UNIVERSITY OF IOANNINA

SCHOOL OF NATURAL SCIENCES

DEPARTMENT OF CHEMISTRY

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The synthesis of 2-substituted phenols, chromans and 2,3-dihydro-1-benzofurans via *o*-quinone methides generated *in situ*

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RESEARCHER

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«Η έγκριση της διδακτορικής διατριβής από το Τμήμα Χημείας της Σχολής Θετικών Επιστημών,του Πανεπιστημίου Ιωαννίνων δεν υποδηλώνει αποδοχή των γνωμών του συγγραφέα Ν. 5343/32, άρθρο 202, παράγραφος 2»

Ημερομηνία αίτησης του κ. SHAIKH ABDUL KADAR: 10-12-13

Ορισμός Τριμελούς Συμβουλευτικής Επιτροπής από τη Γ.Σ.Ε.Σ.: 873^{A}/ 18-11-13

Μέλη Τριμελούς Συμβουλευτικής Επιτροπής:

Επιβλέπων: Βαρβούνης Γεώργιος, Καθηγητής

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Θέμα: «The synthesis of 2-substituted phenols, chromans and 2,3-dihydro-1-benzofurans via *o*-quinone methides generated *in situ*»

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Έγκριση Διδακτορικής Διατριβής με Βαθμό «***ΑΡΙΣΤΑ***» στις 20-11-13

Ο Πρόεδρος του Τμήματος Χημείας

Τσίκαρης Βασίλειος, Καθηγητής

Η Γραμματέας του Τμήματος

Ελένη Αδαμαντίου

ΠΡΑΚΤΙΚΟ ΤΗΣ ΕΠΤΑΜΕΛΟΥΣ ΕΞΕΤΑΣΤΙΚΗΣ ΕΠΙΤΡΟΠΗΣ ΓΙΑ ΤΗΝ ΚΡΙΣΗ ΤΗΣ ΔΙΑΚΤΟΡΙΚΗΣ ΔΙΑΤΡΙΒΗΣ

του υποψήφιου διδάκτορα κ. Shaikh Abdul Kadar Nabilal
κατόχου M.Sc. στην οργανική χημεία από το University of Pune, Maharashtra, India

Η επταμελής εξεταστική επιτροπή που ορίστηκε σύμφωνα με τα άρθρα 12 και 13 του Νόμου 2083/92 και την υπ'αριθμό 873/18-11-2013 απόφαση της Γενικής Συνέλευσης με την ειδική σύνθεση του Τμήματος Χημείας της Σχολής Θετικών Επιστημών του Παν/μίου Ιωαννίνων, για την κρίση της διδακτορικής διατριβής του κ. Shaikh Abdul Kadar Nabilal, συνήλθε σε συνεδρίαση σήμερα Τετάρτη, 20 Νοεμβρίουίου 2013 και ώρα 12.00 το μεσημέρι στην Αίθουσα Συνεδριάσεων του Τμήματος Χημείας στη Δουρούτη, και παρακολούθησε τη δημόσια παρουσίαση της διατριβής του υποψηφίου με τίτλο:

"The synthesis of 2-substituted phenols, chromans and 2,3-dihydro-1-benzofurans via o-quinone methides generated in situ."

Μετά την προφορική παρουσίαση της διατριβής, τα μέλη της εξεταστικής επιτροπής έκαναν ερωτήσεις στον υποψήφιο τόσο γενικού περιεχομένου όσο και σχετικές με το θέμα της διατριβής. Στη συνέχεια και μετά την αποχώρηση του ακροατηρίου και του υποψηφίου ακολούθησε διεξοδική συζήτηση μεταξύ των μελών της επιτροπής.

Τα επτά παρόντα μέλη της επιτροπής δήλωσαν ότι ***η παρούσα διατριβή προάγει την επιστήμη και ότι η προφορική παρουσίαση ήταν ικανοποιητική και υψηλού επιπέδου***.

Η επιτροπή μετά από ψηφοφορία έκρινε ***ομόφωνα*** ότι η διατριβή του κ. Shaikh παρουσιάζει πρωτοτυπία και ότι αποτελεί ουσιαστική συμβολή στην επιστήμη, ο δε υποψήφιος απέκτησε τόσο τις γνώσεις όσο και την τεχνική κατάρτιση ώστε να προσεγγίζει με ωριμότητα σύγχρονα ερευνητικά προβλήματα του επιστημονικού του πεδίου.

Στη συνέχεια η επιτροπή αποφάσισε ***ομόφωνα*** να απονείμει το βαθμό ***ΑΡΙΣΤΑ***.

1. Γ. Βαρβούνης, Καθηγητής Τμήματος Χημείας, Παν/μίου Ιωαννίνων (επιβλέπων)
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Contents

Preface

This work was performed at the Laboratory of Organic Chemistry, University of Ioannina, during the period October 2009 to November 2013. The title of the thesis is "The synthesis of 2-substituted phenols, chromans and 2,3-dihydro-1-benzofurans via *o*-quinone methides generated *in situ*."

First of all, I want to express my gratitude to Professor George Varvounis for the encouragement, inspiration and timely criticism during the course of my work. He supervised the work of my Ph.D. thesis, gave important advice in chemistry and non-chemistry matters. He made me realize that simple experiments can be very enlightening, has the unrivalled ability to realize his visions, almost always allowed me to interrupt his line of thoughts and became a trusted friend as well.

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I would like to wholeheartedly thank my parents, for their staunch support in all areas of my life and the energy that they have offered me, urging me to always strive for the best. Without their support it would not have been possible to achieve the goal.

Financial assistance from the State Scholarship Foundation (IKY), in the form of a fellowship, is gratefully acknowledged.

Finally, thanks to God for his unending faithfulness and his plans for me that have worked towards my well being.

Abdul Kadar Shaikh

Ioannina, November 2013

Abstract

The work described in this research project has been concerned with the investigation of a new method of generating *o*-quinone methide from a 2-silyloxybenzyl nitrate derivative which was trapped (i) with nucleophiles by the Michael addition and dienophiles by cycloaddition, (ii) used as an intermediate in an attempted synthesis of xyloketal H, a natural product, and (iii) used as an intermediate in the synthesis of 2,3-disubstituted or 3-substituted 2,3-dihydrobenzofurans. Furthermore, the non-oxidative generation of *o*-naphthoquinone nitrosomethide from (2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-naphthyl)-methyl nitrate was investigated but without success. However, oxidative generation of *o*-naphthoquinone nitrosomethide from the oxime of 2-hydroxynaphthaldehyde using lead(IV) acetate and pyrrolidine as a nucleophile gave 1-pyrrolidin-1-ylnaphtho[1,2-*d*]-isoxazole, 7a,8,9,10-tetrahydro-12*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazin-12-one and the oxime of the latter compound.

Abbreviations

AIBN	azobisisobutyronitrile
Ar	aryl
ASA	acetylsalicylic acid
Bn	benzyl
CAN	cerium ammonium nitrate
°	degree
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethylazodicarboxylate
DIAD	diisopropyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
EI	electron impact
EtOH	ethanol
EVE	ethyl vinyl ether
GSH	glutathione
HMPA	hexamethylphosphoramide
J	coupling constant
IBD	iodobenzene diacetate
IPA	2-propanol
LAH	lithium aluminium hydride
Lit.	literature
M^+	parent molecular ion
MCPBA	*m*-chloroperbenzoic acid
MeOH	methanol
MIBK	methyl isobutyl ketone

m.p.	melting point
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million
PTSA	*p*-toluene sulfonic acid
rt	room temperature
TBAF	tertiary butyl ammonium fluoride
TBME	methyl *tert*-butyl ether
TBS	(*tert*-butyl)dimethylsilyl
TBSCl	(*tert*-butyl)dimethylsilyl chloride
TBSF	(*tert*-butyl)dimethylsilyl fluoride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPSCl	triisopropylsilyl chloride
TMG	1,1,3,3-tetramethylguanidine
TMS	trimethylsilyl
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TLC	thin layer chromatography

1. Introduction

1.1. Introduction to *o*-Quinone Methide

Quinone methides are highly reactive species with short lifetimes. They are defined as quinone analogues in which one of the carbonyl oxygens is replaced by a methylene group. The term quinone methide appeared in the literature in 1942 but only as a perception and for this reason its initial study was discouraged. Perhaps the field of organic synthesis has become the most frequent benefactor of quinone methides, now that reliable methods are available for their generation and control. The present chapter reviews the chemistry of *o*-quinone methides with only the important applications in chemistry and biology.

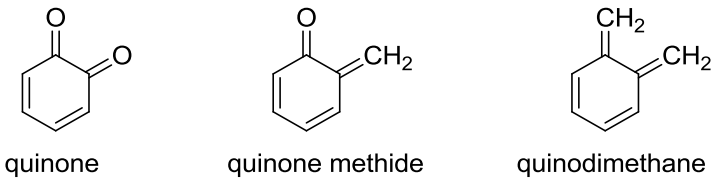


Figure 1.1 *o-Quinone methide and analogs.*

o-Quinone methides (*o*-QMs) are highly polar and highly reactive, much more than their relatives such as α,β-unsaturated ketones. *Ortho*- (**1**) and *para*-quinone methides (**2**) are the most commonly encountered isomers although *meta*-quinone methides (**3**) which are non-Kekule and must be drawn as zwitterionic (**3a**) or biradical (**3b**) structures, are known as well.

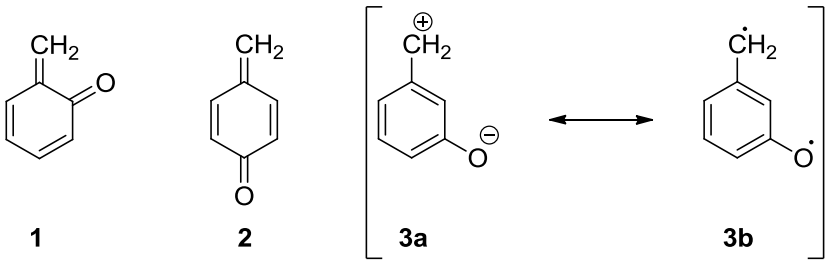
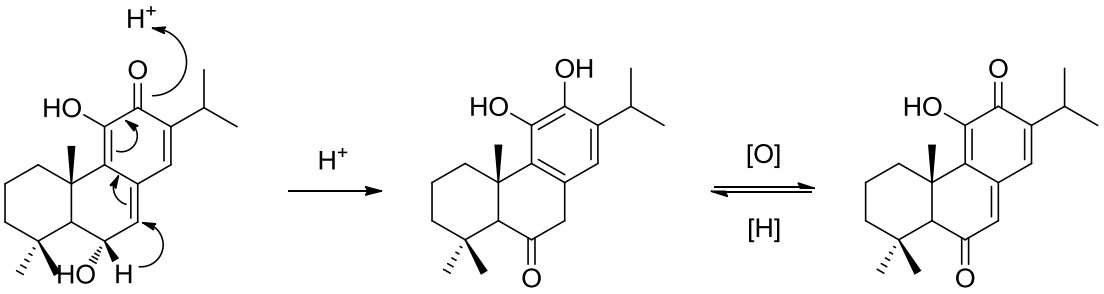


Figure 1.2 *Structures of o-, p- and m-quinone methides.*

Most of the laboratories did not recognize the occurrence and potential applications of quinone methides until 20 years after they were first reported. But now with an ever-increasing appreciation of the structural dependence of numerous important chemical

reactions on quinone methide reactivity, their occurrence in the literature has become more frequent and diverse.

Their role in lignin formation[1] was recognized as early as 1960. Soon after the first stable quinone methide was discovered in the natural product tumour inhibitors taxodione and taxodone.[2,3] This offered a stark contrast to the initial finding describing the fleeting existence of quinone methides (Scheme 1.1).



Scheme 1.1 *Taxodione and taxodone.*

The concept of bioreductive alkylating agents was introduced to form *o*-quinone methide intermediates for treating hypoxic tumors.[4] Both reductive and oxidative metabolisms forming quinone methides have since become a very important topic for quinone methides in drug design as well as drug safety.

Both *o*- and *p*-quinone methides can also have zwitterionic resonance structures that give these species both cationic and anionic centers (Figure 1.3), emphasizing their polarized nature and indicating that they may react with both nucleophiles (similar to carbocations) and electrophiles (similar to phenolates). The nucleophilic attack on an *o*-quinone methide produces an aromatic alcohol (Scheme 1.2), so the significant driving force acting is aromatization which makes *o*-quinone methides much more reactive than simple enones (such as α,β–unsaturated ketones). This electrophilicity is the basis of reactivity of the quinone methides in various biological applications. *o*-Quinone methides

[1] Davin, L. B.; Lewis, N. G. *Curr. Opin. Biotechnol.* **2005**, *16*, 407-415.
[2] Kupchan, S. M.; Karim, A.; Marcks, C. *J. Am. Chem. Soc.* **1968**, *90*, 5923-5924.
[3] Kupchan, S. M.; Karim, A.; Marcks, C. *J. Org. Chem.* **1969**, *34*, 3912-3918.
[4] Moore, H. W.; Czerniak, R. *Med. Res. Rev.* **1981**, *1*, 249-280.

can also readily engage in [4+2] cycloadditions with electron rich dienophiles to give chroman derivatives, again the driving force being aromatization of the ring (Scheme 1.2).

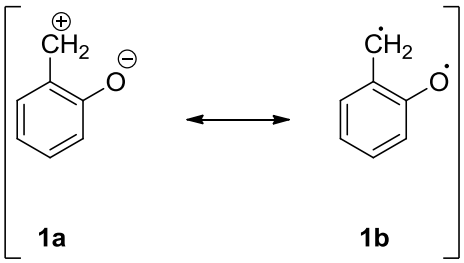
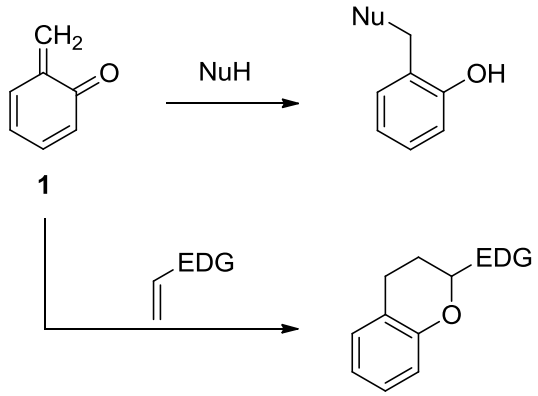


Figure 1.3 *o-Quinone methide zwitterionic structures.*

In the absence of a nucleophile or dienophile *o*-quinone methides tend to dimerize and trimerize as well, the rate of polymerization being dependent upon the steric factors of *o*-quinone methides.[5]



Scheme 1.2 *Trapping of o-quinone methide by Michael addition and inverse hetero Diels-Alder cycloaddition.*

The reaction rates exhibited by quinone methides are highly dependent on the substituents present, solvents and temperature; lifetimes can range from less than 1 ns to several seconds or minutes.

o-Quinone methides have been shown to be important intermediates in chemical synthesis,[6,7] in lignin biosynthesis,[8] and in the activity of antitumor and antibiotic agents.[9]

[5] Cavitt, S. B.; Sarrafizadeh, H.; Gardner, P. D. *J. Org. Chem.* **1962**, *27*, 1211-1216.
[6] Wan, P.; Barker, B.; Diao, L.; Fischer, M.; Shi, Y. *Can. J. Chem.* **1996**, *74*, 465-475.
[7] De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367-5405.
[8] Shevchenko, S. M.; Apushkinskii, A. G. *Russ. Chem. Rev.* **1992**, *61*, 105-131.
[9] Thompson, D. C.; Thompson, J. A.; Sugumaran, M.; Moldeus, P. *Chem. Biol. Interact.* **1993**, *86*, 129-162.

They react with many biologically relevant nucleophiles including alcohols,[6] thiols,[10-12] nucleic acids,[13-15] proteins,[11-16] and phosphodiesters.[17] The reaction of nucleophiles with *o*- and *p*-quinone methides is *p*H dependent and can occur via either acid-catalyzed or uncatalyzed pathways.[18,19] The electron transfer chemistry that is typical of the related quinones does not appear to play a role in the nucleophilic reactivity of quinone methides.[20]

1.1.1. Synthetic methods used to generate *o*-quinone methides

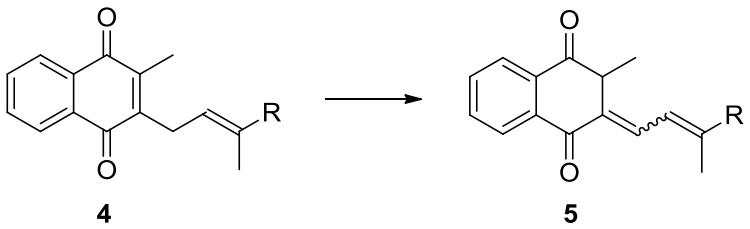
Many of the synthetic techniques for producing *o*-quinone methides, which include (a) tautomerization, (b) oxidation, (c) thermolysis, (d) photolysis, (e) acid promotion, (f) base facilitation, (g) the olefination of quinones and (h) fluoride induction. The conditions associated with the generation of *o*-quinone methides have profound influence on the type of reactions that these species are able to undergo.

1.1.1.1. Initiation by tautomerization

Vitamin K_1 plays an important role in promoting blood coagulation via its redox cycle, it gives the *o*-quinone methide **5** through tautomerization (Scheme 1.3).[21]

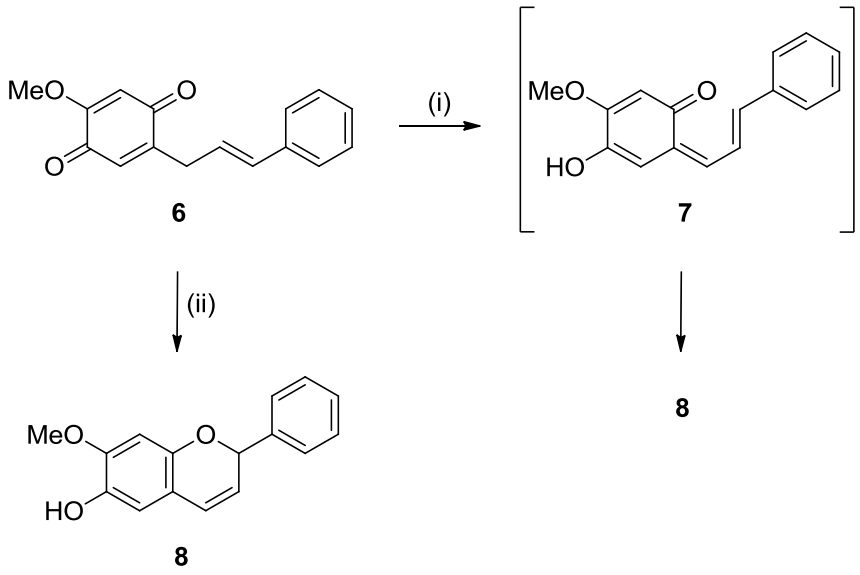
Tautomerization giving rise to the formation of an *o*-quinone methide aimed at initiating a subsequent reaction was first demonstrated by Jurd and co-workers.[22] Quinone **6** was

[10] Ramakrishnan, K.; Fischer, J. *J. Med. Chem.* **1986**, *29*, 1215–1221.
[11] Bolton, J. L.; Turnipseed, S. B.; Thompson, J. A. *Chem. Biol. Interact.* **1997**, *107*, 185-200.
[12] Awad, H. M.; Boersma, M. G.; Boeren, S.; Van Bladeren, P. J.; Vervoort, J.; Rietjens, I. M. *Chem. Res. Toxicol.* **2003**, *16*, 822-831
[13] Lewis, M. A.; Yoerg, D. G.; Bolton, J. L.; Thompson, J. A. *Chem. Res. Toxicol.* **1996**, *9*, 1368-1374.
[14] Pande, P.; Shearer, J.; Yang, J. H.; Greenberg, W. A.; Rokita, S. E. *J. Am. Chem. Soc.* **1999**, *121*, 6773-6779.
[15] Weinert, E. E.; Rokita, S. E. *Chem.Res. Toxicol.* **2005**, *18*, 1970-1970.
[16] Thompson, D. C.; Perera, K.; London, R. *Chem. Biol. Interact.* **2000**, *126*, 1-14
[17] Zhou, Q.; Turnbull, K. D. *J. Org. Chem.* **1999**, *64*, 2847-2851.
[18] Chiang, Y.; Kresge, A. J.; Zhu, Y. *Pure Appl. Chem.* **2000**, *72*, 2299-2308.
[19] Chiang, Y.; Kresge, A. J.; Zhu, Y. *J. Am. Chem. Soc.* **2002**, *124*, 6349-6356.
[20] Ofial, A. R.; Ohkubo, K.; Fukuzumi, S.; Lucius, R.; Mayer, H. *J. Am. Chem. Soc.* **2003**, *125*, 10960-10912.
[21] Swartz, A. M.; Barra, M. *J. Org. Chem.* **2004**, *69*, 3198-3201.
[22] Jurd, L.; Roitman, J. N. *Tetrahedron* **1978**, *34*, 57-62



Scheme 1.3 *Tautomerization of vitamin K_1 to give an o-quinone methide structure.*

heated in benzene and the product obtained was 2*H*-chromen-6-ol **8**, presumably via an unstable *o*-quinone methide **7**, although there was lack of direct evidence. Jurd and co-workers then performed the reaction with ethyl vinyl ether in order to trap the *o*-quinone methide but the product obtained was again **8** (Scheme 1.4).

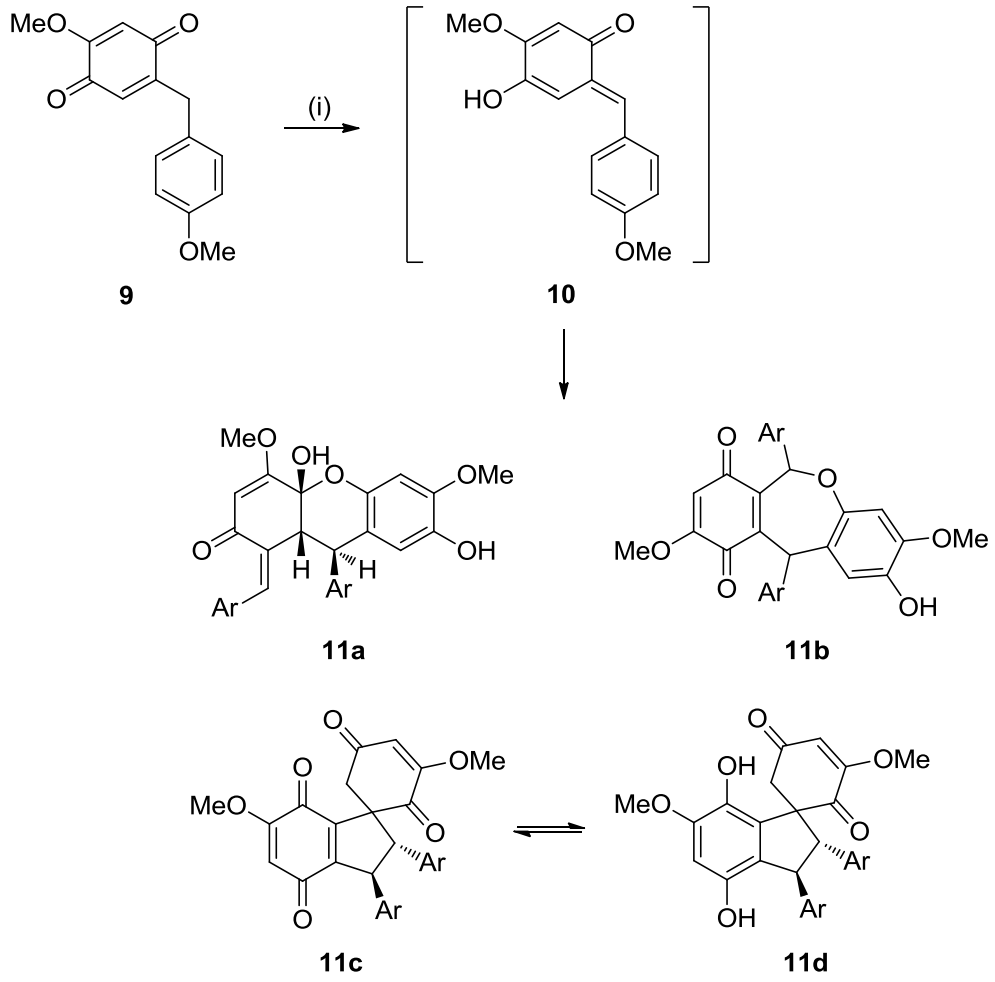


Scheme 1.4 Synthesis of a 2*H*-chromen-6-ol derivative. *(i) benzene, reflux, (ii) benzene, ethyl vinyl ether, reflux.*

In order to confirm the participation of an *o*-quinone methide formed by tautomerization, as shown above, Jurd and co-workers[23] extended their work and warmed solutions of quinone **9** in pyridine or methanolic sodium hydroxide. From these two reactions the authors established the formation of four different dimeric products **11a**, **11b**, **11c** and **11d** (Scheme 1.5). They then confirmed that the formation of these four dimers was possible only via the *o*-quinone methide intermediate **10** formed by tautomerization of

[23] Jurd, L.; Roitman, J. N.; Wong, R. Y. *Tetrahedron* **1979**, *35*, 1041-1054.

quinone **9**. This result confirms the formation of **8** through the *in situ* generation of *o*-quinone methide **7** by tautomerization of quinone **6**.

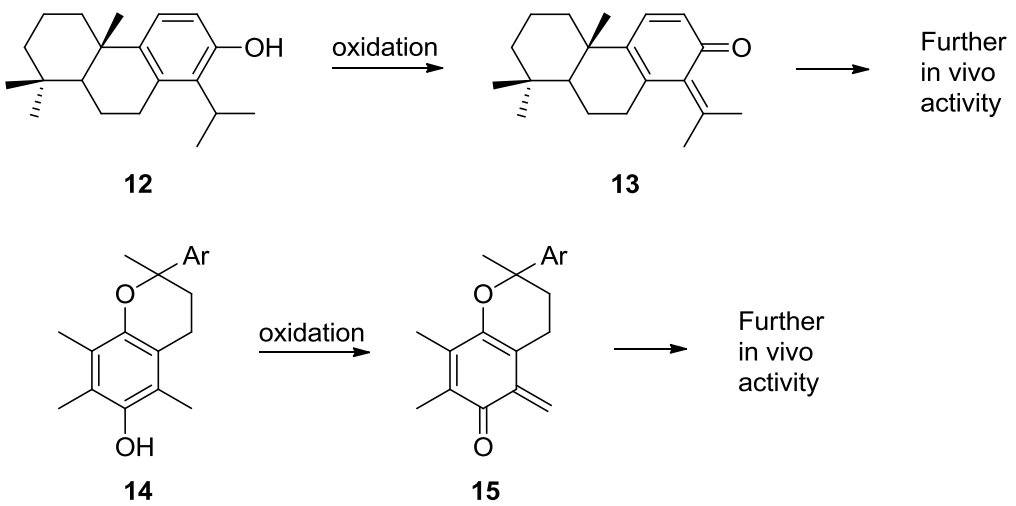


Scheme 1.5 *Synthesis of dimeric derivatives from the o-quinone methide of 2-methoxy-5-(4-methoxybenzyl)-benzo-1,4-quinone. (i) pyridine, heat or methanolic NaOH, heat.*

1.1.1.2. Oxidative initiation

The efficacy of some bioactive entities was found to be due to the oxidative generation of *o*-quinone methide. One such case is the anti-bacterial agent totarol **12**, which is known

to become oxidized to the *o*-quinone methide **13** in vivo.[24] Similar oxidation of anti-diabetic troglitazone **14**[25] gives *o*-quinone methide **15** (Scheme 1.6).

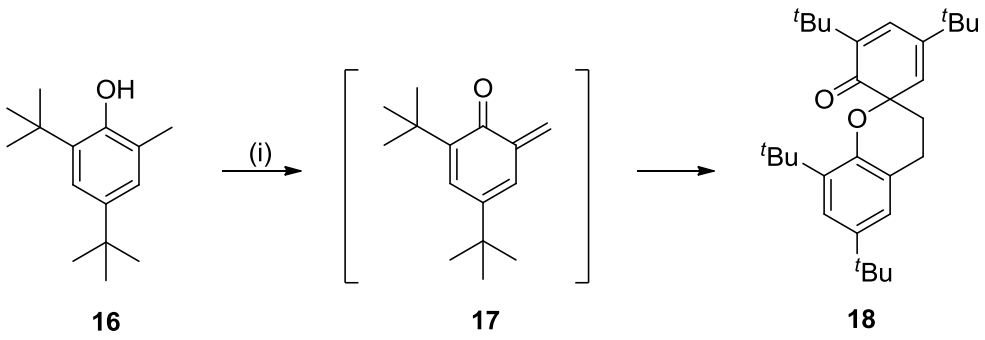


Scheme 1.6 *o-Quinone methide formation by oxidation of totarol and troglitazone natural products.*

The bio-activation of vitamin E is also an example of *o*-quinone methide formation by a biological oxidation process.[26,27]

The generation of *o*-quinone methides using chemical oxidants for synthetic purposes, was first investigated by Waters and co-workers,[28] who studied the oxidation of disubstituted *o*-cresol **16** using silver(I) oxide. The outcome was spiro compound **18** a dimer of *o*-quinone methide **17** generated during the oxidative process (Scheme 1.7).

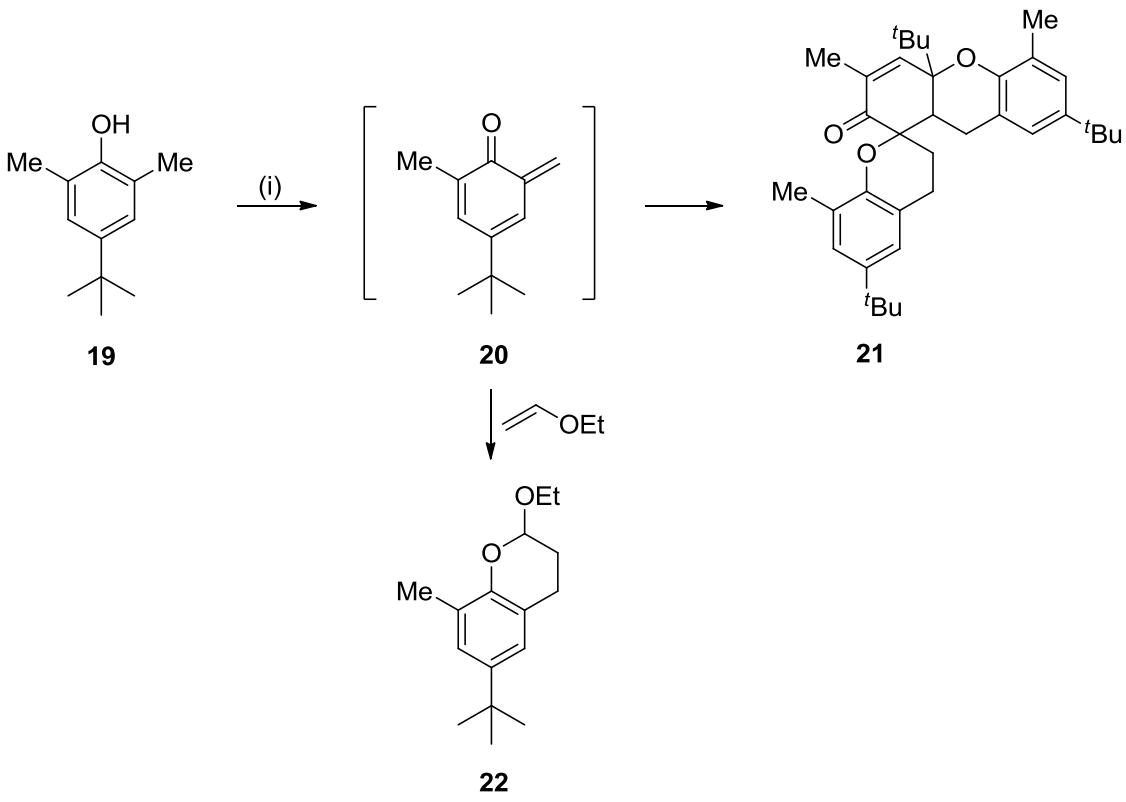
[24] Haraguchi, H.; Oike, S.; Muroi, H.; Kubo, I. *Planta Med.* **1996**, *62*, 122-125.
[25] Kassahun, K.; Pearson, P. G.; Tang, W.; McIntosh, I.; Leung, K.; Elmore, C.; Dean, D.; Wang, R.; Doss, G.; Baillie, T. A. *Chem. Res. Toxicol.* **2001**, *14*, 62–70.
[26] Lloyd, H. A.; Sokoloski, E. A.; Strauch, B. S.; Fales, H. M. *J. Chem. Soc., Chem. Commun.* **1969**, *6*, 299-301.
[27] Bowry, V. W.; Ingold, K. U. *J. Org. Chem.* **1995**, *60*, 5456-5467.
[28] Moore, R. F.; Waters, W.A. *J. Chem. Soc.* **1954**, 243-246.



16 17 18

Scheme 1.7 *Synthesis of a spiro dimeric derivative from the o-quinone methide of 2,4-di-tert-butyl-6-methyl-phenol. (i) Ag_2O, cumene.*

This method was further used by Bolon to get trimer **21** of *o*-quinone methide **20** in benzene as solvent or chroman **22** in the intermolecular hetero Diels-Alder cycloaddition of **20** with ethyl vinyl ether (Scheme 1.8).[29,30]



19 20 21 22

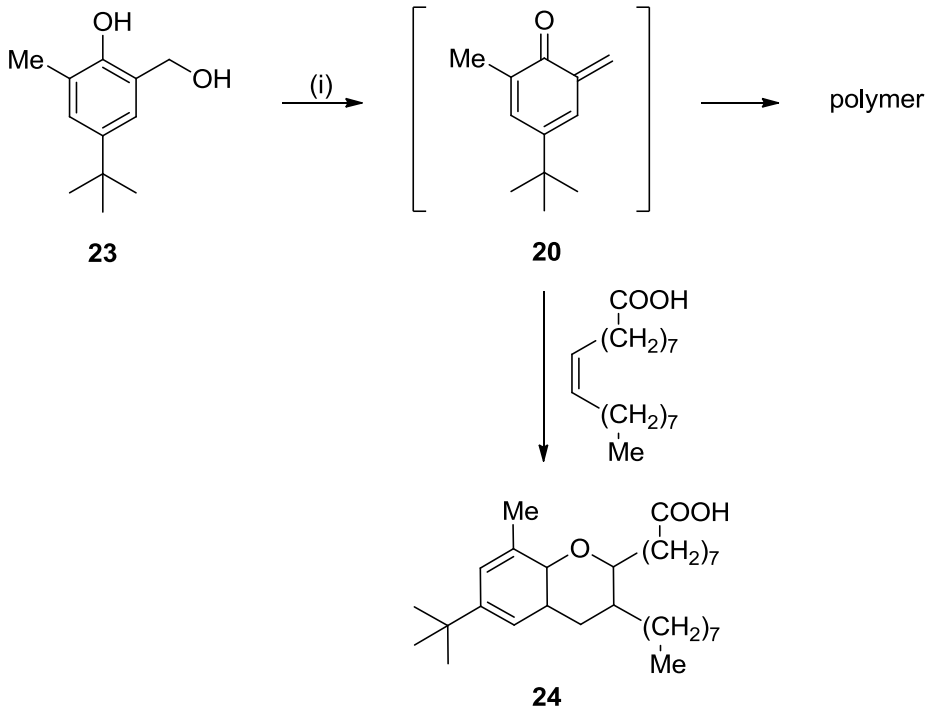
Scheme 1.8 *Cycloaddition reaction of the o-quinone methide derived from 4-tert-butyl-2,6-dimethylphenol. (i) Ag_2O, benzene or ethyl vinyl ether.*

[29] Bolon, D. A. *J. Org. Chem.* **1970**, *35*, 715-719.
[30] Bolon, D. A. *J. Org. Chem.* **1970**, *35*, 3666-3670.

Other reagents used for oxidative generation of *o*-quinone methides are $K_3Fe(CN)_6$, PbO_2,[31] DDQ[32] and DMDO.[33]

1.1.1.3. Thermal initiation

Generation of *o*-quinone methides using thermolysis has been the method of choice among synthetic chemists, although the thermal conditions might affect the nucleophiles used to trap the quinone methide. The temperature range used for each precursor for the initiation depends upon the substituents on it. If a precursor possesses extended conjugation overall temperature requirements are low for initiation but if the process involves significant non-bonded interactions then higher temperatures are required. In thermal initiation, intramolecular cyclisation of the *o*-quinone methide is preferred over intermolecular reactions. During the study of the reactivity between *o*-methylol phenol **23**

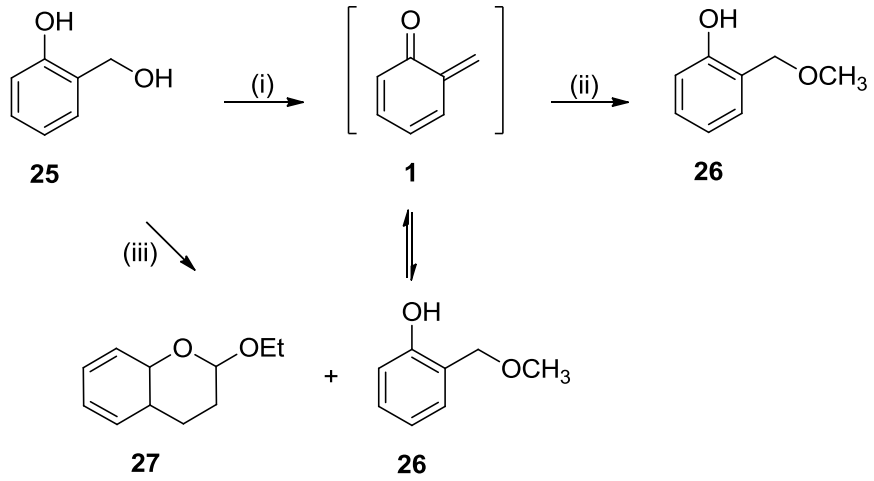


Scheme 1.9 *Cycloaddition to o-quinone methide derived from 4-tert-butyl-2-(hydroxymethyl)-6-methylphenol. (i) 220-230 °C.*

[31] Cook, C. D.; Butler, L. C. *J. Org. Chem.* **1969**, *34*, 227-229.
[32] Kasturi, T.R.; Rajashekhar, B. Raju, G. J.; Reddy, G. M.; Sivaramakrishnan, R.; Ramasubbu, N.; Venkatesan, K. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2375-2382.
[33] Adam, W.; Bialas, J.; Hadjiarapoglou, L.; Sauter, M. *Chem. Ber.***1992**, *125*, 231-234.

and oleic acid, Sprengling and co-workers[34] explain the formation of chromane **24** by the interaction of oleic acid with the in situ thermally generated *o*-quinone methide **20** (Scheme 1.9).

Mulder and co-workers[35] studied the reactivity of *o*-hydroxybenzyl alcohol (**25**) as a model compound for lignin formation, in various solvents, between 390 K and 560 K. They found out that both in polar and apolar solvents the *o*-quinone methide **1** is the reactive intermediate. In alcoholic solvents, the *o*-quinone methide reacts with the solvent to give the corresponding ether **26** whereas if ethyl vinyl ether is added to the same reaction mixture, the outcome is a hetero Diels-Alder cycloaddition to give a mixture containing *o*-(methoxymethyl)phenol **26** and 2-ethoxychroman **27** (Scheme 1.10). It was observed that at 424 K the *o*-hydroxybenzyl alcohol conversion was 49% to give *o*-(methoxymethyl) phenol from methanol and 2-ethoxychroman in a ratio of 40/9. At 475 K *o*-hydroxybenzyl alcohol is quantitatively converted into **27**. The elevation in yield observed for the chroman at higher temperature explains the reversible reaction for the formation of **26** due to the higher energy.



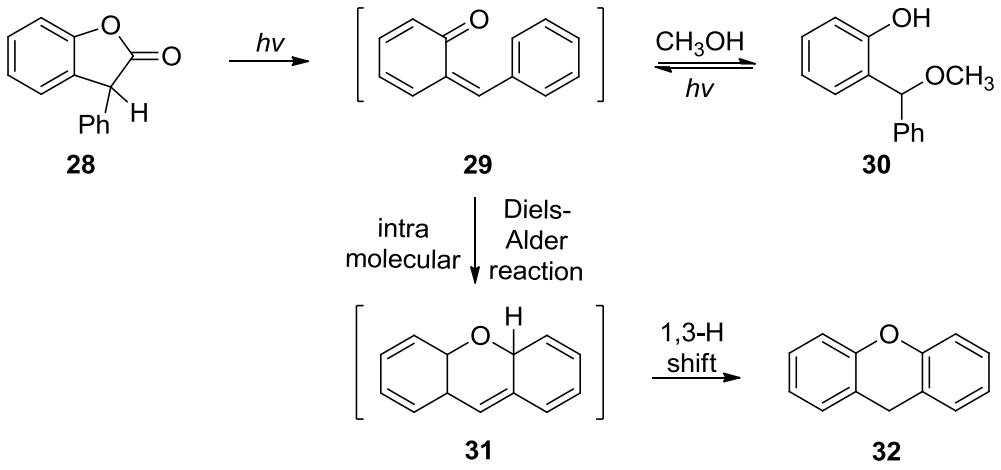
Scheme 1.10 *Cycloaddition and Michael reactions of o-quinone methide produced by 2-(hydroxymethyl)phenol. (i) 424 K (ii) CH_3OH (iii) ethyl vinyl ether, CH_3OH, 475 K.*

[34] Sprengling, G. R. *J. Am. Chem. Soc.* **1952**, *74*, 2937-2940.
[35] Dorrestijn, E.; Kranenburg, M.; Ciriano, M. V.; Mulder, P. *J. Org. Chem.* **1999**, *64*, 3012-3018.

1.1.1.4. Photochemical initiation

The advantage in generating *o*-quinone methide by photochemical excitation is that the reaction can be performed even at lower temperatures. However, by this method, many of the precursors remain unstable and are difficult to purify. The light energy required by most precursors to facilitate the generation of *o*-quinone methide is high (short λ) and this results in unwanted side reactions and difficulties in purification as well. These unwanted side reactions occur because functional groups or nucleophiles used to trap the *o*-quinone methide can be excited into a reactive state, due to the high energy applied. Hence photolysis cannot tolerate a wide range of substituents and solvents.

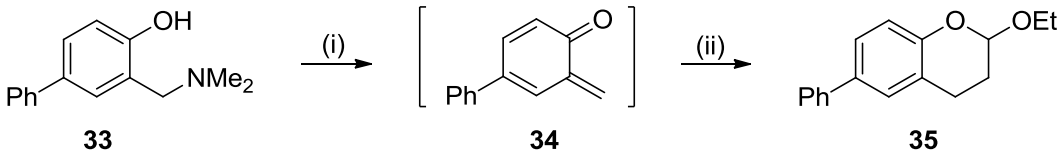
In 1973, Padwa and Lee[36] studied the behavior of the 3-phenyl-1-benzofuran-2(3*H*)-one **28** using light irradiation and the products obtained were *o*-hydroxybenzhydryl methyl ether **30** and xanthene **32** (Scheme 1.11). These two products were derived from the *o*-quinone methide **29** generated by the photochemical excitation of **28**. Michael addition of the solvent, methanol, to the *o*-quinone methide gave ether **30**. In the case of xanthene **32** formation, intramolecular cycloaddition of **29** gives the tricyclic intermediate **31** which undergoes 1,3-hydride shift that leads to the product.



Scheme 1.11 *Michael addition and intramolecular hetero Diels-Alder of the o-QM photochemically generated from 3-phenyl-1-benzofuran-2(3H)-one. (i) hv, CH_3OH.*

[36] Padwa, A.; Lee, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 6147-6149.

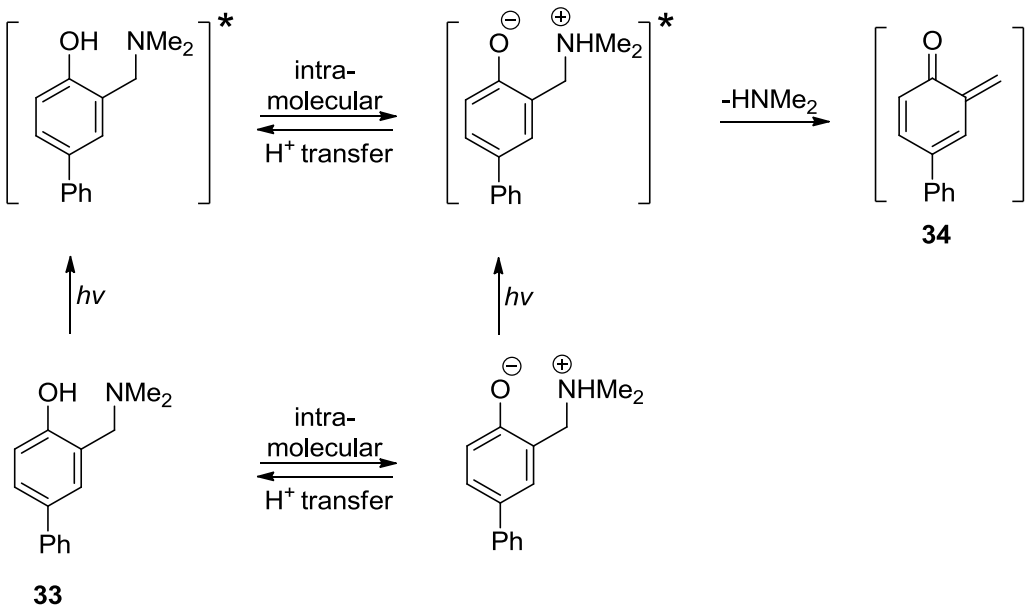
In 1997, Saito and co-workers[37] reported the efficient generation of *o*-quinone methide intermediates from Mannich bases of phenol derivatives in aqueous solvents at neutral pH, by applying low energy UV irradiation (> 300 nm). The existence of an *o*-quinone methide intermediate was evidenced by the addition of excess of ethyl vinyl ether to the reaction mixture (Scheme 1.12). Since formation of the *o*-quinone methide from **33** was found to be



33 **34** **35**

Scheme 1.12 *(i) hv, (> 300 nm), aq. CH_3CN (ii) ethyl vinyl ether.*

highly accelerated in aqueous solvents compared to aprotic solvents, it was suggested that the reaction may proceed via an ionic species. The reactions of **33** at various pH showed that the formation of chroman **35** was most efficient at neutral pH whereas efficiency decreased as the pH increased at alkaline region. Based on these experimental observations, the most likely mechanism for the photochemical generation of *o*-quinone methide from **33** is shown in Scheme 1.13.



