Investigation of Counterion Effects in an Organocatalyzed Iodolactonization and Discovery of an Organocatalyzed Iodolactonization to Give 7-Membered Lactones

By

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Dedicated to my grandfather, John Louis Flach

and

To Kellie, best friend and truest love

ACKNOWLEDGEMENTS

It has been said that victory has 100 fathers, but that defeat is an orphan. The work herein disclosed may not be a great victory, but was assuredly reliant upon a manifold of individuals to reach its fruition, such that it is. Firstly I would like to thank Vanderbilt University, in particular the Chemistry Department, and the NIH for providing funding for this research, and gainful employment for several years. I would also like to thank Dr. Don Stec and Dr. Markus Voehler for maintaining the NMR facilities upon which I have so heavily relied in my time here, and Dr. Jonathan Karty for performing mass spectrometry on the new compounds that were synthesized in the course of this research.

I would also like to thank the members of my preliminary committee, Dr. Jeffrey Johnston, Dr. Steven Townsend, and Dr. Nathan Schley for agreeing to supervise my research, and for providing advice and encouragement throughout it.

In particular I would like to thank Dr. Jeffrey Johnston, who developed the catalyst family employed in this research, and was also the person who suggested trying to use PIDA and KI as an oxidant system within our iodolactonization, a key suggestion that, as will be seen, led directly into the majority of the discoveries disclosed in this work. Dr. Johnston has also served as a rigorous mentor and done his utmost to pass on his attention to detail, hard work ethic, and critical thinking abilities to me although I did not always prove the most apt pupil. Surely it is a credit to him that in three years of working for him in a field abounding with frustrations and stressful situations I have never witnessed him lose his temper or treat someone ungraciously.

I have never met Dr. Mark Dobish, but I am deeply indebted to him for his development of the asymmetric iodolactonization of δ-lactones, since all of the research discussed in this thesis grew directly out of that discovery. Finally, I would like to thank all of the members of the Johnston lab for providing advice, encouragement, and friendship. In particular I would like to thank Dr. Kenneth Schwieter for frequently looking over my presentations, and Matthew Knowe and Thomas Struble for providing excellent chemical advice, both theoretical and practical, and an endless stream of wise counsel.

TABLE OF CONTENTS

Page

LIST OF SCHEMES

LIST OF TABLES

CHAPTER 1. IODOLACTONIZATION AND ITS DISCONTENTS

Introduction: Iodolactonization and the Development of its Asymmetric Variants

The cyclization of a pendent carboxylic acid onto an alkene upon the latter's reaction with an electrophilic halogen species is known as halolactonization, and has been known since before the start of the 20th century in its bromine-mediated incarnation. Bromolactonization, discovered by Fittig and Stobbe contemporaneously was therefore the first reported halolactonization, followed shortly after by the discovery of the iodine-mediated lactonization by Bougault in 1908, and the chlorine-mediated one in 1932.[1,2]

This class of reactions soon found utility in organic synthesis; a use the embrace of which was doubtless hastened by the discovery that the two nascent carbon-heteroatom bonds thereby formed were set in an anti-stereospecific manner, allowing relative stereochemistry of the product to be dictated by the geometry of the preceding olefin. This attribute, in concert with a generally high level of reactivity and selectivity of halogens for the alkene, led to the reaction's acceptance as a robust, predictable classical organic reaction. In particular, the iodine-mediated incarnation was accepted as a particularly useful form of the broader reaction as a consequence of the great flexibility of subsequent potential manipulations that the carbon-iodine bond allowed, as well as iodine's comparative convenience of use and low toxicity relative to the other halogens.[1,3,4]

Seventy years transpired between Bougault's initial discovery of iodolactonization, and a systematic investigation of diastereoselection in the iodolactonization of chiral racemic unsaturated acids, which was undertaken by Bartlett and coworkers (Scheme 1). Initial results showed that substitution in the 3-position (compounds **1a** and **1b**) led to very high degrees of diastereoselection favoring the *trans*-

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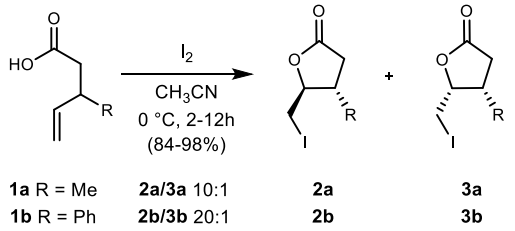
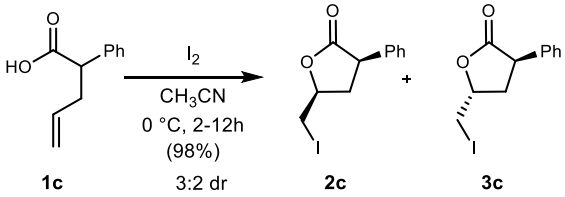
[1] Nolsoe, J. M. J.; Hansen, T. *Eur. J. Org. Chem.* **2014**, 3051-3065.
[2] Bougault, M. J. *Ann. Chim. Phys.* **1908**, *14*, 145-183.
[3] Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950-3952
[4] Bartlett, P. A.; Richardson, D. P.; Myerson, J. *Tetrahedron* **1984**, *40*, 2317-2327

diastereomer (compounds **2a** and **2b**) in the case of γ-lactones when the reaction was performed under thermodynamic conditions.[1,3,4] Furthermore, this relationship was enhanced with increasing size of the 3-substituent yielding greater diastereoselection. Additional substitution in the 2- and 5-positions enhanced this diastereoselection further, but removal of the key substituent in the 3-position dispelled the majority of the observed selectivity (**1c**, Scheme 2), highlighting that position in particular as the critical one for inducing diastereoselection.

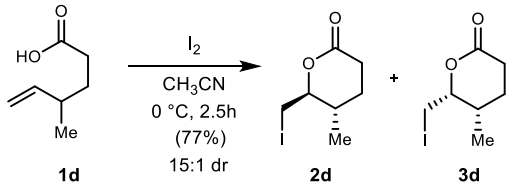
Scheme 1. Diastereoselection of 3-Substituted Pent-4-enoic acids (Bartlett)



Scheme 2. Diastereoselection of 2-Substituted Pent-4-enoic Acids (Bartlett)



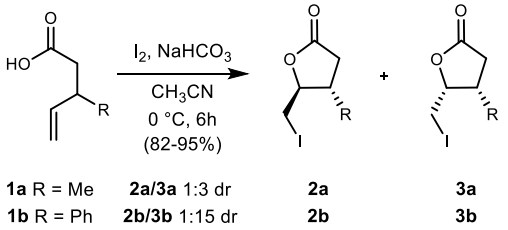
Scheme 3. Diastereoselection of 4-Substituted Hex-5-enoic Acids (Bartlett)



A similar trend was observed in the case of δ-lactones whereby the 4-position proved to be the critical point for inducing diastereoselection (Scheme 3), and again the *trans*-diastereomer (compound **2d**) was preferred. It is not unreasonable to infer from these results that the critical position of a

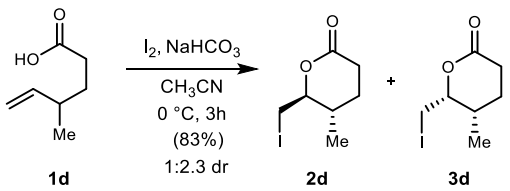
substituent for inducing diastereoselection in an iodolactonization is the allylic position, given that said position proved to be the key position in both γ- and δ-lactones. By way of contrast, substitution of the 2–position gave essentially no facial differentiation, however, it did reinforce diastereoselection when found in concert with substituents in the 4-position.[1,3,4]

Scheme 4. Diastereoselection of 3-Substituted Pent-4-enoic Acids under Kinetic Conditions (Bartlett)



Bartlett also explored the facial selectivity under kinetic conditions, and remarkably found that said conditions caused a reversal of facial selectivity, favoring formation of the *cis*-isomer over the *trans*-, a preference that increased with increasing steric bulk. This observation was explained by invoking formation of an acyl hypoiodite from the carboxylate and iodine which, after delivery of iodine to the hindered face of the alkene, requires rotation of the resultant halonium species in order to accommodate backside attack of the carboxylate, leading to an inversion of diasteroselection. It was discovered that substitution in the 3-position gave rise to a preference of the *cis*-diastereomer of γ-lactones under kinetic conditions, albeit with poor selectivity (3:1 ratio, Scheme 4).[1,3,4] These same kinetic conditions were employed in the iodolactonization towards δ-lactones, with analogous results, albeit less diastereoselection (Scheme 5).[1,3,4]

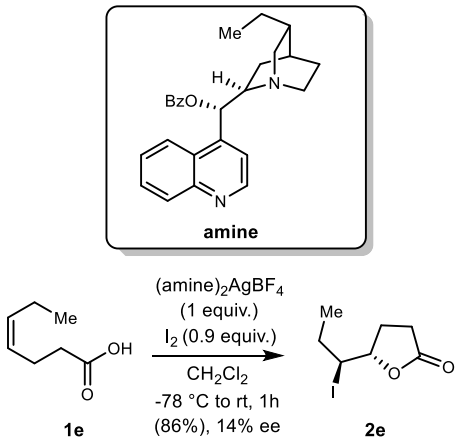
Scheme 5. Diastereoselection of 4-Substituted Hex-5-enoic Acids under Kinetic Conditions (Bartlett)



Reagent-Derived Asymmetry

These initial observations of high diastereoselectivity arising in the iodolactonization reaction gave some measure of hope that enantioselective variants of the reaction could be developed, in particular that catalytic methods could one day be discovered and employed. Notwithstanding these encouraging signs, two decades transpired between Bartlett's pioneering work and the first reports of chiral iodonium reagents inducing enantioselection in an iodolactonization reaction. In 1998, Grossman and coworkers reported the discovery that a quinidine-derived amine in concert with iodine instigated an iodolactonization with a very slight enantioselective preference upon reaction (Scheme 6).[5]

Scheme 6. Iodolactonization with Chiral Quinidine-Based Iodonium (Grossman)

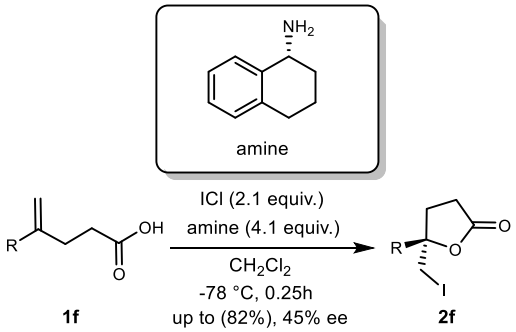


This initial discovery was augmented in the succeeding years by other competent iodonium sources derived from chiral amines. In 2002, Wirth and coworkers reported the enantioselective synthesis of γ-iodolactones through the employ of an enantiopure aminotetraline, and iodine monochloride (Scheme 7).[6] The reaction gave best results when the alkene (compound **1f**) was substituted with an electronically neutral or poor aryl group; electron- rich aromatic rings gave poorer induction, and alkyl substitution gave

[5] Grossman, R. B.; Trupp, R. J. *Can. J. Chem.* **1998**, *76*, 1233-1237.
[6] Haas, J.; Piguel, S.; Wirth, T. *Org. Lett.* **2002**, *4*, 297-300.

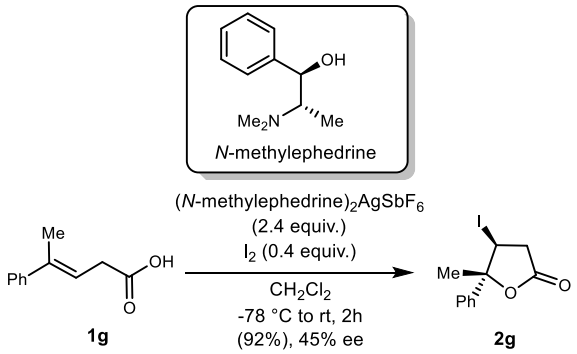
full ablation of enantioselection. Despite these limitations, under favorable conditions, the enantioselection that could be achieved was much higher than Grossman's initial results.

Scheme 7. Iodolactonization with Chiral Aminotetraline-Based Iodonium (Wirth)



Not long after Wirth's reports, Rousseau and coworkers reported a reaction similar to Grossman's initial discovery, albeit with improved enantioselection and a more accessible chiral amine (Scheme 8).[7]

Scheme 8. Iodolactonization with *N*-Methylephedrine-Based Iodonium (Rousseau)



Amongst these advances, the absence of examples featuring δ-lactones is notable. This may be rationalized by invoking different reaction rates for the differing ring sizes since the timing of the formation of the chiral iodine species and subsequent reaction are critical for enantioinduction. Over time, initial induction can be undermined by a variety of alternative pathways, and evidently the δ-lactone

[7] Garnier, J. M.; Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2007**, 3281-3291.

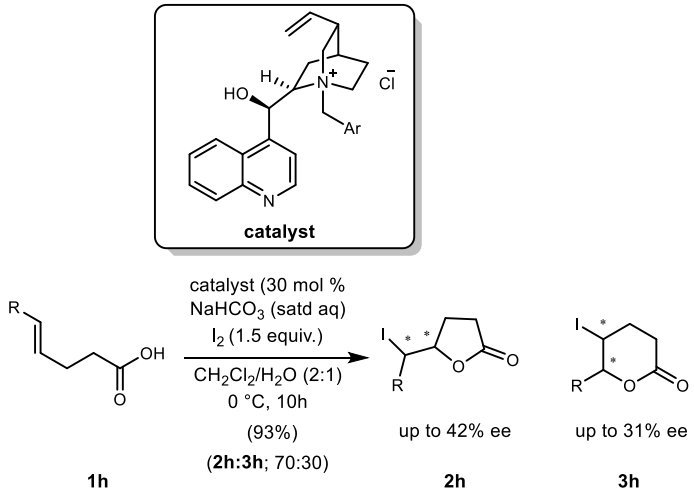
cyclization suffers from kinetic factors that make enantioselective reagent-mediated approaches less viable.[8]

By this point, enantioselective approaches had been well established via a reagent-controlled approach, however enantioselections were relatively poor, and the necessity to rely on stoichiometric or even excess amounts of chiral reagents was an obvious drawback of the reaction. The next substantial advance of the reaction would have to hinge upon not only a substantial improvement in enantioselection, but an ability to induce it in a catalytic manner.

Catalyst-Induced Asymmetry

The first report of an asymmetric iodolactonization arising from a sub-stoichiometric amount of asymmetry-inducing reagent was made by Gao and coworkers, and relied upon the employ of a chiral cinchonidinium phase transfer catalyst salt that, perhaps unsurprisingly, bore very strong structural analogy to Grossman's quinidine-based chiral amine that was vindicated some six years earlier (Scheme 9).[9] Modest enantioselection was seen in both the γ- and δ-lactones (compounds **2h** and **3h**), and the relative ratios of the different lactone sizes (arising from *exo*- vs *endo*-cyclization) was dictated by the electronic properties of the aromatic ring constituting the R-substituent.

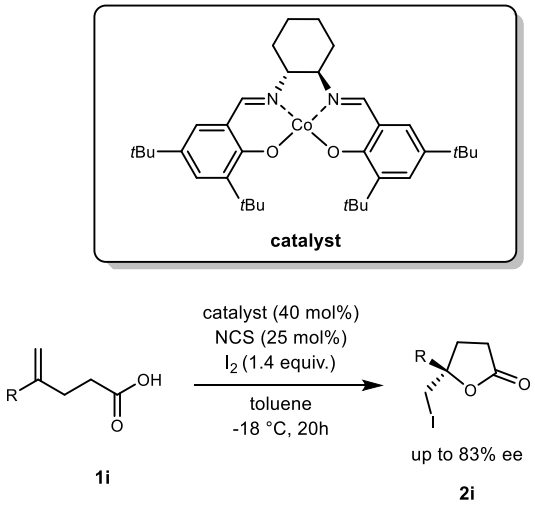
Scheme 9. Iodolactonization with Chiral Cinchonidinium Catalyst (Gao)



[8] Brown, R. S. *Acc. Chem. Res.* **1997**, *30*, 131-137.
[9] Wang, M.; Gao, L. X.; Mai, W. P.; Xia, A. X.; Wang, F.; Zhang, S. B. *J. Org. Chem.* **2004**, *69*, 2874-2876.

The same group also developed a chiral salen-Co^{II} complex that proved competent in a catalytic asymmetric iodolactonization, presumably by acting as a Lewis Acid (Scheme 10).[10] In the presence of iodine monochloride as active iodine source, the reaction proceeded with good enantioselection, and the use of a terminal olefin dictated a single regiochemical outcome favoring the γ-lactone (compound **2i**). Unfortunately, modifications to the salen backbone were unable to further improve the catalyst performance, and employing other *d*-block metals gave significantly poorer outcomes in terms of enantioselection.[10]

Scheme 10. Iodolactonization with Chiral Salen-Co^{II} Catalyst (Gao)

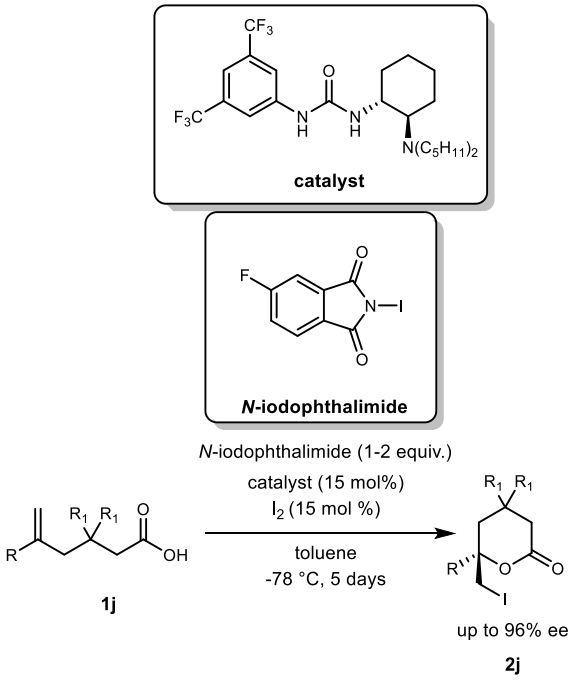


These initial developments were substantial improvements insofar as they represented the first foray into the realm of asymmetric catalytic approaches towards iodolactonization. Despite this, both required very high catalyst loadings, and the cinchonidinium based catalyst gave relatively poor enantioselection. The salen-cobalt catalyst had genuinely impressive enantioselection, but in addition to its very high catalyst loadings, was reliant upon a transition metal, a further liability from a synthetic perspective, especially if the target compound is to be used in a biological or medicinal context.

[10] Ning, Z. L.; Jin, R. H.; Ding, J. Y.; Gao, L. X. *Synlett.* **2009**, 2291-2294.

A massive advance in the methodology was achieved in 2010 by Jacobsen and coworkers with the discovery of a urea-based organocatalyst that gave exceptionally high enantioselections at substantially lower catalyst loadings (Scheme 11).[11]

Scheme 11. Iodolactonization with Chiral Aminourea Catalyst (Jacobsen)



Unusually, it was found that both iodine (as a co-catalyst), and the *N*-iodophthalimide were necessary for reactivity to be observed. The authors proposed that the mechanism proceeded through formation of a triiodide species upon the *N*-iodophthalimide which subsequently iodinated the chiral amine which then acted as the immediate source of asymmetric delivery of electrophilic iodine. The hydrogen-bond donor capacity of the urea N-H bonds was presumed to interact in some manner with the imide species, and potentially the carboxylic acid as well. Furthermore, the catalytic system could be applied towards γ-lactones in addition to the δ-lactones.

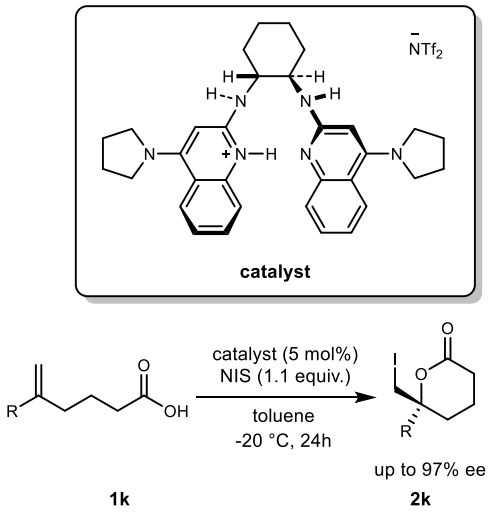
The exceptional degree of enantioselection in forming δ-lactones, combined with the absence of transition metals and lower catalyst loading made the discovery a considerable improvement over existing

[11] Veitch, G. E.; Jacobsen, E. N. *Angew. Chem.* **2010**, *122*, 7490; *Angew. Chem. Int. Ed.* **2010**, *49*, 7332-7335.

methodology, but it still faced the limitations of slow reaction times, extremely cold temperatures being requisite, and a relatively high catalyst loading.

A further improvement was established in 2012 when Johnston and coworkers established a Bis(AMidine)-based catalyst as highly selective for an iodolactonization to give δ-lactones (Scheme 12).[12]

Scheme 12. Iodolactonization with Chiral Bis(AMidine) Catalyst (Johnston)



Impressively, the catalyst loading was able to be substantially lowered, the reaction run at much higher temperatures and within shorter time frames, and the enantioselection achieved was directly comparable to the best results of previous catalysts. The fact that no transition metal was necessary was also an obvious asset. This particular catalytic system is the one employed throughout this thesis, and so further description of the system and some of its idiosyncrasies is deferred to the following chapter. However, its significance within the development of catalytic asymmetric iodolactonization is obvious, and should be noted.

In the same year, Martin and coworkers developed an asymmetric iodolactonization onto an internal alkene using a chiral BINOL derived organocatalyst (Scheme 13).[13]

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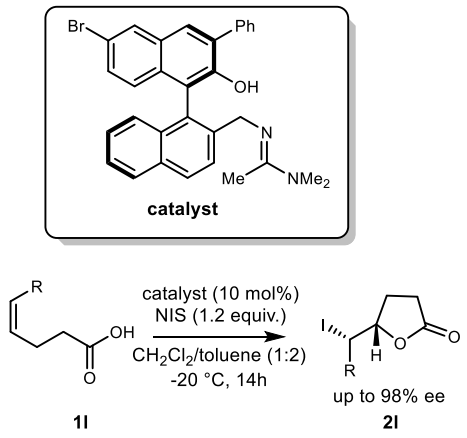
[12] Dobish, M. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2012**, *134*, 6068

[13] Fang, C.; Paull, D. H.; Hethcox, J. C.; Shugrue, C. R.; Martin, S. F. *Org. Lett.* **2012**, *14*, 6290-6293.

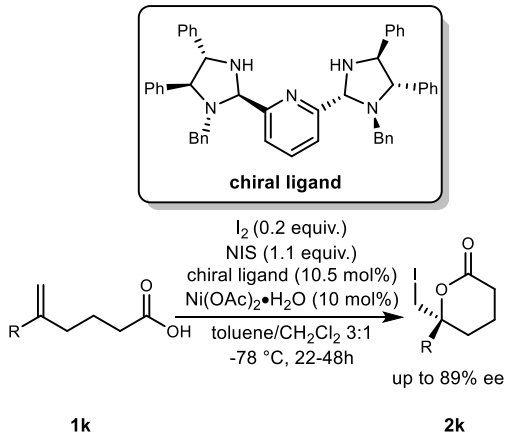
Scheme 13. Iodolactonization with Chiral BINOL Catalyst (Martin)



The enantioselection and regioselection were both excellent, but the reaction was limited to *cis*-alkenes (compound **1l**), and proved inefficacious with their corresponding *trans*-isomers.

The following year, Arai and coworkers were able to induce good enantioselection towards δ-lactones using a chiral PyBidine ligand in concert with a Ni^{II} catalyst (Scheme 14).[14]

Scheme 14. Iodolactonization with PyBidine-Ni^{II} Catalyst (Arai)



This incremental improvement showed that further development of asymmetric iodolactonizations was by no means limited exclusively to organocatalysts, and that various transition metal catalysts had capacity for asymmetric induction as well.

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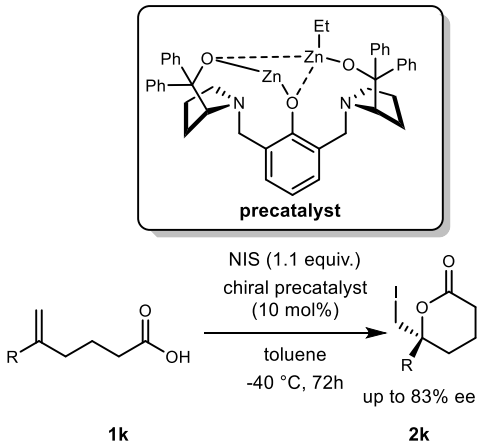
[14] Arai, T.; Kajikawa, S.; Matsumara, E. *Synlett* **2013**, *24*, 2045-2048.

In 2013 also, Stenstrom and coworkers applied Trost's chiral dinuclear zinc complex as a catalyst towards an asymmetric iodolactonization to give δ-lactones, showing yet another metal had some capacity to effect the reaction enantioselectively (Scheme 15).[15]

Scheme 15. Iodolactonization with Zinc Complex (Stenstrom)



The development of asymmetric iodolactonization methodology has obviously improved dramatically since its origins in the late 1990s with respect to enantioselections and yields achieved, as well as with respect to the substoichiometric and even catalytic amounts of asymmetry-inducing reagents employed. More convenient conditions and shorter reaction times have also been observed, and the variety of new catalysts developed provides more options for adaptation to specific lactone precursors. Despite these advances, it should be noted that there are relatively few instances of regioselective control *arising exclusively* from catalyst intervention, and not regiochemical biases arising endogenously from substrate olefin substitution. It should also be noted that the author can find no evidence of asymmetric approaches to lactones of larger ring sizes than the δ-lactone. Finally, mechanistic understanding of the means of asymmetry is by no means commensurate to the empirical discovery of a given competent catalyst. That is to say that all or most catalytic systems within the realm of asymmetric iodolactonization are discovered empirically and not by an a priori understanding of how to induce a given desired

[15] Filippova, L.; Stenstrom Y.; Hansen, T. V. *Tet. Lett.* **2014**, *55*, 419-422.

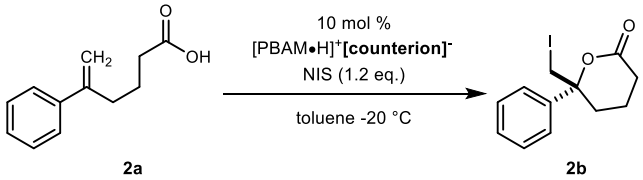
asymmetry. At best such systems are rationalized after the initial discovery by means that are in most cases incompetent towards the a priori rational design of a different catalytic system. At worst they are presented as a point of empirically vindicated data; fully divorced from surrounding context of the wider realm of asymmetric iodolactonization. The observation that mechanistic investigations are significantly more challenging both in terms of intellectual demand and experiment design than initial discovery of a competent catalyst system is not to cast aspersions upon either group of scientists so employed; but is simply to note that there are very few if any examples of a model catalytic system that was developed rationally and found to exhibit enantioselection in accord with previous predictions. The distinction between these challenges is not unlike the difference between catching a fish and designing a living fish from first principles. That the design side has thus far lagged behind the catching side should neither surprise nor perturb us.

It was the desire to gain some mechanistic insight into the Johnston Bis(AMidine) [BAM] catalyst family within the context of asymmetric iodolactonization that led to the initial original efforts documented in this thesis; efforts which, while largely fruitless in fulfilling their stated intention did at least generate some tangential benefits in discovery of novel methodology, and which are discussed in the following chapters.

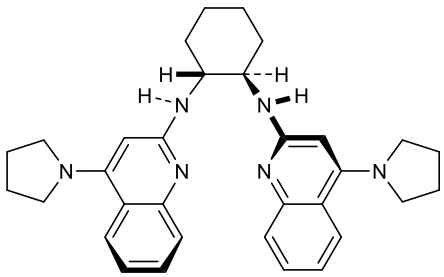
CHAPTER 2. COUNTERION INVESTIGATIONS

It has been mentioned previously that the Bis(AMidine) [BAM] catalyst developed by Johnston and coworkers constituted a significant improvement in the prevailing methodology of asymmetric iodolactonization in terms of simple reaction outcome. In addition to these obvious advantages, the methodology exhibited an unusual counterion effect whereby the same catalyst exhibited significant variations in yield and enantioselection arising exclusively from the identity of its corresponding counterion.

Table 1. Initial Counterion Screen (Dobish and Johnston)



Entry[a]	counterion	I^+ source[b]	yield (%)[c]	ee (%)[d]
1	**$TolSO_3^-$**	NIS	90	20
2	**(-) camphorsulfonate**	NIS	41	29
3	**(+) camphorsulfonate**	NIS	35	29
4	**FSO_3^-**	NIS	35	40
5	**$F_3CSO_3^-$**	NIS	87	53
6	**$CF_3(CF_2)_3SO_3^-$**	NIS	45	49
7	**$F_3CSO_2NH^-$**	NIS	95	24
8	**$(CF_3SO_2)_2N^-$**	NIS	90	84
9	**$F_6C_3S_2O_4N^-$**	NIS	74	82



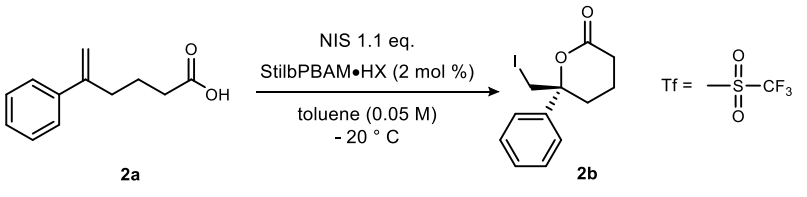
(PBAM)

The initial counterion screen performed with the PBAM catalyst had yielded the observations that chirality in the counterion appeared to have no effect on enantioinduction in the reaction (as evinced by the equal enantioselection induced by both enantiomers of camphorsulfonate), and that stronger acids appeared to give better enantioselection (Table 1).[12] The wide variations in enantioselection which arose from the variations in counterion, in concert with the reaction's apparent indifference to chirality aroused our interest, and we initially set out to explore the role of the counterion in a more controlled manner.

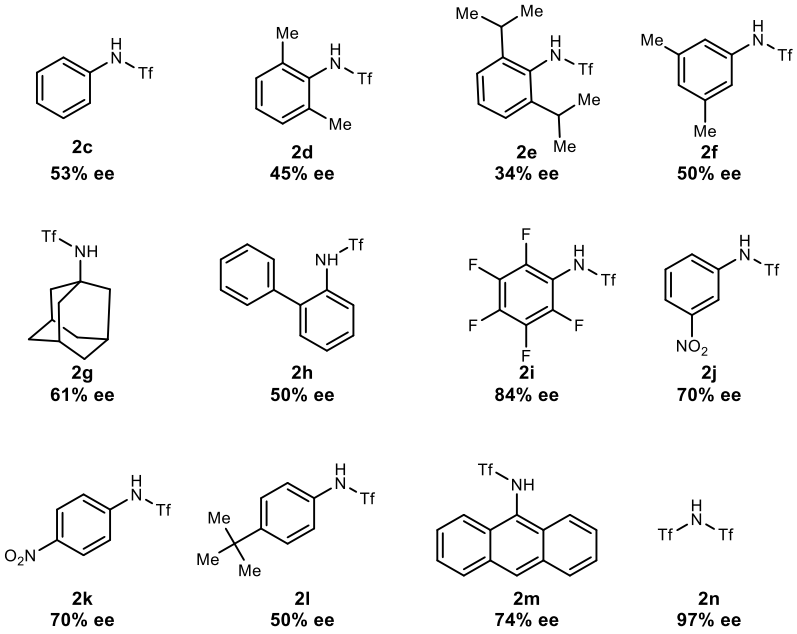
Aniline and its various derivatives proved excellent precursors in this endeavor, since the amine moiety could be readily triflated via reaction with triflic anhydride, and the resultant N-H bond would be sufficiently acidic to protonate the free base StilbPBAM catalyst. The aryl group could then be modified with various functionalities to alter the resulting steric and electronic environs, with the hopes that defined modification of the nascent counterion could offer insight into its mechanism of activity, and ultimately offer an avenue into rational design of catalyst counterions to optimize the BAM-catalyzed iodolactonization and potentially any other reactions catalyzed by BAM salt catalysts (Table 2).

These lofty goals notwithstanding, the results of this inquiry were much more modest than hoped for. After first noting that none of the synthesized counterions matched the excellent enantioselection of 97% previously achieved with triflimide (**2n**), a few identifiable trends do present themselves. The most readily apparent is that seen in procession from the unmodified aniline ring (**2c**) to the 2,6-dimethyl substituted ring (**2d**), and finally the 2,6-diisopropyl substituted ring (**2e**); a fairly clear trend of decreasing enantioselection can be observed corresponding positively with a more sterically congested environment near nitrogen upon the ring. That this is predominantly a steric effect can be reasonably inferred from the minimal effect seen on enantioselection in the 3,5-dimethyl (**2f**) and 4-*tert* butyl (**2l**) substituted cases in which similar alkyl functionalities show essentially no effect when removed from immediate proximity to the putative acid functionality.

Table 2. Results of Aniline-derived Counterions in StilbPBAM Catalyzed Iodolactonization



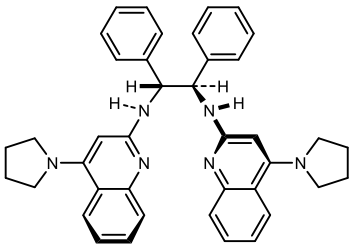
2a **2b**



2c 53% ee | **2d** 45% ee | **2e** 34% ee | **2f** 50% ee

2g 61% ee | **2h** 50% ee | **2i** 84% ee | **2j** 70% ee

2k 70% ee | **2l** 50% ee | **2m** 74% ee | **2n** 97% ee



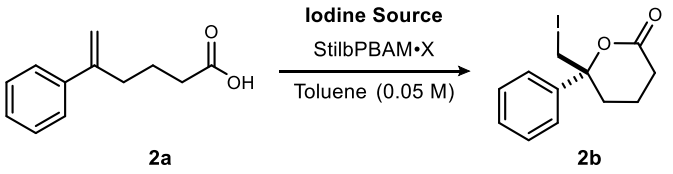
(StilbPBAM)

An additional aryl group in the *ortho*- position (**2h**) appeared to have no impact relative to the unmodified aniline-derived archetype (**2c**), however, the anthracenyl-derived counterion (**2m**) showed substantial improvement in enantioselection over the aniline-derived counterion (**2c**). The pentafluoroaniline-derived counterion (**2i**) gave marked improvement over the aniline-derived archetype (**2c**), an observation that can most readily be attributed to its greater acidity arising from the stabilization of multiple highly electronegative fluorine atoms on the anionic nitrogen. One of the few clear trends observable in Dobish's initial counterion screen (Table 1) was that high acidity of the counterion precursor correlated reasonably well with better enantioselection; the performance of the pentafluoroaniline-derived counterion is in line with these results. Additionally, the 3 and 4-nitro substituted aniline-derived counterions (**2j** and **2k**, respectively) gave significantly improved enantioselections over the archetypal aniline-derived counterion (**2c**) (70% vs. 53%), which can also be explained by invoking the greater acidity of the corresponding acid arising from the anion-stabilizing effect of an electron-withdrawing nitro group on the aniline ring. The position of the nitro functionality on the ring appeared to not matter at all, with both *meta*- and *para*-derivatives giving 70% ee, an unusual outcome in that the *para*-nitro derivative should be somewhat more acidic than its *meta*-nitro cousin.

It should be noted as well that the adamantyl-derived backbone (**2g**) gave an enantioselection corresponding to that of the free base catalyst, which would be an unusual improvement for a markedly less acidic counterion. In addition, a characteristic shift in ^{19}F NMR observed in all of the other counterions upon reaction with free base catalyst to give the resultant catalyst salts was absent in its case alone. These observations, taken in concert, suggest that the adamantyl-derived counterion (**2g**) was not sufficiently acidic to protonate the catalyst free base and produce the corresponding salt, and thus the results observed were simply reaction catalyzed by free base catalyst. This does at least offer some insight into the limits of counterion structure; it appears that in addition to triflation of the nitrogen, at least some form of additional electron-withdrawing group is necessary in order to form an acid capable of protonating the various free base BAM catalysts.

Having seen no success in improving enantioselection beyond the benchmark previously established by Dobish, but having established a panel of counterions with potential utility in reaction screening and tuning, we began examining alternative sources of electrophilic iodine as oxidants in the reaction (Table 3).

Table 3. Screen of Iodine Sources in StilbPBAM-Catalyzed Iodolactonization



	NIS	Iodine	PhI=O	PIDA	PIFA
Free Base	(99%), 57% ee	(73%), racemic	(10%), 65% ee	(99%), 92% ee	(29%), racemic
Tf_2NH	(95%), 98% ee	(82%), racemic	(18%), 77% ee	(99%), 93% ee	

(PhI=O, PIDA, and PIFA had equivalent amount of KI added to form oxidant system)

Values reported as % yield, % ee

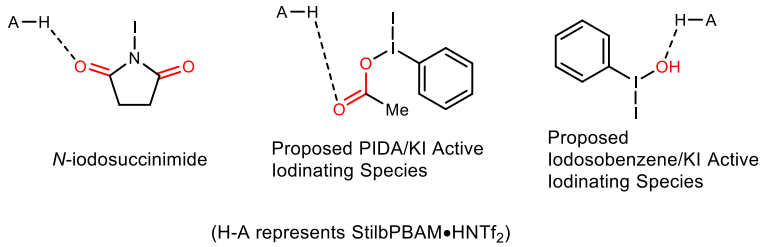
Serendipitously, it was discovered early on in the investigation that a combination of PIDA (phenyliododiacetate), and KI (potassium iodide) in concert, which had previously been employed in the lab as an oxidant towards the diamination of styrenes,[16,17] also acted as an efficient oxidant system in the BAM-catalyzed iodolactonization, affording the iodolactone in good yield and enantioselection. Conversely, the employment of iodine as sole oxidant gave good reactivity, but entirely racemic product, an observation that was rationalized by noting its lack of favorable hydrogen bond acceptor moieties that could interact with the catalyst in a favorable manner. It was also observed that whereas NIS, PIDA, and

[16] Hong, K. B.; Johnston, J. N. *Org. Lett.* **2014**, *16*, 3804-3807.
[17]Danneman, M. W.; Hong, K. B.; Johnston, J. N. *Org. Lett.* **2015**, *17*, 2558-2561.

KI were poorly soluble in toluene under the reaction conditions, molecular iodine was readily solubilized. The solubility of given oxidant has since been regarded as a potentially non-trivial variable in the induction of enantioselection, although no further evidence for an effect has been observed. The success of the PIDA/KI oxidant system led to an interest in structurally related hypervalent iodine species, and so iodosobenzene (PhI=O) with KI, and PIFA (phenyliododi(trifluoroacetate)) with KI were examined. The PIFA/KI system appeared to react quite readily (with PIFA proving fully soluble under the reaction conditions), but upon workup gave racemic material in poor yields, presumably due to multiple operative byproduct pathways. Conversely, iodosobenzene exhibited very poor reactivity, but modest enantioselection was observed. The analogous structures of the oxidants that showed a measure of enantioselection, combined with our understanding of the BAM catalyst as a hydrogen bond donor led us to hypothesize an active species resulting from attack of potassium iodide onto the hypervalent iodine of PIDA, with simultaneous displacement of an acetate leaving group. It was proposed that this active species could act as the electrophilic source of iodine, and that its remaining acetate group could act as a hydrogen bond acceptor in a manner analogous to the amide carbonyls in NIS, thereby coordinating the oxidant to the catalyst and providing a scaffold for enantioselection (Scheme 16). Although the proposed active species is not known, and subsequent discoveries have suggested a different active species as more plausible, it should be stressed that the importance of a carbonyl hydrogen bond-acceptor in the active oxidant in order for good enantioselection to be observed is not an inherently unreasonable assumption.

Furthermore, the mechanistic hypothesis posited below shaped the subsequent investigations for a time and so is duly recorded here. It should be emphasized again that it no longer seems to be the most mechanistically plausible proposal.

Scheme 16. Proposed Catalyst Interaction with Oxidant



N-iodosuccinimide

Proposed PIDA/KI Active Iodinating Species

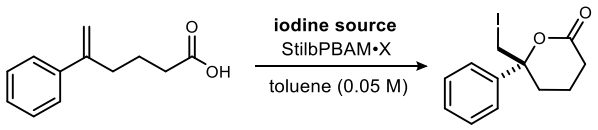
Proposed Iodosobenzene/KI Active Iodinating Species

(H-A represents StilbPBAM•$HNTf_2$)

With iodosobenzene/KI giving poor reactivity, and PIFA/KI and molecular iodine giving racemic product, it became apparent that NIS and PIDA/KI were the two oxidant systems that were competent in the BAM-catalyzed iodolactonization. In the course of examining the PIDA/KI oxidant system, it was observed that the PIDA/KI system had a muted counterion effect relative to that of NIS. Whereas enantioselection dropped from 98% ee to 57% ee when going from the StilbPBAM triflimide salt to the StilbPBAM free base with NIS as an oxidant, no such drop was observed in the PIDA/KI case, with the triflimide salt and free base StilbPBAM catalysts giving 93% ee and 92% ee respectively (Table 4).

This unusual result was further examined by running the iodolactonization across a panel of different catalyst salts, the counterions of which were largely various incarnations of carboxylic acids (Table 4). While NIS showed enantioselections ranging from the mid-fifties up to 98% ee, the enantioselections under the PIDA/KI system proved to be less sensitive to counterion effects across the counterion panel. Interestingly, when using the PIDA/KI system, free base StilbPBAM (**entry 1**), the corresponding mono and bis-triflimide salts (**entries 2 and 3**), and the corresponding mono and bis-acetic acid salts (**entries 5 and 6**) all gave a similar enantioselection of 93-94% ee, with the bis-triflimide salt showing a substantial drop in reactivity relative to the mono-triflimide salt, and the bis-acetic acid salt showing a more modest decline in reactivity (as reflected in lower yields).

Table 4. Counterion Screen of PIDA/KI and NIS

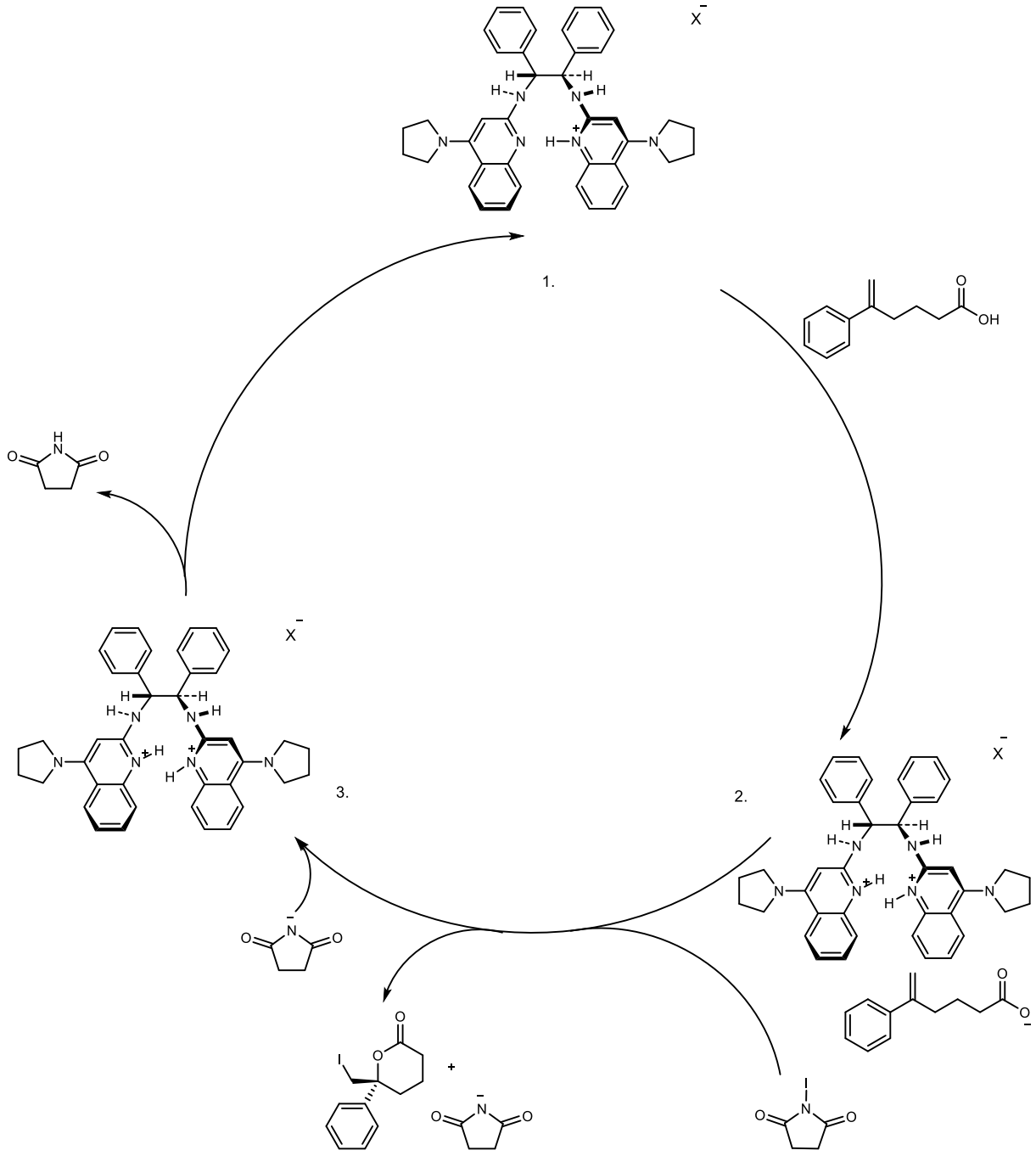


(Values reported as % yield % ee)

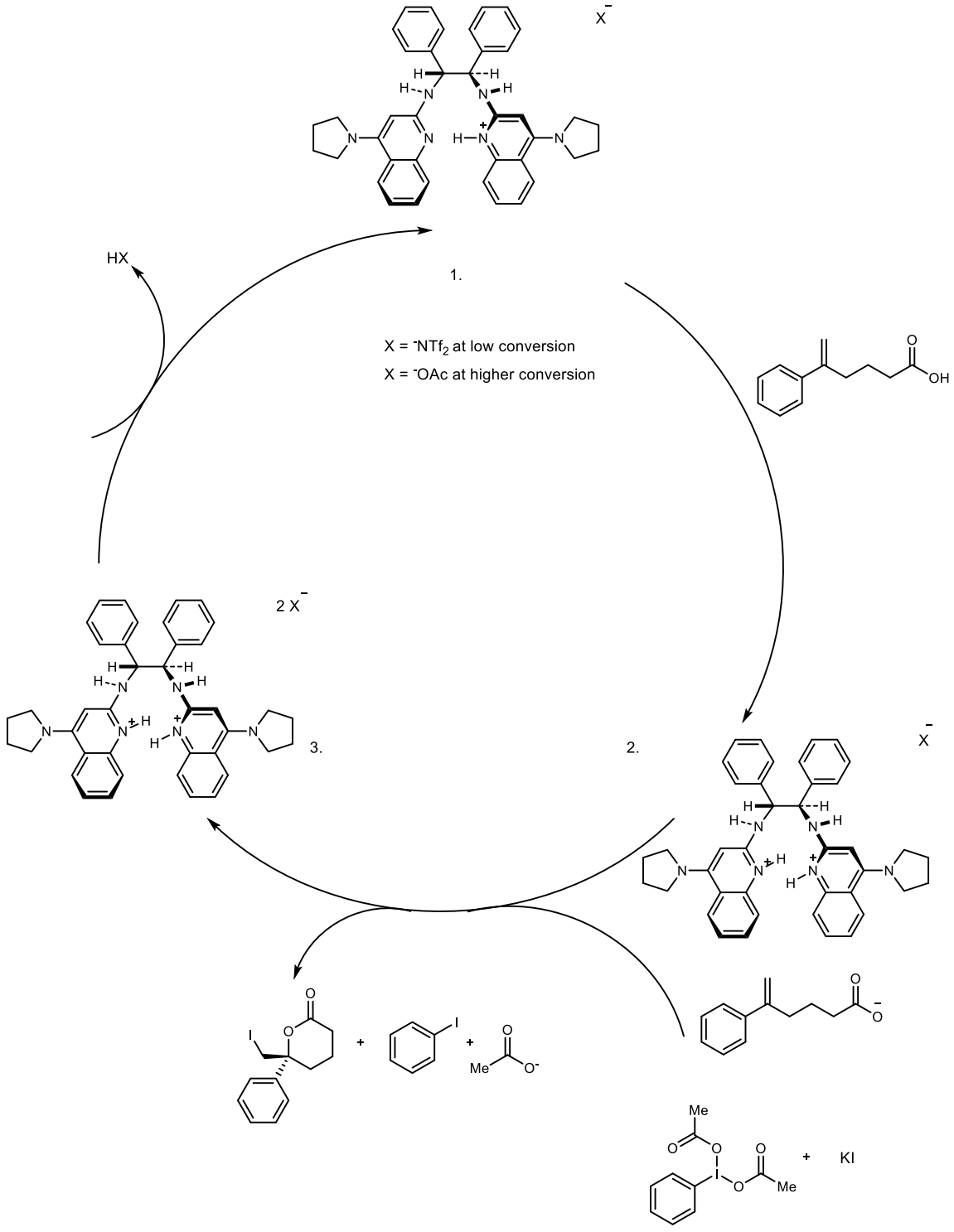
Entry[a]	counterion acid	NIS	PIDA/KI
1	**Free Base$^-$**	99/57	99/92
2	**Tf_2NH**	95/98	99/93
3	**$(Tf_2NH)_2$**	N.R.	28/93
4	**2c$^-$**	34/55	99/77
5	**AcOH$^-$**	58/65	99/94
6	**AcOH (2 equiv.)**	100/49	78/94
7	**$CH_2(COOH)_2^-$**	14/73	60/78

Some variation in enantioselection was seen with the **2c** counterion (**entry 4**), as well as the malonic acid counterion (**entry 7**). The muting of the counterion effect which had proven so significant in the development of the asymmetric iodolactonization with NIS under conditions of PIDA/KI was rationalized by invoking the unambiguous mechanistic distinctions between the two oxidant systems which are illustrated below (Scheme 17 and Scheme 18).

Scheme 17. Proposed Catalytic Cycle with NIS as Oxidant



Scheme 18. Proposed Catalytic Cycle with PIDA/KI as Oxidant



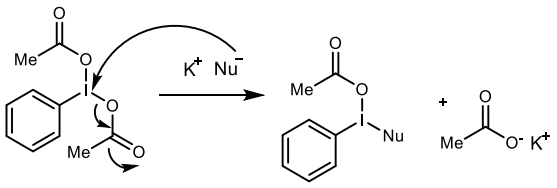
In the NIS based reaction (Scheme 17), after an initial catalyst-mediated deprotonation of acid substrate and subsequent transfer of electrophilic iodine, succinimide anion is generated as a byproduct, which is basic enough to deprotonate the newly doubly protonated catalyst, thereby forming iodolactone, succinimide, and regenerating the catalyst to its initial state of reactivity. In the PIDA/KI mediated reaction (Scheme 18), catalyst deprotonation of substrate proceeds as before as does transfer of electrophilic iodine. While remaining agnostic as to the actual active species of electrophilic iodine we can comfortably assert that the final byproducts after transfer of electrophilic iodine are iodobenzene and two equivalents of acetate. The iodobenzene presumably plays no further role, but it should be noted that our newly formed base (acetate) is by no means equivalent to succinimide in basicity and it is this divergence in basicity that dictates the subsequent divergence in catalytic cycle. Whereas succinimide anion as noted before was sufficiently basic to deprotonate the protonated catalyst, the equilibrium of acetate should actually lie towards favoring protonation of the catalyst- that is, it should act as a second counterion. The fact that these reactions proceed to completion argues that substrate acid has some method whereby it can exchange with a counterion in the case where a doubly protonated catalyst has two counterions. As this reaction proceeds and increasing quantities of acetate are generated, the probability of acetate acting as the counterion to the catalyst in a given reaction sequence increases- especially given that the initial catalyst counterion is present in only catalytic quantities. This hypothesis remains as yet unproven, but does help explain why free base catalyst, mono and bis-triflimide catalyst salt, and mono and bis-acetate catalyst salt give identical enantioselections- all of these reactions are proceeding with acetate as the primary counterion in the majority of cases. The case of malonic acid can be seen as inhibiting this exchange of counterion for acetate by virtue of its being tethered to the catalyst at two protonation sites. Thus two counterion dissociation steps are required to generate the acetate counterion catalyst, making the formation of said catalyst salt much more difficult, and allowing for more of the reaction to occur under conditions where malonic acid is acting as the counterion; a role in which it is presumably worse than acetate, accounting for its somewhat lower enantioselection. The somewhat poorer showing of **2c** as counterion can be rationalized as either the counterion giving extremely poor

enantioselection in a small number of reaction instances before exchanging, or being slower to exchange for acetate relative to triflimide counterion. In any case, the range of enantioselection is far narrower with the PIDA/KI system, and the mechanistic outlines in Scheme 17 and Scheme 18 offer a somewhat compelling rationalization of this effect, albeit one that remains as yet unvindicated.

Attempt to Employ PIDA/Nucleophile as a General Scaffold:

It has been noted previously that the initial discovery of the PIDA/KI system led to a mechanistic postulate that has appeared increasingly unlikely in light of subsequent results. These mechanistic revisions are deferred to a later point in this work for the sake of clarity in explaining the investigations that were undertaken following the discovery of the PIDA/KI system's efficacy in the BAM-catalyzed iodolactonization, and subsequent examination of counterion effects. It had become clear by this point that the PIDA/KI system was, although mechanistically intriguing, especially with regards to its muting of the counterion effect, not quite competitive with the previously reported BAM-catalyzed iodolactonization reported by Dobish using NIS, which was in any case a reaction whose enantioselective iterations were already well established. However, the leading mechanistic hypothesis at that time invoked attack of the nucleophilic iodide onto the PIDA hypervalent iodine, thereby transforming the former nucleophile into a newly electrophilic species. With the remaining acetate of the hypervalent iodine species providing a handle for catalyst coordination, it was hoped that PIDA could be paired with other small nucleophiles to act as a general scaffold for their conversion into electrophilic species that could be manipulated in an enantioselective manner using StilbPBAM as a catalyst (Scheme 19).

Scheme 19. PIDA as a General Platform for Generating Electrophiles from Nucleophiles



In light of subsequent experience, this period of investigation can fairly be described as fully unsuccessful, but can at least be credited with alerting us to potential issues with our mechanistic understanding of the reaction as then posited.

