DISSERTATION

CATALYTICALLY GENERATED ACYL TRIAZOLIUMS AS VERSATILE ACYLATING REAGENTS AND PROGRESS TOWARD THE TOTAL SYNTHESIS OF OKILACTOMYCIN

Submitted by

Philip Andrew Merris Wheeler

Department of Chemistry

In partial fulfillment of the requirements

For the Degree of Doctor of Philosophy

Colorado State University

Fort Collins, Colorado

Spring 2013

Doctoral Committee:

Advisor: Tomislav Rovis

Yian Shi
Eric Ferreira
Matthew Shores
John D. Fisk

ABSTRACT

CATALYTICALLY GENERATED ACYL TRIAZOLIUMS AS VERSATILE ACYLATING REAGENTS AND PROGRESS TOWARD THE TOTAL SYNTHESIS OF OKILACTOMYCIN

The first chapter of this dissertation describes the development of reactions involving the NHC-catalyzed acylation of carbon and nitrogen nucleophiles. The overall goal of this work was to expand the scope of the NHC-redox reaction manifold and improve its applicability to the synthesis of products that would be useful to the organic chemistry community. An efficient and simple procedure for the preparation of amides from amine hydrochloride salts and α,β-unsaturated aldehydes was developed. This procedure was then applied to the asymmetric synthesis of α-fluoroamides which are valuable building blocks for the preparation of fluorinated compounds that are highly sought after in pharmaceutical, material, and agrichemical applications.

The second chapter describes efforts toward the total synthesis of the complex polyketide natural product okilactomycin, enabled by the rhodium-catalyzed desymmetrization of 3,5-dimethylglutaric anhydride developed previously by our group. Progress includes construction of the entire carbon skeleton in two fragments, poised to be unified and elaborated to the natural product by closely precedented steps. This progress demonstrates the potential of the catalytic, enantioselective desymmetrization of anhydrides to build complexity in rapid fashion.

ACKNOWLEDGEMENTS

First, I'd like to thank my advisor, Tom Rovis, for his teaching, guidance, and most importantly patience. This experience would have been unbearable without an advisor as brilliant and flexible as Tom is. He has always inspired me to keep exploring new ideas while delving deeper into current ones, and despite their ever-increasing wear, the words "What else you got?" will stick with me for the foreseeable future.

Many thanks go to my committee members, Yian Shi, Matt Shores, Nick Fisk, and especially Eric Ferreira for agreeing to be a replacement on short notice. Also, I am grateful to John Wood for writing a reference letter.

I'd also like to thank my fellow group members for their input, both scientific and personal. Everyone in the group wants to see one another succeed, and with that in mind, we are always challenging each other's ideas and providing (mostly) constructive criticism. Specifically, I'd like to thank Harit Vora and Stéphane Perrault for their mentorship while I was a young graduate student. Their feedback helped me tremendously.

I would be remiss not to thank a few other scientists who encouraged me to pursue a doctorate in the first place: Mike Achmatowicz, Oliver Thiel, Tiffany Thiel, and Johann Chan. Their mentorship while I was working as an associate was invaluable to my development as a chemist before I came to graduate school, and I am grateful for the opportunity I had to work with them. I'd also like to thank my undergraduate mentor Brian Gerstenberger for putting up with me as a nascent organic chemist and making me believe graduate school could be fun.

Finally, Jen, you were crazy to agree to come on this journey with me, but I am so lucky you did. You have been beyond supportive through this chapter of our lives, and I am so very

grateful to have you for the rest of the chapters. There’s nothing I could write to express how much better my life has been with you in it, so I’ll just say thank you and try to do the same for you.

DEDICATION

This work is dedicated the memory of Marjorie Yost and Roger Fernando.

TABLE OF CONTENTS

Chapter One: Catalytically Generated Acyl Triazoliums as Versatile Acylating Reagents........1

1.1 Introduction..1

1.2. Examination of carbon nucleophiles in the NHC-redox manifold..10

1.3. Development of an operationally simple NHC-redox amidation procedure...............................17

1.4. Development of an asymmetric NHC-catalyzed preparation of α-fluoroamides........................26

1.5. Simultaneous kinetic resolution of racemic secondary amines...38

1.6. Conclusion...44

Chapter Two: Progress Toward the Total Synthesis of Okilactomycin.......................................**45**

2.1 Introduction..45

2.2. Retrosynthetic strategy..56

2.3. Construction of the bottom fragment...58

2.4. Early exploration with unsubstituted furylzinc as the nucleophile..59

2.5. Optimization of protected acetylfuran addition and current route...62

2.6. Conclusion..72

Chapter 1 Experimental..**74**

General methods...74

NHC-redox amidation of amine hydrochlorides...76

Preparation of α-fluoroenals for asymmetric amidation...83

Asymmetric preparation of α-fluoroamides..89

Derivatization of α-fluoroamides...98

Chapter 2 Experimental..**100**

General methods...100

Synthesis of the bottom fragment diene...101

Synthesis of the model system top fragment...106

Exploratory synthesis of top fragment..114

Synthesis of the top fragment..119

Appendix...**126**

Spectral Data for Chapter 1..126

Spectral Data for Chapter 2..216

CHAPTER ONE: CATALYTICALLY GENERATED ACYL TRIAZOLIUMS AS VERSATILE ACYLATING REAGENTS

1.1 Introduction

The reversal of polarity of carbonyl compounds, or *umpolung*,[1] is a concept that furnishes new possibilities for bond disconnection in organic synthesis. By a variety of methods, carbonyl compounds that would normally be considered electrophilic at the carbon can be rendered nucleophilic. Polarity-reversed carbonyl compounds such as these are often referred to as acyl anion equivalents. These species can be utilized to access a number of otherwise challenging intermediates such as 1,4-dicarbonyls, which are important synthons for a number of structural motifs including furans, pyrroles, and thiophenes.[2] Acyl anion equivalents can be formed stoichiometrically in the case of the Corey-Seebach reaction[3] or catalytically in the case of thiamine-mode-of-action-related intermediates.[4] These reactions have been utilized in the synthesis of achiral and racemic products for many years, one notable example being the preparation of atorvastatin (Lipitor™) via a thiamine-catalyzed Stetter reaction (Figure 1.1.1).[5]

---

[1] Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239-258.

[2] (a) Paal, C. *Chem. Ber.* **1884**, *17*, 2756-2767. (b) Knorr, L. *Chem. Ber.* **1884**, 2863-2870.

[3] (a) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40,* 231. (b) Seebach, D.; Wilka, E.-M. *Synlett*, **1976**, 476-477.

[4] (a) Kluger, R.; Tittman, K. *Chem. Rev.* **2008**, *108(6),* 1797-1833. (b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606-5655.

[5] (a) Roth, B. D.; Ortwine, D. F.; Hoefle, M. L.; Stratton, C. D.; Sliskovic, D. R.; Wilson, M. W.; Newton R. S. *J. Med. Chem.* **1990**, *30*, 21-31. (b) Baumann, K. L.; Butler, D. E.; Deering, C. F.; Mennen, K. E.; Millar, A.; Nanninga, T. N.; Palmer, C. W.; Roth, B. D. *Tetrahedron Lett.* **1992**, *33(17)*, 2283-2284.

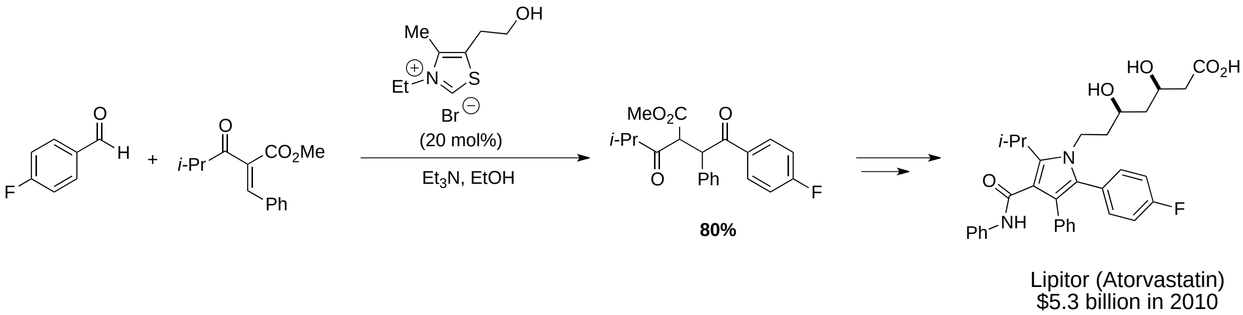


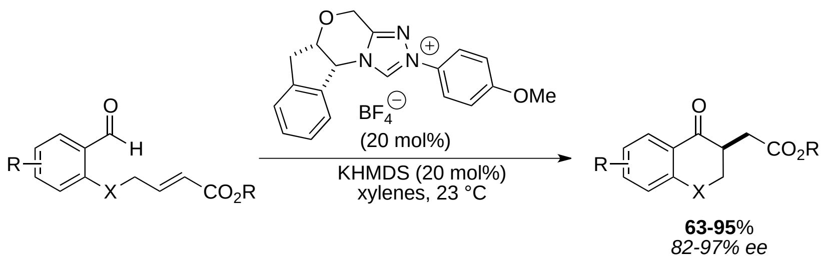
Figure 1.1.1. Thiamine-catalyzed Stetter reaction applied to the synthesis of Lipitor.

Asymmetric variants of the Stetter reaction have been the subject of considerable interest within the field of organocatalysis,[6] and our studies have resulted in the development of a number of chiral triazolium precatalysts that promote highly efficient and enantioselective reactions.[7] Each of these triazoliums can be deprotonated with a variety of bases to form the active *N*-heterocyclic carbene (NHC) catalyst, which when reacted with an aldehyde generates an acyl anion equivalent. In our earliest examples, this acyl anion reacts with a tethered enoate or enone to give chromanone products (eq 1).[7a-c] Later, we reported an intramolecular desymmetrization of dienone substrates (eq 2).[7d] In subsequent work, we have demonstrated highly enantioselective intermolecular Stetter reactions on both alkylidene malonate [7g] (eq 3) and nitroalkene[7h-i] (eq 4) Michael acceptors.

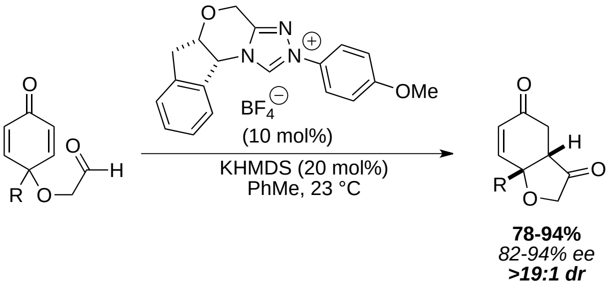
---

[6] Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606-5655.

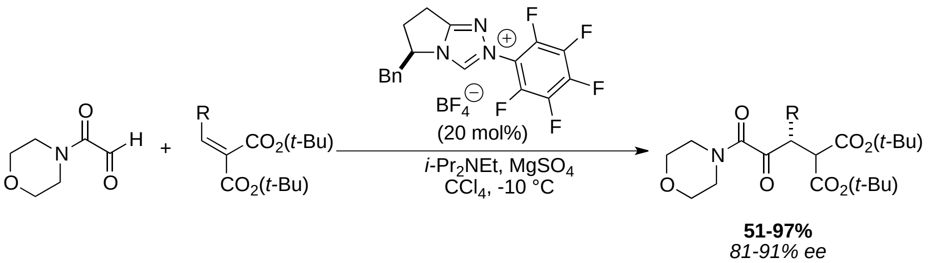
[7] (a) Kerr, M.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.*, **2002**, *124*, 10298–10299. (b) Kerr, M.; Rovis, T. *J. Am. Chem. Soc.*, **2004**, *126*, 8876–8877. (c) Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.*, **2005**, *127*, 6284–6289. (d) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.*, **2006**, *128*, 2552–2553. (e) Liu, Q.; Rovis, T. *Org. Process Res. Dev.*, **2007**, *11*, 598–604. (f) Kerr, M.; Read de Alaniz, J.; Moore, J.; Rovis, T. *J. Org. Chem.*, **2008**, *73*, 2033–2040 (g) Liu, Q.; Perrault, S.; Rovis, T. *J. Am. Chem. Soc.*, **2008**, *130*, 14066–14067. (h) DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 10872-10874. (i) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 10402-10405.


O
H
R
X
CO₂R
O
N
N
N
OMe
BF₄
(20 mol%)
KHMDS (20 mol%)
xylenes, 23 °C
O
R
X
CO₂R
63-95%
82-97% ee

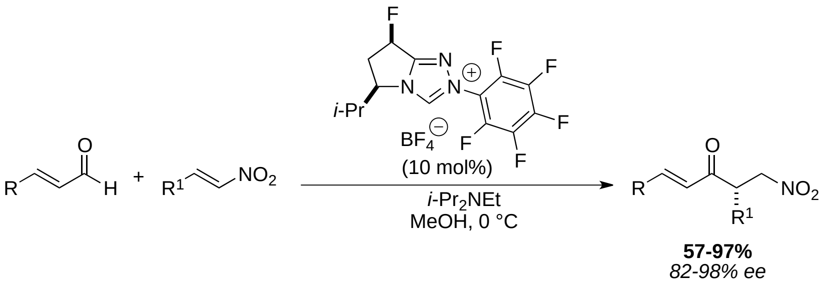
(1)


O
O
H
R
O
N
N
N
OMe
BF₄
(10 mol%)
KHMDS (20 mol%)
PhMe, 23 °C
O
H
O
R
O
78-94%
82-94% ee
>19:1 dr

(2)


O
N
O
O
H
+
R
CO₂(t-Bu)
CO₂(t-Bu)
N
N
N
Bn
F
F
F
F
F
BF₄
(20 mol%)
i-Pr₂NEt, MgSO₄
CCl₄, -10 °C
O
R
N
O
O
CO₂(t-Bu)
CO₂(t-Bu)
51-97%
81-91% ee

(3)


R
O
H
+
R¹
NO₂
F
N
N
N
i-Pr
F
F
F
F
F
BF₄
(10 mol%)
i-Pr₂NEt
MeOH, 0 °C
R
O
NO₂
R¹
57-97%
82-98% ee

(4)

The structure of the active nucleophile in these reactions was first proposed by Ronald Breslow and therefore coined the Breslow intermediate.[8] It is formed by addition of the active catalyst (cyanide or carbene) to the aldehyde followed by proton transfer to generate nucleophilic alkene **I** (Figure 1.1.2). This nucleophilic alkene can also be represented in the resonance form that places an anion at the carbon that was formerly the aldehyde (the acyl anion equivalent) and is the key to the *umpolung* reactivity observed in these reactions.

---

[8] Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719-3726.

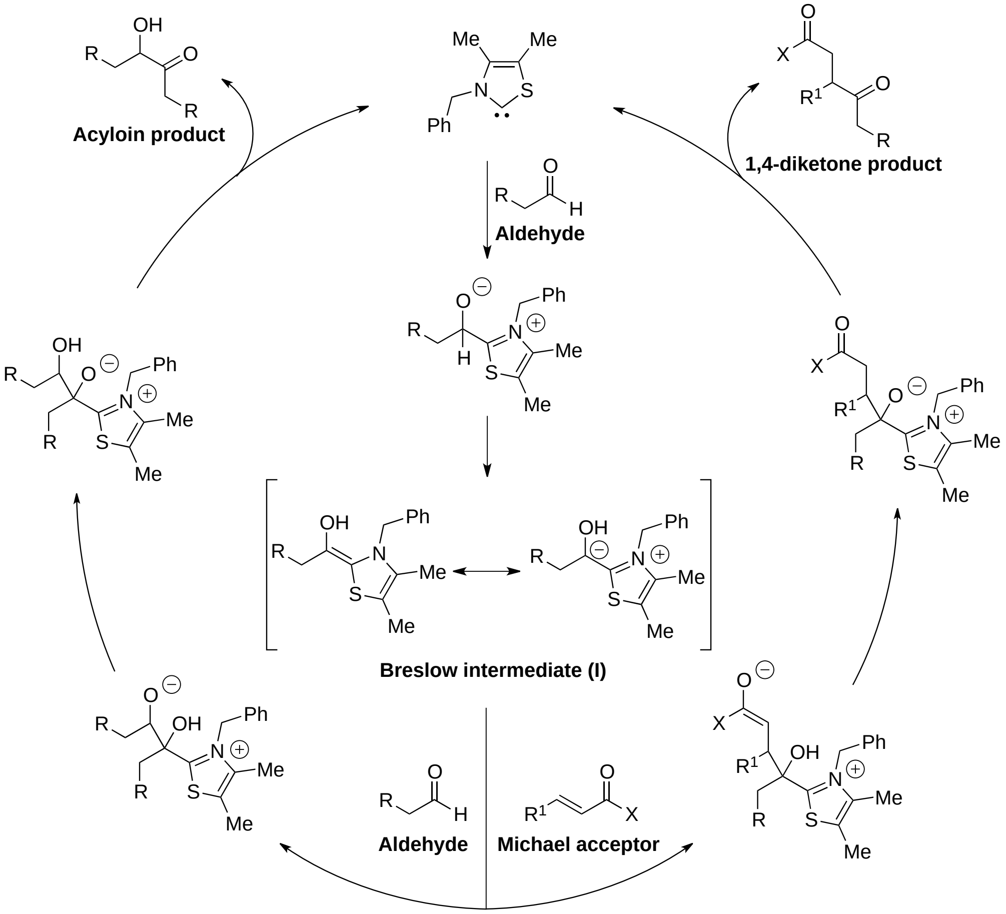
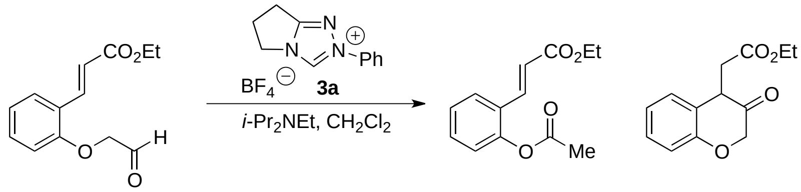

Acyloin product
1,4-diketone product
Aldehyde
Breslow intermediate (I)
Aldehyde
Michael acceptor
Me
Me
N
S
Ph
OH
R
O
X
R¹
Me

Figure 1.1.2. Mechanism of benzoin and Stetter reactions.

During the course of the study of Stetter-type reactions, a pathway distinct from typical acyl anion reactivity was discovered. Namely, we found that aldehyde **1** bearing a phenol at the α-position did not participate in normal Stetter reactivity but rather through an internal redox process wherein the α-leaving group is eliminated and the aldehyde is converted to an acetyl group in the product **2** (eq 5).[9]

---

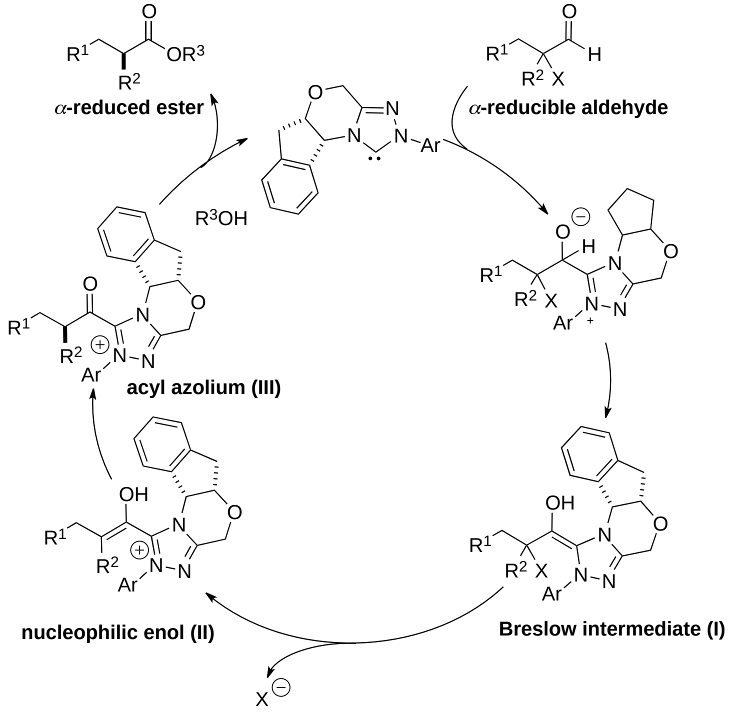
[9] Read de Alaniz, J. Ph. D. Thesis, Colorado State University, Spring 2006.



CO_2Et
$BF_4^{\ominus}$
3a
i-Pr_2NEt, CH_2Cl_2
CO_2Et
Me
CO_2Et

1 2 not observed (5)

This reactivity can be explained by examination of the Breslow intermediate **I** (Figure 1.1.3). When a leaving group such as phenol is present, the nucleophilic alkene, rather than attack an electrophile in a bimolecular process, can unimolecularly eliminate the leaving group to furnish nucleophilic enol **II**. This enol tautomerizes to an activated carboxylate, acyl azolium **III**, which upon displacement with a suitable nucleophile such as an alcohol regenerates the catalyst and gives the observed product.[10]



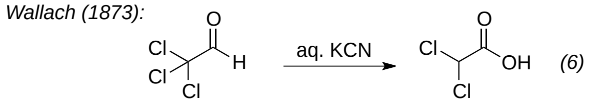
α-reduced ester
α-reducible aldehyde
R^3OH
acyl azolium (III)
nucleophilic enol (II)
Breslow intermediate (I)
$X^{\ominus}$

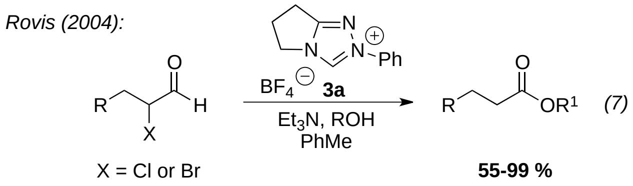
Figure 1.1.3. Mechanism of NHC-redox esterification.

---

[10] (a) Kötz, A. *J. Prakt. Chem.* **1913**, *88*, 531-522. (b) Nowak, R. M. *J. Org. Chem.* **1963**, *28*, 1182.

This reaction manifold was first discovered with cyanide by Wallach (eq 6)[11] and has been applied by our group and others to facilitate to formation of a variety of products from simple esters, amides, and carboxylic acids to numerous heterocycles and carbocycles.[12] For instance, α-chloro and α-bromoaldehydes can be converted to saturated ester products **3** (Equation 7).[13] This family of reactions is characterized by concomitant reduction at the α-position and oxidation at the carbonyl and is commonly referred to as NHC-redox.





In a related example, α,β-unsaturated aldehydes can also be converted to saturated esters **4** by treatment with a benzimidazolium **5** and base in the presence of an alcohol (eq 8).[14] This reaction occurs by addition of the active carbene to the aldehyde, forming the Breslow intermediate **I** (Figure 1.1.4). The presence of an olefin in conjugation with the nucleophilic alkene makes it possible for the Breslow intermediate to react in a vinylogous fashion with an exogenous electrophile, proton in the simplest cases. Substitution at the β-position leads to enol **II** which can tautomerize to the acyl azolium **III**. This is intercepted by a nucleophile to give the observed products.

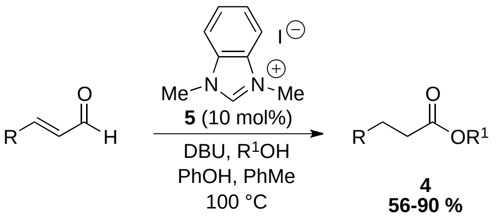
---

[11] Wallach, O. *Annalen* **1873**, *6*, 114-119.

[12] (a) Vora, H. U.; Wheeler, P.; Rovis, T. *Adv. Synth. Catal.* **2012**, *354*, 1617-1639. (b) Rong, Z.-Q.; Zhang, W.; Yang, G.-Q.; You, S.-L. *Curr. Org. Chem.* **2011**, *15*, 3077-3090.

[13] (a) Chow, K. Y.-K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126-8127. (b) Reynolds, N.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.*, **2004**, *126*, 9518-9519. (c) Reynolds, N.; Rovis, T. *J. Am. Chem. Soc.*, **2005**, *127*, 16406–16407.

[14] (a) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905-908. (b) Sohn, S.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3873-3876.



(8)

This alternative *umpolung* has been termed “homoenolate” reactivity because this position in the α,β-unsaturated aldehyde would be normally considered electrophilic, and it is transformed into a nucleophile. This catalytic pathway has been studied by a number of groups, and can lead to a variety of carbon-carbon bond formations to give oxygen heterocycles,[15] nitrogen heterocycles,[16] and carbocycles.[17]

---

[15] (a) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370-14371. (b) Burstein, C.; Glorius, F. *Angew. Chem. Int. Ed.* **2004**, *43*, 6205-6208. (c) Burstein, C.; Tschan, S.; Xie, X.; Glorius, F. *Synthesis* **2006**, 2418-2439. (d) Cohen, D. T. ; Scheidt, K. A. *Chem. Sci.* **2012**, 53-57. (e) Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *Org. Lett.* **2006**, *8*, 507-509. (f) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E.; Viji, S. *Synthesis* **2007**, 3195-3200. (g) Li, Y.; Zhao, Z.-A.; He, H.; You, S.-L. *Adv. Synth. Catal.* **2008**, *350*, 1885-1890. (h) Nair, V.; Poonoth, M.; Vellalath, S.; Suresh, E.; Thirumalai, R. *J. Org. Chem.* **2006**, 8964-8965.

[16] (a) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131-3134. (b) Rommel, M.; Fukuzumi, T.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 17266-17267. (c) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5334-5335. (d) Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2416-2417. (e) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2740-2741. (f) Raup, D. E. A.; Cardinal-David, B.; Holte, D.; Scheidt, K. A. *Nat. Chem.* **2010**, *2*, 766-771. (g) Zhao, X.; DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 12466-12469.

[17] (a) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736-8737. (b) Nair, V.; Babu, B. P.; Vellalath, S.; Suresh, E. *Chem. Commun.* **2008**, 747-749. (c) Verma, P.; Patni, P. A.; Sunoj, R. B. *J. Org. Chem.* **2011**, *76*, 5606-5613. (d) Nair, V.; Babu, B. P.; Vellalath, S.; Varghese, V.; Raveendran, A. E.; Suresh, E. *Org. Lett.* **2009**, *11*, 2507-2510. (e) Chiang, P.-C. Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 3520-3521. (f) Chiang, P.-C.; Rommel, M.; Bode, J. W. *J. Am. Chem. Soc.* **2009**, *131*, 8714-8718. (g) Cardinal-David, B.; Raup, D. E. A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2010**, 5345-5347. (h) Cohen, D. T.; Cardinal-David, B.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 1678-1682. (i) De Sarkar, S.; Studer, A. *Org. Lett.* **2010**, *12*, 1992-1995. (j) De Sarkar, S.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2010**, *132*, 1190-1191. (k) De Sarkar, S.; Biswas, A.; Song, C. H.; Studer, A. *Synthesis* **2011**, 1974-1983.

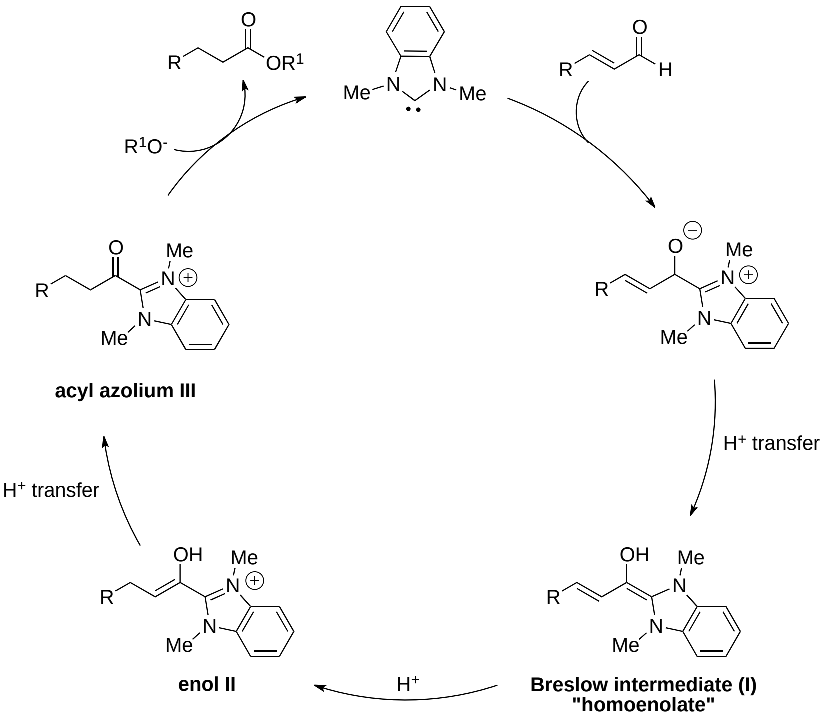


Figure 1.1.4. Homoenolate reactivity.

The scope of the NHC-redox reaction was extended to amines in 2007.[18] Using a catalytic amount of triazolium **3b** and 7-aza-1-hydroxybenzotriazole (HOAt), our group demonstrated that α-chloroamide products **6** can be prepared from a variety α,α-dichloroaldehydes **7** (Figure 1.1.5). This reaction constitutes a waste-reduced, greener alternative to traditional peptide bond forming reactions which commonly use at least one reagent in stoichiometric amount.[19] Furthermore, α,β-epoxy and α,β-aziridinyl aldehydes can be elaborated to β-hydroxy **8** and β-amino amides **9**, respectively, in excellent diastereoselectivity. Saturated amides **10** can also be formed from α,β-unsaturated aldehydes. Using chiral triazolium **11a,** enantioselective formation of α-chloroamide

---

[18] (a) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 13796–13797. (b) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798–13799.

[19] (a) Han, S.-Y.; Kim, Y.-A. *Tetrahedron* **2004**, *60*, 2447-2467. (b) El-Faham, A.; Albericio, F. *Chem. Rev.* **2011**, *111*, 6557-6602.

6a was also demonstrated, but the enantioselectivity of this reaction is modest (eq 9). The reasons for this low selectivity will be discussed in a later section.

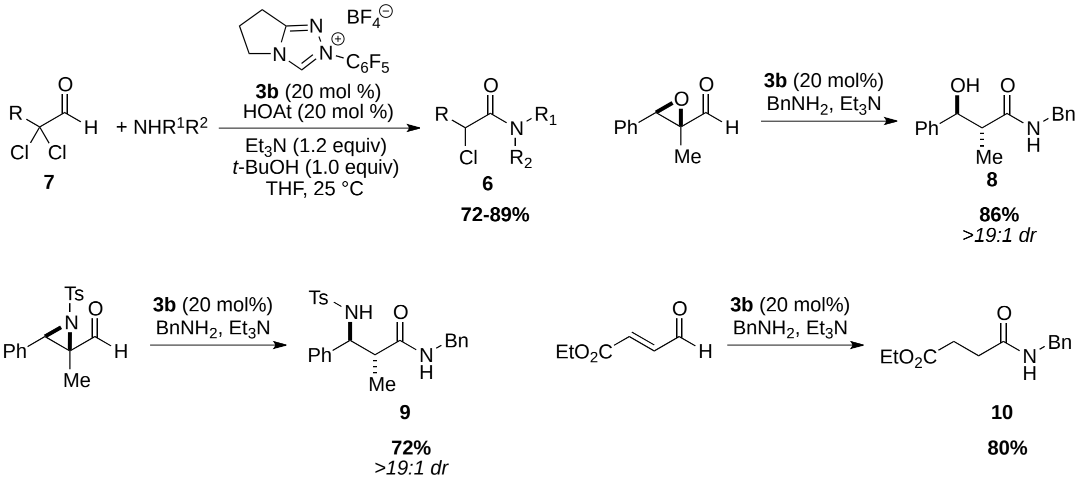
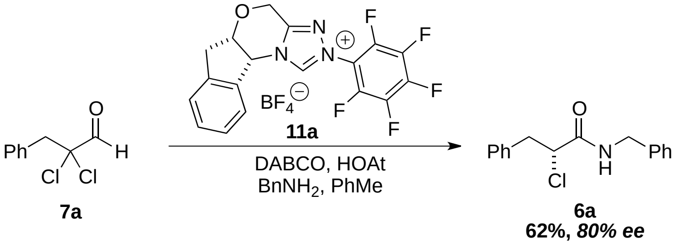

3b (20 mol %)
HOAt (20 mol %)
Et3N (1.2 equiv)
t-BuOH (1.0 equiv)
THF, 25 °C
7
6
72-89%
3b (20 mol%)
BnNH2, Et3N
8
86%
>19:1 dr
9
72%
>19:1 dr
10
80%

Figure 1.1.5. Selected NHC-redox amidation results.


11a
DABCO, HOAt
BnNH2, PhMe
7a
6a
62%, 80% ee

(9)

Since the initial reports by our group and the group of Jeffrey Bode,[18b] many related applications of the NHC-redox amidation have appeared,[20] including an example used in total synthesis.[21] Continued interest in the area speaks to the potential of the NHC-redox manifold, and this chapter will describe my efforts to further expand the scope of this versatile reaction type.

---

[20] a) Li, G.-Q.; Li, Y.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2007**, *9*, 3519–3521. b) Li, G.-Q.; Li, Y.; Dai, L.-X.; You, S.-L. *Adv. Synth. Catal.* **2008**, *350*, 1258–1262. c) Thai, K.; Wang, L.; Dudding, T.; Bilodeau, F.; Gravel, M. *Org. Lett.* **2010**, *12*, 5708–5711. d) Kuwano, S.; Harada, S.; Oriez, R.; Yamada, K. I. *Chem. Commun.* **2012**, 145–147. e) Wang, B.; Forsyth, C. J. *Synthesis* **2009**, 2873–2880.

[21] Forsyth, C. J.; Wang, B.; Huang, P. H.; Chen, C. S. *J. Org. Chem.* **2011**, *76*, 1140–1150.

1.2. Examination of carbon nucleophiles in the NHC-redox manifold

When my work began on this project, alcohols[12,13] and amines[17] had been demonstrated as competent nucleophiles in this reaction manifold to form ester and amide products. Additionally, a number of NHC-catalyzed cycloadditions and annulation reactions of α-reducible aldehydes to form carbon-carbon bonds had also been demonstrated,[14-16] but none of these methods resulted in a carbon-carbon bond forming at the carbonyl of the reducible aldehyde (Figure 1.2.1).

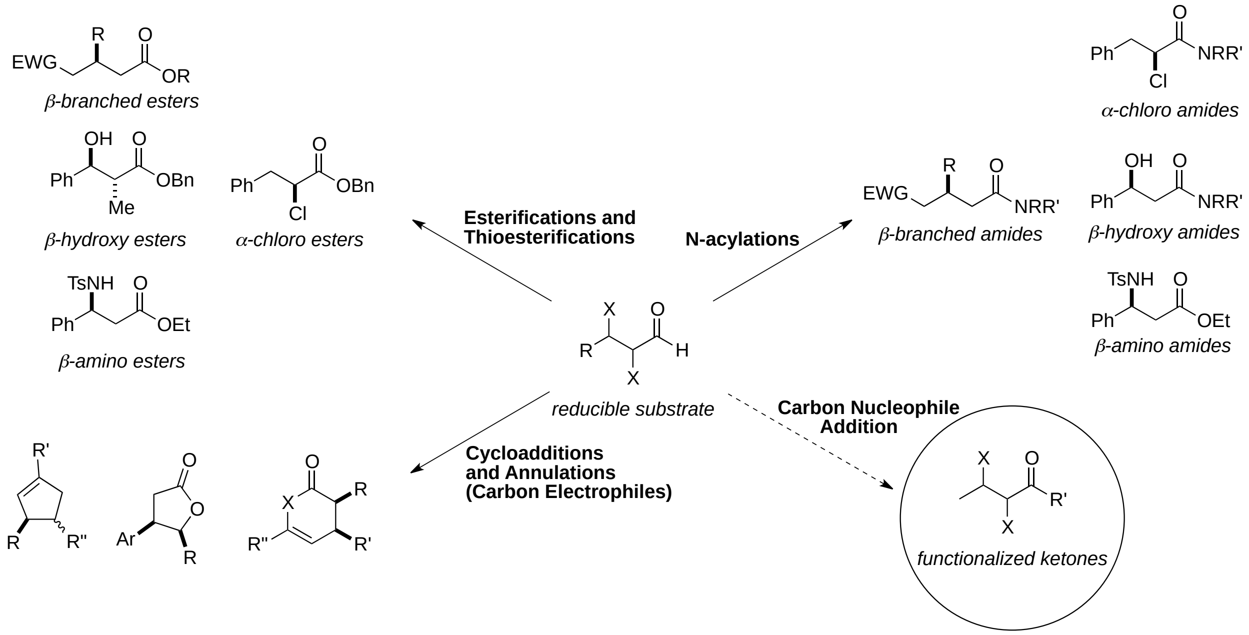

β-branched esters
β-hydroxy esters
α-chloro esters
β-amino esters
Esterifications and Thioesterifications
N-acylations
α-chloro amides
β-branched amides
β-hydroxy amides
β-amino amides
reducible substrate
Cycloadditions and Annulations (Carbon Electrophiles)
Carbon Nucleophile Addition
functionalized ketones

Figure 1.2.1. Representative transformations of reducible aldehyde substrates circa 2007.

We sought to expand the scope of this reaction manifold to include carbon nucleophiles, which could intercept the acyl azolium **III** (Figure 1.1.3) to provide ketones from aldehydes in a single step. Furthermore, this catalytic process could potentially be rendered asymmetric. However, the propensity of many carbon nucleophiles to add directly to aldehydes presented a significant challenge. Phosphorus ylides, enolates, and allylmetals all resulted in direct addition, giving olefin products in the case of ylides and alcohol products in the others. No desired ketone product could be detected under any of these conditions, limiting our possible solutions to the problem of carbon nucleophiles to the acyl azolium (Figure 1.2.2).

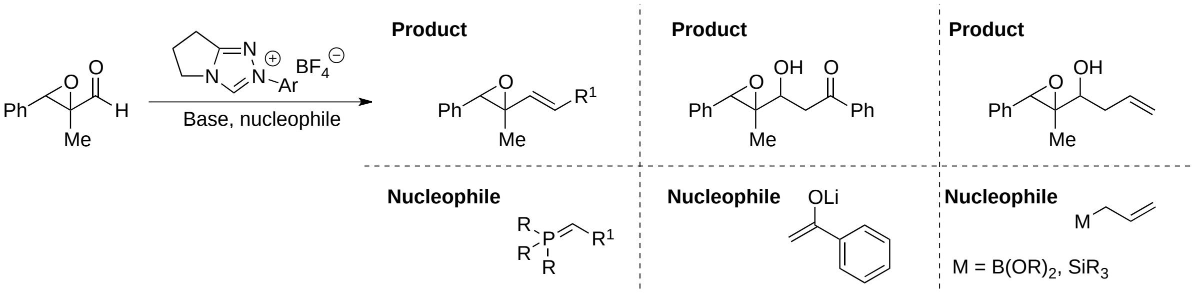


Figure 1.2.2. Attempted carbon nucleophile additions.

One enol nucleophile was found to be effective at displacing the acyl azolium without significant direct addition to the aldehyde: cyclohexanedione (**13**).[22] Under standard conditions using cinnamaldehyde **12** as the α-reducible aldehyde with diisopropylethylamine as the base, triketone **14** could be isolated in modest yield (eq 10). Attempts to optimize this reaction were made by screening solvent and base (Table 1.2.1), but conditions could not be identified to provide the triketone in greater than 55% yield. The mass balance in each of these reactions was made up of hydrocinnamic acid **15**, which could come from hydrolysis of the acyl azolium or from *O*-acylation of cyclohexanedione to give ester **16**, which upon workup would be expected to hydrolyze to the same product. Neither vigorous drying of the reaction vessel nor addition of excess aldehyde reduced the amount of this product; therefore, we hypothesized that *O*-acylation was the issue.

---

[22] This discovery was made by my colleague Stephen Lathrop while investigating another NHC-catalyzed reaction. The carbon addition product was found as a side product in his reaction.

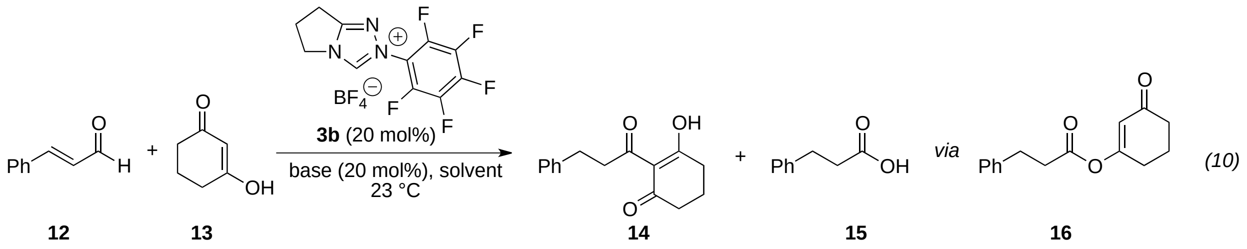


Table 1.2.1. Optimization of cyclohexanedione addition.

Entry	Solvent	Base	Conc (M)	Note	Yield of 14 (%)
1	PhMe	KHMDS	0.2	-	**13**
2	PhMe	KHMDS	0.1	-	**37**
3	CH_2Cl_2	KHMDS	0.2	-	**46**
4	CH_2Cl_2	*t*-BuOK	0.2	-	**38**
5	CH_2Cl_2	Et_3N	0.2	-	**24**
6	CH_2Cl_2	DBU	0.2	-	**20**
7	CH_2Cl_2/*t*-BuOH	*t*-BuOK	0.2	4Å MS added	**45**
8	CH_2Cl_2/*t*-BuOH	*t*-BuOK	0.1	4Å MS added	**50**
9	CH_2Cl_2/*t*-BuOH	*t*-BuOK	0.05	4Å MS added	**45**
10	PhMe/*t*-BuOH	*t*-BuOK	0.1	4Å MS added	**37**
11	CH_2Cl_2/*t*-BuOH	*t*-BuOK	0.2	1.5 equiv **12**	**23**
12	CH_2Cl_2/*t*-BuOH	*t*-BuOK	0.2	2.0 equiv **12**	**30**
13	CH_2Cl_2/*t*-BuOH	*t*-BuOK	0.2	2.0 equiv **12**	**50**

With the goal of preventing *O*-acylation, we looked to methods for selective *C*-acylation of enolate nucleophiles. Particularly, we thought that a benzotriazole amide might be an effective acylating reagent for a carbon nucleophile under the NHC-redox reaction conditions, as Katritzky and others have demonstrated this kind of intermediate as a selective *C*-acylating reagent for enolates.[23] Acylbenzotriazole **17** is prepared in good yield from cinnamaldehyde (Figure 1.2.3) and subsequent reaction with acetophenone under soft enolization conditions gives β-diketone **18** in 53% yield. However, combining these two reactions into a single pot proved unsuccessful. When the reaction is conducted with all reagents present from the start, aldol product **19** is obtained, and when **17** is prepared stoichiometrically and the acetophenone enolate is added slowly to that reaction mixture, no β-diketone **18** is obtained.

---

[23] (a) Katritzky, A.R.; Pastor, A. *J. Org. Chem.*, **2000**, *65*, 3679-3682. (b) Katritzky, A.R.; Abdel-Fattah, A.A.A.; Wang, M. *J. Org. Chem.* **2003**, *68*, 1443-1446. (c) Katritzky, A.R.; Abdel-Fattah, A.A.A.; Wang, M. *J. Org. Chem.* **2003**, *68*, 4932-4934. (d) Katritzky, A.R.; Wang, Z.; Wang, M.; Wilkerson, C.R.; Hall, C.D.; Akhmedov, N.G. *J. Org. Chem.* **2004**, *69*, 6617-6622. (e) Yost, J.M.; Zhou, G.; Coltart, D.M. *Org. Lett.* **2006**, *8*, 1503. (f) Lim, D.; Fang, F.; Zhou, G.; Coltart, D.M. *Org. Lett.* **2007**, *9*, 4139. (g) Zhou, G.; Yost, J.M.; Coltart, D.M. *Synthesis* **2007**, 478. (h) Lim, D.; Zhou, G.; Livanos, A.E.; Fang, F.; Coltart, D.M. *Synthesis*, **2008**, 2148-2152.

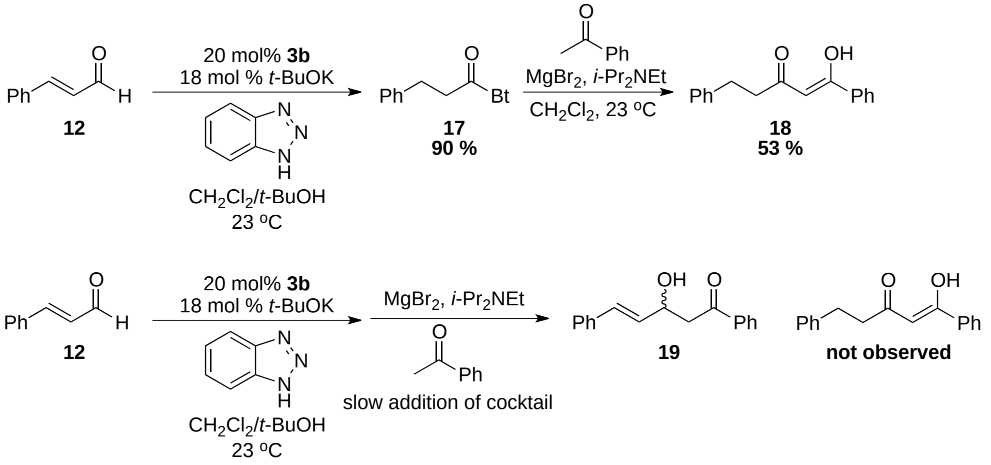

12
20 mol% 3b
18 mol % t-BuOK
CH2Cl2/t-BuOH
23 °C
17
90 %
MgBr2, i-Pr2NEt
CH2Cl2, 23 °C
18
53 %
12
20 mol% 3b
18 mol % t-BuOK
CH2Cl2/t-BuOH
23 °C
MgBr2, i-Pr2NEt
slow addition of cocktail
19
not observed

Figure 1.2.3. Acylbenzotriazole as a selective C-acylation reagent.

Another possible way to circumvent direct addition might be to couple the NHC-redox esterification reaction with a transition metal catalyzed acyl coupling. Since the first report of acid chlorides as suitable partners in the Stille coupling,[24] a number of other acyl electrophiles, including acyl fluorides,[25] anhydrides,[26] thioesters[27] and certain esters[28] have been demonstrated in cross couplings to give ketone products. We were particularly interested in the precedent involving esters and thioesters (eqs 11-14) because the NHC-redox reaction manifold had also been demonstrated to furnish these products efficiently.[12-13] We were aware, however, that NHCs are good ligands for many of the transition metal catalysts employed for these reactions,[29] but despite this fact, a number of examples of transition metal catalyzed processes in the presence of non-coordinated NHCs have been reported.[30] Furthermore, the NHCs used as ligands for transition metals are considerably more Lewis basic that the electron deficient triazolium-derived carbenes we have used to catalyze the NHC-redox reaction.

---

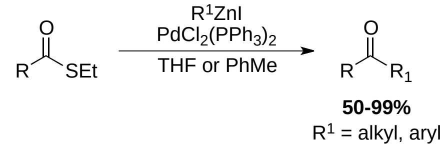
[24] (a) Kosugi, M.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 1423. (b) Kosugi, M.; Shimizu, Y.; Migita, T. *J. Organomet. Chem.* **1977**, *129*, C36. (c) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636. (d) Milstein, D.; Stille, J. K. *J. Org. Chem* **1979**, *44*, 1613. (e) Bumagin, N.A.; Korolev, D.N. *Tetrahedron Lett.* **1999**, *40*, 3057-3060.

[25] Zhang, Y.; Rovis, T *J. Am. Chem. Soc.* **2004**, *126*, 15964-15965.

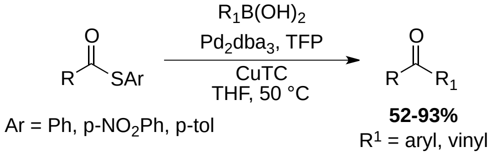
[26] (a) Kakino, R.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn* **2001**, *72*, 799-803. (b) Gooßen, L.J.; Ghosh, K. *Angew. Chem. Int. Ed.* **2001**, *40*, 3458-3460. (c) Gooßen, L.J.; Paetzgold, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1237-1241. (d) Gooßen, L.J.; Ghosh, K. *Eur. J. Org. Chem.* **2002**, *19*, 3254-3267.

[27] (a) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189-3192. (b) Hayashi, Y.; Itoh, T.; Fukuyama, T. *Org. Lett.*, **2003**, *5*, 2235-2238. (c) Tokuyama, H.; Miyazaki, T.; Yokoshima, S.; Fukuyama, T. *Synlett*, **2003**, *10*, 1512-1514. (d) Miyazaki, T.; Han-ya, Y.; Tokuyama, H.; Fukuyama, T. *Synlett*, **2004**, *3*, 477-480. (e) Fukuyama, T.; Tokuyama, H. *Aldrichimica Acta*, **2004**, *37(3)*, 87-96. (f) Savarin, C.; Srogl, J.; Liebeskind, L.S. *Org. Lett.*, **2000**, *2*, 3229-3231. (g) Srogl, J.; Liebeskind, L. *J. Am. Chem. Soc.* **2000**, *122*, 11260-11261. (h) Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L.S. *Org. Lett.*, **2003**, *5*, 3033–3035. (i) Villalobos, J.M.; Srogl, J.; Liebeskind, L.S. *J. Am. Chem. Soc.*, **2007**, *129*, 15734–15735.

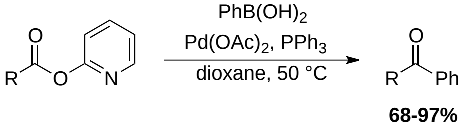
[28] (a) Tatamidani, H.; Kakiuchi, F.; Chatani, N. *Org. Lett.*, **2004**, *6*, 3597–3599. (b) Tatamidani, H.; Yokota, K.; Kakiuchi, F.; Chatani, N. *J. Org. Chem.*, **2004**, *69*, 5615–5621.



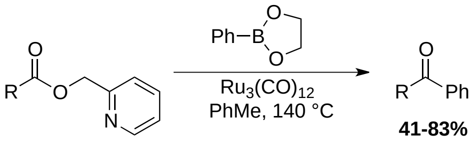
(11)



(12)



(13)



(14)

Because reactive organometallic reagents had been found to add directly to the aldehyde substrates (*vide supra*), we knew a mild nucleophile would be necessary for a successful co-catalytic process. A palladium-catalyzed cross coupling of aryl thioesters with boronic acids is known (eq 12).[25f] I prepared thioester **20** from cinnamaldehyde under standard NHC-redox conditions and reproduced the cross coupling to give hydrochalcone **21** (Figure 1.2.4).

---

[29] Cabeza, J. A.; del Río, I.; Miguel, D.; Pérez-Carreño, E.; Sánchez-Vega, M.G. *Organometallics*, **2008**, *27,* 211-217.

[30] (a) Nemoto, T.; Fukuda, T.; Hamada, Y. *Tetrahedron Lett.* **2006**, *47,* 4365-4368. (b) Lebeuf, R.; Hirano, K.; Glorius, F. *Org. Lett.* **2008**, *10,* 4243-4246. (c) He, J.; Tang, S.; Tang, S.; Liu, J.; Sun, Y.; Pan, X.; She, X. *Tetrahedron Letters* **2009**, *50,* 430–433.

Unfortunately, when the two process were conducted in the same reaction flask, no desired ketone products were obtained. There are many possibilities as to why this reaction fails in one pot. The most likely is that the carbene and transition metal coordinate in such a way to prevent one another from acting as an efficient catalyst.

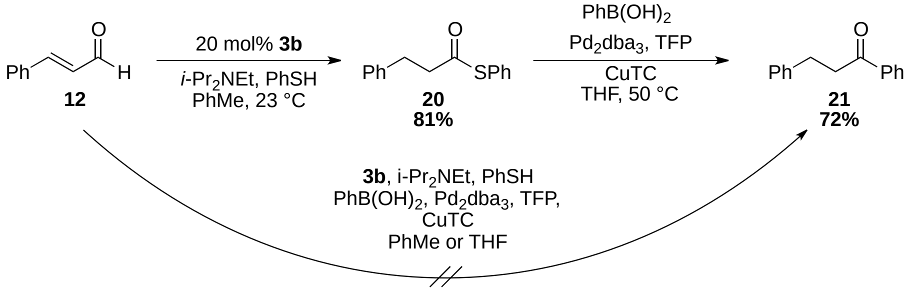
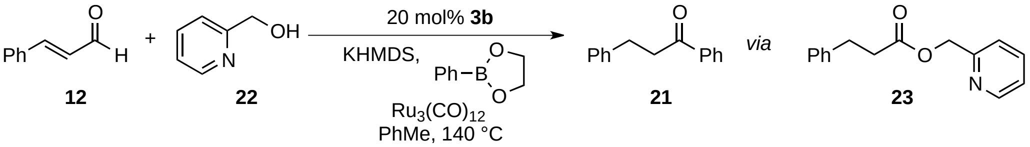


Figure 1.2.4. Redox thioesterification and subsequent cross coupling.

Alternatively, we considered an NHC-redox esterification with pyridinecarbinol **22** and tandem cross coupling as a suitable reaction pair. I prepared pyridinecarbinol ester **23** which Chatani has reported in a ruthenium-catalyzed cross coupling with aryl boronic esters (eq 14). This ester was then treated under Chatani's conditions to give dihydrochalcone **21** in comparable yield to the literature. After screening conditions to combine these reactions in one pot, I found that while the redox esterification with triazolium **3b** is effective in the presence of ruthenium, the desired ketone product **21** can only be obtained when the reaction is run under an atmosphere of carbon monoxide (eq 15, Table 1.2.1). However, the yield of the reaction reflects a single turnover of ruthenium. This suggests that even the electron deficient NHC derived from **3b** deactivates the ruthenium catalyst, and a catalytic process is not feasible.


Ph
O
H
+
N
OH
20 mol% 3b
KHMDS,
Ph−B
O
O
Ru3(CO)12
PhMe, 140 °C
Ph
O
Ph
via
Ph
O
O
N
12
22
21
23

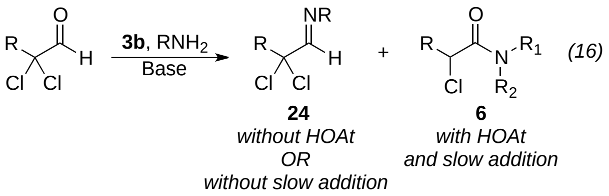
(15)

Table 1.2.2. One-pot redox esterification and cross coupling.

Entry	3b (mol %)	$Ru_3(CO)_{12}$ (mol%)	Atm	Conversion to 23	Yield of 21 (%)
1	5	5	Ar	complete	0
2	5	10	Ar	incomplete	0
3	2.5	5	CO	trace	0
4	5	5	CO	incomplete	0
5	5	10	CO	complete	5
6	5	7.5	CO	incomplete	0
7	7.5	10	CO	complete	5
8	7.5	12.5	CO	complete	5
9	10	13	CO	complete	10
10	10	13	Ar	complete	0

1.3. Development of an operationally simple NHC-redox amidation procedure

At this point, the amidation of α-reducible aldehydes in the co-catalytic process developed by my colleague Harit Vora was revisited. At its inception, this reaction was envisioned to proceed as the earlier esterification had: by catalytic generation of a acyl azolium which could be intercepted by the nucleophilic amine. However, implementation of similar conditions was frustrated by the propensity of the amine to condense on the aldehyde to form an imine **24** (eq 16). This process was non-reversible under the reaction conditions; therefore, a modification was necessary. Namely, slow addition of the amine via syringe pump in the presence of catalytic HOAt or other acyl transfer reagents to accelerate the acylation process enabled the coupling of amines with α-reducible aldehyde substrates to give amide products in excellent yield (Figure 1.1.5). Both of these measures were necessary for efficient reactions; however, with the convenience and simplicity of this method in mind, we would prefer that slow addition was not necessary.



Mechanistically, this reaction is proposed to begin with attack of the carbene on the aldehyde followed by proton transfer to give the Breslow intermediate **I**. Then, the NHC-redox pathway ensues (Figure 1.1.3 or 1.1.4) to give the acyl azolium. Though it is highly efficient at acylating alcohols, the acyl azolium does not react efficiently with amines to give amide products.[31] Rather, HOAt intercepts the acyl azolium to liberate the free carbene and give the activated ester **IV**, which is subsequently attacked by the amine to displace HOAt and give the observed amide product **25**.

---

[31] Mahatthananchai, J.; Zheng, P.; Bode, J. W. *Angew. Chem. Int. Ed.* **2011**, *50*, 1673-1677.

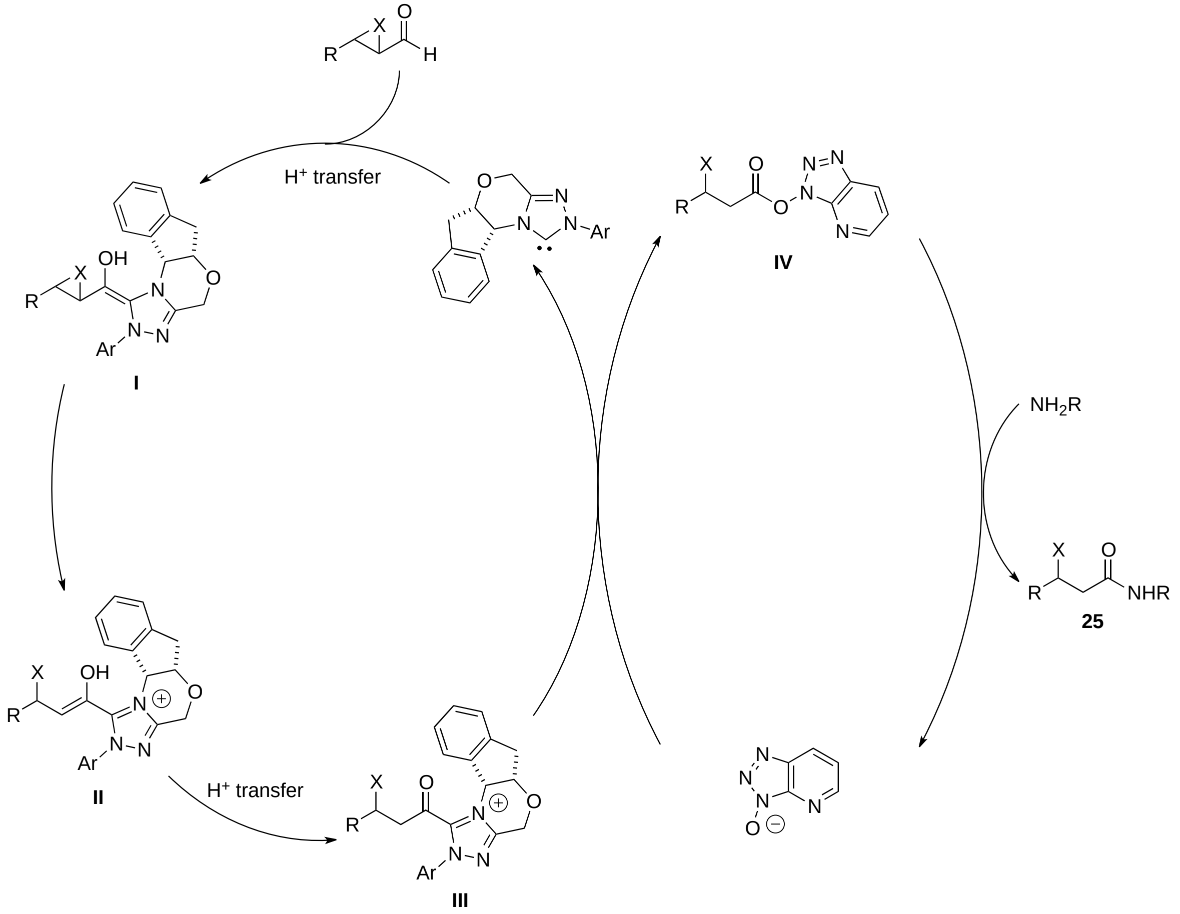
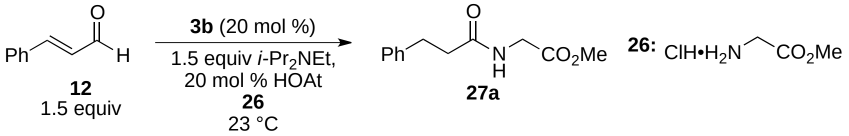


Figure 1.3.1. Proposed co-catalytic cycle for NHC-redox amidation.

Although this work provided a general procedure for the amidation of a variety of α,α-dichloroaldehydes, α,β-epoxyaldehydes and α,β-unsaturated aldehydes, we sought a more convenient and robust method. Namely, we wished to eliminate the need for slow addition of the amine as we saw this as a procedural inconvenience. Early investigation by Dr. Vora into the acylation of amino esters revealed that alkylammonium chloride salts do not lead to imine formation under the reaction conditions. The overall yield of these reactions was low, but it seemed that a door to an alternative to dropwise addition had opened.

After a number of conditions were screened using **12** and glycine methyl ester hydrochloride (**26**) as the substrates, we found that tertiary amine bases in toluene gave the best yields of amide product **27a** with triazolium **3a** (eq 17, Table 1.3.1). Catalyst screening revealed that trichlorophenyl-substituted **3b** was also competent in the reaction, and it was noted that this catalyst gave cleaner crude reactions (eq 18, Table 1.3.2).



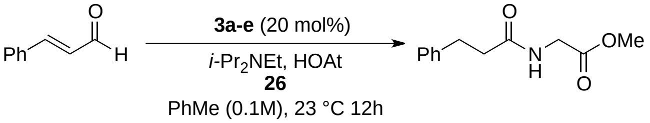
O
Ph
H
12
1.5 equiv
3b (20 mol %)
1.5 equiv i-Pr2NEt,
20 mol % HOAt
26
23 °C
O
Ph
N
H
CO2Me
27a
26: ClH•H2N
CO2Me

(17)

Table 1.3.1. Solvent screening for NHC-redox amidation.

Entry	Solvent	Conc.	Yield	Entry	Solvent	Conc.	Yield
1	THF	0.1M	**<20%***	*5*	CH_3CN	0.1M	**0%**
2	CH_2Cl_2	0.1M	**<20%***	*6*	toluene	0.1M	**32%**
3	ether	0.1M	**trace**	*7*	toluene	0.05M	**23%**
4	dioxane	0.1M	**trace**	*8*	toluene	0.025M	**17%**

* Although product is formed, crude ^{1}H-NMR showed significant impurities and imine formation

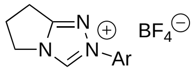


O
Ph
H
3a-e (20 mol%)
i-Pr2NEt, HOAt
26
PhMe (0.1M), 23 °C 12h
O
Ph
N
H
OMe
O

(18)

Table 1.3.2. Catalyst screening for NHC-redox amidation.

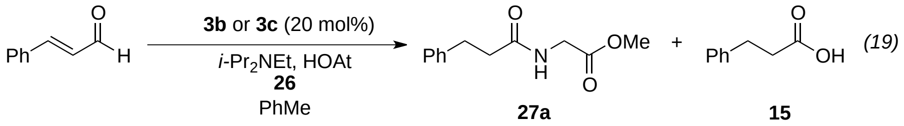
Entry	Catalyst	Yield
1	**3a**	0%*
2	**3b**	32%
3	**3c**	31%
4	**3d**	0%*
5	**3e**	0%*



3a: Ar = phenyl
3b: Ar = pentafluorophenyl
3c: Ar = 2,4,6-trichlorophenyl
3d: Ar = 3,5-bistrifluoromethylphenyl
3e: Ar = *para*-methoxyphenyl

* No desired reaction observed after 24h. Aldehyde is decomposed completely.

A temperature and concentration screen revealed that heating to 70 °C at 0.05M with **3c** as the precatalyst gave the best results, but hydration of the acyl azolium intermediate to give hydrocinnamic acid (**15**) represented a large portion of the reaction mixture (eq 19, Table 1.3.3). Triazolium **3c** also displayed the most favorable yields and ratio of **27a** to **15**.

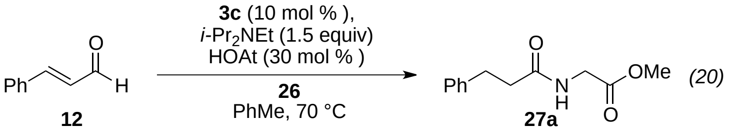


Ph
O
H
3b or **3c** (20 mol%)
i-Pr2NEt, HOAt
26
PhMe
Ph
O
N
H
OMe
O
+
Ph
O
OH
(19)
27a
15

Table 1.3.3. Temperature and concentration screen for NHC-redox amidation.

Entry	Catalyst	Conditions	Yield of 27a	*27a:15*
1	**3b**	0.05M, 23 °C, 12h	**23%**	***3.2:1***
2	**"**	0.1M, 23 °C, 12h	**32%**	***4.9:1***
3	**"**	0.05M, 70 °C, 3h	**23%**	***3.5:1***
4	**"**	0.1M, 70 °C, 3h	**24%**	***3.1:1***
5	**3c**	0.05M, 23 °C, 12h	**37%**	***2.1:1***
6	**"**	0.1M, 23 °C, 12h	**31%**	***1.5:1***
7	**"**	0.05M, 70 °C, 3h	**52%**	***4.3:1***
8	**"**	0.1M, 70 °C, 3h	**50%**	***3.6:1***

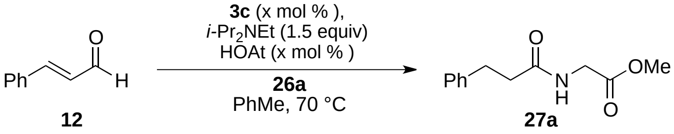
The water necessary to hydrolyze the acyl azolium was presumably being carried in by the hygroscopic amine hydrochloride salt, the drying of which would represent a greater operational challenge than dropwise addition of the amine. Therefore, we screened drying agents and found that the addition of 4Å molecular sieves effectively inhibited hydration. Finally, increasing the equivalents of enal from 1 to 1.5 (eq 20, Table 1.3.4) gave yields in the good to excellent range. Attempts to lower the catalyst loading from 20 mol% led to reduced yield, even when the co-catalyst concentration was increased (eq 21, Table 1.3.5).



3c (10 mol %),
i-Pr2NEt (1.5 equiv)
HOAt (30 mol %)
Ph
O
H
12
26
PhMe, 70 °C
Ph
O
N
H
OMe
O
27a
(20)

Table 1.3.4. Enal equivalents screening for NHC-redox amidation.

Entry	Conditions	Yield of 27a
1	1.0 equiv **12**	**59%**
2	1.1 equiv **12**	**66%**
3	1.2 equiv **12**	**73%**
4	1.3 equiv **12**	**77%**
5	1.5 equiv **12**	**82%**



(21)

Table 1.3.5. Further screening for NHC-redox amidation.

Entry	3c (mol %)	HOAt (mol %)	Temp (°C)	Yield of 27a
1	20	20	70	**87-93%**
2	10	20	70	**69%**
3	5	20	70	**55%**
4	15	30	70	**91%**
5	10	30	70	**82%**
6	5	30	70	**69%**
7	20	20	23	**64%**
8	10	20	23	**41%**
9	10	30	23	**59%**

With optimal conditions in hand, the scope of the reaction was explored. Both secondary and primary amines are tolerated to give tertiary and secondary amide products (Figure 1.3.3). Cinnamaldehydes bearing both electron withdrawing and electron-releasing groups are tolerated, as are a number of aliphatic enals. It was noted, however, that aliphatic enals react more efficiently when 1-hydroxybenzotriazole (HOBt) is used as the acyl transfer reagent. Protected alcohols are tolerated, albeit in reduced yield. Enals bearing α-substitution are unreactive except when an electron withdrawing group is present at the β-position. This observation is consistent with that of the Bode group, and is likely due to allylic strain that would be necessary for the vinylogous Breslow intermediate (homoenolate) to protonate at the β-position (Figure 1.3.4).

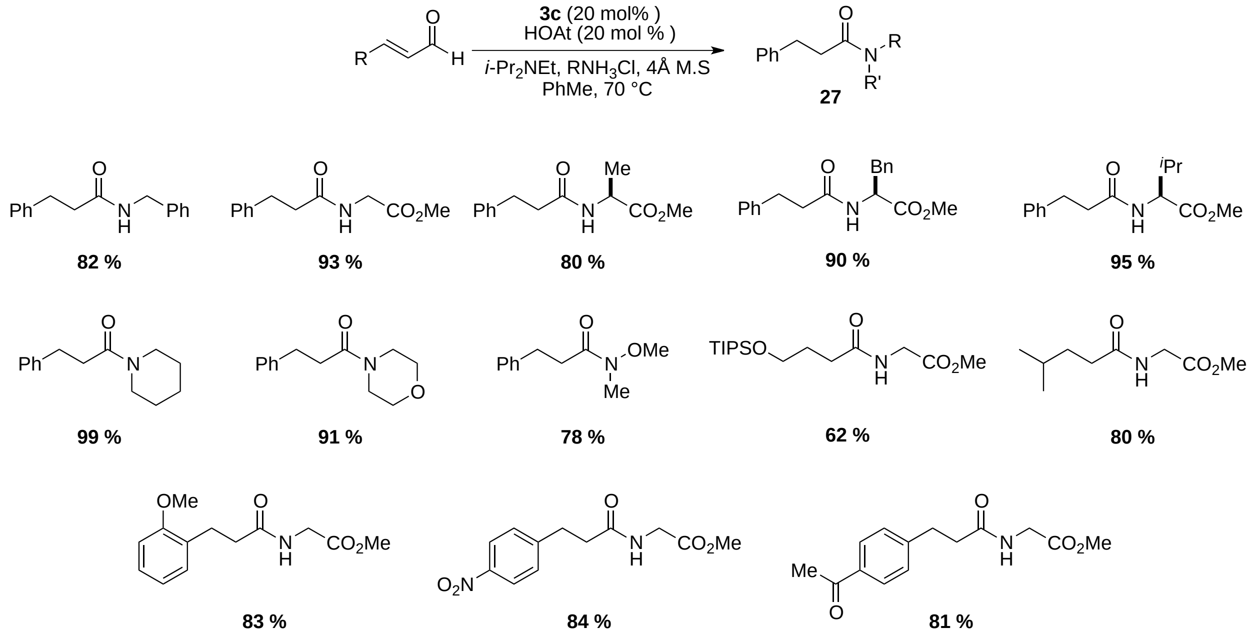


Figure 1.3.2. Scope of NHC-redox amidation.

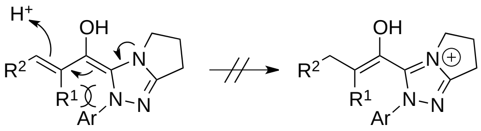
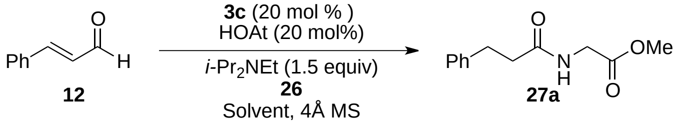


Figure 1.3.3. Possible allylic strain in transition state necessary for β-protonation.

We sought to understand the success of these reactions by elucidating the role of the hydrochloride salt. One hypothesis could be that the presence of a nonpolar proton source accelerates the protonation of extended Breslow intermediate **II** at the β-position to give enol **III** (Figure 1.1.4). However, when 1 equivalent of diisopropylethylammonium chloride is added to the reaction mixture along with an equivalent of benzylamine, imine formation still occurs, and slow degradation of cinamaldehyde is observed. Based on a reexamination of solvents for this reaction (eq 22, Table 1.3.6), we propose that a phase-transfer mechanism is operative. Solubility plays an integral role in product selectivity. In more polar solvents, faster equilibration of the excess diisopropylethylamine with the hydrochloride salt would be expected, resulting in high concentration of free amine in solution and therefore rapid imine formation. In THF, for instance, imine formation is not observed at room temperature (entry 4), but it is the major product at 70 °C (entry 3). We attribute this change to the rapid dissolution of the ammonium salt, leading to rapid deprotonation in solution and condensation of the free amine onto the aldehyde. In solvents where the ammonium salt is less soluble, the tertiary amine base must react with the solid ammonium salt under biphasic conditions, resulting in phase transfer controlled release of the amine free base into solution. This effectively simulates dropwise addition without the need for a syringe pump.



(22)

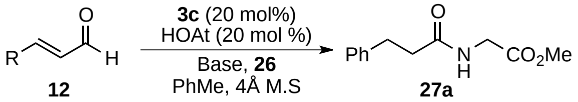
Table 1.3.6. Reexamination of solvent effects.

Entry	Solvent	Temp, Time	Yield	Entry	Solvent	Temp, Time	Yield
1	PhMe	70 °C, 3h	**93 %**	***5***	CH_2Cl_2	23 °C, 12h	**33 %**
2	PhMe	23 °C, 12h	**64 %**	***6***	MeCN	70 °C, 3h	**85 %**
3	THF	70 °C, 3h	**33 %**	***7***	MeCN	23 °C, 12h	**68 %**
4	THF	23 °C, 12h	**82 %**	***8***	MTBE	23 °C, 12h	**7 %**

These heterogeneous reactions are sufficiently rapid at 70 °C such that they are complete within 3h, and with the addition of molecular sieves to the reaction mixture, no pretreatment of any of the reagents is required. Co-catalysts HOAt and HOBt are used directly as received, and the enals are not distilled prior to use. Therefore, this method represents a significant step toward the robustness and procedural simplicity we envisioned.

We thought it might be possible to pre-mix the solid catalyst and co-catalyst, further simplifying the procedure. Ideally, the base would also be present in this pre-mixed reagent mixture such that a researcher could weigh out only an α,β-unsaturated aldehyde substrate, an amine hydrochloride and the reagent mixture, stir them at an appropriate temperature and isolate an amide product. To achieve this goal, a sampling of solid bases were screened, and *N,N*-

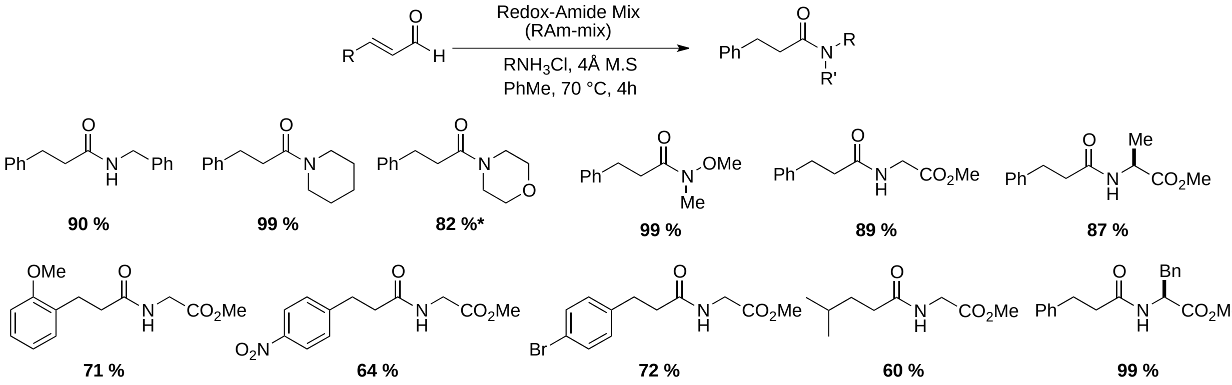
dimethyl-4-aminopyridine (DMAP) was found to be optimal (eq 23, Table 1.3.7). The base, triazolium and HOAt were weighed in appropriate ratio, ground in a scintillation vial, slurried in hexanes, stirred and dried to give a light brown solid. This solid was then tested in a battery of previously studied amidation reactions and found to perform comparably to the standard conditions (Figure 1.3.5). It should be noted, when DMAP is used as the base under the normal amidation conditions, inferior yields are observed without the addition of HOAt. Therefore, the HOAt is necessary for optimal yields.


12
3c (20 mol%)
HOAt (20 mol %)
Base, **26**
PhMe, 4Å M.S
27a
Ph
CO$_2$Me

(23)

Table 1.3.7. Solid base screen.

Entry	Base	Temp, Time	Yield
1	NaOAc	70 °C, 4h	**20 %**
2	NaOAc	23 °C, 16h	**30 %**
3	NaOBz	23 °C, 16h	**27 %**
4	*t*-BuOK	23 °C, 16h	**16 %**
5	DABCO	23 °C, 16h	**59 %**
6	DMAP	23 °C, 16h	**68 %**
7	DMAP	70 °C, 4h	**89 %**


Redox-Amide Mix
(RAm-mix)
RNH$_3$Cl, 4Å M.S
PhMe, 70 °C, 4h
90 %
99 %
82 %*
99 %
89 %
87 %
71 %
64 %
72 %
60 %
99 %

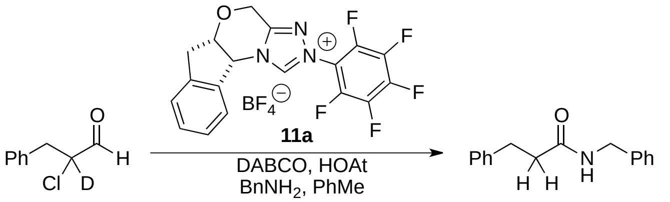
* Stirred 16h at 70° C to obtain complete conversion

Figure 1.3.4. Redox-amide mix reactions.

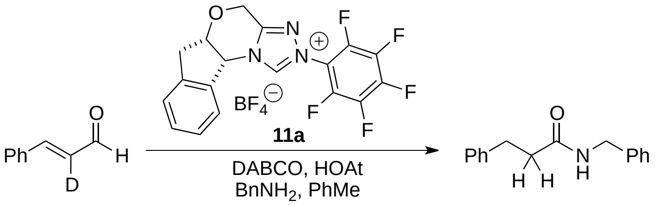
In summary, the use of amine hydrochloride salts in the NHC-redox amidation overcomes the procedural limitation of slow addition. Furthermore, the solid reagents can be weighed, mixed and stored together, making it possible to reduce the number of operations necessary to conduct the reaction even further. As it stands, a synthetic chemist wishing to perform an NHC-redox amidation would, in principle, need only weigh 4Å mol. sieves, an amine hydrochloride and the solid redox-amide mix (RAm-mix) into a reaction vessel, then add a solution of the desired aldehyde and stir for an appropriate period. We hope this brings the NHC-redox amidation closer in terms of practicality to more traditional peptide bond couplings and encourages the wider use of this catalytic amide bond formation.

1.4. Development of an asymmetric NHC-catalyzed preparation of α-fluoroamides

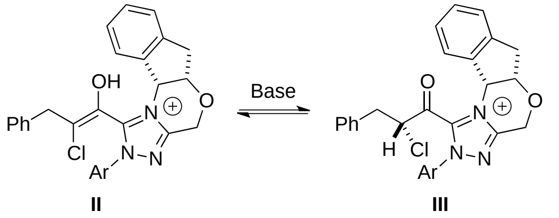
Included in our 2007 report[18a] of NHC-redox amidation was a single asymmetric reaction generating an α-chloro amide in 80% ee (Section 1.1, eq 9). The modest selectivity was probed by a series of studies using deuterium labeled aldehyde starting materials in which Dr. Vora observed complete loss of α-deuteration over the course of the reaction (eqs 24 and 25).[32] This, combined with the observation that enantioenriched product does not epimerize under the reaction conditions led us to invoke the tautomerization of **II** and **III** catalyzed by base, leading to epimerization of the newly installed stereocenter (eq 26).



(24)



(25)



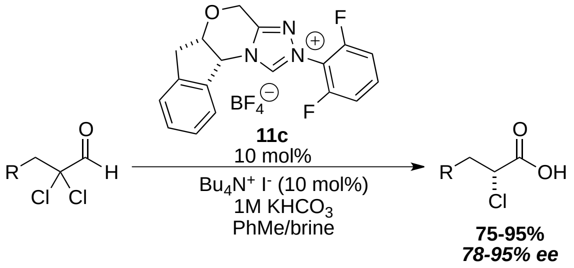
(26)

Dr. Vora applied this hypothesis to develop an NHC-catalyzed hydration to give α-chloro and α-fluoro carboxylic acids in high enantioselectivity (eqs 27 and 28).[33] To overcome the problem of epimerization, he employed an inorganic base and biphasic conditions leading to low effective concentration of base in the organic layer and minimal epimerization of the acyl azolium. We thought that the method I developed, employing amine hydrochloride salts insoluble in the nonpolar solvent, might mimic these conditions and allow for a highly enantioselective amidation. Furthermore, the demonstration of α-fluoroenals as the α-reducible aldehyde component in the hydration opens the door to valuable enantioenriched α-fluoroamides from readily available materials in a single, organocatalytic step (eq 29).

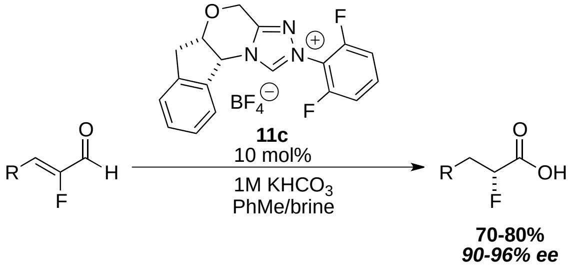
---

[32] Vora, H. U. Ph. D. Thesis, Colorado State University, March 2011.

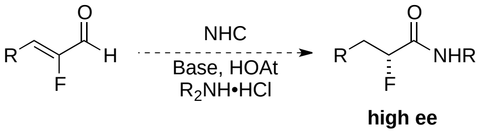
[33] Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 2860–2861.


BF4
11c
10 mol%
Bu4N+ I- (10 mol%)
1M KHCO3
PhMe/brine
75-95%
78-95% ee

(27)


BF4
11c
10 mol%
1M KHCO3
PhMe/brine
70-80%
90-96% ee

(28)


NHC
Base, HOAt
R2NH•HCl
high ee

(29)

Fluorine is a unique and highly valuable element to chemists in many fields. Its high electronegativity and small size make it capable of strong polar interactions that can dramatically influence the physical and chemical properties of organic molecules.[34] For instance, substitution of fluorine for hydrogen can modulate bioavailability, lipophilicity, conformation, and metabolic stability of a drug candidate.[35] However, practical access to fluorinated compounds is limited, and considerable effort has been invested in the development of mild reactions capable of forming carbon-fluorine bonds.[36] A handful of examples of enantioselective installation of sp^3-fluorine substituents have been demonstrated (Fig 1.4.1),[37] but the direct catalytic, asymmetric preparation of α-fluoroamides is a significant challenge that has only very recently been addressed (Fig 1.4.2).[38] Although our approach would not constitute a fluorination *per se*, we felt α-fluoroenals were a sufficiently simple and inexpensive source of a carbon-fluorine bond, and the fact that this position could be protonated asymmetrically to form a fluorine stereocenter makes the potential value of the products extremely high.

---

[34] O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308–319.

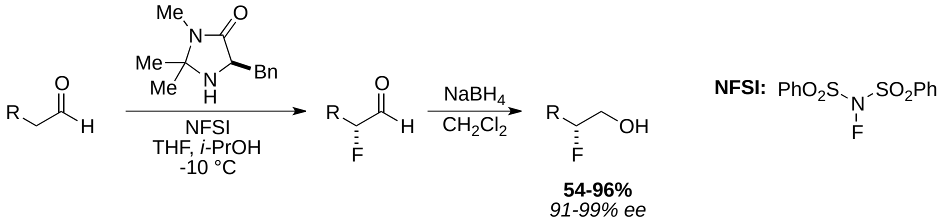

Me
O
N
Me
Me
N
H
Bn
R
O
H
NFSI
THF, i-PrOH
-10 °C
R
O
H
F
NaBH4
CH2Cl2
R
OH
F
54-96%
91-99% ee
NFSI:
PhO2S
N
SO2Ph
F

Figure 1.4.1. MacMillan's catalytic asymmetric fluorination of aldehydes

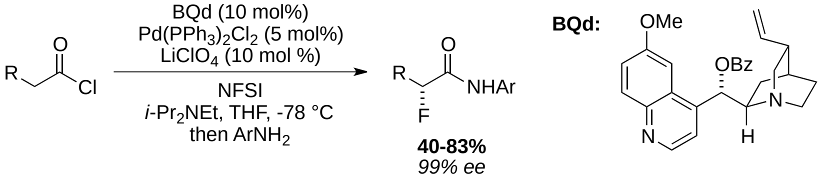

BQd (10 mol%)
Pd(PPh3)2Cl2 (5 mol%)
LiClO4 (10 mol %)
R
O
Cl
NFSI
i-Pr2NEt, THF, -78 °C
then ArNH2
R
O
NHAr
F
40-83%
99% ee
BQd:
OMe
OBz
N
N
H

Figure 1.4.2. Lectka's asymmetric fluorination of acid chlorides

The preparation of the α-fluoroenal starting materials we envisioned as suitable precursors to α-fluoroamides is fairly straightforward from fluorinated Horner-Wadsworth-

---

[35] a) Müller, K.; Faeh, C.; Diederich, F. *Science*, **2007**, *317*, 1881–1886. b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V; *Chem. Soc. Rev.*, **2008**, *37*, 320-330.

[36] Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature*, **2011**, *473*, 470–477.

[37] Beeson, T. D.; MacMillan, D. W. *J. Am. Chem. Soc.* **2005**, *127*, 8826-8828.

[38] Erb, J.; Paull, D. H.; Dudding, T.; Belding, L.; Lectka, T. *J. Am. Chem. Soc.* **2011**, *133*, 7536-7546.

Emmons reagent **28**. Under strongly basic conditions, the α-fluoro-α,β-unsaturated ester **29a** is obtained in excellent yield and >19:1 selectivity for the *E*-isomer (Figure 1.4.3).[39]. Reduction to the allylic alcohol **30a** followed by oxidation with IBX provides the α-fluoroenal **31a** in good yield.

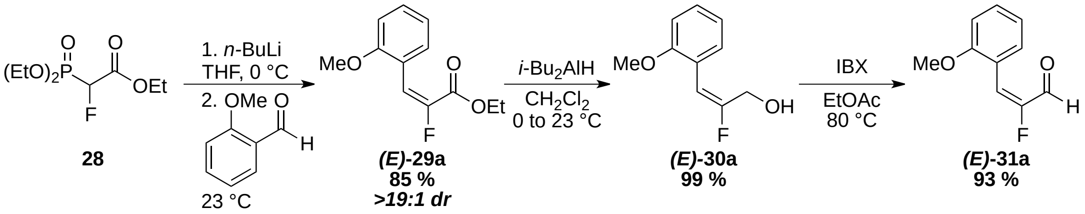

(EtO)2P
OEt
F
28
1. n-BuLi
THF, 0 °C
2. OMe
H
23 °C
MeO
OEt
F
(E)-29a
85 %
>19:1 dr
i-Bu2AlH
CH2Cl2
0 to 23 °C
OH
(E)-30a
99 %
IBX
EtOAc
80 °C
H
(E)-31a
93 %

Figure 1.4.3. Preparation of *E*-α-fluoroenal 31a.

The *E*-α-fluoroenal was subjected to the reaction conditions with a variety of chiral triazolium precatalysts (Figure 1.4.4). The aminoindanol scaffold was found to outperform the phenylalanine scaffold in terms of both enantioselectivity and yield. To our satisfaction, enantioselectivity exceeding 90% ee was observed with trichlorophenyl substituted triazolium **11c**; however, yields were poor (20-40%).

---

[39] Sano, S.; Ando. T.; Yokoyama, K.; Nagao, Y. *Synlett*, **1998**, 777-779.

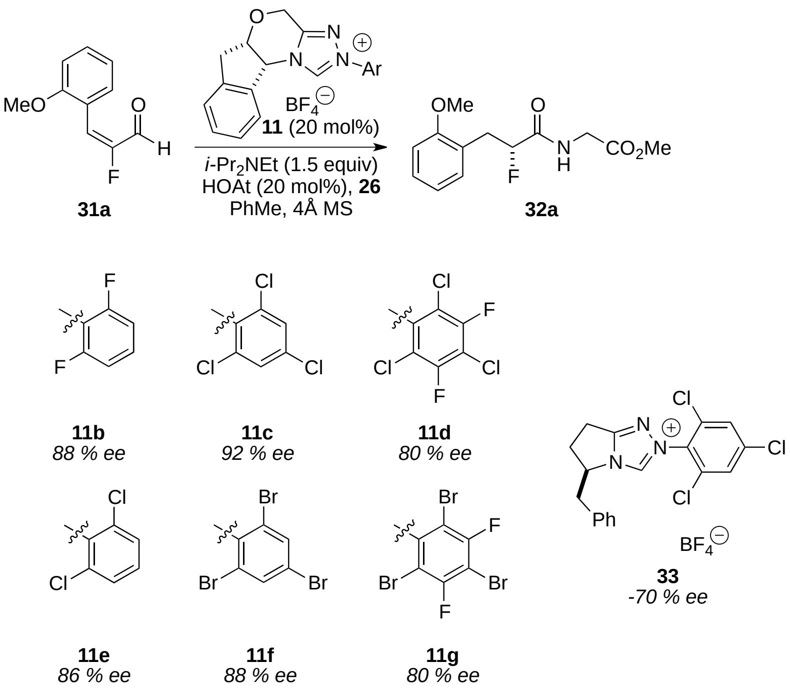

MeO
F
H
O
31a
O
N
N
N
Ar
BF$_4^-$
11 (20 mol%)
i-Pr$_2$NEt (1.5 equiv)
HOAt (20 mol%), **26**
PhMe, 4Å MS
OMe
O
N
H
CO$_2$Me
F
32a
11b
88 % ee
11c
92 % ee
11d
80 % ee
11e
86 % ee
11f
88 % ee
11g
80 % ee
Ph
BF$_4^-$
33
-70 % ee

Figure 1.4.4. Catalyst screen.

We thought the alkene geometry in the α-fluoroenal might play a role in the homoenolate protonation step and therefore affect catalyst turnover,[40] so the *Z*-α-fluoroenal was synthesized by changing the conditions for the Horner-Wadsworth-Emmons reaction. Under soft enolization conditions at elevated temperature (Figure 1.4.5), the *Z* isomer of **29a** is obtained in 10:1 selectivity (Table 1.4.1). This change in selectivity can be attributed to the reversibility of the initial addition of the ylide to the aldehyde, allowing for the thermodynamic product to be formed under the reaction conditions.

The Horner-Wadsworth-Emmons reaction was combined with the reduction to the fluoroalcohol in one pot and used to prepare a number of *Z*-α-fluoroenals in varying yields and diastereoselectivity (**31a-f**, Table 1.4.1). In particular, aromatic fluoroesters **29a-d** can be obtained in high selectivity while aliphatic fluoroesters **29e** and **29f** are obtained in 1:1 dr. Aryl substituted products also proved separable by chromatography; therefore, they were isolated at the alcohol stage as single diastereomers while the aliphatic substrates were carried on as an inseparable mixture of olefin isomers.

---

[40] Vora, H. U. Ph. D. Thesis, Colorado State University, March 2011.

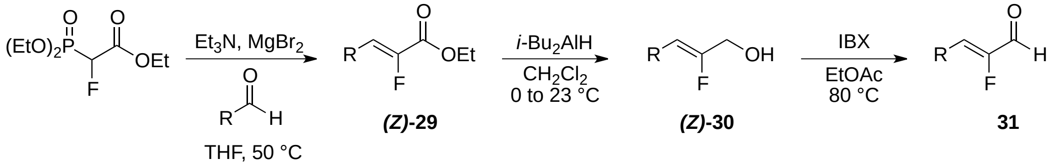
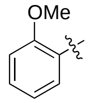
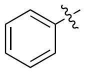
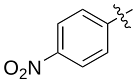
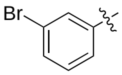
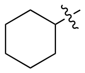
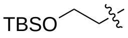


Figure 1.4.5.

Table 1.4.1.

R =	Fluoroester	Fluoroester dr	Yield of 30	Yield of 31
	**29a**	*10:1*	**80%**	**93%**
	**29b**	*7:1*	**77%**	**89%**
	**29c**	*2:1*	**70%**	**55%**
	**29d**	*3:1*	**72%**	**72%**
	**29e**	*1:1*	**90%**	**46%**
	**29f**	*1:1*	**66%**	**78%**

The reaction of *Z*-α-fluoroenal **31a** with glycine methyl ester hydrochloride catalyzed by triazolium **11c** was retried, and the yield improved in comparison to the reaction of the *E* isomer. Further screening of bases revealed that weak acetate bases performed favorably, giving excellent yield and comparable selectivity (Figure 1.4.4). Increasing sterics on the base gave improved enantioselectivity, up to 95% ee in the case of sodium pivalate. These two trends suggest that epimerization is still an issue when an amine base is used, and that the conjugate acid of the chosen base plays a role in the enantiodetermining step (*vide infra*).

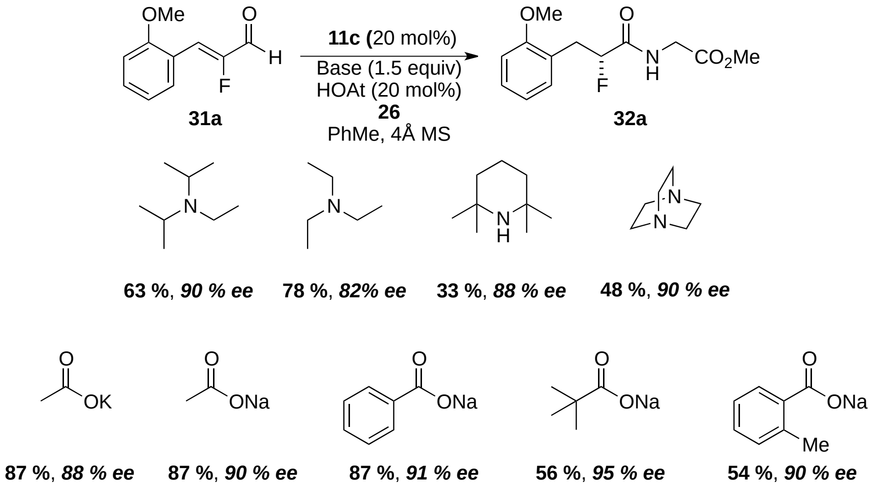

OMe
O
H
F
31a
11c (20 mol%)
Base (1.5 equiv)
HOAt (20 mol%)
26
PhMe, 4Å MS
OMe
O
N
H
CO2Me
F
32a
N
N
N
H
N
N
63 %, 90 % ee
78 %, 82% ee
33 %, 88 % ee
48 %, 90 % ee
O
OK
O
ONa
O
ONa
O
ONa
O
ONa
Me
87 %, 88 % ee
87 %, 90 % ee
87 %, 91 % ee
56 %, 95 % ee
54 %, 90 % ee

Figure 1.4.6. Base screening.

With these optimized conditions in hand, a scope of amine hydrochloride salts nucleophiles was explored. Both primary and secondary alkyl amines are suitable, as is *N,O*-dimethylhydroxylamine to give the Weinreb amide (Figure 1.4.7). The α-fluoroenal scope includes aliphatic substitution at the β-position as well as both electron rich and electron poor aromatic substitution. When L-alanine methyl ester hydrochloride is subjected to the reaction conditions, the resultant amide is obtained as a 97:3 mixture of diastereomers.

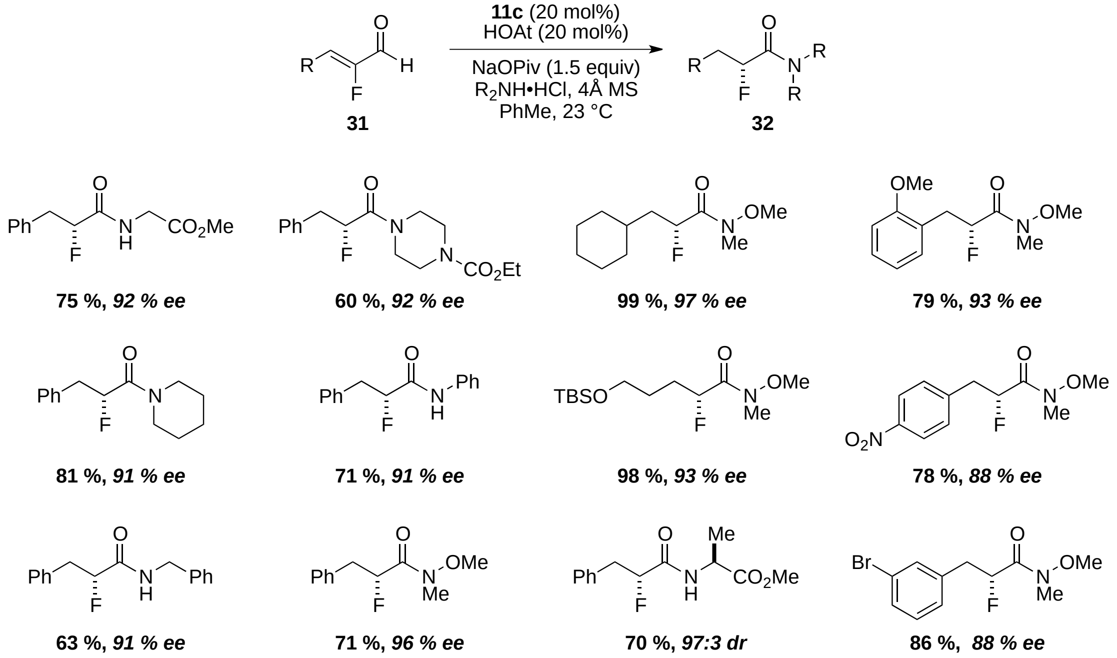

11c (20 mol%)
HOAt (20 mol%)
NaOPiv (1.5 equiv)
R2NH•HCl, 4Å MS
PhMe, 23 °C
31
32
75 %, 92 % ee
60 %, 92 % ee
99 %, 97 % ee
79 %, 93 % ee
81 %, 91 % ee
71 %, 91 % ee
98 %, 93 % ee
78 %, 88 % ee
63 %, 91 % ee
71 %, 96 % ee
70 %, 97:3 dr
86 %, 88 % ee

Figure 1.4.7. Scope of α-fluoroamide preparation.

We propose that this reaction proceeds through the following mechanism (Figure 1.4.8). Generation of enol **II** as in previous examples is followed by the enantiodetermining tautomerization to **III**. The identity of the proton source in this step is crucial, as a significant effect of the size of base used is observed. Larger bases, such as sodium pivalate, lead to greater discrimination of **III** with respect to facial approach (Fig 1.4.6). Enantioselectivity does change with amine nucleophile, indicating that some of the proton transfer in the tautomerization of **II** to **III** is mediated by the amine (or its hydrochloride salt). Additionally, the reversibility of this tautomerization is still an issue when stronger bases are used, leading to lower enantioselectivity (Fig 1.4.6).

Based on our mechanistic hypothesis, the fluorine stereocenter is set before the acyl azolium is displaced by HOAt. The resultant α-fluoroester is intercepted by the amine to give the observed α-fluoroamide product. Thus, the only chiral information on the active acylating reagent is the fluorine stereocenter. While the stereoelectronic impact of a fluorine stereocenter can be significant in many cases,[41] fluorine is isosteric with hydrogen and should have no steric impact on the approach of a nucleophile to α-fluoroester **IV**. Therefore, it seemed feasible that **IV** might acylate either enantiomer of a chiral amine at a similar rate. If this were the case, either enantiomer of catalyst would lead to opposite diastereomers of the α-fluoroamide product in similar selectivity.

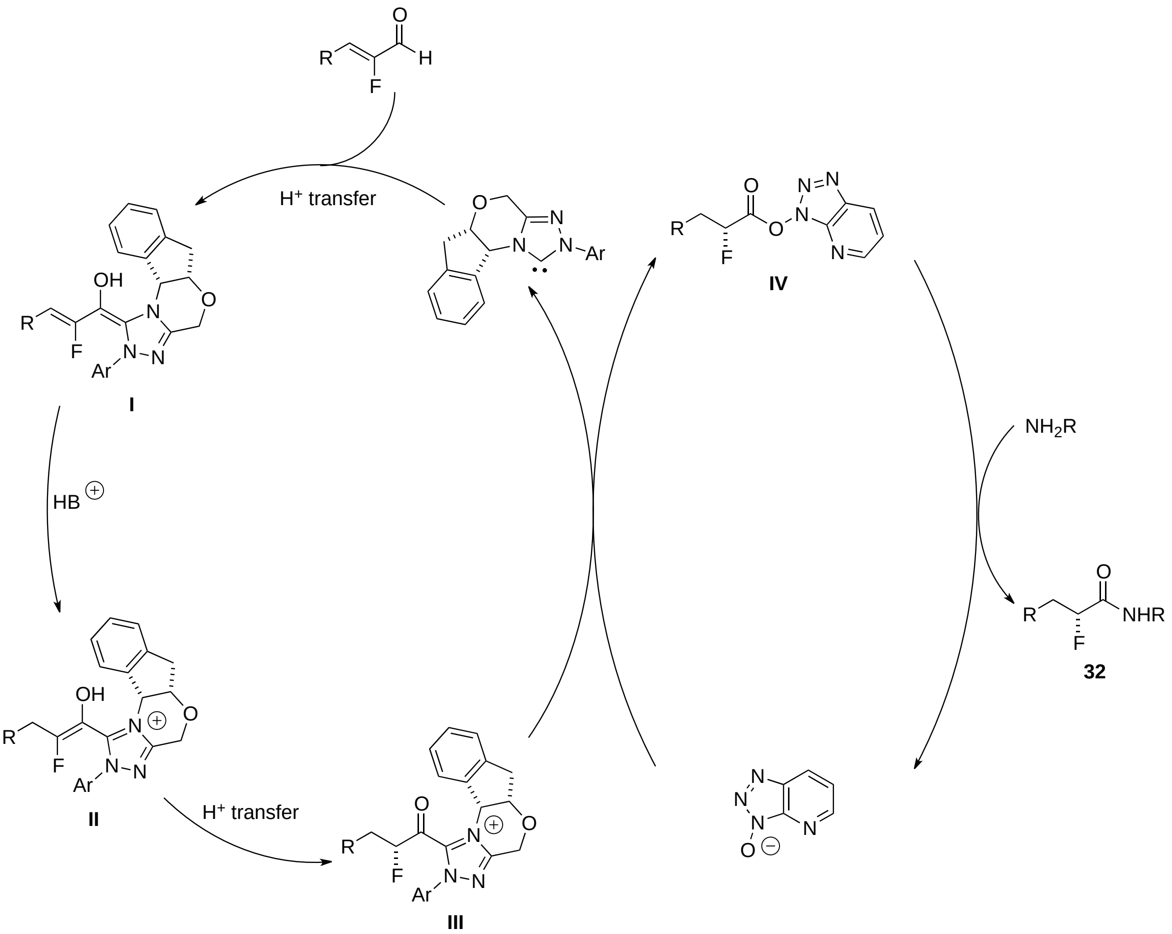


Figure 1.4.8. Proposed mechanism of asymmetric NHC-catalyzed fluoroamide preparation.

---

[41] (a) Eberhardt, E. S., Panasik, N., Jr.; Raines, R. T. *J. Am. Chem. Soc.* **1996**, *118*, 12261-12266. (b) Marson, C. M.; Melling, R. C. *J. Org. Chem.* **2005**, *70*, 9771-9779. (c) Chandler, C. L.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6737-6739. (d) Sparr, C.; Schweizer, W. B.; Senn, H. M.; Gilmour, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 3065-3068. (e) DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 10872-10874.