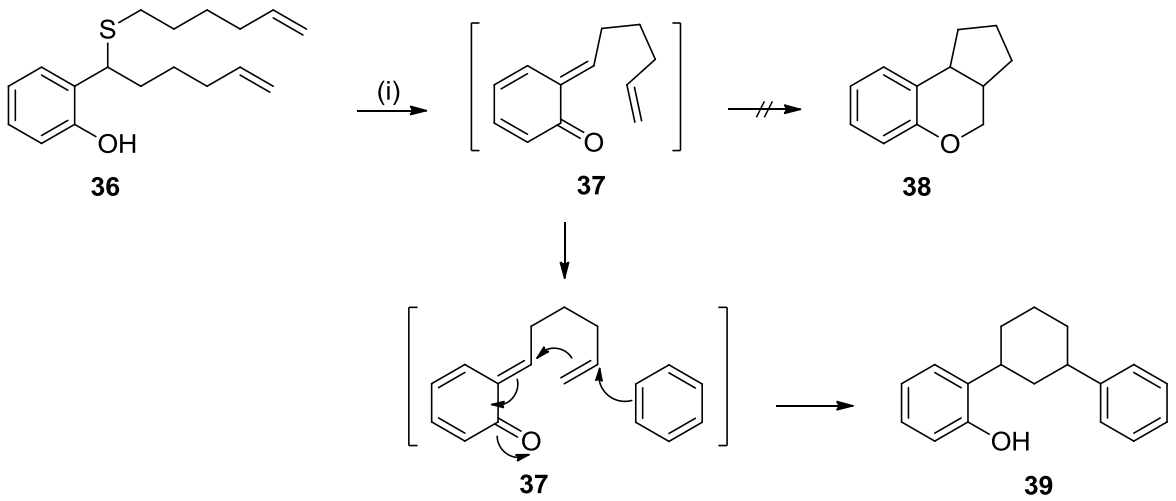
Scheme 1.13 *Photochemical excitation of the Mannich base of a phenol to generate an o-quinone methide.*

[37] Nakatani, K.; Higashida, N.; Saito, I. *Tetrahedron* **1997**, *38*, 1993-2001.

1.1.1.5. Acid facilitation

Addition of small amount of acid induces the thermal and tautomerization processes towards *o*-quinone methide formation to occur at lower temperatures. Acidic silica gel promotes formation of the *o*-quinone methide which in turn undergoes dimerization and trimerization. Except of phenol, acids can generate *o*-quinone methide also from the stable precursors obtained from phenol. These precursors can be prepared from phenols by the protection of the hydroxyl group by an acid labile protecting group, thereby affording some temporary stability to the *o*-quinone methide precursor.

Acidic conditions reduce the range of nucleophiles that can be used to trap the *o*-quinone methide. In 1990, Saito and co-workers[38] reported the generation of *o*-quinone methides using Lewis acid catalysis. Treatment of *o*-[1-(alkylthio)alkyl]phenols, such as compound **36**, with BF_3 did not undergo the intramolecular hetero Diels-Alder reaction to afford hexahydrocyclopenta[*c*]chromene **38** but instead gave 2-(3-phenylcyclohexyl)phenol **39** (Scheme 1.14). It is postulated that *o*-quinone methide **37** generated from the phenol **36** failed to undergo intramolecular hetero Diels-Alder reaction towards **38** but instead the exocyclic alkene group added intramolecularly in Michael fashion followed by addition of benzene to the resulting carbocation, to afford **39**.

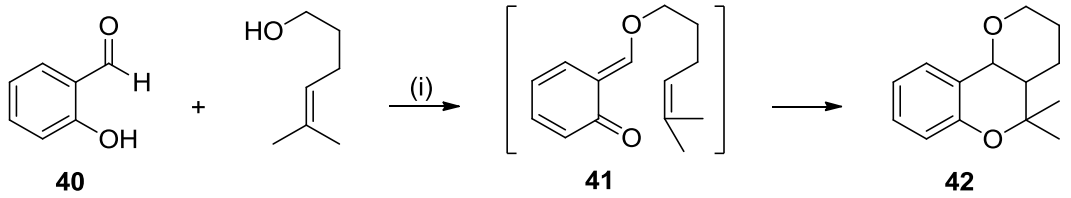


36 **37** **38** **37** **39**

Scheme 1.14 *Intramolecular Michael addition to an o-quinone methide, generated from 2-[1-(hex-5-en-1-ylthio)hex-5-en-1-yl]phenol, with concomitant solvent addition. (i) BF_3OEt_2, benzene, r.t.*

[38] Inoue, T.; Inoue, S.; Saito, K. *Bull. Chem. Soc. Jpn* **1990**, *63*, 1647-1652.

The generation of *o*-quinone methide by using *p*-toluenesulfonic acid as a catalyst is reported by Inoue and co-workers.[39] In this reaction, salicylaldehyde **40** undergoes acetylisation by 5-methylhex-4-en-1-ol in the presence of triethylorthoformate and the resulting *o*-quinone methide adduct **41** is trapped intramolecularly by the side-chain terminal alkene to give a hetero Diels-Alder cycloaddition reaction that produces pyranochromene **42** (Scheme 1.15).



40 **41** **42**

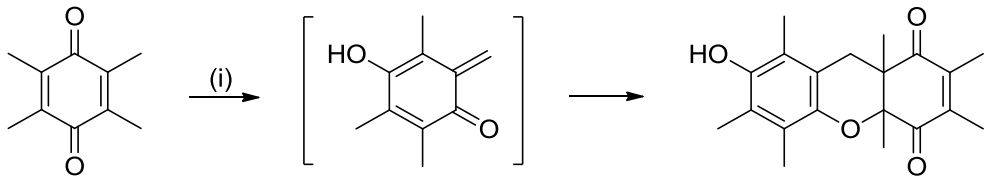
Scheme 1.15 *Formation of pyranochromene derivatives via o-quinone methide intermediates. (i) $CH(OCH_3)_3$, p-toluenesulfonic acid, benzene.*

1.1.1.6. Base facilitation

Similar to acid, base can also induce the thermal and tautomerization processes to occur for the generation of *o*-quinone methides from suitable precursors. Under basic conditions most of the nucleophiles are found to be stable and reactive but the situation differs in case of reactions initiated by thermal, photolytic or acidic conditions.

In 1944, Smith and co-workers[40] found that the addition of base facilitates the tautomerization of quinones that leads to the formation of *o*-quinone methides. Duroquinone **43** when heated with aqueous solution of potassium hydroxide gives the dimer xanthene-1,4-dione **45**, the formation of which is supposed to occur via the in situ generated *o*-quinone methide **44** (Scheme 1.16).

[39] Miyazaki, H.; Honda, Y.; Honda, K.; Inoue, S. *Tetrahedron Lett.* **2000**, *41*, 2643-2647.
[40] Smith, L. I.; Roy Tess, W. H.; Ullyot, G. E. *J. Am. Chem. Soc.* **1944**, *66*, 1320-1323.

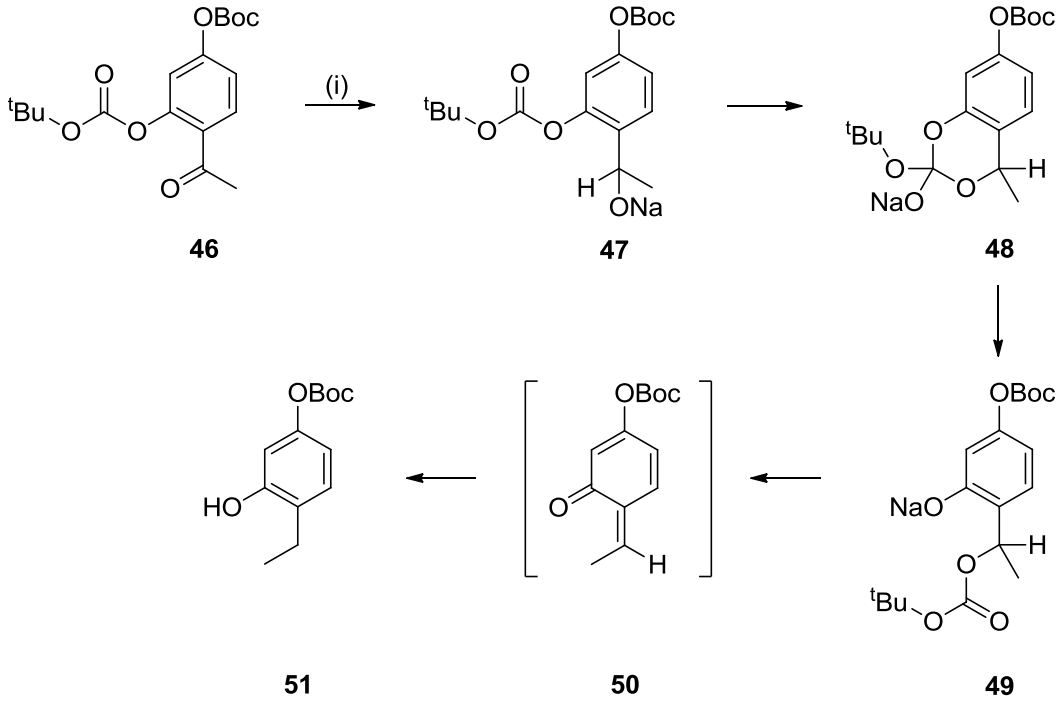


Scheme 1.16 *Formation of a xanthene-1,4-dione derivative via dimerisation of the o-quinone methide of duroquinone. (i) 15% KOH, EtOH.*

In recent years Pettus and co-workers[41,42] have reported the synthesis of *ortho*-ring alkylated phenols from suitably substituted aromatic aldehydes, ketones or esters. For example using ketone **46** as starting material, the reaction is initiated by the addition of hydride ion to the ketone carbonyl to obtain intermediate **47** which undergoes an acyl group transfer via the bicyclic intermediate **48**, to produce the phenoxide **49**. The phenoxide in turn gives the *β*-elimination product **50** which is *o*-quinone methide. The latter undergoes Michael addition by a second hydride ion to restore aromaticity to give the *o*-alkylated phenol **51** (Scheme 1.17).

The reaction can be stopped for a short period of time at intermediate **47** by adding sodium borohydride at low temperature. Treatment of this intermediate with an excess of Grignard reagent reinitiates the cascade to generate *o*-quinone methide **50** and produce the *o*-alkylated phenol.

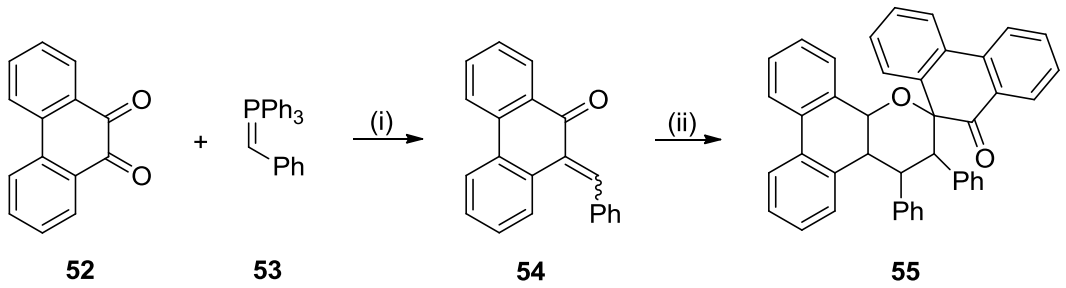
[41] De Water, R. W.; Magdziak, D. J.; Chau, J. N.; Pettus, T. R. R *J. Am. Chem. Soc*. **2000**, *122*, 6502-6503.
[42] Jones, R. M.; De Water, R. W.; Lindsey, C. C.; Hoarau, C.; Ung, T.; Pettus, T. R. R *J. Org. Chem.* **2001**, *66*, 3435-3441.



Scheme 1.17 *Synthesis of an ortho-ring alkylated phenol from an aromatic aldehyde via hydride addition to an o-quinone methide. (i) $NaBH_4$, THF-H_2O (1:1).*

1.1.1.7. Olefination of *o*-quinones

Only a few examples of generating *o*-quinone methides by mono-olefination of *o*-quinone compounds are known in the literature. This is because only a few examples of *o*-quinones are available. In 1969, Shechter and co-workers[43] were the first to report the generation of the stable *o*-quinone methide **54** via olefination of 9,10-phenanthrenequinone

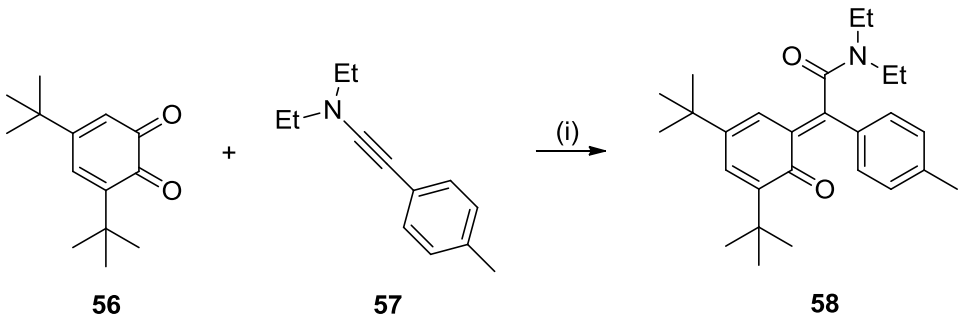


Scheme 1.18 *Formation of a stable o-quinone methide that is heated to dimerise. (i) DMSO, 25 °C, (ii) heat.*

[43] Sullivan, W. W.; Ullman, D.; Shechter, H. *Tetrahedron Lett.* **1969**, *6*, 457-461.

54 with benzylidenetriphenylphosphorane **53**. When heated, *o*-quinone methide **54** undergoes rapid dimerization to give the Diels-Alder adduct **55** (Scheme 1.18).

Bos and co-workers[44] demonstrated that the condensation of 3,5-di-*tert*-butylbenzo-1,2-quinone **56** with ynamine **57** at room temperature yielded the stable *o*-quinone methide **58**. The reaction proceeds through a net [2+2] reaction of the ynamine with one of the carbonyls of the quinone. An electrocyclic reaction then provides the *o*-quinone methide amide **58** (Scheme 1.19). The stability of **58** is due to the extended conjugation while steric hindrance is preventing dimerisation. The compound is stable enough to be isolated.

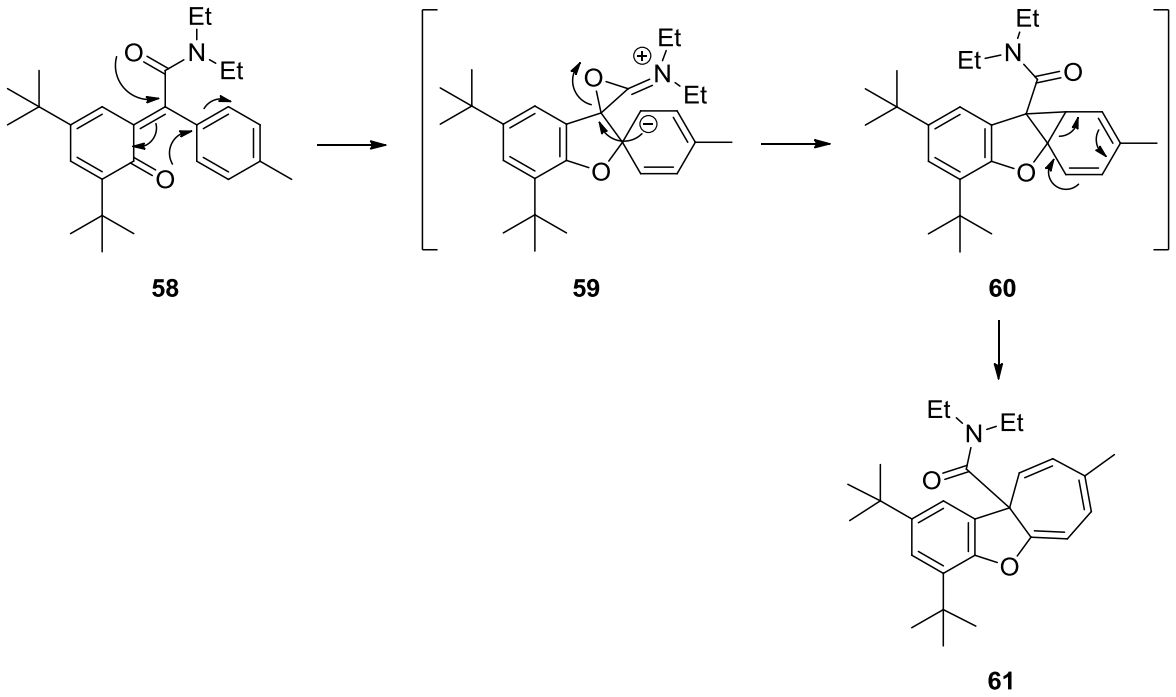


56 **57** **58**

Scheme 1.19 *Formation of a very stable o-quinone methide that does not dimerise (i) $CHCl_3$, rt.*

Photochemical irradiation of **58** gave a rearranged product **61** consisting of a cycloheptatriene ring fused to a benzofuran ring. No dimerisation product was detected. The mechanism of this conversion is shown in Scheme 1.20.

[44] Verboom, W.; Bos, H. J. T. *Tetrahedron Lett.* **1978**, *14*, 1229-1230.



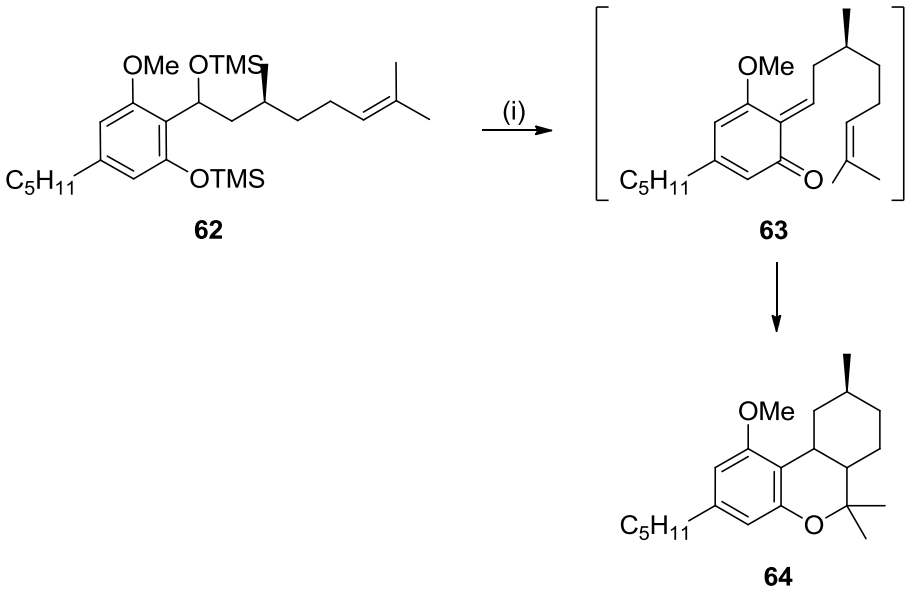
Scheme 1.20 *Mechanism of formation of a benzo[b]cyclohepta[d]furan-10a-carboxamide derivative from an o-quinone methide.*

1.1.1.8. Fluoride induction

This method of generating *o*-quinone methides by exposing an *O*-silylated phenols to the fluoride ion is recently preferred over all the other methods. The method has more advantages compared to all the other methods. Lower temperature, less energy, stable precursors, quick and easy reactions, compatibility of nucleophiles and other functional groups with the fluoride ion and controlled formation of *o*-quinone methide intermediate, are some of the advantages of this method. In the reaction sequence, to generate the *o*-quinone methide, 1,4-elimination of the protecting group occurs followed by phenolic anion induced elimination of a leaving group. This method was used in 1984 by Marino and co-workers,[45] who used cesium fluoride to eliminate the TMS group from the disilyl derivative of *o*-hydroxybenzyl alcohol **62** in order to generate *o*-quinone methide **63** which then underwent intramolecular cycloaddition to afford the methyl ether of the

[45] Marino, J. P.; Dax, S. L. *J. Org. Chem.* **1984**, *49*, 3671-3672.

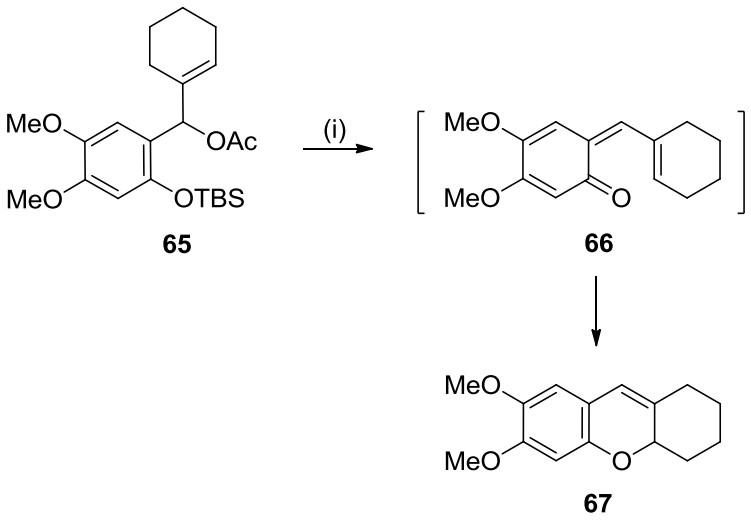
hexahydrocannabinol **64** (Scheme 1.21). Demethylation of the methyl ether gave optically active (-)-hexahydrocannabinol.



62 **63** **64**

Scheme 1.21 *Synthesis of (-)-hexahydrocannabinol using o-quinone methide methodology. (i) CsF, CH_3CN, reflux.*

Recently this method was used for the synthesis of the biologically active natural product puupehedione.[46] The starting material in this reaction, [(2-*tert*-butyldimethylsilyl



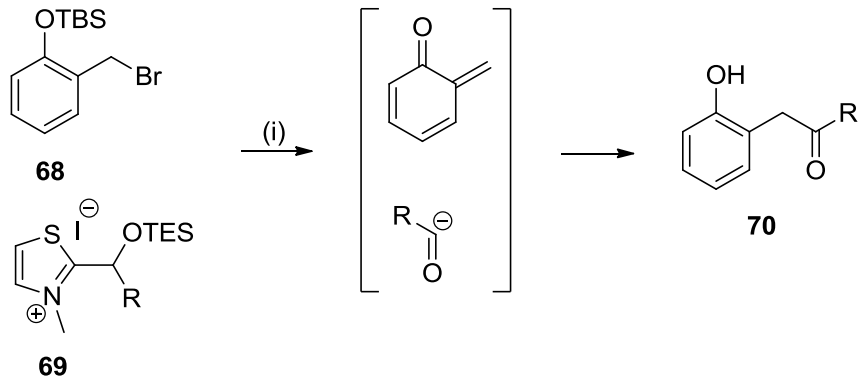
65 **66** **67**

Scheme 1.22 *Synthesis of a puupehedione analogue via an o-quinone methide intermediate. (i) TBAF, benzene, rt.*

[46] Barrero, A. F.; Quilez del Moral, J. F.; Herrador, M. M.; Arteaga, P.; Cortes, M.; Benites, J.; Rosellon, A. *Tetrahedron* **2006**, *62*, 6012-6017.

oxy)-4,5-dimethoxyphenyl)(cyclohexenyl)]methyl acetate **65**, was subjected to *tetra*-butylammonium fluoride (TBAF) as the fluoride ion source which induced 1,4-elimination of the acetate group forced by the deprotection of the oxygen in OTBS to give *o*-quinone methide **66**. Intermediate **66** is then trapped in the intramolecular hetero Diels-Alder cycloaddition to obtain the required product **67** (Scheme 1.22).

Scheidt and co-workers[47] used this method for the synthesis of α-aryl ketones **70** from [2-(bromomethyl)phenoxy](*tert*-butyl)dimethylsilane **68** and triethylsilyl protected thiazolium-carbinol **69** as a source of carbonyl anion. The fluoride ion released from TBAF eliminates TBSF by attacking the silyl atom of **68** and the remainder phenolic anion eliminates bromine ion to give *o*-quinone methide onto which Michael addition takes place from the released carbonyl anion to give product **70** (Scheme 1.23).



Scheme 1.23 *Synthesis of α-aryl ketones. (i) TBAF, CH_2Cl_2, -78 °C.*

1.1.2. Reactivity of *o*-quinone methides

The *o*-quinone methide is highly reactive and very unstable moiety so that it must be generated *in situ* and trapped instantaneously. This property of *o*-quinone methides severely limits the range of reactions they can take part in. This transient species contains an α,β-unsaturated carbonyl group as well as a hetero diene system endowed to give a wide variety of applications in synthetic chemistry. The presence of an exocyclic α,β-unsaturated carbonyl system makes the *o*-quinone methide a Michael acceptor. A more

[47] Mattson, A. E.; Scheidt, K. A . *J. Am. Chem. Soc.* **2007**, *129*, 4508-4509

interesting reactive site in the *o*-quinone methide is the hetero diene system, which is not found in *p*-quinone methide. The hetero diene system can undergo intramolecular as well as intermolecular [4+2] hetero Diel-Alder reactions.

1.1.2.1. [4+2] Cycloadditions

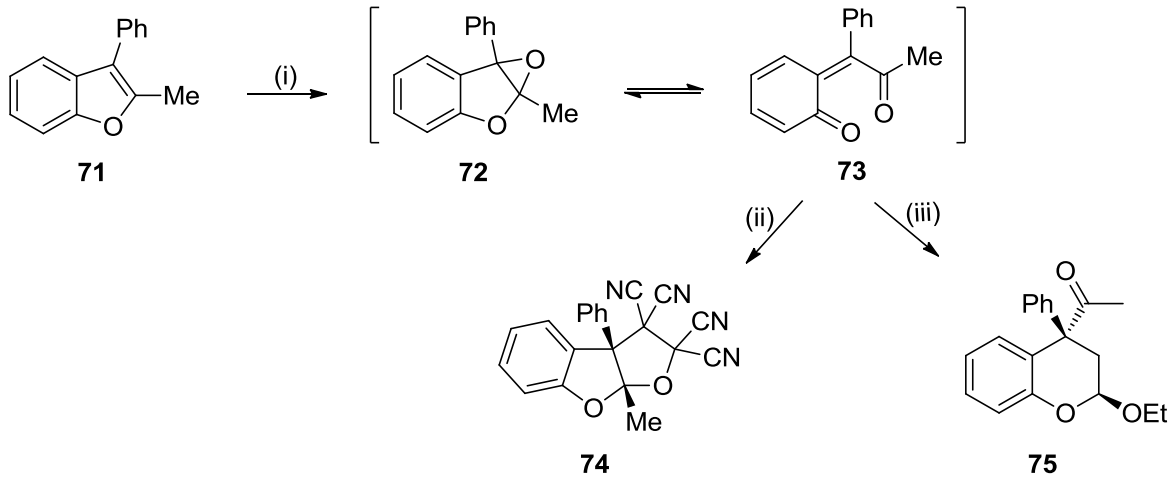
o-Quinone methide actually undergoes inverse-electron demand hetero Diels-Alder reaction wherein the hetero diene is electron poor and the dienophile has to be electron rich. The presence of an electron withdrawing oxygen atom in an *o*-quinone methide makes the hetero diene moiety electron deficient and prone to undergo the inverse electron demand hetero Diels-Alder reaction. In the standard Diels-Alder reaction the strongest orbital interaction is between the HOMO of the diene and LUMO of the dienophile whereas in the inverse-electron demand hetero Diels-Alder reaction the strongest orbital interaction is between the LUMO of the diene and HOMO of the dienophile.

a) Intermolecular cycloadditions

The formation of an adduct by a hetero Diels-Alder reaction derived from an in situ generated *o*-quinone methide in the presence of a dienophile, is indirect evidence of formation of the *o*-quinone methide. The selectivity of the products formed in this reaction depends upon the orientation of the transition state, geometry of the starting *o*-quinone methide and the relative stability of the respective diastereomeric products.

The first *o*-quinone methide reported to be trapped by an intermolecular cycloaddition reaction was in 1952 by Sprengling.[34] (Scheme 1.9). In 1993, Adam and co-workers[48] reported the formation of **74** and **75** explaining that epoxidation of 2-methyl-3-phenylbenzofuran **71** formed first intermediate epoxide **72** which was trapped by tetracyanoethylene in a 1,3-dipolar cycloaddition reaction to afford benzofurofuran **74**. They also reported that chroman **75** was produced from the cycloaddition of **73** with ethyl vinyl ether (Scheme 1.24).

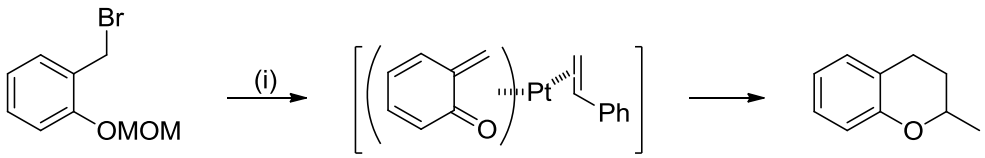
[48] Adam, W.; Hadjiarapoglou, L.; Peters, K.; Sauter, M. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 735-736.



71 **72** **73** **74** **75**

Scheme 1.24 *Ring-opening of 2-methyl-3-phenyl-1-benzofuran during epoxidation and cycloaddition of transient o-quinone methide. (i) dimethyldioxirane, acetone, -70°C to -20°C (ii) tetracyanoethylene, $CDCl_3$ (iii) ethyl vinyl ether, $CDCl_3$.*

Recently *o*-quinone methide generated from 1-(bromomethyl)-2-(methoxymethoxy)benzene using Pt(IV) or Au(III) catalysts was claimed to react with styrene, also activated by the catalysts, and thus providing an improved process of intermolecular 1,3-dipolar cycloaddition (Scheme 1.25).[49]



76 **77** **78**

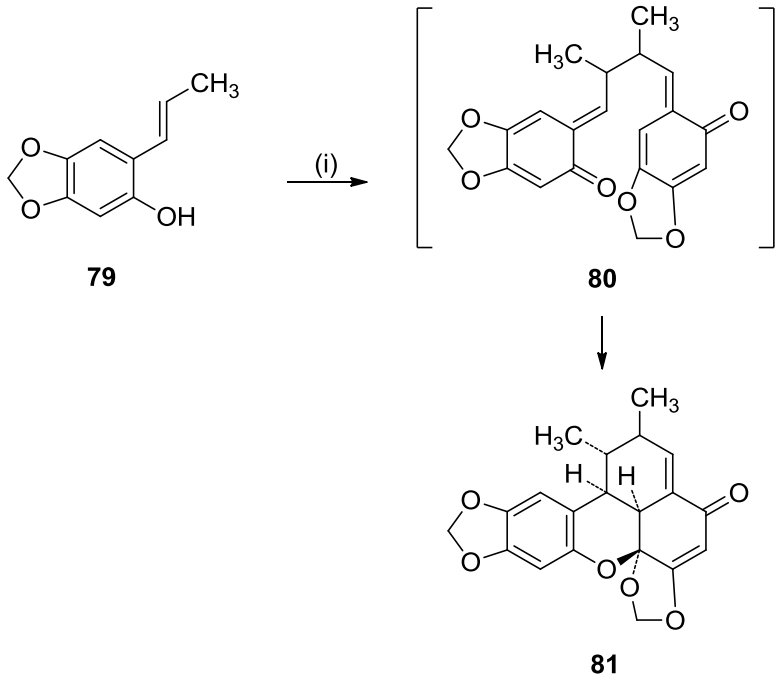
Scheme 1.25 *Synthesis of 2-methylchromane via a Pt(IV) or Au(III) catalysed o-quinone methide and alkene cycloaddition reaction. (i) $PtCl_4$, styrene, CH_2Cl_2.*

b) Intramolecular cycloadditions

These reactions are found to occur in the case of substituted *o*-quinone methides with a substituent that contains an alkene group. After *o*-quinone methide generation cycloaddition with the tethered alkene group gives the cyclic product. This type of reaction is helpful in the synthesis of natural products.

[49] Radomkit, S.; Sarnpitak, P.; Tummatorn, J.; Batsomboon, P.; Ruchirawat, S.; Ploypradith, P. *Tetrahedron* **2011**, *67*, 3904-3914.

Carpanone **81**, a lignin obtained from the bark of the carpano tree, is a significant synthetic challenge. The molecule possesses no element of symmetry and has five contiguous asymmetric centres. In 1971, Chapman and co-workers[50] found a method whereby carpanone is synthesized from 6-[(1*E*)-prop-1-en-1-yl]-1,3-benzodioxol-5-ol **79**. The reaction proceeds by oxidative coupling of the styryl double bonds of two molecules of **79** by palladium(II) chloride. The intermediate *o*-quinone methide **80** produced undergoes intramolecular cycloadditions to afford the product **81** (Scheme 1.26).

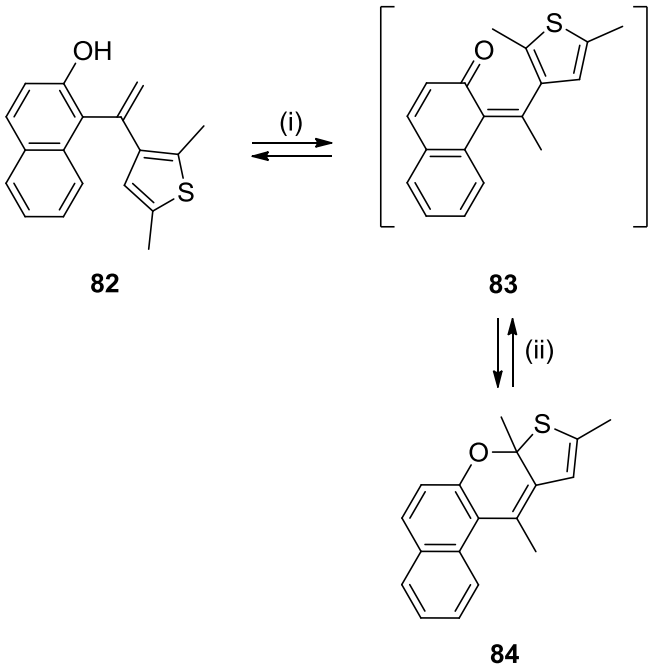


79 **80** **81**

Scheme 1.26 *Synthesis of the lignin carpanone using o-quinone methide methodology. (i) $PdCl_2$, sodium acetate, MeOH, H_2O, 38 °C.*

Uchida and Irie[51] reported photolytic excited state intramolecular proton transfer taking place in 1-[1-(2,5-dimethyl-3-thienyl)vinyl]-2-naphthol to generate of *o*-quinone methide **83** which was then trapped in an intramolecular cycloaddition reaction to afford tetracyclic 7a,9,11-trimethyl-7a*H*-benzo[*f*]thieno[2,3-*b*]chromene **84**. The reaction was found to be photoreversible at different wavelength which proves indirectly the formation of *o*-quinone methide **83**, by an electrocyclic ring opening reaction.

[50] Chapman, O. L.; Engel, M. R.; Springer, J. P.; Clardy, J. C. *J. Am. Chem. Soc.* **1971**, *93*, 6696-6698.
[51] Uchida, M.; Irie, M. *Chem. Lett.* **1991**, 20, 2159-2162.



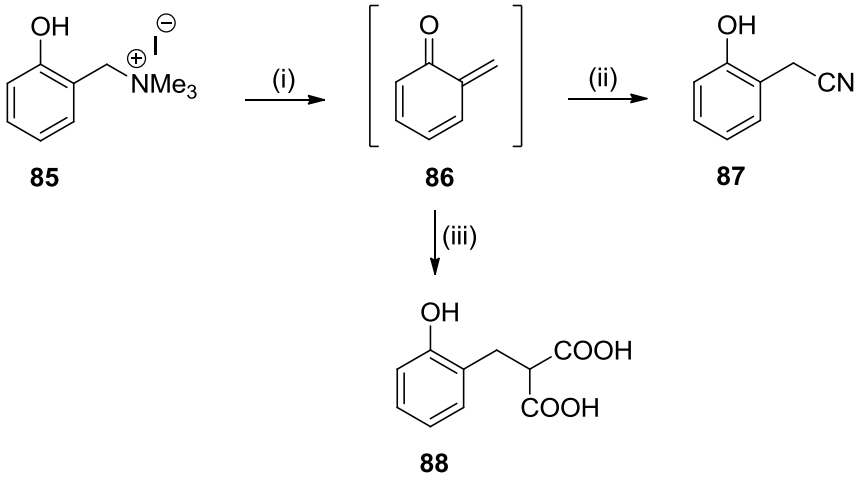
Scheme 1.27 *Synthesis of a benzo[f]thieno[2,3-b]chromene derivative using o-quinone methide methodology. (i) hv, 300 nm, (ii) hv, 400 nm.*

1.1.2.2. Addition of a nucleophile (Michael reaction)

The *o*-quinone methide system is similar to the α,β-unsaturated carbonyl system in Michael addition reactions. The range of nucleophiles which can be used to trap the *o*-quinone methide is limited under conditions used to generate the *o*-quinone methide. Acidic, oxidative or thermal conditions might result in unwanted side reactions with the nucleophile. Also under these conditions the efficiency of *o*-quinone methide to act as a Michael acceptor is reduced as the intermediate tends to dimerise as soon as it is generated.

Gardner and co-workers[52,53] were the first to report this behaviour of *o*-quinone methides. They treated (2-hydroxybenzyl)trimethylammonium iodide **85** with sodium methoxide and then added a nucleophile such as cyanide anion or the potassium salt of diethyl malonate. The first step of the reaction is postulated to give *o*-quinone methide **86** which then undergoes

[52] Gardner, P. D.; Sarrafizadeh, H.; Rafsanjani; Rand, L. *J. Am. Chem. Soc.* **1959**, 81, 3364-3367.
[53] Merijan, A.; Gardner, P. D. *J. Org. Chem.* **1965**, *30*, 3965-3967.

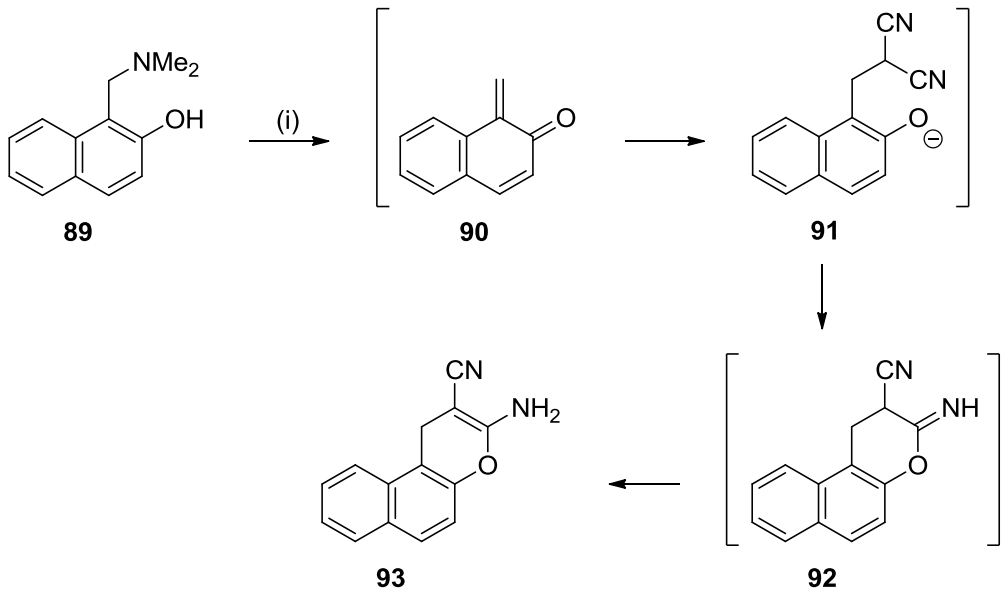


Scheme 1.28 *Synthesis of o-alkylated phenols via an o-quinone methide intermediate. (i) $NaOCH_3$, EtOH, (ii) NaCN, (iii) $CH_2(CO_2Et)_2$, KOH, benzene.*

Michael addition by the nucleophiles to afford phenol derivatives **87** and **88**, respectively (Scheme 1.28).

Recently, Osyanin and co-workers[54] have reported the synthesis of 3-amino-1*H*-benzo[*f*]-chromene-2-carbonitrile **93** by addition of malononitrile to 1-[(dimethylamino)methyl]-2-naphthol **89**. The first step in this reaction is postulated to generate *o*-quinone methide **90** by elimination of dimethylamine from **89** followed by Michael addition of malononitrile carbanion to form **91** which then undergoes intramolecular Pinner reaction to give **92**, that finally tautomerises to benzochromene **93** (Scheme 1.29).

[54] Osipov, D. V.; Osyanin, V. A.; Klimochkin, Y. N. *Russ. J. Org. Chem.* **2013**, *49*, 398-402.



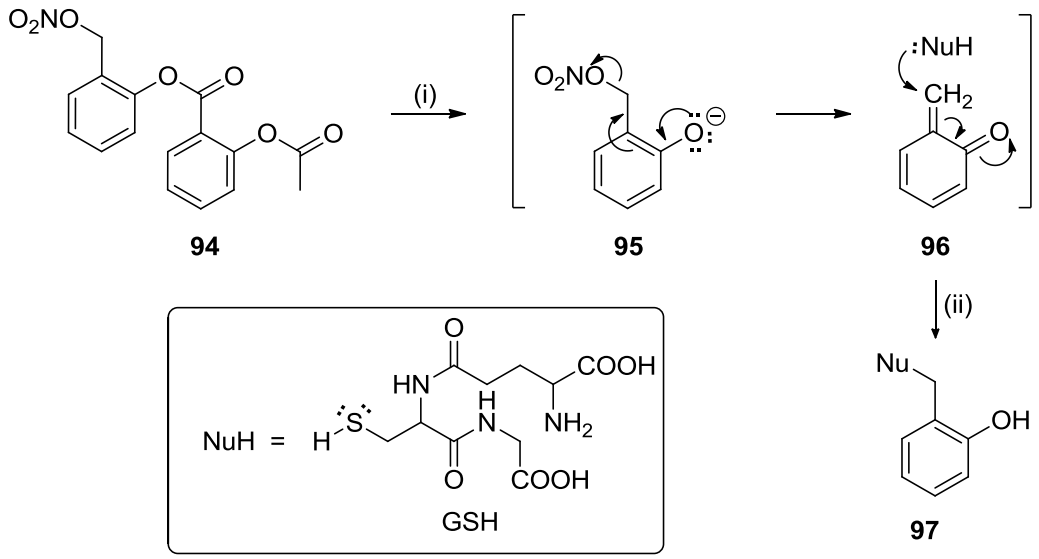
Scheme 1.29 *Synthesis a benzo[f]chromene using o-quinone methide methodology. (i) $CH_2(CN)_2$, EtOH.*

1.1.3. Biologically interesting *o*-quinone methides

o-Quinone methides and their derivatives are common constituents of biological systems. Many quinone methides show pronounced biological activity. They have been implicated as the ultimate cytotoxins responsible for the effects of such agents as antitumor drugs, antibiotics, and DNA alkylators.[55] Oxidation of an appropriate biological molecule to a reactive *o*-quinone methide is the mechanistic basis of many phenolic anti-cancer drugs. Celastrol is a triterpenoid *o*-quinone methide isolated from Tripterygium wilfordi (Thunder of God vine) and Celastrus regelii exhibit antioxidant (15 times the potency of α-tocopherol),[56] anti-inflammatory,[57] anticancer,[58,59] and insecticidal[60] activities.

[55] Wang, P.; Song, Y.; Zhang, L.; He, H.; Zhou, X. *Curr. Med. Chem.* **2005**, *12*, 2893-2913.
[56] Allison, A. C.; Cacabelos, R.; Lombardi,V. R.; Alvarez, X. A.; Vigo, C. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2001**, *25*, 1341-1357.
[57] Kim, D. H.; Shin, E. K.; Kim, Y. H.; Lee, B. W.; Jun, J. G.; Park, J. H.; Kim, J. K. *Eur. J. Clin. Invest.* **2009**, *39*, 819-827.
[58] Lee, J. H; Choi, K. J.; Seo, W. D.; Jang, S. Y.; Kim, M.; Lee, B. W.; Kim, J. Y.; Kang, S.; Park, K. H.; Lee, Y. S.; Bae, S. *Int. J. Mol. Med.* **2011**, *27*, 441-446.
[59] Byun, J. Y.; Kim, M. J.; Eum, D. Y.; Yoon, C. H.; Seo, W. D.; Park, K. H.; Hyun, J. W.; Lee, Y. S.; Lee, J. S.; Yoon, M. Y.; Lee, S. J. *Mol. Pharmacol.* **2009**, *76*, 734-744
[60] Avilla, J.; Teixido, A.; Velazquez, C.; Alvarenga N.; Ferro E.; Canela R. *J. Agric. Food Chem.* **2000**, *48*, 88-92.

A recent example of an *o*-quinone methide in drug chemistry is the NO-ASA hybrid drug **94.**[61] It consists of an ASA (acetylsalicylic acid) molecule and an ONO_2 group connected through a spacer and is at present undergoing preclinical trials aimed at developing an antitumor drug. Until 2007 it was believed that ASA and NO contribute as one molecule to this antitumor effect but later it is shown that rather, the unsubstituted *o*-quinone methide **96** is acting as the sole cytotoxic agent. The proposed mechanism of action is shown in Scheme 1.30. NO-ASA **94** is hydrolysed by the enzyme esterase at the diaryl ester group and the eliminated phenoxide derivative loses nitrate anion to form *o*-quinone methide **96**. The latter is trapped by the cellular nucleophile glutathione, reducing the level of glutathione in the body. Elevated levels of glutathione in tumour cells are able to protect cancerous cells in bone marrow, breast, colon, larynx, and lung cancers.



Scheme 1.30 *Mechanism of action of the NO-ASA hybrid drug. (i) Esterase hydrolysis, (ii) glutathione.*

[61] Hulsman, N.; Medema, J. P.; Bos, C.; Jongejan, A.; Leurs, R.; Smit, M. J.; Esch, I. J. P.; Richel, D.; Wijtmans, M. *J. Med. Chem.* **2007**, *5*, 2424-2431.

