Enantioselective Nucleophile-Catalyzed Cycloadditions

by

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B.A., Chemistry
Oberlin College, 2000

Submitted to the Department of Chemistry in Partial Fulfillment of the Requirements for the Degree of

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Abstract

Chapter 1 describes the development of an asymmetric nucleophile-catalyzed [2+2] cycloaddition of ketenes with aldehydes. This is the first report of a catalytic enantioselective synthesis of trisubstituted β-lactones.

Two enantioselective phosphine-catalyzed [3+2] cycloadditions of allenoates are detailed in Chapter 2. A method for the asymmetric synthesis of cyclopentenes via a [3+2] cycloaddition of allenoates with enones is first discussed. This is followed by a report of our efforts to extend this [3+2] methodology to imine electrophiles.

We conclude, in Chapter 3, with an account of the development of a novel phosphine-catalyzed synthesis of bicyclo[3.3.0]octanones and bicyclo[4.3.0]nonanones. Preliminary results for an enantioselective variant of this method are also disclosed.

Thesis Supervisor: Professor Gregory C. Fu
Title: Professor of Chemistry

Acknowledgments

My time at M. I. T. has presented me with numerous challenges, not all of which have been related to frustrations in the laboratory. Fortunately, I have been surrounded by supportive co-workers, friends, and family to get me through the past five years.

First I'd like to thank Greg for the opportunity and means to explore interesting chemistry, for editing this thesis front to back, and for helping me obtain my future position at Princeton. I'd also like to thank Prof. Danheiser for the feedback and encouragment he provided me with during our yearly meetings.

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Tim, Joe, and Elaine, your loyal friends and I hope that we can maintain our relationships for many years to come. I'm sorry your not here with me now to celebrate this moment but your in my thoughts and I'm proud to have been your classmate.

Sean, you too, have been a loyal friend to me, even when I'm at my worst (which is often). I sincerely appreciate your encouragement and friendship over the last 2 years. My thoughts will certainly be with you as I depart. You will make it, you have a strong will, much stronger than my own, and it will undoubtely serve you well in the remainder of your time here and beyond.

My family has given me unwaivering support over the course of my time here, and throughout my entire life. Mom and Dad, I love you. Dave, you've been a good brother to me. I hope that you can learn from my mistakes, that way they will be worth something.

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I am indebted to all of you, and I hope that throughout the course of my life I will be able to repay this debt. However, there is one person to whom I will never be able to acknowledge or thank enough and that is my wife, Kate. You have seen me at my lowest many times over the past five years, but you have only thought of my best. Every day of this journey you have held my hand and let me know that you will stand by me whether I fail or succeed. This degree and all of my acheivements would not have been possible without your support. I love you and I am forever indebted to you.

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Preface

Parts of this thesis have been adapted from the following articles written and co-written by the author. The following articles were reproduced in part with permission from Wiley Interscience:

"Asymmetric Synthesis of Highly Substituted β-Lactones by Nucleophile-Catalyzed [2+2] Cycloadditions of Disubstituted Ketenes with Aldehydes"
Wilson, J. E.; Fu, G. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 6358.

"Synthesis of Functionalized Cyclopentenes through Catalytic Asymmetric [3+2] Cycloadditions of Allenes with Enones"
Wilson, J. E.; Fu, G. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 1426.

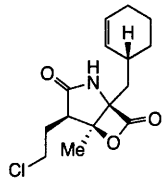
Chapter 1

Asymmetric Synthesis of Highly Substituted β-Lactones via Nucleophile-Catalyzed [2+2] Cycloadditions of Disubstituted Ketenes with Aldehydes

A. Introduction

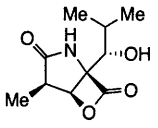
β-Lactones have garnered significant attention because of their diverse biological activity and vast potential as synthetic intermediates.[1] Compounds containing a β-lactone subunit have been shown to be effective as protesome inhibitors, as antitumor agents, and as antibacterials.[2-7] Roche's over-the-counter antiobesity drug, Xenical (Tetrahydrolipstatin), contains a β-lactone substructure.[8]

Scheme 1.1. Structures of β-Lactones Possessing Interesting Biological Activity.



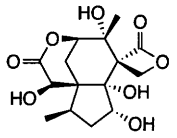
Salinosporamide A

Cytotoxic marine microorganism natural product. Proteasome inhibitor.



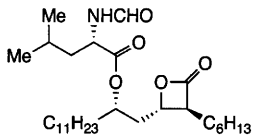
Omuralide

Terrestrial microbial natural product. Proteasome inhibitor.



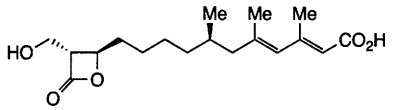
Anisatin

Plant toxin (convulsant) isolated from the Japanese star anise.



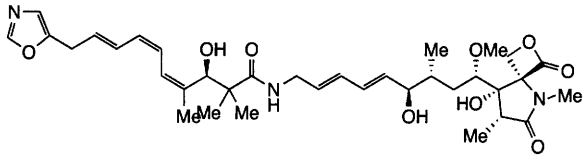
Xenical (Tetrahydrolipstatin)

Patented by Hoffmann-LaRoche for obesity, hyperpaelamia, atherosclerosis, and arteriosclerosis.



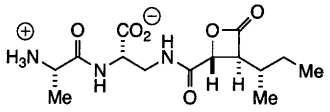
Antibiotic 1233A

Potent and specific inhibitor of HMG-CoA synthase.



Oxazolomycin

Inhibits tumor growth.



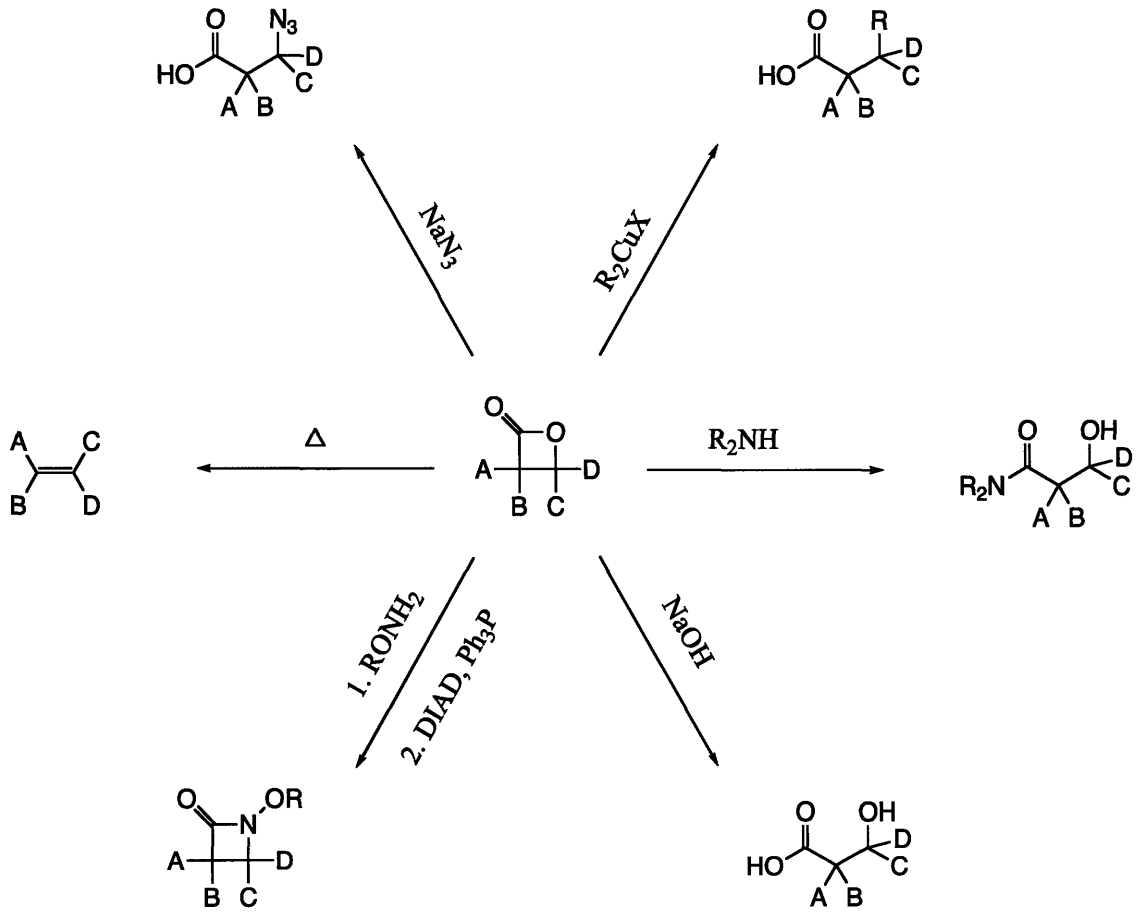
(-)-Belactosin C

Anticancer activity.

In addition to their intriguing biological activity, β-lactones are valuable synthetic intermediates.[9] The strain, inherent in the four membered ring, provides these lactones with interesting electrophilic properties. The heterocycle may be opened at either the carbonyl carbon, through an addition elimination sequence, or at the 4-position, depending on the nature of the nucleophile and reaction conditions. Nucleophiles such as

amines and hydroxide react with β-lactones through an addition/elimination mechanism to provide β-hydroxy amides and β-hydroxy acids, respectively. A two-step procedure, consisting of ring opening by an alkoxyamine and a Mitsunobu reaction, allows for the synthesis of a variety of β-lactam derivatives.[10] On the other hand, organocopper compounds, azides, and thiols add at the C-4 position, providing access to a wide variety of highly substituted carboxylic acid derivatives.[11] Moreover, decarboxylation provides a convenient and stereospecific route to highly substituted olefins.[12]

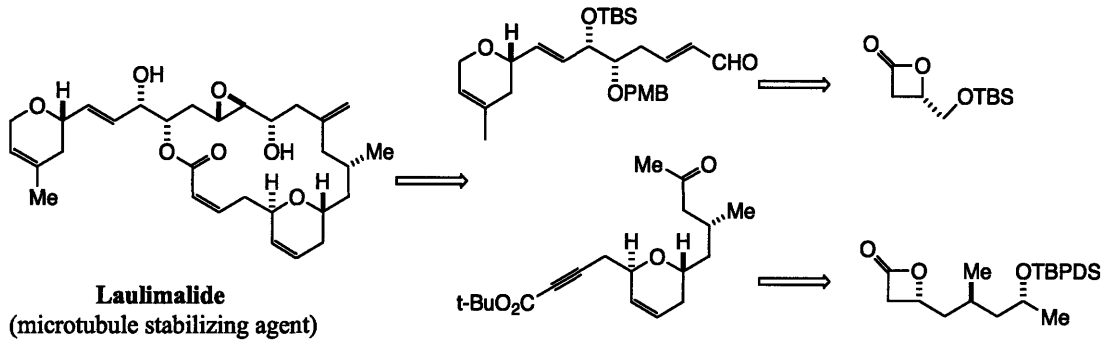
Scheme 1.2. Some Useful Transformations of β-Lactones.



β-Lactones have been used extensively in the synthesis of natural products. Four recent examples are outlined below (Schemes 1.3, 1.4, 1.5, and 1.6).

Nelson's enantioselective synthesis of laulimalide employs a number of enantioenriched β-lactone intermediates that are derived from cycloadditions of ketene with various aldehydes. Four of the nine stereocenters contained within the structure of laulimalide originate from β-lactone starting materials.[13]

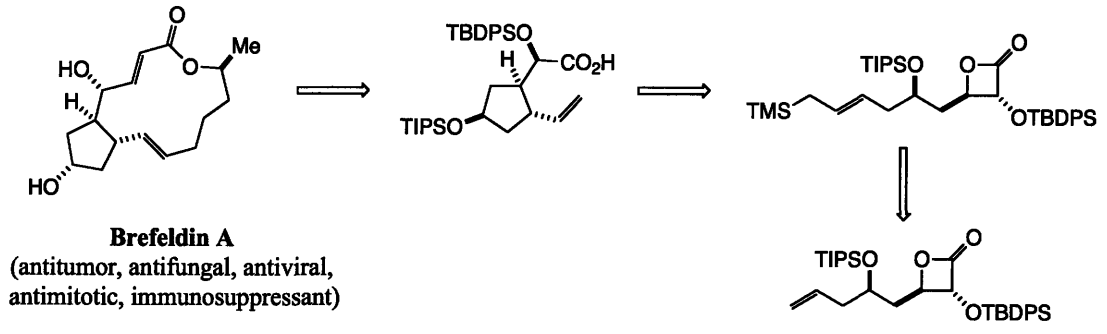
Scheme 1.3. Nelson's β-Lactone Strategy for the Synthesis of Laulamalide.



Laulimalide
(microtubule stabilizing agent)

Romo's synthesis of Brefeldin A employs a β-lactone as a substrate for an intramolecular Lewis Acid mediated S_N2 ring opening reaction with a pendant allyl silane. This novel reaction allows for the synthesis of the densely functionalized cyclopentanol core of brefeldin A.[14]

Scheme 1.4. Romo's β-Lactone Strategy for the Synthesis of Brefeldin A.

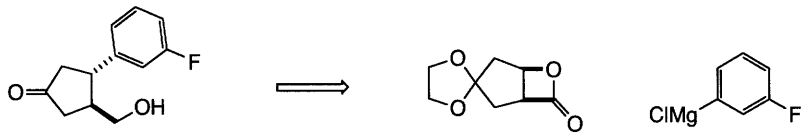


Brefeldin A
(antitumor, antifungal, antiviral, antimitotic, immunosuppressant)

A second application of β-lactone S_N2 ring opening is illustrated in Romo's expeditious synthesis of a Merck CCR5 antagonist intermediate. Here, a copper-

catalyzed S_N2 addition of a Grignard reagent is employed for the formation of the desired cyclopentanone intermediate.[15]

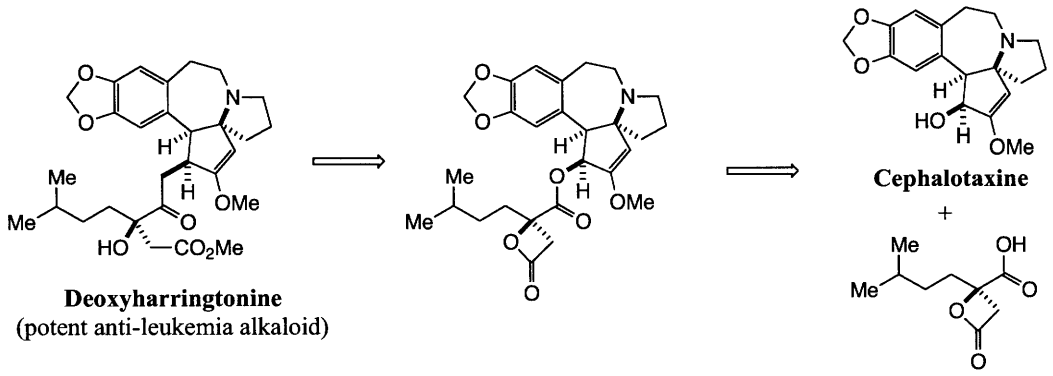
Scheme 1.5. Romo's β-Lactone Ring Opening Strategy for the Synthesis of a Merck anti-HIV Intermediate.



Merck Intermediate
for an anti-HIV CCR5 antagonist

Gin's utilization of a β-lactone intermediate in his synthesis of Deoxyharringtonine allowed for the facile installation of the alkaloid's acyl sidechain. Although numerous approaches to Cephalotaxine have been reported, introduction of the sterically encumbered acyl side, which is necessary for biological activity, has remained a challenge. The success of Gin's coupling of Cephalotaxine with the lactone-acid may be attributed to the small size of the β-lactone intermediate relative to the ring-opened form of the compound.[16]

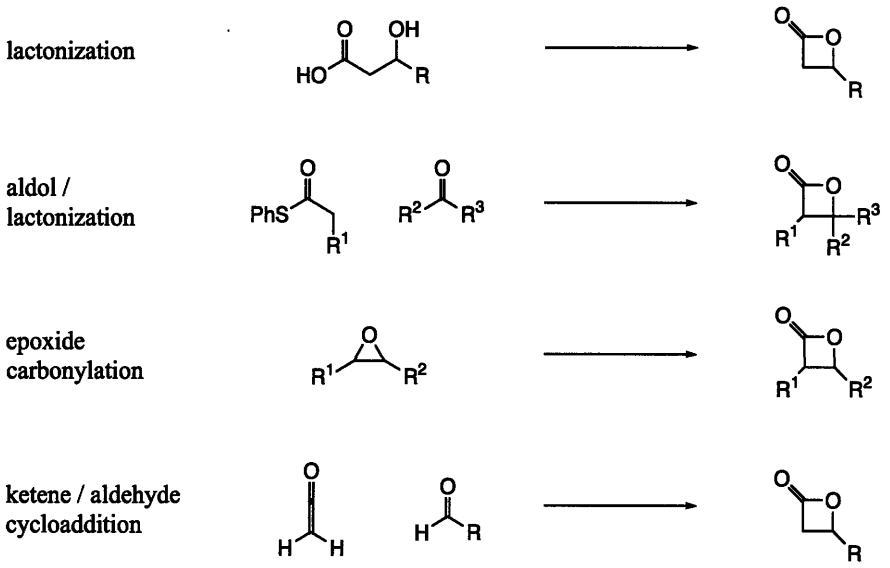
Scheme 1.6. Gin's Use of a β-Lactone Intermediate in the Synthesis of Deoxyharringtonine.



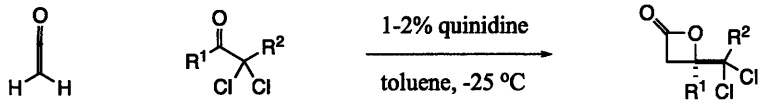
Deoxyharringtonine
(potent anti-leukemia alkaloid)

Due to their significance both as synthetic intermediates and as pharmaceuticals, the development of methods for the synthesis of β-lactones is an important objective. Consequently, considerable effort has been devoted to the development of efficient methods for their synthesis. These strategies include lactonization of β-hydroxy acids, aldol / lactonization sequences, epoxide carbonylation, and [2+2] cycloadditions of ketenes and aldehydes (Scheme 1.7).[17]

Scheme 1.7. Common Synthetic Approaches to β-lactones.



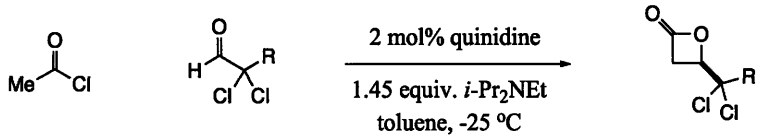
Catalytic asymmetric [2+2] cycloaddition reactions have proven to be the most effective and general methods for the synthesis of enantioenriched β-lactones. Wynberg's pioneering work on cinchona alkaloid-catalyzed [2+2] cycloadditions of ketene with electron deficient aldehydes (eq 1.1) laid the foundations for the development of a series of highly efficient and selective nucleophile-catalyzed cycloadditions.[18] These include Romo's modified version of Wynberg's reaction (eq 1.2)[19], Romo's bicyclic β-lactone synthesis by an intramolecular [2+2] cycloaddition (eq 1.3)[20], and Nelson's [2+2] cycloaddition of acid chlorides and aldehydes (eq 1.4).[21]



(1.1)

R^1 = H, Me, 4-Cl-C_6H_4, 4-NO_2-C_6H_4
R^2 = Cl, H, Me, Et, Ph

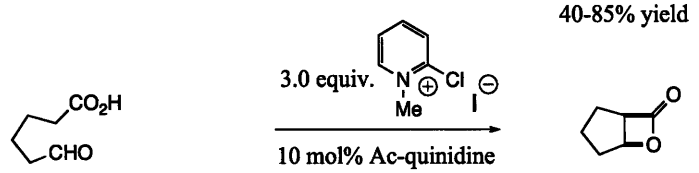
45-98% ee
68-95% yield



(1.2)

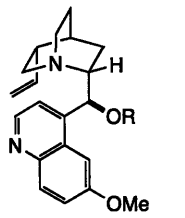
R = Bn, C_6H_{11}, $(CH_2)_2$OPiv, *i*-Pr

93-98% ee
40-85% yield

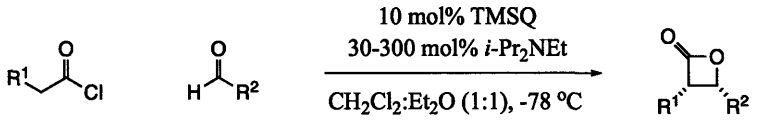


(1.3)

92% ee
54% yield



TMSQ; R = $SiMe_3$
Quinidine; R = H
Ac-quindine; R = Ac



(1.4)

R^1 = H, Me
R^2 = 1° alkyl, 2° alkyl, 3° alkyl, aryl

84-99% ee
76-96% de
68-85% yield

Ketene / aldehdye [2+2] cycloadditions are also catalyzed by Lewis acids. Evans has shown that copper-bisoxazoline complexes catalyze the cycloaddition of trimethlsilylketene with a variety of aldehydes that contain a second coordinating group (eq 1.5).[22] Moreover, Nelson has demonstrated aluminum-triamine complexes to be competent catalysts for the [2+2] cycloaddition of acid bromides with a wide range of aldehydes (eq 1.6).[23] Most recently, Peters has shown that aluminum diamine complexes are effective catalysts for this transformation (eq 1.7).[24]

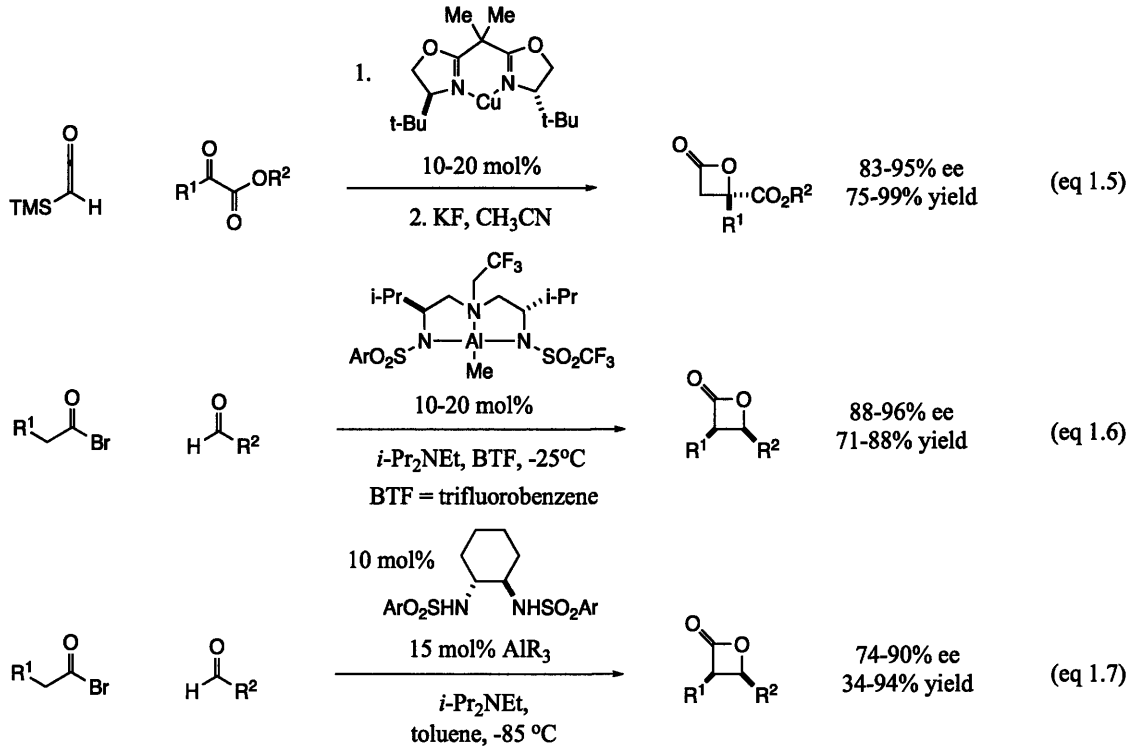
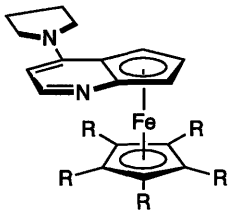
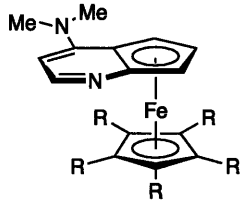


Figure 1.1. Structure of Planar-Chiral Nucleophilic Catalysts.

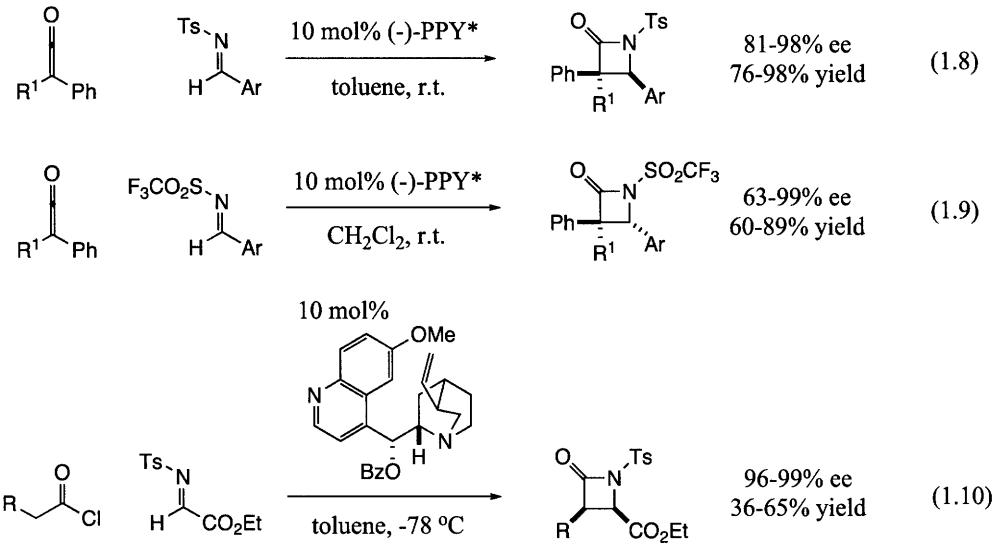


(-)-**1.1** ; R = Me; (-)-PPY*
(-)-**1.2**; R = Ph; (-)-PPY-C_5Ph_5



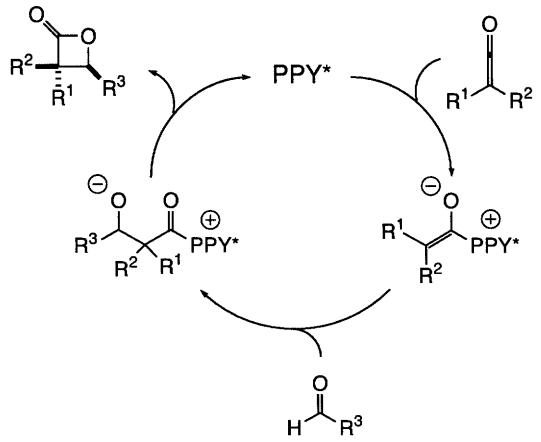
(-)-**1.3**; R = Me; (-)-DMAP*
(-)-**1.4**; R = Ph; (-)-DMAP-C_5Ph_5

Over the last decade our group has developed a family of planar-chiral DMAP and PPY derivatives that are excellent catalysts for a range of asymmetric processes (Figure 1.1).[25] In particular, we have found these compounds to be effective catalysts for processes involving *di*substituted ketenes.[26] Previously, our group has demonstrated that (-)-**1.1** and (-)-**1.3** catalyze the [2+2] cycloaddition of ketenes with imines with high levels of enantioselectivity and diastereoselectivity (eq 1.8 and eq 1.9).[27] Quinidine derivatives have also been shown to be effective catalysts for this process (eq 1.10).[28]



It is generally believed that nucleophile-catalyzed cycloadditions of ketenes with aldehydes occur by the mechanism outlined in Scheme 1.8. Addition of the nucleophilic catalyst to the ketene provides a zwitterionic enolate, which adds to the aldehyde to yield an aldolate intermediate. An addition / elimination sequence ejects the nucleophile to complete the catalytic cycle. An analogous pathway is thought to be operable for the related nucleophile-catalyzed [2+2] cycloadditions of ketenes with imines.

Scheme 1.8. Proposed Mechanism for Nucleophile-Catalyzed [2+2] Cycloadditions of Ketenes with Imines.

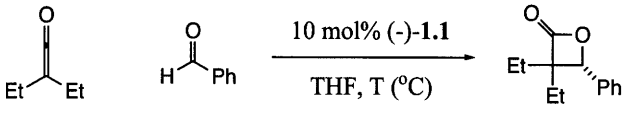


Encouraged by our previous success in the area of nucleophile catalyzed cycloadditions of ketenes with imines, we began our investigation of the [2+2] cycloaddition of *di*substituted ketenes with aldehydes. At the outset of our work, no examples of nucleophile catalyzed [2+2] cycloadditions of *di*substituted ketenes with aldehydes had been reported.

B. Results and Discussion.

We began our studies by examining the [2+2] cycloaddition of diethylketene with benzaldehyde. Interestingly, we found the reaction to have a strong dependence on temperature. At low temperatures, the reaction is highly efficient and selective, but higher temperatures lead to significantly lower yields (Table 1.1).

Table 1.1. Temperature Effects on the Nucleophile-Catalyzed [2+2] Cycloaddition of Diethylketene and Benzaldehyde.

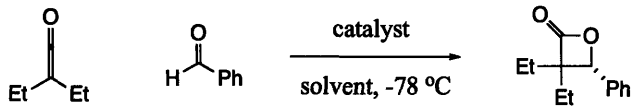


entry	temperature (°C)	ee (%)	yield (%)
1	-78	91	92
2	-70	89	98
3	-60	88	65
4	-50	88	40
5	-40	n.d.	~30
6	-20	n.d.	<5
7	0	n.d.	<5

Other planar-chiral DMAP and PPY derivatives are effective for this cycloaddition. Interestingly, we observe the opposite stereoselectivity when the

cyclopentadienyl ligand is changed from Cp* to C_5Ph_5 ((-)-**1.1** to (-)-**1.2**, Table 1.2, entries 1 and 4). Furthermore, the catalyst loading can be reduced to 5 mol% with little effect on yield or ee, but lower loadings result in decreased efficiency (Table 1.2, entries 2 and 3). Cosolvents have little effect on the outcome of the process (Table 1.2, entries 6 and 7).[29]

Table 1.2. Catalyst and Solvent Optimization for the Nucleophile-Catalyzed [2+2] Cycloaddition of Diethylketene with Benzaldehyde.

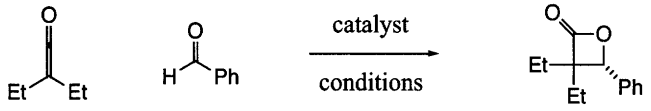


entry	catalyst	solvent	ee (%)	yield (%)
1	8% (-)-**1.1**	THF	89	98
2	4% (-)-**1.1**	THF	90	98
3	1% (-)-**1.1**	THF	n.d.	n.d.
4	8% (-)-**1.2**	THF	-90[a]	30
5	8% (-)-**1.3**	THF	90	96
6	5% (-)-**1.1**	1:1 THF:toluene	87	87
7	5% (-)-**1.1**	1:1 THF:CH_2Cl_2	91	95

[a] A negative value indicates that the opposite enantiomer from that shown in the equation was produced in excess.

Comparison of our reaction conditions to preexisting methodology for enantioselective β-lactone synthesis proved that our system is uniquely effective for [2+2] cycloadditions of *disubstituted* ketenes with aldehydes. Both Wynberg's and Nelson's conditions are unsuccessful for cycloadditions with this type of ketene (Table 1.3).

Table 1.3. Direct Comparison of Cinchona Alkaloid Based Catalyst Systems to (-)-PPY* in the Nucleophile-Catalyzed Enantioselective [2+2] Cycloaddition of Diethylketene and Benzaldehyde.



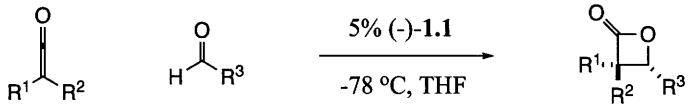
Entry	Catalyst	Conditions	ee (%)	yield (%)
1	10 mol% O-TMS-quinidine, 2 equiv. $LiClO_4$	THF:CH_2Cl_2 (1:1), -78 °C	n.d.	<5
2[a]	10 mol% O-TMS-quinidine, 2 equiv. $LiClO_4$	THF:CH_2Cl_2 (1:1), -78 °C to r.t.	1	21
3	5 mol% quinidine	THF:toluene (1:1), -78 °C to r.t.	n.d.	<5
4	5 mol% (-)-**1.1**	THF:toluene (1:1), -78 °C	89	91

All data are the average of two runs. [a]Because the product could not be separated from a side product, the lactone was reduced to a 1,3-diol with DIBAL-H to determine both the yield and ee.

With an effective set of reaction conditions in hand, the substrate scope of our system was investigated. Both electron-rich and electron-deficient aromatic aldehydes are suitable reaction partners (Table 1.4, Entries 1-5). Moreover, the ketene component can be changed to dimethylketene or hexamethyleneketene with little effect on the enantioselectivity or yield of the process (Table 1.4, Entries 6 and 7). Most interestingly, we are able to employ unsymmetrical ketenes, which yield β-lactones containing two adjacent stereocenters, one tertiary and one quaternary (Table 1.4, Entries 8 and 9). These cycloadditions provide the *cis*-trisubstituted lactone with good levels of enantioselectivity and diastereoselectivity.

We have breifly investigated cycloadditions of aliphatic aldehydes but these experiments have been unsuccessful up to this point. This is most likely due to the acidity of these compounds. Moreover, cycloadditions with cinnamaldehyde and *p*-methoxybenzaldehyde resulted in low yields.

Table 1.4. Scope of Nucleophile-Catalyzed Enantioselective [2+2] Cycloaddition of Ketenes with Aldehydes.

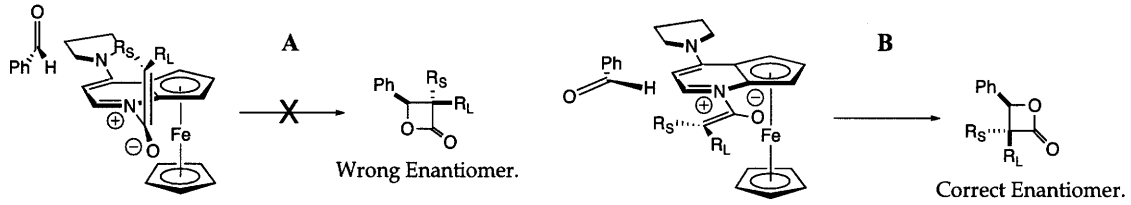


entry	R^1	R^2	R^3	ee (%)[a]	yield[a]
1	Et	Et	Ph	91	92
2	Et	Et	1-naphthyl	89	77
3	Et	Et	*p*-$CF_3C_6H_4$	80	74
4	Et	Et	*p*-$MeCOC_6H_4$	81	76
5	Et	Et	*p*-MeC_6H_4	89	67
6[b, c]	Me	Me	Ph	76	68
7	$(CH_2)_6$		Ph	82	71
8[d]	*i*-Pr	Me	Ph	91	48
9[d]		Me	Ph	88	53

[a] Average of two runs. [b] The product was reduced to the diol for analysis.
[c] 7% (-)-PPY* was used. d. d.r. = 4.2:1 to 4.6:1.

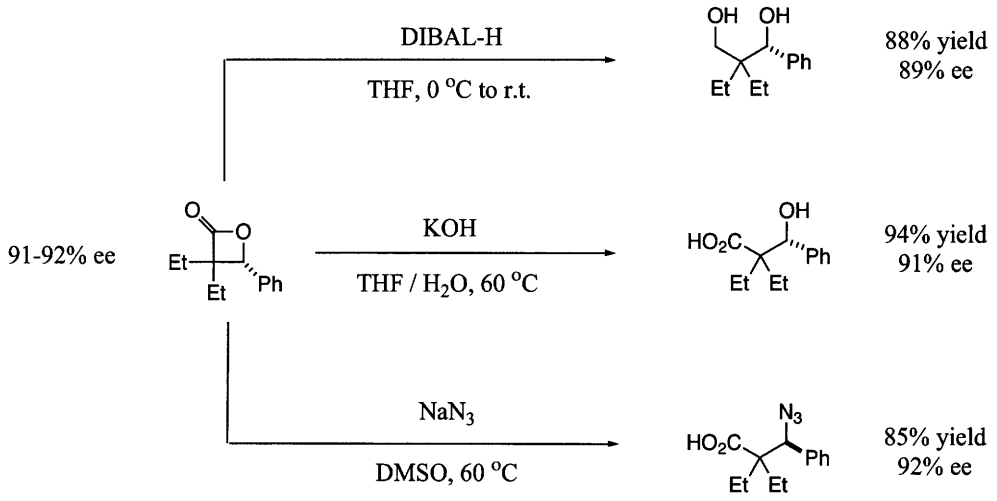
We have developed a model to explain the observed stereochemical outcome of these cycloadditions. Two possible transition states, **A** and **B**, which result from nucleophile-addition to the face of the ketene with the smaller substituent, are shown which could explain the observed *cis*-selectivity of the process (Scheme 1.9). However, only transition state **B**, where the zwitterionic enolate is coplanar with the catalyst framework, accomodates the observed absolute stereochemistry. Although these transition states, **A** and **B**, represent only the two extreme possibities for the structure of the zwitterionic enolate, a structure closely related to **B** seems likely.[30] However, further experiments would be necessary to validate the proposed stereochemical model.

Scheme 1.9. Possible Transition State Ensembles for the PPY*-Catalyzed [2+2] Cycloaddition.



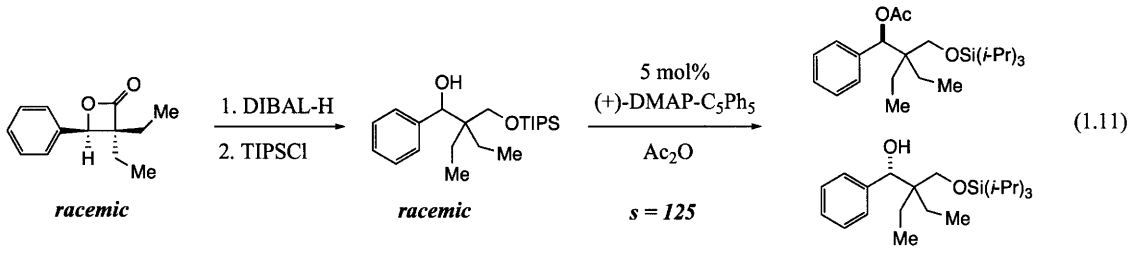
We have established that the sterically hindered trisubstituted β-lactone products from our cycloaddition reactions are subject to a number of ring-opening reactions. Reagents such as DIBAL-H and KOH add to the carbonyl group to deliver the 1,3-diol and β-hydroxyacid, respectively. On the other hand, NaN_3 reacts by an S_N2 mechanism to furnish a β-azido acid, a precursor to a β-amino acid. These functionalizations proceed in good yields and with no deterioration of enantiomeric excess.

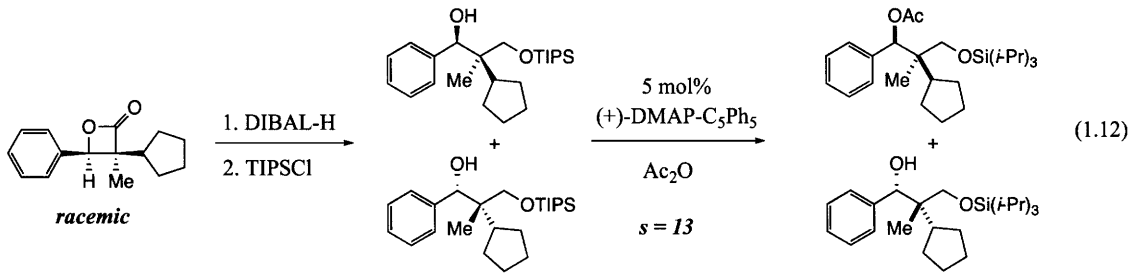
Scheme 1.9. Ring Opening Reactions of Trisubstituted β-lactones.



Interestingly, we employed a kinetic resolution of aryl-alkyl carbinols, previously developed in our group, to assign the absolute stereochemistry of the trisubstituted β-lactones generated from our reaction. Our products can be easily transformed into aryl-alkyl carbinols, which are excellent substrates for kinetic resolutions catalyzed by

(+)-**1.4**.[31] Because a turnover in stereoselectivity has never been observed for this family of secondary alcohol resolutions, we believed this method would provide a straightforward and accurate way to determine the absolute stereochemistry of our β-lactone products. Reduction of the racemic β-lactone with DIBAL-H and selective TIPS protection of the 1° alcohol provided the desired kinetic resolution substrates (eq 1.11 and eq 1.12). The resolution was highly selective in both cases examined. We then reduced and TIPS protected an enantioenriched sample of β-lactone, derived from our cycloaddition. Comparison by HPLC of this sample to a sample resolved with (+)-**1.4** allowed us to determine the absolute stereochemistry of our β-lactone products.





C. Conclusions.

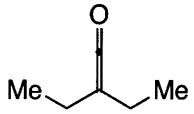
A nucleophile-catalyzed enantioselective [2+2] cycloaddition of ketenes with aromatic aldehydes has been developed. We have shown that this system is uniquely effective for the enantioselective cycloadditions of disubstituted ketenes with aldehydes. Finally, we have established that these products undergo a number of interesting ring-opening reactions.

D. Experimental

I. General

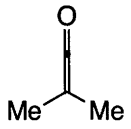
THF was purified by passing it through a neutral alumina column. Zinc metal (Strem) was activated with hydrochloric acid. Benzaldehyde (Aldrich), *p*trifluoromethylbenzaldehyde (Aldrich), *p*-tolualdehyde (Aldrich), and 2-bromo-2-methylpropanoylbromide (Aldrich) were distilled prior to use. Quinidine (Avocado), $LiClO_4$ (Alfa Aesar), 2-napthaldehyde (Aldrich), 4-acetylbenzaldehyde (Aldrich), DIBALH (1.0 M in THF; Aldrich), sodium azide (Alfa Aesar), DMSO (Aldrich), and *n*-propylamine (Aldrich) were used as received. Non-commercially available α-bromoacid bromides were synthesized according to a literature procedure.[32] Catalysts **1.1**,[33] **1.3**,[34] and *O*-TMS-quinidine[35] were prepared as previously reported. All ketenes were prepared by treatement of α-bromoacid bromides with activated Zn^0.[36, 37] All reactions were carried out under an atmosphere of nitrogen or argon in oven dried glassware with magnetic stirring, unless otherwise indicated.

II. Synthesis of Ketenes



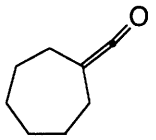
Diethylketene.[37] A sonicated slurry of Zn^0 (105 mg, 1.60 mmol) in THF (0.50 mL) in a Schlenk tube was treated with a solution of 2-bromo-2-ethylbutanoylbromide (128 mg, 0.500 mmol) in THF (0.50 mL). THF (0.25 mL) was used to wash the walls of the Schlenk tube. The reaction mixture was sonicated for 30 minutes at room temperature, and then the resulting solution of the ketene was vacuum transferred into a second Schlenk tube.

To quantify the amount of ketene generated by this procedure, the yellow ketene solution was quenched with *n*-propylamine (300 μL, 3.65 mmol). Evaporation of the solvent and the excess amine furnished a white solid (51.0 mg, 64%), which was identified by ^1H NMR to be 2-ethyl-*N*-propylbutyramide [551906-54-8].



Dimethylketene.[37] A stirred slurry of Zn^0 (82 mg, 1.25 mmol) in THF (0.50 mL) in a Schlenk tube at –78 °C was treated with a solution of 2-bromo-2-methylpropanoylbromide (115 mg, 0.500 mmol) in THF (0.50 mL). THF (0.25 mL) was used to wash thewalls of the Schlenk tube. The reaction mixture was stirred for 10 minutes at –78 °C and then 20 minutes at 0 °C, and then the resulting solution of the ketene was vacuum transferred into a second Schlenk tube.

To quantify the amount of ketene generated by this procedure, the yellow ketene solution was quenched with *n*-propylamine (300 μL, 3.65 mmol). Evaporation of the solvent and the excess amine furnished a white solid (63.0 mg, 97%), which was identified by ^{1}H NMR to be 2-methyl-*N*-propylpropanamide [108122-11-8].



Hexamethyleneketene.[37] A sonicated slurry of Zn^0 (118 mg, 1.80 mmol) in THF (0.60 mL) in a Schlenk tube was treated with a solution of 1-bromocycloheptanoyl-bromide (170 mg, 0.600 mmol) in THF (0.60 mL). THF (0.30 mL) was used to wash the walls of the Schlenk tube. The reaction mixture was sonicated for 30 minutes at 0 °C, and then the resulting solution of the ketene was vacuum transferred into a second Schlenk tube.

To quantify the amount of ketene generated by this procedure, the yellow ketene solution was quenched with *n*-propylamine (300 μL, 3.65 mmol). Evaporation of the solvent and the excess amine furnished a white solid (86.7 mg, 79%), which was identified as *N*-propylcycloheptanamide.

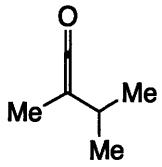
^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.73 (broad, 1H), 3.19-3.12 (m, 2H), 2.23-2.14 (m, 1H), 1.87-1.80 (m, 2H), 1.77-1.68 (m, 2H), 1.65-1.36 (m, 10H), 0.88 (t, J=7.5 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.5, 47.7, 41.1, 31.9, 28.2, 26.8, 23.0, 11.5.

FTIR (NaCl) 3281, 3083, 2927, 2857, 1640, 1558, 1456, 1384, 1235, 1155 cm^{-1}.

HRMS (ESI, M+H) calc. for $C_{11}H_{22}NO$ 184.1696, found 184.1695.

mp = 68° C.



Isopropyl methyl ketene.[37] A sonicated slurry of Zn^0 (105 mg, 1.60 mmol) in THF (0.50 mL) in a Schlenk tube was treated with a solution of 2-bromo-2,3-dimethylbutanoylbromide (129 mg, 0.500 mmol) in THF (0.50 mL). THF (0.25 mL) was used to wash the walls of the Schlenk tube. The reaction mixture was sonicated for 30 minutes at room temperature, and then the resulting solution of the ketene was vacuum transferred into a second Schlenk tube.

To quantify the amount of ketene generated by this procedure, the yellow ketene solution was quenched with *n*-propylamine (500 μL, 6.08 mmol). Evaporation of the solvent and the excess amine furnished a white solid (48.0 mg, 64%), which was identified as 2,3-dimethyl-*N*-propylbutyramide.

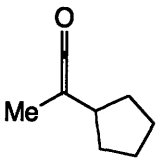
^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.80 (s, 1H), 3.27-3.08 (m, 2H), 1.89-1.73 (m, 2H), 1.49 (m, 2H), 1.07 (d, J=7.0 Hz, 3H), 0.91-0.86 (m, 9H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.5, 48.8, 41.1, 31.5, 23.1, 21.2, 19.7, 15.3, 11.5.

FTIR (NaCl) 3296, 3087, 2874, 1644, 1557, 1461, 1371, 1235, 1157, 1086, 978, 709 cm^{-1}.

HRMS (ESI, M+H) calc. for $C_9H_{20}NO$ 158.1539, found 158.1534.

mp = 50° C.



Cyclopentyl methyl ketene.[37] A sonicated slurry of Zn^0 (105 mg, 1.60 mmol) in THF (0.50 mL) in a Schlenk tube was treated with a solution of 2-bromo-2-cyclopentylpropanoylbromide (142 mg, 0.500 mmol) in THF (0.50 mL). THF (0.25 mL) was used to wash the walls of the Schlenk tube. The reaction mixture was sonicated for 30 minutes at room temperature, and then the resulting solution of the ketene was

vacuum transferred into a second Schlenk tube.

To quantify the amount of ketene generated by this procedure, the yellow ketene solution was quenched with *n*-propylamine (500 μL, 6.08 mmol). Evaporation of the solvent and the excess amine furnished a white solid (70.0 mg, 76%), which was identified as 2-cyclopentyl-*N*-propylpropanamide.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.83 (s, 1H), 3.27-3.07 (m, 2H), 1.96-1.84 (m, 2H), 1.82-1.65 (m, 2H), 1.61-1.43 (m, 6H), 1.16-1.00 (m, 5H), 0.88 (t, J=7.5 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.7, 47.7, 44.0, 41.1, 31.4, 30.7, 25.2, 25.1, 23.1, 17.2, 11.5.

FTIR (NaCl) 3291, 1634, 1557, 1455, 1232, 1156, 711 cm^{-1}.

HRMS (ESI, M+H) calc. for C11H22NO 184.1696, found 184.1691.

III. Asymmetric Synthesis of β-Lactones via Nucleophile-Catalyzed Cycloadditions of Disubstituted Ketenes with Aldehydes (Tables 1.1, 1.2, and 1.3)

Table 1.1. The experiments in Table 1.1 were carried out using the procedure outlined below. See Table 1.4, Entry 1.

Table 1.2. The experiments in Table 1.2 were carried out using the procedure outlined below with the temperature being controlled by a cryocool cooler. See Table 1.4, Entry 1.

Table 1.3, entry 1. A solution of diethylketene (38 mg, 0.38 mmol), prepared as described above immediately before use, in THF (1.5 mL) was vacuum transferred to a Schlenk tube containing a solution of benzaldehyde (20 μL, 0.20 mmol), *O*-TMS-quinidine (8.0 mg, 0.020 mmol), and $LiClO_4$ (41 mg, 0.39 mmol) in CH_2Cl_2 (1.5 mL) at –78 °C. After 20 h at -78 °C, the reaction mixture was filtered through a pad of silica gel with copious washings with Et_2O. The solvent was removed, and the product was purified by silica gel chromatography (10% Et_2O/pentane), which furnished <2 mg of a mixture of the desired β-lactone and an unidentified side product.

HPLC analysis: 1% ee [Daicel CHIRALCEL AD-H column; 1.0 mL/min; solvent system: 10.0% isopropanol in hexanes; retention times: 9.6 min (minor), 12.6 min (major)].

Second run: Diethylketene (38 mg, 0.38 mmol), benzaldehyde (20 μL, 0.20 mmol), *O*-TMS-quinidine (8.0 mg, 0.020 mmol), and $LiClO_4$ (41 mg, 0.39 mmol). Mixture of the desired β-lactone and the unidentified side product: <2 mg. (<5%; 0%ee).

Table 1.3, entry 2. A solution of diethylketene (38 mg, 0.38 mmol), prepared as described above immediately before use, in THF (1.5 mL) was vacuum transferred to a Schlenk tube containing a solution of benzaldehyde (20 μL, 0.20 mmol), *O*-TMS-quinidine (8.0 mg, 0.020 mmol), and $LiClO_4$ (41 mg, 0.39 mmol) in CH_2Cl_2 (1.5 mL) at –78 °C. The resulting solution was immediately placed into a 0 °C ice-water bath, which warmed to room temperature over ~2 h. After 20 h at room temperature, the reaction mixture was filtered through a pad of silica gel with copious washings with Et_2O. The solvent was removed, and the product was purified by silica gel chromatography (10% Et_2O/pentane), which furnished 15.6 mg of a mixture of the desired β-lactone and an unidentified side product.

The mixture was treated with a solution of DIBAL-H in THF (1.0 M; 0.5 mL). After stirring for 6 h at room temperature, the reaction mixture was quenched with NaOH (1.0 N; 0.6 mL). The aqueous layer was extracted with Et_2O (5 x 1 mL), and the combined extracts were filtered through a short pad of silica gel with Et_2O washings. The solvent was removed, and the 1,3-diol was purified by silica gel chromatography (10 -40% Et_2O/pentane), which furnished 9.0 mg (22%) of the 1,3-diol as a clear oil.

HPLC analysis: 1% ee [Daicel CHIRALCEL AD-H column; 1.0 mL/min; solvent system: 10.0% isopropanol in hexanes; retention times: 9.6 min (minor), 12.6 min (major)].

Second run: Diethylketene (38 mg, 0.38 mmol), benzaldehyde (20 μL, 0.20 mmol), *O*-TMS-quinidine (8.0 mg, 0.020 mmol), and $LiClO_4$ (41 mg, 0.39 mmol). Mixture of the desired β-lactone and the unidentified side product: 15.3 mg; 1,3-diol: 8.1 mg (20%; 0%ee).

Table 1.3, entry 3. A solution of diethylketene (38 mg, 0.38 mmol), prepared as described above immediately before use, in THF (1.5 mL) was vacuum transferred to a Schlenk tube containing a solution of benzaldehyde (40 μL, 0.39 mmol) and quinidine (6.5 mg, 0.020 mmol) in toluene (1.5 mL) at –78 °C. The resulting solution was immediately placed into a 0 °C ice-water bath, which warmed to room temperature over ~2 h. After 20 h at room temperature, the reaction mixture was filtered through a pad of silica gel with copious washings with Et_2O. The solvent was removed, and the product was purified by silica gel chromatography (10% Et_2O/pentane), which furnished 2.0 mg of β-lactone (<5%).

Second run: Quinidine (6.5 mg, 0.020 mmol), diethylketene (38 mg, 0.38 mmol), and benzaldehyde (40 μL, 0.39 mmol). <5% yield.

Table 1.3, entry 4. See the procedure in Section IV for Table 1.4, entry 1.

IV. Asymmetric Synthesis of β-Lactones via (-)-1.1-Catalyzed [2+2] Cycloadditions of Disubstituted Ketenes with Aldehydes (Table 1.4).

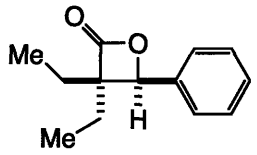


Table 1.4, entry 1. 3,3-Diethyl-4-phenyloxetan-2-one. General Procedure for Table 1.4. A solution of (+)-**1.1** (6.0 mg, 0.016 mmol) in THF (0.40 mL) was added dropwise over 5 min to a –78 °C solution of diethylketene (38 mg, 0.38 mmol), prepared as described above immediately before use, and benzaldehyde (32 μL, 0.32 mmol) in THF (1.5 mL). The reaction mixture was stirred at –78 °C for 5.5 h, and then it was filtered through a short pad of silica gel with copious washings with Et_2O. The solvent was removed, and the product was purified by silica gel chromatography (10% Et_2O/pentane), which furnished 61.0 mg (93%) of a clear oil.

HPLC analysis: 89% ee [Daicel CHIRALCEL AD column; 1.0 mL/min; solvent system: 3.5% isopropanol in hexanes; retention times: 6.4 min (minor), 7.4 min (major)].

Second run: (–)-**1.1** (6.0 mg, 0.016 mmol), diethylketene (38 mg, 0.38 mmol), and

benzaldehyde (32 μL, 0.32 mmol). 92% yield, 92% ee.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43-7.24 (m, 5H), 5.38 (s, 1H), 1.98 (m, 2H), 1.48-1.36 (m, 1H), 1.31-1.19 (m, 1H), 1.13 (t, J=7.5 Hz, 3H), 0.77 (t, J=7.5 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.3, 135.4, 128.7, 128.5, 125.7, 80.9, 64.5, 24.7, 21.9, 8.7, 7.9.

FTIR (NaCl) 1824, 1454, 1248, 1102, 942 cm^{-1}.

HRMS (ESI, M+Na) calc. for $C_{13}H_{16}NaO_2$ 227.1043, found 227.1046.

$[\alpha]^{21.6}_D$ = +62° (c= 0.19, CH_2Cl_2; from reaction with (+)-**1.1**).

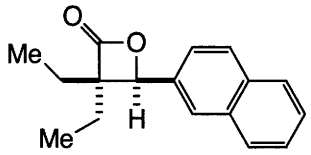


Table 1.4, entry 2. 3,3-Diethyl-4-(2-naphthyl)oxetan-2-one. The general procedure was followed: (+)-**1.1** (6.0 mg, 0.016 mmol), diethylketene (38 mg, 0.38 mmol), and 2-napthaldehyde (50.0 mg, 0.320 mmol). Reaction time: 5.5 hours. Purified by silica gel chromatography (toluene), which provided 61.0 mg (75%) of a white solid.

HPLC analysis: 89% ee [Daicel CHIRALCEL AD column; solvent system: 3.5% isopropanol in hexanes; retention times: 6.8 min (minor), 9.4 min (major)].

Second run: (–)-**1.1** (6.0 mg, 0.016 mmol), diethylketene (38 mg, 0.38 mmol), 2-napthaldehyde (50.0 mg, 0.320 mmol). 80% yield, 89% ee.

$[\alpha]^{21.6}_D$ = –2.9° (c= 0.48, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.91-7.84 (m, 4H), 7.56-7.52 (m, 2H), 7.36-7.32 (m, 1H), 5.54 (s, 1H), 2.03 (m, 2H), 1.53-1.40 (m, 1H), 1.34-1.22 (m, 1H), 1.19 (t, J=7.5 Hz, 3H), 0.77(t, J=7.5 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.3, 133.2, 133.2, 132.9, 128.5, 128.2, 128.0, 126.8, 126.6, 125.0, 123.2, 81.0, 64.8, 24.7, 21.9, 8.3, 8.0.

FTIR (NaCl) 1824, 1458, 1247, 1101 cm^{-1}.

HRMS (ESI, M+Na) calc. for $C_{17}H_{18}NaO_2$ 277.1199, found 277.1204.

$[\alpha]^{21.6}_D$ = –2.9° (c= 0.48, CH_2Cl_2; from reaction with (+)-**1.1**).

mp = 59°C.

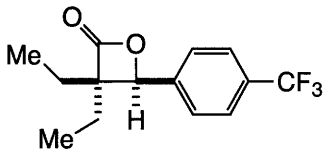


Table 1.4, entry 3. 3,3-Diethyl-4-(4-trifluoromethyl)phenyloxetan-2-one. The general procedure was followed: (+)-**1.1** (6.0 mg, 0.016 mmol), diethylketene (38 mg, 0.38 mmol), and 4-trifluoromethylbenzaldehyde (44 μL, 0.32 mmol). Reaction time: 5.5 hours. Purified by silica gel chromatography (0-20% Et_2O/pentane), which provided 66.6 mg (76%) of a clear oil.

HPLC analysis: 80% ee [Daicel CHIRACEL OJ column; 1.0 mL/min; solvent system: 3.5% isopropanol in hexanes; retention times: 7.6 min (minor), 10.7 min (major)].

Second run: (–)-**1.1** (6.0 mg, 0.016 mmol), diethylketene (38 mg, 0.38 mmol), and 4-trifluoromethylbenzaldehyde (44 μL, 0.32 mmol). 72% yield, 79% ee.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67 (d, J=8.0 Hz, 2H), 7.41 (d, J=8.0 Hz, 2H), 5.41 (s, 1H), 2.08-1.90 (m, 2H), 1.43-1.31 (m, 1H), 1.28-1.17 (m, 1H), 1.13 (t, J=7.5 Hz, 3H), 0.78 (t, J=7.5 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.5, 139.6, 130.7(q), 126.0(d), 125.8(d), 125.7(d), 80.0, 65.2, 24.6, 22.1, 8.8, 8.0.

FTIR (NaCl) 1831, 1622, 1461, 1418, 1326, 1127, 1068, 943, 899 cm^{-1}.

HRMS (ESI, M+Na) calc. for $C_{14}H_{15}F_3NaO_2$ 295.0916, found 295.0926. $[\alpha]^{21.7}_D$ = +31° (c=0.65, CH_2Cl_2; from reaction with (+)-**1.1**).

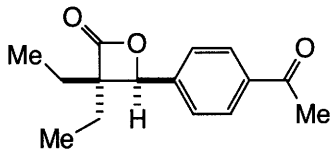


Table 1.4, entry 4. 3,3-Diethyl-4-(4-acetyl)phenyloxetan-2-one. The general procedure was followed: (+)-**1.1** (6.0 mg, 0.016 mmol), diethylketene (38 mg, 0.38 mmol),and 4-acetylbenzaldehyde (47 mg, 0.32 mmol). Reaction time: 5.5 hours. Purified bysilica gel chromatography (5-10% acetone/pentane), which provided 59.3 mg (75%)of a clear oil.

HPLC analysis: 82% ee [Daicel CHIRACEL AD column; 1.0 mL/min; solvent

system: 3.5% isopropanol in hexanes; retention times: 14.3 min (minor), 18.9 min (major)].

Second run: (–)-**1.1** (6.0 mg, 0.016 mmol), diethylketene (38 mg, 0.38 mmol), and 4-acetylbenzaldehyde (47 mg, 0.32 mmol). 77% yield, 80% ee.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.99 (d, J= 8.5 Hz, 2H), 7.38 (d, J=8.5 Hz, 2H), 5.40 (s, 1H), 2.61 (s, 3H), 1.97 (dq, J=2.0 Hz, J=7.5 Hz, 2H), 1.26 (m, 2H), 1.11 (t, J=7.5 Hz, 3H), 0.75 (t, J=7.5 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.6, 173.6, 140.7, 137.1, 128.7, 125.9, 80.2, 65.2, 26.8, 24.6, 22.0, 8.8, 8.0.

FTIR (NaCl) 1825, 1684, 1610, 1459, 1412, 1360, 1267, 1099 cm^{-1}.

HRMS (ESI, M+Na) calc. for $C_{15}H_{18}NaO_3$ 269.1148, found 269.1140.

$[\alpha]^{21.5}_D$ = +36° (c=0.34, CH_2Cl_2; from reaction with (+)-**1.1**).

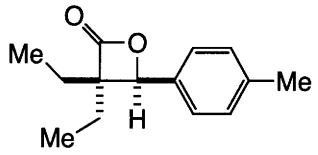


Table 1.4, entry 5. 3,3-Diethyl-4-(4-methyl)phenyloxetan-2-one. The general procedure was followed: (–)-**1.1** (6.0 mg, 0.016 mmol), diethylketene (38 mg, 0.38 mmol), and *p*-tolualdehyde (38 μL, 0.32 mmol). Reaction time: 24 hours. Purified by silica gel chromatography (10% Et_2O/pentane; the remaining aldehyde was removed under vacuum), which provided 48.1 mg (69%) of a clear oil. The β-lactone was reduced to the diol with DIBAL-H for HPLC analysis (for the procedure, see Part IV).

HPLC analysis (1,3-diol): 89% ee [Daicel CHIRACEL AD-H column; 1.0 mL/min; solvent system: 10% isopropanol in hexanes; retention times: 6.5 min (major), 8.9 min (minor)].

Second run: (+)-**1.1** (6.0 mg, 0.016 mmol), diethylketene (38 mg, 0.38 mmol), and *p*-tolualdehyde (38 μL, 0.32 mmol). 64% yield, 88% ee.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23-7.16 (m, 4H), 5.34 (s, 1H), 2.38 (s, 3H), 1.96 (q, J=7.5 Hz, 2H), 1.50-1.37 (m, 1H), 1.31-1.18 (m, 1H), 1.11 (t, J=7.5 Hz, 3H), 0.76 (t, J= 7.5 Hz,3H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.5, 138.4, 132.4, 129.4, 125.7, 81.1, 64.4, 24.7,

21.9, 21.4, 8.5, 8.0.

FTIR (NaCl) 1825, 1459, 1101, 943, 890 cm^{-1}.

HRMS (ESI, M+Na) calc. for $C_{14}H_{18}NaO_2$ 241.1199, found 241.1199.

$[\alpha]^{21.7}_D = -28°$ (c=0.49, CH_2Cl_2; from reaction with (–)-**1.1**).

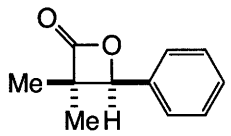


Table 1.4, entry 6. 3,3-Dimethyl-4-phenyloxetan-2-one. [52178-66-2] A solution of (–)-**1.1** (12.5 mg, 0.034 mmol) in THF (0.6 mL) was added dropwise over 8 min to a –78 °C solution of dimethylketene (33 mg, 0.48 mmol) and benzaldehyde (58 μL, 0.57 mmol) in THF (1.75 mL). The reaction mixture was stirred at –78 °C for 22 h, and then it was filtered through a short pad of silica gel with copious washings with Et_2O. The filtrate was immediately treated with LAH (4.8 mmol; 1.0 M in THF), and the resulting mixture was stirred for 1 h at room temperature. The solution was then quenched with 1 N NaOH (5 mL) and H_2O (5 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc. The organic extracts were combined, concentrated under vacuum, and then purified by silica gel chromatography (20-50% Et_2O/pentane), which furnished 55.0 mg (64%) of a white solid (1,3-diol; [33950-46-8]).

HPLC analysis: 78% ee [Daicel CHIRALCEL AD-H column; 1.0 mL/min; solvent system: 5.0% isopropanol in hexanes; retention times: 14.5 min (minor), 15.8 min (major)].

Second run: (–)-**1.1** (18.7 mg, 0.050 mmol), dimethylketene (50 mg, 0.71 mmol), and benzaldehyde (86 μL, 0.85 mmol). 71% yield, 74% ee.

^1H NMR ($CDCl_3$, 300 MHz) δ 7.38-7.30 (m, 5H), 4.64 (s, 1H), 3.61 (d, J=11.0 Hz, 1H), 3.53 (d, J=11.0 Hz, 1H), 2.59 (s, 2H), 0.90 (s, 3H), 0.86 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.6, 127.9, 127.8, 127.7, 82.4, 72.3, 39.2, 23.0, 19.1.

HRMS (ESI, M+Na) calc. for $C_{11}H_{12}NaO_2$ 199.0730, found 199.0732.

$[\alpha]^{20.9}_D = -19.6°$ (c=0.73, CH_2Cl_2; from reaction with (–)-**1.1**).

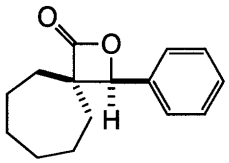


Table 1.4, entry 7. 3,3-Spirocycloheptyl-4-phenyl-oxetan-2-one. A solution of (+)-**1.1**(10.9 mg, 0.029 mmol) in THF (0.90 mL) was added dropwise over 8 min to a –78 °C solution of hexamethyleneketene (60 mg, 0.48 mmol) and benzaldehyde (59 μL, 0.58 mmol) in THF (1.5 mL). The reaction mixture was stirred at –78 °C for 22 hours, and then it was filtered through a short pad of silica gel with copious washings with Et_2O. The solvent was removed, and the product was purified by silica gel chromatography (0-6% Et_2O/hexane), which provided 74.5 mg (68%) of a clear oil.

HPLC analysis: 83% ee [Daicel CHIRALCEL AD column; 1.0 mL/min; solvent system: 2.0% isopropanol in hexanes; retention times: 7.2 min (minor), 9.3 min (major)].

Second run: (–)-**1.1** (10.9 mg, 0.029 mmol), hexamethyleneketene (60 mg, 0.48 mmol), and benzaldehyde (59 μL, 0.58 mmol). 73% yield, 80% ee.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46-7.27 (m, 5H), 5.31 (s, 1H), 2.31-2.22 (m, 1H), 2.18-2.11 (m, 1H), 1.97-1.81 (m, 1H), 1.68-1.50 (m, 4H), 1.48-1.19 (m, 5H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.6, 135.5, 128.8, 128.7, 125.9, 84.3, 64.0, 35.4, 30.4, 29.2, 29.2, 23.8, 22.9.

FTIR (NaCl) 1821, 1497, 1457, 1355, 1112, 939 cm^{-1}.

HRMS (ESI, M+Na) calc. for $C_{15}H_{18}NaO_2$ 253.1199, found 253.1199.

$[\alpha]^{21.6}_D$ = +18° (c=0.57, CH_2Cl_2; from reaction with (+)-**1.1**).

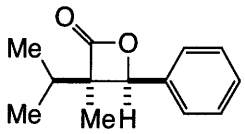


Table 1.4, entry 8. *cis*-3-Isopropyl-3-methyl-4-phenyloxetan-2-one. A solution of (–)-**1.1** (7.0 mg, 0.019 mmol) in THF (0.5 mL) was added dropwise over 5 min to a –78 °C solution of isopropyl methyl ketene (36 mg, 0.37 mmol), prepared as described above immediately before use, and benzaldehyde (113 μL, 1.11 mmol) in THF (1.5 mL). The reaction mixture was stirred for 22 hours, during whichtime it slowly warmed from –78 °C to –10 °C, and then it was filtered through a short pad of silica gel with copious

washings with Et_2O. The crude reaction mixture was analyzed by ^1H NMR to determine the diastereoselectivity (4.1:1 cis:trans). The product was purified by silica gel chromatography (1-5% Et_2O/pentane), which provided 22.5 mg of the cis diastereomer (crystalline solid) and 14.5 mg of a mixture of diastereomers (49% yield, total). Although a sample of the minor diastereomer could not be isolated in pure form the spectral data resemble those of pure isomer of an analogous trans-β-lactone (See the supporting information below for Table 1.4, entry 9). The major isomer was determined by X-ray crystallography to be the cis isomer (see Appendix A).

HPLC analysis: 89% ee [Daicel CHIRALCEL AD column; 1.0 mL/min; solvent system: 2.0% isopropanol in hexanes; retention times (cis diastereomer): 6.7 min (major), 8.7 min (minor)].

Second run: (+)-**1.1** (7.0 mg, 0.019 mmol), isopropyl methyl ketene (36 mg, 0.37 mmol), and benzaldehyde (113 μL, 1.11 mmol). 46% yield, 4.3:1 cis:trans, 92% ee (cis diastereomer).

Major diastereomer (cis): ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45-7.34 (m, 5H), 5.26 (s, 1H), 2.02 (sept, J=7.0 Hz, 1H), 1.50 (s, 3H), 1.02 (d, J=7.0 Hz, 3H), 0.38 (d, J=7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.0, 135.0, 129.1, 128.6, 127.0, 84.3, 63.7, 27.4, 17.7, 15.9,14.8.

FTIR (NaCl) 1821, 1456, 1111, 1078, 939 cm^{-1}.

HRMS (ESI, M+Na) calc. for $C_{13}H_{16}NaO_2$ 227.1043, found 227.1045.

$[\alpha]^{21.7}_D$ = +33° (c=0.20, CH_2Cl_2; from reaction with (+)-**1.1**).

mp = 76° C.

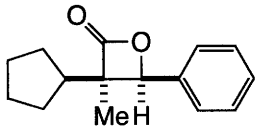


Table 1.4, entry 9. *cis*-3-Cyclopentyl-3-methyl-4-phenyloxetan-2-one. A solution of (+)-**1.1** (8.5 mg, 0.023 mmol) in THF (0.75 mL) was added dropwise over 8 min to a –78 °C solution of cyclopentyl methyl ketene (56 mg, 0.45 mmol) and benzaldehyde (137 μL,1.35 mmol) in THF (1.5 mL). The reaction mixture was stirred at

–78 °C for 72 hours, and then it was filtered through a short pad of silica gel with copious washings with Et_2O. The solvent was removed, and the product was purified by silica gel chromatography (1-2% Et_2O/pentane), which provided 43.3 mg of the major diastereomer and 9.6 mg of the minor diastereomer (51%, 4.5:1 cis:trans).

HPLC analysis: 88% ee (cis diastereomer), 47% ee (trans diastereomer) [Daicel CHIRALCEL AD column; 1.0 mL/min; solvent system: 2.0% isopropanol in hexanes; retention times: cis diastereomer, 6.5 min (minor), 7.1 min (major); trans diastereomer, 6.3 min (minor), 7.6 min (major)].

Second run: (+)-**1.1** (8.5 mg, 0.023 mmol), cyclopentyl methyl ketene (56 mg, 0.45 mmol), and benzaldehyde (137 μL, 1.35 mmol). 55% yield, 4.7:1 cis: trans, 88% ee (cis diastereomer).

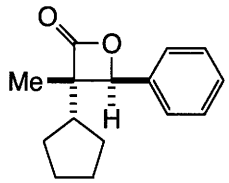
Major diastereomer (cis): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43-7.31 (m, 5H), 5.31 (s, 1H), 2.08-1.97 (m, 1H), 1.55 (s, 3H), 1.53-1.30 (m, 5H), 1.29-1.18 (m, 1H), 1.15-1.03 (m,1H), 1.00-0.89 (m, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.7, 135.6, 128.6, 128.5, 126.1, 83.7, 63.3, 39.8, 28.2, 26.7, 25.8, 25.6, 17.0.

FTIR (NaCl) 1823, 1454, 1382, 1264, 1101, 945, 873 cm^{-1}.

HRMS (ESI, M+Na) calc. for $C_{15}H_{18}NaO_2$ 253.1199, found 253.1193.

$[\alpha]^{21.7}_D$ = +31° (c=0.29, CH_2Cl_2; from reaction with (+)-**1.1**).



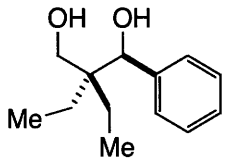
Minor diastereomer (trans): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45-7.32 (m, 3H), 7.27-7.25 (m, 2H), 5.40 (s, 1H), 2.30 (m, 1H), 2.03-1.84 (m, 2H), 1.83-1.53 (m, 5H), 1.51-1.36 (m, 1H), 0.92 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.1, 135.8, 128.8, 128.5, 125.6, 79.6, 63.5, 44.5, 28.5, 28.1, 25.7, 25.6, 15.8.

FTIR (NaCl) 1825, 1454, 1070, 942 cm^{-1}.

$[\alpha]^{21.4}_D$ = +5.0° (c=0.68, CH_2Cl_2; from reaction with (+)-**1.1**).

V. Derivatization of the β-Lactones (Scheme 1.9).

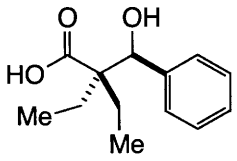


Scheme 1.9, top. 1-Phenyl-2,2-diethyl-1,3-propanediol. [63834-79-7] A solution of DIBAL-H in THF (1.0 M; 0.30 mL, 0.30 mmol) was added to a 0 °C solution of 3,3-diethyl-4-phenyloxetan-2-one (20.0 mg, 0.098 mmol; 91% ee) in THF (0.30 mL). Upon completion of the addition, the reaction mixture was warmed to room temperature over 2 h. Then, a solution of NaOH (1.0 N; 0.40 mL) was added. The aqueous layer was extracted with Et_2O (3 x 5 mL), and the combined extracts were washed with water and then brine. The organic layer was concentrated, and the residue was purified by column chromatography (10-40% Et_2O/pentane), which furnished 18.0 mg (88%) of a clear oil.

HPLC analysis: 89% ee [Daicel CHIRALCEL AD column; 1.0 mL/min; solvent system: 10.0% isopropanol in hexanes; retention times: 7.0 min (minor), 8.9 min (major)].

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38-7.26 (m, 5H), 4.73 (d, J=5.5 Hz, 1H), 3.57 (dd, J=11.5 Hz, J=3.5 Hz, 1H), 3.49 (d, J=4.5 Hz, 1H), 3.44 (dd, J=10.5 Hz, J=5.5 Hz, 1H), 3.24 (dd, J=6.0 Hz, J=4.0 Hz, 1H), 1.84-1.60 (m, 2H), 0.99 (m, 2H), 0.93 (t, J=7.5 Hz, 3H), 0.78 (t, J=7.5 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.8, 128.0, 127.8, 127.6, 80.6, 66.8, 43.3, 22.7, 22.6, 7.7, 7.6.



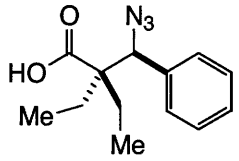
Scheme 1.9, middle. 2,2-Diethyl-3-hydroxy-3-phenylpropanoic acid. [59697-81-3] A solution of KOH (1.0 N; 0.28 mL) was added to a solution of 3,3-diethyl-4-phenyloxetan-2-one (28.4 mg, 0.139 mmol; 92% ee) in wet THF (0.50 mL). The reaction mixture was sealed and heated to 60 °C for 5 h, and then it was cooled to room

temperature and treated with HCl (1.0 N; 0.30 mL). The aqueous layer was extracted with EtOAc/Et_2O (1:1; 5 x 3 mL), and the combined extracts were washed with brine, dried over $MgSO_4$, filtered through a short plug of silica gel, and concentrated to a white solid (29.1 mg, 94%). The ee was determined by reducing the β-hydroxyacid to the 1,3-diol with $LiAlH_4$ in THF
(15 equiv.).

HPLC analysis: 91% ee [Daicel CHIRALCEL AD-H column; 1.0 mL/min; solvent system: 10.0% isopropanol in hexanes; retention times: 7.2 min (major), 9.2 min (minor)].

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.32 (m, 5H), 4.89 (s, 1H), 1.79 (m, 2H), 1.73 (dq, J=15.0 Hz, J=7.5 Hz, 1H), 1.41 (dq, J=15.0 Hz, J=7.5 Hz, 1H), 0.97 (t, J=7.5 Hz, 3H), 0.94 (t, J=7.5 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 181.3, 140.2, 128.4, 128.3, 127.4, 77.1, 54.8, 25.8, 23.4, 8.94, 8.92.



Scheme 1.9, bottom. 2,2-Diethyl-3-azido-3-phenylpropanoic acid. Sodium azide (21.0 mg, 0.323 mmol) was added to a solution of 3,3-diethyl-4-phenyloxetan-2-one (33.0 mg, 0.162 mmol; 92% ee) in DMSO (1.0 mL). The reaction vessel was sealed and heated to 65 °C for 48 h. The reaction was then quenched with HCl (1.0 N; 1.0 mL) and H_2O (1.0 mL). The aqueous layer was extracted with EtOAc (4 x 5 mL), and the organic extracts were combined and washed with H_2O and then brine. The extracts were concentrated, and the residue was purified by column chromatography (1- 4% MeOH/CH_2Cl_2), which furnished 34.0 mg (85%) of the azide. To assay the ee, the acid was converted to the methyl ester by treatment with excess diazomethane in Et_2O .

HPLC analysis: 92% ee [Daicel CHIRALCEL OJ-H column; 1.0 mL/min; solvent system: 5.0% isopropanol in hexanes; retention times: 7.1 min (minor), 7.6 min (major)].

^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.40 (br s, 1H), 7.41-7.31(m, 5H), 4.94 (s, 1H), 1.82-1.58 (m, 4H), 0.95 (m, 6H).

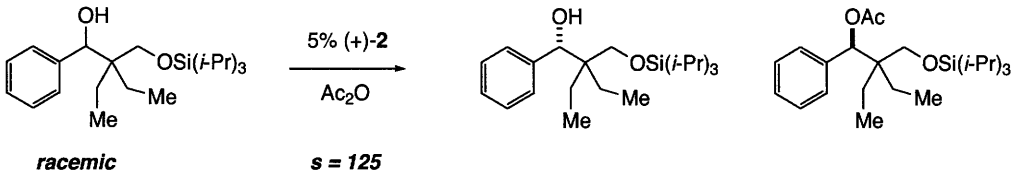
^{13}C NMR ($CDCl_3$, 75 MHz) δ 180.8, 136.2, 128.7, 128.6, 128.5, 70.6, 54.5, 25.4, 24.2, 9.3, 8.9.

FTIR (NaCl) 2973 (broad), 2103, 1699, 1453, 1252, 914, 742 cm^{-1}.

HRMS (ESI, M–H) calc. for $C_{13}H_{16}N_3O_2$ 246.1248, found 246.1244.

$[\alpha]^{21.4}_D$ = +123° (c=0.18, CH_2Cl_2; from reaction with (–)-**1.1**)

VI. Determination of the Absolute Stereochemistry of the β-Lactones



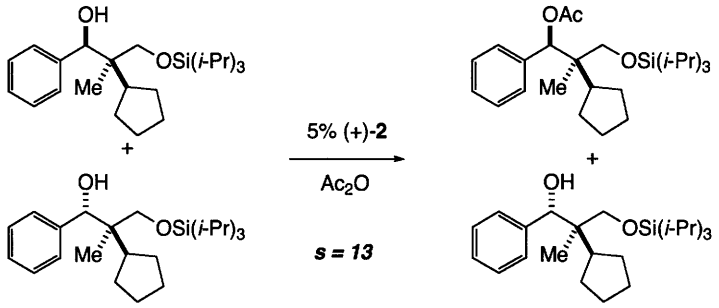
racemic ***s = 125***

Eq 1.11. Kinetic resolution of (+)-2,2-diethyl-3-phenyl-1-triisopropylsiloxy-3-propanol. Ac_2O (6.8 μL, 0.072 mmol) was added to a stirred solution of the racemic alcohol (35 mg, 0.096 mmol), NEt_3 (6.6 μL, 0.072 mmol), and (+)-**1.4** (3.0 mg, 0.0050 mmol) in *t*-amyl alcohol (0.25 mL) at 0 °C.[29] The reaction mixture was stirred for 7 days at 0 °C, and then the reaction was quenched with MeOH (0.50 mL). The reaction mixture was filtered through a pad of silica gel and concentrated. The ^{1}H NMR spectrum of the unpurified reaction mixture indicated ~33% conversion. Purification by silica gel chromatography (0.5-2.0% Et_2O/pentane) yielded 13.0 mg of the acetate and 14.0 mg of the alcohol.

HPLC analysis of the alcohol: 48% ee [Daicel CHIRALCEL AD-H column; 1.0 mL/min; solvent system: 5.0% isopropanol in hexanes; retention times: 3.9 min (minor), 7.8 min (major)].

A sample of 2,2-diethyl-3-phenyl-1-triisopropylsiloxy-3-propanol was then prepared from an enantioenriched sample of 3,3-diethyl-4-phenyloxetan-2-one (obtained from a reaction conducted with (–)-**1.1**). This sample was enriched (HPLC analysis: 90% ee) in the opposite enantiomer of the alcohol to that obtained from the kinetic resolution. On this basis, we assign the absolute stereochemistry of the product of the reaction illustrated in entry 1 of Table 1.4. The stereochemistry of entries 2-7 in Table 1.4 are assigned by analogy (note that the HPLC elution order is the same for all entries: the

major enantiomer elutes more slowly).



Eq. 1.12. Kinetic resolution of (+)-2-cyclopentyl-2-methyl-3-phenyl-1-triisopropylsiloxy-3-propanol (illustrated diastereomer). Ac_2O (4.6 μL, 0.049 mmol) was added to a stirred solution of the racemic alcohol (29.5 mg, 0.076 mmol), NEt_3 (4.5 μL, 0.049 mmol), and (+)-**1.4** (2.5 mg, 0.0040 mmol) in *t*-amyl alcohol (0.40 mL). The reaction mixture wasstirred for 2 days at room temperature, and then additional NEt_3 (4.5 μL, 0.049 mmol) and Ac_2O (4.6 μL, 0.049 mmol) were added. After five more days, the reaction was quenched with MeOH (0.5 mL). The reaction mixture was filtered through a pad of silica gel and concentrated. The ^1H NMR spectrum of the unpurified reaction mixture indicated a 17% conversion. Purification by silica gel chromatography (2.5-5.0% Et_2O/pentane) yielded 5.0 mg of the acetate and 21.0 mg of the partially resolved alcohol.

HPLC analysis of the alcohol: 17% ee [Daicel CHIRALCEL AD-H column; 1.0 mL/min; solvent system: 10.0% isopropanol in hexanes; retention times: 3.5 min (minor), 5.5 min (major)].

A sample of 2-cyclopentyl-2-methyl-3-phenyl-1-triisopropylsiloxy-3-propanol was then prepared from an enantioenriched sample of diastereomerically pure *cis*-3-cyclopentyl-3-methyl-4-phenyloxetan-2-one (obtained from a reaction conducted with (–)-**1.1**). This sample was enriched (HPLC analysis: 89% ee) in the opposite enantiomer of the alcohol to that obtained from the kinetic resolution. On this basis, we assign the absolute stereochemistry of the product of the reaction illustrated in entry 9 of Table 1.4.

E. References and Notes.

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29. We were limited to the use of THF or THF mixtures because the dialkyl ketenes are generated as a solution in THF immediately before use.
30. Any number of zwitterions with geometries between the coplanar structure, **B**, and perpindicular structure, **A**, are possible and have not been considered here.
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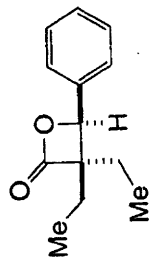
F. ^{1}H NMR Spectra for Selected Compounds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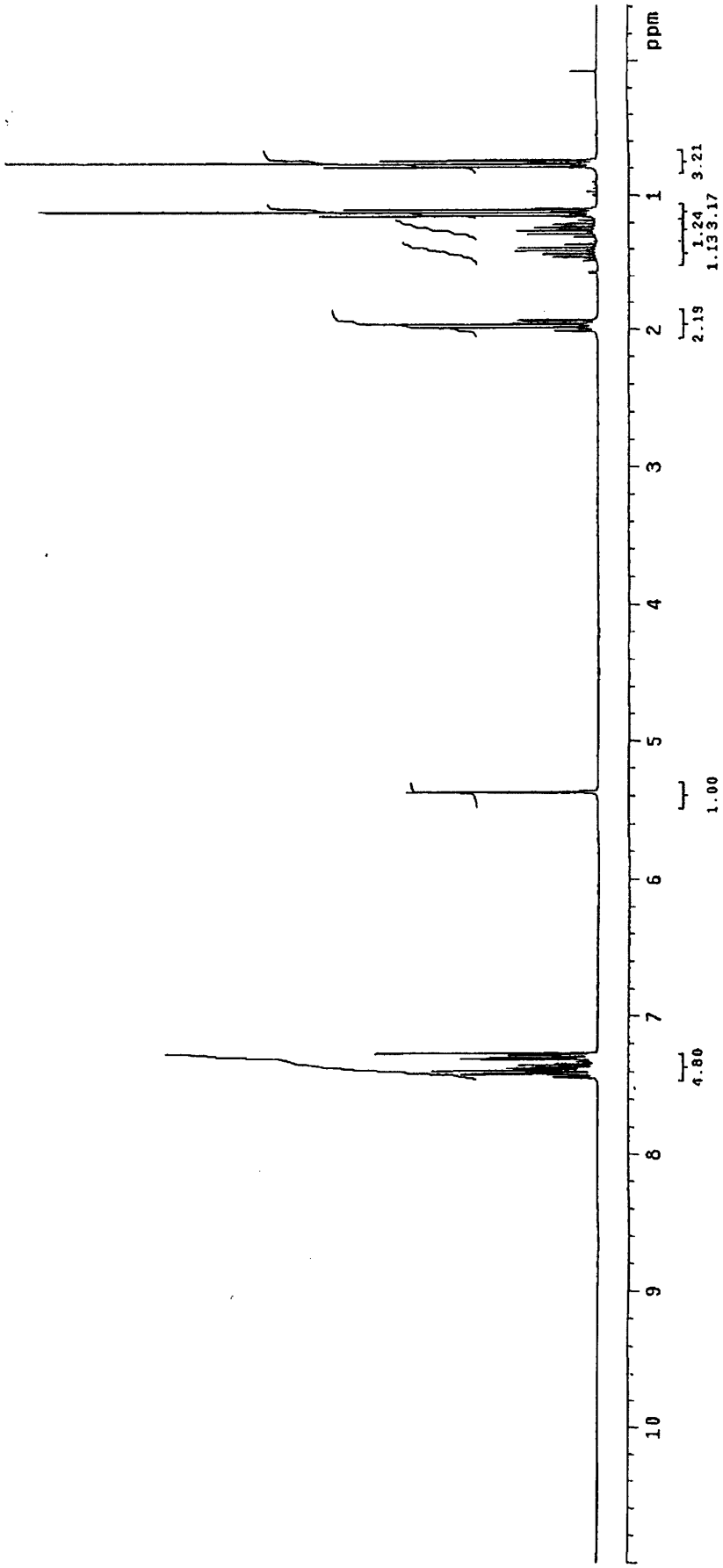
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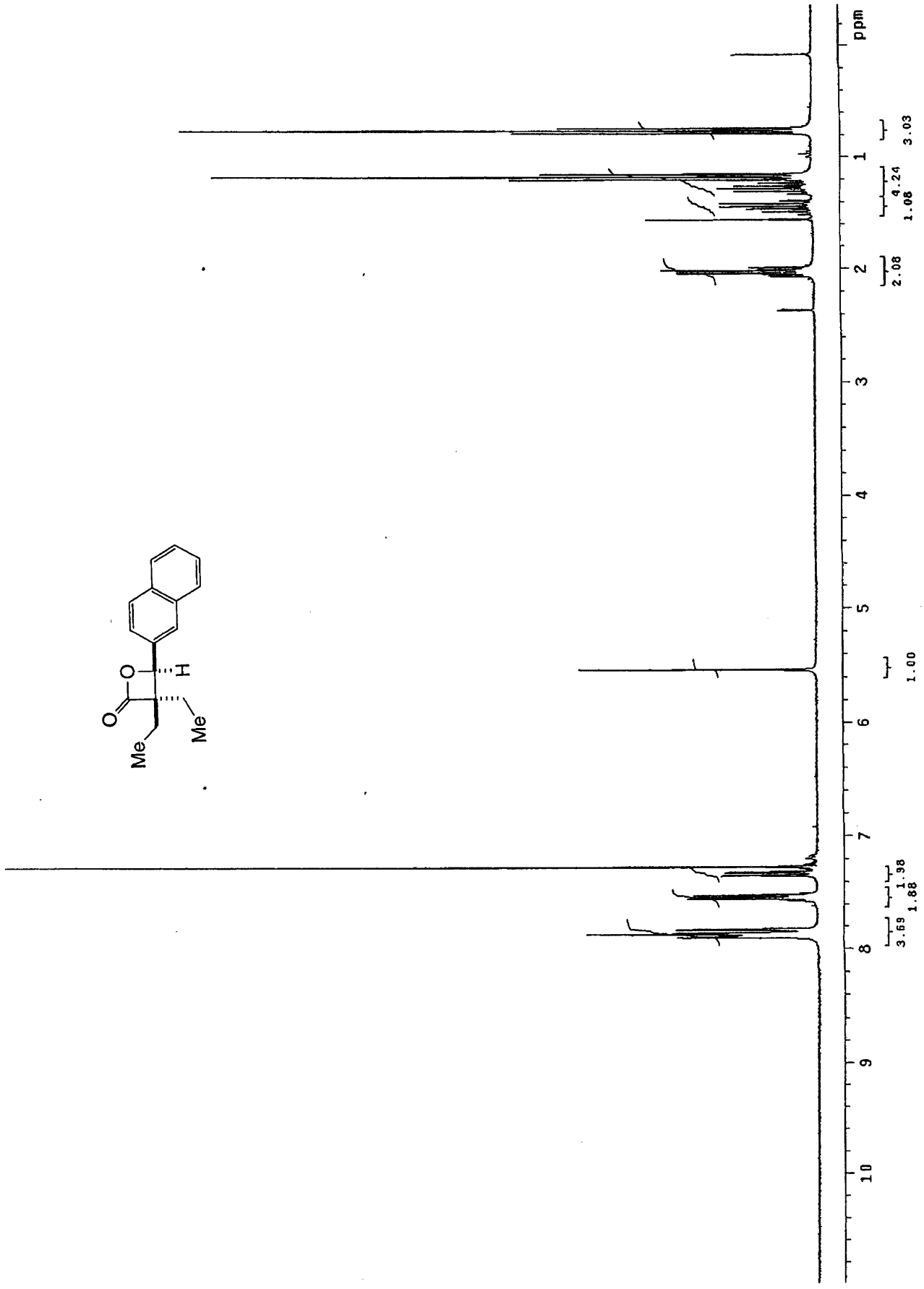
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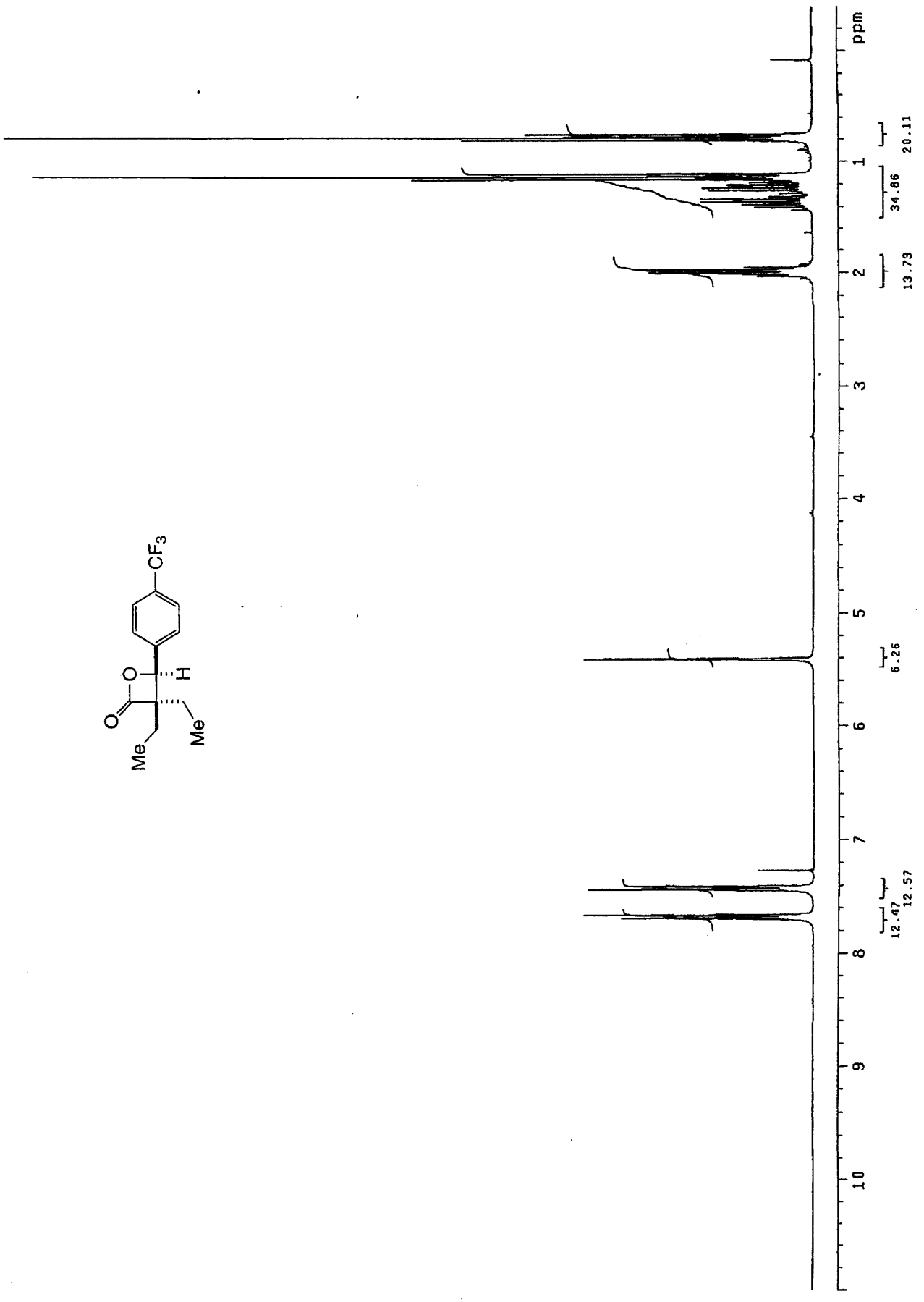
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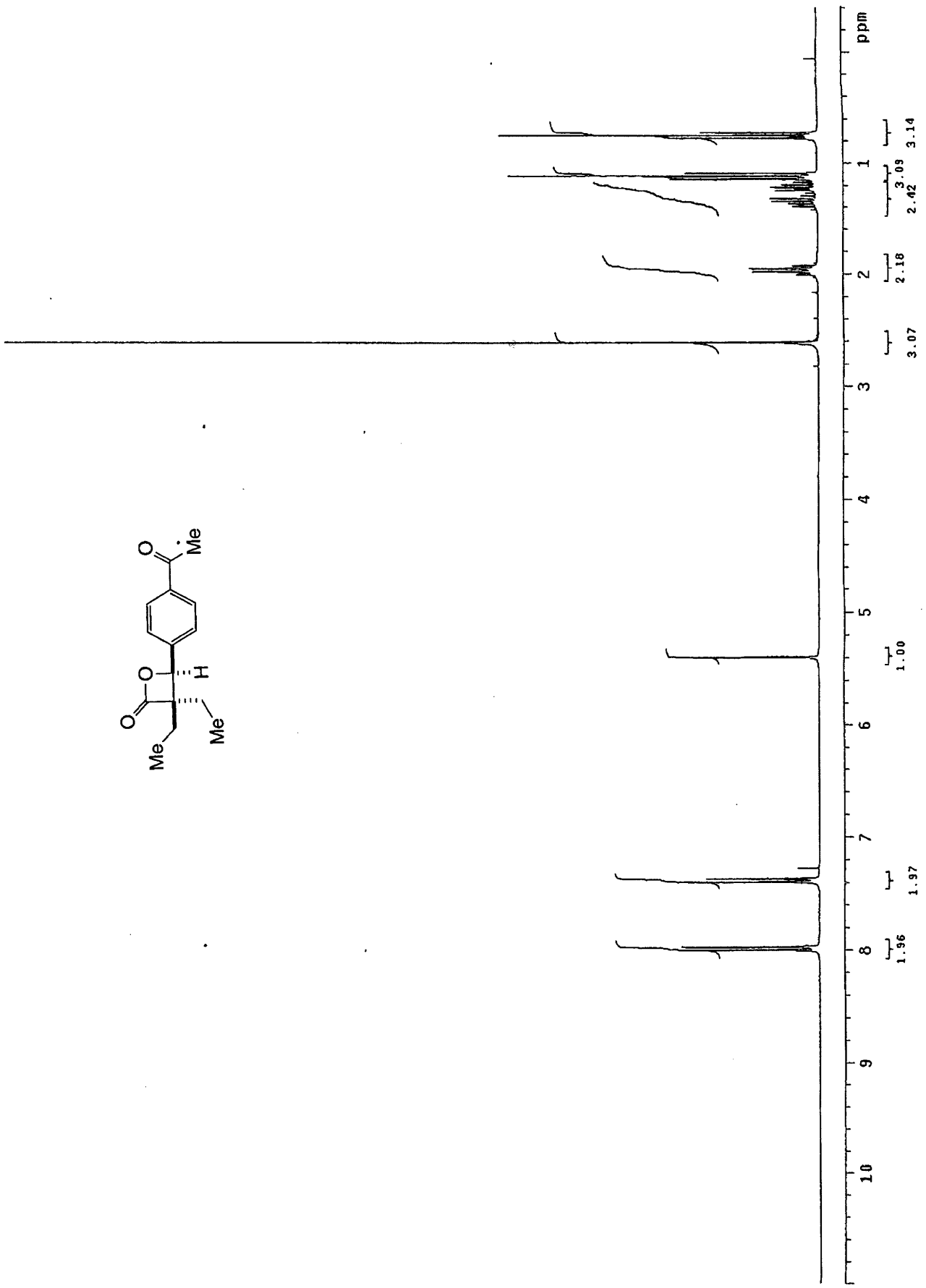
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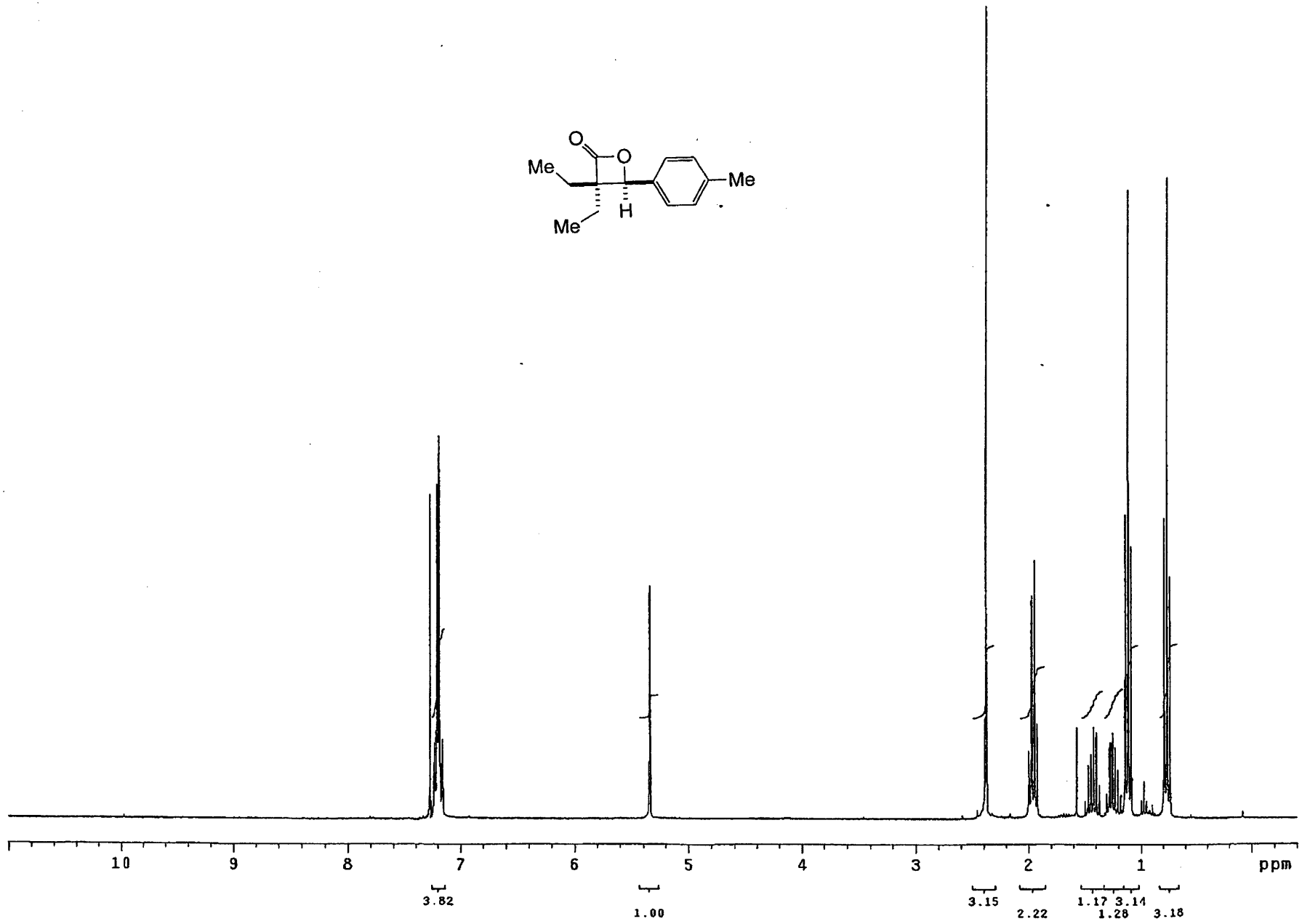
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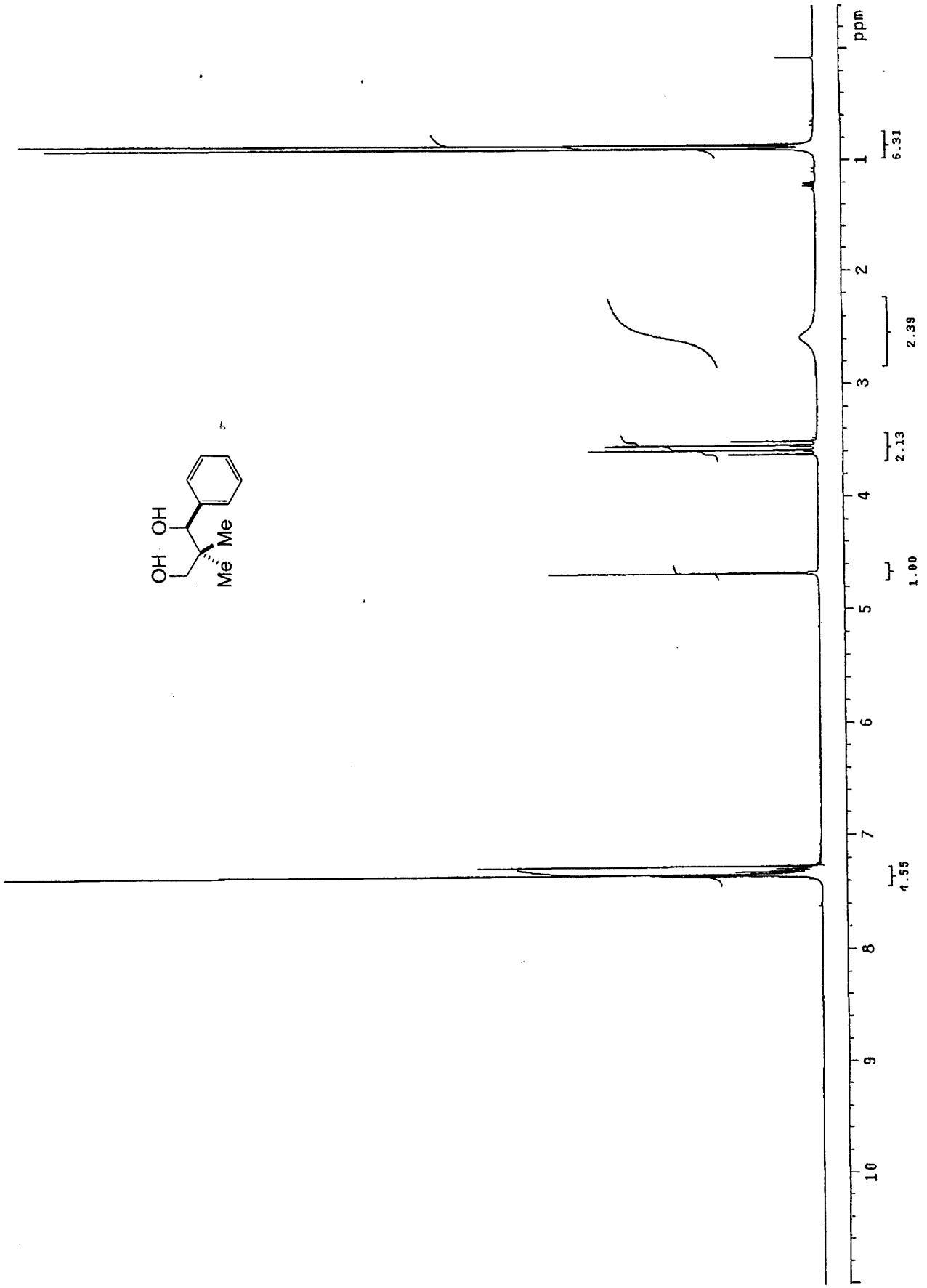
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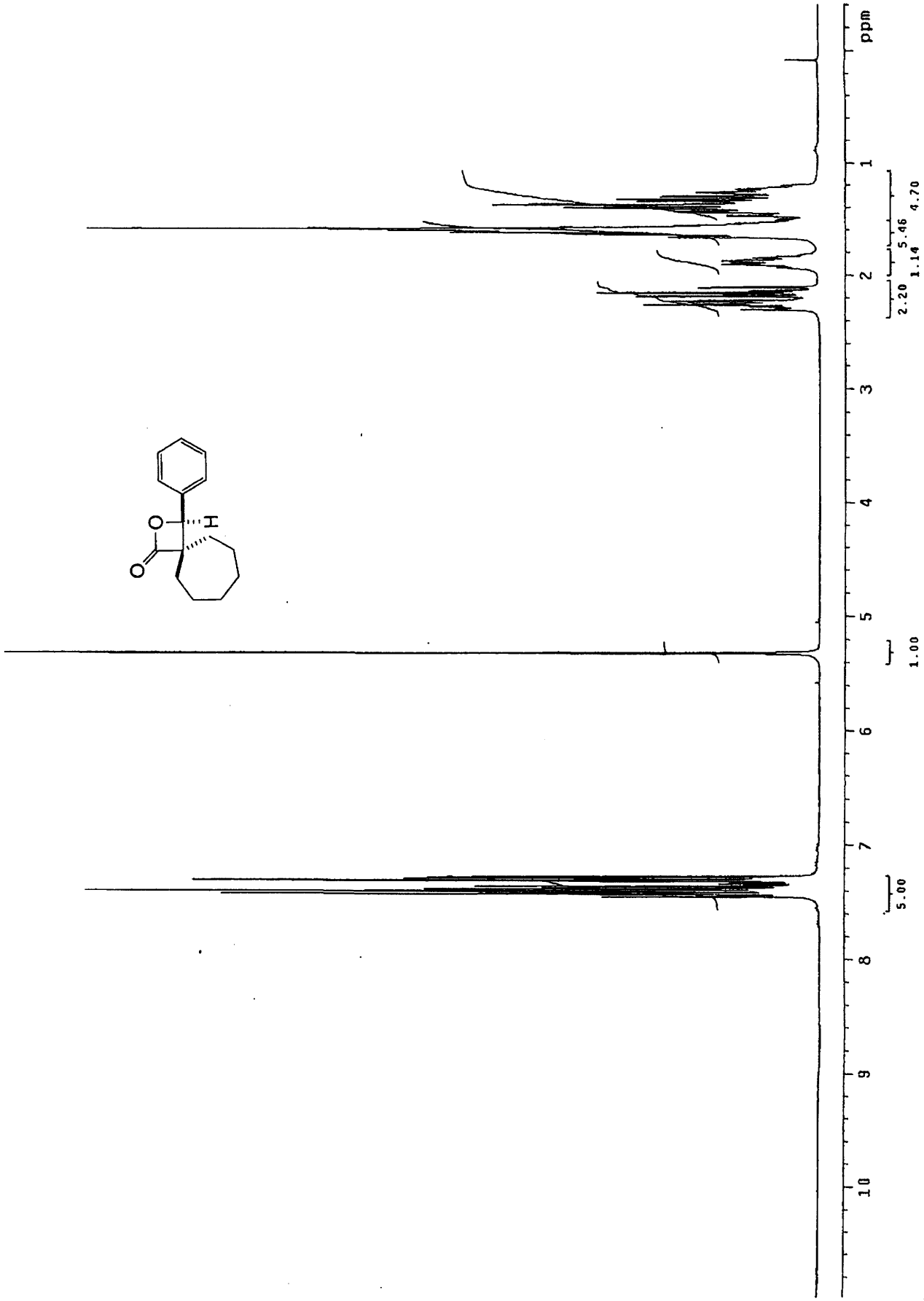
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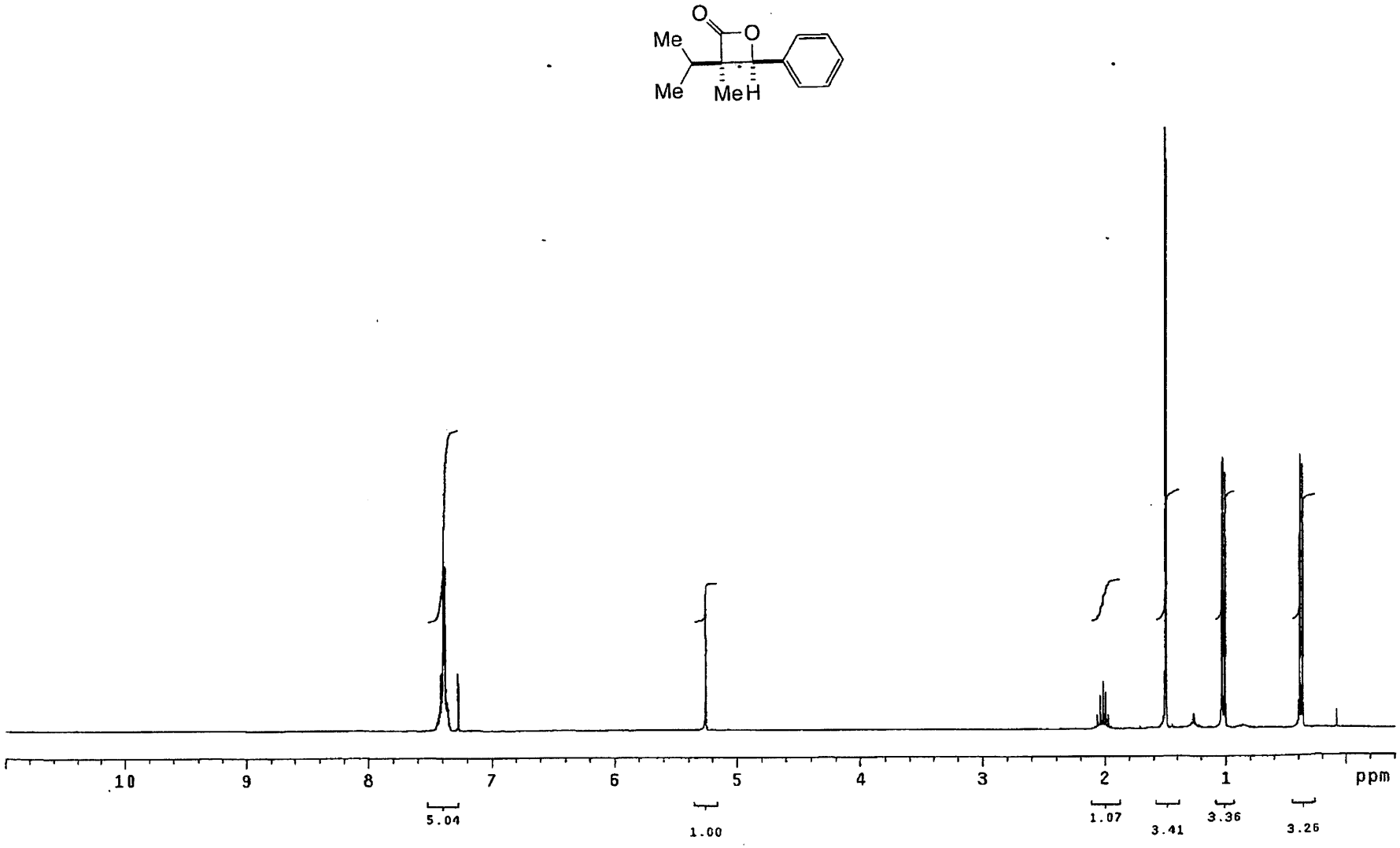
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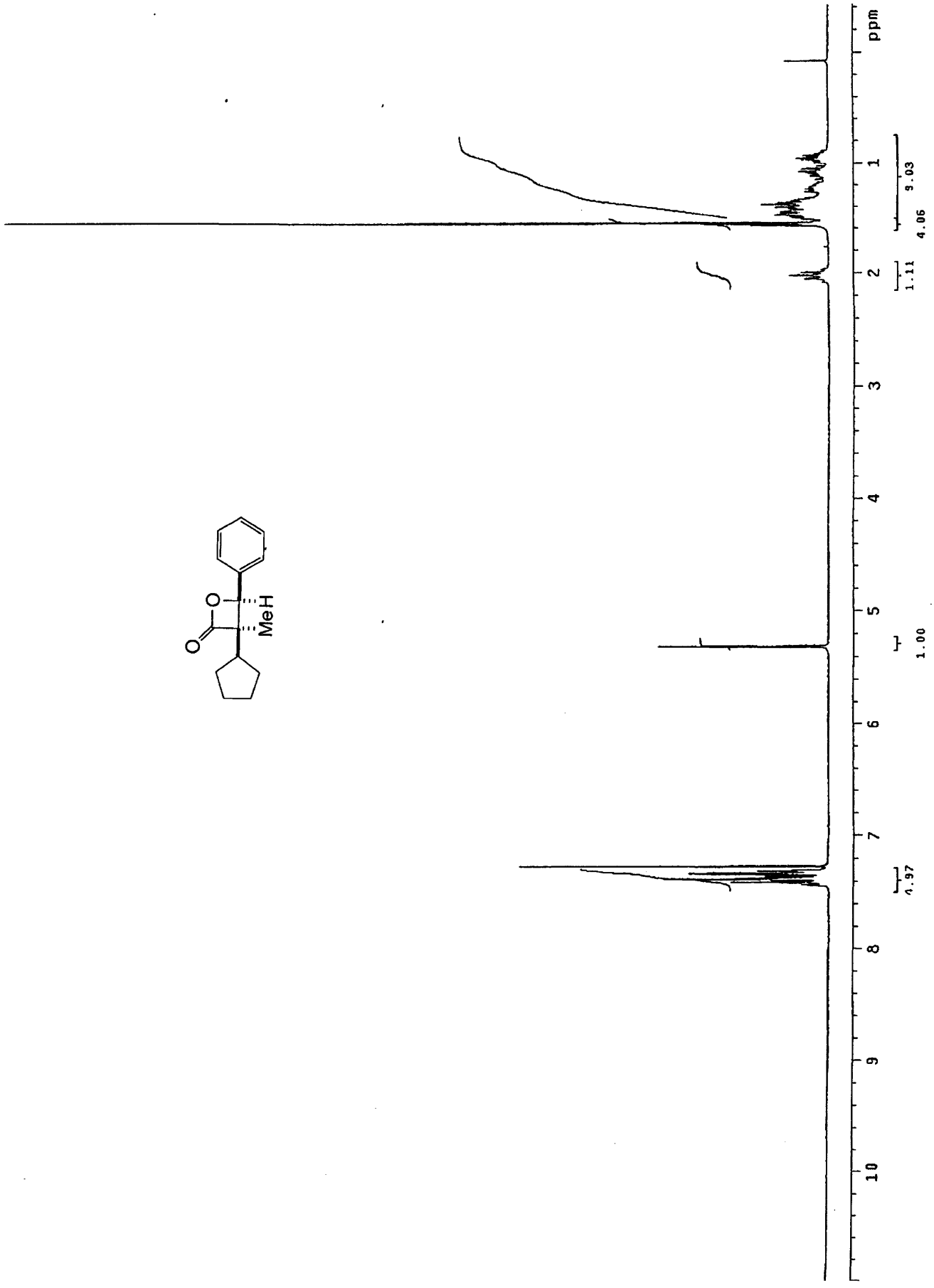
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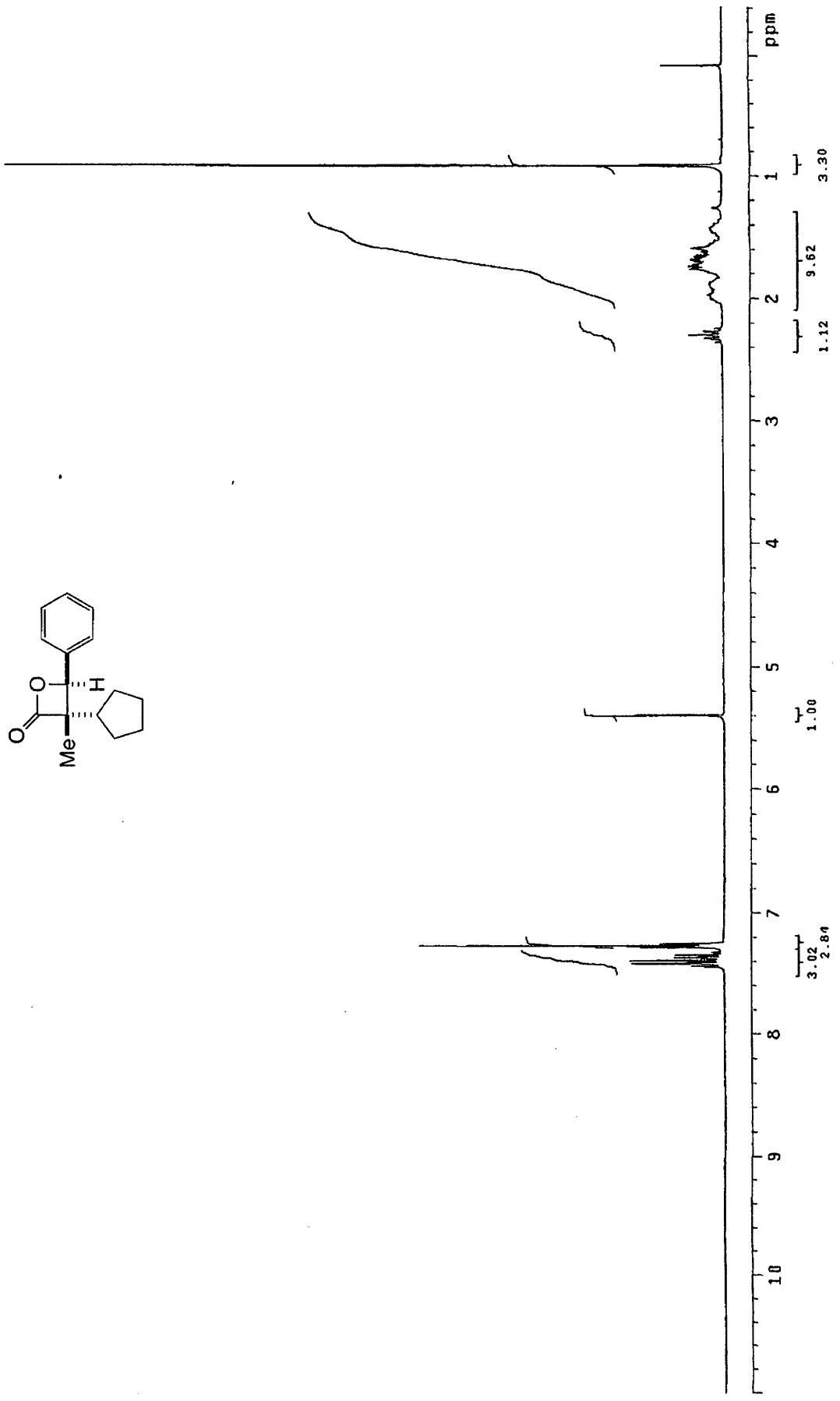
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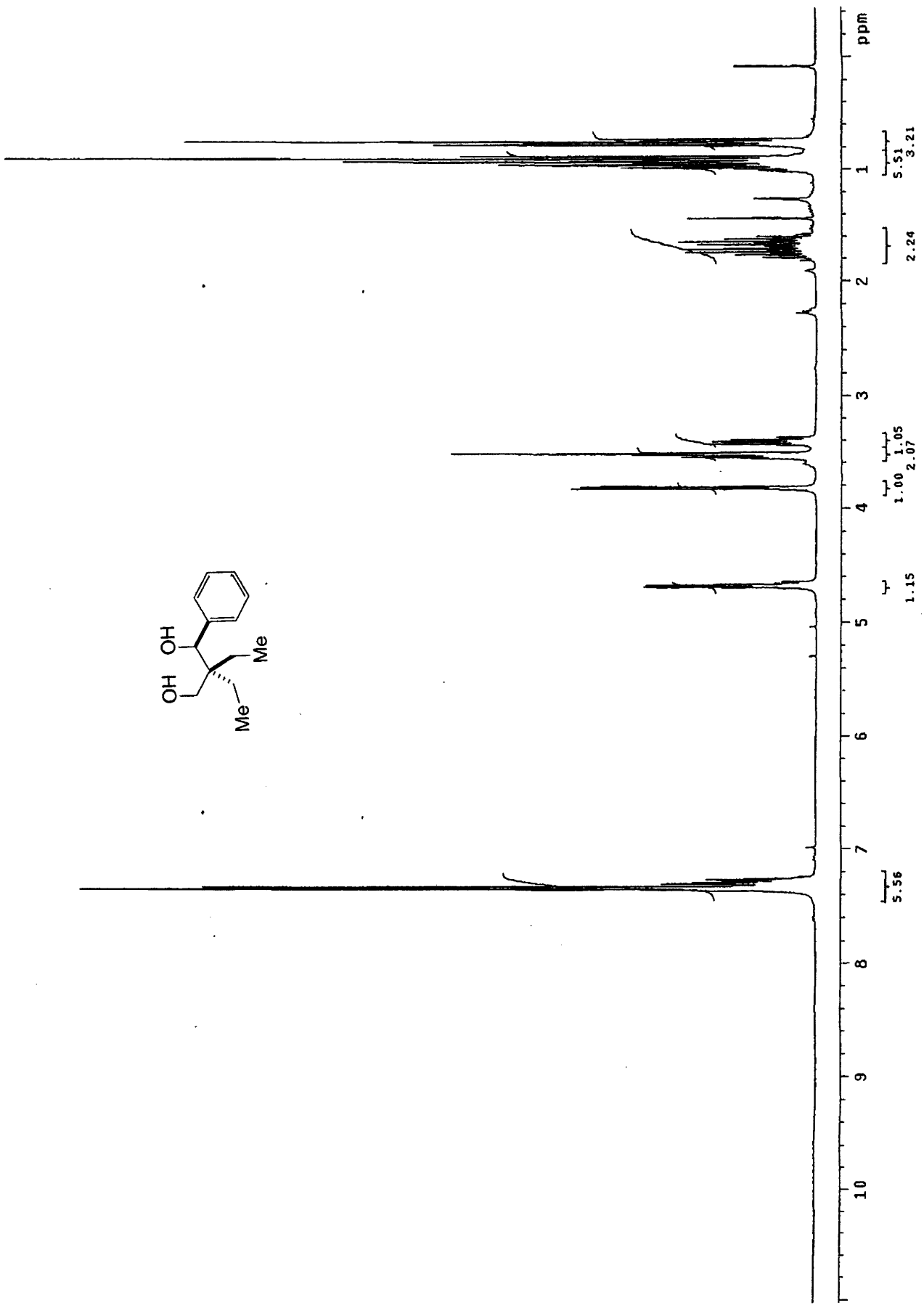
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beta-hydroxy acid