Indeed, we found that chiral primary amines can be elaborated to either diastereomer of α-fluoroamide products **32**. Using either *(+)* or *(-)*-**11c**, L-phenylalanine methyl ester hydrochloride can be acylated to give the *syn* or *anti* diastereomer in good yield and excellent selectivity (Figure 1.4.9). Similarly, either enantiomer of phenethylamine hydrochloride can be acylated with *(-)*-**11c** in excellent selectivity. The small difference in selectivity for each diastereomer of these products again implicates the amine (or its hydrochloride) as a proton source for the enantiodetermining tautomeriazation (*vide supra*). Here, a minimal match/ mismatch between the two diastereomeric transition states is observed.

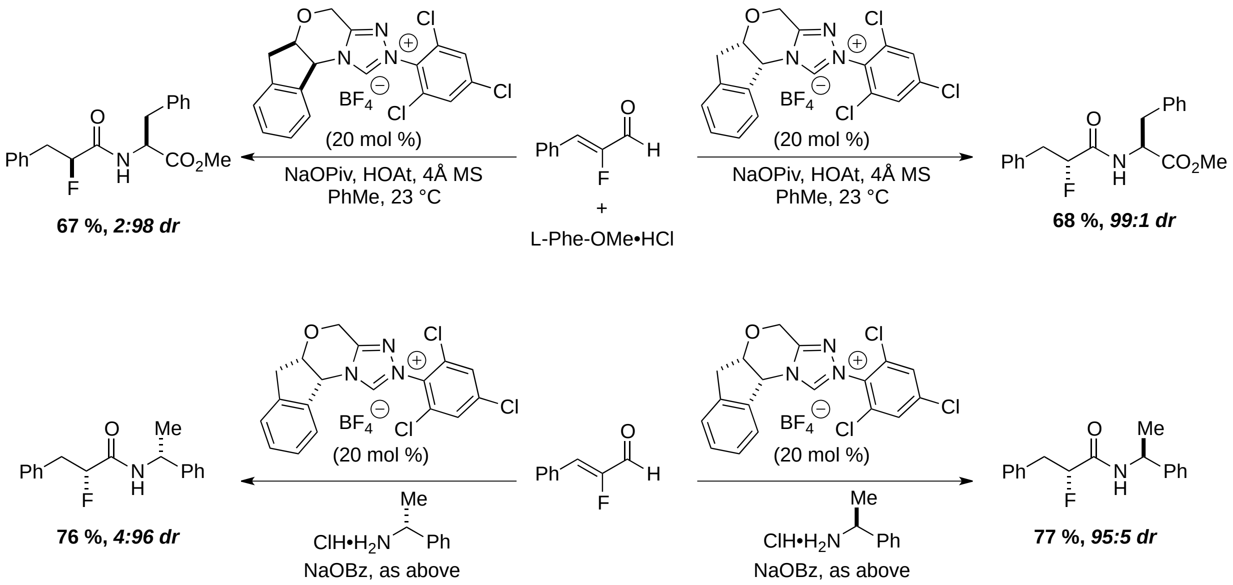
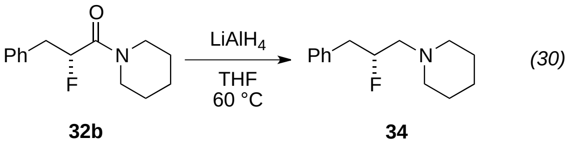


Figure 1.4.9.

The fluoroamide products furnished by this protocol are suitable precursors to a number of other interesting fluorinated motifs. Tertiary amide **32b** can be reduced with lithium aluminum hydride to the corresponding tertiary amine **34** in good yield and retention of enantioenrichment (eq 30).



32b
91 % ee

34
73 %, *90 % ee*

Additionally, Weinreb amide **32c** can be doubly alkylated to fluorohydrin **35** in good diastereoselectivity and no appreciable erosion of enantioenrichment (Figure 1.4.10). Hydride additions to similar α-fluoroketones have been studied, with varying results for facial selectivity.[42] Contrary to our belief that the Ahn-Eisenstein model would correctly predict the stereochemical outcome of the addition to α-fluoroketone **36**,[43] the observed diastereomer contains an *anti* relationship of the fluorine and hydroxyl groups, confirmed by conversion of **35** to epoxide **37** wherein a correlation between the benzyl and methyl protons is observed. This reflects either a traditional Felkin model[44] in which the σ* of the C-F bond is not taken into account when determining the "large" substituent or approach of the nucleophile from the least hindered face of a lithium chelate per the Cram-chelate model.[45] Based on Flowers and coworkers observation of a titanium chelate by ^{19}F-NMR in the diastereoselective reduction of α-fluoroketones,[41b] the Cram-chelate model is the best explanation for this selectivity.

---

[42] (a) Myers, A. G.; Barbay, J. K.; Zhong, B. *J. Am. Chem. Soc.* **2001**, *123*, 7207-7219. (b) Mohanta, P. K.; Davis, T. A.; Gooch, J. A.; Flowers II, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 11896-11987. (c) Kitazume, T.; Kobayashi, T.; Yamamoto, T.; Yamazaki, T. *J. Org. Chem.* **1987**, *52*, 3218-3223.

[43] (a) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. (b) Billing, S. B.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 5171-5177.

[44] Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199-2204.

[45] Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828.

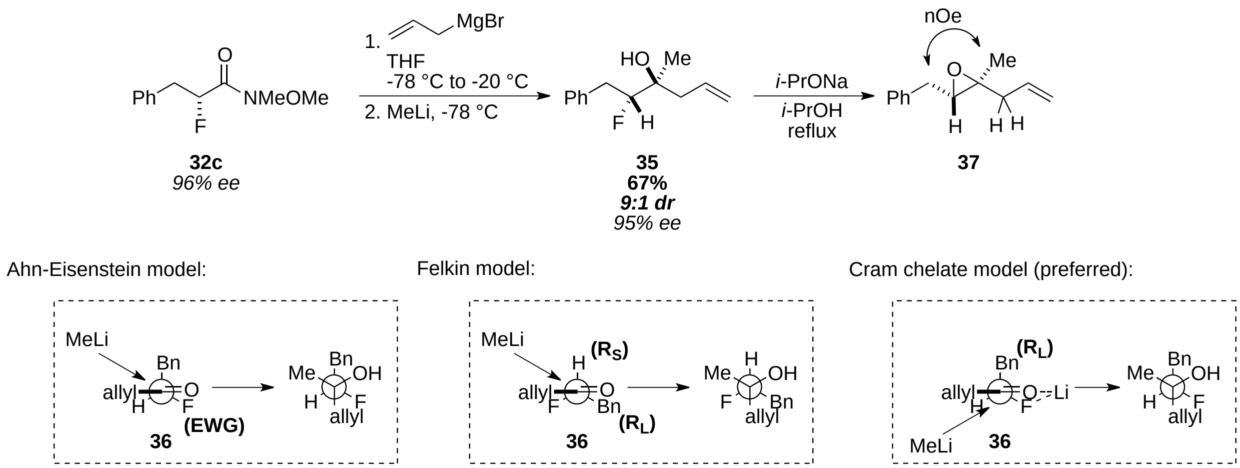

1. MgBr
THF
-78 °C to -20 °C
2. MeLi, -78 °C
Ph
NMeOMe
O
F
32c
96% ee
HO Me
F H
35
67%
9:1 dr
95% ee
i-PrONa
i-PrOH
reflux
nOe
O
Me
H
H H
37
Ahn-Eisenstein model:
Felkin model:
Cram chelate model (preferred):
MeLi
Bn
allyl
H
F
O
(EWG)
36
Me
OH
allyl
(R_S)
(R_L)
Bn
O--Li

Figure 1.4.10. Double alkylation of Weinreb amide and models for addition to α'-fluoroallyl ketone

Other double alkylations were also investigated, each giving poorer selectivity than the above transformation (Fig 1.4.11). The addition of titanium tetrachloride as per the reduction reported by Flowers and coworkers does lead to enhanced diastereoselectivity; however, epimerization of the fluoroketone is also observed. When butyllithium is used in the first alkylation, almost no diastereoselectivity is observed in the second step, suggesting the presence of magnesium is necessary. However, when methyllithium and allyl Grignard are added in the opposite order, only 70:30 selectivity is observed. This is an interesting problem; however, it is unclear how useful a detailed study of the preparation of fluorohydrins from the Weinreb amide would prove. Therefore, further investigation was not pursued.

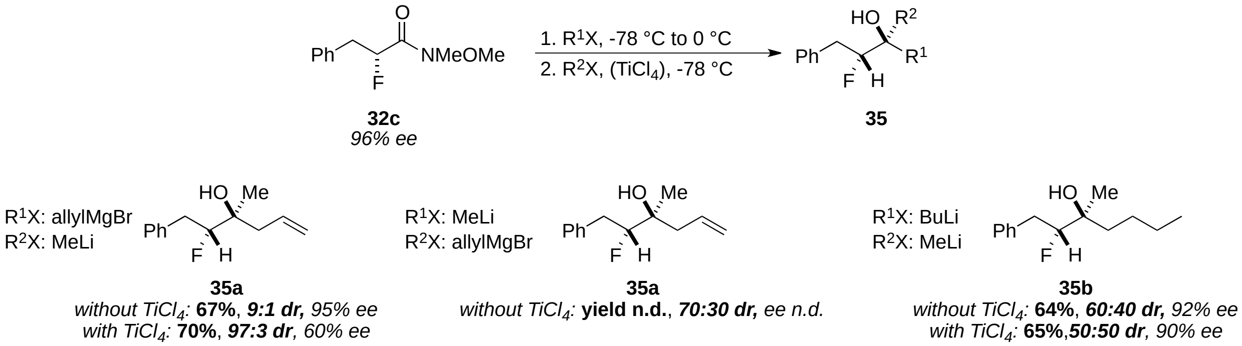
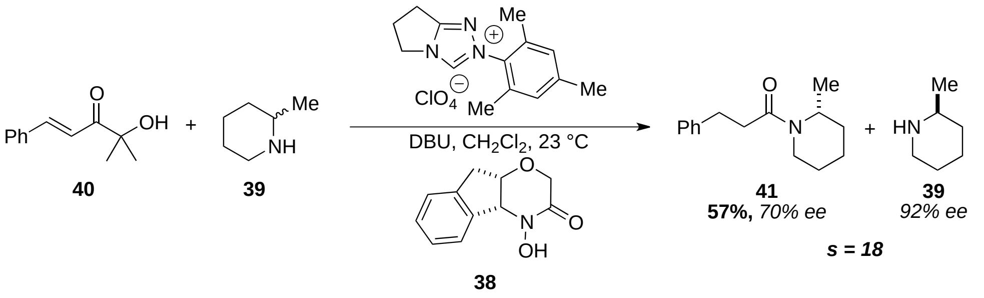

Ph
NMeOMe
O
F
32c
96% ee
1. R1X, -78 °C to 0 °C
2. R2X, (TiCl4), -78 °C
HO R2
R1
F H
35
R1X: allylMgBr
R2X: MeLi
HO Me
35a
without TiCl4: 67%, 9:1 dr, 95% ee
with TiCl4: 70%, 97:3 dr, 60% ee
R1X: MeLi
R2X: allylMgBr
35a
without TiCl4: yield n.d., 70:30 dr, ee n.d.
R1X: BuLi
R2X: MeLi
35b
without TiCl4: 64%, 60:40 dr, 92% ee
with TiCl4: 65%,50:50 dr, 90% ee

Figure 1.4.11. Other conditions for the double alkylation with varying selectivity.

1.5. Simultaneous kinetic resolution of racemic secondary amines

Among the current developments within the field of NHC-catalysis, we were particularly interested in the kinetic resolution of secondary amines reported by Bode and coworkers.[46] When chiral hydroxamic acid co-catalyst **38** is used in the NHC-redox amidation of 2-methylpiperidine **39** with hydroxyketone **40**, the amide product **41** is obtained in 57% yield and 70% ee, corresponding to an k_{rel} of 18 (eq 31). This resolution coupled with the enantioselective protonation demonstrated by our group (Section 1.4) would control stereocenters on either side of a newly formed amide bond, a transformation that is currently unknown. Based on our finding that either enantiomer of phenethylamine is acylated in nearly identical selectivity under the amidation conditions leading to α-fluoroamides (*vide supra*), we believed it should be possible to access any stereoisomer of a given tertiary α-fluoroamide product by changing triazolium and co-catalyst antipode (Figure 1.5.1).



(31)

---

[46] (a) Hsieh, S.-Y.; Binanzer, M.; Kreituss, I.; Bode, J. W. *Chem. Commun.* **2012**, *48*, 8892-8894. (b) Binanzer, M.; Hsieh, S.-Y.; Bode, J. W. *J. Am. Chem. Soc.*, **2011**, *133*, 19698–19701.

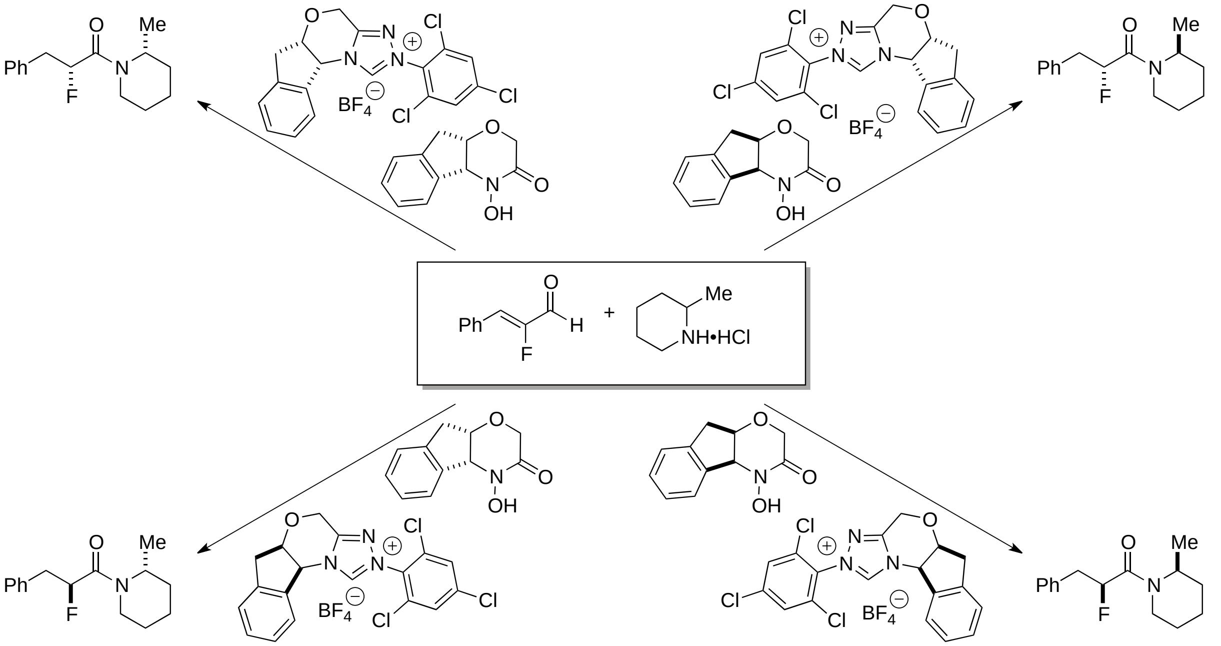
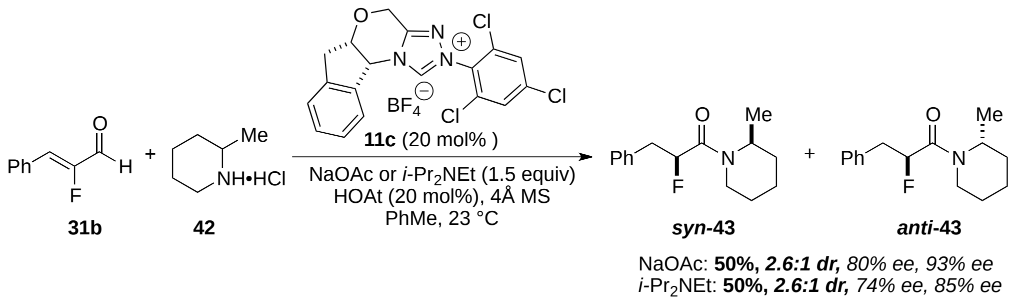

Ph
O
Me
N
F
BF$_4^{\ominus}$
Cl
N
OH
O
NH•HCl
H
+

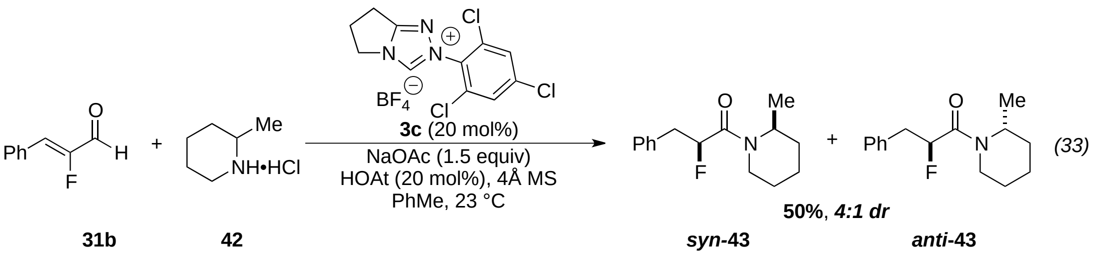
Figure 1.5.1. Potential access to any desired stereoisomer of α-fluoroamide products.

To begin, 2-methylpiperidine hydrochloride **42** was tested in the NHC-redox amidation. Using our best conditions for the enantioselective protonation (sodium pivalate as the base), **42** was not acylated at room temperature. However, the use of sodium acetate or diisopropylethylamine as the base does afford desired product **43** (eq 32).


11c (20 mol%)
NaOAc or i-Pr$_2$NEt (1.5 equiv)
HOAt (20 mol%), 4Å MS
PhMe, 23 °C
31b
42
***syn*-43**
***anti*-43**
NaOAc: **50%, *2.6:1 dr,*** *80% ee, 93% ee*
i-Pr$_2$NEt: **50%, *2.6:1 dr,*** *74% ee, 85% ee*

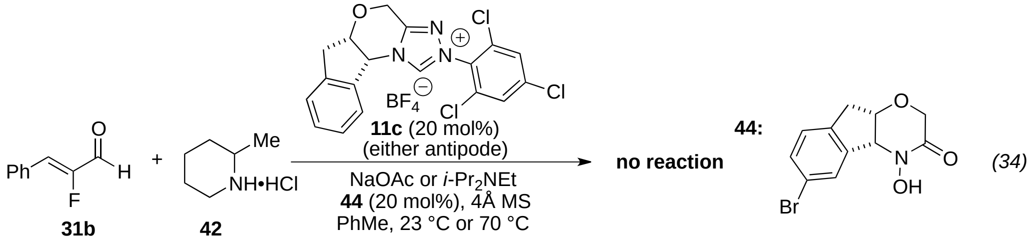
(32)

Surprisingly, using achiral catalyst **3c** under the standard conditions leads to desired product in 4:1 dr (eq 33). This can only be explained by a significant stereoelectronic effect of the fluorine stereocenter in the active acylating reagent, α-fluoroester **IV** (Figure 1.4.8) that discriminates between the enantiomers of amine. This effect is also reflected in the results with chiral triazolium **11c** (eq 32); however, we found it difficult to rationalize those results quantitatively without detailed kinetic experiments.

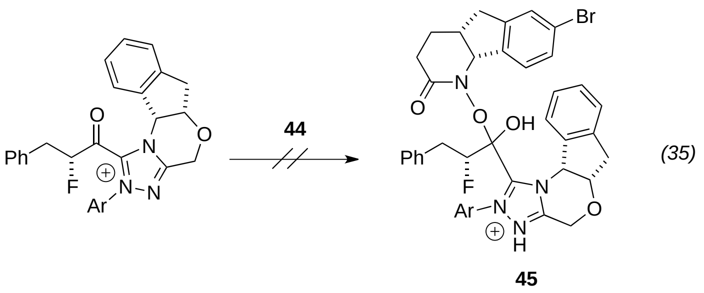


Cl
N
N
N
BF4
Cl
Cl
3c (20 mol%)
NaOAc (1.5 equiv)
HOAt (20 mol%), 4Å MS
PhMe, 23 °C
Ph
O
H
F
+
Me
NH•HCl
31b
42
Ph
O
Me
N
F
+
Ph
O
Me
N
F
(33)
50%, 4:1 dr
syn-43
anti-43

We obtained a sample of chiral hydroxamic acid **44**, generously donated by the Bode group, and screened conditions for the simultaneous kinetic resolution and α-fluoroamide preparation. When **44** is used in conjunction with triazolium **11c**, however, no desired product is obtained, even with additional heat and longer reaction times (eq 34). We attribute the lack of reactivity to the steric demands of tetrahedral intermediate **45** (eq 35). The transition state leading to this catalytic intermediate must be prohibitively high in energy.

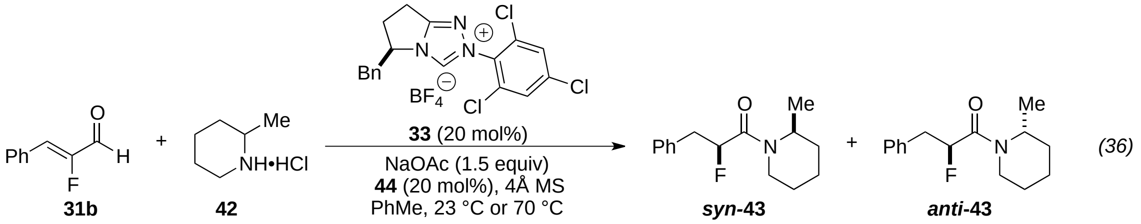


O
N
N
N
Cl
BF4
Cl
Cl
11c (20 mol%)
(either antipode)
NaOAc or i-Pr2NEt
44 (20 mol%), 4Å MS
PhMe, 23 °C or 70 °C
Ph
O
H
F
+
Me
NH•HCl
31b
42
no reaction
44:
O
N
O
OH
Br
(34)



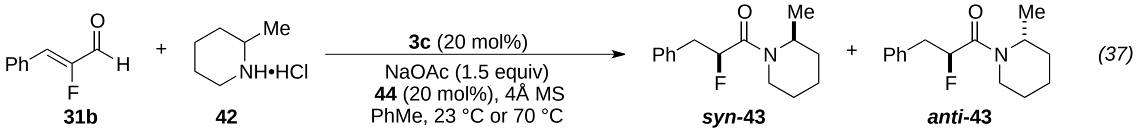
Ph
O
F
N
Ar
N
N
O
44
O
N
O
Br
OH
Ph
F
Ar
N
N
H
N
O
(35)
45

By switching to a less sterically demanding triazolium **33**, we obtained the desired product with **44** as the co-catalyst (eq 36). Diastereoselectivity is modest, and the enantioenrichment of the major diastereomer is close to that obtained under our optimal NHC-redox amidation conditions (using more sterically demanding **11c** as the NHC precursor). The minor diastereomer is enantioenriched with comparable selectivity to that obtained with **33** in the normal amidation reaction (70 % ee, Figure 1.4.4).


Ph
O
H
F
31b
+
Me
NH•HCl
42
Bn
N
N
N
Cl
Cl
Cl
BF_4^-
33 (20 mol%)
NaOAc (1.5 equiv)
44 (20 mol%), 4Å MS
PhMe, 23 °C or 70 °C
Ph
O
Me
N
F
syn-43
+
Ph
O
Me
N
F
anti-43
(36)

36%, ***4.5:1 dr***, *86% ee, 66% ee*

As this reaction was optimized, a discovery was made that changed our approach completely. When achiral triazolium **3c** is used in the reaction, higher diastereoselectivity is obtained, and the enantioenrichment of the products is comparable to that obtained with **33** (eq 37). This result suggests that the chiral triazolium is doing nothing to control the fluorine stereocenter in these reactions.


Ph
O
H
F
31b
+
Me
NH•HCl
42
3c (20 mol%)
NaOAc (1.5 equiv)
44 (20 mol%), 4Å MS
PhMe, 23 °C or 70 °C
Ph
O
Me
N
F
syn-43
+
Ph
O
Me
N
F
anti-43
(37)

25%, ***12:1 dr***, *86% ee, 64% ee*

We began to consider mechanistic possibilities that could explain the selectivity and arrived at the following hypothesis: under these reaction conditions, epimerization of the acyl azolium **III** is competitive with the acylation of amine **39** (Figure 1.5.2). If this is so, the selectivity is determined by the relative rate of acylation of either diastereomer of **IV** (k_4 vs k_4'). Therefore, the selectivity of the protonation leading to acyl azolium **III** is irrelevant, and the fluorine stereocenter is resolved dynamically under the reaction conditions.

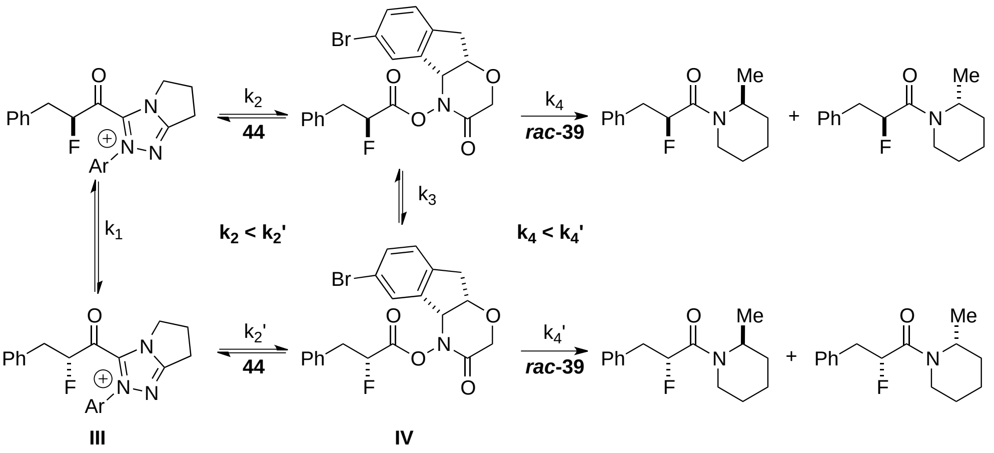
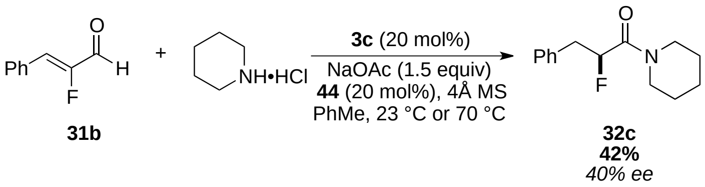
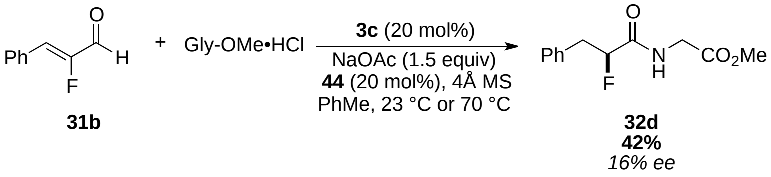


Figure 1.5.2.

If the hydroxamic acid is exerting control over the fluorine stereocenter by the above mechanism, the acylation of any amine by **IV** should lead to enantioenrichment. To test this, I subjected two achiral amines to the reaction with **44** as the co-catalyst. The results were illuminating. When piperidine hydrochloride is used as the nucleophile, α-fluoroamide **32c** is obtained in 40% ee (eq 38), while glycine methyl ester gives **32d** in 16% ee (eq 39). The size of the nucleophile relates directly to the enantioenrichment, suggesting that slower acylation leads to a more efficient dynamic kinetic resolution of the fluorine stereocenter. This is consistent with our hypothesis. When **41** is used as the nucleophile, it seems that the effect of the chiral triazolium is completely overridden by this process.

 (38)

3c (20 mol%)
NaOAc (1.5 equiv)
44 (20 mol%), 4Å MS
PhMe, 23 °C or 70 °C
31b
NH•HCl
32c
42%
40% ee

 (39)

Gly-OMe•HCl
3c (20 mol%)
NaOAc (1.5 equiv)
44 (20 mol%), 4Å MS
PhMe, 23 °C or 70 °C
31b
32d
42%
16% ee

The revelation that the chiral triazolium is not involved in setting the fluorine stereocenter under these conditions led us to reevaluate our strategy. It may be necessary to optimize a new chiral co-catalyst in order to acylate the amine rapidly enough that epimerization does not occur. This project would be suitable for another student in collaboration with Prof. Jeffrey Bode, whose group has synthesized a number of other chiral co-catalysts for the purpose of resolving amines under their NHC-redox amidation conditions. Perhaps the right combination of a less sterically demanding chiral co-catalyst and the inherent effect of the fluorine (observed in experiments without a chiral co-catalyst) will lead to an efficient kinetic resolution.

1.6. Conclusion

Over the course of my study of the NHC-redox reaction manifold, I developed new conditions for the efficient acylation of amine nucleophiles as their hydrochloride salts. These conditions were applied to the development of the first highly selective asymmetric NHC-redox amidation, which furnishes valuable enantioenriched α-fluoroamide products in up to 97% ee. This work also led to early investigation of a simultaneous kinetic resolution and asymmetric NHC-redox amidation protocol, which remains to be studied further. Finally, my exploration into the addition of carbon nucleophiles to the acyl azolium broke new ground, and although I could not develop a practical procedure for the preparation of ketones in the NHC-redox manifold, my results will prove useful for the future exploration of this transformation.

CHAPTER TWO: PROGRESS TOWARD THE TOTAL SYNTHESIS OF OKILACTOMYCIN.

2.1 Introduction

Polyketides are a class of bacterial secondary metabolites with diverse bioactive profiles, ranging from antibiotics[47] and immunosuppressants[48] to cardiovascular[49] and anticancer agents (Figure 2.1.1).[50] Therefore, there has been great interest in the total synthesis of this class of natural product, which has served as the inspiration for the development of numerous synthetic methods. The most prominent among these is the stereoselective aldol reaction, one of the most studied reactions in the history of organic synthesis.[51] Starting with R. B. Woodward's historic synthesis of erythromycin in 1981,[52] the aldol reaction has found use in nearly every polyketide synthesis published in the last thirty years.[53]

---

[47] (a) Kirst, H. A. *Expert Opin. Ther. Pat.* **1998**, *8*, 111-120. (b) Kaneko, T.; McArthur, H.; Sutcliffe, J. *Expert Opin. Ther. Pat.* **2000**, *10*, 403-435. (c) Kalesse, M.; Christmann, M. *Synthesis* **2001**, *8*, 981-1003. (d) Zotchev, S. B. *Curr. Med. Chem.* **2003**, *10*, 211-223. (e) Singh, R. K.; Tiwari, S. P.; Rai, A. K.; Mohapatra, T. M. *J. Antibiot.* **2011**, *64*, 401-412. (f) Herzon, S. B.; Woo, C. M. *Nat. Prod. Rep.* **2012**, *29*, 87-118.

[48] (a) Nielsen, J. B.; Hsu, M. J.; Byrne, K. M.; Kaplan, L. *Biochemistry*, **1991**, *30*, 5789–5796. (b) Schwecke, T.; Aparicio, J. F.; Molnár, I.; König, A.; Khaw, L. E.; Haydock, S. F.; Oliynyk, M.; Caffery, P.; Cortés, J.; Lester, J. B. *Proc. Nat. Acad. Sci. USA* **1995**, *92*, 7839-7843. (c) Reynolds, K. A.; Wallace, K. K.; Handa, S.; Brown, M. S.; McArthur, H. A. I.; Floss, H. G. *J. Antibiot.* **1997**, *50*, 701-703. (d) Motamedi, H.; Shafiee, A. *Eur. J. Biochem.* **1998**, *256*, 528-534. (e) Miyanaga, A.; Janso, J. E.; McDonald, L. He, M.; Liu, H.; Barbieri, L.; Eustaquio, A. S; Fielding, E. N.; Carter, G. T.; Jensen, P. R.; Feng, X.; Leighton, M.; Koehn, F. E.; Moore, B. S. *J. Am. Chem. Soc.*, **2011**, *133*, 13311-13313.

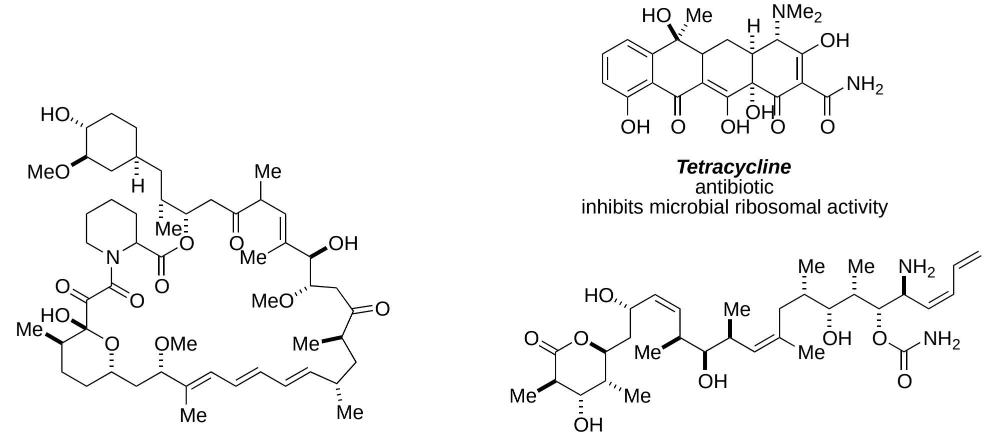
[49] Marinelli, F. *Methods in Enzymology* **2009**, *458*, 29-58.

[50] (a) Hale, K. J.; Hummersone, M. G.; Manaviazar, S.; Frigerio, M. *Nat. Prod. Rep.* **2002**, *19*, 413. (b) Yeung, K.-S.; Paterson, I. *Angew. Chem. Int. Ed.* **2002**, *41*, 4632. (c) Blunt, J. W.; Copp, B. R.; Hu, W. P.; Munro, M. H. G.; Northcote, P. T.**;** Prinsep, M. R. *Nat. Prod. Rep.* **2007**, *24*, 31.

[51] (a) Heathcock, C. H. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *2*, 133-238. (b) Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *2*, 239-275. (c) Paterson, I. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *2*, 301-319.

[52] Woodward, R. B.; Logush, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B. W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chfinevert, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggie, K. W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Rajan Babu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N.-C. *J. Am. Chem. Soc*. **1981**, *103*, 3210-3213.

[53] (a) Yeung, K.-S.; Paterson, I. *Chem. Rev.* **2005**, *105*, 4237. (b) Schetter, B.; Mahrwald, R. *Angew. Chem. Int. Ed.* **2006**, *45*, 7506-7525.

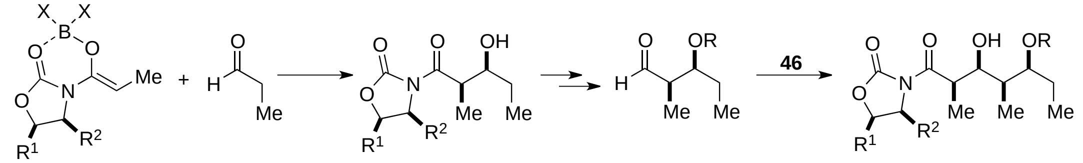

Rapamycin
antifungal, immunosuppressant
inhibits human peripheral blood mononucleation (IC_{50} =1 nM)

Tetracycline
antibiotic
inhibits microbial ribosomal activity

Discodermolide
antifungal, immunosuppressant
hyperstabilizes microtubulin (IC_{50} = 3-80 nM)

Figure 2.1.1. Some polyketide natural products and their biological activities.

Over this period of time, many stereoselective methods have been developed, and among these the Evans auxiliary approach remains the most commonly used.[54] In this protocol, chiral enolate **46** is reacted with an aldehyde, setting two stereocenters simultaneously under auxiliary control. This method allows for the construction of multiple stereocenters with excellent control and gives products that map directly onto portions of polyketide natural products termed polypropionates (Figure 2.1.2). Biosynthetically, these fragments are constructed by iterative Claisen condensations of propionate subunits as their thioesters by a series of enzymes called polyketide synthases (PKS),[55] and the aldol method mimics nature's disconnections.



46

polypropionate

Figure 2.1.2. Evans auxiliary-controlled aldol reactions.

---

[54] (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. "Stereoselective Aldol Condensations," in *Topics in Stereochemistry*, New York, **1982**, *13*, 2.

[55] (a) Staunton, J. *Angew. Chem. Int. Ed.* **1991**, *30*, 1302. (b) Garson, M. J. *Chem. Rev.* **1993**, *93*, 1699. (c) O'Hagan, D. *Nat. Prod. Rep.* **1993**, *9*, 447. (d) Rawlings, B. J. *Nat. Prod. Rep.* **2001**, *18*, 231-281. (e) Rix, U.; Fischer, C.; Remsing, L. L.; Rohr, J. *Nat. Prod. Rep.* **2002**, *19*, 542-580. (f) Heath, R. J.; Rock, C. O. *Nat. Prod. Rep.* **2002**, 581-596. (g) Hill, A. M. *Nat. Prod. Rep.* **2006**, *23*, 256-320. (h) Hertweck, C. *Angew. Chem. Int. Ed.* **2009**, *48*, 4688-4716.

In many polyketides, some of the hydroxyl groups are absent, giving rise to substructures termed deoxypolypropionate subunits. These fragments are commonly constructed by an approach related to the Evans aldol, the Myers alkylation.[56] This method also employs a chiral enolate **47** derived from a psuedoephedrine chiral auxiliary and adds an alkyl iodide with stereochemical control making deoxypolypropionates accessible in high selectivity (Figure 2.1.3).

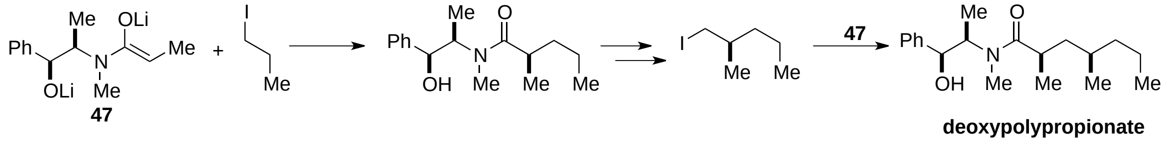


Figure 2.1.3.

Though both the Evans aldol reaction and Myers alkylation are extremely powerful transformations, there are some drawbacks. In both cases, the chiral auxiliary must be cleaved and several manipulations performed before another iteration can be carried out. Furthermore, these methods (and nature's) typically stitch together a target only two or three carbon atoms at a time, leaving room for improvement in terms of convergency. In other words, the use of stoichiometric chiral auxiliaries is not ideal for either atom efficiency and step economy.[57]

The issue of atom efficiency can be addressed directly by asymmetric catalysis. For instance, a number of groups have contributed to the development of the catalytic asymmetric Mukaiyama aldol reaction as an alternative to the Evans aldol.[58] The issue of step economy, on the other hand, may be addressed by a more convergent strategy for the construction of polyketide fragments. Glutaric anhydride derivatives represent 5-carbon fragments from which the functionality present in many polyketides can be revealed (Figure 2.1.4).

---

[56] (a) Meyers, A. I. *J. Am. Chem. Soc.* **1976**, *98*, 3032-3033. (b) Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. *J. Am. Chem. Soc.* **1981**, *103*, 3081-3087. (c) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233-4236 (d) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496-6511.

[57] (a) Trost, B. M. *Angew. Chem. Int. Ed.* **1995**, *34*, 259-281. (b) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40-49.

[58] (a) Carreira, E. M.; Singer, R. A.; Lee, W. S. *J. Am. Chem. Soc.* **1994**, *116*, 8837-8838. (b) Denmark, S. E.; Beutner, G. L.; Wynn, T.; Eastgate, M. D. *J. Am. Chem. Soc.*, **2005**, *127*, 3774-3789.

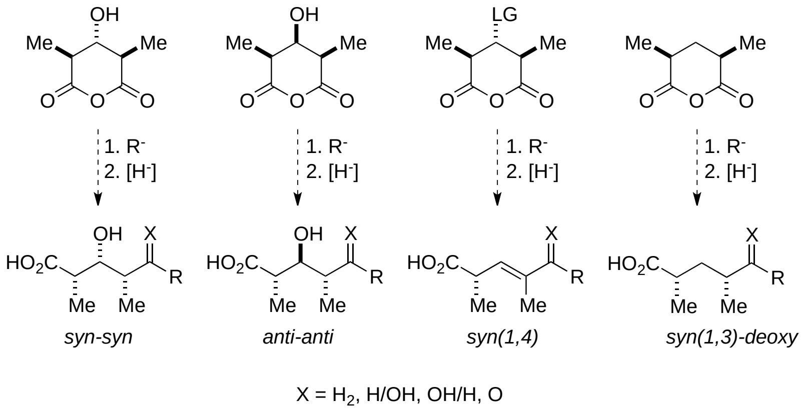
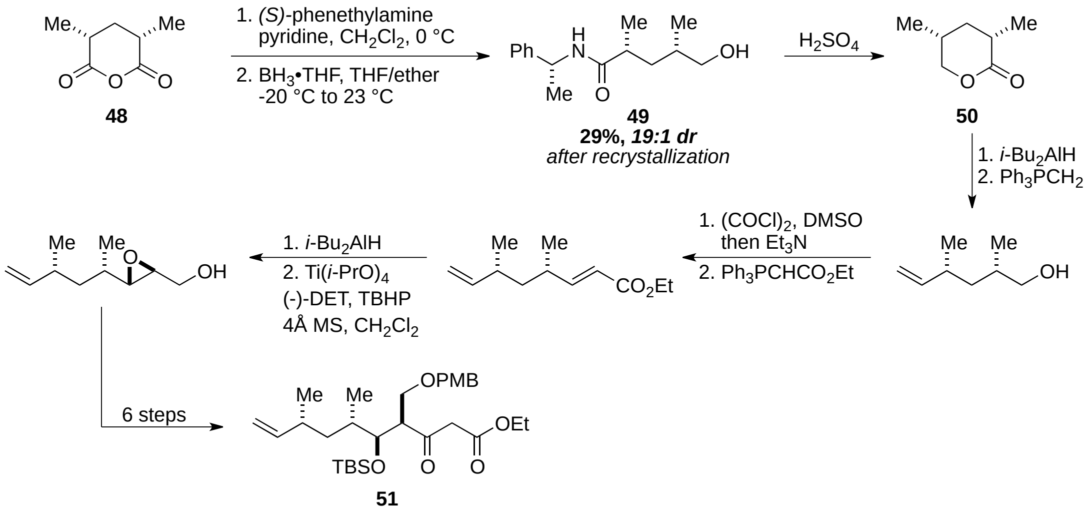


Figure 2.1.4. Desymmetrization strategy toward polyketide substructures

One such compound, *meso*-3,5-dimethylglutaric anhydride **48** has been used by many groups as a starting material for deoxypolypropionate subunits.[59] However, these sequences are lengthy and involve stoichiometric resolving agents. For example, in Paquette's progress toward okilactomycin, **48** is treated with (+)-phenethylamine, reduced with borane and then recrystallized to give amide **49** (Figure 2.1.5). This is closed to lactone **50**, giving an enantioenriched intermediate from *meso*-starting material. However, little complexity has been added to this substrate, and many more steps are necessary to elaborate this lactone to the desired polyketide fragment **51**. Therefore, the advantage over traditional iterative methods is minimal.

---

[59] (a) Paquette, L. A.; Boulet, S. L. *Synthesis* **2002**, 888-894. (b) Paquette, L. A.; Boulet, S. L. *Synthesis* **2002**, 895-900. (c) Lautens, M.; Colucci, J. T.; Hiebert, S.; Smith, N. D.; Bouchain, G. *Org. Lett.* **2002,** *4*, 1879-1882. (d) Zapf, C. W.; Harrison, B. A.; Drahl, C.; Sorenson, E *Angew. Chem. Int. Ed.* **2005**, *44*, 6533-6537.



Me
Me
O
O
O
48
1. (S)-phenethylamine pyridine, CH2Cl2, 0 °C
2. BH3•THF, THF/ether -20 °C to 23 °C
Ph
H
N
Me
O
Me
Me
OH
49
29%, 19:1 dr
after recrystallization
H2SO4
50
1. i-Bu2AlH
2. Ph3PCH2
1. (COCl)2, DMSO then Et3N
2. Ph3PCHCO2Et
CO2Et
1. i-Bu2AlH
2. Ti(i-PrO)4
(-)-DET, TBHP
4Å MS, CH2Cl2
6 steps
OPMB
OEt
TBSO
51

Figure 2.1.5.

Our group has pursued a method for deoxypolypropionate synthesis which addresses the issues of atom efficiency, step economy and convergency: a catalytic, enantioselective desymmetrization of meso anhydrides with organozinc reagents (vide infra). This strategy allows for the introduction of a multiple carbon fragment while simultaneously generating an enantioenriched product, which may be applied to the rapid synthesis of polyketide fragments.

The development of this reaction began with the study of organozinc additions to succinic anhydrides using nickel phosphinooxazoline (PHOX) as the catalyst. Under optimized conditions, ketoacids such as **52** can be prepared in good yield and modest enantioselectivity (Figure 2.1.6).[60] In 2004, we reported an improved catalyst system employing palladium and Josi-Phos to give increased enantioselectivity.[61] A rhodium-catalyzed variant was then applied to the asymmetric total synthesis of the eupomatolone family of natural products.[62]

---

[60] (a) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 174-175. (b) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 247-258. (c) Johnson, J. B.; Bercot, E. A.; Rowley, J. M.; Coates, G. W.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 2718-2725.

[61] Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 10248-10249.

[62] Johnson, J. B.; Bercot, E. A.; Williams, C. M.; Rovis, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 4514-4518.

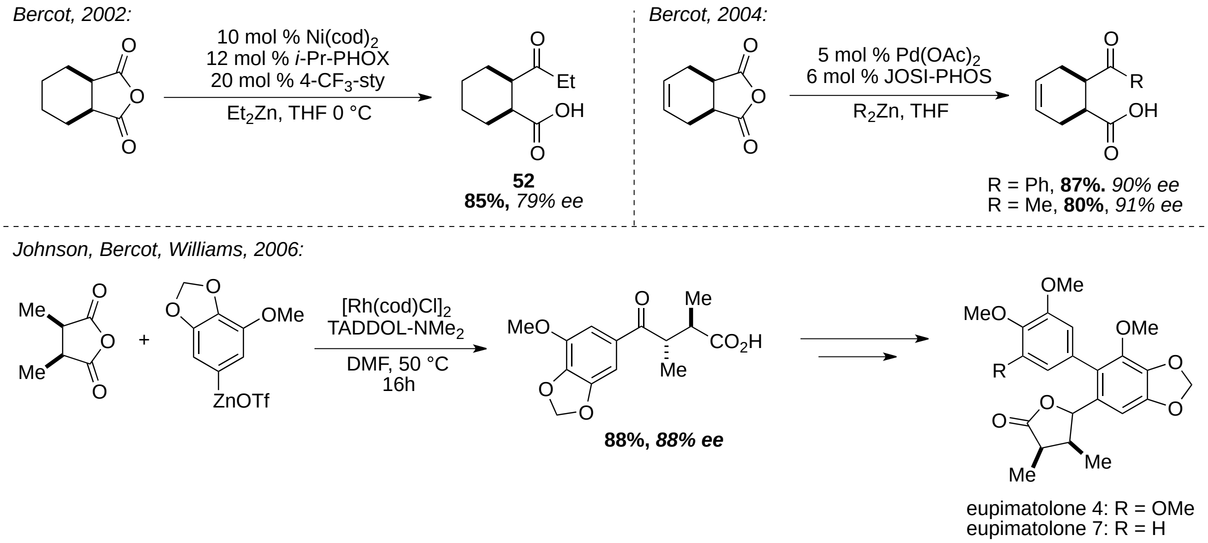

Bercot, 2002:
10 mol % Ni(cod)2
12 mol % i-Pr-PHOX
20 mol % 4-CF3-sty
Et2Zn, THF 0 °C
Et
OH
52
85%, 79% ee
Bercot, 2004:
5 mol % Pd(OAc)2
6 mol % JOSI-PHOS
R2Zn, THF
R
OH
R = Ph, 87%. 90% ee
R = Me, 80%, 91% ee
Johnson, Bercot, Williams, 2006:
Me
Me
OMe
ZnOTf
[Rh(cod)Cl]2
TADDOL-NMe2
DMF, 50 °C
16h
MeO
Me
Me
CO2H
88%, 88% ee
OMe
MeO
OMe
R
Me
Me
eupimatolone 4: R = OMe
eupimatolone 7: R = H

Figure 2.1.6. Transition metal catalyzed desymmetratizations of succinic anhydrides.

In 2007, the scope of electrophile was extended to 3,5-dimethylglutaric anhydride using a rhodium-PHOX catalyst system.[63] A variety of organozincs are competent in this reaction, providing enantioenriched 1,3-dimethyl ketoacids **53** in good yield and excellent selectivity (Figure 2.1.7). It should be noted that alkylzincs give consistently higher enantioselectivity than arylzincs. This method represents a general entry to the catalytic, asymmetric synthesis of deoxypolypropionate subunits.

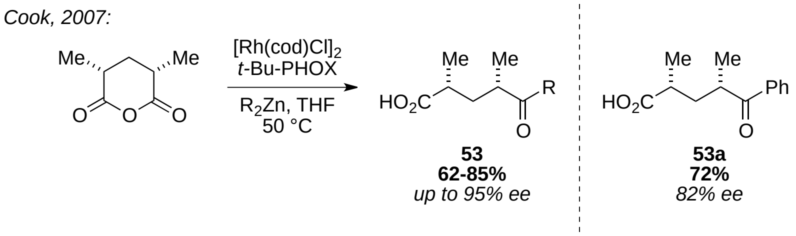

Cook, 2007:
Me
Me
[Rh(cod)Cl]2
t-Bu-PHOX
R2Zn, THF
50 °C
Me Me
HO2C
R
53
62-85%
up to 95% ee
Me Me
HO2C
Ph
53a
72%
82% ee

Figure 2.1.7. Rhodium catalyzed desymmetrization of 3,5-dimethyl glutaric anhydride

Our mechanistic proposal for this reaction begins, in the case of rhodium, with transmetalation of the organozinc to generate an alkylrhodium(I) species **V** (Figure 2.1.8). This then undergoes oxidative addition to the anhydride in a stereoselective fashion to give **VI**, differentiating the carbonyls of **48** by control of the chiral ligand. This Rh(III) intermediate can then reductively eliminate to form the carbon-carbon bond and generate Rh-carboxylate **VII**. This Rh(I) then reenters the catalytic cycle, releasing the ketoacid product **53**.

---

[63] Cook, M. J.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 9302-9303.

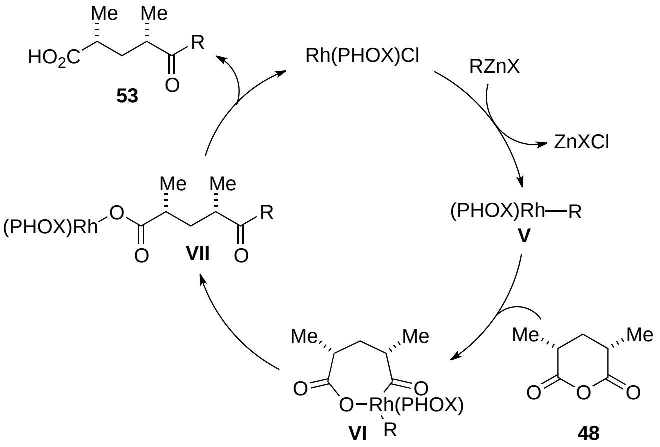


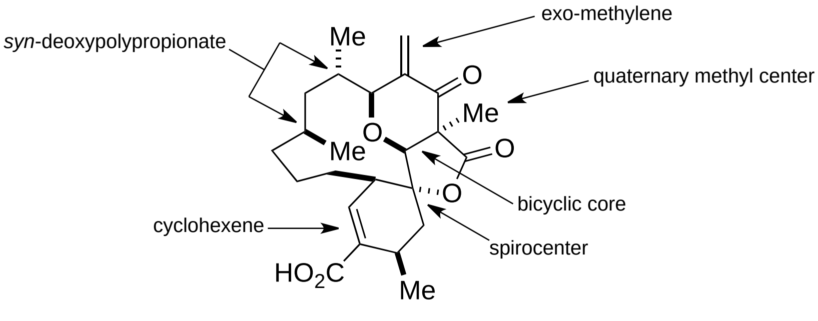
Figure 2.1.8. Proposed catalytic cycle

As stated above, this method provides entry to a variety of deoxypolypropionate structures, and we felt it should be applicable to the total synthesis of a number of natural products. One suitable target is okilactomycin (**54**), a complex polyketide isolated from bacteria found on Zamami Island in Okinawa, Japan.[64] This compound exhibits modest antimicrobial activity against gram-positive cells and promising cytotoxicity against lymphoid leukemia cells (IC_{50} = 0.2 nM) and leukemia P388 cells (IC_{50} = 0.08 nM). Structurally, it contains a *syn*-deoxypolypropionate embedded within a macrocyclic ring, a fused cyclohexene, and a bicyclic pyranone which is itself fused to a spirocyclic lactone. Furthermore, a quaternary methyl stereocenter and sensitive exo-methylene Michael acceptor are present (Figure 2.1.9). This challenging target has been pursued by a number of groups,[65] with two completing the total synthesis of okilactomycin in greater than 25 steps.

---

[64] Imai, H.; Suzuki, K.; Morioka, M.; Numasaki, Y.; Kadota, S.; Nagai, K.; Sato, T.; Iwanami, M.; Saito, T. *J. Antibiot.* **1987**, *40*, 1475-1482.

[65] (a) Paquette, L. A.; Boulet, S. L. *Synthesis* **2002**, 888-894. (b) Paquette, L. A.; Boulet, S. L. *Synthesis* **2002**, 895-900.



syn-deoxypolypropionate
exo-methylene
quaternary methyl center
bicyclic core
spirocenter
cyclohexene
Me
O
O
Me
O
O
Me
HO2C
Me

54
(+)-okilactomycin

Figure 2.1.9. Key structural features of okilactomycin.

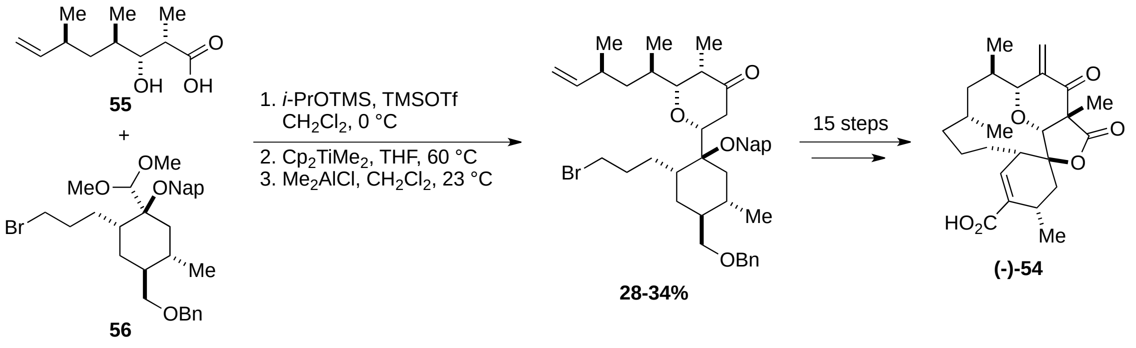
The first total synthesis of okilactomycin was achieved by Amos Smith and coworkers in 2007.[66] Their key step involves a Petasis-Ferrier rearrangement that constructs the spirocyclic core and unites the upper and lower portions of okilactomycin as two chiral fragments **55** and **56** (Figure 2.1.10, a). The macrocyclic ring is closed via a late-stage ring-closing metathesis (RCM). The top fragment **55** arises from a Myers alkylation followed by an Evans auxiliary-controlled aldol (Figure 2.1.10, b) The bottom fragment **56** is made by a Rawal auxiliary-controlled Diels-Alder cycloaddition (Figure 2.1.10, c).[67] Overall, the synthesis of (-)-okilactomycin is achieved in 29 linear steps, and the absolute configuration of the natural compound was confirmed as the enantiomer of Smith's synthetic product.

---

[66] Smith, A.B.; Basu, K.; Bosenac, T *J. Am. Chem. Soc.* **2007**, *129*, 14872-14874.

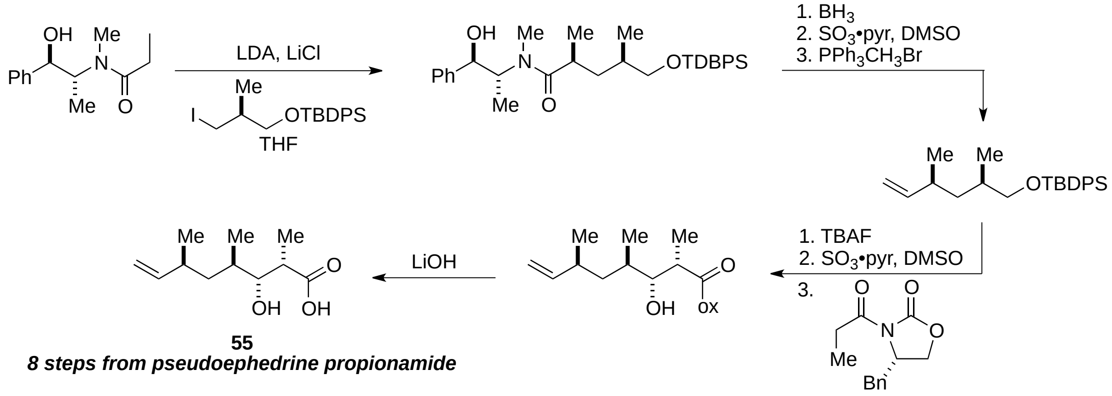
[67] (a) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.*, **1997**, *119*, 7165. (b) Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.*, **1997**, *62*, 5252. (c) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.*, **1999**, *121*, 9562.

(a) Petasis-Ferrier



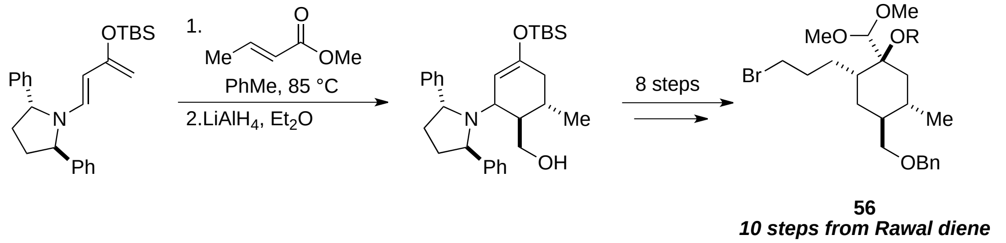
55
+
56
1. *i*-PrOTMS, TMSOTf CH$_2$Cl$_2$, 0 °C
2. Cp$_2$TiMe$_2$, THF, 60 °C
3. Me$_2$AlCl, CH$_2$Cl$_2$, 23 °C
28-34%
15 steps
(-)-54

(b) Top fragment: Myers alkylation and Evans aldol



LDA, LiCl
THF
1. BH$_3$
2. SO$_3$•pyr, DMSO
3. PPh$_3$CH$_3$Br
1. TBAF
2. SO$_3$•pyr, DMSO
3.
LiOH
55
8 steps from pseudoephedrine propionamide

(c) Bottom fragment: Rawal 4+2



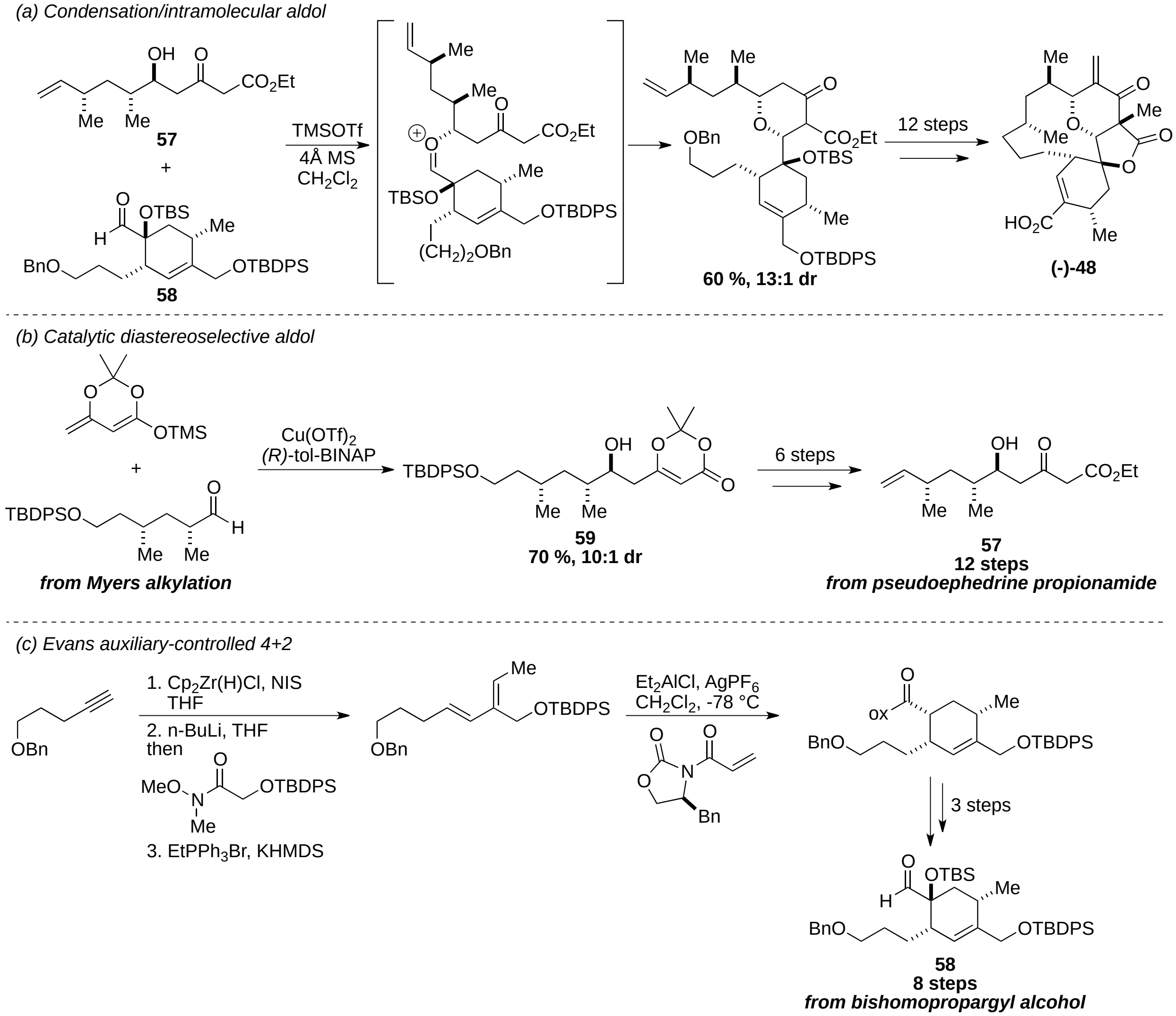
1.
PhMe, 85 °C
2.LiAlH$_4$, Et$_2$O
8 steps
56
10 steps from Rawal diene

Figure 2.1.10. Summary of A. B. Smith's synthesis of (-)-okilactomycin.

While we were working toward our own synthesis of okilactomycin, a second total synthesis was reported by Karl Scheidt and coworkers.[68] Using similar disconnections as Smith, Scheidt unites the upper and lower portions of okilactomycin by a condensation/intramolecular aldol reaction (Figure 2.1.11, a). As in Smith's synthesis, each of the requisite fragments **57** and **58** is prepared stereoselectively by auxiliary-controlled reactions, but Scheidt prepares each fragment in fewer steps. The deoxypolypropionate portion is constructed by a Myers alkylation and then subjected to a diastereoselective copper-catalyzed aldol reaction giving **59**, which is elaborated by further steps to the completed top fragment **57** (Figure 2.1.11, b). The cyclohexene **58** is prepared by an Evans auxiliary-controlled Diels-Alder reaction (Figure 2.1.11, c). Because Scheidt's strategy uses the same natural enantiomers of each auxiliary, he reaches the unnatural enantiomer of okilactomycin as did Smith.

---

[68] Tenenbaum, J. M.; Morris, W. J.; Custar, D. W.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2011**, *50,* 5892-5895.



(a) Condensation/intramolecular aldol

(b) Catalytic diastereoselective aldol

(c) Evans auxiliary-controlled 4+2

57
+
58
TMSOTf
4Å MS
CH2Cl2
60 %, 13:1 dr
12 steps
(-)-48
Cu(OTf)2
(R)-tol-BINAP
from Myers alkylation
59
70 %, 10:1 dr
6 steps
57
12 steps
from pseudoephedrine propionamide
1. Cp2Zr(H)Cl, NIS THF
2. n-BuLi, THF then
3. EtPPh3Br, KHMDS
Et2AlCl, AgPF6
CH2Cl2, -78 °C
3 steps
58
8 steps
from bishomopropargyl alcohol

Figure 2.1.11. Summary of K. A. Scheidt's synthesis of (-)-okilactomycin.

Hoye and coworkers completed okilactomycin D in 2012.[69] This member of the okilactomycin family lacks the closed 4-pyranone, quaternary methyl and exo-methylene of the parent compound but contains the same macrocycle and similar cyclohexene (Scheme 2.1.12). Hoye assembles the macrocycle and fused cyclohexene by an intramolecular Diels-Alder reaction of tetronate **60**. This is built from **61**, which is derived from the unification of the deoxypolypropionate constructed by Myers alkylation with the diene fragment by a Fouquet-Schlosser coupling.[70]

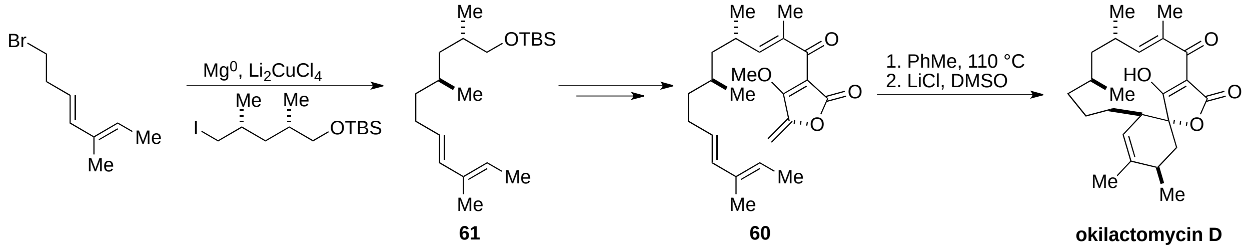

Br
Me
Me
Mg0, Li2CuCl4
Me
Me
I
OTBS
Me
OTBS
Me
Me
Me
61
Me
Me
O
MeO
Me
O
O
Me
Me
60
1. PhMe, 110 °C
2. LiCl, DMSO
Me
Me
O
HO
Me
O
O
Me
Me
okilactomycin D

Figure 2.1.12. Summary of T. R. Hoye's synthesis of okilactomycin D.

---

[69] Niu, D.; Hoye, T. R. *Org. Lett.* **2012**, *14*, 828-831.

[70] (a) Fouquet, G.; Schlosser, M. *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 82-83. (b) Lipshutz, B. H. In *Organometallics in Synthesis*, ed. Schlosser, M.; Wiley, Chichester, U.K. **2002**, 740-763.

2.2. Retrosynthetic strategy

Our retrosynthetic strategy toward okilactomycin would roughly halve the number of steps used by A. B. Smith in its first total synthesis. We planned to accomplish this by an extremely rapid synthesis of the top portion and a more convergent route to elaborate the lower fragment. We thought a late-stage substrate controlled Diels Alder reaction of a tetronic acid similar to that used by Sorenson in his synthesis of abyssomycin[71] could assemble the spirocycle and the cyclohexene simultaneously (Figure 2.2.1). The Diels-Alder substrate **62** could be divided into bottom and top fragments **63** and **64**, united via an sp^3 cross coupling. After our proposal, similar steps were demonstrated by Hoye in his synthesis of okilactomycin D,[72] validating this approach. The diene could be assembled by a fairly straightforward cross-coupling strategy while the dienophile would come from a short sequence employing a Dieckmann-type cyclization of enolcarbonate **65**, which would come from methylenation and oxidative transposition of 3-pyranone **66**. This would, in turn come from an Achmatowicz rearrangement of furyl carbinol **67**. A Rh-catalyzed desymmetrization of **48** with a furylzinc **68** followed by diastereoselective reduction to give **67** would constitute the key enantioselective step. The advantages of this route over the currently published syntheses would include a lower step count, but also the complete elimination of stoichiometric chiral reagents.

---

[71] Zapf, C. W.; Harrison, B. A.; Drahl, C.; Sorenson, E. J.Int. *Angew. Chem. Int. Ed.* **2005**, *44*, 6533-6537.

[72] Niu, D.; Hoye, T. R. *Org. Lett.* **2012**, *14*, 828-831.

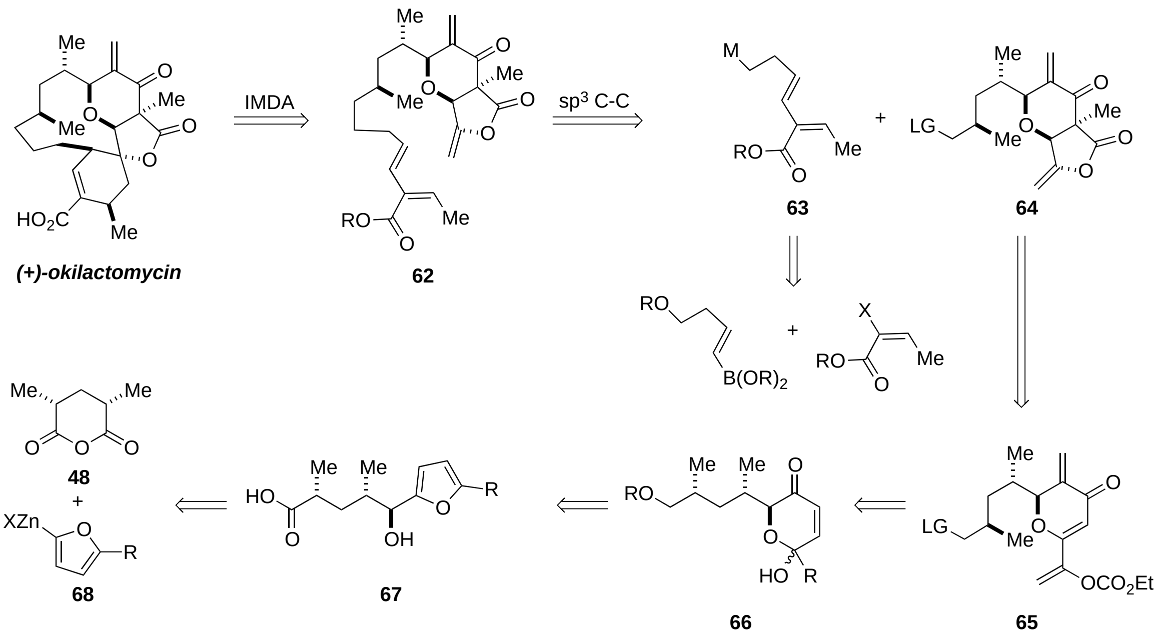

(+)-okilactomycin
IMDA
62
sp3 C-C
63
64
65
66
67
48
68
Me
O
HO2C
RO
M
LG
X
B(OR)2
XZn
R
HO
OH
OCO2Et
+

Figure 2.2.1. Retrosynthesis.

2.3. Construction of the bottom fragment

The synthesis of the diene fragment is fairly straightforward. Starting from homopropargyl alcohol, TBS ether **69** is prepared under standard conditions, then hydroboration, oxidation and condensation of pinacol give the known pinacolboronic ester **70** (Figure 2.3.1).[73] Vinyl iodide **71** is prepared by hydrostannation of ethyl butynoate[74] followed by oxidation with iodine. These fragments are coupled by a Suzuki-Miyaura reaction with $Pd(PPh_3)_2Cl_2$ as the catalyst in the presence of CsF.[75] The TBS ether is cleaved, and Appel reaction[76] with carbon tetrabromide gives the requisite alkyl bromide **72**, setting the stage for activation as the Grignard reagent to be coupled with our proposed top fragment.

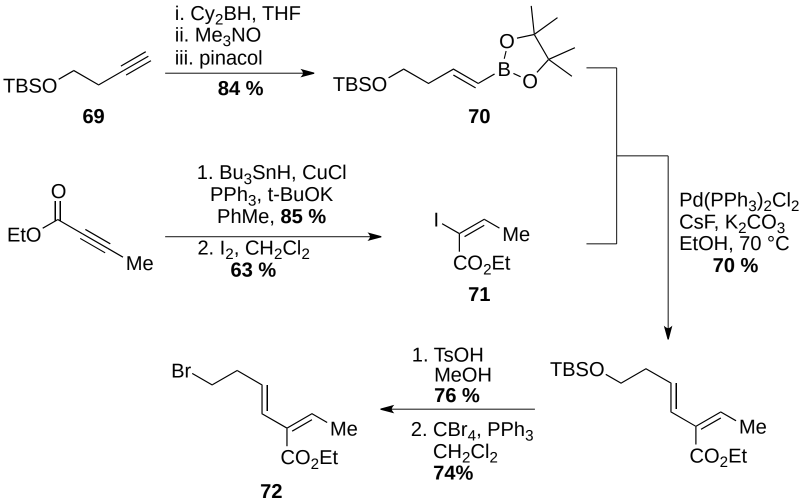

i. Cy2BH, THF
ii. Me3NO
iii. pinacol
84 %
TBSO
69
TBSO
70
O
B
O
1. Bu3SnH, CuCl
PPh3, t-BuOK
PhMe, 85 %
2. I2, CH2Cl2
63 %
EtO
O
Me
I
Me
CO2Et
71
Pd(PPh3)2Cl2
CsF, K2CO3
EtOH, 70 °C
70 %
1. TsOH
MeOH
76 %
2. CBr4, PPh3
CH2Cl2
74%
Br
Me
CO2Et
72
TBSO
Me
CO2Et

Figure 2.3.1

---

[73] (a) Wang, Y. D.; Kimball, G.; Prashad, A. S.; Wang, Y. *Tetrahedron Lett.* **2005**, *46*, 8777-8780. (b) Molander, G. *J. Org. Chem.* **2002**

[74] Bishop, L. M.; Barbarow, J. E.; Bergman, R. G.; Trauner, D. *Angew. Chem. Int. Ed.* **2008**, *47*, 8100-8103.

[75] Bei, X,; Turner, H, W.; Weinberg, W. H.; Guram, A. S.; Petersen, J. L. *J. Org. Chem.* **1999**, *64*, 6797-6803

[76] Appel, R. *Angew. Chem. Int. Ed. Engl*. **1975**, *14*, 801-811.

2.4. Early exploration with unsubstituted furylzinc as the nucleophile

The preparation of furyl carbinol **67** is key to our strategy for constructing the upper portion of okilactomycin. Optimization of our Rh-catalyzed desymmetrization with a furyl nucleophile **68** would give the corresponding ketoacid **73**, which we believed would be reduced diastereoselectively with $LiBHEt_3$ to give **67** (Figure 2.4.1).[77] Furylzincs had been demonstrated previously as nucleophiles for succinic anhydrides,[78] but their use in glutaric anhydride desymmetrizations had been studied only briefly. Therefore, my first task was to optimize desymmetrization of 3,5-dimethyl glutaric anhydride with furylzincs.

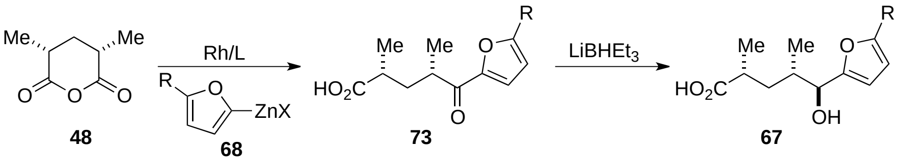
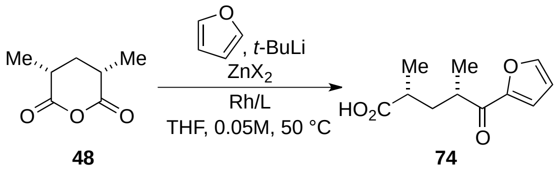


Figure 2.4.1. Planned desymmetrization and subsequent reduction

Initially, I studied the reaction of unsubstituted furylzincs to give ketoacid product **74** (eq 40). A screen of rhodium precursor, ligands, and zinc salts revealed that the reaction was feasible; however, enantioselectivity fell short of satisfactory (Table 2.4.1). It should be noted that preparation of the difurylzinc by addition of 0.5 equiv of a zinc salt gave no desired product.



(40)

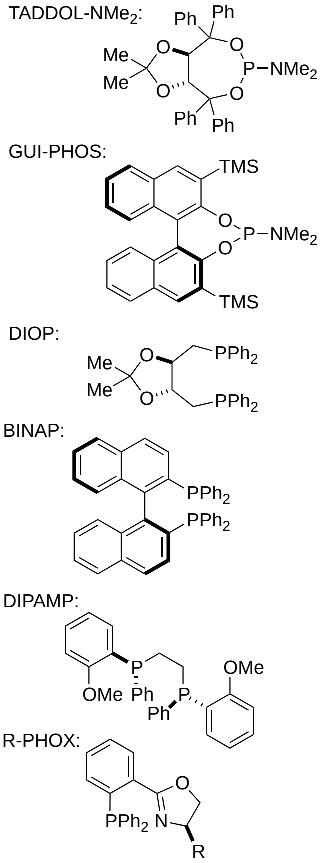
---

[77] Bercot, E. A.; Kindrachuk, D. E.; Rovis, T. *Org. Lett.* **2005**, *7*, 107.

[78] Williams, C. M. Ph. D. Thesis, Colorado State University, March 2010.

Table 2.4.1.

Rh	L	X	Yield (%)	ee (%)
$[Rh(cod)Cl]_2$	TADDOL-NMe_2	I	**<10**	-
$[Rh(cod)Cl]_2$	GUI-PHOS	I	**<10**	-
$[Rh(cod)Cl]_2$	DIOP	Cl	**0**	-
$[Rh(cod)Cl]_2$	NorPHOS	Cl	**0**	-
$[Rh(cod)Cl]_2$	BINAP	Cl	**0**	-
$[Rh(cod)Cl]_2$	DIPAMP	Cl	**0**	-
$[Rh(cod)Cl]_2$	*i*-Pr-PHOX	Cl	**47**	*35*
$[Rh(cod)Cl]_2$	*t*-Bu-PHOX	Cl	**47**	*38*
$[Rh(cod)Cl]_2$	*i*-Pr-PHOX	Br	**50**	*50*
$[Rh(cod)Cl]_2$	*t*-Bu-PHOX	Br	**50**	*38*
$[Rh(cod)Cl]_2$	*i*-Pr-PHOX	I	**50**	*62*
$[Rh(cod)Cl]_2$	*t*-Bu-PHOX	I	**50**	*50*
$[Rh(cod)Cl]_2$	Ph-PHOX	I	**50**	*32*
$[Rh(cod)Cl]_2$	Bn-PHOX	I	**46**	*48*
$[Rh(nbd)Cl]_2$	*i*-Pr-PHOX	I	**50**	*22*
$[Rh(nbd)Cl]_2$	*t*-Bu-PHOX	I	**50**	*32*
$[Rh(nbd)Cl]_2$	Ph-PHOX	I	**57**	*22*
$[Rh(H_2CCH_2)Cl]_2$	*i*-Pr-PHOX	I	**48**	*48*
$[Rh(H_2CCH_2)Cl]_2$	*t*-Bu-PHOX	I	**0**	-
$[Rh(H_2CCH_2)Cl]_2$	Bn-PHOX	I	**36**	*56*
$[Rh(cod)Cl]_2$	*i*-Pr-PHOX	OTf	**42**	*42*
$[Rh(cod)Cl]_2$	*t*-Bu-PHOX	OTf	**0**	-
$[Rh(cod)Cl]_2$	Ph-PHOX	OTf	**35**	*20*
$[Rh(cod)Cl]_2$	Bn-PHOX	OTf	**24**	*10*
$[Rh(cod)Cl]_2$	*i*-Pr-PHOX	furyl	**0**	-
$[Rh(cod)Cl]_2$	*t*-Bu-PHOX	furyl	**0**	-



Regardless, proof of concept had been demonstrated for the initial step, and exploration of the subsequent steps was undertaken. The stereoselective reduction with $LiBHEt_3$ proceeds as expected, with >19:1 dr observed in lactone product **75** (Figure 2.4.2). Reduction to the diol **76** with $LiAlH_4$ followed by protection as the TBS ether **77** and oxidation of the furan ring with NBS gives the rearranged 3-pyranone **78**. At this point, we thought it would be possible to install the requisite acetyl group by forming the thiolate at the lactol center, deprotonating, and adding to an acyl electrophile. Unfortunately, attempts to form thiolate **79** on greater than 10 mg scale led to decomposition.

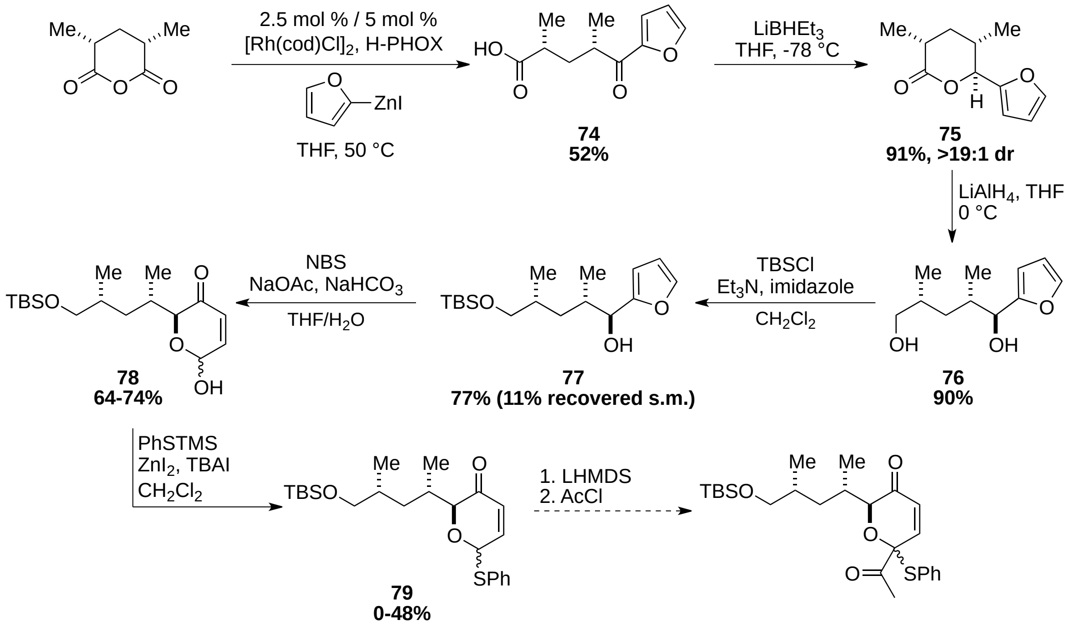
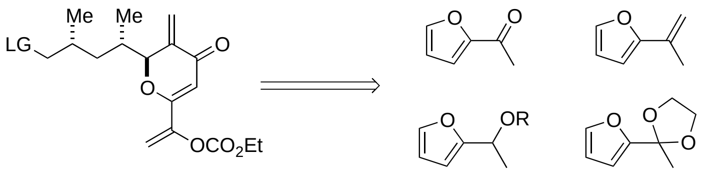

2.5 mol % / 5 mol %
[Rh(cod)Cl]2, H-PHOX
ZnI
THF, 50 °C
74
52%
LiBHEt3
THF, -78 °C
75
91%, >19:1 dr
LiAlH4, THF
0 °C
76
90%
TBSCl
Et3N, imidazole
CH2Cl2
77
77% (11% recovered s.m.)
NBS
NaOAc, NaHCO3
THF/H2O
78
64-74%
PhSTMS
ZnI2, TBAI
CH2Cl2
79
0-48%
1. LHMDS
2. AcCl

Figure 2.4.2.

2.5. Optimization of protected acetylfuran addition and current route

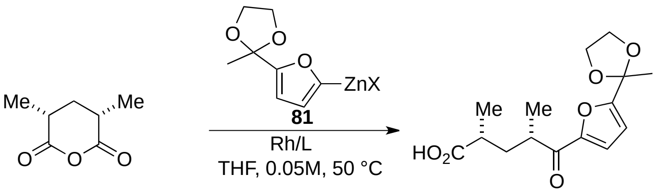
Having demonstrated the desymmetrization with an unsubstituted furylzinc, I moved to furylzincs containing the two carbons that would comprise the dienophile of the late-stage Diels-Alder substrate **65** (Figure 2.5.1). Among these, ketal-protected acetylfuran **80** was both readily accessible and competent in the desymmetrization (eq 41).



65 **80**

Figure 2.5.1. Possible precursors to the 2-carbon dienophile fragment.

I optimized enantioselectivity with furylzinc nucleophile **81** (generated by lithiation and transmetalation of **80**) on 25 mg scale (eq 41) and found that Bn-PHOX and Ph-TADDOL give the highest enantioenrichment of product at 50 °C (Table 2.5.1). However, the yield with TADDOL was less than 10%. On the other hand, 44% yield of keto acid **82** could be isolated using Bn-PHOX as the ligand, and lowering the reaction temperature to 23 °C improved selectivity to 83% ee.

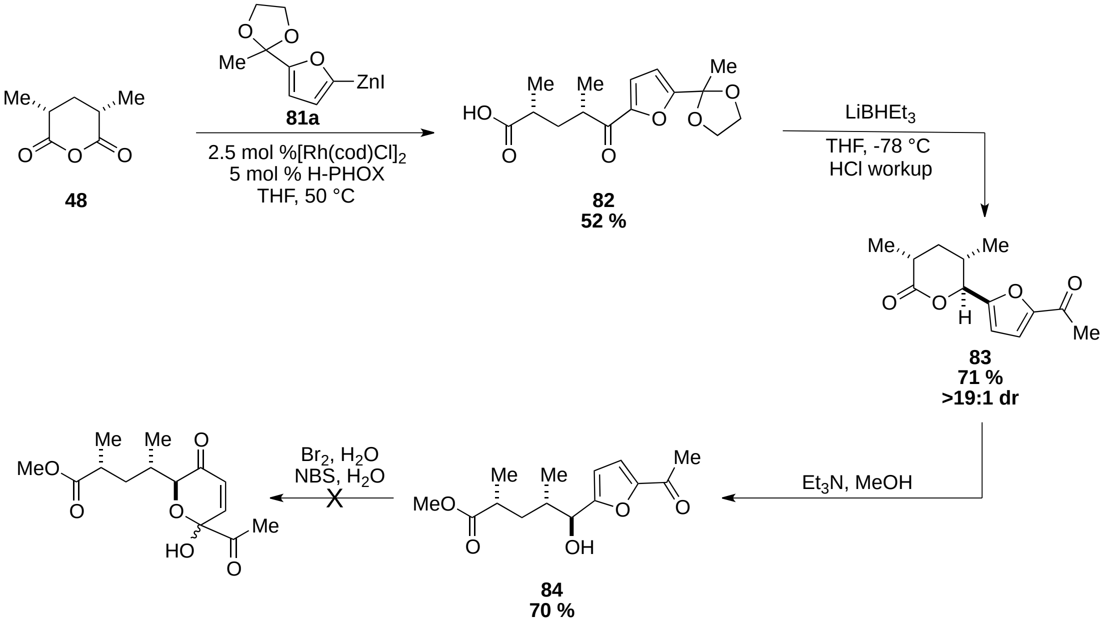


48 **82** (41)

Table 2.5.1.

Rh	L	X	ee (%)	Rh	L	X	ee (%)
$[Rh(cod)Cl]_2$	*i*-Pr-PHOX	Br	*58*	$[Rh(cod)Cl]_2$	GUI-PHOS	I	*n.d.*
$[Rh(cod)Cl]_2$	*t*-Bu-PHOX	Br	*46*	$[Rh(cod)Cl]_2$	Ph-TADDOL-pyr	I	*72%*
$[Rh(cod)Cl]_2$	Bn-PHOX	Br	*73*	$[Rh(cod)Cl]_2$	CK-PHOS	I	*15%*
$[Rh(cod)Cl]_2$	*i*-Pr-PHOX	I	*62*	$[Rh(cod)Cl]_2$	Ph-TADDOL-pip	I	*64%*
$[Rh(cod)Cl]_2$	*t*-Bu-PHOX	I	*58*	$[Rh(cod)Cl]_2$	xylyl-TADDOL-pyr	I	*70%*
$[Rh(cod)Cl]_2$	Bn-PHOX	I	*72*				
$[Rh(nbd)Cl]_2$	*i*-Pr-PHOX	I	*62*	23 °C			
$[Rh(nbd)Cl]_2$	*t*-Bu-PHOX	I	*58*	$[Rh(nbd)Cl]_2$	Bn-PHOX	I	*81%*
$[Rh(nbd)Cl]_2$	Bn-PHOX	I	*72*	$[Rh(cod)Cl]_2$	Bn-PHOX	I	*83%*

With these satisfactory results in hand, I moved on to exploring the forward route toward the top fragment **64** (Figure 2.5.2). The racemic reaction of **48** with furyl zinc iodide **81a** is accomplished in 52% yield using achiral H-PHOX as the ligand. This is followed by diastereoselective reduction of the ketone to give lactone **83**. The acidic workup causes the ketal to hydrolyze, and unprotected ketone is isolated. This intermediate is then transesterified to hydroxyester **84**. At this point, oxidation of the furylcarbinol under a variety of conditions failed, presumably due to the electron withdrawing nature of the acetyl group.



Me
Me
O
O
O
48
O
O
Me
O
ZnI
81a
2.5 mol %[Rh(cod)Cl]2
5 mol % H-PHOX
THF, 50 °C
HO
Me
Me
O
O
O
Me
O
O
82
52 %
LiBHEt3
THF, -78 °C
HCl workup
Me
Me
O
O
H
O
O
Me
83
71 %
>19:1 dr
Et3N, MeOH
MeO
Me
Me
O
O
OH
Me
O
84
70 %
Br2, H2O
NBS, H2O
MeO
Me
Me
O
O
O
HO
Me
O

Figure 2.5.2.

We thought we could prevent deactivation of the ring by keeping the ketal intact after the borohydride reduction, and did so by changing the workup from acidic to basic (Figure 2.5.3). Under these conditions, a mixture of hydroxy acid **85** and lactone **86** is obtained, which can be converted fully to **86** by addition of acetic anhydride. Thus, **86** is prepared in 90% yield and >19:1 dr. Reduction with Red-Al gives the diol which can be TBS protected to give primary silyl ether **87**. The furyl ring can then be oxidized to yield 3-pyranone **88**. A variety of methylenation conditions were screened including the Wittig,[79] Peterson,[80] and Petasis[81] protocols; however, only Tebbe's reagent[82] was found to be effective at preparing diene **89**.

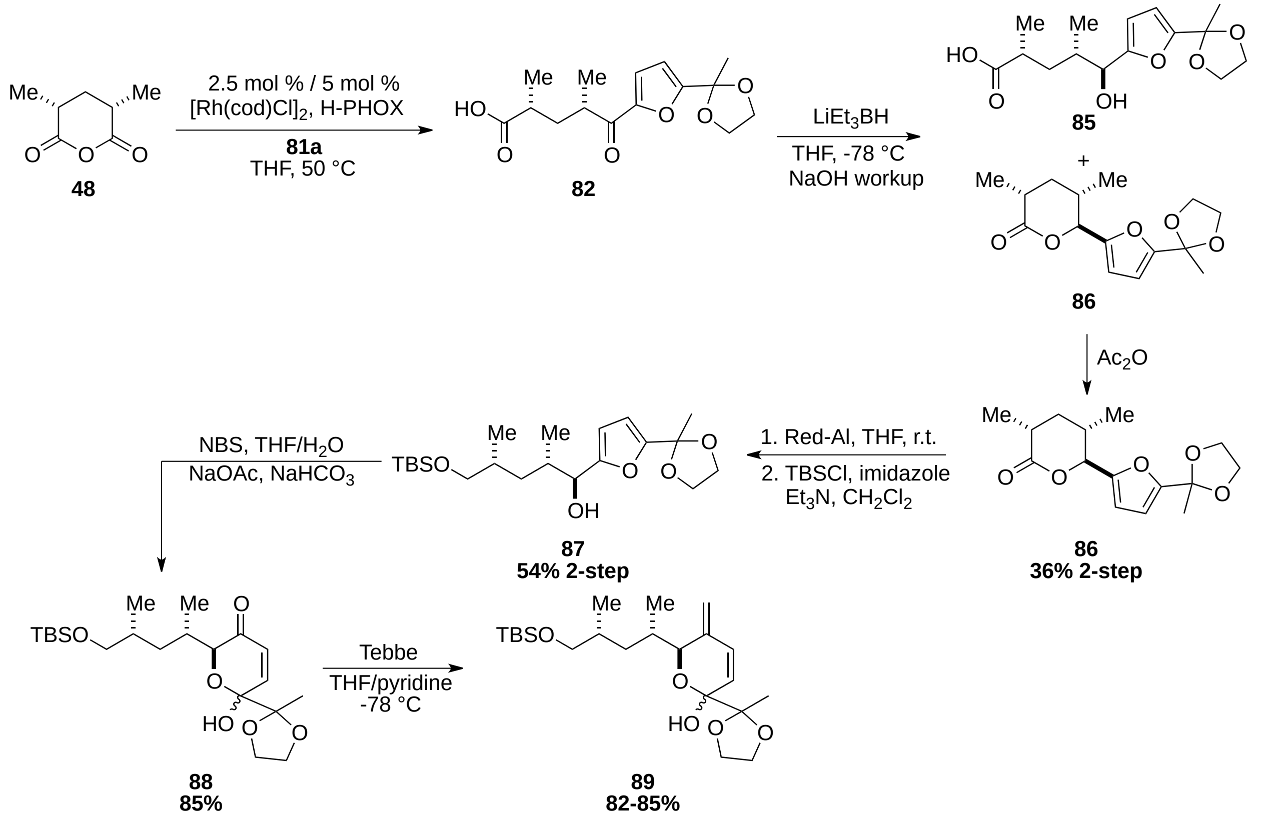

48
2.5 mol % / 5 mol %
[Rh(cod)Cl]$_2$, H-PHOX
81a
THF, 50 °C
82
LiEt$_3$BH
THF, -78 °C
NaOH workup
85
+
86
Ac$_2$O
86
36% 2-step
1. Red-Al, THF, r.t.
2. TBSCl, imidazole
Et$_3$N, CH$_2$Cl$_2$
87
54% 2-step
NBS, THF/H$_2$O
NaOAc, NaHCO$_3$
88
85%
Tebbe
THF/pyridine
-78 °C
89
82-85%

Figure 2.5.3.

---

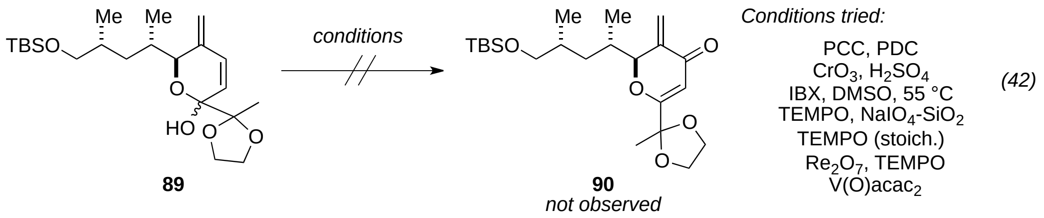
[79] Wittig, G.; Schöllkopf, U. *Chem. Ber.* **1954**, *87*, 1318.

[80] Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780-784

[81] Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**,*112*, 6392-6394.

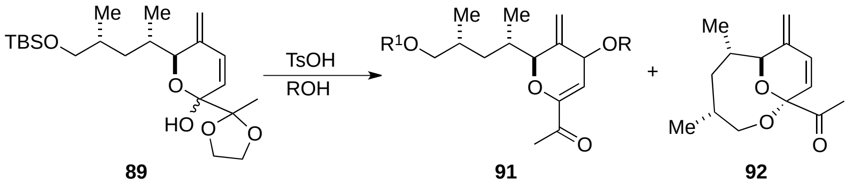
[82] Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611-3613.

Our next envisioned step was the oxidative transposition of the allylic lactol in **89** to give 4-pyranone **90**. This proved to be a difficult task, as many conditions for oxidative transposition failed (eq 42).[83]


Me
Me
TBSO
O
HO
O
O
89
conditions
Me
Me
TBSO
O
O
O
O
90
not observed
Conditions tried:
PCC, PDC
CrO3, H2SO4
IBX, DMSO, 55 °C
TEMPO, NaIO4-SiO2
TEMPO (stoich.)
Re2O7, TEMPO
V(O)acac2

(42)

At this point, we began to consider alternative strategies to prepare 4-pyranone **90**. We sought to isomerize the lactol in **89** by acid catalysis. A screen of conditions and nucleophiles revealed that a number of alcohols could be added at the 4-position of the pyran to give doubly allylic ethers **91** (eq 43). Deprotection of the TBS ether and intramolecular addition of the alcohol to give **92** was also observed in the case of *t*-BuOH. However, the hydration product **91a** (R=H) could not be isolated in appreciable amounts. Oxidation protocols on the allylic ethers were unsuccessful, and this strategy was also abandoned.


Me
Me
TBSO
O
HO
O
O
89
TsOH
ROH
Me
Me
R1O
OR
O
O
91
+
Me
Me
O
O
O
92

(43)

ROH = MeOH, R^1 = H	**45%**	**0%**
ROH = *t*-BuOH, R^1 = TBS	**19%**	**27%**
ROH = PMBOH, R^1 = TBS	**40 %**	**0%**

A second alternative could be the preparation of a lactol thioether **93**, which could be oxidized to sulfoxide **94** (Figure 2.5.4). This could then undergo a Mislow-Evans rearrangement[84] to give oxygenation at the 4-position of the pyrone in **91**a. Unfortunately, treatment of diene **89** under standard conditions to form the thiolate[85] lead to 1,6-addition of the thiol followed by ring opening to **95**.

---

[83] (a) Iwabuchi, *Org. Lett.* **2004**, 4303-4306; (b) Iwabuchi, *Org. Lett.* **2008**, 4715-4718; (c) Iwabuchi, *J. Org. Chem.* **2008**, 4750-4752.

[84] (a) Bickart, P.; Carson, F. W.; Jacobus, J.; Miller, E. G.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4869-4876. (b) Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 2100-2104. (c) Evans, D. A.; Andrews, G. C.; Sims, C. L. *J. Am. Chem. Soc.* **1971**, *93*, 4956-4957.

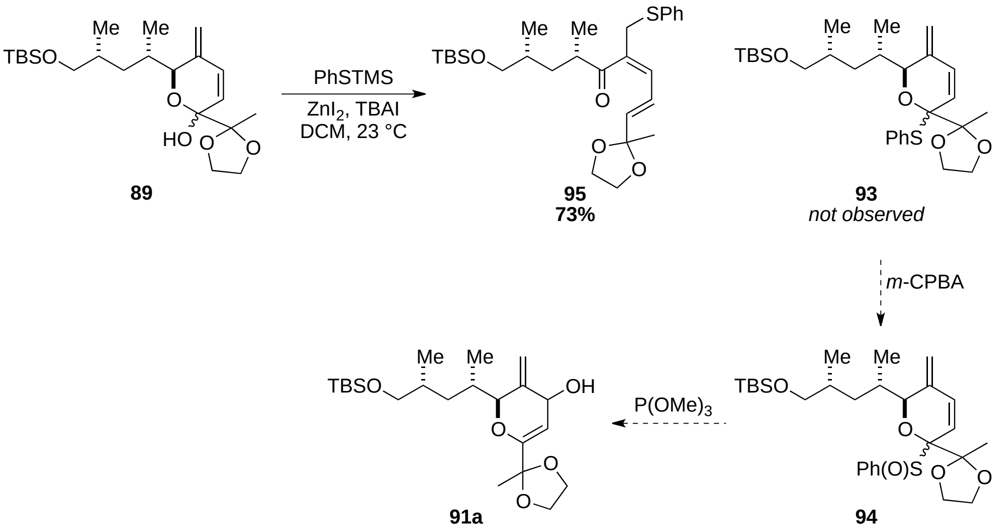

TBSO
Me
Me
HO
89
PhSTMS
ZnI_2, TBAI
DCM, 23 °C
SPh
95
73%
PhS
93
not observed
m-CPBA
Ph(O)S
94
$P(OMe)_3$
OH
91a

Figure 2.5.4.

In order to conserve time and rhodium catalyst, we examined further strategies on a model system, readily accessible from the ketal-protected furan **80** and isobutyraldehyde (Figure 2.5.5). The initial aldehyde addition is followed by Achmatowicz rearrangement to 3-pyrone **96**, and methylenation with Tebbe's reagent gives diene **97**.

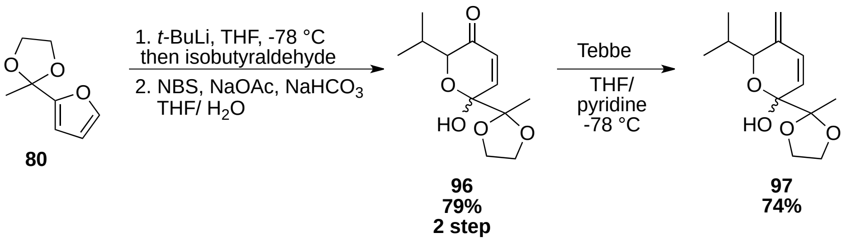

80
1. t-BuLi, THF, -78 °C
then isobutyraldehyde
2. NBS, NaOAc, $NaHCO_3$
THF/ H_2O
HO
96
79%
2 step
Tebbe
THF/
pyridine
-78 °C
97
74%

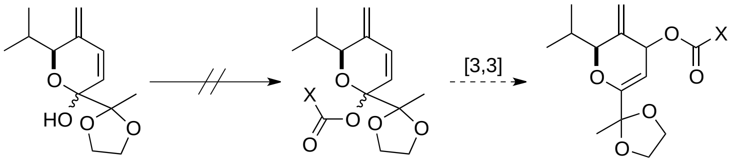
Figure 2.5.5.

We thought a sigmatropic rearrangement of an *O*-acylated allylic lactol might give the correct olefin substitution and leave an oxidation step to prepare the pyranone (Figure 2.5.6).

---

[85] Crimmins, M. T.; Christie, H. S.; Long, A. Chaudhary, K. *Org. Lett.* **2009**, *11*. 831-834.

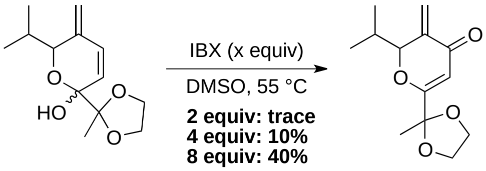
The acetylation of sterically encumbered lactol **97** to give the rearrangement substrate **98** proved very difficult, even under forcing conditions, and this strategy was abandoned.



97 **98**

Figure 2.5.6.

With gram-quantities of model substrate **97** available, I decided to reexamine conditions for the oxidative transposition. Treatment of **97** with 2 equivalents of freshly prepared iodoxybenzoic acid (IBX) gave a trace amount of the desired 4-pyranone product **99**. Increasing to 4 equivalents gave 10% yield, and with 8 equivalents of IBX, 40% yield of the desired 4-pyranone was isolated (eq 44). While modest, this yield was sufficient to try in the real system, and I moved forward with the synthesis.