1.2. Synthesis of xyloketal derivatives

In 2001 Lin, Y. and co-workers[62] isolated five unique metabolites from the mangrove fungus *Xylaria* sp. 2508, found in the South China Sea, namely xyloketals A, B, C, D, and E**.**

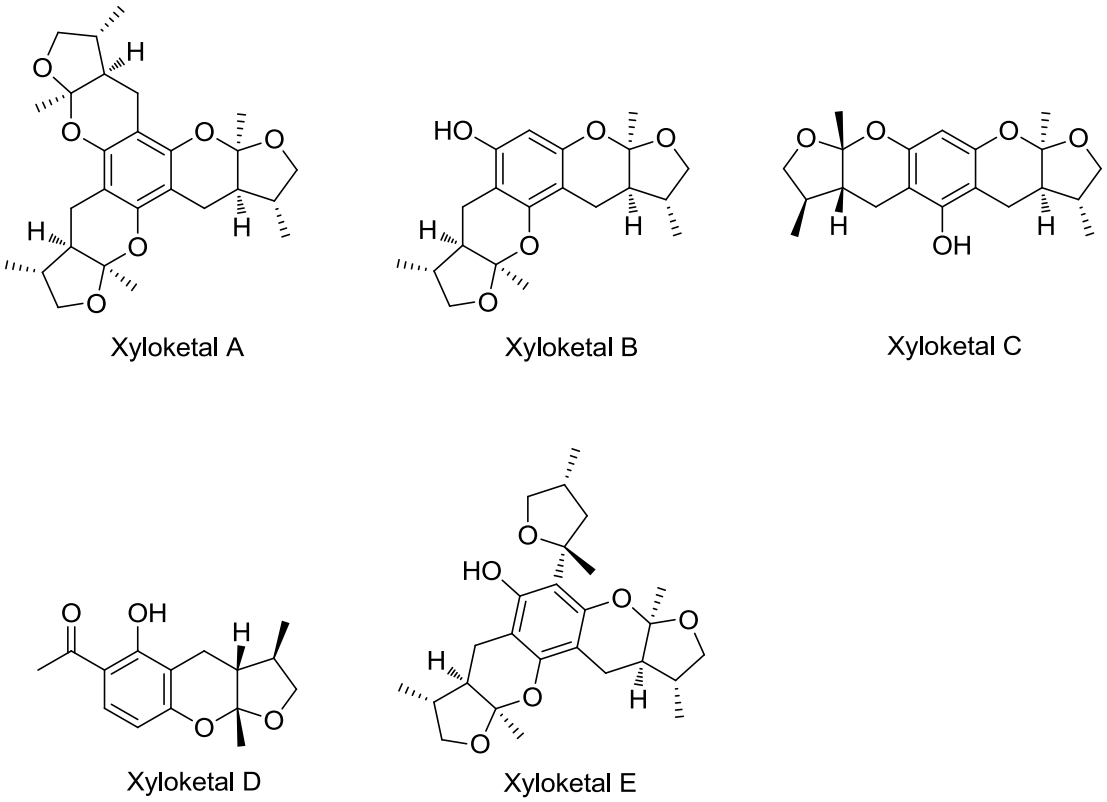
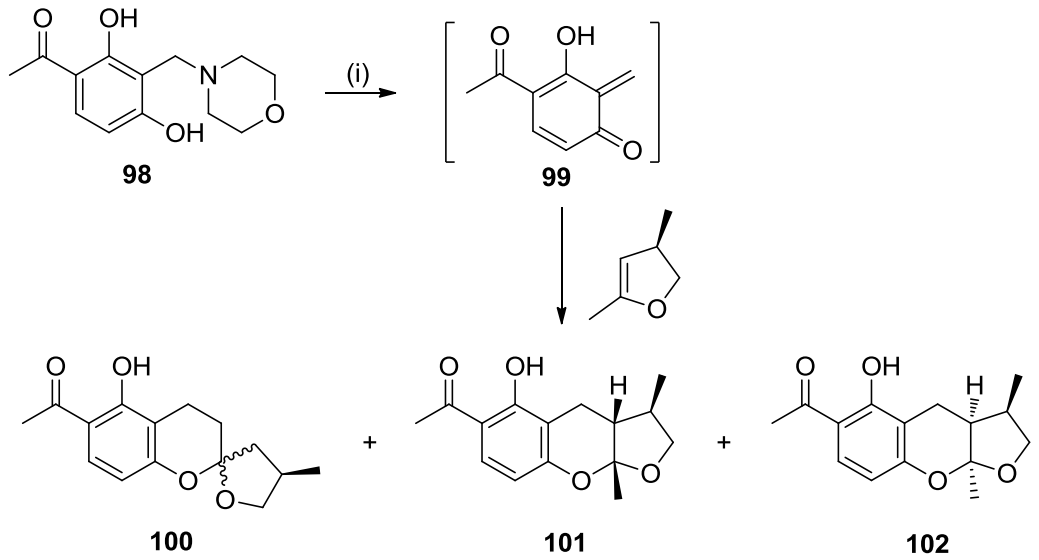


Figure 1.4 *Xyloketal-A, B, C, D, E.*

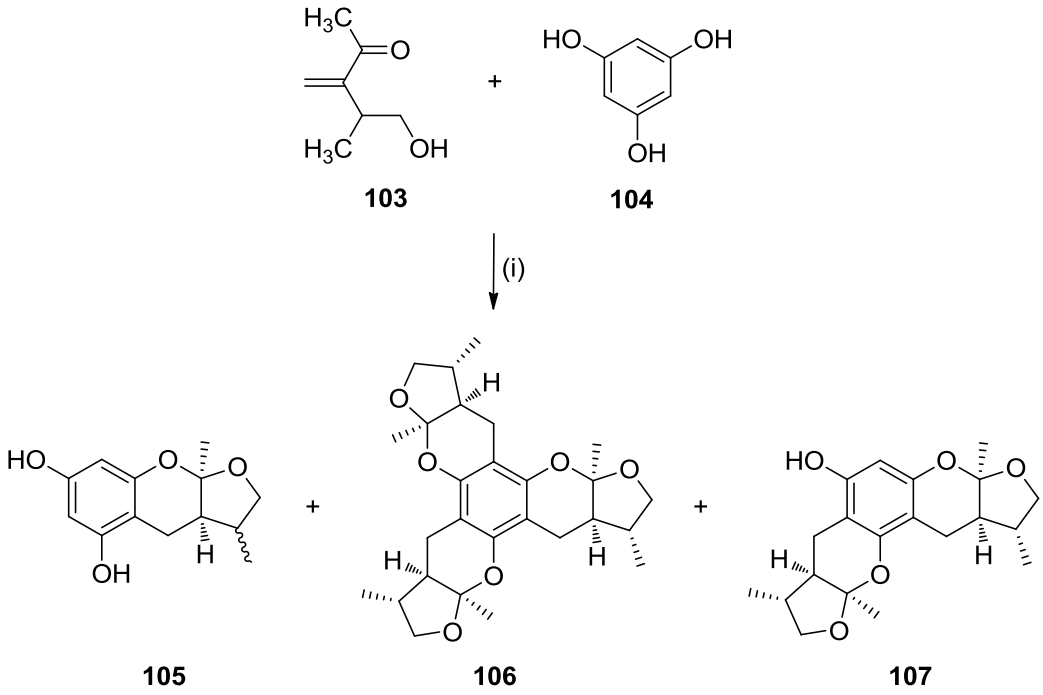
Three years later Wilson and co-workers[63] reported the total synthesis of (-)-xyloketal D (**101**) and its enantiomer (**102**) by the reaction of an *o*-quinone methide **99** with (4*R*)-4,5-dihydro-2,4-dimethylfuran via a diastereoselective inverse electron demand Diels–Alder reaction. This total synthesis confirmed the absolute stereochemistry of the natural product. The *o*-quinone methide was generated by reaction of a functionalized Mannich base with methyl iodide. The diasteromeric spiro acetal **100** is also isolated from the reaction mixture (Scheme 1.31).

[62] Lin, Y.; Wu, X.; Feng, S.; Jiang, G.; Luo, J.; Zhou, S.;Vrijmoed, L. L. P.; Jones, E. B. G.; Krohn, K.; Steingroover, K.; Zsila, F. *J. Org. Chem.* **2001**, *66*, 6252–6256.
[63] Pettigrew, J. D.; Freeman, R. P.; Wilson, P. D. *Can. J. Chem.* **2004**, *82*, 1640–1648.



Scheme 1.31 *Formation of xyloketal D via o-quinone methide methodology. (i) CH_3I, benzene.*

During the non-enantioselective synthesis of xyloketals A and B, Krohn and co-workers[64] reported another member of the xyloketal family *i.e.* xyloketal H, whose structure was later confirmed by Lin and co-workers[65] after isolation and characterization

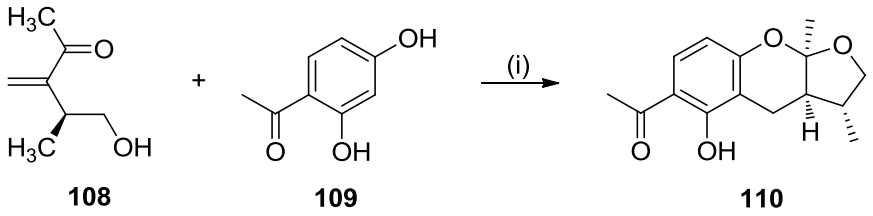


Scheme 1.32 *Formation of xyloketals D, A and B (i) toluene, reflux.*

[64] Krohn, K.; Riaz, M.; Florke, U. *Eur. J. Org. Chem.* **2004**, 1261-1270.
[65] Lin, Y.; Liu, X.; Xu, F.; Zhang, Y.; Liu, L.; Huang, H.;Cai, X.; Chan, W. *Russ. Chem. Bull., Int. Ed.* **2006**, *55*, 1091-1092.

of this natural product from the mangrove fungus *Xylaria* sp. 2508. The condensation of enone **103** (Scheme 1.32) with phloroglucinol **104** lead to the formation of three products xyloketal A, B and H.

Krohn and co-workers[66] later reported the total synthesis of enantiomerically pure (+)-xyloketal D (**110**) by the condensation of the dihydroxy acetophenone with the enantiomerically pure enone **108**.

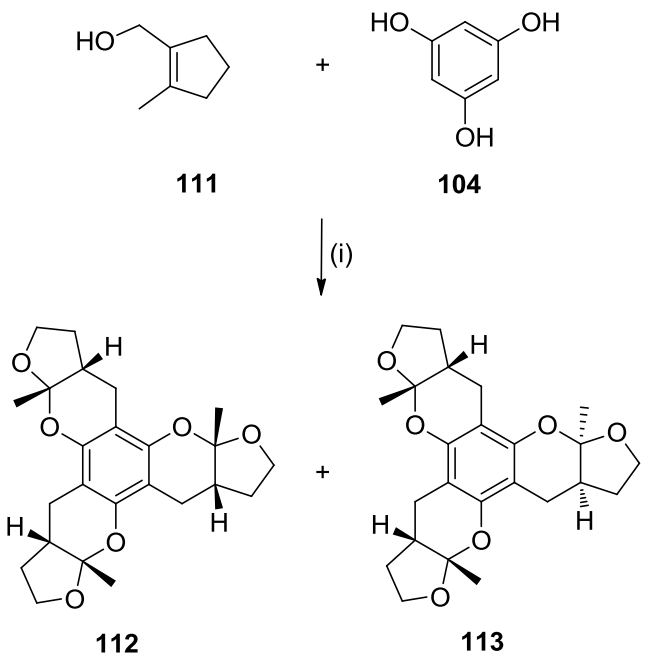


108 **109** **110**

Scheme 1.33 *Formation of (+)-xyloketal D. (i) toluene, reflux.*

Using different methodology, Wilson and co-workers[67] reported the synthesis of two xyloketal A analogues by using a boron trifluoride diethyl etherate-promoted electrophilic aromatic substitution reaction. Treatment of 3-hydroxymethyl-2-methyl-4,5-dihydrofuran **111** with the phloroglucinol **104** produces xyloketal A analogues **112** and **113** (Scheme 1.34).

[66] Krohn, K.; Riaz, M. *Tetrahedron Lett.* **2004**, *45*, 293-294.
[67] Pettigrew, J. D.; Wilson, P. D. *J. Org. Chem.* **2006**, *71*, 1620-1625.



Scheme 1.34 *Synthesis of xyloketal A analogues. (i) BF_3-OEt_2, $MgSO_4$, diethyl ether.*

In 2010 Lin and co-workers[68] prepared a series of xyloketal derivatives to study their application in biology and found out that these compounds can

- relax blood vessels
- enhance angiogenesis
- promote endothelial cell NO production
- attenuate oxLDL-induced oxidative stress

Interestingly, the vasorelaxing action of these derivatives is mediated by both endothelium-independent and endothelium-dependent mechanisms. Furthermore, eNOS-derived NO plays a critical role in endothelium-dependent vasodilatation of xyloketal derivatives.

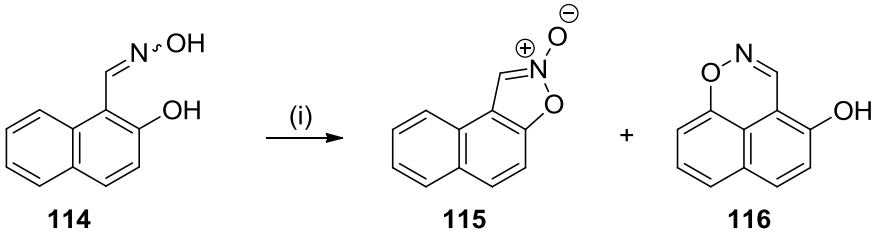
Therefore, they proposed that natural xyloketals and their derivatives will be promising compounds for further evaluation in the treatment of cardiovascular diseases.

[68] Xu, Z.; Li, Y.; Xiang, Q.; Pei, Z.; Liu, X.; Lu, B.; Chen, L.; Wang, G.; Pang, J.; Lin, Y. *J. Med. Chem.* **2010**, *53*, 4642-4653

1.3. *o*-Naphthoquinone nitrosomethide

1.3.1. *o*- and *peri*-Oxidative cyclization

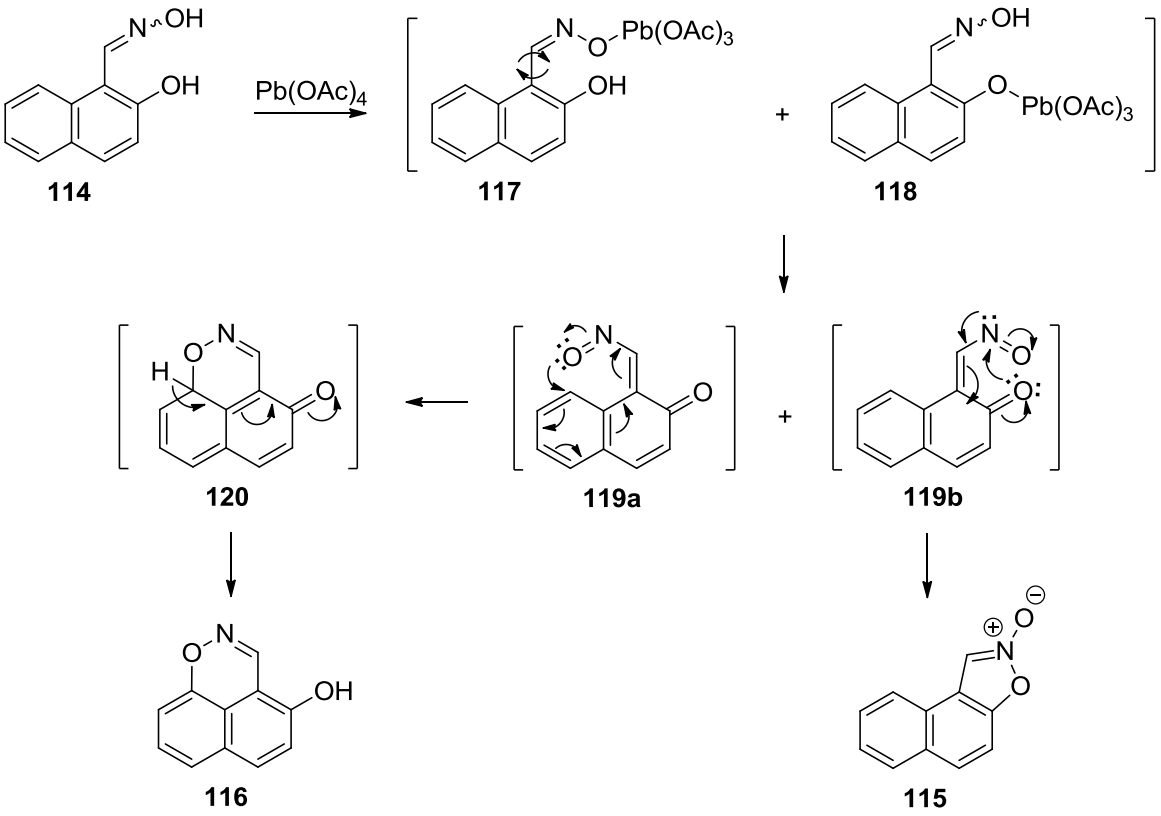
The term *o*-naphthoquinone nitrosomethide was first reported by Varvounis and co-workers[69] in the year 2000. During the course of their study they found out that the treatment of 2-hydroxy-1-naphthaldehyde oxime (**114**) with lead(IV) acetate gives the isomeric naphtho[1,2-*d*]isoxazole 2-oxide (**115**) and naphtho[1,8-*de*][1,2]oxazine (**116**) in a one-pot reaction via *o*- and *peri*-oxidative cyclisation (Scheme 1.35).



Scheme 1.35 *Oxidation of 2-hydroxy-1-naphthaldehyde oxime. (i) $Pb(OAc)_4$, THF, 0 °C.*

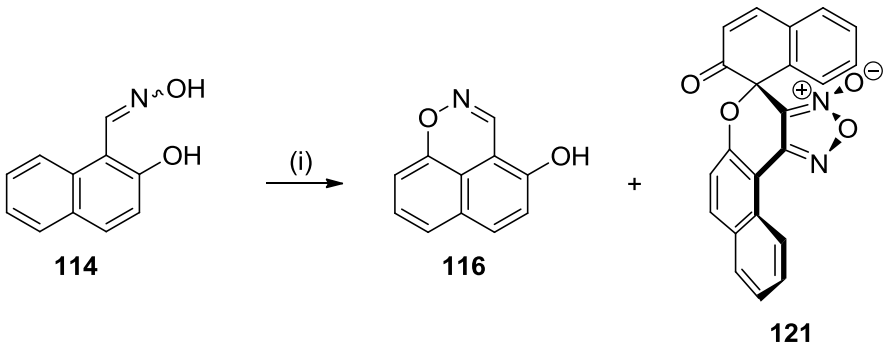
formation of these two products is explained by an intermediate which is produced from two different intermediates. The oxidation of the oxime **114** by lead(IV) acetate can occur at two different positions, either at the oxime oxygen giving rise to intermediate **117** or at the phenolic oxygen giving rise to intermediate **118**. These two intermediates then decompose to either *o*-naphthoquinone nitrosomethide intermediate **119a** or **119b**. These intermediates materialise from the rotation of the side chain before decomposition of the lead acetate complex. The intermediates explain the formation of two different products from the same reaction pot as shown in Scheme 1.36. The formation of **116** is visualised to occur only through the intermediate **119a** as the possibility of rearrangement of **115** to **116** is ruled out since reaction of isoxazole **115** with lead(IV) acetate revealed that the starting material remains unchanged. When this reaction was repeated more than once by the same group, in order to improve the yield of isoxazole **115**, the results obtained were not the same as first.[70]

[69] Supsana, P.; Tsoungas, P. G.; Vavounis, G. *Tetrahedron Lett.* **2000**, *41*, 1845-1847.
[70] Supsana, P.; Tsoungas, P. G.; Aubry, A.; Skoulika, S.; Varvounis, G. *Tetrahedron* **2001**, *57*, 3445-3453.



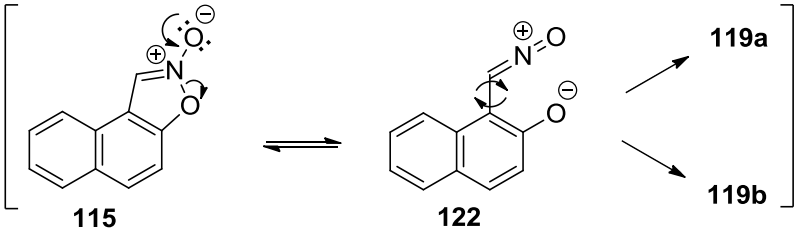
Scheme 1.36 *Oxidation of 2-hydroxy-1-naphthaldehyde oxime and generation of the two forms of o-naphthoquinone nitrosomethide intermediate.*

The results showed that apart from oxazine **116** the second product obtained was not the isoxazole **115** but dimer **121** of the *o*-naphthoquinone nitrosomethide intermediate **119a**/**119b** (Scheme 1.37). This is similar to the dimerisation reaction of *o*-quinone methide in the absence of a nucleophile or a dienophile. The spiro dimer is found to be more stable than the isoxazole-*N*-oxide **115**.



Scheme 1.37 *Oxidation of the oxime (i) Pb(OAc)$_4$, THF, 0°C.*

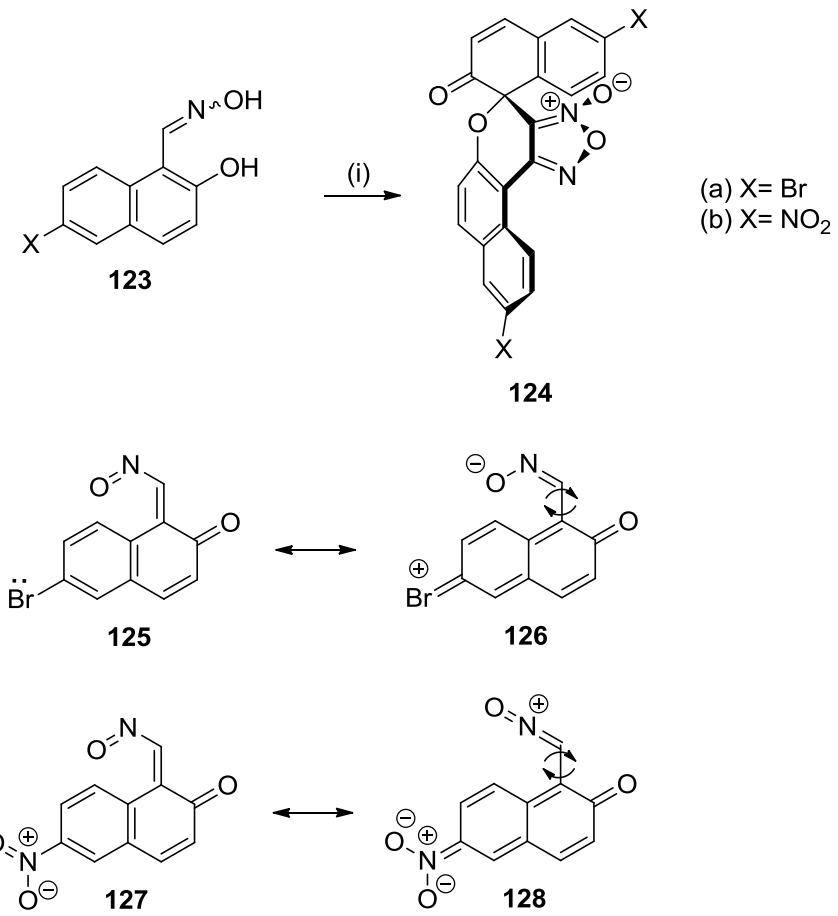
Therefore it is proposed that the isoxazole **115** can be retransformed to the *o*-naphthoquinone nitrosomethide intermediate **119a**/**119b**, via **122**, as shown in Scheme 1.38. Intermediate **119a** will then cyclise into oxazine **116** whereas intermediate **119b** will continue the cycle to isoxazole **115** then **122** and back to **119a**/**119b**, until the occurrence of **119b** in the latter mixture of intermediates is reduced to nothing.



Scheme 1.38 *Reversible conversion of naphthoisoxazole-N-oxide to o-naphthoquinone nitrosomethide.*

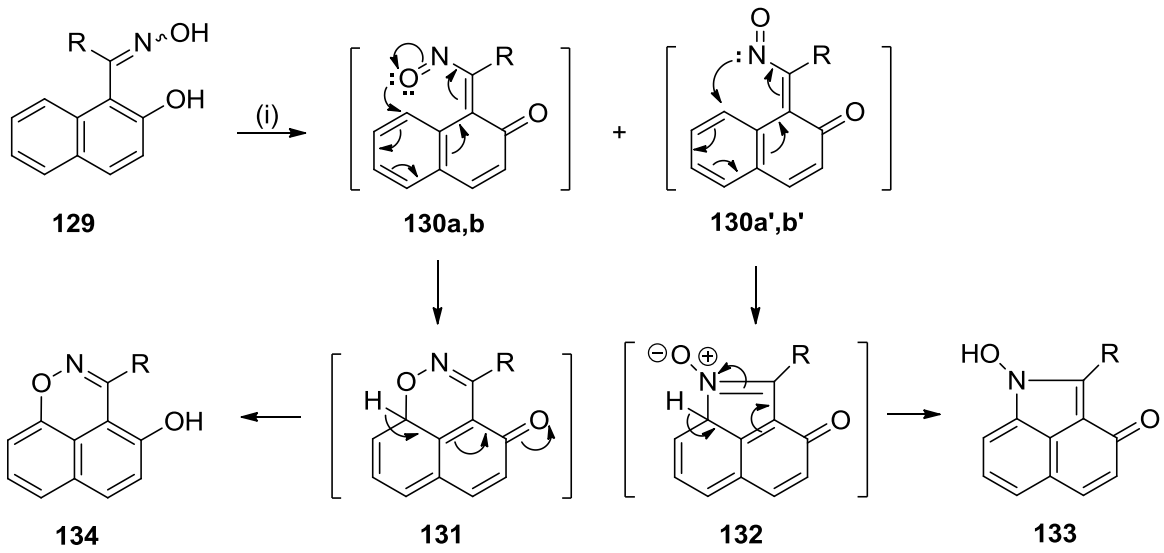
1.3.2. Effect of electron donor and electron attracting substituent

In order to understand the cyclisation behaviour of the *o*-naphthoquinone nitrosomethide intermediate, a marginally electron donating as well as a strongly electron attracting substituent was attached at C-6 of the naphthalene nucleus i.e. compounds **123a** and **123b**. Therefore, oxidation of compounds **123a** and **123b** using lead(IV) acetate afforded the corresponding dimers **124a** and **124b**, as the only isolable products after column chromatography. The absence of oxazines in these reactions is explained by the conjugative effects of the substituent at C-6 of naphthalene nucleus (Scheme 1.39). The resonance structures of the substituted *o*-naphthoquinone nitrosomethides **125** and **127** shows that free rotation of the C–N–O moiety is possible resulting in the blocking of the *peri*-cyclisation and hence not allowing formation of the oxazine derivatives.



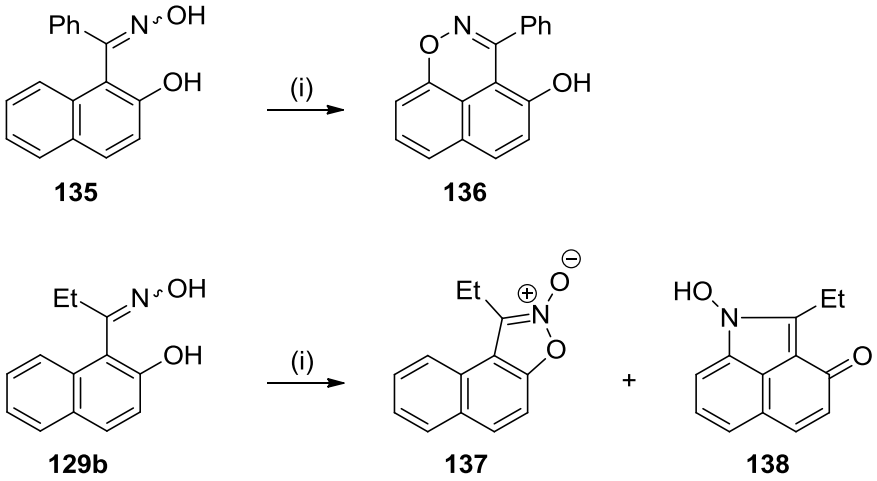
Scheme 1.39 *Oxidation of 6-bromo (or nitro)-2-hydroxy-1-naphthaldehyde oxime. (i) $Pb(OAc)_4$, THF, 0 °C. Resonance forms of intermediate o-naphthoquinone nitrosomethides.*

The same authors carried out the oxidation reaction with ketoximes instead of aldoximes and found out that the outcome was different. When the alkyl substituted ketoximes are treated with lead(IV) acetate the naphthooxazin-4-ols **134** was accompanied by benzoindole-3(1*H*)-ols **133**. The nitrogen from the *o*-naphthoquinone nitrosomethide **130b'** generated *in situ* attacks the C-8 of naphthalene ring to give intermediate **132** which tautomerises into benzoindole **133** (Scheme 1.40).



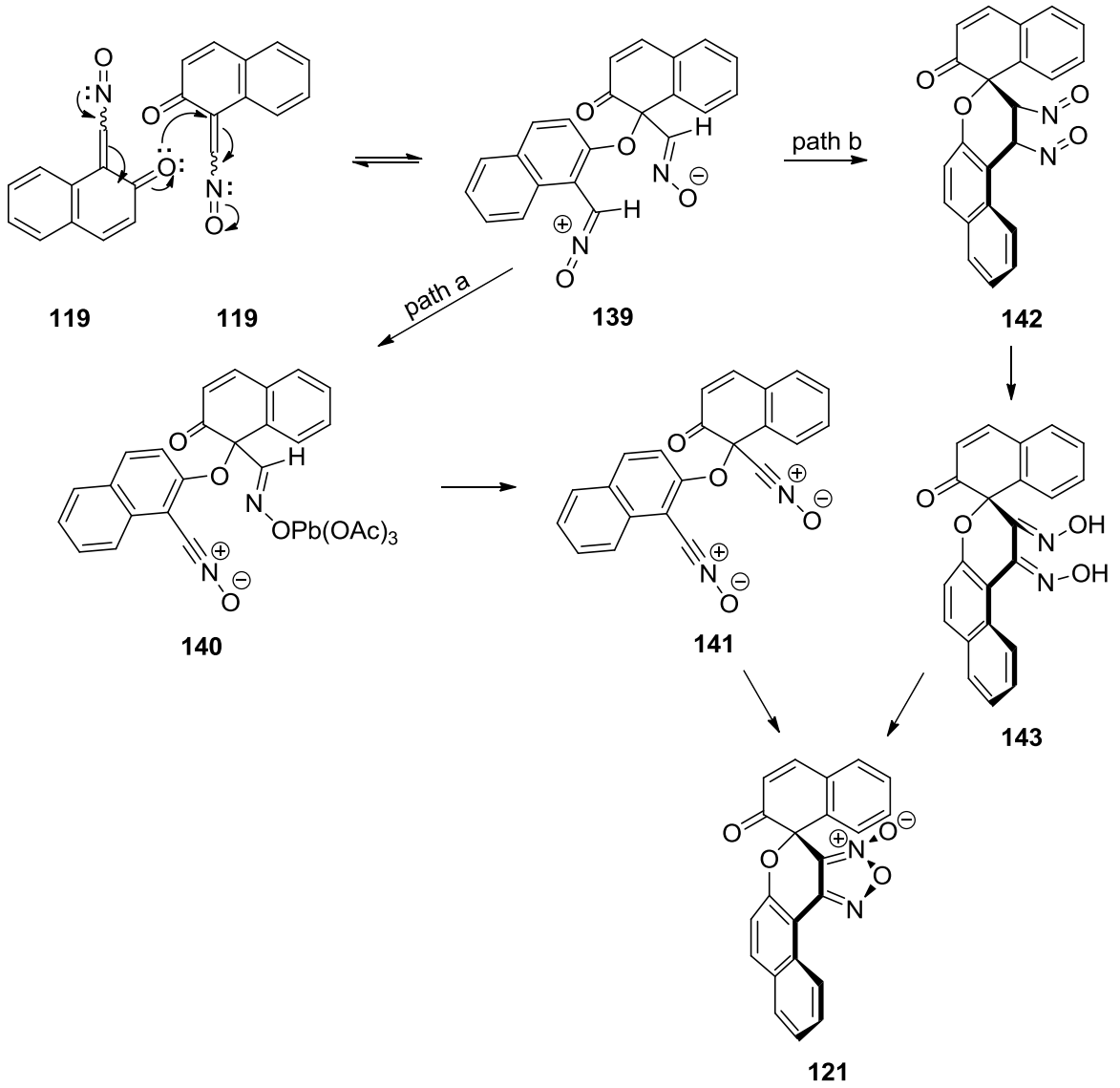
Scheme 1.40 *Oxidation of (E/Z)-1-(2-hydroxy-1-naphthyl)ethanone (or propan-1-one) oxime (i) $Pb(OAc)_4$, THF, 0 °C.*

When the alkyl group in ketoximes **129** is replaced by a phenyl ring to give (*E*/*Z*)-(2-hydroxy-1-naphthyl)(phenyl)methanone oxime **135**, oxidation of this oxime with lead(IV) acetate afforded benzoindole-3(1*H*)-ol **136** as the sole product (Scheme 1.41). When the oxidation reaction of the ketoxime **129b** with lead(IV) acetate was stopped after two hours the products obtained were the naphthoisoxazole-*N*-oxide **137** and the benzoindole **138**. This result provides direct evidence that the naphthooxazine **134b** is formed from the *N*-oxide **137**.



Scheme 1.41 *Oxidation of (E/Z)-1-(2-hydroxy-1-naphthyl)(phenyl)methanone (or propan-1-one) oxime at low temperature. (i) $Pb(OAc)_4$, THF, 0 °C then r.t.*

On the basis of the experimental observations and according to molecular modelling studies of the mechanism by which the spiro dimer **121** was formed from the *o*-naphthoquinone nitrosomethide, the mechanism depicted in Scheme 1.42 is proposed. The first step in the dimerisation is intermolecular cycloaddition of **119**. The reaction is chemoselective in that the nitroso group can activate the exocyclic double bond. Addition of carbonyl oxygen of a second molecule gives the intermediate oxime **139**, this step can be reversible. Intermediate **139** may react with lead(IV) acetate to give the organolead



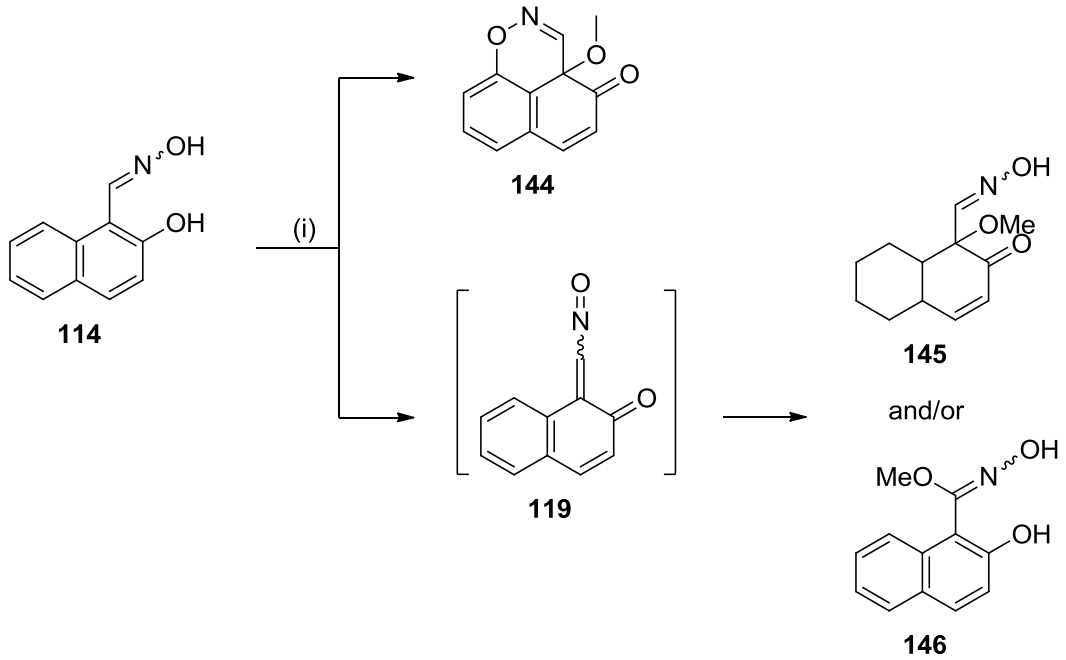
119 119 139 142 140 141 143 121

Scheme 1.42 *Mechanism for the formation of a spiro dimer derived from dimerisation of o-naphthoquinone nitrosomethide intermediate.*

complex **140** (path *a*), which is then converted to the dinitrile oxide **141**, ultimately leading to product **121** via carbon-carbon and nitrogen-oxygen bond formation. Alternatively (path *b*) intermediate **139** undergoes intramolecular cyclisation by carbon-carbon bond formation to furnish dinitroso pyran **142**. The latter tautomerises to dioxime **143** which oxidatively cyclises to **121**.

1.3.3. Alkoxylation reaction

In another publication Varvounis and co-workers[71] reported generation of the *o*-naphthoquinone nitrosomethide using iodobenzene diacetate as an oxidizing agent. Not surprisingly the products obtained were not the products expected. This explains the wide range of reactivity of the *o*-naphthoquinone nitrosomethide intermediate. Again the starting material used for the reaction is the oxime **114** which when treated with iodobenzene diacetate in methanol, the reaction expected to occur was a Michael addition of methanol

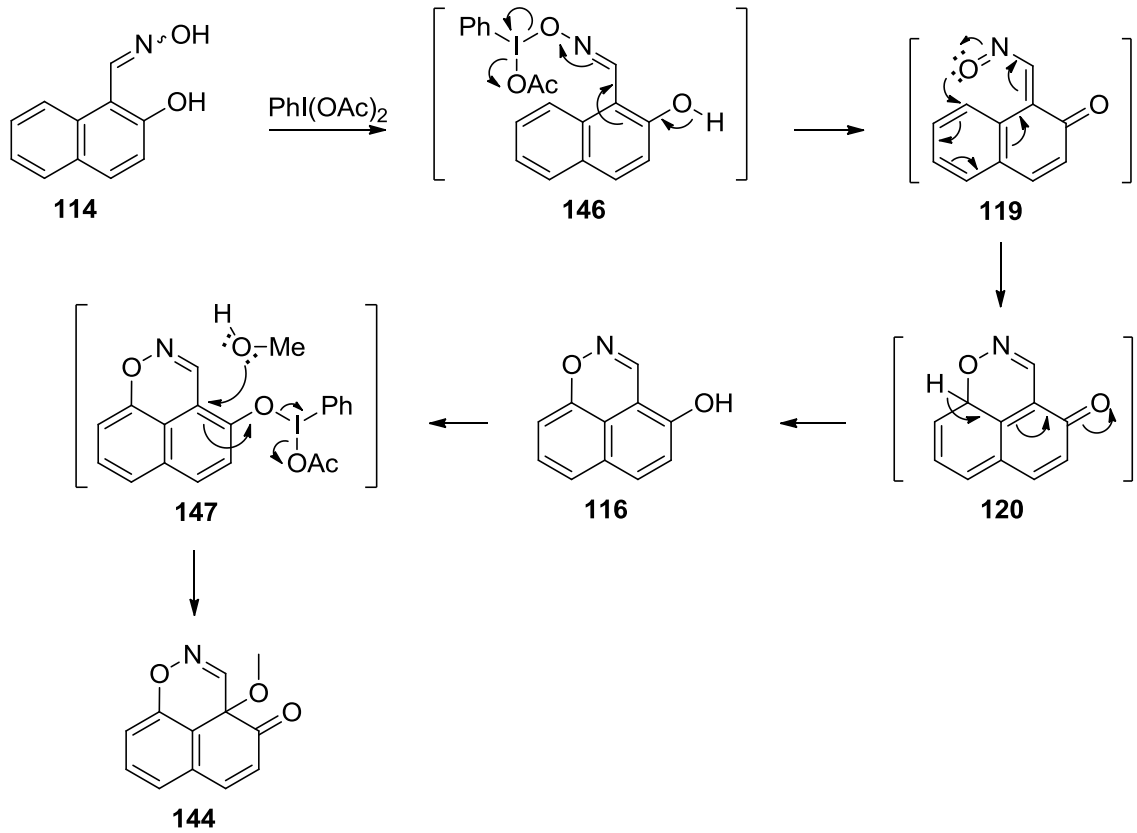


Scheme 1.43 *Oxidation of 2-hydroxy-1-naphthaldehyde oxime with iodobenzene diacetate to 3a-methoxy-naphtho[1,8-de][1,2]oxazin-4(3aH)-one. (i) IBD, MeOH, r.t.*

[71] Dolka, C.; Hecke, K. V.; Meervelt, L. V.; Tsoungas, P. G.; Eycken, E. V. V.; Varvounis, G. *Org. Lett.* **2009**, *11*, 2964–2967.

to the *o*-naphthoquinone nitrosomethide intermediate **119** to give the methoxy substituted oximes (**145** and/or **146**). Instead, the product obtained was 3a-methoxynaphtho[1,8-*de*]-[1,2]oxazin-4(3a*H*)-one **144**.

The formation of oxazine **144** is proposed to occur through the naphthooxazine **116**, derived from an initially formed organoiodo complex **146** that collapses to a *peri*-orientated *o*-naphthoquinone nitrosomethide **119** that cyclises into the naphthooxazine **120** which then tautomerises. The hydroxyl group of intermediate **116** reacts with iodobenzene diacetate and the resulting organoiodo complex **147** is nucleophilically attached at position 3a with concomitant loss of acetic acid and iodobenzene to yield product **144** (Scheme 1.44). To prove the latter sequence of reactions of this proposed mechanism, previously isolated compound **116** was treated with iodobenzene diacetate in methanol and the product obtained was identified as **144**.



Scheme 1.44 *Proposed mechanism for the formation of 3a-methoxynaphtho[1,8-de][1,2]oxazin-4(3aH)-one.*

This reaction was repeated by using various *O*-nucleophiles instead of methanol and the results obtained depicted in (Table 1.1).

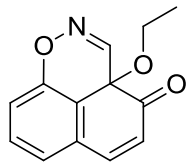
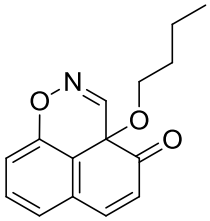
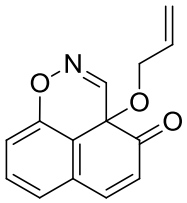
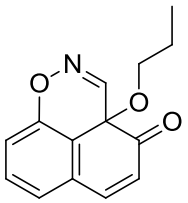
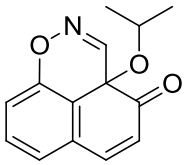
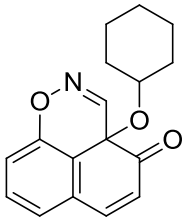
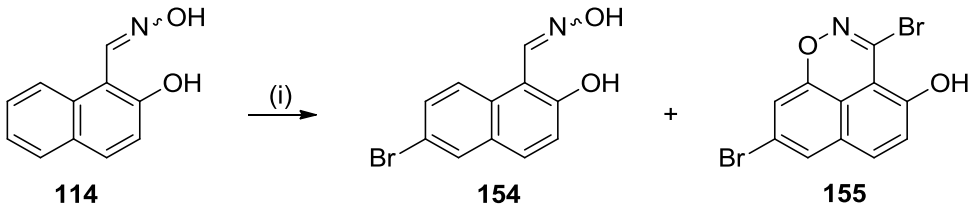
1.  **148**	3.  **150**	5.  **152**
2.  **149**	4.  **151**	6.  **153**

Table 1.1 *Examples of 3a-substituted naphthooxazines by reaction of 2-hydroxy-1-naphthaldehyde oxime with iodobenzene diacetate in the presence of various O-nucleophiles.*

1.3.4. Electrophilic substitution

Up to this point different trends in reactivity of the *o*-naphthoquinone nitrosomethide intermediate have been recorded such as, intramolecular cycloaddition that resulted in the formation of three diverse rings, oxazine, indole and isoxazole-*N*-oxide. Oxazine ring formation was accompanied by a nucleophilic addition in the case where the oxidising agent was iodobenzene diacetate. Intermolecular cycloaddition of the *o*-naphthoquinone nitrosomethide intermediate gave a 6-membered ring spiro dimer. An interesting reaction involving the *o*-naphthoquinone nitrosomethide intermediate is electrophilic substitution at the aromatic ring. In the recent work by Tzinavou[72] the reaction of oxime **114** with *N*-bromosuccinimide in pyridine as a base generated oxidatively the *o*-naphthoquinone nitrosomethide that was then trapped in an electrophilic substitution reaction by a bromine atom (Scheme 1.45).

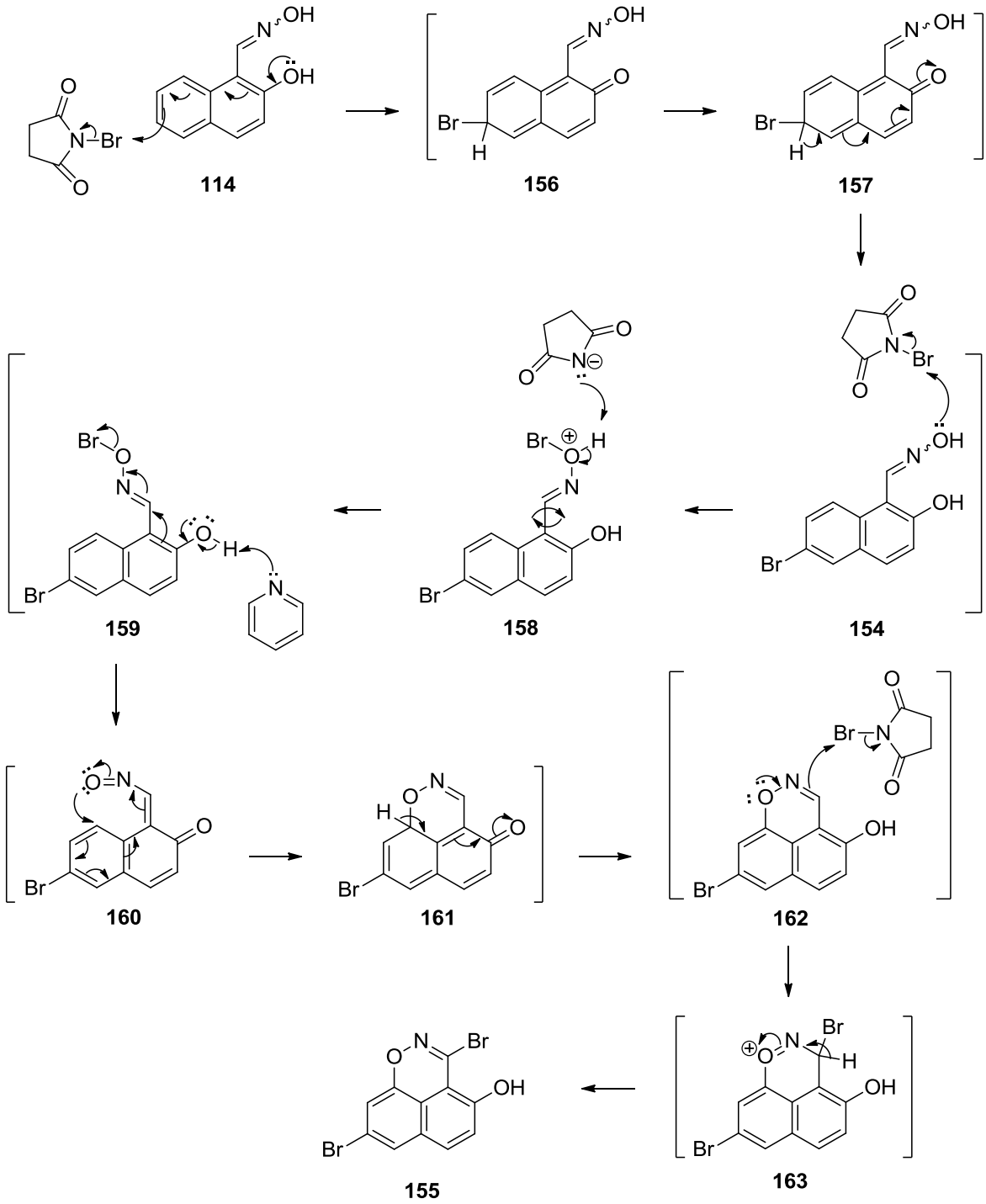
[72] Tzinavou, A. *M.Sc. Thesis*, **2012**, Ioannina.



