DEVELOPMENT OF THE PHOTOREMOVABLE PROTECTING GROUPS FOR VARIOUS HYDROXYL-CONTAINING AND CARBONYL COMPOUNDS.

by

ALEXEY P. KOSTIKOV

(Under the Direction of Vladimir V. Popik)

ABSTRACT

Photoremovable protecting groups (PPG), known as “cages” in biochemistry, allows for the spatial and temporal control of a substrate release, as well as “reagentless” deprotection. PPGs found numerous applications in biochemistry, organic synthesis, fabrication of high density probe array (a.k.a biochips), and time-resolved X-ray crystallography. While a large variety of PPGs has been reported in recent years, few of them are suitable for the direct protection of alcohols, glycols, and carbonyl compounds.

We have developed a novel family of photoremovable protecting groups based on the photochemical reactivity of 2-hydroxybenzyl alcohol and its derivatives. Cleavage of the benzylic C-O bond and release of the substrate are induced by the excited state transfer of a phenolic proton to an adjacent oxygen atom. Attractive advantages of this family of PPGs include fast and efficient liberation of the substrate; *in situ* generation of photolabile group from photostable precursors, and bleaching of the UV band corresponding to the caging chromophore.

Irradiation of alcohols, phenols, and carboxylic acids “caged” with the 2,5-dihydroxybenzyl group (DHB) or its naphthalene analog 1,4-dihydroxy-2-naphthylmethyl

(DHNM) results in deprotection of the substrate in high chemical and quantum yields. These PPGs can be armed *in situ* by the reduction of photochemically inert *p*-quinone precursors. Varying the substitution pattern in the aromatic ring allows for tuning of the chemical and photophysical properties of these PPGs.

We have also developed photochemically removable equivalent of the conventional benzylidene group, widely used in classical organic synthesis for protection of 1,2- and 1,3-glycols. Cyclic acetals of substituted 2-hydroxybenzaldehydes release glycols upon irradiation at appropriate wavelength in excellent chemical yields and good quantum efficiencies. This group can be applied in synthesis of glycerides, carbohydrate chemistry, drug delivery systems *etc*.

Finally, we have designed a new PPG for carbonyl compounds. Cyclic acetals produced by the reaction of 1-(2,5-dihydroxyphenyl)ethane-1,2-diol with various aldehydes and ketones were shown to efficiently liberate substrates upon photolysis. This group is a photochemical analog of ethyleneglycol, a common protecting group for carbonyl compounds in synthetic organic chemistry.

INDEX WORDS: Photoremovable protecting groups, Photocages, UV irradiation, Alcohols, Phenols, Carboxylic acids, Glycols, Carbonyl compounds, Acetals.

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TABLE OF CONTENTS

Page

LIST OF TABLES

Page

LIST OF FIGURES

Page

1. PHOTOREMOVABLE PROTECTING GROUPS (PPG)

1.1. Introduction.

In recent years photoremovable protecting groups have found application in various fields of study.[1-3] In organic synthesis an obvious advantage of PPGs over classical protecting groups is that they do not require any reagent for a deprotection step, thus overcoming complications associated with sensitivity of the substrate to cleaving agents. In cell biology and neurosciences, PPGs allows for time-resolved studies of biological processes due to high spatial and temporal control over photochemically induced release of active substrate. PPGs also found their application in time-resolved X-ray crystallography and photolithographic fabrication of DNA chips.

Requirements for a good photolabile protection groups include:

1) high quantum and chemical yields of deprotection,

2) high extinction coefficients preferably at wavelengths 300 nm and above,

3) stability in the dark,

4) fast release of the substrate (for time-resolved studies),

5) solubility in aqueous media (for biological processes).

It is also very important that photochemical by-products should:

6) not interfere with photochemical reactions; be non-toxic in biological applications

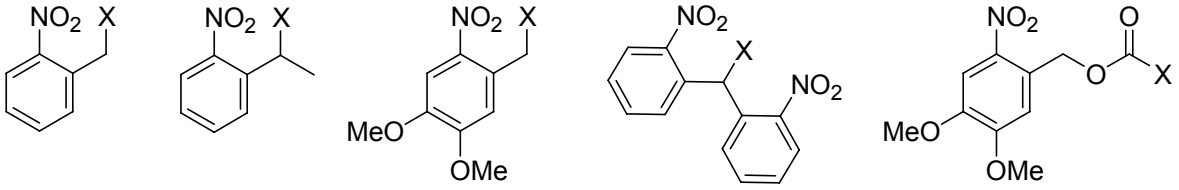
7) have low extinction coefficients at the wavelength of irradiation.

We here wish to review and analyze photoremovable protecting groups for different functionalities reported so far.

1.2. *o*-Nitrobenzyl derivatives.

Various 2-nitrobenzyl derivatives are by far the most widely used photoremovable protecting groups nowadays. This type of PPG beside the parent 2-nitrobenzyl (NB) includes 2-nitrophenethyl (NPE), 6-nitroveratryloxycarbonyl (NVOC), 4,5-dimethoxy-2-nitrobenzyl (DMNB) and 2,2'-dinitrobenzhydrol (DNB) groups (scheme 1.1).

Scheme 1.1



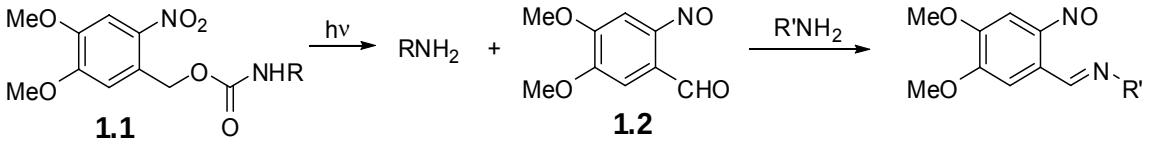
NB **NPE** **DMNB** **DNB** **NVOC**

The first report on using *o*-nitrobenzyl derivatives as a photolabile protecting group for *N*- and *C*-termini of peptides was published in 1966 by Barltrop *et al*.[4] In 1970 Patchornik published a series of communications[5] reporting quantitative release of aminoacids and short peptides from NVOC protected substrates **1.1** (scheme 1.2) upon irradiation at wavelengths longer than 320 nm. This, however, was only achieved in presence of either sulfuric acid or semicarbazide hydrochloride. To avoid the side reactions with the nitroso benzaldehyde intermediate **1.2** α-substituted o-nitrobenzyl derivatives were tested as PRPG. Symmetrical carbinol (DNB) was chosen to prevent formation of diastereomers in the case of optically active protected substrates. Compared to nitroso benzaldehyde, the resulting substituted benzophenone is much less reactive toward amino groups of peptides.

Kaplan *et al.*[6] reported the first biochemical application of the NPE group in his pioneer work published in 1978. Several adenosine phosphates protected with this PRPG on the terminal phosphate were prepared and irradiated. P^3-1-(2-nitro)phenethyl-

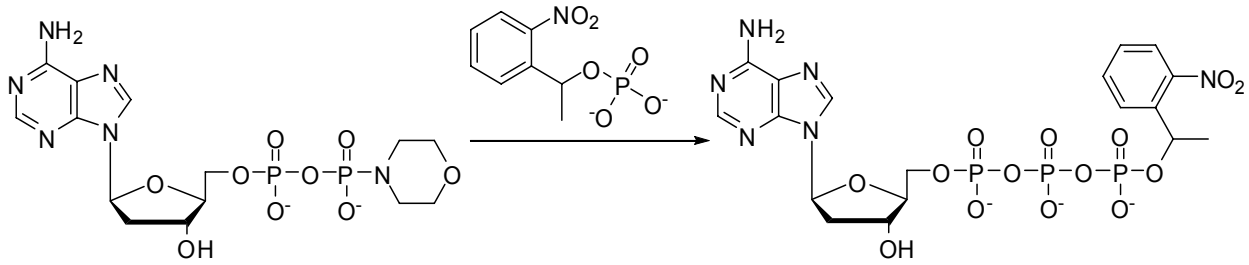
ATP ("caged ATP") **1.3** released adenosine 5'-triphosphate upon irradiation at 340 nm in aqueous solution in about a 70% yield (scheme 1.2).

Scheme 1.2

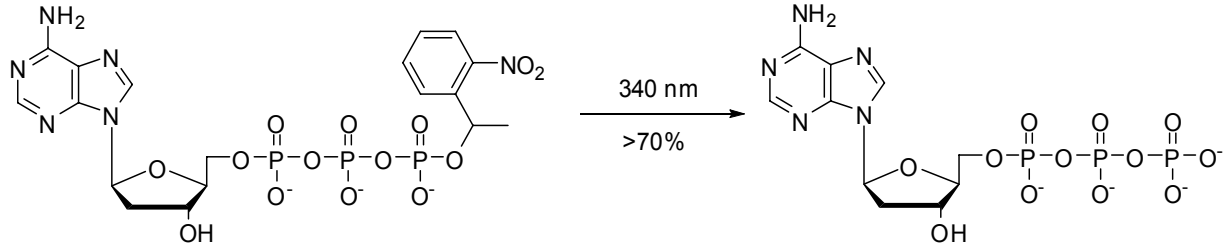


1.1 **1.2**

RNH_2 = Val; Pro; Met; Trp; Phe-Gly; Gly; Ala



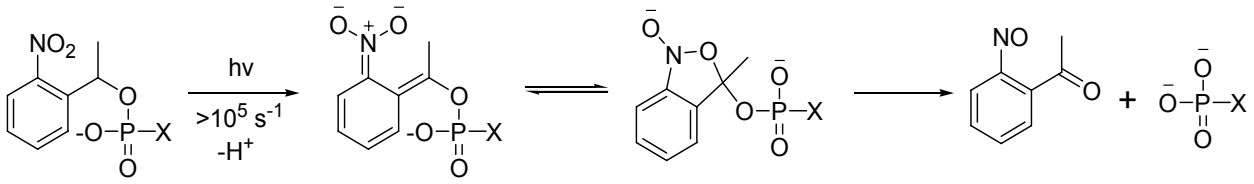
1.3
CAGED ATP



CAGED ATP **ATP**

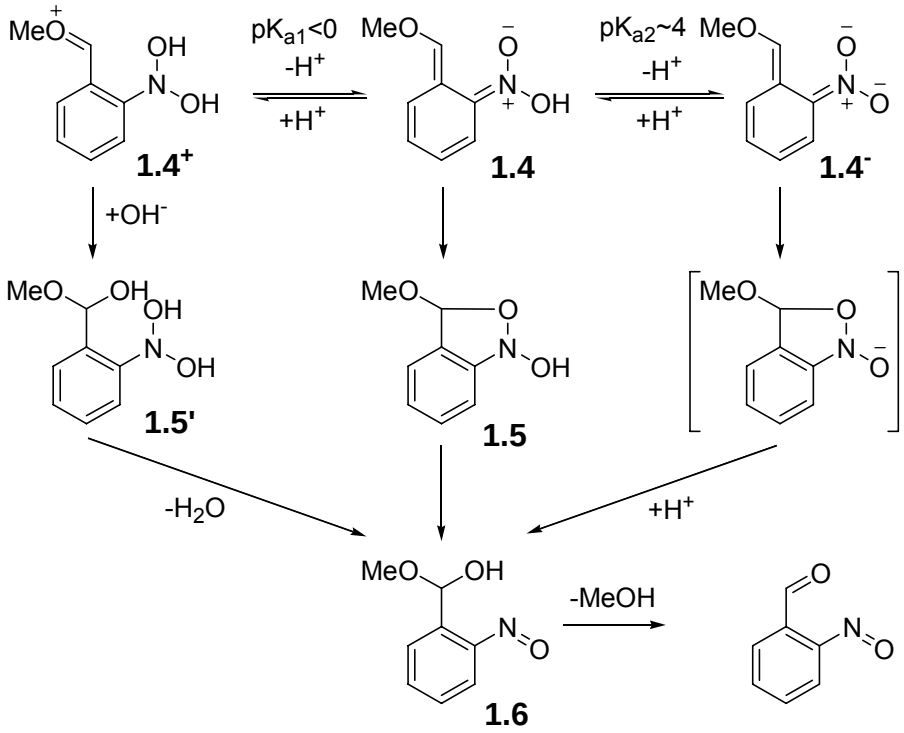
2-Nitrobenzyl derivatives undergo rapid ($k = 2*10^7\ s^{-1}$ for the parent nitrotoluene) reversible tautomerization to the aci-nitro form upon photoexcitation. This is indisputably the first step in a cascade that results in release of the substrate upon irradiation of caged nitrobenzyl derivatives. Walker *et al.* studied the mechanism of the release of caged ATP utilizing the laser flash photolysis technique.[7] The following minimal mechanism consistent with the kinetic results was suggested:

Scheme 1.3



This mechanism was recently revised independently by Corrie and Wirz.[8,9] The photochemical deprotection process was found to be strongly dependent on the solvent and pH. Three intermediates were observed – aci-nitro transient **1.4**, cyclic derivatives **1.5** and 2-nitrosobenzyl hemiacetal **1.6**. In buffered aqueous solution (pH<6) intermediate **1.5'** limits the release rate of the substrate. At pH up to 8-10 decay of intermediate **1.6** becomes the rate-determining step. Finally, at pH values 10 and higher the release of alcohol occurs in a single step from $\mathbf{1.4}^-$, the lifetime of which is independent on pH.

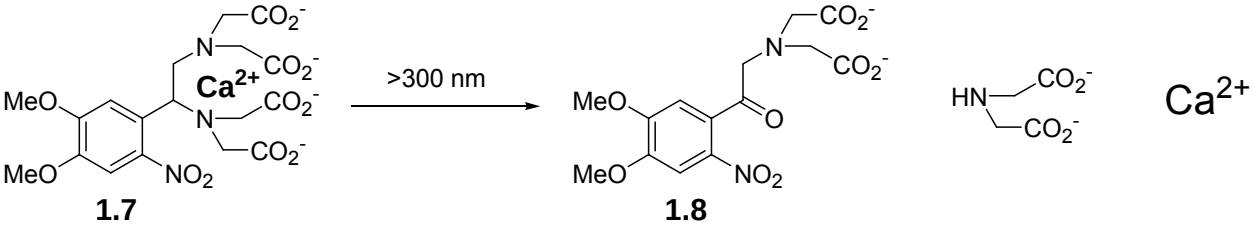
Scheme 1.4



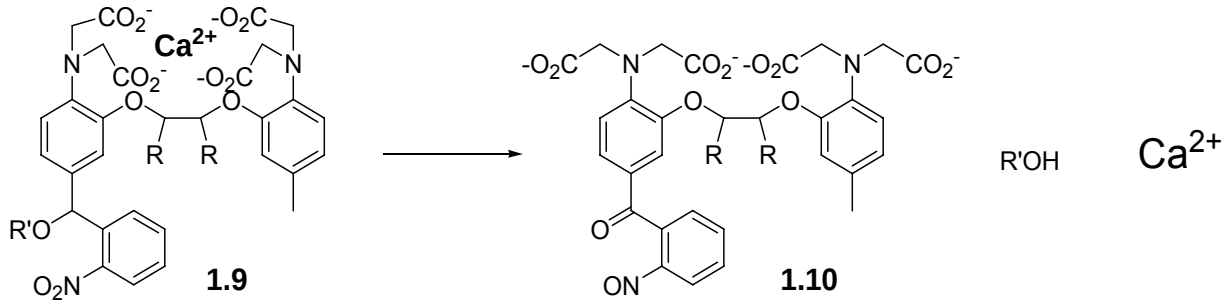
The dependence of quantum efficiency of the photochemical release on substituents in the aromatic ring and side-chain of the chromophore's core was studied by Cameron and Frechet.[10] They found that introduction of the nitro group in the second *o*-position increases the quantum yield of amine release from the nitrobenzyloxycarbonyl group from 0.13 to 0.62. On the other hand, introduction of the substituent in the benzylic position (CH_3, *o*-NO_2-C_6H_4) had much less influence on the quantum efficiency (0.11 and 0.26 respectively).

In 1988, two independent reports on using the nitrobenzyl group as a photolabile chelator for the release of Ca^{2+} appeared. Kaplan *et al.*[11] utilized photochemical cleavage of 1-(2-nitro-4,5-dimethoxyphenyl)-N,N,N',N'-tetrakis [carboxymethyl]-1,2-ethane diamine complex with Ca^{2+} (DM-nitrophen-Ca^{2+}) **1.7**. The resulting iminodiacetate **1.8** has much lower affinity towards Ca^{2+} (6 orders of magnitude) and therefore, the cation is released with a quantum yield of 0.18 at 100-150 μs. Adams and co-workers[12] designed a chelator that upon irradiation does not decompose; however, it releases Ca^{2+} due to significant change in affinity. They utilized the known fact that electron withdrawing substituents lower the binding constant of BAPTA, 1,2-bis(o-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid towards cations. Thus, photochemical transformation of the nitrobenzyl moiety **1.9** to the nitroso benzocarbonyl **1.10** drastically drops the affinity of the chelator and results in liberation of free Ca^{2+} (scheme 1.5).

Scheme 1.5

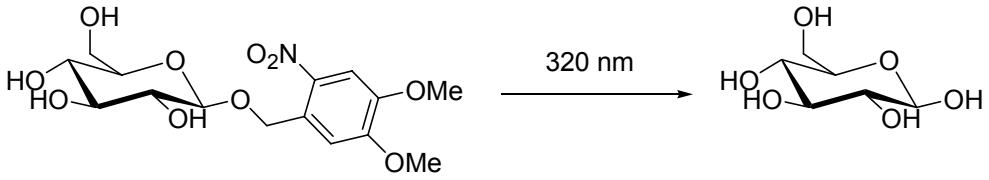


1.7 **1.8**



6-Nitroveratryl and 2-nitrobenzyl β-D-glucopyranosides **1.11** were also found to be labile towards illumination at 320 nm light.[13] These photochemical decompositions result in quantitative release of D-glucose and thus proved to be useful in carbohydrate chemistry such as oligosaccharides modifications and synthesis. In 1978 Ohtsuka et al demonstrated the applicability of the nitrobenzyl protecting group in elongation of ribooligonucleotides chains.[14]

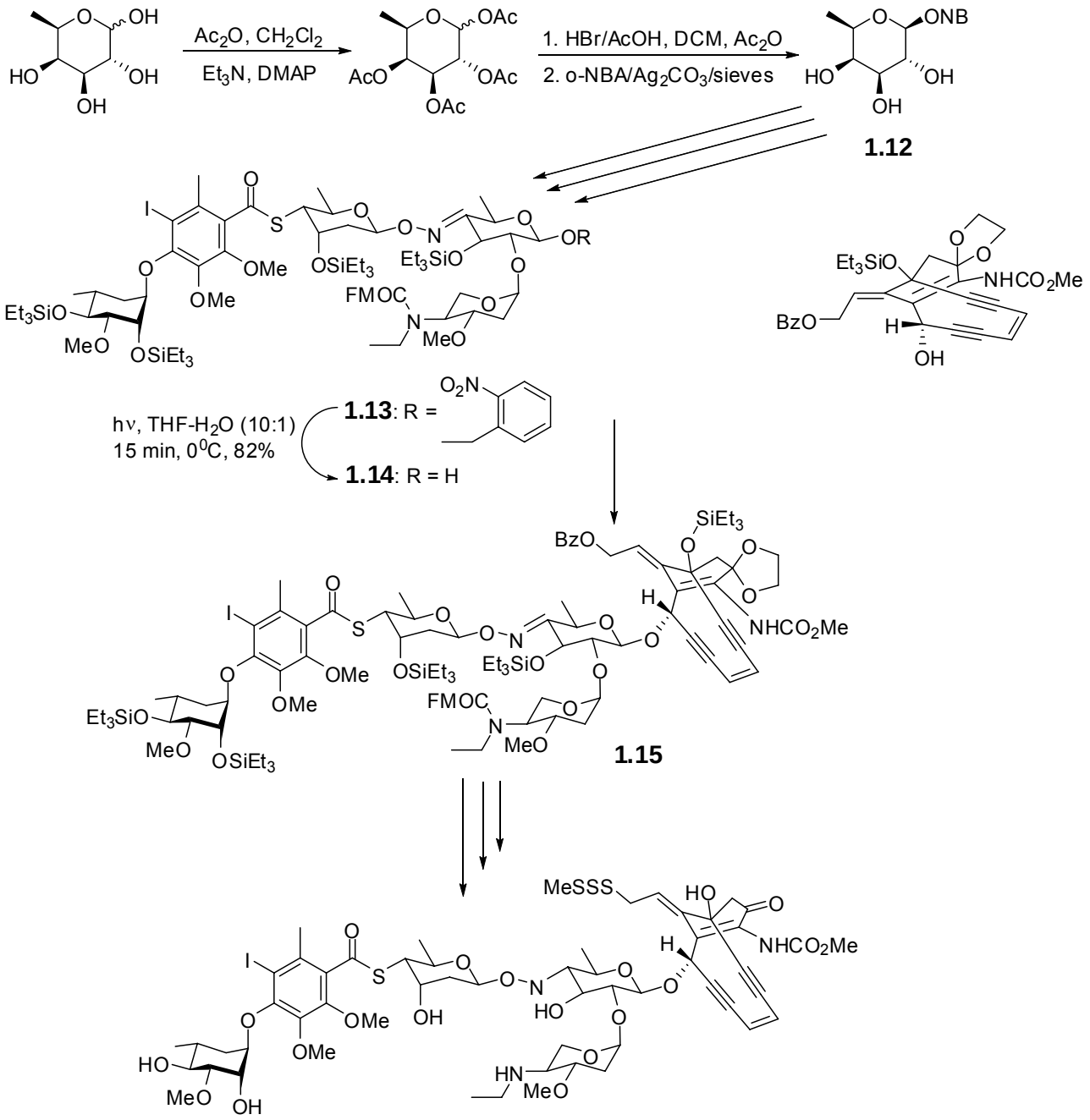
Scheme 1.6



1.11

Application of the nitrobenzyl protecting group in classical organic synthesis was published by Nicolaou.[15] *o*-Nitrobenzyl protected D-fucose **1.12** was synthesized in two steps from commercially available precursors and taken into a multistep synthesis of the antibiotic calicheamicin γ_1^I. The protecting group survived many reaction conditions crucial for classical protection groups and was successfully removed on the final stages of the sequence upon irradiation of **1.13** with a mercury lamp through a Pyrex filter in 82% yield. The resulting lactol **1.14** was then coupled with the enediyne-containing moiety of calicheamicin to obtain **1.15**.

Scheme 1.7

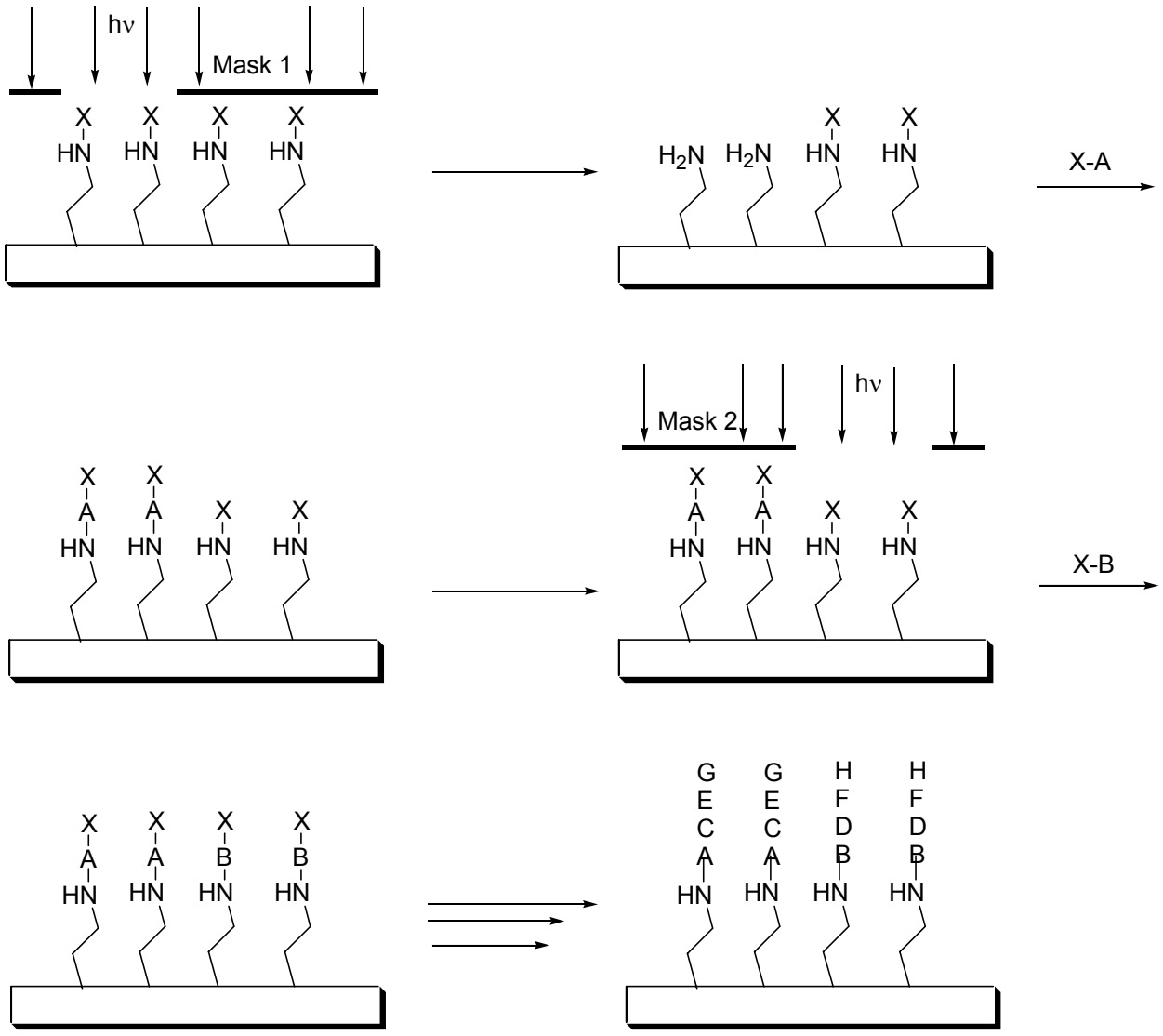


calicheamicin γ_1^I

An amazing application of photolabile protecting groups in spatially addressable parallel chemical synthesis was developed by Fodor *et al.* (scheme 1.8).[16] Polymer-supported linkers with free amino groups at the ends were protected with NVOC.

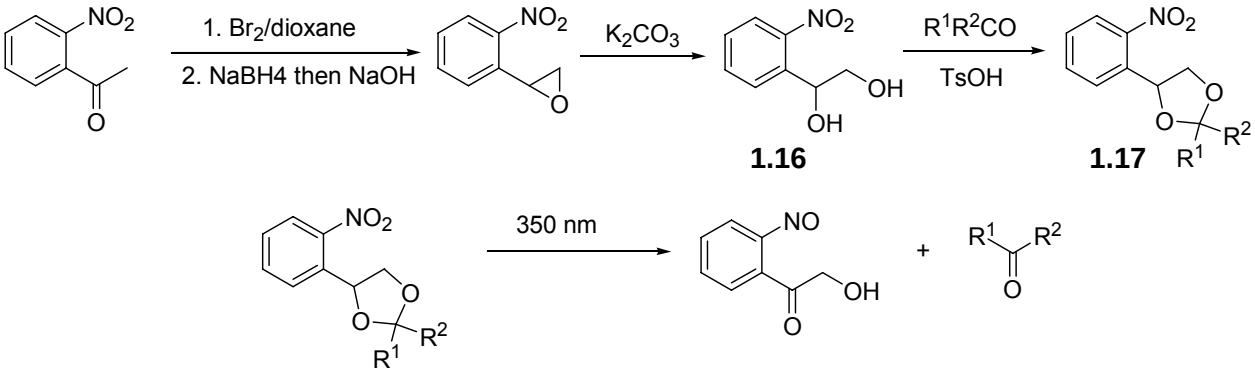
Irradiation of certain areas through a 100 μm x 100 μm checkerboard lithographic mask led to spatially-resolved photodeprotection. Liberated amino groups were coupled with building block A (for example, aminoacid). A second mask was then applied for deprotection of the remaining amino groups to which another building block B was then attached. Repetition of the photodeprotection-coupling cycles led to an array of products in square elements (the authors synthesized pentapeptides YGGFL and PGGFL).

Scheme 1.8.



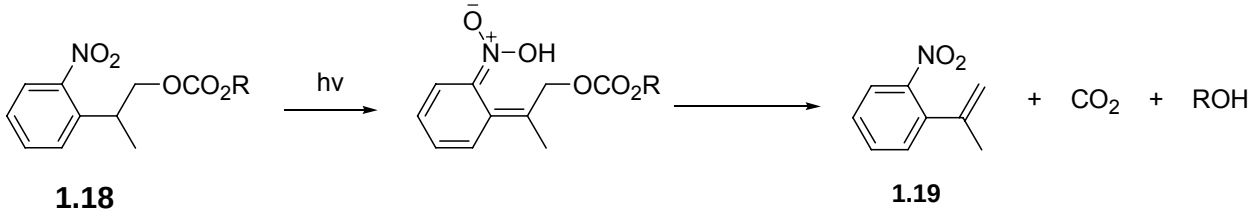
An interesting modification of the 2-nitrobenzyl group was proposed to protect aldehydes or ketones.[17] The authors utilized 2-nitrophenylethylene glycol **1.16** to form cyclic acetals and ketals of various carbonyl compounds **1.17** and illuminated them at 350 nm. The chemical yield of deprotection varied from 31% (testosterone) to 90% (benzophenone), and what is also important, the protected compounds showed relatively good resistance to basic and acidic hydrolysis.

Scheme 1.9



2-(*o*-Nitrophenyl)ethanol derivatives are another noteworthy modification of the *o*-nitrobenzyl photolabile protection group. Thymidine, protected with the 2-(*o*-nitrophenyl)-2-methylethoxycarbonyl group **1.18** was released quantitatively with 0.35 quantum yield.[18] The reaction was proposed to proceed through a formation of aci-form followed by β-elimination of the protecting group to form isopropenylnitrobenzene **1.19**.

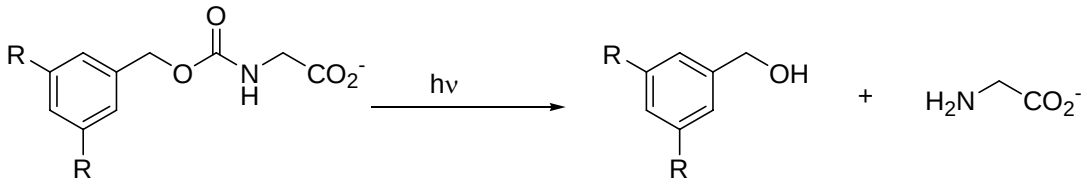
Scheme 1.10



1.3. Benzyl and benzyloxycarbonyl derivatives.

In 1962 Barltrop and Schofield[19] reported the first application of a "photosensitive protecting group" in organic chemistry. They protected the amino-group of glycine as benzyloxycarbonyl derivatives, bearing different substituents in benzene ring, and studied the photochemical decomposition of thus protected aminoacid. It was found that glycine is released upon irradiation of the parent benzyloxycarbonylglycine **1.20** at 254 nm UV-light with up to 75% yield and quantum efficiency of 0.15. Zimmerman and Sandel[20] later found that introduction of a methoxyl group in the *meta* position enhances the efficiency of the photochemical solvolyses of benzyl acetates. Chamberlin[21] first applied 3,5-dimethoxybenzyloxycarbonyl group (**1.21**)as a photosensitive protection for a series of aminoacids and dipeptides. Substrates were released upon illumination with a high-pressure mercury lamp with up to 85% yield in 1.5 hours.

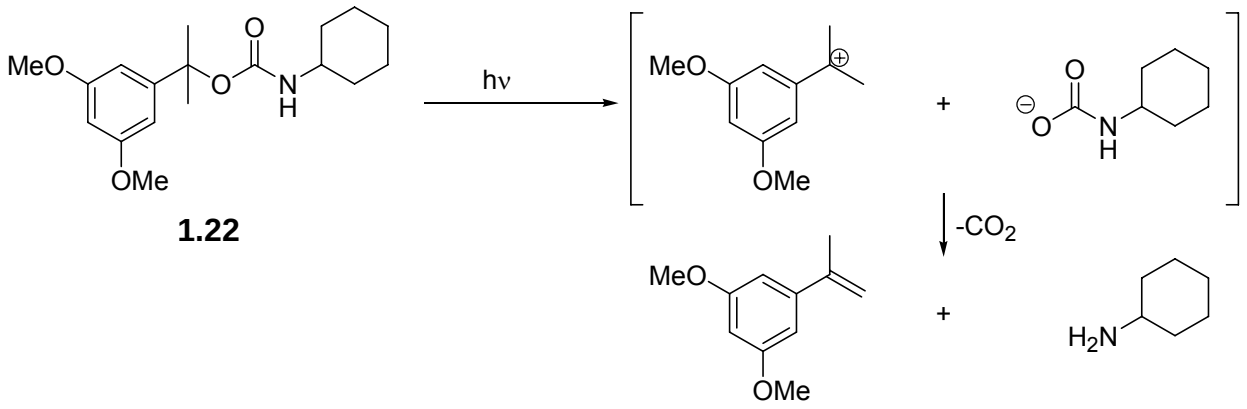
Scheme 1.11



1.20: R=R=H: Q=75%;
1.21: R=R=OMe: Q=85%

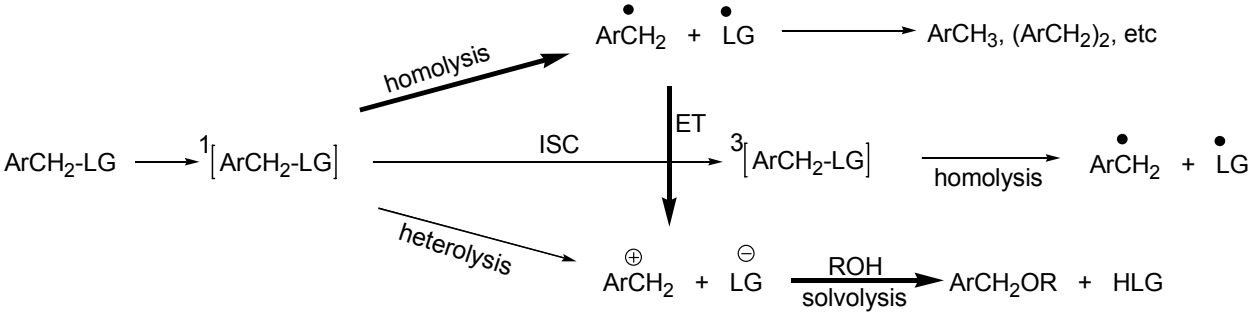
Cameron and Frechet[22] applied the (α,α-dimethyl-3,5-dimethoxybenzyloxy)carbonyl group (**1.22**, Ddz) toward photogeneration of bases. Ddz-based carbamates **1.22** were found to be thermally stable and were photocleaved cleanly in both solution and solid state by irradiation with 450-W medium pressure mercury lamp.

Scheme 1.12



The most detailed mechanistical study of the photochemistry of arylmethyl esters in nucleophilic solvents such as methanol was carried out by Pincock.[23] He showed that among different pathways, homolytic cleavage from the excited singlet state $^1[ArCH_2\text{-}LG]$ to form a radical pair prevails. Electron transfer between two radicals results in formation of an ion pair $[ArCH_2^+ + LG^-]$, which is then trapped by the solvent to give the formal hydrolysis products.

Scheme 1.13



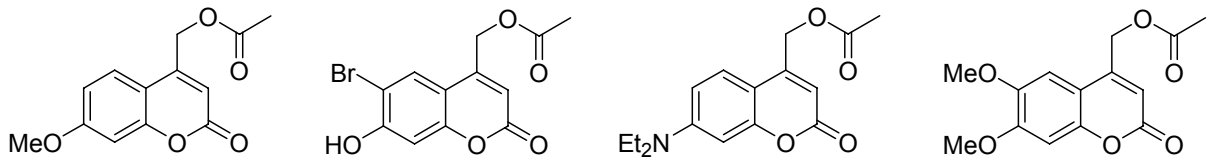
ISC - intersystem crossing; ET - electron transfer

Givens and Matuszewski first discovered the photochemistry of coumarinylmethyl diethyl phosphate, which was used to covalently tag various substrates, including enzymes, with the highly fluorescent coumaryl moiety.[24a] This photochemical reaction, however, had not been applied in chemistry of photoremovable protecting groups until

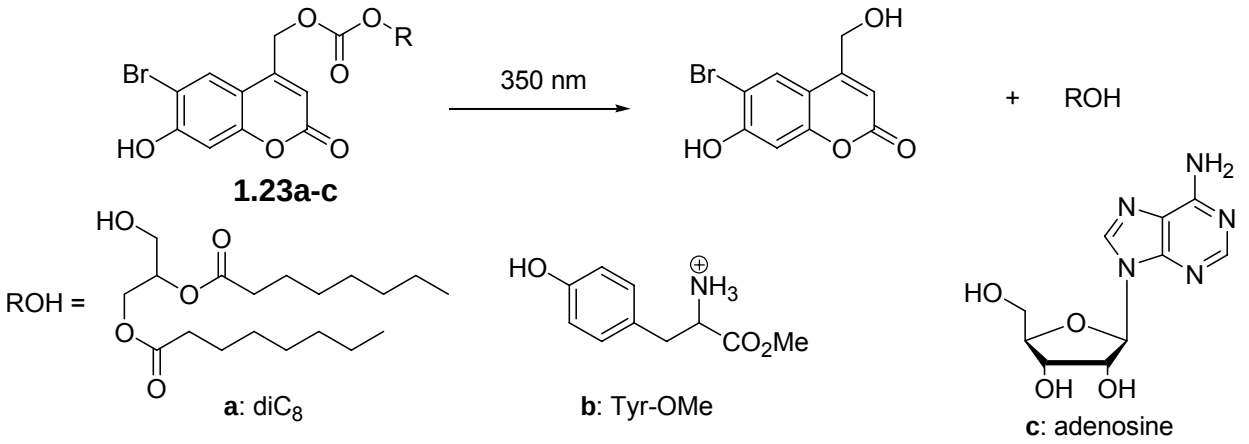
Furuta and co-workers reported the release of adenosine 3',5'-cyclic monophosphate (cAMP) from the corresponding ester on 340 nm irradiation.[24b] The high extinction coefficient, stability in the dark and modest quantum yield (0.07-0.12 depending on solvent) made this protective group attractive for use in biological applications.

Further investigation showed that *N*-(6-bromo-7-hydroxycoumarin-4-yl)methoxycarbonyl-L-glutamic acid (Bhc-glu) has a very suitable cross-section for two-photon excitation in the IR region.[25] Thus, glutamate can be uncaged *in vivo* upon two-photon photolysis with IR pulses. This allowed the first three-dimensional mapping of the glutamate sensitivity of neurons in intact slices. The same group studied quantum efficiencies of the photolyses for a series of coumarin-4-ylmethoxycarbonyl galactose derivatives: 7-methoxycoumarin-4-ylmethyl (MCMoc), 6-bromo-7-hydroxycoumarin-4-ylmethyl (Bhcmoc), 7-diethylaminocoumarin-4-ylmethyl (DEACMoc), and 6,7-dimethoxy coumarin-4-ylmethyl (DMCMoc).[26] Among them, Bhcmoc has the highest $\Phi\varepsilon$ (quantum efficiency x extinction coefficient) value, which is a practically important characteristic for application in caging chemistry. This group was used for protection of different classes of hydroxyl-containing compounds: diC_8, a nonpolar aliphatic alcohol, tyrosine, a phenolic derivative and polar adenosine. The substrates were released quantitatively upon irradiation of the corresponding carbonates **1.23** with moderate quantum yields (0.012-0.022).

Scheme 1.14

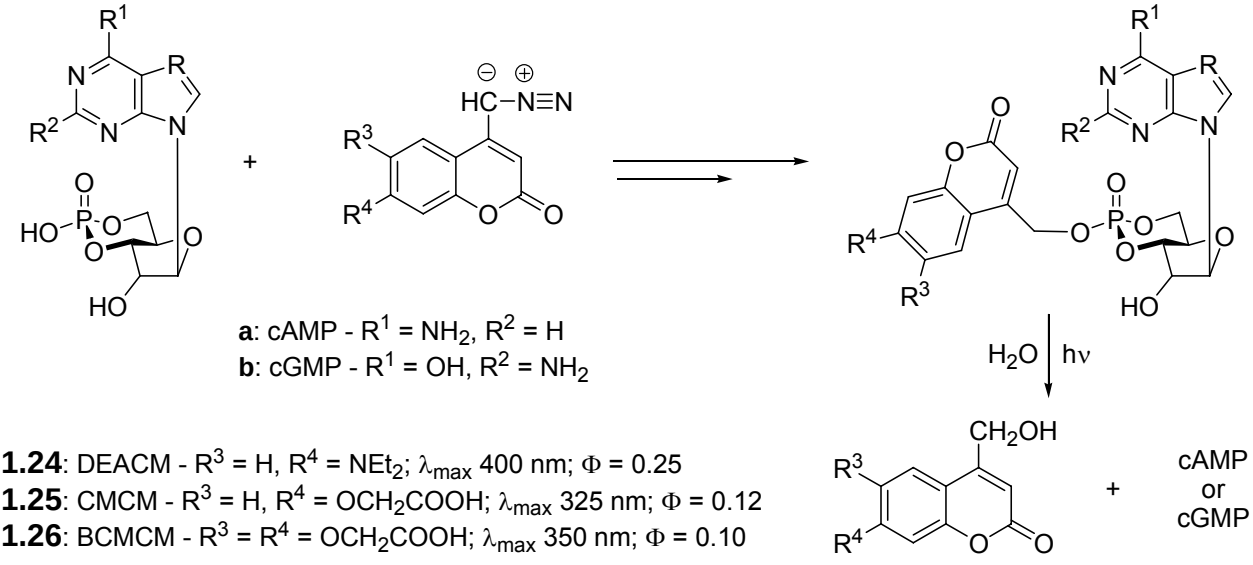


	MCMoc	Bhcmoc	DEACMoc	DMCMoc
$\Phi\varepsilon_{350}$	84	173	37	68



Hagen and co-workers reported application of DEACM, 7-carboxymethoxycoumarin-4-ylmethyl (CMCM), and 6,7-bis(carboxymethoxy)coumarin-4-ylmethyl (BCMCM) groups for caging of the second messengers adenosine 3',5'-cyclic monophosphate (cAMP) and guanosine 3',5'-cyclic monophosphate (cGMP).[27] Uncaging of the phosphates is quantitative when compounds **1.24**-**1.26** are irradiated at the appropriate wavelengths. The advantage of the carboxymethoxy substituted coumarinylmethyl esters **1.25** and **1.26** is their high solubility in aqueous media, whereas caged **1.24** releases cyclic nucleotides under irradiation with tissue-friendly 400 nm light.

Scheme 1.15

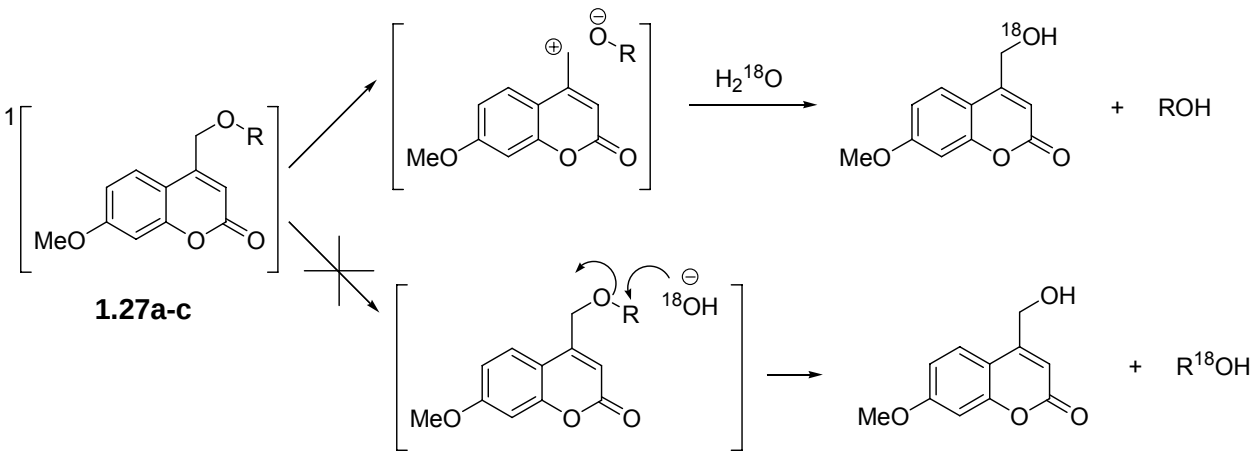


1.24: DEACM - R^3 = H, R^4 = NEt_2; λ_{max} 400 nm; Φ = 0.25
1.25: CMCM - R^3 = H, R^4 = OCH_2COOH; λ_{max} 325 nm; Φ = 0.12
1.26: BCMCM - R^3 = R^4 = OCH_2COOH; λ_{max} 350 nm; Φ = 0.10

The same group later studied the release of cytidine 5'-diphosphate (CDP) from the caged DEACM-CDP upon irradiation at wavelengths between 365 and 436 nm.[28] The rate constant of the formation of cytidine 5'-diphosphate was found to be 2×10^{8} s^{-1} and the quantum efficiency for the disappearance of caged CDP is 0.029. Later on, release of adenosine triphosphate (ATP), diphosphate (ADP) and monophosphate (AMP) from the corresponding 7-dimethylaminocoumarin-4-ylmethyl esters (DMACM) was reported.[29] By using time-resolved fluorescence spectroscopy, a lower limit of 1.6×10^{9} s^{-1} for the rate constant of the release of ATP was determined. The quantum yields of the disappearance of caged ATP, ADP and AMP when irradiated at 330 – 440 nm in aqueous buffer solutions were found to be 0.086, 0.063 and 0.072, respectively.

Studies of the photocleavage of 7-methoxycoumarin-4-ylmethyl esters **1.27a-c** (carboxylate, mesylate and phosphate) allowed determination of the mechanistical pathway.[30] Two possible mechanisms of the photolysis were proposed: solvent assisted photoheterolysis and photosolvolysis. To elucidate the reaction pathway, solutions of **1.27a-c** were irradiated in ^{18}O labeled water. It was shown that the labeled atom was incorporated exclusively in the molecule of 4-hydroxymethyl-7-methoxycoumarin and therefore photocleavage of the excited state of the MCM-caged compounds proceeds via a photo S_N1 mechanism. This mechanism was further confirmed by the dependence of quantum yields (Φ) of photodecomposition on the leaving ability of the leaving group, Φ(mesylate) > Φ(phosphate) > Φ(carboxylate).

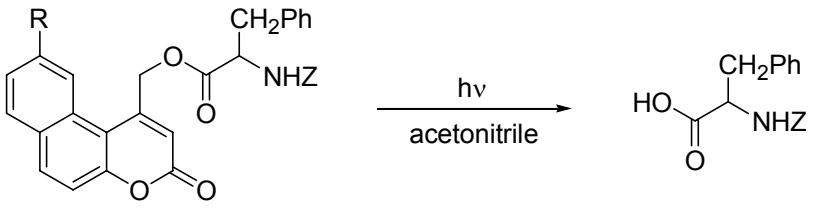
Scheme 1.16



a: R = $C_6H_{13}CO$; **b**: R = CH_3SO_2; **c**: R = $P(OEt)_2O$

Recently oxobenzo[f]benzopyrans **1.28a-c** have been reported as new fluorescent photolabile protecting groups for the *C*-terminus of aminoacids.[31] An additional fused benzene ring slightly red-shifts the wavelength of maximum absorption compared to 7-methoxycoumarin-4-ylmethoxycarbonyl group (360 vs. 343 nm). The studies of the photocleavage of phenylalanine protected with oxobenzo[f]benzopyrans showed that the most suitable wavelength is 350 nm, however 419 nm light also liberates free aminoacid. The results also showed an influence of the substituent at position 9 as the hydroxyl-derivative **1.28b** required more than five times shorter irradiation time for deprotection compared to the unsubstituted compound **1.28a**.

Scheme 1.17

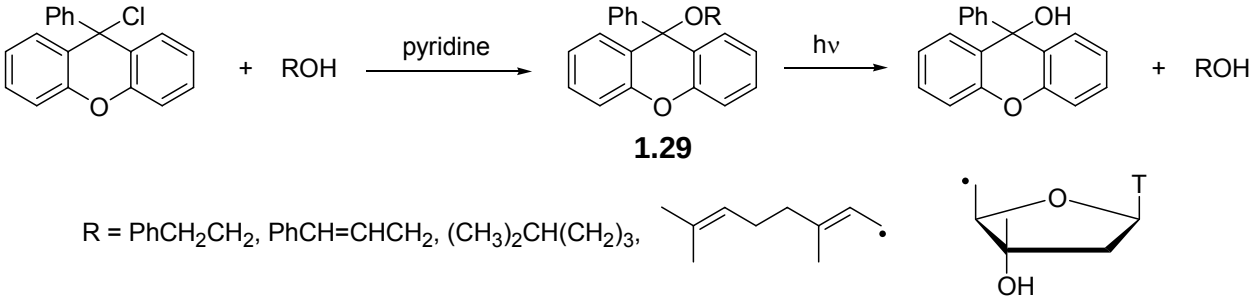


1.28a-c

Compound:	**a**: R = H	**b**: R = OH	**c**: R = OMe
Irradiation time:	22	4	8
Release, %	80	90	81

Most of the photoremovable protecting groups based on the stability of the benzylic cation were discovered in the last decade. The 9-phenylxanthyl (pixyl, Px) has been reported to be a promising photoremovable protecting group for primary alcohols.[32] Pixyl carbocation is extremely stabilized by its highly rigid and planar backbone, thus making this group suitable for protection of alcohols as pixyl ethers **1.29**, without utilization of mixed carbonates. This approach has great advantage because the substrate is released directly from the excited state of the photocage, avoiding the dark decarboxylation of monocarbonate.

Scheme 1.18

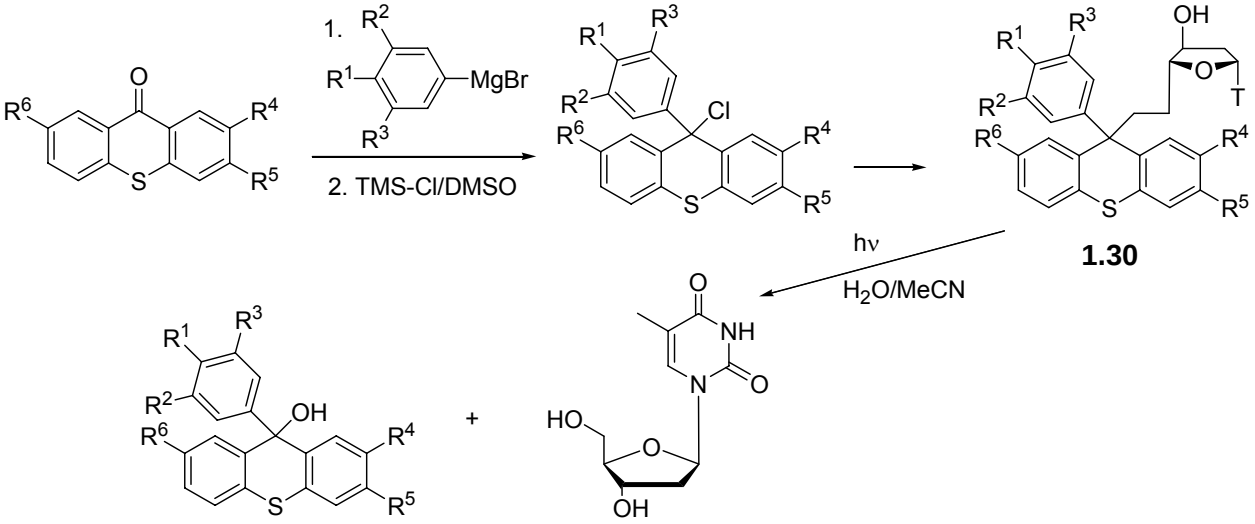


Chemical yield of protection varied in 65-74% range, whereas irradiation of the caged substrates at 254 or 300 nm results in release of the alcohol in 78-97% yield. Based on deprotection of the nucleoside thymidine, authors suggested that pixyl could be an effective protecting group for the combinatorial synthesis of oligoribonucleotides.

Even better results were obtained by the same research group with the 9-phenylthioxanthyl group (**1.30**, S-pixyl, S-Px).[33] Due to a significant bathochromic shift of this chromophore relative to the pixyl group, alcohols including four nucleosides were efficiently deprotected upon irradiation of the caged substrates at 300 nm. It was also shown that *iso*-butyryl and benzoyl protective groups for amino group of a nucleic acid are not affected by the photolysis. The chemical yield of deprotection varied from 75%

for cytidine to 97% for thymidine. Further combinatorial study of several substituted S-pixyl derivatives[34] in the photochemical release of thymidine showed that electron-donating substituents in the position para to the 9-carbon enhance the efficiency of the photolysis. Moreover, some of these compounds proved to be suitable for deprotection under irradiation at 350 nm.

Scheme 1.19

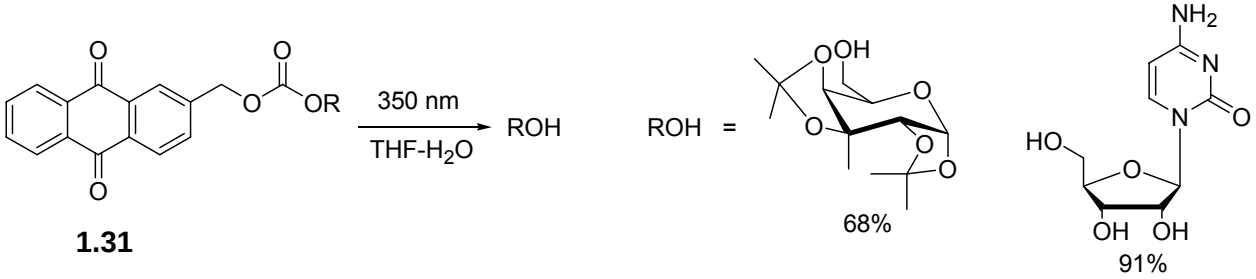


The best results were achieved for 5'-*O*-(3-methoxy-9-phenylthioxanthyl)-2'-deoxythymidine (**1.30**, $R^1 = R^2 = R^3 = R^4 = R^6 = H$; $R^5 = OMe$), which quantitatively releases thymidine with photolytic half-lives ($t_{1/2}$, time for 50% recovery of thymidine) of 3.6 min under 300 nm and 7.3 min under 350 nm irradiation.

A series of polycyclic arylmethanol derivatives has been studied in terms of potential application as photolabile protecting groups by Furuta and co-workers.[35] Carbonates of galactose were chosen for a model studies and anthraquinon-2-ylmethoxycarbonyl **1.31** (Aqmoc) galactose provided highest overall photolysis efficiency $\Phi\varepsilon$ of 150 and rate constant of 4.6×10^6 s^{-1}. However, a serious drawback of the Aqmoc group is the poor yield of the desired 1,2,3,4-di-*O*-isopropylidene-D-galactopyranose (68%) upon the

photolysis of the starting material. Another limitation of this group arises from the low quantum efficiency of uncaging in the absence of THF. 5'-Aqmoc-adenosine (**1.31**, ROH = adenosine) was synthesized in order to test this group for nucleoside protection. Upon photolysis, free adenosine was obtained in 91% yield.

Scheme 1.20

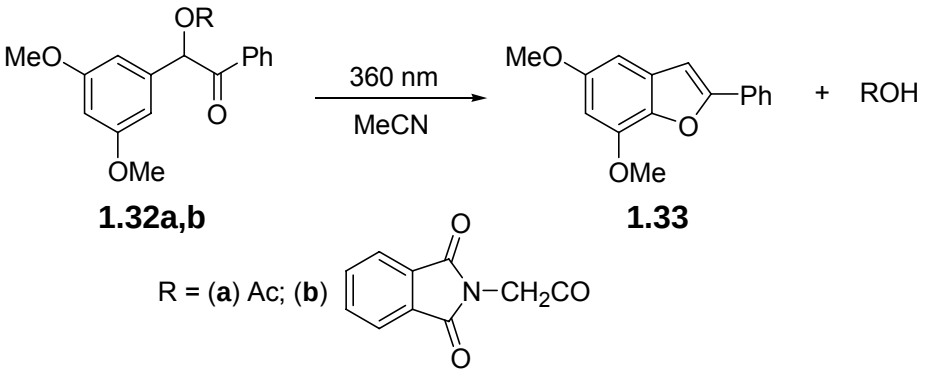


1.31

1.4. Benzoin (desyl) derivatives.

In 1964 Sheehan and Wilson reported photolytic cyclization of benzoin acetate, tosylate and desyl chloride to 2-phenylbenzofuran.[36] The yield of the cyclization varied from 5 to 54% depending on the solvent, substitution pattern and the leaving group. This reaction was assumed to proceed from $n \rightarrow \pi^*$ excitation of the benzoyl carbonyl. The same group later applied methoxy-substituted benzoin esters as a photosensitive protecting group for carboxylic acids.[37] The Influence of the position of the methoxy-group on the yield of benzofuran was studied. It was found that 3',5'-dimethoxybenzoin phthaloyl glycinate **1.32b** yielded 87% of the phthaloylglycine and over 99% of 2-phenyl-5,7-dimethoxybenzofuran **1.33** with quite high quantum efficiency of 0.644 upon irradiation at 360 nm UV light (scheme 1.21).

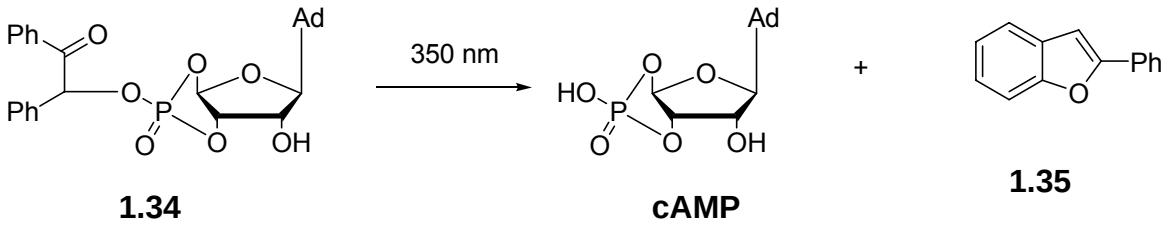
Scheme 1.21



Corrie and Trentham developed the synthesis of the phosphate esters of various methoxy substituted benzoins.[38] These derivatives were examined to study rapid biochemical processes by fast photochemical cleavage. 3'5'-Dimethoxybenzoin phosphate provided the best results, converting into products in 10% with a rate constant of 10^5 s^{-1} by single pulse of 347 nm light.

Givens and co-workers first applied this group as a photoprotecting group for nucleotides.[39] Photolysis of desyl adenosine cyclic 3',5'-monophosphate **1.34** at 350 nm in water/THF mixture produced free adenosine cyclic 3',5'-monophosphate (cAMP) with yield near to quantitative and 2-phenylbenzofuran **1.35**. Quantum efficiency of this process was found to be 0.33 and a rate constant 7.1×10^8 s^{-1} which is 3-6 orders of magnitude faster than C-O cleavage in *o*-nitrobenzyl derivatives.

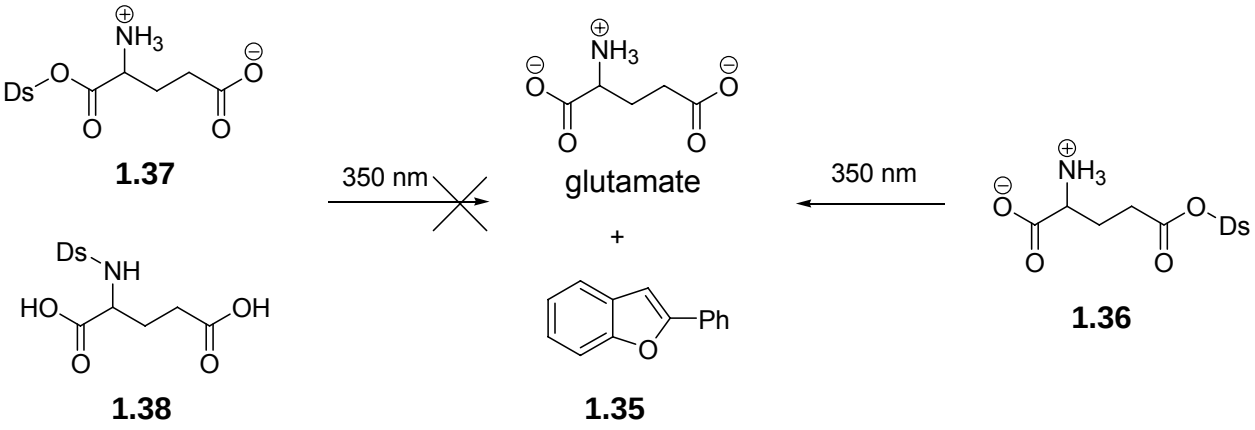
Scheme 1.22



Later, the same group extended their study to protection of amino acids.[40] Thus, development of phototriggers for biologically active neurotransmitters was attempted.

Photocleavage of γ-*O*-desyl glutamate **1.36** and *O*-desyl GABA in water-acetonitrile solutions results in clean release of free glutamate and GABA, respectively, with concomitant formation of 2-phenylbenzofuran **1.35** as the only photo by-product. However, α-O-desyl glutamate **1.37** and N-desyl glutamate **1.38** failed to liberate glutamate upon irradiation, giving benzil as the major detected by-product. The lack of generality of the desyl phototrigger for amino acids discouraged the authors from developing its application in this area any further.

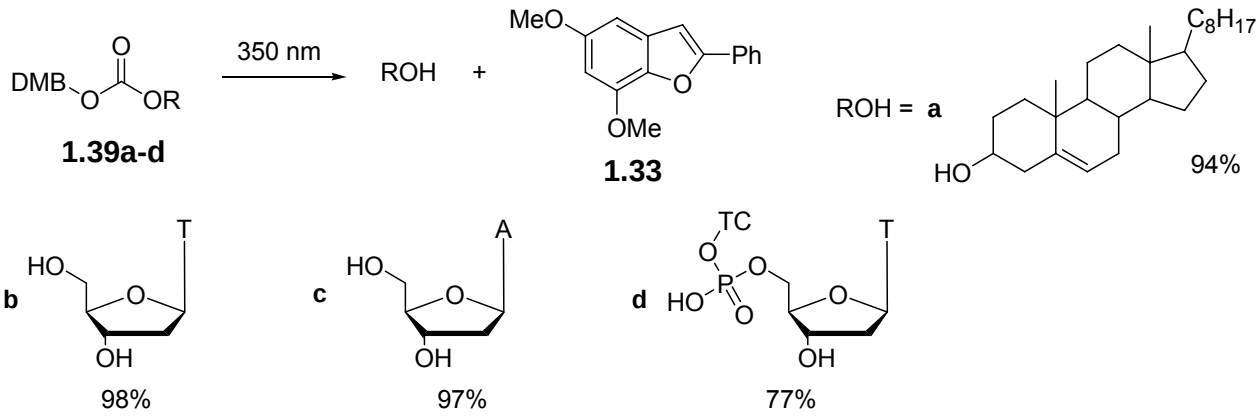
Scheme 1.23



In 1995 Pirrung and Bradley utilized dimethoxybenzoin carbonates as photolabile alcohol protecting groups.[41] A Synthetic procedure for mixed DMB carbonates was developed and alcohols were successfully liberated upon irradiation of these carbonates with 350 nm lamps. Comparison of the photocleavage rates of DMB acetate and DMB carbonate allowed for estimation of the quantum efficiency (0.64). Finally, the DMB carbonate protecting group was proven to be useful for the photochemical synthesis of DNA on solid support in control synthesis of two simple trinucleotides: 5'-CTT and 5'-ATT-3'. It was established that photochemical deprotection does not affect DNA.

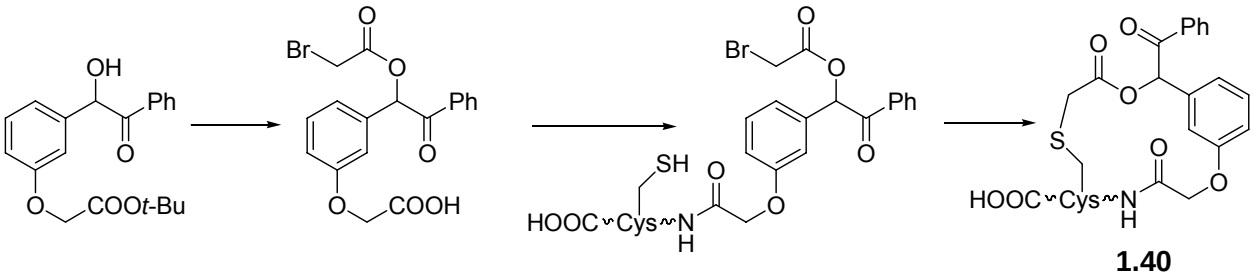
Application of 3',5'-dimethoxybenzoinyloxycarbonyl protected deoxynucleosides **1.39b-d** in photochemically induced DNA array synthesis was developed by the same research group.[42]

Scheme 1.24

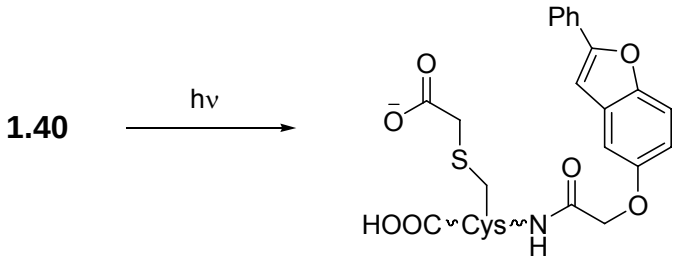


An interesting method for phototriggered protein folding based on the photochemistry of the benzoin group was developed by Chan and co-workers.[43] The cyclized peptide cVHP-34 M12C-CMB **1.40** was prepared through a sequence of standard solid support protocols. This cyclic peptide was photocleaved upon irradiation, converting to the linear form **1.41**. Formation of the benzofuran moiety was detected and changes in CD spectra of the peptide showed the expected formation of α-helical secondary structure. Thus, an irreversible rapid phototriggering method to study protein folding in a nondenaturating environment was successfully developed.

Scheme 1.25



1.40

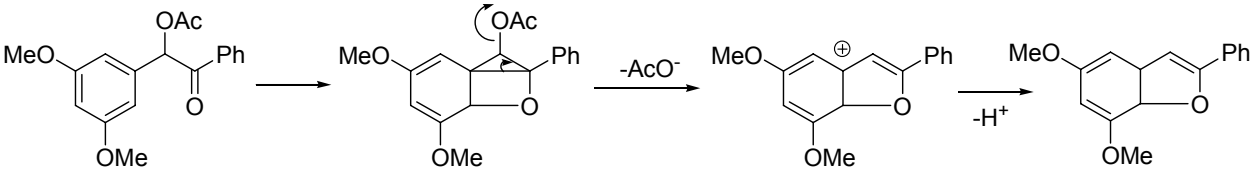


1.41

A report of Cameron and Frechet describes the application of benzoin photochemistry in photogeneration of organic bases – primary and secondary amines.[44] The strategy was based, as in previous publications in this series,[10,22] on caging amines as photocleavable carbamates. Among various substituted derivatives, cyclohexyl carbamates derived from 3',5'-dimethoxybenzoin were especially attractive in terms of their photoefficiency, providing free cyclohexylamine and the corresponding benzofuran in yields close to quantitative. Another striking feature of 3',5'-dimethoxybenzoinyl carbamates as photoremovable protecting groups is that they are photobleachable, i.e. the photochemical products have negligible extinction coefficients at the wavelengths of irradiation, and therefore are suitable to thick film applications. Solid state quantum yield of the cyclohexylamine, photogenerated from the 3,3',5,5'-tetramethoxybenzoinyl carbamate, was calculated to be in the 0.03-0.08 range.

The mechanism of 3',5'-dimethoxybenzoin photochemistry was first proposed by Sheehan *et al*.[37] Formation of a strained bicyclic intermediate **1.42** (oxetane) from n-π^* excited carbonyl was considered to be a key step in this transformation. The methoxy groups then facilitate the loss of the leaving group to form dimethoxycyclohexadienyl cation **1.43** followed by deprotonation to the substituted benzofuran **1.33**.

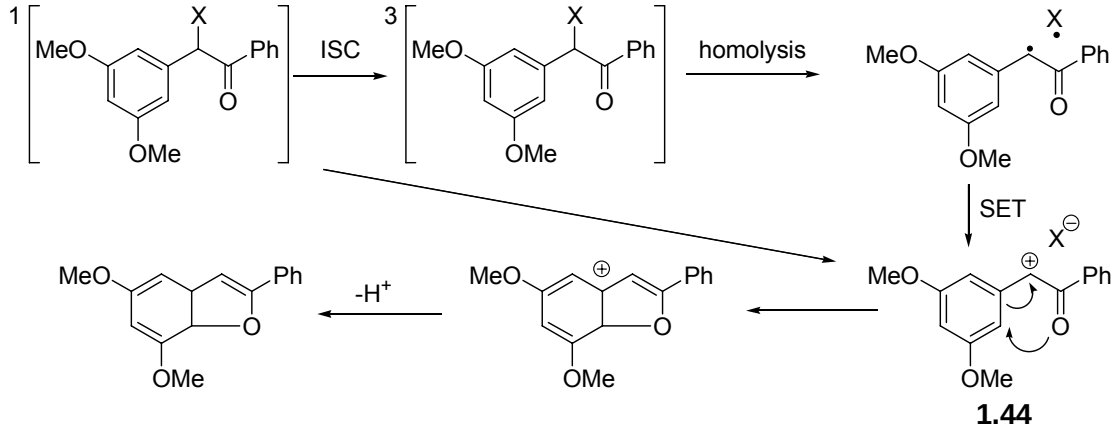
Scheme 1.26



1.42 **1.43** **1.33**

This mechanism was later revised and two alternative pathways, assuming formation of α-keto cation **1.44** by either direct heterolysis of the C-O bond,[45] or *via* homolysis followed by single-electron transfer, have been proposed.

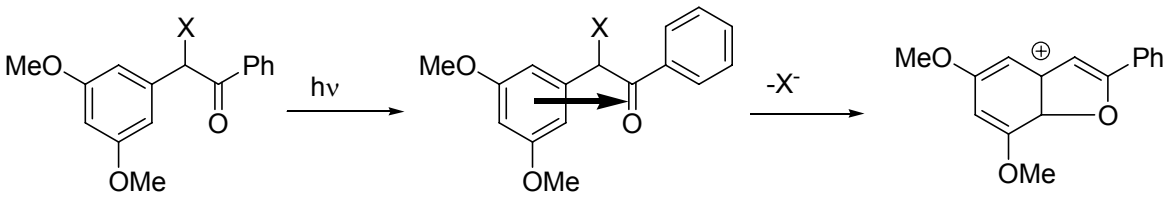
Scheme 1.27



1.44

Most recently, evidence was found supporting a new mechanism,[46] charge-transfer interaction of the electron-rich dimethoxybenzene ring with the electron-deficient oxygen of the n-π* excited carbonyl to form an "intramolecular exciplex" **1.45**. The exciplex can return to the ground state or undergo rearrangement to dimethoxycyclohexadienyl cation, promoted by methoxy substituents. This mechanism explains a) highest yields of benzofuran in case of 3',5'-dimethoxy substituted benzoin; b) absence of solvent-substitution or radical-derived products in such a substitution pattern c) independence of chemical yields of benzofuran on the presence of oxygen (no triplet involved).

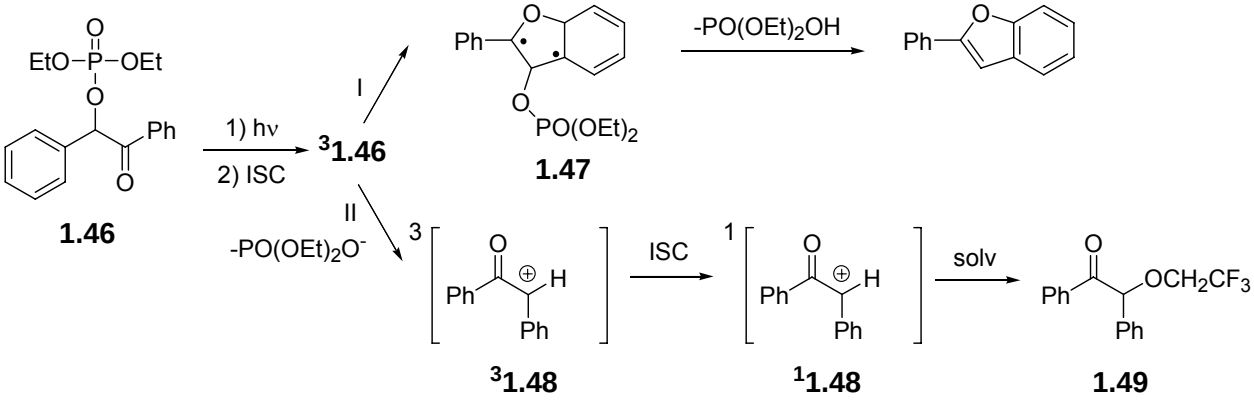
Scheme 1.28



1.45

A different mechanism of photochemical cleavage was proposed for the derivatives of unsubstituted benzoin based on the study of photodissociation of phosphate **1.46** by laser flash photolysis.[47] Two competing, strongly solvent dependent reaction pathways were identified, both of which involve participation of the triplet state ^{3}**1.46**. Reaction path I prevails in most solvents, except water and fluorinated alcohols. The assumed rate-determining step in this mechanism is cyclization of the triplet to the biradical **1.47**, which then rapidly eliminates diethyl phosphoric acid. In trifluoroethanol the yield of 2-phenylbenzofuran drastically drops to 25%, and trifluoroethyl benzoin ether **1.49** is formed as a major product. A new transient intermediate was observed by LFP study, which was assigned to the triplet α-keto cation **1.48**. The decay of the latter is governed by triplet-singlet intersystem crossing, which precedes nucleophilic addition of the solvent.

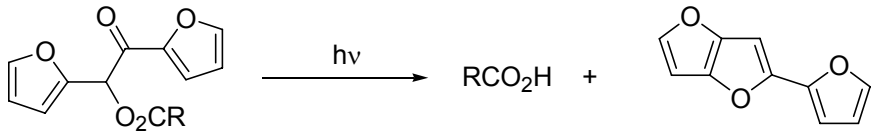
Scheme 1.29



1.46 ^{3}**1.46** **1.47** ^{3}**1.48** ^{1}**1.48** **1.49**

Peach et al. conducted a comparative study of benzoin and furoin esters as photocages for biologically active peptides.[48] Furoin esters **1.50**, despite exhibiting the same photochemistry as benzoin ones, were far less appropriate for this purpose due to low efficiency of photodecomposition.

Scheme 1.30

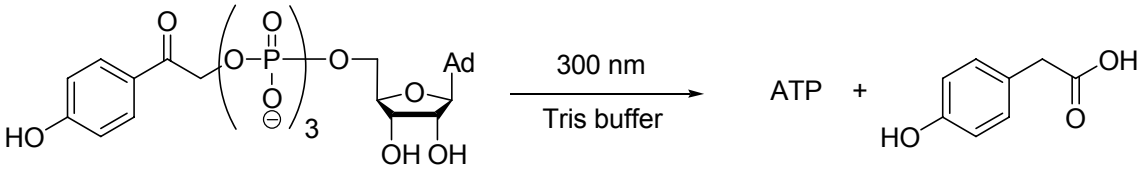


1.50

1.5. *p*-Hydroxy and other phenacyl derivatives.

In 1996 Givens and Park reported an application of the known photoinduced rearrangement of *para*-hydroxyphenacyl derivatives to *p*-hydroxyphenylacetic acid **1.52**[49] in the design of a new phototrigger for rapid ATP release.[50] The photochemical reaction responsible for deprotection of ATP is reproduced in scheme 1.31.

Scheme 1.31



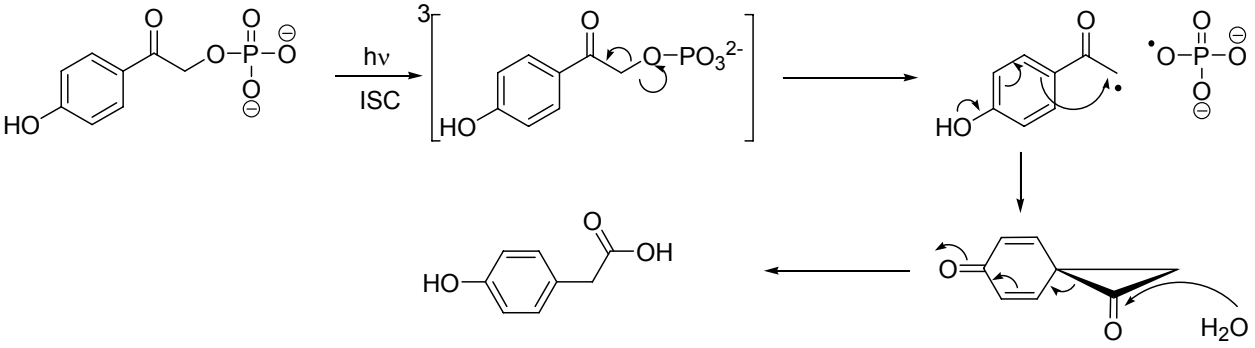
1.51 **1.52**

The *p*-hydroxyphenacyl ATP **1.51** was shown to be synthetically accessible from commercially available p-hydroxyacetophenone in 20% yield and substantially stable in water and buffered media. Other advantages of this photocage include a) excellent aqueous solubility; b) absence of chiral centers; c) high quantum efficiency of ATP photorelease of 0.37; d) hypsochromic shift in the UV spectra of the *p*-

hydroxyphenylacetic acid **1.52** compared to the irradiated material, which allows a greater degree of photoconversion. Comparative study of other variously substituted (*p*- and *m*-methoxy, *p*-amino, *p*-acetamino) phenacyl phosphates proved them far less applicable for release of the substrate.

The mechanism of the photodecomposition, involving triplet excited state, caged radical pair and spiro-intermediate **1.53** was proposed in the later published comprehensive study,[51] and the rate constant was calculated to be 6.0×10^{8} s^{-1}.

Scheme 1.32

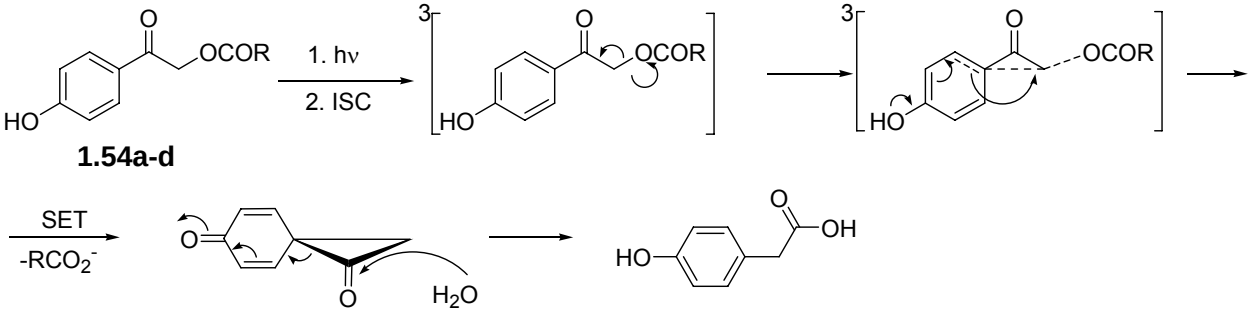


1.52 **1.53**

Further elaboration of *p*-hydroxyphenacyl for phototriggering of excitatory amino acids, often utilized in neurotransmission studies, was carried out by the same research group.[52] They showed that photolysis of *O*-*p*-hydroxyphenacyl γ-aminobutyric acid (GABA)(**1.54a**), γ-*O*-*p*-hydroxyphenacyl L-glutamate (**1.54b**) and *O*-*p*-hydroxyphenacyl ala-ala (**1.54c**) results in the quantitative release of the protected substrate and formation of p-hydroxyphenylacetic acid. The decomposition was again assumed to proceed via phenacyl triplet with quantum efficiencies of 0.35, 0.12 and 0.27 for liberation of GABA, L-glutamate and dipeptide ala-ala, respectively. Stern-Volmer quenching of the release with sodium 2-naphthalenesulfonate allowed calculation of the rate constants of ~10^{7} s^{-1}.

Finally, to demonstrate the efficacy and versatility of *p*-hydroxyphenacyl as a photoremovable group for oligopeptides on a more challenging target, the nonapeptide bradykinin was successfully protected with the pHP group.[53] The release of the peptide upon irradiation of pHP bradykinin (**1.54d**) at 300 nm UV light in water was observed with the rate constant greater than 10^8 s^{-1} and quantum yield of 0.2–0.3. It was shown that a single 337 nm flash released sufficient bradykinin to rapidly increase intracellular calcium concentration. These results proved pHP protected oligopeptides to be useful and powerful tools for high-temporal and spatial control over activation of biological receptors.

Scheme 1.33



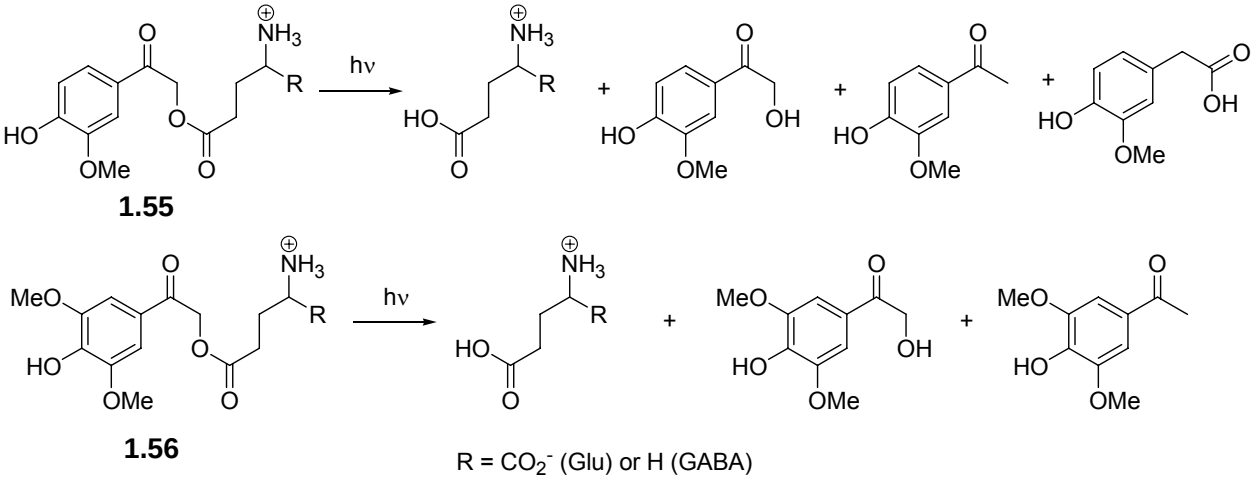
1.54a-d

a: R = $CH_2CH_2CH_2NH_3^+$ (GABA); **b**: R = $CH_2CH_2CH(NH_3^+)CO_2^-$ (L-glutamate); **c**: R = $CH(CH_3)NHCOCH(NH_3^+)CH_3$ (ala-ala); **d**: R = NH_2-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg (bradykinin)

Introduction of 3-methoxy and 3,5-dimethoxy substituents in the *p*-hydroxyphenacyl aromatic ring was explored in order to extend the absorption range of pHP chromophore.[54] The absorption maxima for the modified chromophores shifted from ~320 nm to 350 nm for 3-methoxy-4-hydroxyphenacyl and 370 nm for 3,5-dimethoxy-4-hydroxyphenacyl groups, beyond the absorption range of amino acids and nucleotides. Irradiation of the caged L-glutamate and γ-amino butyrate (GABA) releases amino acids with the rate constant of ~$10^7 s^{-1}$ and poorer quantum efficiencies (0.03–0.04) compared to unsubstituted *p*-hydroxyphenacyl derivatives. Moreover, rearrangement of the pHP

moiety to the phenylacetic acid has become a minor pathway for X and is not observed at all for Y. Overall, despite some drawbacks, 3-methoxy-4-hydroxyphenacyl **1.55** and 3,5-dimethoxy-4-hydroxyphenacyl **1.56** esters are potentially useful as phototriggers of amino acids and peptides upon irradiation at wavelengths longer than 350 nm.

Scheme 1.34

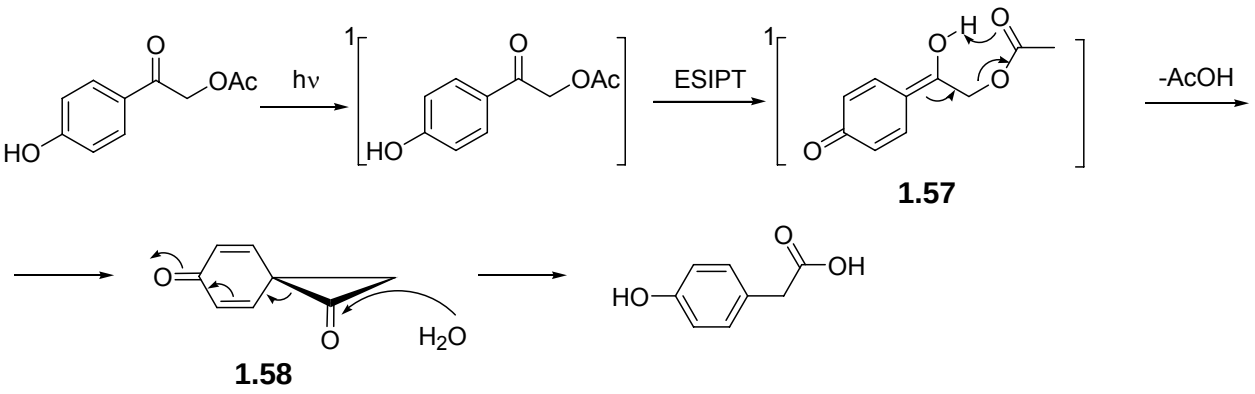


1.55

1.56

Zhang and co-workers challenged the mechanism of photolytic rearrangement of *p*-hydroxyphenacyl esters into *p*-hydroxyphenylacetic acid, proposed earlier by Givens. The results of their studies[55] with triplet quenchers and laser flash photolysis supported a novel mechanism, including solvent-mediated formal intramolecular proton transfer from the phenolic to the carbonyl oxygen in the singlet excited state to generate the corresponding *p*-quinone methide **1.57**. The latter rearranges to a spiroketone intermediate **1.58**, expelling carboxylic acid in a concerted fashion, and *p*-hydroxyphenylacetic acid is formed upon addition of water to the spiroketone.

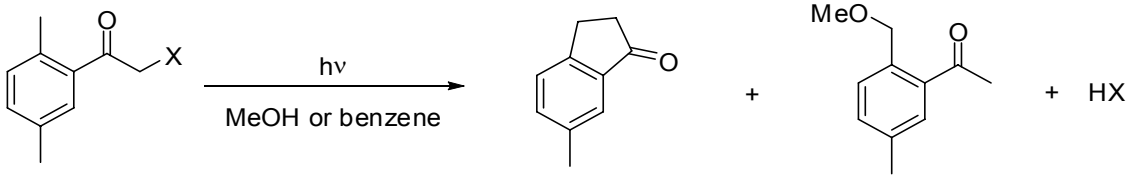
Scheme 1.35



Considering the reported further evidence for a very short-lived (0.4 ns) triplet state participation and adiabatic tautomerization of *p*-hydroxyacetophenone in the triplet state, based on DFT calculations,[56] the mechanism of the photodecomposition of *p*-hydroxyphenacyl derivatives is still not clear.

Recently Klán and co-workers developed 2,5-dimethylphenacyl (DMP) derivatives **1.59** as a new photoremovable protecting groups for carboxylic acids,[57,58] phosphates and sulfonic acids[59] and alcohols and phenols.[60]

Scheme 1.36



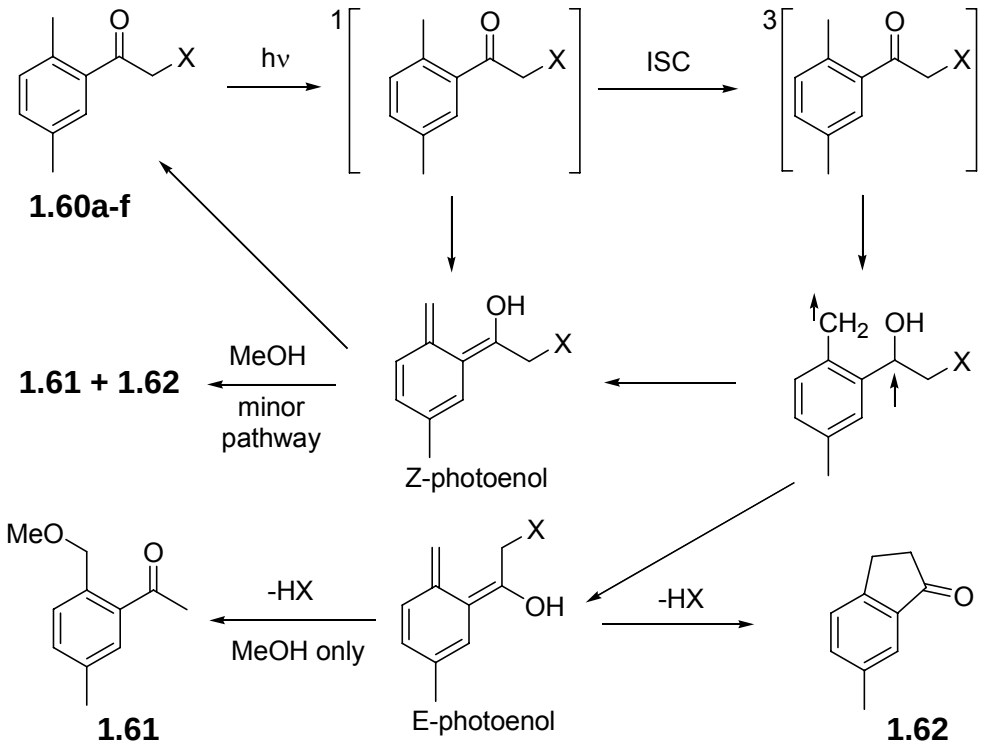
1.59

X = RCOO; RSO_3; $P(OR)_2O$; ROCOO

Efficient enolization (Φ ~ 1) was demonstrated to be the primary step in the photoreaction of the DMP moiety. Investigation of dimethylphenacyl chloride (**1.60a**) photochemistry[61,62] led to the conclusion that reaction in methanol proceeds via the major photoenol (Z)-xylylene (τ = 22 μs), which is predominantly formed from the singlet excited state. On the other hand, upon photolysis in non-polar benzene, both

photoenols are formed and HCl is only released from (E)-xylylene (τ = 10 ms). Release of a poorer leaving group, carboxylate, from the corresponding DMP esters occurs only from (E)-isomer through the triplet pathway.[57,58] That is because the (Z)-photoenol undergoes very rapid intramolecular reketonization. Despite relatively low quantum yields (18 – 25% in benzene; 10% in methanol), the chemical yields for photorelease of carboxylates were quantitative. In contrast, dialkyl phosphoric and alkyl sulfonic acids are released from the corresponding DMP esters with excellent quantum efficiencies in methanol (0.68 – 0.71).[59] Dimethylphenacyl mixed carbonates were tested as photoremovable protecting groups for alcohols and phenols with somewhat more disappointing results. Chemical yields of the substrates were ~70% and quantum efficiencies were similar to that of carboxylate esters (0.1 – 0.2 in methanol; 0.36-0.51 in cyclohexane).

Scheme 1.37

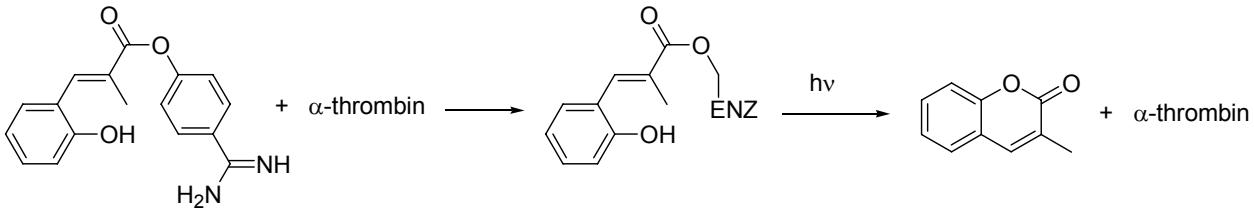


Compound	X	Chemical yield of HX,	Ratio **1.61**:**1.62** (methanol)	Φ (MeOH)	Φ (benzene)
1.60a	Cl		0.69	0.78	0.12
1.60b	PhCOO	86 – 92	1.8	0.09	0.23
1.60c	tosyl	93	0.70	0.68	0.19
1.60d	diethylphosphate	94	0.69	0.71	0.09
1.60e	PhO	>70	~0.63	0.20	0.50
1.60f	$PhCH_2O$	>70	~0.63	0.14	0.48

1.6. Other photoremovable protecting groups.

Porter and co-workers proposed *o*-hydroxy-α-methyl cinnamic acid derivatives as potential photoactive enzyme inhibitors.[63] The human enzyme α-thrombin was inactivated by acylation with p-amidinophenyl *o*-hydroxy-α-methylcinnamate **1.63**, and the resulting ester **1.64** remains inactive and stable in the absence of light. This inhibition, however, becomes reversible upon irradiation of the enzyme, i.e. photolysis results in 80 – 100% reactivation of the enzyme (scheme 1.38).

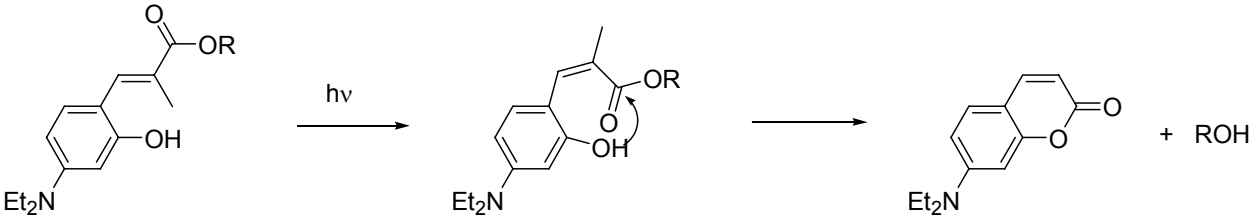
Scheme 1.38



1.63 **1.64** **1.65**

This general approach to photocontrol of enzyme activity was later applied for reversible inhibition of Factor Xa and trypsin.[64] The photoactivation of these enzymes was, however, slow and required irradiation at 254 nm which resulted in sufficient enzyme degradation. Modification of the *o*-hydroxy-α-methylcinnamate chromophore with the diethylamino group allowed for reactivation of the α-thrombin upon irradiation of **1.66** at much more suitable 366 nm light.[65] The key step in *o*-hydroxy-α-methyl-*trans*-cinnamate photochemistry is believed to be trans-cis photoisomerization. The resulting *cis*-isomer (cis-**1.66**) undergoes rapid (~300 μs) lactonization to substituted 3-methylcoumarin **1.67**, thus restoring full enzyme activity.

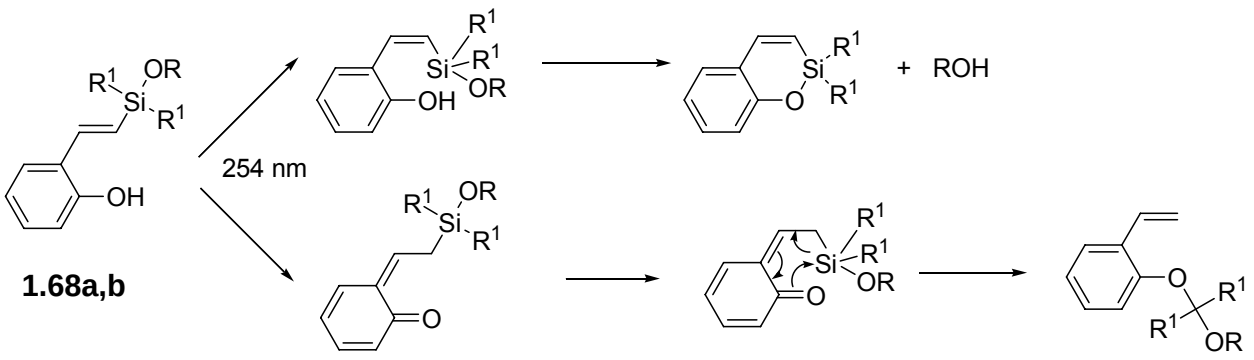
Scheme 1.39



trans-**1.66** cis-**1.66** **1.67**

Pirrung and Lee developed photochemically removable silyl protecting groups, the mechanism of deprotection of which is also based on *trans-cis* photoisomerization.[66] (Hydroxystyryl)dimethylsilyl (HSDMS, **1.68a**, R^1 = Me) and (hydroxystyryl) diisopropylsilyl (HSDIS, **1.68b**, R^1 = *i*-Pr) protecting groups are stable to a variety of reaction conditions, including EtMgBr, $NaBH_4$ and PDC, but are efficiently removed upon irradiation at 254 nm light in acetonitrile. In benzene, however, X is converted to an interesting silylilidene derivative, which was explained by a competing mechanistic pathway.

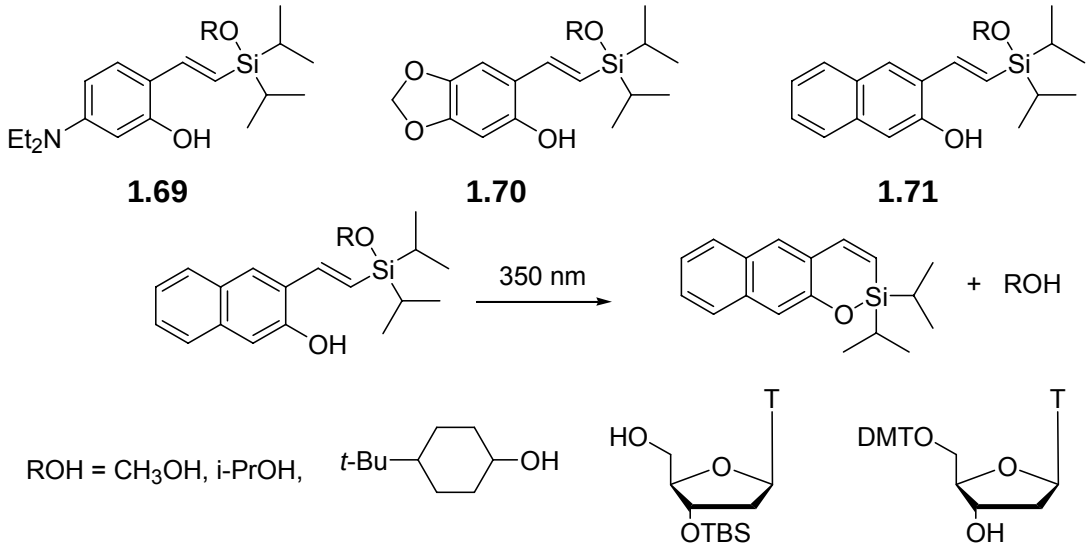
Scheme 1.40



R^1 = (**a**) CH_3; (**b**) $CH(CH_3)_2$

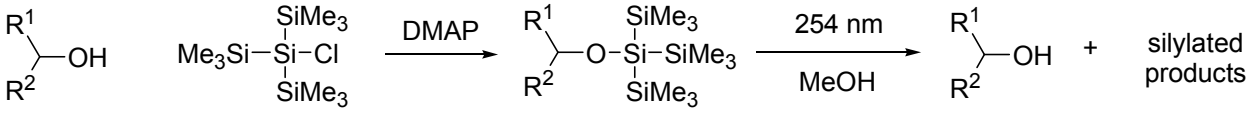
In order to improve long wavelength absorption properties, modification of the benzene ring with diethylamino (**1.69**) and methylenedioxy (**1.70**) substituents was attempted.[67] However, the former was synthetically inaccessible, whereas the latter gave the wrong product upon irradiation at 350 nm. An alternative strategy for red-shifting the absorption maximum, the ((2-hydroxy-3-naphthyl)vinyl)diisopropylsilyl (HNVDS, **1.71**), group was developed. Alcohols, including thymine nucleosides, protected with this group are released upon irradiation at 350 nm with excellent (>90%) isolated yields.

Scheme 1.41

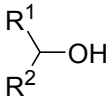


Another silicon-containing photoremovable protecting group was developed by Brook and co-workers.[68] In spite of the absence of a π-system, the tris(trimethylsilyl)silyl (sisyl) group absorbs in the UV-region due to σ-conjugation of Si-Si bonds. Sisyl ethers **1.72** are readily available from the corresponding chlorosilane and were found to be stable towards: oxidation, organometallic reagents and acidic conditions. The photodeprotection of these compounds with a medium pressure mercury lamp (254 nm) in methanol proceeded rapidly to give high yields (70 – 95%) of the starting primary or secondary alcohols.

Scheme 1.42

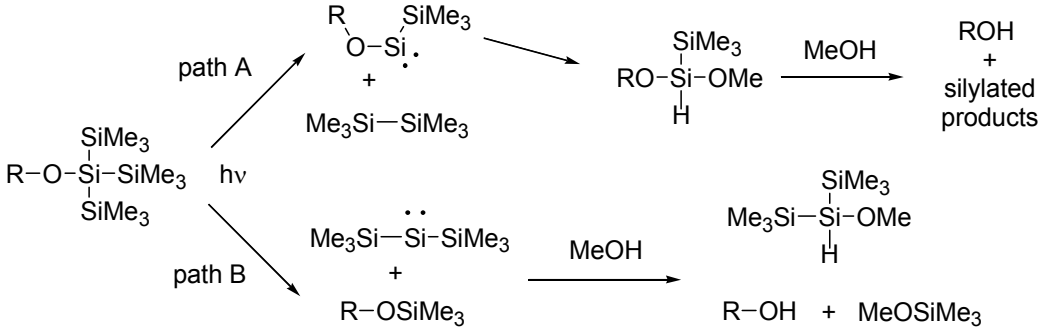


1.72

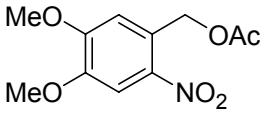

= geraniol, cholesterol, phenylethanol, cyclopentanol, 2-octanol, etc.

It was assumed that the photolysis occurs via silylene formation and the mechanism of deprotection of silyl ethers was examined using 2,3-dimethyl-1,3-butadiene as a silylene trap. Two pathways, both leading to the release of alcohol, have been recognized. It was found that benzyl derivatives preferentially undergo photocleavage path B, whereas the cyclopentyl derivative followed path A.[69]

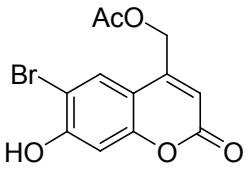
Scheme 1.42



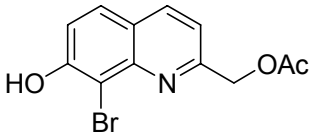
In 2002 Dore and co-workers[70] reported a new photoremovable protecting group for carboxylic acids based on 8-bromo-7-hydroxyquinoline (BHQ). Photodeprotection of acetic acid from BHQ-OAc **1.73** was found to be more efficient compared to 4,5-dimethoxy-4-nitrobenzyl (DMNB) acetate and 6-bromo-7-hydroxycoumarin-4-ylmethyl (Bhc) acetate. Moreover, it is sensitive to two-photon photolysis, as indicated by sufficient uncaging action cross-section δ_u, the product of the two-photon absorbance cross-section δ_a and the uncaging quantum yield Q.



DMNB acetate



Bhc acetate



BHQ-OAc, **1.73**

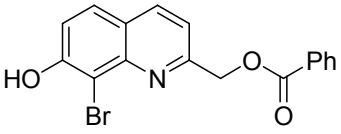
PPG	λ_{max}	ε_{max}	ε_{365}	Φ_{365}	δ_u (740 nm)	δ_u (780 nm)
DMNB	346	6100	5200	0.005	0.03	0.01
Bhc	369	2600	2580	0.29	0.59	0.087
BHQ	370	15000	14800	0.036	0.72	0.21

In a two-photon excitation process, the chromophore simultaneously absorbs two low energy photons via the virtual excited state, resulting in the same effect as upon excitation with a single twice as energetic photon. The advantages of such approach include high three-dimensional spatial resolution of the uncaging (only at the focus of the laser beam) and much deeper and less damaging penetration of the IR light into living tissue since cells are transparent to this light. Other advantages of the BHQ photolabile protecting group are moderate dark hydrolytic stability (τ = 70.9 h at pH 7.2),

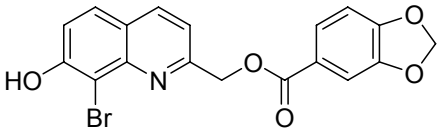
high aqueous solubility of the caged substrate and low fluorescence, which explains high quantum yield of the release.

The BHQ protective group was later applied for caging of benzoic and piperonylic acids; dimethyl phosphoric acid and glycerol derivatives 1-phenoxypropane-2,3-diol and 1-phenylthioxypropane-2,3-diol, **1.74-1.78** respectively.[71]

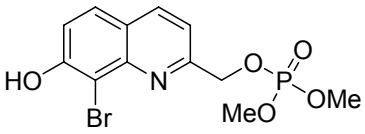
Scheme 1.43



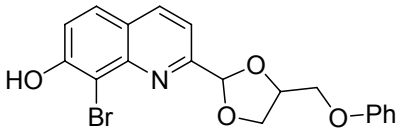
1.74



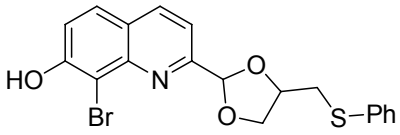
1.75



1.76



1.77

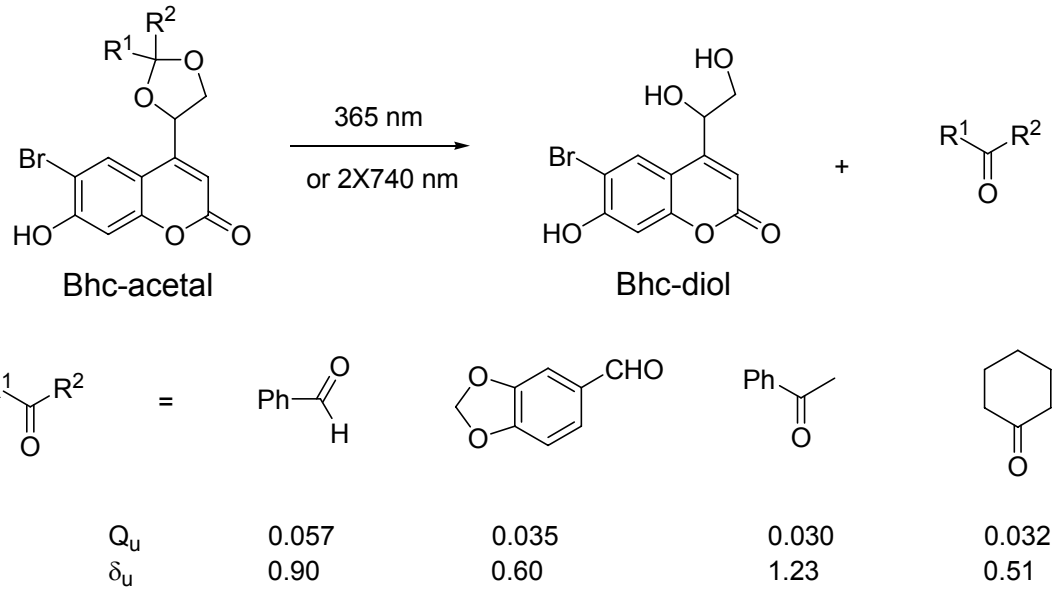


1.78

The carboxylates and diols were photoreleased under simulated physiological conditions by single- (365 nm) or two-photon (740 nm) excitation in good yields (60 – 70%). Kinetic experiments such as Stern-Volmer quenching, time-resolved IR and ^{18}O-labeling supported a solvent-assisted photoheterolysis (S_N1) reaction mechanism that proceeds *via* the singlet excited state of the BHQ.

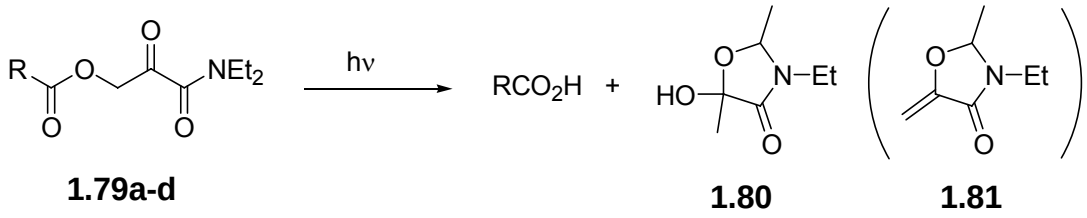
The same group also developed 6-bromo-4-(1,2-dihydroxyethyl)-7-hydroxycoumarin (Bhc-diol) as a photolabile protecting group for aldehydes and ketones.[72] Acetals and ketals of this diol are capable of releasing aldehydes and ketones upon single- or two-photon irradiation in buffer solutions. The carbonyl compounds, however, were only released in 50% yield due to secondary photochemical degradation.

Scheme 1.44



The photorelease of various leaving groups such as carboxylic acids and phenols from α-ketoamides was studied by Steinmetz et al. Benzoic, phenylacetic, acetic and γ-aminobutyric (GABA) acids were liberated from the corresponding compounds **1.79a-d** in aqueous-acetonitrile solutions upon irradiation at $\lambda > 350$ nm light.[73] The yield varied from 70 to 90% and the quantum yields were calculated to be ca 0.3 for this type of compound. The major photocleavage by-product formed in this reaction was the hemiacetal **1.80** with traces of its dehydrated form **1.81**:

Scheme 1.45

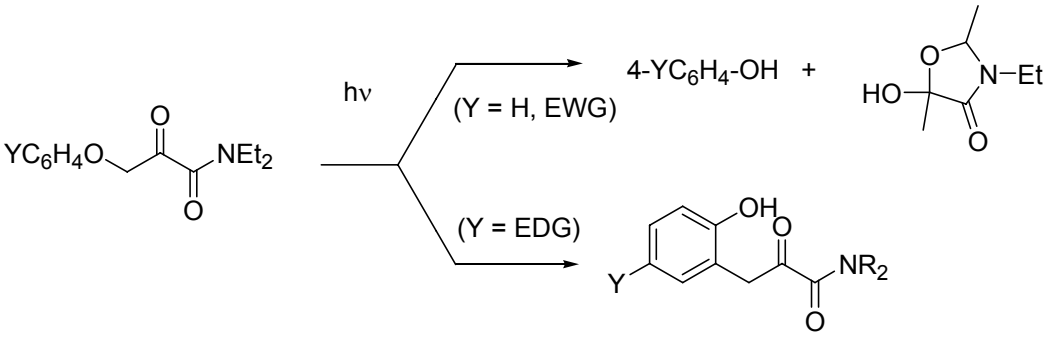


R = (**a**) Ph; (**b**) $PhCH_2$; (**c**) CH_3; (**d**) $H_2NCH_2CH_2CH_2$

Kinetic studies with compound **1.79d** allowed determination of the time constant for release of GABA of 30 ms.