97 **99**

(44)

As I began another batch of starting material to try the oxidative transposition, I thought the TBS protection I had used earlier might be unnecessary. Indeed, the Achmatowicz rearrangement proceeds smoothly on diol **100** to give primary alcohol **101** (Figure 2.5.7). This can then be tosylated for use in the planned Fouquet-Schlosser coupling and methylenated to arrive at diene **103**. Subjection of **103** to the oxidative transposition conditions gave the 4-pyranone in slightly better yield than the model system. This sequence comprises the current optimal route to advanced intermediate **104**. It contains the carbon skeleton and stereochemical relationships present in okilactomycin, minus the 5-membered lactone and quaternary methyl center.

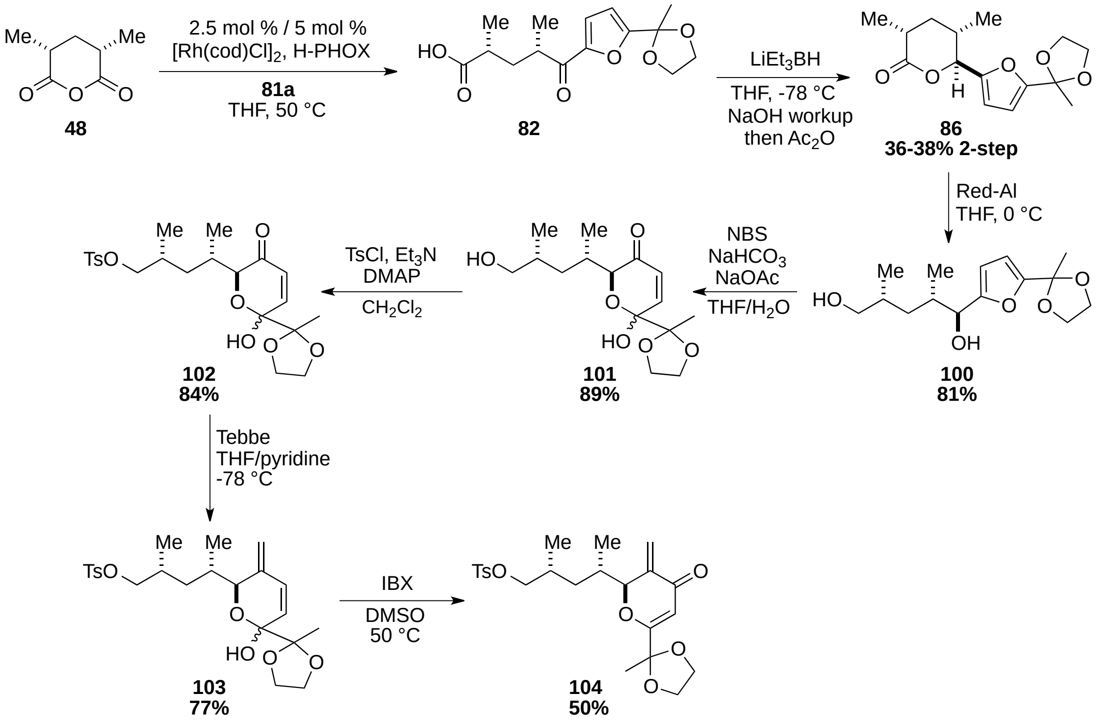
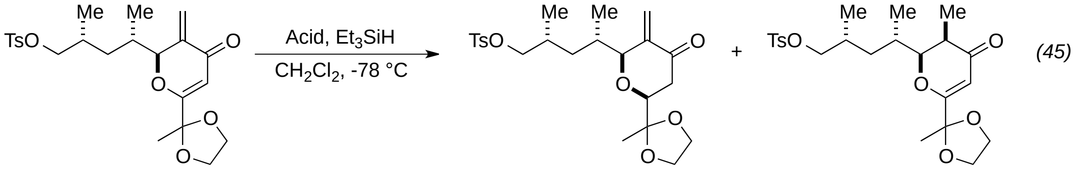

48
2.5 mol % / 5 mol %
[Rh(cod)Cl]2, H-PHOX
81a
THF, 50 °C
82
LiEt3BH
THF, -78 °C
NaOH workup
then Ac2O
86
36-38% 2-step
Red-Al
THF, 0 °C
100
81%
NBS
NaHCO3
NaOAc
THF/H2O
101
89%
TsCl, Et3N
DMAP
CH2Cl2
102
84%
Tebbe
THF/pyridine
-78 °C
103
77%
IBX
DMSO
50 °C
104
50%

Figure 2.5.7. Current optimal route to 104.

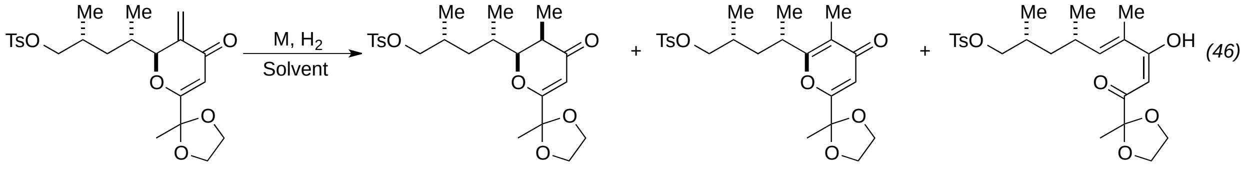
To elaborate **104** to the completed top fragment, we intended to reduce the vinylogous ester to give **105**, still containing the exo-methylene (eq 45). We thought that treatment with a Lewis acid and a mild reductant might favor direct 1,2-reduction of the oxocarbenium and studied to model system to test our hypothesis. Unfortunately, with a variety of Lewis acids and triethylsilane as the reductant, only 1,4-reduction of the exo-methylene Michael acceptor to give **106** is observed.



104 **105** **106**

Acid:	105	106
TMSOTf	**0%**	**10%**
TFA	**0%**	**20%**
BF_3•OEt_2	**0%**	**78%**

Similarly, hydrogenation with Pd/C, Pt/C, Rh/Al_2O_3 or Crabtree's catalyst[86] in a variety of solvents gave exo-methylene reduction to **106** in poor yield. In addition, double bond isomerization to pyrone **107** and 6π-electrocyclic ring opening of **106** to **108** were observed (eq 46). No hydrogenation of the vinylogous ester was observed under any of the conditions tried, despite similar conditions being reported for the hydrogenation of such double bonds.[87]



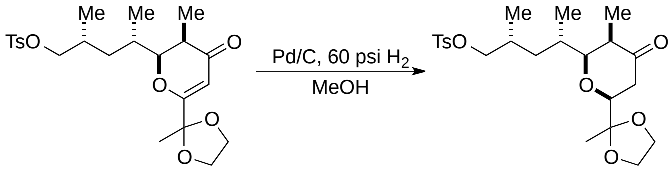
104 **106** 10-25% **107** 20-40% **108** 10-20%

We believed it should still be possible to hydrogenate the olefin in the exo-methylene-reduced product **106** to give saturated pyranone **109**. A screen of conditions was run under 1 atm H_2 and no hydrogenation was observed. Hydrogenation was attempted in a Parr bomb at 50 psi H_2, still with no success. Finally, a glass pressure vessel was charged with 60 psi H_2, the reaction run overnight, and **109** was isolated in 40% yield (eq 47).

---

[86] Crabtree. R. H. *Acc. Chem. Res.* **1979**, *12*, 331-337.

[87] (a) Barrett, A. G. M.; Carr, R. A. E.; Attwood, S. V.; Richardson, G.; Walshe, N. *J. Org. Chem.* **1986**, *51*, 4840-4856. (b) Wipf, P.; Reeves, J. T. *Chem. Commun.* **2002**, 2066-2067.

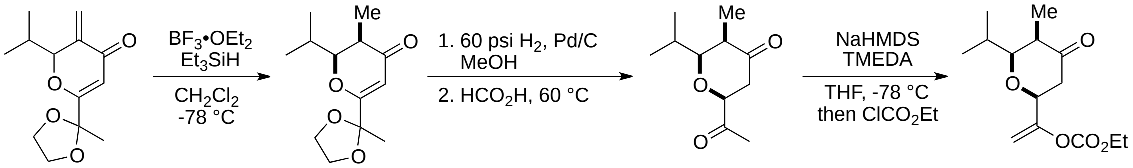

Me
Me
Me
TsO
O
O
O
O
Pd/C, 60 psi H_2
MeOH
Me
Me
Me
TsO
O
O
O
O

(47)

106

109
40%
10:1 dr

Further steps have been explored on the model system. The synthesis of model substrate **110** is carried out in identical steps from **99** (Figure 2.5.8). After reduction of the exo-methylene, pyrone **111** is hydrogenated, then treated immediately with formic acid at 60 °C to cleave the ketal, giving **110**. Then using Trost's conditions for selective *O*-acylation, enolcarbonate **112** can be prepared.[88]


O
O
O
O
BF_3•OEt_2
Et_3SiH
CH_2Cl_2
-78 °C
Me
O
O
O
O
1. 60 psi H_2, Pd/C
MeOH
2. HCO_2H, 60 °C
Me
O
O
O
NaHMDS
TMEDA
THF, -78 °C
then $ClCO_2Et$
Me
O
O
OCO_2Et

99

111
75%

110
54% 2-step

112
94%

Figure 2.5.8.

We hoped treatment with base to generate enolate **113** would result in cyclization onto the carbonyl of the carbonate, giving lactone **114**.[89] So far, a number of bases have failed to close the lactone ring (Figure 2.5.9). The desired enolate does bear a β-leaving group; however, the elimination of the ether to form enone **115** should be reversible and the irreversible condensation of the enolate onto the carbonate should proceed. It is unclear if this ring opening is actually occurring, as epimerization at the 4-position of the Michael acceptor in **115** is not observed.

---

[88] Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343-18357.

[89] He, W.; Huang, J.; Sun, X.: Frontier, A. *J. Am. Chem. Soc.* **2008**, *130*, 300-308.

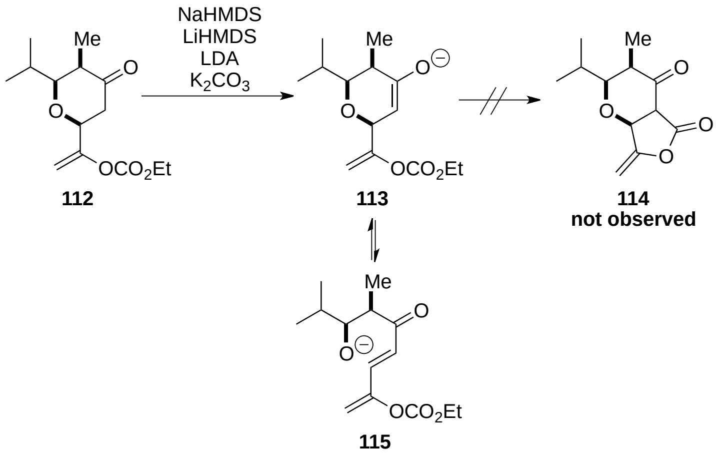
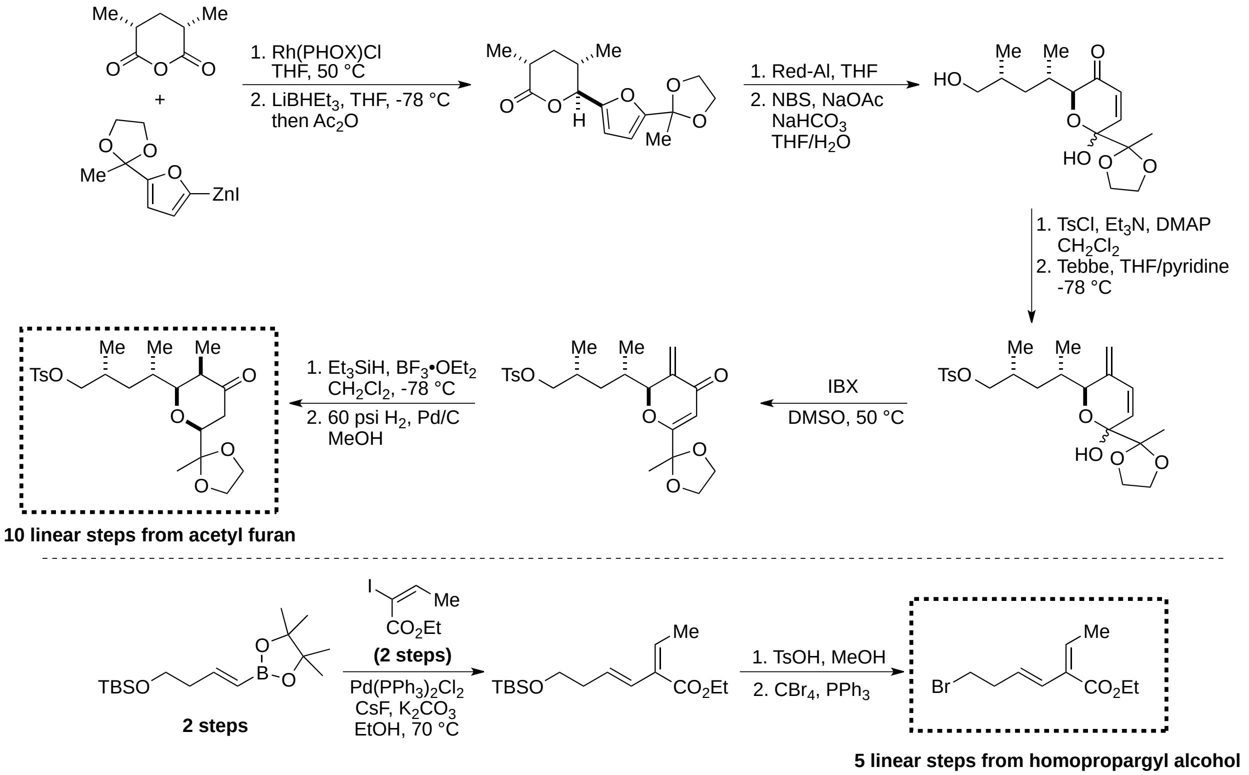

NaHMDS
LiHMDS
LDA
K_2CO_3
Me
O
O
OCO_2Et
112
113
114
not observed
115

Figure 2.5.9.

2.6. Conclusion

At this point, the synthesis of okilactomycin stands with the bottom portion fully assembled and the top fragment a few steps from complete, provided conditions to close the lactone can be identified. The lower fragment alkyl bromide is synthesized in 5 linear steps (7 total) by a Suzuki-Miyaura coupling. The most advanced intermediate toward the top fragment is assembled in 9 steps from 3,5-dimethyl glutaric anhydride (Figure 2.6.1). Though the synthesis is incomplete, the first few steps demonstrate the utility of our asymmetric Rh-catalyzed desymmetrization of 3,5-dimethyl glutaric anhydride to generate complexity in a rapid fashion.

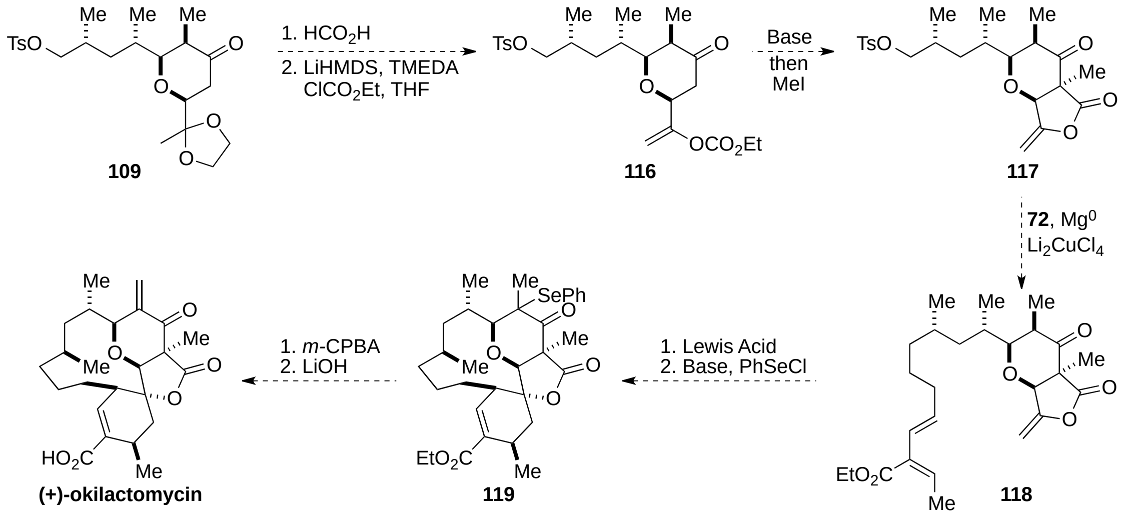


1. Rh(PHOX)Cl THF, 50 °C
2. LiBHEt3, THF, -78 °C then Ac2O
1. Red-Al, THF
2. NBS, NaOAc NaHCO3 THF/H2O
1. TsCl, Et3N, DMAP CH2Cl2
2. Tebbe, THF/pyridine -78 °C
IBX DMSO, 50 °C
1. Et3SiH, BF3•OEt2 CH2Cl2, -78 °C
2. 60 psi H2, Pd/C MeOH
10 linear steps from acetyl furan
2 steps
(2 steps)
Pd(PPh3)2Cl2 CsF, K2CO3 EtOH, 70 °C
1. TsOH, MeOH
2. CBr4, PPh3
5 linear steps from homopropargyl alcohol

Figure 2.6.1

To complete the synthesis, we propose the following sequence. First, intermediate **109** must be elaborated to the completed top fragment by deprotection of the ketal and generation of the enolcarbonate **116** (Figure 2.6.2.), which have been demonstrated on the model system

(Figure 2.5.7). Then, the ketone enolate must be condensed onto the carbonate to generate the lactone, which contains a β-ketoester that will be methylated stereoselectively to give **117** following the precedent of Scheidt. From here, the top and bottom fragments must be coupled by a Fouquet-Schlosser or similar alkyl-alkyl coupling to give the Diels-Alder substrate **118**.[90] The intramolecular Diels-Alder reaction should follow, then installation of the selenide at the ketone of **119** will set up an elimination as per Smith's completed total synthesis. Saponification of the ethyl ester will then deliver okilactomycin. Should these steps be accomplished, our synthesis of okilactomycin would be completed in 18 linear steps.



109
1. HCO_2H
2. LiHMDS, TMEDA $ClCO_2Et$, THF
116
Base then MeI
117
72, Mg^0
Li_2CuCl_4
118
1. Lewis Acid
2. Base, PhSeCl
119
1. *m*-CPBA
2. LiOH
(+)-okilactomycin

Figure 2.6.2.

---

[90] (a) Donkervoort, J. G.; Vicario, J. L.; Jastrzebski, J. T. B. H.; Gossage, R. A.; Cahiez, G.; van Koten, G. *J. Organomet. Chem.* **1998**, *558*, 61-69. (b) Terao, J.; Watanabe, H.; Ikumi, A. Kuniyasu, H. Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222. (c) Terao, J.; Ikumi, A. Kuniyasu, H. Kambe, N. *J. Am. Chem. Soc.* **2003**, *125*, 5646.

CHAPTER 1 EXPERIMENTAL

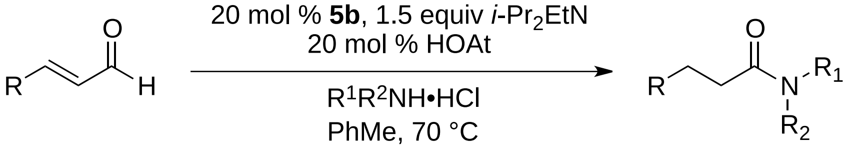
General methods

All reactions were carried out under an atmosphere of argon in flame dried glassware with magnetic stirring. Tetrahydrofuran was degassed with argon and passed through two columns of neutral alumina. Column chromatography was performed on SiliCycle®Silica*Flash*® P60, 40-63μm 60A. Thin layer chromatography was performed on SiliCycle® 250μm 60A plates. Visualization was accomplished with UV quench, $KMNO_4$, or aqueous ceric ammonium molybdate dips followed by heating. Infrared Spectra were obtained on a Bruker Tensor 27 FT-IR spectrometer. ^{1}H spectra were recorded on a Varian 400 MHz spectrometers at ambient temperature. Data are reported as follows: chemical shift is parts per million (δ, ppm) for chloroform ($CHCl_3$) taken as 7.26 ppm, integration, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), and coupling constants (Hz). ^{13}C spectra were recorded on a Varian 400 MHz spectrometers at ambient temperature. Chemical shifts are reported in ppm from $CDCl_3$ taken as 77.0 ppm. Mass spectra were obtained on a Fisions VG Autospec.

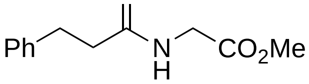
Anhydrous HOAt was purchased from Advanced Chem Tech and used as received. *N,O*-dimethylhydroxylamine hydrochloride, glycine methyl ester hydrochloride, *L*-alanine methyl ester hydrochloride, and *L*-phenylalanine methyl ester hydrochloride were purchased from Aldrich Chemical Co. and used without further purification. Benzylamine hydrochloride, piperidine hydrochloride, piperazine 1-carboxylic acid ethyl ester hydrochloride, *L*-phenethylamine hydrochloride and *D*-phenethylamine hydrochloride were prepared by treatment of the corresponding amine with an equimolar amount of anhydrous hydrogen chloride in ether (purchased from Aldrich Chemical Co. and used as received) followed by filtration. Triethylamine and diisopropylethylamine were distilled over calcium hydride and stored over 4Å MS. 3-((*tert*-butyldimethylsilyl)oxy)propanal was prepared according to known procedures. Other aldehydes were obtained from Aldrich Chemical Co. and used without further purification.

Racemic products were obtained by treating the corresponding fluoroenal with amine hydrochloride and HOAt in the presence of sodium pivalate and achiral triazolium salt in toluene. Enantiomeric ratio was determined by high pressure liquid chromatography on an Agilent Technologies 1100 Series using Daicel™ chiral columns.

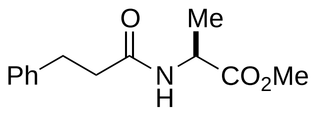
NHC-redox amidation of amine hydrochlorides



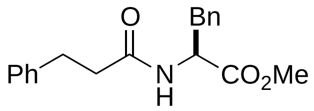
General procedure for NHC-catalyzed amidation reactions of enals: To a 25 mL round-bottom flask equipped with a magnetic stir bar was added ca. 200 mg of molecular sieves (4Å). The sieves were flame activated under vacuum, and the vessel was purged with argon. Glycine methyl ester hydrochloride (50 mg, 0.4 mmol, 1.0 eq.), triazolium catalyst **3c** (30 mg, 0.08 mmol, 0.2 eq.), and 1-hydroxy-7-azabenzotriazole (10.8 mg, 0.08 mmol, 0.2 eq.) were weighed into the flask, which was then evacuated and flushed with argon. Toluene (8 mL) was added, and the reaction vessel was heated to 70 °C. Trans-cinnamaldehyde (75 μL, 0.6 mmol, 1.5 eq.) was added, followed by diisopropylethylamine (104 μL, 0.6 mmol, 1.5 eq.), and the reaction was stirred at 70 °C for 3h. The crude reaction mixture was loaded directly onto silica gel, and the product isolated by column chromatography (3:2 hexanes:ethyl acetate) yielding **32a** as a yellow oil (82 mg, 93% yield).



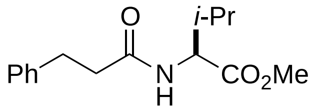
yellow oil **^{1}H-NMR (400 MHz, CDCl$_3$)** δ (ppm) 7.27-7.15 (m, 5H); 6.04 (br s, 1H); 4.54 (d, 2H, J = 5.2 Hz); 3.71 (s, 3H); 2.95 (dd, 2H, J_1 = 7.5 Hz , J_2 = 8.1 Hz); 2.53 (dd, 2H, J_1 = 7.5 Hz, J_2 = 8.1 Hz); **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 172.56; 170.66; 140.83; 128.72; 128.49; 126.46; 52.58; 41.42; 38.14; 31.62



off-white solid, m.p. 82-85 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 7.26-7.15 (m, 5H); 6.13 (br s, 1H); 4.54 (dq, 1H, J_1 = 7.2 Hz, J_2 = 1.7 Hz); 3.67 (s, 3H); 2.95 (t, 2H, J = 7.9 Hz); 2.54-2.41 (m, 2H); 1.29 (d, 3H, J = 7.2 Hz); **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 173.7; 171.9; 140.9; 128.7; 128.5; 126.4; 52.6; 48.1; 38.3; 31.7; 18.6; **IR** (cm^{-1}) 3299.0; 3028.6; 2952.7; 1746.1; 1650.1; 1542.0; 1497.3; 1453.9; 1378.3; 1210.2; 1167.2; **HR-MS (ESI-APCI):** Calc'd (m+h): 236.1208; Found (m+h): 236.1279; **R$_f$** = 0.28 (1:1 Hexanes: Ethyl Acetate)

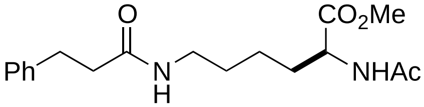


white solid, m.p. 71-73 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 7.28-7.16 (m, 7H); 6.92-6.90 (m, 2H); 5.80 (br d, 1H, J = 7.5 Hz); 4.86 (dt, 1H, J_1 = 7.8 Hz, J_2 = 5.6 Hz); 3.68 (s, 3H); 3.04 (d, 2H, J = 5.6 Hz); 2.94-2.89 (m, 2H); 2.54-2.39 (m, 2H) **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 172.1; 171.6; 140.8; 135.9; 129.4; 128.7; 128.6; 127.3; 126.5; 53.1; 52.5; 38.4; 38.1; 31.6; **IR** (cm^{-1}) 3028.9; 2951.6; 1745.5; 1650.1; 1604.0; 1536.6; 1497.0; 1453.9; 1371.2; 1213.7; 1121.0; 1077.6; 1029.9; **HR-MS (ESI-APCI):** Calc'd (m+h): 312.1521; Found (m+h): 312.1594; **R$_f$** = 0.46 (1:1 Hexanes: Ethyl Acetate)

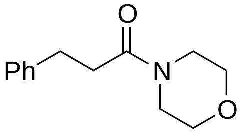


colorless oil, ^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 7.24-7.16 (m, 5H); 5.99 (br d, 1H, J = 8.2 Hz); 4.52 (ddd, 1H, J_1 = 8.7 Hz, J_2 = 5.0 Hz, J_3 = 1.8 Hz); 3.67 (s, 3H); 2.94 (t, 2H, J = 9.7 Hz); 2.55-2.50 (m, 2H); 2.07-2.01 (m, 1H), 0.82-0.77 (m, 6H); **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm)

172.8; 172.2; 140.8; 128.7; 128.5; 126.4; 57.1; 52.3; 38.4; 31.8; 31.4; 19.0; 17.9; **IR** (cm^{-1}) 3028.9; 2965.1; 1744.7; 1651.5; 1540.0; 1497.7; 1454.2; 1436.4; 1373.1; 1310.8; 1265.3; 1206.7; 1156.3; 1076.9; 1024.4; **HR-MS (ESI-APCI):** Calc'd (m+h): 264.1521; Found (m+h): 264.1592; **R_f =** 0.5 (1:1 Hexanes: Ethyl Acetate)

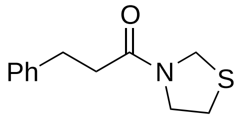


colorless oil, ^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 7.26-7.22 (m, 2H); 7.16 (dd, 3H, J_1 = 7.2 Hz, J_2 = 5.1 Hz); 6.31 (br d; J = 7.6 Hz); 5.70 (br s, 1H); 4.49 (dt, 1H, J_1 = 8.0 Hz, J_2 = 4.0 Hz); 3.69 (s, 3H); 2.92 (t, 2H, J = 7.7 Hz); 2.43 (t, 2H, J = 7.7 Hz); 1.98 (s, 3H); 1.77-1.73 (m, 1H); 1.63 (ddt, 1H, J_1 = 8.1 Hz, J_2 = 3.9 Hz, J_3 = 14.5 Hz); 1.46-1.38 (m, 2H); 1.29-1.20 (m, 2H); **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 173.2; 172.6; 170.3; 141.0; 128.7; 128.5; 126.4; 52.6; 52.0; 38.9; 38.6; 32.0; 32.0; 29.0; 23.3; 22.4; **IR** (cm^{-1}) 3278.6; 3064.7; 2949.4; 2862.7; 2364.2; 1745.0; 1648.1; 1547.1; 1497.1; 1436.8; 1373.4; 1263.0; 1210.6; 1176.6; 1146.5; 1074.8; 1006.0; **HR-MS (ESI-APCI):** Calc'd (m+h): 335.1983; Found (m+h): 335.1971; **R_f =** 0.22 (1:1 Hexanes: Ethyl Acetate)

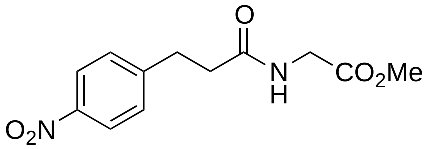


yellow oil, ^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 7.26-7.14 (m, 5H); 3.57 (s, 4H) 3.52 (t, 2H, J = 5.5 Hz); 3.30 (t, 2H, J = 5.5 Hz); 2.94 (t, 2H, J = 8.0 Hz), 2.57 (t, 2H, J = 8.0 Hz); **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 171.04; 141.25; 128.72; 126.46; 67.02; 66.64; 46.15; 42.13; 35.00; 31.68; **IR** (cm^{-1}) 3483.9; 3061.23; 3026.6; 2962.2; 2920.4; 2856.7; 1652.6; 1495.3; 1433.8;

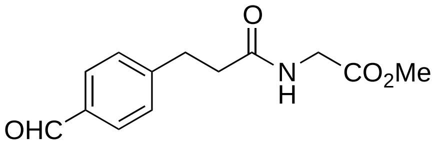
1361.5; 1300.5; 1271.5; 1226.7; 1115.5; 1069.6; 1025.8; **HR-MS (ESI-APCI):** Calc'd (m+h): 220.1259; Found (m+h): 220.1330; **R_f =** 0.15 (1:1 Hexanes: Ethyl Acetate)



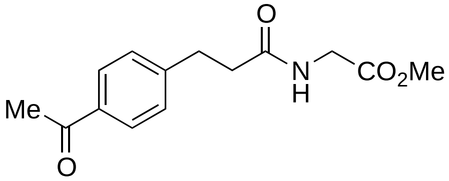
brown oil, ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.29-7.16 (m, 10H, rotamers A and B); 4.56 (s, 2H, rotamer A); 4.33 (s, 2H, rotamer B); 3.82 (t, 2H, *J* = 6.4 Hz, rotamer B); 3.57 (t, 2H, *J* = 6.2 Hz, rotamer A); 3.05-2.86 (m, 8H, rotamers A and B); 2.68-2.51 (m, 4H, rotamers A and B); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ (ppm) 170.7; 170.4; 141.2; 128.7; 128.6; 126.5; 49.2; 48.7; 48.4; 37.4; 37.1; 31.3; 31.2; 29.8; **IR** (cm^{-1}) 3059.9; 3026.2; 2394.7; 2873.5; 1650.1; 1495.7; 1418.3; 1339.3; 1261.0; 1077.6; 1029.7; **HR-MS (ESI-APCI):** Calc'd (m+h): 222.0874; Found (m+h): 222.0942; **R_f =** 0.28 (1:1 Hexanes: Ethyl Acetate)



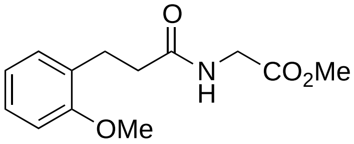
brown solid, m.p. 142-145 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 8.06 (d, 2H, *J* = 8.4 Hz); 7.32 (d, 2H, *J* = 8.4 Hz); 6.22 (br s, 1H); 3.96 (d, 2H, *J* = 5.2 Hz); 3.68 (s, 3H); 3.02 (t, 2H, *J* = 7.7 Hz); 2.56 (t, 2H, *J* = 7.7Hz); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ (ppm) 171.6; 170.5; 142.0; 146.7; 129.5; 123.9; 52.6; 41.4; 37.0; 31.2; **IR** (cm^{-1}) 3287.2; 3092.8, 2955.8; 1742.6; 1649.2; 1598.4; 1554.3; 1515.0; 1431.9; 1386.6; 1344.2; 1215.6; 1108.0; 1021.7; **HR-MS (ESI-APCI):** Calc'd (m+h): 267.0903; Found (m+h): 267.0979; **R_f =** 0.13 (1:1 Hexanes: Ethyl Acetate)



yellow oil ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 9.93 (s, 1H) 7.68 (s, 1H); 7.67 (d, 2H, *J* = Hz); 7.46-7.38 (m, 2H); 6.11 (br s, 1H); 3.98 (d, 2H, *J* = 5.2 Hz); 3.69 (s, 3H); 3.03 (t, *J* = 7.5 Hz); 2.55 (t, 2H *J* = 7.5 Hz); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ (ppm) 192.7; 171.9; 170.5; 142.0; 136.8; 134.9; 129.5; 129.4; 128.2; 52.6; 41.4; 37.5; 31.1; **IR** (cm^{-1}) 3310.3; 3066.7; 2953.7; 2850.4; 2736.4; 1750.0; 1697.8; 1604.8; 1585.8; 1543.6; 1438.7; 1408.9; 1374.5; 1209.9; 1144.5; 1083.4; 1037.8; 1010.4; **HR-MS (ESI-APCI):** Calc'd (m+h): 250.1001; Found (m+h): 250.1076; **R_f =** 0.14 (1:1 Hexanes: Ethyl Acetate)

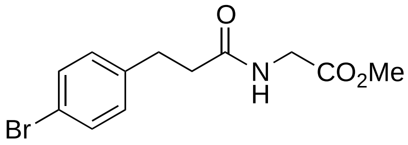


yellow oil ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.83 (d, 2H, *J* = 8.3 Hz); 7.25 (d, 2H, *J* = 8.2 Hz); 6.07 (br s, 1H); 3.98 (d, 2H, *J* = 5.2 Hz); 3.70 (s, 3H); 3.00 (t, *J* = 7.7 Hz); 2.55-2.51 (m, 5H); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ (ppm) 198.0; 171.9; 170.5; 146.7; 135.6; 128.8; 128.7; 52.6; 41.4; 37.4; 31.4; 26.7; **IR** (cm^{-1}) 3324.9; 2954.2; 1750.4; 1680.0; 1606.1; 1534.7; 1413.4; 1360.3; 1269.8; 1207.6; 1183.0; 1017.6; **HR-MS (ESI-APCI):** Calc'd (m+h): 264.1158; Found (m+h): 264.1237; **R_f =** 0.05 (1:1 Hexanes: Ethyl Acetate)

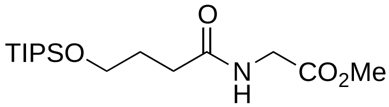


yellow oil ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.17-7.09 (m, 2H); 6.85-6.79 (m, 2H); 6.12 (br s, 1H); 3.98 (d, 2H, *J* = 5.2 Hz); 3.78 (s, 3H); 3.69 (s, 3H); 2.92 (t, *J* = 7.8 Hz); 2.50 (t, *J* = 7.8 Hz); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ (ppm) 173.0; 170.7; 130.2; 129.1; 127.8; 120.7; 110.4; 55.4; 52.5; 41.4; 36.4; 26.7; **IR** (cm^{-1}) 3286.4; 2956.2; 1752.2; 1654.7; 1541.9; 1494.5; 1483.3;

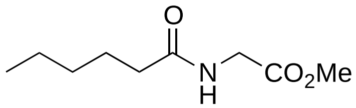
1372.0; 1243.4; 1207.1; 1179.4; 1029.9; **HR-MS (ESI-APCI):** Calc'd (m+h): 252.1158 Found (m+h): 252.1085 **R_f =** 0.22 (1:1 Hexanes: Ethyl Acetate)



white solid ^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 7.38 (d, 2H, *J* = 8.3 Hz); 7.06 (d, 2H, *J* = 8.3 Hz); 5.83 (br s, 1H); 4.00 (d, 2H, *J* = 5.1 Hz); 3.73 (s, 3H); 2.91 (t, 2H, *J* = 7.6 Hz); 2.50 (t, 2H *J* = 7.6 Hz); **IR** (cm^{-1}) 3319.5; 2956.0; 1749.7; 1648.9; 1553.8; 1491.1; 1436.1; 1405.6; 1379.2; 1198.3; **R_f =** 0.21 (1:1 Hexanes: Ethyl Acetate)

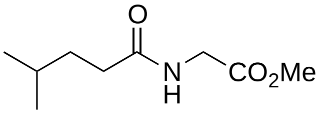


colorless oil; ^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 6.16 (br s, 1H); 4.00 (d, 2H, *J* = 5.2 Hz); 3.72-3.69 (m, 4H); 2.35 (t, *J* = 7.3 Hz); 1.84 (dt, J_1 = 7.3 Hz, J_2 = 13.9 Hz); 1.04-0.99 (m, 18H) **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 173.7; 170.7; 62.5; 52.5; 41.4; 33.0; 28.7; 18.2; 12.1 **DCl$_3$)** δ (ppm) 173.0; 170.7; 130.2; 129.1; 127.8; 120.7; 110.4; 55.4; 52.5; 41.4; 36.4; 26.7; **IR** (cm^{-1}) 2944.1; 2866.9; 1757.9; 1656.3; 1543.3; 1463.5; 1438.5; 1369.2; 1207.6; 1180.6; 1106.0; 1066.3; **HR-MS (ESI-APCI):** Calc'd (m+h): 332.2179 Found (m+h): 332.2231 **R_f =** 0.5 (1:1 Hexanes: Ethyl Acetate)

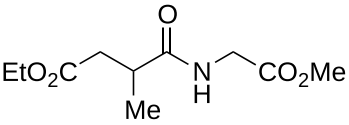


yellow oil; ^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 6.06 (br s, 1H); 4.00 (d, *J* = 5.2 Hz); 3.71 (s, 3H); 2.21 (t, 2H, *J*= 7.4 Hz); 1.58-1.47 (m, 3H), 0.86 (d, 6H, 6.2 Hz); **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 173.7; 170.8; 52.5; 41.3; 34.5; 27.9; 22.5; **IR** (cm^{-1}) 3304.9; 2957.1; 2861.9;

1757.5; 1654.9; 1543.3; 1438.2; 1371.5; 1207.7; **HR-MS (ESI-APCI):** Calc'd (m+h): 188.1208 Found (m+h): 188.1287 **R_f =** 0.28 (1:1 Hexanes: Ethyl Acetate)

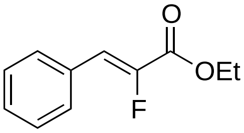


yellow oil; ^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 6.06 (br s, 1H); 4.00 (d, *J* = 5.2 Hz); 3.71 (s, 3H); 2.21 (t, 2H, *J*= 7.4 Hz); 1.58-1.47 (m, 3H), 0.86 (d, 6H, *J* = 6.2 Hz); **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 173.7; 170.8; 52.5; 41.3; 34.5; 27.9; 22.5; **IR** (cm^{-1}) 3078.1, 2957.2; 2871.8; 1757.1; 1654.5; 1542.2; 1438.0; 1408.2; 1368.9; 1207.4; 1088.2; 1039.1; **HR-MS (ESI-APCI):** Calc'd (m+h): 188.1208 Found (m+h): 188.1287 **R_f =** 0.3 (1:1 Hexanes: Ethyl Acetate)



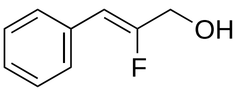
yellow oil; ^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 7.29-7.22 (m, 5H) 6.29 (br s, 1H); 4.39 (d, *J* = 5.8 Hz); 4.05 (q, 2H, *J*= 7.1 Hz); 2.79-2.72 (m, 2H); 2.38-2.29 (m, 1H), 1.22-1.17 (m, 6H) **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 175.2; 172.7; 138.6; 128.8; 127.8; 127.5; 60.8; 43.7; 38.3; 37.3; 18.1; 14.3. **HR-MS (ESI-APCI):** Calc'd (m+h): 232.1117 Found (m+h): 232.1184 **R_f =** 0.35 (1:1 Hexanes: Ethyl Acetate)**.**

Preparation of α-fluoroenals for asymmetric amidation



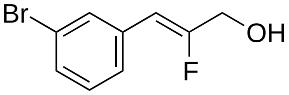
General procedure for preparation of fluoroenoates 29. 2-fluoro-triethylphosphonoacetate (2.42 g, 10 mmol, 1.0 equiv) was dissolved in dry THF (50 mL, 0.2 M) at ambient temperature. Triethylamine (2.8 mL, 20 mmol 2.0 equiv) was added, followed by magnesium bromide (1.84 g, 10 mmol, 1.0 equiv). An exotherm is observed, and while the reaction was hot (ca. 50 °C), benzaldehyde (1.06 g, 10 mmol, 1.0 equiv) was added. The reaction was stirred and monitored by TLC. Upon completion (ca. 1h), the reaction was diluted with 50 mL diethyl ether, then filtered on a medium porosity fritted funnel. The filtrate was washed with saturated ammonium chloride solution, which was then extracted with ether (2x50 mL). The organic layers were combined, washed with brine, dried over magnesium sulfate, filtered and concentrated to give 1.95g of colorless oil, ethyl 2-fluoro-3-phenylacrylate as a 7:1 mixture of olefin isomers favoring *Z* (100 % crude). Spectral data for this compound matched literature, and it was carried to the next step without further purification.

^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 7.53-7.50 (m, 2H); 7.37-7.32 (m, 3H); 6.92 (d, 1H, *J* = 35.2 Hz); 4.36 (q, 2H, *J* = 7.1 Hz); 1.39 (t, 3H, *J* = 7.2 Hz)



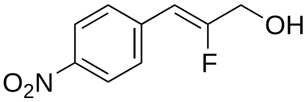
General procedure for the preparation of fluoroalcohols 30. Ethyl 2-fluoro-3-phenylacrylate (1.94 g, 10 mmol, 1 equiv) was dissolved in dry CH$_2$Cl$_2$ (50 mL, 0.2M). The solution was cooled to 0 °C, and 1M diisobutylaluminum hydride solution in hexanes (30 mL, 30 mmol, 3 equiv) was added slowly with stirring. The mixture was warmed to ambient temperature and monitored by TLC. Upon completion (ca. 30 min), the reaction was carefully quenched by addition of saturated Rochelle's salt solution (50 mL). The mixture was stirred vigorously until phase separation was observed (ca. 1h), then extracted into ether (3x50 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give 2-fluoro-3-phenylprop-2-en-1-ol as a light yellow oil (7:1 mixture of olefin isomers). The oil was purified by flash chromatography (10% to 20% EtOAc in hexanes) and the Z isomer isolated as 1.02 g colorless oil (67 %, 2 step, 77 % overall yield).

^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 7.51-7.48 (m, 2H); 7.36-7.22 (m, 3H); 5.77 (d, *J* = 38.7 Hz, 1H); 4.27 (d, *J* = 14.3 Hz, 2H); 1.78 (s, 2H). **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm). 158.1 (d, *J* = 266.8 Hz); 140.8; 132.6; 128.7 (d, *J* = 7.2 Hz); 128.5; 127.5 (d, *J* = 2.3 Hz); 127.0; 107.4 (d, *J* = 6.3 Hz); 61.9 (d, *J* = 32.7 Hz). **LR-MS** Calc'd (m+h): 153.06; Found (m+h) 153.1. **IR** Wavenumber (cm^{-1}, NaCl) 3343.6; 1691.9; 1494.6; 1449.1; 1345.7; 1221.6; 1164.4; 1072.4; 1020.0.

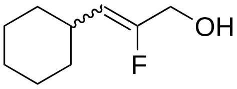


3:1 *Z:E,* 53% 2-step yield of *Z*-isomer (70 % overall). **^{1}H-NMR (400 MHz, CDCl$_3$)** δ (ppm) 7.67 (t, *J* = 1.7 Hz, 1H); 7.43-7.37 (m, 2H); 7.20 (t, *J* = 7.9 Hz, 1H); 5.74 (d, *J* = 38.1 Hz, 1H); 4.29 (d, *J* = 13.3 Hz, 2H); 1.87 (s, 1H). **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 159.1 (d, *J* = 268.6 Hz); 134.7; 131.4 (d, *J* = 7.9 Hz); 130.4; 129.9; 127.2 (d, *J* = 7.0 Hz); 122.5; 106.0 (d, *J* = 6.4 Hz), 61.6 (d, *J* = 33.0 Hz). **LR-MS** Calc'd (m+h): 230.97; Found (m+h) 231.0. **IR**

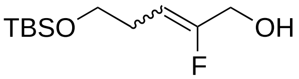
Wavenumber (cm^{-1}, NaCl) 3291.7; 1690.8; 1592.1; 1560.1; 1475.9; 1420.8; 1333.9; 1220.7; 1159.5; 1074.4; 1020.7



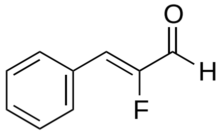
2:1 *Z:E,* 48% 2-step yield of *Z*-isomer (72 % overall).**^{1}H-NMR (400 MHz, CDCl$_3$)** δ (ppm) 8.19 (d, *J* = 9.0 Hz, 2H); 7.65 (d, *J* = 9.0 Hz, 2H); 5.92 (d, *J* = 37.8 Hz, 1H); 4.35 (d, *J* = 11.4 Hz, 2H). **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 139.3, 129.1, 127.0, 123.8, 105.3, 98.4, 61.3 (d, *J* = 33.6 Hz). **LR-MS** Calc'd (m+h): 198.05; Found (m+h) 198.1. **IR** Wavenumber (cm^{-1}, NaCl) 3505.9; 1696.9; 1595.2; 1502.4; 1412.9; 1344.6; 1248.0; 1163.7; 1110.2; 1080.1.



1:1 *Z:E,* inseparable, 90% yield. **^{1}H-NMR (400 MHz, CDCl$_3$)** δ (ppm) *Z*-isomer: 4.70 (dd, *J* = 37.7, 9.3 Hz,), 4.09 (d, *J* = 16.0 Hz, 2H), 2.46-2.43 (m, 1H); 1.73-1.63 (m, 6H), 1.33-1.02 (m, 4H). *E*-isomer: 5.09 (dd, *J* = 21.3, 10.2 Hz, 1H); 4.23 (d, *J* = 21.4 Hz); 2.12-2.04 (m, 1H); 1.73-1.63 (m, 6H), 1.33-1.02 (m, 4H). **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) mixture of *E* and *Z*: 157.8; 155.4; 115.3; 115.1; 114.0; 61.7; 61.4; 57.7; 57.4; 35.0; 33.9; 32.9; 25.9; 25.7; 26.7. **LR-MS** Calc'd (m+h): 151.06; Found (m+h) 151.1. **IR** Wavenumber (cm^{-1}, NaCl) 3331.8; 2926.5; 2852.6; 1699.16; 1449.0; 1287.8; 1245.5; 1162.7; 1120.1; 1069.5; 1025.0.

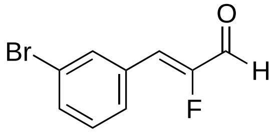


1:1 *Z:E,* inseparable, 66% yield. **^{1}H-NMR (400 MHz, CDCl$_3$)** δ (ppm) *Z*-isomer: 4.87 (dt, *J* = 37.1, 7.5 Hz, 1H); 4.06 (d, J = 15.6 Hz, 2H); 3.60-3.56 (m, 2H); 2.28-2.18 (m, 2H); 0.85 (s, 9H); 0.02 (s, 6H). *E*-isomer: 5.15 (dt, *J* = 20.6, 8.6 Hz, 1H); 4.15 (d, *J* = 19.4 Hz, 2H); 3.60-3.56 (m, 2H); 2.28-2.18 (m, 2H); 0.84 (s, 9H); 0.00 (s, 6H). **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 159.6, 157.3, 105.2 (d, *J* = 21.0 Hz); 104.5(d, *J* = 14.1 Hz); 62.2, 61.5, 61.2, 58.0, 57.7, 28.3, 27.2 -5.5. **LR-MS** Calc'd (m+h): 235.15; Found (m+h) 235.2. **IR** Wavenumber (cm^{-1}, NaCl) 3368.6; 2955.2; 2930.5; 2859.1; 1703.6; 1472.0; 1387.7; 1361.5; 1303.1; 1255.7; 1152.3; 1101.0.

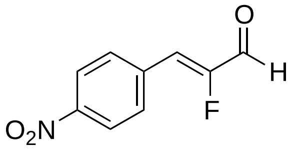


General procedure for preparation of fluoroenals 31. (*Z*)-2-fluoro-3-phenylprop-2-en-1-ol (1.02 g, 6.7 mmol, 1.0 equiv) was dissolved in ethyl acetate (67 mL, 0.1M). IBX (5.63 g, 20.1 mmol, 3 equiv) was added and the slurry was stirred and heated to 80 °C. After consumption of starting material was observed by TLC (ca. 3h), the reaction was cooled to ambient temperature, then diluted with 67 mL diethyl ether. The slurry was then filtered and the cake rinsed with 30 mL diethyl ether. The filtrate was concentrated to give (*Z*)-2-fluoro-3-phenylacrylaldehyde as an off-white solid (0.89 g, 89 %). This was found to be of sufficient purity for the subsequent reaction; however, it can be purified by column chromatography (10% EtOAc in hexanes).

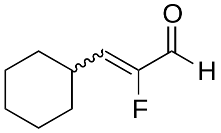
^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 9.37 (d, *J* = 16.9 Hz, 1H); 7.73-7.71 (m, 2H); 7.46-7.45 (m, 3H); 6.63 (d, *J* = 34.2 Hz, 1H). **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 184.0 (d, *J* = 25.1 Hz); 154.8 (d, *J* = 271 Hz); 130.9 (d, *J* = 2.8 Hz); 130.7; 130.6; 129.0; 126.8. **LR-MS** Calc'd (m +h): 151.06; Found (m+h) 151.1. **IR** Wavenumber (cm^{-1}, NaCl) 1691.5; 1647.6; 1494.7; 1450.8; 1396.2; 1358.1; 1322.7; 1295.7; 1170.8.



72 % yield. **^{1}H-NMR (400 MHz, CDCl$_3$)** δ (ppm) 9.30 (d, *J* = 16.4 Hz, 1H); 7.77 (s, 1H); 7.56 (d, *J* = 7.8 Hz, 1H); 7.49 (d, *J* = 8.0 Hz, 1H); 7.25 (t, *J* = 7.9 Hz, 1H), 6.49 (d, *J* = 33.5 Hz, 1H). **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 183.7 (d, *J* = 26.0 Hz); 155.0 (d, *J* = 273.1 Hz); 133.7; 133.2 (d, *J* = 8.5 Hz); 132.5; 130.5; 129.1; 124.6; 123.0. **LR-MS** Calc'd (m+h): 228.96; Found (m+h) 229.0. **IR** Wavenumber (cm^{-1}, NaCl) 1683.7; 1645.7; 1557.5; 1475.0; 1423.7; 1393.0; 1353.5; 1286.5; 1166.2; 1096.9.

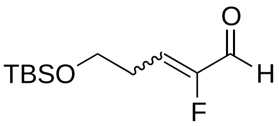


55 % yield. **^{1}H-NMR (400 MHz, CDCl$_3$)** δ (ppm) 9.46 (d, *J* = 15.6 Hz, 1H); 8.30 (d, *J* = 8.9 Hz, 2H); 7.88 (d, *J* = 8.9 Hz, 2H); 6.71 (d, *J* = 33.0 Hz, 1H). **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 183.5 (d, *J* = 27.8 Hz); 157.0; 154.3; 148.4; 136.5; 131.2; 124.1; 122.4. **LR-MS** Calc'd (m+h): 196.03; Found (m+h) 196.1. **IR** Wavenumber (cm^{-1}, NaCl) 1687.2; 1657.5; 1595.6; 1509.6; 1170.6; 1101.9.



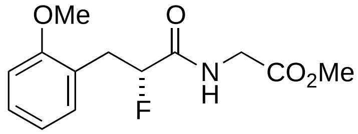
46 % yield. **^{1}H-NMR (400 MHz, CDCl$_3$)** δ (ppm) *Z*-isomer: 9.11 (d, *J* = 18.2 Hz, 1H); 5.73 (dd, *J* = 33.1, 9.6 Hz, 1H); 2.81-2.73 (m, 1H); 1.73-1.61 (m, 4H); 1.31-1.13 (m, 6H). *E*-isomer: 9.70 (d, *J* = 17.2 Hz, 1H); 6.00 (dd, *J* = 18.7, 11.1 Hz, 1H); 2.67-2.57 (m, 1H); 1.73-1.61 (m, 4H); 1.31-1.13 (m, 6H). **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 184.0 (d, *J* = 24.9 Hz); 181.8 (d, *J* = 28.1 Hz); 156.4; 154.2; 153.8; 151.7; 136.2; 133.3; 34.4; 33.8; 33.3; 31.7; 25.6; 25.4; 25.2. **LR-**

MS Calc'd (m+h): 157.10; Found (m+h) 157.1. **IR** Wavenumber (cm^{-1}, NaCl) 2926.4; 2852.8; 1706.9; 1449.3; 1124.6.



78 % yield. **^{1}H-NMR (400 MHz, CDCl$_3$)** δ (ppm) *Z*-isomer: 9.19 (d, *J* = 18.3 Hz, 1H); 6.02 (dt, *J* = 32.7, 7.5 Hz, 1H); 3.73-3.68 (m, 2H); 2.66-2.61 (m, 1H); 2.56-2.51 (m, 1H); 0.85 (s, 9H); 0.02 (s, 6H). *E*-isomer: 9.69 (d, *J* = 16.6 Hz, 1H); 6.20 (dt, *J* = 18.0, 8.9 Hz, 1H); 3.73-3.68 (m, 2H); 2.66-2.61 (m, 1H); 2.56-2.51 (m, 1H); 0.83 (s, 9H); 0.02 (s, 6H). **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 182.9 (d, *J* = 130.0 Hz), 61.2, 60.9, 28.4, 27.7 (d, *J* = 5.6 Hz), 25.8, 25.6, 18.2, -5.5. **LR-MS** Calc'd (m+h): 233.14; Found (m+h) 233.2. **IR** Wavenumber (cm^{-1}, NaCl) 2597.2; 2931.3; 2858.4; 1702.2; 1665.6; 1472.4; 1389.3; 1361.0; 1316.8; 1256.5; 1180.2; 1101.2.

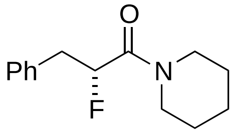
Asymmetric preparation of α-fluoroamides



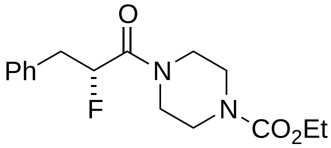
General procedure for NHC-catalyzed amidation reactions of fluoroenals (preparation of 32a): To a 10 mL round-bottom flask equipped with a magnetic stir bar was added ca. 100 mg of molecular sieves (4Å). The sieves were flame activated under vacuum, and the vessel was purged with argon. Glycine methyl ester hydrochloride (25 mg, 0.2 mmol, 1.0 equiv), morpholinone-derived triazolium catalyst **11c** (19 mg, 0.04 mmol, 0.2 equiv), and 1-hydroxy-7-azabenzotriazole (5.4 mg, 0.04 mmol, 0.2 equiv) were weighed into the flask, which was then evacuated and flushed with argon. Toluene (4 mL, 0.05M) was added. (Z)-2-fluoro-3-(2-methoxyphenyl)acrylaldehyde (54 mg, 0.3 mmol, 1.5 equiv) was added, followed by sodium benzoate (44 mg, 0.3 mmol, 1.5 equiv), and the reaction was stirred overnight (ca. 16h). The crude reaction mixture was loaded directly onto silica gel, and the product isolated by column chromatography (3:2 hexanes:ethyl acetate) yielding 5a as a yellow oil (47 mg, 87% yield).

^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 17.21-7.10 (m, 2H); 6.86-6.80 (m, 2H); 6.74 (s, 1H, rotamer 1); 6.10 (s, 1H, rotamer 2); 5.14 (ddd, J = 49.7, 9.5, 3.2 Hz, 1H); 4.03 (d, J = 5.4 Hz, 2H, rotamer 1); 3.97 (d, J = 5.0 Hz, 2H, rotamer 2); 3.77 (s, 3H); 3.72 (s, 3H, rotamer 1); 3.70 (s, 3H, rotamer 2); 3.44 (ddd, J = 36.7, 14.7, 3.2 Hz, 1H); 2.89 (ddd, J = 18.7, 14.7, 9.5 Hz, 1H). **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 178.6; 170.7; 170.0; 169.7; 157.6; 131.2; 128.4; 124.0; 120.4; 90.9 (d, J = 187.2 Hz); 55.3; 52.4; 52.3; 41.3; 40.7; 38.6; 33.6 (d, J = 20.5 Hz); 27.4. **LR-MS** Calc'd (m+h): 218.16; Found (m+h) 218.1. **IR** Wavenumber (cm^{-1}, NaCl) 3366.4; 2957.1; 1753.9; 1672.6; 1602.5; 1589.0; 1530.3; 1496.3; 1464.1; 1439.1; 1407.7; 1369.0; 1290.7;

1246.9; 1207.0; 1181.2; 1117.1; 1051.5. **$[\alpha]_D^{26.2}$** = +32.9 ° (c = 1.5, CH_2Cl_2). **Chiral HPLC Method:** IC column; 30% isopropanol in hexanes; t_R(maj) = 12.9 min, t_R(min) = 11.4 min, 91 % ee.

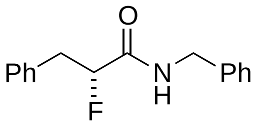


^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.26-7.16 (m, 5H); 5.29-5.14 (m, 1H); 3.55-3.09 (m, 6H); 1.57-1.30 (m, 6H). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ (ppm) 166.4 (d, *J* = 19.6), 136.0, 129.5, 128.5, 126.9, 89.7 (d, *J* = 182.6), 46.3, 43.5, 38.5 (d, *J s*= 21.8 Hz), 26.3, 25.5, 24.5. **LR-MS** Calc'd (m+h): 236.14; Found (m+h) 236.2. **IR** Wavenumber (cm^{-1}, NaCl) 3029.2; 2936.1; 2857.6; 1653.6; 1496.4; 1453.6; 1367.9; 1248.7; 1194.4; 1139.2; 1069.6; 1026.8. **$[\alpha]_D^{26.2}$** = -5.1 ° (c = 2.0, CH_2Cl_2). **Chiral HPLC Method:** OJH column; 10% isopropanol in hexanes; t_R(maj) = 10.0 min, t_R(min) = 11.6 min, 91 % ee.

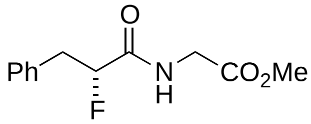


^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.28-7.18 (m, 5H); 5.24 (ddd, 1H, *J* = 48.8, 7.1, 6.5 Hz); 4.07 (q, 2H, *J* = 7.1 Hz), 3.56-3.13 (m, 8H); 1.19 (t, *J* = 7.1 Hz) **^{13}C-NMR (100 MHz, $CDCl_3$)** δ (ppm) 166.8 (d, *J* = 19.9 Hz); 155.2; 135.4; 129.6; 128.6; 127.2; 90.2 (d, *J* = 184.2 Hz); 61.7; 45.0; 42.2; 38.4 (d, *J* = 21.3 Hz); 28.3; 27.1; 14.6. **LR-MS** Calc'd (m+h): 309.15; Found (m+h) 309.2. **IR** Wavenumber (cm^{-1}, NaCl) 2982.3; 2929.1; 2866.5; 1700.2; 1662.1; 1432.0; 1384.9; 1354.8; 1286.7; 1230.9; 1172.7; 1126.6; 1071.1; 1032.9. **$[\alpha]_D^{26.2}$** = -2.0 ° (c = 3.15, CH_2Cl_2).

Chiral HPLC Method: OJH column; 30% isopropanol in hexanes; t_R(maj) = 10.2 min, t_R(min) = 11.3 min, 92 % ee.

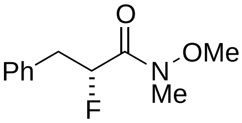


^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.22-7.16 (m, 8H); 7.00-6.97 (m, 2H); 6.38 (br s, 1H); 5.09 (ddd, *J* = 49.3, 6.5, 3.6 Hz, 1H), 4.41 (dd, *J* = 14.8, 6.3 Hz, 1H), 4.25 (dd, *J* = 14.8, 5.3 Hz, 1H), 3.27 (ddd, *J* = 27.2, 14.9, 3.6 Hz, 1H), 3.10 (ddd, *J* = 31.6, 14.9, 6.5 Hz, 1H). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ (ppm) 168.9 (d, *J* =19.1 Hz); 137.3; 135.2; 129.7; 128.7; 128.4; 127.6; 127.5;127.0; 91.8 (d, *J* = 189.0 Hz); 42.9; 38.3 (d, *J* = 19.9 Hz); 27.1. **LR-MS** Calc'd (m+h): 258.13; Found (m+h) 258.1. **IR** Wavenumber (cm^{-1}, NaCl) 1650.1; 1542.1; 1494.7; 1453.3; 1287.2; 1233.4; 1058.1. **$[\alpha]_D^{26.2}$** = +64.6 ° (c = 1.1, CH_2Cl_2). **Chiral HPLC Method:** IC column; 10% isopropanol in hexanes; t_R(maj) = 12.2 min, t_R(min) = 13.0 min, 91 % ee.

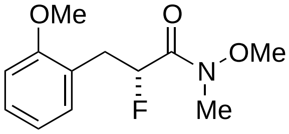


^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 8.13-8.11 (m, 1H), 7.50-7.46 (m, 1H); 7.33-7.24 (m, 3H); 6.75 (br s, 1H); 5.14 (ddd, *J* = 49.3, 7.8, 3.4 Hz, 1H); 4.04 (qd, *J* = 19.7, 5.4 Hz, 2H), 3.75 (s, 3H), 3.34 (ddd, *J* = 31.3, 14.9, 3.4 Hz, 1H), 3.13 (ddd, *J* = 27.0, 14.9, 7.8 Hz, 1H). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ (ppm) 171.0; 169.6 (d, *J* = 7.5 Hz); 135.4; 133.6; 130.1; 129.5; 128.4; 127.0; 91.9 (d, *J* = 189.4 Hz); 52.5; 40.6; 38.4 (d, *J* = 20.0 Hz). **LR-MS** Calc'd (m+h): 240.10; Found (m+h) 240.1. **IR** Wavenumber (cm^{-1}, NaCl) 1752.1; 1684.8; 1541.1; 1452.6; 1438.6; 1373.7; 1215.5; 1121.8; 1068.3. **$[\alpha]_D^{26.2}$** = +3.7° (c = 0.37, CH_2Cl_2). **Chiral HPLC Method:** IC column; 30% isopropanol in hexanes; t_R(maj) = 9.7 min, t_R(min) = 11.6 min, 92 % ee. **$[\alpha]_D^{26.2}$** =

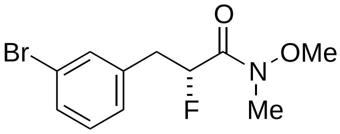
+60.0 ° (c = 0.57, CH_2Cl_2). **Chiral HPLC Method:** ODH column; 20% isopropanol in hexanes; t_R(maj) = 9.1, t_R(min) = 8.3 min, 91 % ee.



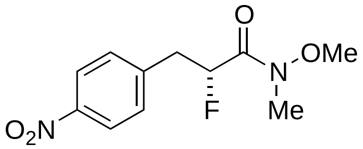
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.27-7.17 (m, 5H); 5.37-5.22 (m, 1H); 3.59 (s, 3H); 3.14-3.05 (m, 5H). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ (ppm) 135.9; 129.3; 128.5; 127.0; 88.4 (d, *J* = 177.9 Hz); 61.6; 38.2 (d, *J* = 22.3 Hz); 32.2; 27.0. **LR-MS** Calc'd (m+h): 212.10; Found (m +h) 212.1. **IR** Wavenumber (cm^{-1}, NaCl) 1677.3; 1496.9; 1454.6; 1391.2; 1331.1; 1178.0; 1062.4; 1014.7. **$[\alpha]_D^{26.2}$** = +8.7° (c = 0.73, CH_2Cl_2). **Chiral HPLC Method:** IC column; 30% isopropanol in hexanes; t_R(maj) = 9.5 min, t_R(min) = 11.2 min, 96 % ee.



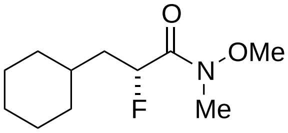
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.20-7.14 (m, 2H); 6.85-6.79 (m, 2H); 5.42 (br d, 1H); 3.76 (s, 3H); 3.60 (s, 3H); 3.26-2.98 (m, 2H) 3.13 (s, 3H) **^{13}C-NMR (100 MHz, $CDCl_3$)** δ (ppm) 157.5; 131.7; 128.4, 123.9; 120.5; 110.2; 86.6 (d, *J* = 176.2 Hz); 61.5; 55.2; 33.2 (d, *J* = 22.6 Hz). **LR-MS** Calc'd (m+h): 242.11; Found (m+h) 242.1. **IR** Wavenumber (cm^{-1}, NaCl) 1683.1; 1602.5; 1495.8; 1465.3; 1440.1; 1391.5; 1330.3; 1291.4; 1246.5; 1177.7; 1120.5; 1050.5; 1030.9. **$[\alpha]_D^{26.2}$** = +81.5 ° (c = 1.4, CH_2Cl_2). **Chiral HPLC Method:** IC column; 30% isopropanol in hexanes; t_R(maj) = 13.6 min, t_R(min) = 13.0 min, 93 % ee.



^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 7.41-7.38 (m, 2H); 7.20-7.18 (m, 2H); 5.41-5.26 (m, 1H); 3.70 (s, 3H); 3.22 (s, 3H); 3.17-3.08 (m, 2H). **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 138.2; 132.3; 130.1; 128.1; 122.5; 88.0 (d, *J* = 180.8 Hz); 61.7, 37.7 (d, *J* = 22.1 Hz); 32.2. **LR-MS** Calc'd (m+h): 290.01; Found (m+h) 290.0. **IR** Wavenumber (cm^{-1}, NaCl) 1683.9, 1595.9; 1568.9; 1474.6; 1428.6; 1391.4; 1328.6; 1178.3; 1071.4. **$[\alpha]_D^{26.2}$** = +17.3 ° (c = 1.6, CH$_2$Cl$_2$). **Chiral HPLC Method:** IC column; 30% isopropanol in hexanes; t_R(maj) = 8.7 min, t_R(min) = 9.4 min, 88 % ee.

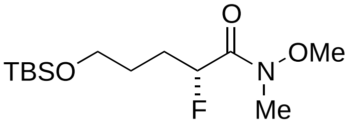


^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 8.11 (d, *J* = 8.8 Hz, 2H); 7.37 (d, *J* = 8.4 Hz, 2H); 5.39-5.23 (m, 1H); 3.67 (s, 3H); 3.25-3.10 (m, 2H); 3.16 (s, 3H). **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 147.1, 143.5, 130.4, 129.2, 123.7, 123.2, 98.4, 87.6 (d, *J* = 181.0 Hz), 61.8, 61.4, 37.8 (d, *J* = 22.0 Hz), 32.2. **LR-MS** Calc'd (m+h): 257.09; Found (m+h) 257.1. **IR** Wavenumber (cm^{-1}, NaCl) 1683.6; 1602.4; 1520.2; 1440.5; 1391.4; 1348.1; 1179.8; 1110.3; 1063.2; 1016.2. **$[\alpha]_D^{26.2}$** = +23.6 ° (c = 1.1, CH$_2$Cl$_2$). **Chiral HPLC Method:** IC column; 30% isopropanol in hexanes; t_R(maj) = 19.0 min, t_R(min) = 20.3 min, 88 % ee.

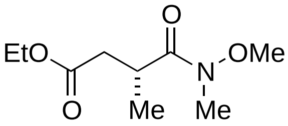


^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 5.30-5.15 (m, 1H); 3.65 (s, 3H); 3.15 (s, 3H); 1.81-1.46 (m, 7H); 1.25-1.07 (m, 4H); 0.98-0.83 (m, 2H). **^{13}C-NMR (100 MHz, CDCl$_3$)** δ 152.9; 86.5 (d, *J* = 177 Hz); 61.4; 39.2 (d, *J* = 21.6 Hz); 33.8; 32.2; 26.3; 26.1; 25.9. **LR-MS** Calc'd (m+h):

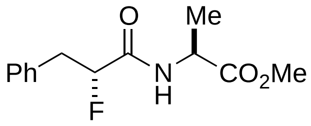
218.16; Found (m+h) 218.1. **IR** Wavenumber (cm^{-1}, NaCl) 2924.9; 2852.6; 1686.4; 1448.9; 1390.8; 1330.3; 1178.5; 1066.2; 1007.8. **$[\alpha]_D^{26.2}$** = +16.5 ° (c = 2.3, CH_2Cl_2). **Chiral HPLC Method:** ODH column; 10% isopropanol in hexanes; t_R(maj) = 5.1 min, t_R(min) = 5.8 min, 97 % ee.



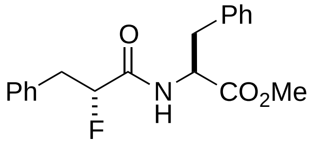
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 5.28-5.13 (m, 1H); 3.67 (s, 3H); 3.63 (dt, *J* = 12.5, 5.8 Hz, 2H); 3.18 (s, 3H); 1.94-1.84 (m, 2H); 1.70-1.60 (m, 2H); 0.84 (s, 9H); 0.00 (s, 6H). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ (ppm) 88.1 (d, *J* = 173.9 Hz); 62.3; 61.5; 28.6; 28.3; 27.9 (d, *J* = 2.9 Hz); 27.0; 25.9; 18.2; -5.4. **LR-MS** Calc'd (m+h): 294.19; Found (m+h) 294.2. **IR** Wavenumber (cm^{-1}, NaCl) 2955.4; 2931.4; 2858.2; 2360.8; 1686.3; 1472.2; 1389.7; 1361.6; 1327.4; 1255.0; 1179.3; 1101.1; 1005.0. **$[\alpha]_D^{26.2}$** = +6.7 ° (c = 2.1, CH_2Cl_2). **Chiral HPLC Method:** IC column; 5% isopropanol in hexanes; t_R(maj) = 5.1 min, t_R(min) = 5.8 min, 93 % ee.



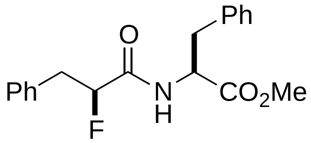
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 4.10 (q, *J* = 7.1, 2H); 3.76 (s, 3H); 3.19 (s, 3H); 2.83 (dd, *J* = 16.8, 9.6 Hz, 1H); 2.30 (dd, *J* = 16.8, 5.1 Hz, 1H); 1.28-1.20 (m, 4H), 1.13 (d, *J* = 7.1 Hz, 3H). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ (ppm) 178.7; 176.2; 172.5; 61.3; 60.4; 37.5; 35.4; 32.0; 17.2; 16.8; 14.1; 14.1. **LR-MS** Calc'd (m+h): 204.12; Found (m+h) 204.1. **IR** Wavenumber (cm^{-1}, NaCl) 2980.6; 2941.3; 1734.4; 1663.0; 1465.6; 1419.9; 1376.8; 1350.8; 1276.7; 1189.4; 1092.1; 1029.6. **$[\alpha]_D^{26.2}$** = +11.1 ° (c = 1.8, CH_2Cl_2). **Chiral HPLC Method:** ODH column; 5% isopropanol in hexanes; t_R(maj) = 6.9 min, t_R(min) = 13.6 min, 71 % ee.



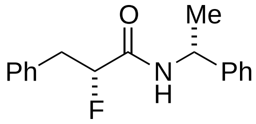
^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 7.25-7.17 (m, 5H); 6.68 (br s, 1H); 5.01 (ddd, *J* = 49.5, 8.2, 3.2 Hz, 1H); 4.55-4.48 (m, 1H); 3.66 (s, 3H); 3.25 (ddd, *J* = 32.8, 14.9, 3.2 Hz, 1H); 3.03 (ddd, *J* = 25.6, 14.9, 8.2 Hz, 1H); 1.36 (d, *J* = 7.2 Hz, 3H). **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 172.5; 168.8 (d, *J* = 19.8 Hz); 135.5; 129.4; 128.4; 127.0; 92.0 (d, *J* = 187.0 Hz); 52.5; 47.6; 38.5 (d, *J* = 20.1 Hz); 18.3. **LR-MS** Calc'd (m+h): 254.12; Found (m+h) 254.1. **IR** Wavenumber (cm^{-1}, NaCl) 3294.0; 2989.5; 2937.2; 1735.2; 1649.72; 1546.1; 1498.0; 1451.0; 1432.2; 1372.4; 1324.0; 1273.3; 1221.0; 1142.3; 1115.1; 1081.9; 1046.3; 1021.8. **[α]$_D$$^{26.2}$** = +77.5 ° (c = 1.1, CH$_2$Cl$_2$). **Chiral HPLC Method:** OJH column; 20% isopropanol in hexanes; t$_R$(maj) = 16.3 min, t$_R$(min) = 9.9 min, 97:3 dr.



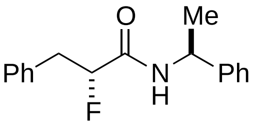
^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 7.22-7.14 (m, 8H); 7.01 (dd, *J* = 7.9, 1.6 Hz, 2H); 6.58 (br s, 1H); 4.96 (ddd, *J* = 49.5, 8.2, 3.2 Hz, 1H); 4.81-4.76 (m, 1H); 3.61 (s, 3H); 3.22 (ddd, *J* = 32.7, 15.0, 3.2 Hz, 1H); 3.10-2.93 (m, 3H). **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 171.1; 168.8 (d, *J* = 19.6 Hz); 135.5; 135.4; 129.4; 129.1; 128.6; 128.4; 127.2; 127.0; 91.9 (d, *J* = 188.9 Hz); 52.7; 52.4; 38.4 (d, *J* = 20.1 Hz); 38.0. **LR-MS** Calc'd (m+h): 330.15; Found (m+h) 330.1. **IR** Wavenumber (cm^{-1}, NaCl) 3031.3; 2953.2; 1804.9; 1745.4; 1678.4; 1528.0; 1497.8; 1454.7; 1216.6; 1124.7; 1064.9; 1030.9. **[α]$_D$$^{26.2}$** = +10.3 ° (c = 1.9, CH$_2$Cl$_2$). **Chiral HPLC Method:** IC column; 10% isopropanol in hexanes; t$_R$(maj) = 13.5 min, t$_R$(min) = 15.9 min, 99:1 dr.



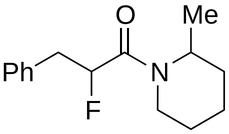
^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 7.26-7.13 (m, 8H); 6.71-6.68 (m, 2H); 6.56 (br s, 1H); 5.03 (ddd, *J* = 49.1, 6.4, 3.7 Hz, 1H); 4.85-4.80 (m, 1H); 3.62 (s, 3H); 3.20 (ddd, *J* = 26.5, 14.8, 3.7 Hz, 1H); 3.10-2.94 (m, 2H); 2.80 (dd, *J* = 13.8, 5.8 Hz, 1H). **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 171.1; 168.4 (d, *J* = 19.8 Hz); 135.2; 135.1; 129.9; 129.1; 128.5; 128.4; 127.2; 127.1; 52.3; 38.3; 38.1 (d, *J* = 3.7 Hz); 27.3; 27.0. **LR-MS** Calc'd (m+h): 330.15; Found (m+h) 330.2. **IR** Wavenumber (cm^{-1}, NaCl) 3031.6; 2954.3; 1804.9; 1745.0; 1679.0; 1524.8; 1497.5; 1454.8; 1367.7; 1215.6; 1124.3; 1079.9; 1050.5; 1012.8. **$[\alpha]_D^{26.2}$** = +190.9 °(c = 0.6, CH$_2$Cl$_2$). **Chiral HPLC Method:** IC column; 10% isopropanol in hexanes; t$_R$(maj) = 11.6 min, t$_R$(min) = 16.7 min, 98:2 dr.



^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 7.20-7.11 (m, 8H); 6.96-6.94 (m, 2H); 6.28 (s, 1H); 5.15-5.00 (m, 2H); 3.23 (ddd, *J* = 26.2, 14.9, 3.8 Hz, 1H); 3.07 (ddd, *J* = 32.5, 14.9, 6.2 Hz, 1H); 1.41 (d, *J* = 7.0 Hz, 3H). **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm)167.9; 142.2; 135.1; 129.7; 128.6; 128.4; 127.3; 126.9; 125.9; 91.8 (d, *J* = 188.7 Hz); 48.1; 38.2 (*J* = 19.5 Hz); 21.6. **LR-MS** Calc'd (m+h): 272.14; Found (m+h) 272.1. **IR** Wavenumber (cm^{-1}, NaCl) 1687.0; 1654.9; 1603.4; 1584.3; 1537.7; 1496.0; 1453.5; 1425.4; 1376.3; 1325.8; 1291.9; 1210.8; 1181.9; 1130.0; 1101.0; 1066.8; 1026.9. **$[\alpha]_D^{26.2}$** = +67.3 ° (c = 0.6, CH$_2$Cl$_2$). **Chiral HPLC Method:** ODH column; 5% isopropanol in hexanes; t$_R$(maj) = 13.3 min, t$_R$(min) = 10.7 min, 96:4 dr.

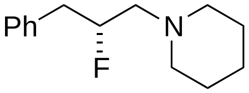


^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 7.45-7.39 (m, 2H); 7.31-7.17 (m, 8H); 6.22 (br s, 1H); 5.12-4.97 (m, 2H); 3.26 (ddd, *J* = 26.4, 14.8, 3.7 Hz, 1H); 3.11 (ddd, *J* = 32.4, 14.8, 6.3 Hz, 1H); 1.23 (d, *J* = 6.9 Hz, 3H). **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 170.5, 133.7, 130.1, 129.7, 128.7, 128.45, 128.35, 127.0, 126.1, 88.5 (d, *J* = 179.0 Hz), 48.2, 38.4 (d, *J* = 19.6 Hz), 21.4. **LR-MS** Calc'd (m+h): 272.14; Found (m+h) 272.1. **IR** Wavenumber (cm^{-1}, NaCl) 1686.4; 1653.2; 1540.8; 1325.9; 1291.8; 1180.7; 1129.0; 1100.8; 1072.9; 1048.4. **$[\alpha]_D^{26.2}$** = -35.8 ° (c = 0.7, CH_2Cl_2). **Chiral HPLC Method:** ODH column; 5% isopropanol in hexanes; t_R(maj) = 8.6 min, t_R(min) = 6.7 min, 95:5 dr.



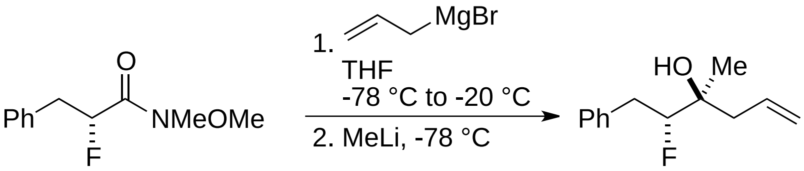
^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 7.25-7.18 (m, 5H); 5.28-5.13 (m, 1H); 4.78 (br s, 0.5 H); 4.39 (br s, 0.5 H); 4.19 (br s, 0.5 H); 3.52 (br s, 0.5 H); 3.18-3.05 (m, 2.5 H); 2.95-2.63 (m, 1.5 H); 1.62-1.23 (m, 6H); 1.1 (d, 3H, *J* = 7.0 Hz). **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 129.5, 128.5; 126.9; 48.5; 44.7; 38.7; 38.5; 29.7; 25.9; 25.4; 18.6; 16.9. **LR-MS** Calc'd (m+h): 250.15; Found (m+h) 250.2. **Chiral HPLC Method:** IC column; 20% isopropanol in hexanes; *syn* diastereomer: t_R = 10.6 min, 11.2 min, *anti* diastereomer: t_R= 11.6 min, 12.6 min.

Derivatization of α-fluoroamides



Reduction of fluoroamide 32b to fluoroamine 34. To an argon purged round bottom flask equipped with a stir bar and reflux condenser was added 2-fluoro-3-phenyl-1-(piperidin-1-yl)propan-1-one (39 mg, 0.166 mmol, 1 equiv) followed by dry THF (1.7 mL, 0.1M). Lithium aluminum hydride (25 mg, 0.66 mmol, 4 equiv) was added portionwise and the reaction heated under argon to reflux. Upon consumption of starting material (monitored by TLC, ca. 1h), the reaction was cooled to ambient temperature and quenched slowly with saturated Rochelle's salt solution (1.7 mL). The product was extracted into ether (3x2 mL), and the combined organic extracts washed with brine (3 mL). The organic extracts were concentrated to give 1-(2-fluoro-3-phenylpropyl)piperidine as a colorless oil (27 mg, 73 % yield).

^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 7.33-7.12 (m, 5H); 5.00-4.77 (m, 1H); 3.00-2.90 (m, 2H); 2.74-2.28 (m, 6H); 1.62-1.40 (m, 6H). **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) **LR-MS** Calc'd (m +h): 222.16; Found (m+h) 222.2. **IR** Wavenumber (cm^{-1}, NaCl) 2934.3; 2582.8; 1496.3; 1453.8; 1157.4; 1119.7; 1075.8; 1030.6. **$[\alpha]_D^{26.2}$** = -5.6 ° (c =0.8, CH$_2$Cl$_2$). **Chiral HPLC Method:** OC column; 3% isopropanol in hexanes; t$_R$(maj) = 4.3 min, t$_R$(min) = 4.5 min, 90 % ee.



Double alkylation of fluoro Weinreb amide 32c to tertiary alcohol 35. To a flame dried, argon purged 10 mL round bottom flask equipped with a stir bar was added **32c** (64 mg, 0.30 mmol), dissolved in 3 mL dry THF (0.1M). The solution was cooled to -20 °C and stirred.

Allylmagnesium bromide (1M in ether, 0.40 mL, 1.33 equiv) was added dropwise and the reaction stirred for 15 min. Upon complete reaction as judged by TLC, saturated ammonium chloride solution (3 mL) was added and the mixture warmed to ambient temperature. The product was extracted into ether (3x3 mL) and the combined organic layers washed with brine (3 mL). The organic extract were then dried over magnesium sulfate, filtered and concentrated to give the allyl ketone as a colorless oil (50 mg crude, 83 %).

The crude ketone was transferred to a 10 mL round bottom flask to which was added an oven dried stir bar, and the flask evacuated and flushed with argon. The ketone was redissolved in dry THF (3 mL), cooled to -78 °C and to it was added MeLi dropwise (1.5M in ether, 0.60 mL, 3.0 equiv). The reaction was stirred at -78 °C until complete reaction was verified by TLC, quenched into cold ammonium chloride solution and extracted into ether (3x3 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated to give tertiary alcohol **35** as a colorless oil. The product was purified by flash chromatography (10% ethyl acetate in hexanes) to yield 42 mg (67% yield).

^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 7.31-7.22 (m, 4H), 5.93-5.86 (m, 1H), 5.18-5.12 (m, 2H), 4.49 (ddd, *J* = 47.8, 8.4, 4.1 Hz, 1H), 2.98-2.88 (m, 2H), 2.37 (dd, *J* = 7.2, 2.9 Hz, 2H), 1.98 (s, 1H), 1.24 (s, 3H). **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 137.8, 132.9, 129.2, 128.4, 126.5, 119.1, 99.4, 97.7, 73.4, 43.1, 35.8, 22.3. **LR-MS** Calc'd (m+h):; Found (m+h). **Chiral HPLC Method:** ODH column; 1% isopropanol in hexanes; First diastereomer: t_{R1} = 12.0 min, t_{R2} = 12.4 min; Second diastereomer: t_{R1} = 12.8 min, t_{R2} = 14.4 min.

CHAPTER 2 EXPERIMENTAL

General methods

All reactions were carried out under an atmosphere of argon in flame dried glassware with magnetic stirring. Tetrahydrofuran, dichloromethane, toluene and diethyl ether used as reaction solvents were degassed with argon and passed through two columns of neutral alumina. ACS reagent grade pyridine was ordered from Sigma-Aldrich and used as received. Column chromatography was performed on SiliCycle®Silica*Flash*® P60, 40-63µm 60A. Thin layer chromatography was performed on SiliCycle® 250µm 60A plates. Visualization was accomplished with UV quench, $KMNO_4$, or aqueous ceric ammonium molybdate dips followed by heating. ^1H spectra were recorded on a Varian 400 MHz spectrometers at ambient temperature. Data are reported as follows: chemical shift is parts per million (δ, ppm) for chloroform ($CHCl_3$) taken as 7.26 ppm, integration, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), and coupling constants (Hz). ^{13}C spectra were recorded on a Varian 400 MHz spectrometers at ambient temperature. Chemical shifts are reported in ppm from $CDCl_3$ taken as 77.0 ppm.

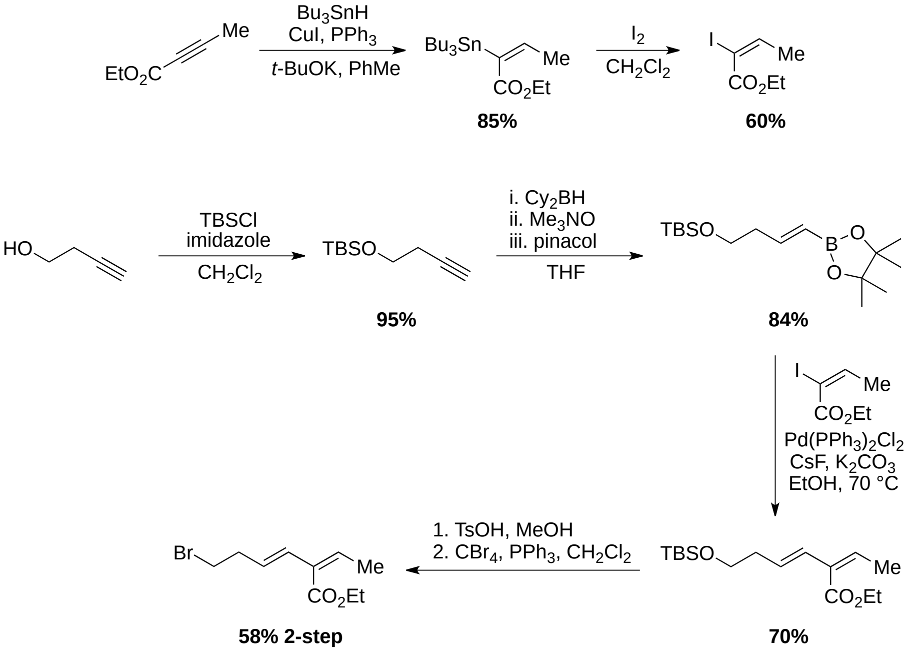
Reagents were purchased from Aldrich and used as received unless otherwise specified. Iodoxybenzoic acid (IBX) was prepared from 2-iodobenzoic acid by known procedures and stored at 0 °C.[91] Tebbe's reagent was synthesized by Grubbs' method and stored in a Schlenk vessel at 0 °C.[92]

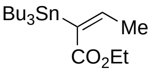
---

[91] Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537-4538.

[92] Cannizo, L. Grubbs, R. H. *J. Org. Chem.* **1985**, *50*, 2386–2387.

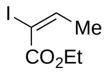
Synthesis of the bottom fragment diene


EtO$_2$C
Me
Bu$_3$SnH
CuI, PPh$_3$
t-BuOK, PhMe
Bu$_3$Sn
Me
CO$_2$Et
85%
I$_2$
CH$_2$Cl$_2$
I
Me
CO$_2$Et
60%
HO
TBSCl
imidazole
CH$_2$Cl$_2$
TBSO
95%
i. Cy$_2$BH
ii. Me$_3$NO
iii. pinacol
THF
TBSO
B
O
O
84%
I
Me
CO$_2$Et
Pd(PPh$_3$)$_2$Cl$_2$
CsF, K$_2$CO$_3$
EtOH, 70 °C
TBSO
Me
CO$_2$Et
70%
1. TsOH, MeOH
2. CBr$_4$, PPh$_3$, CH$_2$Cl$_2$
Br
Me
CO$_2$Et
58% 2-step


Bu$_3$Sn
Me
CO$_2$Et

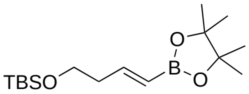
Preparation of vinylstannane 120. To a flame-dried, argon-purged 100 mL round-bottom flask was added copper(I) chloride (99 mg, 1 mmol, 0.1 equiv), triphenylphosphine (393 mg, 1.5 mmol, 0.15 equiv) and potassium *tert*-butoxide (112 mg, 1 mmol, 0.1 equiv). The flask was evacuated and flushed with argon, then dry toluene (20 mL, 0.5M) was added. To the resulting orange-red mixture was added tributyltin hydride (4 mL, 15 mmol, 1.5 equiv). The reaction was stirred for 1h at ambient temperature, at which time a color change to dark red was observed. Ethyl butynoate (1.12g, 10 mmol, 1 equiv) was then added and the reaction stirred overnight at room temperature. When complete consumption of ethyl butynoate was observed by TLC (ca. 16h), the reaction was purified on a short plug of silica gel, then concentrated to a red oil. The crude oil was loaded onto silica gel, then purified by chromatography (0% to 5% EtOAc in hexanes) to yield **120** as a colorless oil (3.42g, 85%).

^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 6.16 (q, *J* = 6.8 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.00 (d, *J* = 6.8 Hz, 3H), 1.49-1.43 (m, 6H), 1.33-1.24 (m, 6H), 0.94-0.85 (m, 15H). **^{13}C-NMR (100 MHz, CDCl$_3$) δ (ppm)** 194.7, 171.2, 147.9, 136.9, 133.6, 59.9, 28.9, 27.3, 18.2, 14.4, 13.6, 10.2.



Preparation of vinyl iodide 71. To a 25 mL argon-purged round-bottom flask equipped with a magnetic stir bar was added a solution of **120** (403 mg, 1 mmol) in dichloromethane (5 mL, 0.2M). Iodine (254 mg, 1 mmol, 1 equiv) was added and the reaction stirred at ambient temperate and monitored by TLC. Upon consumption of **120** (ca. 90 min), the reaction was quenched with saturated sodium thiosulfate solution and extracted into DCM (3x5 mL). The combined organic extracts were washed with KF solution (10 wt%, 5 mL) and brine, then dried over magnesium sulfate, filtered and concentrated to a yellow oil. The crude product was purified by silica gel chromatography (0% to 5% EtOAc in hexanes) to yield **71** as a colorless oil (inseparable mixture 2:1 with Bu$_3$SnI, 145 mg corrected, 60%).

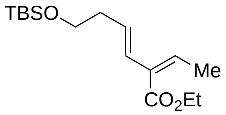
^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 6.98 (q, *J* = 7.4 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.00 (d, *J* = 7.4 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H). **^{13}C-NMR (100 MHz, CDCl$_3$) δ (ppm)** 194.7, 191.8, 150.8, 62.1, 26.8, 17.5.



Preparaton of vinylpinacolboronic ester 70. In a 100 mL round bottom flask equipped with a magnetic stir bar**,** a solution of freshly distilled cyclohexene (1.64 g, 20 mmol, 2 equiv) in THF

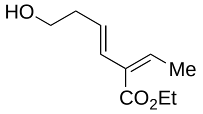
(40 mL, 0.25M) was prepared and cooled to 0 °C. Borane-THF complex (1M in THF, 10 mL, 1 equiv) was added. The resultant solution was stirred and warmed to ambient temperature over 1h, then cooled back to 0 °C. TBS-protected 3-butyn-1-ol **69** (1.84 g, 10 mmol) was then added and the reaction stirred and warmed again to ambient temperature. After 1h, trimethylamine *N*-oxide dihydrate (2.28 g, 20 mmol, 2 equiv) was added, and the reaction was stirred for another hour. Pinacol (1.18 g, 10 mmol, 1 equiv) was then added, and the reaction was stirred overnight (ca. 14h). The reaction was diluted with 40 mL ether, filtered over a sintered glass frit and concentrated to a colorless oil. The crude product was purified by silica gel chromatography (5% to 10% EtOAc in hexanes) to give the **70** as a colorless oil (2.6g, 83%).

^{1}H-NMR (300 MHz, CDCl$_3$) δ (ppm) 6.62-6.54 (m, 1H), 5.49 (d, *J* = 17.9 Hz, 1H), 3.68 (t, *J* = 7.1 Hz, 2H), 2.41-2.35 (m, 2H), 1.24 (d, *J* = 8.3 Hz, 12H), 0.90-0.88 (m, 9H), 0.04 (s, 6H).



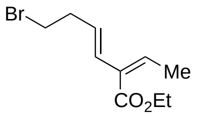
Coupling of vinyl iodide 71 and pinacolboronic ester 70. To a 100 mL round bottom flask equipped with a magnetic stir bar in an inert atmosphere glove box was added cesium fluoride (481 mg, 3.16 mmol, 1 equiv), bistriphenylphosphine palladium chloride (111 mg, 0.18 mmol, 0.05 equiv) and potassium carbonate (1.31 g, 9.5 mmol, 3 equiv). The flask was sealed with a rubber septum, removed from the glove box, evacuated and flushed with argon. Absolute ethanol (32 mL, 0.1M) was added, and the mixture stirred and degassed with argon for 30 min. Vinyl iodide **71** (1.07 g, 3.16 mmol, 1 equiv) was added, followed by vinylboronic ester **70** (0.99 g, 3.16 mmol, 1 equiv). The reaction was heated to 70 °C and stirred overnight (ca. 16h). The mixture was then cooled to ambient temperature and concentrated to remove ethanol. The resultant brown oil was then diluted with ether (30 mL) and water (30 mL) and phase split. The aqueous layer was extracted with ether (2x30 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated to a brown oil. This crude oil was then distilled (130-140 °C at 10 mm Hg) to give diene **121** as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$) δ (ppm) 6.06 (d, *J* = 15.8 Hz, 1H), 5.88 (d, *J* = 7.3 Hz, 1H), 5.68 (d, *J* = 15.9 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.64 (t, *J* = 6.8 Hz, 2H), 2.29 (dd, *J* = 7.6, 7.4 Hz, 2H), 1.86 (d, *J* = 7.3 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H).



Deprotection of TBS ether 121. In a 25 mL round bottom flask equipped with a magnetic stir bar, **121** (606 mg, 2 mmol) was dissolved in methanol (10 ml, 0.2M). Para-toluenesulfonic acid (77 mg, 0.2 equiv) was added, and the reaction was stirred for 2h. The reaction mixture was concentrated and the product distilled directly to give **122** as a colorless oil (280 mg, 76% yield).

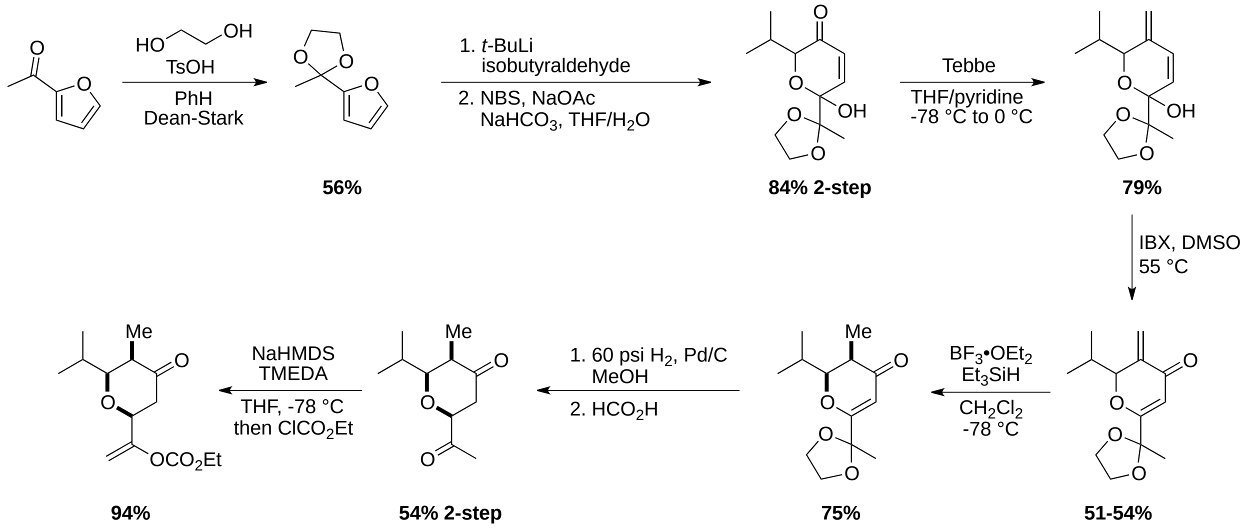
^{1}H-NMR (300 MHz, CDCl$_3$) δ (ppm) 6.15-6.09 (m, 1H), 5.93 (t, *J* = 7.3 Hz, 1H), 5.70-5.65 (m, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.67 (q, *J* = 6.1 Hz, 2H), 2.36 (d, *J* = 6.4 Hz, 2H), 1.87 (d, *J* = 7.3 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).



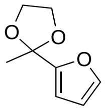
Preparation of bromide 72. In an argon-purged 25 mL round bottom flask equipped with a magnetic stir bar, **72** (280 mg, 1.5 mmol) was dissolved in methylene chloride (15 mL, 0.1M). Carbon tetrabromide (550 mg, 1.65 mmol, 1.1 equiv) and triphenylphosphine (433 mg, 1.65 mmol, 1.1 equiv) were added and the reaction stirred for 24h. The reaction was diluted with water and extracted into methylene chloride (3x10 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated to an oil. The crude product was purified by silica gel chromatography (20% to 50% EtOAc in hexanes) to give **72** as a colorless oil (274 mg, 74%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 6.11 (d, *J* = 15.3 Hz, 1H), 5.97 (q, *J* = 7.4 Hz, 1H), 5.68 (dt, *J* = 15.3, 7.4 Hz, 1H), 4.28 (q, *J* = 7.1, 2H), 3.40-3.36 (m, 2H), 2.64 (q, *J* = 7.1 Hz, 2H), 1.88 (d, *J* = 7.3 Hz, 3H), 1.36-1.31 (m, 3H).

Synthesis of the model system top fragment

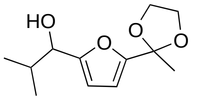


HO OH
TsOH
PhH
Dean-Stark
56%
1. t-BuLi isobutyraldehyde
2. NBS, NaOAc NaHCO3, THF/H2O
84% 2-step
Tebbe
THF/pyridine
-78 °C to 0 °C
79%
IBX, DMSO
55 °C
BF3•OEt2
Et3SiH
CH2Cl2
-78 °C
51-54%
Me
75%
1. 60 psi H2, Pd/C MeOH
2. HCO2H
54% 2-step
NaHMDS
TMEDA
THF, -78 °C
then ClCO2Et
OCO2Et
94%



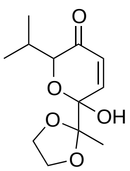
Preparation of dioxolane 80: To a 2L round-bottom flask equipped with a magnetic stir bar, reflux condenser and Dean-Stark apparatus was added 2-acetylfuran (55g, 0.5 mol) and benzene (1L, 0.5M). Ethylene glycol (200 mL, 3.6 mol, 7.2 equiv) was then added, followed by *p*-toluenesulfonic acid (9.5g, 0.05 mol, 0.1 equiv). The reaction mixture was heated to reflux and stirred vigorously until 90% completion could be observed by crude NMR (ca. 2d). At this point, the reaction was cooled to ambient temperature and quenched into 500 mL of a mixture of saturated sodium bicarbonate and ice. The resultant biphasic mixture was phase split and the aqueous later extracted into ether (3x500 mL). The organic layers were combined, washed with brine and dried over magnesium sulfate. The crude mixture was filtered and concentrated to a brown oil. The crude oil was purified by silica gel chromatography (5% to 10% EtOAc in hexanes) then distilled (ca. 70 °C at 10 mm Hg) to give **80** as a colorless oil (43.1g, 56%).

^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 7.35 (dd, *J* = 1.6, 1.1 Hz, 1H), 6.29 (m, 2H), 4.06-3.96 (m, 4H), 1.72 (s, 3H). **^{13}C-NMR (100 MHz, CDCl$_3$)** 194.7, 117.6, 111.6, 81.1, 37.1, 36.2, 32.8, 26.1, 17.1.



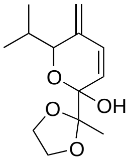
Preparation of furylcarbinol 123. To an argon-purged 500 mL round-bottom flask equipped with a magnetic stir bar was added dry THF (200 mL, 0.1M), then cooled to -78 °C. *t*-butyllithium solution (1.7M in hexanes, 12.3 mL, 21 mmol, 1.05 equiv) was added dropwise. To the resultant yellow solution was slowly added furyldioxolane **80** (3.09 g, 20 mmol). The mixture was warmed to 0 °C with vigorous stirring, then back to -78 °C. Freshly distilled isobutyraldehyde (2.16g, 30 mmol, 1.5 equiv) was then added and the mixture allowed to warm to ambient temperature with stirring then monitored by TLC. When complete consumption of **80** was observed, the reaction was quenched with 200 mL saturated ammonium chloride solution and extracted into ether (3x200 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give **123** as a yellow oil (4.45g, 99% crude).

^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 6.22 (d, *J* = 3.2 Hz, 1H), 6.12-6.11 (m, 1H), 4.33 (d, *J* = 5.2 Hz, 1H), 4.01-3.95 (m, 4H), 2.05 (m, *J* = 6.8 Hz, 1H), 1.69 (s, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H). **^{13}C-NMR (100 MHz, CDCl$_3$)** 156.1, 153.3, 106.9, 106.6, 104.6, 73.4, 65.0, 33.3, 24.2, 18.6, 18.1.



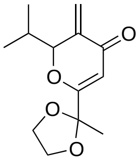
Preparation of 3-pyrone 96. To an argon-purged 500 mL round-bottom flask equipped with a magnetic stir bar was added crude **123** (4.45g, 20 mmol), dissolved in 100 mL THF (0.2 M). To this solution was added water (33 mL). To this vigorously stirred solution was added sodium bicarbonate (3.36g, 40 mmol, 2 equiv) and sodium acetate (1.64g, 20 mmol, 1 equiv). Upon dissolution of the salts, *N*-bromosuccinimide (3.56g, 20 mmol, 1 equiv) was added, and the reaction mixture stirred at ambient temperature and monitored by TLC. Upon consumption of **123** (ca 3h), the reaction was diluted with water (66 mL) and extracted into ether (3x100 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give crude **96** as a yellow oil. The crude oil was purified by silica gel chromatography (20% to 40% EtOAc in hexanes) to give **96** as a colorless oil (4.07g, 84% over 2 steps).

^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 7.03 (d, *J* = 10.4 Hz, 1H), 6.14 (d, *J* = 10.3 Hz, 1H), 4.37 (s, 1H), 4.16-4.04 (m, 5H), 2.45 (td, *J* = 6.9, 2.6 Hz, 1H), 1.37 (s, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H). **^{13}C-NMR (100 MHz, CDCl$_3$)** δ (ppm) 196.4, 144.6, 129.8, 110.0, 95.0, 78.4, 66.3, 65.7, 28.7, 20.7, 19.0, 16.2.