Scheme 1.45 *Bromination and oxidative cyclisation of 2-hydroxy-1-naphthaldehyde oxime. (i) NBS, pyridine, CH_2Cl_2.*

The reaction (Scheme 1.46) is initiated by the naphthyl hydroxyl group that attacks via position C6 either free bromine, generated from the reaction of NBS with traces of HBr, or the bromine atom of NBS as shown in Scheme 1.46, to give the 6-bromo addition intermediate **156**. It is reasonable to assume that **156** aromatises to the 6-bromooxime **154.** Intermediate **154** is then brominated at the oxime hydroxyl group to give intermediate O-Br **159** via **158**. In the next step, the organobromo complex **159** collapses into the 6-bromo *o*-naphthoquinone nitrosomethide **160**. This intermediate after cycloaddition and tautomerization forms the naphthoooxazine **162** from which the dibromo naphthooxazine **155** is formed after a second electrophilic substitution.

The reactions described so far in this chapter, compared to the reactions that have taken place with the structurally simpler *o*-quinone methide, are much more diversified.



Scheme 1.46 *Mechanism for the dibromination and oxidative cyclisation of 2-hydroxy-1-naphthaldehyde oxime by NBS.*

1.4. Synthesis of 2,3-dihydro-1-benzofurans

As the name implies, 1-benzofuran, otherwise called benzo[*b*]furan, contains a ring system derived by the fusion of a benzene nucleus with a furan ring in the manner of formula **164** (Figure 1.5). The corresponding formal hydrogenation of the furan ring gives the 2,3-dihydro-1-benzofuran **165** nucleus. The 2,3-dihydro-1-benzofuran ring-system constitutes the core skeleton of an increasing number of biologically active compounds.

164 **165**

Figure 1.5 *1-Benzofuran and 2,3-dihydro-1-benzofuran.*

The dihydro-1-benzofuran moiety has been known for a long time, and a first report on its synthesis dates back to 1892.[73] Successively, various methods have been applied for the preparation of 2,3-dihydro-1-benzofurans.[74]

1.4.1. Natural occurrence of 2,3-dihydro-1-benzofurans

The 1-benzofuran nucleus is common in natural products and appears in many forms including several examples of 2,3-dihydro-1-benzofurans. A well-known example of an aromatic hemiterpene containing the 2,3-dihydro-1-benzofuran skeleton is anisoxide, isolated from star anise oil (*Illicium verum*) in 1937.[75] This compound is peculiar in being optically inactive although containing a chiral centre. More recently, benzodihydrofuran derivatives, all possessing interesting biological activities, have been found in several species of higher plants and in particular in Asteraceae (Figure 1.6).[76]

[73] Alexander, H. *Ber.* **1892**, *25*, 2409.
[74] Mustafa, A. *The Chemistry of Heterocyclic Compounds*, Vol. 29, p. 143, Weissberger, A, Taylor, E.C. eds. John Wiley & Sons, Inc., New York, 1974.
[75] Jackson R. W.; Short, W. F. *J. Chem. Soc.* **1937**, 513-516.
[76] Proksch P.; Rodriquez, E. *Phytochemistry* **1983**, *22*, 2335-2348.

Quite recently, a new dihydrobenzofuran derivative having antioxidant properties, 2,3,4-trimethyl-5,7-dihydroxy-2,3-dihydro-1-benzofuran **166**, was isolated from a culture broth of *Penicillum citrinum F5* (Figure 1.6).[77]

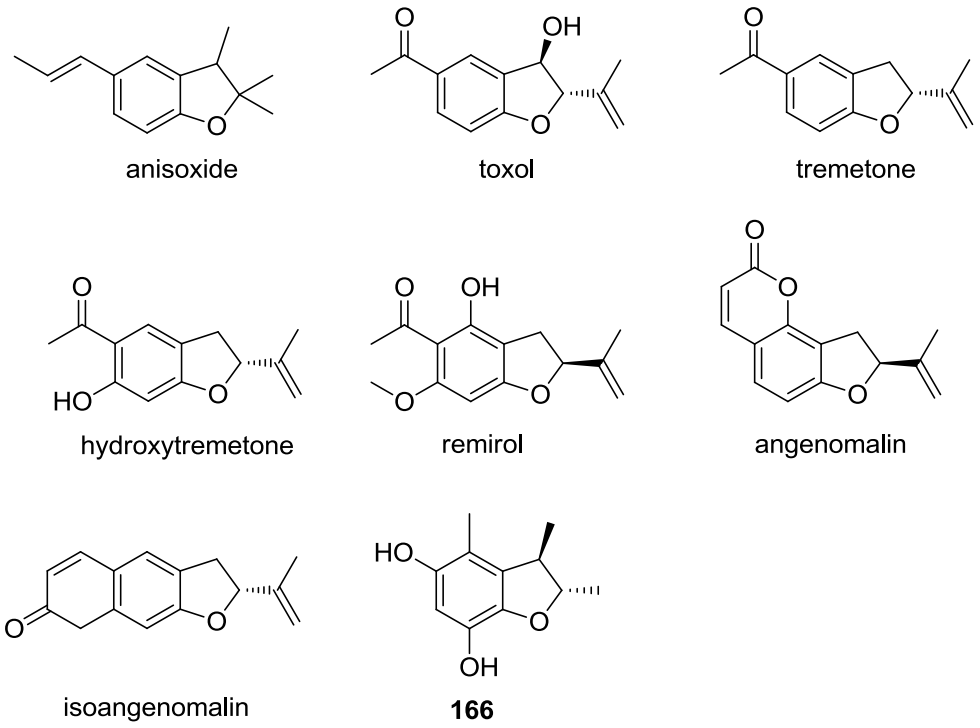


Figure 1.6 *Natural products containing a 2,3-dihydro-1-benzofuran ring system.*

The 2,3-dihydro-1-benzofuran ring system can be found as a key structural element in the neo-lignans, which are a diverse family of biologically active plant metabolites.[78] These compounds exhibit a broad range of biological activities including, for some classes, antitumor and antiproliferative activities. For example, (2*R*,3*S*)-3´,4-di-*O*-methylcedrusin **167**, identified as one of the minor constituents of the red latex called "dragon blood" ("sangre de drago") in traditional medicine, was found to act as an inhibitor of cell proliferation, stimulating the synthesis of analogs based on this scaffold.[79]

Obtusafuran **168**, a simple dihydrobenzofuran isolated from several Dalbergia species, was shown recently to have potent induction of the anticarcinogenic marker enzyme,

[77] Chen, C.-H.; Shaw, C.-Y.; Chen C.-C.; Tsai, Y.-C. *J. Nat. Prod.* **2002**, *65*, 740-741.
[78] Wars, R. S. *Chem. Soc. Rev.* **1982,** *11***,** 75-125**.**
[79] Pieters, L.; Van Dyck, S.; Gao, M.; Bai, R.; Hamel, E.; Vlietinck, A.; Lemiere, G. *J. Med. Chem.* **1999,** *42*, 5475-5481.

quinone reductase (Figure 1.7).[80] Also, neolignan kadsurenone (**169**) has attracted the most attention due to its biological activity as a platelet-activating (PAF) antagonist.[81]

From the plant kingdom, in particular from dipterocarpaceous plants, it is also possible to isolate oligostilbenes having dihydrobenzofuran moieties. These high molecular weight compounds are resveratrol (3,5,4´-trihydroxystilbene) oligomers and possess multifunctional bioactivities.[82]

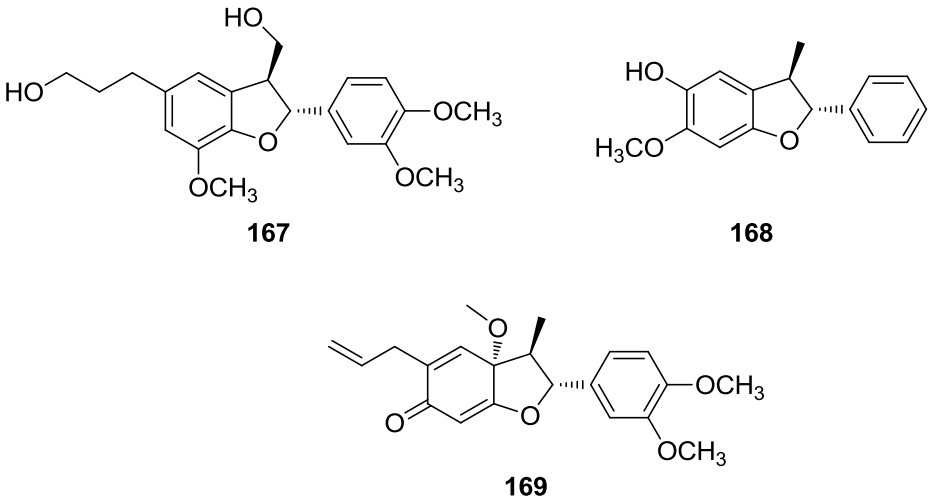


Figure 1.7 *Biologically important 2,3-dihydro-1-benzofuran derivatives.*

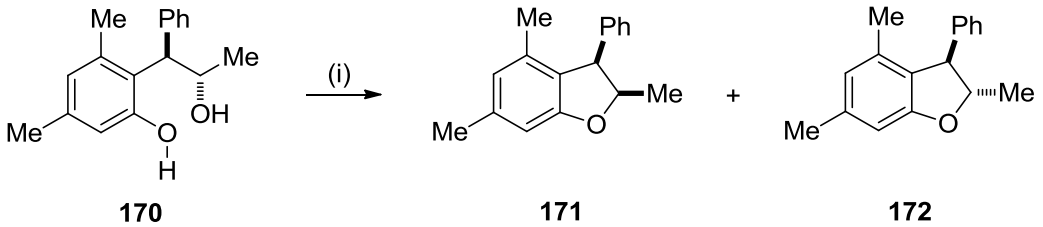
1.4.2. Methods of Synthesis of 2,3-dihydro-1-benzofurans

1.4.2.1. Synthesis by dehydrative methods

A simple synthesis of 2,3-dihydro-1-benzofurans can be achieved by intramolecular dehydration of a molecule containing both a phenol and an alcohol functionality. The use of a Mitsunobu type dehydration (PPh_3, DEAD) to perform this transformation was first reported by Aristoff and co-workers in 1984.[83] The complete inversion of configuration, together with the high yields generally obtained, are the major advantages of the

[80] Yin, H.-Q.; Lee, B.-W.; Kim, Y.-C.; Sohn D.-H.; Lee, B.-H. *Arch. Pharm. Res.***2004**, *27*, 919-922.
[81] Shen, T. Y.; Hwang, S.-B.; Chang, M. N.; Doebber, T.W.; Lam, M.-H. T.; Wu, M. S.; Wang, X.; Han, G.-Q.; Li, R. Z. *Proc. Natl. Acad. Sci. USA*, **1985**, *82*, 672-676.
[82] Ito, T.; Tanaka, T.; Iinuma, M.; Nakaya, K.-i.; Takahashi, Y.; Sawa, R.; Naganawa, H.; Chelladurai, V. *Tetrahedron* **2003**, *59*, 1255-1264.
[83] Aristoff, P. A.; Harrison, A. H.; Huber, A.M. *Tetrahedron Lett.* **1984**, *25*, 3955-3958.

Mitsunobu type cyclization, especially when substituted chiral hydroxy phenols are employed. For example, Pineschi and co-workers[84] reported recently that 2-(2-hydroxypropyl)phenols *e.g.* **170**, were suitable precursors to prepare 3-aryl-2,3-dihydro-1-benzofurans such as **171** and **172** by a simple cyclodehydration (Scheme 1.47). Treatment of hydroxyphenol **170** with catalytic amounts of *p*-TsOH in refluxing toluene gave an inseparable 68/32 mixture of diastereoisomeric *cis*-**171** and *trans*-2-methyl-3-phenyl-5,7-dimethyl-2,3-dihydro-1-benzofurans **172**, while when the cyclodehydration was effected by means of an intramolecular Mitsunobu type protocol (PPh_3, DEAD, THF, rt), compound **171** was isolated in 80% yield and a high diastereocontrol.

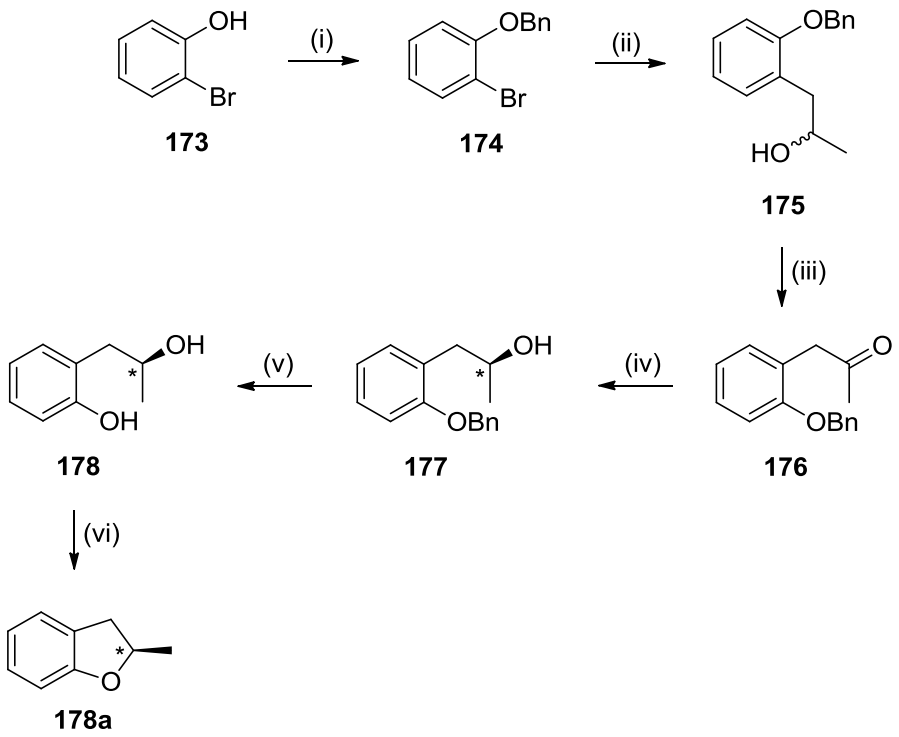


170 **171** **172**

Scheme 1.47 *Synthesis of 2,3-dihydro-1-benzofuran derivatives by dehydration of 2-[(1R,2S)-2-hydroxy-1-phenylpropyl]-3,5-dimethylphenol. (i) PPh_3, DEAD, THF.*

Optically active 2-methyl-2,3-dihydro-1-benzofuran **178a** has been prepared by a simple synthesis and chemoenzymatic asymmetric strategy by Gotor and co-workers.[85] This synthetic approach is based on the combination of a bioreduction of a ketone such as 1-[2-(benzyloxy)phenyl]acetone **176** with alcohol dehydrogenase A (ADH A) to give enantiopure (*S*)-1-[2-(benzyloxy)phenyl]propan-2-ol **177** from which the protecting benzyl group was removed to afford enantiopure (*S*)-2-(2-hydroxypropyl)phenol **178**. Diol **178** underwent cyclodehydration under Mitsunobu reaction conditions to yield enantiopure (*R*)-2-methyl 2,3-dihydro-1-benzofuran **178a**. Ketone **177** was prepared synthetically from 2-bromophenol **173** which was protected in the presence of benzyl bromide to yield 1-(benzyloxy)-2-bromobenzene **174** that was subsequently reacted with *n*-BuLi and 2-methyloxirane in the presence of a Lewis acid to afford racemic 1-[2-(benzyloxy)phenyl]propan-2-ol **175**. Dess Martin oxidation of the latter alcohol afforded ketone **176** (Scheme 1.48).

[84] Bertolini, F.; Crotti, P.; Di Bussolo, V.; Macchia, F.; Pineschi, M. *J. Org. Chem.* **2007**, *72*, 7761-7764.
[85] Mangas-Sanchez, J.; Busto, E.; Gotor-Fernandez, V.; Gotor, V. *Org. Lett.* **2010**, *12*, 3498-3501.

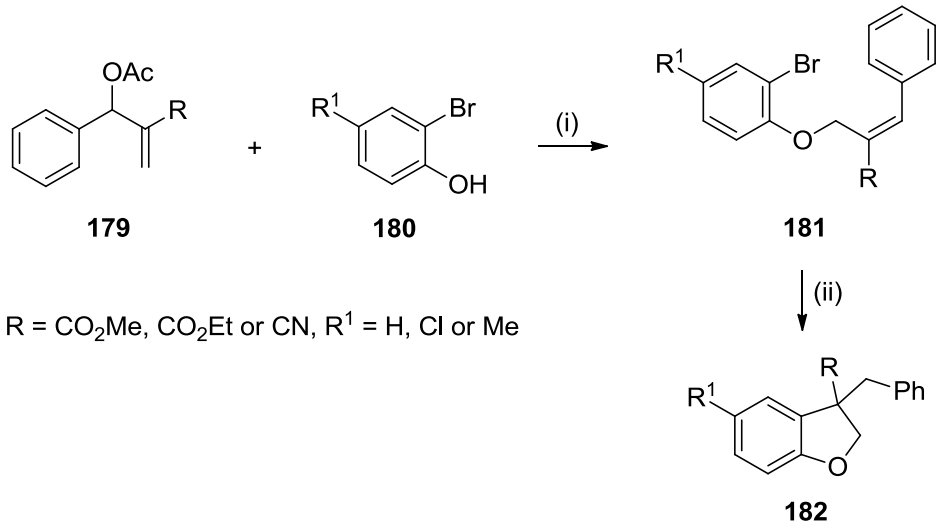


Scheme 1.48 *Chemoenzymatic synthesis of (R)-2-methyl-2,3-dihydro-1-benzofuran. (i) BnBr, K_2CO_3, DMF, (ii) (a) n-BuLi, THF, -78 °C, (b) 2-methyloxirane, $BF_3.Et_2O$, THF, -78 °C, (iii) Dess Martin, CH_2Cl_2, (iv) alcohol dehydrogenase A, aq. solution, (v) H_2, Pd-C, MeOH, (vi) PPh_3, DIAD, THF.*

1.4.2.2. Radical cyclisations

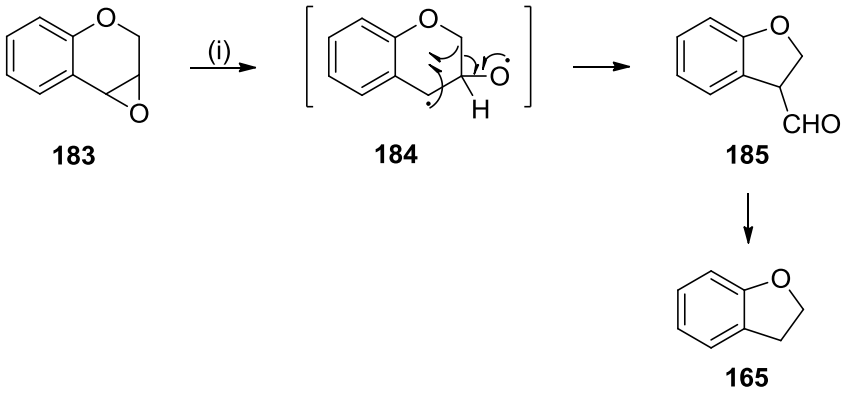
Kim and co-workers[86] reported a method wherein 3,3-disubstituted 2,3-dihydro-1-benzofuran derivatives **182** were obtained by radical cyclization of precursors of type **181**, easily prepared by the reaction of Baylis-Hilman adducts **179** and 2-bromophenol, 2-bromo-3-chlorophenol or 2-bromo-3-methylphenol (Scheme 1.49).

[86] Park, D. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1440-1442.



Scheme 1.49 *Radical catalyzed synthesis of 2,3-dihydro-1-benzofurans. (i) K_2CO_3, aq. THF, (ii) n-Bu_3SnH, AIBN, benzene.*

During the study of photochemical behaviour of 3,4-epoxyprecocene **183**, Ariamala and Balasubramanian[87] have reported synthesis of 2,3-dihydro-1-benzofuran **165**. They found that upon irradiation of **183** in cyclohexane it undergoes photoisomerisation via diradical intermedidate **184** to give aldehyde **185** which is photodecarbonylated to yield the 2,3-dihydro-1-benzofuran **165**.



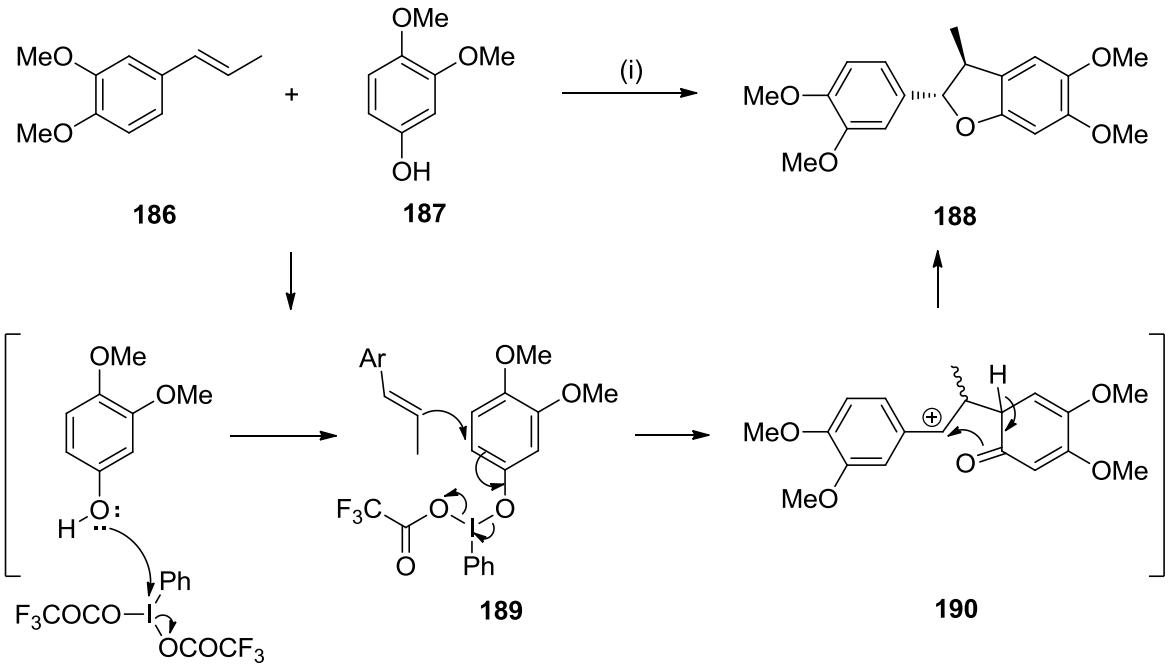
Scheme 1.50 *Photoisomerisation and photodecarbonylation reactions of 1a,7b-dihydro-2H-oxireno[c]-chromene. (i) hv (125W), cyclohexane.*

[87] Ariamala, G.; Balasubramanian, K. K. *Tetrahedron* **1989**, *45*, 3769-3774.

1.4.2.3. Biomimetic couplings and cycloadditions

Over the years, the use of biomimetic-inspired reactions has been used extensively for the synthesis of many families of natural products. These biomimetic reactions represent also one of the most common approaches for the preparation of a great number of biological active compounds in which the 2,3-dihydro-1-benzofuran ring system represents the core skeleton.

Swenton and co-workers[88] reported that neolignans, a group of secondary plant metabolites possessing a dihydrobenzofuran skeleton, can be obtained in good yields and high stereoselectivities by oxidation of *p*-methoxy-substituted phenols **187** with iodobenzene bis(trifluoroacetate) in the presence of electron-rich styrene derivatives **186** (Scheme 1.51).

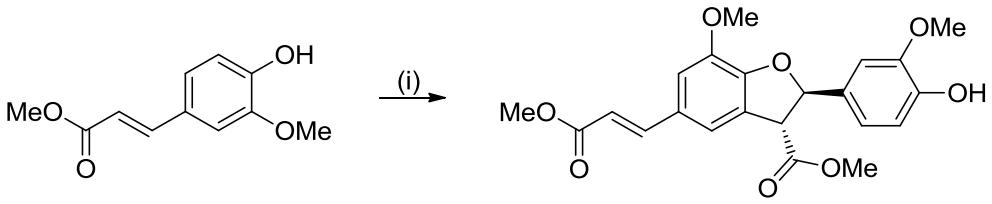


Scheme 1.51 *Oxidative synthesis of a neolignan derivative. (i) $PhI(OCOCF_3)_2$, CH_3CN.*

A different approach for the preparation of neolignans with a dihydrobenzofuran skeleton was reported by Lemiere and co-workers.[89] The oxidative biomimetic

[88] Wang, S.; Gates, B. D.; Swenton, J. S. *J. Org. Chem.* **1991**, *56*, 1979-1981.
[89] Lemiere, G.; Gao, M.; De Groot, A.; Dommisse, R.; Lepoivre, J.; Pieters, L.; Buss, V. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1775-1779.

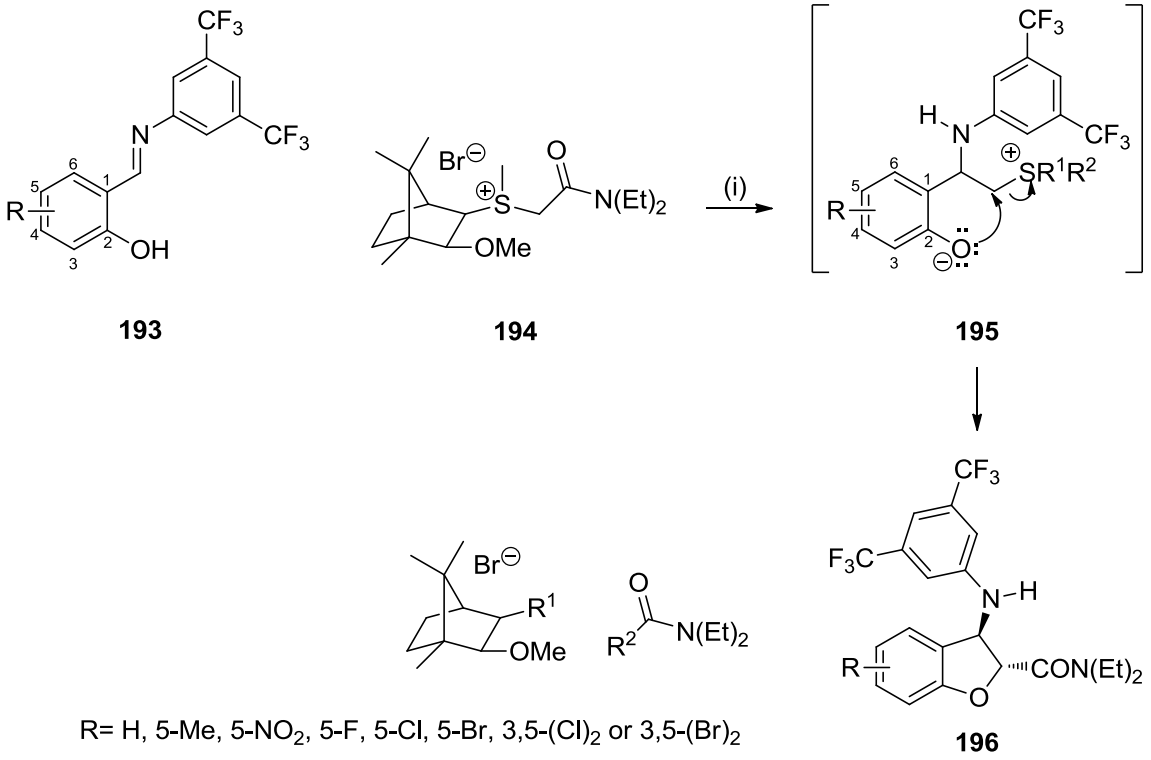
dimerization of ferulic acid methyl ester **191** with Ag_2O allowed the isolation of the corresponding *trans*-2,3-dihydro-1-benzofuran **192** with high stereoselectivity and in moderate yield.



191 **192**

Scheme 1.52 *Oxidative biomimetic dimerization of methyl (2E)-3-(4-hydroxy-3-methoxyphenyl)acrylate towards a neolignan derivative. (i) Ag_2O, acetone, benzene.*

Xiao and co-workers[90] reported an asymmetric formal [4 + 1] cycloadditions of camphor-derived sulfonium salt **194** with electron-poor and -rich aldimines **193**, to afford exclusively *trans*-3-{[3,5-bis(trifluoromethyl)phenyl]amino}-*N*,*N*-diethyl-2,3-dihydro-1-



193 **194** **195**

R= H, 5-Me, 5-NO_2, 5-F, 5-Cl, 5-Br, 3,5-$(Cl)_2$ or 3,5-$(Br)_2$

196

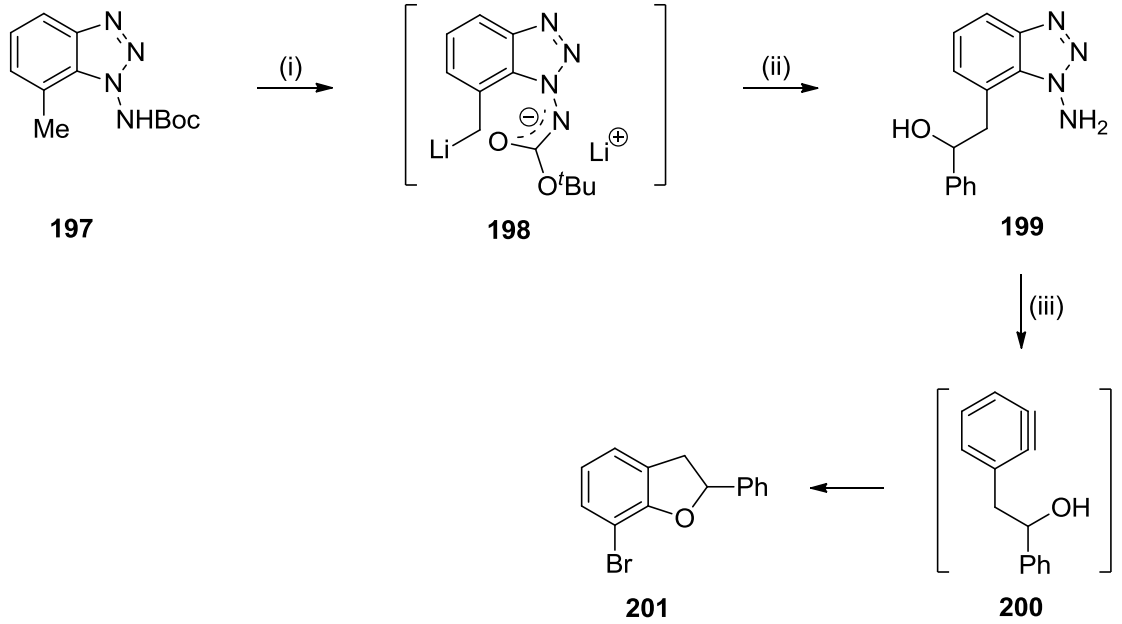
Scheme 1.53 *Synthesis of trans-2,3-disubstituted-2,3-dihydro-1-benzofurans from phenolic aldimines using sulfonium salts via {4 + 1] cycloadditions reactions. (i) TMG, 4Å molecular sieves, toluene, 0 °C.*

[90] Cheng, Y.; Hu, X.-Q.; Gao, S.; Lu, L.-Q. Chen, J.-R.; Xiao, W.-J. *Tetrahedron* **2013**, *69*, 3810-3816.

benzofuran-2-carboxamides **196** in moderate to good yields with high diastereo- (up to >95:5 dr) and enantio-selectivities (up to 93% ee). The reaction takes place with 1,1,3,3-tetramethylguanidine (TMG) as the base in toluene at 0 °C.

1.4.2.4. Synthesis of 2,3-dihydro-1-benzofurans *via* benzyne intermediates

Substituted arynes are utilized as versatile synthetic intermediates and has been used in well known organic transformations such as Diels-Alder reactions. Knight and co-workers[91] more recently reported the use of 7-substitued-1-aminobenzotriazoles for the synthesis of 2,3-dihydro-1-benzofurans. In particular, the exposure of compound **199**, derived from the Boc-triazole **197** after treatment first with an aldehyde in presence of *n*-BuLi and tetramethylethylendiamine (TMEDA) followed by deprotection of the Boc protecting group by trifluoroacetic acid in dichloromethane, to 2 equivalents of NBS in dichloromethane at room temperature leads to the formation of the corresponding benzyne intermediate **200**, which rapidly attracts electrophilically the hydroxyl group to give dihydrobenzofuran **201** (Scheme 1.54).

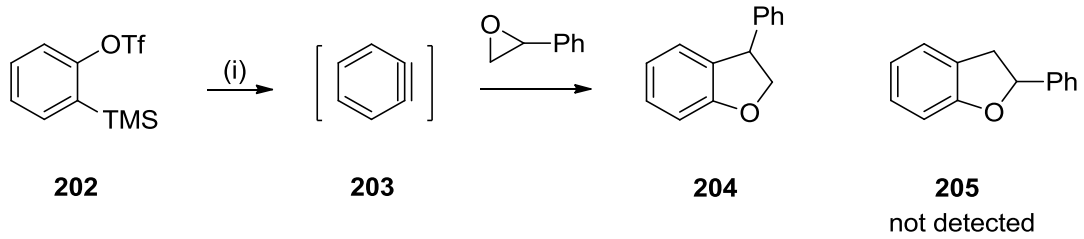


197 **198** **199** **200** **201**

Scheme 1.54 *Formation of 7-bromo-2-phenyl-2,3-dihydro-1-benzofuran via a benzyne intermediate. (i) n-BuLi, TMEDA, THF, (ii) (a) PhCHO, THF, (b) TFA, CH_2Cl_2, (iii) NBS, CH_2Cl_2.*

[91] Birkett, M. A.; Knight, D. W.; Mitchell, M. B. *Tetrahedron Lett.* **1993**, *34*, 6939-6940.

Another example of the preparation of 2,3-dihydro-1-benzofurans *via* a benzyne intermediate has been described recently by Pena and co-workers.[92] In this work, the formation of the benzyne intermediate **203** was achieved under mild conditions by treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate with CsF in MeCN at room temperature. The benzyne intermediate then inserts into the C-O bond of styrene oxide to give the 3-phenyl-2,3-dihydro-1-benzofuran **204** in 32% yield. Although the low yield indicated the formation of a mixture of products, the regioisomeric dihydrobenzofuran **205** was not detected in the reaction mixture.

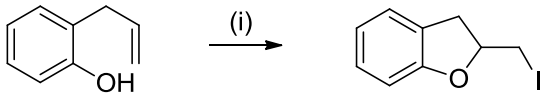


202 **203** **204** **205** not detected

Scheme 1.55 *Formation of 3-phenyl-2,3-dihydro-1-benzofuran via a benzyne intermediate. (i) CsF, MeCN.*

1.4.2.5. Intramolecular substitutions

Fousteris and co-workers[93] developed an elegant method for the synthesis of 2-(iodomethyl)-2,3-dihydro-1-benzofurans *via* water promoted iodocyclization of 2-allylphenols (Scheme 1.56). The cyclisation occurs through an *exo* process, as generally observed in these cases. This simple procedure is easy to perform and allows the transformation of various substituted 2-allylphenols in the absence of any additive and organic solvents.

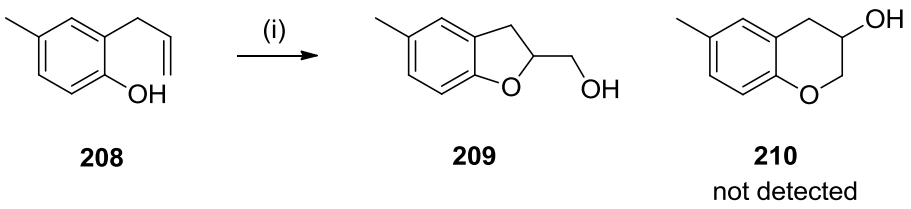


206 **207**

Scheme 1.56 *Iodocyclisation of 2-allylphenols. (i) I_2, water.*

[92] Beltran-Rodil, S.; Pena, D.; Guitan, E. *Synlett* **2007**, 1308-1310.
[93] Fousteris, M.; Chevrin, C.; Le Bras, J.; Muzart, J. *Green Chem.* **2006**, *8*, 522-523.

Ramadas and Krupadanam[94] showed that the double bond of an allylphenol can also be rendered electrophilic by epoxidation using *m*-chloroperbenzoic acid (MCPBA). Subsequent ring-opening of the epoxide intermediate by the phenolic oxygen gives 2-hydroxymethyl-2,3- dihydro-1-benzofuran **209** through an *exo* ring-opening. The isomeric *endo* ring-opening of the oxirane to give 3-hydroxy-6-methylchroman **210**, is not observed.



208 **209** **210**
not detected

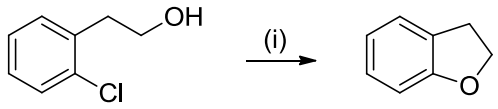
Scheme 1.57 *Intramolecular oxidative cyclization of 2-allyl-4-methylphenol via epoxide into 2-hydroxymethyl-2,3-dihydro-1-benzofuran. (i) MCPBA, $CHCl_3$.*

1.4.2.6. Transition metal-catalyzed processes

a) Transition metal-catalyzed nucleophilic substitutions

The intramolecular C-O formation between aryl halides and alcohols represents another possible approach for the construction of the 2,3-dihydrobenzo-1-furan skeleton. In this respect, historically one of the most representative examples of this class of transformation is provided by the Ullman reaction. Zhu and co-workers[95] have reported a copper(I)-catalyzed Ullman type reaction leading to 2,3-dihydro-1-benzofuran. Copper(I) chloride is used as a catalyst along with sodium hydride in toluene with 5 mol% ethyl acetate for the cyclisation of 2-(2-chlorophenyl)ethanol **211** to yield 2,3-dihydro-1-benzofuran **165**, in 74% yield. Similar yields of the corresponding dihydrobenzofuran were recorded from the cyclisation of 2-(2,4-dichlorophenyl)ethanol and 2-(2,6-dichlorophenyl)ethanol. The reaction is initiated by the deprotonation of hydroxy group with sodium hydride, oxidative addition if copper whereby the chlorine atom is replaced by a Cu(I) atom followed by cyclisation to form an intramolecular benzofuran-copper adduct followed by reductive elimination of copper to give the product.

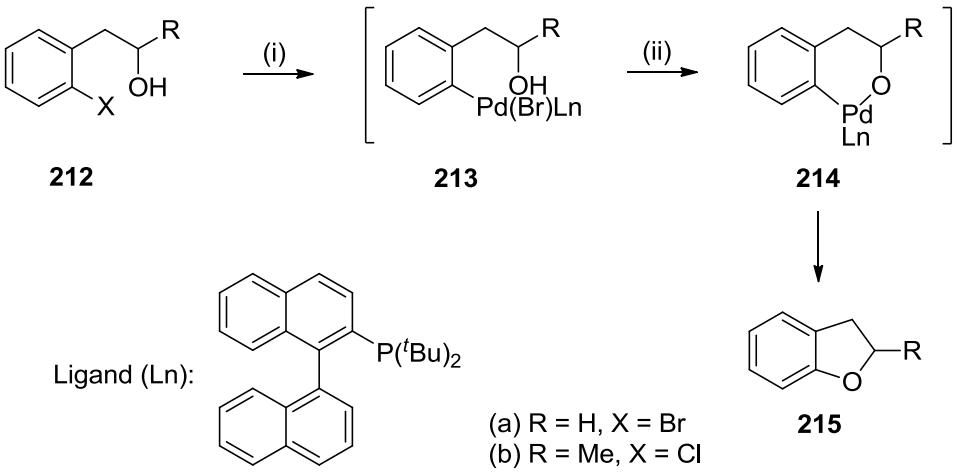
[94] Ramadas, S.; Krupadanam, G. L. D. *Tetrahedron: Asymmetry* **2000**, *11*, 3375-3393.
[95] Zhu, J.; Price, B. A.; Zhao, S. X.; Skonezny, P. M. *Tetrahedron Lett.* **2000**, *41*, 4011-4014.



211 **165**

Scheme 1.58 *Intramolecular Ullman reaction of 2-(2-chlorophenyl)ethanol and derivatives. (i) NaH, CuCl, toluene.*

Buchwald and co-workers[96] have reported a catalytic C-O bond formation leading to five- and six-membered oxygen heterocycles. The electron rich binaphthyl ligand containing a di-*tert*-butylphosphino moiety, shown in Scheme 1.59, was used as a catalyst along with a palladium catalyst for the cyclization of 2-(2-bromophenyl)ethanol **212a** or 1-(2-chlorophenyl)propan-2-ol **212b** to afford 2,3-dihydro-1-benzofuran **215a** or 2-methyl-2,3-dihydro-1-benzofuran **215b**. The reaction is initiated by the formation of the organopalladium complex **213** which is cyclized into a six-membered palladacycle **214** by the addition of base. The latter undergoes reductive elimination that leads to the products **215a,b**.

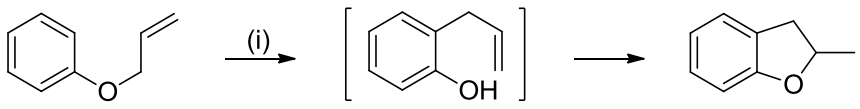


Scheme 1.59 *Ligand promoted Pd-catalysed cyclisation-reductive elimination of 2(or 1)-[2-bromo(or chloro)phenyl]ethanol(or propan1-ol) into 2,3-dihydro-1-benzofurans. (i) $Pd(OAc)_2$, ligand, toluene, (ii) Cs_2CO_3.*

[96] Torraca, K. E.; Kuwabe, S. I.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12907-12908.

b) Transition metal-catalyzed intramolecular hydroaryloxylations

Grant and Liu[97] have reported a metal catalyzed tandem Claisen rearrangement and intramolecular hydroaryloxylation of ally aryl ethers which provides a mild method to prepare dihydrobenzofurans. The simplest example involves treatment of phenyl allyl ether **216** with a catalytic amount of iridium(III) chloride in the presence of silver triflate as an additive, to afford 2-methyl-2,3-dihydro-1-benzofuran **218** in 65% yield. This method is applicable to substrates with functional groups such as methoxy, methylenedioxy, and chloro on the benzene ring. The reaction was also observed tolerant of alkyl substitution at either side of the olefin bond.



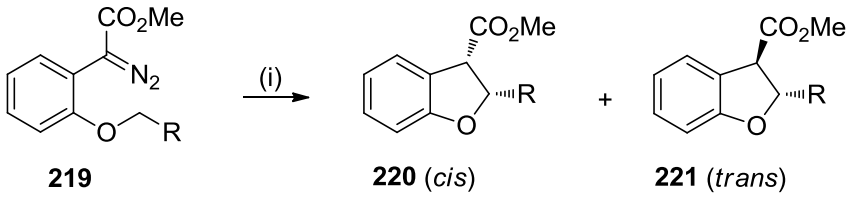
216 **217** **218**

Scheme 1.60 *Claisen rearrangement of phenyl allyl ether (i) $IrCl_3$, AgOTf, 1,2-dichloroethane.*

c) Transition metal-catalyzed insertion-cyclisations

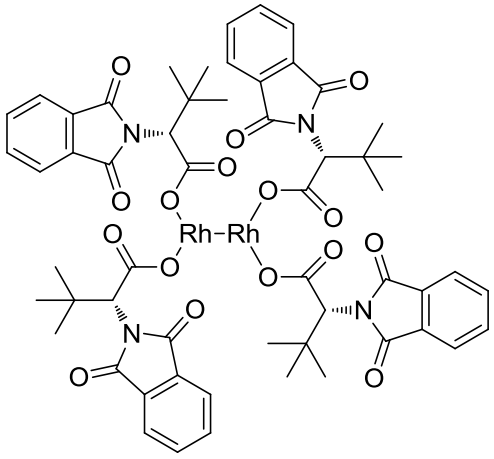
Hashimoto and co-workers[98] have reported synthesis of 2,3-dihydro-1-benzofuran by the enantioselective intramolecular C-H insertion reaction of aryldiazoacetates with use of dirhodium(II) carboxylate catalysts, which incorporate *N*-phthaloyl- or *N*-benzene-fused phthaloyl-(*S*)-amino acids as chiral bridging ligands. For example, the intramolecular C-H insertion of methyl [2-(benzyloxy or substituted benzyloxy)phenyl](diazo)acetates **219** is carried out by using 1 mol % of Rh_2(*S*-PTTL)$_4$. The reaction proceeds at -60 °C to completion within 0.5 h, giving the corresponding methyl 2-substituted-2,3-dihydo-1-benzofuran-3-carboxylates **220** and **221** in a >99:1 ratio of *cis* to *trans* isomers (Scheme 1.61).

[97] Grant, V. H.; Liu, B. *Tetrahedron Lett.* **2005**, *46*, 1237-1239.
[98] Saito, H.; Oishi, H.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Org. Lett.* **2002**, *22*, 3887-3890.