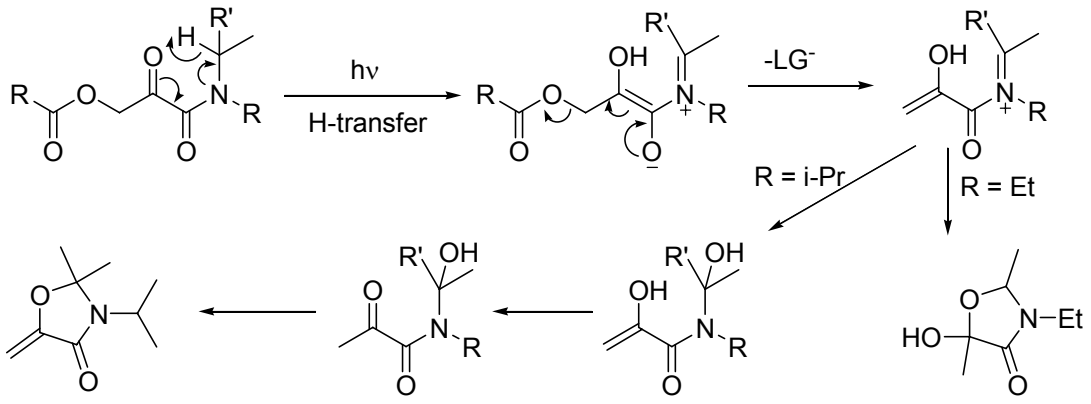
Photorelease of the phenols upon irradiation of the analogous phenoxy-compounds[74] occurred only in case of parent phenol (in 52% yield) or if Y is an electron-withdrawing group such as cyano (98% yield). However, if Y is an electron donating group, the 1,3-photorearrangement product is formed with only traces of the released phenol. These results were explained as the result of competing ArO–C_α bond scission to radicals followed by recombination.

Scheme 1.46



It was later shown that in case of *N,N*-diisopropyl α-keto amides, the leaving group ability has much smaller effect on the release of the substrate than for *N,N*-diethyl amides.[75] Moreover, the photochemical by-products are different: product **1.81b** is exclusively formed upon irradiation of *N,N*-diisopropyl α-keto amides; whereas *N,N*-diethyl amides form hemiacetal **1.80** under similar conditions. The following mechanism has been proposed:

Scheme 1.47

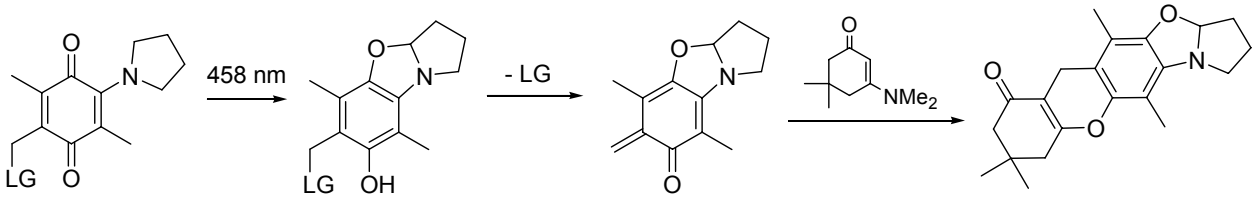


1.81b **1.80**

Overall, substituted α-keto amides efficiently release various carboxylic acids with quantum yields of 0.2-0.4 and rate constants of 20-150 μs depending on the leaving group and alkyl substituents on nitrogen.

Another photochemically removable protecting group developed by this research group is pyrrolidino-substituted 1,4-benzoquinones.[76] 5-Acyloxymethyl-2-pyrrolidino-1,4-benzoquinones **1.82** undergoes photochemically induced isomerisation to oxazolidines **1.83** upon irradiation with visible light. The latter spontaneously eliminates a carboxylic acid to form *o*-quinone methide intermediate **1.84** which reacts with the starting material or can be trapped with a Diels-Alder alkene such as 3-dimethylamino-5,5-dimethyl-cyclohex-2-enone (scheme 1.48).

Scheme 1.48

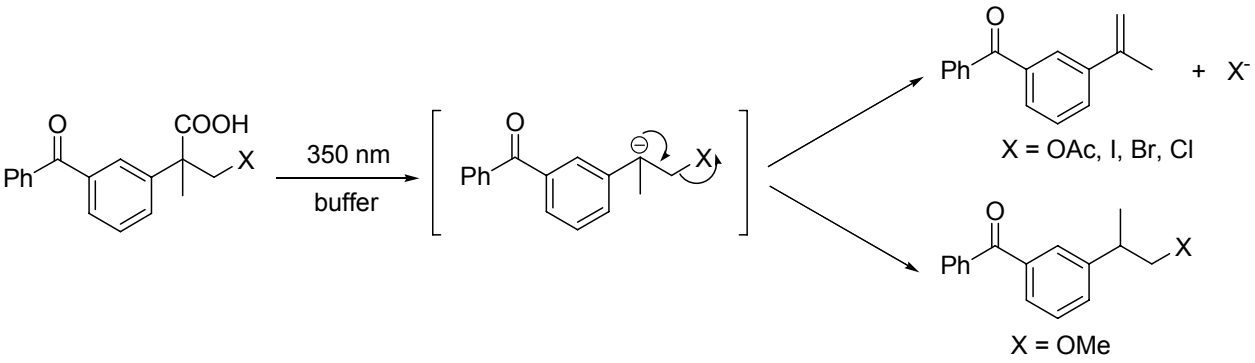


1.82 **1.83** **1.84** **1.85**

Carboxylic acids were released in 79% to 92% yield and the cycloadduct **1.85** is formed in ca. 85% yield. Irradiation of 5-phenoxymethyl-2-pyrrolidino-1,4-benzoquinones (LG = C_6H_5O) led to a cyclised oxazolidine which was isolated in quantitative yield. This compound eliminates phenol in basic media, thus making this photochemically removable protecting group suitable for phenols under certain conditions.

A novel carbanion-mediated mechanism for photodeprotection was proposed by Lukeman and Scaiano based on the photochemical decarboxylation of ketoprofen.[77] Elimination of the leaving group from the β-position to the carbanion is accompanied with formation of 3-isopropenylbenzophenone.

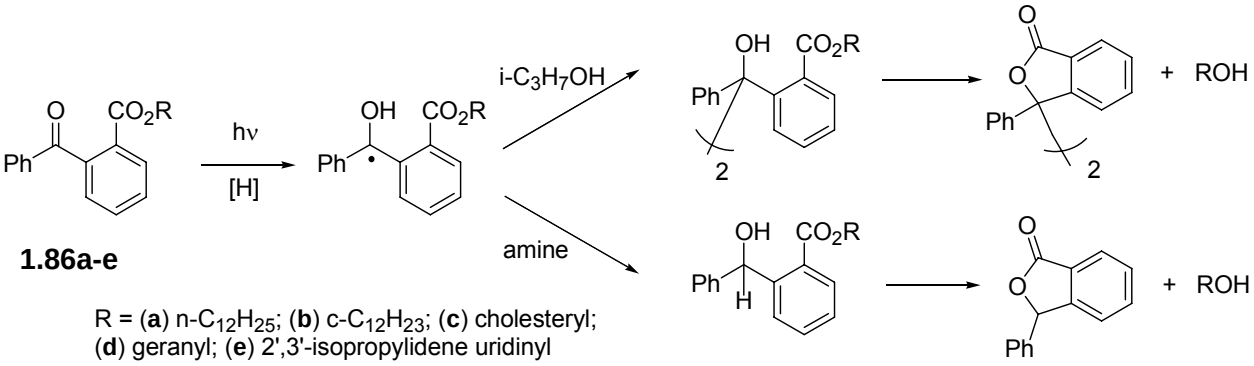
Scheme 1.49



Upon irradiation of acetyl and halide derivatives, only 3-isopropenylbenzophenone was observed in the reaction mixture, which led the authors to the conclusion that carboxylic acids and halides are released quantitatively. The very high quantum efficiency of this reaction ($\Phi \sim 0.7$) in combination with the fast rate constant ($\tau > 10^8\ s^{-1}$) makes "ketoprofenate" photocages very suitable for carboxylate functionalities. However, irradiation of the methoxy derivative afforded only 20% of 3-isopropenylbenzophenone along with 80% of the product of formal decarboxylation.

Esters of 2-benzoylbenzoic acid **1.86a-e** were shown to be effective photolabile protecting groups for primary and secondary alcohols as well as for thiols in the presence of hydrogen or electron donor (*iso*-propanol and cyclohexylamine respectively).[78] Despite the difference in photochemical by-products, alcohols are released with high to excellent chemical yields (85 – 100%) upon irradiation of these esters with a medium pressure mercury lamp through a filter in both cases.

Scheme 1.50



1.86a-e

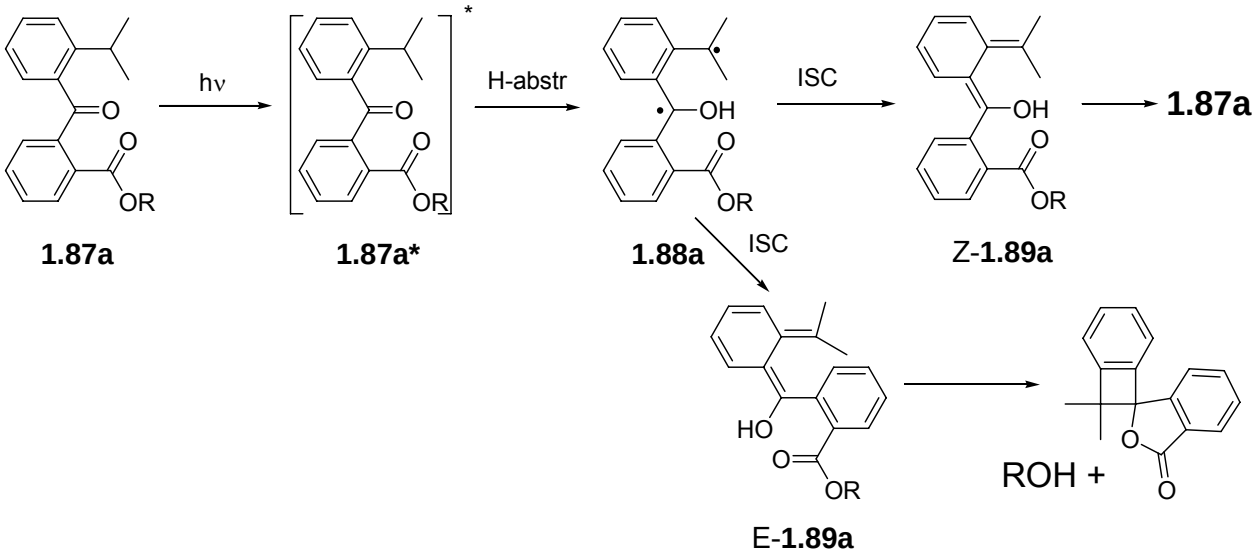
R = (**a**) n-$C_{12}H_{25}$; (**b**) c-$C_{12}H_{23}$; (**c**) cholesteryl; (**d**) geranyl; (**e**) 2',3'-isopropylidene uridinyl

Thus, alcohols and thiols can be easily caged and photochemically uncaged from their *o*-benzoylbenzoate esters. However, the presence of a reducing agent is vital for this photochemical transformation.

Gudmundsdottir and co-workers later modified this protecting group by introducing an *iso*-propyl substituent *ortho* to the ketone in order to provide a donor for intramolecular hydrogen abstraction.[79] Thus, photolysis of 2-(2-isopropylbenzoyl)benzoate esters **1.87a** results in release of the alcohol independently of the reaction media. The photochemical transformation was proposed to proceed through the triplet excited state of the ketone (**1.87a***, τ ~ 0.08 – 0.8 ns), which then undergoes intramolecular hydrogen transfer to form a biradical **1.88a** (τ = 17 ns).

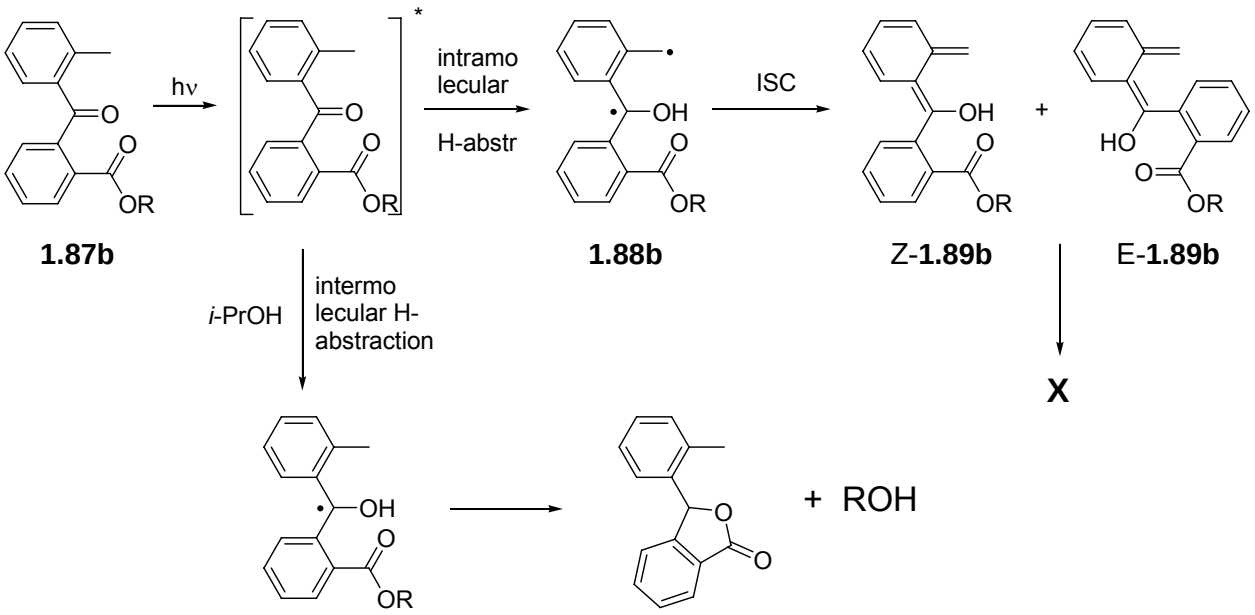
Intersystem crossing of the latter produce photoenol Z-**1.89a** (τ ~ 3μs), which rearranges to the starting material, and E-**1.89a** (τ > 1 ms), which releases alcohol through an intramolecular lactonization:

Scheme 1.51



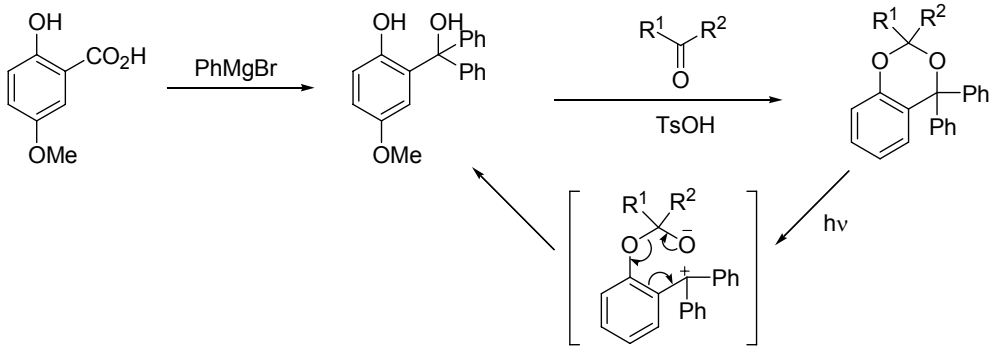
Unfortunately, the photochemistry of the methyl analog **1.87b**, which is easier to synthesize than **1.87a**, is quite different.[80] This compound releases alcohol only in 2-propanol, but fails to do so in benzene or dichloromethane. The reason for such behavior is rapid rearrangement of the photoenol E-**1.89b** back to the starting **1.87b** instead of lactonization. In 2-propanol, where intermolecular hydrogen transfer occurs, the resulting radical does release the alcohol through an intramolecular lactonization.

Scheme 1.52



Most recently Wang and co-authors invented a new photolabile protecting group for carbonyl compounds based on 5-methoxysalicylic alcohol.[81] It was shown that readily accessible cyclic acetals and ketals of this formal diol undergo photochemical cleavage to liberate aldehydes or ketones, respectively, presumably *via* a zwitterionic intermediate in high yields (75 – 90%). The protected form was remarkably stable towards various reagents including metalloorganic (PhLi, $LiAlH_4$, *t*-BuOK); strong acids (AcOH, TFA, conc HCl) and mild oxidants (DDQ). Unfortunately, quantum efficiencies of the photochemical release were not reported.

Scheme 1.51

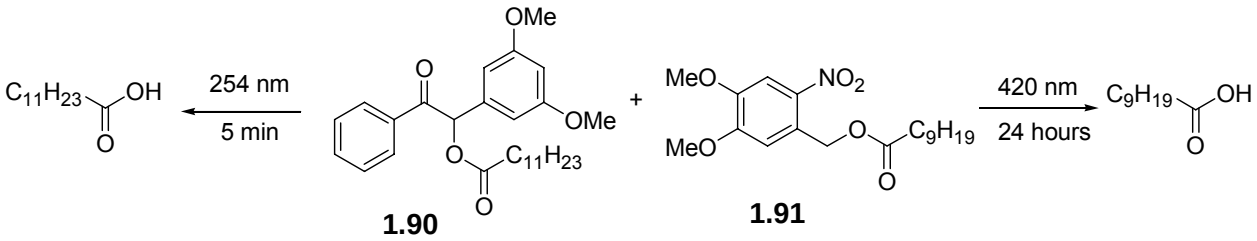


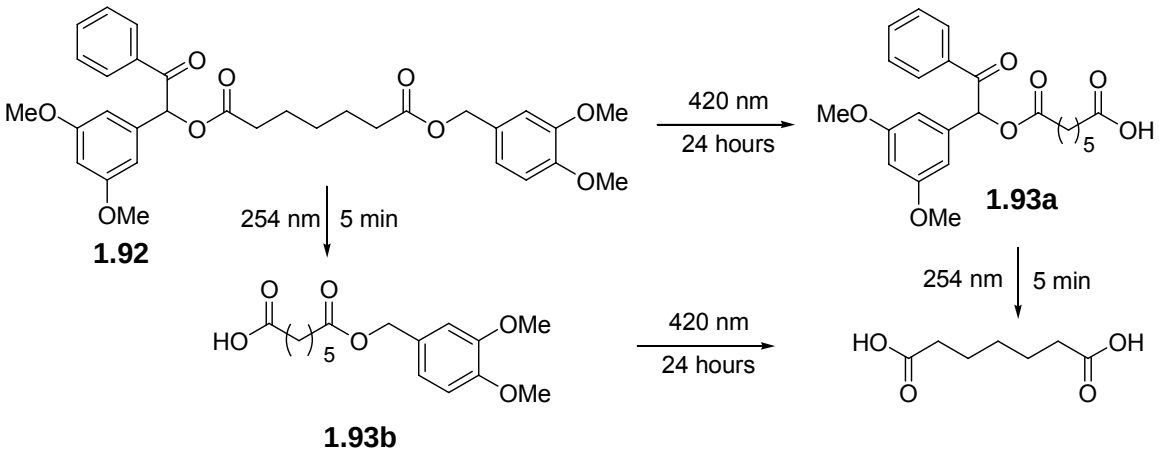
1.7. Current trends in photoremovable protecting groups.

Recently Bochet introduced an elegant concept of "wavelength-controlled orthogonal photolysis of protecting groups".[82] In other words, one photolabile protecting group might be removed in the presence of another one and vice versa if their stability is different at different wavelengths. The 3',5'-dimethoxybenzoin esters can be efficiently cleaved upon short irradiation at 254 nm light (Φ = 0.64), whereas *o*-nitrobenzyl derivatives are much less reactive, but sensitive towards longer wavelengths of 420 nm. Thus the mixture of esters of two different aliphatic carboxylic acids[82a] **1.90** and **1.91** gave upon irradiation at 254 nm for 5 minutes dodecanoic acid; on the other hand photolysis at 420 nm for 24 hours afforded decanoic acid.

Furthermore,[82b] irradiation of the mixed adipate **1.92**, bearing the dimethoxybenzoin moiety at one site and nitrobenzyl on the other one at different wavelengths leads to different monoesters of adipic acid **1.93a** and **b**. Both of them can be deprotected further by photolysis at another wavelength.

Scheme 1.52

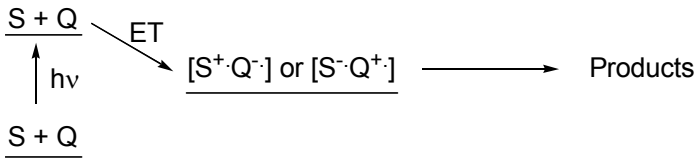




Thus, the concept of chromatic orthogonality was illustrated in both inter- and intramolecular cases and applied to wavelength-controlled photorelease of the compounds.

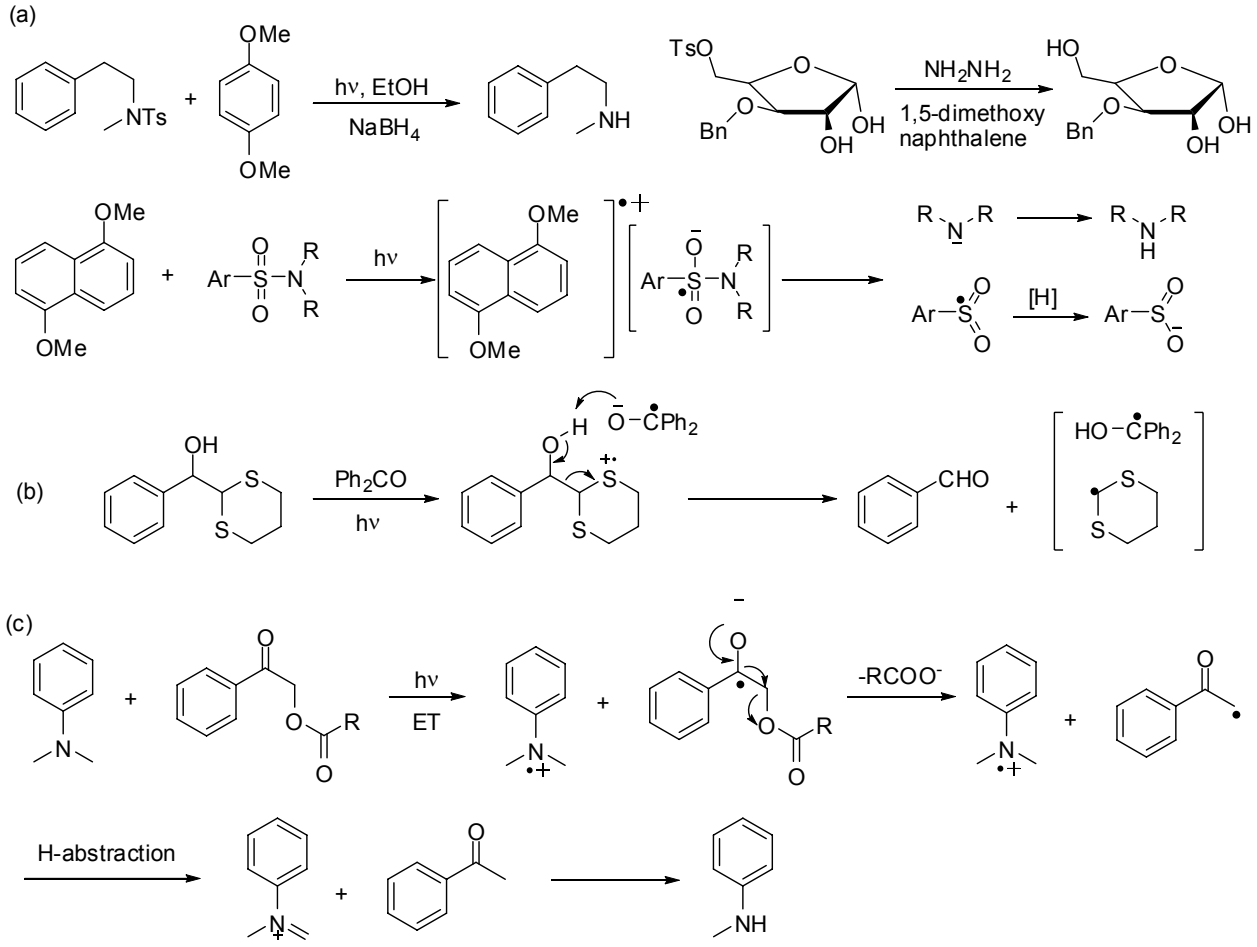
Another promising approach which arose in the last decade is photorelease mediated by photoinduced electron transfer.[83] This concept includes absorption of a photon by photosensitizer ('antenna') followed by a bond-breaking step to release the substrate from the different compound.

Scheme 1.53



Numerous types of protecting groups, removable using photoinduced electron transfer protocol have been developed. Some of them require advantageous long-wavelength irradiation at λ > 350 nm. The most attractive among them are sulfonamides,[84] dithianes[85] and phenacyl esters[86] (scheme 1.54; a, b, c respectively)

Scheme 1.54

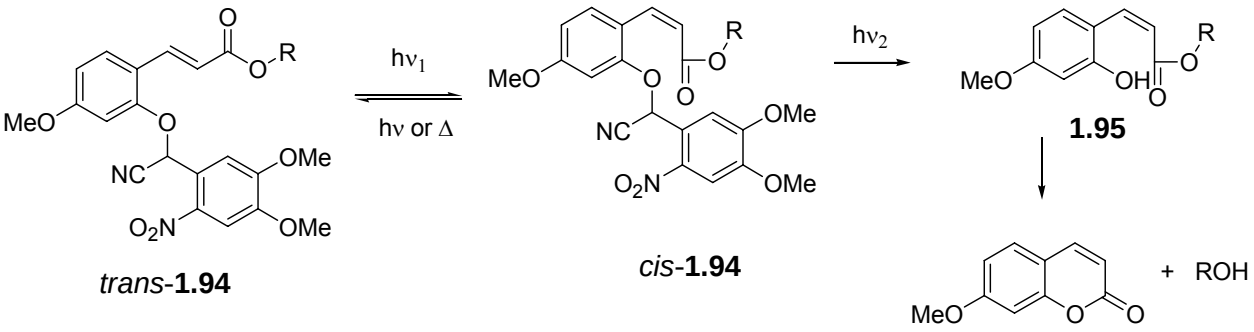


An advantage and at the same time a drawback of such an indirect approach is that the photorelease is divided in two independent processes: light absorption and electron transfer to (or from) the photoremovable protecting group followed by the cleavage of the latter. This allows controlling the wavelengths of irradiation; on the other hand photochemical release requires extra reagents.

Two-photon excitation provides a powerful tool for conducting photochemical processes with high spatial resolution since two-photon absorption probability depends quadratically on the light intensity. Therefore, absorption as well as consequent processes is confined in a very small area at the light focus. Protecting groups,

removable upon excitation with two IR photons were mentioned before.[25,70] Pirrung *et al.* in their combinatorial study have discovered a new PPG which is removed upon excitation with two UV photons and can be applied in photolithography or peptide synthesis.[87] Compound **1.94** contains two photolabile chromophores: a nitrobenzyl moiety and hydroxycinnamate group, also mentioned above.[63-65] The following pathway has been proposed: absorption of the first photon promotes reversible cis-trans isomerization, whereas the second photon cleaves off the nitrobenzyl group and the product **1.95** spontaneously lactonizes, eliminating free alcohol

Scheme 1.55



trans-**1.94**

cis-**1.94**

This two-photon approach provides excellent spatial resolution of photorelease and therefore might be useful in high-quality stereolithography or drug delivery systems.

1.8. Conclusions.

A large variety of photochemically removable protecting groups has been developed to-date and this family is extensively growing. While this manuscript was in preparation at least two novel PPGs were reported.[88,89] We hope that review above along with other brilliant summaries of the field[2,3] will help to classify these PPGs by class, mechanism of photorelease and possible applications.

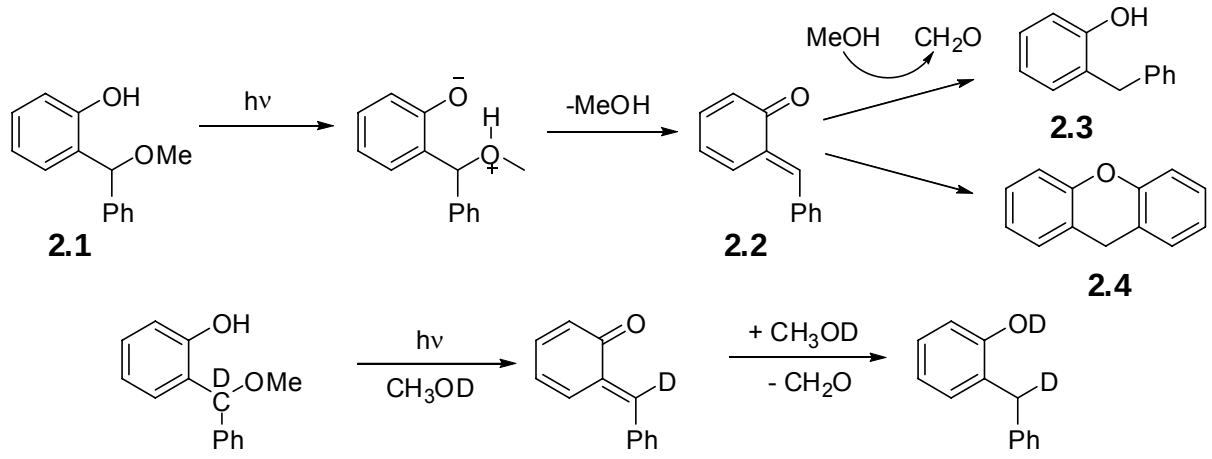
All photoremovable protecting groups can be divided into two groups based on the mechanism of releasing the substrate. For the first type of PRPGs, irradiation induces the cascade reaction and the substrate is released from the ground state of a reactive intermediate generated from the irradiated compound. These groups are well represented by the family of the most commonly used 2-nitrobenzyl (NB) protecting groups. Absorption of a photon gives rise to a reactive *aci*-tautomer and the following cascade does not require light. Another example is dimethoxybenzyl carbonates which release alcohols through the dark decarboxylation of the photochemically generated monoalkyl carbonate. Direct release of the substrate from the excited state of the photocage usually proceeds much faster and therefore is more advantageous for time-resolved studies. Most commonly used PRPGs of this type include benzoin and *p*-hydroxyphenacyl esters.

Although most of the PPGs developed so far photochemically release carboxylic acids, phosphates and halides with excellent yields, photolabile protection of alcohols or phenols is more difficult. In order to promote their poor ability as a leaving group, utilization of mixed carbonates is required with rare exceptions.[32-34] Overall, a substrate is released through the dark decarboxylation of the photochemically generated monoalkyl carbonates which have the lifetimes up to several seconds. There are also a very few reports on photochemically protected carbonyl compounds. Therefore, despite tremendous progress in the field in recent years, the need to develop novel efficient and reliable groups for some functionalities still exists.

2. PHOTOGENERATION OF *ORTHO* QUINONE METHIDE

The formation of transient *o*-quinone methides upon irradiation of the derivatives of o-hydroxybenzyl alcohol was first reported by Padwa in the series of papers concerning the photochemistry of isocoumaranone and chromanone systems.[90] It was found that irradiation of benzhydryl methyl ether **2.1** at 254 nm results in formation of o-benzylphenol **2.3** and xanthene **2.4**. The intermediacy of quinone methide **2.2**. has been suggested and the mechanism, involving phenolic hydrogen transfer to the departing methoxy group was proposed and confirmed by the experiment with the deuterated analog in deuteromethanol.

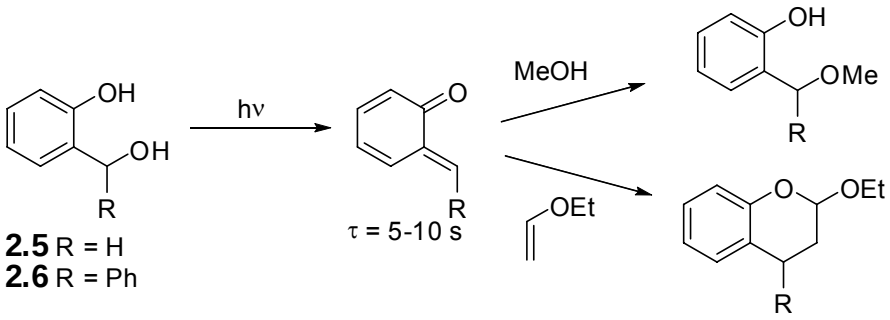
Scheme 2.1



Despite the numerous applications that *o*-quinone methides (*o*-QM) found in organic synthesis, particularly in “reverse electron demand” Diels-Alder [4+2] cycloaddition to electron-rich olefins,[91] this reaction had not been proven useful until the mid 90’s when Wan and co-workers reported a mild general method for the photogeneration of quinone methides.[92] They showed that photolysis of the simplest o-hydroxybenzyl alcohols **2.5**

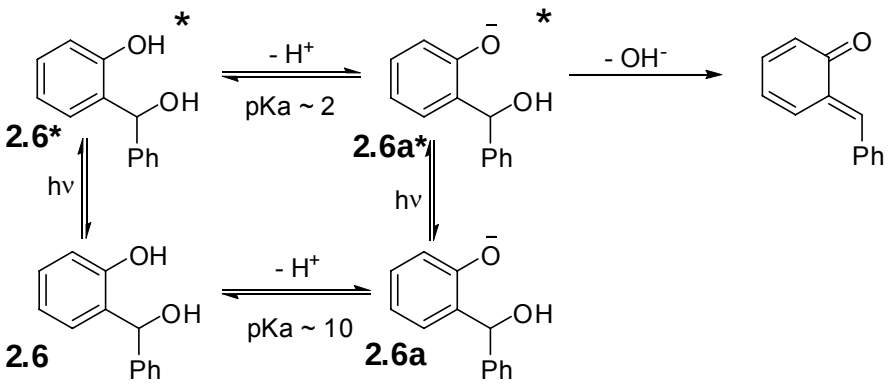
and **2.6** in aqueous methanol results in formation of the corresponding methyl ethers with high quantum yields. On the other hand, photolysis in aqueous acetonitrile in presence of ethyl vinyl ether, dihydropyran or dihydrofuran gives the corresponding [4+2] cycloaddition adducts quantitatively. Laser flash photolysis experiments allowed detection of the long-lived (τ = 5-10 s), strongly absorbing at 350 – 450 nm. These observations clearly indicate formation of *o*-QMs as intermediates upon irradiation of the corresponding *o*-hydroxybenzyl alcohols in aqueous solutions.

Scheme 2.2



The mechanism of the *o*-QM formation was proposed based on the plot of quantum yield of its formation versus pH for the compound **2.6**.

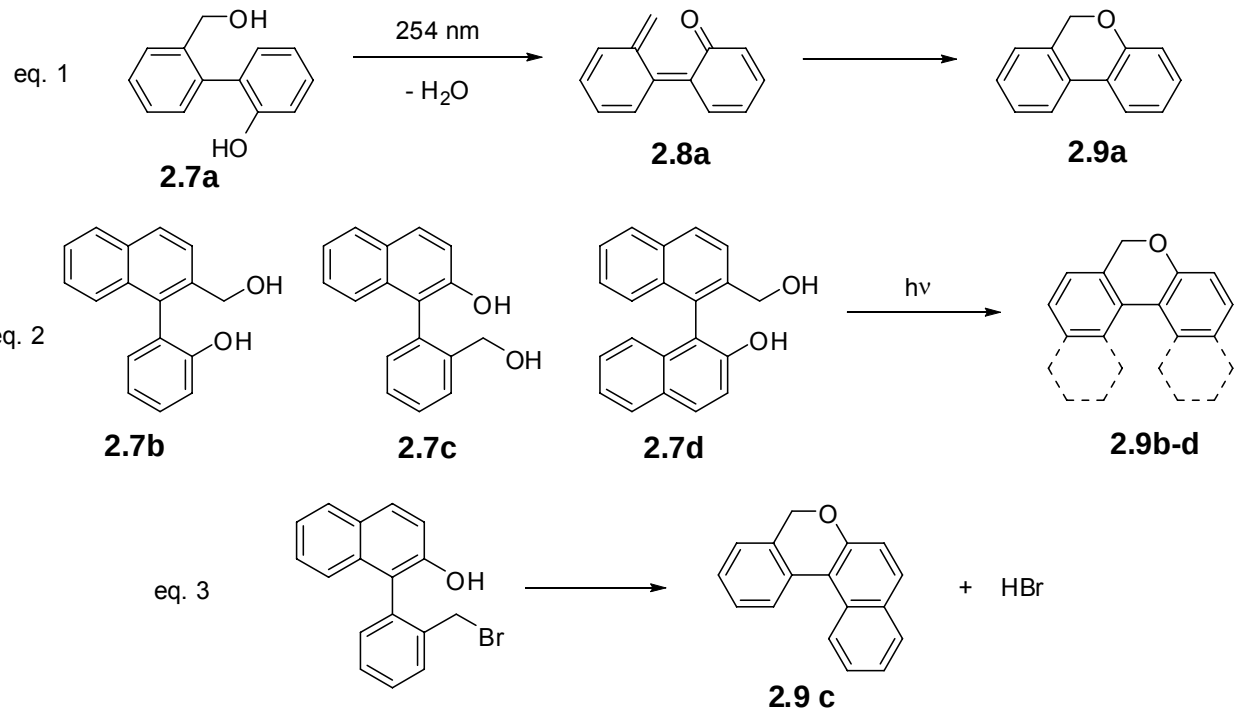
Scheme 2.3



In basic (pH > 10) media excitation of the phenolate anion **2.6a** results in formation of singlet **2.6a*** with high quantum yield, which loses hydroxide anion to give *o*-QM. At 2 < pH < 8 light is absorbed by phenol to form excited **2.6*** which readily dissociates, producing **2.6a***; the overall quantum yield of this process is somewhat lower. Finally, in acidic media (pH < 1) quantum yield of the quinone methide formation drops to 0 which indicates that dissociation of the O-H bond is a necessary step in the mechanism.[93]

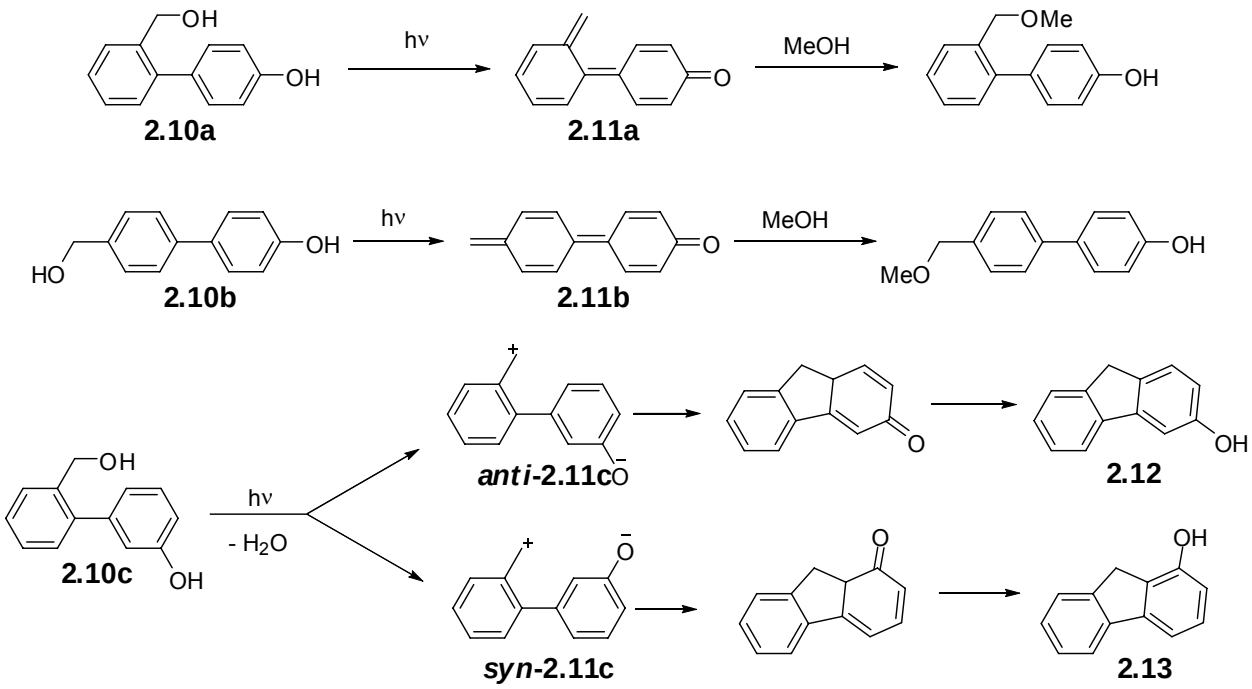
Further investigation of quinone methide chemistry by this research group revealed a very interesting photocyclization reaction of biaryl quinone methides leading to planarization of the highly twisted system. As an example, photolysis of 2-(2'-hydroxyphenyl)benzyl alcohol **2.7a** in aqueous or acetonitrile solution gave 5*H*-dibenzo[*b,d*]pyran **2.9a** via the *o,o'*-biphenyl quinone methide intermediate **2.8a** with high quantum yield of 0.5 (eq. 1).[94a] The same electrocyclic ring closure reaction was then observed for a series of other biarylmethyl alcohols **2.7b-d**, which were cleanly and almost quantitatively converted into the corresponding pyrans upon irradiation at 254 nm (eq. 2).[94b] It was also shown that irradiation of the bromide derivative of **2.7c** results in a dramatic decrease in the pH from 7 to 2.6, indicating release of the hydrobromic acid (eq. 3).

Scheme 2.4



Biaryl derivatives possessing functionalities required for formation of quinone methides, that are, however, not capable of electrocyclic ring closure, have also been studied. Photolysis of biphenyl alcohols **2.10a** and **b** at 254 nm produces the corresponding quinone methides **2.11a, b**, which have lifetimes in the microsecond range and can be trapped with methanol to give the corresponding methyl ethers in high yield.[95] Interestingly, photolysis of alcohol **2.10c** gives rise to the isomeric hydroxyfluorenes **2.12** and **2.13**, and only traces of the corresponding methyl ether.[96] This photolysis was suggested to proceed via meta-quinone methide, which can only exist in zwitterionic forms ***anti*-2.11c** and ***syn*-2.11c** both of which cyclize to the fluorene products.

Scheme 2.5

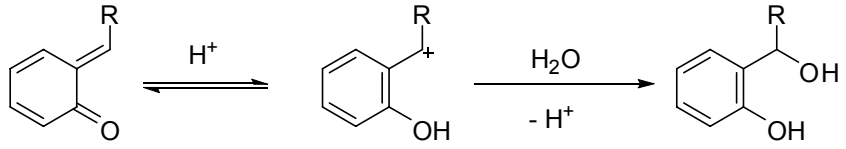


Thus, a variety of quinone methides with lifetimes ranging from subnanoseconds to milliseconds has been generated and investigated upon irradiation of the corresponding hydroxymethyl substituted phenols. The fate of these species largely depends on their structure and chemical environment such as solvent, *etc*.

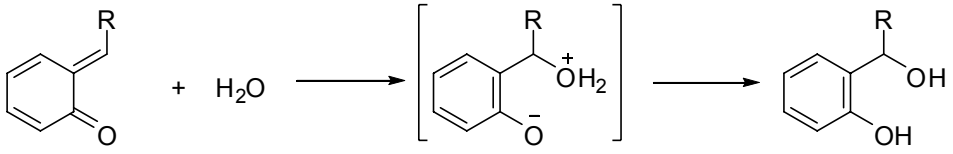
A series of reports on the mechanism of hydration of *o*-QM in aqueous solutions provided great insights into the photogeneration and reactivity of these species. Quinone methides **2.14a-c**, generated from the corresponding alcohols in flash photolysis experiments, were shown to undergo reverse hydration reactions in both acid-catalyzed and uncatalyzed fashions.[97] An inverse isotope effect on the acid-catalyzed hydration indicates the following mechanism of this reaction: rapid reversible protonation on the carbonyl atom followed by the rate-determining attack of the molecule of water on the carbocation (preequilibrium substrate-protonation mechanism).

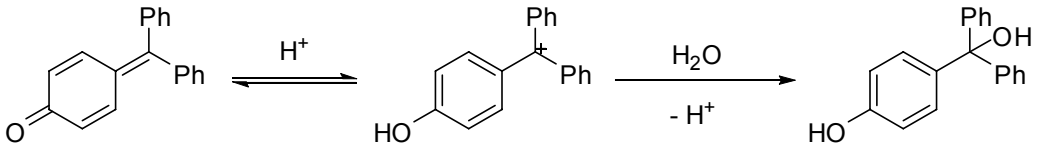
An uncatalyzed reaction is initiated by nucleophilic attack of water on the quinone methide with most probably concerted hydrogen transfer to the phenolic oxygen. These two mechanisms were found to be valid for a series of α-substituted quinone methides, such as *o*-quinone α-phenylmethide **2.14b** and *o*-quinone α-(*p*-anisyl)methide **2.14c**[98] as well as for *p*-quinone α,α-diphenylmethide **2.15**.[99]

Scheme 2.6



2.14a: R = H; b: R = Ph; c: R = An



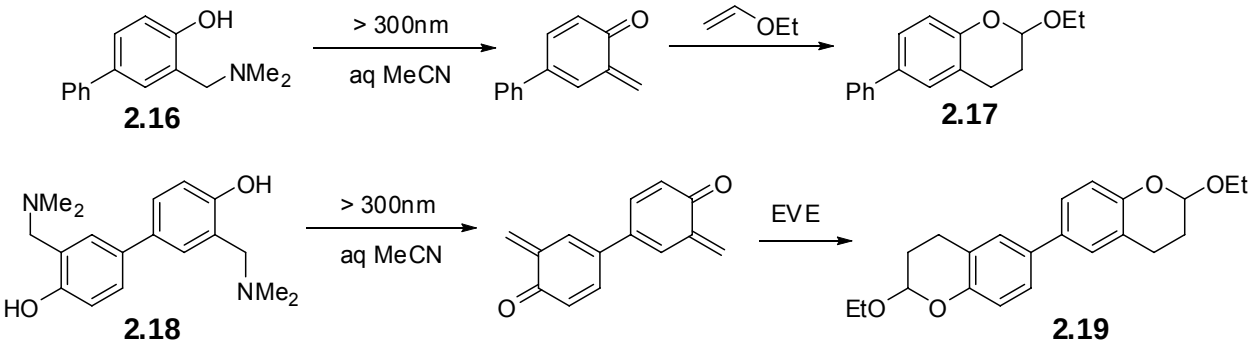


2.15

Saito *et al.* developed a slightly different method for generation of *o*-quinone based methides on photolysis of Mannich bases of phenol and naphthol.[100] The main advantage of these compounds is that formation of the *o*-QM requires irradiation at longer wavelengths (λ > 300 nm), which causes less damage to the living tissues than highly energetic 254 nm light. The resulting *o*-QMs were trapped with ethyl vinyl ether and 4-phenyl substituted compound **2.16** provided the highest yield of the [4+2] cycloaddition adduct **2.17**. The authors proposed the same mechanism of quinone

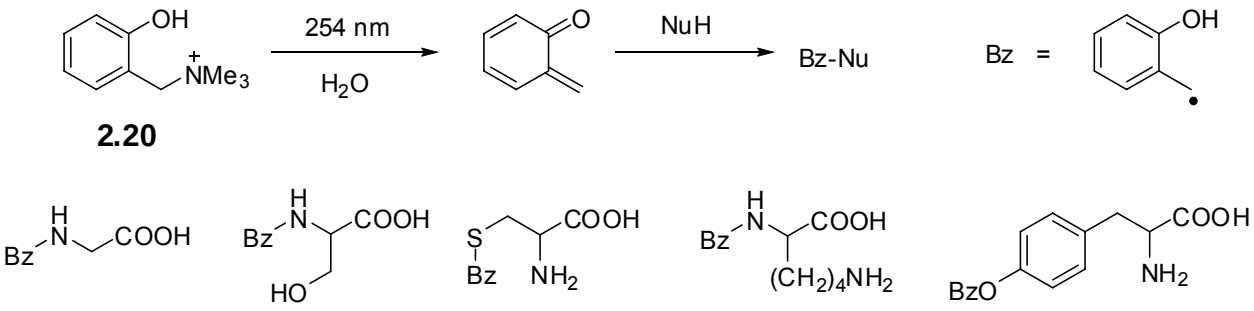
methide generation from Mannich bases as from benzyl alcohols and suggested the use of these compounds as DNA alkylation (**2.16**) or cross-linking agents (**2.18**).

Scheme 2.7



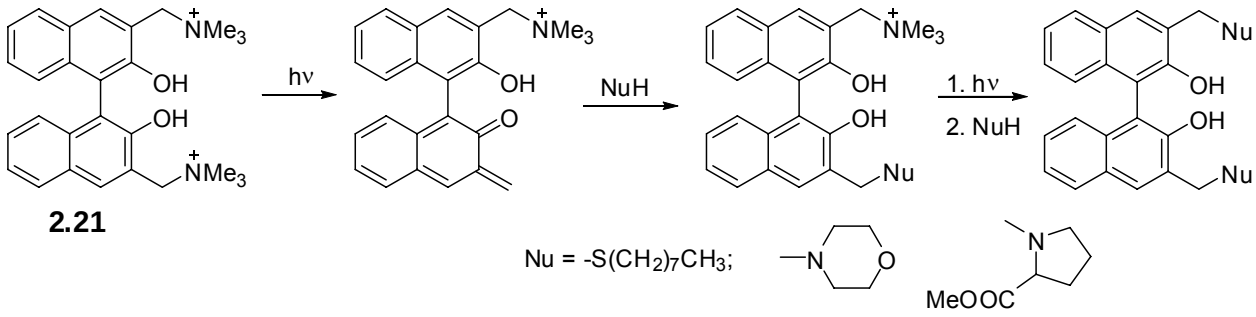
Freccero and co-workers successfully generated *o*-QMs upon irradiation of tertiary ammonium salts **2.20** in water and carried out Michael addition reactions of these species to nitrogen, oxygen and sulphur nucleophiles of aminoacids.[101] The obvious advantages of such an approach is the high aqueous solubility of the quinone methides precursors, low nucleophilicity, and great quantum efficiency, approaching unity (Φ = 0.98). The nucleophilicity scale toward *o*-QM in alkylation reactions changes in the following order: $RS^- >> R_3N > PhO^- > RSH > RNH_2 > OH^- >> H_2O$, ROH. Thus, the side-chains of different aminoacids were very efficiently alkylated with quinone methide and the possible application of the latter as a covalent protein linker has been clearly shown.

Scheme 2.8



More recently, the DNA cross-linking ability of binol quaternary ammonium salts **2.21** was investigated and found to be very promising.[102] These derivatives have two sites of possible quinone methide formation and therefore might serve as precursors of bisalkylating binol-QM, thus DNA cross-linking is possible via a "tandem quinone methide generation".

Scheme 2.9



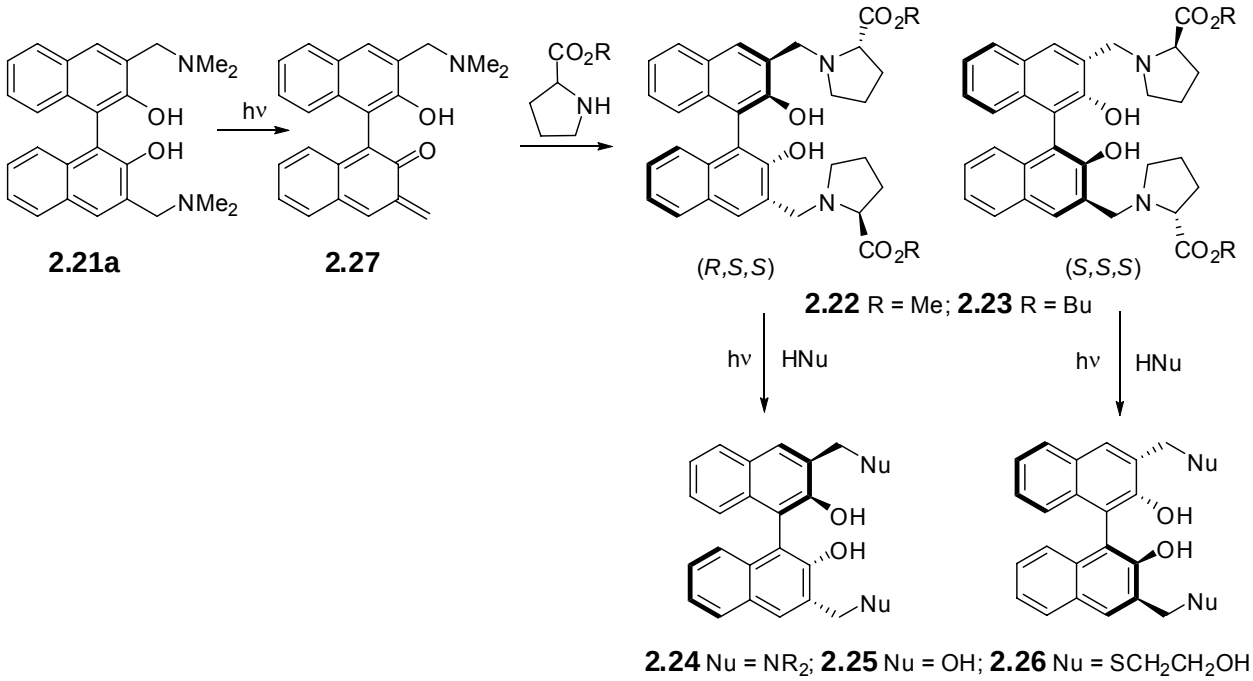
2.21

A model study was carried out by irradiation of **2.21** in the presence of octane-1-thiol, morpholine or L-proline methyl ester and gave the corresponding bisalkylated adducts quantitatively. A DNA cross-linking experiment using a negatively coiled plasmid DNA in an alkaline agarose gel assay showed a remarkable potency of **2.21** as an interstrand cross-linking agent.

Compound **2.21a** was also applied in the photoinduced synthesis of new chiral BINOL ligands, very useful chiral ligands in asymmetric synthesis.[103] The preparative irradiation of racemic **2.21a** in the presence of L-proline methyl or butyl ester afforded corresponding adducts **2.22** or **2.23** as diastereomeric mixtures, that can be easily separated. These compounds, in turn, are also photochemically active and can be converted into various ligands, most important of which are chiral BINOLAMs **2.24**,

tetradentate alcohol ligand **2.25** and thioether **2.26**, upon irradiation at 310 nm, with complete retention of the BINOL moiety configuration. The key intermediate in all of these transformations is the quinone methide of the general structure **2.27**.

Scheme 2.10



In summary, *ortho* quinone methides has been photochemically generated upon photolysis of hydroxybenzyl alcohols, Mannich bases or their quaternary ammonium salts. These highly reactive electrophilic transients can undergo “reverse electron demand” Diels-Alder [4+2] cycloaddition to electron-rich olefins; Michael addition with different nucleophiles, or, if properly oriented, electrocyclic ring closure reaction. Application of this photochemical reaction is limited to few examples in organic synthesis, development of photoactivatable systems, interstrand cross-linking agent and precursor in synthesis of chiral ligands.

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3. RESULTS AND DISCUSSION

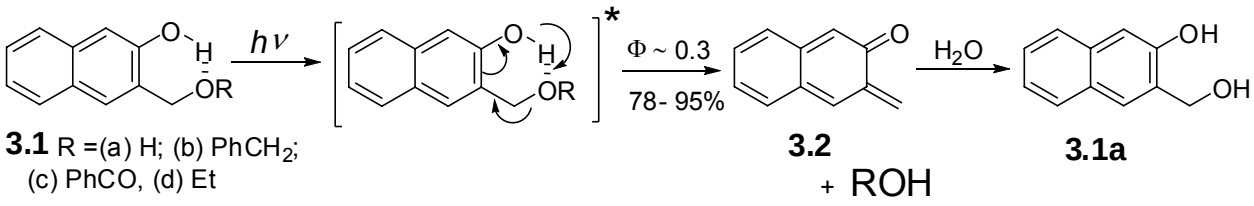
3.1. Photoremovable protecting groups for alcohols, phenols and carboxylic acids.

3.1.1. Introduction. Among common functional groups, alcohols are one of the most difficult functionalities to cage. Several examples of successful release of alcohols and carbohydrates caged with *o*-nitrobenzyl-based PPGs have been reported.[1-3] However, substrate release can take minutes after irradiation since this reaction proceeds via several slow dark steps.[4,5] Other common PPGs, such as 3',5'-dimethoxybenzoin,[6] *p*-hydroxyphenacyl,[7] and a family of cages utilizing photochemical heterolysis of the C – O bond, allow for the rapid release of a substrate but work well only with good leaving groups and are rarely suitable for the direct caging of alcohols. The quantum and chemical yield of alcohol photo-release can be improved substantially by the introduction of a carbonate linker between the substrate and the cage.[8] In this case, however, the relatively slow dark decarboxylation of a mono-carbonate becomes the rate-determining step of the alcohol release. Photo-removable protecting groups based on photo-induced electron transfer often allow for the efficient deprotection of alcohols but require the addition of a sensitizer and/or an electron donor.[9]

Our research group is interested in developing new PPGs based on the photochemistry of *o*-hydroxybenzyl ethers and esters. *o*-Hydroxybenzyl alcohol and its derivatives lose water upon irradiation, generating reactive *o*-quinone methides.[10] The formation of an *o*-quinone methide is usually complete within the nanosecond laser

pulse. It apparently proceeds via the excited state proton transfer, accompanied by a concerted C–O bond cleavage (Scheme 3.1). Recently we have shown that ethers and esters of (3-hydroxymethyl)naphthalen-2-ol **3.1b-d** efficiently release the corresponding hydroxy compounds upon irradiation (Scheme 3.1).[11] (3-Hydroxymethyl)naphthalen-2-ol was chosen over *o*-hydroxybenzyl alcohol because it allows for the use of longer irradiation wavelengths for deprotection.

Scheme 3.1



3.1 R =(a) H; (b) $PhCH_2$; (c) PhCO, (d) Et

3.2 + ROH

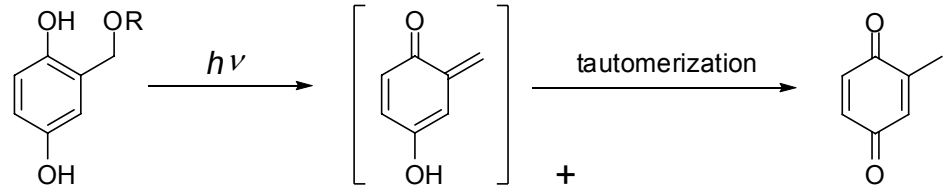
3.1a

In aqueous solvents, water rapidly adds to the intermediate *o*-quinone methide **3.2** to form the parent diol **3.1a**. This cage is well-suited for the time-resolved release of hydroxyl compounds in aqueous media. Under steady-state irradiation, however, accumulation of (3-hydroxymethyl)naphthalen-2-ol **3.1a**, which has the same chromophore as the caged compound, causes the filtering effect and reduces yields of deprotection.

3.1.2. 2,5-Dihydroxybenzyl (DHB) protecting group. To alleviate this problem, we have designed a new PPG, the 2,5-dihydroxybenzyl (DHB) group (**3.3**, Scheme 2). The 4-hydroxy-1-quinone-2-methide intermediate (i.e. **3.4**) formed upon deprotection of the substrate undergoes rapid tautomerization to stable 2-methyl-1,4-benzoquinone (**3.5**). Thus, the DHB protective group has several advantages over the previously explored **3.1**:

1. 1,4-Hydrobenzoquinones are known to have an absorption maxima at 300 nm – a suitable wavelength for irradiation in Rayonet photoreactor.
2. 1,4-Benzoquinones have absorption maxima at about 250 nm and are nearly transparent at 300 nm. Therefore, the expected photochemical reaction should result in bleaching at the wavelength of irradiation allowing for selective irradiation of the caged compound even at high concentrations.
3. Compounds of this type are easily synthetically accessible, which is an extremely desired feature for the protective group.

Scheme 3.2



3.3a-d **3.4** **3.5**

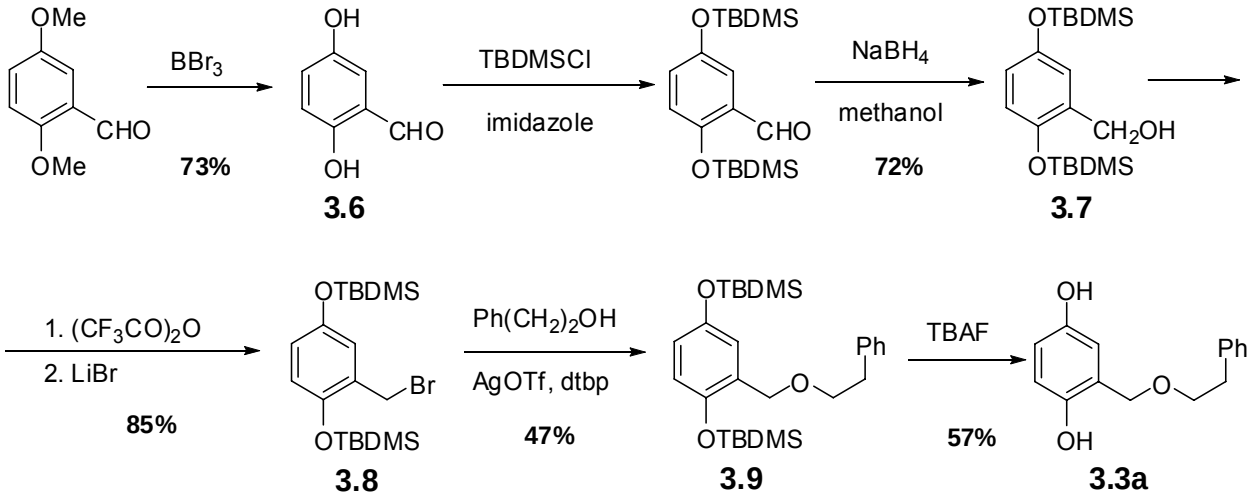
R= (a) $PhCH_2CH_2$; (b) *p*-Cl-C_6H_4; (c) PhCO; (d) $(CH_3)_3CCO$

In order to examine the ability of the DHB group to photochemically release hydroxyl-containing substrates we needed to synthesize a series of protected compounds. We focused our attention on alkyl ethers, aryl ethers and esters of dihydroxybenzyl alcohol. To be able to monitor released substrates by means of HPLC we chose the ones, containing phenyl rings: 2-phenylethanol, 4-chlorophenol and benzoic acid as the model alcohol, phenol and carboxylic acid, respectively. We also synthesized dihydroxybenzyl pivalate.

Compound **3.3a** was synthesized via two independent routes. The first approach starts with protection of dihydroxybenzaldehyde **3.6** with *t*-butyldimethylsilyl group[12] followed by successful reduction with sodium borohydride to afford the corresponding

alcohol **3.7** with 72% yield over two steps. The latter was converted into the bromide **3.8** in two step *via* trifluoroacetate with 85% yield.[13] Etherification with 2-phenylethanol in presence of silver triflate and di-*tert*-butylpyridine[14] afforded benzyl ether **3.9** which upon deprotection by tetrabutylammonium fluoride in THF gave 2-phenethyloxymethyl-1,4-hydroquinone **3.3a** (scheme 3.3).[15]

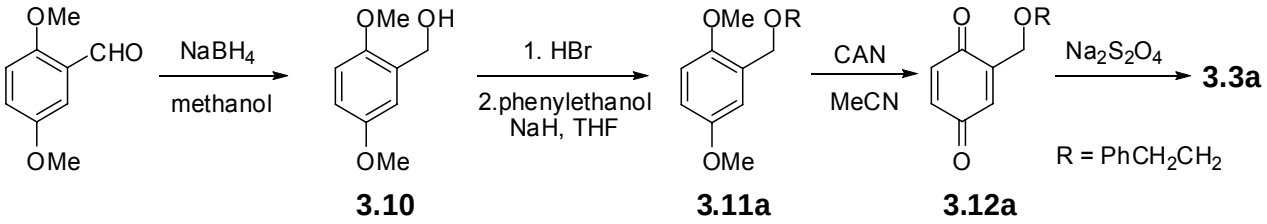
Scheme 3.3



This 7-step procedure, using some exotic and expensive reagents, is inconvenient for introduction of the protecting group and another shorter, straightforward sequence was developed and successfully applied. 2,5-Dimethoxybenzyl alcohol **3.10**, readily available by reduction of the corresponding aldehyde, was converted into 2,5-dimethoxybenzyl bromide,[16] which was then reacted with 2-phenylethoxide in THF[17] to afford **3.11a**. 1,4-Dimethoxy-2-phenethyloxymethylbenzene was converted into corresponding quinone **3.12a** by the oxidation with ceric ammonium nitrate (CAN).[18] The hydroquinone **3.3a** was prepared by reduction of 2-phenethyloxymethylbenzo-1,4-quinone with sodium dithionite in a bi-phasic water-chloroform system (Scheme 3.4).[19]

This two step procedure is exclusively suitable for demethylation of 1,2- and 1,4-dimethoxyarenes providing the corresponding hydroquinones in high yields.

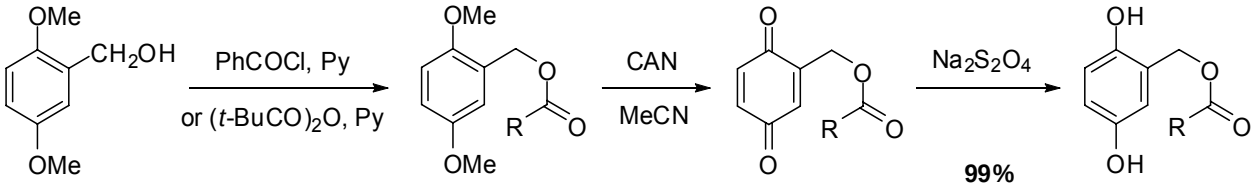
Scheme 3.4



3.10 **3.11a** **3.12a**

A similar sequence was applied for the syntheses of **3.3c** and **d**. 2,5-Dimethoxybenzyl alcohol **3.10** was acylated with either benzoyl chloride or pivalic anhydride. The resulting esters **3.11c** and **d** were oxidized with cerium ammonium nitrate (CAN), yielding quinones **3.12c, d**, respectively, which were then reduced with sodium dithionite in quantitative yields, giving desired esters **3.3c** and **d** (scheme 3.5).

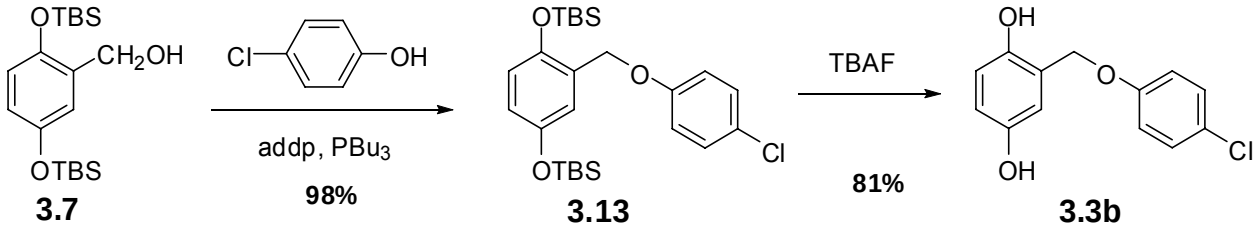
Scheme 3.5



3.10 **3.11 c R=Ph** **d R=*t*-Bu** **3.12c R=Ph** **d R=*t*-Bu** **3.3 c R=Ph** **d R=*t*-Bu**

2-(4-Chloro-phenoxymethyl)-1,4-hydroquinone was obtained from benzyl alcohol **3.7** in 2 steps. A modified Mitsunobu coupling (azodicarbonyldipiperidine, tributyl phosphine)[20] with 4-chlorophenol afforded **3.13**, which was then deprotected by TBAF to obtain the desired ether **3.3b** with 80% overall yield (scheme 3.6). It is noteworthy that the same set of reactions with 4-nitrophenol failed on the deprotection step, yielding the starting phenol back.

Scheme 3.6



2,5-Dihydroxybenzyl-caged compounds **3.3a-d** are stable in the dark in the solid state, as well as in acetonitrile-water or methanol solutions. UV spectra of these compounds contain the characteristic band of 2,5-dihydroxybenzyl group at λ_{max} = 297 nm. The expected product of the uncaging reaction, methyl p-benzoquinone **3.5**, has virtually no absorption at this wavelength (Figure 3.1).

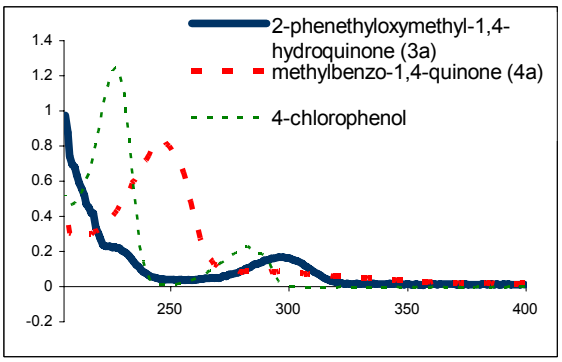


Figure 3.1. UV-spectra of ca. $5*10^{-5}$ M methanol solutions of **3.3a** (solid line), methylbenzoquinone (**3.5**, dashed line), and p-chlorophenol (dotted line).

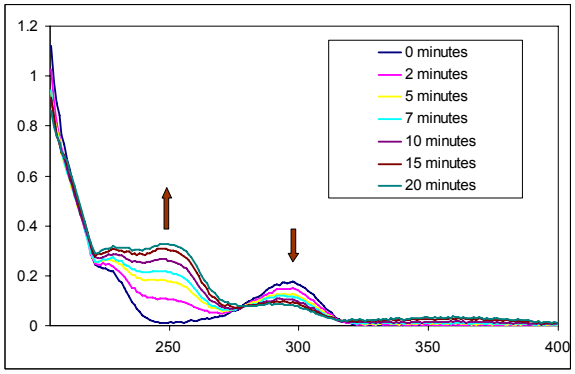


Figure 3.2. Photochemical decomposition of **3.3a** ($5*10^{-5}$ M solution in methanol).

Irradiation of ca. 0.001 M solutions of compounds **3.3a-d** in various solvents using 300 nm light resulted in the rapid bleaching of the 297 nm band and the formation of a new band at 246 nm, which corresponds to methyl *p*-benzoquinone (**3.5**, Figure 3.2). The release of substrates was monitored by HPLC or GC, while the quantum yields of un-caging were calculated using chemical actinometry (Table 3.1).[21]

The photo-deprotection of 2,5-dihydroxybenzyl caged substrates is quite efficient ($\Phi_{300\ nm}$ = 0.2 - 0.5), with the exception of benzoic acid. We believe that relatively low quantum and chemical yields of substrate release from **3.3c** can be explained by energy transfer from the caging chromophore to the benzoate moiety. Pivalic acid, for which such process is not viable, was deprotected quantitatively. The yield of *p*-chlorophenol at complete consumption of **3.3b** was in the range of 50 – 60% and HPLC analysis of reaction mixture indicated the presence of numerous minor by-products. This can be explained by secondary photochemical decomposition of the phenol since its longer wavelength band (λ_{max} = 290 nm, dotted line in Fig. 3.1) overlaps with the emission of the source. In fact, the yield of *p*-chlorophenol at 40% conversion of **3.3b** is above 80%.

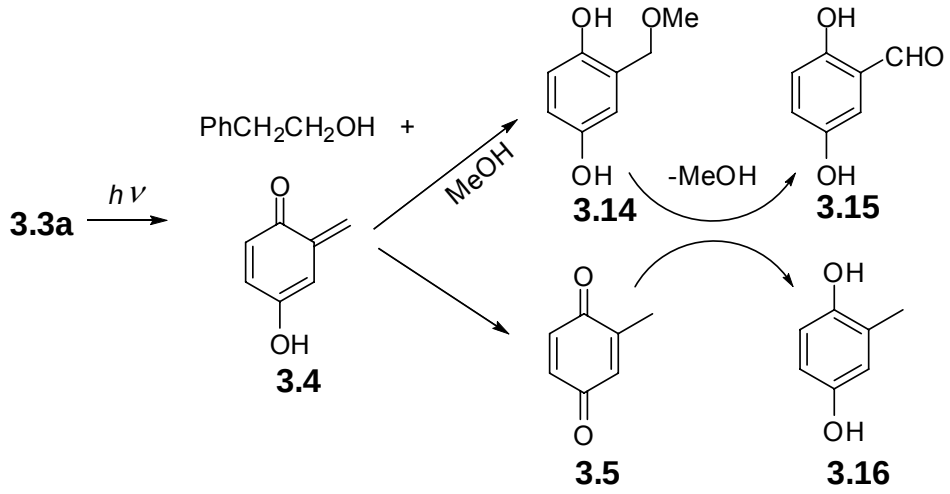
Table 3.1. Photochemical release of substrates from caged compounds **3.3a-d**

	Solvent	$\lambda_{Irradiation}$ (nm)	Φ (%)	Yield of the substrate (%)	Yield of quinone **6** or $\mathbf{6_N}$ (%)
3.3a	MeOH	300	19	79	28
	MeCN / H_2O[a)]	300	30	80	traces
3.3b	MeOH	300	31	49	14
	MeOH / H_2O[a)]	300	50	58 (84)[b)]	26
3.3c	MeOH	300	6	59	21
	MeCN / H_2O[a)]	300	11	55	traces
3.3d	H_2O	300	31	Quantitative	traces

[a)] 1/1 ratio; [b)] 40% conversion

While deprotection of hydroxyl compounds from **3.3a**-**d** works well and is accompanied by pronounced bleaching of the cage chromophore, the formation of expected 2-methyl benzoquinone never exceeded 30% in methanol and only traces were observed in aqueous reaction mixtures (Table 3.1). Moreover, the bleaching of the band at 297 nm in UV spectra is not complete as can be clearly seen from the plot (Figure 3.2). To test whether **3.5** undergoes subsequent photoconversion under steady-state irradiation, we have conducted preparative photolyses of **3.3a** under various conditions. Irradiation of **3.3a** in the flow photoreactor[21] allowed us to achieve complete conversion of the starting material but limit exposure of the photoproducts. Only methyl *p*-quinone (**3.5**) and 2,5-dihydroxybenzyl methyl ether **3.14** (in addition to 2-phenylethanol) were isolated from the photolysate. Ether **3.14** is apparently formed by a competitive nucleophilic addition of methanol to the transient quinone methide **3.4** (Scheme 3.7).

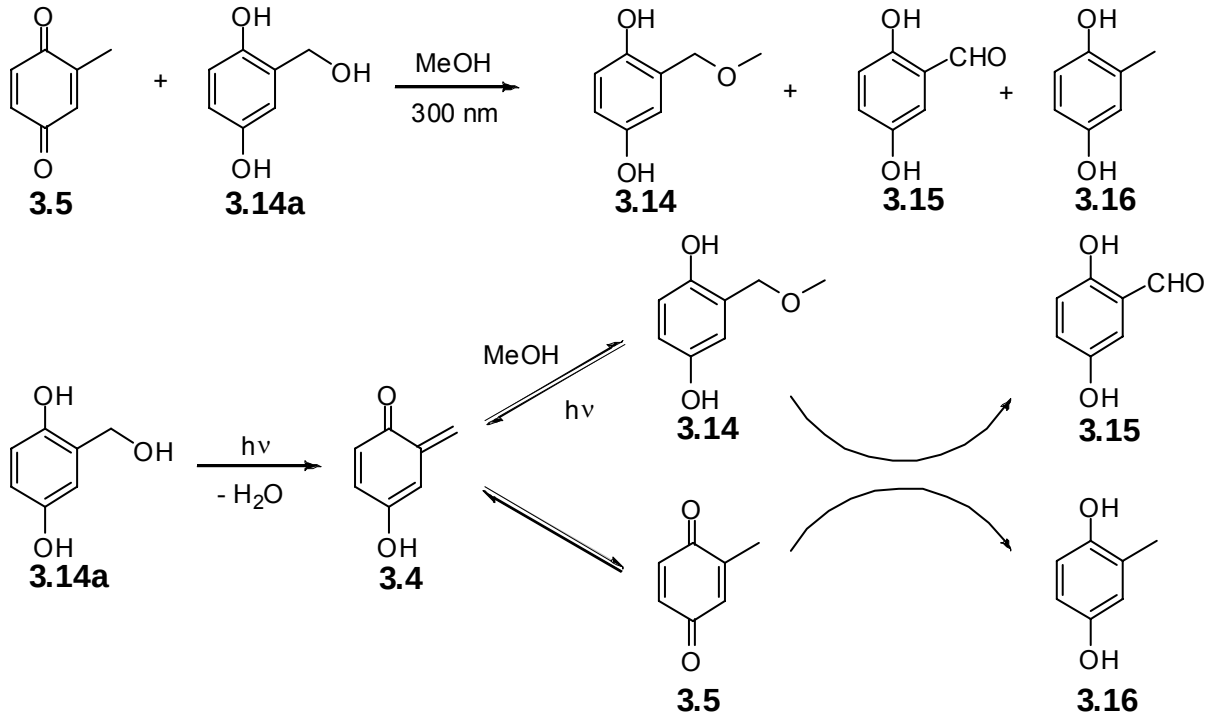
Scheme 3.7



After 1 hour of steady-state irradiation of a methanol solution of **3.3a** with a 450 W medium-pressure Hg lamp, the reaction mixture did not contain compounds **3.5** or **3.14**. 2,5-Dihydroxybenzaldehyde (**3.15**) and methyl-*p*-hydroquinone (**3.16**) were the only isolated by-products. These observations suggest that quinone **3.5** oxidizes methyl benzyl ether **3.14** to aldehyde **3.15** in a photochemically-driven redox reaction. In aqueous solution quinone **3.5** can be detected by HPLC at low conversion of the substrate but only **3.15** and **3.16** are isolated after uncaging of the substrate is complete. Apparently, the oxidation of 2,5-dihydroxybenzyl alcohol, which is expected to be produced in the presence of water, is much faster than that of **3.14**. This photochemical reaction also explains the residual band at 300 nm in the UV spectra of the irradiated reaction mixture, which corresponds to the absorption of hydroquinone **3.16**.

In order to test this suggestion we conducted co-irradiation of 2,5-dihydroxybenzyl alcohol **3.14a** and methyl-*p*-quinone in methanol at 300 nm and monitored this reaction by GCMS. We observed rapid accumulation of methyl benzyl ether **3.14**, concomitant with the disappearance of the corresponding alcohol. On longer irradiation, peaks corresponding to quinone and **3.14** slowly disappeared, giving rise to dihydroxybenzaldehyde (**3.15**) and methyl-*p*-hydroquinone (**3.16**) (Scheme 3.8). Thus, an interesting example of a photochemically induced formal disproportion reaction has been revealed.

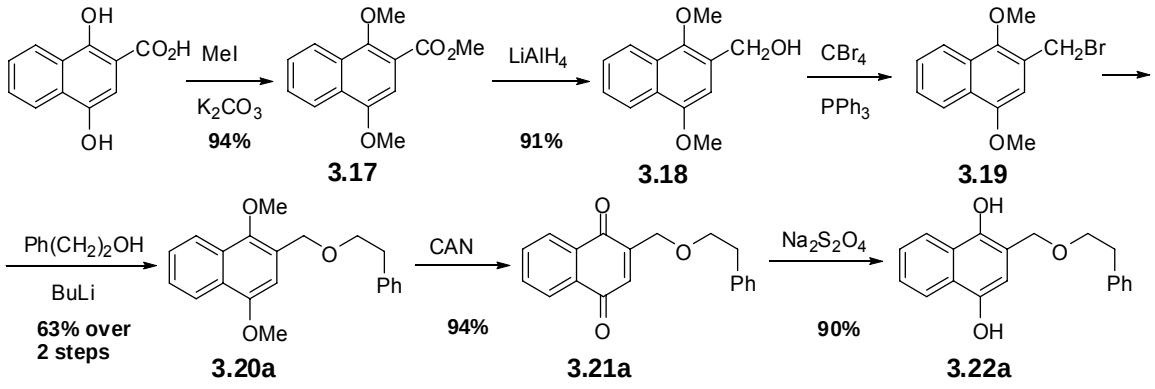
Scheme 3.8



3.1.3. 1,4-Dihydroxy-2-naphthylmethyl (DHNM) protecting group. In order to increase the chemical yield of phenol and benzoic acid release and make it more suitable for biochemical applications we have to modify the DHB protecting group so that it can be irradiated at longer wavelength. This can be achieved by proper substitution in the phenyl ring or by utilizing the higher conjugated naphthalene system. We have chosen the second strategy and developed another photolabile protecting group – 1,4-dihydroxy-2-naphthylmethyl (DHNM). In addition to the bathochromic shift of the λ_{max} we expected a larger extinction coefficient of this chromophore compared to DHB. This, in turn, leads to improvement of the effective quantum yield which is simply the combination of photolysis quantum yield (Φ) and extinction coefficient (ε).[22]

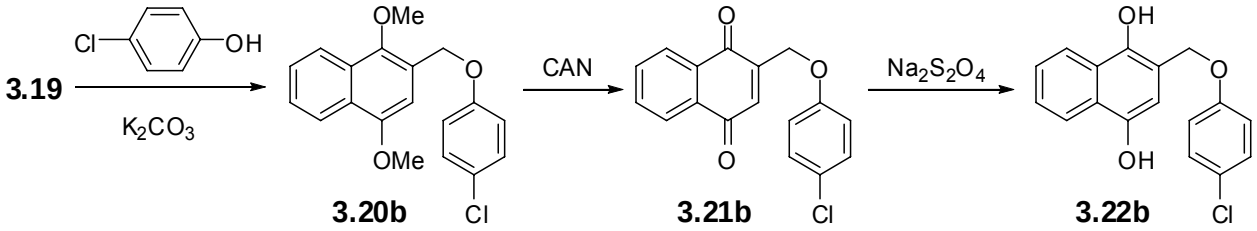
The general synthetic approach to the series of DHNM-caged compounds is nearly identical to the procedures used for the series **3.3a-d**. The synthetic sequence started with commercially available 1,4-dihydroxy-2-naphthoic acid, which was treated with iodomethane in the presence of potassium carbonate in refluxing acetone. The resulting methyl 1,4-dimethoxy-2-naphthoate **3.17** was reduced with lithium aluminum hydride to the corresponding alcohol **3.18**,[23] which was converted to the bromide **3.19**[24] upon treatment with carbon tetrabromide in the presence of triphenyl phosphine. The reaction of the 1,4-dimethoxy-2-naphthylmethylbromide with 2-phenylethoxide anion in THF lead to the formation of ether **3.20a** which was then successfully deprotected in two steps yielding the desired 2-phenethyloxymethyl-1,4-hydronaphthoquinone **3.22a** (45% overall yield, Scheme 3.9). Considering the stability of the bromide **3.19**, the alcohol is protected in three easy steps, giving a high yield of the protected substrate.

Scheme 3.9



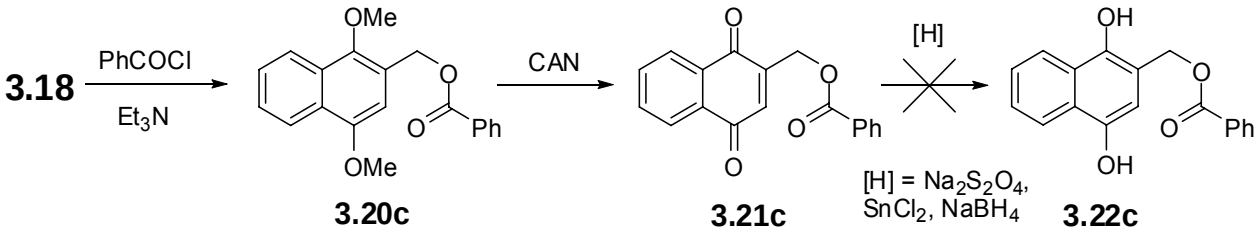
Similarly, 2-(4-chlorophenoxymethyl)-1,4-hydronaphthoquinone **3.22b** was obtained by conversion of naphthylmethyl bromide **3.19** into phenyl ether **3.20b** upon refluxing it with 4-chlorophenol in acetone in presence of potassium carbonate, followed by the two-step oxidative demethylation (59% overall yield, Scheme 3.10).

Scheme 3.10



Interestingly, the corresponding ester 1,4-dihydroxy-naphthalen-2-ylmethyl benzoate **3.22c** is synthetically inaccessible. The corresponding quinone **3.21c** was obtained by benzoylation of alcohol **3.18** followed by oxidation with CAN. However reduction of **3.21c** with various agents such as sodium dithionite, stannous chloride or sodium borohydride leads to complicated mixture of products with no traces of **3.22c**. We believe that because of the good ability of the carboxylate leaving group this compound decomposes upon formation, undergoing the same type of chemistry as **3.22a** and **b** in the dark (Scheme 3.11).

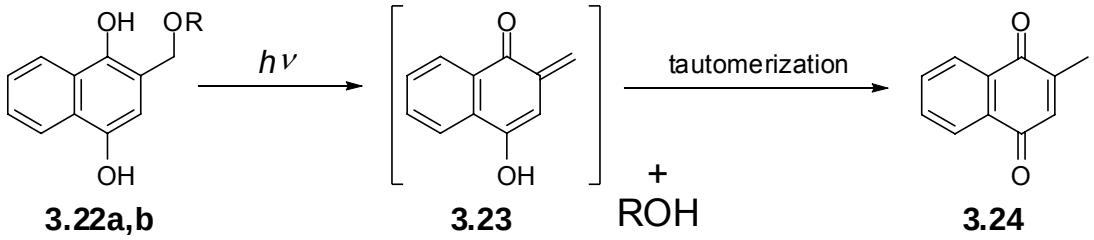
Scheme 3.11



The absorbance of the (1,4-dihydroxy-2-naphthyl)methyl chromophore extends up to 400 nm, allowing for the use of longer wavelengths for uncaging than in the case of the 2,5-dihydroxybenzyl chromophore (Figure 3.3). The liberation of the substrate is accompanied with the transient formation of naphthoquinone methide **3.23**, whose

behaviour should resemble benzoquinone methide **3.4**. Formation of methyl naphthoquinone was therefore highly anticipated (**3.24**, Scheme 3.12).

Scheme 3.12



3.22a,b **3.23** **3.24**

R= (a) $PhCH_2CH_2$; (b) *p*-Cl-C_6H_4

Irradiation of **3.22a** at either 300 or 350 nm results in bleaching of the starting material (Figure 3.3) and efficient deprotection of the substrate (Table 3.2). In aqueous acetonitrile, release of 2-phenylethanol is almost quantitative, while yields are slightly lower in methanol. Photolysis of (1,4-dihydroxy-2-naphthyl)methyl - caged *p*-chlorophenol **3.22b** at 350 nm regenerated the substrate in 85% yield at full conversion. This result supports the suggestion that the poor yield of *p*-chlorophenol in high conversion photolysis of **3.3b** is due to secondary photochemical transformations of the substrate (Table 3.2).

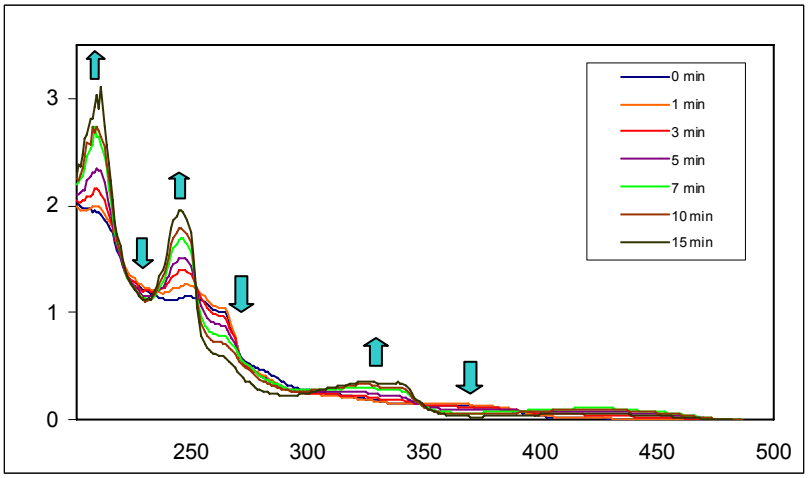


Figure 3.3. Photochemical decomposition of **3.22a** ($5*10^{-5}$ M solution in methanol).

Table 3.2. Photochemical release of substrates from caged compounds **3.22a,b**

	Solvent	$\lambda_{Irradiation}$ (nm)	Φ (%)	Yield of the substrate (%)	Yield of quinone **3.24**
3.22a	MeOH	300	31	99	43
	MeOH	350	29	94	35
	MeCN / H_2O[a)]	300	20	87	traces
	MeCN / H_2O[a)]	350	25	70	traces
3.22b	MeOH	350	7	85	traces

As with compounds **3.3a-d**, the formation of methyl 1,4-naphthoquinone **3.24** was observed only in methanol. The overall photochemical process, however, is more complicated and along with naphthoquinone and released substrate we detected 1,4-dimethoxy-2-methoxymethyl naphthalene and 1,4-dimethoxy-2-naphthaldehyde. The formation of these products could be explained by the nucleophilic addition of methanol to the transient quinone methide followed by photochemical methylation of the resulting hydroquinone.

The poor stability of the compounds **3.22a,b** is disappointing. Derivatives of 1,4-hydronaphthoquinone are labile towards oxidation with air, unless they have strong electron withdrawing substituents. DHNM derivatives are not exceptions and therefore care should be taken when these compounds are isolated. They have to be kept under inert gas, preferably in dilute solution or irradiated right away. This, indeed, is a serious drawback for any protective group, which has to be relatively stable towards various conditions by definition. Naphthoquinone precursors **3.21a**,**b**, on the other hand, are perfectly stable in solution and in the solid state. The photochemical stability of these quinones is also noteworthy. Irradiation of these compounds at 300 or 350 nm for the

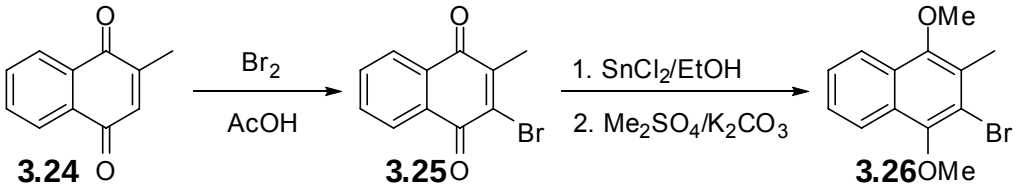
period of time required for the complete consumption of and **3.22a**,**b** does not result in any detectable decomposition of quinones or release of the caged substrates. Since quinones **3.21a**,**b** are quantitatively reduced to the target hydroquinones **3.22a**,**b** under very mild conditions, stable protecting groups can be generated *in situ* by using a suitable reducing agent.

Overall, the (1,4-dihydroxy-2-naphthyl)methyl protecting group provides better yields of photochemical release of the substrates, especially for phenols. Moreover, shifting irradiation to the 350 nm wavelength without sacrificing the quantum yield makes this protective group suitable for physiological applications. The fact that this group suffers from somewhat lower hydrolytic stability than 2,5-hydroxybenzyl derivatives can be alleviated by *in situ* arming of the perfectly stable naphthoquinones **3.21a**,**b** by simple reduction.

3.1.4. 2-Cyano-1,4-dihydroxy-3-naphthylmethyl (CDHNM) protecting group. Strong electron-withdrawing groups are known to stabilize the naphthohydroquinone moiety. We decided to introduce such EWG into the DHNM photolabile protecting group, which suffers from poor stability towards oxidation. The other reason for such substitution was to shift the wavelength of absorption maximum further to the red region of the UV spectrum. Among the groups we intended to introduce into the naphthalene ring were -Br; -CF_3; -CN and -SO_3R, where R = CH_3 or H. The synthetic approach to these compounds started with the bromination of menadione (**3.24**) in acetic acid in the presence of anhydrous sodium acetate.[25] The resulting 2-bromo-3-methyl-1,4-naphthoquinone **3.25** is converted into the corresponding dimethoxynaphthalene **3.26** in

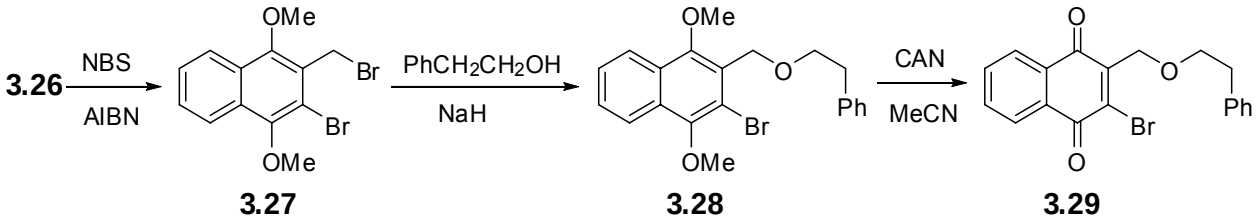
two steps using reduction with stannous chloride followed by methylation with dimethyl sulfate (Scheme 3.13).[26]

Scheme 3.13



The resulting 2-bromo-1,4-dimethoxy-3-methyl-naphthalene was used as a precursor for several synthetic sequences. First of all, it was used in synthesis of the 3-bromo substituted analog of (1,4-dihydroxy-2-naphthyl)methyl protected substrates. **3.26** was treated with *N*-bromosuccinimide in presence of a radical chain initiator to obtain dibromoderivative **3.27**,[27] which was then converted to the phenethyl ether **3.28** using standard procedure. 2-Bromo-1,4-dimethoxy-3-phenethyloxymethylnaphthalene **3.28** was then oxidized to the corresponding quinone **3.29** (Scheme 3.14). Unfortunately, the hydronaphthoquinone obtained by the reduction of 2-bromo-3-phenethyloxymethyl-1,4-naphthoquinone does not possess greater stability than derivative **3.22a**, quickly oxidizing to the complicated mixture of products. This is probably because bromine is not strong enough of an electron-withdrawing group to make these derivatives stable toward oxidation. We therefore decided not to investigate this type of compound in terms of their photolability because we did not expect results to be much different from the DHNM photocage.

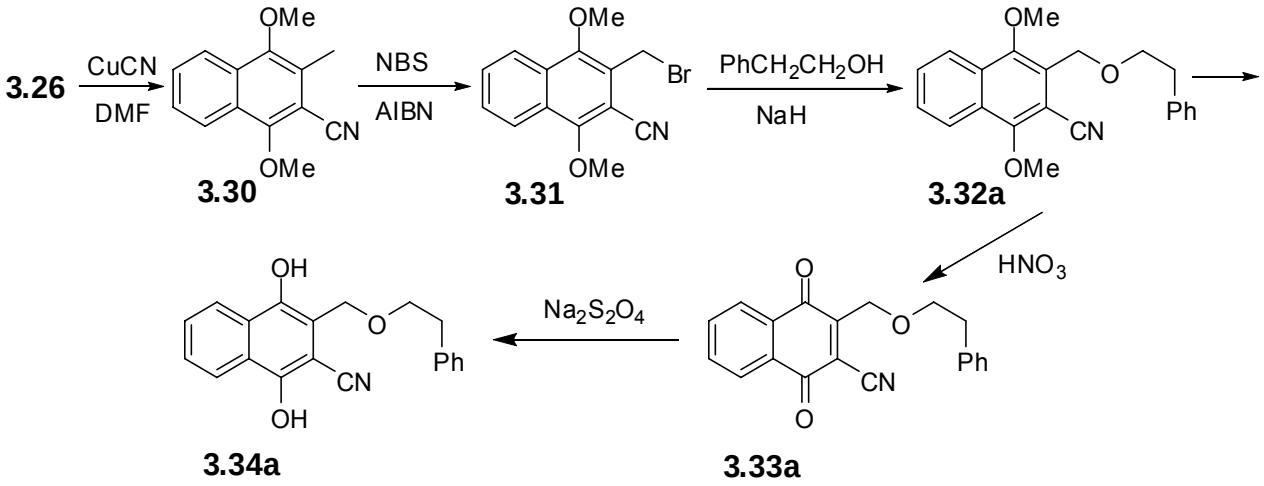
Scheme 3.14



3.27 **3.28** **3.29**

Compound **3.26** may undergo aromatic nucleophilic substitution with various agents. Thus treatment of **3.26** with cupric cyanide in DMF leads to 2-cyano-1,4-dimethoxy-3-methyl-naphthalene **3.30**.[28] Bromination of the latter with *N*-bromosuccinimide in carbon tetrachloride followed by treatment with 2-phenethyloxide anion in THF afforded 2-cyano-1,4-dimethoxy-3-phenethyloxymethylnaphthalene **3.32a**. Oxidation of this compound with cerium ammonium nitrate failed to give the corresponding quinone **3.33a**, but worked well when concentrated nitric acid was used as an oxidant instead.[29] Finally, 2-cyano-3-phenethyloxymethyl-1,4-naphthoquinone was reduced with sodium dithionite to the corresponding naphthohydroquinone **3.34a** (Scheme 3.15).

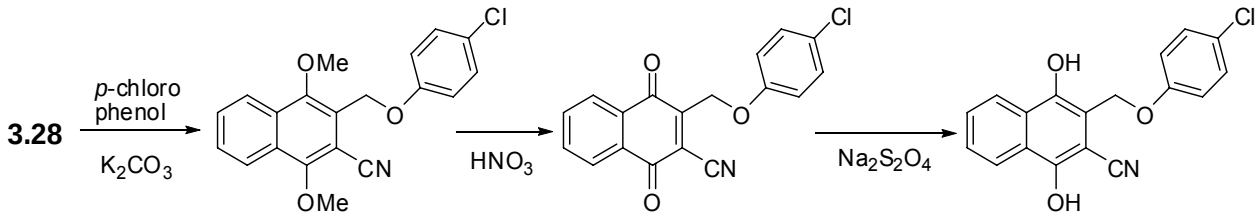
Scheme 3.15



3.30 **3.31** **3.32a** **3.33a** **3.34a**

Similarly, 2-cyano-3-(4-chlorophenoxymethyl)-1,4-hydronaphthoquinone **3.31b** was obtained from the naphthylmethyl bromide **3.28** by treatment with 4-chlorophenoxide anion followed by two step demethylation:

Scheme 3.16



3.32b **3.33b** **3.34b**

The solid-state stability of the 2-cyano-1,4-dihydroxy-3-naphthylmethyl (CDHNM) derivatives **3.34 a,b** is remarkably higher compared to the unsubstituted analogues **3.22a,b**. These compounds could be isolated and do not undergo oxidation upon standing on air. We therefore were able to explore them in terms of their photolytic decomposition and ability to release the corresponding substrates. The solution of **3.34a** in methanol was irradiated at 362 nm (Figure 3.4), and as in previous case, the reaction mixture after photolysis was analyzed using HPLC. The yield of photochemical release of 2-phenylethanol is comparable to the previously discussed photocages; however, the quantum yield is somewhat lower. Compound **3.34a** also suffers from relatively low hydrolytic stability, as conversion of the starting material after 24 hours in the dark was 15%. Compound **3.34b** quickly solvolyzes in methanol, so in order to obtain the release of *p*-chlorophenol we had to irradiate the solution in THF (Figure 3.4) where the irradiated compound is relatively stable. We managed to determine the yield of the phenol which was only about 50%, much lower than anticipated.

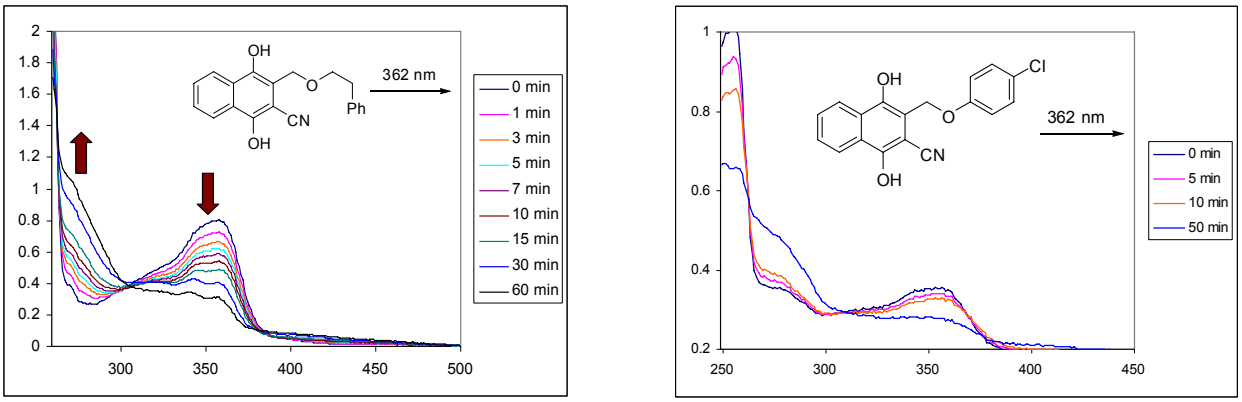
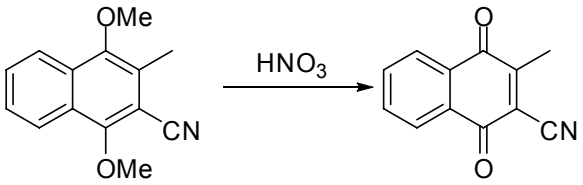


Figure 3.4. Photochemical decomposition of the CDHNM protected **3.34a** and **b**.

The photochemical behaviour of CDHNM compounds **3.34a** and **b** differs from the pathway observed for the DHB and DHNM protective groups. Thus, the expected by-product 2-cyano-3-methylnaphtho-1,4-quinone **3.35**, which was independently synthesized by oxidation of **3.30** (Scheme 3.17), is not formed under any circumstances probably due to the strong interference of the cyano group with the formation or reactivity of the quinone methide

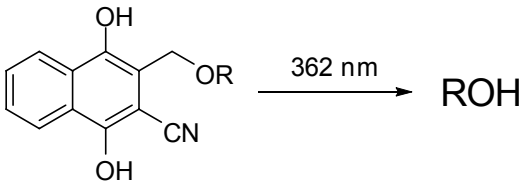
Scheme 3.17



3.30 **3.35**

Quantitative data collected from the analysis of the reaction mixtures after photolyses of the compounds **3.34a** and **b** (scheme 3.18) are summarized in table 3.3

Scheme 3.18



3.34a,b

Table 3.3. Photochemical release of substrates from caged compounds **3.34a,b**

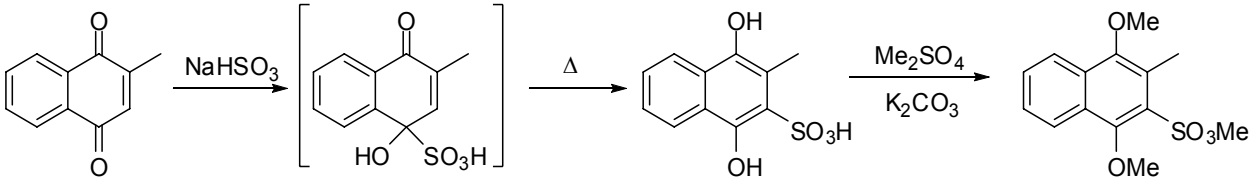
	Solvent	$\lambda_{Irradiation}$ (nm)	Φ (%)	Yield of the substrate (%)	Yield of quinone **3.35**
3.34a	MeOH	362	4	87	0
3.34b	MeOH	362	N/A	decomposes in the dark	0
3.34b	THF	362	N/A	48	0

The main disadvantage of the CDHNM photolabile protecting group is poor hydrolytic stability. Apparently, the introduction of a strong electron-withdrawing cyano group into the aromatic ring makes the phenolic hydrogen in the ground state acidic enough to promote slow elimination of the leaving group. On the other hand, stability towards oxidation and longer wavelength, required for deprotection of the hydroxyl-containing compounds makes CDHNM an attractive group for protection of poor leaving groups such as alcohols.

We also attempted to develop water-soluble derivatives of the DHNM photolabile protecting groups. Introduction of a highly polar sulfonate group should drastically increase the aqueous solubility of such derivatives. We started our synthetic route from the known synthesis of 1,4-dihydroxy-3-methylnaphthalene-2-sulfonic acid **3.36**.[30] The

methylation of **3.36** with an excess of dimethyl sulfate afforded methyl 1,4-dimethoxy-3-methylnaphthalene-2-sulfonate **3.37** (Scheme 3.19)

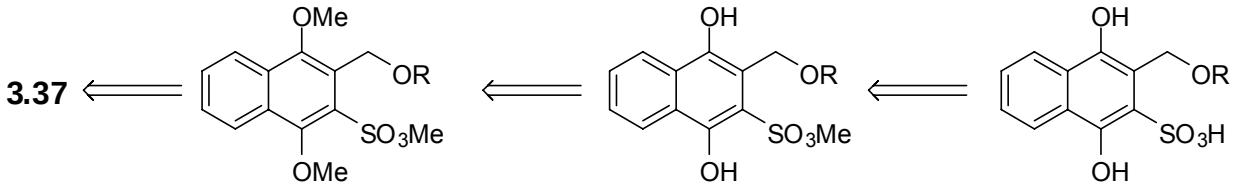
Scheme 3.19



3.36 **3.37**

Our original synthetic scheme included radical benzylic bromination of **3.37** followed by etherification with 2-phenethyloxide or *p*-chlorophenoxide anion, demethylation of the resulting product and final hydrolysis to obtain sulfonic acid (Scheme 3.20).

Scheme 3.20

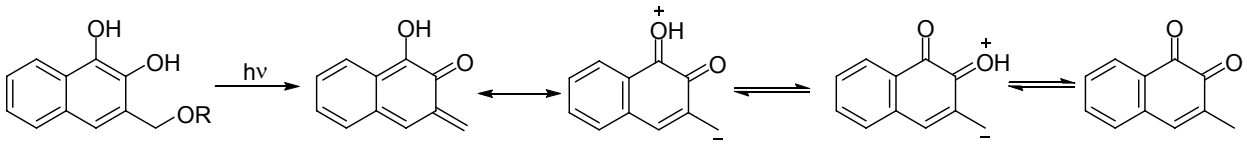


The product of bromination of **3.37** is not stable on silica gel and therefore was not isolated. Treatment of the latter with phenylethoxide did not yield the desired methyl sulfonate, giving instead a messy mixture of products. Definitely, the methoxysulfonyl group somehow interferes with the reactivity of benzyl bromide and leads to the products of either intra- or intermolecular re-esterification.

3.1.5. 1,2-Dihydroxy-3-naphthylmethyl (iDHNM) protecting group. Since 1,4- and 1,2-hydroquinones are very similar compounds we decided to explore the photochemistry of 1,2-dihydroxy-3-naphthylmethyl derivatives, regioisomers of 1,4-dihydroxy-2-naphthylmethyl derivatives. These compounds are more stable than 1,4-

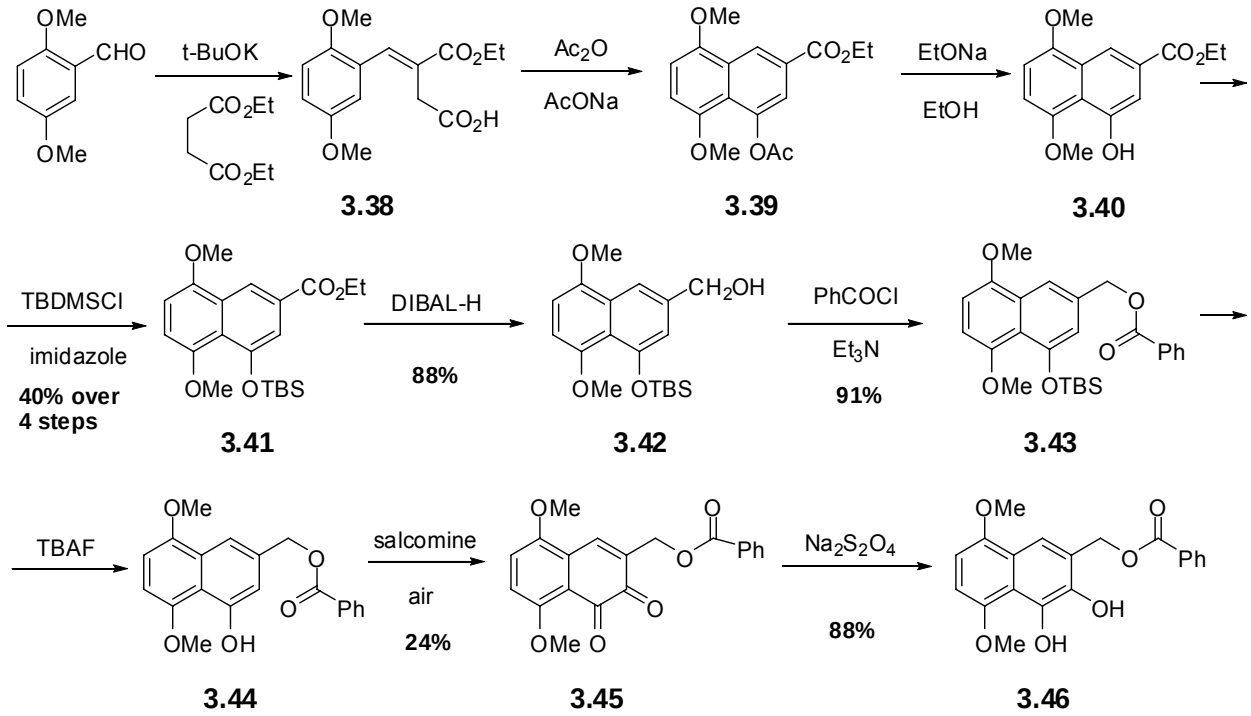
naphthohydroquinones. Furthermore, we proposed the assistance of the carbonyl group in tautomerization of the intermediate hydroxyl quinone methide as represented on scheme 3.21. The hydrogen transfer proceeds intramolecularly bypassing the necessity of using protic solvents.