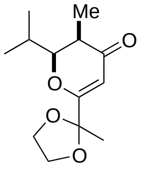
Preparation of diene 97. To a flame-dried, argon purged 500 mL round bottom flask equipped with a magnetic stir bar was added **96** (1.21g, 5 mmol), dissolved in dry THF (40 mL) and ACS reagent grade pyridine (10 mL, 0.1M total). The solution was cooled to -78 °C and stirred, then Tebbe's reagent (0.5-0.9M in toluene, pre-titrated, 10 mmol, 2 equiv) was added dropwise. The reaction is checked by TLC to ensure complete conversion, and more Tebbe's reagent is added if necessary. Then, the reaction is warmed to 0 °C and stirred (*Note: the reaction goes to* *completion in the capillary when it warms, the reaction must be warmed to 0 °C to ensure complete conversion).* After stirring for 1h, the reaction is quenched carefully with 15% NaOH (10 mL) in an ice bath. *Note: HAZARD. The aqueous solution must be added slowly. Vigorous methane gas evolution and exotherm are observed.* The resultant red to green slurry is stirred and warmed to ambient temperature, then diethyl ether is added (100 mL). The resultant orange solid is removed by filtration over a bed of Celite and the filtrate concentrated by rotary evaporation (*Note: the remaining pyridine is codistilled by several additions of toluene and reconcentration).* The crude product is then purified by silica gel chromatography (10% to 20% EtOAc in hexanes) and isolated as a yellow wax (1.90g, 79%).

^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 6.36 (d, *J* = 10.2 Hz, 1H), 5.94 (d, *J* = 10.1 Hz, 1H), 5.02-4.97 (m, 2H), 4.46 (d, *J* = 2.1 Hz, 1H), 4.12-4.00 (m, 4H), 2.24 (td, *J* = 6.8, 2.2 Hz, 1H), 1.31 (s, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H). **^{13}C-NMR (100 MHz, CDCl$_3$) δ (ppm)** 140.3, 132.4, 125.5, 112.1, 98.4, 95.6, 72.9, 66.1, 65.6, 28.3, 20.4, 20.0, 15.2.



Preparation of 4-pyrone 99. To an argon-purged 100 mL round bottom flask equipped with a magnetic stir bar was added **97** (481 mg, 2 mmol), dissolved in DMSO (20 mL, 0.1M). IBX (4.48g, 16 mmol, 8 equiv) was then added and the reaction mixture heated to 50 °C and stirred until complete consumption of starting material is observed by TLC (ca. 6h). The reaction mixture was then cooled to 0 °C and quenched by the addition of 20 mL of sat. NaCl solution. The resultant slurry was extracted into ether (3x20 mL). The combined organic extracts were washed successively with sat. NaHCO$_3$ (20 mL) and brine (20 mL), dried over magnesium sulfate and filtered to give crude **99** as a yellow oil. The crude oil was purified by silica gel chromatography (10% to 20% EtOAc in hexanes) to give **99** as a colorless oil (240 mg, 50%).

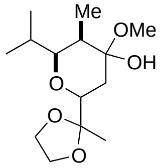
^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 6.14 (s, 1H), 5.67 (s, 1H), 5.25 (s, 1H), 4.71 (dt, *J* = 7.4, 1.2 Hz, 1H), 3.98-3.85 (m, 4H), 2.10-1.99 (m, 1H), 1.53 (s, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H). **^{13}C-NMR (100 MHz, CDCl$_3$) δ (ppm)** 172.2, 139.7, 121.9, 105.9, 101.3, 88.2, 65.2, 31.5, 22.9, 18.7, 18.1.



Preparation of 4-pyranone 111. To an argon-purged 50 mL round bottom flask equipped with a magnetic stir bar was added **99** (240 mg, 1 mmol) dissolved in dry CH_2Cl_2 (10 mL, 0.1M). The solution was cooled to -78 °C, and BF_3•OEt_2 (126 μL, 1 mmol, 1 equiv) was added. The mixture was stirred and warmed to 0 °C, then triethylsilane (595 μL, 4 mmol, 4 equiv) was added and the reaction allowed to warm to ambient temperature. When complete consumption of starting material was observed by TLC (ca. 20h), the reaction was cooled to 0 °C and quenched with sat. $NaHCO_3$ (10 mL). The mixture was phase split and extracted into ether (3x10 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give crude **111** as a brown oil. The crude product was purified by silica gel chromatography (10% to 20% EtOAc in hexanes) to give **111** as a yellow oil (180 mg, 75%).

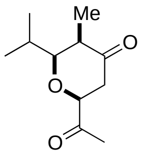
^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 5.46 (s, 1H), 4.28 (d, *J* = 6.5 Hz, 1H), 3.76 (d, *J* = 10.2 Hz, 1H), 2.36-2.34 (m, 1H), 2.02-1.98 (m, 1H), 1.36 (dd, *J* = 6.7, 3.1 Hz, 3H), 1.03 (d, *J* = 6.5

Hz, 3H), 0.97 (d, *J* = 7.4 Hz, 2H), 0.83 (d, *J* = 6.8 Hz, 3H). **^{13}C-NMR (100 MHz, CDCl$_3$) δ (ppm)** 99.6, 87.6, 67.4, 41.5, 28.5, 20.8, 19.4, 17.7, 9.5.



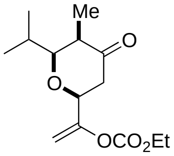
Preparation of saturated hemiketal 124. To an argon purged glass pressure vessel equipped with a regulator and a magnetic stir bar was added **111** (180 mg, 0.75 mmol) dissolved in MeOH (7.5 mL, 0.1M). Pd/C (10 wt%, 180 mg) was added, and the vessel pressurized to 60 psi with hydrogen gas. The mixture was stirred at ambient temperature for 6h, then hydrogen pressure released and the vessel purged with argon (*Note: to avoid fire, make sure there is no hydrogen left in the reaction vessel*). The reaction mixture was run down a short plug of silica, eluted with EtOAc. The eluent was concentrated to a yellow oil (180 mg, 100% crude). Crude **124** was carried to the next step without further purification.

^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 3.95-3.91 (m, 4H), 3.37 (dd, *J* = 11.9, 2.4 Hz, 1H), 3.15 (d, *J* = 4.5 Hz, 3H), 3.09 (dd, *J* = 10.0, 2.1 Hz, 1H), 1.92-1.90 (m, 1H), 1.80-1.64 (m, 2H), 1.33 (s, 3H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.85 (dd, *J* = 11.6, 7.1 Hz, 2H), 0.79 (q, *J* = 6.0 Hz, 4H). **^{13}C-NMR (100 MHz, CDCl$_3$) δ (ppm)** 194.7, 109.2, 101.9, 85.3, 83.1, 80.5, 78.4, 65.6, 65.0, 47.4, 46.7, 35.5, 29.4, 27.1, 20.4, 17.9, 7.6.



Preparation of dione 110. To an argon purged 50 mL round bottom flask equipped with a stir bar was added crude **124** (180 mg, 0.75 mmol). Formic acid (5 mL) was added and the reaction heated to 60 °C and stirred for 2h. Sat. $NaHCO_3$ (10 mL) was added and the mixture extracted into ether (3x10 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give crude **110** as a brown oil. The crude product was purified by silica gel chromatography (10% to 20% EtOAc in hexanes) to give **110** as a yellow oil (80 mg, 54%).

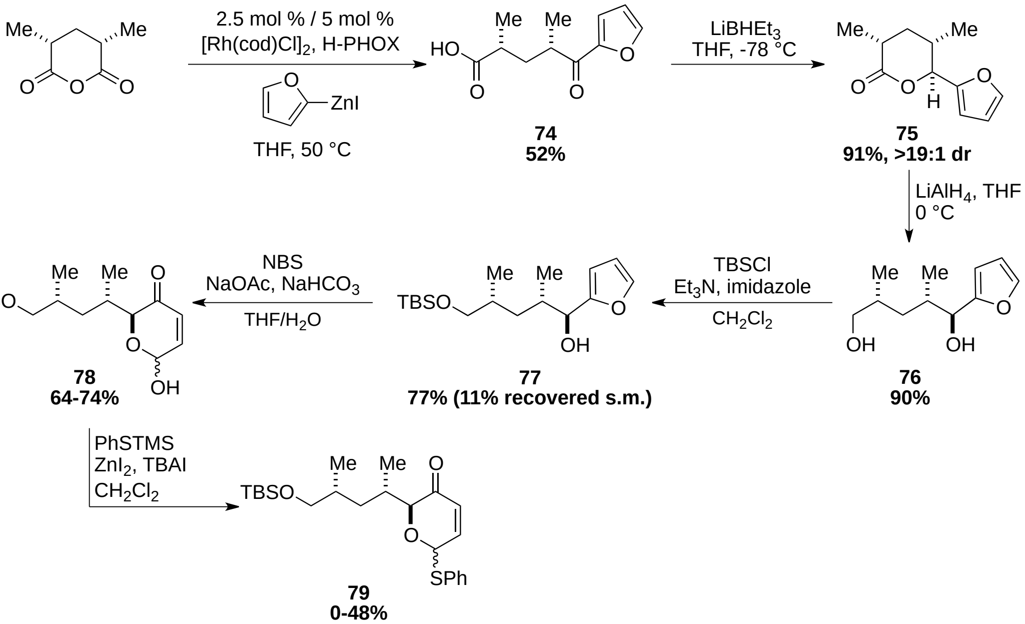
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 3.95 (dd, *J* = 11.8, 3.8 Hz, 1H), 3.12 (dd, *J* = 9.7, 2.4 Hz, 1H), 2.57-2.46 (m, 3H), 2.28 (s, 3H), 1.91 (dt, *J* = 9.7, 6.6 Hz, 1H), 1.09 (t, *J* = 6.8 Hz, 6H), 0.82 (d, *J* = 6.8 Hz, 3H). **^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm)** 209.9, 206.3, 85.6, 81.3, 47.2, 39.2, 29.0, 26.1, 20.0, 17.6, 10.4.

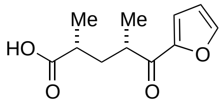


Preparation of enol carbonate 112. To an argon purged 10 mL round bottom flask equipped with a stir bar was added NaHMDS (55 mg, 0.3 mmol, 1.2 equiv). Dry THF was added (1.5 mL) and the slurry was cooled to - 78 °C. TMEDA (45 μL, 0.3 mmol, 1.2 equiv) was added and the mixture stirred and allowed to warm until a clear solution was observed. The mixture was cooled back to -78 °C, followed by the addition of **110** (50 mg, 0.25 mmol) in 1 mL dry THF (2.5 mL total, 0.1M). The reaction was stirred at -78 °C for 30 min, then ethyl chloroformate (29 μL, 0.3 mmol, 1.2 equiv) was added. The reaction was stirred at -78 °C for 30 min, then quenched with sat. NH_4Cl (2.5 mL). After warming to ambient temperature, the mixture was extracted into ether (3x5mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give crude **112** as a brown oil. The crude product was purified by silica gel chromatography (10% to 20% EtOAc in hexanes) to give **112** as a yellow oil (60 mg, 94%).

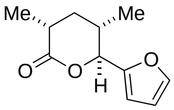
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 5.14-5.07 (m, 2H), 4.28-4.17 (m, 2H), 3.23-3.09 (m, 1H), 2.69-2.32 (m, 2H), 1.93-1.80 (m, 1H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.14-1.04 (m, 6H), 0.84 (dd, *J* = 15.5, 6.8 Hz, 3H).

Exploratory synthesis of top fragment


2.5 mol % / 5 mol %
[Rh(cod)Cl]2, H-PHOX
ZnI
THF, 50 °C
74
52%
LiBHEt3
THF, -78 °C
75
91%, >19:1 dr
LiAlH4, THF
0 °C
76
90%
TBSCl
Et3N, imidazole
CH2Cl2
77
77% (11% recovered s.m.)
NBS
NaOAc, NaHCO3
THF/H2O
78
64-74%
PhSTMS
ZnI2, TBAI
CH2Cl2
79
0-48%

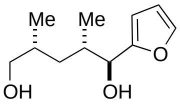


Preparation of ketoacid 74. To a flame-dried, argon purged 250 mL round-bottom flask equipped with a magnetic stir bar was added THF (100 mL, 0.05M), cooled to -78 °C. *t*-BuLi was added (4.4 mL, 1.7 M, 7.5 mmol, 1.5 equiv), followed by furan (510 mg, 7.5 mmol, 1.5 equiv). The resultant solution was stirred and warmed until a colorless solution was observed. The solution was then cooled back to -78 °C and transferred by cannula to another flame-dried 250 mL round bottom flask containing zinc iodide (3.19 g, 10 mmol, 2 equiv). The resultant slurry was warmed to ambient temperature and stirred for 2h. Then, Rh(cod)Cl dimer (62 mg, 0.125 mmol, 0.025 equiv) and H-PHOX (83 mg, 0.25 mmol, 0.05 equiv) were added, followed by 3,5-dimethylglutaric anhydride (711 mg, 5 mmol). The resultant dark red mixture was heated to 50 °C and stirred for 24h. The reaction was cooled to ambient temperature and quenched with sat. $NaHCO_3$ (100 mL). The mixture was extracted into ether (2x100 mL). The organic extracts were then washed with water (100 mL). The aqueous layers were combined and acidified with hydrochloric acid to pH = 1. This aqueous layer was then extracted into ether (3x100 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give crude **74** as a brown oil. The crude product was taken to the next step without further purification.



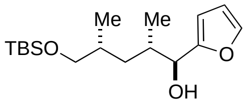
Preparation of lactone 75. In an argon purged 250 mL round bottom flask equipped with a magnetic stir bar was dissolved **74** (5 mmol theor.) in dry THF (50 mL, 0.1M). The solution was cooled to -78 °C and stirred. Lithium triethylborohydride (1M in THF, 10 mL, 2 equiv) was added dropwise and the reaction monitored by crude NMR of aliquots. After complete reaction (ca. 2h), 1M HCl (50 mL) was added and the reaction stirred vigorously while warming to ambient temperature. The reaction mixture was extracted into ether (3x200 mL), and the combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give crude **75** as a brown oil. The crude lactone was then purified by silica gel chromatography (30% to 40% EtOAc in hexanes) to give **75** as a colorless oil (456 mg, 47 % 2-step).

^{1}H-NMR (300 MHz, CDCl$_3$) δ (ppm) 7.41 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.37 (dd, *J* = 5.8, 1.3 Hz, 2H), 4.91 (d, *J* = 10.7 Hz, 1H), 2.68-2.60 (m, 1H), 2.41 (dddd, *J* = 12.2, 10.6, 6.6, 3.4 Hz, 1H), 2.06 (ddd, *J* = 13.3, 6.3, 3.1 Hz, 1H), 1.53-1.40 (m, 1H), 1.32 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H).



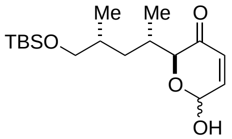
Synthesis of diol 76. To an argon-purged 100 mL round bottom flask containing **75** (456 mg, 2.35 mmol) was added THF (23.5 mL, 0.1M) and a magnetic stir bar. The resultant solution was cooled to 0 °C and stirred vigorously. Lithium aluminum hydride (178 mg, 4.7 mmol, 2 equiv) was then added portionwise and the reaction monitored by TLC. When complete consumption of starting material was observed (ca. 1h), the reaction was quenched with water (0.18 mL), then 15% NaOH solution was added (0.18 mL) followed by water (0.54 mL). The resultant slurry was filtered over Celite and the filtrate concentrated to give a colorless oil (452 mg, 97% crude). The crude product was purified by silica gel chromatography (50% to 80% EtOAc in hexanes) to give **76** as a colorless oil (419 mg, 90%).

^{1}H-NMR (300 MHz, CDCl$_3$) δ (ppm) 7.37-7.36 (m, 1H), 6.33 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.24 (dd, *J* = 2.6, 0.7 Hz, 1H), 4.46-4.44 (m, 1H), 3.76-3.72 (m, 1H), 3.50 (dt, *J* = 5.0, 2.4 Hz, 2H), 2.11-2.02 (m, 1H), 1.87-1.83 (m, 1H), 1.76-1.64 (m, 3H), 0.99-0.96 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H).



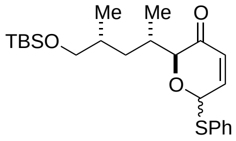
Synthesis of TBS ether 77. To a solution of **76** (419 mg, 2.1 mmol, 1.05 equiv) in methylene chloride (20 mL, 0.1M) was added TBSCl (301 mg, 2 mmol), imidazole (163 mg, 2.4 mmol, 1.2 equiv), and triethylamine (334 µL, 2.4 mmol, 1.2 equiv). The resultant solution was stirred at ambient temperature for 24h, then quenched with sat. ammonium chloride solution (20 mL). The mixture was extracted into DCM (3x20 mL) and the combined organic extracts were washed with brine (20 mL), dried over magnesium sulfate, filtered, and concentrated to give a colorless oil. The crude product was purified by silica gel chromatography (30% to 50% EtOAc in hexanes) to give **77** as a colorless oil (481 mg, 77%).

^{1}H-NMR (300 MHz, CDCl$_3$) δ (ppm) 7.36 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.32 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.23-6.22 (m, 1H), 4.46 (dd, *J* = 6.5, 5.2 Hz, 1H), 3.48 (dd, *J* = 9.8, 5.3 Hz, 1H), 3.36 (dd, *J* = 9.8, 6.3 Hz, 1H), 2.10-2.05 (m, 1H), 1.76-1.56 (m, 2H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.89 (s, 9H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.04 (s, 6H).



Synthesis of 3-pyranone 78. In an argon purged 100 mL round bottom flask equipped with a magnetic stir bar was dissolved **77** (481 mg, 1.54 mmol) in THF (7.5 mL) and water (2.5 mL, 0.15M total). NaHCO$_3$ (259 mg, 3.08 mmol, 2 equiv) and NaOAc (126 mg, 1.54 mmol, 1 equiv) were added and the mixture stirred vigorously until the salts dissolve. Then, *N*-bromosuccinimide (279 mg, 1.54 mmol, 1 equiv) was added and the mixture stirred at ambient temperature and monitored by TLC. After complete consumption of starting material was observed (ca. 2h), the reaction was diluted with water (10 mL) and extracted into ether (3x10 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give crude **78** as a yellow oil. The crude product was then purified by silica gel chromatography (20% to 30% EtOAc in hexanes) to give **78** as a colorless oil (374 mg, 74%).

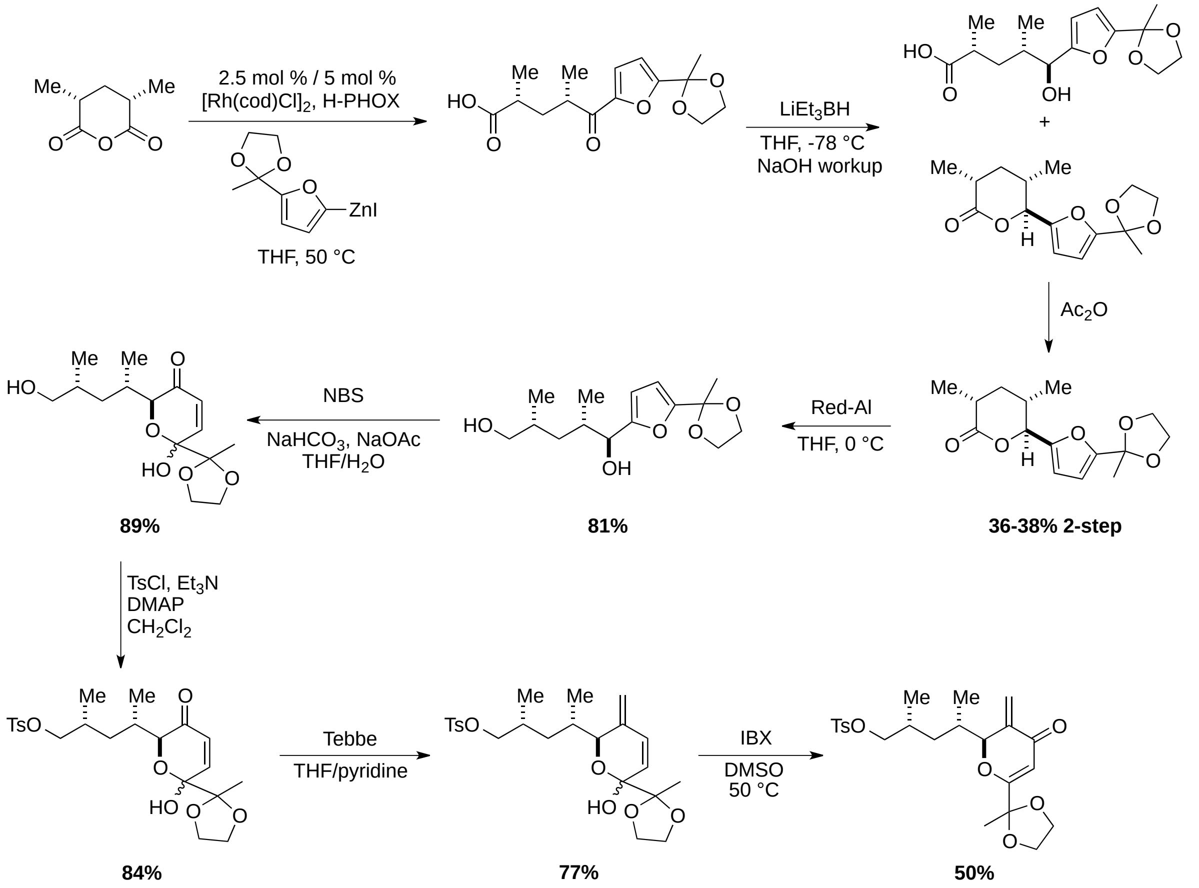
^{1}H-NMR (300 MHz, CDCl$_3$) δ (ppm) 6.91-6.85 (m, 1H), 6.10 (dd, *J* = 10.3, 4.7 Hz, 1H), 5.68-5.66 (m, 1H), 4.42 (dd, *J* = 2.9, 0.8 Hz, 1H), 3.54-3.49 (m, 1H), 3.26 (ddd, *J* = 9.8, 6.9, 0.9 Hz, 1H), 2.84-2.83 (m, 1H), 2.40-2.37 (m, 1H), 1.60-1.56 (m, 2H), 1.03 (d, *J* = 7.0, 3H), 0.88 (m, 12H), 0.03 (s, 6H).

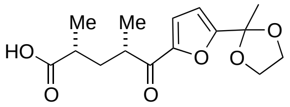


Preparation of thiolate 79. To a solution of **78** (33 mg, 0.1 mmol) in methylene chloride (1mL, 0.1M) was added zinc iodide (96 mg, 0.3 mmol, 3 equiv), tetrabutylammonium iodide (37 mg, 0.1 mmol, 1 equiv) and PhSTMS (18 mg, 0.1 mmol, 1 equiv). The reaction was monitored by TLC, and when complete consumption of starting material was observed (ca. 2h), the reaction was quenched with sat. sodium bicarbonate solution (1 mL). The mixture was extracted into methylene chloride (3x1 mL) and the combined organic extracts washed with brine, dried over magnesium sulfate, filtered and concentrated to a brown oil. The crude product was purified by silica gel chromatography (5% EtOAc in hexanes) to give **79** as a yellow oil (20 mg, 48%)

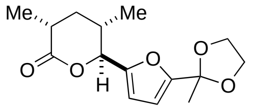
^{1}H-NMR (300 MHz, $CDCl_3$) 7.56-7.48 (m, 3H), 7.34-7.30 (m, 2H), 7.07 (dd, *J* = 10.0, 4.0 Hz, 1H), 6.07 (dd, *J* = 10.0, 1.2 Hz, 1H), 5.94 (dd, *J* = 4.0, 1.1 Hz, 1H), 3.53 (dd, *J* = 9.9, 4.9 Hz, 1H), 3.25 (dd, *J* = 9.8, 7.1 Hz, 1H), 2.52-2.47 (m, 1H), 1.61-1.55 (m, 1H), 1.35 (ddd, *J* = 13.5, 8.1, 5.2 Hz, 1H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.88 (m, 12H), 0.03 (s, 6H).

Synthesis of the top fragment


2.5 mol % / 5 mol %
[Rh(cod)Cl]$_2$, H-PHOX
ZnI
THF, 50 °C
LiEt$_3$BH
THF, -78 °C
NaOH workup
+
Ac$_2$O
Red-Al
THF, 0 °C
NBS
NaHCO$_3$, NaOAc
THF/H$_2$O
89%
81%
36-38% 2-step
TsCl, Et$_3$N
DMAP
CH$_2$Cl$_2$
Tebbe
THF/pyridine
IBX
DMSO
50 °C
84%
77%
50%

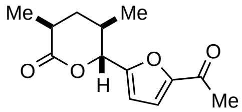


Preparation of keto acid 82. To a flame-dried, argon purged 500 mL round bottom flask was added dry THF (200 mL), cooled to -78 °C. *t*-BuLi was added (14.7 mL, 1.7 M, 25 mmol, 1.25 equiv), followed by furyl dioxolane **80** (3.92 g, 25 mmol, 1.25 equiv). The mixture was stirred and warmed until the orange color fades to pale yellow. In a separate 1000 mL 3-neck RBF equipped with a magnetic stir bar, ZnI$_2$ (9.58 g, 30 mmol, 1.5 equiv) was flame-dried, then slurried in 200 mL dry THF. The solution of lithiated furan was cooled back to -78 °C, then cannulated to the slurry of ZnI$_2$. The reaction was allowed to warm to ambient temperature and stirred for 2h. Rh(cod)Cl dimer (247 mg, 0.5 mmol, 0.025 equiv) and H-PHOX (331 mg, 1.0 mmol, 0.05 equiv) were added and the mixture heated to 50 °C and stirred for 10 min. 3,5-dimethylglutaric anhydride (2.48 g, 20 mmol) was then added and the reaction was stirred at 50 °C for 24h. The reaction was cooled to ambient temperature and quenched with sat. $NaHCO_3$ (200 mL). The mixture was extracted into ether (2x400 mL). The organic extracts were then washed with water (100 mL). The aqueous layers were combined and acidified with glacial acetic acid to pH = 4. This aqueous layer was then extracted into ether (3x400 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give crude **82** as a brown oil. The crude product was taken to the next step without further purification.

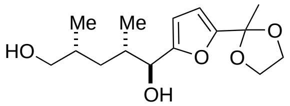


Preparation of lactone 86. In an argon purged 500 mL round bottom flask equipped with a magnetic stir bar was dissolved **82** (20 mmol theor.) in dry THF (200 mL, 0.1M). The solution was cooled to -78 °C and stirred. Lithium triethylborohydride (1M in THF, 40 mL, 2 equiv) was added dropwise and the reaction monitored by crude NMR of aliquots. After complete reaction (ca. 2h), 15% aq. NaOH (100 mL) is added and the reaction stirred vigorously while warming to ambient temperature. After 1h, the mixture is acidified with glacial acetic acid to pH = 4 and extracted into ether (3x200 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give crude **86** as a brown oil. Acetic anhydride (ca. 10 mL) was added to the crude product (a mixture of lactone and hydroxy acid), then concentrated by rotary exaporation. Toluene (ca. 10 mL) was then added and concentrated again. The crude lactone was then purified by silica gel chromatography (30% to 40% EtOAc in hexanes) to give **86** as a colorless oil (2.4g, 43 % 2-step).

^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 6.29-6.25 (m, 2H), 4.86 (d, *J* = 10.7 Hz, 1H), 4.04-3.92 (m, 4H), 2.61 (t, *J* = 6.6 Hz, 1H), 2.42-2.35 (m, 1H), 2.02-2.01 (m, 1H), 1.69 (s, 3H), 1.30 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H). **^{13}C-NMR (100 MHz, CDCl$_3$) δ (ppm)** 173.5, 154.9, 150.6, 110.0, 107.1, 104.5, 98.6, 81.5, 65.0, 37.3, 36.2, 32.5, 24.4, 17.3, 17.1.

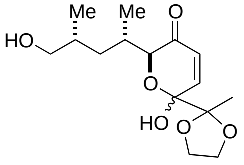


Characterization data for side product 83. ^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) ^{1}H-NMR (400 MHz; CDCl$_3$): δ 7.12 (d, *J* = 3.5 Hz, 1H), 6.51 (d, *J* = 3.5 Hz, 1H), 4.96 (d, *J* = 10.8 Hz, 1H), 2.66 (dt, *J* = 13.1, 6.5 Hz, 1H), 2.46-2.40 (m, 4H), 2.07 (ddd, *J* = 13.6, 6.2, 3.3 Hz, 1H), 1.49 (dd, *J* = 25.9, 12.5 Hz, 2H), 1.32 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H). **^{13}C-NMR (100 MHz, CDCl$_3$) δ (ppm)** 222.3, 194.7, 172.9, 117.6, 111.6, 81.1, 37.1, 36.2, 32.8, 26.1, 17.1.



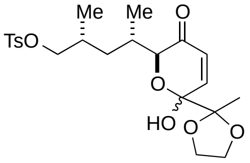
Preparation of diol 100. In an argon purged 250 mL round bottom flask equipped with a magnetic stir bar was dissolved **86** (2.26 g, 3.8 mmol) in dry THF (80 mL, 0.1M). The solution was cooled to 0 °C and stirred. Red-Al (3.73 g, 65 wt%, 12 mmol, 1.5 equiv) was added dropwise and the reaction monitored by TLC. After complete consumption of starting material was observed (ca. 2h), the reaction was quenched with water (40 mL) then sat. NH$_4$Cl (40 mL). The mixture was extracted into EtOAc (3x80 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give crude **100** as a brown oil. The crude product was then purified by silica gel chromatography (30% to 50% EtOAc in hexanes) to give **100** as a colorless oil (1.84 g, 81%).

^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 6.23 (d, *J* = 3.2 Hz, 1H), 6.13 (d, *J* = 3.2 Hz, 1H), 4.42 (d, *J* = 6.5 Hz, 1H), 4.01-3.95 (m, 4H), 3.44 (dd, *J* = 7.5, 5.0 Hz, 2H), 2.03 (s, 1H), 1.68 (s, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H). **^{13}C-NMR (100 MHz, CDCl$_3$) δ (ppm)** 194.8, 156.0, 153.2, 107.1, 106.8, 104.6, 72.6, 67.0, 65.1, 36.2, 35.9, 33.2, 24.2, 18.1, 16.6.



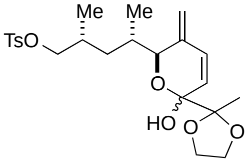
Preparation of 3-pyranone 101. In an argon purged 250 mL round bottom flask equipped with a magnetic stir bar was dissolved **100** (1.84 g, 6.5 mmol) in THF (34 mL) and water (9 mL, 0.15M total). NaHCO$_3$ (1.09 g, 13 mmol, 2 equiv) and NaOAc (533 mg, 6.5 mmol, 1 equiv) were added and the mixture stirred vigorously until the salts dissolve. Then, *N*-bromosuccinimide (1.16 g, 6.5 mmol, 1 equiv) was added and the mixture stirred at ambient temperature and monitored by TLC. After complete consumption of starting material was observed (ca. 2h), the reaction was diluted with water (45 mL) and extracted into ether (3x65 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give crude **101** as a yellow oil. The crude product was then purified by silica gel chromatography (50% to 70% EtOAc in hexanes) to give **101** as a colorless oil (1.74 g, 89%).

^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 7.02 (d, *J* = 10.4 Hz, 1H), 6.14 (d, *J* = 10.3 Hz, 1H), 4.41 (s, 1H), 4.15-3.99 (m, 4H), 3.49-3.43 (m, 2H), 2.39 (dt, *J* = 4.4, 2.3 Hz, 1H), 1.59-1.53 (m, 1H), 1.35 (s, 3H), 1.09-0.99 (m, 3H), 0.93-0.86 (m, 3H). **^{13}C-NMR (100 MHz, CDCl$_3$) δ (ppm)** δ 197.0, 144.9, 129.6, 109.9, 95.1, 78.5, 67.1, 66.2, 65.7, 35.4, 33.2, 31.0, 20.6, 18.1, 17.0.



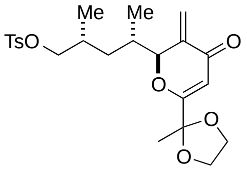
Preparation of tosylate 102. In an argon purged 250 mL round bottom flask equipped with a magnetic stir bar was dissolved **101** (1.74 g, 5.8 mmol) in CH_2Cl_2 (29 mL, 0.2M). Triethylamine (3.23 mL, 23.2 mmol, 4 equiv) and *p*-toluenesulfonyl chloride (2.21g, 11.6 mmol, 2 equiv) were added, followed by DMAP (71 mg, 0.58 mmol, 0.1 equiv). The reaction was stirred at ambient temperature and monitored by TLC. After complete consumption of starting material was observed (6-18h), the reaction was quenched with sat. NH_4Cl (29 mL) and extracted into ether (3x30 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give crude **102** as a yellow oil. The crude product was then purified by silica gel chromatography (20% to 50% EtOAc in hexanes) to give **102** as a colorless oil (2.21 g, 84%).

^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) 7.74 (d, *J* = 8.3 Hz, 2H), 7.33-7.28 (m, 2H), 6.13 (dd, *J* = 5.4, 0.6 Hz, 1H), 4.99 (d, *J* = 10.3 Hz, 1H), 4.23 (s, 1H), 3.84-3.76 (m, 2H), 2.93 (dd, *J* = 6.5, 4.1 Hz, 1H), 2.42 (s, 3H), 1.69 (td, *J* = 6.6, 3.5 Hz, 1H), 1.45 (ddd, *J* = 13.7, 10.6, 4.0 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 2H), 1.05 (dd, *J* = 11.2, 6.7 Hz, 3H), 0.85 (dd, *J* = 11.8, 6.7 Hz, 3H). **^{13}C-NMR (100 MHz, CDCl$_3$) δ (ppm)** 169.9, 149.2, 144.7, 143.6, 139.3, 132.9, 129.8, 127.8, 121.9, 119.3, 75.2, 40.1, 31.3, 29.1, 21.6, 21.3, 15.9.



Preparation of diene 103. To a flame-dried, argon purged 100 mL round bottom flask equipped with a magnetic stir bar was added **103** (2.21 g, 4.9 mmol). Dry THF (20 mL) was added and the solution cooled to -78 °C. Pyridine (5 mL, 0.2M total) was then added, followed by Tebbe's reagent (20 mL, 0.5M in PhMe, 10 mmol, 2 equiv). The reaction was monitored by TLC (mini workup with HCl to remove pyridine). After complete consumption of starting material was observed, the reaction was warmed to 0 °C and stirred for 30 min (*Note: the reaction goes to completion in the capillary when it warms, the reaction must be warmed to 0 °C to ensure complete conversion*). The reaction was then quenched with 15% NaOH (10 mL) at 0 °C. *Note: HAZARD. The aqueous solution must be added slowly. Vigorous methane gas evolution and exotherm are observed.* The resultant red to green slurry is stirred and warmed to ambient temperature, then diethyl ether is added (25 mL). The resultant orange solid is removed by filtration over a bed of Celite and the filtrate concentrated by rotary evaporation (*Note: the remaining pyridine is codistilled by several additions of toluene and reconcentration).* The crude product is then purified by silica gel chromatography (30% to 40% EtOAc in hexanes) and isolated as a yellow oil (1.71g, 77%).

^{1}H-NMR (300 MHz, CDCl$_3$) δ (ppm) 7.78 (d, *J* = 7.9 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 6.36 (d, *J* = 10.1 Hz, 1H), 5.96-5.93 (m, 1H), 5.00 (d, *J* = 0.6 Hz, 1H), 4.91 (d, *J* = 0.6 Hz, 1H), 4.48 (t, *J* = 0.7 Hz, 1H), 4.13-3.84 (m, 6H), 3.01 (s, 1H), 2.45 (s, 3H), 2.13-2.04 (m, 1H), 1.88-1.82 (m, 1H), 1.57-1.46 (m, 2H), 1.28 (d, *J* = 0.7 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.89 (dd, *J* = 6.7, 0.6 Hz, 3H).

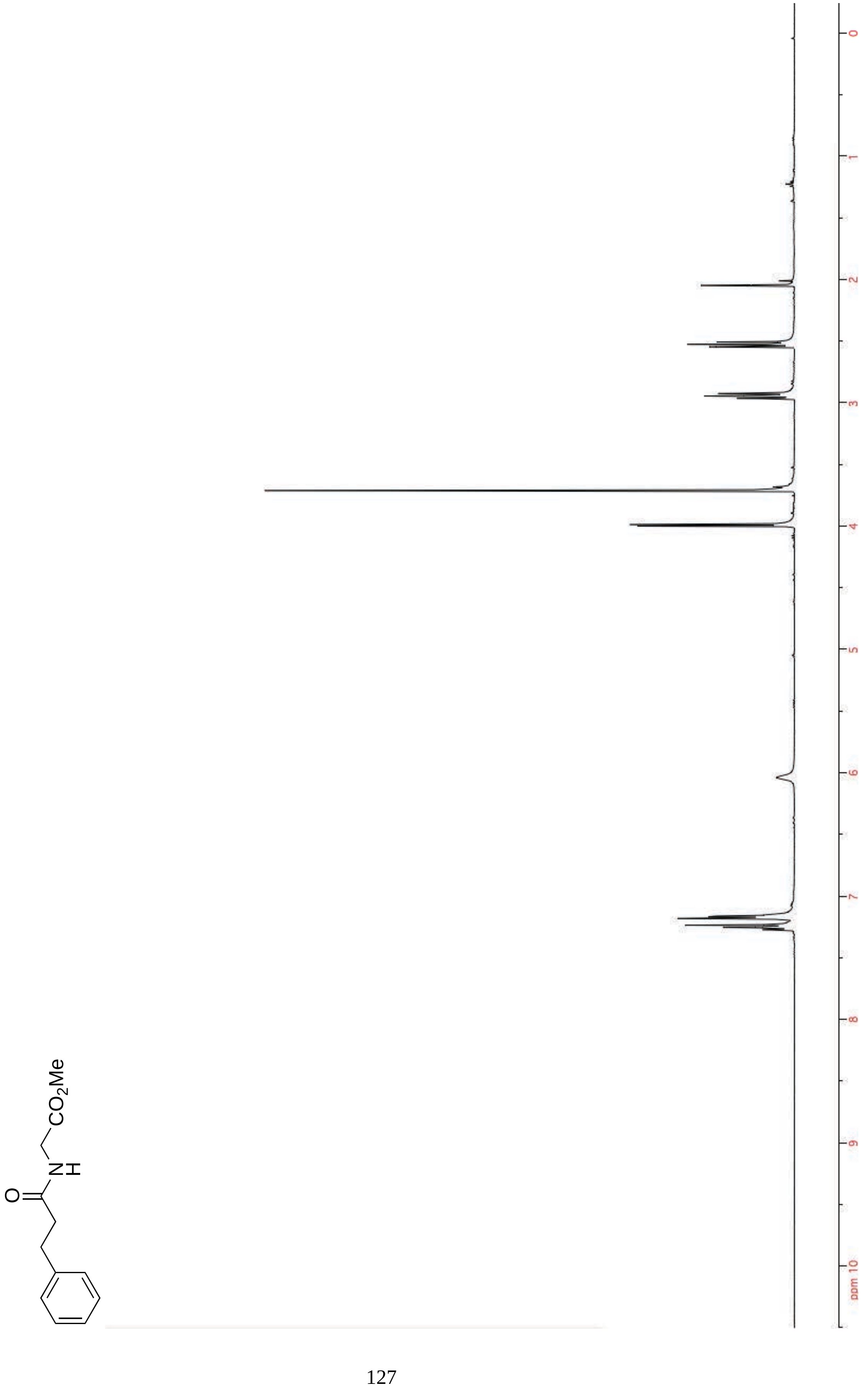


Preparation of 4-pyrone 104. In an argon purged 100 mL round bottom flask equipped with a magnetic stir bar was dissolved **103** (1.71 g, 3.8 mmol) in DMSO (38 mL, 0.1M). IBX (8.51 g, 30.4 mmol, 8 equiv) was then added and the reaction was heated to 50 °C, stirred and monitored by TLC. After complete consumption of starting material was observed, the reaction mixture was then cooled to 0 °C and quenched by the addition of 38 mL of sat. NaCl solution. The resultant slurry was extracted into ether (3x40 mL). The combined organic extracts were washed successively with sat. $NaHCO_3$ (40 mL) and brine (40 mL), dried over magnesium sulfate and filtered to give crude **104** as a yellow oil. The crude oil was purified by silica gel chromatography (30% to 50% EtOAc in hexanes) to give **104** as a colorless oil (856 mg, 50%).

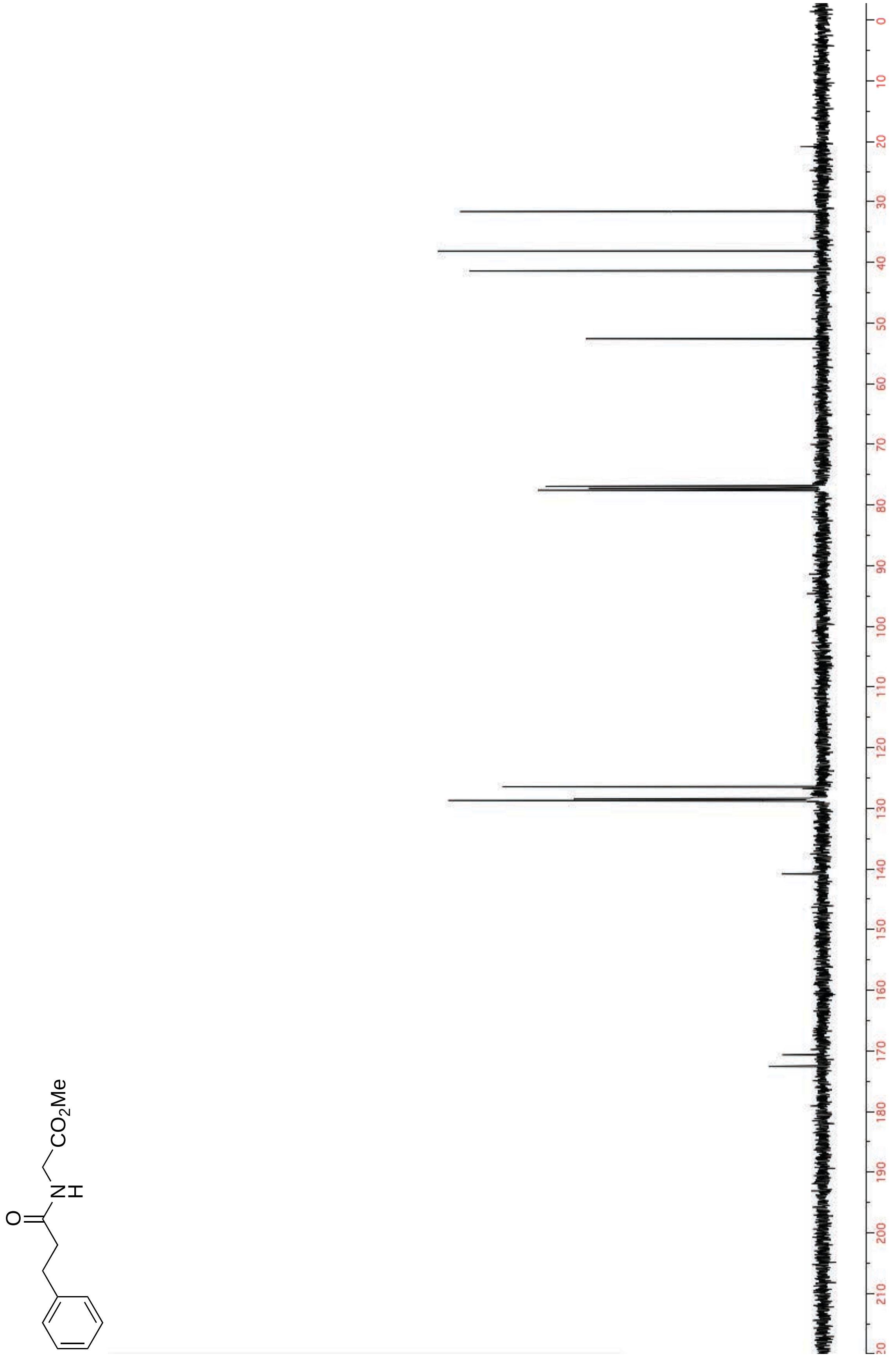
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.83-7.73 (m, 2H), 7.36-7.30 (m, 2H), 6.20 (s, 1H), 5.71 (d, *J* = 0.7 Hz, 1H), 5.29 (t, *J* = 0.5 Hz, 1H), 4.81-4.77 (m, 2H), 4.04-3.73 (m, 6H), 2.44 (d, *J* = 6.3 Hz, 3H), 1.97-1.88 (m, 2H), 1.71-1.50 (m, 6H), 1.10-1.02 (m, 2H), 0.95-0.81 (m, 6H).

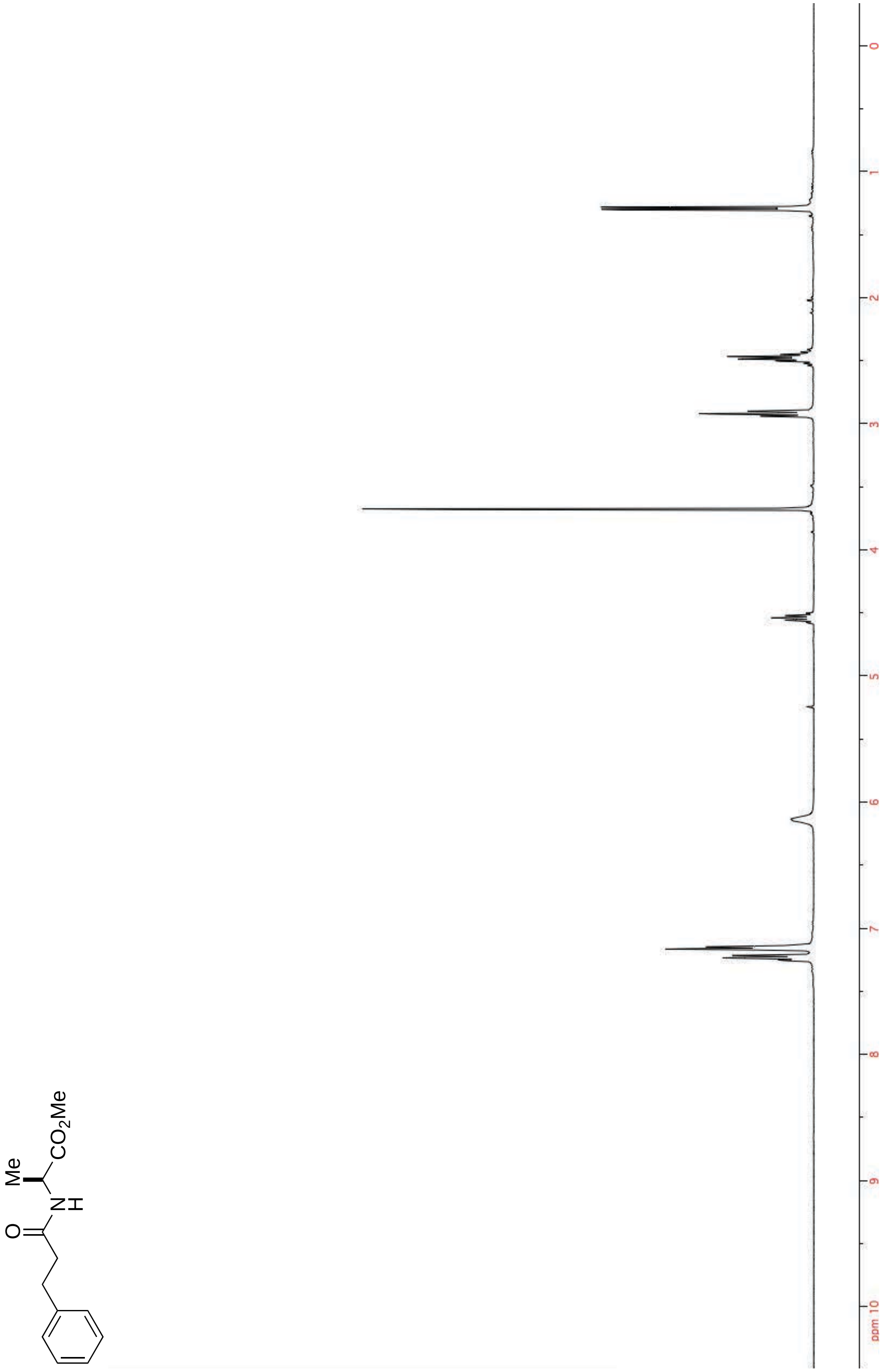
APPENDIX

Spectral Data for Chapter 1

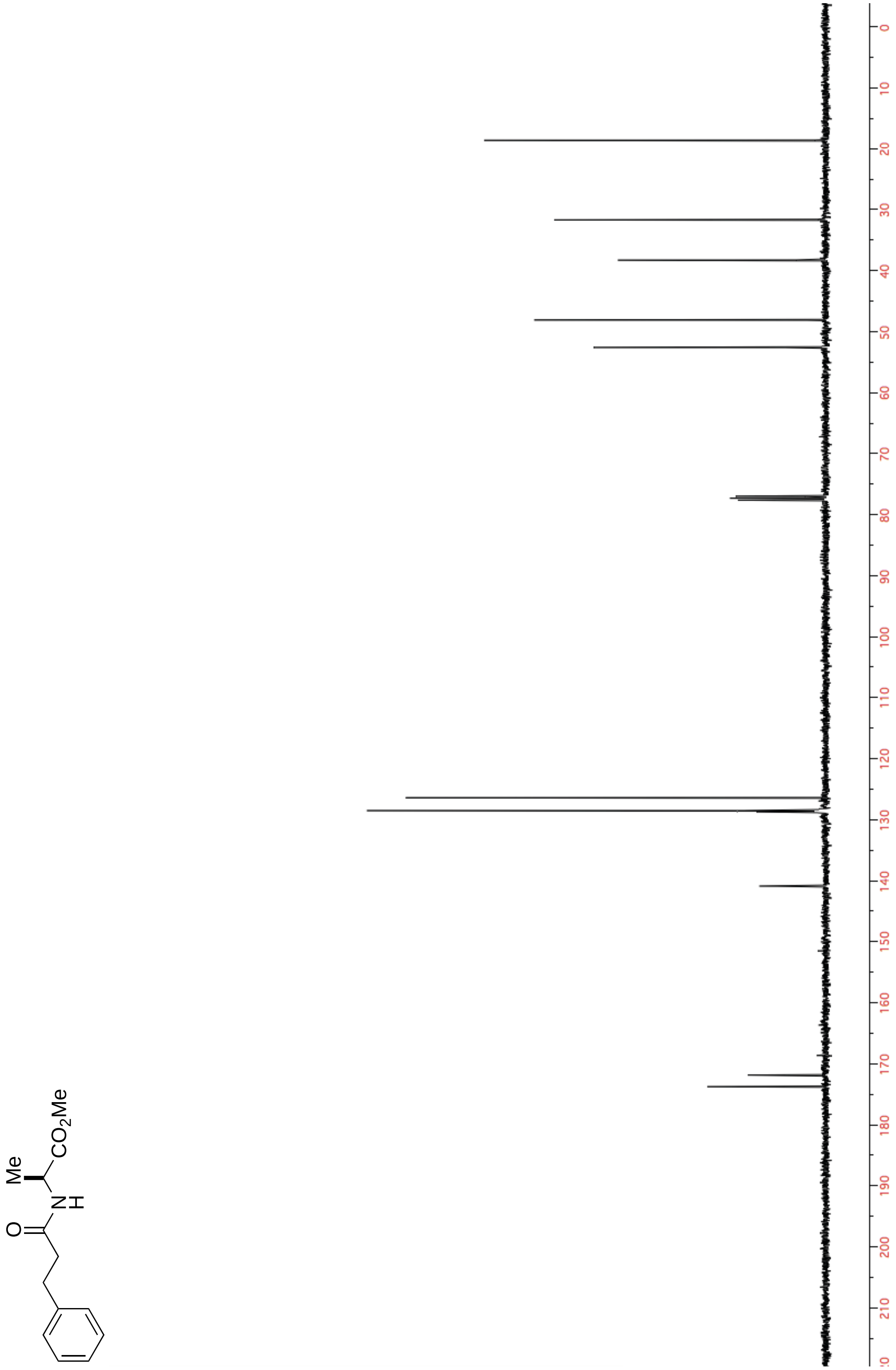


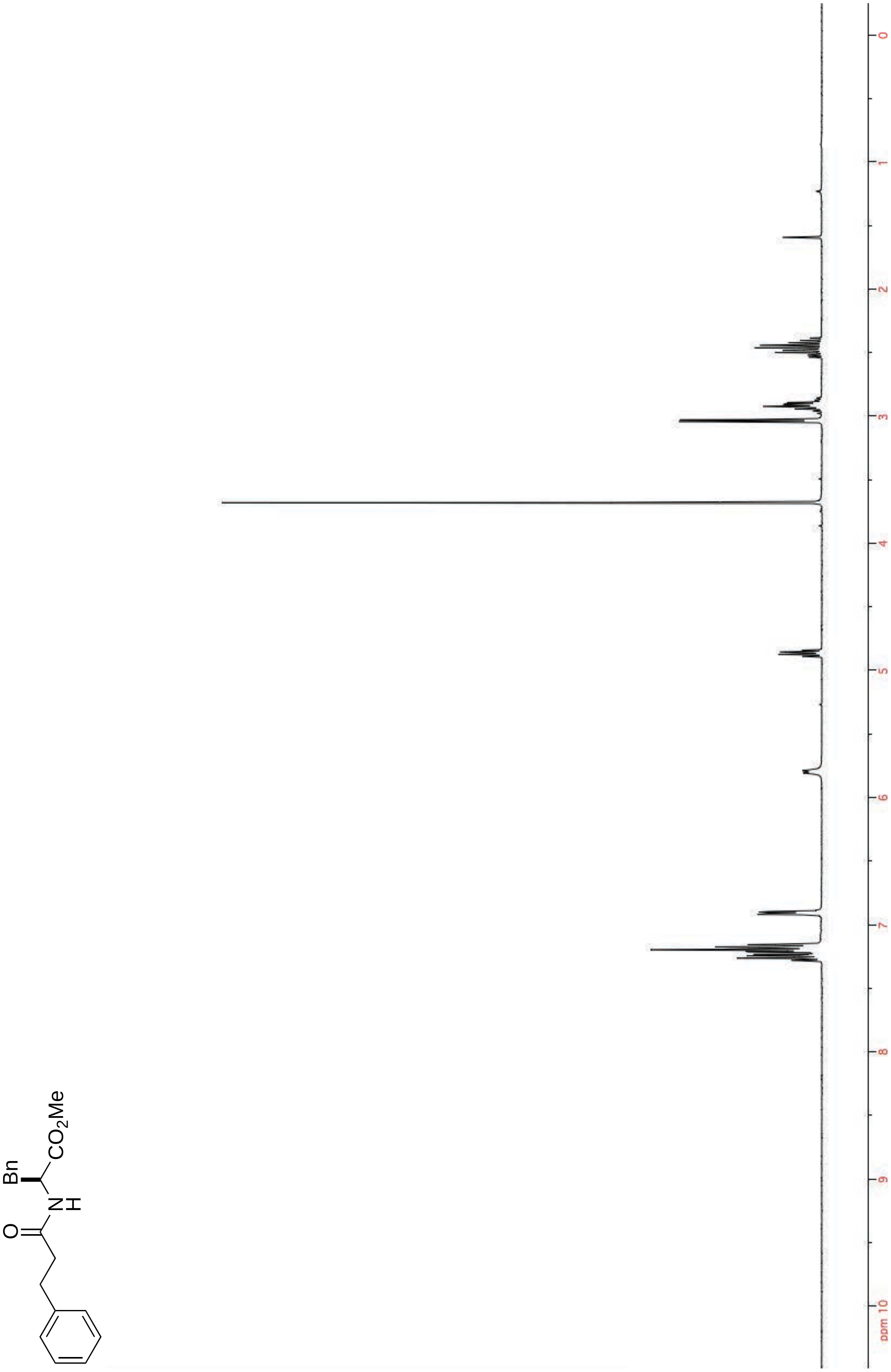
O
N
H
CO2Me
ppm 10
9
8
7
6
5
4
3
2
1
0

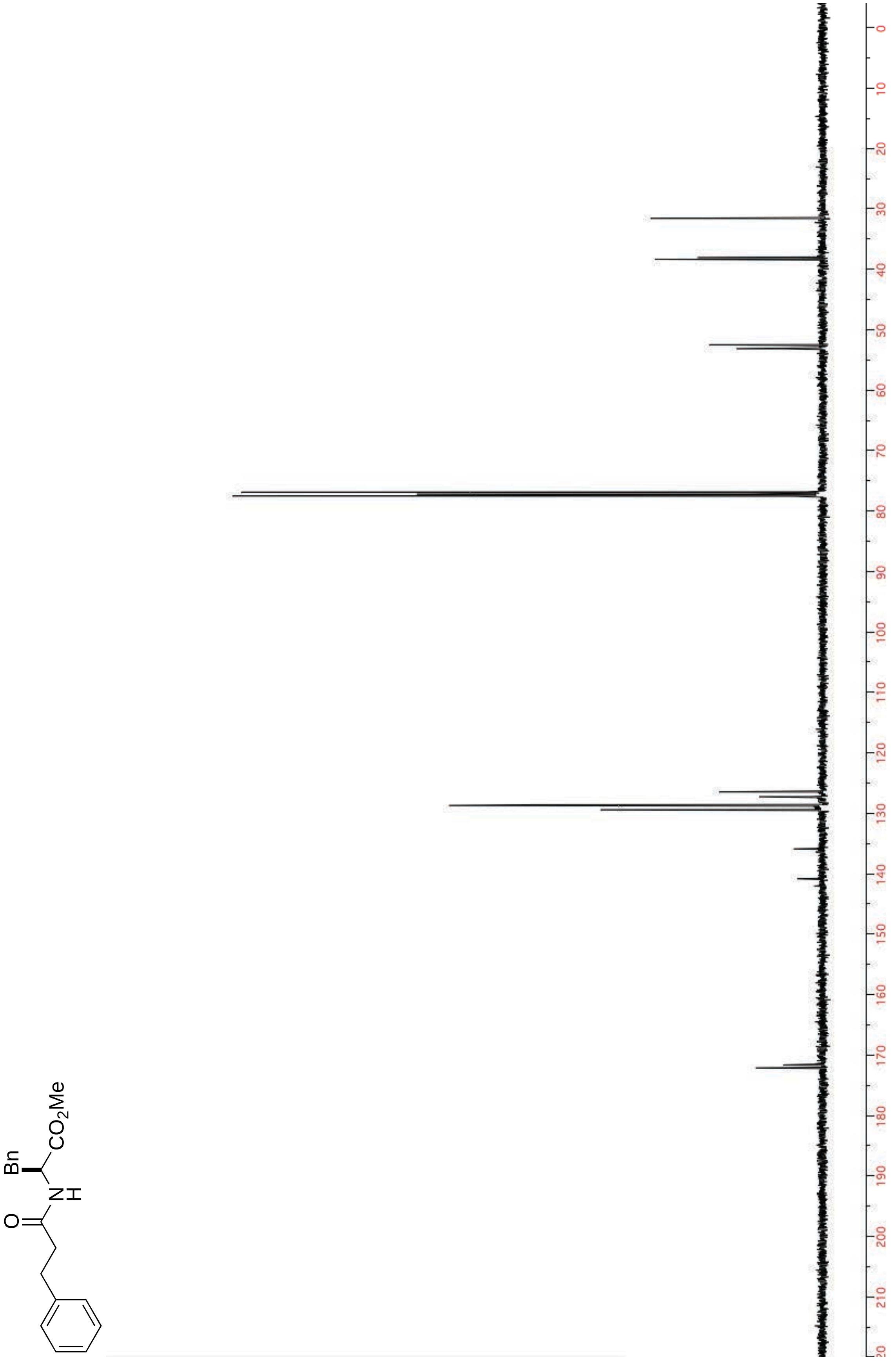

CO2Me
N
H
O
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

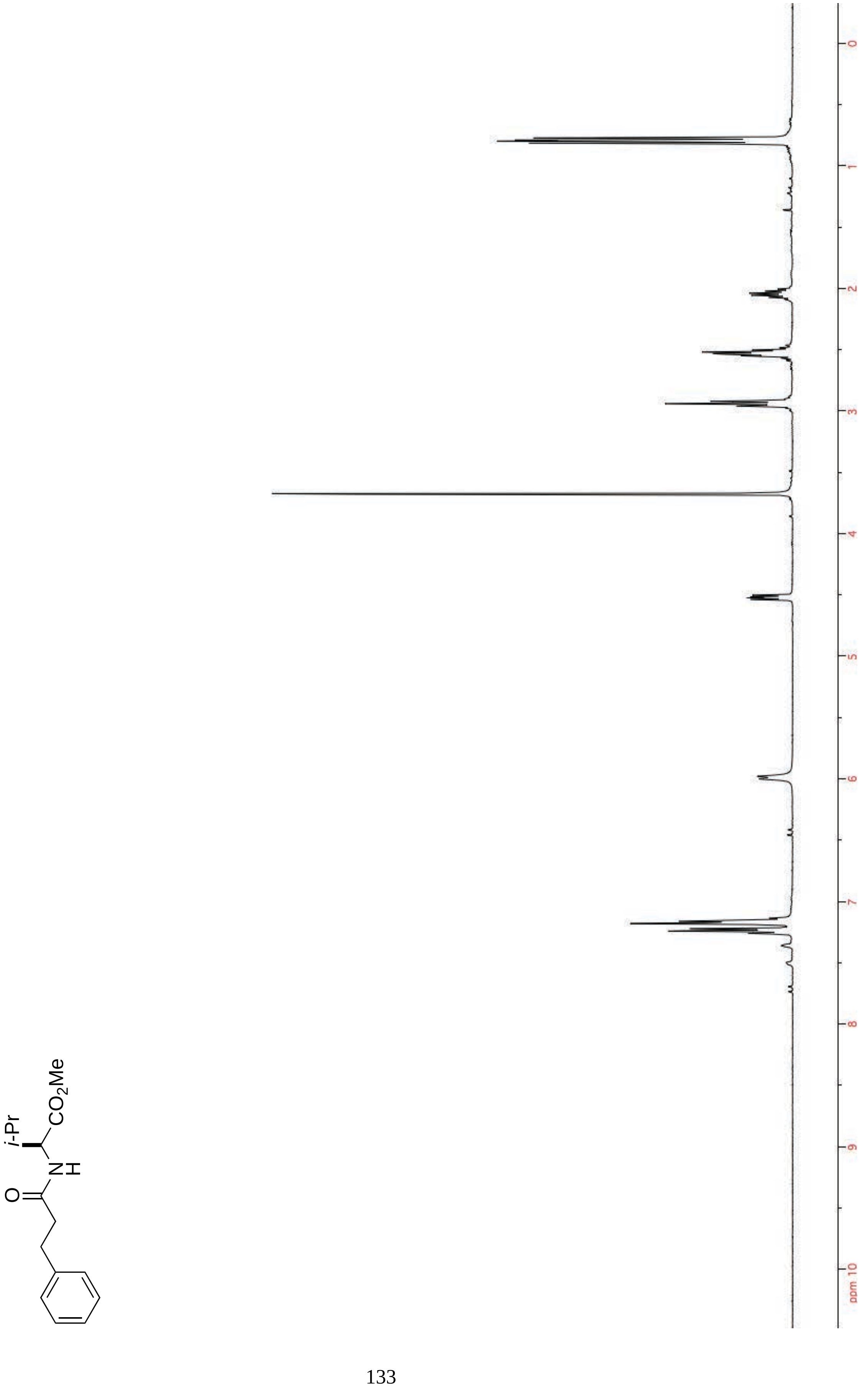


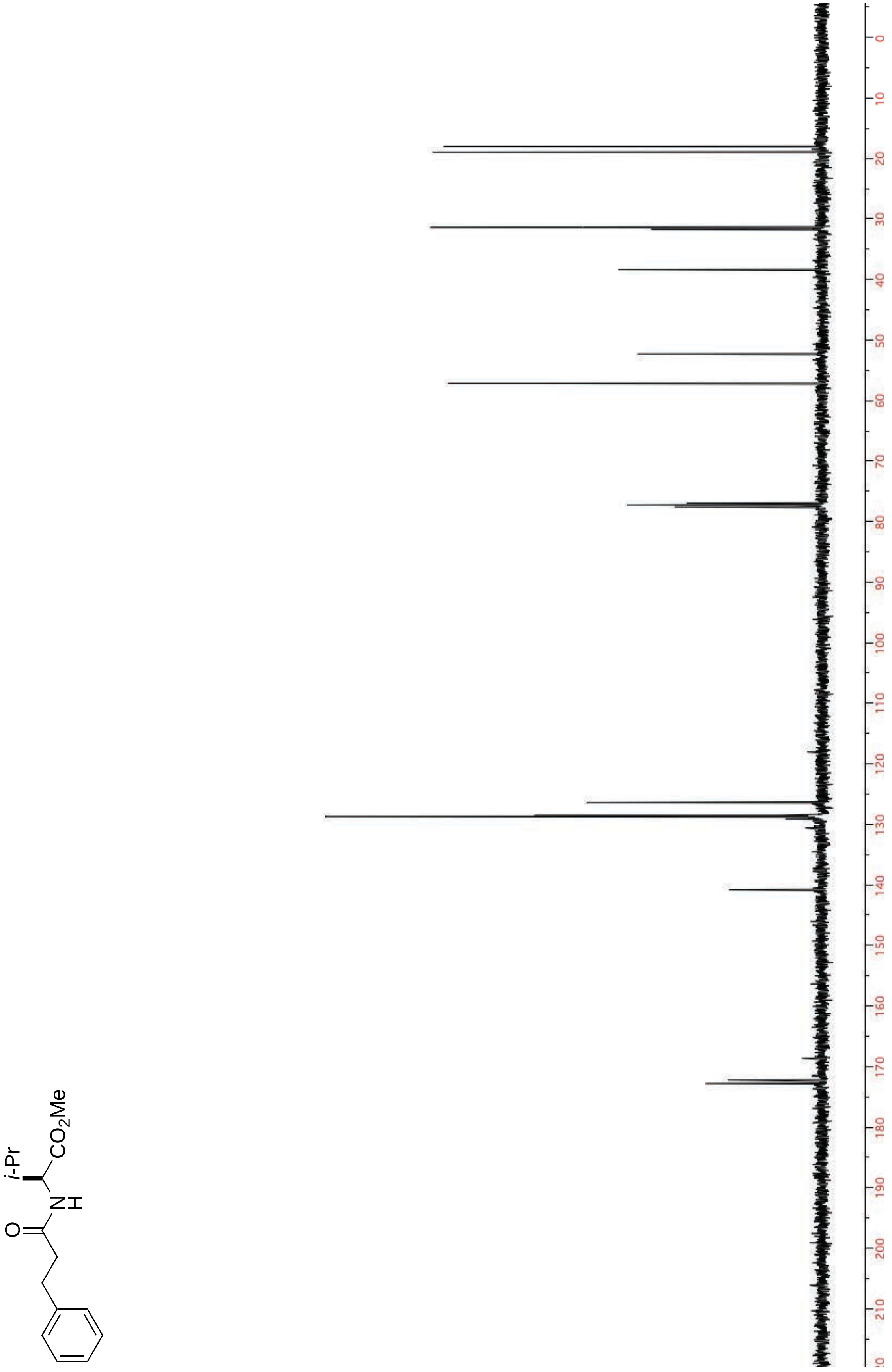
O
N
H
Me
CO2Me
ppm 10
9
8
7
6
5
4
3
2
1
0

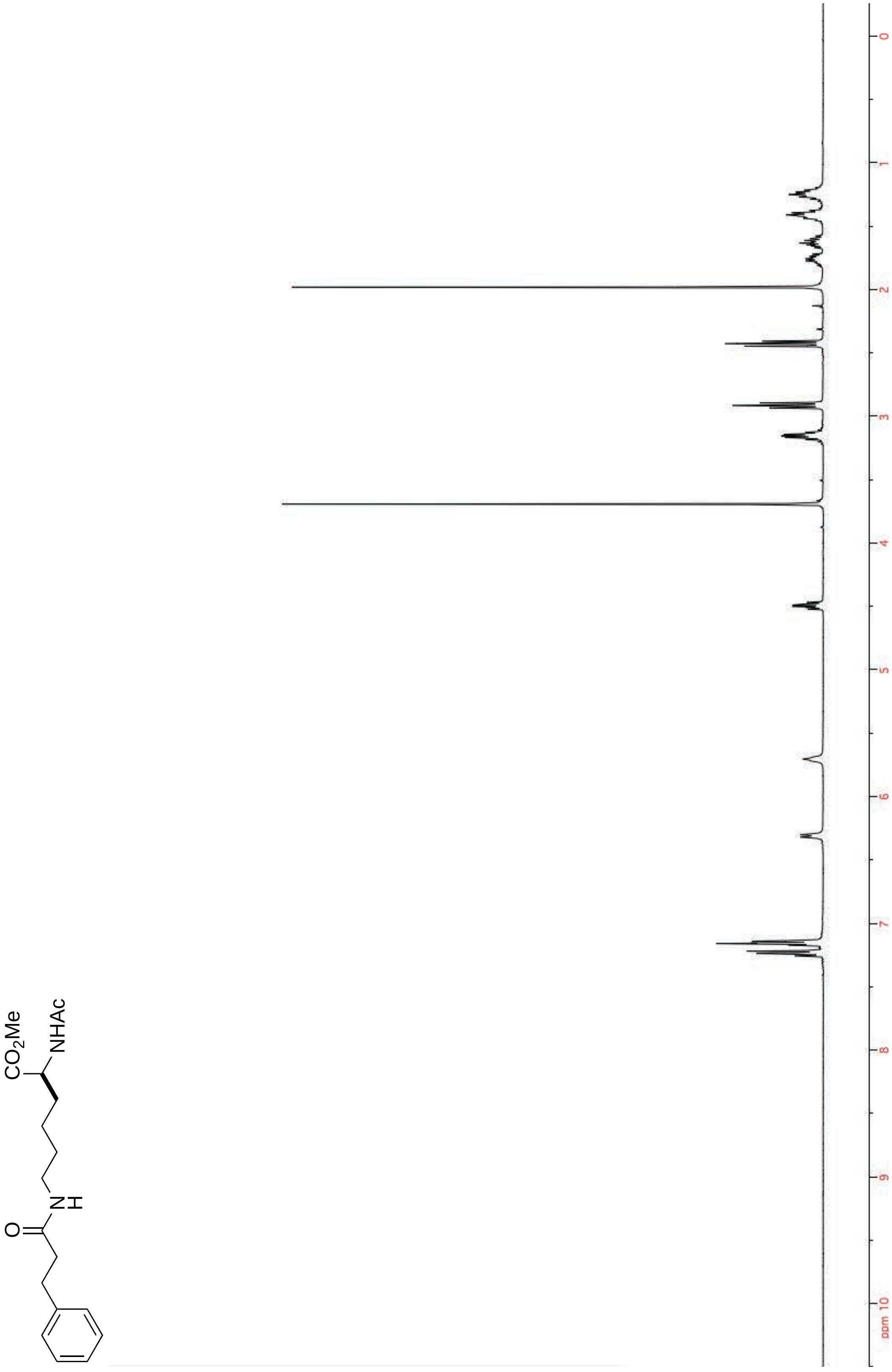

O
N
H
Me
CO$_2$Me
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

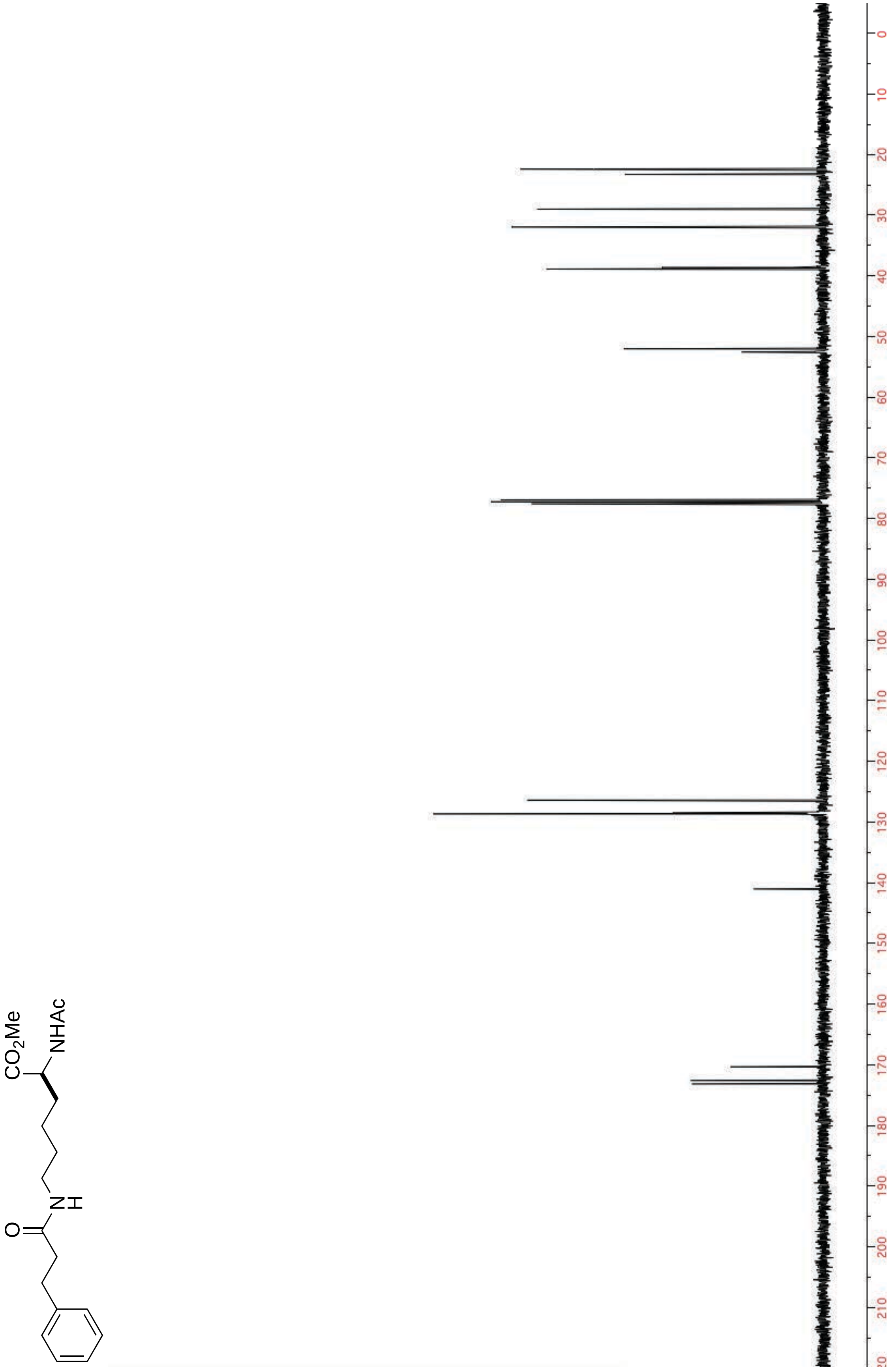

O
N
H
Bn
CO_2Me
ppm
0
1
2
3
4
5
6
7
8
9
10


O
N
H
Bn
CO2Me
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

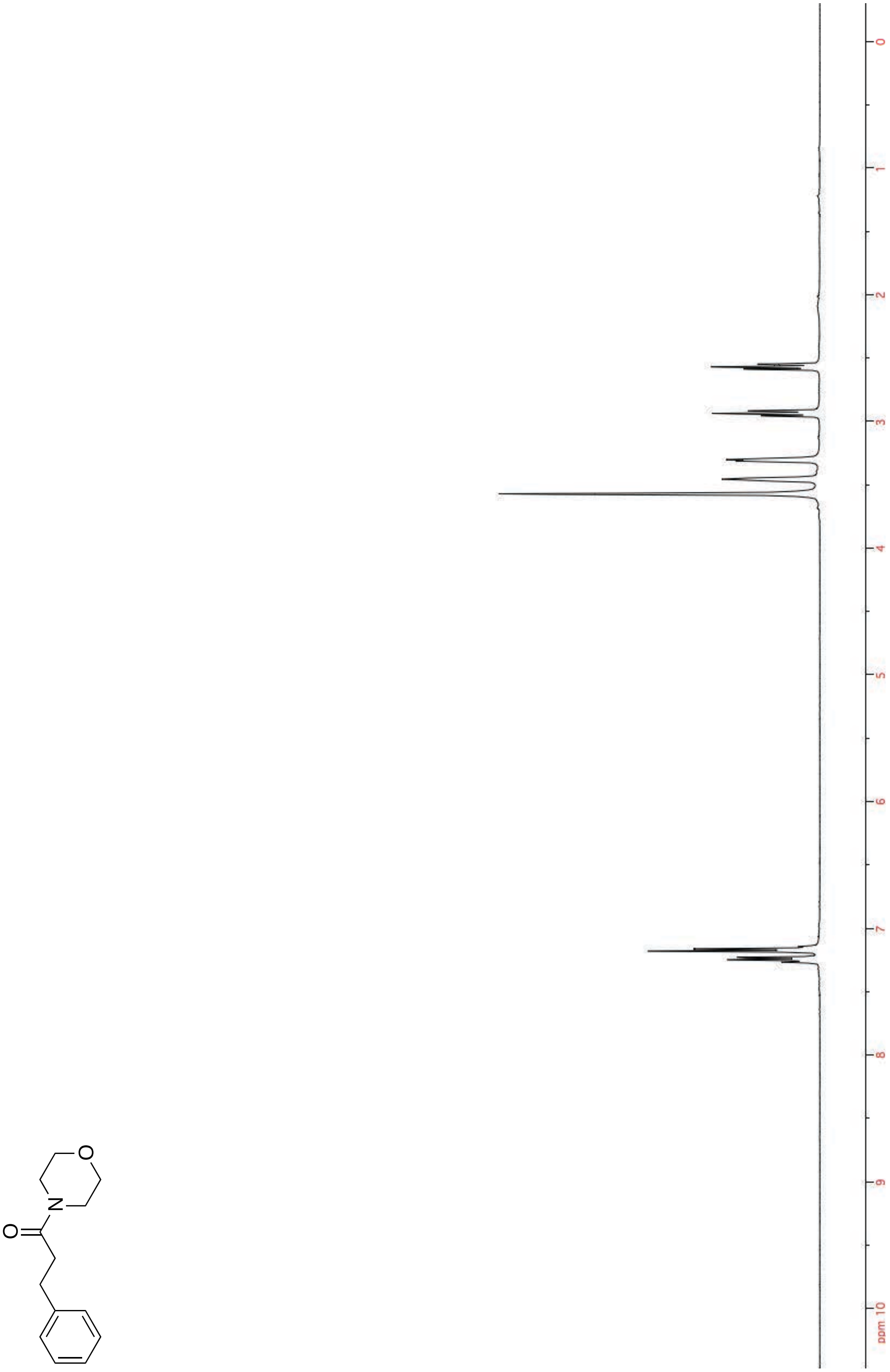

O
N
H
i-Pr
CO2Me
ppm 10
9
8
7
6
5
4
3
2
1
0

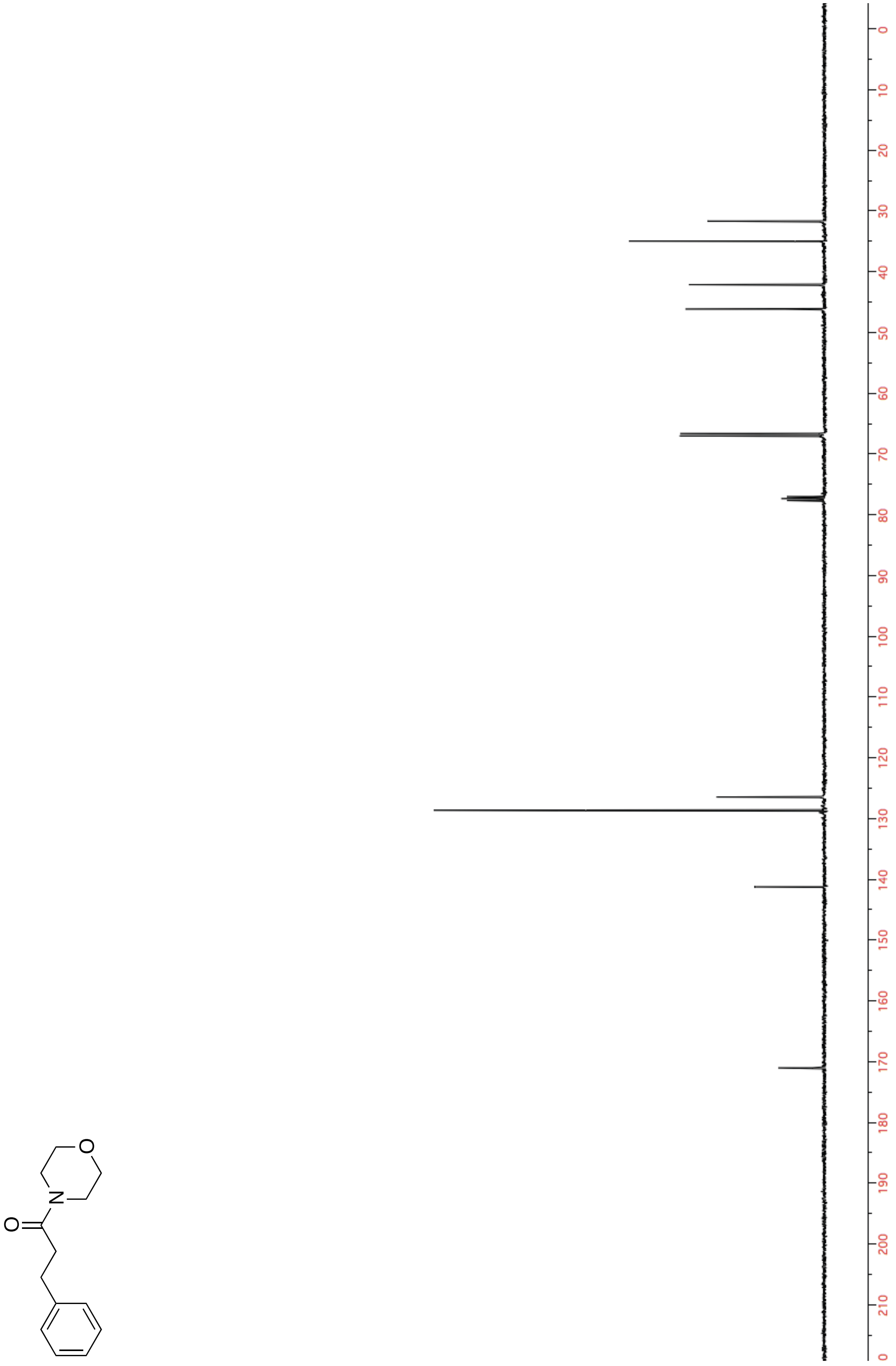

O
N
H
i-Pr
CO2Me
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210


CO2Me
NHAc
O
N
H
0
1
2
3
4
5
6
7
8
9
ppm 10

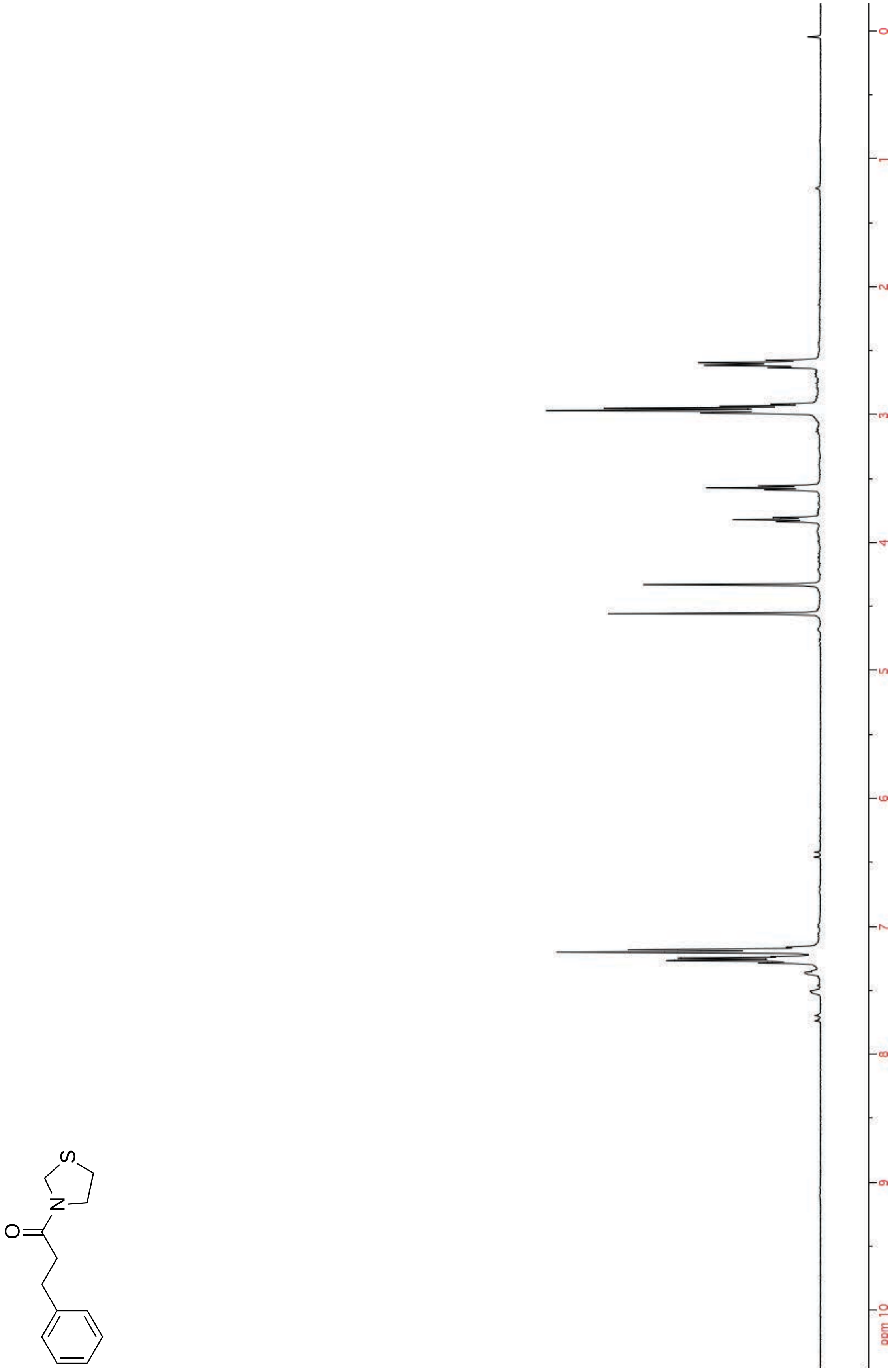


CO$_2$Me
NHAc
O
N
H
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

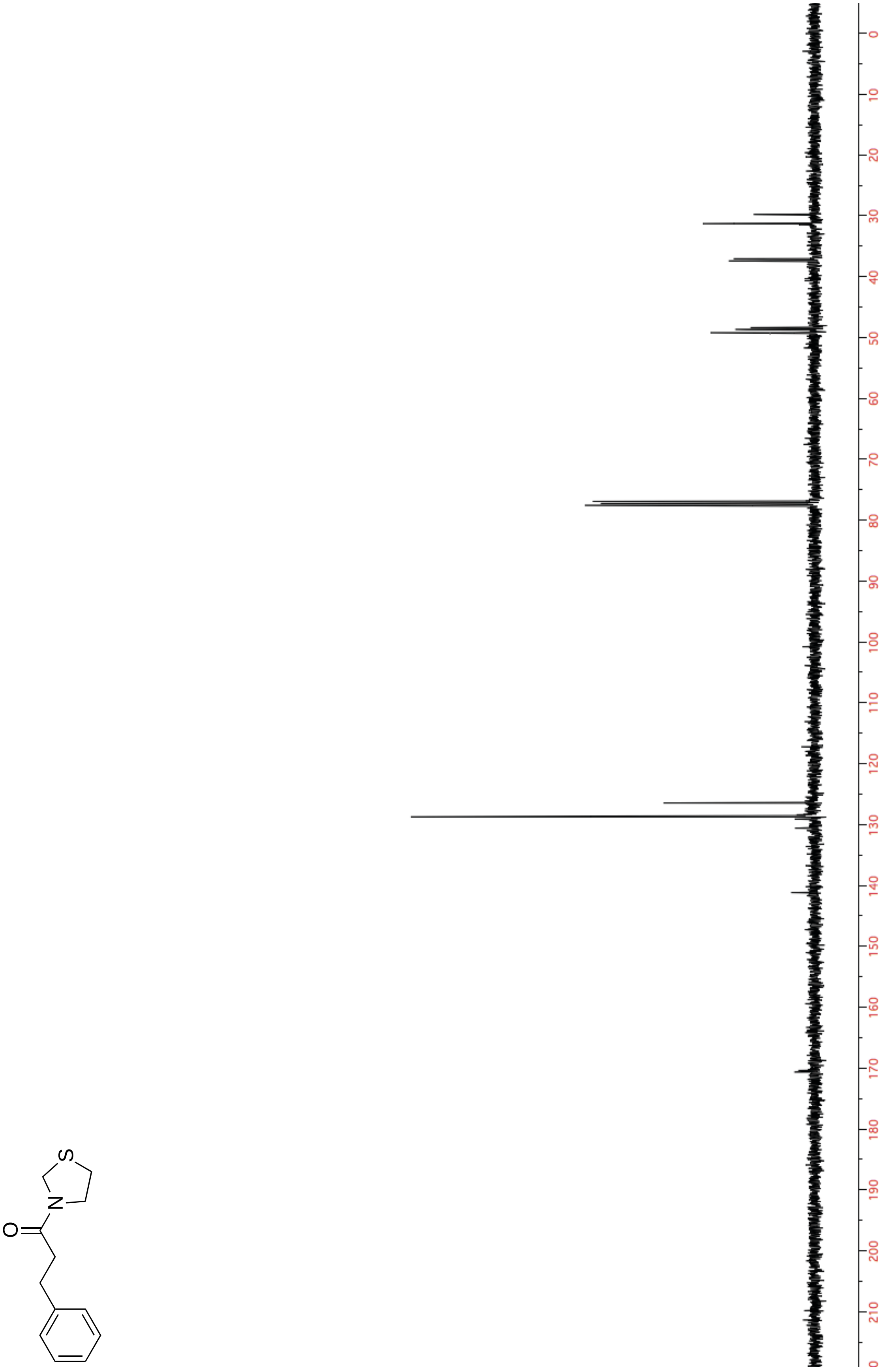

O
N
O
ppm 10
9
8
7
6
5
4
3
2
1
0



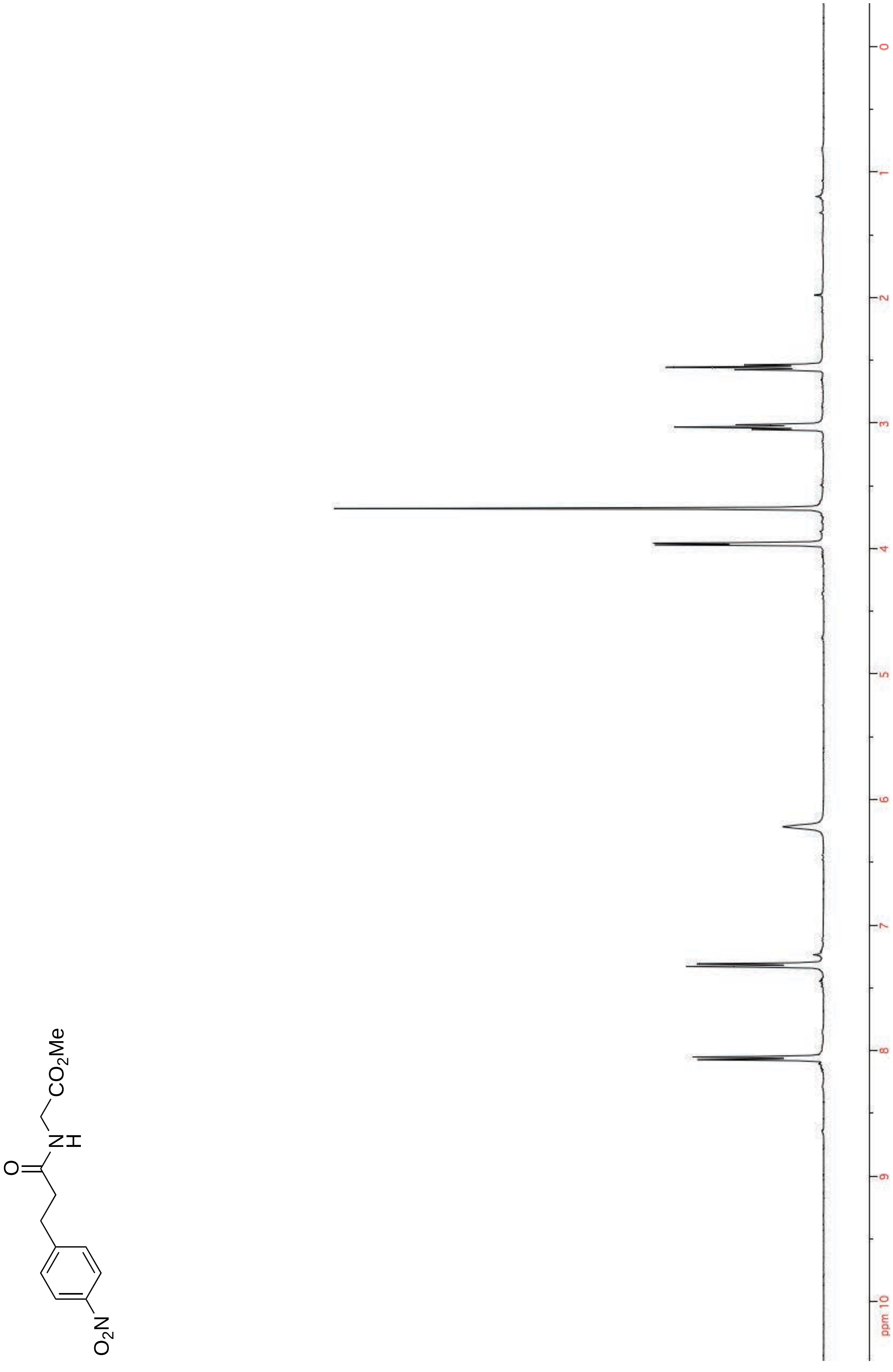
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
0
O
N
O



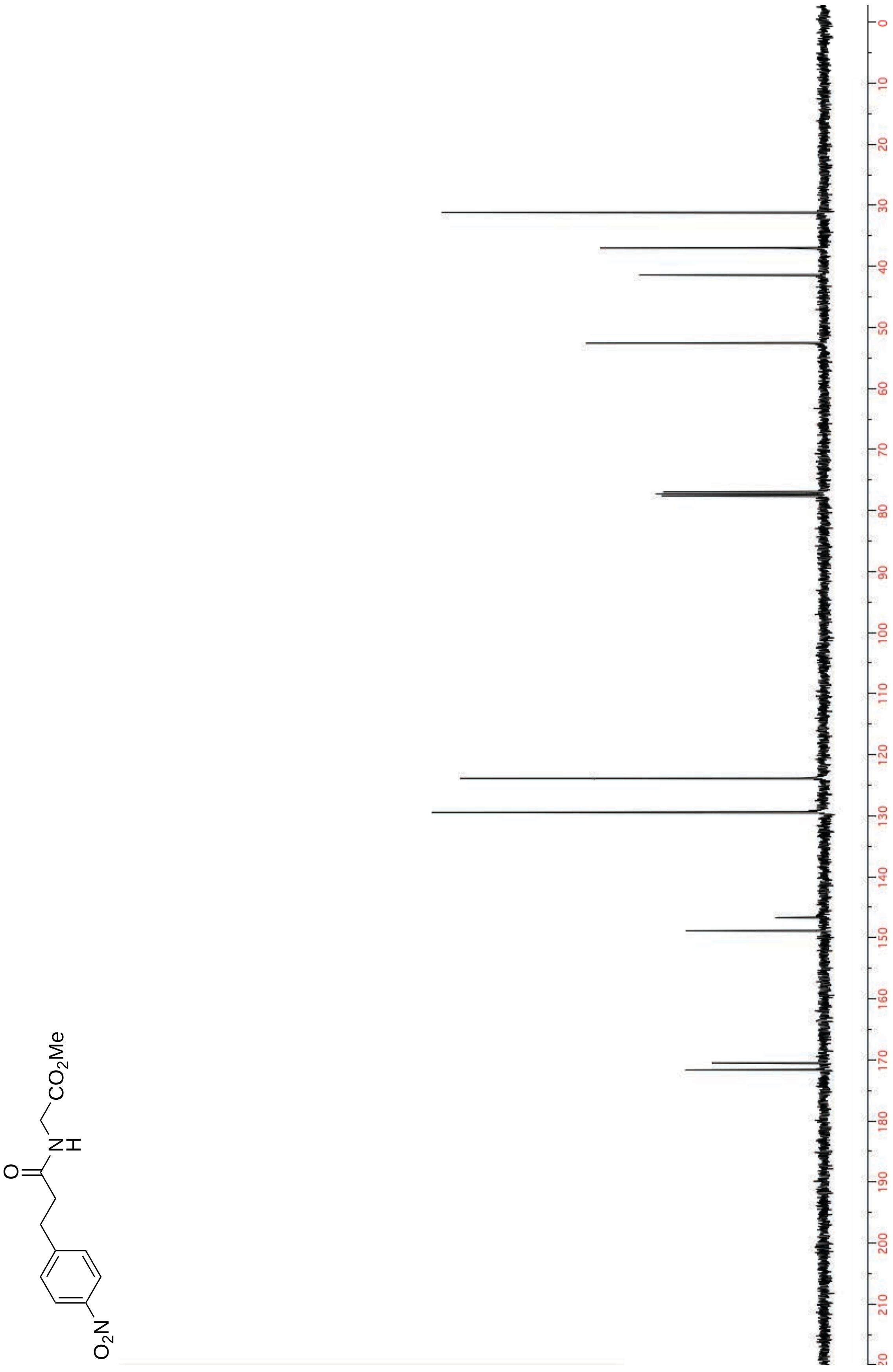
S
N
O
ppm 10
9
8
7
6
5
4
3
2
1
0

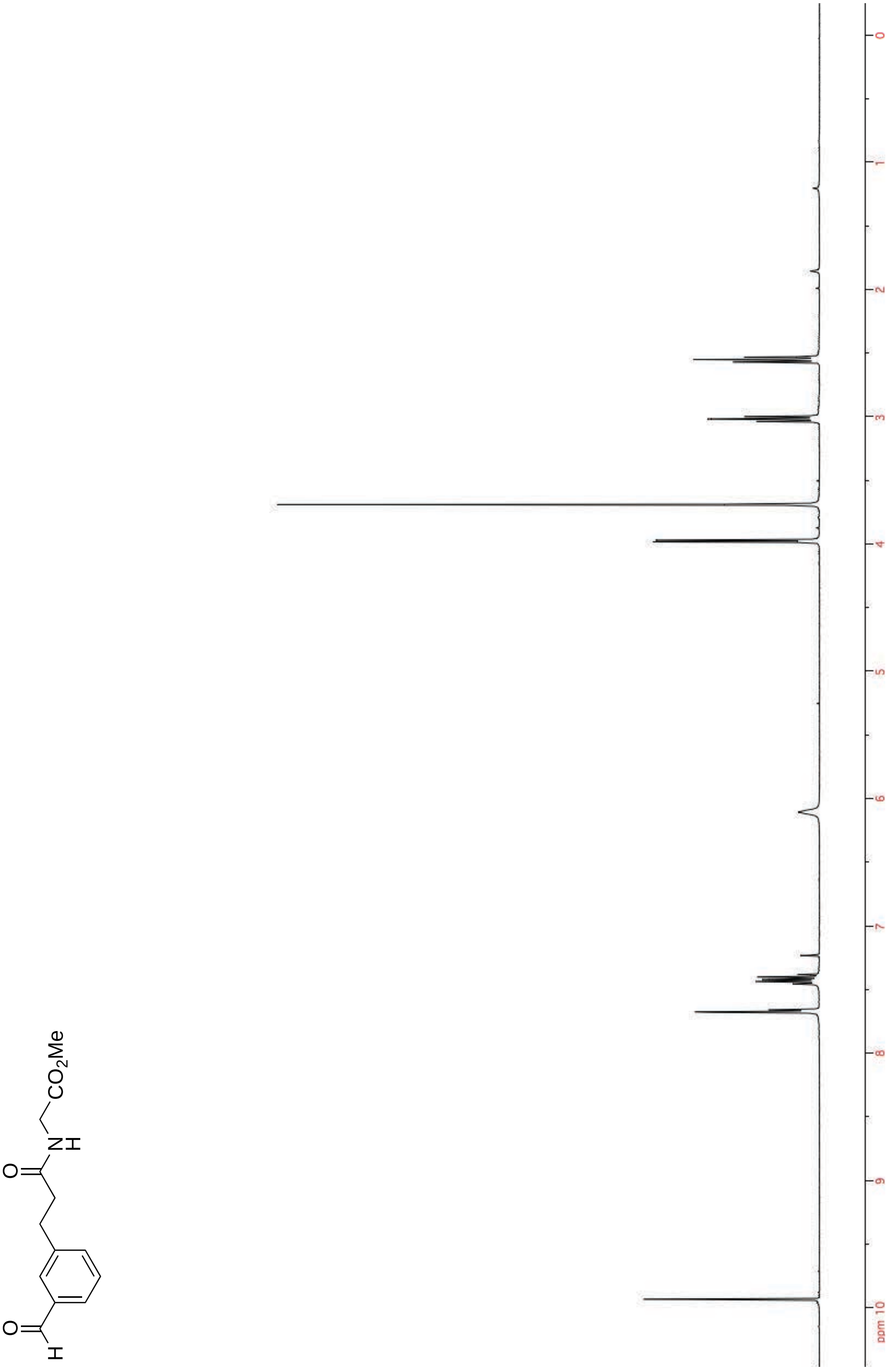


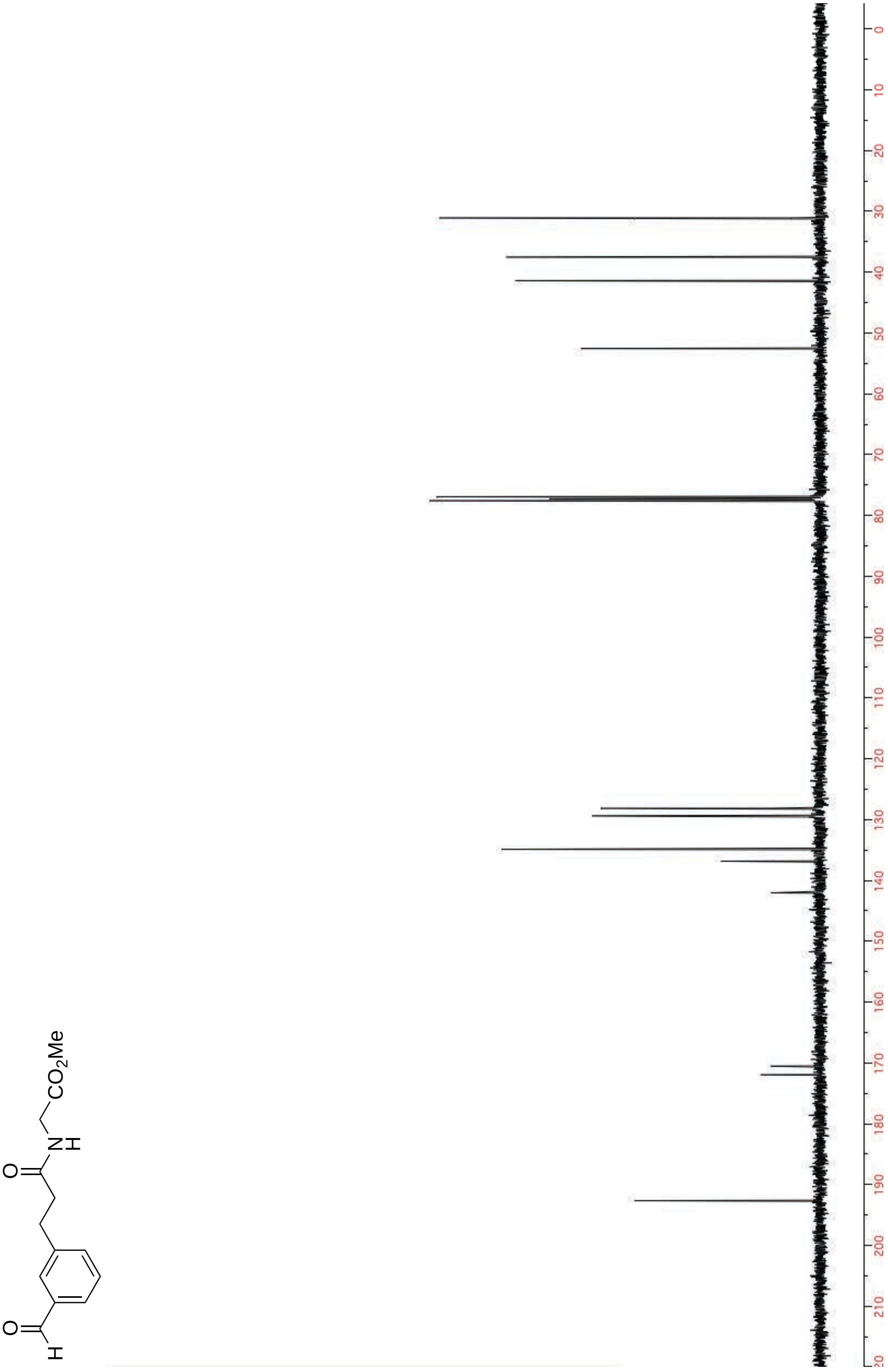
O
N
S
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
0