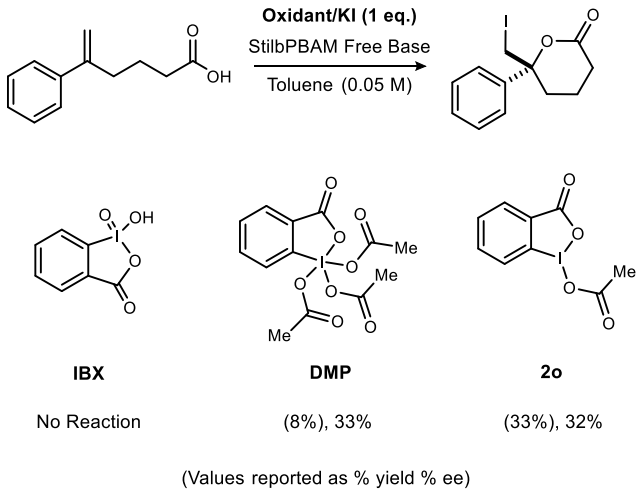
The investigation of alternative nucleophiles began with potassium bromide (KBr), in the hopes that a halide not dissimilar to KI offered the best hope for success in expanding the repertoire of nucleophiles that could be controlled. Unfortunately, although a small amount of bromolactone was recovered (11%) under reaction conditions (the same as those employed in the iodolactonization), the product was racemic. Although discouraged by the lack of enantioselection, we were encouraged somewhat by even the minimal amount of product formation, and resolved to press onward with the examination of other nucleophiles. We decided to examine sodium azide (NaN_3) and potassium cyanide (KCN) next on the basis of novelty if we were to meet with even limited success. No success was seen in either case, with both reactions returning mostly starting material. To our initial surprise, the PIDA/NaN_3 conditions returned a substantial amount of the corresponding ketone arising from oxidative cleavage of the substrate alkene. Although it is unclear why, it appears that the presence of sodium azide accelerates this oxidative cleavage process. The capacity of PIDA to effect this transformation is not unknown[18], however, it has generally been understood to do so from the corresponding diol. It seems most likely that PIDA very slowly oxidizes the alkene to the diol, which is then quickly oxidatively cleaved by another equivalent of PIDA. This very same reactivity was observed under the reaction conditions with the exclusion of sodium azide, albeit at a far slower rate, whereas no ketone formation was observed under reaction conditions when sodium azide was present but PIDA was excluded. When potassium cyanide was employed as nucleophile, starting material was recovered largely intact, with slight formation of ketone – by all appearances the potassium cyanide did not accelerate the oxidative cleavage process in the manner in which sodium azide had. Subsequent attempts to employ TMSCN and $TMSN_3$ as alternative sources of the nucleophiles failed as well, largely giving decomposition of the starting material. By this

[18] Nicolaou, K. C.; Adsool, V. A.; Hale, C. R. H. *Org. Lett.* **2010**, *12*, 1552-1555

point it had become evident that the use of PIDA in concert with various nucleophiles and BAM-based catalysts as a general scaffold for enantioselective reactions with alkenes was unsuccessful, and no further nucleophiles were pursued. Emphasis shifted back towards investigating other oxidants competent in the already vindicated BAM-catalyzed iodolactonization.

Towards this end, it was discovered that although 2-iodoxybenzoic acid (IBX) in concert with KI exhibited no reactivity, Dess-Martin periodinane (DMP) with KI under the standard reaction conditions gave 8% yield of the iodolactone with 33% ee (Scheme 20).

Scheme 20. Exploration of Other Hypervalent Iodine Oxidants



Although it was somewhat surprising that the reactivity of PIDA with KI could be expanded even modestly to a hypervalent iodine(V) species with some preservation of enantioselection, the result could not be readily expanded or improved, and offered no realistic synthetic utility. Benzoiodoxole **2o** was synthesized, and assayed under reaction conditions to see the effect of a presumably more sterically demanding environment on the (at the time) putative active intermediate. In this regard the benzoiodoxole (**2o**) was assumed to behave analogously to PIDA, but with one of the acetate ligands tethered directly to the aryl ring. This resulted in modest reactivity and enantioselection, but with both poorer than those seen with PIDA under the same conditions. Finally, the PIDA/KI system in concert with StilbPBAM catalyst

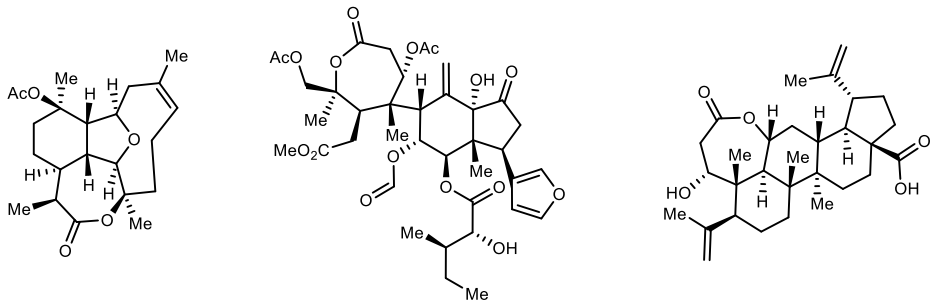
was assayed in an intermolecular reaction using alpha-methylstyrene and acetic acid; while product was observed in low yields, it proved to be racemic.

The investigations into the BAM-catalyzed iodolactonization reaction had, by this point, exhausted many avenues of investigation, and, with the notable exception of the discovery of the PIDA/KI system, yielded very little results of any synthetic utility. The initial investigation which had centered on synthesizing and exploring various counterions had failed to improve on the admittedly excellent selectivity previously achieved by Dobish with the triflimide counterion. The discovery of the PIDA/KI system proved remarkably efficacious in the previously developed reaction, but even so did not improve on the previously reported yield and enantioselection achieved using NIS as oxidant. Unfortunately, the initial discovery proved to be relatively limited, with efforts to replace PIDA with other oxidants proving largely unsuccessful, and efforts to exchange potassium iodide for other nucleophiles completely so. We had found a reagent system in search of a reaction in many ways. That reaction would eventually be found, and though it proved more modest of an innovation than initially hoped, it nevertheless proved to be the greatest triumph of the PIDA/KI system, a genuine expansion of the preceding methodology, the discovery and development of which comprises the second part of this treatise.

CHAPTER 3. ε-LACTONES: PREVALENCE AND SYNTHESIS

The ε-lactone functionality is found in a considerable number of natural products isolated from a diverse range of organisms, most of which are terpenoid in nature.[19] Of these terpenoid ε-lactones, the majority arise from plants, although a large number were isolated from marine organisms as well.[19] Research into the biological activities of this diverse class has found that many of the compounds exhibit antimicrobial, insecticidal, and anticancer properties. Others are used as plant growth inhibitors.[19] Several examples of this naturally arising structural motif are illustrated in Scheme 21 below.

Scheme 21. ε-Lactone Functionality Arising within Natural Products



Briarellin J (**3a**) was first isolated from marine coral, and has been a target of synthetic efforts due to both its intriguing structure as well as the antimalarial activity it has demonstrated.[20] Prieurianin (**3b**) has been shown to have activity in stabilization of the actin cytoskeleton in cells.[21] Chiisanogenin (**3c**) has shown significant anti-inflammatory effects in rats.[22]

In the grander context of natural product structures, the ε-lactone motif is a rarity in drugs, and synthetic efforts more generally, nor is it particularly prevalent in natural products relative to its

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[19] Ishmuratov, G. Y.; Vydrina, V. A.; Galkina, Y. A.; Yakovleva, M. P.; Ishmuratova, N. M.; Tolstikov, A. G. *Chem. Nat. Compd.* **2015**, *51*, 1011-1034.
[20] Crimms, M. T.; Mans, M. C.; Rodriguez, A. D. *Org. Lett.* **2010,** *12*, 5028-5031.
[21] Toth, R.; Gerding-Reimers, C.; Deeks, M. J.; Menninger, S.; Gallegos, R. M.; Tonaco, I. A. N.; Hubel, K.; Hussey, P. J.; Waldmann, H.; Coupland, G. *The Plant Journal*, **2012**, *71*, 338-352.
[22] Jung, H. J.; Nam, J. H.; Choi, J.; Lee, K. T.; Park, H. J. *J. Ethnopharmacol.*, **2005**, *97*, 359-367.

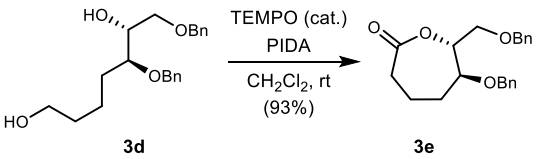
homologous cousins the γ- and δ-lactones. Despite this, and in light of its presence in bioactive compounds, methods towards the synthesis of ε-lactones, in particular *asymmetric* methods could potentially offer access into new chemical space.

Prevailing Synthetic Methods

Current methodology towards the synthesis of ε-lactones can be roughly broken down into the four major categories of diol oxidation, Baeyer-Villiger oxidation of ketones, Yamaguchi macrolactonization, and halolactonization.[23]

An example of diol oxidation with subsequent lactone formation is illustrated in Scheme 22.[24]

Scheme 22. Diol Oxidation to Give ε-Lactones (Sasaki)



3d **3e**

This method relies upon oxidation of the primary alcohol to the aldehyde, cyclization to the lactol, and subsequent oxidation to the lactone **3e**. Aside from the obvious reliance on prior asymmetry, this method is an excellent one for the synthesis of ε-lactones.

The Baeyer-Villiger reaction is another common method for the synthesis of ε-lactones, perhaps the most widely known to the broader community of organic chemists. An example of the reaction can be seen in Scheme 23 wherein compound **3f** is oxidized to give brassinolide **3g**.[25]

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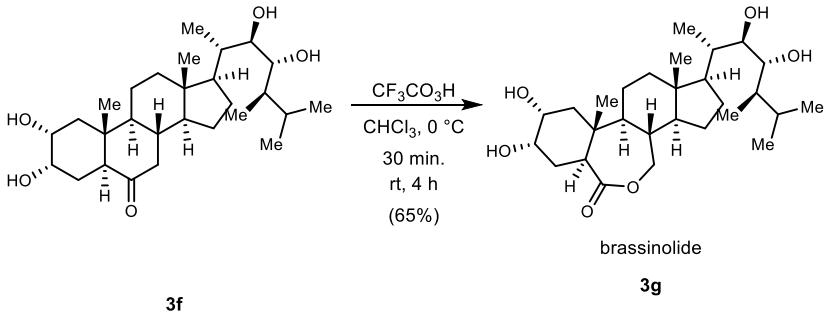
[23] Piva, O. *Synthesis of Saturated Oxygenated Heterocycles II*, Topics in Heterocyclic Chemistry 36, **2014**, 283-320.
[24] Ebine, M.; Suga, Y.; Fuwa, H.; Sasaki, M. *Org. Biomol. Chem.* **2010**, *8*, 39-42.
[25] Marek, A. M.; Patil, M. R.; Klepetarova, B.; Kohout, L.; Elbert, T. *Tet. Lett.* **2012**, *53*, 2048 – 2050.

Scheme 23. Baeyer-Villiger Ring Expansion to Give Brassinolide (Elbert)

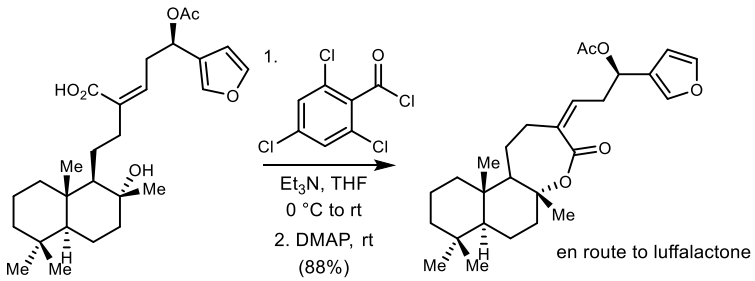


3f **3g**

The use of the Baeyer-Villiger reaction here is particularly impressive in light of the fact that no protecting groups were used on a complex steroid architecture (**3f**) and that a relatively high yield was still achieved.

The Yamaguchi macrolactonization conditions are widely used in the synthesis of larger ring sizes than ε-lactones, but have also proven competent in the synthesis of ε-lactones (Scheme 24).[26]

Scheme 24. Yamaguchi Macrolactonization to Give ε-Lactones (Urones)



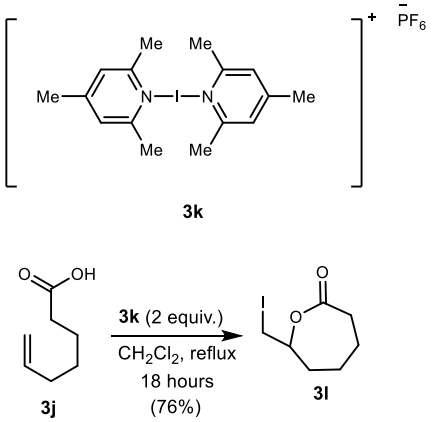
3h **3i**

Finally, halolactonization has been employed in the synthesis of ε-lactones, but has proven to be far more challenging and less broadly applicable a reaction than the halolactonizations towards γ- and δ-lactones. Examples of halolactonizations to give ε-lactones are relatively sparse, and tend to be reliant upon electrophilic halogen species that can charitably be described as unusual.[27] Rousseau and coworkers

[26] Basabe, P.; Bodero, O.; Marocs, I. S.; Diez, D.; Blanco, A.; de Roman, M.; Urones, J.G. *J. Org. Chem.* **2009**, *74*, 7750 - 7754.
[27] Simonot, B.; Rousseau, G. *J. Org. Chem.* **1993**, *58*, 4-5.

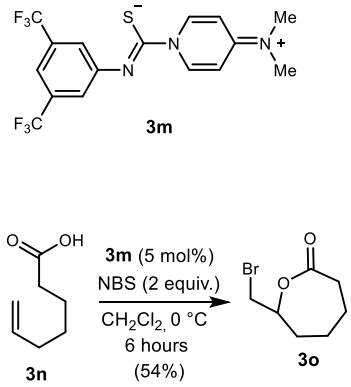
relied upon bis(*sym*-collidine)iodine(I) hexafluorophosphate (**3k**) as the requisite electrophile in the work they have accomplished in this field, which is considerable (Scheme 25).[27, 28]

Scheme 25. Bis(*sym*-collidine)iodine(I) Hexafluorophosphate-Mediated Iodolactonization (Rousseau)



A final testament to the challenge inherent in the field can be witnessed by the fact that as recently as 2012, Yeung and coworkers published a catalytic bromolactonization in which the operation of the catalyst acted exclusively to improve reactivity, and induced no enantioselection in the product (Scheme 26).[29]

Scheme 26. Organocatalyzed Bromolactonization to Give ε-Lactones (Yeung)



[28] Simonot, B.; Rousseau, G. *J. Org. Chem.* **1994**, *59*, 5912-5919.
[29] Cheng, Y. A.; Chen, T.; Tan, C. K.; Heng, J. J.; Yeung, Y. Y. *J. Am. Chem. Soc.* **2012**, 16492-16495.

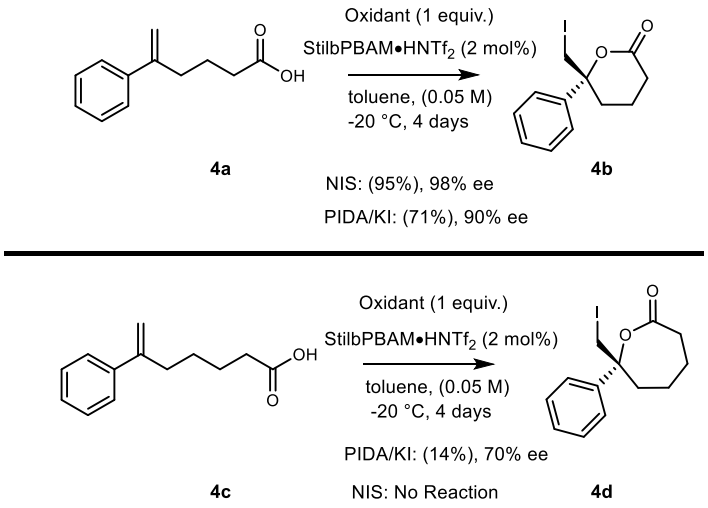
This reaction and its disclosure serves as an indication of the substantial challenges that are arrayed against halolactonization towards larger ring sizes. That the catalyst (**3m**) can induce new reactivity is undoubtedly impressive, but also serves to emphasize that common electrophilic halogen species are often not competent in the synthesis of halolactones larger than δ-lactones without catalyst intervention. The following chapter shall disclose an alternative approach centered on catalyst control of a significantly more potent halogenating species; one that upon full development was able to rely upon catalyst intervention in order to bias desired product formation against an irksome byproduct, as well as induce an appreciable degree of enantioselection.

CHAPTER 4. DISCOVERY AND DEVELOPMENT OF AN ENANTIOSELECTIVE IODOLACTONIZATION TO GIVE ε-LACTONES

It should be noted here in a brief preface that at this time chronologically, issues with reproducibility of the StilbPBAM-catalyzed iodolactonization to give δ-lactones using PIDA/KI briefly arose, which were quickly dispelled upon the cessation of flame-drying the glassware. In other words, the reaction is reproducible under conditions of ambient moisture, but more rigorous drying protocols can lead to significantly poorer enantioselections and yields.

After the discovery of PIDA/KI as a competent oxidant system in concert with StilbPBAM catalysis to effect asymmetric iodolactonization, efforts were undertaken to develop an application of the system that would be genuinely unique. These efforts were rewarded when it was discovered that the PIDA/KI conditions allowed for the cyclization of a longer carboxylic acid to give an ε-lactone (7-membered lactone) with relatively good enantioselection (Scheme 27).

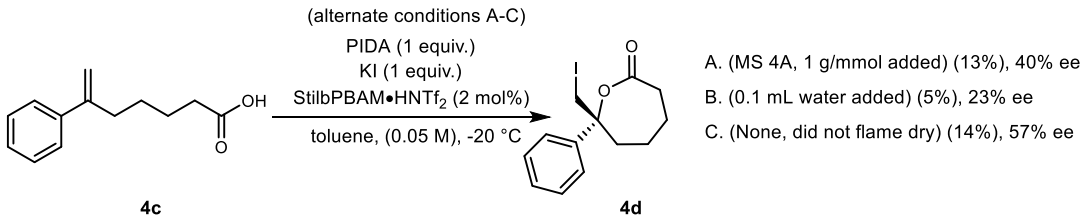
Scheme 27. The Discovery of an Enantioselective Iodolactonization to give ε-Lactones



Scheme 27 shows the typical conditions used towards the δ-lactone, as well as the discovery that PIDA/KI yielded a small amount of ε-lactone (**4d**), which NIS was not competent to form under the same conditions. Although the enantioselection was relatively good as a starting point, higher selectivity remained a goal. Furthermore, the reactivity of the 7-membered iodolactonization was remarkably poor under the given conditions, yielding only 14% after 4 days of reaction time. Moving forward, the immediate goal was to improve yield considerably while preserving or improving enantioselection.

These initial efforts focused on employing water as an additive given the effect we had seen it have on the 6-membered iodolactonization (Scheme 28).

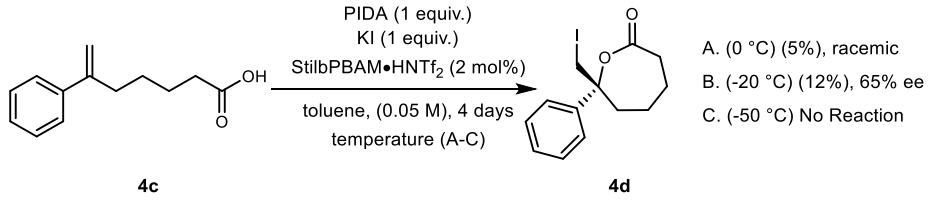
Scheme 28. Effect of Water on 7-Membered Iodolactonization



As can be seen in conditions A-C in Scheme 28, the addition of molecular sieves lowered enantioselection moderately, whereas the addition of water directly lowered both enantioselection and yield significantly. Neglecting to flame dry the given glass vessel and employing no other additive gave the best outcome of the three conditions tried in terms of yield and enantioselection. Although an admittedly imperfect investigation of the variable, it seemed relatively clear that ambient amounts of moisture gave better results than the alternatives, and so that particular variable was set and maintained moving forward.

The most obvious variable to assay next was reaction temperature, and so the reaction was run at several different temperatures (Scheme 29).

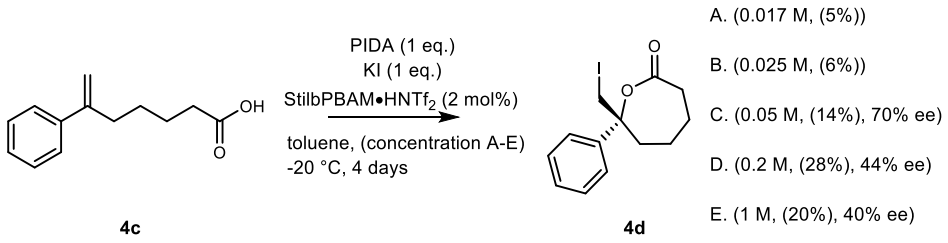
Scheme 29. Effect of Temperature on 7-Membered Iodolactonization



Again, the result was relatively unambiguous. At 0 °C, the product was racemic, and at -50 °C no product formation was observed. It was clear that -20 °C was the ideal temperature at which the reaction would proceed. The variable was set and maintained.

The effect of solvent concentration was then explored (Scheme 30).

Scheme 30. Effect of Concentration on 7-Membered Iodolactonization

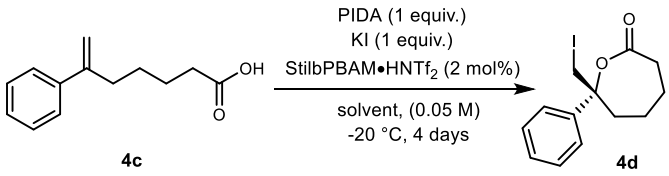


The results made sense insofar as highly dilute conditions (A. and B. in Scheme 30) gave even lower reactivity (such that pure compound could not be recovered to determine enantioselection), while more concentrated conditions (D. and E. in Scheme 30) gave greater conversion, but substantial decreases in enantioselection. Ultimately, it was determined that the starting concentration (C. in Scheme 30) was better than the alternatives, and so was set as a variable, and efforts turned to other potential avenues of reaction improvement.

The next major effort of exploring the reaction centered on probing different solvents.

The majority of solvents assayed gave no formation of product and are duly enumerated in Scheme 31.

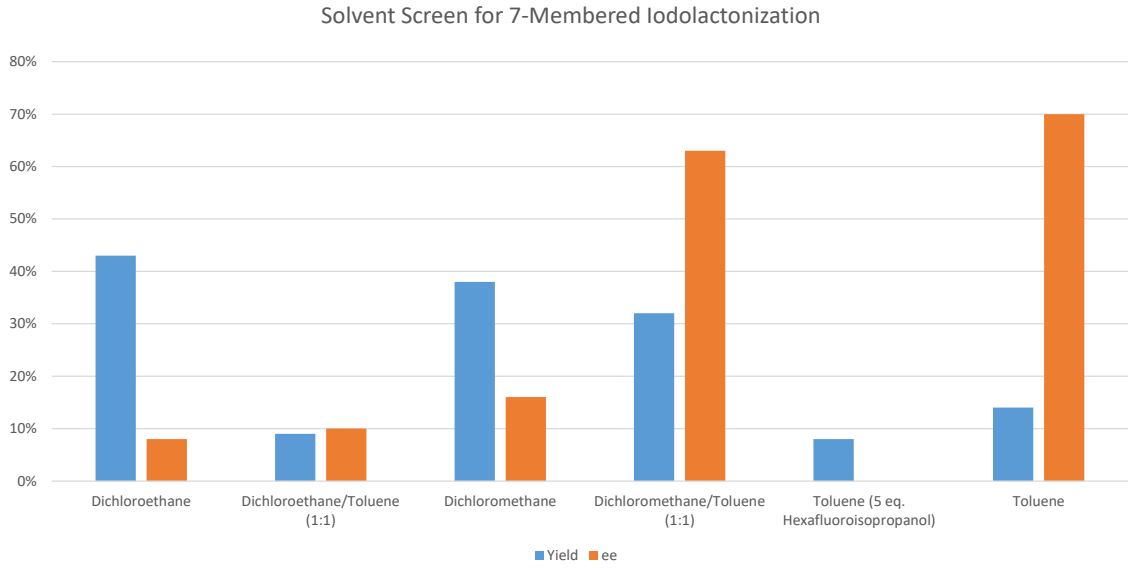
Scheme 31. Solvent Screen (Unsuccessful Solvents)



Solvents tried that gave no reaction: acetonitrile, chloroform, chloroform/toluene (1:3), diethyl ether, hexafluoroisopropanol, trifluorotoluene

Those solvents that showed some measure of conversion can be seen in Table 5.

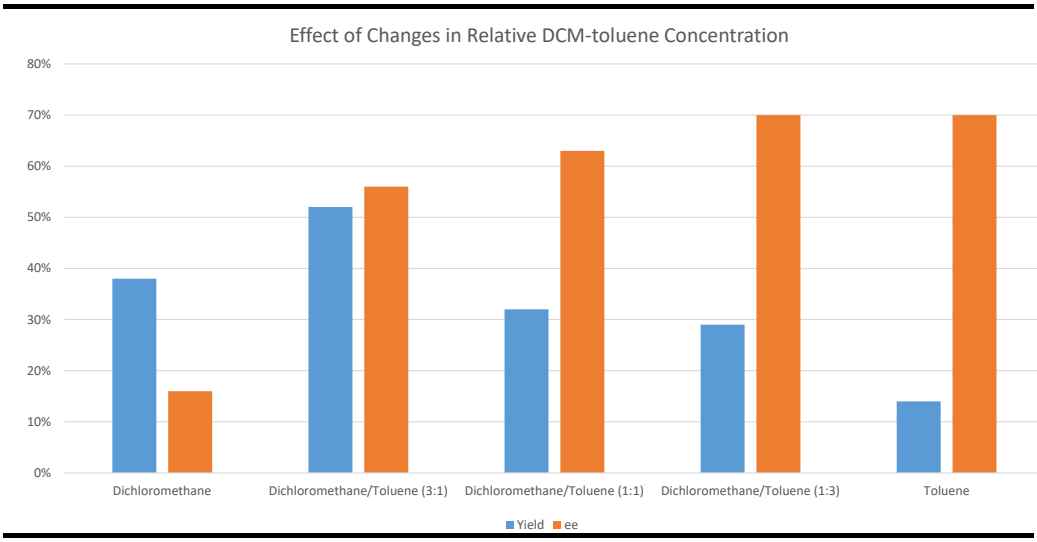
Table 5. Solvent Screen (Solvents that Gave Conversion)



Toluene was the only solvent to show significant enantioselection, but halogenated solvents showed better conversion. To our modest pleasure, it was discovered that a 1:1 mixture of toluene and dichloromethane was able to preserve most of the benefits of each individual solvent; it roughly doubled the reactivity over that of toluene alone, while only slightly decreasing enantioselection. This discovery led to an examination of various ratios of dichloromethane and toluene as solvent under the reaction

conditions to see if the 1:1 ratio was ideal (Table 6). Keeping other reaction variables constant, the relative ratios of dichloromethane and toluene were altered to see effect on yield and enantioselection.

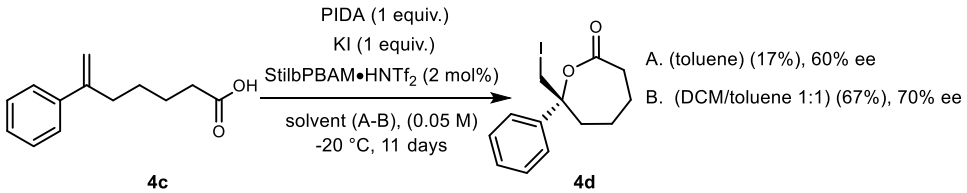
Table 6. Effect of Changes in Relative Dichloromethane-Toluene Concentration



The results trended well with the previous understanding that dichloromethane imparts higher reactivity and toluene greater selectivity. However, it seemed clear that a 1:1 ratio offered the best balance of high yield and enantioselection, and so was set as the solvent system to be employed moving forward.

Interestingly, it was observed at this point that the dichloromethane and toluene solvent system offered an additional advantage over toluene alone; namely, that the reaction with exclusively toluene appeared to stall at around 20% yield even at extended reaction times, an issue not observed with the new solvent system (Scheme 32).

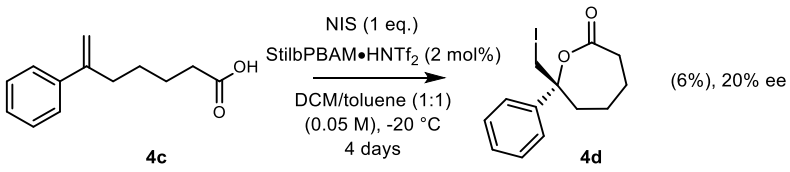
Scheme 32. Full Conversion under New Solvent Conditions



Unusually, this effect seemed to reverse when the free base catalyst was employed, with toluene as a single solvent giving higher yields at long reaction times than the free base catalyst in the dichloromethane and toluene solvent system.

It was also noted at this point that under these new optimized reaction conditions, some slight reactivity could now be observed when employing NIS as the oxidant (Scheme 33).

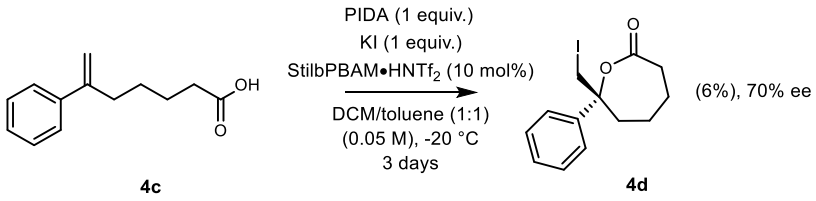
Scheme 33. NIS Shows Reactivity under New Solvent Conditions



Some measure of enantioselection was even observed, but both reactivity and enantioselection were so unambiguously worse than the PIDA/KI system that no efforts were made to try to optimize the reaction under NIS conditions.

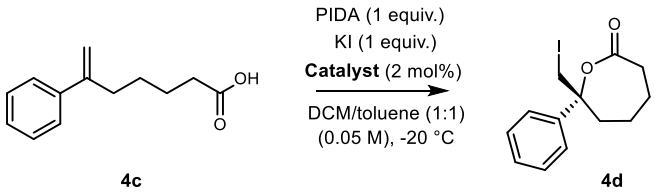
In an effort to increase reactivity further while also shortening the very long reaction times, the reaction was run under increased catalyst loading. To the author's surprise, this seemed to have a detrimental effect on the yield of the reaction and no effect on enantioselection (Scheme 34).

Scheme 34. Results of Increased Catalyst Loading

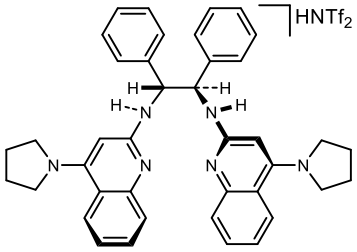


Having exhausted several of the more obvious avenues of reaction manipulation, efforts were turned towards an examination of different catalyst structures (Table 7).

Table 7. Examination of Catalyst Modifications

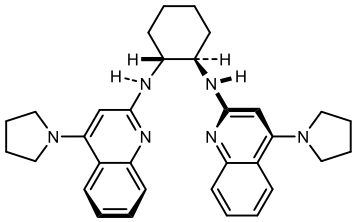


4c **4d**



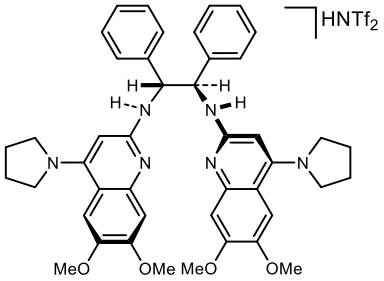
StilbBAM•HNTf$_2$ (4e)

(32%), 63%



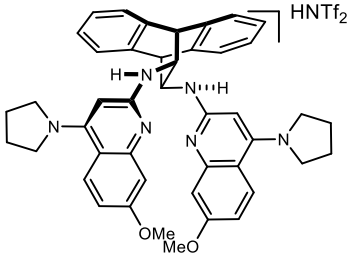
PBAM Free Base (4f)

(0%)



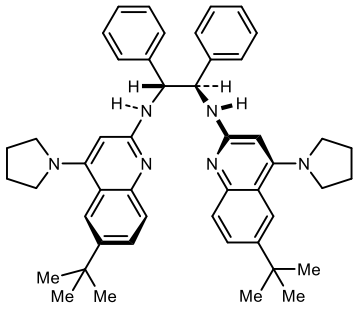
^{6,7}(MeO)$_2$StilbPBAM•HNTf$_2$ (4g)

(0%)



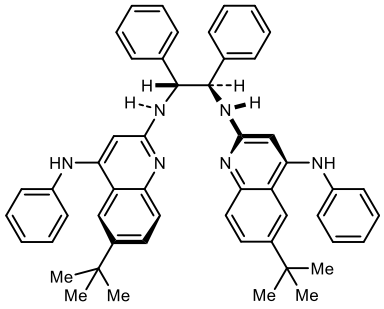
^{7}(MeO)$_2$AnthPBAM•HNTf$_2$ (4h)

(18%), 15% ee
opposite enantiomer



^{6}(*t*Bu)$_2$StilbPBAM Free Base (4i)

3 days, (12%), racemic



^{6}(*t*Bu)$_2$StilbAnBAM (4j)

3 days, (3%), racemic

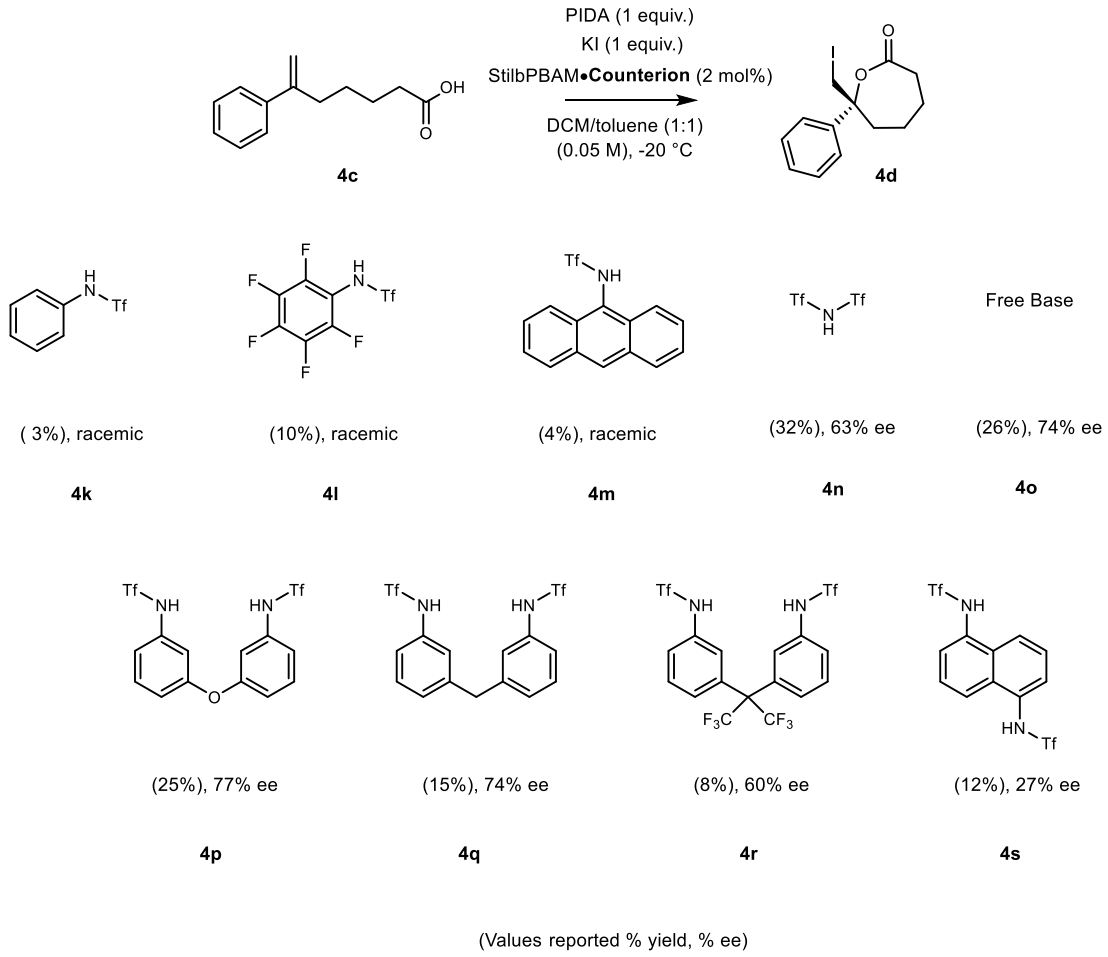
(Values reported % yield, % ee)

This examination was determined largely by immediate catalyst availability, and was rather unpromising in terms of its prospects. Most of the catalysts tested ablated either reactivity, enantioselectivity, or both. The most interesting observation was that the anthracenyl-backboned catalyst

(**4h**) appeared to invert the enantioinduction of the reaction, but the yield and enantioselection were so poor it wasn't pursued further.

Having seen little promise in improving the reaction by catalyst modification, the investigation turned towards examining a variety of different counterions (Table 8).

Table 8. Examination of Counterion Effect on 7-Membered Iodolactonization

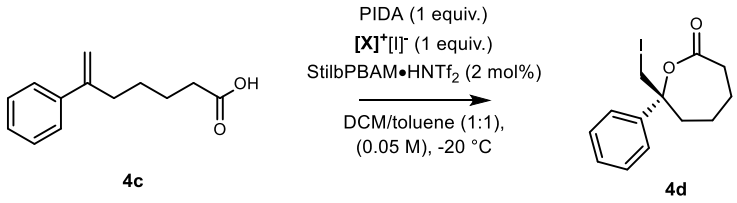


Counterions **4k**, **4l**, and **4m** had previously been synthesized and tested in the 6-membered asymmetric iodolactonization, but appeared to fully ablate enantioselection in the 7-membered iodolactonization. A panel of bis-triflyl aniline-derived diacids **4p**, **4q**, **4r**, and **4s** (synthesized and provided by a postdoctoral researcher - Mahesh Vishe) were tested and exhibited comparable yields and enantioselections to those of triflimide (**4n**). Interestingly, there appeared to be a clear trend of increasing

electron richness (with **4p** being most electron rich, followed by **4q**, and then **4r**, which is relatively electron poor) of the aryl ring improving both yield and enantioselection. The counterion results were doubtless intriguing, but had not significantly improved the reaction outcome, and so triflimide (**4n**) was kept as the default counterion.

By this point, most of the obvious variables within the reaction had been examined in at least a preliminary manner, with the prime exception being that we had not attempted alternative sources of iodide (specifically) or oxidant more generally within the reaction. This was then undertaken, with fairly underwhelming results (Table 9)

Table 9. Screen of Iodide Sources



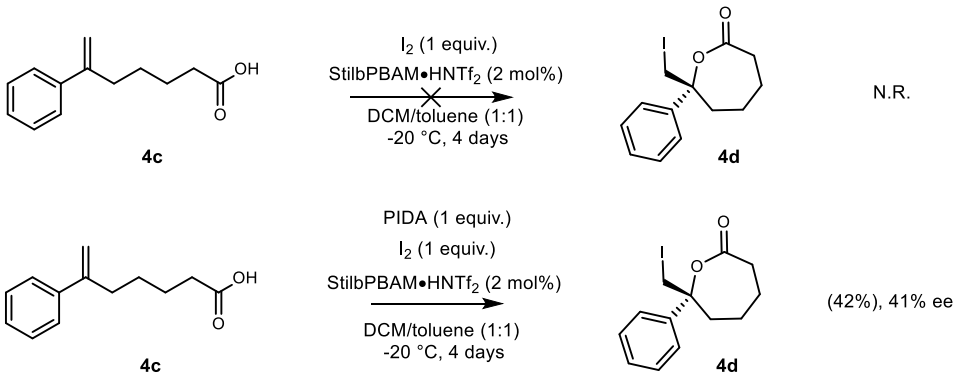
4c **4d**

Entry[a]	**X**	yield (%)[c]	ee (%)[d]
1	$\mathbf{NH_4^+}$	13	50
2	$\mathbf{(CH_3CH_2CH_2CH_2)_4N^+}$	N.R.	
3	$\mathbf{Cu^+}$	2	64
4	$\mathbf{(CH_3)_3SO^+}$	N.R.	
5	$\mathbf{(CH_3)_3S^+}$	N.R.	
6	$\mathbf{Li^+}$	3	70
7	$\mathbf{Na^+}$	27	59
8	$\mathbf{(CH_3)_2CHP(Ph)_3^+}$	N.R.	

The alkali metals appeared to be the best iodide counterion in terms of conversion, and appeared to give better conversion with increasing size (Table 9, entries 6 and 7). The ammonium species (Table 9, entry 1) gave some conversion surprisingly, with moderate enantioselection as well, but none of the

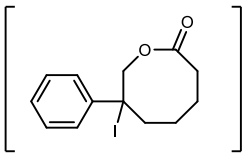
sources screened appeared to be an improvement over potassium iodide. It was at this time however, that a visiting professor, Dr. Robert Hinkle, suggested that we try an alternative iodinating system. PIDA with molecular iodine has been utilized previously as a source of highly electrophilic iodine via formation of acetyl hypoiodite.[30] Accordingly, we tried these conditions (PIDA/I_2) in the reaction as well as molecular iodine alone (Scheme 35).

Scheme 35. Results with I_2 and PIDA/I_2 Oxidant Systems



Surprisingly, iodine alone exhibited no reaction whereas the PIDA/I_2 system exhibited significantly higher reactivity than that seen with the PIDA/KI system coinciding with an encouraging degree of enantioselection. The only immediate drawback to this discovery was that an appreciable amount of byproduct was also generated under these conditions (13% by ^{1}H NMR). At the time, it was believed that the byproduct was an iodolactone arising from an 8-*endo* cyclization (Scheme 36, **4t**), as this structure seemed consistent with what little information could be gleaned from the ^{1}H NMR of the crude reaction mixture.

Scheme 36. Initial Proposal for Byproduct Structure



4t

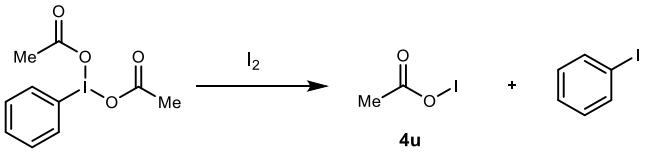
[30] Gottam, H.; Vinod, T. K. *J. Org. Chem.* **2011**, *76*, 974-977.

Mechanism of the Asymmetric Iodolactonization to give ε-Lactones

Upon the discovery of the PIDA/I_2 oxidant system, efforts immediately turned towards optimization of the improved conditions, and little thought was spared towards its mechanism, or the identity of the byproduct, which proved challenging to isolate. Therefore, the question of mechanism remained unresolved for a long period, and its positioning here is anachronistic with regards to the optimization process which will be discussed subsequently. Nevertheless, the discussion has been placed here in the hopes that it may allow for a better understanding of the reaction that the remainder of this text grapples with, however inadequately.

It was mentioned previously that the paper which inspired the testing of the PIDA/I_2 oxidant system proposed the active iodinating species to be acetyl hypoiodite (Scheme 37, **4u**).[30] A further perusal of the literature revealed that the evidence for PIDA/I_2 forming acetyl hypoiodite as the active iodinating species was quite strong, and widely accepted.[31,32,33] In particular, the *e-EROS* article alerted us that the reagent system had been widely used in radical generation for decades under the moniker of Suárez's reagent.[33]

Scheme 37. Formation of Acetyl Hypoiodite from PIDA/I_2

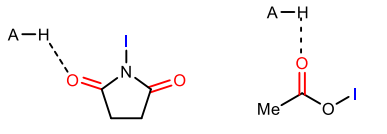


Occam's razor dictated that a common active iodinating species would be more probable than two distinct mechanistic pathways with distinct active species that could both be controlled by the BAM catalyst to give decent enantioselection. Accordingly, we proposed that both the PIDA/KI and PIDA/I_2 oxidant systems served as precursors to the common active species of acetyl hypoiodite (**4u**), a proposal

[31] Li, W.; Gan, J.; Fan, R. *Tet. Lett.* **2010**, *51*, 4275-4277.
[32] Fan, R.; Li, W.; Pu, D.; Zhang, L. *Org. Lett.* **2009**, *11*, 1425-1428.
[33] Giri, R.; Yu, J. Q. **2008** Iodine Monoacetate, e-*EROS Encyclopedia of Reagents for Organic Synthesis.*

that has found some measure of support in other publications which have shown PIDA/KI to also be capable of generating acetyl hypoiodite.[34,35] That the BAM catalyst family could interact favorably with acetyl hypoiodite to induce enantioselection was not surprising, as its structure had potential for hydrogen bond acceptance from the protonated catalyst, a condition believed to be important for catalyst coordination of the active iodinating species. Furthermore, its structure mapped onto that of NIS remarkably well, NIS being of course, the electrophilic iodine species that was most well established in giving enantioselection in the 6-membered iodolactonization (Scheme 38).

Scheme 38. NIS and Acetyl Hypoiodite as Structural Analogies

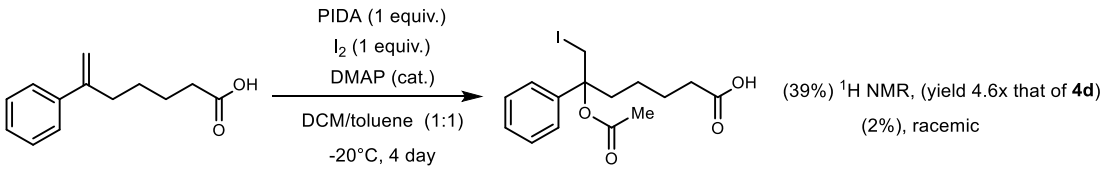


N-iodosuccinimide acetyl hypoiodite (**4u**)

(H-A represents StilbPBAM•$HNTf_2$)

It was also discovered in the course of our investigations that replacing the BAM catalyst with dimethylaminopyridine (DMAP), favored formation of the byproduct over that of the lactone product **4d**. Armed with the capacity to favor the elusive pathway, we were at last able to purify and characterize the byproduct, revealing it to be not the 8-*endo* lactone **4t**, but the iodoacetate **4v** (Scheme 39).

Scheme 39. The Elusive Byproduct Revealed



4c **4v**

[34] Kim, H. J.; Cho, S. H.; Chang, S. *Org. Lett.* **2012**, *14*, 1424-1427.
[35] Doleschall, G.; Toth, G. *Tetrahedron*, **1980**, *36*, 1649.

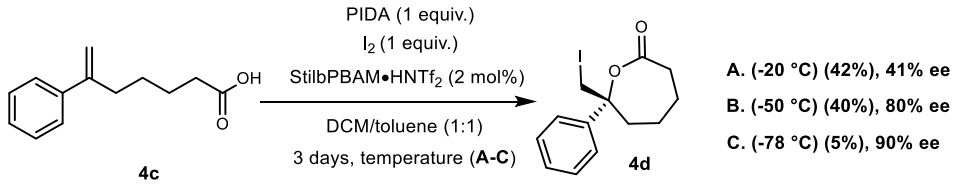
This revelation served as further evidence for the role of acetyl hypoiodite as the active iodinating species, since the byproduct **4v** most likely arises from acetate addition into the benzylic cation arising after iodonium formation. The proximity of acetate after the immediate transfer of iodine from acetyl hypoiodite (**4u**) presumably allows the acetate to outcompete the pendent carboxylic acid which would normally have an advantage arising from its cyclization being an intramolecular, rather than intermolecular, reaction.

This discovery also highlighted the importance of the catalyst not just in the induction of asymmetry in the lactone product **4d**, but in biasing the reaction towards an intramolecular cyclization of the pendent carboxylic acid instead of benzylic carbocation interception by acetate. This catalyst intervention could arise from either steric blocking of the acetate nucleophile, or a full coordination of the carboxylic acid into an adventitious position whereby it could outcompete acetate in attack upon the benzylic carbocation.

Optimization of the PIDA/I_2 Oxidant System

The PIDA/I_2 oxidant system evinced an improvement over the PIDA/KI system in terms of reactivity so significant, that there were hopes that it could be cooled to lower temperatures, and thereby receive at least a marginal boost in enantioselection. Accordingly, the effect of temperature was probed using the new oxidant system (Scheme 40).

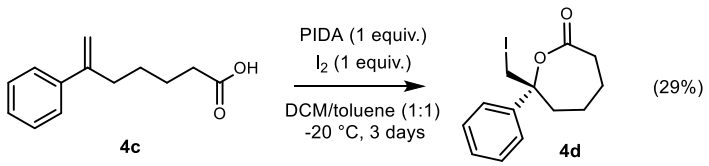
Scheme 40. Effect of Temperature with PIDA/I_2 System



Remarkably, the enantioselection effectively doubled when run at -50 °C (**B.**), with no significant loss in reactivity, and the ratio of formation of iodolactone **4d** to byproduct **4v** dropped to 15:1 favoring the iodolactone **4d**. The enantioselection improved still further at -78 °C, but at the cost of an intolerable

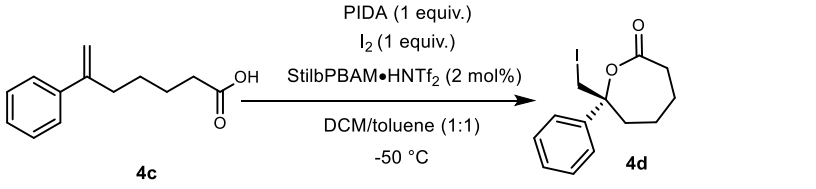
loss in reactivity. This dramatic improvement implied a substantial background reaction rate at -20 °C, a suspicion which was confirmed upon running a background reaction at said temperature (Scheme 41).

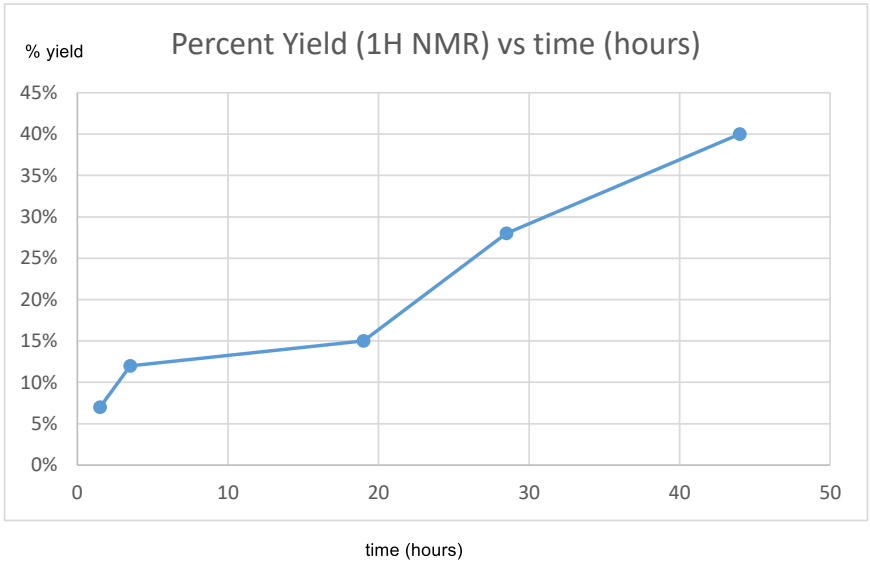
Scheme 41. Substantial Background Reaction Revealed



The reaction proceeded readily at this temperature in the absence of catalyst, and the disfavoring of this background reaction at lower temperatures was presumed to be the source of the significant improvements observed upon cooling the reaction to -50 °C. It should also be noted that the background reaction without any basic catalyst gave a roughly 1:1 ratio of iodolactone **4d** and byproduct **4v**, again

Table 10. Reaction Progess Study of the PIDA/I_2 Mediated Iodolactonization





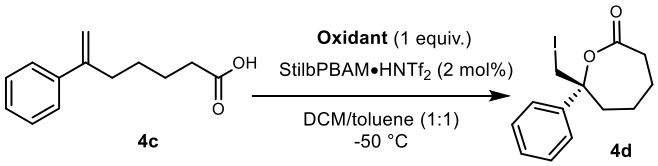
(Reaction progress evaluated by 5 simultaneous reactions quenched at specific time intervals)

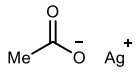
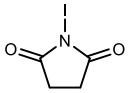
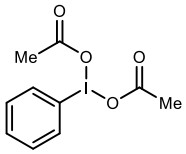
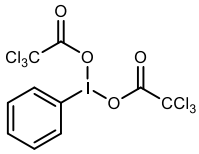
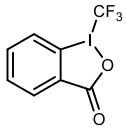
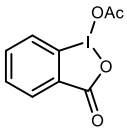
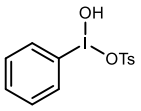
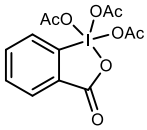
emphasizing the role of the BAM catalyst in favoring intramolecular cyclization over intermolecular attack of acetate.

Although the application of the PIDA/I_2 oxidant system at -50 °C proved to be a significant improvement, there were still concerns over the middling yields, and a simple kinetic study was undertaken to see if the reaction might be stalling out due to arrested catalyst turnover (Table 10). The results of this study suggested that product was formed at a steady rate, with no clear signs of product inhibition or catalyst saturation. It was concluded that the substrate and reagents simply suffered from a low inherent reactivity.

With both the discovery and major improvement of the asymmetric iodolactonization of ε-lactones arising through the employ of new oxidant systems, it was hoped that a further examination of different oxidant systems might yield further benefits (Table 11).

Table 11. Further Examination of Various Oxidant Systems



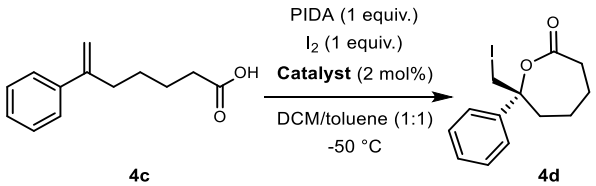
 **4w** With I_2, ((2%), 12% ee, 4 days)	 **NIS** N.R. (2 days)	 **PIDA** With KI, ((14%), 70% ee) (4 days, -20 °C) With I_2 ((40%), 80% ee) (4 days)	 **4x** With I_2 ((13%), racemic) (2 days)
 **4y** N.R. (4 days, -20 °C) With KI, (N.R.) (4 days, -20 °C) With I_2, (5%) (2 days, -20 °C)	 **4z** With I_2, ((24%), 80% ee) (4 days)	 **4aa** With I_2, ((11%), racemic) (5 days)	 **4ab** With I_2, ((11%), 37% ee) (2 days)

These efforts bear some discussion, though none of them improved upon the PIDA/I_2 conditions previously employed. Silver acetate (**4w**) was tested as it is a known precursor of acetyl hypoiodite (**4u**) when mixed with molecular iodine.[33] It did indeed form a small measure of product, but in terrible yield and enantioselection, a result perhaps arising from the poor solubility of **4w** under reaction conditions. NIS gave no reaction at the lower temperature of -50 °C, and the results of PIDA with I_2 have already been noted. The PIDA analog **4x** was employed in an effort to increase the reactivity of PIDA in the reaction; regrettably, it decreased yield and fully ablated enantioselection while forming a considerable amount of the trichloroacetate analog of byproduct **4v**. Various other hypervalent iodine(III) species (**4y**, **4z**, **4aa**) were employed to see if they could form acetyl hypoiodite (**4u**) in a manner more conducive to high enantioselection. Togni's reagent (**4y**), gave no reaction on its own, or with potassium iodide, but gave a small amount of product when employed with iodine, along with a much more considerable

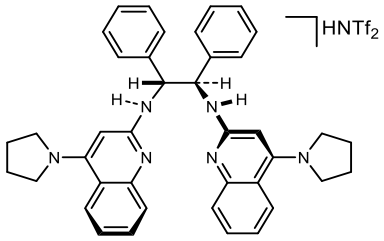
amount of byproduct**s**. The close PIDA analog **4z** gave equivalent amounts of byproduct **4v** and iodolactone **4d**, but the iodolactone showed a high level of enantioselection. Koser's reagent **4aa** in concert with iodine, gave a small amount of product, but with full loss of enantioselection. Finally, the hypervalent iodine(V) Dess-Martin periodinane (**4ab**) with iodine gave a small amount of product **4d** with modest enantioselection, along with a roughly equivalent amount of byproduct **4v**. As noted previously, none of the conditions were superior to the PIDA/I_2 oxidant system, however, it was of some interest that multiple hypervalent iodine(III) species in concert with molecular iodine could be induced to form a measure of product **4d**, presumably in every case through either formation of acetyl hypoiodite **4u** directly, or through some sort of analogous species.

With no further success in oxidant examination forthcoming, efforts turned again towards modifying the catalyst to improve reaction outcome (Table 12). Thanks are extended to lab members Matt Knowe, Thomas Struble, and Kenneth Schwieter in particular and the lab more generally for providing the majority of the catalysts tested.