219 **220** (*cis*) **221** (*trans*)

R = Ph, 4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$ or 4-MeOC$_6$H$_4$

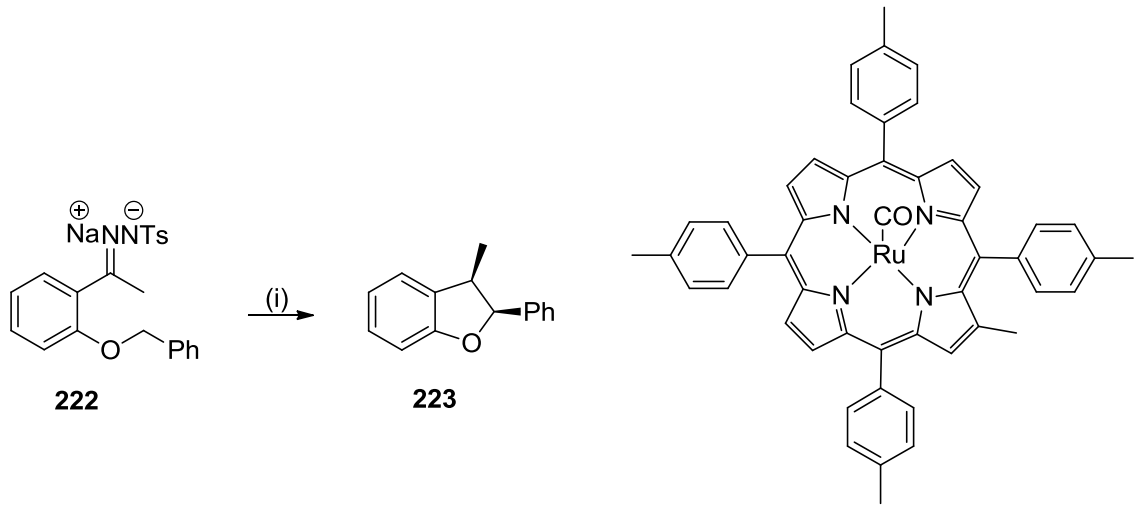


dirhodium tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate], Rh$_2$(*S*-PTTL)$_4$

Scheme 1.61 *Rh(II)-catalyzed C-H insertion process for the synthesis of methyl 2-substituted-2,3-dihydro-1-benzofuran-3-carboxylates. (i) Rh_2(S-PTTL)$_4$, toluene.*

A ruthenium porphyrin-catalyzed stereoselective intramolecular carbenoid C-H insertion is described by Che and co-workers.[99] Using [Ru^{II}(TTP)(CO)] as catalyst, aryl tosylhydrazones are converted to 2,3-dihydro-1-benzofurans. Aryl tosylhydrazones are used as precursors for *in situ* generation of diazo compounds, where handling or accumulation of unstable intermediates can be avoided. A typical example is treatment of the sodium salt of benzophenone tosylhydrazone **222** with [Ru^{II}-(TTP)(CO)] and *n*-Bu$_4$NBr as phase-transfer catalyst in toluene at 60-70 °C to afford 3-methyl-2-phenyl-2,3-dihydro-1-benzofuran **223** in 89% isolated yield where the *cis*-disubstituted product was predominantly formed (*cis*/*trans* = 98:2) (Scheme 1.62).

[99] Cheung, W.-H.; Zheng, S.-L.; Yu, W.-Y.; Zhou, G.-C.; Che, C.-M. *Org. Lett.* **2003**, *5*, 2535–2538.



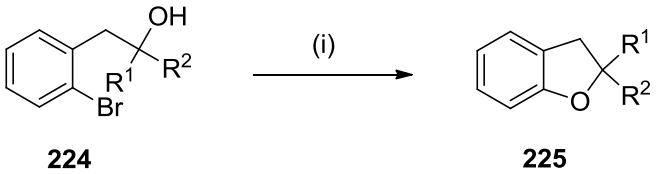
Scheme 1.62 *Ru^{II}-porphyrin catalyzed C-H insertion process (i) Ru^{II}(TTP)(CO), n-Bu_4NBr, toluene.*

d) Palladium-catalyzed intramolecular etherification of aryl halides

The development of ligand structures for palladium catalyzed cross-coupling processes has advanced dramatically in recent years and has led to the activation of aryl halides under mild conditions enabling a variety of intramolecular reactions, one of them leading to the synthesis of 2,3-dihydro-1-benzofurans.

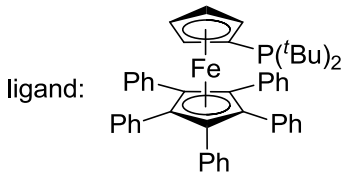
Kataoka and co-workers[100] have developed sterically hindered ferrocenyl di-*tert*-butylphosphines for palladium catalyzed C-C, C-N, and C-O bond forming cross coupling reactions. Pentaphenylferrocenyl di-*tert*-butylphosphine [$Ph_5FcP(t\text{-}Bu)_2$] has been prepared in high yield and used as a catalyst in combination with 5 mol % $Pd(dba)_2$ for the cyclisation of 2-bromophenethyl alcohol **224a**, 1-(2-bromophenyl)propan-2-ol **224b** or 1-(2-bromophenyl)-2-methylpropan-2-ol **224c** to the corresponding 2,3-dihydro-1-benzofurans **225a,b,c**.

[100] Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553-5566.



224 **225**

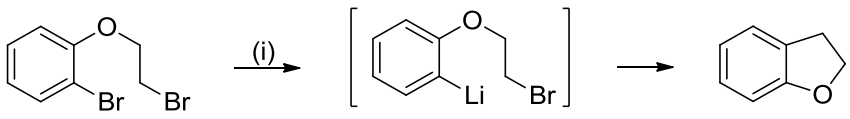
(a) $R^1 = R^2 = H$, (b) $R^1 = H$, $R^2 = Me$, (c) $R^1 = R^2 = Me$



Scheme 1.63 *Intramolecular ligand catalyzed palladium cross-coupling of o-alkylhydroxyaryl halides to 2,3-dihydro-1-benzofurans. (i) ^{t}BuONa, Pd(dba)$_2$, ligand, toluene.*

e) Anionic cyclization

The intramolecular addition of *ortho*-substituted metallated aryloxy ethers bearing appropriate leaving groups or unsaturations through a 5-*exo*-*trig* cyclization process occupies a place of choice in the arsenal of synthetic strategies for the assembling of five-membered heterocyclic systems. In particular, the Parham cyclization process, which hinges upon aromatic lithiation, usually carried out by lithium-halogen exchange, has been exploited for this purpose. Bradsher and Reames have reported[101] the synthesis of 2,3-dihydro-1-benzofuran using the Parham cyclialkylation reaction. The addition of butyllithium at -100 °C to ω-bromoalkyl ethers of *o*- bromophenol led to preferential exchange of the aryl bromine at position 2. The resulting organolithium reagents, under suitable conditions, cyclised to afford 2,3-dihydro-1-benzofuran.



226 **227** **165**

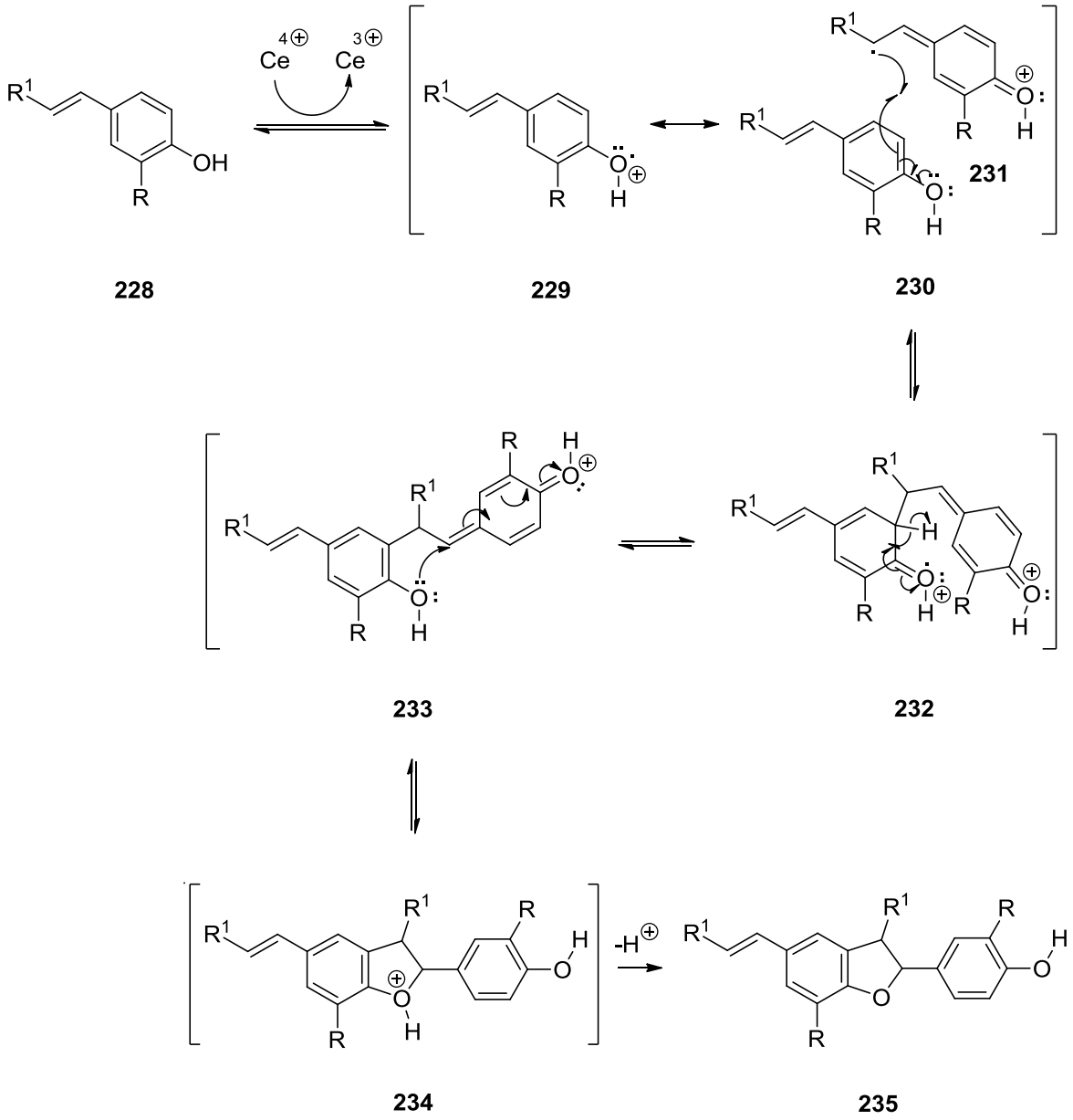
Scheme 1.64 *Parham cycloalkylation reaction (i) BuLi, THF, -100 °C.*

[101] Bradsher, C. K.; Reames, D. C. *J. Org. Chem.* **1981**, *46*, 1384-1388.

f) Oxidative dimerisation

A new method for the preparation of substituted dihydrobenzofurans is described by Wang and co-workers.[102] The *p*-alkenylphenols **228** treated slowly with 1.5 equivalents of cerium ammonium nitrate (CAN) at low temperature in THF, were induced to undergo oxidative dimerization to generate *trans*-2,3-disubstituted 2,3-dihydro-1-benzofurans **235**. The mechanism proposed for this reaction is depicted in Scheme 1.65. Initially, mediated by CAN, one lone pair electron on oxygen of *p*-alkenylphenol **228** is oxidatively abstracted by Ce^{4+} to give a transient radical cation **229** which has stabilized by transient **230** with resonance. Then, transient radical cation **230** is coupled with *p*-alkenylphenol radical cation **231** to generate the intermediate adduct **232**. Subsequently, by restoring aromaticity, intramolecular conjugated addition occurs to the 4-methylenecyclohexa-2,5-dienone-like cation in **233** to afford protonated dihydrobenzofuran **234**. Loss of a proton from the latter produces the desired products **235**.

[102] Chen, P.-Y.; Wu, Y.-H.; Hsu, M.-H.; Wang, T.-P.; Wang, E.-C. *Tetrahedron* **2013**, *69*, 653-657.

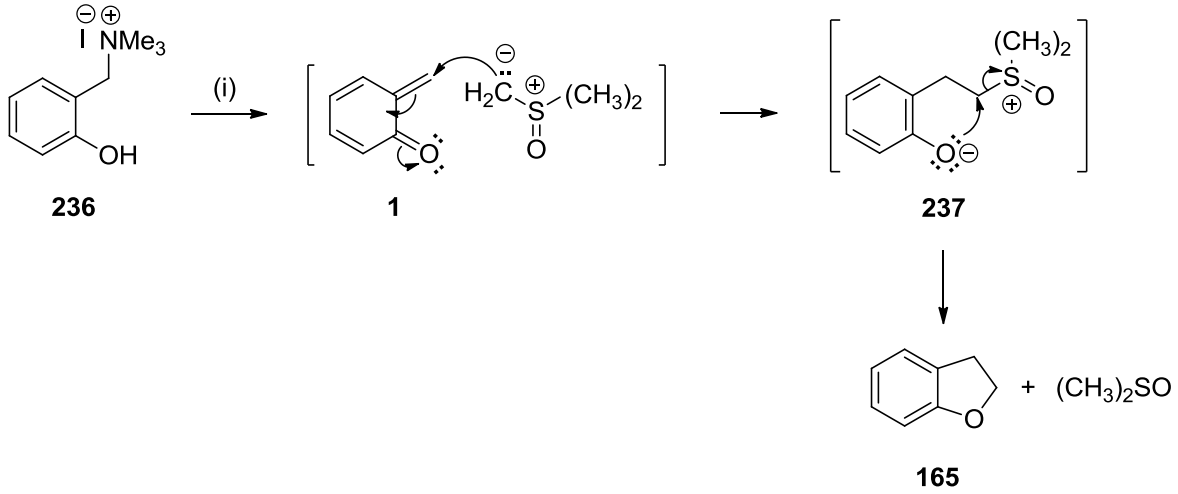


(a) R = H, R^1 = CH_3 (conocarpin), (b) R = OCH_3, R^1 = CH_3 (licarin A), (c) R = R^1 = H, (d) R = H, R^1 = *iso*-C_3H_9, (e) R = OCH_3, R^1 = H, (f) R = H, R^1 = $COCH_3$, (g) R = OCH_3, R^1 = $COCH_3$

Scheme 1.65 *The proposed mechanism for the formation of trans-2,3-disubstituted or 2-substituted 2,3-dihydro-1-benzofurans from p-alkenylphenols mediated by CAN. (i) CAN (1.5 equiv.), THF, 0 °C.*

1.4.2.7. Synthesis of 2,3-dihydro-1-benzofurans *via o*-quinone methide intermediates

Melumad and Breuer[103] were the first to report a route involving *o*-quinone methide as an intermediate intermediate in the synthesis of 2,3-dihydro-1-benzofuran **165**. The *o*-quinone methide **1** generated *in situ* from *o*-hydroxybenzyltrimethylammonium iodide **236** is trapped by a Michael addition reaction provided by dimethyl sulfoxonium methylide that leads to 2,3-dihydro-1-benzofuran **165**.

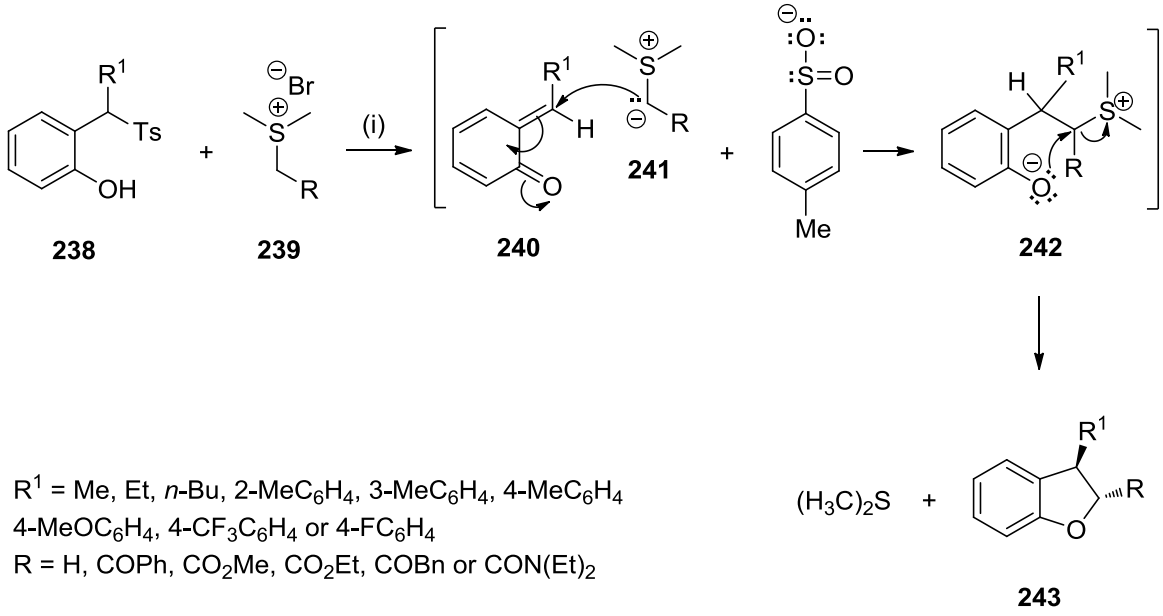


236 **1** **237** **165**

Scheme 1.66 *Formation of 2,3-dihydro-1-benzofuran from o-quinone methide and dimethyl sulfoxonium methylide generated in situ. (i) $(CH_3)_2S(O)CH_2$, DMSO.*

A similar approach was recently reported by Zhou and co-workers.[104] In the presence of caesium carbonate abstraction of the phenolic proton of 2-{(aryl)[(4-methylphenyl)-sulfonyl]methyl}phenols **238** induces the elimination of toluene-*para*-sulfinate anion to give *o*-quinone methides **240** which are trapped by the sulphur ylides **241** formed after removal of a methylene proton from sulfonium salts **239**. The resulting intermediate phenoxides **242** undergo nucleophilic attack of the oxygen anion on the carbon atom of the trimethylsulfonium moiety, to furnish via a *trans*-elimination–cyclization process 2,3-dihydro-1-benzofurans **243** in excellent yield and > 20:1 *trans*/*cis* selectivity.

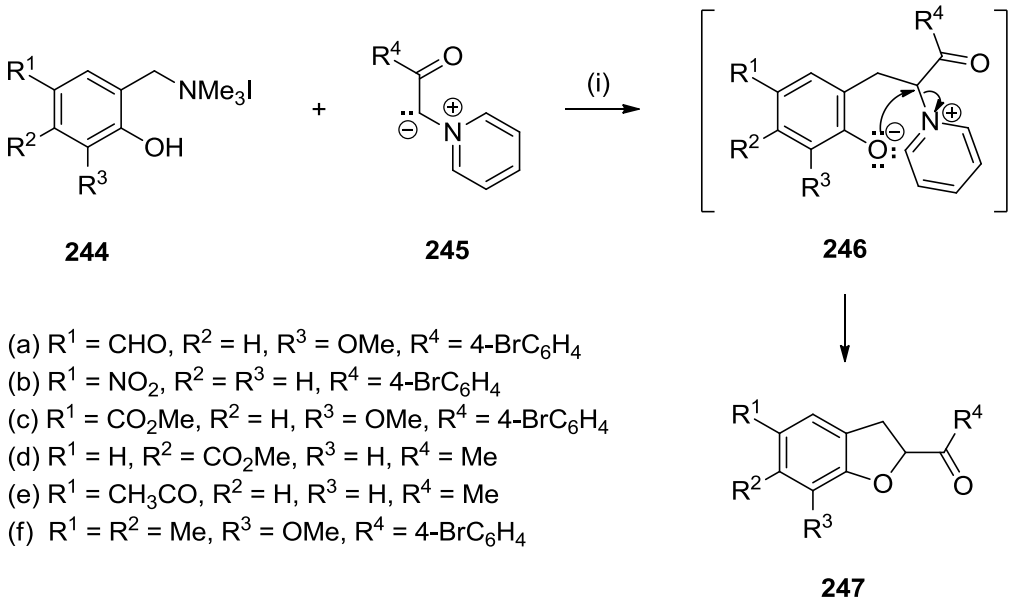
[103] Breuer, E.; Melumad, D. *Tetrahedron Lett.* **1969**, *10*, 1875-1877.
[104] Chen, M.-W.; Cao, L.-L.; Ye, Z.-S.; Jiang, G.-F.; Zhou, Y.-G. *Chem. Commun.* **2013**, *49*, 1660-1662.



Scheme 1.67 *Synthesis of 2,3-dihydro-1-benzofurans derived from in situ generated o-quinone methides followed by Michael addition of a substituted sulfonium ylide and eliminative cyclisation. (i)* Cs_2CO_3, CH_2Cl_2.

Osyanin and co-workers[105] have reported that the reaction of quaternary ammonium salts with DBU in refluxing acetonitrile produces the corresponding *o*-quinone methides which in the presence of pyridinium acylmethylides **245** react by Michael addition to give adducts **246**, that cyclise by elimination of pyridine to give only the respective 2,3-dihydro-1-benzofurans **247** in moderate to good yields.

[105] Osyanin, V. A.; Osipov, D. V.; Klimochkin, Y. N. *J. Org. Chem.* **2013**, *78*, 5505-5520.

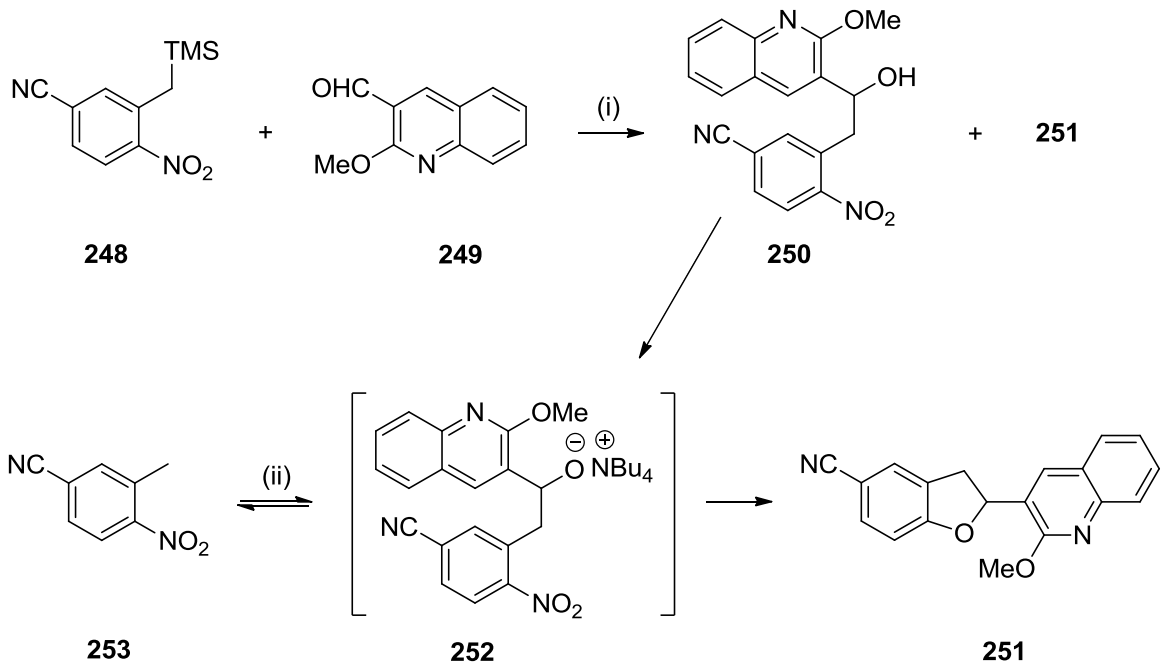


Scheme 1.68 *Synthesis of 2,3-dihydro-1-benzofurans derived from o-quinone methides generated in situ followed by pyridinium acylmethylide Michael addition and eliminative cyclisation. (i) DBU, MeCN, reflux.*

1.4.2.8. Other methods

Kuethe and co-workers[106] developed an effective strategy for the rapid and efficient one-pot synthesis of 2-aryl-5-substituted-2,3-dihydro-1-benzofurans from readily available *o*-nitrotoluenes and aromatic aldehydes. The reaction requires that a mixture of 4-nitro-3-[(trimethylsilyl)methyl]benzonitrile **248** and 2-methoxyquinoline-3-carbaldehyde **249** is treated with a catalytic amount of TBAF to afford the expected alcohol **250** in 79% yield together with a trace amount of 2,3-dihydro-1-benzofuran **251**. Compound **251** is envisaged to occur via a denitrocyclisation reaction. On the other hand, treatment of alcohol **250** with TBAF at room temperature gave a mixture of aldehyde **249** (20%), 2,3-dihydro-1-benzofuran **251** (40%), and nitrotoluene **253** (20%). This product distribution suggests that a reversible carbonyl addition process may be occurring so that **253** reacts with **249** in presence of TBAF to afford intermediate **252** that may provide **251** directly. For the validation of this hypothesis, reaction of **253** and **249** with TBAF gave **251** in 57% yield.

[106] Kuethe, J. T.; Wong, A.; Journet, M.; Davies, I. W. *J. Org. Chem.* **2005**, *70*, 3727-3729.

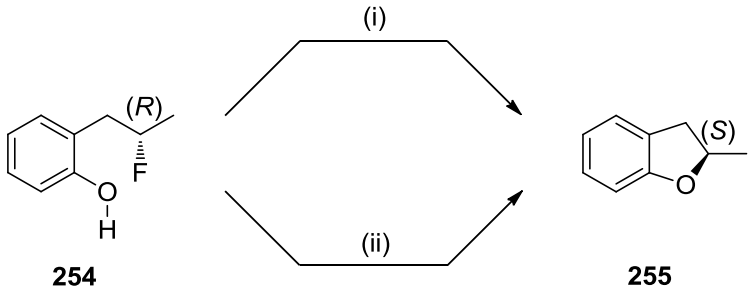


Scheme 1.69 *Synthesis of a 2,3-dihydro-1-benzofuran by a denitrocyclisation reaction. (i) TBAF, THF, (ii) TBAF, THF, reflux.*

Intramolecular S_N2 reaction of alkyl fluorides, have not attracted much attention for a long time probably due to the "common sense" that the C-F bond is highly stable known from the decreasing relative leaving group reactivity of four the halides: I- (30 000) > Br- (10 000) > Cl- (200) > F- (1). Therefore, it is widely realized that, unlike other alkyl halides, alkyl fluorides are either inert to S_N2 reactions or very slow. There are however enzyme-catalysed conditions[107] for example, nucleophilic displacement of C(sp3)-F bonds by hydroxide ion which can be explained by the proximity effect, that is, enzyme binds both alkyl fluoride and the hydroxide together to make the reaction an intramolecular process. Using this lead, Hu and co-workers[108] used intramolecular nucleophilic substitution of alkyl fluoride to synthesize, among other benzo-fused nitrogen and oxygen heterocycles, (2*S*)-2-methyl-2,3-dihydro-1-benzofuran, by treating 2-(*2R*)-2-(2-fluoropropyl)phenol **254** in 91% ee, $[\alpha]_D^{25}$ –11.5 (*c*, 1.2 in $CHCl_3$), with sodium hydride in either THF or DMF as solvents at 70 °C (Scheme 1.70). It was found that the reaction proceeded well to give product **255** in good yield and with high enantiospecificity [in THF, 89% yield, 91% ee, $[\alpha]_D^{25}$ –13.3 (*c*, 1.2 in $CHCl_3$); in DMF, 93% yield, 91% ee, $[\alpha]_D^{25}$ –

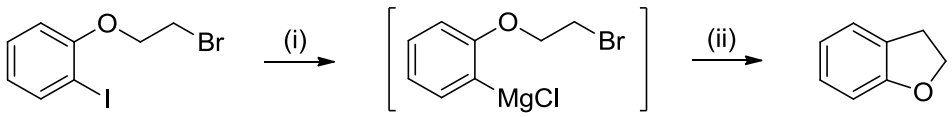
[107] Menger, F. M. *Acc. Chem. Res.* **1993**, *26*, 206-212.
[108] Zhang, L.; Zhang, W.; Liu, J.; Hu, J. *J. Org. Chem.* **2009**, *74*, 2850–2853.

17.2 (*c*, 1.0 in $CHCl_3$). The absolute configuration of **254** was determined by X-ray crystallography whereas to determine the absolute configuration of compound **255** it was synthesised unequivocally as (2*S*)-2-methyl-2,3-dihydro-1-benzofuran with 99% ee, $[\alpha]_D^{25}$ –20.1 (*c*, 1.1 in $CHCl_3$) and found to be identical with the compound derived from the intramolecular S_N2 defluorinative cyclization.



Scheme 1.70 *Synthesis of 2-methyl-2,3-dihydro-1-benzofuran by intramolecular nucleophilic substitution of fluoride anion. (i) NaH, THF, 70 °C, 48 h, 89%, 91% ee, (ii) NaH, DMF, 70 °C, 12 h, 93%, 91% ee.*

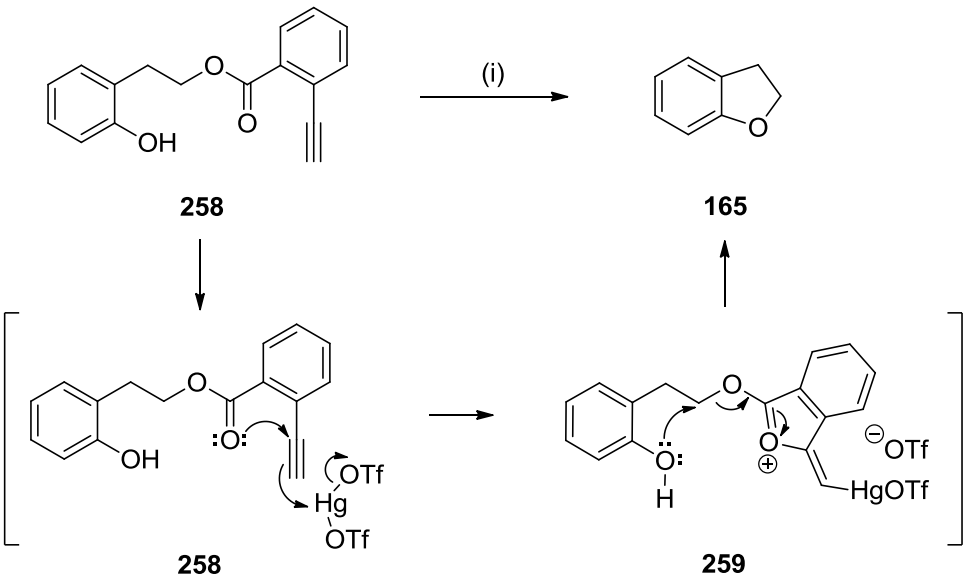
Kneisel and co-workers[109] have reported, an intramolecular cyclization reaction of Grignard reagent [2-(2-bromoethoxy)phenyl](chloro)magnesium **257** by transition-metal catalysis, using CuCN.2LiCl salt, to afford 2,3-dihydro-1-benzofuran **165**. The Grignard reagent was prepared by iodine-magnesium exchange reaction between 1-(2-bromoethoxy)-2-iodobenzene **256** with *i*-PrMgCl in THF at low temperature (Scheme 1.71).



Scheme 1.71 *Synthesis of 2,3-dihydro-1-benzofuran by an intramolecular elimination reaction involving an o-substituted aryl Grignard reagent. (i) i-PrMgCl, THF,-20 °C, (ii) CuCN.2LiCl, 25 °C.*

[109] Kneisel, F. F.; Monguchi, Y.; Knapp, K. M.; Zipse, H.; Knochel, P. *Tetrahedron Lett.* **2002**, *43*, 4875-4879.

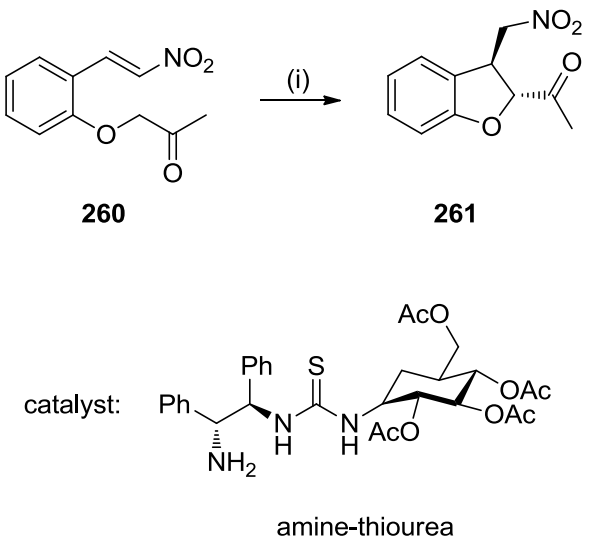
Catalytic activation of an alkynyl group leading to an exo-dig cyclization has been reported by Nishiwaza and co-workers.[110] 2-Ethynylbenzoate **258** when treated with mercuric triflate [$Hg(OTf)_2$] was found to give 2,3-dihydro-1-benzofuran **165**. $Hg(OTf)_2$ showed highly efficient catalytic activity based upon a significant affinity for the alkynyl group. The reaction is initiated by π-complexation of an alkynyl group with $Hg(OTf)_2$ and then nucleophilic attack by a lone electron pair of the carbonyl group to the electron deficient alkynyl to give an intermediate oxocarbenium cation **259**. This cationic residue acts as the highly efficient leaving group for the intramolecular S_N2 reaction initiated by the phenolic oxygen atom that leads to 2,3-dihydro-1-benzofuran **165**.



Scheme 1.72 *Catalytic activation of an ethynyl benzoate group tethered at position 2 of phenol leads by intramolecular elimination to 2,3-dihydro-1-benzofuran. (i) $Hg(OTf)_2$, CH_2Cl_2.*

Zhou and co-workers[111] have described a convenient and scalable procedure for the preparation of *trans*-2,3-dihydro-1-benzofurans, such as **261**, in high yields with excellent diastereo- and enantio-selectivities. For example, 1-{2-[(*E*)-2-nitrovinyl]phenoxy}acetone **260** was cyclised via a primary amine-thiourea organocatalysed intramolecular Michael addition. The presence of co-catalyst *p*-nitrobenzoic acid was found to accelerate the reaction as well improving the diastereo- and enantio-selectivity of the product obtained.

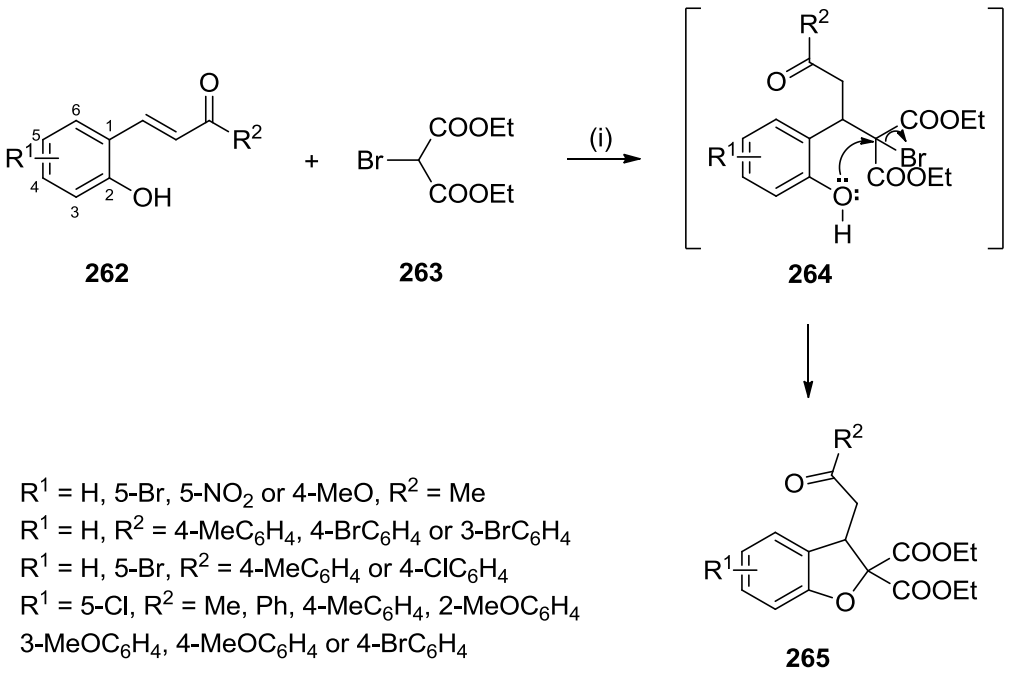
[110] Yamamoto, H.; Pandey, G.; Asai, Y.; Nakano, M.; Kinoshita, A.; Namba, K.; Imagawa, H.; Nishizawa, M. *Org. Lett.* **2007**, *9*, 4029-4032.
[111] Lu, A.; Hu, K.; Wang, Y.; Song, H.; Zhou, Z.; Fang, J.; Tang, C. *J. Org. Chem.* **2012**, *77*, 6208-6214.



Scheme 1.73 *Intramolecular Michael addition methodology leading to 2,3-dihydro-1-benzofurans. (i) catalyst, p-nitrobenzoic acid, THF.*

Xie and co-workers[112] reported a base catalyzed synthesis of 2,3-dihydro-1-benzofurans from 2-hydroxyaryl-*α*,*β*-unsaturated ketones. When potassium carbonate is added to a solution of *α*-bromomalonate in acetone followed by 2-hydroxyaryl-*α*,*β*-unsaturated ketones **262** at room temperature, it is postulated that first a Michael addition takes place to give the intermediate addition products **264** which cyclise by nucleophilic attack of the hydroxyl oxygen atom to the C-Br group displacing bromine anion to afford the corresponding diethyl 3-[2-(substituted)-2-oxoethyl]-1-benzofuran-2,2(3*H*)-dicarboxylates **265**. In the place of 2-hydroxyaryl-*α*,*β*-unsaturated ketones the authors report the use of 2-hydroxyarylnitroalkenes, 2-hydroxyarylimines, and salicylic aldehydes to give 2,3-dihydrobenzofuran derivatives which possess other useful groups at position 3, such as nitro, amino, and hydroxyl groups.

[112] Li, Q.-B.; Zhou, F.-T.; Liu, Z.-G.; Li, X.-F.; Zhu, W.-D.; Xie, J.-W. *J. Org. Chem.* **2011**, *76*, 7222-7228.

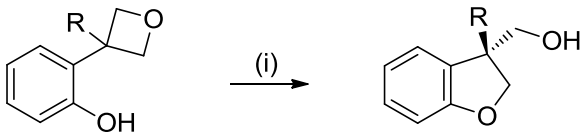


262 **263** **264** **265**

Scheme 1.74 *Synthesis of 2,3-dihydro-1-benzofurans from 2-hydroxyaryl-α,β-unsaturated ketones by Michael addition with carbon nucleophiles followed by cyclisation. (i) K_2CO_3, acetone.*

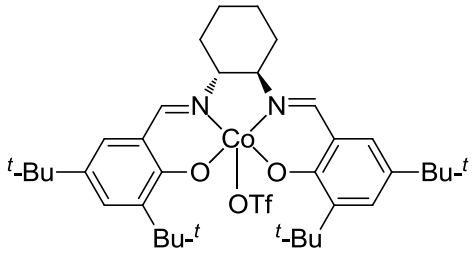
Intramolecular ring opening of achiral 3-substituted oxetanes activated by (salen)Co(III) complexes followed by reaction with *O*-centered nucleophiles has been used by Loy and Jacobsen[113] to synthesise functionalised 2,3-dihydro-1-benzofurans in high yields and enantioselectivities. Thus, 2-oxetan-3-ylphenol **266a**, 2-(3-methyloxetan-3-yl)phenol **266b** and 3-(2-hydroxy-phenyl)oxetan-3-ol **266c** were ring opened in the presence of 5, 10 and 10 mol% of catalyst, respectively, under solvent-free conditions for the first two compounds and in small amounts of methyl *tert*-butyl ether for the latter compound, to afford after cyclisation enantioenriched [2,3-dihydro-1-benzofuran-3-yl]methanols (*S*)-**267a** in 94% yield, 93% ee, (*S*)-**267b** in 77% yield, 96% ee and (*R*)-**267c** in 79% yield, 84% ee.

[113] Loy, R. N.; Jacobsen, E. N. *J. Amer. Chem. Soc*. **2009**, *131*, 2786-2787.



266 **267**

(a) R = H, (b) R= Me, (c) R = OH



cyclic oligomeric
(salen)CoOTf catalyst

Scheme 1.75 *Synthesis of 2,3-dihydro-1-benzofurans by catalytic ring-opening followed by ring-closure of achiral 3-substituted oxetanes. (i) 5 or 10 mol% catalyst, solvent-free conditions or small amount of TBME.*

2. Results and Discussion

2.1. Synthesis of *o*-quinone methide precursor and trapping reactions

The *o*-quinone methides selected for our study are as shown in Figure 2.1 these were generated *in situ* from the appropriate precursors and trapped by either a nucleophile giving a Michael addition product or by a dienophile to yield the hetero Diels-Alder adduct.

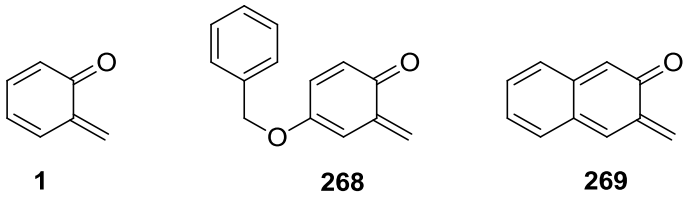
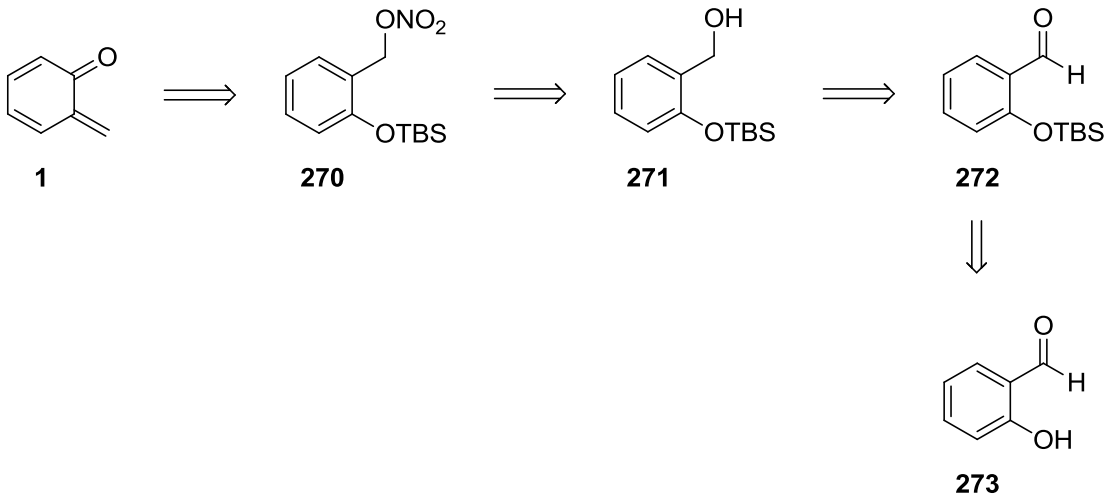


Figure 2.1 *o-Quinone methide intermediates targeted in this study*.

2.1.1 Generation and reactivity of *o*-quinone methide intermediate

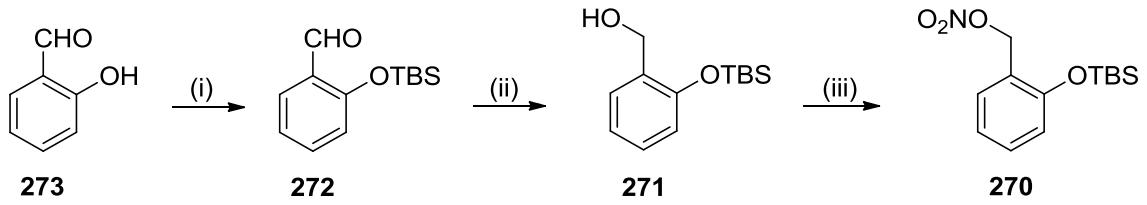
The simple retrosynthetic analysis shown in Scheme 2.1 indicates that the formation of the *o*-quinone methide precursors *i.e.* the nitrate ester can be done starting from the commercially available reagent salicylaldehyde **273**.



Scheme 2.1 *Retrosynthetic analysis of o-quinone methide generation.*

The first step was the protection of the hydroxy group in salicylaldehyde[46] **273** using triethyl- amine (1.2 equiv.) and *tert*-butyldimethylsilyl chloride (TBSCl) (1.2 equiv.) in the

presence of catalytic 4-dimethylaminopyridine (DMAP) at 0 ^{o}C (Scheme 2.2). The reaction went to near completion within 1 hour but even after a longer period, the reaction was found to be incomplete, as shown by TLC. The addition of excess of triethylamine (2 equiv.) and the extension of reaction time up to 12 hours resulted in the formation of 2-{[*tert*-butyl-(dimethyl)silyl]oxy}benzaldehyde **272** in 97% yield, without any trace of starting material. Since the reaction of salicylaldehyde **273** with TBSCl releases HCl, it is quite possible that the acid is converting the silyl ether **272** back to **273** and TBSCl whereas addition of excess of triethylamine must be effectively neutralizing the acid. In the second step the aldehyde **272** was reduced by sodium borohydride (1.2 equiv.) in methanol to the secondary alcohol **271** (96% yield). The third step was more crucial because the alcohol was to be converted to the nitrate ester. At first the procedure reported by Froyen[114] using triphenyl phosphine, NBS and silver nitrate was implemented but no spot other than the starting material was observed after examining the reaction mixture with TLC. Hakimelahi[115] prepared thionyl chloride nitrate as nitrating agent by reacting thionyl chloride and silver nitrate which was used for the nitrosation of alcohols. This method was applied to benzyl alcohol **271** which was dissolved in THF at room temperature followed by slow addition of powdered silver nitrate and then dropwise addition of thionyl chloride. The resulting ester, 2-{[*tert*-butyl(dimethyl)-silyl]oxy}benzyl nitrate **270**, was isolated in 55% yield.



Scheme 2.2 *Synthesis of 2-{[tert-butyl(dimethyl)silyl]oxy}benzyl nitrate. (i) TBSCl, NEt_3, DMAP, CH_2Cl_2, 0 °C, (ii) $NaBH_4$, MeOH, (iii) $AgNO_3$, $SOCl_2$, THF.*

The ^{1}H NMR spectrum of the nitrate ester **270** is shown in the Figure 2.2. The signal at 4.63 ppm that integrates to two protons and belongs to the benzyl methylene is a singlet whereas in the case of the alcohol **271**, the corresponding protons appear as a doublet because of coupling with the hydroxy proton (appearing as a triplet at 2.10 ppm). There

[114] Froyen, P. *Phosphorus, Sulfur and Silicon*, **1997**, *129*, 89-97.
[115] Hakimelahi, G. H.; Sharghi, H.; Zarrinmayeh, H.; Khalafi-Nezhad, A. *Helv. Chim. Acta* **1984**, *67*, 906-915.

was no trace of the hydroxy proton in the spectrum of compound **270**, as expected, while the peak at m/z 281.9 in the ESI mass spectrum, run by in methanol solution, corresponds to loss of H^+ and thus offers further confirmation of the structure.