Scheme 3.21



Compound **3.39** was prepared from commercially available 2,5-dimethoxybenzaldehyde and diethyl succinate by application of standard Stobbe condensation conditions (potassium *tert*-butoxide in *tert*-butanol or sodium hydride in toluene) followed by cyclization of **3.38** in acetic anhydride. The resulting acetate was re-esterified with sodium ethoxide in ethanol and then naphthol **3.40** is protected with the *t*-butyldimethylsilyl group to afford **3.41** in 40% over 4 steps.[31a,b] The reduction of the latter with DIBAL-H produces naphthylmethanol **3.42** in 88% yield, which is benzoylated to affords **3.43**. Deprotection of the TBDMS group with tetrabutylammonium fluoride followed by salcomine-catalyzed aerial oxidation,[31b,c] produces the brightly red colored *o*-naphthoquinone **3.45**. Reduction of the latter leads to the desired 3,4-dihydroxy-naphthalen-2-ylmethyl benzoate **3.46** with 7% overall yield (Scheme 3.22).

Scheme 3.22



A solution of 3,4-dihydroxy-5,8-dimethoxy-naphthalen-2-ylmethyl benzoate in THF (9.23×10^{-4}M) or THF/water (1/1, 9.23×10^{-4}M) was irradiated in a Rayonet photoreactor with 362 nm lamps. The reaction mixture was analyzed by HPLC and quantum and chemical yields of deprotection were calculated. The data are summarized in the table 3.4.

Table 3.4. Photochemical release of the substrate from caged compound **3.46**

Solvent	$\lambda_{Irradiation}$ (nm)	Φ (%)	Yield of the acid (%)	Yield of quinone **3.47**
THF	362	2.8	70[a]	N/A
THF/H2O	362	3.2	72[a]/85[b]	N/A

a – 85% conversion; b – 55% conversion.

Benzoic acid is released in 85% yield at about half-conversion, but the yield drops to only 70% at full consumption of **3.46** independently of the solvent. The very low quantum yield requires longer irradiation time and that, in turn, causes some secondary photochemical processes to take place. A possible explanation of such poor quantum yield is the presence of alternative sites for hydrogen bonding. The desired hydrogen transfer, therefore, becomes less efficient. The complicated synthesis is another problem associated with this protecting group. So far, we were not able to synthesize protected alcohols and phenols. On the other hand, the noteworthy feature of the compound **3.46** is its stability in both solid state and aqueous solution. Moreover, the suitable absorption UV spectrum makes it possible to carry out the photolysis at 362 nm (Figure 3.5).

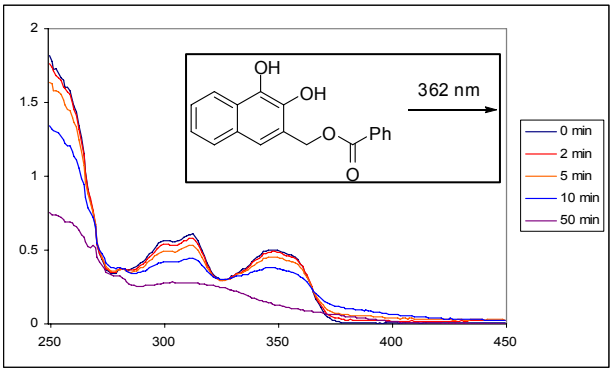
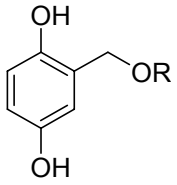
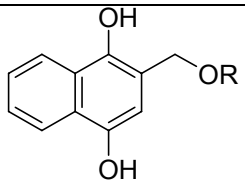
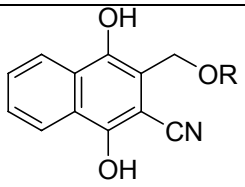
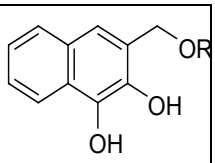


Figure 3.5. Photochemical decomposition of **3.46** ($5*10^{-5}$ solution in THF/water)

Photoremovable protecting groups for hydroxyl-containing compounds that were studied within this project are summarized in table 3.5.

Table 3.5. Summary of the explored protecting groups for hydroxyl compounds

				
Abbreviation	DHB	DHNM	CDHNM	*i*-DHNM
$\lambda_{irradiation}$	300 nm	300 or 350 nm	362 nm	362 nm
Stability in the dark	High	Poor	Very poor	High
Yield of deprotection	Depends on substrate	High	Moderate	Moderate
Quantum efficiency	High	High	Low	Low
Other advantages	1. Stable crystalline cmpd 2. pronounced bleaching at irradiation wavelength	1. Can be reductively armed from the corresponding quinones	1. Can be irradiated at long wavelengths	1. Can be irradiated at long wavelengths 2. Stable crystalline cmpd

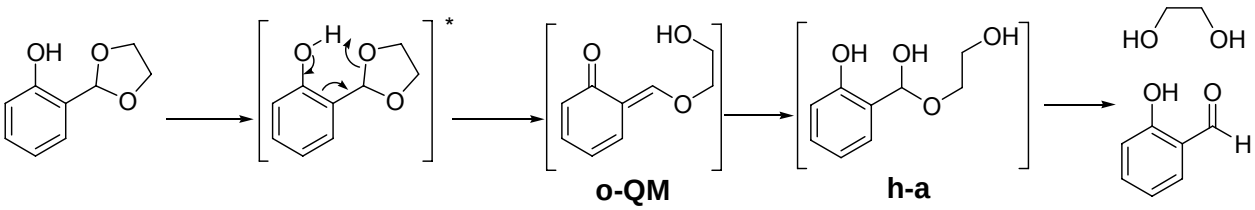
3.2. Photoremovable benzylidene protecting groups for 1,2- and 1,3-diols.

1,2- and 1,3-Diol functionalities are most often protected as acetals – 1,3-dioxanes and dioxolanes, respectively – of simple aldehydes and ketones in carbohydrate chemistry and synthesis of glycerides[32,33]. These compounds are formed upon acid-catalyzed reaction of the carbonyl compound with the corresponding glycol and are stable to relatively strong bases (alkoxides and amides), weak acids, mild oxidants and metal hydrides. Acid-catalysed hydrolysis is the most common method for the cleavage of this protecting group[33,34]. The conditions required for deprotection are quite harsh (pH ~ 1, elevated temperature)[32-34] and might lead to decomposition of the substrate. Other methods include transacetalization,[35] catalytic hydrogenation,[36] treatment with dilute solution of iodine in methanol,[37] oxidative cleavage,[38] NBS-catalyzed cleavage[39]. Apparently, if an organic molecule is sensitive to these reagents, deprotection might lead to complete degradation of the substrate. Therefore, it would be extremely beneficial for synthetic organic chemistry and especially carbohydrate chemistry to develop a photolabile protecting group for diols.

Pursuing this purpose we have explored possible application of 2-hydroxy-benzaldehydes as photoremovable protection for 1,2- and 1,3-diols. Excitation of the 2-1,3-dioxolan-2-yl-phenol (or 2-1,3-dioxan-2-yl-phenol) provides a driving force for hydrogen transfer from the phenolic to acetal oxygen to form the *ortho*-quinone methide (***o*-QM**), which then undergoes nucleophilic addition of water. The resulting hemi-acetal (**h-a**) hydrolyzes to yield the target diol and 2-hydroxy-benzaldehyde (Scheme 3.23). The conjugation of a carbonyl group with a benzene ring makes this chromophore

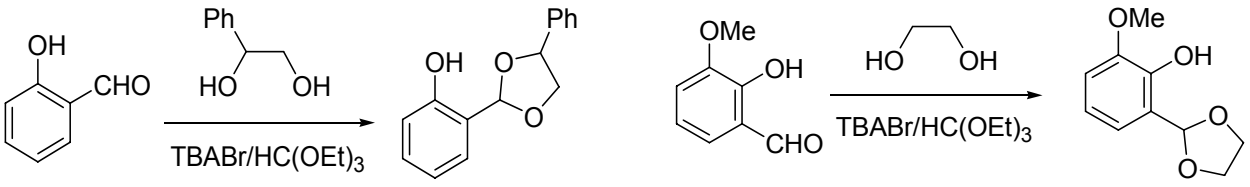
substantially different from the irradiated compound. Thus, selective irradiation can be achieved as described for previous model.

Scheme 3.23.



o-QM **h-a**

Synthesis of the cyclic acetals of *o*-hydroxybenzaldehydes is a challenging task. Azeotropic distillation of water from the reaction mixture containing such an aldehyde, diol and catalytic amount of *para*-toluenesulfonic acid in benzene or toluene produces a complicated mixture of products. Only one example of a synthetic procedure for synthesis of such compounds is reportedin the literature.[40] The reaction of salicaldehyde with a diol is carried out in triethyl orthoformate at room temperature, using a catalytic amount of tetrabutyl ammonium tribromide as the acid. This approach was successfully applied in synthesis of 2-(4-phenyl-1,3-dioxolan-2-yl)-phenol **3.48**. Unfortunately, the transparency of this compound in the UV-spectrum at both 254 and 300 nm (Figure 3.6) makes it inconvenient for irradiation in a Rayonet photoreactor. Derivatives of *o*-vanilin (2-hydroxy-3-methoxybenzaldehyde) **3.49** are not suitable as photolabile benzylidene protecting groups for the same reason (Figure 3.6).



3.48 **3.49**

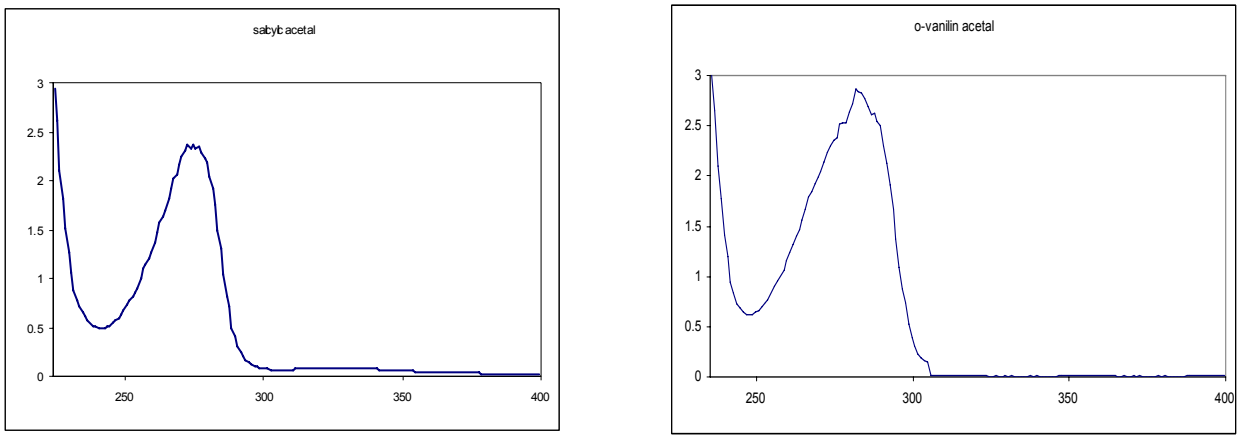
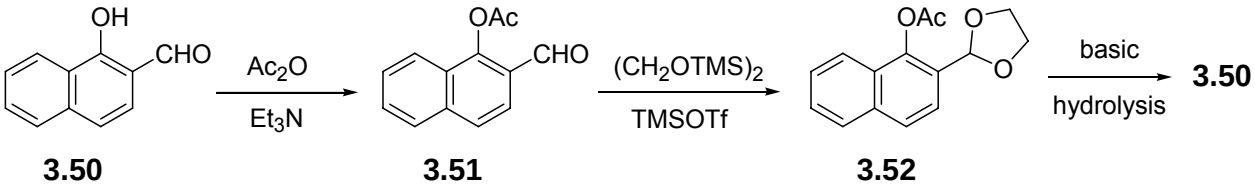


Figure 3.6. Synthesis and UV-spectra of **3.48** (left) and **3.49** (right) ($1*10^{-3}$M solution in methanol)

In order to extend the conjugation of the π-system and thus shift the absorption maxima we attempted to synthesize the acetal of 1-hydroxy-2-naphthaldehyde **3.50**. The direct approach using tetrabutyl ammonium tribromide and triethyl orthoformate failed in this case. We then tried to first protect the hydroxyl group with acetyl to obtain **3.51**, then derivatize the aldehyde with 1,2-bis-((trimethylsilyl)oxy)ethane[41] to **3.52**, and finally hydrolyze an acetate. However, the last step failed under any conditions conveniently used for hydrolysis of esters, giving 1-hydroxy-2-naphthaldehyde **3.50** back (Scheme 3.24). Thus, 2-1,3-dioxolan-2-ylnaphthalen-1-ol is synthetically inaccessible.

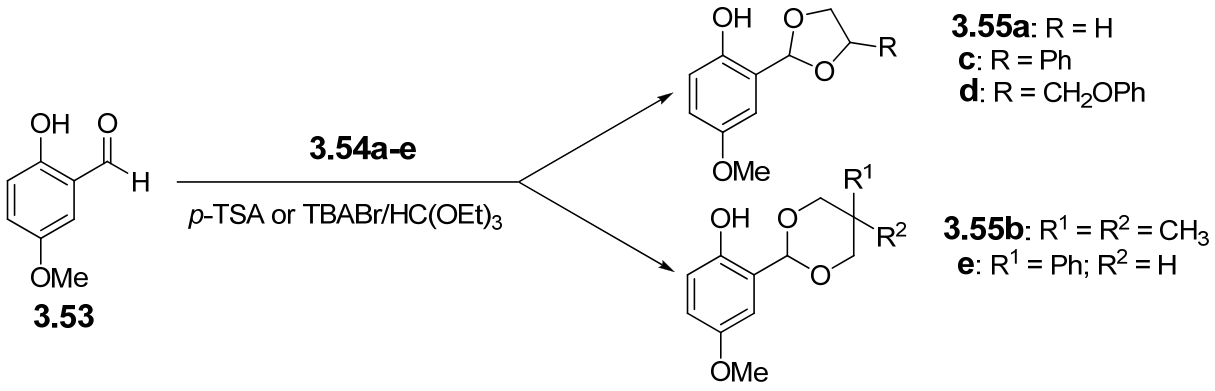
Scheme 3.24



3.50 **3.51** **3.52**

Finally, diols **3.54a-e** were protected with commercially available 2-hydroxy-5-methoxybenzaldehyde **3.53** with satisfactory yields, using either *p*-toluenesulfonic acid or tetrabutyl ammonium tribromide as an acid, triethyl orthoformate as a water-trapping agent and dichloromethane as a solvent (Scheme 3.25).

Scheme 3.25



These compounds have an absorption maximum at 295 nm (Figure 3.7), which matches the emission wavelength of the UV lamps used in a Rayonet photoreactor (300 nm). 2-Hydroxy-5-methoxybenzaldehyde, on the other hand, does not absorb at this wavelength, as is clearly seen from its UV spectra. Therefore, if the liberation of the diol, concomitant with a formation of benzaldehyde takes place upon irradiation of **3.55a-e**, we should expect pronounced bleaching at this wavelength. This is clearly the case as it is shown on the plots of photochemical decomposition of compounds **3.55a-e**. We achieved complete bleaching of the band at 300 nm, corresponding to the starting

material in less than 30 minutes of irradiation (Figure 3.7 a; c-e). The UV-spectrum of the reaction mixture after full conversion completely corresponds to that of **3.53**.

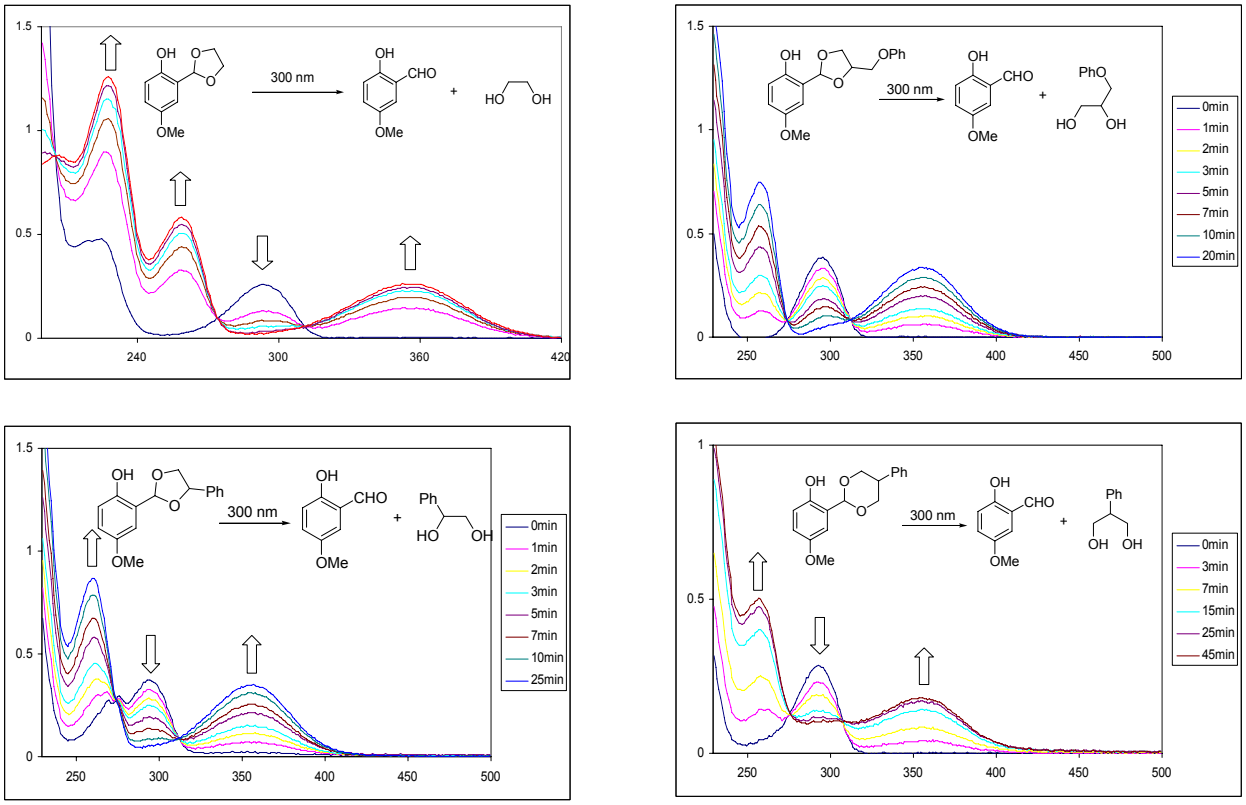


Figure 3.7. Photochemical decomposition of **3.55a** and **c-e** ($1*10^{-4}$M aqueous solutions)

We monitored the decomposition of compounds **3.55a** and **3.55b** by NMR spectroscopy. Disappearance of the dioxolane (δ ~ 5.95 ppm; **3.55a**) and dioxane proton signal (δ ~ 5.50 ppm; **3.55b**) and rising of the aldehydic proton (δ ~ 9.9 ppm) indicates decomposition of the acetals and formation of the 2-hydroxy-5-methoxybenzaldehyde **3.53**. Formation of the corresponding diols, ethyleneglycol **3.54a** and neopentylglycol **3.54b**, respectively, can also be clearly monitored. It is noteworthy that no other peaks arise upon photolysis, indicating a very clean reaction (Figure 3.8).

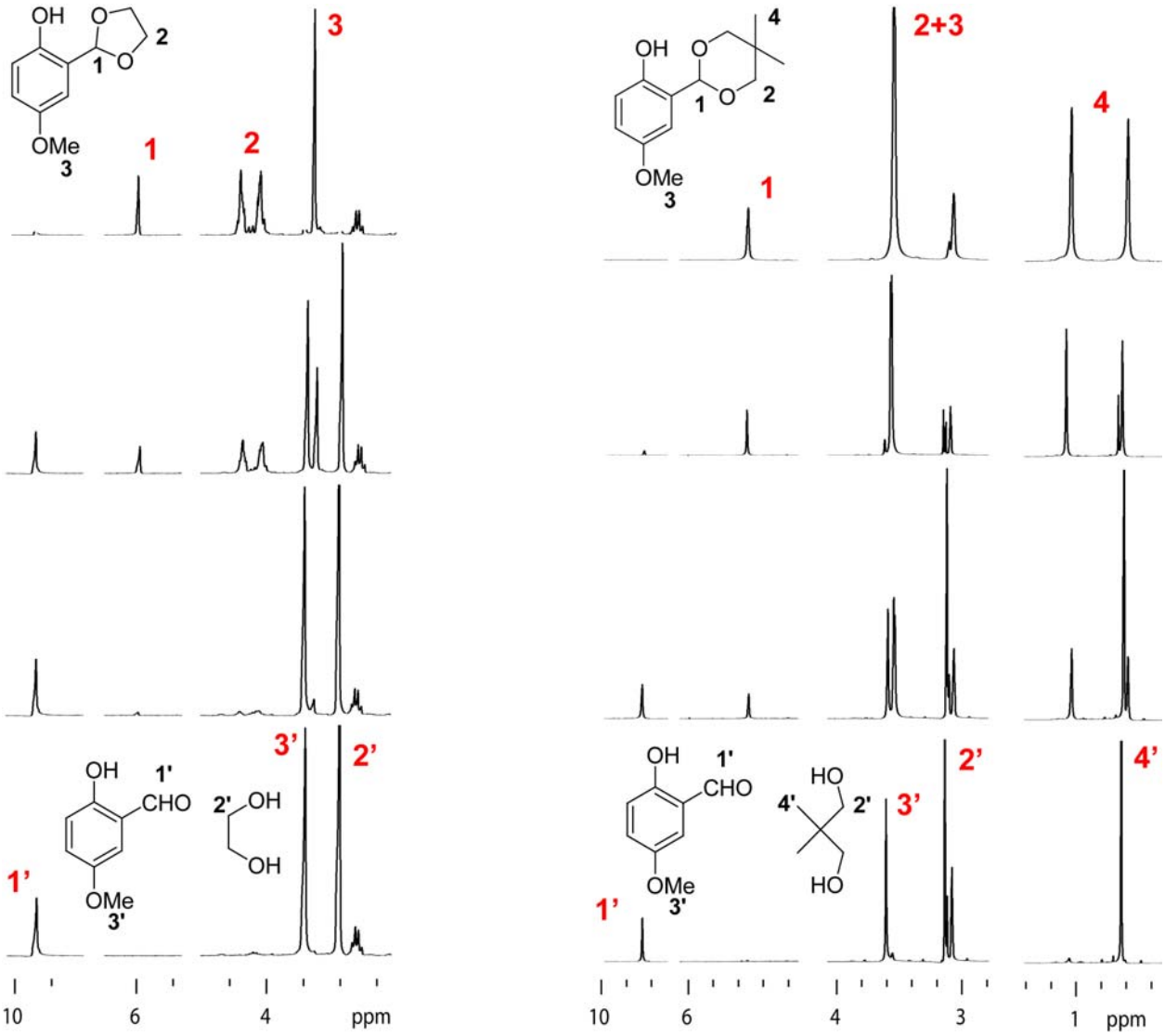


Figure 3.8. Changes in NMR spectra upon photolysis of **3.55a** (left) and **b** (right): disappearance of peaks, corresponding to the acetals (1, 2, 3, 4) and formation of **3.53** (1' and 3') and diols **3.54a** (left, 2') and **b** (right, 2' and 4').

Photolysis of compounds **3.55c-e** was performed in 20% aqueous methanol and monitored by HPLC. Irradiation of the cyclic acetals in all cases led to the formation of 2-hydroxy-5-methoxybenzaldehyde and the corresponding diol as the only products. Quantitative data, including yields of protection and deprotection and quantum yields of the photolyses are summarized in table 3.6.

Table 3.6. Yields of protection, deprotection and quantum yields of diols **3.54a-e**

	Yield of protection, %	Yield of deprotection, %	Quantum yield	Stability (τ, h)[e]
ethyleneglycol	89[a]	100[c]	0.36	50
neopentylglycol	74[a]	100[c]	0.1	500
3.54c	37[a]	91[d]	0.24	90
3.54d	75[b]	96[d]	0.27	45
3.54e	74[b]	59[d]	0.03	N/A

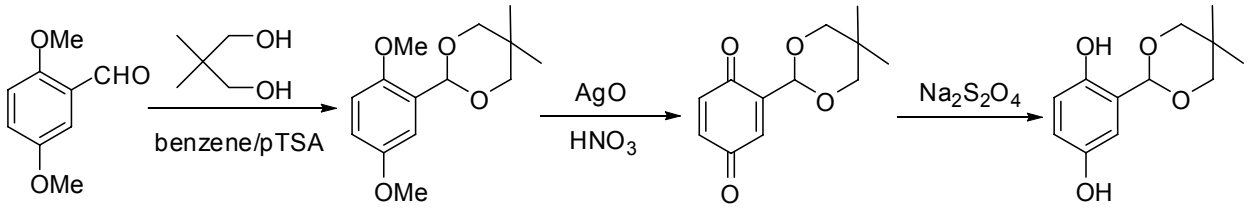
a – Method A; b – method B; c –by NMR; d – by HPLC; e – 80% water, 20% methanol

Cyclic acetals **3.55a-e** are unstable in the neat state and in chloroform solutions, decomposing to the starting materials in the dark. We believe that intramolecular hydrogen bondings in these conditions promote efficient hydrogen transfer even in the ground state of the chromophore. On the other hand, these compounds are stable in methanol and ethereal solutions, where molecules of solvent bind phenolic hydrogen intermolecularly. In aqueous solutions, 1,3-dioxanes **3.55b** and **3.55e** are relatively stable toward hydrolysis, whereas stability of 1,3-doxolanes **3.55a,c,d** is somewhat lower. Quantum yields of the substrate in 20% aqueous methanol are notably higher for 1,2-diols compared to 1,3-diols as was expected taking into account the higher stability of 1,3-dioxane.

In order to overcome the stability issue of the explored photoremovable protecting group we desired to replace the methoxy group with the free phenol. This modified design allows us to arm the photolabile protecting group in situ from the corresponding quinone by treatment with the simple reducing agent. Quinones, in turn, can be

obtained by oxidation of the corresponding acetal of 2,5-dimethoxybenzaldehyde. We performed the model synthesis of the 2-(5,5-dimethyl-1,3-dioxan-2-yl)benzene-1,4-diol **3.58** – protected neopentylglycol. 2,5-Dimethoxybenzaldehyde was first reacted with glycol in standard conditions (benzene, catalytic amount of *p*-TSA) to obtain acetal **3.56**. Oxidation of the latter was a challenging task, since traditionally used cerium ammonium nitrate is also known as a very efficient agent for cleavage of cyclic acetals. We, therefore, applied silver (II) oxide in the presence of nitric acid[49] to oxidize **3.56** into 2-(5,5-dimethyl-1,3-dioxan-2-yl)benzo-1,4-quinone **3.57** leaving acetal moiety intact. The latter was reduced with sodium dithionite to the target compound **3.58** (Scheme 3.26).

Scheme 3.26



3.56 **3.57** **3.58**

A solution of **3.58** in CD_3OD/D_2O was irradiated at 300 nm and the progress of decomposition was monitored by both UV and NMR (Figures 3.9 and 3.10 respectively). Complete bleaching of the band at 300 nm is achieved in 50 minutes of irradiation and indicates complete consumption of the starting material (Figure 3.9) and the UV-spectrum of the reaction mixture corresponds to 2,5-dihydroxybenzaldehyde. The changes in NMR spectra (Figure 3.10) also confirm decomposition of the starting material **3.58** and formation of neopentylglycol and 2,5-dihydroxybenzaldehyde as the only products of the photochemical cleavage. The chemical yield of diol release is nearly quantitative as concluded from NMR spectra and the quantum yield is 0.18.

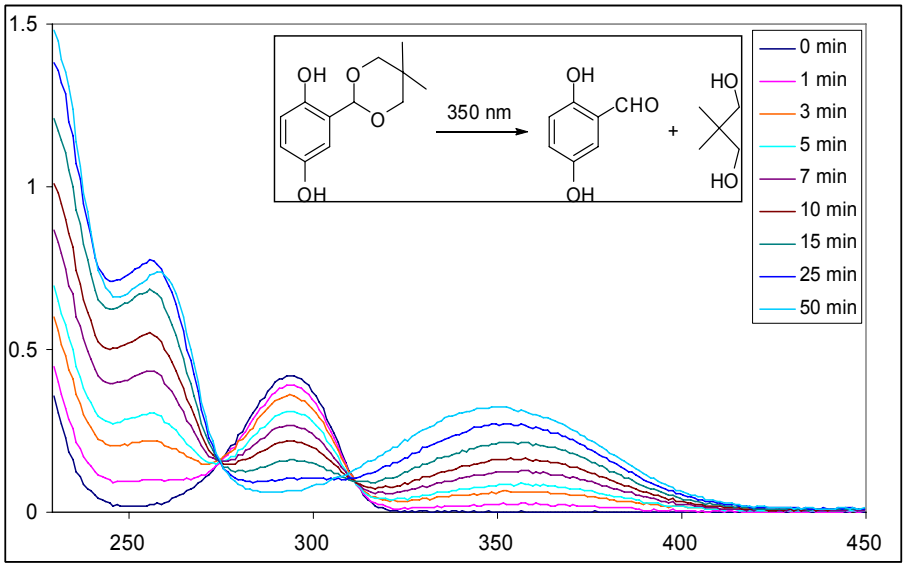


Figure 3.9. Photochemical decomposition of **3.58** ($1*10^{-4}$M solution in D_2O/CD_3OD) concomitant with formation of 2,5-dihydroxy-benzaldehyde

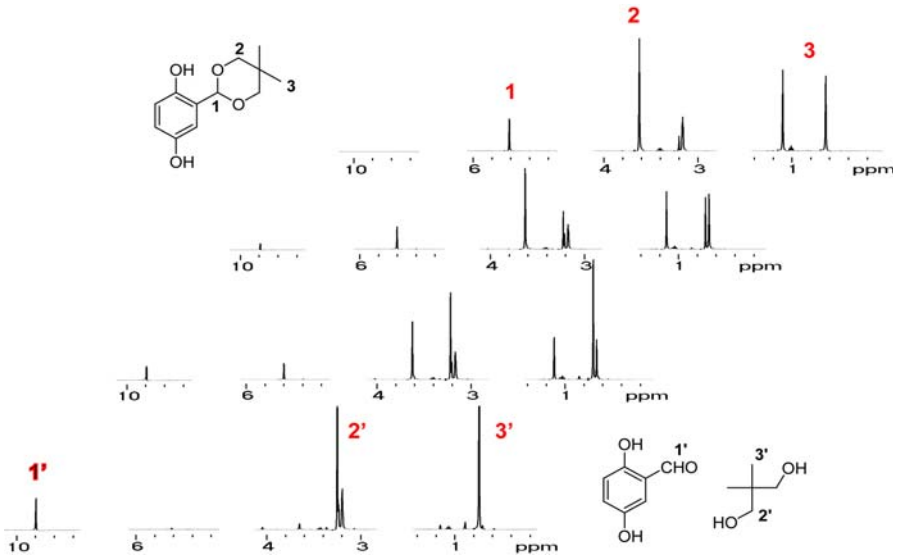


Figure 3.10. Changes in NMR spectra upon photolysis of **3.58**: disappearance of peaks 1 (5.6 ppm), 2 (3.6 ppm) and 3 (0.7; 1.1 ppm) and formation of peaks 1' (9.8 ppm), 2' (3.3 ppm) and 3' (0.8 ppm)

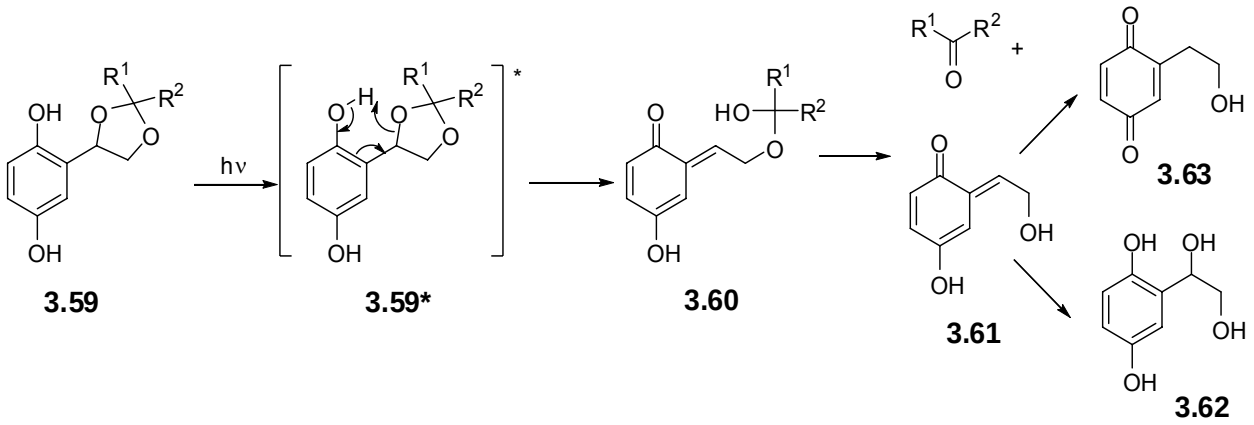
In conclusion, we have designed novel photochemically removable benzylidene protection group for diols. Protected substrates are released in excellent chemical yields with good quantum efficiencies. Potential applications of this group include synthesis of glycerides, carbohydrate chemistry and drug delivery systems.

3.3. Photoremovable protecting group for carbonyl compounds.

The majority of photolabile groups are designed to protect carboxylic acids, phosphates and alcohols. Surprisingly, such a versatile functionality as the carbonyl group has attracted little attention in terms of protection with photoremovable groups. For example, *O*-nitrophenylethylene glycol[42] and *bis*(*o*-nitrophenyl)ethanediol[43] cyclic acetals were shown to release carbonyl moiety upon irradiation at 350 nm with good yields; however, the quantum yields were not reported. Moreover, these groups should suffer from the known disadvantages of the nitrobenzyl group, including slow release of the substrate, reactive nitroso byproduct and poor aqueous solubility. Deprotection of carbonyl compounds upon photolysis of their dithiane adducts[44] requires addition of an electron transfer photosensitizer such as benzophenone. The coumarinylethyleneglycol photoremovable protecting group[45] releases the carbonyl substrates in low yields. Methoxysalicyl alcohol has been shown very recently to successfully cage and release various carbonyl compounds;[46] however, the quantum yields of deprotection were not reported.

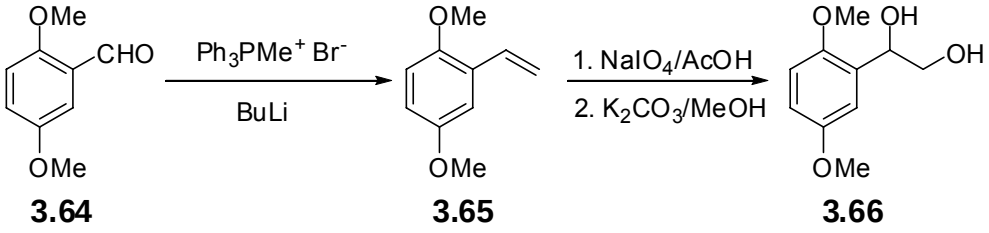
We designed a photoremovable protecting group for carbonyl compounds based on the photochemistry of *o*-hydroxybenzyl derivatives in order to expand the scope of possible applications of this moiety. The following mechanism of uncaging was proposed: the initial excitation of an acetal **3.59** promotes intramolecular hydrogen transfer from phenol group to dioxolane. The resulting hemi-acetal **3.60** should undergo hydrolysis to liberate the carbonyl compound and quinone methide **3.61**. The latter either adds water to convert into the parent 1-(2,5-dihydroxyphenyl)ethane-1,2-diol **3.62** or undergoes tautomerization to 2-hydroxyethyl-1,4-benzoquinone **3.63** (Scheme 3.27).

Scheme 3.27



(2,5-Dimethoxyphenyl)ethanediol **3.66**, a feasible precursor in the synthesis of **3.59**, was synthesized as shown in Scheme 2. 2,5-Dimethoxybenzaldehyde **3.64** was reacted with methyltriphenyl phosphonium bromide in the presence of butyllithium to obtain 2,5-dimethoxystyrene **3.65**.[47] Oxidation of the latter with sodium periodate in hot acetic acid, followed by hydrolysis of the resulting mixture of acetates with potassium carbonate in methanol afforded **3.66** (Scheme 3.28).[48]

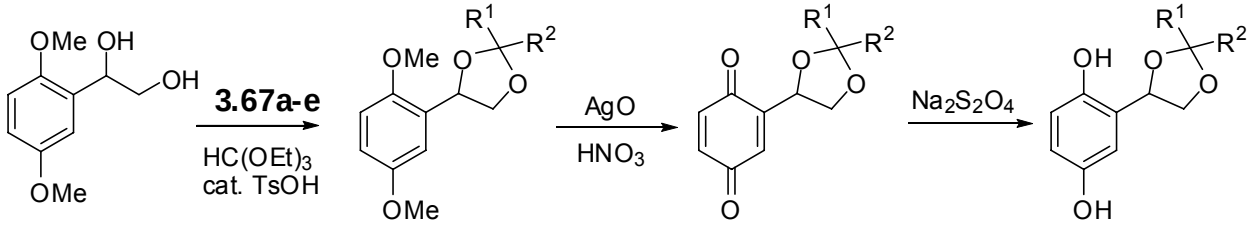
Scheme 3.28.



Starting from **3.66** a series of carbonyl compounds were protected as 2-1,3-dioxolan-4-ylhydroquinone derivatives **3.59a-e**. We have synthesized derivatives of aromatic and aliphatic aldehydes and ketones – 3-pentanone (**3.67a**), benzaldehyde (**3.67b**), cyclohexanone (**3.67c**), acetophenone (**3.67d**) and 3-phenylpropionaldehyde (**3.67e**). Treatment of the carbonyl compound with **3.60** and triethylorthoformate in

dichloromethane in presence of catalytic amount of p-toluenesulfonic acid leads to acetals **3.68a-e**. Oxidation with silver oxide in presence of nitric acid[49] followed by reduction of the resulting quinones **3.69a-e** with sodium dithionite afforded the desired **3.59a-e** (Scheme 3.29). Yields of protection are summarized in table 3.7.

Scheme 3.29



3.66 **3.68a-e** **3.69a-e** **3.59a-e**

a: $R^1 = R^2 =$ Et; **b**: R^1 = Ph, R^2 = H; **c**: $R^1 = R^2 = -(CH_2)_5-$;
d: R^1 = Ph, R^2 = Me; **e**: $R^1 = PhCH_2CH_2$, R^2 = H

2,5-Dihydroxybenzyl-caged compounds **3.59a-e** are stable in the dark in the solid state, as well as in aqueous methanol solutions. UV spectra of these compounds contain the characteristic band of the hydro-1,4-quinone moiety at λ_{max} = 297 nm. Solutions of **3.59a-e** in aqueous methanol ($1*10^{-3}$M, up to 30% MeOH v/v for solubility) were photolyzed in a Rayonet photoreactor with 300 nm lamps and the course of the reaction was monitored by UV spectroscopy. Changes in UV-spectra taken at several timepoints during irradiation reflect smooth decomposition of the starting material and formation of the product (Figure 3.11, representative photolysis of **3.59b** and **3.59d**).

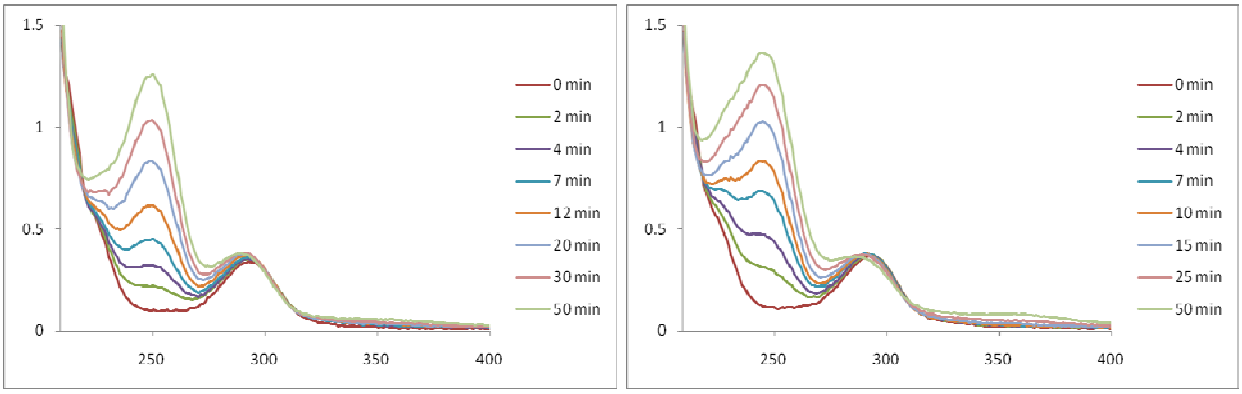


Figure 3.11. Photochemical decomposition of **3.59b** (left) and **3.59d** (right)

Yield of the substrates release was measured by either NMR (**3.59a**, Figure 3.12), GC (**3.59c**) or HPLC (**3.59b,d,e**), while the quantum yields of uncaging were calculated using chemical actinometry. The data are summarized in table 3.7.

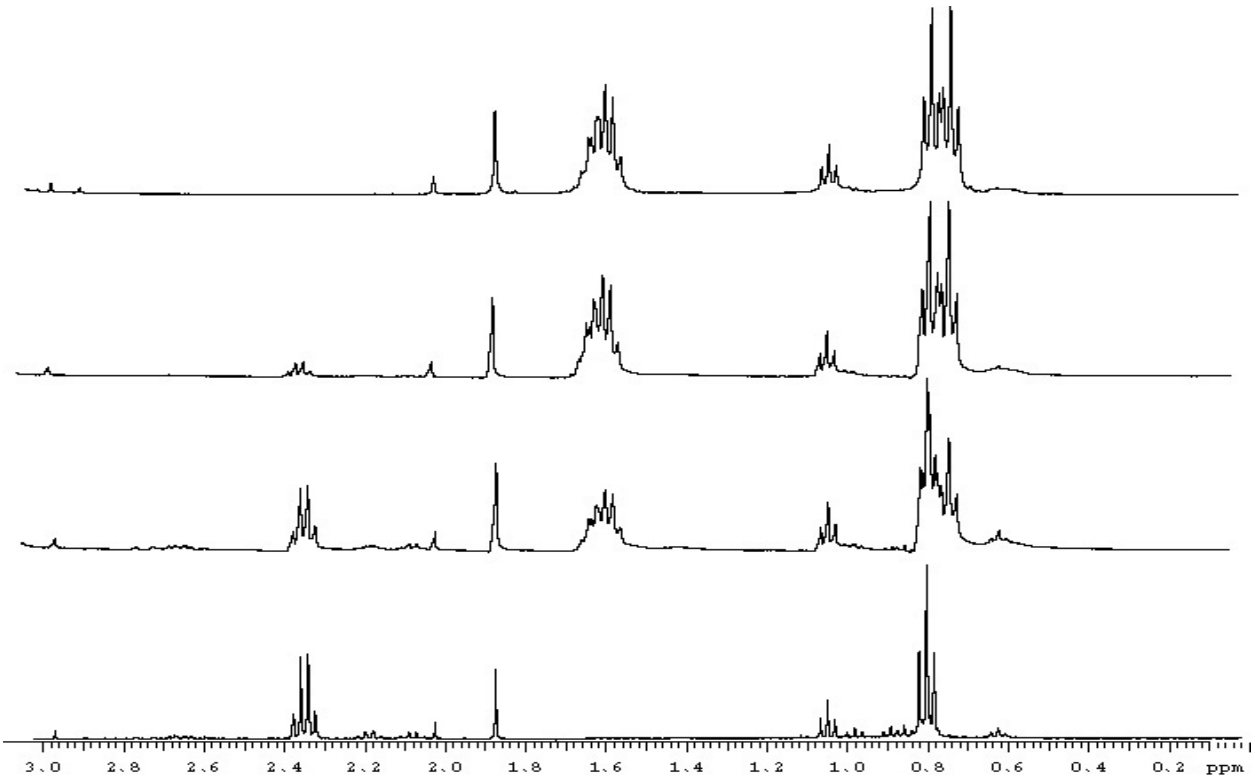


Figure 3.12. Decomposition of **3.59a** concomitant with formation of pentanone-3 (**3.67a**)

Table 3.7. Yields of protection, deprotection and quantum yield of the carbonyl compounds

Entry	Compound	Protection, %	Release of the substrate	Quantum yield
1	**3.59a**	37	~90[a]	0.08
2	**3.59b**	40	88	0.12
3	**3.59c**	39	59[b]	0.04
4	**3.59d**	47	94	0.15
5	**3.59e**	43	100	0.17

a – measured by NMR; b – measured by GC

We have thus designed another novel photochemically removable protecting group based on the chemistry of *o*-hydroxybenzyl compounds. Carbonyl compounds protected as cyclic acetals with 1-(2,5-dihydroxyphenyl)ethane-1,2-diol are released in excellent chemical yields with good quantum efficiencies. The potential applications of this group include classical organic synthesis, chemistry of photocaged compounds and drug delivery systems.

4. EXPERIMENTAL PART

Methods and materials: 2,5-dimethoxybenzaldehyde, 2-methyl-*p*-benzoquinone (**3.5**), 2,5-dihydroxybenzaldehyde (**3.15**), 2-methyl-*p*-hydroquinone (**3.16**), 2-methyl-1,4-naphthoquinone (**3.24**), 1,4-dihydroxy-2-naphthoic acid, diethylsuccinate, salicylic aldehyde, *o*-vanillin, 2-hydroxy-5-methoxybenzaldehyde were purchased from commercial sources and used as received without further purification. Samples of compounds **3.3a-d**, **3.22a,b**, **3.34a,b**, **3.46**, **3.55a-e**, **3.58** and **3.59 a-e** were irradiated in Rayonet photoreactor with conventional UV lamps (4W, 300, 350 or 362 nm). Water, methanol and acetonitrile (HPLC grade) were purchased from commercial sources and used without further purification; concentrations of the irradiated solutions were kept around $1*10^{-3}$ M. Reaction mixtures after photolysis were analyzed by NMR, HPLC or GC and deprotection yields were calculated using calibration plots. Quantum efficiencies of photochemical decomposition were measured by actinometry.

2,5-*bis*-(*tert*-Butyldimethylsilanyloxy)benzyl alcohol (**3.7**): *t*-Butyldimethylsilyl chloride (3.15 g, 21 mmol) was added to a solution of 2,5-dihydroxybenzaldehyde (1.38 g, 10 mmol) and imidazole (2.85 g, 42 mmol) in DMF (10 mL); reaction mixture was stirred for 1 h, and poured into aqueous sodium bicarbonate (10%, 100 mL). Aqueous phase was extracted with ether (3x50 mL) and combined organic layers were washed with water, dried over anhydrous sodium sulfate, and passed through a layer of silica gel. Solvent was removed under reduced pressure, the residue dissolved in methanol, and sodium borohydride (750 mg, 20 mmol) was slowly added at 0^0C. Reaction mixture

was allowed to warm to room temperature, stirred for additional 3 h, and quenched with aqueous ammonium chloride (10%, 50 mL). Methanol was removed under reduced pressure, aqueous phase was extracted with ether (3x50 mL), ether solution was dried over anhydrous sodium sulfate, passed through a thin layer of silica gel, and concentrated under reduced pressure. Column chromatography of the residue (hexane:ether = 9:1) gave 2.9g (7.9 mmol, 79%) of alcohol **3.7** as colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.17 (s, 6H), 0.22 (s, 6H), 0.97 (s, 9H), 1.0 (s, 9H), 2.15 (t, *J* = 6.4 Hz, 1H), 4.60 (d, *J* = 6.4 Hz, 2H), 6.63-6.70 (m, 2H), 6.79 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR δ -4.2, -4.0, 18.4, 25.9, 26.0, 62.2, 119.2, 119.6, 132.4, 147.8, 149.9. MS: 368 (6), 311 (100), 293 (33), 255 (5), 253 (5), 237 (3), 73 (32). HRMS: calcd. for $C_{19}H_{36}O_3Si_2$ 368.2203; found 368.2198.

2,5-*bis*-(*tert*-Butyldimethylsilanyloxy)benzyl bromide (3.8): Trifluoroacetic anhydride (1.7g, 8 mmol) was added with stirring to a solution of benzyl alcohol **3.7** (2.67 g, 7.25 mmol) in dry tetrahydrofuran (50 mL), and the mixture was refluxed for 30 min. After cooling to room temperature the reaction mixture was poured into saturated sodium bicarbonate (100 mL), extracted with ether (3x25 mL) and washed with aqueous sodium bicarbonate. Ether layer was dried over anhydrous Na_2SO_4, passed through a thin layer of silica and the solvent was removed *in vacuo*. Resulting trifluoroacetate (97% yield) was dissolved in dry THF (25 mL) and dry lithium bromide (1.8 g, 21 mmol, 3 equiv) was added with stirring. The mixture was refluxed overnight, cooled to room temperature, poured in water (100 mL) and extracted 3 times with hexane. The hexane layers were concentrated leaving benzyl bromide **6** as a colorless oil in 85% yield over two steps (2.77g, 6.2 mmol). ^{1}H NMR ($CDCl_3$): δ 0.17 (s, 6H), 0.25 (s, 6H), 0.97 (s, 9H),

1.04 (s, 9H), 4.46 (s, 2H), 6.65 (d, 2H), 6.81 (d, 1H); ^{13}C NMR -4.2, -3.9, 18.4, 18.5, 26.0, 26.1, 29.5, 119.5, 121.4, 122.5, 129.1, 148.3, 149.6.

2-(Phenethoxymethyl)-1,4-bis-(*tert*-butyldimethylsilanyloxy)benzene (3.9): To a suspension of the 2-phenylethanol (3.0 mmol, 370 mg), 2,6-di-*tert*-butylpyridine (4.5 mmol, 861 mg, 1 ml) and silver triflate (3.3 mmol, 850 mg) in dry chloroform (5 mL) at 0^0C was added *bis*-(*t*-butyldimethylsilanyloxy)benzyl bromide **3.8** (3.5 mmol, 1.5 g) with stirring. The reaction mixture was stirred for 3 hours, then concentrated *in vacuo* and applied on top of the silica gel column. 2-(Phenethoxymethyl)-1,4-bis-(*tert*-butyldimethylsilanyloxy)benzene **3.9** was isolated in 54% yield. ^{1}H NMR ($CDCl_3$): δ 0.16 (s, 6H), 0.17 (s, 6H), 0.97 (s, 9H), 0.98 (s, 9H), 2.94 (t, 2H), 3.69 (t, 2H), 4.48(s, 2H), 6.60-6.62 (m, 2H), 6.845 (d, 1H), 7.20-7.30 (m, 5H); ^{13}C NMR δ -4.5, -4.3, 18.18, 18.22, 25.7, 25.8, 67.6, 67.9, 71.5, 118.9, 119.1, 120.0, 120.1, 126.1, 128.3, 129.0, 129.8, 147.1, 149.5. MS: 472 (M^+, 7), 415 (15), 399 (12), 398 (33), 397 (100), 323 (22), 311 (12), 295 (25), 237 (15), 117(11), 105 (67), 75 (19), 73 (82).

2,5-Dimethoxybenzyl alcohol (**3.10**): Sodium borohydride (3.8 g, 100 mmol) was added slowly to the solution of 2,5-dimethoxybenzaldehyde (8.3 g, 50 mmol) in methanol (100 mL) at 0^0C. Reaction mixture was allowed to reach room temperature, was stirred for 2 h, and quenched with dilute aqueous ammonium chloride (200 mL). Methanol was evaporated under reduced pressure and aqueous layer was extracted with ether. Ether solution was dried over anhydrous sodium sulfate and concentrated. Flash chromatography (hexane:ether = 7:3) of the residue gave desired 2,5-dimethoxybenzyl alcohol as colorless liquid in 99% yield (8.31 g, 49 mmol). ^{1}H NMR ($CDCl_3$): δ 2.44 (t, *J* = 6.0 Hz, 1H), 3.77 (s, 3H), 3.81 (s, 3H), 4.65 (d, *J* = 6.0 Hz, 2H),

6.79 (m, 2H), 6.87 (m, 1H); ^{13}C NMR: δ 56.0, 62.3, 111.3, 113.2, 115.0, 130.3, 151.7, 153.8. MS: 168 (100, M^+), 139 (33), 135 (31), 125 (52), 110 (23), 93 (22), 77 (25), 65 (34). Lit[16]: ^{1}H NMR ($CDCl_3$): δ 3.8 (s, 6H), 4.2(s, 2H), 6.85 (m, 3H).

2,5-Dimethoxybenzyl bromide (3.10a): A mixture of 2,5-dimethoxybenzyl alcohol (1.68 g, 10 mmol) and aqueous hydrobromic acid (40%, 5 mL) was stirred for 30 minutes at 0^0C, poured in water, and extracted with ether (3x30mL). Combined organic layers were washed with aqueous solution of $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, filtered through silica gel, and evaporated, leaving benzyl bromide (2.1 g, 9.1 mmol) as white solid (mp 69-70 ^{0}C) in 91% yield. ^{1}H NMR ($CDCl_3$): δ 3.77 (s, 3H), 3.86 (s, 3H), 4.54 (s, 2H), 6.83 (m, 2H), 6.91 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR: δ 29.2, 56.0, 56.4, 112.4, 115.2, 116.6, 127.1, 151.9, 153.6. MS: 232 (23), 230 (M^+, 23), 151 (100), 121 (47), 108 (18), 91 (35), 77 (28). Lit[16]: ^{1}H NMR ($CDCl_3$): δ 3.8 (s, 6H), 4.1 (s, 2H), 6.83 (m, 3H).

1,4-Dimethoxy-2-phenethyloxymethylbenzene (**3.11a**): 2-Phenylethanol (171 mg, 1.4 mmol) was added to the suspension of NaH (5 mmol, 200 mg of the 60% suspension in oil) in THF. Resulting mixture was stirred for 60 min and then 2,5-dimethoxybenzyl bromide **3.10a** (231 mg, 1mmol) was added. The resulting mixture was stirred overnight at 50^0C. Excess of sodium hydride was then carefully quenched with water and product was extracted with ether (3x30 mL). Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered through a layer of silica gel, and evaporated. Column chromatography (hexane:ether = 9:1) afforded the desired product **3.11a** as colorless oil in 85% yield (231 mg, 0.85 mmol). ^{1}H NMR ($CDCl_3$): δ 2.96 (t, *J* = 7.0 Hz, 2H), 3.74 (s+t, 5H), 3.77 (s, 3H), 4.56 (s, 2H), 6.77 (m, 2H), 6.94 (m,

1H), 7.18-7.31 (m, 5H); ^{13}C NMR: δ 36.6, 56.0, 56.2, 67.7, 71.8, 111.6, 113.3, 114.5, 126.4, 128.3, 128.5, 129.2, 139.4, 151.3, 153.9. MS: 272 (70, M^+), 151 (100), 121 (42), 105 (11), 91 (33), 77 (20). HRMS: calcd. for $C_{17}H_{20}O_3$ 272.1412; found 272.1404.

2-(Phenethyloxymethyl)-1,4-benzoquinone (**3.12a**): Aqueous solution of cerium ammonium nitrate (2.74 g, 5 mmol) was added to the solution of **3.11a** (0.77 mmol, 231 mg) in acetonitrile (25 mL) and stirred at room temperature for 30 min. The reaction mixture was extracted with ether (3x30 mL); combined organic layers washed with brine, dried over anhydrous Na_2SO_4, and solvents removed in vacuum. Chromatographic purification (hexane:ether = 4:1) gave 148 mg (0.61 mmol, 79%) of quinone **3.12a** as bright yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.94 (t, *J* = 7.0 Hz, 2H), 3.77 (t, *J* = 7.0 Hz, 2H), 4.35 (d, *J* = 2.0 Hz, 2H), 6.72-6.75 (m, 3H), 7.22-7.31 (m, 5H); ^{13}C NMR: δ 36.5, 66.2, 72.7, 126.7, 128.7, 129.1, 131.6, 136.6, 136.8, 138.8, 145.9, 187.2, 187.7. MS: 244 (10, $[M+2]^+$), 122 (29), 104 (44), 91 (100), 77 (12). HRMS: calcd. for $C_{15}H_{14}O_3$ 244.1099 (M+2); found 244.1088. Note that both MS and HRMS give molecular ion peak corresponding to the hydroquinone. This was actually the case for some other simple quinines we worked with (not reported here). However, retention time of the product in GC/MS and difference in fragmentation pattern clearly indicate that this is not a hydroquinone (see **3a** below).

2-Phenethyloxymethylbenzene-1,4-diol (**3.3a**): An aqueous solution (25 mL) of sodium dithionite (870 mg, 5 mmol) was added to a solution of **3.12a** (128 mg, 0.53 mmol) in chloroform (25 mL). The mixture was vigorously stirred until the complete disappearance of yellow color, dilute ammonium chloride (10%, 100 mL) was added. Aqueous layer was extracted with ether (2x 50 mL), combined organic layers were

washed with ca. 10% ammonium chloride (2x50 mL), dried over anhydrous Na_2SO_4, and solvents removed under reduced pressure. Column chromatography (hexane:ether = 1:1) gave 128 mg of **3.3a** as white solid (0.53 mmol, 99%). Mp 105-107 ^{0}C; ^{1}H NMR ($CDCl_3$): δ 2.93 (t, *J* = 7.0 Hz, 2H), 3.75 (t, *J* = 7.0 Hz, 2H), 4.59 (s, 2H), 6.48 (d, *J* = 2.8 Hz, 1H), 6.64 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.87(s, broad, 1H, O**H**), 7.20-7.25 (m, 3H), 7.29-7.33 (m, 2H); ^{13}C NMR: δ 36.1, 71.6, 72.2, 114.8, 115.9, 117.3, 123.1, 126.6, 128.6, 128.8, 138.2, 148.6, 149.7. MS: 244 (M^+, 28), 123 (35), 122 (100), 105 (22), 94 (31), 92 (25), 91 (55), 77 (12), 67 (10), 65 (20). HRMS: calcd. for $C_{15}H_{16}O_3$ 244.1095; found 244.1088.

2,5-Dimethoxybenzyl benzoate (**3.11c**): Benzoyl chloride (3.22 g, 23 mmol) was added to a solution of 2,5-dimethoxybenzyl alcohol (3.5 g, 21 mmol) and pyridine (20 mL) in dichloromethane (100 mL) and left overnight. The reaction mixture was diluted with ether (ca. 200 mL), washed with brine (2x100 mL), organic layer was dried over anhydrous Na_2SO_4, and solvents were removed under reduced pressure. Recrystallizaton of the residue from hexane gave 4.57 g of colorless crystals of **3.11c** (81%). Mp 62-63 ^{0}C; ^{1}H NMR ($CDCl_3$): δ 3.78 (s, 3H), 3.82 (s, 3H), 5.40 (s, 2H), 6.84 (s, 2H), 7.02 (s, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.6 Hz, 1H), 8.09 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR: δ 55.8, 56.1, 62.0, 11.6, 113.4, 115.5, 125.6, 128.4, 129.7, 130.3, 132.9, 151.6, 153.5, 166.5. MS: 272 (M^+, 75), 167 (61), 151 (19), 139 (20), 121 (31), 105 (100), 77 (64). HRMS: calcd. for $C_{16}H_{16}O_4$ 272.1049; found 272.1043.

2,5-Dimethoxybenzyl pivalate (**3.11d**) was prepared using the same procedure in 87% yield. Colorless oil; ^{1}H NMR ($CDCl_3$): δ 1.23 (s, 9H), 3.77 (s, 3H), 3.78 (s, 3H), 5.12 (s, 2H), 6.80 (m, 2H), 6.91 (m, 1H); ^{13}C NMR: δ 27.2, 40.4, 55.9, 56.2, 61.7, 11.7, 113.3,

114.9, 126.3, 151.6, 153.7, 185.2. MS: 252 (80, M^+), 167 (26), 151 (100), 121 (59), 91 (22), 77 (20), 57 (65). HRMS: calcd. for $C_{14}H_{20}O_4$ 252.1362; found 252.1351.

(3,6-Dioxo-cyclohexa-1,4-dienyl)methyl benzoate (**3.12c**): was obtained following the procedure used for **3.12a**. Yellow oil, 71%. ^{1}H NMR ($CDCl_3$): δ 5.26 (d, *J* = 2.0 Hz, 2H), 6.79-6.83 (m, 3H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.62 (t, *J* = 7.6 Hz, 1H), 8.09 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR: δ 59.9, 128.6, 129.1, 129.8, 131.4, 133.7, 136.6, 136.7, 143.3, 165.6, 186.2, 187.0. MS: 242 (M^+, 2), 122 (41), 105 (100), 94 (8), 82 (6), 77 (55), 66 (7), 51 (21). HRMS: calcd. for $C_{14}H_{10}O_4$ 242.0579; found 242.0574.

(3,6-Dioxo-cyclohexa-1,4-dienyl)methyl pivalate (**3.12d**): was obtained following the procedure used for **3.12a**. Yellow oil, 73% yield. ^{1}H NMR ($CDCl_3$): δ 1.24 (s, 9H), 4.96 (d, *J* = 2.0 Hz, 2H), 6.63 (t, *J* = 2.0 Hz, 1H), 6.77 (m, 2H); ^{13}C NMR: δ 27.2, 39.2, 59.6, 131.3, 136.7, 136.8, 143.8, 177.8, 186.4, 187.2. MS: 224 (1), 222 (1, M^+), 138 (3), 122 (14), 94 (4), 85 (6), 69 (10), 65 (8), 57 (100). HRMS: calcd. for $C_{12}H_{14}O_4$ 222.0892; found 222.0888.

2,5-Dihydroxybenzyl benzoate (**3.3c**): was obtained following the procedure used for **3.3a**. Colorless oil, 99%. ^{1}H NMR ($CDCl_3$): δ 5.00 (s, broad, 1H, O**H**), 5.30 (s, 2H), 6.78 (dd, *J* = 7.6, 2.8 Hz, 1H), 6.84-6.87 (m, 2H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.65 (s, 1H, O**H**), 8.05 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR: δ 63.5, 118.1, 118.2, 118.9, 122.6, 128.5, 129.2, 130.0, 133.7, 149.2, 168.7. HRMS: calcd. for $C_{14}H_{12}O_4$ 244,0736; found 244.0731

2,5-Dihydroxybenzyl pivalate (**3.3d**): was obtained following procedure for **3.3a**. Colorless oil, 97%. ^{1}H NMR ($CDCl_3$): δ 1.19(s, 9H), 5.04 (s, 2H + s, broad, 1H), 6.77 (m,

2H), 6.82 (m, 1H), 7.54 (s, broad, 1H); ^{13}C NMR: δ 27.3, 39.2, 63.4, 118.1, 118.2, 119.0, 122.9, 149.4, 181.3. HRMS: calcd. for $C_{12}H_{16}O_4$ 224.1049; found 224.1042.

1,4-*bis*-(*tert*-Butyldimethylsilanyloxy)-2-(4-chlorophenoxymethyl)benzene (3.13): Tributyl phosphine (404 mg, 2 mmol) was added to a solution of alcohol **3.7** (368 mg, 1 mmol) followed by the solution of ADDP (504 mg, 2 mmol) in anhydrous benzene (40 mL). After 10 minutes 4-chlorophenol (1.28g, 10 mmol) was added, the mixture was stirred at room temperature overnight, and quenched with water. The aqueous layer was extracted with ether (2x50 mL), and the combined organic layers were washed with brine (2x50 mL) and dried over anhydrous Na_2SO_4. All volatiles were removed under reduced pressure and the residue was purified by chromatography on silica gel (hexane:ether = 19:1) to give 470 mg (0.98 mmol, 98%) of **3.13** as colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.12 (s, 6H), 0.20 (s, 6H), 0.94 (s, 9H), 0.97 (s, 9H), 4.98 (s, 2H), 6.63-6.70 (m, 2H), 6.86 (s+d, 3 H), 7.22 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR δ -4.5, -4.3, 18.2, 18.2, 25.7, 25.7, 65.5, 116.0, 119.1, 119.9, 120.2, 125.5, 127.8, 129.3, 147.2, 149.7, 157.3. MS: 480 (M^+, 2), 478 (M^+, 4), 351 (100), 295 (100), 237 (14), 73 (93). HRMS: calcd. for $C_{25}H_{39}ClO_3Si_2$ 421.1422 (M-57); found 421.1401.

2-(4-Chlorophenoxymethyl)benzene-1,4-diol (**3.3b**): Tetra-*n*-butylammonium fluoride (1M solution in THF, 3 mL, 3 mmol) was added dropwise to a solution of **3.13** (440 mg, 0.92 mmol) in THF (20 mL) at 0^0C. Reaction mixture was stirred for 15 minutes, quenched with brine (100 mL), extracted with ether (3x30ml), organic solution is washed with saturated aqueous ammonium chloride and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatographic separation of the residue (hexane:ether = 3:2) afforded 200 mg (0.81 mmol, 88%) of **3.3b** as white solid.

Mp 141-143 ^{0}C; ^{1}H NMR (acetone-d6): δ 5.08 (s, 2H), 6.65 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 2.4 Hz, 1H), 7.02 (d, *J* = 9.0 Hz, 2H), 7.30 (d, *J* = 9.0 Hz, 2H), 7.77 (s, 1H, O**H**), 8.00 (s, 1H, O**H**); ^{13}C NMR δ 66.0, 116.2, 116.3, 116.8, 117.2, 124.8, 125.7, 130.1, 148.5, 151.4, 158.7. HRMS: calcd. for $C_{13}H_{11}ClO_3$ 250,0397; found 250.0393.

Methyl 2,5-dixydroxybezyl ether (**3.14**): ^{1}H NMR ($CDCl_3$, 400 MHz): 3.40 (s, 3H), 4.53 (s, 2H), 6.23 (s, br, 1H), 6.54 (d, 1H), 6.64 (dd, 1H), 6.70 (d, 1H), 7.16 (s, br, 1H); MS: 154 (26, M+), 123 (15), 122 (100), 94 (87), 82 (11), 66 (38), 55 (17).

Methyl 1,4-dimethoxy-2-naphthoate (3.17): Potassium carbonate (31g, 0.23 mol) and iodomethane (27.5 mL, 0.44 mol) were added to a solution of 1,4-dihydroxy-2-naphthoic acid (6 g, 0.03 mol) in acetone (120 mL). The mixture was refluxed overnight, allowed to cool and diluted with water until the precipitate dissolved. Acetone was removed under reduced pressure and the aqueous layer was extracted with ether (3x50 mL). Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered through silica gel, and evaporated. Column chromatography of the residue (hexane:ether = 4:1) gave 6.82 g (94%) of **3.17** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.99 (s, 3H), 4.00 (s, 3H), 4.01 (s, 3H), 7.16 (s, 1H), 7.57-7.59 (m, 2H), 8.21-8.26 (m, 2H); ^{13}C NMR δ 52.3, 55.7, 63.3, 103.5, 118.7, 122.3, 123.5, 127.1, 127.8, 128.8, 129.2, 151.4, 152.1, 166.8. MS: 246 (M^+, 93), 231 (100), 215 (15), 175 (27), 157 (15), 129 (20), 115 (11), 114 (12), 101 (19), 75 (12). Lit:[21] ^{1}H NMR ($CDCl_3$): δ 4.00 (s, 3H), 4.01 (s, 3H), 4.02 (s, 3H), 7.16 (s, 1H), 7.59 (m, 2H), 8.24 (m, 2H).

(1,4-Dimethoxy-2-naphthyl)methanol (**3.18**): Solution of methyl 1,4-dimethoxy-2-naphthoate (6.82 g, 27.7 mmol) in THF (30 mL) was added to a solution of $LiAlH_4$ in

THF (1M, 30 mL, 30 mmol) at 25^{0}C over 45 min. The resulting mixture was stirred for 30 min, cooled to 0^{0}C, and quenched with methanol (5 mL) and aqueous HCl (10%, 50 ml). Aqueous layer was extracted with ether (2x50 mL), and combined organic layers were washed with 10% ammonium chloride solution (70 mL), brine (70 mL), dried over anhydrous Na_2SO_4, and evaporated. Chromatography of the crude mixture (hexane:ether = 3:2) produced 5.57 g (25 mmol, 91%) of **3.18** as a white solid. Mp 75-77 ^{0}C; ^{1}H NMR ($CDCl_3$): δ 2.17 (t, *J* = 5.6 Hz, 1H), 3.92 (s, 3H), 3.99 (s, 3H), 4.89 (d, *J* = 5.6 Hz, 2H), 6.81 (s, 1H), 7.46-7.57 (m, 2H), 8.04 (d, *J* = 8.4 Hz, 1H), 8.23 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR δ 55.7, 61.1, 62.6, 103.8, 121.8, 122.4, 125.5, 126.3, 126.7, 128.4, 128.5, 147.0, 152.2. MS: 218 (M^+, 86), 203 (14), 175 (100), 160 (39), 159 (11), 157 (11), 144 (16), 115 (51), 77 (13). Lit[21]: ^{1}H NMR ($CDCl_3$): δ 1.95 (t, 1H), 3.92 (s, 3H), 3.99 (s, 3H), 4.89 (s, 2H), 6.82 (s, 1H), 7.52 (m, 2H), 8.03 (dd, 1H), 8.23 (dd, 1H).

1,4-Dimethoxy-2-phenethyloxymethylnaphthalene (**3.20a**): Carbon tetrabromide (1.5 equiv, 1.5 g, 4.5 mmol) was added to a solution of **3.18** (670 mg, 3 mmol) and triphenylphosphine (1.5 equiv, 1.18 g, 4.5 mmol) in acetonitrile (25 mL) at 0^{0}C. The reaction mixture was stirred overnight, allowing temperature to reach 25^{0}C and all volatiles were removed under reduced pressure. The residue was passed through a thin layer of silica gel and resulting 1,4-dimethoxy-2-bromomethylnaphthalene **3.19** was used without further purification.

n-Butyllithium (2.5M in hexane, 4 mL, 10 mmol) was added to the solution of 2-phenylethanol (610 mg, 5 mmol) in THF (30 mL) at –78^{0}C. Resulting solution was stirred for 30 minutes and crude 2-bromomethyl-1,4-dimethoxynaphthalene was added. Reaction mixture was gradually warmed to room temperature, stirred overnight, and

quenched with aqueous ammonium chloride (10%, 100 mL). The product was extracted with ether (3x50 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated. Column chromatography of the residue (hexane:ether 3:1) gave 1.01 g of **3.20a** (3.14 mmol, 63%) as colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.97 (t, *J* = 7.0 Hz, 2H), 3.77 (t, *J* = 7.0 Hz, 2H), 3.85 (s, 3H), 3.91 (s, 3H), 4.75 (s, 2H), 6.76 (s, 1H), 7.18-7.32 (m, 5H), 7.45-7.57 (m, 2H), 8.04 (d, *J* = 8.2 Hz, 1H), 8.22 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR δ 36.4, 55.6, 62.7, 67.4, 71.3, 103.9, 121.9, 122.3, 125.4, 126.2, 126.2, 126.2, 126.5, 128.3, 128.4, 129.0, 139.1, 147.3, 152.0. MS: 322 (100, M^+), 201 (28), 186 (12), 128 (12), 115 (10), 105 (55), 91 (11). HRMS: calcd. for $C_{21}H_{22}O_3$ 322.1569; found 322.1556

2-(4-Chloro-phenoxymethyl)-1,4-dimethoxynaphthalene (**3.20b**): A solution of crude 2-bromomethyl-1,4-dimethoxynaphthalene **3.19** in THF (5 mL) was added to a stirred mixture of *p*-chlorophenol (1.28 g, 10 mmol) and potassium carbonate (1.38 g, 10 mmol) in THF (20 mL). The reaction mixture was stirred overnight at 60^0C, poured into HCl (10%, 50 mL) and the product was extracted with ether (3x50 mL). The combined organic layers were washed with aqueous NaOH (1M, 2x50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered through silica gel, and evaporated under reduced pressure. The residue was purified by chromatography on silica gel column (hexane:ether 3:1) to give **3.20b** in 93% yield as colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.93 (s, 3H), 3.97 (s, 3H), 5.24 (s, 2H), 6.84 (s, 1H), 6.97 (m, 2H), 7.24 (m, 2H), 7.50 (td, 1H), 7.56 (td, 1H), 8.07 (dd, 1H), 8.24 (dd, 1H); ^{13}C NMR δ 55.9, 63.4, 65.7, 104.0, 116.4, 122.2, 122.7, 124.6, 126.1, 126.1, 126.9, 127.0, 128.6, 129.6, 147.9, 152.5, 157.6. MS:

330 (4), 328 (11, M^+), 201 (100), 186 (84), 170 (14), 128 (15), 115 (12), 99 (7). HRMS: calcd. for $C_{19}H_{17}ClO_3$ 328.0866; found 328.0851.

2-(Phenethyloxymethyl)-1,4-naphthoquione (**3.21a**) was obtained following the procedure used for **3.12a**. Yellow crystals, 87%, mp 74-75 ^{0}C; ^{1}H NMR ($CDCl_3$): δ 2.98 (t, *J* = 7.2 Hz, 2H), 3.82 (td, *J* = 7.2, 0.8 Hz, 2H), 4.52 (dd, *J* = 1.2, 0.8 Hz, 2H), 6.99 (t, *J* = 1.2 Hz, 2H), 7.21-7.35 (m, 5H), 7.72-7.79 (m, 2H), 8.04-8.12 (m, 2H); ^{13}C NMR δ 36.3, 66.4, 72.5, 126.3, 126.3, 126.4, 128.5, 128.9, 132.0, 132.0, 133.5, 133.7, 134.0, 138.6, 147.8, 184.8, 184.9. MS: 292 (1, M^+), 201 (24), 171 (59), 143 (39), 115 (42), 105 (45), 104 (100), 91 (63), 89 (12). HRMS: calcd. for $C_{19}H_{16}O_3$ 201.0552 (M-91); found 201.0546

2-Phenethyloxymethylnaphthalene-1,4-diol (**3.22a**) was obtained following the procedure used for **3.3a**. Air-sensitive white solid, 90%. ^{1}H NMR ($CDCl_3$): δ 2.90 (t, *J* = 7.0 Hz, 2H), 3.69 (t, *J* = 7.0 Hz, 2H), 4.55 (s, 2H), 5.90 (s, 1H), 6.22 (s, 1H), 7.15-7.29 (m, 5H), 7.40-7.47 (m, 2H), 7.67 (s, 1H), 8.03-8.07 (m, 1H), 8.14-8.18 (m, 1H); ^{13}C NMR δ 36.7, 72.0, 72.9, 108.6, 114.7, 121.7, 122.3, 125.2, 126.0, 126.07, 126.11, 126.9, 128.9, 129.1, 138.4, 144.7, 145.6. HRMS: calcd. for $C_{19}H_{18}O_3$ 294,1256; found 294.1245

2-(4-Chlorophenoxymethyl)-1,4-naphthoquione (**3.21b**) was obtained following the procedure used for **3.12a**. Yellow crystals, 92%, mp 159-161 ^{0}C; ^{1}H NMR ($CDCl_3$): δ 5.05 (d, *J* = 2.0 Hz, 2H), 6.94 (dd, *J* = 9.0, 1.6 Hz, 2H), 7.16 (t, *J* = 2.0 Hz, 1H), 7.28 (d, *J* = 9.0, 1.6 Hz, 2H), 7.75-7.80 (m, 2H), 8.09-8.15 (m, 2H); ^{13}C NMR δ 63.8, 116.0, 126.4, 126.4, 126.7, 129.6, 131.9, 132.0, 133.9, 134.0, 134.2, 145.7, 156.4, 184.5, 184.6. MS: 300 (12, M^+), 298 (28, M^+), 283 (33), 281 (100), 269 (8), 263 (10), 143 (22),

115 (35), 99 (10), 89 (10), 76 (14). HRMS: calcd. for $C_{17}H_{11}ClO_3$ 298.0397; found 298.0390

2-(4-Chloro-phenoxymethyl)-naphthalene-1,4-diol (**3.22b**) was obtained following the procedure used for **3.3a**. Air-sensitive white solid, 92%. ^{1}H NMR ($CDCl_3$): δ 5.29 (s, 2H), 6.94 (s, 1H), 7.03 (dd, *J* = 6.8, 2.4 Hz, 2H), 7.28 (dd, *J* = 6.8, 2.4 Hz, 2H), 7.47-7.52 (m, 2H), 7.98 (s, 1H), 8.20-8.27 (m, 2H), 8.61 (s, 1H); ^{13}C NMR δ 66.6, 109.1, 117.2, 118.5, 122.7, 123.0, 125.8, 125.9, 126.4, 126.5, 127.5, 130.0, 143.8, 147.5, 128.5. HRMS: calcd. for $C_{17}H_{13}ClO_3$ 281.0369 (M-19); found 281.0360.

2-Bromo-3-methyl-1,4-naphthoquinone (3.25): Bromine (2 mL, 6.3 g, 39 mmol) was added to a solution of 2-methyl-1,4-naphthoquinone (5.5 g, 32 mmol) and anhydrous sodium acetate (11 g, 134 mmol) in glacial acetic acid (50 mL) with stirring. The flask was stoppered and allowed to stand in the dark for one week, then poured in water (300 mL) and filtered. The precipitate was thoroughly washed with water and recrystallized from methanol to obtain 2-methyl-3-bromo-1,4-naphthoquinone as bright yellow needles (mp148-150^{0}C); yield 6.18 g (77%). ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H), 7.73-7.77 (m, 2H), 8.11-8.17 (m, 2H); ^{13}C NMR: δ 18.10, 127.34, 127.73, 131.40, 131.76, 134.13, 134.34, 139.27, 148.72, 177.76, 182.18. MS: 252 (100), 250 (100, M^+), 171 (60), 143 (50), 115 (85), 89 (21), 76 (32). Lit[25]: mp 151-152^{0}C.

2-Bromo-1,4-dimethoxy-3-methylnaphthalene (3.26): A solution of $SnCl_2$ (8.9 g, 40 mmol) in concentrated HCl (20 mL) was added to the suspension of 3-bromo-2-methyl-1,4-naphthoquinone **3.25** (3 g, 11.9 mmol) in absolute ethanol (80 mL) for 10 min. The resulting solution was stirred at ambient temperature for 1 h and then concentrated *in vacuo*. Residue was poured in water (300 mL) and the precipitate

filtered, washed with brine and air dried for 30 min. It was washed away from the filter with acetone and the resulting solution dried over anhydrous $MgSO_4$. Drying agent was then removed by filtration and potassium carbonate (13.8 g, 100 mmol) followed by dimethyl sulfate (6 mL, 8 g, 63 mmol) was added to the filtrate. Resulting solution was stirred under reflux overnight, cooled down and filtered. All volatiles were evaporated *in vacuo* and the residue was applied on top of the chromatographic column. Desired 3-bromo-1,4-dimethoxy-2-methylnaphthalene was eluted with hexane-ether 4:1. Yield – 60% (2.02 g, 7.2 mmol). ^{1}H NMR ($CDCl_3$): δ 2.54 (s, 3H), 3.88 (s, 3H), 3.97 (s, 3H), 7.52 (td+td, 2H), 8.07 (dd+dd, 2H); ^{13}C NMR: δ 16.90, 61.51, 61.89, 117.47, 122.60, 122.63, 126.42, 126.76, 127.52, 127.77, 128.05, 150.05, 150.70. MS: 282 (66, $[M+2]^+$), 280 (75, M^+), 267 (99), 265 (100), 171 (36), 143 (32), 128 (15), 127 (16), 115 (43). Lit[26]: ^{1}H NMR ($CDCl_3$): δ 2.55 (s, 3H), 3.88, 3.97 (each 3H, s), 7.41-7.56 (m, 2H), 8.01-8.08 (m, 2H).

2-Bromo-3-bromomethyl-1,4-dimethoxynaphthalene (3.27): AIBN (~ 50 mg) was added to a solution of 2-bromo-1,4-dimethoxy-3-methylnaphthalene **3.26** (1.4 g, 5 mmol) and NBS (890 mg, 5 mmol) in CCl_4 (50 mL) and the reaction mixture was refluxed for 2 h. After cooling to room temperature it was filtered through a thin layer of silica gel and eluted with CH_2Cl_2. Evaporation of the solvents yielded colorless oil of dibromide **3.27** in 95% yield (1.71 g, 4.75 mmol). ^{1}H NMR ($CDCl_3$): δ 4.00 (s, 3H), 4.10 (s, 3H), 4.94 (s, 2H), 7.57-7.59 (m, 2H), 8.07-8.12 (m, 2H); ^{13}C NMR: δ 29.15, 61.67, 63.03, 115.44, 122.93, 123.34, 127.07, 127.25, 127.94, 128.00, 129.57, 150.86, 152.41. MS: 362 (21, $[M+4]^+$), 360 (45, $[M+2]^+$), 358 (23, M^+), 281 (100), 279 (95), 200 (60), 185 (86), 170 (10), 142 (12), 127 (27), 114 (27).

2-Bromo-1,4-dimethoxy-3-(phenethoxymethyl)naphthalene (3.28): 2-Phenylethanol (854 mg, 7 mmol) was added dropwise to a stirred suspension of sodium hydride (1 g of 60% dispersion in oil, 25 mmol) in dry THF (30 mL) and the resulting mixture was stirred for 1 hr. at ambient temperature. Then solution of dibromide **3.27** from the reaction above in THF (20 mL) was added and the reaction mixture was stirred for 2 h at 45^0C under argon. Unreacted NaH was carefully quenched with water, diluted with aqueous NH_4Cl (5%, 100 mL) and extracted with ether (3x40 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated. Column chromatography of the residue afforded ether **3.28** (1.72 g, 4.29 mmol, 90%) as a colorless oil which solidifies in the fridge. ^{1}H NMR ($CDCl_3$): δ 2.98 (t, 2H), 3.87 (t, 2H), 3.91 (s, 3H), 3.98 (s, 3H), 4.84 (s, 2H), 7.15-7.30 (m, 5H), 7.54-7.57 (m, 2H), 8.07-8.12 (m, 2H); ^{13}C NMR: δ 36.57, 61.59, 64.22, 67.47, 72.05, 116.73, 122.77, 123.29, 126.38 126.91, 127.59, 128.15, 128.53, 129.20, 129.44, 139.20, 150.39, 152.95. MS: 402 (100, $[M+2]^+$), 400 (87, M^+), 281 (70), 279 (72), 200 (79), 185 (65), 170 (10), 127 (18), 105 (47).

2-Bromo-3-(phenethoxymethyl)naphthalene-1,4-dione (3.29): Aqueous cerium ammonium nitrate (5.48 g, 10 mmol in 20 mL) was added to the solution of ether **3.28** (857 mg, 2.15 mmol) in acetonitrile (20 mL) and reaction mixture was stirred for 30 min at room temperature. It was then diluted with brine (100 mL) and the product extracted with CH_2Cl_2 (3x40 mL). The combined organic phase was washed with brine (2x70 mL), dried over anhydrous Na_2SO_4 and evaporated. Column chromatography of the residue afforded quinone **3.29** (480 mg, 1.3 mmol, 60%) as a yellow-browhish solid. ^{1}H NMR ($CDCl_3$): δ 2.91 (t, 2H), 3.82 (t, 2H), 4.71 (s, 2H), 7.11-7.24 (m, 2H), 7.75-7.80 (m, 2H),

8.11-8.17 (m, 2H); ^{13}C NMR: δ 36.52, 67.08, 72.88, 126.48, 127.49, 127.82, 128.57, 129.15, 131.27, 131.65, 134.26, 134.67, 138.79, 142.60, 145.75, 178.14, 181.52. MS: 281 (7, $[M+2–PhCH_2]^+$), 279 (9, $[M–PhCH_2^+]$), 251 (26), 249 (24), 223 (12), 221(12), 142 (8), 114 (16), 104 (100), 91 (88).

1,4-Dimethoxy-3-methyl-2-naphthonitrile (3.30): Copper (I) cyanide (360 mg, 62 mmol) was added to a solution of 2-bromo-3-methyl-1,4-dimethoxynaphthalene **3.26** (8.8 g, 31 mmol), in anhydrous DMF (50 mL). The reaction mixture was refluxed overnight. After cooling down it was poured into aqueous ammonia and extracted with ether (3x30 mL). The combined organic extracts were washed with brine (2x50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by silica gel chromatography afforded 1,4-dimethoxy-3-methyl-2-naphthonitrile **3.30** in 84% yield (6 g, 26 mmol) as yellowish solid. ^{1}H NMR ($CDCl_3$): δ 2.58 (s, 3H), 3.89 (s, 3H), 4.19 (s, 3H), 7.56 (td, 1H), 7.66 (td, 1H), 8.09 (d, 1H), 8.16 (td, 1H); ^{13}C NMR: δ 14.51, 61.78, 63.30, 103.36, 116.22, 122.55, 123.44, 126.57, 126.82, 127.08, 129.60, 131.37, 150.14, 158.47. MS: 227 (58, M^+), 213 (14), 212 (100), 184 (12), 115 (14), 76 (14).

3-(Bromomethyl)-1,4-dimethoxy-2-naphthonitrile (3.31): AIBN (~100 mg) was added with stirring to the suspension of 1,4-dimethoxy-3-methyl-2-naphthonitrile **3.30** (2 g, 8.8 mmol) and NBS (1.6 g, 9 mmol) in carbon tetrachloride (100 mL), and the reaction mixture refluxed for 2 hours. It was then cooled down to room temperature, filtered through thin layer of silica gel, eluted with ether and the filtrate evaporated in vacuo. The resulting crude 3-(bromomethyl)-1,4-dimethoxy-2-naphthonitrile **3.31** (2.6 g, 8.5 mmol) was used further without purification. MS: 307 (14), 305 (15, M^+), 226 (100), 211 (24), 195 (46), 184 (10), 140 (16), 113 (13), 76 (18).

1,4-Dimethoxy-3-(phenethoxymethyl)-2-naphthonitrile (3.32a): 2-Phenylethanol (1.71 g, 14 mmol) was added to the suspension of sodium hydride (50 mmol, 2 g of the 60% suspension in oil) in THF. The resulting mixture was stirred for 1 h and then crude 3-(bromomethyl)-1,4-dimethoxy-2-naphthonitrile **3.31** from the reaction above (2.6 g, 8.5 mmol) was added and the reaction mixture was stirred overnight at 50^0C. Excess sodium hydride was then carefully quenched with water (100 mL) and the product extracted with ether (3x40 mL). The combined organic phases were washed with brine, dried over anhydrous sodium sulfate and evaporated *in vacuo*. Column chromatography afforded desired 1,4-dimethoxy-3-(phenethoxymethyl)-2-naphthonitrile **3.32a** as yellow oil (1.65 g, 4.8 mmol) in 55% yield over 2 steps. ^{1}H NMR ($CDCl_3$): δ 2.99 (t, 2H), 3.87 (s, 3H), 3.89 (t, 2H), 4.21 (s, 3H), 4.79 (s, 3H), 7.15-7.27 (m, 5H), 7.62 (t, 1H), 7.68 (t, 1H), 8.12 (s, 1H), 8.19 (d, 1H); ^{13}C NMR: δ 36.48, 63.34, 64.10, 65.83, 72.52, 102.69, 115.85, 123.24, 123.59, 126.37, 126.40, 127.91, 128.55, 128.58, 129.21, 129.72, 131.32, 139.04, 151.76, 158.85. MS: 347 (57, M^+), 226 (100), 211 (16), 195 (38), 105 (14), 91 (18).

1,4-Dihydroxy-3-(phenethoxymethyl)-2-naphthonitrile (3.34a): To a stirred suspension of 1,4-dimethoxy-3-(phenethoxymethyl)-2-naphthonitrile **3.32a** (114 mg, 0.5 mmol) in glacial acetic acid (10 mL) was added dropwise concentrated nitric acid (2 mL) at room temperature. The resulting bright yellow solution was stirred for 30 min, poured in water and extracted with dichloromethane (3x30 mL). The combined organic extracts were washed consequently with diluted $NaHCO_3$ (2x50 ml) and water (50 mL), and then treated with aqueous solution of sodium dithionite (870 mg, 5 mmol) under vigorous stirring. After 30 min layers were separated, and an aqueous layer was extracted with

dichloromethane (2x50 mL). Combined organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Chromatography of the residue afforded desired hydroquinone **3.34a** (114 mg, 0.36 mmol) in 42% yield over 2 steps as yellowish solid. ^{1}H NMR ($CDCl_3$): δ 3.01 (t, 2H), 3.90 (t, 2H), 4.97 (s, 2H), 6.57 (s, br, 1H), 7.23-7.35 (m, 5H), 7.57 (t, 1H), 7.64 (td, 1H), 8.16-8.19 (s+d, 3H); ^{13}C NMR: δ 36.25, 70.96, 72.49, 91.00, 110.91, 116.14, 122.63, 122.82, 124.17, 126.94, 127.37, 128.61, 128.93, 129.03, 129.40, 138.04, 146.28, 151.98. MS:

3-(4-Chlorophenoxymethyl)-1,4-dimethoxy-2-naphthonitrile (3.32b): A solution of crude 3-(bromomethyl)-1,4-dimethoxy-2-naphthonitrile **3.31** in THF (10 mL) was added to a stirred mixture of 4-chlorophenol (2.55 g, 20 mmol) and K_2CO_3 (2.75 g, 20 mmol) in THF (40 mL). The reaction mixture was stirred at 60^{0}C for 5 h, then poured into dilute aqueous NH_4Cl (150 mL) and the product was extracted with ether (3x50mL). Organic phase was washed with sodium hydroxide (1M, 2x50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. Chromatography of the residue afforded 1.287 g (3.6 mmol, 60% yield over 2 steps) of the desired ether **3.32b** as white solid. ^{1}H NMR ($CDCl_3$): δ 3.98 (s, 3H), 4.24 (s, 3H), 5.29 (s, 2H), 7.02 (d, 2H), 7.28 (d, 2H), 7.66 (t, 1H), 7.72 (t, 1H), 8.16 (d, 1H), 8.23 (d, 1H); ^{13}C NMR δ 63.37, 63.78, 64.34, 101.98, 115.56, 116.65, 123.31, 123.75, 124.46, 126.65, 128.33, 128.91, 129.69, 130.01, 131.18, 151.10, 157.47, 159.14. MS: 355 (<1), 353 (M^+, 2), 226 (100), 211 (16), 195 (38), 184 (8), 168 (4), 153 (7), 140 (8), 99 (7).

3-(4-Chlorophenoxymethyl)-1,4-dihydroxy-2-naphthonitrile (3.34b): Concentrated nitric acid (5 mL) was added dropwise to a stirred suspension of 3-(4-chlorophenoxymethyl)-1,4-dimethoxy-2-naphthonitrile **3.32b** (177 mg, 0.5 mmol) in

glacial acetic acid (10 mL) at room temperature. Resulting bright yellow solution was stirred for 3 h, poured in water (100 mL) and extracted with dichloromethane (3x20 mL). The combined organic extracts were washed consequently with diluted $NaHCO_3$ (50 ml) and water (50 mL), and then vigorously stirred with aqueous solution of sodium dithionite (870 mg, 5 mmol, 25 mL) for 1 h. The layers were separated and an aqueous phase was extracted with ether (2x30 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, passed through thin layer of celite and solvent was evaporated *in vacuo*. The residue was then recrystallized from chloroform to give the desired 3-(4-chlorophenoxymethyl)-1,4-dihydroxy-2-naphthonitrile **3.34b** (52 mg, 0.16 mmol, 32%) as a white solid. ^{1}H NMR (acetone): δ 5.39 (s, 2H), 7.10 (dd, 2H), 7.34 (dd, 2H), 7.71 (t, 1H), 7.76 (t, 1H), 8.36 (d, 2H); ^{13}C NMR δ 64.06, 95.83, 115.103, 115.76, 116.67, 122.93, 123.10, 125.57, 126.00, 127.65, 129.07, 129.17, 129.45, 145.57, 152.60, 157.99.

3-Methyl-1,4-dioxo-1,4-dihydronaphthalene-2-carbonitrile (3.35): Concentrated nitric acid (2 mL) was added dropwise to a stirred suspension of 1,4-dimethoxy-3-methyl-2-naphthonitrile **3.30** (114 mg, 0.5 mmol) in glacial acetic acid (10 mL) at room temperature. The resulting bright yellow solution was stirred for 30 min, poured in water and extracted with dichloromethane (3x30 mL). The combined organic extracts were washed consequently with dilute sodium bicarbonate (10%, 2x50 mL) and water (50 mL), dried over anhydrous Na_2SO_4, filtered and evaporated to obtain essentially pure quinone **3.35** (94 mg, 0.48 mmol) as a yellow solid in 95% yield. ^{1}H NMR ($CDCl_3$): δ 2.52 (s, 3H), 7.82-7.85 (m, 2H), 8.14-8.17 (m, 2H); ^{13}C NMR: δ 16.76, 112.67, 122.45,

127.32, 127.54, 131.23, 131.77, 135.04, 135.12, 156.76, 178.69, 182.80. MS: 197 (100, M^+), 169 (32), 141 (42), 114 (21), 104 (76), 76 (90), 50 (55).

Potassium 1,4-dihydroxy-3-methylnaphthalene-2-sulfonate (3.36): A solution of menadione (17.2 g, 100 mmol) and sodium bisulfite (12 g, 116 mmol) in water (30 mL) was refluxed for 22 h and then cooled down to room temperature and filtered. Saturated aqueous KCl (30 mL) was added to the filtrate and the resulting solution was kept at – 18^0C overnight in the freezer. Precipitated sulfonate **3.36** was filtered and recrystallized from water (10 mL). Yield – 9.5 g, 33 mmol, 33%. ^{1}H NMR (D_2O): δ 2.39 (s, 3H), 7.18 (t, 1H), 7.30 (t, 1H), 7.69 (d, 1H), 7.81 (d, 1H); ^{13}C NMR: δ 13.01, 117.29, 118.69, 120.93, 122.94, 123.41, 125.73, 127.93, 128.44, 141.15, 145.29.

Methyl 1,4-dimethoxy-3-methylnaphthalene-2-sulfonate (3.37): Potassium carbonate (27.5 g, 0.2 mol) followed by dimethyl sulfate (10 mL) was added to the suspension of potassium 1,4-dihydroxy-3-methylnaphthalene-2-sulfonate **3.36** in acetone. The resulting solution was refluxed overnight, cooled, and filtered. The volatiles were evaporated *in vacuo* and the residue was applied on top of the chromatographic column. Methyl 1,4-dimethoxy-3-methylnaphthalene-2-sulfonate **3.37** was eluted with hexane-ether 3:1. Yield – 5.90 g (20 mmol, 61%), colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.70 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 4.08 (s, 3H), 7.59 (td, 1H), 7.68 (td, 1H), 8.11 (d, 1H), 8.19 (td, 1H); ^{13}C NMR: δ 14.00, 56.58, 61.78, 64.85, 122.79, 124.39, 125.41, 125.56, 127.11, 127.77, 129.80, 131.55, 151.38, 154.51. MS: 296 (100, M^+), 281 (30), 249 (43), 185 (21), 143 (12), 128 (20), 115 (29).

(*E*)-4-(2,5-Dimethoxyphenyl)-3-(ethoxycarbonyl)but-3-enoic acid (3.38): Potassium *t*-butoxide (2.24 g, 20 mmol) was added in portions to a stirred solution of

dimethoxybenzaldehyde (1.66 g, 10 mmol) and diethylsuccinate (4.35 g, 25 mmol) in *tert*-butanol. The reaction mixture was stirred at 25^0C for 1 h (monitored by TLC) then poured into aqueous HCl (10%, 50 mL), and extracted with ethyl acetate (3x50 mL). The combined organic extracts were treated with aqueous sodium carbonate (0.25M, 2x100 mL) and the resulting aqueous solution was washed with ethyl acetate (50 mL), acidified with an excess of saturated HCl to pH 1 and extracted with ethyl acetate (3x50 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, passed through silica gel and evaporated *in vacuo* to afford crude carboxylic acid **3.38** as an oil. MS: 294 (100, M^+), 206 (16), 193 (10), 167 (16), 166 (49), 165 (36), 151 (18), 91 (10), 55 (40).

Ethyl 4-acetoxy-5,8-dimethoxy-2-naphthoate (3.39): Anhydrous sodium acetate (1 g, 12.2 mmol) was added to the solution of carboxylic acid **3.38** in acetic anhydride (15 mL) with stirring. Reaction mixture was refluxed for 2 h, cooled to 25^0C, poured into iced water and the product was extracted with ethyl acetate (3x50 mL). The combined organic extracts were thoroughly washed with sodium bicarbonate (4x50 mL), dried over anhydrous Na_2SO_4, passed through silica gel and evaporated under reduced pressure to obtain crude oily acetate **3.39**. MS: 318 (32, M^+), 276 (100), 261 (69), 233 (14).

Ethyl 4-hydroxy-5,8-dimethoxy-2-naphthoate (3.40): Sodium ethoxide (3 g, 44 mmol) was added to the suspension of crude acetate **3.39** in ethanol (250 mL). The resulting mixture was refluxed for 3 h, cooled to ambient temperature, concentrated to half of the initial volume *in vacuo* and poured into aqueous HCl (10%, 75 mL). The product was extracted with ether (3x100 mL) and the combined organic extracts were

washed with brine (2x100 mL), dried over anhydrous Na_2SO_4, passed through silica gel and evaporated under reduced pressure. Naphthol **3.40** was obtained as yellow oil and loaded to the next reaction without further purification. MS: 276 (100, M^+), 261 (79), 233 (25), 231 (7).

Ethyl 4-(*tert*-butyldimethylsilyloxy)-5,8-dimethoxy-2-naphthoate (3.41): Imidazole (13.6 g, 200 mmol) and *t*-butyldimethylsilylchloride (15 g, 100 mmol) were added to the solution of crude naphthol **3.40** in DMF (100 mL). The reaction mixture was stirred overnight, then poured into aqueous sodium bicarbonate (30%, 100 mL) and the product was extracted with ether (3x70 mL). The organic extracts were washed consequently with sodium bicarbonate (10%, 2x50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography (toluene-hexane) on the residue afforded desired product **3.41** in 40% yield over 4 steps (1.55 g, 4 mmol) as yellowish oil. ^{1}H NMR ($CDCl_3$): δ 0.24 (s, 1H), 1.06 (s, 9H), 1.43 (t, 3H), 3.87 (s, 3H), 3.96 (d, 3H), 4.42 (q, 2H), 6.74 (d, 1H), 6.79 (d, 1H), 7.47 (d, 1H), 8.60 (d, 1H); ^{13}C NMR: δ -4.36, 14.39, 18.59, 25.94, 55.77, 61.01, 104.39, 107.06, 115.80, 117.83, 118.02, 122.46, 127.59, 128.27, 150.14, 150.68, 152.43, 166.74. MS: 390 (8, M^+), 333 (19), 319 (24), 318 (100), 303 (23), 275 (12).

(4-(*tert*-Butyldimethylsilyloxy)-5,8-dimethoxynaphthalen-2-yl)methanol (3.42): DIBAL-H (1.21M in toluene, 8 mL, 9.7 mmol) was successfully added to the solution of ethyl naphthoate **3.41** (1.55 g, 4 mmol) in CH_2Cl_2 (50 mL) at –78^{0}C. The reaction mixture was stirred at the same temperature for 2 h, quenched with methanol (5 mL) and warmed up to ambient temperature. It was then poured in aqueous HCl (15%, 100 mL), layers were separated and aqueous layer was extracted with ether (3x30 mL). The

combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, passed through silica gel and evaporated at reduced pressure. Column chromatography of the residue afforded desired alcohol **3.42** in 94% yield (1.31 g, 3.75 mmol) as an oil, which crystallizes in the fridge (mp 73-75^{0}C). ^{1}H NMR ($CDCl_3$): δ 0.22 (s, 6H), 1.05 (s, 9H), 1.72 (t, broad, 1H), 3.85 (s, 3H), 3.94 (s, 3H), 4.77 (d, 2H), 6.67 (d, 1H), 6.70 (d, 1H), 6.91 (d, 1H), 7.83 (d, 1H); ^{13}C NMR: δ -4.31, 18.62, 25.97, 55.61, 55.74, 65.54, 104.11, 104.45, 112.71, 115.83, 119.80, 128.94, 138.71, 149.22, 150.90, 152.61. MS: 348 (14, M^+), 291 (12), 278 (5), 277 (20), 276 (100), 274 (6), 262 (8), 261 (36), 73 (8).

(4-(*tert*-Butyldimethylsilyloxy)-5,8-dimethoxynaphthalen-2-yl)methyl benzoate (3.43): Benzoyl chloride (350 mg, 2.5 mmol) was added dropwise to the solution of alcohol **3.42** (770mg, 2.2 mmol) in dichloromethane (50 mL) and triethylamine (5 mL). The reaction mixture was stirred overnight at 25^{0}C, and then concentrated under reduced pressure. The crude residue was suspended in ether (75 mL), washed with brine (3x40 mL), dried over anhydrous Na_2SO_4, filtered through silica gel and evaporated *in vacuo*. Column chromatography of the residue afforded benzoate **3.43** in 91% yield (904 g, 2 mmol). ^{1}H NMR ($CDCl_3$): δ 0.20 (s, 6H), 1.03 (s, 9H), 3.85 (s, 3H), 3.94 (s, 3H), 5.44 (s, 2H), 6.69-6.71 (m, 2H), 7.00 (s, 1H), 7.52-7.55 (m, 2H), 7.92 (s, 1H), 8.09 (d, 1H), 8.17 (dd, 2H); ^{13}C NMR: δ -4.4, 18.6, 25.9, 55.67, 55.74, 66.9, 104.2, 104.9, 114.6, 116.6, 126.3, 128.3, 128.9, 129.7, 130.6, 133.0, 134.5, 149.3, 150.8, 152.6, 166.4.

(4-Hydroxy-5,8-dimethoxynaphthalen-2-yl)methyl benzoate (3.44): Tetra-*n*-butylammonium fluoride (1.04 g, 4 mmol) was dissolved in minimal volume of THF and added dropwise to a stirred solution of benzoate **3.43** (904 g, 2 mmol) in THF (50 mL) at

0^0C. After 15 min reaction was quenched with dilute aqueous NH_4Cl (100 mL) and extracted with ether (3x50 mL). Combined organic extract was washed with brine (2x75 mL), dried over anhydrous Na_2SO_4 and evaporated. Column chromatography afforded 700 mg of the crude material, containing unseparatable on silica gel mixture of 2 compounds one of which was desired naphthol **3.44**. MS: 338 (100, M^+), 323 (17), 233 (11), 205 (18), 187 (7), 159 (7), 105 (33), 77 (17).

(5,8-Dimethoxy-3,4-dioxo-3,4-dihydronaphthalen-2-yl)methyl benzoate (3.45): Salcomine (N,N'-disalicylalethylenediamine cobalt (II), 140 g, 0.43 mmol) was added with stirring to the solution of crude naphthol **3.44** in acetonitrile (50 mL) at 25^0C. The air was bubbled through the solution overnight, and then extra amount of salcomine (280 mg, 0.85 mmol) was added and the reaction mixture was stirred in opened to air flask for 2 more days. The resulting solution was filtered through silica gel and evaporated in vacuo. Column chromatography of the residue afforded naphtho-1,2-quinone **3.45** (170 mg, 0.48 mmol) as a copper-red solid (mp 147-150^0C). ^{1}H NMR ($CDCl_3$): δ 3.89 (s, 3H), 3.96 (s, 3H), 5.21 (d, 2H), 7.08 (d, 1H), 7.20 (d, 1H), 7.45 (t, 2H), 7.57 (t, 1H), 8.07 (d, 1H), 8.09 (d, 2H); ^{13}C NMR: δ 56.51, 56.61, 61.04, 116.96, 119.23, 120.59, 123.13, 128.42, 129.77, 129.82, 132.31, 133.19, 137.48, 151.07, 157.20, 166.26, 117.97, 179.77.

(3,4-Dihydroxy-5,8-dimethoxynaphthalen-2-yl)methyl benzoate (3.46): Aqueous sodium dithionite (870 mg, 5 mmol) was added dropwise to the solution of quinone **3.45** (170 mg, 0.48 mmol) in chloroform (30 mL) with vigorous stirring. Upon completion of the reaction (30 min) the layers were separated and the product was extracted with CH_2Cl_2 (2x30 mL). The combined organic extracts were washed with brine, dried over

anhydrous Na_2SO_4 and evaporated under reduced pressure. Column chromatography of the residue afforded hydronaphthoquinone **3.46** (114 mg, 0.32 mmol) in 67% yield as white solid (mp 102-105^{0}C). ^{1}H NMR ($CDCl_3$): δ 3.92 (s, 3H), 4.00 (s, 3H), 5.58 (s, 2H), 6.04 (s, 1H), 6.48 (d, 1H), 6.64 (d, 1H), 7.42 (t, 2H), 7.54 (t, 1H), 7.83 (s, 1H), 8.10 (d, 2H), 9.31 (s, 1H); ^{13}C NMR δ 55.62, 56.27, 62.70, 100.52, 103.95, 114.27, 115.65, 121.31, 123.82, 128.29, 129.80, 130.30, 132.88, 138.33, 139.77, 148.68, 150.41, 166.71.

2-(4-Phenyl-1,3-dioxolan-2-yl)phenol (3.48): Tetra-*n*-butylammonium tribromide (Bu_4NBr_3, 43 mg, 0.1 mmol) was added to the solution of salicaldehyde (5 mmol, 610 mg) and phenylethyleneglycol (5 mmol, 700 mg) in triethylorthoformate (20 mmol, 3 g). The reaction mixture was stirred overnight, then diluted with ether (70 mL), washed with brine (2x50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Chromatographic separation of the residue afforded both diastereoisomers of desired acetal: I (290 mg, 25%) and II (400 mg, 35%). Diasteroisomer I: ^{1}H NMR ($CDCl_3$): δ 3.90 (t, 1H), 4.52 (dd, 1H), 5.22 (t, 1H), 6.34 (s, 1H), 6.89-6.93 (m, 2H), 7.23-7.43 (m, 7H), 7.79 (s, 1H); ^{13}C NMR: δ 72.43, 77.89, 105.05, 117.50, 120.28, 121.59, 126.30, 128.19, 128.72, 129.07, 131.00, 138.78, 155.55. MS: 242 (6, M^+), 123 (12), 122 (100), 121 (56), 107 (12), 103 (21), 91 (31), 77 (23). Diastereoisomer II: ^{1}H NMR ($CDCl_3$): δ 3.96 (t, 1H), 4.38 (t, 1H), 5.21 (t, 1H), 6.09 (s, 1H), 6.89-6.93 (m, 2H), 7.27-7.40 (m, 7H), 7.75 (s, 1H); ^{13}C NMR: δ 72.00, 79.04, 105.43, 117.51, 120.24, 120.74, 126.74, 128.72, 128.94, 129.12, 131.12, 138.38, 155.67. MS: 242 (5, M^+), 123 (12), 122 (100), 121 (59), 107 (12), 103 (21), 91 (32), 77 (23).

2-(1,3-Dioxolan-2-yl)-6-methoxyphenol (3.49): Tetra-*n*-butylammonium tribromide (75 mg, 0.15 mmol) was added to the solution of *o*-vanillin (751 mg, 5 mmol) in triethyl orthoformate (1.8 mL, 1.6 mg, 11 mmol) and ethylene glycol (2.2 mL, 2.5 g, 40 mmol). The reaction mixture was stirred at room temperature for 5 h and then directly applied on silica gel impregnated with triethylamine (5%). The product was eluted with ether (40-95%)-hexane (55-0%)-Et_3N (5%) eluent. Acetal **3.49** was obtained as a colorless oil in 62% yield (611 mg, 3.1 mmol). ^{1}H NMR ($CDCl_3$): δ 3.78 (s, 3H), 3.97 (m, 2H), 4.05 (m, 2H), 6.04 (s, 1H), 6.78 (m, 2H), 6.95 (dd, 1H); ^{13}C NMR δ 56.26, 65.30, 100.91, 111.83, 119.15, 119.70, 122.90, 144.55, 147.17. MS: 196 (M^+, 68), 152 (47)137 (18), 122 (17), 109 (25), 106 (100), 73 (35).

2-Formylnaphthalen-1-yl acetate (3.51): Acetic anhydride (12 mmol) was added with stirring to the solution of 2-hydroxy-1-naphthaldehyde **3.50** (1.72 g, 10 mmol) in dichloromethane (50 mL) and triethylamine (10 mL). The reaction mixture was stirred overnight at room temperature and then all volatiles were removed *in vacuo*. The resulting residue was purified on silica gel column (ether-hexane 1:3) to obtain desired 2-acetoxy-1-naphthaldehyde **3.51** in 90 % yield (1.92 g, 9 mmol) as yellowish solid (mp 79-83^{0}C). ^{1}H NMR ($CDCl_3$): δ 2.37 (s, 3H), 7.19 (dd, 1H), 7.49 (td, 1H), 7.61 (td, 1H), 7.81 (dd, 1H), 8.03 (d, 1H), 9.07 (dd, 1H), 10.64 (s, 1H); ^{13}C NMR: δ 21.11, 121.58, 121.82, 125.25, 126.87, 128.67, 129.83, 131.33, 131.97, 136.69, 154.59, 169.42, 190.20. MS: 214 (10, M^+), 172 (100), 171 (52), 144 (53), 115 (54), 89 (13).

2-(1,3-Dioxolan-2-yl)naphthalen-1-yl acetate (3.52): Trimethylsilyl triflate (3 drops) followed by **3.51** were added to the solution of 1,2-*bis*((trimethylsilyl)oxy)ethane (3 mmol, 618 mg) in CH_2Cl_2 (50 mL) at -78^{0}C. The reaction was monitored by TLC and

quenched with triethylamine (0.2 mL) after 2 h. It was then warmed up to ambient temperature, washed with sodium bicarbonate and brine, dried over anhydrous Na_2SO_4 and filtered through silica gel to obtain desired acetal **3.52** in 95% yield (617 mg, 2.4 mmol). ^{1}H NMR ($CDCl_3$): 2.37 (s, 3H), 4.13 (td, 2H), 4.34 (td, 2H), 6.37 (s, 1H), 7.17 (d, 1H), 7.52 (m, 2H), 7.87 (d+d, 2H), 8.37 (d, 1H); δ; ^{13}C NMR: δ 21.24, 65.54, 100.34, 121.76, 121.92, 125.36, 125.88, 126.98, 128.80, 131.75, 132.22, 132.55, 148.32, 169.68. MS: 258 (9, M^+), 216 (50), 199 (54), 171 (59), 157 (14), 144 (68), 127 (17), 115 (55), 87 (100).

2-(1,3-Dioxolan-2-yl)-4-methoxyphenol (3.55a): General procedure (method A): Tetra-*n*-butylammonium tribromide (ca. 25 mg) was added to the solution of 2-hydroxy-5-methoxybenzaldehyde (751 mg, 5 mmol) in triethyl orthoformate (0.91 mL, 810 mg, 5.5 mmol) and ethylene glycol (1.11 mL, 1.24 g, 20 mmol). The reaction mixture was stirred at room temperature overnight and then directly applied on the column packed with silica gel impregnated with triethylamine (5%). The product was eluted with ether (40-95%)-hexane (55-0%)-Et_3N (5%) eluent. Acetal **3.55a** was obtained as a colorless oil in 89% yield (870 mg, 4.4 mmol). ^{1}H NMR ($CDCl_3$): δ 3.75 (s, 3H), 4.07 (m, 2H), 4.13 (m, 2H), 5.92 (s, 1H), 6.79 – 6.83 (m, 3H); ^{13}C NMR δ 56.0, 65. 0, 104.0, 112.9, 116.8, 118.2, 121.6, 149.3, 153.2. MS: 196 (78, M^+), 152 (100), 151 (22), 137 (85), 109 (19), 95 (11), 81 (13), 73 (16), 65 (14).