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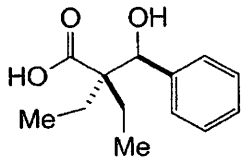

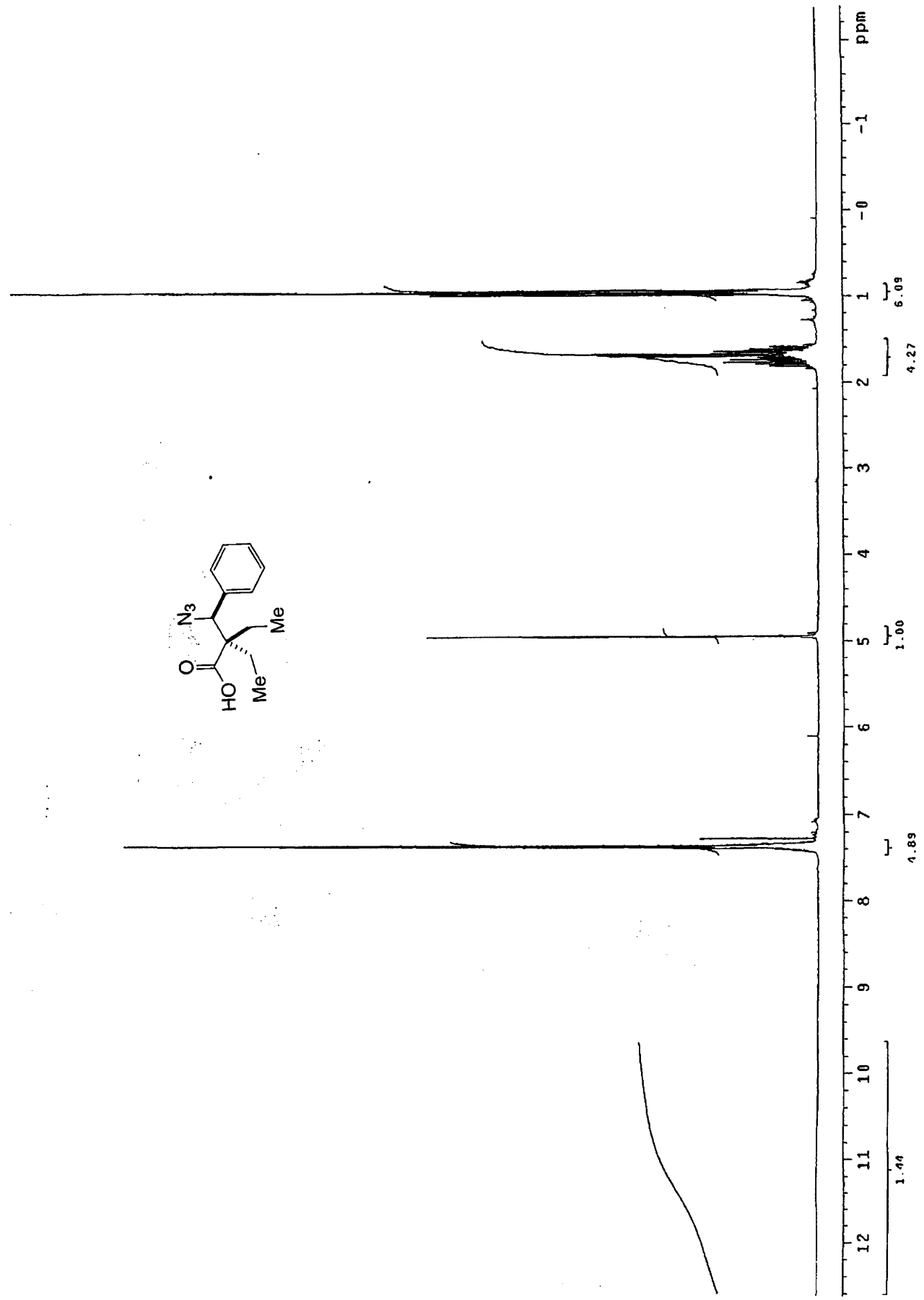
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Chapter 2

Enantioselective Phosphine-Catalzed [3+2] Cycloadditions of Allenoates

Section 2.1

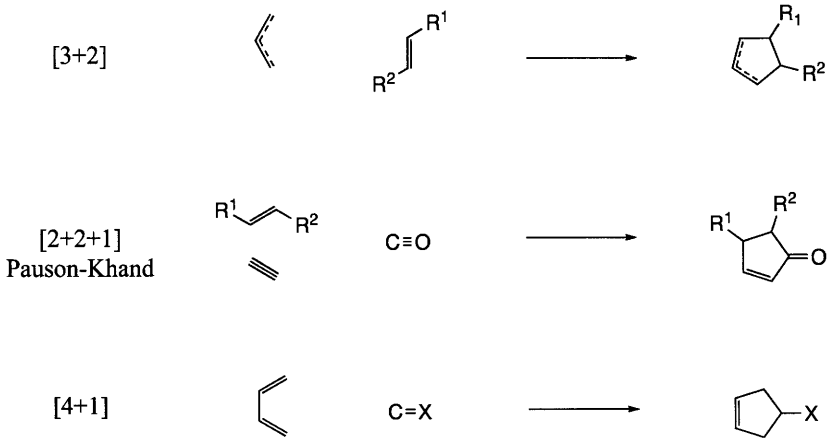
Enantioselective Phosphine-Catalyzed [3+2] Cycloadditions of Allenes with Enones

A. Introduction.

Cyclopentanoids are ubiquitous in natural products, pharmaceuticals, and materials. Therefore, numerous methods for the synthesis of five-membered carbocycles have been devised.[1] Undoubtedly, cycloadditions represent the most convergent route to not only five-membered rings, but to all cyclic compounds as these strategies allow the target structure to be made from two similarly complex starting materials.[2, 3]

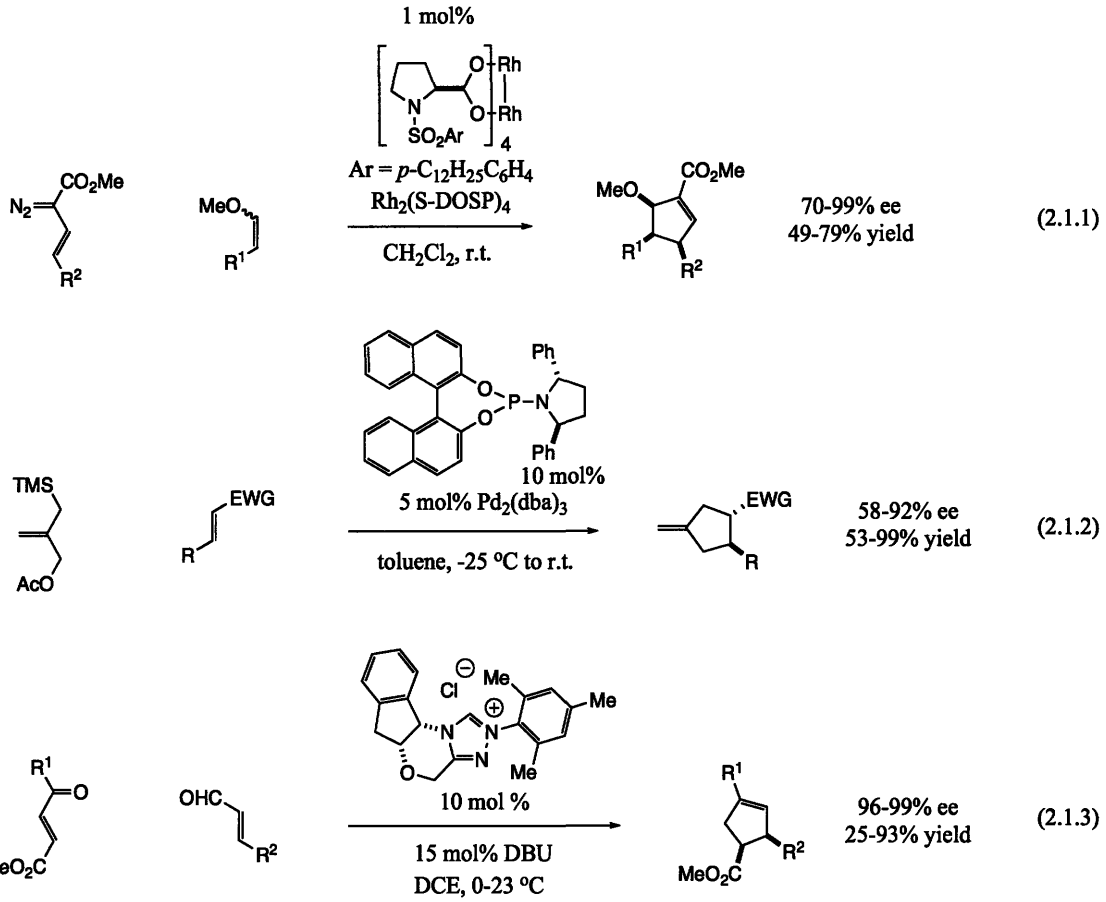
It is not surprising then that cycloaddition and annulation reactions are popular strategies for the synthesis of cyclopentanes and their derivatives (e.g., cyclopentenes, cyclopentanols, and cyclopentanones). These strategies include [4+1] cycloadditions,[4] [2+2+1] cycloadditions (e.g., the Pauson-Khand reaction),[5] and [3+2] cycloadditions (Scheme 2.1.2).[6] Although considerable progress has been made in these areas, very few general catalytic asymmetric methods for the synthesis of cyclopentane derivatives exist. No catalytic asymmetric [4+1] cycloadditions have been demonstrated to date. And while a number of strategies have been developed for asymmetric intramolecular [2+2+1] cycloadditions,[7] no general catalytic intermolecular variants have been described.[8] However, a number of catalytic asymmetric [3+2] cycloadditions have emerged.

Scheme 2.1.1. Common Strategies for Cyclopentanoid Synthesis.

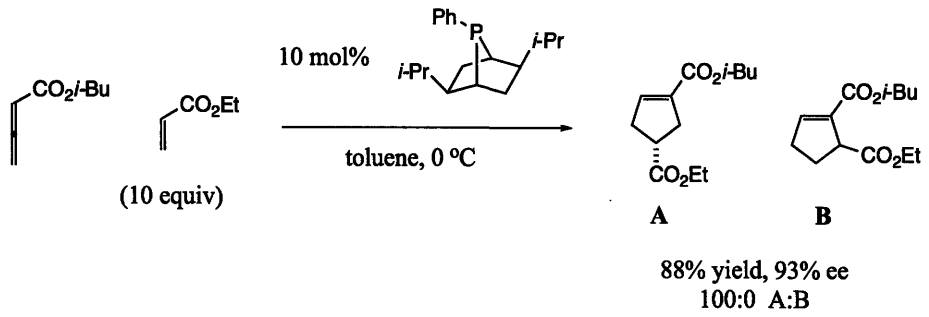


Davies has reported a highly enantioselective [3+2] cycloaddition of diazo compounds with vinyl ethers catalyzed by rhodium-DOSP (eq 2.1.1).[9] More recently,

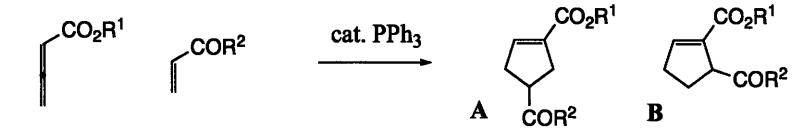
Trost has reported a palladium-catalyzed asymmetric [3+2] trimethylenemethane cycloaddition (eq 2.1.2).[10] Furthermore, Bode has developed a *N*-heterocyclic carbene-catalyzed enantioselective benzoin-oxy-Cope annulation of α,β-unsaturated aldehydes with enones (eq 2.1.3).[11]



In 1997, Zhang reported the first enantioselective phosphine-catalyzed [3+2] cycloaddition of allenoates with acrylates (eq 2.1.4).[12] This work was based on Lu's studies of Ph_3P- and $(n\text{-}Bu)_3P$-catalyzed cycloadditions of allenoates (eq 2.1.5 and eq 2.1.6).[13] Although a number of related phosphine-catalyzed cycloadditions and annulation reactions have appeared in the interim,[14] few of them are asymmetric.[15] Kwon has reported preliminary results of (*S,S*)-DIPAMP catalyzing the [4+2] cycloaddition of allenoates with imines with up to 34% ee (eq 2.1.7).[16] Additionally, researchers at Pfizer have reported up to 20% ee when (*R,R*)-Me-BPE is used as the catalyst in their phosphine-mediated [4+2] annulation of bis(enones) (eq 2.1.8).[17]

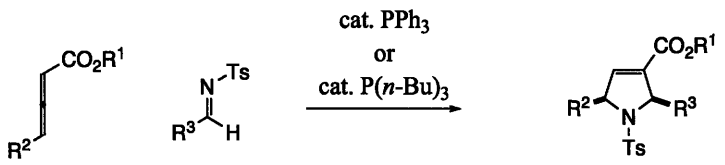


(2.1.4)



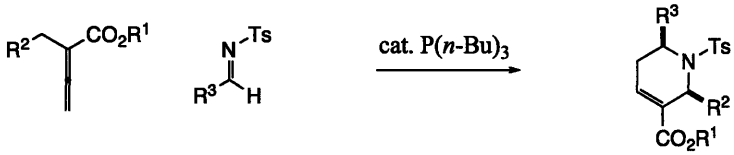
61-91% yield
3:1-10:1 A:B

(2.1.5)



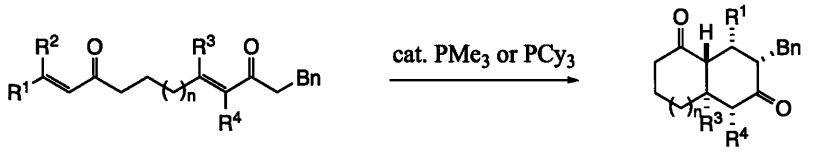
57-99% yield

(2.1.6)



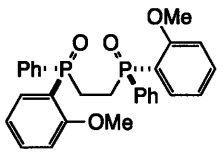
80-99% yield
up to 34% ee
w/ (*S,S*)-DIPAMP

(2.1.7)

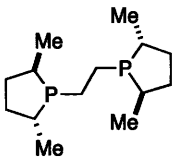


33-79% yield
up to 20% ee
w/ (*R,R*)-Me-BPE

(2.1.8)



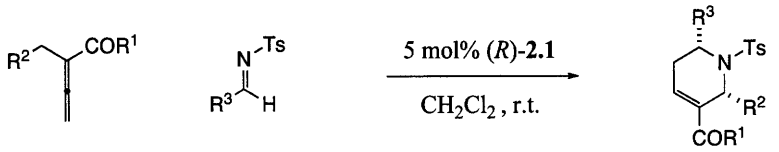
(*S,S*)-DIPAMP



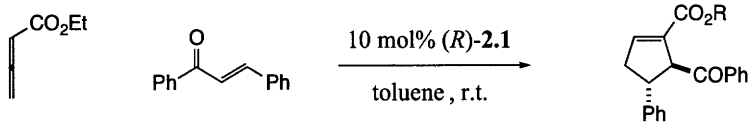
(*R,R*)-Me-bpe

Our group has recently initiated efforts towards the development of a number of asymmetric phosphine-catalyzed reactions. Dr. Ryan Wurz has demonstrated that phosphepine **2.1** is an excellent catalyst for an enantioselective variant of Kwon's [4+2] cycloaddition of 1,1-disubstitued allenoates with imines (eq 2.1.9).[18] The following

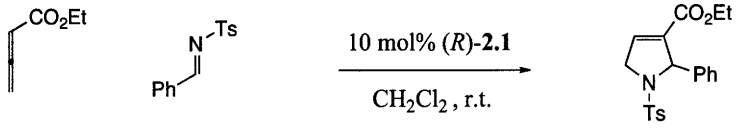
chapter describes my work on phosphepine **2.1**-catalyzed [3+2] cycloadditions of allenoates with enones and allenoates with imines (eq 2.1.10 and eq 2.1.11).



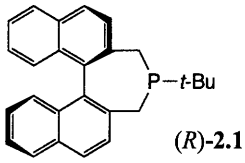
60-99% ee
42-99% yield (2.1.9)



74-95% ee
32-97% yield (2.1.10)



70-80% ee
75-85% yield (2.1.11)



(*R*)-**2.1**

B. Results and Discussion.

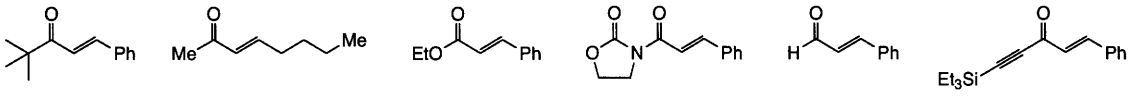
Our group has a standing interest in asymmetric nucleophile-catalyzed processes. Most of our efforts up to this point have employed 4-dimethylaminopyridine and 4-pyrrolidinopyridine derivatives as catalysts. This family of compounds has proven effective for a wide array of enantioselective nucleophile-catalyzed reactions, including acyl transfer reactions, enantioselective protonations, and cycloadditions.[19] We have found these compounds to be particularly effective for addition reactions and cycloadditions of *di*substitued ketenes. Encouraged by our success with asymmetric [2+2] cycloadditions of ketenes catalyzed by **1.1** and **1.2**, we decided to explore the utility of these nucleophiles as catalysts for the [3+2] cycloaddition of an electron-deficient allene (a cumulene that is electronically similar to a ketene) with an imine or electron deficient-olefin. Unfortunately, our efforts in this vein proved to be fruitless.

However, we were well aware that tertiary phosphines were effective catalysts for this subset of cycloadditions. Zhang's enantioselective phosphine-catalyzed synthesis of cyclopentenes was the only example of asymmetric catalysis for this type of reaction at the outset of our investigation. Although, Zhang's cycloaddition is highly enantioselective, the scope of the reaction is severely limited with respect to the olefin.[20]

With the hope of expanding the scope of these cycloadditions, we began our studies by investigating the [3+2] cycloaddition of ethyl-2,3-butadienoate[21] with a range of β-substituted electron-deficient olefins. Of the olefins examined, chalcone proved to be the most reactive, so we focused our attention on this class of compounds. Other enones examined are shown in Figure 2.1.1. Alkyl ketones, β-substituted, α,β-unsaturated enoates, amides, and aldehydes were poor reaction partners.

We also briefly pursued reactions of δ-substituted allenes, both phenyl and ethyl, but the [3+2] adducts were generally obtained in poor yields.

Figure 2.1.1. Olefins Tested in the Phosphine-Catalyzed [3+2] Cycloaddition.

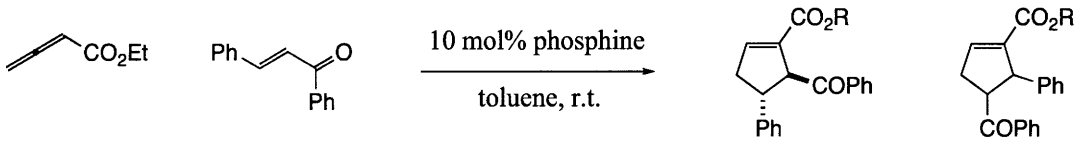


A range of commercially available mono- and bi-dentate phosphines, traditionally used as ligands for transition metals, were surveyed as catalysts for the [3+2] cycloaddition of ethyl-2,3-butadienoate with chalcone (Table 2.1.1).[22] Phosphepine **2.1**,[23] which can be prepared in enantiomerically pure form from (*R*)- or (*S*)-BINOL, affords the targeted cyclopentene in good yield, enantioselectivity, and regioselectivity, in contrast to a number of commercially available phosphines, which were either ineffective as catalysts (Table 2.1.1, entries 1,5, and 6) or provided inferior enantioselectivity and regioselectivity (Table 2.1.1, entries 2, 3, and 4). Use of a derivative of **2.1** with a smaller P-substituent increased the yield of the cycloaddition but significantly decreased the enantioselectivity (Table 2.1.1, Entry 8). With the hope of rendering our reaction more user-friendly, we explored the possibility of employing the

air-stable HBF_4 adduct of **2.1** in conjunction with bases such as NEt_3 and K_2CO_3, but these combinations failed to catalyzed the cycloaddition.

Interestingly, we observe the formation of cyclopentenes with the opposite regioselectivity compared with previous phosphine-catalyzed [3+2] cycloadditions of allenes with enones. Others have observed the same trend for phosphine-catalyzed [3+2] cycloadditions of allenes with β-substituted enones.[15b]

Table 2.1.1. Phosphine Screening for the Asymmetric [3+2] Cycloaddition of Ethyl-2,3-butadienoate with Chalcone.



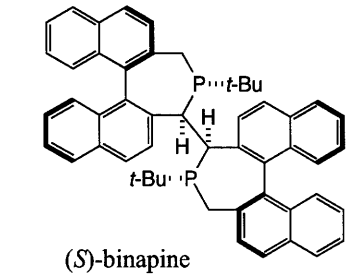
A **B**

entry	phosphine	yield (%)[a]	ee(%)[b]	**A:B**
1	(*S*)-BINAPINE	0	n.d.	n.d.
2	(*R,R*)-Me-BPE	61	-4	6:1
3	(*R,R*)-Et-DUPHOS	61	58	7:1
4	(*R,R*)-Ferrotane	64	11	7:1
5	(*R*)-BINAP	2	50	>20:1
6	(*R*)-NMDPP	4	-4	11:1
7	(*R*)-**2.1**	66	88	13:1
8	(*R*)-**2.2**	88	43	10:1

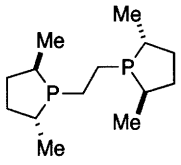
All data are the average of two experiments except for entry 8. [a]Isolated yield of **A** and **B**. [b]Enantiomeric excess of **A**. A negative value for the ee signifies that the illustrated enantiomer of cyclopentene **A** is the minor, rather than the major, product.

The reasons for **2.1**'s superiority in phosphine-catalyzed cycloadditions of allenoates is not currently well understood. Attempts to construct models, either with ball and stick models or computationally, which accommodate both the sense of absolute stereochemistry and regiochemistry for these cycloadditions have been unsuccessful.

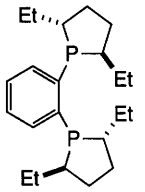
Figure 2.1.2. Structures of the Phosphines Surveyed in Table 2.1.1.



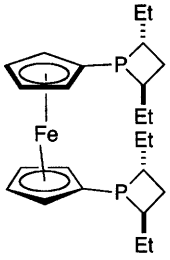
(*S*)-binapine



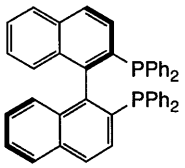
(*R*,*R*)-Me-bpe



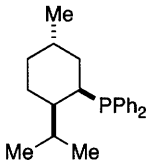
(*R*,*R*)-Et-DuPhos



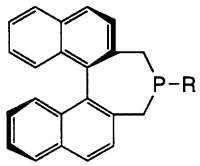
(*R*,*R*)-ferrotane



(*R*)-BINAP



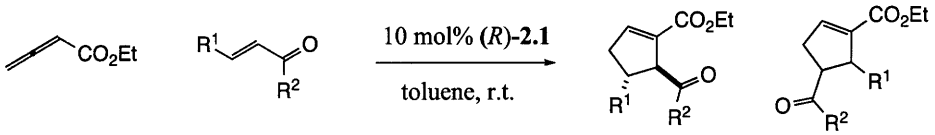
(*R*)-NMDPP



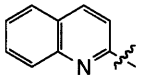
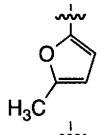
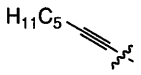
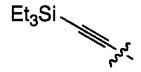
(*R*)-**2.1**; R = *t*-Bu
(*R*)-**2.2**; R = *i*-Pr
(*R*)-**2.3**; R = Et
(*R*)-**2.4**; R = Ph
(*R*)-**2.5**; R = 4-OMe-Ph
(*R*)-**2.6**; R = NEt_2

Phosphepine **2.1** catalyzes the cycloaddition of ethyl-2,3-butadienoate with a wide range of enones. The ee of the cycloaddition is insensitive to electronic perturbations on either the ketone substituent or the β-substituent (Table 2.1.2, entries 2-6). However, reactions of electron-rich substrates are less efficient and require the use of two equivalents of allene to obtain good yields (Table 2.1.2, entries 4 and 6).[24] A variety of enones bearing heterocyclic substituents are also suitable reaction partners (Table 2.1.2, entries 7, 8, 9, and 10). In addition to β-(hetero)aryl enones, we have found β-alkynyl (Table 2.1.2, entries 12 and 13) and β-alkyl enones (Table 2.1.2, entry 14) to be suitable reaction partners. Although, the later reaction is sluggish, it is highly regioselective and the balance of the enone may be recovered.

Table 2.1.2. Asymmetric Phosphine-Catalyzed [3+2] Cycloadditions of Allenes with Various Enones.



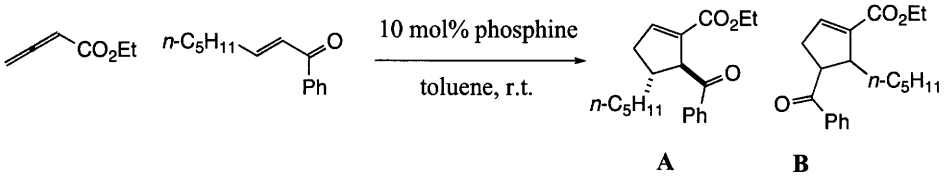
A **B**

entry	R^1	R^2	yield (%)[a]	ee (%)[b]	**A:B**
1	C_6H_5	C_6H_5	64	88	13:1
2	C_6H_4	4-Cl-C_6H_4	76	82	7:1
3	C_6H_4	4-CH_3-C_6H_4	61	87	20:1
4	C_6H_4	4-OCH_3-C_6H_4	54	88	>20:1
5	4-Cl-C_6H_4	C_6H_5	74	87	9:1
6	4-OCH_3-C_6H_4	C_6H_5	67	87	10:1
7		C_6H_5	69	88	3:1
8[c]		C_6H_5	52	88	20:1
9[c]	4-Cl-C_6H_4		54	89	>20:1
10	C_6H_5		74	90	6:1
11		C_6H_5	65	85	6:1
12		C_6H_5	70	87	>20:1
13	C_5H_{11}	C_6H_5	39[d]	75	>20:1
14	4-OBn-C_6H_4	4-Br-C_6H_4	62	86	7:1

All data are the average of two experiments except for entry 14. All cycloadditions employed 1.2 equiv. of allene, except for entries 4, 6, 8, and 14, for which 2.0 equiv. were used. [a]Isolated yield of **A** and **B**. [b]Enantiomeric excess of **A**. [c]Because of the low solubility of the enone in toluene, CH_2Cl_2 was employed as a cosolvent. [d]The enone can be recoverd in 56% yield.

We surveyed a family of phosphepines related to **2.1** for the cycloaddition of the β-alkyl enone. However, the selectivity is reduced, drastically in some instances, as the size of phosphorous substituent is decreased. Although this is only an empirical observation at this stage, this trend does seem to be general for all phosphine-catalyzed allenoate cycloadditions we have investigated to date.

Table 2.1.3. Phosphine Survey for the [3+2] Cycloaddition of Ethyl-2,3-butadientoate with a β-Alkyl Enone.

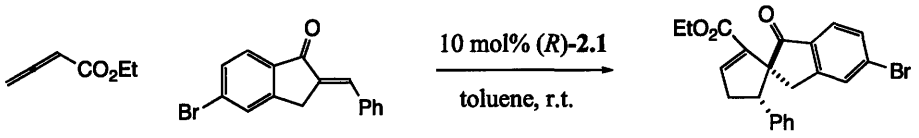


A **B**

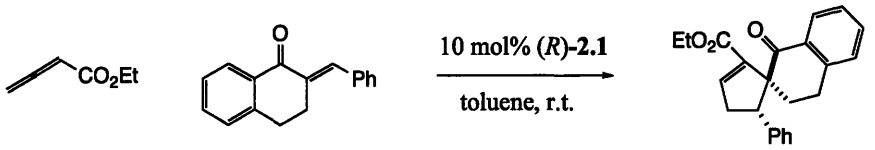
entry	phosphine	yield (%)[a]	ee (%)[b]	**A:B**
1	(*R*)-**2.2**	68	10	6:1
2	(*R*)-**2.3**	67	64	9:1
3	(*R*)-**2.5**	53	5	4:1

All cycloadditions employed 1.1 equiv. of allene. [a]Isolated yield of **A** and **B**.
[b]Enantiomeric excess of **A**.

Catalyst **2.1** is also effective for cycloadditions of *tri*substituted enones. This unprecedented phosphine-catalyzed cycloaddition allows for the synthesis of densely functionalized spirocyclic compounds containing adjacent quaternary and tertiary stereocenters.[25, 26] Moreover, a single regioisomer and diastereomer is observed in both cases (eq 2.1.12 and eq 2.1.13).



97% yield, 89% ee (2.1.12)

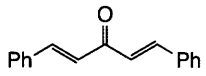
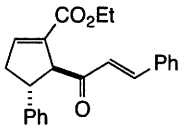
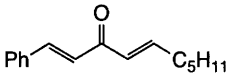
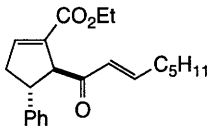
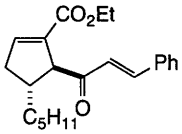
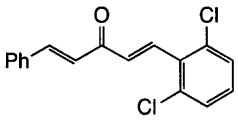
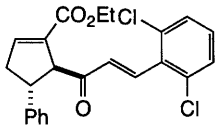
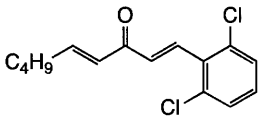
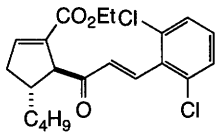
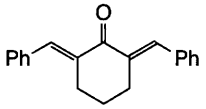
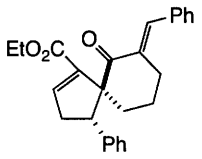
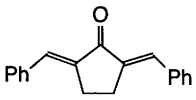
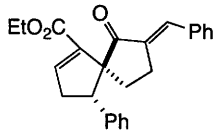


32% yield, 95% ee (2.1.13)

This cycloaddition process is not limited to the use of aryl ketones. Cycloaddition of dibenzylideneacetone (dba) with ethyl-2,3-butadienoate yields the desired cyclopentene in excellent yield, regioselectivity, and enantioselectivity. Because β-alkyl enones were observed to be less efficient reaction partners, we speculated that a site selective cycloaddition of an unsymmetrical dienone containing two electronically differentiated β-substituents (i.e., one β-aryl substituent and one β-alkyl substituent) would be possible. Unfortunately, this type of electronic differentiation was insufficient for the realization of this goal (Table 2.1.4, Entry 2). Further exploration of this idea led us to discover that a β-2,6-dichlorophenyl substituent effectively blocks one olefin from undergoing the cycloaddition. Although this group decreases the enantioselectivity of the process, it does allow for highly regio- and site selective [3+2] cycloadditions of both β-aryl (Table 2.1.4, Entry 3) and β-alkyl dienones (Table 2.1.4, Entry 4).

Not surprisingly, in light of our success with trisubstituted exocyclic enones (Scheme 2.1.8), dibenzylidenecyclohexanone and dibenzylidene cyclopentanone are excellent substrates for the process. These substrates provide access to [4.4] and [4.5] spirocyclic compounds containing adjacent quaternary and tertiary stereocenters as well as two differentiated enones (Table 2.1.4, Entries 5 and 6).

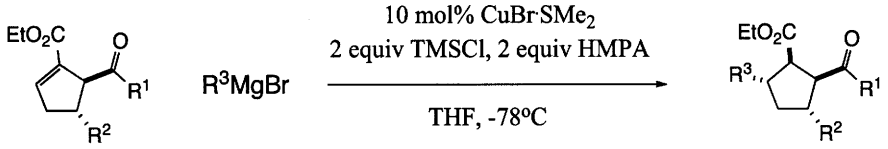
Table 2.1.4. Phosphine Catalyzed Asymmetric [3+2] Cycloadditions of Ethyl-2,3-Butadienoate with Various Dienones.

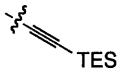
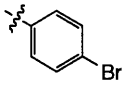
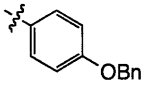
entry	dienone	cycloadduct(s)	yield (%)[a]	ee (%)
1			75	89
2[b, c]		 	n.d.	
3			68	73
4[b]			60	
5			57	93
6			81	89

All data are the average of two experiments, except for entries 2 and 4. All cycloadditions employed 2.0 equiv. of ethyl- 2,3-butadienoate and 10 mol% of (*R*)-**2.1** unless noted otherwise. [a]Only one regioisomer is observed in all cases unless otherwise noted. [b]10 mol% PPh_3 was used as catalyst. [c]1:1 mixture of regioisomers was determined by ^1H NMR analysis of a crude reaction mixture.

We hypothesized that our cyclopentene products may be prone to diastereoselective transformations that would result in the generation of multiple contiguous stereocenters. This is exemplified by the highly diastereoselective copper-catalyzed 1,4-addition of alkyl Grignard reagents shown in Table 2.1.5.[27, 28]

Table 2.1.5. Copper (I)-Catalyzed 1,4-Additions of Alkyl Grignards to [3+2] Cycloadducts.



entry	R^1	R^2	R^3MgBr	yield (%)	d.r.
1			EtMgBr	62	>95:5
2			EtMgBr	65	>95:5

C. Conclusions.

We have developed a phosphine catalyzed asymmetric [3+2] cycloaddition of allenes with enones. For the first time, we have demonstrated that a variety of β-substituted enones and *tri*substituted enones are efficient reaction partners for this process. Moreover, a regio- and site-selective asymmetric [3+2] cycloaddition of unsymmetrical dienones was developed by employing a sterically demanding blocking group. Finally, we established that our cyclopentene products undergo a highly diastereoselective copper-catalyzed 1,4-addition reaction.

D. Experimental

I. General

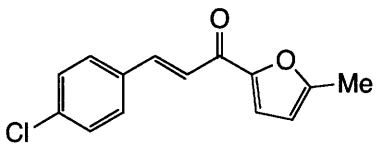
All reactions were carried out in oven-dried glassware under an atmosphere of nitrogen or argon with magnetic stirring, unless otherwise indicated.
Toluene and CH_2Cl_2 were purified by passage through a neutral alumina column. Chalcone (Avocado) was recrystallized from EtOH before use. Ethyl 2,3-butanedienoate (Aldrich), 4-chlorochalcone (Avocado), 4-methoxychalcone (Aldrich), 4'-chlorochalcone (Avocado), 4'-methoxychalcone (Aldrich), 2,5-dibenzylidenecyclopentanone (Alfa Aesar), 2-benzylidene-1-tetralone (Lancaster), 2,6-dibenzylidenecyclohexanone (Alfa Aesar), 2-cinnamoylthiophene (TCI), dibenzylideneacetone (Avocado), 2-Acetyl-5-methylfuran (Avocado), benzaldehyde (Alfa Aesar) 4-chlorobenzaldehyde (Aldrich), 4'-methylacetophenone (Aldrich), acetophenone (Aldrich), 2-furaldehyde (Alfa Aesar), 2-quinolinecarboxaldehyde (Aldrich), *trans*-4-phenyl-3-buten-2-one (Aldrich), 2,6-dichlorobenzaldehyde (Alfa Aesar), 2-octynal (Aldrich), benzoylmethylenetriphenylphosphorane (Alfa Aesar), and 5-bromo-1-indanone (Alfa Aesar) were used as received.

3-Triethylsilylpropynal[29] and catalyst **2.1**[23] were prepared according to literature procedures.

All NMR spectra were recorded in $CDCl_3$ unless noted otherwise.

II. Preparation of Substrates

These yields have not been optimized.



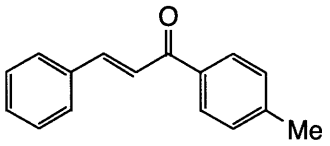
General procedure for aldol-dehydration. 2-Acetyl-5-methylfuran (2.33 mL, 20.0 mmol) and 4-chlorobenzaldehyde (2.84 g, 20.2 mmol) were dissolved in ethanol (30 mL) and water (20 mL). After being cooled to 0 °C, the solution was treated with 1 N NaOH (10.0 mL). The solution was allowed to warm to room temperature and then stirred for 18 h. The reaction mixture was diluted with water (50 mL) and treated with 1 N HCl (10.0 mL). This mixture was extracted with CH_2Cl_2 (2 x 75 mL), and the extracts were combined, washed with water and then brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was washed with cold 1:1 toluene:CH_2Cl_2 (20 mL) to provide 3.17 g (64%) of a white solid.

^{1}H NMR (300 MHz) δ 7.76 (d, J=15.9 Hz, 1H), 7.54 (m, 2H), 7.39-7.31 (m, 3H), 7.24 (m, 1H), 6.20 (dd, J=3.6 Hz, J=0.8 Hz, 1H), 2.42 (s, 3H).

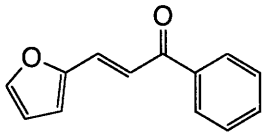
^{13}C NMR (75 MHz) δ 177.1, 158.5, 152.6, 141.9, 136.4, 133.5, 129.7, 129.3, 121.9, 119.9, 109.6, 14.4.

FTIR (thin film) 1651, 1600, 1510, 1489 cm^{-1}.

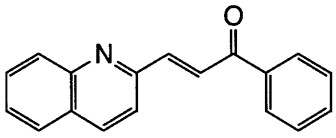
MS (EI) calc. for $C_{14}H_{11}ClO_2$ [M] 246.04, found 246.04.



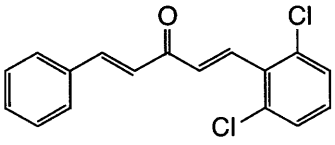
[4224-87-7] This compound was prepared by the general procedure for aldol-dehydration: 4'-methylacetophenone (2.67 mL, 20.0 mmol) and benzaldehyde (2.23 mL, 22.0 mmol). The product (2.65 g, 60%) was recrystallized from hot EtOH.



[39511-12-1] This compound was prepared by the general procedure for aldol-dehydration: acetophenone (2.33 mL, 20.0 mmol) and 2-furaldehyde (1.69 mL, 20.4 mmol). The product (3.54 g, 89%) was purified by flash chromatography (5-20% Et_2O/pentane).



[119118-42-2] This compound was prepared by the reaction of benzoylmethylene-triphenylphosphorane (2.00 g, 5.25 mmol) and 2-quinolinecarboxaldehyde (0.785 g, 5.00 mmol) in 1,2-dichloroethane at room temperature for 18 h. The product (1.10 g, 85%) was purified by flash chromatography (5-50% Et_2O/pentane).



Trans-4-phenyl-3-buten-2-one (1.53 g, 10.5 mmol) and 2,6-dichlorobenzaldehyde (1.83 g, 10.5 mmol) were dissolved in ethanol (10 mL) and water (5 mL). After being

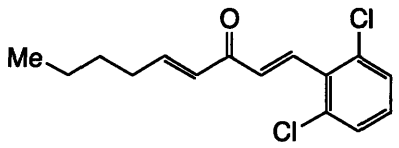
cooled to 0 °C, the solution was treated with 1 N NaOH (5.0 mL). The solution was allowed to warm to room temperature and then stirred for 18 h. The reaction mixture was diluted with water (20 mL) and extracted with ~50:1 Et_2O:CH_2Cl_2 (2 x 100 mL). The extracts were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (~1-10% Et_2O/pentane), which furnished 1.61 g (51%) of a viscous yellow oil that solidified upon standing.

^{1}H NMR (300 MHz) δ 7.79 (d, J=16.1 Hz, 1H), 7.74 (d, J=16.1 Hz, 1H), 7.61 (m, 2H), 7.44-7.39 (m, 3H), 7.37 (d, J=8.1 Hz, 2H), 7.23 (d, J=16.2 Hz, 1H), 7.19 (dd, J=8.6 Hz, J=7.6 Hz, 1H), 7.06 (d, J=16.2 Hz, 1H).

^{13}C NMR (75 MHz) δ 188.9, 144.3, 136.7, 135.3, 134.8, 133.3, 132.7, 130.9, 130.0, 129.2, 129.0, 128.7, 125.6.

FTIR (thin film) 1676, 1657, 1623, 1595, 1576, 1427, 1333, 1186 cm^{-1}.

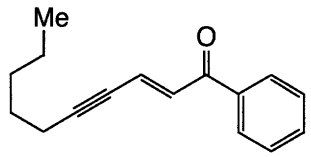
MS (EI) calc. for $C_{17}H_{12}Cl_2O$ [M+Na] 302.03, found 302.02.



Trans-oct-3-en-2-one (0.600 g, 4.76 mmol) was added dropwise over 10 minutes to a -78 °C solution of LiHMDS (15.0 mL of 0.33 M solution in THF, 5.0 mmol). After the mixture was stirred for 1 hour, 2,6-dichlorobenzaldehyde (0.840 g, 4.80 mmol) was added as a solution in THF (5.0 mL). After 45 minutes, the reaction was quenched with saturated NH_4Cl solution. The aqueous layer was extracted with Et_2O, washed with H_2O, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude material was then treated with $MeSO_2Cl$ (0.385 mL, 4.80 mmol) and NEt_3 (1.0 mL, 7.50 mmol). This mixture was stirred for 24 hours at room temperature. The solution was diluted with Et_2O and washed with H_2O. The extracts were dried over $MgSO_4$, filtered, and concentrated. The crude mixture was purified by flash chromatography (2-7% Et_2O in pentane) to yield 0.445 g (25%) of a yellow oil.

^{1}H NMR (500 MHz) δ 7.70 (d, J=16.3 Hz, 1H), 7.37 (d, J=8.2 Hz, 2H), 7.20 (t, J=8.2 Hz, 1H), 7.12 (d, J=16.3 Hz, 1H), 7.02 (dt, J=15.5 Hz, J=7.0 Hz, 1H), 6.42 (dt,

J=15.9 Hz, J=1.5 Hz, 1H), 2.32-2.28 (m, 2H), 1.51 (m, 2H), 1.38 (m, 2H), 0.94 (t, J=7.3 Hz, 3H).



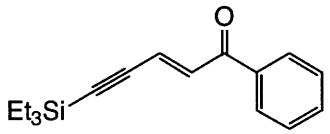
2-Octynal (1.14 mL, 8.00 mmol) and benzoylmethylenetriphenylphosphorane (3.35 g, 8.80 mmol) were combined in 1,2-dichloroethane (40 mL) and stirred for 18 h at room temperature. The reaction mixture was concentrated, redissolved in toluene (5 mL), and purified by flash chromatography (1-8% Et_2O/pentane), which furnished 1.53 g (85%) of a yellow oil.

^1H NMR (300 MHz) δ 7.95 (m, 2H), 7.57 (m, 1H), 7.47 (m, 2H), 7.27 (dt, J=15.6 Hz, J=0.6 Hz, 1H), 6.90 (dt, J=15.6 Hz, J=2.2 Hz, 1H), 2.41 (m, 2H), 1.59 (m, 2H), 1.46-1.28 (m, 4H), 0.92 (m, 3H).

^{13}C NMR (75 MHz) δ 189.4, 137.5, 133.2, 132.7, 128.8, 128.7, 126.5, 102.4, 79.4, 31.3, 28.4, 22.4, 20.1, 14.1.

FTIR (thin film) 3062, 2956, 2932, 2860, 2212, 1660, 1589, 1448 cm^{-1}.

MS (EI) calc. for $C_{16}H_{18}O$ [M] 226.14, found 226.14.



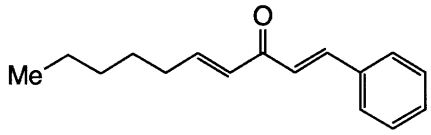
3-Triethylsilylpropynal (1.21 g, 7.16 mmol) and benzoylmethylene-triphenylphosphorane (2.99 g, 7.87 mmol) were combined in 1,2-dichloroethane (35 mL) and stirred at room temperature for 18 h. The reaction mixture was then concentrated, redissolved in toluene (5 mL), and purified by flash chromatography (1-2% Et_2O in pentane), which furnished 1.62 g (85%) of a yellow oil (trans isomer).

^1H NMR (300 MHz) δ 7.98 (m, 2H), 7.60 (m, 1H), 7.50 (m, 2H), 7.39 (d, J=15.6 Hz, 1H), 6.91 (d, J=15.7 Hz, 1H), 1.04 (t, J=7.9 Hz, 9H), 0.68 (q, J=7.9 Hz, 6H).

^{13}C NMR (75 MHz) δ 189.1, 137.3, 134.3, 133.4, 128.9, 128.7, 125.2, 104.1, 104.0, 7.6, 4.3.

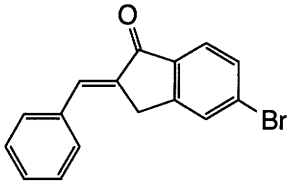
FTIR (thin film) 2956, 2936, 2875, 1662, 1598, 1586, 1457, 1448 cm^{-1}.

MS (EI) calc. for $C_{17}H_{22}OSi$ [M+Na] 270.14, found 270.14.



LiHMDS (3.75 mL of a 1.0 M solution in THF, 3.75 mmol) was added to a -78 °C solution of *Trans*-4-phenyl-3-buten-2-one (0.520 g, 3.56 mmol). After stirring for 1 hour a -78 °C, hexanal (0.442 mL, 3.60 mmol) was added all at once. After 10 minutes, the reaction was quenched with saturated NH_4Cl solution. The aqueous layer was extracted with Et_2O. the extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. This material was then purified by flash chromatography (10-50% Et_2O in pentane) to 425 mg of the aldol product. The aldol product (0.405 g, 1.64 mmol) was dissolved in THF (10 mL) and treated sequentially with $MeSO_2Cl$ (0.134 mL, 1.73 mmol) and NEt_3 (0.468 mL, 3.36 mmol) and then stirred for 24 hours. The reaction mixture was diluted with Et_2O and the organic layer was washed with H_2O and brine. The extracts were dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography yielded 0.245 g (65%) of a clear oil.

^{1}H NMR (500 MHz) δ 7.65 (d, J=15.9 Hz, 1H), 7.59 (m, 2H), 7.41-7.39 (m, 3H), 7.02 (dt, J=15.4 Hz, J=7.0 Hz, 1H), 6.99 (d, J=15.9 Hz, 1H), 6.44 (dt, J=15.4 Hz, J=1.5 Hz), 2.29 (m, 2H), 1.52 (m, 2H), 1.35 (m, 4H), 0.91 (m, 3H).



5-Bromo-1-indanone (1.11 g, 5.26 mmol) and benzaldehyde (560 mL, 5.52 mmol) were combined in EtOH (7.0 mL). The reaction vessel was purged with argon, and concentrated HCl (5 drops) was added. The reaction mixture was refluxed for

18 h, and then cooled to room temperature. The solid was filtered and washed with ethanol (3 x 5 mL) to provide 1.17 g of a white solid (75%).

^{1}H NMR (300 MHz) δ 7.79-7.64 (m, 5H), 7.57 (m, 1H), 7.51-7.39 (m, 3H), 4.03 (d, J=1.1 Hz, 2H).

^{13}C NMR (75 MHz) δ 193.3, 151.4, 137.1, 135.3, 134.9, 134.1, 131.5, 131.0, 130.1, 129.9, 129.6, 129.2, 125.9, 32.3.

FTIR (thin film) 1697, 1621, 1598, 1447, 1420 cm^{-1}.

HRMS (EI) calc. for $C_{16}H_{11}BrNaO$ [M+Na] 320.9885, found 320.9897.

III. Catalytic Asymmetric [3+2] Cycloadditions

General Procedures for Phosphine Catalyzed [3+2] Cycloadditions (Table 2.1.1, Table 2.1.2, Table 2.1.3, Table 2.1.4, and Scheme 2.1.8):

Method A. In a glove box, a solution of (*R*)-**2.1** (14.7 mg, 0.040 mmol) in toluene (0.5 mL) was added to a stirring solution of the enone (0.400 mmol) and ethyl 2,3-butanedienoate (56 μL, 0.48 mmol) in toluene (1.5 mL). The mixture was stirred at ambient temperature for 16 h, and then the product was directly purified by flash chromatography.

Method B. In a glove box, a solution of (*R*)-**2.1** (14.7 mg, 0.040 mmol) in toluene (0.5 mL) was added to a stirring solution of the enone (0.400 mmol) and ethyl 2,3-butanedienoate (46 μL, 0.40 mmol) in toluene (1.5 mL). After 3 h, ethyl 2,3-butanedienoate (46 μL, 0.40 mmol) was added, and the mixture was stirred for an additional 16 h. The product was directly purified by flash chromatography.

Table 2.1.1, Entry 1. Method A was used. (*S*)-BINAPINE (14.7 mg, 0.020 mmol), 2,3-ethylbutadienoate (28.0 μL, 0.240 mmol), and chalcone (41.7 mg, 0.200 mmol). The reaction mixture was filtered through a pad of silica gel with Et_2O and concentrated. Analysis of the resulting residue by ^1H NMR showed no desired cycloadduct.

Second run: (*S*)-BINAPINE (14.7 mg, 0.020 mmol), 2,3-ethylbutadienoate (28.0 μL, 0.240 mmol), and chalcone (41.7 mg, 0.200 mmol). The reaction mixture was filtered through a pad of silica gel with Et_2O and concentrated. Analysis of the resulting residue by ^1H NMR showed no desired cycloadduct.

Table 2.1.1, Entry 2. Method A was used. (*R*,*R*)-Me-BPE (10.3 mg, 0.040 mmol), 2,3-ethylbutadienoate (56.0 μL, 0.480 mmol), and chalcone (83.3 mg, 0.400 mmol). Purification by silica gel chromatography (2-30% Et_2O in pentane) yields the product as a 4.5:1.0 mixture of inseperable regioisomers (78.6 mg, 61%, -2% ee).

Second run: (*R*,*R*)-Me-BPE (10.3 mg, 0.040 mmol), 2,3-ethylbutadienoate (56.0 μL, 0.480 mmol), and chalcone (83.3 mg, 0.400 mmol). 78.9 mg (61%), 6.6:1.0 rs, -5% ee.

Table 2.1.1, Entry 3. Method A was used. (*R*,*R*)-Et-DUPHOS (14.5 mg, 0.040 mmol), 2,3-ethylbutadienoate (56.0 μL, 0.480 mmol), and chalcone (83.3 mg, 0.400 mmol). Purification by silica gel chromatography (2-30% Et_2O in pentane) yields the product as a 4.4:1.0 mixture of inseperable regioisomers (77.1 mg, 60%, 60% ee).

Second run: (*R*,*R*)-Et-DUPHOS (14.5 mg, 0.040 mmol), 2,3-ethylbutadienoate (56.0 μL, 0.480 mmol), and chalcone (83.3 mg, 0.400 mmol). 80.0 mg (62%), 8.6:1.0 rs, 56% ee.

Table 2.1.1, Entry 4. (*R*,*R*)-Et-FerroTANE. Method A was used. (R,R)-Et-FerroTANE (17.7 mg, 0.040 mmol), 2,3-ethylbutadienoate (56.0 μL, 0.480 mmol), and chalcone (83.3 mg, 0.400 mmol). Purification by silica gel chromatography (2-30% Et_2O in pentane) yields the product as a 5.6:1.0 mixture of inseperable regioisomers (82.0 mg, 64%, 11% ee).

Second run: (*R*,*R*)-Et-FerroTANE (17.7 mg, 0.040 mmol), 2,3-ethylbutadienoate (56.0 μL, 0.480 mmol), and chalcone (83.3 mg, 0.400 mmol). 82.1mg (64%), 7.4:1.0 rs, 11% ee.

Table 2.1.1, Entry 5. Method A was used. (*R*)-BINAP (10.3 mg, 0.020 mmol), 2,3-ethylbutadienoate (28.0 μL, 0.240 mmol), and chalcone (41.7 mg, 0.200 mmol). Purification by silica gel chromatography (2-30% Et_2O in pentane) yields the product as a 40:1 mixture of inseperable regioisomers (<1.0 mg, 2%, 50% ee).

Second run: (*R*)-BINAP (10.3 mg, 0.020 mmol), 2,3-ethylbutadienoate (28.0 μL, 0.240 mmol), and chalcone (41.7 mg, 0.200 mmol). (<1.0 mg, 30:1 rs, 2%, 50% ee).

Table 2.1.1, Entry 6. Method A was used. (*R*)-NMDPP (17.7 mg, 0.040 mmol), 2,3-ethylbutadienoate (56.0 μL, 0.480 mmol), and chalcone (83.3 mg, 0.400 mmol).

Purification by silica gel chromatography (2-30% Et_2O in pentane) yields the product as a 12.4:1.0 mixture of inseperable regioisomers (4.9 mg, 4%, -4% ee).

Second run: (*R*)-NMDPP (17.7 mg, 0.040 mmol), 2,3-ethylbutadienoate (56.0 μL, 0.480 mmol), and chalcone (83.3 mg, 0.400 mmol). 3.5 mg (3%), 9.2:1.0 rs, -3% ee.

Table 2.1.1, Entry 7. See Table 2.2, Entry 1.

Table 2.1.1, Entry 8. Method A was used. (*R*)-**2.2** (7.0 mg, 0.020 mmol), 2,3-ethylbutadienoate (58.0 μL, 0.240 mmol), and chalcone (41.6 mg, 0.200 mmol). Purification by silica gel chromatography (2-30% Et_2O in pentane) yields the product as a 10.0:1.0 mixture of inseperable regioisomers (56.5 mg, 88%, 43% ee).

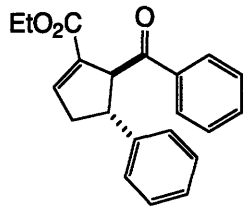


Table 2.1.2, entry 1. Method A was employed: Enone (83.3 mg, 0.400 mmol), ethyl 2,3-butanedienoate (56 μL, 0.48 mmol), and (*R*)-**2.1** (14.7 mg, 0.040 mmol). Purification by flash chromatography (~2-30% Et_2O in pentane) furnished the product as a 10:1 mixture of regioisomers (80.5 mg, 63%).

HPLC analysis: 88% ee [Daicel CHIRALCEL OD-H; solvent system: 10% isopropanol/hexanes; retention times: (minor) 9.6 min, (major) 14.4 min].

Second run: Enone (83.3 mg, 0.400 mmol), ethyl 2,3-butanedienoate (56 μL, 0.48 mmol), and (*S*)-**2.1** (14.7 mg, 0.040 mmol). 81.9 mg (64%), 15:1 rs, 87% ee.

$[a]^{20}_D = +224°$ (c=0.20, CH_2Cl_2).

^1H NMR (300 MHz) δ 7.78 (m, 2H), 7.50 (t, J=7.3 Hz, 1H), 7.38-7.17 (m, 7H), 7.11 (m, 1H), 4.89 (m, 1H), 4.13 (m, 2H), 3.58 (dt, J=9.1 Hz, J=4.7 Hz, 1H), 3.19 (ddt, J=18.7 Hz, J=9.0 Hz, J=2.5 Hz, 1H), 2.72 (m, 1H), 1.15 (t, J=7.2 Hz, 3H).

^{13}C NMR (75 MHz) δ 200.9, 164.2, 145.4, 145.1, 136.7, 135.8, 133.2, 129.1, 128.9, 128.6, 127.2, 126.9, 60.7, 60.4, 49.1, 42.3, 14.2.

FTIR (thin film) 3084, 3062, 3028, 2981, 2934, 2906, 1963, 1715, 1681, 1640, 1597, 1493, 1448 cm^{-1}.

HRMS (ESI) calc. for $C_{21}H_{20}NaO_3$ [M+Na] 343.1304, found 343.1320.

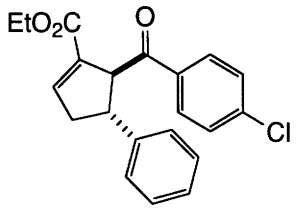


Table 2.1.2, entry 2. Method A was employed: 4'-chlorochalcone (97.1 mg, 0.400 mmol), ethyl 2,3-butanedienoate (56 μL, 0.48 mmol), and (*R*)-**2.1** (14.7 mg, 0.040 mmol). Purification by flash chromatography (2-15% Et_2O in pentane) furnished the product as a 6:1 mixture of regioisomers (110 mg, 78%).

HPLC analysis: 82% ee [Daicel CHIRALCEL OD-H; solvent system: 10% isopropanol/hexanes; retention times: (minor) 8.2 min, (major) 38.9 min].

Second run: 4'-chlorochalcone (97.1 mg, 0.400 mmol), ethyl 2,3-butanedienoate (56 μL, 0.48 mmol), and (*R*)-**2.1** (14.7 mg, 0.040 mmol). 105 mg (74%), 8:1 rs, 82% ee.

^1H NMR (300 MHz) δ 7.69 (m, 2H), 7.34-7.24 (m, 5H), 7.19 (m, 2H), 7.09 (m, 1H), 4.82 (m, 1H), 4.12 (m, 2H), 3.55 (dt, J=9.0 Hz, J=5.5 Hz, 1H), 3.18 (ddt, J=18.9 Hz, J=9.1 Hz, J=2.5 Hz, 1H), 2.73 (m, 1H), 1.16 (t, J=7.0 Hz, 3H).

^{13}C NMR (75 MHz) δ 199.8, 164.1, 145.3, 144.8, 139.7, 135.7, 135.1, 130.3, 129.2, 128.9, 127.3, 126.9, 60.7, 60.5, 49.2, 42.3, 14.2.

FTIR (thin film) 3063, 3029, 2981, 2934, 2906, 2843, 1716, 1683, 1636, 1588, 1571, 1489, 1455 cm^{-1}.

HRMS (ESI) calc. for $C_{21}H_{19}ClNaO_3$ [M+Na] 377.0915, found 377.0916.

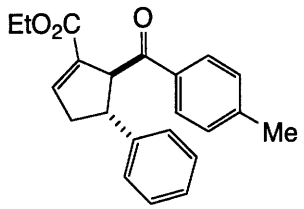


Table 2.1.2, entry 3. Method A was employed: Enone (89.0 mg, 0.400 mmol), ethyl 2,3-butanedienoate (56 μL, 0.48 mmol), and (*R*)-**2.1** (14.7 mg, 0.040 mmol). Purification by flash chromatography (5-20% Et_2O in pentane) furnished the product as a 20:1 mixture of regioisomers (83.1 mg, 62%).

HPLC analysis: 87% ee [Daicel CHIRALCEL OD-H; solvent system: 10% isopropanol/hexanes; retention times: (minor) 8.6 min, (major) 18.8 min].

Second run: Enone (89.0 mg, 0.400 mmol), ethyl 2,3-butanedienoate (56 μL, 0.48 mmol), and (*S*)-**2.1** (14.7 mg, 0.040 mmol). 80.9 mg (60%), 20:1 rs, 87% ee.

$[a]^{20}_D = +219°$ (c=0.15, CH_2Cl_2).

^{1}H NMR (300 MHz) δ 7.69 (m, 2H), 7.35-7.12 (m, 7H), 7.10 (m, 1H), 4.86 (m, 1H), 4.13 (m, 2H), 3.56 (dt, J=9.1 Hz, J=5.0 Hz, 1H), 3.18 (ddt, J=19.0 Hz, J=9.1 Hz, J=2.5 Hz, 1H), 2.71 (m, 1H), 2.36 (s, 3H), 1.16 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 200.4, 164.2, 145.3, 145.1, 144.0, 135.9, 134.1, 129.3, 129.1, 129.0, 127.1, 127.0, 60.6, 60.3, 49.1, 42.3, 21.8, 14.2.

FTIR (thin film) 3061, 3029, 2981, 2929, 2872, 1715, 1689, 1639, 1606, 1572, 1493, 1454 cm^{-1}.

HRMS (ESI) calc. for $C_{22}H_{22}NaO_3$ [M+Na] 357.1461, found 357.1462.

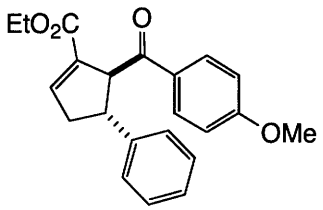


Table 2.1.2, entry 4. Method B was employed: Enone (95.3 mg, 0.400 mmol), ethyl 2,3-butanedienoate (93 μL, 0.80 mmol), and (*R*)-**2.1** (14.7 mg, 0.040 mmol).

Purification by flash chromatography (2-30% Et_2O in pentane) furnished the product (78.6 mg, 56%; >20:1 rs).

HPLC analysis: 88% ee [Daicel CHIRALCEL OD-H; solvent system: 10% isopropanol/hexanes; retention times: (minor) 13.7 min, (major) 34.3 min].

Second run: Enone (95.3 mg, 0.400 mmol), ethyl 2,3-butanedienoate (93 μL, 0.80 mmol), and (*S*)-**2.1** (14.7 mg, 0.040 mmol). 73.0 mg (52%), >20:1 rs, 87% ee.

$[a]^{20}_D = +186°$ (c=0.24, CH_2Cl_2).

^1H NMR (300 MHz) δ 7.76 (dt, J=8.8 Hz, J=1.9 Hz, 2H), 7.35-7.23 (m, 3H), 7.23-7.17 (m, 2H), 7.09 (m, 1H), 6.82 (dt, J=9.0 Hz, J=1.9 Hz, 2H), 4.82 (m, 1H), 4.12 (m, 2H), 3.82 (s, 3H), 3.55 (dt, J=9.0 Hz, J=4.9 Hz, 1H), 3.18 (ddt, J=18.8 Hz, J=8.8 Hz, J=2.6 Hz, 1H), 2.70 (m, 1H), 1.16 (t, J=6.9 Hz, 3H).

^{13}C NMR (75 MHz) δ 199.3, 164.3, 163.9, 145.4, 145.1, 135.9, 131.3, 129.7, 129.1, 127.1, 127.0, 113.8, 60.6, 60.2, 55.6, 49.1, 42.3, 14.2.

FTIR (thin film) 3062, 3027, 2980, 2935, 2840, 1715, 1673, 1599, 1575, 1510, 1493, 1510 cm^{-1}.

HRMS (ESI) calc. for $C_{22}H_{22}NaO_4$ [M+Na] 373.1410, found 373.1427.

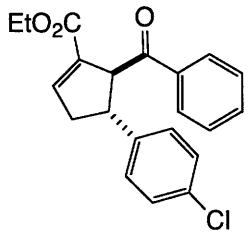


Table 2.1.2, entry 5. Method A was employed: Enone (97.1 mg, 0.400 mmol), ethyl 2,3-butanedienoate (56 μL, 0.48 mmol), and (*R*)-**2.1** (14.7 mg, 0.040 mmol). Purification by flash chromatography (5-20% Et_2O in pentane) furnished the product as an 8:1 mixture of regioisomers (107 mg, 75%).

HPLC analysis: 87% ee [Daicel CHIRALCEL OD-H; solvent system: 10% isopropanol/hexanes; retention times: (minor) 9.2 min, (major) 15.1 min].

Second run: Enone (97.1 mg, 0.400 mmol), ethyl 2,3-butanedienoate (56 μL, 0.48 mmol), and (*S*)-**2.1** (14.7 mg, 0.040 mmol). 104 mg (73%), 9:1 rs, 87% ee.

^{1}H NMR (300 MHz) δ 7.78 (m, 2H), 7.51 (m, 1H), 7.37 (m, 2H), 7.27 (m, 2H), 7.17-7.06 (m, 3H), 4.83 (m, 1H), 4.11 (m, 2H), 3.55 (m, 1H), 3.18 (ddt, J=19.0 Hz, J=9.1 Hz, J=2.5 Hz, 1H), 2.66 (m, 1H), 1.14 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 200.6, 163.9, 144.9, 143.6, 136.6, 135.8, 133.4, 132.8, 129.2, 128.9, 128.7, 128.4, 60.7, 60.2, 48.4, 42.2, 14.2.

FTIR (thin film) 3085, 3063, 2981, 2935, 1714, 1682, 1639, 1596, 1580, 1492, 1447 cm^{-1}.

HRMS (ESI) calc. for $C_{21}H_{19}ClNaO_3$ [M+Na] 377.0915, found 377.0912.

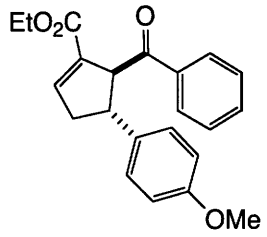


Table 2.1.2, entry 6. Method B was employed: Enone (95.3 mg, 0.400 mmol), ethyl 2,3-butanedienoate (93 μL, 0.80 mmol), and (*R*)-**2.1** (14.7 mg, 0.040 mmol). Purification by flash chromatography (~2-30% Et_2O in pentane) furnished the product as a 10:1 mixture of regioisomers (94.8 mg, 68%).

HPLC analysis: 87% ee [Daicel CHIRALCEL OD-H; solvent system: 10% isopropanol/hexanes; retention times: (minor) 11.8 min, (major) 18.3 min].

Second run: Enone (95.3 mg, 0.400 mmol), ethyl 2,3-butanedienoate (56 μL, 0.48 mmol), and (*S*)-**2.1** (14.7 mg, 0.040 mmol). 91.5 mg (65%), 10:1 rs, 86% ee.

$[a]^{20}_D$ = +235° (c=0.16, CH_2Cl_2).

^{1}H NMR (300 MHz) δ 7.78 (m, 2H), 7.50 (m, 1H), 7.36 (t, J=8.0 Hz, 2H), 7.15-7.07 (m, 3H), 6.83 (m, 2H), 4.83 (m, 1H), 4.12 (m, 2H), 3.79 (s, 3H), 3.53 (dt, J=8.8 Hz, J=5.2 Hz, 1H), 3.15 (ddt, J=19.0 Hz, J=9.1 Hz, J=2.5 Hz, 1H), 2.67 (m, 1H), 1.15 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 200.9, 164.2, 158.7, 145.2, 137.2, 136.7, 135.8, 133.2, 128.9, 128.6, 127.9, 114.3, 60.64, 60.60, 55.4, 48.4, 42.4, 14.2.

FTIR (thin film) 3062, 3032, 2981, 2935, 2907, 2837, 1716, 1683, 1636, 1611, 1596, 1581, 1514, 1447 cm^{-1}.

HRMS (ESI) calc. for $C_{22}H_{22}NaO_4$ [M+Na] 373.1410, found 373.1422.

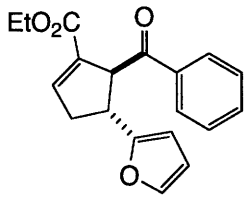


Table 2.1.2, entry 7. Method B was employed: Enone (79.3 mg, 0.400 mmol), ethyl 2,3-butanedienoate (93 μL, 0.48 mmol), and (*R*)-**2.1** (14.7 mg, 0.040 mmol). Purification by flash chromatography (2-25% Et_2O in pentane) furnished the product (60.1 mg, 48%; 22.9 mg, 18%, of the regioisomer).

HPLC analysis: 88% ee [Daicel CHIRALCEL OD-H; solvent system: 10% isopropanol/hexanes; retention times: (minor) 9.0 min, (major) 11.8 min].

Second run: Enone (79.3 mg, 0.400 mmol), ethyl 2,3-butanedienoate (93 μL, 0.48 mmol), and (*S*)-**2.1** (14.7 mg, 0.040 mmol). 66.3 mg (53%), 87% ee. 20.0 mg (16%) of the regioisomer.

$[a]^{20}_D = +239°$ (c=0.16, CH_2Cl_2).

^1H NMR (300 MHz) δ 7.91 (m, 2H), 7.54 (m, 1H), 7.42 (m, 2H), 7.35 (dd, J=1.9 Hz, J=0.9 Hz, 1H), 7.03 (dt, J=1.7 Hz, J=2.4 Hz, 1H), 6.28 (dd, J=3.0 Hz, J=1.7 Hz, 1H), 6.02 (m, 1H), 4.99 (m, 1H), 4.09 (m, 2H), 3.73 (dt, J=8.5 Hz, J=5.8 Hz, 1H), 3.04 (ddt, J=18.4 Hz, J=8.8 Hz, J=2.5 Hz, 1H), 2.82 (m, 1H), 1.11 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 200.9, 164.0, 156.2, 144.6, 141.9, 136.9, 135.8, 133.3, 128.9, 128.6, 110.4, 105.6, 60.7, 56.9, 42.6, 38.6, 14.1.

FTIR (thin film) 3118, 3064, 2981, 2937, 1716, 1682, 1637, 1596, 1580, 1507, 1448 cm^{-1}.

HRMS (ESI) calc. for $C_{19}H_{18}NaO_4$ [M+Na] 333.1097, found 333.1109.

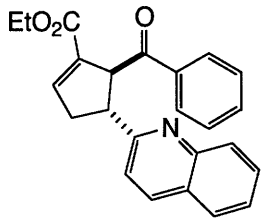


Table 2.1.2, entry 8. Method A was employed, except that CH_2Cl_2 (0.2 mL)/toluene (2.0 mL) was used as the solvent, due to the low substrate solubility of the enone in toluene: Enone (104 mg, 0.400 mmol), ethyl 2,3-butanedienoate (56 μL, 0.48 mmol), and (*R*)-**2.1** (14.7 mg, 0.040 mmol). Purification by flash chromatography (5-40% Et_2O in pentane) furnished the product (77.1 mg, 53%; 18:1 rs).

HPLC analysis: 88% ee [Daicel CHIRALCEL OD-H; solvent system: 10% isopropanol/hexanes; retention times: (minor) 13.0 min, (major) 23.1 min].

Second run: Enone (104 mg, 0.400 mmol), ethyl 2,3-butanedienoate (56 μL, 0.48 mmol), and (*S*)-**2.1** (14.7 mg, 0.040 mmol). 74.3 mg (50%), >20:1 rs, 88% ee.

$[a]^{20}_D = +407°$ (c=0.15, CH_2Cl_2).

^{1}H NMR (300 MHz) δ 8.01 (m, 4H), 7.78 (dd, J=8.0 Hz, J=1.4 Hz, 1H), 7.71 (td, J=8.3 Hz, J=1.4 Hz, 1H), 7.53-7.43 (m, 2H), 7.33 (t, J=8.0 Hz, 2H), 7.18 (d, J=8.6 Hz, 1H), 7.07 (dd, J=4.4 Hz, J=2.5 Hz, 1H), 5.64 (m, 1H), 4.18-4.02 (m, 3H), 3.25 (ddt, J=18.7 Hz, J=9.1 Hz, J=2.5 Hz, 1H), 2.97 (m, 1H), 1.12 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 201.9, 164.2, 162.4, 147.9, 144.4, 137.1, 137.0, 136.4, 133.1, 129.8, 129.4, 129.1, 128.5, 127.7, 127.2, 126.4, 120.7, 60.6, 56.6, 51.6, 40.4, 14.2.

FTIR (thin film) 3059, 2981, 2934, 2842, 1714, 1681, 1639, 1618, 1598, 1503, 1447 cm^{-1}.

HRMS (ESI) calc. for $C_{24}H_{21}NNaO_3$ [M+Na] 394.1413, found 394.1421.

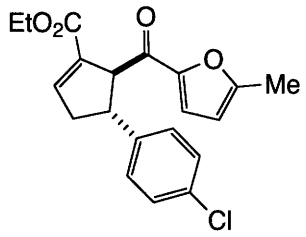


Table 2.1.2, entry 9. Method A was employed, except that CH_2Cl_2 (0.2 mL)/toluene (2.0 mL) was used as the solvent, due to the low substrate solubility of the enone in toluene: Enone (98.7 mg, 0.400 mmol), ethyl 2,3-butanedienoate (56 μL, 0.48 mmol), and (*R*)-**2.1** (14.7 mg, 0.040 mmol). Purification by flash chromatography (5-40% Et_2O in pentane) furnished the product (80.0 mg, 56%; >20:1 rs).

HPLC analysis: 89% ee [Daicel CHIRALCEL OD-H; solvent system: 10% isopropanol/hexanes; retention times: (minor) 12.4 min, (major) 22.3 min].

Second run: Enone (98.7 mg, 0.400 mmol), ethyl 2,3-butanedienoate (56 μL, 0.48 mmol), and (*S*)-**2.1** (14.7 mg, 0.040 mmol). 73.0 mg (51%), >20:1 rs, 89% ee.

$[a]^{20}_D$ = +250° (c=0.24, CH_2Cl_2).

^{1}H NMR (300 MHz) δ 7.24 (dt, J=8.5 Hz, J=2.0 Hz, 2H), 7.12 (dt, J=8.5 Hz, J=2.0 Hz, 2H), 7.03 (m, 1H), 6.86 (d, J=3.6 Hz, 1H), 6.06 (dd, J=3.6 Hz, J=0.9 Hz, 1H), 4.51 (m, 1H), 4.10 (q, J=7.1 Hz, 2H), 3.59 (dt, J=9.1 Hz, J=6.0 Hz, 1H), 3.14 (ddt, J=18.8 Hz, J=8.8 Hz, J=2.5 Hz, 1H), 2.64 (m, 1H), 2.29 (s, 3H), 1.15 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 188.2, 163.9, 158.7, 151.2, 145.2, 143.2, 135.2, 132.7, 128.9, 128.5, 120.7, 109.3, 60.7, 60.5, 48.8, 41.8, 14.2.

FTIR (thin film) 3122, 3063, 3027, 2982, 2927, 1715, 1668, 1588, 1515, 1493, 1444 cm^{-1}.

HRMS (ESI) calc. for $C_{20}H_{19}ClNaO_4$ [M+Na] 381.0864, found 381.0879.

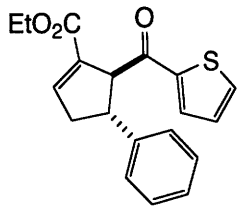


Table 2.1.2, entry 10. Method A was employed: Enone (85.7 mg, 0.400 mmol), ethyl 2,3-butanedienoate (56 μL, 0.48 mmol), and (*R*)-**2.1** (14.7 mg, 0.040 mmol). Purification by flash chromatography (5-25% Et_2O in pentane) furnished the product as a 5:1 mixture of regioisomers (96.9 mg, 74%).

HPLC analysis: 90% ee [Daicel CHIRALCEL OD-H; solvent system: 10% isopropanol/hexanes; retention times: (minor) 11.9 min, (major) 14.8 min].

Second run: Enone (85.7 mg, 0.400 mmol), ethyl 2,3-butanedienoate (56 μL, 0.48 mmol), and (*S*)-**2.1** (14.7 mg, 0.040 mmol). 95.7 mg (73%), 6:1 rs, 89% ee.

^{1}H NMR (300 MHz) δ 7.59 (dd, J=5.0 Hz, J=1.1 Hz, 1H), 7.38 (dd, J=3.8 Hz, J=1.1 Hz, 1H), 7.35-7.16 (m, 6H), 7.10 (m, 1H), 4.69 (m, 1H), 4.12 (m, 2H), 3.64 (dt, J=9.1 Hz, J=5.5 Hz, 1H), 3.19 (ddt, J=19.0 Hz, J=9.6 Hz, J=2.5 Hz, 1H), 2.73 (m, 1H), 1.15 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 193.5, 163.9, 145.5, 144.8, 144.2, 135.3, 134.4, 132.9, 129.0, 128.2, 127.2, 127.0, 61.9, 60.7, 49.5, 42.2, 14.1.

FTIR (thin film) 3086, 3063, 3028, 2981, 2934, 2905, 1715, 1652, 1603, 1517, 1493 cm^{-1}.

HRMS (ESI) calc. for $C_{19}H_{18}NaO_3S$ [M+Na] 349.0869, found 349.0878.

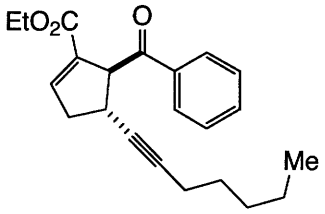


Table 2.1.2, entry 11. Method A was employed: Enone (90.5 mg, 0.400 mmol), ethyl 2,3-butanedienoate (56 μL, 0.48 mmol), and (*R*)-**2.1** (14.7 mg, 0.040 mmol).

Purification by flash chromatography (2-15% Et_2O in pentane) furnished the product as a 6:1 mixture of regioisomers (85.3 mg, 63%).

HPLC analysis: 84% ee [Regis (*R,R*)-Whelk-O2; solvent system: 10% isopropanol/hexanes; retention times: (minor) 13.2 min, (major) 21.6 min].

Second run: Enone (90.5 mg, 0.400 mmol), ethyl 2,3-butanedienoate (56 μL, 0.48 mmol), and (*R*)-**2.1** (14.7 mg, 0.040 mmol). 89.1 mg (66%), 5:1 rs, 85% ee.

^{1}H NMR (300 MHz) δ 8.12 (m, 2H), 7.58 (tt, J=7.0 Hz, J=1.0 Hz, 1H), 7.47 (m, 2H), 6.93 (dd, J=2.5 Hz, J=1.5 Hz, 1H), 4.86 (m, 1H), 4.08 (m, 2H), 3.20 (m, 1H), 2.99 (m, 1H), 2.66 (m, 1H), 2.15 (m, 2H), 1.46 (m, 2H), 1.37-1.24 (m, 4H), 1.11 (t, J=7.0 Hz, 3H), 0.87 (m, 3H).

^{13}C NMR (75 MHz) δ 200.7, 163.9, 144.3, 136.9, 135.7, 133.4, 129.1, 128.7, 82.9, 81.9, 60.7, 58.9, 41.2, 34.6, 31.2, 28.7, 22.4, 18.9, 14.2.

FTIR (thin film) 3063, 1716, 1683, 1640, 1597, 1580, 1465, 1448 cm^{-1}.

HRMS (ESI) calc. for $C_{22}H_{26}NaO_3$ [M+Na] 361.1774, found 361.1789.

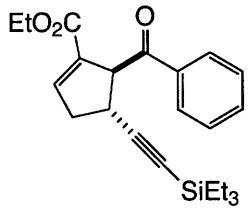


Table 2.1.2, entry 12. Method A was employed: Enone (109 mg, 0.400 mmol), ethyl 2,3-butanedienoate (56 μL, 0.48 mmol), and (*R*)-**2.1** (14.7 mg, 0.040 mmol). Purification by flash chromatography (5-20% Et_2O in pentane) furnished the product (109 mg, 71%; >20:1 rs).

HPLC analysis: 86% ee [Regis (*R,R*)-Whelk-O2; solvent system: 10% isopropanol/hexanes; retention times: (minor) 10.5 min, (major) 14.5 min].

Second run: Enone (109 mg, 0.400 mmol), ethyl 2,3-butanedienoate (56 μL, 0.48 mmol), and (*S*)-**2.1** (14.7 mg, 0.040 mmol). 104 mg (68%), >20:1 rs, 87% ee.

$[a]^{20}_D = +188°$ (c=0.23, CH_2Cl_2).

^{1}H NMR (300 MHz) δ 8.14 (m, 2H), 7.59 (m, 1H), 7.48 (m, 2H), 6.93 (m, 1H), 4.94 (m, 1H), 4.10 (m, 2H), 3.26 (dt, J=9.1 Hz, J=6.6 Hz, 1H), 3.06 (ddt, J=18.3 Hz, J=8.9 Hz, J=2.5 Hz, 1H), 2.74 (m, 1H), 1.13 (t, J=7.1 Hz, 3H), 0.97 (t, J=7.7 Hz, 9H), 0.58 (q, J=8.0 Hz, 6H).

^{13}C NMR (75 MHz) δ 200.5, 163.8, 143.9, 136.9, 135.6, 133.4, 129.1, 128.6, 109.2, 84.3, 60.7, 58.8, 41.1, 35.2, 14.1, 7.6, 4.5.

FTIR (thin film) 3063, 2173, 1716, 1684, 1642, 1597, 1580, 1448 cm^{-1}.

HRMS (ESI) calc. for $C_{23}H_{30}NaO_3Si$ [M+Na] 405.1856, found 405.1874.

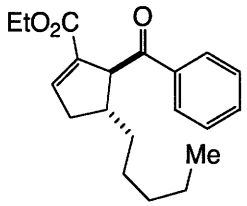


Table 2.1.2, entry 13. Method B was employed: Enone (76 mg, 0.38 mmol), ethyl 2,3-butanedienoate (93 μL, 0.80 mmol), and (*R*)-**2.1** (14.7 mg, 0.040 mmol). Purification by flash chromatography (~2-12% Et_2O in pentane) furnished the product (48.9 mg, 41%; >20:1 rs).

HPLC analysis: 75% ee [Daicel CHIRALCEL OD-H; solvent system: 10% isopropanol/hexanes; retention times: (minor) 10.5 min, (major) 14.5 min].

Second run: Enone (76 mg, 0.38 mmol), ethyl 2,3-butanedienoate (93 μL, 0.80 mmol), and **(*R*)-2.1** (14.7 mg, 0.040 mmol). 43.0 mg (56%) of the enone was recovered. 43.5 mg (37%), >20:1 rs, 75% ee.

$[a]^{20}_D = -125°$ (c=1.5, $CDCl_3$).

^{1}H NMR (300 MHz) δ 8.03 (d, J=7.3 Hz, 2H), 7.58 (t, J=7.3 Hz, 1H), 7.49 (t, J=7.4 Hz, 2H), 7.00 (m, 1H), 4.50 (m, 1H), 4.08 (m, 2H), 2.84 (m, 1H), 2.48 (m, 1H), 2.26 (m, 1H), 1.62-1.45 (m, 2H), 1.32-1.18 (m, 6H), 1.11 (t, J=7.1 Hz, 3H), 0.83 (t, J=6.7 Hz, 3H).

^{13}C NMR (75 MHz) δ 202.3, 164.5, 145.9, 137.5, 136.1, 133.2, 128.9, 128.8, 60.6, 57.7, 44.5, 39.1, 36.2, 31.9, 27.5, 22.8, 14.24, 14.21.

FTIR (thin film) 2956, 2927, 2855, 2871, 1714, 1681, 1637, 1447, 1372 cm^{-1}.

HRMS (ESI) calc. for $C_{20}H_{26}NaO_3$ [M+Na] 337.1774, found 337.1782.

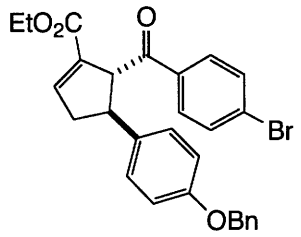


Table 2.1.2, Entry 14. Method A was employed: Enone (157 mg, 0.400 mmol), ethyl 2,3-butanedienoate (56μL, 0.48 mmol), and (*S*)-**2.1** (14.7 mg, 0.040 mmol). Purification by flash chromatography (2-25% Et_2O in hexanes) furnished the product as a 7:1 mixture of regioisomers (125mg, 62%).

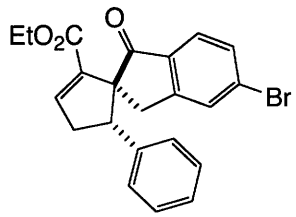
HPLC analysis: 86% ee [Daicel CHIRALCEL AD-H; solvent system: 10% isopropanol/hexanes; retention times: (minor) 19.2 min, (major) 24.2 min].

^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (m, 2H), 7.51-7.35 (m, 7H), 7.14-7.07 (m, 3H), 6.93 (m, 2H), 5.07 (s, 2H), 4.78 (m, 1H), 4.14 (m, 2H), 3.52 (dt, J=9.1 Hz, J=5.5 Hz, 1H), 3.16 (ddt, J=19.0 Hz, J=9.1 Hz, J=2.4 Hz, 1H), 2.70 (m, 1H), 1.18 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 164.1, 157.9, 145.3, 137.02, 136.99, 135.5, 135.4, 131.9, 130.4, 128.7, 128.4, 128.2, 128.0, 127.64, 127.60, 115.4, 70.1, 60.7, 60.6, 48.5, 42.4, 14.2.

FTIR (thin film) 3064, 3033, 2980, 2934, 2870, 1716, 1683, 1568, 1584, 1511 cm^{-1}.

HRMS (ESI) calc. for $C_{28}H_{25}NaO_4$ [M+Na] 527.0828, found 527.0844.



Eq 2.1.12. Method B was employed: Enone (110 mg, 0.400 mmol), ethyl 2,3-butanedienoate (93 μL, 0.80 mmol), and (*R*)-**2.1** (14.7 mg, 0.040 mmol). Purification by

flash chromatography (2-25% Et_2O in pentane) furnished the product as a single regioisomer (159 mg, 97%).

HPLC analysis: 89% ee [Daicel CHIRALCEL OD-H; solvent system: 10% isopropanol/hexanes; retention times: (minor) 8.6 min, (major) 11.6 min].

Second run: Enone (110 mg, 0.400 mmol), ethyl 2,3-butanedienoate (93 μL, 0.80 mmol), and (*S*)-**2.1** (14.7 mg, 0.040 mmol). 158 mg (96%), 88% ee.

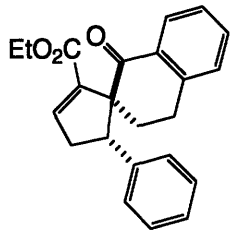
$[a]^{20}_D = +91.4°$ (c=0.14, CH_2Cl_2).

^1H NMR (300 MHz) δ 7.63 (d, J=8.0 Hz, 1H), 7.42 (dd, J=1.2 Hz, J=8.0 Hz, 1H), 7.26 (s, 1H), 7.16 (t, J=2.5 Hz, 1H), 7.15-7.09 (m, 3H), 7.01-6.95 (m, 2H), 4.10 (t, J=8.8 Hz, 1H), 4.01 (t, J=7.1 Hz, 2H), 2.96 (m, 2H), 2.93 (br s, 2H), 1.02 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 208.1, 163.4, 154.7, 146.1, 139.7, 138.3, 136.1, 130.8, 130.1, 129.2, 128.4, 127.9, 127.3, 124.9, 64.6, 60.6, 53.7, 36.4, 34.4, 13.9.

FTIR (thin film) 3407, 3061, 3029, 2981, 1700, 1628, 1596, 1496 cm^{-1}.

HRMS (EI) calc. for $C_{22}H_{19}BrO_3$ [M] 410.0512, found 410.0523.



Eq 2.1.13. Method B was employed: Enone (93.7 mg, 0.400 mmol), ethyl 2,3-butanedienoate (93 μL, 0.80 mmol), and (*R*)-**2.1** (14.7 mg, 0.040 mmol). Purification by flash chromatography (2-30% Et_2O in pentane) furnished the product as a single regioisomer (46.0 mg, 33%).

HPLC analysis: 96% ee [Daicel CHIRALCEL OD-H; solvent system: 10% isopropanol/hexanes; retention times: (minor) 8.4 min, (major) 9.6 min].

Second run: Enone (93.7 mg, 0.400 mmol), ethyl 2,3-butanedienoate (93 μL, 0.80 mmol), and (*S*)-**2.1** (14.7 mg, 0.040 mmol). 42.4 mg (31%), 93% ee.

$[a]^{20}_D = +106°$ (c=0.21, CH_2Cl_2).

^{1}H NMR (300 MHz) δ 8.10 (dd, J=7.7 Hz, J=1.4 Hz, 1H), 7.38 (ddd, J=8.4 Hz, J=8.4 Hz, J=1.6 Hz, 1H), 7.28 (m, 1H), 7.24-7.16 (m, 5H), 7.12 (dd, J=2.4 Hz, J=2.4 Hz, 1H), 6.98 (d, J=7.7 Hz, 1H), 4.30 (dd, J=9.6 Hz, J=8.1 Hz, 1H), 4.05 (q, J=7.1 Hz, 2H), 3.00 (ddd, J=9.6 Hz, J=8.5 Hz, J=2.2 Hz, 1H), 2.84 (ddd, J=10.1 Hz, J=7.9 Hz, J=3.1 Hz, 1H), 2.48 (m, 1H), 2.36-2.23 (m, 1H), 2.06-1.88 (m, 2H), 1.05 (t, J=7.2 Hz, 3H).

^{13}C NMR (75 MHz) δ 200.1, 163.9, 145.1, 144.0, 142.3, 139.6, 133.4, 133.2, 128.6, 128.4, 127.9, 127.4, 126.6, 61.3, 60.6, 54.3, 35.7, 28.1, 25.6, 13.9.

FTIR (thin film) 3063, 3029, 2981, 2933, 1953, 1715, 1674, 1633, 1600, 1496, 1455 cm^{-1}.

HRMS (ESI) calc. for $C_{23}H_{22}NaO_3$ [M+Na] 369.1461, found 369.1475.

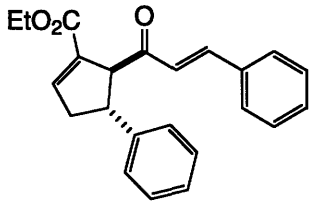


Table 2.1.4, Entry 1. Method B was employed: Enone (93.7 mg, 0.400 mmol), ethyl 2,3-butanedienoate (93 μL, 0.80 mmol), and (*R*)-**2.1** (14.7 mg, 0.040 mmol). Purification by flash chromatography (2-30% Et_2O in pentane) furnished the product (104 mg, 75%; >20:1 rs).

HPLC analysis: 89% ee [Daicel CHIRALCEL OD-H; solvent system: 10% isopropanol/hexanes; retention times: (minor) 10.2 min, (major) 34.4 min].

Second run: Enone (93.7 mg, 0.400 mmol), ethyl 2,3-butanedienoate (93 μL, 0.80 mmol), and (*R*)-**2.1** (14.7 mg, 0.040 mmol). 103 mg (74%), >20:1 rs, 89% ee.

$[a]^{20}_D = -166°$ (c=0.050, CH_2Cl_2).

^{1}H NMR (300 MHz) δ 7.42-7.29 (m, 8H), 7.29-7.23 (m, 3H), 7.06 (m, 1H), 6.76 (d, J=16.2 Hz, 1H), 4.41 (m, 1H), 4.18 (m, 2H), 3.61 (dt, J=8.6 Hz, J=5.9 Hz, 1H), 3.18 (ddt, J=9.9 Hz, J=8.9 Hz, J=2.6 Hz, 1H), 2.73 (ddt, J=19.0 Hz, J=5.8 Hz, J=2.2 Hz, 1H), 1.25 (t, J=6.9 Hz, 3H).

^{13}C NMR (75 MHz) δ 200.1, 164.2, 145.1, 144.9, 144.1, 135.5, 134.6, 130.6, 129.1, 128.9, 128.5, 127.1, 127.1, 125.7, 63.3, 60.7, 48.8, 42.0, 14.3.

FTIR (thin film) 3061, 3027, 1714, 1687, 1660, 1609, 1576, 1494, 1449 cm^{-1}.

HRMS (ESI) calc. for $C_{23}H_{22}NaO_3$ [M+Na] 369.1461, found 369.1478.

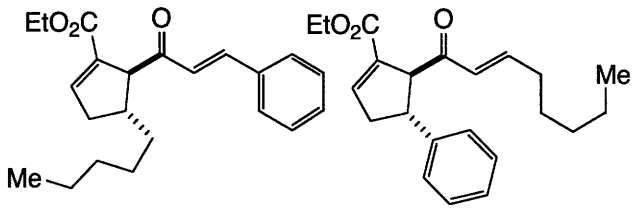


Table 2.1.4, Entry 2. Ethyl-2,3-butadienoate (15 mg, 0.134 mmmol) and the enone (30.5 mg, 0.134 mmol) were combined in toluene (0.75 mL) and PPh_3 (3.5 mg, 0.013 mmmol) was added. The solution was stirred for 22 h at room temperature. The reaction mixture was purified directly by flash chromatography (2-10% Et_2O in pentane) to yield 30.5 mg (67%) of a clear oil determined to be approximately a 1:1 mixture of the above isomers by ^1H NMR.

(left isomer, aromatic protons are unassigned) ^1H NMR (500 MHz) δ 7.67 (d, J=15.9 Hz, 1H), 6.98 (m, 1H), 6.88 (d, J=15.9 Hz, 1H), 4.21-4.11 (m, 2H), 3.87 (m, 1H), 2.84 (ddt, J=18.6 Hz, J=8.3 Hz, J=2.5 Hz, 1H), 2.48 (m, 1H), 2.24 (ddt, J=18.6 Hz, J=4.6 Hz, J=2.4 Hz, 1H), 1.58 (m, 1H), 1.49 (m, 1H), 1.36-1.18 (m, 9H), 0.87 (m, 3H).

(right isomer, aromatic protons are unassigned) ^1H NMR (500 MHz) δ 7.02 (m, 1H), 6.62 (dt, J=15.8 Hz, J=7.0 Hz, 1H), 6.11 (dt, J=15.8 Hz, J=1.5 Hz, 1H), 4.30 (m, 1H), 4.21-4.11 (m, 2H), 3.49 (m, 1H), 3.13 (ddt, J=18.9 Hz, J=8.9 Hz, J=2.5 Hz, 1H), 2.68 (ddt, J=18.9 Hz, J=5.8 Hz, J=2.3 Hz, 1H), 2.11 (m, 1H), 1.36-1.18 (m, 9H), 0.89 (m, 3H).

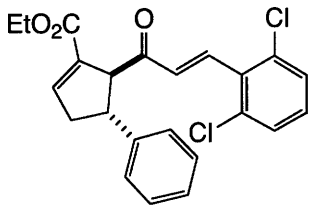


Table 2.1.4, Entry 3. Method B was employed: Enone (121 mg, 0.400 mmol), ethyl 2,3-butanedienoate (93 μL, 0.48 mmol), and (*R*)-**2.1** (14.7 mg, 0.040 mmol). Purification by flash chromatography (~25% Et_2O in pentane) furnished the product (109 mg, 66%; >20:1 rs).

HPLC analysis: 74% ee [Daicel CHIRALCEL OD-H; solvent system: 10% isopropanol/hexanes; retention times: (minor) 10.5 min, (major) 16.4 min].

Second run: Enone (121 mg, 0.400 mmol), ethyl 2,3-butanedienoate (93 μL, 0.48 mmol), and (*S*)-**2.1** (14.7 mg, 0.040 mmol). 114 mg (69%), >20:1 rs, 72% ee.

$[a]^{20}_D = +156°$ (c=0.33, CH_2Cl_2).

^1H NMR (300 MHz) δ 7.57 (d, J=16.5 Hz, 1H), 7.34-7.22 (m, 7H), 7.14 (dd, J=7.5 Hz, J=8.5 Hz, 1H), 7.07 (dd, J=2.5 Hz, J=4.5 Hz, 1H), 6.89 (d, J=16.5 Hz, 1H), 4.37 (m, 1H), 4.19 (m, 2H), 3.69 (dt, J=8.8 Hz, J=6.0 Hz, 1H), 3.16 (ddt, J=19.0 Hz, J=9.1 Hz, J=2.5 Hz, 1H), 2.72 (ddt, J=19.0 Hz, J=5.9 Hz, J=2.4 Hz, 1H), 1.25 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 199.7, 164.0, 145.4, 144.4, 136.9, 135.3, 135.2, 133.3, 132.3, 129.9, 129.0, 128.9, 127.1, 127.05, 63.5, 60.8, 48.7, 41.4, 14.3.

FTIR (thin film) 3063, 3028, 2981, 1715, 1669, 1616, 1578, 1556, 1494 cm^{-1}.

HRMS (EI) calc. for $C_{23}H_{20}Cl_2O_3$ [M] 414.0784, found 414.0777.

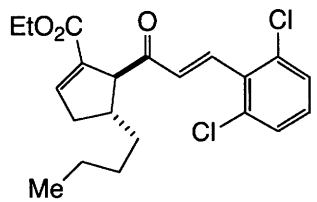


Table 2.1.4, Entry 4. Ethyl-2,3-butadienoate (122 mg, 1.087 mmmol) and the enone (308 mg, 1.087 mmol) were combined in toluene (3.0 mL) and PPh_3 (29 mg,

0.109 mmmol) was added. The solution was stirred for 16 h at room temperature. The reaction mixture was purified directly by flash chromatography (2-12% Et_2O in pentane) to yield 297 mg (69%) of a yellow oil.

^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J=16.5 Hz, 1H), 7.36 (d, J=8.2 Hz, 2H), 7.19 (t, J=8.2 Hz, 1H), 6.99 (d, J=16.5 Hz, 1H), 6.99 (m, 1H), 4.21-4.11 (m, 2H), 3.86 (m, 1H), 2.83 (ddt, J=18.6 Hz, J=8.2 Hz, J=2.5 Hz, 1H), 2.49 (m, 1H), 2.25 (ddt, J=18.6 Hz, J=4.9 Hz, J=2.5 Hz, 1H), 1.63 (m, 1H), 1.50 (m, 1H), 1.35-1.30 (m, 4H), 1.24 (t, J=7.2 Hz, 3H), 0.89 (m, 3H).

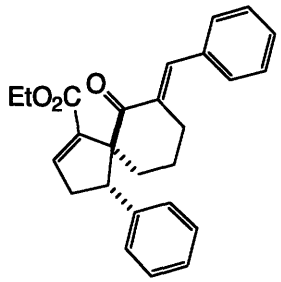


Table 2.1.4, Entry 5. Method B was employed: Enone (110 mg, 0.400 mmol), ethyl 2,3-butanedienoate (93 μL, 0.80 mmol), and (*R*)-**2.1** (14.7 mg, 0.040 mmol). Purification by flash chromatography (~2-25% Et_2O in pentane) furnished the product (84.4 mg, 55%).

HPLC analysis: 93% ee [Daicel CHIRALCEL OD-H; solvent system: 10% isopropanol/hexanes; retention times: (minor) 7.3 min, (major) 10.4 min].
Second run: Enone (110 mg, 0.400 mmol), ethyl 2,3-butanedienoate (93 μL, 0.80 mmol), and (*S*)-**2.1** (14.7 mg, 0.040 mmol). 92.0 mg (59%), 93% ee.

$[a]^{20}_D$ = +442° (c=0.13, CH_2Cl_2).

^1H NMR (300 MHz) δ 7.69 (m, 1H), 7.43-7.21 (m, 10H), 7.02 (dd, J=3.0 Hz, J=2.2 Hz, 1H), 4.25-4.16 (m, 3H), 2.97 (ddd, J=18.1 Hz, J=10.4 Hz, J=2.1 Hz, 1H), 2.84-2.76 (m, 1H), 2.76-2.71 (m, 1H), 2.57 (m, 1H), 2.05-1.87 (m, 2H), 1.40-1.25 (m, 1H), 1.26 (t, J=7.0 Hz, 3H), 0.39 (m, 1H).

^{13}C NMR (75 MHz) δ 205.2, 163.9, 143.6, 143.5, 138.9, 137.2, 136.14, 136.09, 130.4, 128.7, 128.50, 128.48, 128.39, 127.40, 62.7, 60.6, 56.1, 35.4, 29.1, 28.3, 20.1, 14.2.

FTIR (thin film) 3060, 3027, 2934, 2870, 1715, 1674, 1594, 1491, 1446 cm^{-1}.

HRMS (EI) calc. for $C_{25}H_{26}O_3$ [M] 386.1876, found 386.1887.

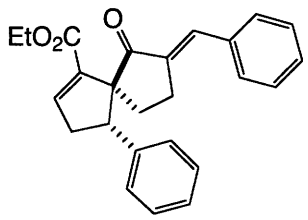


Table 2.1.4, Entry 6. Method B was employed: Enone (104 mg, 0.400 mmol), ethyl 2,3-butanedienoate (93 μL, 0.80 mmol), and (*R*)-**2.1** (14.7 mg, 0.040 mmol). Purification by flash chromatography (2-25% Et_2O in pentane) furnished the product (118 mg, 79%).

HPLC analysis: 89% ee [Daicel CHIRALCEL OD-H; solvent system: 10% isopropanol/hexanes; retention times: (minor) 8.2 min, (major) 18.2 min].

Second run: Enone (104 mg, 0.400 mmol), ethyl 2,3-butanedienoate (93 μL, 0.80 mmol), and (*S*)-**2.1** (14.7 mg, 0.040 mmol). 122 mg (82%), 89% ee. $[a]^{20}_D = +100°$ (c=0.23, CH_2Cl_2).

^1H NMR (300 MHz) δ 7.50 (m, 1H), 7.43-7.18 (m, 10H), 7.10 (dd, J=2.4 Hz, J=2.4 Hz, 1H), 4.14 (q, J=7.2 Hz, 2H), 3.94 (app t, J=8.7 Hz, 1H), 2.96 (ddd, J=18.1 Hz, J=9.6 Hz, J=1.9 Hz, 1H), 2.85 (ddd, J=18.2 Hz, J=8.3 Hz, J=2.9 Hz, 1H), 2.73 (m, 1H), 2.05 (m, 2H), 1.70 (m, 1H), 1.22 (t, J=7.2 Hz, 3H).