Table 12. Catalyst Screen with the PIDA/I_2 Oxidant System

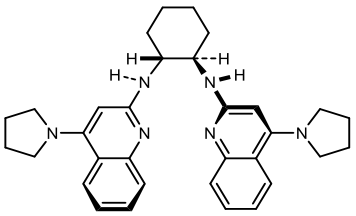


4c **4d**



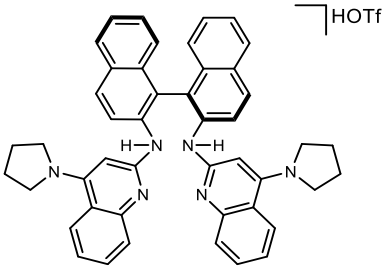
StilbPBAM•$HNTf_2$ (4e)

(30%), 79% ee (3 days)



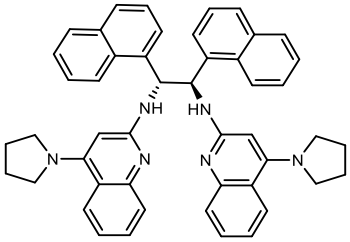
PBAM (4f)

(31%), 67% ee (4 days)



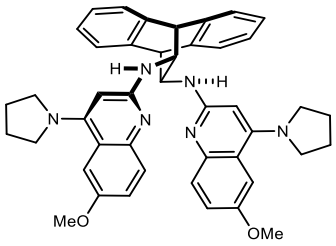
BINAMBAM•TfOH (4ac)

(20%), 25% ee (4 days)



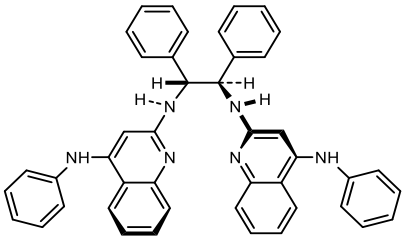
1-NpPBAM (4ad)

(32%), 34% ee (4 days)



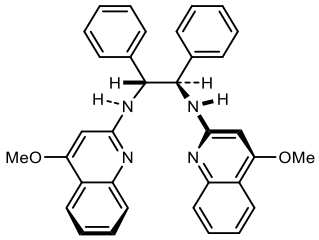
6-MeO(AnthPBAM) (4ae)

(31%), 18% ee (opposite enantiomer, 4 days)



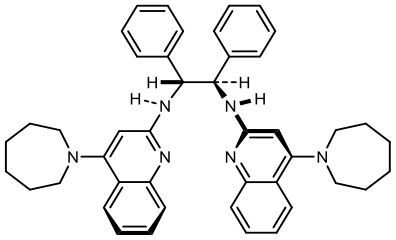
StilbAnBAM (4af)

(24%), 41% ee (2 days)



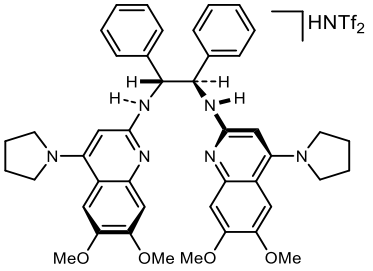
4-MeOStilbBAM (4ag)

(33%), 27% ee (2 days)



StilbAzBAM (4ah)

(18%), 59% ee (2 days)



$^{6,7}(MeO)_2$StilbPBAM•$HNTf_2$ (4g)

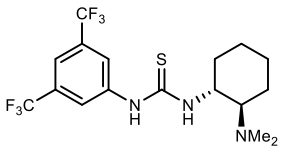
(23%), 71% ee (2 days)

In procession from **4e** through **4f**, **4ac**, **4ad**, and **4ae** the effect of varying catalyst backbones can be discerned. The stilbene-backbone catalyst salt (StilbPBAM, **4e**) remained the best in enantioselection, although the cyclohexane-backed catalyst (PBAM, **4f**) was only slightly worse. The unusual BINAM-inspired **4ac** gave significantly worse enantioselection, while still showing some enantioinduction. Turning the stilbene aryl rings into respective napthalenes (**4ad**) significantly lowered enantioselection as well. Finally, the anthracene-backbone derived catalyst **4ae** gave a minor amount of enantioselection of the opposite enantiomer to all other catalysts; a result seen previously when a similar catalyst was tested using PIDA/KI oxidant conditions (Table 7, **4h**). None of the alternative backbones compared favorably with StilbPBAM (**4e**).

Substitution of the pyrrolidine rings with substituents of diverse electronics and (in particular) sterics, was likewise fruitless. Aniline substitution in the 4-position of the quinoline rings (**4af**) lowered enantioselection considerably relative to the pyrrolidine substituent (**4e**). Methoxy substitution in the same 4-position (**4ag**) lowered the enantioselection still further, leading to the suspicion that perhaps a sterically bulky electron donating group may be necessary. Azepane substitution in the same position (**4ah**) proved superior to the other substituents (**4af**, **4ag**), but still significantly worse than StilbPBAM salt (**4e**). Finally, increasing electron richness of the quinoline rings via methoxy disubstitution in the 6- and 7-positions **(4g**) seemed to have only a negligible impact on enantioselection, but offered no clear improvements over **4e.**

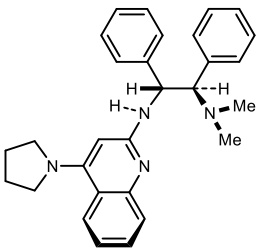
A brief and cursory effort was also made to test the reaction conditions with non-BAM catalysts (Table 13).

Table 13. Brief Inquiry of Non-BAM Catalysts



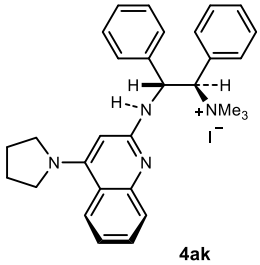
Takemoto's Thiourea (4ai)

(12%), racemic (2 days)



4aj

(24%), racemic, (4 days)



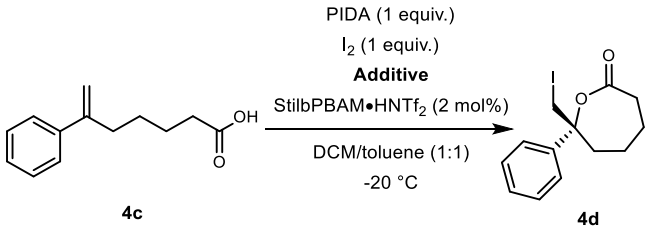
4ak

(39%), racemic (4 days)

Takemoto's Thiourea (**4ai**) proved incapable of inducing any enantioselection, and the racemic result of both **4aj** and **4ak** suggested that the overarching [BAM] moiety was critical for any success in the reaction from an asymmetric standpoint.

With the catalyst examinations showing no obvious avenue for improvement, the weary author turned to the final refuge open to those buffeted by the storm of unrelenting failure upon the plains of chemical methodology development- namely, the employ of additives. Regrettably, this bastion proved no more redoubtable than those previously occupied, but did show effects that, as seen so frequently in the course of this journey, may be of interest in understanding the reaction, but of little practical consequence (Table 14).

Table 14. Screen of Additives



Entry[a]	additive	Additive amount	yield (%)[c]	ee (%)[d]
1	DMAP	2 equiv.	3	N/A
2	K_2CO_3	2 equiv.	17	36
3	Et_3N	2 equiv.	3	N/A
4	Na Salt of Substrate	N/A	14	59
5	AcOH	1 equiv.	45	72
6	AcOH	10 equiv.	18	53
7	H_2O	10 µL	61	74
8	H_2O	100 µL	42	75
9	None	N/A	48	74

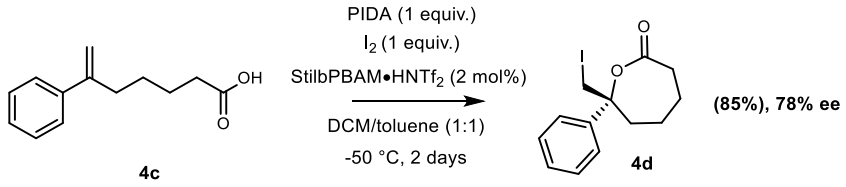
Surprisingly, the addition of two equivalents of dimethylaminopyridine (Table 14, DMAP**,** entry 1) and triethylamine (Table 14, entry 3) reduced reactivity to the point of only trace product formation. Potassium carbonate (Table 14, entry 2) also exhibited a deleterious effect, but a far milder one, giving poorer yields and significantly worse enantioselection, but still an appreciable measure of both. The sodium carboxylate salt of substrate (Table 14, entry 4) was used in lieu of the acid substrate and generated beforehand by deprotonating the substrate with an equivalent of sodium hydride. This undermined reactivity, but had only a marginal negative impact on enantioselection. It was noted that both DMAP (Table 14, entry 1) and triethylamine (Table 14, entry 3) were fully soluble under reaction conditions whereas potassium carbonate (Table 14, entry 2), and the substrate sodium salt (Table 14, entry 4), were not. Therefore it was reasoned that stoichiometric base for whatever reason almost fully ablated reactivity and that entry 2 was spared this fate to some degree by virtue of its appertaining base being largely insoluble and thereby prevented from inducing further chemical mischief. The distinction between the natures of the bases may also be significant; a mild carboxylate base is apparently more tolerable than an amine base.

Entries 5 and 6 (Table 14) examined the effect of adding acetic acid: increasing equivalents lowered yield substantially, and enantioselection more modestly. The precipitous drop in yield arose primarily by virtue of the acetic acid additive favoring formation of byproduct **4v** over iodolactone **4d**, with entry 5 giving a ratio of product to byproduct of a mere 6:1 (by ^{1}H NMR), and entry 6 actually favoring byproduct **4v** formation over iodolactone **4d** by a 2:1 ratio. At the time this observation proved an inexplicable mystery, but in light of the characterization of byproduct **4v** is readily rationalized, since increasing quantities of acetic acid should in fact favor formation of the iodoacetate **4v** (since intercept by acetic acid or acetate rather than pendent carboxylic acid is how the byproduct **4v** arises to begin with).

Finally, the addition of water seemed to have little effect, but did at least demonstrate that the reaction is not particularly water sensitive. None of the additives tested led to improved conditions, and most of the avenues for reaction improvement had been at least well-trodden if not fully explored. A change to running the reaction in microwave vials in lieu of flat-bottom vials, and the discovery that

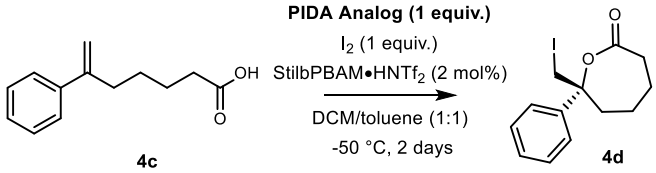
product material was being lost due to poor purification technique led to the not insignificant improvement of the reaction yield to its best and final result (Scheme 42).

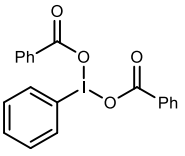
Scheme 42. Final Result of the Asymmetric Iodolactonization towards ε-Lactones



Subsequent to this, a brief inquiry into PIDA analogs was again attempted, with the results being far more interesting than those previously seen arising from the manipulation of that particular parameter. Previous efforts towards employing direct PIDA analogs had focused on increasing its reactivity by making its acetate analog components comparatively better leaving groups (see PIFA in Table 3, and **4x** in Table 11). These efforts gave poor yields of racemic product. However, modifying the structure of the acetate ligands without an eye towards increasing immediate reactivity proved somewhat more fruitful (Scheme 43).

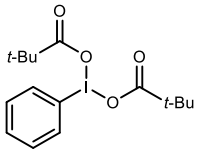
Scheme 43. A Brief Inquiry into PIDA Analogs





4al

(37%), 55% ee



4am

(88%) 79% ee

The benzoic acid-derived species **4al** gave lower yield and enantioselection, the latter of which may have arisen as a result of more substantial background reaction, possibly due to the iodine monobenzoate active species being significantly more reactive than the corresponding acetyl hypoiodite **4u**. Its results fall reasonably in line with those observed with PIFA and **4x** insofar as increasing the reactivity of the active iodinating species lowers enantioselection and yield (likely through multiple side reactions) in proportion to the increase of reactivity.

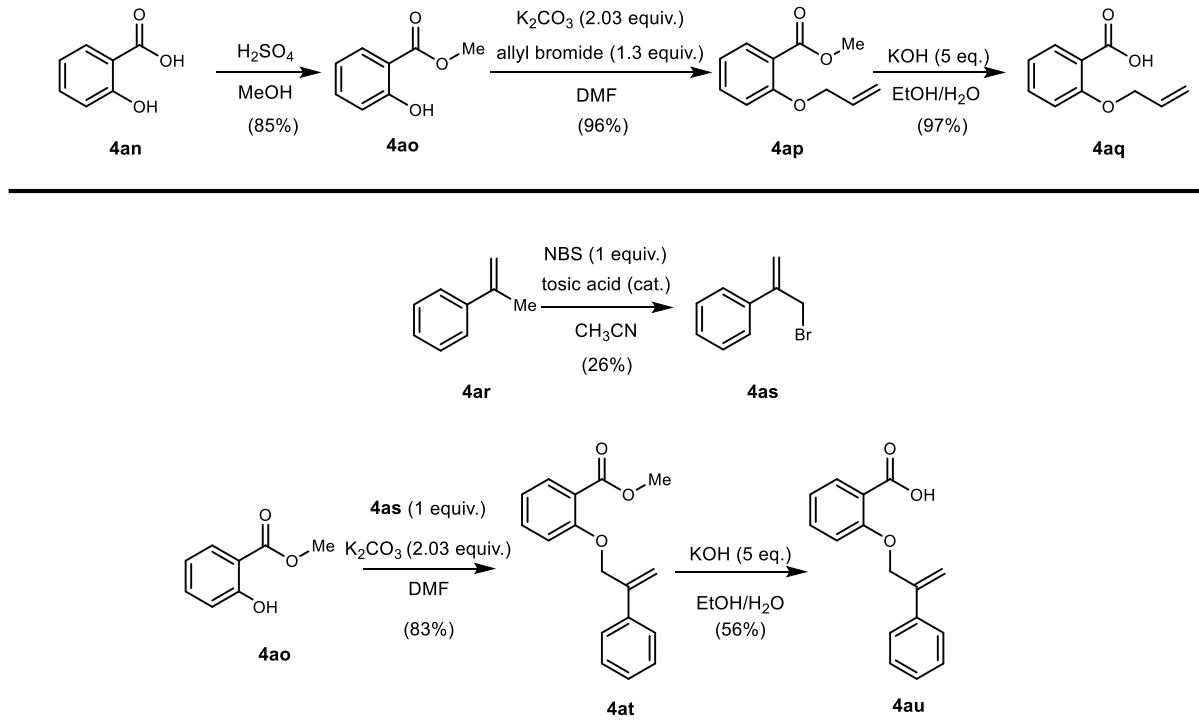
Far more interesting was the reactivity of analog **4am**. Replacing the acetate ligands with pivalate ligands gave yields and enantioselections directly comparable to those achieved with PIDA, with the additional benefit that no trace of byproduct **4v** (or its analog) was observed. Like the observation that acetic acid additives favored byproduct **4v** formation (Table 14), this result was inexplicable until the byproduct identity was finally discovered, at which point it became obvious that the considerably more sterically demanding environment of the pivalate species made it so inefficacious a nucleophile relative to the substrate pendent carboxylic acid that formation of the corresponding iodopivalate was fully precluded. The ablation of byproduct formation offers significant advantages, but the cheapness and commercial availability of PIDA, when taken in combination with the results of **4am** and PIDA being roughly at parity in terms of yield and enantioselection, led to the continuation of PIDA being used in the oxidant system. Nevertheless, the capacity of **4am** to destroy the byproduct **4v** (and analog) pathway could find utility wherever the PIDA/I_2 oxidant system is employed with undesired byproduct arising from acetate addition into the iodinated substrate species. Indeed the discovery is such a direct and logical (in hindsight) resolution to a thorny problem, that it is surprising and unfortunate that it was not developed consciously, but stumbled upon serendipitously.

Synthesis of Substrates and Initial Substrate Scope

Having optimized the asymmetric iodolactonization towards ε-lactones up to a respectable, albeit not stellar, yield and degree of enantiomeric excess, efforts were then undertaken towards an initial

investigation of the scope of the reaction via synthesis and assay of structurally diverse substrates. The first of these, derived from salicylic acid (**4an**) can be seen in Scheme 44.

Scheme 44. Synthesis of Salicylate-Derived Substrates **4aq** and **4au**



The salicylic acid (**4an**) backbone was chosen due to the affordability of starting materials as well as its ability to orient an alkene and carboxylic acid with the proper degree of separation from each other quickly and *within the context of an aryl ring tether*. This latter goal was pursued in the hopes that the aforementioned tether might improve reactivity by virtue of forcing the reactive moieties into closer proximity to each other.

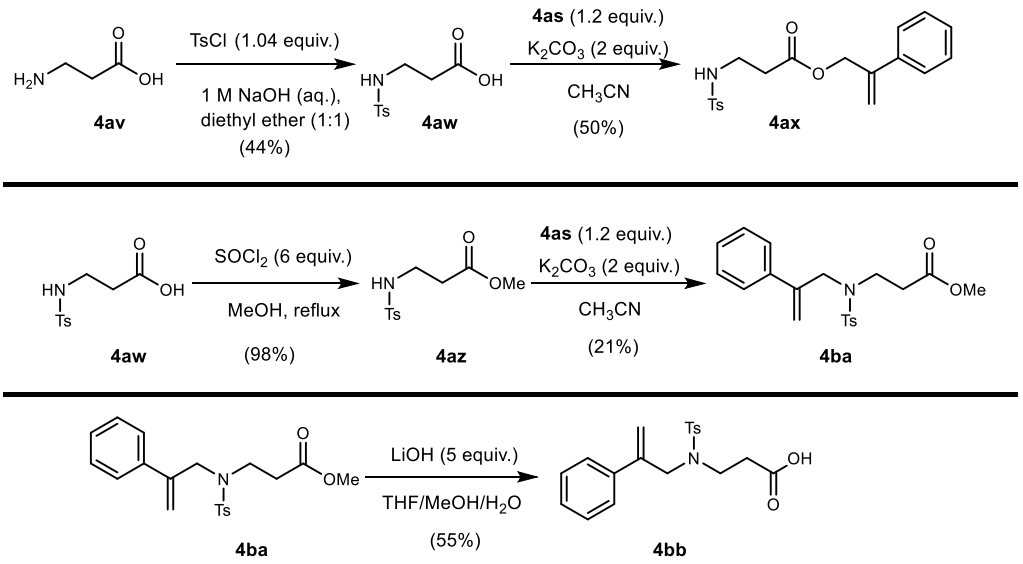
The monosubstituted alkene **4aq** was synthesized by first esterifying salicylic acid (**4an**) to give the corresponding methyl ester **4ao** in 85% yield. Subsequent *O*-alkylation of the phenol by way of

potassium carbonate and allyl bromide gave the ester **4ap** in 96% yield. The ester **4ap** was then saponified using potassium hydroxide to give the desired substrate acid **4aq** in 97% yield.

The styrenyl-alkene derived substrate **4au** was synthesized in an analogous manner, by reacting the salicylic acid methyl ester **4ao** with potassium carbonate and the bromide **4as** to give the corresponding *O*-alkylation product **4at** in 83% yield. The ester **4at** was subsequently saponified using potassium hydroxide to give the desired substrate acid **4au** in 56% yield.

With these substrates in hand, efforts turned towards the design of a substrate with a significant degree of steric bulk along its alkyl chain tether in the hopes that such a substrate may show greater reactivity arising from a Thorpe-Ingold type effect. It was decided to attempt to use a tosylamine moiety to create a more sterically-demanding environment along the chain because the synthetic access appeared to be both brief and affordable. Accordingly, efforts towards synthesizing substrate **4bb** began (Scheme 45).

Scheme 45. Synthesis of Tosylamino-Linked Substrate **4bb**

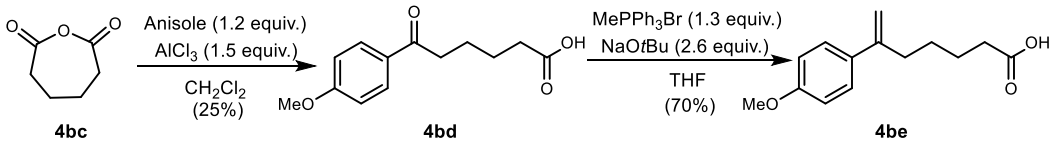


beta-Alanine **4av** was readily tosylated using tosyl chloride to give tosylamine **4aw** in 44% yield. The subsequent effort to alkylate the tosylamine **4aw** using bromide **4as** and potassium carbonate unexpectedly gave the ester **4ax** in 50% yield. The simplest response to this chemical intransigence was

simply to protect the offending carboxylic acid moiety as its methyl ester **4az**, which was achieved by the addition of thionyl chloride with subsequent refluxing in methanol. The methyl ester **4az** was then alkylated (albeit in a poor yield of 21%) with **4as** and potassium carbonate to give **4ba**. Ester **4ba** was readily saponified via lithium hydroxide to give the desired tosylamino acid substrate **4bb** in 55% yield.

The final substrate synthesized was intended to probe the reaction's tolerance for electron rich alkenes and aryl rings, and is shown in Scheme 46.

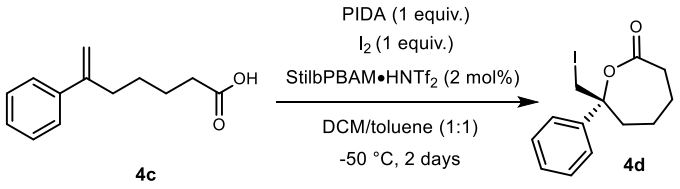
Scheme 46. Synthesis of *para*-Methoxy Substrate **4be**

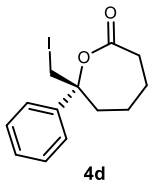


Friedel-Crafts acylation of anisole using adipic anhydride **4bc** gave the keto-acid **4bd** in 25% yield. Subsequent Wittig olefination of keto-acid **4bd** gave the corresponding *para*-methoxy substrate **4be**.

With these four new substrates in hand, the limits of the reaction were tested by subjecting all of them to reaction conditions, the results of which can be seen in Table 15.

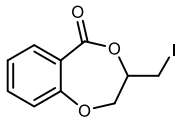
Table 15. Preliminary Substrate Scope of the Asymmetric Iodolactonization Towards ε-Lactones





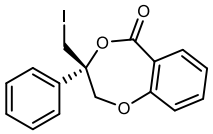
4d

(85%), 78% ee, 2 days



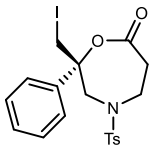
4bf

(10%), racemic, 2 days



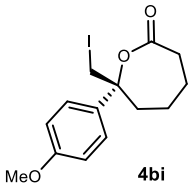
4bg

(64%), 65% ee, 4 days



4bh

(51%), 88% ee, 4 days



4bi

(49%), 50% ee, 4 days

The product **4bf** arising from monosubstituted alkene **4aq** was recovered in poor yield and with no enantioselection, indicating that some degree of substitution is requisite upon the pertinent alkene in order for the reaction to proceed with any enantioselection. This was the clearest delineation of a structural aspect being necessary in order for enantioselection to be induced. The lactone **4bg** arising from acid **4au** unfortunately did not show an improvement in either enantioselection or reactivity arising from its aryl tether, but did show decent results for both, demonstrating that the incorporation of aryl tethers are tolerated and that heteroatom incorporation into the lactone backbone could be tolerated as well. It also demonstrated that a benzoic acid could be controlled in the same manner as an alkyl carboxylic acid, which was a further open question before this examination. All told, the result is not unimpressive given the numerous structural modifications made in the single substrate that are enumerated above. The tosylamino lactone **4bh** arising from tosylamino acid **4bb** gave an enantiomeric excess approaching 90%, but showed significantly poorer reactivity, an ironic outcome given that the substrate was designed with

the intention of increasing reactivity. Nevertheless, the result was encouraging, and again showed that the reaction had some measure of versatility in substitution that could be undertaken within the alkyl chain; both in terms of heteroatom substitution and the appertaining electronic effects, as well as the raw steric bulk arising from a tosyl group which was well-tolerated. Finally, the methoxy-substituted lactone **4bi** arising from the substrate **4be** appeared to show another limitation of the reaction; one that is largely ubiquitous throughout the wider realm of asymmetric iodolactonization.[12] The increased electron richness upon the aryl ring and conjugated alkene arising from the methoxy substituent notably accelerates reactivity in the majority of cases, leading to a more significant background reaction and a resultant significant loss of enantioselection.[12] This same effect was observed in the case of **4bi**, with enantiomeric excess dropping to 50%, and yield proving lower as well, possibly due either to decomposition of product or alternative reaction pathways. It should further be noted that lactone **4bi** was quite unstable and prone to spontaneous decomposition presumably through a retro-lactonization pathway with loss of iodine. This irksome tendency could be tempered, but not wholly mastered by keeping the product somewhat diluted in solvent and storing it at -78 °C. Although the result of **4bi** is relatively poor, the fact that a considerable amount of product could even be isolated is a source for some encouragement given that acetyl hypoiodite (**4u**) is known to be efficacious in the iodination of electron-rich aryl rings.[33] From this perspective, the fact that the substrate (**4bi**) showed a reasonable preference for reaction at the alkene is itself a small victory.

Conclusions and Reflections

Without a doubt the greatest achievement of this work is the discovery of an asymmetric iodolactonization to give ε-iodolactones. That this may be testament to an underlying dearth of accompanying accomplishments is fair enough critique, and such an assertion could be pressed still further by noting that the 7-membered iodolactonization is not a reaction of particular synthetic utility, that this methodology is neither exceptional in yield nor in enantioselection, and that the rough outlines of the reaction limits can already be gleaned by perusing the (only very preliminary) substrate scope.

The rejoinder is this: that the author has seen no instances of an asymmetric iodolactonization performed towards 7-membered rings prior to this discovery, and that the discovery may therefore throw itself upon the mercy of novelty; that much sought after and abused currency of science. If such a claim may merit some measure of skepticism from the wary scholastic eye, wisely mistrustful of this supposed inexhaustible world in which unending novelties abound, seemingly unconnected from all precedents or glory-thieving connections; it may only be asserted that the author sympathizes with such feelings, and has endeavored insofar as possible to ground his modest discoveries within the larger framework of wiser persons and greater accomplishments. That this work has stood chiefly upon the previous work done by Mark Dobish and others within the Johnston lab is indisputable, and that it constitutes only a narrow expansion of that methodology is a defensible proposition. The reaction appears to proceed by formation of acetyl hypoiodite, a known scion of PIDA and I_2, the use of which to iodinate alkenes is at least half a century old.[33] Thus the mechanism shows little novelty, although the ability to control so vigorous an iodinating reagent and guide its reactivity into productive avenues is not altogether unimpressive.

The methodology appears to be new with respect to ring size and old in all else. That it may be applied towards genuine synthetic targets does not strike the author as particularly probable given the remarkable lack of demand for access to 7-membered lactones. The obvious counter to this observation is that there is clearly unexplored chemical space within that particular class of compound. It would be disingenuous to assert a wide synthetic utility arising from this methodology in particular, or even catalyst-mediated asymmetric iodolactonization more generally. This author was grimly amused by the synthetic examples cited in Hansen's indispensable review on the development of asymmetric iodolactonization[1]; of those conditions used in the total syntheses cited, all relied upon previously installed asymmetry and conditions not unknown to Bartlett, a sure sign that despite real advances, when it comes to the installation of lactone functionality in an asymmetric manner, most synthetic chemists prefer the old Irish directions, "Don't start from here".

It is perhaps the doom of methodology to advance a legion of unconvincing justifications for its undertaking, but the development must stand or fall upon its own merits, and need not claim immediate

practical utility in order to be of value. The vision of our science passes still through a glass, darkly, and none may know what outward cascade of action a minor discovery may instigate. The discoveries herein described are inarguably minor and modest. They are perhaps the dimmest of an infinitude of lights. But they are lights, and they may add some small flicker to the grand torch of human knowledge, which passes onward as common inheritance to all mankind, our last and greatest shield against the outer dark which always and everywhere surrounds us.[36]

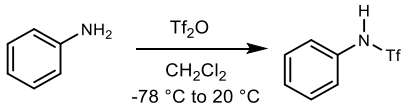
[36] Lovecraft, H. P. *The Call of Cthulu*. Weird Tales, 1928.

CHAPTER 5. EXPERIMENTAL METHODS

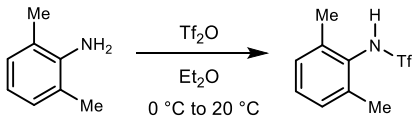
All reagents and solvents used were commercial grade and purified prior to use when necessary. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2) and toluene were dried by passage through a column of activated alumina as described by Grubbs.[37] This was done to accurately quantitate the amount of water in each reaction. Thin layer chromatography (TLC) was performed using glass-backed silica gel (250 μm) plates and flash chromatography utilized 230–400 mesh silica gel from Sorbent Technologies. UV light, and/or the use of potassium permanganate solutions were used to visualize products. IR spectra were recorded on a Nicolet Avatar 360 spectrophotometer and are reported in wavenumbers (cm^{-1}). All compounds were analyzed as neat films on a NaCl plate (transmission). Nuclear magnetic resonance spectra (NMR) were acquired on a Bruker AV-400 (400 MHz) instrument. Chemical shifts are measured relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.16 for $CDCl_3$. Mass spectra were recorded on a Thermo Electron Corporation MAT 95XP-Trap mass spectrometer by use of chemical ionization (CI), electron impact ionization (EI) or electrospray ionization (ESI) by the Indiana University Mass Spectrometry Facility. A post-acquisition gain correction was applied using sodium formate or sodium iodide as the lock mass. Optical rotations were measured on a Perkin Elmer-341 polarimeter. Chiral HPLC analysis was conducted on an Agilent 1100 series instrument using the designated Chiralcel-OD-H column. *N*-Triflyl-aniline-derived counterions with structures that had been previously reported were synthesized according to the method described by Linder and Sundermeyer.[38] Synthesis of alkenoic acid substrates that had been previously reported were synthesized as described by Dobish and Johnston.[12] The BAM-catalyzed asymmetric iodolactonization to give δ-iodolactones was run as described by Dobish and Johnston when using NIS as oxidant, and in the same manner when using PIDA and KI, deviating only in oxidant identity.[12] The BAM-catalyzed asymmetric iodolactonization to give ε-

[37] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.
[38] Kogel, J. F.; Linder, T.; Schroder, F. G.; Sundermeyer, J.; Goll, S. K.; Himmel, D.; Krossing, I.; Kutt, K.; Saame, J.; Leito, I. *Chem. Eur. J.* **2015**, *21*, 5769-5782.

iodolactone **4d** is described below using PIDA and I_2 as oxidants; the reaction using PIDA and KI was run in the same manner, deviating only in the use of KI instead of I_2. PIDA, I_2, and KI were used as purchased without additional purification.

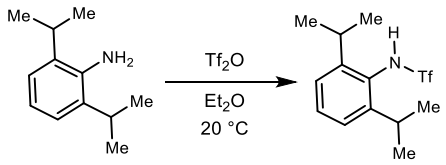


***N*-Phenyl-1,1,1-trifluoromethanesulfonamide (2c)**. Freshly distilled trifluoromethanesulfonic anhydride (740 μL, 4.40 mmol) was dissolved in dichloromethane (9 mL). The solution was stirred and cooled to -78 °C. Aniline (400 μL, 4.40 mmol) in dichloromethane (9 mL) was added, and the resulting solution was left to stir and warm overnight. After 16 hours, the reaction mixture was washed twice with water, dried ($MgSO_4$), filtered, and concentrated to give a white-clear solid with red discoloration. Flash chromatography (SiO_2, 20% ethyl acetate in hexanes) gave the product as a white solid (321 mg, 32 %). Mp = 55-60 °C; R_f = 0.41 (20% EtOAc/hexanes); IR (film) 3292, 1433, 1364, 1198 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.38 (m, 2H), 7.35-7.29 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 133.7, 129.8, 127.7, 123.7, 119.8 (q, $^1J_{CF}$ = 322 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) ppm -75.4; HRMS (EI): Exact mass calcd for $C_7H_7F_3NO_2S$ $[M+H]^+$ 226.0144, found 226.0150.

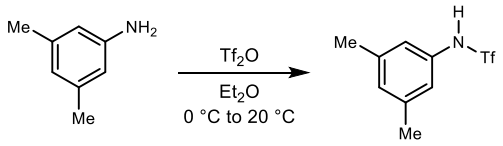


***N*-(2,6-Dimethylphenyl)-1,1,1-trifluoromethanesulfonamide (2d).** Under argon atmosphere, freshly distilled 2,6-dimethylaniline (540 μL, 4.40 mmol) was dissolved in ether (12 mL), and cooled to 0 °C. Freshly distilled trifluoromethanesulfonic anhydride (740 μL, 4.40 mmol) in ether (9 mL) was added to the 2,6-dimethylaniline solution and left to warm up overnight. After 16 hours, the reaction mixture was poured into 3 M aq HCl and washed with brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to give a white solid. Flash column chromatography (SiO_2, 10-20% ethyl acetate in

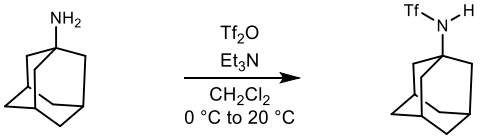
hexanes), gave the product as a white solid (486 mg, 44%). Mp = 83-85 °C; R_f = 0.53 (20% EtOAc/hexanes); IR (film) 3285, 1419, 1371, 1135 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 2H), 6.74 (br s, 1H), 2.43 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 138.1, 130.6, 129.3, 129.1, 119.6 (q, $^1J_{CF}$ = 322 Hz), 18.7; ^{19}F NMR (376 MHz, $CDCl_3$) ppm -75.4; HRMS (CI): Exact mass calcd for $C_9H_{11}F_3NO_2S$ $[M+H]^+$ 254.0457, found 254.0456.



***N*-(2,6-Diisopropylphenyl)-1,1,1-trifluoromethanesulfonamide (2e).** Under argon atmosphere, freshly distilled 2,6-diisopropylaniline (733 μL, 4.40 mmol) was dissolved in diethyl ether (10 mL), and freshly distilled trifluoromethanesulfonic anhydride (740 μL, 4.40 mmol) in diethyl ether (10 mL) was added. The resulting solution was stirred at room temperature for 2 days and then concentrated to give a clear-white residue. The residue was dissolved in dichloromethane and product was extracted with 1 M aq NaOH. The aqueous layer was then acidified using 3 M aq HCl, extracted with dichloromethane, dried ($MgSO_4$), filtered, and concentrated to give a white solid (148 mg, 11%). Mp = 65-67 °C; R_f = 0.73 (25% EtOAc/hexanes); IR (film) 3275, 2963, 1420, 1373, 1227, 1194, 1134, 955 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.7 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 2H), 6.56 (br s, 1H), 3.28 (septet, *J* = 6.8 Hz, 2H), 1.14 (d, *J* = 6.8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 148.7, 130.2, 127.1, 124.6, 119.8 (q, $^1J_{CF}$ = 322 Hz), 28.9, 24.1; ^{19}F NMR (376 MHz, $CDCl_3$) ppm -75.9; HRMS (CI): Exact mass calcd for $C_{13}H_{19}F_3NO_2S$ $[M+H]^+$ 310.1083, found 310.1078.

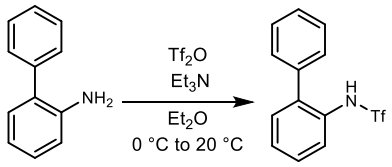


***N*-(3,5-Dimethylphenyl)-1,1,1-trifluoromethanesulfonamide (2f).** Freshly-distilled 3,5-dimethylaniline (550 µL, 4.40 mmol) was dissolved in ether (11 mL) and cooled to 0 °C. Freshly-distilled trifluoromethanesulfonic anhydride (740 µL, 4.40 mmol) was dissolved in ether (10 mL) and added dropwise. The solution was stirred overnight and the bath was allowed to warm to room temperature over 16 hours. The reaction mixture was poured over 1 M aq HCl, extracted with diethyl ether, and washed with brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to give a red crystalline solid. Flash chromatography (SiO_2, 10% ethyl acetate in hexanes), gave the product as a white solid (500 mg, 45%). Mp = 74-76 °C; R_f = 0.37 (10% EtOAc/hexanes); IR (film) 3297, 3256, 2367, 1599, 1418, 1184 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 6.89 (s, 1H), 6.87 (s, 2H), 2.27 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 139.7, 133.5, 129.4, 121.3, 119.9 (q, $^1J_{CF}$ = 322 Hz), 21.1; ^{19}F NMR (376 MHz, $CDCl_3$) ppm -75.3; HRMS (CI): Exact mass calcd for $C_9H_{11}F_3NO_2S$ $[M+H]^+$ 254.0457, found 254.0449.

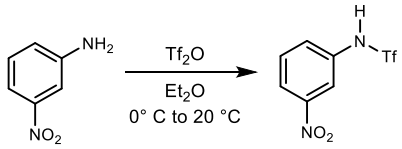


***N*-((3s,5s,7s)-Adamantan-1-yl)-1,1,1-trifluoromethanesulfonamide (2g).** Freshly-distilled triethylamine (300 µL, 2.18 mmol) and 1-adamantylamine (300 mg, 1.98 mmol) were dissolved in dichloromethane (15 mL) and cooled to 0 °C. Freshly-distilled trifluoromethanesulfonic anhydride (366 µL, 2.18 mmol) was dissolved in dichloromethane and added. The reaction was stirred and the bath was allowed to warm overnight. After 16 hours, the reaction mixture was washed with brine and concentrated to give a viscous red liquid. The liquid was dissolved in dichloromethane, washed with water, and then with brine. The organic layer was dried ($MgSO_4$) and concentrated to a tan solid that was recrystallized from EtOH/H_2O to give the product as a white solid (171 mg, 30%). Mp = 95-99 °C; IR (film) 3280,

2924, 1447, 1368, 1190, 1144 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (br s, 1H), 2.14 (br s, 3H), 1.99 (d, *J* = 2.8 Hz, 6H), 1.67 (d, *J* = 2.1, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 58.5, 43.1, 35.5, 30.8, 29.6; ^{19}F NMR (376 MHz, $CDCl_3$) ppm -78.0; HRMS (CI): Exact mass calcd for $C_{11}H_{16}F_3NO_2S$ $[M]^+$ 283.0848, found 283.0844.

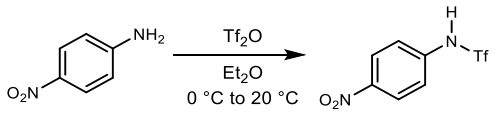


***N*-([1,1'-Biphenyl]-2-yl)-1,1,1-trifluoromethanesulfonamide (2h).** 2-Phenyl aniline (500 mg, 2.96 mmol) was dissolved in dichloromethane (25 mL), and cooled to 0 °C. Freshly-distilled trifluoromethanesulfonic anhydride (548 µL, 3.26 mmol) in dichloromethane (25 mL) was added. After 1 hour, triethylamine (452 µL, 3.26 mmol) was added, and the reaction was allowed to stir for 30 minutes. The mixture was then poured over brine, extracted with DCM, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (SiO_2, 10% ethyl acetate in hexanes) gave the product as a colorless viscous oil. R_f = 0.23 (10% EtOAc/hexanes); IR (film) 3320, 3050, 1503, 1433, 1371, 1218, 1142 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.2 Hz, 1H), 7.54-7.37 (m, 4H), 7.34-7.29 (m, 4H), 6.74 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 136.9, 134.9, 131.7, 130.9, 129.5, 129.2, 129.1, 128.8, 126.7, 121.7, 119.7 (q, $^{1}J_{CF}$ = 322 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) ppm -75.9; HRMS (ESI): Exact mass calcd for $C_{13}H_{10}F_3NO_2S$ $[M]^+$ 301.0379, found 301.0386.

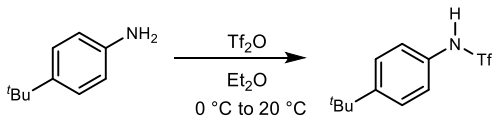


***N*-(3-Nitrophenyl)-1,1,1-trifluoromethanesulfonamide (2j)**. 3-Nitroaniline (1.14 g, 8.25 mmol) was dissolved in diethyl ether (10 mL), and cooled to 0 °C. Freshly-distilled trifluoromethanesulfonic anhydride (1.39 mL, 8.25 mmol) was dissolved in diethyl ether (12 mL) and added. The solution was

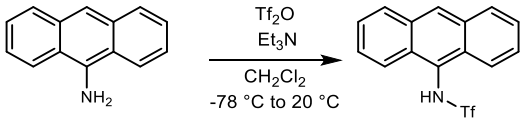
stirred and the bath was allowed to warm to rt over 16 hours. The reaction mixture was poured over 1 M HCl, washed with water and then with brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to give a yellow solid. Flash column chromatography (SiO_2, 1-4 % methanol in dichloromethane), gave the product as a dark yellow solid (646 mg, 29%). Mp = 53-56 °C; R_f = 0.08 (30% EtOAc/hexanes); IR (film) 3271, 2925, 2855, 1537, 1433, 1350, 1225, 1142, 961 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19-8.15 (m, 2H), 7.66-7.69 (m, 1H), 7.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 148.9, 135.4, 130.9, 128.7, 122.2, 119.7 (q, $^1J_{CF}$ = 322 Hz), 118.0; ^{19}F NMR (376 MHz, $CDCl_3$) ppm -75.4; HRMS (CI): Exact mass calcd for $C_7H_6F_3N_2O_4S$ $[M+H]^+$ 270.9995, found 271.0003.



***N*-(4-Nitrophenyl)-1,1,1,trifluoromethanesulfonamide (2k).** 4-Nitroaniline (792 μL, 8.25 mmol) was dissolved in diethyl ether (15 mL) and cooled to 0 °C. Freshly-distilled trifluoromethanesulfonic anhydride (1.39 mL, 8.25 mmol) was dissolved in diethyl ether (15 mL) and added. The solution was stirred and the bath allowed to warm to room temperature. After 16 hours, the reaction solution was poured over 1 M HCl, and washed with water, and then with brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to give a yellow solid. Flash column chromatography (SiO_2, 1-4 % methanol in dichloromethane), gave the product as a yellow solid (134 mg, 6 %). Mp = 54-58 °C; R_f = 0.03 (30% EtOAc/hexanes); IR (film) 3264, 2924, 2855, 1613, 1517, 1343, 1218, 1142, 941 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.3 Hz, 2H), 7.60 (br s, 1H), 7.44 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 145.8, 140.2, 125.6, 121.4, 118.1; ^{19}F NMR (376 MHz, $CDCl_3$) ppm -75.6; HRMS (CI): Exact mass calcd for $C_7H_6F_3N_2O_4S$ $[M+H]^+$ 270.9995, found 270.9989.

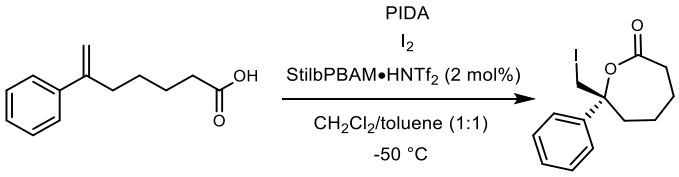


***N*-(4-(*tert*-Butyl)phenyl)-1,1,1-trifluoromethanesulfonamide (2l)**. Freshly-distilled 4-*tert*-butylaniline (100 µL, 620 µmol) was dissolved in diethyl ether (8 mL) and cooled to 0 °C. Freshly-distilled trifluoromethanesulfonic anhydride (100 µL, 620 µmol) in diethyl ether (8 mL) was added, and the solution was stirred as the bath was allowed to warm. The reaction mixture was poured over 1 M aq HCl and washed with brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (SiO_2, 25% ethyl acetate in hexanes) gave the product as a white solid (30 mg, 17%). Mp = 77-79 °C; R_f = 0.65 (25% EtOAc/hexanes); IR (film) 3315, 2951, 2362, 1531, 1391, 1154, 1212 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.7 Hz, 2H), 7.21 (d, *J* = 8.7 Hz, 2H), 6.99 (br s, 1H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 151.2, 130.9, 126.7, 123.9, 119.9 (q, $^1J_{CF}$ = 322 Hz), 34.8, 31.4; ^{19}F NMR (376 MHz, $CDCl_3$) ppm -75.3; HRMS (CI): Exact mass calcd for $C_{11}H_{14}F_3NO_2S$ $[M]^+$ 281.0692, found 281.0688.

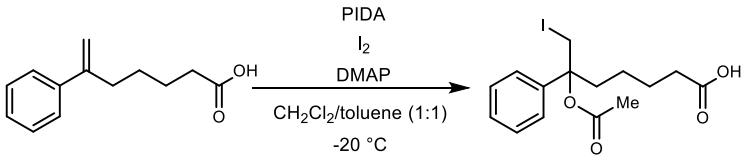


***N*-(Anthracen-9-yl)-1,1,1-trifluoromethanesulfonamide (2m).** 9-Aminoanthracene (200 mg, 1.04 mmol) was dissolved in dichloromethane (20 mL), cooled to -78 °C, and distilled triethylamine (144 µL, 1.04 mmol) was added. Freshly distilled trifluoromethanesulfonic anhydride (175 µL, 1.04 mmol) was added. The reaction was stirred for 16 hours and allowed to warm to 20 °C. The mixture was then directly loaded onto a flash chromatography column. Flash chromatography (SiO_2, 10% ethyl acetate in hexanes) gave the product as a white solid which coeluted with a yellow residue which could be rinsed off of the pure solid using dichloromethane (4 mg, 1%). Mp = 210-214 °C; R_f = 0.10 (10% EtOAc/hexanes); IR (film) 3241, 2397, 1420, 1335, 1166 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.32 (d, *J* = 8.9 Hz, 2H), 8.06 (d, *J* = 8.9 Hz, 2H), 7.68-7.64 (m, 2H), 7.57-7.53 (m, 2H), 7.08 (br s, 1H); ^{13}C NMR (100

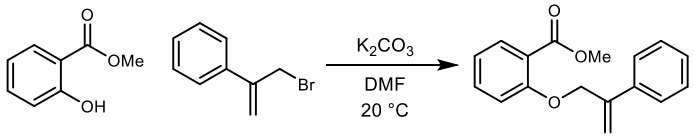
MHz, $CDCl_3$) ppm 131.8, 131.1, 130.6, 130.1, 128.9, 127.8, 125.9, 123.3, 122.8; ^{19}F NMR (376 MHz, $CDCl_3$) ppm -75.3; HRMS (CI): Exact mass calcd for $C_{15}H_{10}O_2NF_3S$ $[M]^+$ 325.0379, found 325.0369.



(*R*)-7-(Iodomethyl)-7-phenyloxepan-2-one (4d). The carboxylic acid (20.0 mg, 100 µmol) and StilbPBAM·$HNTf_2$ (1.8 mg, 2.0 µmol, 2% loading) were added to a microwave vial with rounded bottom and dissolved in a 1:1 solution of dichloromethane and toluene (2 mL). The mixture was cooled to -50 °C and treated with PIDA (32 mg, 100 µmol) and iodine (25 mg, 100 µmol). The reaction mixture was stirred for 48 hours and then cooled to -78 °C before directly loading it onto a plug of silica (SiO_2). It was flushed with hexanes (10 mL), eluted with 50% ethyl acetate in hexanes (10 mL), and directly concentrated. Flash chromatography (SiO_2, 20% ethyl acetate in hexanes) gave the product as a colorless oil (28 mg, 85%). The product was determined to be 78% ee by chiral HPLC analysis (Chiralcel OD-H, 10% ^{i}PrOH/hexanes, 1 mL/min, t_r(*e*$_1$, minor) = 8.81 min, t_r(*e*$_2$, major) = 9.90 min); R_f = 0.40 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ -54 (*c* 0.56, $CHCl_3$); IR (film) 2950, 2349, 1730, 1509, 1435, 1258, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.32 (m, 5H), 3.53 (d, *J* = 10.8 Hz, 1H), 3.41 (d, *J* = 10.8 Hz, 1H), 2.70-2.63 (m, 1H), 2.60-2.53 (m, 1H), 2.40 (ddd, *J* = 3.4, 12.7, 16.0 Hz, 1H), 2.01-1.68 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 174.5, 139.1, 129.4, 128.6, 126.2, 83.1, 37.5, 36.8, 24.6, 23.0, 21.3; HRMS (ESI): Exact mass calcd for $C_{13}H_{15}IO_2Na$ $[M+Na]^+$ 353.0015, found 353.0018.

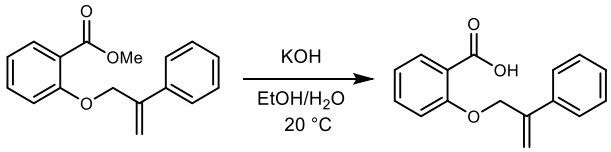


6-Acetoxy-7-iodo-6-phenylheptanoic acid (4v). The carboxylic acid (102 mg, 500 µmol) and DMAP (6.10 mg, 50.0 µmol, 10% loading) were added to a microwave vial with rounded bottom and dissolved in a 1:1 solution of dichloromethane and toluene (2 mL). The mixture was cooled to -20 °C and then treated with PIDA (161 mg, 500 µmol) and iodine (127 mg, 500 µmol). The reaction mixture was stirred for 96 hours and then cooled to -78 °C before directly loading it onto a plug of silica (SiO_2). It was flushed with hexanes (10 mL), eluted with 50% ethyl acetate in hexanes (10 mL), and directly concentrated. Flash chromatography (SiO_2, 30% ethyl acetate in hexanes) gave the product as a colorless oil (14 mg, 7%). R_f = 0.14 (30% EtOAc/hexanes); IR (film) 3737, 2949, 2374, 1749, 1431, 1362, 1224 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.28 (m, 5H), 4.26 (d, *J* = 10.5 Hz, 1H), 3.97 (d, *J* = 10.5 Hz, 1H), 2.56-2.48 (m, 1H), 2.25 (t, *J* = 7.5 Hz, 2H), 2.16 (s, 3H), 2.07-1.99 (m, 2H), 1.64-1.48 (m, 3H), [O*H* not observed]; ^{13}C NMR (100 MHz, $CDCl_3$) ppm 178.0, 169.7, 140.9, 128.5, 127.7, 125.2, 84.0, 38.0, 33.5, 24.6, 23.6, 22.2, 15.3; HRMS (CI): Exact mass calcd for $C_{15}H_{18}IO_4$ $[M-H]^-$ 389.0244, found 389.0245.

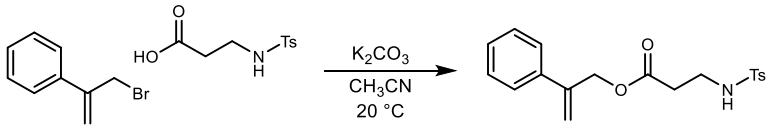


Methyl 2-((2-phenylallyl)oxy)benzoate (4at). Methyl 2-hydroxybenzoate (540 mg, 3.55 mmol) was dissolved in dimethylformamide (40 mL), and then treated with (3-bromoprop-1-en-2-yl)benzene (700 mg, 3.55 mmol) and potassium carbonate (1.00 g, 7.21 mmol). The resulting mixture was stirred for 4 days and then poured over water and extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (SiO_2, 20% ethyl acetate in hexanes) gave the product as an oil (326 mg, 34%). R_f = 0.51 (30% EtOAc/hexanes); IR (film) 2994, 2349, 1725, 1607, 1503, 1427, 1316, 1232, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 7.7, 1.7 Hz, 1H),

7.49-7.43 (m, 3H), 7.39-7.30 (m, 3H), 7.03-6.99 (m, 2H), 5.63 (d, *J* = 1.3 Hz, 1H), 5.60 (d, *J* = 1.3 Hz, 1H), 4.97 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 167.1, 158.0, 142.8, 138.6, 133.5, 132.0, 128.6, 128.1, 126.3, 120.9, 120.8, 114.6, 113.8, 70.4, 52.1; HRMS (ESI): Exact mass calcd for $C_{17}H_{16}NaO_3$ $[M+Na]^+$ 291.0997, found 291.0988.

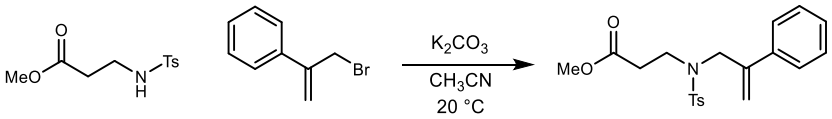


2-((2-Phenylallyl)oxy)benzoic acid (4au). Methyl 2-((2-phenylallyl)oxy)benzoate (326 mg, 1.22 mmol) was dissolved in ethanol (50 mL) and water (10 mL), potassium hydroxide (342 mg, 6.10 mmol) was added, and the resulting mixture was stirred for 5 days. The reaction mixture was acidified with 5 M aq HCl and extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give the product as a white solid (300 mg, 97%). Mp = 70-74 °C; R_f = 0.21 (30% EtOAc/hexanes); IR (film) 3282, 3054, 2904, 2353, 1749, 1599, 1457, 1392, 1314, 1229 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.48 (br s, 1H), 8.18 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.57 (ddd, *J* = 8.4, 7.4, 1.9 Hz, 1H), 7.44-7.35 (m, 5H), 7.17-7.11 (m, 2H), 5.68 (s, 1H), 5.50 (s, 1H), 5.17 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 165.3, 157.3, 141.9, 137.2, 135.1, 134.1, 129.1, 128.9, 126.2, 122.6, 118.1, 117.3, 113.0, 72.1; HRMS (ESI): Exact mass calcd for $C_{16}H_{14}NaO_3$ $[M+Na]^+$ 277.0841, found 277.0841.

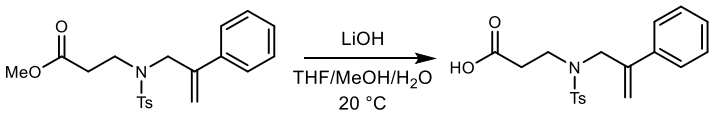


2-Phenylallyl 3-((4-methylphenyl)sulfonamido)propanoate (4ax). 3-((4-Methylphenyl)sulfonamido)propanoic acid (500 mg, 2.06 mmol) was dissolved in acetonitrile (25 mL), and (3-bromoprop-1-en-2-yl)benzene (492 mg, 2.50 mmol), and potassium carbonate (730 mg, 4.12 mmol) were added. The reaction solution was stirred overnight and concentrated directly after 16 hours.

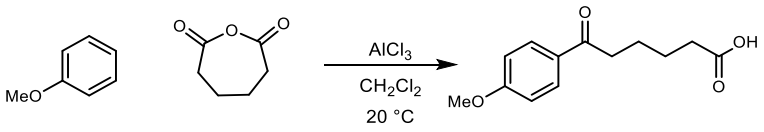
The residue was treated with 1 N aqueous HCl and extracted with DCM, dried ($MgSO_4$), and concentrated. Flash chromatography (SiO_2 30-50% ethyl acetate in hexanes) afforded the product as an oil (372 mg, 50%). R_f =0.27 (30% EtOAc/hexanes); IR (film) 3306, 3057, 2925, 2869, 1739, 1586, 1440, 1323, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.33-7.18 (m, 7H), 5.47 (s, 1H), 5.25 (s, 1H), 4.98 (br s, 1H), 4.90 (s, 2H), 3.09 (td, *J* = 6.3 Hz, 6.3 Hz, 2H), 2.45 (t, *J* = 6.3 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 171.8, 143.6, 142.2, 137.9, 137.1, 129.9, 128.7, 128.4, 127.1, 126.0, 115.9, 66.3, 38.8, 34.2, 21.6; HRMS (ESI): Exact mass calcd for $C_{19}H_{21}NNaO_4S$ $[M+Na]^+$ 382.1089, found 382.1085.