2-(5,5-Dimethyl-1,3-dioxan-2-yl)-4-methoxyphenol (3.55b): General procedure (method B): *p*-Toluenesulfonic acid (ca. 25 mg) was added to the solution of 2-hydroxy-5-methoxybenzaldehyde (751 mg, 5 mmol) neopentyl glycol (572 mg, 5.5 mmol) and triethyl orthoformate (0.91 mL, 810 mg, 5.5 mmol) in dichloromethane (10 mL). The

reaction mixture was stirred at room temperature overnight and then applied on the silica gel column. Acetal **3.55b** was eluted with ether (40-95%)-hexane (55-0%)-Et_3N (5%) as a colorless oil in 74% yield (880 mg, 3.7 mmol). ^{1}H NMR ($CDCl_3$): δ 0.82 (s, 3H), 1.28 (s, 3H), 3.67 (d, 2H), 3.74 (s, 3H), 3.81 (d, 2H), 5.51 (s, 1H), 6.75 – 6.84 (m, 3H), 7.58 (s, br, 1H); ^{13}C NMR δ 22.0, 23.2, 30.6, 56.1, 102.9, 112.8, 116.6, 118.2, 122.4, 149.3, 153.1. MS: 238 (32, M^+), 153 (9), 152 (100), 137 (35), 109 (5), 95 (3), 81 (4), 69 (6), 65 (5).

4-Methoxy-2-(4-phenyl-1,3-dioxolan-2-yl)phenol (3.55c) was synthesized according to method A in 37% yield as a colorless oil containing unseparatable mixture of diastereomers. ^{1}H NMR ($CDCl_3$): diastereomer I: δ 3.77 (s, 3H), 3.92 (t, 1H), 4.42 (t, 1H), 5.22 (t, 1H), 6.10 (s, 1H), 6.87 (m, 3H), 7.34 – 7.42 (m, 5H); diastereomer II: δ 3.77 (s, 3H), 3.97 (t, 1H), 4.52 (t, 1H), 5.24 (t, 1H), 6.35 (s, 1H), 6.87 (m, 3H), 7.34 – 7.42 (m, 5H).

4-Methoxy-2-(4-(phenoxymethyl)-1,3-dioxolan-2-yl)phenol (3.55d) was synthesized according to method B in 75% total yield of both diastereomers (separated) as colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.65 (s, 3H), 4.12 (m, 4H), 4.55 (m, 1H), 6.05 (s, 1H), 6.71 – 6.79 (m, 2H), 6.91 – 6.98 (m, 3H), 7.00 (d, 1H), 7.26 (m, 2H); ^{13}C NMR δ 55.0, 67.1, 68.3, 74.7, 101.3, 112.6, 114.4, 114.5, 116.3, 116.5, 121.0, 123.1, 129.4, 149.9, 153.0. MS: 302 (100, M^+), 211 (13), 208 (10), 152 (83), 137 (37), 121 (19), 107 (17), 105 (11), 95 (18), 79 (13), 77 (41).

4-Methoxy-2-(5-phenyl-1,3-dioxan-2-yl)phenol (3.55e) was synthesized according to method B in 74% total yield of both diastereomers (separated) as colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.73 (s, 3H), 4.06 – 4.11 (m, 3H), 4.22 – 4.27 (m, 2H), 5.89 (s, 1H),

6.76 (m, 2H), 7.05 (d, 1H), 7.23 – 7.35 (m, 5H); ^{13}C NMR δ 55.0, 60.4, 72.2, 98.2, 112.1, 115.7, 116.3, 124.9, 127.3, 127.7, 128.6, 137.8, 148.7, 153.0. MS: 286 (34, M^+), 152 (100), 137 (22), 104 (12), 91 (37), 78 (11), 77 (12).

2-(2,5-Dimethoxyphenyl)-5,5-dimethyl-1,3-dioxane (3.56): *p*-Toluenesulfonic acid (~ 25 mg) was added to the solution of dimethoxybenzaldehyde (830 mg, 5 mmol) and neopentyl glycol (2.08 g, 20 mmol) in benzene (100 mL). The reaction mixture was refluxed overnight, cooled to room temperature and then washed with sodium bicarbonate (10%, 2x75 mL). The organic phase was dried over anhydrous Na_2SO_4 and all volatiles were evaporated *in vacuo*. The product was obtained essentially pure in 97% yield (1.22g, 4.85 mmol) and used without further purification. ^{1}H NMR (acetone-d6, 400 MHz): δ 0.78 (s, 3H), 1.27 (s, 3H), 3.64 (d, 2H), 3.67 (d, 2H), 3.75 (s, 3H), 3.77 (s, 3H), 5.69 (s, 1H), 6.89 (m, 2H), 7.17 (d, *J* = 3.2, 1H); ^{13}C NMR (acetone-d6, 400 MHz): δ 21.9, 23.4, 30.7, 55.8, 56.6, 78.1, 97.4, 113.0, 114.0, 115.2, 129.1, 129.3, 151.8, 154.5. MS: 252 (77, M^+), 221 (21), 166 (100), 151 (23), 138 (30), 135 (24), 120 (26), 69 (59).

2-(5,5-Dimethyl-1,3-dioxan-2-yl)-1,4-benzoquinone (3.57): Silver oxide (490 mg, 4 mmol) followed by nitric acid (6M, 1 mL) were added to the solution of 2-(2,5-dimethoxyphenyl)-5,5-dimethyl-1,3-dioxane **3.56** (504 mg, 2 mmol) in dioxane (50 mL). The resulting suspension was stirred for 30 min and then quenched with sodium bicarbonate (10%, 100 mL) and the product was extracted with dichloromethane (3x30 mL). The combined organic layers were washed with $NaHCO_3$, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. Column chromatography on the residue afforded 330 mg (1.5 mmol, 75%) of the desired **3.57** as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.79

(s, 3H), 1.24 (s, 3H), 3.63 (d, *J* = 10.8, 2H), 3.72 (d, *J* = 11.2, 2H), 5.46 (s, 1H), 6.77 (s, 2H), 7.04 (s, 1H); ^{13}C NMR: δ 22.0, 23.1, 30.6, 77.9, 94.7, 133.2, 136.5, 136.8, 143.2, 185.8, 188.0. MS: 224 (18, $[M+2]^+$), 138 (92), 137 (38), 136 (83), 108 (35), 69 (40), 56 (100).

2-(5,5-Dimethyl-1,3-dioxan-2-yl)benzene-1,4-diol (3.58): Aqueous solution of sodium dithionite (870 mg, 5 mmol, 25 mL) was added to the solution of 2-(5,5-dimethyl-1,3-dioxan-2-yl)-1,4-benzoquinone **3.57** (330 mg, 1.5 mmol) in dichloromethane (25 mL). The resulting suspension was vigorously stirred for 5 min and the layers were separated. The product was extracted with ether (3x30 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and then evaporated *in vacuo*. Column chromatography of the residue afforded title hydroquinone **3.58** in 62% yield (205 mg, 0.9 mmol). ^{1}H NMR (acetone-d_6, 400 MHz): δ 0.80 (s, 3H), 1.26 (s, 3H), 3.68 (d, *J* = 10.4, 2H), 3.73 (d, *J* = 10.8, 2H), 5.62 (s, 3H), 6.67 (m, 2H), 6.89 (m, 1H), 7.64 (s, 1H), 7.72 (s, 1H); ^{13}C NMR: δ 21.9, 23.2, 30.8, 78.0, 100.6, 115.0, 117.2, 117.5, 125.6, 148.8, 150.9. MS: 224 (20, M^+), 138 (100), 137 (29), 120 (4), 109 (3), 92 (4), 81 (6), 69 (8).

2,5-Dimethoxystyrene (3.65): Methyltriphenyl phosphonium bromide (35.7 g, 100 mmol) was suspended in THF (300 mL) and *n*-butyllithium in hexane (2.2M, 50 mL, 110 mmol) was added dropwise under nitrogen. The resulting yellow solution was stirred for 3 h at room temperature, and then 2,5-dimethoxybenzaldehyde (16.6 g, 100 mmol) in THF (100 mL) was added dropwise. The reaction mixture was refluxed overnight, then cooled to room temperature, filtered, and washed consequently with aqueous ammonium chloride (10%, 3x100 mL) and brine (100 mL). The organic solution was

dried over anhydrous Na_2SO_4, filtered, and all volatiles were removed *in vacuo*. Column chromatography on the residue afforded dimethoxystyrene **3.65** in 79% yield (13g, 79 mmol) as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.79 (s, 3H), 3.81 (s, 3H), 5.27 (dd, 1H), 5.72 (dd, 1H), 6.80 (m, 2H), 7.03 (m, 2H); ^{13}C NMR δ 56.0, 56.5, 113.1, 112.5, 114.0, 114.9, 127.8, 131.7, 151.4, 153.9. MS: 164 (100, M+), 149 (52), 121 (66), 91 (83), 89 (16), 78 (34), 77 (39).

(2,5-Dimethoxyphenyl)ethanediol (3.66): Glacial acetic acid (100 mL) was added to the mixture of dimethoxystyrene **3.65** (13 g, 79 mmol), sodium periodate (5.14 g, 24 mmol, 30 mol%) and dry lithium bromide (1.4 g, 16 mmol, 20 mol%). The reaction mixture was stirred at 100^{0}C overnight, then cooled, partially concentrated in vacuo and poured in water (250 mL). The product was extracted with ethyl acetate (3x50 mL), and combined organic layers were washed with aqueous sodium bicarbonate (2x75 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was redissolved in methanol (100 mL) and stirred with potassium carbonate (16.5 g, 120 mmol) for 20 h. The resulting mixture was then filtered, concentrated *in vacuo* and the residue redissolved in ethyl acetate (150 mL), washed with brine (3x50 mL) dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The resulting crude product was purified by column chromatography to afford pure diol in 71% yield (11.1 g, 56 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.65 (q, 1H), 3.72 (q, 1H), 3.77 (s, 3H), 3.79 (s, 3H), 5.02 (dd, 1H), 6.79 (m, 2H), 6.99 (d, 1H); ^{13}C NMR δ 55.97, 56.03, 66.8, 71.3, 11.7, 113.3, 113.5, 129.8, 150.8, 154.0. MS: 198 (22), 167 (100), 152 (18), 139 (59), 137 (40), 124 (36), 109 (15), 108 (12), 77 (14).

4-(2,5-Dimethoxyphenyl)-2,2-diethyl-1,3-dioxolane (3.68a): General procedure: *p*-Toluenesulfonic acid (ca. 25 mg) was added to the solution of pentanone-3 (950 mg, 11 mmol), (2,5-dimethoxyphenyl)ethanediol **3.66** (2 g, 10 mmol) and triethyl orthoformate (1.8 mL, 1.62 g, 11 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at room temperature overnight and then applied on the silica gel column. Acetal **3.68a** was obtained in 77% yield (2.05 g, 7.7 mmol). ^{1}H NMR ($CDCl_3$): δ 0.99 (m, 6H), 1.77 (m, 4H), 3.55 (t, 1H), 3.77 (s, 3H), 3.79 (s, 3H), 4.45 (td, 1H), 5.30 (td, 1H), 6.77 (d, 2H), 7.19 (d, 1H); ^{13}C NMR δ 8.4, 8.5, 29.7, 30.1, 55.9, 56.0, 71.3, 73.6, 111.1, 112.1, 112.9, 113.0, 129.8, 150.7, 154.0. MS: 266 (44, M^+),238 (14), 237 (100), 181 (35), 151 (14), 149 (17), 121 (19), 100 (20), 91 (20), 77 (20).

4-(2,5-Dimethoxyphenyl)-2-phenyl-1,3-dioxolane (3.68b): Colorless liquid, 85% yield, mixture of diastereomers in 1:1 ratio. ^{1}H NMR ($CDCl_3$): δ 3.69-3.87 (4s, 12H + 2t, 2H), 4.46 (t, 1H), 4.67 (t, 1H), 5.47 (2t, 2H), 5.98 (s, 1H), 6.08 (s, 1H), 6.79 (m, 4H), 7.12 (m, 1H), 7.19 (m, 1H), 7.40 – 7.54 (m, 5H), 7.55 – 7.59 (m, 5H). MS: 286 (100, M^+), 227 (11), 180 (48), 164 (17), 149 (40), 119 (44), 105 (39), 91 (74), 89 (16), 77 (53).

2-(2,5-Dimethoxyphenyl)-1,4-dioxaspiro[4.5]decane (3.68c): Colorless liquid, 72% yield. ^{1}H NMR ($CDCl_3$): δ 1.43 – 1.75 (m, 10H), 3.59 (t, 1H), 3.76 (s, 3H), 3.79 (s, 3H), 4.43 (td, 1H), 5.33 (t, 1H), 6.76 (d, 2H), 7.16 (s, 1H); ^{13}C NMR δ 24.17, 24.24, 25.5, 35.7, 36.2, 55.95, 56.03, 70.6, 73.0, 109.9, 111.1, 112.4, 112.7, 130.4, 150.7, 154.0. MS: 278 (66, M^+), 235 (29), 180 (60), 164 (56), 151 (42), 137 (12), 121 (22), 97 (11), 91 (16), 77 (14).

4-(2,5-Dimethoxyphenyl)-2-methyl-2-phenyl-1,3-dioxolane (3.68d): Colorless liquid, 63% yield. ^{1}H NMR ($CDCl_3$): δ 1.81 (s, 3H), 3.70 (s, 3H), 3.72 (m, 1H), 3.82 (s,

3H), 4.18 (t, 1H), 5.18 (t, 1H), 6.72 – 6.78 (m, 3H), 7.27 – 7.50 (m, 5H). MS: 300 (56, M^+), 285 (15), 180 (17), 149 (12), 133 (72), 105 (100), 91 (16), 77 (36).

4-(2,5-Dimethoxyphenyl)-2-phenethyl-1,3-dioxolane (3.68e): was not isolated.

2-(2,2-Diethyl-1,3-dioxolan-4-yl)benzo-1,4-quinone (3.69a): General procedure: Silver oxide (1.22 g, 10 mmol) followed by nitric acid (6M, 1 mL) were added to the solution of 4-(2,5-dimethoxyphenyl)-2,2-diethyl-1,3-dioxolane **3.68a** (2.05 g, 7.7 mmol) in dioxane (50 mL). The resulting suspension was stirred for 30 min and then quenched with sodium bicarbonate (10%, 100 mL) and the product was extracted with dichloromethane (3x30 mL). The combined organic phases were washed with $NaHCO_3$ (2x50 mL), dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. Column chromatography on the residue afforded 1.3 g (5.5 mmol, 71%) of **3.69a** as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.95 (m, 6H), 1.72 (m, 4H), 3.56 (t, 1H), 4.49 (td, 1H), 4.99 (td, 1H), 6.76 (d, 2H), 6.96 (d, 1H); ^{13}C NMR δ 8.2, 8.4, 29.1, 29.8, 70.2, 72.5, 114.1, 130.7, 136.6, 137.0, 147.6, 187.5, 187.7. MS: 207 (26, $[M-29]^+$), 152 (17), 135 (10), 133 (38), 123 (11), 107 (6), 77 (6), 57 (100).

2-(2-Phenyl-1,3-dioxolan-4-yl)benzo-1,4-quinone (3.69b): Yellow oil, 59% yield, mixture of diastereomers in 1:1 ratio. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.71 (m, 1H), 3.92 (dd, 1H), 4.45 (t, 1H), 4.66 (td, 1H), 5.15 (m, 2H), 5.92 (s, 1H), 5.99 (s, 1H), 6.78 (m, 4H), 6.89 (d, 1H), 7.01 (d, 2H), 7.40 – 7.43 (m, 10H). MS: 258 (8, $[M+2]^+$), 255 (9), 152 (100), 137 (15), 134 (30), 123 (54), 105 (83), 91 (47), 77 (91).

2-(1,4-Dioxaspiro[4.5]decan-2-yl)benzo-1,4-quinone (3.69c): Yellow oil, 77% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.42 – 1.72 (m, 10H), 3.64 (td, 1H), 4.45 (td, 1H), 5.02 (td, 1H), 6.76 (d, 2H), 6.93 (d, 1H); ^{13}C NMR δ 24.0, 24.1, 25.3, 35.0, 36.1, 69.3,

71.9, 111.0, 130.9, 136.6, 137.0, 148.0, 187.6, 187.8. MS: 248 (7, M+), 205 (21), 152 (19), 133 (86), 123 (6), 106 (17), 97 (6), 82 (16), 78 (15).

2-(2-Methyl-2-phenyl-1,3-dioxolan-4-yl)benzo-1,4-quinone (3.69d): was not isolated.

2-(2-Phenethyl-1,3-dioxolan-4-yl)benzo-1,4-quinone (3.69e): Yellow oil, 57% yield over 2 steps. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.09 (m, 2H), 2.81 (m, 2H), 3.51 (m, 1H), 4.25 (td, 1H), 5.01 (m, 1H+1H), 6.77 (d, 2h), 6.88 (d, 1H), 7.20 – 7.33 (m, 5H). MS: 286 (7, $[M+2]^+$), 180 (15), 152 (60), 133 (67), 123 (42), 105 (38), 91 (100), 77 (31).

2-(2,2-Diethyl-1,3-dioxolan-4-yl)benzene-1,4-diol (3.59a): General procedure: Aqueous solution of sodium dithionite (1.74 g, 10 mmol, 25 mL) was added to the solution of 2-(2,2-diethyl-1,3-dioxolan-4-yl)benzo-1,4-quinone **3.69a** (1.3 g, 5.5 mmol) in dichloromethane (25 mL). The resulting suspension was vigorously stirred for 5 min and the layers were separated. The product was extracted with ether (3x30 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. Column chromatography of the residue afforded hydroquinone **3.59a** in 67% yield (875 mg, 3.7 mmol). ^{1}H NMR (acetone-d6, 400 MHz): δ 0.95 (m, 6H), 1.71 (m, 4H), 3.48 (t, 1H), 4.41 (td, 1H), 5.27 (td, 1H), 6.58 (dd, 1H), 6.67 (d, 1H), 7.01 (d, 1H), 7.81 (s, br, 1H), 7.93 (s, br, 1H). ^{13}C NMR δ 7.86, 7.94, 29.5, 29.9, 71.0, 74.0, 112.5, 112.9, 114.6, 115.8, 127.2, 147.1, 150.7. MS: 238 (13, M^+), 209 (11), 152 (90), 135 (62), 123 (42), 107 (32), 95 (6), 77 (13), 57 (100).

2-(2-Phenyl-1,3-dioxolan-4-yl)benzene-1,4-diol (3.59b): Colorless oil, 80% yield, mixture of diastereomers in 1:1 ratio. ^{1}H NMR (acetone-d6, 400 MHz): δ 3.77 (m, 1H+1H), 4.42 (td, 1H), 4.62 (td, 1H), 5.37 (t, 1H), 5.42 (t, 1H), 5.90 (s, 1H), 6.04 (s, 1H),

6.54 (m, 2H), 6.63 (m, 2H), 6.94 (m, 1H+1H), 7.39 – 7.69 (m, 12H). MS: 258 (5, M^+), 152 (100), 137 (14), 135 (23), 123 (44), 107 (13), 105 (16), 91 (10), 77 (32).

2-(1,4-Dioxaspiro[4.5]decan-2-yl)benzene-1,4-diol (3.59c): Colorless oil, 70% yield. ^{1}H NMR (acetone-d6, 400 MHz): δ 1.40 – 1.71 (m, 10H), 3.55 (t, 1H), 4.38 (td, 1H), 5.27 (t, 1H), 6.57 (dd, 1H), 6.67 (d, 1H), 6.97 (d, 1H), 7.75 (s, 1H), 7.87 (s, 1H); ^{13}C NMR δ 24.0, 24.1, 28.6, 35.4, 36.2, 70.3, 73.5, 109.3, 113.1, 114.5, 115.8, 127.7, 147.1, 150.7. MS: 250 (12, M^+), 152 (100), 135 (32), 123 (38), 107 (18), 95 (7), 77 (11), 55 (37).

2-(2-Methyl-2-phenyl-1,3-dioxolan-4-yl)benzene-1,4-diol (3.59d): Colorless oil, 75% yield over 2 steps, mixture of diastereomers in 4:5 ratio. ^{1}H NMR (acetone-d6, 400 MHz): δ 1.77 (s, 3H), 1.82 (s, 3.75H), 3.79 (t, 1H), 3.98 (t, 1.25H), 4.17 (t, 1.25H), 4.43 (t, 1H), 4.94 (t, 1.25H), 5.27 (t, 1H), 6.52 – 6.79 (m, 7H), 6.95 (s, br, 1H), 7.30 – 7.55 (m, 11H). MS: 272 (5, M^+), 152 (100), 135 (29), 123 (40), 107 (13), 105 (27), 95 (6), 77 (34).

2-(2-Phenethyl-1,3-dioxolan-4-yl)benzene-1,4-diol (3.59e): Colorless oil, 75% yield, mixture of diastereomers in ca. 1:2 ratio. 2.05 (m, 2H), 2.82 (m, 2H), [3.57 (dd) + 3.66 (dd), 1H], [4.25 (t) + 4.53 (t), 1H], [5.06 (t) + 5.18 (t), 1H], 5.26 (m, 1H), 6.59 (m, 1H), 6.69 (m, 1H), [6.92 (d) + 7.00 (d), 1H], 7.15 – 7.32 (m, 5H), [7.72 (s) + 7.76 (s), 1H], [7.91 (s) + 7.95 (s), 1H]. MS: 286 (13, M+), 152 (100), 135 (28), 123 (61), 107 (21), 91 (42), 77 (24).

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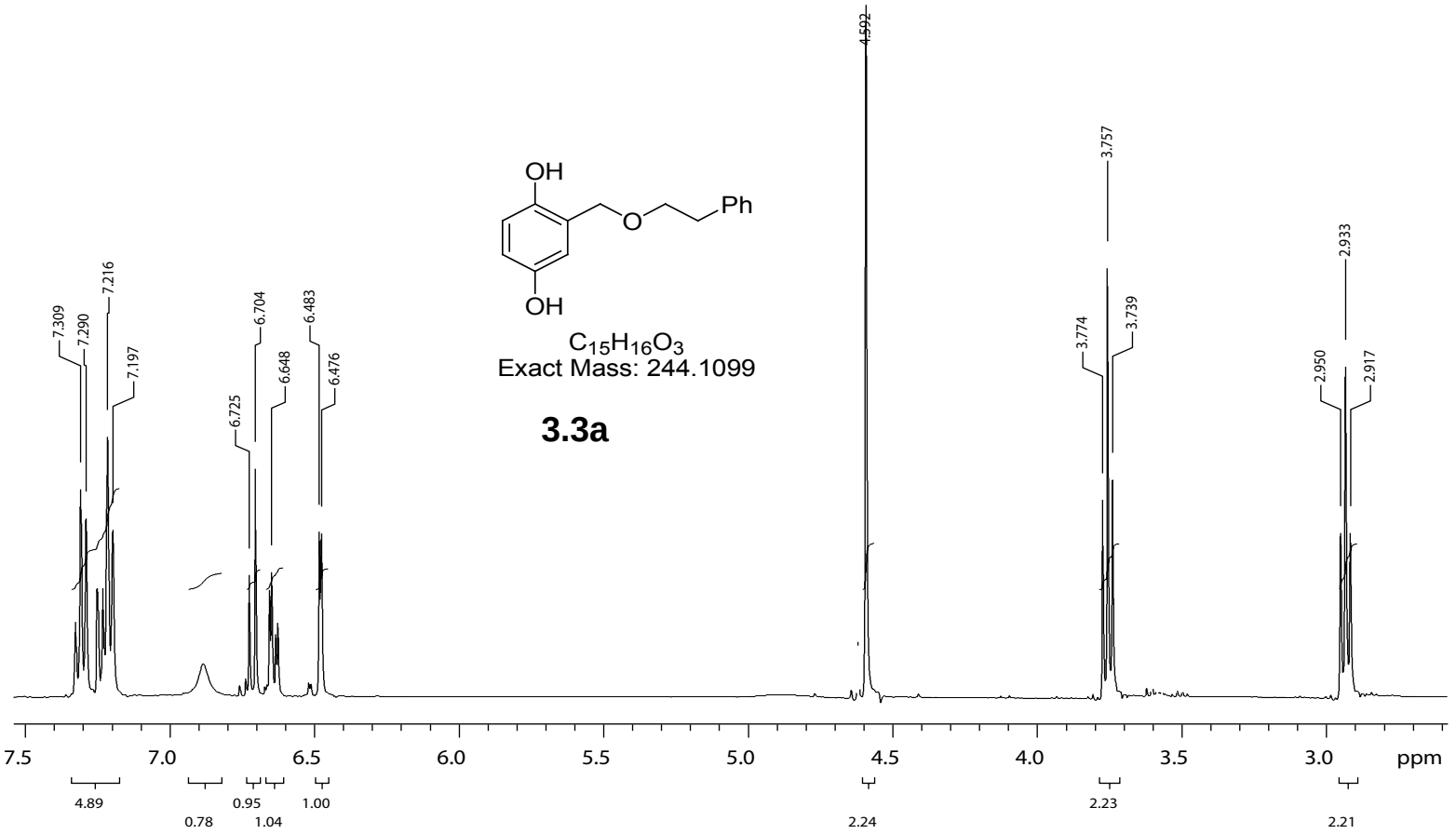
APPENDICES

Characterization of the compounds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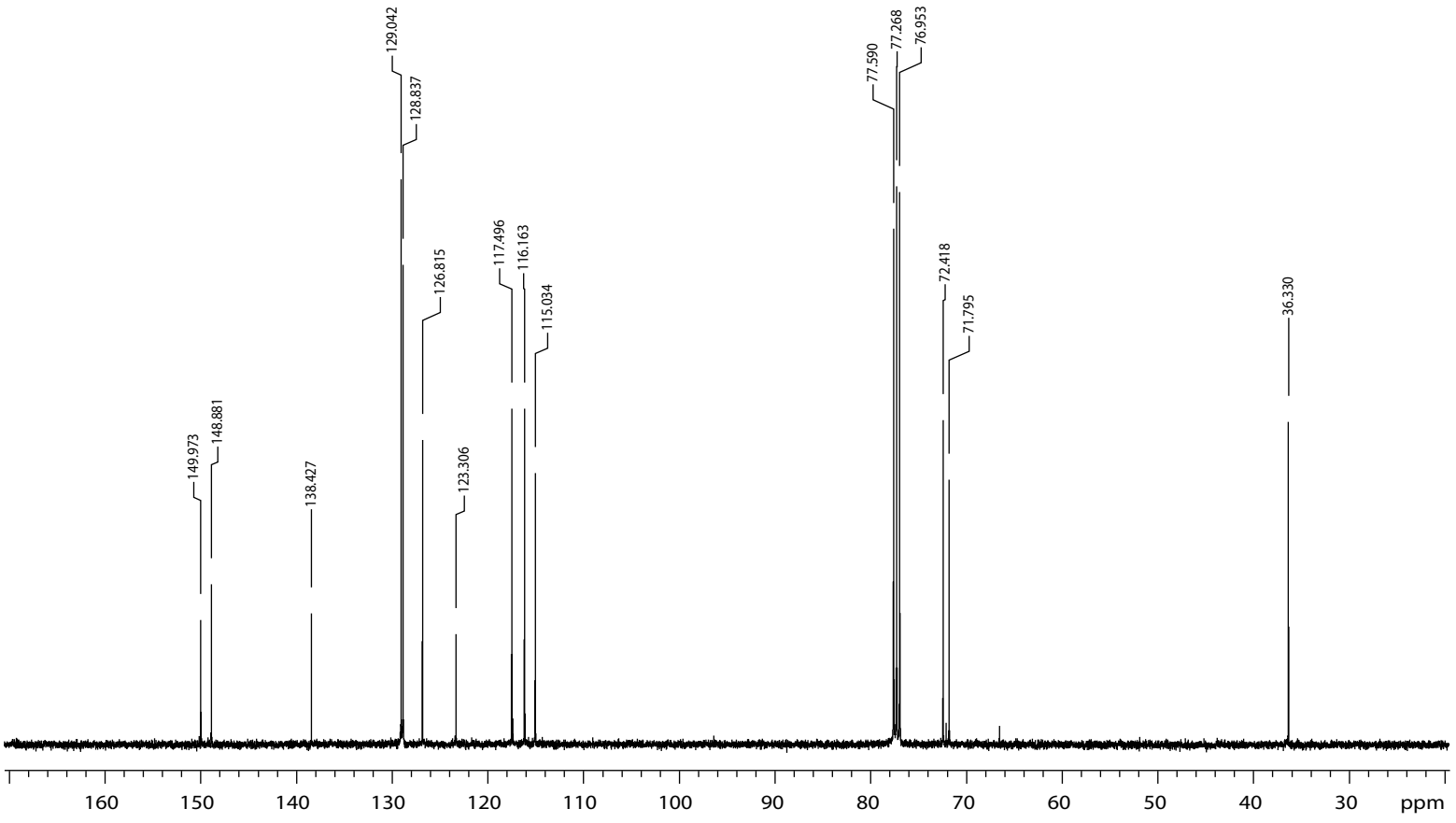
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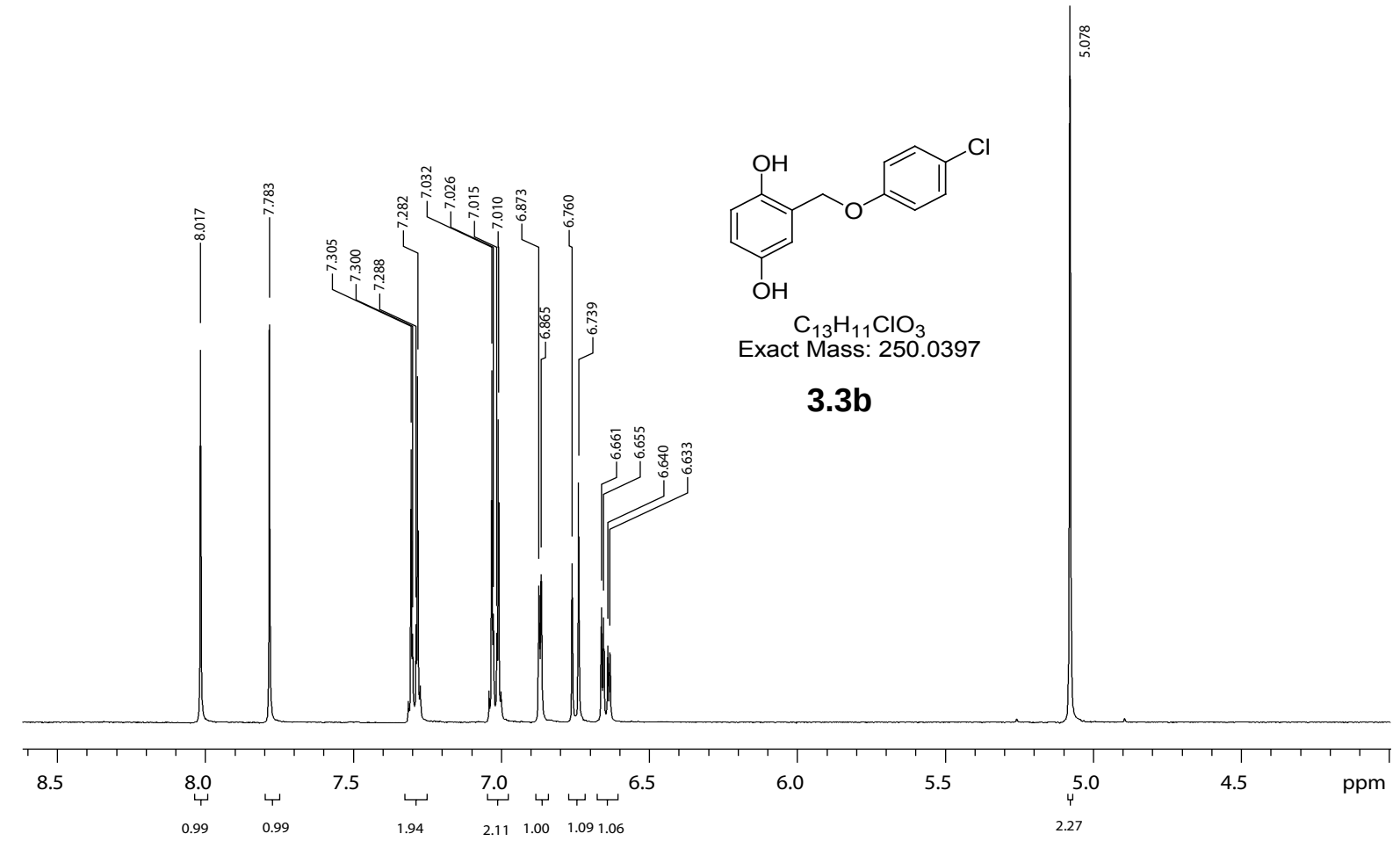
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6.633
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OH
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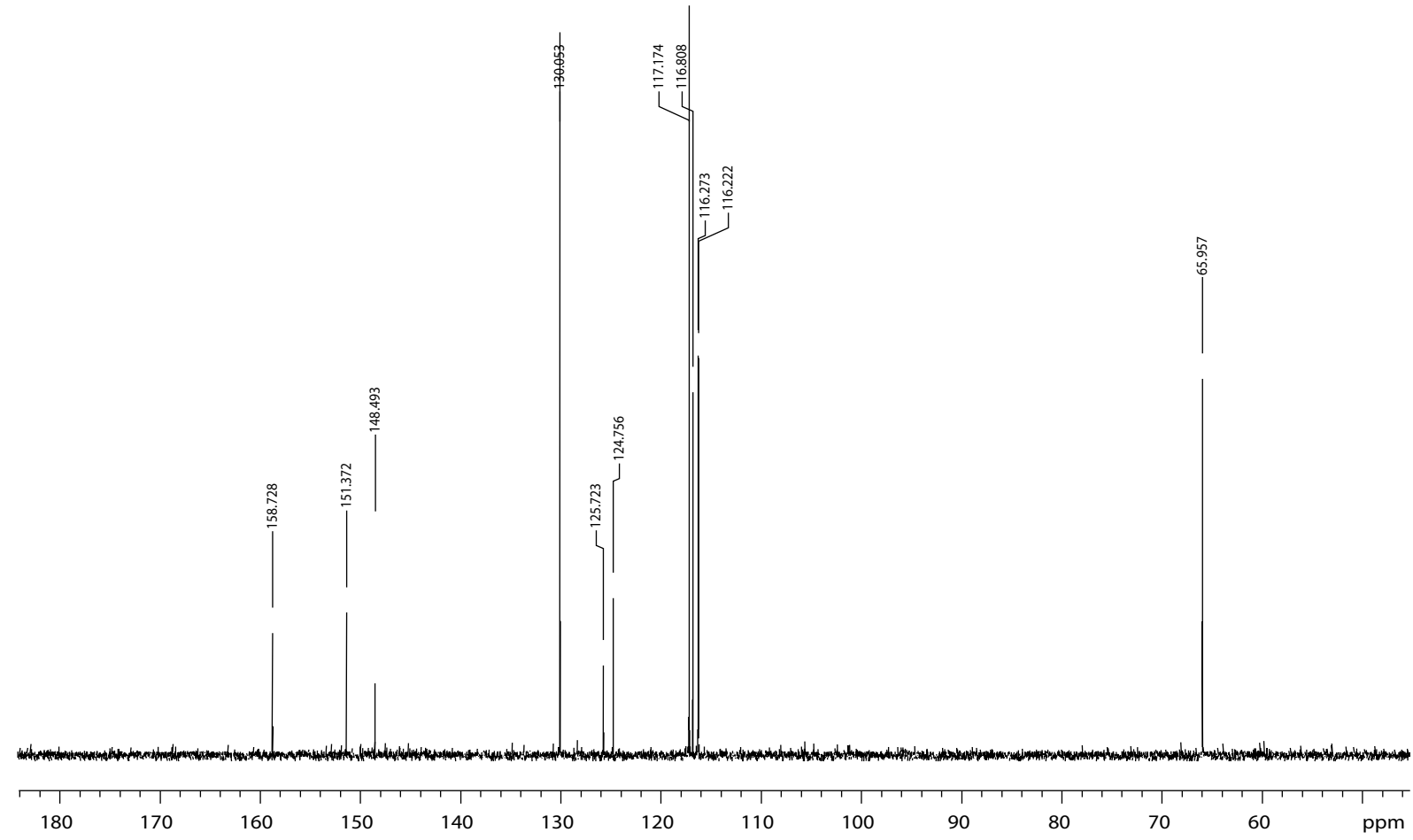
2.27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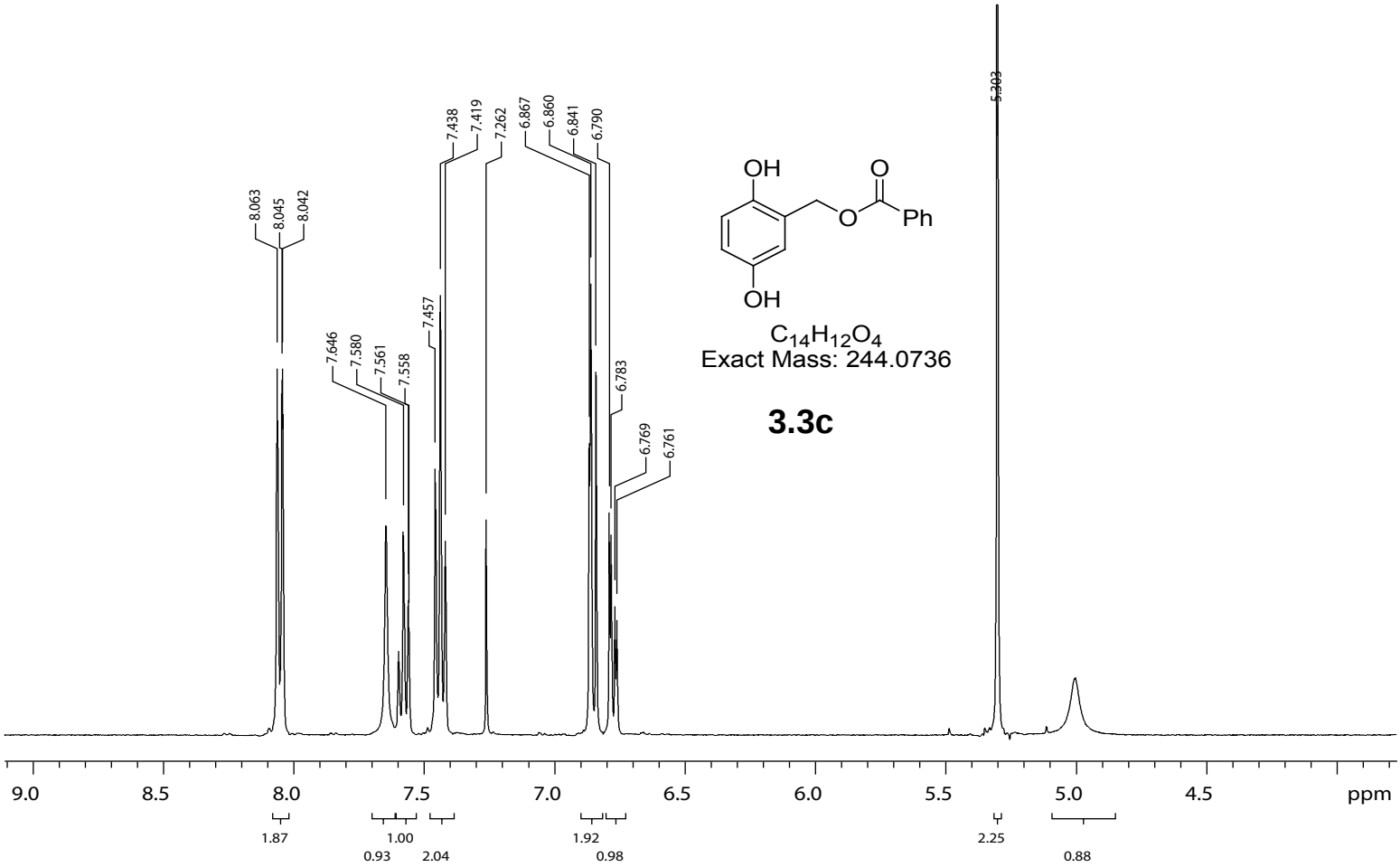
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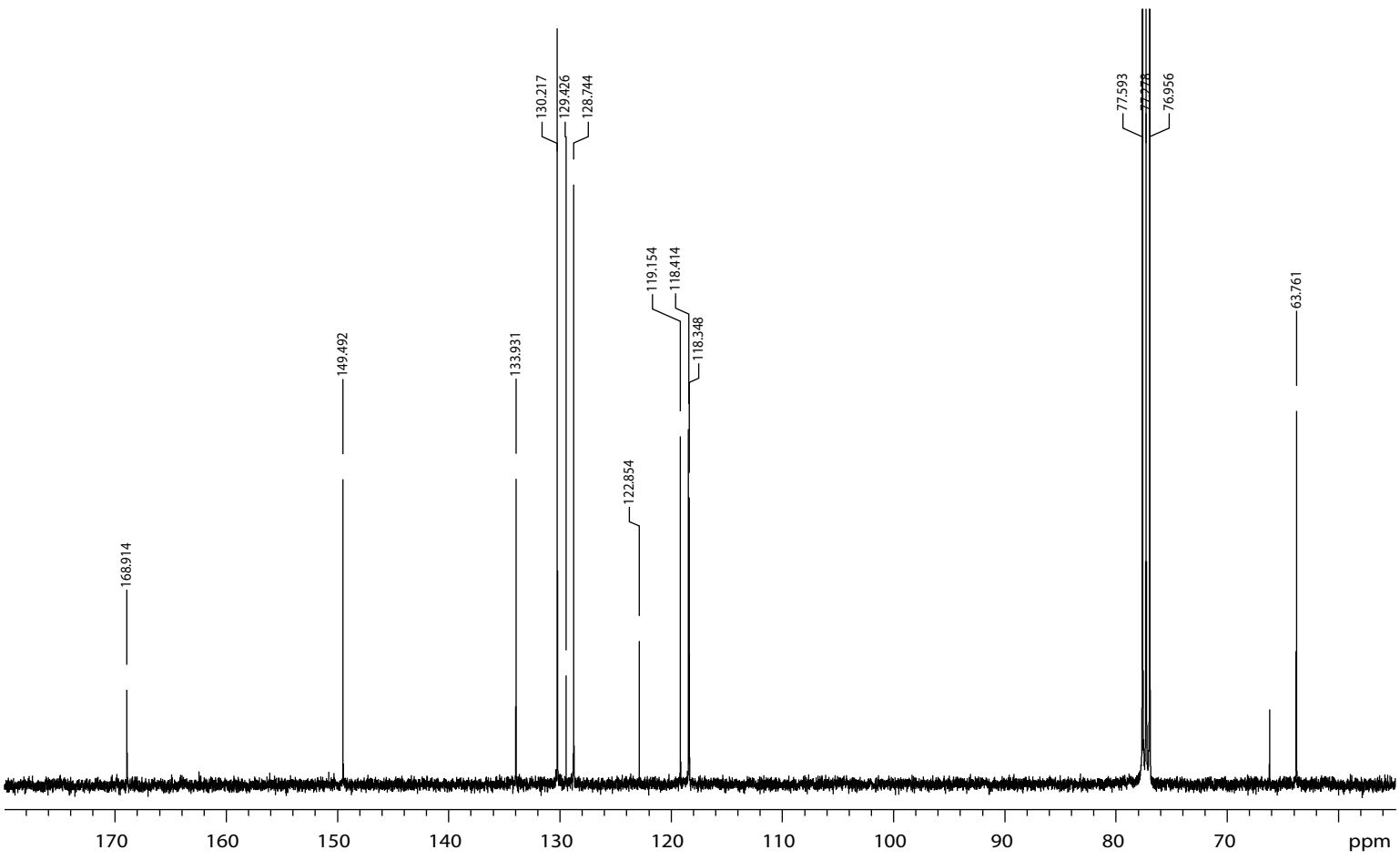
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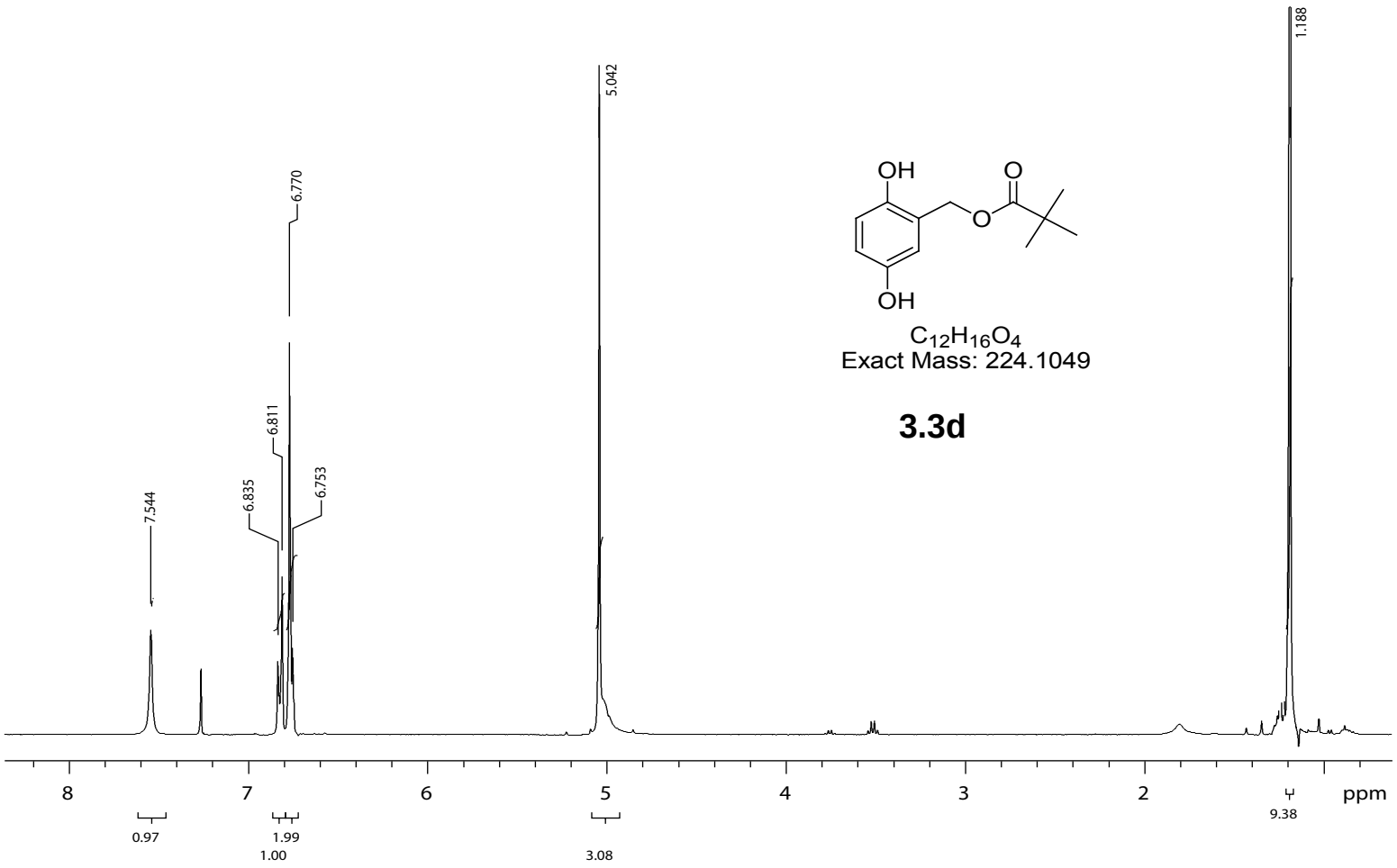
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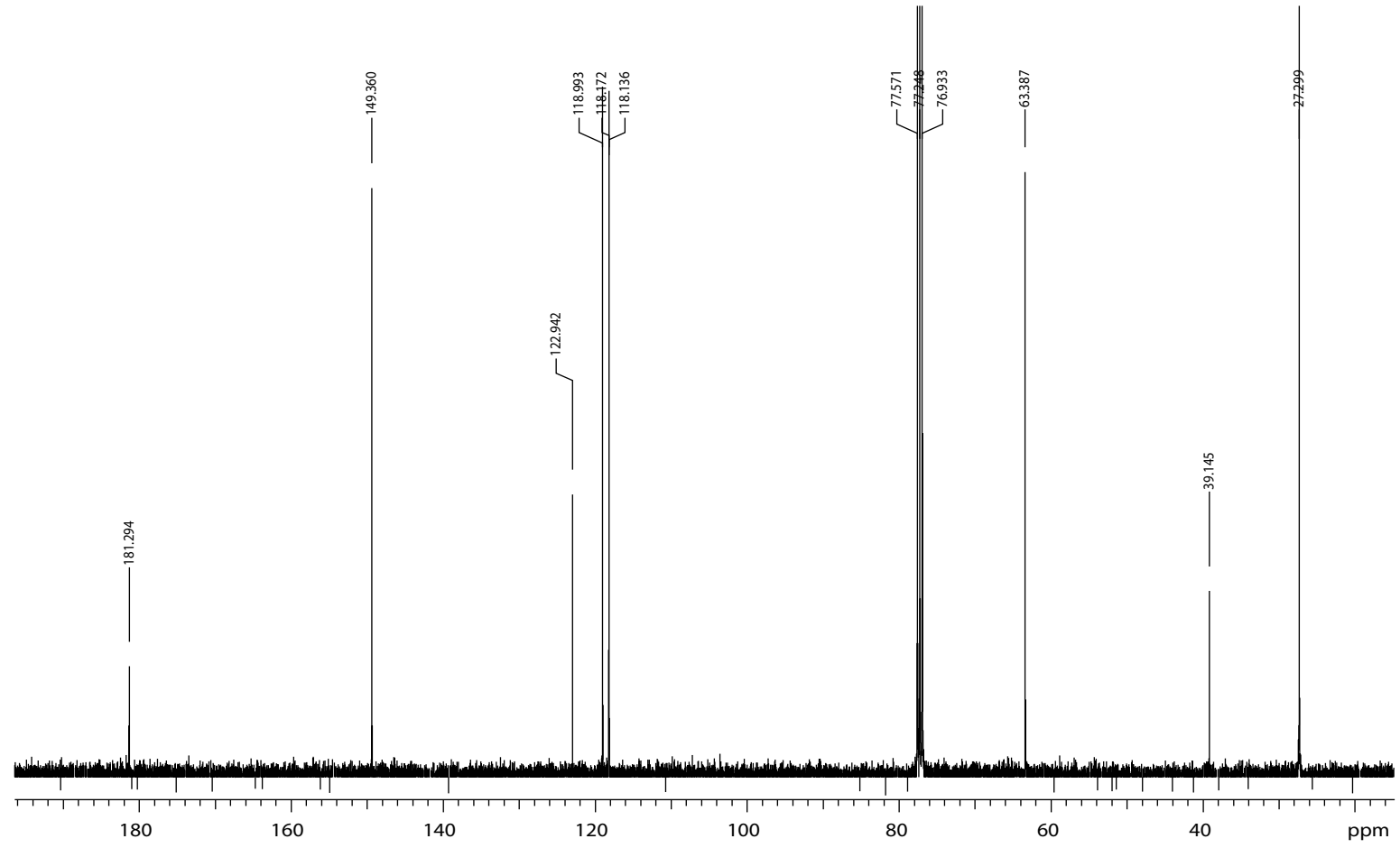
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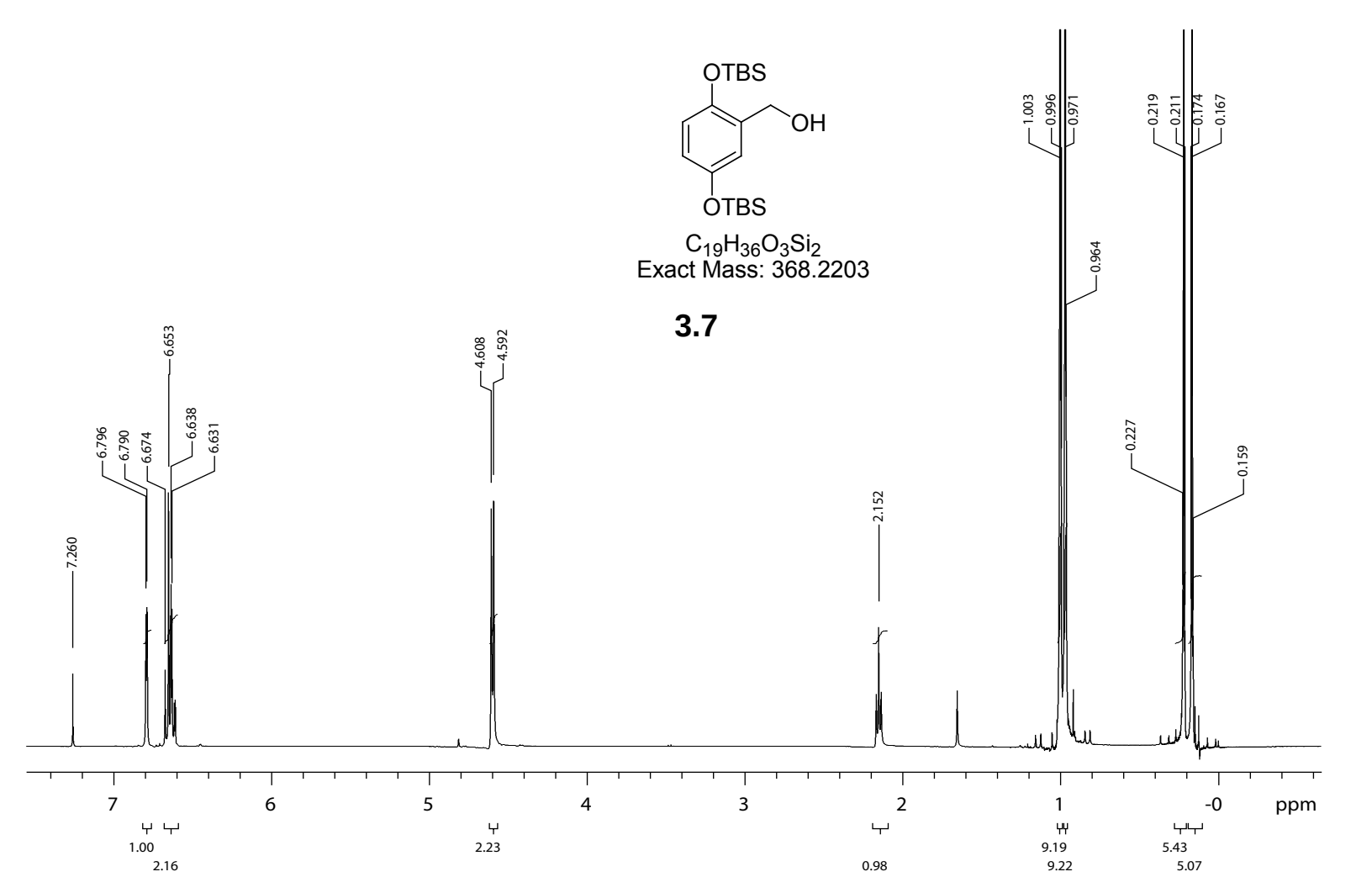
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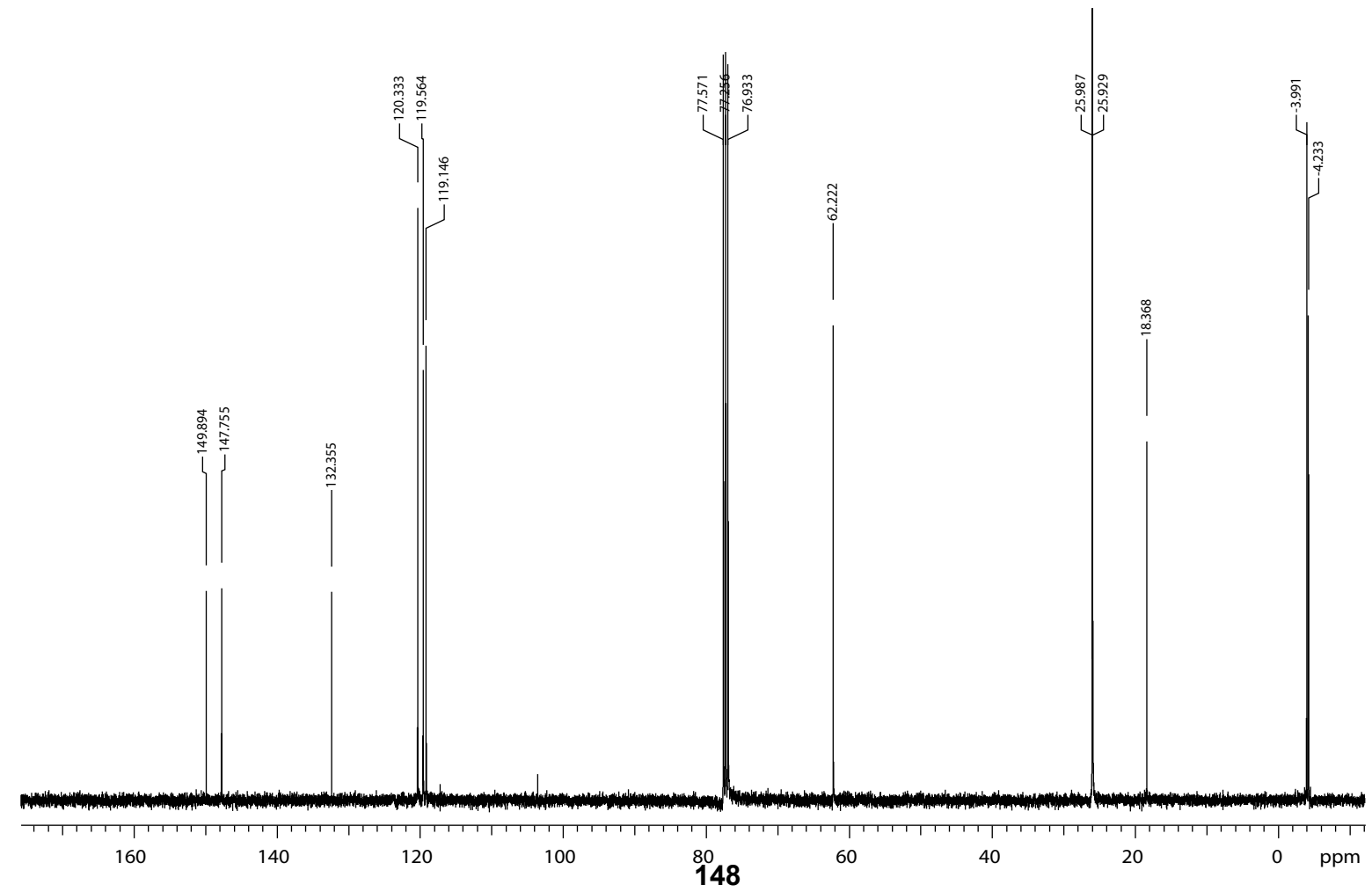
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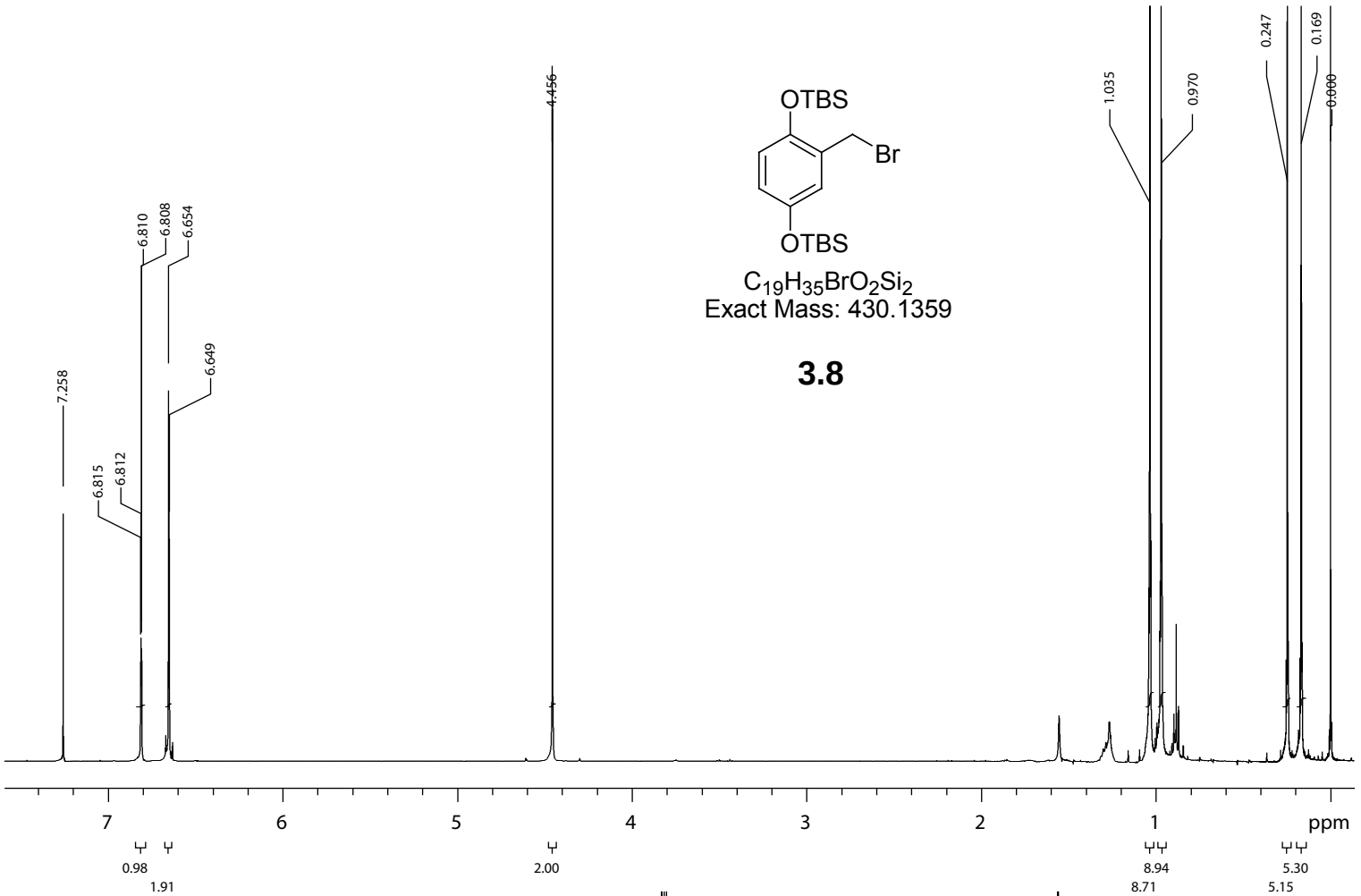

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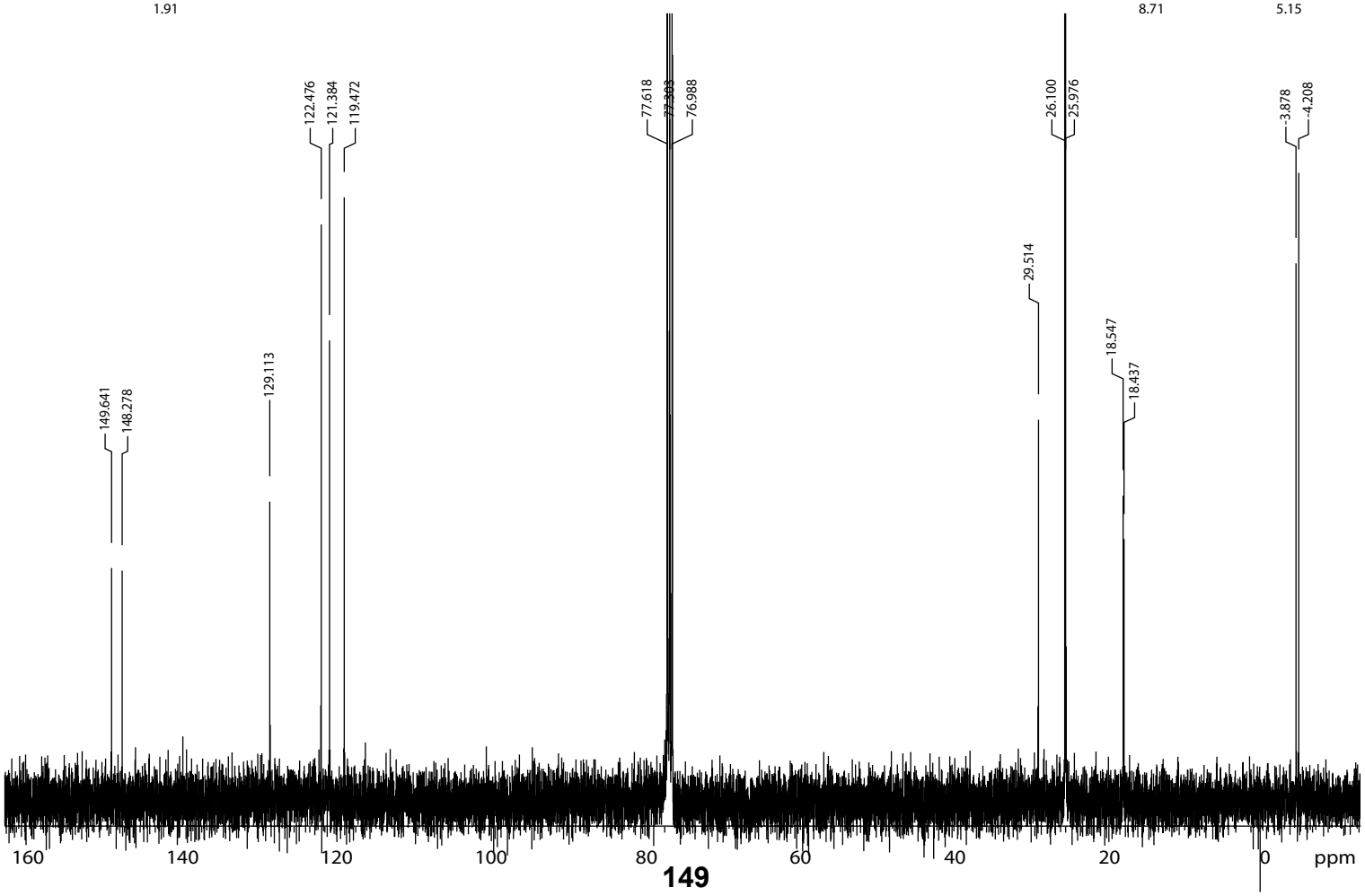

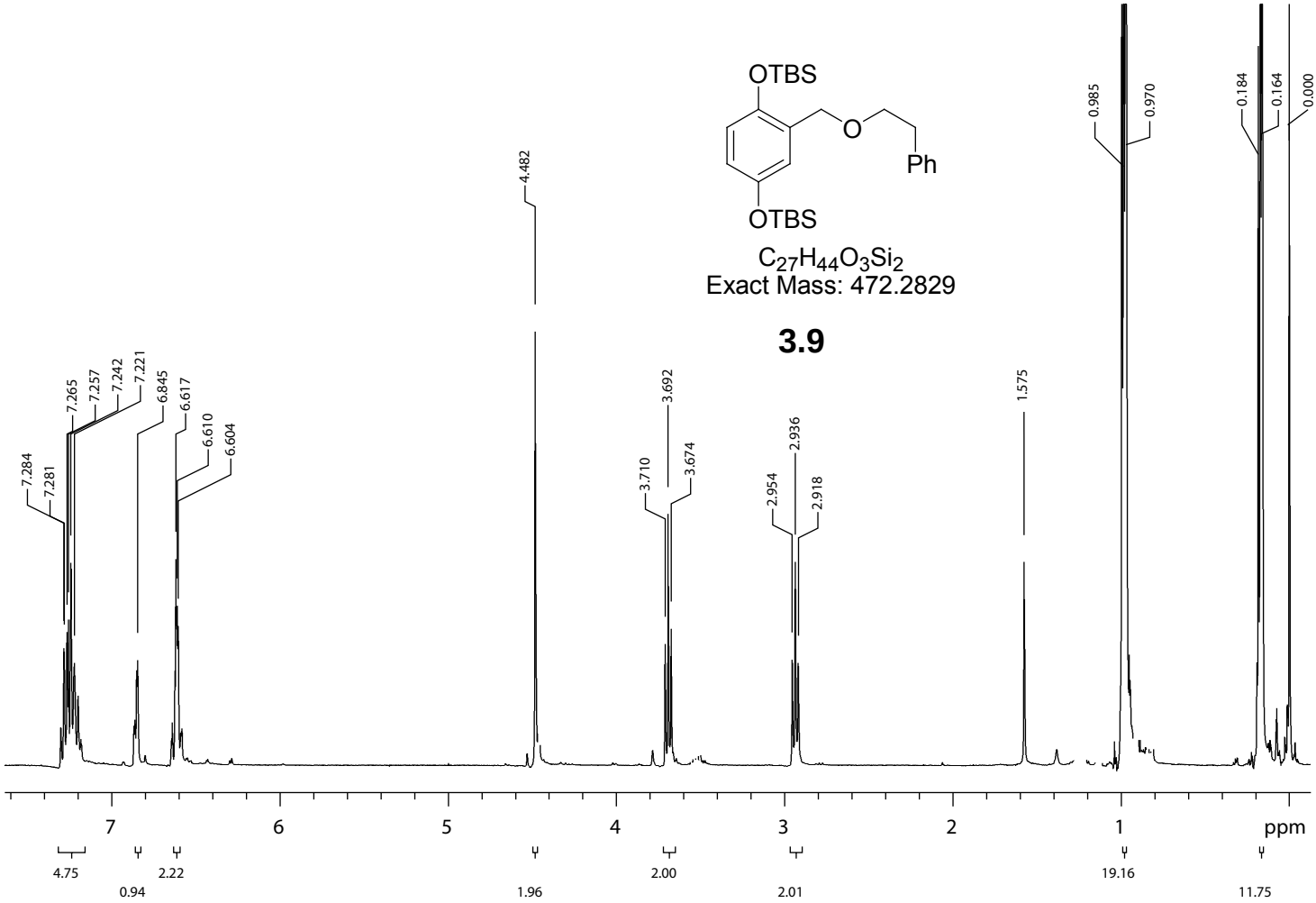
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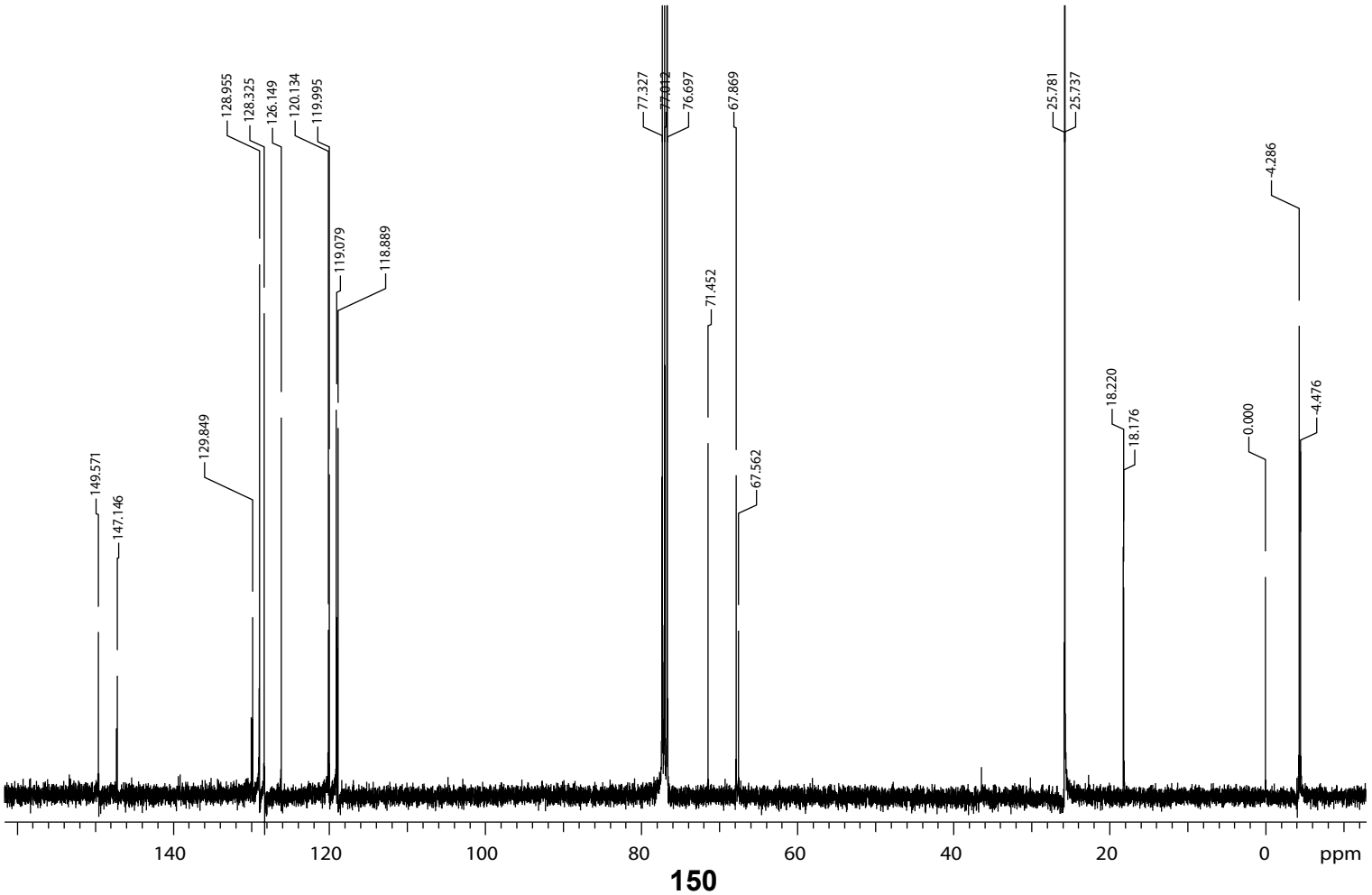
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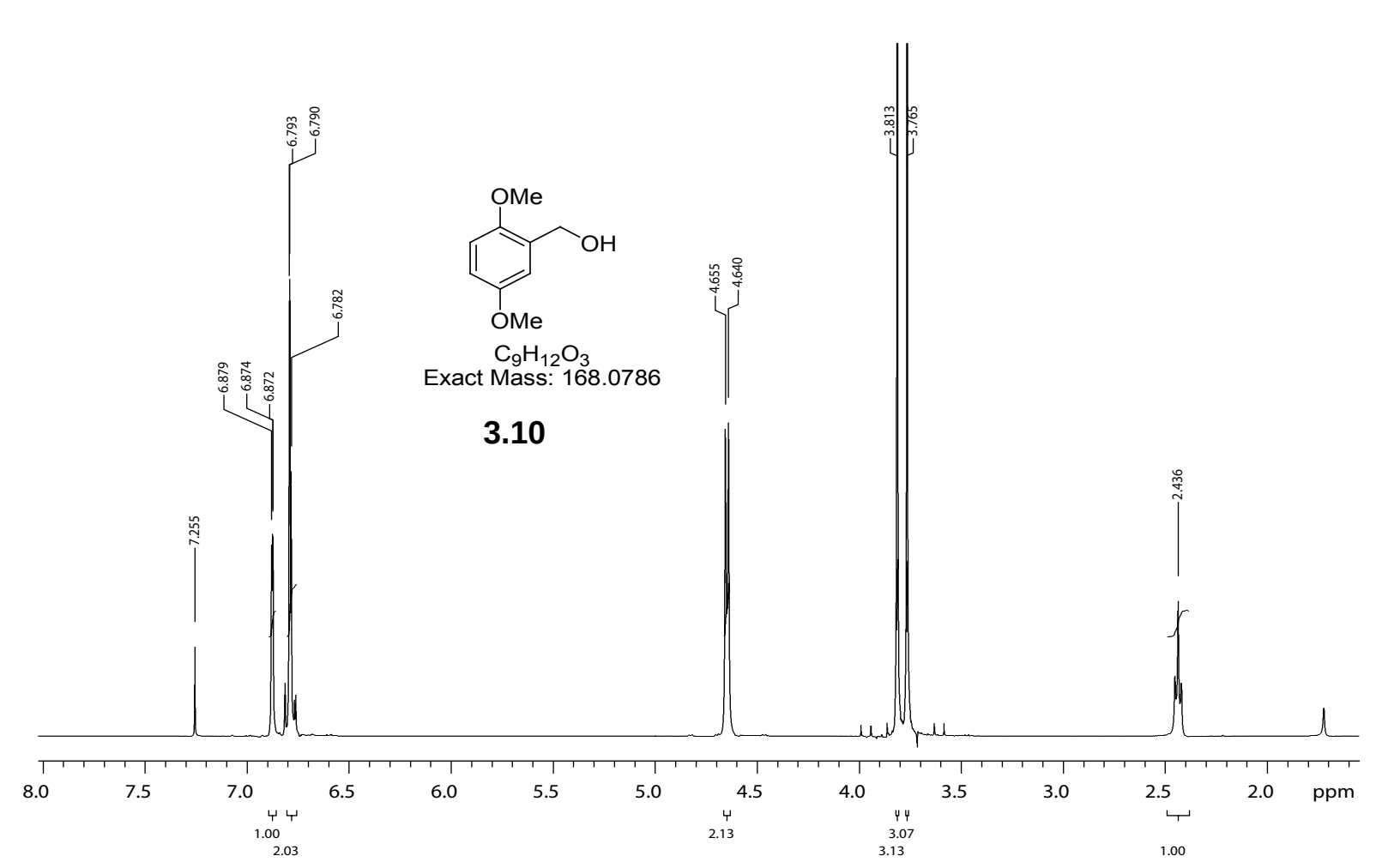
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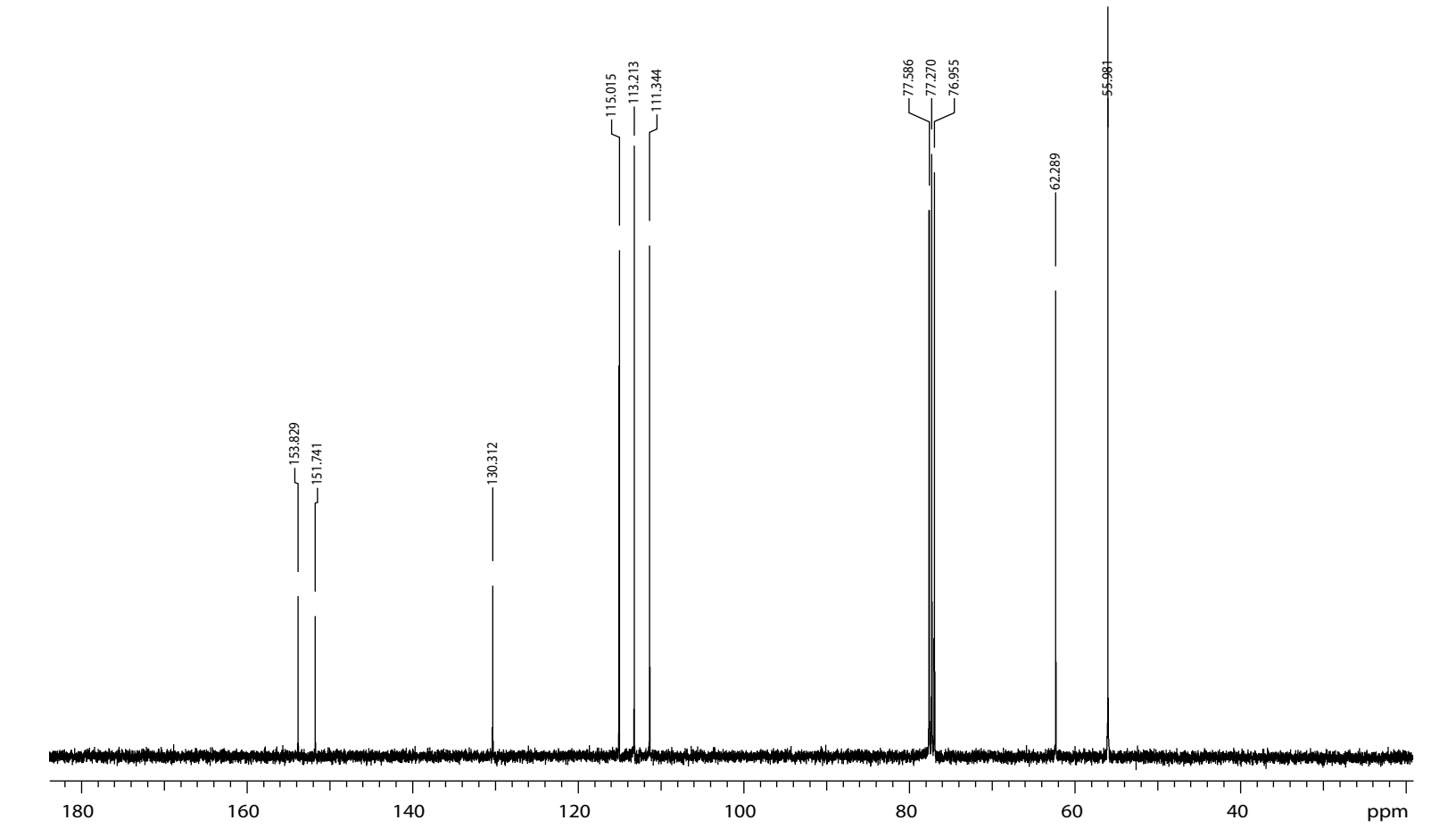
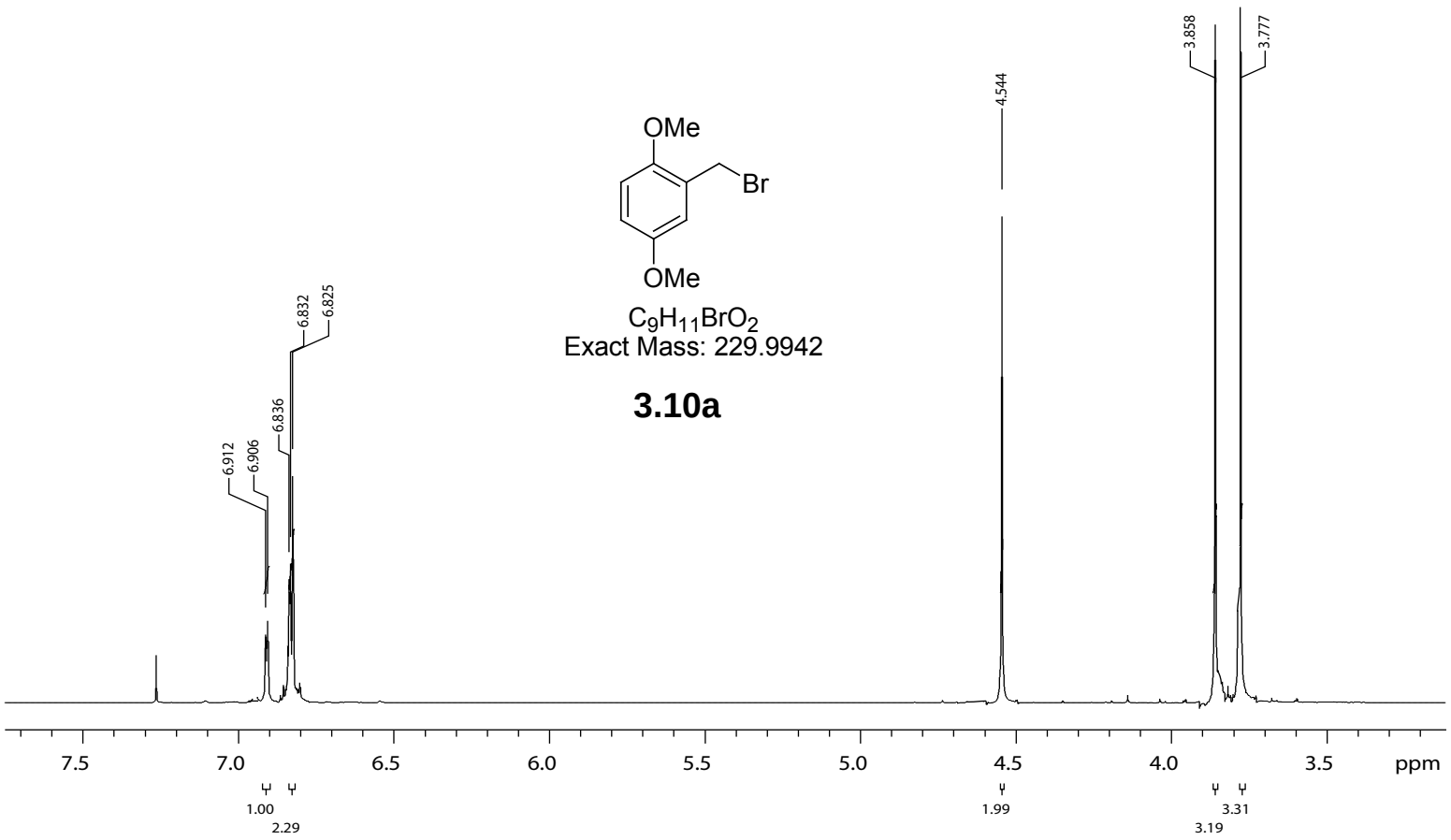
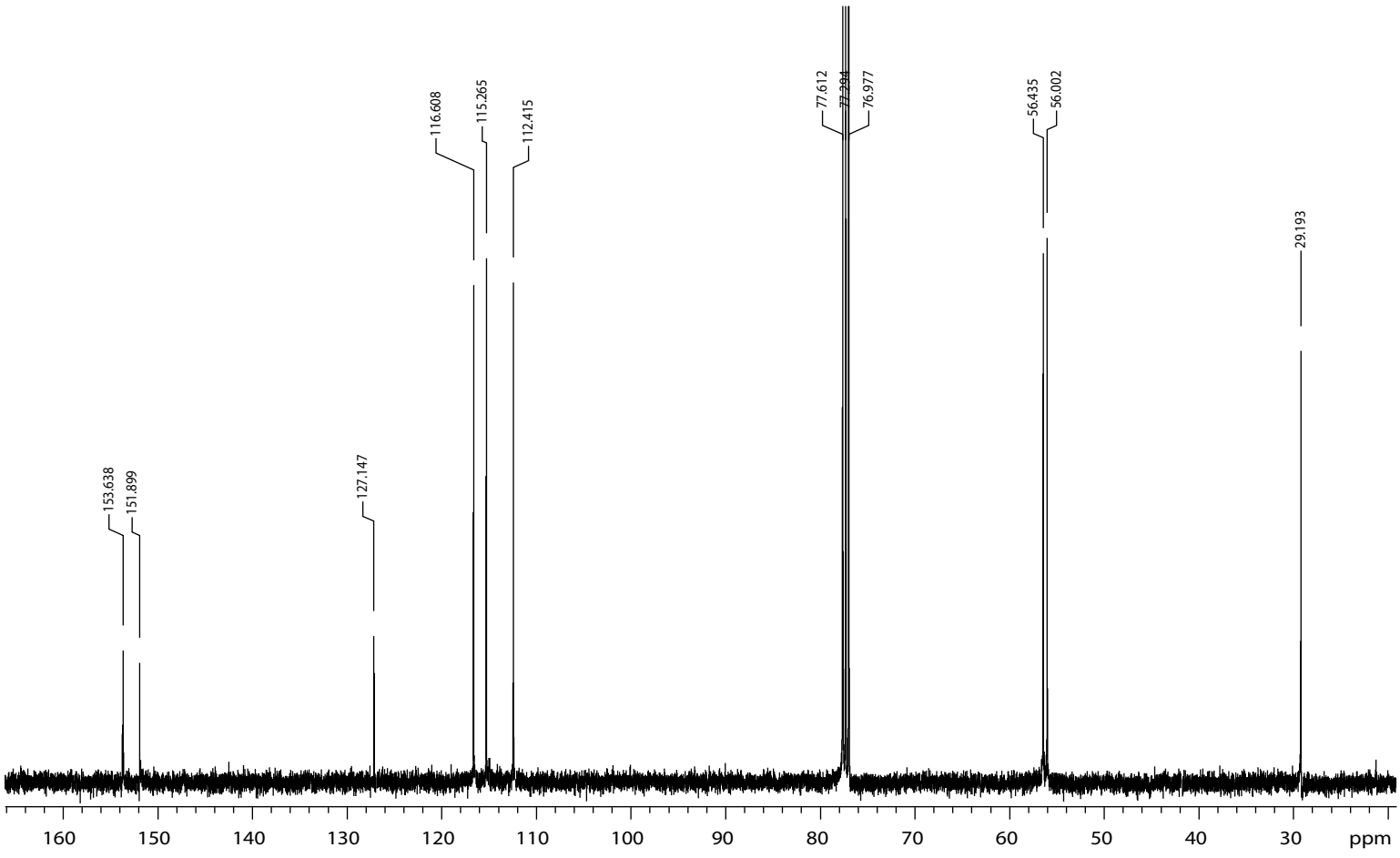
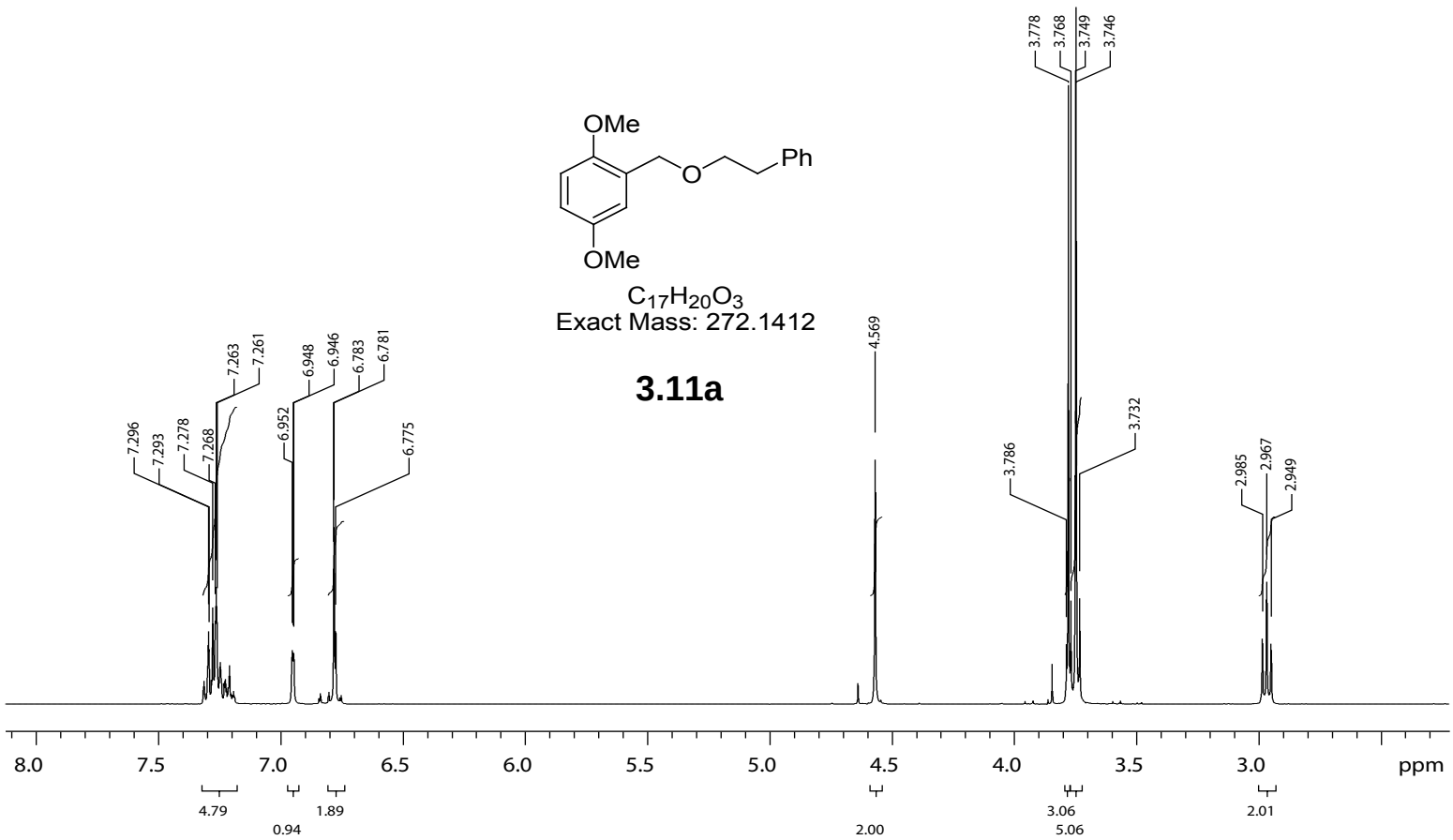
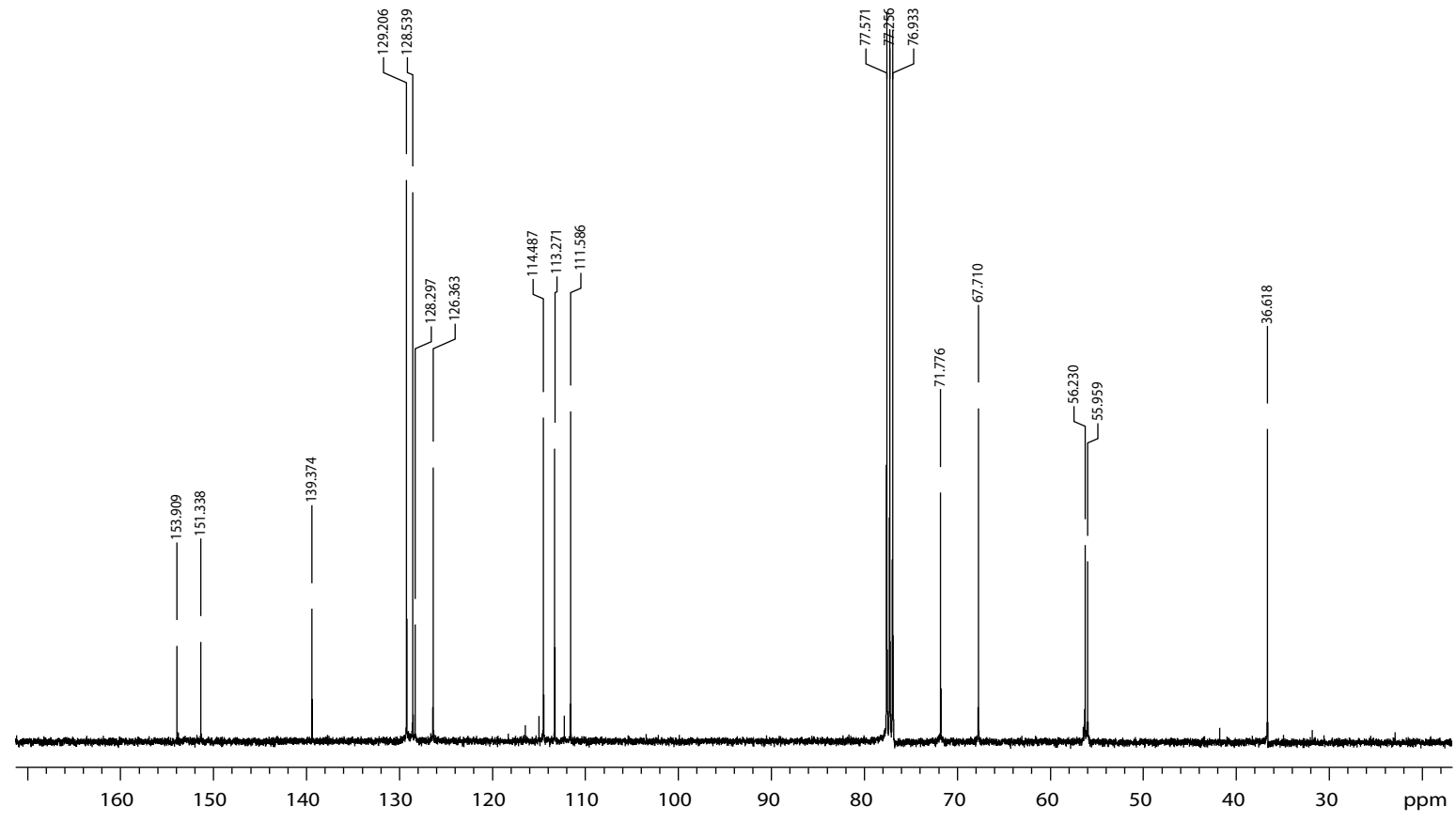
3.13
1.00

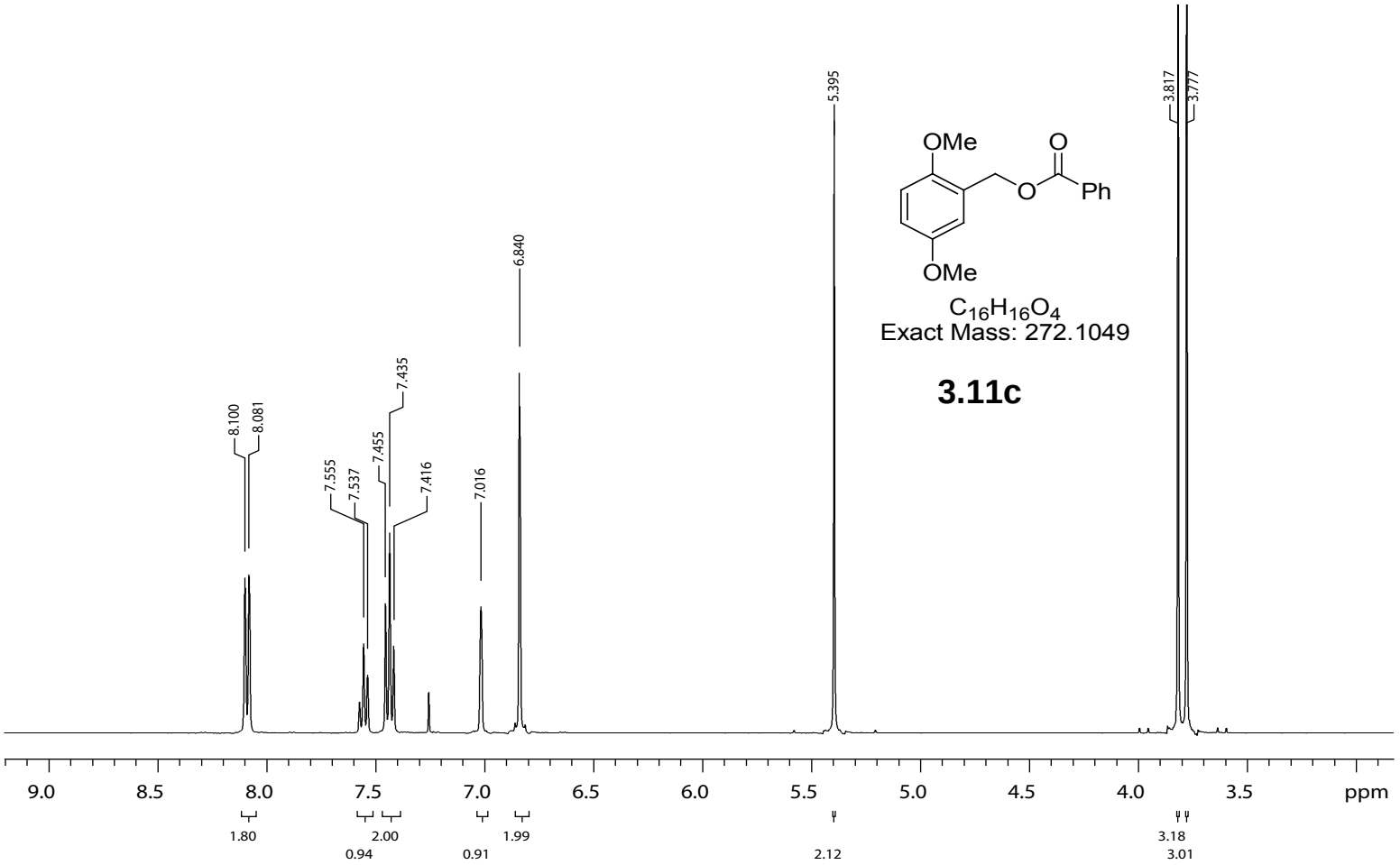

153.829
151.741
130.312
115.015
113.213
111.344
77.586
77.270
76.955
62.289
55.981
180
160
140
120
100
80
60
40
ppm

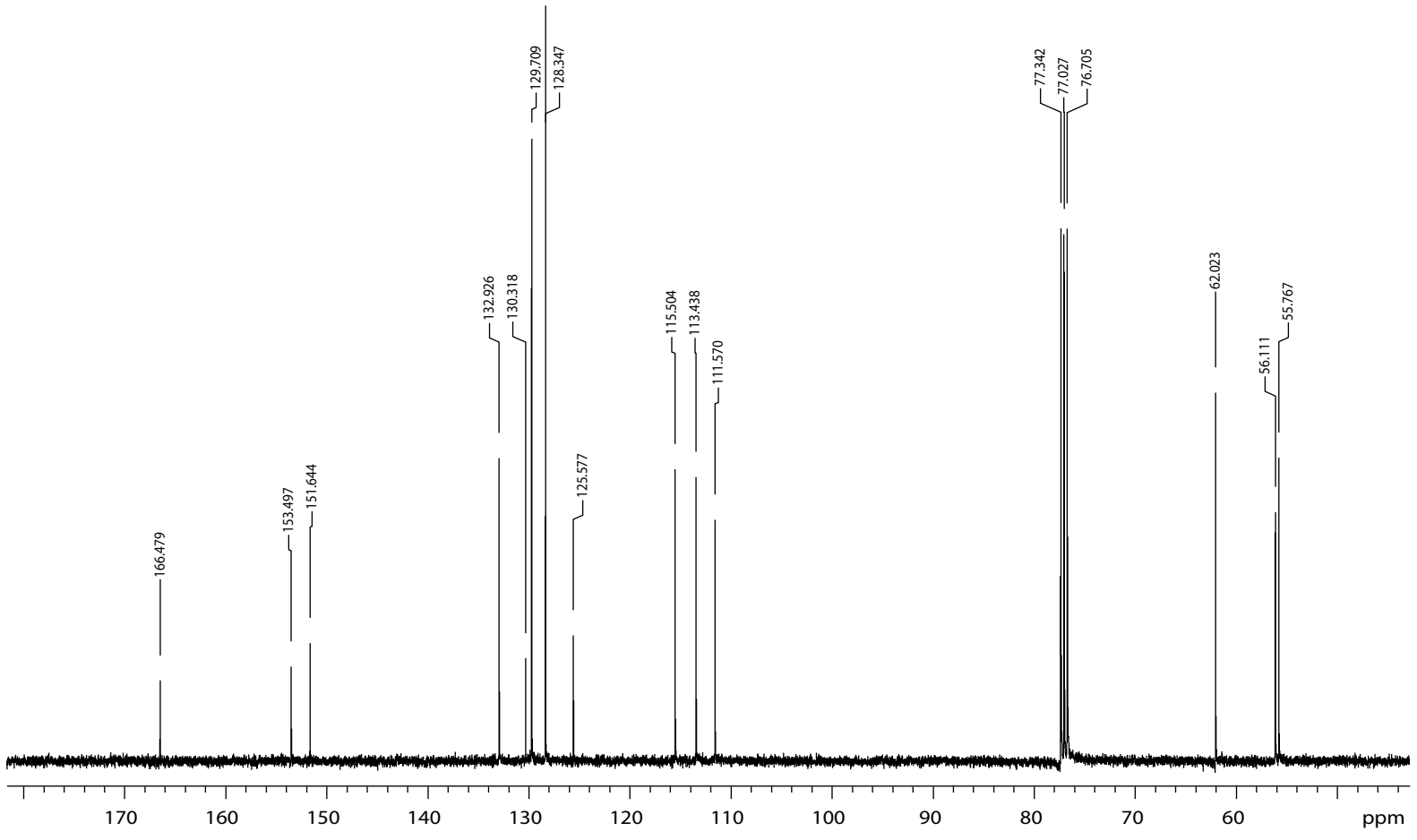

OMe
Br
OMe
$C_9H_{11}BrO_2$
Exact Mass: 229.9942
3.10a
6.912
6.906
6.836
6.832
6.825
4.544
3.858
3.777
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm
1.00
2.29
1.99
3.19
3.31

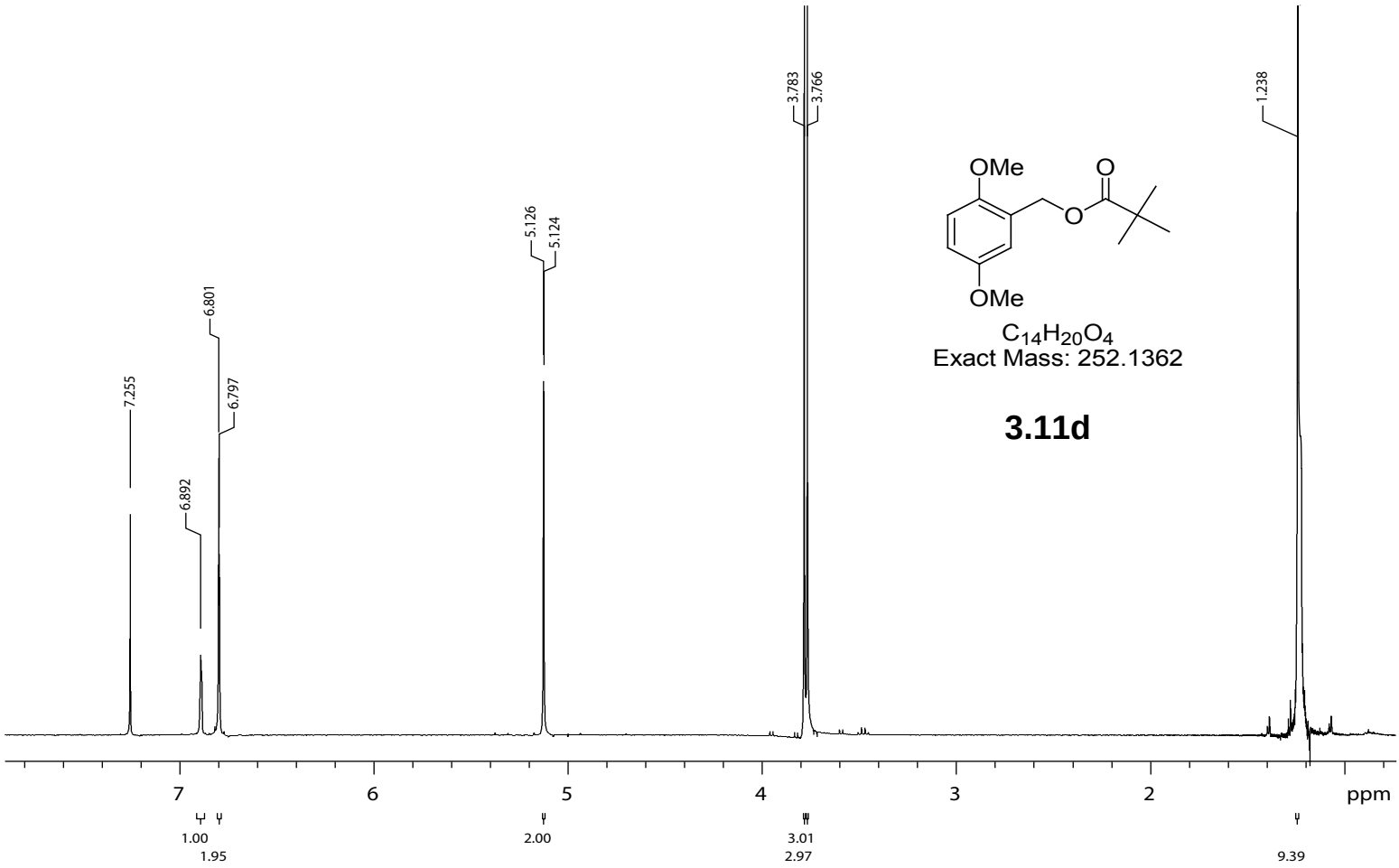

153.638
151.899
127.147
116.608
115.265
112.415
77.612
77.294
76.977
56.435
56.002
29.193
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

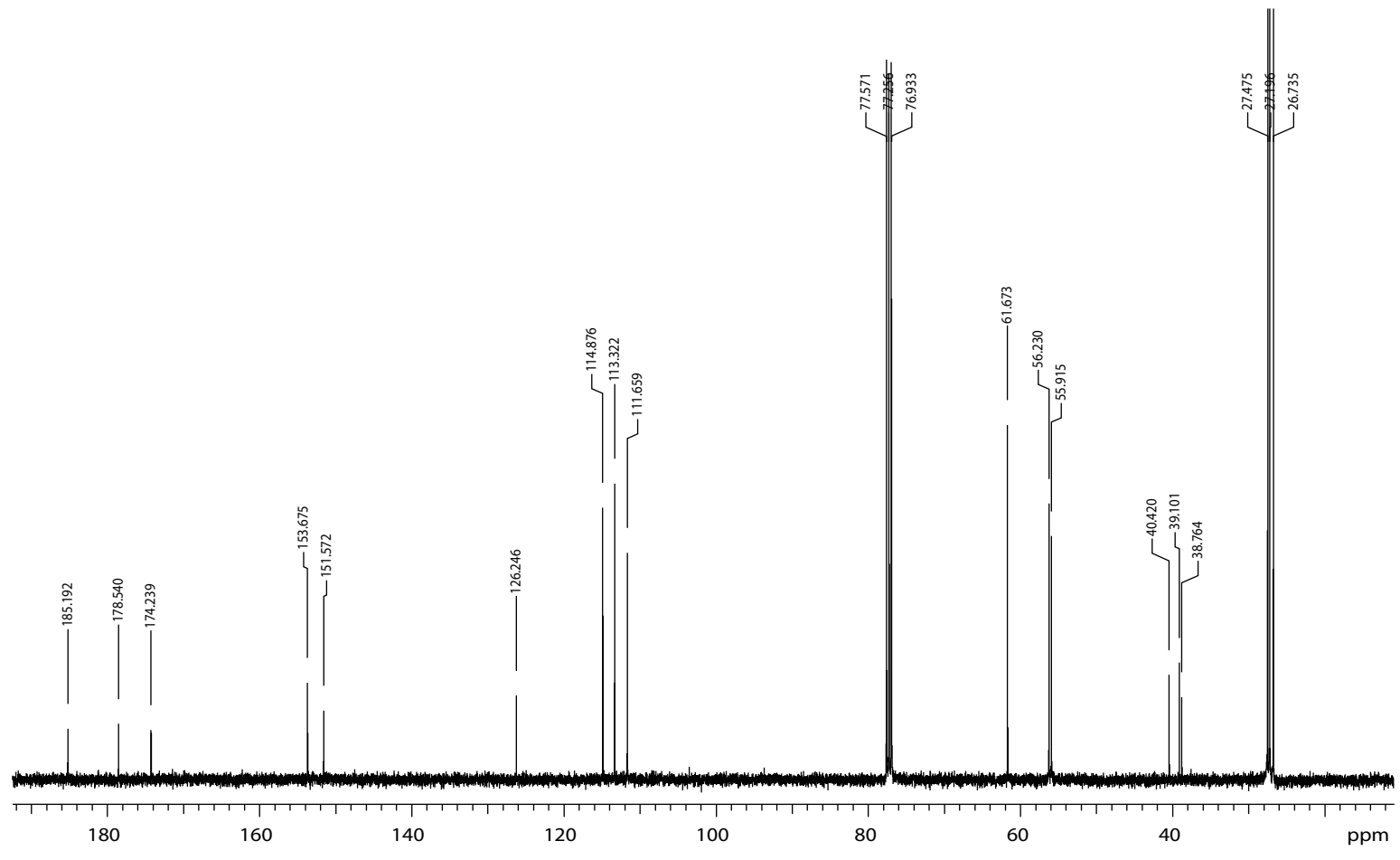

OMe
Ph
O
OMe
$C_{17}H_{20}O_3$
Exact Mass: 272.1412
3.11a
7.296
7.293
7.278
7.268
7.263
7.261
6.952
6.948
6.946
6.783
6.781
6.775
4.569
3.786
3.778
3.768
3.749
3.746
3.732
2.985
2.967
2.949
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm
4.79
0.94
1.89
2.00
3.06
5.06
2.01