^{13}C NMR (75 MHz) δ 210.7, 163.6, 145.3, 140.5, 138.8, 136.7, 135.8, 132.9, 130.8, 129.3, 128.7, 128.5, 128.4, 127.4, 64.5, 60.6, 54.4, 36.5, 27.2, 26.7, 14.2.

FTIR (thin film) 3061, 3027, 2979, 2938, 1700, 1623, 1574, 1492, 1448 cm^{-1}.

HRMS (EI) calc. for $C_{25}H_{24}O_3$ [M] 372.1720, found 372.1716.

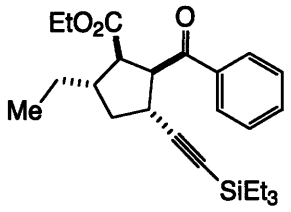


Table 2.1.5, Entry 1. To a slurry of $CuBr{\cdot}SMe_2$ (2.8 mg, 0.014 mmol) in THF (1.25 mL) at –78 °C was added HMPA (48 μL, 0.28 mmol), followed by EtMgBr (3.0 M in Et_2O; 138 mL, 0.41 mmol). After 5 min, a solution of the [3+2] adduct (53.0 mg, 0.138 mmol; 86% ee; derived from a cycloaddition catalyzed by (*R*)-**2.1** and TMSCl (35 μL, 0.28 mmol) in THF (1.25 mL) was added dropwise. The mixture was stirred for 2 h at –78 °C. Then, a solution of saturated NH_4Cl was added, and the aqueous layer was extracted with Et_2O (5 x 3 mL). The extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by flash chromatography (2-10% Et_2O in pentane), which furnished 33.5 mg (62%) of the desired compound.

HPLC analysis: 84% ee [Regis (*R,R*)-Whelk-O2; solvent system: 10% isopropanol/hexanes; retention times: (minor) 6.3 min, (major) 8.1 min].

Second run: $CuBr{\cdot}SMe_2$ (2.7 mg, 0.013 mmol), HMPA (44 mL, 0.25 mmol), EtMgBr (3.0 M in Et_2O; 125 mL, 0.375 mmol), [3+2] adduct (48.0 mg, 0.125 mmol, 86% ee; from (*R*)-**2.1**, and TMSCl (32 μL, 0.25 mmol). 31.5 mg (61%), 85% ee. $[a]^{20}_D = -79°$ (c=0.050, CH_2Cl_2).

^{1}H NMR (300 MHz) δ 7.98 (m, 2H), 7.56 (m, 1H), 7.45 (m, 2H), 4.22 (dd, J=9.9 Hz, J=7.1 Hz, 1H), 3.83 (q, J=7.2 Hz, 2H), 3.19 (dt, J=9.4 Hz, J=6.9 Hz, 1H), 2.93 (m, 1H), 2.49-2.35 (m, 2H), 1.76 (m, 1H), 1.49 (m, 1H), 1.33 (m, 1H), 0.90-0.97 (m, 15H), 0.53 (q, J=7.9 Hz, 6H).

^{13}C NMR (75 MHz) δ 199.6, 173.1, 137.0, 133.3, 128.8, 128.7, 110.1, 83.2, 60.6, 55.9, 53.2, 44.1, 39.5, 34.5, 28.2, 14.0, 12.6, 7.7, 4.6.

FTIR (thin film) 2957, 2911, 2875, 2168, 1737, 1683, 1597, 1459, 1448 cm^{-1}.

HRMS (ESI) calc. for $C_{25}H_{36}NaO_3Si$ [M+Na] 435.2326, found 435.2322.

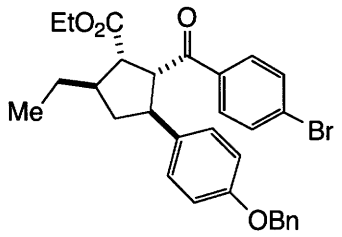


Table 2.1.5, Entry 2. The procedure used for Table 2.1.5, entry 1 was employed: CuBr·SMe_2 (2.5 mg, 0.012 mmol) in THF (1.0 mL), then HMPA (43 μL, 0.25 mmol), EtMgBr (3.0 M in Et_2O; 125 μL, 0.37 mmol), the [3+2] adduct (62.0 mg, 0.123 mmol; 86% ee), and TMSCl (32 μL, 0.25 mmol) in THF (1.0 mL). Yield: 43.0 mg (65%).

Crystals suitable for X-ray crystallography were grown by dissolving the compound in a boiling solution of hexane/Et_2O and allowing thesolution to cool to r.t.

HPLC analysis: 84% ee [Daicel CHIRALCEL AD-H; solvent system: 10% isopropanol/hexanes; retention times: (minor) 9.8 min, (major) 15.2 min].

$[\alpha]^{20}_D = +54°$ (c=0.065, CH_2Cl_2).

^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (m, 2H), 7.50 (m, 2H), 7.43-7.31 (m, 5H), 7.15 (m, 2H), 6.87 (m, 2H), 5.01 (s, 2H), 4.04 (dd, J=10.5 Hz, J=9.3 Hz, 1H), 3.83 (m, 2H), 3.63 (m, 1H), 3.02 (dd, J=10.5 Hz, J=9.0 Hz, 1H), 2.57-2.37 (m, 2H), 1.78 (m, 1H), 1.54 (m, 1H), 1.39 (m, 1H), 0.96 (t, J=7.4 Hz, 3H), 0.94 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 173.3, 157.7, 137.2, 136.1, 135.7, 131.9, 130.2, 128.8, 128.5, 128.3, 128.2, 127.7, 115.1, 70.2, 60.7, 56.9, 54.2, 47.4, 45.1, 41.2, 28.1, 14.0, 12.7.

FTIR (thin film) 3062, 3033, 2961, 2931, 2858, 1733, 1678, 1584, 1512 cm^{-1}.

HRMS (ESI) calc. for $C_{30}H_{31}BrNaO_4$ [M+Na] 557.1298, found 557.1298.

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20. Only ethyl acrylate and dimethyl maleate are suitable reaction partners.
21. Ethyl-2,3-butadienoate is commercially available from Aldrich.
22. Other commercially available chiral phosphines that were tested include: (*R,R*)-Me-DUPHOS, (*R,R*)-i-Pr-DUPHOS, (*R,R*)-Et-BPE, (*R,R*)-Ph-BPE, (*S,S*)-DIOP, (*R*)-MONOPHOS, (*S,S,R,R*)-TANGPHOS, and (*R*)-BINAPHANE.
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24. Allene dimerization is also catalyzed by phosphines and is a competing side reaction. Because electron-rich enones react slower than electron-deficient enones the allene dimerization becomes a competing side reaction.
25. Lu has demonstrated that cycloadditions of 1,1-disubstituted enones with allenes are possible, but at the time our work was published no examples of cycloadditions of *tri*substituted enones had been described.
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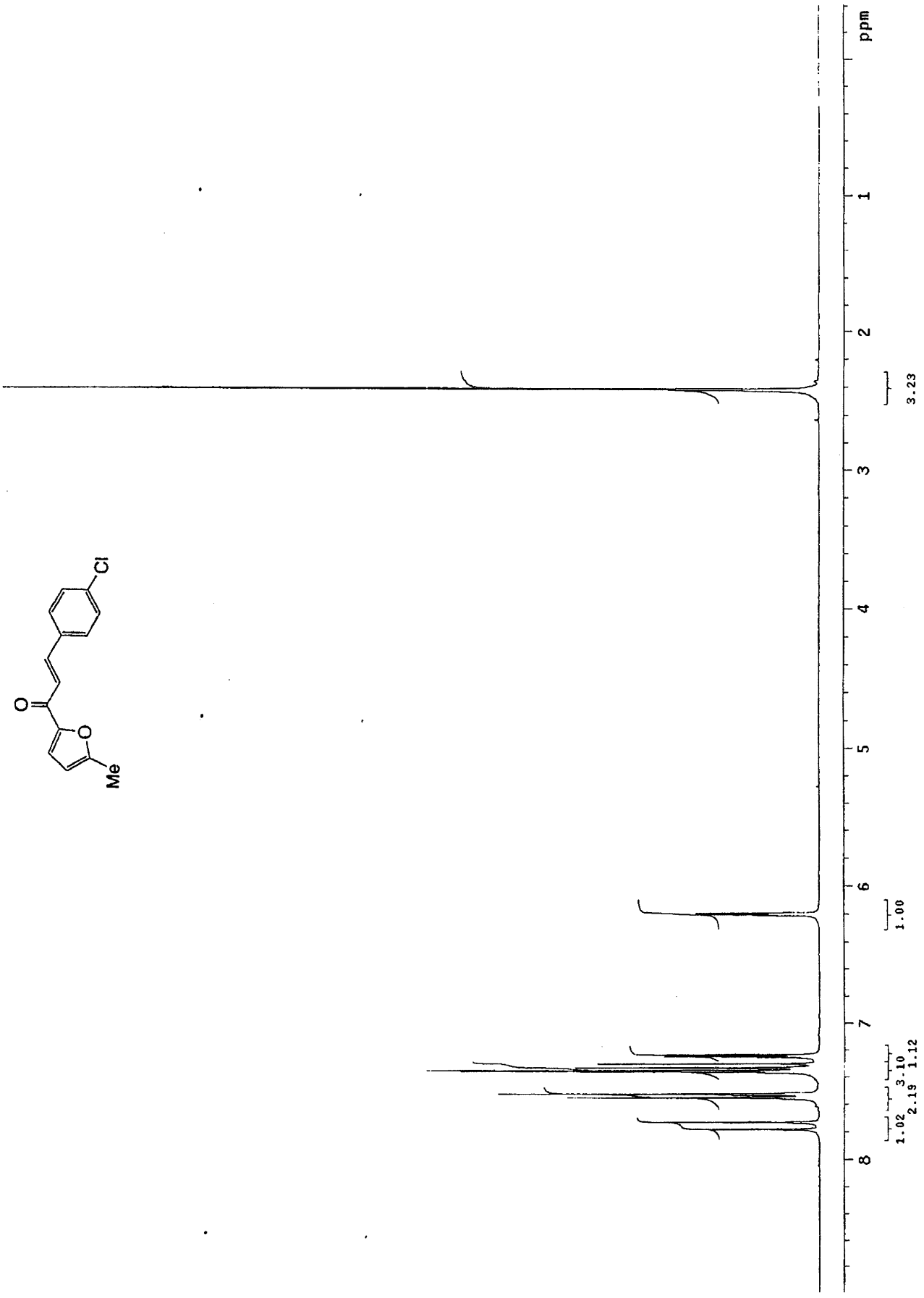
28. We have found that isobutyl magnesium bromide works in the 1,4-addition as well, but isopropyl magnesium bromide and phenylmagnesium bromide do not add under these conditions.
29. Chauvin, R. *Tetrahedron Lett.* **1995**, *36*, 401-404.

F. ^{1}H NMR for Selected Compounds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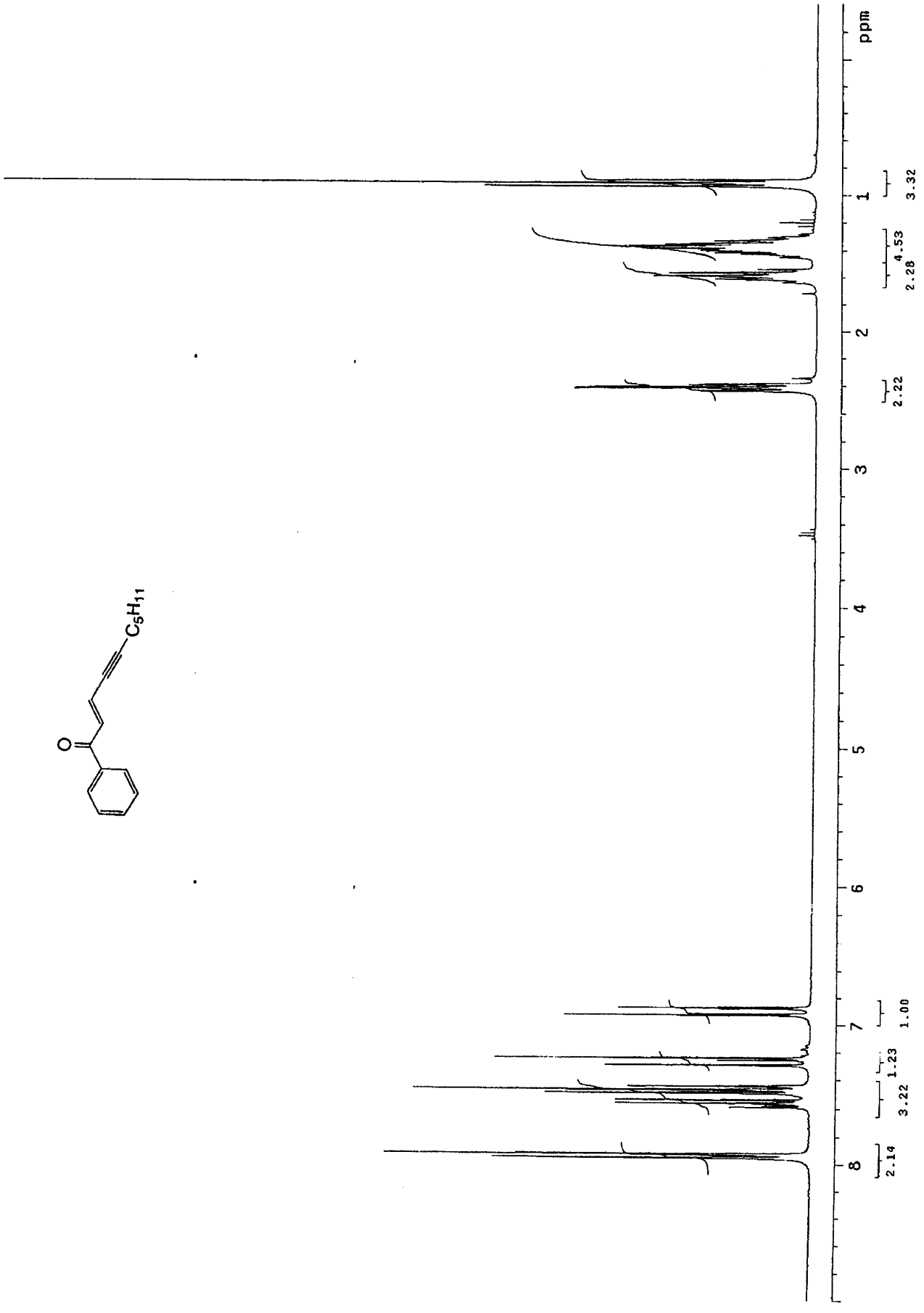
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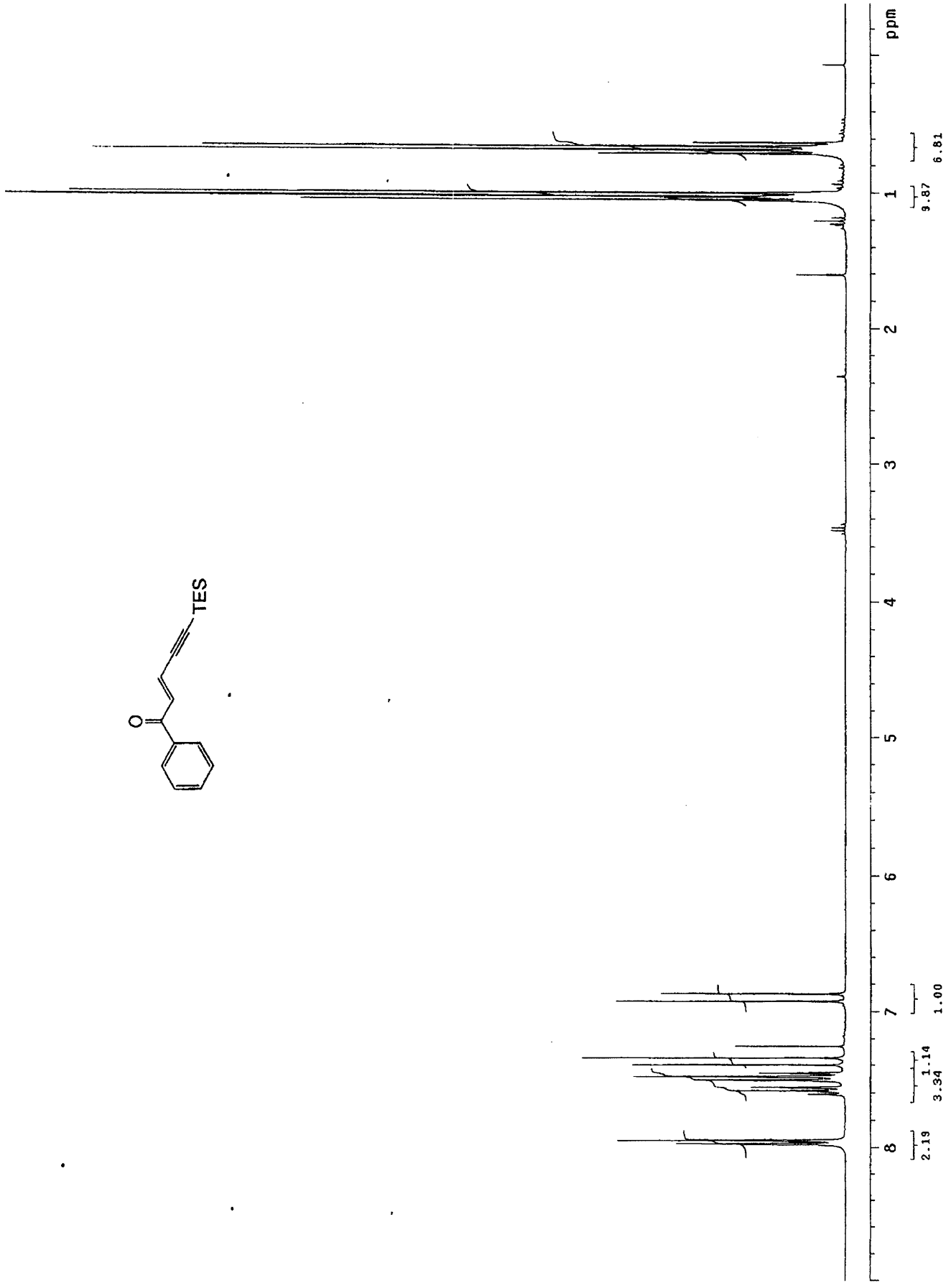
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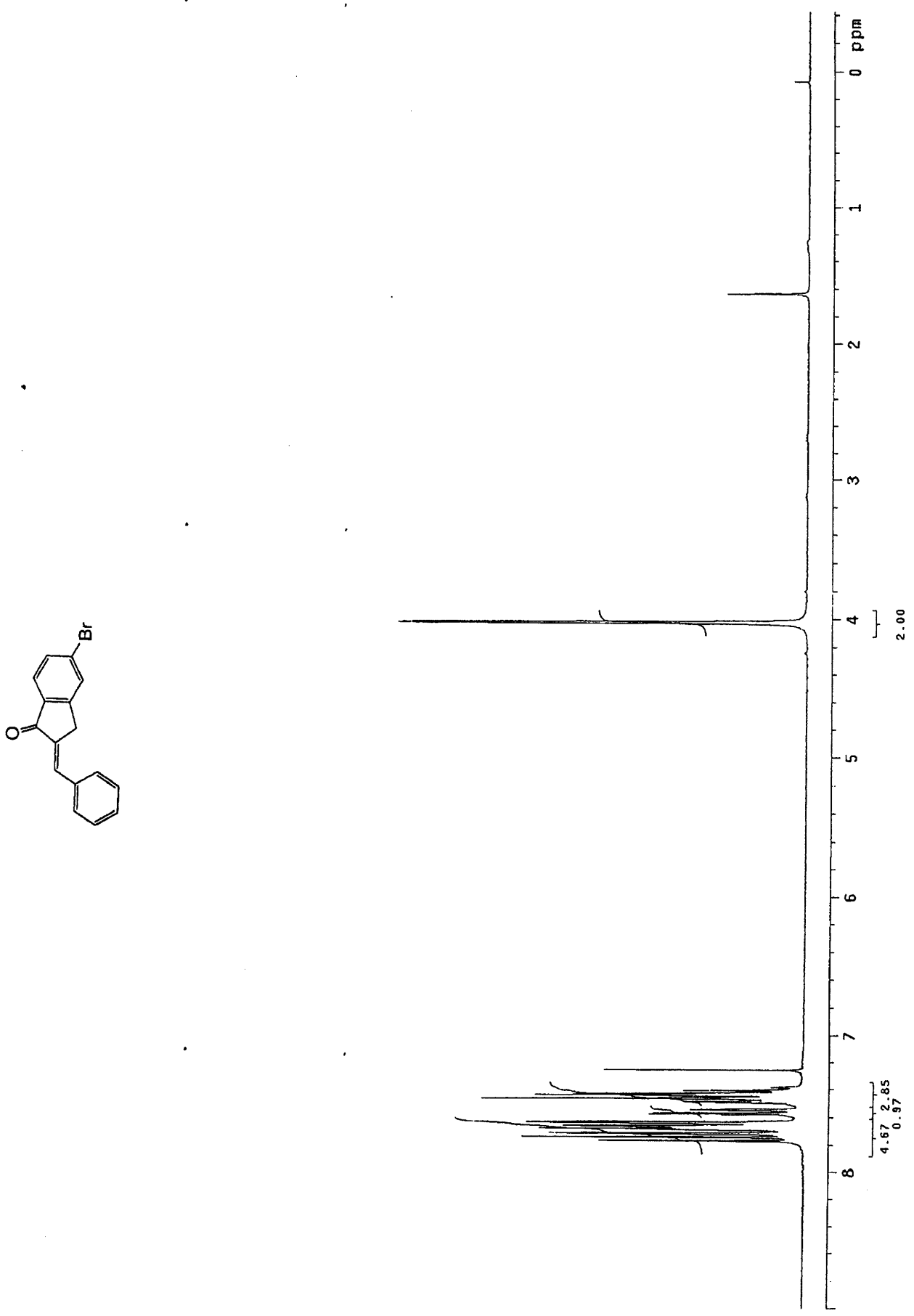
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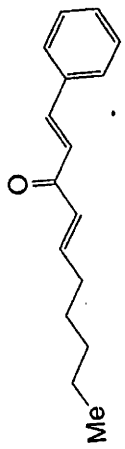
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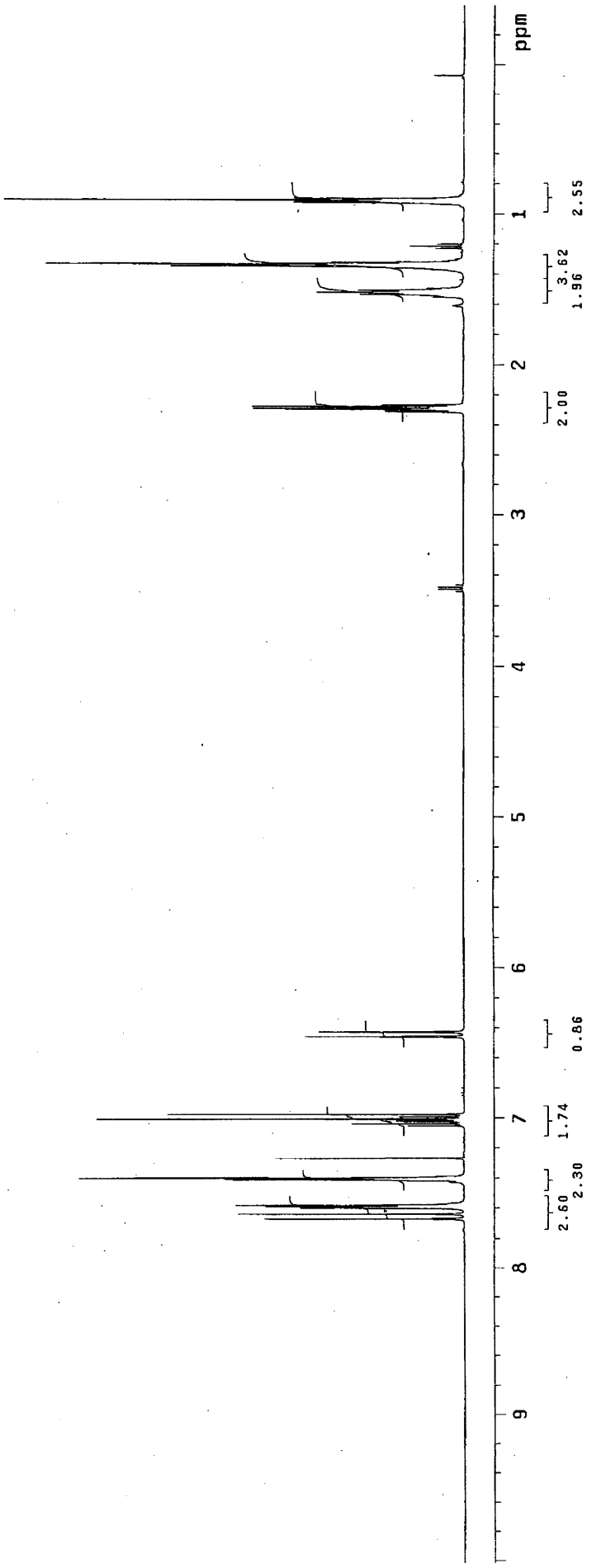
Me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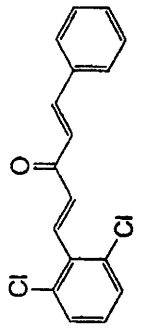
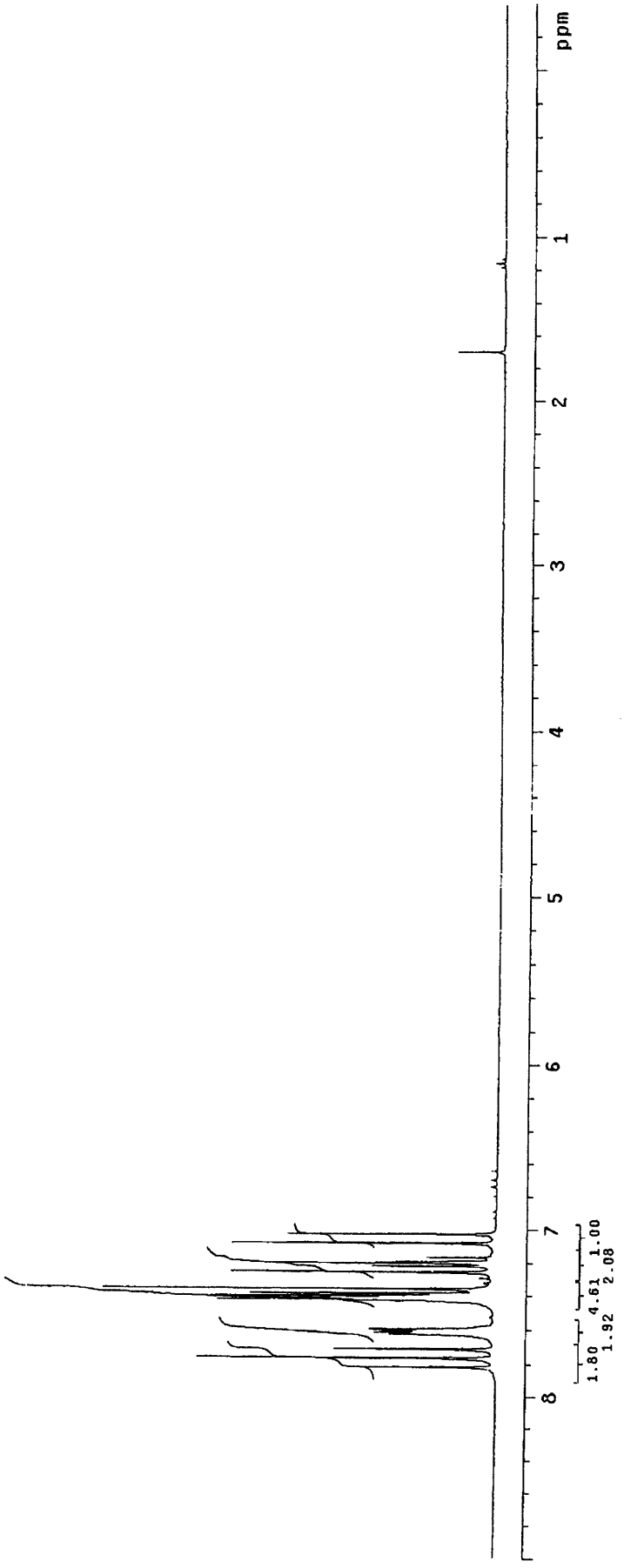

O
Cl
Cl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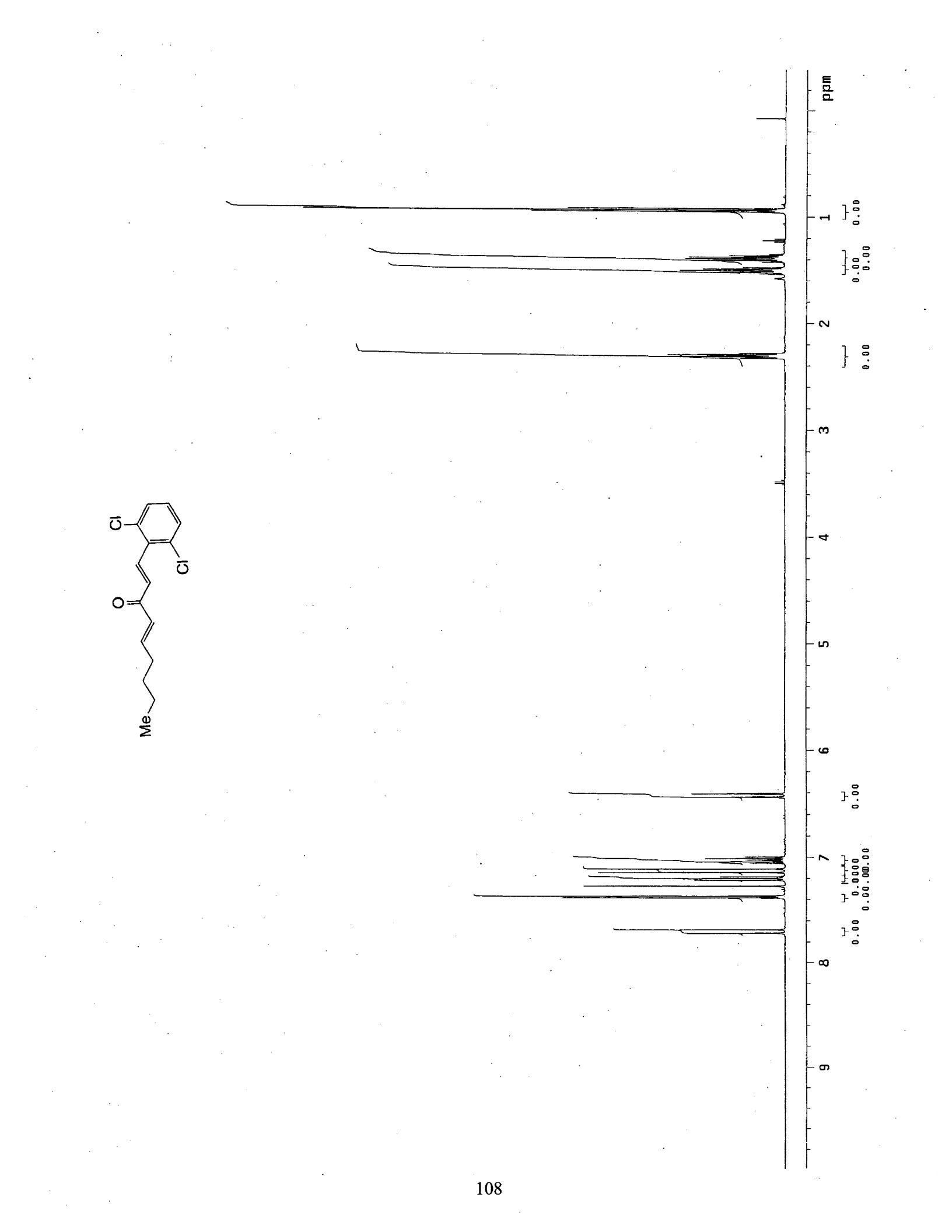
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Cl
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Me
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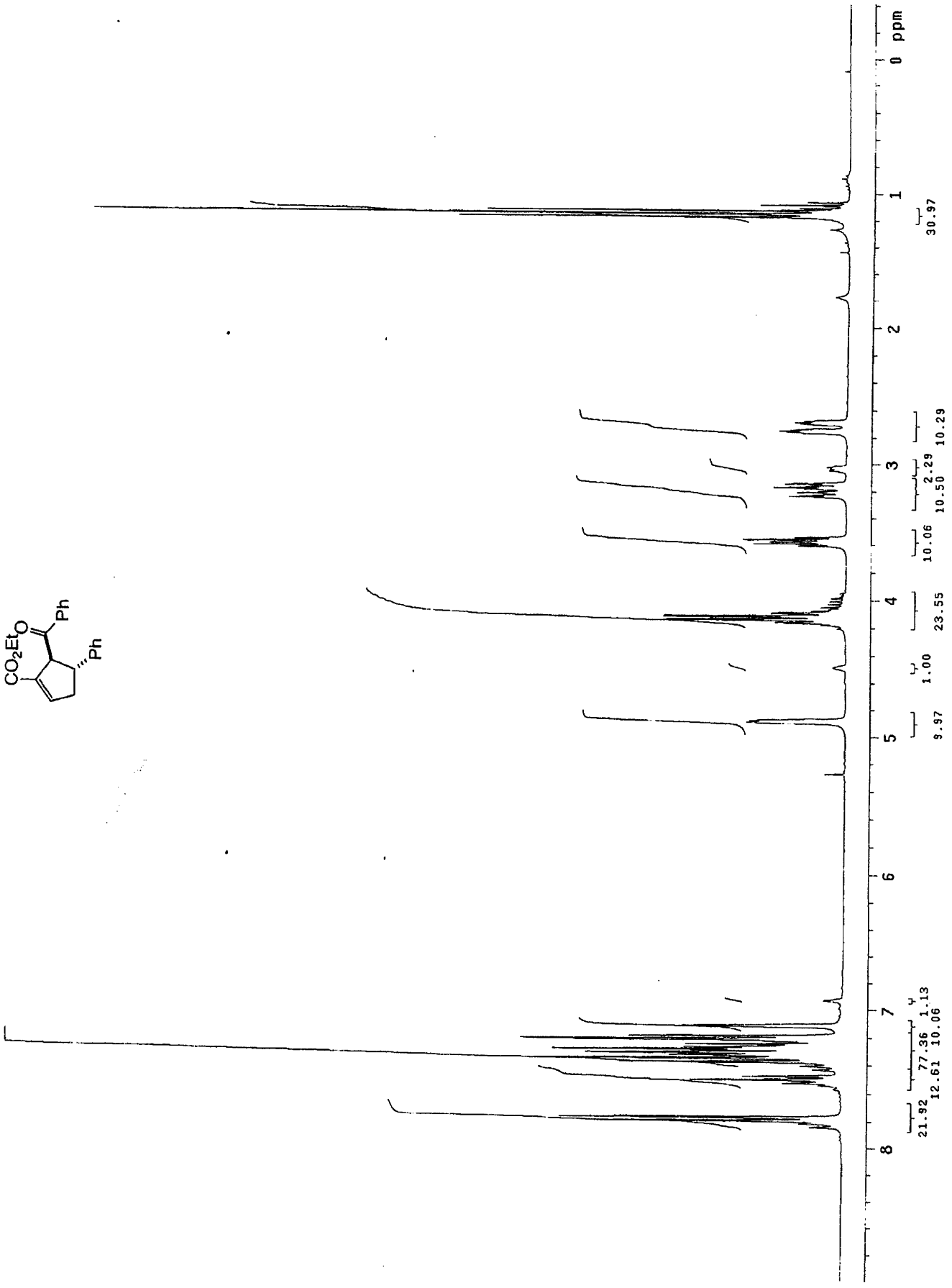
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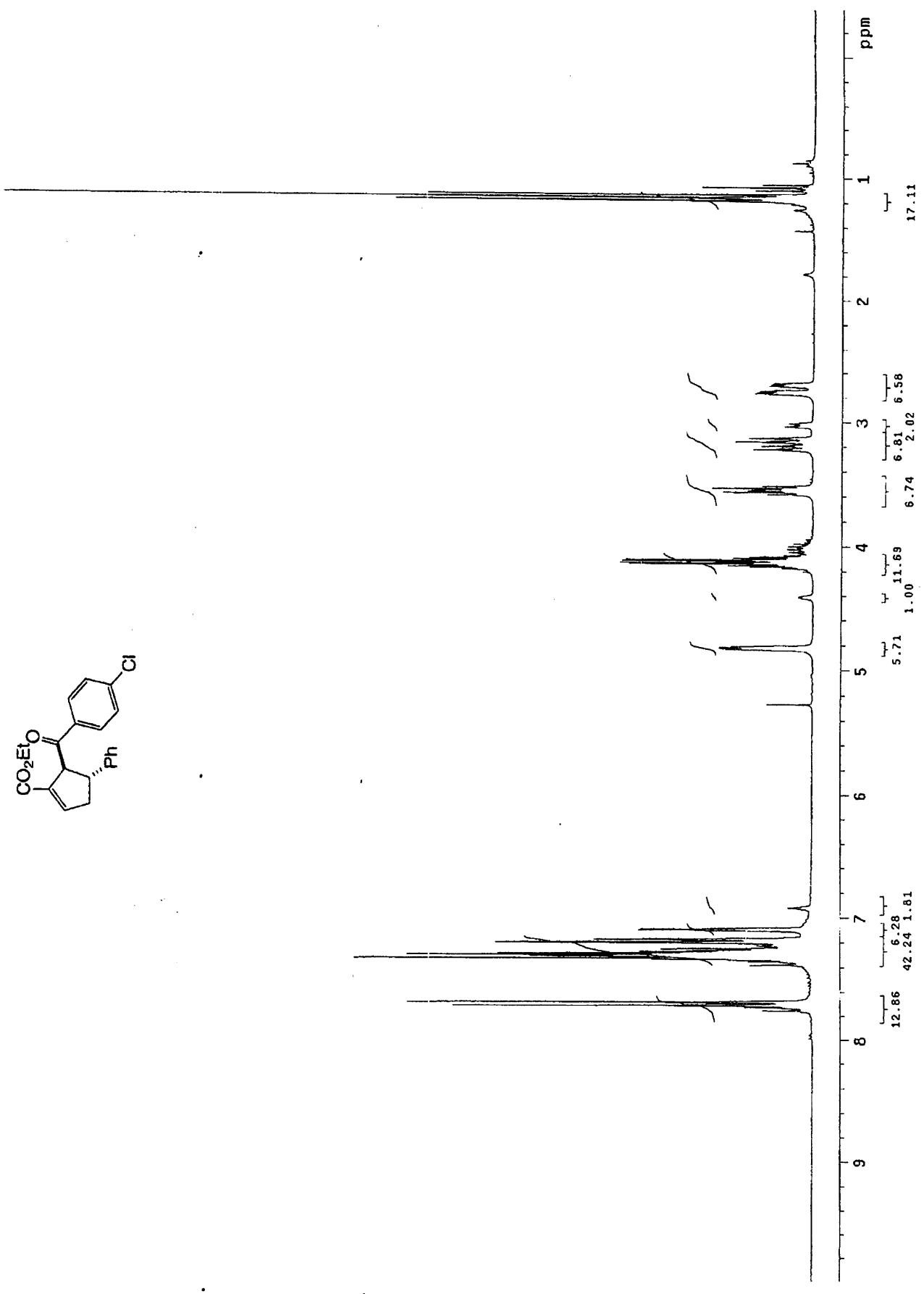
30.97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CO2Et
Ph
ppm
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3
4
5
6
7
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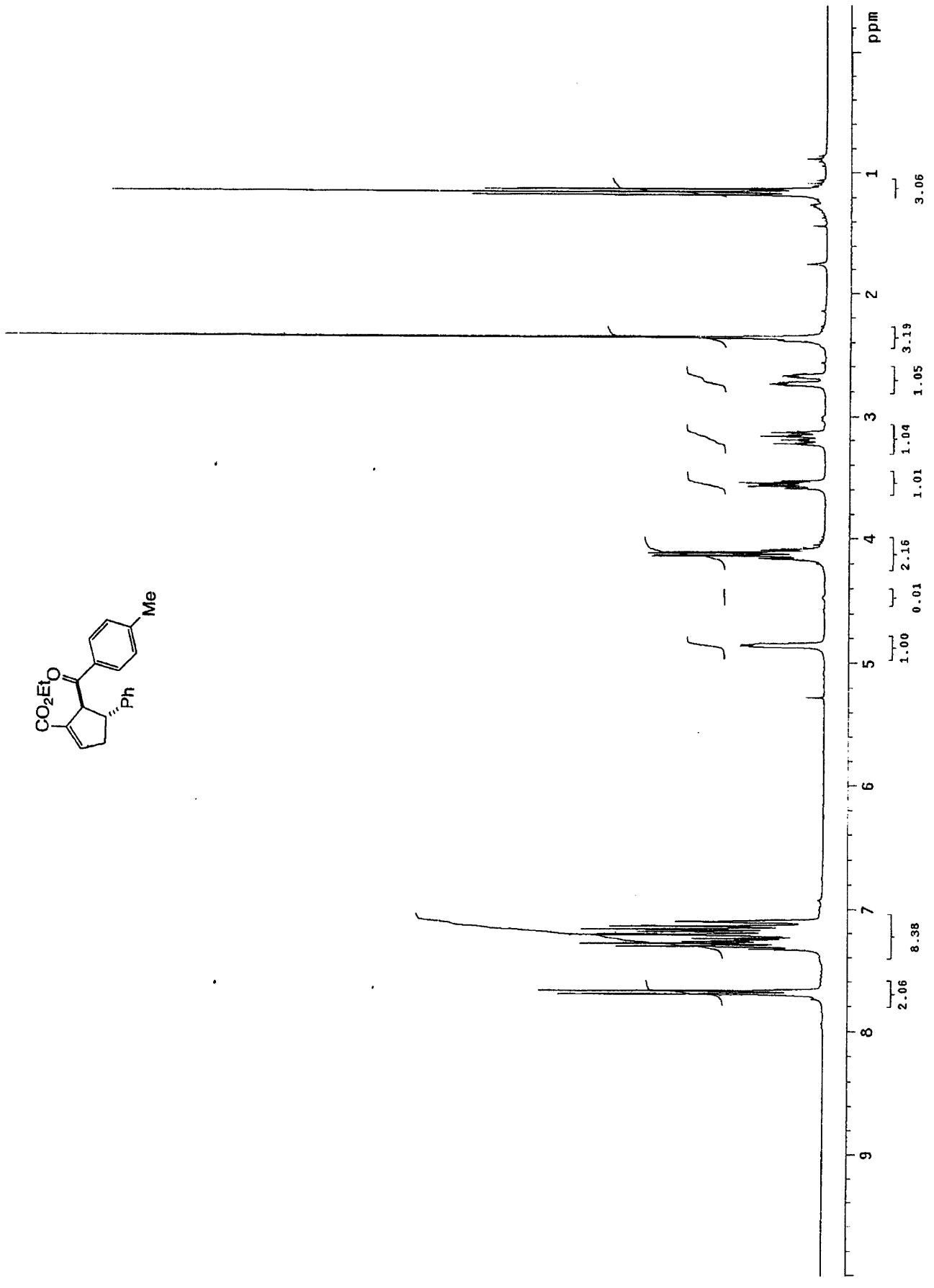
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CO2Et
Ph
ppm
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3
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5
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1.01
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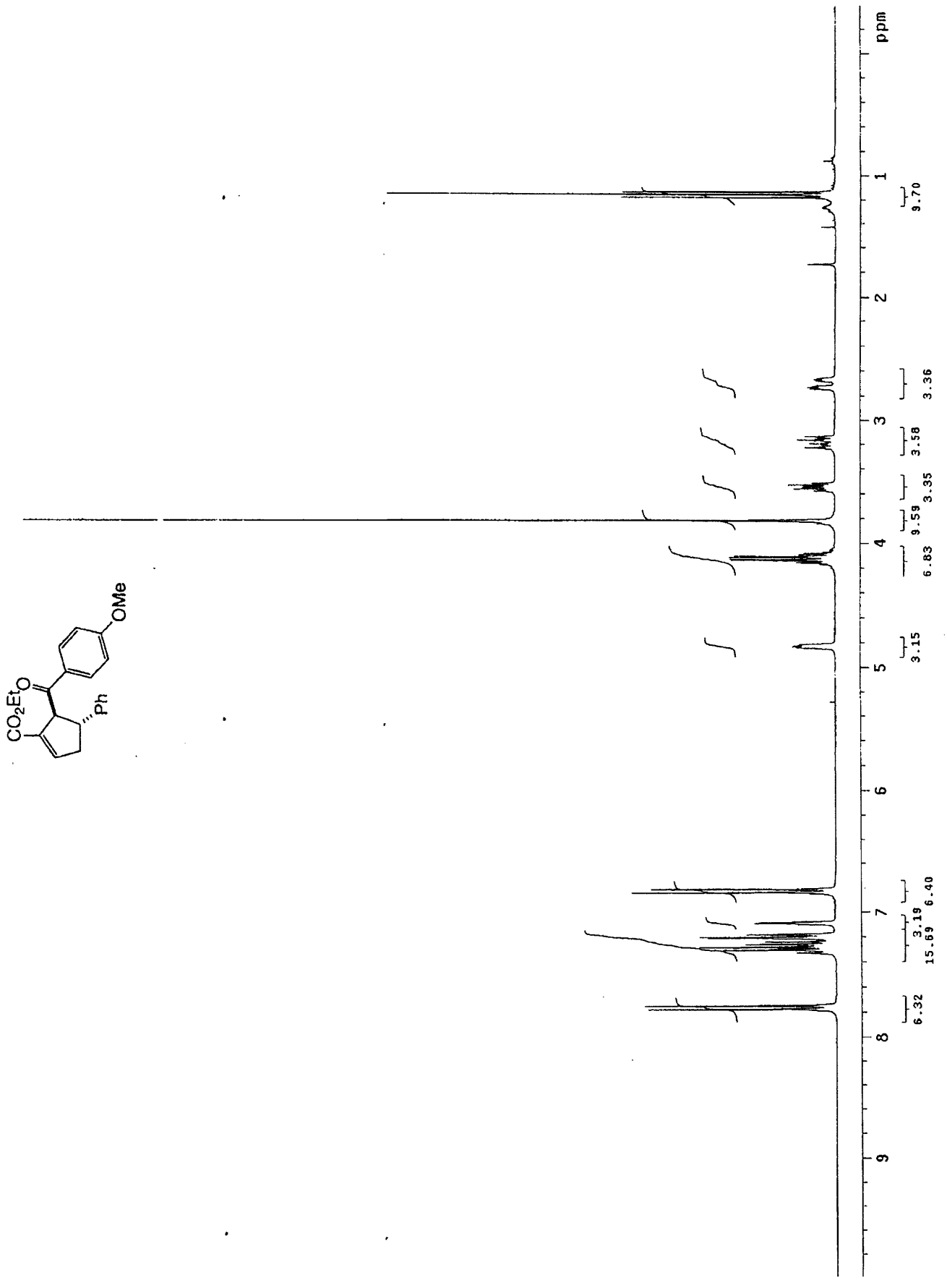
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Ph
CO2Et
O
ppm
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3
4
5
6
7
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3.15
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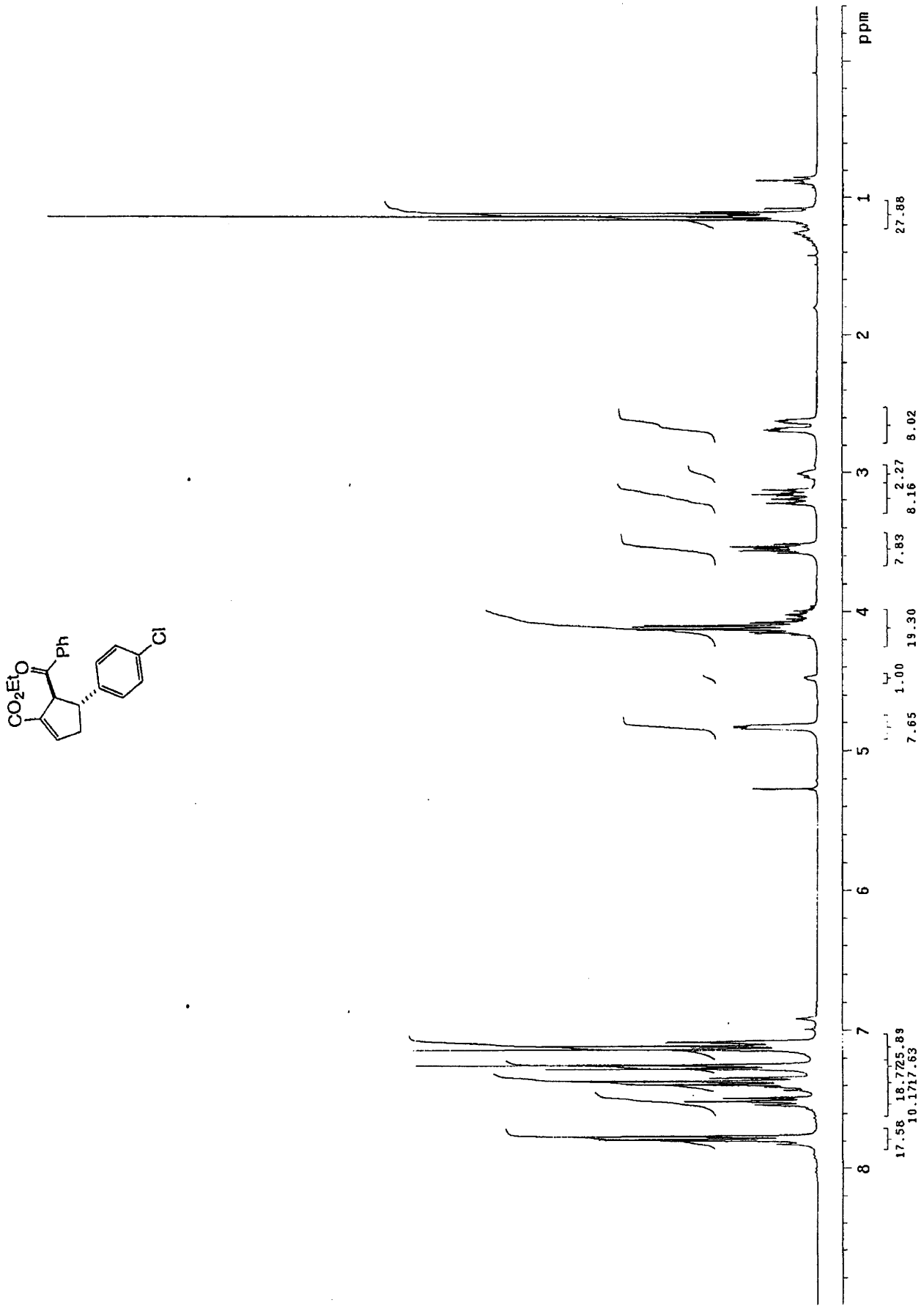
6.32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O
Ph
Cl
ppm
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3
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5
6
7
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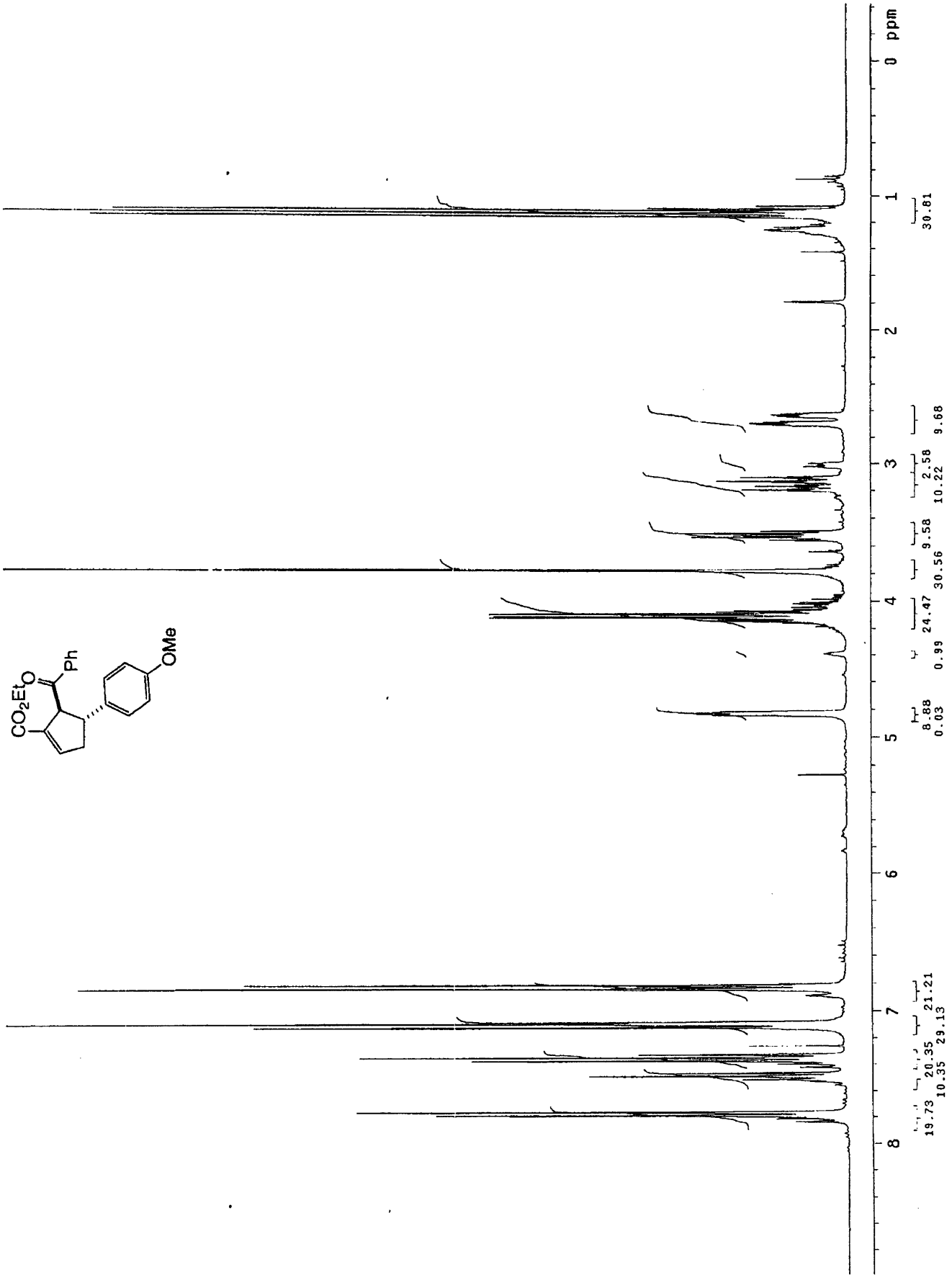
10.1717.63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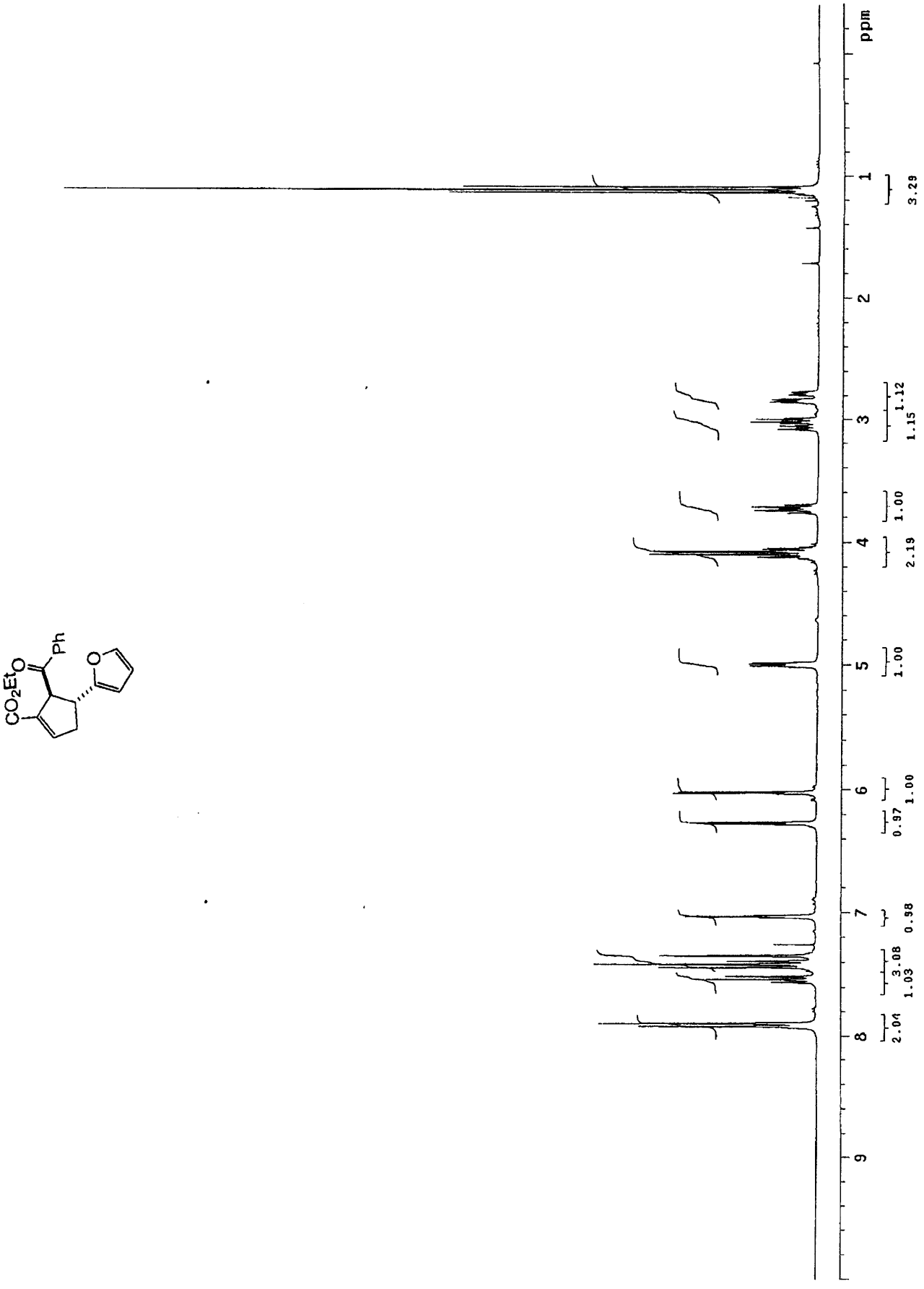
19.73
10.35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Ph
O
ppm
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6
7
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2.19
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1.00
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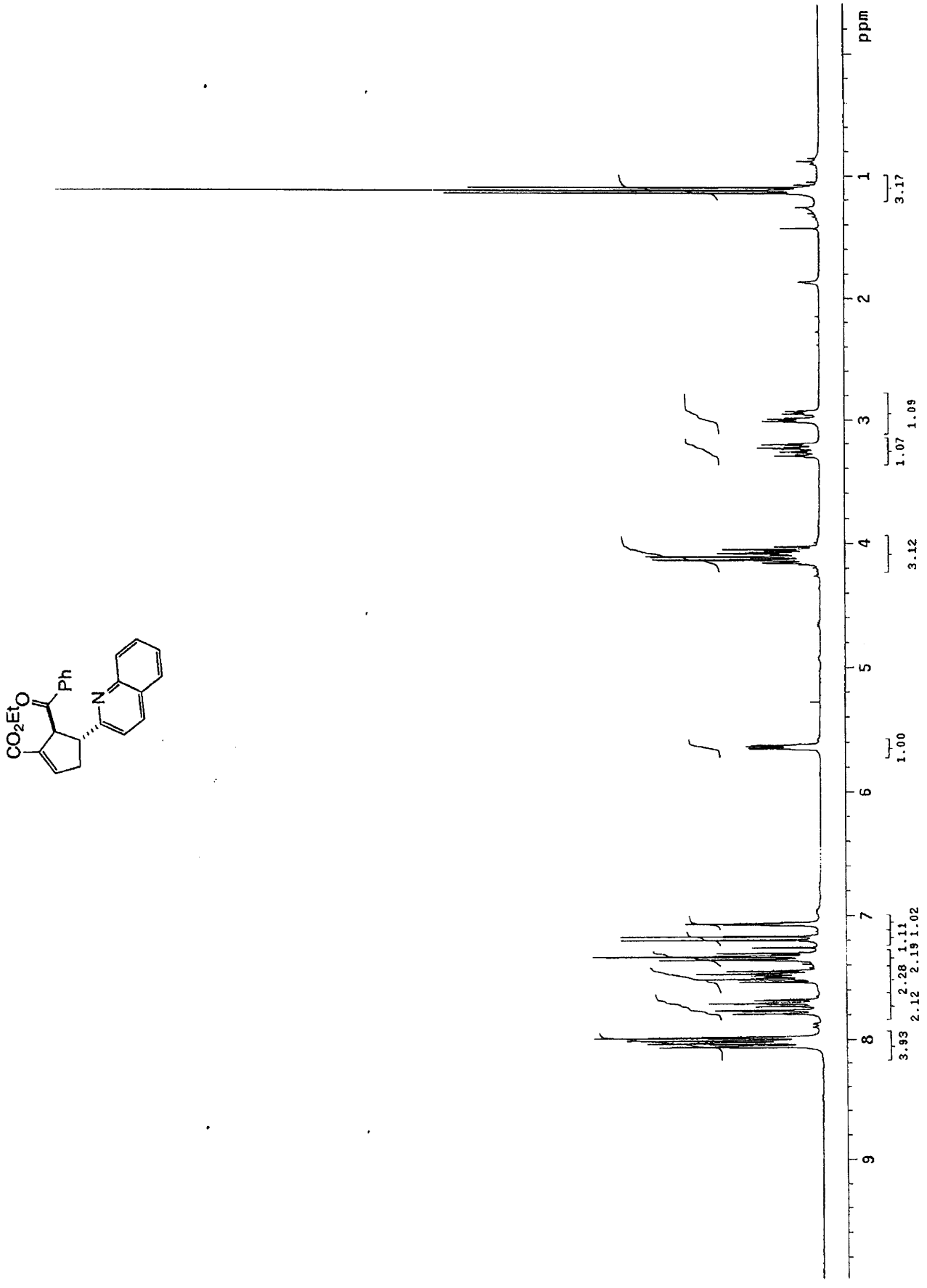
2.04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Ph
N
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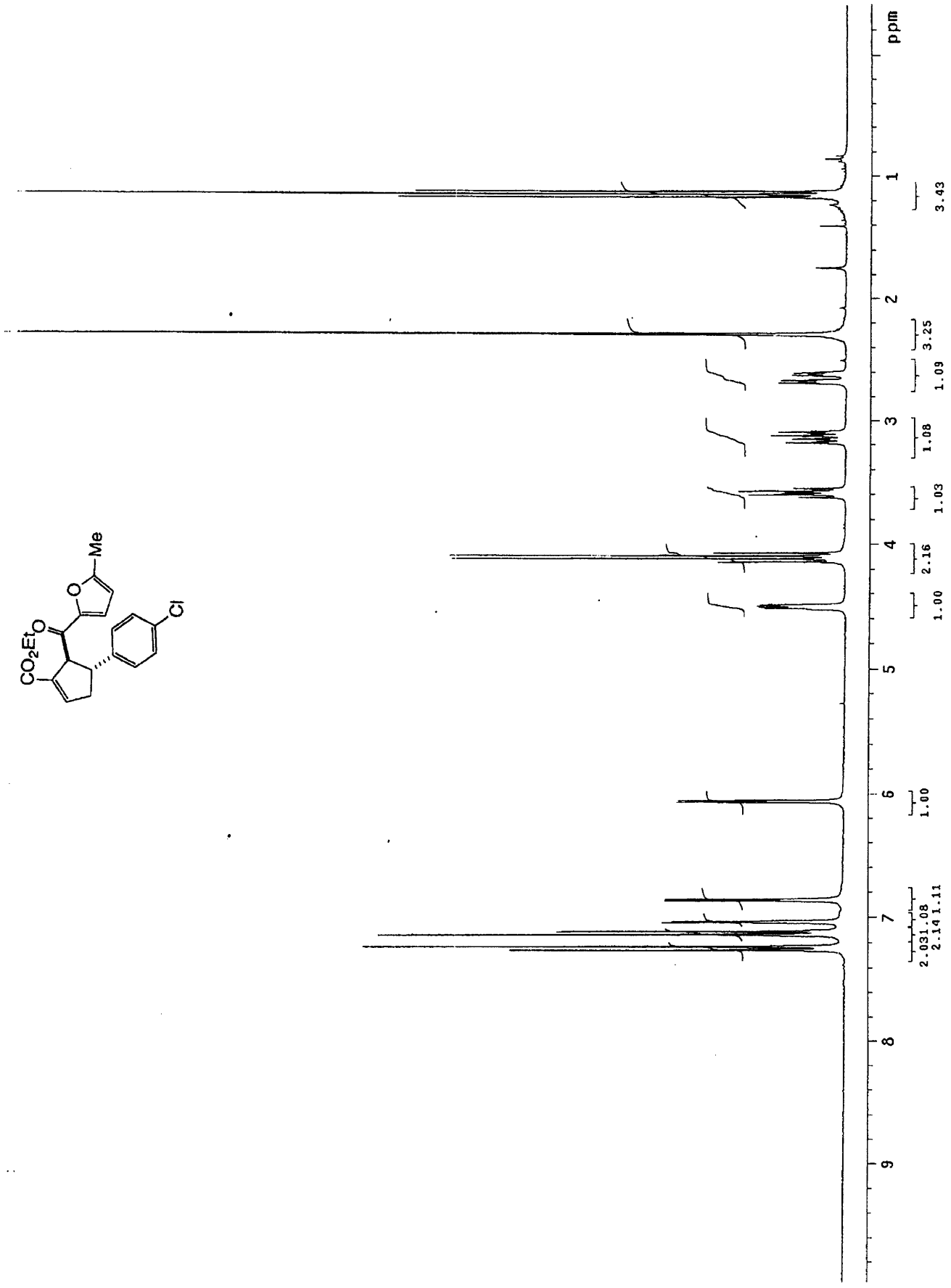
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O
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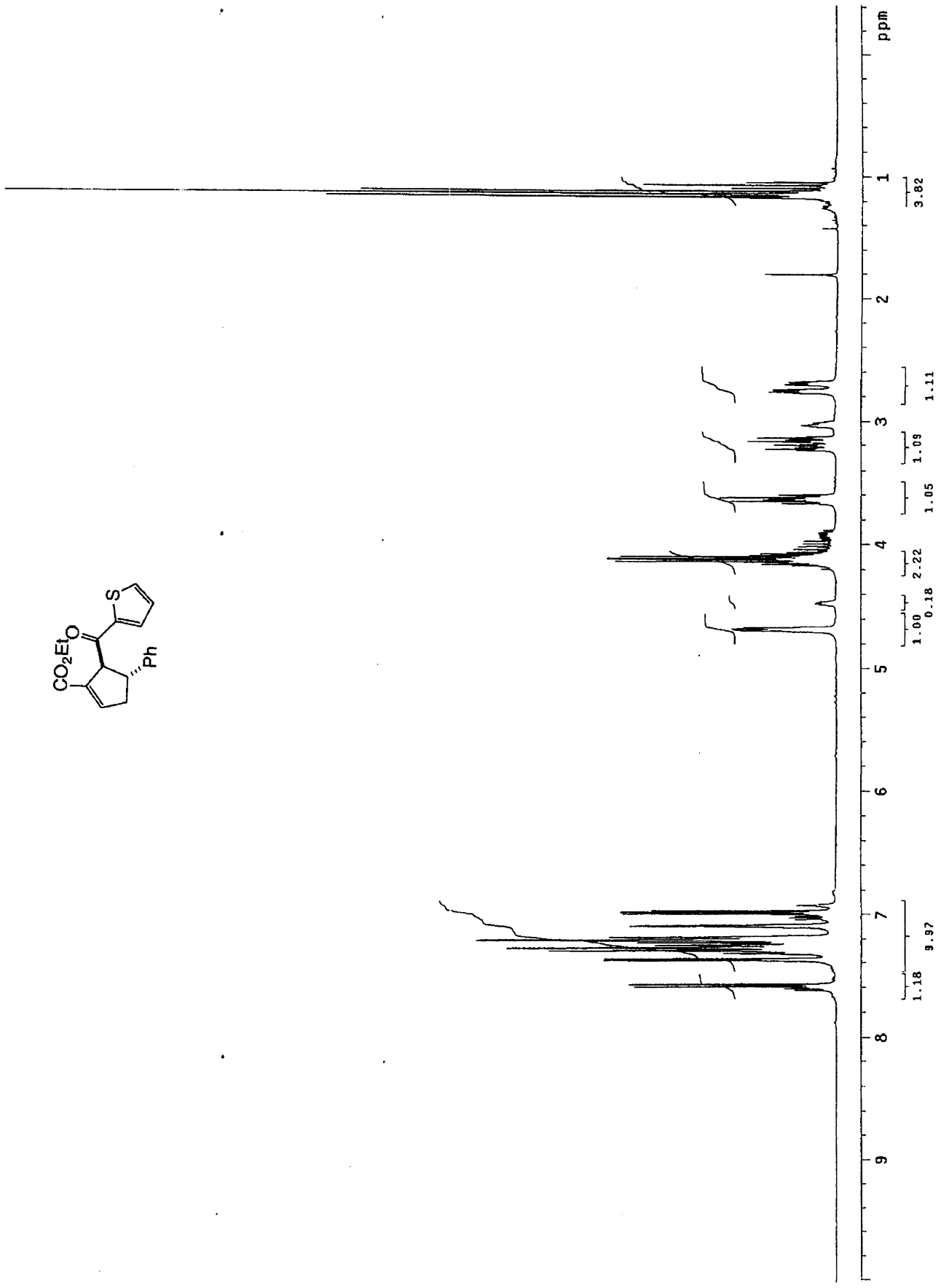
2.14
1.11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Ph
ppm
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3
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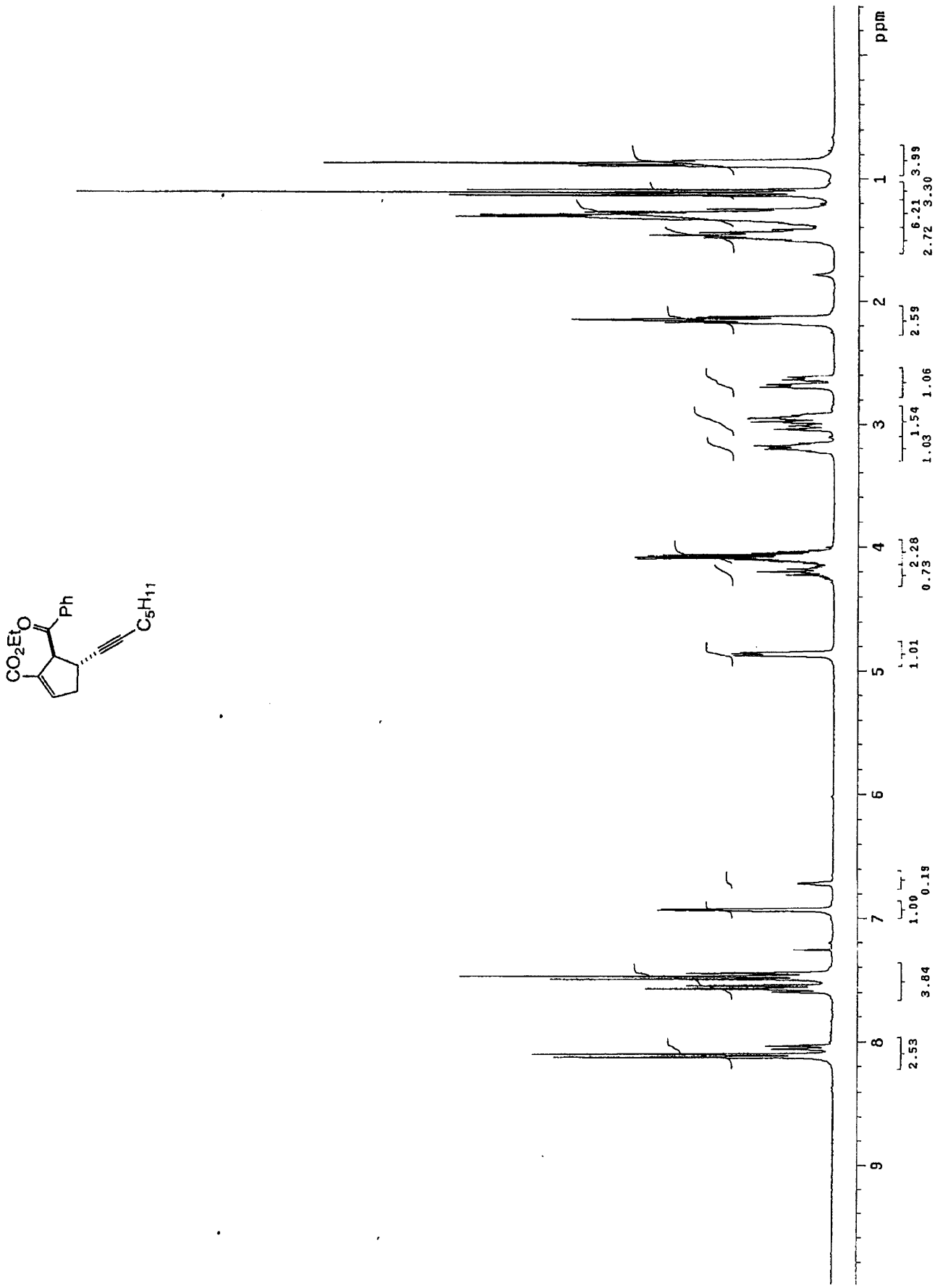
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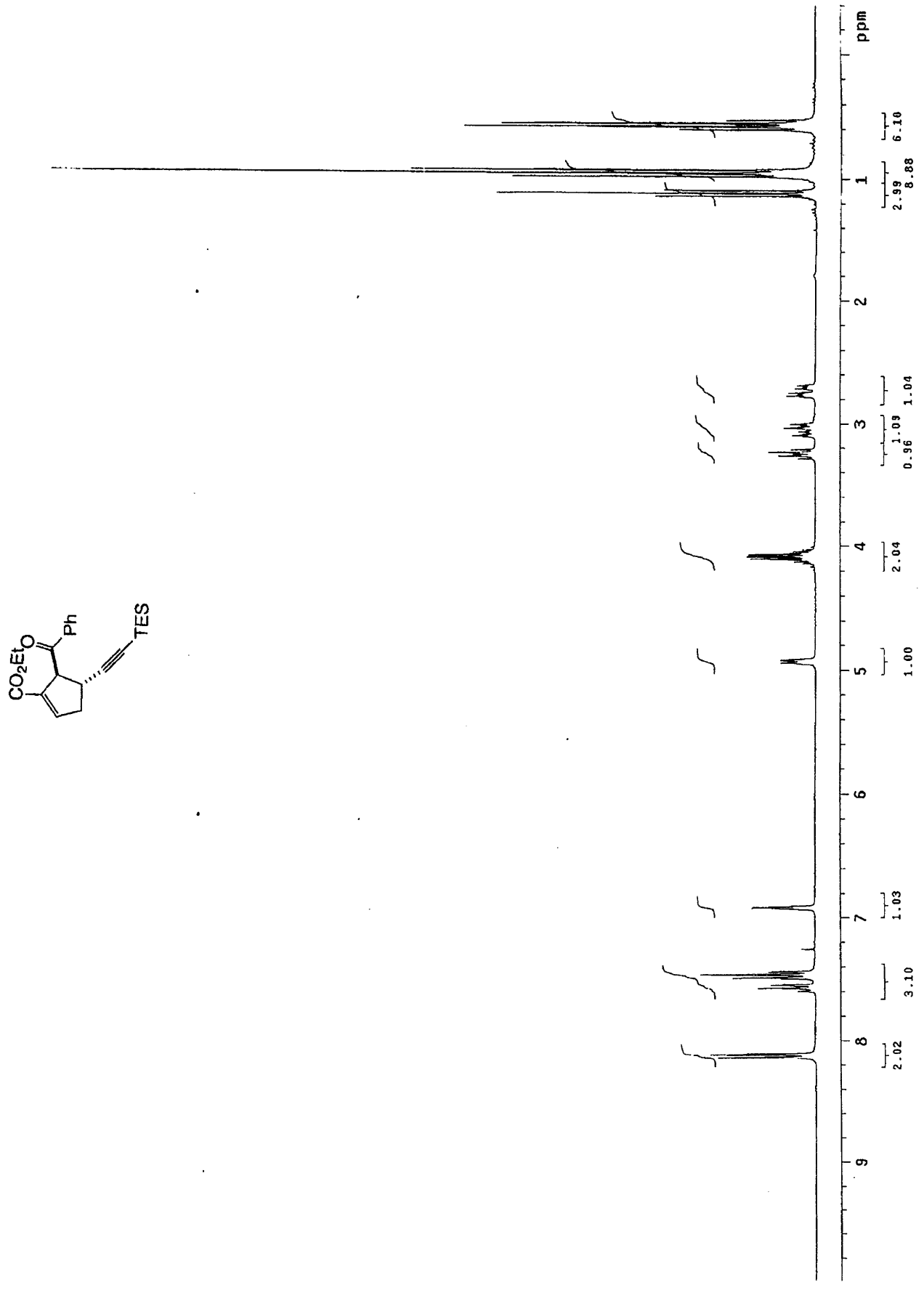
2.53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Ph
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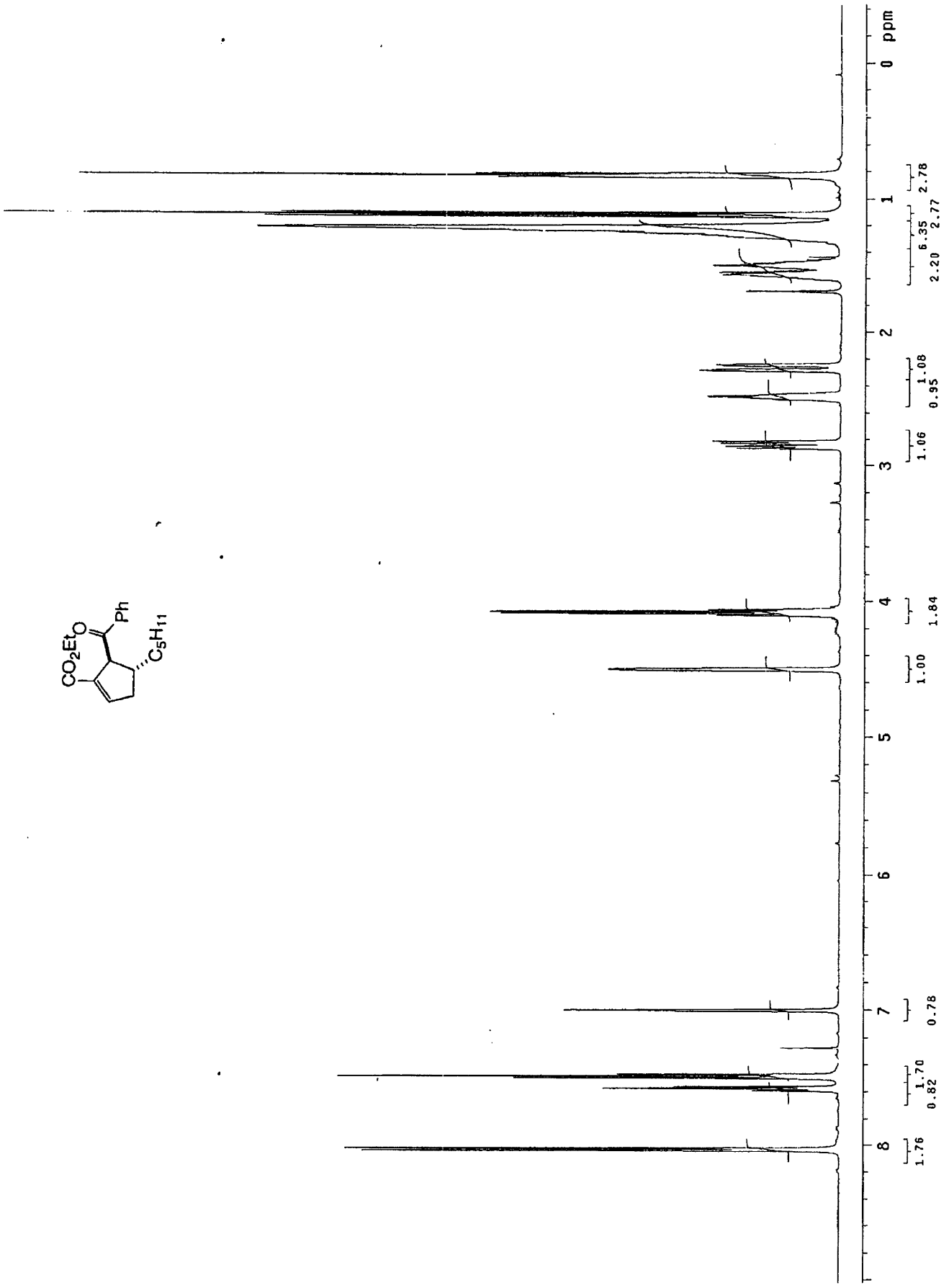
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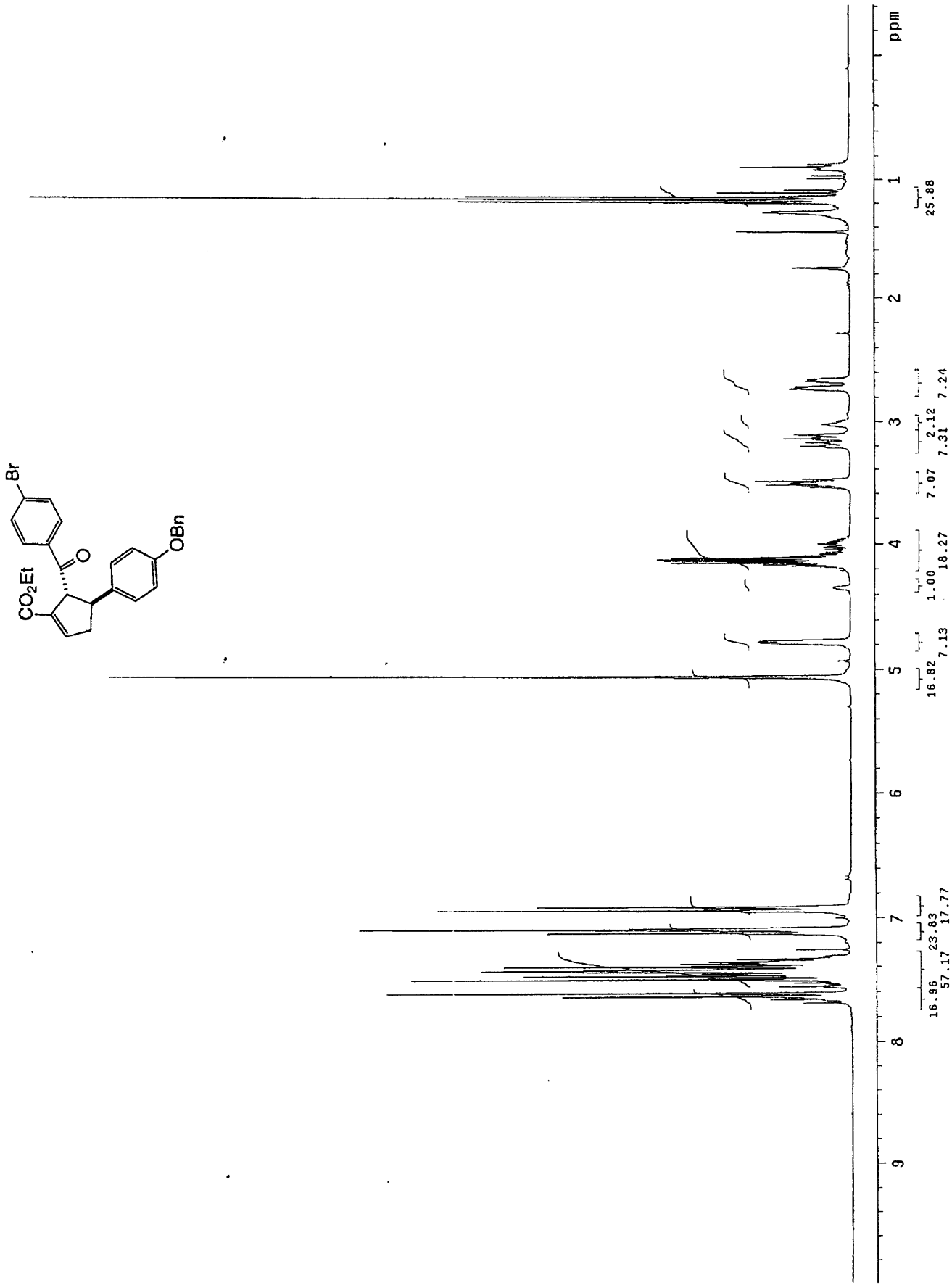
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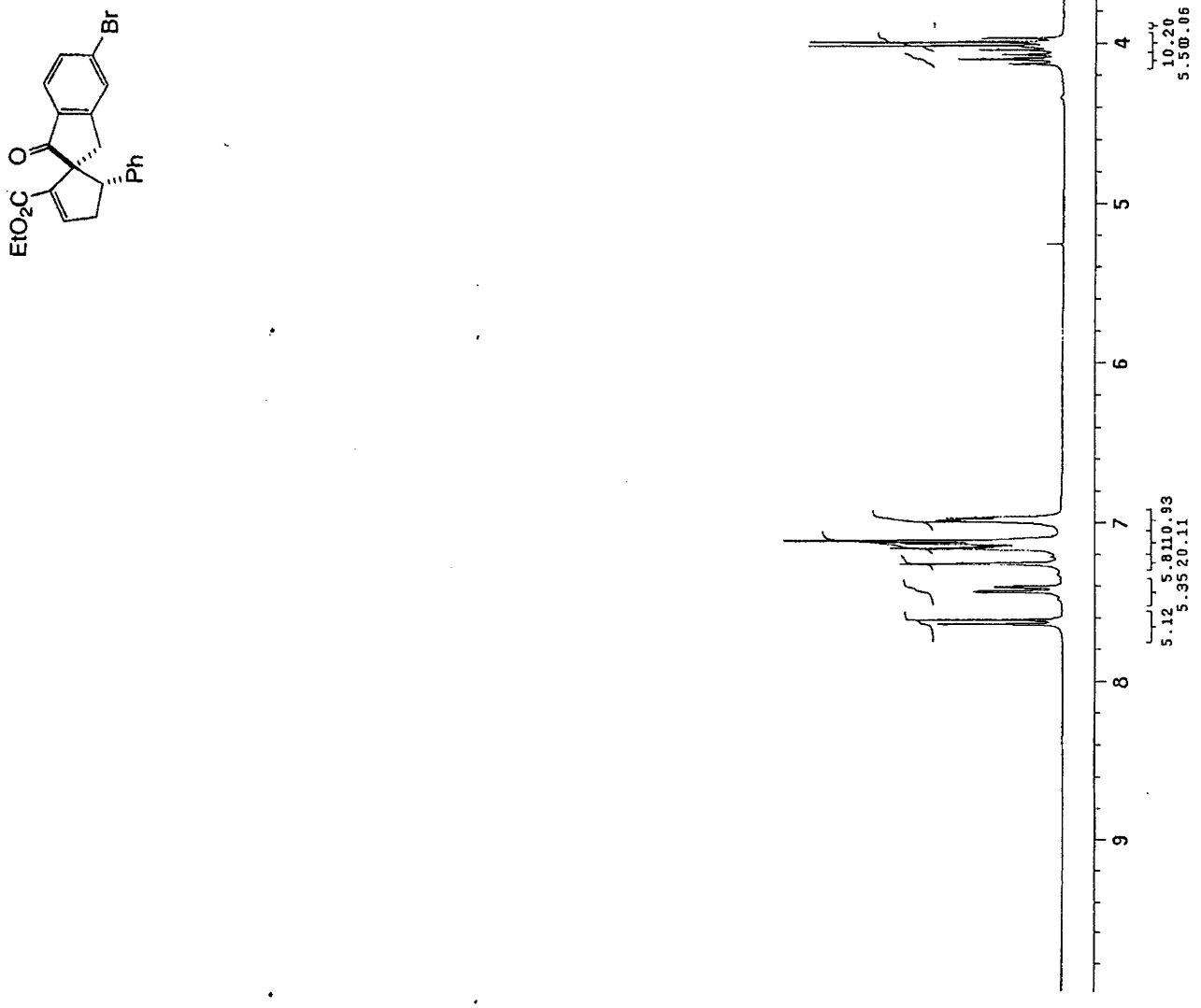
17.77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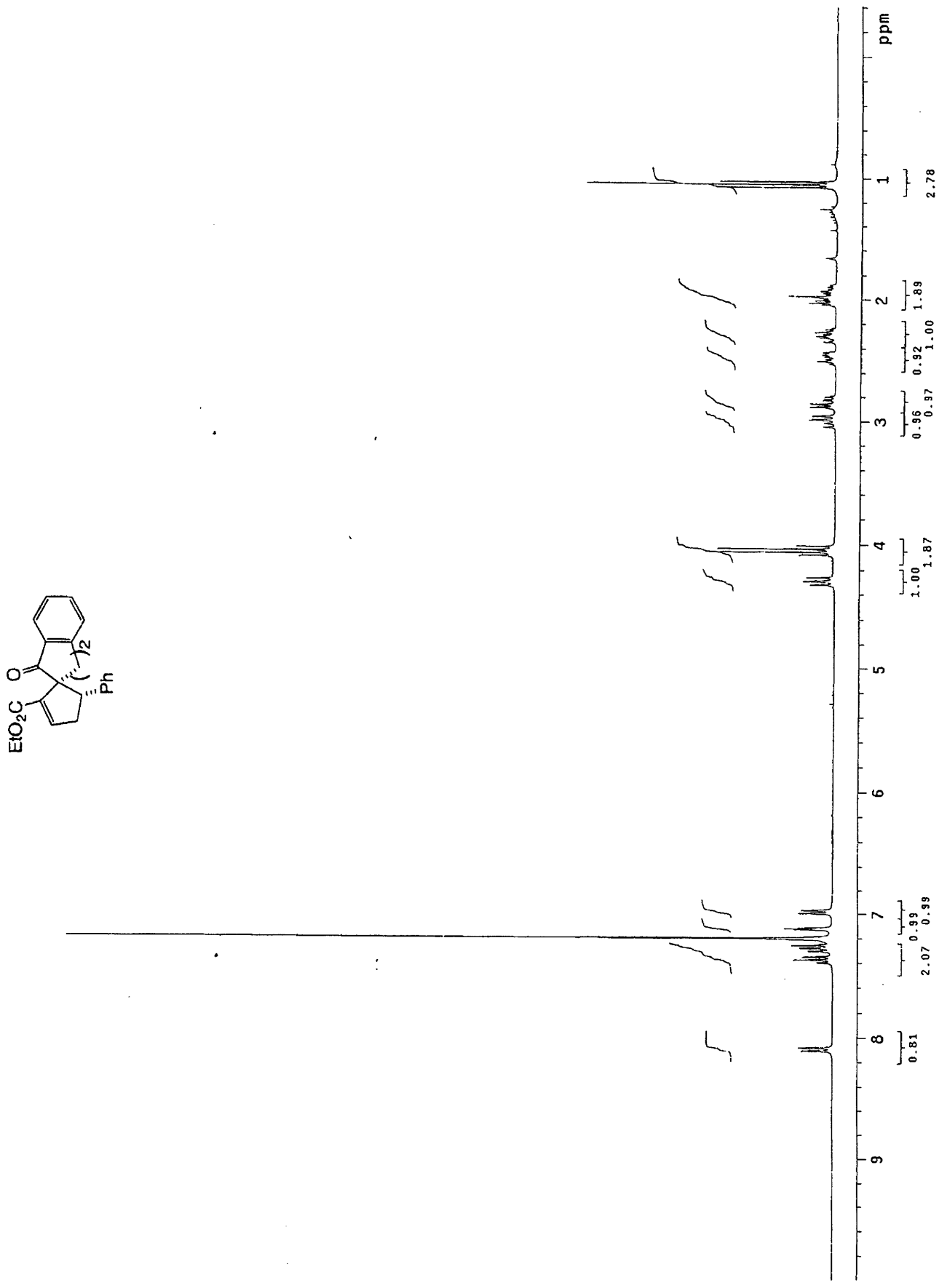
5.35
20.11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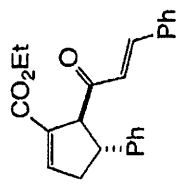
2.78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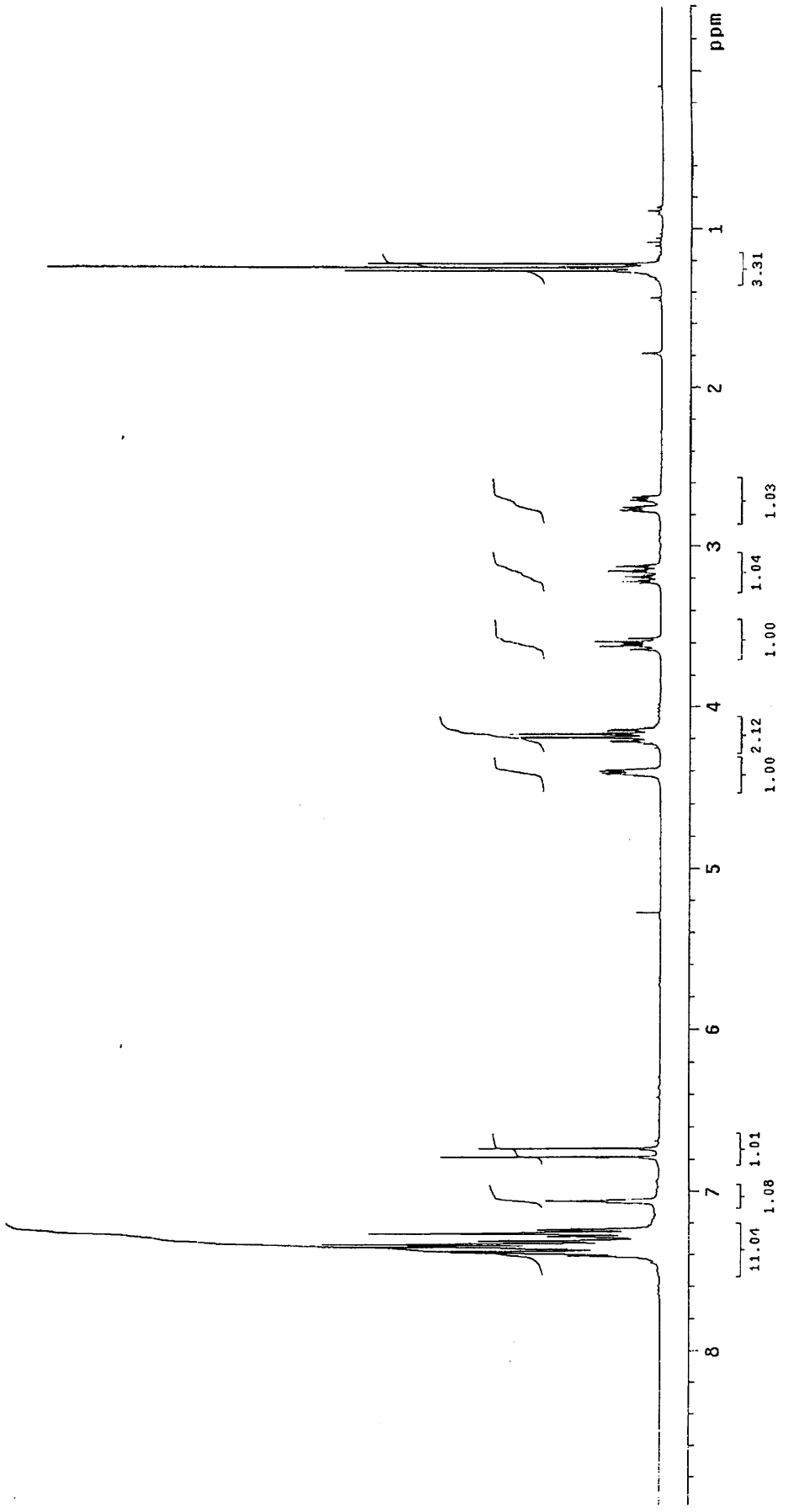
Ph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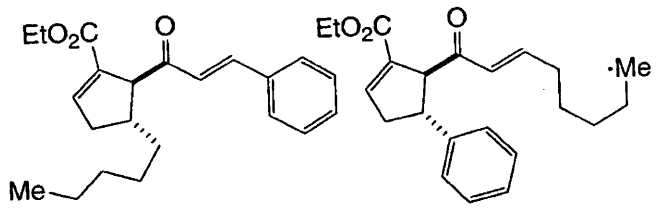
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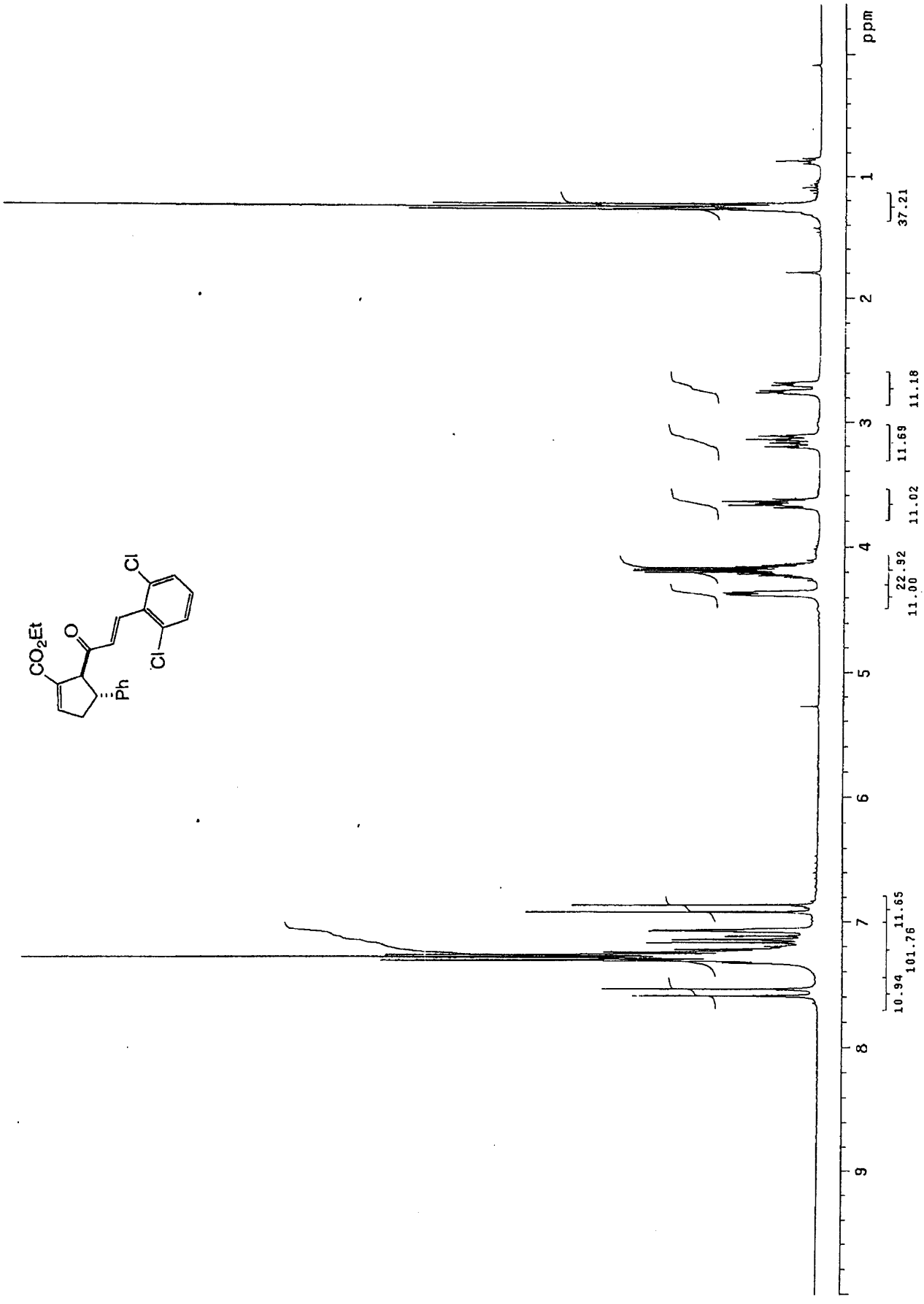
EtO2C
O
Me
Me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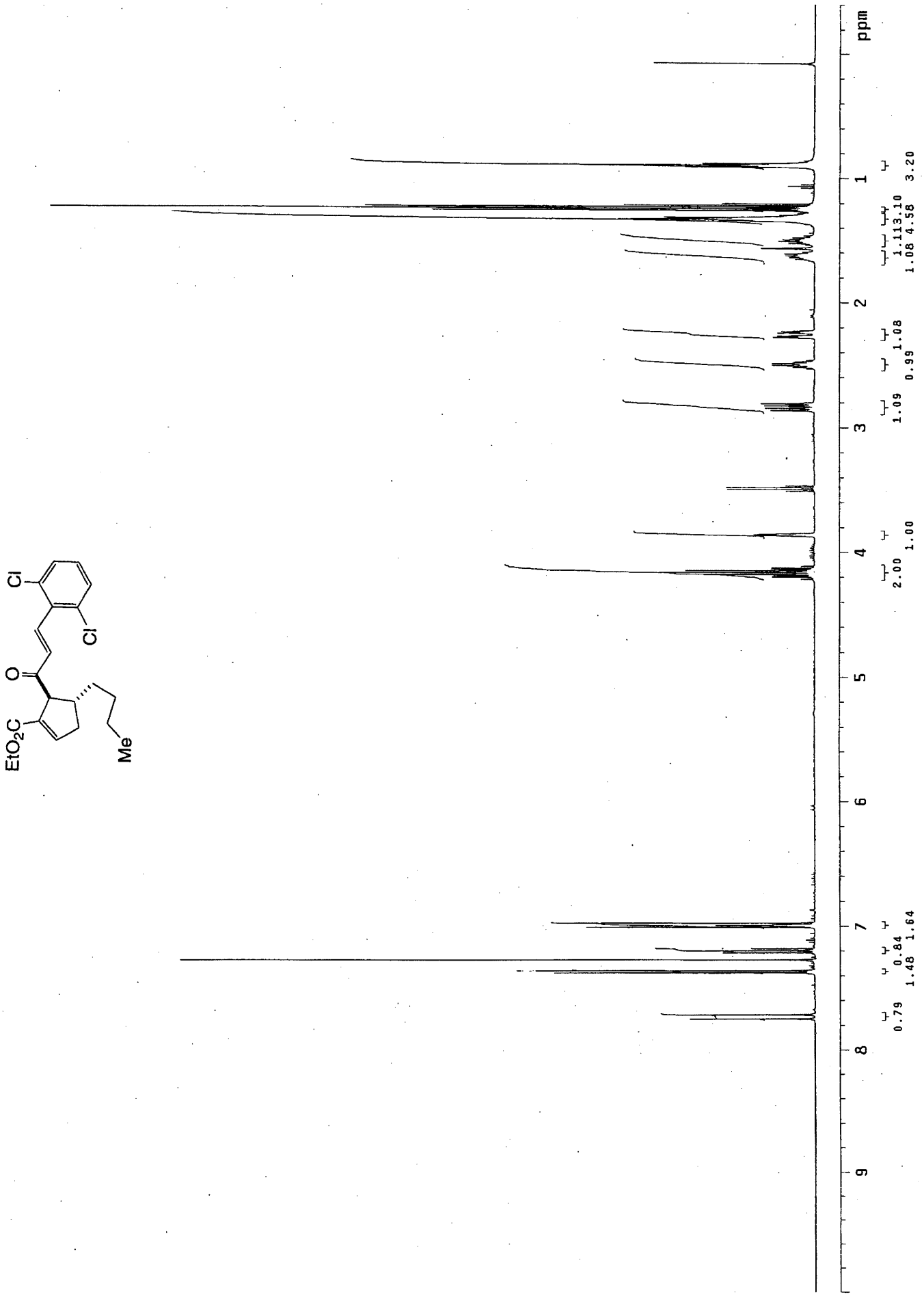
101.76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Cl
O
EtO2C
Me
ppm
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3
4
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6
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9
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1.00
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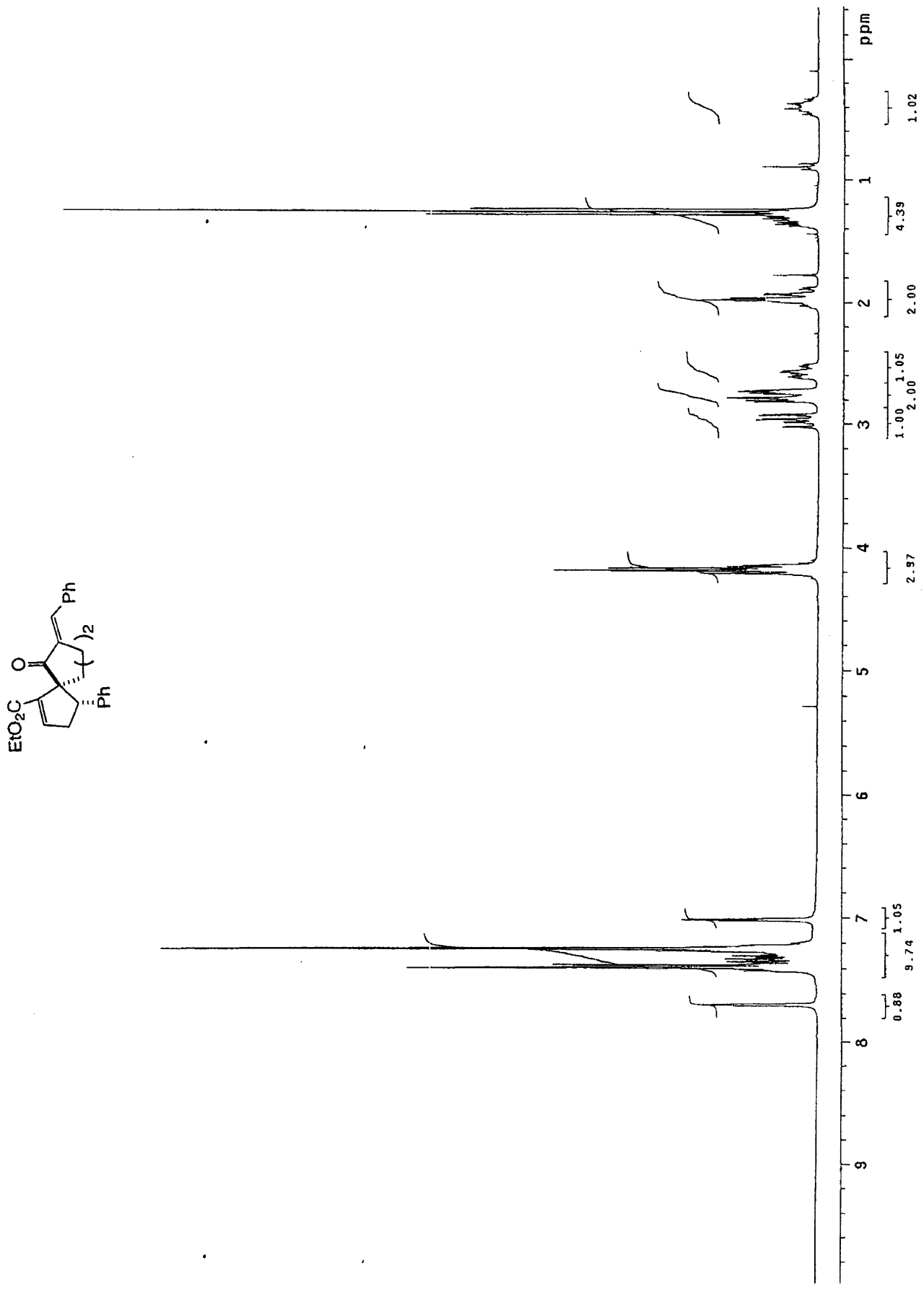
1.48 1.64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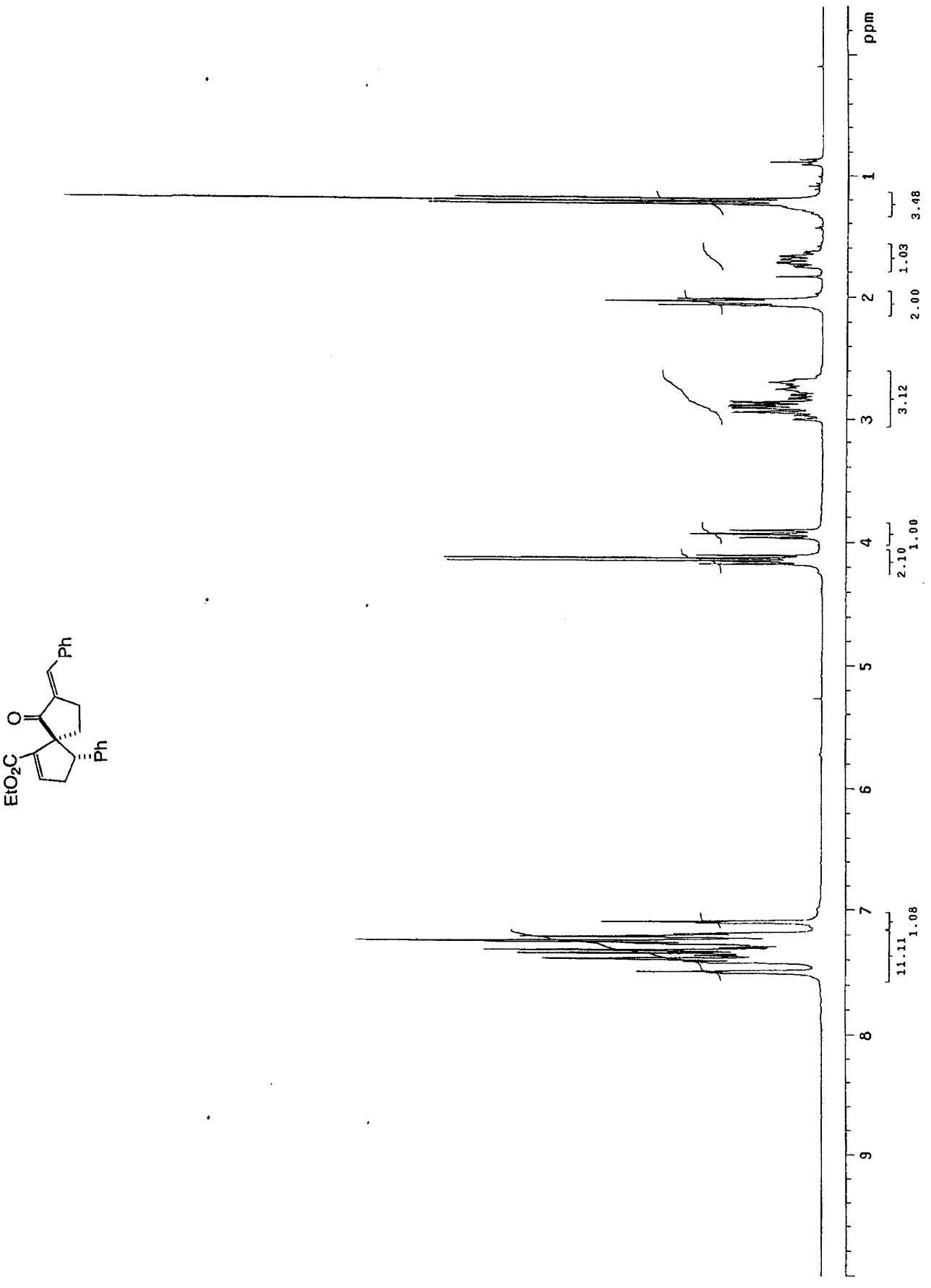
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EtO2C
Ph
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3.12
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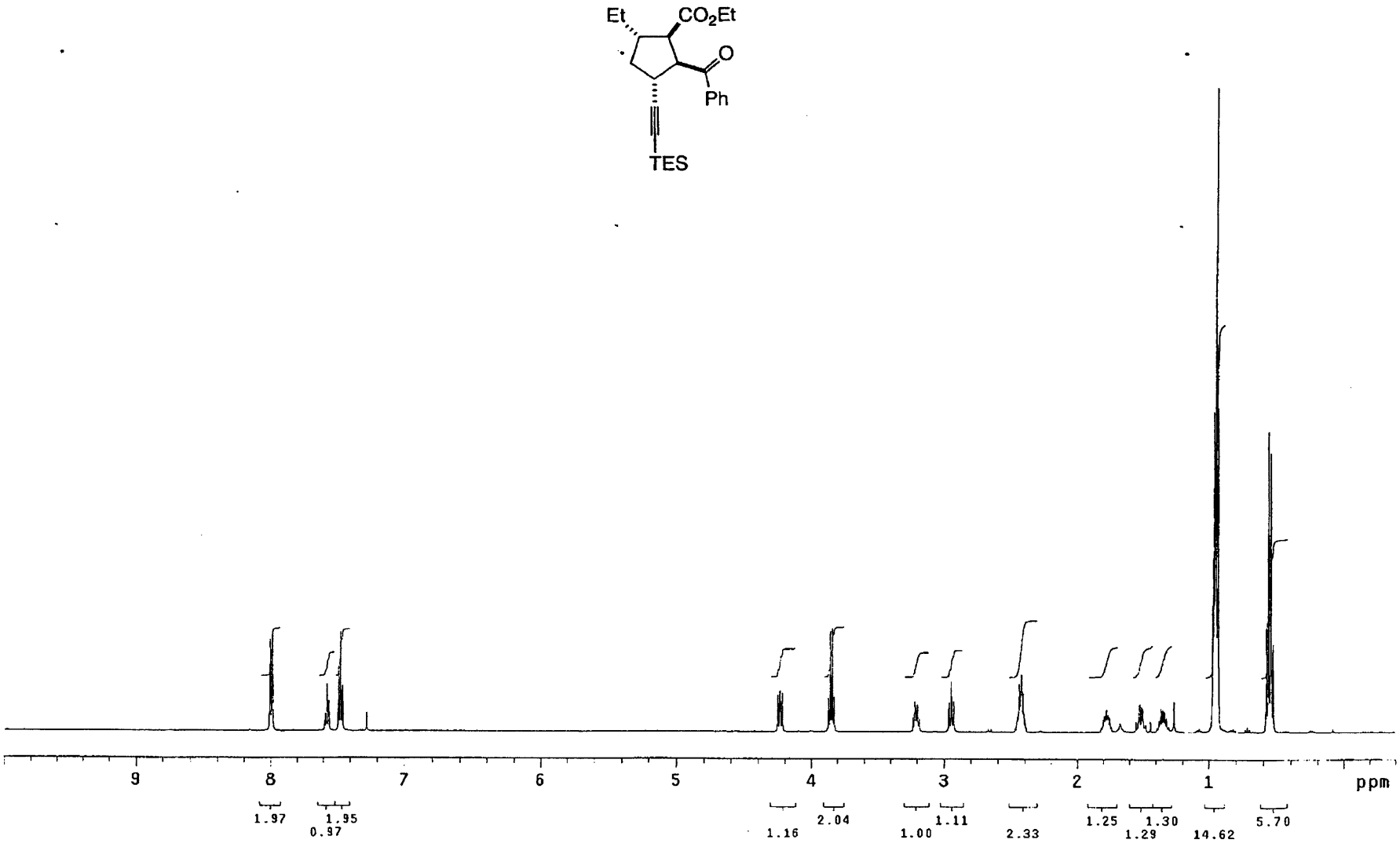
1.08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O
Ph
TES
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7
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5
4
3
2
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ppm
1.97
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1.25
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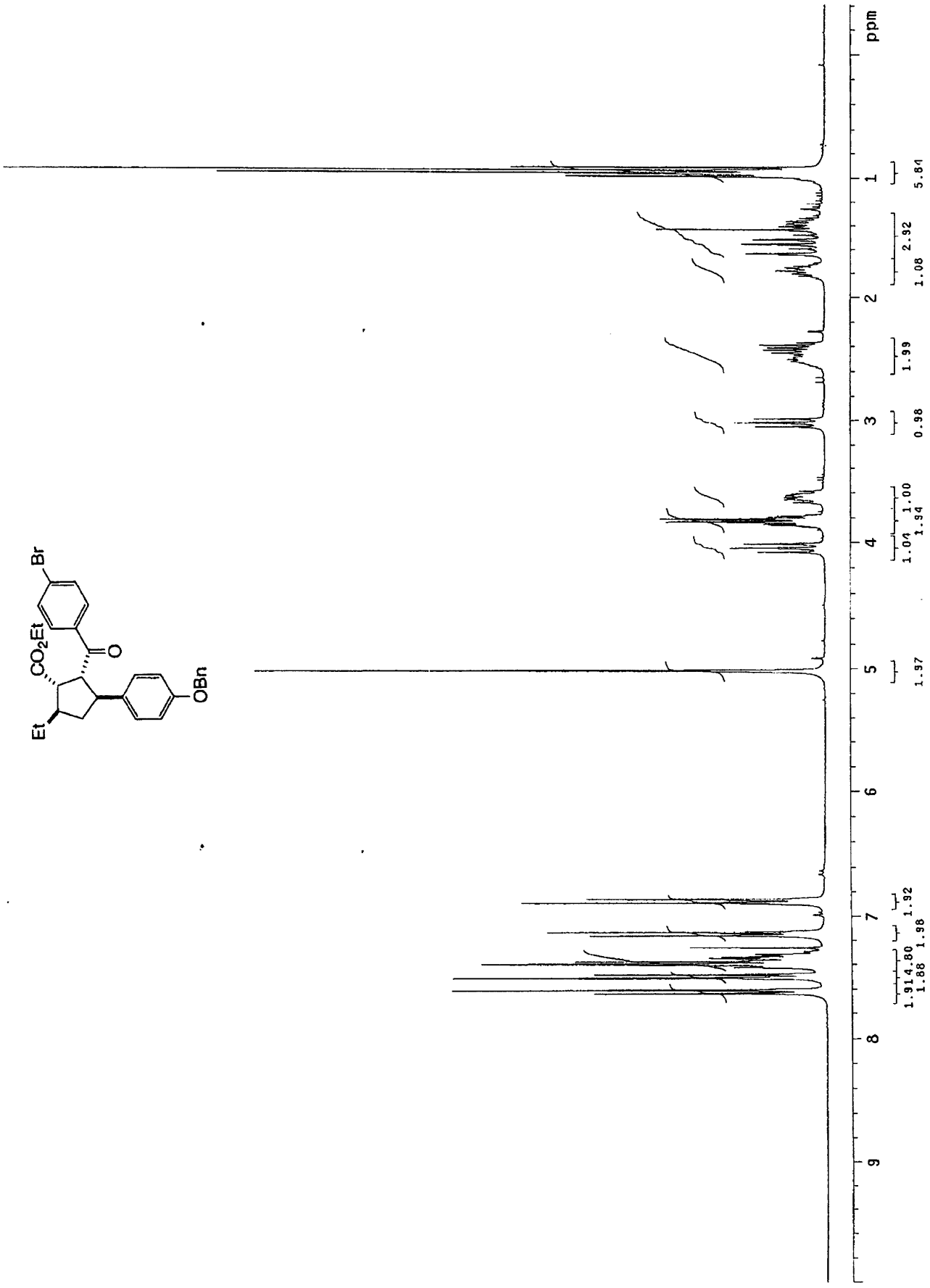
1.29
14.62
5.70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CO2Et
O
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OBn
ppm
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9
5.84
2.92
1.08
1.99
0.98
1.00
1.04
1.94
1.97
1.92
1.98
4.80
1.91
1.88

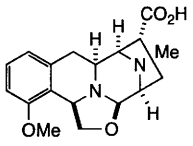
Section 2.2

Synthesis of Pyrrolines via Phosphine-Catalyzed Asymmetric [3+2] Cycloadditions of Allenes with Imines

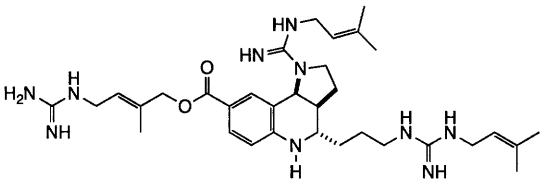
A. Introduction

Pyrrolidines, compounds readily accessed from pyrrolines, are a common subunit in a number of pharmaceuticals and natural products with important biological activity (Scheme 2.2.1).[1, 2, 3] Proline, a pyrrolidine-based amino acid, and its derivatives play a crucial role in the folding of peptides and peptide-mimics.[4] Furthermore, a number of useful organocatalytic processes that make use of pyrrolidine-based catalysts have been developed.[5] Considering the broad utility of pyrrolidine derivatives, the development of methods for the asymmetric synthesis of this class of heterocycles is an important objective.