Methyl 3-((4-methyl-N-(2-phenylallyl)phenyl)sulfonamido)propanoate (4ba). (3-Bromoprop-1-en-2-yl)benzene (1.30 g, 6.60 mmol) and methyl 3-((4-methylphenyl)sulfonamido)propanoate (1.70 g, 6.60 mmol) were dissolved in acetonitrile (100 mL) and treated with potassium carbonate (1.82 g, 13.2 mmol). The reaction mixture was stirred at room temperature for 3 days and then poured into 1 N aq HCl, extracted with dichloromethane, dried ($MgSO_4$), filtered, and concentrated to an oil. Flash chromatography (SiO_2, 30-50-100% ethyl acetate in hexanes) of the crude oil gave the product as a colorless oil (1.70 g, 69%). R_f = 0.40 (30% EtOAc/hexanes); IR (film) 2952, 1734, 1438, 1341, 1203, 1160, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.5 Hz, 2H), 7.38-7.36 (m, 2H), 7.28-7.18 (m, 5H), 5.42 (s, 1H), 5.16 (s, 1H), 4.13 (s, 2H), 3.52 (s, 3H), 3.26-3.23 (m, 2H), 2.41-2.37 (m, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 171.9, 143.7, 142.9, 138.0, 135.8, 129.9, 128.6, 128.3, 127.5, 126.6, 116.8, 53.0, 51.7, 43.4, 33.7, 21.6; HRMS (ESI): Exact mass calcd for $C_{20}H_{23}NNaO_4S$ $[M+Na]^+$ 396.1245, found 396.1236.

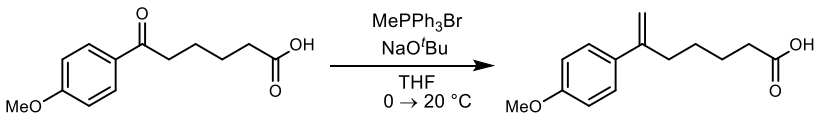


3-((4-Methyl-N-(2-phenylallyl)phenyl)sulfonamido)propanoic acid (4bb). Methyl 3-((4-methyl-*N*-(2-phenylallyl)phenyl)sulfonamido)propanoate (1.70 g, 4.55 mmol) was dissolved in tetrahydrofuran/methanol/water (3:1:1, 50 mL) and treated with lithium hydroxide (550 mg, 22.8 mmol). The mixture was stirred overnight at room temperature, concentrated until the aqueous layer remained, and then diluted with 1 N aq NaOH. The aqueous layer was washed with diethyl ether, acidified using 6 M aq HCl, and extracted with dichloromethane. The organic layers were dried ($MgSO_4$), filtered, and concentrated to give the product as a white solid (890 mg, 55%). Mp = 130-133 °C; R_f = 0.43 (100% EtOAc); IR (film) 3750, 2918, 2370, 1718, 1329, 1149 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.5 Hz, 2H), 7.46-7.43 (m, 2H), 7.36-7.29 (m, 5H), 5.50 (s, 1H), 5.23 (s, 1H), 4.20 (s, 2H), 3.31-3.27 (m, 2H), 2.51-2.47 (m, 2H), 2.44 (s, 3H) [O*H* not observed]; ^{13}C NMR (100 MHz, $CDCl_3$) ppm 175.8, 143.8, 142.9, 137.0, 135.7, 130.0, 128.7, 128.4, 127.6, 126.6, 117.0, 53.2, 43.0, 33.5, 21.7; HRMS (ESI): Exact mass calcd for $C_{19}H_{22}NO_4S$ $[M+H]^+$ 360.1270, found 360.1260.

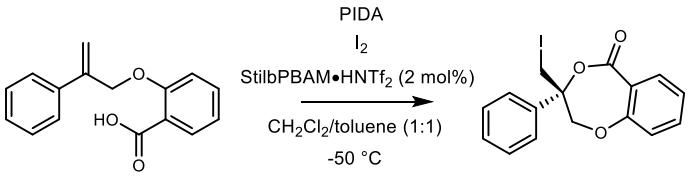


6-(4-Methoxyphenyl)-6-oxohexanoic acid (4bd). Adipic anhydride (5.00 g, 39.1 mmol) was dissolved in dichloromethane (80 mL) and anisole (4.67 mL, 43.0 mmol) was added. Aluminum trichloride (11.4 g, 86.0 mmol) was added, and the reaction mixture was stirred for 18 hours, cooling as necessary. The reaction mixture was quenched with 1 N aq HCl, extracted with dichloromethane, dried (Na_2SO_4), and concentrated. The recovered solid was dissolved in dichloromethane and extracted with 1 N aq NaOH. The aqueous layer was washed with dichloromethane, acidified with 2 N aq HCl, and extracted with dichloromethane. The organic layers were dried (Na_2SO_4), and concentrated to give the product as a white solid (2.3 g, 25%). Mp = 117-122 °C; R_f = 0.06 (30% EtOAc/hexanes); IR (film) 3744, 3040, 2945,

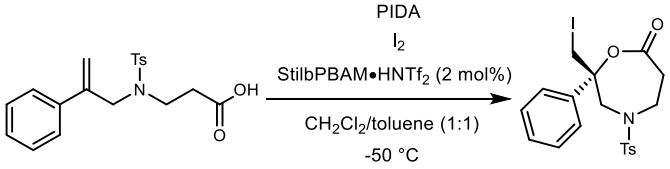
2373, 1714, 1593, 1250, 1168 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.9 Hz, 2H) 6.93 (d, *J* = 8.9 Hz, 2H), 3.87 (s, 3H), 2.95 (t, *J* = 6.9 Hz, 2H), 2.42 (t, *J* = 6.9 Hz, 2H), 1.84-1.69 (m, 4H), [O*H* not observed]; ^{13}C NMR (100 MHz, $CDCl_3$) ppm 198.6, 178.4, 163.6, 130.4, 130.2, 113.9, 55.6, 37.9, 33.8, 24.5, 23.9; HRMS (ESI): Exact mass calcd for $C_{13}H_{16}O_4Na$ $[M+Na]^+$ 259.0946, found 259.0939.



6-(4-Methoxyphenyl)hept-6-enoic acid (4be). Methyltriphenylphoshonium bromide (1.98 g, 5.55 mmol) was suspended in THF (100 mL), and cooled to 0 °C. Sodium *tert*-butoxide (1.06 g, 11.1 mmol) was added and the reaction mixture was stirred for 1 hour at room temperature. The reaction mixture was cooled to 0 °C, the carboxylic acid was added, and the reaction mixture was stirred for 48 hours at room temperature. The reaction mixture was concentrated, the residue was dissolved in 1 M aq NaOH, and washed with dichloromethane. The aqueous layer was acidified with 2 N aq HCl and extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated to give the product as a white solid (700 mg, 70%). Mp = 97-100 °C; R_f = 0.21 (30% EtOAc/hexanes); IR (film) 3074, 2933, 2844, 1699, 1606, 1510, 1427, 1286, 1042 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.9 Hz, 2H), 6.86 (d, *J* = 8.9 Hz, 2H), 5.21 (d, *J* = 1.4 Hz, 1H), 4.98 (d, *J* = 1.4 Hz, 1H), 3.81 (s, 3H), 2.51 (t, *J* = 7.9 Hz, 2H), 2.35 (t, *J* = 7.5 Hz, 2H), 1.71-1.64 (m, 2H), 1.54-1.47 (m, 2H), [O*H* not observed]; ^{13}C NMR (100 MHz, $CDCl_3$) ppm 180.1, 159.1, 147.4, 133.6, 127.3, 113.8, 111.1, 55.4, 35.1, 34.0, 27.7, 24.4; HRMS (ESI): Exact mass calcd for $C_{14}H_{18}O_3Na$ $[M+Na]^+$ 257.1154, found 257.1149.

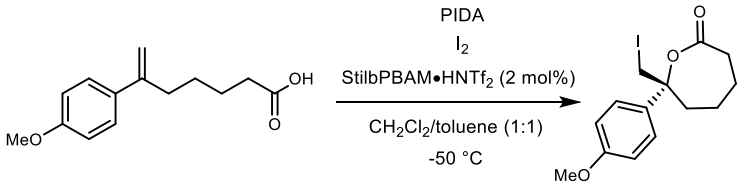


(*S*)-3-(Iodomethyl)-3-phenyl-2,3-dihydro-5H-benzo[e][1,4]dioxepin-5-one (4bg). The carboxylic acid (25.0 mg, 100 µmol) and StilbPBAM·$HNTf_2$ (1.8 mg, 2.0 µmol, 2% loading) were added to a microwave vial with rounded bottom and dissolved in a 1:1 solution of dichloromethane and toluene (2 mL). The mixture was cooled to -50 °C and treated with PIDA (32 mg, 100 µmol) and iodine (25 mg, 100 µmol). The reaction mixture was stirred for 48 hours and then cooled to -78 °C before directly loading it onto a plug of silica (SiO_2). It was flushed with hexanes (10 mL), eluted with 50% ethyl acetate in hexanes (10 mL), and directly concentrated. Flash chromatography (SiO_2, 10% ethyl acetate in hexanes) gave the product as a colorless oil (24 mg, 64%). The product was determined to be 65% ee by chiral HPLC analysis (Chiralcel OD-H, 10% ^{i}PrOH/hexanes, 1 mL/min, t_r(*e*$_1$, minor) = 13.76 min, t_r(*e*$_2$, major) = 16.65 min); R_f = 0.50 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ +10 (*c* 1.3, $CHCl_3$); IR (film) 3050, 1711, 1614, 1498, 1439, 1291, 1129 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 1.7, 8.3 Hz, 1H), 7.42-7.38 (m, 2H), 7.34-7.27 (m, 4H), 6.98-6.94 (m, 1H), 6.80 (dd, *J* = 1.2, 8.4 Hz, 1H), 4.92 (d, *J* = 14.0 Hz, 1H), 4.79 (d, *J* = 14.0 Hz, 1H), 3.60 (d, *J* = 11.1 Hz, 1H), 3.56 (d, *J* = 11.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 165.9, 156.4, 137.0, 135.3, 135.0, 128.8 (2C), 125.9, 121.8, 119.6, 116.7, 82.1, 75.9, 12.1; HRMS (ESI): Exact mass calcd for $C_{16}H_{13}IO_3Na$ $[M+Na]^+$ 402.9807, found 402.9820.



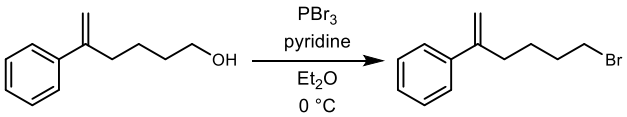
(*S*)-2-(Iodomethyl)-2-phenyl-4-tosyl-1,4-oxazepan-7-one (4bh). The carboxylic acid (36.0 mg, 100 µmol) and StilbPBAM·$HNTf_2$ (1.8 mg, 2.0 µmol, 2% loading) were added to a microwave vial with rounded bottom and dissolved in a 1:1 solution of dichloromethane and toluene (2 mL). The mixture was

cooled to -50 °C and treated with PIDA (32 mg, 100 µmol) and iodine (25 mg, 100 µmol). The reaction mixture was stirred for 48 hours and then cooled to -78 °C before directly loading it onto a plug of silica (SiO_2). It was flushed with hexanes (10 mL), eluted with 50% ethyl acetate in hexanes (10 mL), and directly concentrated. Flash chromatography (SiO_2, 30% ethyl acetate in hexanes) gave the product as a colorless oil (24 mg, 51%). The product was determined to be 88% ee by chiral HPLC analysis (Chiralcel OD-H, 20% ^{i}PrOH/hexanes, 1 mL/min, t_r(*e*$_1$, minor) = 15.46 min, t_r(*e*$_2$, major) = 20.12 min); R_f = 0.35 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ -37 (*c* 1.4, $CHCl_3$); IR (film) 3755, 3041, 2385, 1735, 1369, 1253, 1156 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.7 Hz, 2H), 7.56 (d, *J* = 7.7 Hz, 2H), 7.49-7.38 (m, 5H), 4.77 (dd, *J* = 2.0, 14.4 Hz, 1H), 3.77-3.72 (m, 1H), 3.54 (d, *J* = 11.0 Hz, 1H), 3.42 (d, *J* = 11.0 Hz, 1H), 3.24 (d, *J* = 14.4 Hz, 1H), 2.66-2.61 (m, 1H), 2.55-2.49 (m, 1H), 2.47 (s, 3H), 2.37-2.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 171.4, 144.8, 137.5, 133.0, 130.4, 129.5, 129.2, 127.6, 126.6, 81.3, 57.3, 43.8, 36.9, 21.8, 15.7; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}INO_4NaS$ $[M+Na]^+$ 508.0055, found 508.0043.



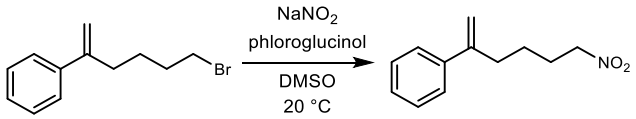
(*R*)-7-(Iodomethyl)-7-(4-methoxyphenyl)oxepan-2-one (4bi). The carboxylic acid (23.0 mg, 100 µmol) and StilbPBAM·$HNTf_2$ (1.8 mg, 2.0 µmol, 2% loading) were added to a microwave vial with rounded bottom and dissolved in a 1:1 solution of dichloromethane and toluene (2 mL). The mixture was cooled to -50 °C and treated with PIDA (32 mg, 100 µmol) and iodine (25 mg, 100 µmol). The reaction mixture was stirred for 48 hours and then cooled to -78 °C before directly loading it onto a plug of silica (SiO_2). It was flushed with hexanes (10 mL), eluted with 50% ethyl acetate in hexanes (10 mL), and directly concentrated. Flash chromatography (SiO_2, 30% ethyl acetate in hexanes) gave the product as a colorless oil (18 mg, 49%). The product was determined to be 50% ee by chiral HPLC analysis (Chiralcel OD-H, 2% ^{i}PrOH/hexanes, 1 mL/min, t_r(*e*$_1$, minor) = 41.06 min, t_r(*e*$_2$, major) = 43.73 min); R_f = 0.31 (30%

EtOAc/hexanes); IR (film) 2925, 2835, 1732, 1621, 1517, 1454, 1253, 1156, 1010 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 3.83 (s, 3H), 3.51 (d, *J* = 10.6 Hz, 1H), 3.38 (d, *J* = 10.6 Hz, 1H), 2.65-2.59 (m, 1H), 2.58-2.52 (m, 1H), 2.42-2.34 (m, 1H), 2.03-1.95 (m, 1H), 1.93-1.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 174.6, 159.6, 130.9, 127.5, 114.7, 82.9, 55.5, 37.4, 36.8, 24.7, 23.0, 21.7. HRMS (ESI): Exact mass calcd for $C_{14}H_{17}IO_3$ $[M]^+$ 360.02, found N/A.[39,40]

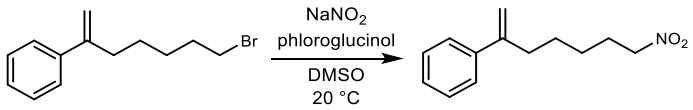


(6-Bromohex-1-en-2-yl)benzene (x1). Phosphorous tribromide (215 µL, 2.27 mmol) was dissolved in diethyl ether (10 mL), and cooled in an ice-water bath. Pyridine (230 µL, 2.84 mmol) and 5-phenylhex-5-en-1-ol (1.00 g, 5.67 mmol) were dissolved in diethyl ether (10 mL) and added. The reaction mixture was stirred for three hours and then quenched by the addition of water, extracted with diethyl ether, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (SiO_2, 10% ethyl acetate in hexanes) gave the product as a colorless oil (170 mg, 13%). R_f = 0.68 (30% EtOAc/hexanes); IR (film) 3060, 2925, 1640, 1479, 1447, 1253 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.27 (m, 5H), 5.29 (d, *J* = 1.3 Hz, 1H), 5.07 (d, *J* = 1.3 Hz, 1H), 3.39 (t, *J* = 6.8 Hz, 2H), 2.54 (t, *J* = 7.5 Hz, 2H), 1.89 (tt, *J* = 6.9, 7.7 Hz, 2H), 1.60 (tt, *J* = 6.9, 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 148.0, 141.1, 128.5, 127.6, 126.2, 112.8, 34.5, 33.7, 32.4, 26.8; HRMS (CI): Exact mass calcd for $C_{12}H_{15}Br$ $[M]^+$ 238.0352, found 238.0355.

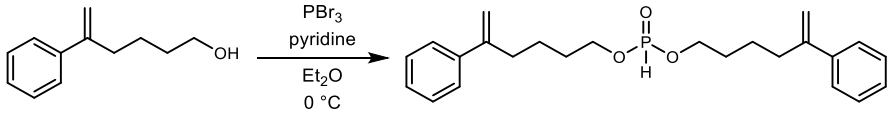
[39] HRMS was collected but the expected mass was not observed due to the observed instability of the compound. All other spectra were consistent with the identified structure.
[40] Note that the compound **4bi** is unstable when concentrated and is prone to decomposition when concentrated and/or heated, even mildly (i.e. rotary evaporation).



(6-Nitrohex-1-en-2-yl)benzene (x2). (6-Bromohex-1-en-2-yl)benzene (1.4 g, 5.9 mmol) was dissolved in dimethyl sulfoxide (20 mL) and treated with sodium nitrite (814 mg, 11.8 mmol) and phloroglucinol (744 mg, 5.9 mmol). The reaction mixture was stirred for 16 hours and then poured over ice, extracted with diethyl ether, dried ($MgSO_4$), and concentrated. Flash chromatography (SiO_2, 10% ethyl acetate in hexanes) of the residue gave the product as a colorless oil (600 mg, 50%). R_f = 0.56 (30% EtOAc/hexanes); IR (film) 3051, 2923, 1752, 1544, 1390 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.28 (m, 5H), 5.30 (s, 1H), 5.08 (s, 1H), 4.36 (t, *J* = 7.0 Hz, 2H), 2.58 (t, *J* = 7.5 Hz, 2H), 2.03 (tt, *J* = 7.3, 7.3 Hz, 2H), 1.58-1.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 147.4, 140.8, 128.6, 127.7, 126.2, 113.3, 75.6, 34.6, 27.0, 24.8; HRMS (CI): Exact mass calcd for $C_{12}H_{15}NO_2$ $[M]^+$ 205.1097, found 205.1106.



(7-Nitrohept-1-en-2-yl)benzene (x3). (7-Bromohept-1-en-2-yl)benzene (2.00 g, 7.90 mmol) was dissolved in dimethyl sulfoxide (20 mL). Sodium nitrite (1.09 g, 15.8 mmol), and phloroglucinol (1.00 g, 7.90 mmol) were subsequently added, and the reaction was stirred overnight. After 16 hours, the reaction solution was poured over ice, extracted with diethyl ether, dried ($MgSO_4$), and concentrated. Flash chromatography (SiO_2 10-50% ethyl acetate in hexanes), afforded the product as a colorless oil (350 mg, 21%). R_f = 0.63 (30% EtOAc/hexanes); IR (film) 2933, 2861, 1551, 1493, 1434, 1383 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.27 (m, 5H), 5.27 (d, *J* = 1.2 Hz, 1H), 5.05 (d, *J* = 1.2 Hz, 1H), 4.34 (t, *J* = 7.2 Hz, 2H), 2.53 (t, *J* = 7.2 Hz, 2H), 2.00 (tt, *J* = 7.2, 7.2 Hz, 2H), 1.54-1.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 148.1, 141.1, 128.5, 127.6, 126.2, 112.8, 75.7, 35.1, 27.5, 27.3, 25.9; HRMS (CI): Exact mass calcd for $C_{13}H_{17}NO_2$ $[M]^+$ 219.1254, found 219.1264.



bis(5-Phenylhex-5-en-1-yl) phosphonate (x4). Phosphorous tribromide (215 µL, 2.27 mmol) was dissolved in diethyl ether (10 mL) and cooled in an ice-water bath. Pyridine (230 µL, 2.84 mmol) and 5-phenylhex-5-en-1-ol (1.00 g, 5.67 mmol) were dissolved in diethyl ether (10 mL) and added. The reaction was stirred for three hours and then quenched by the addition of water, extracted with diethyl ether, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (SiO_2, 10-100% ethyl acetate in hexanes) gave the product as an oil (675 mg, 60%). R_f = 0.12 (30% EtOAc/hexanes); IR (film) 3512, 3091, 2932, 2435, 1631, 1460, 1275, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.12 (m, 10H), 6.63 (d $^1J_{PH}$ = 693.0 Hz, 1H), 5.18 (d, *J* = 1.3 Hz, 2H), 4.96 (d, *J* = 1.3 Hz, 2H), 3.96-3.85 (m, 4H), 2.43 (t, *J* = 7.6 Hz, 4H), 1.62-1.55 (m, 4H), 1.47-1.39 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 147.8, 140.9, 128.3, 127.4, 126.1, 112.7, 65.4 (d, $^2J_{PC}$ = 6.1 Hz), 34.7, 29.9 (d, $^3J_{PC}$ = 6.2 Hz), 24.0; ^{31}P NMR (162 MHz, $CDCl_3$) ppm 7.7; HRMS (ESI): Exact mass calcd for $C_{24}H_{32}O_3P$ $[M+H]^+$ 399.2089, found 399.2075.

Chapter 6. Spectra (SI2)

Figure 1. ^{1}H NMR (400 MHz, $CDCl_3$) of **2c**

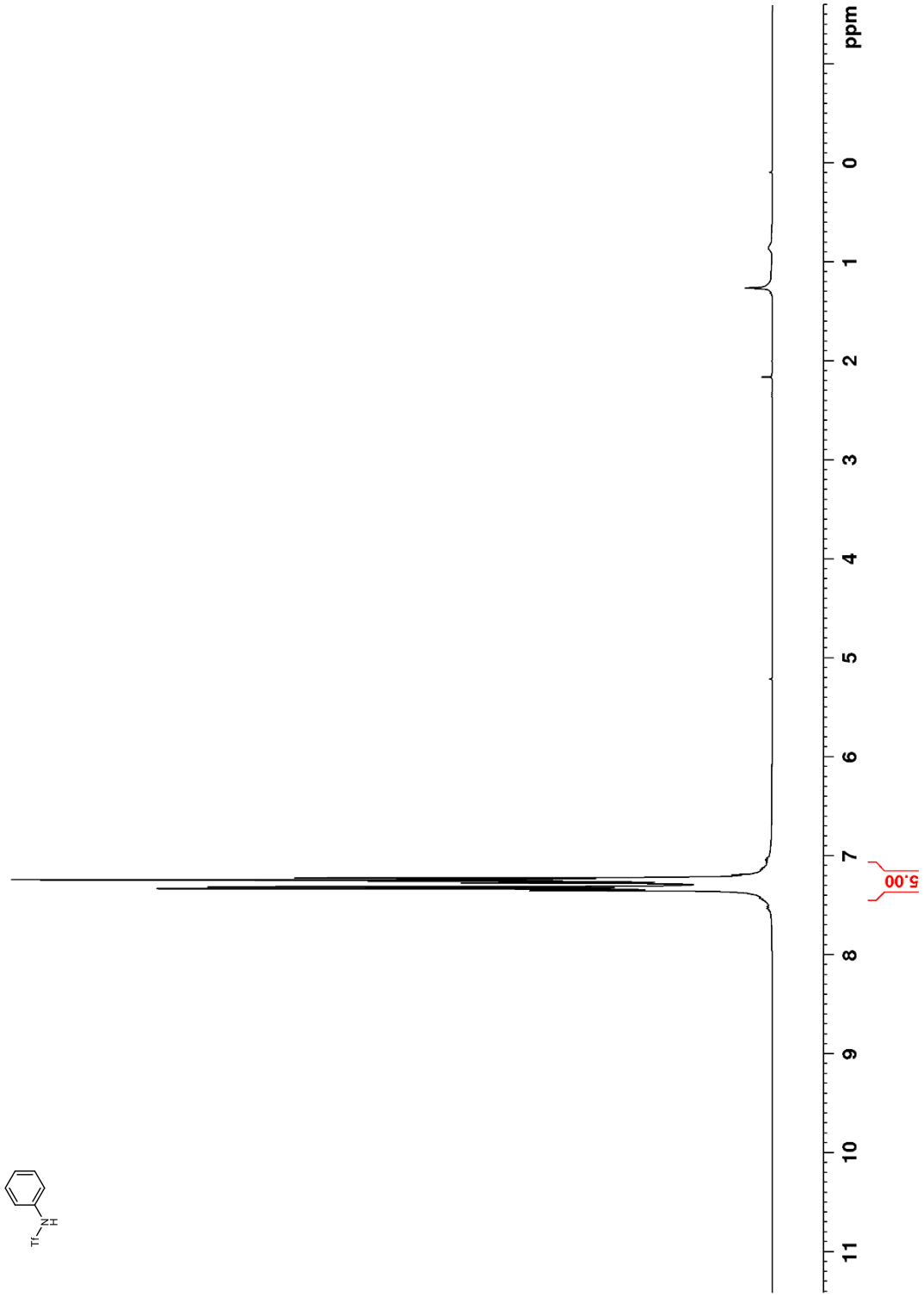


Figure 2. ^{13}C NMR (100 MHz, $CDCl_3$) of **2c**

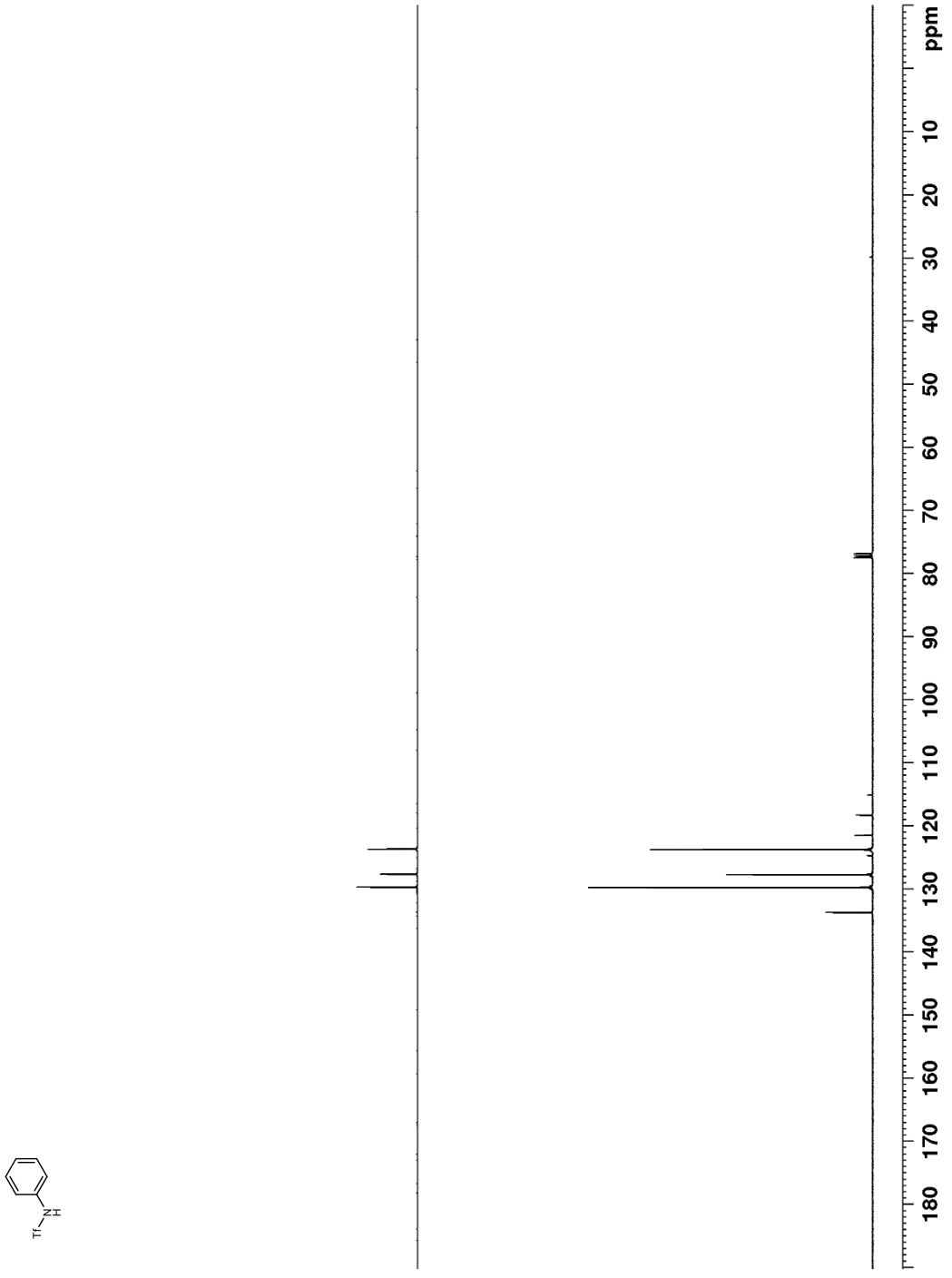


Figure 3. ^{19}F NMR (376 MHz, $CDCl_3$) of **2c**

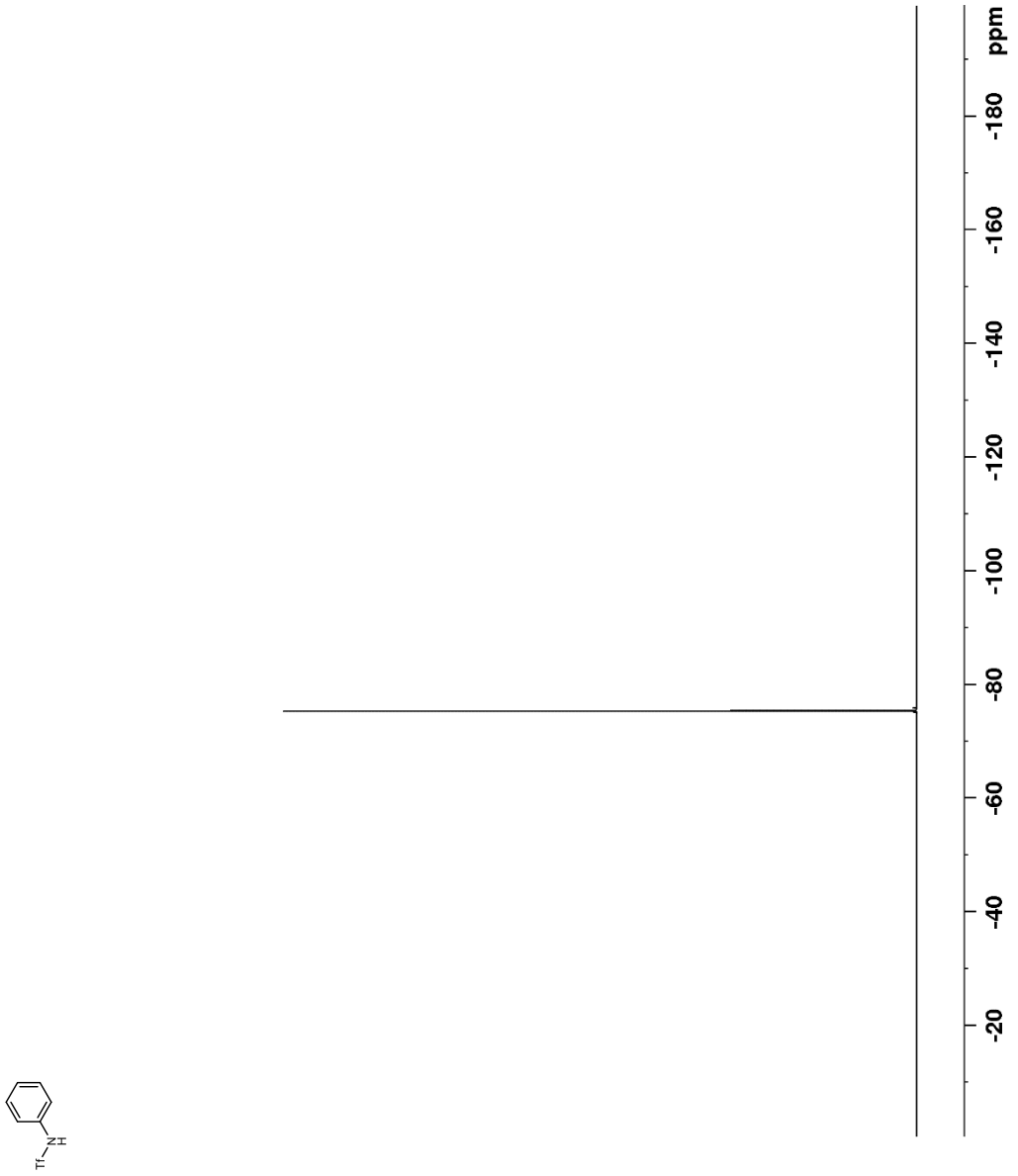


Figure 4. ^{1}H NMR (400 MHz, $CDCl_3$) of **2d**

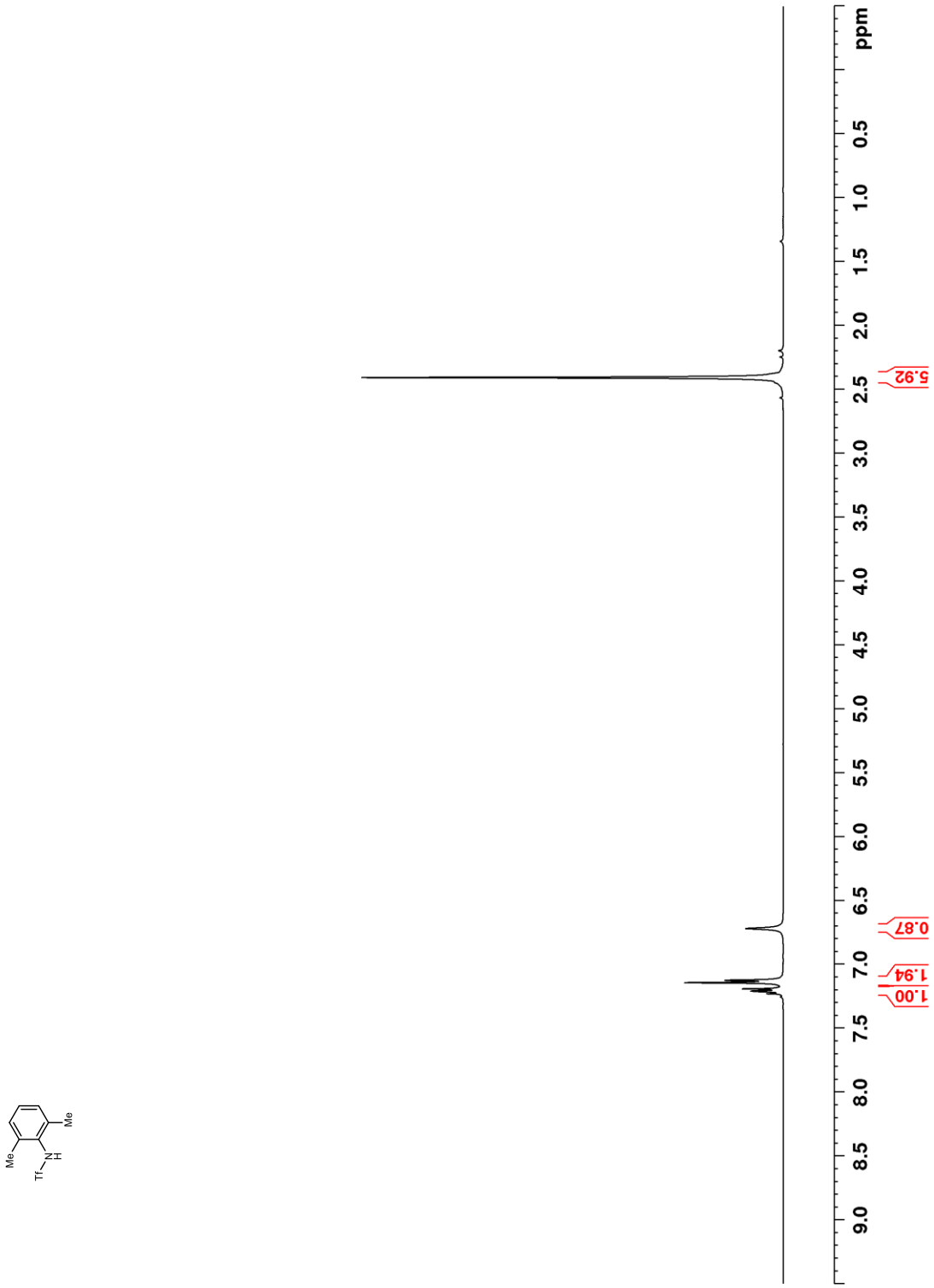


Figure 5. ^{13}C NMR (100 MHz, $CDCl_3$) of **2d**

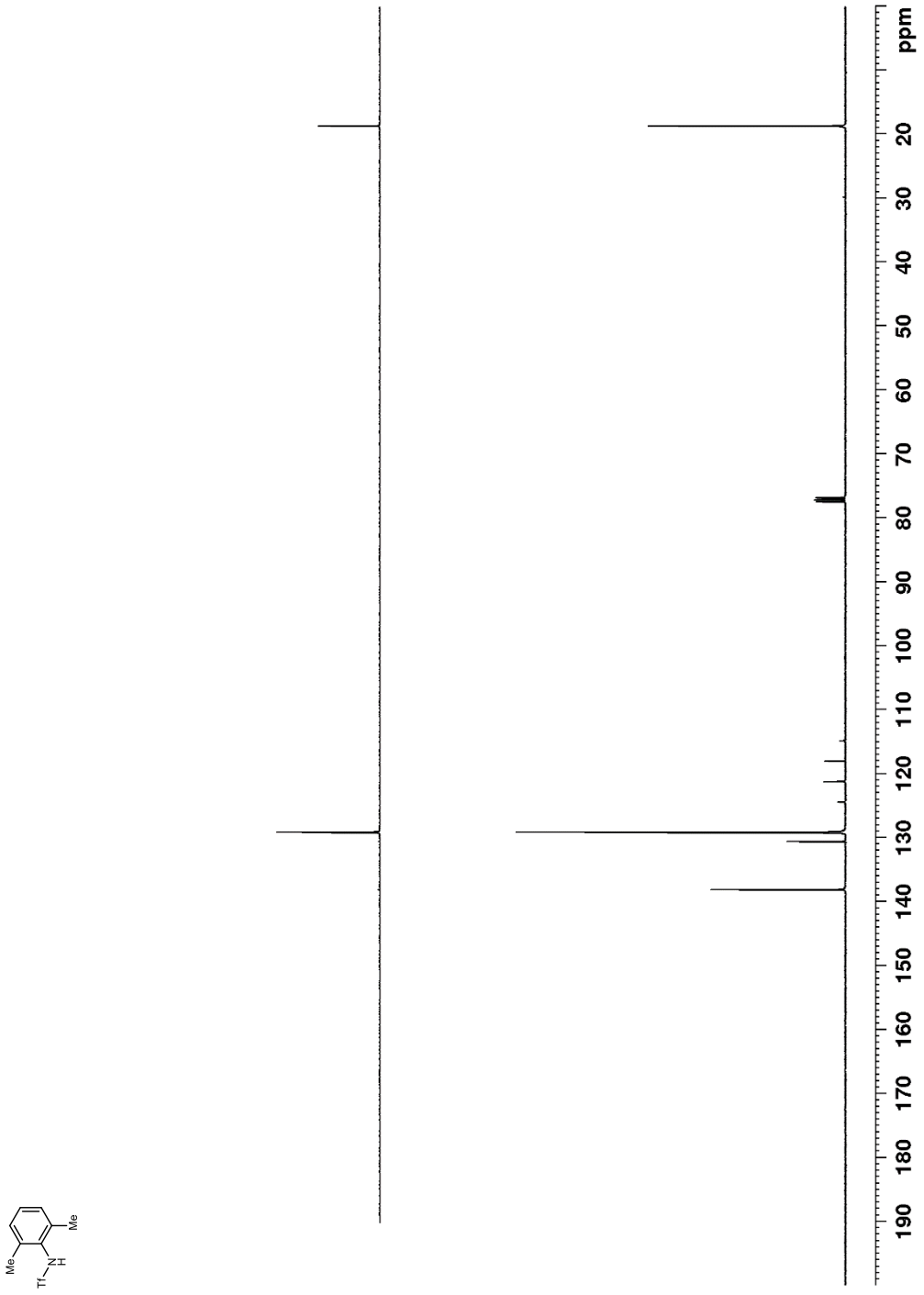


Figure 6. ^{19}F NMR (376 MHz, $CDCl_3$) of **2d**

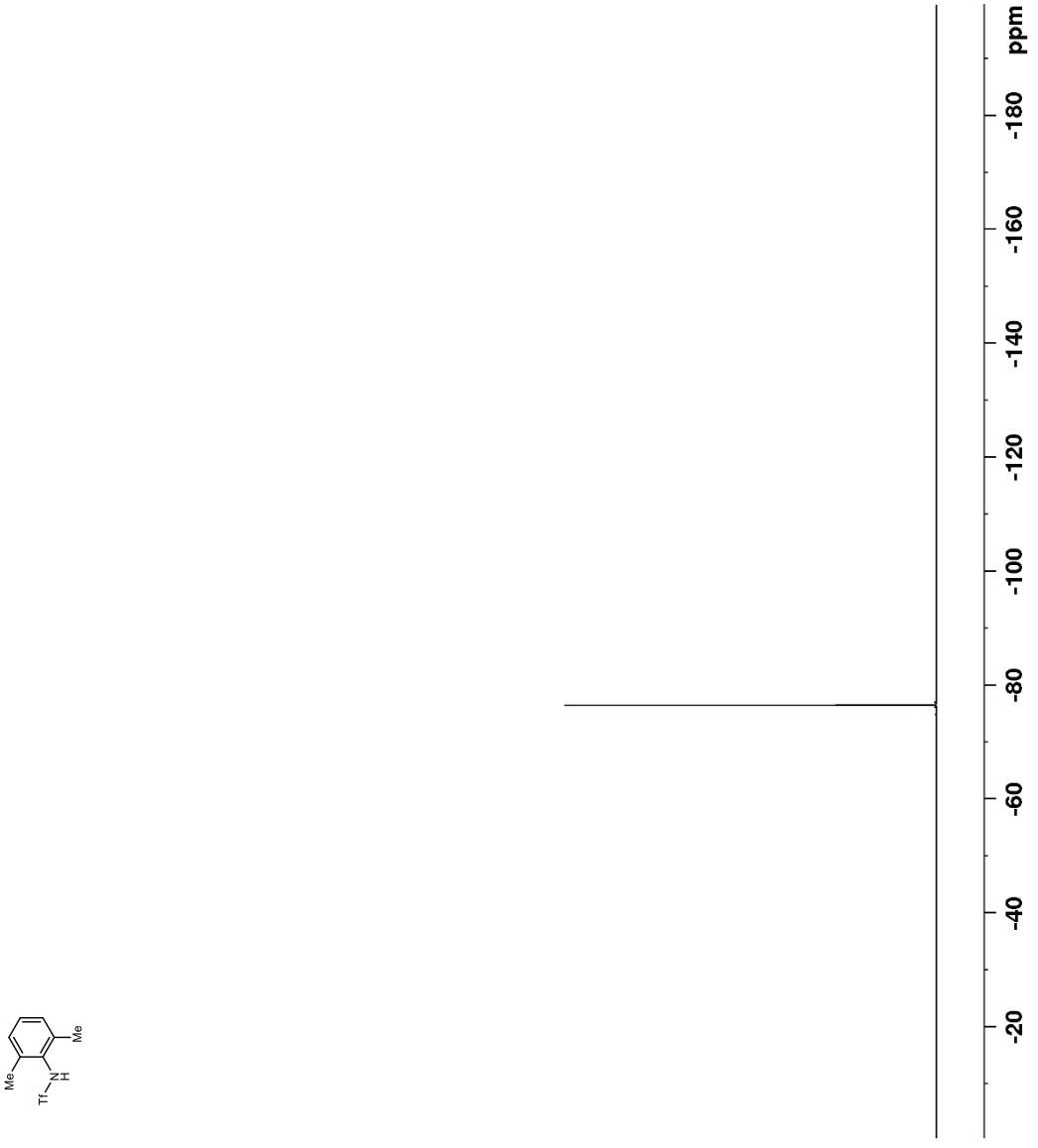


Figure 7. ^{1}H NMR (400 MHz, $CDCl_3$) of **2e**

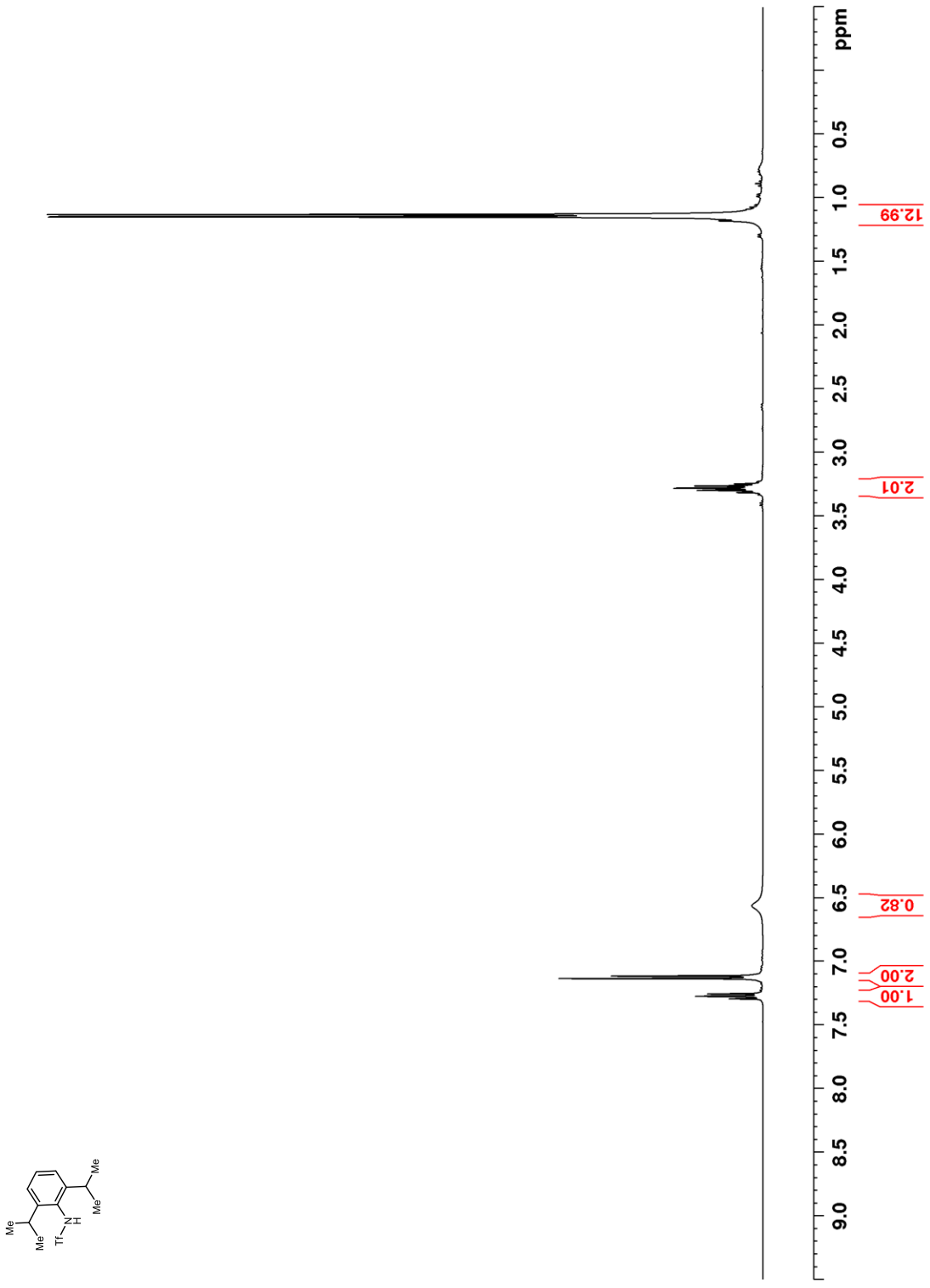


Figure 8. ^{13}C NMR (100 MHz, $CDCl_3$) of **2e**

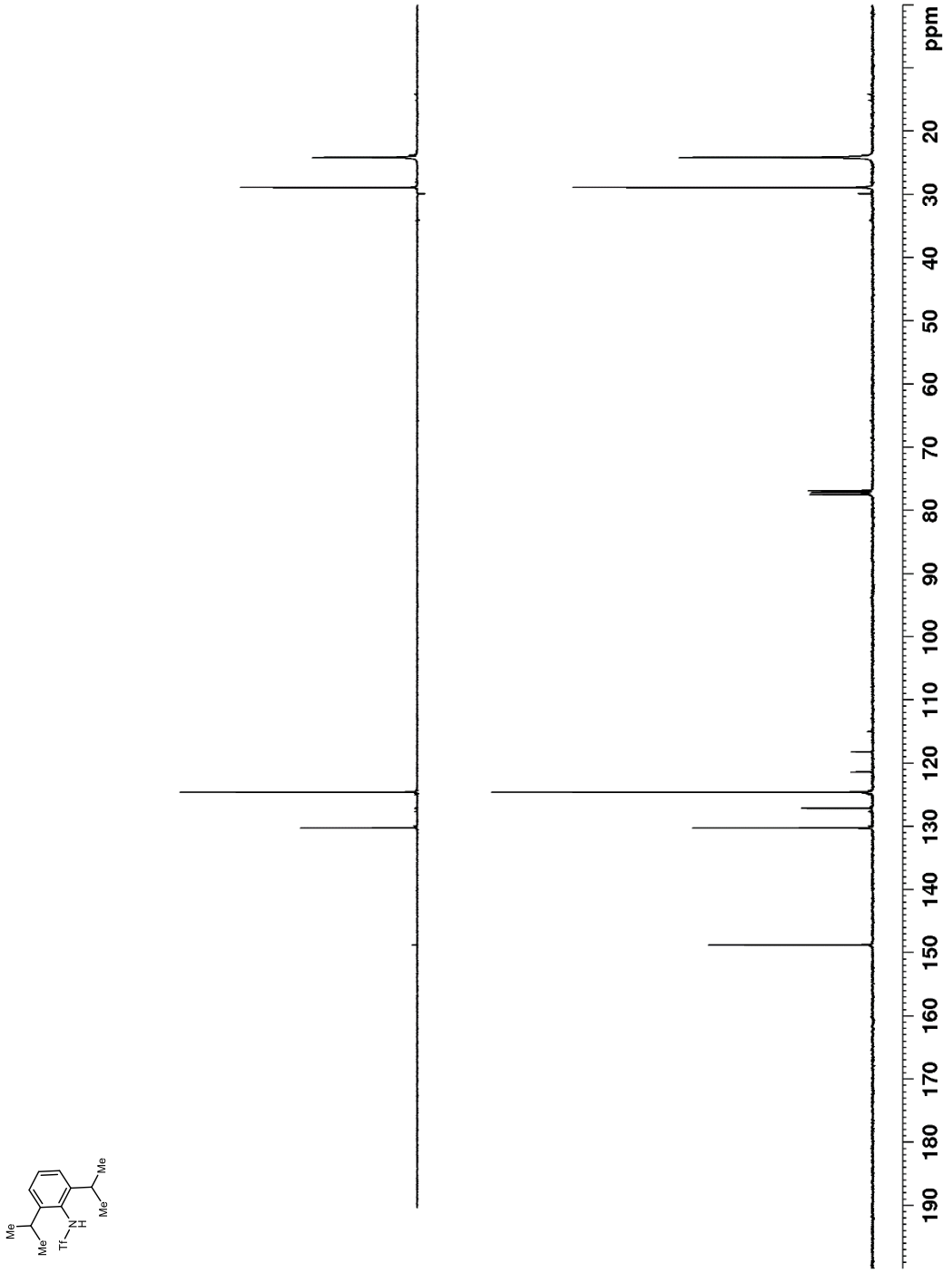


Figure 9. ^{19}F NMR (376 MHz, $CDCl_3$) of **2e**

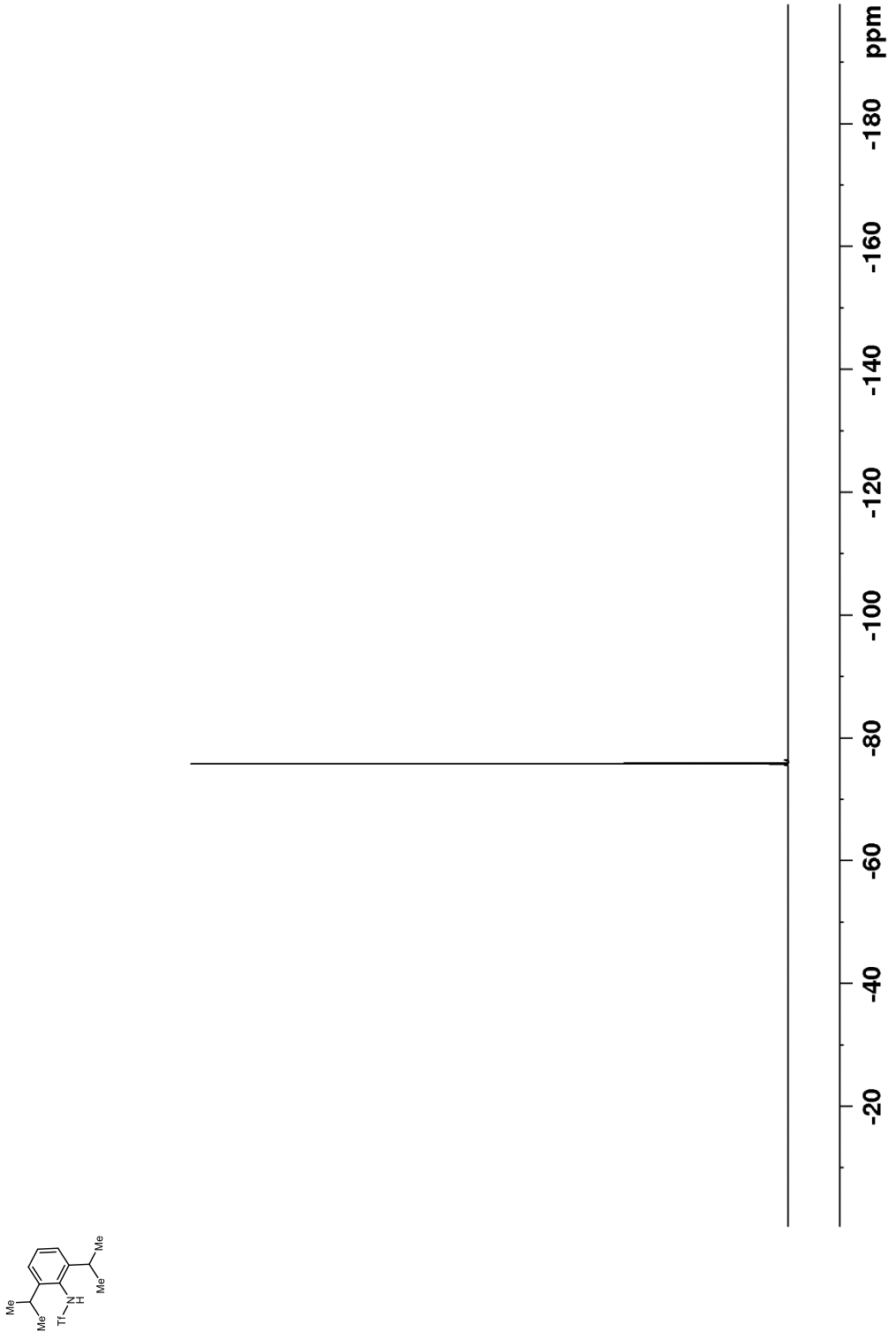


Figure 10. ^{1}H NMR (400 MHz, $CDCl_3$) of **2f**

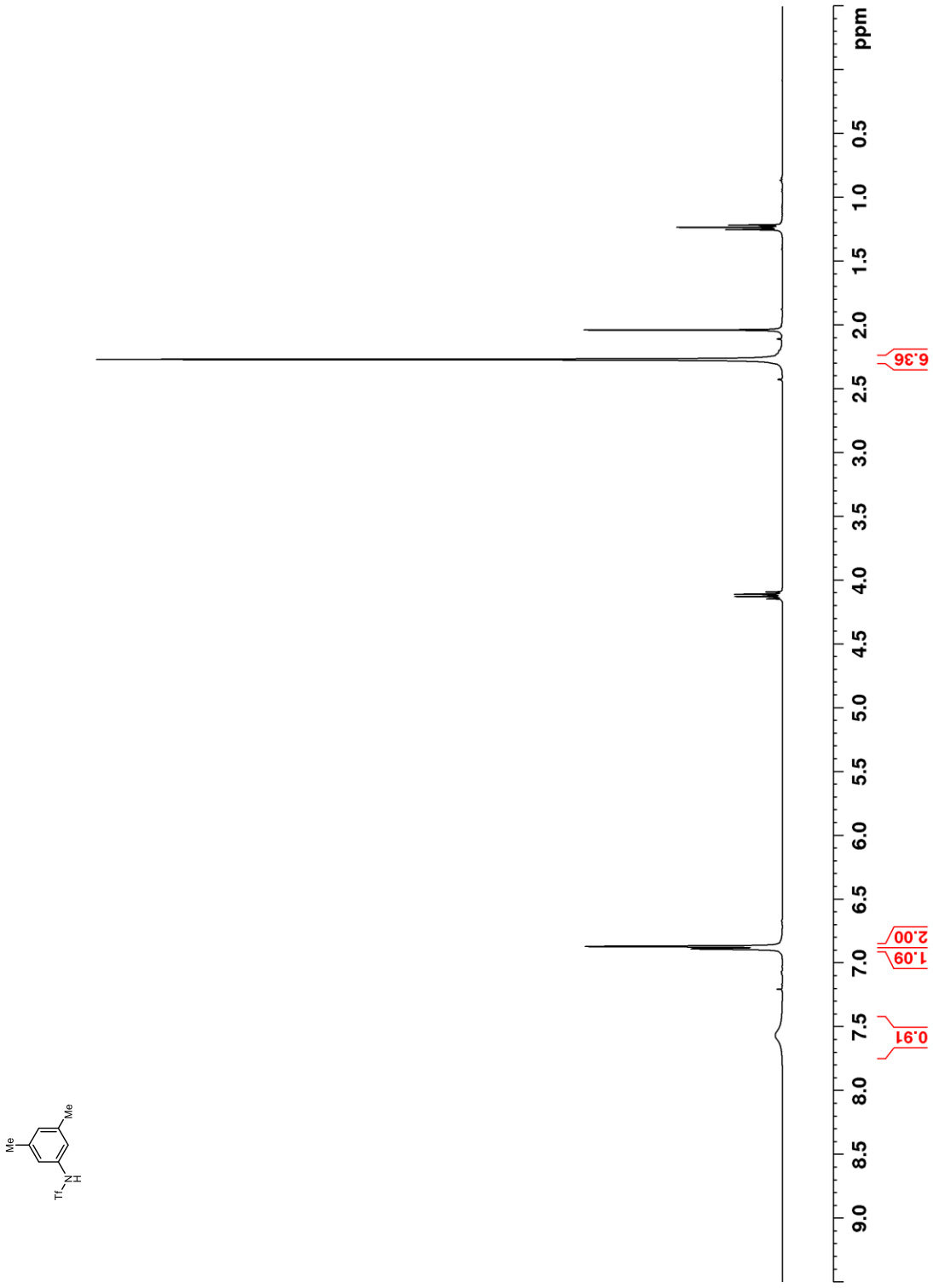


Figure 11. ^{13}C NMR (100 MHz, $CDCl_3$) of **2f**

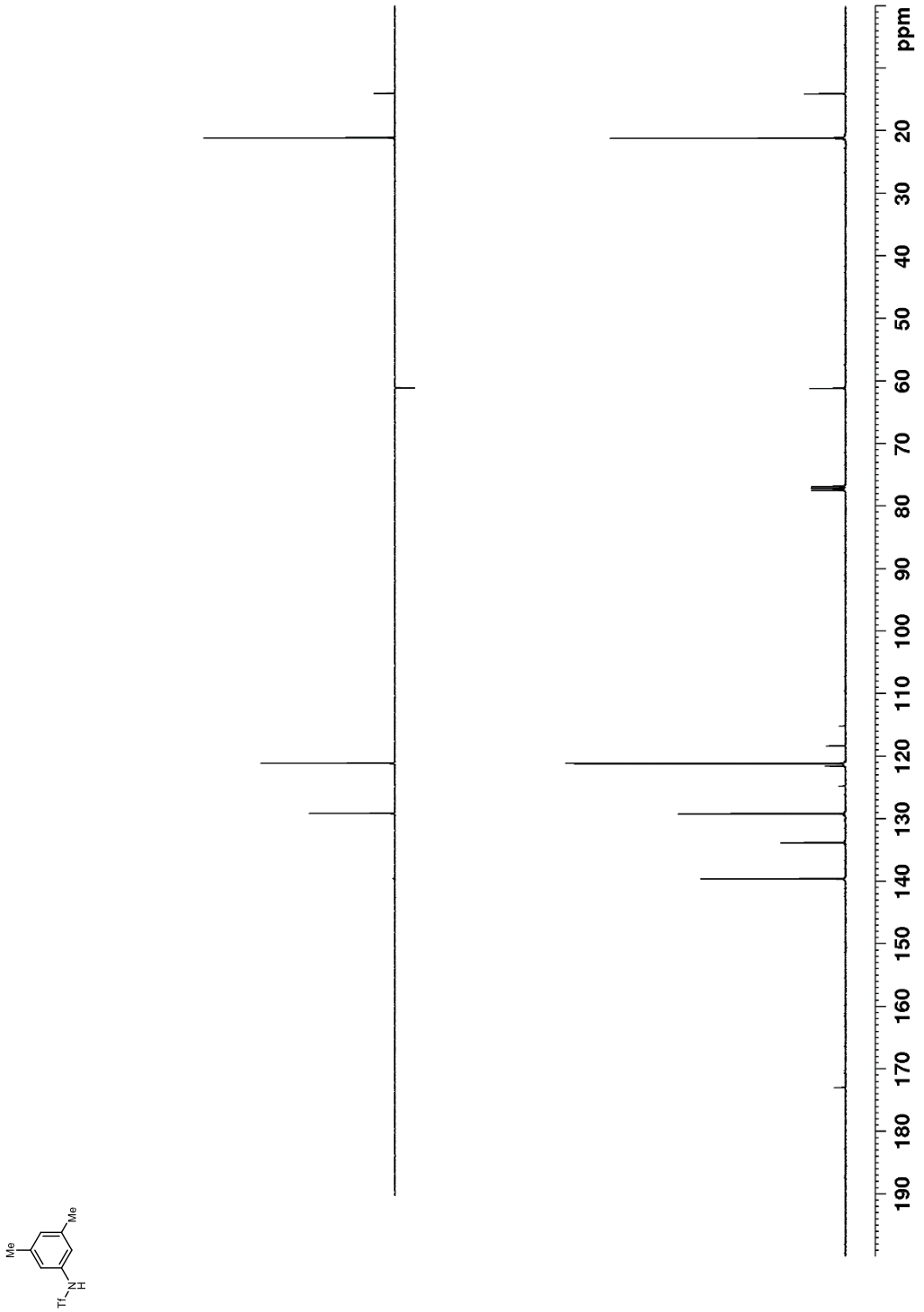


Figure 12. ^{19}F NMR (376 MHz, $CDCl_3$, internal standard of fluorobenzene) of **2f**