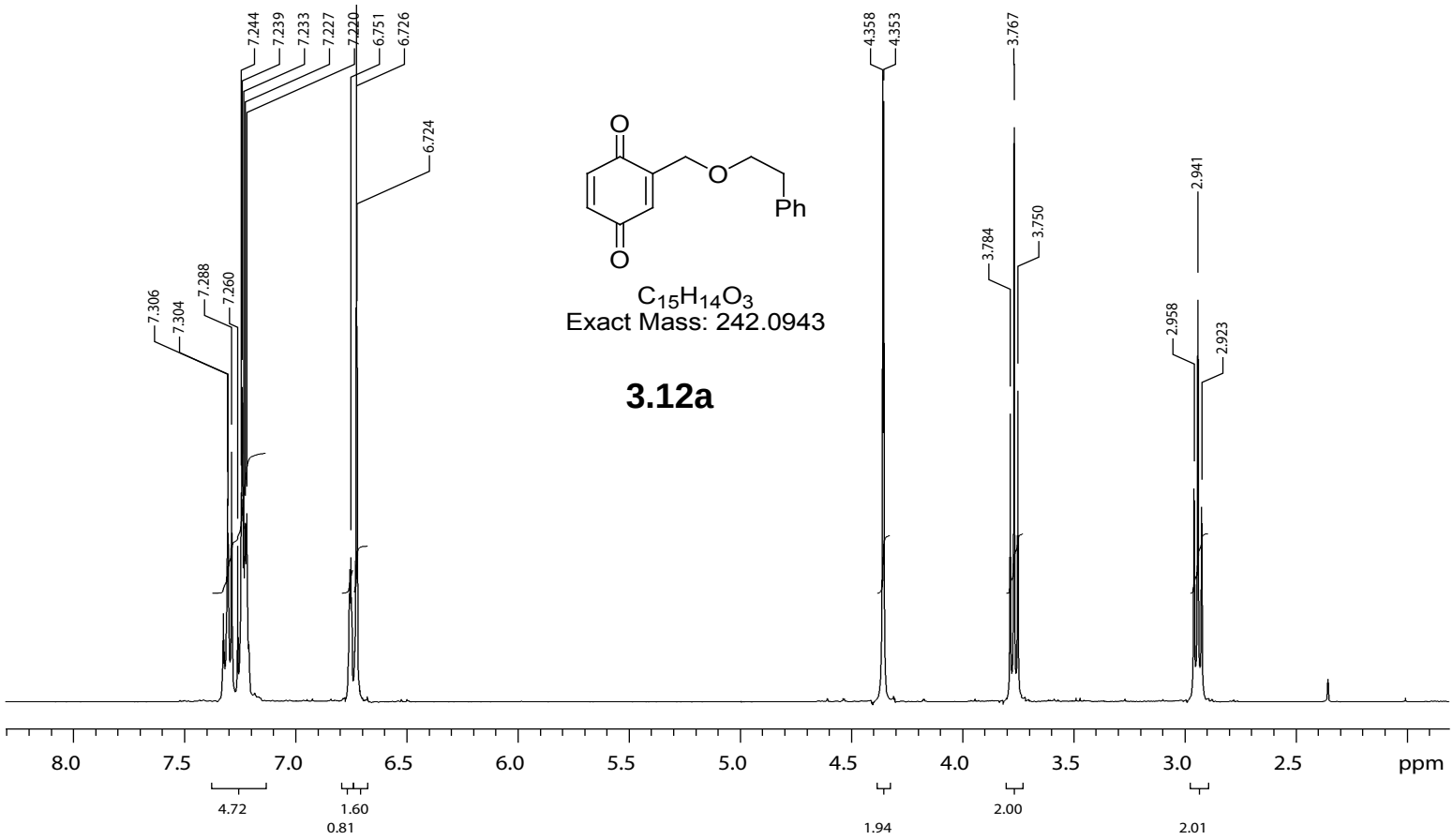

129.206
128.539
128.297
126.363
114.487
113.271
111.586
153.909
151.338
139.374
77.571
77.256
76.933
71.776
67.710
56.230
55.959
36.618
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm


OMe
O
O
Ph
OMe
$C_{16}H_{16}O_4$
Exact Mass: 272.1049
3.11c
8.100
8.081
7.555
7.537
7.455
7.435
7.416
7.016
6.840
5.395
3.817
3.777
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm
1.80
0.94
2.00
0.91
1.99
2.12
3.18
3.01


166.479
153.497
151.644
132.926
130.318
129.709
128.347
125.577
115.504
113.438
111.570
77.342
77.027
76.705
62.023
56.111
55.767
170
160
150
140
130
120
110
100
90
80
70
60
ppm

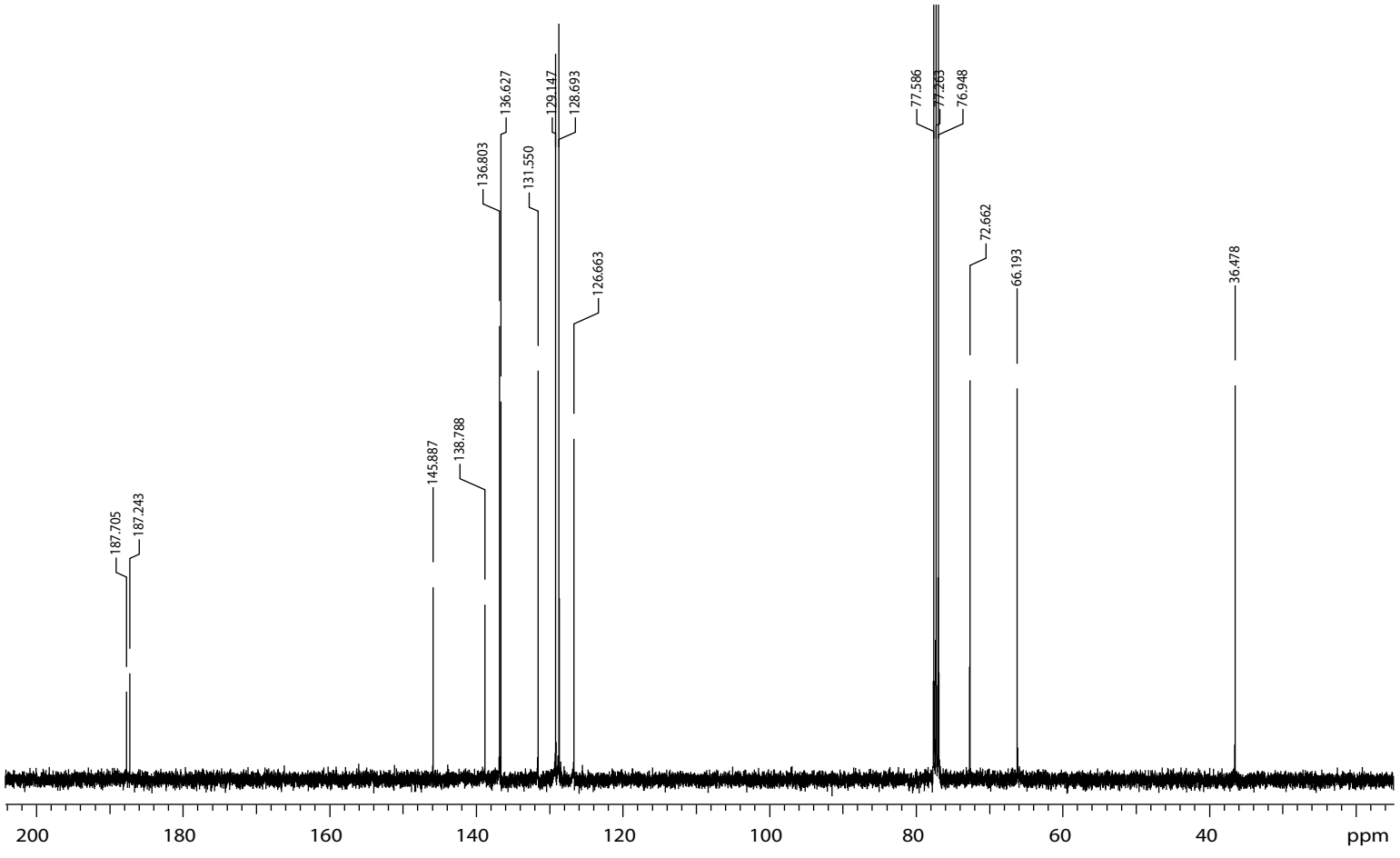

7.255
6.892
6.801
6.797
5.126
5.124
3.783
3.766
1.238
OMe
O
O
OMe
$C_{14}H_{20}O_4$
Exact Mass: 252.1362
3.11d
7
6
5
4
3
2
ppm
1.00
1.95
2.00
3.01
2.97
9.39

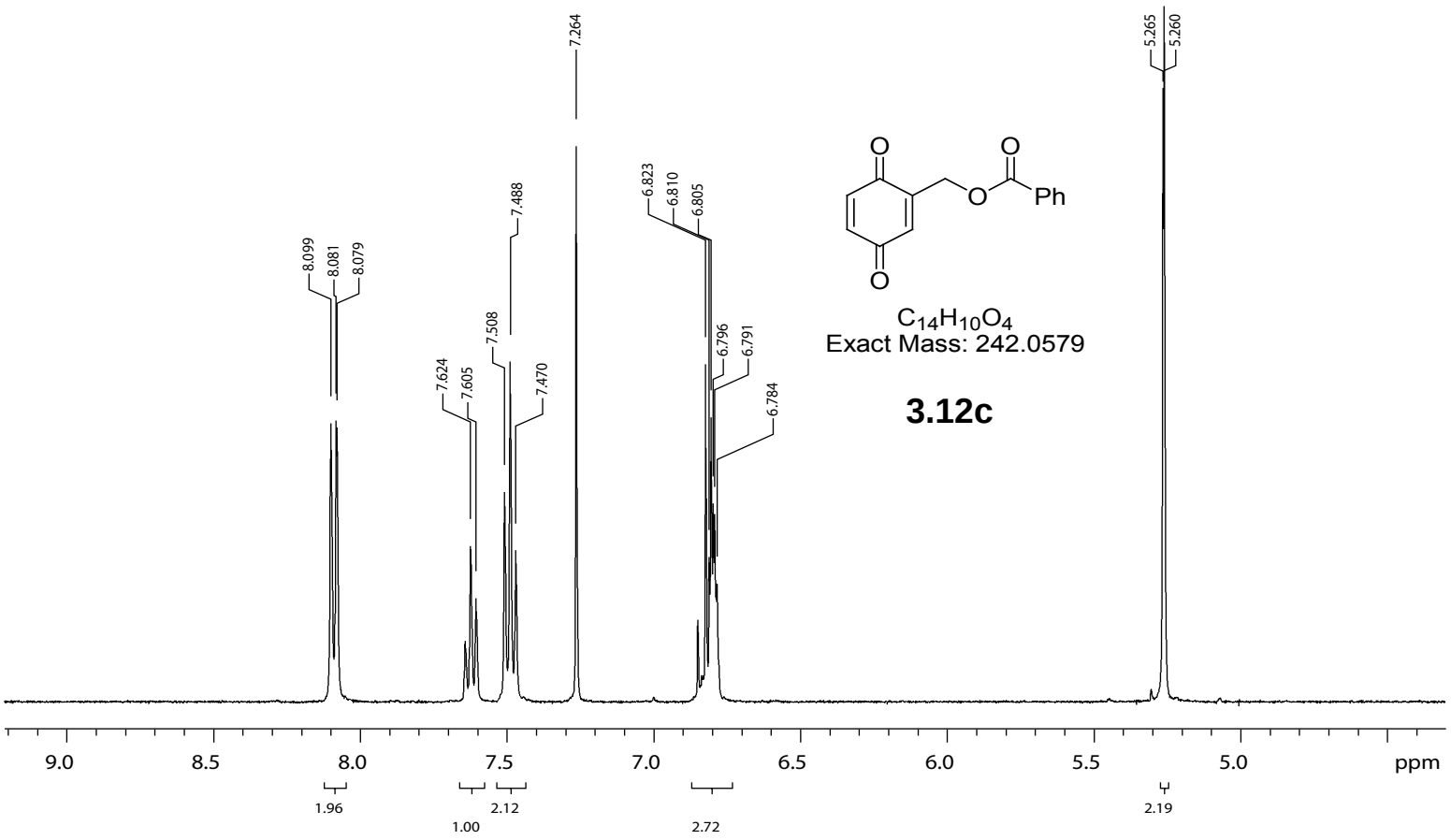

185.192
178.540
174.239
153.675
151.572
126.246
114.876
113.322
111.659
77.571
76.933
61.673
56.230
55.915
40.420
39.101
38.764
27.475
26.735
180
160
140
120
100
80
60
40
ppm

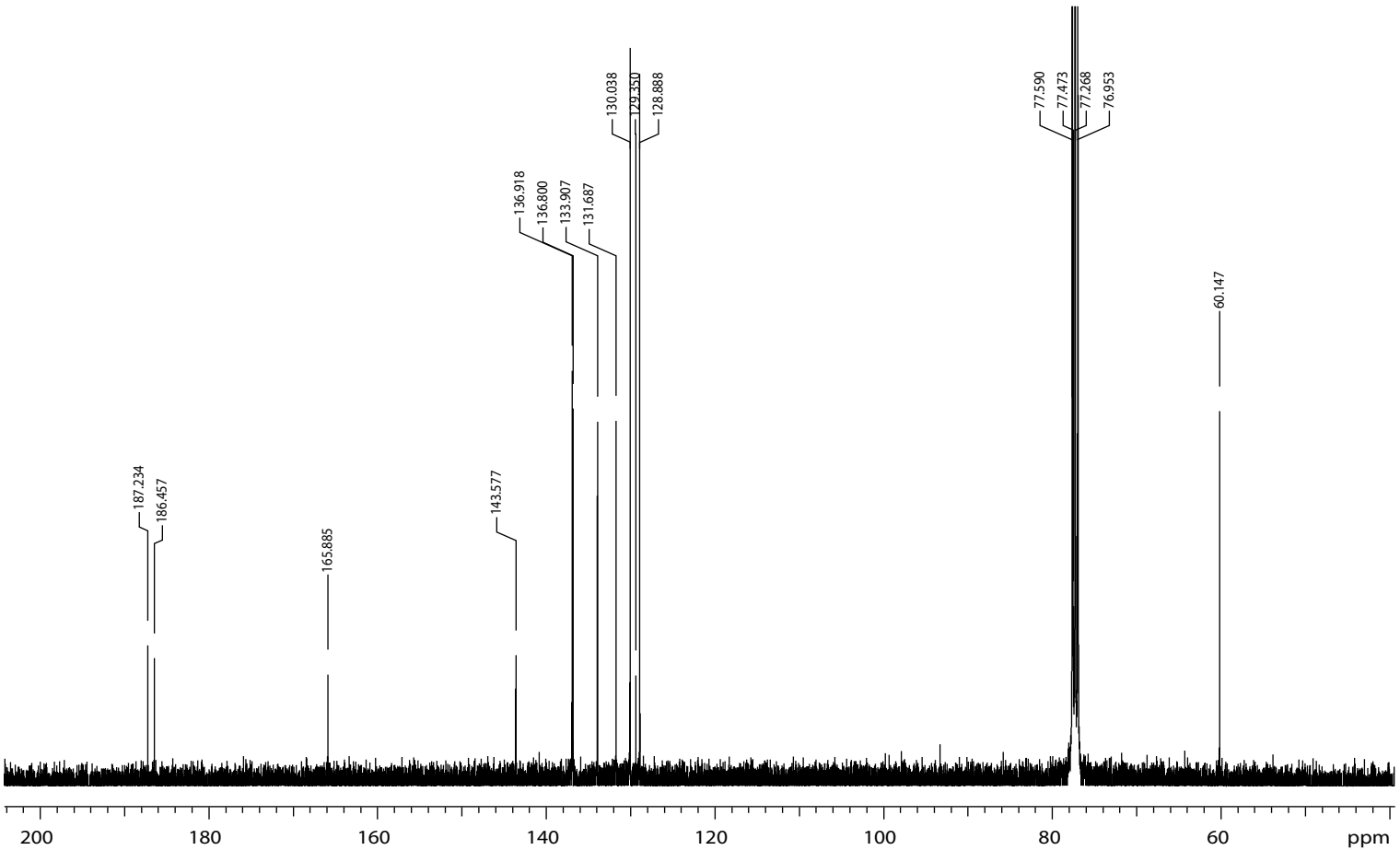


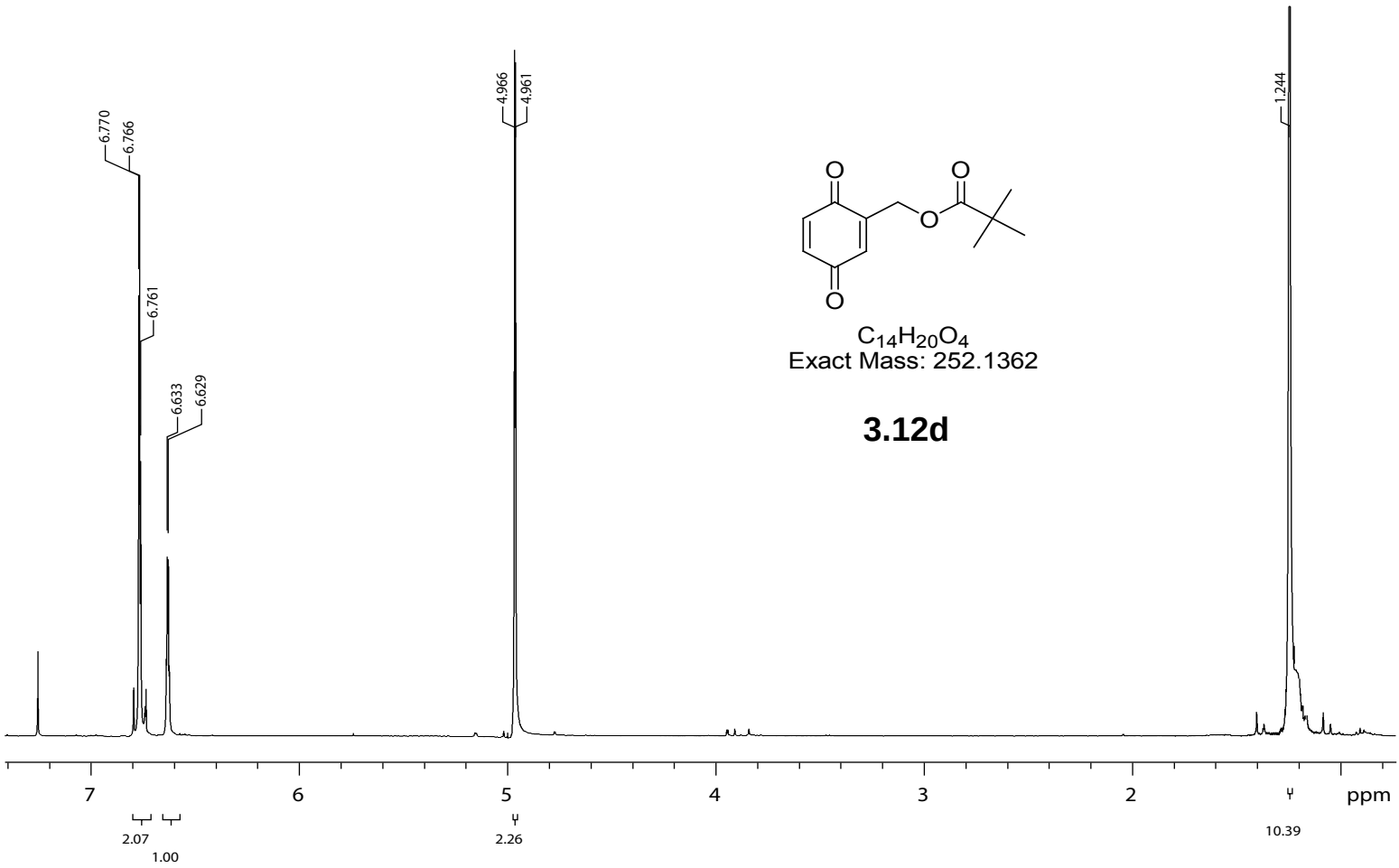
$C_{15}H_{14}O_3$
Exact Mass: 242.0943

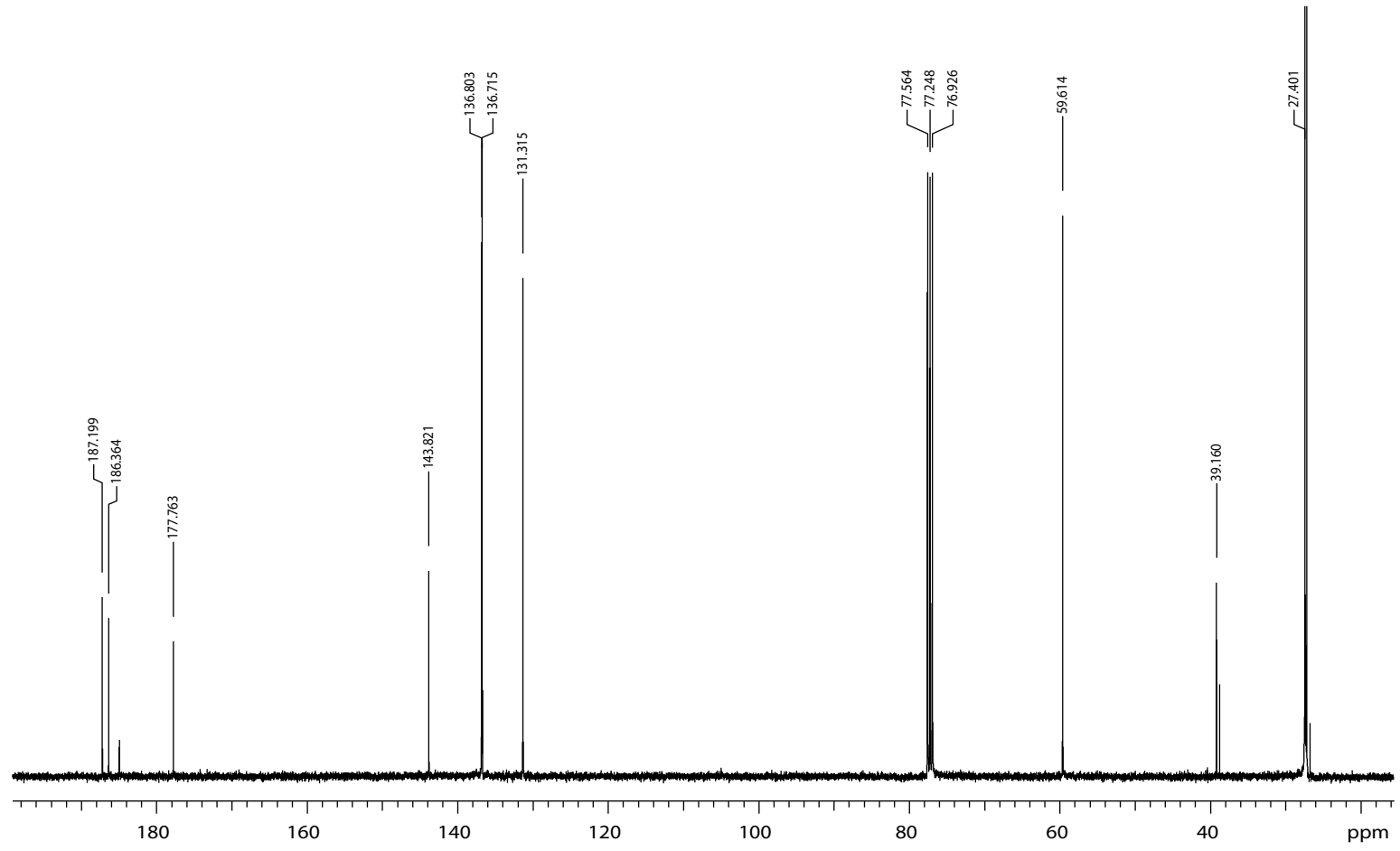
3.12a

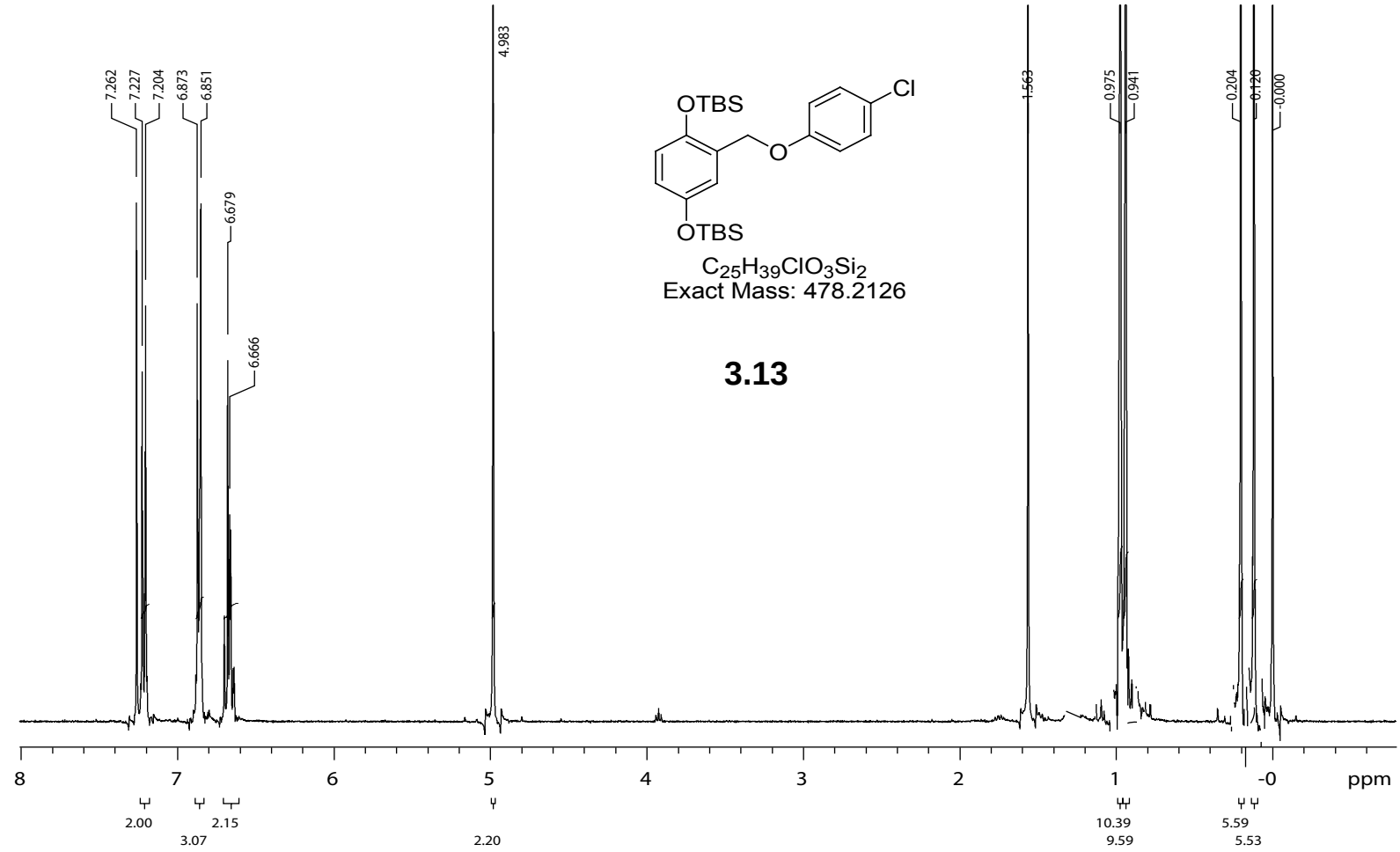



8.099
8.081
8.079
7.624
7.605
7.508
7.488
7.470
7.264
6.823
6.810
6.805
6.796
6.791
6.784
5.265
5.260
O
O
O
O
Ph
C14H10O4
Exact Mass: 242.0579
3.12c
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
ppm
1.96
1.00
2.12
2.72
2.19


187.234
186.457
165.885
143.577
136.918
136.800
133.907
131.687
130.038
129.350
128.888
77.590
77.473
77.268
76.953
60.147
200
180
160
140
120
100
80
60
ppm

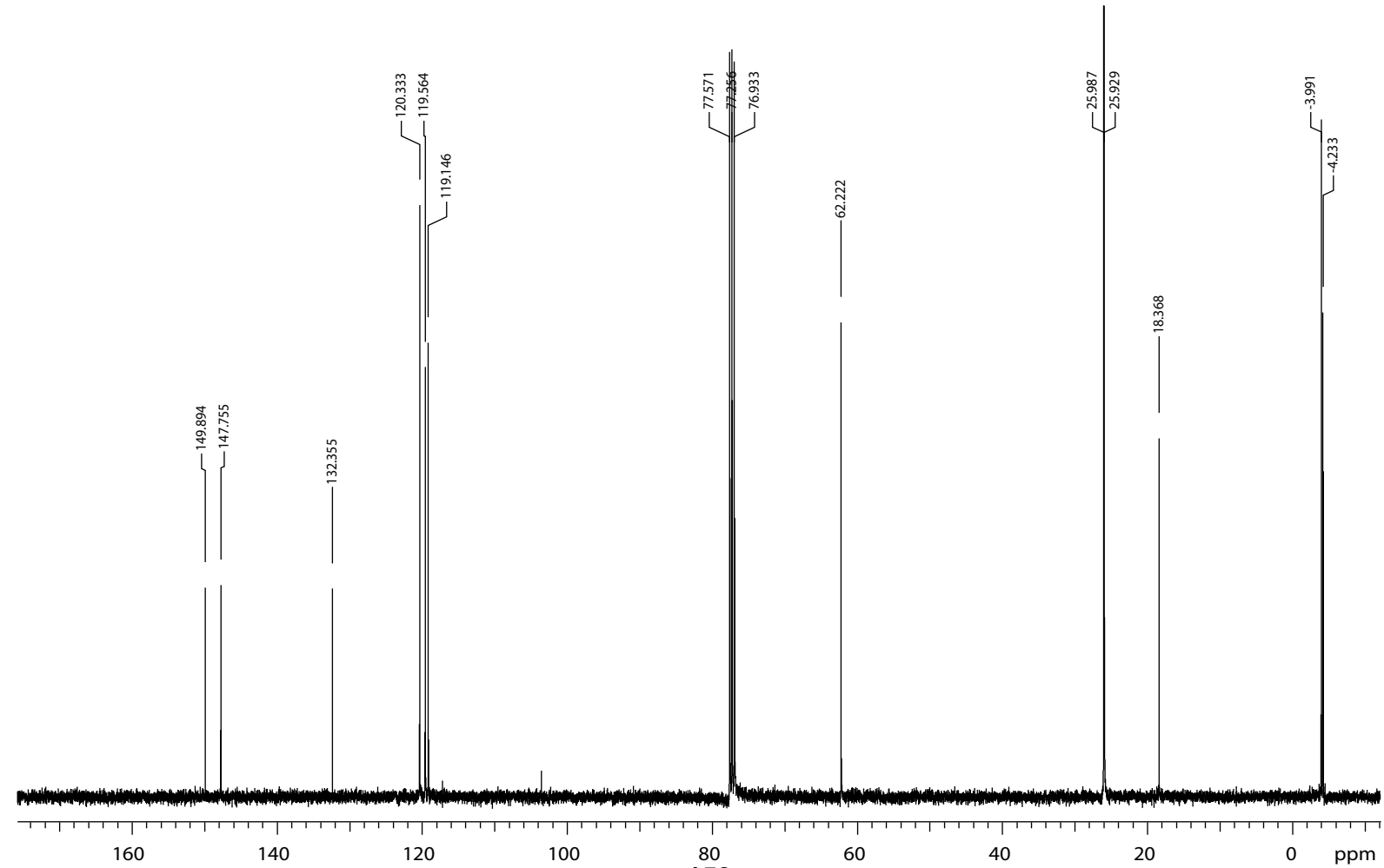

6.770
6.766
6.761
6.633
6.629
4.966
4.961
1.244
O
O
O
O
$C_{14}H_{20}O_4$
Exact Mass: 252.1362
3.12d
7
6
5
4
3
2
ppm
2.07
1.00
2.26
10.39

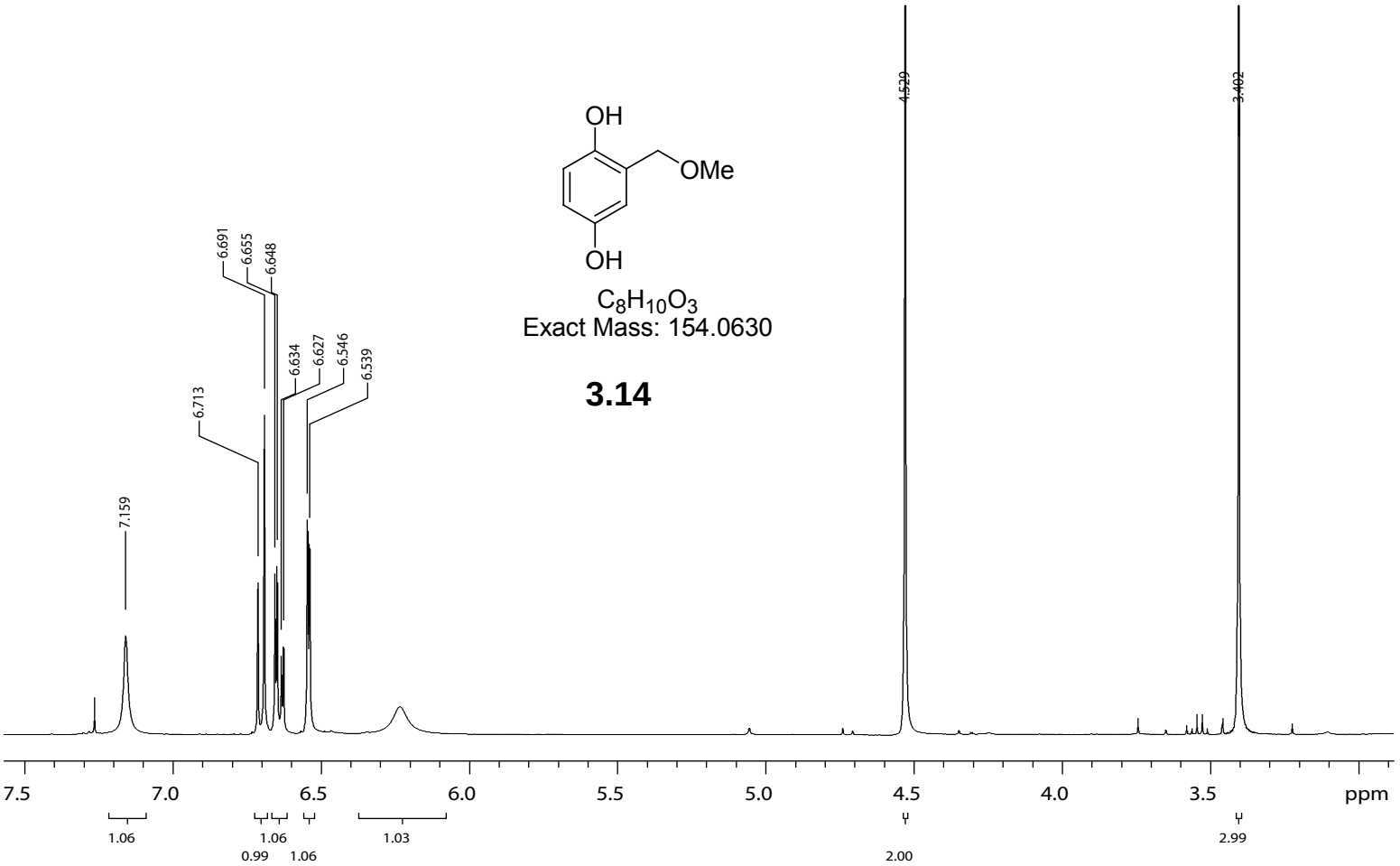

187.199
186.364
177.763
143.821
136.803
136.715
131.315
77.564
77.248
76.926
59.614
39.160
27.401
180
160
140
120
100
80
60
40
ppm

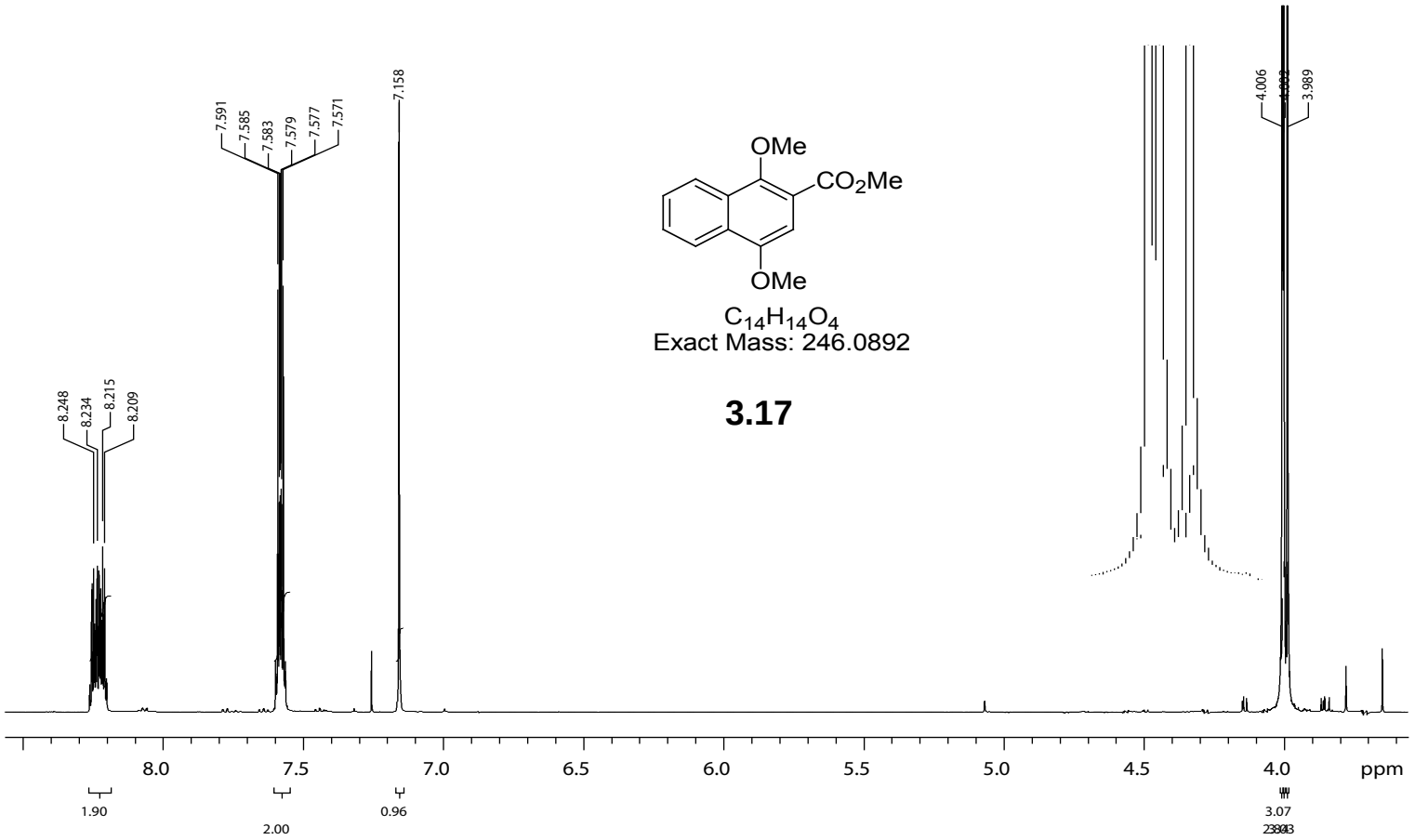


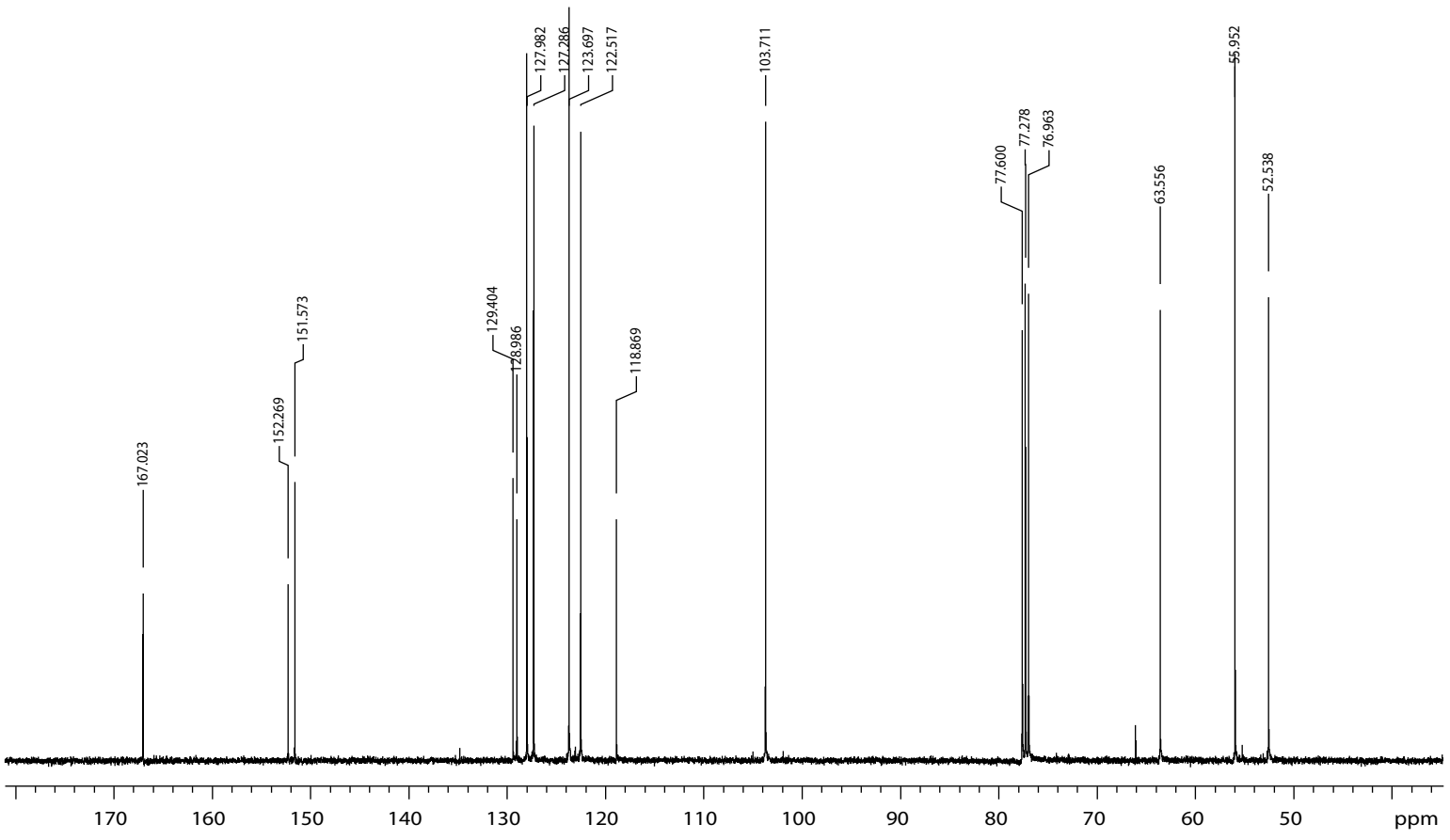
$C_{25}H_{39}ClO_3Si_2$
Exact Mass: 478.2126

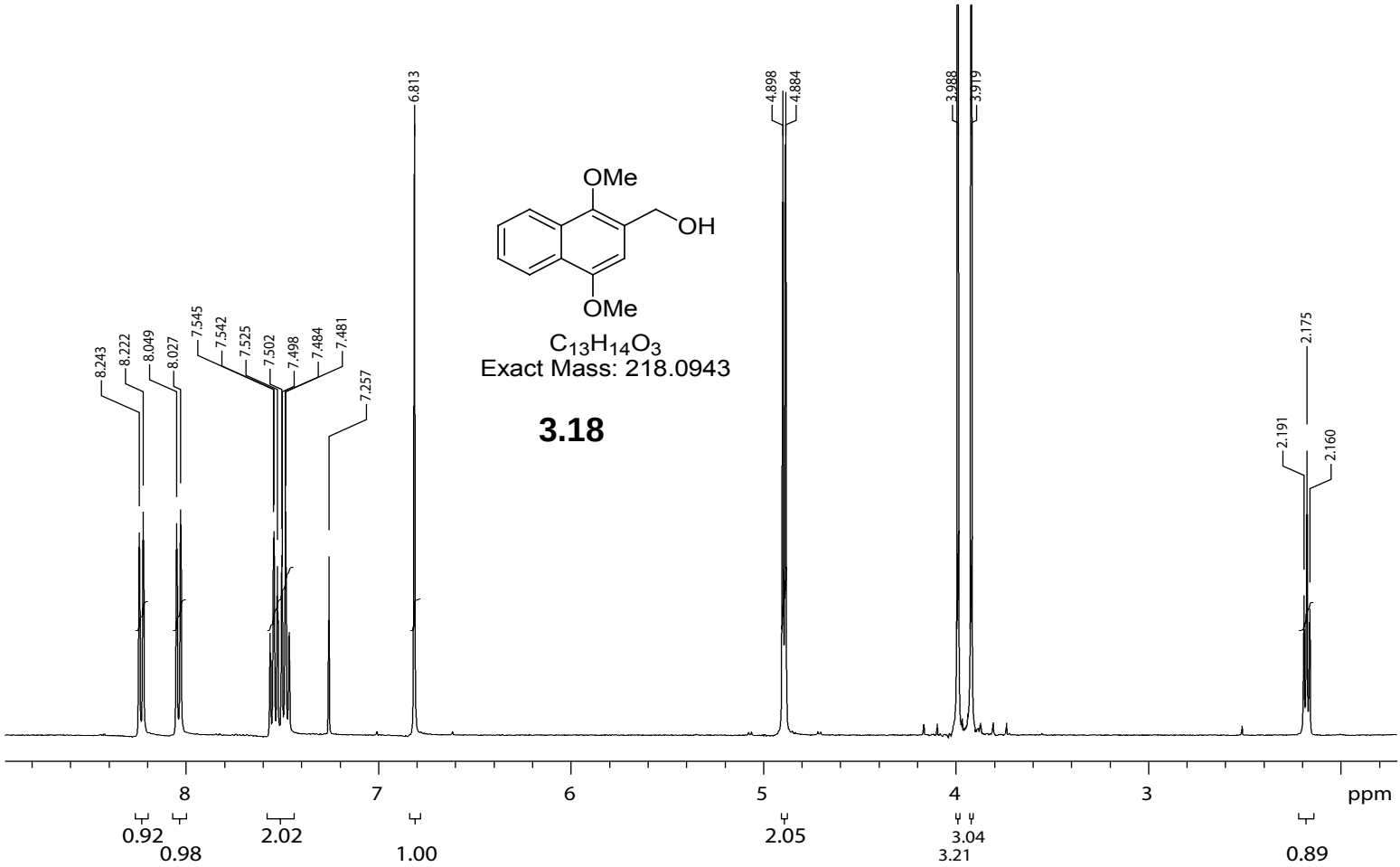
3.13

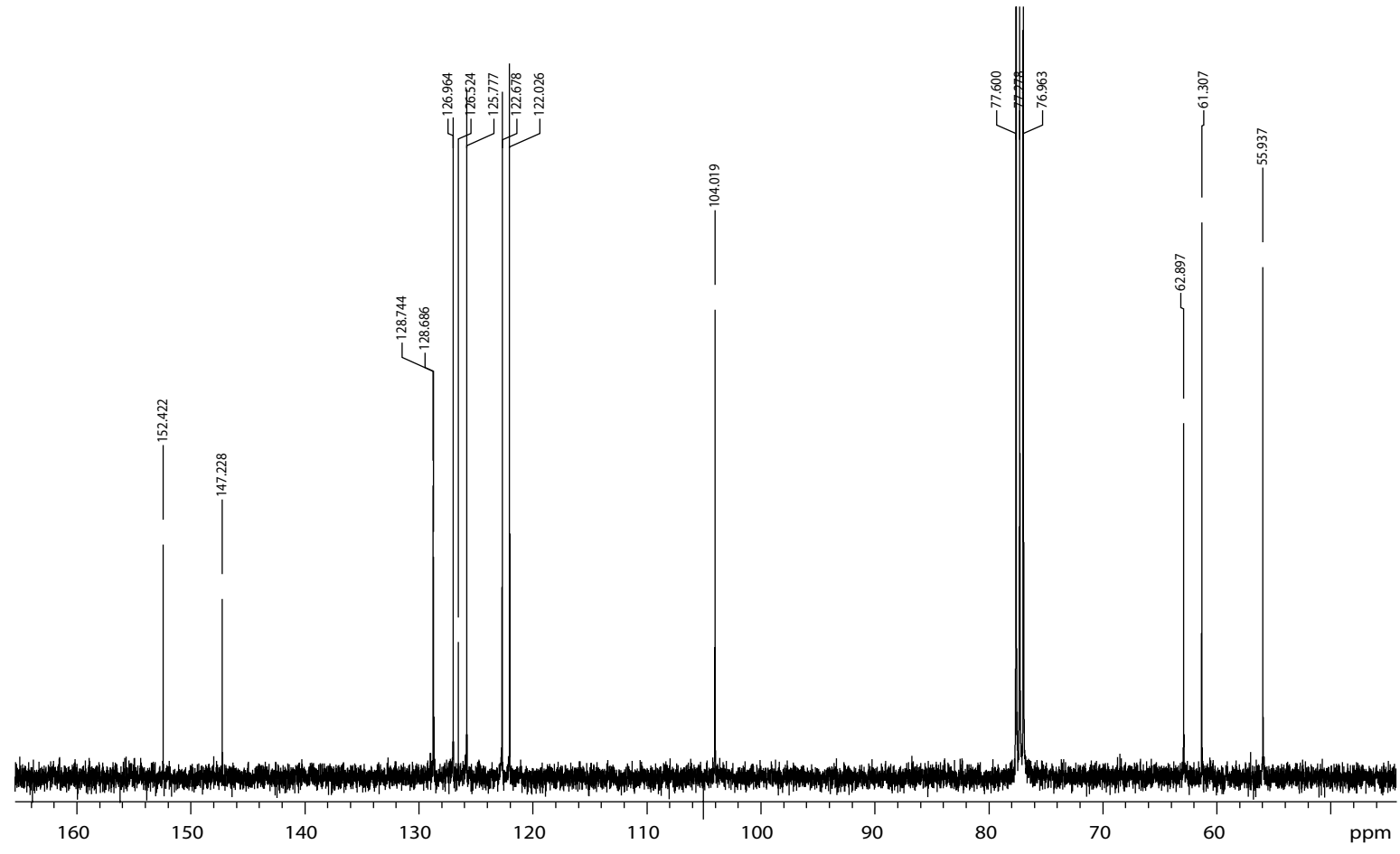


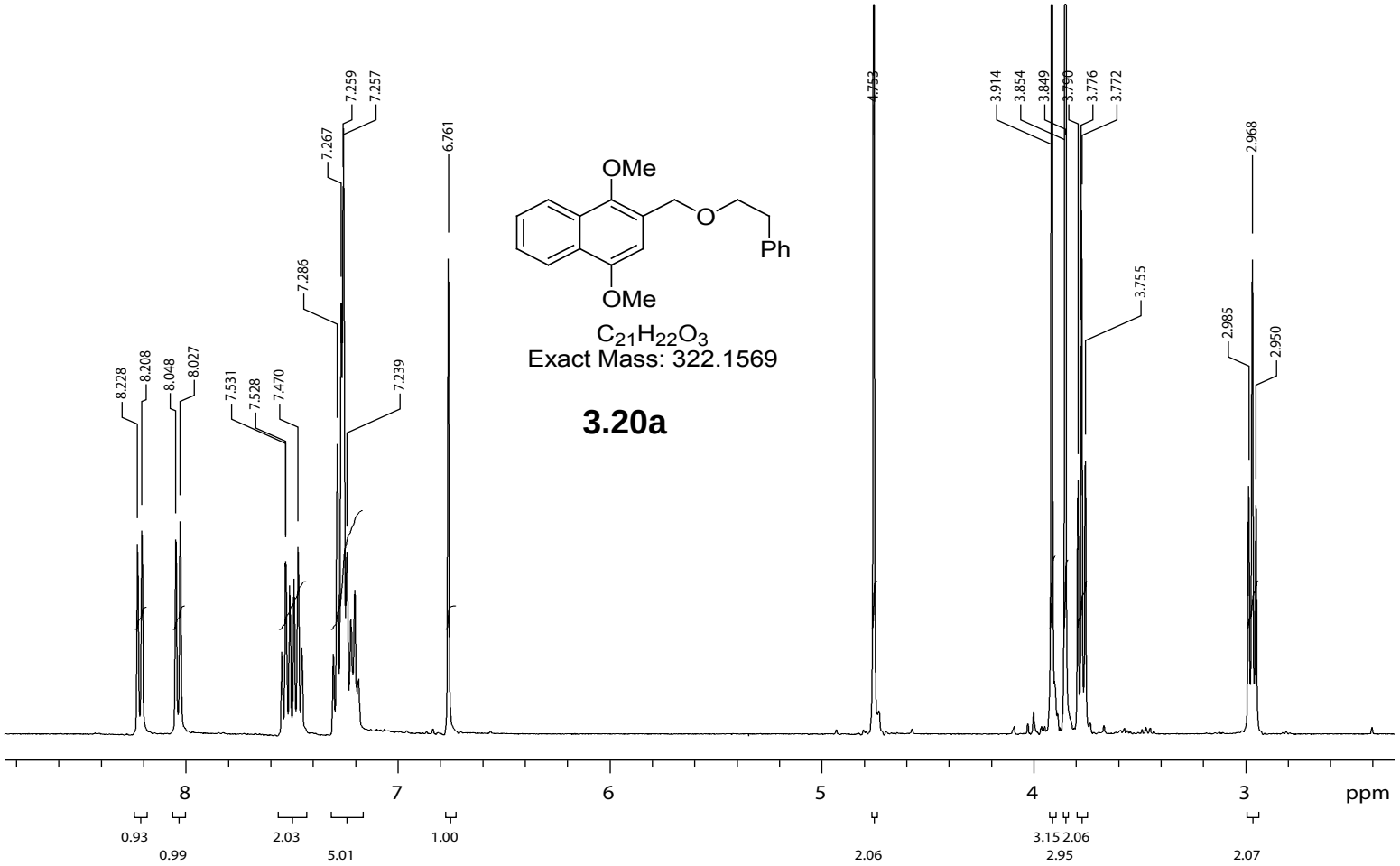

OH
OMe
OH
$C_8H_{10}O_3$
Exact Mass: 154.0630
3.14
6.691
6.655
6.648
6.713
6.634
6.627
6.546
6.539
7.159
4.529
3.402
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm
1.06
1.06
0.99
1.06
1.03
2.00
2.99


OMe
CO2Me
OMe
C14H14O4
Exact Mass: 246.0892
3.17
8.248
8.234
8.215
8.209
7.591
7.585
7.583
7.579
7.577
7.571
7.158
4.006
3.989
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
ppm
1.90
2.00
0.96
3.07


167.023
152.269
151.573
129.404
128.986
127.982
127.286
123.697
122.517
118.869
103.711
77.600
77.278
76.963
63.556
55.952
52.538
170
160
150
140
130
120
110
100
90
80
70
60
50
ppm


OMe
OH
OMe
$C_{13}H_{14}O_3$
Exact Mass: 218.0943
3.18
8.243
8.222
8.049
8.027
7.545
7.542
7.525
7.502
7.498
7.484
7.481
7.257
6.813
4.898
4.884
3.988
3.919
2.191
2.175
2.160
ppm
0.92
0.98
2.02
1.00
2.05
3.04
3.21
0.89


152.422
147.228
128.744
128.686
126.964
126.524
125.777
122.678
122.026
104.019
77.600
77.278
76.963
62.897
61.307
55.937
ppm


OMe
O
Ph
OMe
$C_{21}H_{22}O_3$
Exact Mass: 322.1569
3.20a
8.228
8.208
8.048
8.027
7.531
7.528
7.470
7.286
7.267
7.259
7.257
7.239
6.761
4.753
3.914
3.854
3.849
3.790
3.776
3.772
3.755
2.985
2.968
2.950
ppm
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0.99
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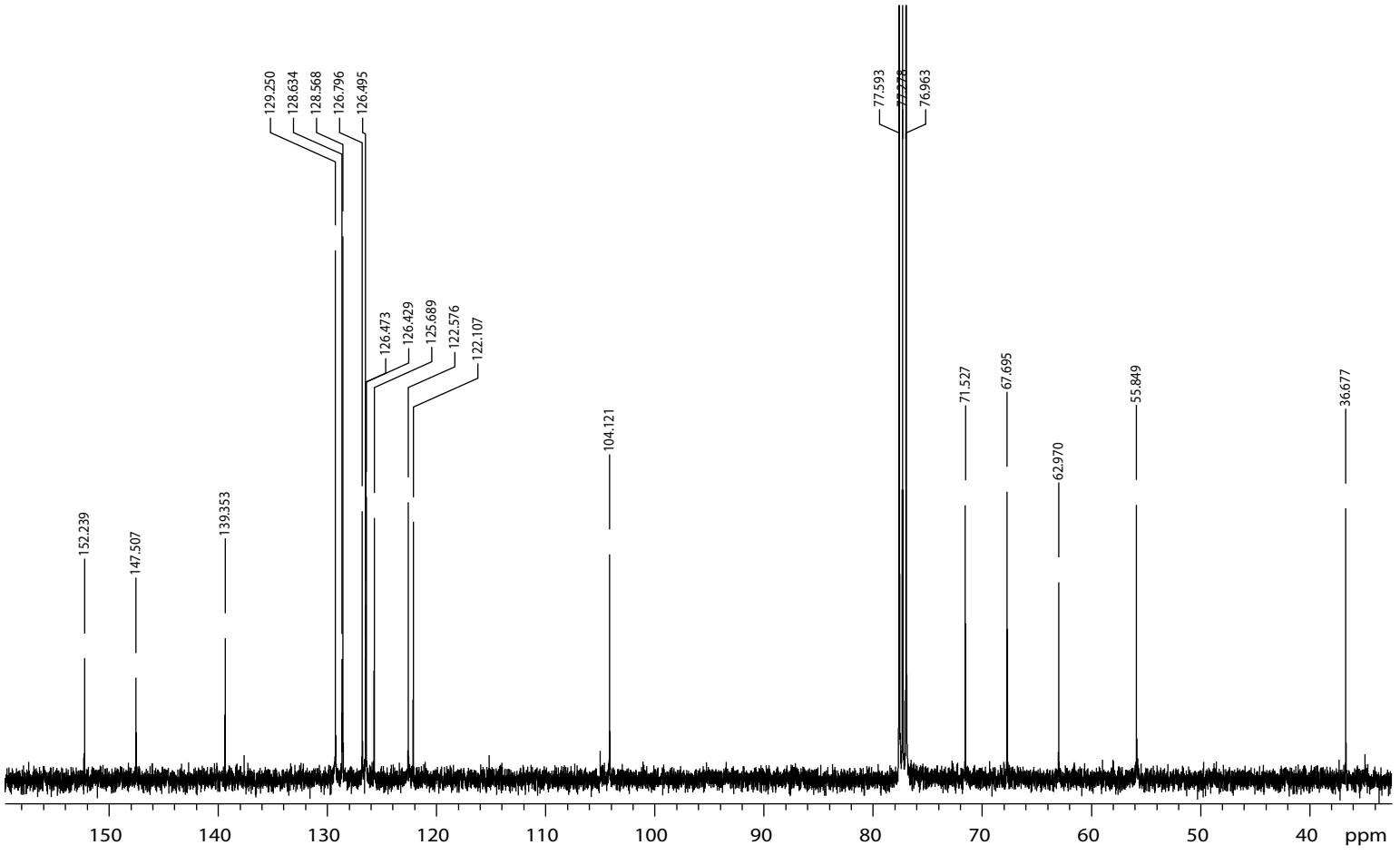
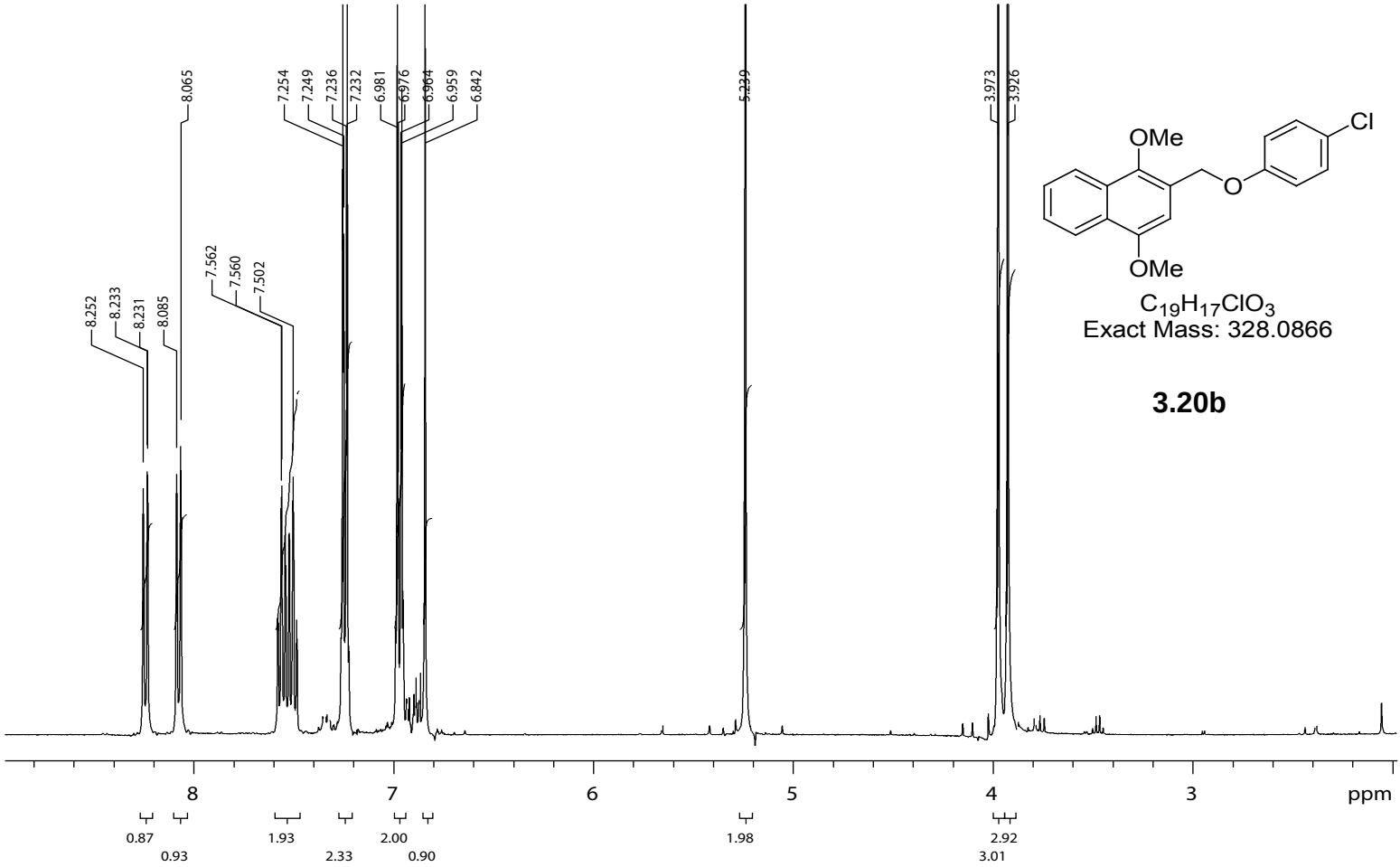
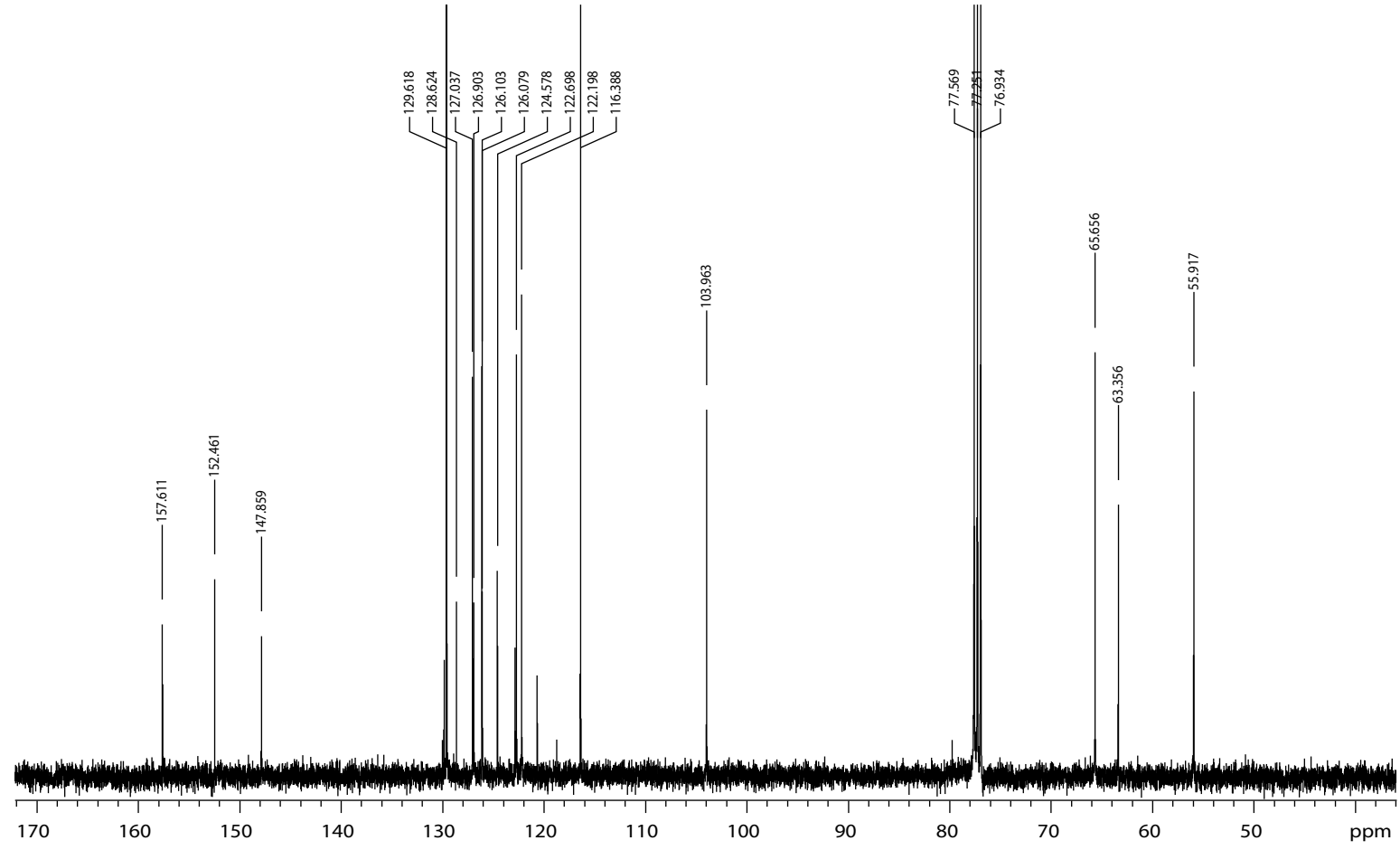
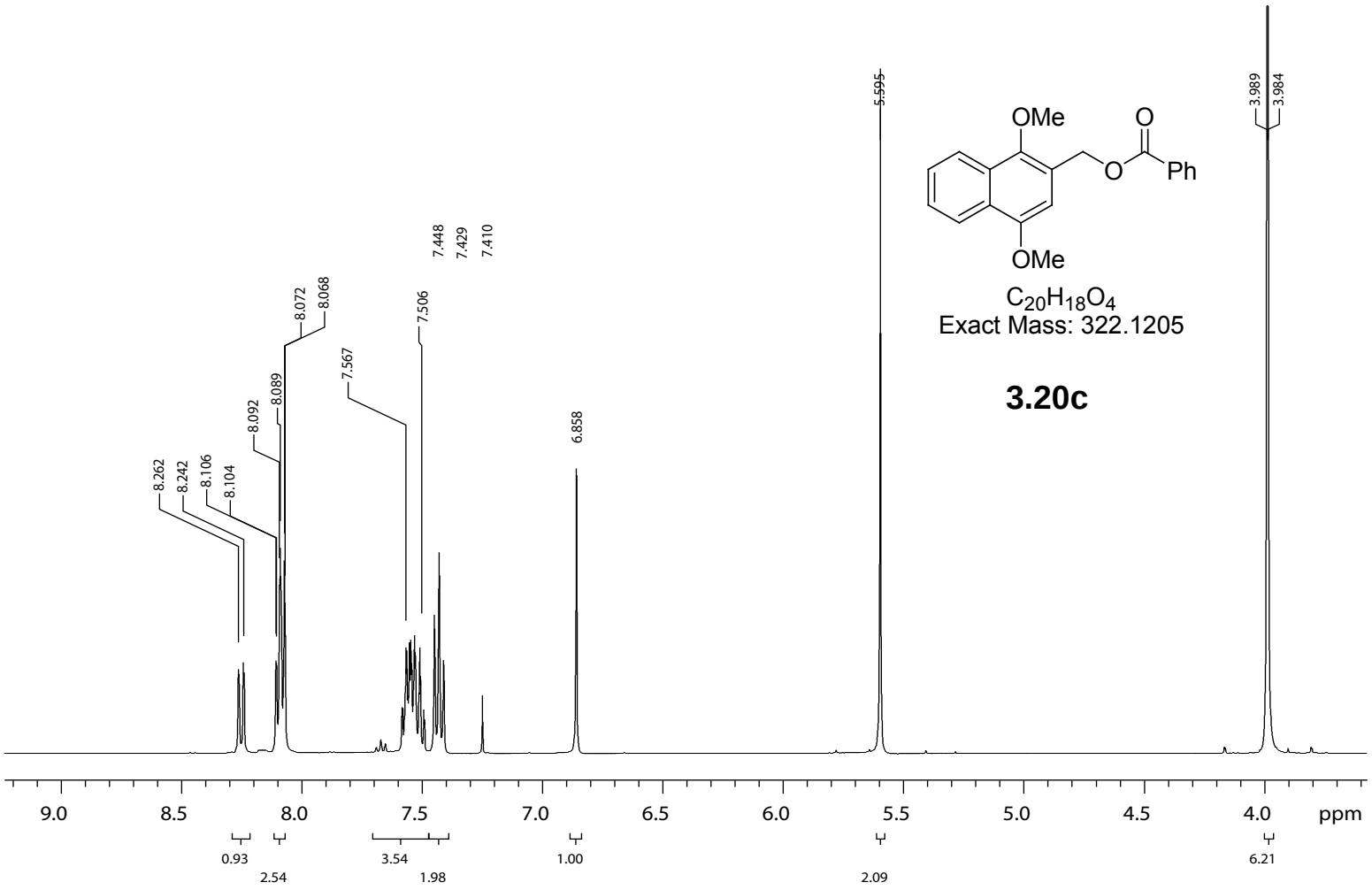
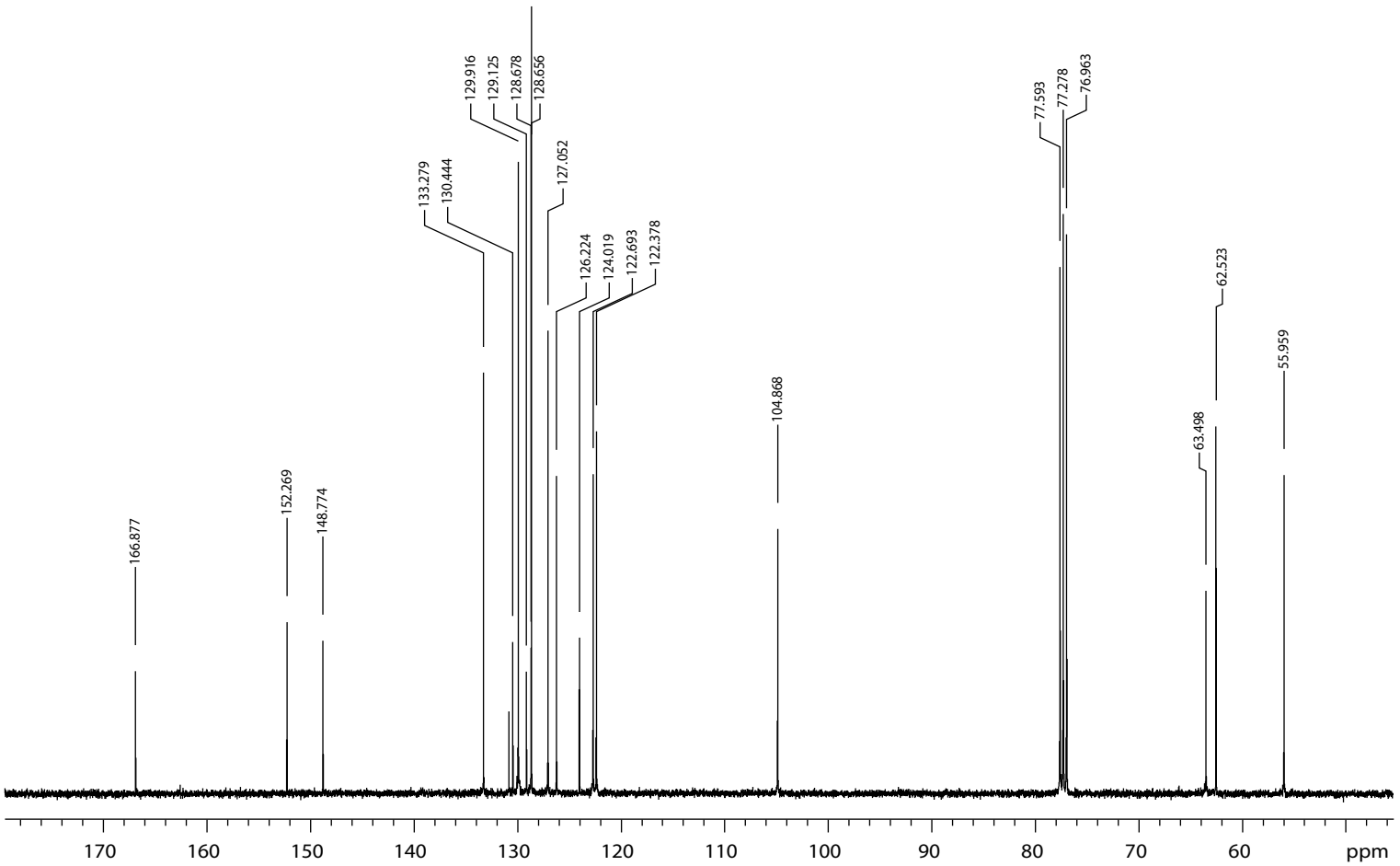
5.01
1.00
2.06
3.15
2.06
2.95
2.07

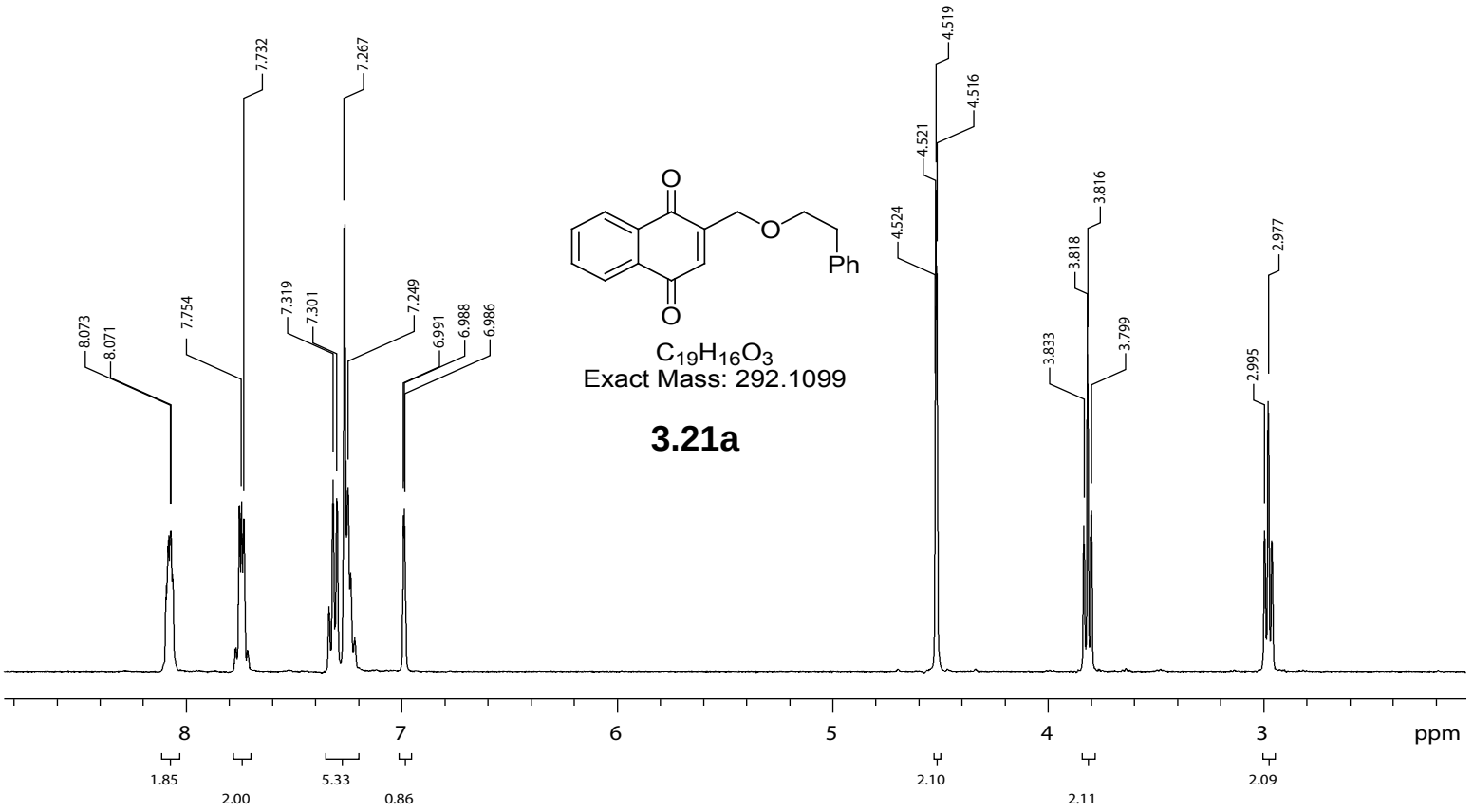

152.239
147.507
139.353
129.250
128.634
128.568
126.796
126.495
126.473
126.429
125.689
122.576
122.107
104.121
77.593
77.378
76.963
71.527
67.695
62.970
55.849
36.677
ppm


8.252
8.233
8.231
8.085
8.065
7.562
7.560
7.502
7.254
7.249
7.236
7.232
6.981
6.976
6.964
6.959
6.842
5.239
3.973
3.926
OMe
O
Cl
OMe
$C_{19}H_{17}ClO_3$
Exact Mass: 328.0866
3.20b
8
7
6
5
4
3
ppm
0.87
0.93
1.93
2.33
2.00
0.90
1.98
2.92
3.01


129.618
128.624
127.037
126.903
126.103
126.079
124.578
122.698
122.198
116.388
77.569
77.251
76.934
157.611
152.461
147.859
103.963
65.656
63.356
55.917
170
160
150
140
130
120
110
100
90
80
70
60
50
ppm

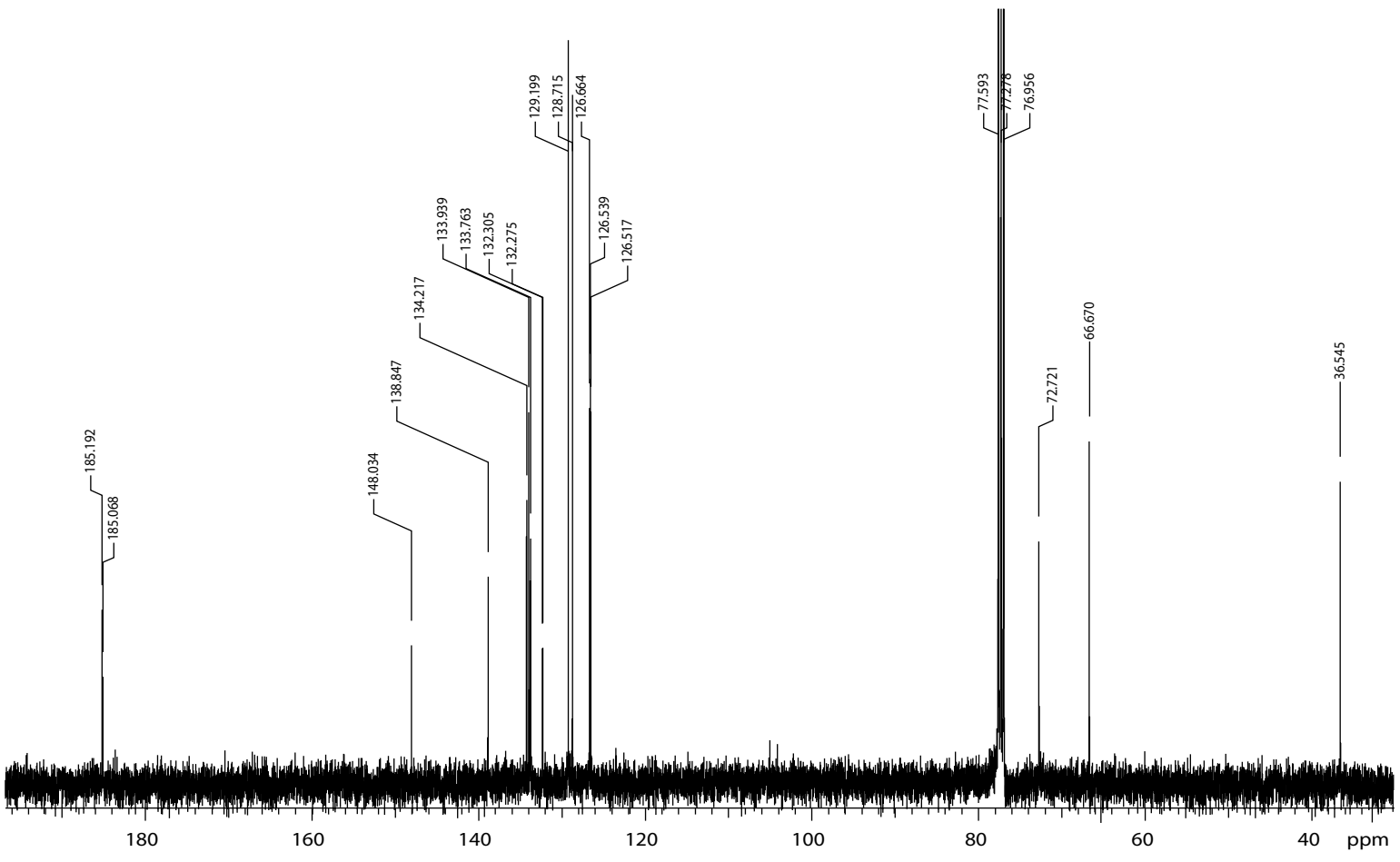

OMe
O
O
Ph
OMe
$C_{20}H_{18}O_4$
Exact Mass: 322.1205
3.20c
8.262
8.242
8.106
8.104
8.092
8.089
8.072
8.068
7.567
7.506
7.448
7.429
7.410
6.858
5.595
3.989
3.984
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
ppm
0.93
2.54
3.54
1.98
1.00
2.09
6.21

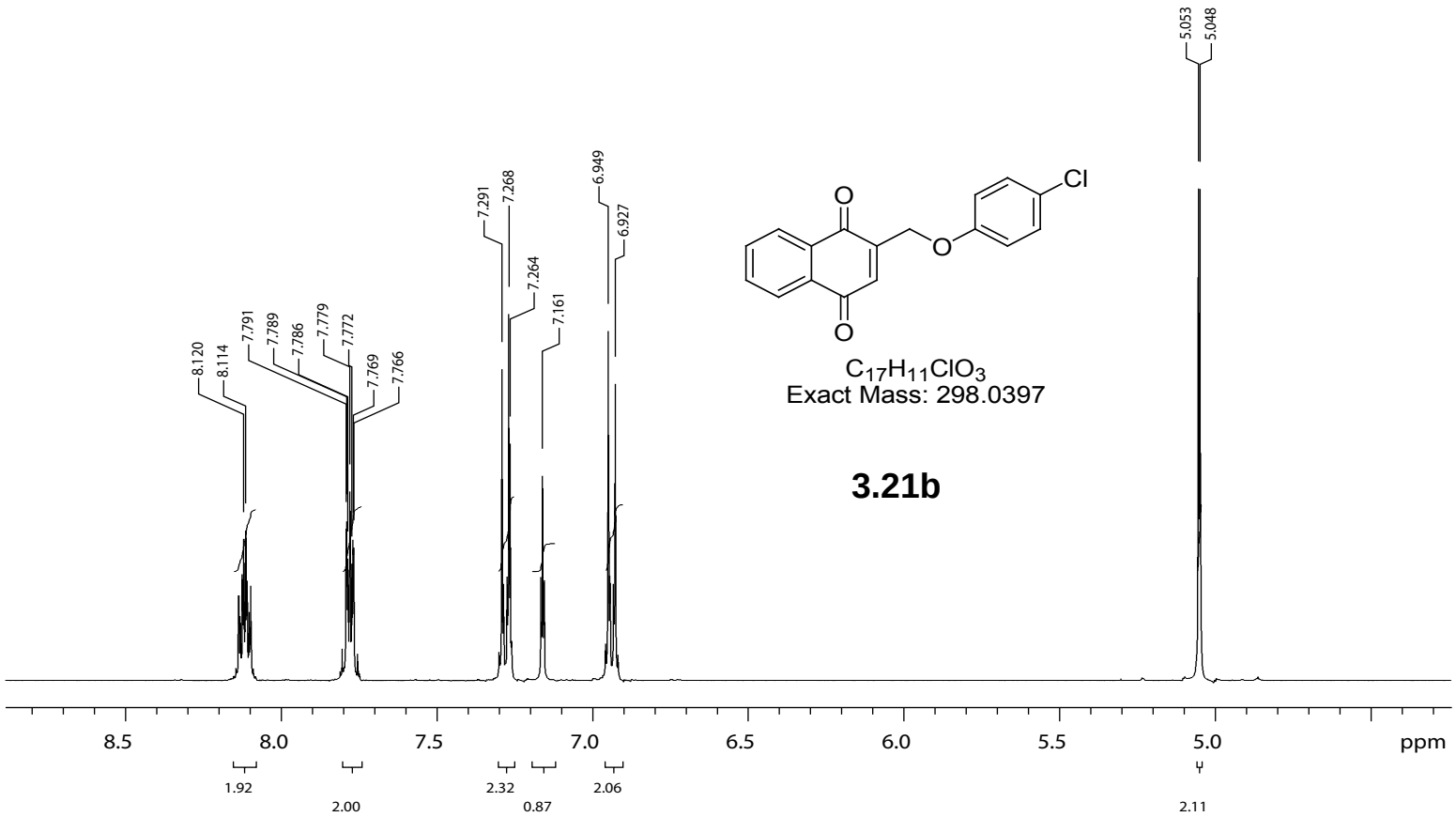

166.877
152.269
148.774
133.279
130.444
129.916
129.125
128.678
128.656
127.052
126.224
124.019
122.693
122.378
104.868
77.593
77.278
76.963
63.498
62.523
55.959
170
160
150
140
130
120
110
100
90
80
70
60
ppm

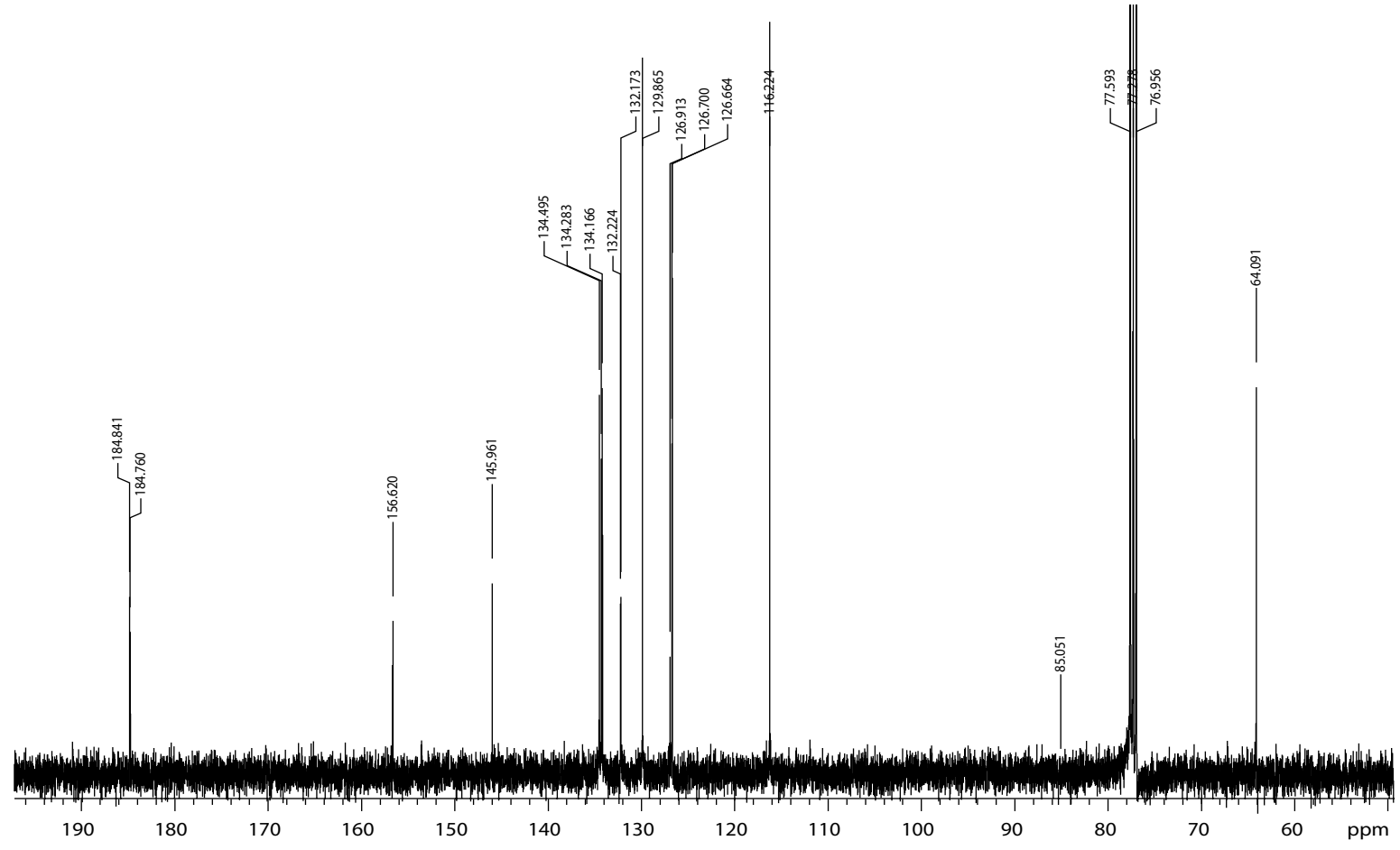


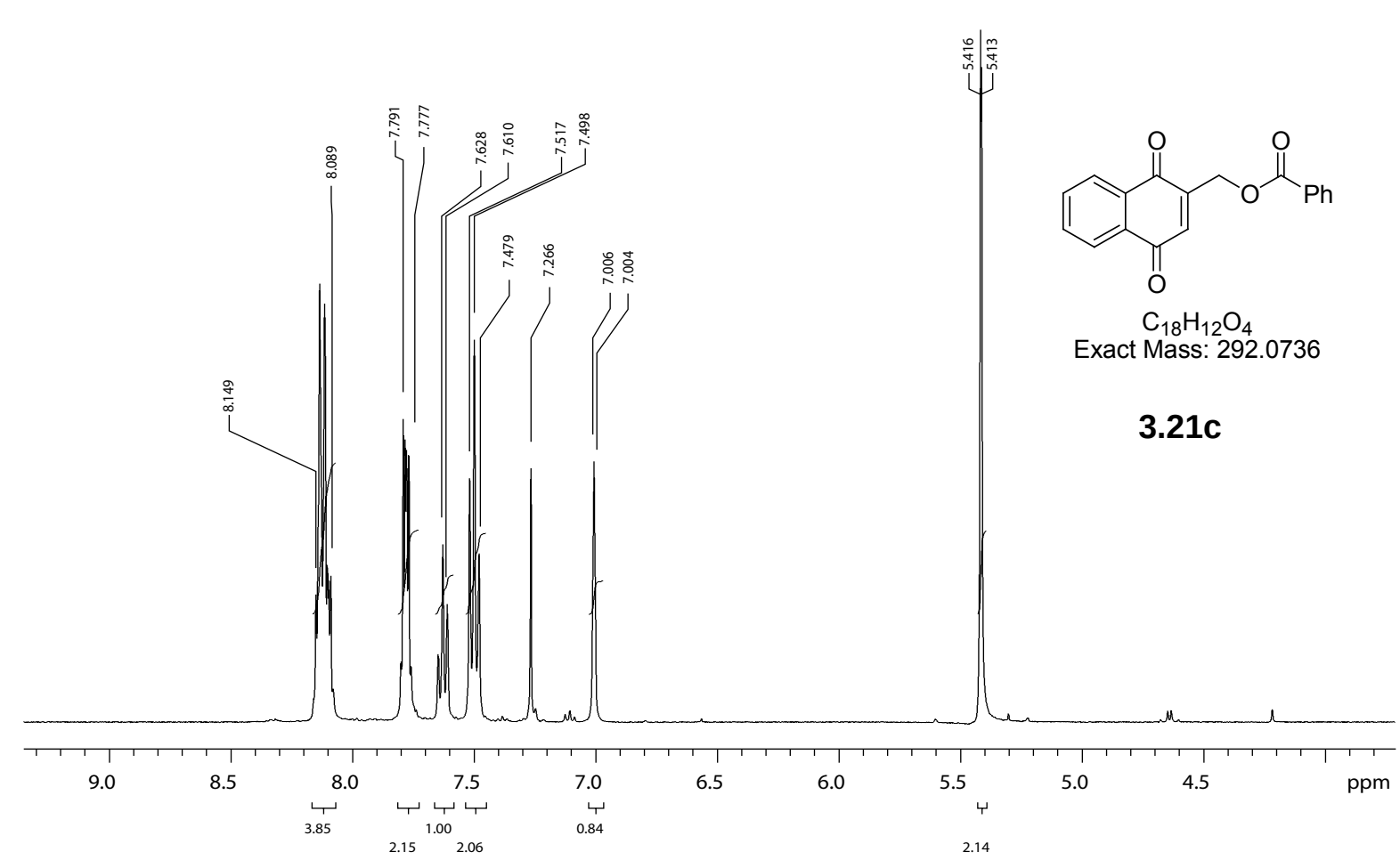
$C_{19}H_{16}O_3$
Exact Mass: 292.1099

3.21a



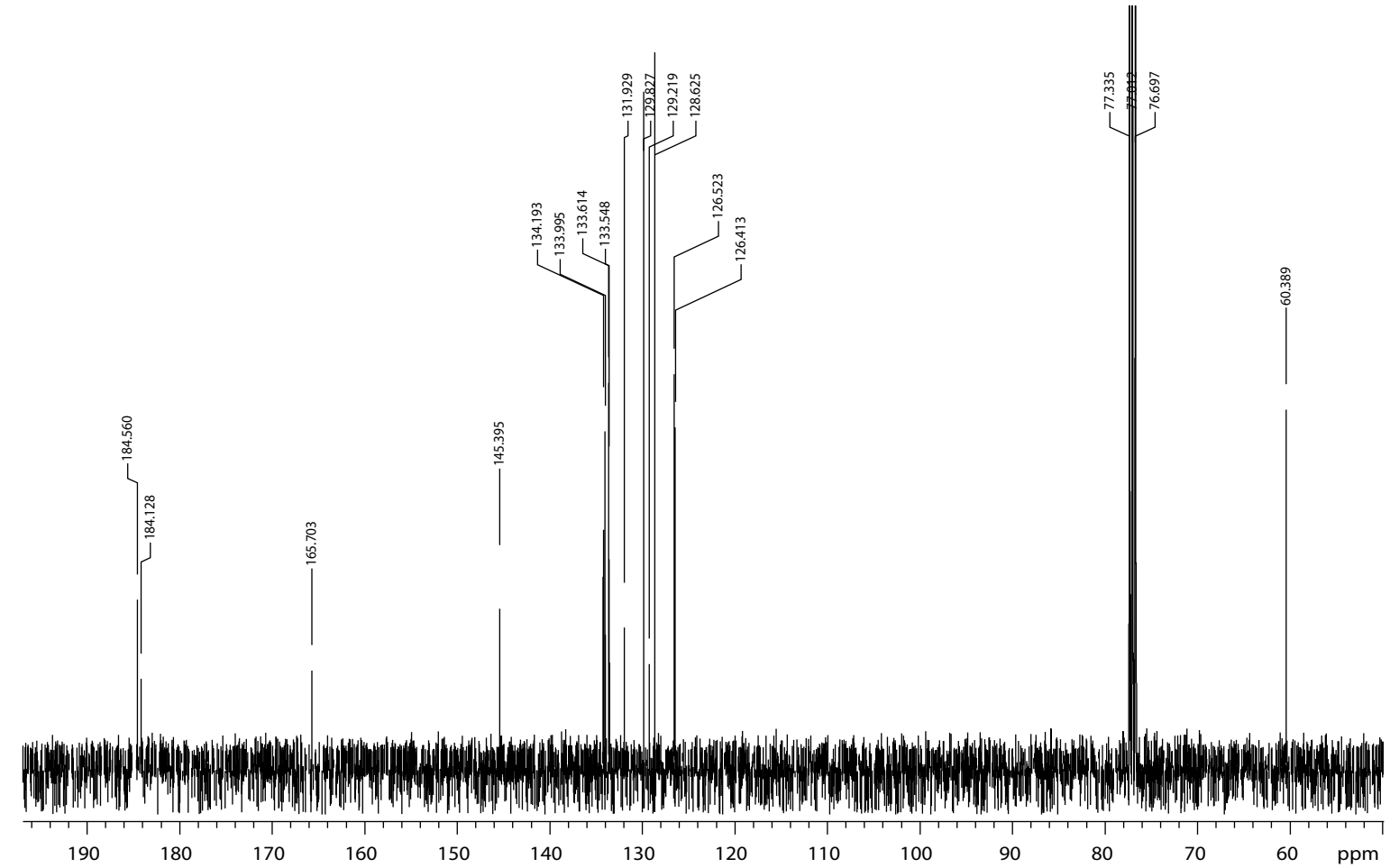

5.053
5.048
8.120
8.114
7.791
7.789
7.786
7.779
7.772
7.769
7.766
7.291
7.268
7.264
7.161
6.949
6.927
Cl
O
O
O
$C_{17}H_{11}ClO_3$
Exact Mass: 298.0397
3.21b
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
ppm
1.92
2.00
2.32
0.87
2.06
2.11

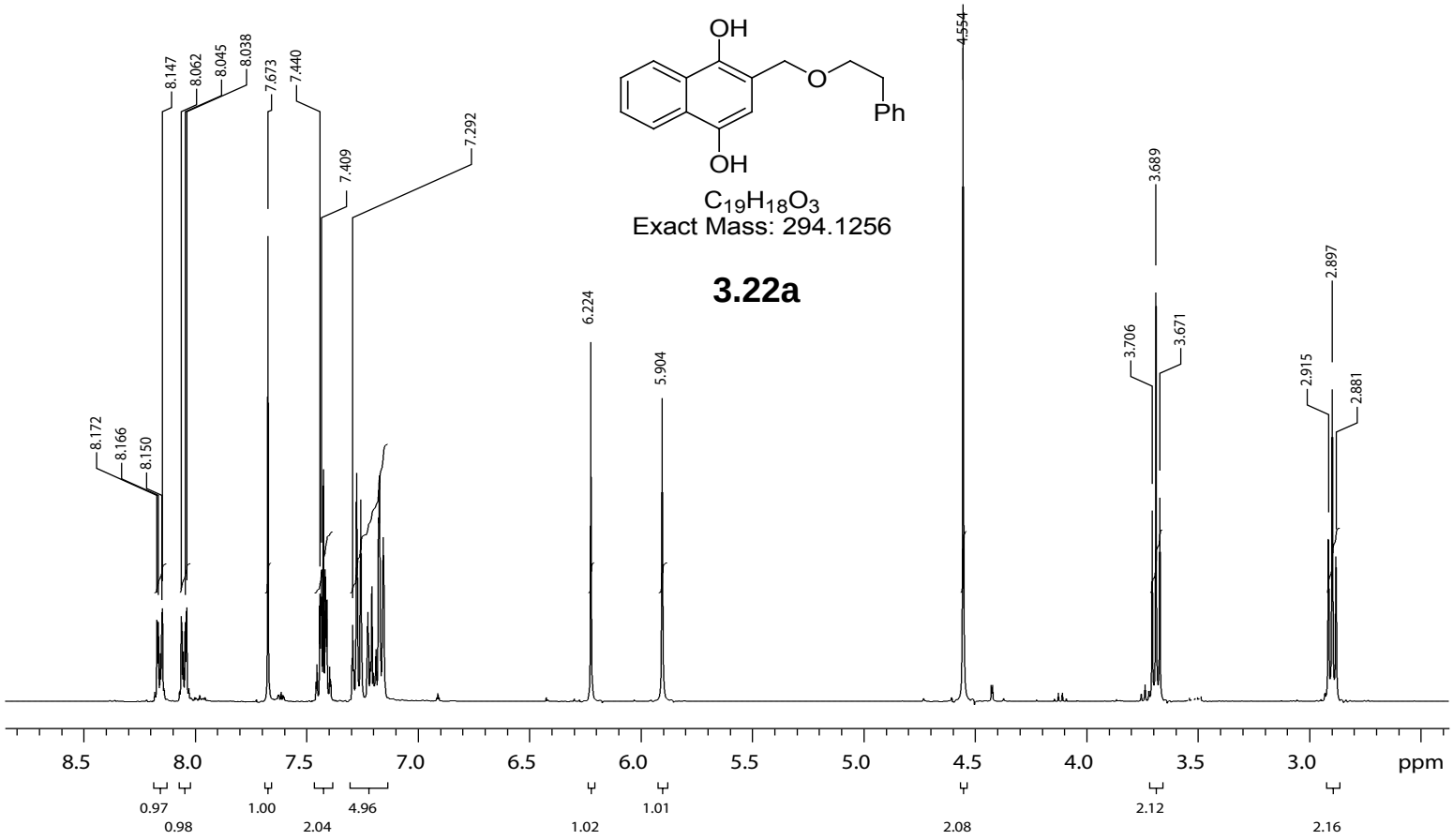

184.841
184.760
156.620
145.961
134.495
134.283
134.166
132.224
132.173
129.865
126.913
126.700
126.664
116.324
85.051
77.593
77.378
76.956
64.091
190
180
170
160
150
140
130
120
110
100
90
80
70
60
ppm