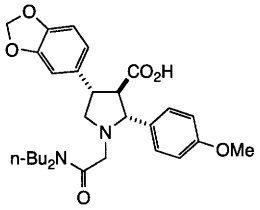
Scheme 2.2.1. Structures of Pyrrolidines with Interesting Biological Activity.



(-)-Quinocarcin

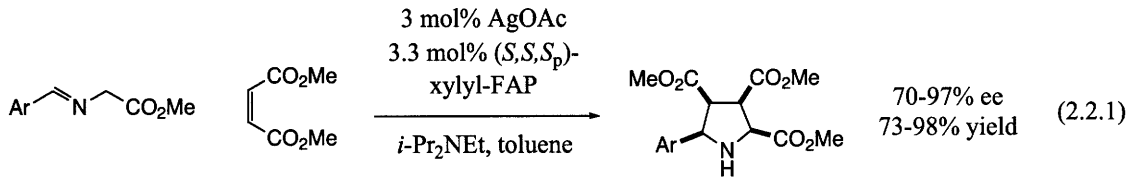


Martinelline
Vine extracts traditionally used to treat conjunctivitis.

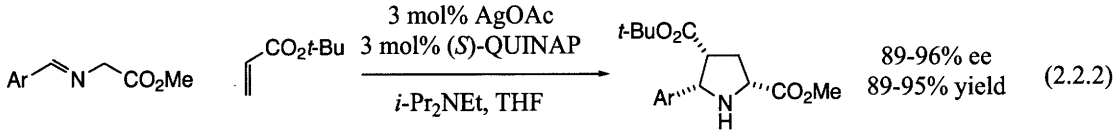


Atrasentan (Xinlay)
In Phase III clinical trials for the treatment of prostate cancer.

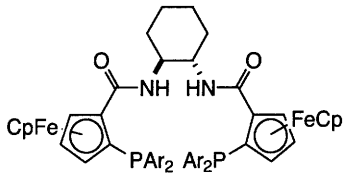
Popular approaches to enantioselective pyrrolidine synthesis include [3+2] cycloadditions of azomethine ylids with olefins, olefin-hydroamination, and reduction of cyclic imines.[6] Both Zhang and Schreiber have developed Ag(I)-catalyzed asymmetric [3+2] cycloadditions (eq 2.2.1 and eq 2.2.2).[7]



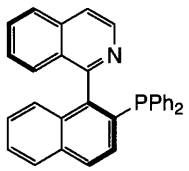
(2.2.1)



(2.2.2)

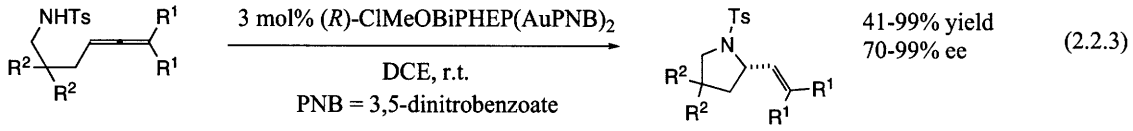


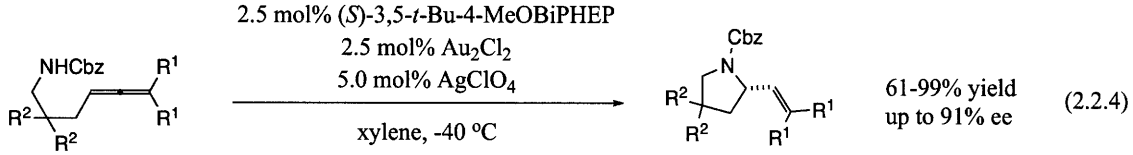
(*S*, *S*, S_p)-xylyl-FAP
Ar = 3,5-diMe-C_6H_3

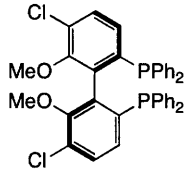


(*S*)-QUINAP

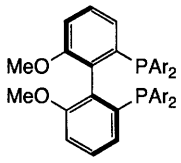
More recently, Toste and Widenhoefer have devised enantioselective intramolecular allene hydroamination reations that are based on Au(I)-alkyne activation (eq 2.2.3 and eq 2.2.4).[8] This methodology is applicable to both the synthesis of pyrrolidines and piperidines.







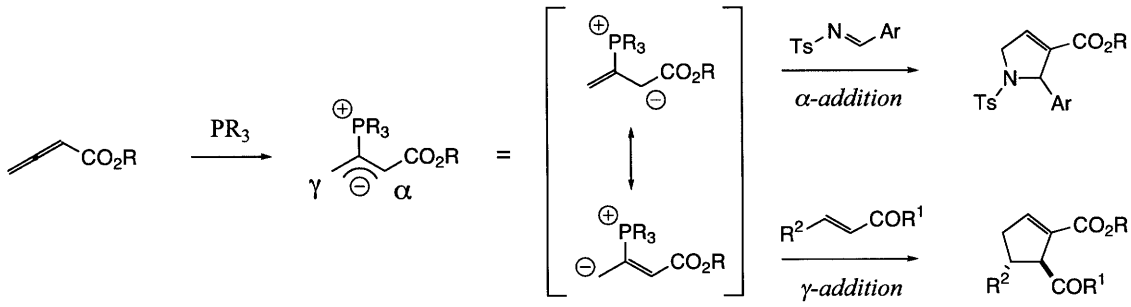
(*R*)-ClMeOBiPHEP



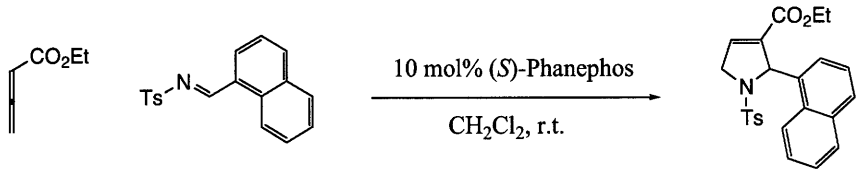
(*S*)-3,5-t-Bu-4-MeOBiPHEP
Ar = 3,5-t-Bu-C_6H_3

In 1997, Lu and coworkers reported a phosphine-catalyzed [3+2] cycloaddition of allenes and imines that provides access to a wide variety of 2,3-disubstituted pyrrolines (see eq 2.1.6).[9] In 2005, Kwon reported an extension of this work that describes the synthesis of 2,3,5-trisubstituted pyrrolines.[10] The mechanism of the cycloaddition is believed be similar to that of the phosphine-catalyzed [3+2] cycloaddition of allenoates with acrylates. However, the phosphonium zwitterion reacts with the imine to form a bond with the α-carbon initially, whereas reactions with β-substituted olefins proceed by attack from the γ-carbon (Figure 2.2.1).[11]

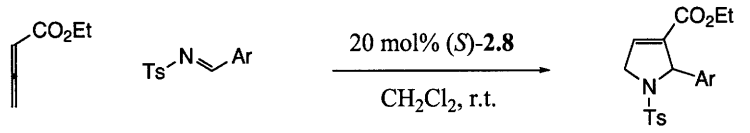
Scheme 2.2.2. Divergent Regiochemical Pathways for Phosphine-Catalyzed [3+2] Cycloadditions.



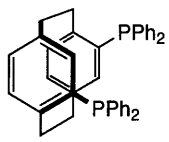
Recently, Marinetti and Gladysz have disclosed their efforts towards the development of catalytic asymmetric variants of this process (eq 2.2.4 and eq 2.2.6).[12,13] However, these methods are not general and do not provide pyrrolines with synthetically useful levels of enantiomeric excess.



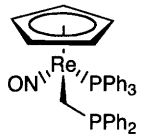
64% ee
32% yield (2.2.5)



52-60% ee
90-93% yield (2.2.6)



(*S*)-Phanephos



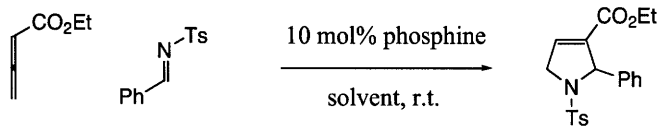
(*S*)-**2.8**

Considering our earlier success in the application of catalyst **2.1** to both [3+2] and [4+2] cycloadditions of allenes,[14] we were optimistic that we could improve upon the systems reported by Marinetti and Gladysz.

B. Results and Discussion

We commenced our studies by examining derivatives of phosphepine **2.1**, because of its utility in related asymmetric phosphine-catalyzed cycloadditions. Again, the *t*-butyl phosphepine **2.1** proved to be optimal. Routine reaction optimization led us to find that the cycloadditions occur with the highest levels of enantioselectivity in CH_2Cl_2.[15] Adjustment of other parameters, such as temperature, concentration, and additives, were found to have no positive impact on the enantioselectivity.[16]

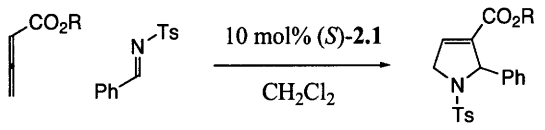
Table 2.2.1. Survey of Phosphines for the Enantioselective [3+2] Cycloaddition of Allenoates and Imines.

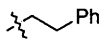
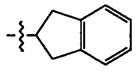
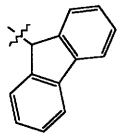
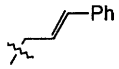
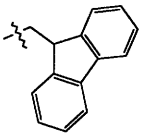
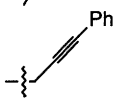
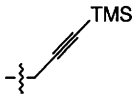
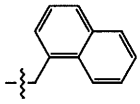
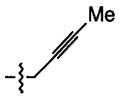
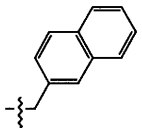


entry	phosphine	solvent	yield (%)	ee(%)
1	(*R*)-**2.1**	toluene	80	55
2	(*R*)-**2.3**	toluene	79	9
3	(*R*)-**2.1**	CH_2Cl_2	80	69
4	(*R*)-**2.6**	CH_2Cl_2	69	9
5	(*R*)-**2.4**	CH_2Cl_2	65	33

We then turned our attention to the modification of the allenoate ester. A secondary alkyl ester provided little improvement (Table 2.2.2, entry 2) and a *t*-butyl ester resulted in a substantial decrease in selectivity (Table 2.2.2, entry 3). Although we obtained encouraging initial results with benzylic (Table 2.2.2, entries 5, 7, 16, and 17), allylic (Table 2.2.2, entries 4 and 8), and propargylic esters (Table 2.2.2, entries 9, 10, and 11), the enantioselectivity of the process remained modest. Other derivatives that were explored included homobenzylic (Table 2.2.2, entries 12 and 13), fluorenyl (Table 2.2.2, entry 14), and methylenefluorenyl (Table 2.2.2, entry 15). Although, this final example provided pyrrolines with exceptional enantiomeric excess, the ester substituent underwent elimination when trialkylphosphines (e.g. **2.1**) were employed resulting in catalyst deactivation by phosphine protonation.

Table 2.2.2. Allene Optimization in the Enantioselective [3+2] Cycloaddition of Allenoates and Imines.

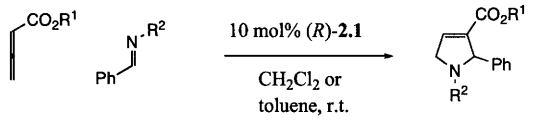


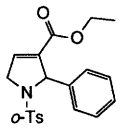
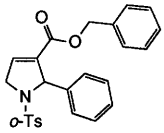
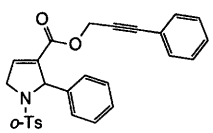
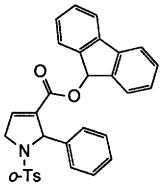
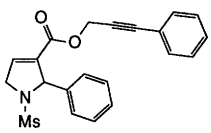
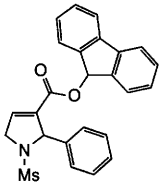
entry	R	yield (%)[a]	ee (%)	entry	R	yield (%)[a]	ee (%)
1	Et	75	69	12		99	70
2	Cy	87	>70				
3	*t*-Bu	86	32	13		85	70
4	allyl	66	76				
5	Bn	81	75				
6	Ph	32	51	14		85	82
7	$CHPh_2$	89	79				
8		84	75	15		8	88
9		89	81				
10		87	83	16		80	76
11		89	73	17		91	79

[a] Isolated yield.

The effect of the imine protecting group was also investigated. In the hope that we would uncover a pair of substrates that would interact cooperatively to provide increased levels of enantioselectivity, we investigated *o*-tosyl- and methanesulfonyl-protected imines with a selection of our most promising allenes from Table 2.2.2. *o*-Tosyl-protected imines when paired with a variety of allenes lead to decreased yields while leaving the ee unaffected (Table 2.2.3, Entries 1-4). Methanesulfonyl-protected imines provide no advantage over the *p*-tosyl-protecting group with a variety of allenes (Table 2.2.3, Entries 5 and 6).

Table 2.2.3. Imine Optimization in Enantioselective [3+2] Cycloaddition of Allenoates and Imines.



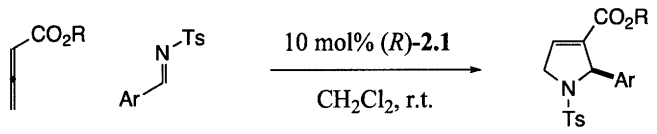
					
Entry 1, 68% ee 68% yield	Entry 2, 70% ee, 62% yield	Entry 3, 76% ee, 39% yield	Entry 4, 81% ee, 40% yield	Entry 5, 66% ee, 88% yield	Entry 6, 82% ee, 98% yield

o-Ts = *o*-$CH_3C_6H_4SO_2$-; Ms = CH_3SO_2-

We then investigated a selection of *p*-tosyl-imines with one of our more promisting allene substrates to probe the electronic effects of the imine substituent. Both electron-rich and electron-deficient imines are suitable reaction partners. However, the enantioselectivity decreases for both electron-poor imines and imines containing an ortho substituent.[17] Heterocyclic imines react to provide pyrrolines in good yield and modest selectivity.

We have also surveyed a number of aliphatic imines, but the yields and enantioselectivity for cycloadditions with these imines is significantly worse than cycloadditions of aromatic imines.

Table 2.2.4. Examples of Enantioselective [3+2] Cycloadditions of Allenes and Imines.



entry	Ar	yield (%)[a]	ee(%)
1	4-OMe-C_6H_4	87	81
2	4-Cl-C_6H_4	84	70
3	3-furyl	88	63
4	3,4-OMe-C_6H_4	88	70

R = CH_2-2-naphthyl. Data are for the average of two runs.
[a]Isolated yield.

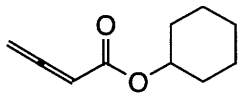
C. Conclusions.

An efficient, enantioselective phosphine-catalyzed [3+2] cycloaddition of allenoates with imines has been developed. The selectivity of the reaction has been shown to be sensitive to modifications of the allenoate ester substituent. Although the system we have developed is the most general and highly enantioselective reported for this process to date, much remains to be accomplished.

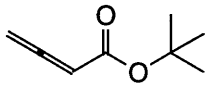
D. Experimental.

I. Substrate Preparation.

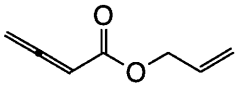
Allenes were generally prepared in three steps starting with the acylation of the appropriate alchol with bromoacetylbromide, followed by reaction with triphenylphosphine, and finally allene formation by reaction of the corresponding phosphorane with ketene, generated from treatment of acetyl chloride with NEt_3.[19]



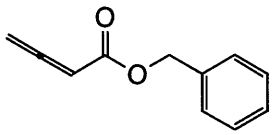
[884868-77-7] A solution of (cyclohexyloxycarbonylmethyl)-triphenylphosphonium bromide (7.00 g, 14.48 mmol) in CH_2Cl_2 (70 mL) was treated with NEt_3 (4.04 mL, 28.96 mmol) and stirred for 3 h. Then AcCl (1.03 mL, 14.48 mmol) was added dropwise as a solution in CH_2Cl_2 (10 mL) over 20 min. This mixture was stirred overnight. The reaction was washed with water, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (1-10% Et_2O in hexanes) yield the 723 mg (30%) of a pale yellow oil.



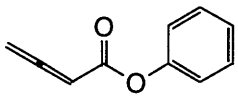
[189078-68-0] A solution of (*t*-butoxycarbonylmethyl)triphenylphosphonium bromide (1.0 g, 20.0 mmol) in CH_2Cl_2 (100 mL) was treated with NEt_3 (5.85 mL, 42.0 mmol) and stirred for 3 h. Then AcCl (1.50 mL, 21.0 mmol) was added dropwise as a solution in CH_2Cl_2 (10 mL) over 20 min. This mixture was stirred overnight. The reaction was concentrated and the resulting solids were washed with copious amounts of pentane. The solution of allene in pentane was concentrated and the product was purified by column chromatography (1-5% Et_2O in pentane) to yield 41 mg (11%) of an pale orange oil.



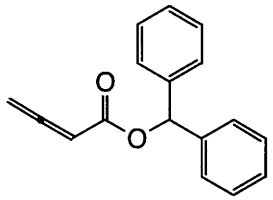
[91747-23-8] A solution of (allyloxycarbonylmethyl)triphenylphosphonium bromide (8.83 g, 20.0 mmol) in CH_2Cl_2 (100 mL) was treated with NEt_3 (5.85 mL, 42.0 mmol) and stirred for 3 h. Then AcCl (1.50 mL, 21.0 mmol) was added dropwise as a solution in CH_2Cl_2 (10 mL) over 20 min. This mixture was stirred overnight. The reaction was concentrated and the resulting solids were washed with copious amounts of pentane. The solution of allene in pentane was concentrated and the product was purified by distillation under reduced pressure to yield 540 mg (22%) of an orange oil.



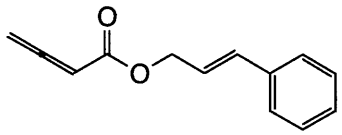
[187661-86-5] A solution of (benzyloxycarbonylmethyl)triphenylphosphonium bromide (4.00 g, 8.14 mmol) in THF (40 mL) cooled to -78 °C was treated with *n*-BuLi (5.13 mL of a 1.6 M solution in hexanes, 8.22 mmol) and stirred for 2 h. The solution was warmed to room temperature and treated with NEt_3 (1.13 mL, 8.14 mmol). Then AcCl (0.580 mL, 8.14 mmol) was added dropwise as a solution in CH_2Cl_2 (10 mL) over 20 min. This mixture was stirred overnight. The reaction was washed with water, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (1-10% Et_2O in hexanes) yielded 825 mg (58%) of a pale yellow oil.



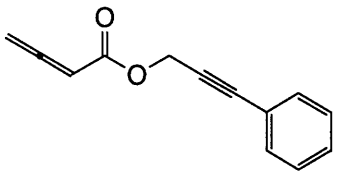
[102690-46-0] A solution of (phenyloxycarbonylmethyl)triphenylphosphonium bromide (4.78 g, 10.01 mmol) in CH_2Cl_2 (60 mL) was treated with NEt_3 (2.90 mL, 20.53 mmol) and stirred for 3 h. Then AcCl (0.715 mL, 10.01 mmol) was added dropwise as a solution in CH_2Cl_2 (10 mL) over 20 min. This mixture was stirred overnight. The reaction was washed with water, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (2-5% Et_2O in pentane) yielded 355 mg (22%) of a pale yellow oil.



[68809-49-4] A solution of (diphenylmethoxycarbonylmethyl)-triphenylphosphonium bromide (1.85 g, 3.26 mmol) in CH_2Cl_2 (30 mL) was treated with NEt_3 (1.00 mL, 7.70 mmol) and stirred for 3 h. Then AcCl (0.245 mL, 3.42 mmol) was added dropwise as a solution in CH_2Cl_2 (10 mL) over 20 min. This mixture was stirred overnight. The reaction mixture was concentrated and purified by flash chromatography (2-5% Et_2O in pentane) to yield 275 mg (31%) of a white solid.



[104892-30-0] A solution of (cinnamyloxycarbonylmethyl)triphenylphosphonium bromide (0.515 g, 0.995 mmol) in THF (8 mL) cooled to -78 °C was treated with *n*-BuLi (0.655 mL of a 1.6 M solution in hexanes, 1.05 mmol) and stirred for 1 h. The solution was warmed to room temperature and treated with NEt_3 (0.139 mL, 0.995 mmol). Then AcCl (0.071 mL, 0.995 mmol) was added dropwise. This mixture was stirred overnight. The reaction was washed with water, extracted with Et_2O, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (2-10% Et_2O in hexanes) yielded 92 mg (46%) of a pale yellow oil.



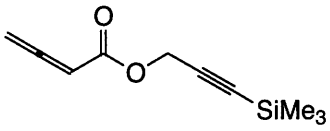
A solution of (3-phenylprop-2-ynoxycarbonylmethyl)triphenylphosphonium bromide (2.00 g, 3.88 mmol) in THF (20 mL) cooled to -78 °C was treated with *n*-BuLi (0.655 mL of a 1.6 M solution in hexanes, 1.05 mmol) and stirred for 1 h. The solution was warmed to room temperature and treated with NEt_3 (0.540 mL, 3.88 mmol). Then AcCl (0.275 mL, 3.88 mmol) was added dropwise. This mixture was stirred overnight. The reaction was washed with water, extracted with Et_2O, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (2-10% Et_2O in hexanes) yielded 362 mg (47%) of a pale yellow oil.

^1H NMR (300 MHz) δ 7.47-7.44 (m, 2H), 7.34-7.30 (m, 3H), 5.71 (t, J=6.5 Hz, 1H), 5.27 (d, J=6.5 Hz, 2H), 4.98 (s, 2H).

^{13}C NMR (75 MHz) δ 216.4, 165.2, 132.1, 128.9, 128.5, 122.3, 87.7, 86.7, 83.0, 79.9, 53.5.

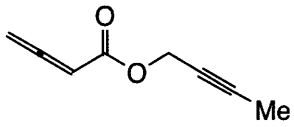
FTIR (thin film) 3067, 2992, 2360, 2339, 2239, 1969, 1939, 1722, 1490, 1373, 1332, 1243, 1151 cm^{-1}.

LC-MS calc. for $C_{13}H_{10}O_2$ [M+1] 199.1, found 199.0.



A solution of (3-trimethylsilyl-1-prop-2-ynoxy)triphenylphosphonium bromide (2.00 g, 3.91 mmol) in CH_2Cl_2 (30 mL) was treated with NEt_3 (1.65 mL, 11.73 mmol) and stirred for 4 h. Then AcCl (0.280 mL, 3.91 mmol) was added dropwise as a solution in CH_2Cl_2 (8 mL) over 20 min. This mixture was stirred overnight. The reaction was washed with water, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (1-5% Et_2O in pentane) yielded 289 mg (38%) of a clear oil.

^{1}H NMR (300 MHz) δ 5.69 (t, J=6.3 Hz, 1H), 5.27 (d, J=6.3 Hz, 2H), 4.76 (s, 2H), 0.19 (s, 9H).



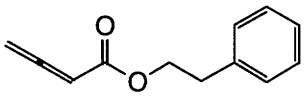
A solution of (but-2-yn-1-oxycarbonylmethyl)triphenylphosphonium bromide (1.28 g, 2.28 mmol) in THF (15 mL) cooled to -78 °C was treated with *n*-BuLi (1.85 mL of a 1.6 M solution in hexanes, 2.96 mmol) and stirred for 1 h. The solution was warmed to room temperature and treated with NEt_3 (0.395 mL, 2.82 mmol). Then AcCl (0.200 mL, 2.82 mmol) was added dropwise. This mixture was stirred overnight. The reaction was washed with water, extracted with Et_2O, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (2-10% Et_2O in hexanes) yielded 167 mg (43%) of a clear oil (this material was contaminated with ~20% acetyl but-2-yn-1-ol).

^{1}H NMR (300 MHz) δ 5.61 (t, J=6.6 hz, 1H), 5.21 (d, J=6.6 Hz, 2H), 4.65 (q, J=2.4 Hz, 2H), 1.80 (t, J=2.4 Hz, 3H).

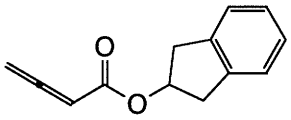
^{13}C NMR (75 MHz) δ 216.2, 165.1, 87.6, 83.4, 79.7, 73.1, 53.4, 3.7.

FTIR (thin film) 3069, 2992, 2323, 2241, 1970, 1941, 1716, 1438, 1373, 1331, 1245, 1185, 1083, 992 cm^{-1}.

LC-MS calc. for $C_8H_8O_2$ [M+H] 136.0, found 136.0.



A solution of (2-phenylethoxycarbonylmethyl)triphenylphosphonium bromide (1.74 g, 3.44 mmol) in THF (25 mL) cooled to -78 °C was treated with *n*-BuLi (2.25 mL of a 1.6 M solution in hexanes, 3.62 mmol) and stirred for 1 h. The solution was warmed to room temperature and treated with NEt_3 (0.480 mL, 3.44 mmol). Then AcCl (0.245 mL, 3.44 mmol) was added dropwise. This mixture was stirred overnight. The reaction was washed with water, extracted with Et_2O, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (2-10% Et_2O in hexanes) yielded 275 mg (43%) of a clear oil.



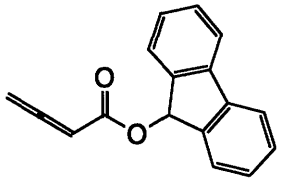
A solution of (2-indanoxycarbonylmethyl)triphenylphosphonium bromide (2.95 g, 5.71 mmol) in THF (30 mL) cooled to -78 °C was treated with *n*-BuLi (3.75 mL of a 1.6 M solution in hexanes, 5.99 mmol) and stirred for 1 h. The solution was warmed to room temperature and treated with NEt_3 (0.955 mL, 6.85 mmol). Then AcCl (0.490 mL, 6.85 mmol) was added dropwise. This mixture was stirred overnight. The reaction was washed with water, extracted with Et_2O, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (2-10% Et_2O in hexanes) yielded 639 mg (56%) of a clear oil (this material is contaminated with ~20% of acetyl 2-indanol).

^1H NMR (300 MHz) δ 7.29-7.20 (m, 4H), 5.65 (t, J=6.7 Hz, 1H), 5.62 (m, 1H), 5.22 (d, J=6.7 Hz, 2H), 3.37 (dd, J=17.0 Hz, J=6.6 Hz, 2H), 3.09 (dd, J=17.0 Hz, J=3.2 Hz, 2H).

^{13}C NMR (75 MHz) δ 215.9, 165.7, 140.4, 126.8, 124.7, 88.2, 79.5, 76.0, 39.6.

FTIR (thin film) 3069, 3025, 2989, 2903, 1970, 1715, 1483, 1422, 1365, 1335, 1260, 1166 cm^{-1}.

LC-MS calc. for $C_{13}H_{12}O_2$ [M+Na] 223.1, found 223.0.



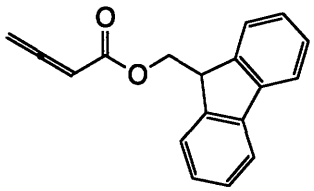
A solution of (9-fluorenoxycarbonylmethyl)triphenylphosphonium bromide (10.54 g, 18.64 mmol) in THF (125 mL) cooled to -78 °C was treated with *n*-BuLi (12.2 mL of a 1.6 M solution in hexanes, 19.57 mmol) and stirred for 1 h. The solution was warmed to room temperature and treated with NEt_3 (2.60 mL, 18.64 mmol). Then AcCl (1.33 mL, 18.64 mmol) was added dropwise. This mixture was stirred overnight. The reaction was washed with water, extracted with Et_2O, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (2-15% Et_2O in hexanes) yielded 2.75 g (59%) of a yellow solid (contaminated with acetyl fluorenol which is inseparable).

^1H NMR (300 MHz) δ 7.69-7.66 (m, 2H), 7.62-7.57 (m, 2H), 7.45-7.40 (m, 2H), 6.98 (td, J=7.4 Hz, J=1.2 Hz, 2H), 6.87 (s, 1H), 5.78 (t, J=6.5 Hz, 1H), 5.25 (d, J=6.5 Hz, 2H).

^{13}C NMR (75 MHz) δ 216.3, 166.8, 142.1, 141.2, 129.7, 128.0, 126.2, 120.2, 88.1, 79.9, 75.8.

FTIR (thin film) 3068, 2991, 2928, 1968, 1715, 1611, 1453, 1421, 1352, 1246, 1154 cm^{-1}.

LC-MS calc. for $C_{17}H_{12}O_2$ [M+1] 249.1, found 249.0.



A solution of (1-fluorenylmethoxycarbonylmethyl)triphenylphosphonium bromide (1.35 g, 2.33 mmol) in THF (15 mL) cooled to -78 °C was treated with *n*-BuLi (1.53 mL of a 1.6 M solution in hexanes, 2.45 mmol) and stirred for 1 h. The solution was warmed to room temperature and treated with NEt_3 (0.325 mL, 2.33 mmol). Then AcCl (0.166 mL, 2.33 mmol) was added dropwise. This mixture was stirred overnight. The reaction was washed with water, extracted with Et_2O, dried over $MgSO_4$, filtered,

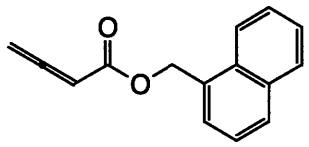
and concentrated. Flash chromatography (2-10% Et_2O in hexanes) yielded 250 mg (41%) of a clear oil.

^1H NMR (300 MHz) δ 7.79 (d, J=6.7 Hz, 2H), 7.67-7.62 (m, 2H), 7.46-7.40 (m, 2H), 7.36-7.31 (m, 2H), 5.76 (t, J=6.5 Hz, 1H), 5.33 (d, J=6.5 Hz, 2H), 4.43 (d, J=7.5 Hz, 2H), 4.27 (t, J=7.5 Hz, 1H).

^{13}C NMR (75 MHz) δ 216.4, 165.9, 143.9, 141.5, 128.0, 127.3, 125.4, 120.2, 88.1, 79.7, 67.2, 46.9.

FTIR (thin film) 3066, 2360, 2341, 1969, 1717, 1450, 1256, 1160, 1080, 1017, 856 cm^{-1}.

LC-MS calc. for $C_{18}H_{14}O_2$ [M+Na] 285.1, found 285.0.



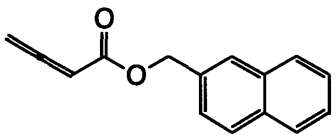
A solution of (1-naphthylmethoxycarbonylmethyl)triphenylphosphonium bromide (2.01 g, 3.71 mmol) in THF (30 mL) cooled to -78 °C was treated with *n*-BuLi (2.44 mL, 3.90 mmol) and stirred for 1 h. The solution was warmed to room temperature and treated with NEt_3 (0.517 mL, 3.71 mmol). Then AcCl (0.265 mL, 3.71 mmol) was added dropwise. This mixture was stirred overnight. The reaction was washed with water, extracted with Et_2O, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (2-10% Et_2O in hexanes) yielded 510 mg (61%) of a clear oil.

^1H NMR (300 MHz) δ 8.08-8.05 (m, 1H), 7.92-7.86 (m, 2H), 7.61-7.45 (m, 4H), 5.74 (t, J=6.6 Hz, 1H), 5.67 (s, 2H), 5.23 (d, J=6.6 Hz, 2H).

^{13}C NMR (75 MHz) δ 216.2, 165.7, 133.8, 131.6, 131.4, 129.4, 128.8, 127.6, 126.7, 126.1, 125.4, 123.7, 87.9, 79.7, 65.1.

FTIR (thin film) 3066, 2990, 1969, 1716, 1599, 1512, 1330, 1243, 1154, 1083 cm^{-1}.

LC-MS calc. for $C_{15}H_{12}O_2$ [M+Na] 247.1, found 247.0.



A solution of (2-naphthylmethoxycarbonylmethyl)triphenylphosphonium bromide (1.34 g, 2.47 mmol) in THF (20 mL) cooled to -78 °C was treated with *n*-BuLi (1.62 mL of 1.6 M solution in hexanes, 2.59 mmol) and stirred for 1 h. The solution was warmed to room temperature and treated with NEt_3 (0.345 mL, 2.47 mmol). Then AcCl (0.176 mL, 2.47 mmol) was added dropwise. This mixture was stirred overnight. The reaction was washed with water, extracted with Et_2O, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (2-10% Et_2O in hexanes) yielded 510 mg (61%) of a clear oil.

^1H NMR (300 MHz) δ 7.75-7.48 (m, 4H), 7.53-7.48 (m, 3H), 5.76 (t, J=6.6 Hz, 1H), 5.38 (s, 2H), 5.26 (d, J=6.6 Hz, 2H).

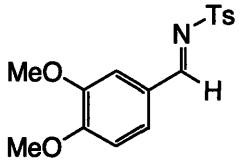
^{13}C NMR (75 MHz) δ 216.2, 165.7, 133.4, 133.3, 128.5, 128.2, 128.1, 127.9, 127.5, 126.5, 126.4, 126.0, 88.0, 79.7, 67.0

FTIR (thin film) 3058, 2990, 1969, 1940, 1603, 1510, 1422, 1331, 1251, 1160 cm^{-1}.

LC-MS calc. for $C_{15}H_{12}O_2$ [M+Na] 247.1, found 247.0.

All of the sulfonyl imines used in the above studies are known compounds. [135822-88-7], [357417-22-2], [51608-60-7], and [194878-04-1].

This is a sample procedure for the preparation of sulfonyl imines:



[137845-39-7] A flask was charged with 3,4-dimethoxybenzaldehyde (0.783 g, 4.71 mmol), p-toluenesulfonamide (1.61 g, 9.42 mmol), Amberlite IR-120 (plus) ion exchange resin (0.120 g), and 4Å MS (0.950 g). The flask was then purged with argon and toluene (12 mL) was introduced. A Dean-Stark trap was attached and the mixture

was refluxed for 24 h. After cooling to room temperature, the mixture was filtered over a pad of celite washing with CH_2Cl_2 (60 mL). The organic extracts were washed with 1 N NaOH (4x20 mL), dried over $MgSO_4$, filtered, and concentrated. The material was dried under vacuum overnight to yield 1.33 g (92%) of a white solid which was used without further purification.

^{1}H NMR (300 MHz) δ 8.9 (s, 1H), 7.87 (d, J=8.3 Hz, 2H), 7.50 (d, J=1.9 Hz, 1H), 7.42 (dd, J=8.3 Hz, J=1.9 Hz, 1H), 7.33 (d, J=8.3 Hz, 2H), 6.93 (d, J=8.3 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.42 (s, 3H).

^{13}C NMR (75 MHz) δ 169.8, 155.5, 149.8, 144.6, 135.8, 130.0, 129.5, 128.2, 125.7, 110.8, 110.3, 56.5, 56.3, 21.9.

II. Phosphine-Catalyzed Asymmetric [3+2] Cycloadditions of Allenoates with Imines (Table 2.2.1, Table 2.2.2, and Table 2.2.3):

Table 2.2.1. See Table 2.2.2, Entry 1, for the experimental procedure.

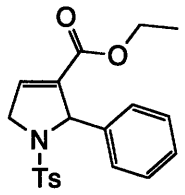


Table 2.2.2, Entry 1. In a nitrogen filled glove box, a solution of (*R*)-**2.1** (1.4 mg, 0.004 mmol) in CH_2Cl_2 (0.10 mL) was added to a solution of allene (4.8 mg, 0.043 mmol) and N-benzylidene-*p*-toluenesulfonamide (10.0 mg, 0.039 mmol) in CH_2Cl_2 (0.4 mL). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (5-50% Et_2O in hexanes) to yield 10.8 mg (75%) of the pyrroline as a white solid.

HPLC analysis: 69% ee. (Diacel CHIRALCEL AD-H column; 0.9 mL/min; solvent system: 20% isopropanol in hexanes; retention times 18.8 min (major), 15.5 min (minor).

^{1}H NMR (500 MHz) δ 7.42 (d, J=1.7 Hz, 1H), 7.41 (d, J=1.7 Hz, 1H), 7.25-7.20 (m, 5H), 7.15-7.13 (m, 2H), 6.79 (dd, J=4.0 Hz, J=2.0 Hz, 1H), 5.73 (m, 1H), 4.51 (dt,

J=17.0 Hz, J=2.4 Hz, 1H), 4.39 (ddd, J=17.0 Hz, J=5.8 Hz, J=2.0 Hz, 1H), 4.09-3.59 (m, 2H), 2.37 (s, 3H), 1.10 (t, J=7.1 Hz, 3H).

^{13}C NMR (125 MHz) δ 162.0, 143.5, 139.7, 136.3, 135.8, 135.7, 129.7, 128.5, 128.2, 128.1, 127.3, 69.3, 61.1, 55.1, 21.7, 14.1.

FTIR (thin film) 1721, 1643, 15988, 1494, 1456, 1346, 1265, 1163, 1092 cm^{-1}.

LC-MS calc. for $C_{20}H_{21}NO_4S$ [M+1] 372.1, found 372.1.

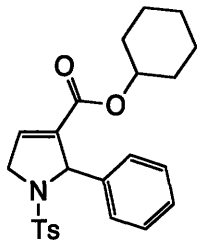


Table 2.2.2, Entry 2. In a nitrogen filled glove box, a solution of allene (10.0 mg, 0.06 mmol) and N-benzylidene-*p*-toluenesulfonamide (13.0 mg, 0.050 mmol) in CH_2Cl_2 (0.5 mL) was added to (*S*)-**2.1** (1.8 mg, 0.005 mmol). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (5-50% Et_2O in hexanes) to yield 18.4 mg (87%) of the pyrroline.

HPLC analysis: 70% ee. (Diacel CHIRALCEL AD-H column; 0.9 mL/min; solvent system: 20% isopropanol in hexanes; retention times 12.9 min (major), 12.0 min (minor).

^{1}H NMR (500 MHz) δ 7.39-7.38 (m, 2H), 7.23-7.19 (m, 5H), 7.13-7.11 (m, 2H), 6.81 (m, 1H), 5.74 (d, J=5.8 Hz, 1H), 4.64 (m, 1H), 4.51 (m, 1H), 4.36 (ddd, J=17.0 Hz, J=5.9 Hz, J=1.4 Hz, 1H), 2.36 (s, 3H), 1.69 (m, 1H), 1.62 (m, 1H), 1.49 (m, 1H), 1.44-1.11 (m, 8H).

^{13}C NMR (125 MHz) δ161.6, 143.4, 139.7, 136.7, 136.0, 135.7, 129.6, 128.4, 128.2, 128.1, 127.3, 73.4, 69.2, 55.0, 31.5, 31.1, 25.4, 23.5, 23.3, 21.7.

FTIR (thin film) 2938, 1716, 1649, 1598, 1494, 1454, 1351, 1262, 1163, 1089, 1015 cm^{-1}.

LC-MS calc. for $C_{24}H_{28}NO_4S$ [M+1] 426.2, found 426.1.

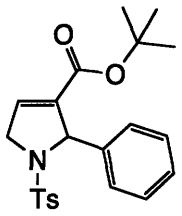


Table 2.2.2, Entry 3. In a nitrogen filled glove box, a solution of allene (6.0 mg, 0.043 mmol) and N-benzylidene-*p*-toluenesulfonamide (10.0 mg, 0.039 mmol) in CH_2Cl_2 (0.30 mL) was added to (*R*)-**2.1** (1.4 mg, 0.004 mmol). After stirring for 24 h at room temperature this mixture was directly purified by silica gel chromatography (5-50% Et_2O in hexanes) to yield 13.4 mg (86%) of the pyrroline.

HPLC analysis: 32% ee. (Diacel CHIRALCEL AD-H column; 0.9 mL/min; solvent system: 20% isopropanol in hexanes; retention times x min (major), x min (minor).

^{1}H NMR (500 MHz) δ 7.39 (d, J=8.1 Hz, 2H), 7.23-7.17 (m, 5H), 7.12 (d, J=8.1 Hz, 2H), 6.73 (m, 1H), 5.67 (d, J=5.9 Hz, 1H), 4.49 (dt, J=16.8 Hz, J=2.1 Hz, 1H), 4.33 (ddd, J=16.8 Hz, J=5.8 Hz, J=1.5 Hz, 1H), 2.36 (s, 3H), 1.24 (s, 9H).

^{13}C NMR (125 MHz) δ 161.4, 143.4, 139.8, 137.7, 136.0, 134.9, 129.6, 128.4, 128.2, 128.1, 127.3, 81.9, 69.3, 54.9, 28.0, 21.7.

FTIR (thin film) 1714, 1649, 1598, 1494, 1456, 1349, 1283, 1163, 1092, 1074 cm^{-1}.

LC-MS calc. for $C_{22}H_{25}NO_4S$ [M+1] 400.1, found 400.1.

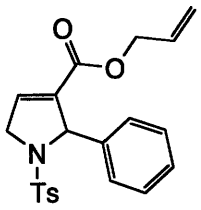


Table 2.2.2, Entry 4. In a nitrogen filled glove box, a solution of allene (8.0 mg, 0.06 mmol) and N-benzylidene-*p*-toluenesulfonamide (13.0 mg, 0.050 mmol) in CH_2Cl_2 (0.5 mL) was added to (*S*)-**2.1** (1.8 mg, 0.005 mmol). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (5-50% Et_2O in hexanes) to yield 12.6 mg (66%) of the pyrroline.

HPLC analysis: 76% ee.(Diacel CHIRALCEL AD-H column; 0.9 mL/min; solvent system: 20% isopropanol in hexanes; retention times 13.3 min (major), 15.8 min (minor).

^{1}H NMR (500 MHz) δ 7.42-7.41 (m, 2H), 7.25-7.21 (m, 5H), 7.15-7.13 (m, 2H), 6.83 (dd, J=3.7 Hz, J=2.0 Hz, 1H), 5.77-5.69 (m, 2H), 5.13 (dd, J=10.5 Hz, J=1.2 Hz, 1H), 5.08 (dt, J=17.2 Hz, J=1.4 Hz, 1H), 4.54-4.50 (m, 2H), 4.44 (ddt, J=13.5 Hz, J=5.5 Hz, J=1.3 Hz, 1H), 4.39 (ddd, J=17.2 Hz, J=5.9 Hz, J=1.9 Hz, 1H), 2.37 (s, 3H).

^{13}C NMR (125 MHz) δ 161.7, 143.5, 139.7, 136.2, 135.9, 135.8, 131.6, 129.7, 128.6, 128.3, 128.1, 127.3, 118.5, 69.2, 65.5, 55.1, 21.7.

FTIR (thin film) 1723, 1648, 1598, 1494, 1456, 1348, 1259, 1163, 1094, 988 cm^{-1}.

LC-MS calc. for $C_{21}H_{21}NO_4S$ [M+1] 384.1, found 384.1.

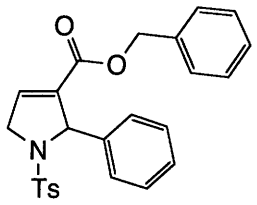


Table 2.2.2, Entry 5. In a nitrogen filled glove box, a solution of allene (10.5 mg, 0.06 mmol) and N-benzylidene-*p*-toluenesulfonamide (13.0 mg, 0.050 mmol) in CH_2Cl_2 (0.5 mL) was added to (*S*)-**2.1** (1.8 mg, 0.005 mmol). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (5-50% Et_2O in hexanes) to yield 17.5 mg (81%) of the pyrroline.

HPLC analysis: 75% ee. (Diacel CHIRALCEL AD-H column; 0.9 mL/min; solvent system: 20% isopropanol in hexanes; retention times 21.1 min (major), 23.6 min (minor).

^{1}H NMR (500 MHz) δ 7.41-7.40 (m, 2H), 7.30-7.20 (m, 8H), 7.14-7.12 (m, 2H), 7.06-7.04 (m, 2H), 6.85 (m, 1H), 5.76 (d, J=5.8 Hz, 1H), 5.08 (d, J=12.5 Hz, 1H), 4.94 (d, J=12.5 Hz, 1H), 4.51 (dt, J=17.1 Hz, J=2.1 Hz, 1H), 4.38 (ddd, J=17.1 Hz, J=5.8 Hz, J=1.8 Hz, 1H), 2.37 (s, 3H).

^{13}C NMR (125 MHz) δ 161.8, 143.5, 139.5, 136.6, 135.84, 135.77, 135.4, 129.7, 128.7, 128.6, 128.5, 128.3, 128.2, 128.1, 127.3, 69.2, 66.8, 55.1, 21.7.

FTIR (thin film) 1721, 1645, 1598, 1495, 1455, 1348, 1265, 1163, 1089 cm^{-1}.

LC-MS calc. for $C_{25}H_{23}NO_4S$ [M+1] 434.1, found 434.1.

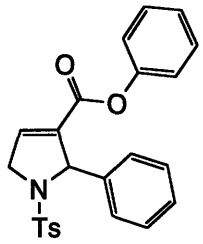


Table 2.2.2, Entry 6. In a nitrogen filled glove box, a solution of allene (10.0 mg, 0.06 mmol) and N-benzylidene-*p*-toluenesulfonamide (13.0 mg, 0.050 mmol) in CH_2Cl_2 (0.5 mL) was added to (*S*)-**2.1** (1.8 mg, 0.005 mmol). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (5-50% Et_2O in hexanes) to yield 13.0 mg (62%) of the pyrroline.

HPLC analysis: 51% ee. (Diacel CHIRALCEL AD-H column; 0.9 mL/min; solvent system: 20% isopropanol in hexanes; retention times 16.5 min (major), 18.9 min (minor).

^1H NMR (500 MHz) δ 7.46-7.44 (m, 2H), 7.30-7.25 (m, 7H), 7.19-7.16 (m, 3H), 7.02 (dd, J=3.6 Hz, J=1.7 Hz, 1H), 6.84-6.83 (m, 2H), 5.86 (m, 1H), 4.61 (dt, J=17.3 Hz, J=2.4 Hz, 1H), 4.47 (ddd, J=17.3 Hz, J=5.9 Hz, J=1.9 Hz, 1H), 2.39 (s, 3H).

^{13}C NMR (125 MHz) δ 160.3, 150.2, 143.6, 139.5, 137.8, 135.7, 129.8, 129.6, 128.6, 128.4, 128.1, 127.4, 126.3, 121.4, 69.3, 55.3, 21.8.

FTIR (thin film) 1738, 1645, 1597, 1491, 1456, 1350, 1253, 1194, 1162, 1102, 1053 cm^{-1}.

LC-MS calc. for $C_{24}H_{21}NO_4S$ [M+1] 420.1, found 420.1.

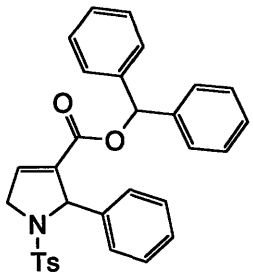


Table 2.2.2, Entry 7. In a nitrogen filled glove box, a solution of allene

(15.0 mg, 0.06 mmol) and N-benzylidene-*p*-toluenesulfonamide (13.0 mg, 0.050 mmol) in CH_2Cl_2 (0.5 mL) was added to (*S*)-**2.1** (1.8 mg, 0.005 mmol). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (5-50% Et_2O in hexanes) to yield 22.5 mg (89%) of the pyrroline.

HPLC analysis: 79% ee. (Diacel CHIRALCEL AD-H column; 0.9 mL/min; solvent system: 20% isopropanol in hexanes; retention times 37.2 min (major), 41.0 min (minor).

^{1}H NMR (500 MHz) δ 7.37-7.34 (m, 2H), 7.34-7.23 (m, 8H), 7.21-7.15 (m, 3H), 7.13-7.10 (m, 4H), 6.95 (dd, J=3.9 Hz, J=2.0 Hz, 1H), 6.75-6.71 (m, 3H), 5.84-5.82 (m, 1H), 4.53 (dt, J=17.2 Hz, J=2.4 Hz, 1H), 4.36 (ddd, J=17.2 Hz, J=5.9 Hz, J=1.9 Hz, 1H), 2.36 (s, 3H).

^{13}C NMR (125 MHz) δ 161.1, 143.5, 139.8, 139.7, 139.4, 137.5, 135.9, 135.8, 129.7, 128.8, 128.7, 128.6, 128.42, 128.41, 128.3, 127.9, 127.3, 127.2, 126.7, 77.9, 69.1, 54.9, 21.7.

FTIR (thin film) 1723, 1646, 1598, 1495, 1455, 1348, 1259, 1163, 1086, 987 cm^{-1}.

LC-MS calc. for $C_{31}H_{27}NO_4S$ [M+Na] 532.1, found 532.1.

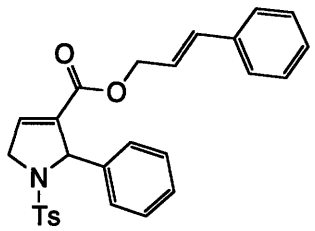


Table 2.2.2, Entry 8. In a nitrogen filled glove box, a solution of allene (12.0 mg, 0.06 mmol) and N-benzylidene-*p*-toluenesulfonamide (13.0 mg, 0.050 mmol) in CH_2Cl_2 (0.5 mL) was added to (*S*)-**2.1** (1.8 mg, 0.005 mmol). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (5-50% Et_2O in hexanes) to yield 19.3 mg (84%) of the pyrroline.

HPLC analysis: 75% ee. (Diacel CHIRALCEL AD-H column; 0.9 mL/min; solvent system: 20% isopropanol in hexanes; retention times 26.9 min (major), 35.1 min (minor).

^{1}H NMR (500 MHz) δ 7.44-7.42 (m, 2H), 7.34-7.29 (m, 4H), 7.28-7.25 (m, 6H), 7.15-7.14 (m, 2H), 6.84 (dd, J=4.0 Hz, J=1.9 Hz, 1H), 6.44 (d, J=15.8 Hz, 1H), 6.07 (dt, J=15.9 Hz, J=6.3 Hz, 1H), 5.77 (m, 1H), 4.70 (ddd, J=13.1 Hz, J=6.3 Hz, J=1.3 Hz, 1H), 4.59 (ddd, J=13.1 Hz, J=6.3 Hz, J=1.3 Hz, 1H), 4.52 (dt, J=17.2 Hz, J=2.3 Hz, 1H), 4.40 (ddd, J=17.2 Hz, J=5.8 Hz, J=1.9 Hz, 1H), 2.37 (s, 3H).

^{13}C NMR (125 MHz) δ 161.8, 143.5, 139.6, 136.3, 136.2, 136.0, 134.5, 129.7, 128.8, 128.6, 128.4, 128.3, 128.1, 127.3, 126.8, 122.6, 69.2, 65.5, 55.2, 21.7 (coincident resonance).

FTIR (thin film) 1720, 1645, 1598, 1494, 1455, 1349, 1260, 1163, 1094, 969 cm^{-1}.

LC-MS calc. for $C_{27}H_{25}NO_4S$ [M+1] 460.2, found 460.1.

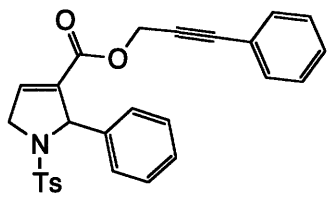


Table 2.2.2, Entry 9. In a nitrogen filled glove box, a solution of allene (12.0 mg, 0.06 mmol) and N-benzylidene-*p*-toluenesulfonamide (13.0 mg, 0.050 mmol) in CH_2Cl_2 (0.5 mL) was added to (*S*)-**2.1** (1.8 mg, 0.005 mmol). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (5-50% Et_2O in hexanes) to yield 20.3 mg (89%) of the pyrroline.

HPLC analysis: 81% ee. (Diacel CHIRALCEL IA column; 0.9 mL/min; solvent system: 20% isopropanol in hexanes; retention times 16.4 min (major), 17.6 min (minor).

^{1}H NMR (500 MHz) δ 7.46-7.42 (m, 2H), 7.41-7.37 (m, 2H),7.35-7.29 (m, 3H), 7.27-7.22 (m, 5H), 7.16-7.13 (m, 2H), 6.88 (m, 1H), 5.78 (m, 1H), 4.84 (d, J=15.7 Hz, 1H), 4.78 (d, J=15.7 Hz, 1H), 4.54 (dt, J=17.2 Hz, J=2.5 Hz, 1H), 4.41 (ddd, J=17.2 Hz, J=5.8 Hz, J=2.0 Hz, 1H), 2.36 (s, 3H).

^{13}C NMR (125 MHz) δ 161.7, 144.1, 139.9, 137.3, 136.2, 135.9, 132.5, 130.2, 129.6, 129.03, 129.01, 128.8, 128.5, 127.8, 122.6, 87.5, 82.9, 69.7, 55.7, 53.9, 22.2.

FTIR (thin film) 1727, 1644, 1598, 1491, 1456, 1346, 1256, 1163, 1084 cm^{-1}.

LC-MS calc. for $C_{27}H_{23}NO_4S$ [M+Na] 480.1, found 480.1.

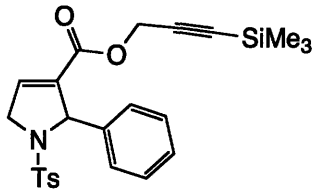


Table 2.2.2, Entry 10. In a nitrogen filled glove box, a solution of allene (15.0 mg, 0.06 mmol) and N-benzylidene-*p*-toluenesulfonamide (13.0 mg, 0.050 mmol) in CH_2Cl_2 (0.5 mL) was added to (*S*)-**2.1** (1.8 mg, 0.005 mmol). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (5-50% Et_2O in hexanes) to yield 19.6 mg (87%) of the pyrroline.

HPLC analysis: 83% ee. (Diacel CHIRALCEL IA column; 0.9 mL/min; solvent system: 20% isopropanol in hexanes; retention times 9.1 min (major), 8.6 min (minor).

^{1}H NMR (500 MHz) δ 7.43 (d, J=8.2 Hz, 2H), 7.25-7.22 (m, 5H), 7.15 (d, J=8.2 Hz, 2H), 6.86 (m, 1H), 5.76 (d, J=5.8 Hz, 1H), 4.62-4.51 (m, 3H), 4.41 (ddd, J=17.2 Hz, J=5.7 Hz, J=1.4 Hz, 1H), 2.38 (s, 3H), 0.16 (s, 9H).

^{13}C NMR (125 MHz) δ 161.1, 143.6, 139.5, 136.8, 135.8, 135.4, 129.7, 128.5, 128.3, 128.0, 127.4, 98.4, 92.8, 69.2, 55.2, 53.3, 21.7, -0.12.

FTIR (thin film) 1730, 1645, 1598, 1494, 1456, 1346, 1251, 1164, 1085, 846 cm^{-1}.

LC-MS calc. for $C_{24}H_{27}NO_4S$ [M+1] 454.1, found 454.1.

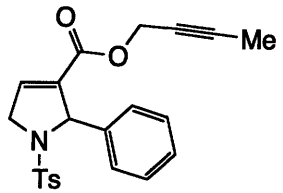


Table 2.2.2, Entry 11. In a nitrogen filled glove box, a solution of allene (10.0 mg, 0.06 mmol) and N-benzylidene-*p*-toluenesulfonamide (13.0 mg, 0.050 mmol) in CH_2Cl_2 (0.5 mL) was added to (*S*)-**2.1** (1.8 mg, 0.005 mmol). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (5-50% Et_2O in hexanes) to yield 17.5 mg (89%) of the pyrroline.

HPLC analysis: 79% ee. (Diacel CHIRALCEL AS-H column; 0.9 mL/min; solvent system: 20% isopropanol in hexanes; retention times 44.1 min (major), 66.0 (broad) min (minor).

^{1}H NMR (300 MHz) δ 7.43 (m, 2H), 7.24 (m, 5H), 7.15 (m, 2H), 6.83 (m, 1H), 5.75 (m, 1H), 4.56-4.48 (m, 3H), 4.40 (ddd, J=17.2 Hz, J=5.8 Hz, J=2.0 Hz, 1H), 2.37 (s, 3H), 1.80 (t, J=2.4 Hz, 3H).

^{13}C NMR (125 MHz) δ 161.8, 144.0, 139.9, 136.9, 136.2, 136.0, 131.3, 130.2, 129.0, 128.7, 128.5, 127.8, 84.3, 73.2, 69.7, 55.7, 53.8, 22.2.

FTIR (thin film) 1726, 1645, 1598, 1494, 1456, 1345, 1256, 1163, 1083 cm^{-1}.

LC-MS calc. for $C_{22}H_{21}NO_4S$ [M+1] 396.1, found 396.1.

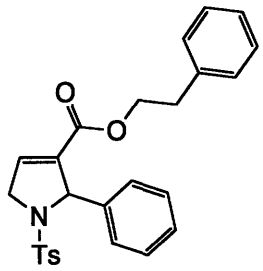


Table 2.2.2, Entry 12. In a nitrogen filled glove box, a solution of allene (11.3 mg, 0.06 mmol) and N-benzylidene-*p*-toluenesulfonamide (13.0 mg, 0.050 mmol) in CH_2Cl_2 (0.5 mL) was added to (*S*)-**2.1** (1.8 mg, 0.005 mmol). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (5-50% Et_2O in hexanes) to yield 22.0 mg (99%) of the pyrroline.

HPLC analysis: 70% ee. (Diacel CHIRALCEL IA column; 0.9 mL/min; solvent system: 10% isopropanol in hexanes; retention times 23.6 min (major), 22.1 min (minor).

^{1}H NMR (500 MHz) δ 7.41 (d, J=8.3 Hz, 2H), 7.29-7.18 (m, 8H), 7.14 (d, J=8.0 Hz, 2H), 7.07 (d, J=8.3 Hz, 2H), 6.75 (dd, J=3.9 Hz, J=2.0 Hz, 1H), 5.71 (m, 1H), 4.49 (dt, J=17.2 Hz, J=2.4 Hz, 1H), 4.37 (ddd, J=17.2 Hz, J=5.8 Hz, J=1.9 Hz, 1H), 4.20 (m, 2H), 2.78 (t, J=6.9 Hz, 2H), 2.37 (s, 3H).

^{13}C NMR (125 MHz) δ 161.9, 143.5, 139.6, 137.7, 136.1, 136.0, 135.8, 129.7, 129.0, 128.7, 128.6, 128.3, 128.0, 127.3, 126.8, 69.2, 65.5, 55.1, 35.0, 21.7.

FTIR (thin film) 1720, 1645, 1598, 1495, 1455, 1349, 1264, 1163, 1092 cm^{-1}.

LC-MS calc. for $C_{26}H_{25}NO_4S$ [M+Na] 470.1, found 470.1.

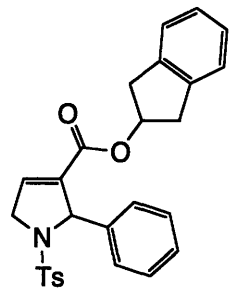


Table 2.2.2, Entry 13. In a nitrogen filled glove box, a solution of allene (12.0 mg, 0.06 mmol) and N-benzylidene-*p*-toluenesulfonamide (13.0 mg, 0.050 mmol) in CH_2Cl_2 (0.5 mL) was added to (*S*)-**2.1** (1.8 mg, 0.005 mmol). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (5-50% Et_2O in hexanes) to yield 19.5 mg (85%) of the pyrroline.

HPLC analysis: 70% ee. (Diacel CHIRALCEL OD-H column; 1.0 mL/min; solvent system: 10% isopropanol in hexanes; retention times 37.9 min (major), 34.0 min (minor).

^{1}H NMR (300 MHz) δ 7.39-7.34 (m, 2H), 7.26-7.06 (m, 11H), 6.76 (m, 1H), 5.65 (m, 1H), 5.41 (m, 1H), 4.49 (dt, J=17.0 Hz, J=2.5 Hz, 1H), 4.34 (ddd, J=17.0 Hz, J=5.9 Hz, J=2.0 Hz, 1H), 3.22 (dd, J=17.1 Hz, J=6.3 Hz, 1H), 3.11 (dd, J=17.1 Hz, J=6.3 Hz, 1H), 2.90 (dd, J=17.1 Hz, J=2.9 Hz, 1H), 2.59 (dd, J=17.0 Hz, J=2.7 Hz, 1H), 2.36 (s, 3H).

^{13}C NMR (500 MHz) δ 161.9, 143.4, 140.32, 140.27, 139.6, 136.3, 135.98, 135.88, 129.6, 128.4, 128.1, 128.0, 127.3, 127.0, 124.84, 124.78, 76.0, 69.2, 55.1, 39.7, 39.5, 21.7.

FTIR (thin film) 1717, 1647, 1598, 1457, 1347, 1269, 1163, 1091 cm^{-1}.

LC-MS calc. for $C_{27}H_{25}NO_4S$ [M+1] 460.1, found 460.1.

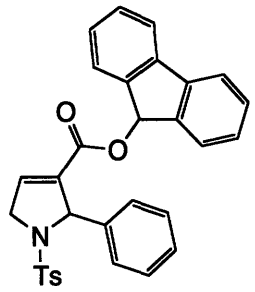


Table 2.2.2, Entry 14. In a nitrogen filled glove box, a solution of allene (15.0 mg, 0.06 mmol) and N-benzylidene-*p*-toluenesulfonamide (13.0 mg, 0.050 mmol) in CH_2Cl_2 (0.5 mL) was added to (*S*)-**2.1** (1.8 mg, 0.005 mmol). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (5-50% Et_2O in hexanes) to yield 21.5 mg (85%) of the pyrroline.

HPLC analysis: 82% ee. (Diacel CHIRALCEL AD-H column; 0.9 mL/min; solvent system: 20% isopropanol in hexanes; retention times 24.1 min (major), 27.2 min (minor).

^{1}H NMR (500 MHz) δ 7.64 (d, J=3.9 Hz, 1H), 7.62 (d, J=3.9 Hz, 1H), 7.42-7.30 (m, 5H), 7.29-7.11 (m, 9H), 6.89 (m, 1H), 6.86 (dd, J=3.8 Hz, J=1.1 Hz, 1H), 6.61 (s, 1H), 5.73 (m, 1H), 4.50 (dt, J=17.2 Hz, J=2.4 Hz, 1H), 4.38 (ddd, J=17.2 Hz, J=5.8 Hz, J=2.0 Hz, 1H), 2.36 (s, 3H),

^{13}C NMR (500 MHz) δ 162.8, 143.5, 141.8, 141.3, 141.0, 139.5, 137.0, 135.8, 135.7, 129.8, 129.7, 128.6, 128.3, 128.2, 128.0, 127.9, 127.4, 126.3, 126.0, 120.2, 120.1, 75.7, 69.1, 55.2, 21.7.

FTIR (thin film) 1719, 1646, 1598, 1494, 1453, 1349, 1258, 1163, 1098 cm^{-1}.

LC-MS calc. for $C_{31}H_{25}NO_4S$ [M+1] 508.1, found 508.1.

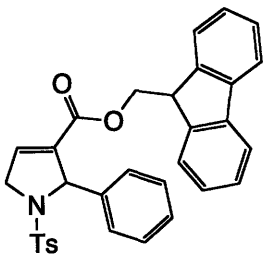


Table 2.2.2, Entry 15. In a nitrogen filled glove box, a solution of allene

(16.0 mg, 0.06 mmol) and N-benzylidene-*p*-toluenesulfonamide (13.0 mg, 0.050 mmol) in CH_2Cl_2 (0.5 mL) was added to (*S*)-**2.1** (1.8 mg, 0.005 mmol). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (5-50% Et_2O in hexanes) to yield 2.0 mg (8%) of the pyrroline.

HPLC analysis: 88% ee. (Diacel CHIRALCEL IA column; 0.9 mL/min; solvent system: 20% isopropanol in hexanes; retention times 21.4 min (major), 18.2 min (minor).

^{1}H NMR (500 MHz) δ 7.76 (d, J=3.1 Hz, 1H), 7.74 (d, J=2.6 Hz, 1H), 7.41-7.33 (m, 5H), 7.27-7.20 (m, 8H), 7.16-7.14 (m, 2H), 6.85 (s, 1H), 5.75 (d, J=5.6 Hz, 1H), 4.53 (m, 1H), 4.39 (dd, J=17.2 Hz, J=5.8 Hz, 1H), 4.33 (d, J=6.7 Hz, 1H), 4.08 (t, J=6.7 Hz, 1H), 2.38 (s, 3H).

^{13}C NMR (125 MHz) δ 162.0, 143.7, 143.6, 143.5, 141.5, 141.4, 139.4, 136.8, 135.8, 129.7, 128.7, 128.4, 128.1, 128.0, 127.4, 127.32, 127.30, 125.01, 124.98, 120.3, 120.2, 69.1, 67.0, 55.1, 46.8, 21.7.

FTIR (thin film) 1720, 1645, 1598, 1451, 1348, 1263, 1163, 1091 cm^{-1}.

LC-MS calc. for $C_{32}H_{27}NO_4S$ [M+1] 522.1, found 522.1.

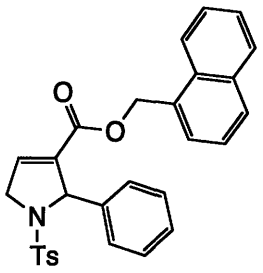


Table 2.2.2, Entry 16. In a nitrogen filled glove box, a solution of allene (13.0 mg, 0.06 mmol) and N-benzylidene-*p*-toluenesulfonamide (13.0 mg, 0.050 mmol) in CH_2Cl_2 (0.5 mL) was added to (*S*)-**2.1** (1.8 mg, 0.005 mmol). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (5-50% Et_2O in hexanes) to yield 19.4 mg (80%) of the pyrroline.

HPLC analysis: 76% ee. (Diacel CHIRALCEL AD-H column; 0.9 mL/min; solvent system: 20% isopropanol in hexanes; retention times 31.2 min (major), 26.1 min (minor).

^{1}H NMR (500 MHz) δ 7.87 (d, J=8.8 Hz, 1H), 7.83 (d, J=8.2 Hz, 1H), 7.76 (d, J=8.3 Hz, 1H), 7.53-7.46 (m, 2H), 7.39-7.36 (m, 3H), 7.28 (d, J=6.8 Hz, 1H), 7.23-7.19

(m, 1H), 7.18-7.15 (m, 4H), 7.10 (d, J=8.1 Hz, 2H), 6.80 (dd, J=3.8 Hz, J=2.1 Hz, 1H), 5.73 (m, 1H), 5.52 (d, J=12.6 Hz, 1H), 5.43 (d, J=12.6 Hz, 1H), 4.47 (dt, J=17.2 Hz, J=2.4 Hz, 1H), 4.35 (ddd, J=17.2 Hz, J=5.8 Hz, J=2.0 Hz, 1H), 2.35 (s, 3H).

^{13}C NMR (500 MHz) δ 161.9, 143.5, 139.4, 136.6, 135.9, 135.6, 133.9, 131.7, 130.9, 129.7, 129.6, 128.9, 128.5, 128.3, 128.0, 127.6, 127.3, 126.9, 126.2, 125.4, 123.5, 69.2, 65.0, 55.1, 21.7.

FTIR (thin film) 1721, 1646, 1598, 1456, 1349, 1259, 1163, 1089 cm^{-1}.

LC-MS calc. for $C_{29}H_{25}NO_4S$ [M+1] 484.1, found 484.1.

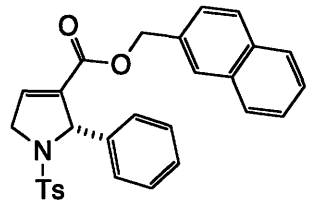


Table 2.2.2, Entry 17. In a nitrogen filled glove box, a solution of allene (13.5 mg, 0.06 mmol) and N-benzylidene-*p*-toluenesulfonamide (13.0 mg, 0.050 mmol) in CH_2Cl_2 (0.5 mL) was added to (*S*)-**2.1** (1.8 mg, 0.005 mmol). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (5-50% Et_2O in hexanes) to yield 22.0 mg (91%) of the pyrroline.

HPLC analysis: 79% ee. (Diacel CHIRALCEL AS-H column; 0.9 mL/min; solvent system: 20% isopropanol in hexanes; retention times 53.1 min (major), 71.0 min (minor).

^{1}H NMR (500 MHz) δ 7.82 (dd, J=5.9 Hz, J=3.3 Hz, 1H), 7.76-7.74 (m, 2H), 7.53 (s, 1H), 7.50 (d, J=3.3 Hz, 1H), 7.48 (d, J=3.1 Hz, 1H), 7.40 (d, J=8.2 Hz, 2H), 7.28-7.22 (m, 5H), 7.13-7.12 (m, 3H), 6.87 (m, 1H), 5.77 (d, J=5.5 Hz, 1H), 5.25 (d, J=12.5 Hz, 1H), 5.09 (d, J=12.5 Hz, 1H), 4.51 (dt, J=17.2 Hz, J=2.1 Hz, 1H), 4.39 (ddd, J=17.2 Hz, J=5.8 Hz, J=1.6 Hz, 1H), 2.36 (s, 3H).

^{13}C NMR (125 MHz) δ 161.2, 143.6, 139.5, 136.9, 135.7, 135.4, 132.1, 129.7, 129.1, 128.6, 128.5, 128.3, 128.0, 127.4, 122.2, 87.0, 82.5, 69.2, 55.3, 53.4, 21.7 (coincident resonances).

FTIR (thin film) 1722, 1646, 1598, 1494, 1456, 1346, 1262, 1163, 1088 cm^{-1}.

LC-MS calc. for $C_{29}H_{25}NO_4S$ [M+1] 484.1, found 484.1.

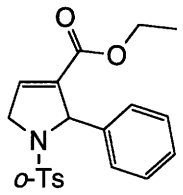


Table 2.2.3, Entry 1. In a nitrogen filled glove box, a solution of allene (6.8 mg, 0.06 mmol) and N-benzylidene-*o*-toluenesulfonamide (13.0 mg, 0.050 mmol) in CH_2Cl_2 (0.5 mL) was added to (*S*)-**2.1** (1.8 mg, 0.005 mmol). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (5-50% Et_2O in hexanes) to yield 12.5 mg (68%) of the pyrroline.

HPLC analysis: 68% ee. (Diacel CHIRALCEL AS-H column; 0.9 mL/min; solvent system: 20% isopropanol in hexanes; retention times 12.6 min (major), 19.1 min (minor).

^{1}H NMR (500 MHz) δ 7.73 (d, J=7.9 Hz, 1H), 7.29 (t, J=7.4 Hz, 1H), 7.16-7.02 (m, 7H), 6.90 (m, 1H), 5.77 (m, 1H), 4.75 (ddd, J=17.1 Hz, J=2.4 Hz, J=2.4 Hz, 1H), 4.40 (ddd, J=17.1 Hz, J=5.8 Hz, J=1.8 Hz, 1H), 4.09-3.97 (m, 2H), 2.36 (s, 3H).

^{13}C NMR (125 MHz) δ 162.1, 139.3, 138.4, 137.4, 136.3, 135.8, 133.0, 132.6, 130.8, 129.8, 128.2, 128.1, 127.7, 126.1, 100.0, 68.9, 61.1, 55.0, 20.3, 14.1.
FTIR (thin film) 2341, 2360, 1719, 1652, 1456, 1321, 1264, 1161, 1133, 1071 cm^{-1}.
LC-MS calc. for $C_{20}H_{21}NO_4S$ [M+Na] 394.1, found 394.0.

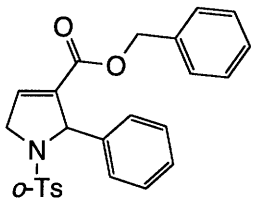


Table 2.2.3, Entry 2. In a nitrogen filled glove box, a solution of allene (10.5 mg, 0.06 mmol) and N-benzylidene-*p*-toluenesulfonamide (13.0 mg, 0.050 mmol) in CH_2Cl_2 (0.5 mL) was added to (*S*)-**2.1** (1.8 mg, 0.005 mmol). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (5-50% Et_2O in hexanes) to yield 13.5 mg (62%) of the pyrroline.

HPLC analysis: 70% ee. (Diacel CHIRALCEL AS-H column; 0.9 mL/min; solvent system: 20% isopropanol in hexanes; retention times 17.1 min (major), 24.7 min (minor).

^{1}H NMR (500 MHz) δ 7.73 (d, J=7.8 Hz, 1H), 7.30-7.24 (m, 4H), 7.15-7.08 (m, 4H), 7.05-7.03 (m, 5H), 6.97 (d, J=1.8 Hz, 1H), 5.79 (m, 1H), 5.09 (d, J=12.4 Hz, 1H), 4.94 (d, J=12.4 Hz, 1H), 4.75 (ddd, J=17.2 Hz, J=2.4 Hz, J=2.4 Hz, 1H), 4.40 (ddd, J=17.2 Hz, J=5.9 Hz, J=1.8 Hz, 1H), 2.35 (s, 3H).

^{13}C NMR (125 MHz) δ 161.9, 139.1, 138.4, 137.4, 136.8, 135.9, 135.4, 133.0, 132.6, 129.8, 128.7, 128.4, 128.3, 128.2, 128.1, 127.8, 126.1, 68.8, 66.8, 55.0, 20.3.

FTIR (thin film) 1720, 1456, 1321, 1265, 1161, 1133, 1070 cm^{-1}.

LC-MS calc. for $C_{25}H_{23}NO_4S$ [M+1] 434.1, found 434.1.

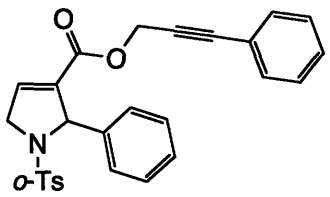


Table 2.2.3, Entry 3. In a nitrogen filled glove box, a solution of allene (12.0 mg, 0.06 mmol) and N-benzylidene-*p*-toluenesulfonamide (13.0 mg, 0.050 mmol) in CH_2Cl_2 (0.5 mL) was added to (*S*)-**2.1** (1.8 mg, 0.005 mmol). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (5-50% Et_2O in hexanes) to yield 9.0 mg (39%) of the pyrroline.

HPLC analysis: 76% ee. (Diacel CHIRALCEL OD-H column; 0.9 mL/min; solvent system: 20% isopropanol in hexanes; retention times 40.5 min (major), 27.5 min (minor).

^{1}H NMR (500 MHz) δ 7.74 (d, J=7.8 Hz, 1H), 7.40-7.38 (m, 2H), 7.34-7.26 (m, 4H), 7.15 (t, J=7.4 Hz, 1H), 7.12-7.00 (m, 6H), 5.83 (m, 1H), 4.86-4.76 (m, 3H), 4.44 (ddd, J=17.3 Hz, J=5.9 Hz, J=1.9 Hz, 1H), 2.37 (s, 3H).

^{13}C NMR (125 MHz) δ 161.3, 139.0, 138.4, 137.4, 136.9, 135.5, 133.1, 132.6, 132.1, 129.8, 129.1, 128.5, 128.3, 128.2, 127.7, 126.1, 122.2, 87.1, 82.5, 68.9, 55.1, 53.4, 20.3.

FTIR (thin film) 1728, 1646, 1491, 1456, 1379, 1322, 1256, 1162, 1133,

1070 cm^{-1}.

LC-MS calc. for $C_{27}H_{23}NO_4S$ [M+Na] 480.1, found 480.1.

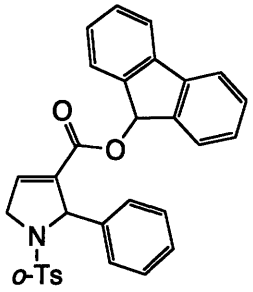


Table 2.2.3, Entry 4. In a nitrogen filled glove box, a solution of allene (15.0 mg, 0.06 mmol) and N-benzylidene-*p*-toluenesulfonamide (13.0 mg, 0.050 mmol) in CH_2Cl_2 (0.5 mL) was added to (*S*)-**2.1** (1.8 mg, 0.005 mmol). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (5-50% Et_2O in hexanes) to yield 10 mg (40%) of the pyrroline.

HPLC analysis: 81% ee. (Diacel CHIRALCEL AD-H column; 0.9 mL/min; solvent system: 20% isopropanol in hexanes; retention times 17.9 min (major), 13.0 min (minor).

^{1}H NMR (500 MHz) δ 7.72 (d, J=7.9 Hz, 1H), 7.62 (t, J=8.4 Hz, 2H), 7.41-7.34 (m, 3H), 7.28-7.21 (m, 2H), 7.16-7.07 (m, 4H), 7.00-6.99 (m, 4H), 6.86 (d, J=7.5 Hz, 1H), 6.63 (s, 1H), 5.77 (m, 1H), 4.77 (m, 1H), 4.40 (ddd, J=17.3 Hz, J=5.9 Hz, J=1.5 Hz, 1H), 2.33 (s, 3H).

^{13}C NMR (125 MHz) δ 162.9, 141.8, 141.3, 141.0, 139.0, 138.4, 137.3, 137.1, 135.8, 133.0, 132.5, 129.9, 129.8, 129.7, 128.3, 128.10, 128.06, 127.9, 127.8, 126.3, 126.04, 126.02, 120.2, 120.1, 100.0, 75.7, 68.8, 55.0, 20.2.

FTIR (thin film) 1720, 1647, 1454, 1321, 1258, 1162, 1133, 1069 cm^{-1}.

LC-MS calc. for $C_{31}H_{25}NO_4S$ [M+Na] 530.1, found 530.1.

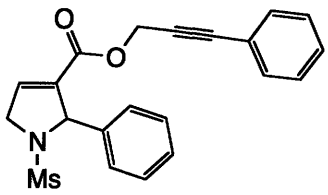


Table 2.2.3, Entry 5. In a nitrogen filled glove box, a solution of allene

(12.0 mg, 0.06 mmol) and N-benzylidene-*p*-toluenesulfonamide (9.0 mg, 0.050 mmol) in toluene (0.5 mL) was added to (*S*)-**2.1** (1.8 mg, 0.005 mmol). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (5-50% Et_2O in hexanes) to yield 16.7 mg (88%) of the pyrroline.

HPLC analysis: 66% ee. (Diacel CHIRALCEL AD-H column; 0.9 mL/min; solvent system: 20% isopropanol in hexanes; retention times 26.6 min (major), 17.9 min (minor).

^{1}H NMR (500 MHz) δ 7.41-7.30 (m, 10H), 7.03 (s, 1H), 5.84 (m, 1H), 4.88 (d, J=15.7 Hz, 1H), 4.84 (d, J=15.7 Hz, 1H), 4.66 (m, 1H), 4.43 (ddd, J=17.1 Hz, J=5.8 Hz, J=1.3 Hz, 1H), 2.44 (s, 3H).

^{13}C NMR (125 MHz) δ 161.2, 139.0, 136.9, 135.4, 132.1, 129.1, 129.0, 128.9, 128.6, 128.1, 122.2, 87.1, 82.4, 68.8, 55.0, 53.5, 39.6.

FTIR (thin film)1726, 1491, 1338, 1256, 1154, 1072, 989, 758 cm^{-1}.

LC-MS calc. for $C_{21}H_{19}NO_4S$ [M+Na] 404.1, found 404.0.

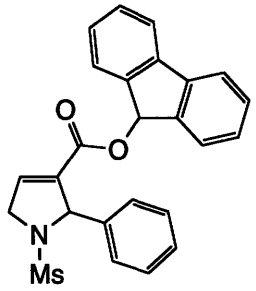


Table 2.2.3, Entry 6. In a nitrogen filled glove box, a solution of allene (15.0 mg, 0.06 mmol) and N-benzylidene-*p*-toluenesulfonamide (9.0 mg, 0.050 mmol) in CH_2Cl_2 (0.5 mL) was added to (*S*)-**2.1** (1.8 mg, 0.005 mmol). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (5-50% Et_2O in hexanes) to yield 21.0 mg (98%) of the pyrroline.

HPLC analysis: 82% ee. (Diacel CHIRALCEL AD-H column; 0.9 mL/min; solvent system: 20% isopropanol in hexanes; retention times 14.9 min (major), 13.3 min (minor).

^{1}H NMR (500 MHz) δ 7.64 (m, 2H), 7.42-7.31 (m, 8H), 7.24 (m, 1H), 7.15 (t, J=7.4 Hz, 1H), 7.00 (m, 1H), 6.66 (s, 1H), 5.79 (m, 1H), 4.63 (dt, J=17.1 Hz, J=2.4 Hz, 1H), 4.41 (ddd, J=17.1 Hz, J=6.1 Hz, J=1.9 Hz, 1H), 2.41 (s, 3H).

^{13}C NMR (125 MHz) δ 162.8, 141.8, 141.3, 141.2, 141.1, 139.0, 137.0, 135.7, 129.9, 129.7, 129.0, 128.8, 128.2, 128.1, 127.9, 126.3, 125.9, 120.3, 120.2, 75.8, 68.7, 55.0, 39.6.

FTIR (thin film) 1719, 1453, 1337, 1258, 1155, 1072, 966 cm^{-1}.

LC-MS calc. for $C_{25}H_{21}NO_4S$ [M+Na] 454.1, found 454.0.

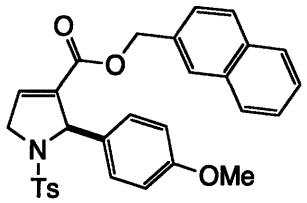


Table 2.2.4, Entry 1. In a nitrogen filled glove box, a solution of (*R*)-**2.1** (7.4 mg, 0.020 mmol) in CH_2Cl_2 (1.0 mL) was added to a solution of allene (53.8 mg, 0.240 mmol) and N-(4-methoxy)benzylidene-*p*-toluenesulfonamide (57.7 mg, 0.200 mmol) in CH_2Cl_2 (1.0 mL). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (5-30% EtOAc in hexanes) to yield 86.0 mg (84%) of the pyrroline as a white solid.

This compound was recrystallized from 1:1 Et_2O:hexanes to yield crystals suitable for X-ray crystallography (See Appendix A).

HPLC analysis: 80% ee. (Diacel CHIRALCEL IA column; 1.0 mL/min; solvent system: 25% EtOAc in hexanes; retention times 14.8 min (major), 18.4 min (minor).

Second run: (*S*)-**2.1** (7.4 mg, 0.020 mmol), allene (53.8 mg, 0.240 mmol), and N-(4-methoxy)benzylidene-*p*-toluenesulfonamide (57.7 mg, 0.200 mmol). 89% yield, 81% ee.

^{1}H NMR (300 MHz) 7.84-7.79 (m, 1H), 7.76-7.71 (m, 2H), 7.51-7.46 (m, 3H), 7.43-7.39 (m, 2H), 7.17-7.10 (m, 5H), 6.84 (dd, J=3.9 Hz, J=2.2 Hz, 1H), 6.76-6.71 (m, 2H), 5.73 (m, 1H), 5.28 (d, J=12.9 Hz, 1H), 5.08 (d, J=12.9 Hz, 1H), 4.48 (dt, J=17.1 Hz, J=2.5 Hz, 1H), 4.35 (ddd, J=17.1 Hz, J=5.7 Hz, J=1.9 Hz, 1H), 3.77 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (300 MHz) 161.9, 159.6, 143.4, 136.4, 135.8, 133.3, 132.9, 131.8, 129.7, 129.3, 128.5, 128.2, 127.9, 127.32, 127.27, 126.53, 126.51, 125.8, 113.9, 68.7, 66.8, 55.5, 54.9, 21.7.

FTIR (thin film) 1721, 1610, 1511, 1457, 1345, 1251, 1162, 1085, 816 cm^{-1}.

LC-MS calc. for $C_{30}H_{27}NO_5S$ [M+1] 514.1, found 514.1.

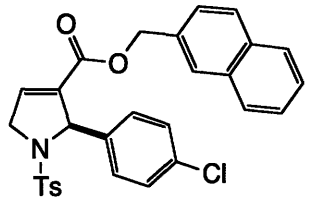


Table 2.2.4, Entry 2. In a nitrogen filled glove box, a solution of (*R*)-**2.1** (7.4 mg, 0.020 mmol) in CH_2Cl_2 (1.0 mL) was added to a solution of allene (53.8 mg, 0.240 mmol) and N-(4-chloro)benzylidene-*p*-toluenesulfonamide (58.5 mg, 0.200 mmol) in CH_2Cl_2 (1.0 mL). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (5-30% EtOAc in hexanes) to yield 87.0 mg (84%) of the pyrroline as a white solid.

HPLC analysis: 70% ee. (Diacel CHIRALCEL IA column; 1.0 mL/min; solvent system: 25% EtOAc in hexanes; retention times 12.9 min (major), 15.6 min (minor). Second run: (*S*)-**2.1** (7.4 mg, 0.020 mmol), allene (53.8 mg, 0.240 mmol), and N-(4-chloro)benzylidene-*p*-toluenesulfonamide (58.5 mg, 0.200 mmol). 83% yield, 70% ee.

^{1}H NMR (300 MHz) δ 7.85-7.82 (m, 1H), 7.78-7.74 (m, 2H), 7.54 (s, 1H), 7.53-7.47 (m, 2H), 7.46-7.42 (m, 2H), 7.19-7.12 (m, 7H), 6.87-6.85 (m, 1H), 5.72-5.69 (m, 1H), 5.27 (d, J=12.4 Hz, 1H), 5.08 (d, J=12.4 Hz, 1H), 4.50 (dt, J=17.2 Hz, J=2.5 Hz, 1H), 4.39 (ddd, J=17.2 Hz, J=5.7 Hz, J=2.0 Hz, 1H), 2.37 (s, 3H).

^{13}C NMR (75 MHz) δ 161.7, 143.8, 138.3, 137.0, 135.5, 135.4, 134.1, 133.3, 133.2, 132.6, 129.8, 129.5, 128.7, 128.5, 128.1, 127.9, 127.5, 127.3, 126.6, 125.8, 68.4, 67.0, 55.2, 21.7.

FTIR (thin film) 1722, 1647, 1597, 1490, 1346, 1265, 1163, 1091, 815 cm^{-1}.

LC-MS calc. for $C_{29}H_{24}ClNO_4S$ [M+1] 518.1, found 518.1.

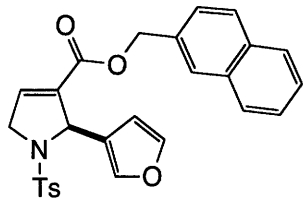


Table 2.2.4, Entry 3. In a nitrogen filled glove box, a solution of (*R*)-**2.1** (7.4 mg, 0.020 mmol) in CH_2Cl_2 (1.0 mL) was added to a solution of allene (53.8 mg, 0.240 mmol) and N-(3-furylidene)-*p*-toluenesulfonamide (50.0 mg, 0.200 mmol) in CH_2Cl_2 (1.0 mL). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (5-30% EtOAc in hexanes) to yield 82.0 mg (87%) of the pyrroline as a white solid.

HPLC analysis: 62% ee. (Diacel CHIRALCEL IA column; 1.0 mL/min; solvent system: 25% EtOAc in hexanes; retention times 12.7 min (major), 15.7 min (minor).

Second run: (*S*)-**2.1** (7.4 mg, 0.020 mmol), allene (53.8 mg, 0.240 mmol), and N-(3-furylidene)-*p*-toluenesulfonamide (50.0 mg, 0.200 mmol). 89% yield, 63% ee.

^{1}H NMR (300 MHz) δ 7.85-7.79 (m, 3H), 7.65 (s, 1H), 7.59-7.55 (m, 2H), 7.53-7.47 (m, 2H), 7.44-7.43 (m, 1H), 7.29-7.26 (m, 2H), 7.22-7.19 (m, 2H), 6.80-6.78 (m, 1H), 6.23-6.22 (m, 1H), 5.85-5.82 (m, 1H), 5.32 (d, J=12.5 Hz, 1H), 5.20 (m, 1H), 4.44 (dt, J=17.3 Hz, J=2.3 Hz, 1H), 4.30 (ddd, J=17.3 Hz, J=5.3 Hz, J=1.9 Hz, 1H), 2.37 (s, 3H).

^{13}C NMR (75 MHz) δ 162.8, 144.6, 144.1,141.8, 137.9, 136.2, 135.6, 134.0,133.6, 130.6, 129.3, 129.3, 128.9, 128.7, 128.14,128.12, 127.4, 126.5, 125.4, 110.0, 67.4, 61.2, 54.9, 21.8.

FTIR (thin film) 1721, 1646, 1598, 1346, 1163, 1089, 1020, 815 cm^{-1}.

LC-MS calc. for $C_{27}H_{23}NO_5S$ [M+1] 474.1, found 474.1.

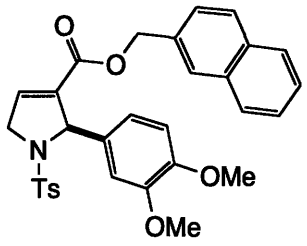


Table 2.2.4, Entry 4. In a nitrogen filled glove box, a solution of (*R*)-**2.1** (7.4 mg, 0.020 mmol) in CH_2Cl_2 (1.0 mL) was added to a solution of allene (53.8 mg, 0.240 mmol) and N-(3,4-dimethoxy)benzylidene-*p*-toluenesulfonamide (63.7 mg, 0.200 mmol) in CH_2Cl_2 (1.0 mL). After stirring for 16 h at room temperature this mixture was directly purified by silica gel chromatography (10-40% EtOAc in hexanes) to yield 94.0 mg (87%) of the pyrroline as a white solid.

HPLC analysis: 70% ee. (Diacel CHIRALCEL IA column; 1.0 mL/min; solvent system: 25% EtOAc in hexanes; retention times 17.6 min (major), 16.4 min (minor).

Second run: (*S*)-**2.1** (7.4 mg, 0.020 mmol), allene (53.8 mg, 0.240 mmol), and N-(3,4-dimethoxy)benzylidene-*p*-toluenesulfonamide (63.7 mg, 0.200 mmol). 88% yield, 71% ee.

^{1}H NMR (300 MHz) δ 7.84-7.79 (m, 1H), 7.76-7.72 (m, 2H), 7.53 (s, 1H), 7.50 (t, J=2.3 Hz, 1H), 7.46 (t, J=2.3 Hz, 1H), 7.39 (m, 2H), 7.36 (m, 1H), 7.16-7.10 (m, 2H), 6.87-6.85 (m, 1H), 6.77 (dd, J=8.3 Hz, J=2.0 Hz, 1H), 6.66 (d, J=8.2 Hz, 1H), 6.57 (d, J=2.0 Hz, 1H), 5.76-5.73 (m, 1H), 5.27 (d, J=12.5 Hz, 1H), 5.09 (d, J=12.5 Hz, 1H), 4.52 (dt, J=17.1 Hz, J=2.4 Hz, 1H), 4.35 (ddd, J=17.1 Hz, J=5.8 Hz, J=2.0 Hz, 1H), 3.84 (s, 3H), 3.62 (s, 3H), 2.34 (s, 3H).

^{13}C NMR (75 MHz) δ 162.0, 149.0, 148.3, 143.4, 136.4, 135.9, 135.8, 133.24, 133.21, 132.8, 131.7, 129.5, 128.5, 128.1, 127.9, 127.3, 127.2, 126.6, 125.8, 120.7, 110.8, 69.0, 66.9, 56.0, 55.7, 54.9, 21.6.

FTIR (thin film) 1721, 1647, 1596, 1514, 1464, 1421, 1344, 1261, 1163, 1141, 1087, 1027, 815 cm^{-1}.

LC-MS calc. for $C_{31}H_{29}NO_6S$ [M+1] 544.1, found 544.1.

E. References and Notes:

1. For information regarding Atrasentan (Xinlay), see: (a) Thakkar, S. G.; Chouveiri, T. K.; Garcia, J. A. *Current Oncology Reports* **2006**, *8*, 108-113. (b) Buchholz, M.; Reissig, H. U. *Eur. J. Org. Chem.* **2003**, *18*, 3524-3533. (c) Wittenberger, S. J.; McLaughlin, M. A. *Tet. Lett.* **1999**, *40*, 7175-7178. (d) Tasker, A. S.; Sorensen, B. K.; Jae, H.-S.; Winn, M.; von Geldern, T. W.; Dixon, D. B.; Chiou, W. J.; Dayton, B. D.; Calzadila, S.; Hernandez, L.; Marsh, K. C.; WuWong, J. R.; Opgenorth, T. J. *J. Med. Chem.* **1997**, *40*, 322-340. (e) Winn, M.; von Geldern, T. W.; Opgenorth, T. J.; Jae, H.-S.; Tasker, A. S.; Boyd, S. A.; Kester, J. A.; Mantei, R. A. Bal, R., Sorensen, B. K.; WuWong, J. R.; Chiou, W. J.; Dixon, D. B.; Novosad, E. I.; Hernandez, L.; Marsh, K. C. *J. Med. Chem.* **1996**, *39*, 1039-1048.
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9. For reviews on phosphine catalyzed cycloadditions, see references 12-17 in Chapter 2.1. For references on the non-asymmetric phosphine-catalyzed [3+2] cycloaddition of allenoates with imines, see: (a) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031. (b) Xu, Z.; Lu, X. *Tet. Lett.* **1997**, *38*, 3461. (c) Xu, Z.; Lu, X. *Tet. Lett.* **1999**, *40*, 549.
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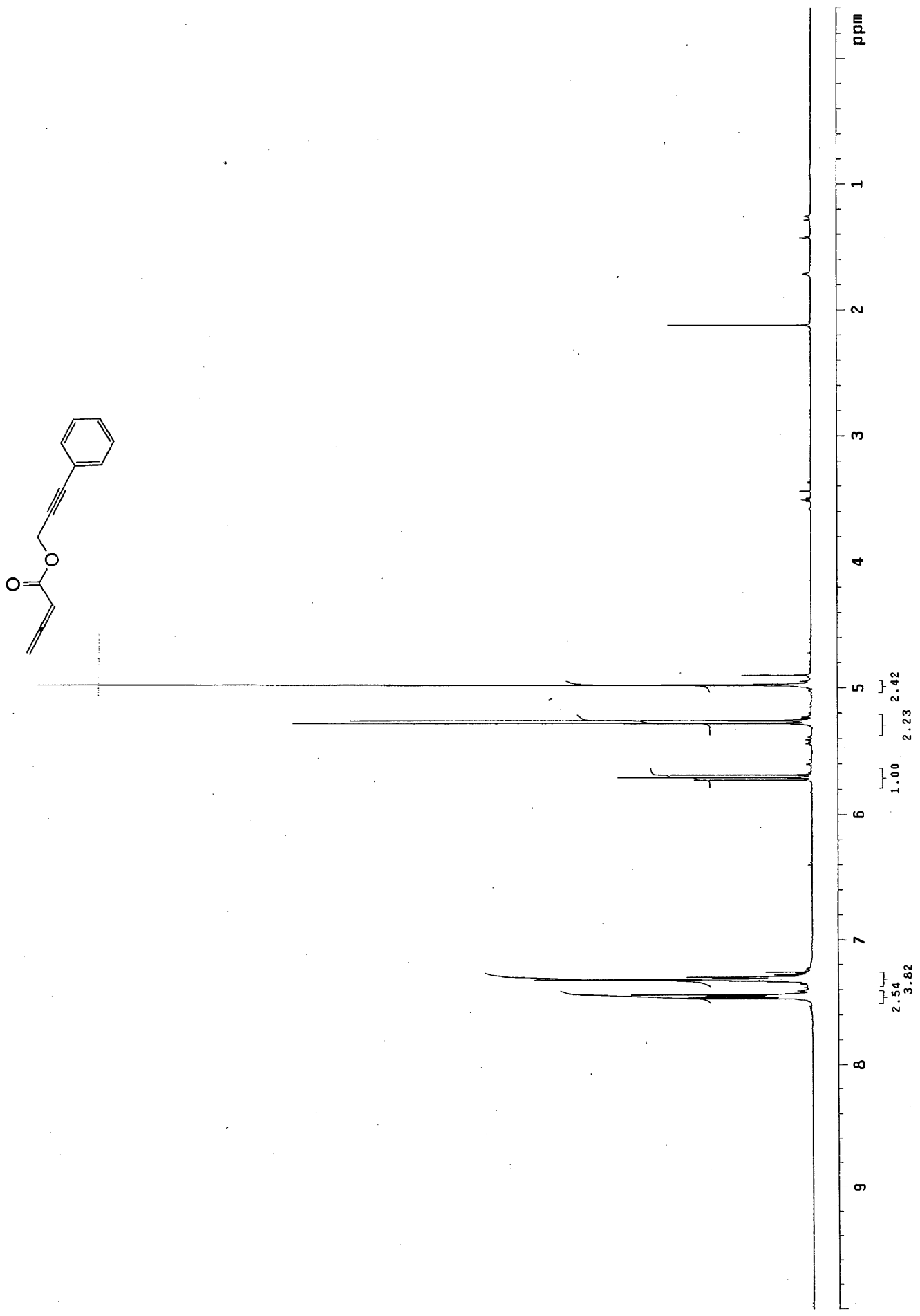
15. 1,2-dichloroethane gave comparable results to CH_2Cl_2. Halogenated solvents such as chlorobenzed, chloroform, and trifluorotoluene provided inferior selectivities. Other solvents such as toluene, EtOAc, Et_2O, THF, MeOH, EtOH, *t*-amylalcohol, benzene, and dioxane gave inferior results.
16. Concentration had little impact on the ee of the cycloaddition, but reactions run at very high concentrations yielded complex mixtures. Reactions run at elevated temperatures gave decreased selectivities. The reaction rate drastically slowed at 0 °C.
17. We have observed similar trends when other allenoates are used as reaction partners.
18. Cycloadditions with a cyclohexyl, *i*-butyl, and cyclopropyl substituted imine gave yields between 30-50% and enantioselectivity of 10-60%.
19. The allenoate synthesis was adopted from: Lang, R. W.; Hansen, H.-J. *Organic Syntheses* **1984**, *62*, 202.