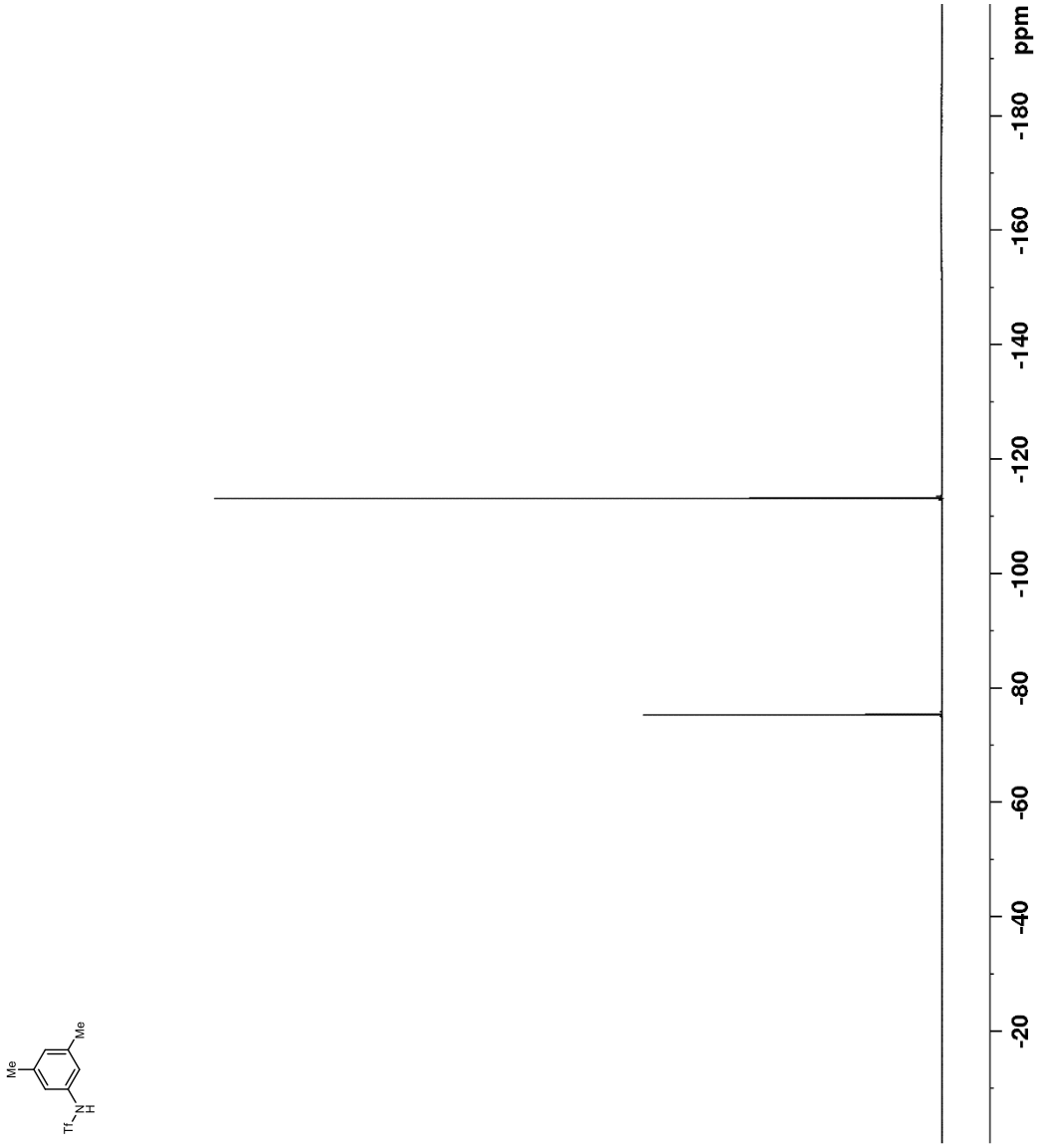


Figure 13. ^{1}H NMR (400 MHz, $CDCl_3$) of **2l**

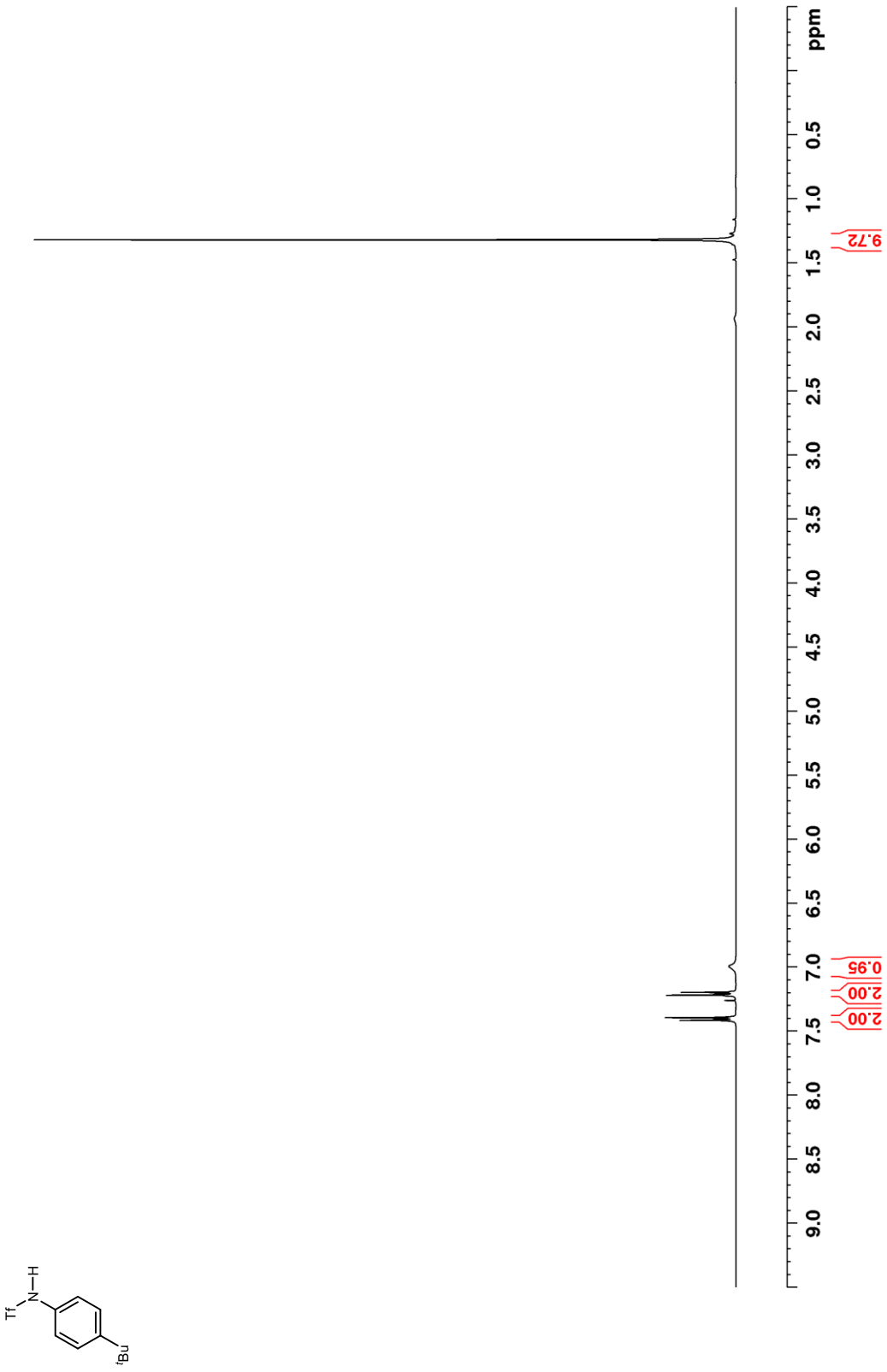


Figure 14. ^{13}C NMR (100 MHz, $CDCl_3$) of **2l**

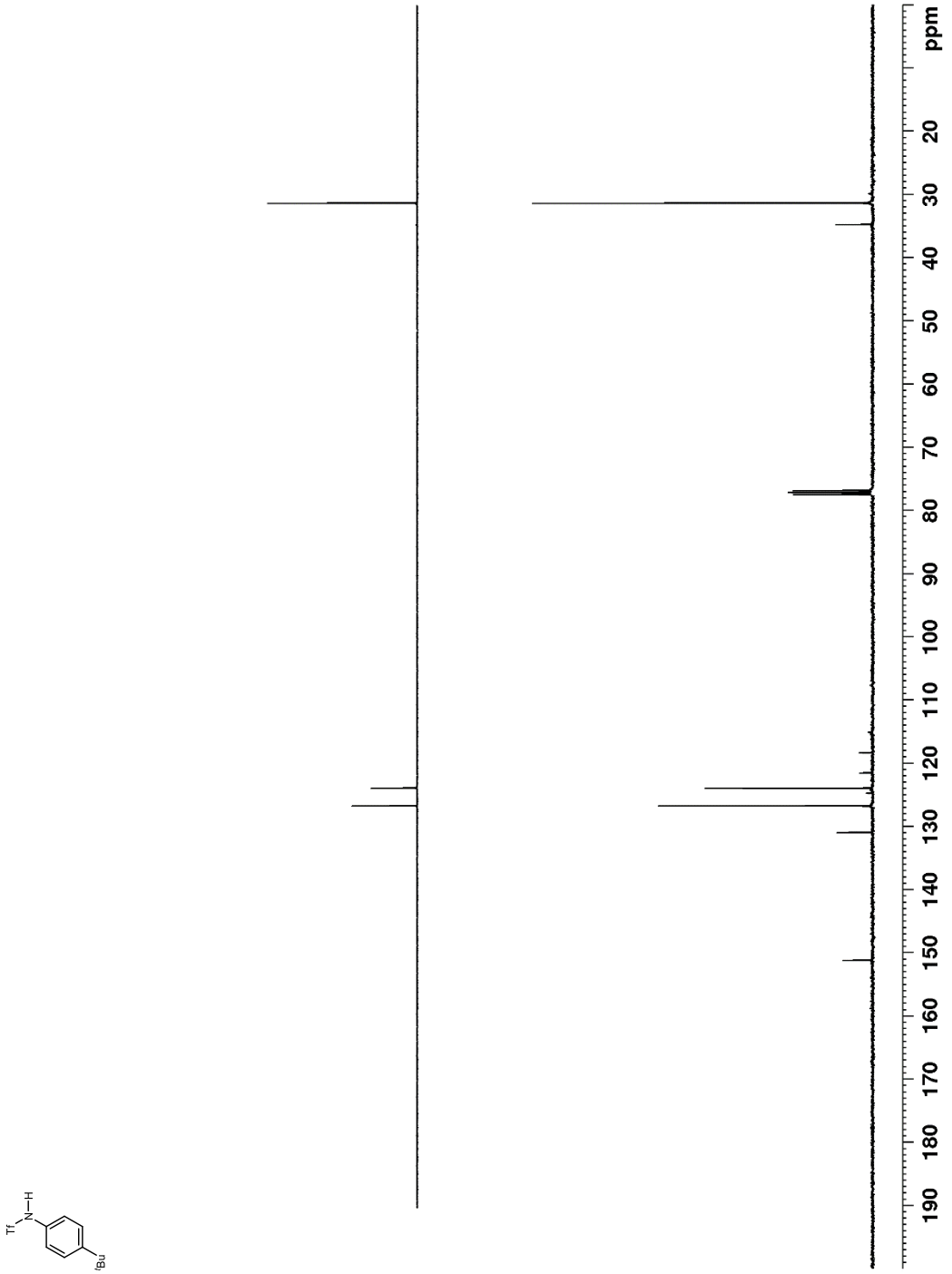


Figure 15. ^{19}F NMR (376 MHz, $CDCl_3$) of **2l**

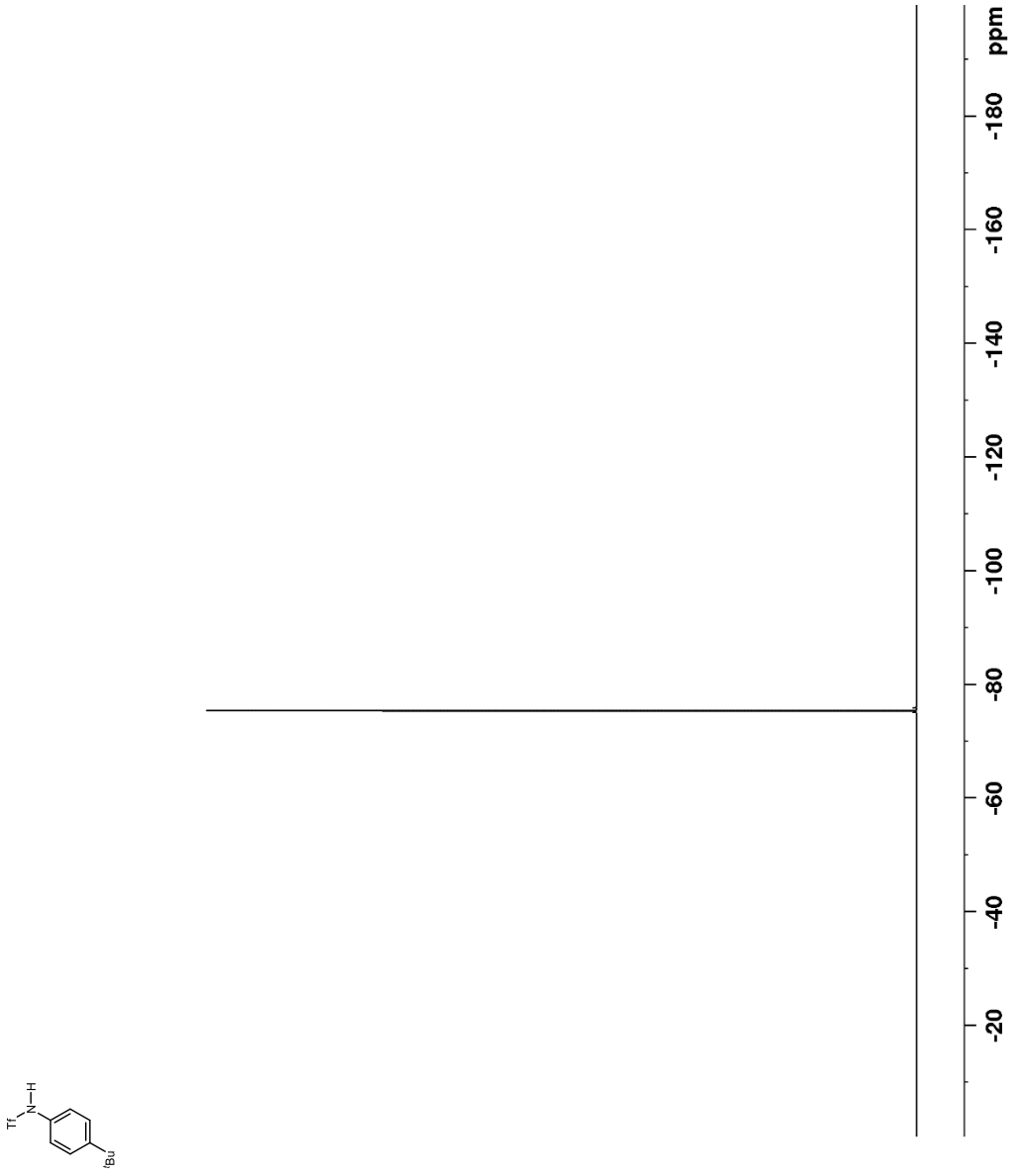


Figure 16. ^{1}H NMR (400 MHz, $CDCl_3$) of **2g**

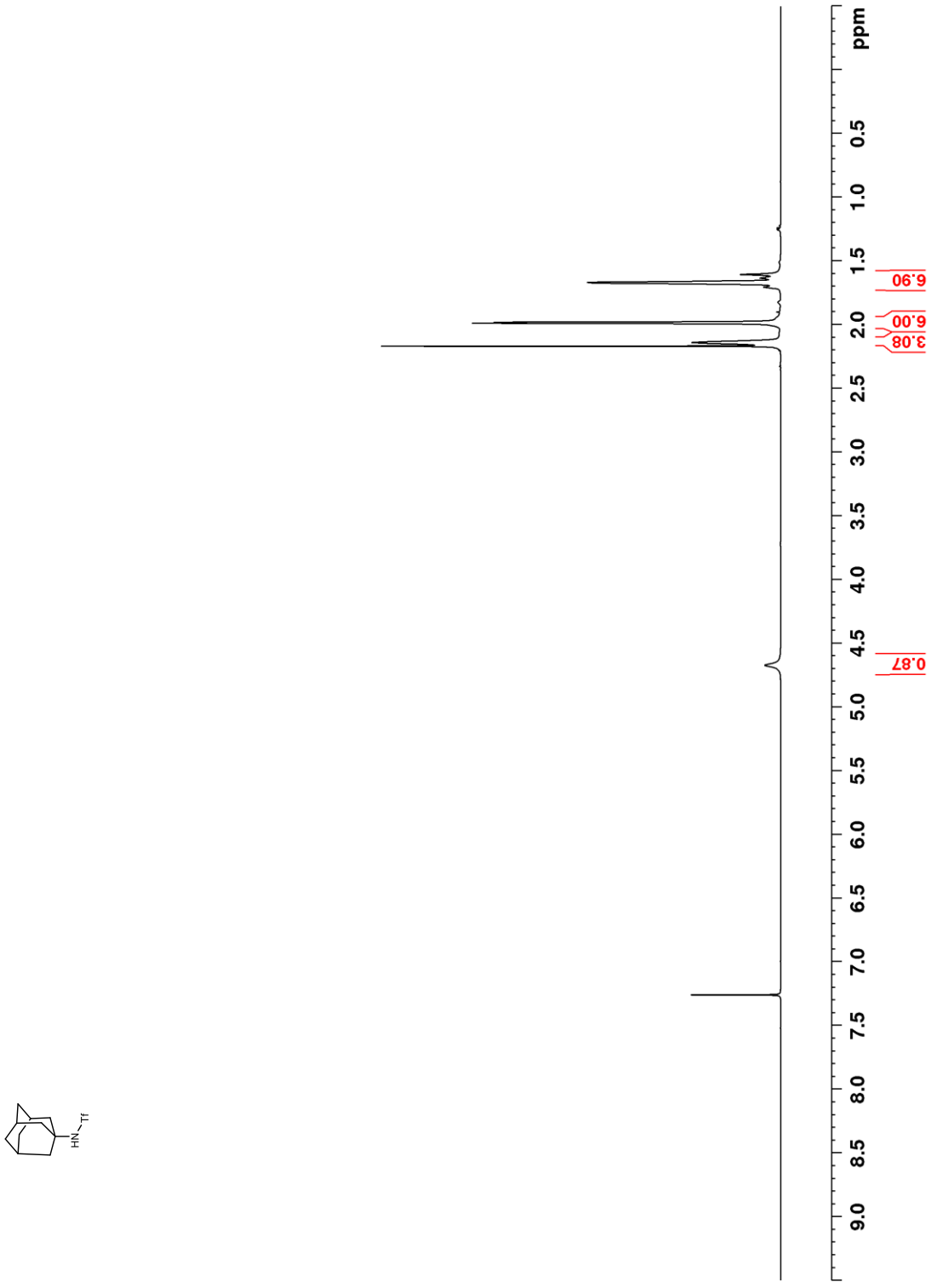


Figure 17. ^{13}C NMR (100 MHz, $CDCl_3$) of **2g**

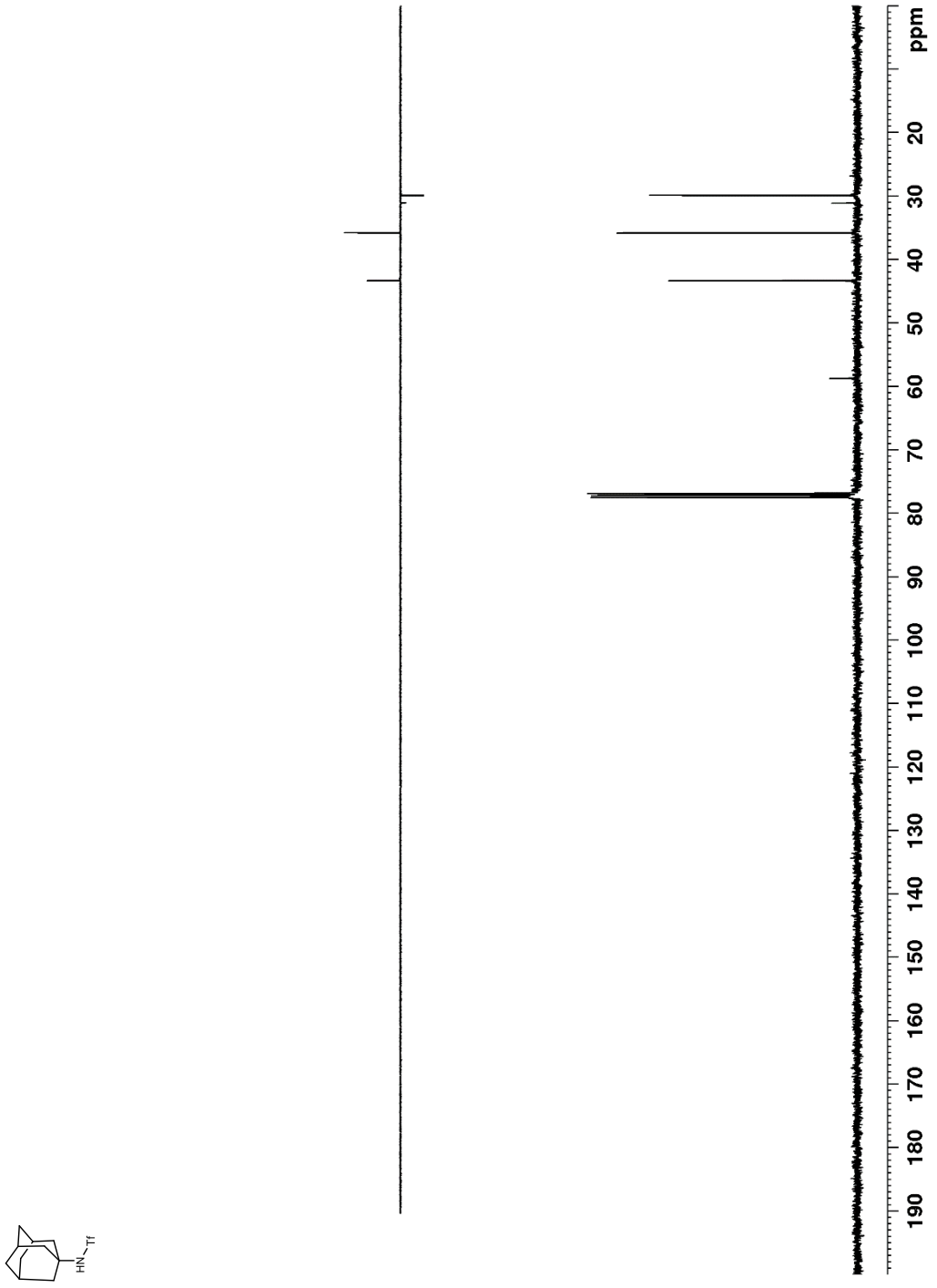


Figure 18. ^{19}F NMR (376 MHz, $CDCl_3$) of **2g**

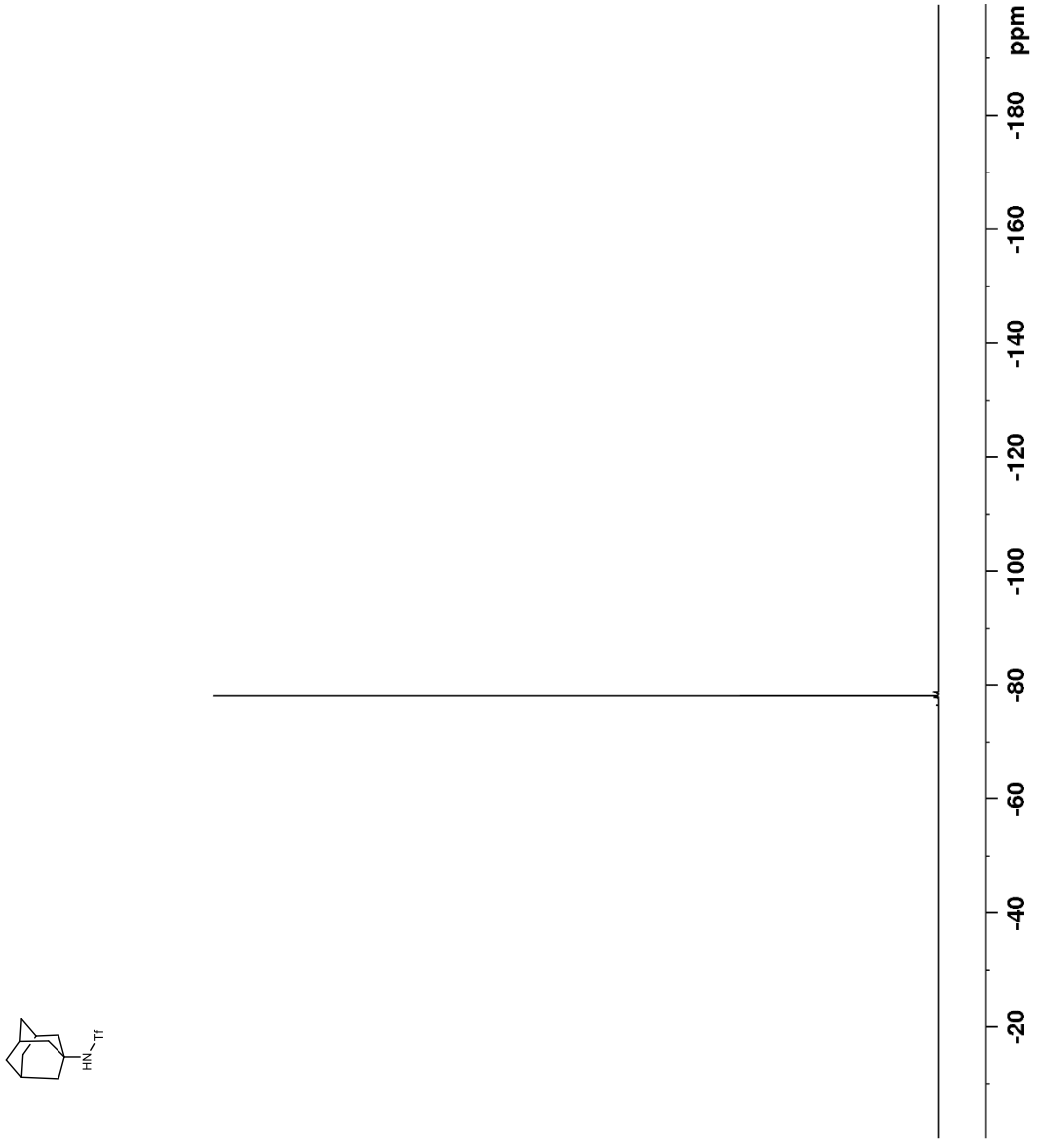


Figure 19. ^{1}H NMR (400 MHz, $CDCl_3$) of **2h**

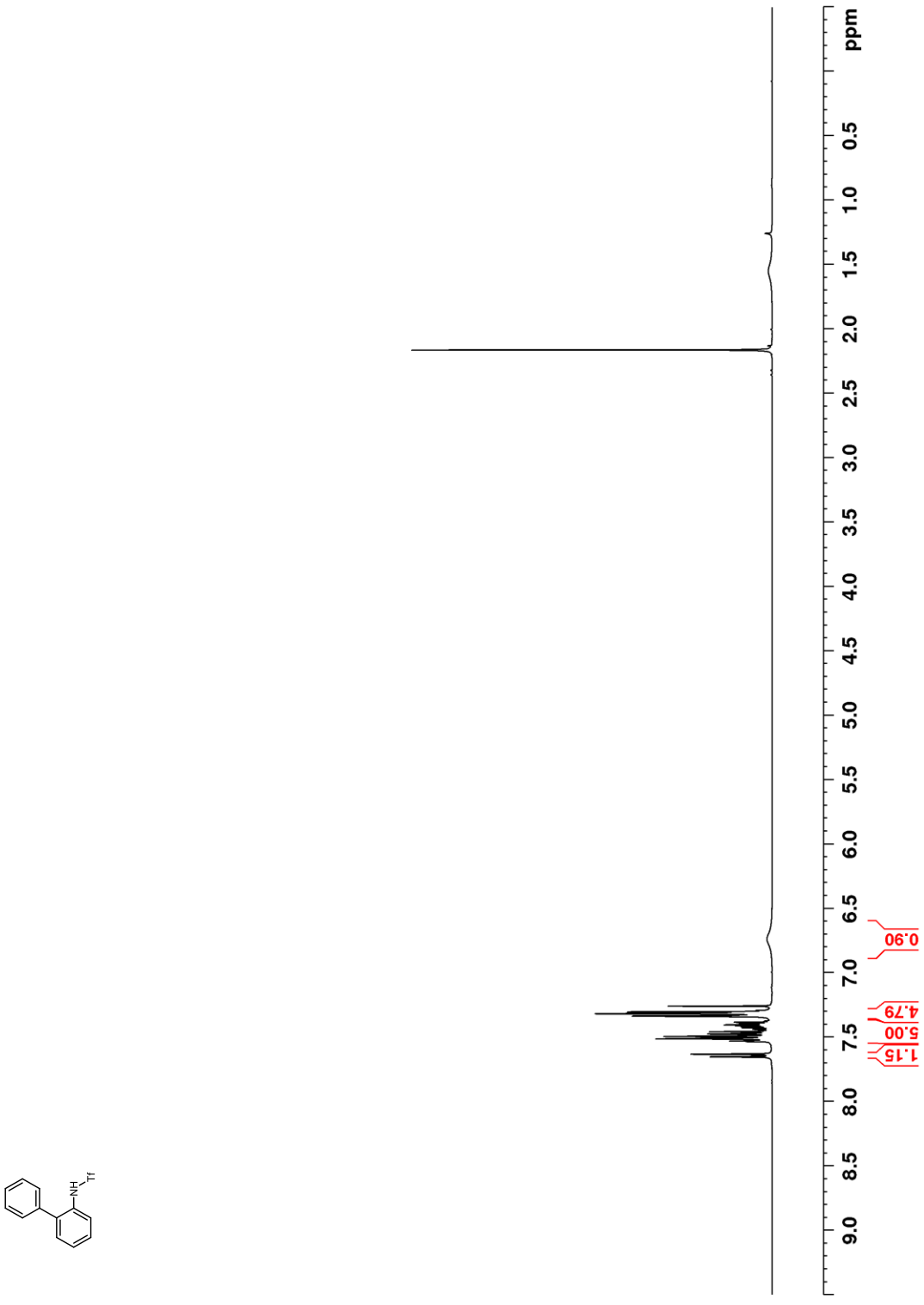


Figure 20. ^{13}C NMR (100 MHz, $CDCl_3$) of **2h**

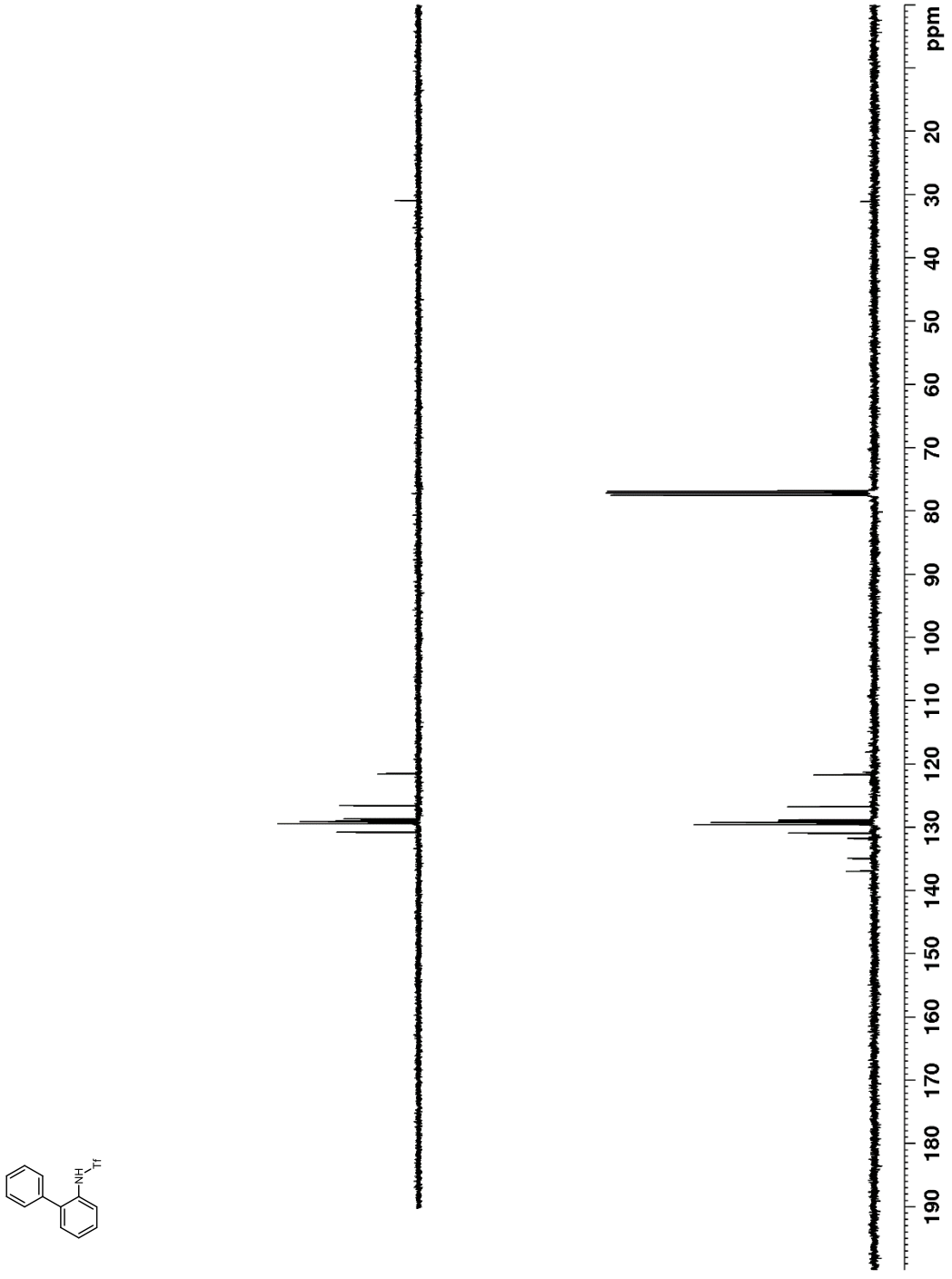


Figure 21. ^{19}F NMR (376 MHz, $CDCl_3$) of **2h**

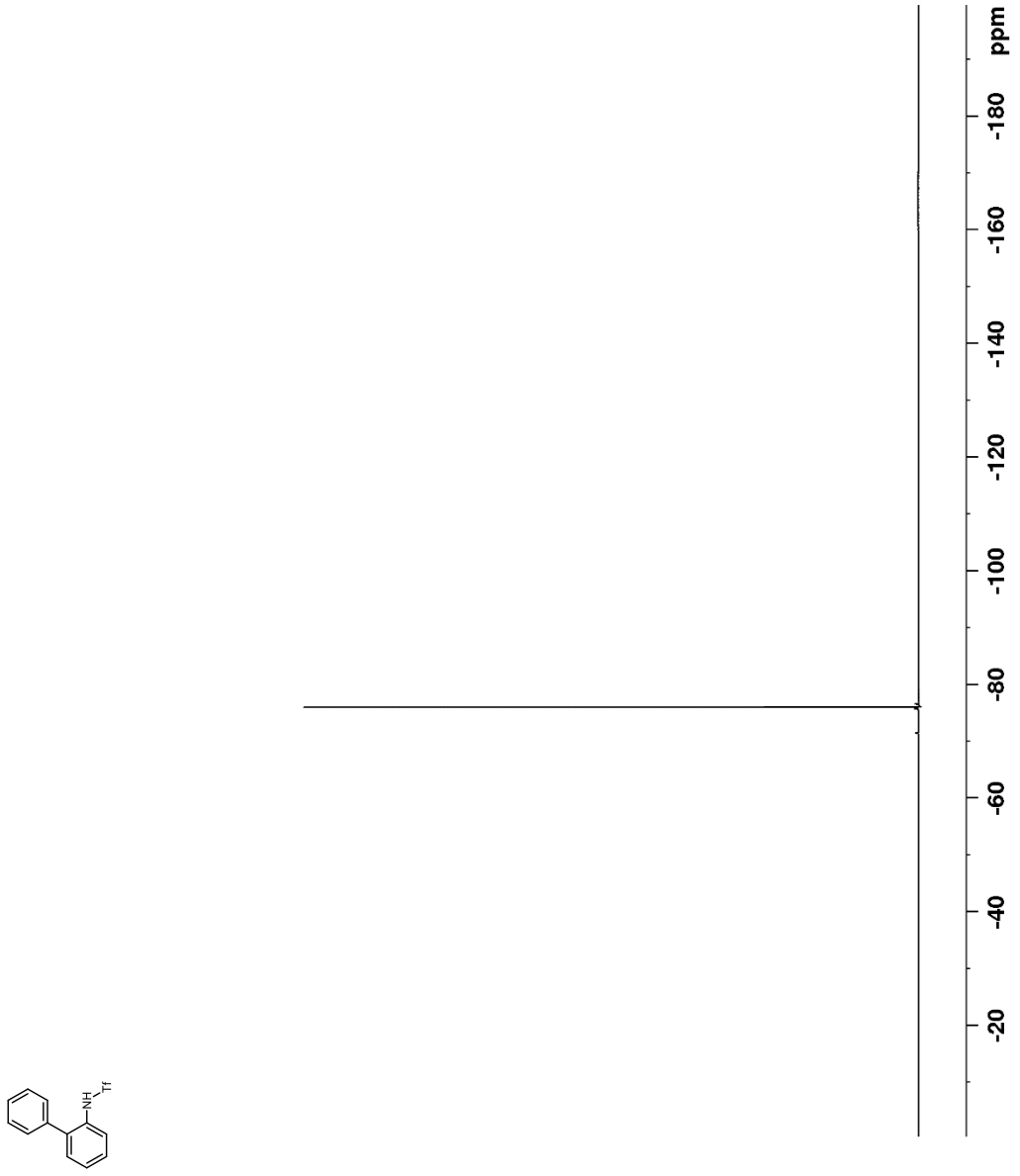


Figure 22. ^{1}H NMR (400 MHz, $CDCl_3$) of **2k**

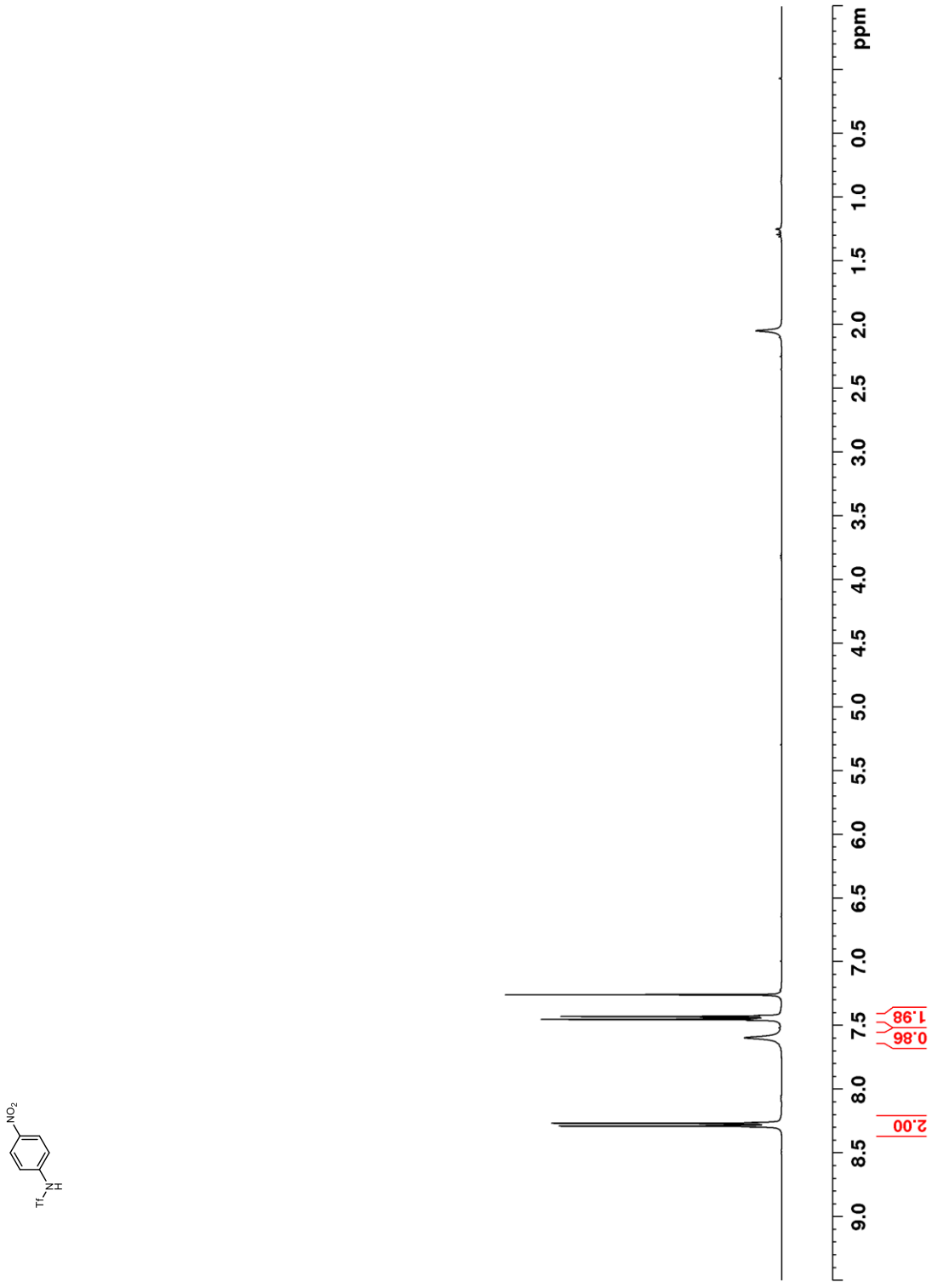


Figure 23. ^{13}C NMR (100 MHz, $CDCl_3$) of **2k**

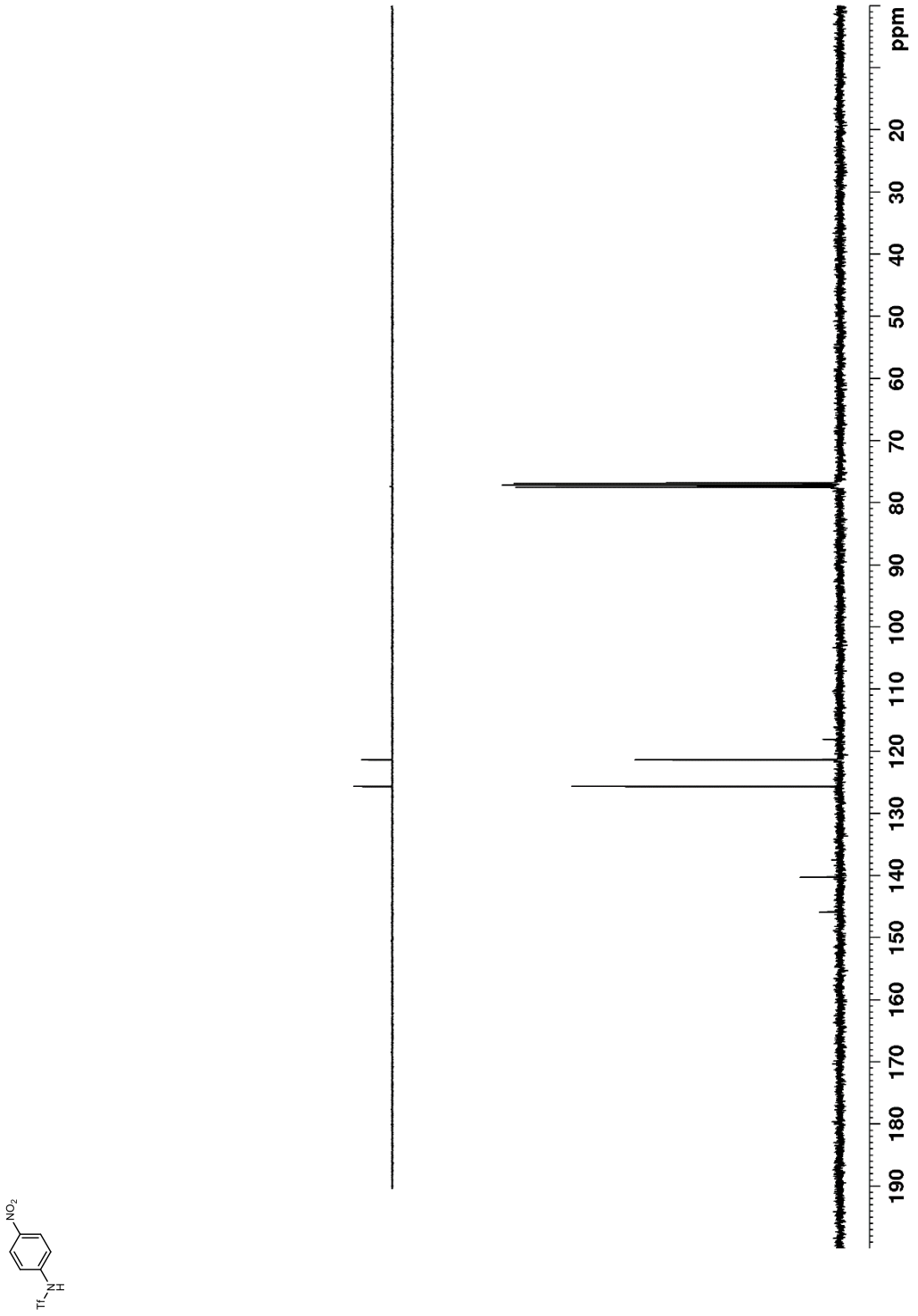


Figure 24. ^{19}F NMR (376 MHz, $CDCl_3$) of **2k**

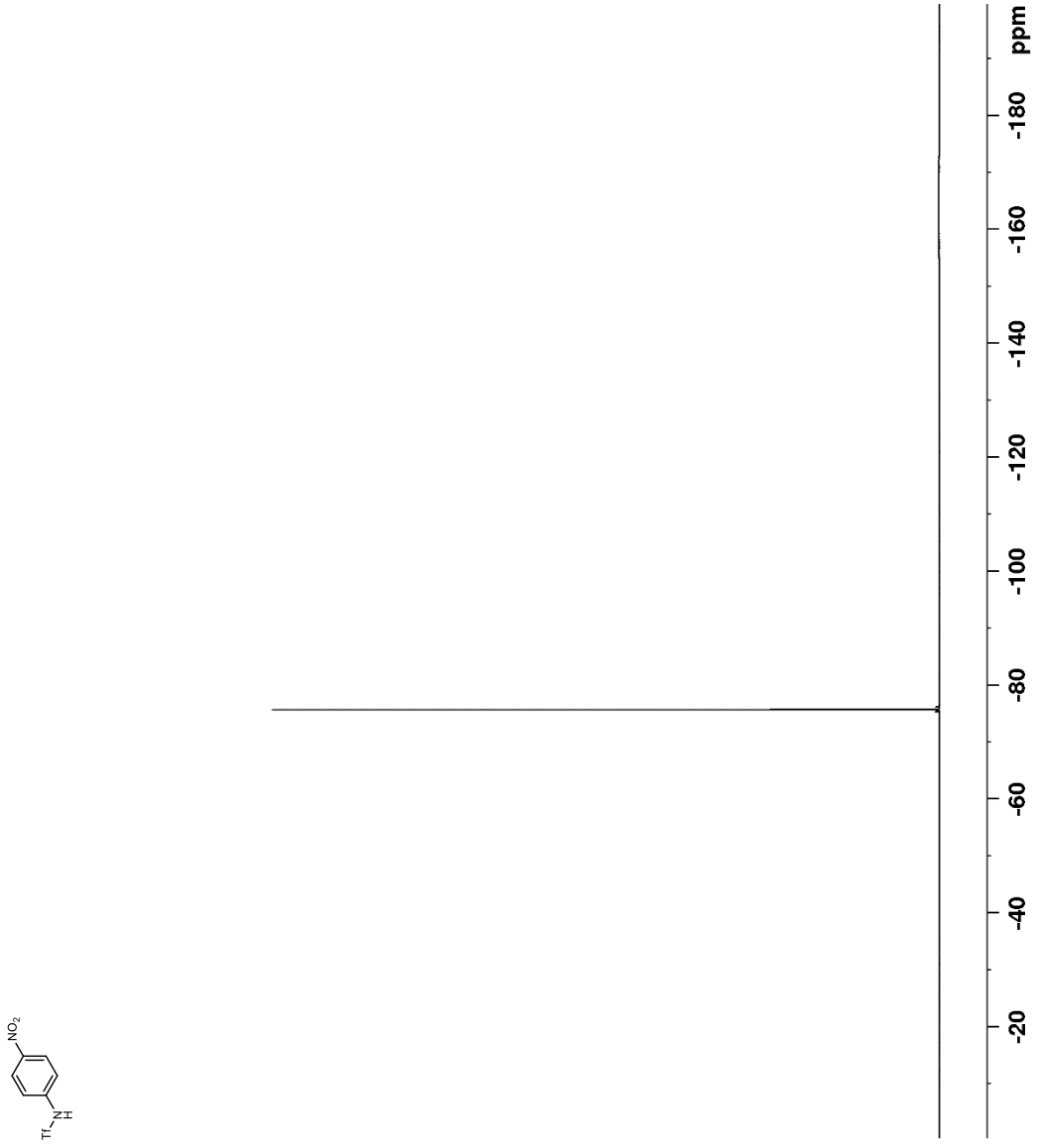


Figure 25. ^{1}H NMR (400 MHz, $CDCl_3$) of **2j**

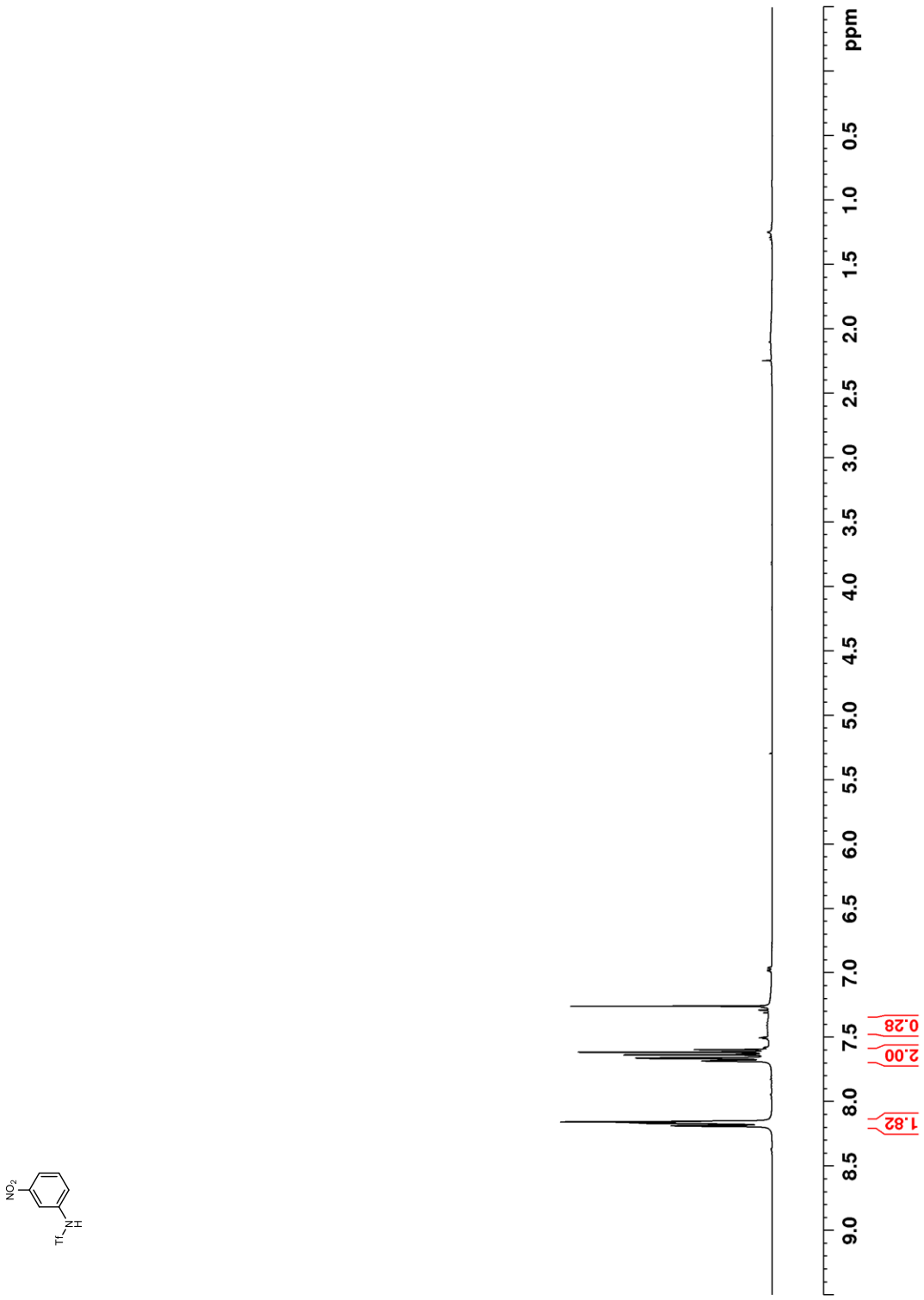