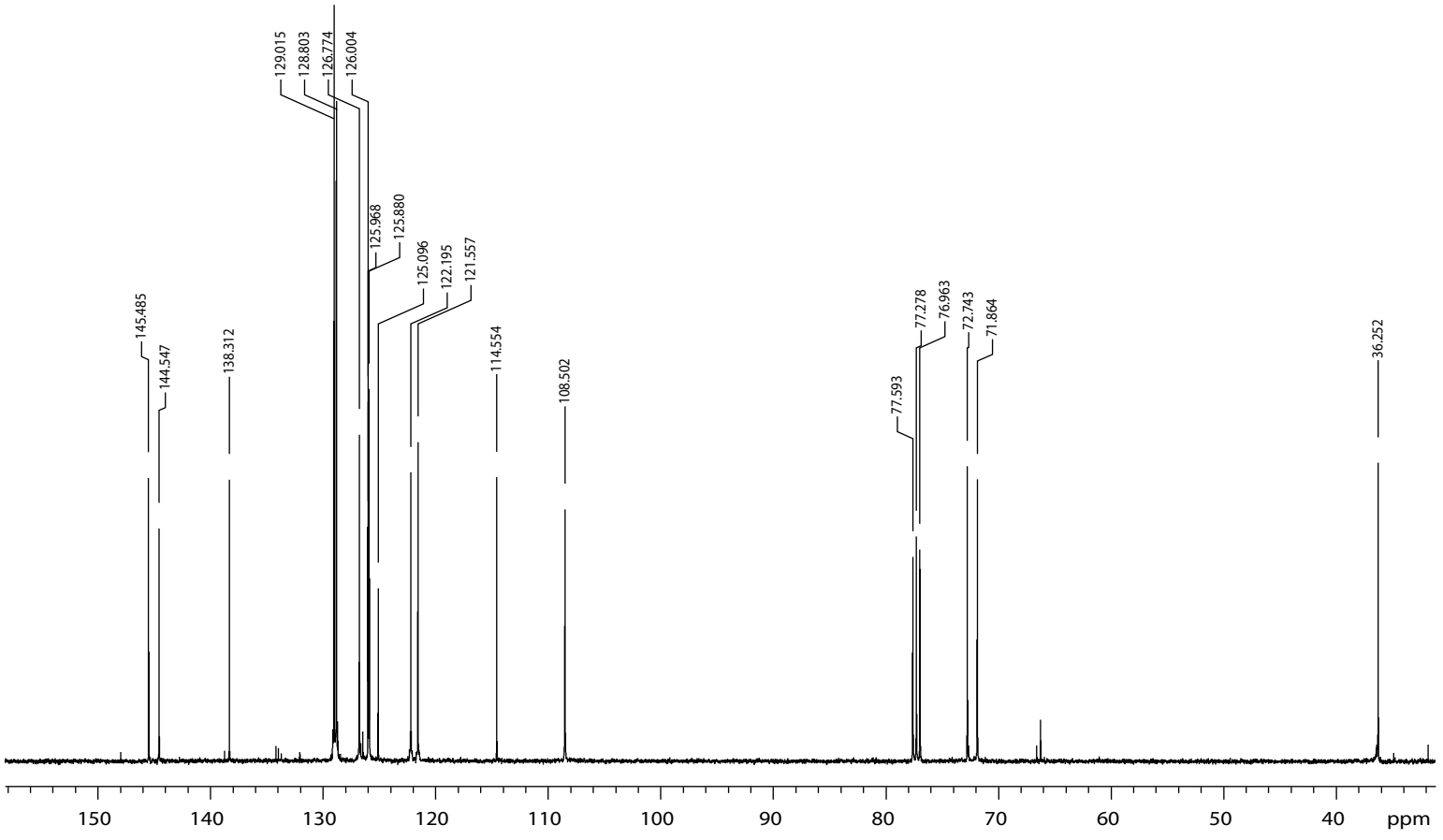


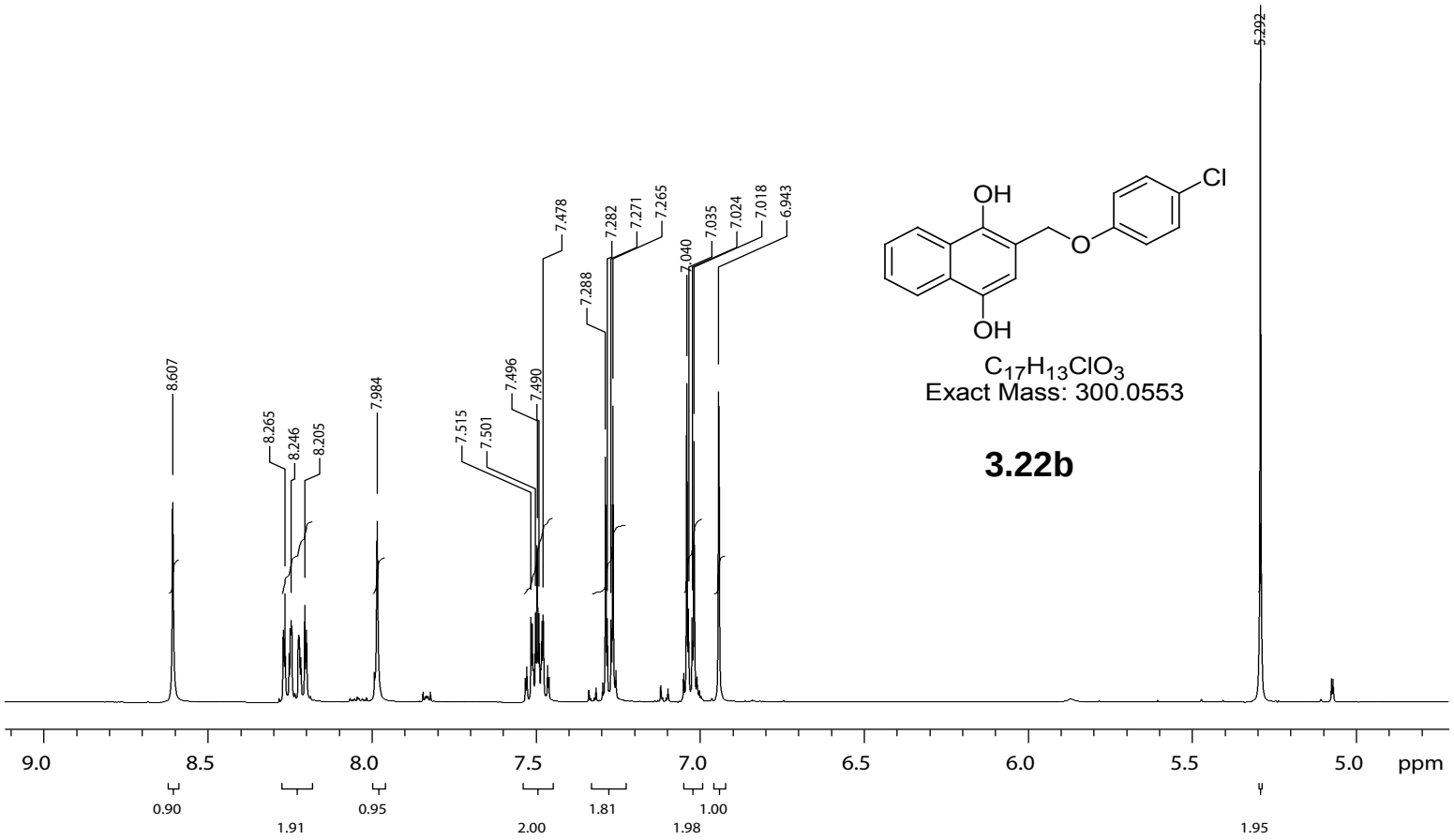
$C_{18}H_{12}O_4$
Exact Mass: 292.0736

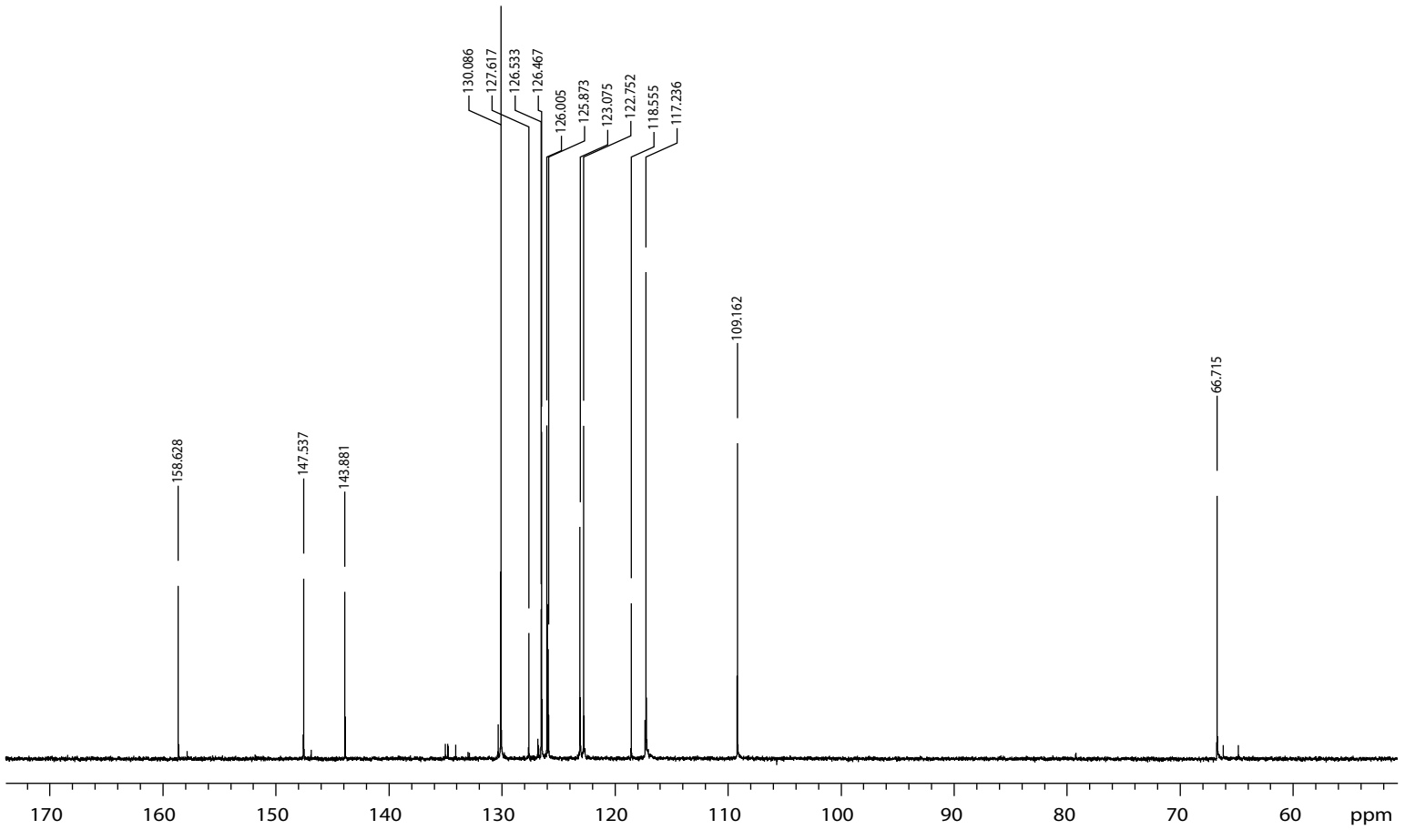
3.21c

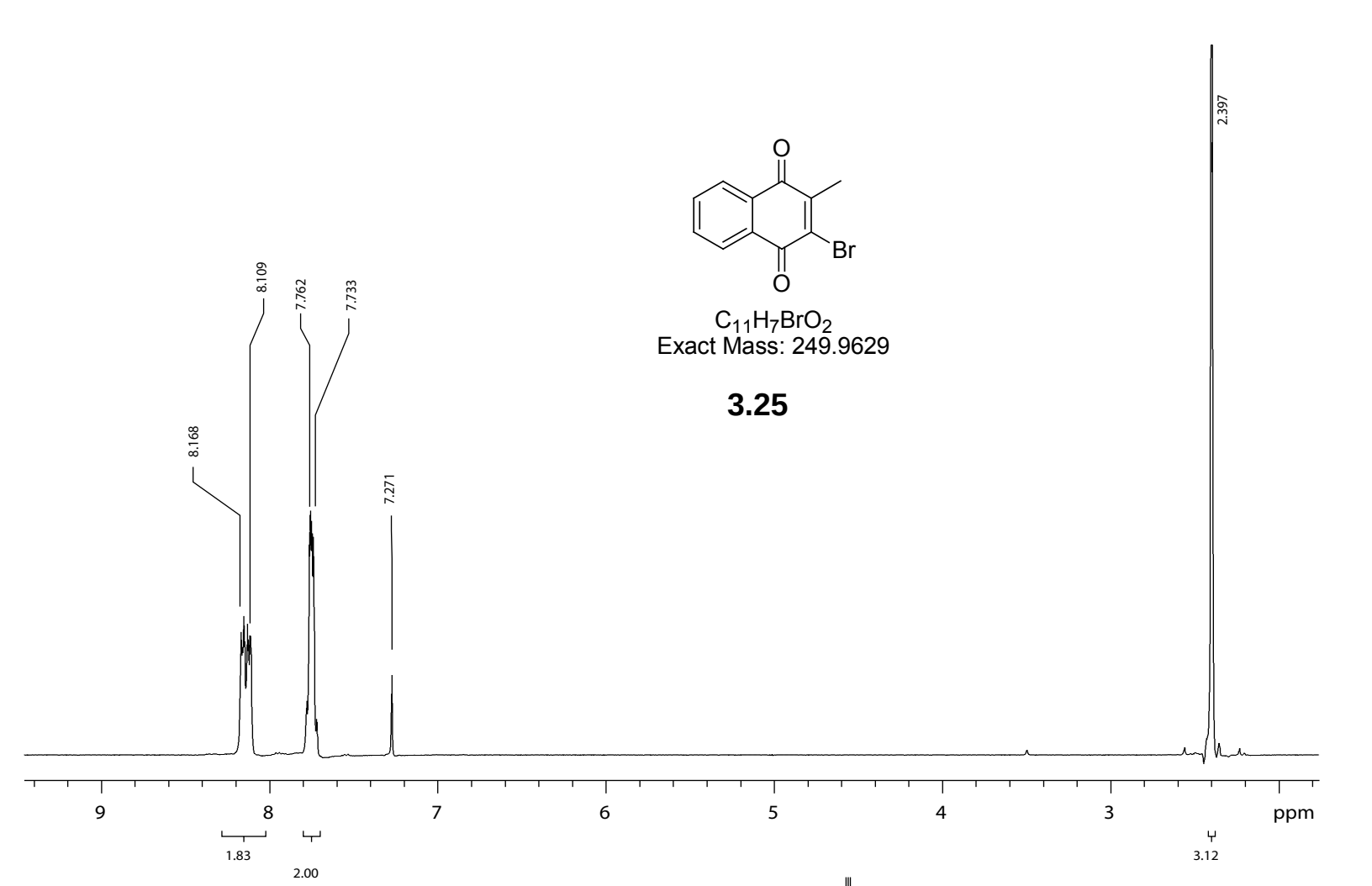


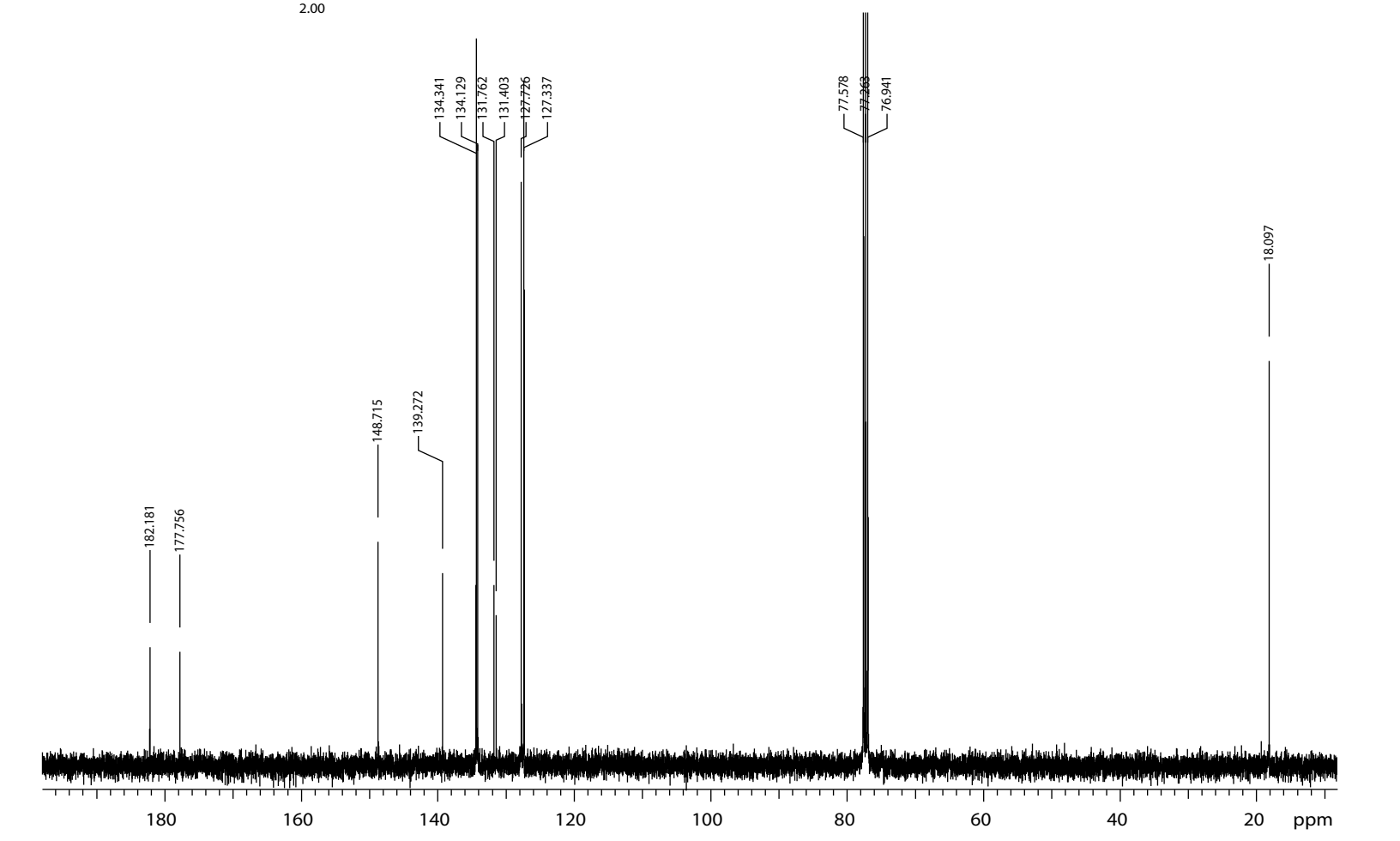

OH
O
Ph
OH
$C_{19}H_{18}O_3$
Exact Mass: 294.1256
3.22a
8.172
8.166
8.150
8.147
8.062
8.045
8.038
7.673
7.440
7.409
7.292
6.224
5.904
4.554
3.706
3.689
3.671
2.915
2.897
2.881
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm
0.97
0.98
1.00
2.04
4.96
1.02
1.01
2.08
2.12
2.16

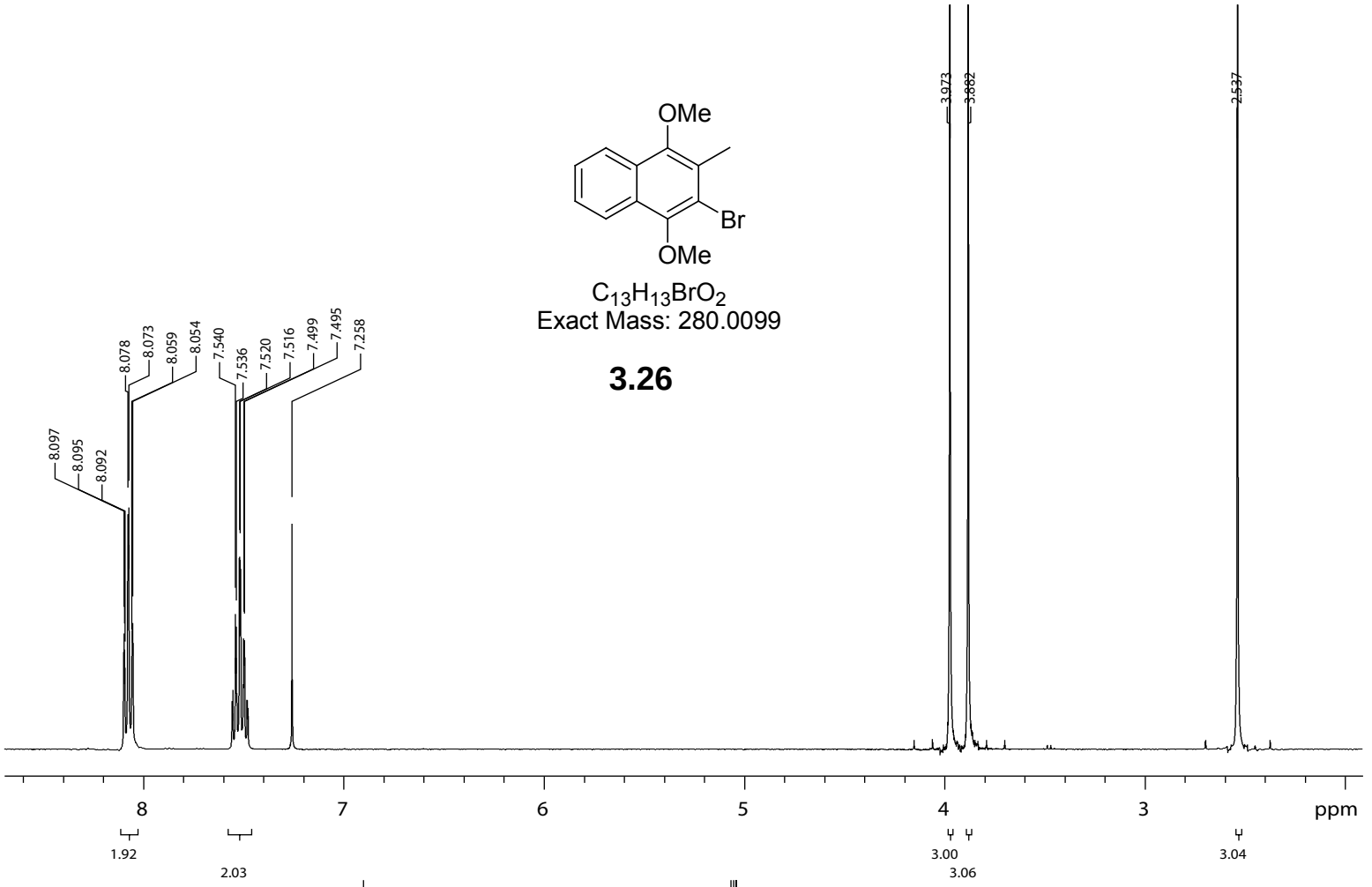

145.485
144.547
138.312
129.015
128.803
126.774
126.004
125.968
125.880
125.096
122.195
121.557
114.554
108.502
77.593
77.278
76.963
72.743
71.864
36.252
150
140
130
120
110
100
90
80
70
60
50
40
ppm


5.292
8.607
8.265
8.246
8.205
7.984
7.515
7.501
7.496
7.490
7.478
7.288
7.282
7.271
7.265
7.040
7.035
7.024
7.018
6.943
OH
Cl
O
OH
$C_{17}H_{13}ClO_3$
Exact Mass: 300.0553
3.22b
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
ppm
0.90
1.91
0.95
2.00
1.81
1.98
1.00
1.95


130.086
127.617
126.533
126.467
126.005
125.873
123.075
122.752
118.555
117.236
109.162
66.715
158.628
147.537
143.881
170
160
150
140
130
120
110
100
90
80
70
60
ppm

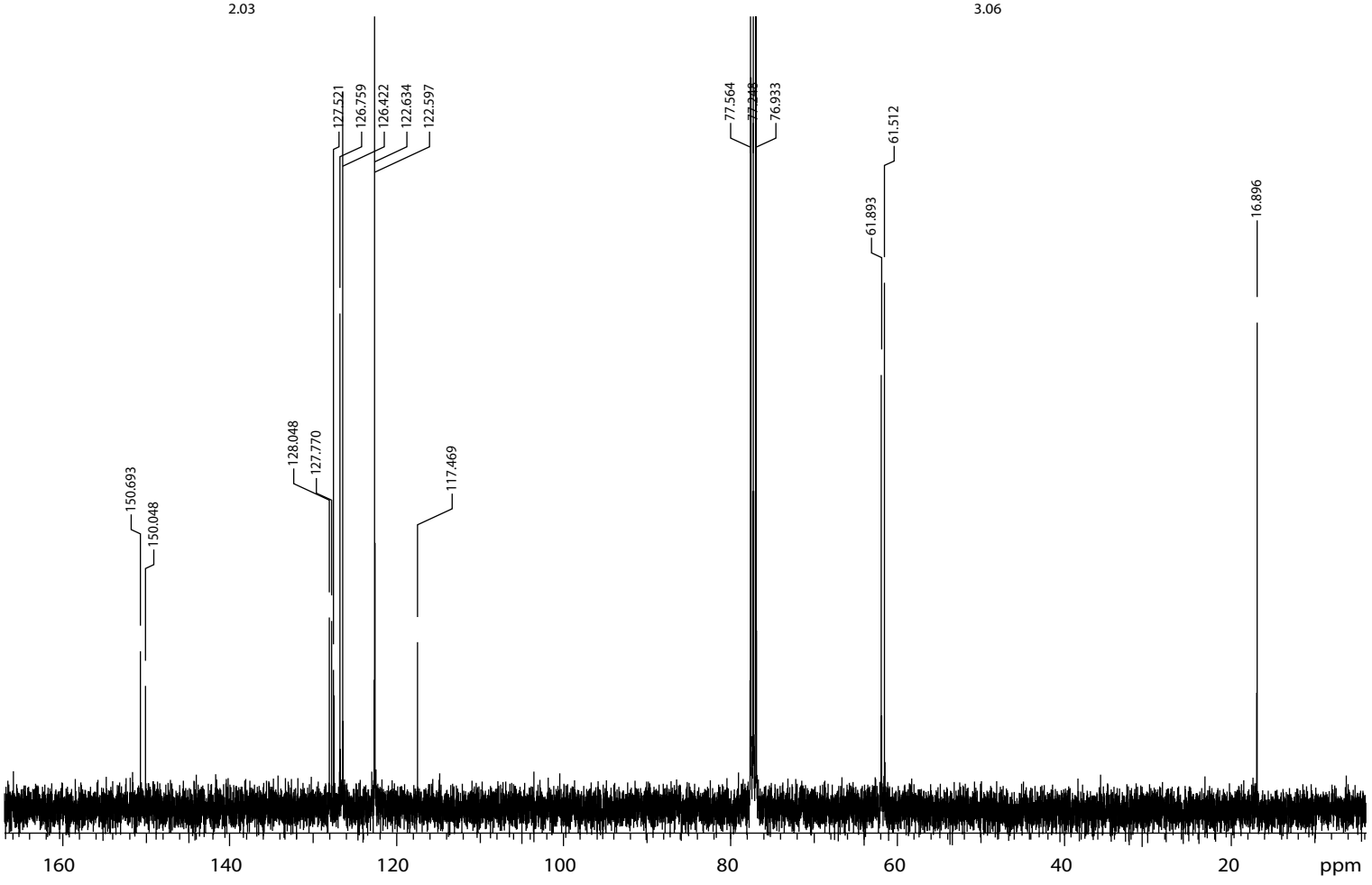

O
Br
O
C11H7BrO2
Exact Mass: 249.9629
3.25
8.168
8.109
7.762
7.733
7.271
2.397
9
8
7
6
5
4
3
ppm
1.83
2.00
3.12

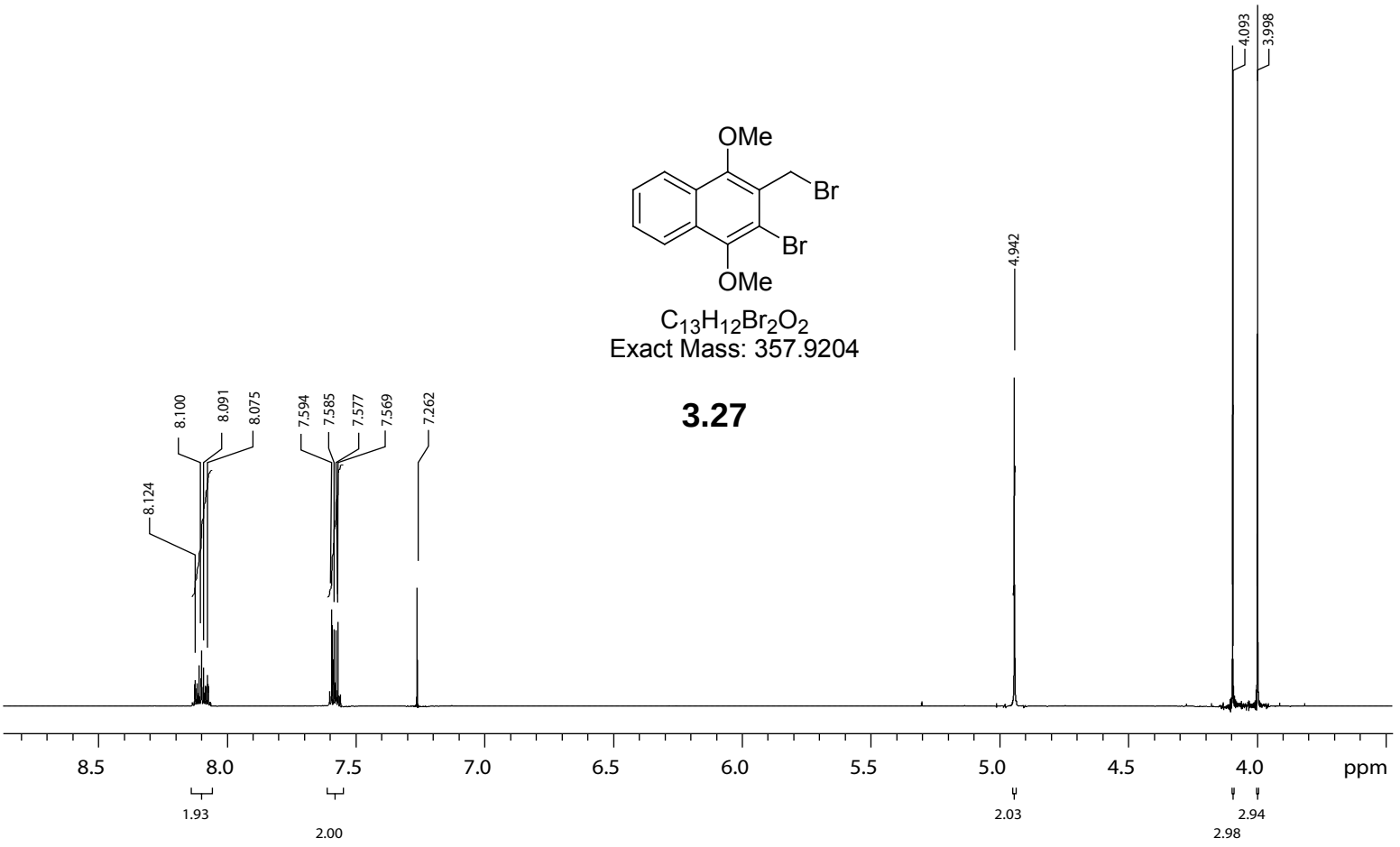

134.341
134.129
131.762
131.403
127.726
127.337
77.578
77.263
76.941
18.097
182.181
177.756
148.715
139.272
180
160
140
120
100
80
60
40
20
ppm

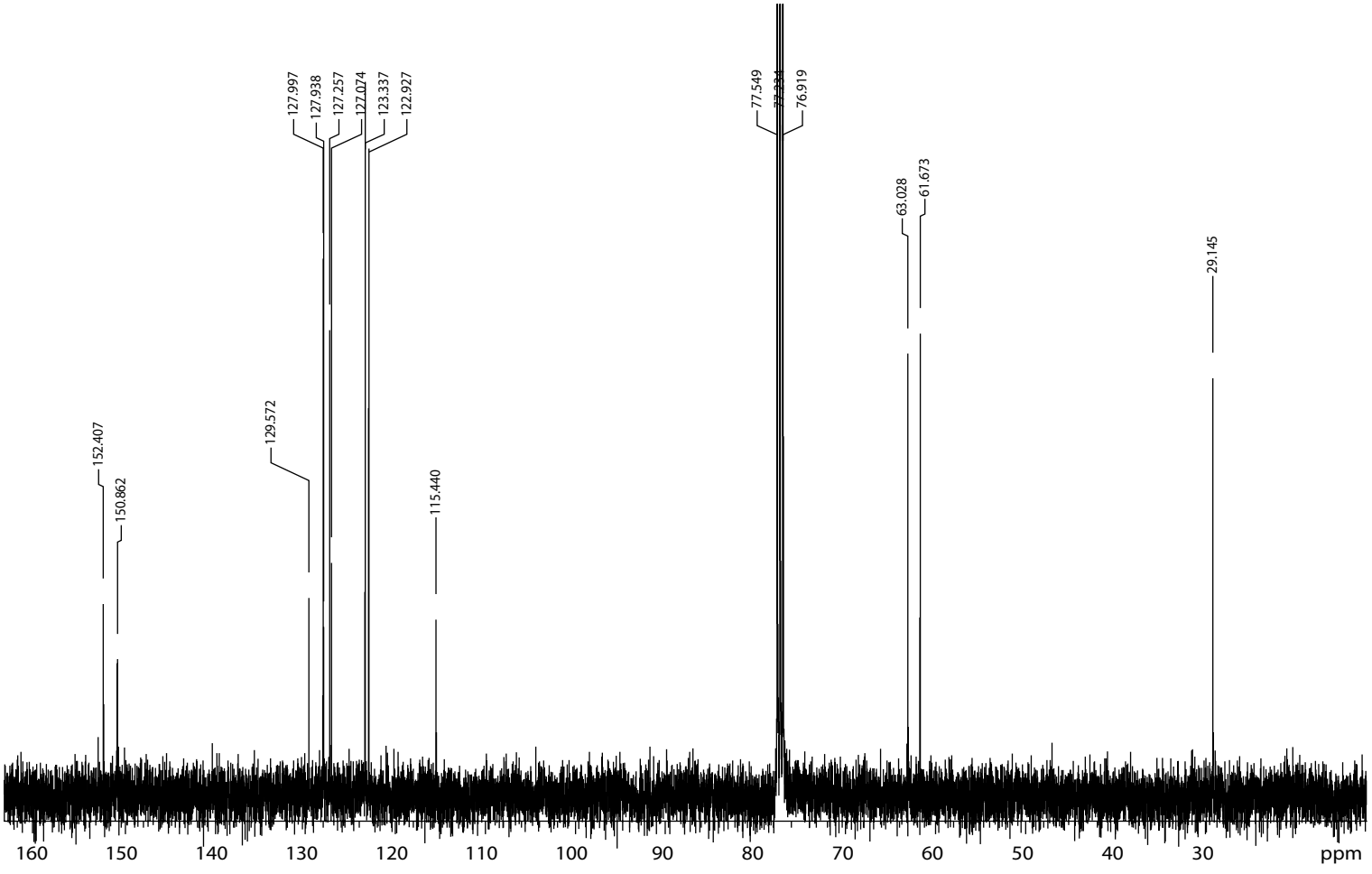


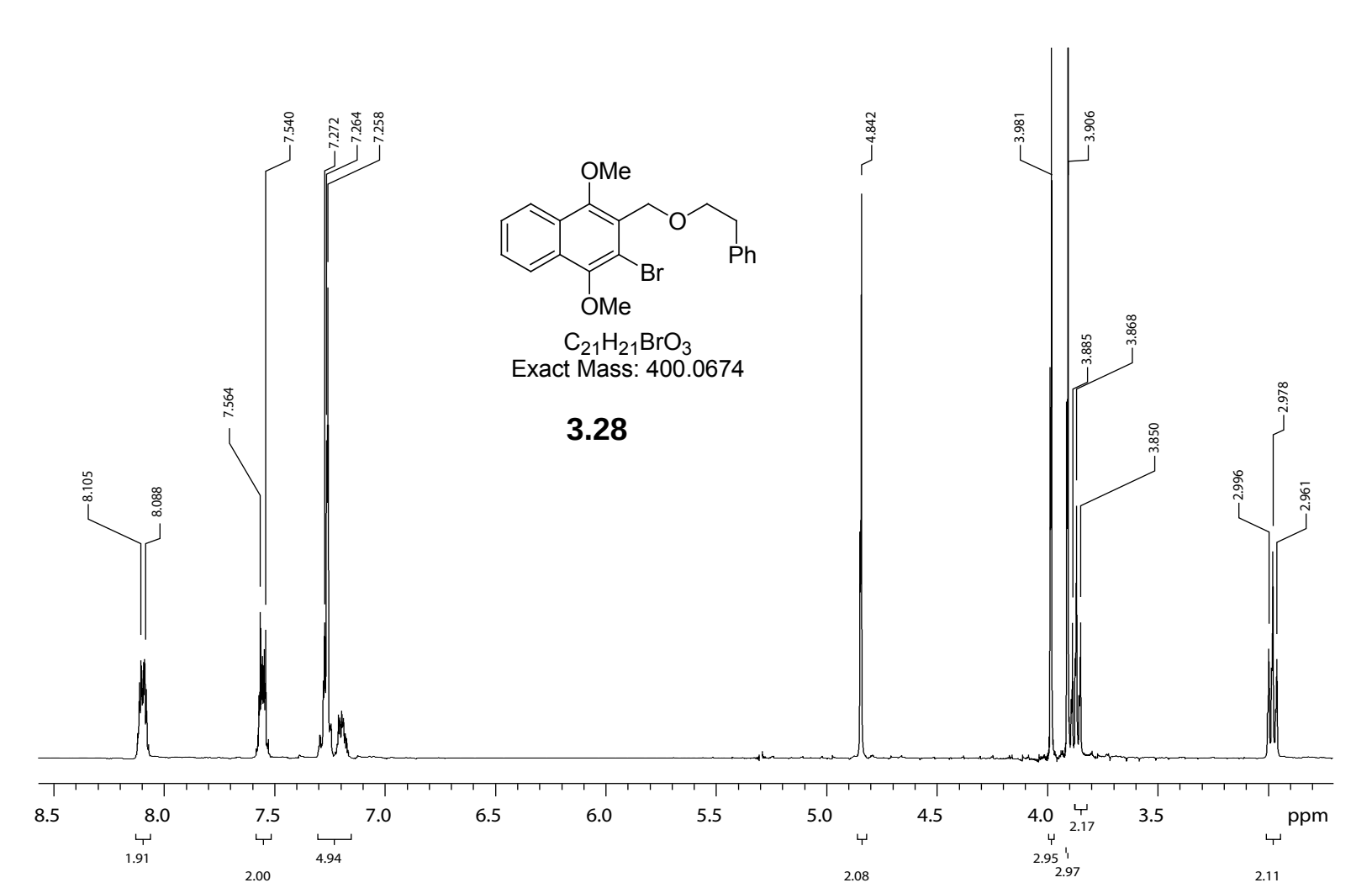
$C_{13}H_{13}BrO_2$
Exact Mass: 280.0099

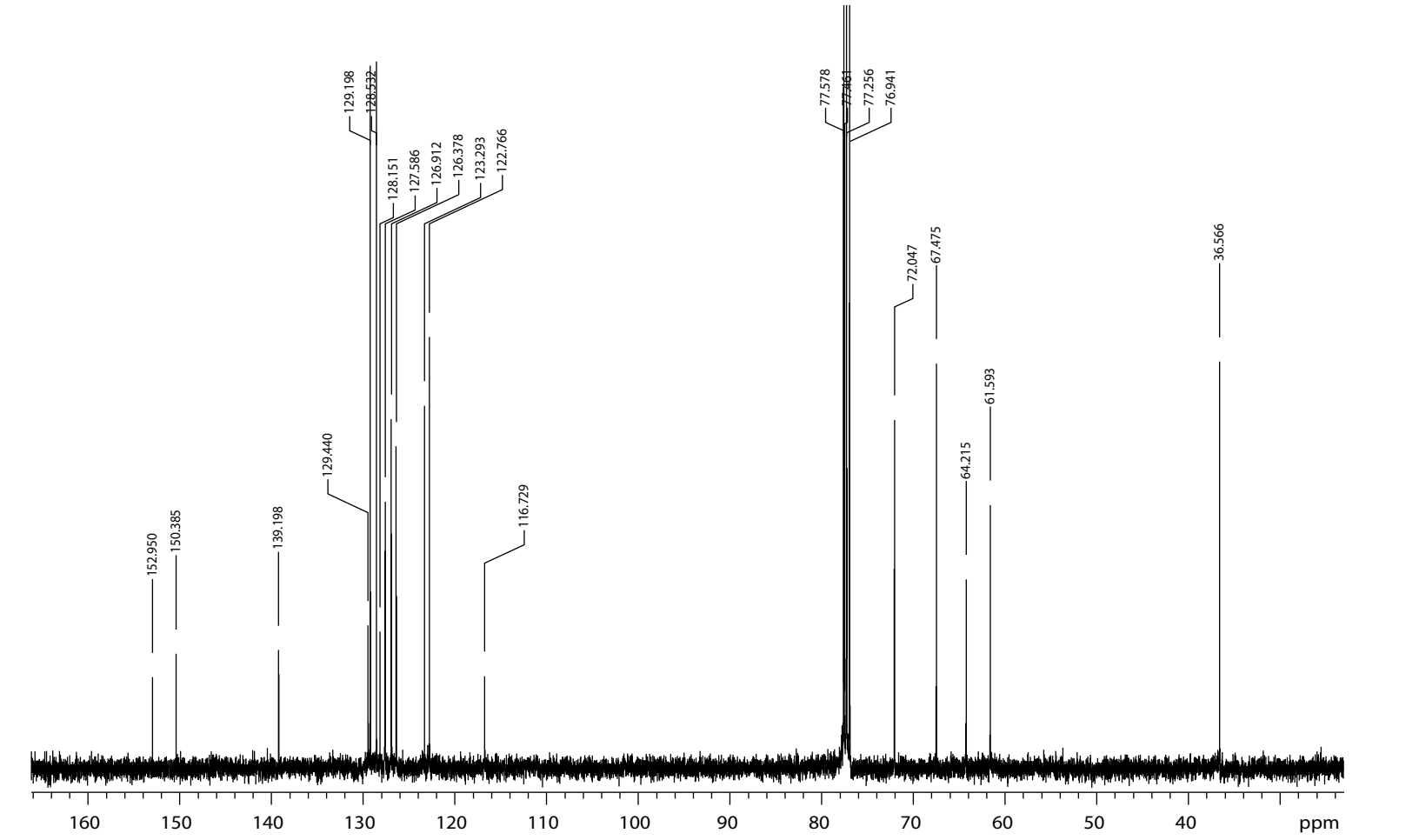
3.26

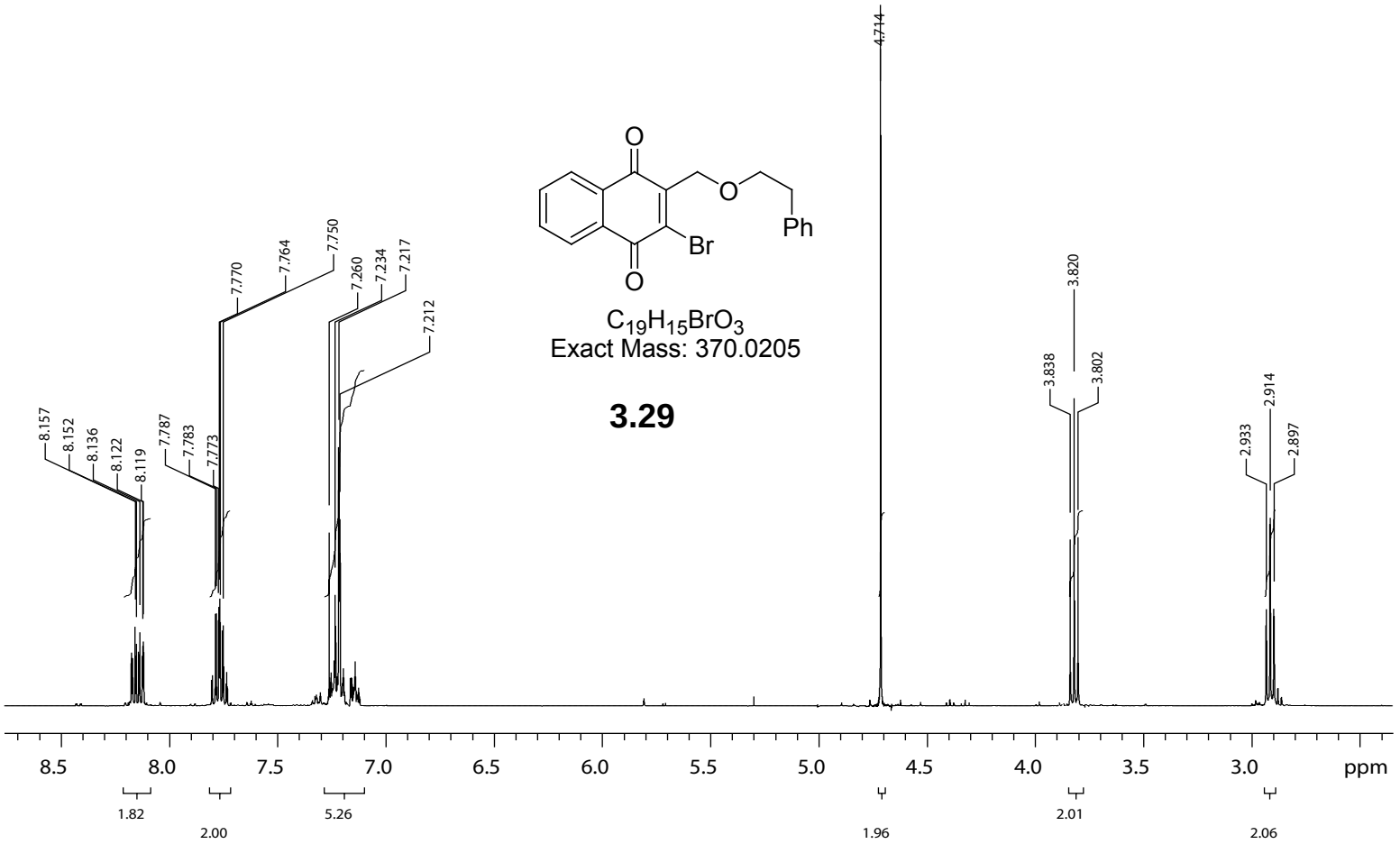


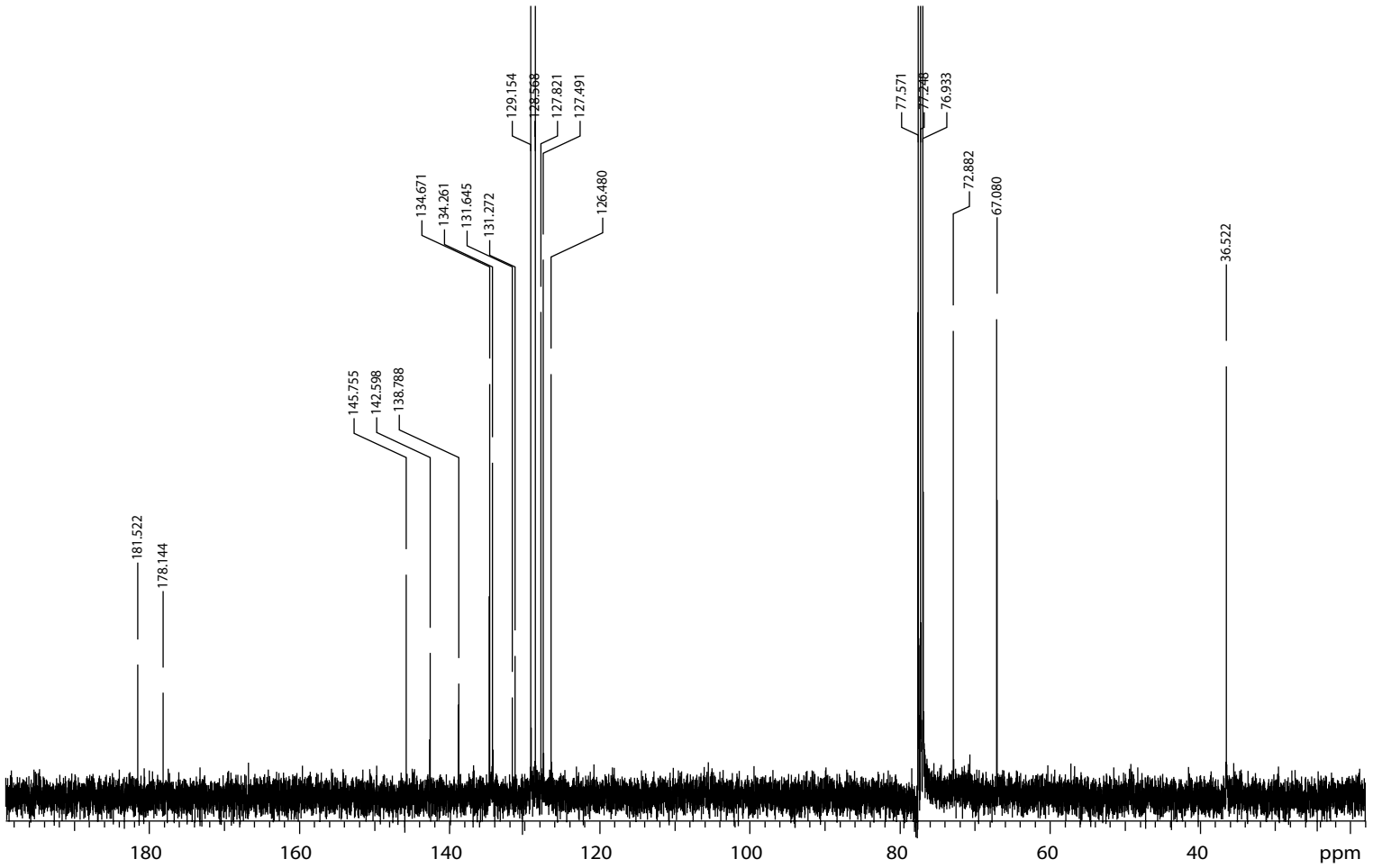

OMe
Br
Br
OMe
$C_{13}H_{12}Br_2O_2$
Exact Mass: 357.9204
3.27
8.124
8.100
8.091
8.075
7.594
7.585
7.577
7.569
7.262
4.942
4.093
3.998
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
ppm
1.93
2.00
2.03
2.94
2.98

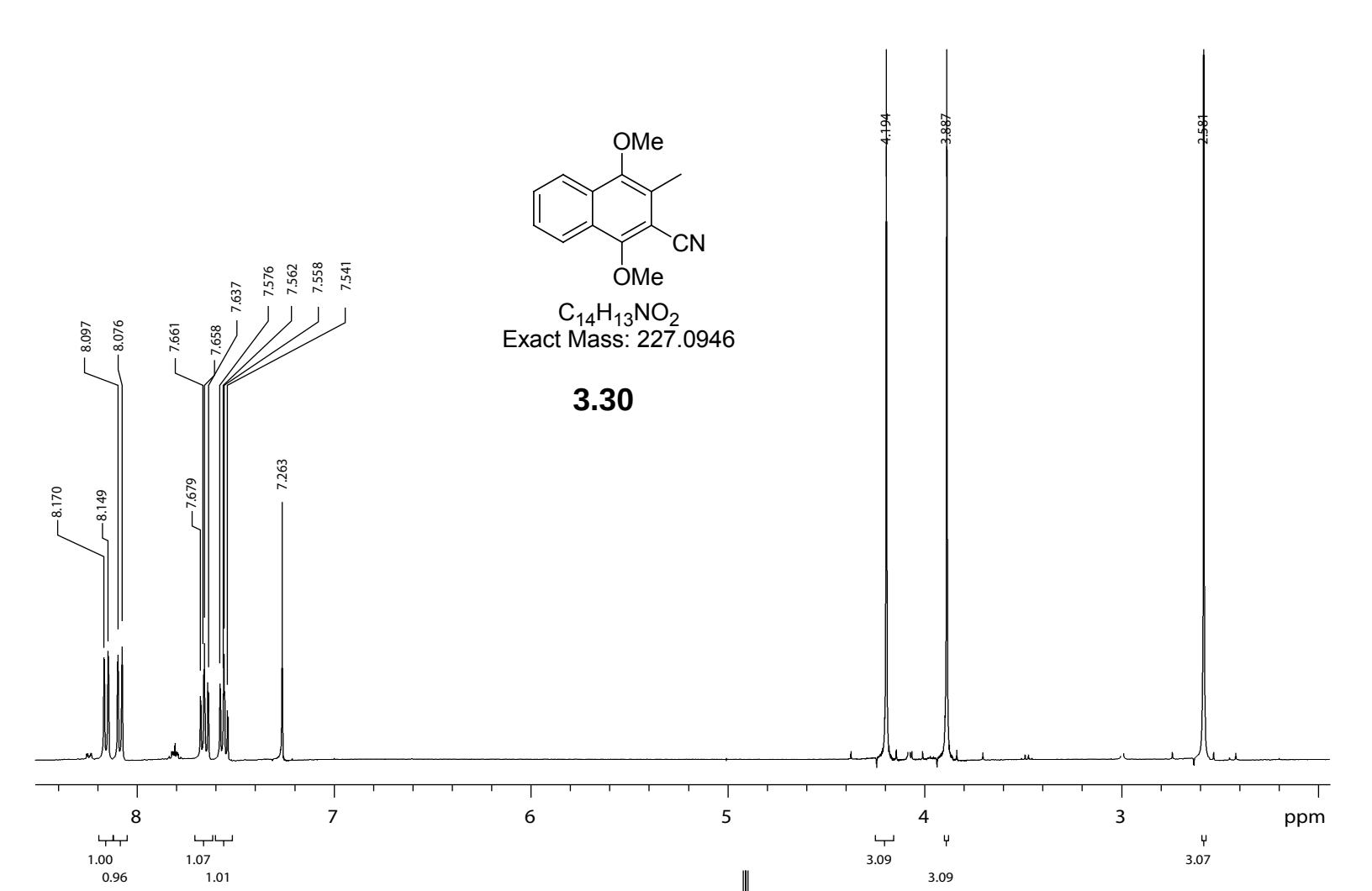

152.407
150.862
129.572
127.997
127.938
127.257
127.074
123.337
122.927
115.440
77.549
76.919
63.028
61.673
29.145
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

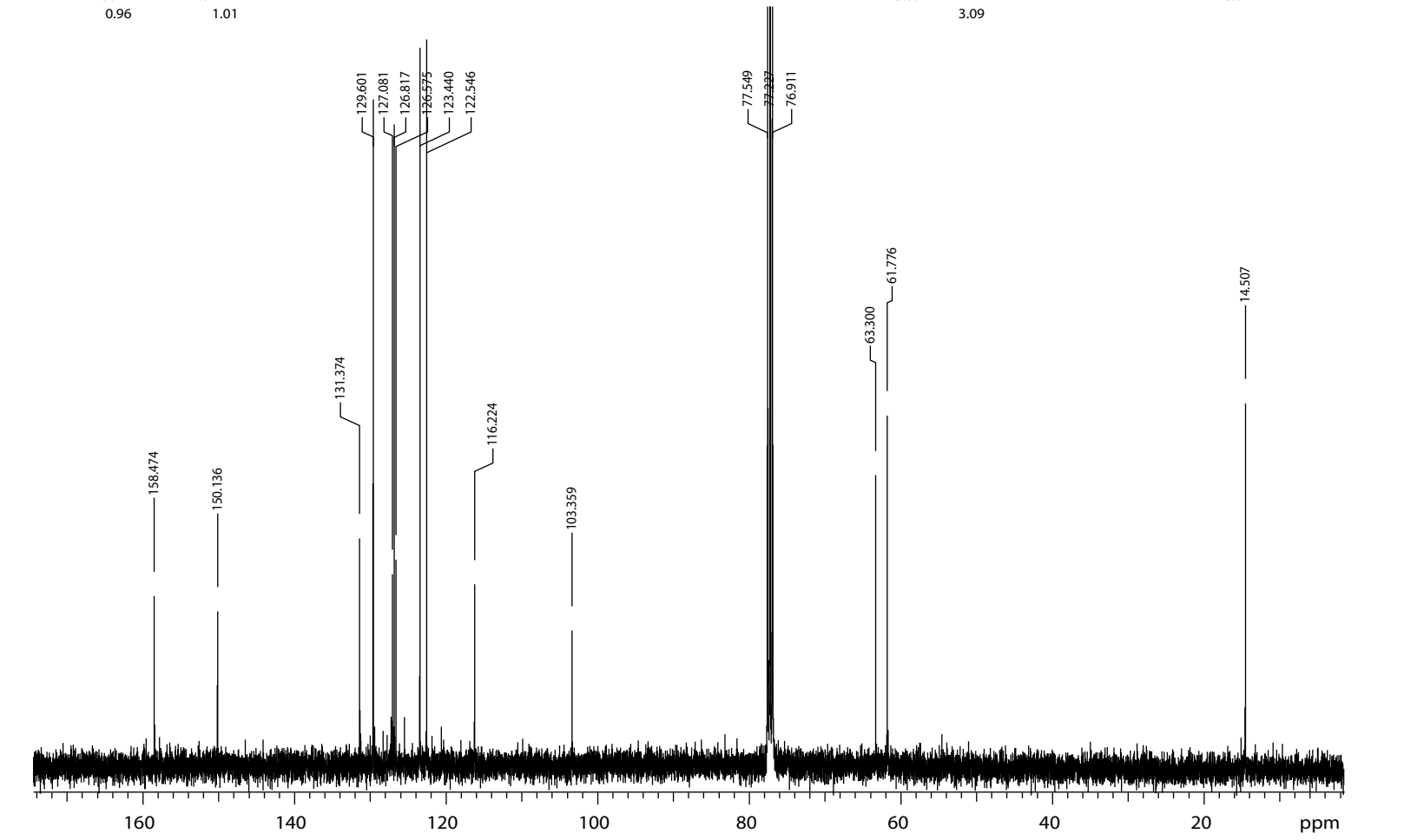

OMe
O
Ph
Br
OMe
$C_{21}H_{21}BrO_3$
Exact Mass: 400.0674
3.28
8.105
8.088
7.564
7.540
7.272
7.264
7.258
4.842
3.981
3.906
3.885
3.868
3.850
2.996
2.978
2.961
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm
1.91
2.00
4.94
2.08
2.95
2.97
2.17
2.11

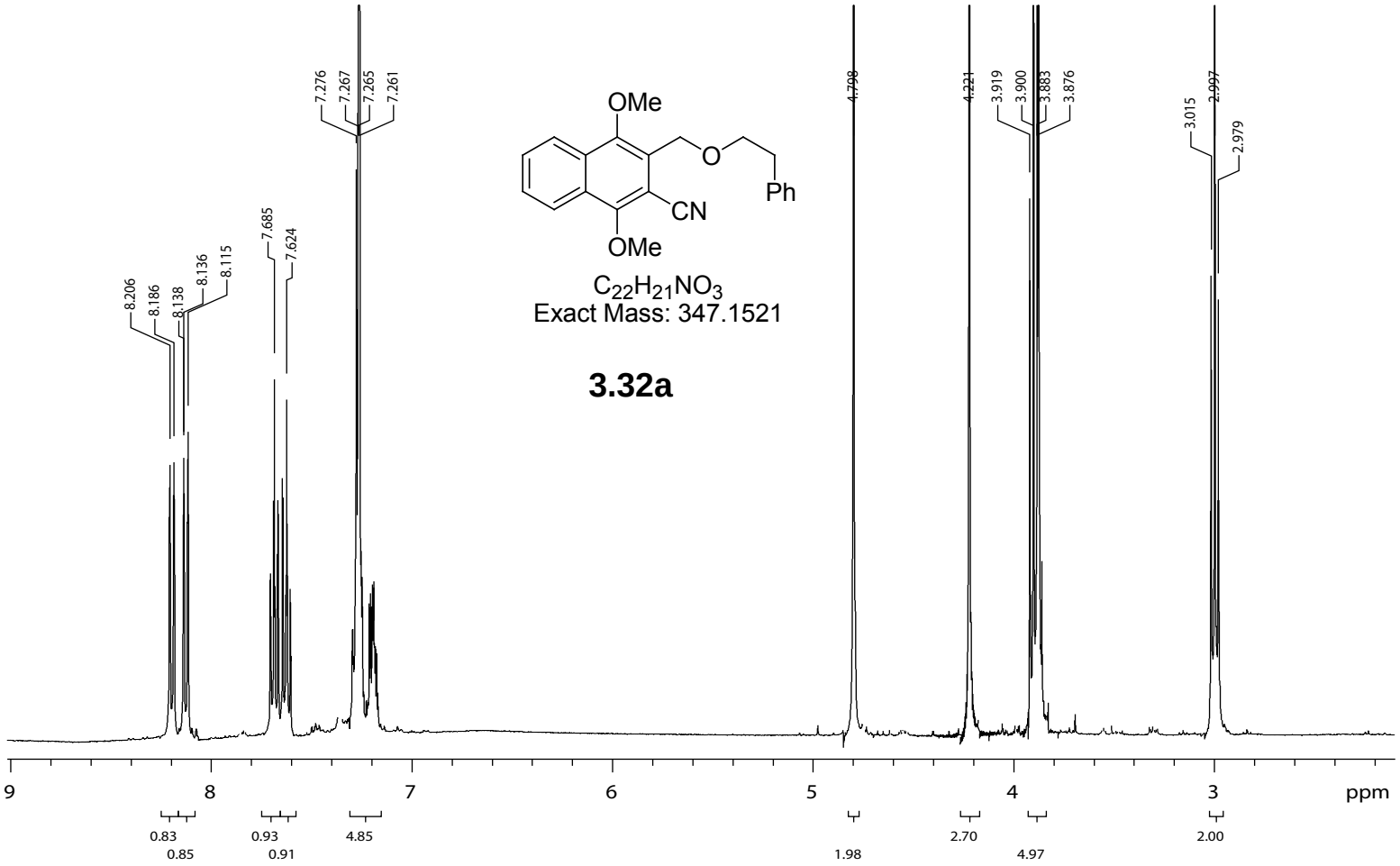

129.198
128.532
128.151
127.586
126.912
126.378
123.293
122.766
129.440
116.729
152.950
150.385
139.198
77.578
77.461
77.256
76.941
72.047
67.475
64.215
61.593
36.566
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm

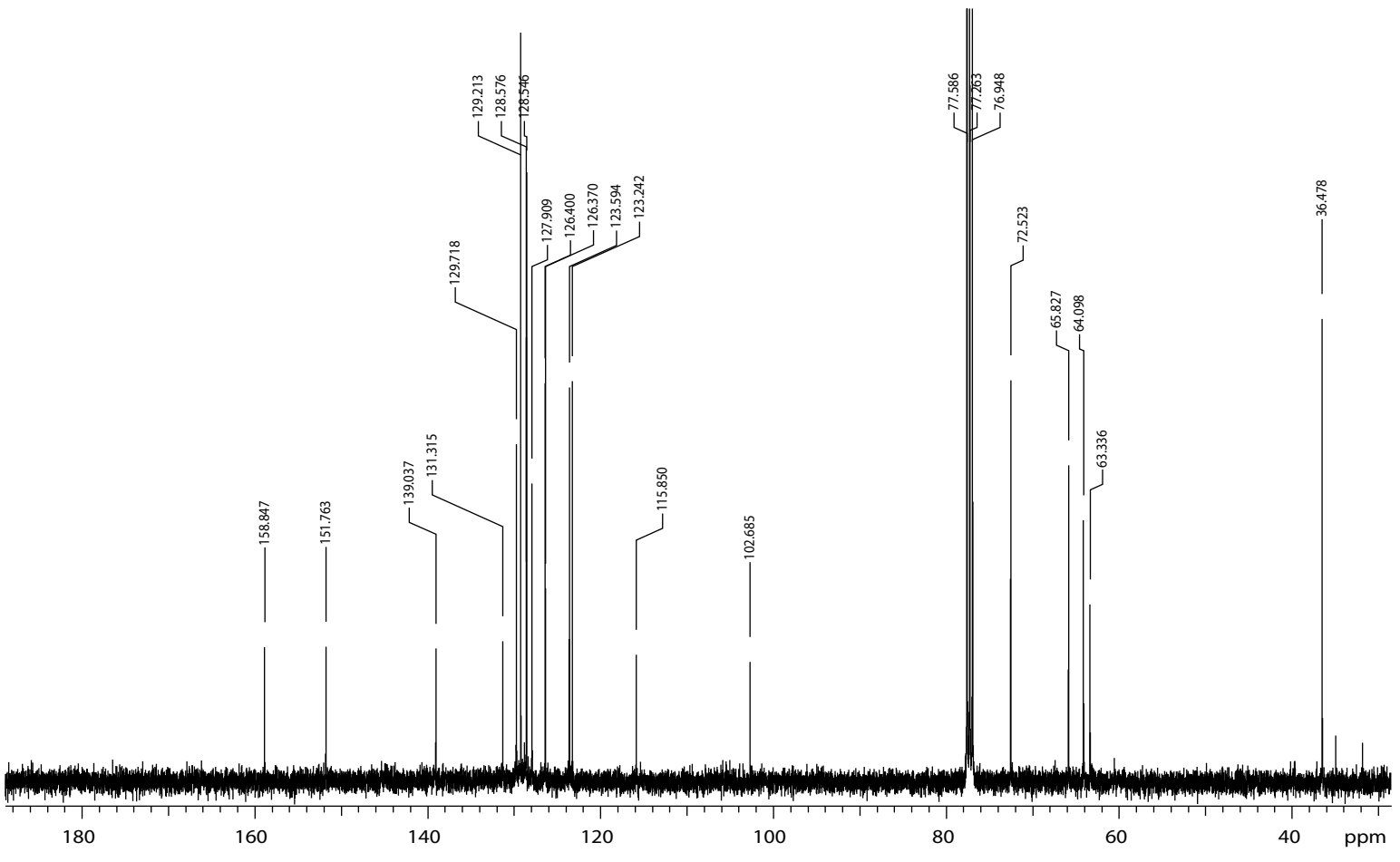

4.714
7.770
7.764
7.750
7.260
7.234
7.217
7.212
8.157
8.152
8.136
8.122
8.119
7.787
7.783
7.773
3.820
3.838
3.802
2.914
2.933
2.897
O
O
O
Br
Ph
$C_{19}H_{15}BrO_3$
Exact Mass: 370.0205
3.29
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm
1.82
2.00
5.26
1.96
2.01
2.06

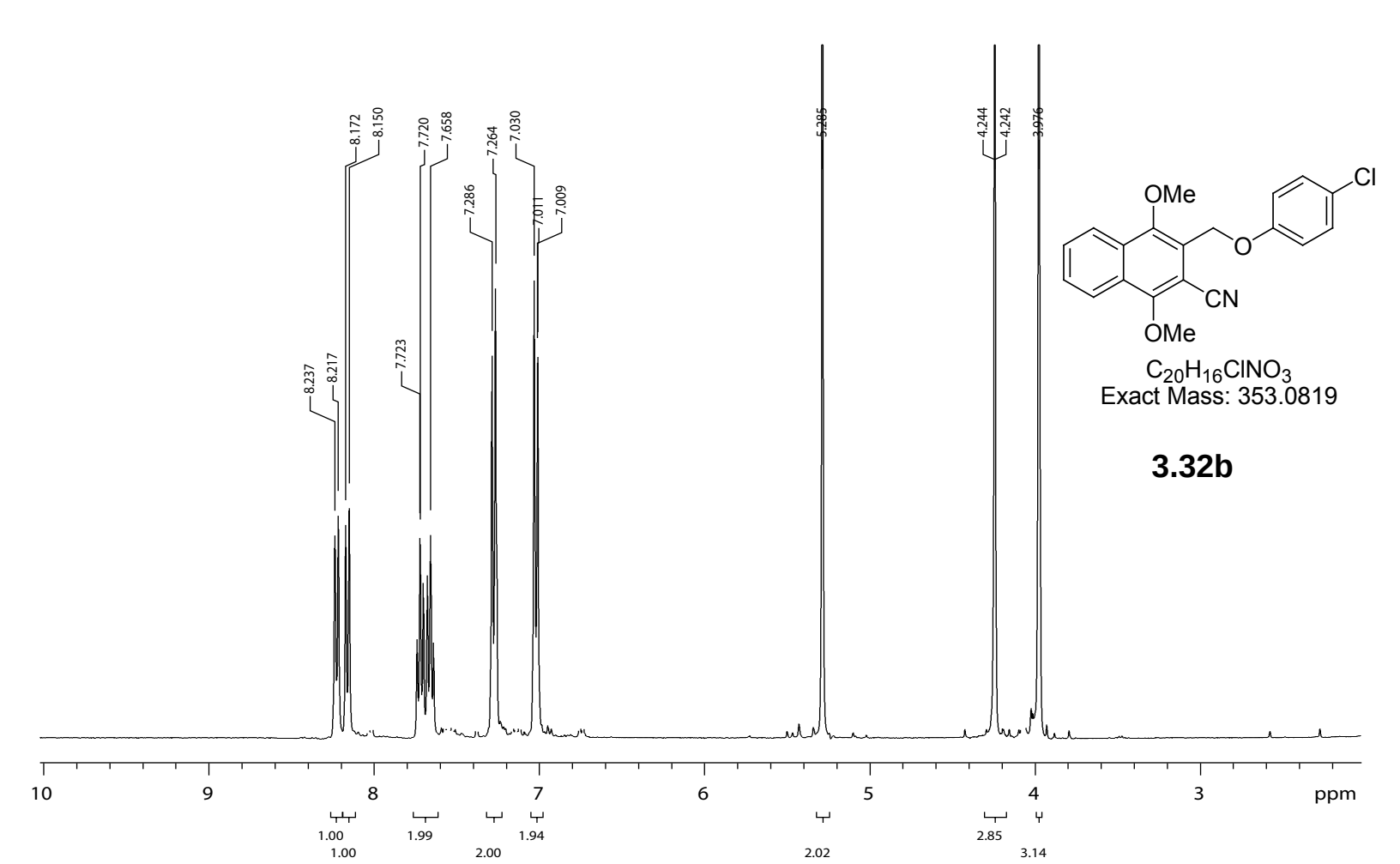

129.154
128.568
127.821
127.491
126.480
134.671
134.261
131.645
131.272
145.755
142.598
138.788
181.522
178.144
77.571
77.248
76.933
72.882
67.080
36.522
180
160
140
120
100
80
60
40
ppm


OMe
CN
OMe
$C_{14}H_{13}NO_2$
Exact Mass: 227.0946
3.30
8.170
8.149
8.097
8.076
7.679
7.661
7.658
7.637
7.576
7.562
7.558
7.541
7.263
4.194
3.887
2.581
ppm
1.00
0.96
1.07
1.01
3.09
3.09
3.07


158.474
150.136
131.374
129.601
127.081
126.817
126.575
123.440
122.546
116.224
103.359
77.549
77.337
76.911
63.300
61.776
14.507
ppm

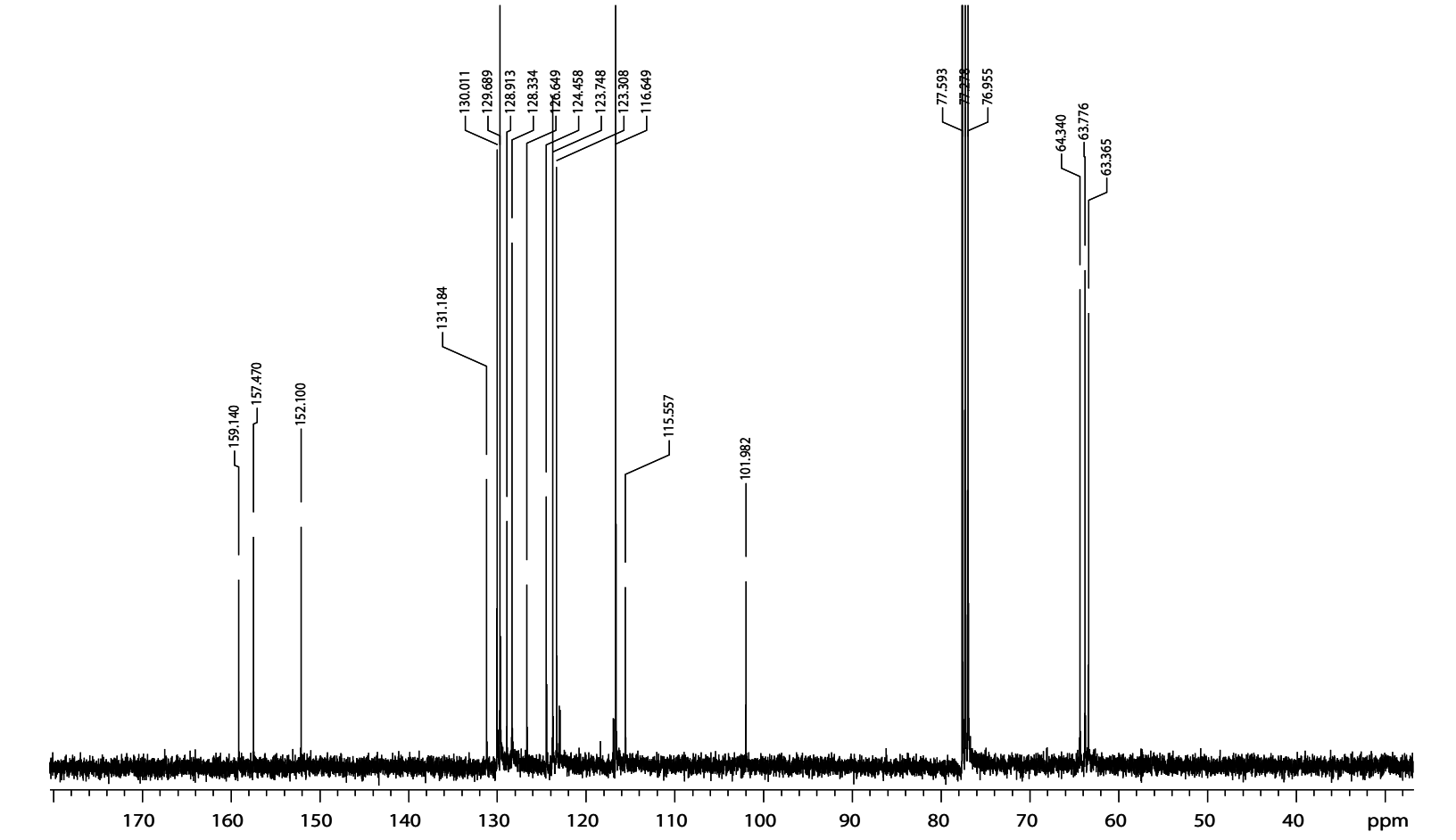

OMe
O
Ph
CN
OMe
$C_{22}H_{21}NO_3$
Exact Mass: 347.1521
3.32a
8.206
8.186
8.138
8.136
8.115
7.685
7.624
7.276
7.267
7.265
7.261
4.798
4.221
3.919
3.900
3.883
3.876
3.015
2.997
2.979
9
8
7
6
5
4
3
ppm
0.83
0.85
0.93
0.91
4.85
1.98
2.70
4.97
2.00

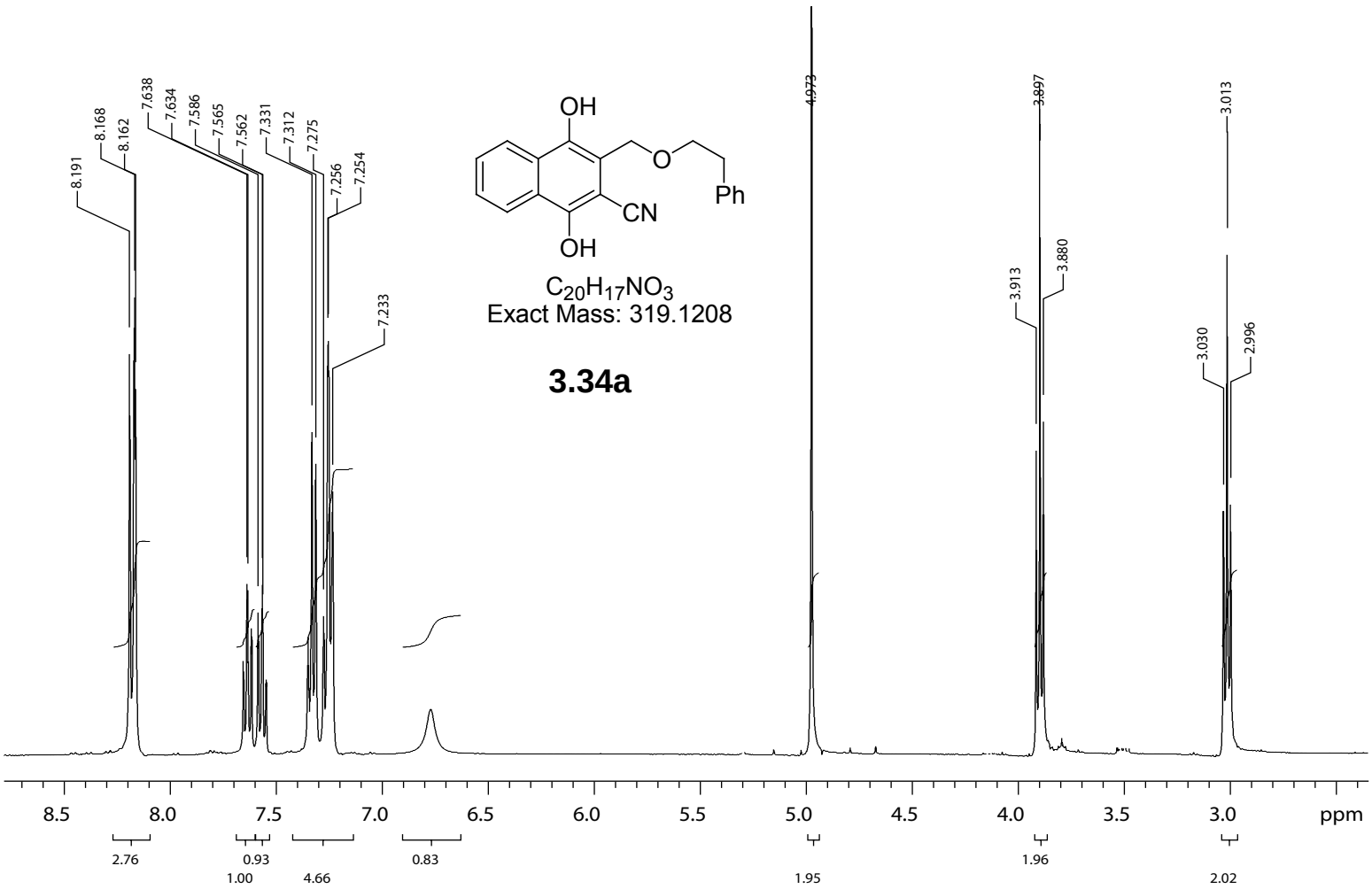

129.213
128.576
128.546
127.909
126.400
126.370
123.594
123.242
129.718
77.586
77.263
76.948
72.523
65.827
64.098
63.336
36.478
158.847
151.763
139.037
131.315
115.850
102.685
180
160
140
120
100
80
60
40
ppm



$C_{20}H_{16}ClNO_3$
Exact Mass: 353.0819

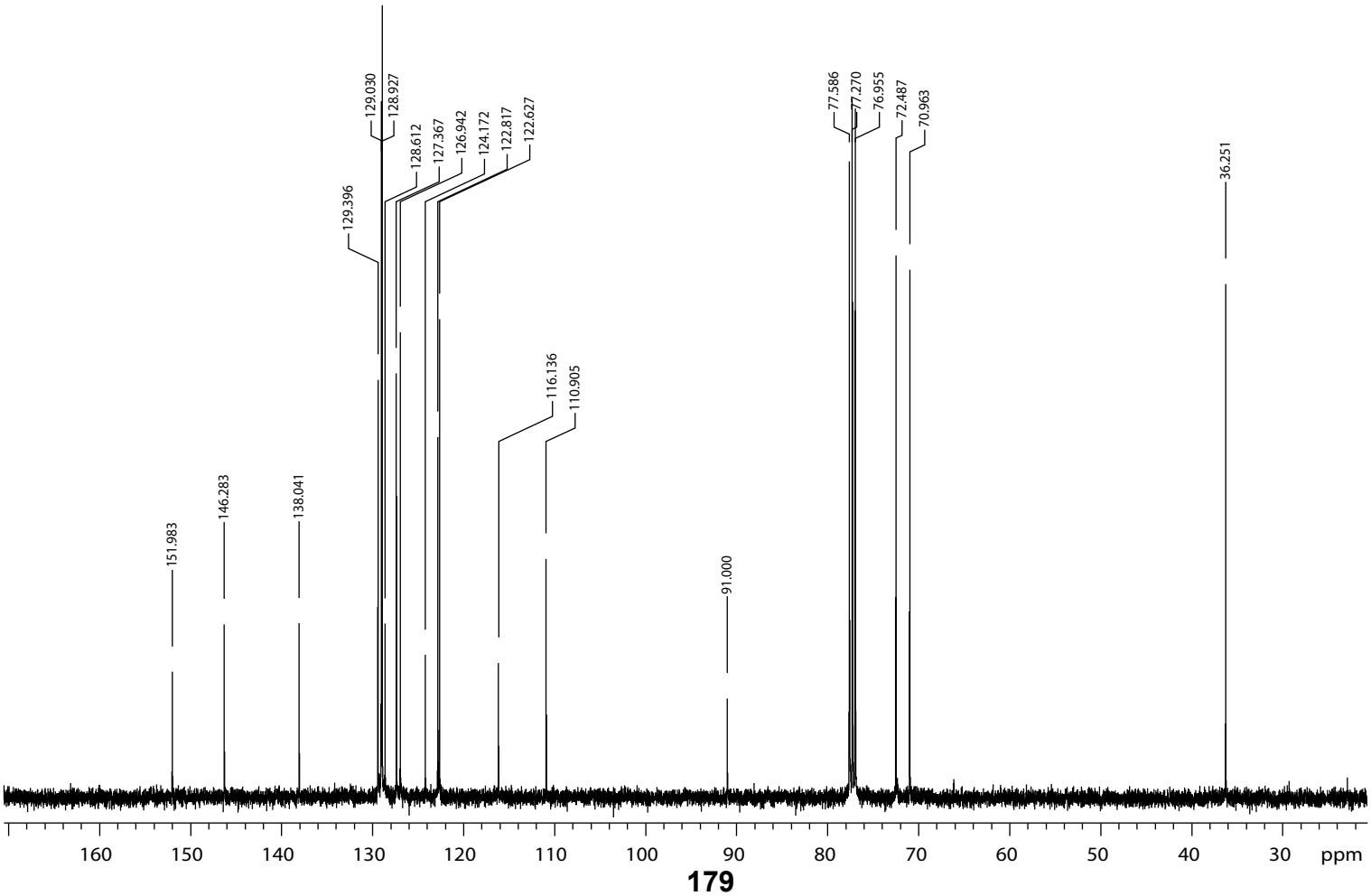
3.32b

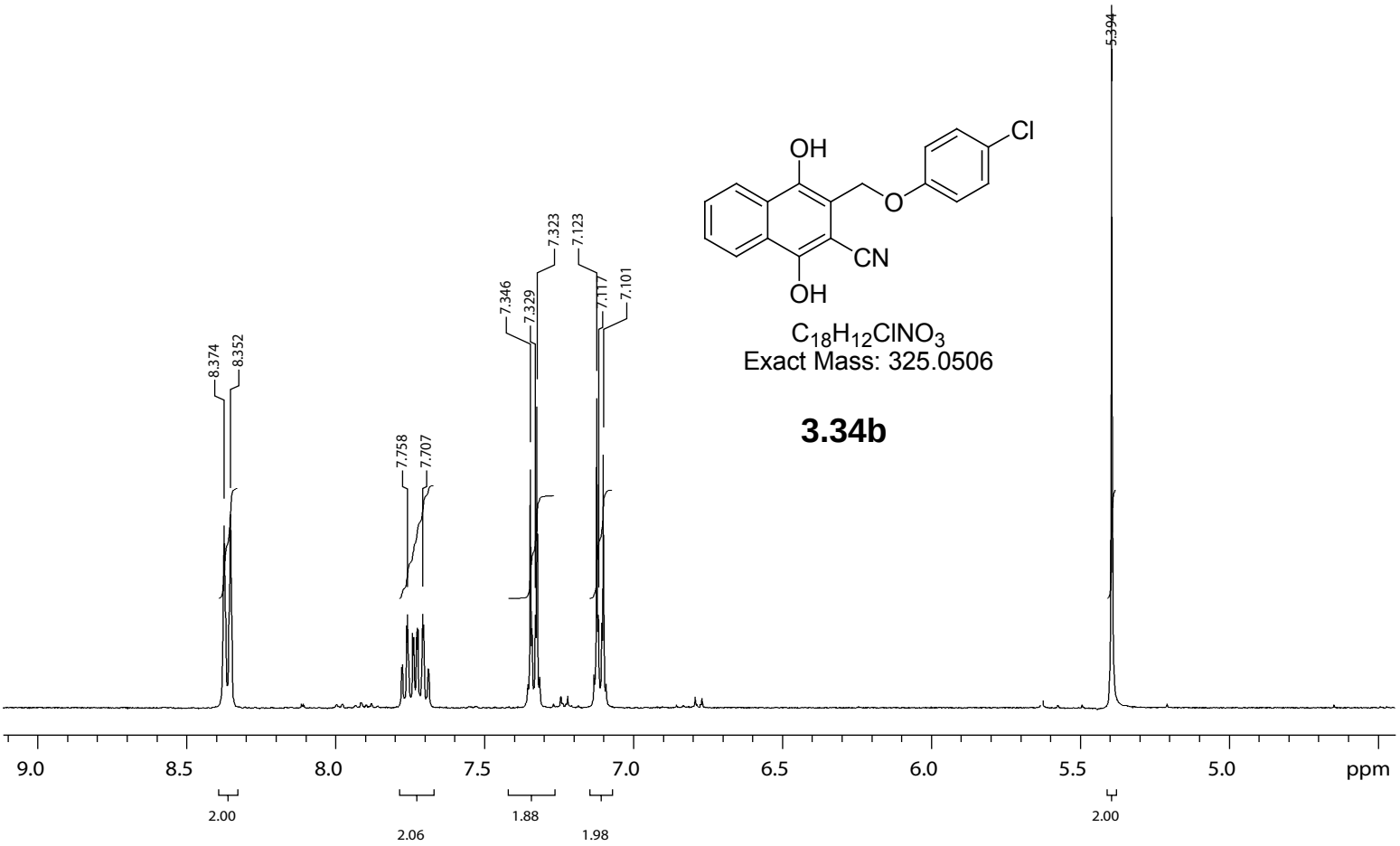


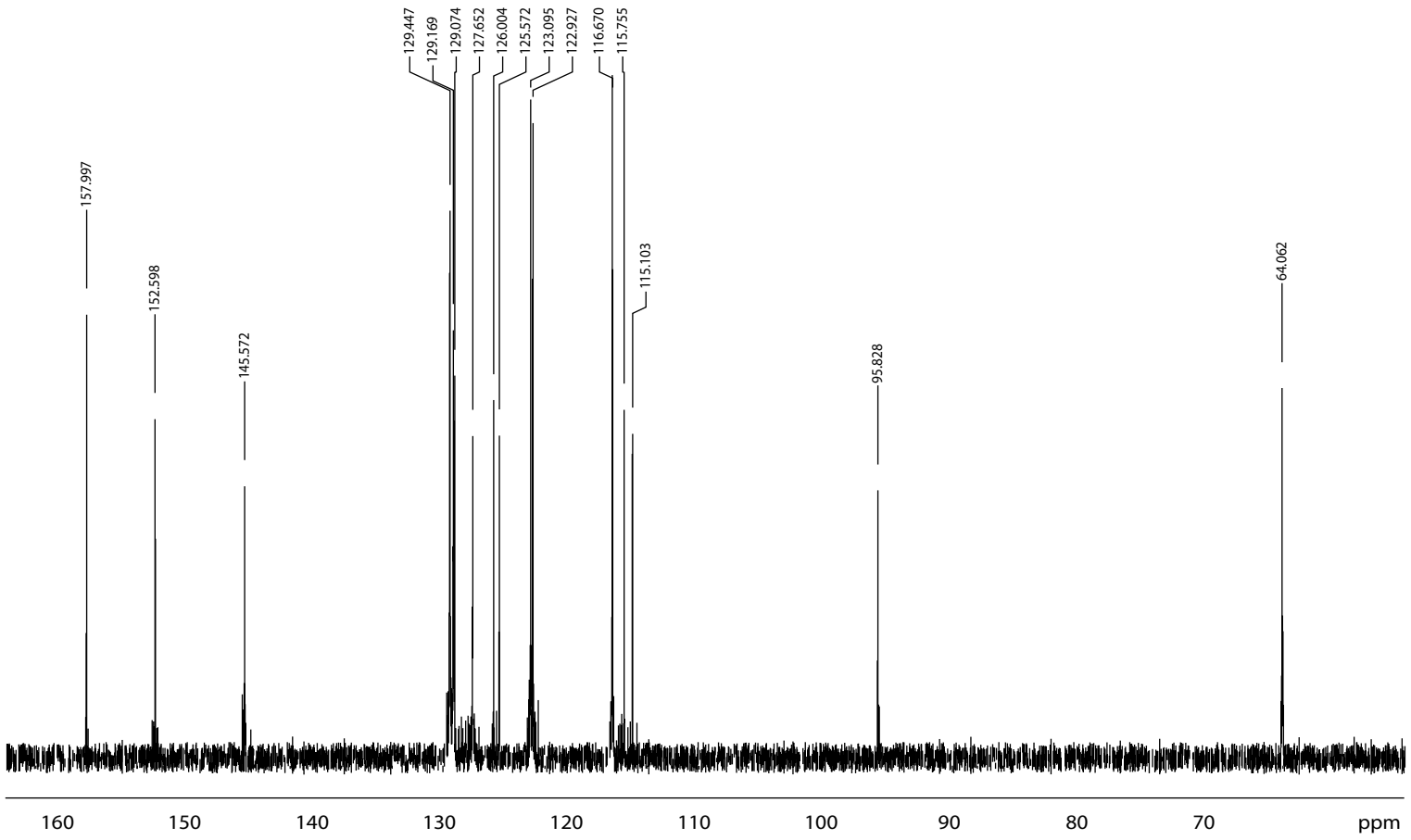


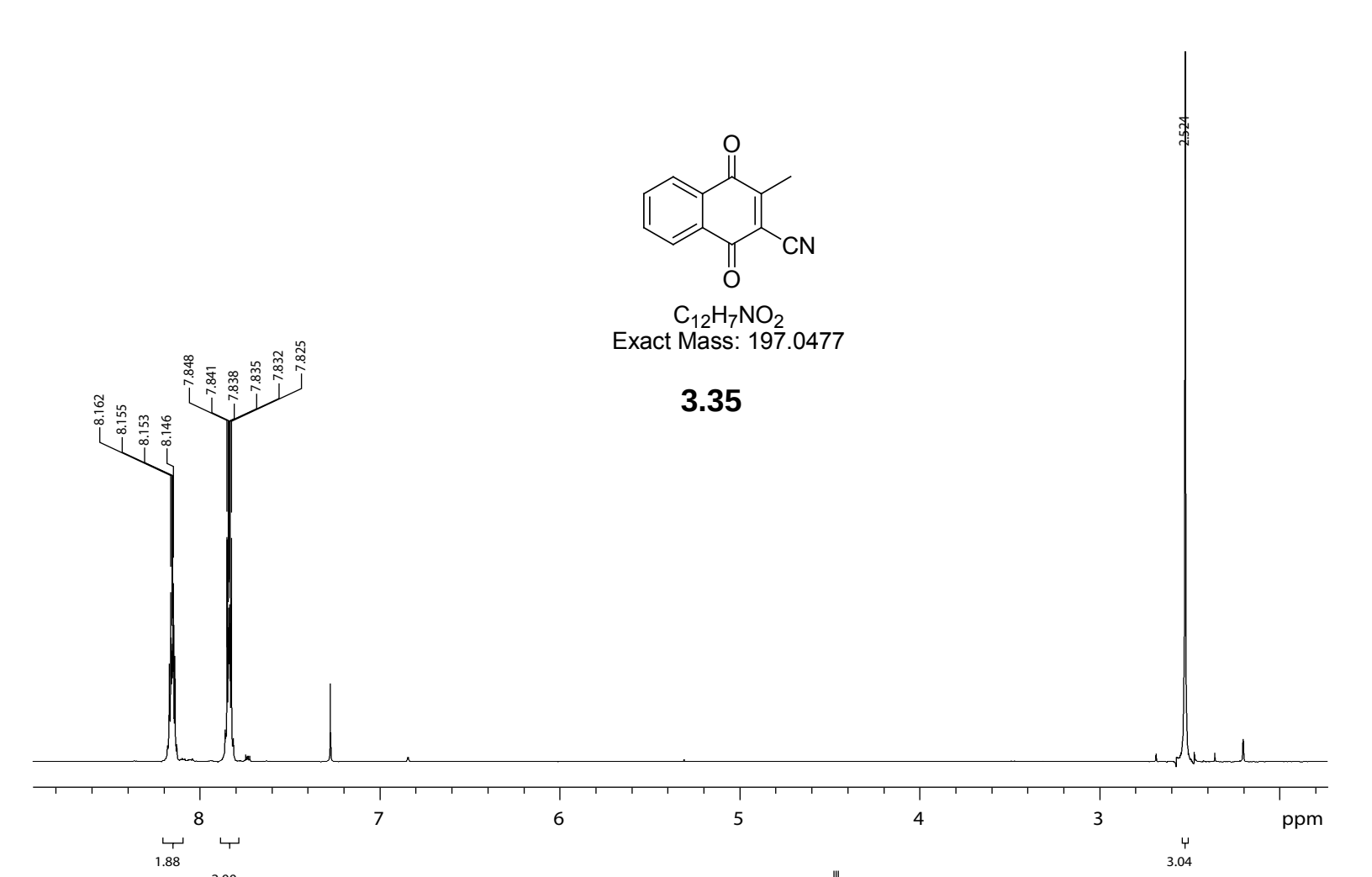
$C_{20}H_{17}NO_3$
Exact Mass: 319.1208

3.34a



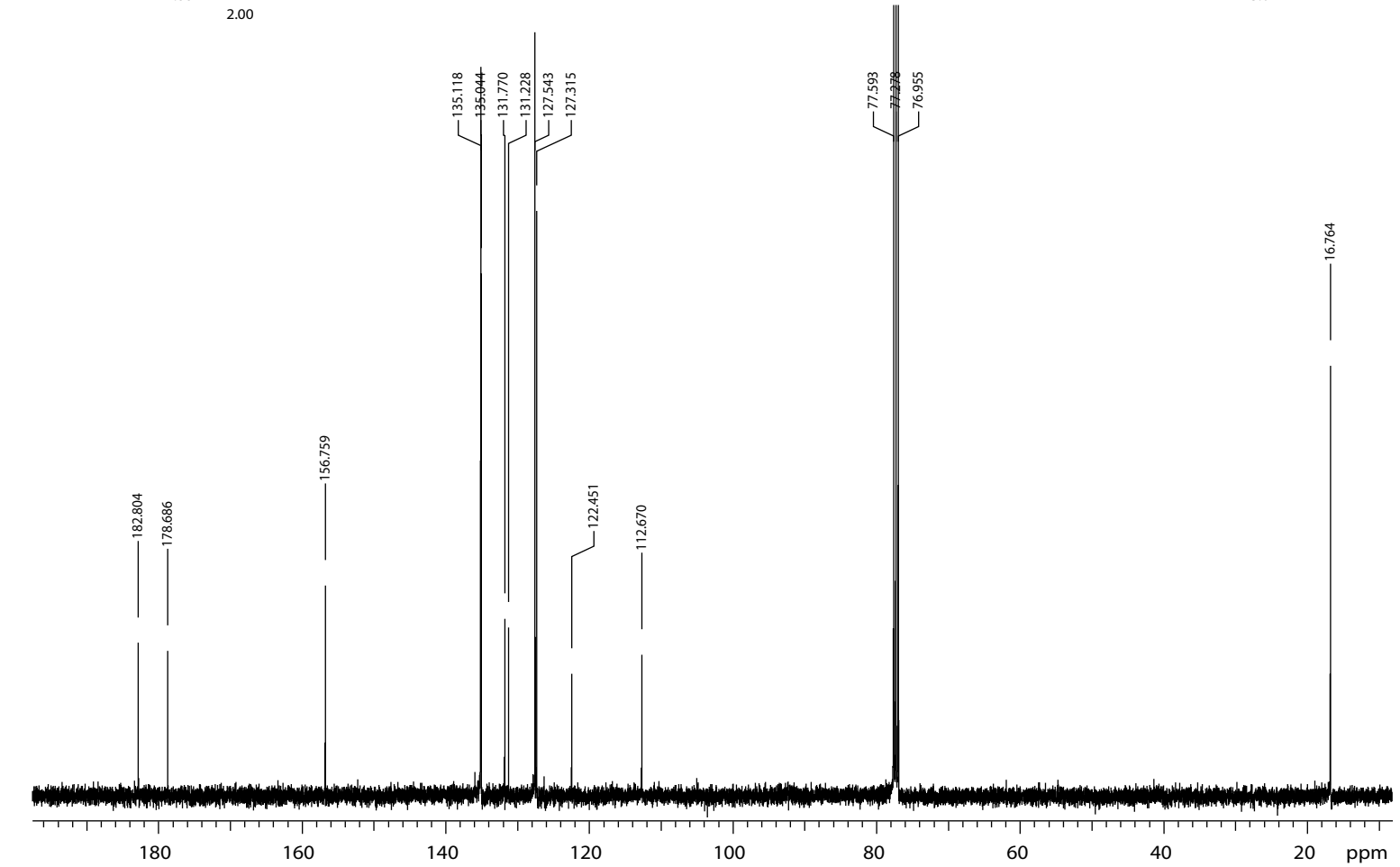

8.374
8.352
7.758
7.707
7.346
7.329
7.323
7.123
7.117
7.101
5.394
OH
Cl
O
CN
OH
$C_{18}H_{12}ClNO_3$
Exact Mass: 325.0506
3.34b
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
ppm
2.00
2.06
1.88
1.98
2.00

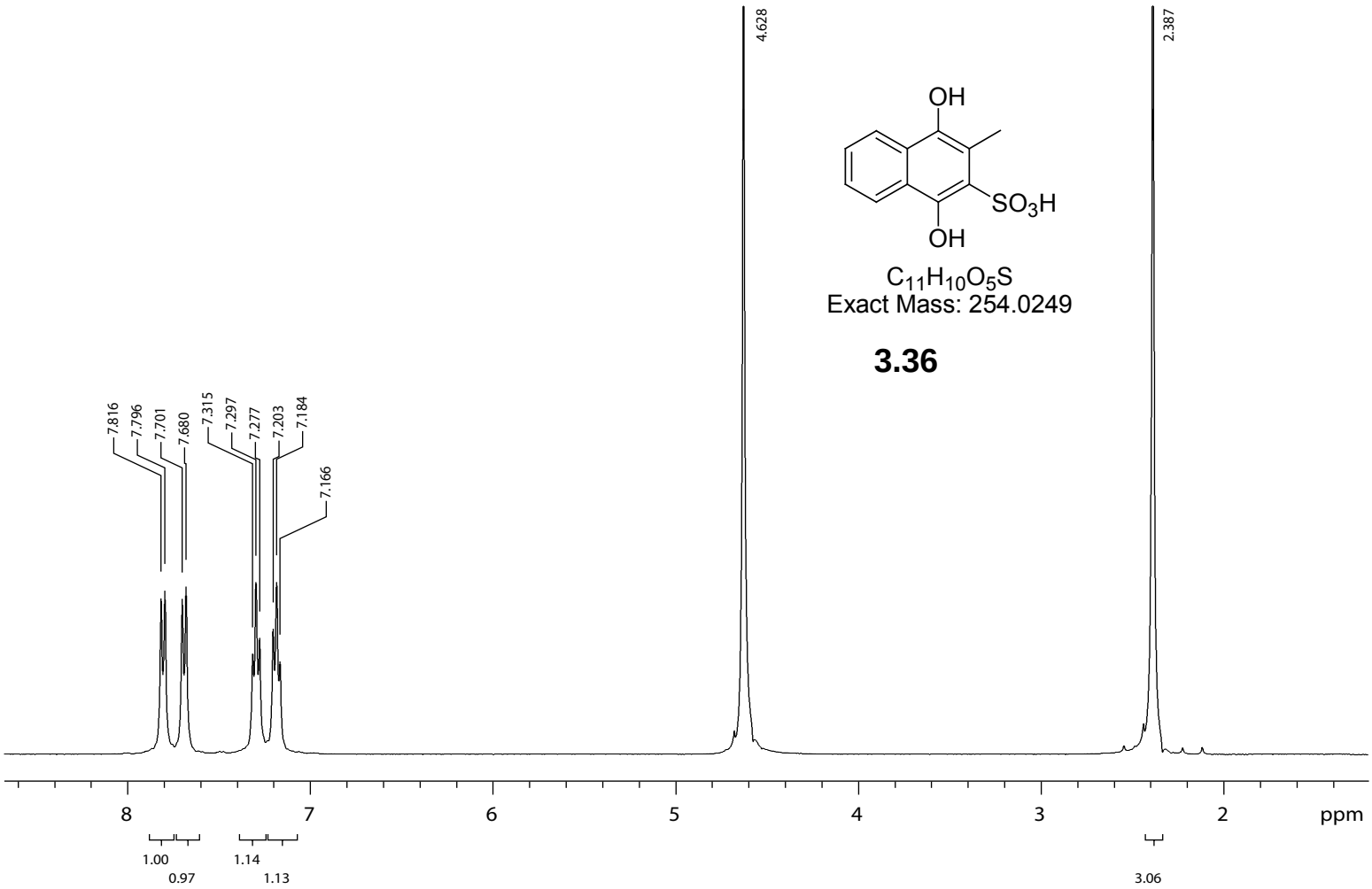

157.997
152.598
145.572
129.447
129.169
129.074
127.652
126.004
125.572
123.095
122.927
116.670
115.755
115.103
95.828
64.062
160
150
140
130
120
110
100
90
80
70
ppm

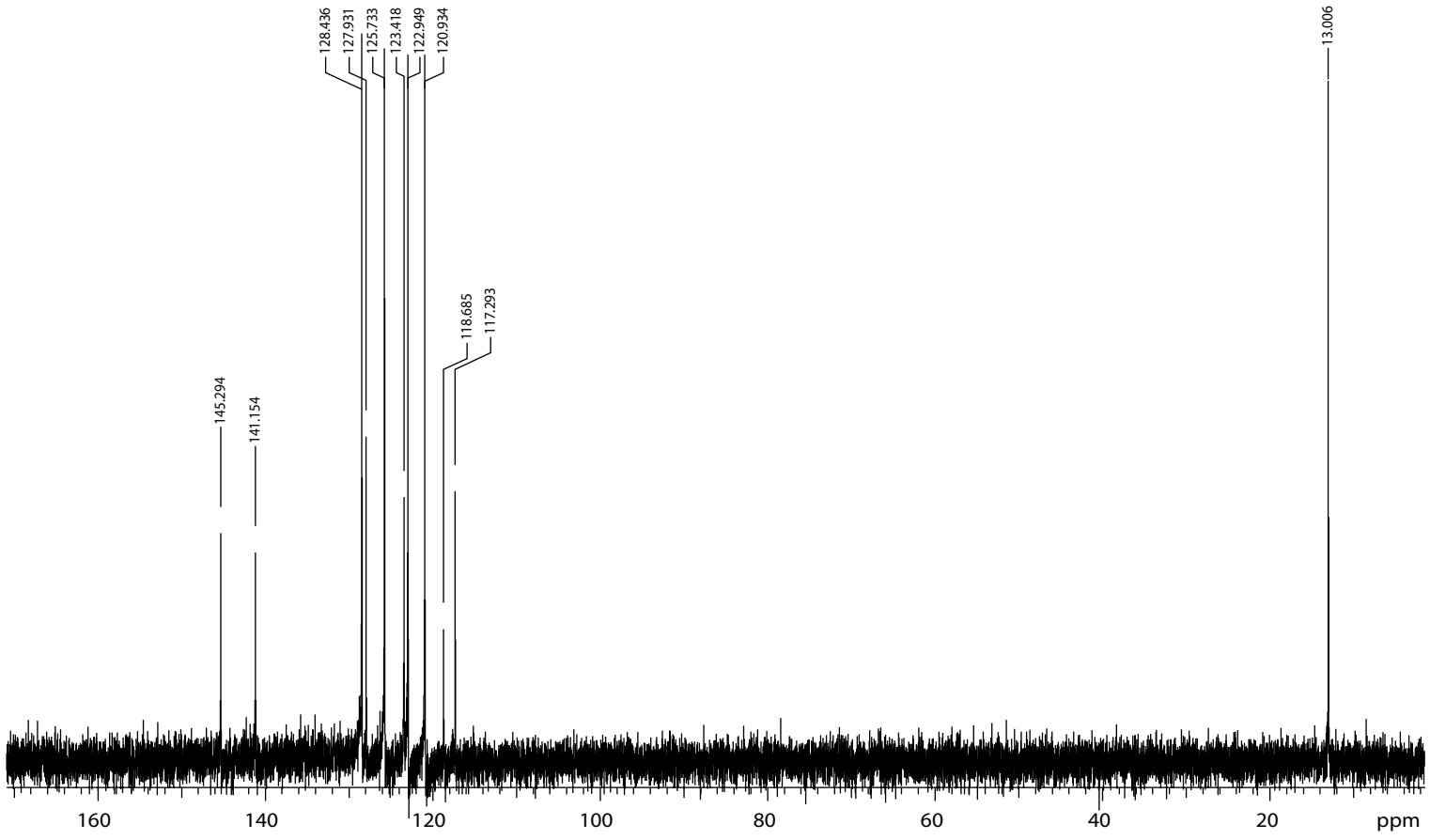


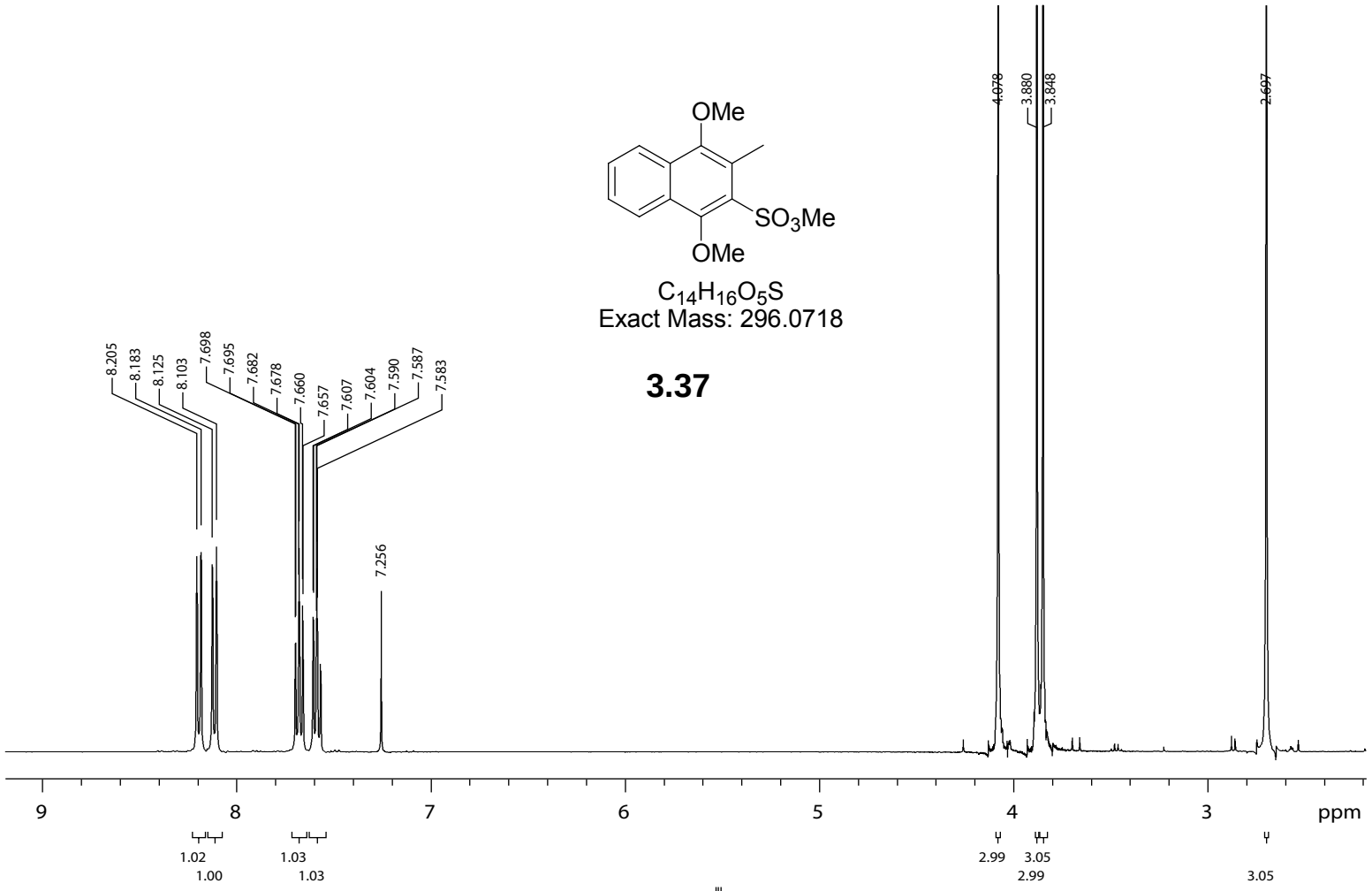
$C_{12}H_7NO_2$
Exact Mass: 197.0477

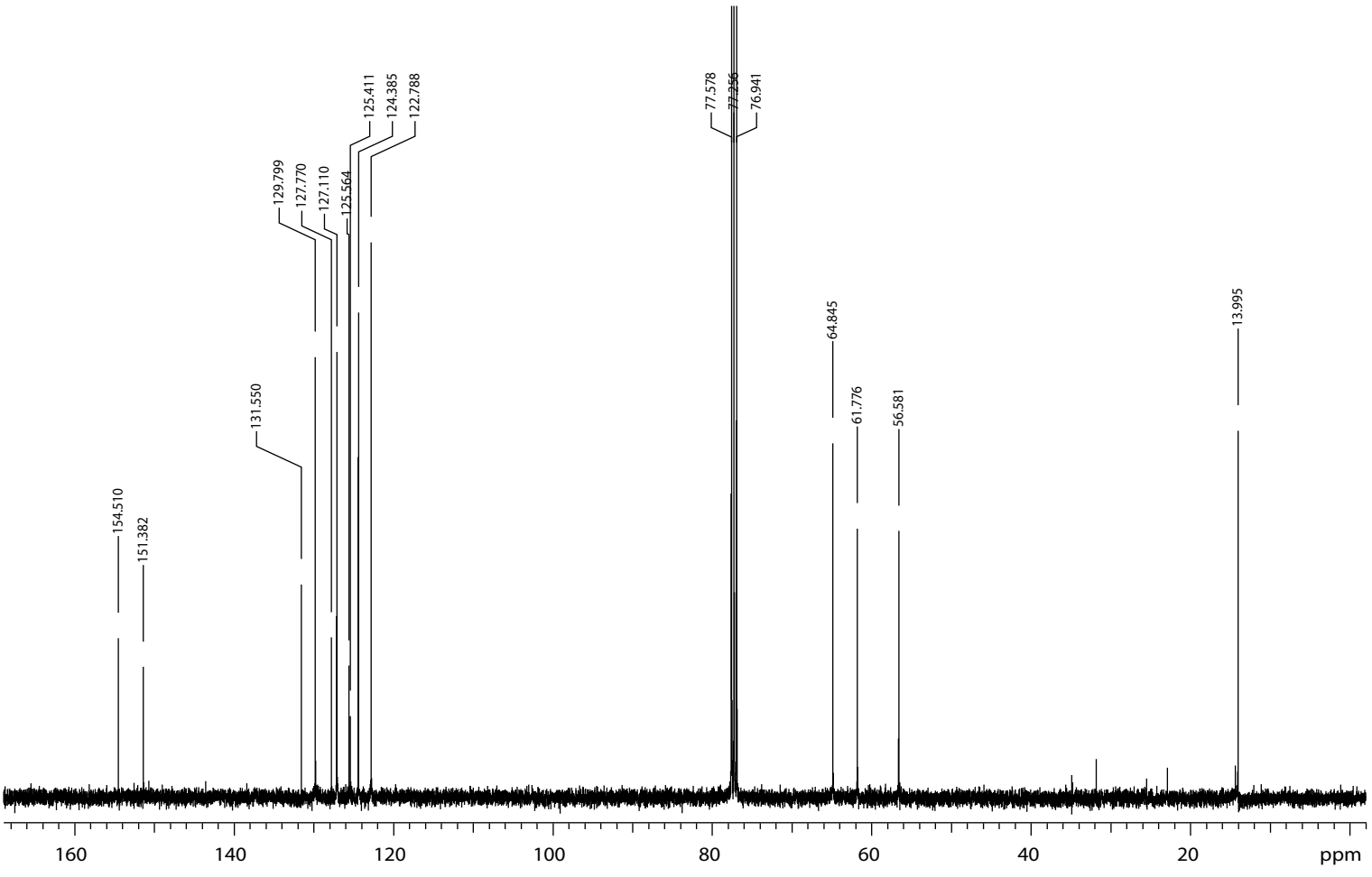
3.35

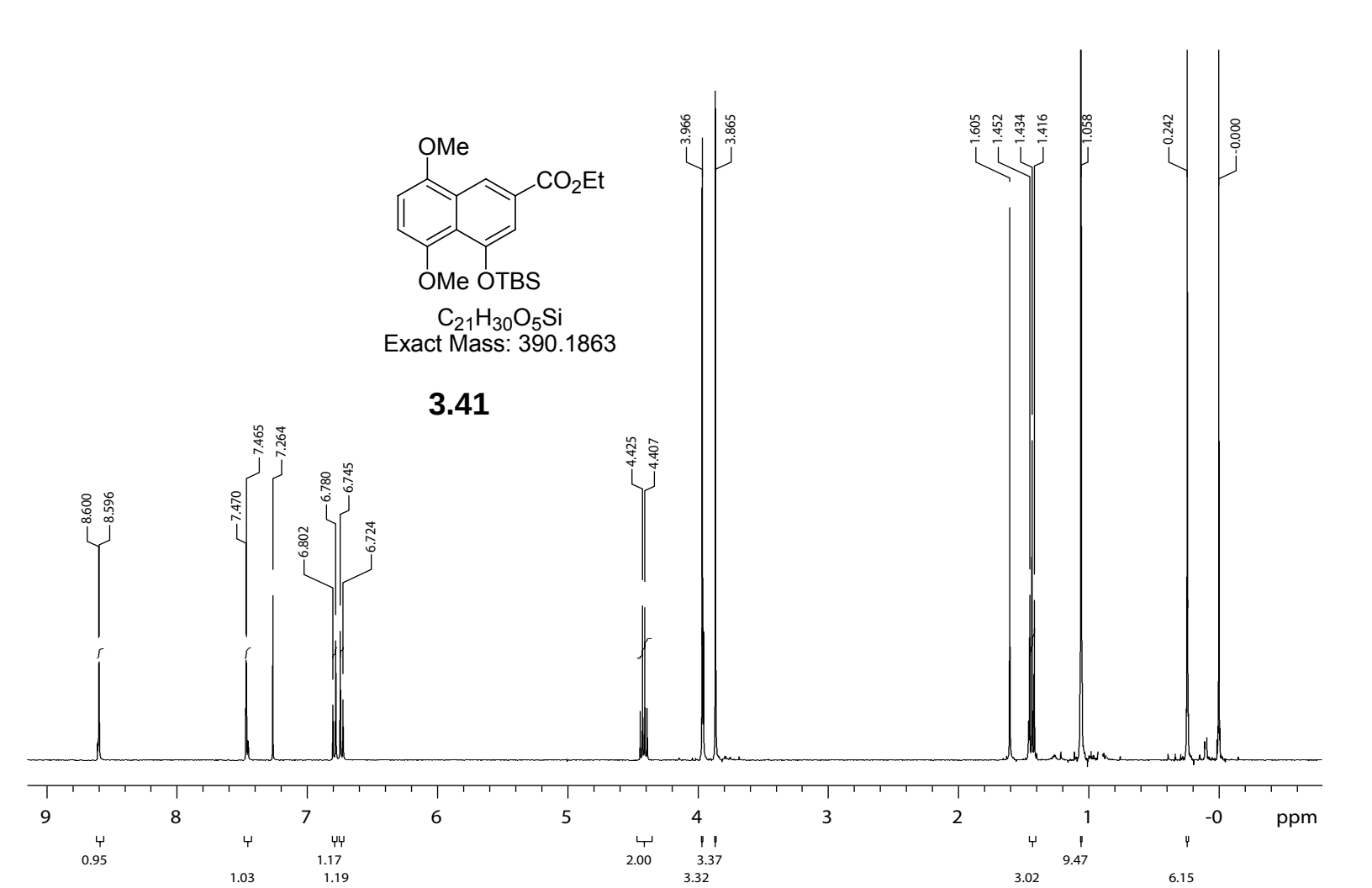


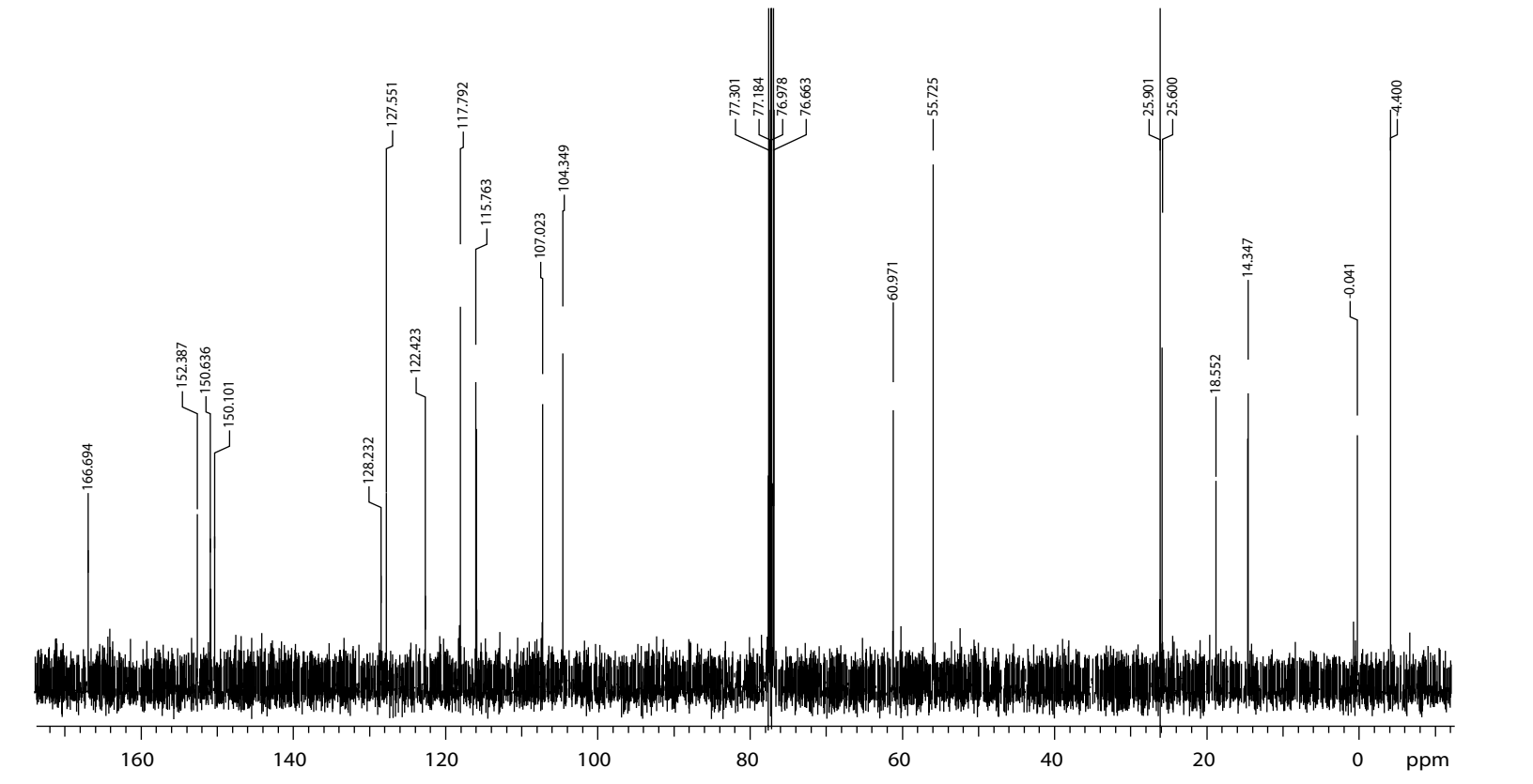

4.628
2.387
OH
SO3H
OH
C11H10O5S
Exact Mass: 254.0249
3.36
7.816
7.796
7.701
7.680
7.315
7.297
7.277
7.203
7.184
7.166
8
7
6
5
4
3
2
ppm
1.00
0.97
1.14
1.13
3.06