F. ^{1}H NMR Spectra for Selected Compounds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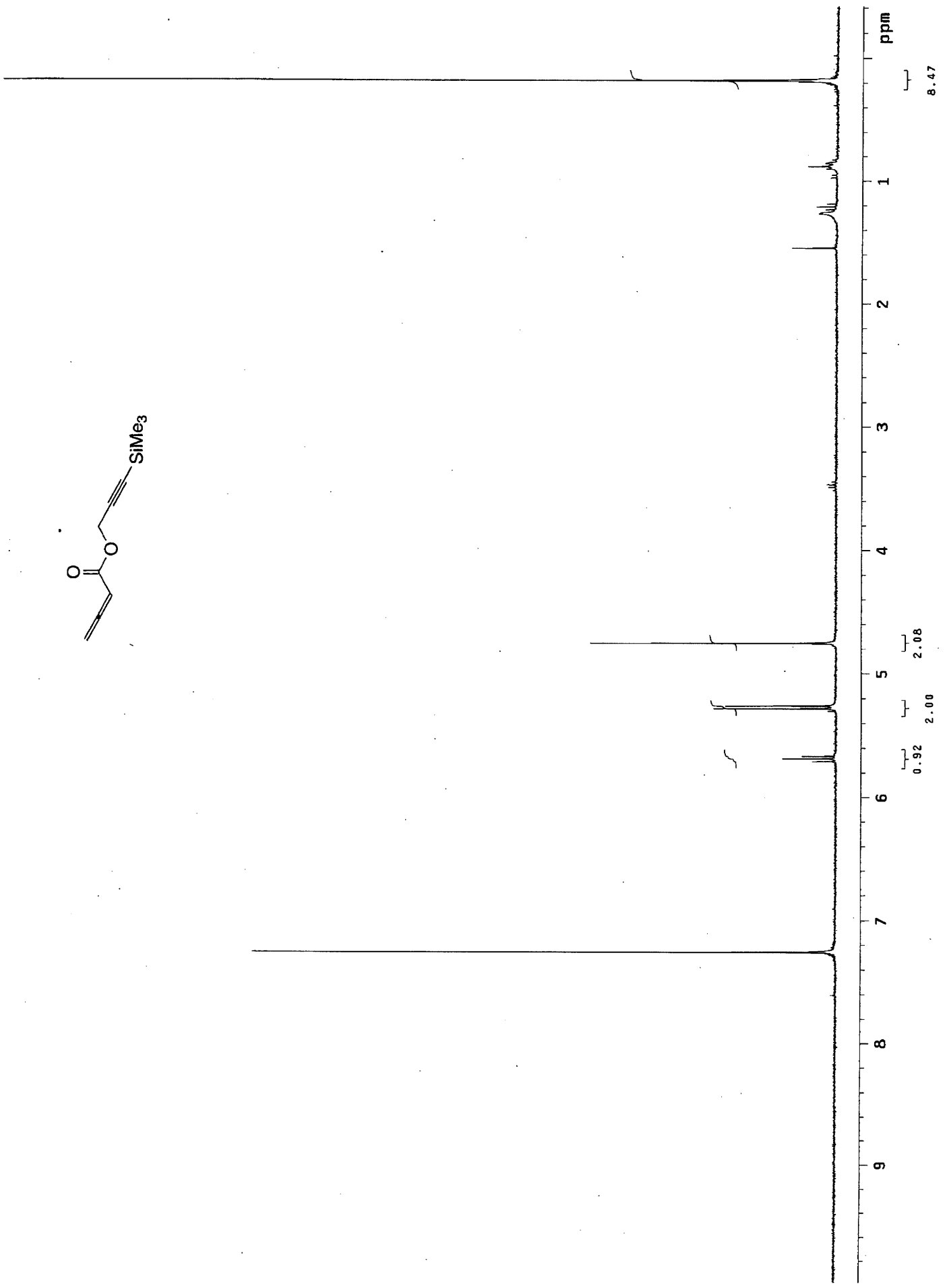
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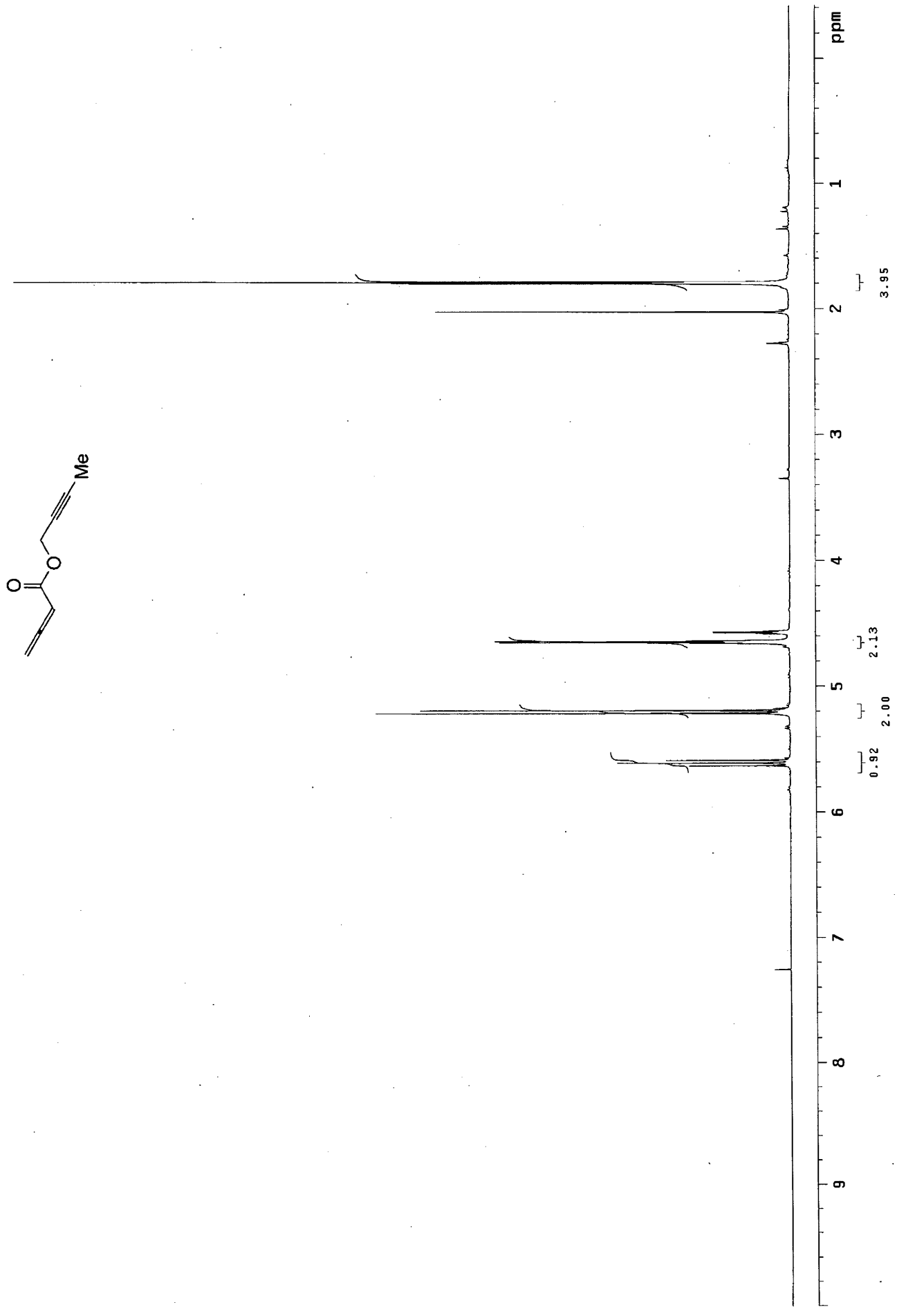
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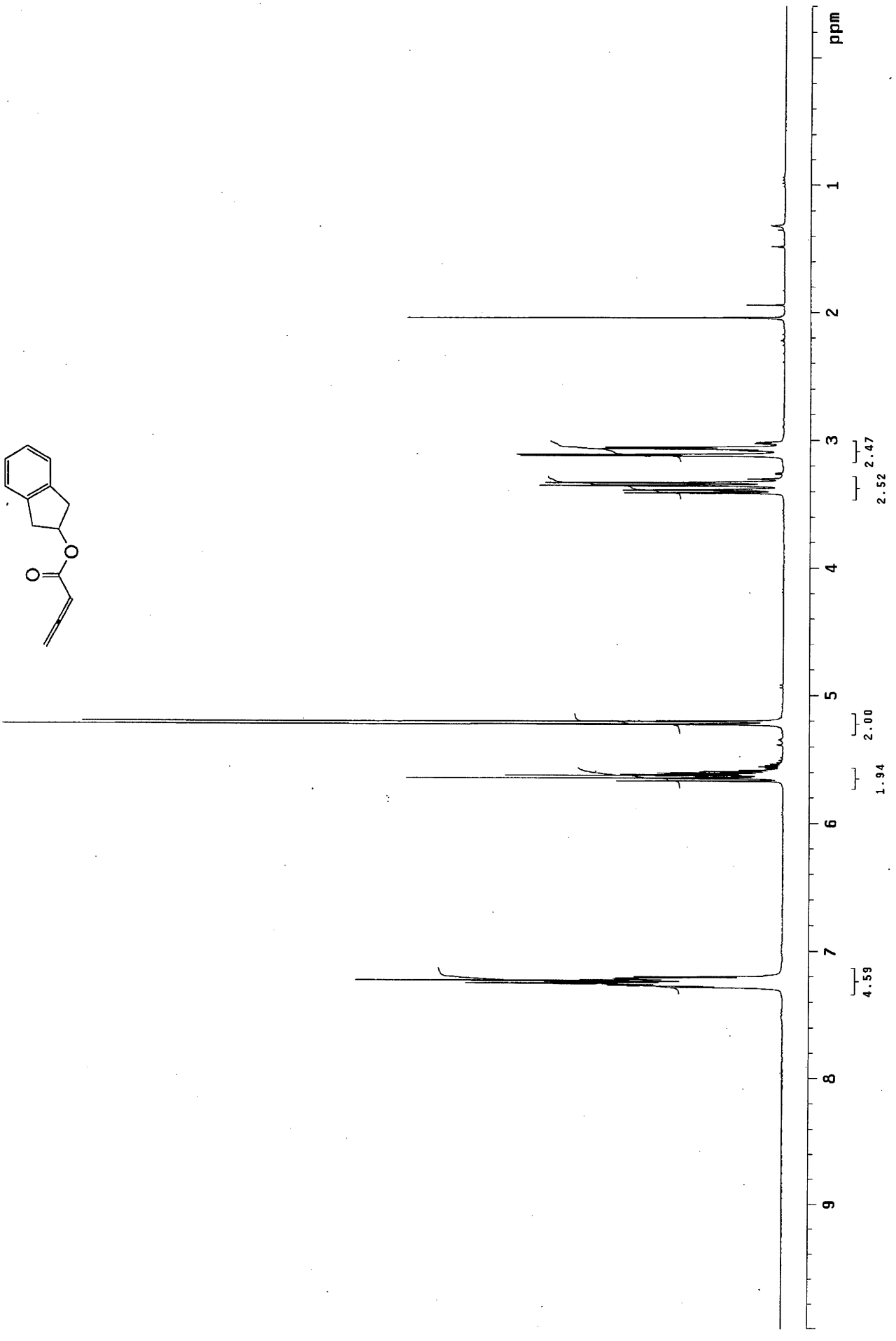
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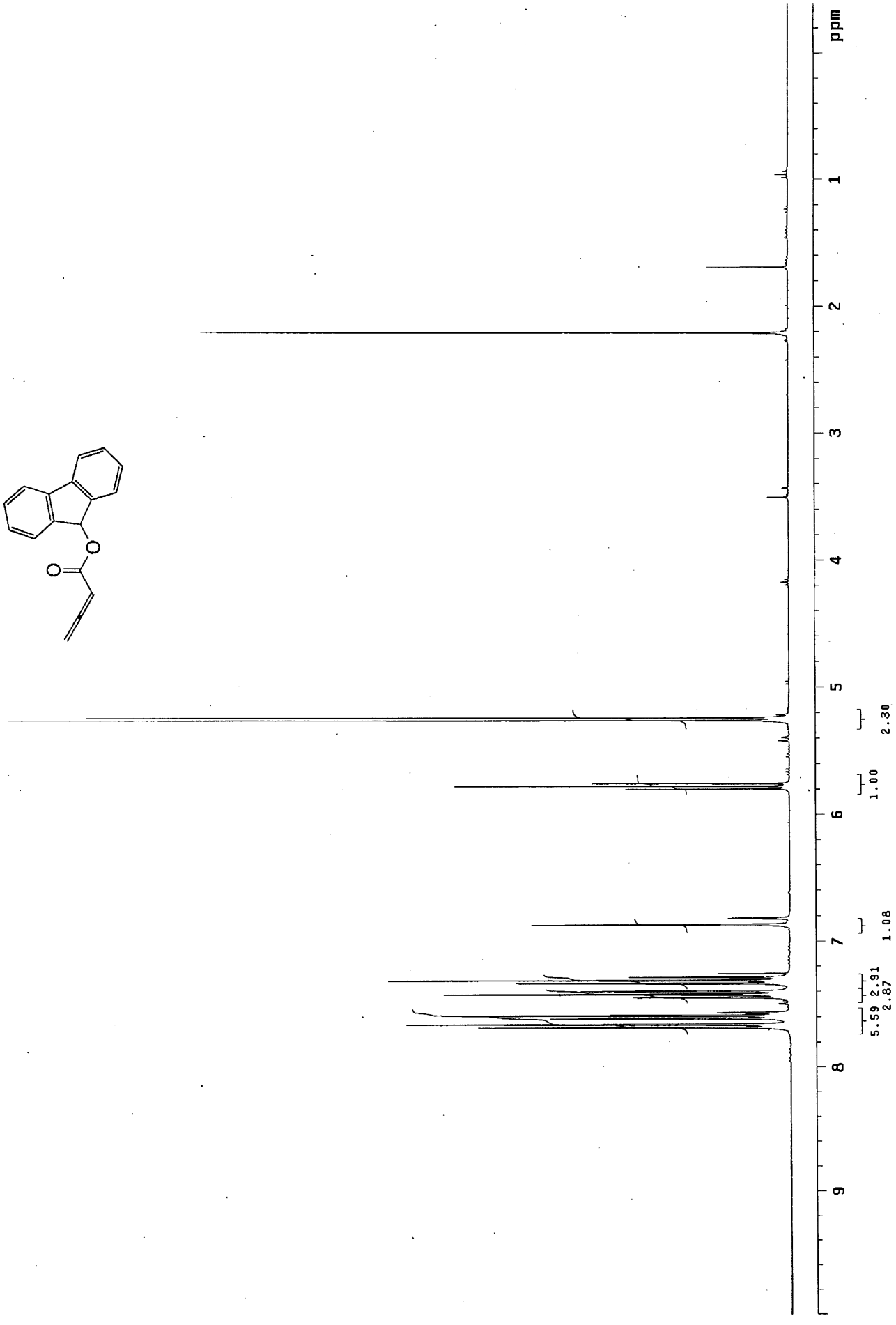
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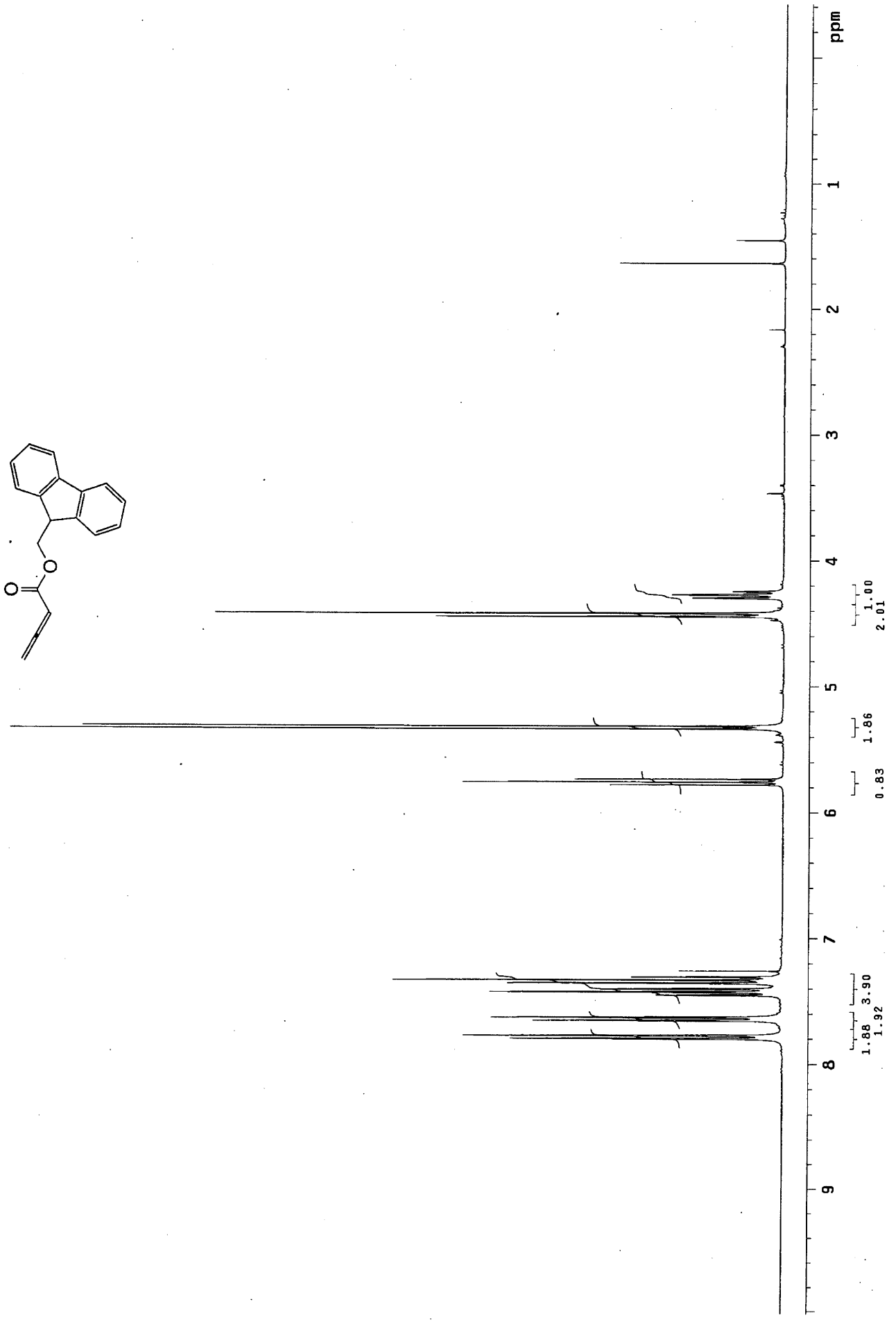
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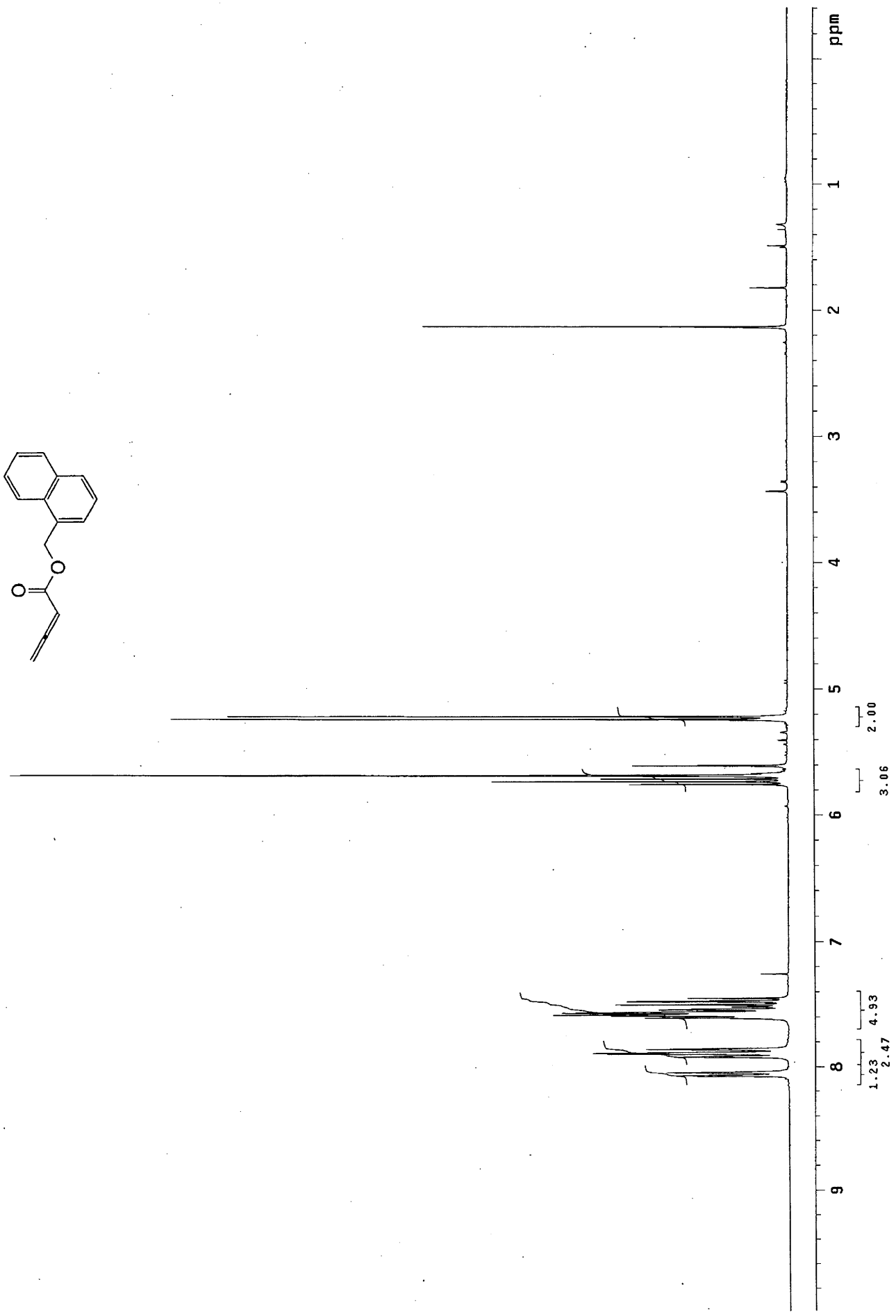
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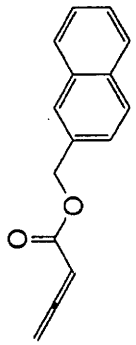

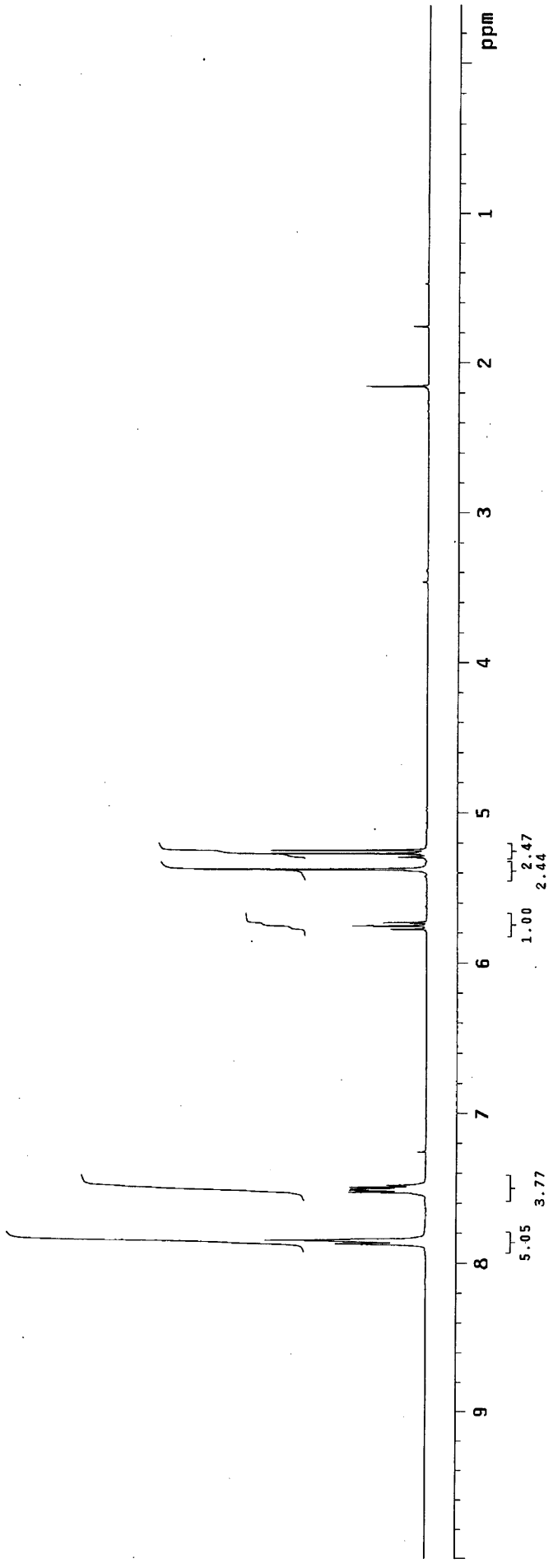
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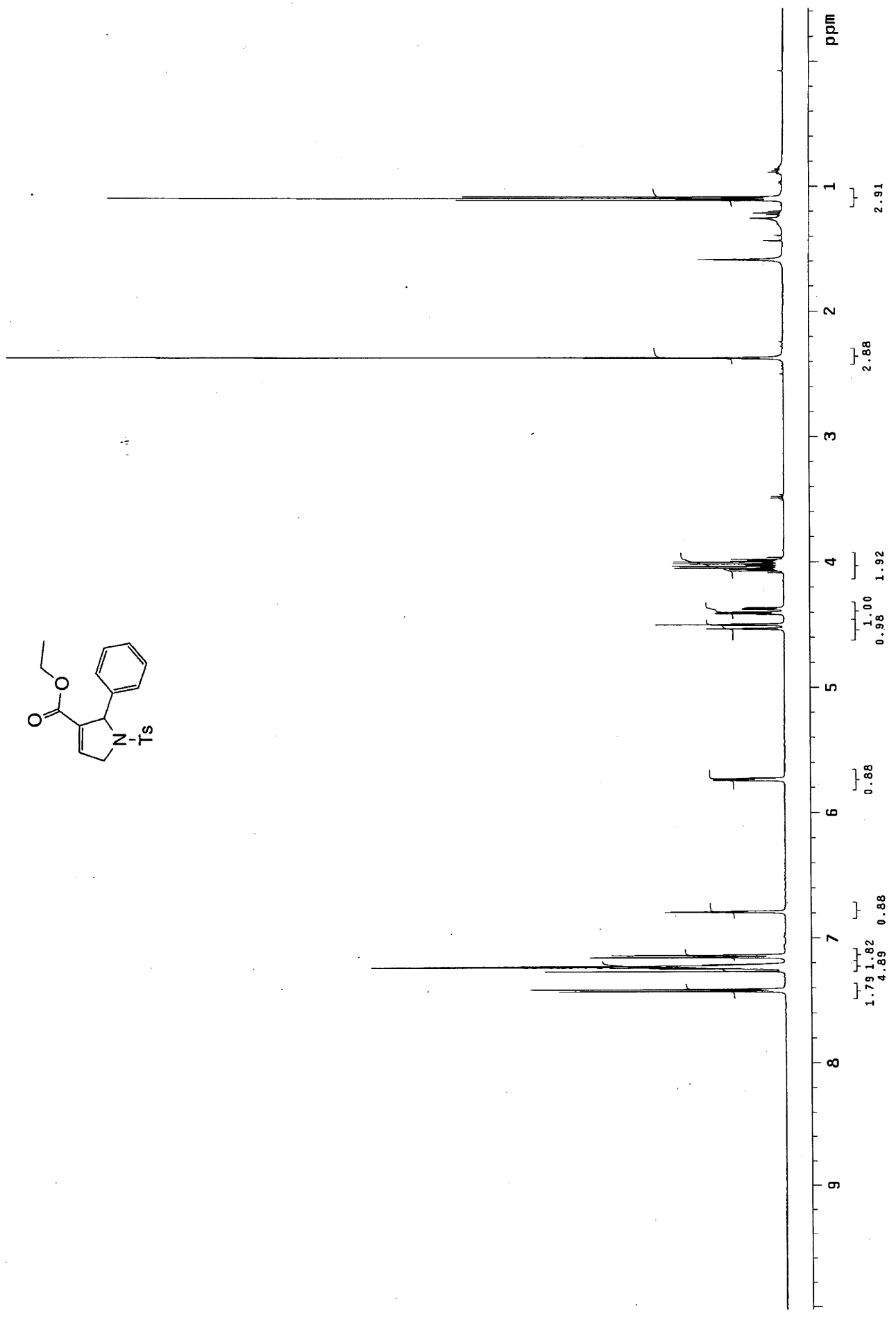
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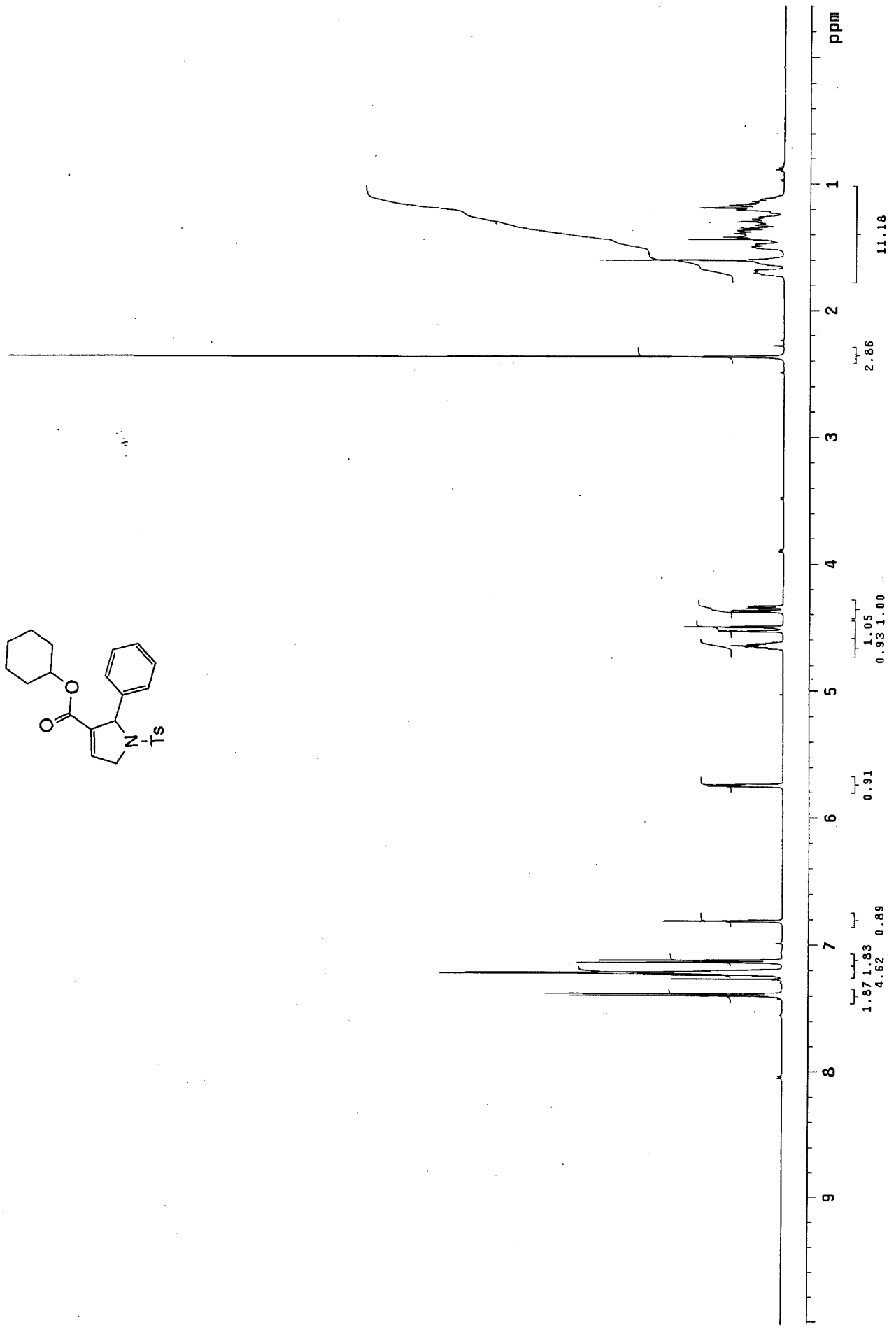
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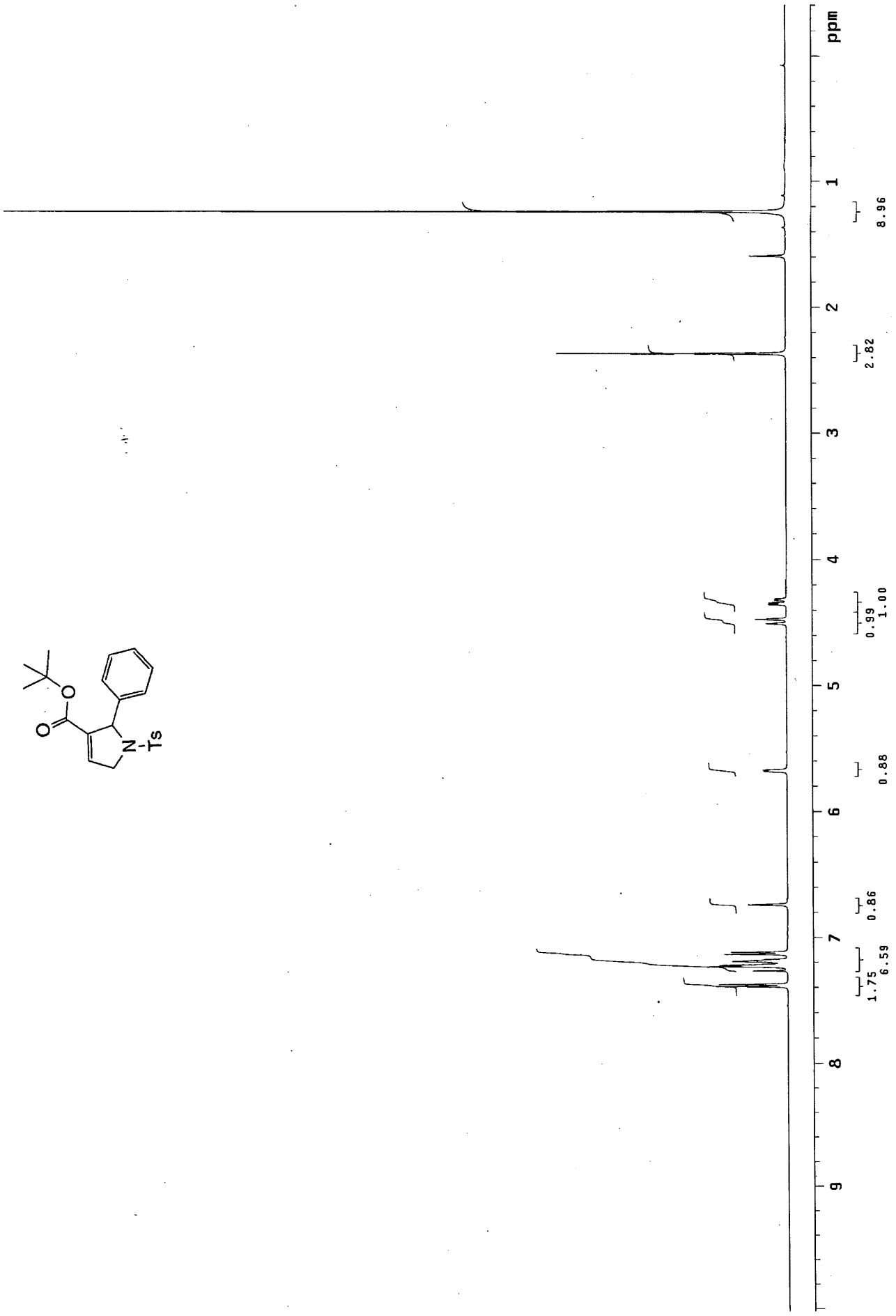
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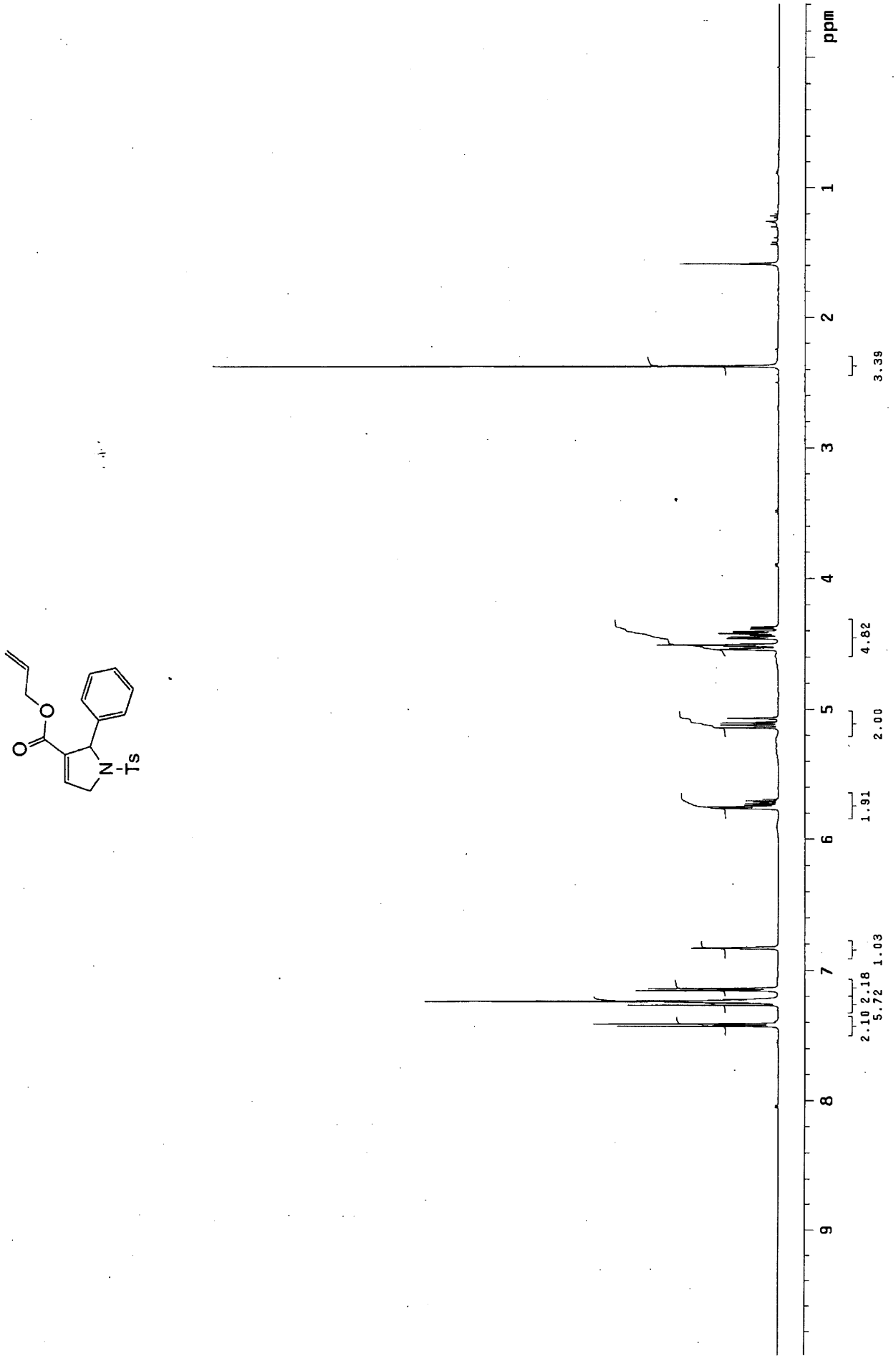
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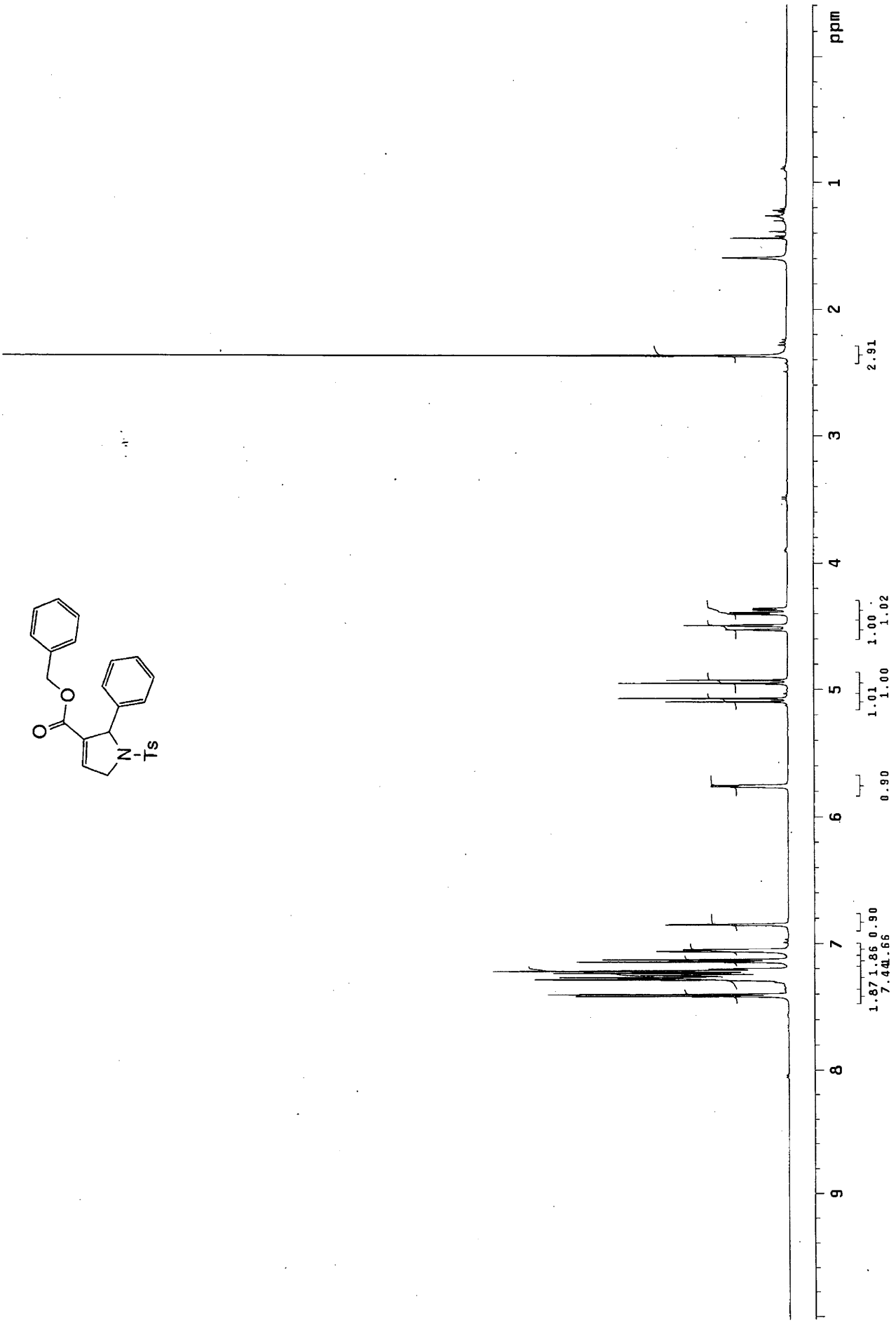
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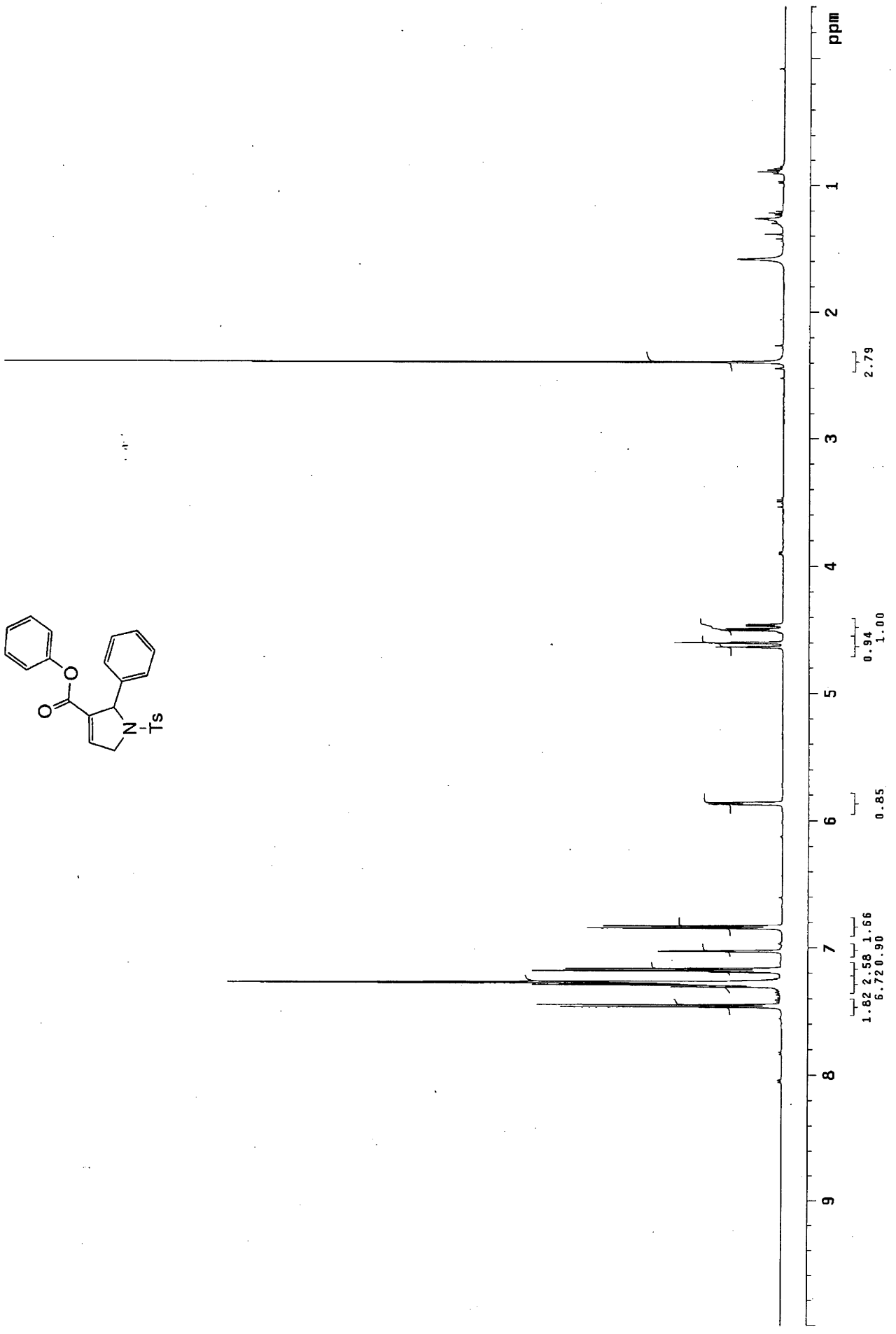
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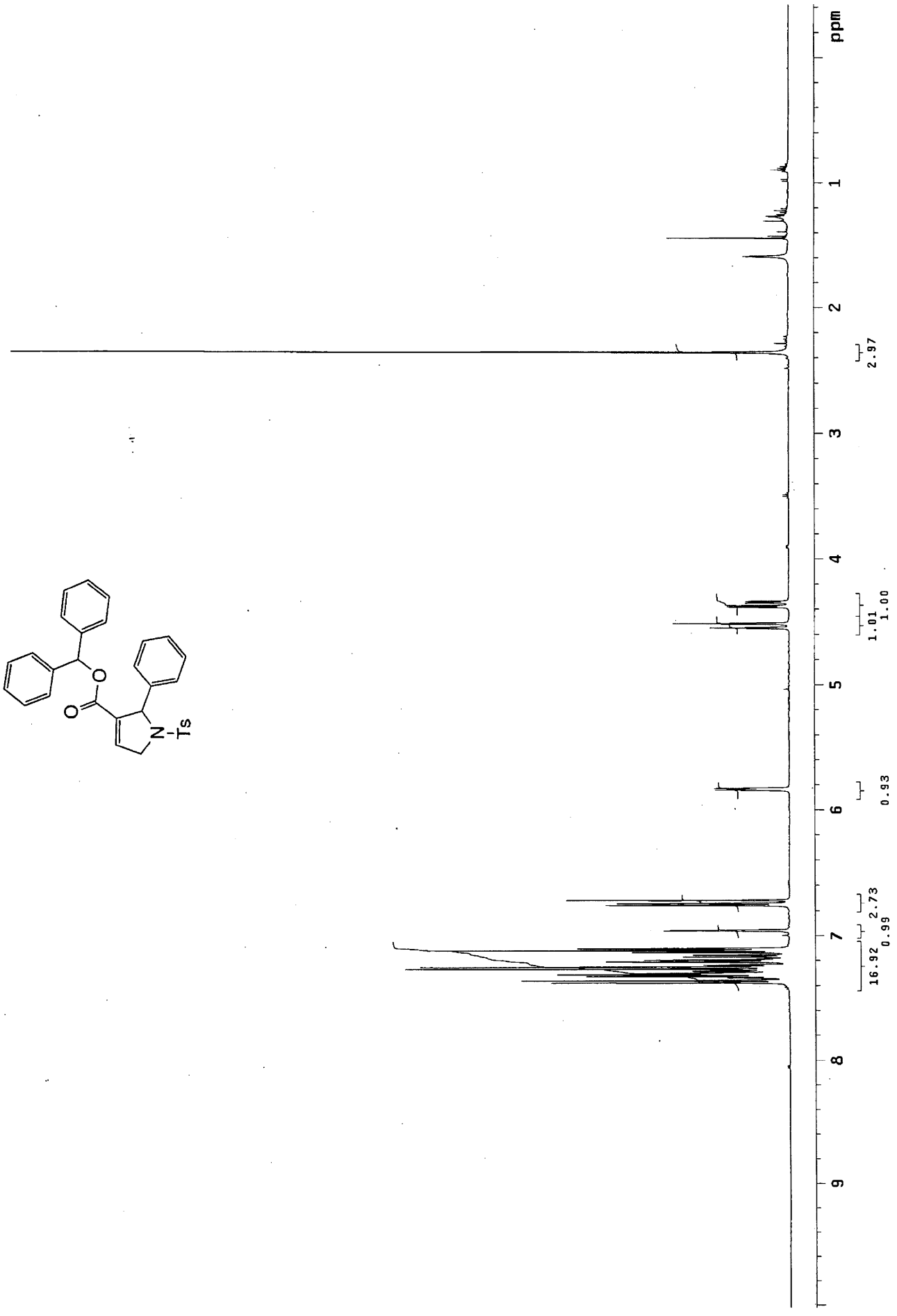
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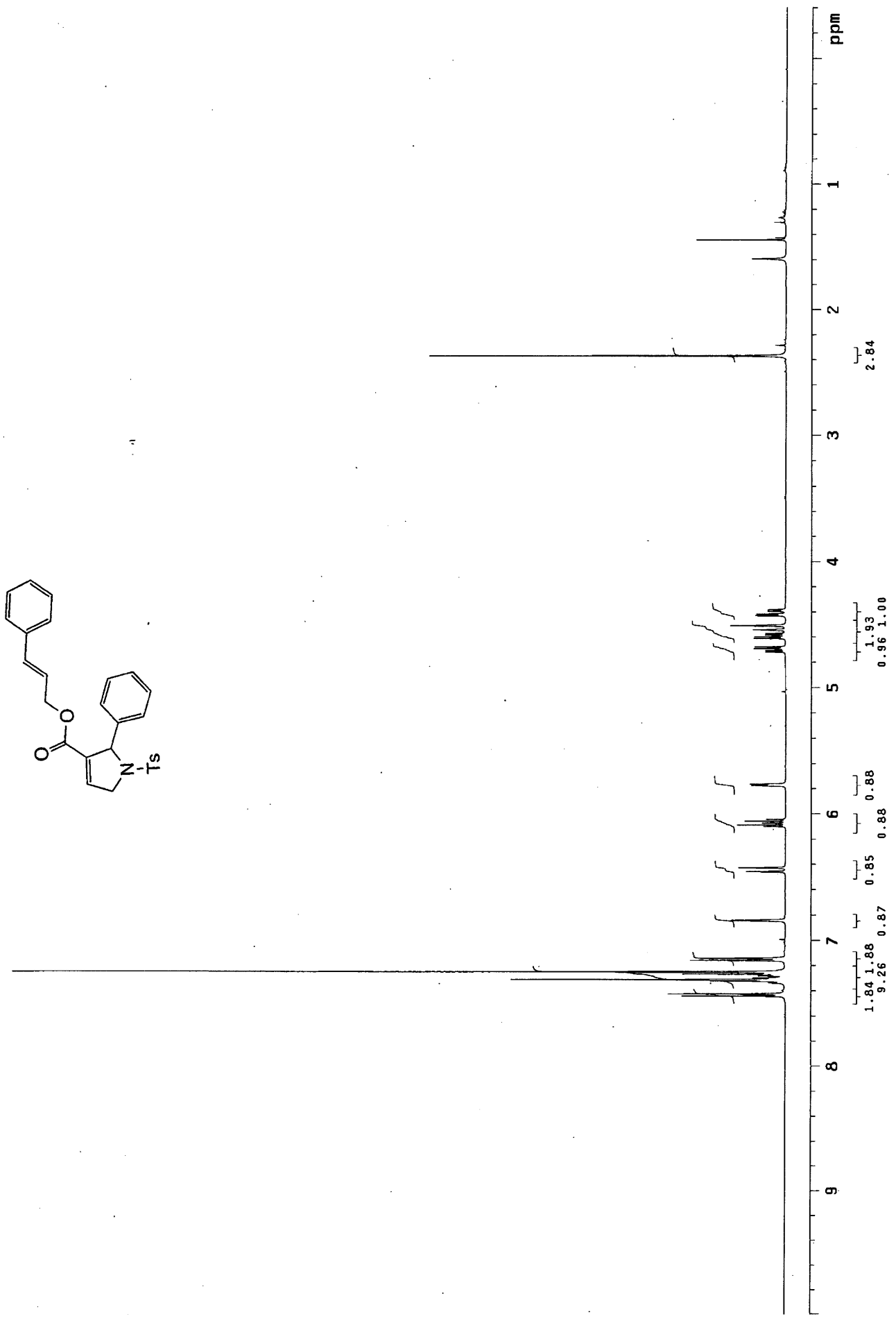
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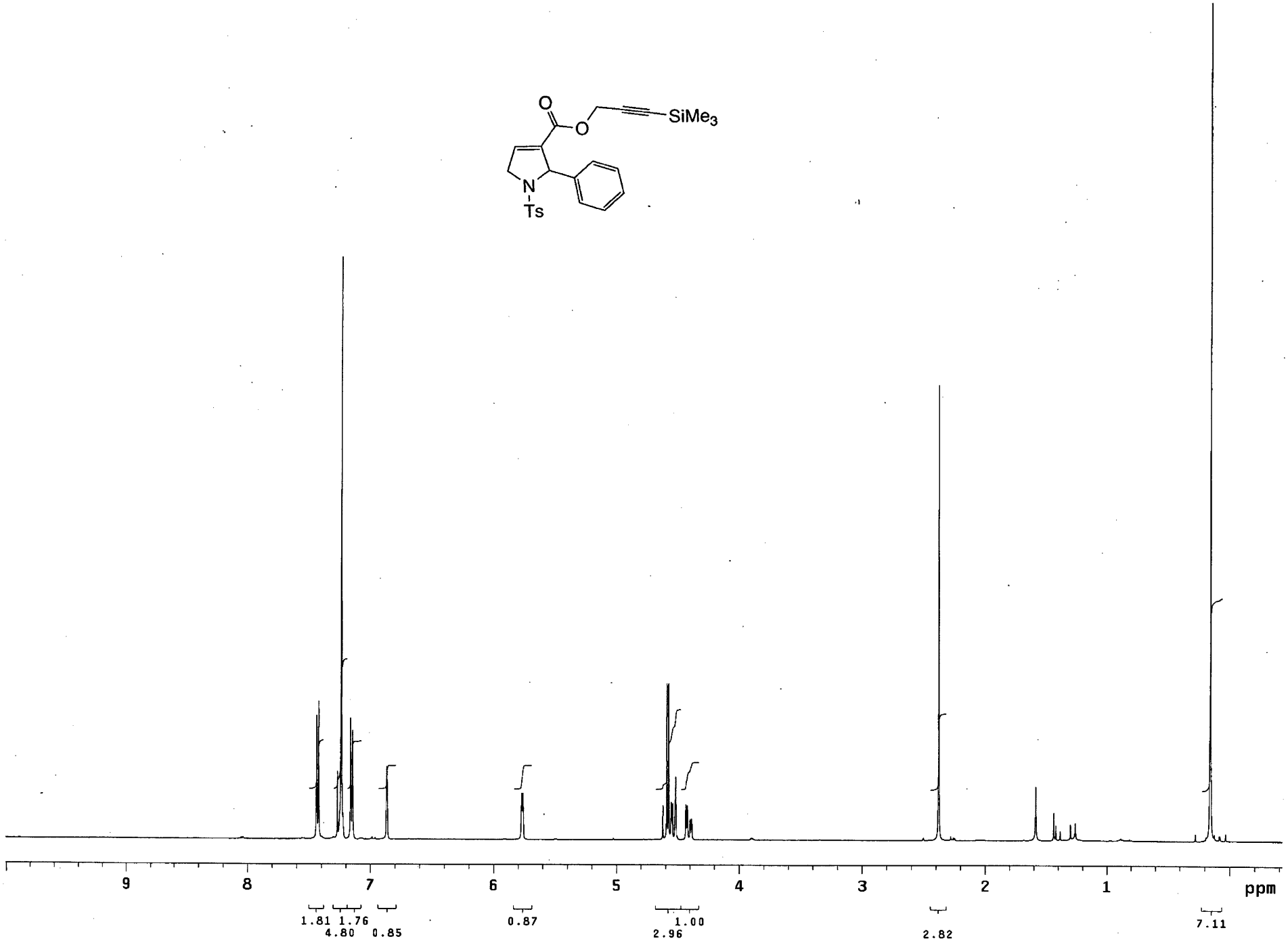
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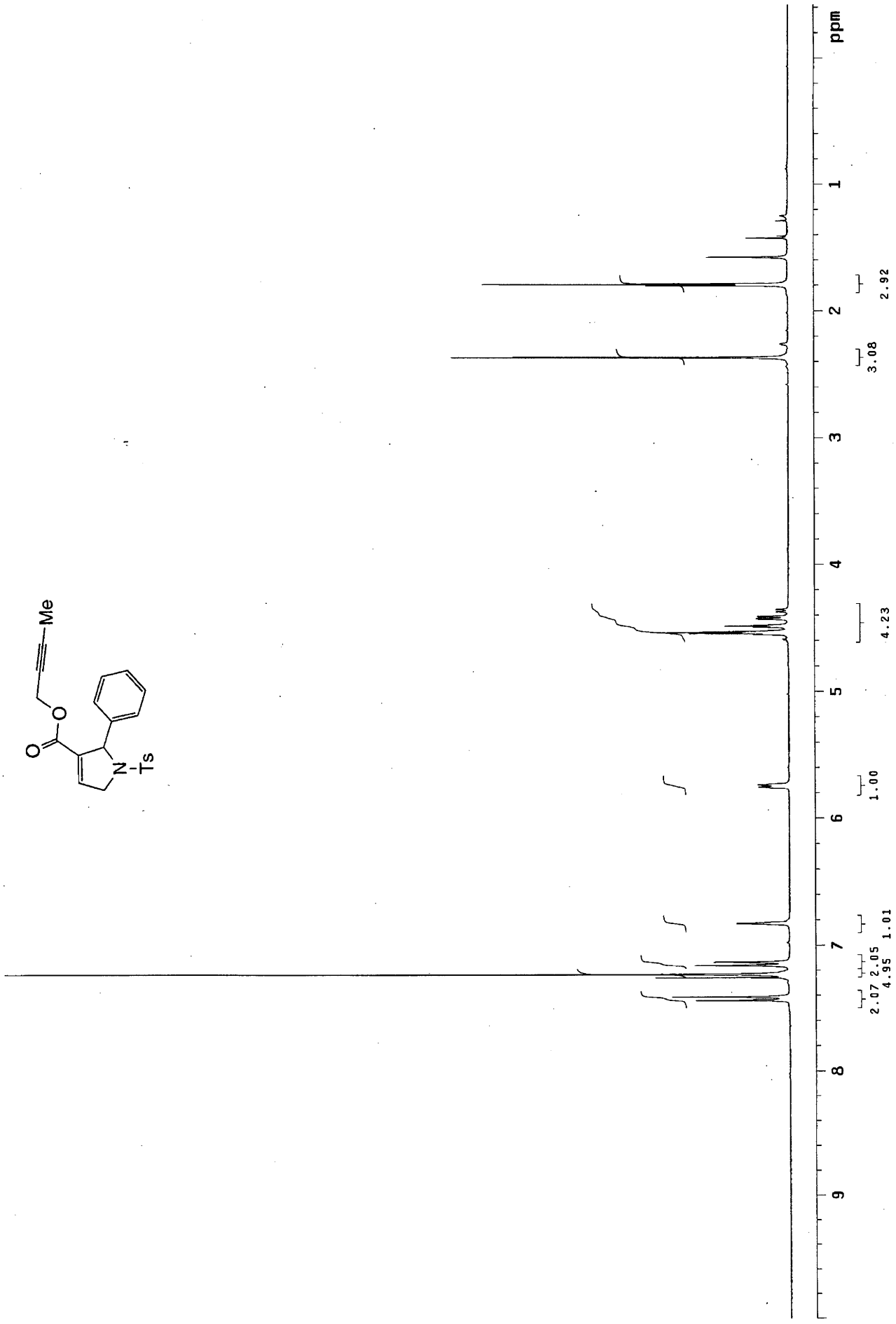
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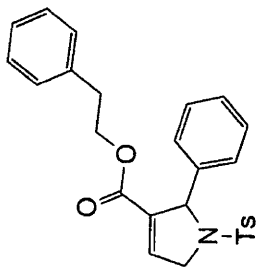
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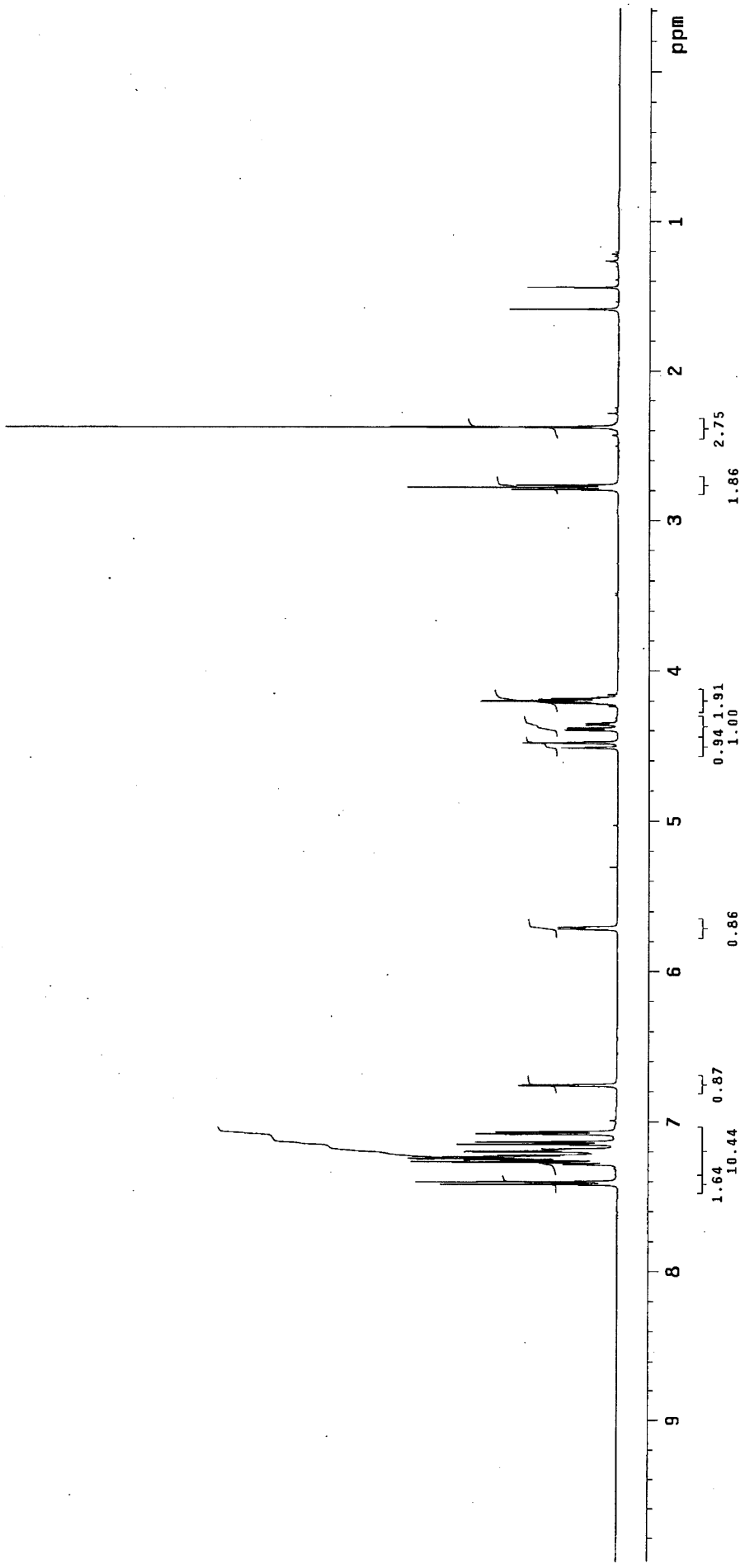
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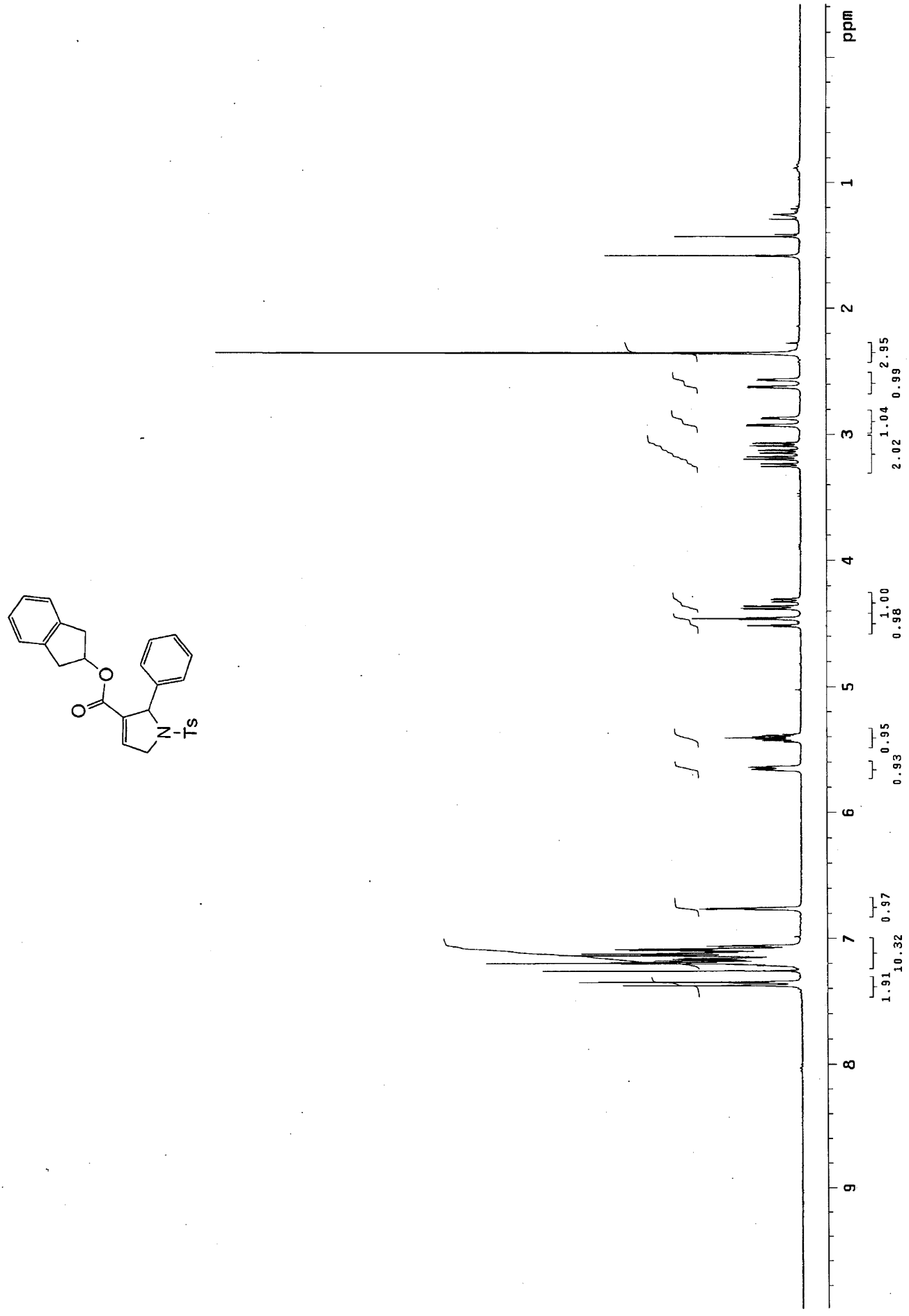
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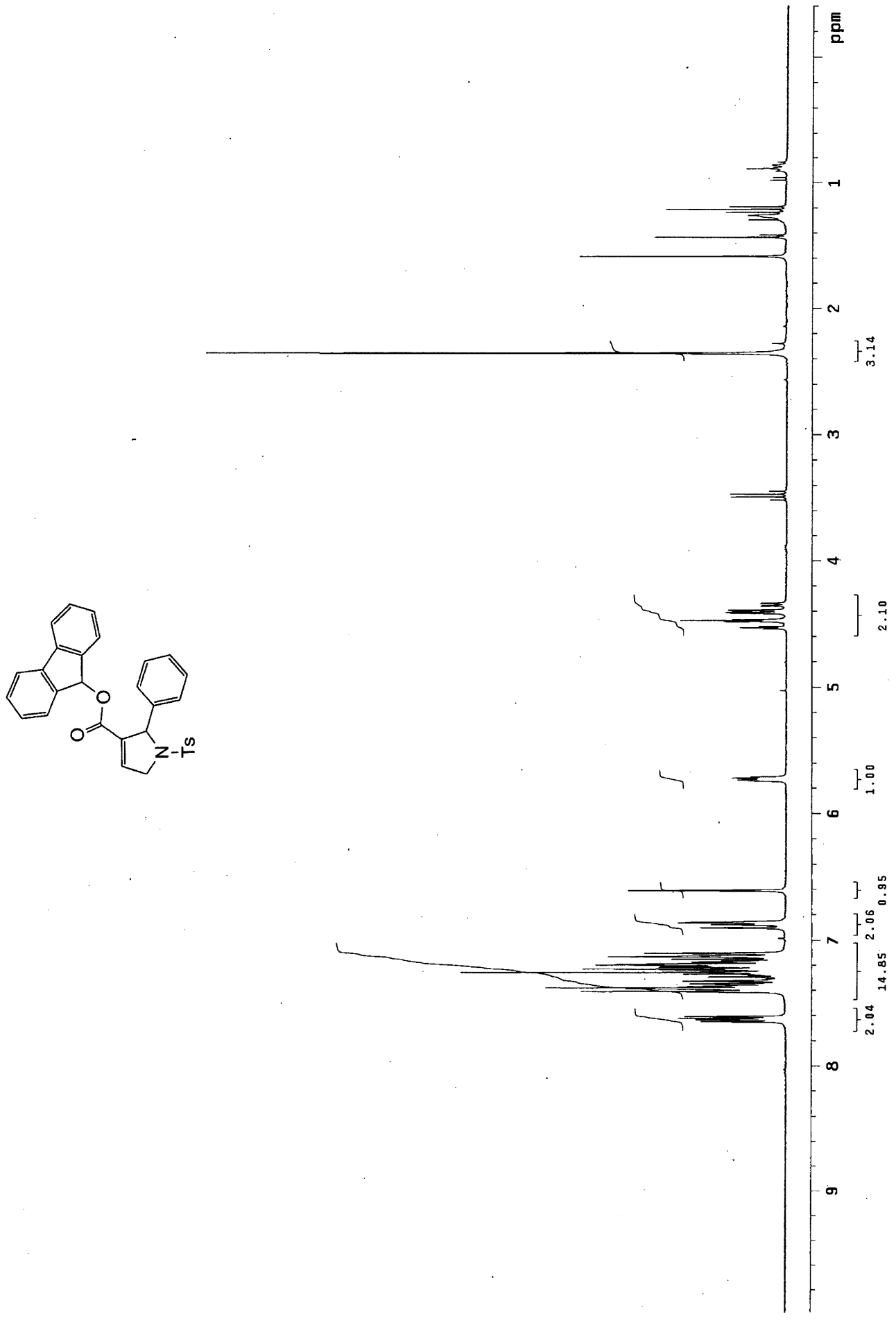
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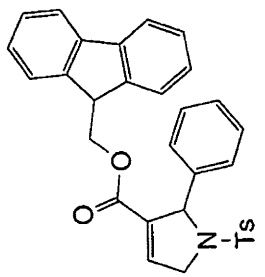
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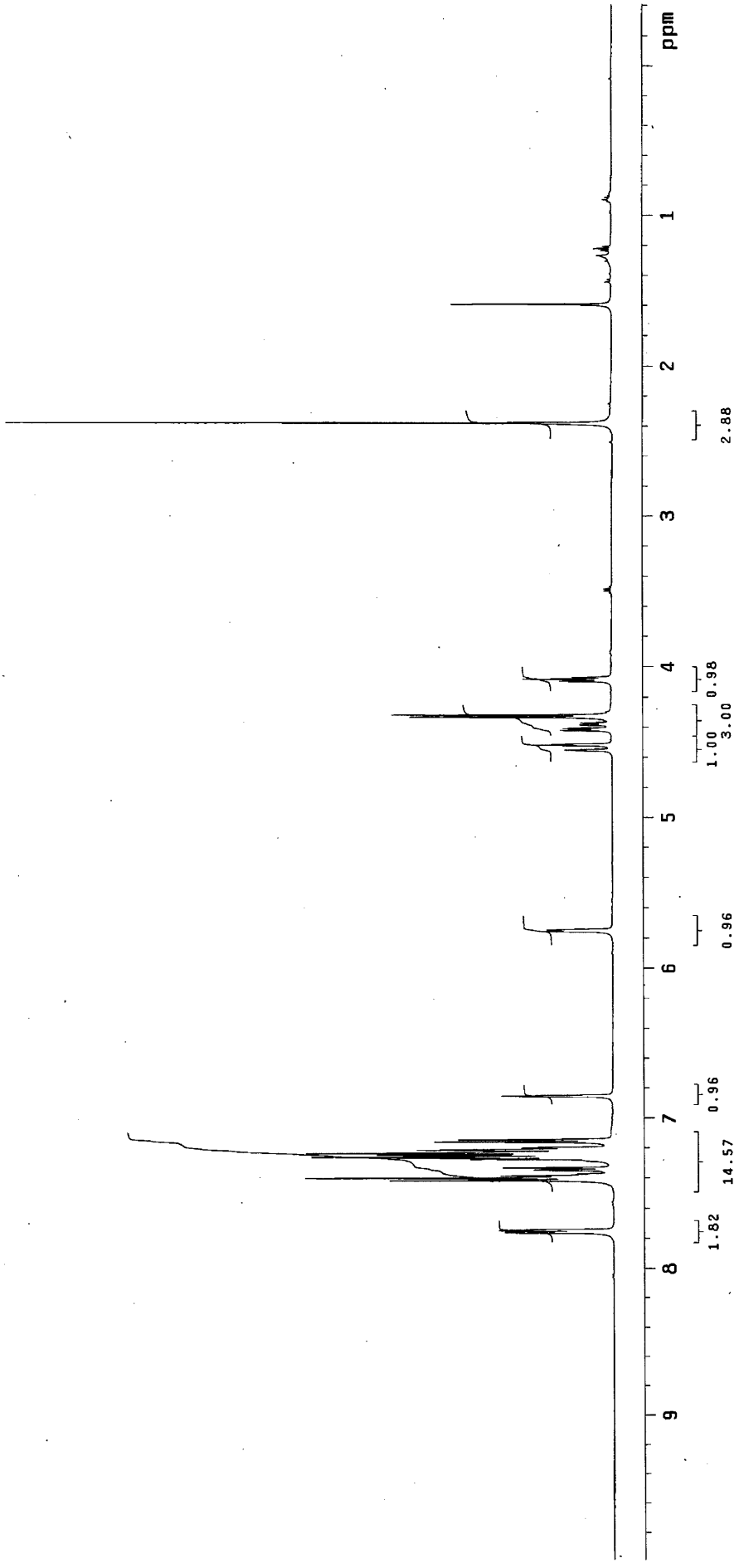
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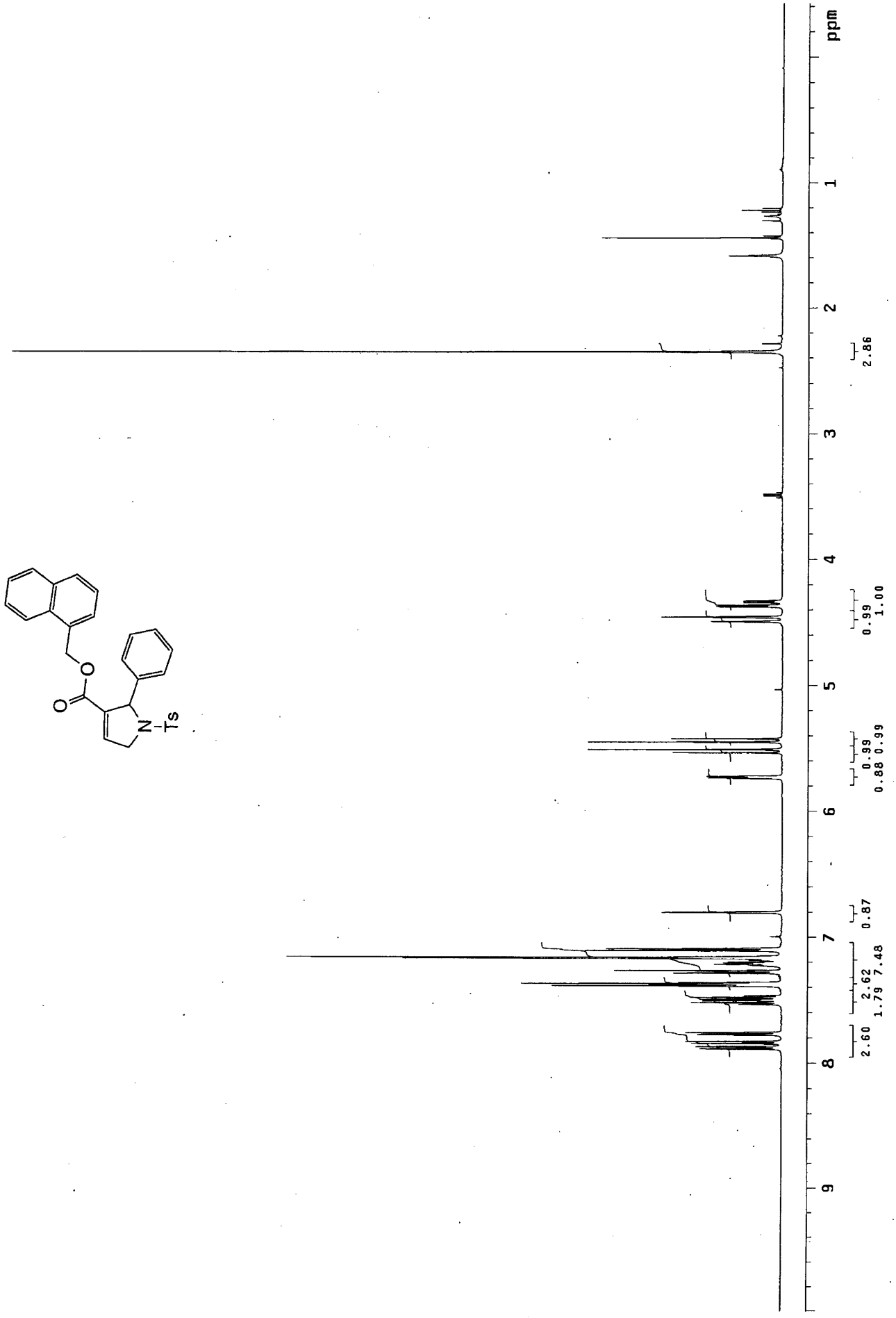
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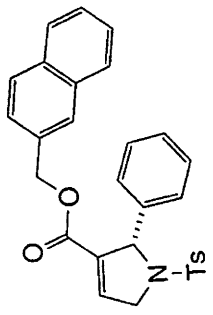
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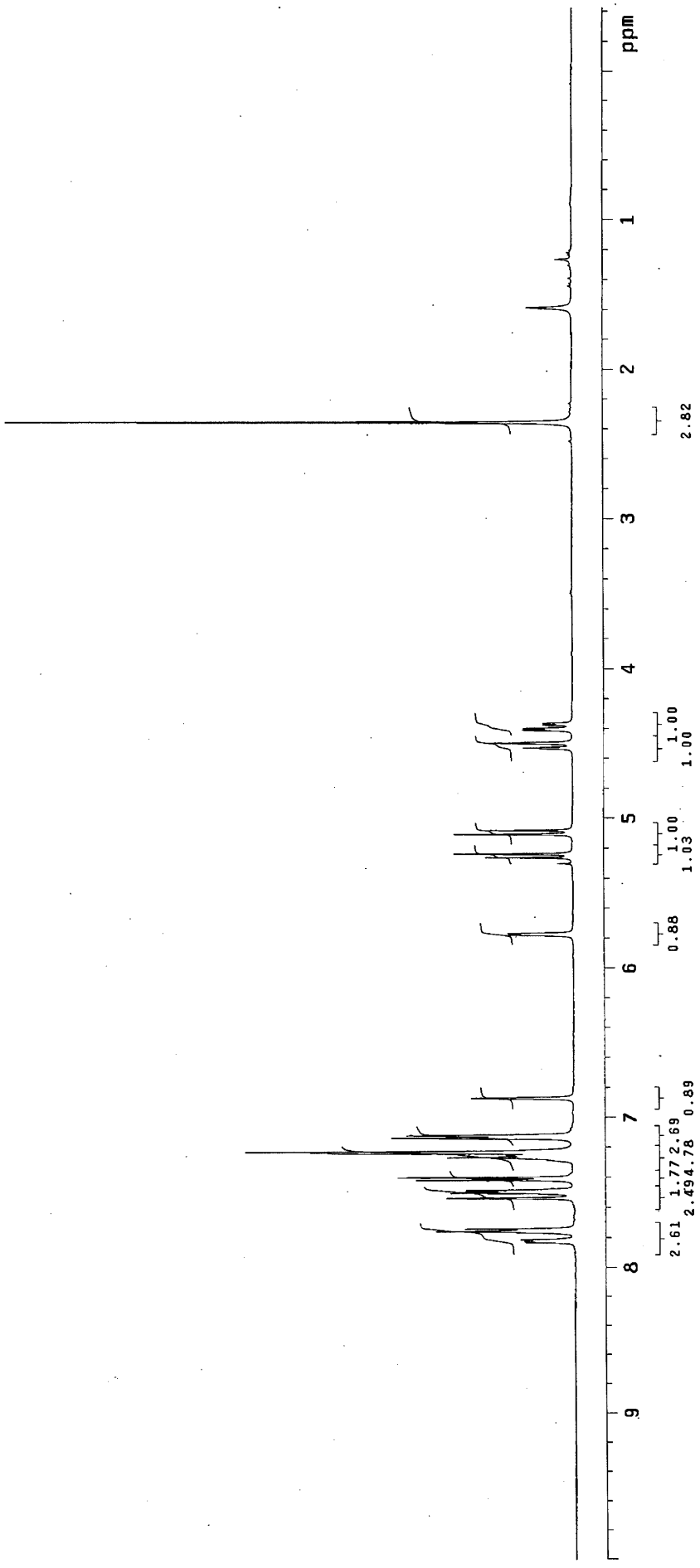
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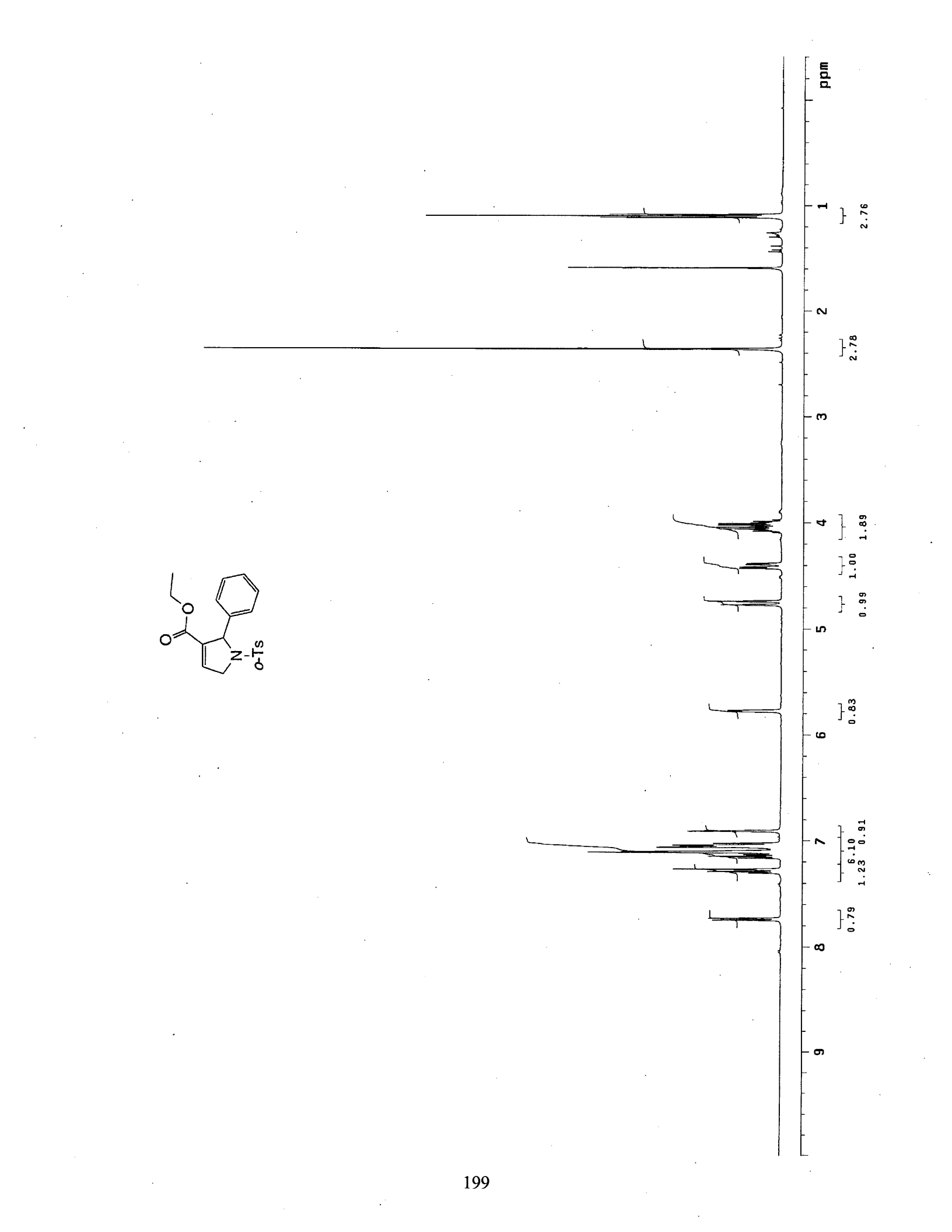
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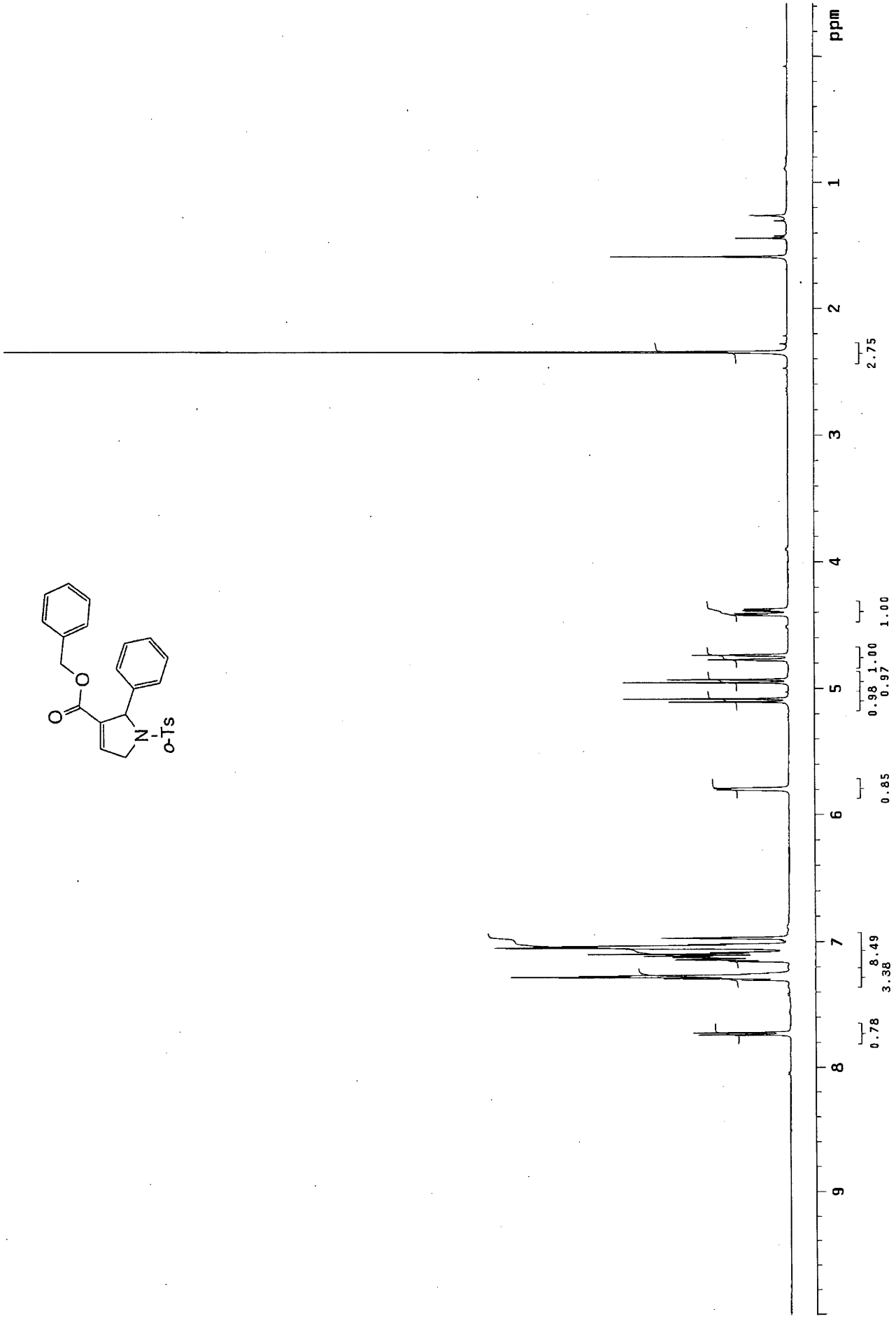
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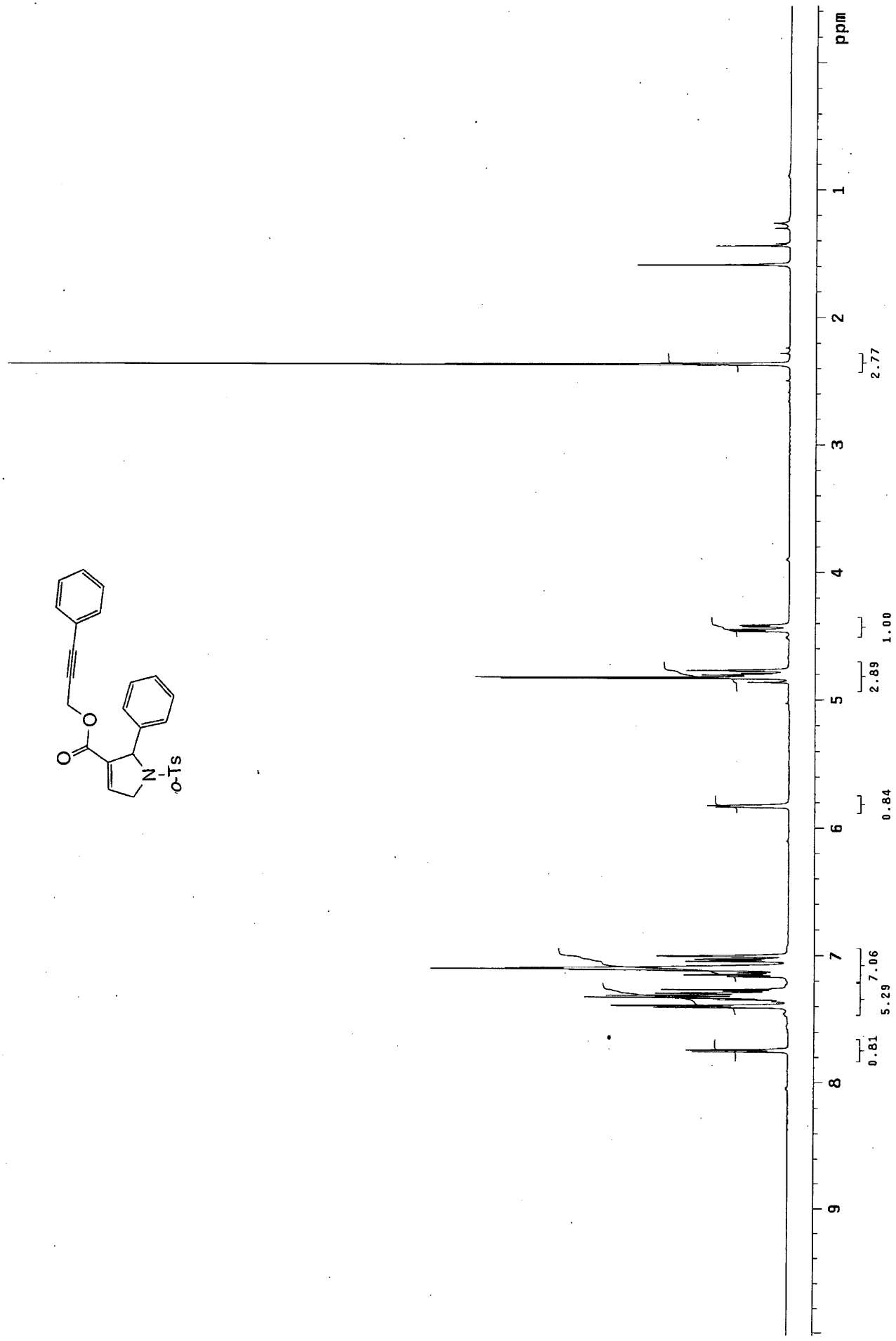
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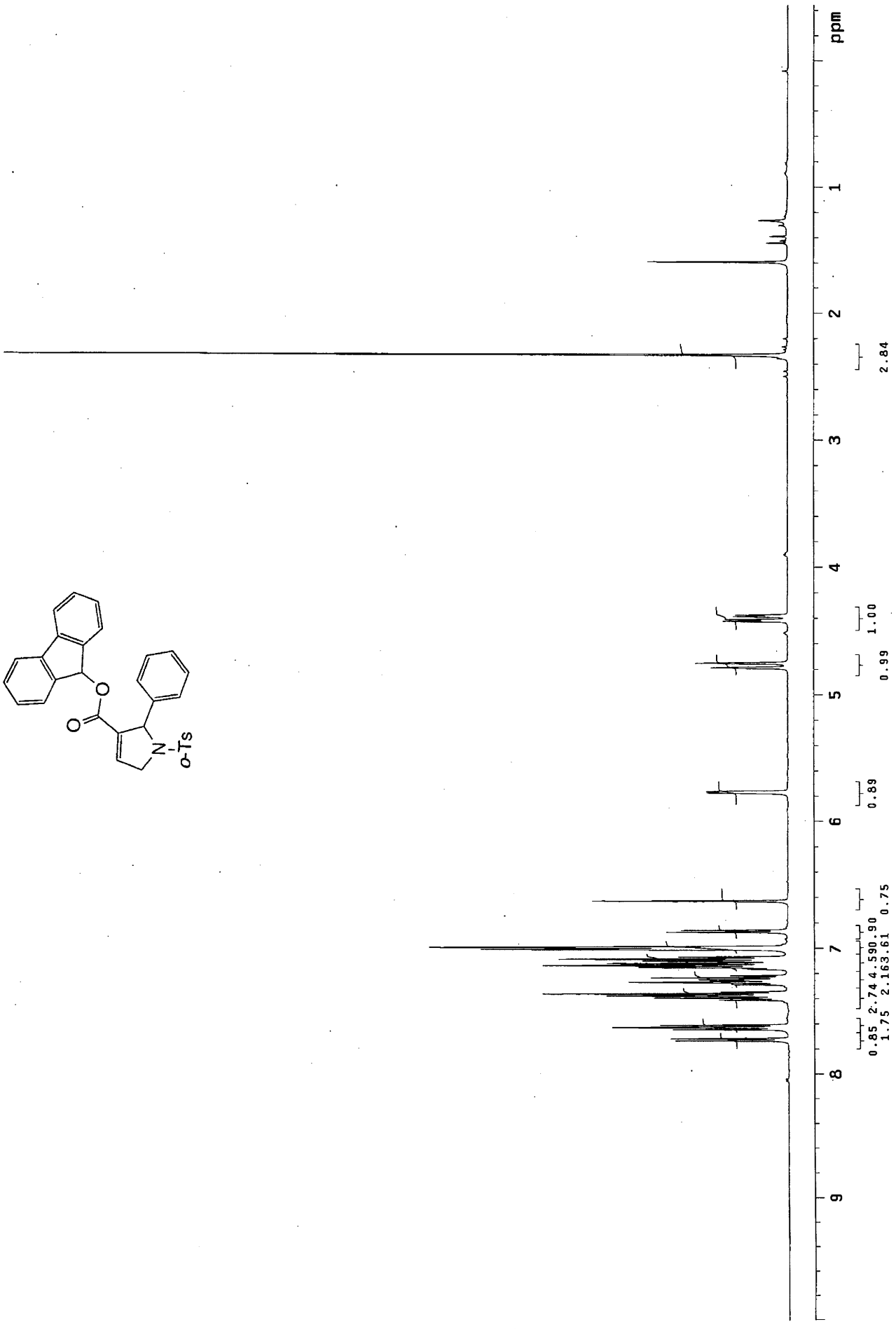
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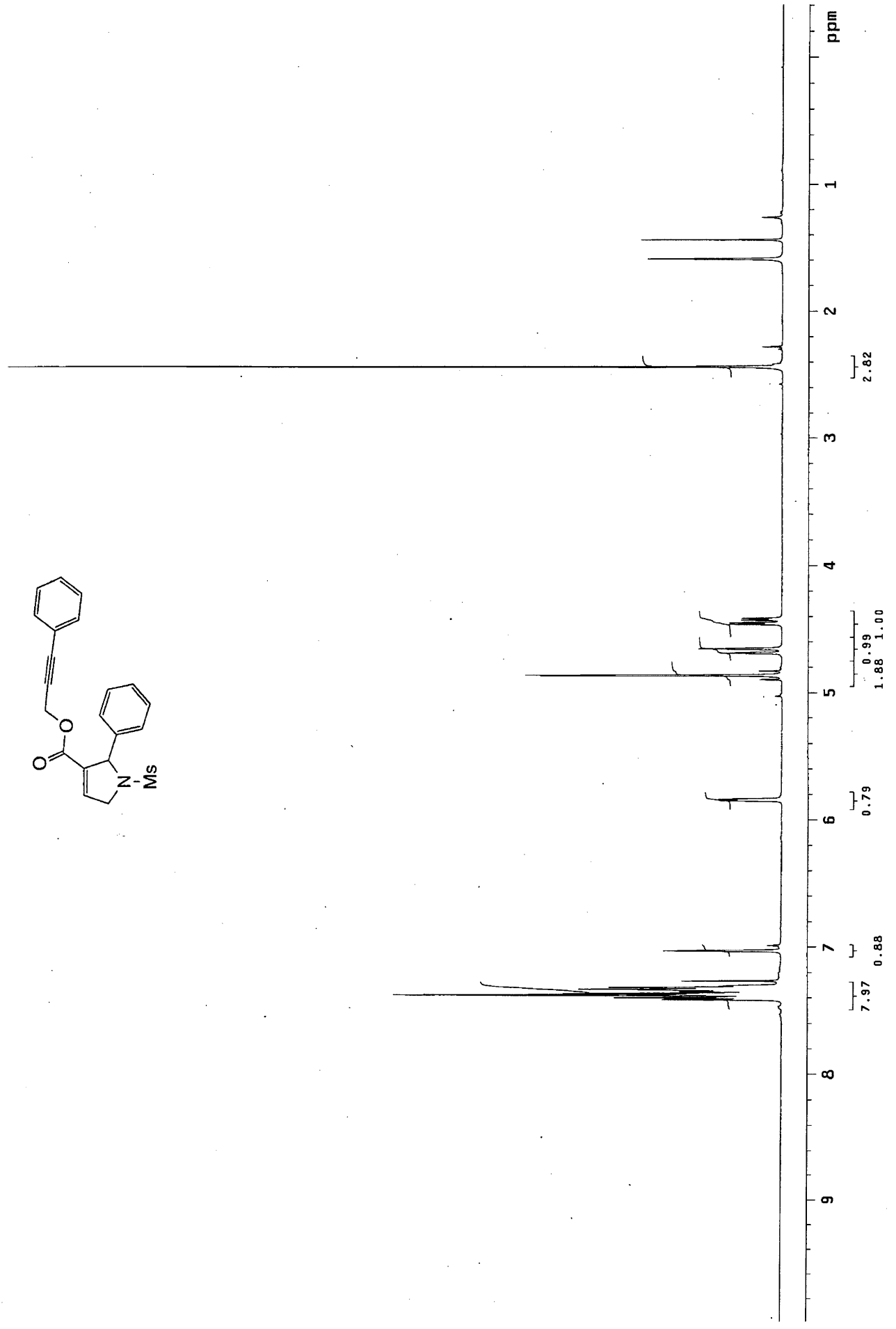
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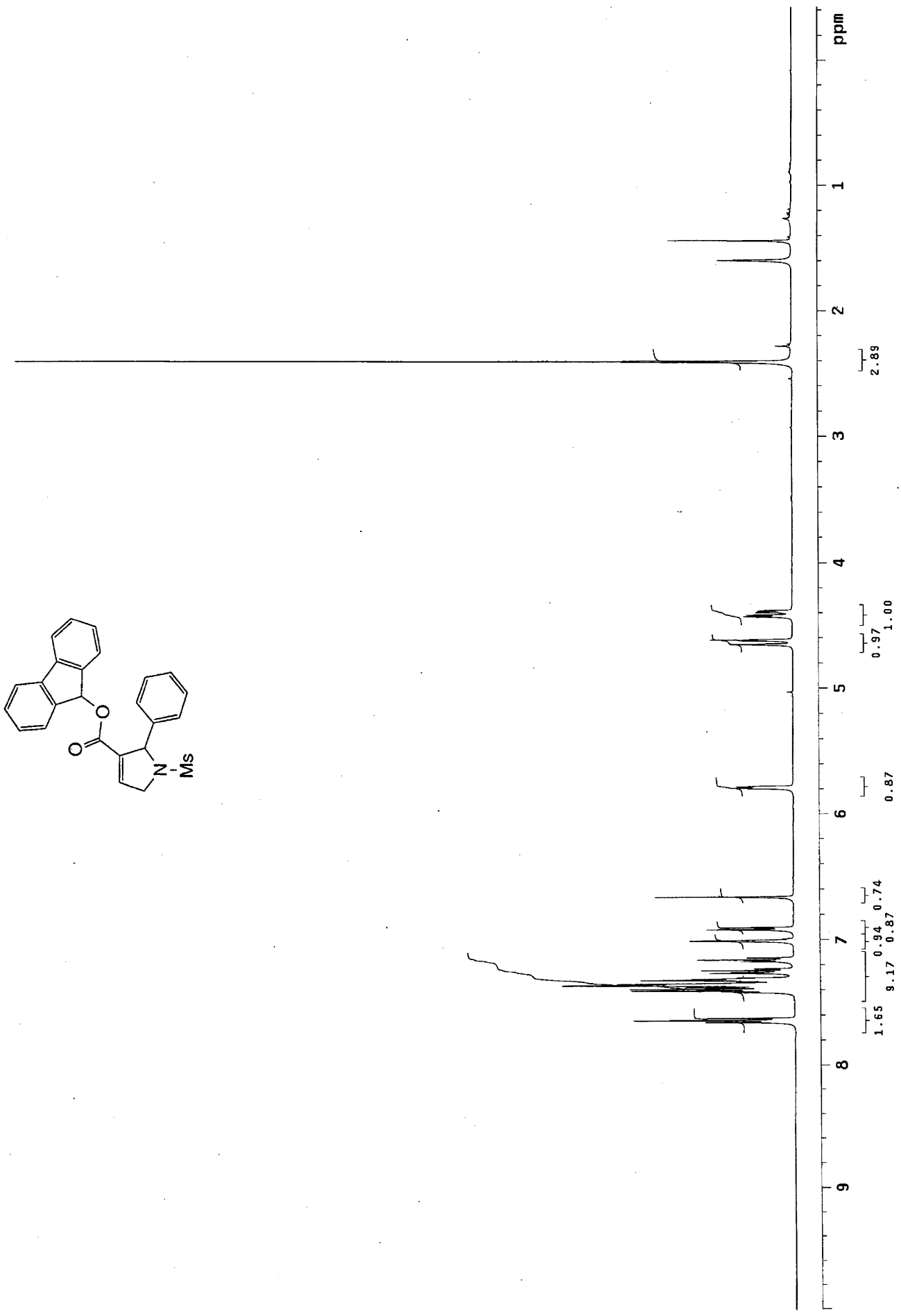
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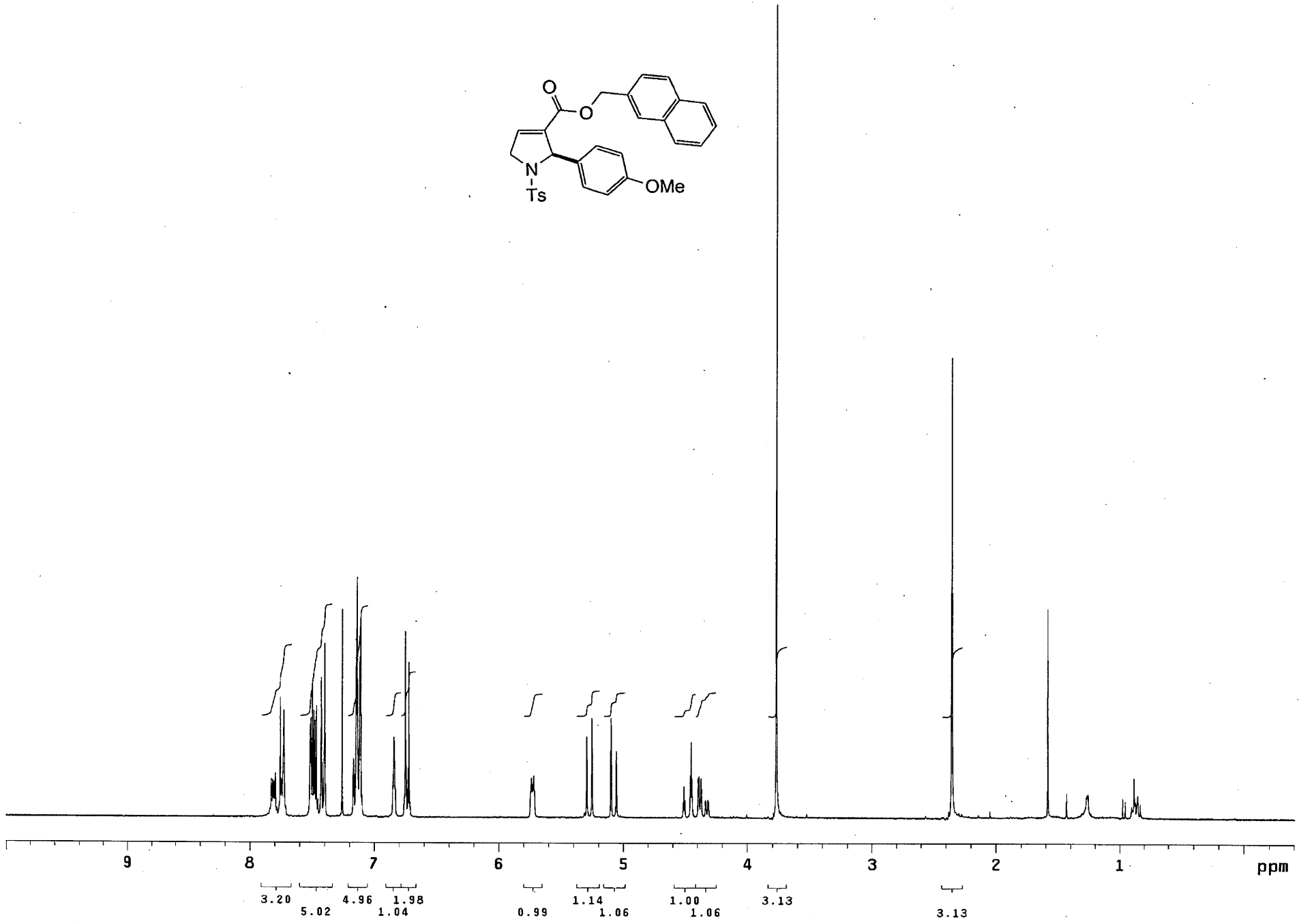
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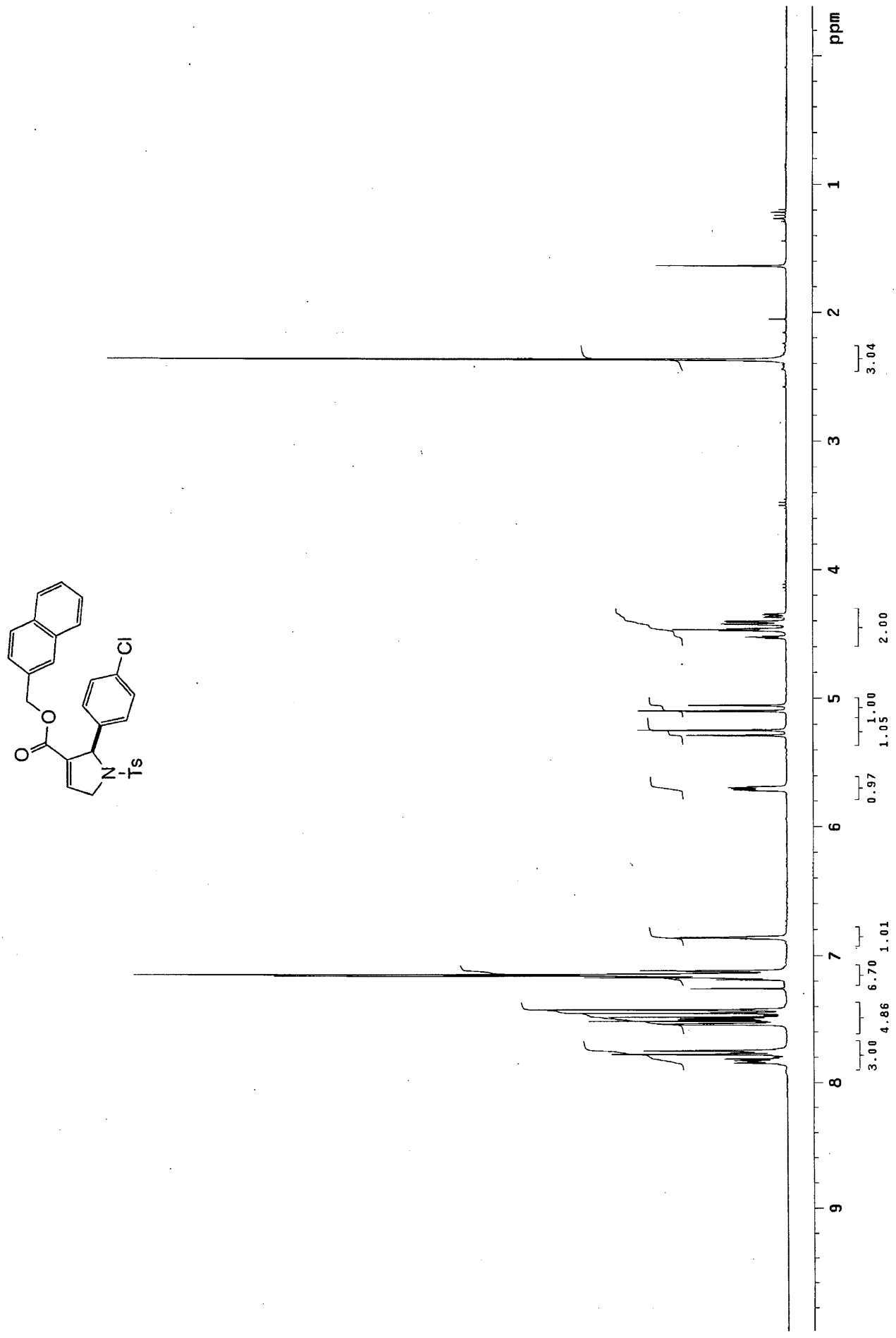
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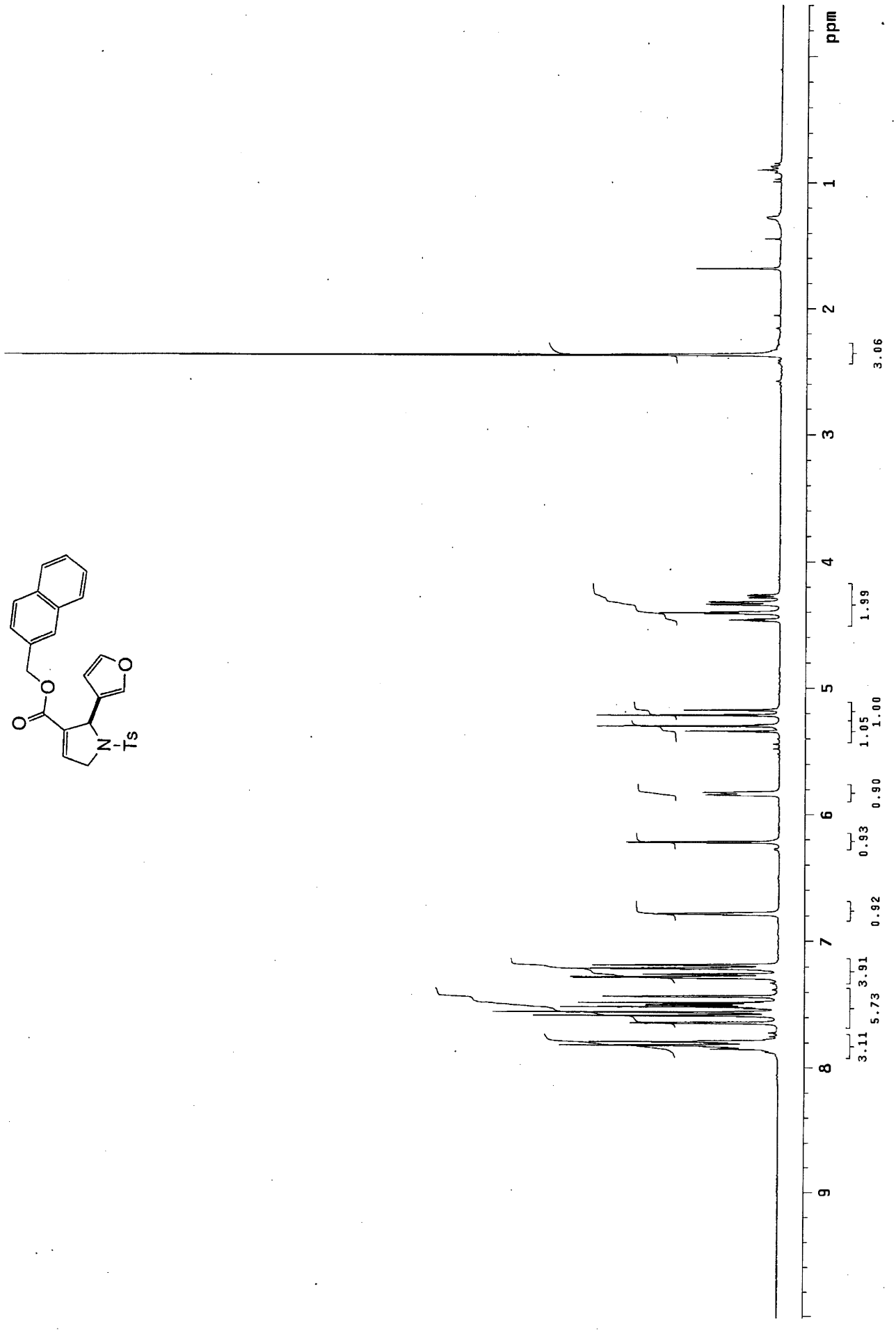
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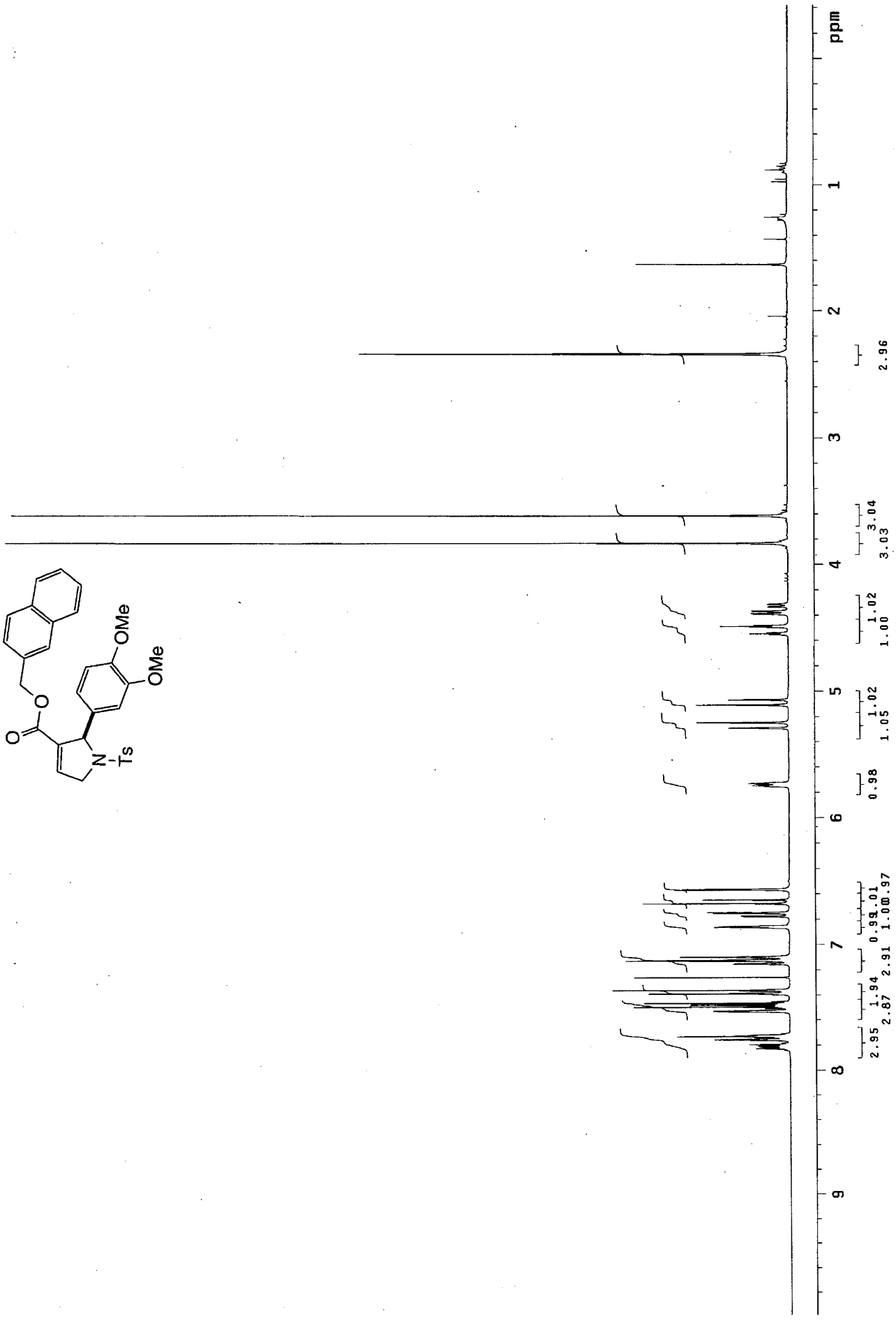
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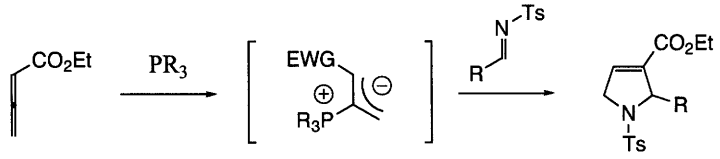
Chapter 3

Phosphine-Catalyzed Synthesis of Bicyclo[3.3.0]octanones and Bicyclo[4.3.0]nonanones from Ynone-Enoates

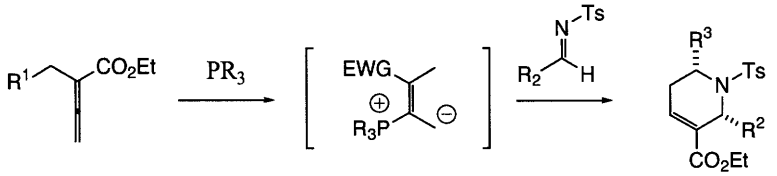
A. Introduction.