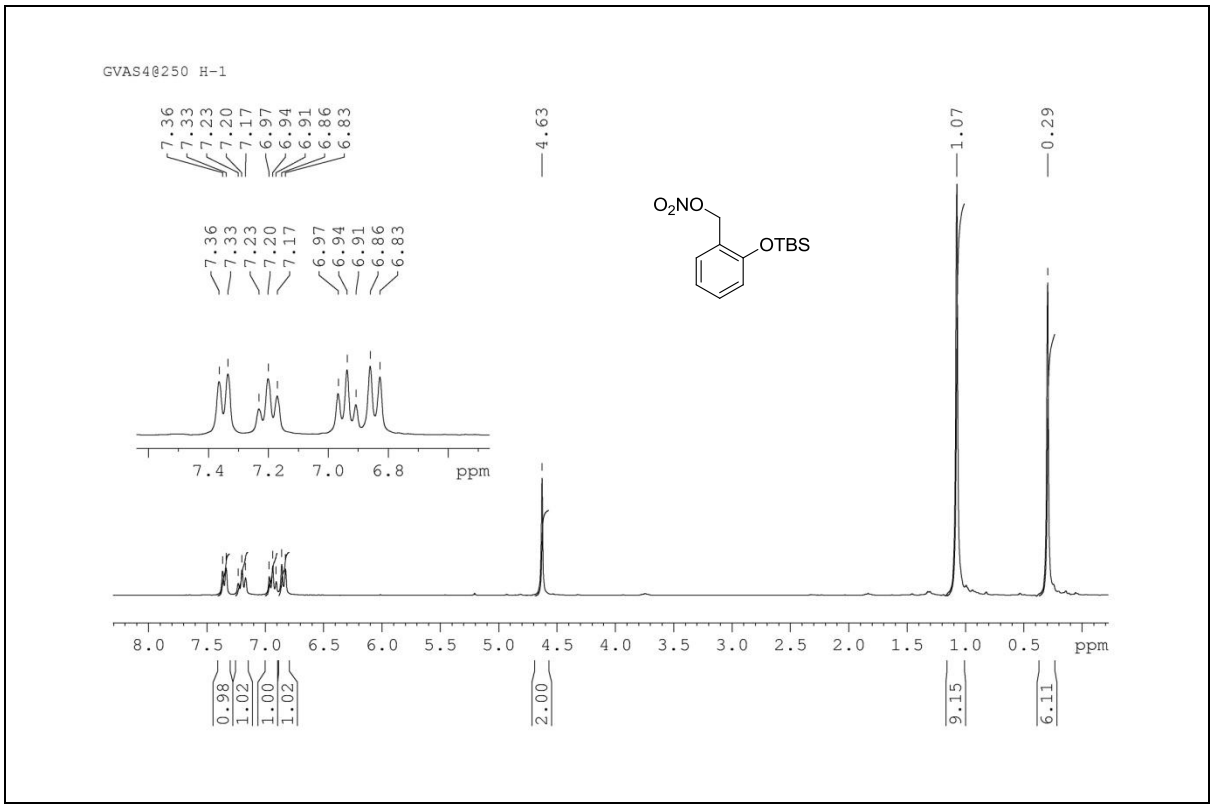
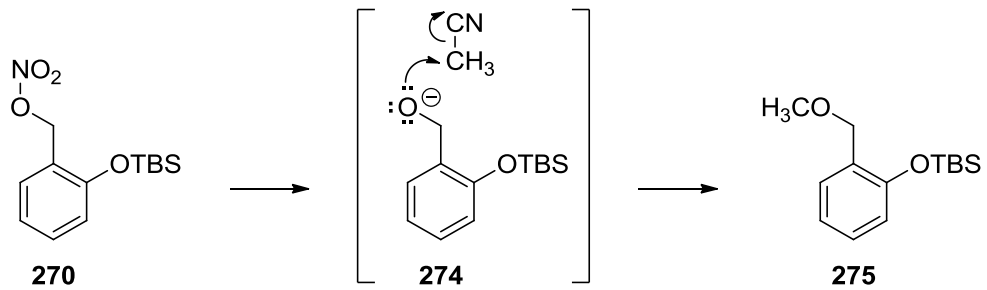


Figure 2.2 *^{1}H NMR (250 MHz, $CDCl_3$) of compound **270**.*

It is interesting that in the ESI HRMS spectrum of compound **270** (Figure 2.4), run in acetonitrile solution, the molecular ion at m/z = 275.1428 $[M + Na]^+$ corresponds to loss of $^+NO_2$ and addition of CH_3 (derived from acetonitrile), as shown in Scheme 2.3.



Scheme 2.3 *Ionisation of 2-{[tert-butyl(dimethyl)silyl]oxy}benzyl nitrate in acetonitrile.*

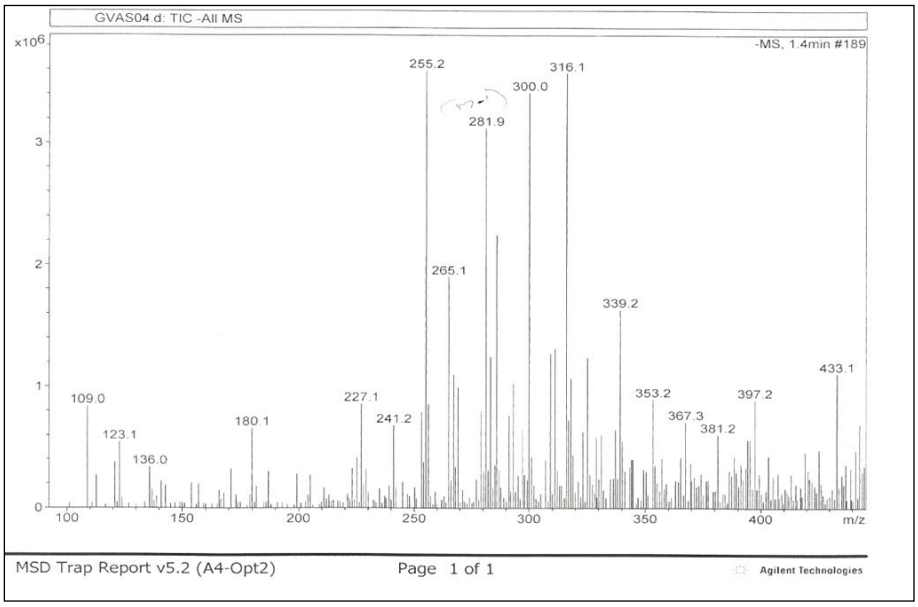


Figure 2.3 *Low resolution ESI mass spectrum of compound **270** in MeOH.*

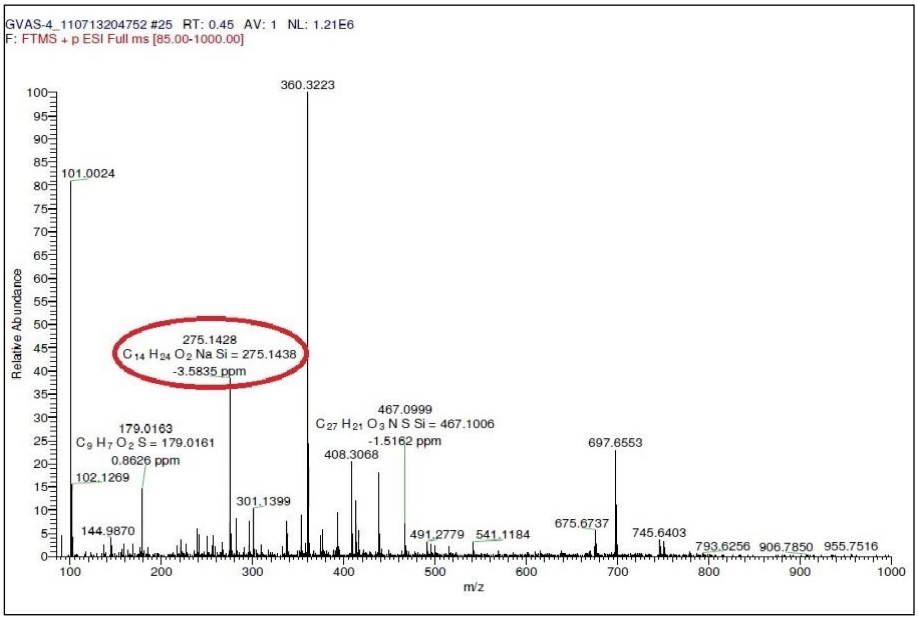
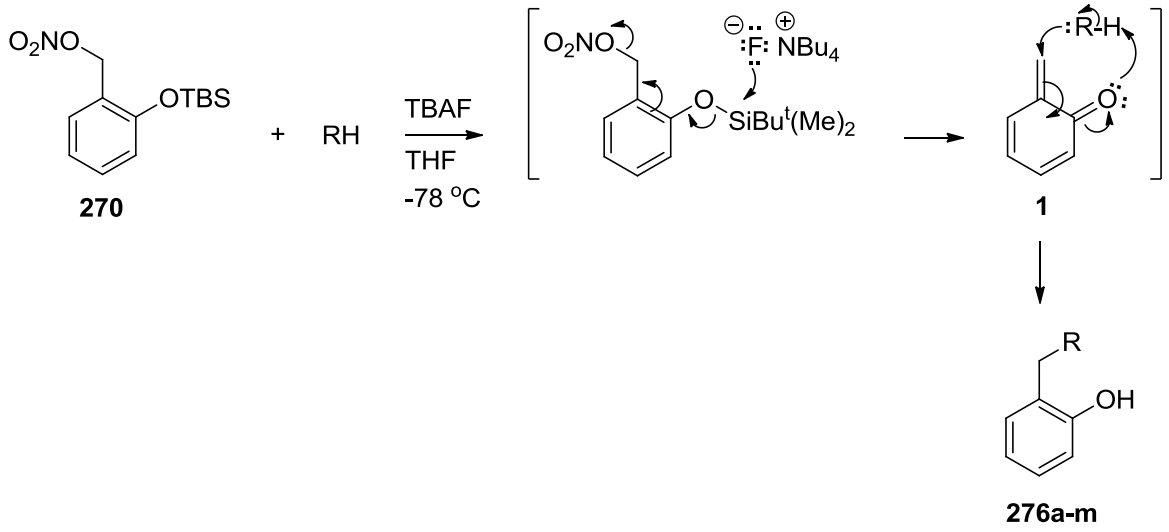


Figure 2.4 *High resolution ESI mass spectrum of compound **270** in CH_3CN.*

a) <u>Michael addition</u>

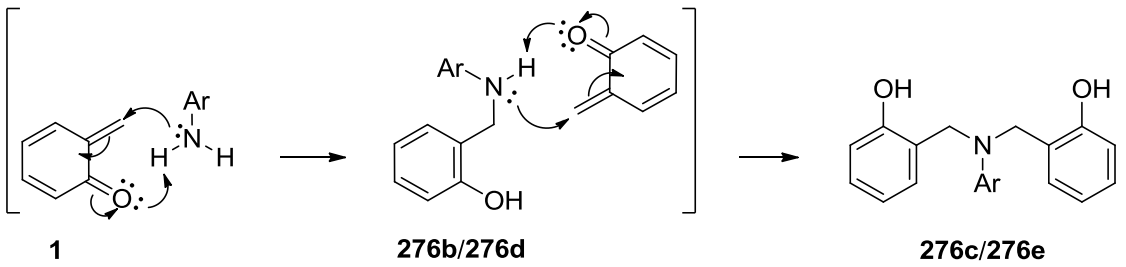
The next step was generation of the *o*-quinone methide from the nitrate ester using fluoride ion and trapping this intermediate by a Michael reaction using C, O, N and S nucleophiles. The reaction was carried out by the addition of the appropriate nucleophile to

the nitrate ester **270** in THF at -78 °C followed by dropwise addition of the fluoride ion source *i.e.* TBAF in THF and then stirring the reaction mixture for a further 10 minutes (Scheme 2.4).



Scheme 2.4 *Generation of o-quinone methide and trapping by the Michael addition.*

The reaction is postulated to proceed by attack of the fluoride anion onto the silyl ether, breakage of the Si-O bond, and elimination of a nitrate anion to generate the corresponding *o*-quinone methide **1** *in situ*. Table 2.1 shows the nucleophiles used and the products obtained together with the yields. In case of the primary amines there was mixture of two products as the Michael addition was found to occur twice (Table 2.1, entry 2 and 3). The appropriate primary amine, benzylamine or *p*-methoxyaniline, adds to the first molecule of the *o*-quinone methide to give the secondary amino addition product **276b** or **276d**, which then reacts further with a second molecule of *o*-quinone methide by another Michael addition to produce the tertiary amino product **276c** or **276e**.



Scheme 2.5 *Trapping of two o-quinone methide molecules by a double sequence of Michael additions from a secondary amine.*

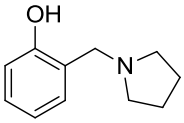
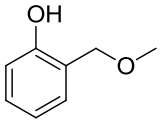
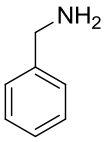
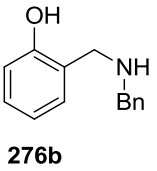
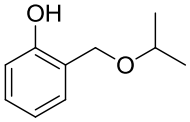
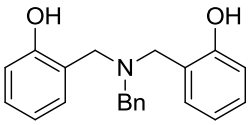
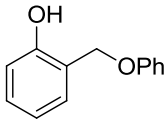
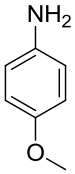
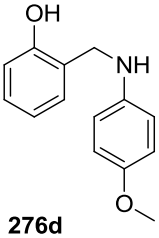
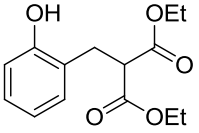
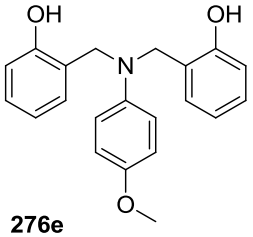
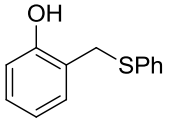
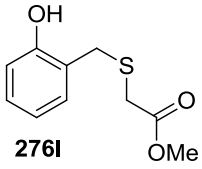
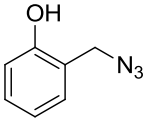
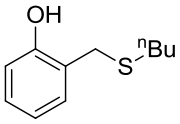
entry	RH	product	yield (%)	entry	RH	product	yield (%)
1		 **276a**	80	5	MeOH	 **276g**	94
2		 **276b**	13	6	*i*-PrOH	 **276h**	65
		 **276c**	20	7	PhOH	 **276i**	52
3		 **276d**	30	8	$CH_2(CO_2Et)_2$	 **276j**	60
		 **276e**	20	9	PhSH	 **276k**	68
				10	HSCO_2Me	 **276l**	56
4	NaN_3	 **276f**	63	11	*n*-BuSH	 **276m**	66

Table 2.1 *Products obtained from the Michael addition of the C, O, N and S nucleophiles to o-quinone methide generated in situ.*

In the ^{1}H NMR spectrum of compound **276e** the broad peak at 9.59 ppm that corresponds to the two protons of the phenolic hydroxyl groups, the eight aromatic protons in the region of 7.06-6.53 ppm, the singlet at 4.45 ppm that corresponds to the four protons of the two methylene groups and the singlet at 3.61 ppm that corresponds to the three protons of the methyl group, together with the molecular ion at m/z = 336.1 $[M + H]^+$ in

the ESI mass spectrum, coincide without doubt with the proposed structure of this tertiary amine. The ^{1}H NMR and mass spectrometry data of tertiary amine **276c** also support fully the structure of this compound.

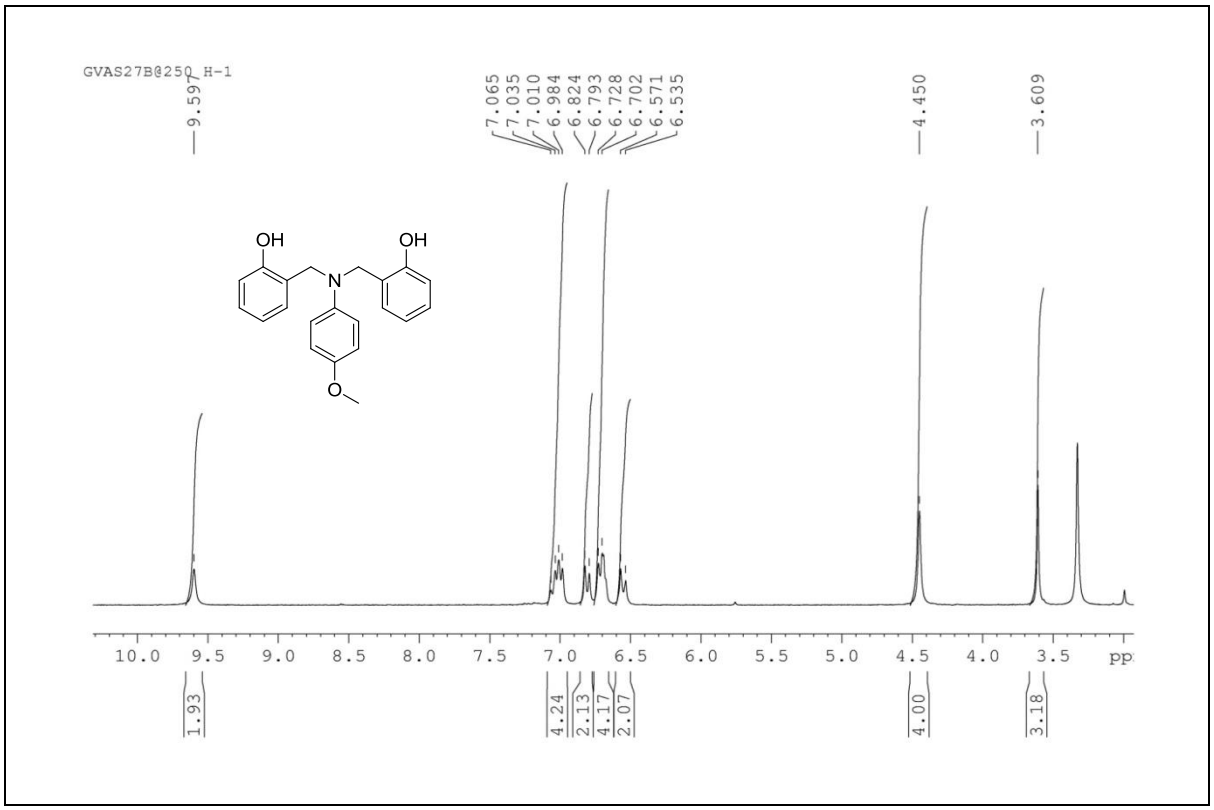
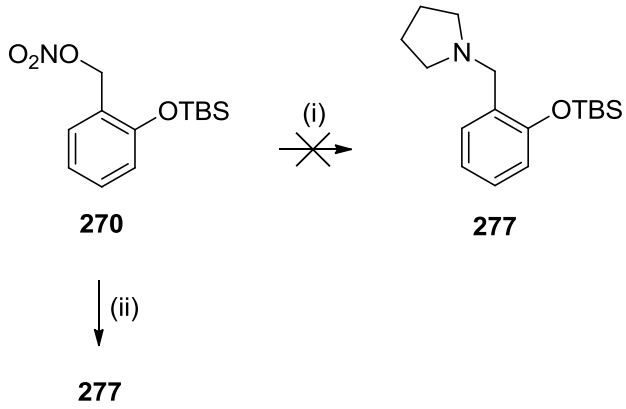


Figure 2.5 *^{1}H NMR (250 MHz, DMSO-d_6) of compound **276e**.*

In case of methanol and 2-propanol (Table 2.1, entry 5 and 6) the solvent itself was used as a nucleophile. The reactions were carried out in the respective solvents, instead of using THF, in order to get better yields of the products. In case of diethyl malonate (Table 2.1 entry 8) the addition of sodium hydride at 0 °C produced the corresponding carbanion which was added to the nitrate ester **270**, the reaction mixture cooled to -78 ^{o}C, and then TBAF was added dropwise to generate gradually *o*-quinone methide and for the Michael reaction to occur.

To confirm that these products were obtained via the *in situ* generated *o*-quinone methide and not by a simple nucleophilic substitution followed by TBS deprotection, nitrate ester **270** and pyrrolidine were stirred in THF at -78 °C for 6 hours, no product was not detected by TLC. However, when this reaction mixture was heated for 24 hours

compound **277** was produced in 45% yield, which supports the assumption that an intermediate *o*-quinone methide must be involved in the above Michael addition reactions.



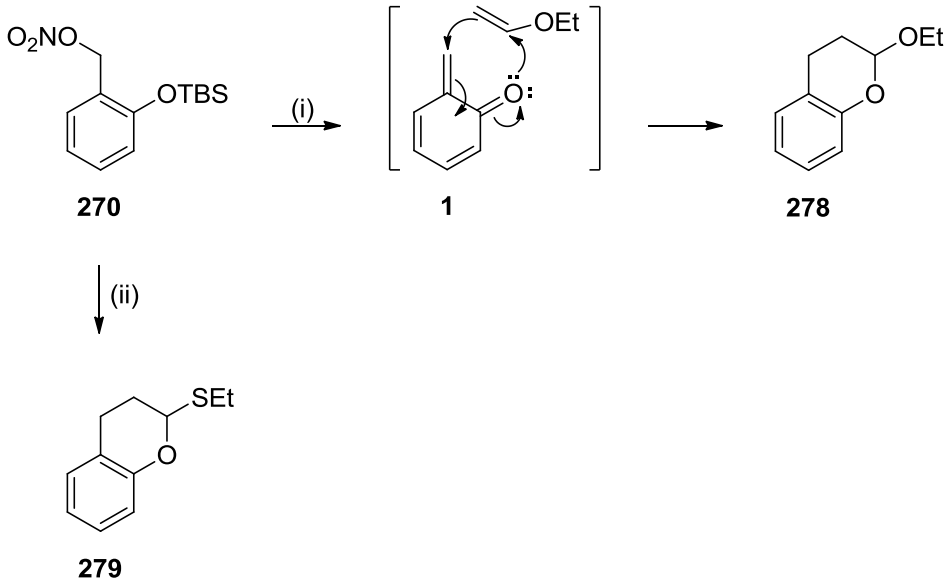
Scheme 2.6 *Nucleophilic substitution of nitrate anion in 2-{[tert-butyl(dimethyl)silyl]oxy}benzyl nitrate. (i) pyrrolidine, THF, -78 °C, 6 h, (ii) pyrrolidine, THF, reflux, 24 h.*

b) "Inverse electron demand" hetero-Diels-Alder reaction

The fingerprint reaction that confirms the existence of the *in situ* generated *o*-quinone methide intermediate is the Diels-Alder cycloaddition reaction. It therefore seemed imperative to obtain the Diels-Alder products from the nitrate ester **270**. Thus, the nitrate ester **270** was dissolved in dry toluene under an argon atmosphere, the temperature was lowered to -78 °C, and then a 100-fold excess of the appropriate dienophile, ethyl vinyl ether (EVE), or ethyl vinyl sulfide was added slowly, followed by dropwise addition of TBAF. The *o*-quinone methide generated in this reaction acts as a heterodiene which reacts with the respective dienophile and undergoes "inverse electron demand" hetero-Diels-Alder reaction to yield the corresponding chromanes **278** and **279** in 20 and 17% yields, respectively. The low yield of these reactions may be accounted for by the competing facile trimerization of the very reactive *o*-quinone methide. The insoluble material from the reaction mixtures of **278** and **279** was recrystallized from acetone, and the melting point was found to be the same as that of the trimer **288** (mechanism of formation of this trimer

is given in Scheme 2.11) reported by Cavitt et al.[116] and confirmed later by Mao and Boekelheide.[117]

The reaction was repeated several times as there was no detection of the product from the reaction mixture but later it was found out that the ethoxy chromane obtained from this reaction is not stable and is decomposing during its purification by column chromatography. A different purification procedure was therefore sought that is, trituration of the crude product with hexane followed by filtration and preparative TLC of the filtrate.



Scheme 2.7 *Hetero-Diels-Alder reaction of the in situ generated o-quinone methide (i) ethyl vinyl ether, TBAF, toluene, -78 °C, (ii) ethyl vinyl sulfide, TBAF, toluene, -78 °C.*

The ^{1}H NMR spectrum of chromane **278** is shown in Figure 2.6. Proton H-2 at 5.25 ppm appears as a triplet derived from the inner line overlapping of two doublets due to coupling (J = 2.5 Hz) to the adjacent protons H-3a and H-3b. Each of the protons H-3a and H-3b appear as a multiplet at 3.96-3.84 ppm and 3.71-3.61 ppm arising from four consecutive doublets. The benzylic protons at C-4 appear as two triplets at 2.98 ppm and 2.62 ppm derived from three consecutive doublets. The two protons of the CH_2 of the ethoxy group appear as a multiplet at 2.09-1.88 ppm and since they are in the vicinity of the chiral C-2 proton they are diastereotopic. Each one therefore splits into two quartets of a doublet.

[116] Cavitt, S. B.; Sarrafizadeh, H. R.; Gardner, P. D. *J. Org. Chem.* **1962**, *27*, 1211-1216.
[117] Mao, Y. L.; Boekelheide, V. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 1732-1735.

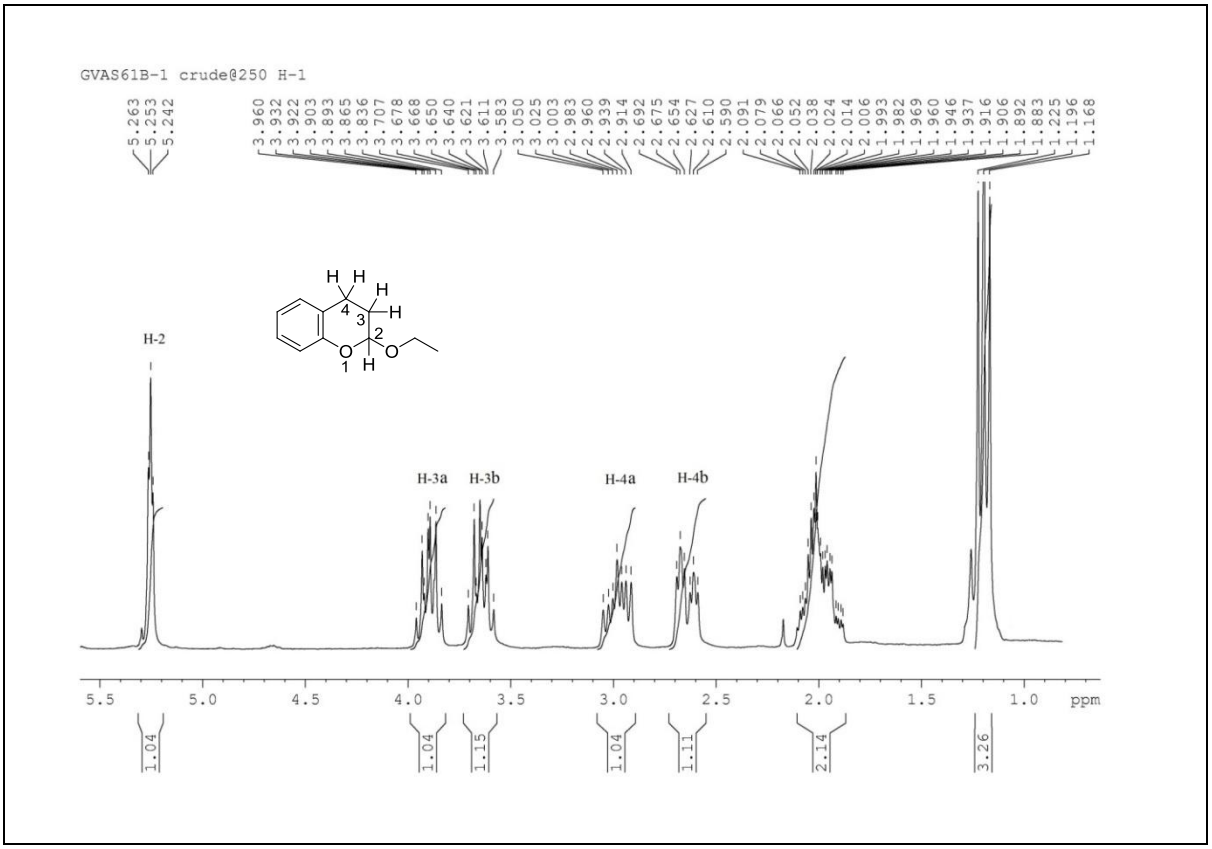
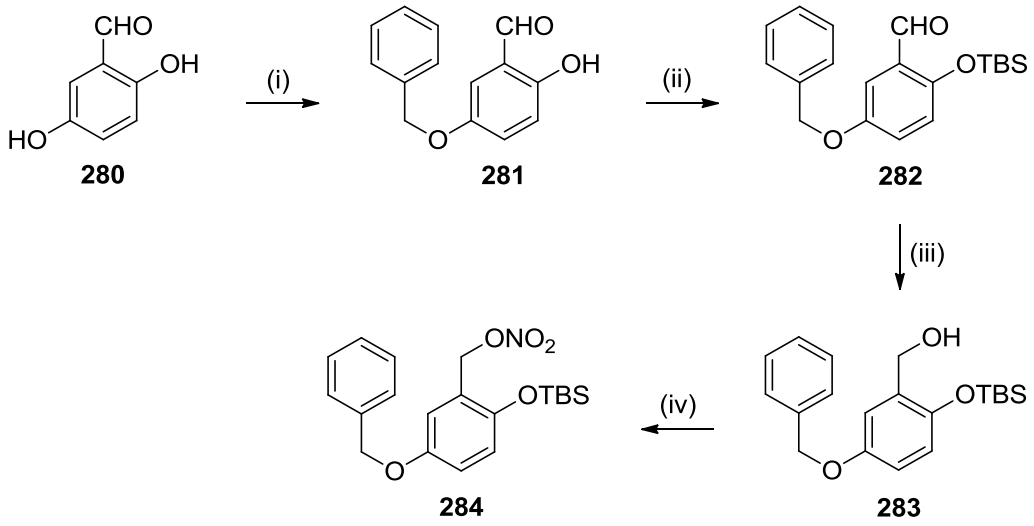


Figure 2.6 *^{1}H NMR (250 MHz, $CDCl_3$) of compound **278**.*

2.1.2 Generation and reactivity of substituted *o*-quinone methide intermediate

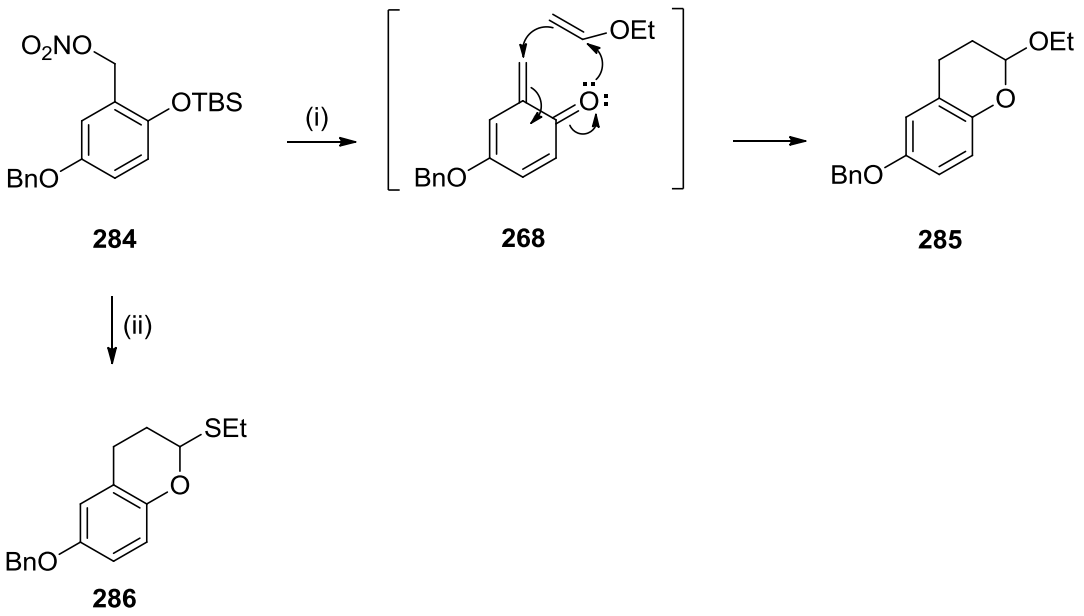
From the results above it has been established that *o*-quinone methide **1** generated from nitrate ester **270** acts as a heterodiene and undergoes "inverse electron demand" hetero-Diels-Alder reaction with the dienophile. The requirement for an "inverse electron demand" hetero-Diels-Alder reaction is that the diene has to be electron-deficient and the dienophile electron-rich. Therefore it was decided to introduce an electron withdrawing substituent *para* to the oxygen of the *o*-quinone methide to investigate if there will be an increase in the yield of the Diels-Alder reaction product. For this reason, *meta*-benzyloxy nitrate ester **284** (Scheme 2.8) was chosen as a substituted *o*-quinone methide precursor, that was synthesized starting from the commercially available 2,5-dihydroxybenzaldehyde where the 5-hydroxy group was selectively transformed into a benzyloxy group by a simple benzylation process (in 30% yield) using benzyl bromide and sodium bicarbonate. The aldehyde **281** was then transformed into 5-(benzyloxy)-2-{[*tert*-butyl(dimethyl)

silyl]oxy}-benzyl nitrate **284** (in 55% yield) by the reaction sequence shown in Scheme 2.8. The chemistry used in this reaction sequence is similar to that used for the synthesis of parent nitro ester **270** (Scheme 2.2).



Scheme 2.8 *Synthesis of 5-(benzyloxy)-2-{[tert-butyl(dimethyl)silyl]oxy}benzyl nitrate. (i) $NaHCO_3$, KI, benzyl bromide, CH_3CN, reflux, 24 h, (ii) TBSCl, NEt_3, DMAP, CH_2Cl_2, 0 °C, (iii) $NaBH_4$, MeOH, (iv) $AgNO_3$, $SOCl_2$, THF.*

Nitro ester **284** was then subjected to TBAF in the presence of ethyl vinyl ether or ethyl vinyl sulfide, to give, via the *in situ* generated *o*-quinone methide (4-(benzyloxy)-6-methylenecyclohexa-2,4-dien-1-one) **268**, chromanes **285** and **286** in 84% and 74 % yield, respectively. It turns out that the yields obtained for chromanes **285** and 2**86** are comparatively higher than the yields of chromanes **278** and **279** (Scheme 2.7) obtained from unsubstituted *o*-quinone methide **1**. This increase in the yield of the products points out to a more efficient cycloaddition reaction between the electron-poor heterodiene and electron-rich dienophiles, in the "inverse electron demand" hetero-Diels-Alder reaction.

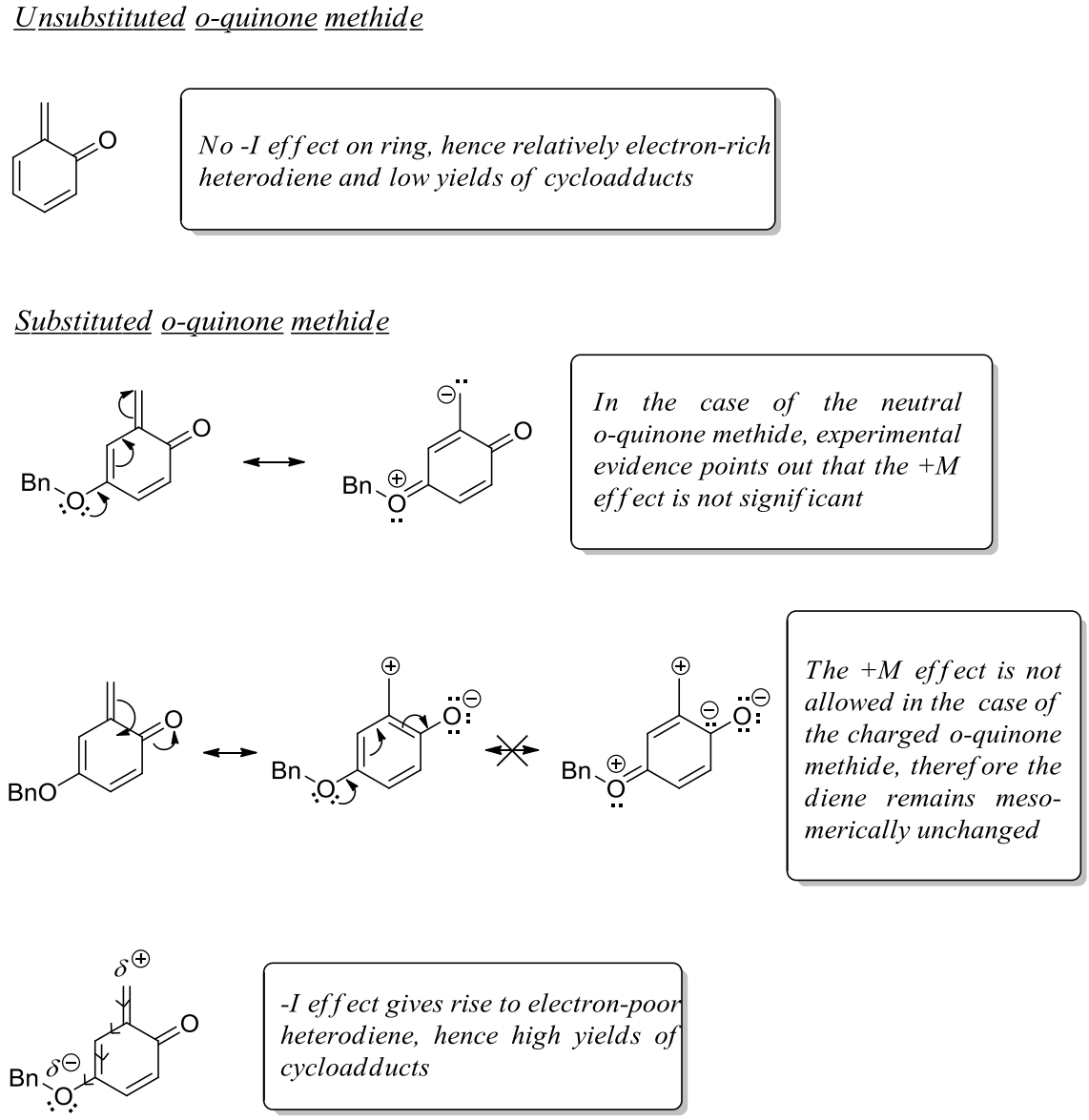


284 **268** **285**

286

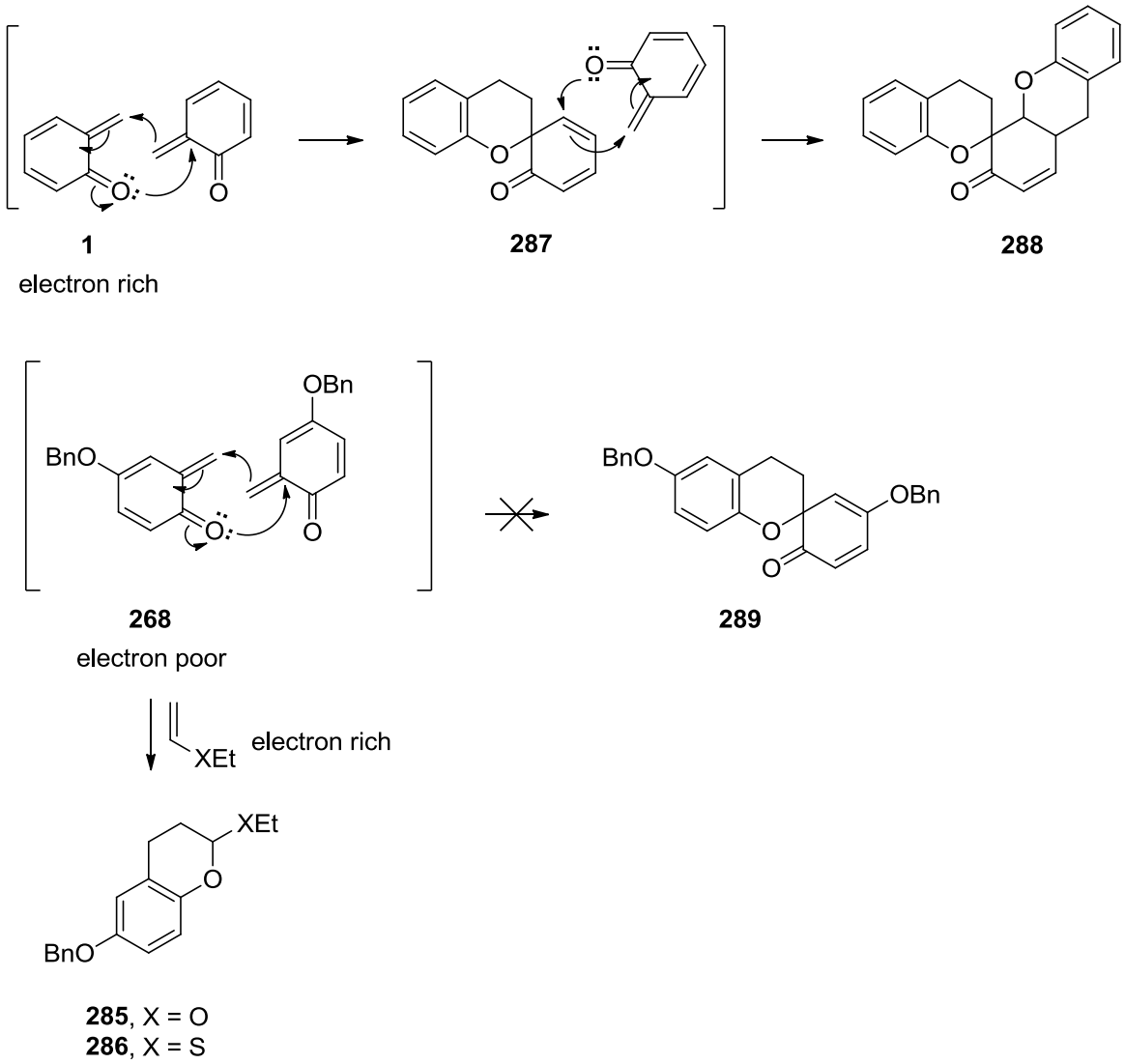
Scheme 2.9 *Hetero-Diels-Alder reaction of in situ generated 4-(benzyloxy)-6-methylenecyclohexa-2,4-dien-1-one with electron-rich dienophiles. (i) ethyl vinyl ether, TBAF, toluene, -78 °C, (ii) ethyl vinyl sulfide, TBAF, toluene, -78 °C.*

The explanation for the above result is as follows. Similar to the methoxy group the benzyloxy group acts as electron donor in the concept of the resonance effect in an aromatic compound or a polyene but for this to occur the group has to be at *para* position to the negative charge thereof developed. Hence, in the described case, from the high yields of cycloadducts **285** and **286** it can be deduced that the +M effect of the benzyloxy group in *o*-quinone methide **268** (Scheme 2.9 and see also Scheme 2.10) is by no means significant. On the other hand, negative inductive effect (-I) of the benzyloxy group must be more significant in *o*-quinone methide **268** (Scheme 2.9 and see also Scheme 2.10) and therefore the heterodiene moiety of this molecule turns out to be more electron-deficient than the heterodine moiety of unsubstituted *o*-quinone methide in Scheme 2.7.



Scheme 2.10 *Explanation of the +M and –I effects taking place in o-quinone methide intermediates.*

In case of the benzyloxy substituted *o*-quinone methide **268**, the dimerization process cannot occur as the heterodiene is electron poor and tends to react with the electron-rich dienophile (ethyl vinyl ether or ethyl vinyl sulfide) instead of reacting with a second molecule of itself to give high yields of **285** or **286** (Scheme 2.9). By comparison, the parent *o*-quinone methide **1** is electron-rich compared to **268** and reacts with the electron-rich dienophiles to give **278** or **279** (Scheme 2.7) in less than 20% yield while trimerization occurs to give the trimer **288** as the major product (Scheme 2.11).

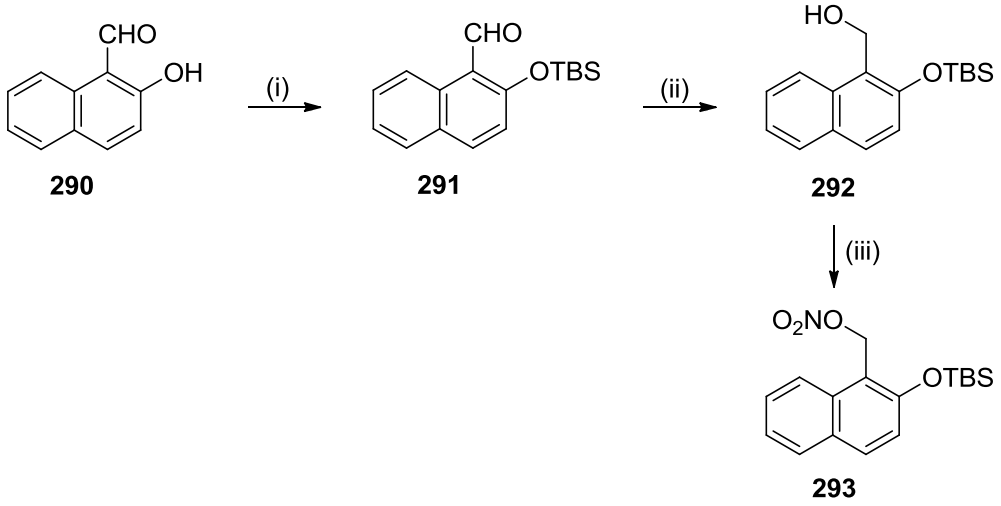


Scheme 2.11 *The role of electronic effects in the hetero-Diels–Alder reaction of o-quinone methides.*

2.1.3 Generation and reactivity of *o*-naphthoquinone methide intermediate

The study of the generation and reactivity of *o*-naphthoquinone methide, using the conditions described above, was an interesting outcome of this work. The required precursor, (2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-naphthyl)methyl nitrate **293** was prepared in a manner similar to that used for the synthesis of nitrate ester **270** (Scheme 2.2). In order to prepare nitrate ester **293** (Scheme 2.12) commercially available 2-hydroxy-1-naphthaldehyde **290** was used as starting material. *tert*-Butyl(dimethyl)silylation of **290**

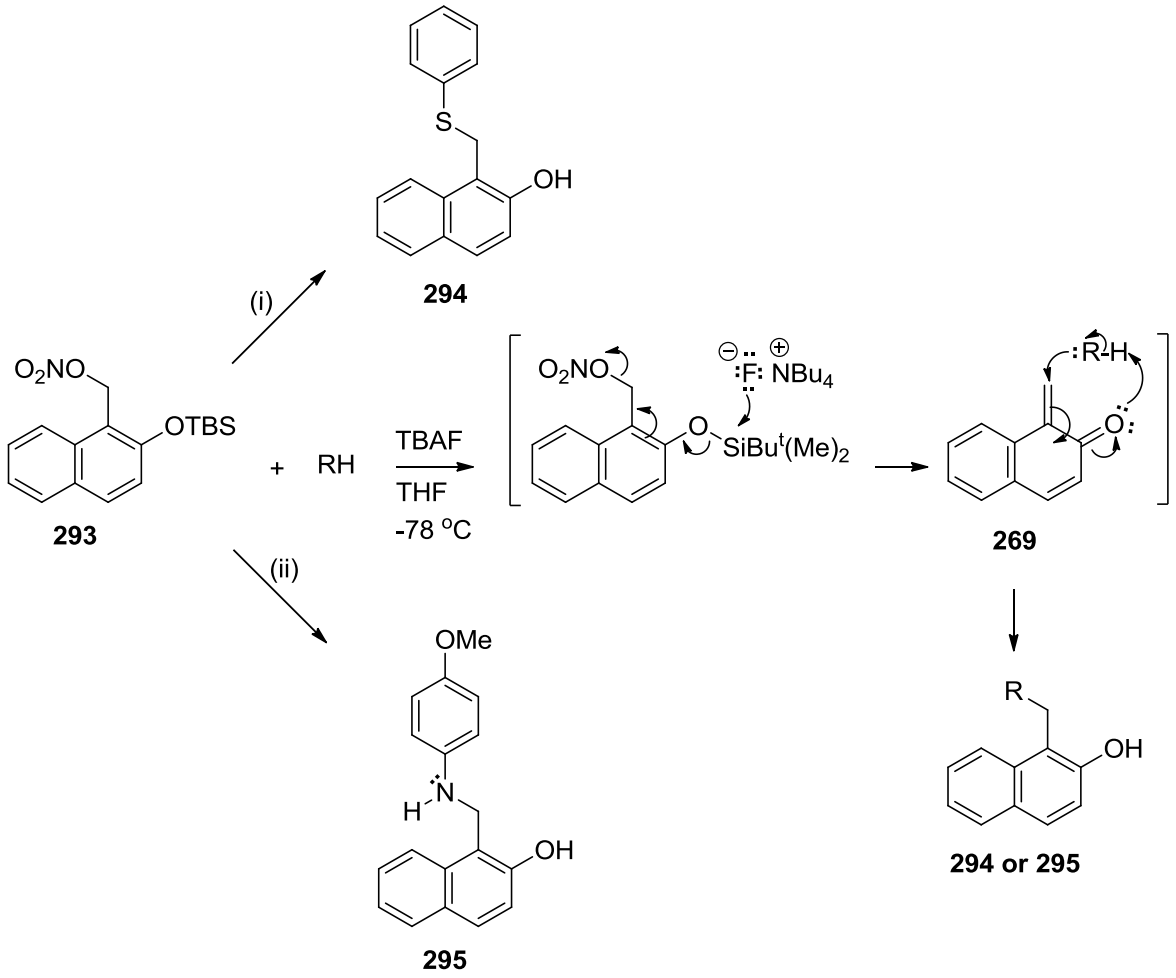
produced silyl ether **291** in 96% yield. Reduction of the aldehyde group in **291** gave alcohol **292** in 89% yield while nitration of **292** afforded nitrate ester **293** in 63% yield.