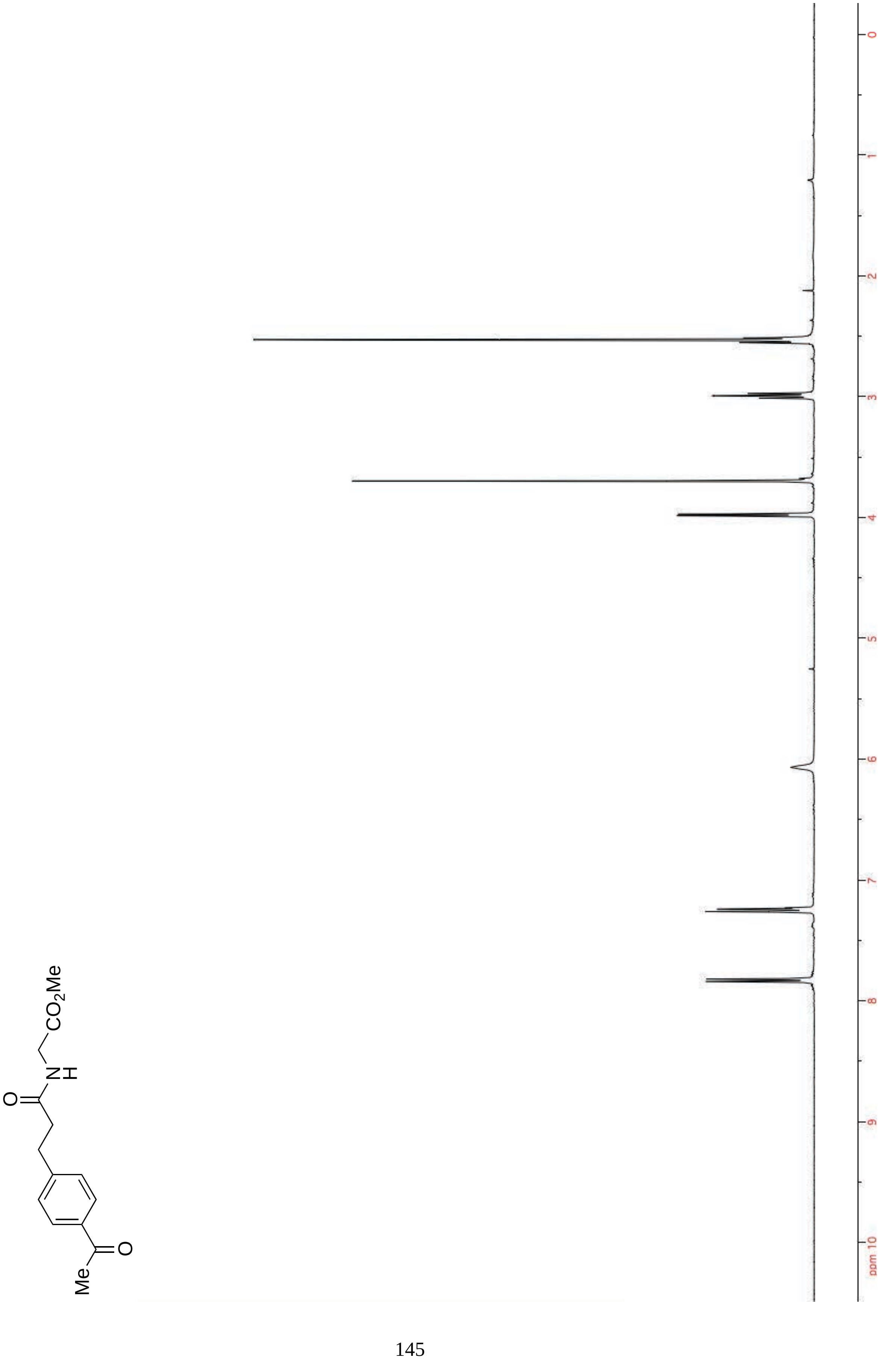
O
N
H
CO$_2$Me
O$_2$N
ppm
10
9
8
7
6
5
4
3
2
1
0


O2N
O
N
H
CO2Me
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

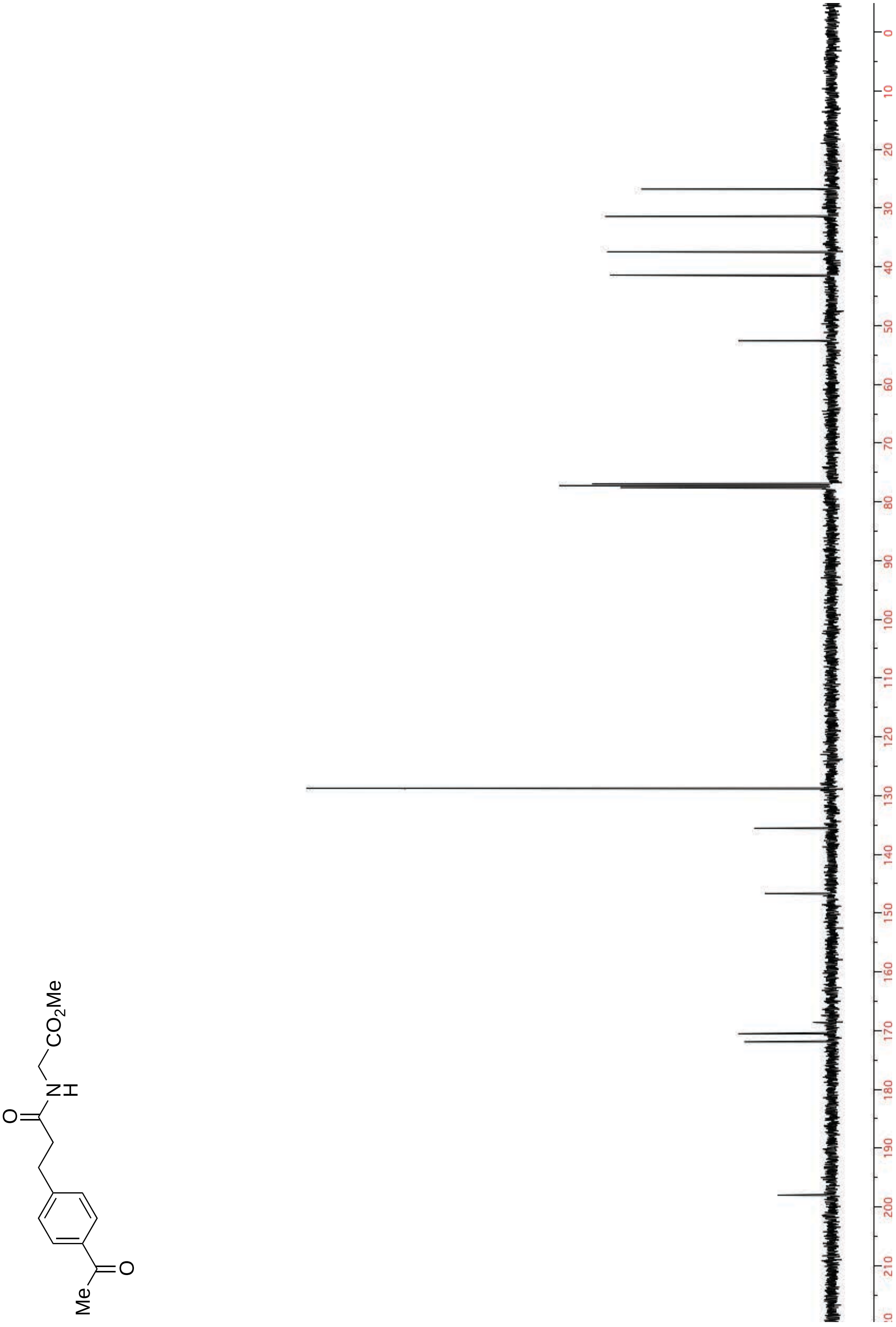

H
O
N
H
O
CO2Me
ppm 10
9
8
7
6
5
4
3
2
1
0

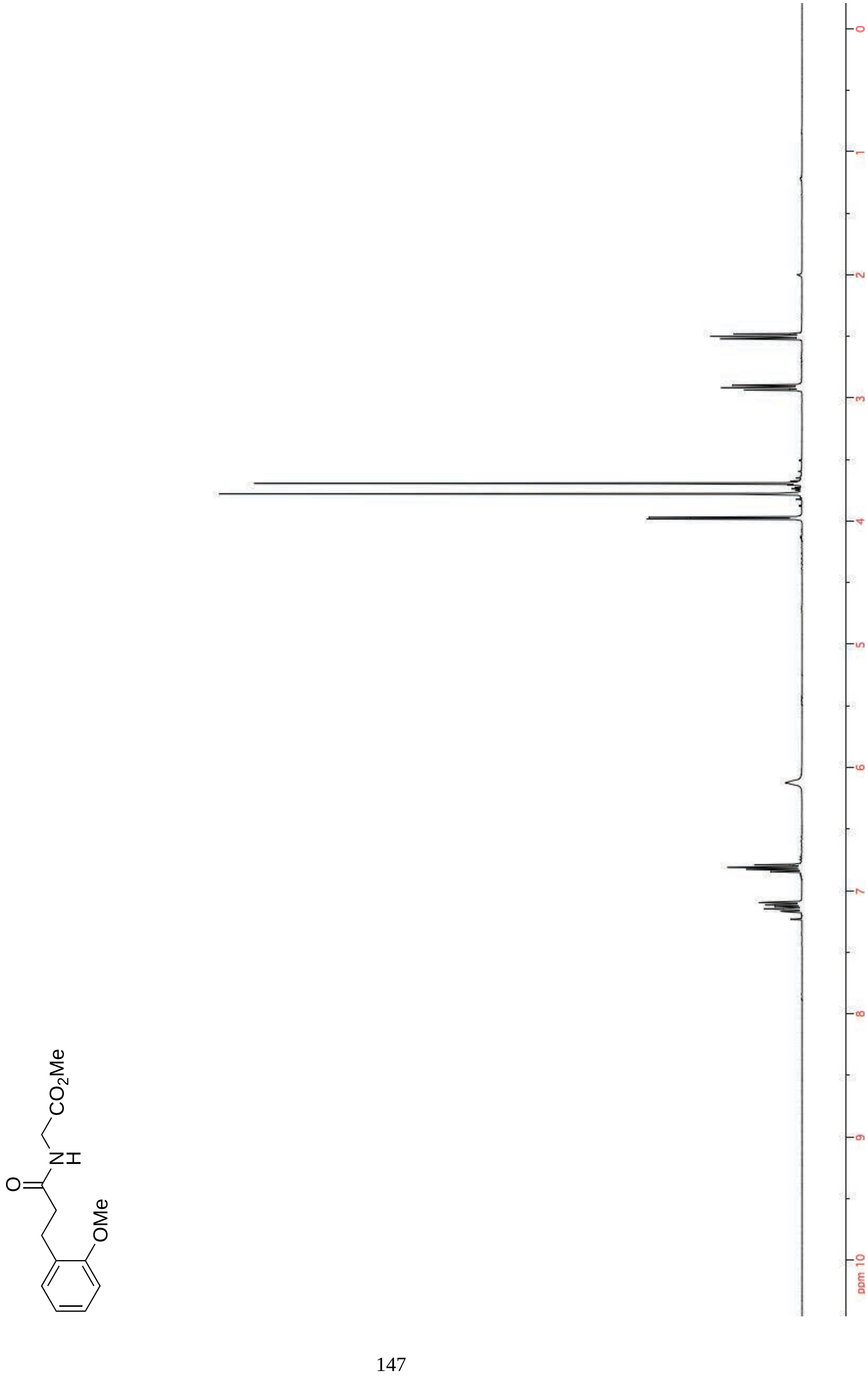


CO2Me
N
H
O
O
H
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

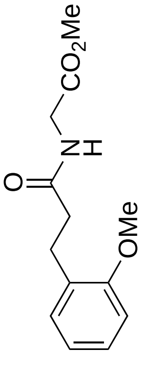


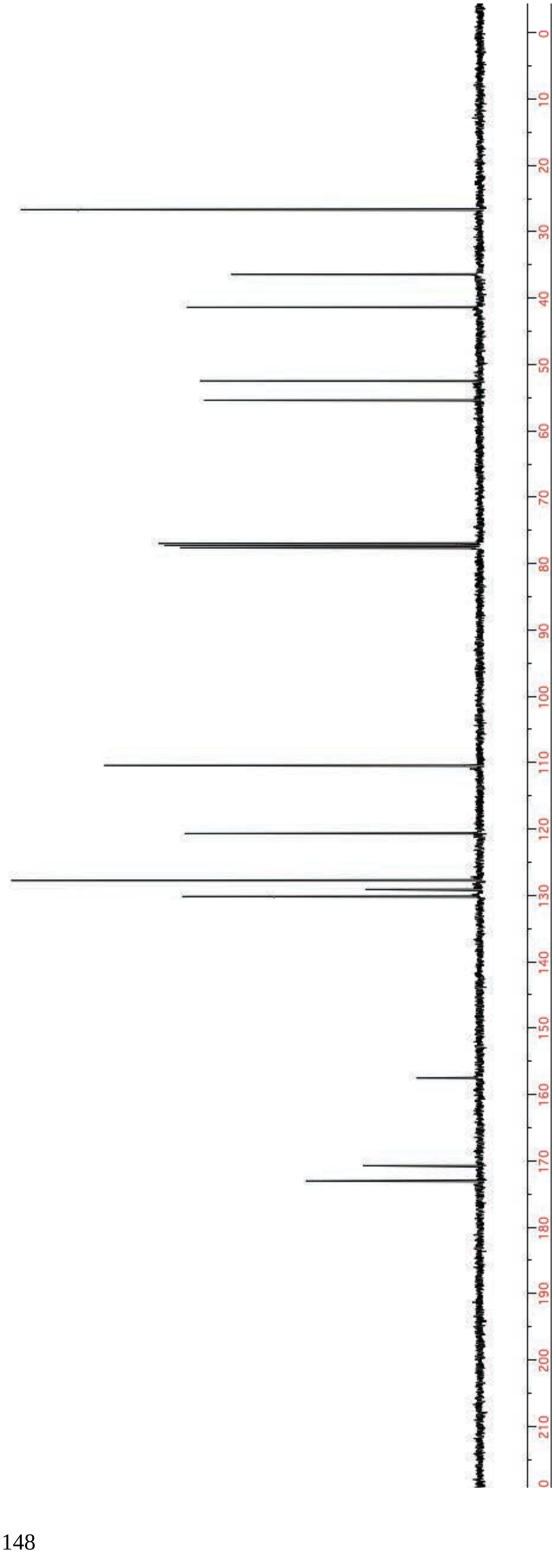
Me
O
O
N
H
CO_2Me
ppm 10
9
8
7
6
5
4
3
2
1
0

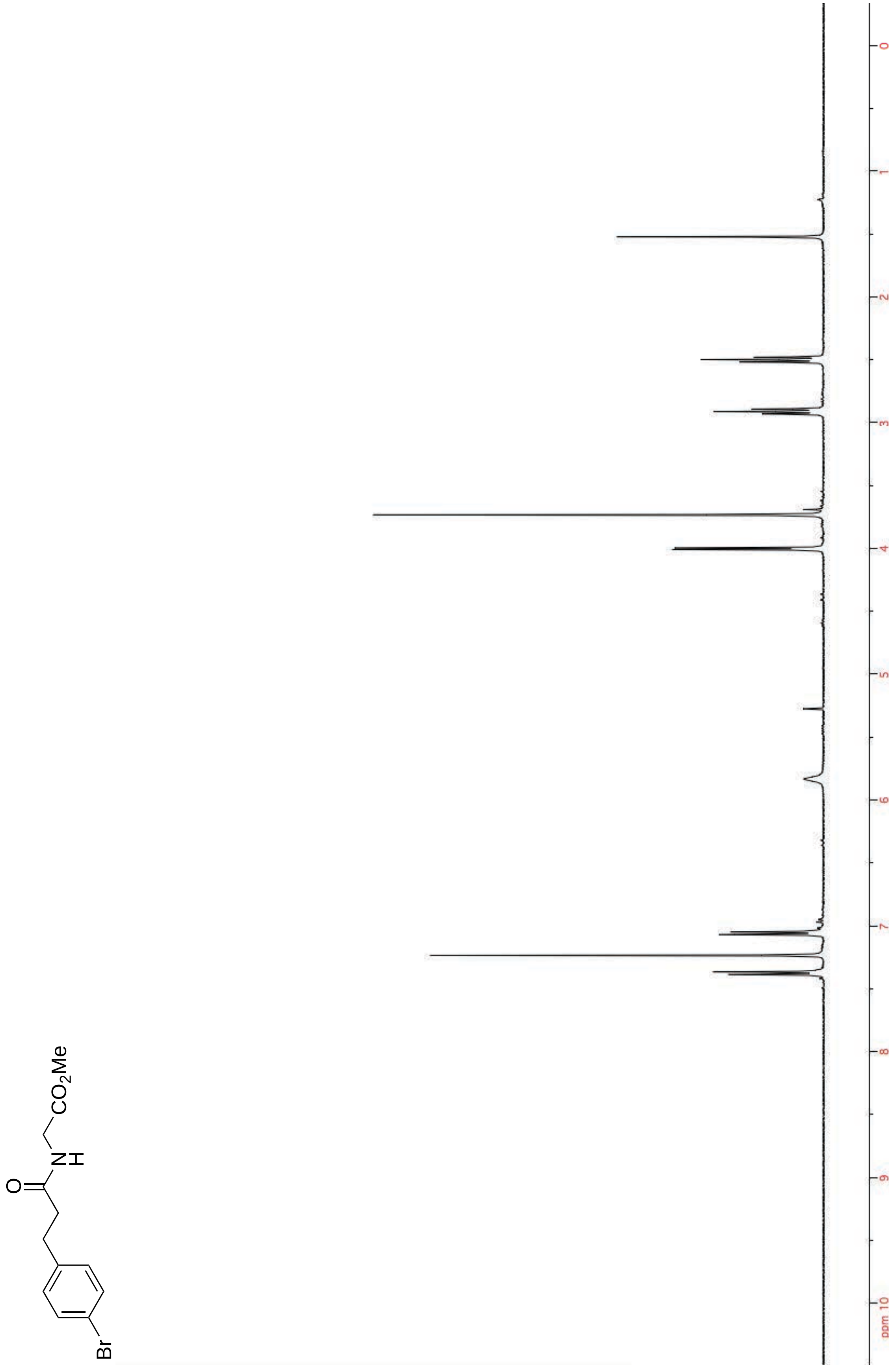

Me
O
N
H
CO2Me
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

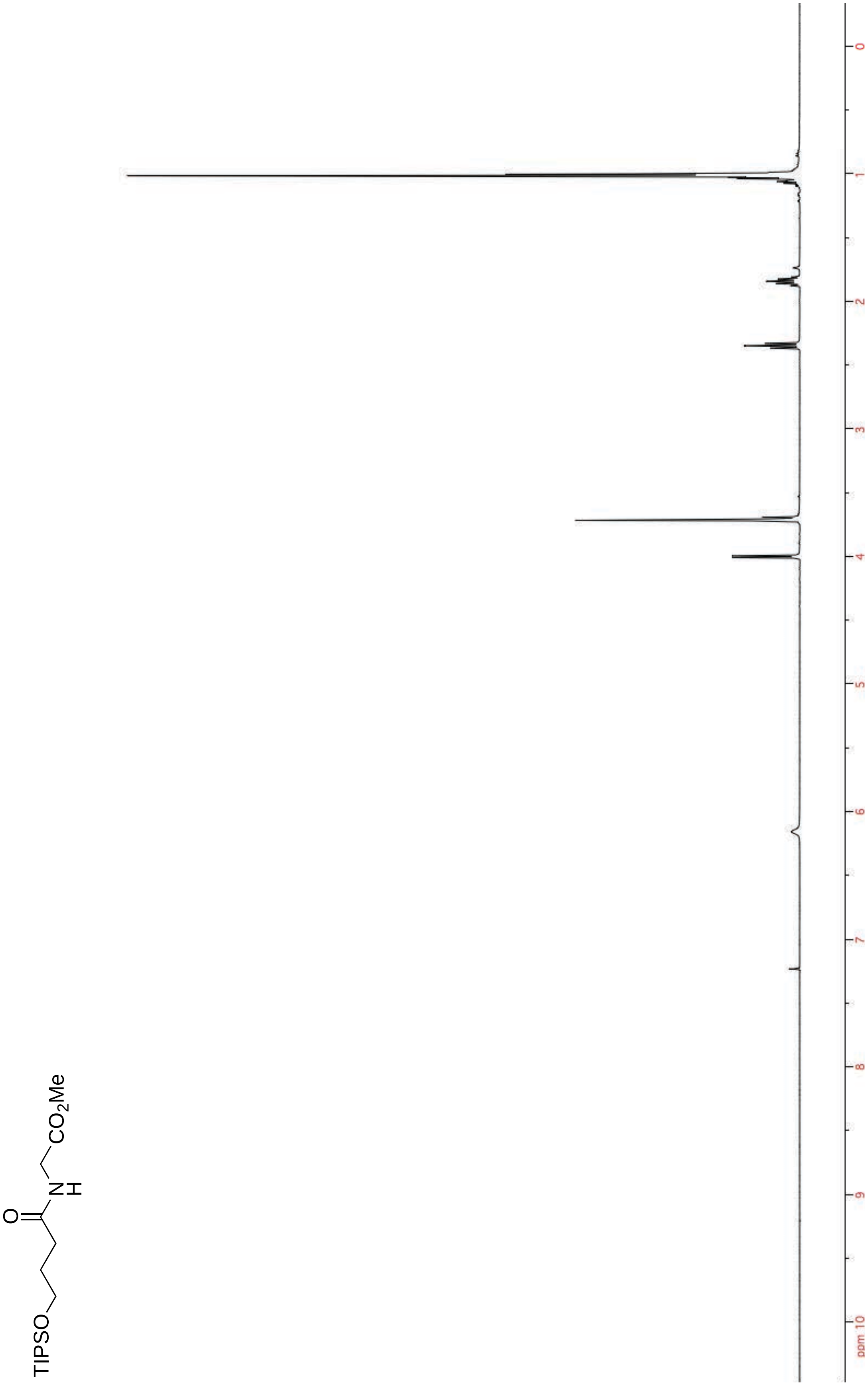


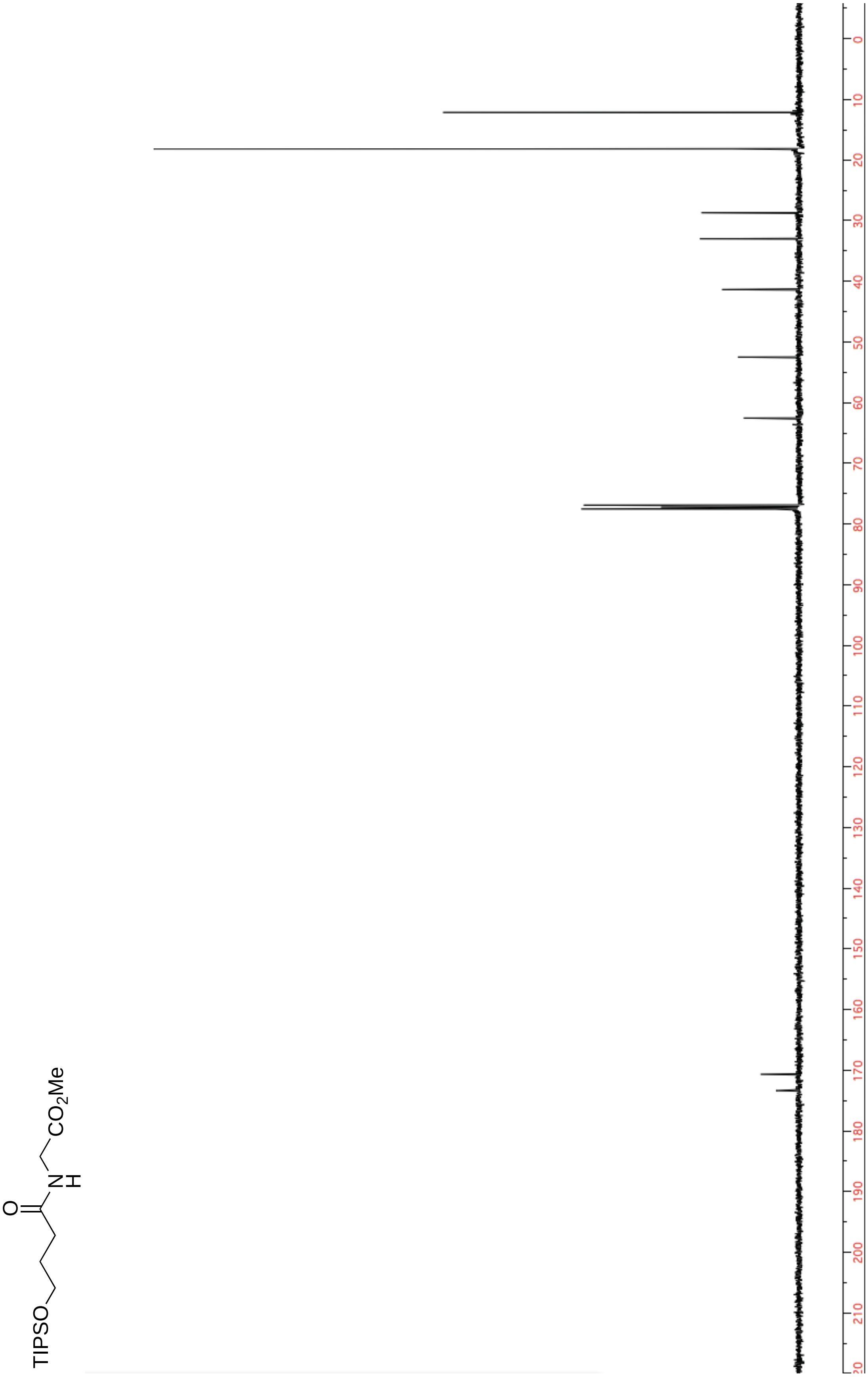
CO2Me
N
H
O
OMe
ppm 10
9
8
7
6
5
4
3
2
1
0

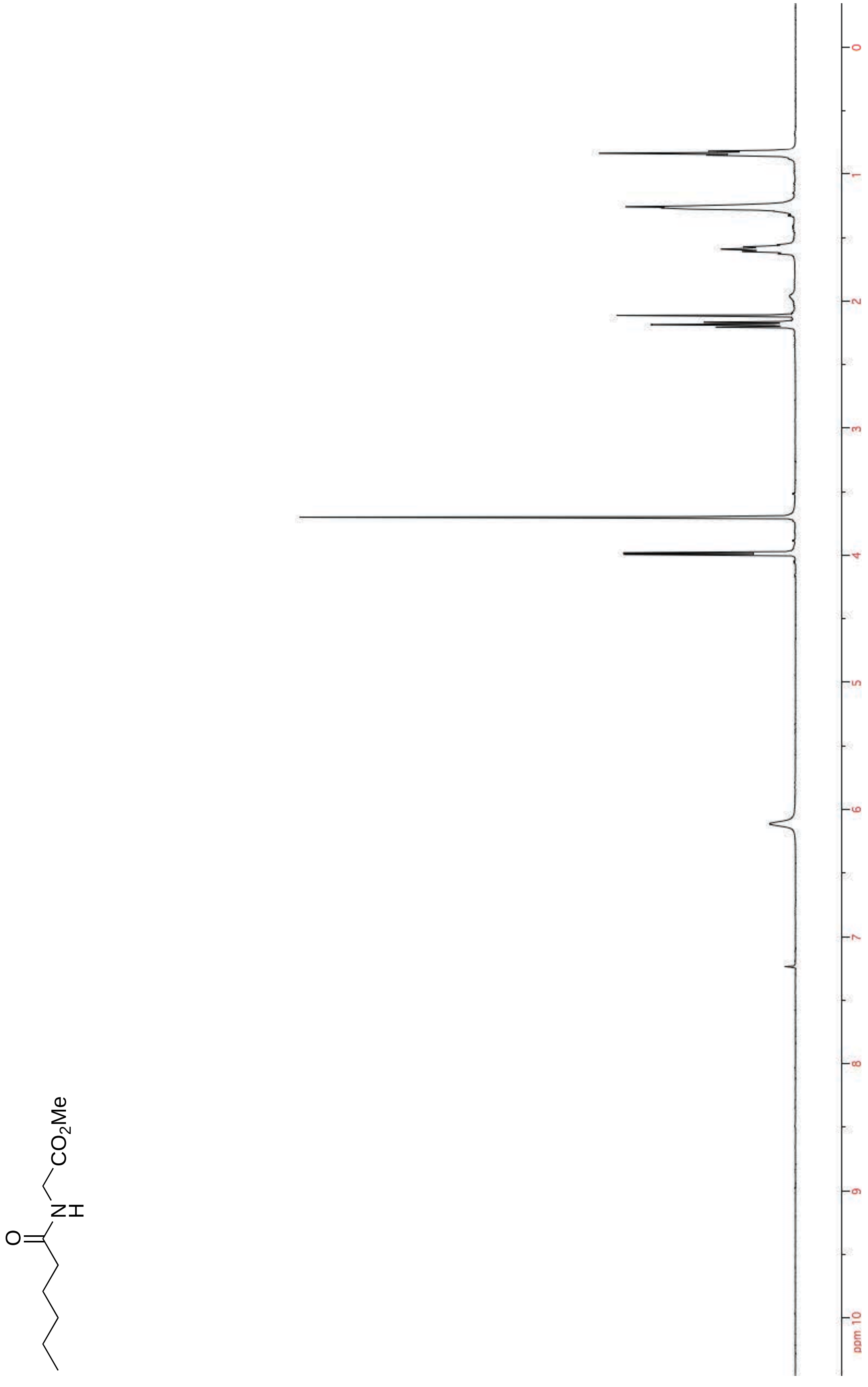

O
N
H
CO2Me
OMe

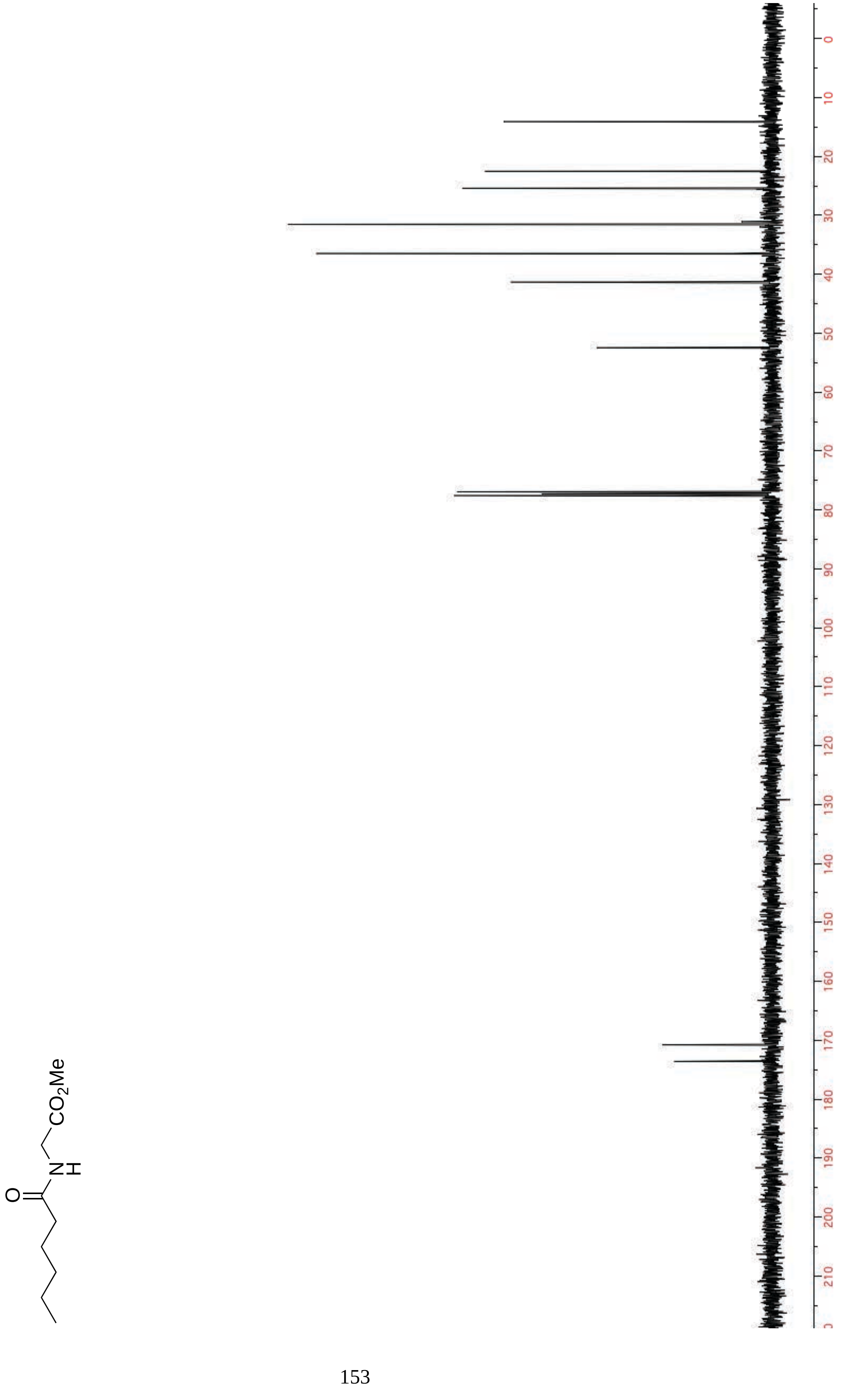

0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

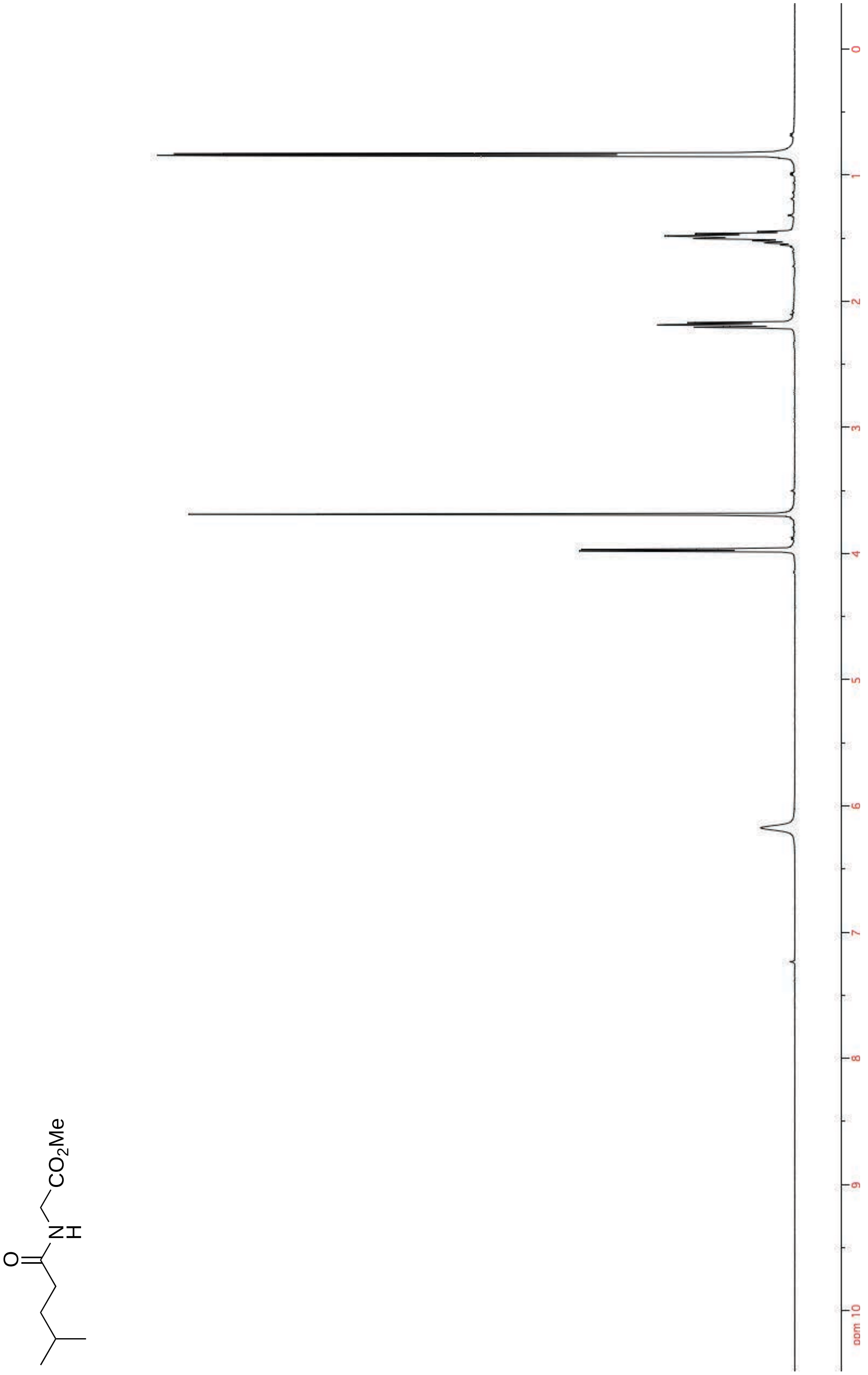

Br
O
N
H
CO2Me
ppm 10
9
8
7
6
5
4
3
2
1
0

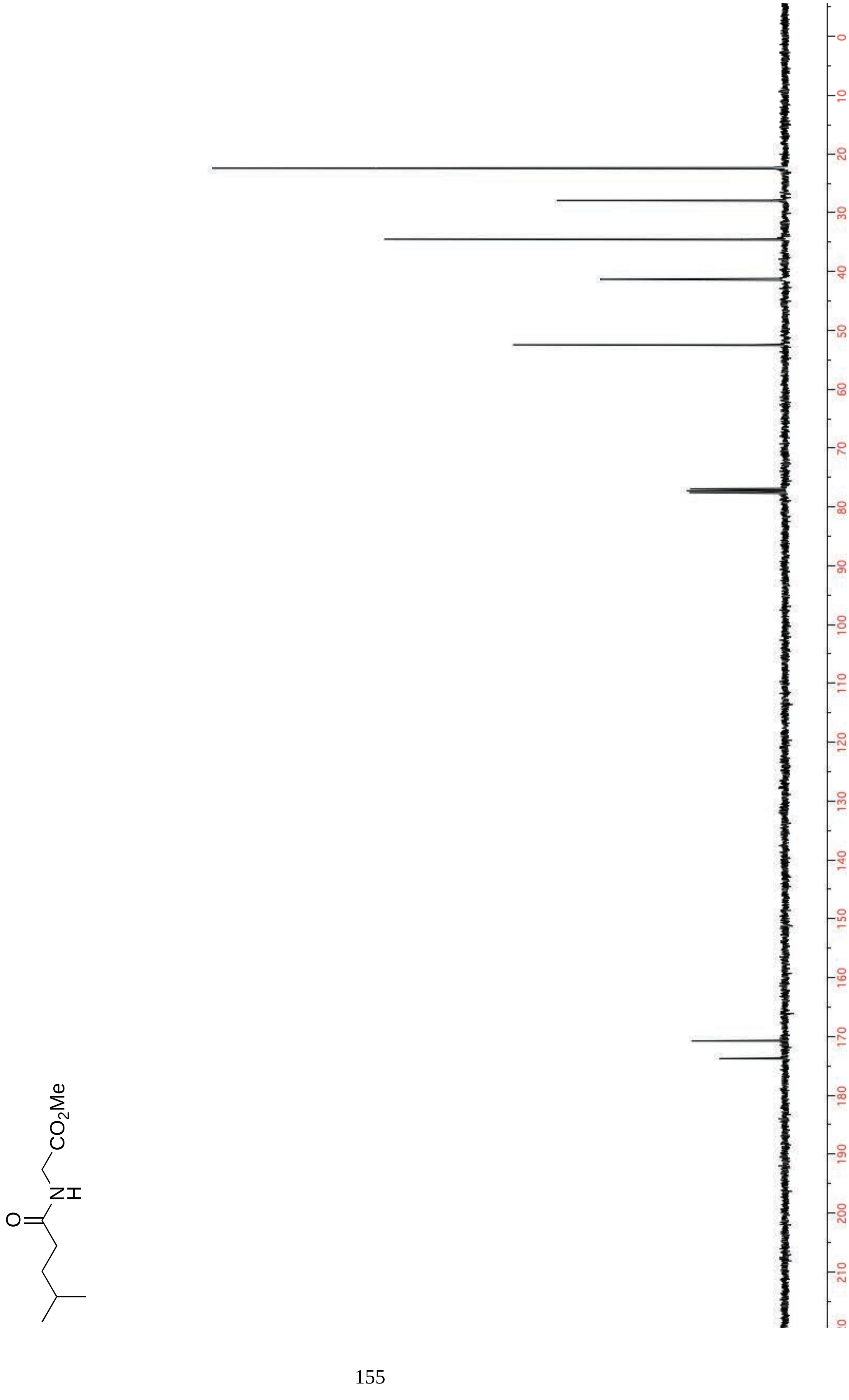

TIPSO
O
N
H
CO2Me
ppm 10
9
8
7
6
5
4
3
2
1
0


TIPSO
O
N
H
CO2Me
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

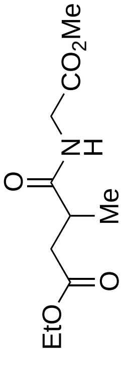

O
N
H
CO2Me
0
1
2
3
4
5
6
7
8
9
ppm 10

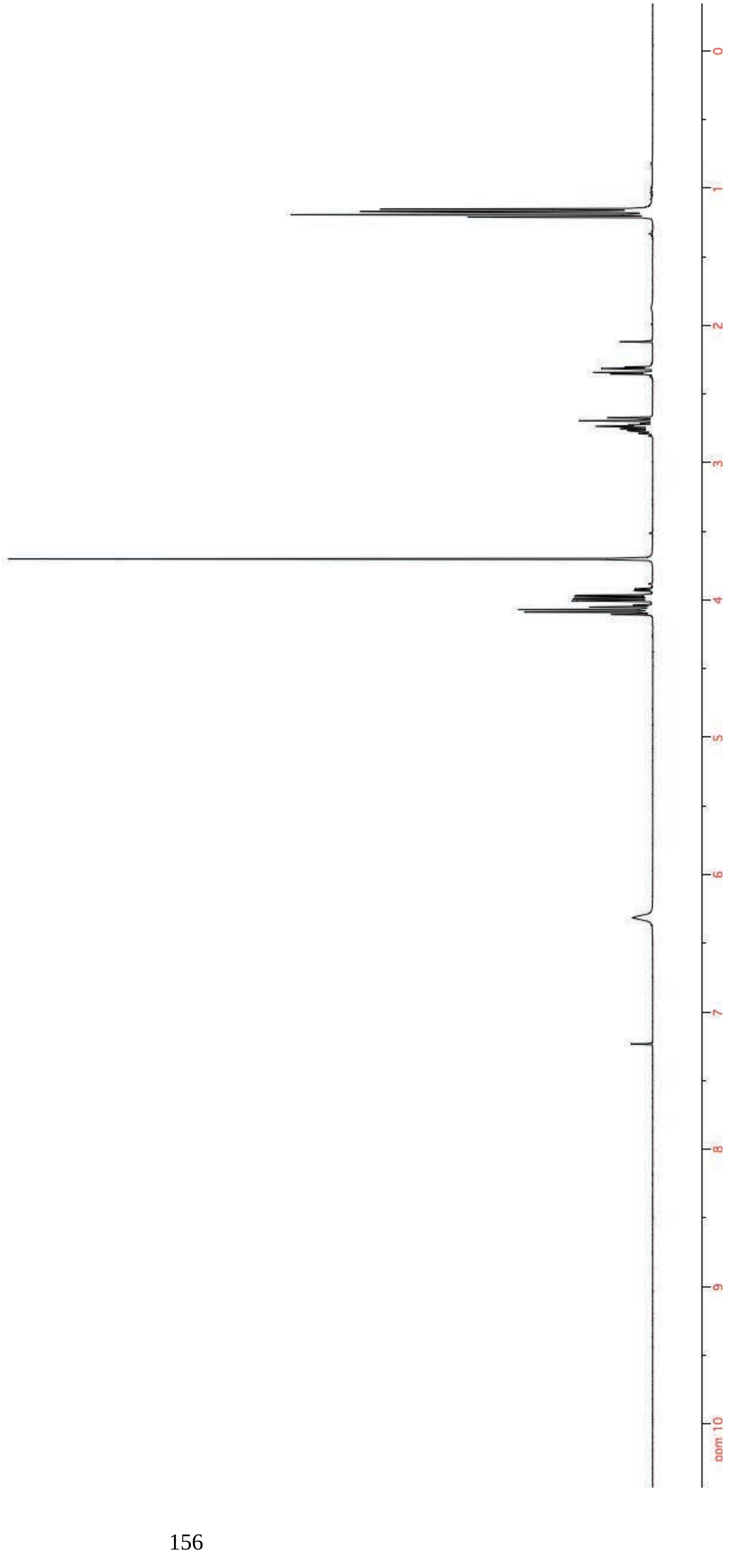

O
N
H
CO2Me
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

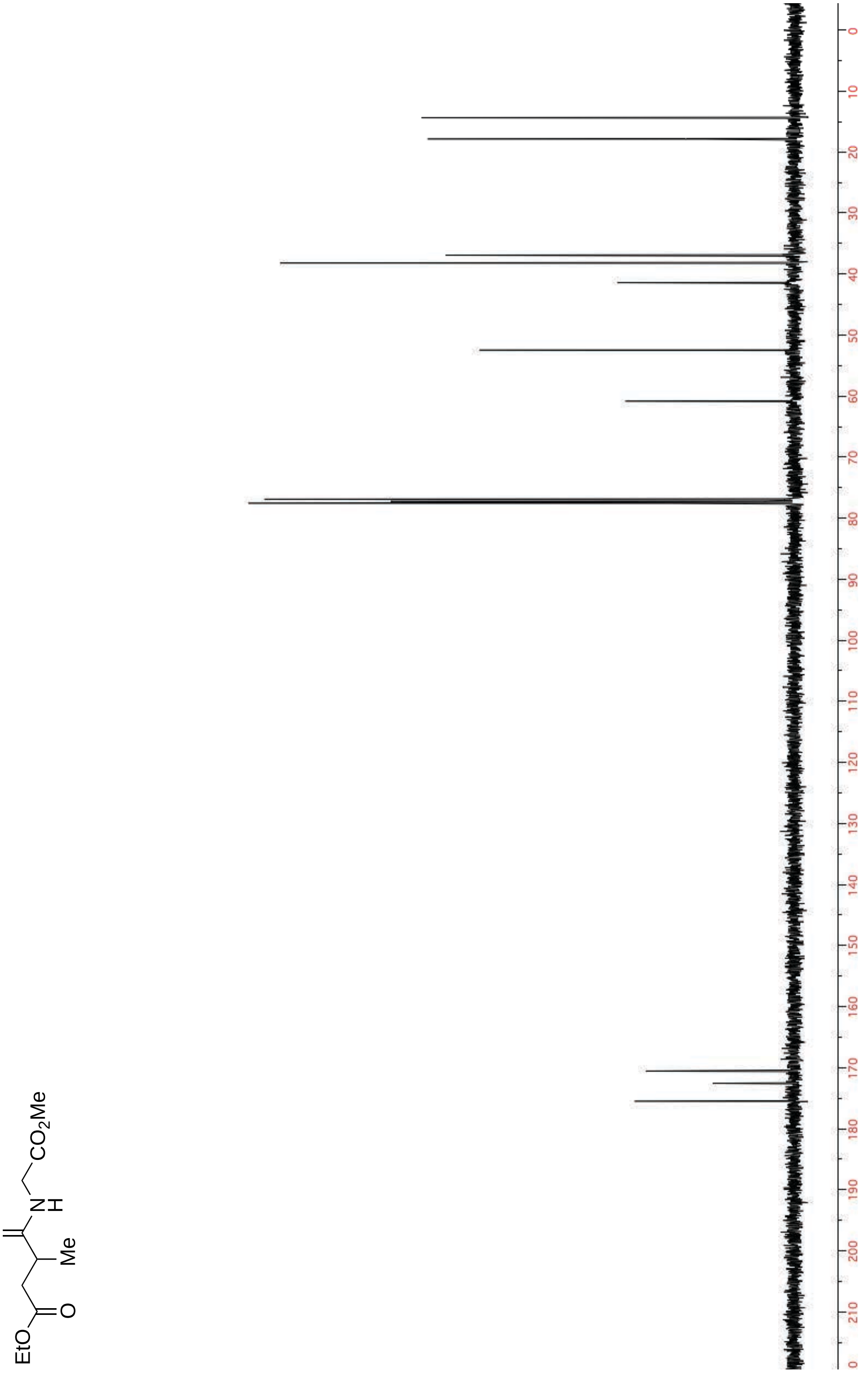

O
N
H
CO2Me
ppm
10
9
8
7
6
5
4
3
2
1
0



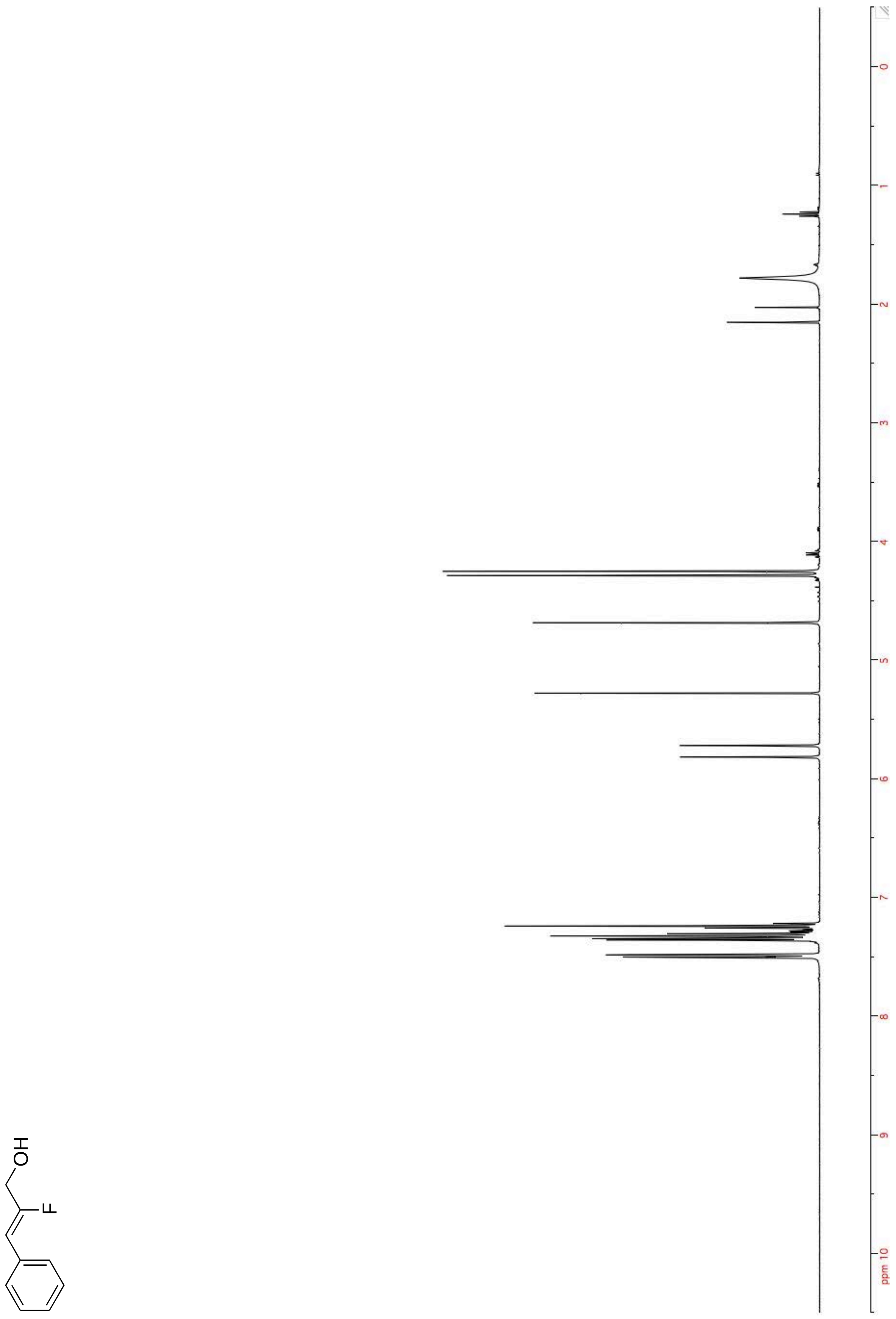
O
N
H
CO2Me
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

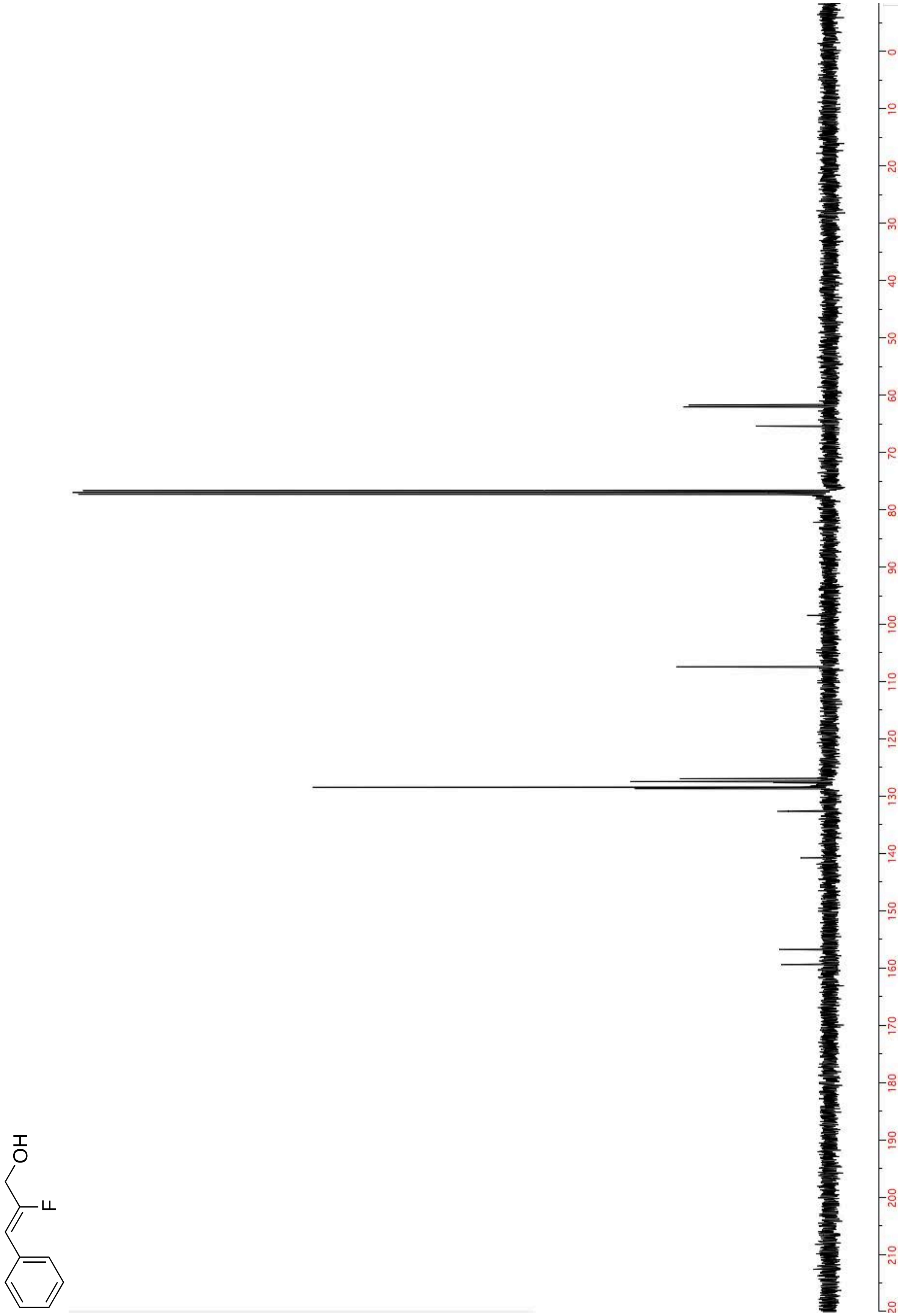

EtO
O
Me
O
N
H
CO2Me

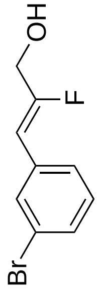

0
1
2
3
4
5
6
7
8
9
ppm 10

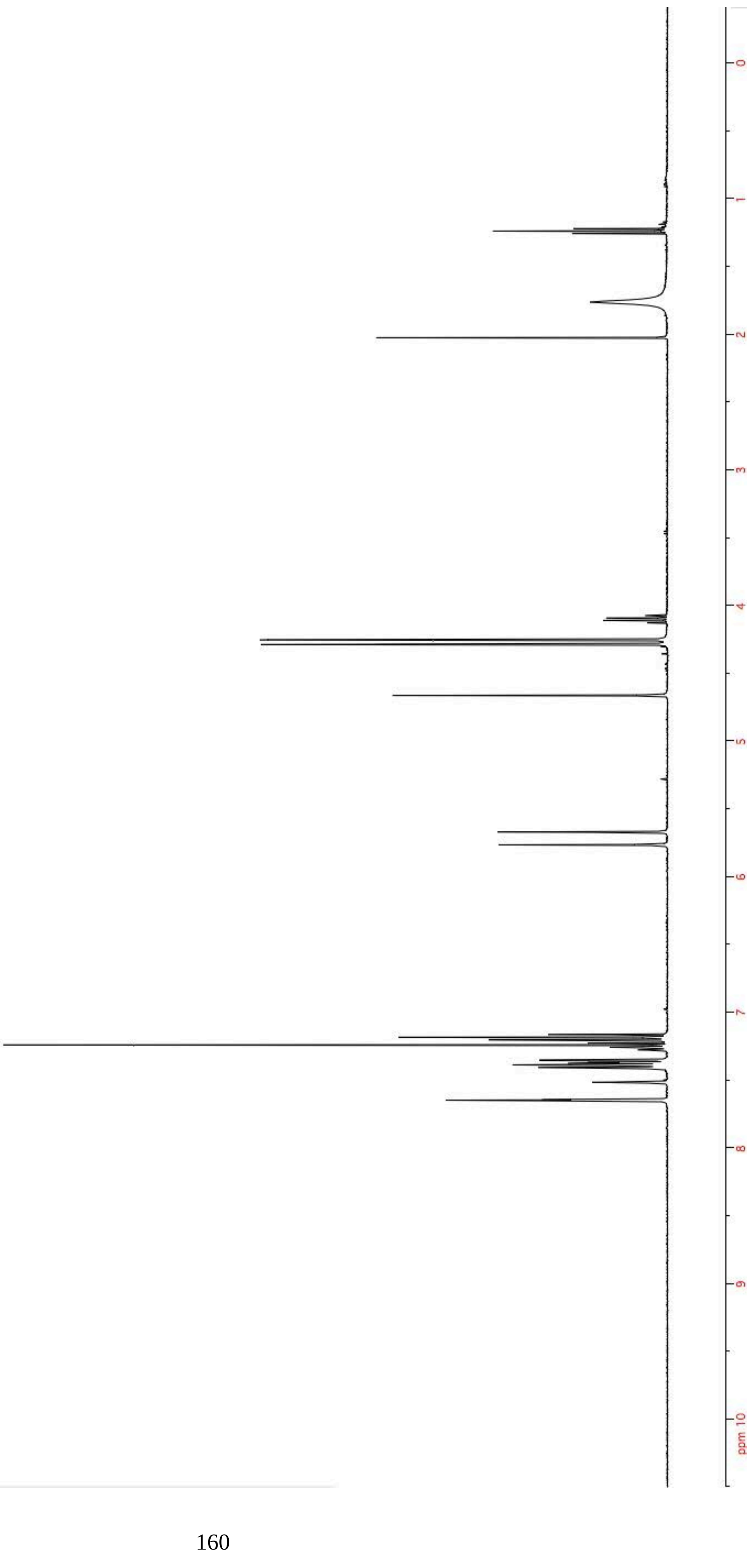


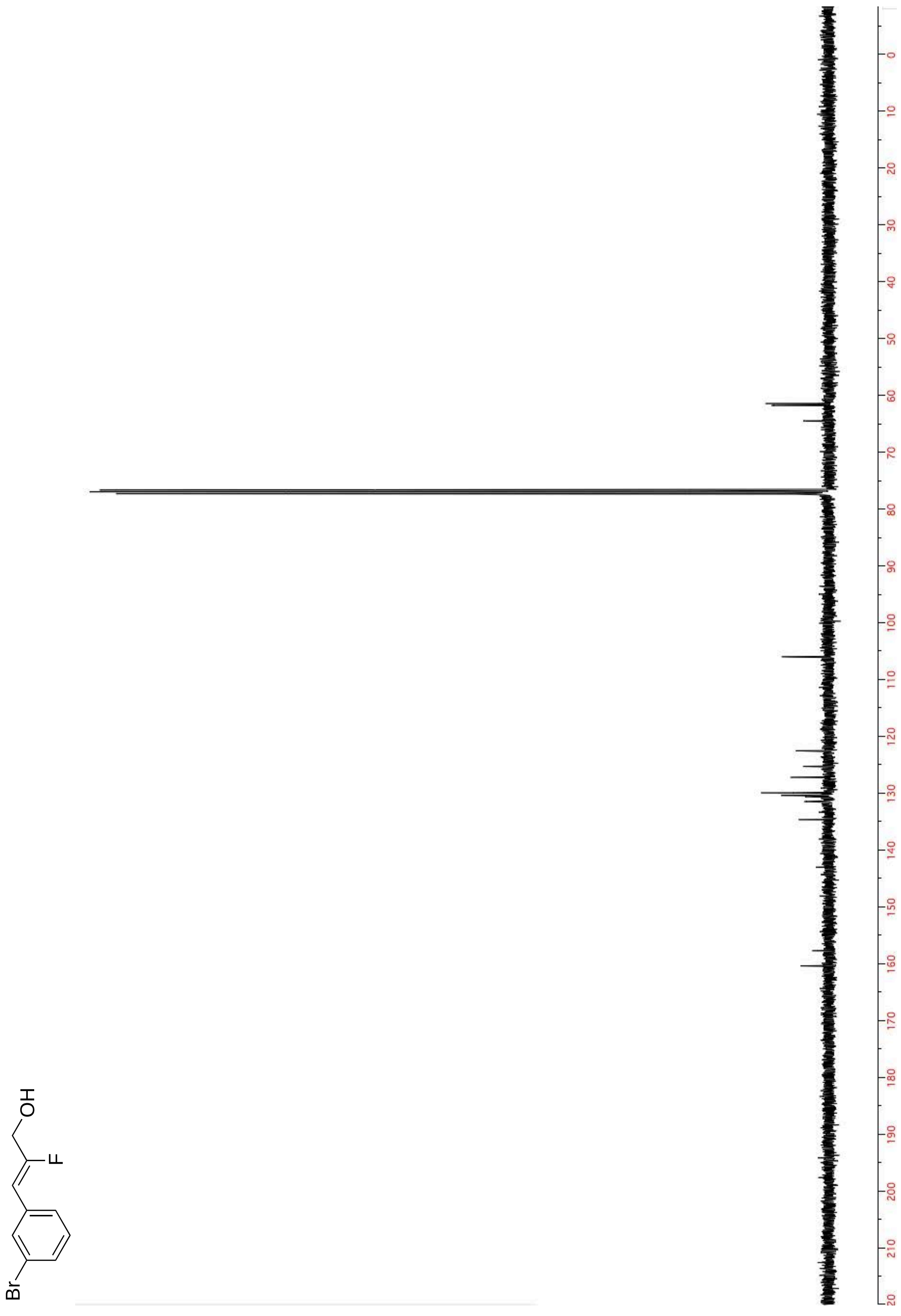
EtO
O
O
Me
N
H
CO2Me
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