Cycloadditions allow for the construction of cyclic compounds containing multiple stereogenic elements in a single step. This characteristic has rendered these reactions powerful tools for the synthesis of complex natural products and pharmaceuticals. Although considerable effort has been devoted to the study of pericyclic reactions over the years, this family of processes continues to inspire and fascinate researchers resulting in creative and valuable chemical transformations.[1]

More than 60 years ago, Lewis acids were found to be efficient catalysts for many types of cycloadditions. Since this time, much effort has been devoted to the development of Lewis acid-catalyzed cycloadditions, and these reactions have seen broad application in synthesis.[2] More recently, our group and others have reported methods that employ nucleophiles, more precisely, amines and phosphines, as catalysts for cycloadditions.[3] In contrast to Lewis acid-catalyzed cycloadditions, which generally rely on electrophile activation, tertiary amines and phosphines catalyze cycloadditions by activation of a latent nucleophile, usually an electron deficient alkene or alkyne. The activated alkene or alkyne usually takes the form of a zwitterionic enolate/ylide.[4] Examples of this include phosphine-catalyzed [3+2] and [4+2] cycloadditions of allenoates with imines (eq 3.1 and eq 3.2).[5, 6]

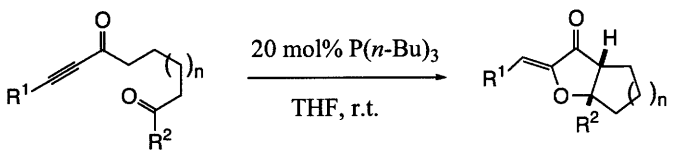


(3.1)



(3.2)

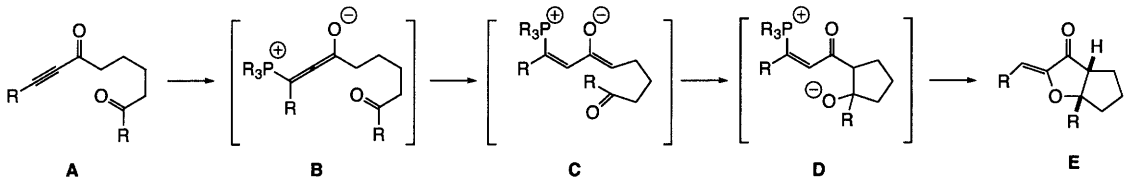
Recently, Tomita reported a novel phosphine-catalyzed intramolecular annulation reaction for the synthesis of bicyclic furanones (eq 3.3).[7]



R^1 = Ph, *n*-Bu
R^2 = *n*-Bu-CC, Ph-CC, Me, H
n = 1, 2
41-73% yield (3.3)

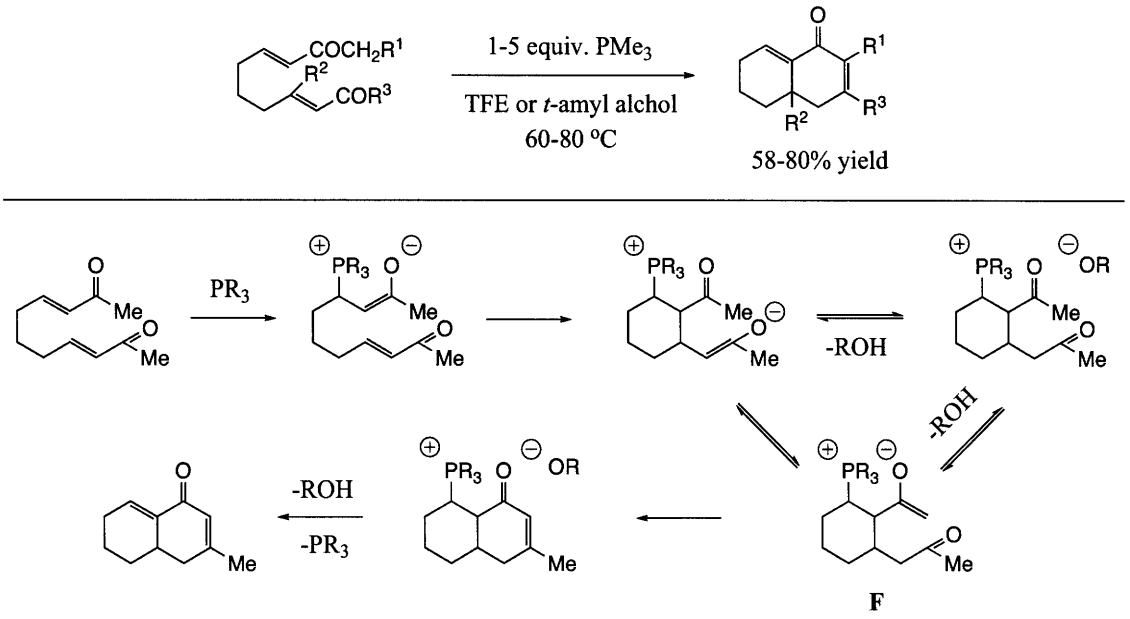
Tomita proposes that the reaction proceeds through a conjugated phosphonium stabilized enolate **C**, which is thought to arise from tautomerization of allenoate **B**. Aldol cyclization provides **D**, which undergoes C-O bond formation by alkoxide addition to the vinyl phosphonium moiety. Subsequent proton transfer and elimination of the phosphine provides the furanone **E** (Scheme 3.1).

Scheme 3.1. Proposed Mechanism of Tomita's Phosphine-Catalyzed Ynone-Carbonyl Annulation.

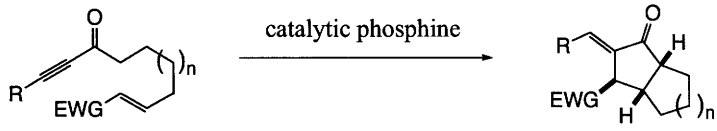


While Tomita's reaction is the only study, to the best of our knowledge, that makes use of a conjugated zwitterionic enolate such as **C**, other related phosphine-mediated annulation reactions that implicate similar intermediates have been reported.[8] Roush has evidence that a phosphonium-stabilized enolate is responsible for the high levels of regioselectivty observed in his phosphine-mediated tandem Rauhut-Currier/aldol reaction. His proposed mechanism invokes enolate **F**, which is a saturated analog of Tomita's posited intermediate **C**.[9]

Scheme 3.2. Roush's Phosphine-Mediated Tandem Rauhut-Currier/Aldol Reaction.



We became interested in the prospect of developing a reaction analogous to Tomita's involving the cyclization of an ynone moiety with a Michael acceptor. This type of reaction would provide access to [3.3.0] and [4.3.0] bicyclic systems, which are prevalent substructures of numerous natural products (eq 3.4).

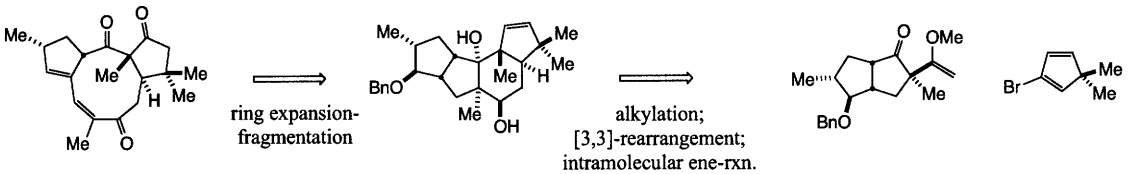


(3.4)

Moreover, the products of the proposed reaction, bicyclo[3.3.0]octan-2-ones, have been employed as intermediates for the synthesis of structurally complex natural products. The versatility of these compounds is exemplified by the imaginative synthesis outlined below.

In Paquette's jatrophatrione synthesis, a bicyclo[3.3.0]octan-2-one dictates the stereochemical course of a cascade reaction leading to a complex tetracyclic-1,3-diol that is subsequently converted to the [5.9.5] tricyclic core of Jatrophatrione via a ring-expanding fragmentation process.[10]

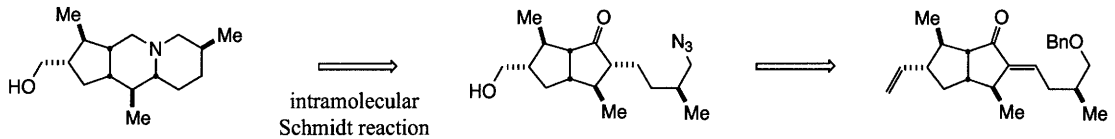
Scheme 3.3. Paquette's Use of a Bicyclo[3.3.0]octanone in a Synthesis of Jatrophatrione.



Jatrophatrione
diterpenoid tumor-inhibition agent

Aube employs a bicyclo[3.3.0]octan-2-one in his elegant synthesis of indolizidine 251F. The bicyclic ketone is used here as a substrate for a ring-expanding Schmidt rearrangement that establishes the alkaloid's tricyclic core.[11]

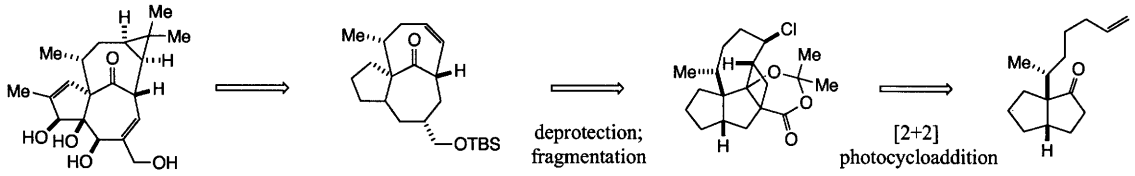
Scheme 3.4. Aube's Use of a Bicyclo[3.3.0]octanone in a Synthesis of Indolizidine 251F.



Indolizidine 251F
alkaloid from the dendrobates bombetes species of frog

A third instance of the utility of bicyclo[3.3.0]octan-2-ones is demonstrated in Winkler's synthesis of ingenol. Again, the bicycle serves as a substrate for a ring-expanding fragmentation that provides the "inside-outside" ingenane carbon skeleton.[12]

Scheme 3.5. Winkler's Use of a Bicyclo[3.3.0]octanone in a Synthesis of Ingenol.



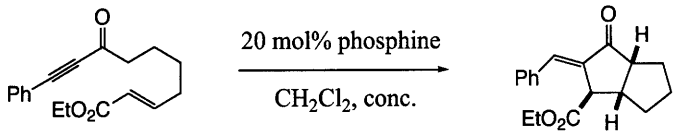
Ingenol
anti-leukemic and
anti-HIV agent

It is apparent from the preceeding examples that the development of a general method for the preparation of bicyclo[3.3.0]octan-2-ones would be a worthy undertaking. Even more useful would be the development of a catalytic asymmetric variant of this process. The following chapter describes the development of the process outlined in equation 3.4.

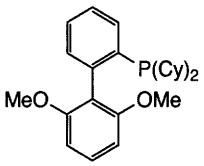
B. Results and Discussion.

Our investigation commenced by examining the phosphine-catalyzed cyclization of substrate **3.1**. Tomita's conditions for intramolecular ynone-carbonyl cyclizations, 20 mol% P(*n*-Bu)$_3$ in THF (0.5 M), provide only small quantities of the bicyclo[3.3.0]octanone (Table 3.1, Entry 1).[7] However, the replacement of THF with CH_2Cl_2 led to a dramatic increase in yield.[13] More dilute conditions further improve the efficiency of the cyclization, presumably due to the suppression of undesired intermolecular processes (Table 3.1, Entries 2-6). Other phosphines catalyzed the process, but less efficiently than P(*n*-Bu)$_3$. Trialkylphosphines smaller than P(*n*-Bu)$_3$ lead to more oligomerization (Table 3.1, Entries 7-9). Trialkylphosphines larger than P(*n*-Bu)$_3$ either fail to catalyze the cyclization or do so very slowly (Table 3.1, Entries 10-14). A variety of triarylphosphines failed to catalyze the cyclization (Table 3.1, Entries 16-19).

Table 3.1. Reaction Optimization: Effects of Solvent and Phosphine.



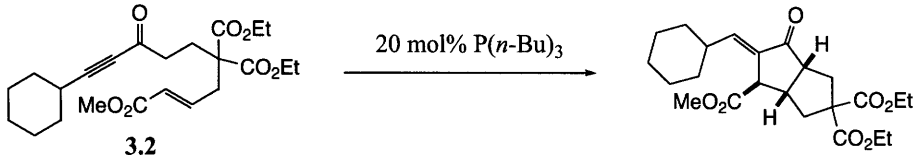
3.1

entry	phosphine	conc. [M]	product : oligomer : SM[b]
1[a]	P(*n*-Bu)$_3$	0.50	08 : 72 : 20
2	P(*n*-Bu)$_3$	0.10	64 : 36 : 00
3	P(*n*-Bu)$_3$	0.05	81 : 19 : 00
4	P(*n*-Bu)$_3$	0.03	86 : 14 : 00
5	P(*n*-Bu)$_3$	0.02	88 : 12 : 00
6	P(*n*-Bu)$_3$	0.01	91 : 09 : 00
7	PMe_3	0.01	51 : 49 : 00
8	PEt_3	0.01	64 : 36 : 00
9	P(*n*-propyl)$_3$	0.01	64 : 17 : 17
10	P(*i*-Bu)$_3$	0.01	36 : 41 : 23
11	P(*n*-hexyl)$_3$	0.01	15 : 42 : 43
12	P(benzyl)$_3$	0.01	traces : 00 : 95
13	P(cyclopentyl)$_3$	0.01	83 : 17 : 00
14	P(cyclohexyl)$_3$	0.01	46 : 22 : 32
15	PEt_2Ph	0.01	78 : 22 : 00
16	P(4-OMe-C_6H_4)$_3$	0.01	trace : 00 : 95
17	P(4-OMe-C_6H_4)$_2$Ph	0.01	00 : 00 : 100
18	P(4-NMe_2-C_6H_4)Ph_2	0.01	trace : 00 : 95
19		0.01	00 : 00 : 100

[a] THF is used instead of CH_2Cl_2. [b]Ratios are estimated by analysis of a crude reaction mixture by ^{1}H NMR.

Although preliminary studies indicated that the scope of this process would be broad, we were puzzled to discover that substrate **3.2** was reluctant to cyclize under the conditions developed for our model substrate **3.1**. ^{1}H NMR analysis showed that the substrate was consumed under the reaction conditions but only trace amounts of the

bicyclic product were observed. Further investigation led us to uncover a pronounced solvent effect. The use of a CH_2Cl_2:EtOAc (1:1) solvent system led to efficient cyclization of **3.2** (eq 3.5).

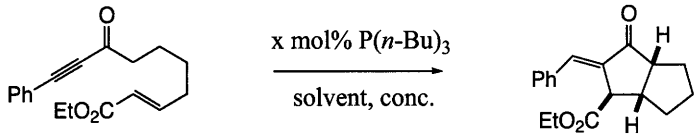


3.2 (3.5)

CH_2Cl_2 (0.01 M), r.t. = complete conversion, no desired product
(1:1) CH_2Cl_2:EtOAc (0.01 M) = complete conversion, 70-80% by ^1H NMR

We were pleased to find that these new conditions were effective for the cyclization of ynone **3.1** as well (Table 3.2, Entry 6). Detailed examination of the CH_2Cl_2:EtOAc ratio led to an improvement over our initial reaction conditions (Table 3.2, Entries 1-7). Hopeful that our new conditions may allow for a reduction in catalyst loading or an increase in concentration, we reexamined these parameters. Unfortunately, lower catalyst loadings (Table 3.2, Entries 8-11) or increased concentration (Table 3.2, Entries 12 and 13) led to increases in oligomerization, as before. We also examined the possibility of using the catalyst precursor $(n\text{-Bu})_3P{\cdot}HBF_4$ with K_2CO_3 or NEt_3, but this combination failed to promote the reaction.

Table 3.2. Reaction Optimization: Effects of Cosolvents, Concentration, and Catalyst Loading.

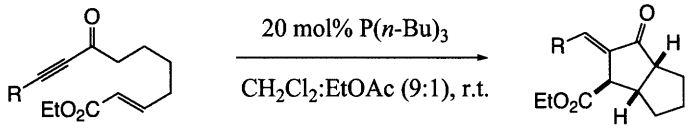


entry	x mol% $P(n\text{-}Bu)_3$	solvent	conc. [M]	product : oligomer : SM[a]
1	20	CH_2Cl_2:EtOAc (19:1)	0.01	93 : 07 : 00
2	20	CH_2Cl_2: EtOAc (9:1)	0.01	94 : 06 : 00
3	20	CH_2Cl_2:EtOAc (4:1)	0.01	91 : 09 : 00
4	20	CH_2Cl_2:EtOAc (7:3)	0.01	87 : 13 : 00
5	20	CH_2Cl_2:EtOAc (3:2)	0.01	79 : 21 : 00
6	20	CH_2Cl_2:EtOAc (1:1)	0.01	74 : 26 : 00
7	20	CH_2Cl_2:EtOAc (1:9)	0.01	52 : 48 : 00
8	15	CH_2Cl_2:EtOAc (9:1)	0.01	93 : 07 : 00
9	10	CH_2Cl_2:EtOAc (9:1)	0.01	86 : 14 : 00
10	5	CH_2Cl_2:EtOAc (9:1)	0.01	46 : 34 : 12
11	2	CH_2Cl_2:EtOAc (9:1)	0.01	15 : 10 : 75
12	20	CH_2Cl_2:EtOAc (9:1)	0.02	90 : 10 : 00
13	20	CH_2Cl_2:EtOAc (9:1)	0.05	75 : 25 : 00

[a] Ratios are estimated by analysis of a crude reaction mixture by ^1H NMR.

These reaction conditions are effective for the cyclization of a range of ynone-enoate substrates. Both aromatic- and alkenyl-substituted ynones cyclize smoothly furnishing bicyclo[3.3.0]octan-2-ones in excellent yields (Table 3.3, entries 1-3). Alkyl-ynones are more problematic. It is necessary to employ 1 equivalent of $P(n\text{-}Bu)_3$ for efficient cyclization of a 2°-alkyl-ynone (Table 3.3, Entry 4).

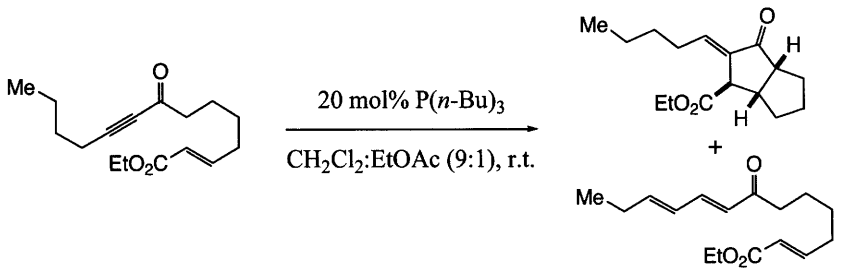
Table 3.3. Phosphine-Catalyzed Synthesis of Bicyclo[3.3.0]octanones.



Entry 1, 89% yield	Entry 2, 83%[a]	Entry 3, 84% yield	Entry 4, 45% yield[b]

All data are the average of two runs. [a]CH_2Cl_2:EtOAc (1:1) was used. [b]1 equiv of P(n-Bu)$_3$ was used.

Although, phosphine-catalyzed ynone to dieneone isomerization is not an issue for aryl-ynones, this problem does arise for alkyl-substituted ynones.[14] Under our optimized conditions we observe significant amounts of the undesired dienone side product according to analysis of the crude reaction mixture by ^{1}H NMR spectroscopy (eq 3.6). We do not observe the ynone to dienone isomerization in the case of the 2°-alkyl-ynone (Table 3.3, Entry 4).

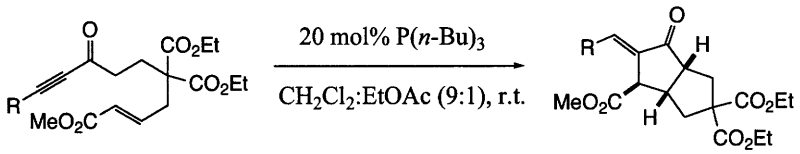


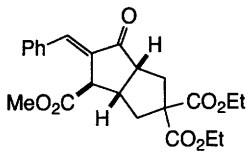
(3.6)

This difficulty can be overcome through the use of the Thorpe-Ingold effect. No dienone is observed in the cyclization of an alkyl-ynone containing a geminal diester moiety in the backbone (Table 3.4, Entry 4). Presumably, the inclusion of a geminal diester substituent increases the rate of cyclization but does not significantly affect the rate of the ynone to dienone isomerization. Not surprisingly, aryl-, alkenyl-, methyl-, and

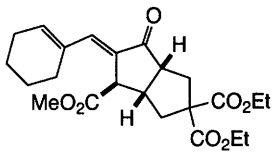
2°alkyl-ynones containing a geminal diester moiety cyclize as well (Table 3.4, Entries 1, 2, 3, and 5).

Table 3.4. Phosphine-Catalyzed Ynone Cyclizations of Thorpe-Ingold Substrates.

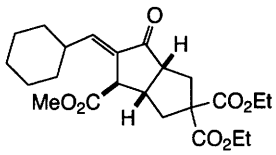




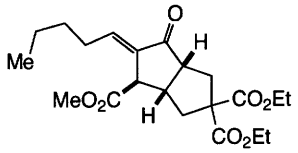
Entry 1, 89% yield



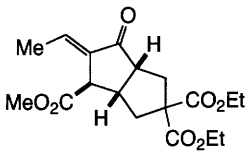
Entry 2, 87% yield



Entry 3, 74% yield



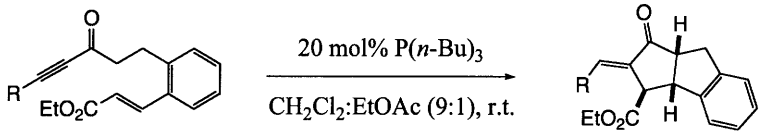
Entry 4, 77% yield



Entry 5, 56% yield

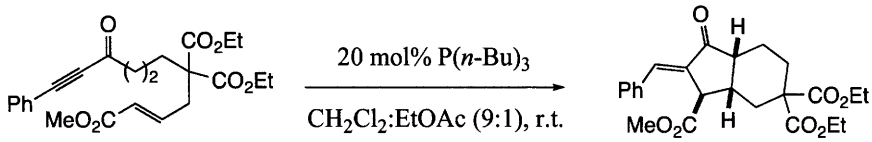
All data are the average of two runs.

A benzo-fused alkyl-ynone-enoate cyclizes, indicating that other types of backbone substitution are capable of rendering the cyclization competitive with the undesired isomerization process (eq 3.7, top).[15] The phenyl-substituted analog of this substrate also cyclizes smoothly to deliver the tricyclic ketone in excellent yield (eq 3.7, bottom).

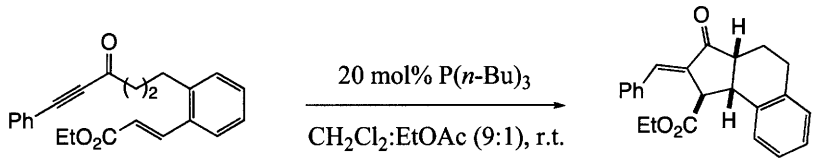


R = *n*-pentyl; 55% yield
R = Ph; 88% yield (3.7)

Homologated ynone-enoates cyclize efficiently under our optimized reaction conditions to furnish bicyclo[4.3.0]nonanones (eq 3.8 and 3.9). Currently, this class of cyclization is limited to backbone-substituted ynone-enoates.[16]

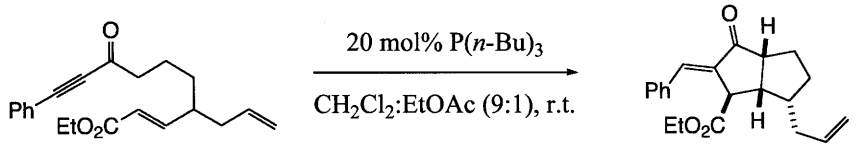


(3.8)



(3.9)

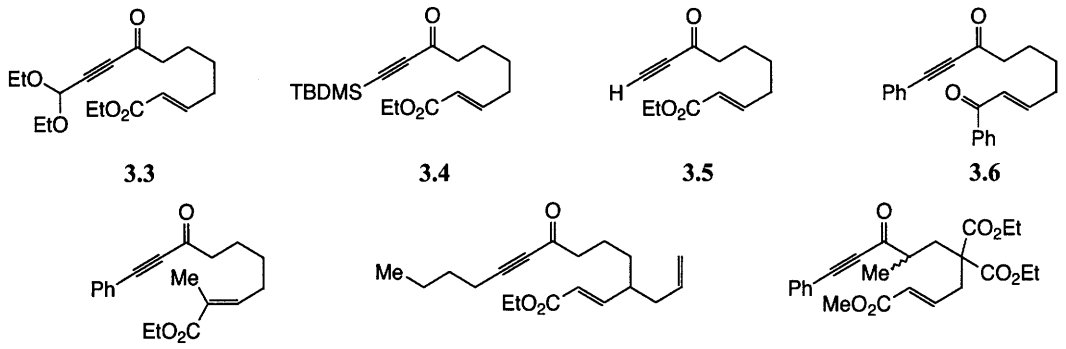
Preliminary investigations show promise for the future development of diastereoselective ynone-enoate cyclizations (eq 3.10). Suprisingly, the more sterically-congested isomer is formed preferentially.



(3.10)

Although successful in many instances, we have found some limitations of this new methodology. Compounds **3.3** and **3.5** decompose under the reaction conditions, providing an intractable reaction mixture. Silyl-ynone **3.4** is recovered quantitatively, indicating that the initial phosphine addition most likely does not occur. Complex reaction mixtures are obtained when **3.6** is employed as a substrate. This may be due to competitive addition to the enone. Attempts with substrates **3.7** and **3.9** to synthesize bicycles containing a quaternary stereocenter either adjacent to the ester or at the ring junction failed even under more forcing conditions.

Scheme 3.6. Limitations of the Phosphine-Catalyzed Bicycl0[3.3.0]octan-2-one Synthesis.

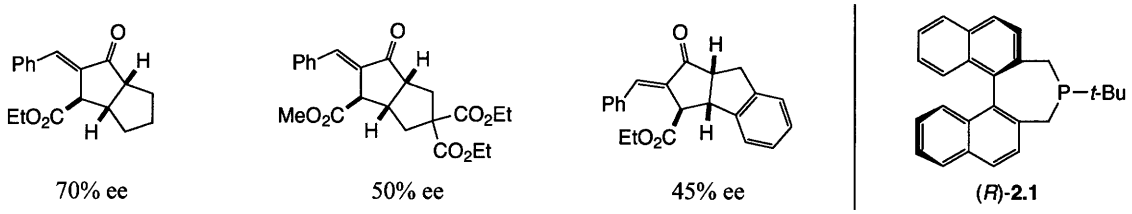


3.3 **3.4** **3.5** **3.6**

3.7 **3.8** **3.9**

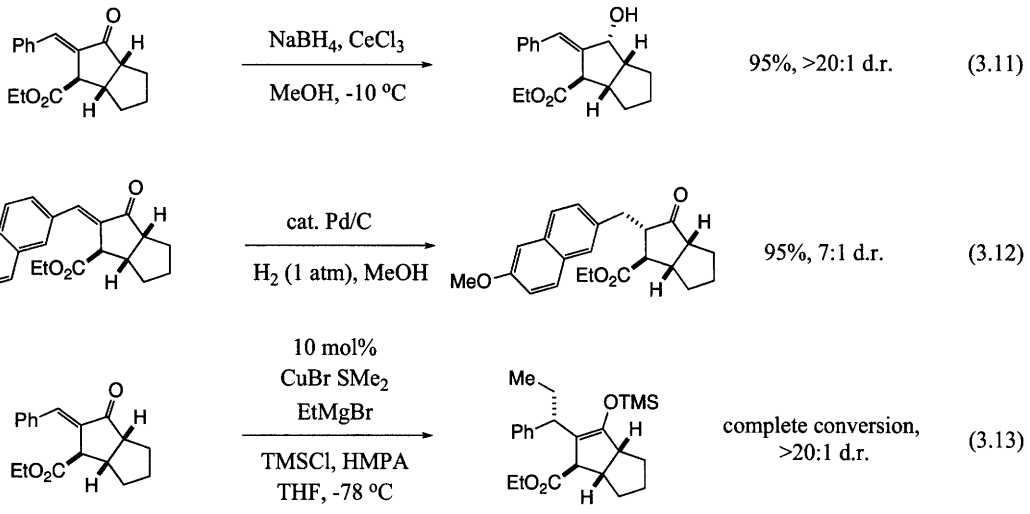
Because the phosphine catalyst is bound to the substrate during the C-C bond-forming event, catalytic enantioselective cyclizations should be feasible. Indeed, when P(*n*-Bu)$_3$ is replaced with chiral phosphine **2.1**, we observe modest enantioselectivity for a range of ynone-enoate cyclizations (Scheme 3.7). Ester analogs of **3.1** (MeO-, BnO-, *t*-BuO-, and PhO-) were prepared in the hopes of improving these initial results. Unfortunately, these modifications offered no advantages.

Scheme 3.7. Examples of Enantioselective Bicyclo[3.3.0]octanone Synthesis Catalyzed by **2.1**.



70% ee 50% ee 45% ee (*R*)-**2.1**

The bicyclic products from the phosphine-catalyzed ynone-enoate cyclization may be functionalized with high stereoselectivity. The carbonyl group is reduced under Luche conditions (eq 3.11), while hydrogenation with catalytic Pd/C reduces the olefin (eq 3.12). Furthermore, Cu(I)-catalyzed 1,4-addition reactions of Grignard reagents proceeds with excellent diastereoselectivity (eq 3.13).[17]



C. Conclusions.

A diastereoselective phosphine-catalyzed synthesis of bicyclo[3.3.0]octan-2-ones and bicyclo[4.3.0]nonan-2-ones was developed. Initial studies indicate that an effective asymmetric variant of the process may be feasible. Finally, some useful derivatizations of the bicyclic products were developed.

D. Experimental

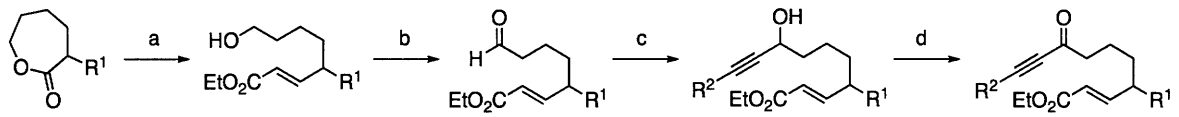
I. General

All reactions were carried out in oven-dried glassware under an atmosphere of argon or nitrogen with magnetic stirring, unless otherwise noted. P(*n*-Bu)$_3$ (97%) was purchased from Aldrich. All purchased materials were used as received. EtOAc (anhydrous) was purchased from Fluka. CH_2Cl_2 was purified by passage through neutral alumina.

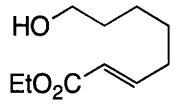
All NMR spectra were recorded in $CDCl_3$, unless otherwise noted.

II. Substrate Preparation

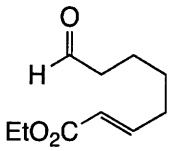
Substrates for Table 3.3 and Eq 3.10:



a. DIBAL-H, toluene, –78 °C; then Ph_3PCHCO_2Et. b. Swern oxidation. c. R^2CCLi, THF, –78 °C to 0 °C. d. cat. TPAP, NMO, 4A MS, CH_2Cl_2:CH_3CN (10:1), r.t.



[75958-95-1]. DIBAL-H (1.0 M solution in toluene; 25.0 mL, 25.0 mmol) was added to a solution of the ε-lactone (2.77 mL, 25.00 mmol) in toluene (50.0 mL) at –78 °C. The mixture was stirred for 2 h at –78 °C, and then EtOAc (75 mL) and a saturated solution of disodium tartrate (30 mL) were added. This solution was warmed to room temperature and stirred for 1 h (until the aqueous layer and organic layer separate easily). The layers were separated, and the aqueous layer was extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude lactol was dissolved in $CHCl_3$ (75 mL), treated with (ethoxycarbonylmethylene)triphenylphosphorane (8.70 g, 25.0 mmol), and stirred at room temperature for 18 h. Next, the reaction mixture was concentrated and directly purified by flash chromatography (20-60% EtOAc in hexanes), which provided 2.77 g (60%) of a clear, colorless oil.

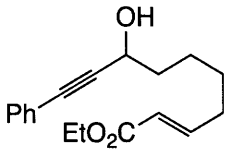


[98525-85-0]. DMSO (3.20 mL, 44.7 mmol) was added dropwise to a solution of oxalyl chloride (1.95 mL, 22.4 mmol) in CH_2Cl_2 (50 mL) at –78 °C. After 10 min, a

solution of the alcohol (2.77 g, 14.9 mmol) in CH_2Cl_2 (50 mL) was added dropwise via cannula. The solution was stirred for 30 min, and then it was treated with NEt_3 (10.4 mL, 74.5 mmol). This mixture was stirred at –78 °C for 20 min, and then it was warmed to room temperature and stirred for an additional 30 min. The reaction was quenched with a saturated solution of $NaHCO_3$ (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2x50 mL). The combined organic layers were washed with 1 N HCl (100 mL) and brine, dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by flash chromatography (10-30% EtOAc in hexanes), which furnished 2.58 g (94%) of a clear, colorless oil.

^{1}H NMR (300 MHz) δ 9.75 (t, J=1.5 Hz, 1H), 6.92 (dt, J=15.7 Hz, J=7.0 Hz, 1H), 5.80 (dt, J=15.7 Hz, J=1.6 Hz, 1H), 4.16 (q, J=7.1 Hz, 2H), 2.44 (td, J=7.2 Hz, J=1.6 Hz, 2H), 2.21 (qd, J=7.1 Hz, J=1.5 Hz, 2H), 1.69-1.59 (m, 2H), 1.53-1.44 (m, 2H), 1.26 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 202.4, 166.8, 148.5, 121.9, 60.4, 43.8, 32.1, 27.6, 21.7, 14.5.



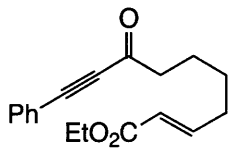
n-BuLi (1.6 M in hexanes; 3.88 mL, 6.21 mmol) was added to a solution of phenylacetylene (0.682 mL, 6.21 mmol) in THF (20 mL) at –78 °C. After 30 min, this solution was added by cannula into a flask that contained a solution of the aldehyde (1.14 g, 6.21 mmol) in THF (25 mL) at –78 °C. The resulting solution was stirred for 20 min at –78 °C, and then it was warmed to 0 °C and stirred for an additional 30 min. The reaction was quenched by the addition of a saturated solution of NH_4Cl. The layers were separated, and the aqueous layer was extracted with Et_2O (2x30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (5-40% EtOAc in hexanes), which provided 1.56 g (88%) of a pale-yellow oil.

^{1}H NMR (300 MHz) δ 7.43 (m, 2H), 7.31-7.26 (m, 3H), 6.96 (dt, J=15.7 Hz, J=7.0 Hz, 1H), 5.82 (dt, J=15.7 Hz, J=1.4 Hz, 1H), 4.59 (t, J=6.5 Hz, 1H), 4.17 (q, J=7.1 Hz, 2H), 2.32 (br s, 1H), 2.21 (m, 2H), 1.83-1.76 (m, 2H), 1.56-1.51 (m, 4H), 1.26 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 167.0, 149.3, 131.8, 128.6, 128.5, 122.8, 121.6, 90.2, 85.1, 62.9, 60.4, 37.7, 32.3, 27.9, 25.0, 14.5.

FTIR (thin film) 3423 (broad), 2981, 2938, 2860, 1716, 1652, 1490, 1443, 1490, 1443, 1368, 1270, 1187, 1043, 980, 757, 692 cm^{-1}.

LC-MS calc. for $C_{18}H_{22}O_3$ [M+1] 287.2, found, 287.1.



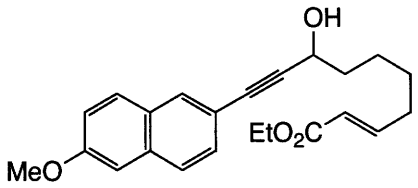
A mixture of the propargylic alcohol (1.53 g, 5.34 mmol), 4A MS (2.67 g), and NMO (0.941 g, 8.01 mmol) in 10:1 CH_2Cl_2:CH_3CN (27 mL) at 0 °C was treated with TPAP (0.056 g, 0.160 mmol). The mixture was immediately warmed to room temperature, and then it was stirred for 2 h. Next, the reaction mixture was filtered through a short pad of silica gel with Et_2O washings (150 mL). The filtrate was concentrated, and the residue was purified by flash chromatography (5→30% Et_2O in hexanes), which provided 1.18 g (78%) of a pale-yellow oil.

^{1}H NMR (300 MHz) δ 7.58-7.55 (m, 2H), 7.48-7.35 (m, 3H), 6.94 (dt, J=15.6 Hz, J=7.0 Hz, 1H), 5.83 (dt, J=15.6 Hz, J=1.3 Hz, 1H), 4.16 (q, J=7.2 Hz, 2H), 2.68 (t, J=7.2 Hz, 2H), 2.24 (tdd, J=7.0 Hz, J=7.0 Hz, J=1.4 Hz, 2H), 1.75 (m, 2H), 1.53 (m, 2H), 1.27 (t, J=7.2 Hz, 3H).

^{13}C NMR (75 MHz) δ 187.8, 166.8, 148.6, 133.3, 131.0, 128.9, 122.0, 120.1, 91.1, 87.9, 60.4, 45.4, 32.1, 27.5, 23.7, 14.5.

FTIR (thin film) 3059, 2981, 2937, 2865, 2202, 1715, 1673, 1489, 1444, 1366, 1271, 1221, 1186, 1098, 1043, 981 cm^{-1}.

LC-MS calc. for $C_{18}H_{20}O_3$ [M+1] 285.1, found 285.1.



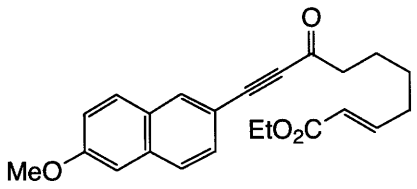
n-BuLi (1.6 M in hexanes; 2.59 mL, 4.15 mmol) was added to a solution of 2-ethynyl-6-methoxynaphthalene (0.758 g, 4.15 mmol) in THF (20 mL) at –78 °C. After 30 min, this solution was transferred by cannula into a flask containing a solution of the aldehyde (0.756 g, 4.11 mmol) in THF (20 mL) at –78 °C. The resulting solution was stirred for 1 h at –78 °C, and then it was warmed to 0 °C and stirred for an additional 30 min. Next, the reaction was quenched with a saturated solution of NH_4Cl. The layers were separated, and the aqueous layer was extracted with Et_2O (3x30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (10-40% EtOAc in hexanes), which provided 1.09 g (72%) of a pale-yellow oil.

^{1}H NMR (300 MHz) δ 7.86 (s, 1H), 7.67 (d, J=6.4 Hz, 1H), 7.65 (d, J=6.1 Hz, 1H), 7.42 (dd, J=8.5 Hz, J=1.7 Hz, 1H), 7.14 (dd, J=9.0 Hz, J=2.5 Hz, 1H), 7.09 (d, J=2.5 Hz, 1H), 6.98 (dt, J=15.7 Hz, J=7.0 Hz, 1H), 5.83 (dt, J=15.7 Hz, J=1.6 Hz, 1H), 4.63 (m, 1H), 4.17 (q, J=7.1 Hz, 2H), 3.91 (s, 3H), 2.27-2.20 (m, 3H), 1.85-1.79 (m, 2H), 1.63-1.52 (m, 4H), 1.26 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 167.0, 158.8, 149.3, 134.4, 131.6, 129.5, 129.2, 128.6, 127.0, 121.7, 119.7, 117.6, 105.9, 90.0, 85.7, 63.0, 60.4, 55.6, 37.8, 32.3, 27.9, 25.0, 14.5.

FTIR (thin film) 3428 (broad), 3059, 2938, 2860, 2224, 1716, 1699, 1630, 1602, 1499, 1484, 1390, 1368, 1270, 1246, 1198, 1122, 1031, 891, 854 cm^{-1}.

LC-MS calc. for $C_{23}H_{26}O_4$ [M+Na] 389.2, found, 389.1.



A mixture of the propargylic alcohol (1.06 g, 2.88 mmol), 4A MS (1.44 g), and NMO (0.509 g, 4.33 mmol) in 10:1 CH_2Cl_2:CH_3CN (15.4 mL) at 0 °C was treated with

TPAP (0.050 g, 0.144 mmol). The mixture was immediately warmed to room temperature, and then it was stirred for 3 h. Next, the mixture was filtered through a short pad of silica gel with Et_2O washings (150 mL). The filtrate was concentrated, and the residue was purified by flash chromatography (5-50% Et_2O in hexanes), which provided 0.843 g (80%) of a pale-yellow oil, which solidified upon being stored in a freezer overnight.

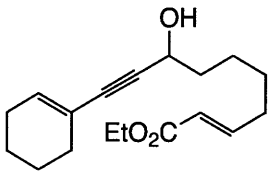
Mp=59 °C

^{1}H NMR (300 MHz) δ 8.05 (s, 1H), 7.73 (d, J=8.4 Hz, 1H), 7.70 (d, J=8.0 Hz, 1H), 7.52 (dd, J=8.5 Hz, J=1.7 Hz, 1H), 7.18 (dd, J=9.0 Hz, J=2.5 Hz, 1H), 7.11 (d, J=2.5 Hz, 1H), 6.96 (dt, J=15.7 Hz, J=7.0 Hz, 1H), 5.84 (dt, J=15.7 Hz, J=1.6 Hz, 1H), 4.16 (q, J=7.1 Hz, 2H), 3.92 (s, 3H), 2.70 (t, J=7.2 Hz, 2H), 2.25 (qd, J=7.2 Hz, J=1.5 Hz, 2H), 1.79 (m, 2H), 1.55 (m, 2H), 1.26 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 187.9, 166.8, 159.5, 148.7, 135.7, 134.5, 130.0, 129.4, 128.3, 127.4, 121.9, 120.2, 114.7, 106.0, 92.3, 88.1, 60.4, 55.6, 45.3, 32.1, 27.5, 23.8, 14.5.

FTIR (thin film) 2939, 2360, 2341, 2191, 1715, 1662, 1624, 1499, 1461, 1391, 1335, 1259, 1167, 1124, 1030, 978 cm^{-1}.

LC-MS calc. for $C_{23}H_{24}O_4$ [M+1] 365.1, found 365.1.



n-BuLi (1.6 M in hexanes; 7.29 mL, 11.7 mmol) was added to a solution of cyclohex-1-enylacetylene (1.37 mL, 11.7 mmol) in THF (30 mL) at –78 °C. After 30 min, this solution was added by cannula into a flask that contained a solution of the aldehyde (2.15 g, 11.7 mmol) in THF (40 mL) at –78 °C. The resulting solution was stirred for 45 min at –78 °C, and then it was warmed to 0 °C and stirred for an additional 20 min. The reaction was quenched by the addition of a saturated solution of NH_4Cl. The layers were separated, and the aqueous layer was extracted with Et_2O (2x30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and

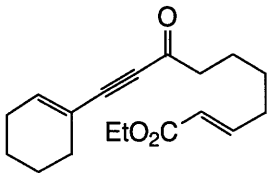
concentrated. The residue was purified by flash chromatography (10-40% EtOAc in hexanes), which provided 2.88 g (85%) of a pale-yellow oil.

^{1}H NMR (300 MHz) δ 6.93 (dt, J=15.6 Hz, J=7.0 Hz, 1H), 6.05 (quintet, J=1.9 Hz, 1H), 5.78 (m, 1H), 4.44 (m, 1H), 4.14 (q, J=7.2 Hz, 2H), 2.27 (d, J=4.2 Hz, 1H), 2.19 (m, 2H), 2.08-2.05 (m, 4H), 1.72-1.44 (m, 10H), 1.25 (td, J=7.2 Hz, J=0.4 Hz, 3H).

^{13}C NMR (75 MHz) δ 166.9, 149.3, 135.3, 121.5, 120.2, 87.5, 86.8, 62.8, 60.4, 37.8, 32.3, 29.3, 27.8, 25.7, 24.9, 22.4, 21.6, 14.4.

FTIR (thin film) 3427 (broad), 2980, 2934, 2859, 2217, 1717, 1652, 1447, 1436, 1368, 1309, 1269, 1185, 1043, 981, 919 cm^{-1}.

LC-MS calc. for $C_{18}H_{24}O_3$ [M+1] 289.2, found, 289.1.



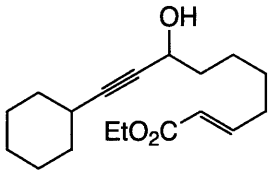
A mixture of the propargylic alcohol (2.85 g, 9.82 mmol), 4A MS (4.91 g), and NMO (1.73 g, 14.7 mmol) in 10:1 CH_2Cl_2:CH_3CN (55 mL) at 0 °C was treated with TPAP (0.104 g, 0.295 mmol). The mixture was immediately warmed to room temperature, and then it was stirred for 3 h. Next, the mixture was filtered through a short pad of silica gel with Et_2O washings (150 mL). The filtrate was concentrated, and the residue was purified by flash chromatography (5-30% Et_2O in hexanes), which provided 2.05 g (72%) of a pale-yellow oil.

^{1}H NMR (300 MHz) δ 6.92 (dt, J=15.7, J=7.0 Hz, 1H), 6.43 (quintet, J=2.0 Hz, 1H), 5.80 (dt, J=15.7 Hz, J=1.5 Hz, 1H), 4.16 (q, J=7.1 Hz, 2H), 2.56 (t, J=7.2 Hz, 2H), 2.21 (m, 2H), 2.17-2.11 (m, 4H), 1.73-1.43 (m, 8H), 1.26 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 188.1, 166.8, 148.7, 142.8, 121.9, 119.1, 93.7, 86.3, 60.4, 45.2, 32.1, 28.5, 27.5, 26.3, 23.8, 22.1, 21.3, 14.5.

FTIR (thin film) 2980, 2935, 2861, 2184, 1716, 1667, 1622, 1448, 1436, 1367, 1307, 1273, 1183, 1096, 1043, 981 cm^{-1}.

LC-MS calc. for $C_{18}H_{24}O_3$ [M+1] 289.1, found 289.1.



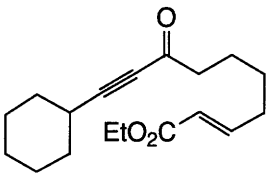
n-BuLi (1.6 M in hexanes; 2.33 mL, 3.73 mmol) was added to a solution of cyclohexylacetylene (0.480 mL, 3.73 mmol) in THF (25 mL) at –78 °C. After 1 h, this solution was transferred by cannula into a flask containing a solution of the aldehyde (0.680 g, 3.69 mmol) in THF (15 mL) at –78 °C. The resulting solution was stirred for 1 h at –78 °C, and then it was warmed to 0 °C and stirred for an additional 30 min. Next, the reaction was quenched with a saturated solution of NH_4Cl. The layers were separated, and the aqueous layer was extracted with Et_2O (2x30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (10-40% EtOAc in hexanes), which provided 0.849 g (79%) of a clear, colorless oil.

^{1}H NMR (300 MHz) δ 6.94 (dt, J=15.6 Hz, J=6.9 Hz, 1H), 5.79 (dt, J=15.6 Hz, J=1.4 Hz, 1H), 4.34 (dt, J=6.5 Hz, J=1.7 Hz, 1H), 4.15 (q, J=7.1 Hz, 2H), 2.35 (m, 1H), 2.23-2.16 (m, 2H), 2.00 (br s, 1H), 1.79-1.61 (m, 6H), 1.53-1.32 (m, 7H), 1.32-1.21 (m, 6H).

^{13}C NMR (75 MHz) δ 166.9, 149.3, 121.6, 89.9, 81.2, 62.6, 60.4, 38.0, 32.8, 32.3, 29.1, 27.9, 26.0, 25.01, 24.96, 14.5.

FTIR (thin film) 3427 (broad), 2931, 2855, 1716, 1651, 1449, 1367, 1267, 1185, 1040, 981 cm^{-1}.

LC-MS calc. for $C_{18}H_{28}O_3$ [M+1] 293.2, found, 293.2.



A mixture of the propargylic alcohol (0.694 g, 2.37 mmol), 4A MS (1.19 g), and NMO (0.418 g, 3.56 mmol) in 10:1 CH_2Cl_2:CH_3CN (12.0 mL) at 0 °C was treated with TPAP (0.042 g, 0.119 mmol). The mixture was immediately warmed to room

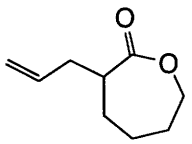
temperature, and then it was stirred for 2 h. Next, the mixture was filtered through a short pad of silica gel with Et_2O washings (100 mL). The filtrate was concentrated, and the residue was purified by flash chromatography (5-30% Et_2O in hexanes), which provided 0.589 g (85%) of a clear, colorless oil.

^1H NMR (300 MHz) δ 6.92 (dt, J=15.7 Hz, J=6.9 Hz, 1H), 5.80 (dt, J=15.7 Hz, J=1.5 Hz, 1H), 4.16 (q, J=7.1 Hz, 2H), 2.58-2.49 (m, 3H), 2.20 (qd, J=7.0 Hz, J=1.5 Hz, 2H), 1.86-1.77 (m, 2H), 1.73-1.63 (m, 4H), 1.56-1.42 (m, 5H), 1.39-1.26 (m, 3H), 1.26 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 188.3, 166.8, 148.7, 121.9, 94.8, 81.0, 60.4, 45.4, 32.1, 31.8, 29.3, 27.5, 25.8, 24.8, 23.8, 14.5.

FTIR (thin film) 2980, 2933, 2857, 2206, 1716, 1673, 1449, 1367, 1314, 1268, 1235, 1182, 1042, 981 cm^{-1}.

LC-MS calc. for $C_{18}H_{26}O_3$ [M+1] 291.1, found 291.1.



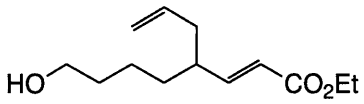
[85930-85-4]. A solution of ε-caprolactone (2.22 mL, 20.0 mmol) in THF (20 mL) was added dropwise over 45 min to a solution of LiHMDS in THF (22.0 mL of a 1.0 M solution in THF + 28 mL of THF) at –78 °C. This mixture was stirred for an additional 30 min, and then a solution of allyl bromide (2.08 mL, 24.0 mmol) in HMPA (distilled from CaH_2 prior to use; 3.0 mL) was added over 10 min. The reaction mixture was warmed to –30 °C and stirred for 3 h at this temperature. Next, the reaction was quenched with a saturated solution of NH_4Cl, the layers were separated, and the aqueous layer was extracted with Et_2O (100 mL). The combined organic layers were washed with H_2O (3x20 mL) and brine, dried over $MgSO_4$, filtered, and concentrated. The crude material was then purified by flash chromatography (5→30% EtOAc in hexanes), which provided 2.07 g (67%) of a clear, colorless oil.

^{1}H NMR (500 MHz) δ 5.81 (m, 1H), 5.09-5.04 (m, 2H), 4.30-4.20 (m, 2H), 2.63 (m, 2H), 2.14 (m, 1H), 2.00-1.90 (m, 2H), 1.86-1.83 (m, 1H), 1.76-1.68 (m, 1H), 1.63-1.54 (m, 1H), 1.45-1.36 (m, 1H).

^{13}C NMR (75 MHz) δ 177.4, 136.1, 117.4, 68.7, 42.6, 36.8, 29.3, 29.1, 28.5.

FTIR (thin film) 3076, 2933, 2860, 1732, 1641, 1474, 1454, 1393, 1291, 1174, 1122, 1054, 915 cm^{-1}.

LC-MS calc. for $C_9H_{14}O_2$ [M+1] 155.1, found, 155.1.



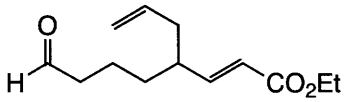
DIBAL-H (1.0 M solution in hexanes; 5.04 mL, 5.04 mmol) was added to a solution of the lactone in toluene (12.0 mL) at –78 °C. After stirring for 2 h at –78 °C, the reaction mixture was quenched with EtOAc (30 mL) and a saturated solution of disodium tartrate (15 mL). This mixture was warmed to room temperature and stirred for 1 h. The layers were separated, and the aqueous layer was extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude lactol was dissolved in $CHCl_3$ (15 mL) and treated with (ethoxycarbonylmethylene)triphenylphosphorane (1.72 g, 4.94 mmol). The mixture was stirred at room temperature for 18 h. Then, it was concentrated and directly purified by flash chromatography (10-40% EtOAc in hexanes), which provided 1.05 g (94%) of a clear, colorless oil.

^{1}H NMR (300 MHz) δ 6.74 (dd, J=8.8 Hz, J=15.6 Hz, 1H), 5.75 (d, J=15.6 Hz, 1H), 5.68 (m, 1H), 5.03-4.97 (m, 2H), 4.15 (qd, J=7.1 Hz, J=0.6 Hz, 2H), 3.59 (m, 2H), 2.26-2.08 (m, 3H), 1.72 (s, 1H), 1.57-1.43 (m, 3H), 1.39-1.23 (m, 3H), 1.26 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 166.9, 152.7, 135.9, 121.5, 116.9, 62.9, 60.5, 42.5, 38.9, 33.7, 32.9, 23.7, 14.4.

FTIR (thin film) 3418 (broad), 3077, 2980, 2933, 2861, 1716, 1699, 1651, 1461, 1445, 1392, 1370, 1310, 1183, 1041, 986, 915 cm^{-1}.

LC-MS calc. for $C_{13}H_{22}O_3$ [M+1] 227.2, found, 227.1.



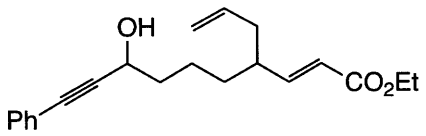
DMSO (0.974 mL, 13.7 mmol) was added dropwise to a solution of oxalyl chloride (0.596 mL, 6.83 mmol) in CH_2Cl_2 (20 mL) at –78 °C. After 10 min, a solution of the alcohol (1.03 g, 4.55 mmol) in CH_2Cl_2 (20 mL) was added dropwise via cannula. The solution was stirred for 30 min, and then it was treated with NEt_3 (3.17 mL, 22.8 mmol). This mixture was stirred at –78 °C for 20 min, and then it was warmed to room temperature and stirred for an additional 30 min. The reaction was quenched with a saturated solution of $NaHCO_3$ (30 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2x30 mL). The combined organic layers were washed with 1 N HCl (30 mL) and brine, dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by flash chromatography (5-30% EtOAc in hexanes), which provided 0.931 g (91%) of a clear, colorless oil.

^{1}H NMR (300 MHz) δ 9.73 (t, J=1.7 Hz, 1H), 6.73 (dd, J=15.7 Hz, J=8.8 Hz, 1H), 5.78 (dt, J=15.7 Hz, J=0.7 Hz, 1H), 5.68 (m, 1H), 5.05-4.98 (m, 2H), 4.17 (q, J=7.1 Hz, 2H), 2.41 (m, 2H), 2.29-2.17 (m, 1H), 2.17-2.12 (m, 2H), 1.69-1.44 (m, 3H), 1.40-1.27 (m, 1H), 1.28 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 202.4, 166.7, 151.9, 135.7, 121.9, 117.2, 60.5, 44.0, 42.4, 38.8, 33.2, 19.9, 14.5.

FTIR (thin film) 3077, 2980, 2932, 2722, 1716, 1651, 1369, 1310, 1268, 1185, 1159, 1040, 987, 917 cm^{-1}.

LC-MS calc. for $C_{13}H_{20}O_3$ [M+1] 225.2, found, 225.1.



n-BuLi (1.6 M in hexanes; 2.52 mL, 4.03 mmol) was added to a solution of phenylacetylene (0.442 mL, 4.03 mmol) in THF (20 mL) at –78 °C. After 30 min, this solution was transferred by cannula into a flask containing a solution of the aldehyde

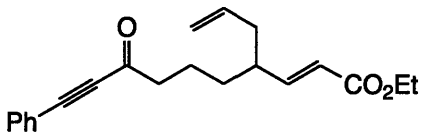
(0.903 g, 4.03 mmol) in THF (20 mL) at –78 °C. The resulting solution was stirred for 20 min at –78 °C, and then it was warmed to 0 °C and stirred for an additional 30 min. The reaction was quenched with a saturated solution of NH_4Cl. The layers were separated, and the aqueous layer was extracted with Et_2O (2x30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (10-40% EtOAc in hexanes), which provided 1.19 g (91%) of a clear, pale-yellow oil.

^1H NMR (300 MHz) δ 7.42-7.39 (m, 2H), 7.32-7.27 (m, 3H), 6.77 (dd, J=15.7 Hz, J=8.8 Hz, 1H), 5.79 (dd, J=15.7 Hz, J=0.7 Hz, 1H), 5.69 (m, 1H), 5.04-4.98 (m, 2H), 4.57 (qd, J=6.5 Hz, J=1.7 Hz, 1H), 4.16 (qd, J=7.1 Hz, J=1.5 Hz, 2H), 2.28-2.08 (m, 4H), 1.81-1.72 (m, 2H), 1.56-1.37 (m, 4H), 1.26 (td, J=7.1 Hz, J=1.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 166.9, 152.6, 135.9, 131.9, 128.5, 122.8, 121.6, 117.0, 90.2, 85.1, 62.9, 60.5, 42.4, 38.8, 37.9, 33.4, 23.1, 23.0, 14.4.

FTIR (thin film) 3419 (broad), 3077, 2979, 2939, 2862, 1720, 1716, 1699, 1694, 1490, 1443, 1370, 1310, 1224, 1184, 1038, 986, 915 cm^{-1}.

LC-MS calc. for $C_{21}H_{26}O_3$ [M+1] 327.2, found, 327.1.



A mixture of the propargylic alcohol (1.18 g, 3.62 mmol), 4A MS (1.81 g), and NMO (0.637 g, 5.42 mmol) in 10:1 CH_2Cl_2:CH_3CN (19.8 mL) at 0 °C was treated with TPAP (0.063 g, 0.108 mmol). The mixture was immediately warmed to room temperature and then stirred for 2 h. The mixture was filtered through a short pad of silica gel with Et_2O washings (100 mL). The filtrate was concentrated and purified by flash chromatography (5-30% Et_2O in hexanes), which provided 1.01 g (86%) of a pale-yellow oil.

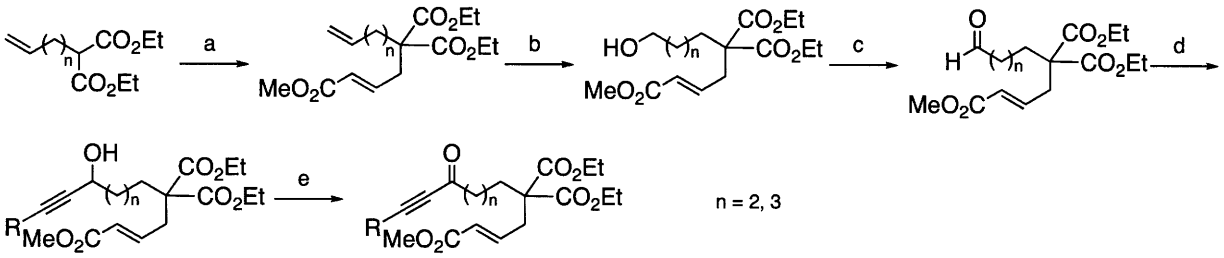
^1H NMR (300 MHz) δ 7.58-7.55 (m, 2H), 7.45 (m, 1H), 7.38 (m, 2H), 6.77 (dd, J=15.7 Hz, J=7.8 Hz, 1H), 5.81 (dd, J=15.7 Hz, J=0.8 Hz, 1H), 5.69 (m, 1H), 5.04 (m, 1H), 5.00 (m, 1H), 4.17 (q, J=7.1 Hz, 2H), 2.65 (t, J=7.4 Hz, 2H), 2.34-2.09 (m, 3H), 1.82-1.48 (m, 3H), 1.45-1.32 (m, 1H), 1.27 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 187.8, 166.7, 152.0, 135.7, 133.3, 131.0, 128.9, 121.9, 120.1, 117.2, 91.1, 87.9, 60.5, 45.5, 42.4, 38.9, 33.0, 21.9, 14.5.

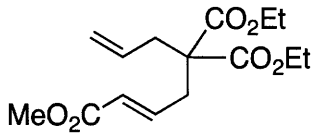
FTIR (thin film) 3076, 2979, 2931, 2870, 2202, 1715, 1668, 1489, 1444, 1368, 1309, 1222, 1096, 1039, 987, 917 cm^{-1}.

LC-MS calc. for $C_{21}H_{24}O_3$ [M+1] 325.2, found, 325.1.

Substrates for Table 3.4 and Eq 3.8:



a. NaH, DMF; then $BrCH_2CH{=}CHCO_2Me$. b. 9-BBN, THF, r.t.; then $NaBO_3/H_2O$. c. Swern oxidation. d. RCCLi, THF, –78 °C to 0 °C. e. cat. TPAP, NMO, 4A MS, CH_2Cl_2:CH_3CN (10:1), r.t.



Diethyl allylmalonate (9.86 mL, 50.0 mmol) was added to a slurry of NaH (1.20 g, 50.0 mmol) in DMF (100 mL) at 0 °C. The mixture was warmed to room temperature and stirred until it became clear (approximately 30 min). This solution was cooled to 0 °C and then treated with methyl 4-bromocrotonate (85%; 6.92 mL, 50.0 mmol) over a 5-min period. The resulting mixture was stirred for 18 h at room temperature, and then it was diluted with H_2O (100 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (2x150 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude mixture was purified by flash chromatography (5-20% EtOAc in hexanes), which provided 10.5 g (70%) of a clear, colorless oil.

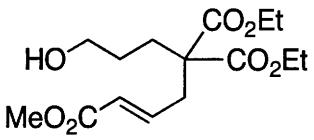
^{1}H NMR (300 MHz) δ 6.79 (dt, J=15.5 Hz, J=7.7 Hz, 1H), 5.87 (dt, J=15.5 Hz, J=1.4 Hz, 1H), 5.69-5.55 (m, 2H), 5.17-5.09 (m, 2H), 4.19 (q, J=7.1 Hz, 4H), 3.71 (s,

3H), 2.75 (dd, J=7.7 Hz, J=1.5 Hz, 2H), 2.64 (dt, J=7.4 Hz, J=1.1 Hz, 2H), 1.24 (t, J=7.1 Hz, 6H).

^{13}C NMR (75 MHz) δ 170.4, 166.5, 143.1, 131.9, 124.9, 120.0, 61.8, 57.1, 51.8, 37.4, 35.4, 14.3.

FTIR (thin film) 3080, 2983, 2954, 1733, 1660, 1643, 1465, 1438, 1276, 1191, 1096, 1037, 925 cm^{-1}.

LC-MS calc. for $C_{15}H_{22}O_6$ [M+1] 299.1, found 299.1.



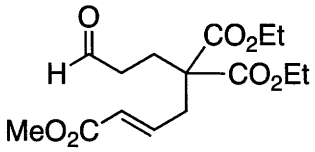
A solution of the olefin (3.58 g, 12.0 mmol) in THF (60 mL) at 0 °C was treated with a solution of 9-BBN (0.5 M solution in THF; 24.2 mL, 12.1 mmol) and then stirred vigorously at room temperature for 5 h. Next, H_2O (20 mL) and $NaBO_3{\cdot}4H_2O$ (6.10 g, 39.6 mmol) were added, and the mixture was stirred for 2 h at room temperature. The layers were separated, and the aqueous layer was extracted with Et_2O (2x50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting crude material was purified by flash chromatography (10-70% EtOAc in hexanes), which provided 3.07 g (81%) of a clear, colorless oil.

^{1}H NMR (300 MHz) δ 6.78 (dt, J=15.5 Hz, J=7.7 Hz, 1H), 5.86 (dt, J=15.5 Hz, 1.4 Hz, 1H), 4.17 (q, J=7.1 Hz, 4H), 3.69 (s, 3H), 3.61 (m, 2H), 2.77 (dd, J=7.7 Hz, J=1.4 Hz, 2H), 1.92 (m, 2H), 1.47 (m, 2H), 1.23 (t, J=7.1 Hz, 6H).

^{13}C NMR (75 MHz) δ 170.8, 166.5, 143.1, 124.8, 62.7, 61.8, 57.1, 51.8, 35.8, 29.3, 27.5, 14.3.

FTIR (thin film) 3441(broad), 2982, 2875, 1738, 1732, 1716, 1659, 1651, 1463, 1439, 1177, 1095, 1035, 859 cm^{-1}.

LC-MS calc. for $C_{15}H_{24}O_7$ [M+Na] 339.2, found 339.1.



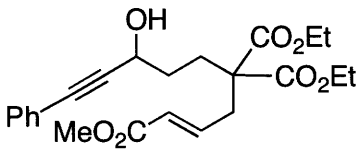
DMSO (0.728 mL, 10.2 mmol) was added dropwise to a solution of oxalyl chloride (0.447 mL, 5.12 mmol) in CH_2Cl_2 (10 mL) at –78 °C. After 10 min, a solution of the alcohol (1.08 g, 3.41 mmol) in CH_2Cl_2 (12 mL) was added dropwise. The solution was stirred for 30 min, and then NEt_3 (2.38 mL, 17.0 mmol) was added. This mixture was stirred at –78 °C for 20 min, and then it was warmed to room temperature and stirred for an additional hour. The reaction was quenched with a saturated solution of $NaHCO_3$ (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2x15 mL). The combined organic layers were washed with 1 N HCl (20 mL) and brine, dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by flash chromatography (15-30% EtOAc in hexanes), which provided 0.970 g (90%) of a clear, colorless oil.

^{1}H NMR (300 MHz) δ 9.72 (t, J=1.1 Hz, 1H), 6.77 (dt, J=15.5 Hz, J=7.7 Hz, 1H), 5.87 (dt, J=15.5 Hz, 1.4 Hz, 1H), 4.18 (qd, J=14.1 Hz, J=1.1 Hz, 4H), 3.70 (s, 3H), 2.75 (dd, J=7.6 Hz, J=1.4 Hz, 2H), 2.49 (m, 2H), 2.17 (m, 2H), 1.24 (t, J=7.1 Hz, 6H).

^{13}C NMR (75 MHz) δ 200.6, 170.4, 166.3, 142.5, 125.2, 62.0, 56.4, 51.8, 39.3, 36.6, 25.5, 14.3.

FTIR (thin film) 2983, 2954, 1907, 2842, 1738, 1732, 1716, 1659, 1439, 1390, 1275, 1192, 1097, 1034, 859 cm^{-1}.

LC-MS calc. for $C_{15}H_{22}O_7$ [M+1] 315.1, found 315.1.



n-BuLi (1.6 M in hexanes; 2.94 mL, 4.71 mmol) was added to a solution of phenylacetylene (0.518 mL, 4.71 mmol) in THF (20 mL) at –78 °C. After 30 min, this solution was transferred by cannula into a flask containing a solution of the aldehyde (1.47 g, 4.67 mmol) in THF (20 mL) at –78 °C. The resulting solution was stirred for 20

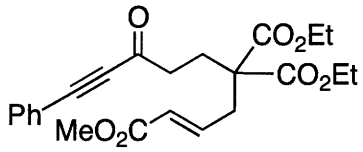
min at –78 °C, and then it was warmed to 0 °C and stirred for an additional 30 min. The reaction was quenched with a saturated solution of NH_4Cl. The layers were separated, and the aqueous layer was extracted with Et_2O (2x30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (10-40% EtOAc in hexanes), which provided 1.62 g (83%) of a clear, pale-yellow oil.

^1H NMR (300 MHz) δ 7.42-7.38 (m, 2H), 7.32-7.27 (m, 3H), 6.81 (dt, J=15.3 Hz, J=7.7 Hz, 1H), 5.89 (dt, J=15.3 Hz, J=1.4 Hz, 1H), 4.58 (m, 1H), 4.19 (q, J=7.1 Hz, 4H), 3.65 (s, 3H), 2.79 (dd, J=7.7 Hz, J=1.4 Hz, 2H), 2.25 (d, J=5.3 Hz, 1H), 2.18-2.06 (m, 2H), 1.77-1.68 (m, 2H), 1.23 (t, J=7.2 Hz, 3H), 1.23 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 170.73, 170.71, 166.5, 143.0, 131.9, 128.7, 128.5, 124.9, 122.6, 89.4, 85.5, 62.7, 61.9, 56.9, 51.8, 35.8, 32.6, 28.6, 14.3.

FTIR (thin film) 3493 (broad), 2981, 1727, 1727, 1659, 1490, 1442, 1368, 1177, 1095, 1032 cm^{-1}.

LC-MS calc. for $C_{23}H_{28}O_7$ [M+Na] 439.2, found 439.1.



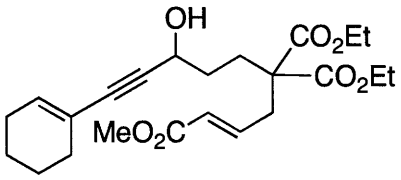
A mixture of the propargylic alcohol (1.62 g, 3.90 mmol), 4A MS (1.95 g), and NMO (0.687 g, 5.85 mmol) in 10:1 CH_2Cl_2:CH_3CN (22 mL) at 0 °C was treated with TPAP (0.041 g, 0.117 mmol). The mixture was immediately warmed to room temperature and then stirred for 2 h. Next, the mixture was filtered through a short pad of silica gel with Et_2O washings (150 mL). The filtrate was concentrated, and the residue was purified by flash chromatography (5-30% Et_2O in hexanes), which provided 1.19 g (74%) of a pale-yellow oil.

^1H NMR (300 MHz) δ 7.58-7.55 (m, 2H), 7.48-7.34 (m, 3H), 6.81 (dt, J=15.4 Hz, J=7.7 Hz, 1H), 5.90 (dt, J=15.5 Hz, J=1.3 Hz, 1H), 4.21 (qd, J=7.1 Hz, J=1.5 Hz, 4H), 3.69 (s, 3H), 2.79 (dd, J=7.7 Hz, J=1.3 Hz, 2H), 2.72 (m, 2H), 2.28 (m, 2H), 1.25 (t, J=7.1 Hz, 6H).

^{13}C NMR (75 MHz) δ 186.1, 170.4, 166.3, 142.6, 133.3, 131.1, 128.9, 125.1, 119.9, 91.6, 87.7, 62.0, 56.5, 51.8, 40.8, 36.6, 27.1, 14.3.

FTIR (thin film) 2982, 2953, 2204, 1731, 1673, 1490, 1444, 1368, 1271, 1191, 1045 cm^{-1}.

LC-MS calc. for $C_{23}H_{26}O_7$ [M+1] 415.2, found, 415.1.



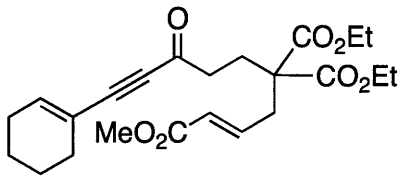
n-BuLi (1.6 M in hexanes; 1.88 mL, 3.00 mmol) was added to a solution of 1-ethynylcyclohexene (0.353 mL, 3.00 mmol) in THF (15 mL) at –78 °C. After 30 min, this solution was transferred by cannula into a flask containing a solution of the aldehyde (0.943 g, 3.00 mmol) in THF (15 mL) at –78 °C. The resulting solution was stirred for 20 min at –78 °C, and then it was warmed to 0 °C and stirred for an additional 30 min. The reaction was quenched with a saturated solution of NH_4Cl. The layers were separated, and the aqueous layer was extracted with Et_2O (2x30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (10-40% EtOAc in hexanes), which provided 1.01 g (80%) of a clear, pale-yellow oil.

^{1}H NMR (300 MHz) δ 6.79 (dt, J=15.5 Hz, J=7.7 Hz, 1H), 6.07 (m, 1H), 5.87 (dt, J=15.5 Hz, J=1.3 Hz, 1H), 4.45 (m, 1H), 4.18 (q, J=7.1 Hz, 4H), 3.69 (s, 3H), 2.76 (dd, J=7.7 Hz, J=1.3 Hz, 2H), 2.08-2.00 (m, 7H), 1.65-1.51 (m, 6H), 1.23 (t, J=7.1 Hz, 6H).

^{13}C NMR (75 MHz) δ 170.72, 170.70, 166.4, 143.0, 135.7, 124.8, 120.1, 87.3, 86.7, 62.7, 61.8, 56.9, 51.8, 35.8, 32.8, 32.1, 29.3, 28.6, 25.8, 22.4, 21.6, 14.3.

FTIR (thin film) 3508, 2980, 2936, 2860, 2217, 1732, 1659, 1435, 1368, 1271, 1178, 1095, 1033, 919 cm^{-1}.

LC-MS calc. for $C_{23}H_{32}O_7$ [M+Na] 443.2, found 443.1.



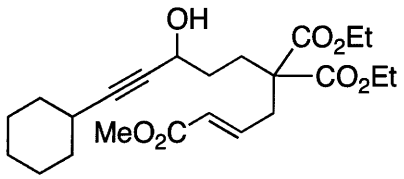
A mixture of the propargylic alcohol (0.927 g, 2.20 mmol), 4A MS (1.10 g), and NMO (0.390 g, 3.30 mmol) in 10:1 CH_2Cl_2:CH_3CN (12 mL) at 0 °C was treated with TPAP (0.023 g, 0.066 mmol). The mixture was immediately warmed to room temperature and then stirred for 2 h. Next, the mixture was filtered through a short pad of silica gel with Et_2O washings (150 mL). The filtrate was concentrated, and the residue was purified by flash chromatography (5-30% Et_2O in hexanes), which provided 0.638 g (69%) of a pale-yellow oil.

^{1}H NMR (300 MHz) δ 6.79 (dt, J=15.5 Hz, J=7.6 Hz, 1H), 6.45 (q, J=2.0 Hz, 1H), 5.88 (dt, J=15.5 Hz, 1.3 Hz, 1H), 4.19 (qd, J=14.1 Hz, J=1.6 Hz, 4H), 3.70 (s, 3H), 2.76 (dd, J=7.7 Hz, J=1.4 Hz, 2H), 2.62-2.57 (m, 2H), 2.25-2.20 (m, 2H), 2.16-2.12 (m, 4H), 1.68-1.57 (m, 4H), 1.24 (t, J=7.1 Hz, 6H).

^{13}C NMR (75 MHz) δ 186.3, 170.4, 166.3, 143.2, 142.7, 125.1, 119.0, 94.3, 86.0, 61.9, 56.5, 51.8, 40.7, 36.5, 28.5, 27.4, 26.4, 22.1, 21.3, 14.3.

FTIR (thin film) 2982, 2937, 2863, 2185, 1715, 1673, 1621, 1436, 1366, 1222, 1093 cm^{-1}.

LC-MS calc. for $C_{23}H_{30}O_7$ [M+1] 419.2, found, 419.1.



n-BuLi (1.6 M in hexanes; 3.05 mL, 4.88 mmol) was added to a solution of cyclohexylacetylene (0.629 mL, 4.88 mmol) in THF (25 mL) at –78 °C. After 30 min, this solution was transferred by cannula into a flask containing a solution of the aldehyde (1.52 g, 4.84 mmol) in THF (25 mL) at –78 °C. The resulting solution was stirred for 20 min at –78 °C, and then it was warmed to 0 °C and stirred for an additional 30 min. Next, the reaction was quenched with a saturated solution of NH_4Cl. The layers were

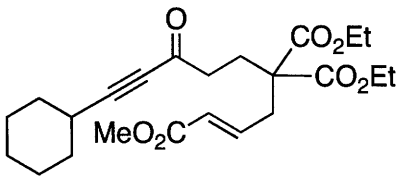
separated, and the aqueous layer was extracted with Et_2O (2x30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (10-40% EtOAc in hexanes), which provided 1.54 g (75%) of a clear, pale-yellow oil.

^1H NMR (300 MHz) δ 6.78 (dt, J=15.5 Hz, J=7.7 Hz, 1H), 5.86 (dt, J=15.5 Hz, J=1.3 Hz, 1H), 4.33 (qd, J=5.2 Hz, J=1.6 Hz, 1H), 4.18 (q, J=7.1 Hz, 4H), 3.68 (s, 3H), 2.75 (dd, J=7.7 Hz, J=1.3 Hz, 2H), 2.34 (m, 1H), 2.05-1.97 (m, 3H), 1.79-1.21 (m, 12H), 1.23 (t, J=7.1 Hz, 6H).

^{13}C NMR (75 MHz) δ 170.73, 170.72, 166.4, 143.0, 124.8, 90.4, 80.5, 62.4, 61.8, 56.9, 51.7, 35.7, 32.9, 32.8, 29.1, 28.5, 26.0, 25.0, 14.3.

FTIR (thin film) 3508, 2931, 2855, 2229, 1738, 1732, 1716, 1651, 1463, 1446, 1435, 1342, 1176, 1095, 1033, 860 cm^{-1}.

LC-MS calc. for $C_{23}H_{34}O_7$ [M+Na] 445.2, found 445.1.



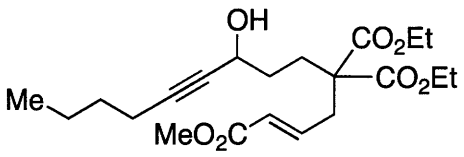
A mixture of the propargylic alcohol (1.50 g, 3.55 mmol), 4A MS (1.78 g), and NMO (0.626 g, 5.33 mmol) in 10:1 CH_2Cl_2:CH_3CN (19.8 mL) at 0 °C was treated with TPAP (0.037 g, 0.107 mmol). The mixture was immediately warmed to room temperature and then stirred for 2 h. Next, the mixture was filtered through a short pad of silica gel with Et_2O washings (150 mL). The filtrate was concentrated, and the residue was purified by flash chromatography (10-40% Et_2O in hexanes), which provided 1.23 g (82%) of a pale-yellow oil.

^1H NMR (300 MHz) δ 6.77 (dt, J=15.5 Hz, J=7.7 Hz, 1H), 5.86 (dt, J=15.5 Hz, J=1.4 Hz, 1H), 4.18 (qd, J=7.1 Hz, J=1.4 Hz, 4H), 3.69 (s, 3H), 2.74 (dd, J=7.7 Hz, J=1.3 Hz, 2H), 2.58-2.47 (m, 3H), 2.19 (m, 2H), 1.86-1.76 (m, 2H), 1.73-1.63 (m, 2H), 1.54-1.40 (m, 3H), 1.36-1.26 (m, 3H), 1.23 (t, J=7.1 Hz, 6H).

^{13}C NMR (75 MHz) δ 186.4, 170.4, 166.3, 142.6, 125.0, 98.9, 80.6, 61.9, 56.5, 51.8, 40.8, 36.5, 31.7, 29.3, 27.2, 25.7, 24.8, 14.2.

FTIR (thin film) 2982, 2934, 2857, 2206, 1732, 1674, 1447, 1367, 1270, 1173, 1096, 1035, 983, 860 cm^{-1}.

LC-MS calc. for $C_{23}H_{32}O_7$ [M+1] 421.2, found, 421.1.



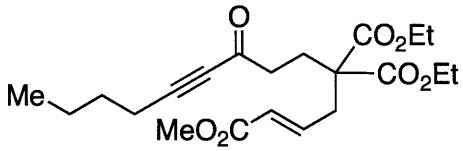
n-BuLi (1.6 M in hexanes; 2.48 mL, 3.96 mmol) was added to a solution of 1-hexyne (0.470 mL, 4.16 mmol) in THF (10 mL) at –78 °C. After 30 min, this solution was transferred by cannula into a flask containing a solution of the aldehyde (1.24 g, 3.96 mmol) in THF (15 mL) at –78 °C. The resulting solution was stirred for 20 min at –78 °C, and then it was warmed to 0 °C and stirred for an additional 30 min. The reaction was quenched with a saturated solution of NH_4Cl. The layers were separated, and the aqueous layer was extracted with Et_2O (3x25 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (10-40% EtOAc in hexanes), which provided 0.758 g (48%) of a clear, pale-yellow oil.

^1H NMR (300 MHz) 6.79 (dt, J=15.5 Hz, J=7.8 Hz, 1H), 5.87 (dt, J=15.5 Hz, J=1.4 Hz, 1H), 4.33 (m, 1H), 4.19 (q, J=7.2 Hz, 4H), 3.70 (s, 3H), 2.77 (dd, J=7.7 Hz, J=1.4 Hz, 2H), 2.18 (td, J=7.0 Hz, J=1.9 Hz, 2H), 2.07-1.99 (m, 2H), 1.87 (d, J=5.2 Hz, 1H), 1.62-1.54 (m, 2H), 1.52-1.34 (m, 4H), 1.24 (t, J=7.2 Hz, 6H), 0.89 (t, J=7.2 Hz, 3H).

^{13}C NMR (75 MHz) 170.8, 170.7, 166.5, 143.1, 124.8, 86.4, 80.6, 62.5, 61.8, 56.9, 51.8, 35.8, 32.9, 30.8, 28.6, 22.1, 18.5, 14.3, 13.8.

FTIR (thin film) 3508 (broad), 2958, 2873, 2232, 1731, 1659, 1438, 1368, 1179, 1095, 1036 cm^{-1}.

LC-MS calc. for $C_{21}H_{32}O_7$ [M+Na] 419.2, found 419.1.



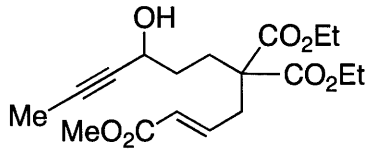
A mixture of the propargylic alcohol (0.662 g, 1.67 mmol), 4A MS (0.835 g), and NMO (0.294 g, 2.50 mmol) in 10:1 CH_2Cl_2:CH_3CN (8.8 mL) at 0 °C was treated with TPAP (0.025 g, 0.069 mmol). The mixture was immediately warmed to room temperature and then stirred for 2 h. Next, the mixture was filtered through a short pad of silica gel with Et_2O washings (100 mL). The filtrate was concentrated, and the residue was purified by flash chromatography (10-40% Et_2O in hexanes), which provided 0.500 g (76%) of a clear, colorless oil.

^{1}H NMR (500 MHz) 6.78 (dt, J=15.4 Hz, J=7.5 Hz, 1H), 5.87 (d, J=15.4 Hz, 1H), 4.22-4.14 (m, 4H), 3.70 (s, 3H), 2.75 (d, J=7.6 Hz, 2H), 2.56 (m, 2H), 2.34 (t, J=7.1 Hz, 2H), 2.20 (m, 2H), 1.54 (m, 2H), 1.41 (m, 2H), 1.24 (t, J=7.2 Hz, 6H), 0.90 (t, J=7.3 Hz, 3H).

^{13}C NMR (125 MHz) 186.3, 170.4, 166.3, 142.6, 125.1, 100.0, 95.4, 80.7, 62.0, 56.5, 51.8, 40.7, 36.5, 29.9, 27.1, 22.2, 18.8, 14.2, 13.7.

FTIR (thin film) 2959, 2874, 2213, 1731, 1674, 1437, 1368, 1270, 1173, 1096, 1032, 860 cm^{-1}.

LC-MS calc. for $C_{21}H_{30}O_7$ [M+1] 395.2, found, 395.1.



Propynylmagnesium bromide (0.5 M solution; 5.32 mL, 2.66 mmol) was added to a solution of the aldehyde (0.796 g, 2.53 mmol) in THF (15 mL) at –78 °C. The resulting solution was stirred at –78 °C for 20 min, and then it was warmed to 0 °C and stirred for an additional 30 min. The reaction was quenched with a saturated solution of NH_4Cl. The layers were separated, and the aqueous layer was extracted with Et_2O (2x30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and

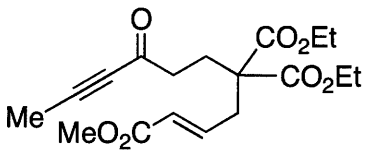
concentrated. The residue was purified by flash chromatography (10-60% EtOAc in hexanes), which provided 0.503 g (57%) of a clear, colorless oil.

^{1}H NMR (300 MHz) δ 6.78 (dt, J=15.5 Hz, 7.6 Hz, 1H), 5.86 (dt, J=15.5 Hz, J=1.4 Hz, 1H), 4.29 (m, 1H), 4.17 (q, J=7.1 Hz, 4H), 3.68 (s, 3H), 2.75 (dd, J=7.7 Hz, J=1.4 Hz, 2H), 2.11 (d, J=5.2 Hz, 1H), 2.02-1.97 (m, 2H), 1.80 (d, J=2.1 Hz, 3H), 1.59-1.51 (m, 2H), 1.22 (t, J=7.1 Hz, 6H).

^{13}C NMR (75 MHz) δ ^{13}C NMR (75 MHz) δ 170.75, 170.73, 166.5, 143.1, 124.8, 81.7, 79.9, 62.4, 61.8, 56.9, 51.8, 35.6, 32.8, 28.4, 14.3, 3.7.

FTIR (thin film) 3509(broad), 2982, 1738, 1732, 1716, 1659, 1439, 1435, 1273, 1190, 1095, 1032 cm^{-1}.

LC-MS calc. for $C_{18}H_{26}O_7$ [M+Na] 377.2, found 377.1.



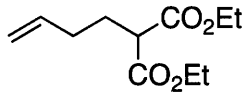
A mixture of the propargylic alcohol (0.415 g, 1.40 mmol), 4A MS (0.700 g), and NMO (0.246 g, 2.09 mmol) in 10:1 CH_2Cl_2:CH_3CN (7.7 mL) at 0 °C was treated with TPAP (0.025 g, 0.069 mmol). The mixture was immediately warmed to room temperature and then stirred for 2 h. Next, the mixture was filtered through a short pad of silica gel with Et_2O washings (100 mL). The filtrate was concentrated, and the residue was purified by flash chromatography (10-50% Et_2O in hexanes), which provided 0.255 g (52%) of a pale-yellow oil.

^{1}H NMR (300 MHz) δ 6.77 (dt, J=15.5 Hz, J=7.6 Hz, 1H), 5.86 (dt, J=15.5 Hz, J=1.4 Hz, 1H), 4.17 (qd, J=7.1 Hz, J=1.1 Hz, 4H), 3.69 (s, 3H), 2.73 (dd, J=7.7 Hz, J=1.2 Hz, 2H), 2.55 (m, 2H), 2.19 (m, 2H), 1.99 (s, 3H), 1.23 (t, J=7.1 Hz, 6H).

^{13}C NMR (75 MHz) δ 186.2, 170.3, 166.3, 142.6, 125.1, 91.1, 80.1, 61.9, 56.4, 51.8, 40.6, 36.5, 26.9, 14.2, 4.3.

FTIR (thin film) 2983, 2848, 2221, 1731, 1674, 1436, 1368, 1274, 1096, 1033 cm^{-1}.

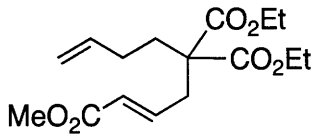
LC-MS calc. for $C_{18}H_{24}O_7$ [M+1] 353.2, found, 353.1.



[31696-00-1]. Diethylmalonate (6.07 mL, 40.0 mmol) was added to a slurry of NaH (0.960 g, 40.0 mmol) in DMF (125 mL) at 0 °C. The mixture was warmed to room temperature and stirred until it became clear (approximately 30 min). This solution was cooled to 0 °C and then treated with 1-bromo-3-butene (4.06 mL, 40.0 mmol) over a 5-min period. After stirring for 18 h at room temperature, the solution was diluted with H_2O (100 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2x150 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude mixture was purified by flash chromatography (5-20% EtOAc in hexanes), which provided 6.13 g (72%) of a clear, colorless oil.

^{1}H NMR (300 MHz) δ 5.73 (ddt, J=17.0 Hz, J=10.3 Hz, J=6.5 Hz, 1H), 5.04-4.95 (m, 2H), 4.16 (q, J=7.1 Hz, 4H), 3.32 (t, J=7.1 Hz, 1H), 2.11-1.92 (m, 4H), 1.23 (t, J=7.1 Hz, 6H).

^{13}C NMR (75 MHz) δ 169.6, 137.1, 116.1, 61.5, 51.3, 31.5, 27.9, 14.2.



Diethyl (3-butenyl)malonate (3.00 g, 14.0 mmol) was added to a slurry of NaH (0.338 g, 14.1 mmol) in DMF (30 mL) at 0 °C. The mixture was warmed to room temperature and stirred until it became clear (approximately 30 min). This solution was cooled to 0 °C and then treated with methyl 4-bromocrotonate (85%; 1.94 mL, 14.0 mmol) over a 5-min period. After stirring for 18 h at room temperature, the solution was diluted with H_2O (50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2x75 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude mixture was purified by flash

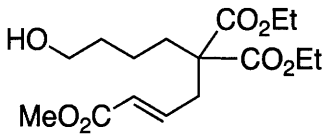
chromatography (5-25% EtOAc in hexanes), which provided 3.26 g (75%) of a clear, colorless oil.

^{1}H NMR (300 MHz) δ 6.78 (dt, J=15.4 Hz, J=7.7 Hz, 1H), 5.86 (d, J=15.4 Hz, 1H), 5.74 (m, 1H), 5.04-4.94 (m, 2H), 4.18 (q, J=7.1 Hz, 4H), 3.70 (s, 3H), 2.78 (d, J=7.7 Hz, 2H), 1.96 (m, 2H), 1.95 (m, 2H), 1.23 (t, J=7.1 Hz, 6H).

^{13}C NMR (75 MHz) δ 170.8, 166.5, 143.2, 137.3, 124.7, 115.8, 61.8, 57.1, 51.8, 35.7, 32.1, 28.5, 14.3.

FTIR (thin film) 3079, 2982, 1733, 1659, 1642, 1435, 1342, 1270, 1195, 1096, 1035, 917, 860 cm^{-1}.

LC-MS calc. for $C_{16}H_{24}O_6$ [M+Na] 335.1, found 335.1.



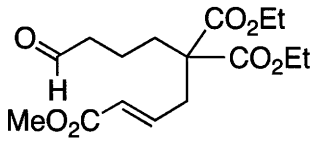
A solution of the olefin (3.23 g, 10.3 mmol) in THF (10 mL) at 0 °C was treated with a solution of 9-BBN (0.5 M solution in THF; 20.9 mL, 10.4 mmol), and the resulting mixture was stirred at room temperature for 7 h. Then, H_2O (20 mL) and $NaBO_3 \cdot 4H_2O$ (5.25 g, 39.6 mmol) were added, and the mixture was stirred vigorously for 2 h at room temperature. The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 75 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (20-80% EtOAc in hexanes), which provided 2.70 g (79%) of a clear, colorless oil.

^{1}H NMR (300 MHz) δ 6.75 (dt, J=15.5 Hz, J=7.7 Hz, 1H), 5.84 (dt, J=15.5 Hz, 1.4 Hz, 1H), 4.15 (q, J=7.1 Hz, 4H), 3.68 (s, 3H), 3.58 (m, 2H), 2.74 (m, 2H), 1.88-1.82 (m, 3H), 1.53 (quintet, J=7.2 Hz, 2H), 1.30-1.18 (m, 2H), 1.21 (t, J=7.1 Hz, 6H).

^{13}C NMR (75 MHz) δ 170.9, 166.5, 143.3, 124.6, 62.3, 61.7, 57.3, 51.8, 35.5, 32.7, 32.5, 20.4, 14.2.

FTIR (thin film) 3442 (broad), 2953, 2872, 1739, 1733, 1716, 1699, 1658, 1463, 1435, 1368, 1344, 1176, 1097, 1035, 860 cm^{-1}.

LC-MS calc. for $C_{16}H_{26}O_7$ [M+1] 331.2, 331.1.



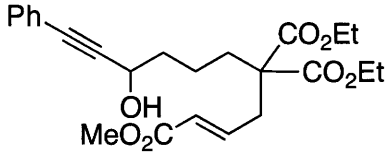
DMSO (1.71 mL, 23.9 mmol) was added dropwise to a solution of oxalyl chloride (1.04 mL, 11.9 mmol) in CH_2Cl_2 (30 mL) at –78 °C. After 10 min, a solution of the alcohol (2.64 g, 7.98 mmol) in CH_2Cl_2 (30 mL) was added dropwise via cannula. The solution was stirred for 30 min, and then it was treated with NEt_3 (5.56 mL, 39.1 mmol). This mixture was stirred at –78 °C for 20 min, and then it was warmed to room temperature and stirred for an additional 30 min. The reaction was quenched with a saturated solution of $NaHCO_3$ (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2x30 mL). The combined organic layers were washed with 1 N HCl (50 mL) and brine, dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by flash chromatography (15-30% EtOAc in hexanes), which provided 2.41 g (92%) of a clear, colorless oil.

^{1}H NMR (300 MHz) δ 9.71 (t, J=1.2 Hz, 1H), 6.74 (dt, J=15.5 Hz, 7.8 Hz, 1H), 5.85 (dt, J=15.5 Hz, 1.4 Hz, 1H), 4.16 (q, J=7.1 Hz, 4H), 3.67 (s, 3H), 2.75 (dd, J=7.8 Hz, J=1.4 Hz, 2H), 2.43 (td, J=7.0 Hz, J=1.2 Hz, 2H), 1.83 (m, 2H), 1.55-1.45 (m, 2H), 1.21 (t, J=7.1 Hz, 6H).

^{13}C NMR (75 MHz) δ 201.5, 170.5, 166.4, 142.9, 124.8, 61.8, 57.2, 51.7, 43.8, 35.5, 32.2, 16.8, 14.2.

FTIR (thin film) 2983, 2842, 2727, 2739, 1733, 1716, 1699, 1659, 1458, 1439, 1435, 1342, 1177, 1097, 1035, 860cm^{-1}.

LC-MS calc. for $C_{16}H_{24}O_7$ [M+1] 329.1, 329.1.



n-BuLi (1.6 M in hexanes; 1.91 mL, 3.06 mmol) was added to a solution of phenylacetylene (0.336 mL, 3.06 mmol) in THF (15 mL) at –78 °C. After 30 min, this solution was transferred by cannula into a flask containing a solution of the aldehyde

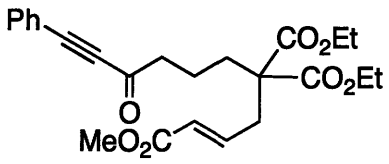
(1.01 g, 3.06 mmol) in THF (15 mL) at –78 °C. The resulting solution was stirred for 20 min at –78 °C, and then it was warmed to 0 °C and stirred for an additional 30 min. Next, the reaction was quenched with a saturated solution of NH_4Cl. The layers were separated, and the aqueous layer was extracted with Et_2O (3x20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (10-40% EtOAc in hexanes), which provided 1.16 g (88%) of a pale-yellow oil.

^1H NMR (300 MHz) δ 7.41-7.37 (m, 2H), 7.32-7.26 (m, 3H), 6.79 (dt, J=15.5 Hz, J=7.7 Hz, 1H), 5.87 (dt, J=15.5 Hz, J=1.4 Hz, 1H), 4.59 (m, 1H), 4.17 (qd, J=7.1 Hz, J=1.6 Hz, 4H), 3.69 (s, 3H), 2.78 (dd, J=7.8 Hz, J=1.4 Hz, 2H), 4.41 (d, J=4.4 Hz, 1H), 1.94 (m, 2H), 1.79 (m, 2H), 1.49-1.38 (m, 2H), 1.21 (td, J=7.1 Hz, J=1.4 Hz, 6H).

^{13}C NMR (75 MHz) δ 170.8, 166.5, 143.2, 131.9, 128.6, 128.5, 124.7, 122.7, 89.9, 85.2, 62.5, 61.8, 57.4, 51.8, 37.9, 35.5, 32.4, 19.9, 14.3.

FTIR (thin film) 3496 (broad), 2981, 2953, 2732, 1658, 1490, 1442, 1368, 1279, 1097, 1032, 917, 859 cm^{-1}.

LC-MS calc. for $C_{24}H_{30}O_7$ [M+Na] 453.2, found 453.1.



A mixture of the propargylic alcohol (1.11 g, 2.58 mmol), 4A MS (1.30 g), and NMO (0.455 g, 3.87 mmol) in 10:1 CH_2Cl_2:CH_3CN (14.3 mL) at 0 °C was treated with TPAP (45 mg, 0.129 mmol). The mixture was immediately warmed to room temperature and then stirred for 2 h. Next, the mixture was filtered through a short pad of silica gel with Et_2O washings (100 mL). The filtrate was concentrated, and the residue was purified by flash chromatography (10-50% Et_2O in hexanes), which provided 0.953 g (86%) of a pale-yellow oil.

^1H NMR (300 MHz) δ 7.57-7.54 (m, 2H), 7.45 (m, 1H), 7.37 (m, 2H), 6.79 (dt, J=15.5 Hz, J=7.7 Hz, 1H), 5.88 (dt, J=15.5 Hz, J=1.4 Hz, 1H), 4.19 (q, J=7.1 Hz, 4H),

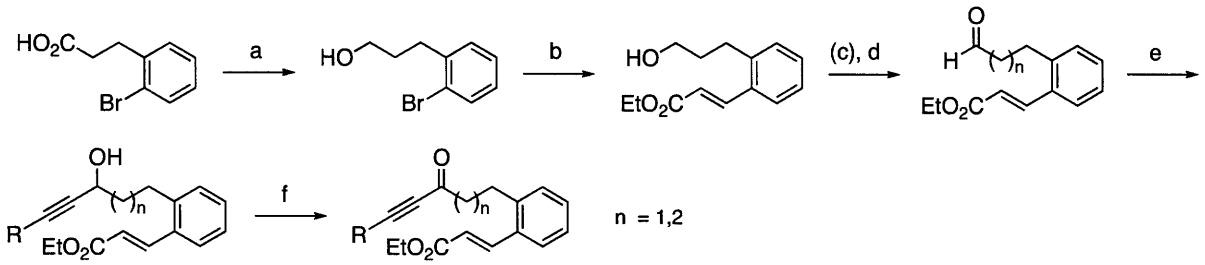
3.70 (s, 3H), 2.80 (dd, J=7.8 Hz, 1.4 Hz, 2H), 2.69 (t, J=7.4 Hz, 2H), 1.92 (m, 2H), 1.69-1.58 (m, 2H), 1.24 (t, J=7.1 Hz, 6H).

^{13}C NMR (75 MHz) δ 187.0, 170.6, 166.4, 143.0, 133.3, 131.0, 128.9, 124.9, 120.0, 91.2, 87.8, 61.9, 57.3, 51.8, 45.4, 35.6, 32.1, 18.8, 14.3.

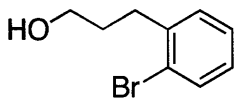
FTIR (thin film) 3059, 2982, 2905, 2201, 1732, 1669, 1490, 1444, 1343, 1276, 1174, 1094, 1038, 860 cm^{-1}.

LC-MS calc. for $C_{24}H_{28}O_7$ [M+1] 429.2, found, 429.1.

Substrates for Eq 3.7 and eq. 3.9:



a. LAH, Et_2O, 0 °C to r.t. b. cat. $Pd_2(dba)_3/P(t\text{-}Bu)_3$, $CH_2{=}CHCO_2Et$, Cy_2NEt, 1,4-dioxane, 65 °C. c. Swern oxidation. d. $Ph_3PCHOMe$, THF, –78 °C to r.t. e. RCCLi, THF, –78 °C to 0 °C. f. cat. TPAP, NMO, 4A MS, CH_2Cl_2:CH_3CN (10:1), r.t.



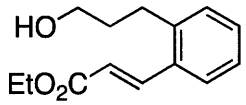
$LiAlH_4$ (1.0 M solution in Et_2O; 100 mL, 100 mmol) was added dropwise to a solution of 3-(2-bromophenyl)propionic acid (11.5 g, 50.2 mmol) in Et_2O (60 mL) at 0 °C. The mixture was then warmed to room temperature and stirred for 4 h. Next, the mixture was cooled to 0 °C, and H_2O (50 mL) was added cautiously dropwise over 30 min. The layers were separated, and the aqueous layer was extracted with EtOAc (2x100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was passed through a short pad of silica gel with Et_2O washings (250 mL), yielding 10.3 g (96%) of a clear, colorless oil.

^{1}H NMR (300 MHz) δ 7.53 (d, J=7.9 Hz, 1H), 7.25-7.23 (m, 2H), 7.09-7.01 (m, 1H), 3.70 (m, 2H), 2.83 (m, 2H), 1.89 (m, 2H), 1.71 (t, J=5.2 Hz, 1H).

^{13}C NMR (75 MHz) δ 141.3, 133.0, 130.6, 127.9, 127.7, 124.7, 62.3, 32.9, 32.6.

FTIR (thin film) 3334 (broad), 3065, 2939, 2867, 1566, 1471, 1438, 1058, 1019, 748 cm^{-1}.

LC-MS calc. for $C_9H_{11}BrO$ [M+Na] 238.9, found 238.9.



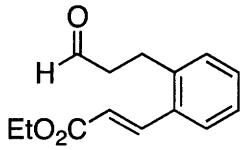
In a glove box, P(*t*-Bu)$_3$ (0.202 g, 1.00 mmol) and Pd_2dba_3 (0.458 g, 0.500 mmol) were combined and dissolved in 1,4-dioxane (50 mL). NCy_2Me (6.43 mL, 30.0 mmol), 3-(2-bromophenyl)propanol (5.39 g, 25.0 mmol), and ethyl acrylate (4.00 mL, 37.5 mmol) were added sequentially to this solution. The mixture was then heated to 70 °C for 18 h. Next, the reaction mixture was cooled and then filtered through a short pad of silica gel with Et_2O washings (200 mL) to remove the ammonium salt, catalyst, etc. The crude mixture was concentrated, and the residue was purified by flash chromatography (20-60% EtOAc in hexanes), which provided 5.53 g (94%) of a pale-yellow oil.

^{1}H NMR (300 MHz) δ 8.03 (d, J=15.8 Hz, 1H), 7.57 (dd, J=6.1 Hz, J=1.9 Hz, 1H), 7.33-7.19 (m, 3H), 6.37 (d, J=15.8 Hz, 1H), 4.26 (q, J=7.1 Hz, 2H), 3.67 (m, 2H), 2.86 (m, 2H), 2.01 (m, 1H), 1.84 (m, 2H), 1.33 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 167.4, 142.3, 141.9, 133.2, 130.3, 126.79, 126.78, 119.7, 62.1, 60.8, 34.5, 29.6, 14.5 (coincident resonances).

FTIR (thin film) 3419 (broad), 3063, 2980, 2940, 2873, 1706, 1716, 1703, 1699, 1694, 1647, 1634, 16000, 1483, 1455, 1367, 1316, 1216, 1179, 1097, 1035, 981, 863, 766 cm^{-1}.

LC-MS calc. for $C_{14}H_{18}O_3$ [M+1] 235.1, found 235.1.



3.10. DMSO (5.00 mL, 70.1 mmol) was added dropwise to a solution of oxalyl chloride (3.06 mL, 35.0 mmol) in CH_2Cl_2 (60 mL) at –78 °C. After 10 min, a solution of the alcohol (5.49 g, 23.4 mmol) in CH_2Cl_2 (60 mL) was added dropwise via cannula. The

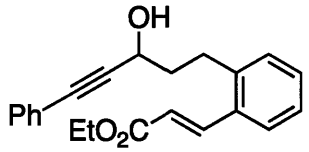
solution was stirred for 30 min before being treated with NEt_3 (16.3 mL, 116 mmol). This mixture was stirred at –78 °C for 20 min, and then it was warmed to room temperature and stirred for an additional 30 min. Next, the reaction was quenched with a saturated solution of $NaHCO_3$ (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2x50 mL). The combined organic layers were washed with 1 N HCl (100 mL) and brine, dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by flash chromatography (15-30% EtOAc in hexanes), which provided 4.95 g (91%) of a clear, colorless oil.

^{1}H NMR (300 MHz) δ 9.80 (t, J=1.1 Hz, 1H), 7.94 (d, J=15.8 Hz, 1H), 7.55 (dd, J=7.2 Hz, J=1.6 Hz, 1H), 7.34-7.19 (m, 3H), 6.37 (d, J=15.8 Hz, 1H), 4.26 (q, J=7.1 Hz, 2H), 3.09 (t, J=7.6 Hz, 2H), 2.73 (td, J=7.6 Hz, J=1.1 Hz, 2H), 1.33 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 201.0, 167.0, 141.6, 140.0, 133.3, 130.4, 130.1, 127.2, 127.1, 120.5, 60.8, 45.2, 25.6, 14.5.

FTIR (thin film) 3064, 2981, 2902, 2825, 1716, 1634, 1600, 1485, 1389, 1366, 1315, 1271, 1216, 1179, 1096, 1035, 980, 864, 766 cm^{-1}.

LC-MS calc. for $C_{14}H_{16}O_3$ [M+1] 233.1, found 233.0.



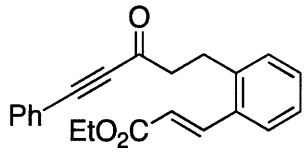
n-BuLi (1.6 M in hexanes; 3.54 mL, 5.67 mmol) was added to a solution of phenylacetylene (0.622 mL, 5.67 mmol) in THF (25 mL) at –78 °C. After 30 min, this solution was transferred by cannula into a flask containing a solution of the aldehyde (1.32 g, 5.67 mmol) in THF (25 mL) at –78 °C. The resulting solution was stirred for 20 min at –78 °C, and then it was warmed to 0 °C and stirred for an additional 30 min. The reaction was quenched with a saturated solution of NH_4Cl. The layers were separated, and the aqueous layer was extracted with Et_2O (2x30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (10-50% EtOAc in hexanes), which provided 1.83 g (96%) of a clear, pale-yellow oil.

^{1}H NMR (300 MHz) δ 8.08 (d, J=15.8 Hz, 1H), 7.57 (m, 1H), 7.46-7.41 (m, 2H), 7.34-7.20 (m, 6H), 6.39 (d, J=15.8 Hz, 1H), 4.62 (m, 1H), 4.24 (q, J=7.1 Hz, 2H), 3.02 (m, 2H), 2.64 (d, J=5.4 Hz, 1H), 2.13-2.02 (m, 2H), 1.30 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 167.3, 142.2, 141.2, 133.3, 131.9, 130.41, 130.36, 128.6, 128.5, 126.93, 126.90, 122.7, 119.9, 89.9, 85.4, 62.2, 60.8, 39.5, 29.1, 14.5.

FTIR (thin film) 3411 (broad), 3062, 3020, 2980, 2954, 2873, 1716, 1632, 1600, 1489, 1443, 1366, 1316, 1279, 1219, 1183, 1097, 1035, 979, 757 cm^{-1}.

LC-MS calc. for $C_{22}H_{22}O_3$ [M+Na] 357.2, found 357.1.



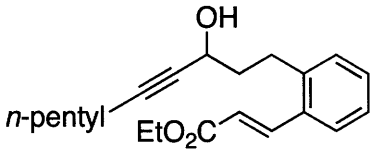
A mixture of the propargylic alcohol (1.83 g, 5.16 mmol), 4A MS (2.58 g), and NMO (0.910 g, 7.74 mmol) in 10:1 CH_2Cl_2:CH_3CN (27.5 mL) at 0 °C was treated with TPAP (0.090 g, 0.26 mmol). The mixture was immediately warmed to room temperature and then stirred for 2 h. Next, the mixture was filtered through a short pad of silica gel with Et_2O washings (150 mL). The filtrate was concentrated, and the residue was purified by flash chromatography (5-30% Et_2O in hexanes), which provided 1.26 g (73%) of a pale-yellow oil.

^{1}H NMR (300 MHz) δ 8.01 (d, J=15.6 Hz, 1H), 7.59-7.54 (m, 3H), 7.48-7.21 (m, 6H), 6.39 (d, J=15.6 Hz, 1H), 4.26 (q, J=7.2 Hz, 2H), 3.20 (m, 2H), 2.96 (m, 2H), 1.33 (t, J=7.2 Hz, 3H).

^{13}C NMR (75 MHz) δ 186.4, 167.0, 141.6, 139.9, 133.3, 131.0, 130.4, 130.2, 128.8, 127.3, 127.1, 120.5, 119.9, 91.6, 87.8, 60.8, 46.8, 27.4, 14.5 (coincident resonances).

FTIR (thin film) 3063, 2980, 2938, 2901, 2203, 1714, 1674, 1633, 1600, 1488, 1444, 1365, 1314, 1280, 1218, 1177, 1093, 1034, 980 cm^{-1}.

LC-MS calc. for $C_{22}H_{20}O_3$ [M+1] 333.1, found, 333.1.



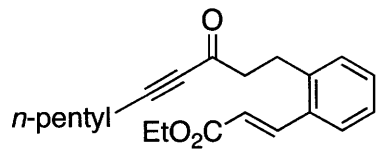
n-BuLi (1.6 M in hexanes; 5.26 mL, 8.42 mmol) was added to a solution of 1-heptyne (1.10 mL, 8.42 mmol) in THF (30 mL) at –78 °C. After 60 min, this solution was transferred by cannula into a flask containing a solution of the aldehyde (1.96 g, 8.42 mmol) in THF (30 mL) at –78 °C. The resulting solution was stirred for 1 h at –78 °C, and then it was warmed to 0 °C and stirred for an additional 30 min. Next, the reaction was quenched with a saturated solution of NH_4Cl. The layers were separated, and the aqueous layer was extracted with Et_2O (2x30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (10-30% EtOAc in hexanes), which provided 2.38 g (86%) of a clear, pale-yellow oil.