Scheme 2.12 *Synthesis of (2-{[tert-butyl(dimethyl)silyl]oxy}-1-naphthyl)methyl nitrate. (i) TBSCl, NEt_3, DMAP, CH_2Cl_2, 0 °C, (ii) $NaBH_4$, MeOH, (iii) $AgNO_3$, $SOCl_2$, THF.*

a) Michael addition

The reaction was carried out by the addition of thiophenol or 4-methoxyaniline to the nitrate ester **293** in THF at -78 °C followed by dropwise addition of the fluoride ion source *i.e.* TBAF in THF and then stirring the reaction mixture for a further 10 minutes. The reaction proceeds by attack of the fluoride anion onto the silyl ether, breakage of the Si-O bond, and elimination of a nitrate anion to generate the corresponding *o*-naphthoquinone methide **269** *in situ* which reacted with the thiophenol present in the reaction mixture, to afford Michael addition product, 1-[(phenylthio)methyl]-2-naphthol **294**, in 75% yield or with 4-methoxyaniline to afford a secondary amine, 1-{[(4-methoxyphenyl)amino] methyl}-2-naphthol **295**, in 47% yield. It is interesting to note that in contrast to the reaction of 4-methoxyaniline with two molecules of *o*-quinone methide **1** that gave tertiary amine **3e** (Scheme 2.5 and entry 3 Table 2.1), where the Michael addition occurred twice, the inability of compound **295** to react with a second molecule of *o*-naphthoquinone methide **269** may be due to steric hinderance.

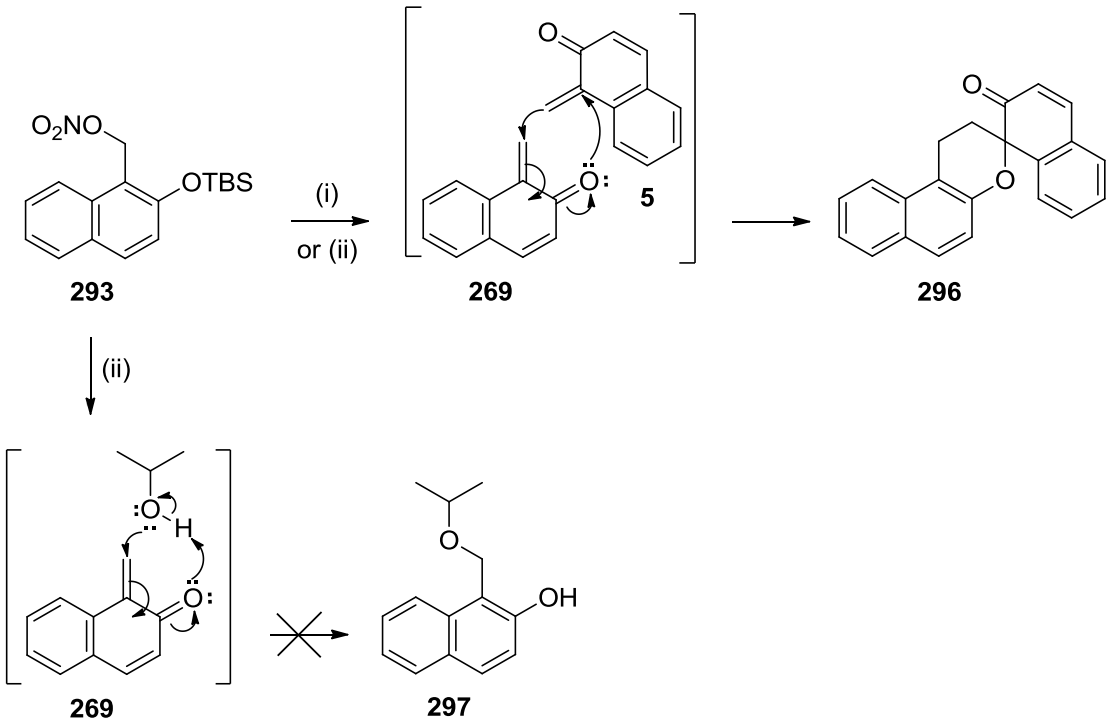


Scheme 2.13 *Generation of o-naphthoquinone methide and trapping by the Michael addition of N and S nucleophiles. (i) thiophenol, TBAF, THF, -78 °C, 10 min, (ii) 4-methoxyaniline, TBAF, THF, -78 °C, 10 min.*

b) "Inverse electron demand" hetero-Diels-Alder reaction

When the reaction of silyl ether **293** was repeated in the absence of a dienophile in THF, with dropwise addition of TBAF, the transient *o*-naphthoquinone methide **269** underwent diene-dienophile cycloaddition to give the spiro dimer **296** (Scheme 2.14), in 40% yield. The absence of the trimerisation product in this reaction is presumably because the benzene ring of the naphthalen-2(1*H*)-one **296** blocks the γ- and δ-carbons of the cyclohexa-2,4-dien-1-one ring and stops further diene-dienophile cycloadditions. To our surprise, when silyl ether **293** was stirred in 2-propanol and *tetra*-butylammonium fluoride was added dropwise at -78 °C, after workup, purification and characterization of the

isolated material, the product turned out to be dimer **296** and not the Michael addition ether **297**.



Scheme 2.14 *Unexpected trapping of o-naphthoquinone methide by Diels-Alder reaction (i) THF, TBAF, -78 °C, 10 min, (ii) 2-propanol, TBAF, -78 °C, 10 min.*

In the ^{1}H NMR spectrum of compound **296** (Figure 2.7) the region at 7.34-7.83 ppm corresponds to the aromatic protons of the benzene and naphthalene rings including H-9 which appears downfield due to the conjugation of the double bond with the carbonyl group. The doublet at 6.17 ppm (J = 10 Hz) corresponds to H-8. Due to the presence of asymmetric C-6 the two protons at C-5 and the two protons at C-4 are not equivalent, the two methylene groups are diastereotopic. Each proton has a different chemical shift, is coupled to one geminal and two vicinal protons and is therefore split into multiplets. We assign H-5a to the multiplet at 3.12 ppm, H-5b to the multiplet at 2.86 ppm, H-4a to the multiplet at 2.50 ppm and H-4b to the multiplet at 2.18 ppm.

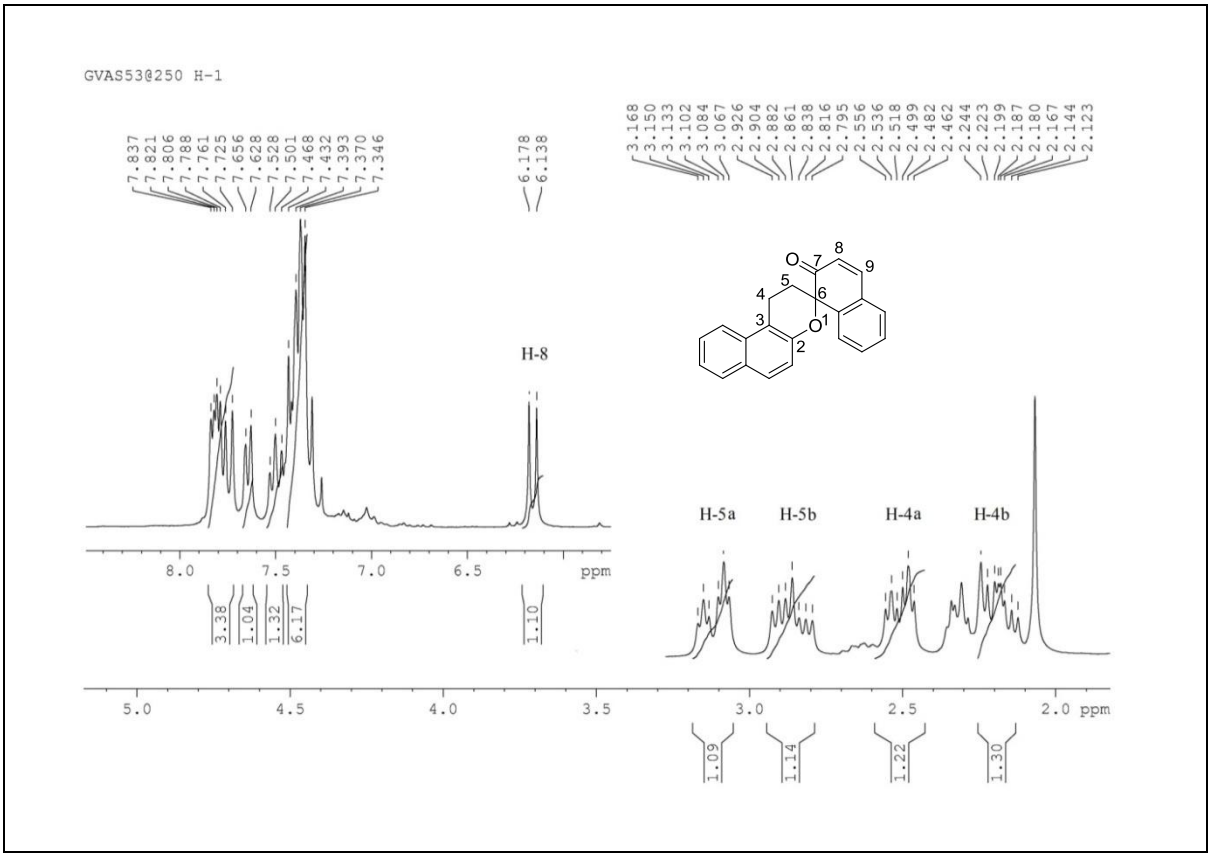


Figure 2.7 *^{1}H-NMR (250 MHz, $CDCl_3$) of compound **296**.*

In the ^{13}C NMR spectrum of compound **296** (Figure 2.8) the 8 quaternary carbons as well as the 12 aromatic CH carbons are in the region 201.63 ppm to 83.59 ppm and the asymmetric quaternary carbon C-6 appears as a signal at 83.59 ppm. The carbonyl carbon peak of the α,β-unsaturated group is at 201.63 ppm whereas the two methylene carbon peaks are as expected in the aliphatic region, C-5 at 34 ppm and C-4 at 19 ppm.

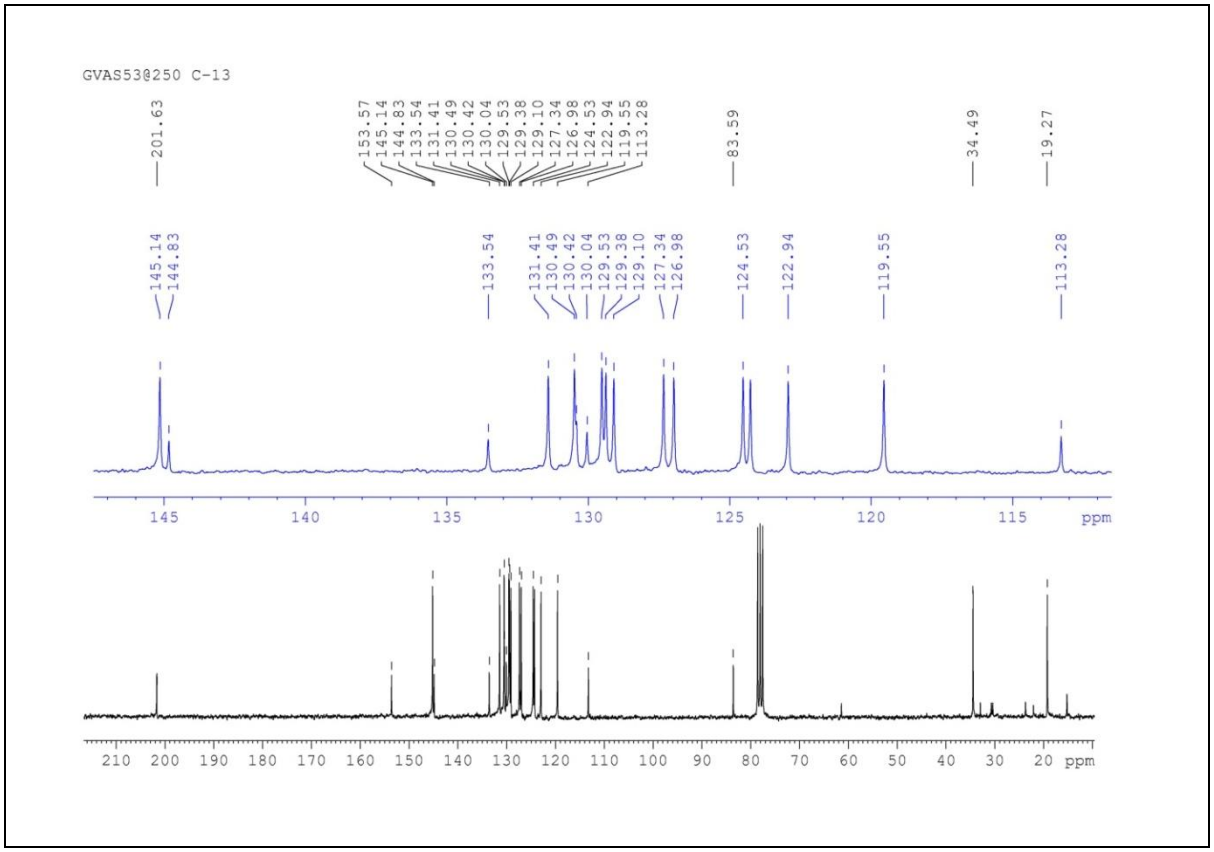
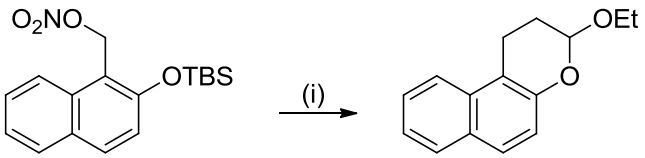


Figure 2.8 *^{13}C NMR (250 MHz, $CDCl_3$) of compound **296**.*

The ability of the *o*-naphthoquinone methide, generated *in situ* from nitro ester **293**, to undergo the "inverse electron demand" hetero-Diels-Alder reaction was further tested by applying the reaction conditions used for the Michael additions but substituting the nucleophiles for an electron rich dienophile, ethyl vinyl ether (EVE). The outcome was to isolate the hetero-Diels-Alder adduct, 3-ethoxy-2,3-dihydro-1*H*-benzo[*f*]chromene **298**, in 23% yield (Scheme 2.15). An even lower yield (20%) was obtained for chromane **278** (Scheme 2.7) from the analogous hetero-Diels-Alder cycloaddition of *o*-quinone methide **1** and EVE. It is reasonable to assume that benzene ring of the *o*-naphthoquinone methide **269** exerts a very weak electron-withdrawing effect to the heterodiene moiety of the molecule, rendering it slightly more electron-poor than its *o*-quinone methide counterpart and hence making it a marginally more reactive (than the *o*-quinone methide) heterodiene for the "inverse electron demand" hetero-Diels-Alder with EVE.

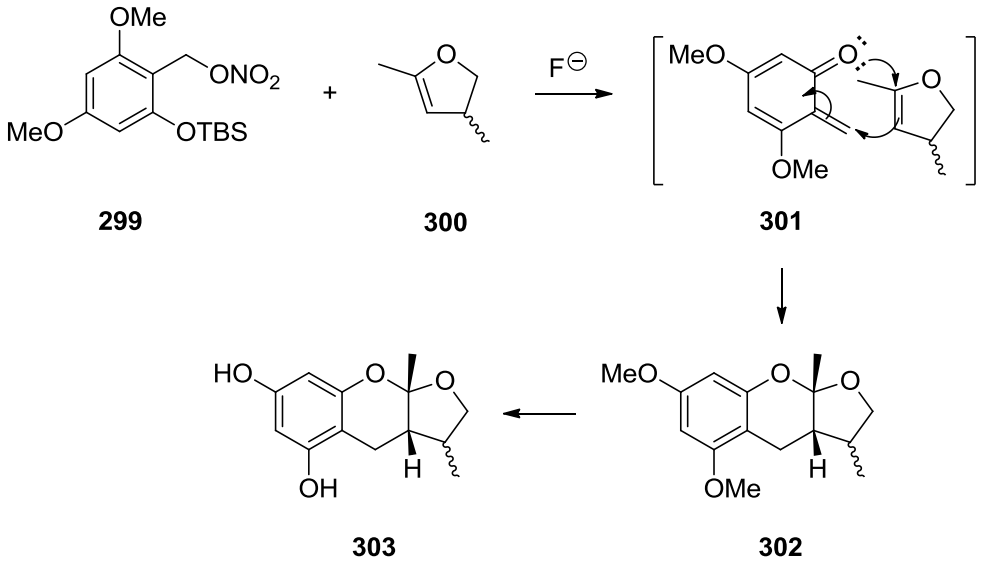


293 **298**

Scheme 2.15 *Trapping of o-naphthoquinone methide generated in situ from (2-{[tert-butyl(dimethyl)silyl]oxy}-1-naphthyl)methyl nitrate by a hetero-Diels-Alder reaction with an electron rich dienophile. (i) ethyl vinyl ether, TBAF, THF, -78 °C, 10 min.*

2.2 Synthesis of xyloketal H

In order to advantageously apply the above method for generating an *o*-quinone methide from a nitrate ester, we turned towards the synthesis of a recently reported natural product xyloketal H.[62] It was planned to react the *o*-quinone methide precursor **299** with the cyclic dienophile **300** in the presence of fluoride ion leading towards the "inverse electron demand" hetero-Diels-Alder reaction **301** to afford, after demethylation of compound **302**, xyloketal H **303**.



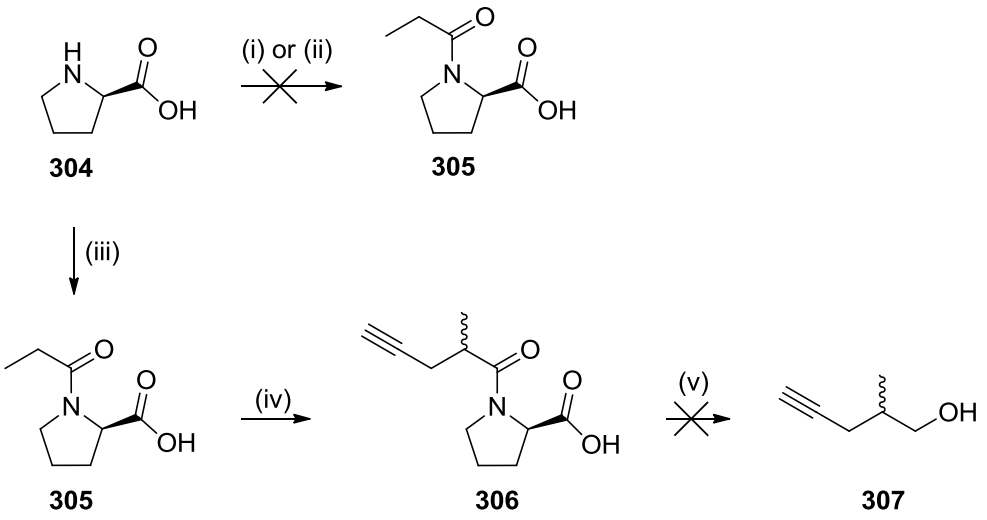
Scheme 2.16 *Synthesis of xyloketal H.*

2.2.1 Synthesis of dienophile 3,5-dimethyl-2,3-dihydrofuran

The major step in Scheme 2.16 was the preparation of 3,5-dimethyl-2,3-dihydrofuran **300** and the *o*-quinone methide precursor **299**. We chose to prepare dienophile **300** as a racemic mixture in order to test the feasibility of the reaction knowing that we would end up with a racemic mixture of xyloketal H. The first attempt to prepare 3,5-dimethyl-2,3-dihydrofuran **300** (Scheme 2.16) was from 2-methylpentynol **307** (Scheme 2.17). There are several methods reported in the literature[63,118] for the synthesis of **307**. The method

[118] Pettigrew, J. D.; Wilson, P. D. *Org. Lett.* **2006**, *8*, 1427-1429.

reported by Wilson and Pettigrew[5] was finally chosen. The first step[119] was attempted preparation of amide **305** from proline and propionyl chloride (Scheme 2.17) using *n*-butyl lithium in THF at -78 °C. In our hands this reaction did not work even when it was repeated using propionic anhydride instead of propionyl chloride. However, reaction of proline **304** with propionic anhydride in water at 50 °C, according to Markovich and co-workers[120] afforded compound **305**, in 40% yield. In the second step amide **305** reacted with propargyl bromide, *n*-butyl lithium, diisopropylamine, hexamethylphosphoramide (HMPA), in THF at 0 °C to afford compound **306** in 50% yield. An attempt to reduce **306** using one equivalent of lithium aluminium hydride (LAH) or even after addition of three equivalents of LAH, did not give the required alcohol **307**.

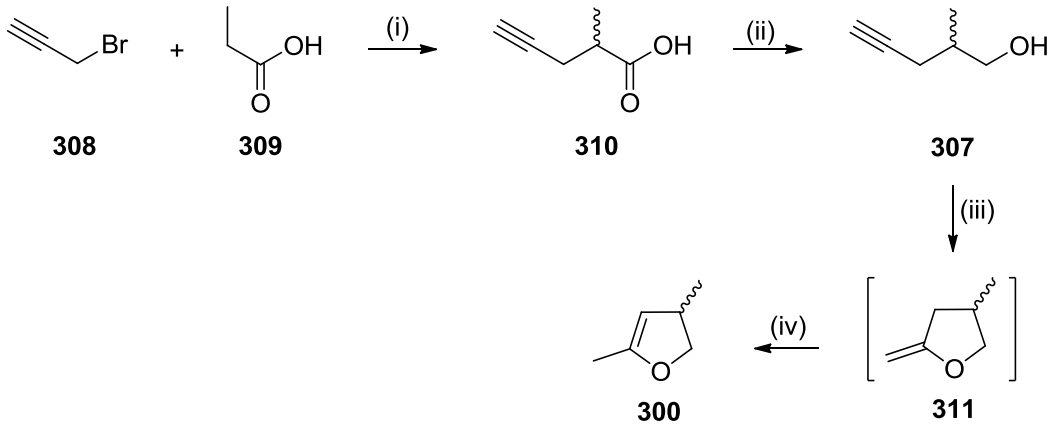


Scheme 2.17 *Synthesis of 2-methylpent-4-yn-1-ol. (i) propionyl chloride, n-butyl lithium, THF, -78 °C (ii) $(CH_3CH_2CO)_2O$, n-BuLi,, THF, -78 °C, (iii) $(CH_3CH_2CO)_2O$, water, 50 °C, (iv) propargyl bromide, n-BuLi, $(i\text{-}Pr)_2NH$, HMPA, THF, 0 °C, (v) $LiAlH_4$, THF, 0 °C.*

In another method, reported by Wilson and co-workers,[63] compound **307** was synthesised by reduction of 2-methylpent-4-ynoic acid **307** (Scheme 2.18). Compound **307** was prepared, in 25% yield, from the reaction of propargyl bromide **308** with propionic acid **309** to give carboxylic acid **310** that was then reduced with LAH to alcohol **307**, in a manner similar to the preparation of proline amide **306** (Scheme 2.17). Alcohol **307** reacted

[119] Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 83-87.
[120] Kuvaeva, Z. I.; Lopatik, D. V.; Nikolaeva, T. A.; Knizhnikova, A. N.; Naidenov, V. E.; Markovich, M. M. *Pharm. Chem. J.* **2010**, *44*, 307-309.

with a sub-stoichiometric amount of sodium amide to afford the exocyclic dihydrofuran (±)-**311**, which was isomerised thermally to afford the required dihydrofuran (±)-**300** in 58% yield (Scheme 2.18).

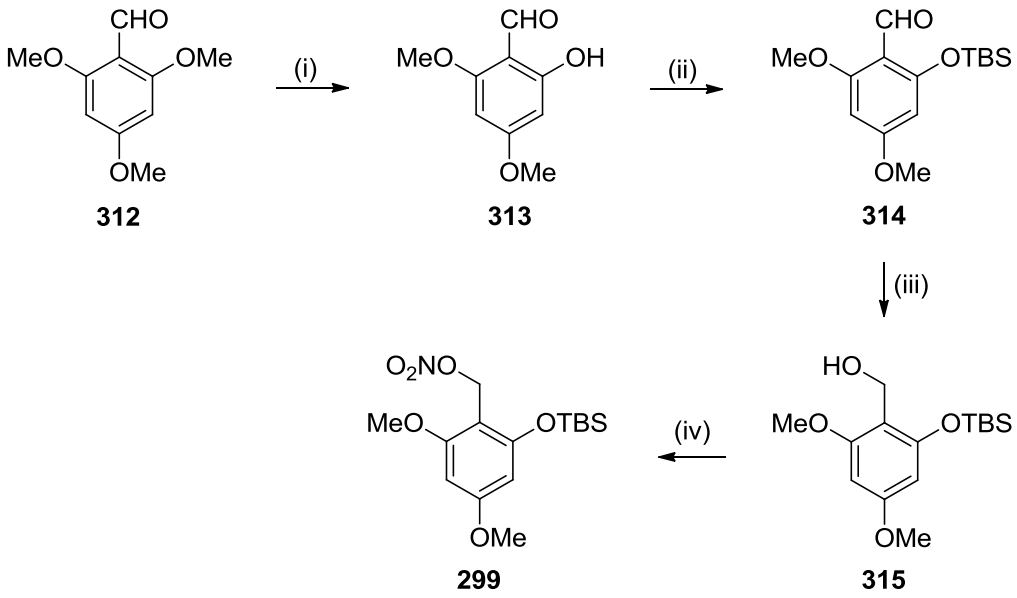


Scheme 2.18 *Synthesis of 3,5-dimethyl-2,3-dihydrofuran. (i) n-BuLi, (i-Pr)$_2$NH, HMPA, THF, 0 °C, (ii) LiAlH$_4$, THF, 0 °C, (iii) NaNH$_2$, reflux, 4 h, (iv) reflux, 16 h.*

2.2.2 Synthesis of the *o*-quinone methide precursor for the attempted synthesis of xyloketal H

The preparation of the *o*-quinone methide precursor *i.e.* the disubstituted nitrate ester **299**, entailed, in the first step, a selective demethylation[121] reaction on 2,4,6-trimethoxybenzaldehyde **312** using boron tribromide in dichloromethane, to give 4,6-dimethoxysalicyaldehyde in 64% yield. The next step, protection of the phenolic hydroxyl group, reaction with TBSCl to give silyl ether **314**, reduction of the aldehyde group of **314** with sodium borohydride afford the alcohol **315** and then reaction of **315** with silver nitrate and thionyl chloride in THF to give 2-{[tert-butyl(dimethyl)silyl]oxy}-4,6-dimethoxybenzyl nitrate **299**, in 16% yield.

[121] Roelens, F.; Huvaere, K.; Dhooge, W.; Cleemput, M. V.; Comhaire, F.; Keukeleire, D. D. *Eur. J. Med. Chem.* **2005**, *40*, 1042-1051.



Scheme 2.19 *Synthesis of 2-{[tert-butyl(dimethyl)silyl]oxy}-4,6-dimethoxybenzyl nitrate. (i) BBr_3, CH_2Cl_2, -78 °C, (ii) TBSCl, NEt_3, DMAP, CH_2Cl_2, 0 °C, (iii) $NaBH_4$, MeOH, (iv) $AgNO_3$, $SOCl_2$, THF.*

In the ^{1}H NMR spectrum of **299** (Figure 2.9) the two doublets at 6.13 ppm and 6.02 ppm with J = 2.5 Hz correspond to the two aromatic protons situated *meta* to one another. The benzylic protons appear at 4.86 ppm as a singlet. Two singlets at 3.82 ppm and 3.50 ppm correspond to the two methoxy groups whereas the signals at 1.07 ppm and 0.24 ppm correspond to the 9 protons from the *tert*-butyl group and two methyl groups attached to the silyl atom, respectively.

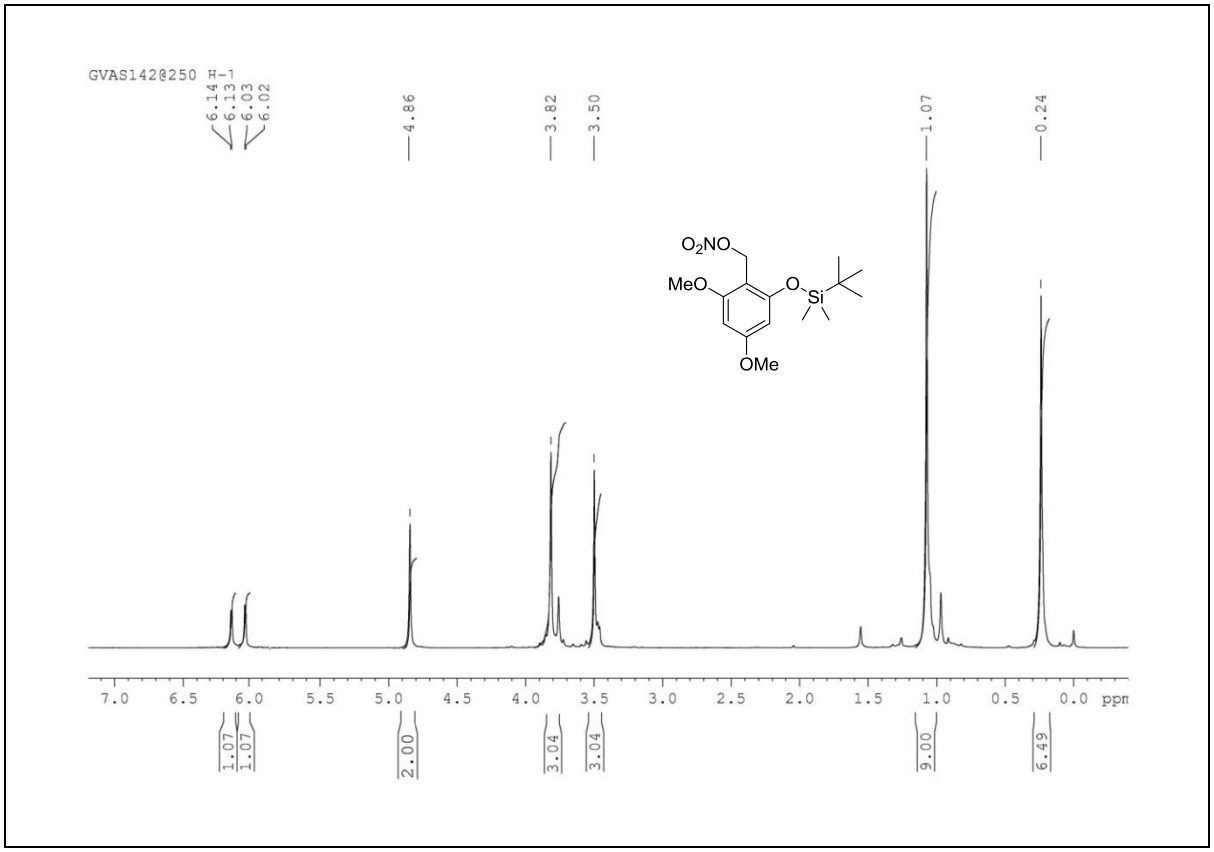
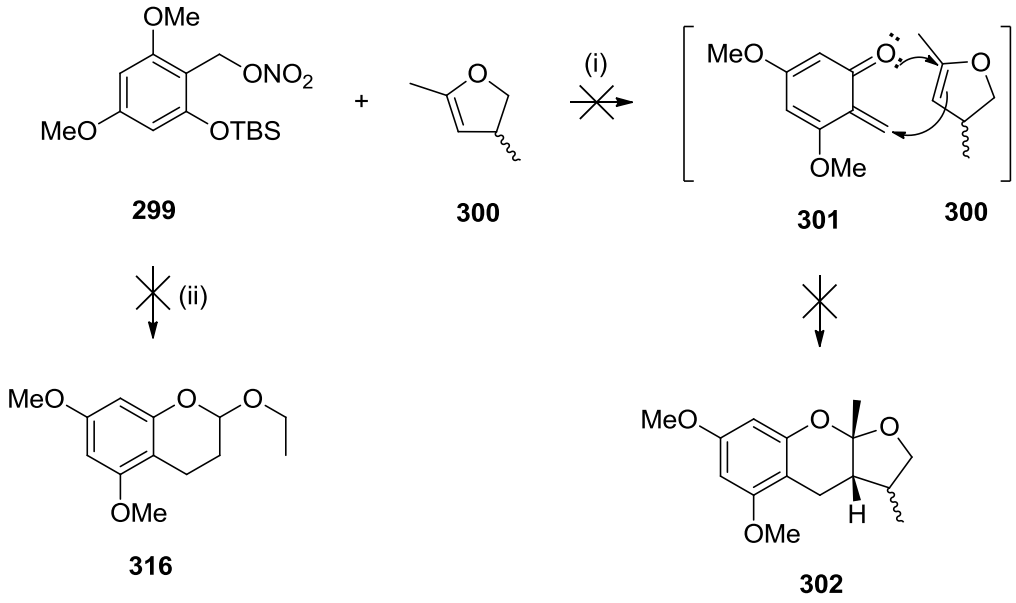


Figure 2.9 *[1]H-NMR (250 MHz, $CDCl_3$) of compound **299**.*

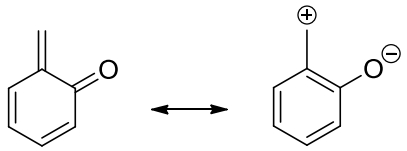
The final reaction was designed so that it could lead to xyloketal H **303** (Scheme 2.16). The key step involved the hetero Diels-Alder reaction between the *in situ* generated substituted *o*-quinone methide **301** and 3,5-dimethyl-2,3-dihydrofuran **300**. The reaction was performed in a manner similar to the preparation of the chromanes (Scheme 2.7) that is, by adding TBAF to a solution containing nitrate ester **299** and five equivalents of the dienophile **300** in toluene at low temperature. Workup of the reaction mixture and running the NMR spectrum of the residual oil did not reveal any trace of the required product **302**. Product **302** was not detected by NMR even when the reaction was repeated with seventy equivalents of dienophile. In order to confirm if the "inverse electron demand" hetero-Diels-Alder reaction took place, a previously successful dienophile was chosen and the reaction was repeated with one hundred equivalents of ethyl vinyl ether instead of dihydrofuran **300**. However no reaction occurred since the expected product **316** was not detected by NMR (Scheme 2.20).



Scheme 2.20 *Attempted hetero Diels-Alder reaction for the synthesis of xyloketal H. (i) TBAF, toluene, -78* °C, *(ii) ethyl vinyl ether, TBAF, toluene, –78* °C.

The choice of nitrate ester **299** and electron-rich dienophile **300** in the above reaction Scheme was based upon the availability of starting materials and the number of steps leading to xyloketal H **303** (Scheme 2.16), it was initially thought that dimethoxy *o*-quinone methide in the ionic resonance form (Scheme 2.21) is stable enough so that the two methoxy groups would exert a stronger –I effect than a +M effect. On the contrary, the +M effect is stronger than a –I effect which reduces the electrophilic character of the exocyclic methylene group. The –I and +M effects of unsubstituted *o*-quinone methide, benzyloxy *o*-quinone methide and dimethoxy *o*-quinone methide are summarised in Scheme 2.21. The outcome of these effects agrees entirely with experimental facts. The benzyloxy group of the mono-substituted *o*-quinone methide is in the *meta* position with respect to the exocyclic methylene group and has no +M effect on it but instead a –I effect is experienced (Scheme 2.10). This heterodiene is therefore more electron-deficient than the unsubstituted *o*-quinone methide and the hetero-Diels–Alder reaction is favoured (higher yield). On the other hand, the disubstituted *o*-quinone methide is comparatively electron-rich and hence the hetero-Diels-Alder does not occur.

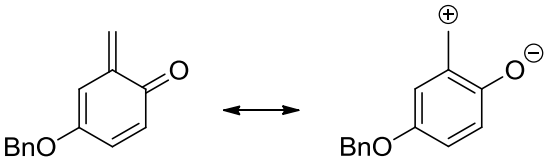
Unsubstituted o-quinone methide



Exocyclic methyl carbocation not affected since there are no ring substituents

Low yield of hetero-Diels-Alder reaction

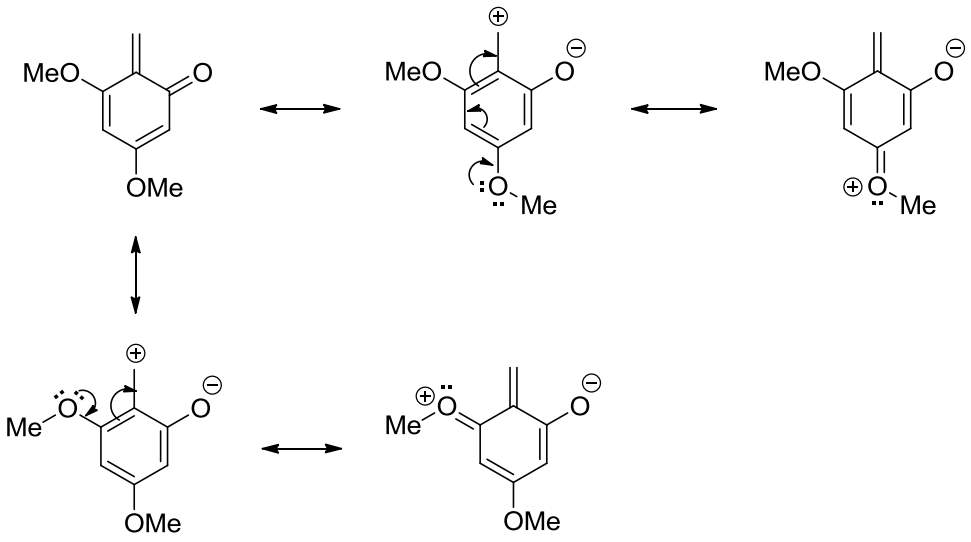
Mono-substituted o-quinone methide, benzyloxy group orientated meta to exocyclic methylene and para to carbonyl group



The +M effect of the benzyloxy group does not affect the exocyclic methyl carbocation

High yield of hetero-Diels-Alder reaction

Di-substituted o-quinone methide methoxy groups both oriented meta to the carbonyl group while one oriented ortho and the other oriented para to the exocyclic methylene group



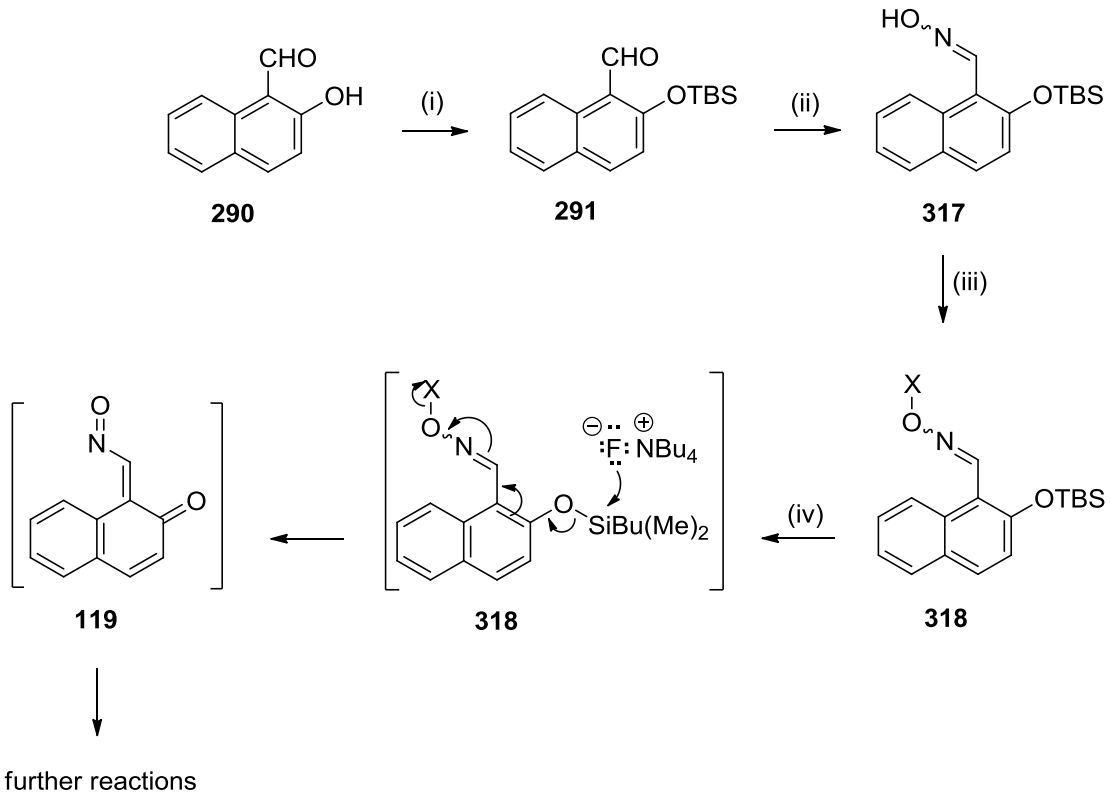
The +M effect of the methoxy groups reduces the electrophilic character of the exocyclic methyl carbocation rendering the heterodiene more electron-rich than unsubstituted and mono-substituted o-quinone methides

No hetero-Diels-Alder reaction

Scheme 2.21 *Explanation to the +M and –I effects taking place in various o-quinone methide intermediates.*

2.3 An investigation to produce the *o*-quinone nitrosomethide and *o*-naphthoquinone nitrosomethide intermediates *in situ* from suitable precursors

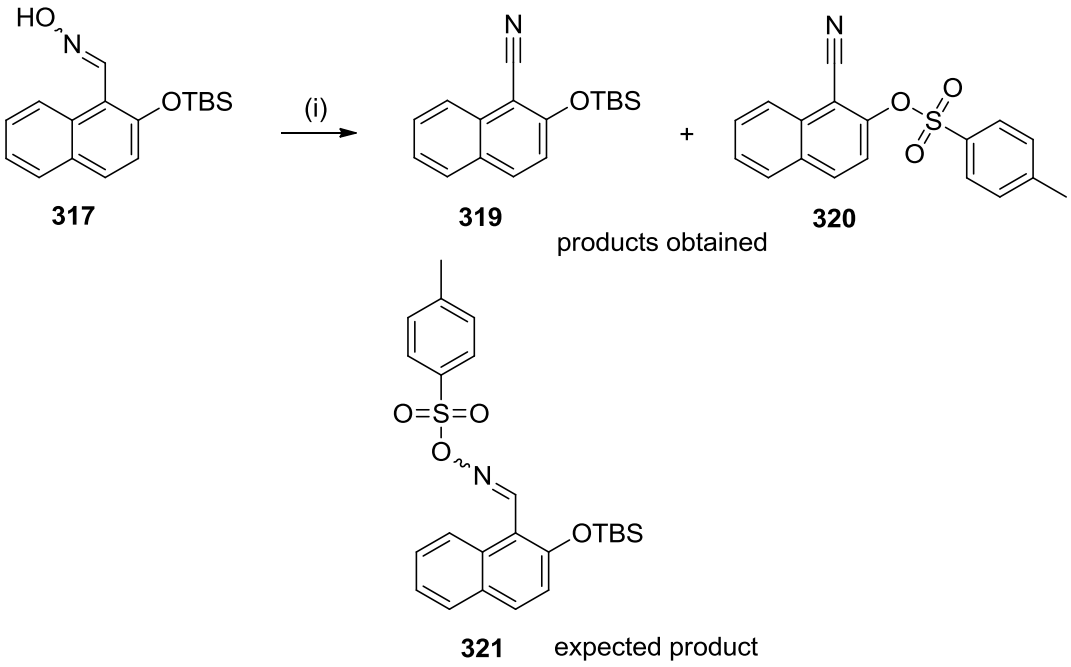
In this chapter a study on the synthesis of suitable precursors for the generation of *o*-naphthoquinone nitrosomethide **119** *in situ* is presented. The overall strategy (Scheme 2.22) requires protection of the hydroxyl group of 2-hydroxy-1-naphthaldehyde **290** with *tert*-butylsilyl chloride to give *tert*-butylsilyl protected aldehyde **291**, reaction of **291** with hydroxylamine hydrochloride in base to afford *tert*-butylsilyl protected oxime **317** in 78% yield, reaction of **317** with a suitable reagent that would substitute the hydrogen atom of the oxime hydroxyl group to give precursor **318** containing a potentially good leaving group X bound to the oxygen atom. The addition of fluoride ion to precursor **318** would cause desilylation to create a –ve charge on the naphtholic oxygen atom wherein triggering a positive resonance effect along the conjugated system of **318** to produce *o*-naphthoquinone nitrosomethide **119**, after elimination of leaving group X^-.