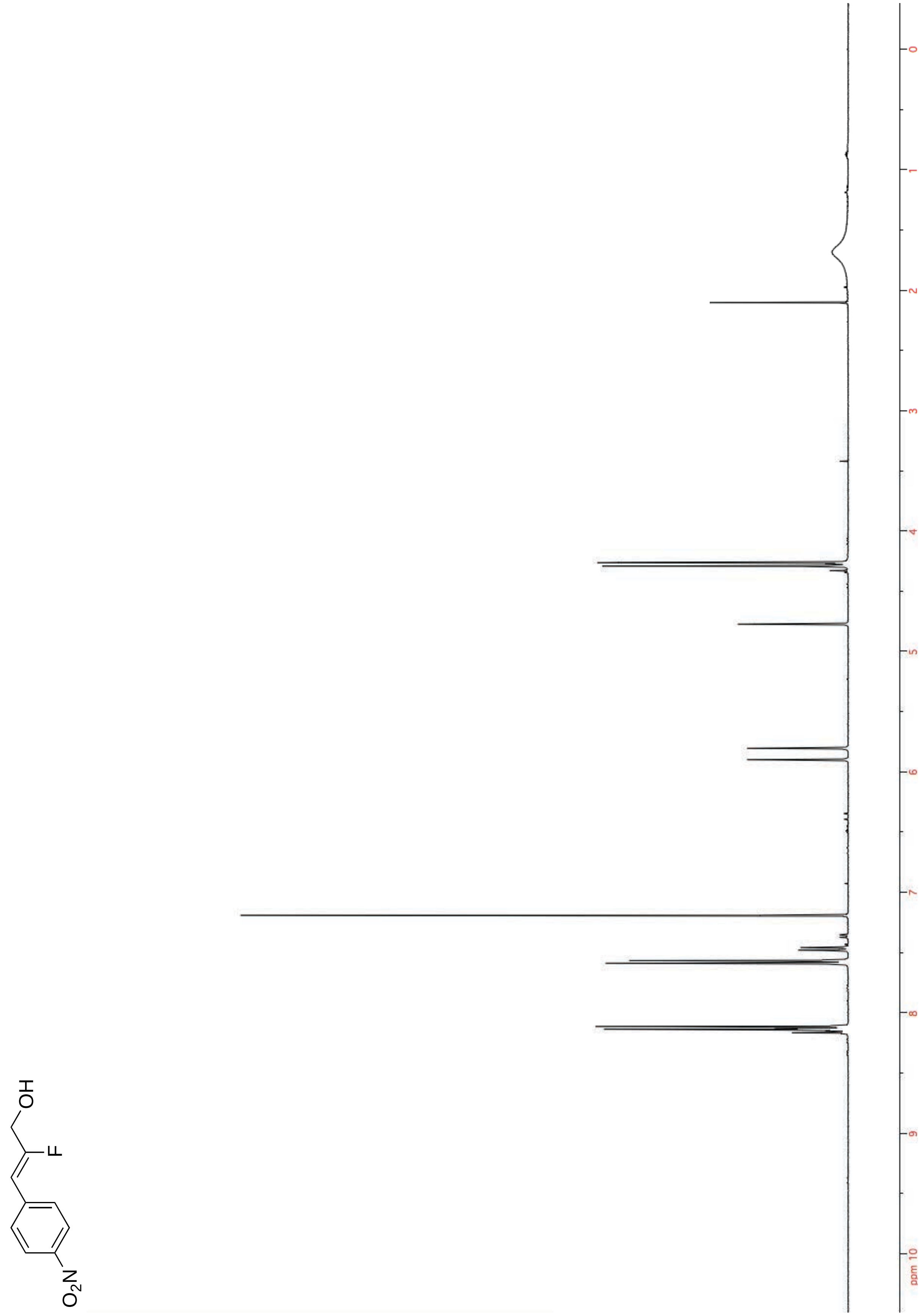

OH
F
ppm
0
1
2
3
4
5
6
7
8
9
10


F
OH
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
20

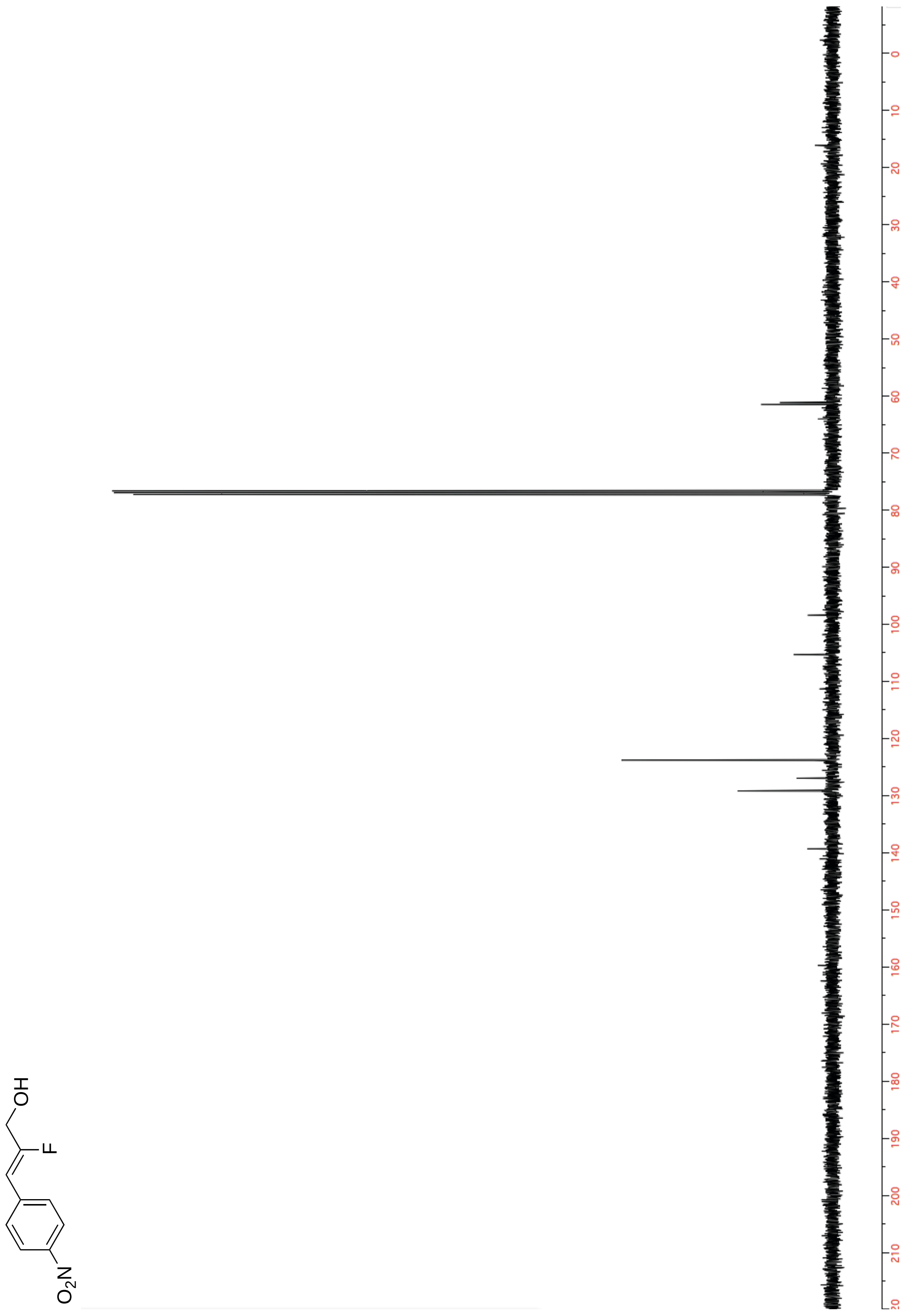

Br
F
OH

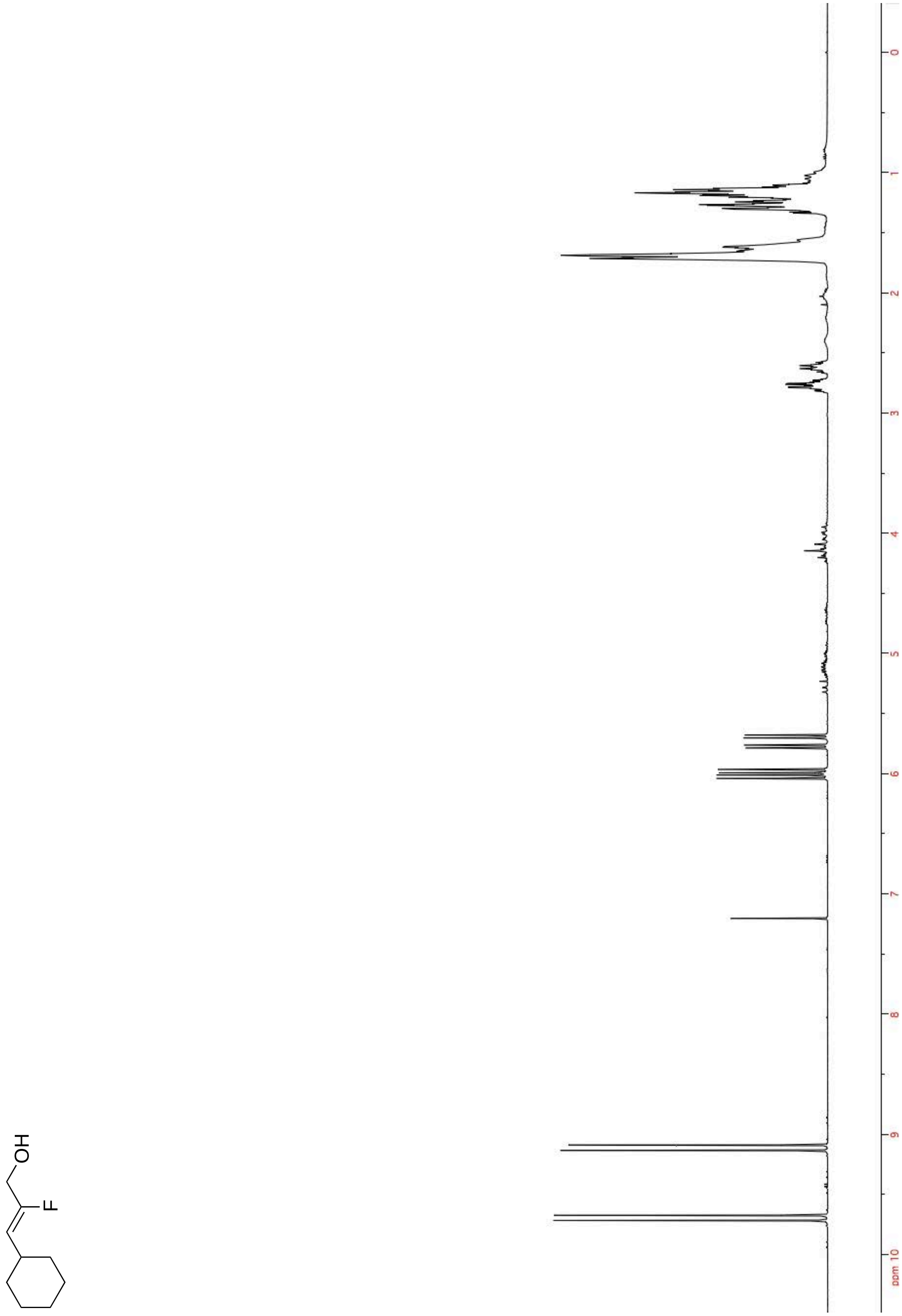

0
1
2
3
4
5
6
7
8
9
ppm 10

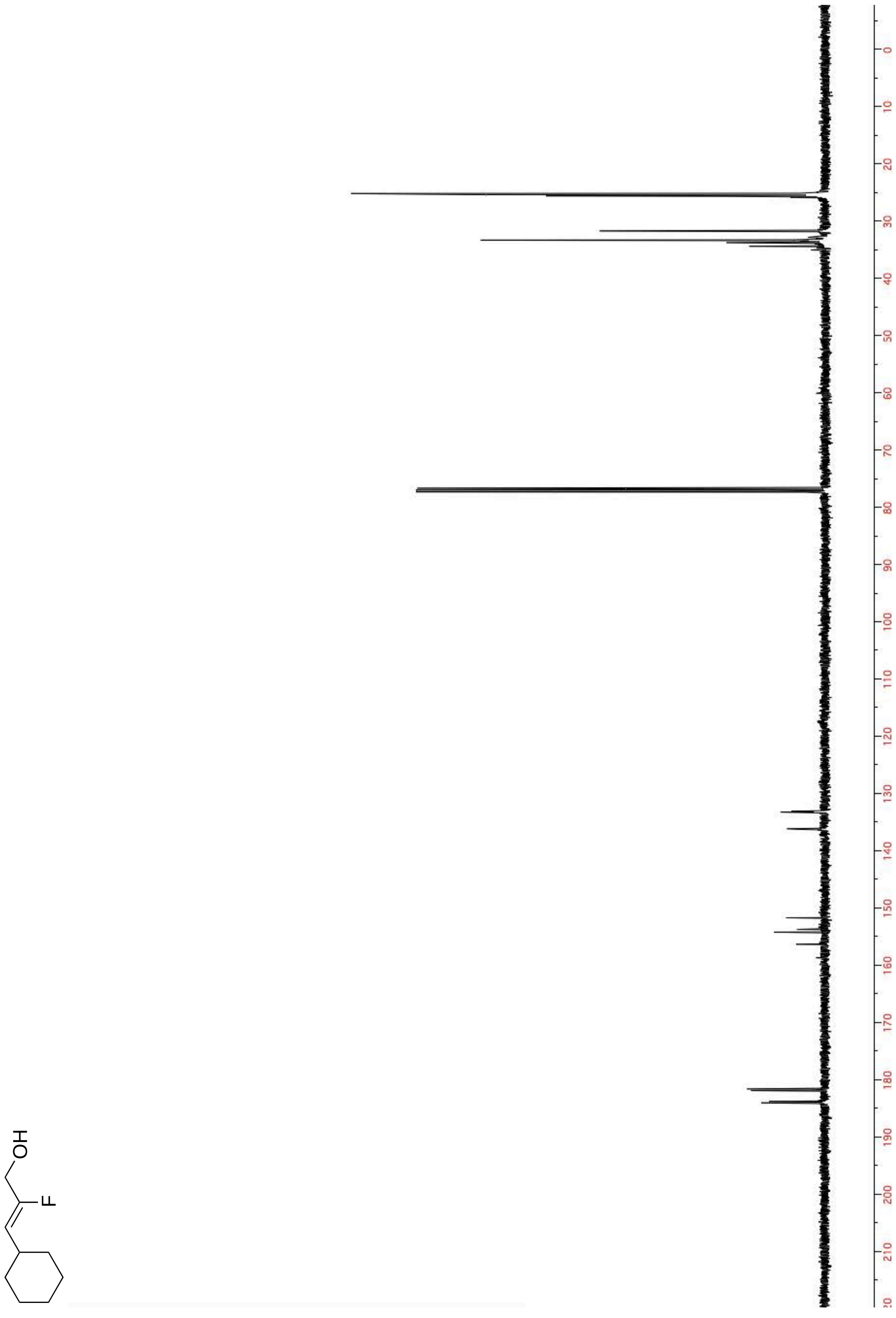

Br
F
OH
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

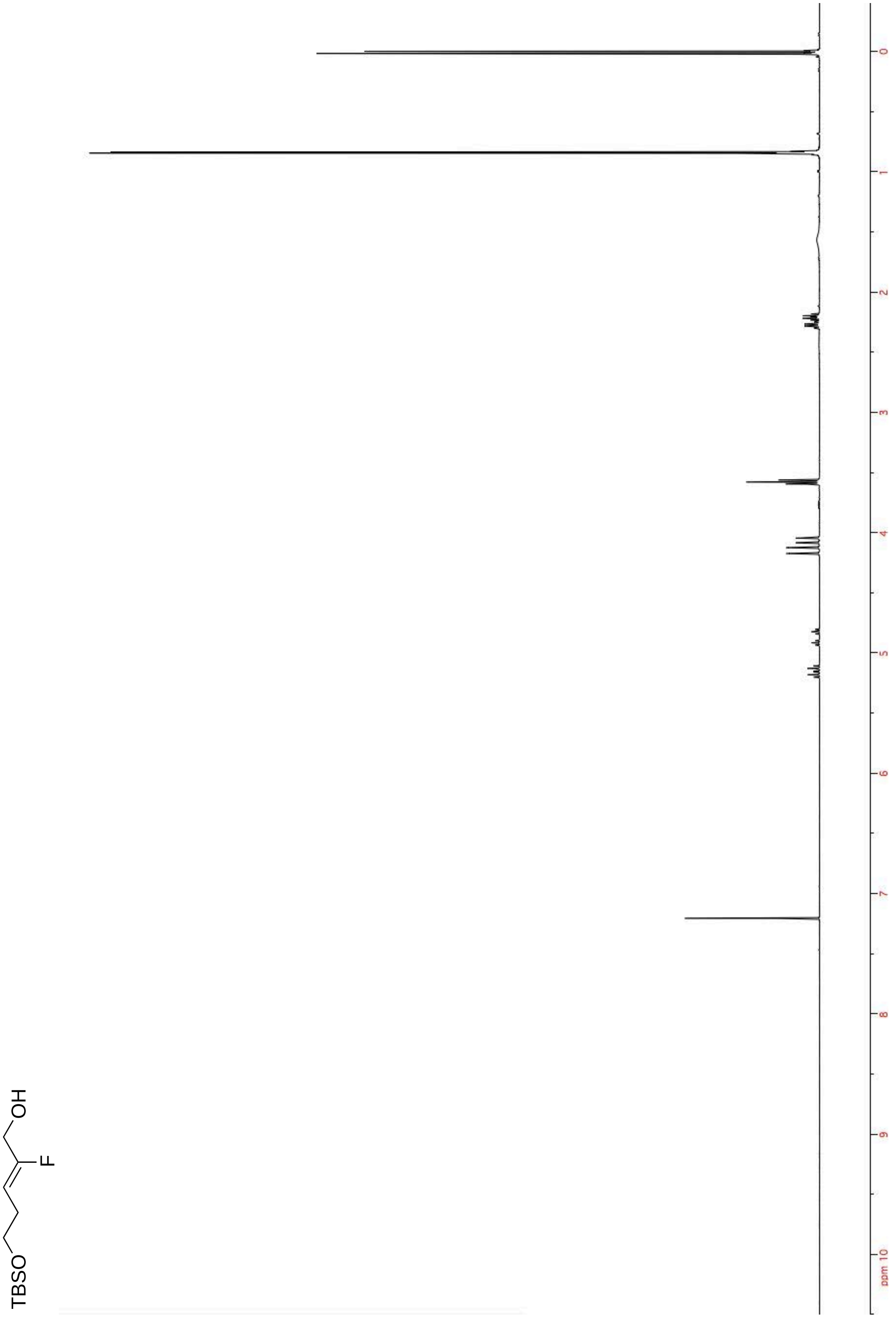


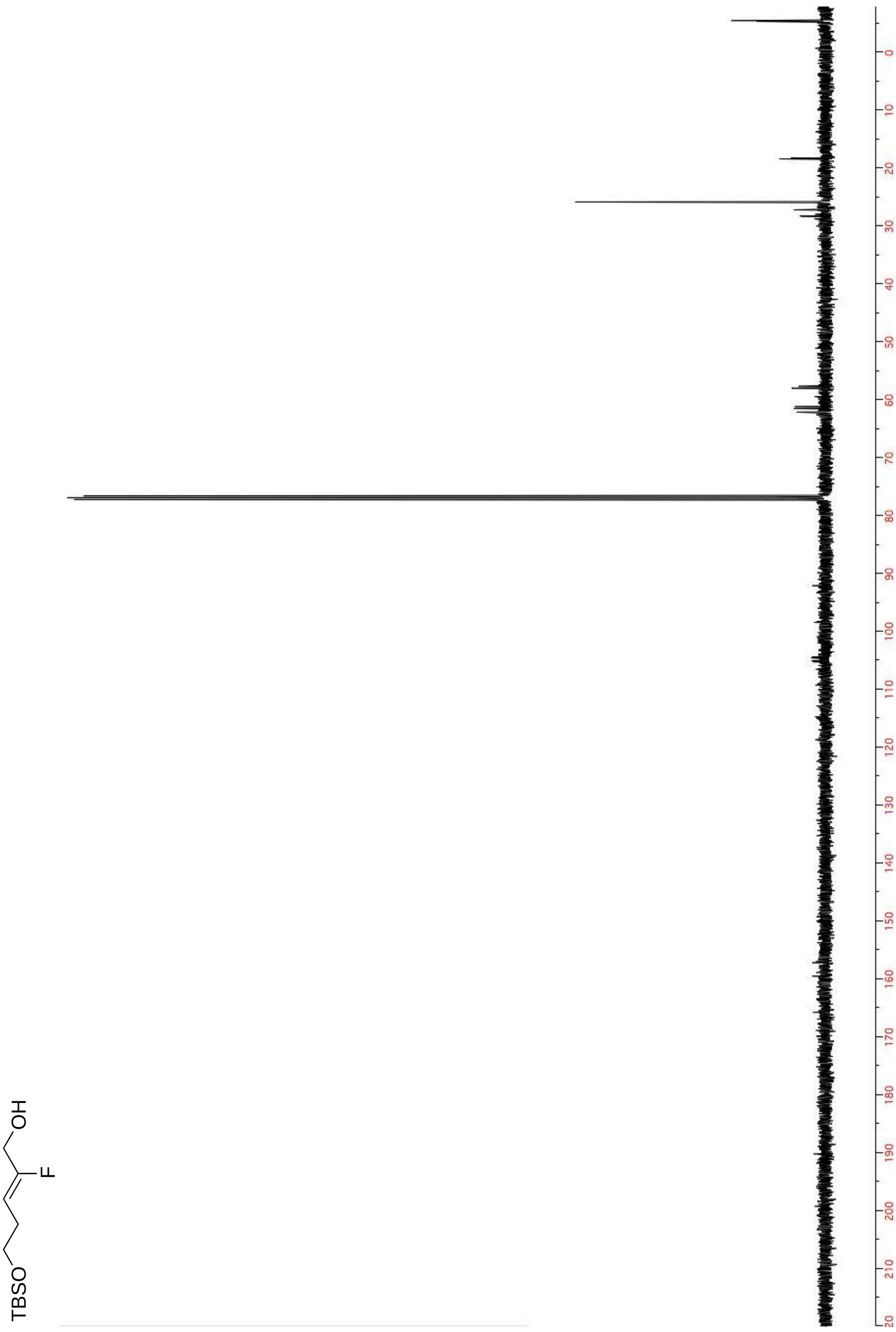
O2N
F
OH
ppm 10
9
8
7
6
5
4
3
2
1
0

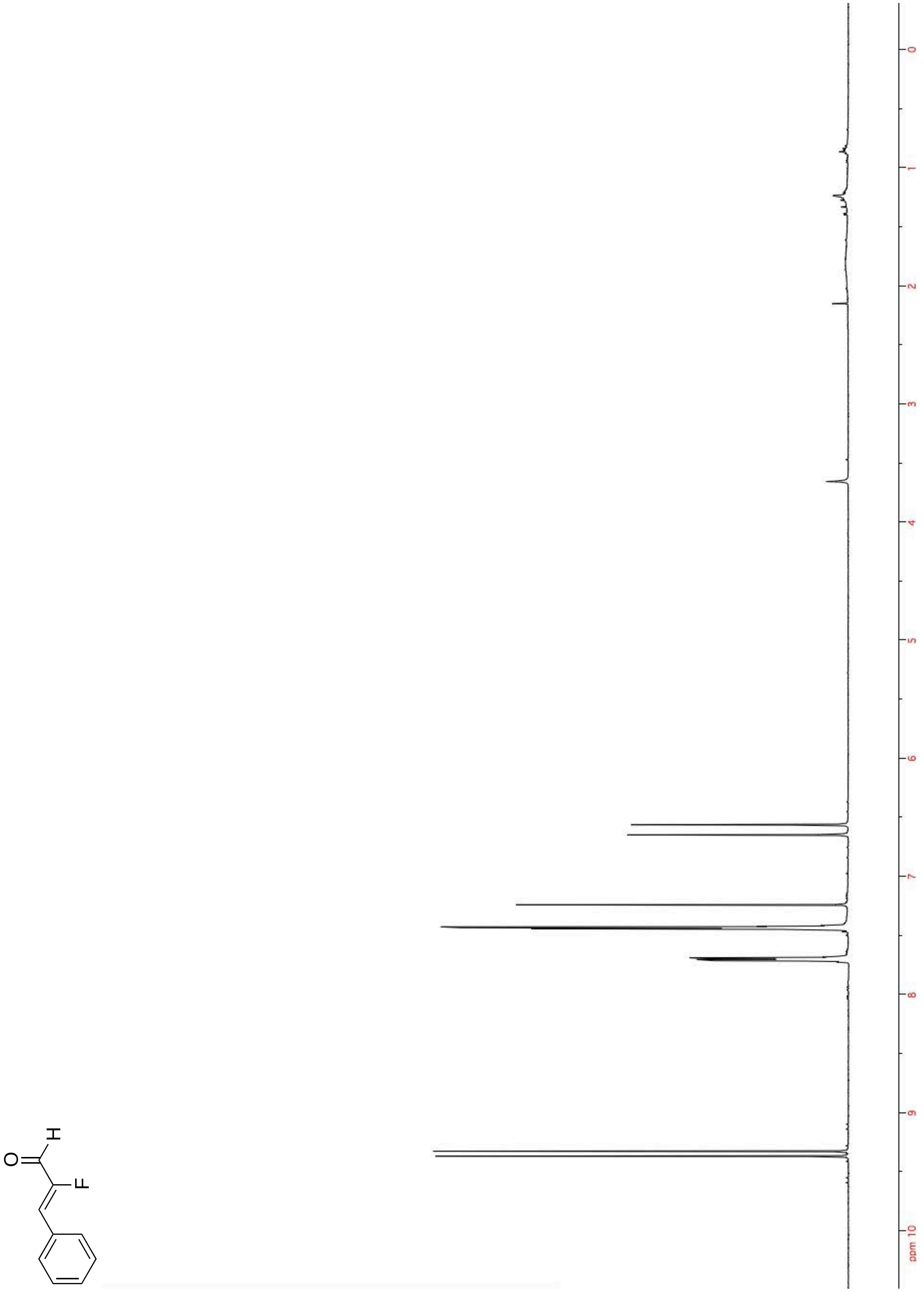

OH
F
O2N
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210


OH
F
0
1
2
3
4
5
6
7
8
9
ppm 10

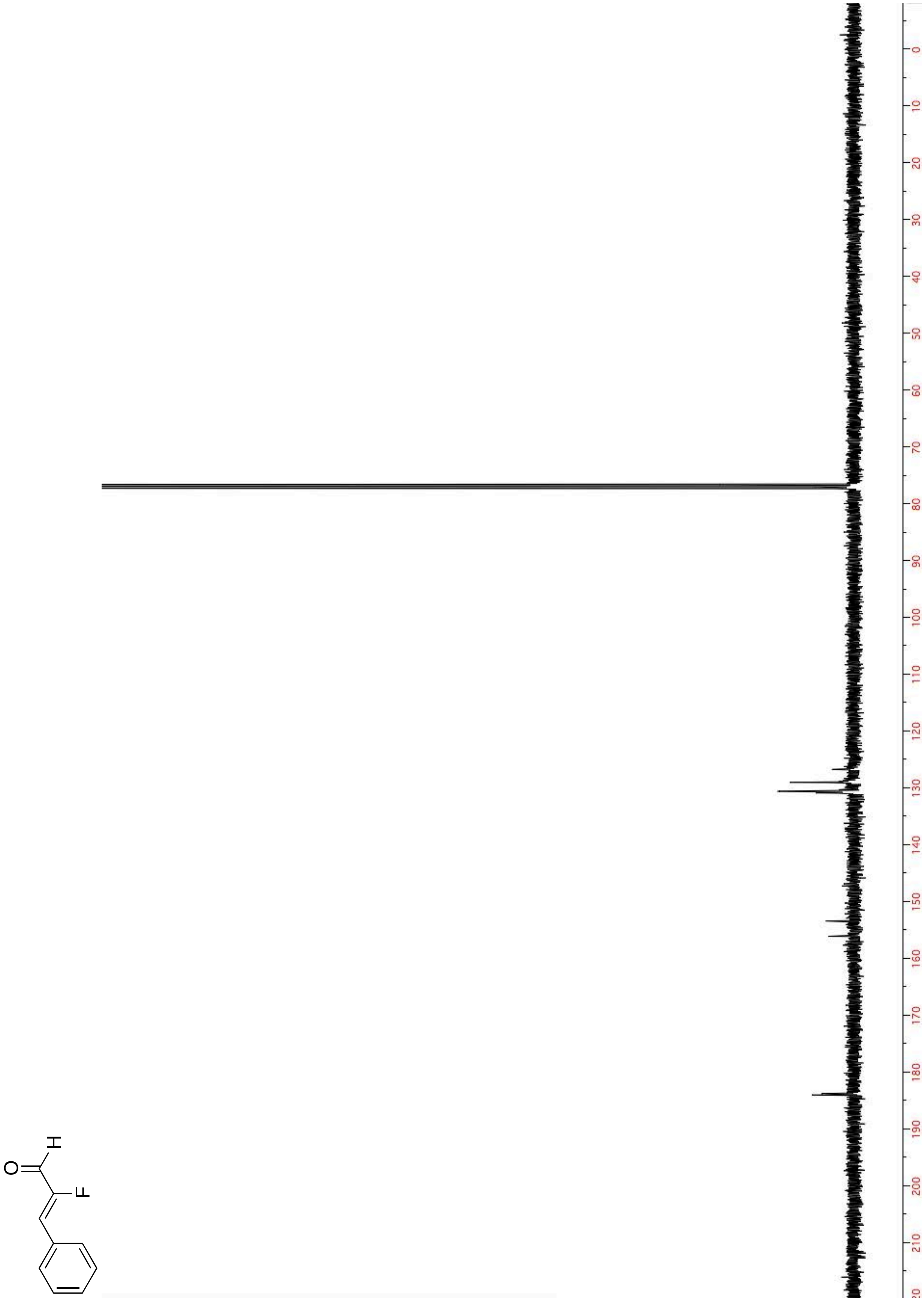

OH
F
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

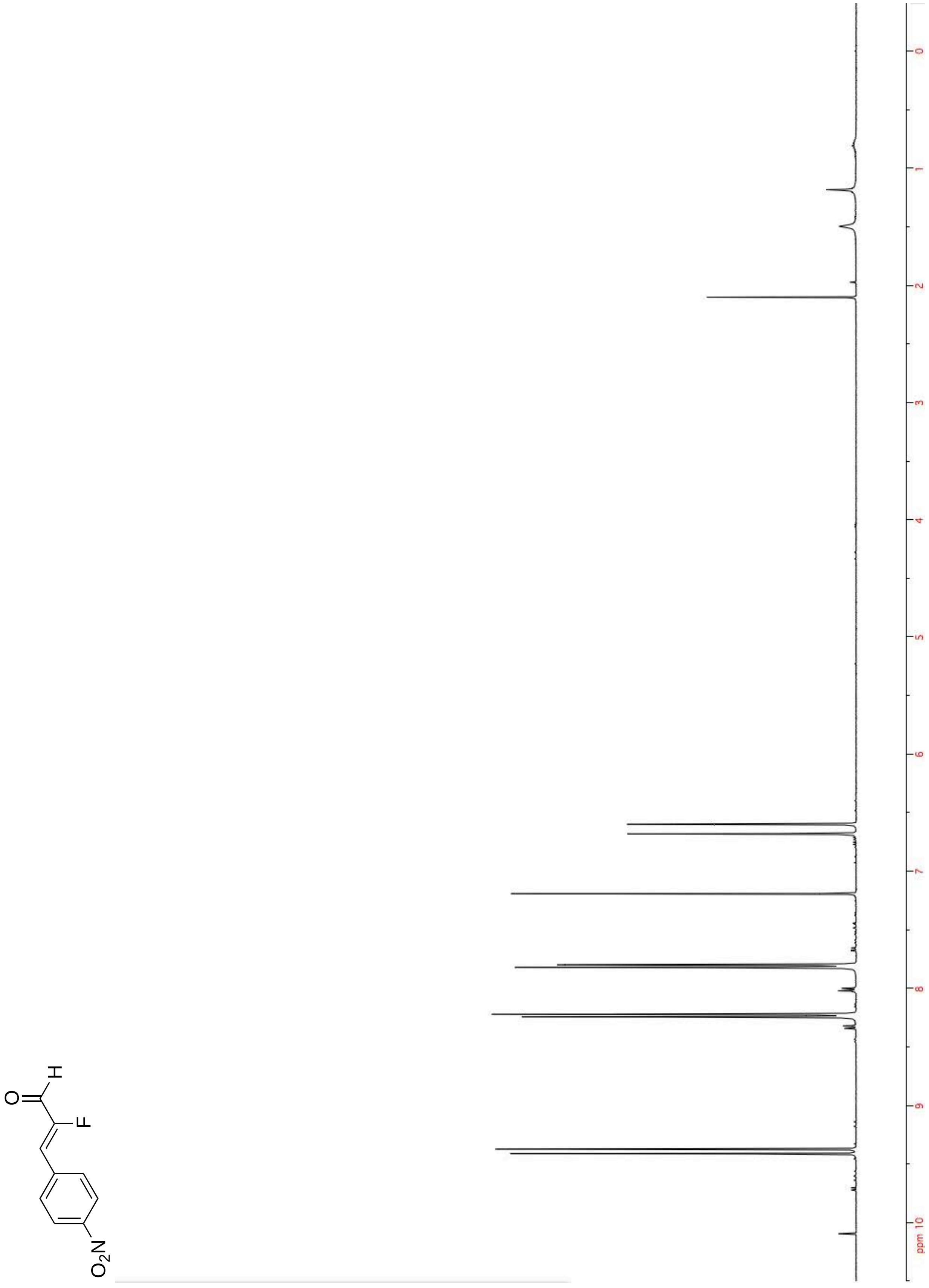

TBSO
F
OH
0
1
2
3
4
5
6
7
8
9
ppm 10

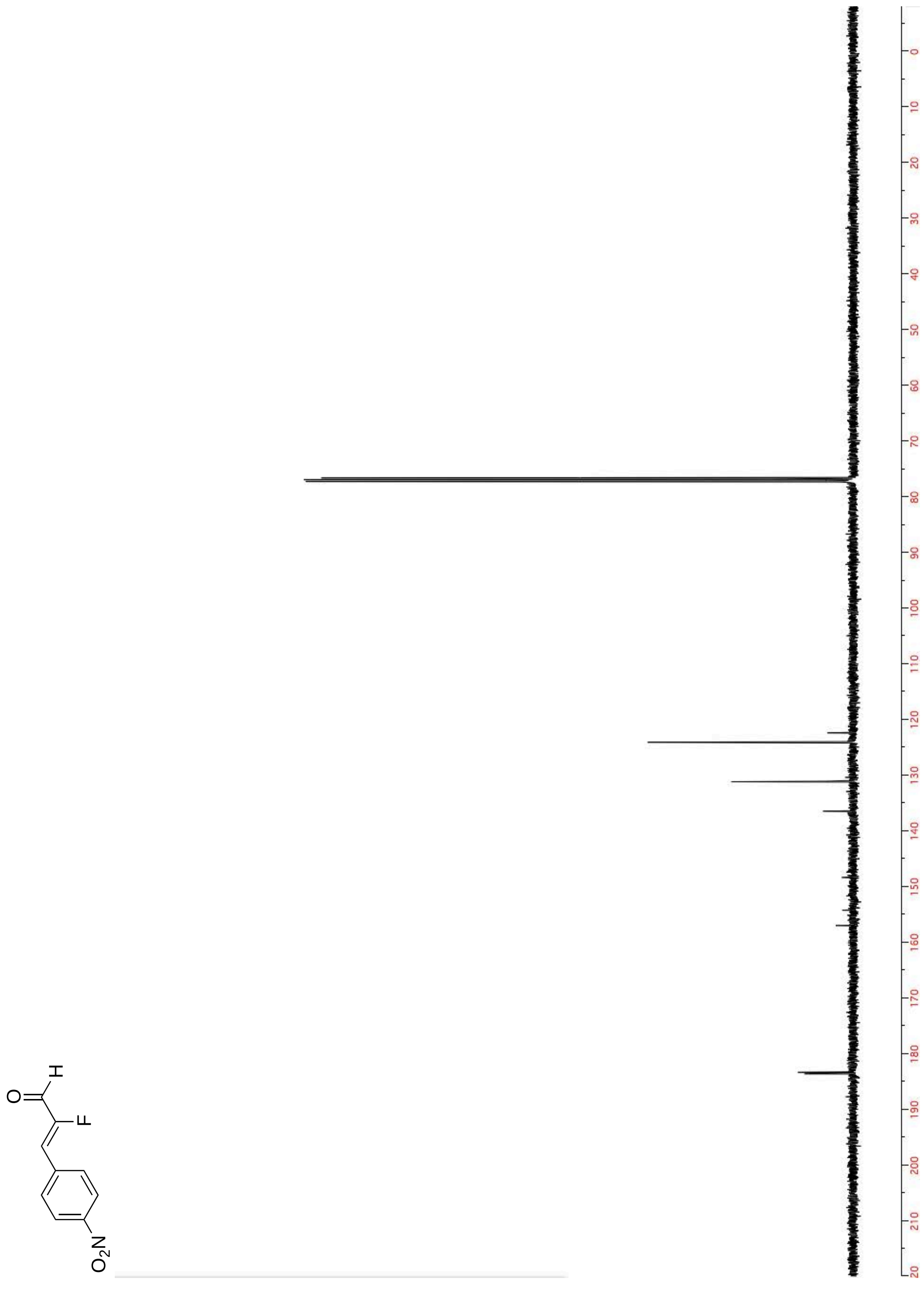

TBSO
F
OH
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

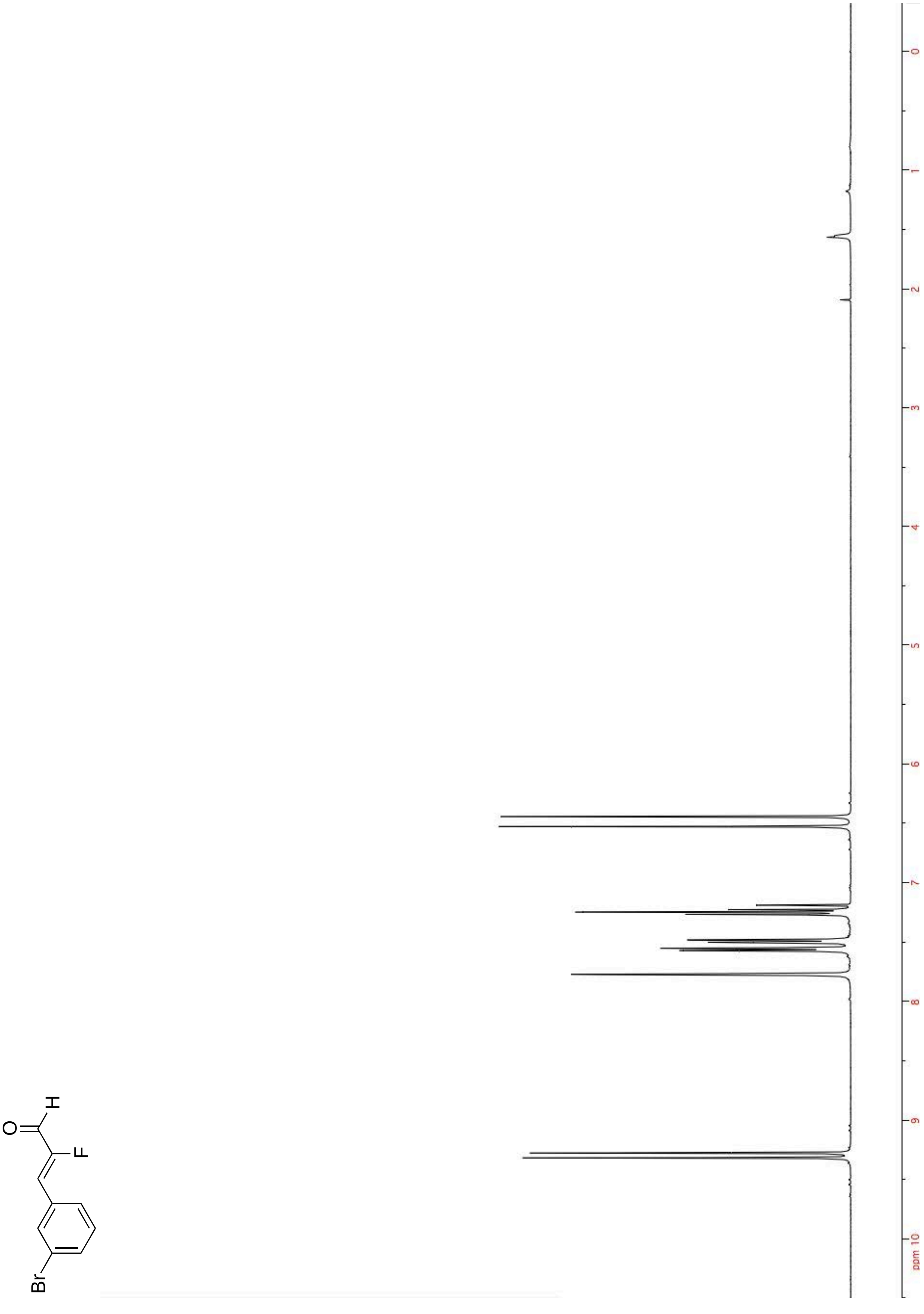


O
H
F
0
1
2
3
4
5
6
7
8
9
ppm 10

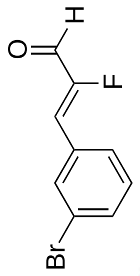

O
H
F
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

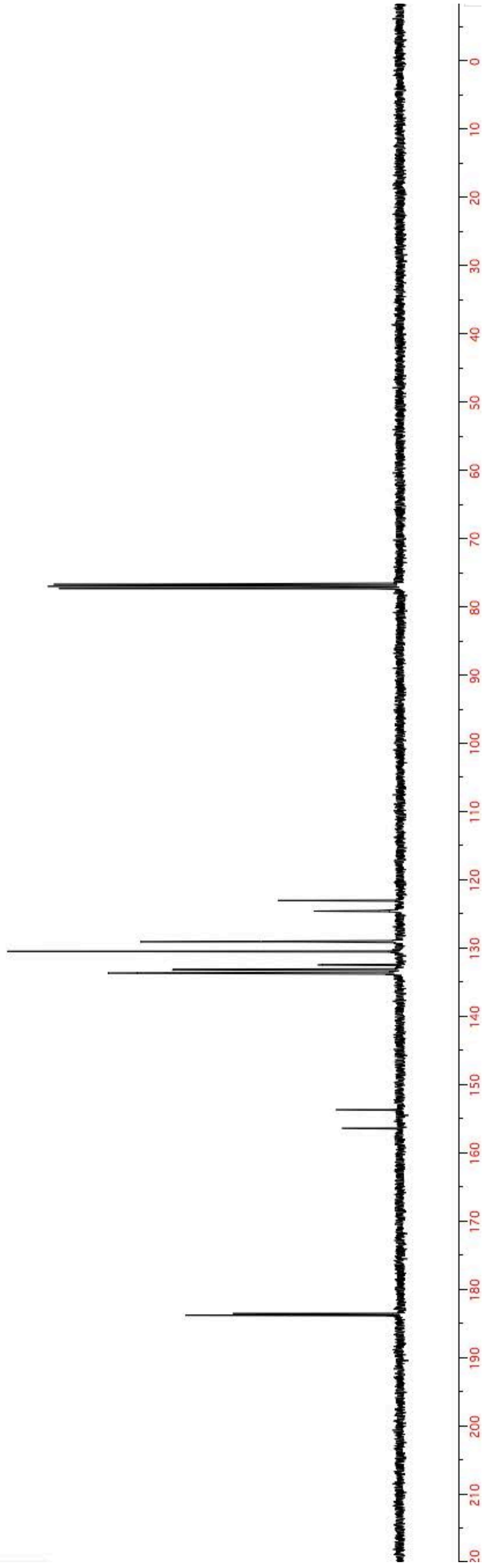

O
H
F
O_2N
0
1
2
3
4
5
6
7
8
9
ppm 10

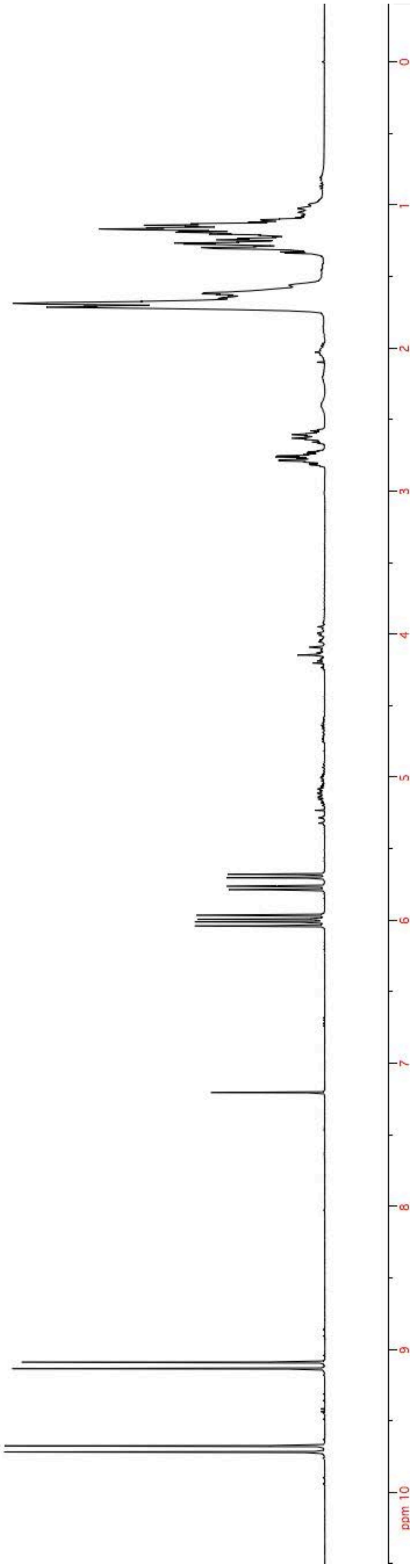

O
H
F
O2N
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
20

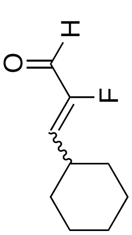


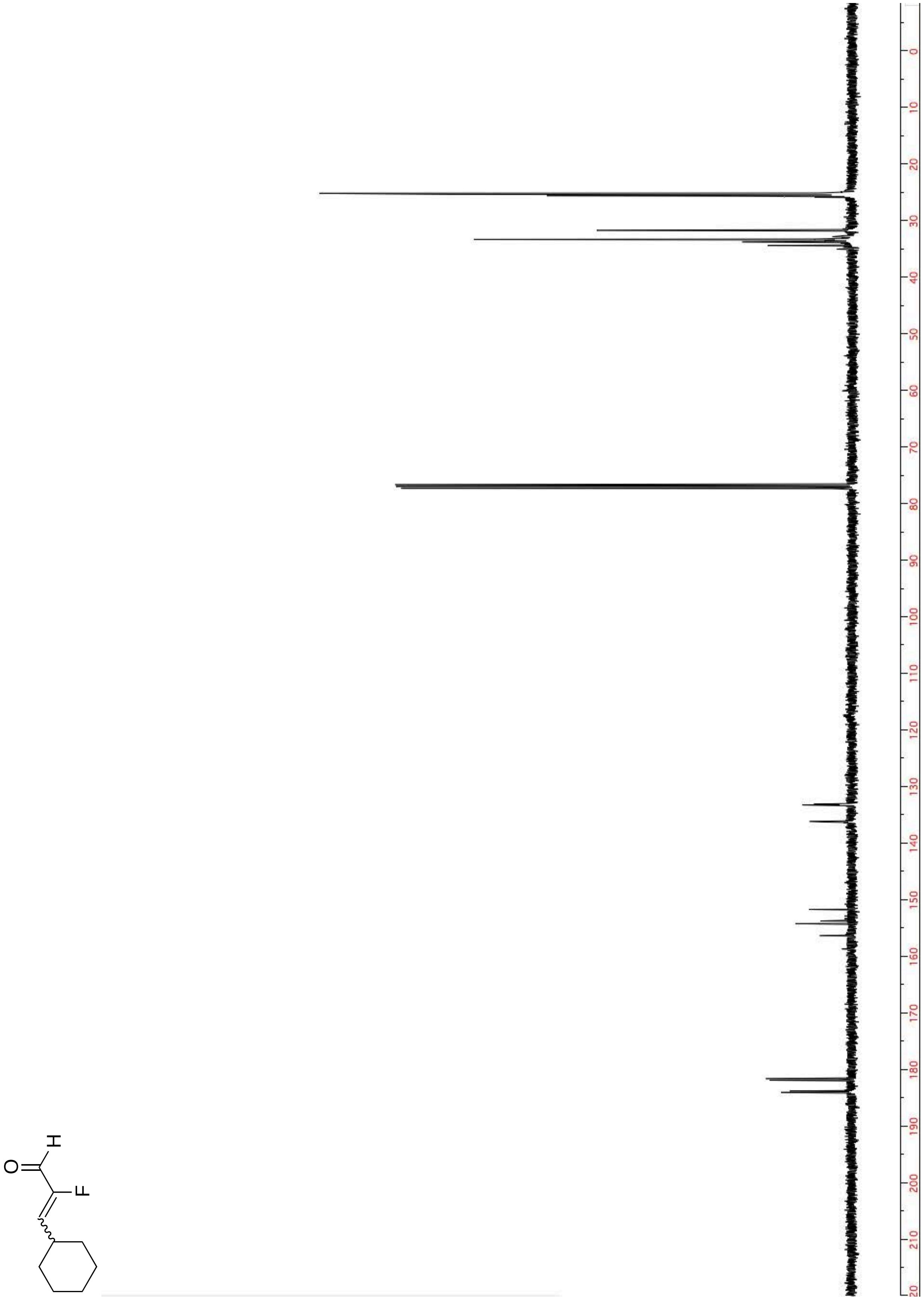
Br
F
O
H
0
1
2
3
4
5
6
7
8
9
ppm 10


Br
F
O
H

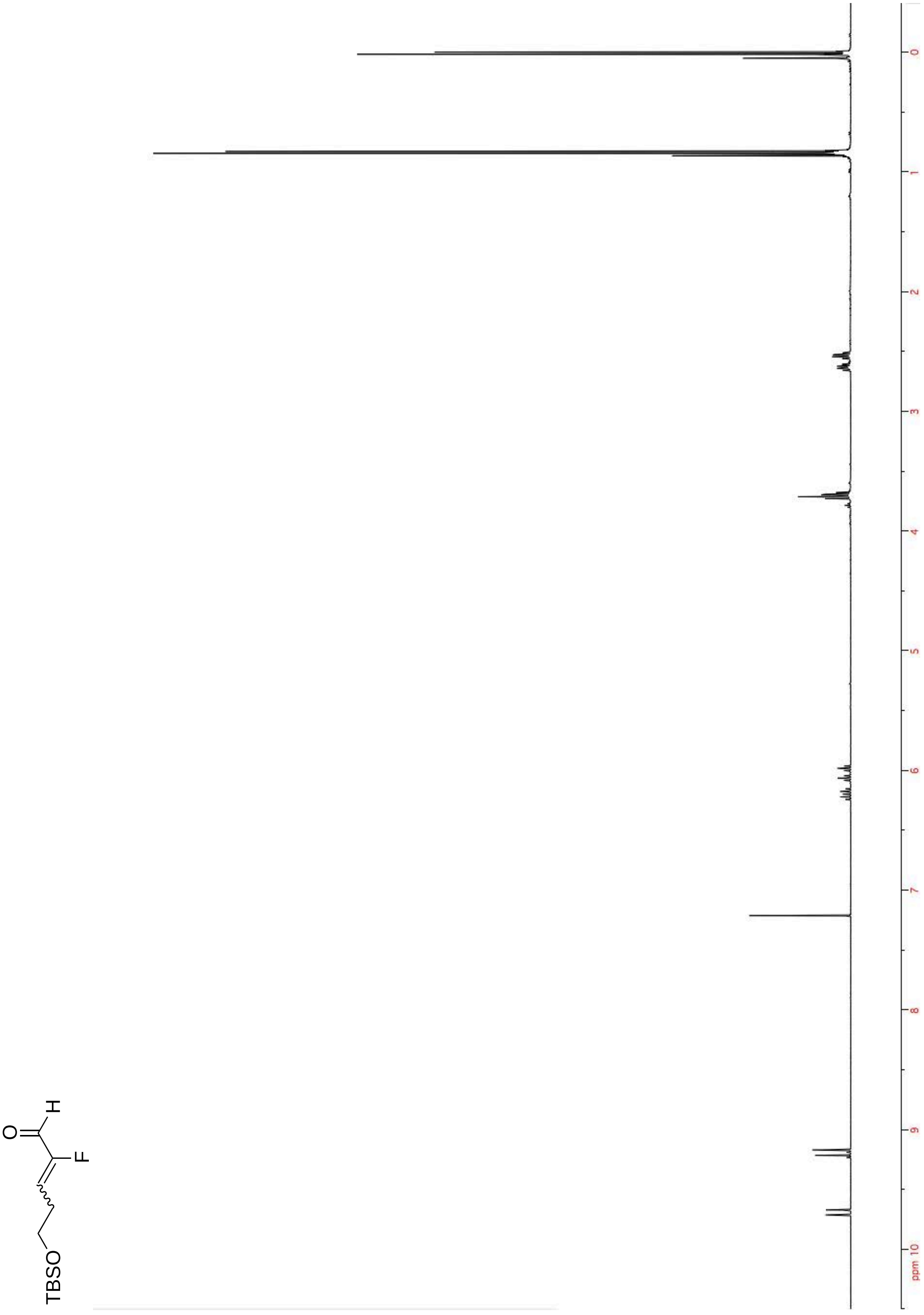

0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

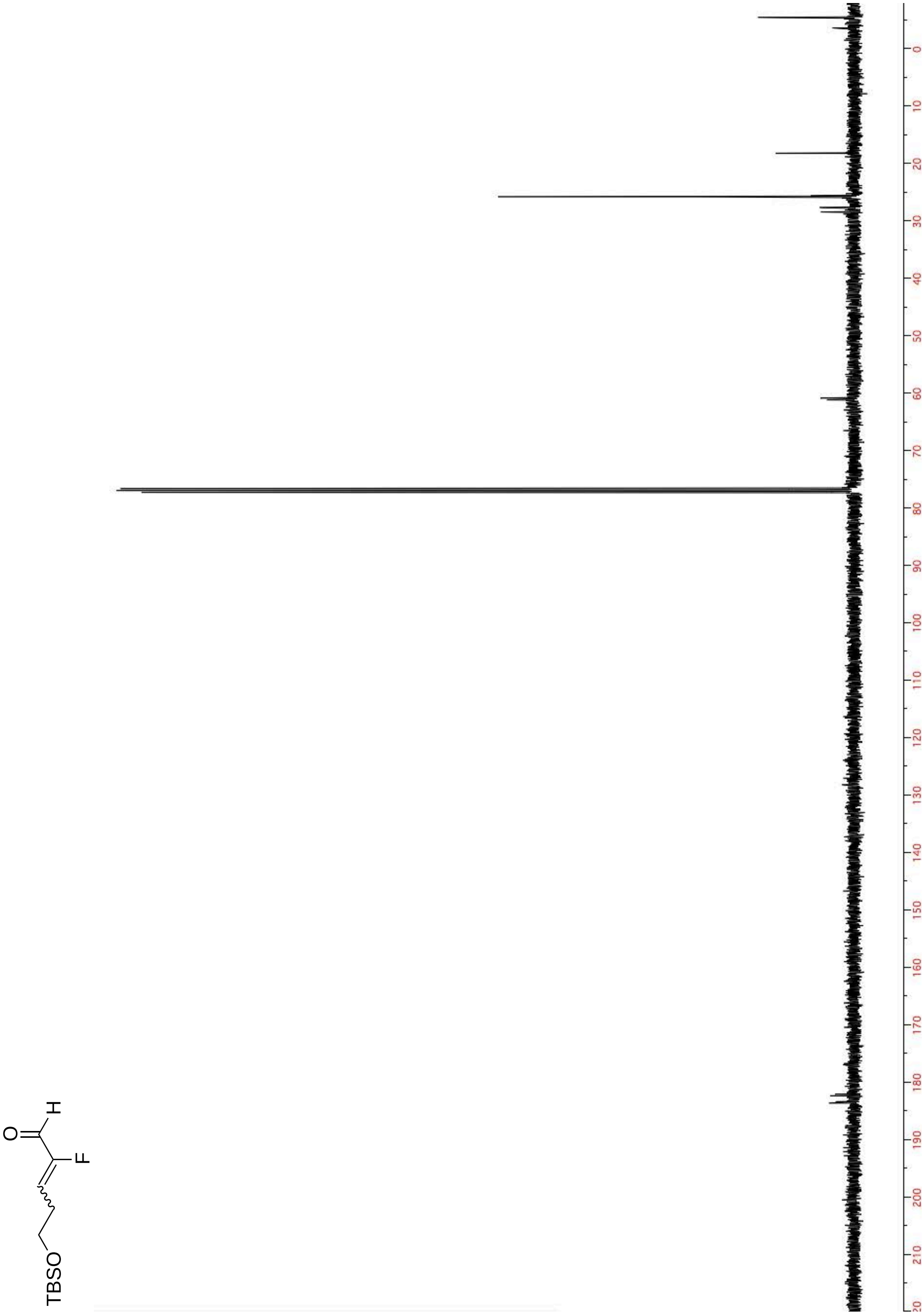

0
1
2
3
4
5
6
7
8
9
ppm 10

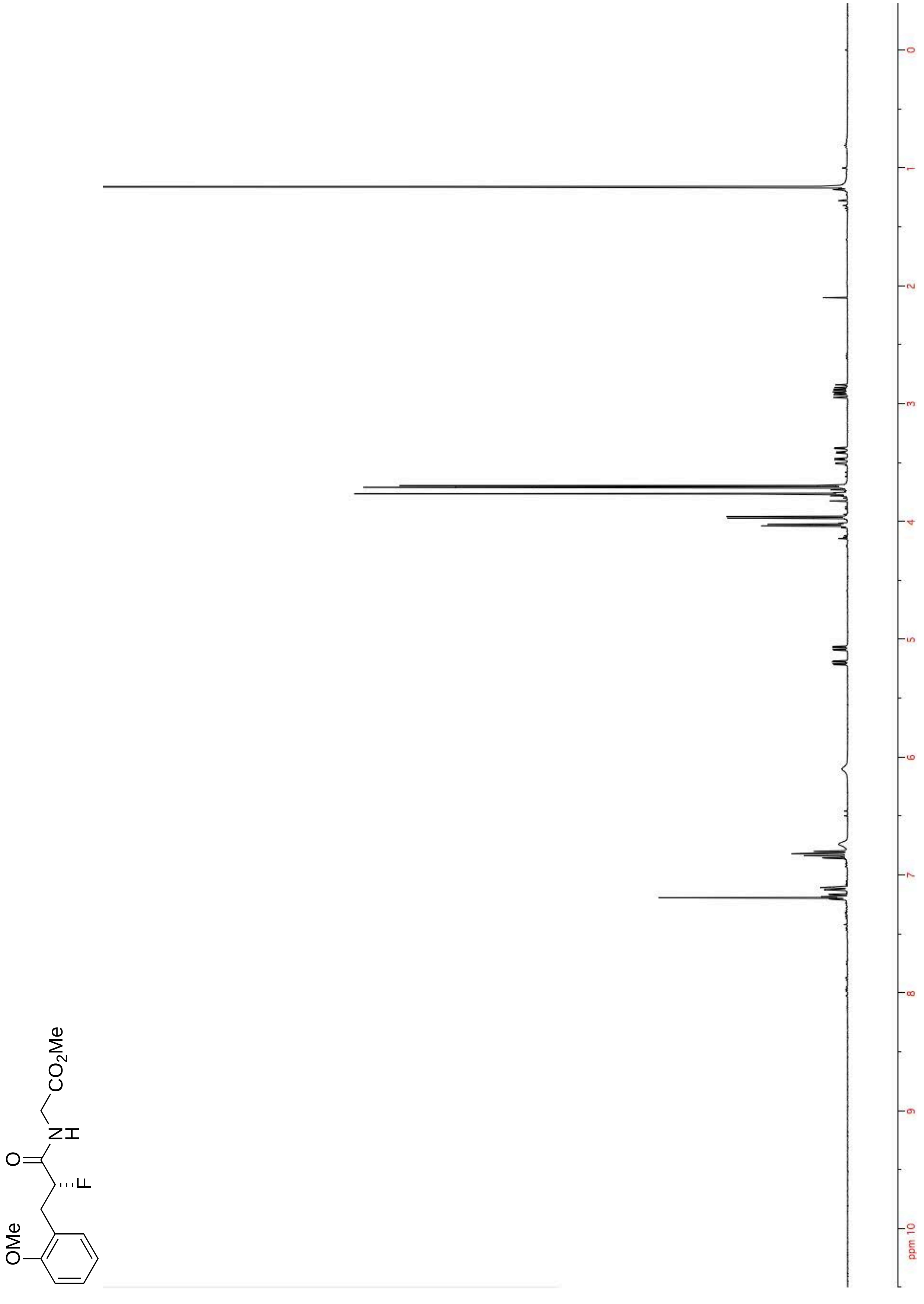

O
H
F

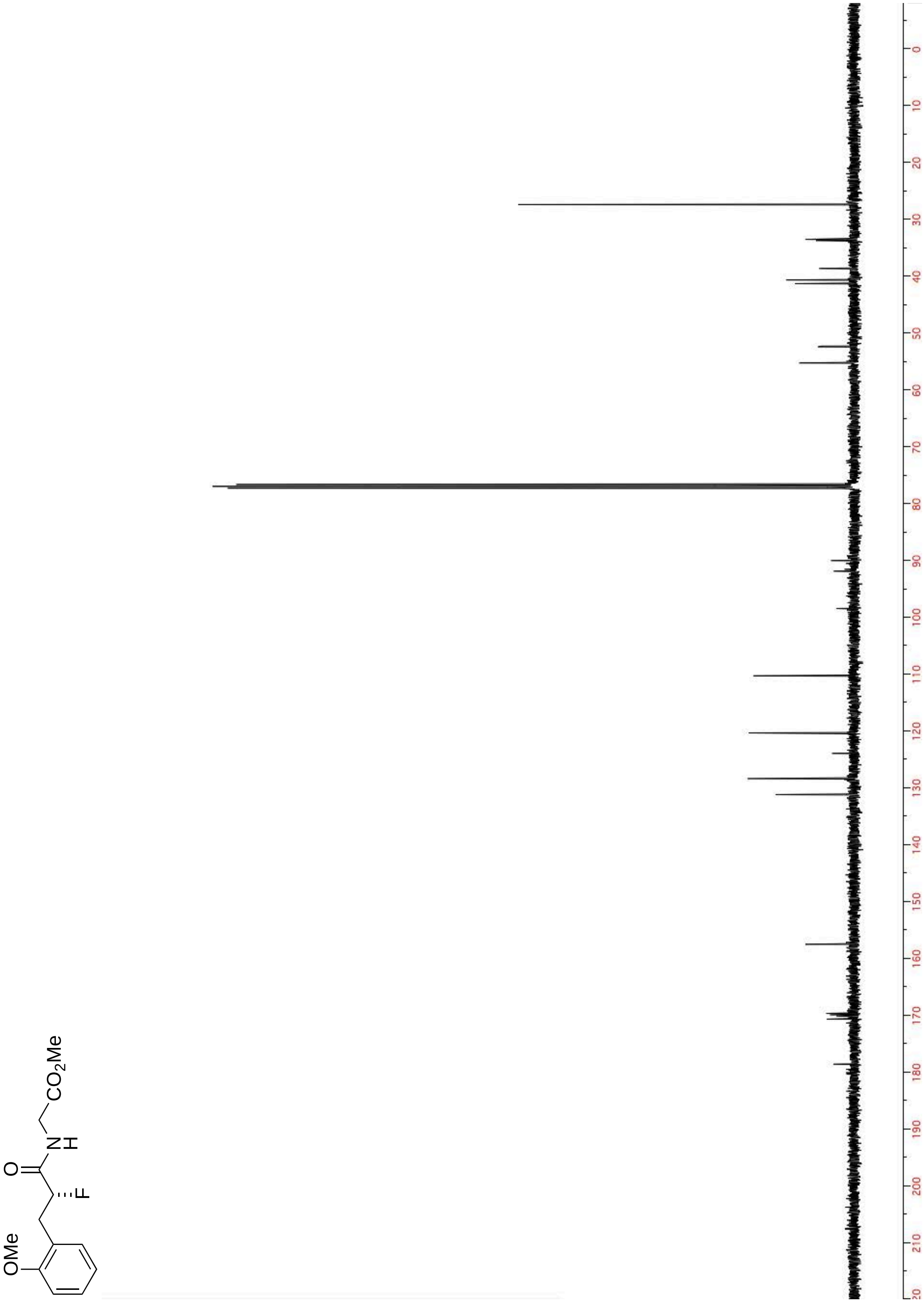


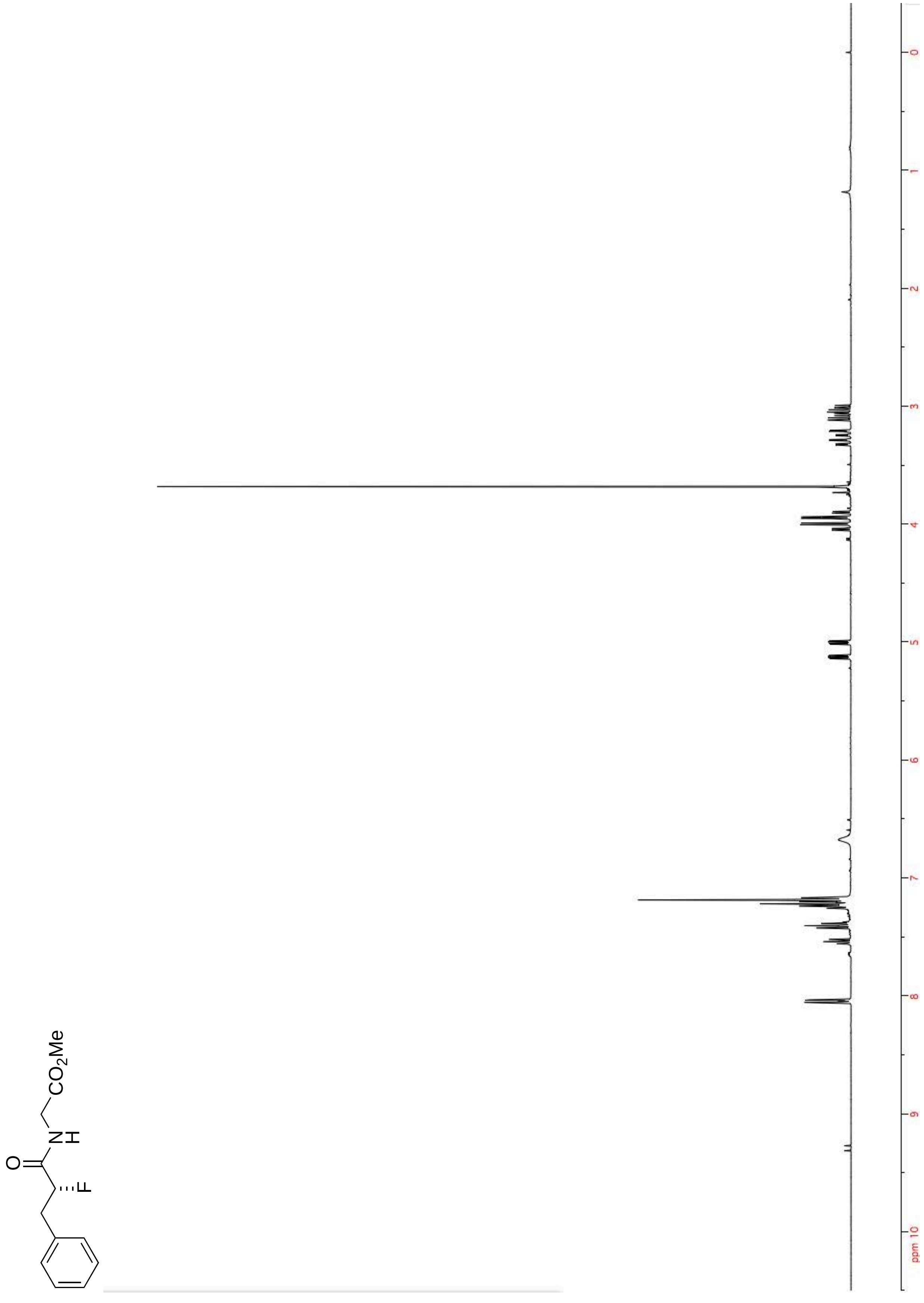
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
O
H
F