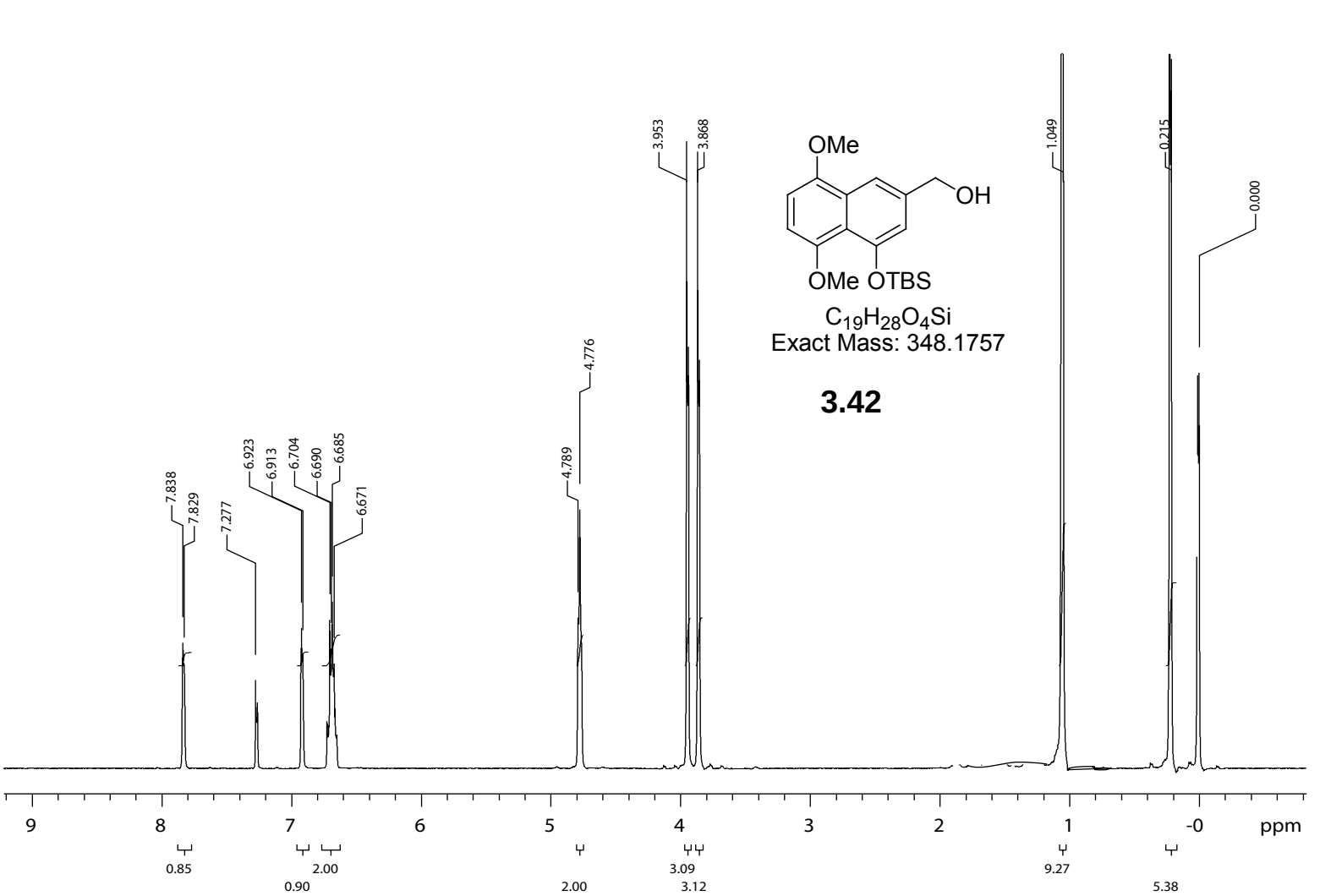

128.436
127.931
125.733
123.418
122.949
120.934
118.685
117.293
145.294
141.154
13.006
160
140
120
100
80
60
40
20
ppm

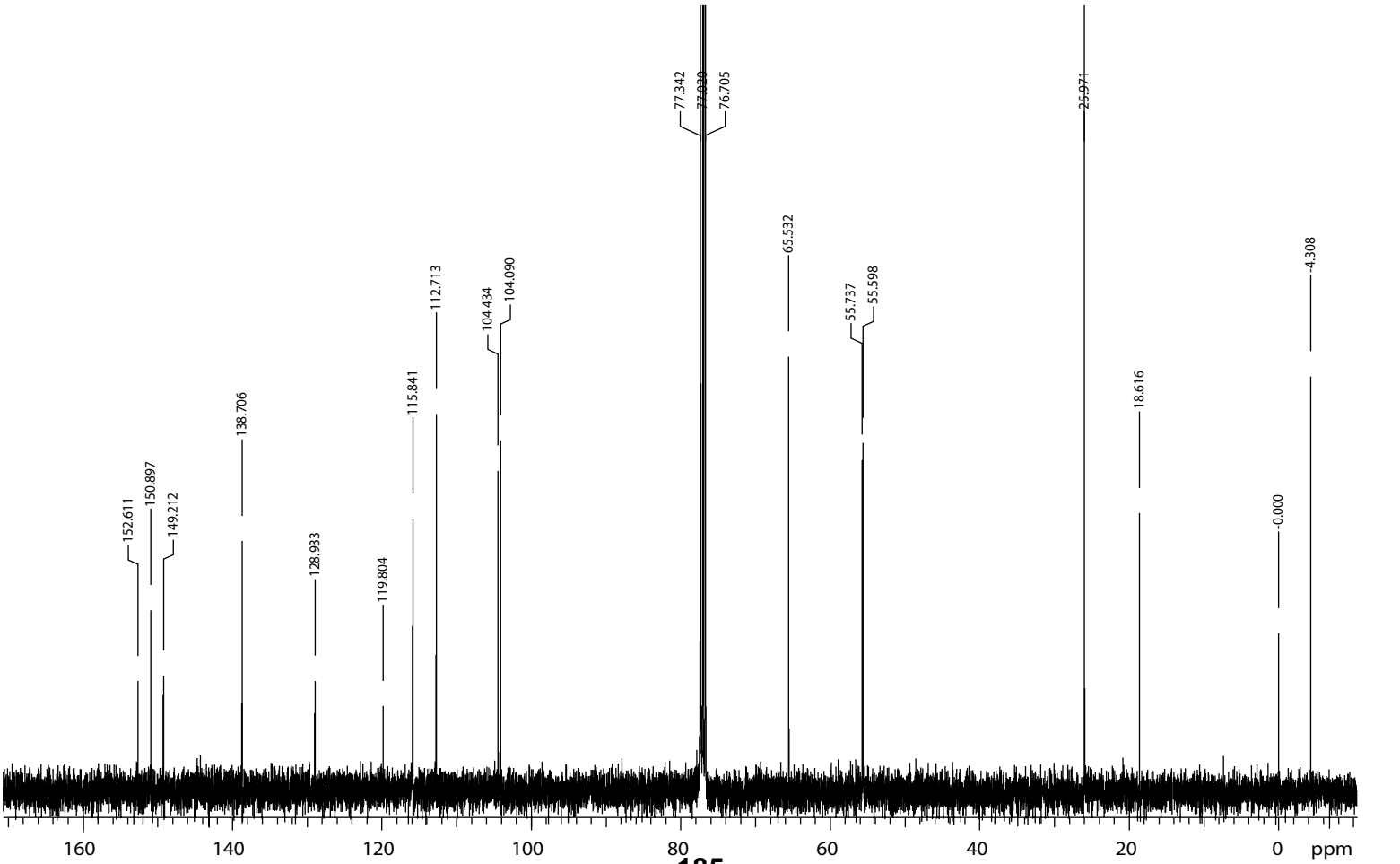

OMe
SO3Me
OMe
C14H16O5S
Exact Mass: 296.0718
3.37
8.205
8.183
8.125
8.103
7.698
7.695
7.682
7.678
7.660
7.657
7.607
7.604
7.590
7.587
7.583
7.256
4.078
3.880
3.848
2.697
9
8
7
6
5
4
3
ppm
1.02
1.00
1.03
1.03
2.99
3.05
2.99
3.05

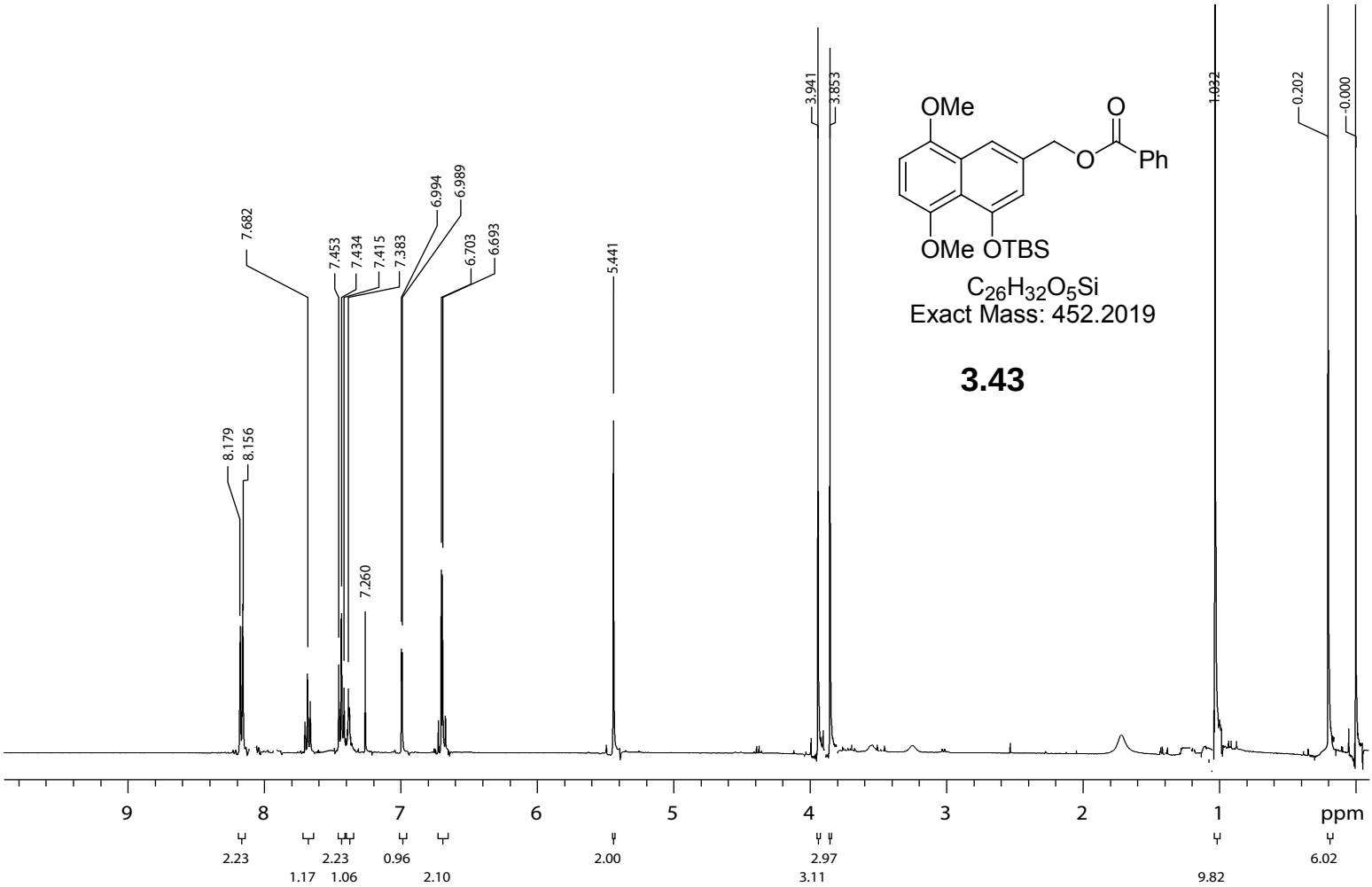

154.510
151.382
131.550
129.799
127.770
127.110
125.564
125.411
124.385
122.788
77.578
77.256
76.941
64.845
61.776
56.581
13.995
160
140
120
100
80
60
40
20
ppm

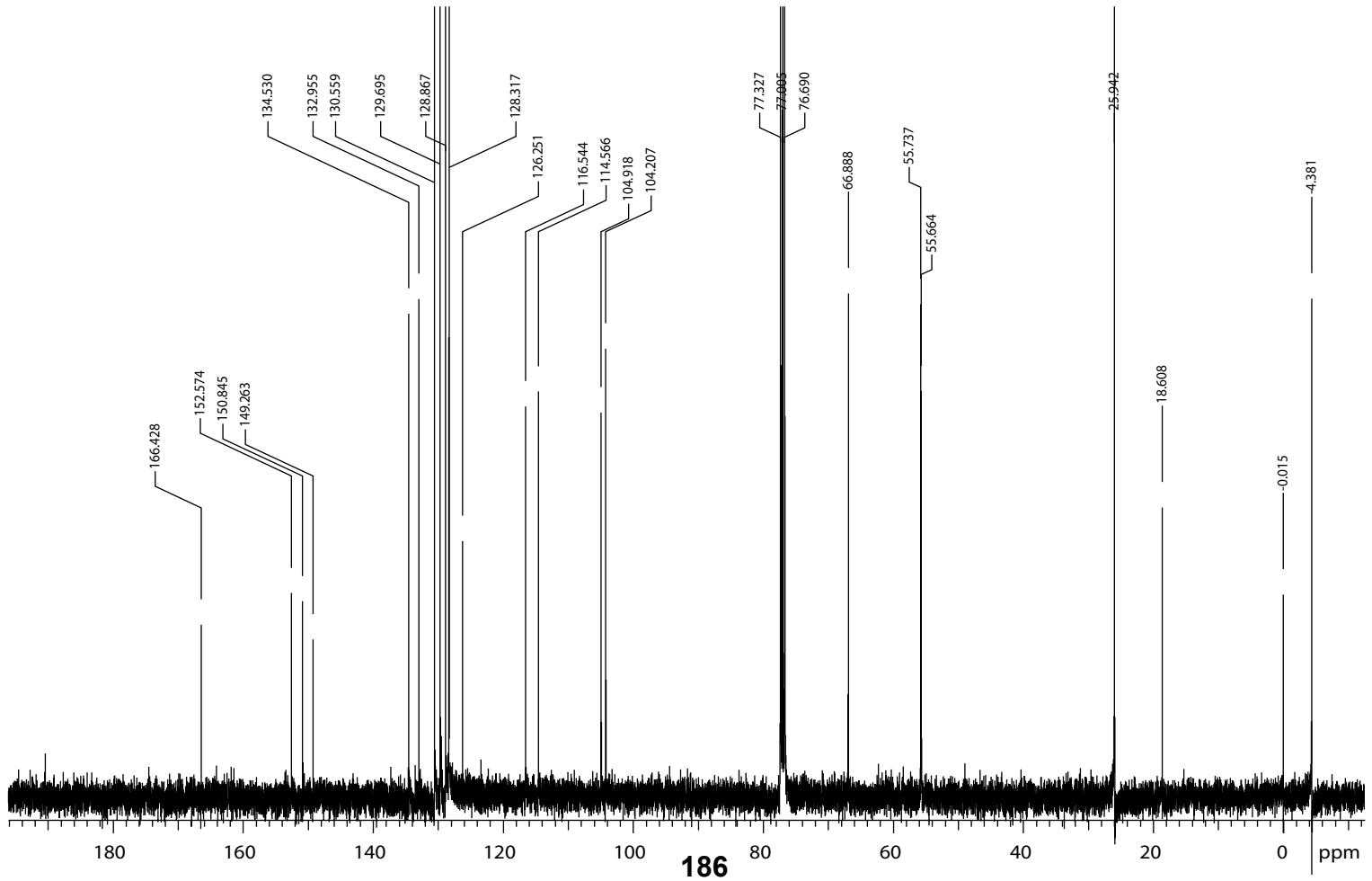

OMe
CO2Et
OMe OTBS
C21H30O5Si
Exact Mass: 390.1863
3.41
8.600
8.596
7.470
7.465
7.264
6.802
6.780
6.745
6.724
4.425
4.407
3.966
3.865
1.605
1.452
1.434
1.416
1.058
0.242
-0.000
ppm
0.95
1.03
1.17
1.19
2.00
3.37
3.32
3.02
9.47
6.15

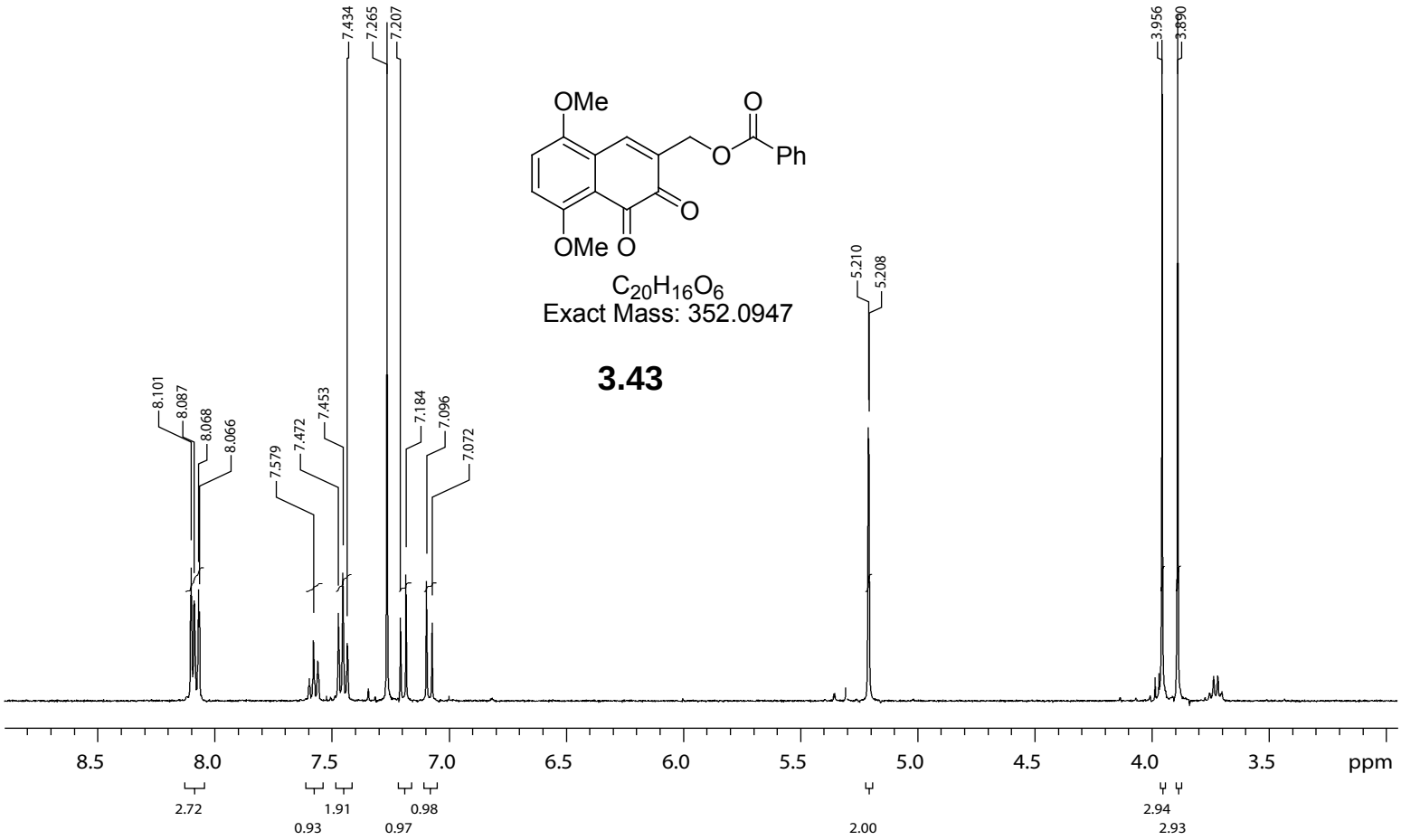

166.694
152.387
150.636
150.101
128.232
127.551
122.423
117.792
115.763
107.023
104.349
77.301
77.184
76.978
76.663
60.971
55.725
25.901
25.600
18.552
14.347
-0.041
-4.400
ppm

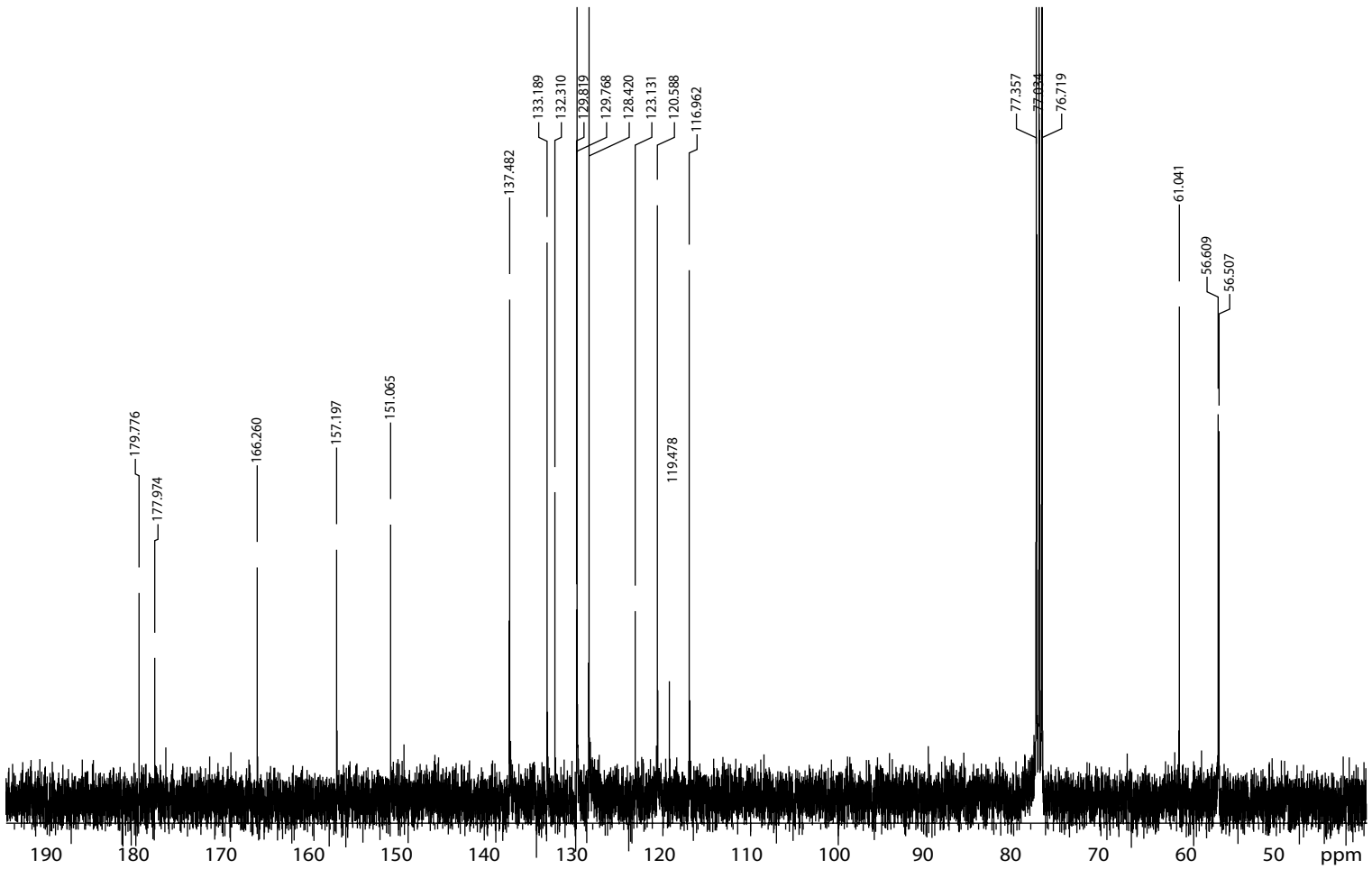

OMe
OH
OMe OTBS
$C_{19}H_{28}O_4Si$
Exact Mass: 348.1757
3.42
3.953
3.868
1.049
0.215
0.000
4.776
4.789
6.923
6.913
6.704
6.690
6.685
6.671
7.838
7.829
7.277
9
8
7
6
5
4
3
2
1
-0
ppm
0.85
2.00
0.90
2.00
3.09
3.12
9.27
5.38

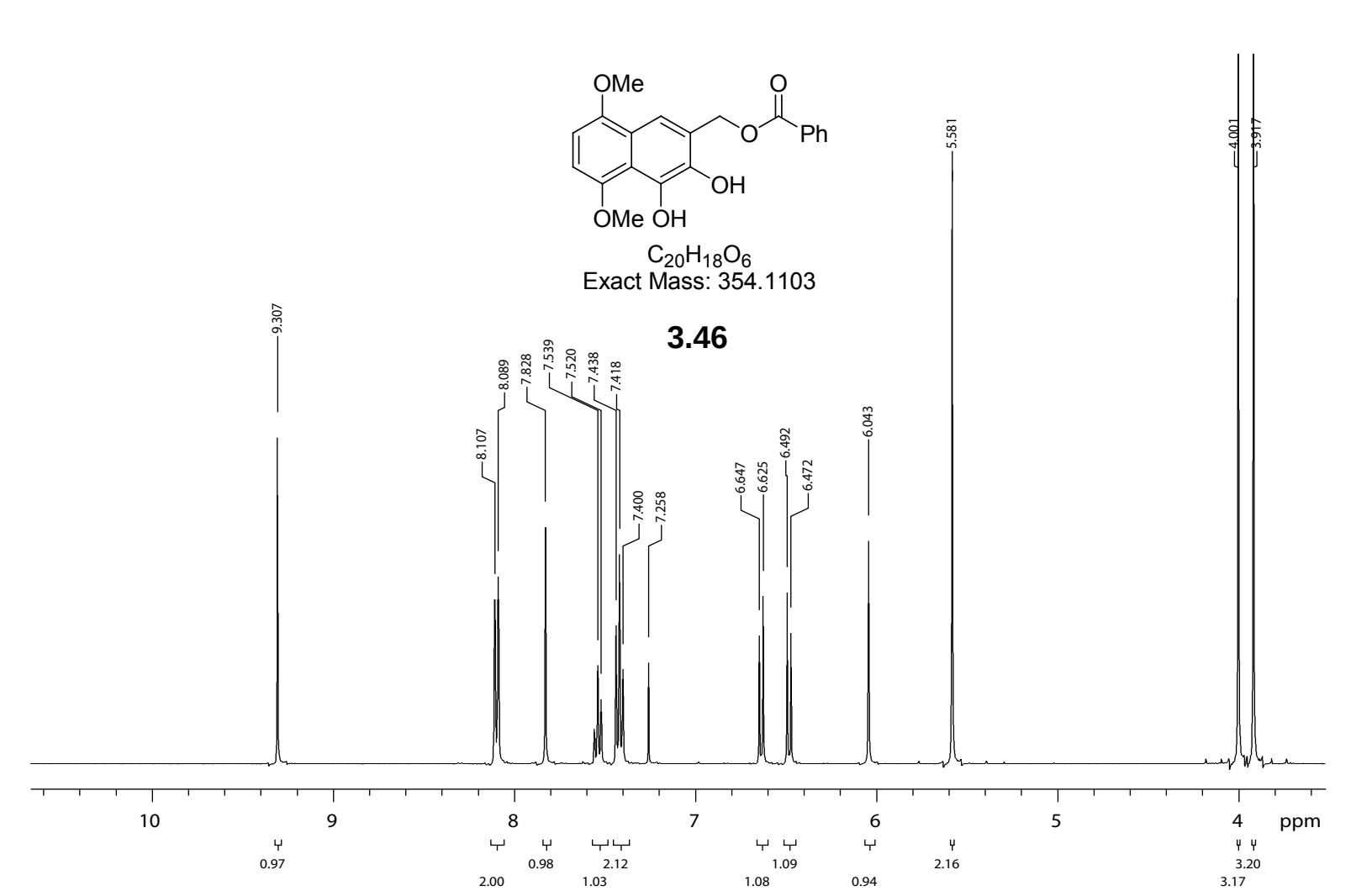

77.342
77.030
76.705
25.971
65.532
55.737
55.598
18.616
-4.308
-0.000
104.434
104.090
112.713
115.841
138.706
152.611
150.897
149.212
128.933
119.804
160
140
120
100
80
60
40
20
0
ppm

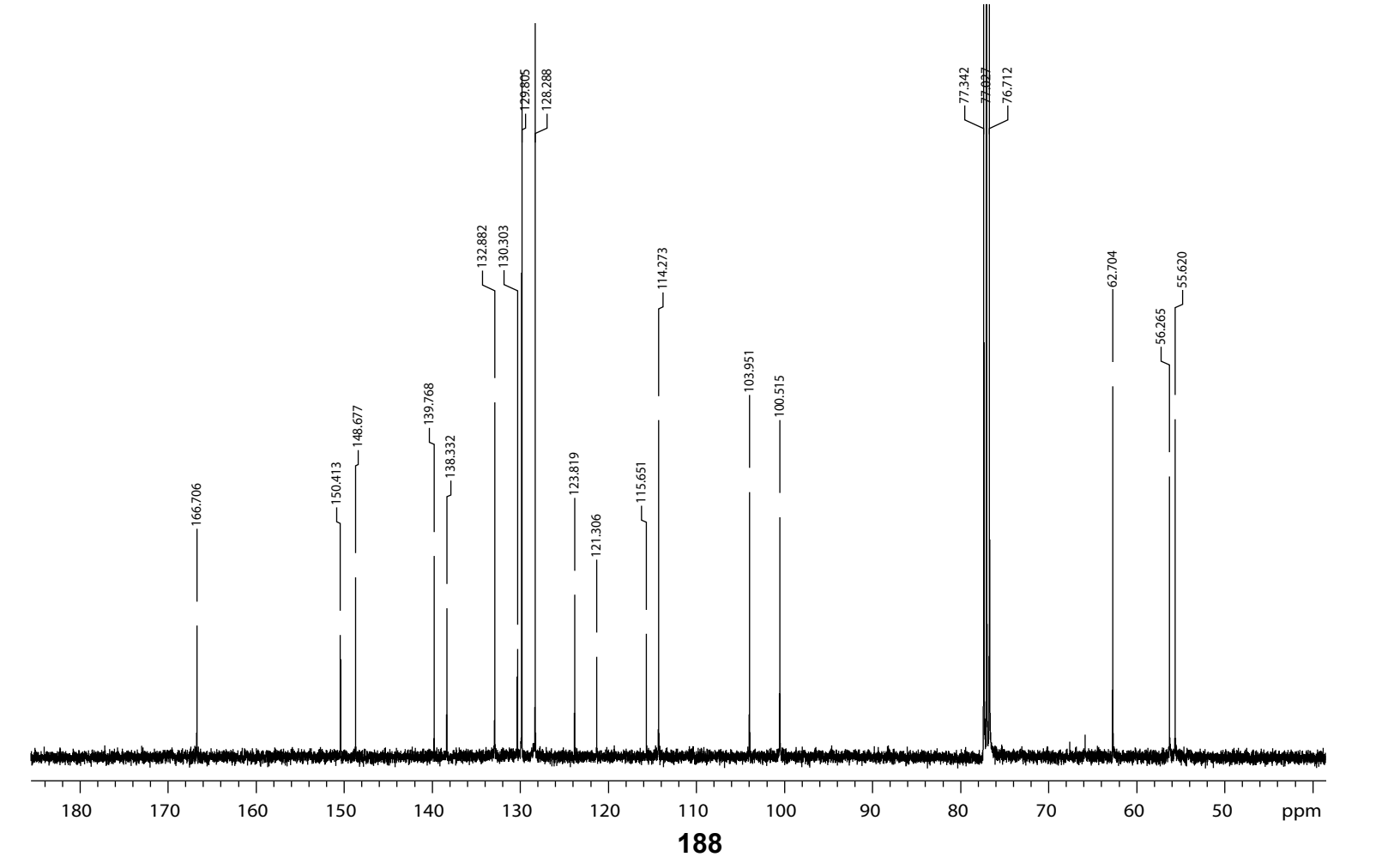

OMe
O
O
Ph
OMe OTBS
$C_{26}H_{32}O_5Si$
Exact Mass: 452.2019
3.43
8.179
8.156
7.682
7.453
7.434
7.415
7.383
7.260
6.994
6.989
6.703
6.693
5.441
3.941
3.853
1.832
0.202
-0.000
ppm
2.23
1.17
2.23
1.06
0.96
2.10
2.00
2.97
3.11
9.82
6.02

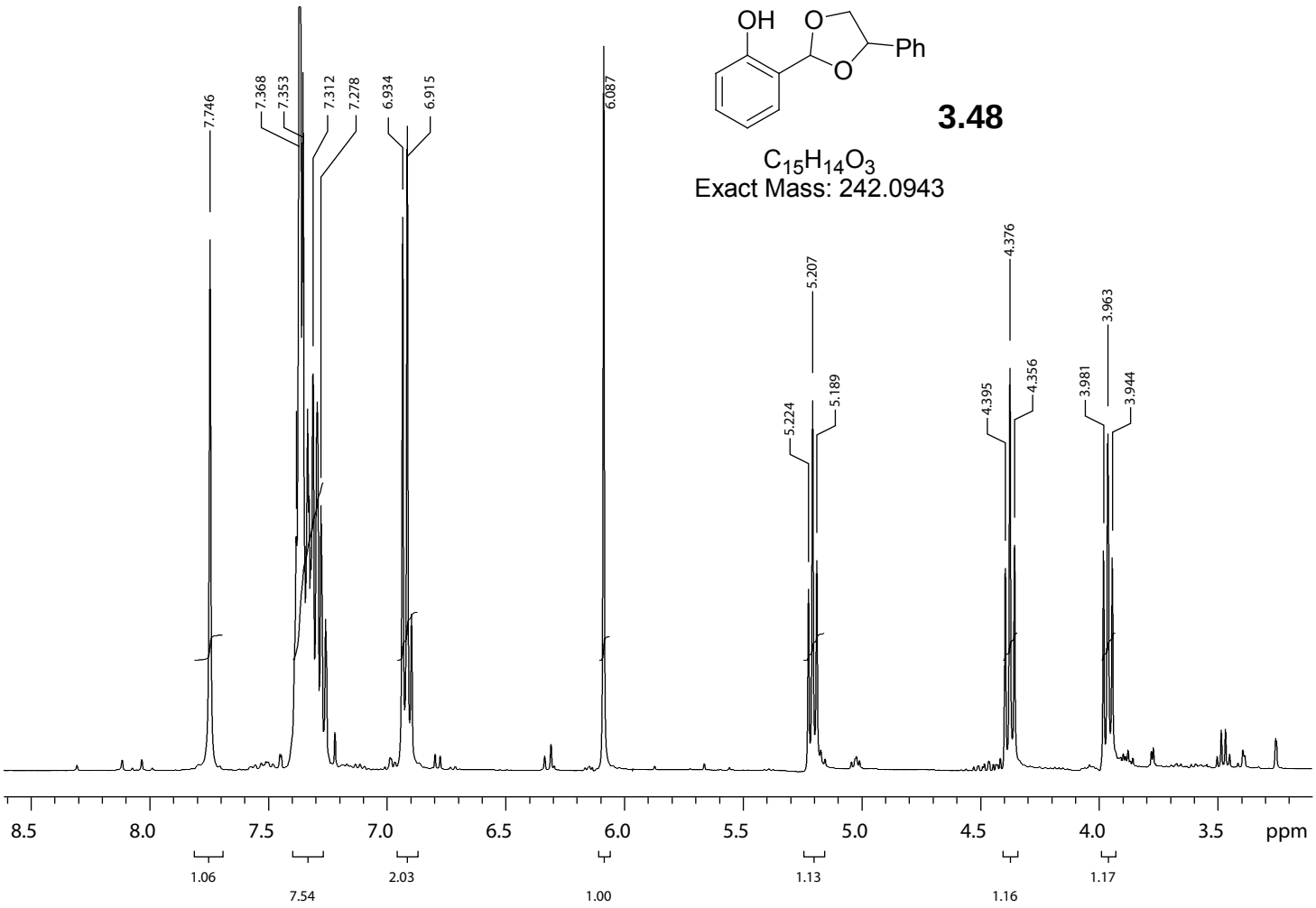

166.428
152.574
150.845
149.263
134.530
132.955
130.559
129.695
128.867
128.317
126.251
116.544
114.566
104.918
104.207
77.327
77.005
76.690
66.888
55.737
55.664
25.942
18.608
-4.381
-0.015
ppm

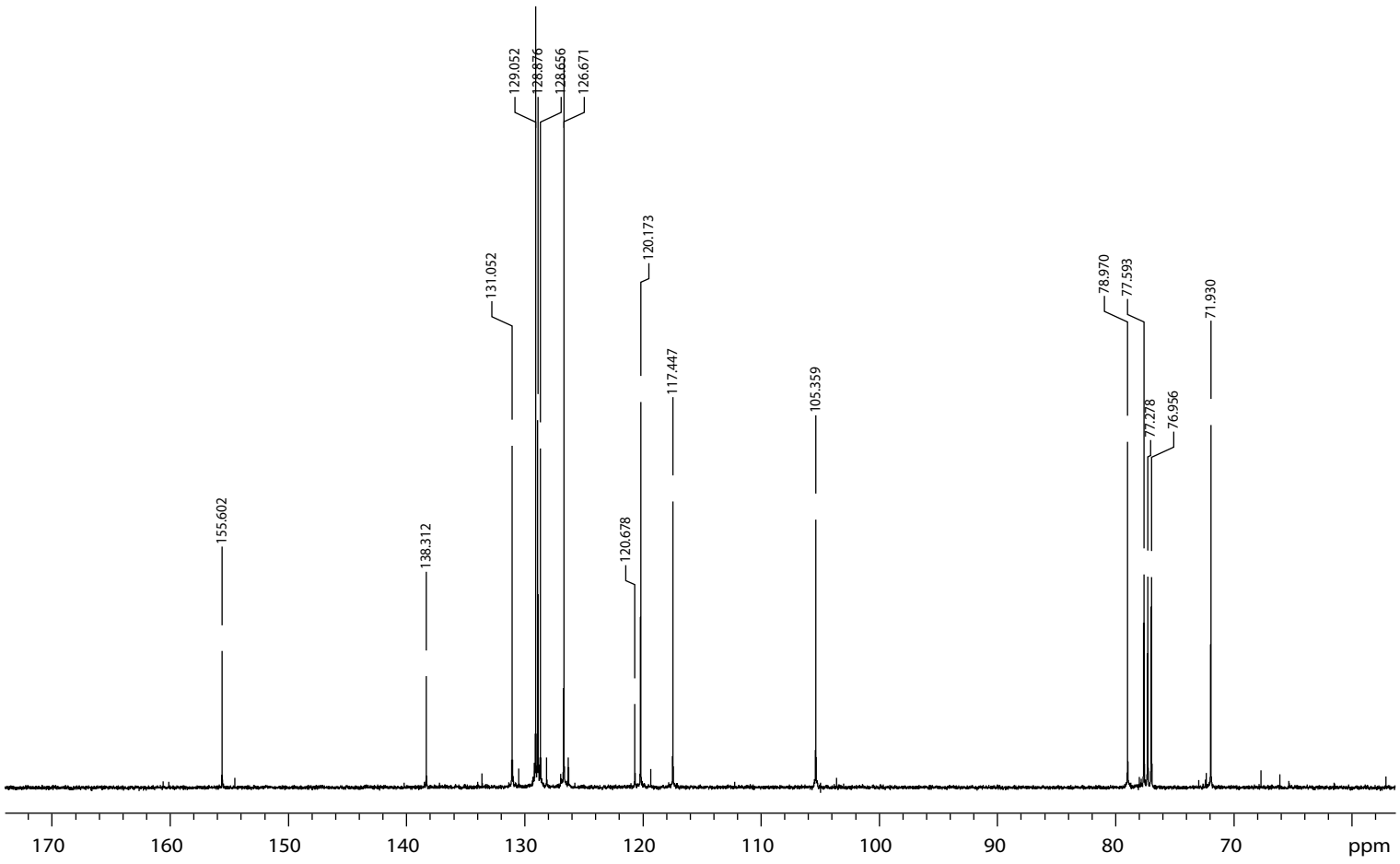

OMe
O
O
Ph
O
OMe O
$C_{20}H_{16}O_6$
Exact Mass: 352.0947
3.43
7.434
7.265
7.207
3.956
3.890
5.210
5.208
8.101
8.087
8.068
8.066
7.579
7.472
7.453
7.184
7.096
7.072
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm
2.72
0.93
1.91
0.97
0.98
2.00
2.94
2.93

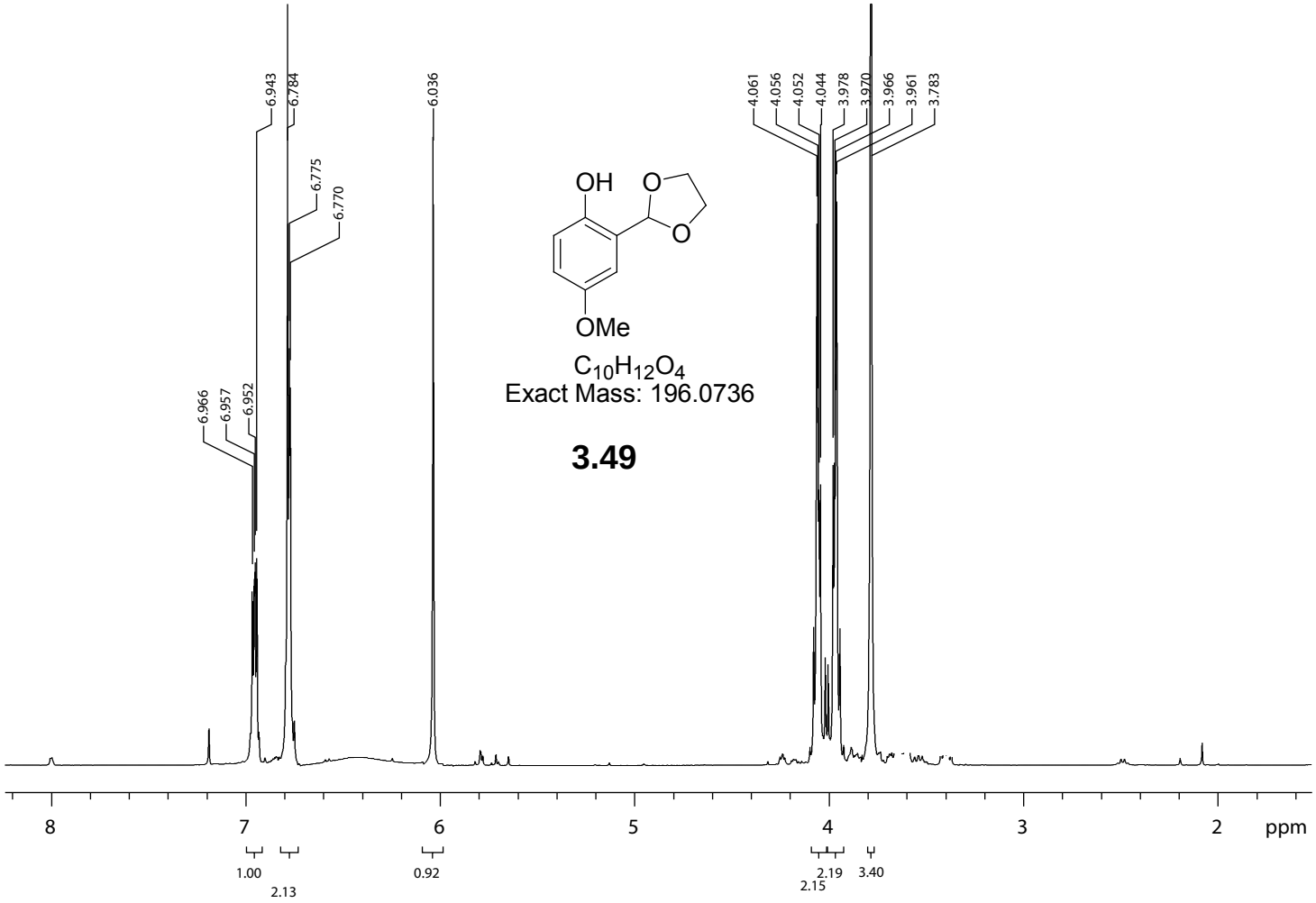

179.776
177.974
166.260
157.197
151.065
137.482
133.189
132.310
129.819
129.768
128.420
123.131
120.588
116.962
119.478
77.357
77.034
76.719
61.041
56.609
56.507
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
ppm

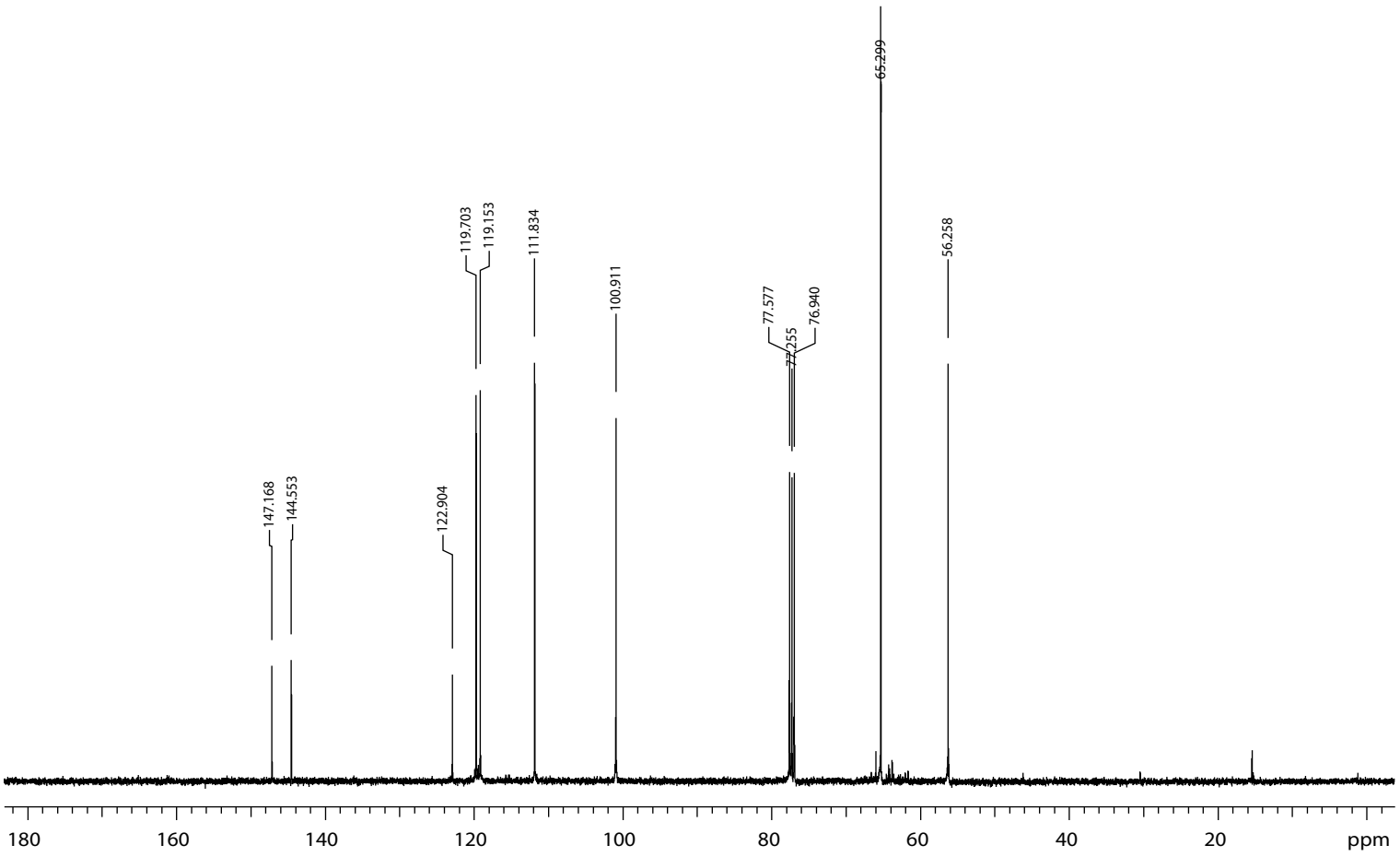

OMe
O
O
Ph
OH
OMe OH
$C_{20}H_{18}O_6$
Exact Mass: 354.1103
3.46
9.307
8.107
8.089
7.828
7.539
7.520
7.438
7.418
7.400
7.258
6.647
6.625
6.492
6.472
6.043
5.581
4.001
3.917
10
9
8
7
6
5
4
ppm
0.97
2.00
0.98
1.03
2.12
1.08
1.09
0.94
2.16
3.17
3.20

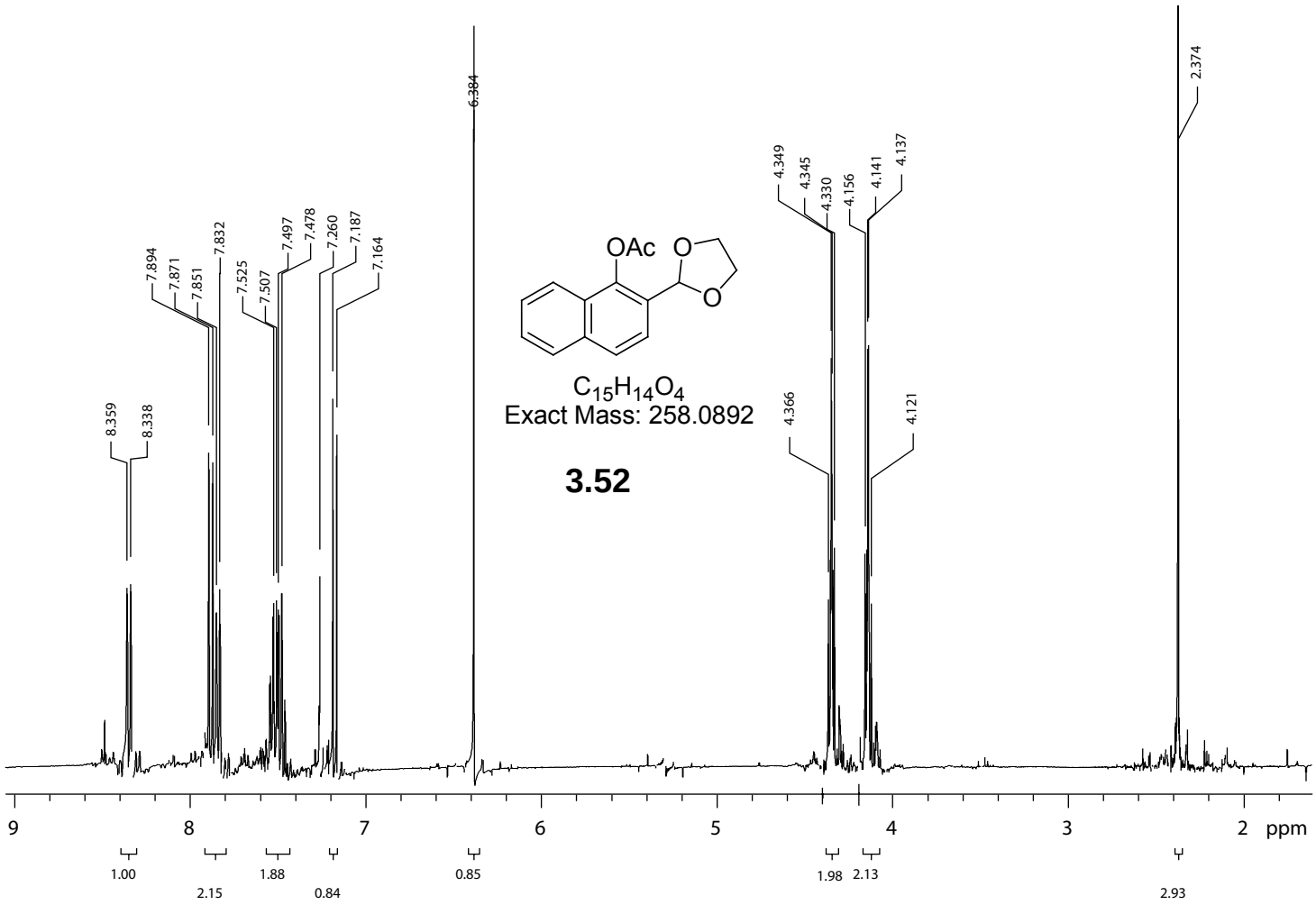

166.706
150.413
148.677
139.768
138.332
132.882
130.303
129.805
128.288
123.819
121.306
115.651
114.273
103.951
100.515
77.342
77.037
76.712
62.704
56.265
55.620
180
170
160
150
140
130
120
110
100
90
80
70
60
50
ppm

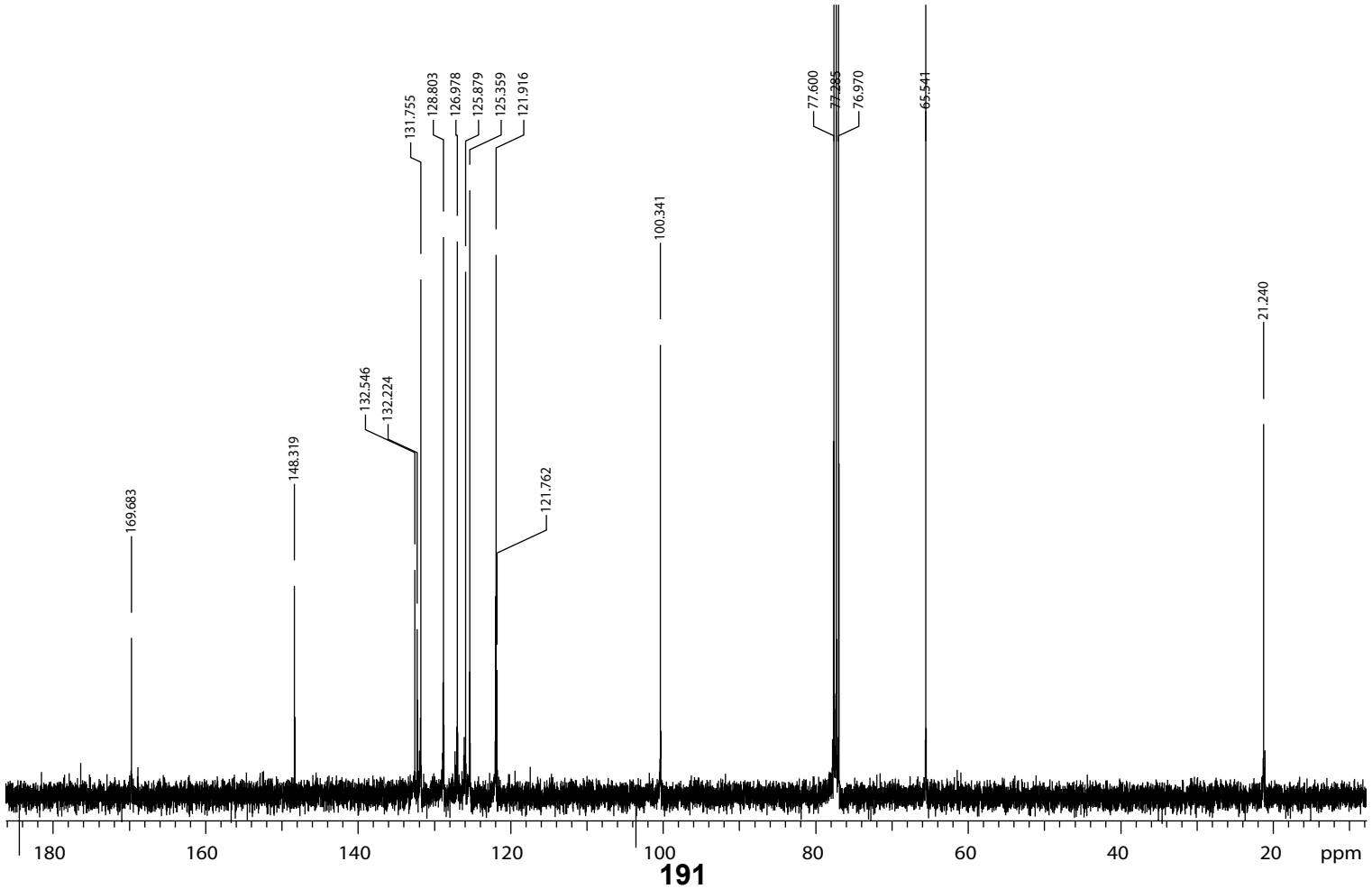

OH
O
O
Ph
3.48
C15H14O3
Exact Mass: 242.0943
7.746
7.368
7.353
7.312
7.278
6.934
6.915
6.087
5.207
5.224
5.189
4.376
4.395
4.356
3.981
3.963
3.944
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm
1.06
7.54
2.03
1.00
1.13
1.16
1.17

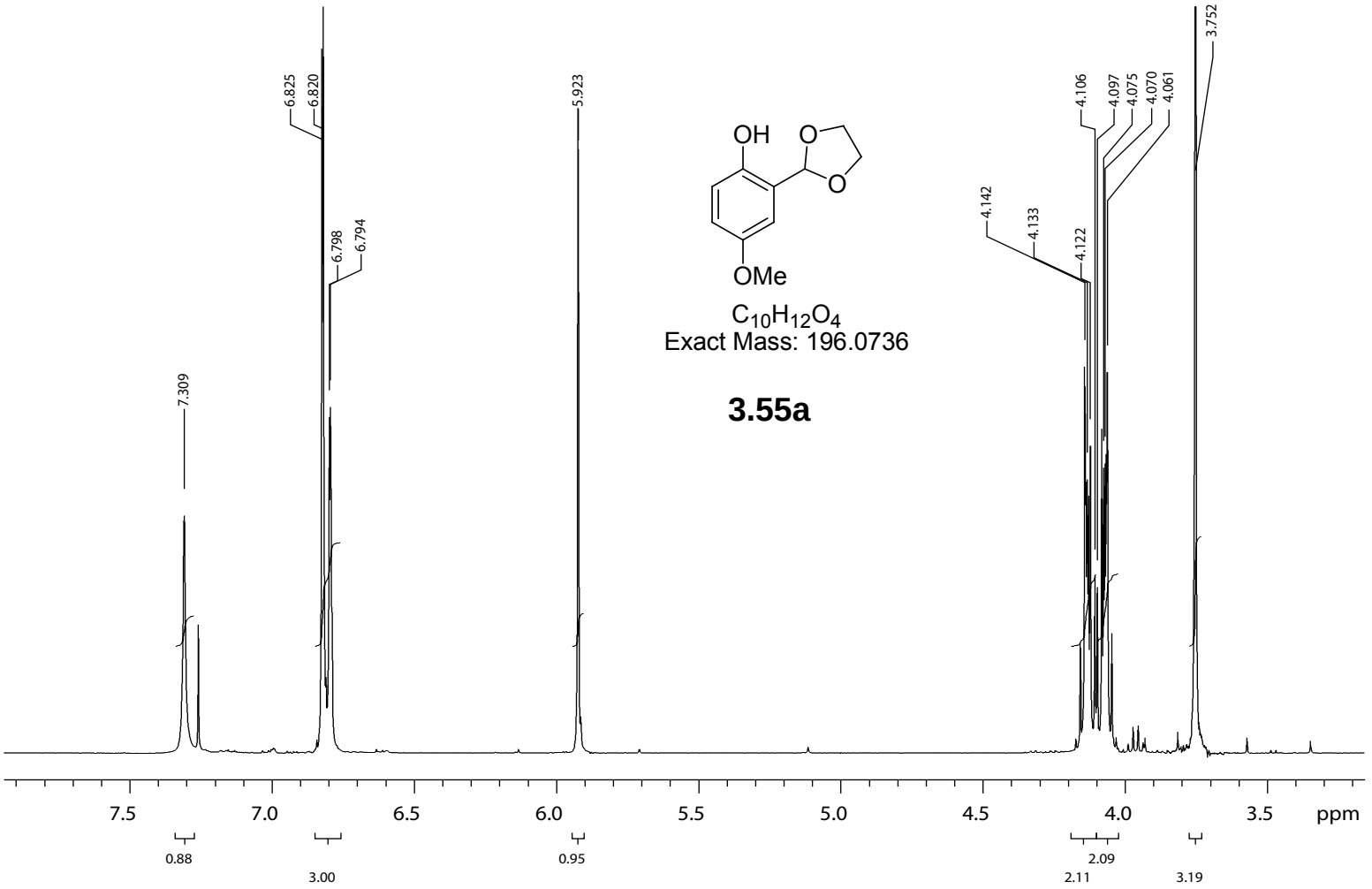

155.602
138.312
131.052
129.052
128.876
128.656
126.671
120.678
120.173
117.447
105.359
78.970
77.593
77.278
76.956
71.930
170
160
150
140
130
120
110
100
90
80
70
ppm

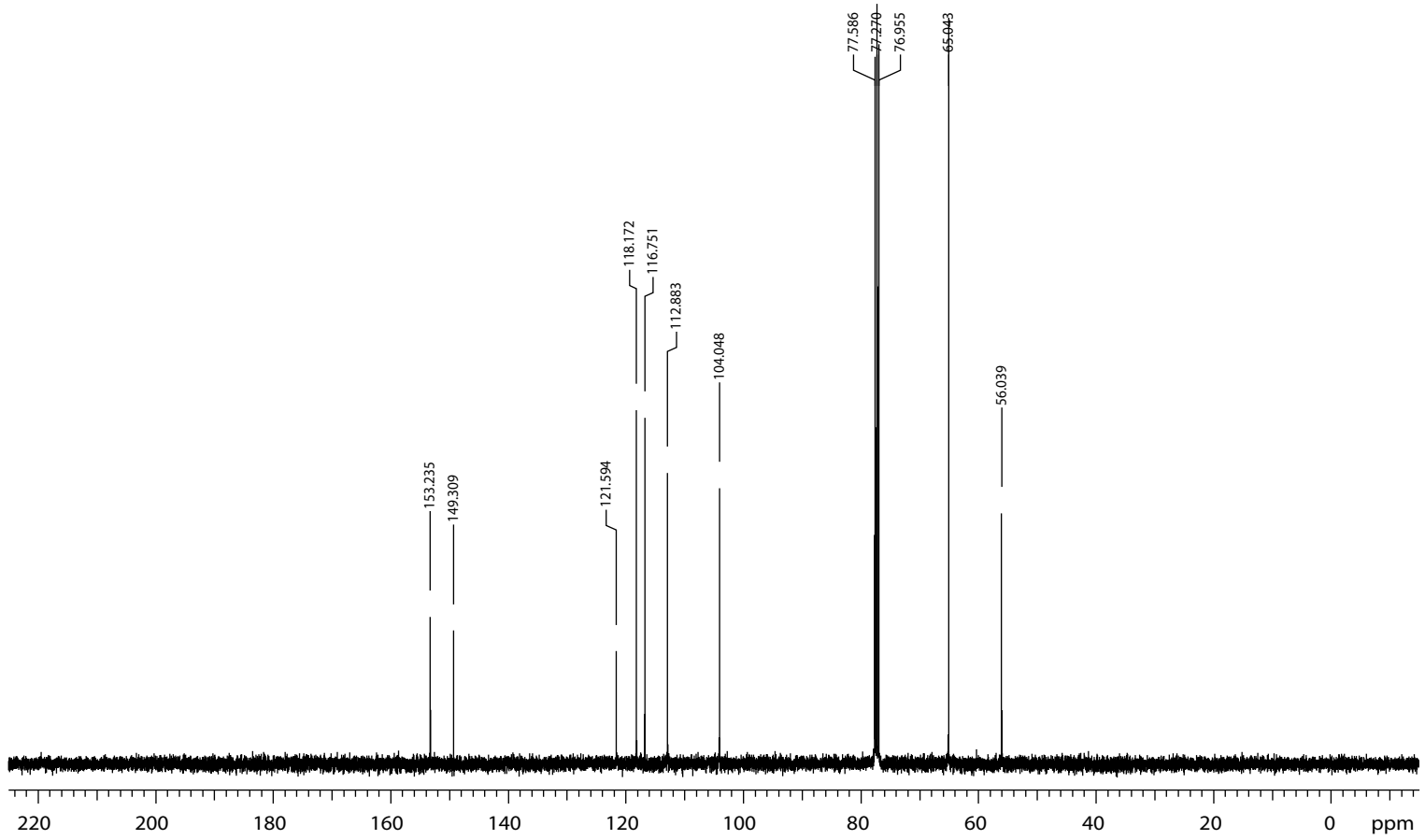

6.943
6.784
6.775
6.770
6.036
6.966
6.957
6.952
4.061
4.056
4.052
4.044
3.978
3.970
3.966
3.961
3.783
OH
O
O
OMe
$C_{10}H_{12}O_4$
Exact Mass: 196.0736
3.49
8
7
6
5
4
3
2
ppm
1.00
2.13
0.92
2.15
2.19
3.40

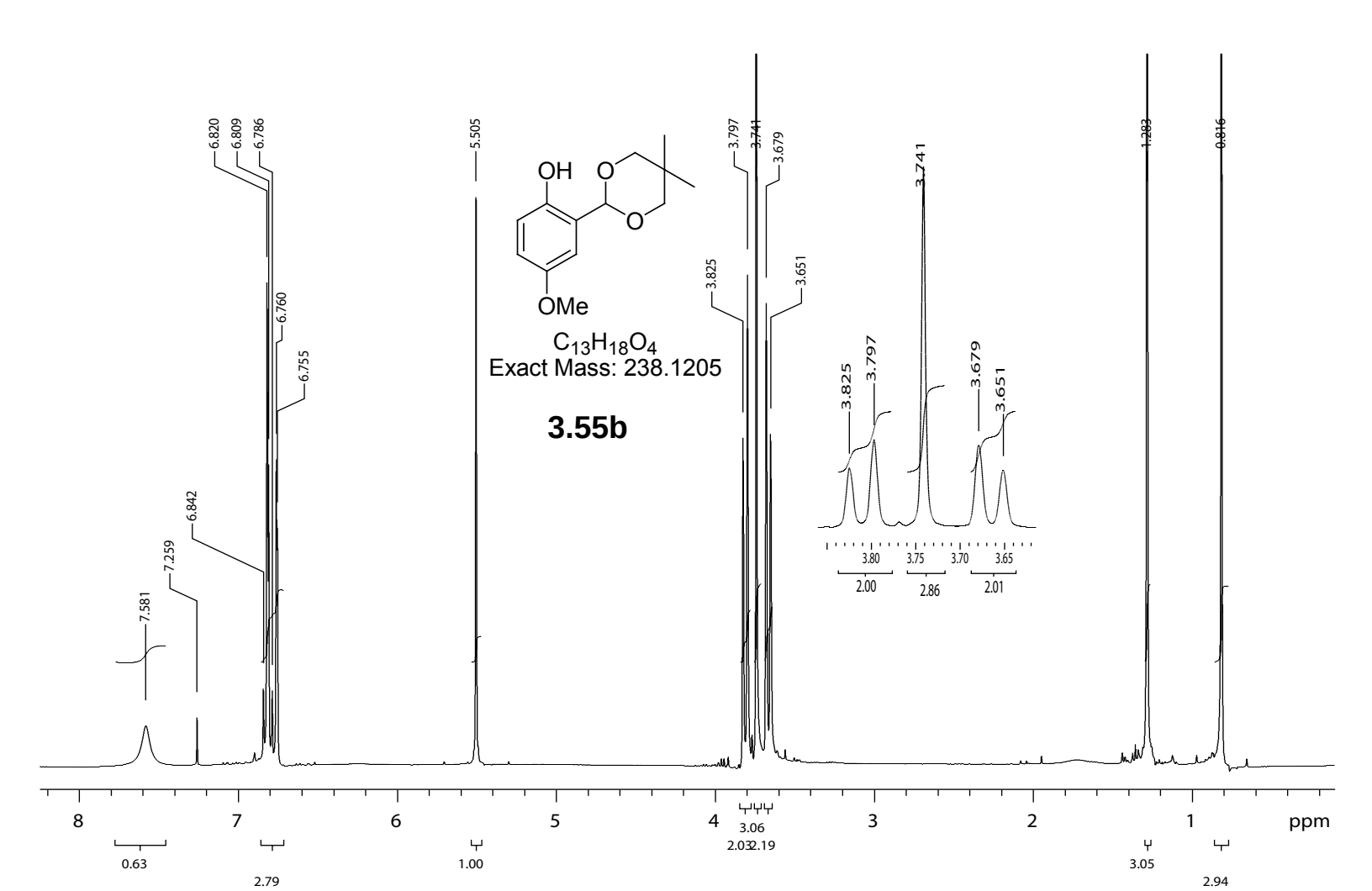

65.299
119.703
119.153
111.834
100.911
77.577
77.255
76.940
56.258
147.168
144.553
122.904
180
160
140
120
100
80
60
40
20
ppm


8.359
8.338
7.894
7.871
7.851
7.832
7.525
7.507
7.497
7.478
7.260
7.187
7.164
6.384
4.349
4.345
4.330
4.156
4.141
4.137
4.366
4.121
2.374
OAc
O
O
$C_{15}H_{14}O_4$
Exact Mass: 258.0892
3.52
9
8
7
6
5
4
3
2
ppm
1.00
2.15
1.88
0.84
0.85
1.98
2.13
2.93


169.683
148.319
132.546
132.224
131.755
128.803
126.978
125.879
125.359
121.916
121.762
100.341
77.600
77.385
76.970
65.541
21.240
180
160
140
120
100
80
60
40
20
ppm


6.825
6.820
6.798
6.794
5.923
7.309
4.142
4.133
4.122
4.106
4.097
4.075
4.070
4.061
3.752
OH
O
O
OMe
$C_{10}H_{12}O_4$
Exact Mass: 196.0736
3.55a
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm
0.88
3.00
0.95
2.09
2.11
3.19


77.586
77.270
76.955
65.043
118.172
116.751
112.883
104.048
153.235
149.309
121.594
56.039
220
200
180
160
140
120
100
80
60
40
20
0
ppm


6.820
6.809
6.786
6.760
6.755
6.842
7.259
7.581
5.505
3.797
3.741
3.679
3.825
3.651
1.283
0.816
OH
O
O
OMe
C13H18O4
Exact Mass: 238.1205
3.55b
3.825
3.797
3.741
3.679
3.651
3.80
3.75
3.70
3.65
2.00
2.86
2.01
8
7
6
5
4
3
2
1
ppm
0.63
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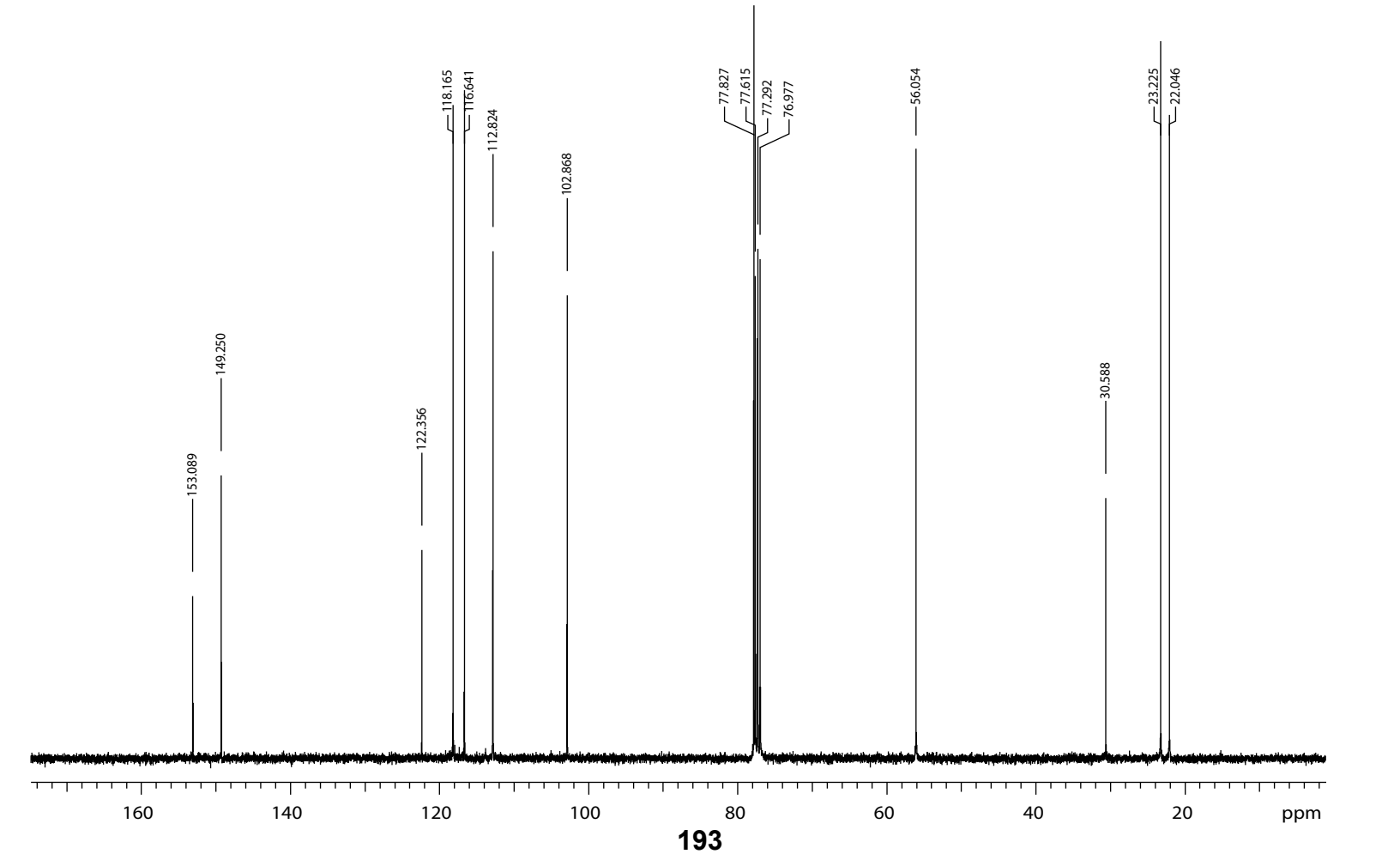
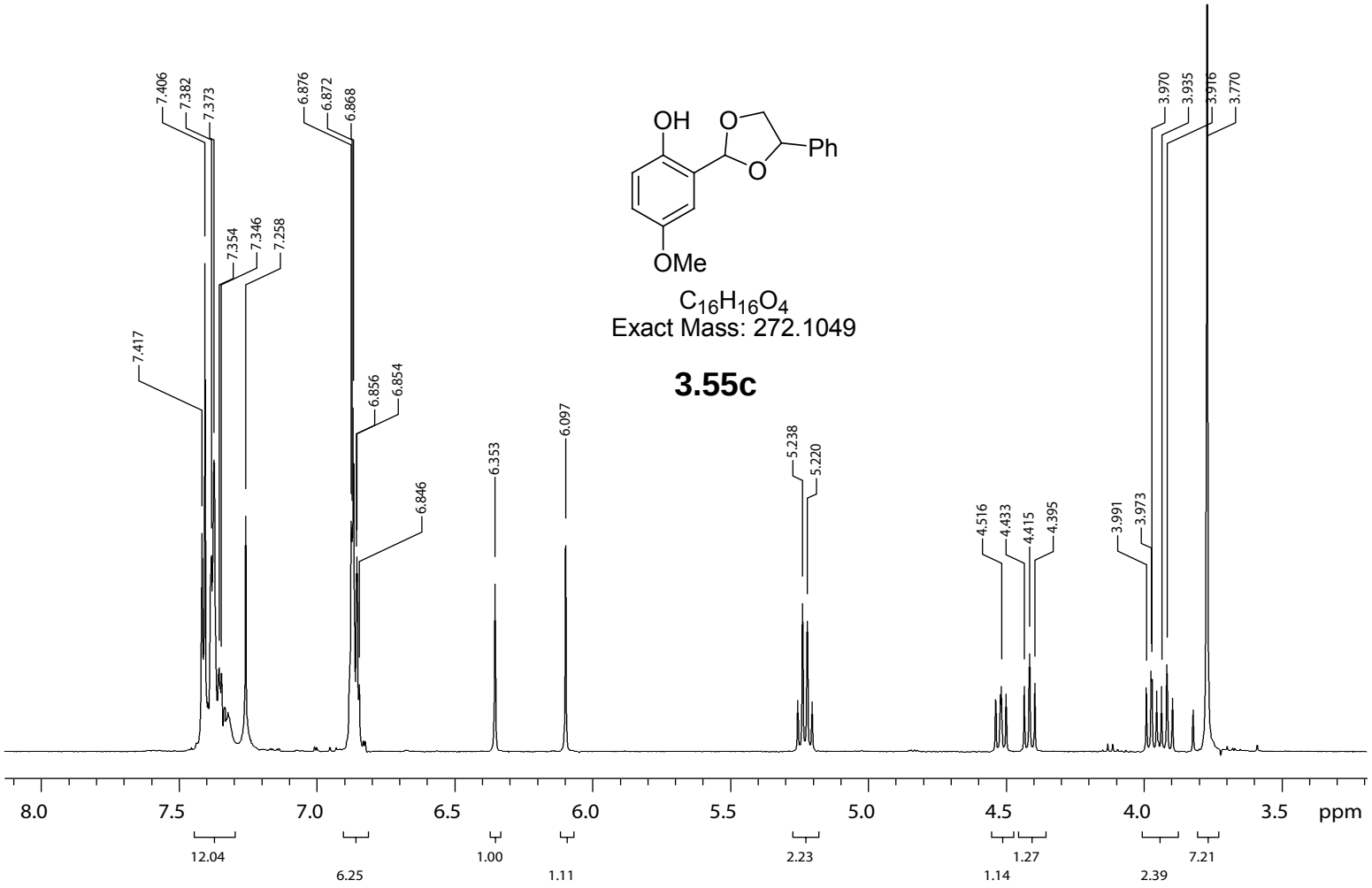
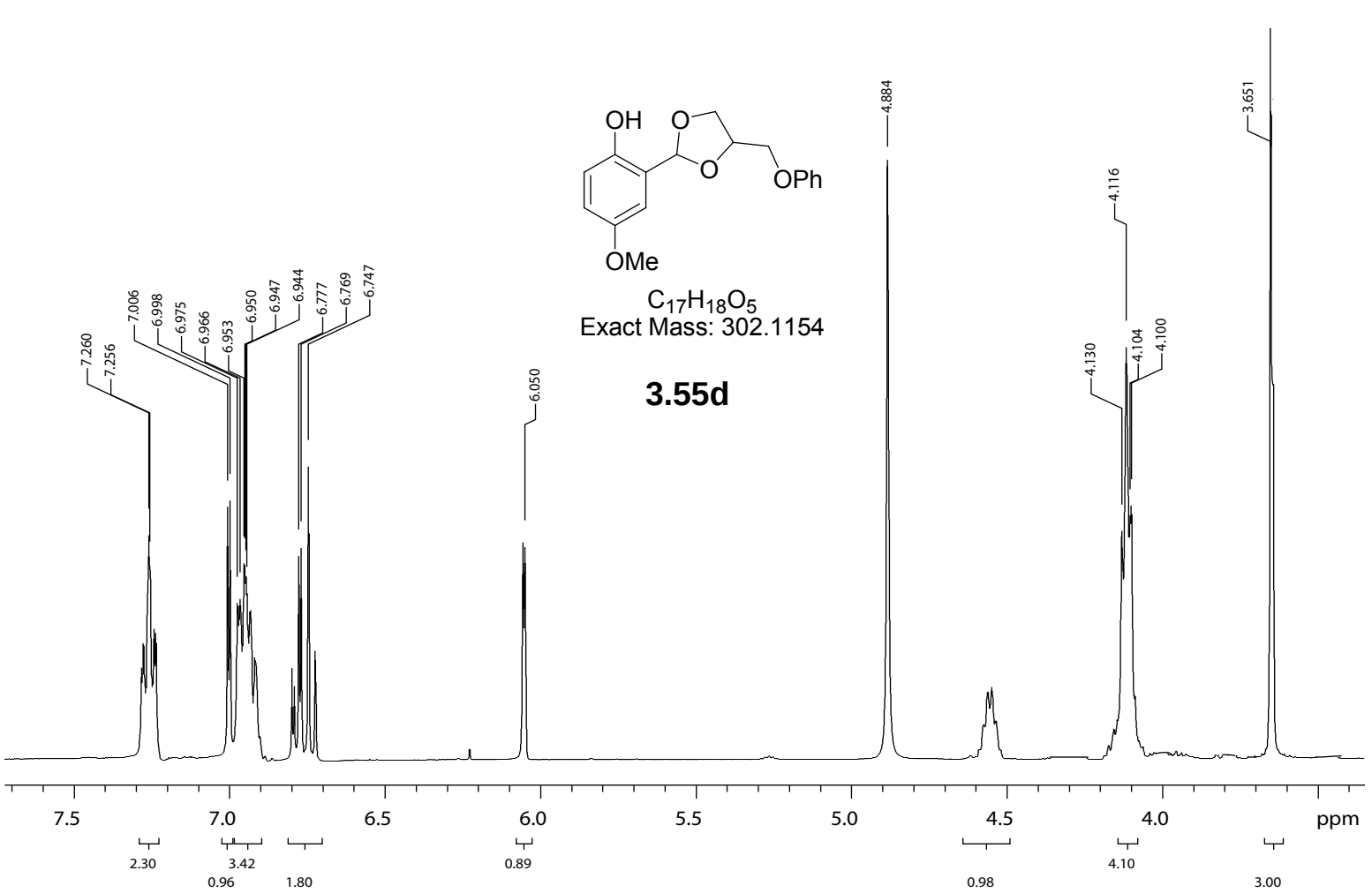
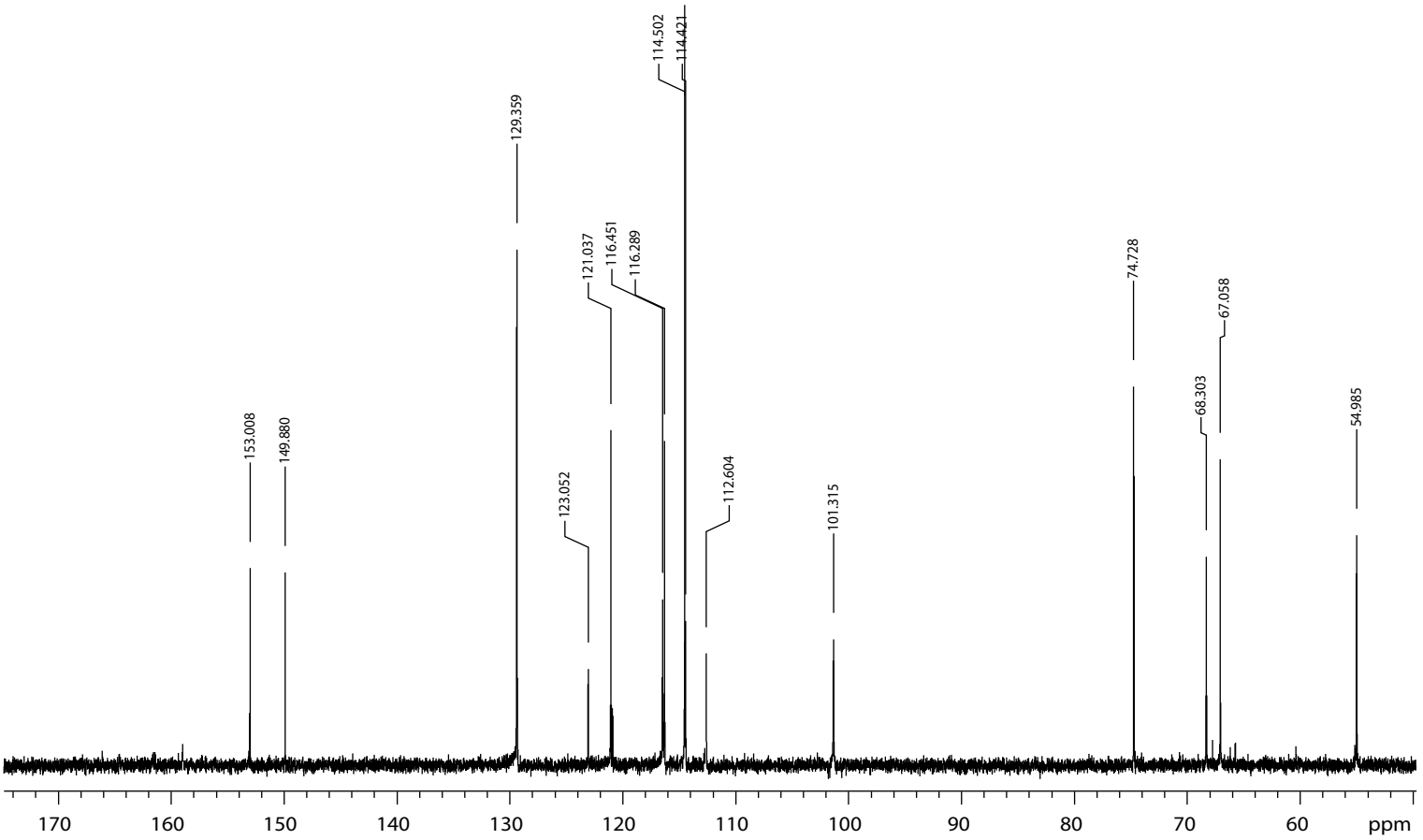
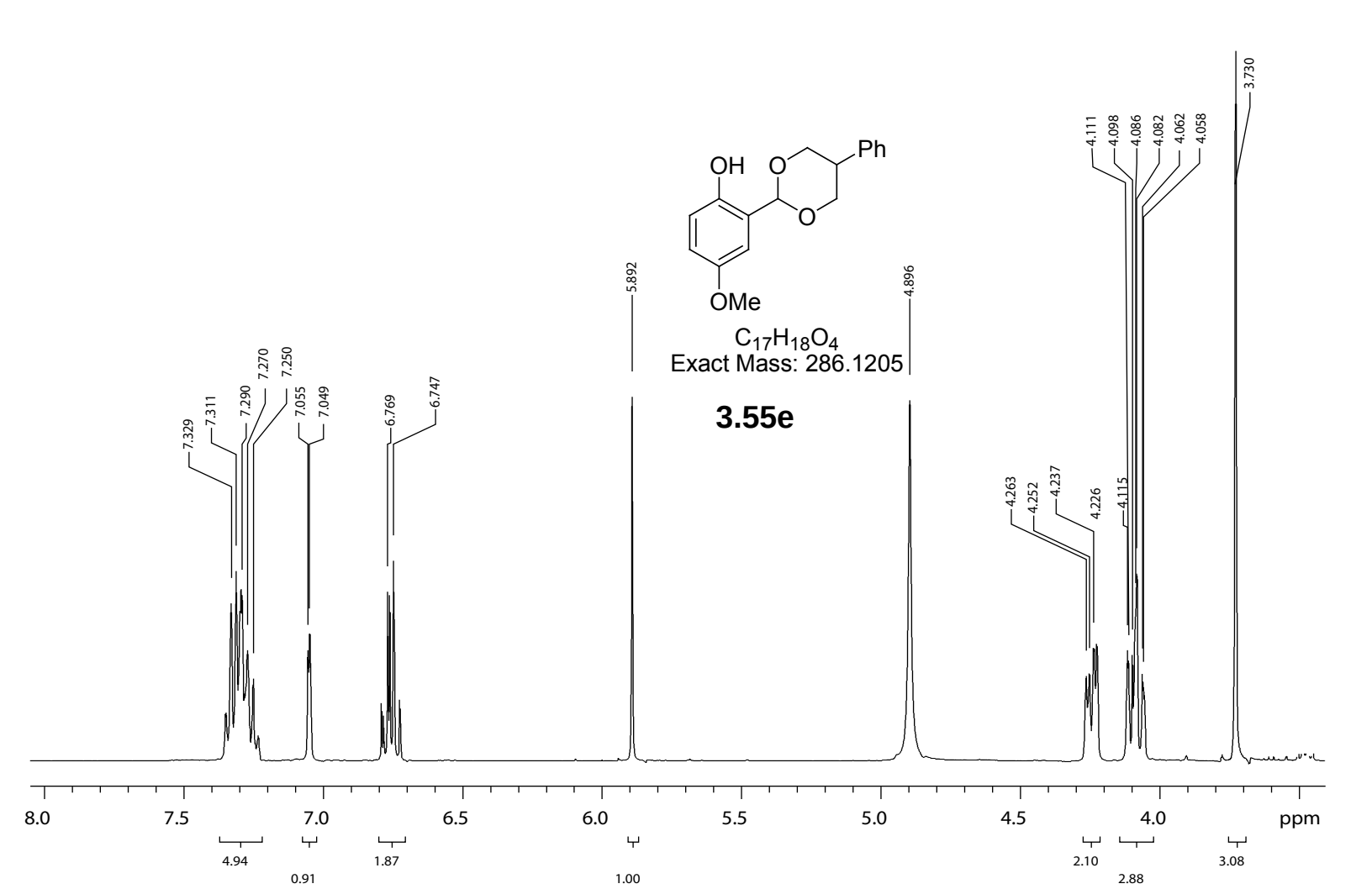
1.00
3.06
2.03
2.19
3.05
2.94

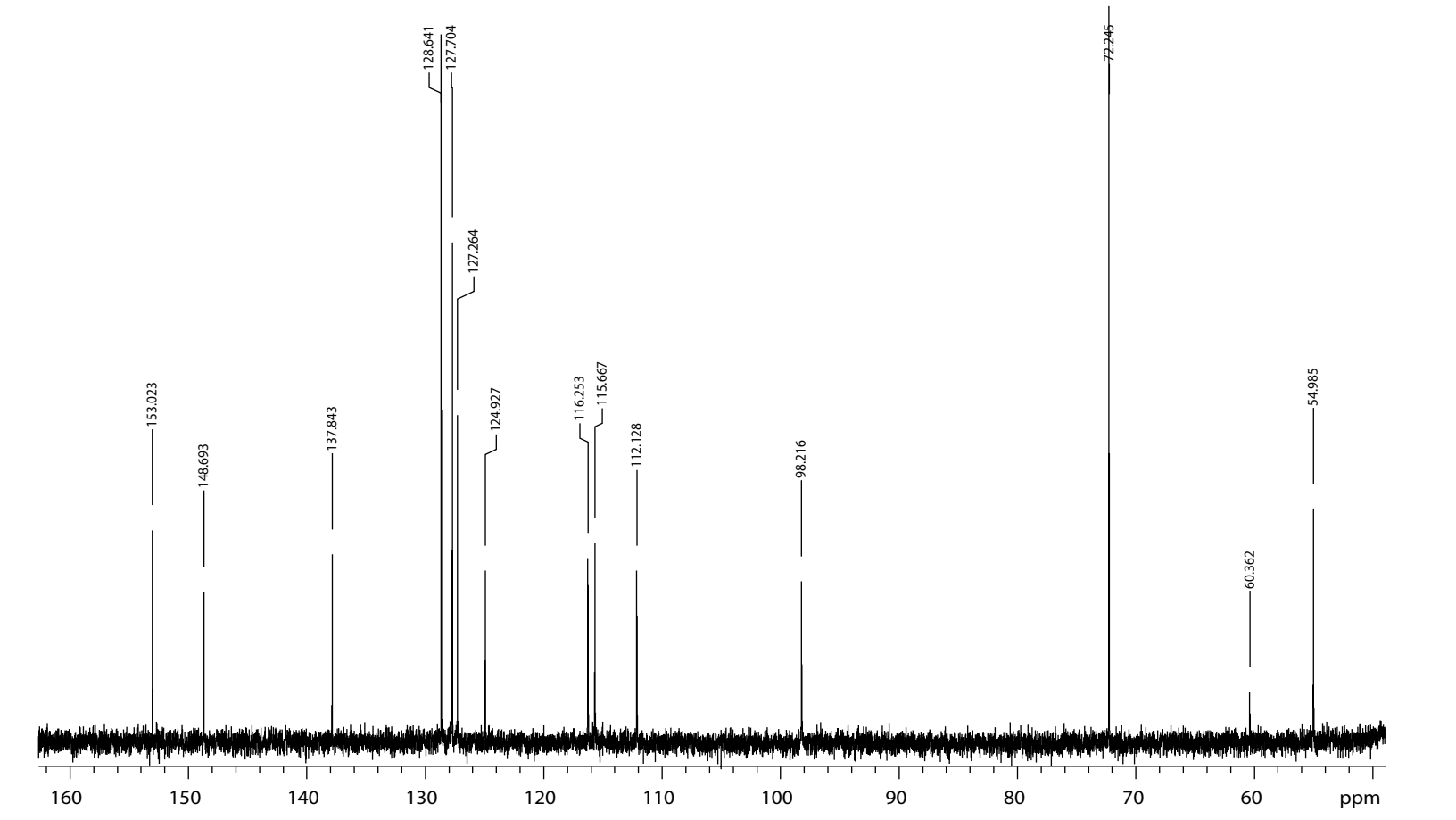

153.089
149.250
122.356
118.165
116.641
112.824
102.868
77.827
77.615
77.292
76.977
56.054
30.588
23.225
22.046
160
140
120
100
80
60
40
20
ppm

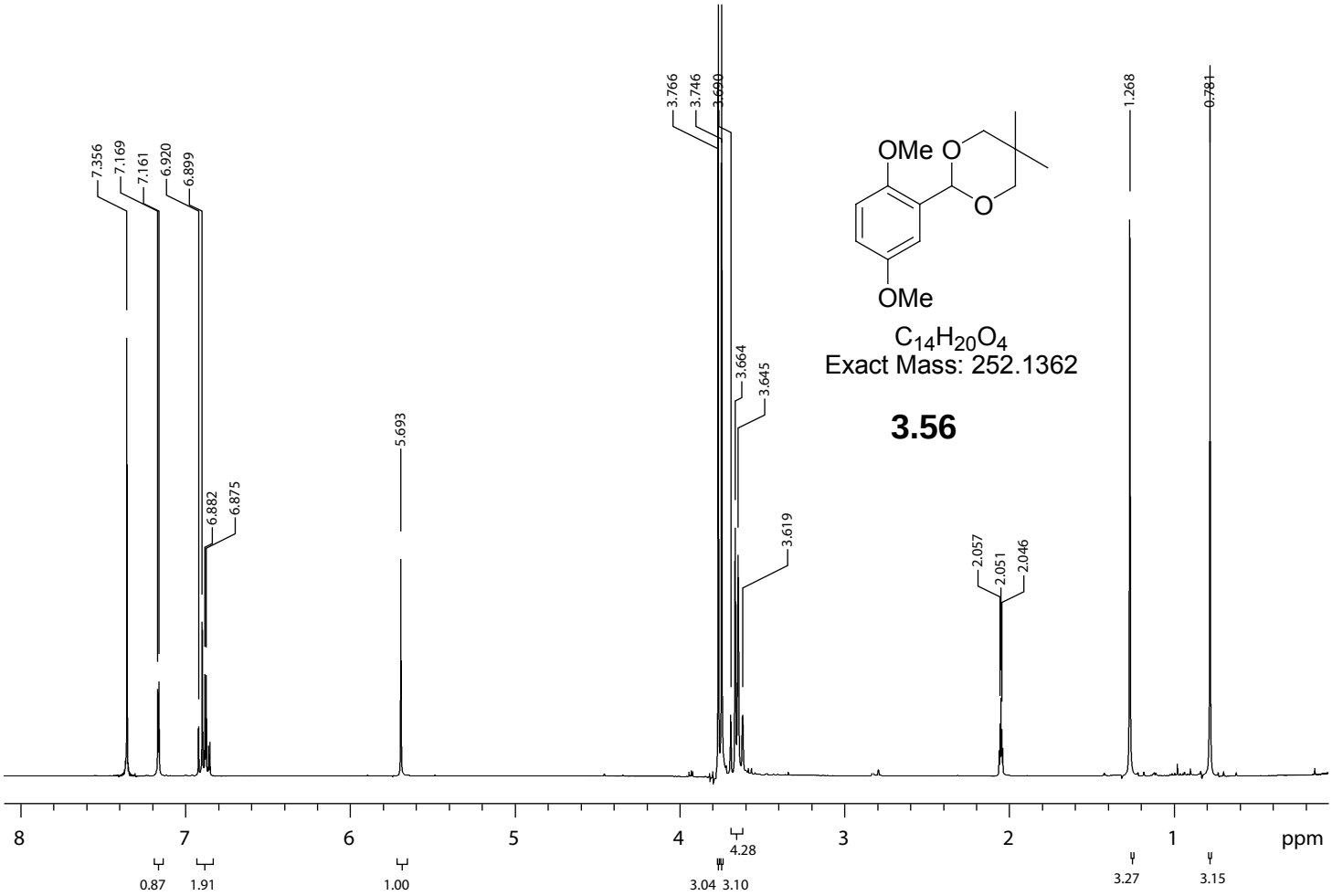

OH
O
Ph
O
OMe
$C_{16}H_{16}O_4$
Exact Mass: 272.1049
3.55c
7.406
7.382
7.373
7.354
7.346
7.258
7.417
6.876
6.872
6.868
6.856
6.854
6.846
6.353
6.097
5.238
5.220
4.516
4.433
4.415
4.395
3.991
3.973
3.970
3.935
3.916
3.770
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm
12.04
6.25
1.00
1.11
2.23
1.14
1.27
2.39
7.21

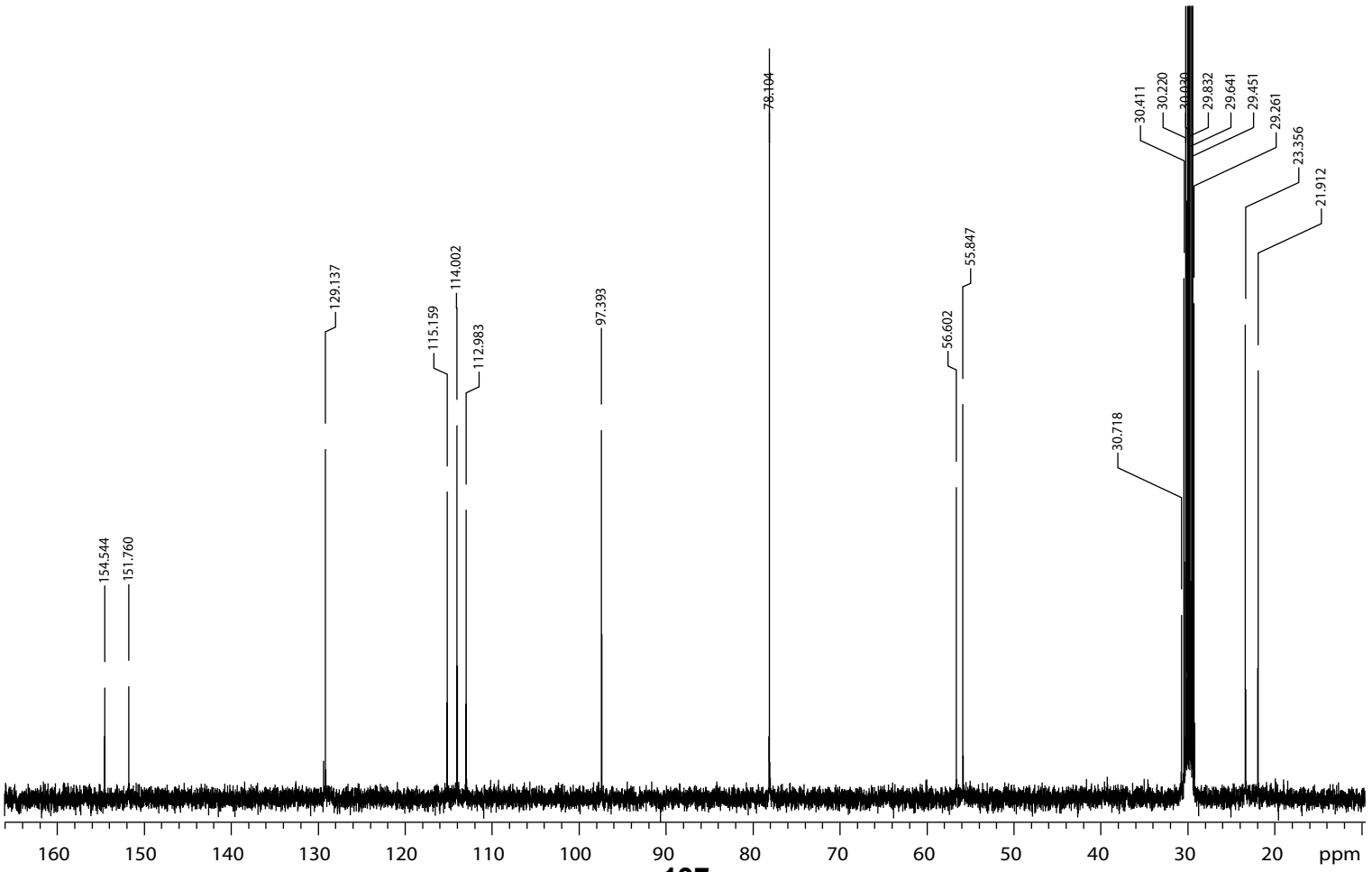

OH
O
O
OPh
OMe
$C_{17}H_{18}O_5$
Exact Mass: 302.1154
3.55d
7.260
7.256
7.006
6.998
6.975
6.966
6.953
6.950
6.947
6.944
6.777
6.769
6.747
6.050
4.884
4.130
4.116
4.104
4.100
3.651
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
ppm
2.30
3.42
0.96
1.80
0.89
0.98
4.10
3.00

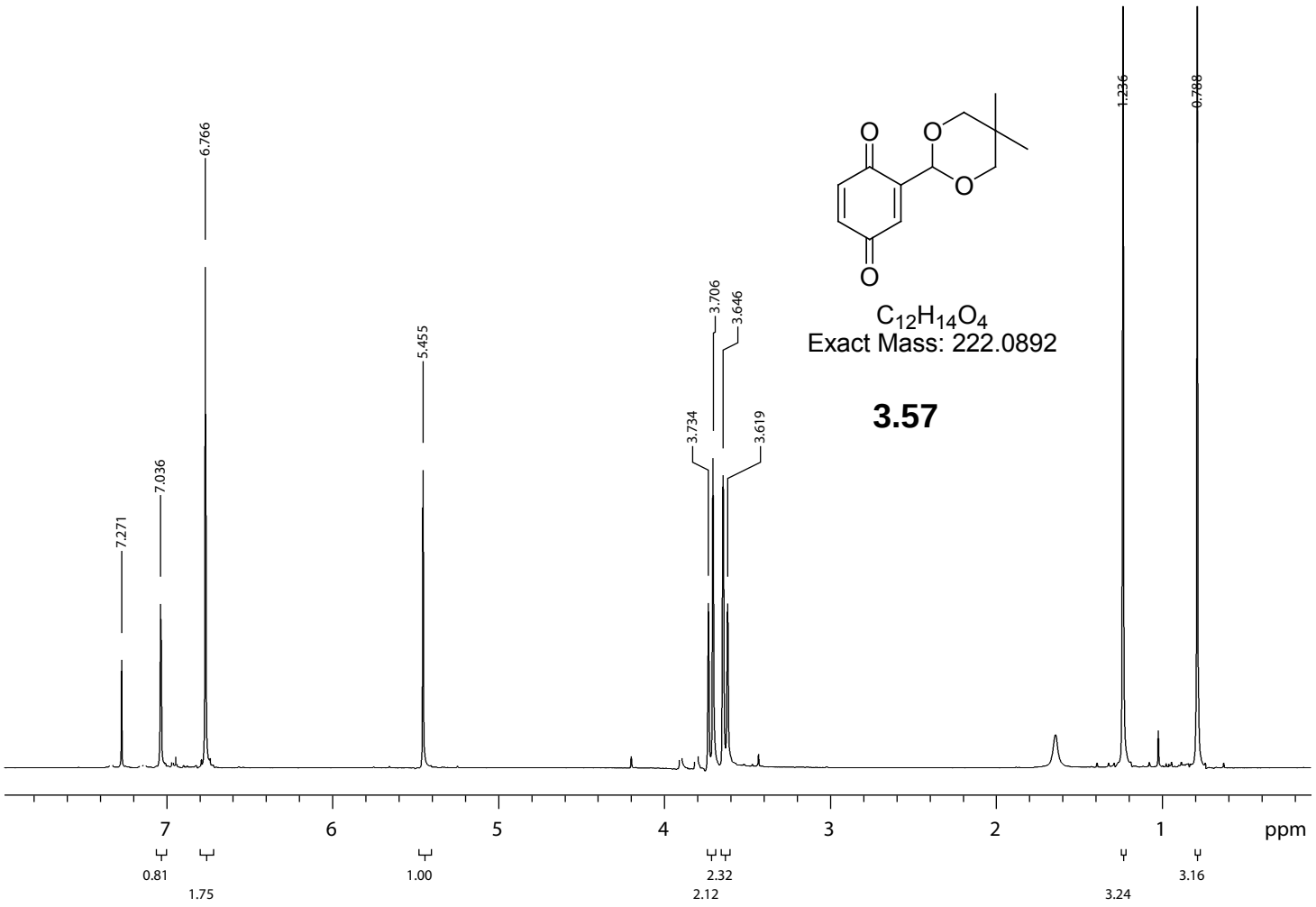

153.008
149.880
129.359
123.052
121.037
116.451
116.289
114.502
114.421
112.604
101.315
74.728
68.303
67.058
54.985
170
160
150
140
130
120
110
100
90
80
70
60
ppm