Figure 26. ^{13}C NMR (100 MHz, $CDCl_3$) of **2j**

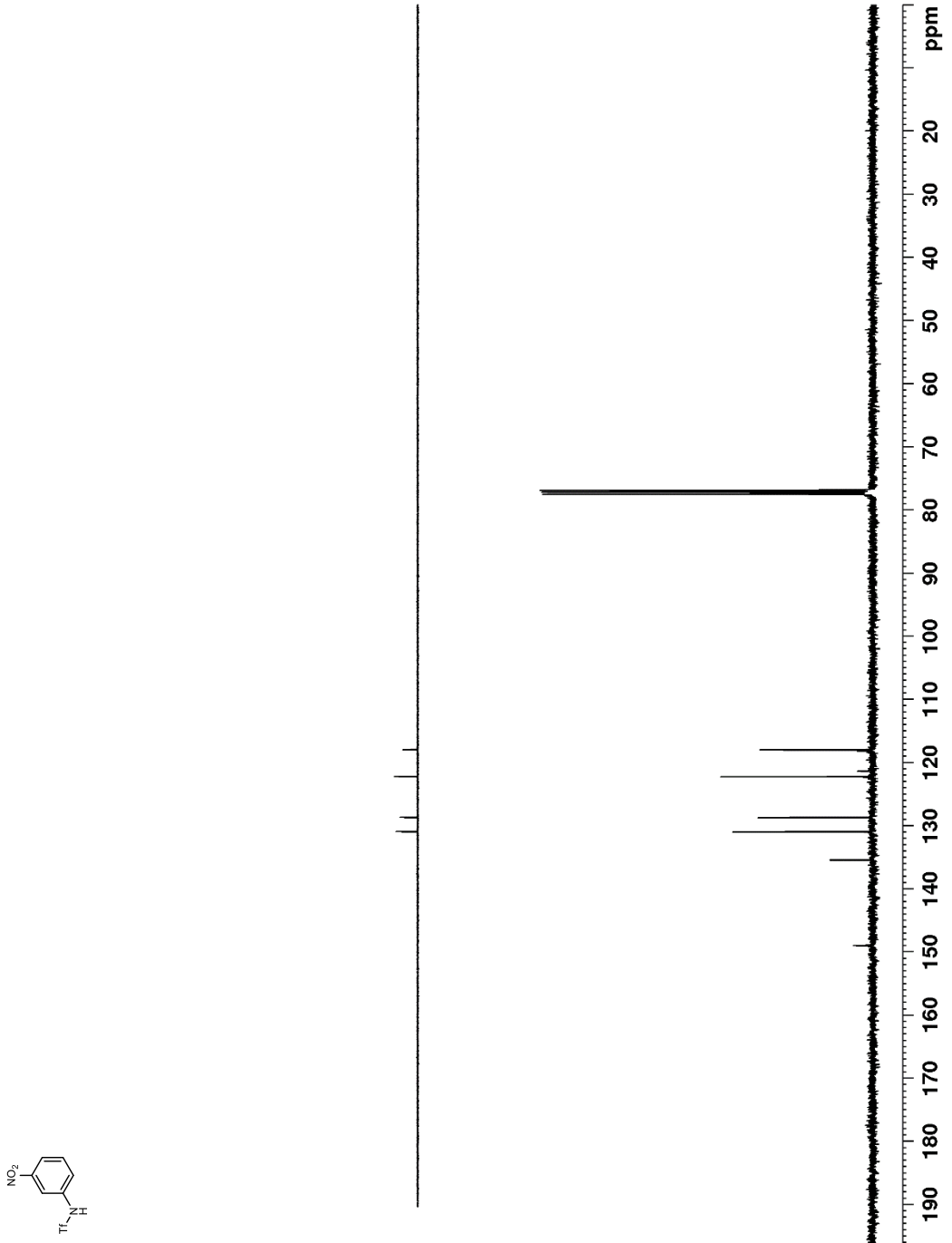


Figure 27. ^{19}F NMR (376 MHz, $CDCl_3$) of **2j**

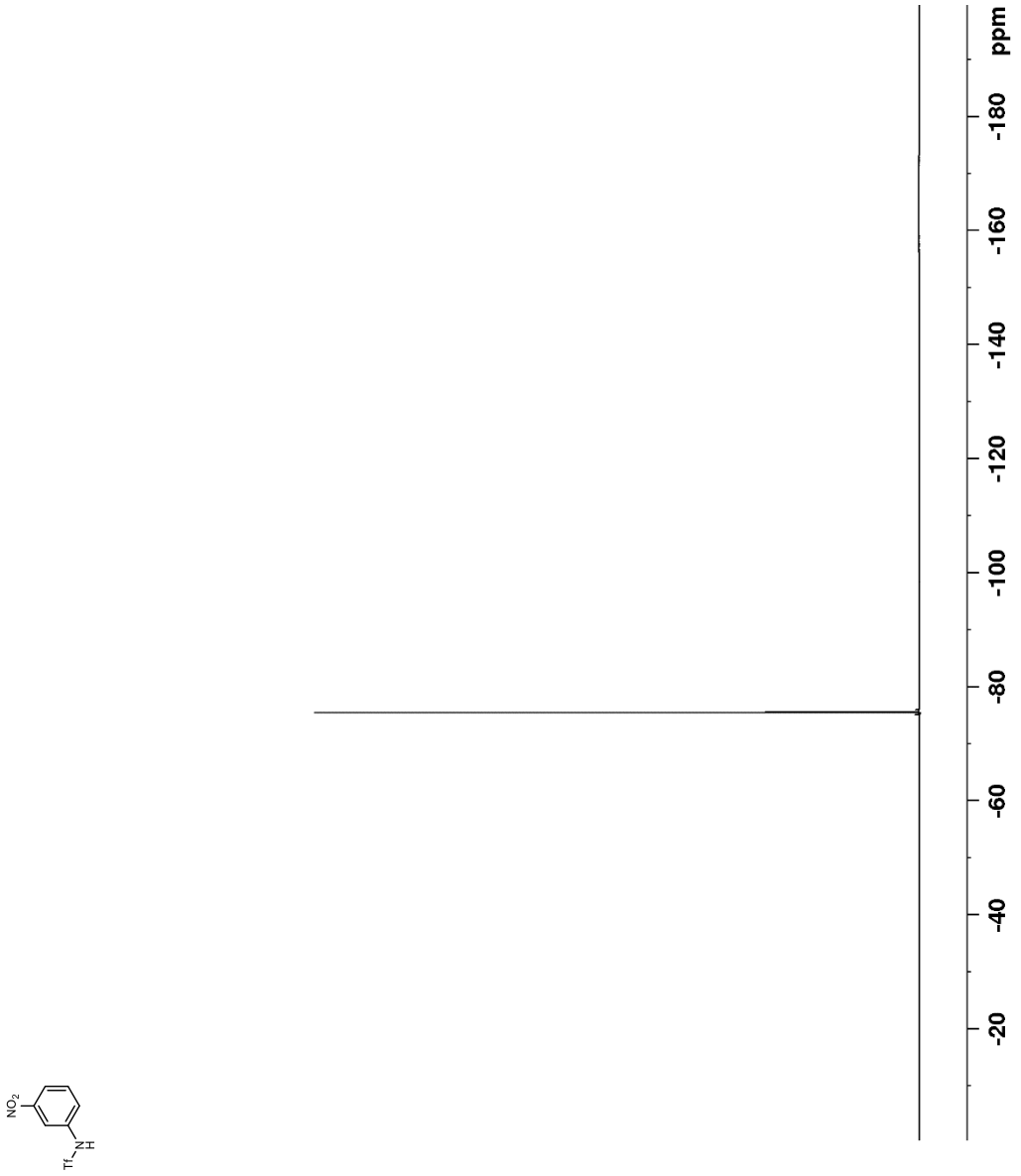


Figure 28. ^{1}H NMR (400 MHz, $CDCl_3$) of **2m**

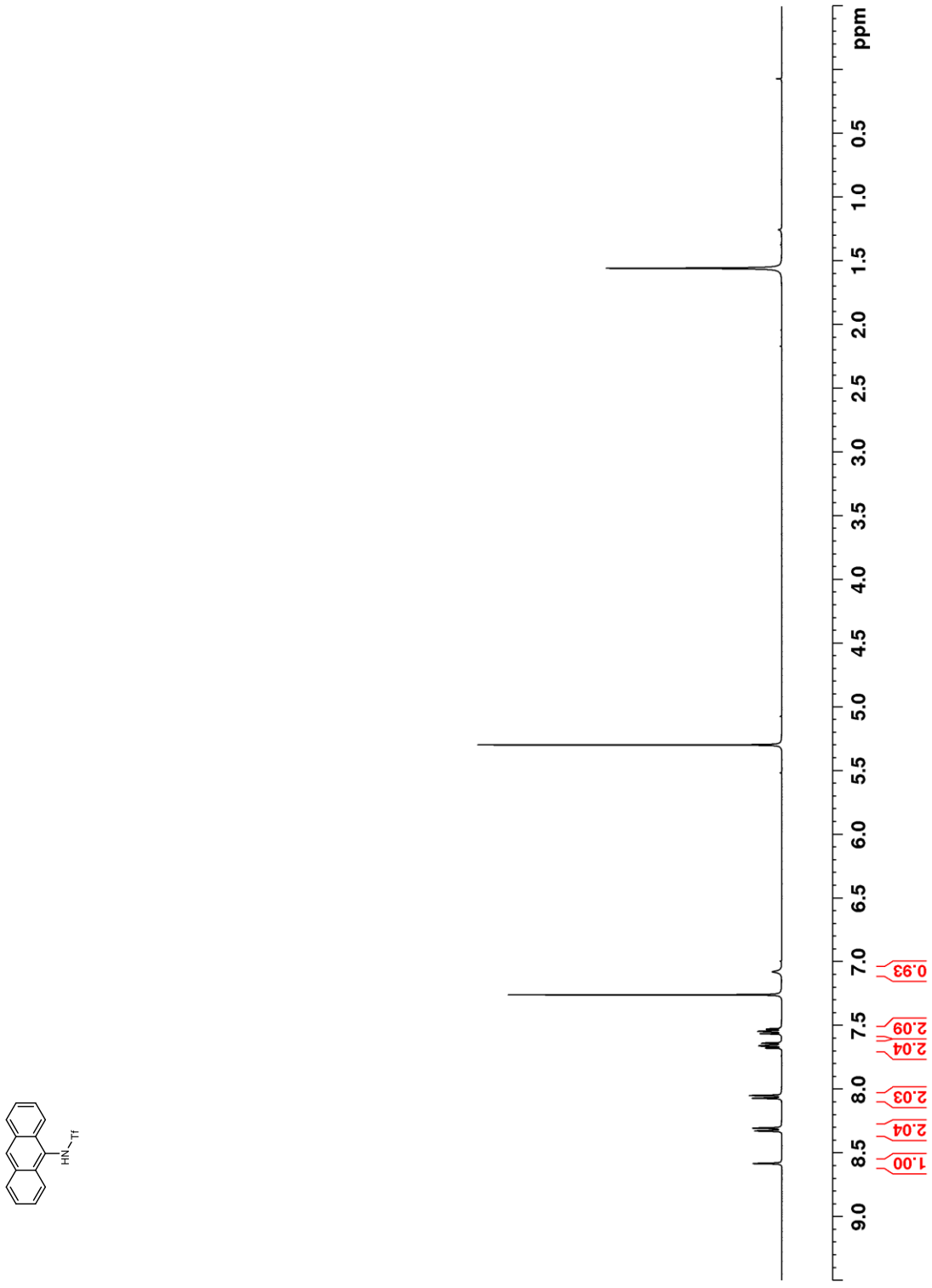


Figure 29. ^{13}C NMR (100 MHz, $CDCl_3$) of **2m**

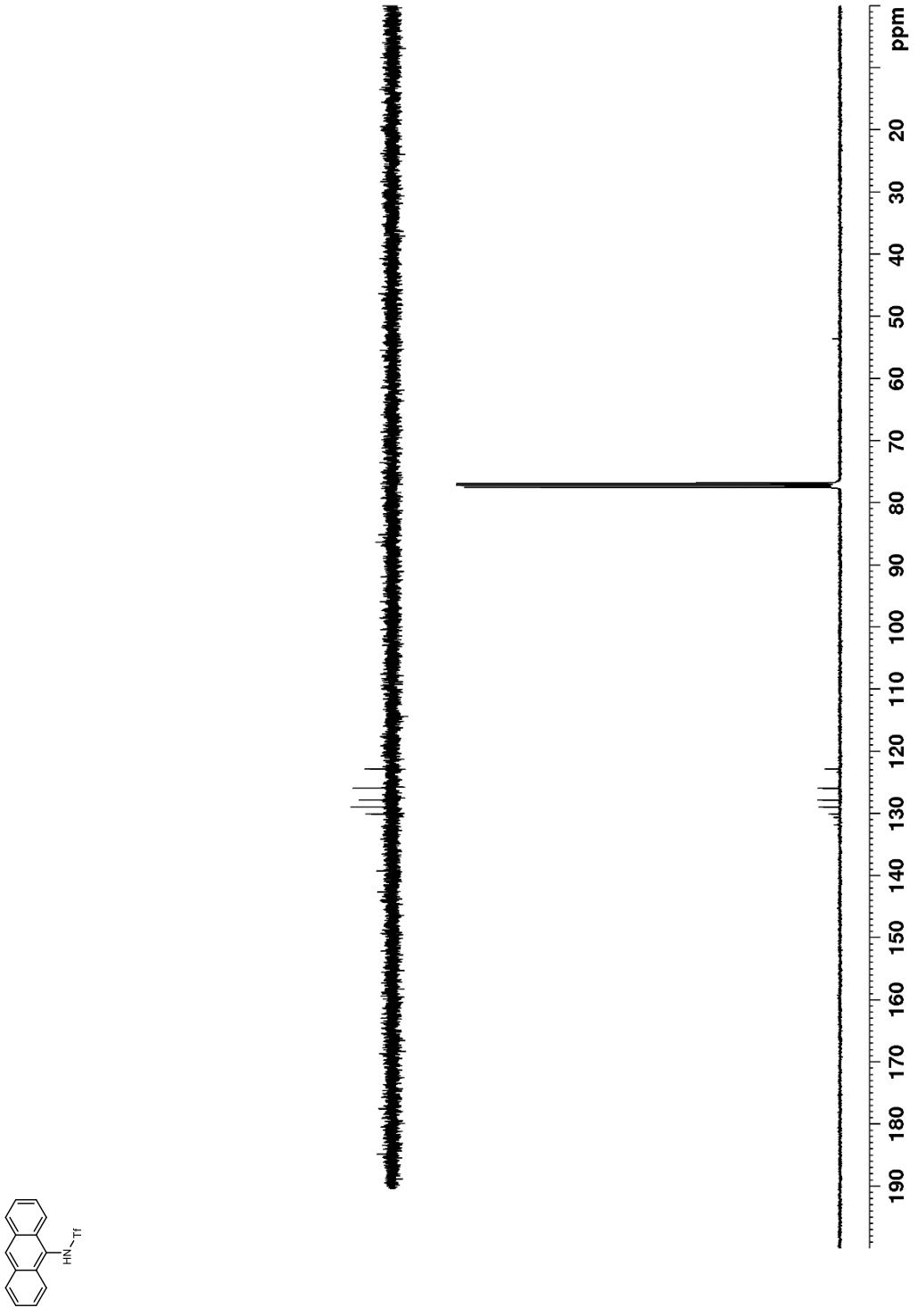


Figure 30. ^{19}F NMR (376 MHz, $CDCl_3$) of **2m**

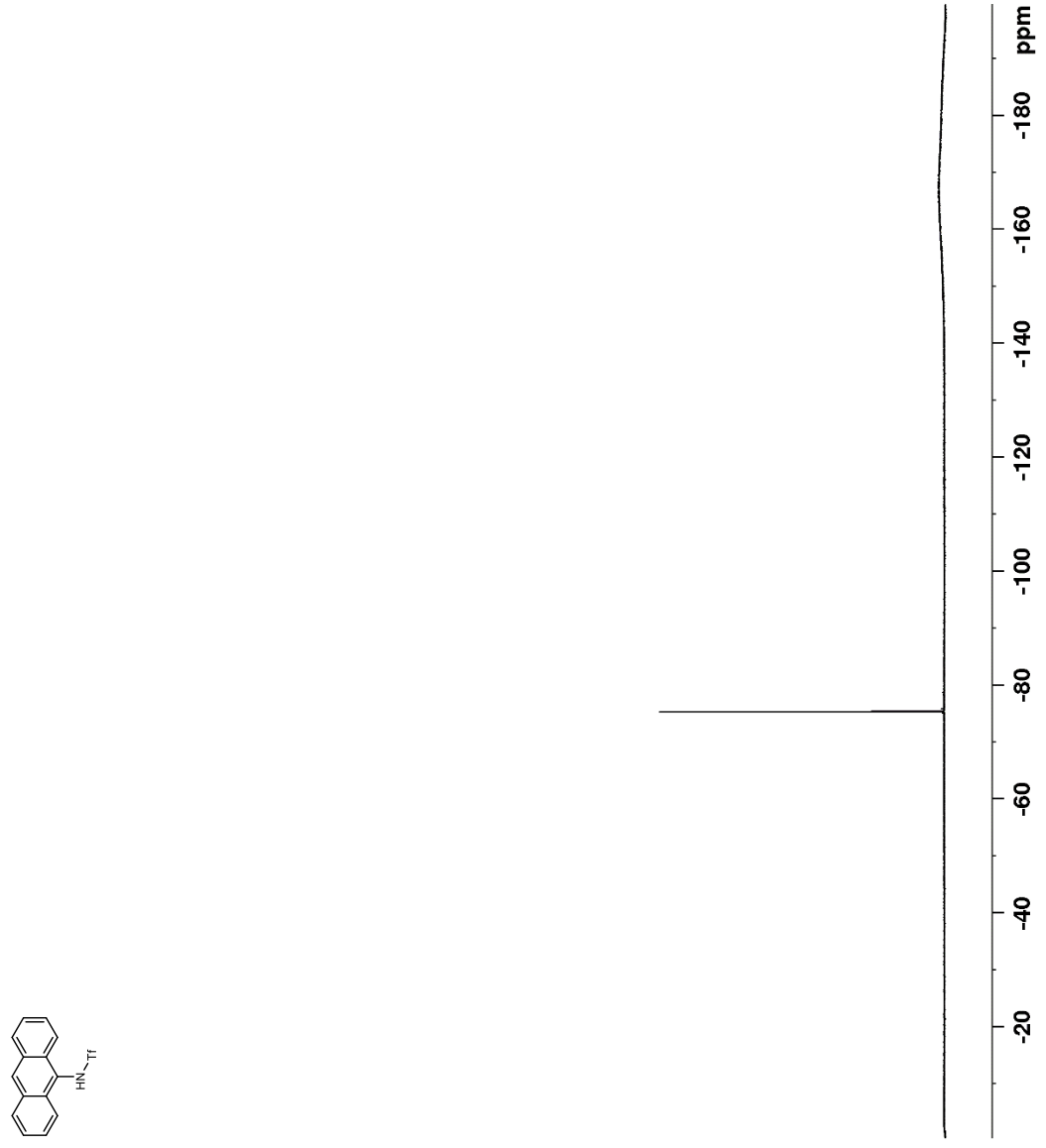


Figure 31. ^{1}H NMR (400 MHz, $CDCl_3$) of **4d**

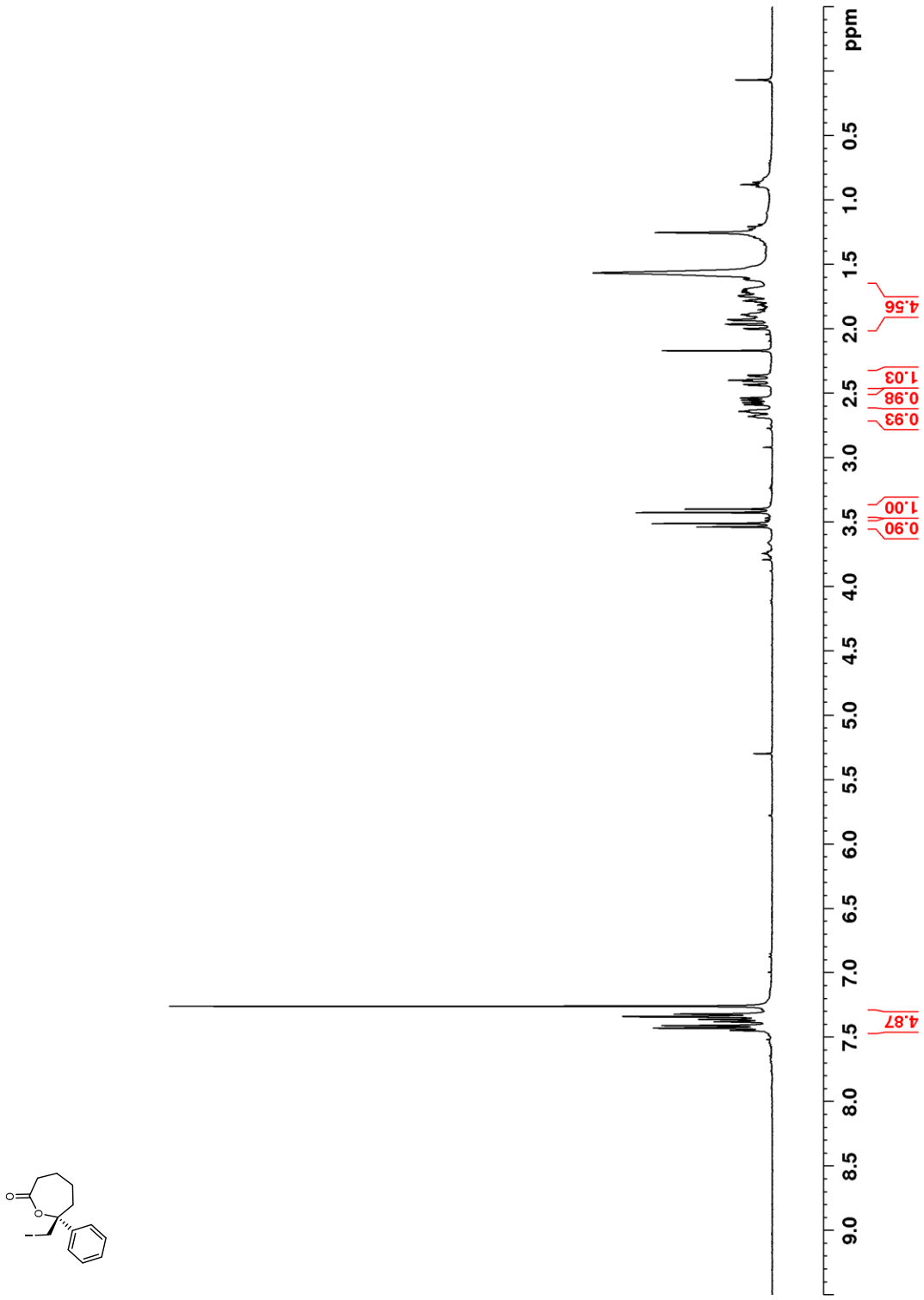


Figure 32. ^{13}C NMR (100 MHz, $CDCl_3$) of **4d**

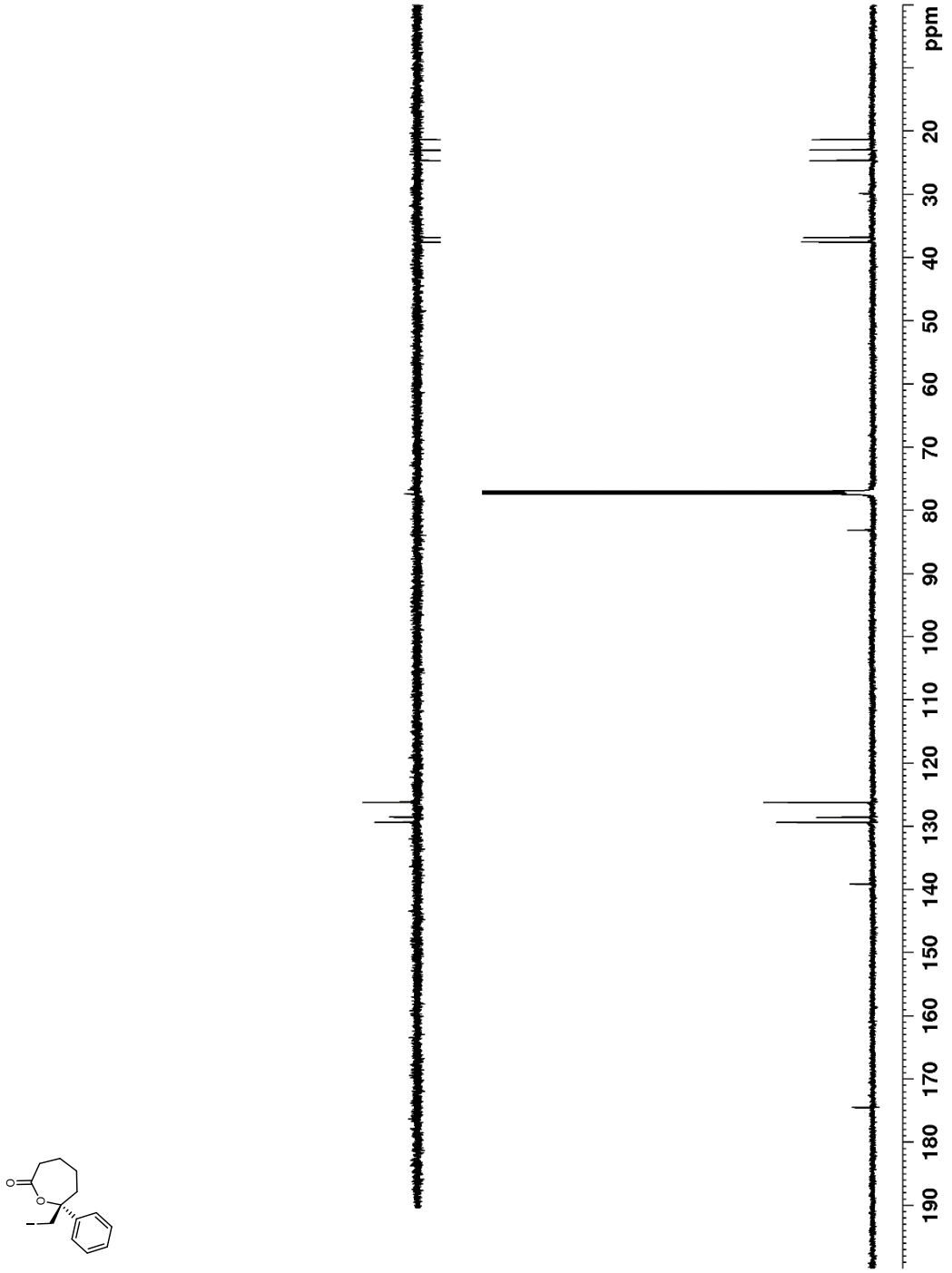


Figure 33. ^{1}H NMR (400 MHz, $CDCl_3$) of **4v**

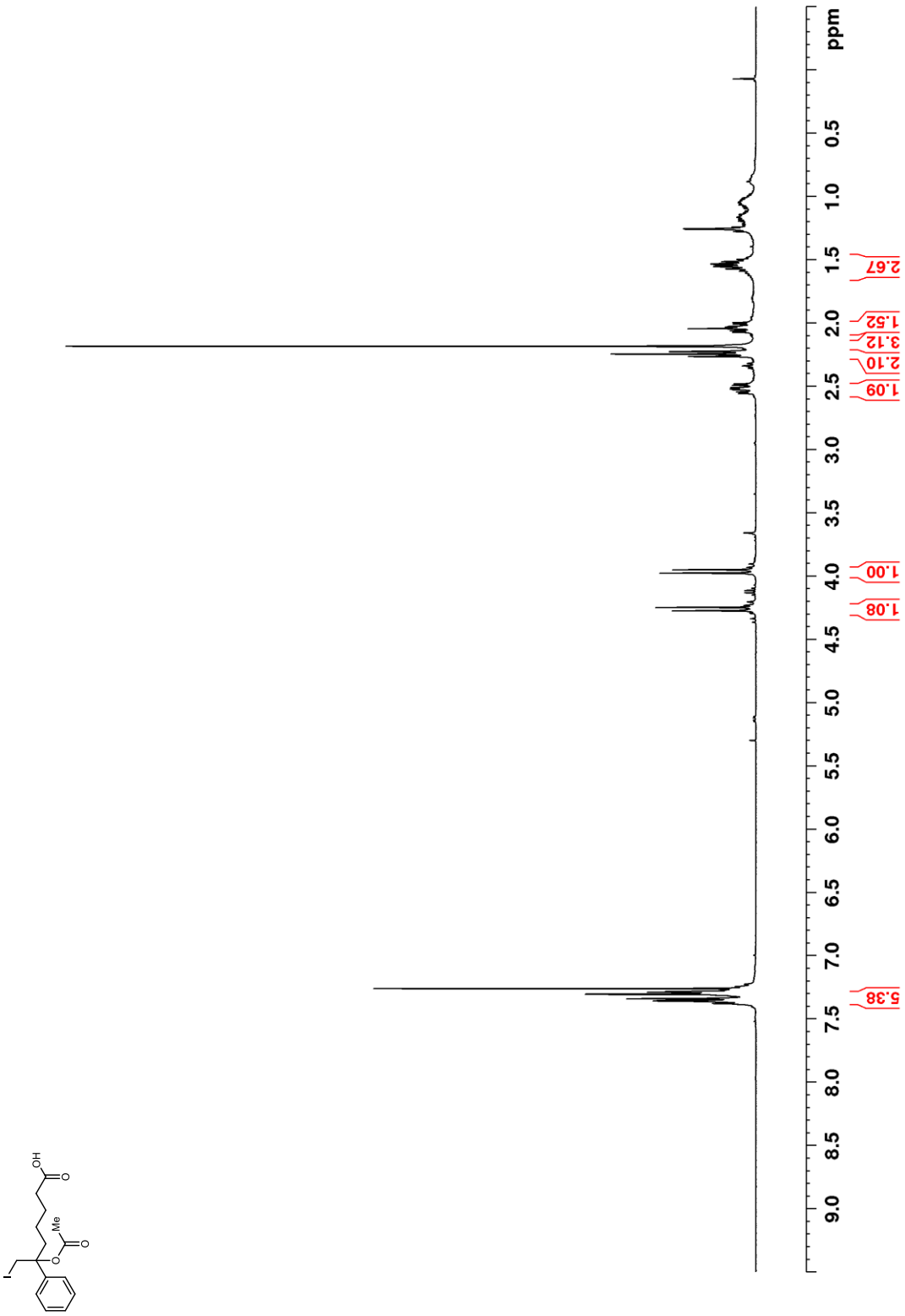


Figure 34. ^{13}C NMR (100 MHz, $CDCl_3$) of **4v**

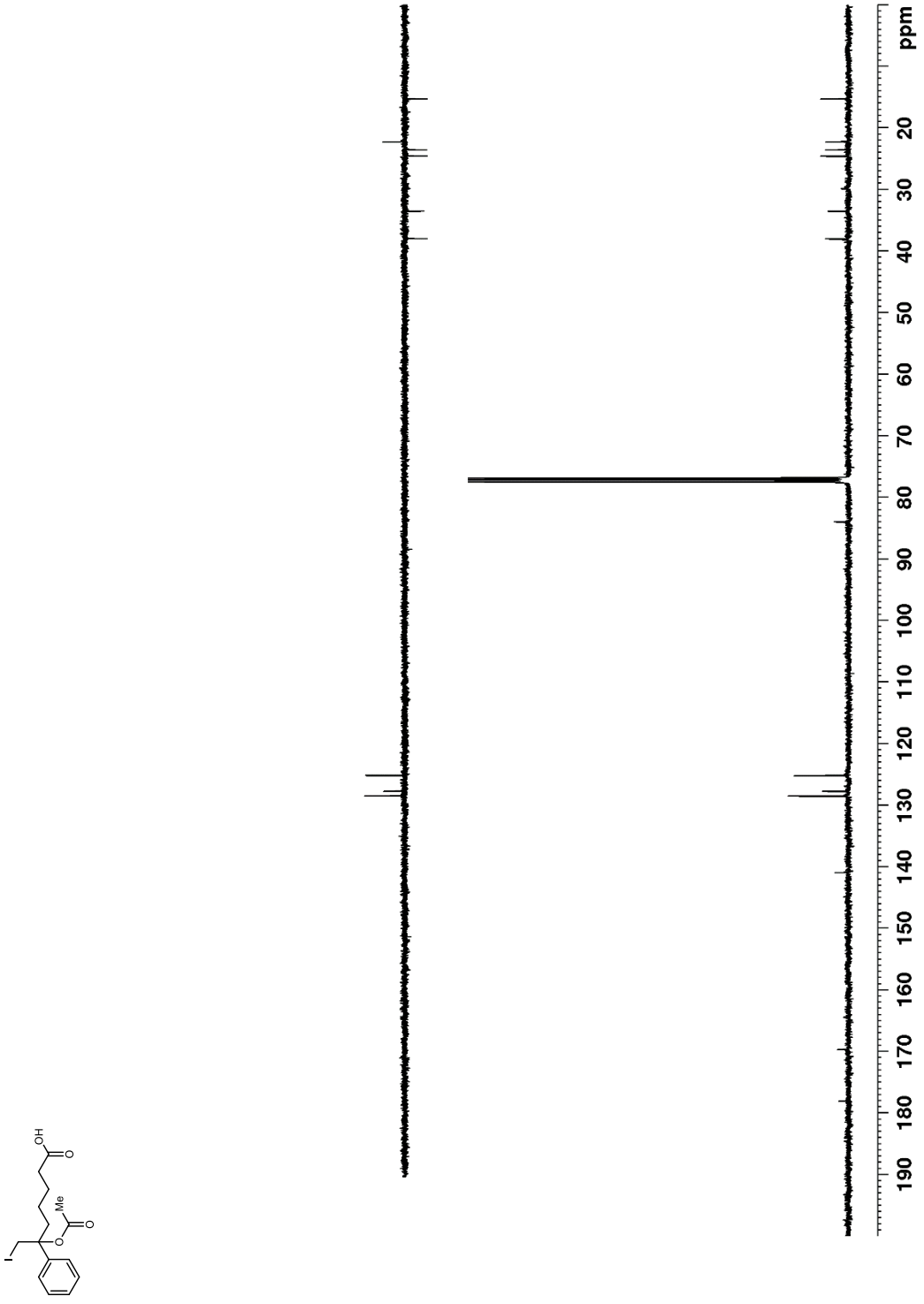


Figure 35. ^{1}H NMR (400 MHz, $CDCl_3$) of **4ba**

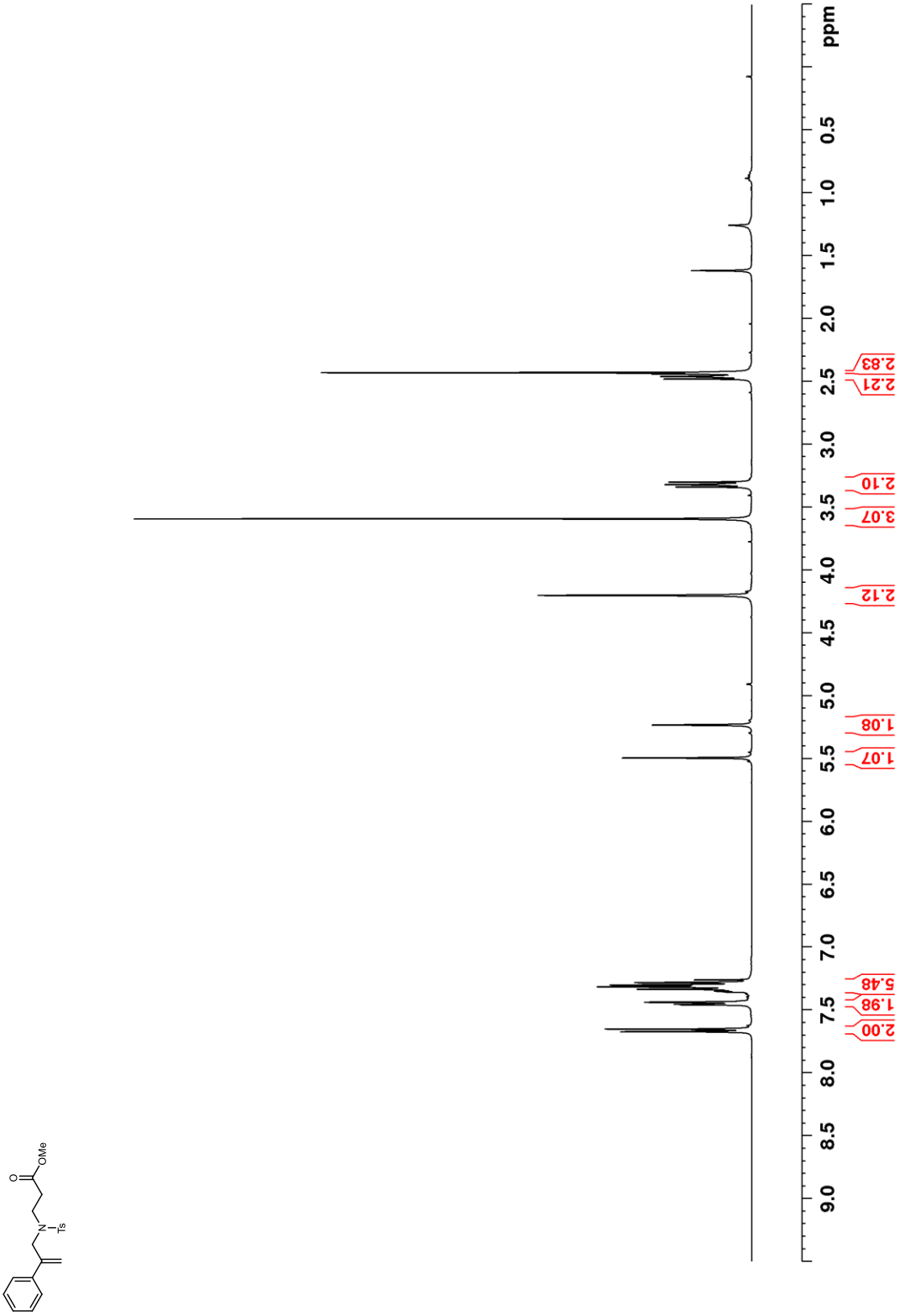


Figure 36. ^{13}C NMR (100 MHz, $CDCl_3$) of **4ba**

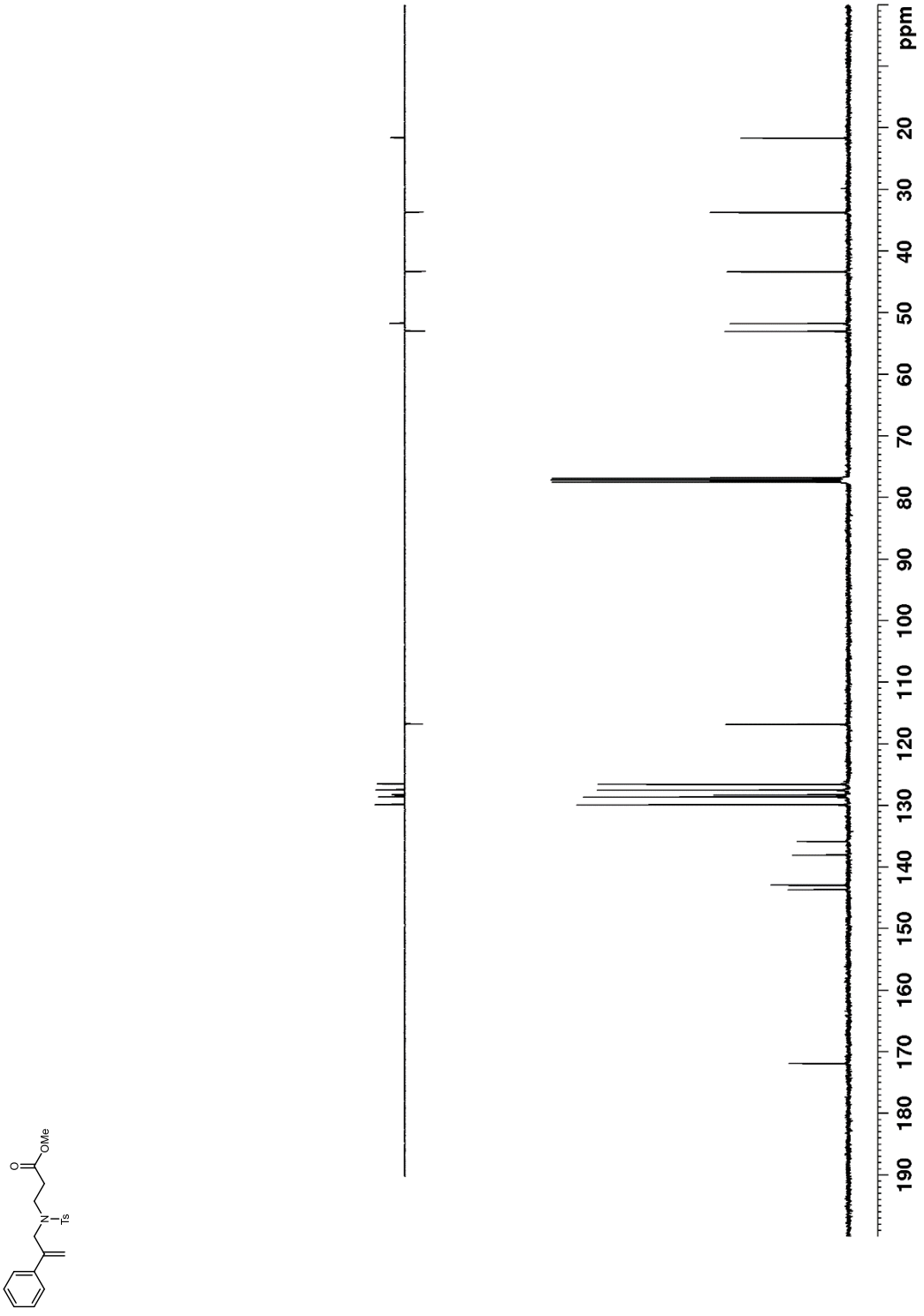


Figure 37. ^{1}H NMR (400 MHz, $CDCl_3$) of **4bb**

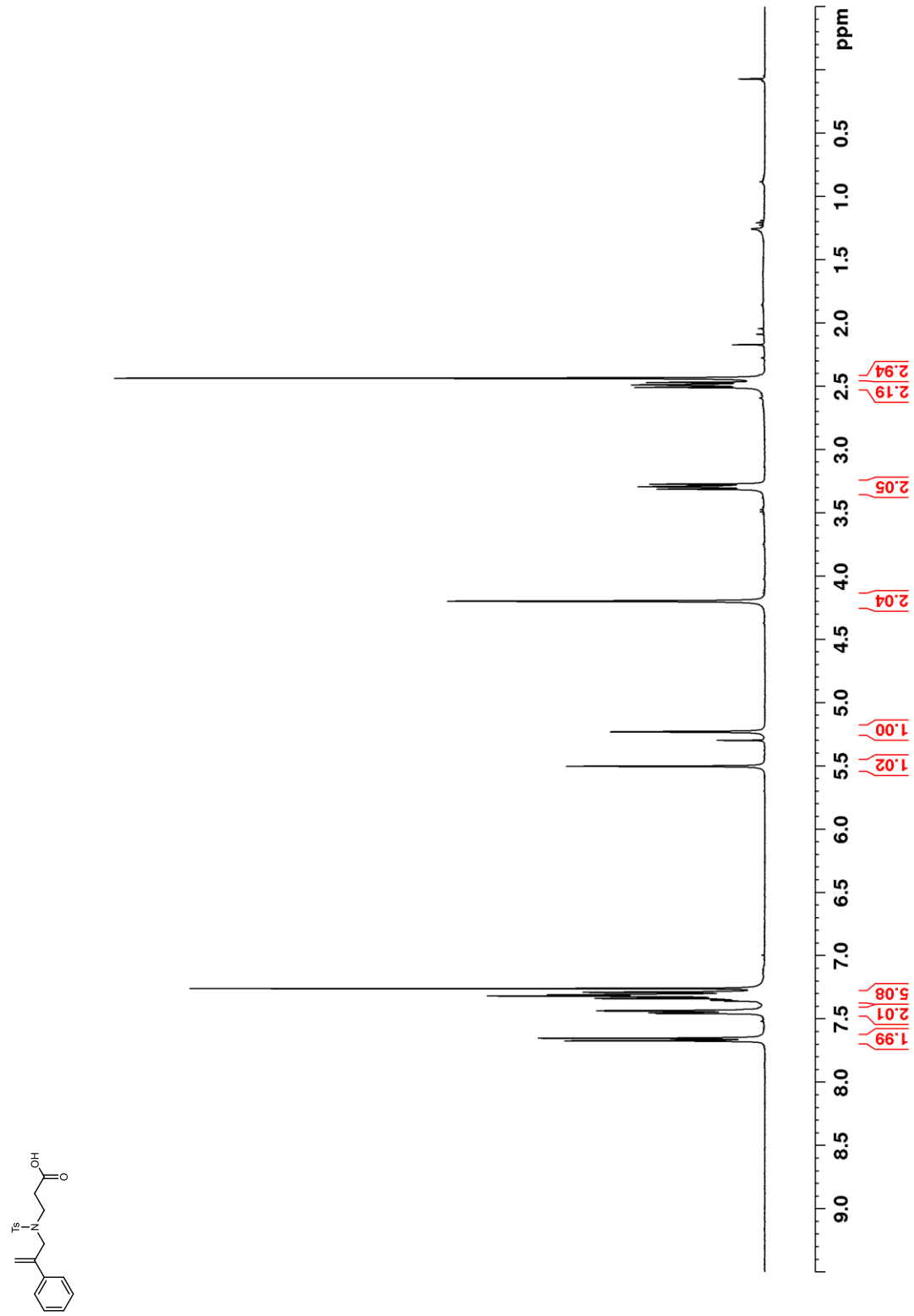


Figure 38. ^{13}C NMR (100 MHz, $CDCl_3$) of **4bb**

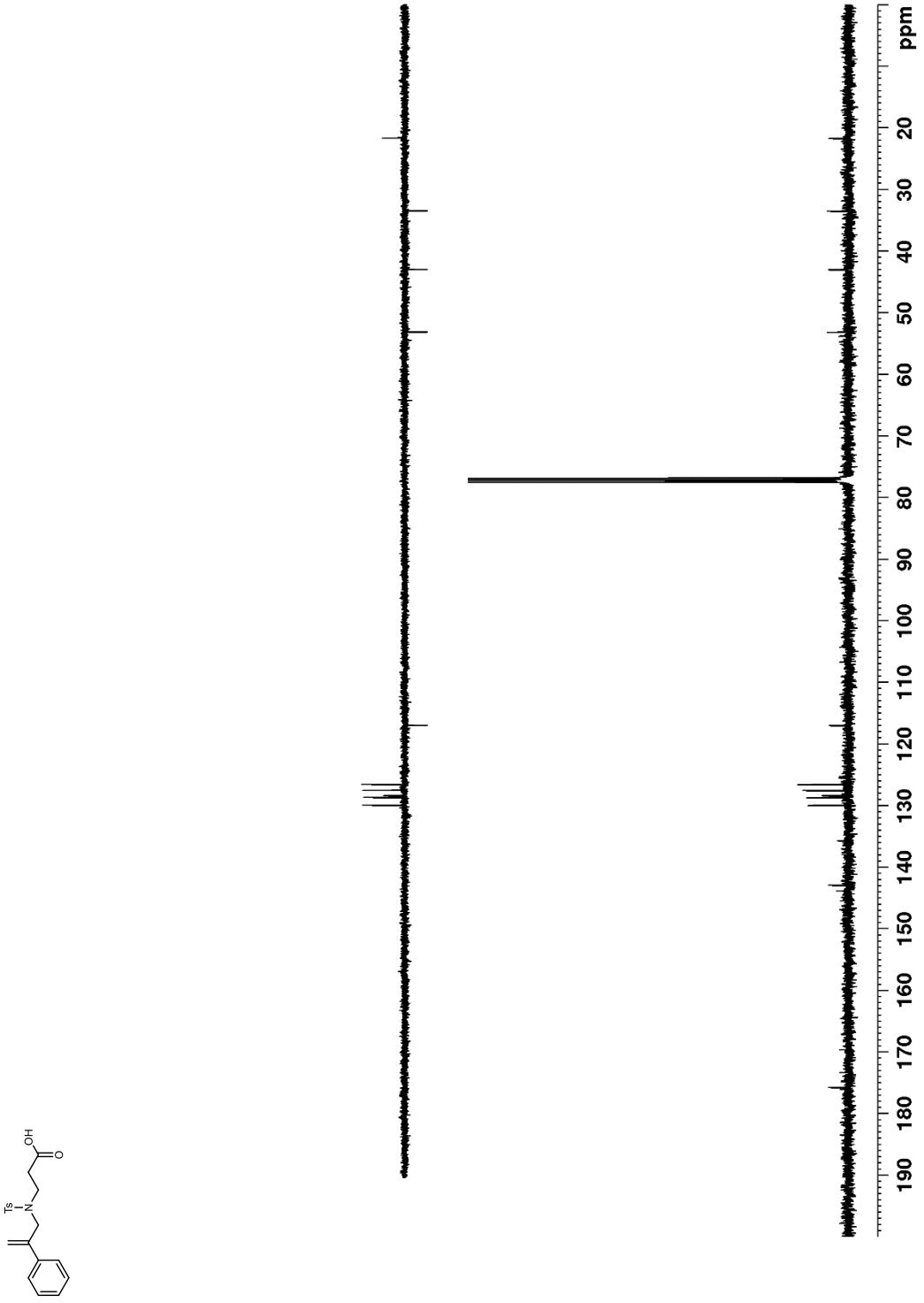