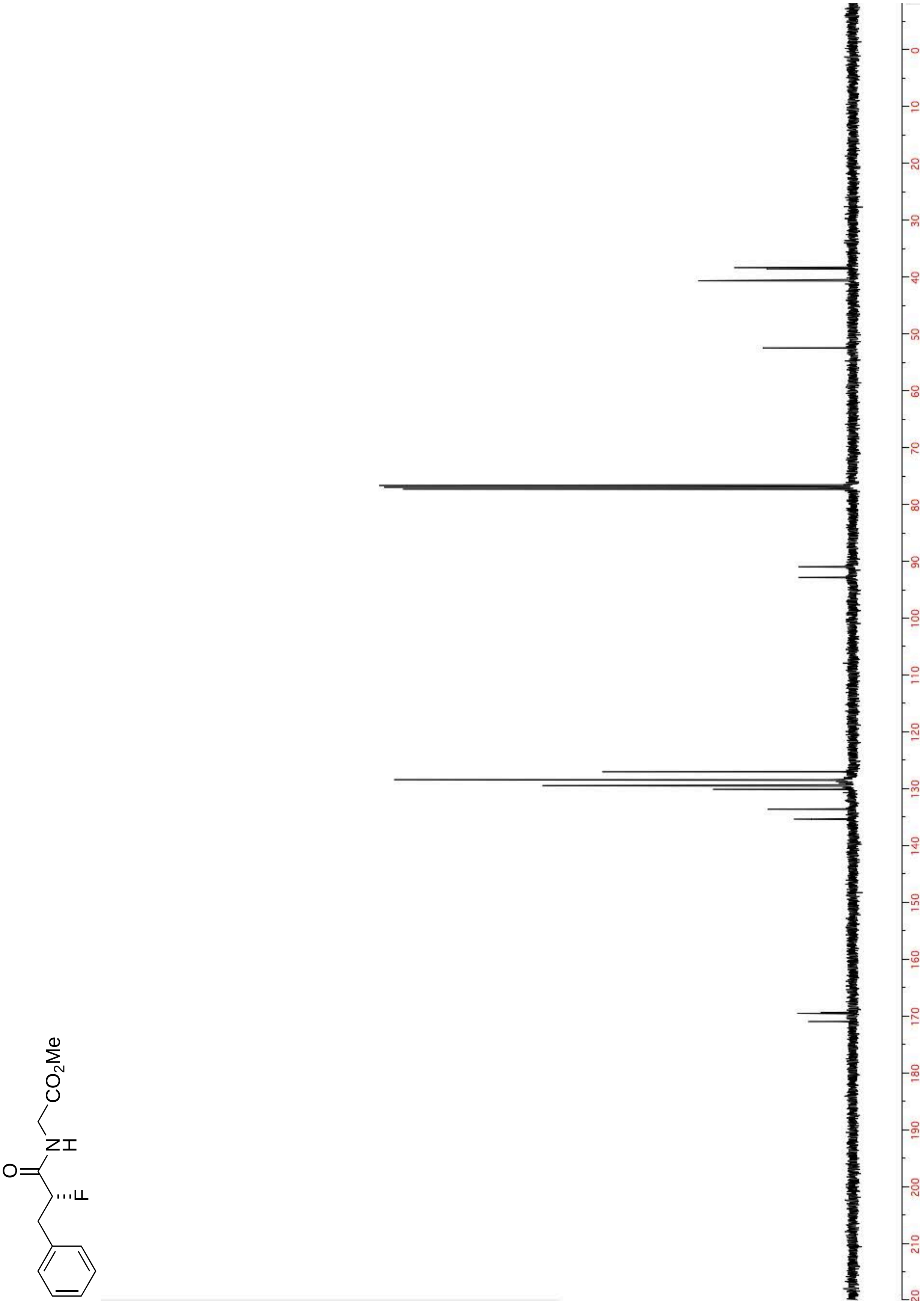

TBSO
O
H
F
ppm 10
9
8
7
6
5
4
3
2
1
0

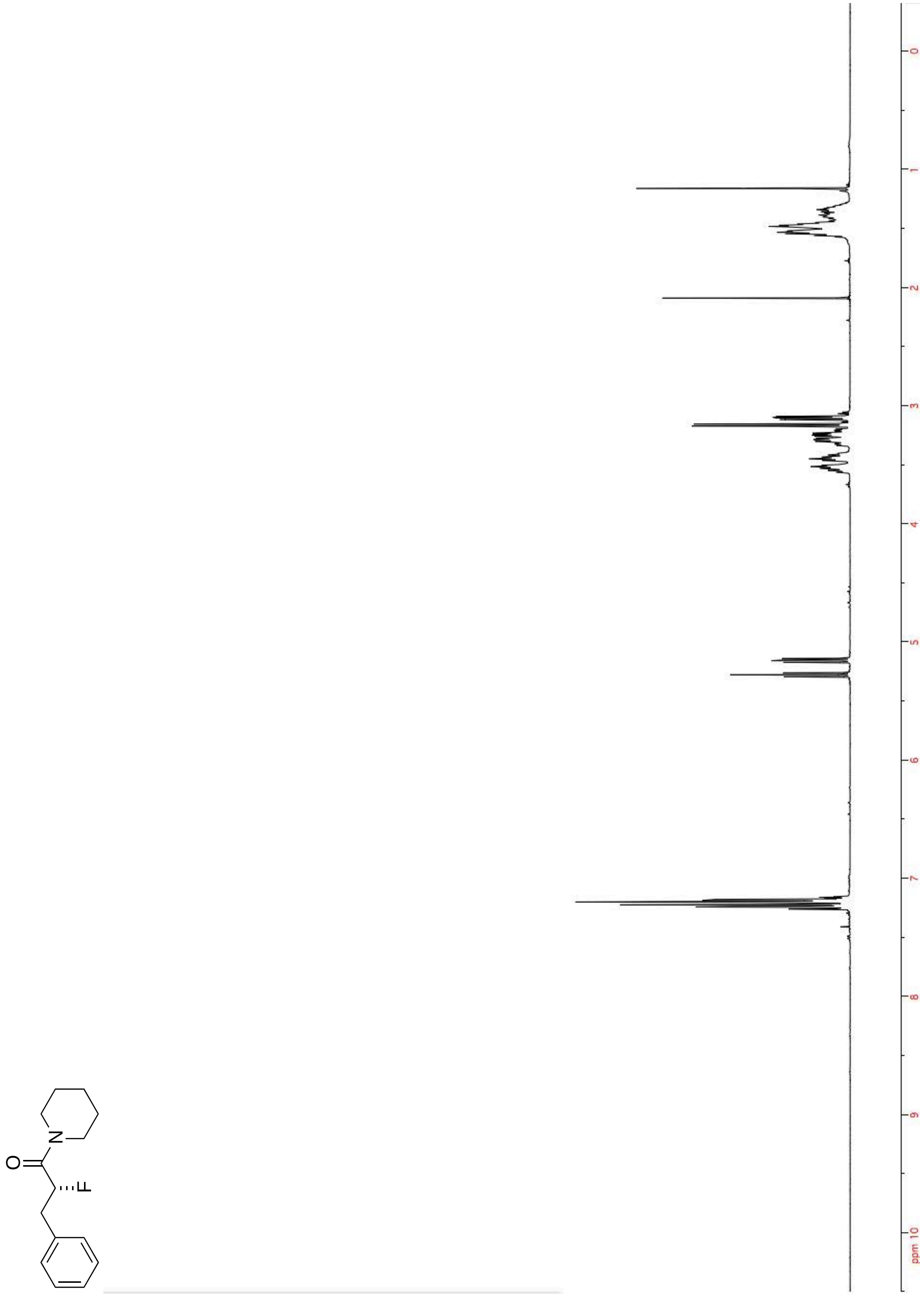

TBSO
O
H
F
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
20

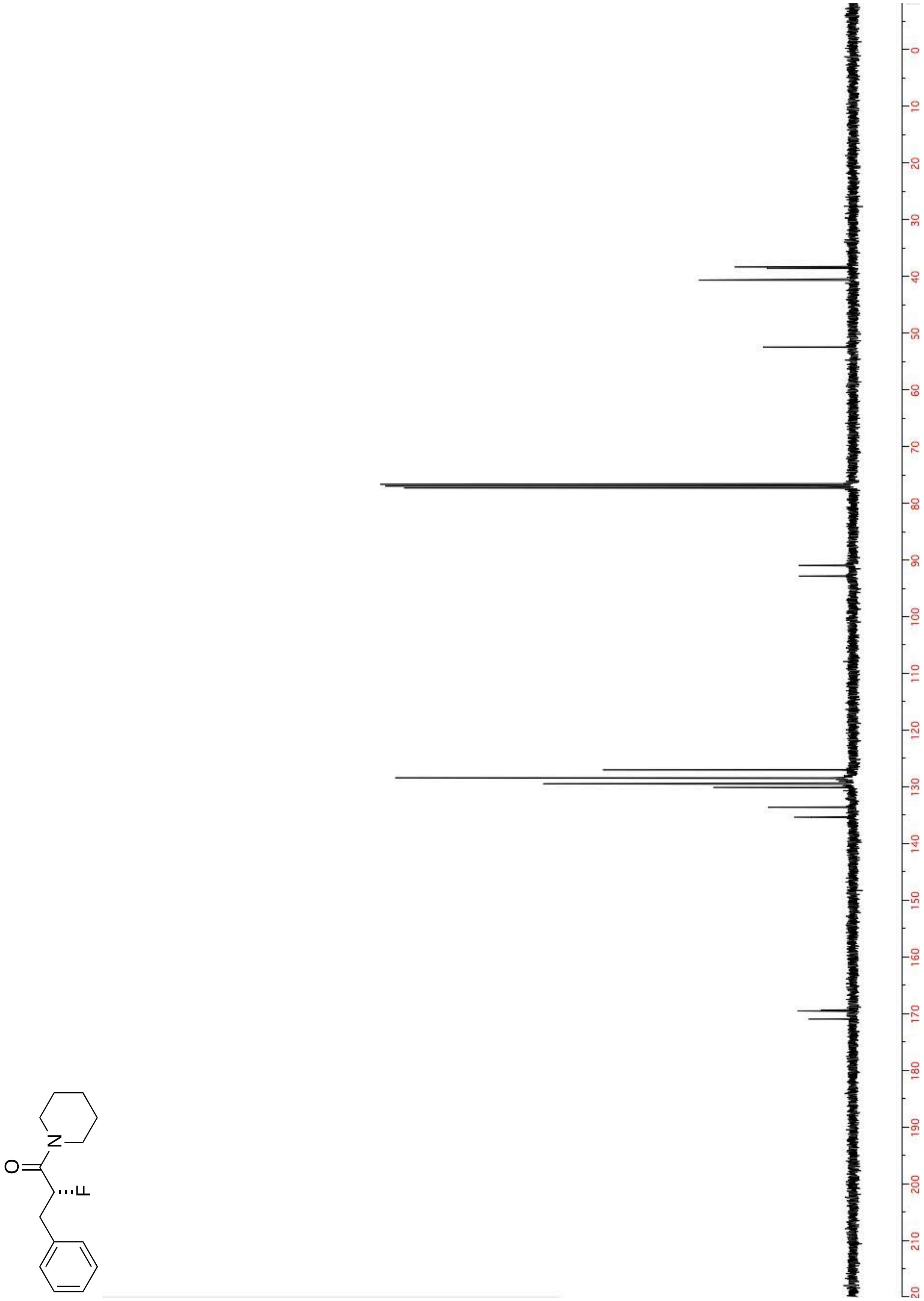

OMe
O
N
H
F
CO2Me
ppm
0
1
2
3
4
5
6
7
8
9
10

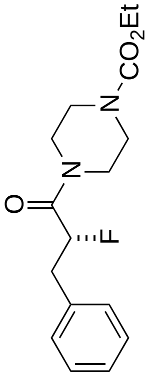

OMe
F
O
N
H
CO2Me
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

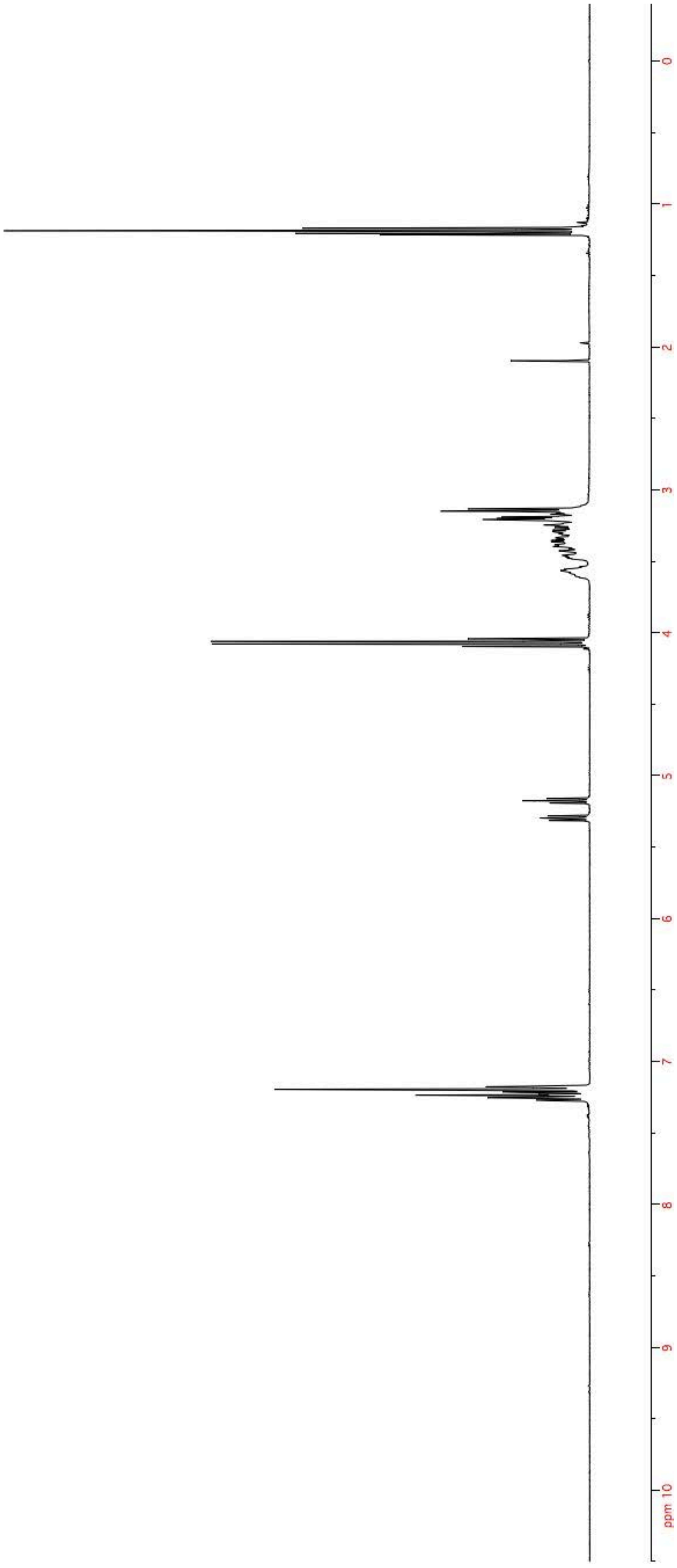

O
N
H
F
CO2Me
0
1
2
3
4
5
6
7
8
9
ppm 10

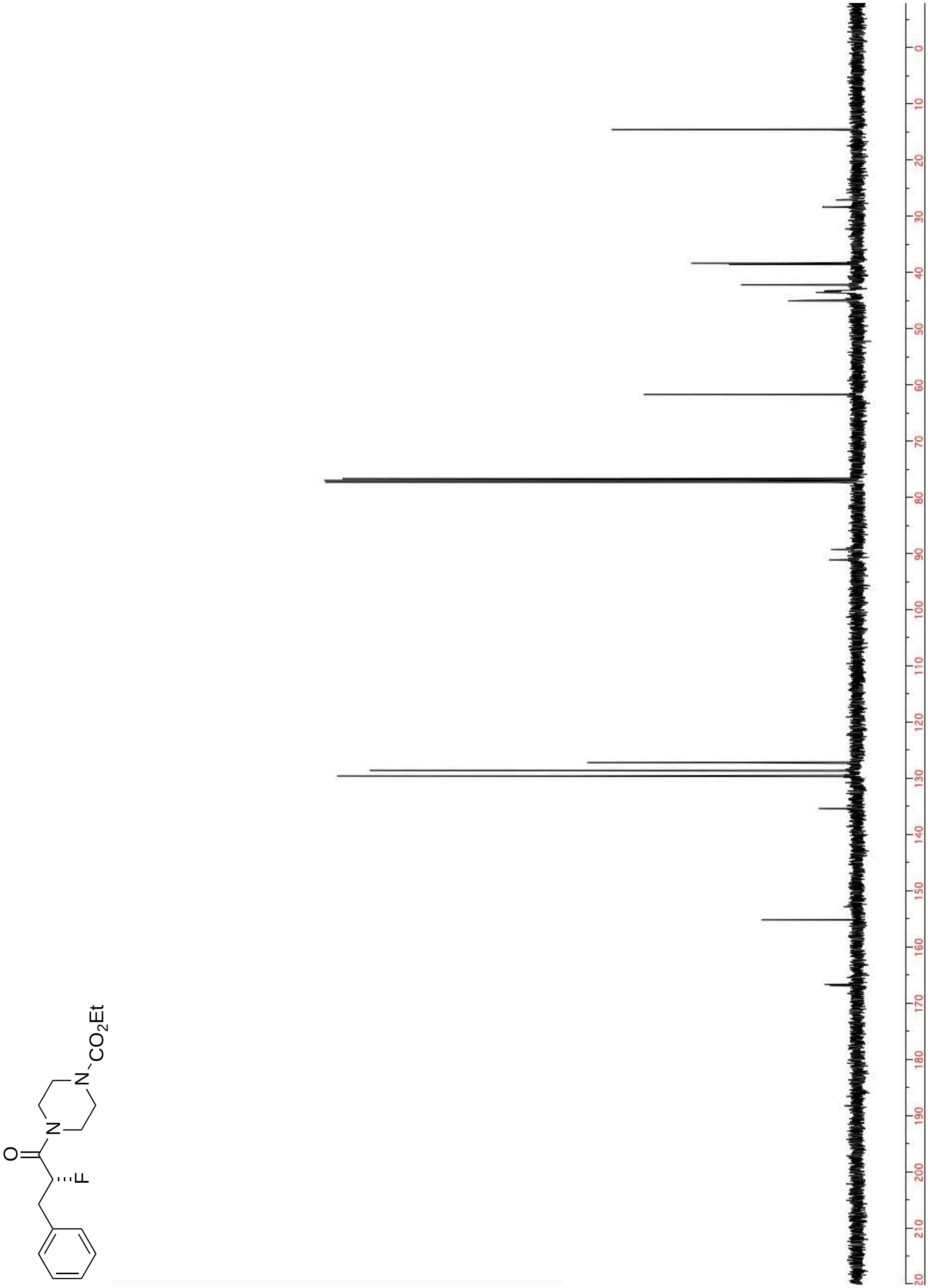

O
N
H
CO2Me
F
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

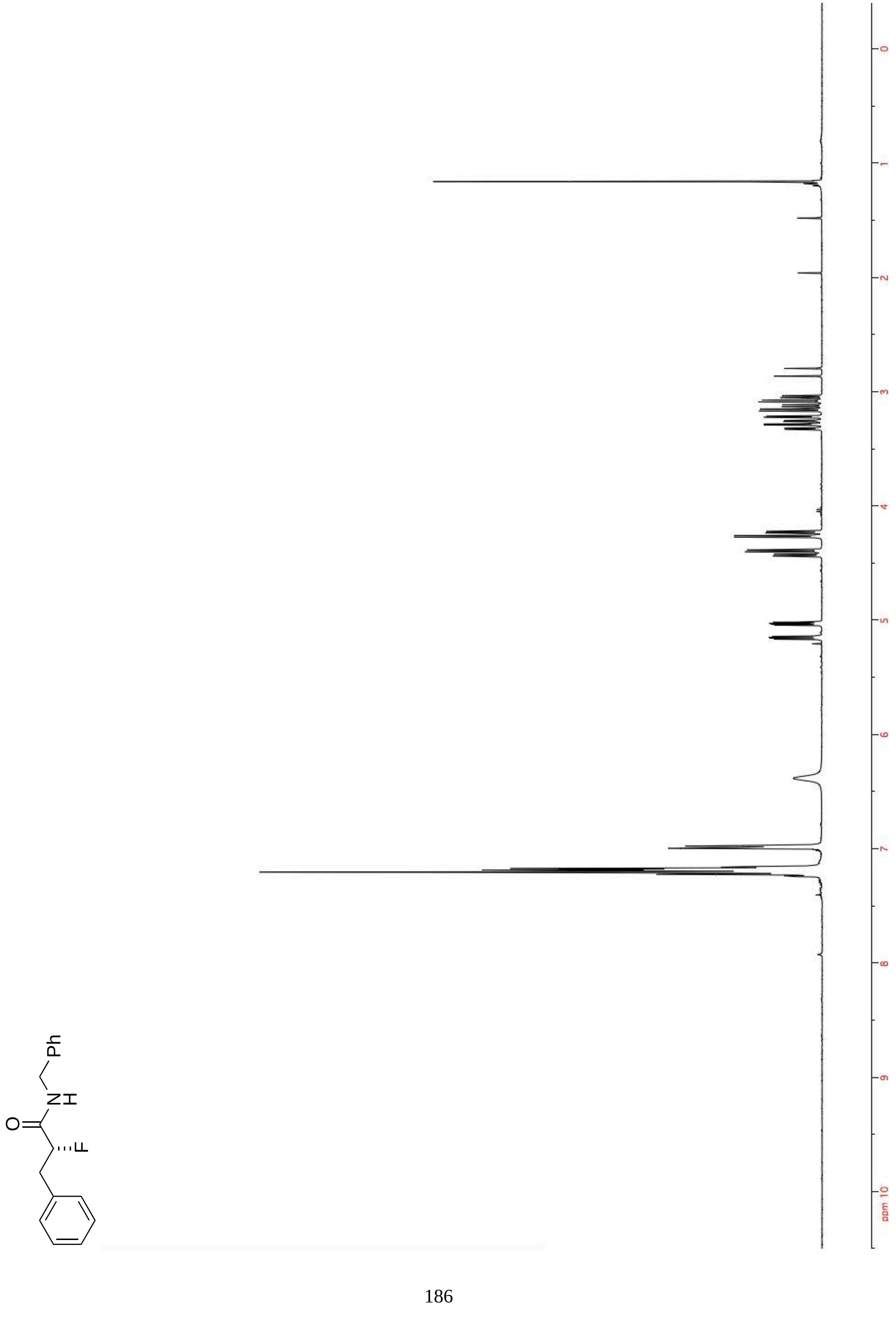

O
N
F
0
1
2
3
4
5
6
7
8
9
ppm 10

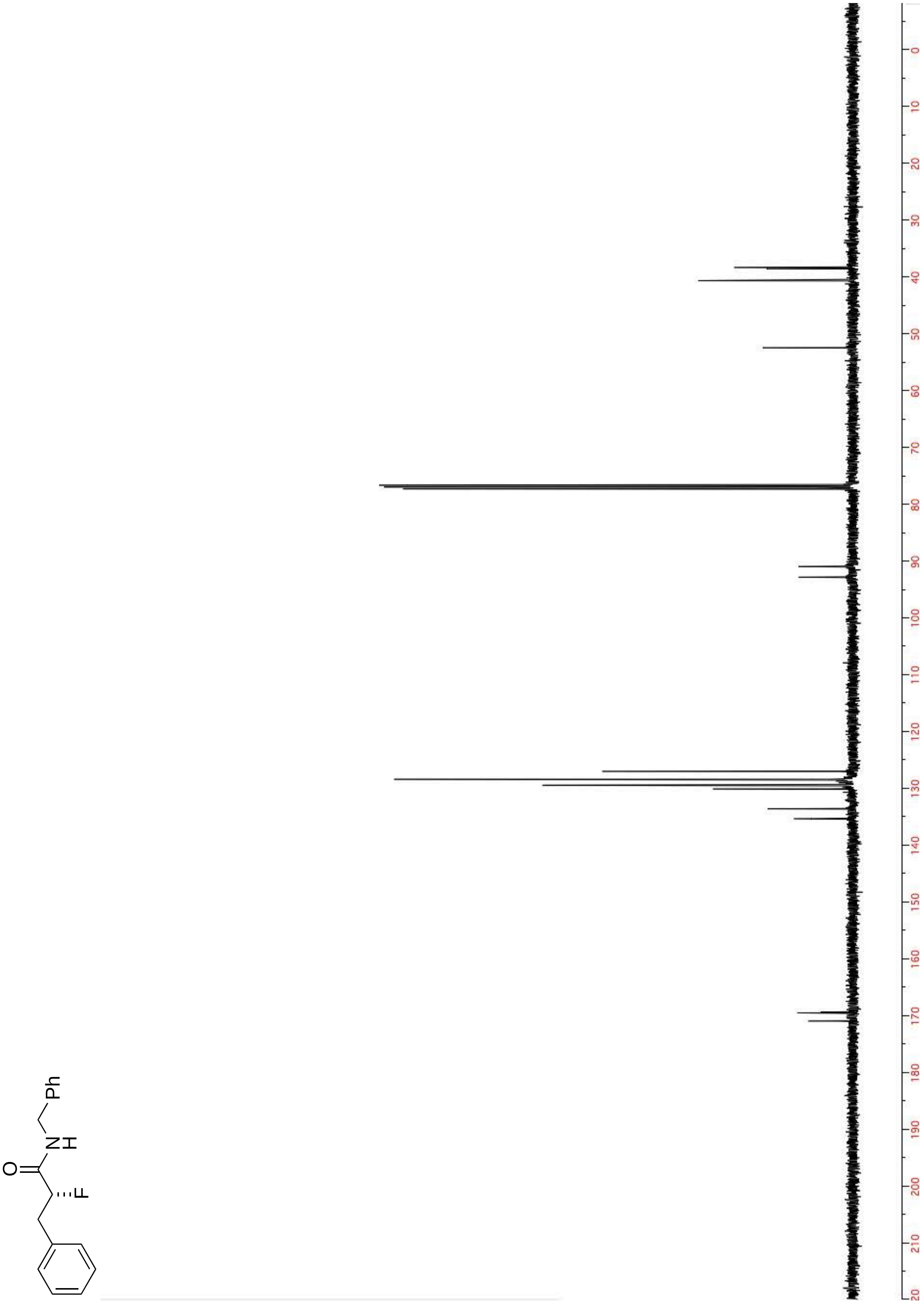

O
N
F
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
20

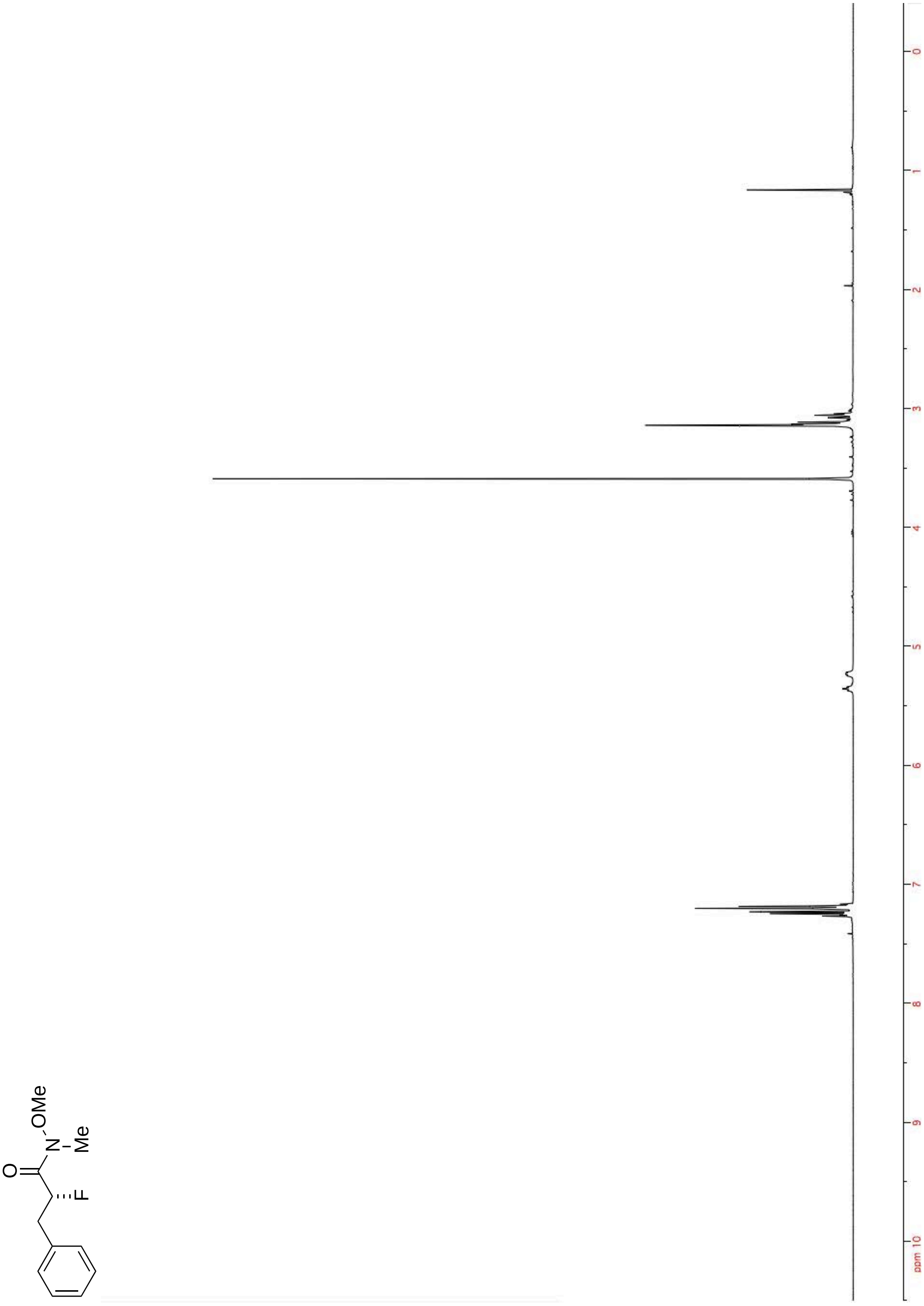

O
N
N
CO2Et
F


0
1
2
3
4
5
6
7
8
9
ppm 10

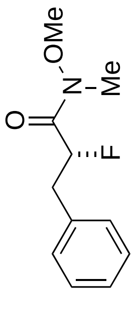

O
N
N
CO2Et
F
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

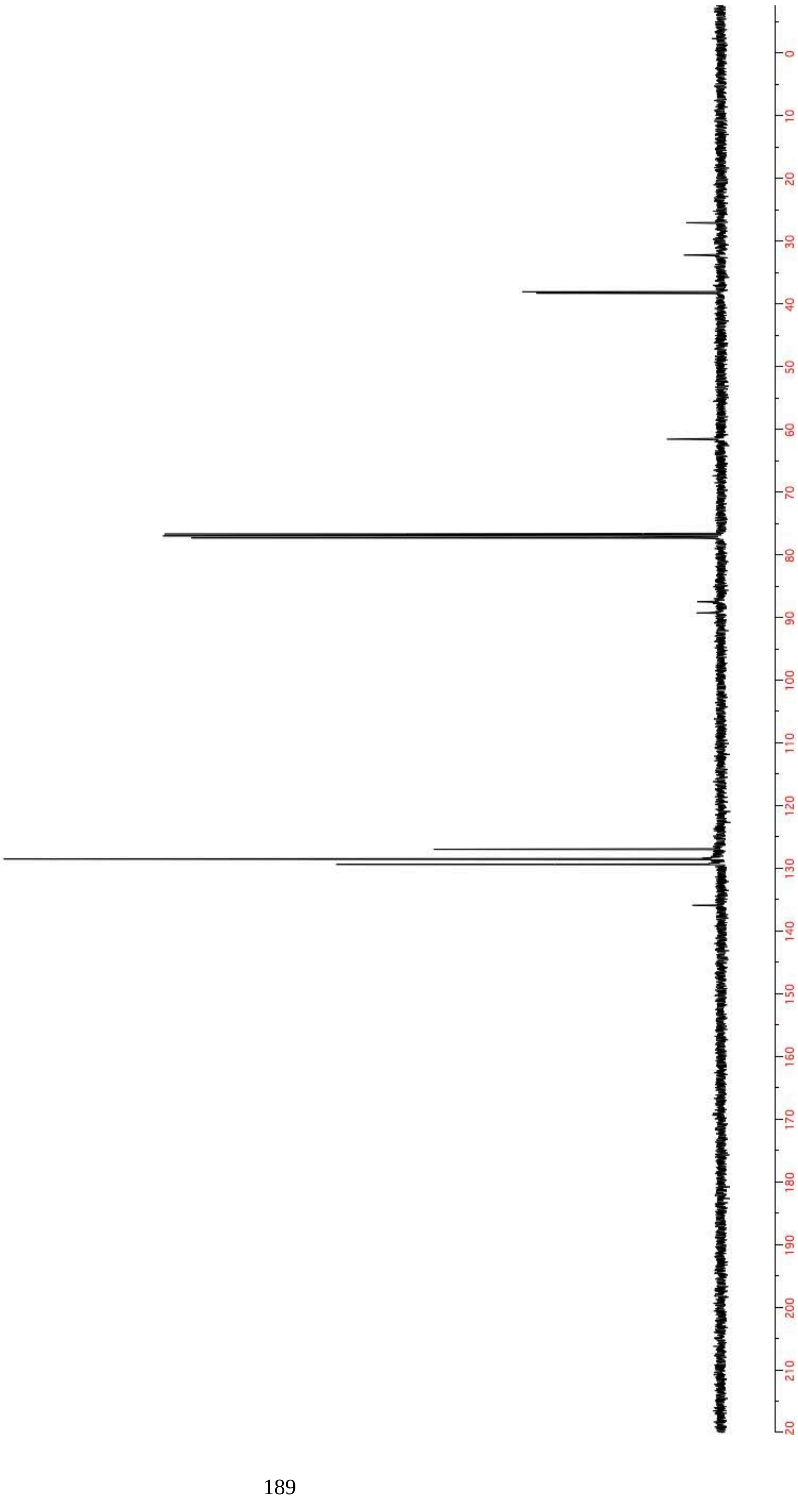

O
N
H
Ph
F
ppm 10
9
8
7
6
5
4
3
2
1
0

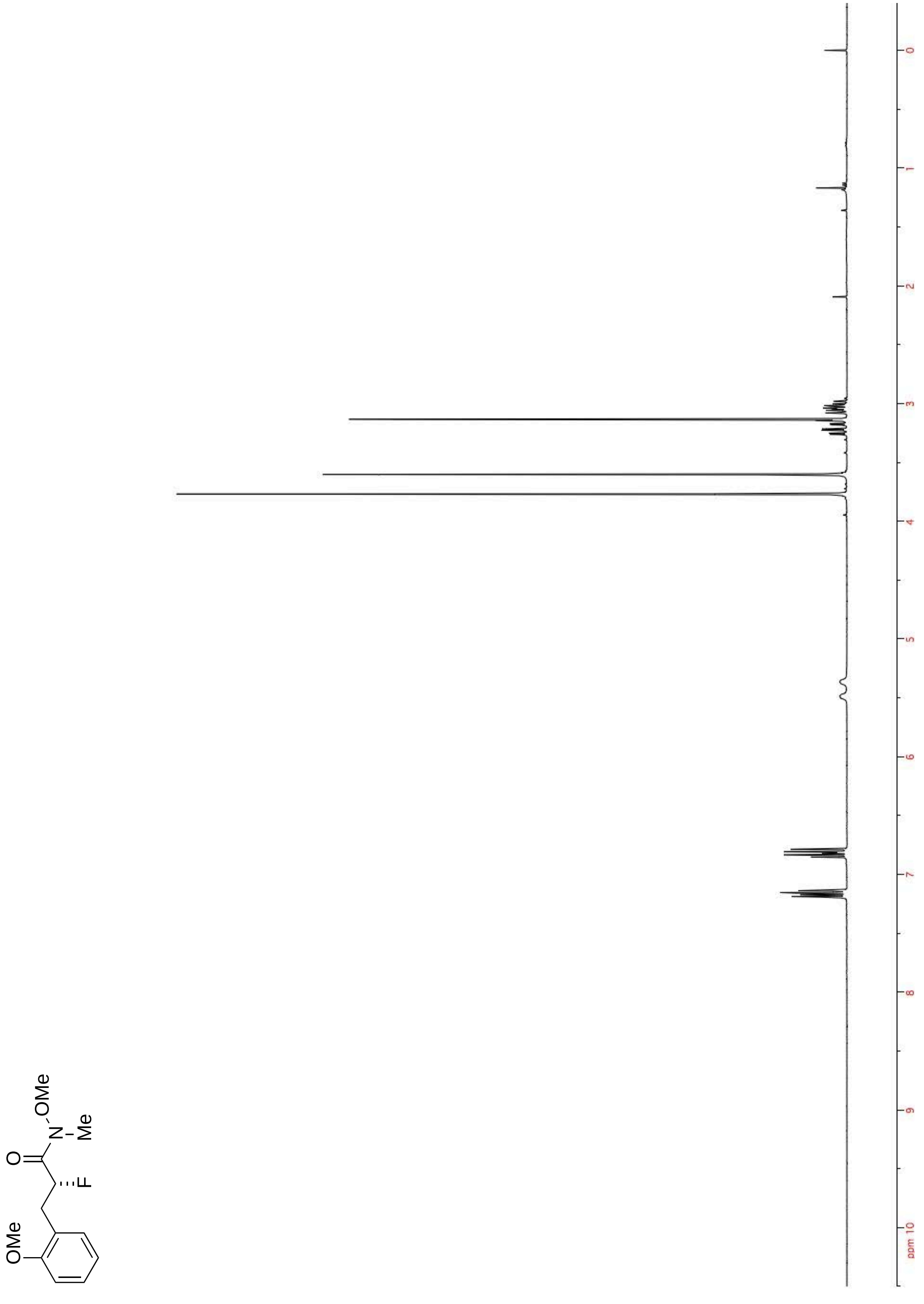

O
N
H
Ph
F
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
20

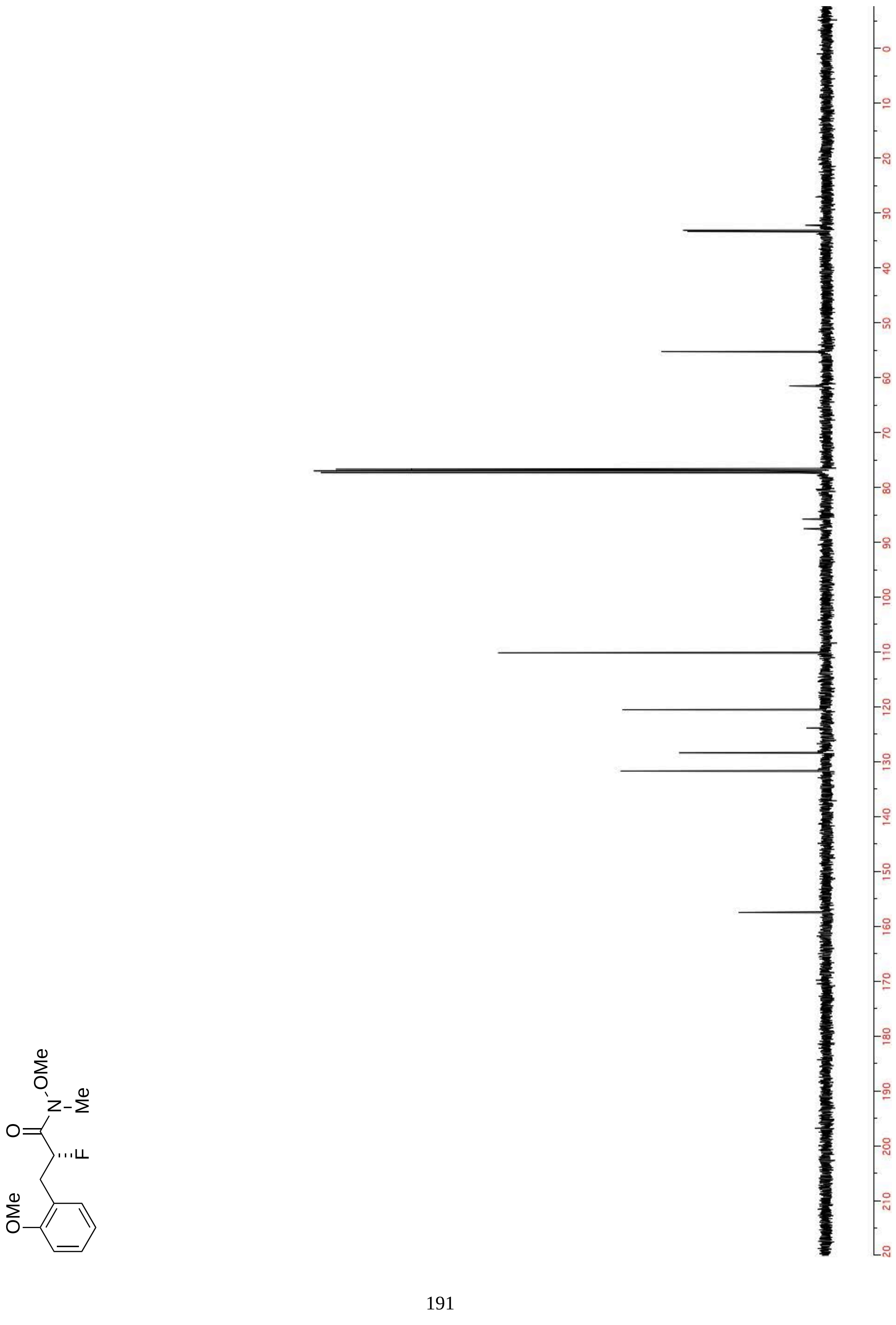


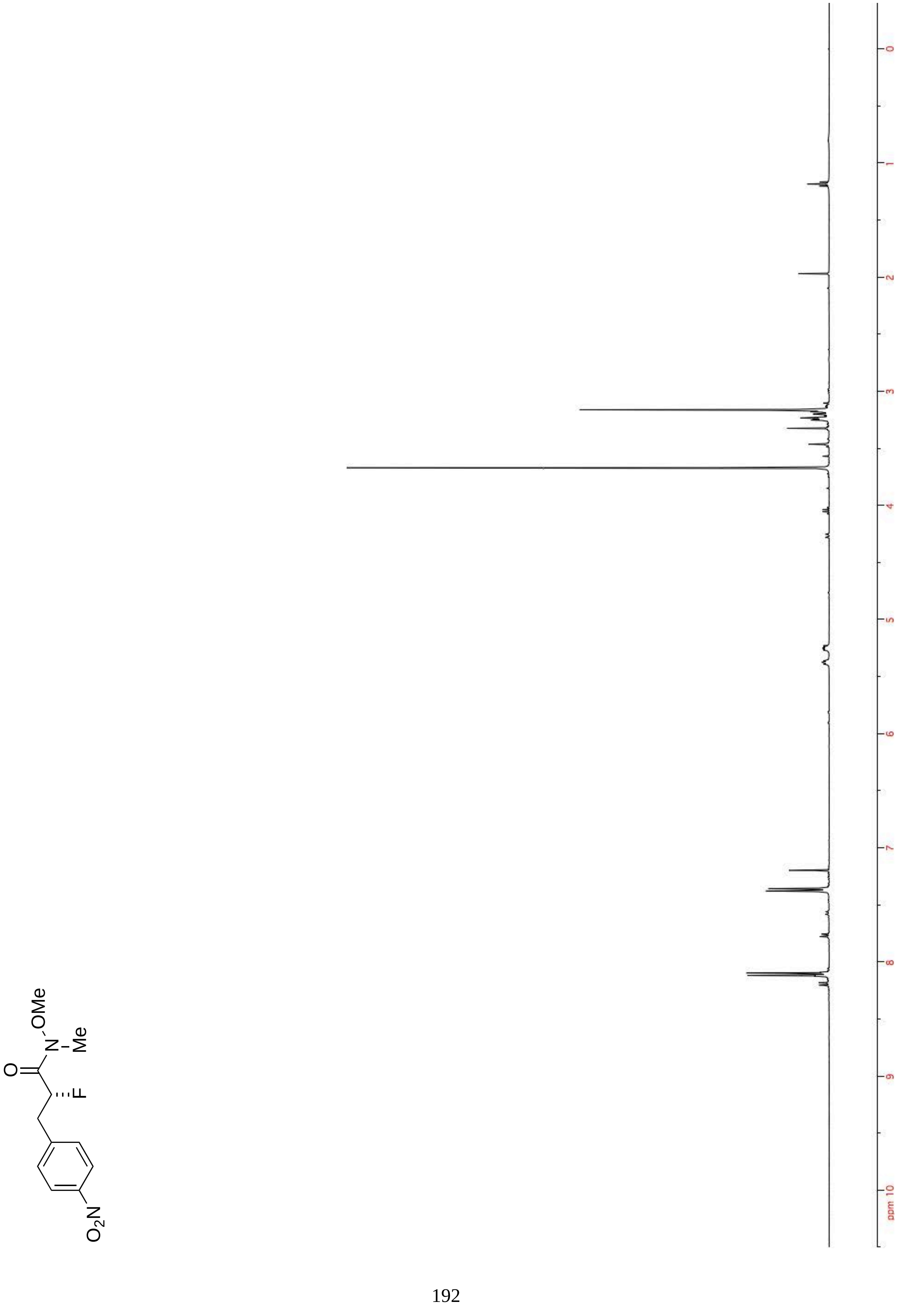
OMe
N
Me
O
F
ppm
0
1
2
3
4
5
6
7
8
9
10

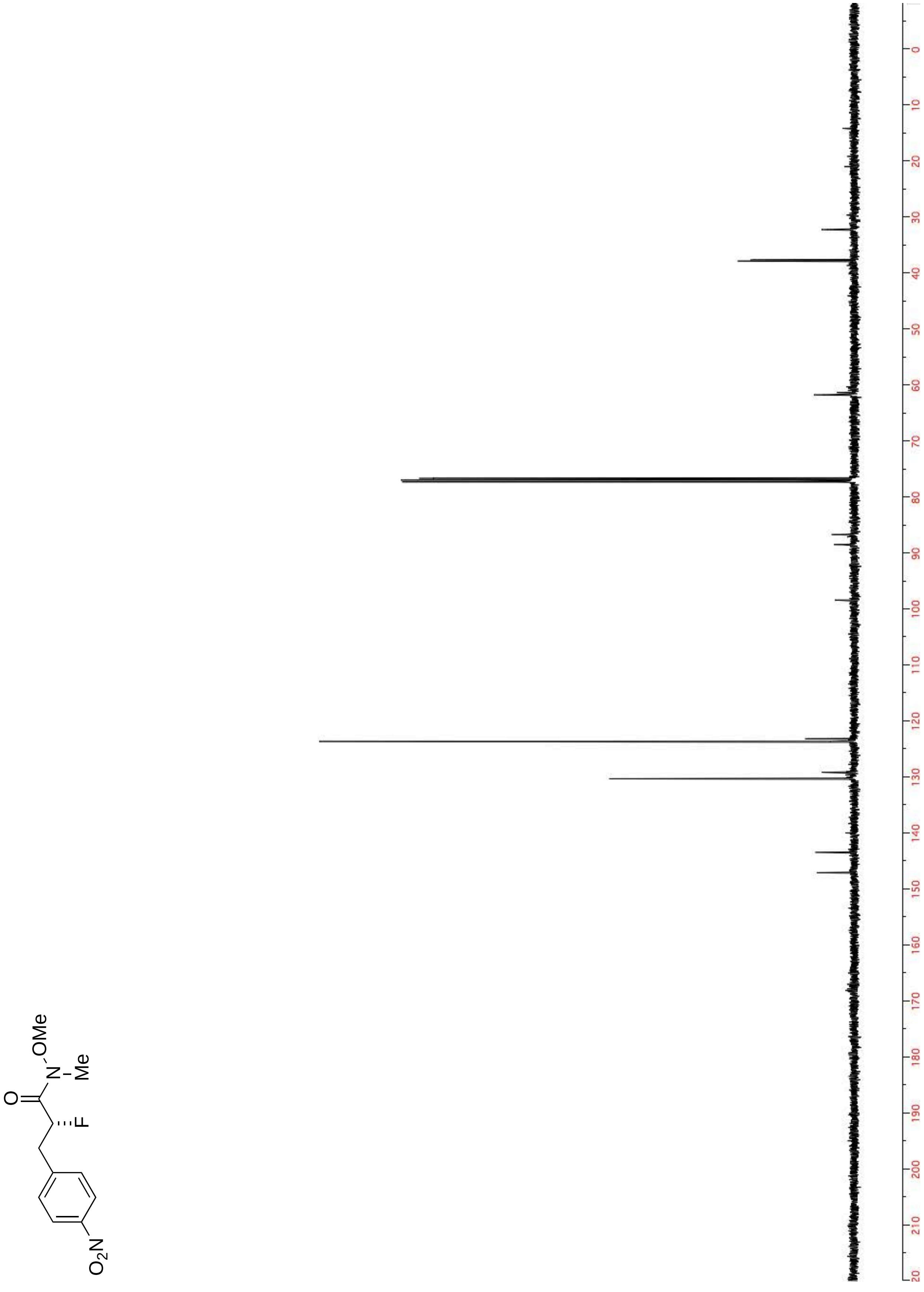

O
N
OMe
Me
F

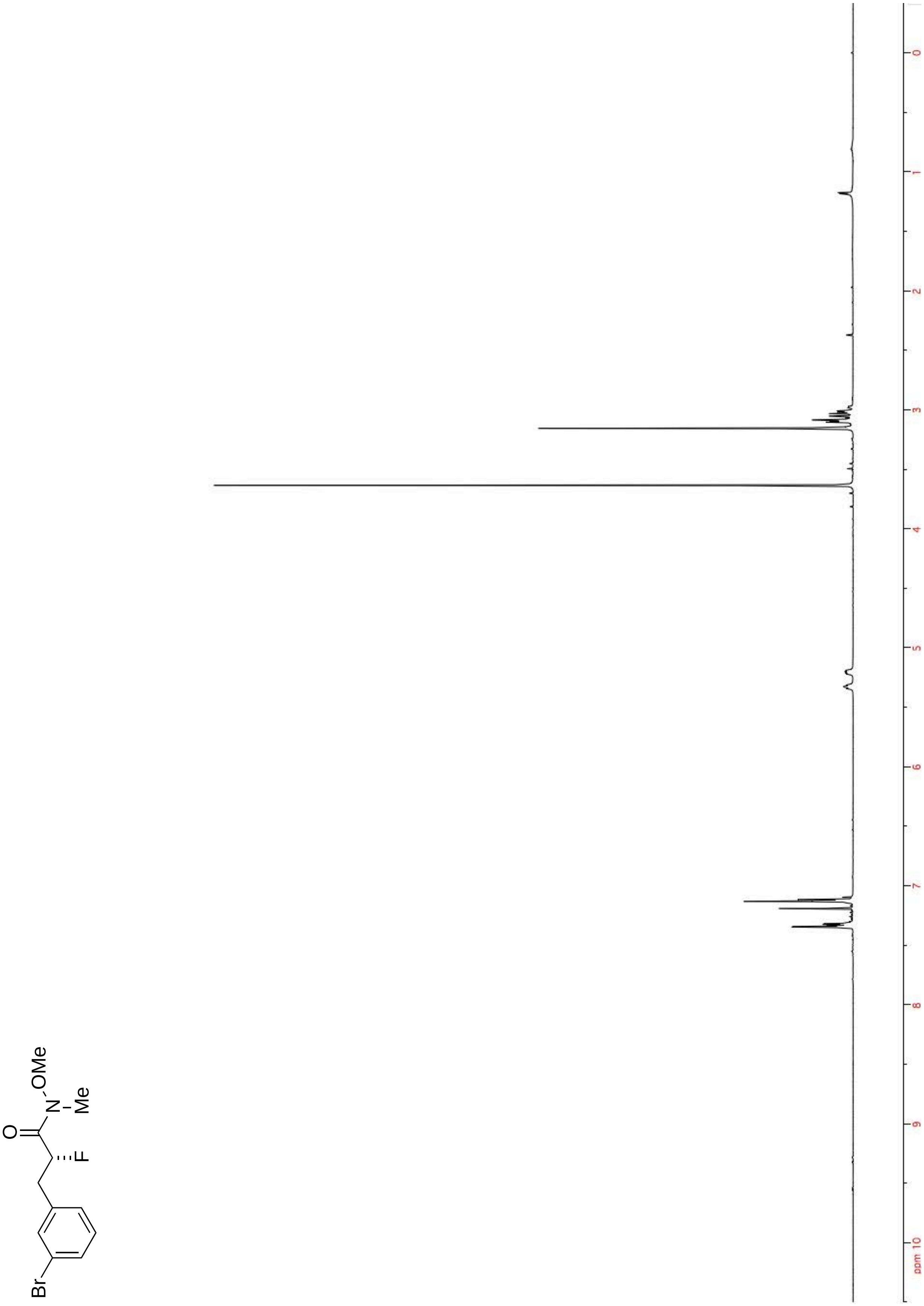

0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
20

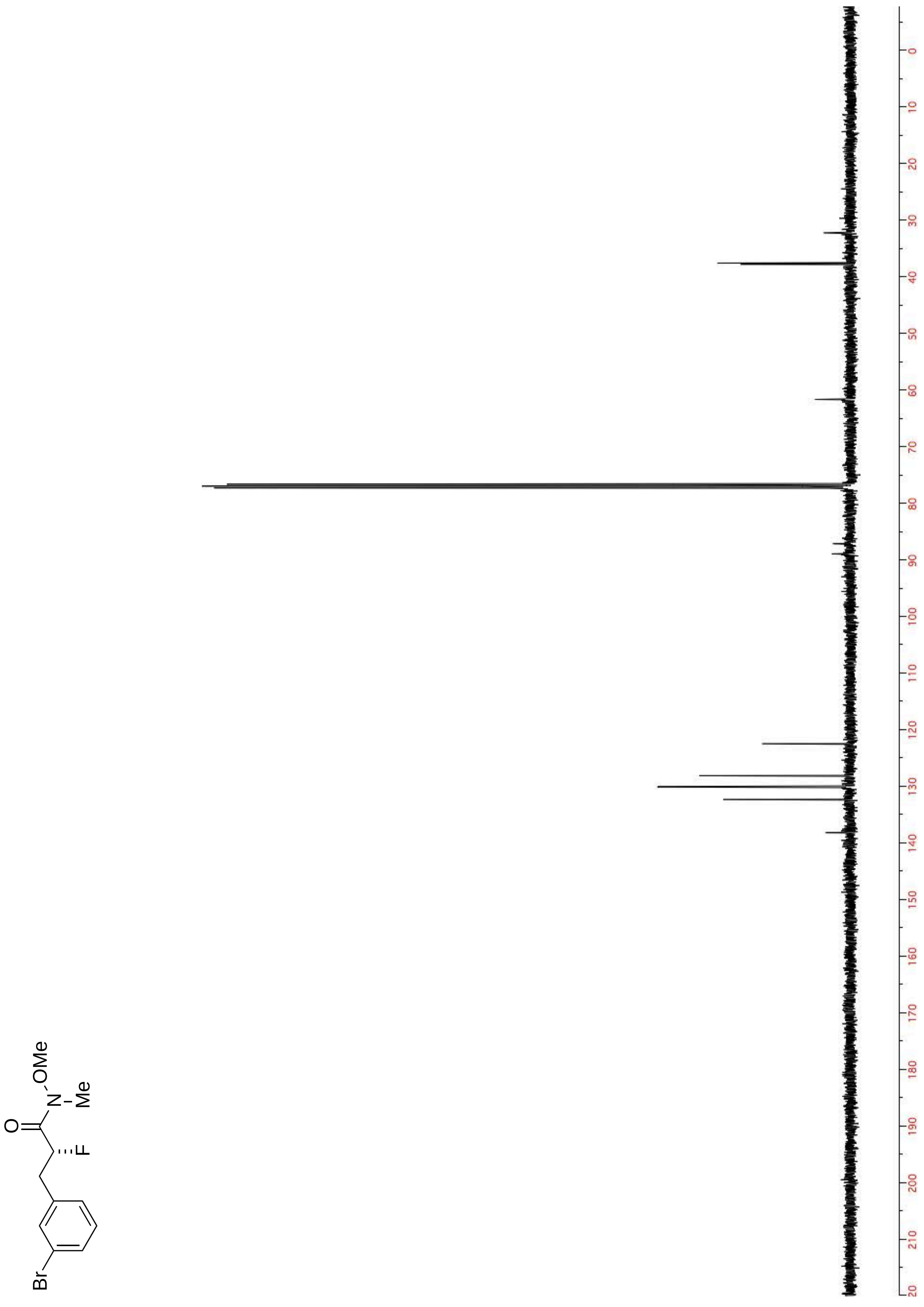

OMe
O
N
OMe
Me
F
0
1
2
3
4
5
6
7
8
9
ppm 10

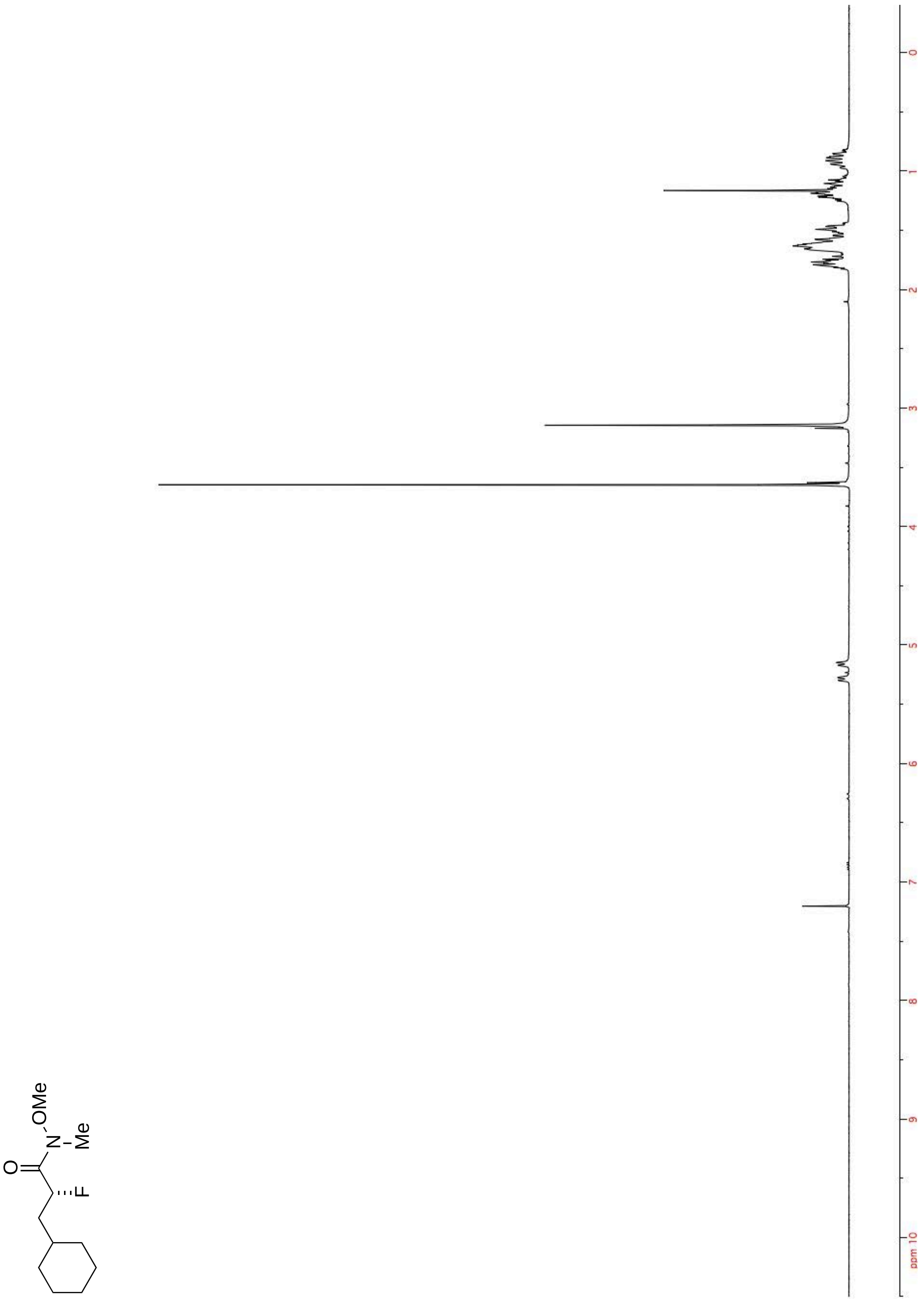

OMe
O
N
OMe
Me
F
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
20

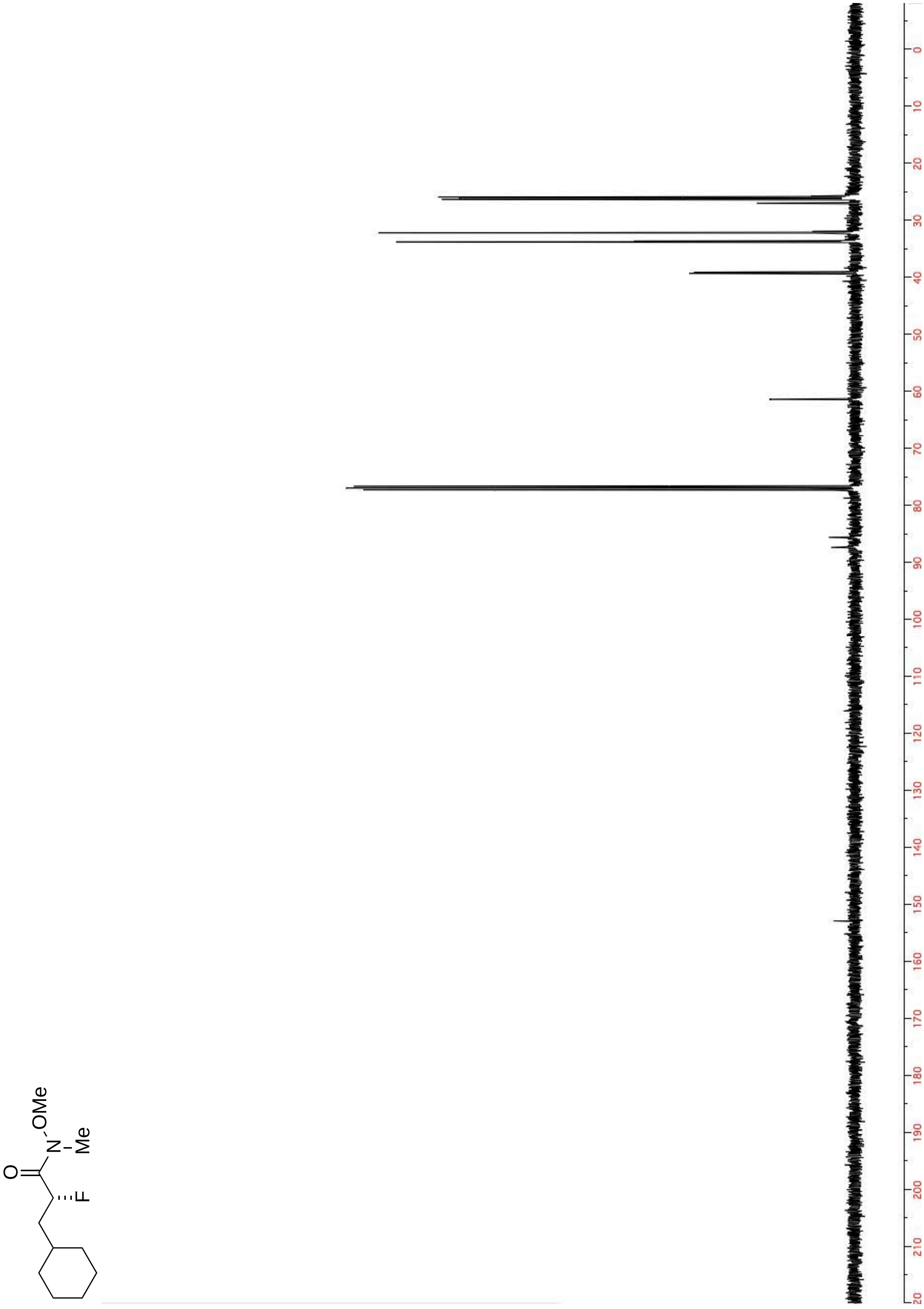

O
N
OMe
Me
F
O2N
ppm
0
1
2
3
4
5
6
7
8
9
10

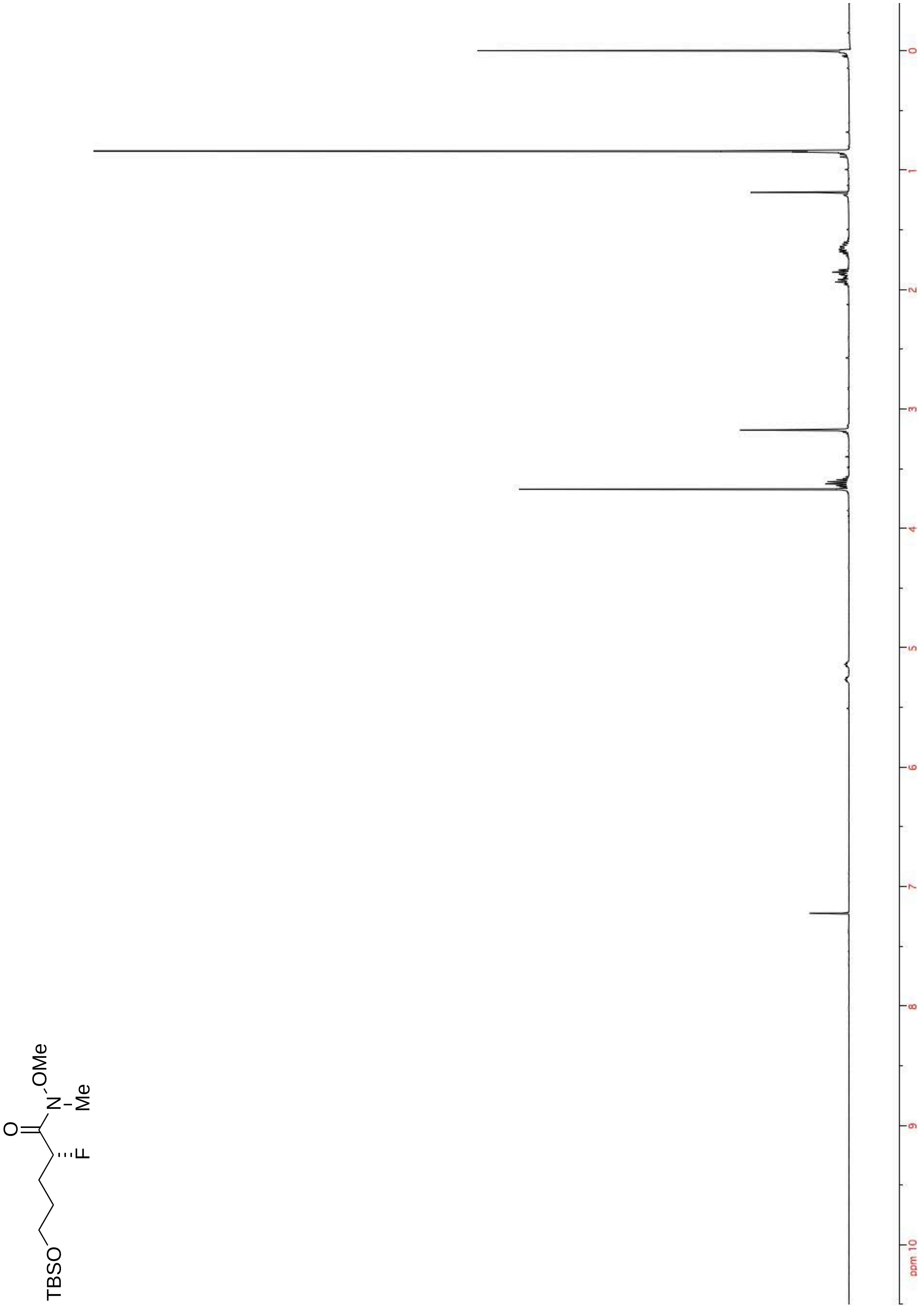

O
N
OMe
Me
F
O2N
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
20

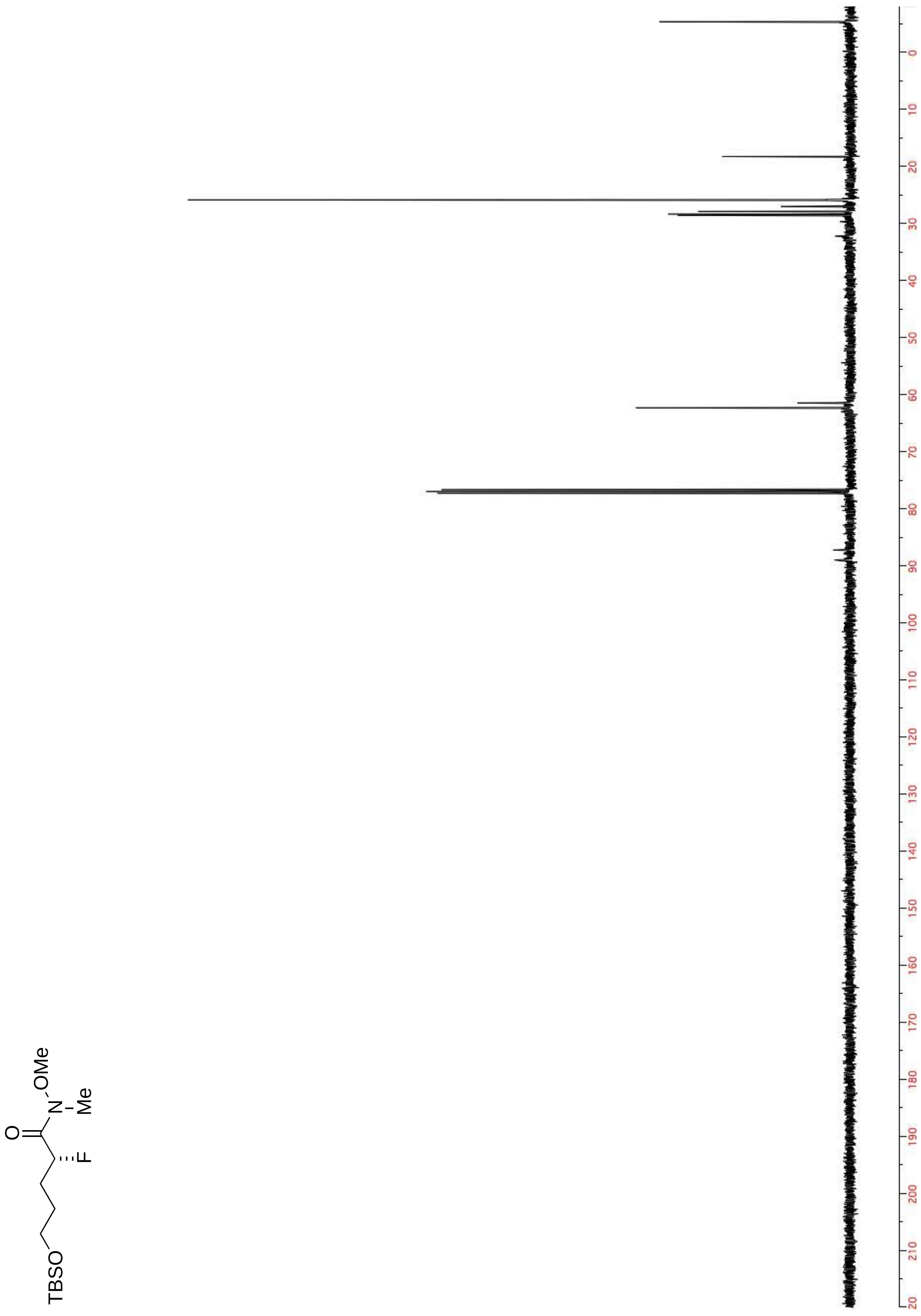

Br
O
N
OMe
Me
F
0
1
2
3
4
5
6
7
8
9
ppm 10

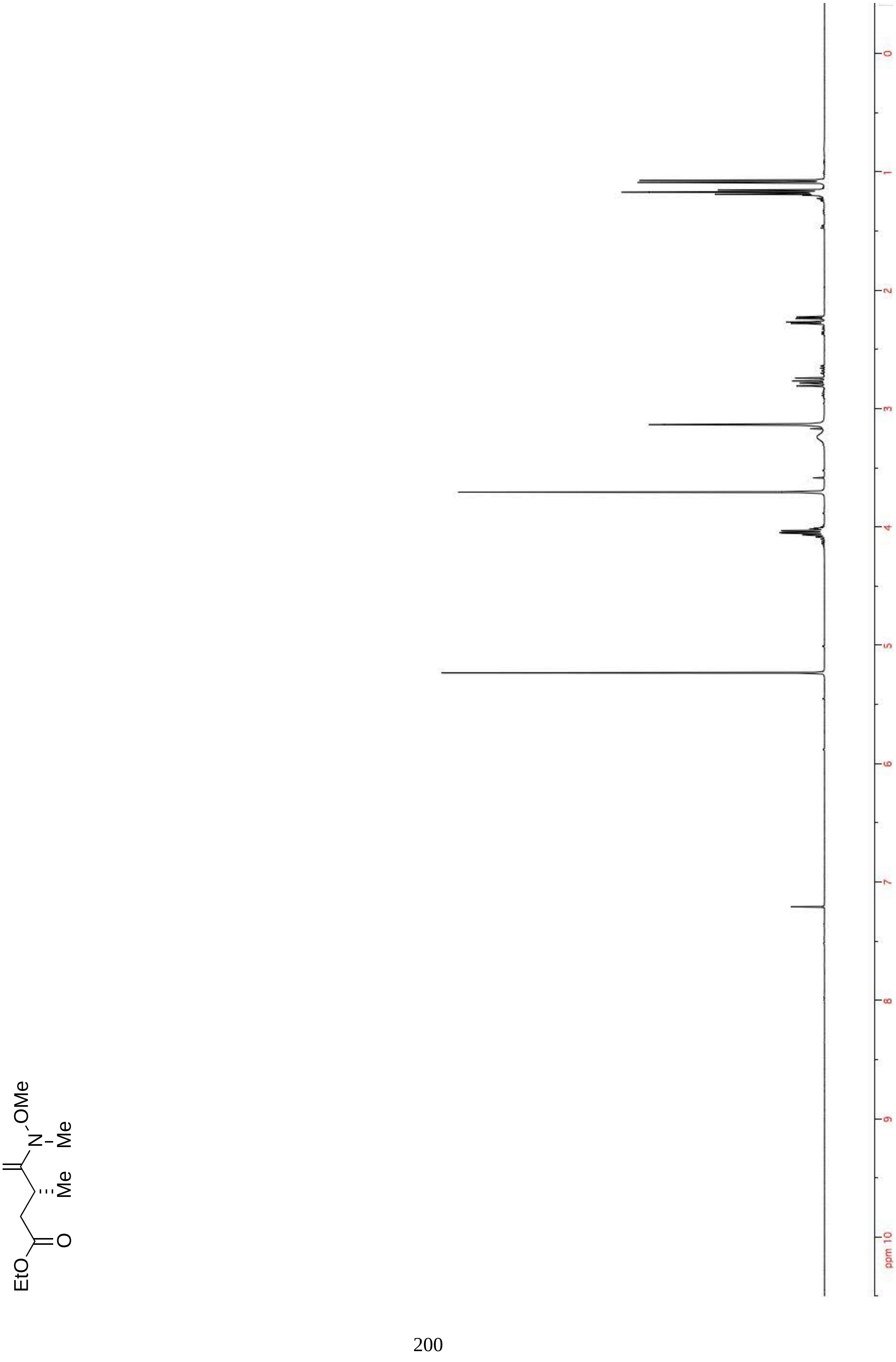

Br
F
O
N
OMe
Me
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

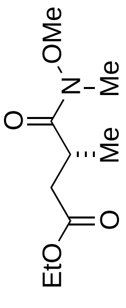

O
N
OMe
Me
F
0
1
2
3
4
5
6
7
8
9
ppm 10

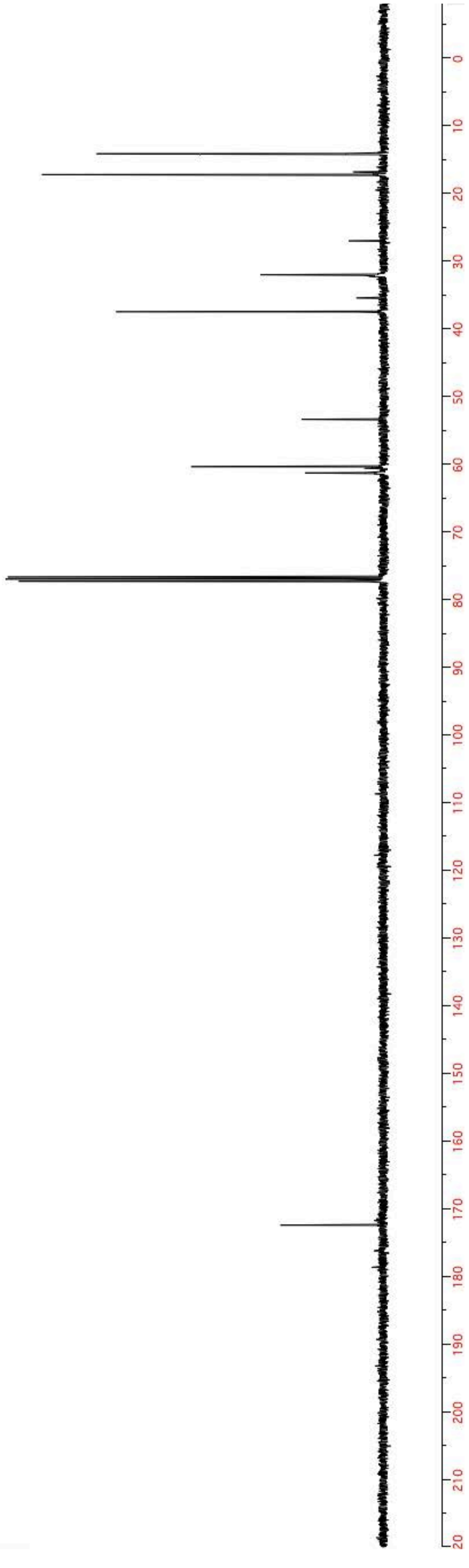

O
N
OMe
Me
F
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

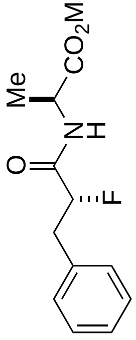

TBSO
O
N
OMe
Me
F
ppm
0
1
2
3
4
5
6
7
8
9
10

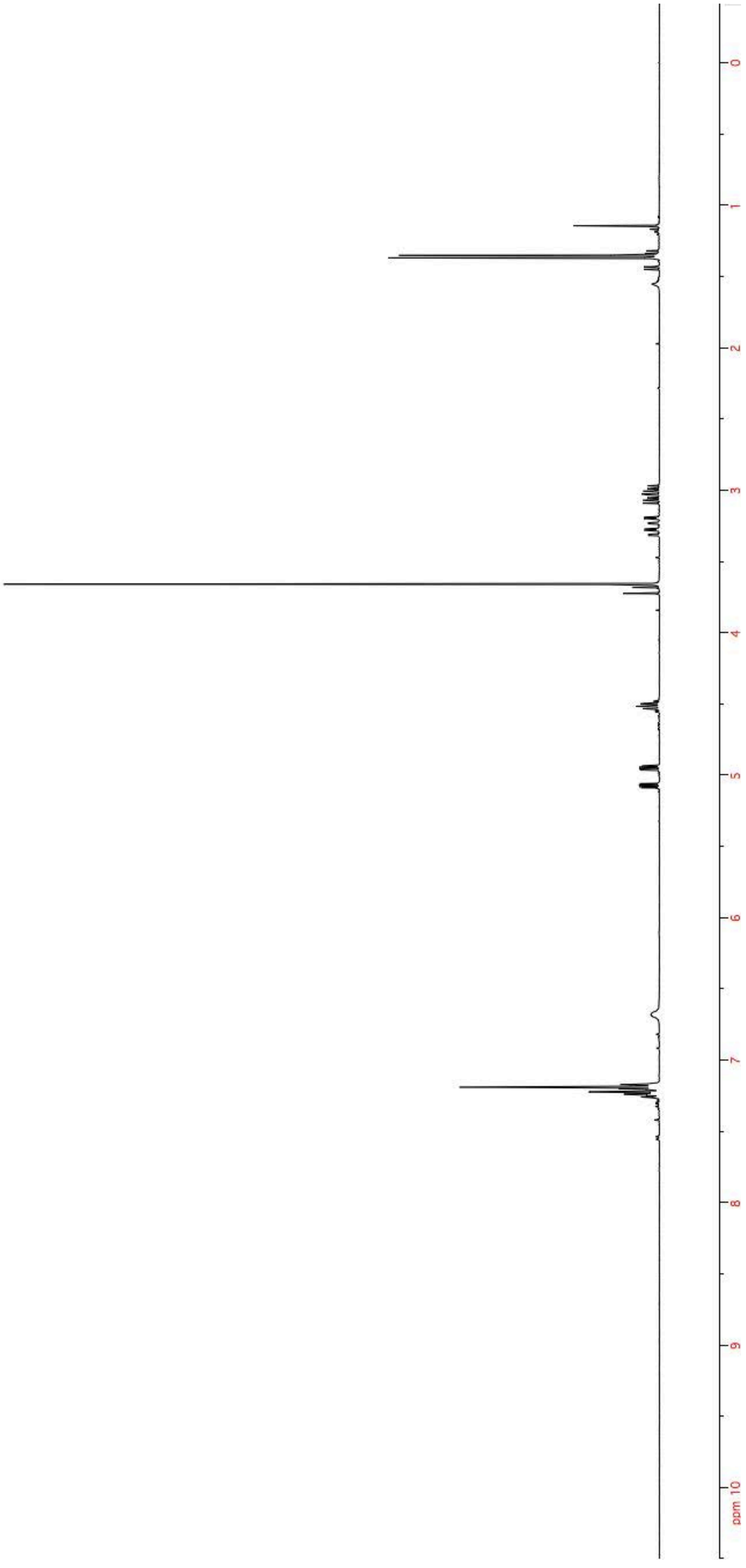

TBSO
O
N
OMe
Me
F
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

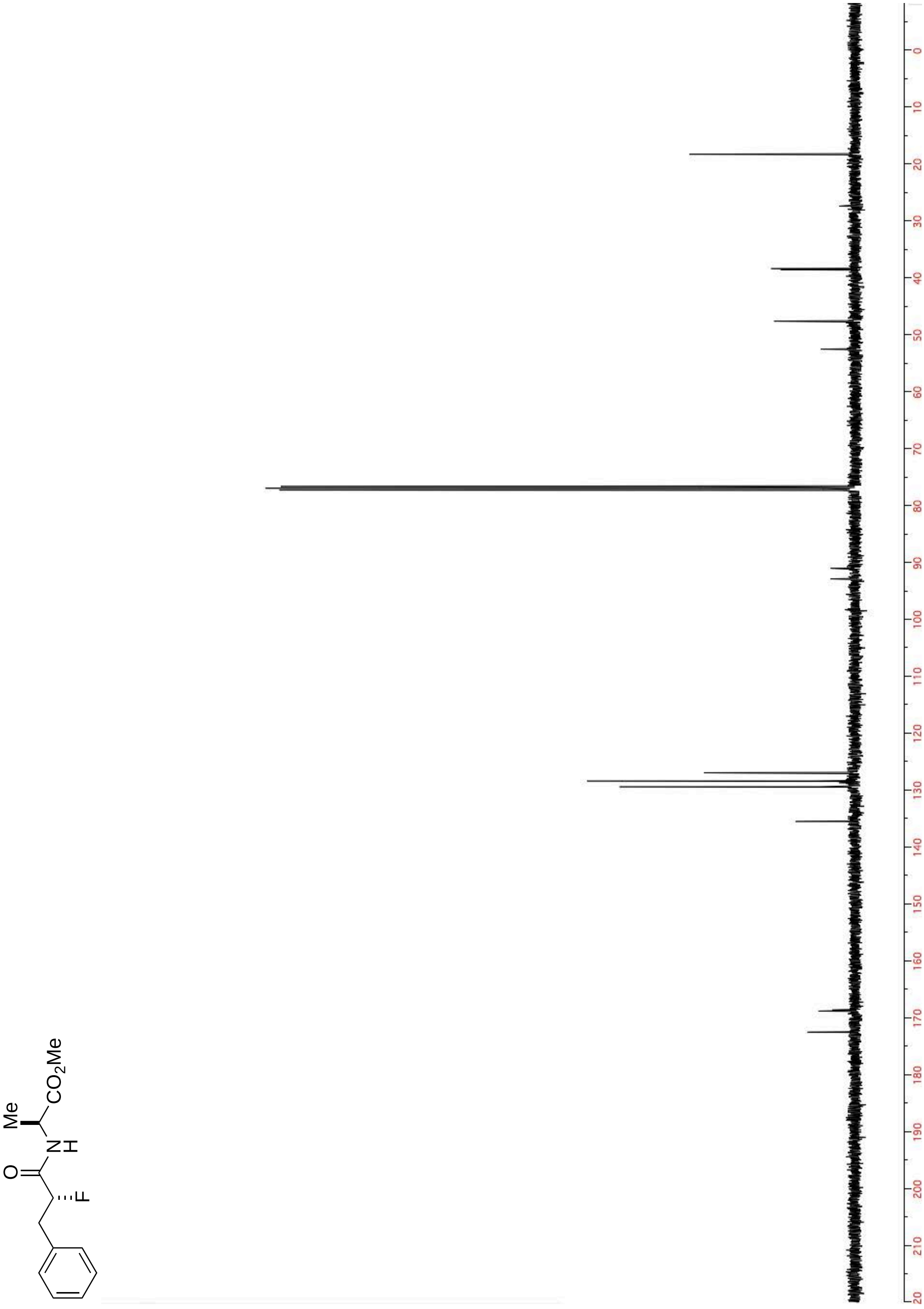

EtO
O
O
Me
N
OMe
Me
ppm
0
1
2
3
4
5
6
7
8
9
10

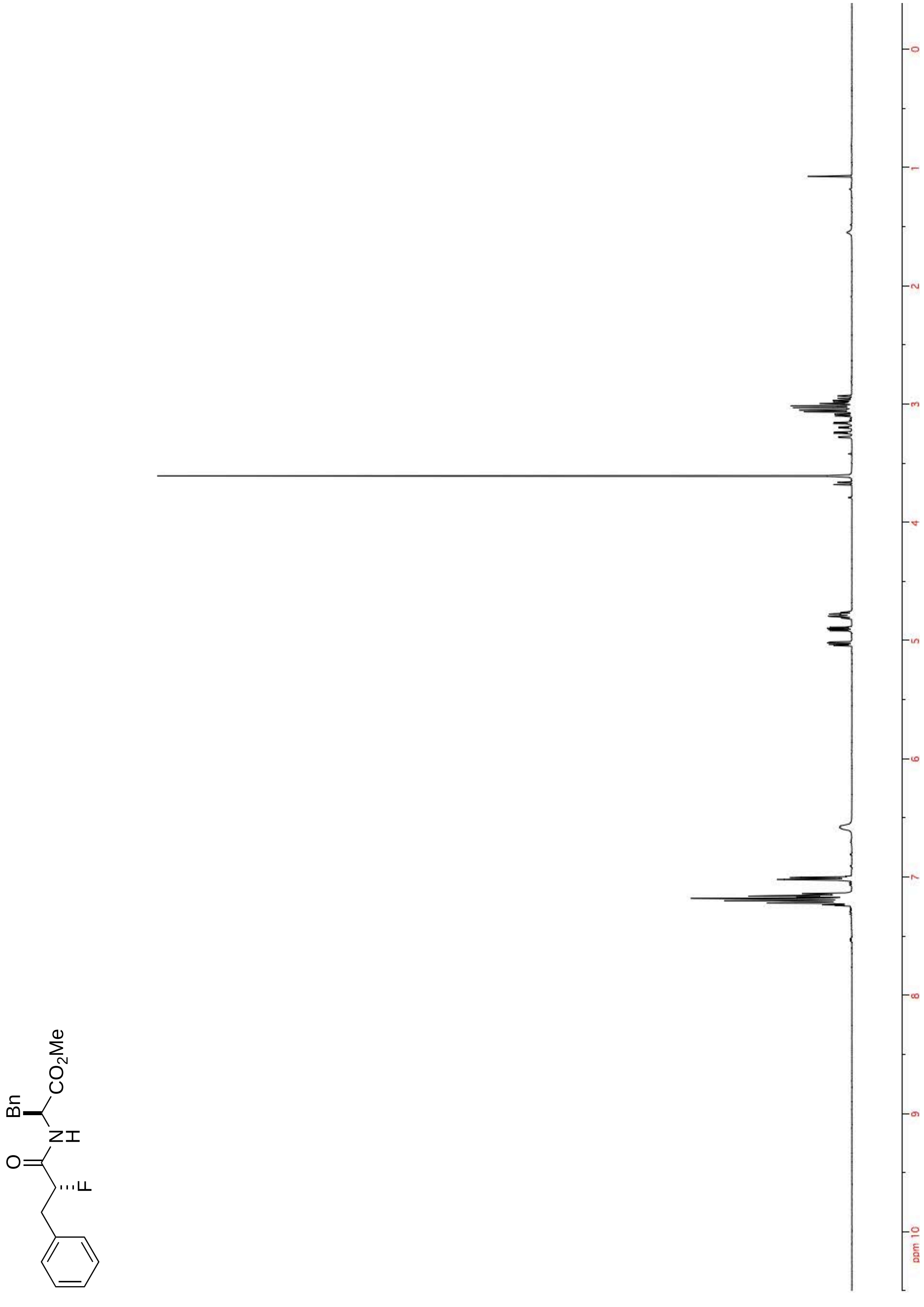

EtO
O
O
Me
N
OMe
Me

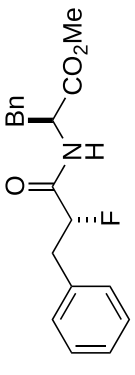

0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

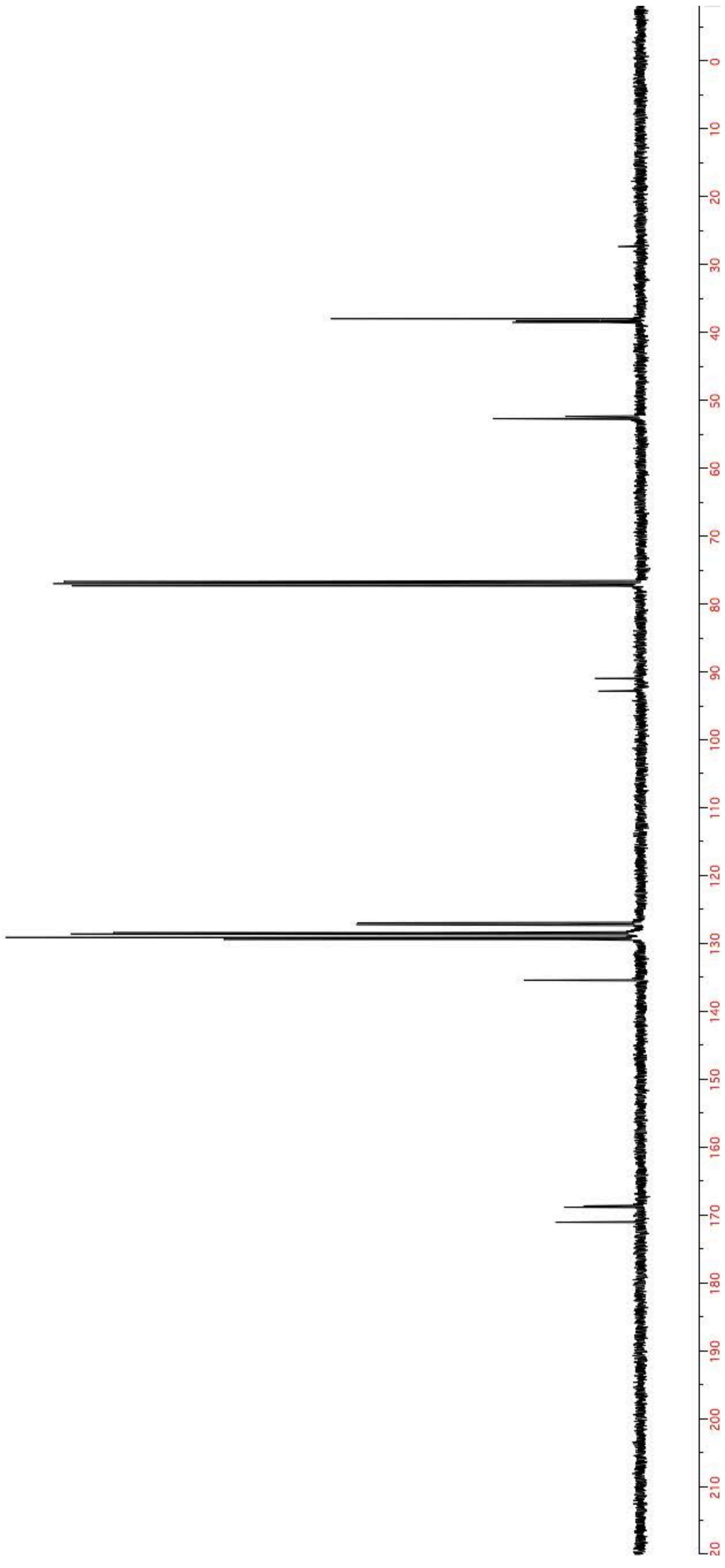

O
N
H
Me
CO2Me
F

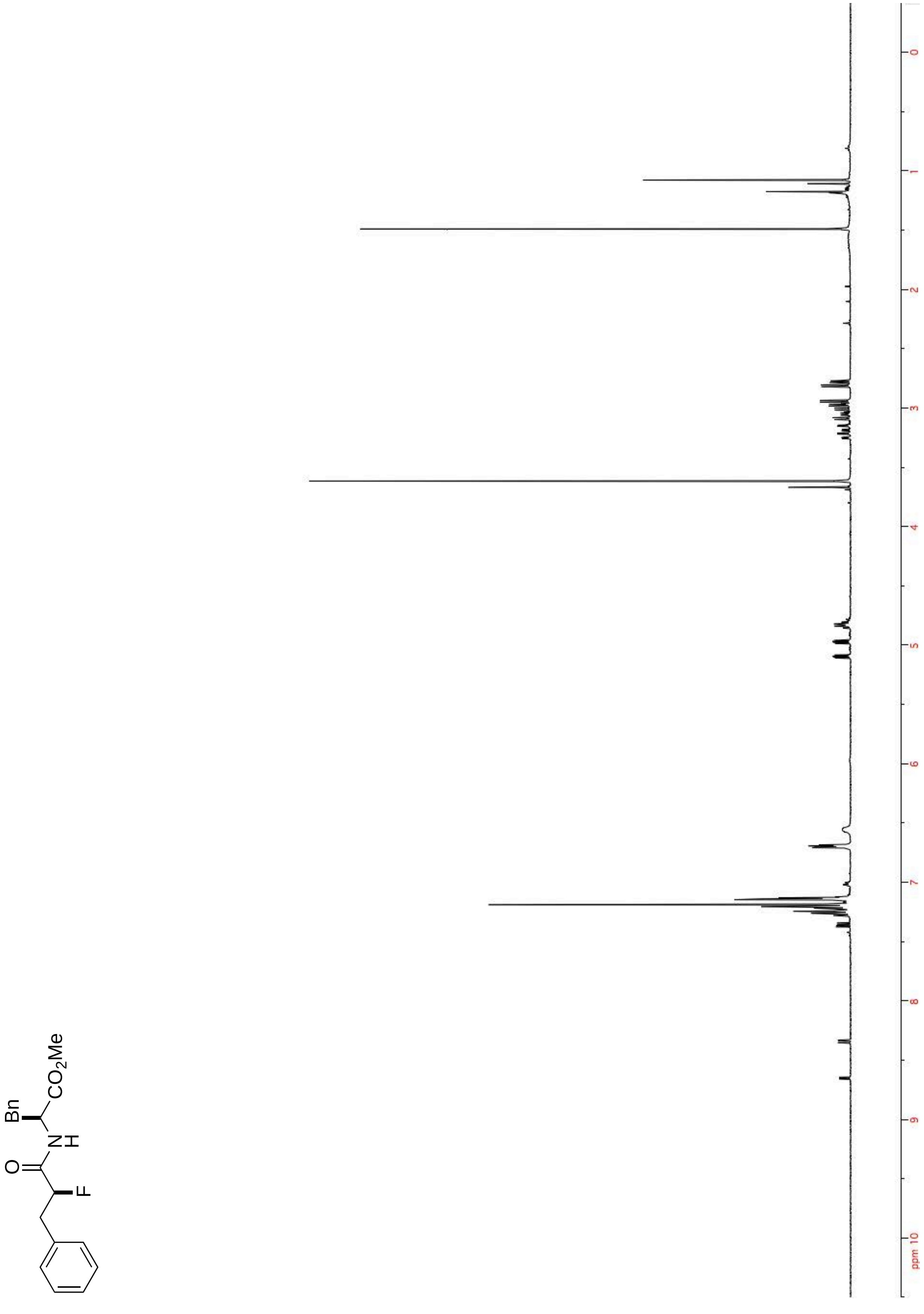

0
1
2
3
4
5
6
7
8
9
ppm 10

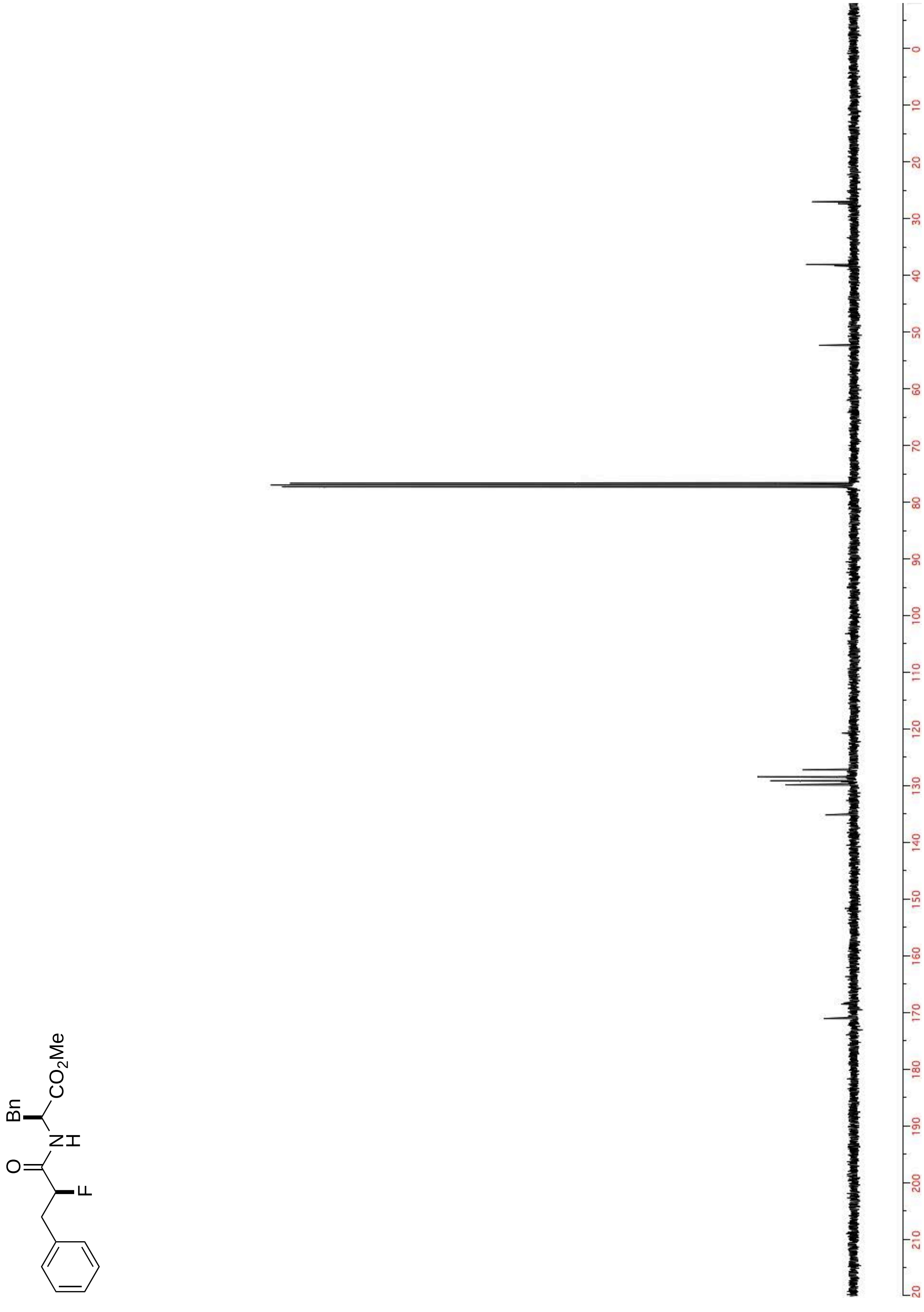

O
N
H
Me
CO2Me
F
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

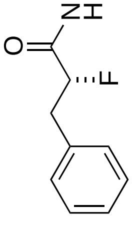

O
N
H
F
Bn
CO2Me
ppm 10
9
8
7
6
5
4
3
2
1
0

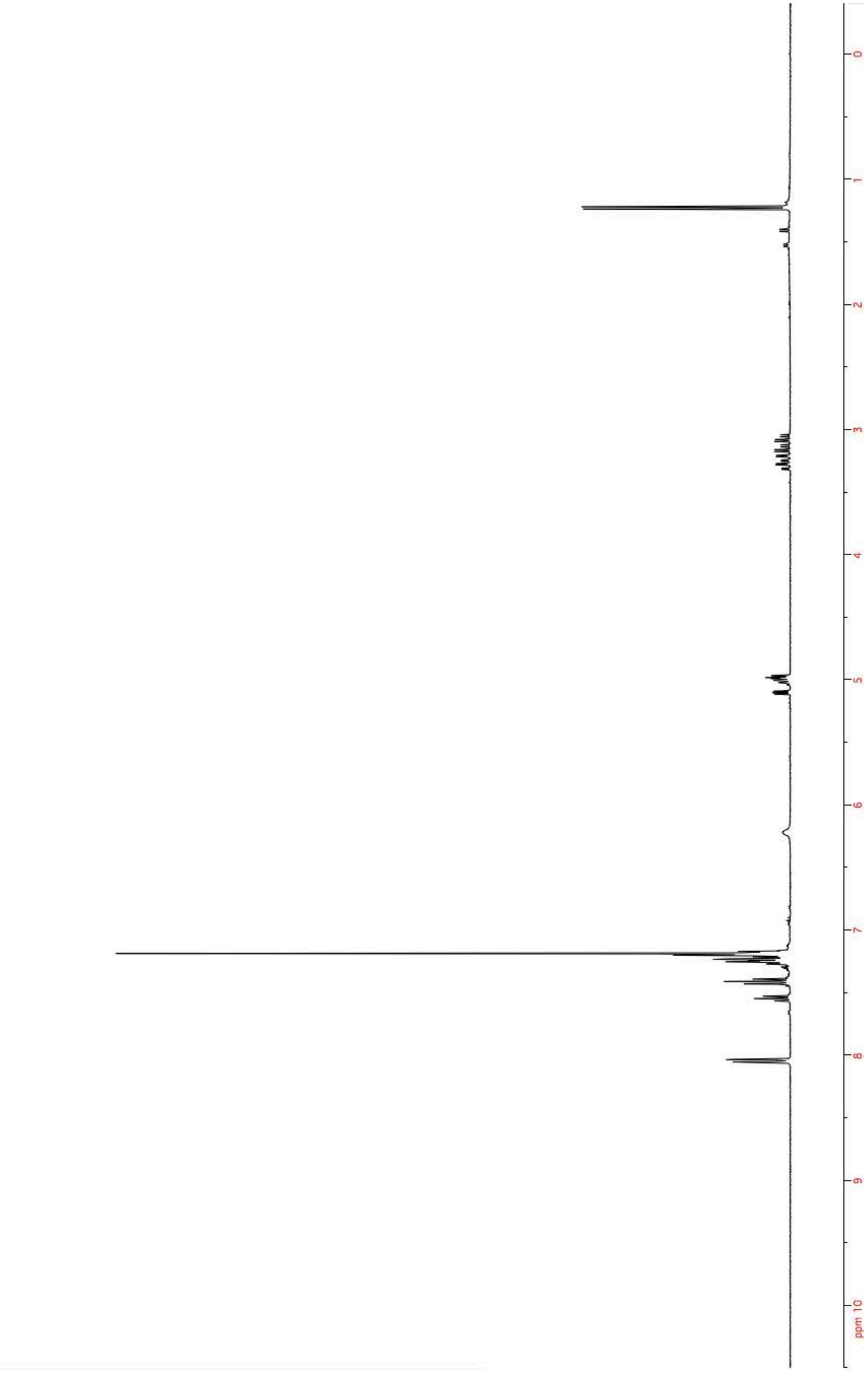

O
N
H
Bn
CO2Me
F

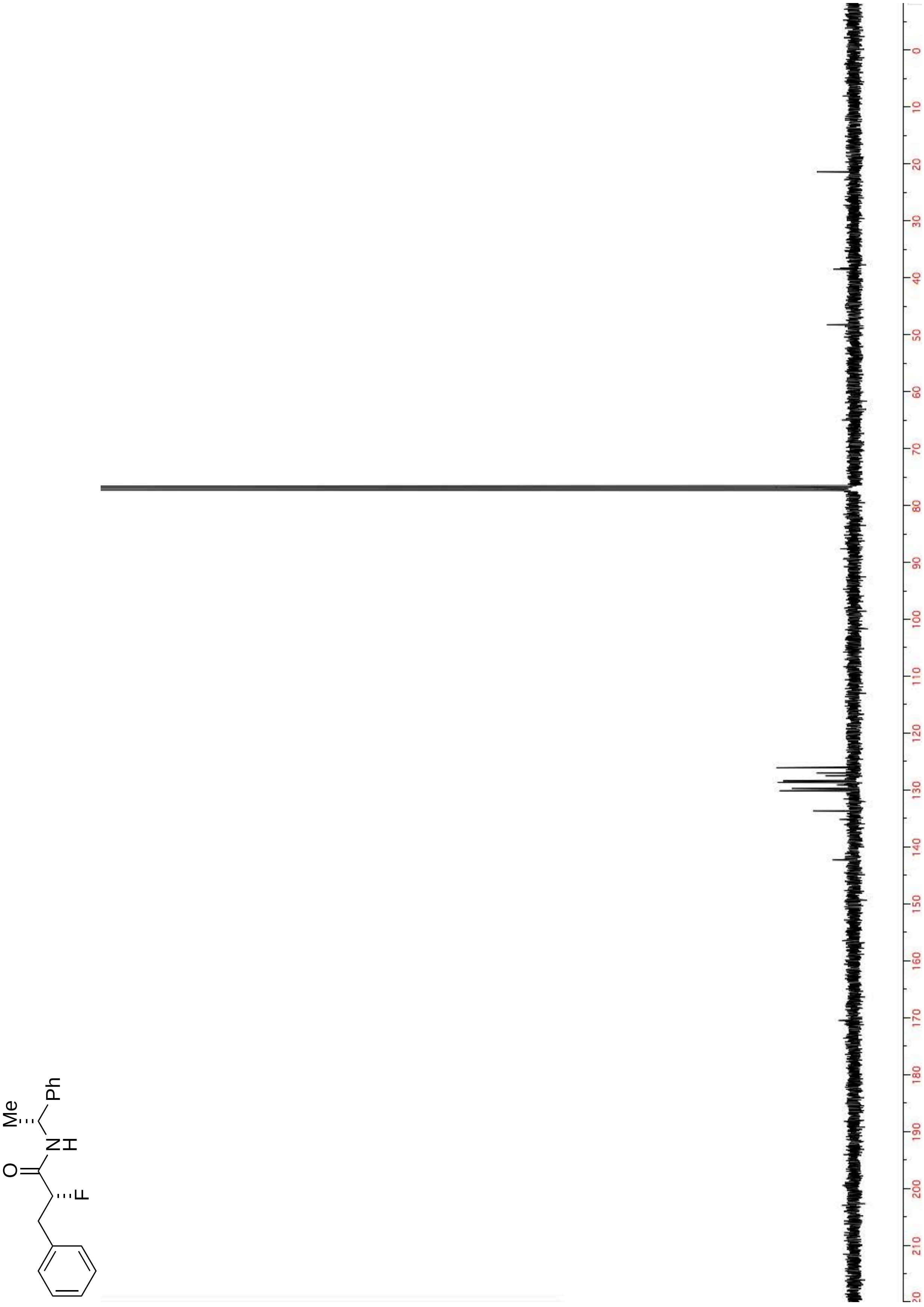

0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220


Bn
O
N
H
F
CO2Me
ppm
0
1
2
3
4
5
6
7
8
9
10

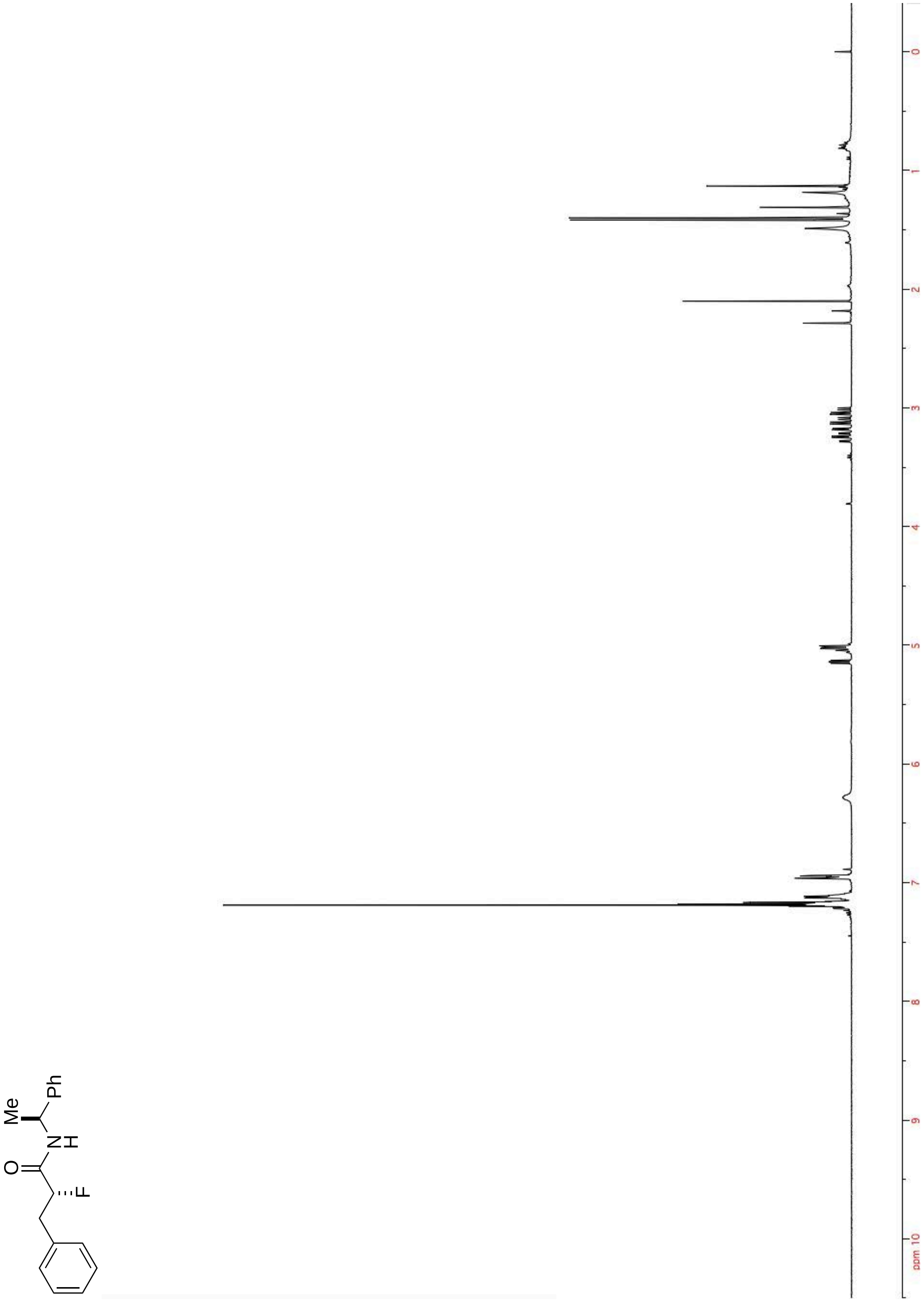

O
N
H
Bn
CO2Me
F
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

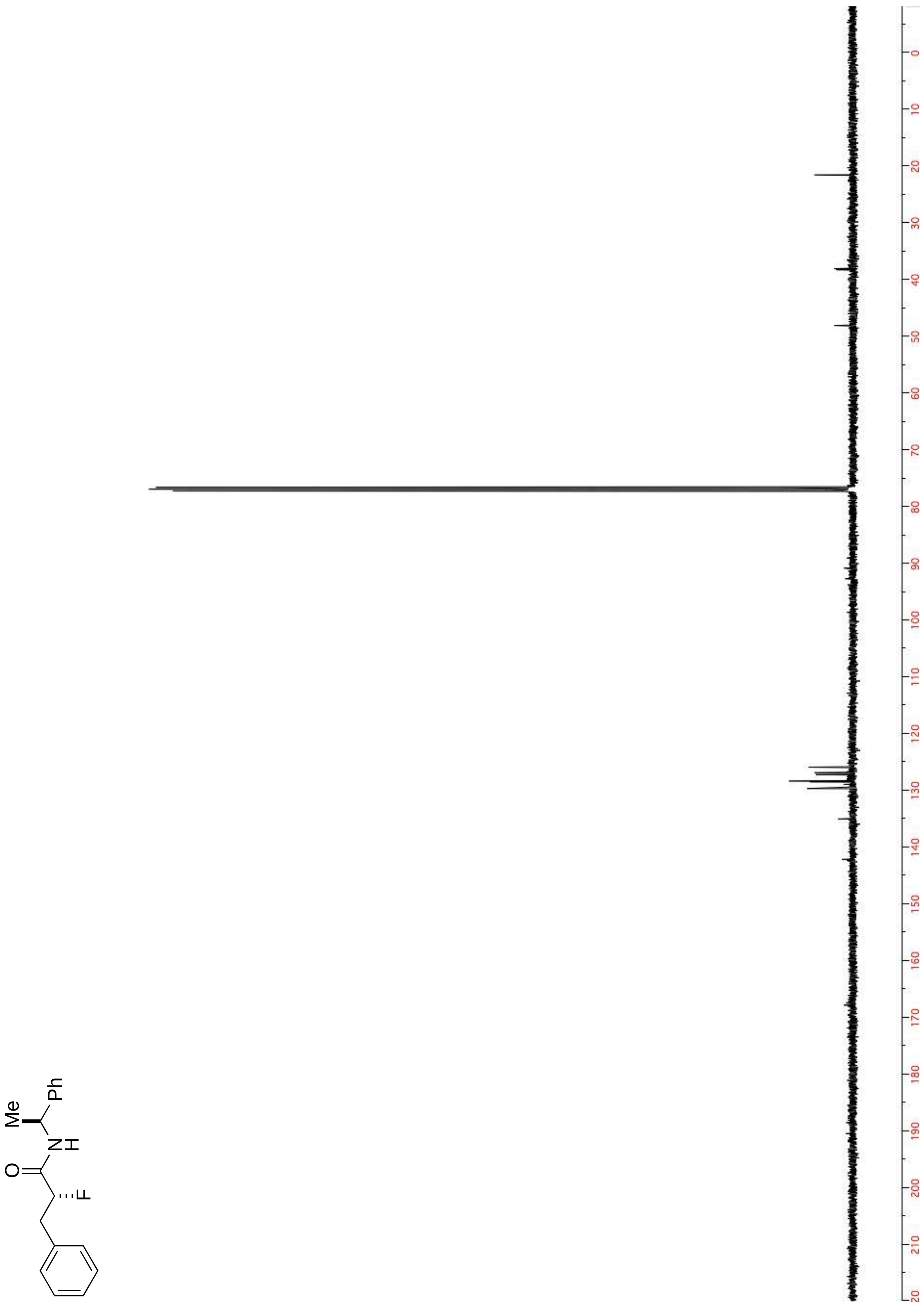

O
N
H
Me
Ph
F


0
1
2
3
4
5
6
7
8
9
ppm 10

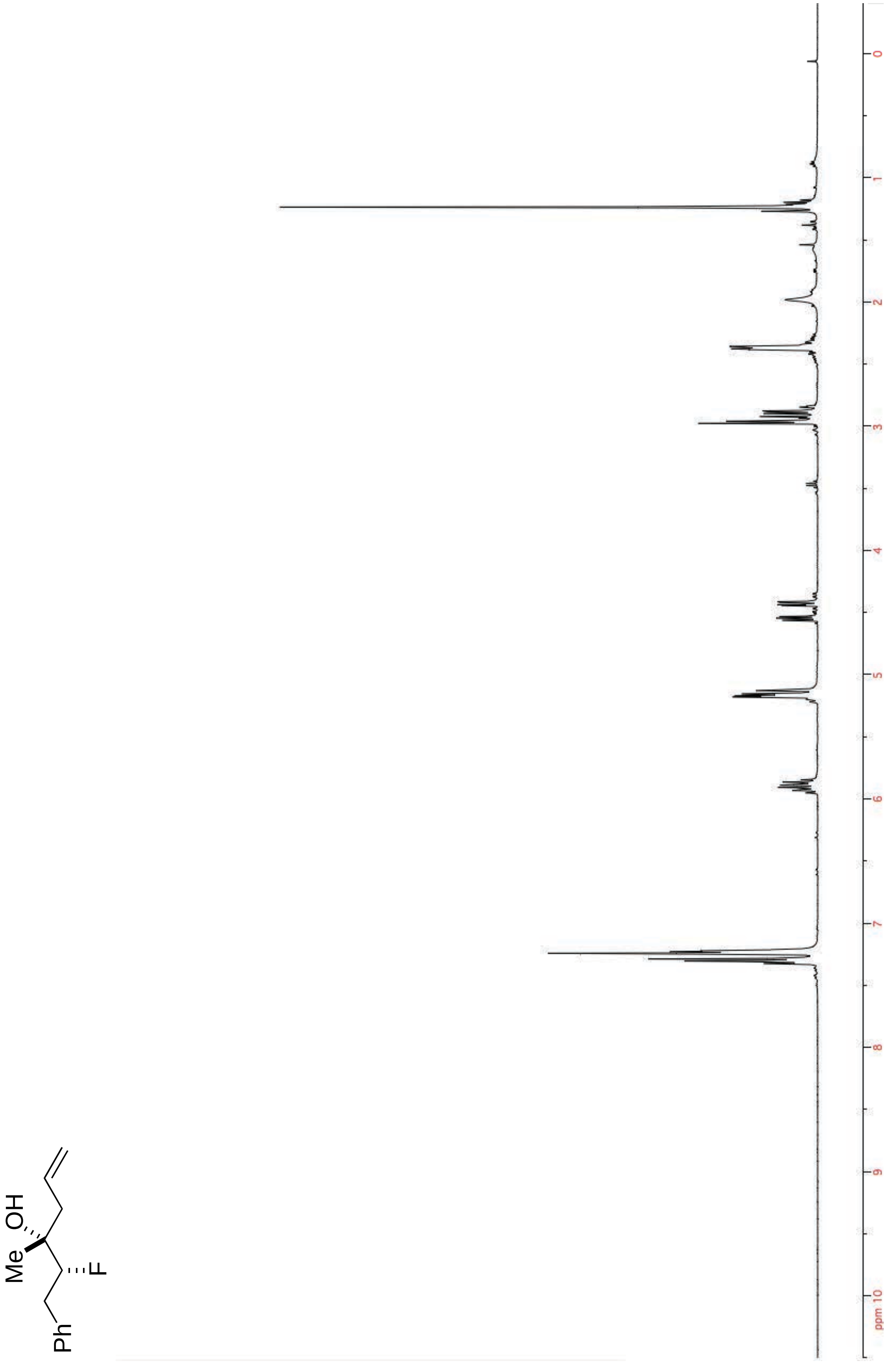


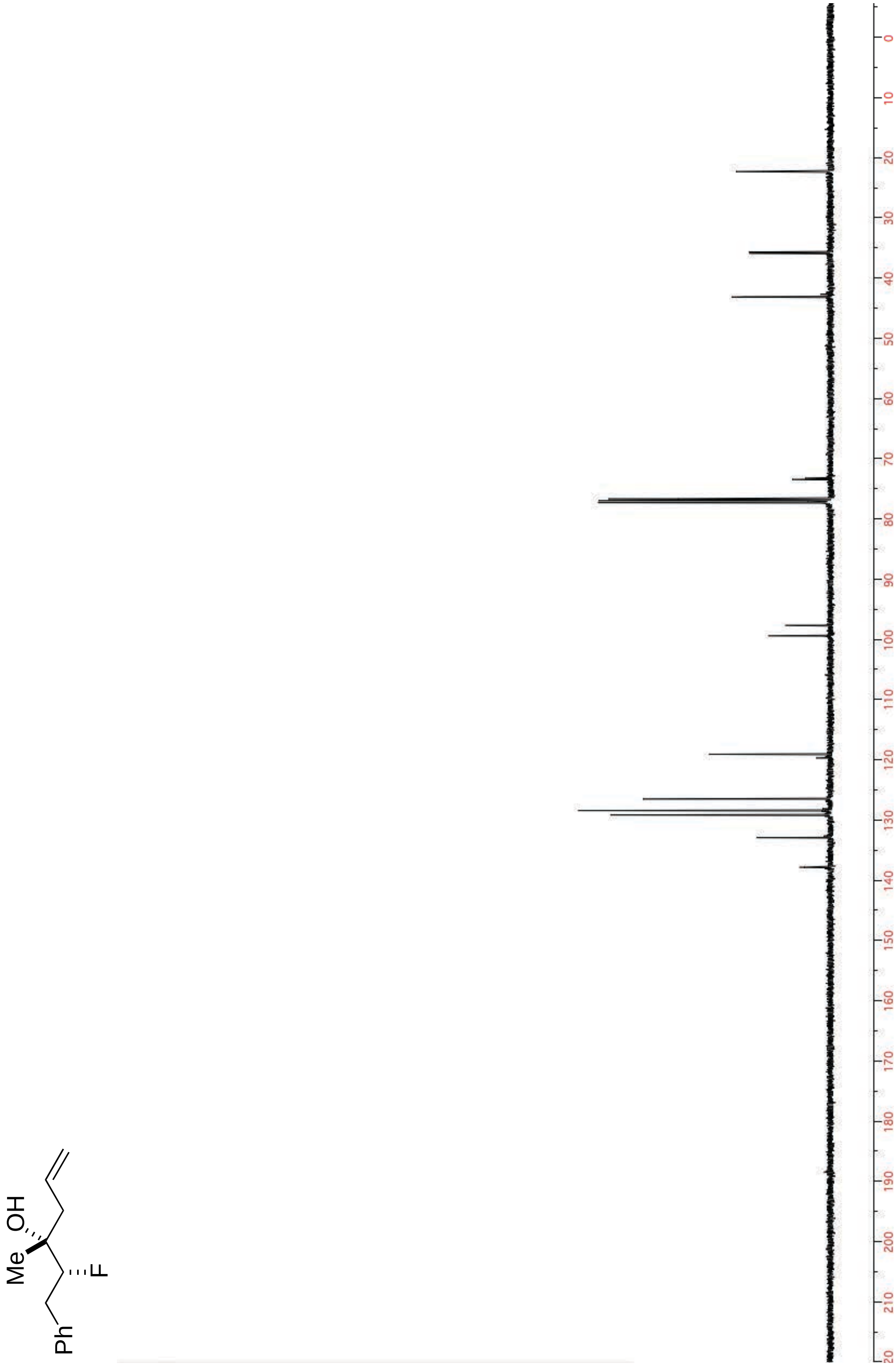
O
N
H
Me
Ph
F
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