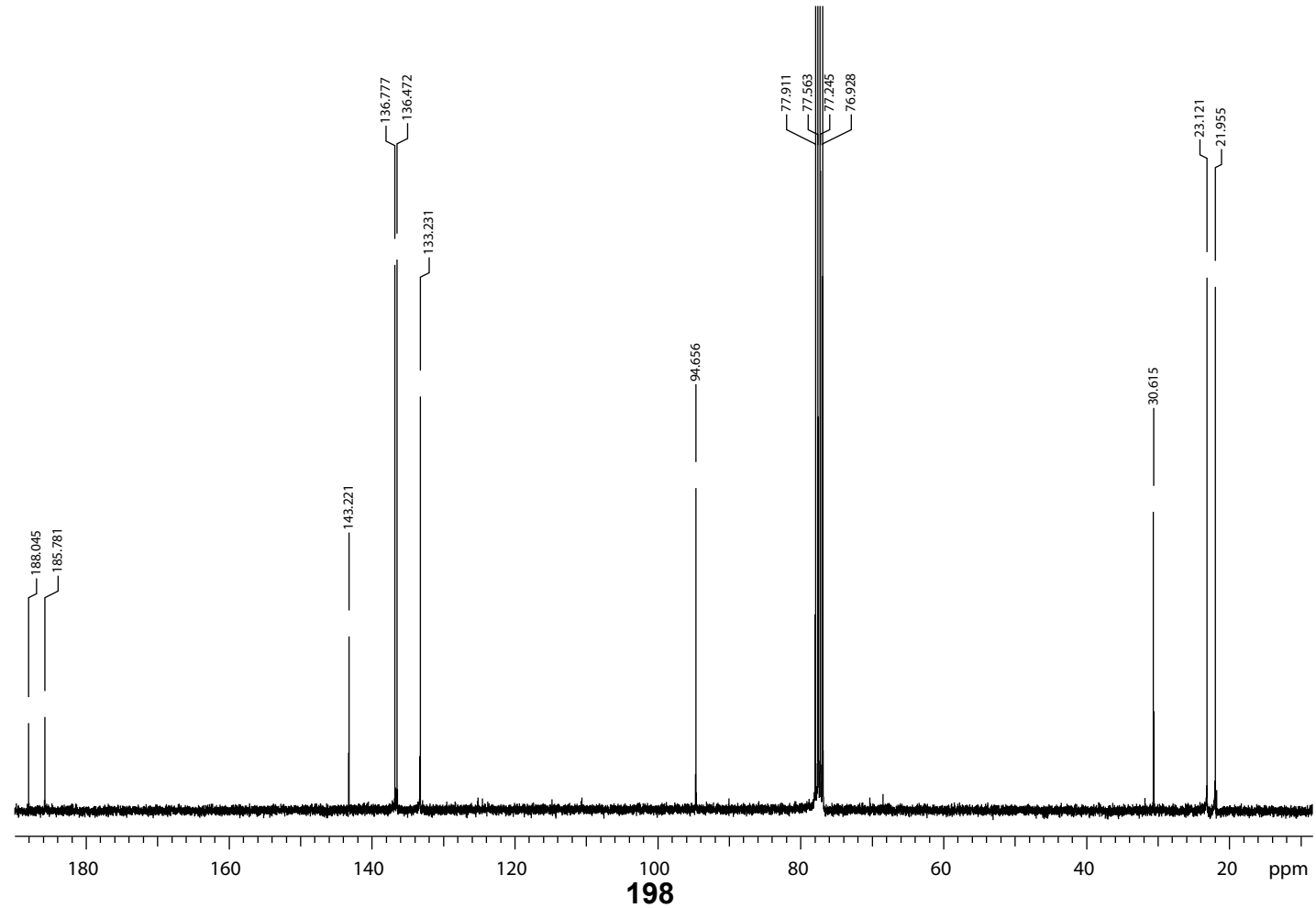

OH
O
Ph
O
OMe
$C_{17}H_{18}O_4$
Exact Mass: 286.1205
3.55e
7.329
7.311
7.290
7.270
7.250
7.055
7.049
6.769
6.747
5.892
4.896
4.263
4.252
4.237
4.226
4.115
4.111
4.098
4.086
4.082
4.062
4.058
3.730
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
ppm
4.94
0.91
1.87
1.00
2.10
2.88
3.08

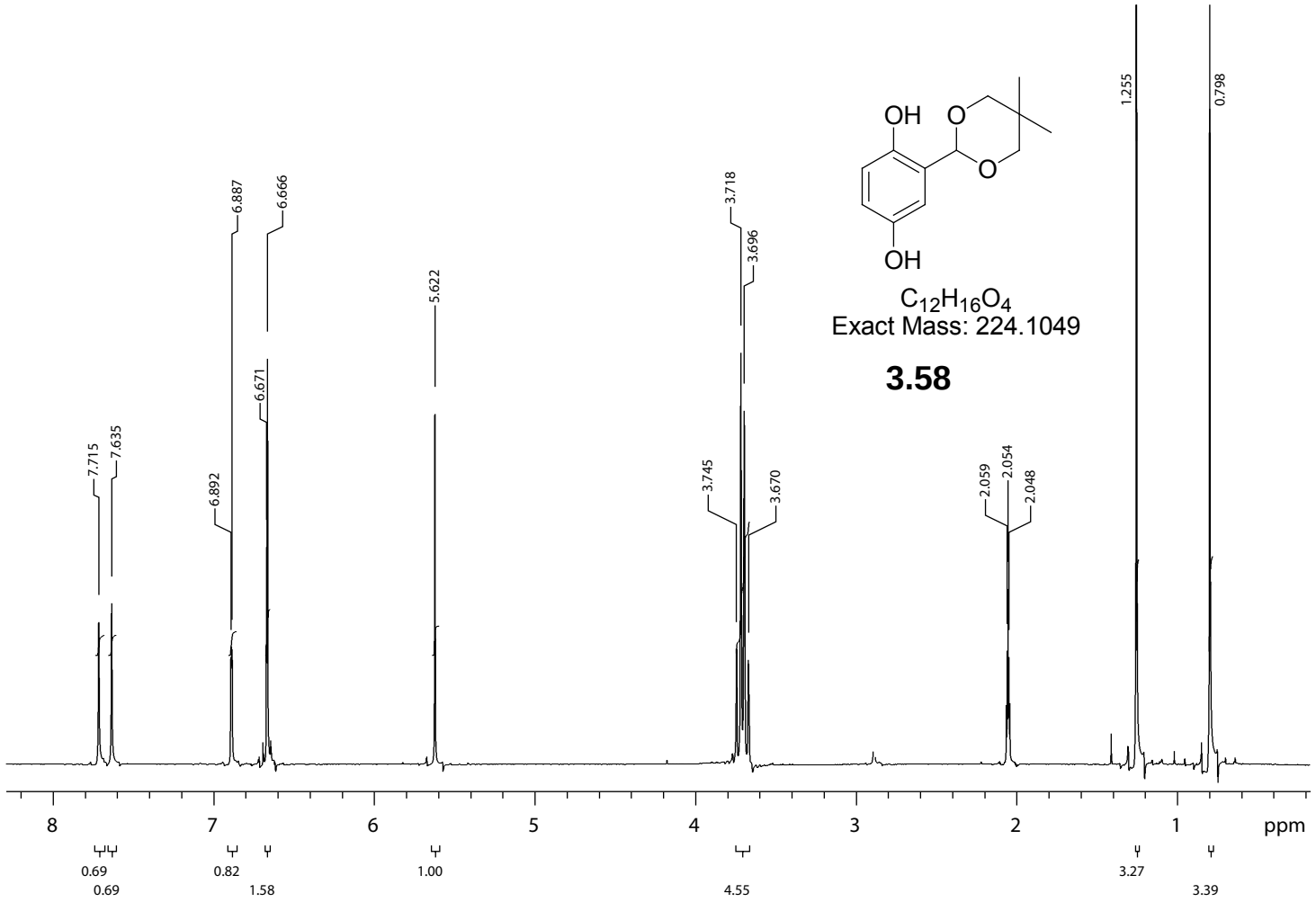

153.023
148.693
137.843
128.641
127.704
127.264
124.927
116.253
115.667
112.128
98.216
72.245
60.362
54.985
160
150
140
130
120
110
100
90
80
70
60
ppm

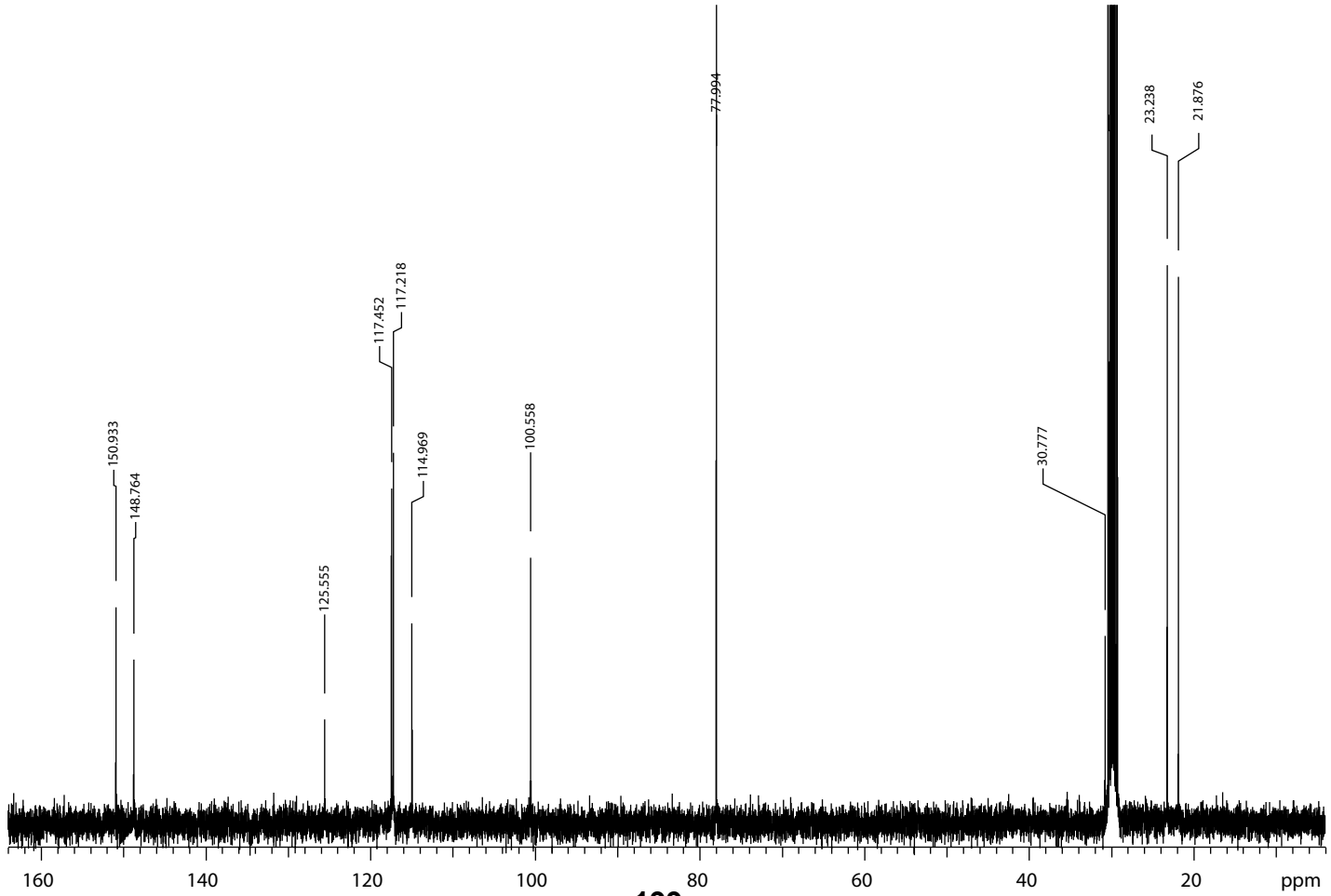

7.356
7.169
7.161
6.920
6.899
6.882
6.875
5.693
3.766
3.746
3.690
3.664
3.645
3.619
2.057
2.051
2.046
1.268
0.781
OMe
O
O
OMe
$C_{14}H_{20}O_4$
Exact Mass: 252.1362
3.56
8
7
6
5
4
3
2
1
ppm
0.87
1.91
1.00
3.04
4.28
3.10
3.27
3.15

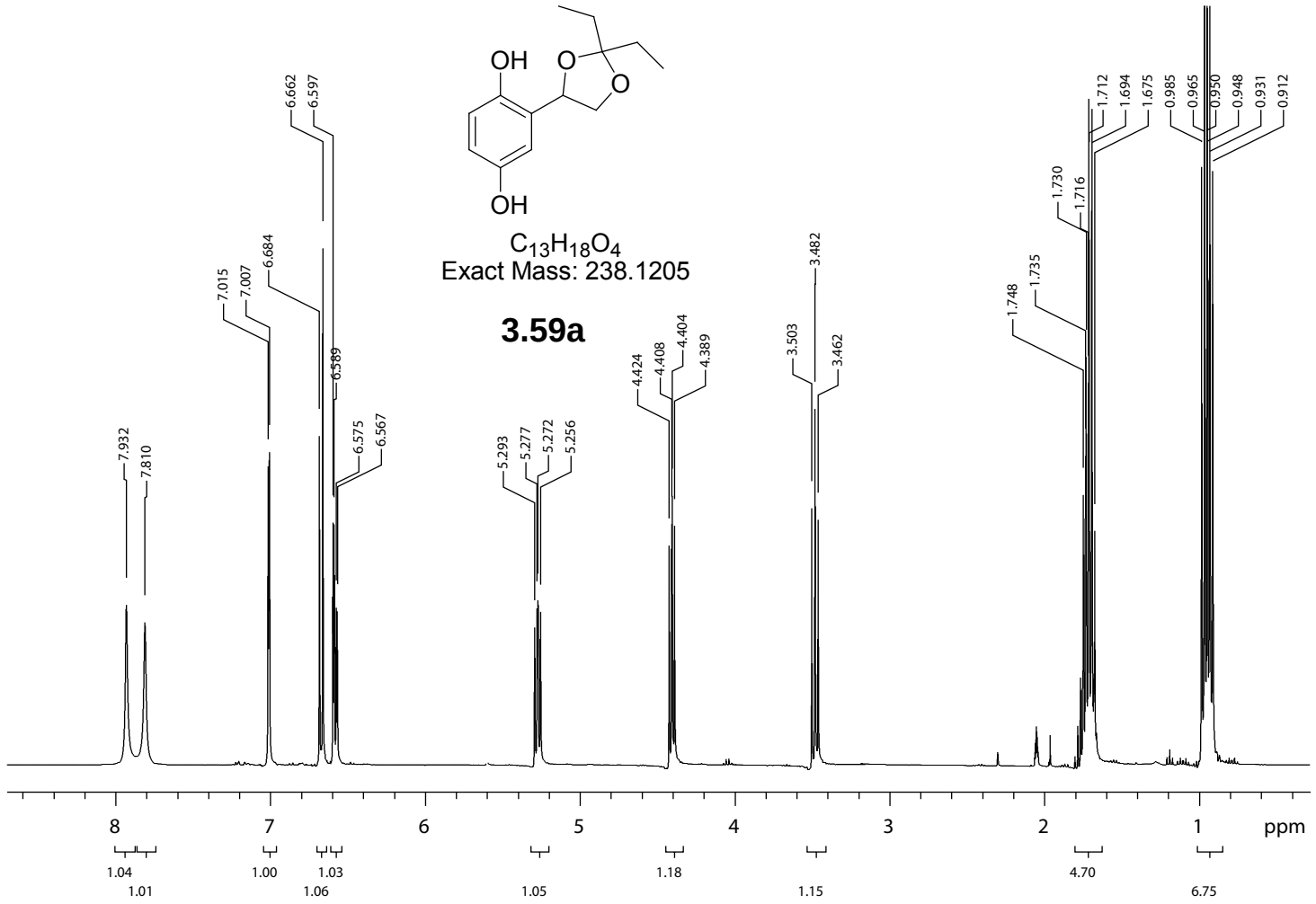

154.544
151.760
129.137
115.159
114.002
112.983
97.393
78.104
56.602
55.847
30.718
30.411
30.220
30.030
29.832
29.641
29.451
29.261
23.356
21.912
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

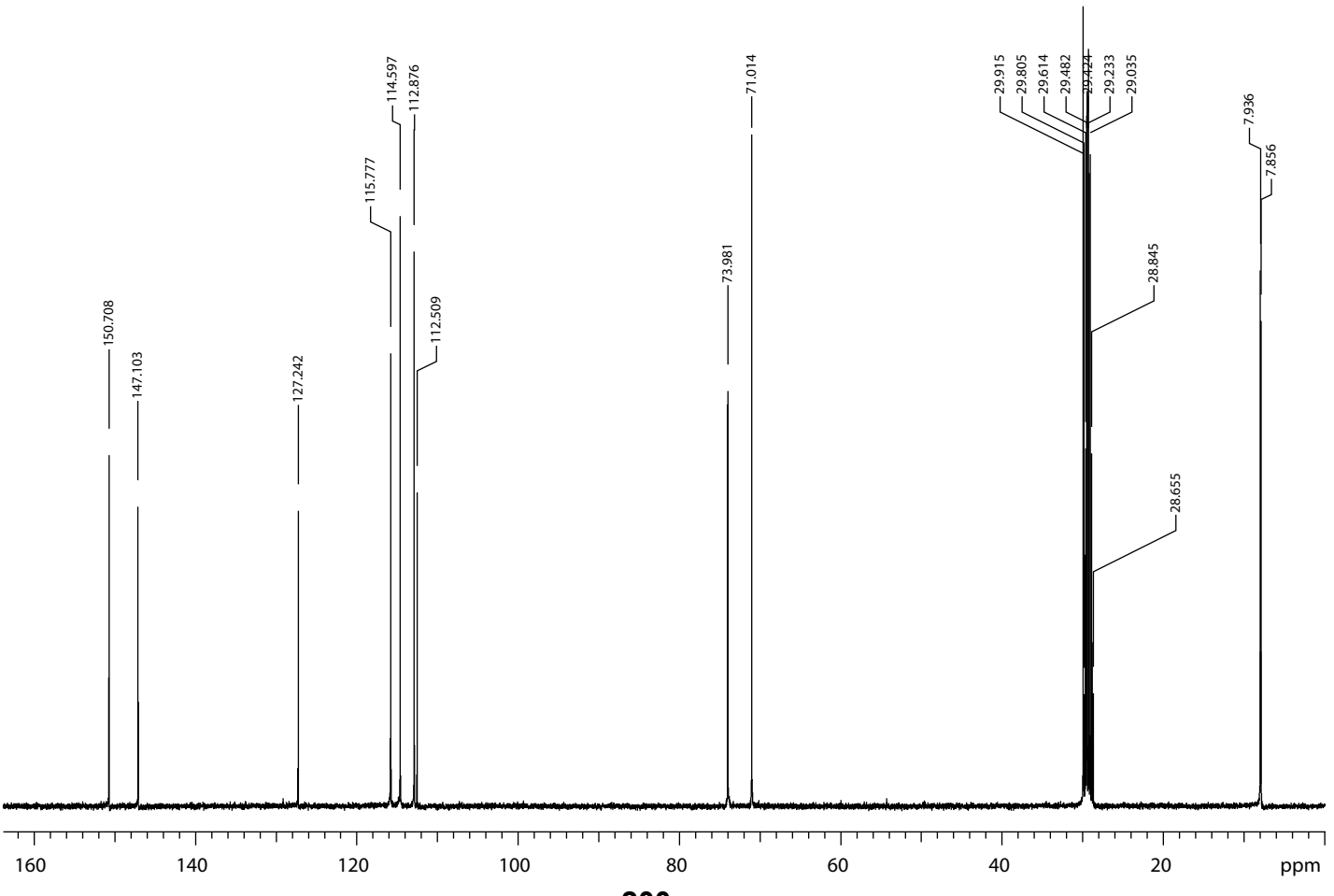

7.271
7.036
6.766
5.455
3.734
3.706
3.646
3.619
1.236
0.788
O
O
O
O
$C_{12}H_{14}O_4$
Exact Mass: 222.0892
3.57
7
6
5
4
3
2
1
ppm
0.81
1.75
1.00
2.32
2.12
3.24
3.16

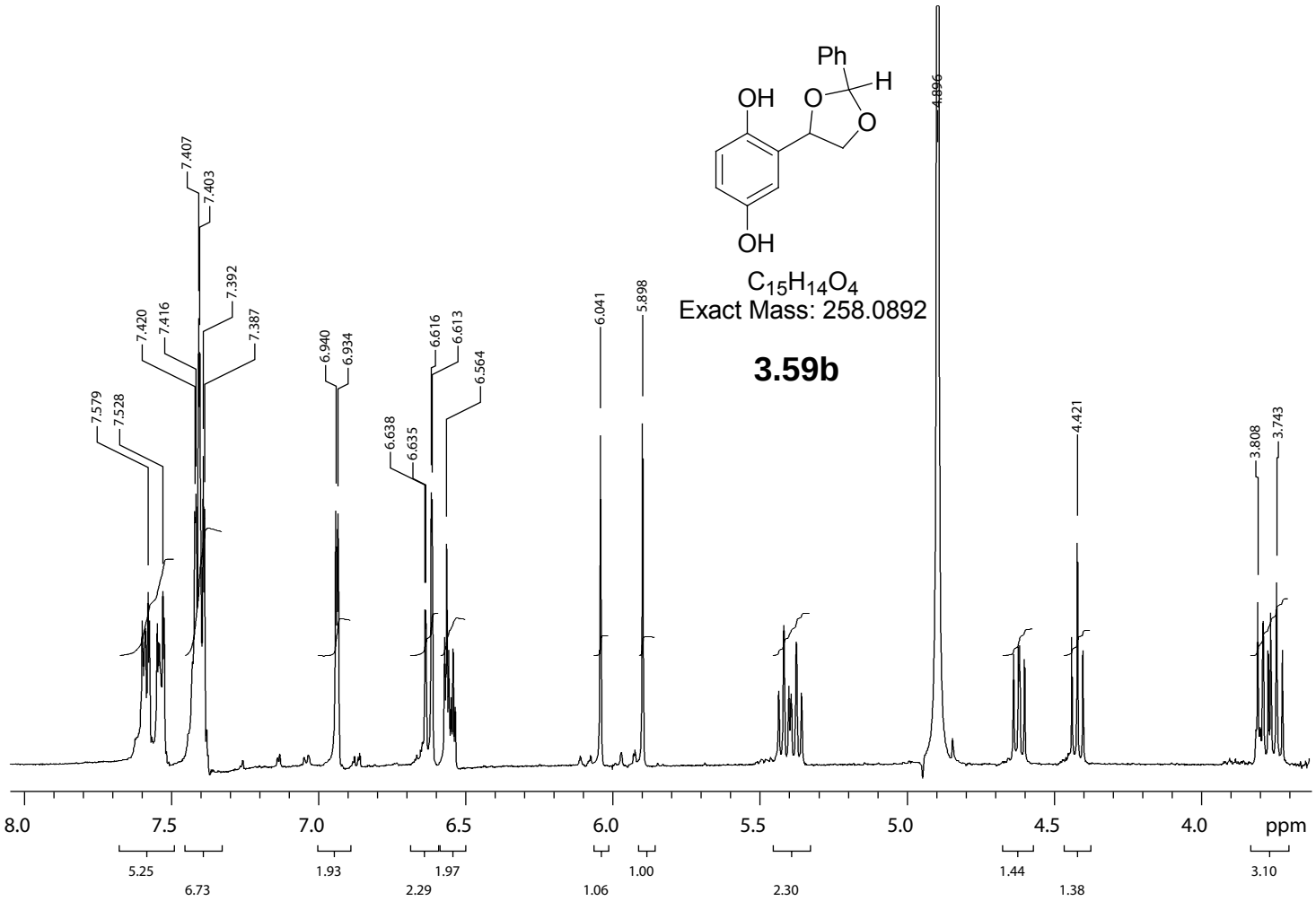

188.045
185.781
143.221
136.777
136.472
133.231
94.656
77.911
77.563
77.245
76.928
30.615
23.121
21.955
180
160
140
120
100
80
60
40
20
ppm

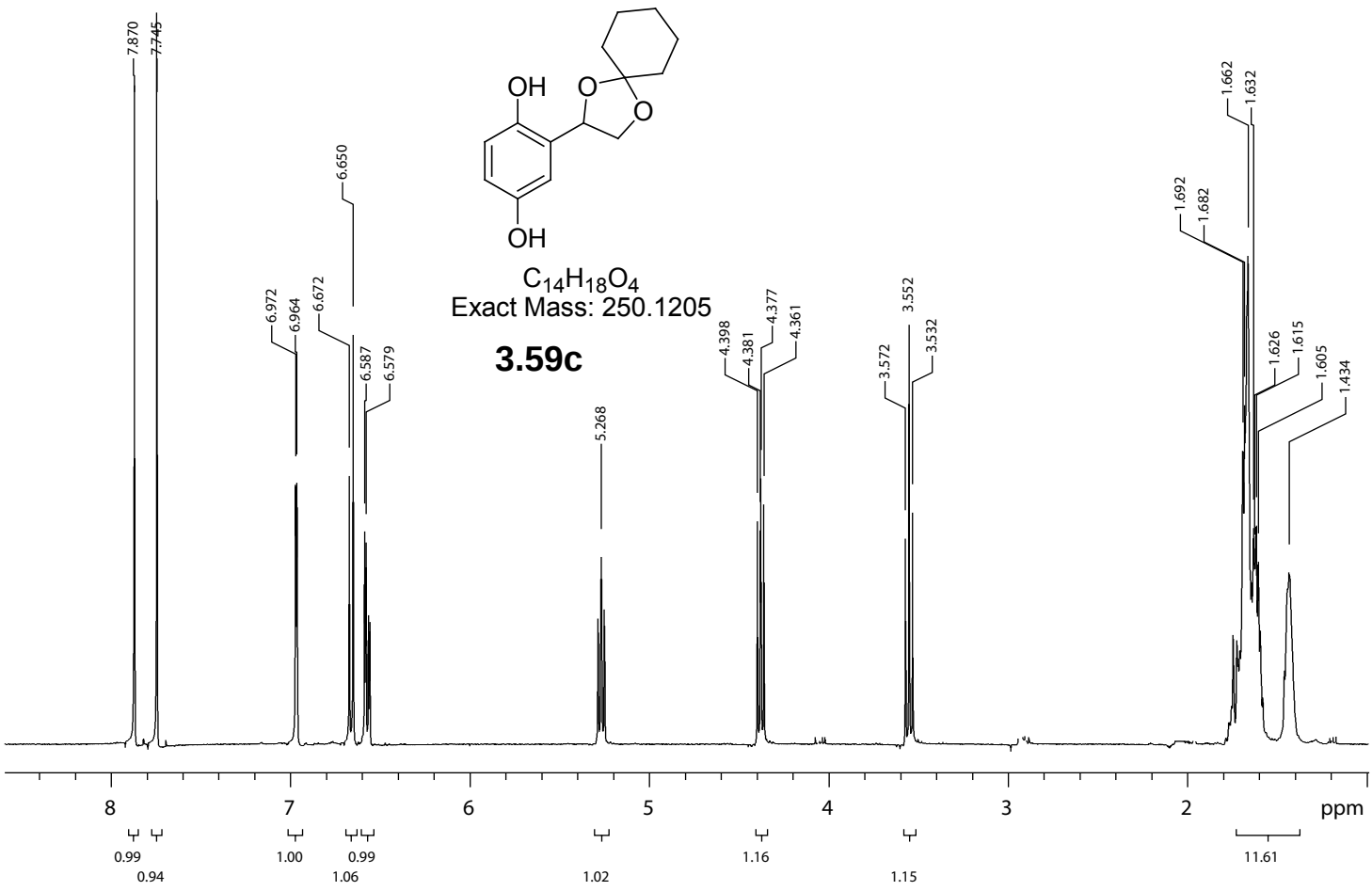

OH
O
O
OH
$C_{12}H_{16}O_4$
Exact Mass: 224.1049
3.58
7.715
7.635
6.892
6.887
6.671
6.666
5.622
3.745
3.718
3.696
3.670
2.059
2.054
2.048
1.255
0.798
8
7
6
5
4
3
2
1
ppm
0.69
0.69
0.82
1.58
1.00
4.55
3.27
3.39

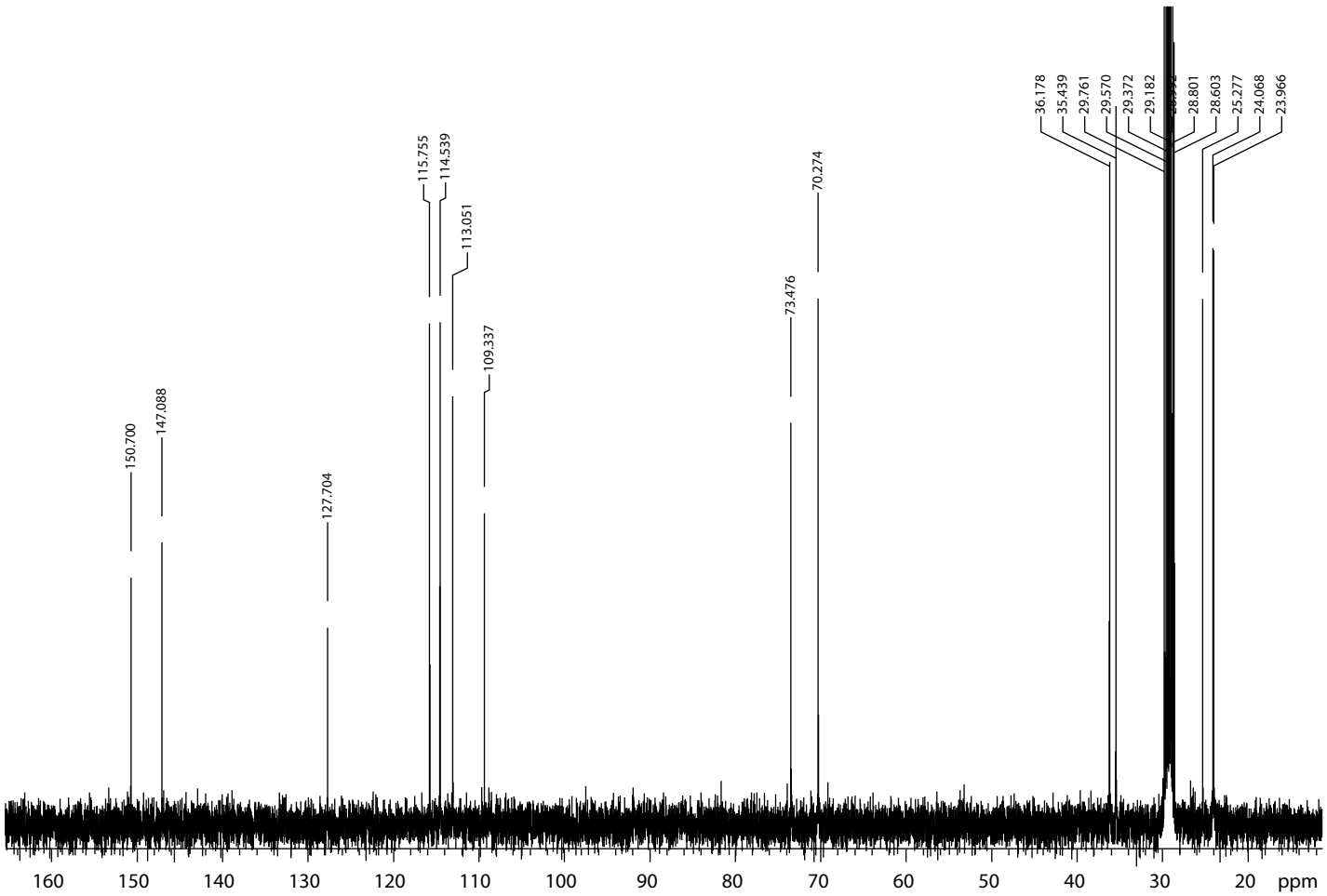

150.933
148.764
125.555
117.452
117.218
114.969
100.558
77.994
30.777
23.238
21.876
160
140
120
100
80
60
40
20
ppm

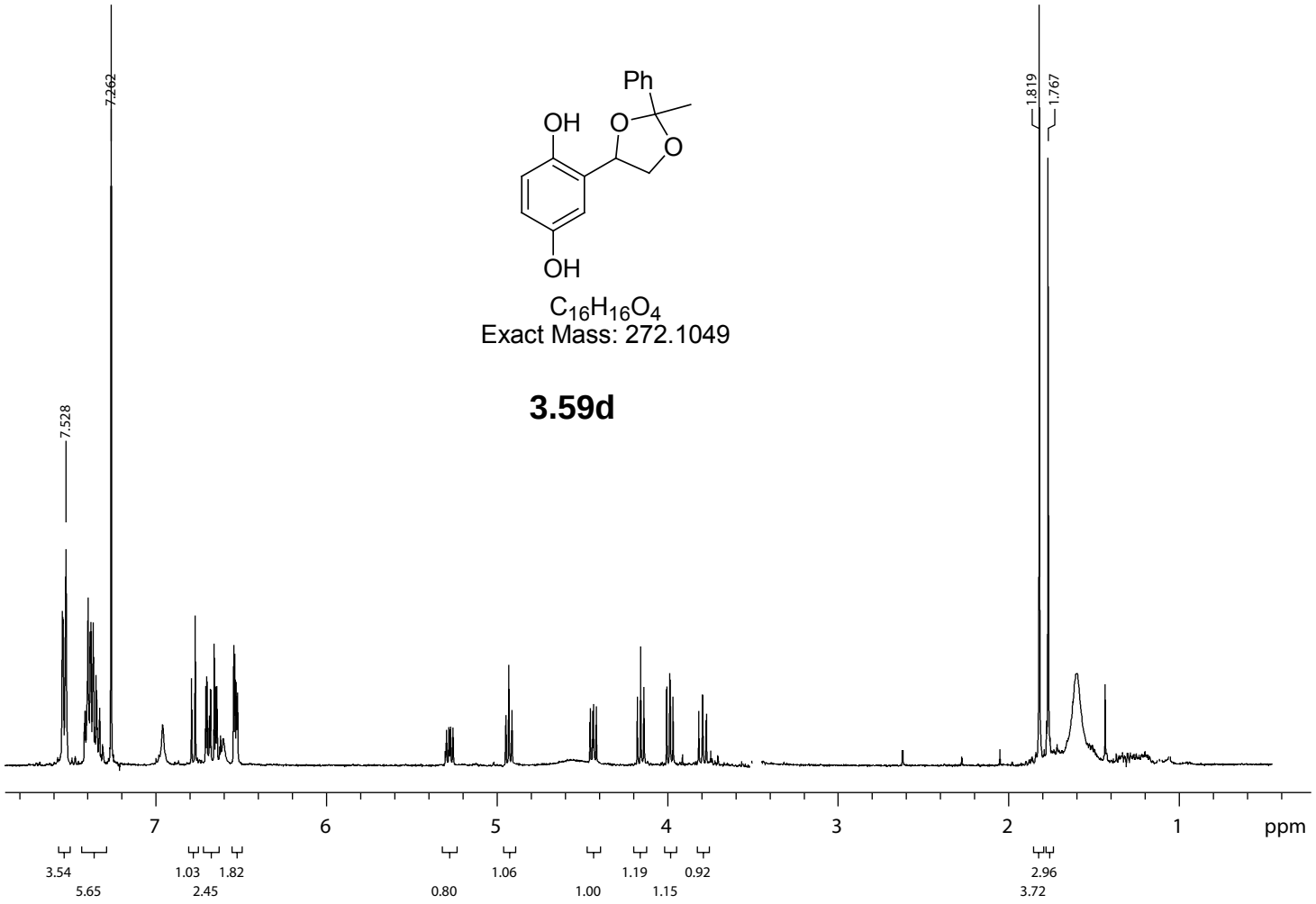

OH
O
O
OH
$C_{13}H_{18}O_4$
Exact Mass: 238.1205
3.59a
7.932
7.810
7.015
7.007
6.684
6.662
6.597
6.589
6.575
6.567
5.293
5.277
5.272
5.256
4.424
4.408
4.404
4.389
3.503
3.482
3.462
1.748
1.735
1.730
1.716
1.712
1.694
1.675
0.985
0.965
0.950
0.948
0.931
0.912
8
7
6
5
4
3
2
1
ppm
1.04
1.01
1.00
1.03
1.06
1.05
1.18
1.15
4.70
6.75


150.708
147.103
127.242
115.777
114.597
112.876
112.509
73.981
71.014
29.915
29.805
29.614
29.482
29.424
29.233
29.035
28.845
28.655
7.936
7.856
160
140
120
100
80
60
40
20
ppm


Ph
H
OH
O
O
OH
$C_{15}H_{14}O_4$
Exact Mass: 258.0892
3.59b
7.579
7.528
7.420
7.416
7.407
7.403
7.392
7.387
6.940
6.934
6.638
6.635
6.616
6.613
6.564
6.041
5.898
4.896
4.421
3.808
3.743
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
ppm
5.25
6.73
1.93
2.29
1.97
1.06
1.00
2.30
1.44
1.38
3.10

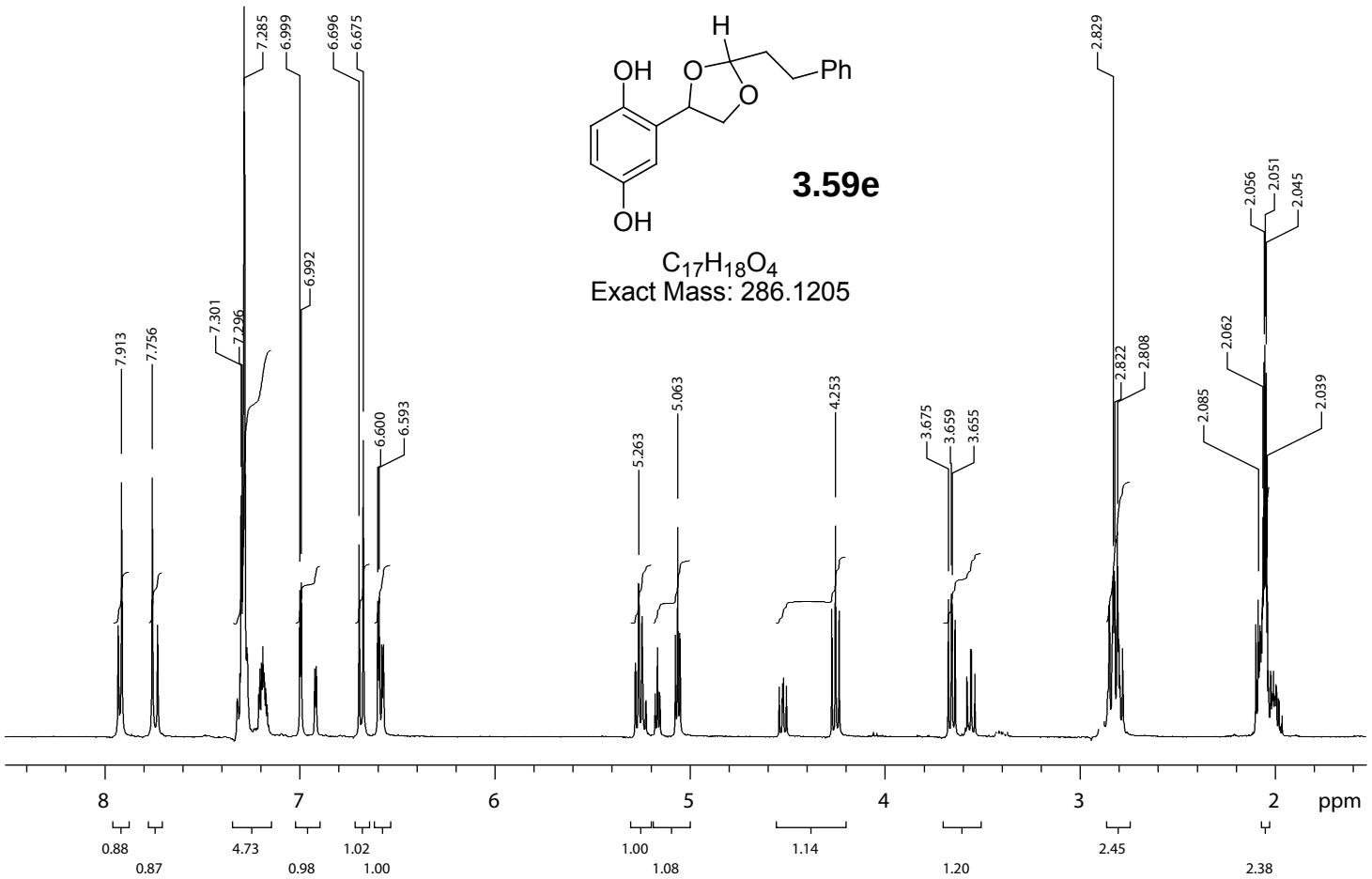

OH
O
O
OH
$C_{14}H_{18}O_4$
Exact Mass: 250.1205
3.59c
7.870
7.745
6.972
6.964
6.672
6.650
6.587
6.579
5.268
4.398
4.381
4.377
4.361
3.572
3.552
3.532
1.692
1.682
1.662
1.632
1.626
1.615
1.605
1.434
8
7
6
5
4
3
2
ppm
0.99
0.94
1.00
0.99
1.06
1.02
1.16
1.15
11.61

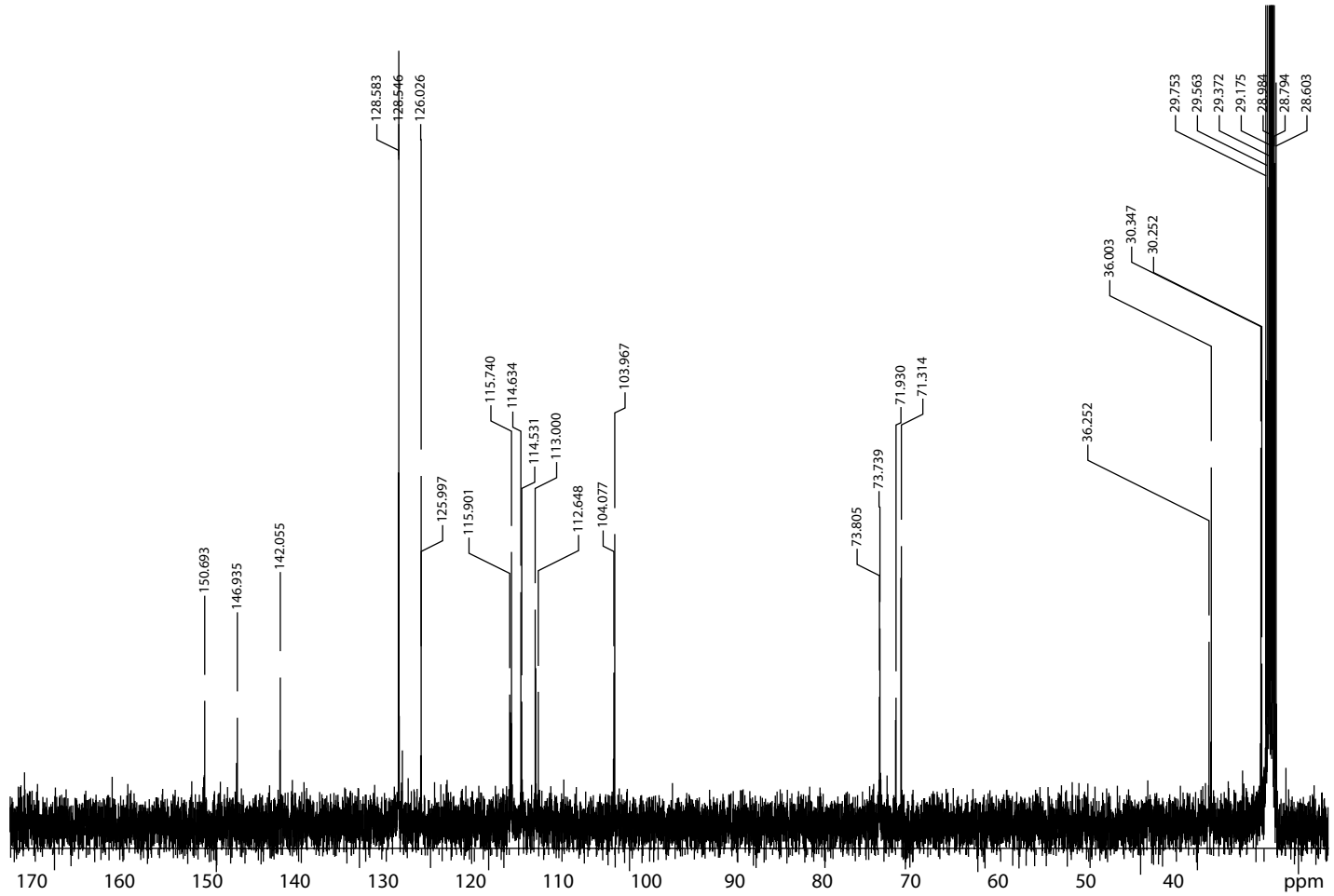

150.700
147.088
127.704
115.755
114.539
113.051
109.337
73.476
70.274
36.178
35.439
29.761
29.570
29.372
29.182
28.801
28.603
25.277
24.068
23.966
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

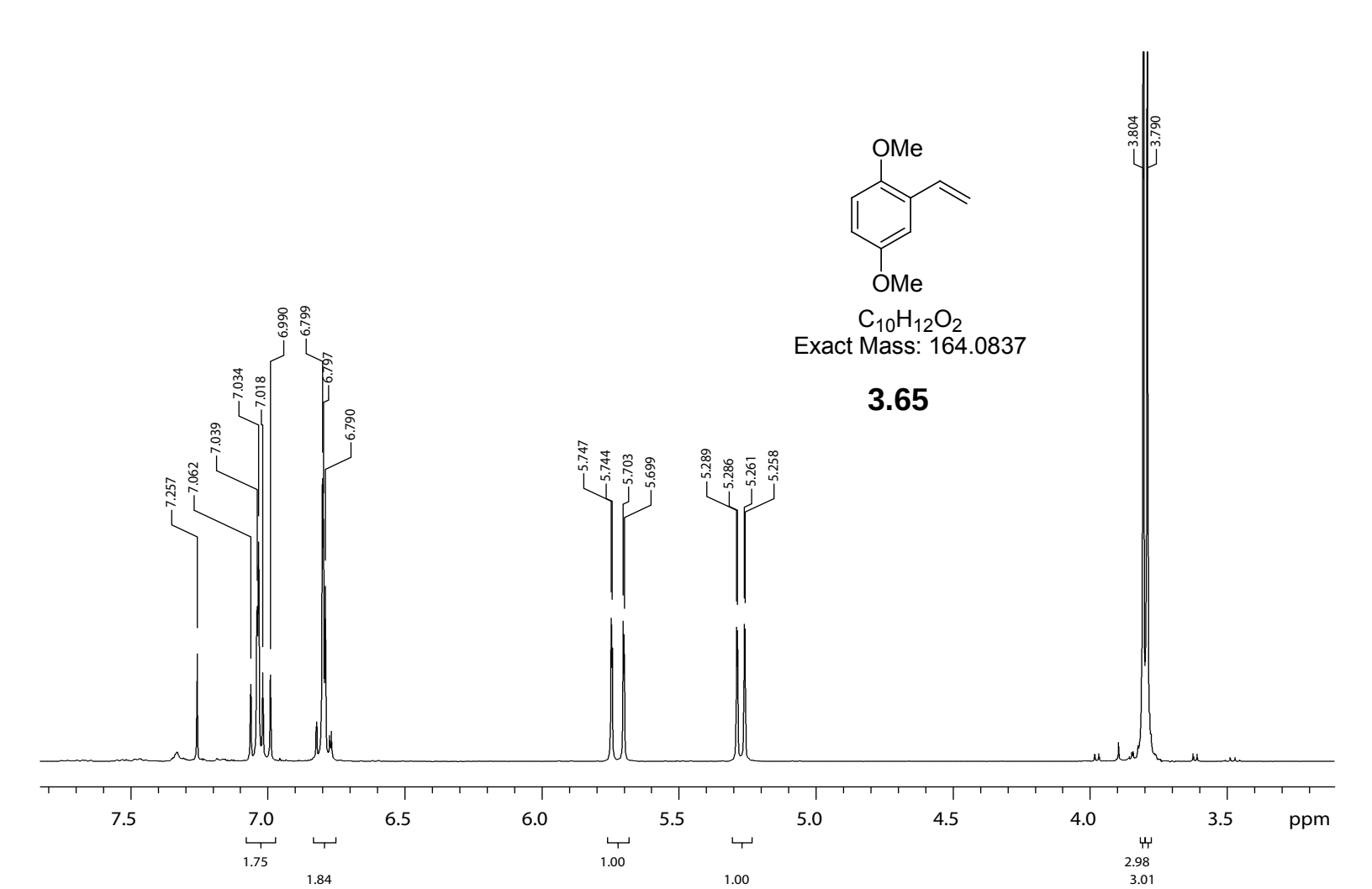


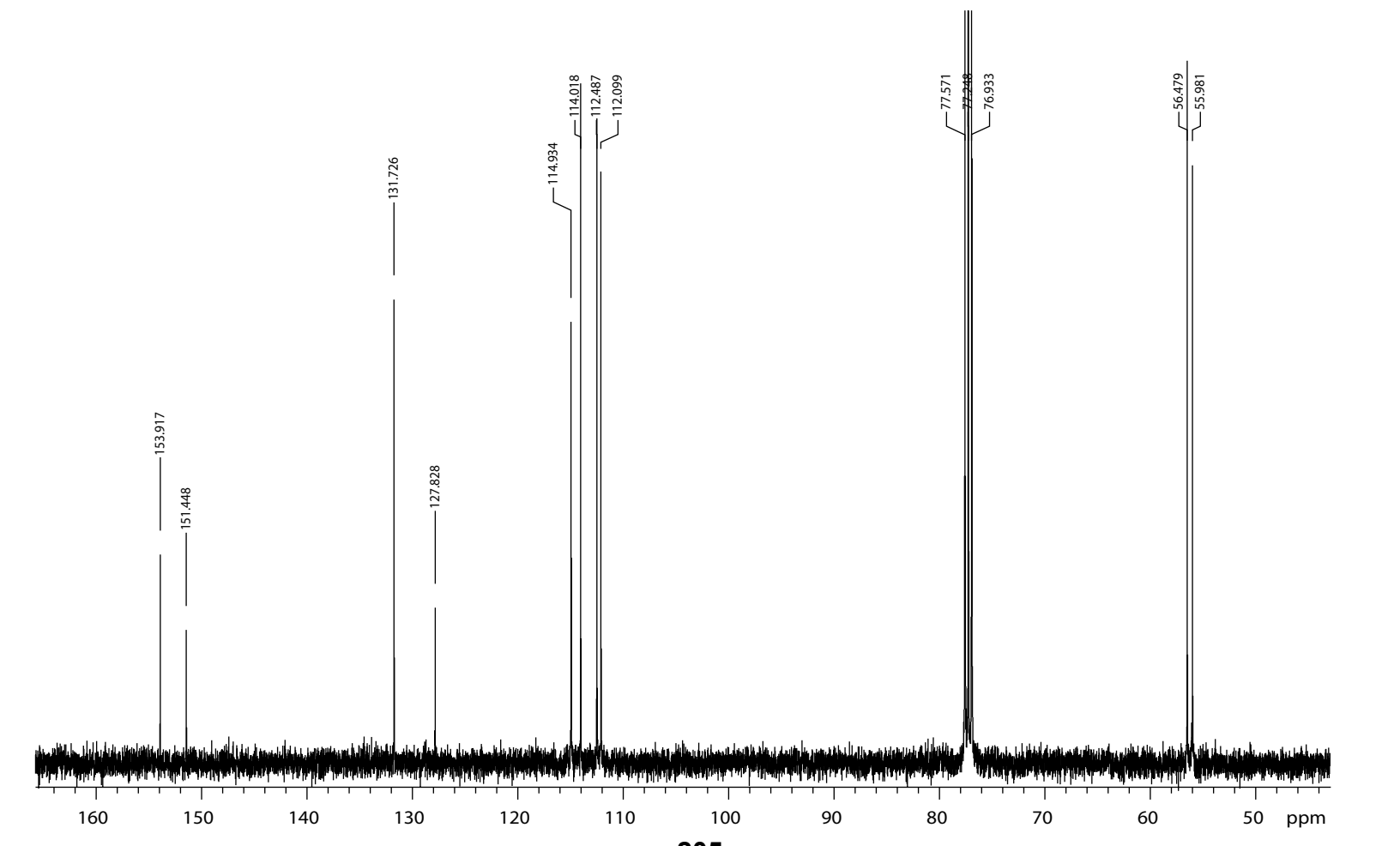
$C_{16}H_{16}O_4$
Exact Mass: 272.1049

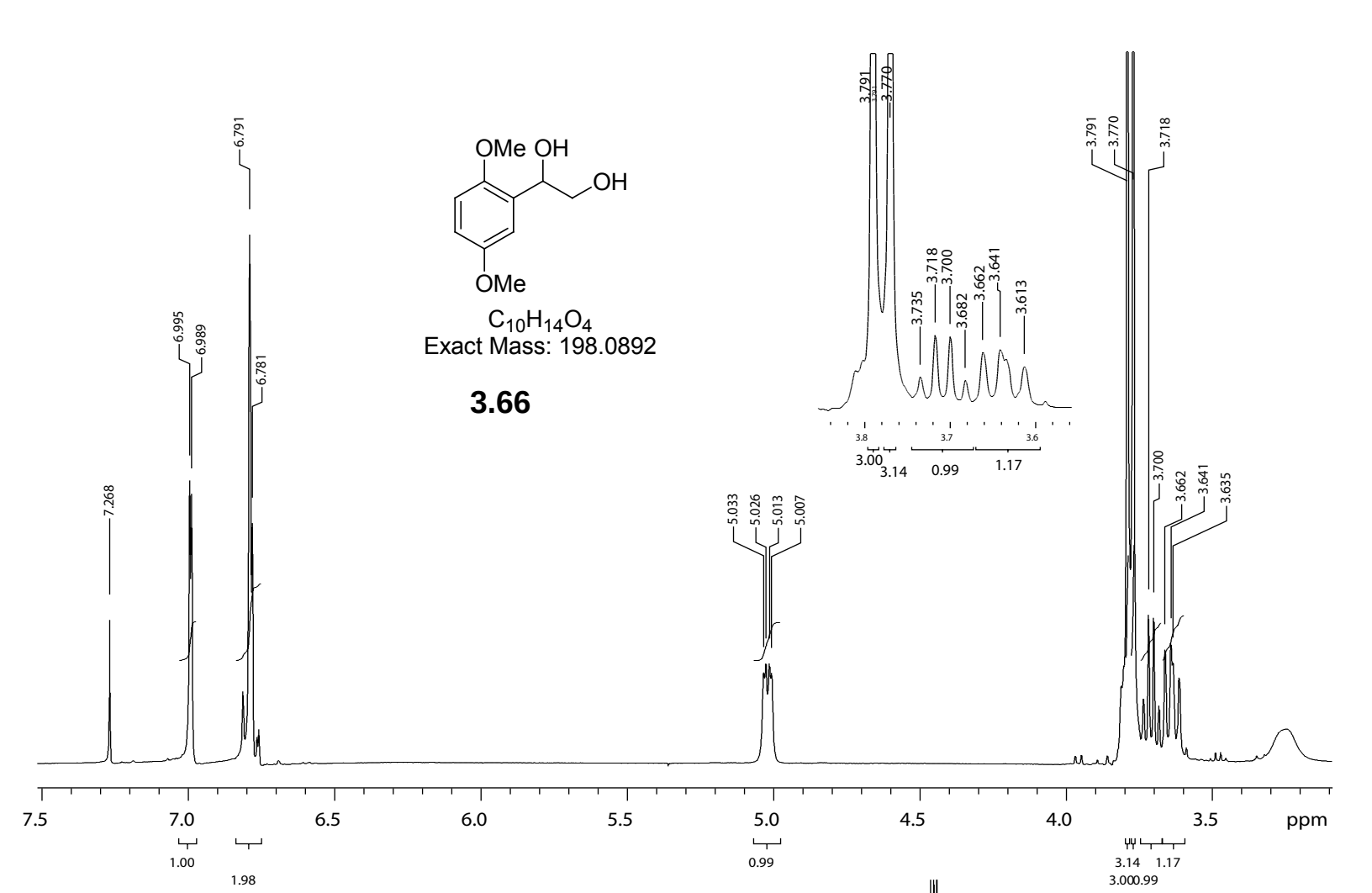
3.59d

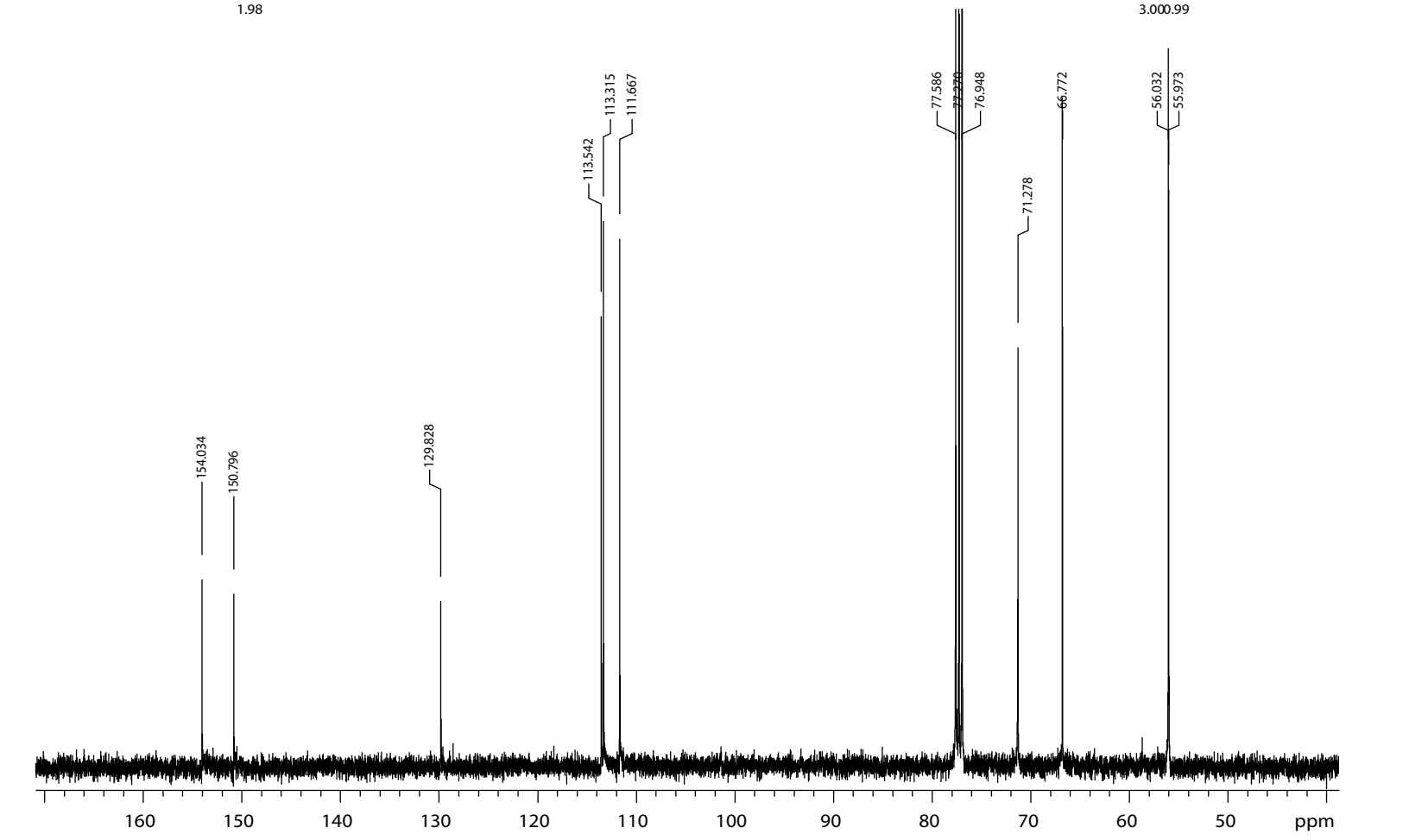

H
OH
O
O
Ph
OH
3.59e
C17H18O4
Exact Mass: 286.1205
7.913
7.756
7.301
7.296
7.285
6.999
6.992
6.696
6.675
6.600
6.593
5.263
5.063
4.253
3.675
3.659
3.655
2.829
2.822
2.808
2.085
2.062
2.056
2.051
2.045
2.039
8
7
6
5
4
3
2
ppm
0.88
0.87
4.73
0.98
1.02
1.00
1.00
1.08
1.14
1.20
2.45
2.38

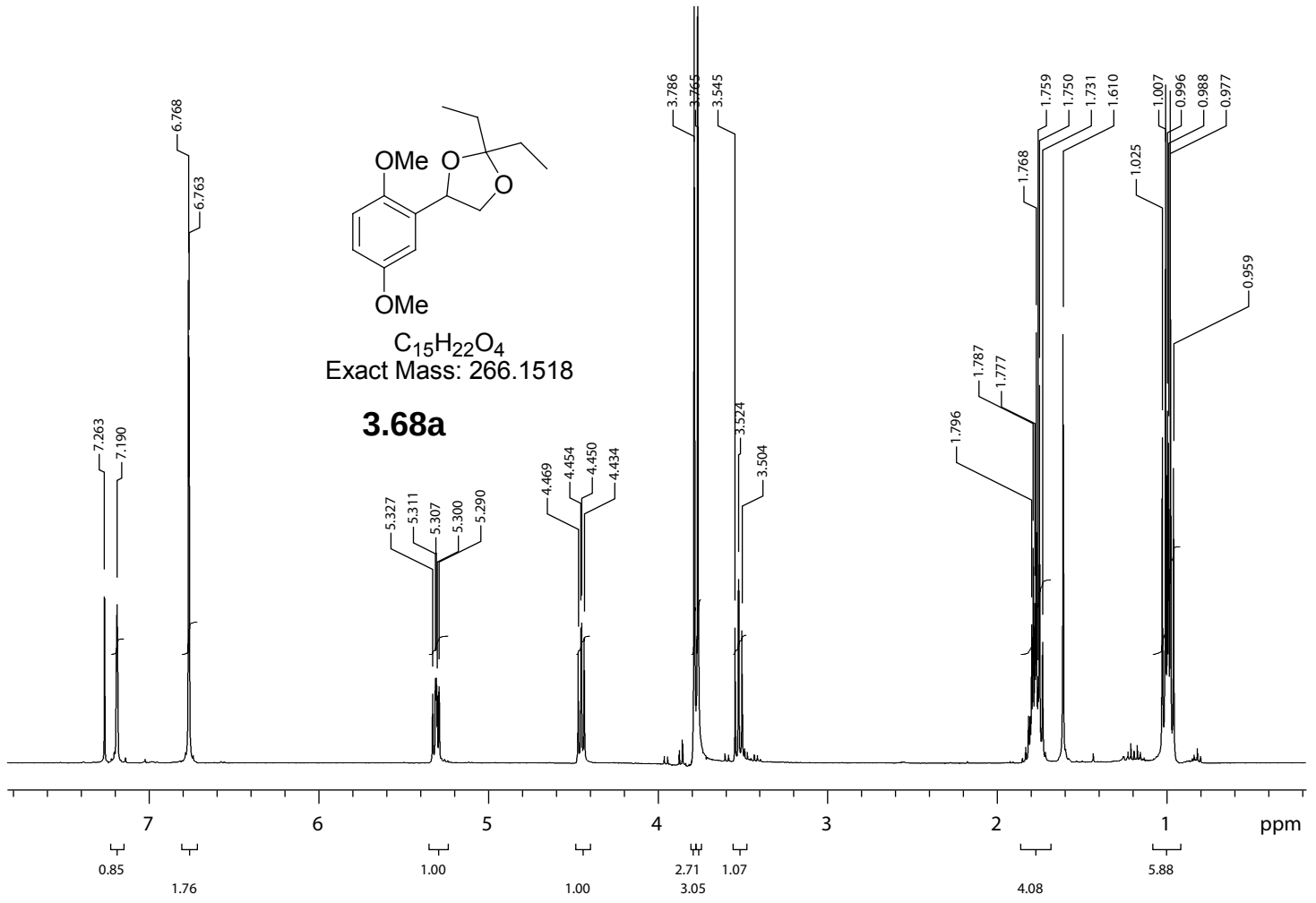

128.583
128.546
126.026
125.997
115.901
115.740
114.634
114.531
113.000
112.648
104.077
103.967
150.693
146.935
142.055
73.805
73.739
71.930
71.314
36.252
36.003
30.347
30.252
29.753
29.563
29.372
29.175
28.984
28.794
28.603
170
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm

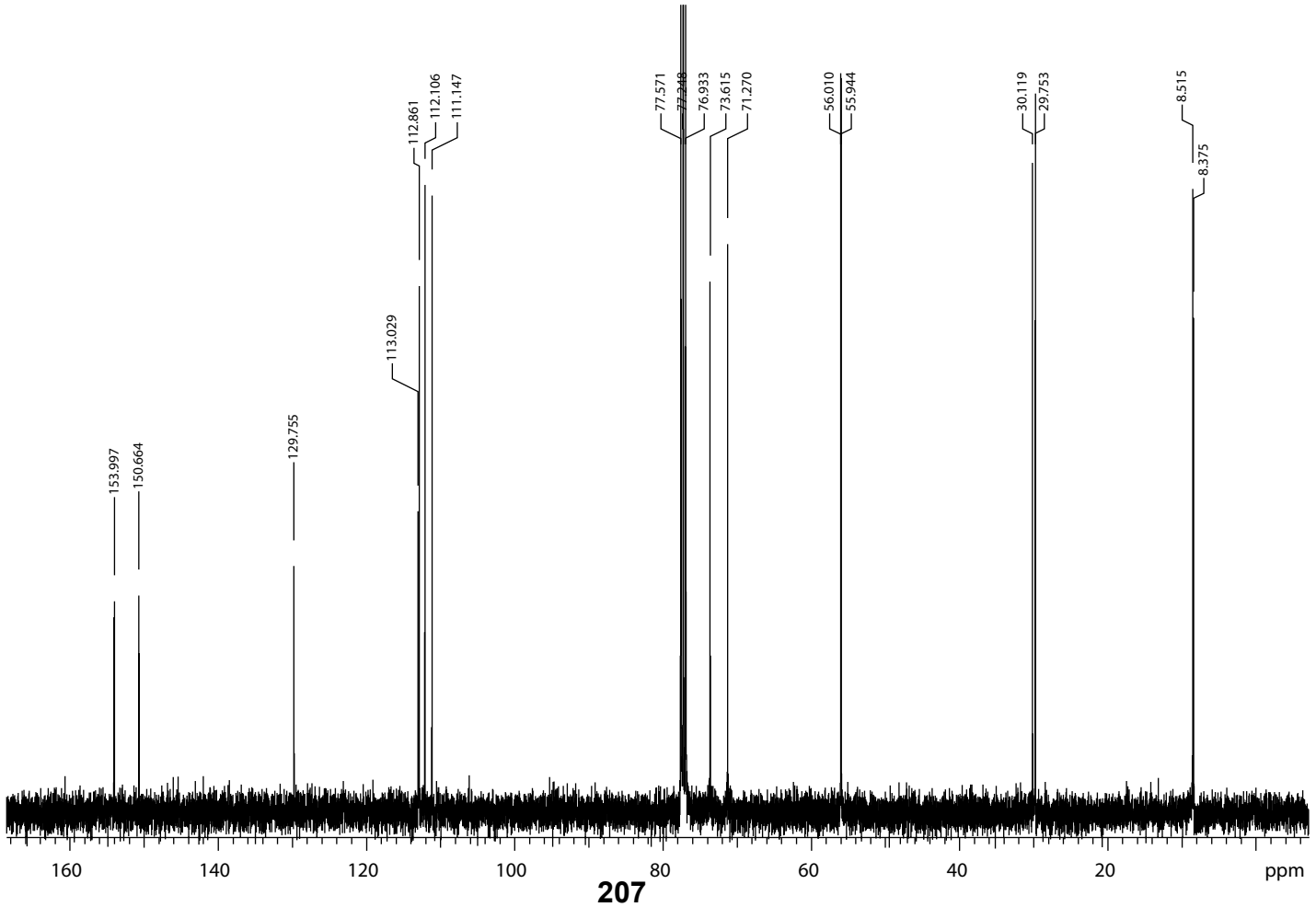

OMe
OMe
$C_{10}H_{12}O_2$
Exact Mass: 164.0837
3.65
7.257
7.062
7.039
7.034
7.018
6.990
6.799
6.797
6.790
5.747
5.744
5.703
5.699
5.289
5.286
5.261
5.258
3.804
3.790
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm
1.75
1.84
1.00
1.00
2.98
3.01

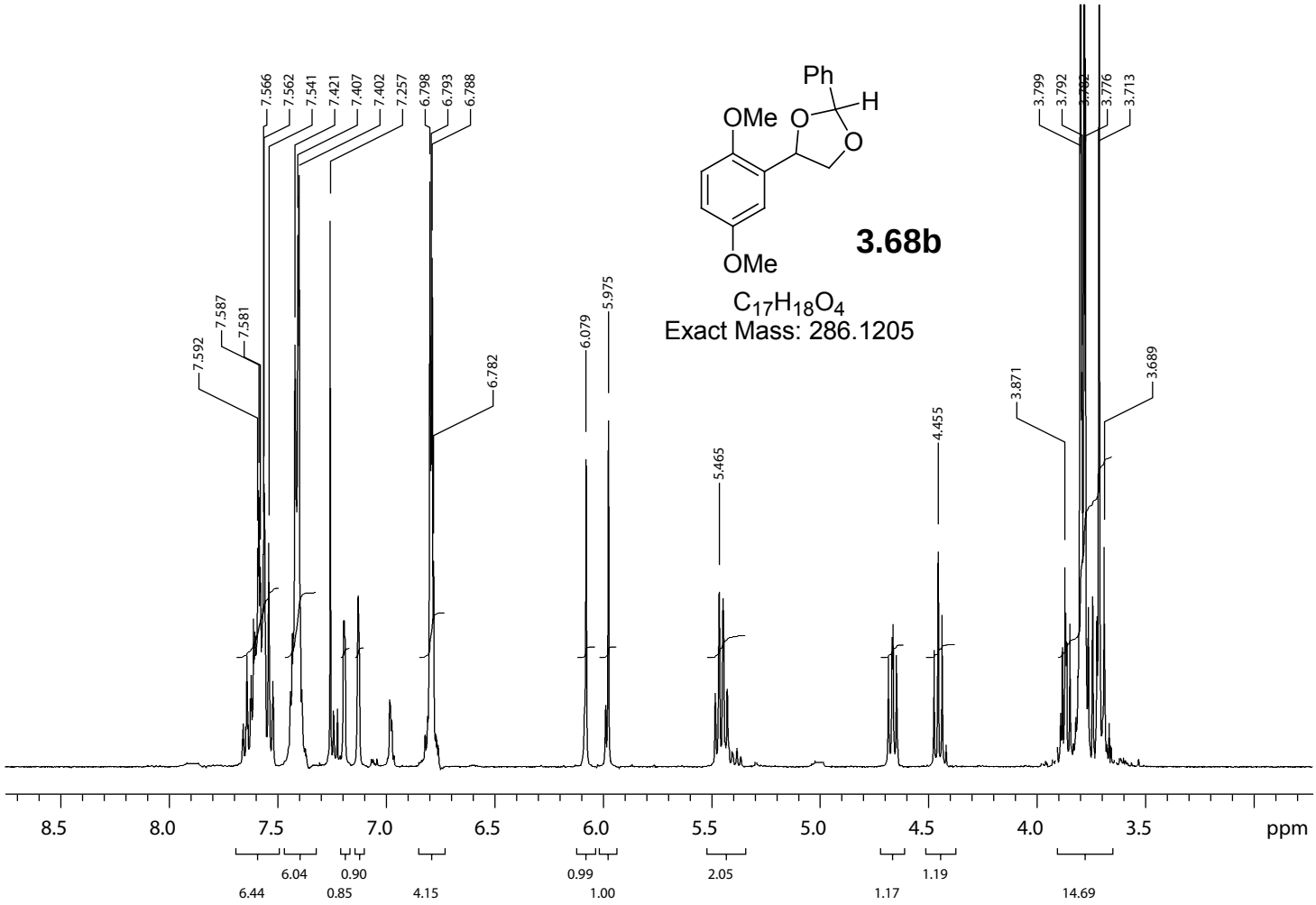

153.917
151.448
131.726
127.828
114.934
114.018
112.487
112.099
77.571
77.248
76.933
56.479
55.981
160
150
140
130
120
110
100
90
80
70
60
50
ppm

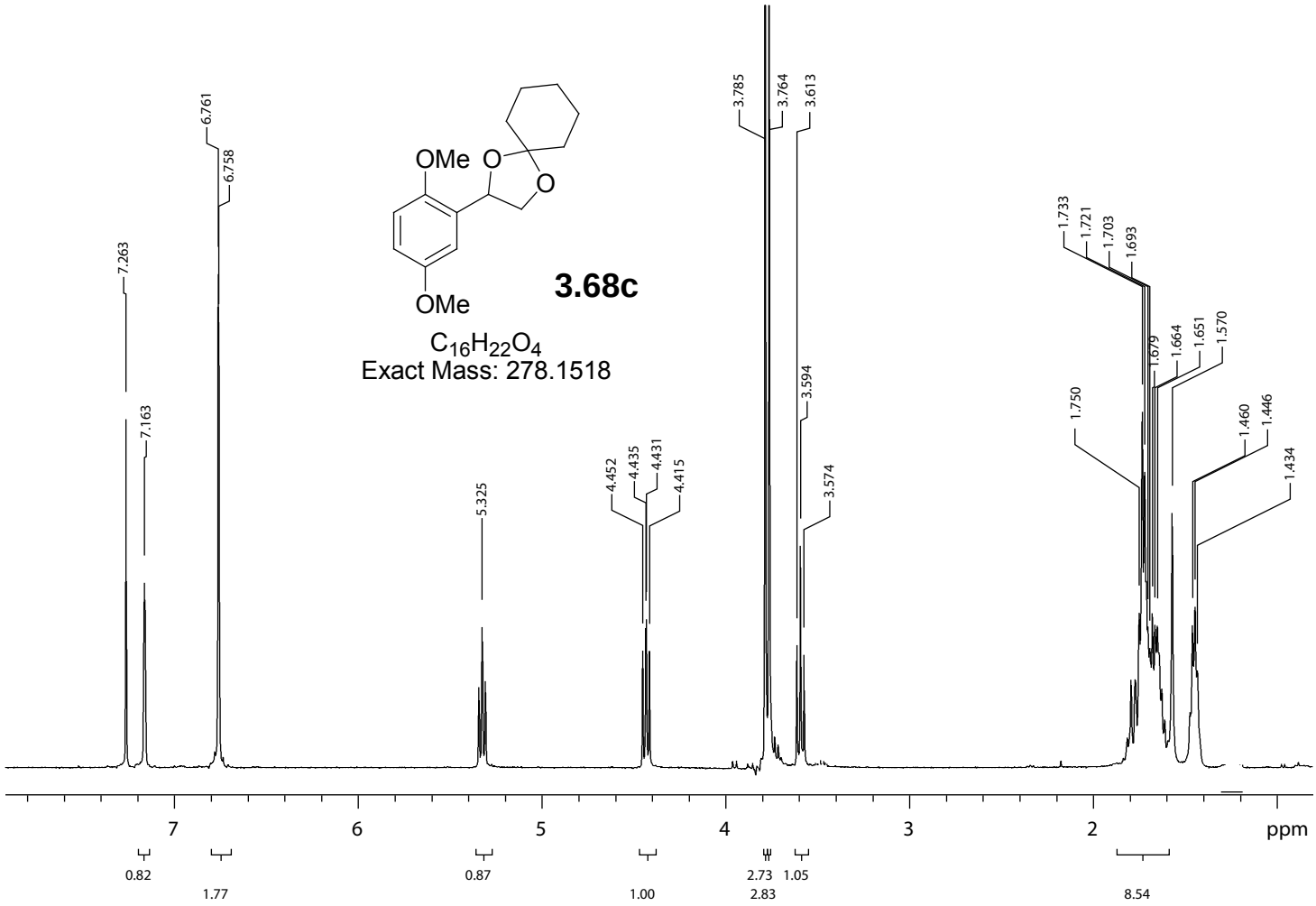

OMe OH
OH
OMe
$C_{10}H_{14}O_4$
Exact Mass: 198.0892
3.66
7.268
6.995
6.989
6.791
6.781
5.033
5.026
5.013
5.007
3.791
3.770
3.718
3.700
3.682
3.662
3.641
3.635
3.735
3.613
3.8
3.7
3.6
3.00
3.14
0.99
1.17
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm
1.00
1.98
0.99
3.14
1.17
3.00
0.99

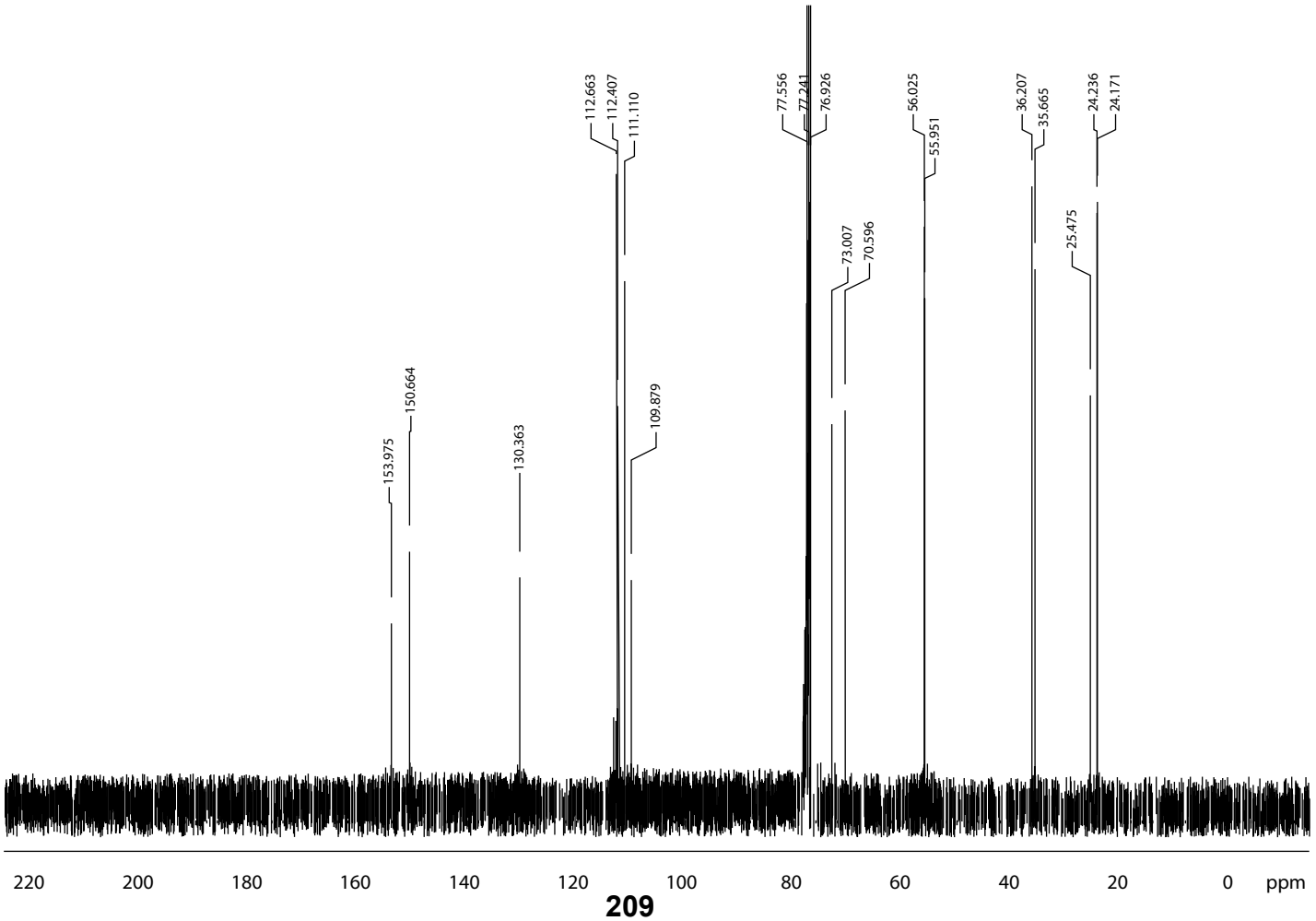

154.034
150.796
129.828
113.542
113.315
111.667
77.586
77.278
76.948
71.278
66.772
56.032
55.973
160
150
140
130
120
110
100
90
80
70
60
50
ppm

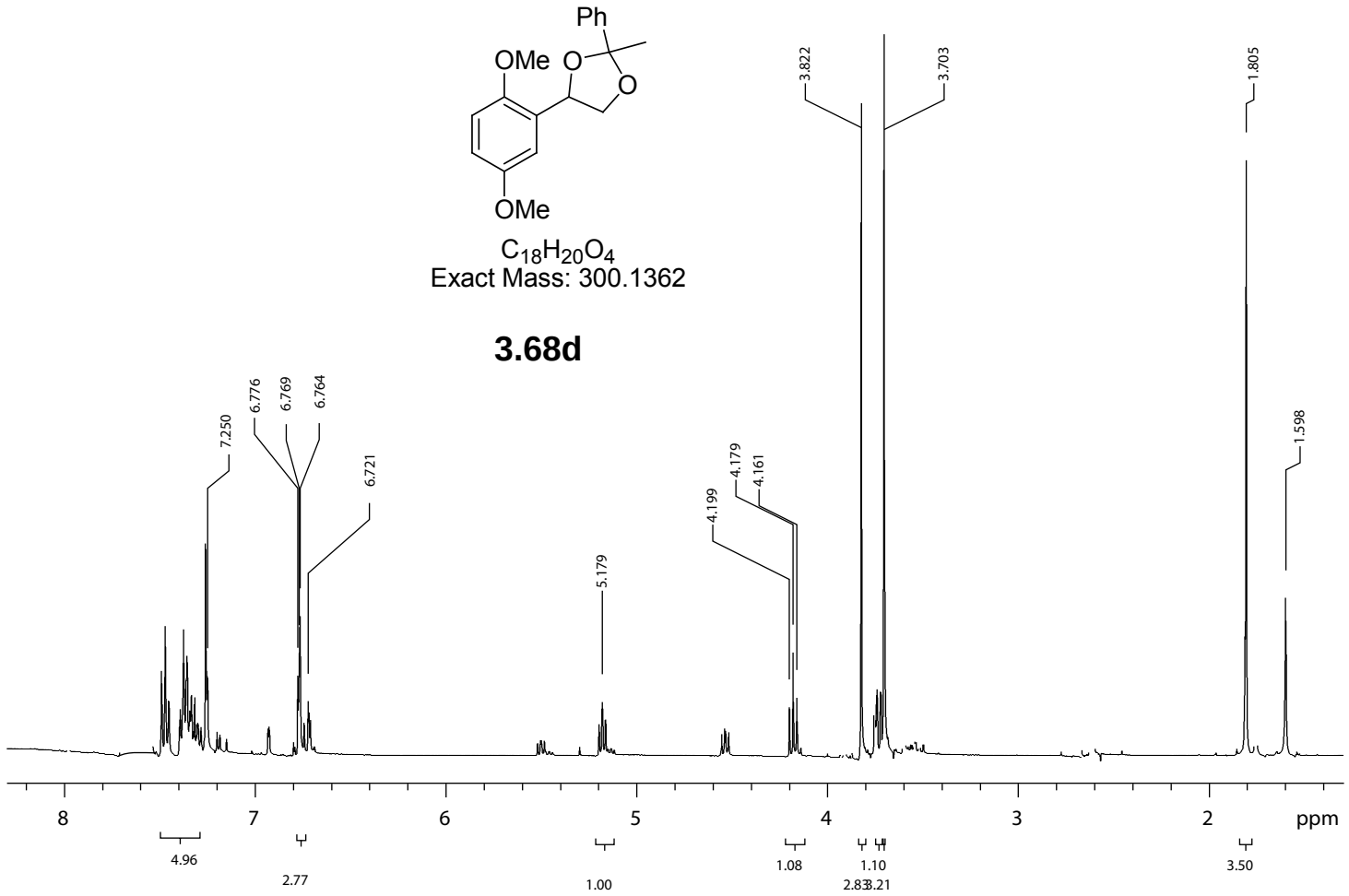

OMe
O
O
OMe
$C_{15}H_{22}O_4$
Exact Mass: 266.1518
3.68a
7.263
7.190
6.768
6.763
5.327
5.311
5.307
5.300
5.290
4.469
4.454
4.450
4.434
3.786
3.765
3.545
3.524
3.504
1.796
1.787
1.777
1.768
1.759
1.750
1.731
1.610
1.025
1.007
0.996
0.988
0.977
0.959
ppm
0.85
1.76
1.00
1.00
2.71
3.05
1.07
4.08
5.88

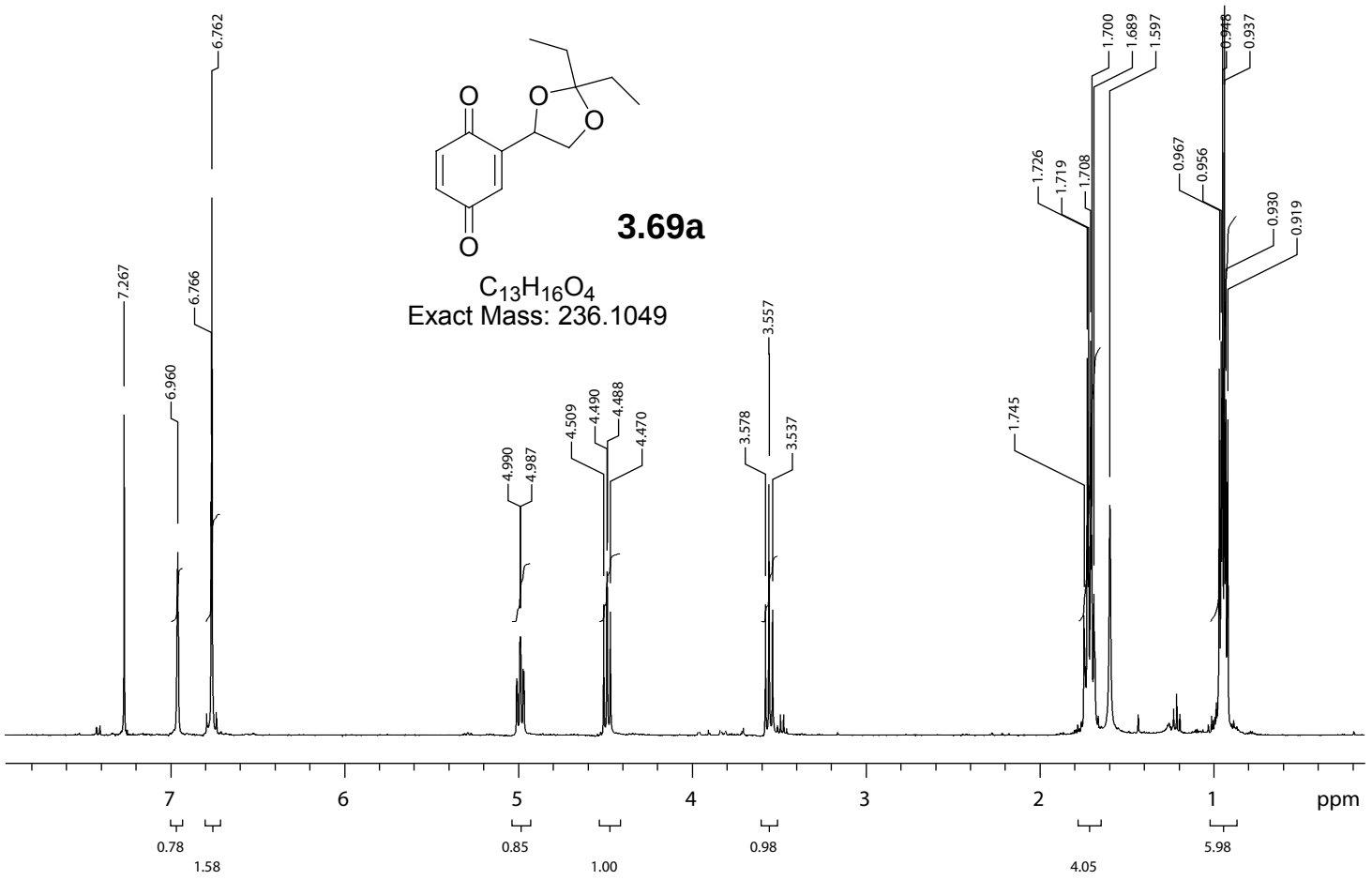

153.997
150.664
129.755
113.029
112.861
112.106
111.147
77.571
77.248
76.933
73.615
71.270
56.010
55.944
30.119
29.753
8.515
8.375
ppm

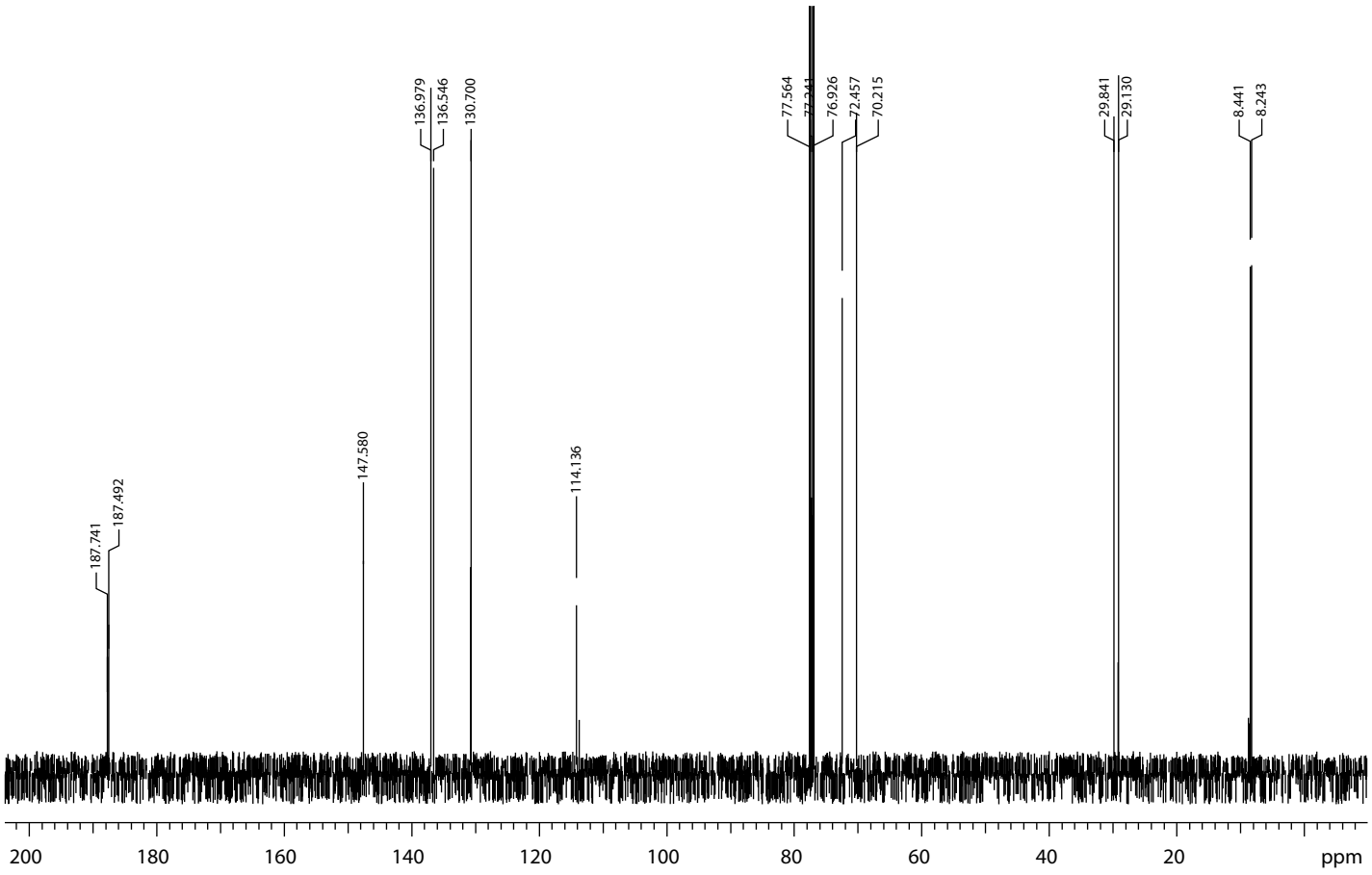

Ph
OMe
O
H
O
OMe
3.68b
C17H18O4
Exact Mass: 286.1205
7.566
7.562
7.541
7.421
7.407
7.402
7.257
6.798
6.793
6.788
7.592
7.587
7.581
6.782
6.079
5.975
5.465
4.455
3.871
3.799
3.792
3.776
3.713
3.689
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm
6.44
6.04
0.85
0.90
4.15
0.99
1.00
2.05
1.17
1.19
14.69

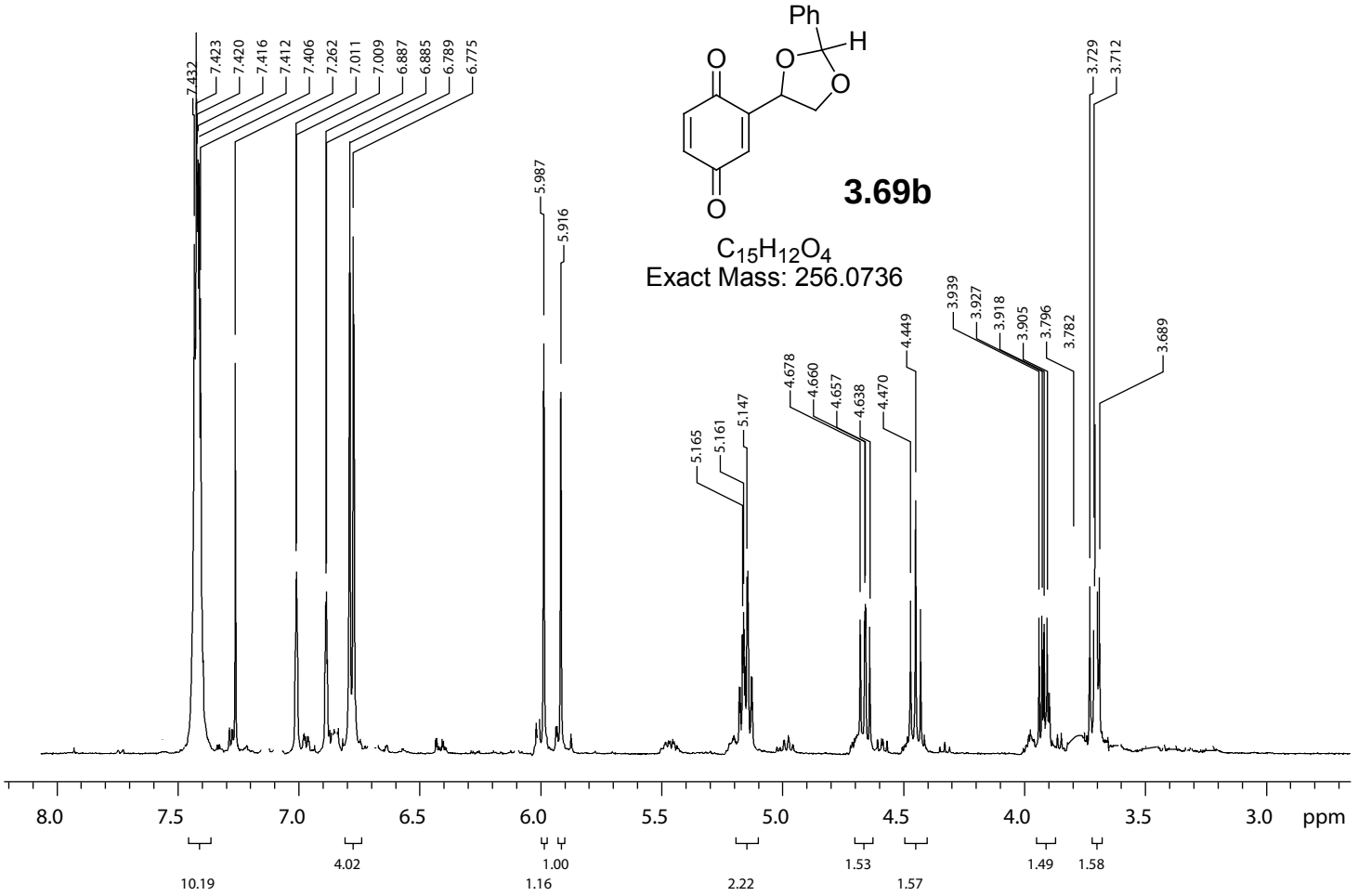

OMe
O
O
OMe
3.68c
$C_{16}H_{22}O_4$
Exact Mass: 278.1518
7.263
7.163
6.761
6.758
5.325
4.452
4.435
4.431
4.415
3.785
3.764
3.613
3.594
3.574
1.733
1.721
1.703
1.693
1.679
1.664
1.651
1.570
1.750
1.460
1.446
1.434
7
6
5
4
3
2
ppm
0.82
1.77
0.87
1.00
2.73
2.83
1.05
8.54

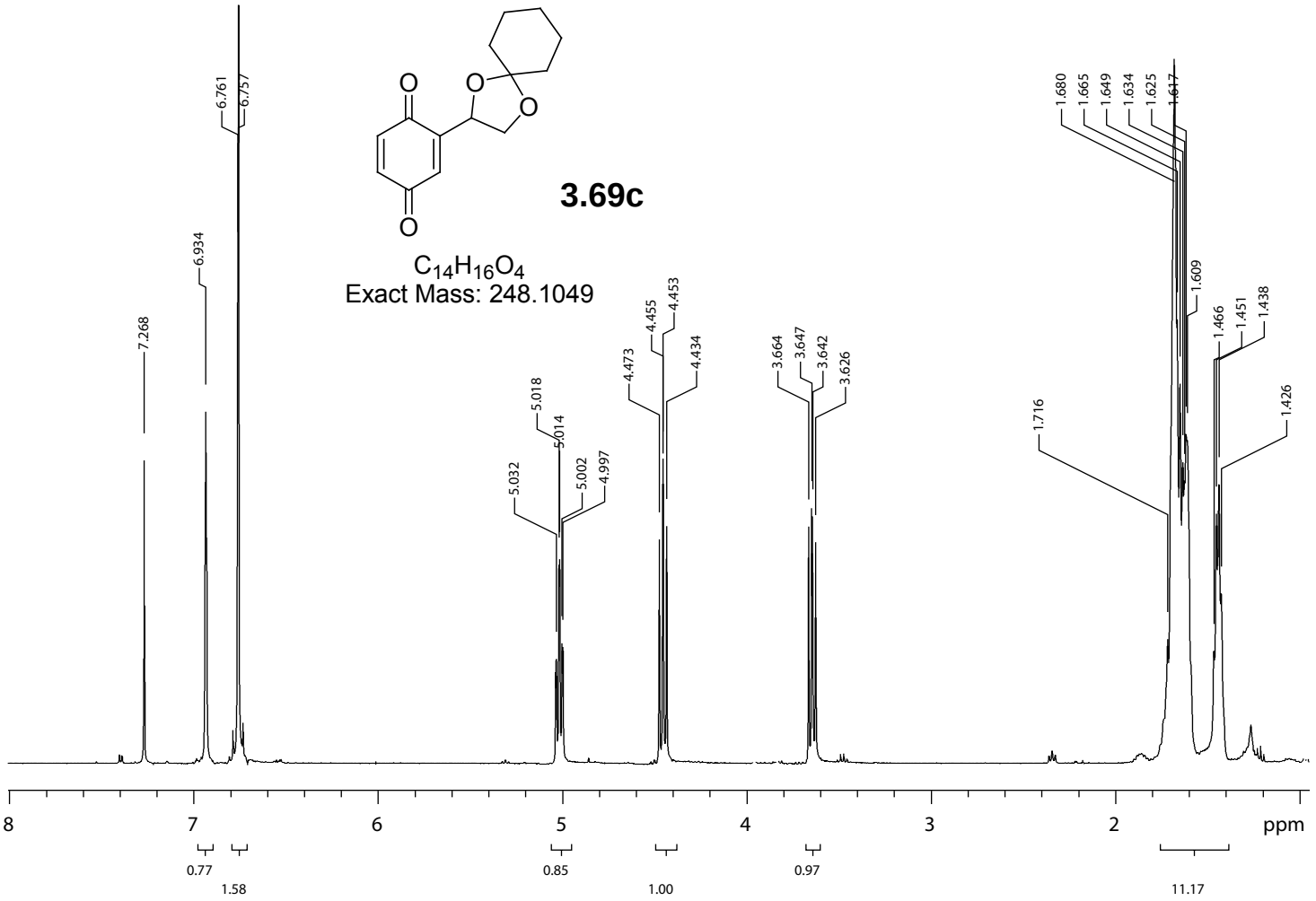

153.975
150.664
130.363
112.663
112.407
111.110
109.879
77.556
77.241
76.926
73.007
70.596
56.025
55.951
36.207
35.665
25.475
24.236
24.171
220
200
180
160
140
120
100
80
60
40
20
0
ppm

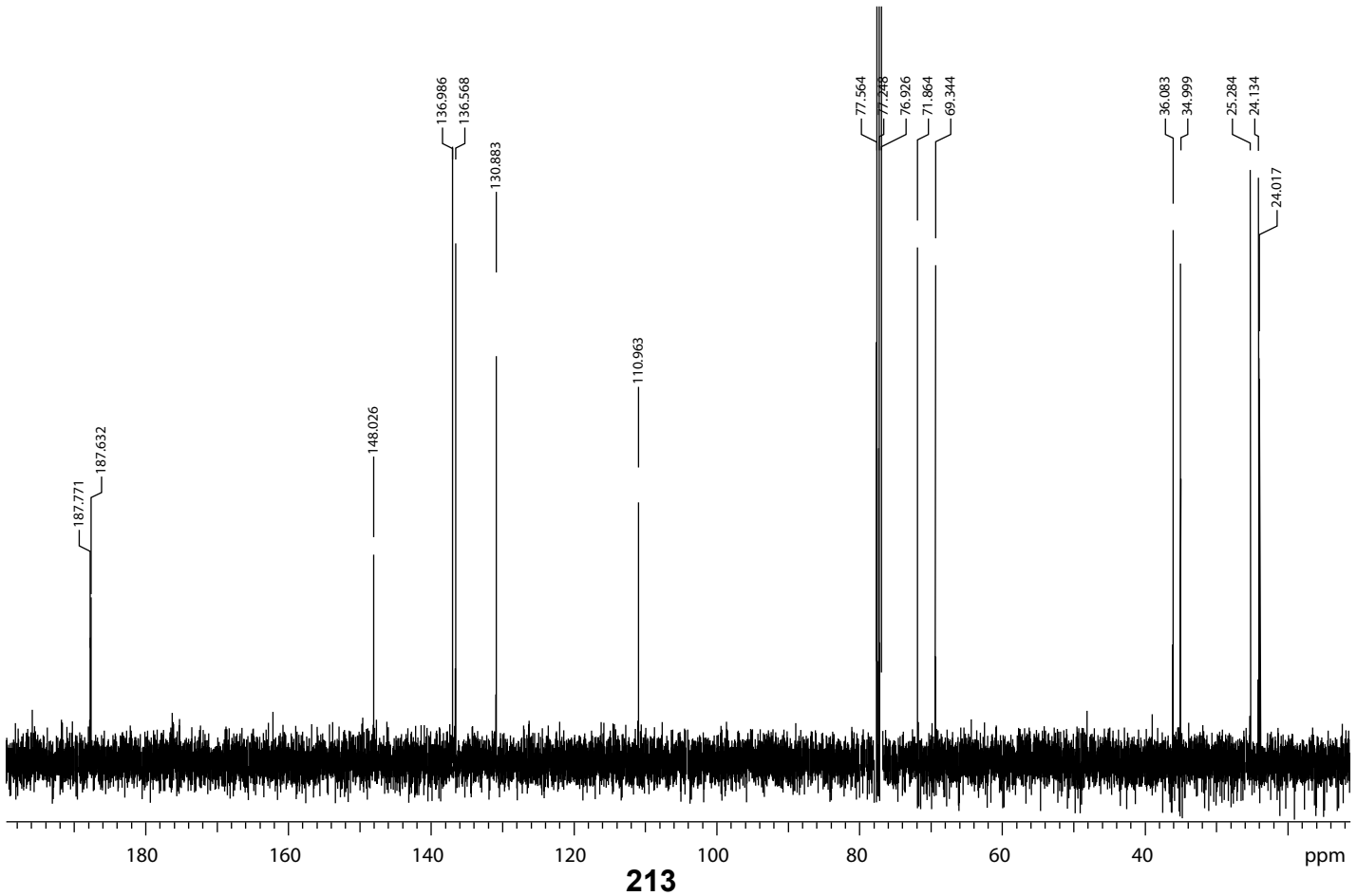

Ph
OMe
O
O
OMe
$C_{18}H_{20}O_4$
Exact Mass: 300.1362
3.68d
7.250
6.776
6.769
6.764
6.721
5.179
4.199
4.179
4.161
3.822
3.703
1.805
1.598
8
7
6
5
4
3
2
ppm
4.96
2.77
1.00
1.08
1.10
2.83
3.21
3.50

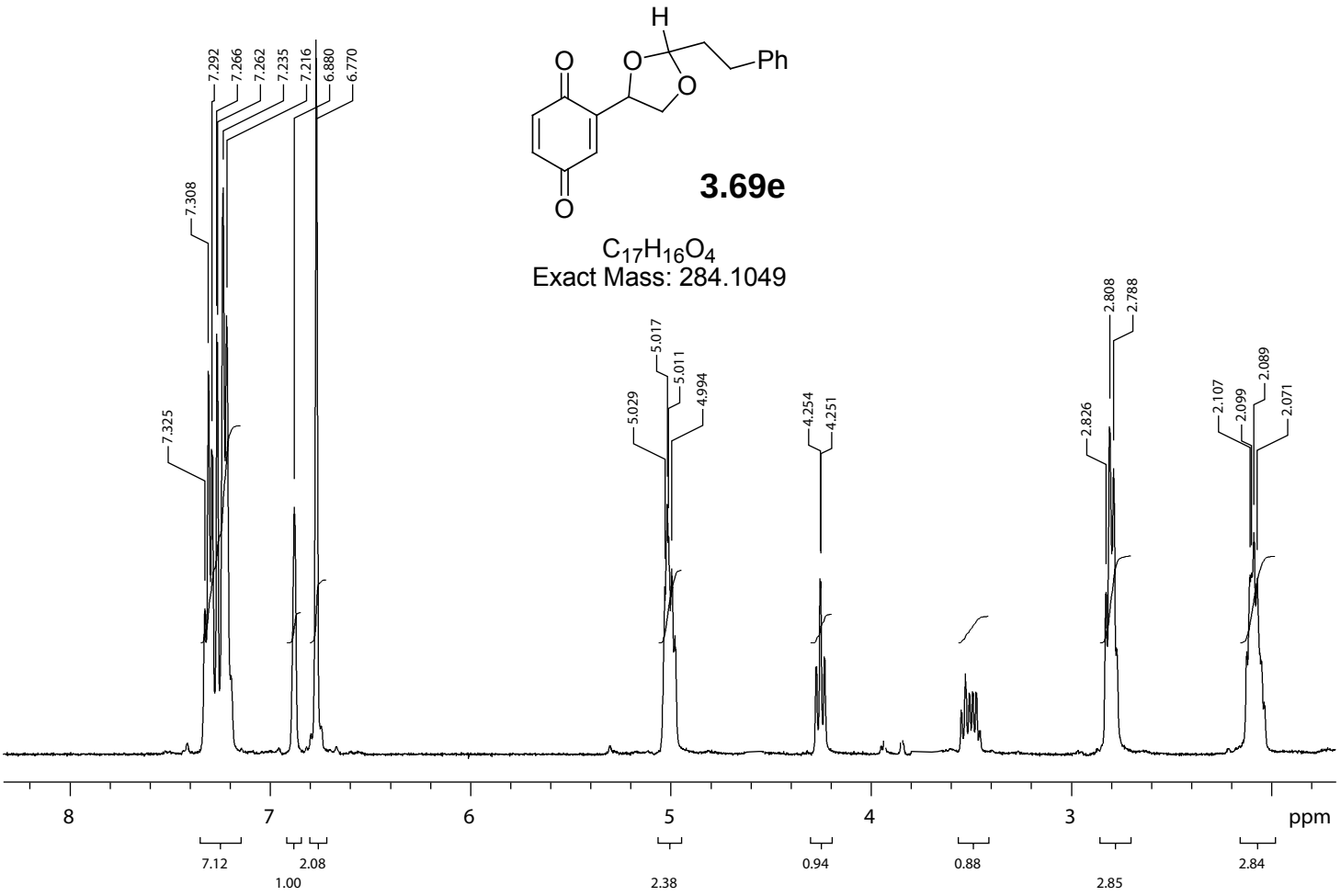

3.69a
C13H16O4
Exact Mass: 236.1049
7.267
6.960
6.766
6.762
4.990
4.987
4.509
4.490
4.488
4.470
3.578
3.557
3.537
1.745
1.726
1.719
1.708
1.700
1.689
1.597
0.967
0.956
0.948
0.937
0.930
0.919
ppm
0.78
1.58
0.85
1.00
0.98
4.05
5.98


187.741
187.492
147.580
136.979
136.546
130.700
114.136
77.564
77.241
76.926
72.457
70.215
29.841
29.130
8.441
8.243
ppm


Ph
H
O
O
O
O
3.69b
C15H12O4
Exact Mass: 256.0736
7.432
7.423
7.420
7.416
7.412
7.406
7.262
7.011
7.009
6.887
6.885
6.789
6.775
5.987
5.916
5.165
5.161
5.147
4.678
4.660
4.657
4.638
4.470
4.449
3.939
3.927
3.918
3.905
3.796
3.782
3.729
3.712
3.689
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm
10.19
4.02
1.16
1.00
2.22
1.53
1.57
1.49
1.58


3.69c
$C_{14}H_{16}O_4$
Exact Mass: 248.1049
6.761
6.757
6.934
7.268
5.018
5.014
5.032
5.002
4.997
4.473
4.455
4.453
4.434
3.664
3.647
3.642
3.626
1.716
1.680
1.665
1.649
1.634
1.625
1.617
1.609
1.466
1.451
1.438
1.426
8
7
6
5
4
3
2
ppm
0.77
1.58
0.85
1.00
0.97
11.17


136.986
136.568
130.883
77.564
77.248
76.926
71.864
69.344
36.083
34.999
25.284
24.134
24.017
110.963
148.026
187.632
187.771
180
160
140
120
100
80
60
40
ppm


H
O
O
O
Ph
O
3.69e
C17H16O4
Exact Mass: 284.1049
7.292
7.266
7.262
7.235
7.216
6.880
6.770
7.308
7.325
5.029
5.017
5.011
4.994
4.254
4.251
2.826
2.808
2.788
2.107
2.099
2.089
2.071
8
7
6
5
4
3
ppm
7.12
2.08
1.00
2.38
0.94
0.88
2.85
2.84