^{1}H NMR (300 MHz) δ 8.04 (d, J=15.8 Hz, 1H), 7.56 (d, J=7.9 Hz, 1H), 7.33-7.19 (m, 3H), 6.37 (d, J=15.8 Hz, 1H), 4.36 (m, 1H), 4.26 (q, J=7.1 Hz, 2H), 2.94 (m, 2H), 2.22 (td, J=7.1 Hz, J=1.9 Hz, 2H), 2.02 (d, J=5.8 Hz, 1H), 1.98-1.89 (m, 2H), 1.56-1.46 (m, 2H), 1.41-1.24 (m, 4H), 1.34 (t, J=7.1 Hz, 3H), 0.89 (t, J=7.0 Hz, 3H).

^{13}C NMR (75 MHz) δ 167.3, 142.2, 141.4, 133.3, 130.4, 130.3, 126.89, 126.87, 119.9, 86.5, 80.9, 62.1, 60.8, 39.8, 31.3, 29.0, 28.6, 22.4, 18.9, 14.6, 14.2.

FTIR (thin film) 3430 (broad), 3064, 2933, 2860, 2231, 1716, 1699, 1634, 1600, 1484, 1466, 1455, 1367, 1315, 1279, 1178, 1095, 1033, 982, 765 cm^{-1}.

LC-MS calc. for $C_{21}H_{28}O_3$ [M+1] 329.2, found 329.2.



A mixture of the propargylic alcohol (2.37 g, 7.20 mmol), 4A MS (3.60 g), and NMO (1.27 g, 10.8 mmol) in 10:1 CH_2Cl_2:CH_3CN (39 mL) at 0 °C was treated with TPAP (0.126 g, 0.360 mmol). The mixture was immediately warmed to room temperature and then stirred for 3 h. Next, the mixture was filtered through a short pad of

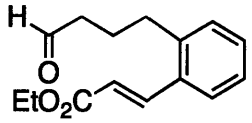
silica gel with Et_2O washings (150 mL). The filtrate was concentrated, and the residue was purified by flash chromatography (5-20% Et_2O in hexanes), which provided 1.82 g (77%) of a pale-yellow oil.

^1H NMR (300 MHz) δ 7.97 (d, J=15.8 Hz, 1H), 7.55 (m, 1H), 7.34-7.21 (m, 3H), 6.37 (d, J=15.8 Hz, 1H), 4.27 (q, J=7.2 Hz, 2H), 3.11 (m, 2H), 2.82 (m, 2H), 2.35 (t, J=7.1 Hz, 2H), 1.61-1.52 (m, 2H), 1.42-1.25 (m, 4H), 1.34 (t, J=7.2 Hz, 3H), 0.89 (m, 3H).

^{13}C NMR (75 MHz) δ 186.7, 167.1, 141.9, 140.0, 133.3, 130.4, 130.2, 127.2, 127.0, 120.4, 95.5, 80.9, 60.8, 46.8, 31.2, 27.6, 27.4, 22.3, 19.2, 14.6, 14.1.

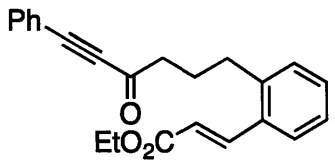
FTIR (thin film) 3064, 2934, 2871, 2214, 1714, 1674, 1633, 1600, 1485, 1463, 1366, 1313, 1271, 1177, 1035, 980 cm^{-1}.

LC-MS calc. for $C_{21}H_{26}O_3$ [M+1] 327.2, found, 327.1.



A solution of KHMDS (0.310 g, 1.55 mmol) in THF (2.0 mL) was added to a -78 °C suspension of (triphenylphosphonium)methoxymethyl chloride (0.514 g, 1.50 mmol) in THF (3.0 mL). This solution was stirred for 45 minutes at -78 °C before adding a solution of aldehyde 3.10 (0.233 g, 1.00 mmol) in THF (2.0 mL). The resulting mixture was allowed to warm to room temperature over 1 hour and then stirred for an additional hour at room temperature. 1 N HCl (6.0 mL) was added and the mixture was stirred vigorously for 3 hours. The aqueous was extracted with Et_2O (2 x 20 mL). The extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (10-30% EtOAc in hexanes) furnished 0.130 g (53%) of the aldehyde.

^1H NMR (300 MHz) δ 9.77 (t, J=1.4 Hz, 1H), 7.99 (d, J=15.7 Hz, 1H), 7.58 (dd, J=7.6 Hz, J=1.4 Hz, 1H), 7.32 (td, J=7.4 Hz, J=1.4 Hz, 1H), 7.27-7.18 (m, 2H), 6.38 (d, J=15.7 Hz, 1H), 4.28 (q, J=7.1 Hz, 2H), 2.80 (t, J=7.7 Hz, 2H), 2.49 (td, J=7.2 Hz, J=1.4 Hz, 2H), 1.89 (m, 2H), 1.35 (t, J=7.1 Hz, 3H).



n-BuLi (1.6 M in hexanes; 0.350 mL, 0.559 mmol) was added to a solution of phenylacetylene (0.061 mL, 0.559 mmol) in THF (3.0 mL) at –78 °C. After 30 min, this solution was transferred by cannula into a flask containing a solution of the aldehyde (0.130 g, 0.532 mmol) in THF (3.0 mL) at –78 °C. The resulting solution was stirred for 20 min at –78 °C, and then it was warmed to 0 °C and stirred for an additional 30 min. The reaction was quenched with a saturated solution of NH_4Cl. The layers were separated, and the aqueous layer was extracted with Et_2O (2x10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated.

The resulting material was combined with 4A MS (2.58 g), and NMO (0.910 g, 7.74 mmol) in 10:1 CH_2Cl_2:CH_3CN (1.1 mL) and was treated with TPAP (0.005 g, 0.014 mmol). The mixture was stirred for 2 h at room temperature. Next, the mixture was filtered through a short pad of silica gel with Et_2O washings (50 mL). The filtrate was concentrated, and the residue was purified by flash chromatography (5-30% Et_2O in hexanes), which provided 0.075 g (41% over two steps) of a pale-yellow oil.

^{1}H NMR (300 MHz) δ 8.02 (d, J=15.8 Hz, 1H), 7.58-7.54 (m, 3H), 7.47-7.21 (m, 6H), 6.38 (d, J=15.8 Hz, 1H), 4.25 (q, J=7.1 Hz, 2H), 2.84 (t, J=7.7 Hz, 2H), 2.71 (t, J=7.2 Hz, 2H), 2.02 (m, 2H), 1.33 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 187.5, 167.1, 141.9, 141.1, 133.2, 130.9, 130.34, 130.28, 128.8, 127.0, 126.9, 120.1, 120.0, 91.0, 87.9, 60.7, 44.8, 32.4, 25.7, 14.5.

FTIR (thin film) 2360, 2202, 1711, 1668, 1633, 1600, 1488, 1444, 1313, 1271, 1178, 1101, 1038, 980 cm^{-1}.

LC-MS calc. for $C_{23}H_{22}O_3$ [M+1] 346.2, found 346.1.

III. Phosphine-Catalyzed Cyclizations

General Procedure for Cyclizations: A flask was charged with the substrate, and then it was evacuated and refilled with argon three times. The appropriate volume of CH_2Cl_2:EtOAc (9:1) was added to make a 0.01 M solution of the substrate. P(*n*-Bu)$_3$

(0.20 equiv) was added by syringe, and the solution was stirred for 20 h at room temperature. Then, the reaction mixture was exposed to air for 1 h, filtered through a short pad of silica gel with Et_2O washings (100 mL), and concentrated. The crude material was purified by flash chromatography to afford the pure cyclized product.

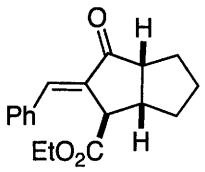


Table 3.3, entry 1. The general procedure was followed. Ynone (114 mg, 0.400 mmol), P(*n*-Bu)$_3$ (20 μL, 0.080 mmol). Purification by flash chromatography (5-25% Et_2O in hexanes) furnished the product (104 mg, 91%) as a pale-yellow oil.

Second run: Ynone (114 mg, 0.400 mmol), P(*n*-Bu)$_3$ (20 μL, 0.080 mmol). Product: 98.9 mg, 87%.

^{1}H NMR (300 MHz) δ 7.60-7.57 (m, 2H), 7.52 (d, J=1.6 Hz, 1H), 7.44-7.38 (m, 3H), 4.22-4.03 (m, 2H), 3.88 (s, 1H), 3.02 (td, J=9.2 Hz, J=3.7 Hz, 1H), 2.87 (q, J=7.4 Hz, 1H), 2.11-1.86 (m, 3H), 1.61-1.52 (m, 2H), 1.17 (t, J=7.1 Hz, 3H), obscured peak under the triplet at 1.17 (m, 1H).

^{13}C NMR (75 MHz) δ 210.3, 173.4, 137.0, 134.5, 133.5, 131.0, 130.3, 129.0, 61.4, 51.3, 50.5, 44.5, 33.9, 29.9, 26.1, 14.3.

FTIR (thin film) 3057, 3026, 2957, 2871, 1731, 1622, 1575, 1494, 1448, 1367, 1293, 1233, 1173, 1117, 1094, 942 cm^{-1}.

LC-MS calc. for $C_{18}H_{20}O_3$ [M+1] 285.1, found 285.1.

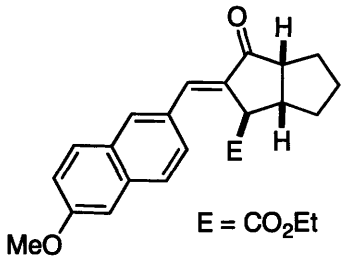


Table 3.3, entry 2. The general procedure was followed, except CH_2Cl_2:EtOAc (1:1) was used. Ynone (109 mg, 0.300 mmol), P(*n*-Bu)$_3$ (15 μL, 0.060 mmol). Purification by flash chromatography (5-40% Et_2O in hexanes) furnished the product (91.5 mg, 84%) as a yellow solid.

Second run: Ynone (109 mg, 0.300 mmol), P(*n*-Bu)$_3$ (15 μL, 0.060 mmol). Product: 89.6 mg, 82%.

Mp=87 °C.

^{1}H NMR (300 MHz) δ 8.05 (s, 1H), 7.78 (d, J=9.3 Hz, 1H), 7.74 (d, J=8.9 Hz, 1H), 7.67-7.64 (m, 2H), 7.17 (dd, J=8.9 Hz, J=2.5 Hz, 1H), 7.12 (d, J=2.5 Hz, 1H), 4.15 (m, 2H), 4.00 (s, 1H), 3.93 (s, 3H), 3.06 (m, 1H), 2.90 (m, 1H), 2.12-1.89 (m, 3H), 1.63-1.53 (m, 2H), 1.19 (t, J=7.2 Hz, 3H), 1.31-1.17 (m, 1H).

^{13}C NMR (75 MHz) δ 210.6, 173.7, 159.3, 137.5, 135.5, 132.5, 132.0, 130.6, 129.8, 128.8, 128.1, 127.5, 119.8, 105.8, 61.4, 55.6, 51.4, 50.7, 44.5, 34.0, 29.9, 26.1, 14.4.

FTIR (thin film) 2957, 2870, 1727, 1610, 1482, 1394, 1268, 1249, 1173, 1029 cm^{-1}.

LC-MS calc. for $C_{23}H_{24}O_4$ [M+1] 365.1, found 365.1.

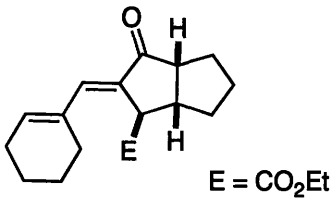


Table 3.3, entry 3. The general procedure was followed. Ynone (115 mg, 0.400 mmol), P(*n*-Bu)$_3$ (20 μL, 0.080 mmol). Purification by flash chromatography (5-25% Et_2O in hexanes) furnished the product (97.0 mg, 84%) as a pale-yellow oil.

Second run: Ynone (115 mg, 0.400 mmol), P(*n*-Bu)$_3$ (20 μL, 0.080 mmol). Product: 96.3 mg, 83%.

^{1}H NMR (300 MHz) δ 7.01 (s, 1H), 6.28 (t, J=3.9 Hz, 1H), 4.21-4.03 (m, 2H), 3.84 (s, 1H), 2.88 (td, J=9.3 Hz, J=3.6 Hz, 1H), 2.72 (q, J=8.3 Hz, 1H), 2.31-2.24 (m, 2H), 2.24-2.17 (m, 2H), 2.04-1.79 (m, 3H), 1.68-1.49 (m, 6H), 1.20 (t, J=7.1 Hz, 3H), 1.24-1.10 (m, 1H).

^{13}C NMR (75 MHz) δ 210.6, 174.1, 142.3, 140.9, 135.3, 129.4, 61.2, 51.1, 49.9, 44.2, 33.9, 29.8, 27.0, 26.9, 26.1, 22.6, 21.6, 14.3.

FTIR (thin film) 2936, 2866, 1737, 1603, 1447, 1388, 1367, 1308, 1219, 1156, 1116, 1094, 1032 cm^{-1}.

LC-MS calc. for $C_{18}H_{24}O_3$ [M+1] 289.1, found 289.1.

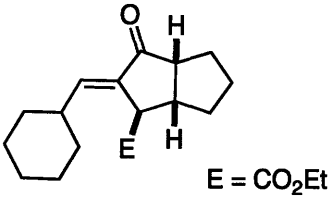


Table 3.3, entry 4. The general procedure was followed, except 1:1 CH_2Cl_2:EtOAc was used. Ynone (87.1 mg, 0.300 mmol), P(*n*-Bu)$_3$ (75 μL, 0.30 mmol). Purification by flash chromatography (5-25% Et_2O in hexanes) furnished the product (38.1 mg, 44%) as a colorless oil.

Second run: Ynone (87.1 mg, 0.300 mmol), P(*n*-Bu)$_3$ (75 μL, 0.30 mmol). Product: 39.8 mg, 46%.

^{1}H NMR (300 MHz) δ 6.53 (dd, J=10.6 Hz, J=1.9 Hz, 1H), 4.11 (q, J=7.1 Hz, 2H), 3.56 (m, 1H), 2.96 (m, 1H), 2.82 (m, 1H), 2.31 (m, 1H), 2.05-1.51 (m, 10H), 1.32-1.06 (m, 6H), 1.23 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 209.8, 173.9, 146.4, 133.4, 61.2, 52.4, 48.5, 43.2, 39.2, 33.7, 31.9, 31.5, 29.6, 26.2, 25.9, 25.51, 25.47, 14.3.

FTIR (thin film) 2927, 2853, 1732, 1645, 1448, 1368, 1294, 1266, 1246, 1174, 1031, 935 cm^{-1}.

LC-MS calc. for $C_{18}H_{26}O_3$ [M+1] 291.1, found 291.1.

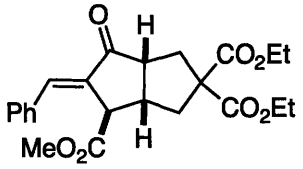


Table 3.4, entry 1. The general procedure was followed, except 1:1 CH_2Cl_2:EtOAc was used. Ynone (124 mg, 0.300 mmol), P(*n*-Bu)$_3$ (15 μL, 0.060 mmol). Purification by flash chromatography (5-40% Et_2O in hexanes) furnished the product (110 mg, 89%) as a pale-yellow oil.

Second run: Ynone (109 mg, 0.300 mmol), P(*n*-Bu)$_3$ (15 μL, 0.060 mmol). Product: 109 mg, 88%.

^{1}H NMR (300 MHz) δ 7.60-7.56 (m, 3H), 7.46-7.39 (m, 3H), 4.20 (m, 2H), 4.10 (q, J=7.1 Hz, 2H), 3.91 (s, 1H), 3.67 (s, 3H), 3.15 (m, 1H), 3.02 (m, 1H), 2.84 (ddd, J=14.4 Hz, J=10.1 Hz, J=1.5 Hz, 1H), 2.52 (dd, J=13.5 Hz, J=7.0 Hz, 1H), 2.35 (dd, J=14.4 Hz, J=4.3 Hz, 1H), 1.71 (dd, J=13.5 Hz, J=11.5 Hz, 1H), 1.24 (t, J=7.1 Hz, 3H), 1.18 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 207.9, 173.2, 171.7, 170.9, 138.8, 134.1, 131.9, 131.2, 130.7, 129.2, 62.1, 61.9, 61.1, 52.8, 50.0, 48.9, 43.1, 40.1, 36.1, 14.22, 14.16.

FTIR (thin film) 3057, 2982, 2874, 1731, 1621, 1494, 1448, 1367, 1261, 1097, 1064, 1028, 955 cm^{-1}.

LC-MS calc. for $C_{23}H_{26}O_7$ [M+1] 415.2, found, 415.1.

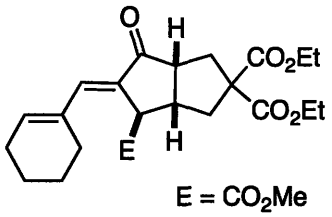


Table 3.4, entry 2. The general procedure was followed. Ynone (126 mg, 0.300 mmol), P(*n*-Bu)$_3$ (15 μL, 0.060 mmol). Purification by flash chromatography (10-40% Et_2O in hexanes) furnished the product (113 mg, 90%) as a pale-yellow oil.

Second run: Ynone (126 mg, 0.300 mmol), P(*n*-Bu)$_3$ (15 μL, 0.060 mmol). Product: 106 mg, 85%.

^{1}H NMR (300 MHz) δ 7.06 (s, 1H), 6.32 (t, J=3.7 Hz, 1H), 4.18 (m, 2H), 4.10 (q, J=7.1 Hz, 2H), 3.89 (broad, 1H), 3.66 (s, 3H), 3.01 (m, 1H), 2.87 (m, 1H), 2.79 (ddd, J=14.3 Hz, J=10.2 Hz, J=1.4 Hz, 1H), 2.49 (dd, J=13.3 Hz, J=7.0 Hz, 1H), 2.29-2.21 (m, 5H), 1.74 (dd, J=13.3 Hz, J=11.5 Hz, 1H), 1.68-1.54 (m, 4H), 1.23 (t, J=7.1 Hz, 3H), 1.19 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 208.2, 173.9, 171.8, 171.0, 143.6, 142.8, 135.2, 127.8, 62.0, 61.8, 61.1, 52.6, 49.8, 48.3, 42.8, 40.1, 36.1, 27.1, 26.8, 22.5, 21.5, 14.22, 14.18.

FTIR (thin film) 2981, 2935, 2862, 1715, 1603, 1436, 1366, 1222, 1096, 1064, 1028, 941, 860 cm^{-1}.

LC-MS calc. for $C_{23}H_{30}O_7$ [M+1] 419.2, found, 419.1.

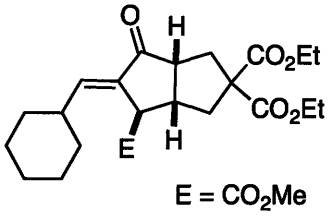


Table 3.4, entry 3. The general procedure was followed, except 1:1 CH_2Cl_2:EtOAc was used. Ynone (126 mg, 0.300 mmol), P(*n*-Bu)$_3$ (15 μL, 0.060 mmol). Purification by flash chromatography (5-40% Et_2O in hexanes) furnished the product (90.5 mg, 72%) as a colorless oil.

Second run: Ynone (126 mg, 0.300 mmol), P(*n*-Bu)$_3$ (15 μL, 0.060 mmol). Product: 96.0 mg, 76%.

^{1}H NMR (300 MHz) δ 6.60 (dd, J=10.6 Hz, J=1.8 Hz, 1H), 4.21-4.13 (m, 2H), 4.11 (q, J=7.1 Hz, 2H), 3.65 (s, 3H), 3.60 (s, 1H), 2.94 (m, 1H), 2.78 (ddd, J=14.3, J=10.2 Hz, J=1.5 Hz, 1H), 2.49 (m, 1H), 2.33-2.25 (m, 2H), 1.76-1.59 (m, 5H), 1.52-1.44 (m, 1H), 1.36-1.10 (m, 6H), 1.23 (t, J=7.1 Hz, 3H), 1.19 (t, J=7.2 Hz, 3H).

^{13}C NMR (75 MHz) δ 207.2, 173.6, 171.7, 171.0, 148.2, 132.1, 62.0, 61.9, 61.1, 52.5, 51.2, 46.9, 41.8, 39.9, 39.4, 35.8, 31.8, 31.4, 25.9, 25.5, 25.3, 14.23, 14.17.

FTIR (thin film) 2982, 2929, 2853, 1732, 1644, 1447, 1367, 1259, 1185, 1099, 1064, 1028, 932 cm^{-1}.

LC-MS calc. for $C_{23}H_{32}O_7$ [M+1] 421.2, found, 421.2.

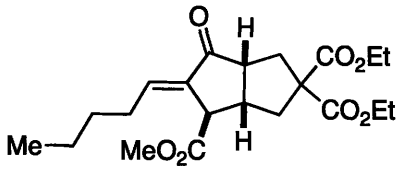


Table 3.4, entry 4. The general procedure was followed. Ynone (79 mg, 0.20 mmol), P(*n*-Bu)$_3$ (10 μL, 0.040 mmol). Purification by flash chromatography (5-40% Et_2O in hexanes) furnished the product (60.4 mg, 77%) as a colorless oil.

Second run: Ynone (79 mg, 0.20 mmol), P(*n*-Bu)$_3$ (10 μL, 0.040 mmol). Product: 61.0 mg, 77%.

^{1}H NMR (300 MHz) δ 6.78 (td, J=7.7 Hz, J=1.9 Hz, 1H), 4.18 (m, 2H), 4.11 (q, J=7.1 Hz, 2H), 3.65 (s, 3H), 3.57 (broad, 1H), 3.08 (m, 1H), 2.94 (m, 1H), 2.78 (ddd, J=14.4 Hz, J=10.2 Hz, J=1.3 Hz, 1H), 2.49 (dd, J=13.3 Hz, J=7.1 Hz, 1H), 2.27 (dd, J=14.4 Hz, J=4.2 Hz, 1H), 2.21 (m, 2H), 1.70 (dd, J=13.4 Hz, J=10.6 Hz, 1H), 1.46-1.20 (m, 4H), 1.23 (t, J=7.1 Hz, 3H), 1.19 (t, J=7.1 Hz, 3H), 0.87 (t, J=7.2 Hz, 3H).

^{13}C NMR (75 MHz) δ 206.6, 173.3, 171.7, 171.0, 144.1, 134.2, 62.0, 61.9, 61.1, 52.5, 51.2, 47.0, 41.8, 39.9, 35.9, 30.5, 29.9, 22.7, 14.23, 14.18, 14.08.

FTIR (thin film) 2958, 2873, 1732, 1645, 1587, 1445, 1367, 1261, 1187, 1100, 1064, 1028, 935, 861 cm^{-1}.

LC-MS calc. for $C_{21}H_{30}O_7$ [M+1] 395.2, found, 395.1.

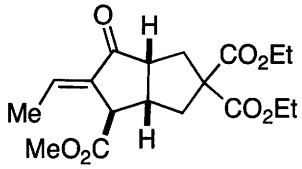


Table 3.4, entry 5. The general procedure was followed. Ynone (70.5 mg, 0.200 mmol), P(*n*-Bu)$_3$ (10 μL, 0.040 mmol). Purification by flash chromatography (5-40% Et_2O in hexanes) furnished the product (39.8 mg, 56%) as a colorless oil.

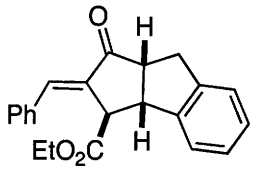
Second run: Ynone (70.5 mg, 0.200 mmol), P(*n*-Bu)$_3$ (10 μL, 0.040 mmol). Product: 38.8 mg, 55%.

^{1}H NMR (300 MHz) δ 6.87 (qd, J=7.2 Hz, J=1.8 Hz, 1H), 4.18 (m, 2H), 4.11 (q, J=7.1 Hz, 2H), 3.66 (s, 3H), 3.59 (broad, 1H), 3.08 (m, 1H), 2.97 (m, 1H), 2.78 (ddd, J=14.4 Hz, J=10.2 Hz, J=1.4 Hz, 1H), 2.49 (dd, J=13.3 Hz, J=7.1 Hz, 1H), 2.27 (dd, J=14.4 Hz, J=4.0 Hz, 1H), 1.88 (dd, J=7.3 Hz, J=1.0 Hz, 3H), 1.71 (dd, J=13.4 Hz, J=11.4 Hz, 1H), 1.24 (t, J=7.1, 3H), 1.19 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 206.3, 173.1, 171.7, 171.0, 138.9, 135.4, 62.0, 61.9, 61.1, 52.5, 51.3, 46.9, 41.6, 39.9, 35.9, 15.8, 14.23, 14.17.

FTIR (thin film) 2983, 2875, 1732, 1651, 1585, 1437, 1367, 1262, 1186, 1100, 1064, 1029, 919, 860 cm^{-1}.

LC-MS calc. for $C_{18}H_{24}O_7$ [M+1] 353.2, found, 353.1.



Eq 3.7, bottom. The general procedure was followed. Ynone (133 mg, 0.400 mmol), P(*n*-Bu)$_3$ (20 μL, 0.080 mmol). Purification by flash chromatography (5-40% Et_2O in hexanes) furnished the product (115 mg, 86%) as a pale-yellow oil.

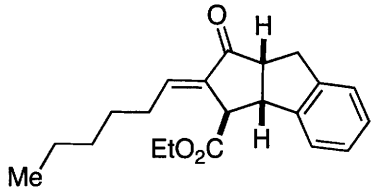
Second run: Ynone (133 mg, 0.400 mmol), P(*n*-Bu)$_3$ (20 μL, 0.080 mmol). Product: 121 mg, 91%.

^{1}H NMR (300 MHz, C_6D_6) δ 7.60 (d, J=1.6 Hz, 1H), 7.37 (m, 1H), 7.35 (m, 1H), 6.98 (m, 2H), 6.93-6.80 (m, 5H), 4.42 (d, J=1.6 Hz, 1H), 3.99-3.78 (m, 3H), 3.47 (d, J=16.2 Hz, 1H), 3.21 (m, 1H), 2.90 (dd, J=16.1 Hz, J=8.7 Hz, 1H), 0.81 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz, C_6D_6) δ 208.0, 173.0, 143.4, 143.3, 137.5, 135.0, 133.7, 131.5, 130.4, 129.2, 128.3, 127.9, 125.5, 124.5, 61.6, 52.1, 50.6, 50.1, 36.3, 14.4.

FTIR (thin film) 3068, 3024, 2980, 2936, 2909, 2835, 1715, 1622, 1575, 1448, 1315, 1290, 1222, 1199, 1154, 1095, 1029, 957 cm^{-1}.

LC-MS calc. for $C_{22}H_{20}O_3$ [M+1] 333.1, found, 333.1.



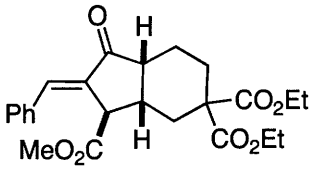
Eq 3.7, top. The general procedure was followed. Ynone (97.9 mg, 0.300 mmol), P(*n*-Bu)$_3$ (15 μL, 0.060 mmol). Purification by flash chromatography (5-40% Et_2O in hexanes) furnished the product (51.3 mg, 52%) as a colorless oil.
Second run: Ynone (97.9 mg, 0.300 mmol), P(*n*-Bu)$_3$ (15 μL, 0.060 mmol). Product: 55.3 mg, 56%.

^{1}H NMR (300 MHz, C_6D_6) δ 7.01-6.85 (m, 4H), 6.71 (td, J=7.7 Hz, J=1.8 Hz, 1H), 4.02 (broad, 1H), 3.98-3.87 (m, 3H), 3.42 (d, J=16.1 Hz, 1H), 3.22 (app t, J=8.1 Hz, 1H), 2.87 (dd, J=16.1 Hz, J=8.6 Hz, 1H), 2.07-1.81 (m, 2H), 1.06-0.84 (m, 6H), 0.90 (t, J=7.1 Hz, 3H), 0.69 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz, C_6D_6) δ 206.3, 172.7, 143.3, 143.2, 141.7, 135.2, 127.9, 127.3, 125.3, 124.1, 61.0, 51.5, 49.9, 48.6, 35.8, 31.7, 29.9, 28.0, 22.7, 14.2, 14.1.

FTIR (thin film) 2929, 2857, 1732, 1645, 1459, 1444, 1367, 1328, 1313, 1269, 1235, 1163, 1133, 1028, 939 cm^{-1}.

LC-MS calc. for $C_{21}H_{26}O_3$ [M+1] 327.2, found, 327.2.



Eq 3.8. The general procedure was followed. Ynone (128 mg, 0.300 mmol), P(*n*-Bu)$_3$ (15 μL, 0.060 mmol). Purification by flash chromatography (5-40% Et_2O in hexanes) furnished the product (73.0 mg, 57%) as a colorless oil.

Second run: Ynone (128 mg, 0.300 mmol), P(*n*-Bu)$_3$ (15 μL, 0.060 mmol). Product: 79.8 mg, 62%.

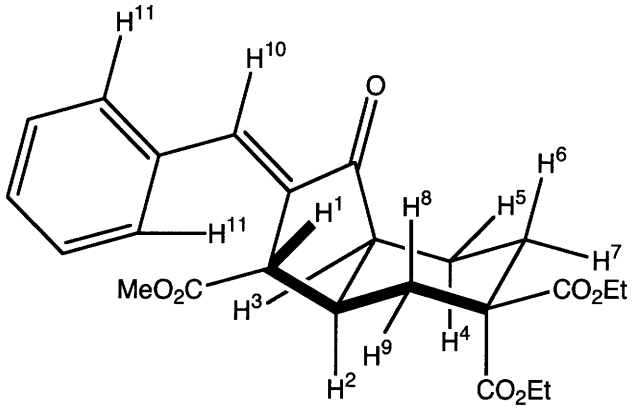
^{1}H NMR (300 MHz) δ 7.66 (d, J=1.2 Hz, 1H), 7.57-7.54 (m, 2H), 7.46-7.39 (m, 3H), 4.23 (q, J=7.2 Hz, 2H), 4.08 (qd, J=7.1 Hz, J=1.2 Hz, 2H), 3.72 (s, 3H), 3.71 (s, 1H), 3.00 (m, 1H), 2.83 (m, 1H), 2.44-2.32 (m, 2H), 2.17 (m, 1H), 1.64 (m, 1H), 1.44 (m, 1H), 1.27 (t, J=7.1 Hz, 3H), 1.17 (t, J=7.2 Hz, 3H), 1.10 (t, J=13.0 Hz, 1H).

^{13}C NMR (75 MHz) δ 205.4, 172.8, 171.7, 170.5, 137.7, 134.2, 132.1, 131.0, 130.5, 129.2, 61.8, 61.6, 54.2, 52.7, 51.0, 45.3, 36.3, 34.5, 27.3, 19.1, 14.3, 14.2.

FTIR (thin film) 2980, 2954, 1732, 1627, 1448, 1367, 1315, 1229, 1175, 1127, 1050, 1018 cm^{-1}.

LC-MS calc. for $C_{24}H_{28}O_7$ [M+1] 429.2, found, 429.1.

Relative Stereochemistry:

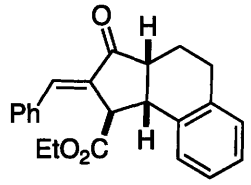


Protons were assigned based upon a gCOSY experiment and J couplings.

Relative stereochemistry of H^1 to H^2 is based upon the lack of a J coupling. H^1 appears as a singlet and shows no cross peak in the gCOSY, indictating a dihedral angle of 80-90°, which is consistent with the assigned structure.

Relative stereochemistry of H^2 to H^3 is assigned based upon a strong NOESY cross peak. Moreover, H^2 has a large J coupling to H^8, which is an apparent triplet ($J_H{}^2{}_H{}^8=J_H{}^8{}_H{}^9$;$J_H{}^{axial}{}_H{}^{axial}=J^{geminal}$). H^2 must be in an axial-axial relationship with H^8. So if H^3 were axial (it is not, it is equatorial), H^2 should be an apparent td (two $J_H{}^{axial}{}_H{}^{axial}$, one $J_H{}^{axial}{}_H{}^{eq}$).

Olefin Geometry: NOESY crosspeak between H^1 and H^{11}.



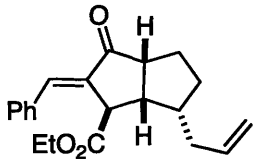
Eq 3.9. The general procedure was followed. Ynone (66.5 mg, 0.192 mmol), P(*n*-Bu)$_3$ (9.5 μL, 0.038 mmol). Purification by flash chromatography (5-30% Et_2O in hexanes) furnished the product (48.0 mg, 72%) as a pale yellow oil.

^{1}H NMR (300 MHz) δ 7.57 (d, J=1.8 Hz, 1H), 7.53-7.49 (m, 2H), 7.42-7.36 (m, 4H), 7.19 (td, J=7.5 Hz, J=1.3 Hz, 1H), 7.11 (td, J=7.4 Hz, J=0.8 Hz, 1H), 7.03 (d, J=7.5 Hz, 1H), 4.26-4.16 (m, 3H), 3.95 (d, J=8.8 Hz, 1H), 3.17 (m, 1H), 2.72-2.56 (m, 2H), 2.41 (m, 1H), 1.89 (m, 1H), 1.23 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 207.3, 173.1, 137.6, 137.0, 136.7, 134.3, 132.9, 131.0, 130.4, 129.32, 129.30, 129.0, 126.9, 126.8, 61.7, 55.0, 46.0, 42.2, 26.4, 22.1, 14.3.

FTIR (thin film) 3059, 3023, 1980, 2934, 1723, 1622, 1575, 1493, 1449 cm^{-1}.

LCMS calc. for $C_{23}H_{22}O_3$ [M+1] 347.2, found 347.1.



Eq 3.10. The general procedure was followed. Ynone (130 mg, 0.400 mmol), P(*n*-Bu)$_3$ (20 μL, 0.080 mmol). Purification by flash chromatography (5-25% Et_2O in hexanes) furnished the product (93 mg, 72%) as a pale-yellow oil.

Second run: Ynone (130 mg, 0.400 mmol), P(*n*-Bu)$_3$ (20 μL, 0.080 mmol). Product: 98.7 mg, 76%.

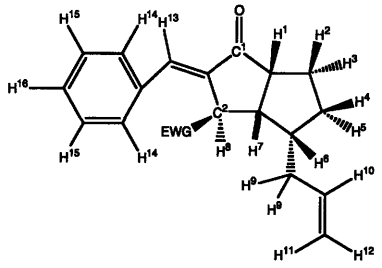
^{1}H NMR (300 MHz) δ 7.63-7.55 (m, 3H), 7.48-7.41 (m, 3H), 5.77 (ddt, J=17.1 Hz, J=10.1 Hz, J=7.0 Hz, 1H), 5.09-4.99 (m, 2H), 4.24-4.06 (m, 2H), 3.91 (broad, 1H), 3.09 (m, 1H), 2.48 (t, J=9.2 Hz, 1H), 2.43-2.34 (m, 1H), 2.22-2.01 (m, 2H), 1.90-1.77 (m, 2H), 1.49-1.25 (m, 2H), 1.20 (t, J=7.2 Hz, 3H).

^{13}C NMR (75 MHz) δ 210.1, 173.2, 137.4, 136.6, 134.5, 133.1, 131.1, 130.4, 129.7, 129.1, 128.7, 116.6, 61.4, 51.3, 50.0, 49.0, 45.9, 37.8, 32.2, 27.8, 14.3.

FTIR (thin film) 3073, 2956, 1716, 1622, 1494, 1448, 1367, 1255, 1159, 1098, 1030, 993, 921 cm^{-1}.

LC-MS calc. for $C_{21}H_{24}O_3$ [M+1] 325.2, found, 325.1.

Determination by NMR of the stereochemistry of the product. The protons were assigned on the basis of a gCOSY experiment.

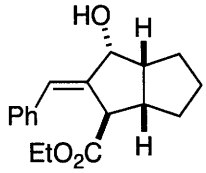


Stereochemistry of the allyl group: There is a NOESY cross peak between H^8 and H^9. The relative volume of the cross peaks (H^8,H^9):(H^8,H^7) is 781:432, which indicates that there is direct transfer from H^8 to H^9. H^7 is an apparent triplet, indicating that $J_{H^7H^1} \cong J_{H^7H^6}$, which is consistent with the proposed structure.

Olefin geometry: There are NOESY cross peaks between H^8 and H^{14}. The gHMBC relative cross peak volume for H^{13},C^1:H^{13},C^2 is 3.7:4.4, so H^{13} is 180° from C^2 and 0° from C^1.

The NMR spectra for all other [3.3.0] systems are similar with regard to chemical shifts and splitting patterns, and the structures are therefore assigned by analogy with the above.

IV. Derivatizations



Eq 3.11. $CeCl_3$ (64 mg, 0.26 mmol) was added to a stirred solution of enone (49 mg, 0.17 mmol) in MeOH (3.5 mL) under argon. This solution was stirred for 10 min at room temperature, and then it was cooled to –10 °C. Next, a solution of $NaBH_4$ (7.6 mg, 0.21 mmol) in MeOH (1.0 mL) was added dropwise. The resulting mixture was stirred at –10 °C for 20 min, and then it was warmed to room temperature and stirred for an additional hour. The reaction was quenched with H_2O (5 mL), and the mixture was extracted with Et_2O (3x10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by flash chromatography (10-40% EtOAc in hexanes), which provided 44.5 mg (90%) of a clear, colorless oil.

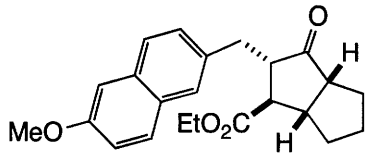
Second run: $CeCl_3$ (68 mg, 0.28 mmol), enone (52 mg, 0.28 mmol), $NaBH_4$ (8.2 mg, 0.22 mmol). Product: 47.1 mg (89%).

^1H NMR (300 MHz) δ 7.37-7.23 (m, 5H), 6.62 (m, 1H), 5.02 (d, J=7.1 Hz, 1H), 4.25-4.08 (m, 2H), 3.29 (s, 1H), 2.77-2.66 (m, 2H), 2.06 (broad, 1H), 1.91 (m, 1H), 1.59 (m, 1H), 1.49-1.40 (m, 3H), 1.32 (m, 1H), 1.26 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 174.5, 143.1, 136.8, 128.8, 128.5, 127.1, 123.7, 76.1, 61.2, 52.0, 45.3, 45.2, 35.4, 26.1, 25.7, 14.4.

FTIR (thin film) 3439 (broad), 2952, 2867, 1715, 1599, 1494, 1446, 1368, 1320, 1259, 1222, 1142, 1029, 921 cm^{-1}.

LC-MS calc. for $C_{18}H_{22}O_3$ [M+Na] 309.1, found 309.1.



Eq. 3.12. The enone (0.043 g, 0.118 mmol) was added to a flask as a solution in MeOH (1.5 mL) containing Pd/C (degussa type) (0.005 g, 5% weight on carbon). The flask was purged with a balloon of H_2 and then a fresh balloon was attached and the mixture was stirred vigorously for 3 h at room temperature. The mixture was then filtered through silica gel with Et_2O washings (60 mL) and concentrated to yield 41 mg (95%) of a clear oil which was determined to be a 7:1 mixture of diastereomers by ^1H NMR analysis. A pure sample of the major isomer could be obtained by column chromatography (5-30% Et_2O in hexanes).

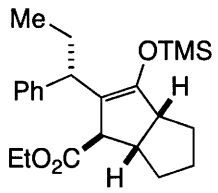
Second run: Enone (0.039 g, 0.107 mmol) and Pd/C (0.005 g). 0.038 g product, 97%, 8:1 d.r.

^1H NMR (500 MHz, C_6D_6) δ 7.52-7.50 (m, 2H), 7.45 (d, J=8.9 Hz, 1H), 7.33 (dd, J=8.5 Hz, J=1.6 Hz, 1H), 7.12 (obscured by solvent peak, 1H), 6.86 (d, J=2.3 Hz, 1H), 3.71-3.58 (m, 2H), 3.33 (s, 3H), 3.24 (dd, J=13.9 Hz, J=5.3 Hz, 1H), 3.07 (m, 1H), 2.95 (dd, J=13.9 Hz, J=6.5 Hz, 1H), 2.52 (m, 1H), 2.37 (m, 1H), 2.17 (dd, J=12.1 Hz, J=8.9 Hz, 1H), 1.80 (m, 1H), 1.45 (dd, J=12.6 Hz, J=6.4 Hz, 1H), 1.35-1.20 (m, 2H), 1.16-1.09 (m, 1H), 0.85 (m, 1H), 0.73 (t, J=7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.8, 174.9, 157.5, 134.0, 133.4, 129.2, 129.1, 128.5, 128.0, 127.0, 118.9, 105.8, 61.0, 55.7, 55.5, 51.7, 50.9, 43.5, 31.1, 32.9, 29.4, 25.2, 14.2.

FTIR (thin film) 2954, 2868, 1738, 1732, 1634, 1606, 1506, 1484, 1264, 1227 cm^{-1}.

LC-MS calc. for $C_{23}H_{26}O_4$ [M+Na] 367.1, found 367.0.



Eq 3.13. EtMgBr (0.065 mL of a 3.0 M solution in Et_2O, 0.189 mmol) was added to a -78 °C solution of HMPA (0.022 mL, 0.126 mmol) and CuBr·SMe_2 (1.3 mg, 0.006 mmol) in THF (0.75 mL). A solution of the enone (Table 3.3, entry 1) (18 mg, 0.063 mmol) and TMSCl (0.016 mL, 0.126 mmol) in THF (0.75 mL) was added dropwise. This solution was stirred a -78 °C for 2h, diluted with Et_2O, and then quenched with saturate NH_4Cl solution. After warming to room temperature the layers were separated, and the aqueous was extracted again with Et_2O. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to yield a 18.5 mg of a clear oil (70%). ^1H NMR showed primarily one diastereomer (>10:1).

E. References

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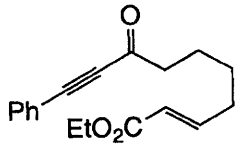
13. Other solvents such as Et_2O, toluene, and $CHCl_3$ were less effective.
14. (a) Trost, B. M.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933. (b) Rychnovsky, S. D.; Kim, J. *J. Org. Chem.* **1994**, *59*, 2659.
15. The isomerization product has been isolated as a side product.
16. The homologous substrate of **3.1** that would lead to [4.3.0] bicycle cyclizes but much less efficiently than **3.1** and the substrates shown in eq 3.8 and eq 3.9.
17. The relative stereochemistry shown in eq 3.12 and eq 3.13 is tentatively assigned as that shown in the text.

F. ^{1}H NMR Spectra of Selected Compounds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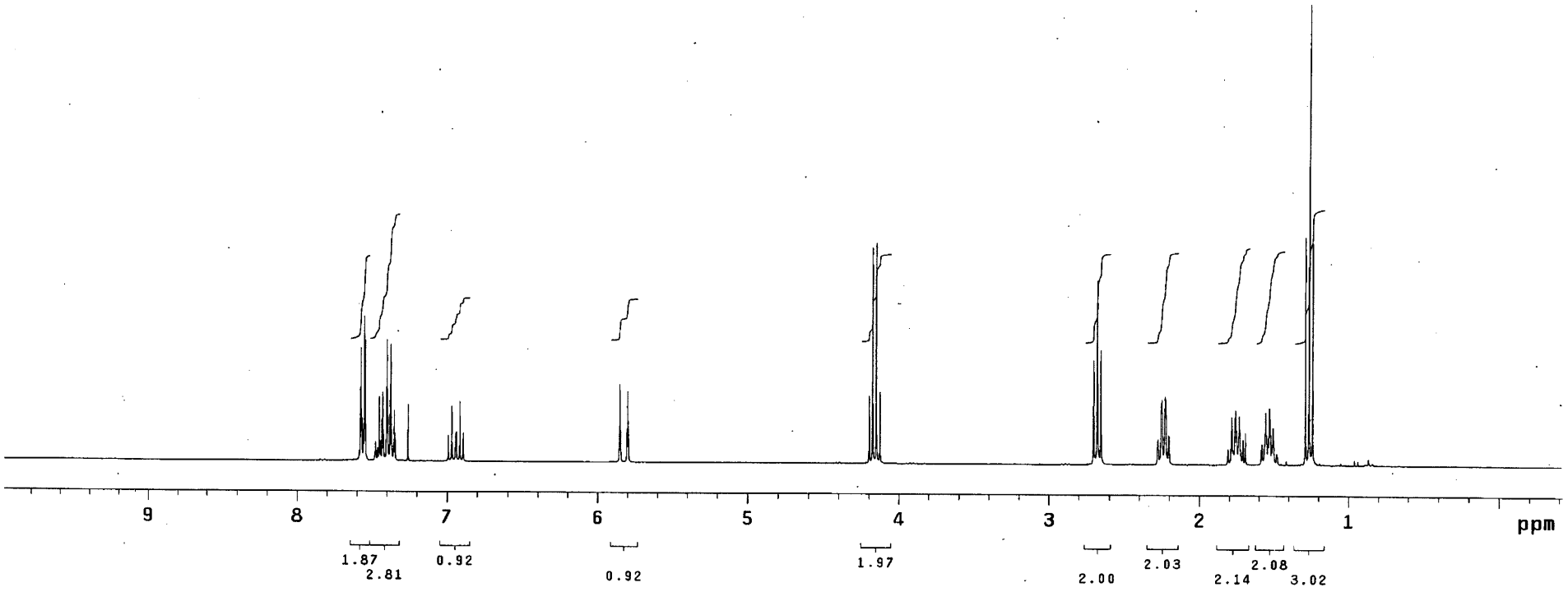
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0.92
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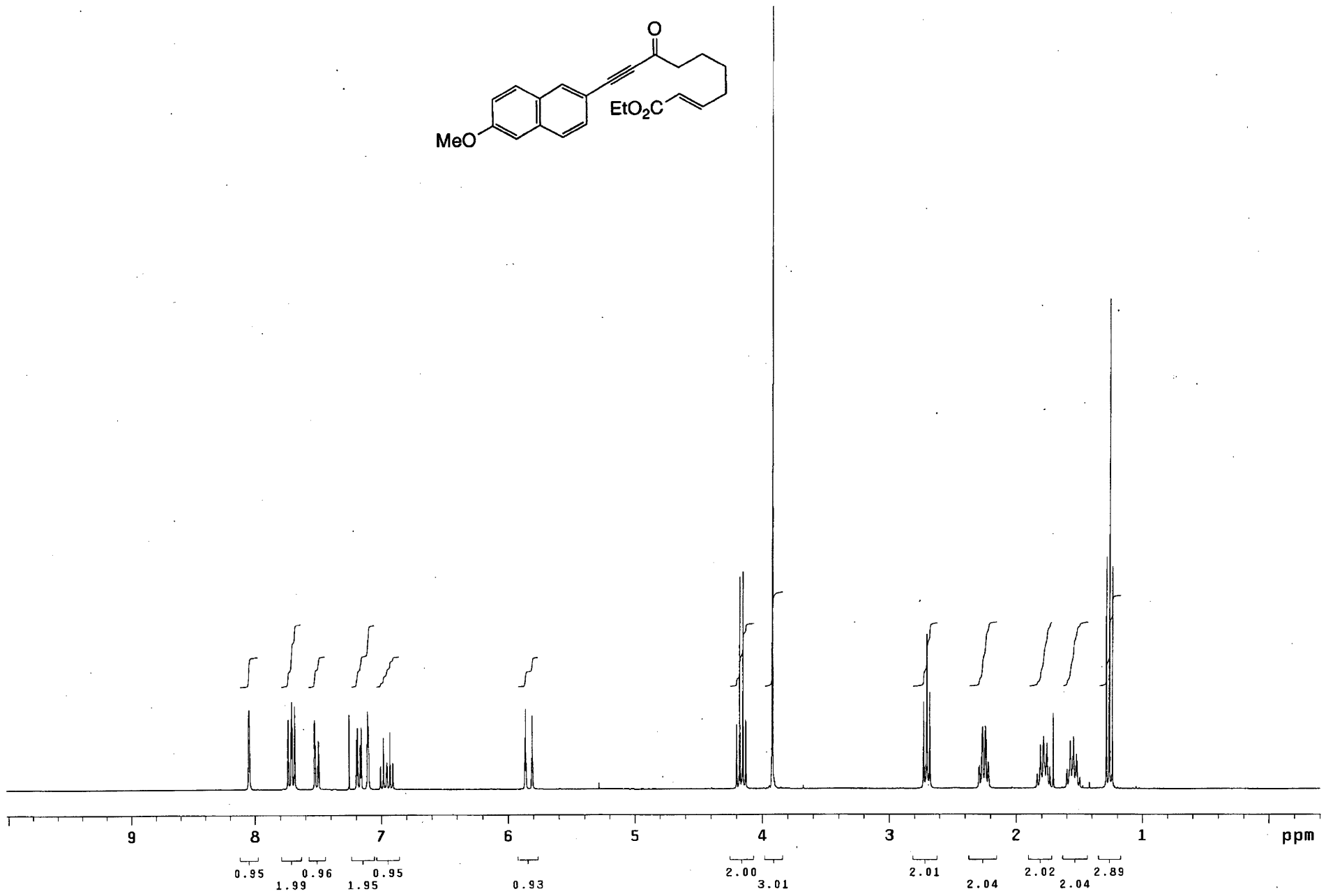
2.08
3.02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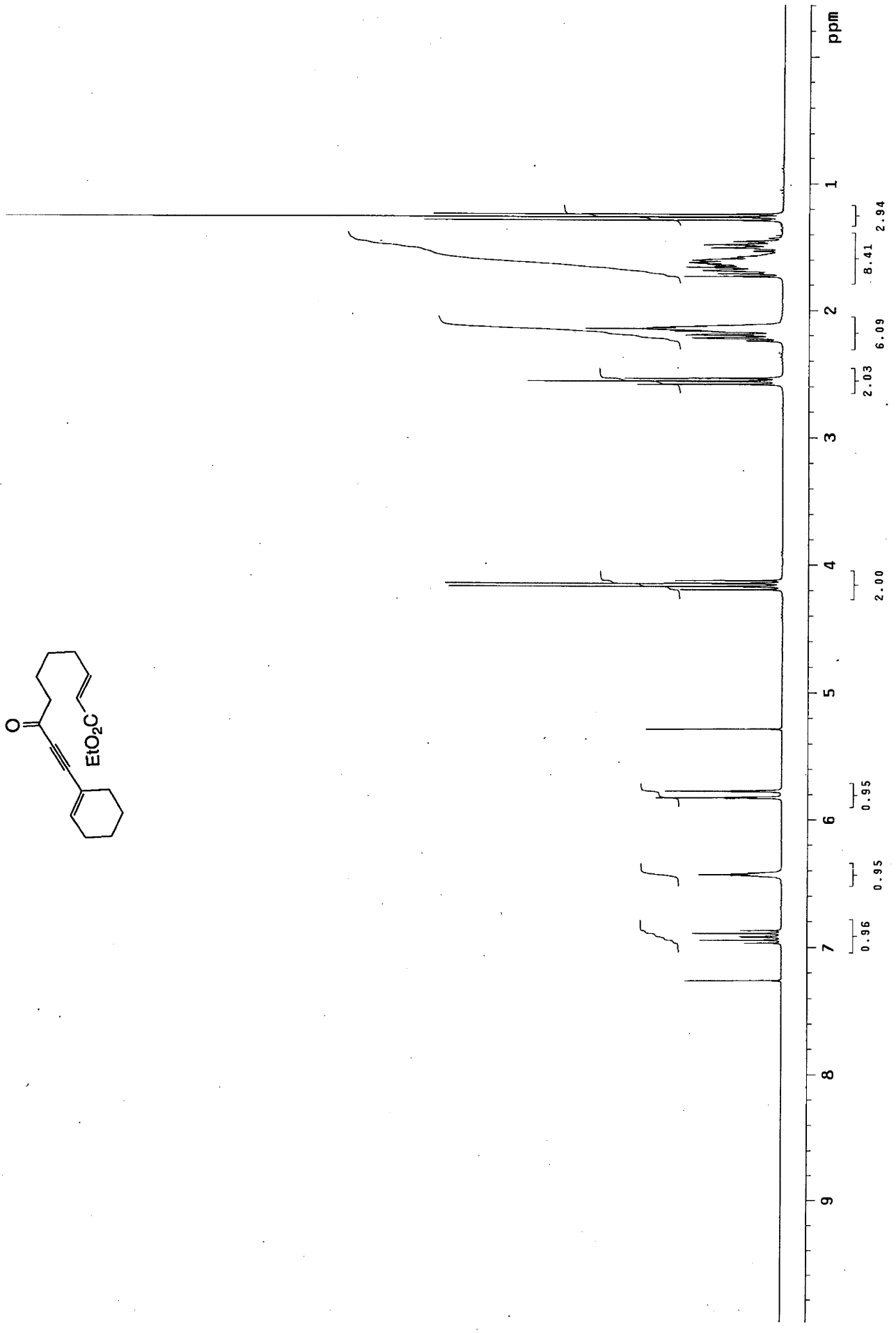
2.89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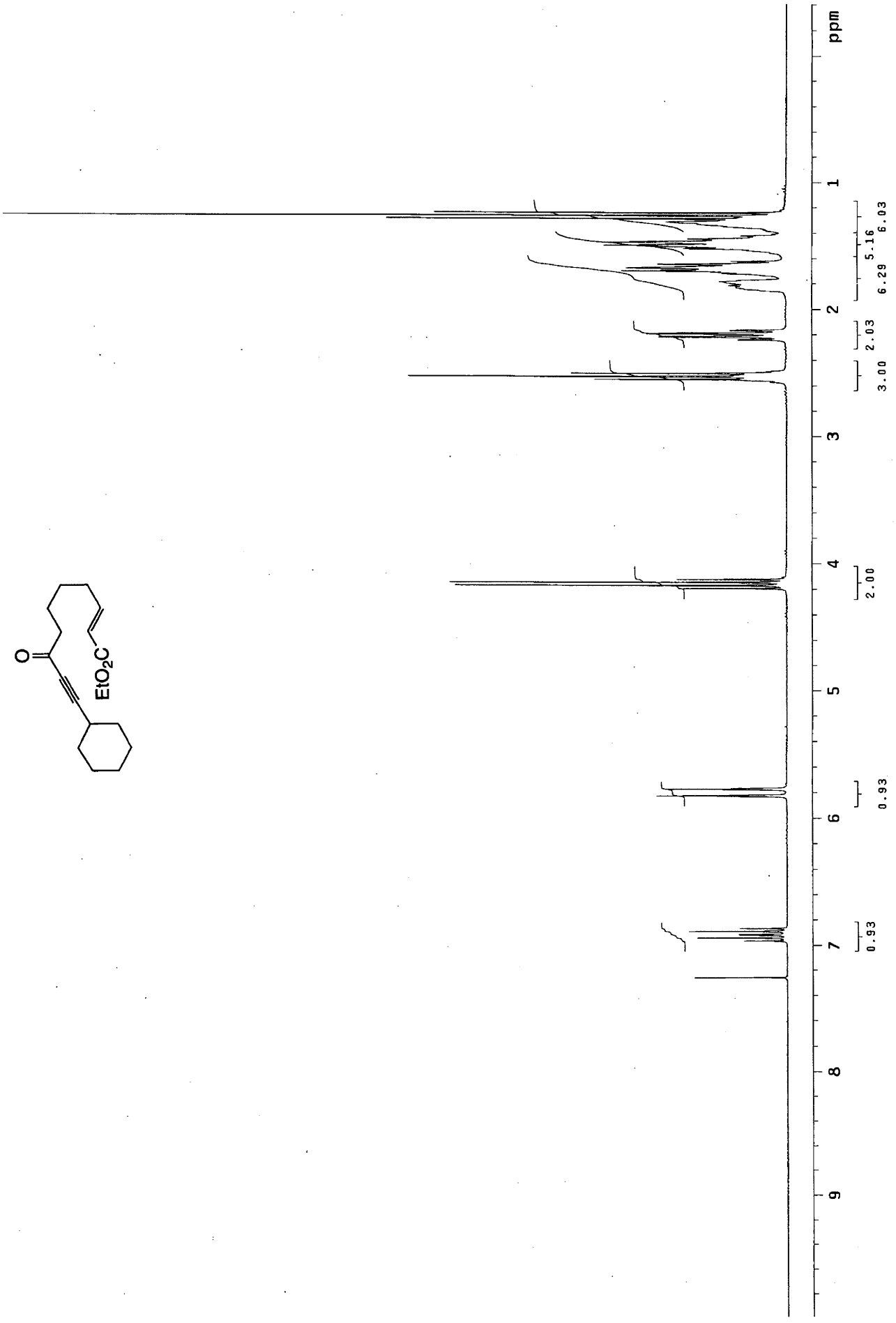
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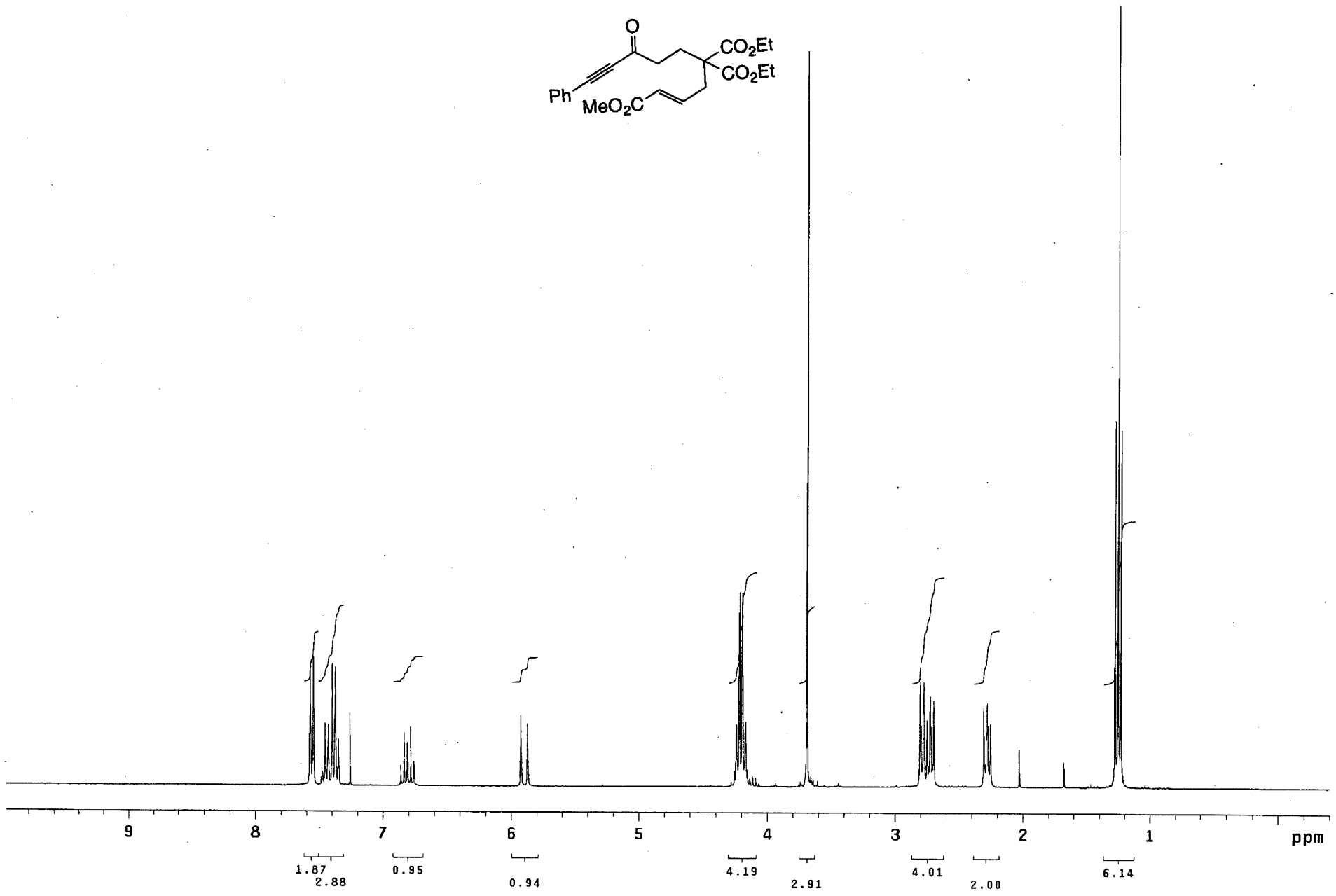
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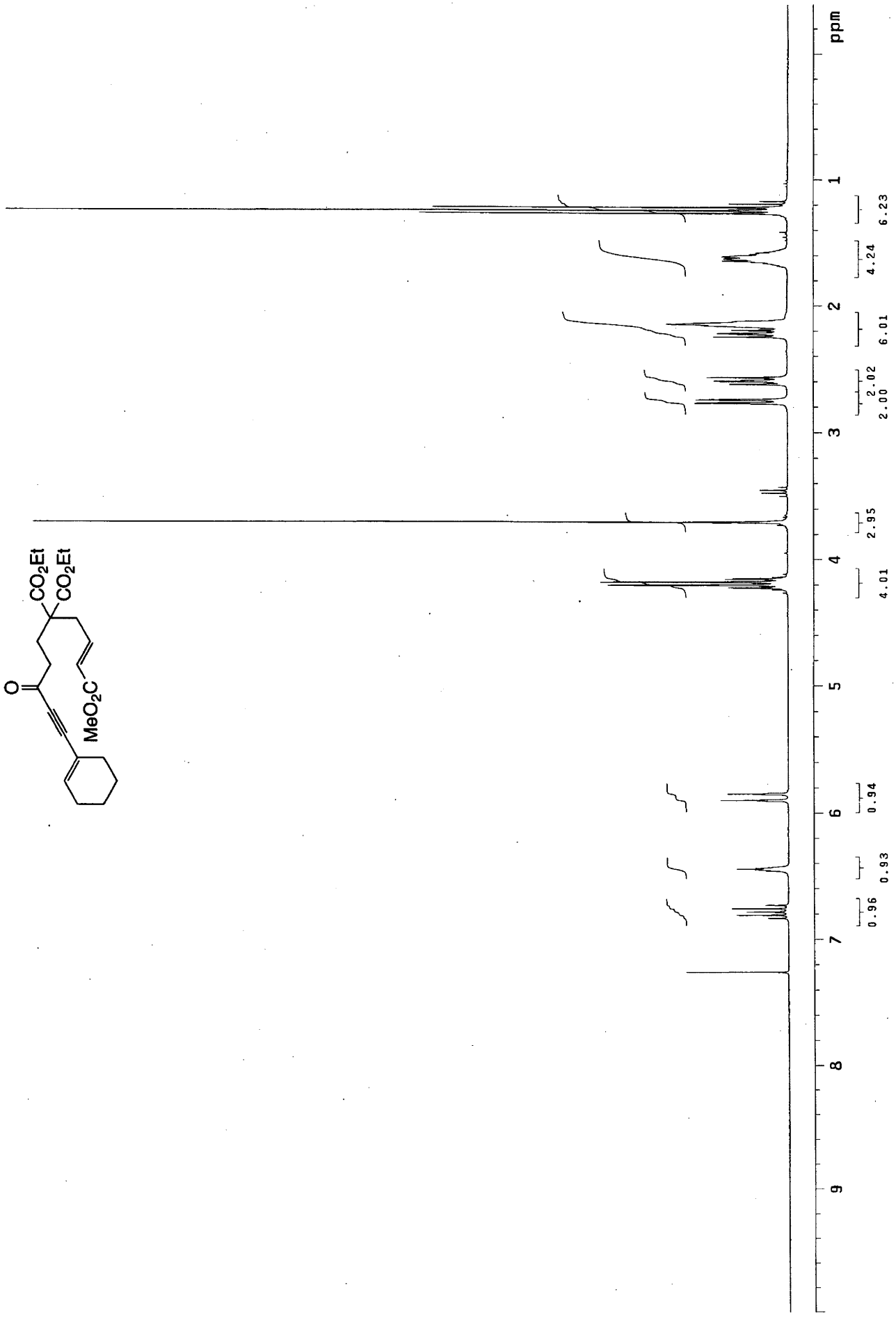
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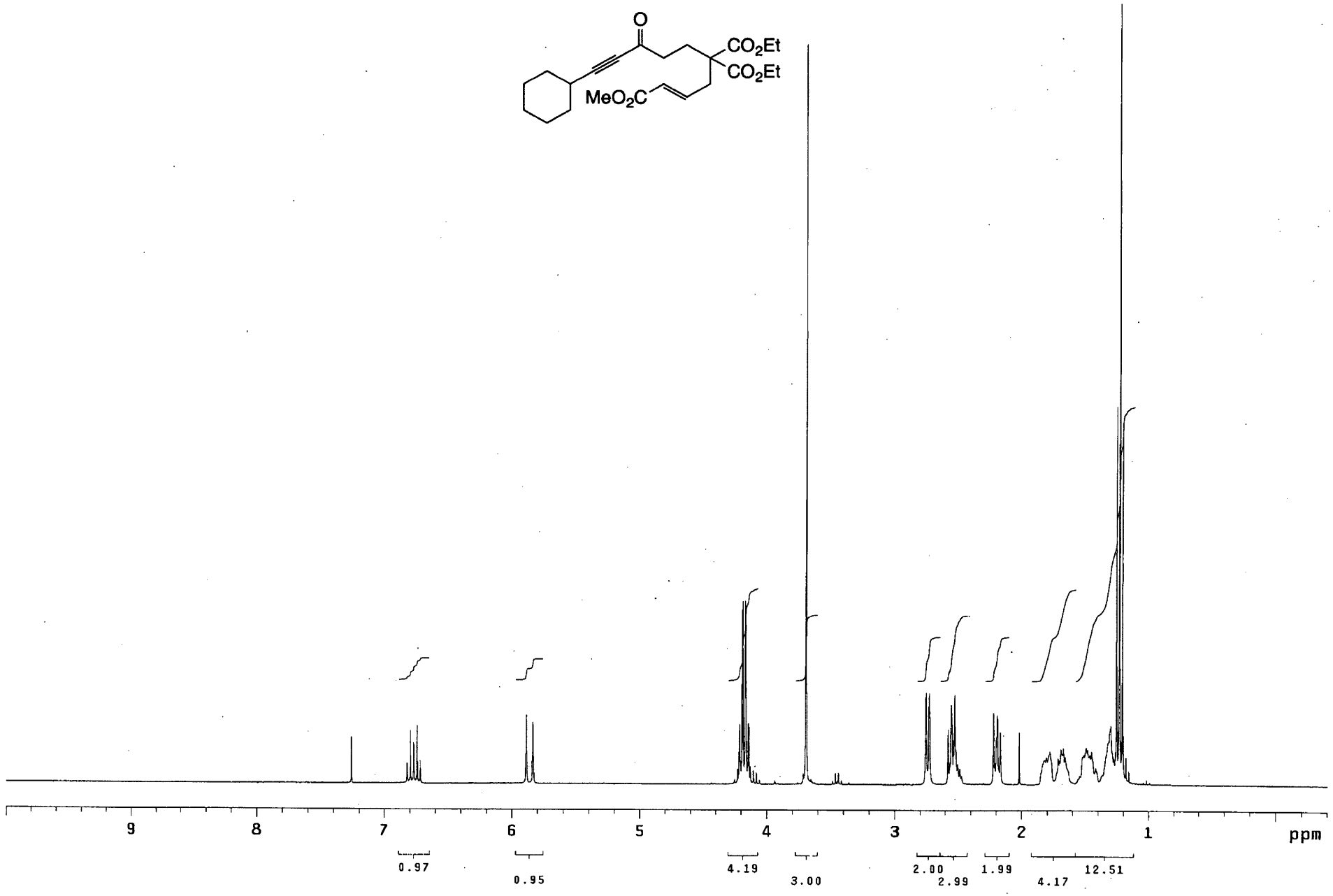
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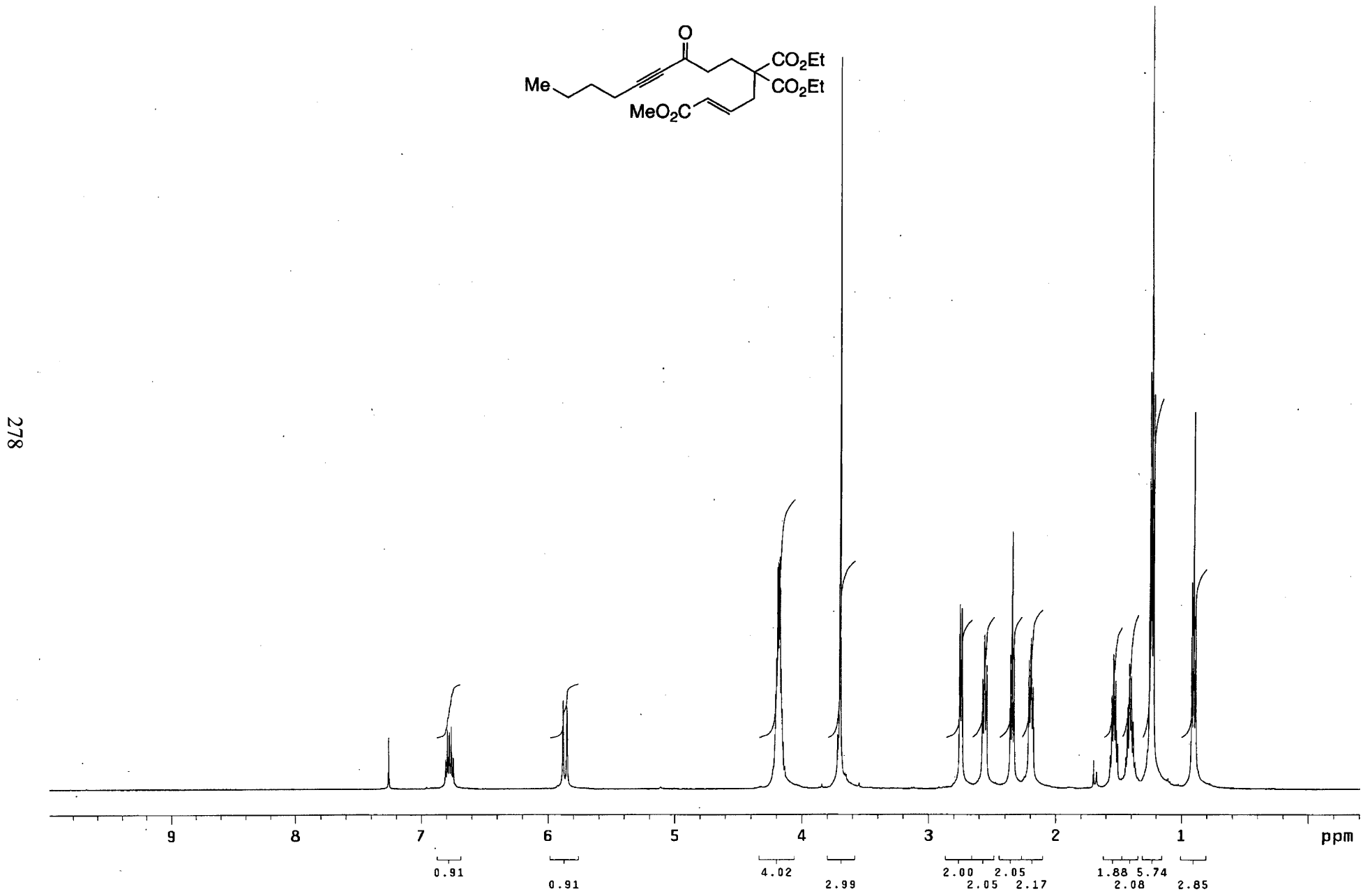
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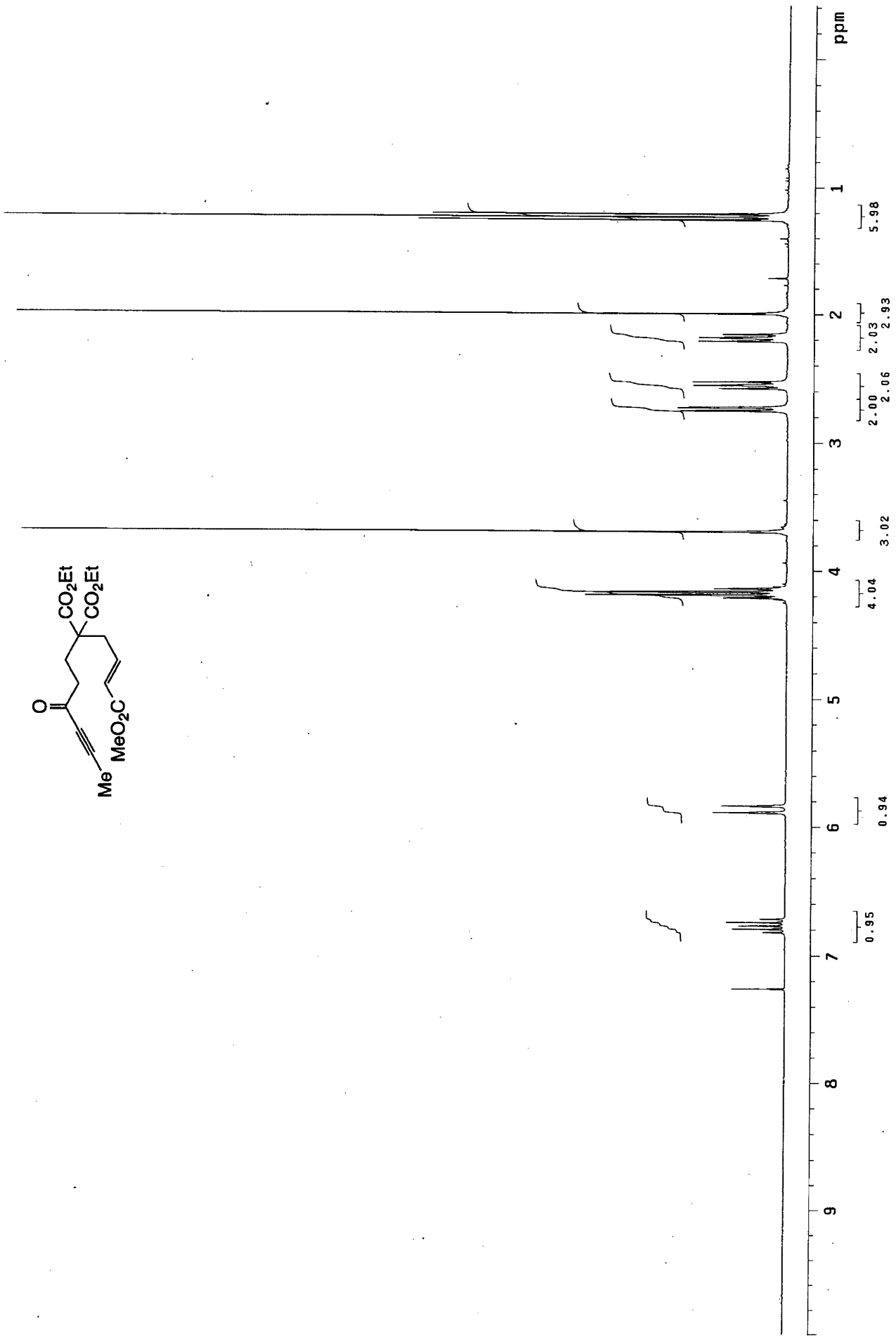
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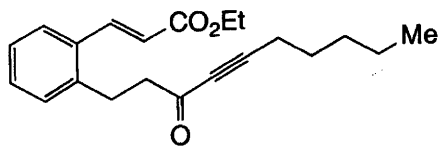
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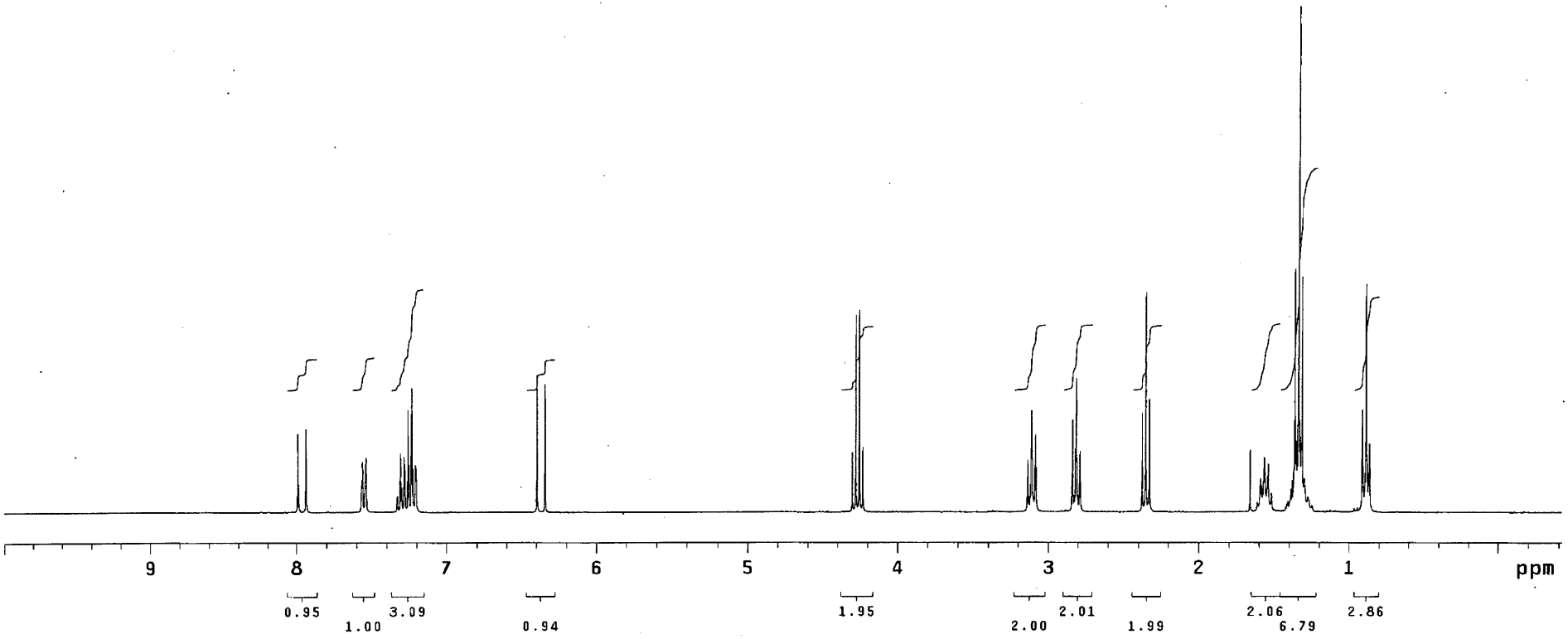
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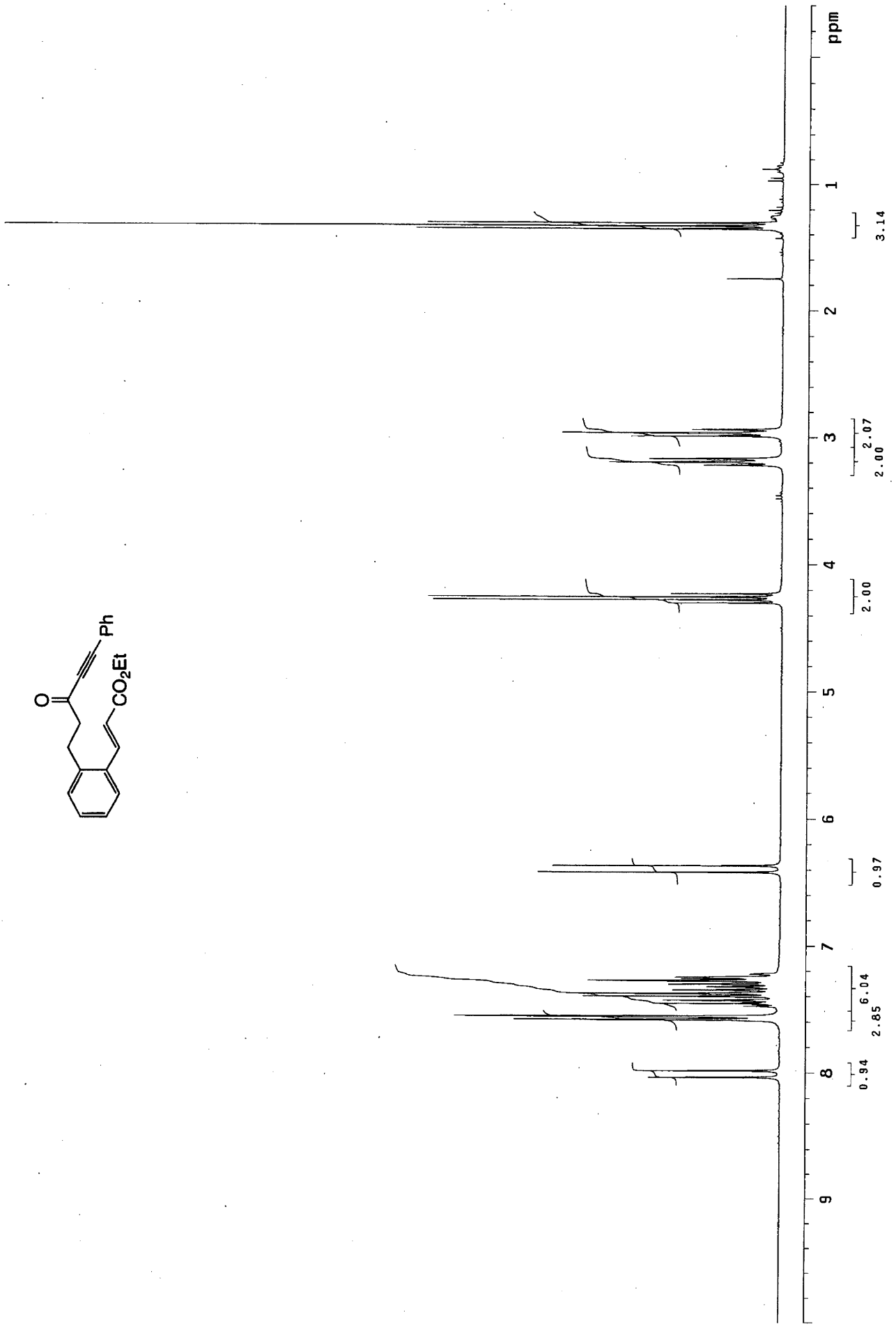
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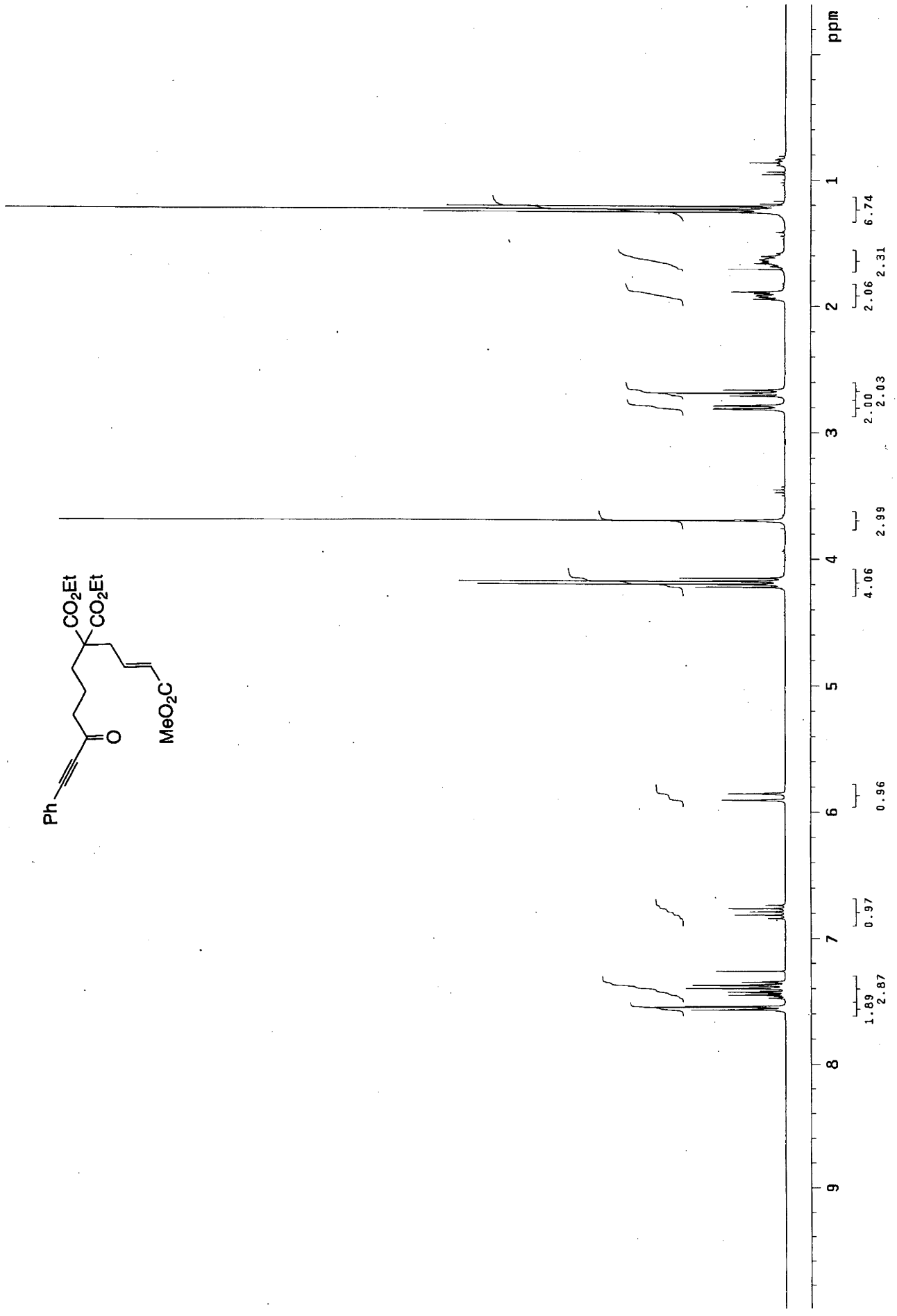
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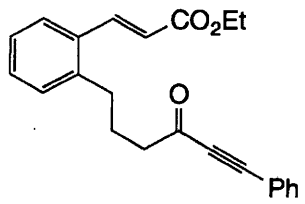
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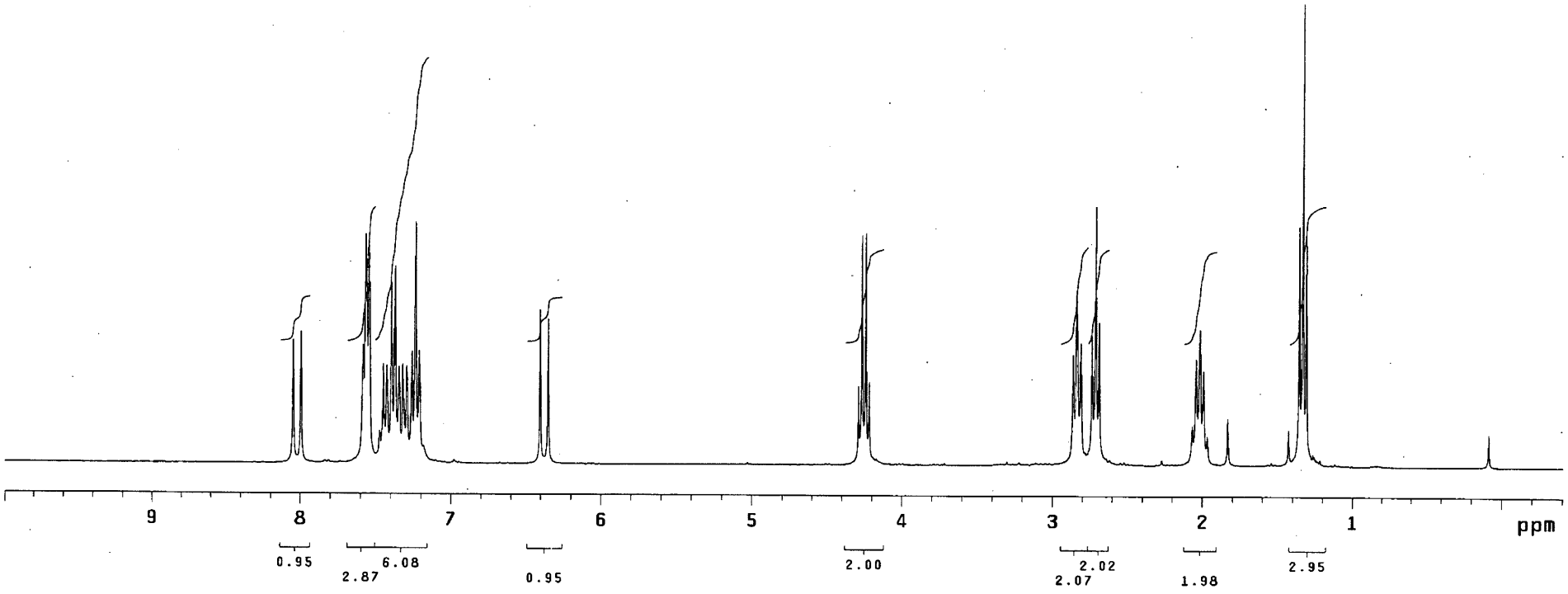
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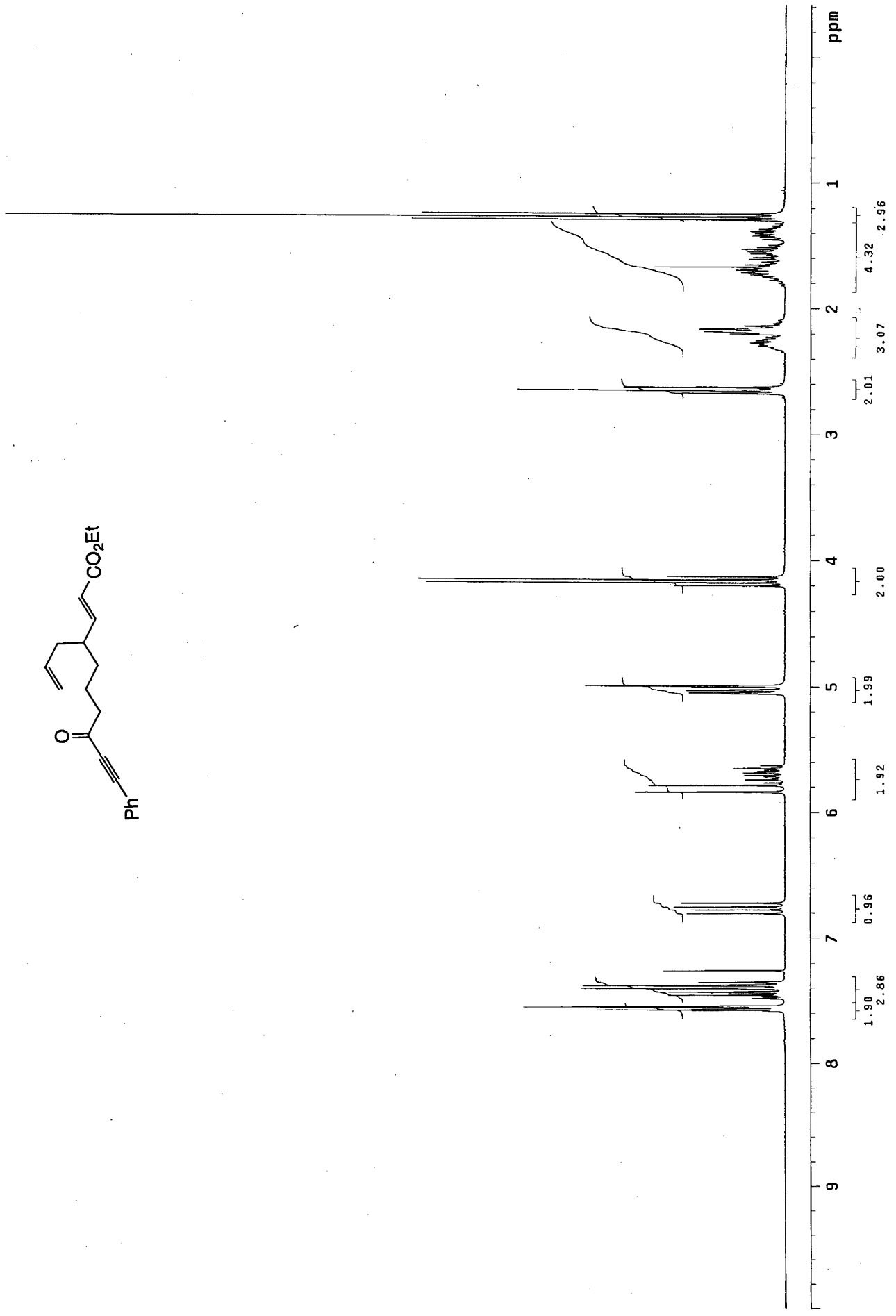
2.95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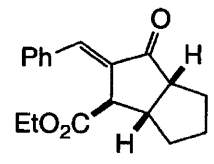
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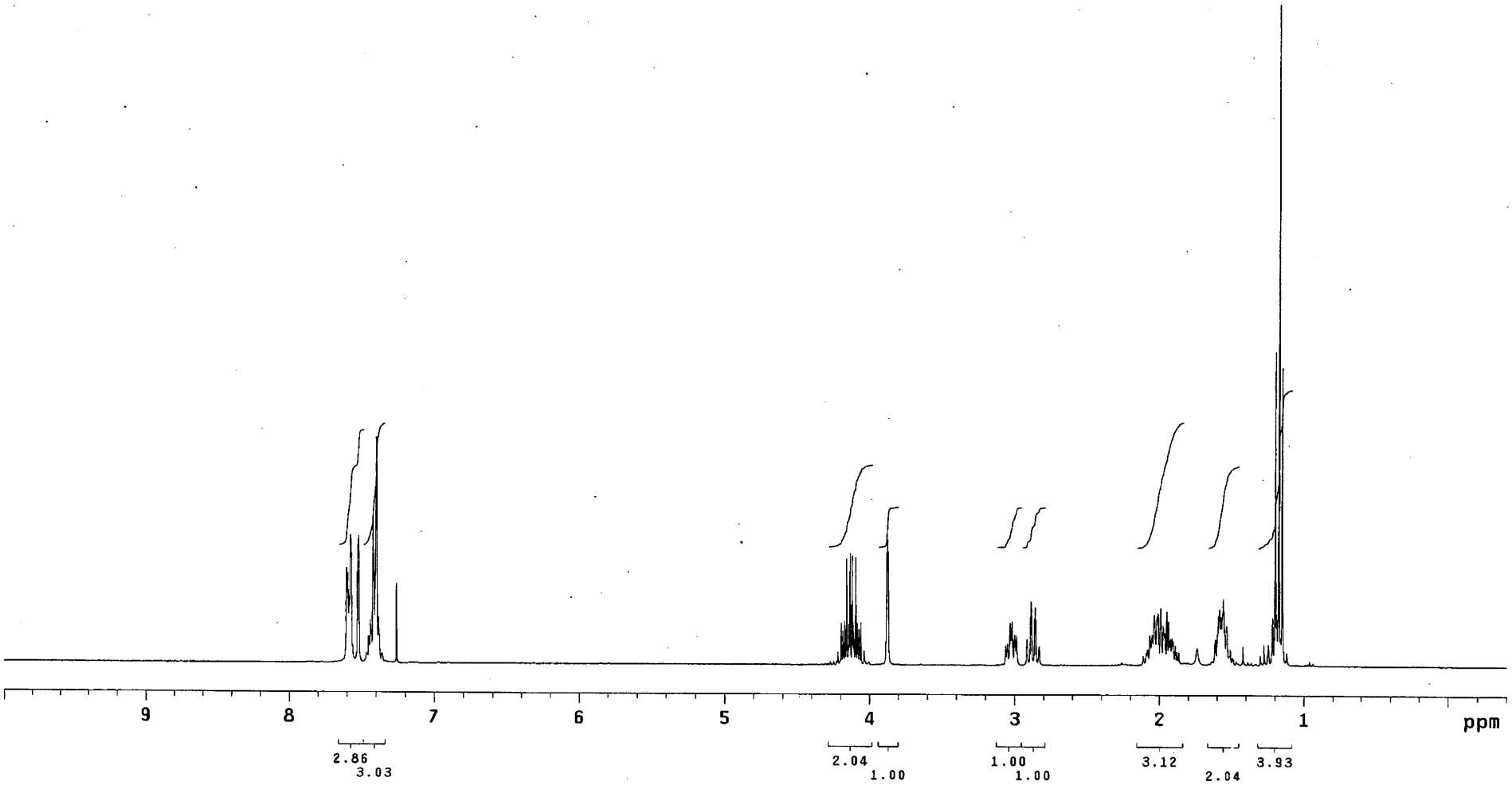
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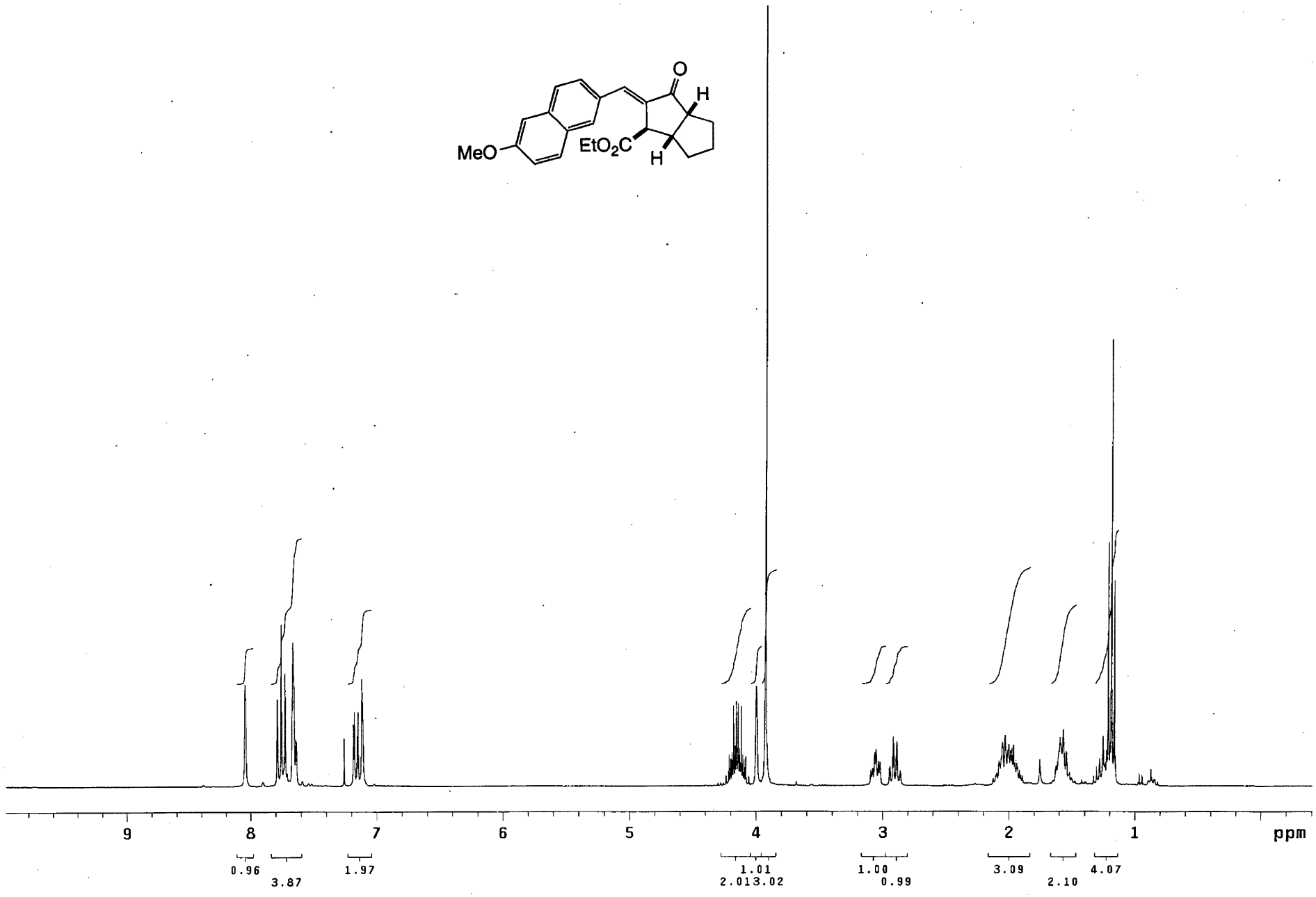
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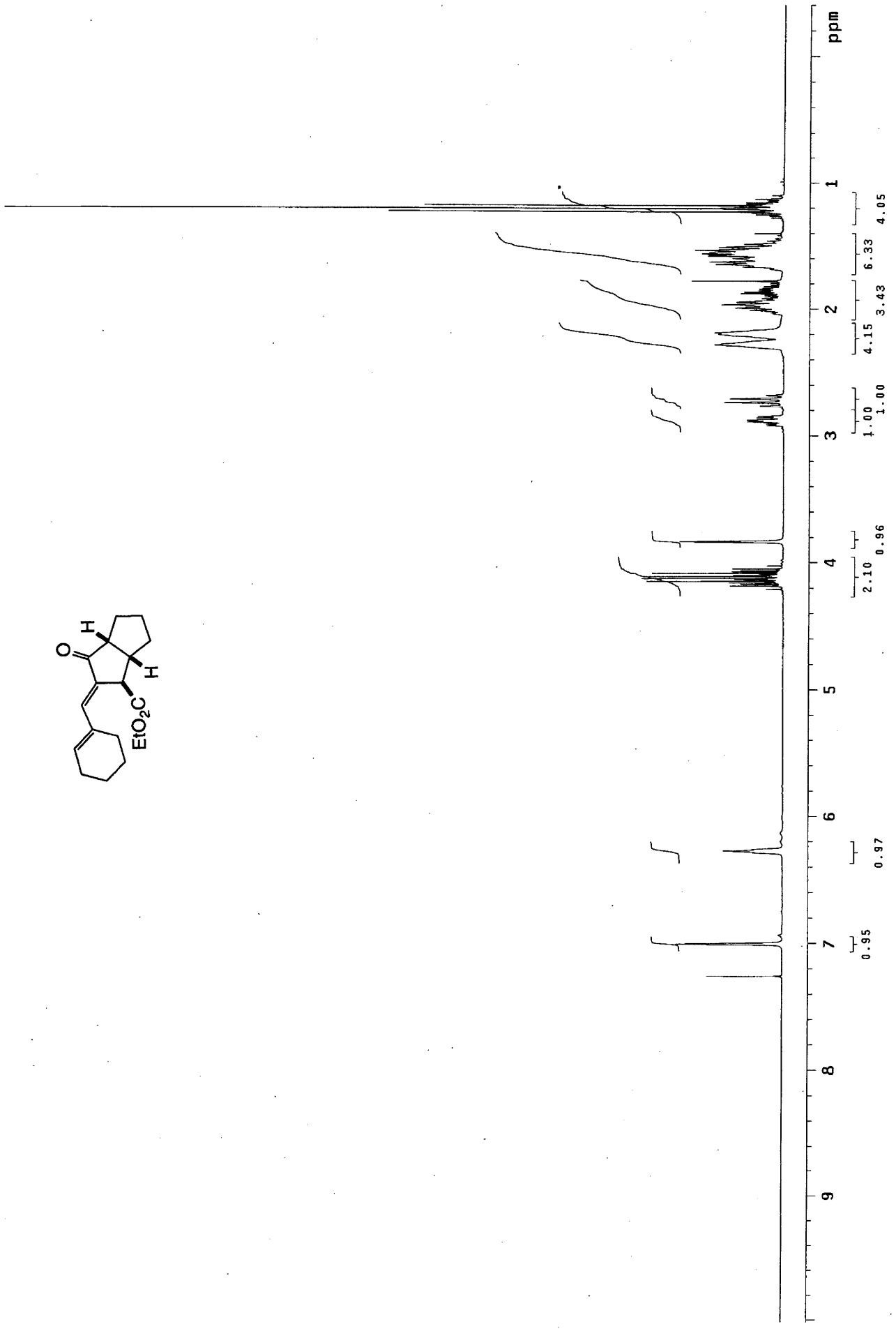
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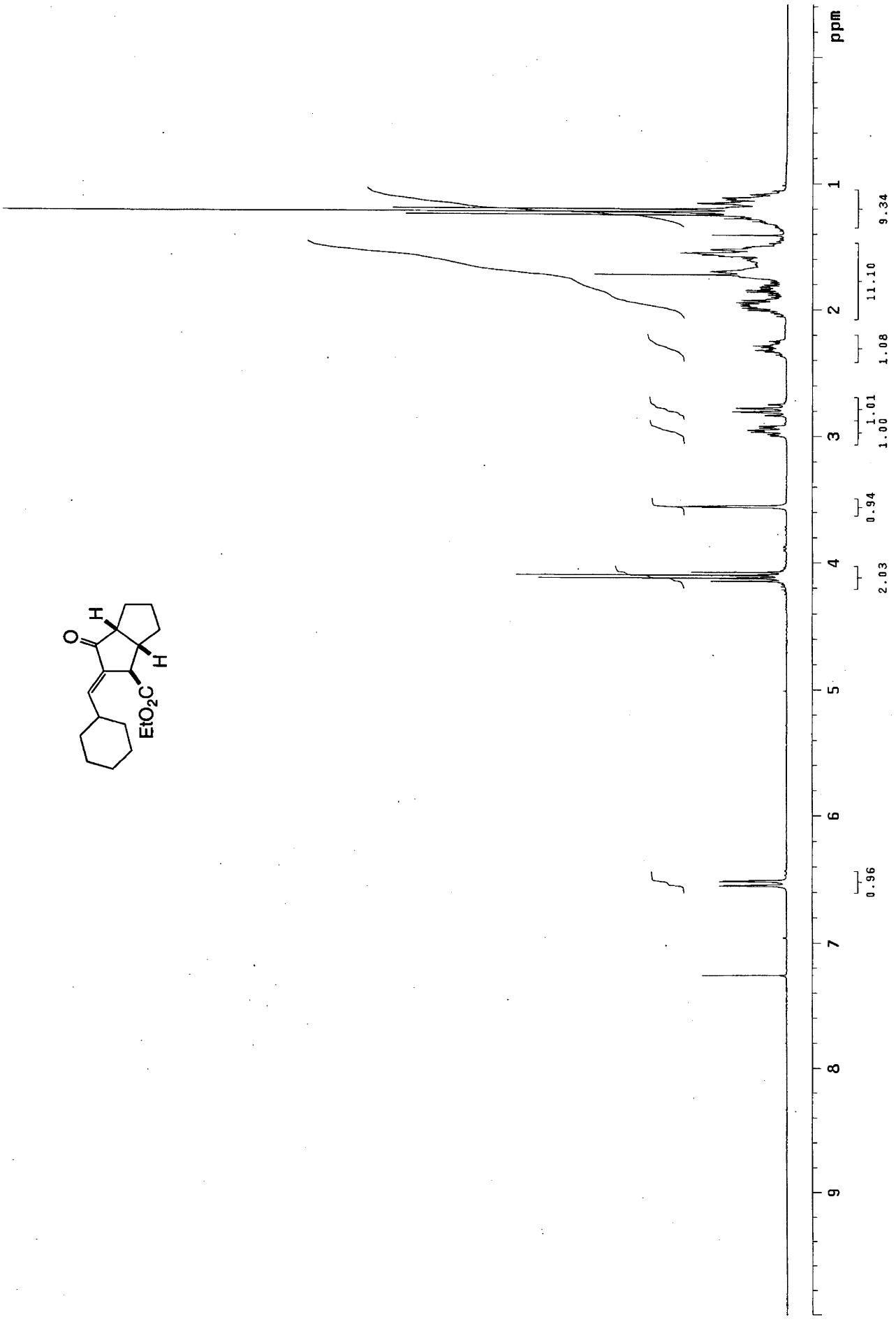
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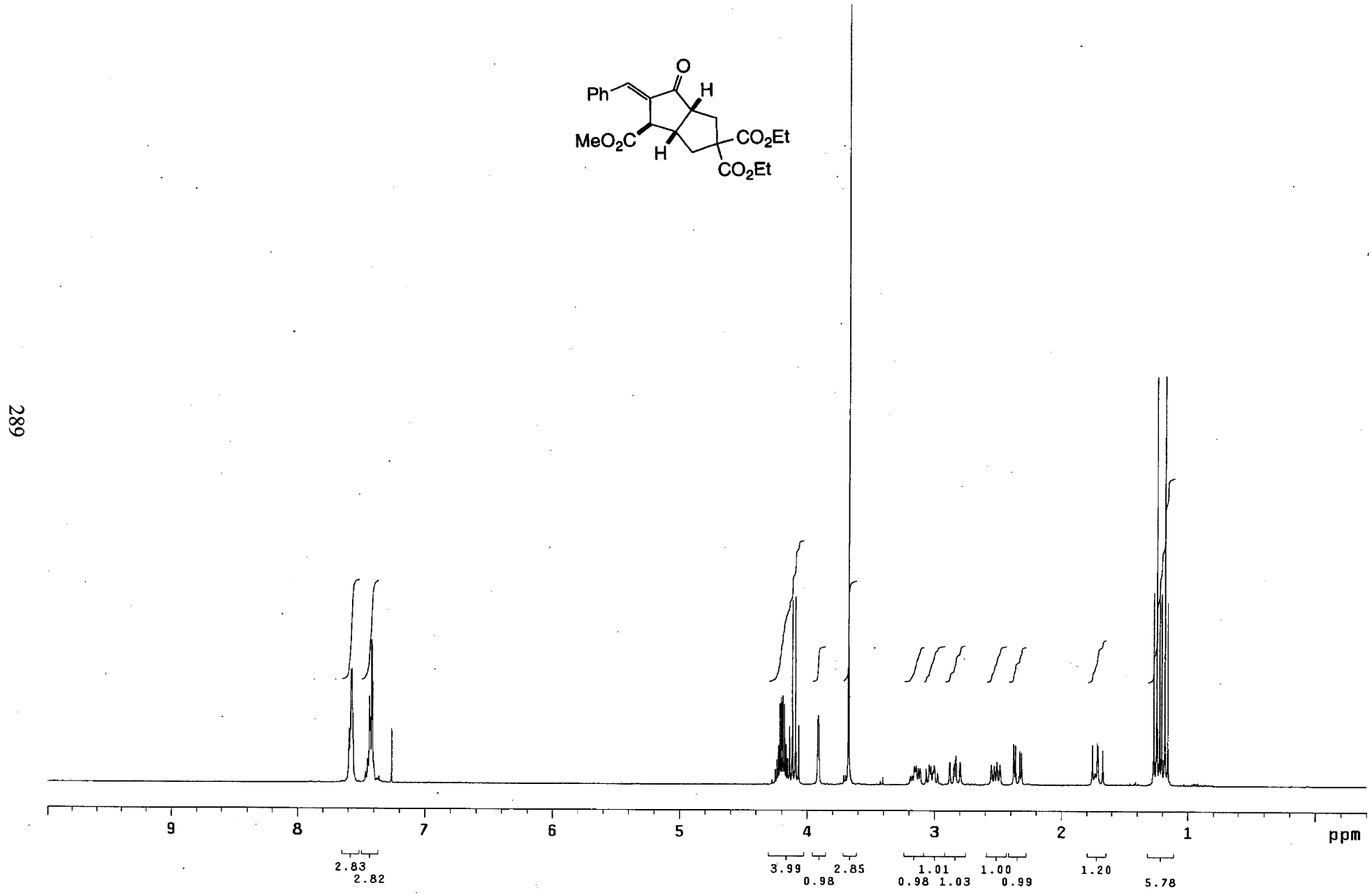
0.96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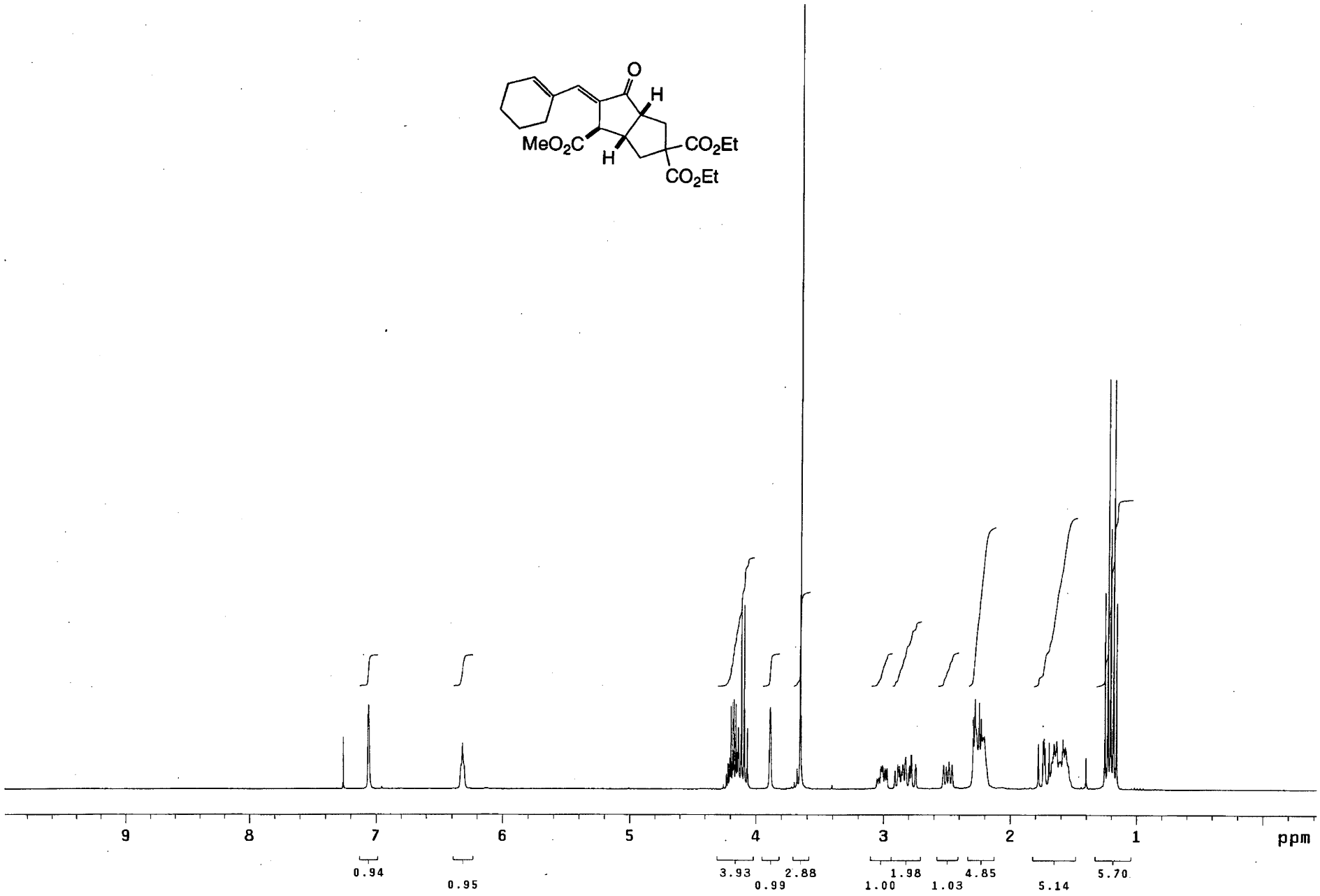
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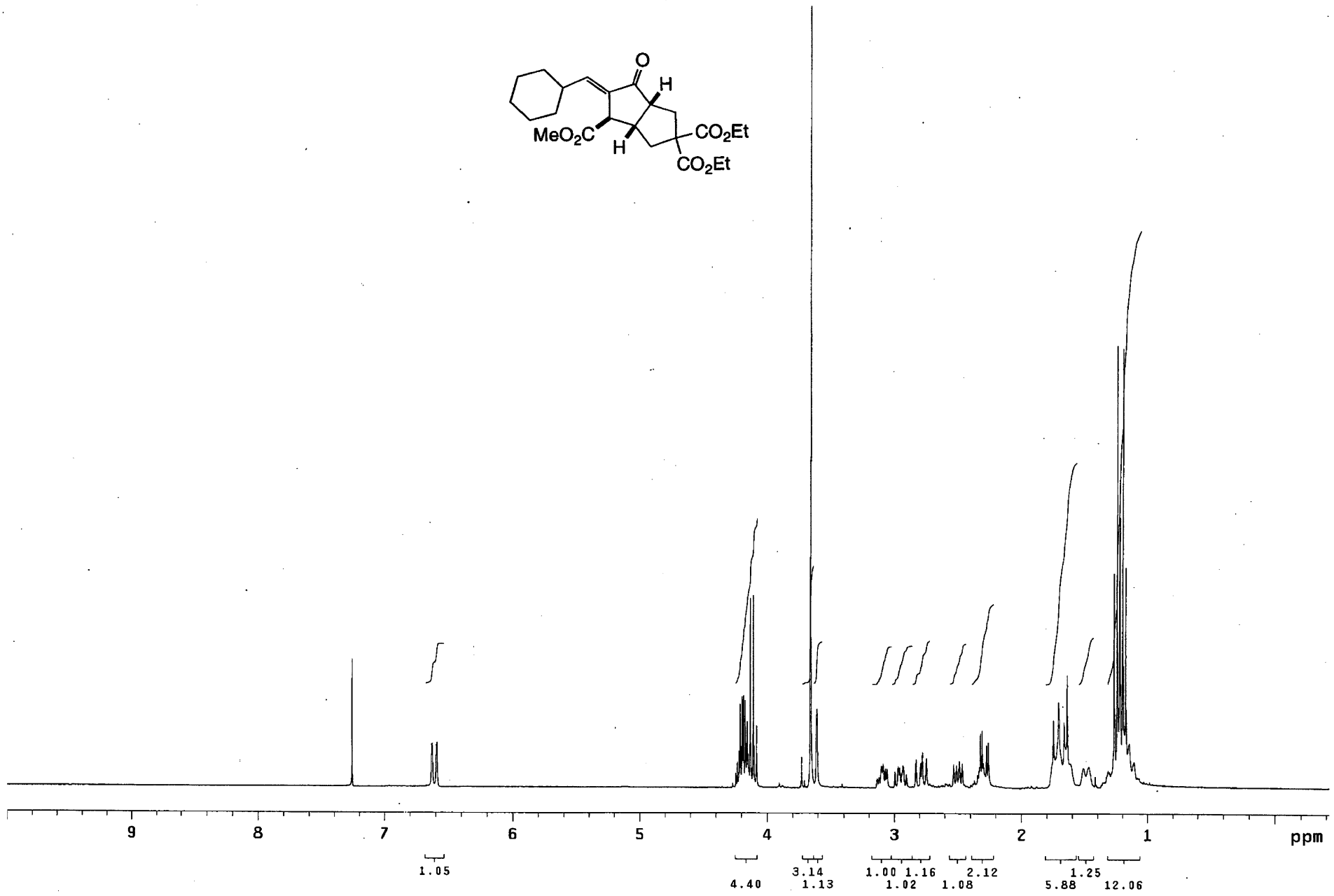
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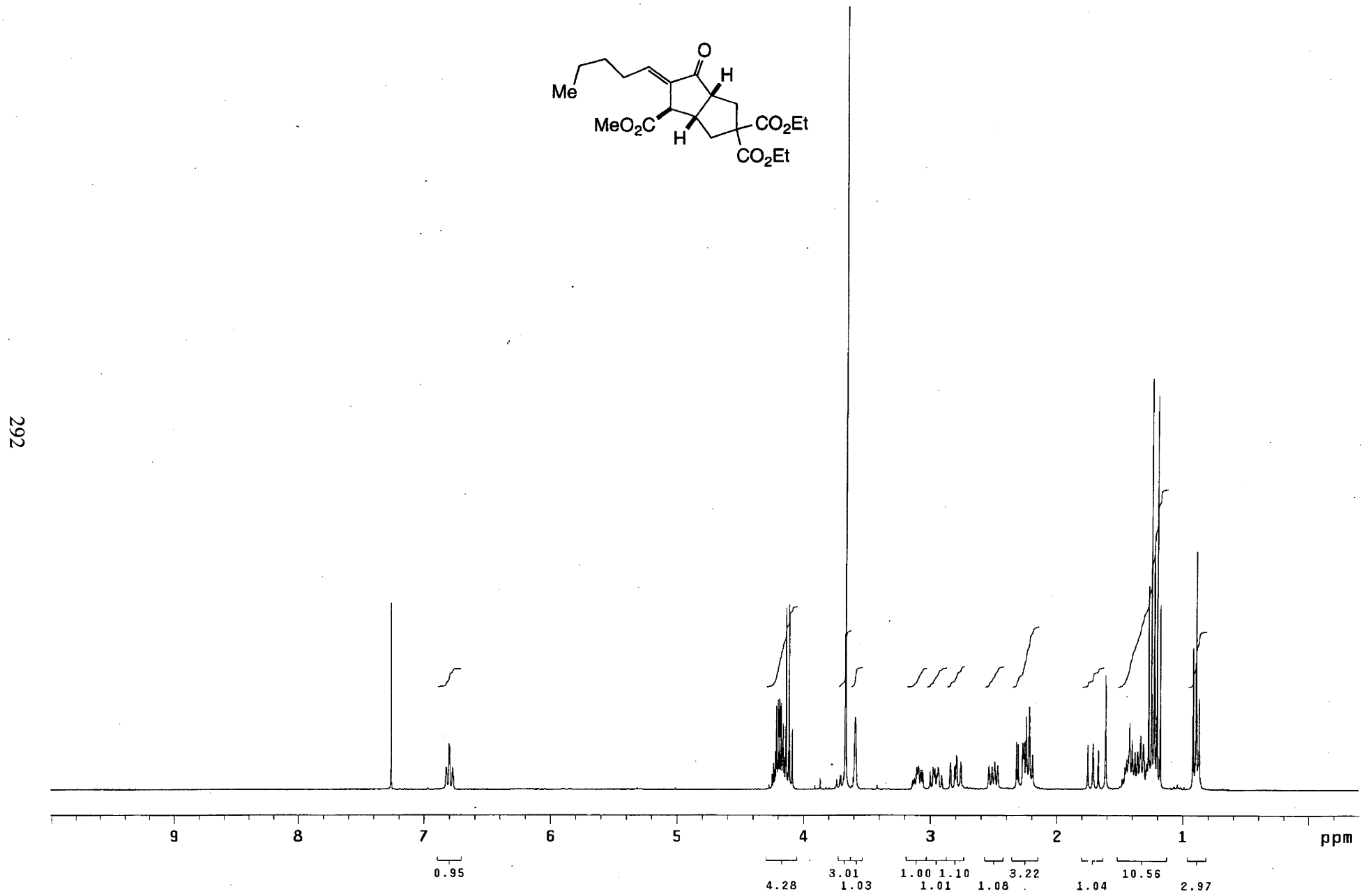
12.06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CO2Et
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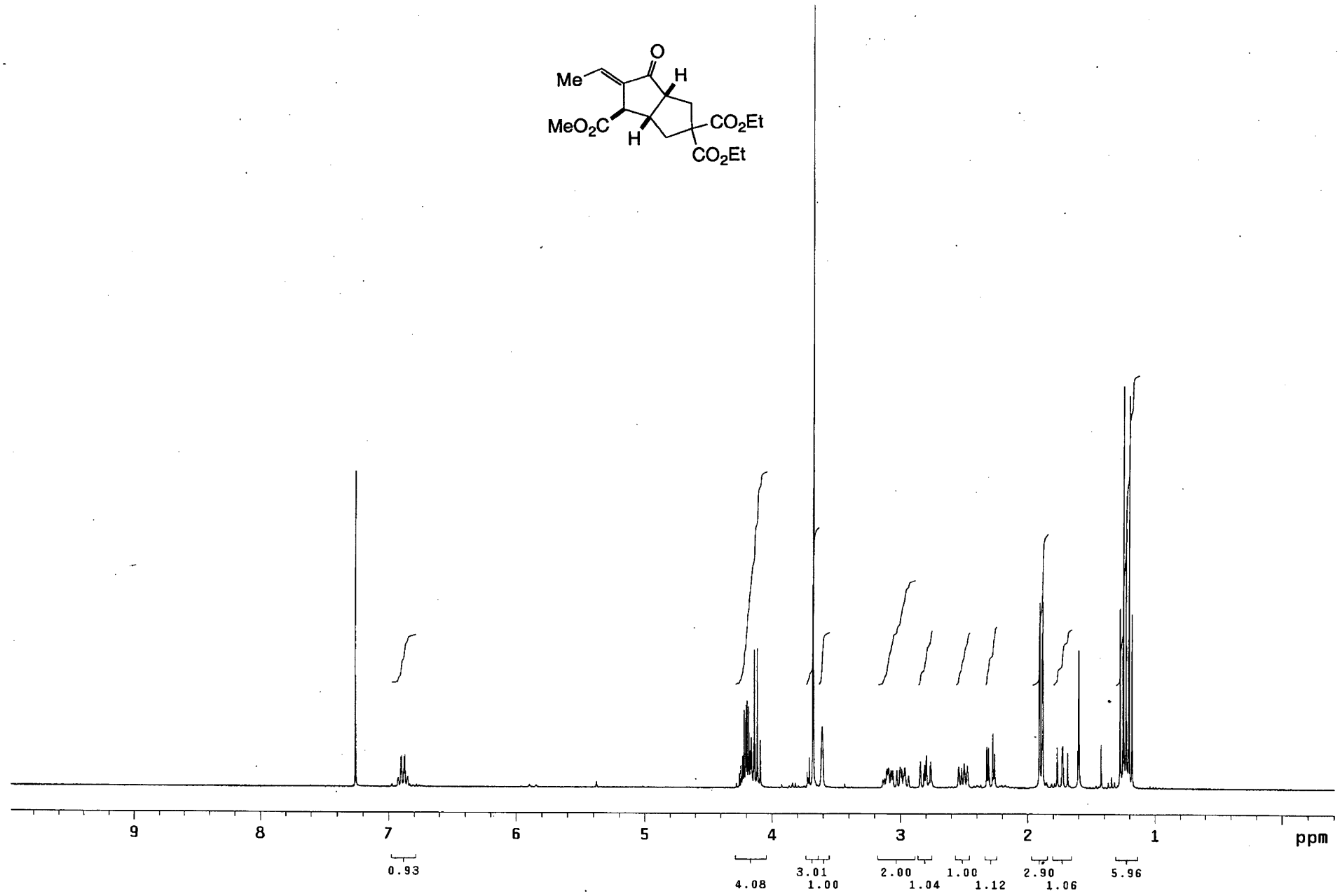
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MeO2C
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CO2Et
CO2Et
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8
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2
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ppm
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1.00
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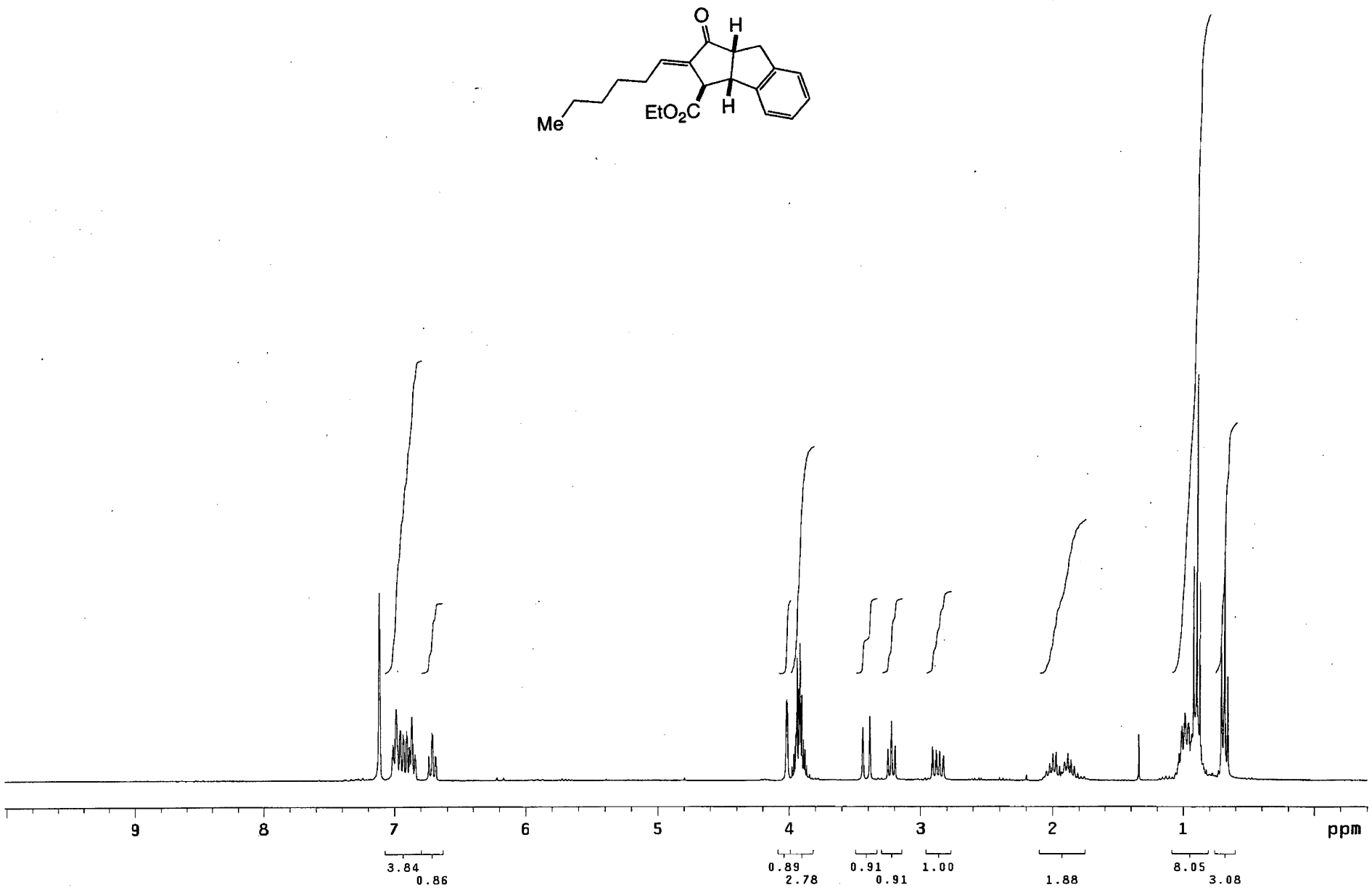
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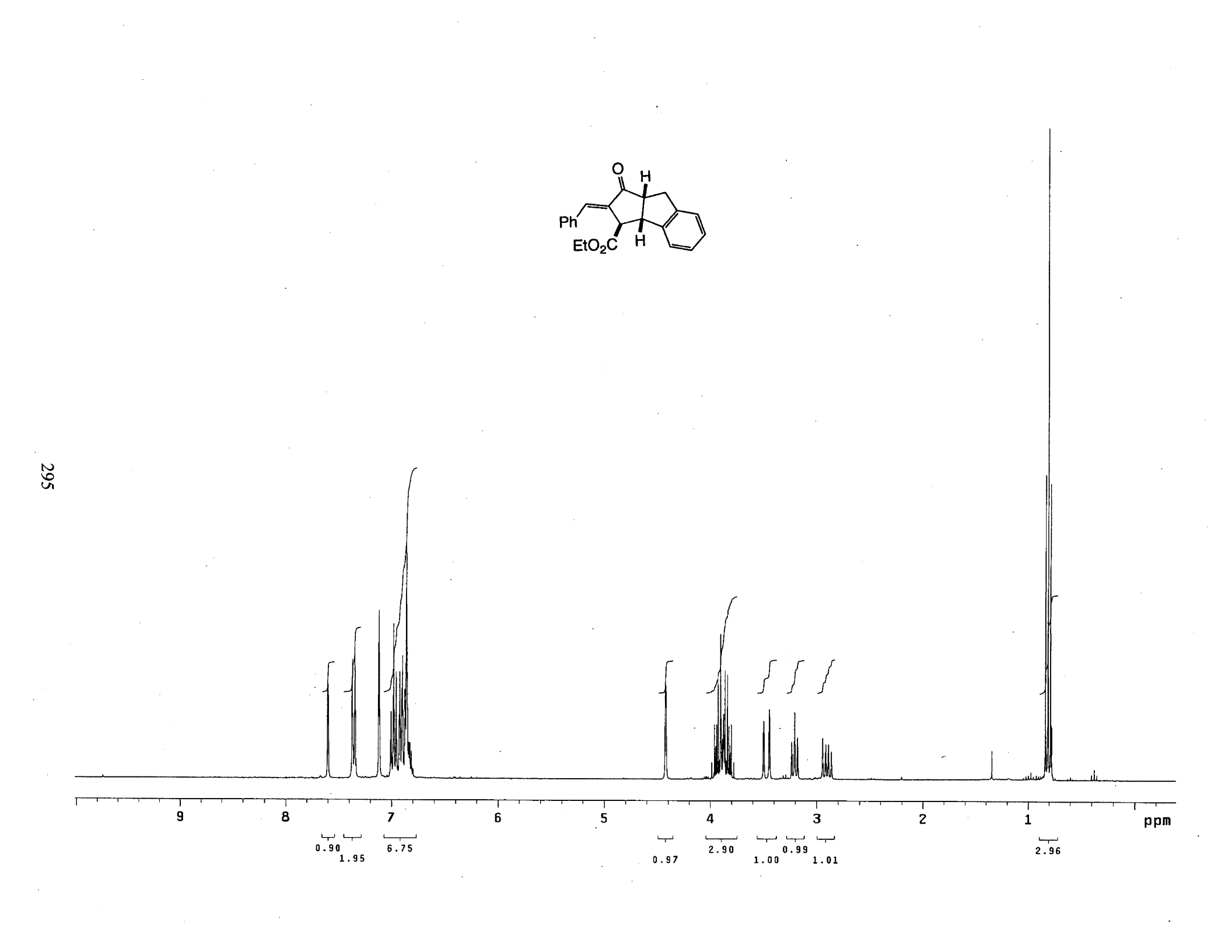
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EtO2C
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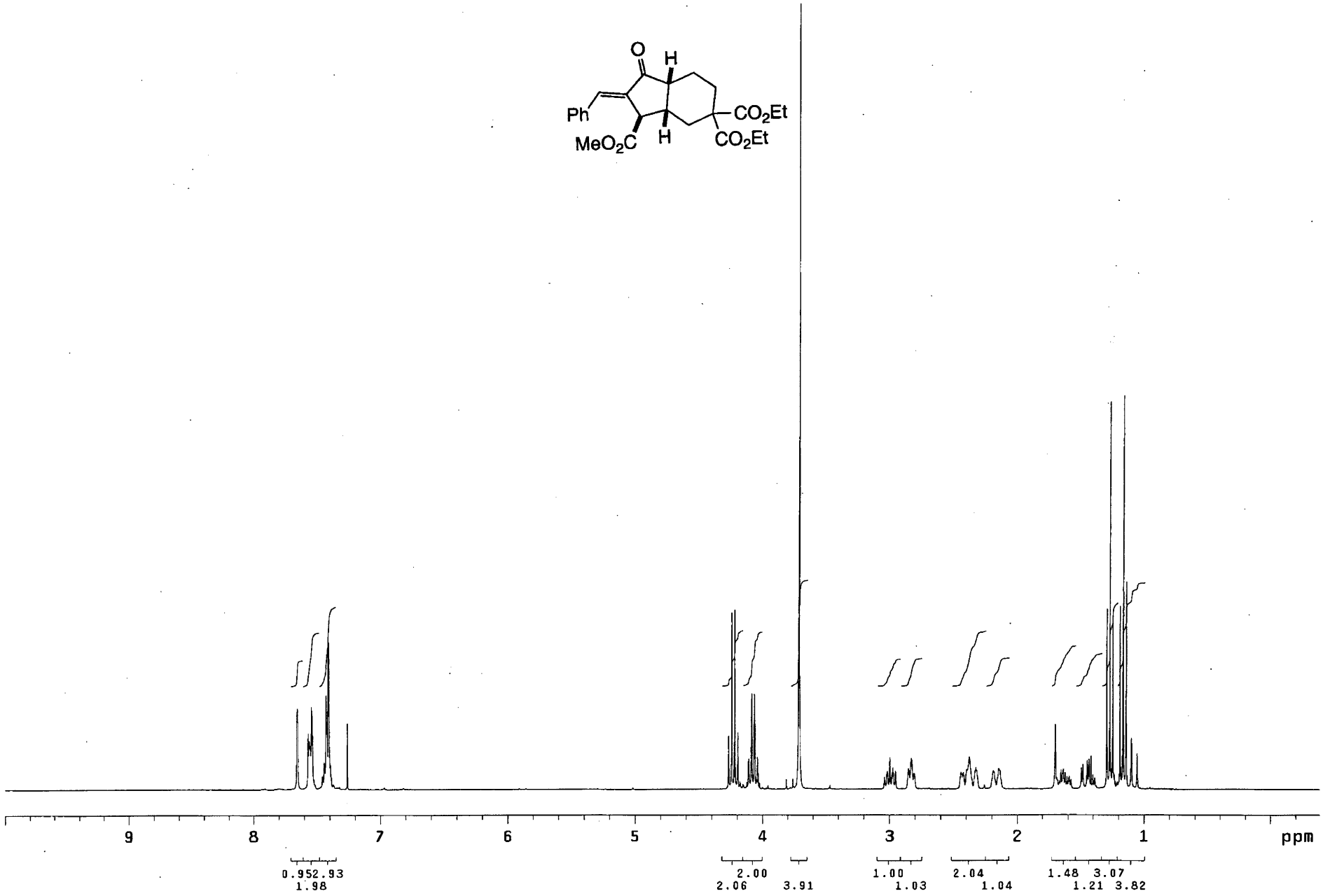
2.96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CO2Et
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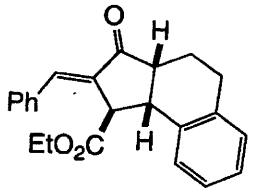
1.21 3.82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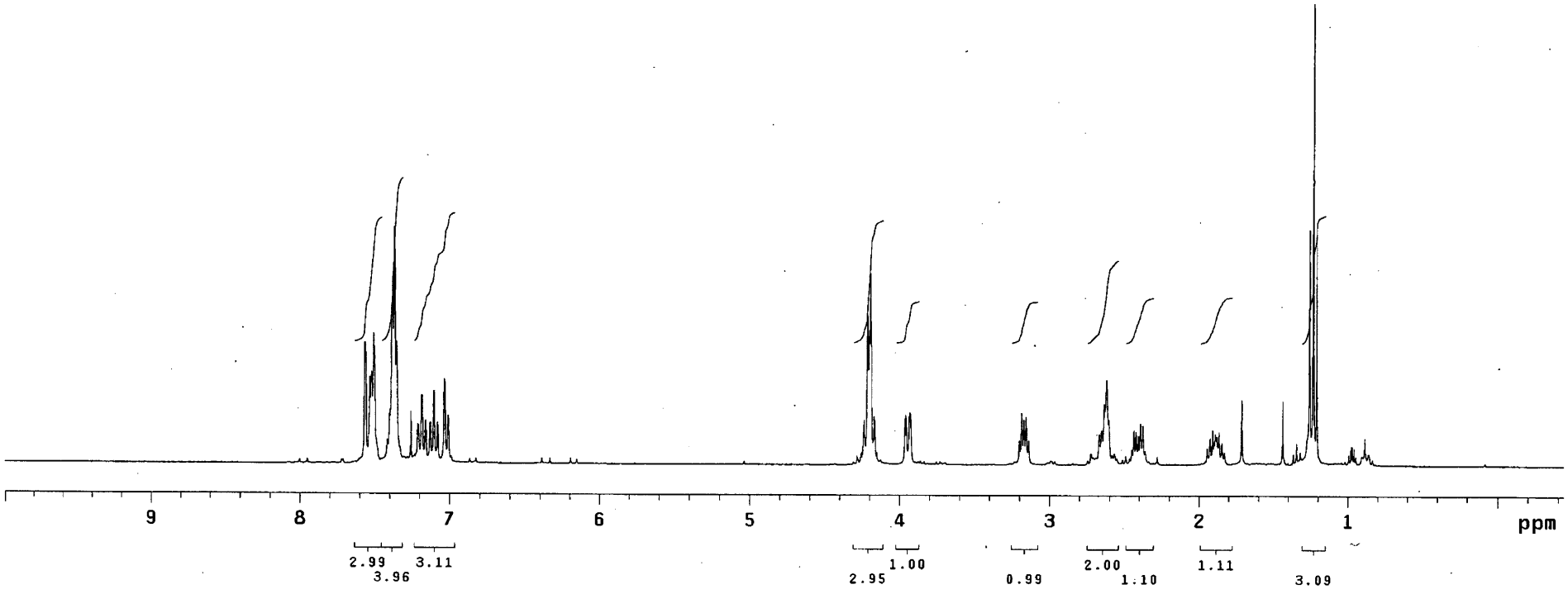
Ph
EtO2C
H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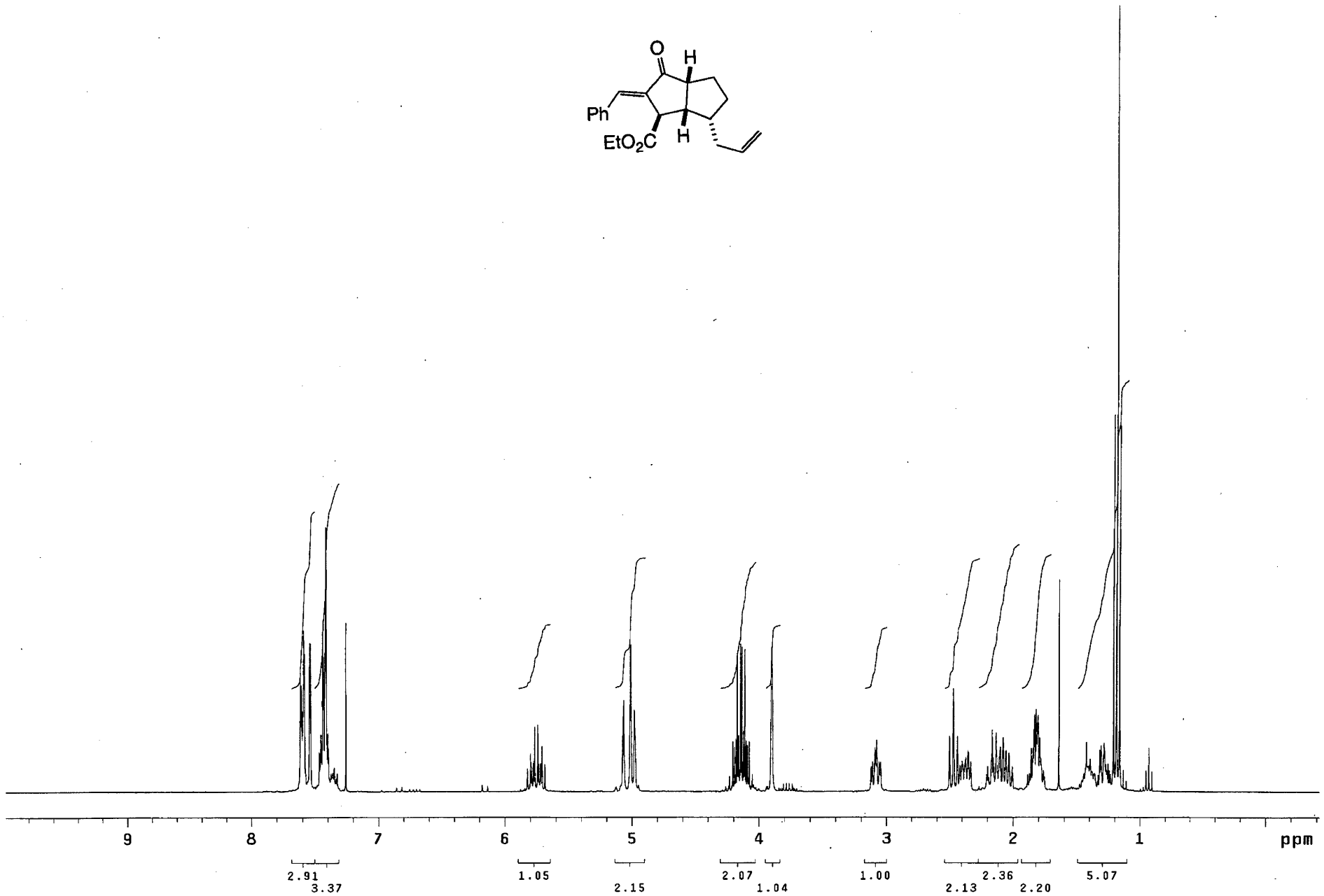
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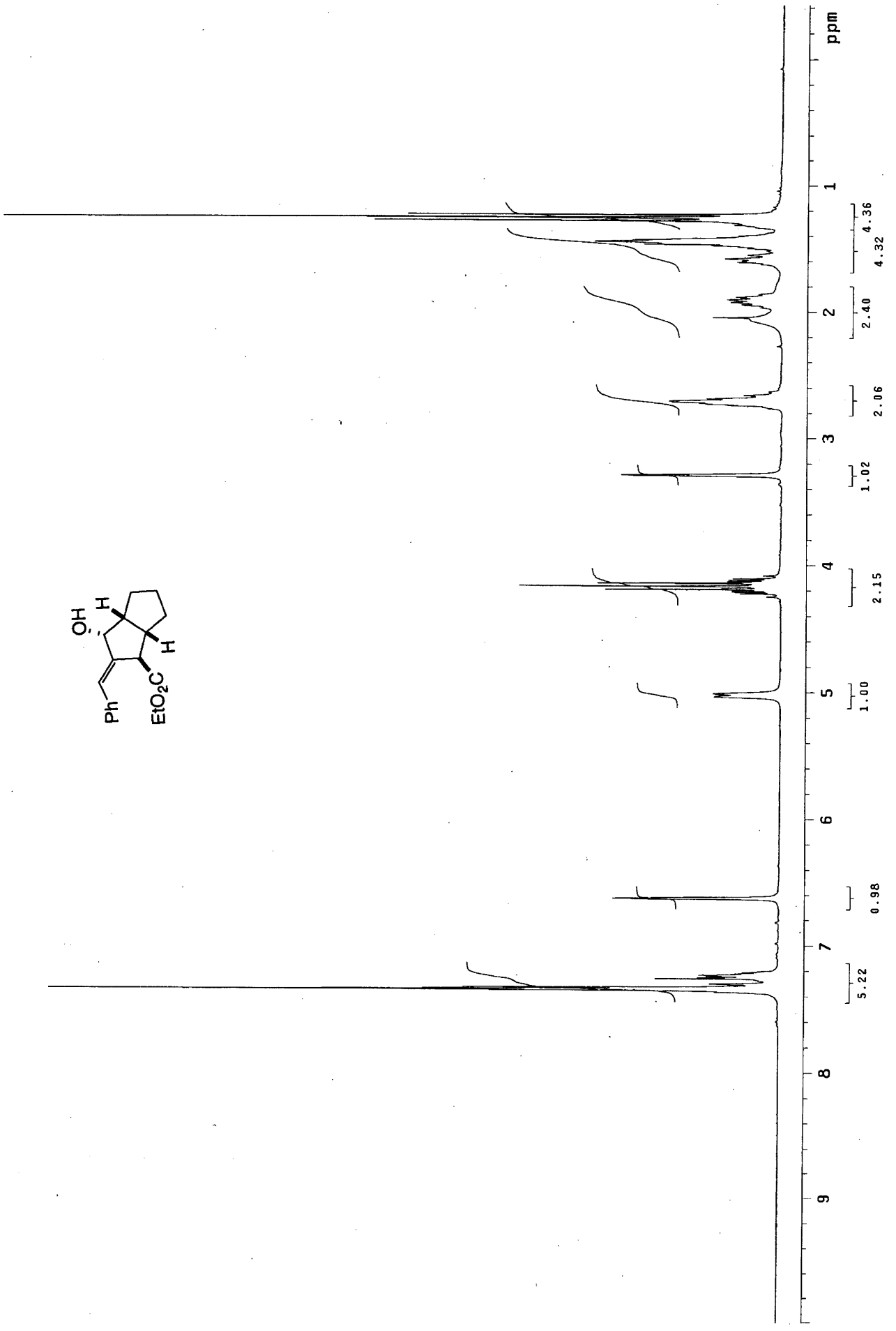
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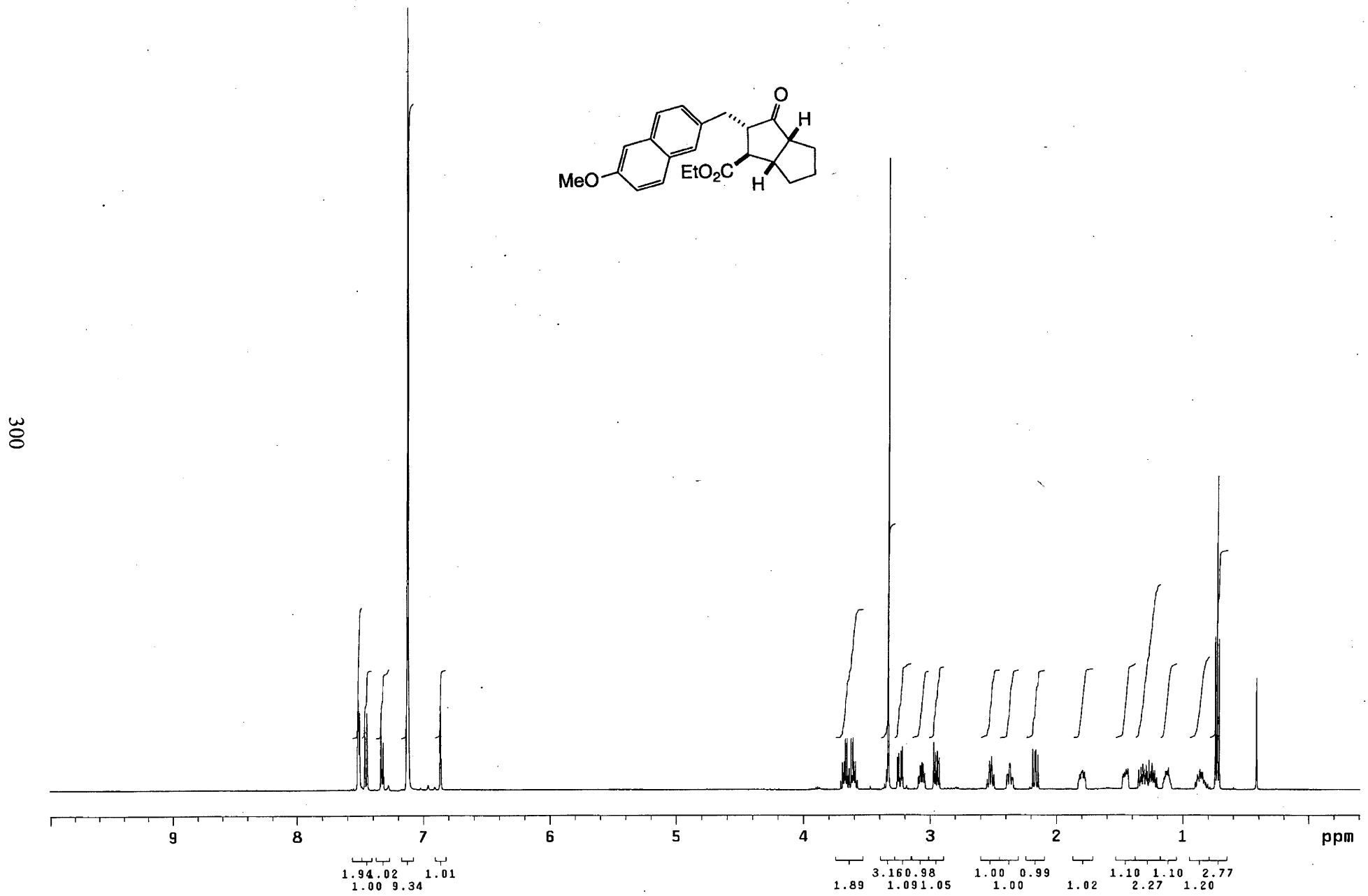
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1.02
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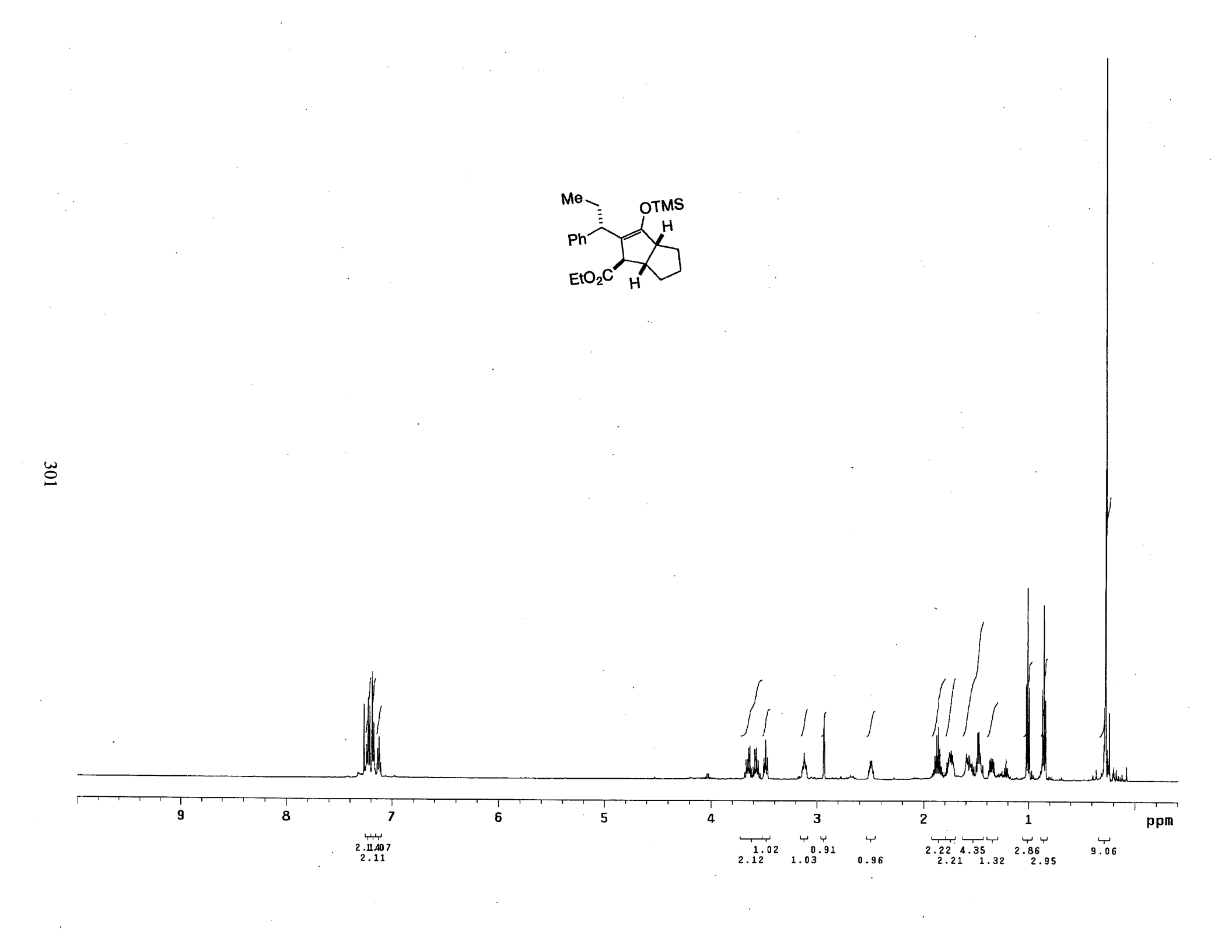
2.27 1.20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2.12
1.02
1.03
0.91
0.96
2.21
2.22
1.32
4.35
2.95
2.86
9.06