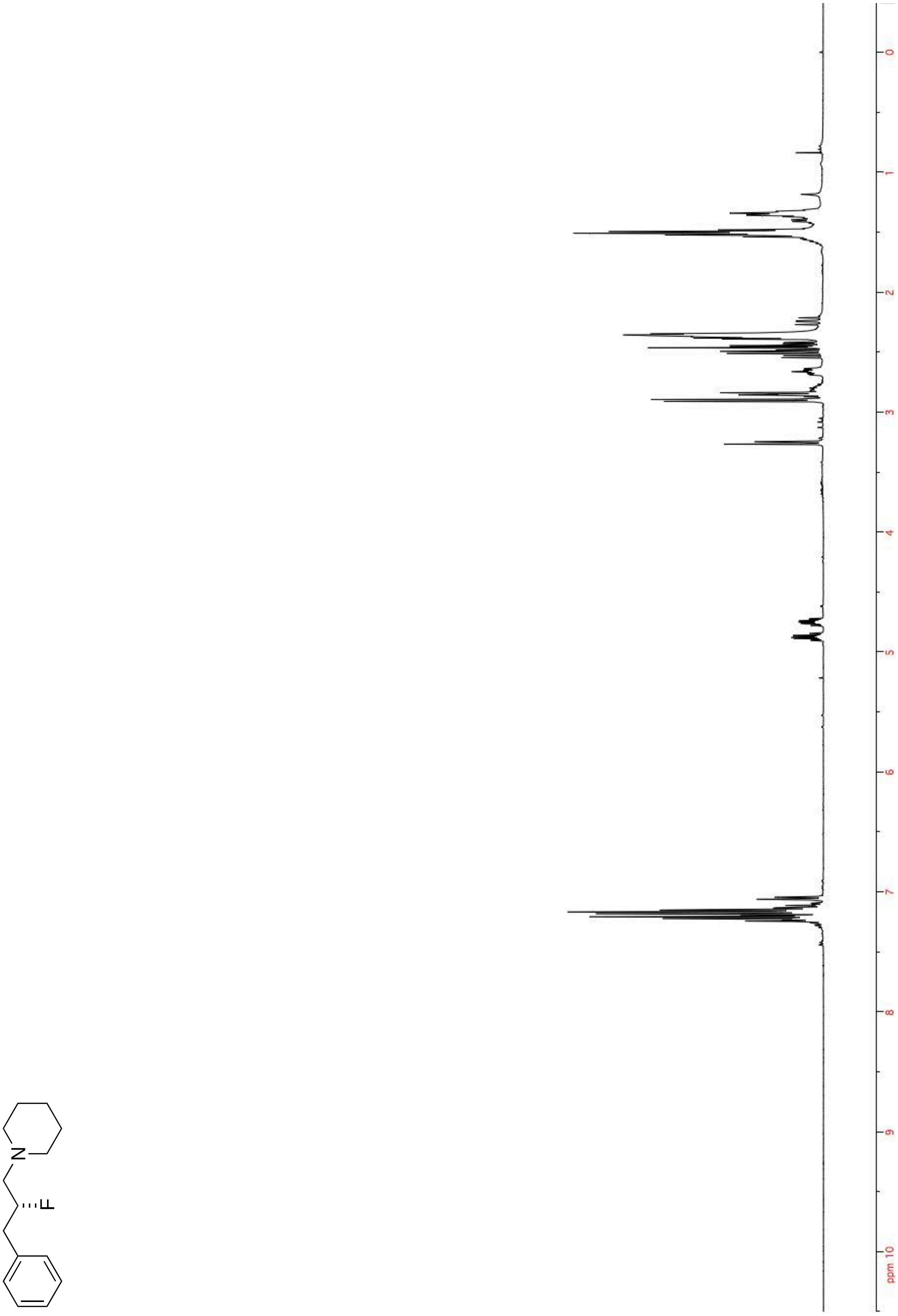

O
N
H
Me
Ph
F
ppm
0
1
2
3
4
5
6
7
8
9
10

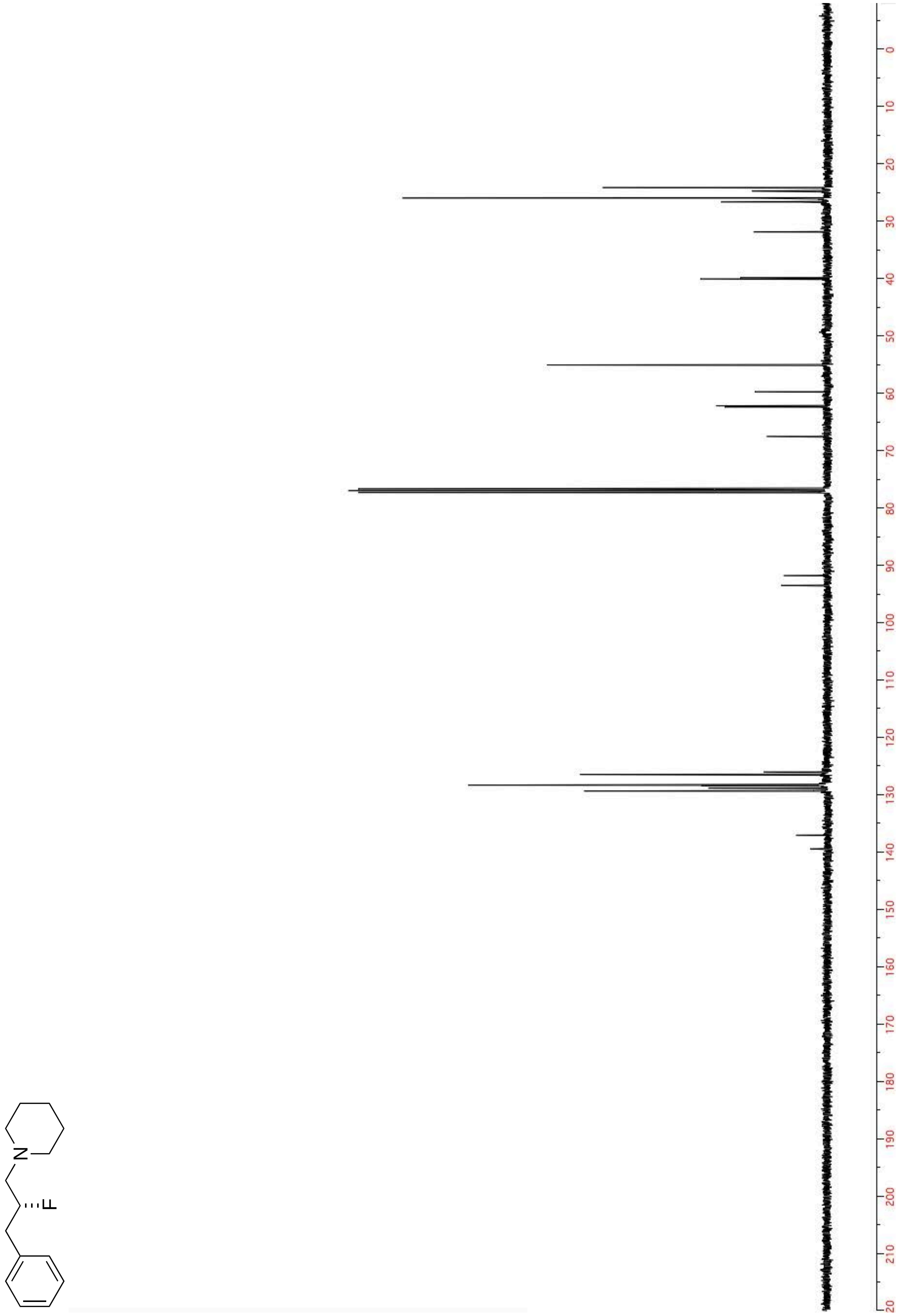


Me
Ph
O
N
H
F
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
20

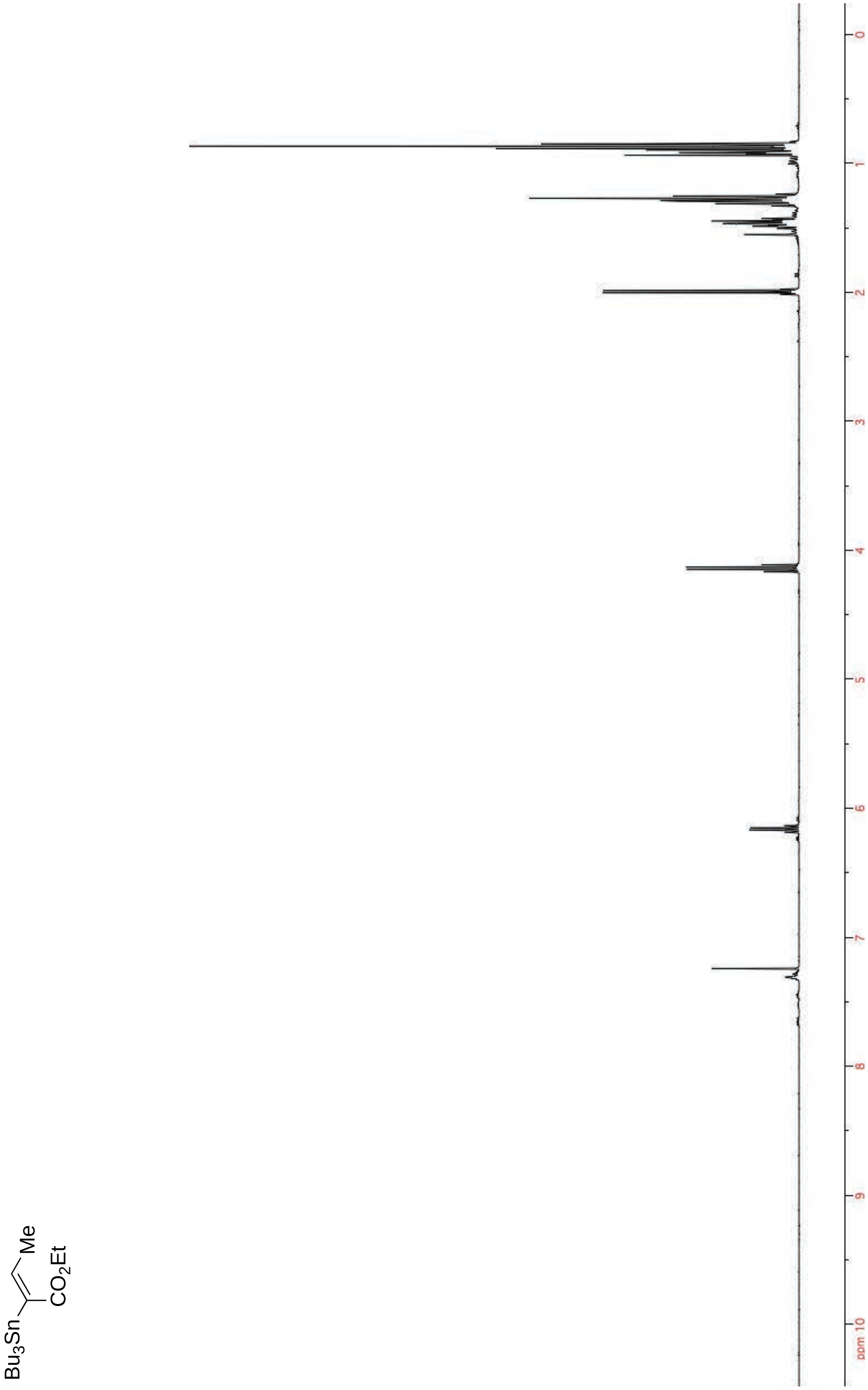

Me
OH
F
Ph
ppm 10
9
8
7
6
5
4
3
2
1
0

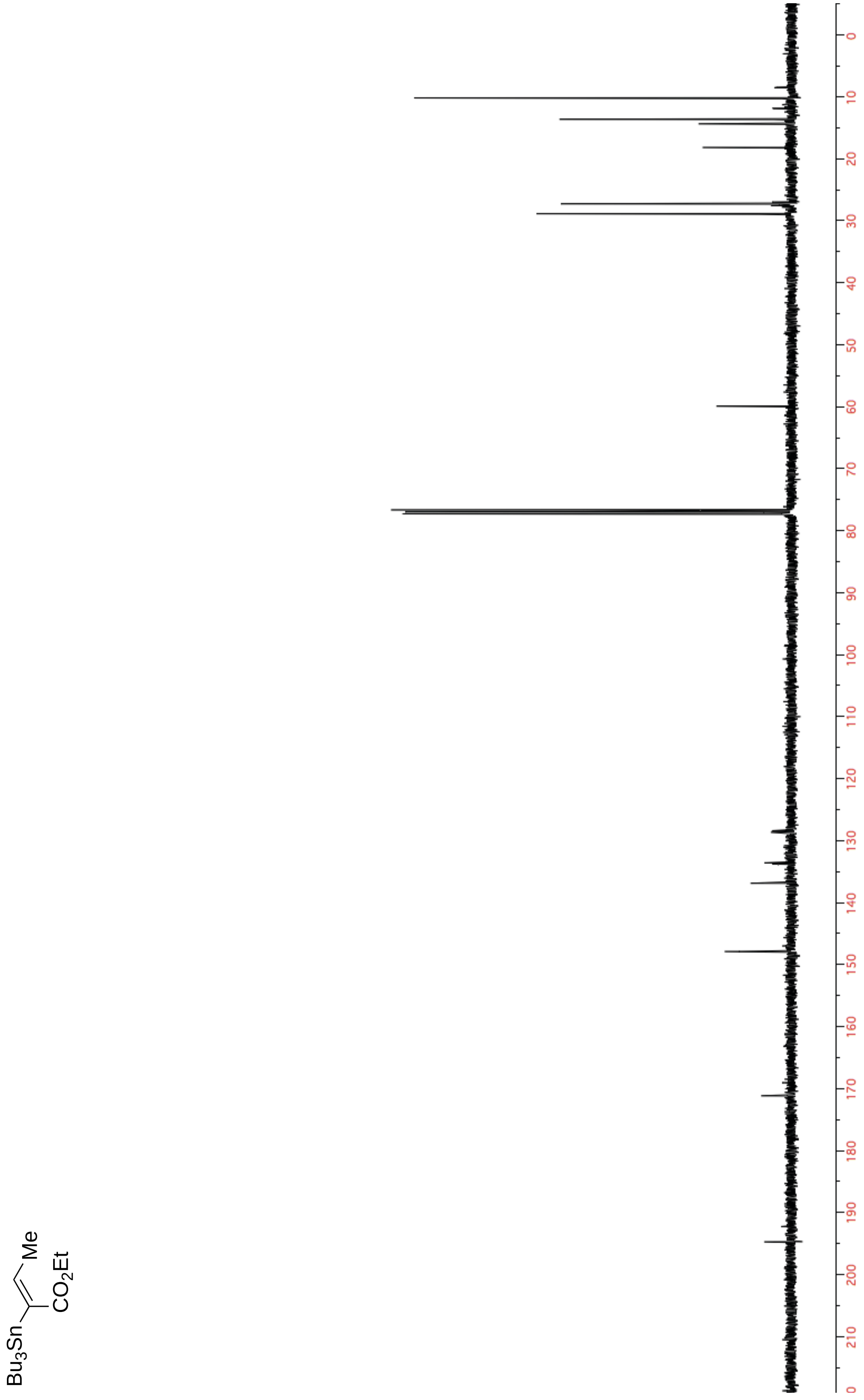

Me
OH
F
Ph
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

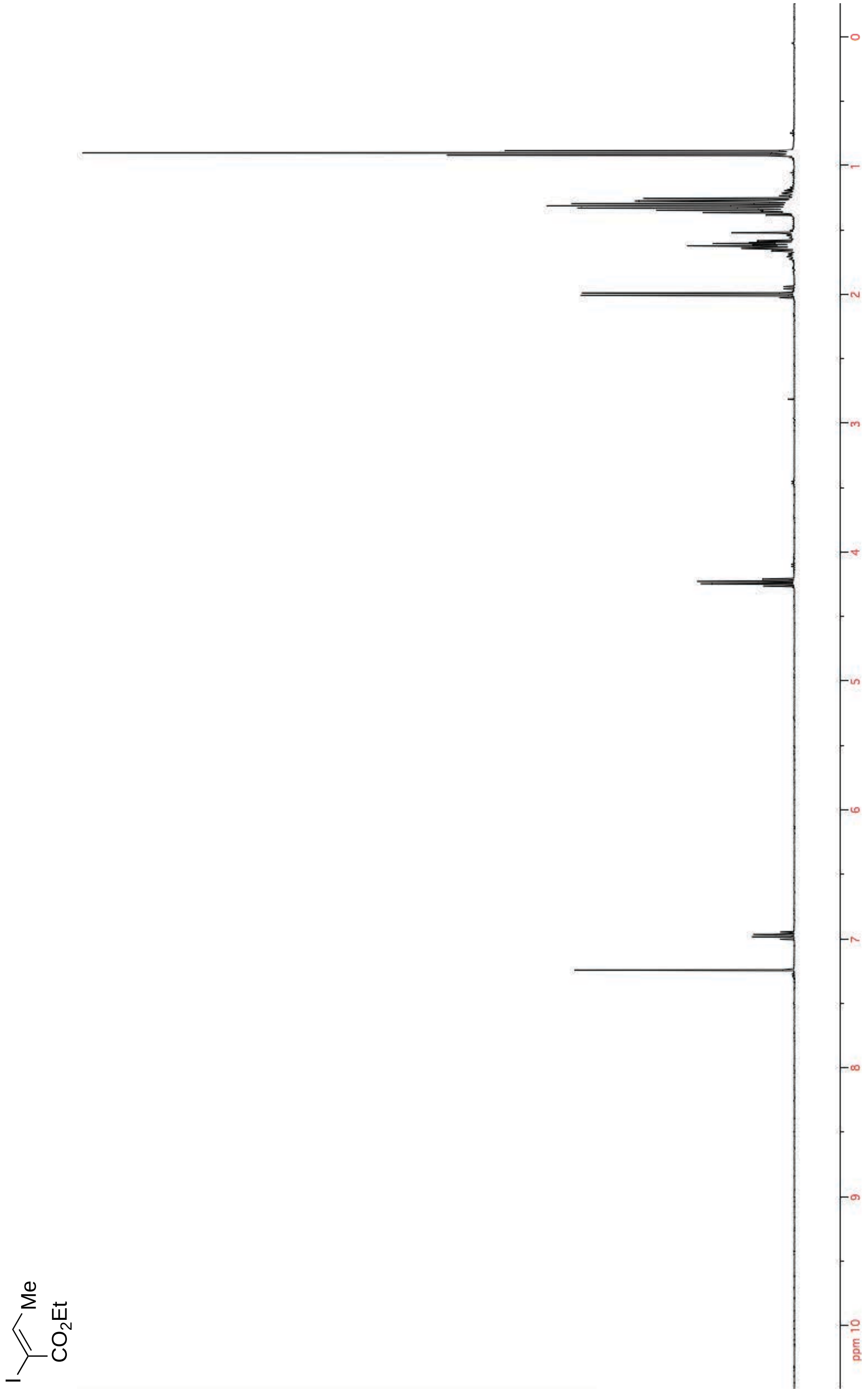

N
F
ppm 10
9
8
7
6
5
4
3
2
1
0

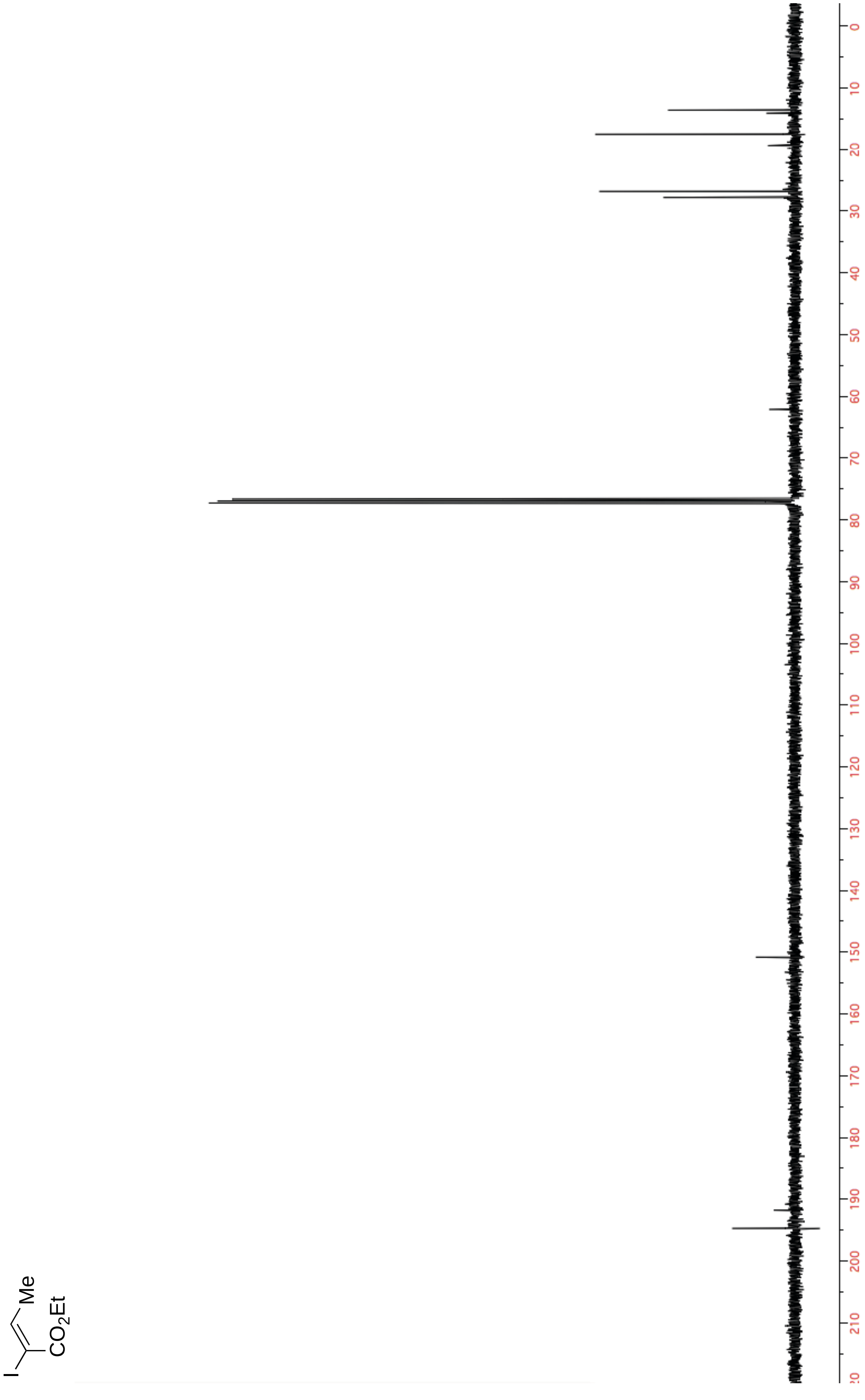

0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
20
N
F

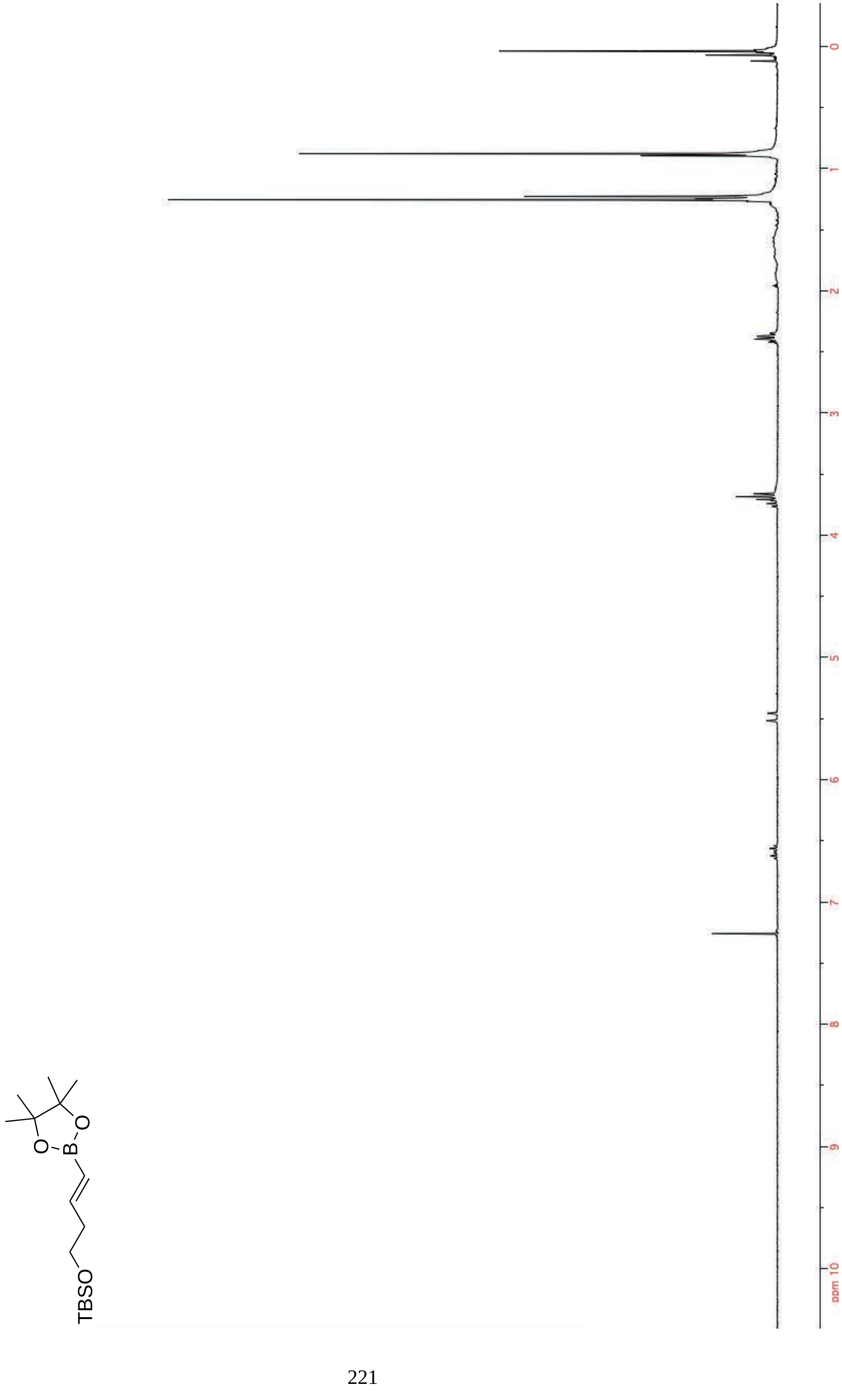
Spectral Data for Chapter 2

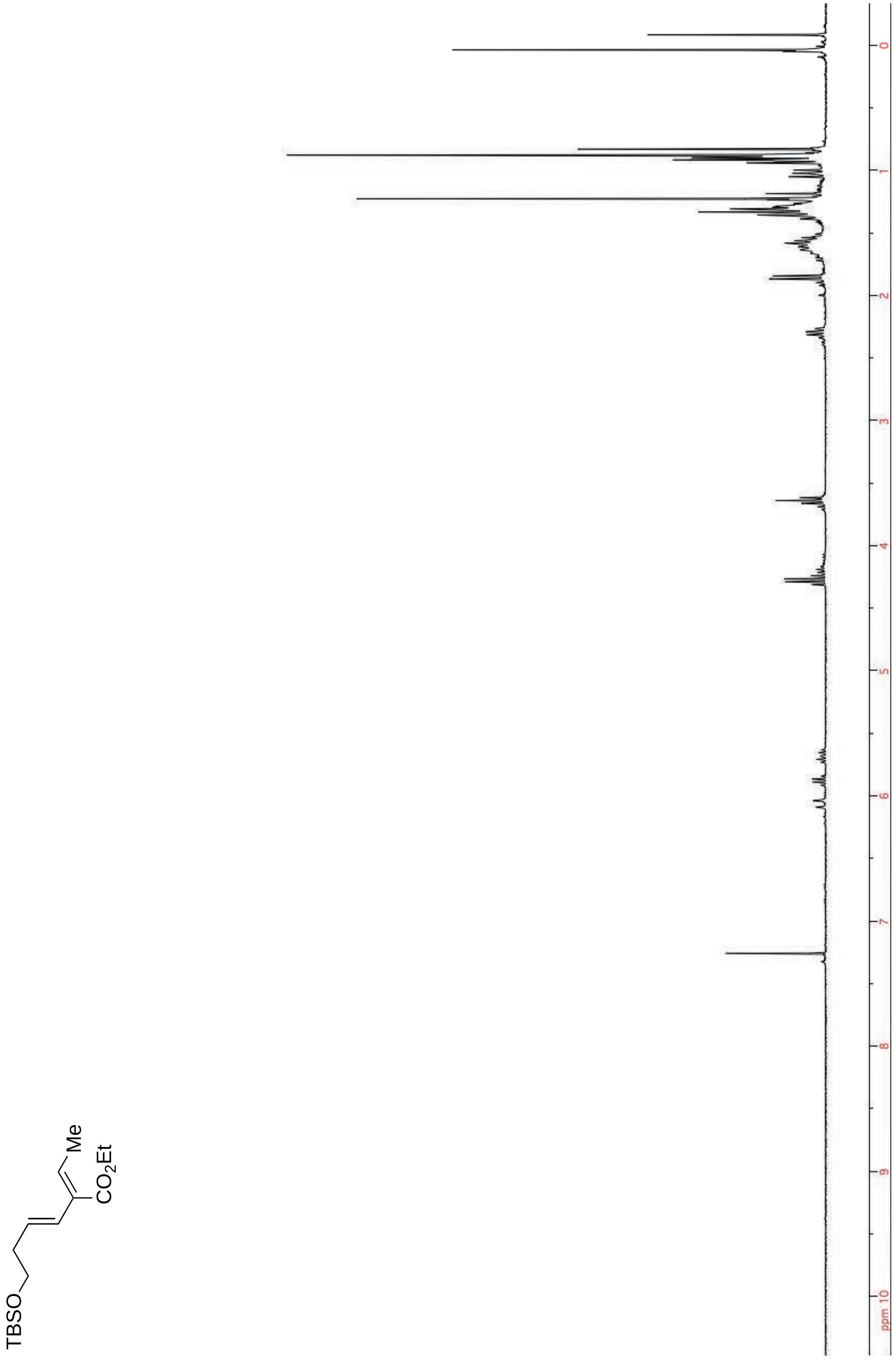

Bu3Sn
Me
CO2Et
0
1
2
3
4
5
6
7
8
9
ppm 10

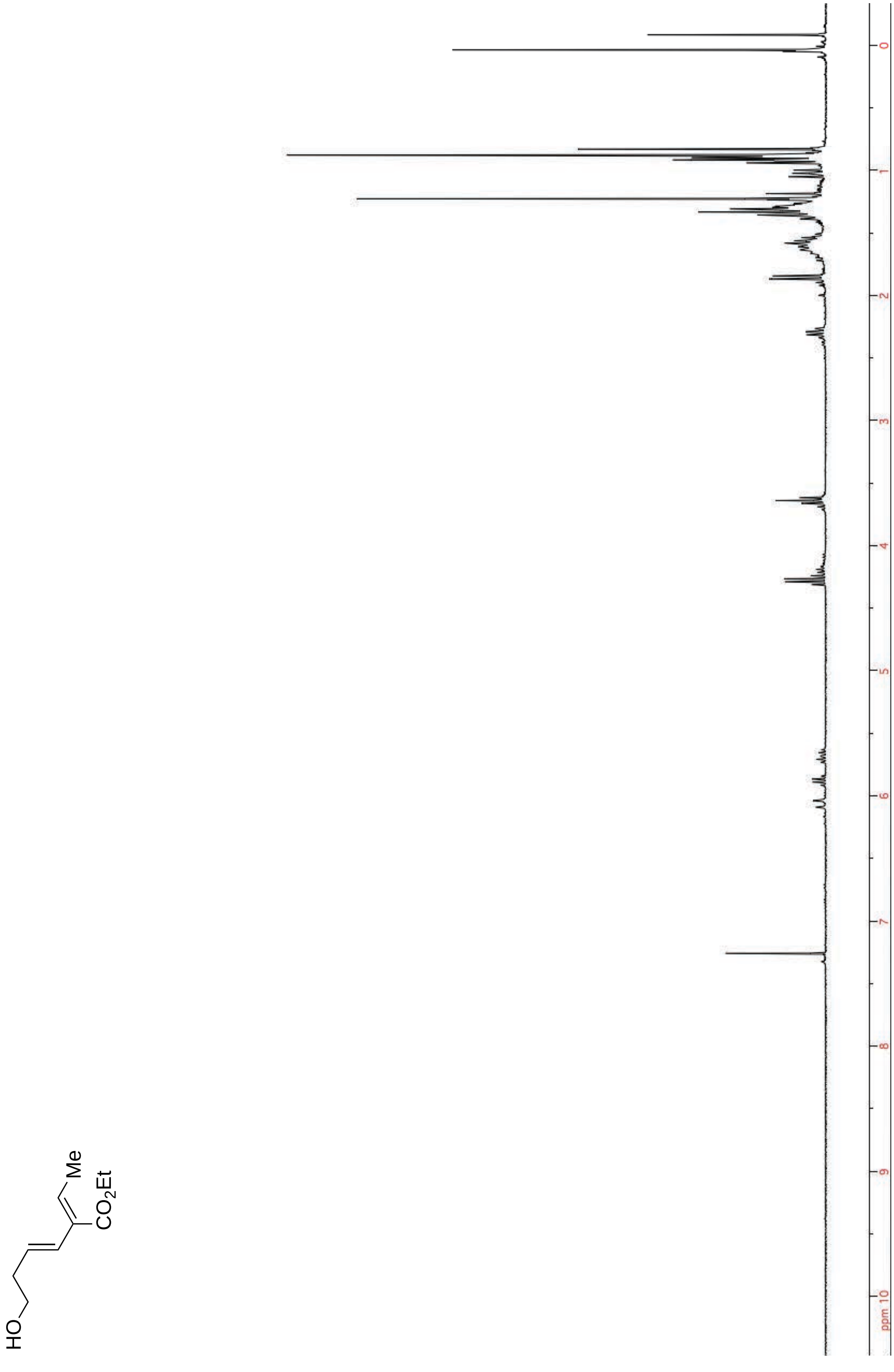

Bu3Sn
Me
CO2Et
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
0

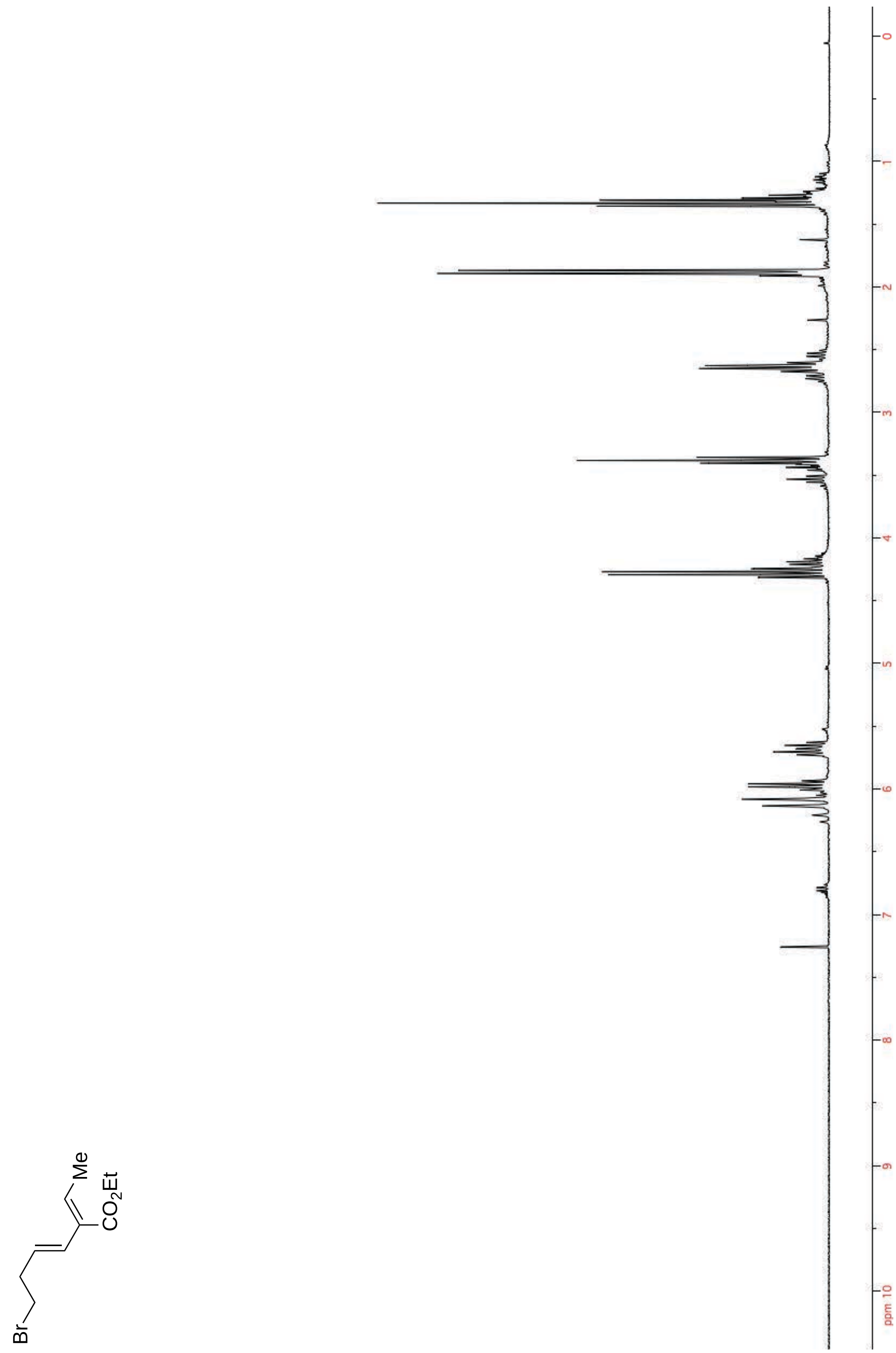

I
CO2Et
Me
ppm 10
9
8
7
6
5
4
3
2
1
0

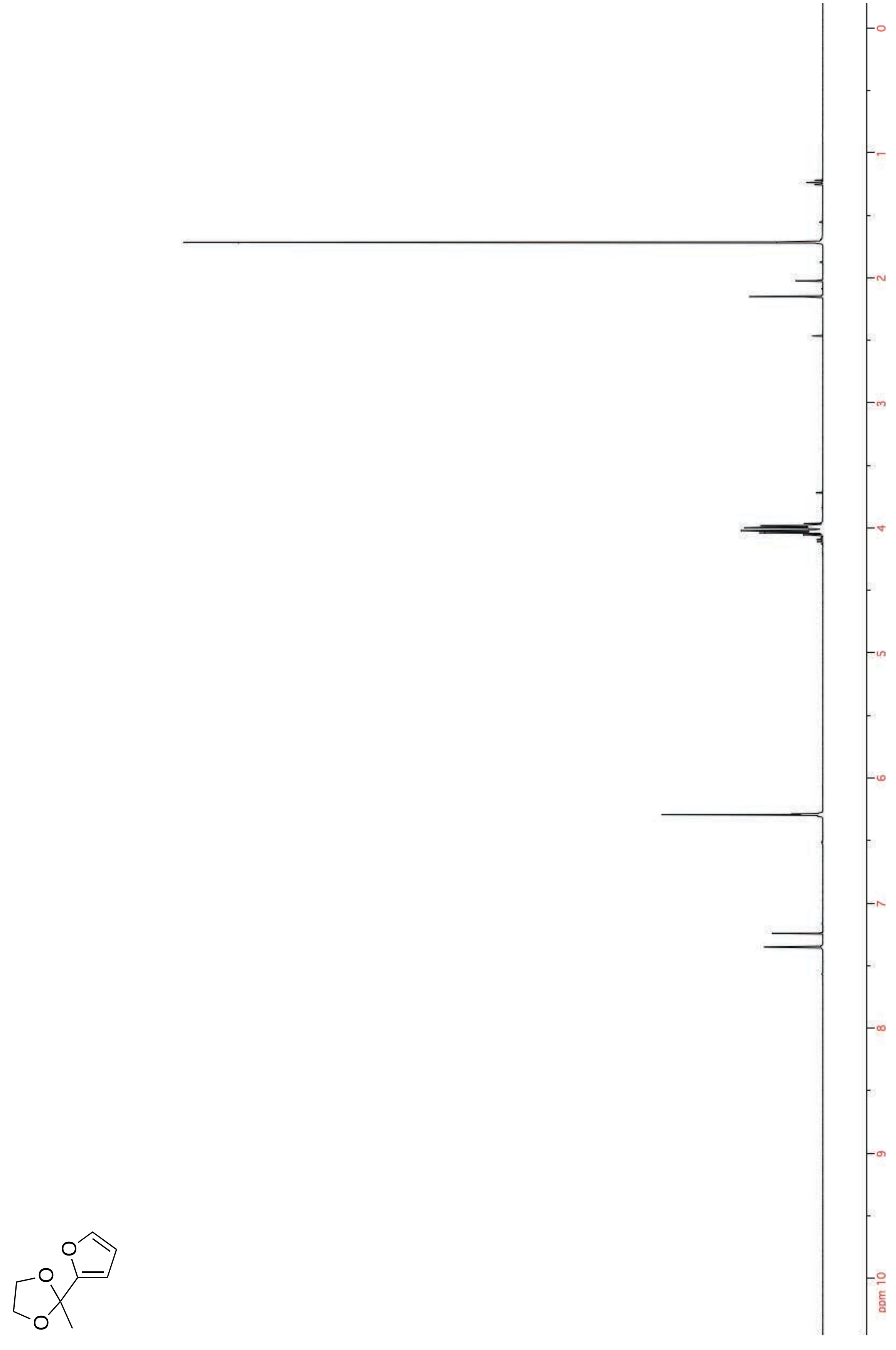

I
CO$_2$Et
Me
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

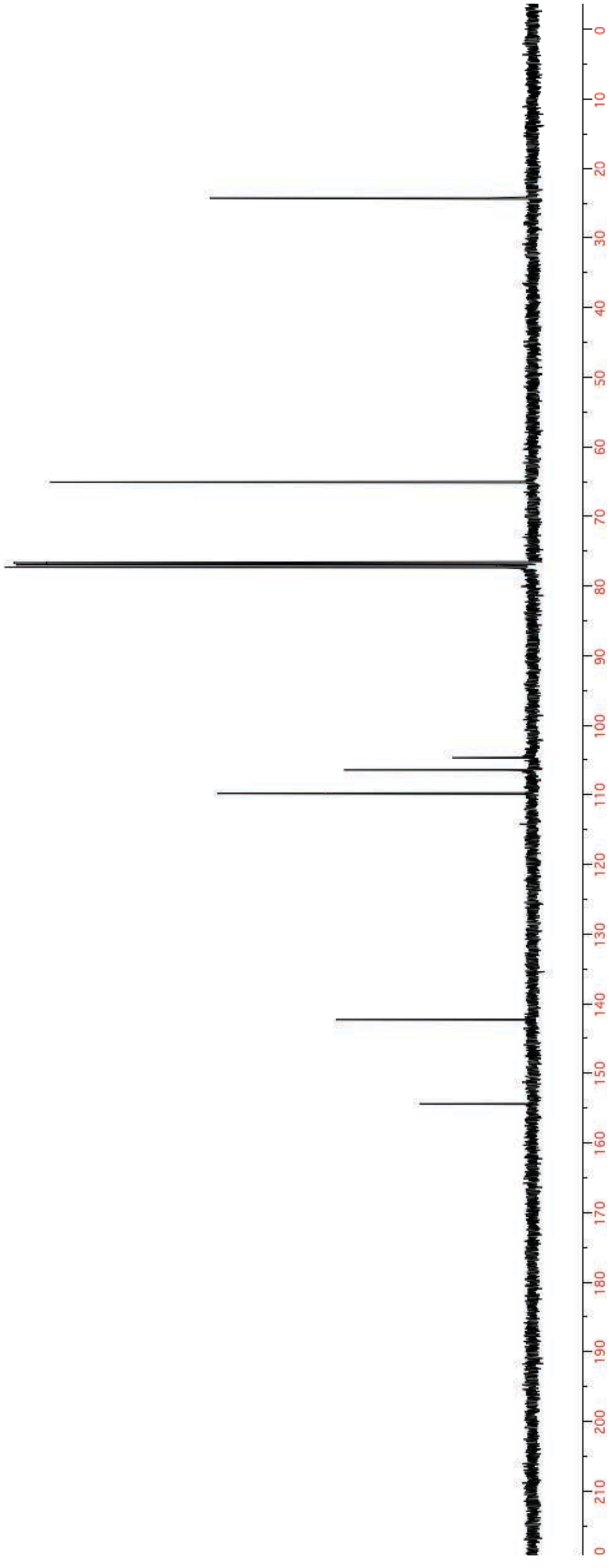

TBSO
O
B
O
ppm 10
9
8
7
6
5
4
3
2
1
0

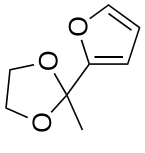

TBSO
Me
CO2Et
0
1
2
3
4
5
6
7
8
9
ppm 10

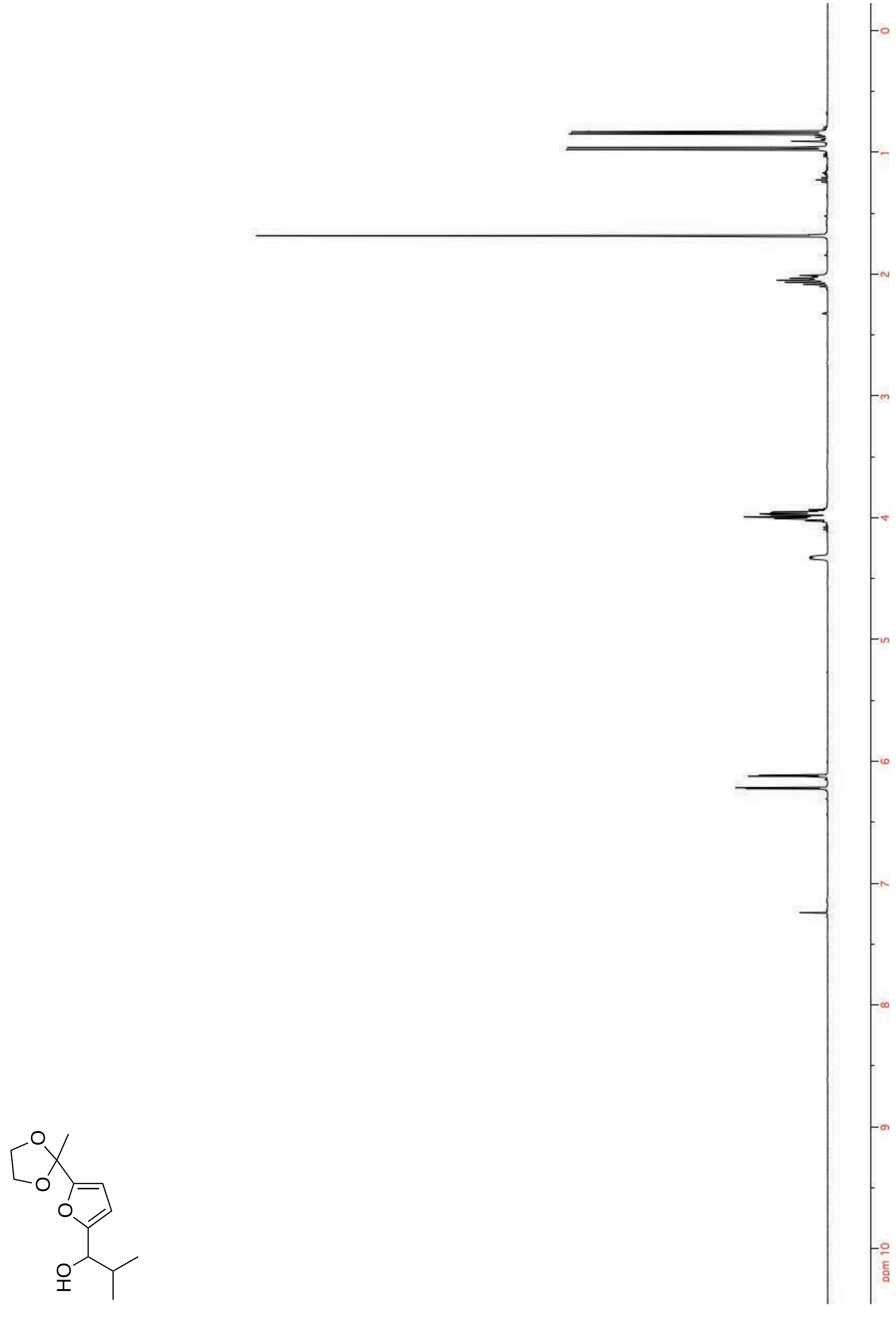

HO
Me
CO2Et
ppm
0
1
2
3
4
5
6
7
8
9
10

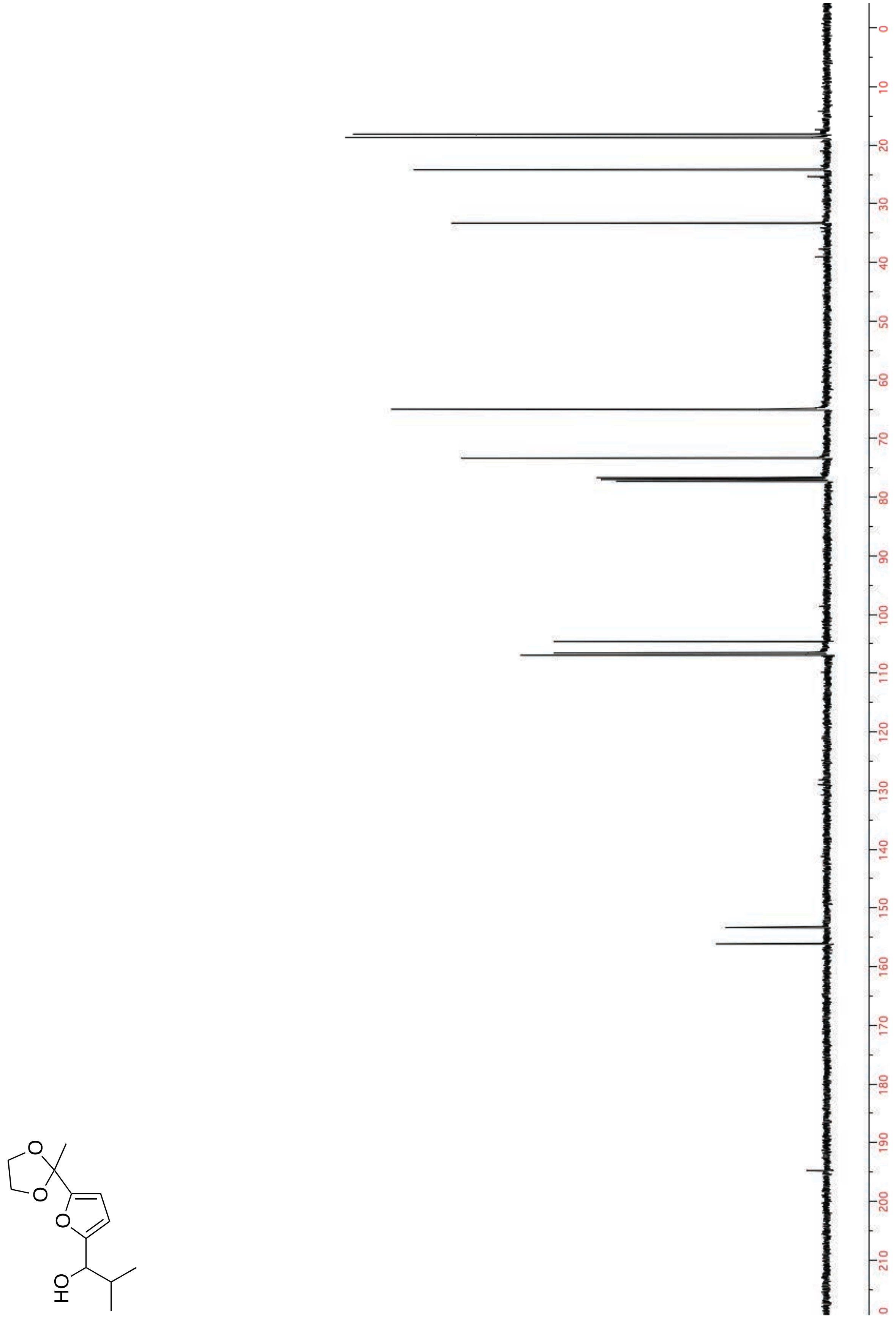

Br
CO2Et
Me
ppm 10
9
8
7
6
5
4
3
2
1
0


0
1
2
3
4
5
6
7
8
9
ppm 10
O
O
O

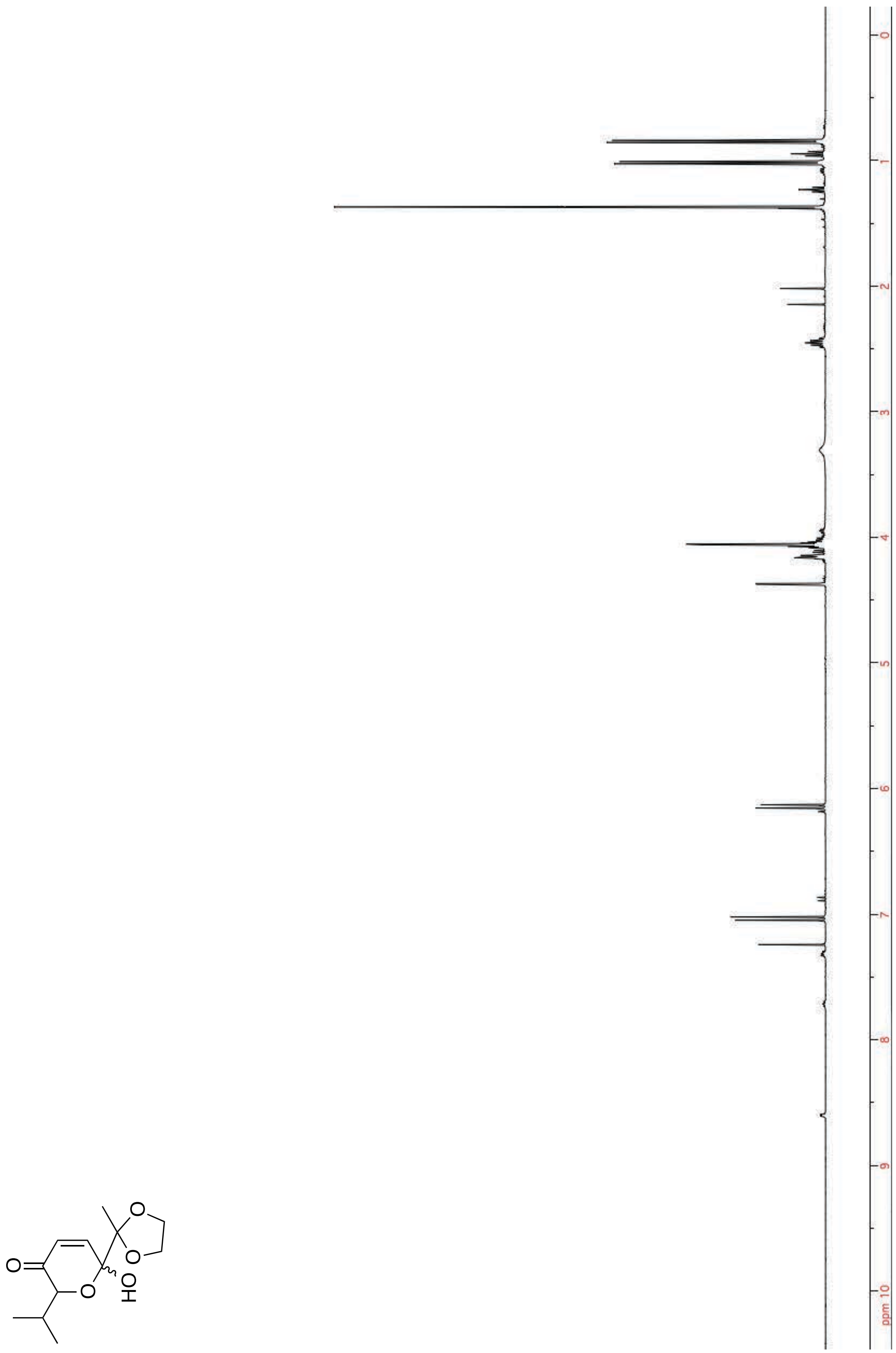

0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

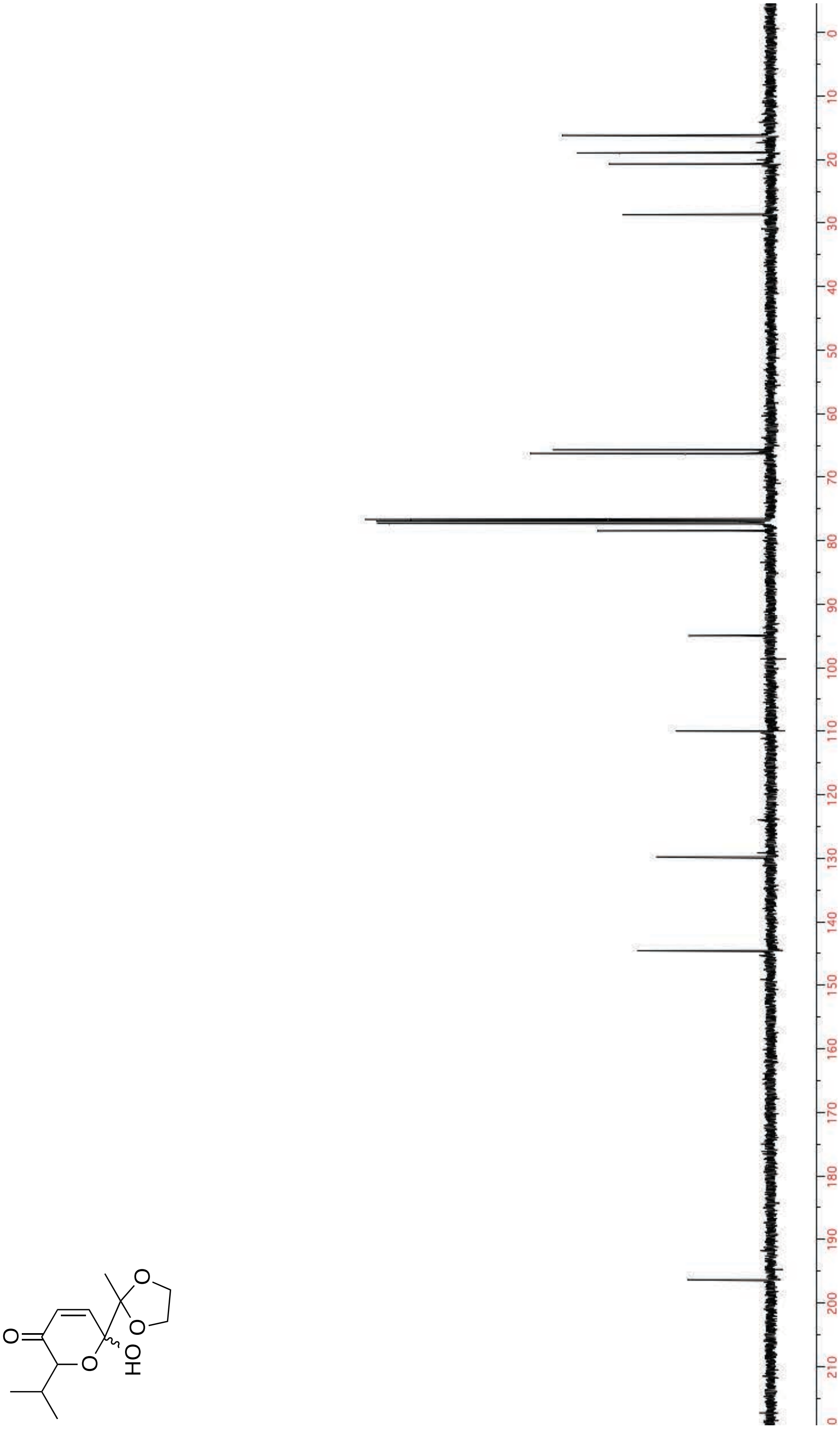



0
1
2
3
4
5
6
7
8
9
ppm 10
O
O
O
HO

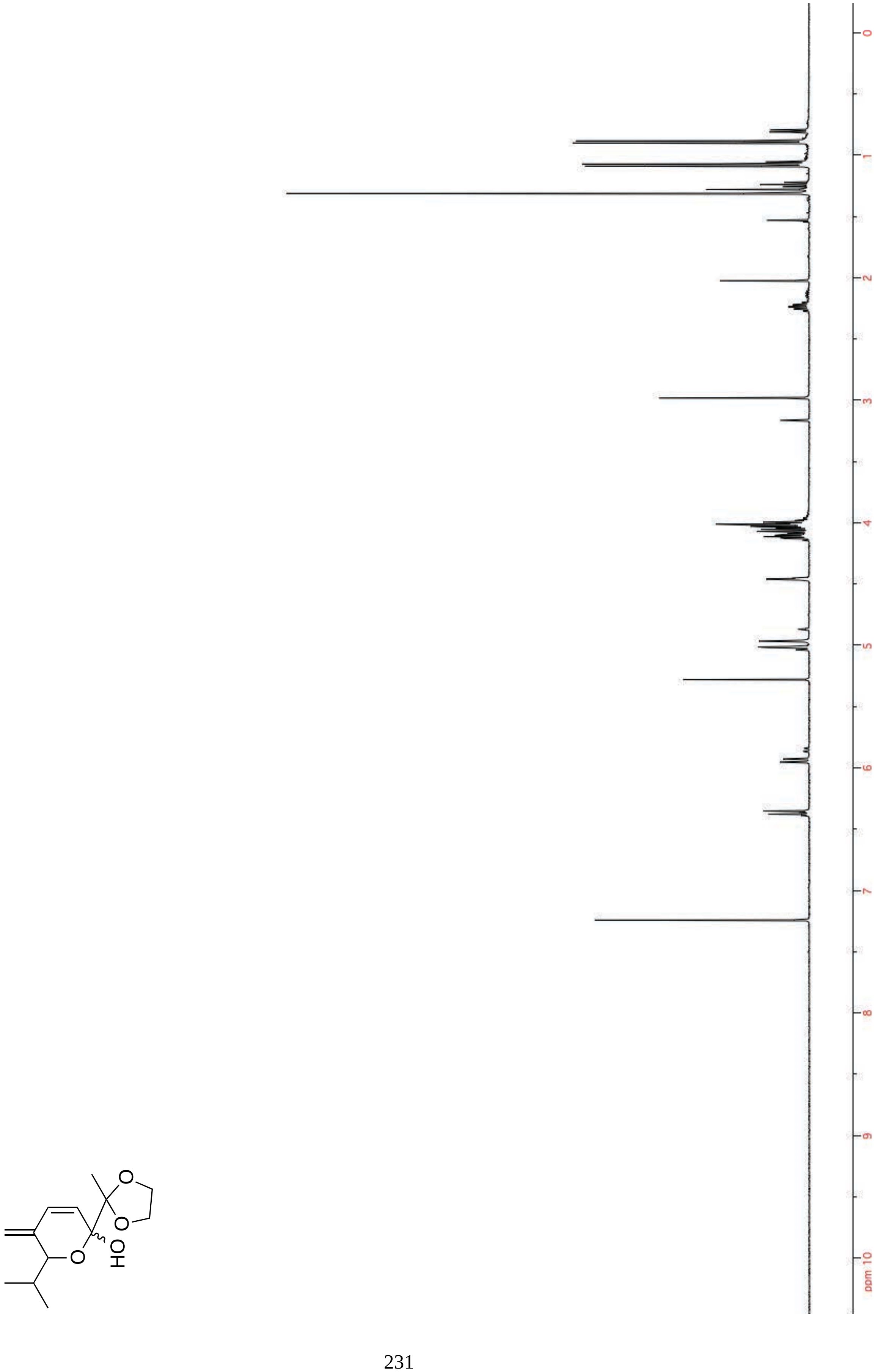


O
O
O
HO
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

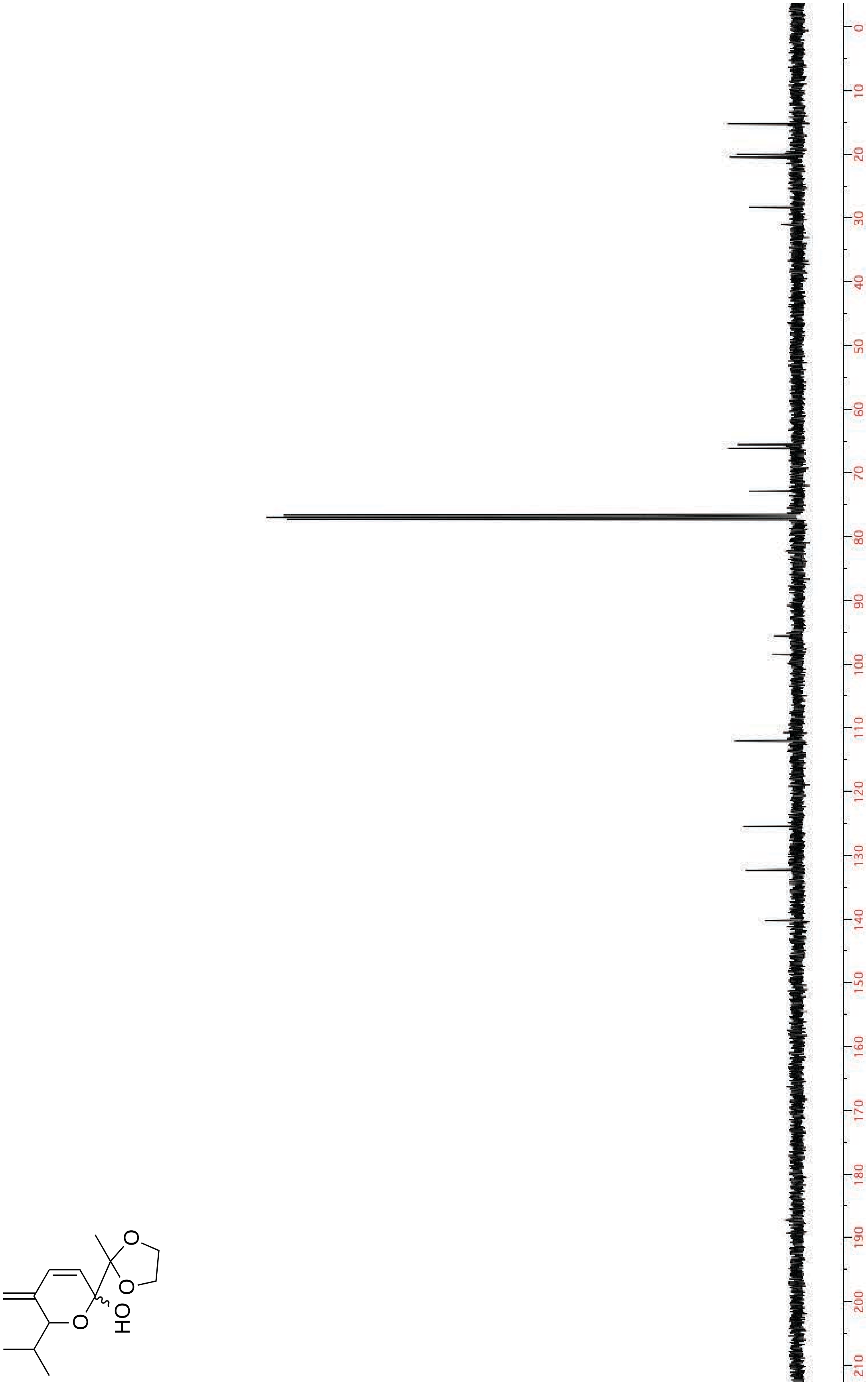

ppm
0
1
2
3
4
5
6
7
8
9
10
O
HO

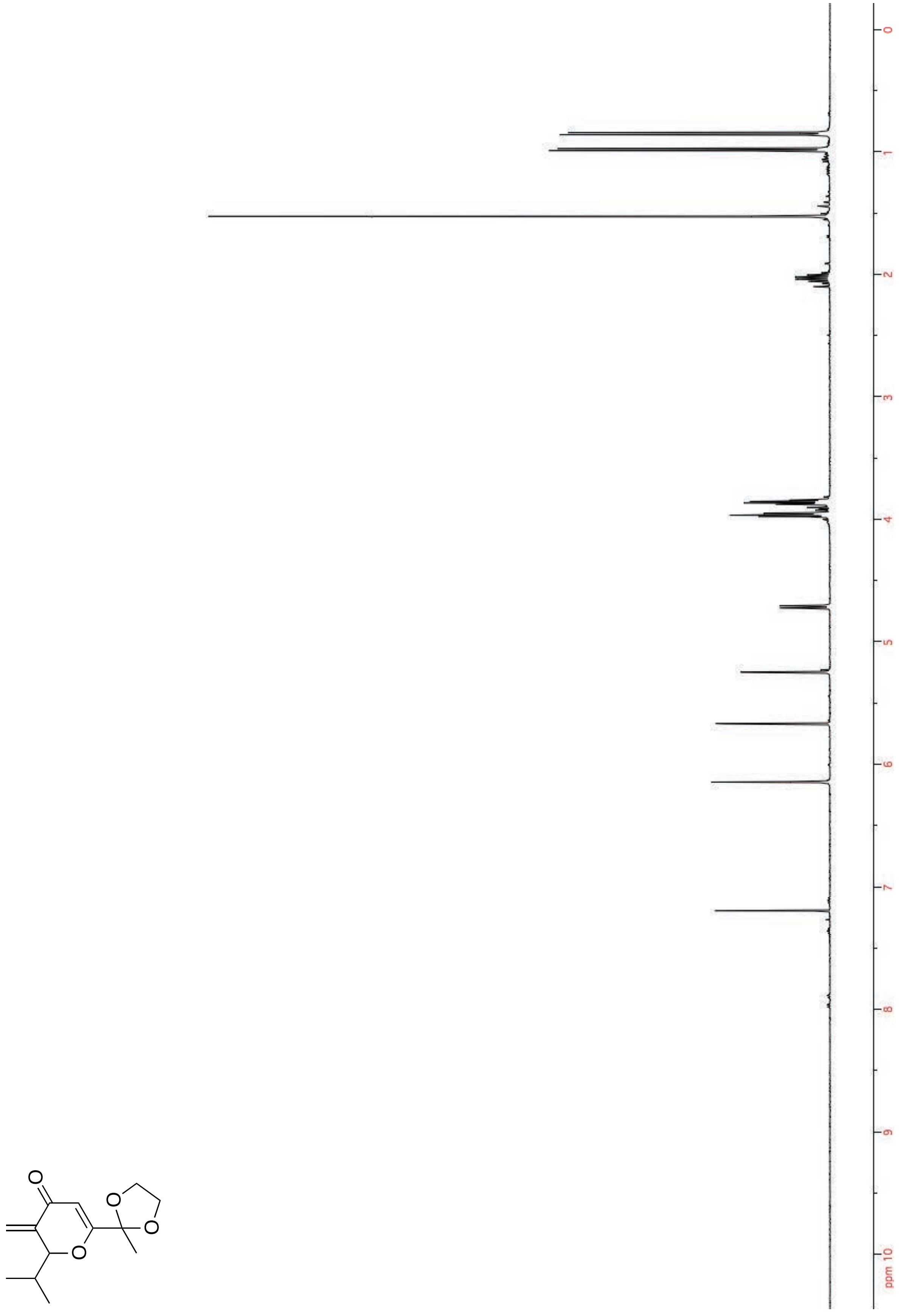


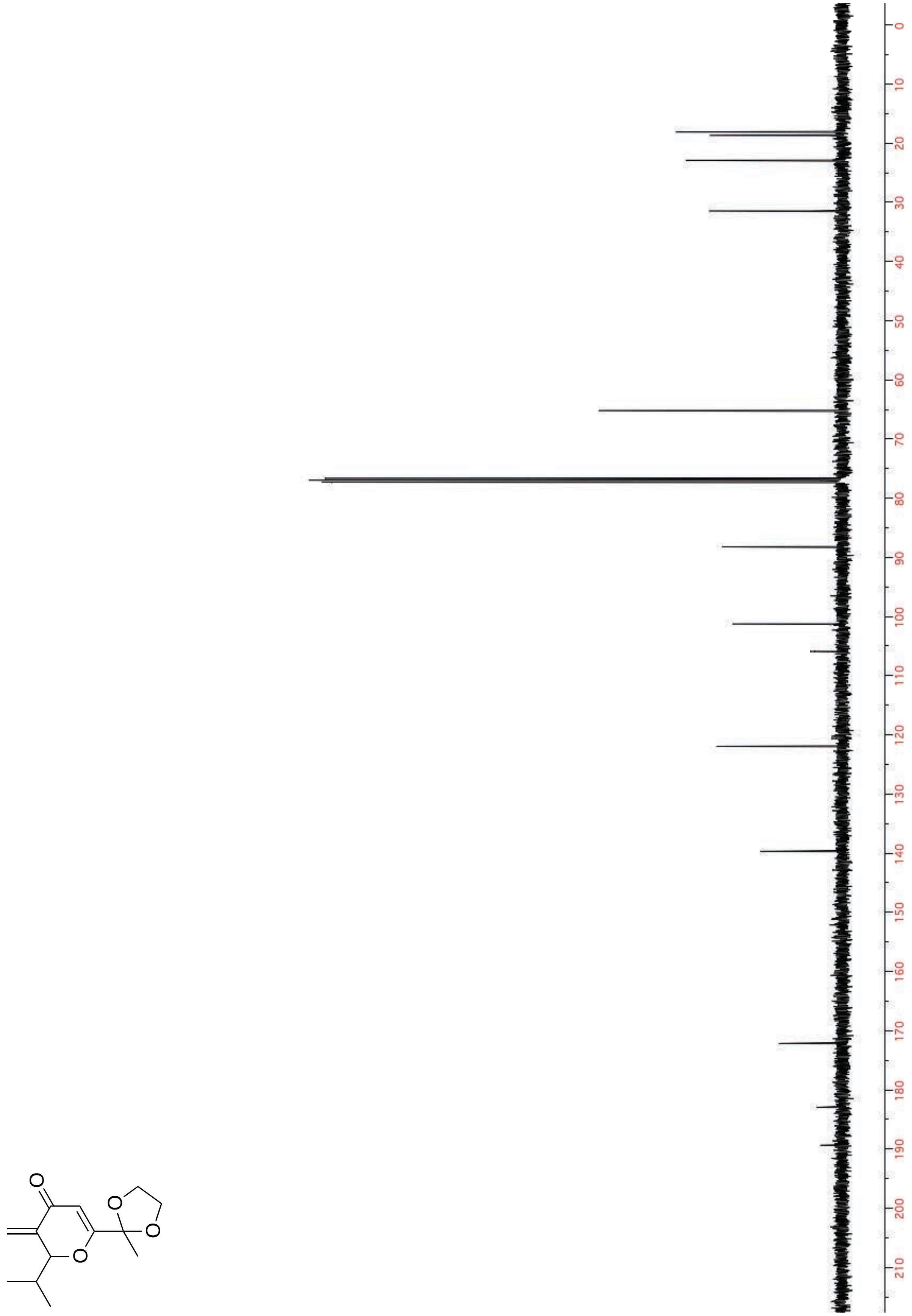
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
O
O
O
O
HO

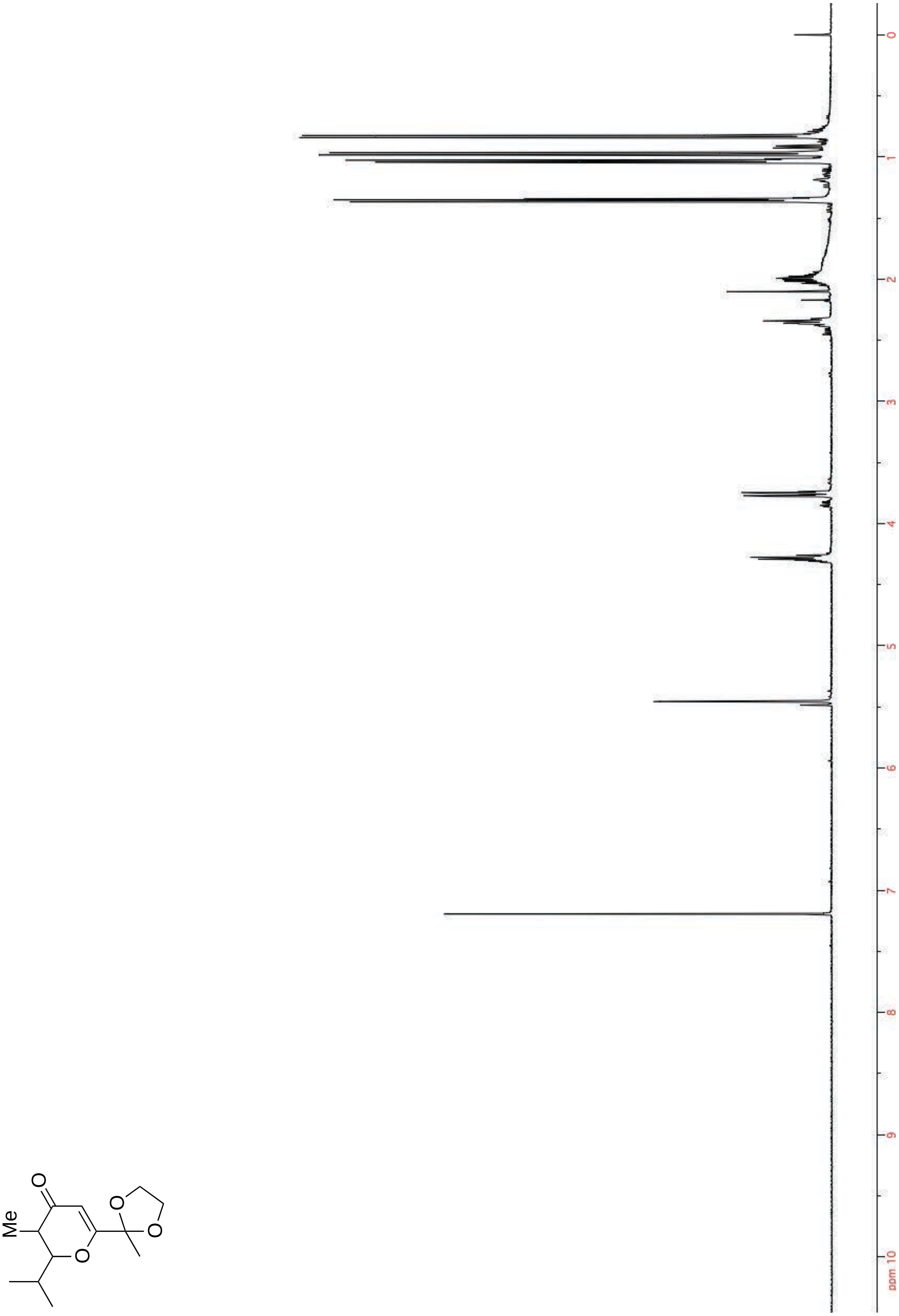


O
O
O
HO
ppm
0
1
2
3
4
5
6
7
8
9
10

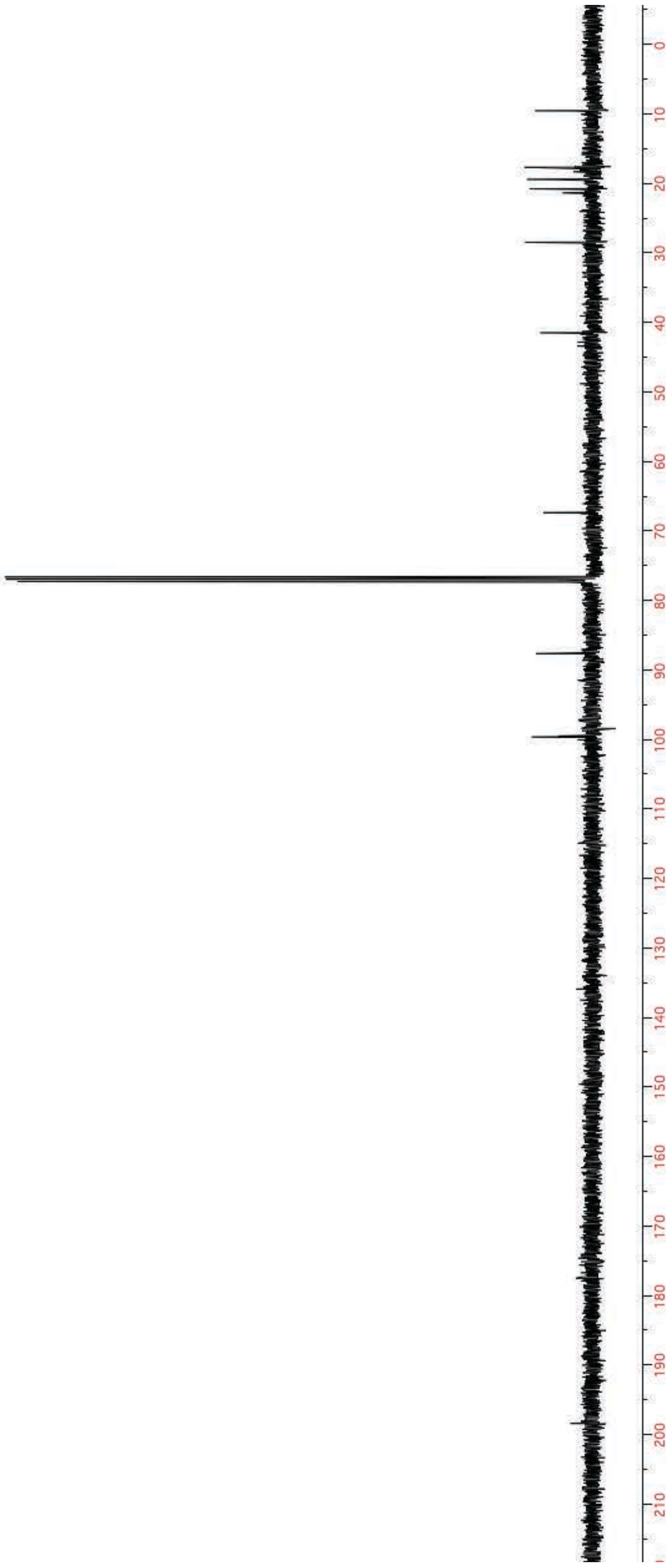

0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
O
O
O
HO

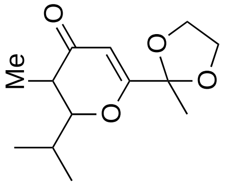

ppm
0
1
2
3
4
5
6
7
8
9
10
O
O
O
O

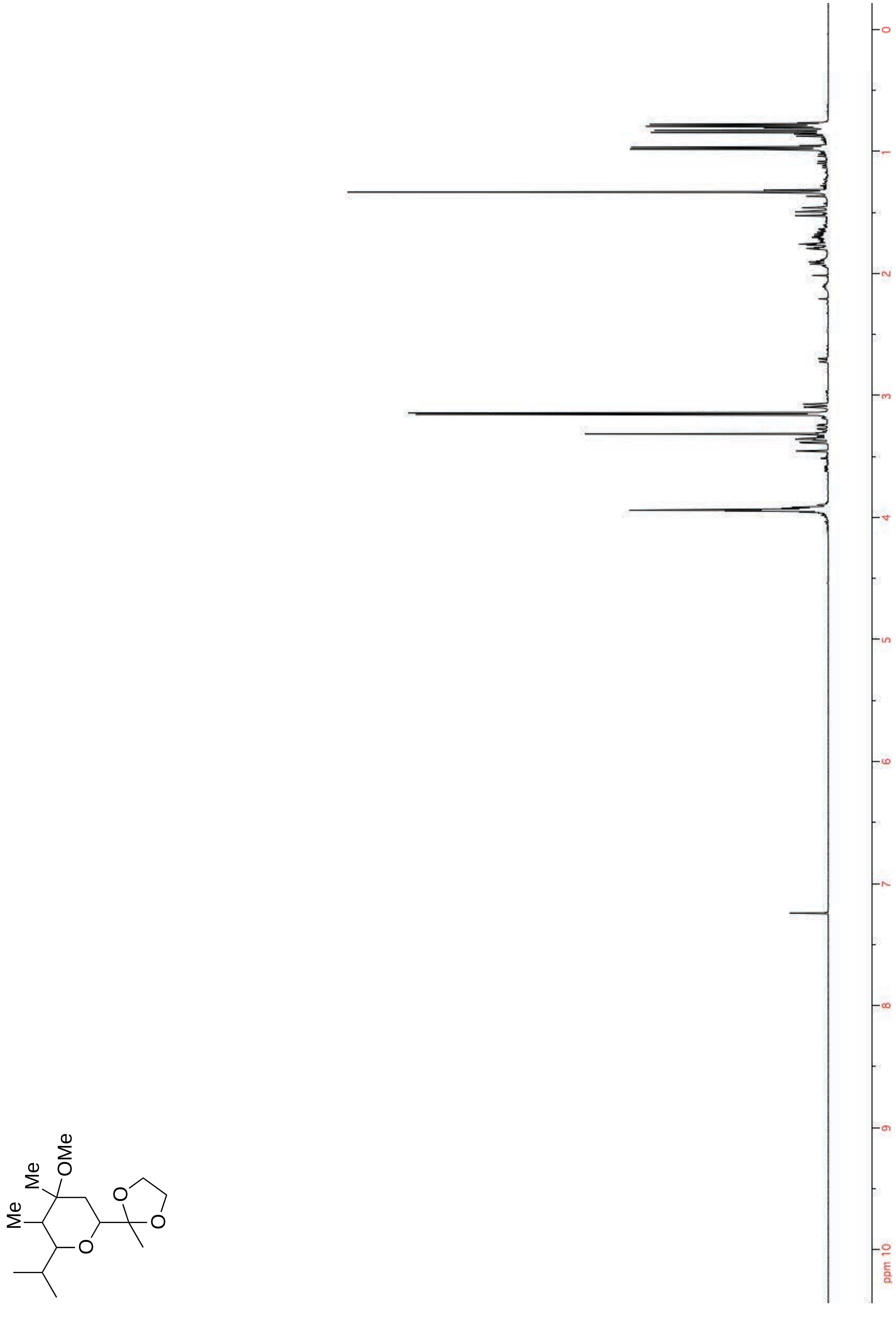

0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

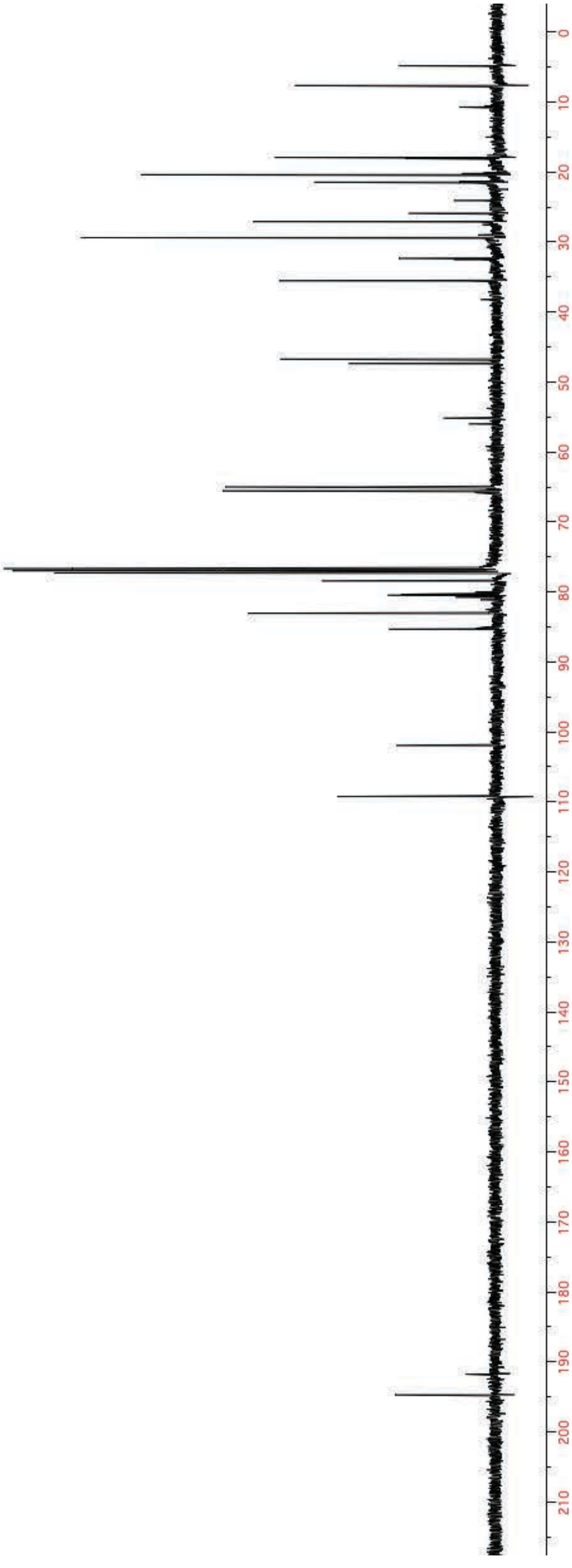


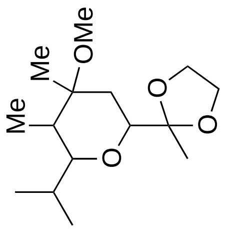
Me
O
0
1
2
3
4
5
6
7
8
9
ppm 10

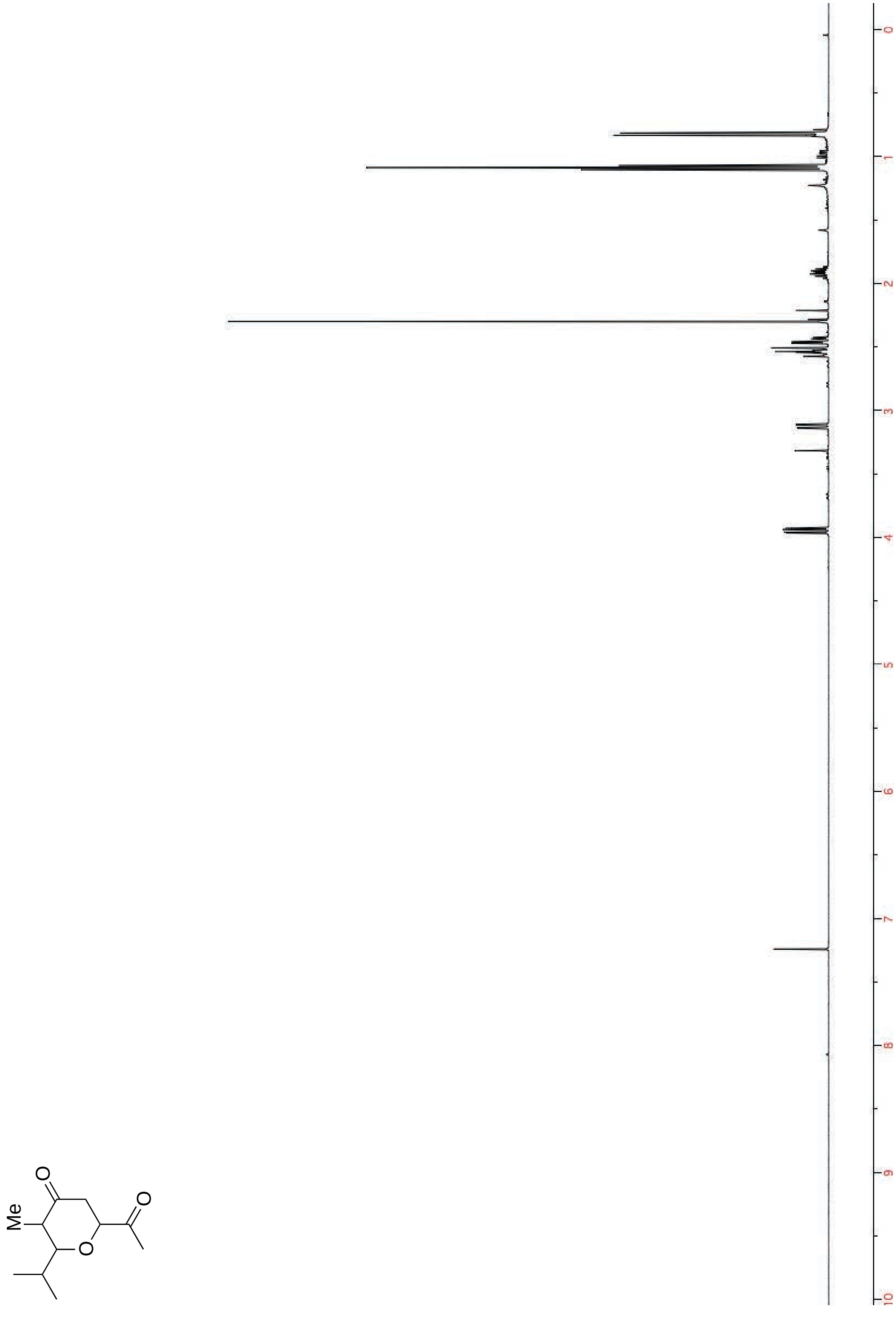

0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

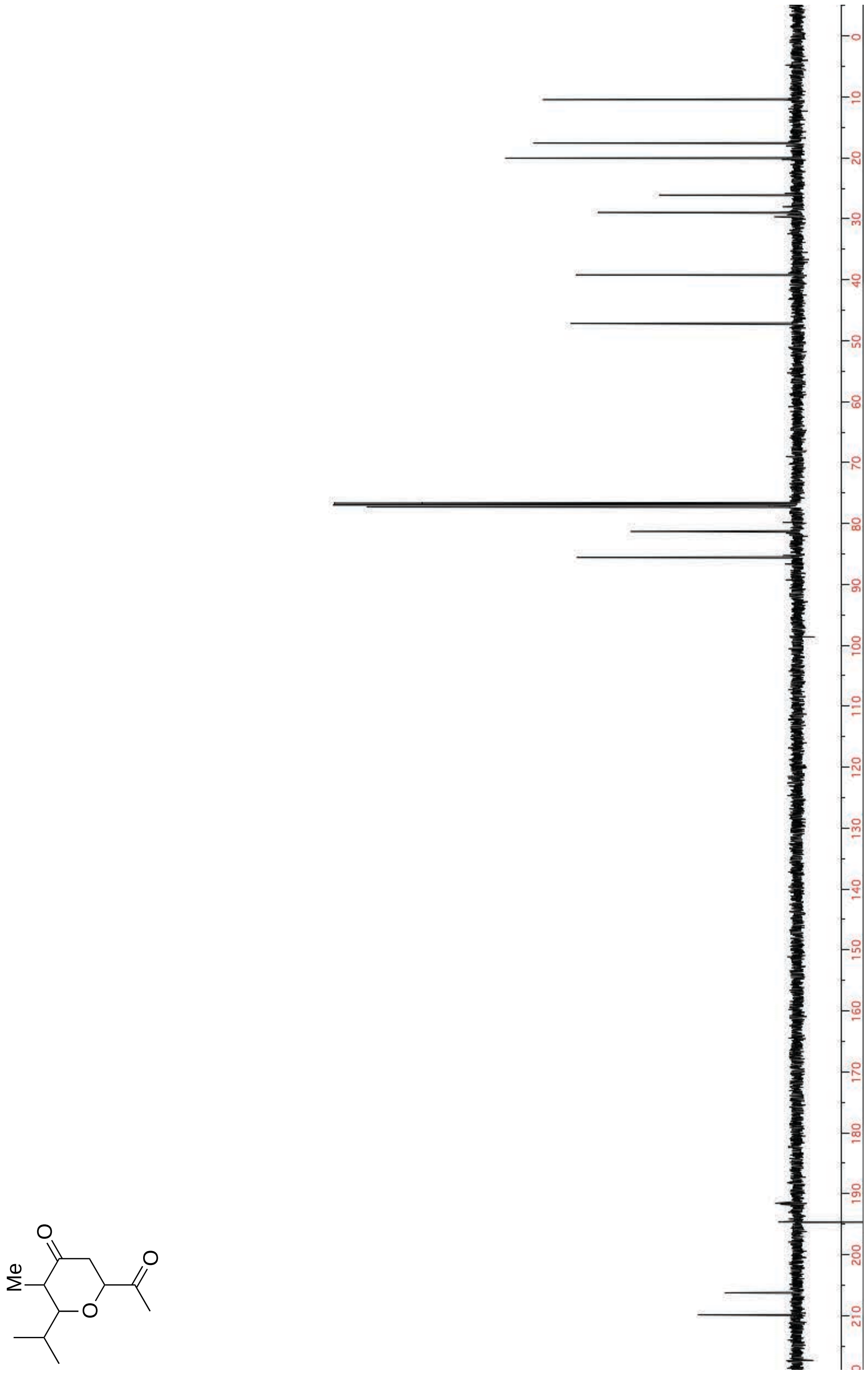

Me
O
O
O
O

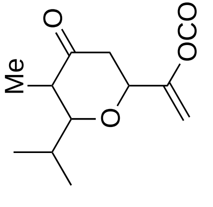

Me
Me
OMe
O
O
O
ppm 10
9
8
7
6
5
4
3
2
1
0

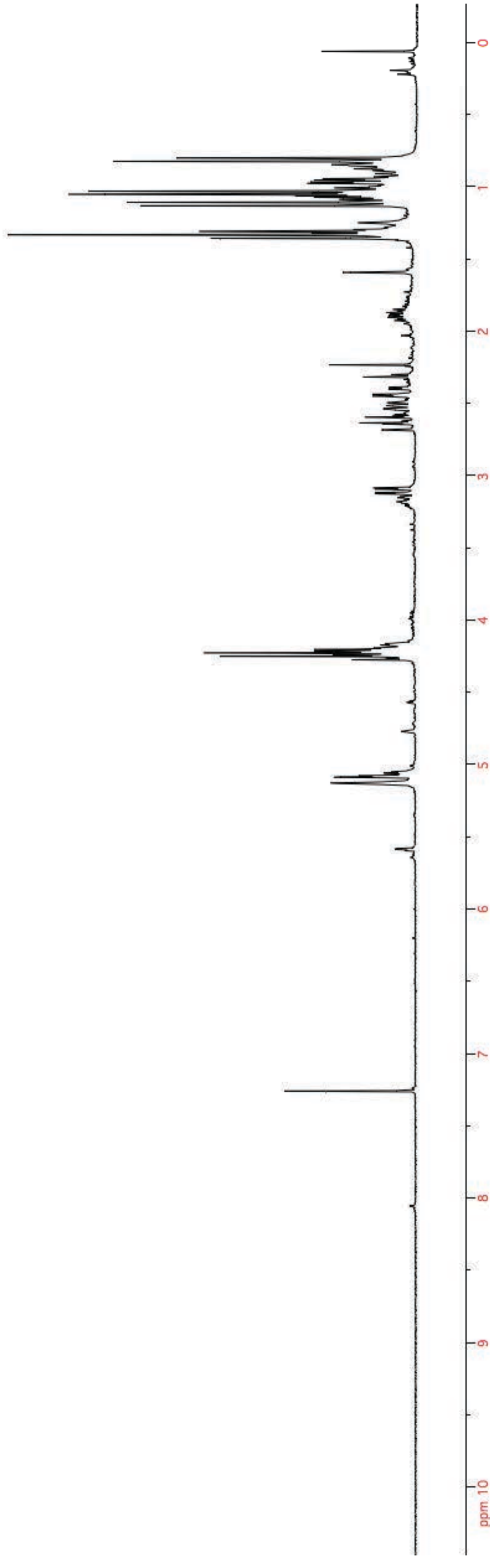

0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

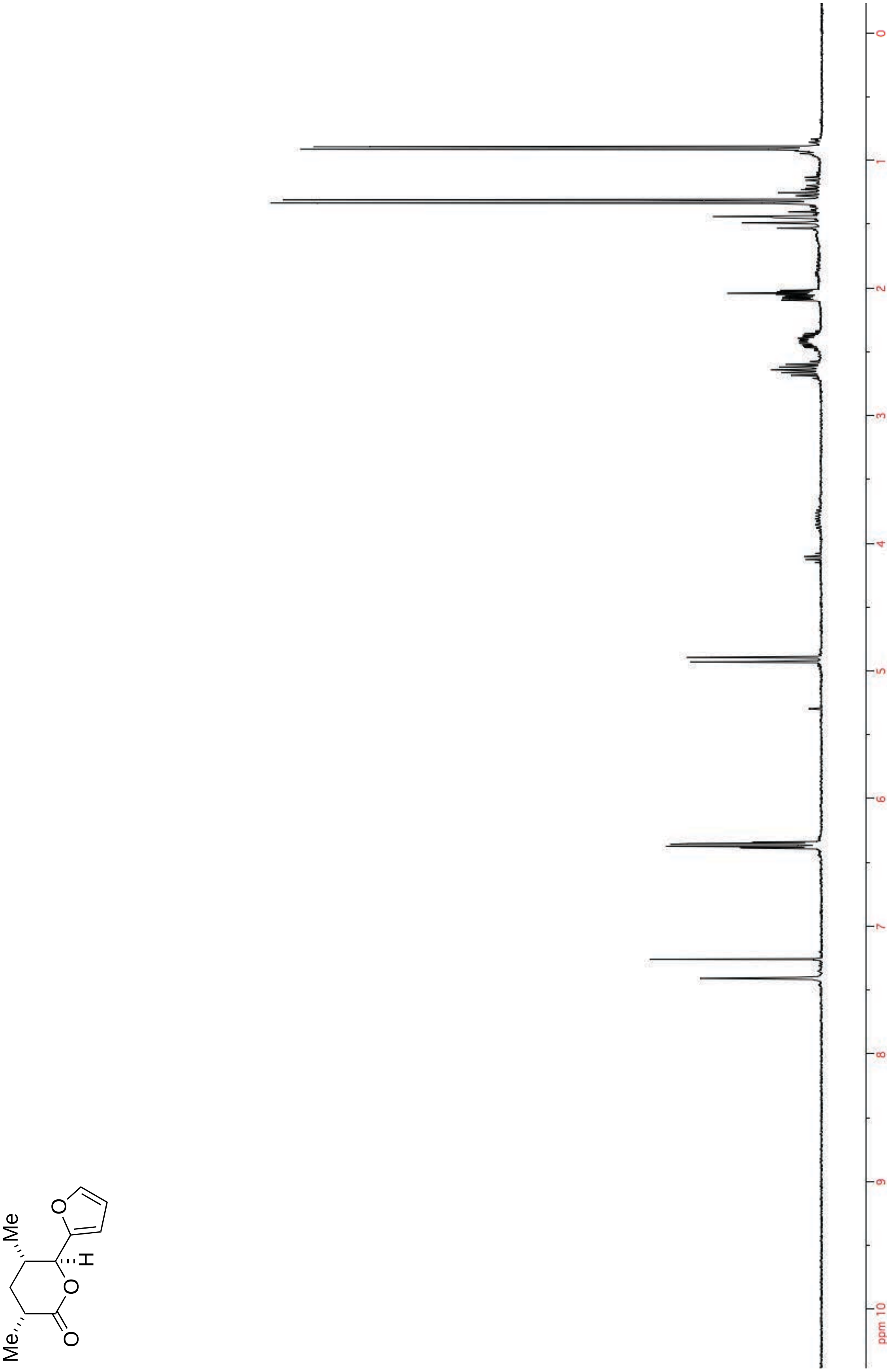

Me
Me
OMe
O
O
O

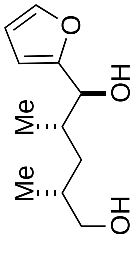

0
1
2
3
4
5
6
7
8
9
10
Me
O
O
O

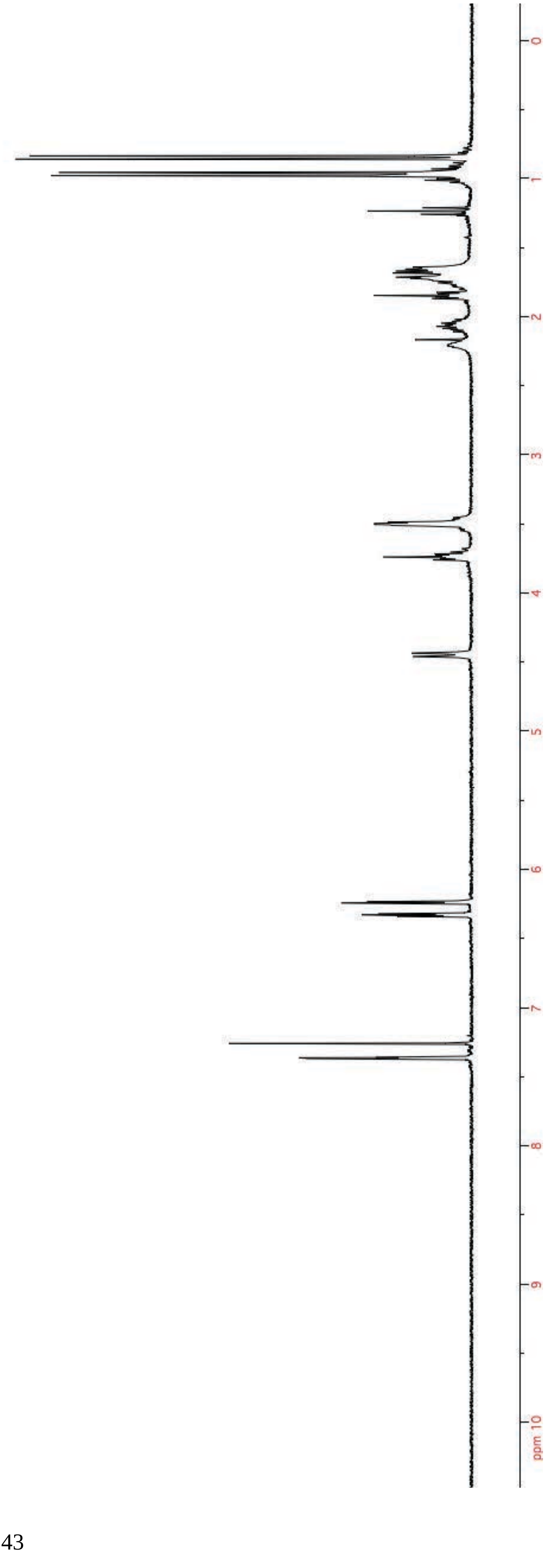

Me
O
O
O
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

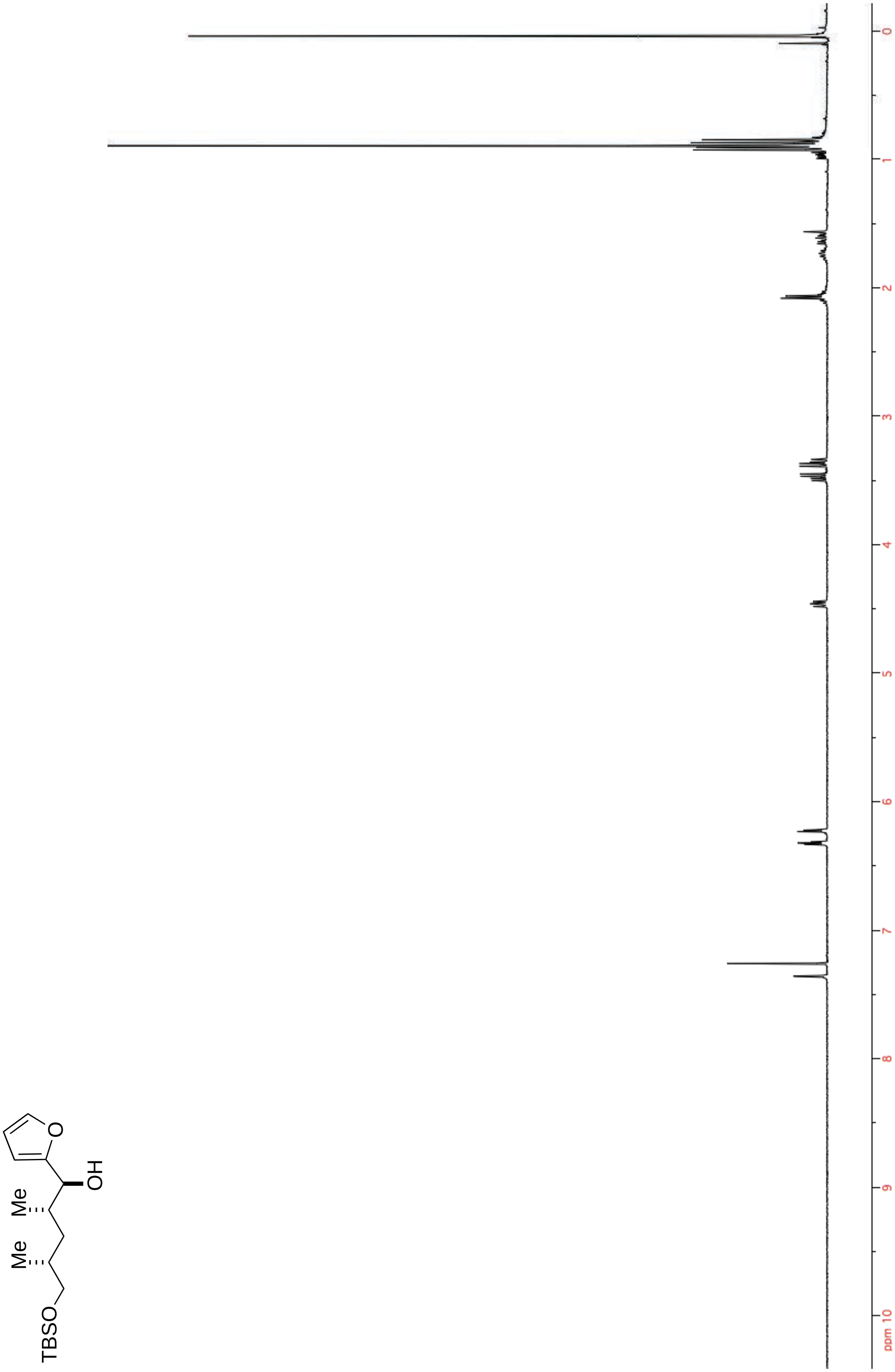

Me
O
O
OCO2Et

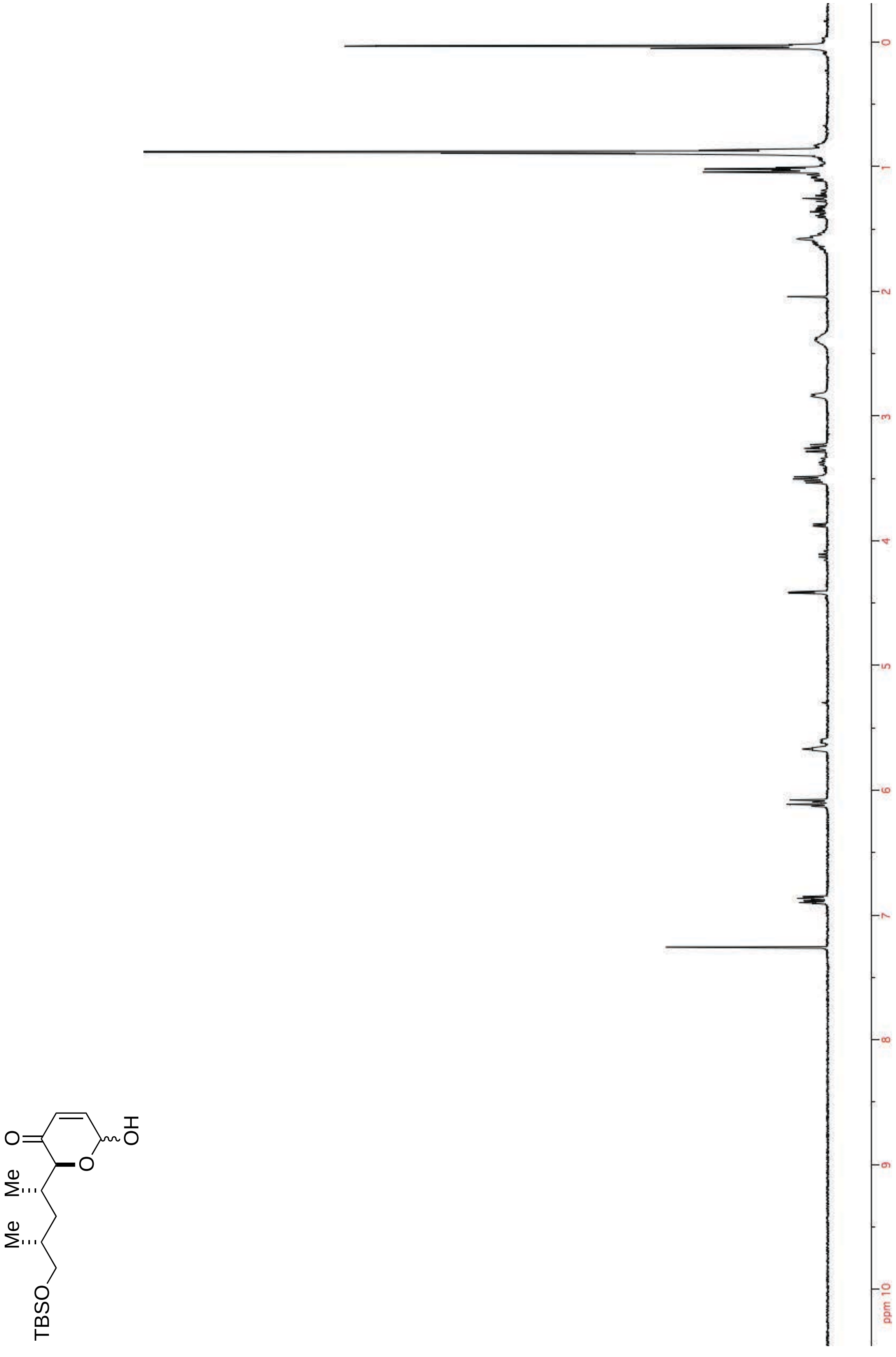

0
1
2
3
4
5
6
7
8
9
ppm 10

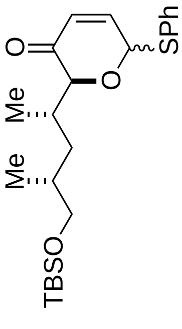

Me
Me
O
O
O
H
ppm
0
1
2
3
4
5
6
7
8
9
10

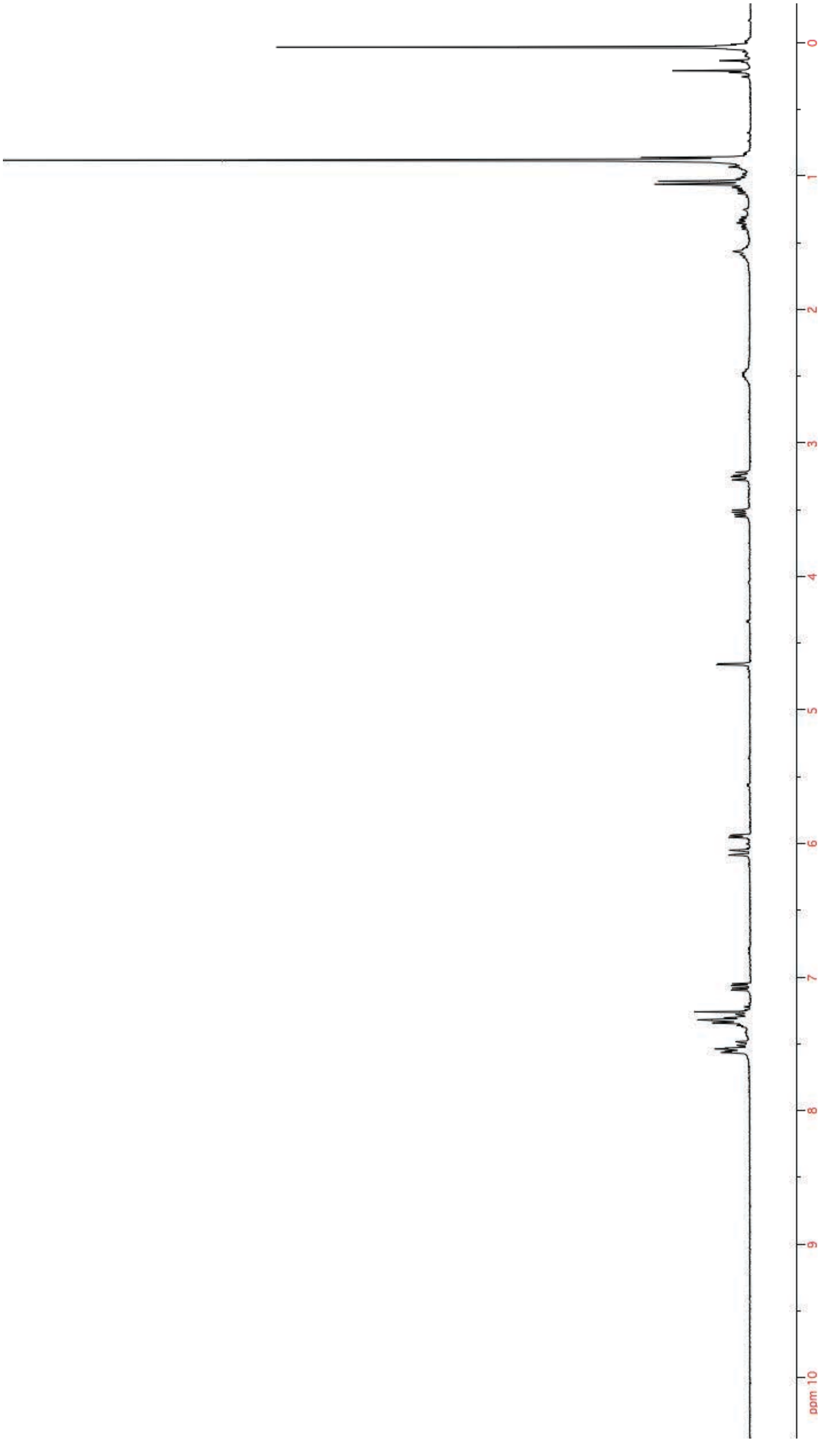

Me
Me
OH
OH
O

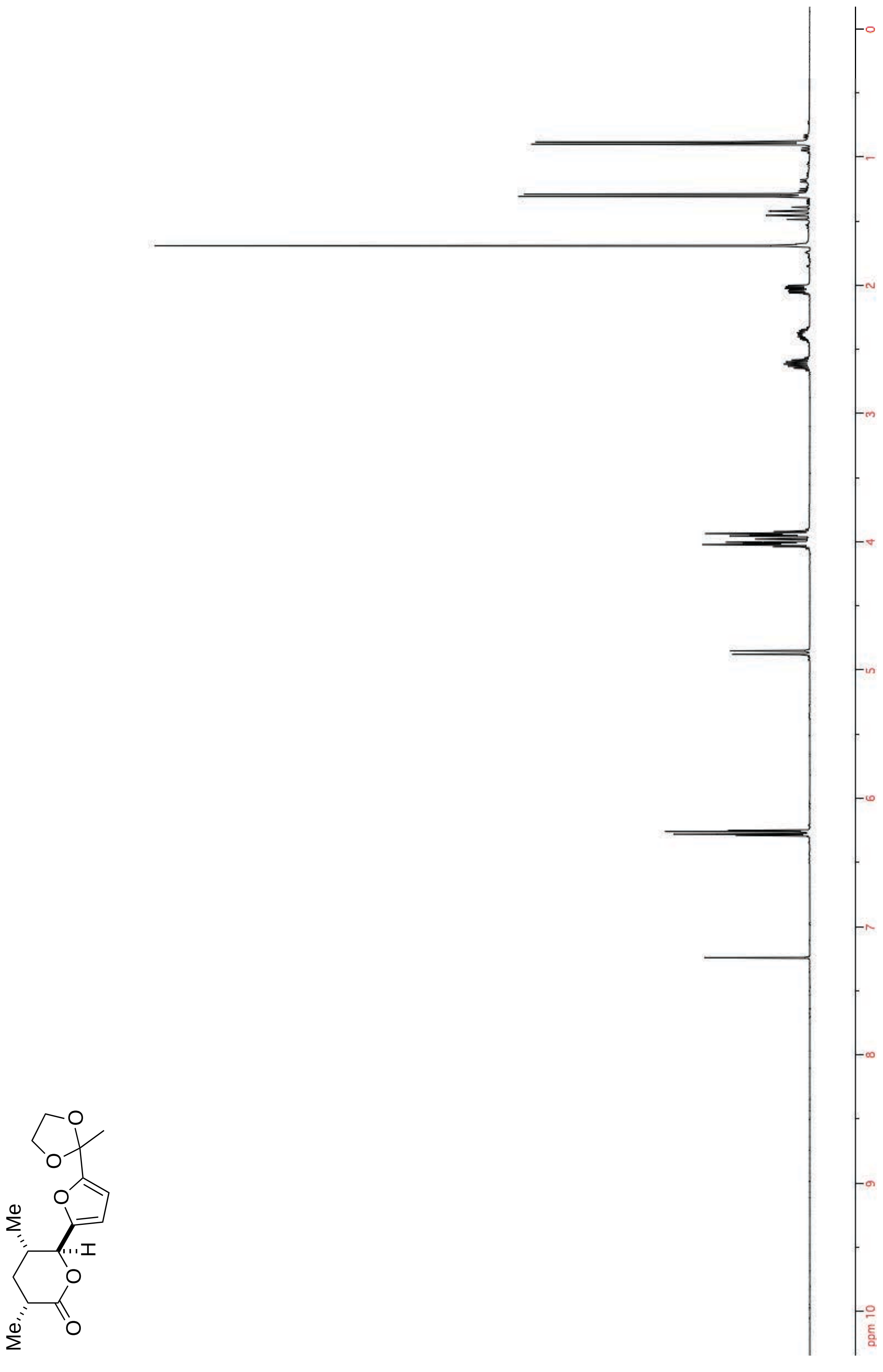

0
1
2
3
4
5
6
7
8
9
ppm 10

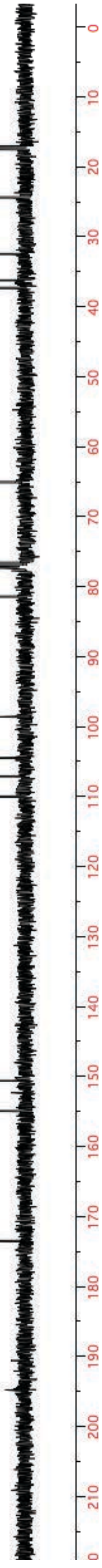

TBSO
Me
Me
OH
O
ppm 10
9
8
7
6
5
4
3
2
1
0

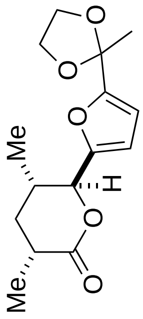

TBSO
Me
Me
O
O
OH
ppm
0
1
2
3
4
5
6
7
8
9
10

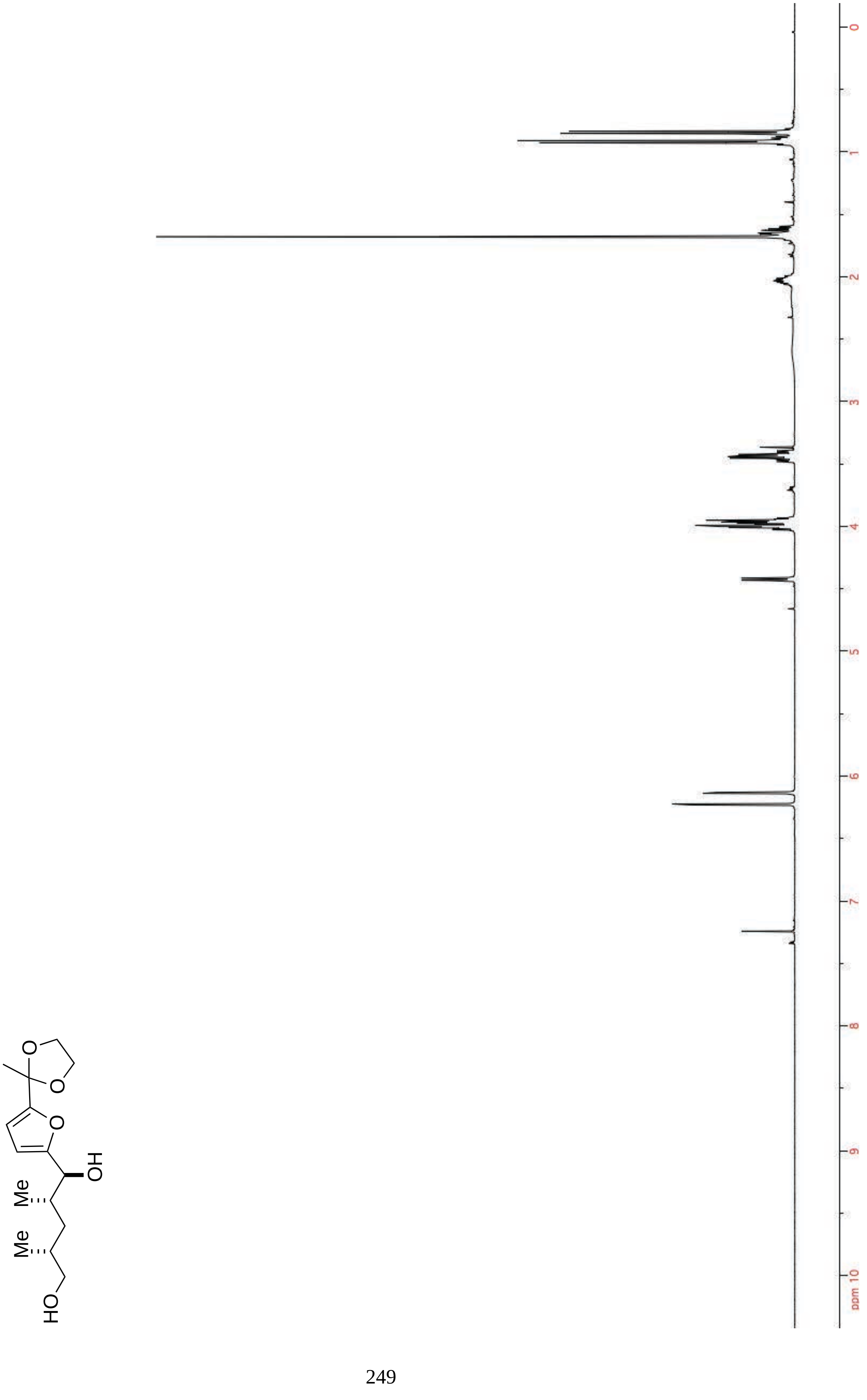

TBSO
Me
Me
O
O
SPh

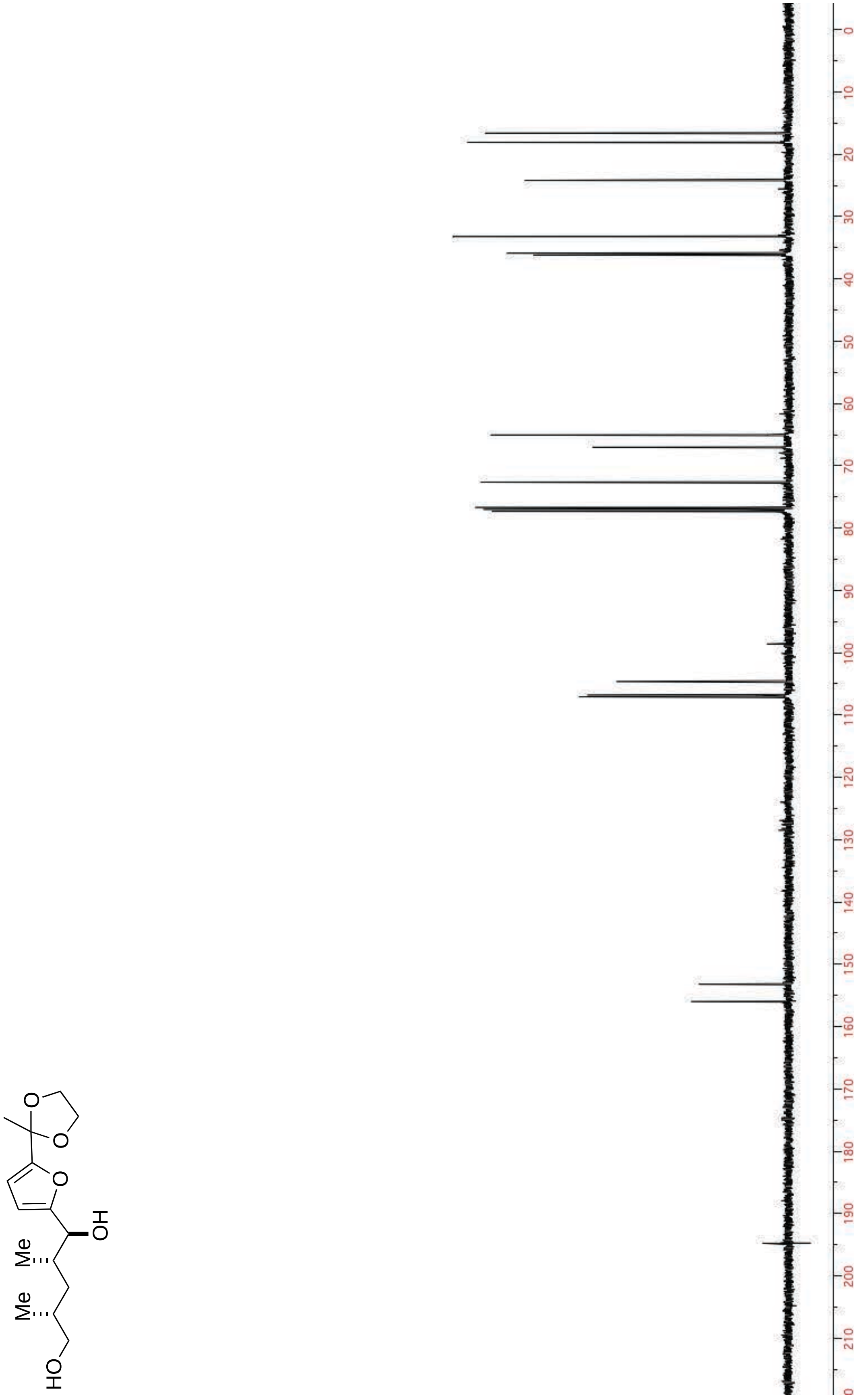

0
1
2
3
4
5
6
7
8
9
ppm 10


Me
Me
O
O
H
O
O
O
0
1
2
3
4
5
6
7
8
9
ppm 10

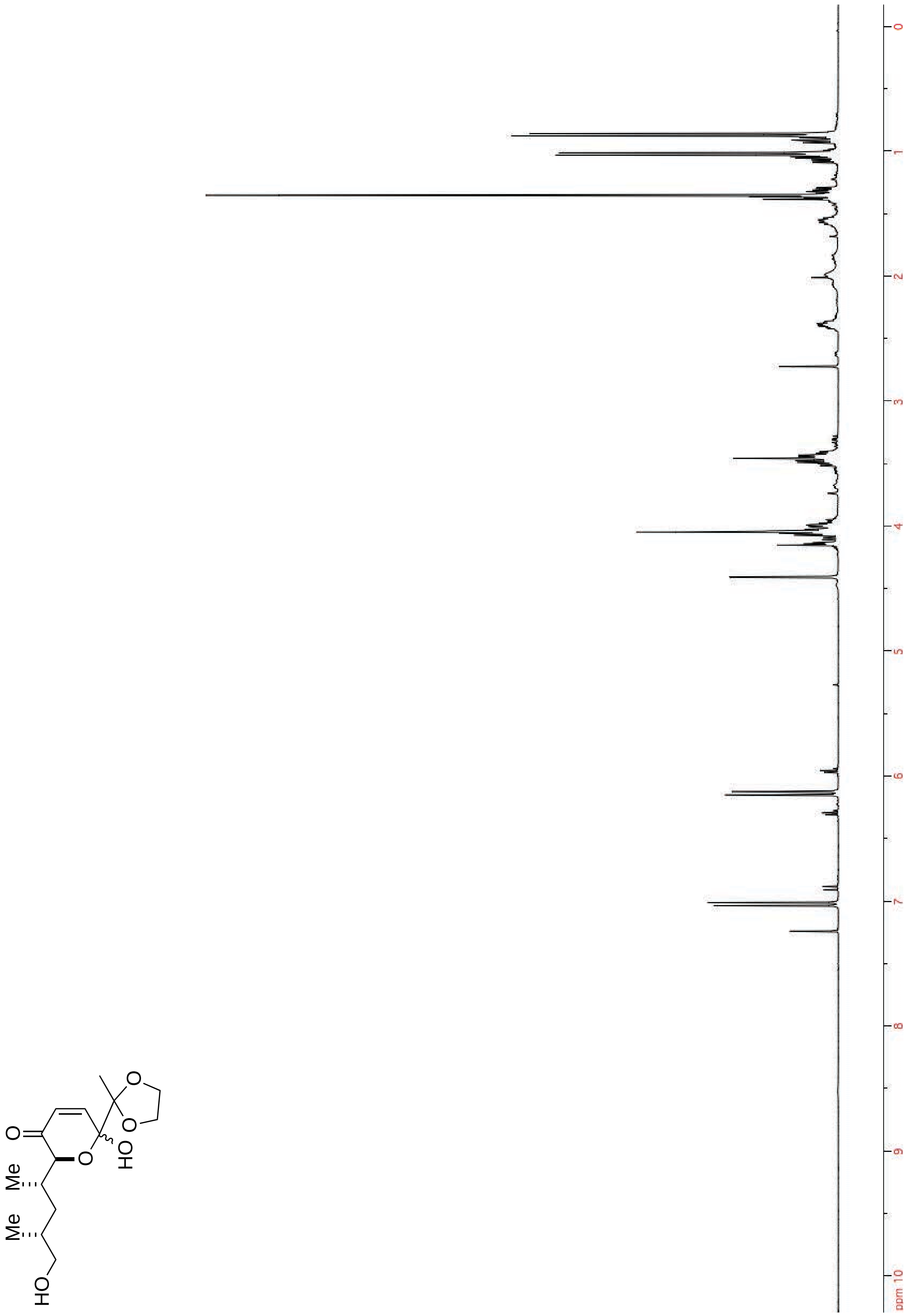

0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

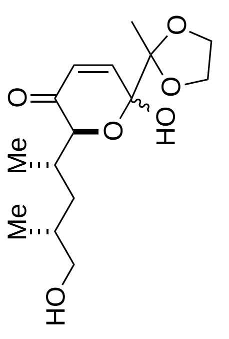

Me
Me
O
O
H
O
O
O

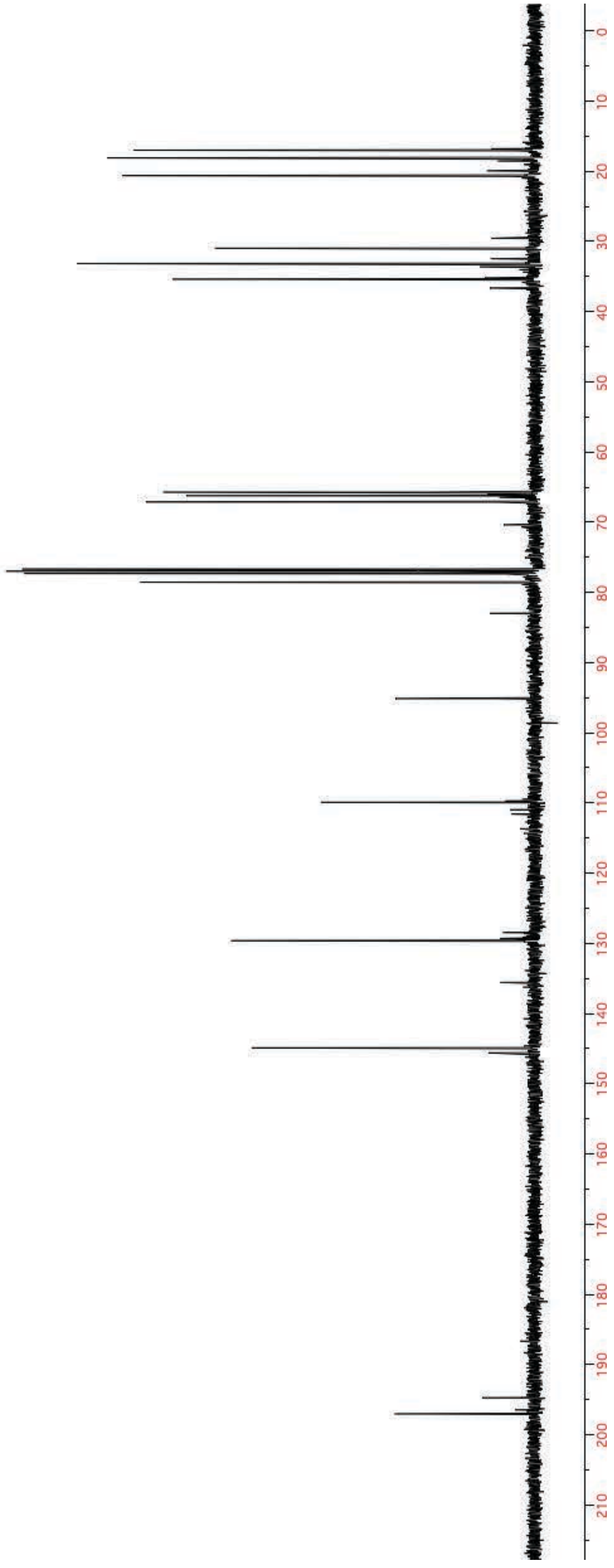

HO
Me
Me
OH
O
O
O
0
1
2
3
4
5
6
7
8
9
ppm 10

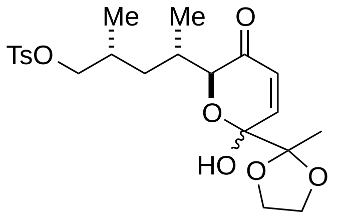


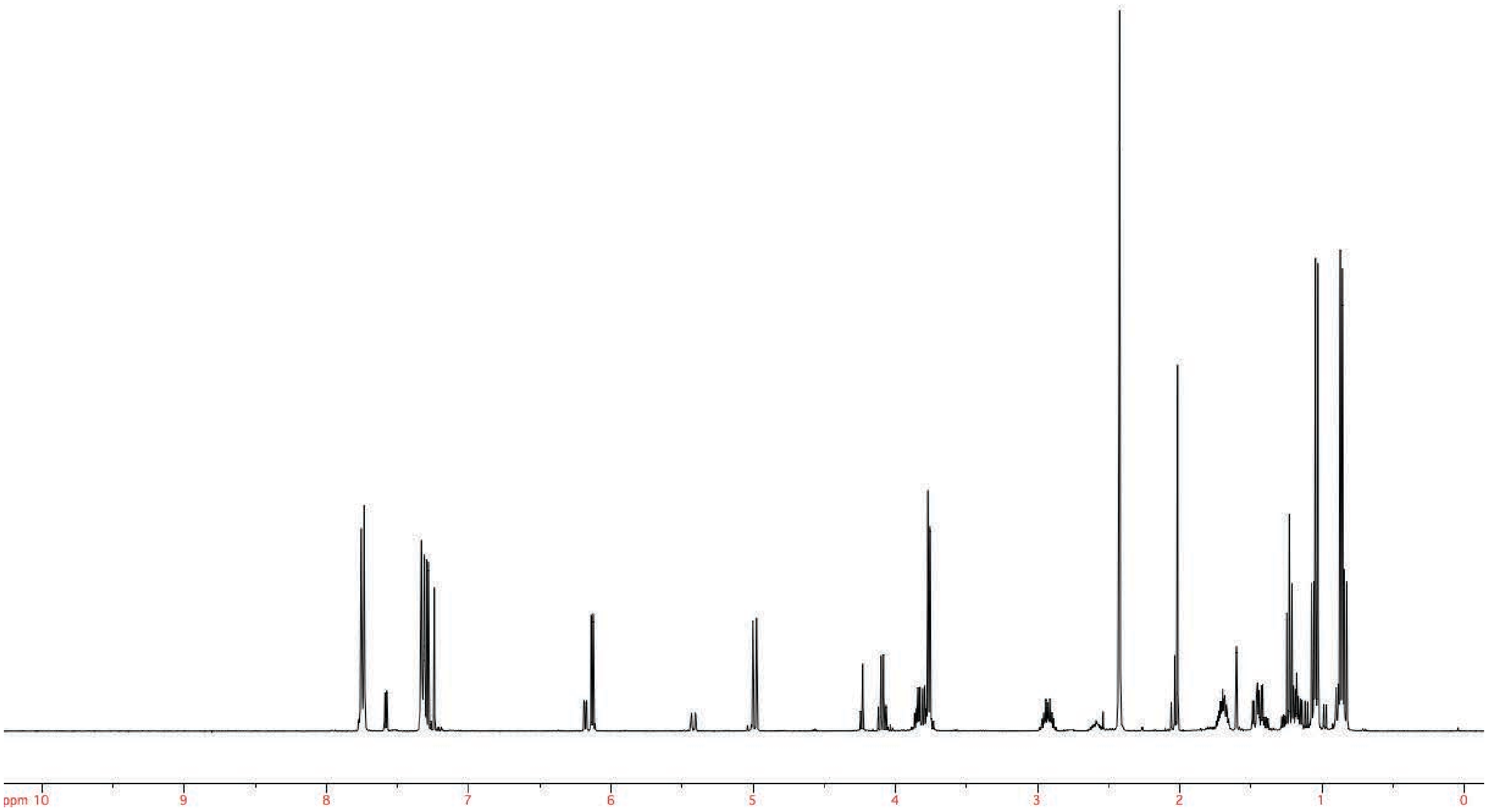
HO
Me
Me
OH
O
O
O
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

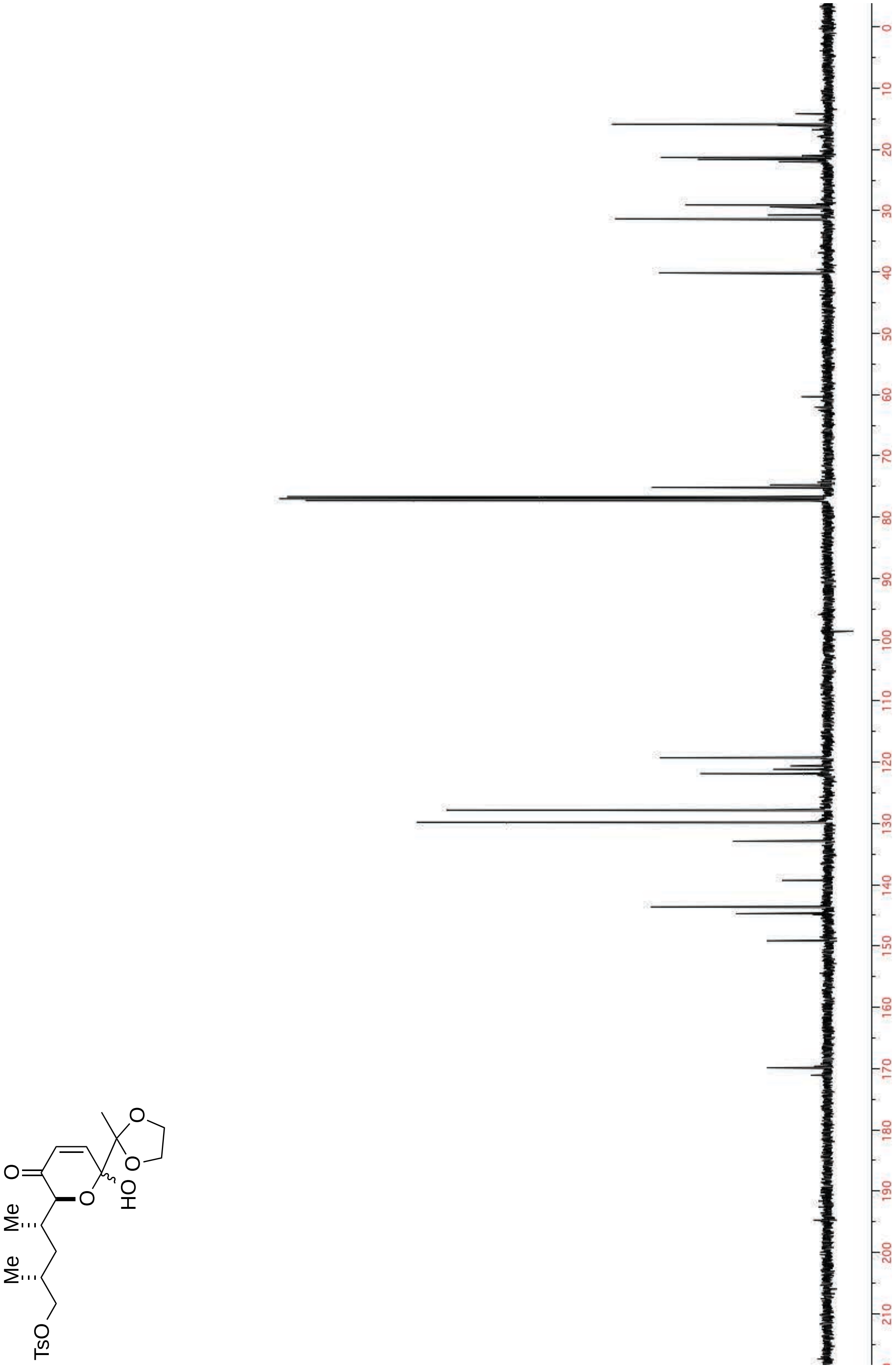

HO
Me
Me
O
O
HO
O
O
ppm 10
9
8
7
6
5
4
3
2
1
0


O
Me
Me
HO
O
HO
O
O

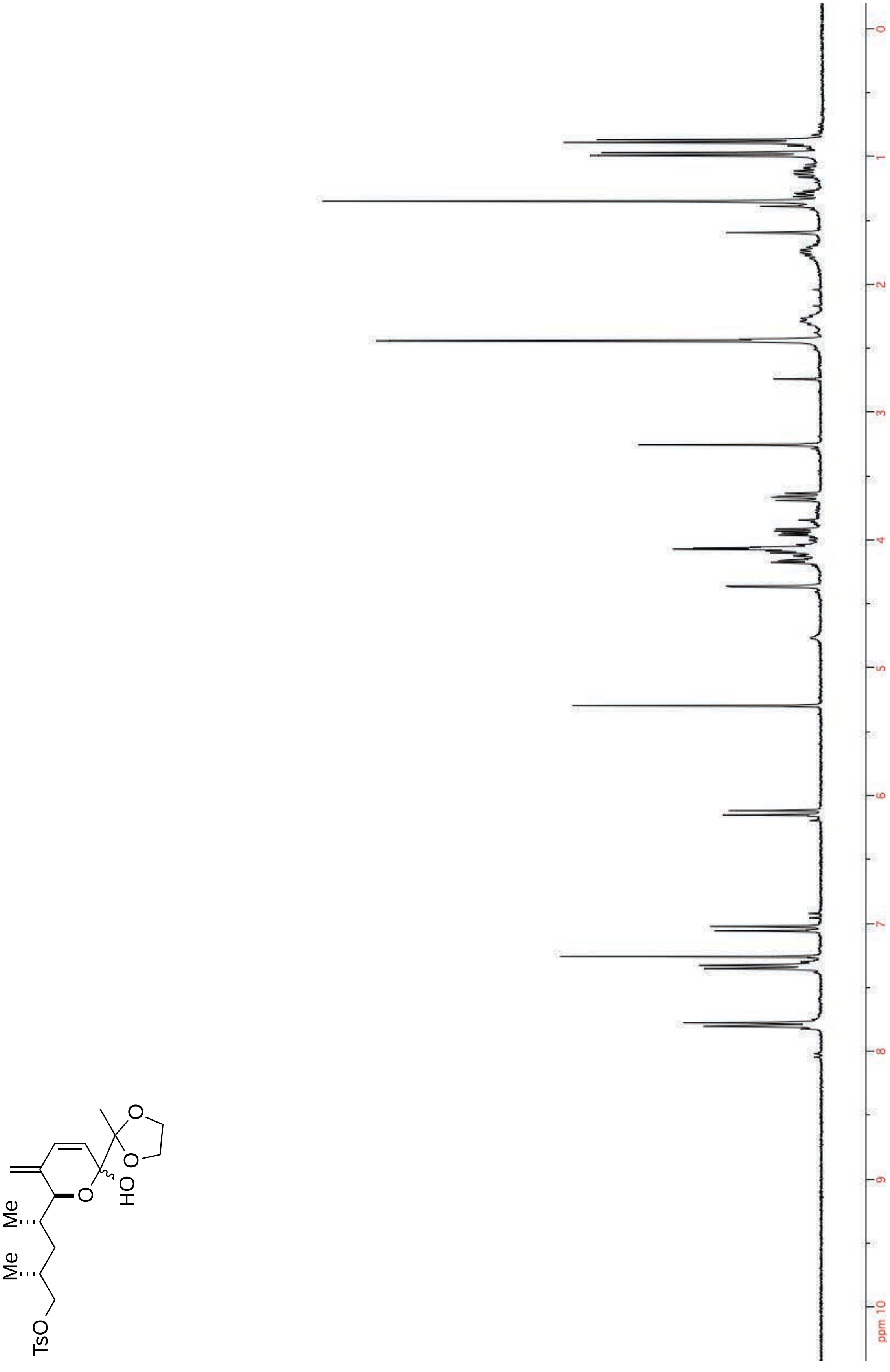

0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

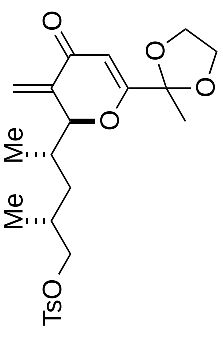

TsO
Me
Me
O
O
HO
O
O


ppm 10
9
8
7
6
5
4
3
2
1
0

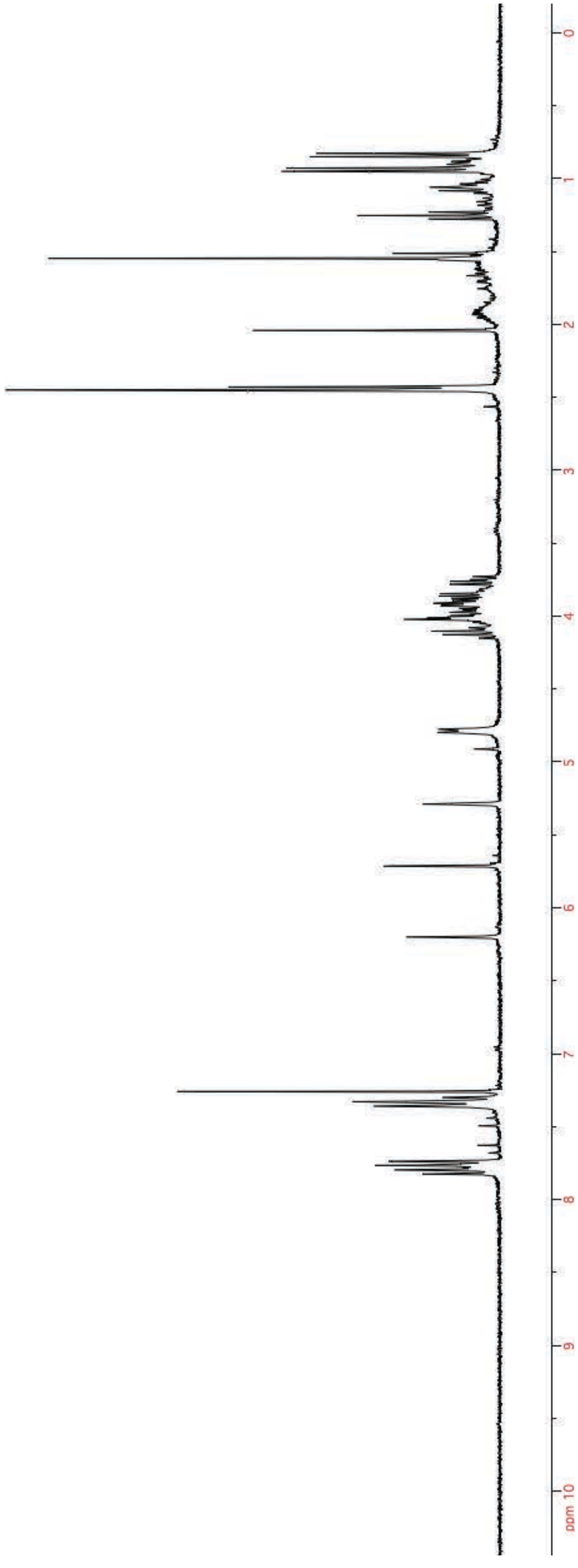


TsO
Me
Me
O
O
O
O
HO
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210


TsO
Me
Me
O
HO
O
O
ppm
0
1
2
3
4
5
6
7
8
9
10



O
O
O
O
Me
Me
TsO



0
1
2
3
4
5
6
7
8
9
ppm 10