Figure 39. ^{1}H NMR (400 MHz, $CDCl_3$) of **4bh**

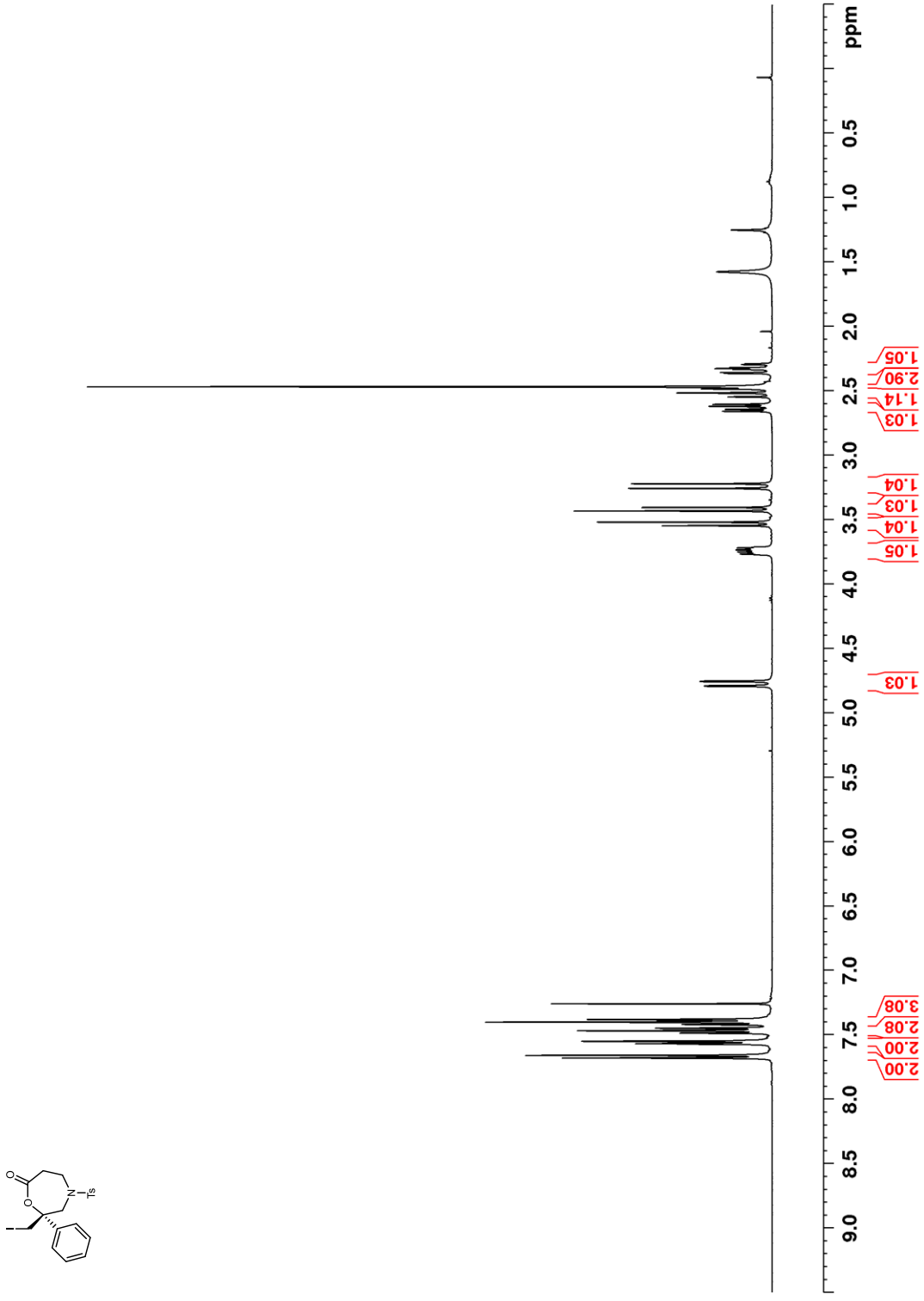


Figure 40. ^{13}C NMR (100 MHz, $CDCl_3$) of **4bh**

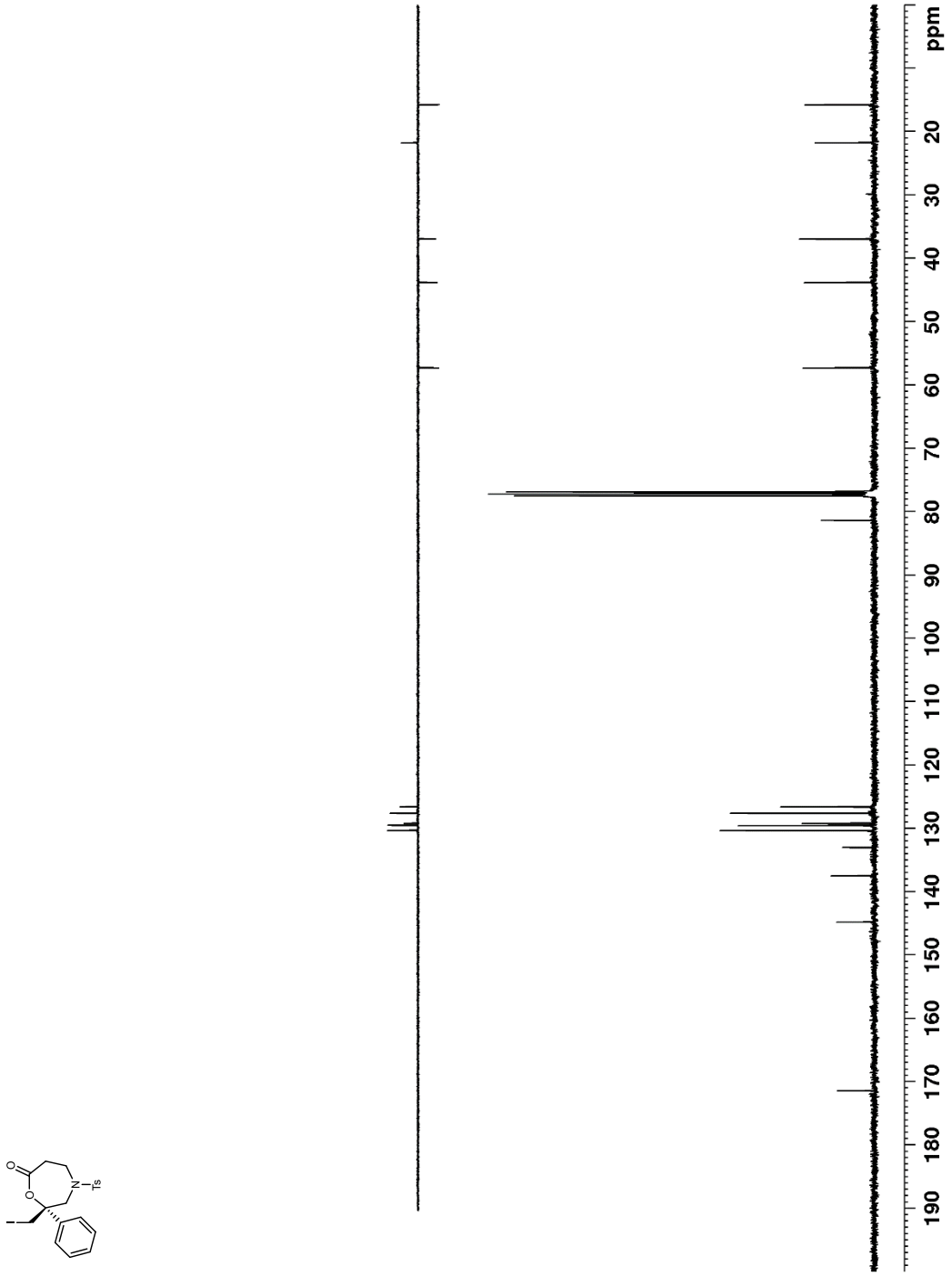


Figure 41. ^{1}H NMR (400 MHz, $CDCl_3$) of **4at**

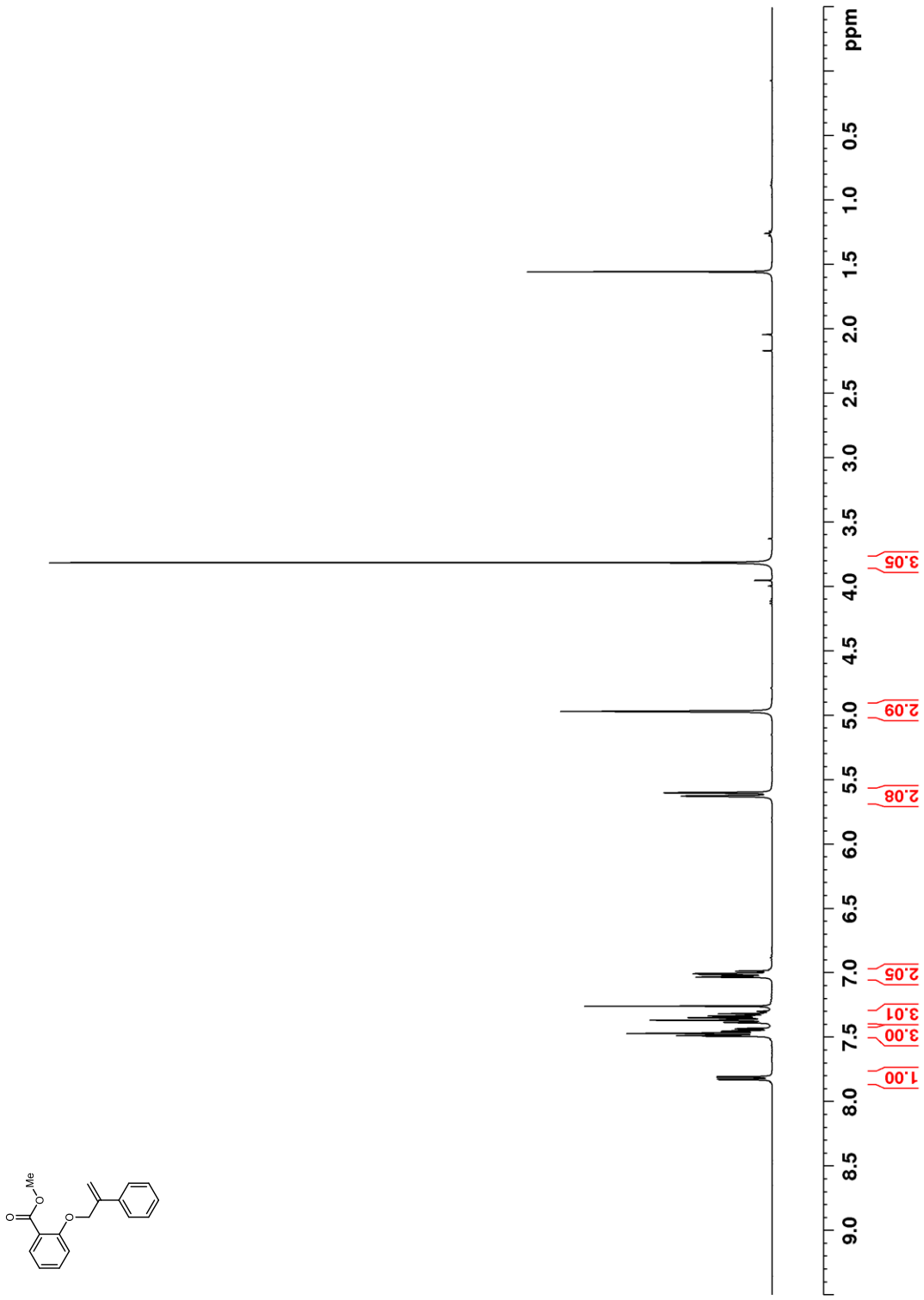


Figure 42. ^{13}C NMR (100 MHz, $CDCl_3$) of **4at**

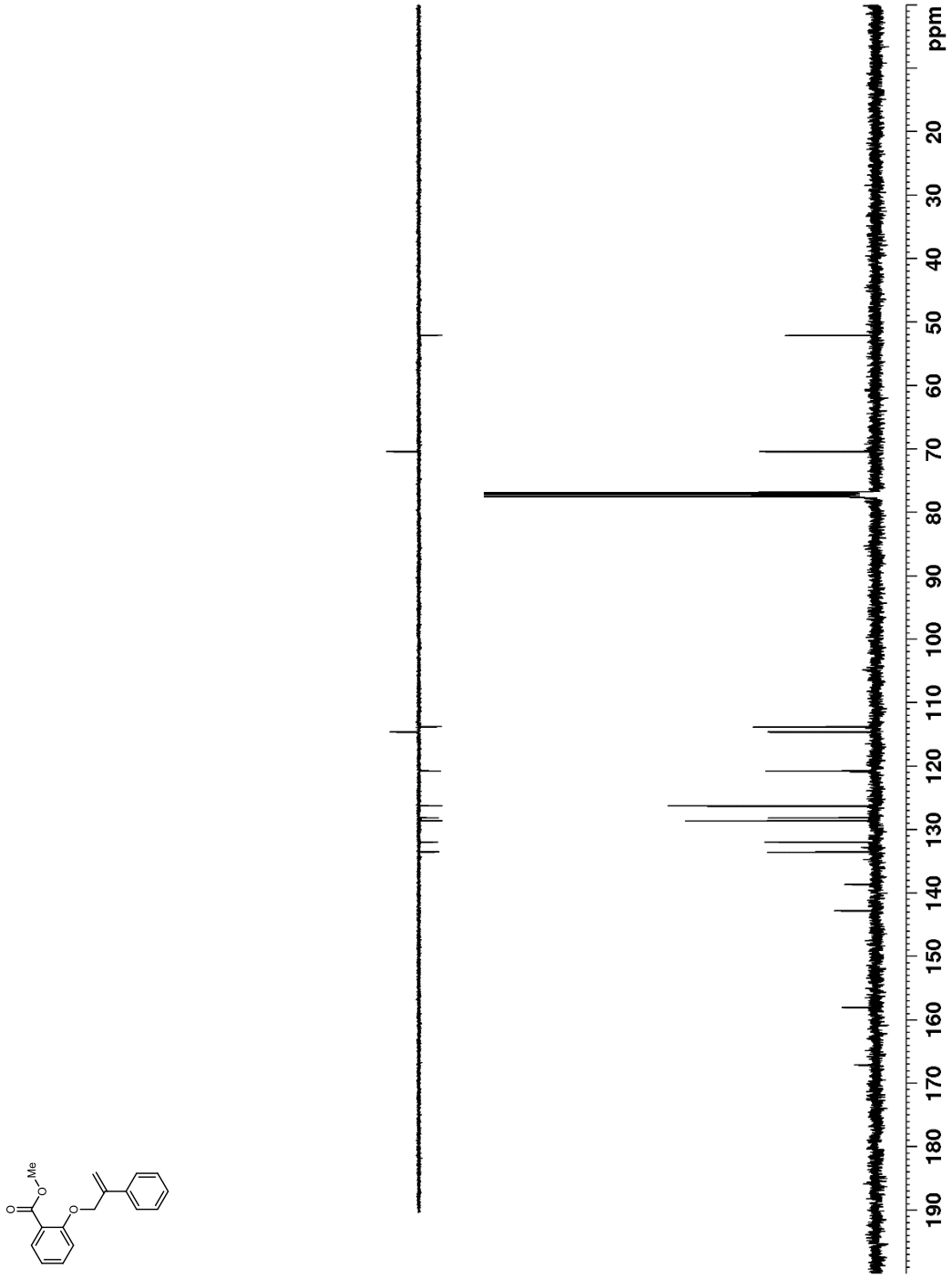


Figure 43. ^{1}H NMR (400 MHz, $CDCl_3$) of **4au**

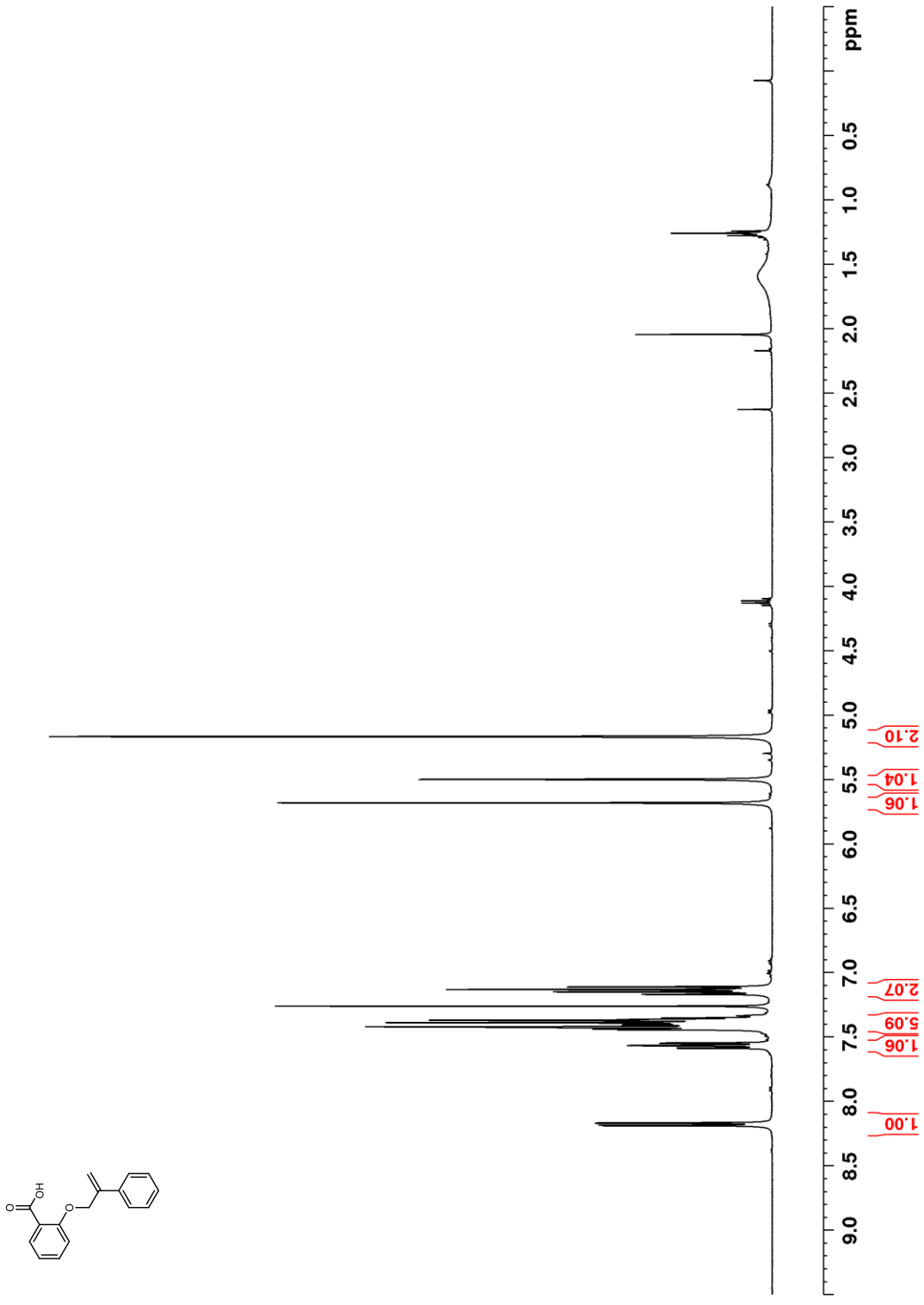


Figure 44. ^{13}C NMR (100 MHz, $CDCl_3$) of **4au**

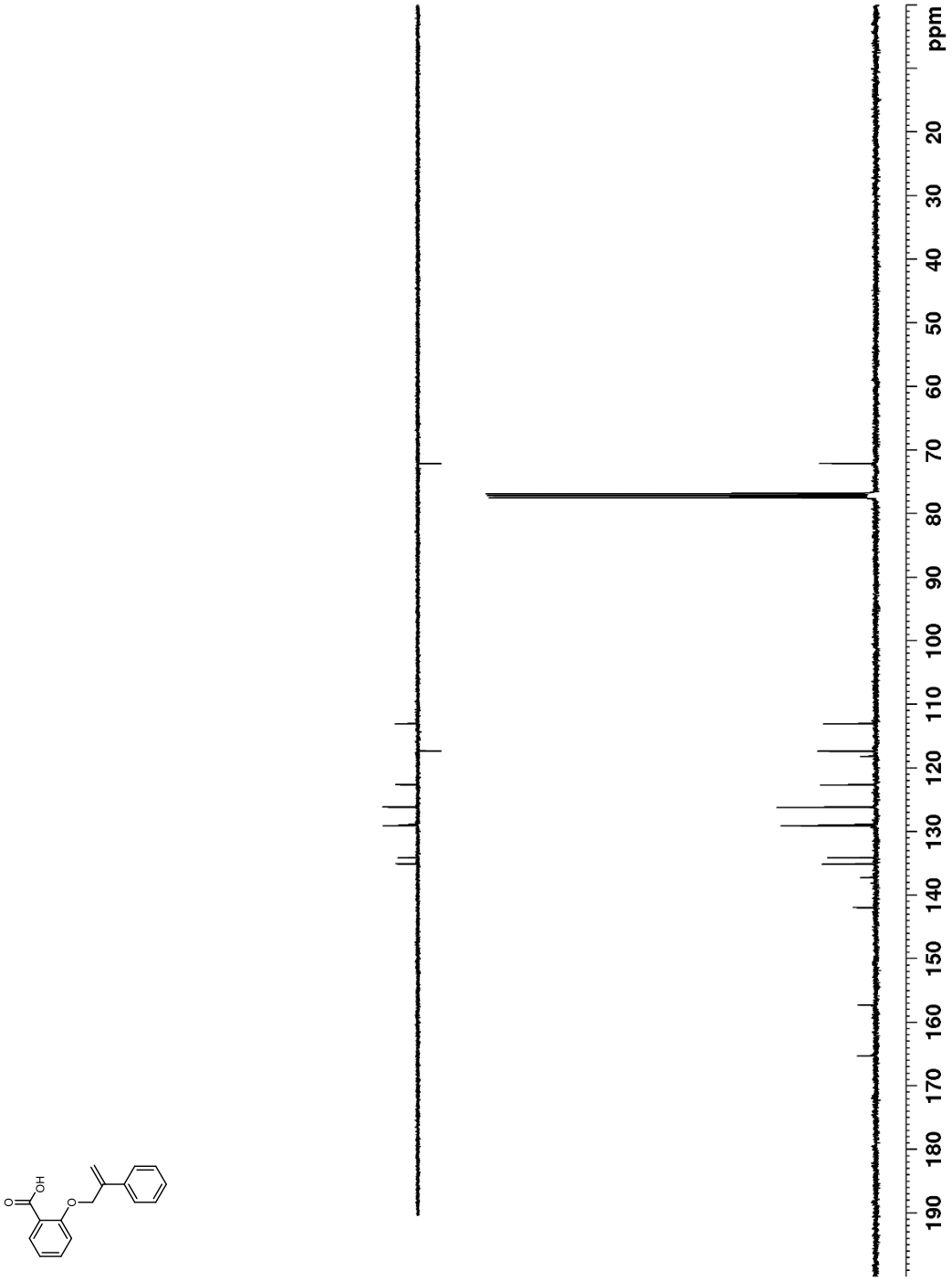


Figure 45. ^{1}H NMR (400 MHz, $CDCl_3$) of **4bg**

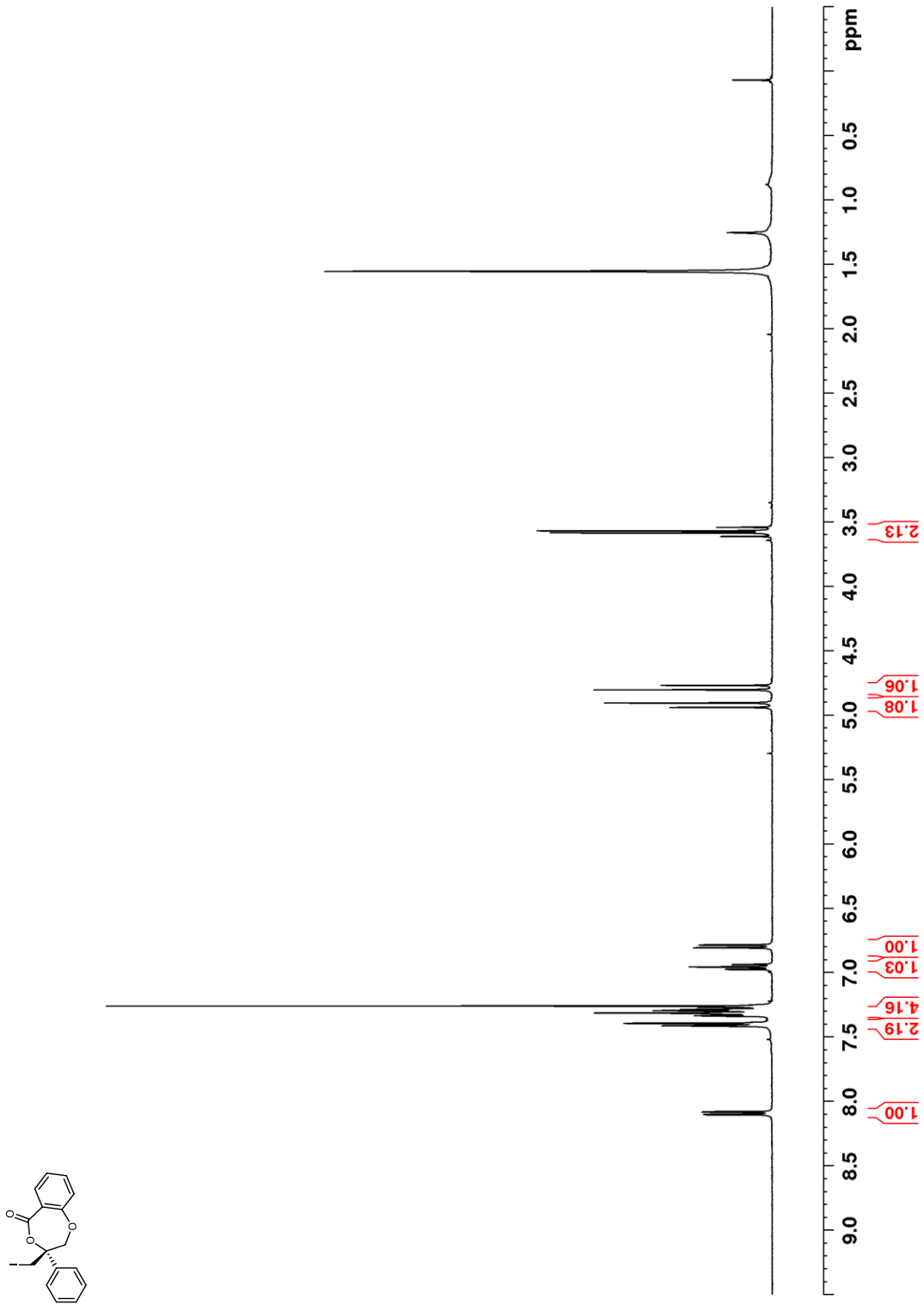


Figure 46. ^{13}C NMR (100 MHz, $CDCl_3$) of **4bg**

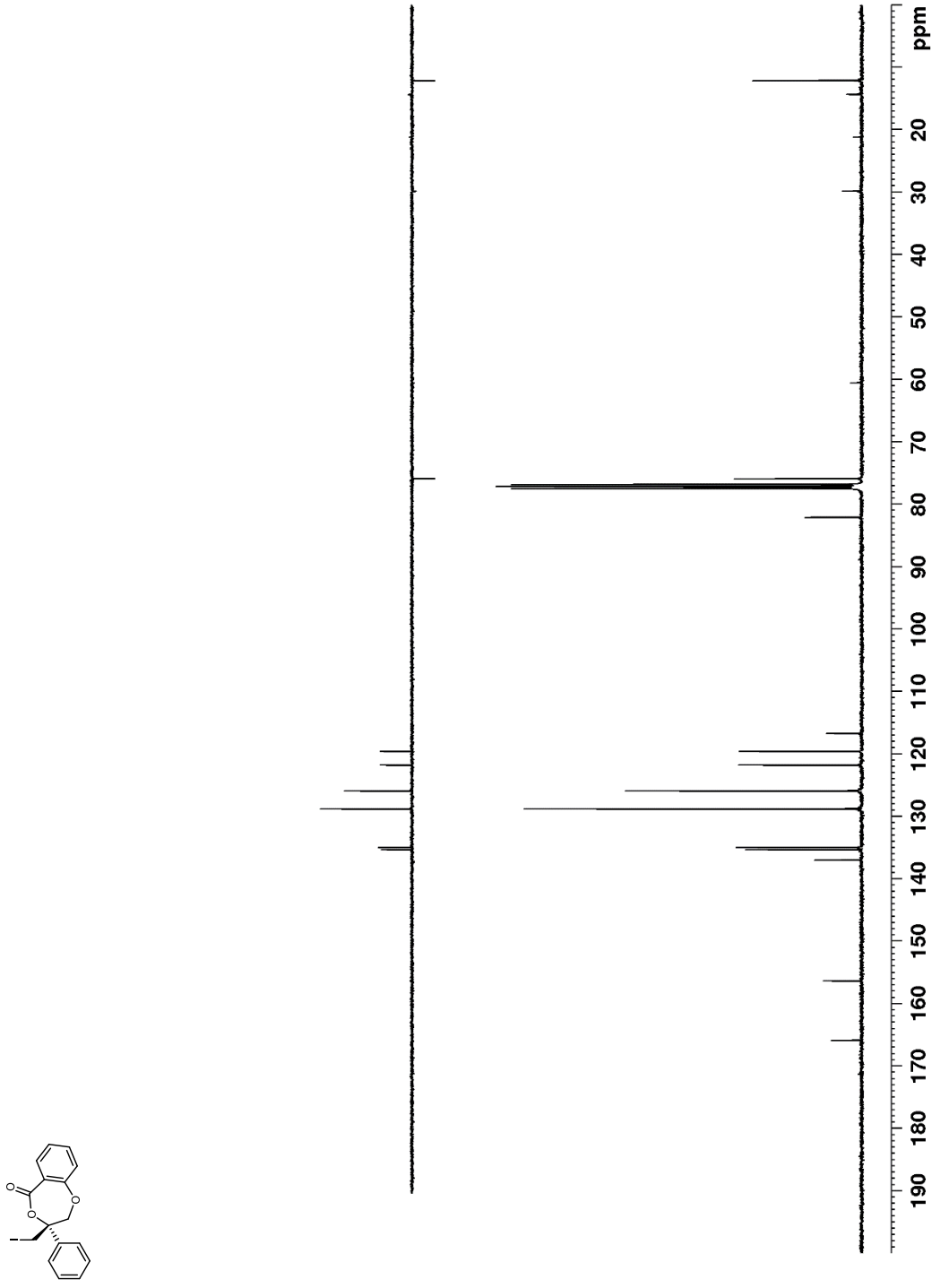


Figure 47. ^{1}H NMR (400 MHz, $CDCl_3$) of **4bd**

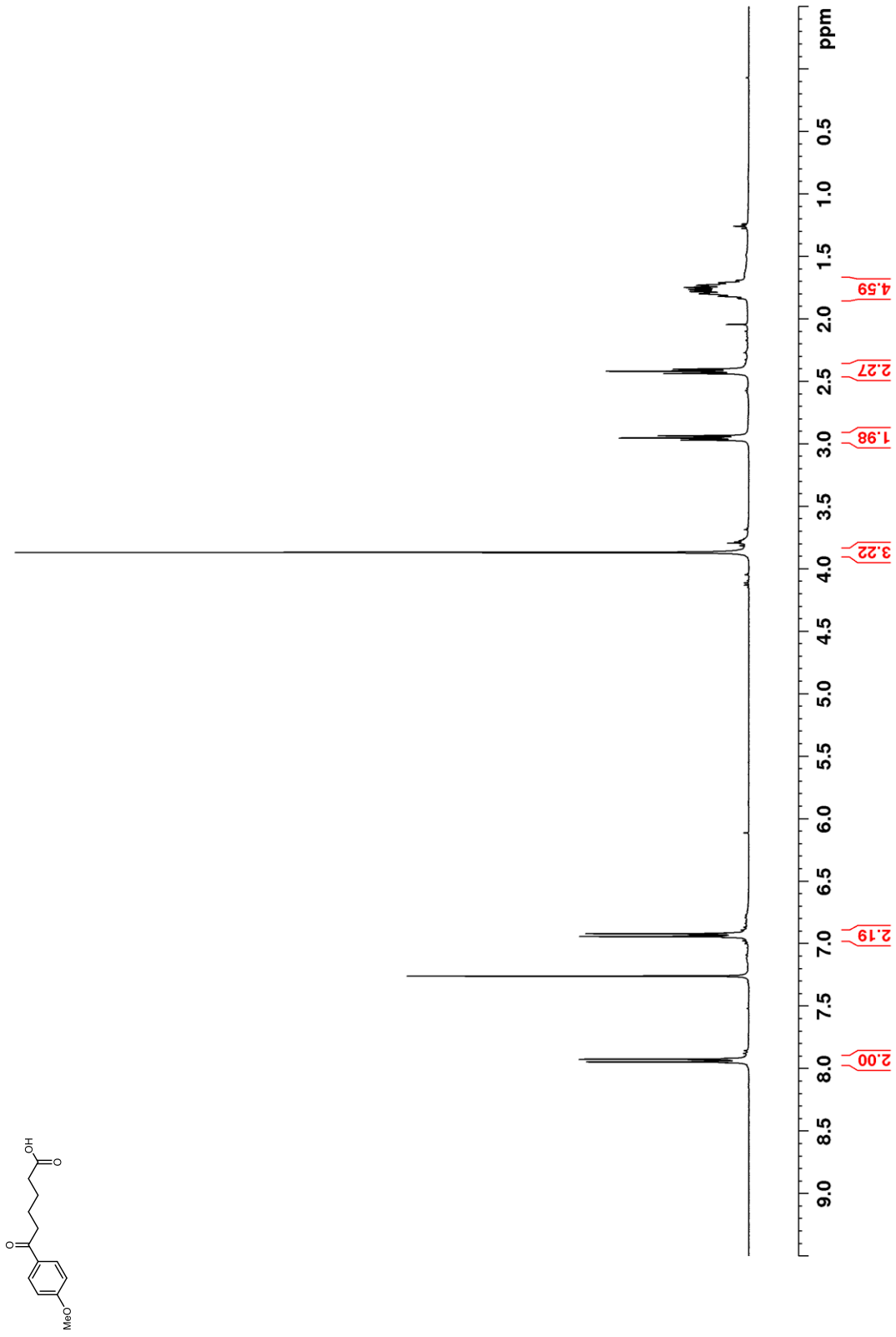


Figure 48. ^{13}C NMR (100 MHz, $CDCl_3$) of **4bd**

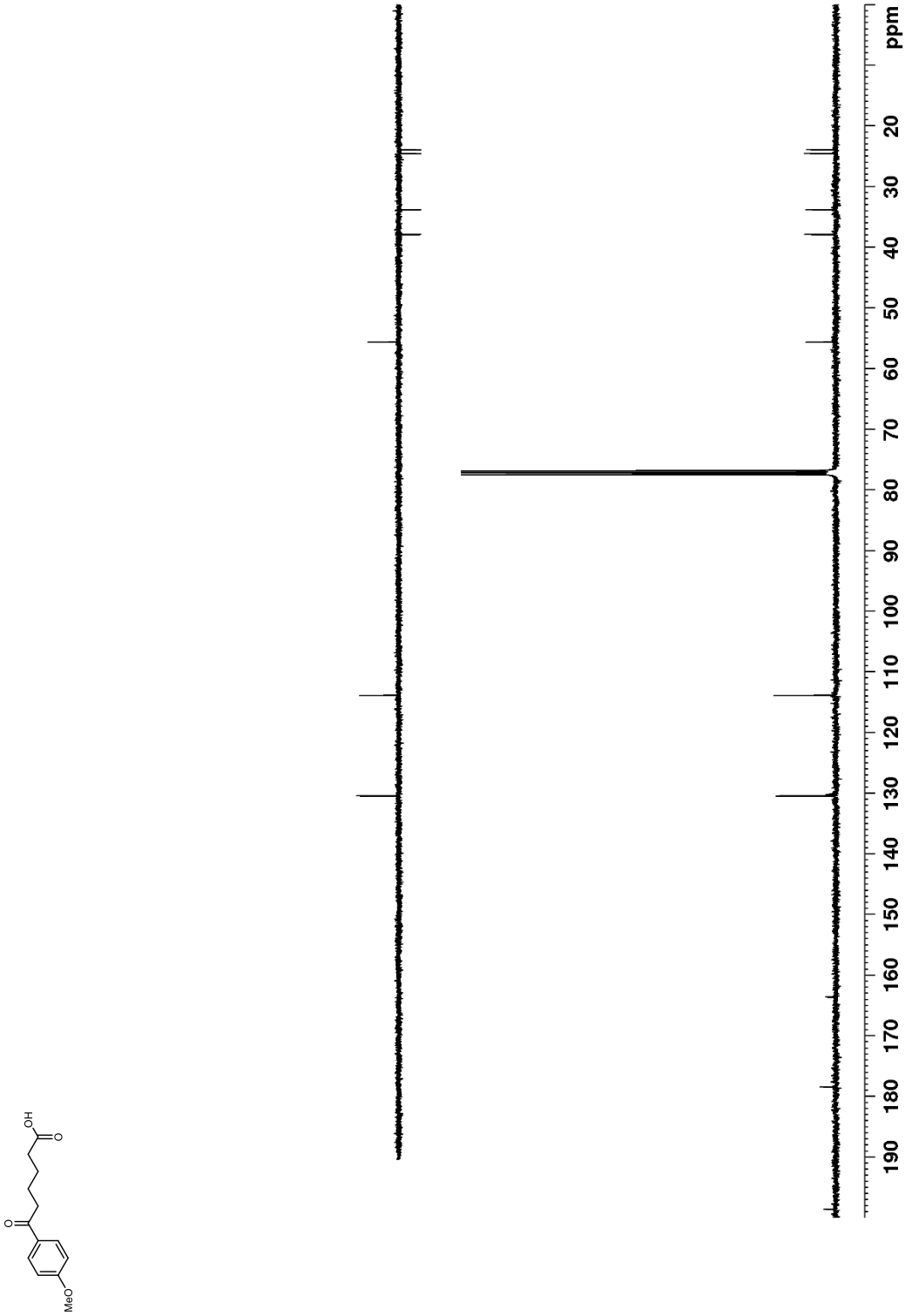


Figure 49. ^{1}H NMR (400 MHz, $CDCl_3$) of **4be**

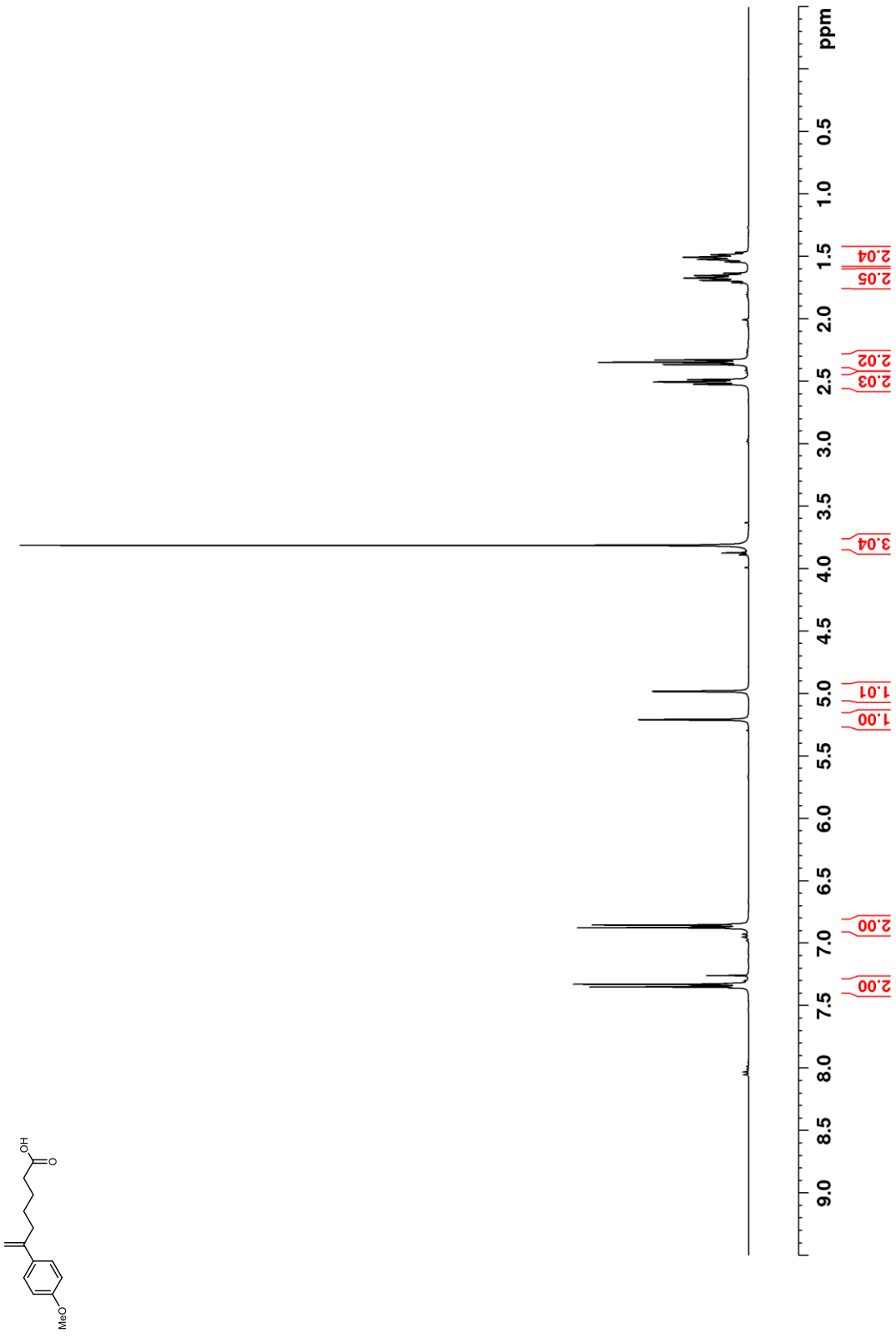


Figure 50. ^{13}C NMR (100 MHz, $CDCl_3$) of **4be**

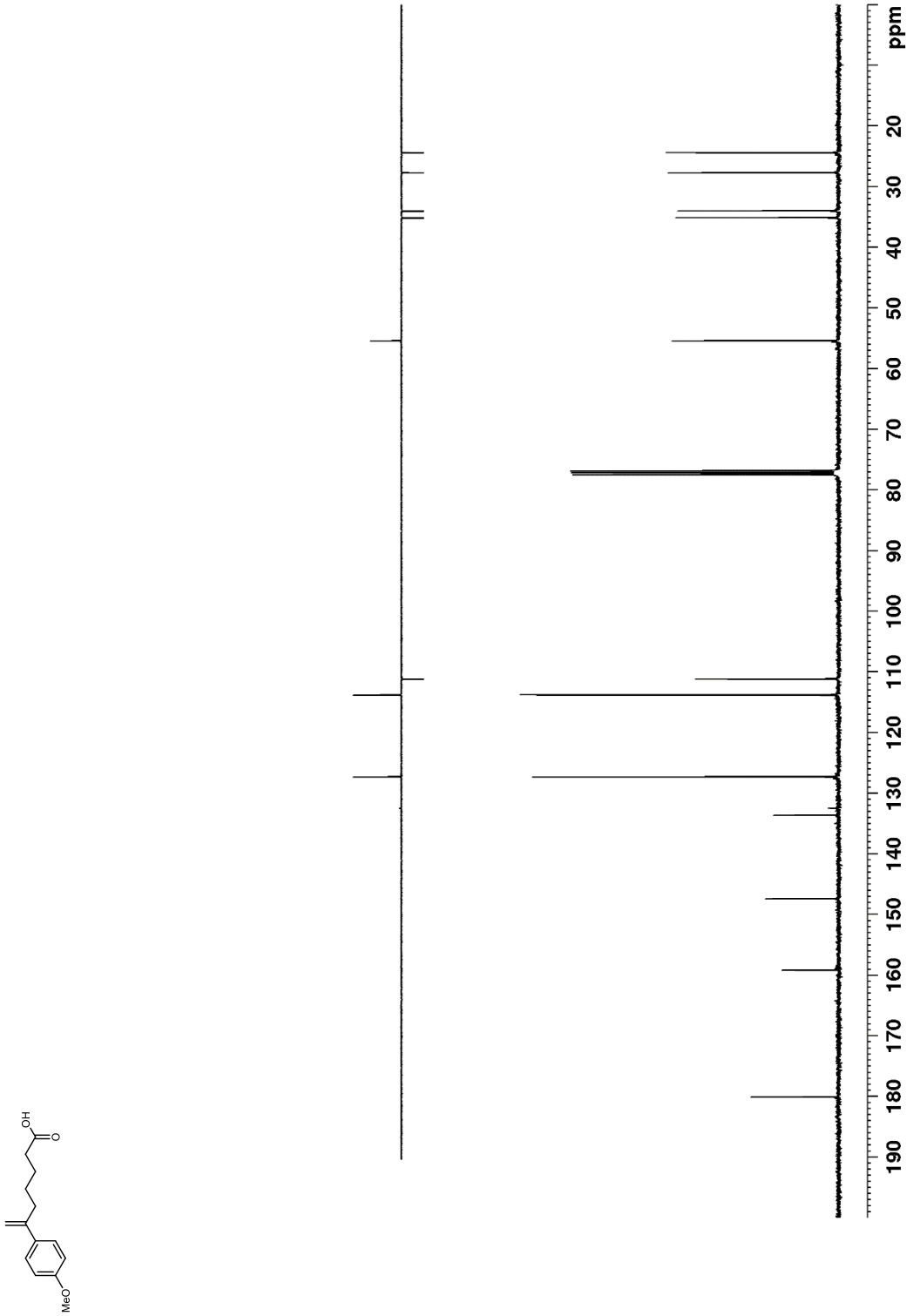


Figure 51. ^{1}H NMR (400 MHz, $CDCl_3$) of **4bi (**EtOAc and DCM also present due to compound decomposing when pure)