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EXPERIENCE

2002-present	**Graduate student with Professor Gregory C. Fu** Massachusetts Institute of Technology
2000-2002	**Research Assistant with Dr. Linda Chang** Merck Research Laboratories, Rahway, NJ
1999-2000	**Researcher with Professor Albert Matlin** Oberlin College
1998	**Researcher with Professor Robert Thompson** Oberlin College

EDUCATION

2002-present	Ph.D. candidate, Chemistry, Massachusetts Institute of Technology
2000	B.A., Chemistry, Oberlin College

AWARDS AND FELLOWSHIPS

2003	**NIH Cancer Training Grant,** Massachusetts Institute of Technology
2002	**Presidential Fellowship,** Massachusetts Institute of Technology
2000	**Tarbell Organic Chemistry Award,** Oberlin College
1999	**NCAC Scholar Athlete Award,** Oberlin College
1999	**Harold and Virginia Baker Chemistry Scholarship,** Oberlin College
1998	**Frank Fanning Jewett Award,** Oberlin College

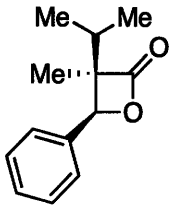
PUBLICATIONS

Wilson, J. E.; Fu, G. C. **Synthesis of Functionalized Cyclopentenes via Catalytic Asymmetric [3+2] Cycloadditions of Allenes with Enones.** *Angew. Chem. Int. Ed.* **2006,** *45,* 1426.

Wilson, J. E.; Fu, G. C. **Asymmetric Synthesis of β-Lactones via Nucleophile-Catalyzed [2+2] Cycloadditions of Disubstituted Ketenes with Aldehydes.** *Angew. Chem. Int. Ed.* **2004,** *43,* 6358.

Hagmann, W. K.; Durette, P. L.; Lanza, T.; Kevin, N. J.; deLaszlo, S. E.; Kopka, I. E.; Young, D.; Magriotis, P. A.; Li, B.; Lin, L. S.; Yang, G.; Kamenecka, T.; Chang, L. L.; **Wilson, J. E.;** MacCoss, M.; Mills, S. G.; Van Riper, G.; McCauley, E.; Egger, L. A.; Kidambi, U.; Lyons, K.; Vincent, S.; Stearns, R.; Colletti, A.; Teffera, J.; Tong, S.; Fenyk-Melody, J.; Owens, K.; Levorse, D.; Kim, P.; Schmidt, J. A.; Mumford. R. A. **The Discovery of Sulfonylated Dipeptides as Potent VLA-4 Antagonists.** *Bioorg. & Med. Chem. Lett.* **2001,** *11,* 2709.

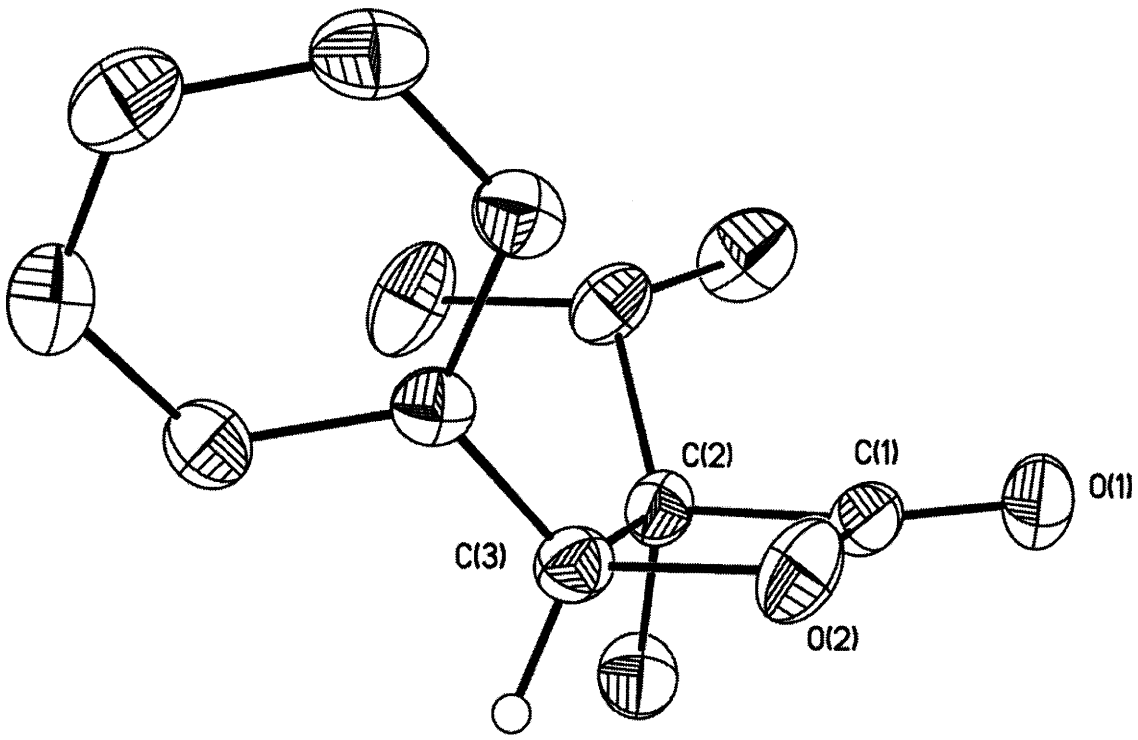
Appendix A. X-ray Crystal Structure Data



Chapter 1. A colorless ether / pentane (1:1) solution of **1** was prepared. Crystals suitable for X-ray structural analysis were obtained by solvent evaporation.

A colorless block of dimensions 0.41 x 0.29 x 0.19 mm^3 was mounted under STP and transferred to a Bruker AXS/CCD three-circle diffractometer equipped with a cold stream of N_2 gas. An initial unit cell was determined by harvesting reflections $I > 20\ s(I)$ from 45 x 10-s frames of 0.30° ω scan data with monochromated Mo K_α radiation (l = 0.71073 Å). The cell thus determined was orthorhombic.

A hemisphere of data was then collected using ω scans of 0.30° and 10-s frames. The raw data frames were integrated using the Bruker program SAINT+ for NT version 6.01. The data that were collected (8734 total reflections, 2926 unique, $R_{int} = 0.0454$) had the following Miller index ranges: –5 to 10 in h, –14 to 14 in k, and –17 to 17 in l. No absorption correction was performed. All aspects of the solution and refinement were handled by SHELXTL NT version 5.10. The structure was solved by direct methods in the orthorhombic space group P2(1)2(1)2(1), a = 8.1417(5) Å; b = 10.8215(6) Å; c = 13.4224(8) Å; α = 90°; β = 90°; γ = 90°, and refined using standard difference Fourier techniques. Final, full-matrix least-squares refinement (2926 data for 140 parameters) on F^2 yielded residuals of R_1 and wR_2 of 0.0408 and 0.1112 for data $I > 2s(I)$, and 0.0442 and 0.1140, respectively, for all data. During the final refinement, all non-hydrogen atoms were treated anisotropically. Hydrogen atoms were included in calculated positions and refined isotropically on a riding model. Residual electron density amounted to a maximum of 0.202 e/$Å^3$ and a minimum of –0.219 e/$Å^3$.


C(2)
C(1)
O(1)
C(3)
O(2)

Tables 1-6 provide the full crystallographic data for the X-ray structure.

Table 1. Crystal data and structure refinement for 04075JWm.

Identification code	04075jwm
Empirical formula	C13 H16 O2
Formula weight	204.26
Temperature	193(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 8.1417(5) Å α = 90 °
	b = 10.8215(6) Å β = 90 °
	c = 13.4224(8) Å γ = 90 °
Volume	1182.59(12) $Å^3$
Z, Calculated density	4, 1.147 Mg/m^3
Absorption coefficient	0.076 mm^{-1}
F(000)	440
Crystal size	0.41 x 0.29 x 0.19 mm
Theta range for data collection	2.42 to 28.28 °
Limiting indices	-5<=h<=10, -14<=k<=14, -17<=l<=17
Reflections collected / unique	8734 / 2926 [R(int) = 0.0454]
Completeness to theta = 28.28	99.9 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2926 / 0 / 140
Goodness-of-fit on F^2	1.007
Final R indices [I>2sigma(I)]	R1 = 0.0408, wR2 = 0.1112
R indices (all data)	R1 = 0.0442, wR2 = 0.1140
Absolute structure parameter	-0.1(10)
Extinction coefficient	0.041(6)
Largest diff. peak and hole	0.202 and -0.219 e.$Å^{-3}$

Table 2. Atomic coordinates ($Å^2$ x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 04075JWm. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	1212(2)	6343(1)	9649(1)	54(1)
O(2)	3613(1)	6696(1)	8833(1)	49(1)
C(1)	2073(2)	6985(1)	9145(1)	39(1)
C(2)	2027(2)	8258(1)	8668(1)	36(1)
C(3)	3793(2)	7904(1)	8313(1)	37(1)
C(4)	2022(2)	9269(1)	9470(1)	49(1)
C(5)	696(2)	8396(1)	7856(1)	44(1)
C(6)	-1041(2)	8250(2)	8291(1)	65(1)
C(7)	843(2)	9628(2)	7301(1)	69(1)
C(8)	4224(2)	7726(1)	7237(1)	34(1)
C(9)	5092(2)	8644(1)	6745(1)	41(1)
C(10)	5585(2)	8500(1)	5764(1)	50(1)
C(11)	5223(2)	7420(2)	5266(1)	54(1)
C(12)	4328(2)	6497(1)	5735(1)	48(1)
C(13)	3826(2)	6647(1)	6718(1)	39(1)

Table 3. Bond lengths [Å] and angles [°] for 04075JWm.

O(1)-C(1)	1.1966(17)
O(2)-C(1)	1.3585(17)
O(2)-C(3)	1.4891(14)
C(1)-C(2)	1.5196(16)
C(2)-C(4)	1.5347(16)
C(2)-C(5)	1.5433(18)

C(2)-C(3)	1.5626(18)
C(3)-C(8)	1.4991(17)
C(5)-C(7)	1.532(2)
C(5)-C(6)	1.538(2)
C(8)-C(9)	1.3863(18)
C(8)-C(13)	1.3979(16)
C(9)-C(10)	1.3859(19)
C(10)-C(11)	1.378(2)
C(11)-C(12)	1.388(2)
C(12)-C(13)	1.3896(19)
C(1)-O(2)-C(3)	91.91(9)
O(1)-C(1)-O(2)	125.54(12)
O(1)-C(1)-C(2)	138.62(14)
O(2)-C(1)-C(2)	95.83(10)
C(1)-C(2)-C(4)	110.51(9)
C(1)-C(2)-C(5)	113.74(11)
C(4)-C(2)-C(5)	115.10(11)
C(1)-C(2)-C(3)	83.31(9)
C(4)-C(2)-C(3)	113.01(11)
C(5)-C(2)-C(3)	117.05(10)
O(2)-C(3)-C(8)	111.25(9)
O(2)-C(3)-C(2)	88.95(9)
C(8)-C(3)-C(2)	122.73(10)
C(7)-C(5)-C(6)	110.21(13)
C(7)-C(5)-C(2)	111.88(13)
C(6)-C(5)-C(2)	111.58(11)
C(9)-C(8)-C(13)	118.68(11)
C(9)-C(8)-C(3)	119.06(11)
C(13)-C(8)-C(3)	122.23(11)
C(10)-C(9)-C(8)	121.28(12)
C(11)-C(10)-C(9)	119.62(13)

C(10)-C(11)-C(12)	120.19(13)
C(13)-C(12)-C(11)	120.06(12)
C(12)-C(13)-C(8)	120.14(12)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for 04075JWm.

The anisotropic displacement factor exponent takes the form:

-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	72(1)	45(1)	45(1)	10(1)	3(1)	-10(1)
O(2)	58(1)	46(1)	43(1)	12(1)	-1(1)	15(1)
C(1)	51(1)	36(1)	31(1)	2(1)	-6(1)	-1(1)
C(2)	43(1)	32(1)	32(1)	3(1)	1(1)	2(1)
C(3)	40(1)	35(1)	36(1)	1(1)	-6(1)	2(1)
C(4)	61(1)	39(1)	46(1)	-8(1)	7(1)	0(1)
C(5)	43(1)	52(1)	37(1)	4(1)	-1(1)	13(1)
C(6)	43(1)	91(1)	61(1)	4(1)	-1(1)	16(1)
C(7)	75(1)	71(1)	61(1)	28(1)	6(1)	31(1)
C(8)	33(1)	33(1)	37(1)	-2(1)	-4(1)	4(1)
C(9)	41(1)	36(1)	47(1)	-3(1)	0(1)	-1(1)
C(10)	49(1)	50(1)	50(1)	7(1)	9(1)	1(1)
C(11)	57(1)	65(1)	39(1)	-6(1)	4(1)	12(1)
C(12)	53(1)	42(1)	49(1)	-14(1)	-9(1)	9(1)
C(13)	40(1)	32(1)	46(1)	-2(1)	-6(1)	4(1)

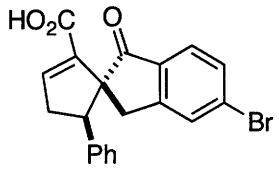
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 04075JWm.

x	y	z	U(eq)
H(3)	4634	8429	8653	44
H(4A)	949	9286	9800	73
H(4B)	2234	10072	9159	73
H(4C)	2879	9093	9962	73
H(5)	864	7718	7360	53
H(6A)	-1288	8956	8723	97
H(6B)	-1100	7485	8680	97
H(6C)	-1843	8217	7747	97
H(7A)	88	9632	6732	103
H(7B)	1972	9734	7063	103
H(7C)	562	10307	7753	103
H(9)	5354	9387	7088	49
H(10)	6170	9142	5436	60
H(11)	5586	7308	4599	64
H(12)	4059	5761	5385	58
H(13)	3211	6014	7037	47

Table 6. Torsion angles [°] for 04075JWm.

C(3)-O(2)-C(1)-O(1)	-178.90(13)
C(3)-O(2)-C(1)-C(2)	-0.27(9)
O(1)-C(1)-C(2)-C(4)	66.5(2)
O(2)-C(1)-C(2)-C(4)	-111.85(12)
O(1)-C(1)-C(2)-C(5)	-64.77(19)
O(2)-C(1)-C(2)-C(5)	116.92(11)

O(1)-C(1)-C(2)-C(3)	178.57(17)
O(2)-C(1)-C(2)-C(3)	0.26(9)
C(1)-O(2)-C(3)-C(8)	-124.71(11)
C(1)-O(2)-C(3)-C(2)	0.26(9)
C(1)-C(2)-C(3)-O(2)	-0.23(8)
C(4)-C(2)-C(3)-O(2)	109.24(10)
C(5)-C(2)-C(3)-O(2)	-113.51(11)
C(1)-C(2)-C(3)-C(8)	114.55(12)
C(4)-C(2)-C(3)-C(8)	-135.98(11)
C(5)-C(2)-C(3)-C(8)	1.27(17)
C(1)-C(2)-C(5)-C(7)	-172.39(11)
C(4)-C(2)-C(5)-C(7)	58.67(15)
C(3)-C(2)-C(5)-C(7)	-77.70(14)
C(1)-C(2)-C(5)-C(6)	63.61(16)
C(4)-C(2)-C(5)-C(6)	-65.33(16)
C(3)-C(2)-C(5)-C(6)	158.30(13)
O(2)-C(3)-C(8)-C(9)	-153.09(11)
C(2)-C(3)-C(8)-C(9)	103.82(14)
O(2)-C(3)-C(8)-C(13)	24.85(16)
C(2)-C(3)-C(8)-C(13)	-78.25(15)
C(13)-C(8)-C(9)-C(10)	-0.98(19)
C(3)-C(8)-C(9)-C(10)	177.03(12)
C(8)-C(9)-C(10)-C(11)	-0.6(2)
C(9)-C(10)-C(11)-C(12)	1.8(2)
C(10)-C(11)-C(12)-C(13)	-1.4(2)
C(11)-C(12)-C(13)-C(8)	-0.19(19)
C(9)-C(8)-C(13)-C(12)	1.37(17)
C(3)-C(8)-C(13)-C(12)	-176.57(12)



Chapter 2.1. The [3+2] adduct (77.0 mg, 0.187 mmol) from the reaction catalyzed by (*S*)-**2** was dissolved in THF (2.0 mL) and treated with 1 N NaOH (1.87 mL, 1.87 mmol). The reaction mixture was heated to 60 °C for 24 h, and then 1N HCl (2.0 mL) was added.The mixture was extracted with Et_2O (3 x 5 mL), and the combined extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flashchromatography (0-2% MeOH in CH_2Cl_2), which provided 49.8 mg (70%) of the carboxylic acid.

Recrystallization by diffusion of pentane into a solution of the acid in CH2Cl2 provided crystals suitable for X-ray crystallography.

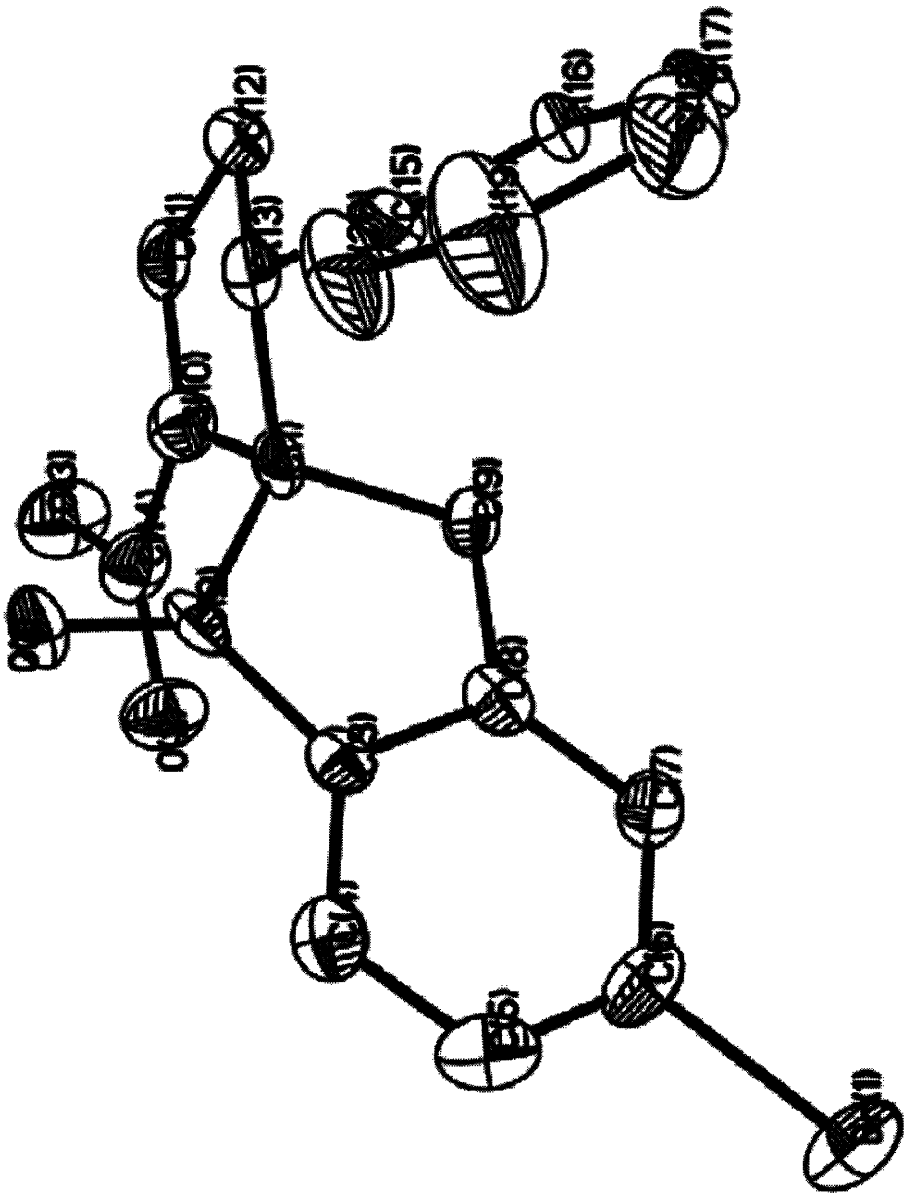
^{1}H NMR (300 MHz) δ 9.80-8.60 (br s, 1H), 7.57 (m, 1H), 7.40 (m, 1H), 7.24 (m, 2H), 7.12 (m, 3H), 6.99-6.91 (m, 2H), 4.03 (t, J=8.8 Hz, 1H), 3.03-2.93 (m, 2H), 2.91 (s, 2H).

^{13}C NMR (75 MHz) δ 208.0, 168.6, 154.6, 149.5, 138.8, 138.0, 135.9, 130.9, 130.3, 129.3, 128.5, 128.2, 127.5, 125.2, 64.5, 54.2, 36.7, 34.1.

$[\alpha]^{20}_D$ = +88° (c=0.13, CH_2Cl_2).

FTIR (thin film) 3560-2650 (broad), 1710, 1685, 1626, 1596, 1426, 1318, 1268 cm-1.

HRMS (ESI) calc. for $C_{20}H_{14}BrO_3$ [M-H] 381.0121, found 381.0122.



Low-temperature diffraction data were collected on a Siemens Platform three-circle diffractometer coupled to a Bruker-AXS Apex CCD detector with graphite monochromated Mo K*a* radiation (*l* = 0.71073Å), performing *j*- and *w*-scans. Raw data frames were integrated using the Bruker program SAINT+ for NT version 6.01. All structures were solved by direct methods using SHELXS and refined against F^2 on all data by full-matrix least squares with SHELXL-97 (Sheldrick, G. M. *SHELXL 97*,

Universität Göttingen, Göttingen, Germany, 1997). SADABS absorption correction was performed. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of the hydrogen atoms were fixed to 1.2 times the *U* value of the atoms they are linked to (1.5 times for methyl groups).

05143:

A colorless plate of dimensions 0.08 x 0.03 x 0.03 mm^3 was mounted under STP and transferred to a Siemens Platform three-circle diffractometer equipped with a cold stream of N_2 gas. The data that were collected (28404 total reflections, 2865 unique, Rint = 0.0590) had the following Miller index ranges: (- 10 to 10 in h, -10 to 10 in k, and – 39 to 40 in l). The structure was solved in the monoclinic space group *P3(1)21, a* = 9.2451(7) Å, *b* = 9.2451(7) Å, *c* = 35.204(6) Å, a = 90°; b = 90°; g = 120°, and refined using standard difference Fourier techniques. Final, full-matrix least squares refinement (2865 data for 218 parameters) on F^2 yielded residuals of R1 and wR2 of 0.0557 and 0.1378 for data I > 2s(I), and 0.0592 and 0.1393, respectively, for all data. Residual electron density amounted to a maximum of 0.885 e/$Å^3$ and a minimum of -0.615 e/ $Å^3$. The absolute structure (Flack) parameter for the correct enantiomer is 0.064(19), thus confirming the absolute stereochemistry.

Table 1. Crystal data and structure refinement for 05143.

Identification code	05143	
Empirical formula	$C_{20}H_{14}BrO_3$	
Formula weight	382.22	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Trigonal	
Space group	P3(1)21	
Unit cell dimensions	a = 9.2451(7) Å	a= 90°.
	b = 9.2451(7) Å	b= 90°.

	c = 35.204(6) Å g = 120°.
Volume	2605.8(5) $Å^3$
Z	6
Density (calculated)	1.461 Mg/m^3
Absorption coefficient	2.380 mm^{-1}
F(000)	1158
Crystal size	0.08 x 0.03 x 0.03 mm^3
Theta range for data collection	2.54 to 24.40°.
Index ranges	-10<=h<=10, -10<=k<=10, -39<=l<=40
Reflections collected	28404
Independent reflections	2865 [R(int) = 0.0590]
Completeness to theta = 24.40°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9320 and 0.8324
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2865 / 0 / 218
Goodness-of-fit on F^2	1.216
Final R indices [I>2sigma(I)]	R1 = 0.0557, wR2 = 0.1378
R indices (all data)	R1 = 0.0592, wR2 = 0.1393
Absolute structure parameter	0.064(19)
Largest diff. peak and hole	0.885 and -0.615 $e.Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 05143. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	8439(1)	2829(1)	410(1)	50(1)
O(1)	3786(5)	4102(5)	-973(1)	34(1)

O(2)	4961(6)	1483(5)	-1343(1)	39(1)
O(3)	5052(6)	1780(6)	-1973(1)	47(1)
C(1)	6601(6)	5052(7)	-1212(2)	25(1)
C(2)	5155(7)	4264(7)	-919(2)	24(1)
C(3)	5768(7)	3847(6)	-578(2)	22(1)
C(4)	4904(8)	3115(8)	-246(2)	31(1)
C(5)	5723(9)	2871(7)	52(2)	36(2)
C(6)	7357(8)	3286(8)	5(2)	35(2)
C(7)	8262(8)	4009(7)	-327(2)	31(1)
C(8)	7437(7)	4290(7)	-620(2)	25(1)
C(9)	8087(7)	4990(8)	-1013(2)	25(1)
C(10)	6184(7)	4231(8)	-1595(2)	31(1)
C(11)	6739(7)	5295(8)	-1882(2)	32(1)
C(12)	7590(8)	7064(8)	-1739(2)	36(2)
C(13)	6924(7)	6825(7)	-1330(2)	29(1)
C(14)	5348(8)	2371(8)	-1629(2)	34(1)
C(15)	7933(7)	8250(7)	-1044(2)	32(1)
C(16)	9695(7)	9207(8)	-1059(2)	39(2)
C(17)	10517(9)	10456(8)	-775(2)	52(2)
C(18)	9670(12)	10693(9)	-503(3)	65(2)
C(19)	7909(11)	9769(11)	-489(3)	71(3)
C(20)	7055(9)	8541(9)	-760(2)	53(2)

Table 3. Bond lengths [Å] and angles [°] for 05143.

Br(1)-C(6)	1.908(6)
O(1)-C(2)	1.213(7)
O(2)-C(14)	1.233(7)
O(3)-C(14)	1.301(7)
C(1)-C(10)	1.499(8)
C(1)-C(2)	1.551(8)
C(1)-C(13)	1.568(8)
C(1)-C(9)	1.568(7)
C(2)-C(3)	1.459(8)
C(3)-C(4)	1.387(8)
C(3)-C(8)	1.392(8)
C(4)-C(5)	1.375(9)
C(5)-C(6)	1.370(10)
C(6)-C(7)	1.396(9)
C(7)-C(8)	1.385(8)
C(8)-C(9)	1.516(8)
C(10)-C(11)	1.324(8)
C(10)-C(14)	1.496(9)
C(11)-C(12)	1.504(9)
C(12)-C(13)	1.536(9)
C(13)-C(15)	1.547(8)
C(15)-C(20)	1.395(10)
C(15)-C(16)	1.413(8)
C(16)-C(17)	1.426(11)
C(17)-C(18)	1.323(12)
C(18)-C(19)	1.412(13)
C(19)-C(20)	1.389(11)
C(10)-C(1)-C(2)	114.6(5)

C(10)-C(1)-C(13)	99.1(4)
C(2)-C(1)-C(13)	109.6(4)
C(10)-C(1)-C(9)	113.1(5)
C(2)-C(1)-C(9)	104.5(4)
C(13)-C(1)-C(9)	116.4(5)
O(1)-C(2)-C(3)	127.9(5)
O(1)-C(2)-C(1)	123.8(5)
C(3)-C(2)-C(1)	108.2(4)
C(4)-C(3)-C(8)	121.1(5)
C(4)-C(3)-C(2)	128.2(5)
C(8)-C(3)-C(2)	110.8(5)
C(5)-C(4)-C(3)	119.5(6)
C(6)-C(5)-C(4)	118.9(6)
C(5)-C(6)-C(7)	123.2(6)
C(5)-C(6)-Br(1)	118.4(5)
C(7)-C(6)-Br(1)	118.4(5)
C(8)-C(7)-C(6)	117.3(6)
C(7)-C(8)-C(3)	119.9(5)
C(7)-C(8)-C(9)	128.5(5)
C(3)-C(8)-C(9)	111.5(5)
C(8)-C(9)-C(1)	104.8(4)
C(11)-C(10)-C(14)	125.3(6)
C(11)-C(10)-C(1)	113.9(6)
C(14)-C(10)-C(1)	120.6(5)
C(10)-C(11)-C(12)	110.4(5)
C(11)-C(12)-C(13)	101.8(5)
C(12)-C(13)-C(15)	117.4(5)
C(12)-C(13)-C(1)	104.6(5)
C(15)-C(13)-C(1)	115.9(5)
O(2)-C(14)-O(3)	123.3(6)
O(2)-C(14)-C(10)	120.8(5)

O(3)-C(14)-C(10)	115.9(5)
C(20)-C(15)-C(16)	120.4(6)
C(20)-C(15)-C(13)	118.0(5)
C(16)-C(15)-C(13)	121.6(6)
C(15)-C(16)-C(17)	117.5(7)
C(18)-C(17)-C(16)	121.5(7)
C(17)-C(18)-C(19)	121.6(8)
C(20)-C(19)-C(18)	118.9(8)
C(19)-C(20)-C(15)	120.1(7)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 05143. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	63(1)	65(1)	33(1)	10(1)	-4(1)	40(1)
O(1)	15(2)	35(2)	48(3)	6(2)	1(2)	11(2)
O(2)	53(3)	32(2)	29(2)	-1(2)	-2(2)	19(2)
O(3)	65(3)	44(3)	30(2)	-5(2)	-4(2)	25(3)
C(1)	13(3)	25(3)	38(3)	4(2)	-1(2)	9(2)
C(2)	13(3)	14(3)	37(3)	1(2)	4(2)	1(2)
C(3)	22(3)	14(2)	27(3)	-2(2)	1(2)	8(2)
C(4)	29(3)	32(3)	33(3)	-3(3)	0(3)	17(3)
C(5)	52(4)	33(3)	31(3)	4(3)	13(3)	27(3)
C(6)	49(4)	41(4)	23(3)	-4(3)	-7(3)	29(3)
C(7)	28(3)	31(3)	33(3)	-1(3)	-5(3)	14(3)
C(8)	23(3)	19(3)	35(3)	-2(2)	2(3)	12(2)
C(9)	18(3)	30(3)	29(3)	2(3)	0(2)	14(3)
C(10)	29(3)	37(3)	31(3)	3(3)	3(3)	19(3)
C(11)	18(3)	46(4)	32(3)	3(3)	-1(2)	16(3)
C(12)	22(3)	38(4)	41(4)	15(3)	2(3)	9(3)
C(13)	19(3)	26(3)	37(3)	2(3)	-6(3)	8(3)
C(14)	36(3)	44(4)	24(3)	0(3)	0(3)	22(3)
C(15)	18(3)	23(3)	51(4)	14(3)	2(3)	6(2)
C(16)	19(3)	27(3)	53(4)	14(3)	-14(3)	-2(3)
C(17)	27(4)	22(4)	83(6)	22(4)	-17(4)	-6(3)
C(18)	64(6)	35(4)	90(7)	-18(4)	-32(5)	20(4)
C(19)	55(5)	54(5)	98(7)	-41(5)	-14(5)	23(4)
C(20)	35(4)	34(4)	83(6)	-23(4)	-13(4)	11(3)

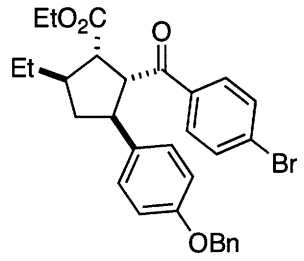
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 05143.

	x	y	z	U(eq)
H(3)	4741	2327	-2107	71
H(4)	3755	2784	-224	37
H(5)	5165	2423	285	43
H(7)	9399	4296	-350	37
H(9A)	8392	4257	-1154	30
H(9B)	9079	6121	-995	30
H(11)	6616	4986	-2143	38
H(12A)	7268	7763	-1889	44
H(12B)	8821	7574	-1743	44
H(13)	5799	6727	-1348	35
H(17)	11699	11133	-782	62
H(18)	10262	11504	-312	78
H(19)	7317	9984	-297	85
H(20)	5870	7898	-753	64

Table 6. Hydrogen bonds for 05143 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(3)-H(3)...Br(1)#1	0.84	2.94	3.386(4)	115.7

Symmetry transformations used to generate equivalent atoms:
#1 -x+y+1,-x+1,z-1/3



Chapter 2.1. Low-temperature diffraction data were collected on a Siemens Platform three-circle diffractometer coupled to a Bruker-AXS Apex CCD detector with graphite monochromated Mo K*a* radiation (*l* = 0.71073Å), performing *j*- and *w*-scans. Raw data frames were integrated using the Bruker program SAINT+ for NT version 6.01. All structures were solved by direct methods using SHELXS and refined against F^2 on all data by full-matrix least squares with SHELXL-97 (Sheldrick, G. M. *SHELXL 97*, Universität Göttingen, Göttingen, Germany, 1997). SADABS absorption correction was performed. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of the hydrogen atoms were fixed to 1.2 times the *U* value of the atoms they are linked to (1.5 times for methyl groups).

05195:

A colorless plate of dimensions 0.50 x 0.15 x 0.04 mm^3 was mounted under STP and transferred to a Siemens Platform three-circle diffractometer equipped with a cold stream of N_2 gas. The data that were collected (23224 total reflections, 6799 unique, Rint

= 0.0323) had the following Miller index ranges: (- 40 to 40 in h, -7 to 7 in k, and – 21 to 21 in l). The structure was solved in the monoclinic space group *C2*, a = 31.348(6) Å, b = 5.6825(9) Å, c = 15.832(3) Å, a = 90°; b = 115.239(5)°; g = 90°, and refined using standard difference Fourier techniques. Final, full-matrix least squares refinement (6799 data for 318 parameters) on F^2 yielded residuals of R1 and wR2 of 0.0276 and 0.0614 for data I > 2s(I), and 0.0317 and 0.0625, respectively, for all data. Residual electron density amounted to a maximum of 0.637 e/Å^3 and a minimum of -0.232 e/ Å^3. The absolute structure (Flack) parameter for the correct enantiomer is 0.008(5), thus confirming the absolute stereochemistry.

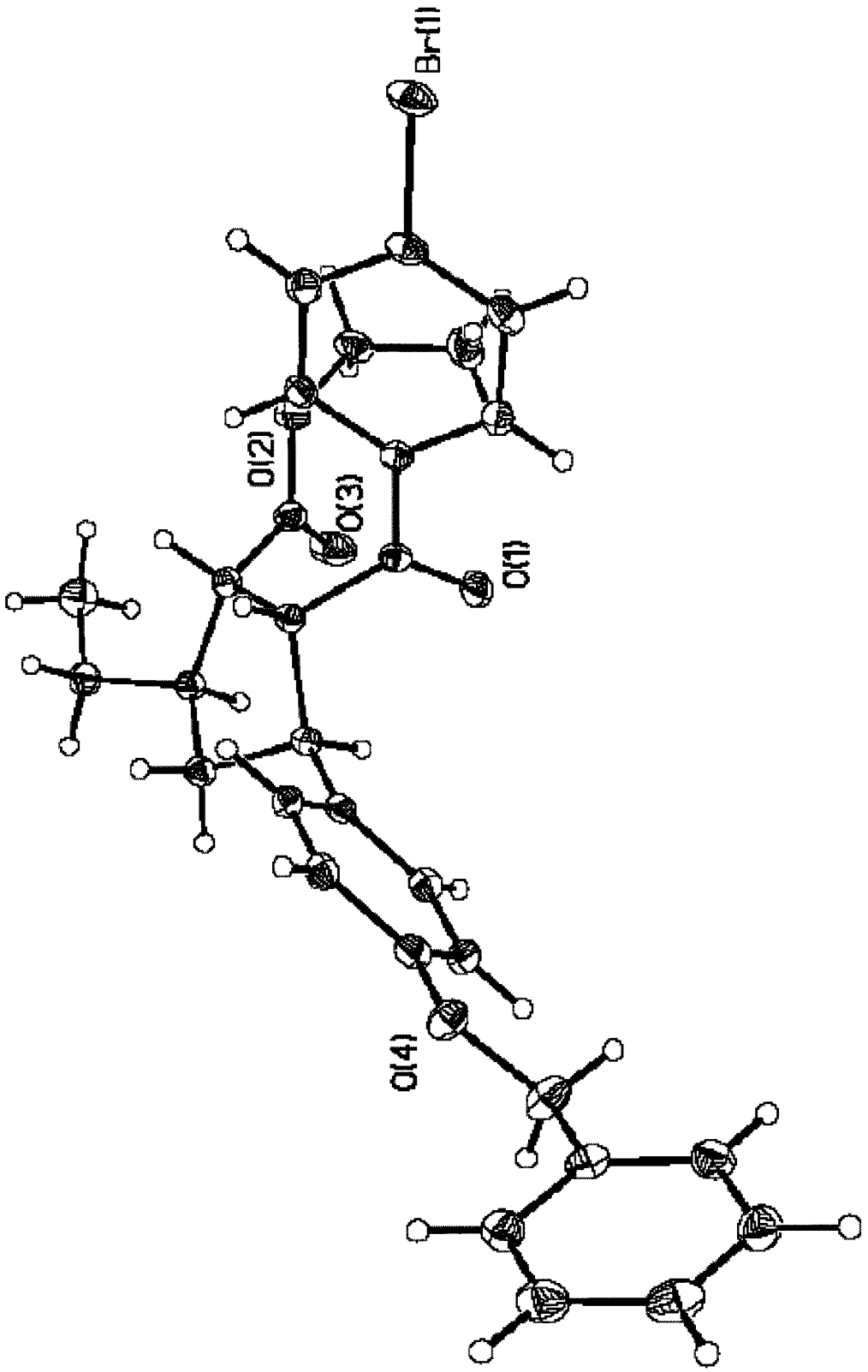

Br(1)
O(2)
O(3)
O(1)
O(4)

Table 1. Crystal data and structure refinement for 05195.

Identification code	05195	
Empirical formula	$C_{30}H_{31}BrO_4$	
Formula weight	535.46	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2	
Unit cell dimensions	a = 31.348(6) Å	a= 90°.
	b = 5.6825(9) Å	b= 115.239(5)°.
	c = 15.832(3) Å	g = 90°.
Volume	2551.0(8) $Å^3$	
Z	4	
Density (calculated)	1.394 Mg/m^3	
Absorption coefficient	1.645 mm^{-1}	
F(000)	1112	
Crystal size	0.50 x 0.15 x 0.04 mm^3	
Theta range for data collection	2.41 to 29.13°.	
Index ranges	-40<=h<=42, -7<=k<=7, -21<=l<=21	
Reflections collected	23224	
Independent reflections	6799 [R(int) = 0.0323]	
Completeness to theta = 29.13°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9371 and 0.4934	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6799 / 1 / 318	
Goodness-of-fit on F^2	0.984	
Final R indices [I>2sigma(I)]	R1 = 0.0276, wR2 = 0.0614	
R indices (all data)	R1 = 0.0317, wR2 = 0.0625	
Absolute structure parameter	0.008(5)	

Largest diff. peak and hole 0.637 and -0.232 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for 05195. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	1954(1)	3189(1)	1331(1)	25(1)
O(1)	3930(1)	-1961(3)	1320(1)	22(1)
C(1)	4213(1)	1985(3)	1399(1)	14(1)
O(2)	4251(1)	1363(2)	3412(1)	20(1)
C(2)	4592(1)	2646(3)	2420(1)	15(1)
O(3)	4876(1)	-721(2)	3472(1)	31(1)
C(3)	5069(1)	2780(3)	2343(1)	16(1)
C(4)	4929(1)	2974(4)	1289(1)	16(1)
O(4)	3544(1)	867(2)	-3099(1)	20(1)
C(5)	4513(1)	1223(3)	883(1)	14(1)
C(6)	4255(1)	1134(3)	-171(1)	14(1)
C(7)	3964(1)	2975(4)	-705(1)	16(1)
C(8)	3738(1)	2843(3)	-1672(1)	17(1)
C(9)	3796(1)	863(3)	-2139(1)	17(1)
C(10)	4086(1)	-979(3)	-1630(1)	17(1)
C(11)	4310(1)	-818(3)	-652(1)	16(1)
C(12)	3850(1)	129(3)	1344(1)	15(1)
C(13)	3386(1)	944(3)	1310(1)	14(1)
C(14)	3338(1)	3136(4)	1662(1)	16(1)
C(15)	2913(1)	3784(3)	1685(1)	18(1)
C(16)	2534(1)	2237(3)	1325(1)	18(1)
C(17)	2570(1)	53(3)	956(1)	19(1)
C(18)	2999(1)	-585(3)	963(1)	17(1)

C(19)	4601(1)	887(3)	3154(1)	17(1)
C(20)	4192(1)	-249(3)	4075(1)	23(1)
C(21)	3899(1)	-2367(3)	3579(1)	28(1)
C(22)	5398(1)	4742(3)	2926(1)	19(1)
C(23)	5530(1)	4547(3)	3972(1)	26(1)
C(24)	3578(1)	-1218(3)	-3581(1)	23(1)
C(25)	3241(1)	-1025(3)	-4604(1)	19(1)
C(26)	2930(1)	-2863(3)	-5035(1)	23(1)
C(27)	2630(1)	-2755(3)	-5991(1)	24(1)
C(28)	2643(1)	-813(4)	-6507(1)	26(1)
C(29)	2948(1)	1039(3)	-6078(1)	26(1)
C(30)	3247(1)	941(3)	-5129(1)	22(1)

Table 3. Bond lengths [Å] and angles [°] for 05195.

Br(1)-C(16)	1.9029(17)
O(1)-C(12)	1.218(2)
C(1)-C(12)	1.527(2)
C(1)-C(5)	1.549(2)
C(1)-C(2)	1.589(2)
O(2)-C(19)	1.350(2)
O(2)-C(20)	1.463(2)
C(2)-C(19)	1.526(2)
C(2)-C(3)	1.553(2)
O(3)-C(19)	1.209(2)
C(3)-C(22)	1.532(2)
C(3)-C(4)	1.537(2)
C(4)-C(5)	1.545(2)
O(4)-C(9)	1.382(2)
O(4)-C(24)	1.438(2)
C(5)-C(6)	1.514(2)
C(6)-C(11)	1.397(2)
C(6)-C(7)	1.408(2)
C(7)-C(8)	1.389(2)
C(8)-C(9)	1.400(2)
C(9)-C(10)	1.395(2)
C(10)-C(11)	1.404(2)
C(12)-C(13)	1.505(2)
C(13)-C(14)	1.398(3)
C(13)-C(18)	1.399(2)
C(14)-C(15)	1.400(2)
C(15)-C(16)	1.389(2)
C(16)-C(17)	1.396(2)
C(17)-C(18)	1.390(2)

C(20)-C(21)	1.514(3)
C(22)-C(23)	1.531(2)
C(24)-C(25)	1.513(2)
C(25)-C(26)	1.394(2)
C(25)-C(30)	1.398(2)
C(26)-C(27)	1.401(3)
C(27)-C(28)	1.384(3)
C(28)-C(29)	1.389(3)
C(29)-C(30)	1.392(3)

C(12)-C(1)-C(5)	112.52(13)
C(12)-C(1)-C(2)	115.94(13)
C(5)-C(1)-C(2)	104.07(12)
C(19)-O(2)-C(20)	117.31(14)
C(19)-C(2)-C(3)	112.81(13)
C(19)-C(2)-C(1)	112.48(12)
C(3)-C(2)-C(1)	105.06(12)
C(22)-C(3)-C(4)	114.16(14)
C(22)-C(3)-C(2)	114.34(13)
C(4)-C(3)-C(2)	104.42(12)
C(3)-C(4)-C(5)	101.87(13)
C(9)-O(4)-C(24)	116.47(13)
C(6)-C(5)-C(4)	116.15(13)
C(6)-C(5)-C(1)	115.52(13)
C(4)-C(5)-C(1)	101.23(12)
C(11)-C(6)-C(7)	117.51(14)
C(11)-C(6)-C(5)	119.64(14)
C(7)-C(6)-C(5)	122.83(14)
C(8)-C(7)-C(6)	121.12(16)
C(7)-C(8)-C(9)	120.41(16)
O(4)-C(9)-C(10)	124.26(15)

O(4)-C(9)-C(8)	115.94(14)
C(10)-C(9)-C(8)	119.77(15)
C(9)-C(10)-C(11)	119.02(15)
C(6)-C(11)-C(10)	122.17(15)
O(1)-C(12)-C(13)	120.62(15)
O(1)-C(12)-C(1)	121.03(15)
C(13)-C(12)-C(1)	118.35(14)
C(14)-C(13)-C(18)	119.21(14)
C(14)-C(13)-C(12)	121.71(14)
C(18)-C(13)-C(12)	118.98(15)
C(13)-C(14)-C(15)	120.67(15)
C(16)-C(15)-C(14)	118.64(16)
C(15)-C(16)-C(17)	121.88(16)
C(15)-C(16)-Br(1)	117.98(13)
C(17)-C(16)-Br(1)	120.14(13)
C(18)-C(17)-C(16)	118.56(16)
C(17)-C(18)-C(13)	121.00(15)
O(3)-C(19)-O(2)	123.63(16)
O(3)-C(19)-C(2)	126.07(15)
O(2)-C(19)-C(2)	110.30(14)
O(2)-C(20)-C(21)	111.13(14)
C(23)-C(22)-C(3)	113.61(14)
O(4)-C(24)-C(25)	109.40(13)
C(26)-C(25)-C(30)	119.43(16)
C(26)-C(25)-C(24)	119.60(15)
C(30)-C(25)-C(24)	120.94(16)
C(25)-C(26)-C(27)	120.20(17)
C(28)-C(27)-C(26)	119.86(17)
C(27)-C(28)-C(29)	120.20(17)
C(28)-C(29)-C(30)	120.21(17)
C(29)-C(30)-C(25)	120.09(17)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 05195. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

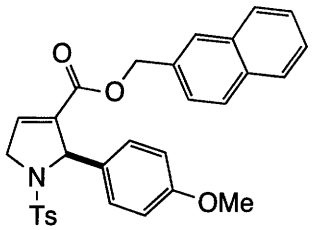
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	16(1)	30(1)	34(1)	8(1)	15(1)	5(1)
O(1)	22(1)	16(1)	32(1)	1(1)	16(1)	0(1)
C(1)	13(1)	15(1)	15(1)	1(1)	7(1)	1(1)
O(2)	21(1)	23(1)	19(1)	0(1)	12(1)	0(1)
C(2)	15(1)	16(1)	16(1)	-1(1)	7(1)	1(1)
O(3)	33(1)	31(1)	36(1)	15(1)	23(1)	12(1)
C(3)	15(1)	17(1)	16(1)	-1(1)	7(1)	0(1)
C(4)	13(1)	18(1)	17(1)	0(1)	7(1)	0(1)
O(4)	21(1)	21(1)	14(1)	-1(1)	5(1)	3(1)
C(5)	14(1)	16(1)	15(1)	1(1)	7(1)	0(1)
C(6)	12(1)	16(1)	16(1)	-1(1)	7(1)	-3(1)
C(7)	16(1)	16(1)	19(1)	-2(1)	9(1)	-2(1)
C(8)	17(1)	16(1)	19(1)	2(1)	8(1)	0(1)
C(9)	15(1)	20(1)	17(1)	1(1)	7(1)	-2(1)
C(10)	18(1)	17(1)	17(1)	-2(1)	9(1)	0(1)
C(11)	13(1)	16(1)	18(1)	1(1)	6(1)	1(1)
C(12)	14(1)	18(1)	13(1)	1(1)	6(1)	0(1)
C(13)	15(1)	17(1)	12(1)	1(1)	7(1)	1(1)
C(14)	15(1)	15(1)	18(1)	1(1)	8(1)	-1(1)
C(15)	21(1)	17(1)	20(1)	3(1)	12(1)	2(1)
C(16)	13(1)	24(1)	19(1)	6(1)	8(1)	4(1)
C(17)	15(1)	23(1)	18(1)	2(1)	5(1)	-4(1)
C(18)	19(1)	17(1)	15(1)	1(1)	7(1)	-1(1)

C(19)	18(1)	19(1)	15(1)	-1(1)	8(1)	-1(1)
C(20)	25(1)	33(1)	15(1)	-2(1)	12(1)	-7(1)
C(21)	35(1)	30(1)	21(1)	0(1)	14(1)	-10(1)
C(22)	19(1)	20(1)	19(1)	-2(1)	8(1)	-3(1)
C(23)	24(1)	31(1)	19(1)	-3(1)	6(1)	-2(1)
C(24)	29(1)	22(1)	17(1)	-1(1)	7(1)	6(1)
C(25)	18(1)	23(1)	16(1)	-1(1)	8(1)	4(1)
C(26)	26(1)	23(1)	22(1)	2(1)	13(1)	0(1)
C(27)	20(1)	29(1)	23(1)	-7(1)	8(1)	-4(1)
C(28)	21(1)	37(1)	17(1)	0(1)	6(1)	6(1)
C(29)	31(1)	29(1)	21(1)	5(1)	13(1)	3(1)
C(30)	21(1)	23(1)	22(1)	-1(1)	10(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 05195.

	x	y	z	U(eq)
H(1)	4039	3453	1096	17
H(2)	4516	4240	2585	18
H(3)	5236	1246	2564	19
H(4A)	5192	2501	1135	19
H(4B)	4828	4592	1059	19
H(5)	4639	-388	1107	17
H(7)	3922	4331	-398	20
H(8)	3543	4103	-2019	21
H(10)	4131	-2323	-1940	21
H(11)	4506	-2078	-306	19
H(14)	3597	4195	1888	19
H(15)	2883	5253	1942	22
H(17)	2306	-975	706	23
H(18)	3031	-2082	729	20
H(20A)	4036	587	4415	28
H(20B)	4506	-781	4538	28
H(21A)	3599	-1838	3086	42
H(21B)	3839	-3338	4028	42
H(21C)	4071	-3297	3303	42
H(22A)	5691	4706	2832	23
H(22B)	5244	6280	2698	23
H(23A)	5246	4755	4079	38
H(23B)	5760	5769	4309	38
H(23C)	5666	2993	4198	38
H(24A)	3499	-2620	-3305	28

H(24B)	3905	-1399	-3516	28
H(26)	2920	-4193	-4680	28
H(27)	2418	-4011	-6284	29
H(28)	2443	-747	-7157	31
H(29)	2954	2376	-6434	31
H(30)	3454	2213	-4838	26



Chapter 2.2. Low-temperature diffraction data were collected on a Siemens Platform three-circle diffractometer coupled to a Bruker-AXS Apex CCD detector with graphite monochromated Mo K*a* radiation (*l* = 0.71073Å), performing *j*- and *w*-scans. Raw data frames were integrated using the Bruker program SAINT+ for NT version 6.01. All structures were solved by direct methods using SHELXS and refined against F^2 on all data by full-matrix least squares with SHELXL-97 (Sheldrick, G. M. *SHELXL 97*, Universität Göttingen, Göttingen, Germany, 1997). SADABS absorption correction was performed. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of the hydrogen atoms were fixed to 1.2 times the *U* value of the atoms they are linked to (1.5 times for methyl groups).

07091:

A colorless needle of dimensions 0.40 x 0.35 x 0.30 mm^3 was mounted under STP and transferred to a Siemens Platform three-circle diffractometer equipped with a cold stream of N_2 gas. The data that were collected (27299 total reflections, 6844 unique, Rint = 0.0219) had the following Miller index ranges: (- 15 to 15 in h, -15 to 15 in k, and – 14 to 15 in l). The structure was solved in the monoclinic space group *P2(1)*, *a* = 11.0860(3) Å, *b* = 11.1996(3) Å, *c* = 11.1086(3) Å, a = 90°; b = 117.6786(4)°; g = 90°, and refined using standard difference Fourier techniques. Final, full-matrix least squares refinement (6844 data for 336 parameters) on F^2 yielded residuals of R1 and wR2 of 0.0284 and 0.0774 for data I > 2s(I), and 0.0292 and 0.0782, respectively, for all data. Residual electron density amounted to a maximum of 0.327 e/$Å^3$ and a minimum of -0.236 e/ $Å^3$. The absolute structure (Flack) parameter for the correct enantiomer is 0.00(4), thus confirming the absolute stereochemistry.

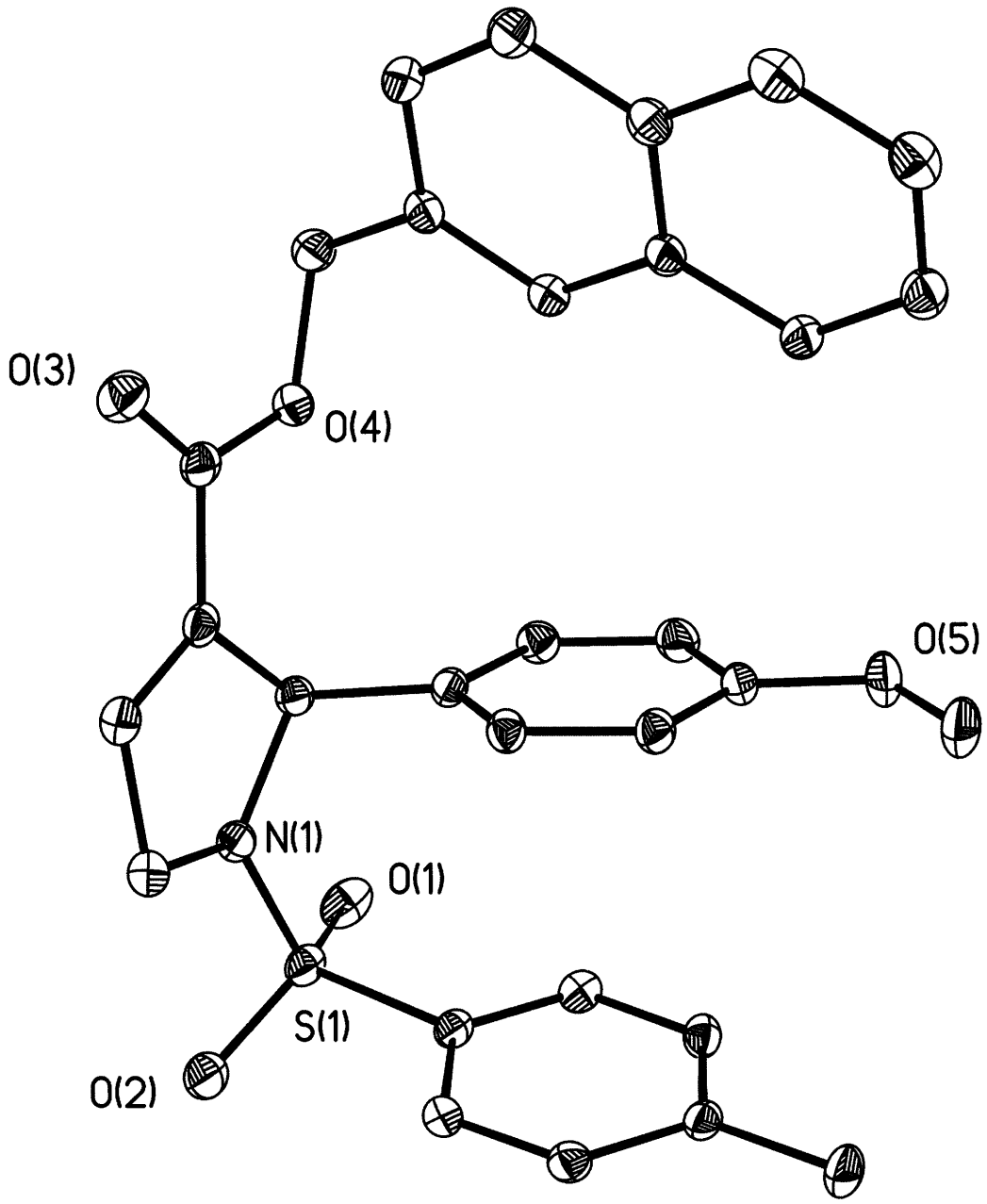

O(3)
O(4)
O(5)
N(1)
O(1)
S(1)
O(2)

Table 1. Crystal data and structure refinement for 07091.

Identification code	07091	
Empirical formula	$C_{30}H_{27}NO_5S$	
Formula weight	513.59	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 11.0860(3) Å	a= 90°.
	b = 11.1996(3) Å	b= 117.6786(4)°.
	c = 11.1086(3) Å	g = 90°.
Volume	1221.40(6) $Å^3$	
Z	2	
Density (calculated)	1.396 Mg/m^3	
Absorption coefficient	0.176 mm^{-1}	
F(000)	540	
Crystal size	0.40 x 0.35 x 0.30 mm^3	
Theta range for data collection	2.07 to 29.57°.	
Index ranges	-15<=h<=15, -15<=k<=15, -14<=l<=15	
Reflections collected	27299	
Independent reflections	6844 [R(int) = 0.0219]	
Completeness to theta = 29.57°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9490 and 0.9329	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6844 / 1 / 336	
Goodness-of-fit on F^2	1.055	
Final R indices [I>2sigma(I)]	R1 = 0.0284, wR2 = 0.0774	
R indices (all data)	R1 = 0.0292, wR2 = 0.0782	
Absolute structure parameter	0.00(4)	

Largest diff. peak and hole 0.327 and -0.236 e.$Å^{-3}$

Table 2. Atomic coordinates ($Å^2$x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 07091. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	8780(1)	379(1)	8437(1)	17(1)
O(1)	8310(1)	-747(1)	8682(1)	24(1)
O(2)	10217(1)	630(1)	9055(1)	26(1)
O(3)	5319(1)	3897(1)	9979(1)	24(1)
O(4)	4546(1)	2023(1)	9276(1)	18(1)
O(5)	2761(1)	367(1)	3376(1)	24(1)
N(1)	8129(1)	1404(1)	8997(1)	17(1)
C(1)	8620(1)	2653(1)	9163(1)	20(1)
C(2)	7625(1)	3273(1)	9506(1)	19(1)
C(3)	6602(1)	2557(1)	9342(1)	15(1)
C(4)	6710(1)	1330(1)	8820(1)	15(1)
C(5)	5439(1)	2927(1)	9574(1)	17(1)
C(6)	3295(1)	2297(1)	9338(1)	20(1)
C(7)	2275(1)	2886(1)	8040(1)	17(1)
C(8)	2091(1)	2480(1)	6796(1)	16(1)
C(9)	1089(1)	2992(1)	5570(1)	15(1)
C(10)	829(1)	2549(1)	4274(1)	16(1)
C(11)	-169(1)	3042(1)	3105(1)	20(1)
C(12)	-936(1)	4030(1)	3173(1)	20(1)
C(13)	-697(1)	4483(1)	4408(1)	20(1)
C(14)	298(1)	3966(1)	5640(1)	16(1)
C(15)	511(1)	4374(1)	6934(1)	20(1)
C(16)	1466(1)	3839(1)	8105(1)	20(1)

C(17)	5623(1)	1117(1)	7364(1)	14(1)
C(18)	5410(1)	1941(1)	6343(1)	15(1)
C(19)	4469(1)	1723(1)	4995(1)	16(1)
C(20)	3713(1)	668(1)	4667(1)	18(1)
C(21)	3900(1)	-156(1)	5681(1)	20(1)
C(22)	4849(1)	71(1)	7018(1)	18(1)
C(23)	2552(1)	1190(1)	2310(1)	29(1)
C(24)	8117(1)	558(1)	6669(1)	15(1)
C(25)	7139(1)	-231(1)	5789(1)	16(1)
C(26)	6562(1)	-43(1)	4391(1)	16(1)
C(27)	6946(1)	933(1)	3871(1)	15(1)
C(28)	7949(1)	1703(1)	4775(1)	16(1)
C(29)	8548(1)	1522(1)	6169(1)	17(1)
C(30)	6313(1)	1174(1)	2368(1)	22(1)

Table 3. Bond lengths [Å] and angles [°] for 07091.

S(1)-O(1)	1.4380(10)
S(1)-O(2)	1.4388(9)
S(1)-N(1)	1.6266(10)
S(1)-C(24)	1.7595(11)
O(3)-C(5)	1.2063(14)
O(4)-C(5)	1.3453(14)
O(4)-C(6)	1.4534(13)
O(5)-C(20)	1.3696(13)
O(5)-C(23)	1.4319(18)
N(1)-C(1)	1.4808(16)
N(1)-C(4)	1.4931(14)
C(1)-C(2)	1.4951(16)
C(2)-C(3)	1.3304(16)

C(3)-C(5)	1.4869(15)
C(3)-C(4)	1.5170(15)
C(4)-C(17)	1.5217(15)
C(6)-C(7)	1.5095(16)
C(7)-C(8)	1.3774(15)
C(7)-C(16)	1.4171(16)
C(8)-C(9)	1.4181(15)
C(9)-C(10)	1.4205(15)
C(9)-C(14)	1.4237(15)
C(10)-C(11)	1.3710(16)
C(11)-C(12)	1.4186(17)
C(12)-C(13)	1.3683(17)
C(13)-C(14)	1.4223(16)
C(14)-C(15)	1.4200(16)
C(15)-C(16)	1.3761(17)
C(17)-C(18)	1.3941(15)
C(17)-C(22)	1.3971(15)
C(18)-C(19)	1.3926(15)
C(19)-C(20)	1.3962(16)
C(20)-C(21)	1.3947(17)
C(21)-C(22)	1.3882(16)
C(24)-C(25)	1.3889(15)
C(24)-C(29)	1.3953(15)
C(25)-C(26)	1.3941(15)
C(26)-C(27)	1.3910(15)
C(27)-C(28)	1.3969(15)
C(27)-C(30)	1.5048(15)
C(28)-C(29)	1.3869(15)

O(1)-S(1)-O(2)	119.93(6)
O(1)-S(1)-N(1)	106.36(5)

O(2)-S(1)-N(1)	105.62(5)
O(1)-S(1)-C(24)	108.14(5)
O(2)-S(1)-C(24)	107.85(5)
N(1)-S(1)-C(24)	108.49(5)
C(5)-O(4)-C(6)	115.99(9)
C(20)-O(5)-C(23)	117.21(10)
C(1)-N(1)-C(4)	111.89(9)
C(1)-N(1)-S(1)	120.72(8)
C(4)-N(1)-S(1)	122.56(8)
N(1)-C(1)-C(2)	101.41(9)
C(3)-C(2)-C(1)	111.60(10)
C(2)-C(3)-C(5)	124.11(10)
C(2)-C(3)-C(4)	112.59(10)
C(5)-C(3)-C(4)	123.23(10)
N(1)-C(4)-C(3)	99.50(9)
N(1)-C(4)-C(17)	114.48(9)
C(3)-C(4)-C(17)	112.59(9)
O(3)-C(5)-O(4)	125.04(10)
O(3)-C(5)-C(3)	124.76(10)
O(4)-C(5)-C(3)	110.20(9)
O(4)-C(6)-C(7)	110.81(9)
C(8)-C(7)-C(16)	119.90(10)
C(8)-C(7)-C(6)	120.67(10)
C(16)-C(7)-C(6)	119.40(10)
C(7)-C(8)-C(9)	120.93(10)
C(8)-C(9)-C(10)	122.11(10)
C(8)-C(9)-C(14)	119.04(10)
C(10)-C(9)-C(14)	118.84(10)
C(11)-C(10)-C(9)	120.96(11)
C(10)-C(11)-C(12)	120.21(11)
C(13)-C(12)-C(11)	120.07(11)

C(12)-C(13)-C(14)	121.08(11)
C(15)-C(14)-C(13)	122.20(11)
C(15)-C(14)-C(9)	119.01(10)
C(13)-C(14)-C(9)	118.78(10)
C(16)-C(15)-C(14)	120.65(11)
C(15)-C(16)-C(7)	120.44(10)
C(18)-C(17)-C(22)	118.79(10)
C(18)-C(17)-C(4)	120.80(10)
C(22)-C(17)-C(4)	120.38(10)
C(19)-C(18)-C(17)	121.19(10)
C(18)-C(19)-C(20)	119.22(10)
O(5)-C(20)-C(21)	115.84(10)
O(5)-C(20)-C(19)	123.97(11)
C(21)-C(20)-C(19)	120.19(10)
C(22)-C(21)-C(20)	119.88(11)
C(21)-C(22)-C(17)	120.71(11)
C(25)-C(24)-C(29)	120.79(10)
C(25)-C(24)-S(1)	119.85(8)
C(29)-C(24)-S(1)	119.31(8)
C(24)-C(25)-C(26)	119.44(10)
C(27)-C(26)-C(25)	120.74(10)
C(26)-C(27)-C(28)	118.75(10)
C(26)-C(27)-C(30)	121.76(10)
C(28)-C(27)-C(30)	119.48(10)
C(29)-C(28)-C(27)	121.39(10)
C(28)-C(29)-C(24)	118.84(10)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for 07091. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	17(1)	23(1)	11(1)	3(1)	5(1)	7(1)
O(1)	33(1)	23(1)	19(1)	7(1)	14(1)	10(1)
O(2)	16(1)	42(1)	15(1)	0(1)	4(1)	8(1)
O(3)	26(1)	23(1)	24(1)	-4(1)	12(1)	2(1)
O(4)	15(1)	22(1)	15(1)	0(1)	6(1)	1(1)
O(5)	20(1)	30(1)	16(1)	-7(1)	3(1)	-2(1)
N(1)	14(1)	21(1)	15(1)	-2(1)	6(1)	2(1)
C(1)	18(1)	25(1)	17(1)	-4(1)	8(1)	-3(1)
C(2)	19(1)	22(1)	15(1)	-3(1)	7(1)	-1(1)
C(3)	16(1)	18(1)	10(1)	-1(1)	4(1)	2(1)
C(4)	14(1)	17(1)	13(1)	1(1)	6(1)	2(1)
C(5)	17(1)	20(1)	11(1)	2(1)	5(1)	3(1)
C(6)	17(1)	30(1)	14(1)	1(1)	8(1)	1(1)
C(7)	13(1)	21(1)	15(1)	-2(1)	6(1)	-3(1)
C(8)	14(1)	19(1)	16(1)	-1(1)	7(1)	-1(1)
C(9)	13(1)	17(1)	15(1)	-1(1)	7(1)	-3(1)
C(10)	16(1)	20(1)	15(1)	-1(1)	8(1)	-2(1)
C(11)	19(1)	24(1)	16(1)	1(1)	9(1)	-2(1)
C(12)	19(1)	21(1)	19(1)	6(1)	7(1)	0(1)
C(13)	18(1)	16(1)	24(1)	3(1)	9(1)	1(1)
C(14)	15(1)	16(1)	18(1)	-1(1)	7(1)	-2(1)
C(15)	19(1)	19(1)	21(1)	-4(1)	8(1)	0(1)
C(16)	18(1)	24(1)	18(1)	-7(1)	8(1)	-3(1)
C(17)	14(1)	16(1)	12(1)	-1(1)	6(1)	1(1)
C(18)	15(1)	15(1)	14(1)	-1(1)	5(1)	1(1)
C(19)	16(1)	18(1)	13(1)	1(1)	5(1)	2(1)

C(20)	13(1)	23(1)	15(1)	-5(1)	4(1)	1(1)
C(21)	18(1)	19(1)	23(1)	-4(1)	10(1)	-3(1)
C(22)	18(1)	17(1)	18(1)	0(1)	9(1)	-1(1)
C(23)	25(1)	43(1)	14(1)	-3(1)	3(1)	4(1)
C(24)	14(1)	17(1)	12(1)	2(1)	6(1)	5(1)
C(25)	19(1)	14(1)	17(1)	2(1)	9(1)	3(1)
C(26)	17(1)	16(1)	14(1)	-2(1)	6(1)	0(1)
C(27)	15(1)	19(1)	12(1)	1(1)	6(1)	3(1)
C(28)	16(1)	18(1)	16(1)	1(1)	8(1)	-1(1)
C(29)	14(1)	21(1)	15(1)	-2(1)	6(1)	-1(1)
C(30)	23(1)	28(1)	11(1)	1(1)	5(1)	1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 07091.

	x	y	z	U(eq)
H(1A)	8580	2967	8312	24
H(1B)	9563	2725	9908	24
H(2)	7712	4078	9804	23
H(4)	6655	699	9429	18
H(6A)	3499	2836	10115	24
H(6B)	2900	1552	9484	24
H(8)	2643	1847	6758	19
H(10)	1354	1902	4216	20
H(11)	-347	2720	2247	23
H(12)	-1616	4377	2360	24
H(13)	-1204	5153	4443	23
H(15)	-12	5023	6992	24
H(16)	1585	4110	8964	24
H(18)	5915	2665	6572	18

H(19)	4343	2286	4307	20
H(21)	3379	-870	5456	24
H(22)	4973	-492	7706	21
H(23A)	2269	1964	2504	44
H(23B)	1842	882	1444	44
H(23C)	3403	1286	2253	44
H(25)	6864	-894	6137	20
H(26)	5900	-586	3786	20
H(28)	8226	2364	4428	20
H(29)	9239	2044	6773	20
H(30A)	5753	489	1869	32
H(30B)	7032	1301	2104	32
H(30C)	5740	1889	2153	32