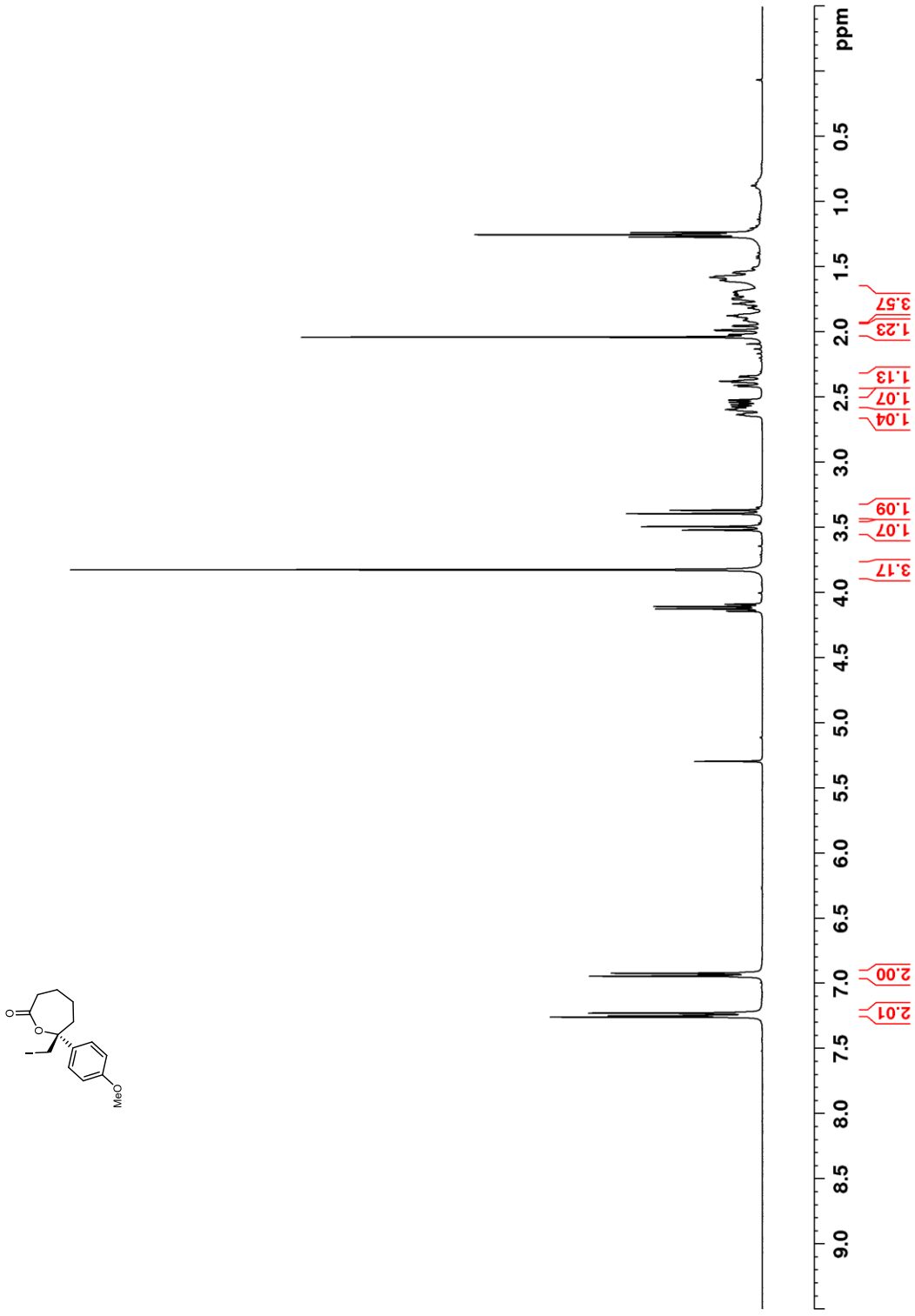


Figure 52. ^{13}C NMR (100 MHz, $CDCl_3$) of **4bi**

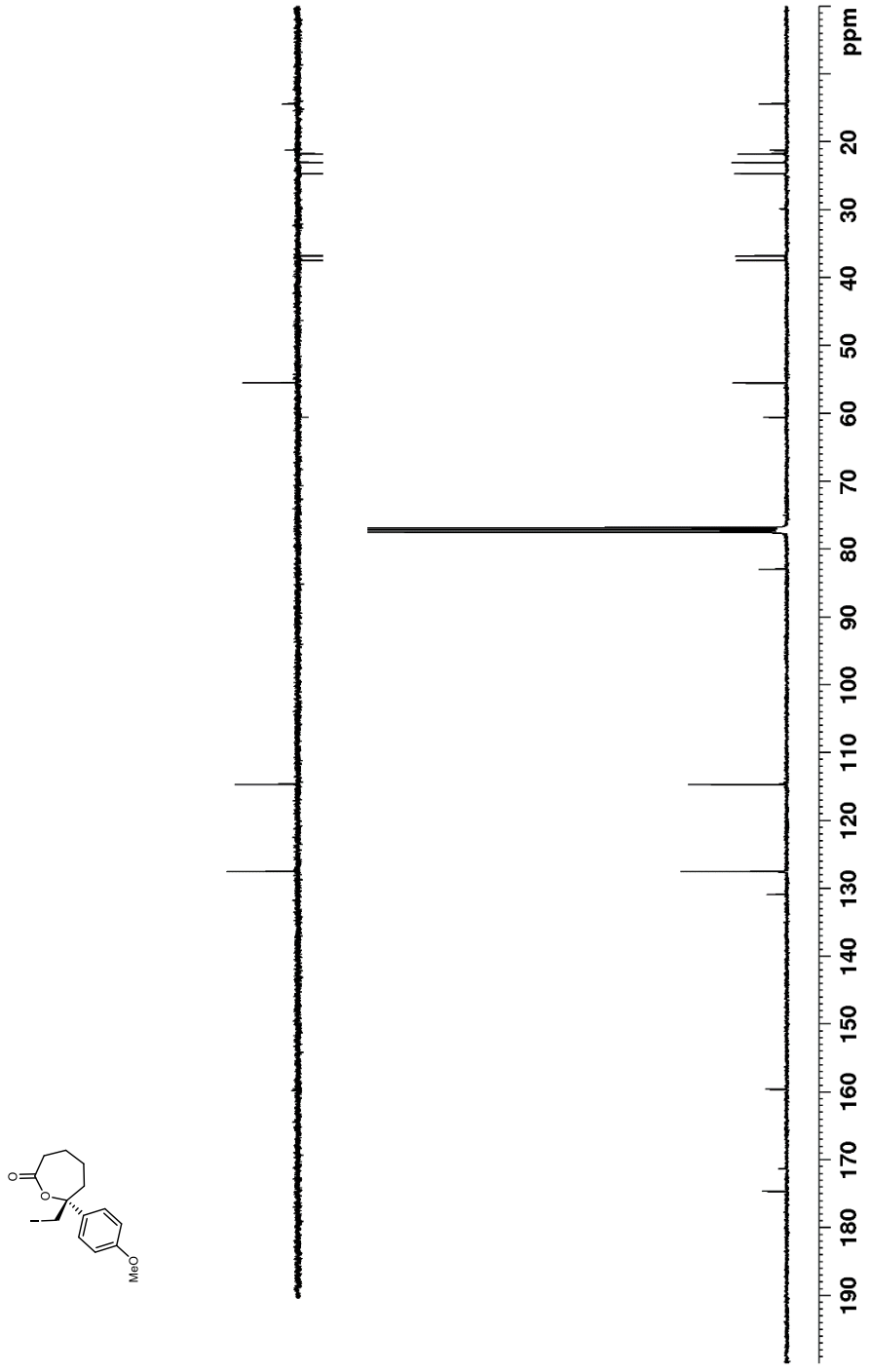


Figure 53. ^{1}H NMR (400 MHz, $CDCl_3$) of **4ax**

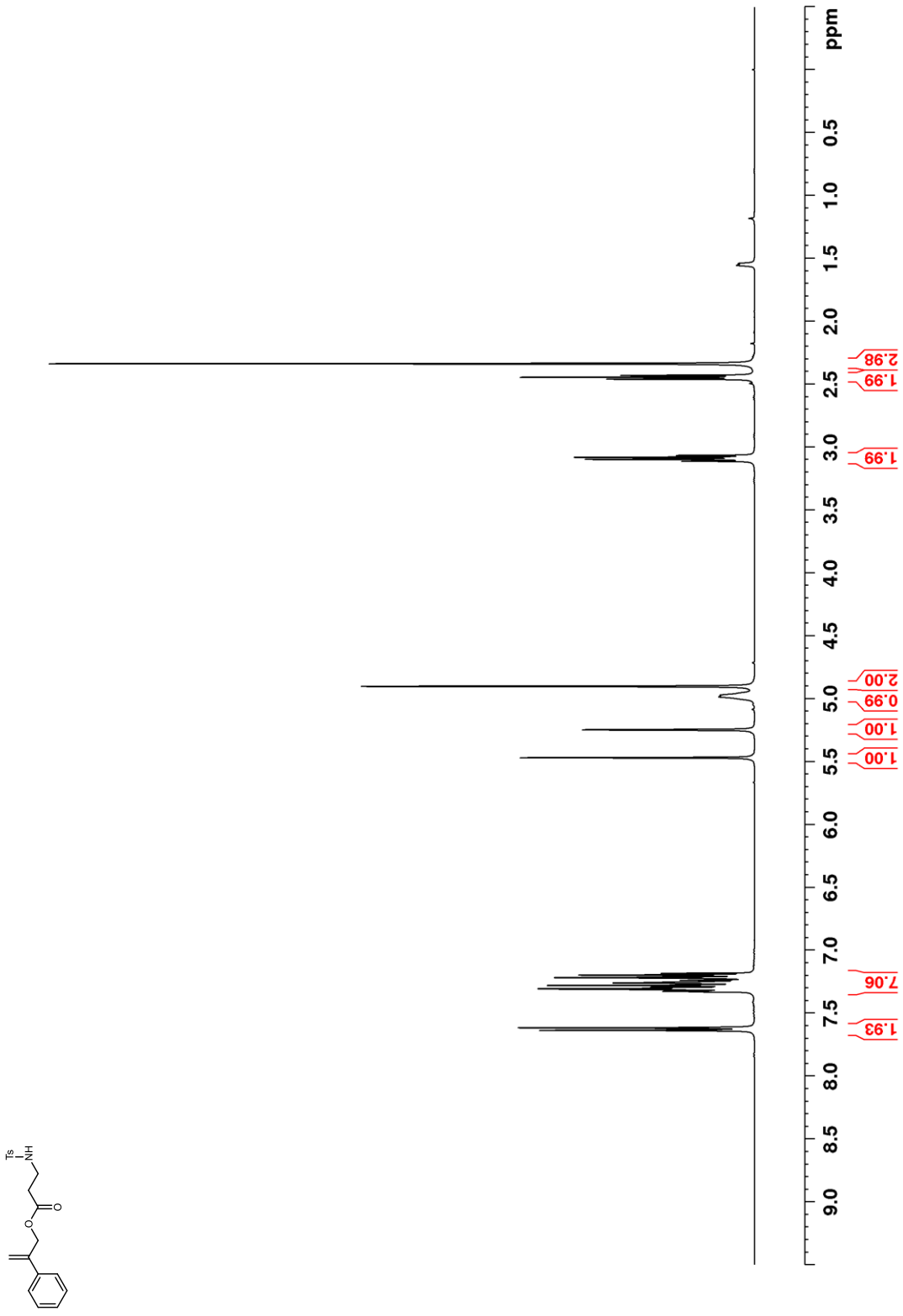


Figure 54. ^{13}C NMR (100 MHz, $CDCl_3$) of **4ax**

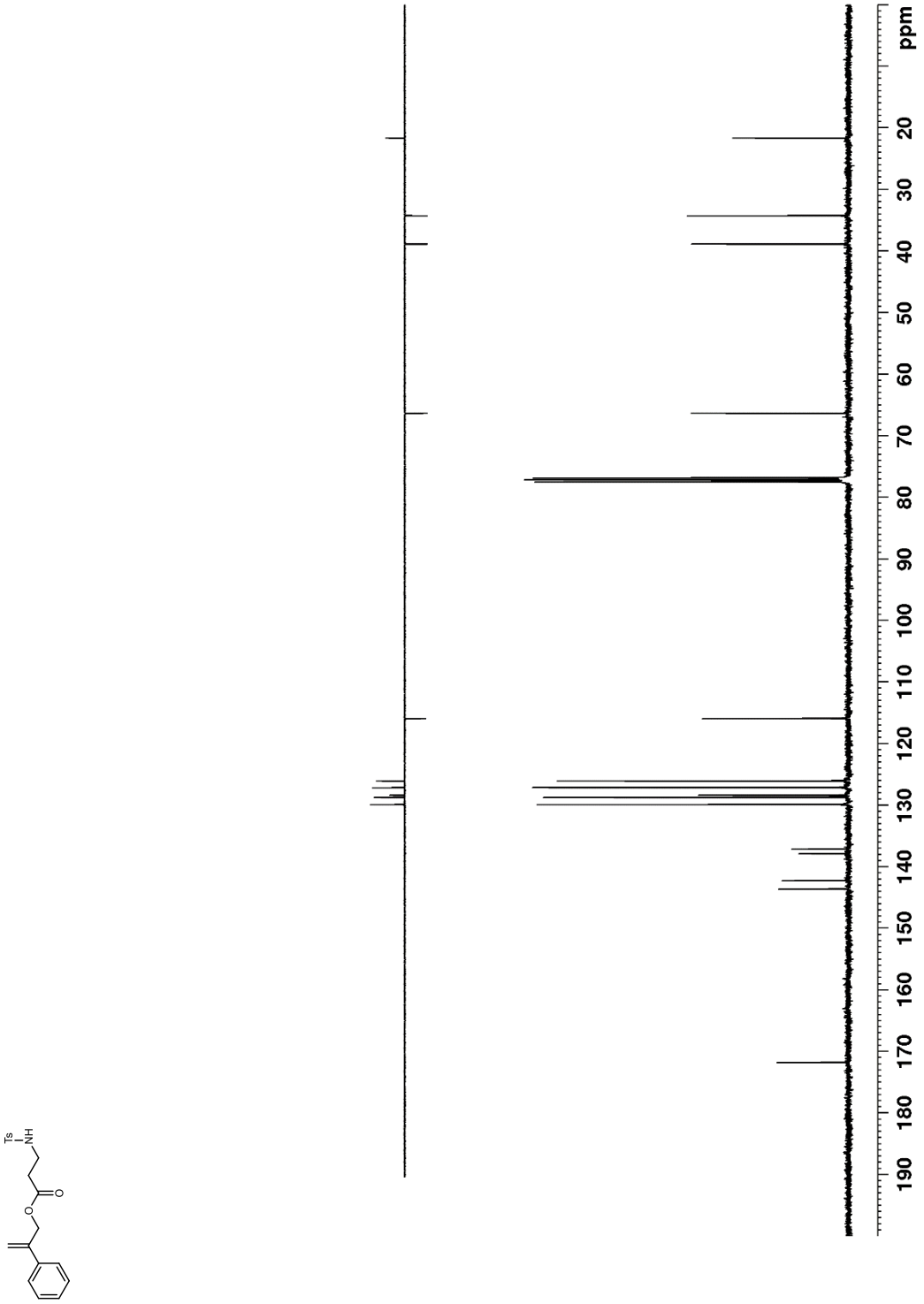


Figure 55. ^{1}H NMR (400 MHz, $CDCl_3$) of **x1**

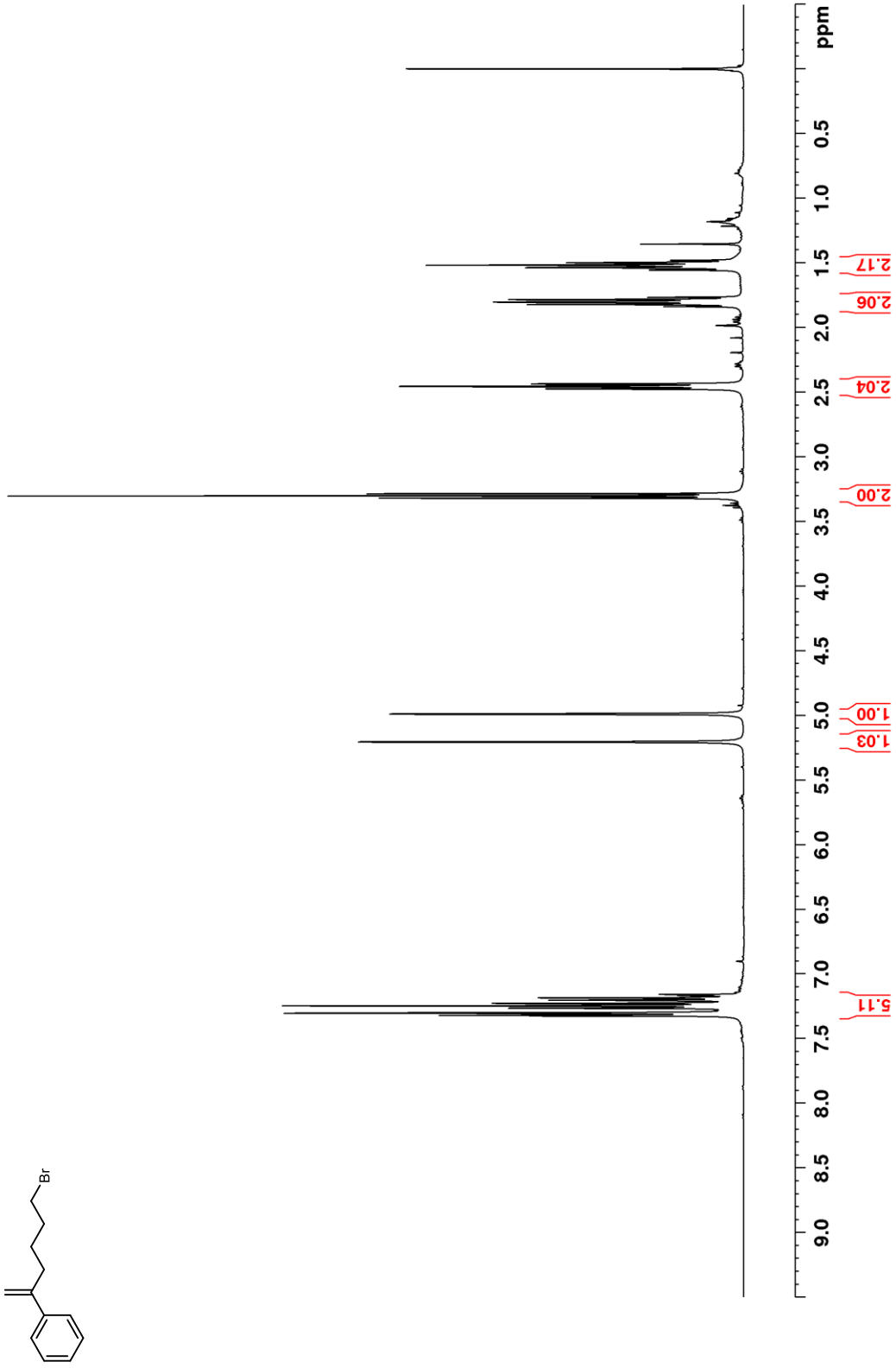


Figure 56. ^{13}C NMR (100 MHz, $CDCl_3$) of **x1**

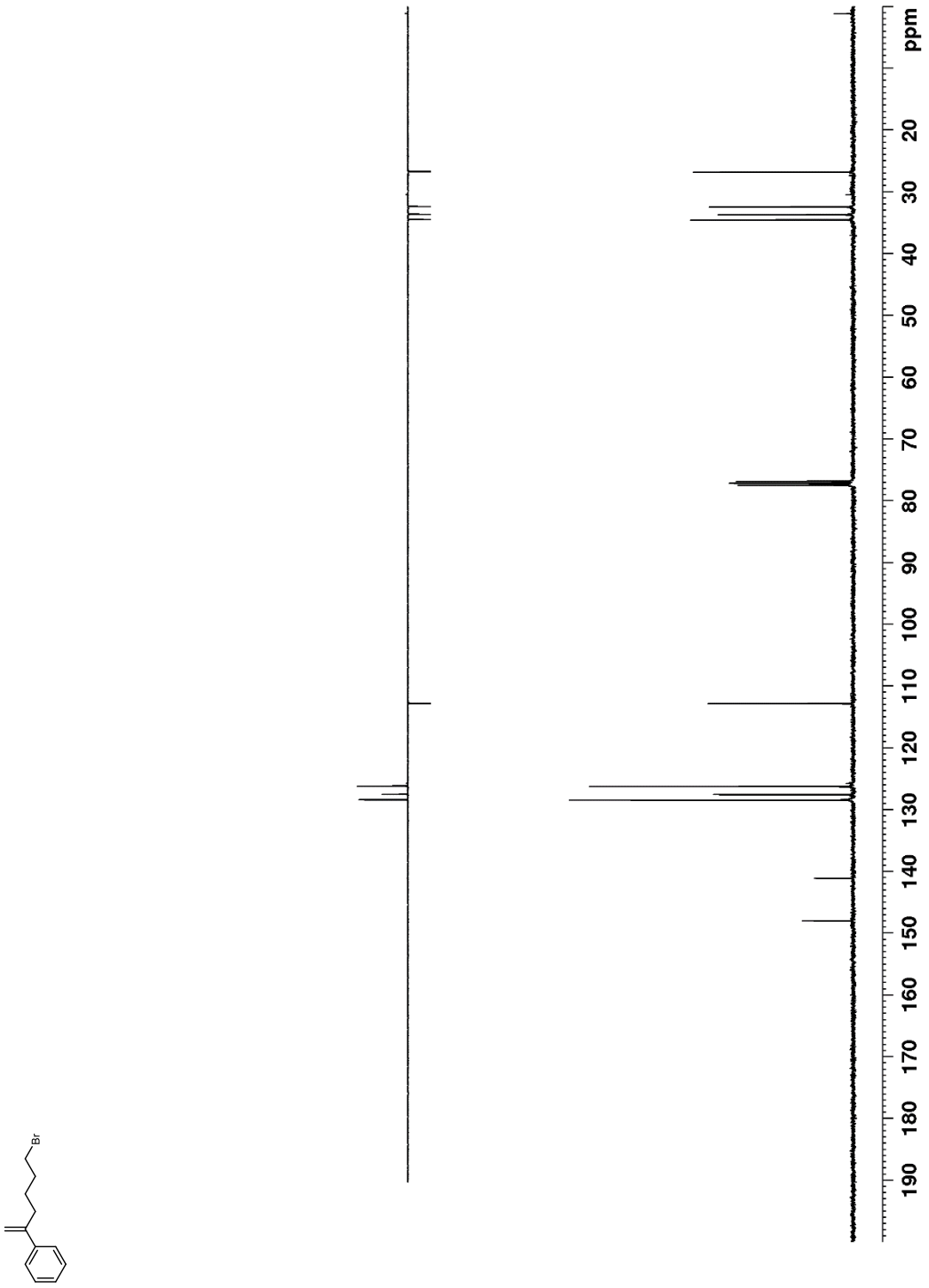


Figure 57. ^{1}H NMR (400 MHz, $CDCl_3$) of **x2**

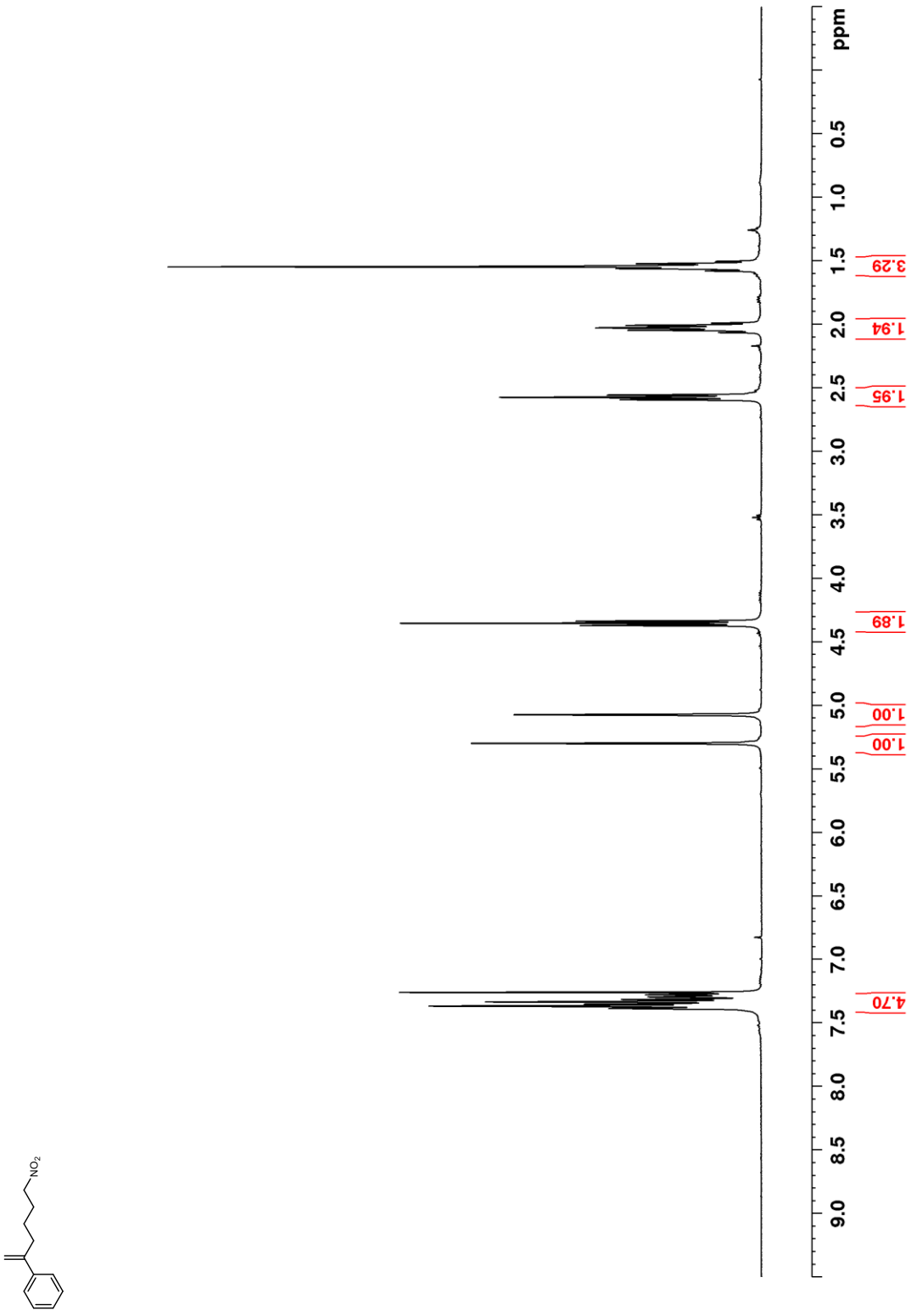


Figure 58. ^{13}C NMR (100 MHz, $CDCl_3$) of **x2**

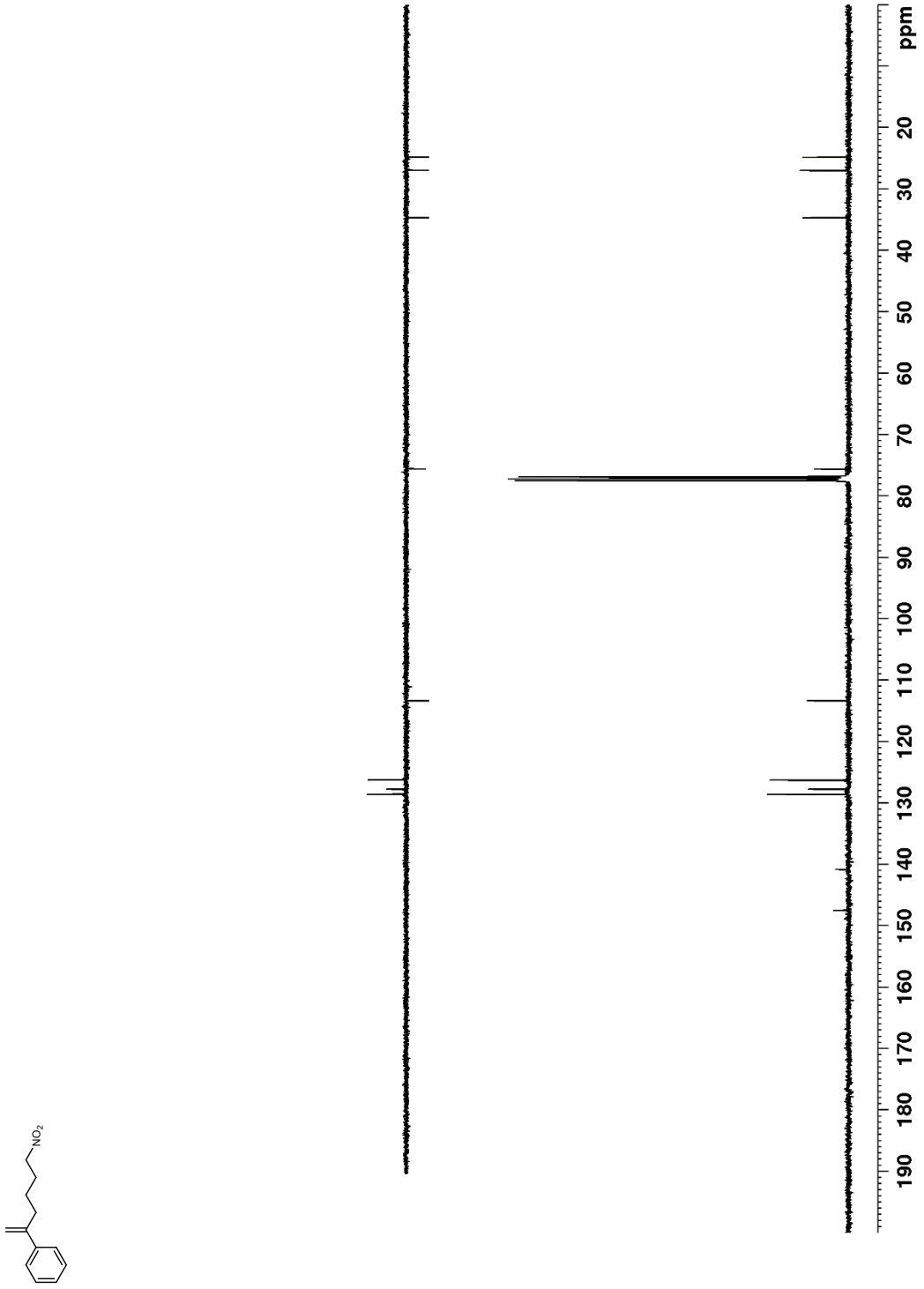


Figure 59. ^{1}H NMR (400 MHz, $CDCl_3$) of **x3**

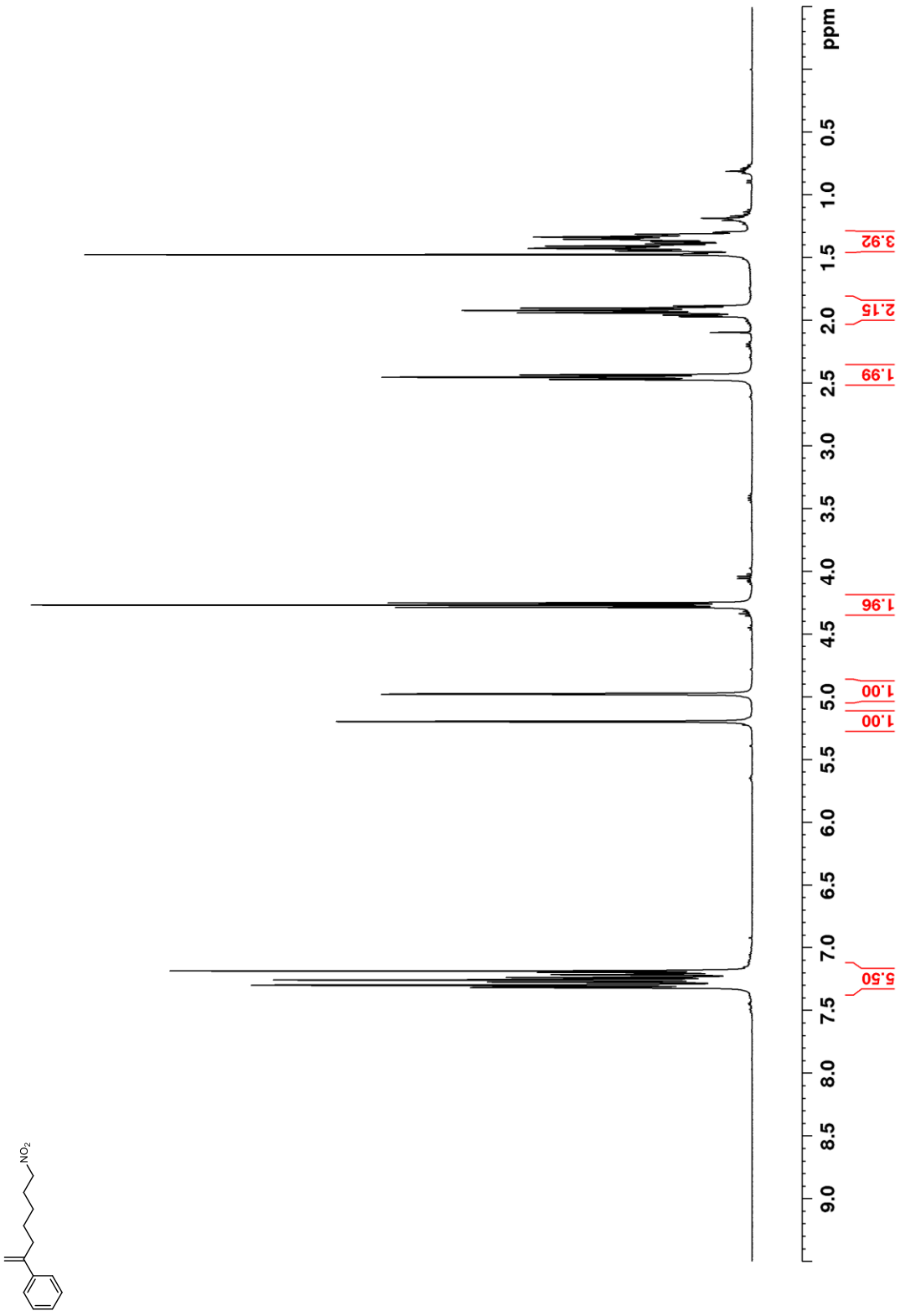


Figure 60. ^{13}C NMR (100 MHz, $CDCl_3$) of **x3**

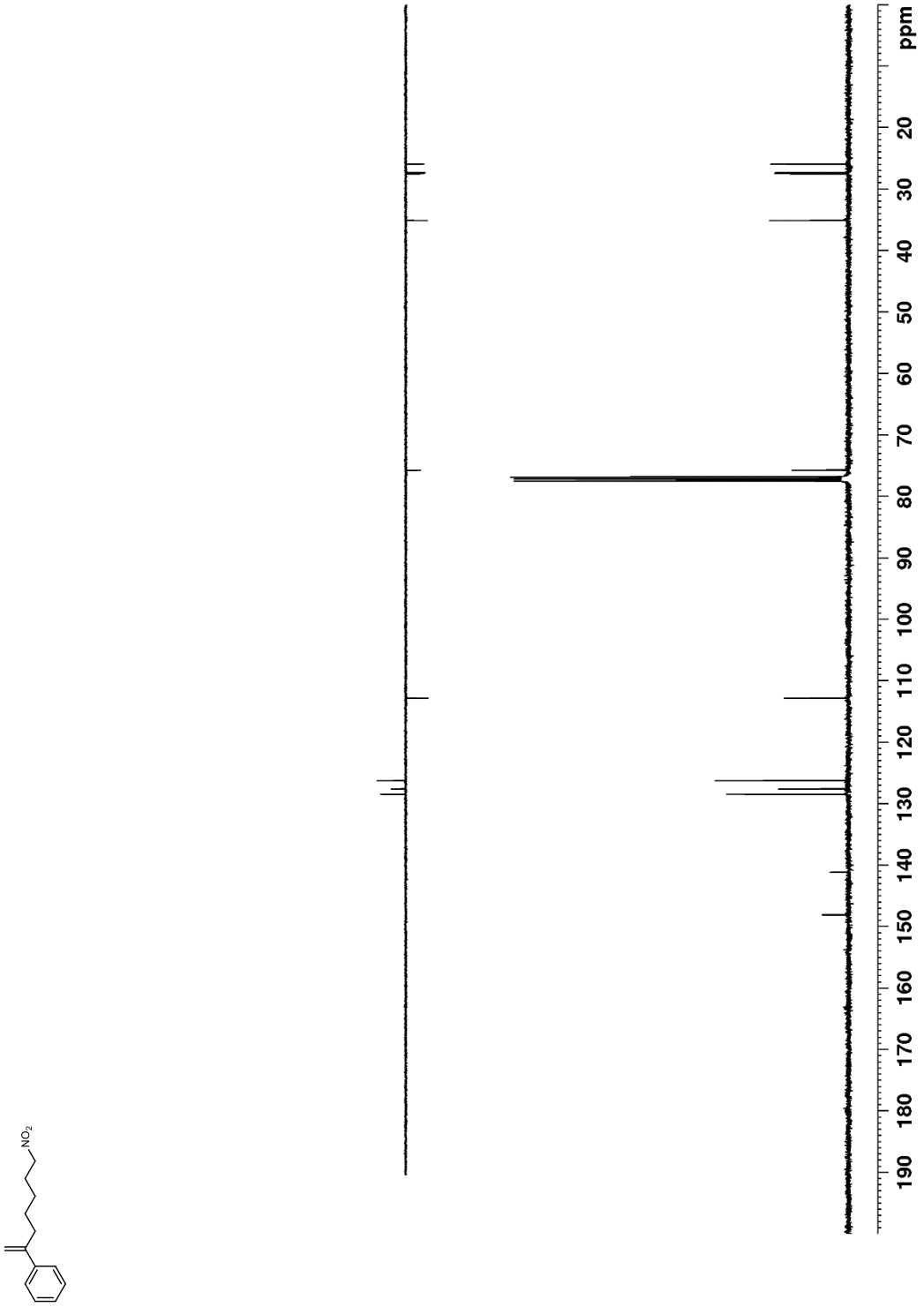


Figure 61. ^{1}H NMR (400 MHz, $CDCl_3$) of **x4**

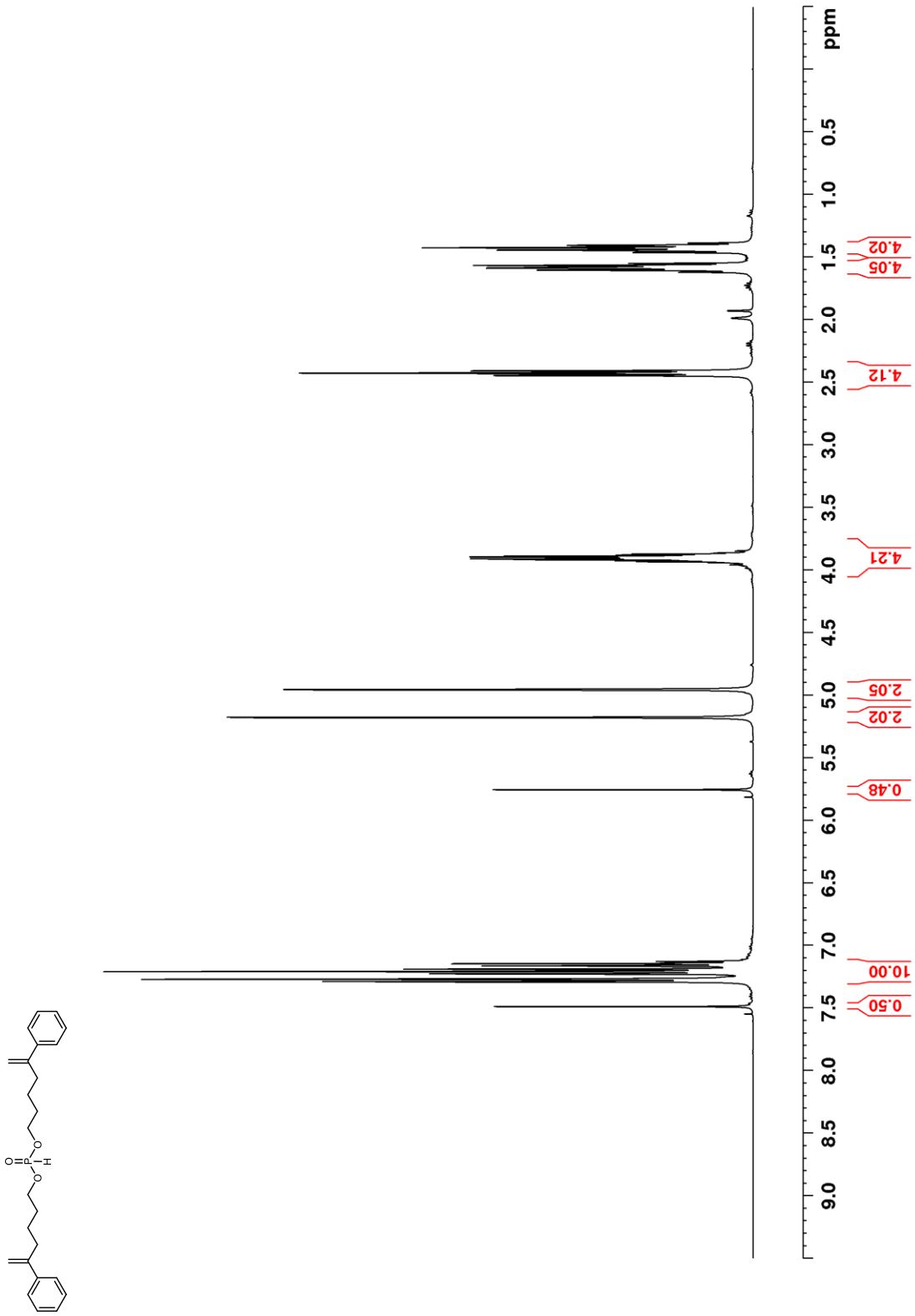


Figure 62. ^{13}C NMR (100 MHz, $CDCl_3$) of **x4**

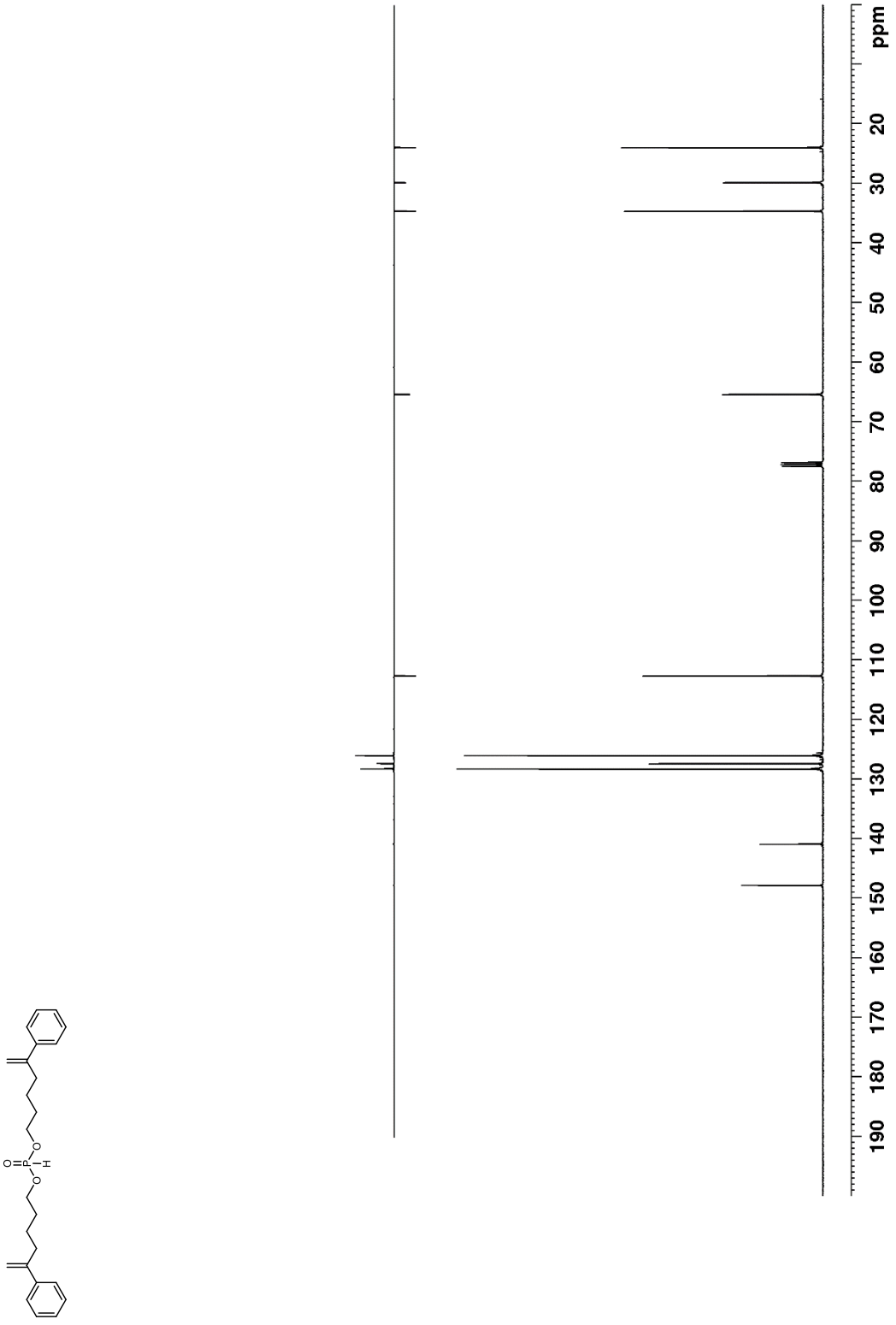


Figure 63. ^{31}P NMR (400 MHz, $CDCl_3$) of **x4**

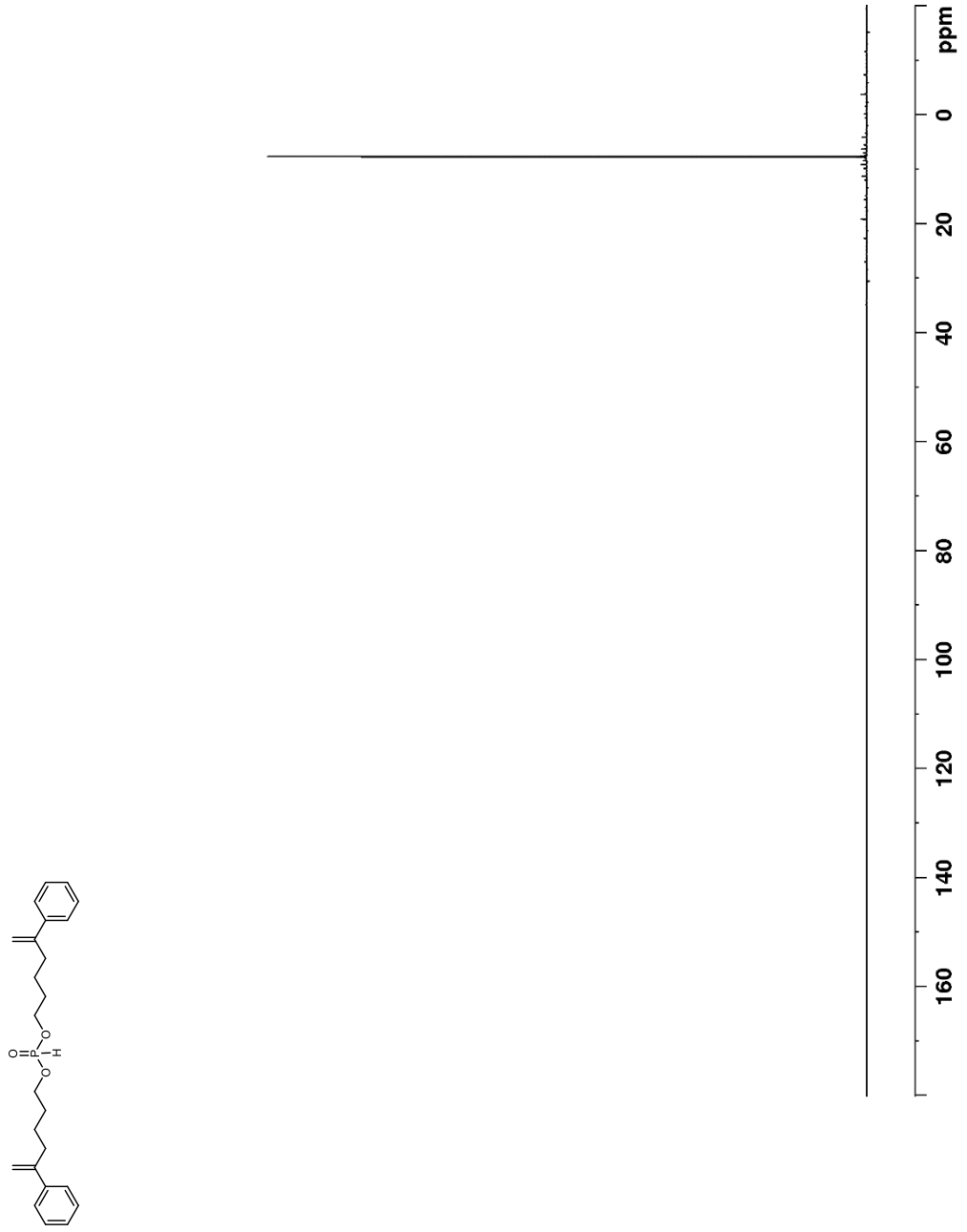
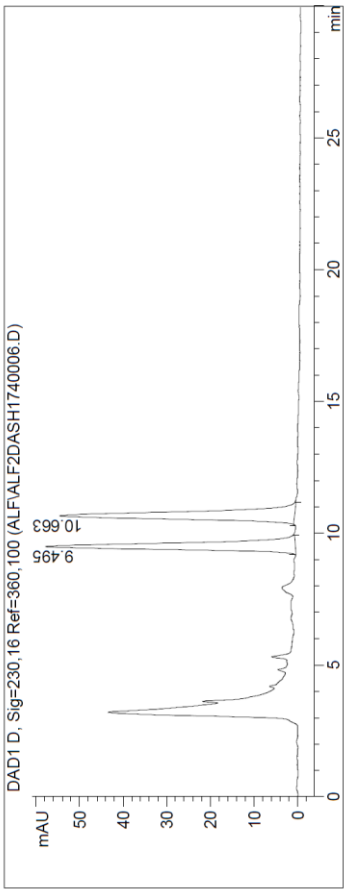
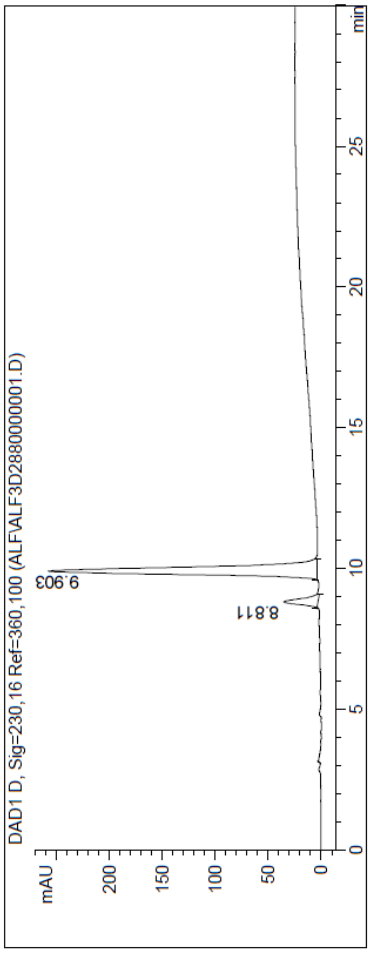


Figure 64. HPLC trace of **4d**. Chiralcel-OD-H 10% ^{i}PrOH/hexanes, 1.0 mL/min, 20 ºC



Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RT [min]	Width [min]	Area	Area %
1	9.495	0.267	918.937	48.387
2	10.663	0.303	980.203	51.613



Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RT [min]	Width [min]	Area	Area %
1	8.811	0.234	447.881	9.479
2	9.903	0.281	4277.110	90.521

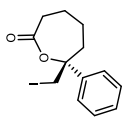
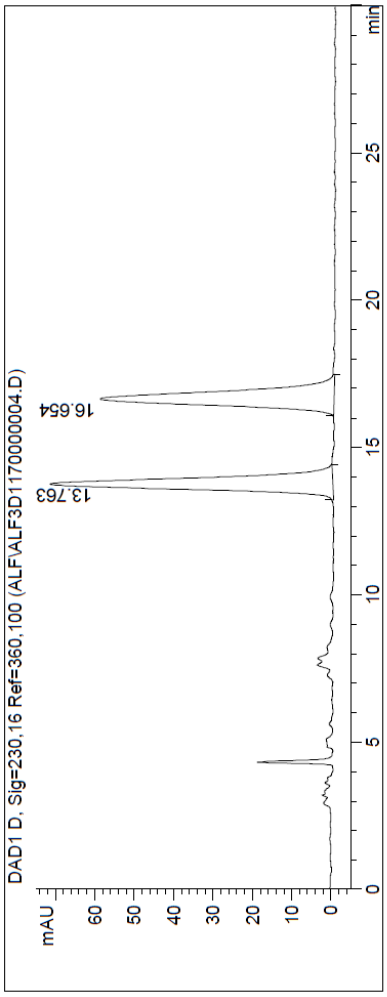
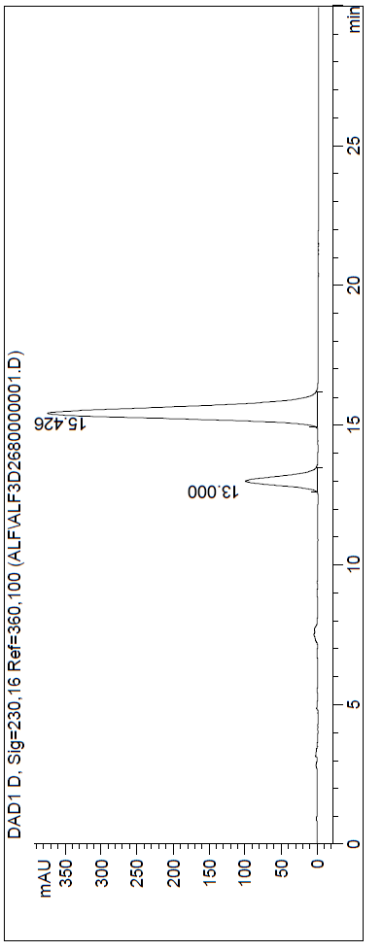


Figure 65. HPLC trace of **4bg**. Chiralcel-OD-H 10% ^{i}PrOH/hexanes, 1.0 mL/min, 20 ºC



Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RT [min]	Width [min]	Area	Area %
1	13.763	0.421	1815.320	49.826
2	16.654	0.513	1827.979	50.174



Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RT [min]	Width [min]	Area	Area %
1	13.000	0.371	2213.740	17.053
2	15.426	0.479	10767.708	82.947

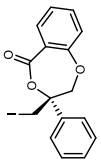
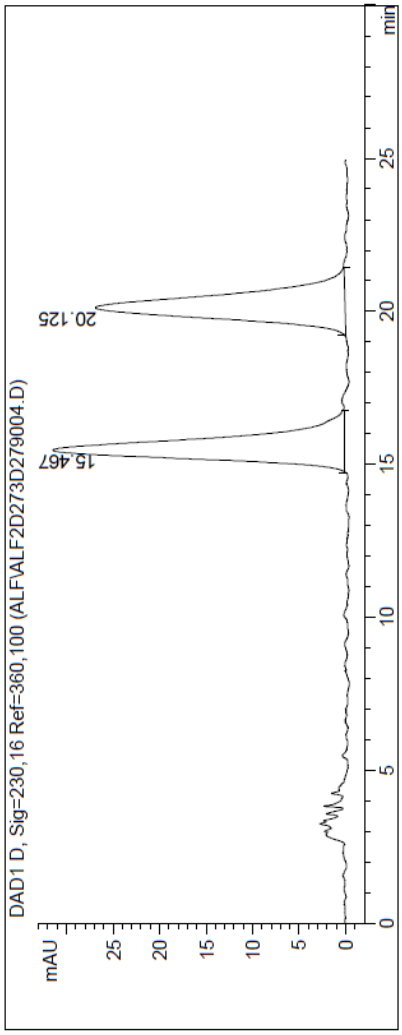
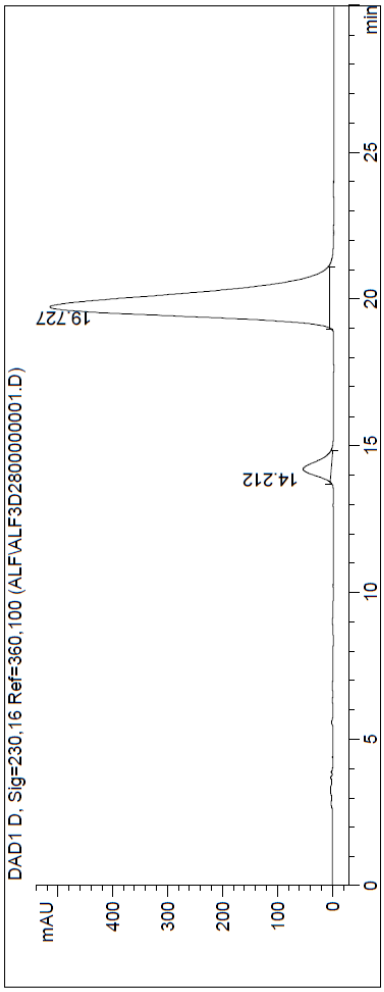


Figure 66. HPLC trace of **4bh**. Chiralcel-OD-H 20% ^{i}PrOH/hexanes, 1.0 mL/min, 20 ºC



Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RT [min]	Width [min]	Area	Area %
1	15.467	0.725	1359.783	49.948
2	20.125	0.848	1362.634	50.052



Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RT [min]	Width [min]	Area	Area %
1	14.212	0.552	1690.831	6.010
2	19.727	0.864	26442.414	93.990

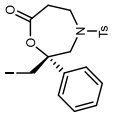
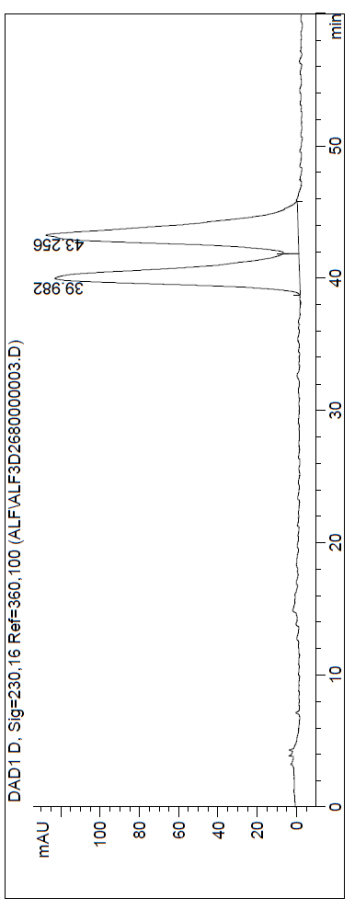
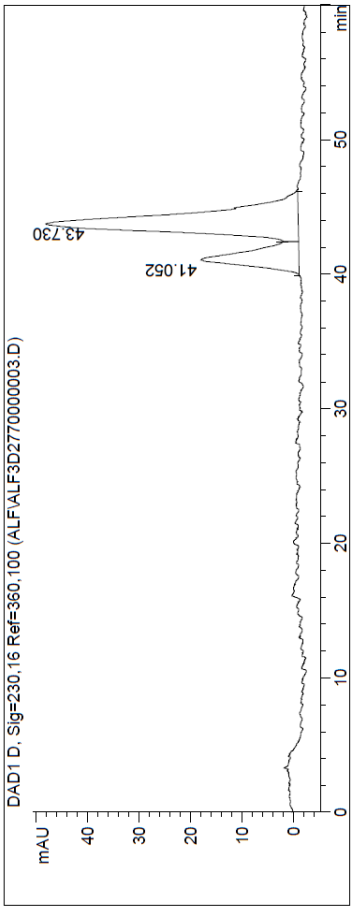


Figure 67. HPLC trace of **4bi**. Chiralcel-OD-H 2% ^{i}PrOH/hexanes, 1.0 mL/min, 20 ºC



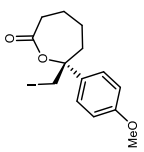
Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RT [min]	Width [min]	Area	Area %
1	39.982	1.380	10315.561	46.349
2	43.256	1.548	11940.668	53.651



Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RT [min]	Width [min]	Area	Area %
1	41.052	1.207	1381.017	24.098
2	43.730	1.479	4349.737	75.902



REFERENCES

1. Nolsoe, J. M. J.; Hansen, T. *Eur. J. Org. Chem.* **2014**, 3051-3065.
2. Bougault, M. J. *Ann. Chim. Phys.* **1908**, *14*, 145-183.
3. Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950-3952
4. Bartlett, P. A.; Richardson, D. P.; Myerson, J. *Tetrahedron* **1984**, *40*, 2317-2327
5. Grossman, R. B.; Trupp, R. J. *Can. J. Chem.* **1998**, *76*, 1233-1237.
6. Haas, J.; Piguel, S.; Wirth, T. *Org. Lett.* **2002**, *4*, 297-300.
7. Garnier, J. M.; Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2007**, 3281-3291.
8. Brown, R. S. *Acc. Chem. Res.* **1997**, *30*, 131-137.
9. Wang, M.; Gao, L. X.; Mai, W. P.; Xia, A. X.; Wang, F.; Zhang, S. B. *J. Org. Chem.* **2004**, *69*, 2874-2876.
10. Ning, Z. L.; Jin, R. H.; Ding, J. Y.; Gao, L. X. *Synlett.* **2009**, 2291-2294.
11. Veitch, G. E.; Jacobsen, E. N. et. al. *Angew. Chem.* **2010**, *122*, 7490; *Angew. Chem. Int. Ed.* **2010**, *49*, 7332-7335.
12. Dobish, M. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2012**, *134*, 6068
13. Fang, C.; Paull, D. H.; Hethcox, J. C.; Shugrue, C. R.; Martin, S. F. *Org. Lett.* **2012**, *14*, 6290-6293.
14. Arai, T.; Kajikawa, S.; Matsumara, E. *Synlett* **2013**, *24*, 2045-2048.
15. Filippova, L.; Stenstrom, Y.; Hansen, T. V. *Tet. Lett.* **2014**, *55*, 419-422.
16. Hong, K. B.; Johnston, J. N. *Org. Lett.* **2014**, *16*, 3804-3807.
17. Danneman, M. W.; Hong, K. B.; Johnston, J. N. *Org. Lett.* **2015**, *17*, 2558-2561.
18. Nicolaou, K. C.; Adsool, V. A.; Hale, C. R. H. *Org. Lett.* **2010**, *12*, 1552-1555
19. Ishmuratov, G. Y.; Vydrina, V. A.; Galkina, Y. A.; Yakovleva, M. P.; Ishmuratova, N. M.; Tolstikov, A. G. *Chem. Nat. Compd.* **2015**, *51*, 1011-1034.
20. Crimms, M. T.; Mans, M. C.; Rodriguez, A. D. *Org. Lett.* **2010,** *12*, 5028-5031.
21. Toth, R.; Gerding-Reimers, C.; Deeks, M. J.; Menninger, S.; Gallegos, R. M.; Tonaco, I. A. N.; Hubel, K.; Hussey, P. J.; Waldmann, H.; Coupland, G. *The Plant Journal*, **2012**, *71*, 338-352.
22. Jung, H. J.; Nam, J. H.; Choi, J.; Lee, K. T.; Park, H. J. *J. Ethnopharmacol.*, **2005**, *97*, 359-367.
23. Piva, O. *Synthesis of Saturated Oxygenated Heterocycles II*, Topics in Heterocyclic Chemistry 36, **2014**, 283-320.

24. Ebine, M.; Suga, Y.; Fuwa, H.; Sasaki, M. *Org. Biomol. Chem.* **2010**, *8*, 39-42.

25. Marek, A. M.; Patil, M. R.; Klepetarova, B.; Kohout, L.; Elbert, T. *Tet. Lett.* **2012**, *53*, 2048 – 2050.

26. Basabe, P.; Bodero, O.; Marocs, I. S.; Diez, D.; Blanco, A.; de Roman, M.; Urones, J.G. *J. Org. Chem.* **2009**, *74*, 7750 - 7754.

27. Simonot, B.; Rousseau, G. *J. Org. Chem.* **1993**, *58*, 4-5.

28. Simonot, B.; Rousseau, G. *J. Org. Chem.* **1994**, *59*, 5912-5919.

29. Cheng, Y. A.; Chen, T.; Tan, C. K.; Heng, J. J.; Yeung, Y. Y. *J. Am. Chem. Soc.* **2012**, 16492-16495.

30. Gottam, H.; Vinod, T. K. *J. Org. Chem.* **2011**, *76*, 974-977.

31. Li, W.; Gan, J.; Fan, R. *Tet. Lett.* **2010**, *51*, 4275-4277.

32. Fan, R.; Li, W.; Pu, D.; Zhang, L. *Org. Lett.* **2009**, *11*, 1425-1428.

33. Giri, R.; Yu, J. Q. **2008** Iodine Monoacetate, e-*EROS Encyclopedia of Reagents for Organic Synthesis*

34. Kim, H. J.; Cho, S. H.; Chang, S. *Org. Lett.* **2012**, *14*, 1424-1427.

35. Doleschall, G.; Toth, G. *Tetrahedron*, **1980**, *36*, 1649.

36. Lovecraft, H. P. *The Call of Cthulu*. Weird Tales, 1928.

37. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518- 1520.

38. Kogel, J. F.; Linder, T.; Schroder, F. G.; Sundermeyer, J.; Goll, S. K.; Himmel, D.; Krossing, I.; Kutt, K.; Saame, J.; Leito, I. *Chem. Eur. J.* **2015**, *21*, 5769-5782.