Scheme 2.22 *General plan to synthesise a precursor of o-naphthoquinone nitrosomethide and to apply a desilylation method to generate it. (i) TBSCl, NEt_3, DMAP, CH_2Cl_2, 0 °C, (ii) $NH_3OH.Cl$, $NaOCOCH_3$, IPA, r.t., (iii) reaction with suitable electrophiles, (iv) TBAF, THF, -78 °C.*

2.3.1. Attempted synthesis of 1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-*N*-[(methyl sulfonyl)oxy]methanimine and 1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-naphthyl)-*N*-[(methylsulfonyl)oxy]methanimine

Sulfinate ions are better known as ambidentate species: they can react via their softer sulfur anion centre to give sulfones, or via their harder oxyanion centres to yield sulfinate esters. Sulfinate ions can discriminate between hard and soft Lewis acid centres. They are produced by the redox reaction of zinc dust on *p*-toluenesulfonyl chloride.[122] Sulfinate ions are scarcely known as leaving groups although at least one report is known in the literature.[123] The use of the sulfinate ion as a leaving group in the formation of *o*-naphthoquinone nitrosomethide **119** is both challenging and novel. In the first attempt, oxime **317** was treated with triethylamine (1.1 equivalent) and tosyl chloride (1 equivalent) in THF in the hope of preparing tosyl substituted oxime **321**. However, the products obtained were, instead, the dehydration products **319** (32% yield) and **320** (60% yield). It is quite possible that compound **320** is derived from **319** after deprotection of the silyl group and reaction of the free oxygen atom with tosyl chloride.



317 **319** **320**

products obtained

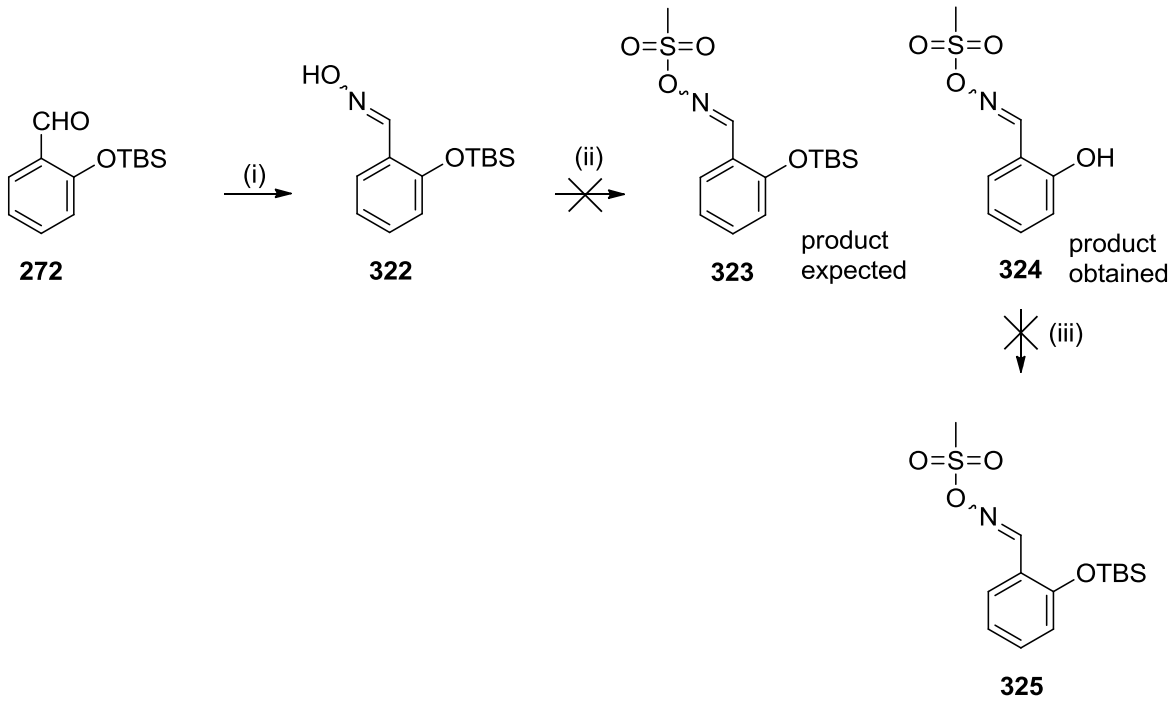
321 expected product

Scheme 2.23 *Sulfonation of 2-{[tert-butyl(dimethyl)silyl]oxy}-1-naphthaldehyde oxime . (i) NEt_3, TsCl, THF.*

[122] Okuyama, T. Sulfinate ions as nucleophiles, in Sulphinic Acids, Esters and Derivatives (1990) (ed S. Patai), John Wiley & Sons, Inc., Chichester, UK.
[123] Kirmse, W.; Herpers, E. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1018-1020.

Repeating the reaction of Scheme 2.23 with pyridine instead of triethylamine, even for 48 hours, produced no change in the starting material. On the other hand, treatment of the oxime **317** with sodium hydride and tosyl chloride in THF lead to the formation of nitrile **319**, in 22% yield.

In order to prepare a precursor that would lead, after treatment with fluoride anion, to intermediate *o*-quinone nitrosomethide **329** (Scheme 2.26), further reactions were carried out using the *tert*-butylsilyl protected benzoxime **322**. 2-{[*tert*-Butyl(dimethyl)silyl]oxy}-benzaldehyde oxime **322** was prepared in two steps from salicylaldehyde using similar reaction conditions to those used to prepare oxime **317** in Scheme 2.22.



Scheme 2.24 *Synthesis of 2-((E)-{[(methylsulfonyl)oxy]imino}methyl)phenol and attempted silylation. (i) $NH_3OH.Cl$, $NaOCOCH_3$, IPA, (ii) pyridine, mesityl chloride or NaH, mesityl chloride , THF, (iii) TBSCl, NEt_3, DMAP, CH_2Cl_2.*

Before abandoning the sulfinate ion as a potential leaving group in our reaction to produce the intermediate **330** (Scheme 2.26), oxime **322** was reacted with mesityl chloride in pyridine or mesityl chloride in THF with sodium hydride in order to synthesise the methylsulfonyloxy derivative **325**. The yield of **324** obtained with the former reaction was 70% while with the latter it gave the dehydration product similar to **319** (Scheme 2.23). In

the ^{1}H NMR spectrum of the isolated product the oxime hydroxy proton signal at 11.23 ppm and the signals of the 15 protons of the *tert*-butyldimethyl silyl group at 0.98 ppm and at 0.21 ppm are absent whereas there are five aromatic protons between 8.98-7.95 ppm, a singlet due to the imine C-H and another singlet at 2.90 ppm corresponding to the methyl group that support the structure of compound **324**. A peak at m/z = 216 $[M + H]^{+}$ confirms further the structure of this compound.

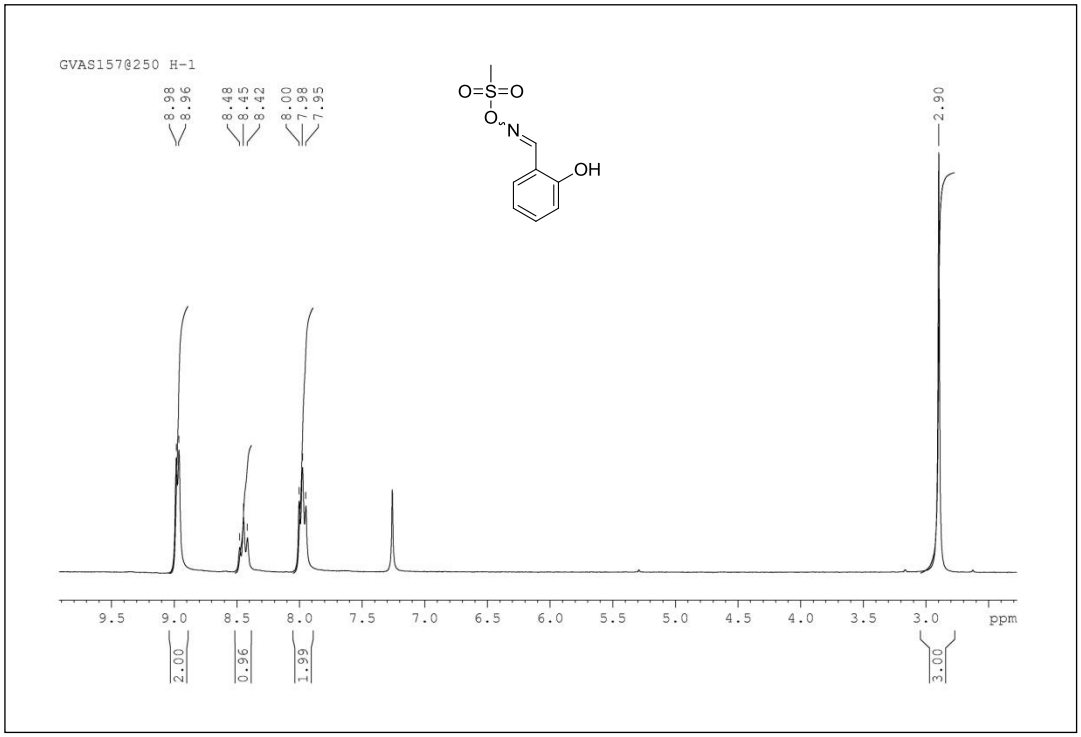
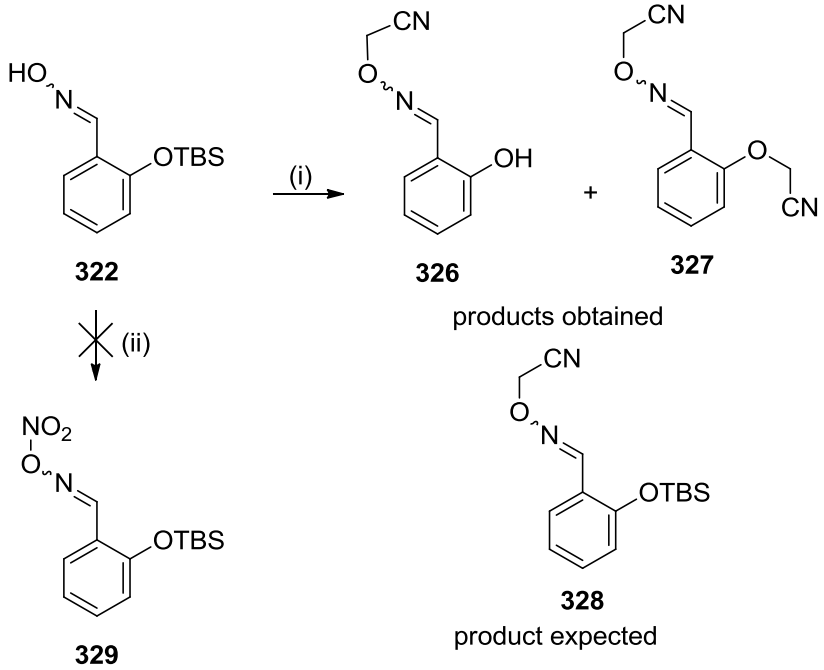


Figure 2.10 *^{1}H-NMR (250 MHz, $CDCl_3$) of compound **324**.*

Several attempts to silylate the phenolic hydroxyl group of compound **324** with our standard conditions, using *tert*-butyldimethylsilyl chloride, triethylamine, 4-dimethylaminopyridine in dichloromethane, failed since there was unchanged starting material according to TLC examination of the reaction mixture and the ^{1}H NMR spectrum of the material isolated after workup.

2.3.2. Synthesis of {[(2-{[tert-butyl(dimethyl)silyl]oxy}benzylidene)amino]oxy} acetonitrile

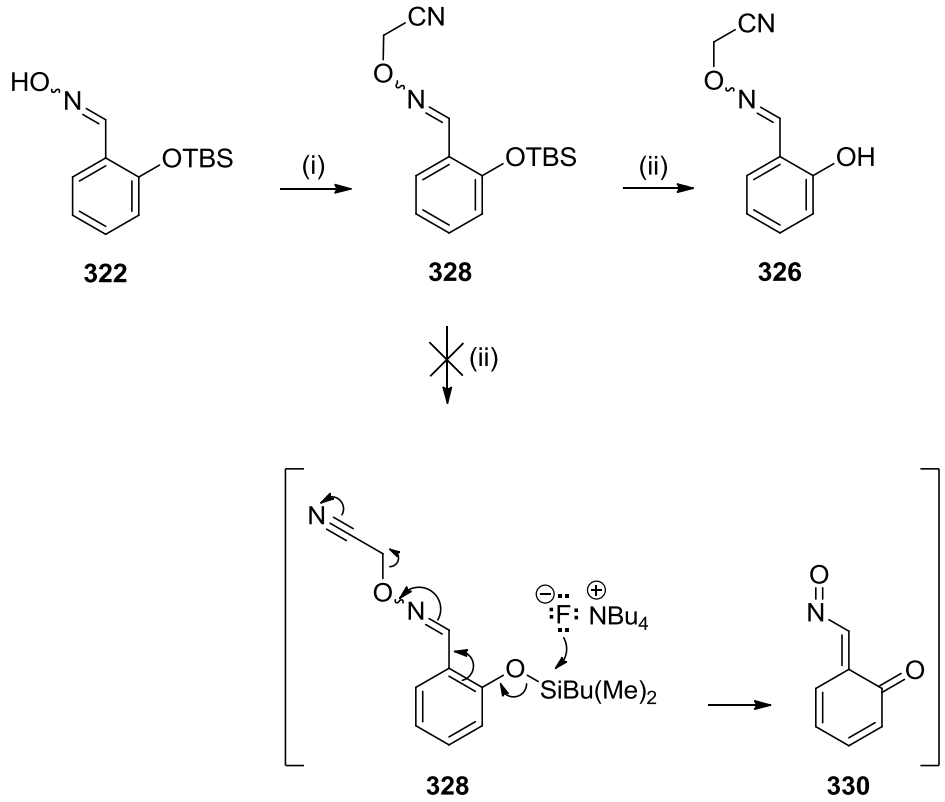
When oxime **322** was reacted with bromoacetonitrile in THF with potassium *tert*-butoxide (Scheme 2.25) the expected product **328** was not formed but instead compounds **326** and **327** were isolated, in 16 and 15% yield, respectively. The former product was probably derived after deprotection of the silyl ether group of **322** and by alkylation of the oxime with bromoacetonitrile while the latter product evolves from alkylation of the phenolic hydroxyl group of **326** with another molecule of bromoacetonitrile. Due to the failure of obtaining precursor **328** under basic reaction conditions, nitrosation of oxime **322** was attempted using thionyl chloride and silvar nitrate in THF (as previously used for other hydroxy groups in this thesis) but there was no formation of the desired precursor **329**. Nitration of oxime **322** was also attempted using isopropyl nitrite with either 1 equivalent of triethylamine or two equivalents of pyridine. Curiously only starting material was retrieved from both reactions.



Scheme 2.25 *Attempted synthesis of o-quinone nitrosomethide precursors. (i) t-BuOK, $BrCH_2CN$, THF, (ii) $AgNO_3$, $SOCl_2$, THF or NEt_3, isopropyl nitrite, CH_2Cl_2 or pyridine, isopropyl nitrite, CH_2Cl_2.*

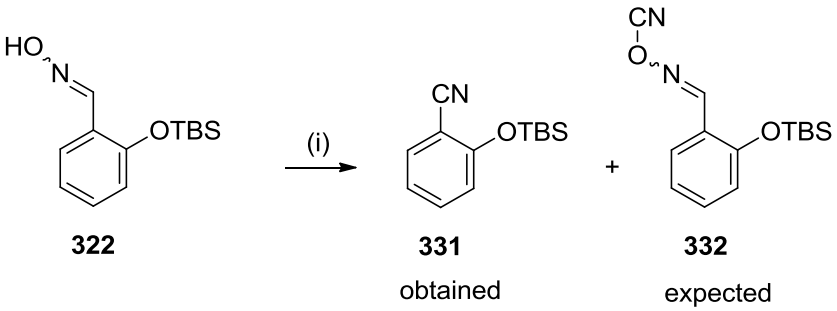
By changing the base in the reaction of oxime **322** with bromoacetonitrile from potassium *tert*-butoxide to sodium hydride and lowering the temperature of the reaction to

0 °C, the alkylation product **328** was obtained in 37% yield (Scheme 2.26). This compound was then treated with *tetra*-butylammonium fluoride and pyrrolidine in THF but the only product obtained was the deprotected oxime **326**. This indicated that the generation of *o*-quinone nitrosomethide **330** intermediate had not occurred.



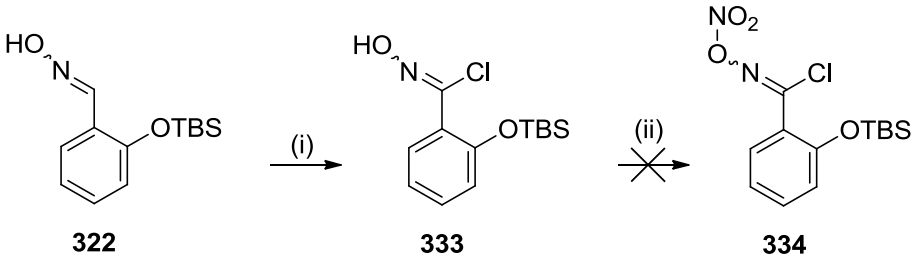
Scheme 2.26 *Synthesis of a precursor for generating o-quinone nitrosomethide in situ and then trapping it by a nucleophile. (i) NaH, $BrCH_2CN$, THF, (ii) pyrrolidine, TBAF, THF, -78 °C.*

Although it was reasoned that the acetonitrile carbanion is a good, resonance stabilised, leaving group, the above experiments indicate that, at least the cleavage of the O-C bond in O-CH_2CN is not favoured. Oxime **322** was therefore reacted with cyanogen bromide in the presence of sodium hydride (Scheme 2.27) but this resulted in base catalysed dehydration of the oxime to afford only cyano compound **331**, in 81% yield.



Scheme 2.27 *Attempted synthesis of a new precursor for generating in situ the o-quinone nitrosomethide intermediate. (i) NaH, CNBr, THF.*

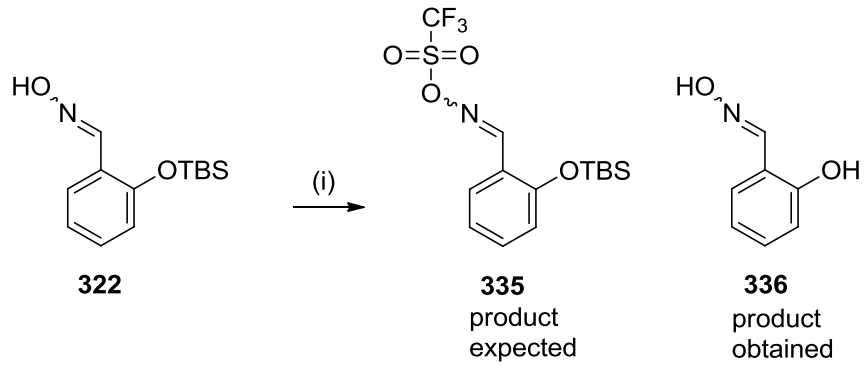
In order to avoid reactions leading to the dehydration of the oxime or formation of other side products during attempted substitutions (Schemes 2.23-2.27), the chloro substituted oxime **333** was prepared in 81% yield by reacting oxime **322** with *N*-chlorosuccinimide in pyridine (Scheme 2.28). A first attempt to convert chloro oxime **333** to nitrate **334** by our well established nitration reaction using silver nitrate and thionyl chloride, resulted in unchanged starting material. A second attempt to nitrate chloro oxime **333** using triphenyl phosphine, *N*-bromosuccinimide and silver nitrate, also failed.



Scheme 2.28 *Synthesis of 2-{[tert-butyl(dimethyl)silyl]oxy}-N-hydroxybenzenecarboximidoyl chloride and attempted nitration. (i) N-chlorosuccinimide, pyridine, $CHCl_3$, 40 °C, (ii) $AgNO_3$, $SOCl_2$, THF or PPh_3, NBS, $AgNO_3$, CH_3CN, CH_2Cl_2.*

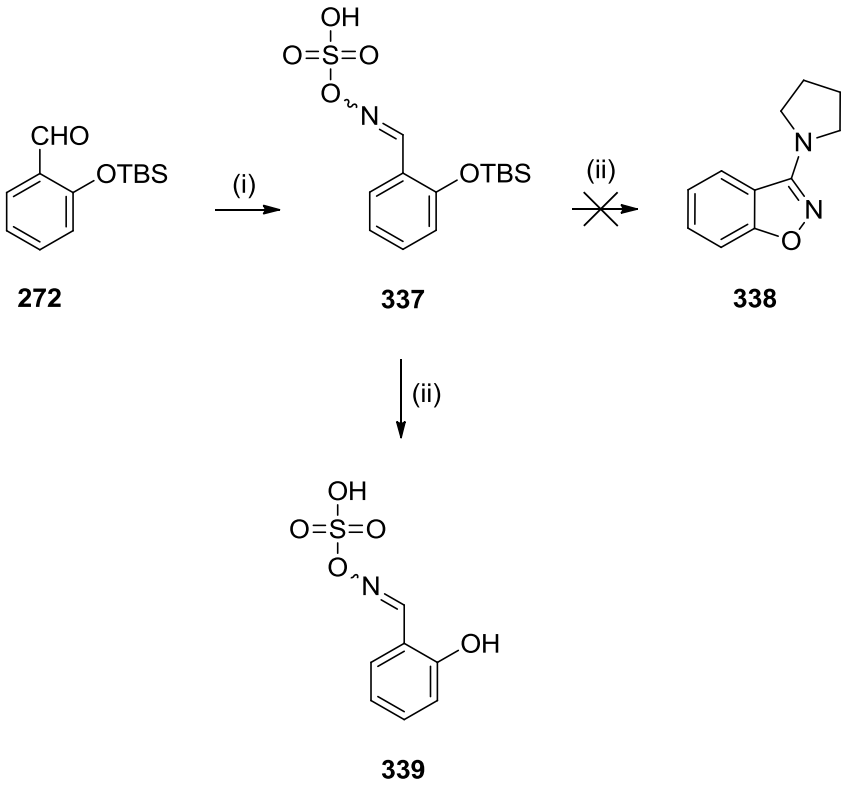
2.3.3. Synthesis of 1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-*N*-(sulfooxy)methanimine

As a promising leaving group triflic ion was the next choice. However, using standard conditions, such as reaction of the oxime **322** with triflic anhydride and triethylamine, failed to give triflic substituted oxime **335** and instead gave the deprotected oxime **336**.



Scheme 2.29 *Attempted synthesis of (E)-1-(2-{[tert-butyl(dimethyl)silyl]oxy}phenyl)-N-{[(trifluoromethyl)-sulfonyl]oxy}methanimine. (i) NEt_3, triflic anhydride, CH_2Cl_2.*

None of the above options for obtaining a suitable precursor that would lead to *o*-quinone nitrosomethide **330** (Scheme 2.26) were applicable to oxime **322**. An alternative approach was therefore considered whereby silyloxy protected aldehyde **272** (Scheme 2.30) was directly reacted with an appropriate *O*-substituted hydroxylamine. The reaction went smoothly when **272** was reacted with hydroxylamine-*O*-sulfonic acid in 2-propanol to afford (*E*)-1-(2-{[*tert*-butyl-(dimethyl)silyl]oxy}phenyl)-*N*-(sulfooxy)methanimine **337**, in 42% yield. Attempted generation of *o*-quinone nitrosomethide in the presence of fluoride followed by trapping of this intermediate by pyrrolidine and then cyclisation to give benzoisoxazole **338**, failed. Instead, deprotection of the silyl ether of compound **337** occurred to yield phenol **339** in 63% yield.

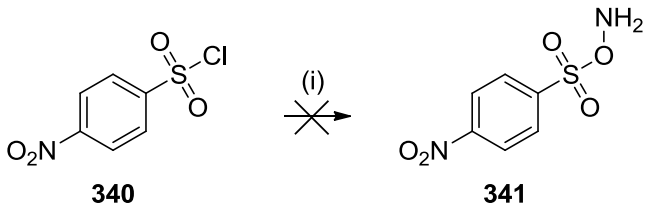


Scheme 2.30 *Synthesis of (E)-1-(2-{[tert-butyl-(dimethyl)silyl]oxy}phenyl)-N-(sulfooxy)methanimine and attempted formation of a 2,3-dihydro-1-benzofuran. (i) hydroxylamine-O-sulfonic acid, CH_3CO_2Na, i-PrOH, (ii) pyrrolidine, TBAF, THF, -78 °C.*

2.3.4. Attempted synthesis of 1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-*N*-{[(4-nitrophenyl)sulfonyl]oxy}methanimine

In the above reaction (Scheme 2.30) the sulfinic acid ion proved to be an inefficient leaving group and therefore we tried to prepare *O*-substituted hydroxylamine **341** which can be used in the reaction with aldehyde **272** (Scheme 2.2) to give the corresponding oxime (Scheme 2.31). Unfortunately reaction of 4-nitrobenzenesulfonyl chloride **340** with hydroxyl amine hydrochloride in the presence of sodium bicarbonate,[124] in a mixture THF-water, failed.

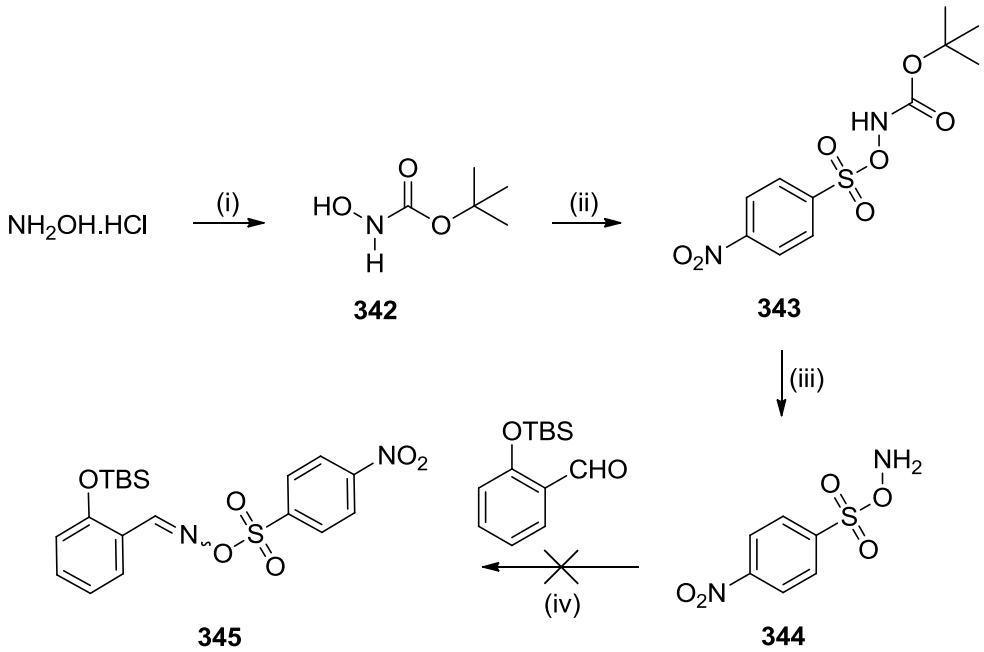
[124] Fioravanti, S.; Pellacani, L.; Tardella, P. A. *Tetrahedron* **2009**, *65*, 5747-5751.



340 **341**

Scheme 2.31 *Attempted synthesis of 1-[(aminooxy)sulfonyl]-4-nitrobenzene. (i) $NH_3OH.Cl$, sodium bicarbonate, THF-water.*

The failure of the above reaction led us to prepare *tert*-butyl {[(4-nitrophenyl)sulfonyl]oxy}-carbamate **342** (Scheme 2.32) by a literature method.[125] Boc protected hydroxylamine was reacted with 4-nitrobenzenesulfonyl chloride (nosyl chloride) with triethylamine in THF to afford **343**, in 28% yield. Compound **343** was converted into sulfonyl hydroxylamine **344**, in 85% yield, using trifluoroacetic acid. Unfortunately attempts to condense **344** with 2-{[*tert*-butyl(dimethyl)silyl]oxy} benzaldehyde failed to give the required oxime **345**.



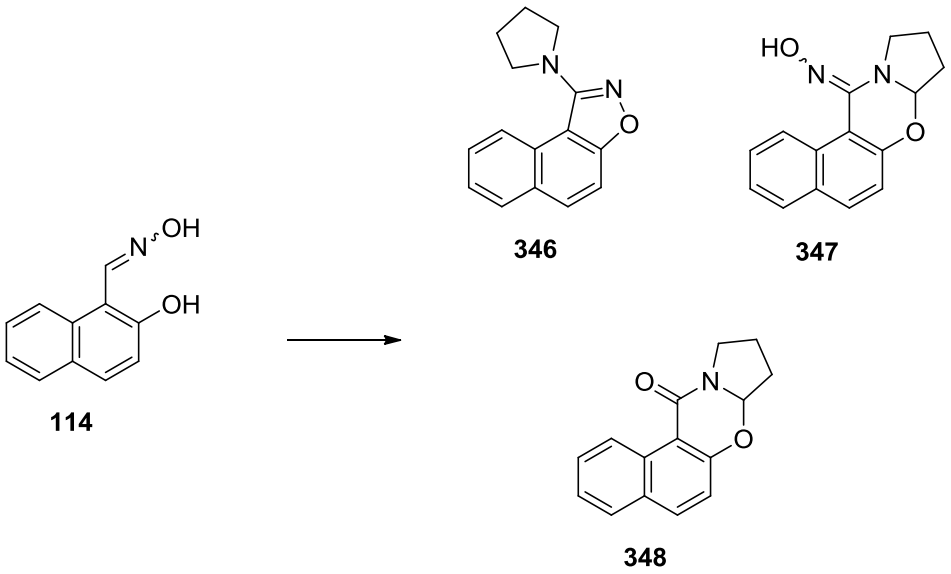
342 **343** **344** **345**

Scheme 2.32 *Synthesis of 1-[(aminooxy)sulfonyl]-4-nitrobenzene and attempted condensation with 2-{[tert-butyl(dimethyl)silyl]oxy}benzaldehyde. (i) Boc anhydride, $NaHCO_3$, THF-H_2O, (ii) NEt_3, nosyl chloride, THF, (iii) TFA, (iv) 2-propanol, molecular sieves, reflux.*

[125] Lajiness, J. P.; Robertson, W. M.; Dunwiddie, I.; Broward, M. A.; Vielhauer, G. A. Weir, S. J.; Boger, D. L. *J. Med. Chem.* **2010**, *53*, 7731–7738.

2.3.5. Oxidative generation of *o*-naphthoquinone nitrosomethide

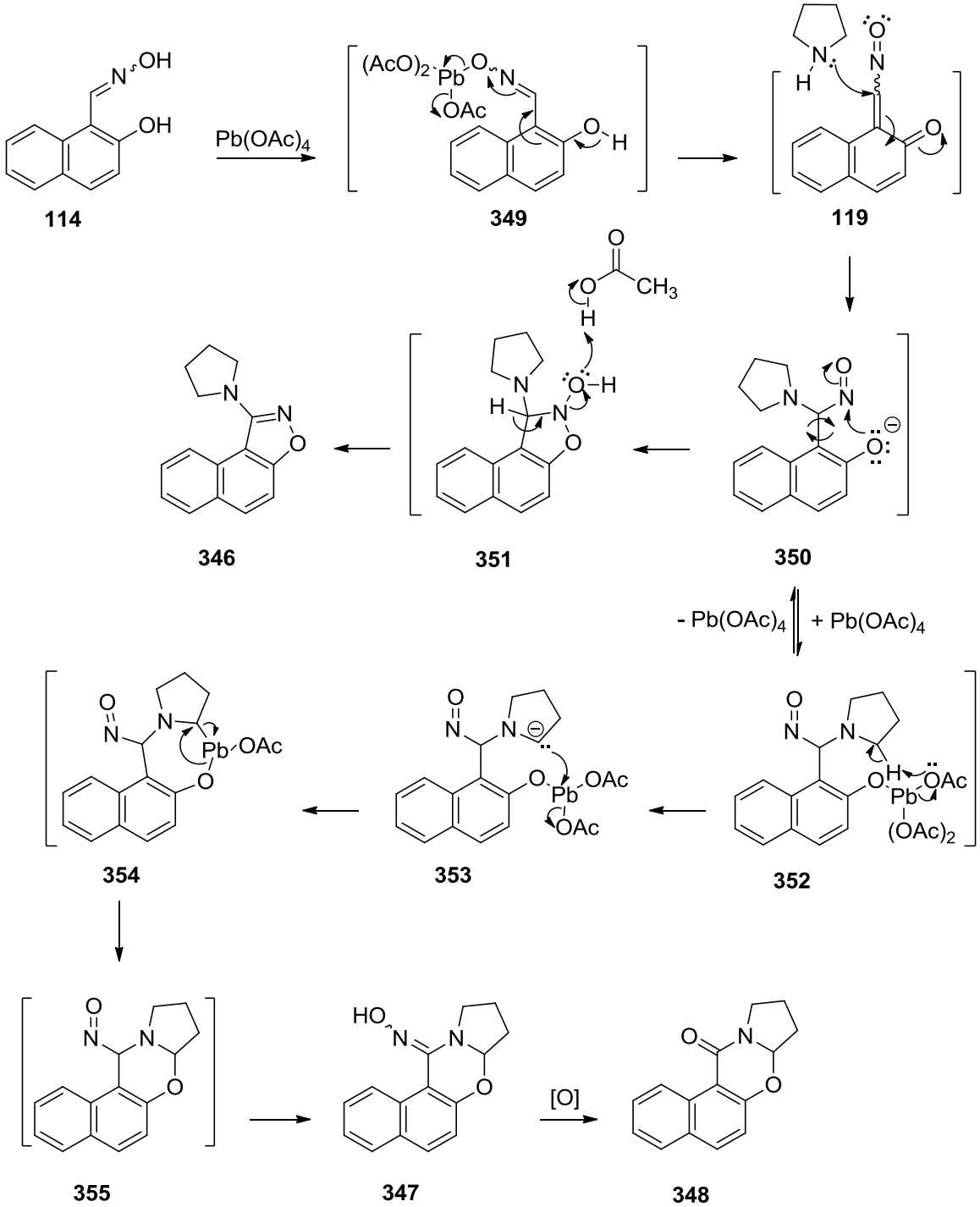
After several failed attempts to find suitable routes in order to prepare a precursor for the generation of *o*-quinone nitrosomethide or *o*-naphthoquinone nitrosomethide by using non-oxidative conditions we finally chose oxidation as the method for generating these intermediates. When oxime **114** was reacted with lead(IV) acetate (2 equivalents) in the presence of pyrrolidine in THF, after workup and column chromatography, three interesting products were isolated **346**, **347** and **348**, in 18, 15 and 10% yield, respectively. A mechanism is proposed for their formation as depicted in Scheme 2.34.



Scheme 2.33 *Products obtained after oxidation of 2-hydroxy-1-naphthaldehyde oxime in the presence of pyrrolidine. (i) $Pb(OAc)_4$, THF, 0 °C.*

In the first step of the proposed mechanism, the oxygen atom of oxime **114**, being more nucleophilic than the phenolic oxygen atom, nucleophilically attacks lead(IV) acetate displacing acetate anion to form the organolead intermediate **349**. Conjugate addition of an electron-pair from the phenolic oxygen atom into the aromatic ring ends up forming an N=O bond after displacing lead((II) acetate. The formed *o*- naphthoquinone nitrosomethide **119** then undergoes Michael addition by pyrrolidine at the exocyclic alkene carbon of the α,β-unsaturated carbonyl system to afford naphthoxide ion adduct **350**. Cyclisation of **350** by a 5-exo-trig addition reaction and protonation gives 1-pyrrolidin-1-ylnaphtho[1,2-*d*]isoxazol-2(1*H*)-ol **351**. Intermediate **351** undergoes acid catalysed dehydration to yield

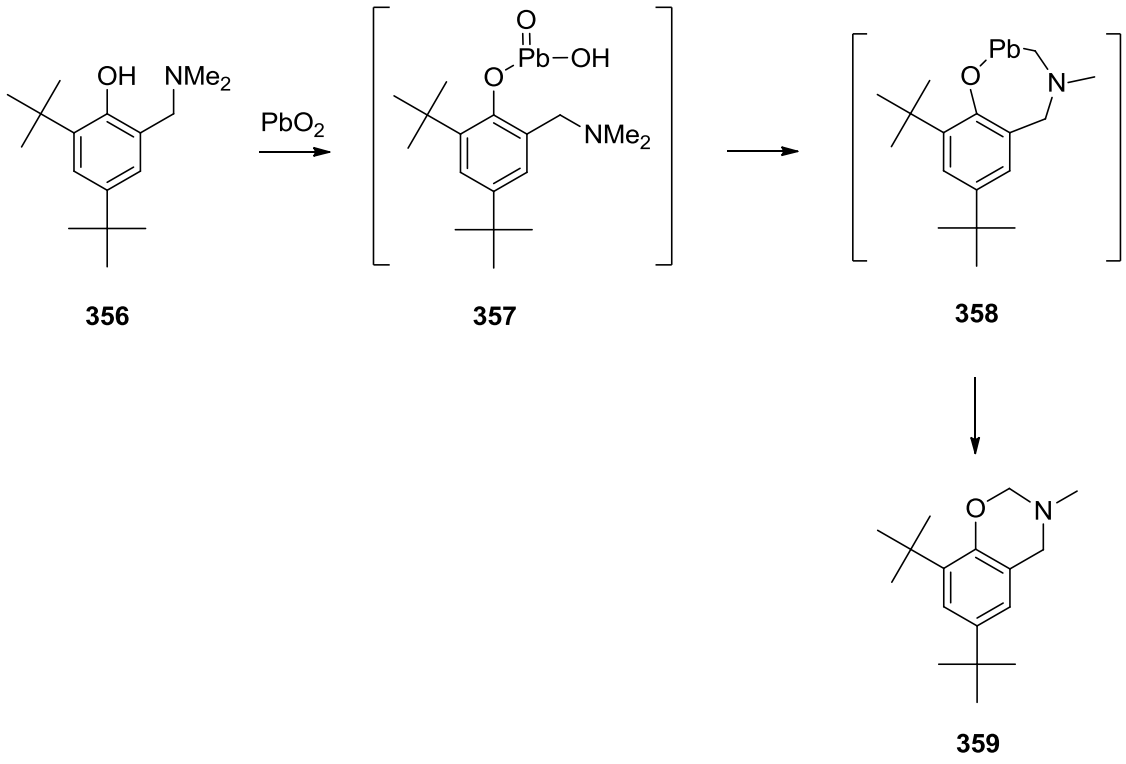
the aromatic derivative **346**. During the transformations in this reaction sequence, free rotation around the σ-bond of the benzylic group allows the free naphthoxide ion to react with lead(IV) acetate to give the organolead adduct **352**. The acidic proton of the



Scheme 2.34 *Proposed mechanism for oxidative generation of o-naphthoquinone nitrosomethide from 2-hydroxy-1-naphthaldehyde oxime, Michael addition and further reactions.*

pyrrolidine group in adduct **352** is abstracted intramolecularly by the departing acetate ion to afford carbanionic organolead species **353** which undergoes cyclisation to intermediate naphthopyrrolooxazaplumbepine **351**, by forming a C–Pb bond with concomitant elimination of acetate ion. Rearrangement of the lead and oxygen atoms in compound **354** affords 12-nitrosonaphthopyrrolooxazine **355** which in the presence of acid tautomerises to the oxime **347**. The oxime is unstable in the presence of lead(IV) acetate and is oxidised to the ketone **348**.

A similar type of reaction was reported by Belostotskaya and co-workers[126] who oxidatively cyclised 2,4-di-*tert*-butyl-6-[(dimethylamino)methyl]phenol **356** into 6,8-di-*tert*-butyl-3-methyl-3,4-dihydro-2*H*-1,3-benzoxazine **359** (Scheme 2.35). The organolead intermediate **358** proposed in this reaction is analogous to intermediate **354** we have proposed in Scheme 2.34.



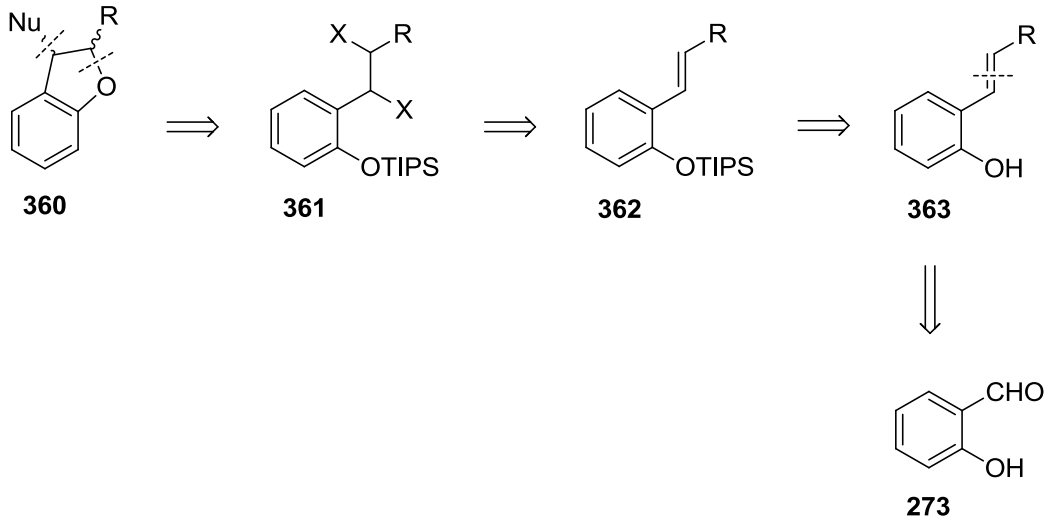
356 **357** **358** **359**

Scheme 2.35 *Proposed mechanism by Belostotskaya and co-workers.*

[126] Belostotskaya, I. S.; Voleva, V. B.; Komissarova, N. L.; Dekaprilevich, M. O.; Khrustalev, V. N.; Karmilov, A. Yu.; Ershov, V. V. *Russ. Chem. Bull.* **1997**, *46*, 1272-1280.

2.4 Synthesis of 2,3-dihydro-1-benzofurans via *o*-quinone methide intermediates

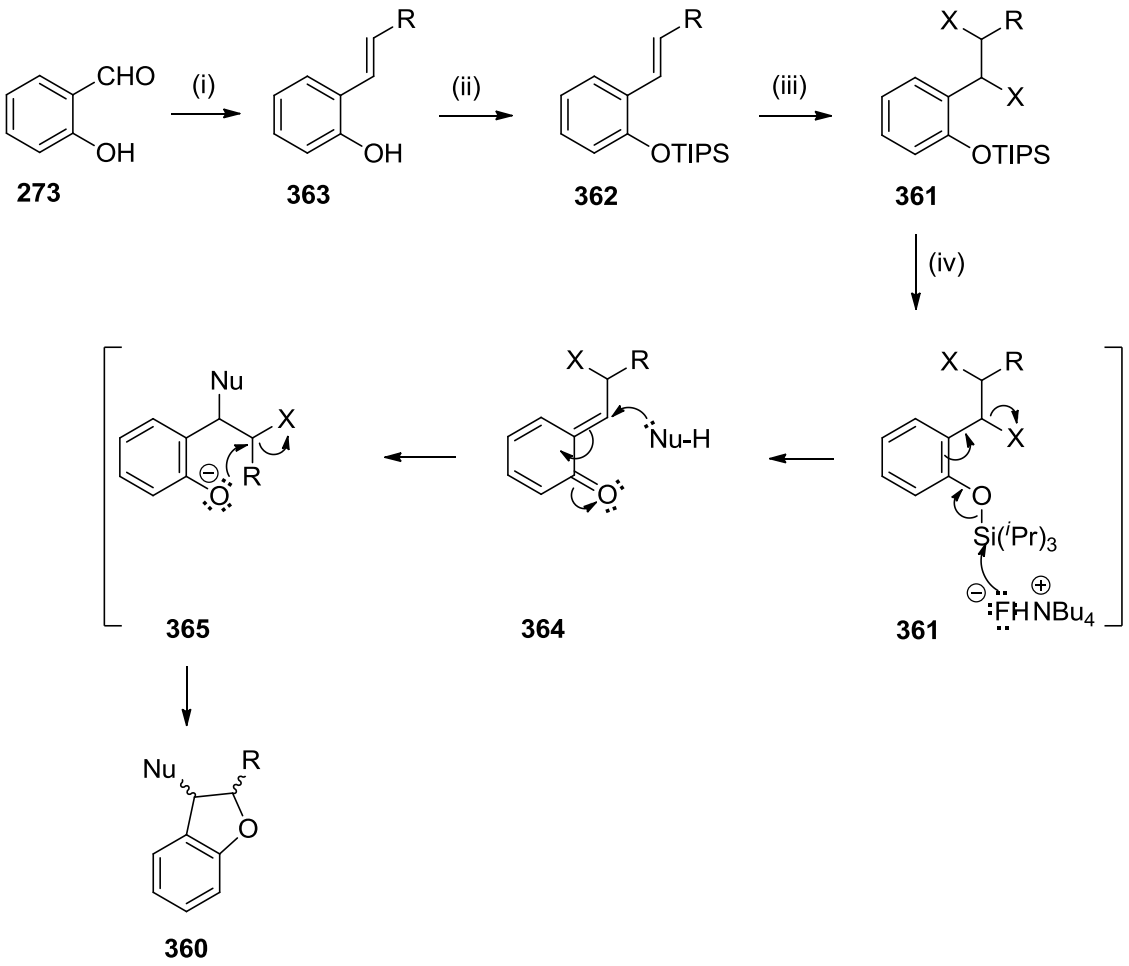
This chapter describes the search for a new method to synthesise 2,3-dihydro-1-benzofurans via *o*-quinone methide intermediates. We specifically wanted a one pot reaction to proceed by an elimination reaction, triggered by fluoride ion, of a suitable precursor leading to the generation of *o*-quinone methide *in situ* that would then undergo an intramolecular cyclization reaction by a second elimination. The requirement for the precursor was the existence of two leaving groups adjacent to each other. The retrosynthetic analysis for the above reasoning is shown in Scheme 2.36.



360 **361** **362** **363** **273**

Scheme 2.36 *Retrosynthetic analysis for the formation of 2,3-dihydro-1-benzofurans.*

The synthesis of a suitable precursor was approached by starting from the commercially available salicyaldehyde **273** (Scheme 2.37). In the first step, aldehyde **273** is converted an acrylate **363** using a Wittig reaction. In the second step, the hydroxy group of **363** is protected by a triisopropylsilyl group to afford silyl ether **362**. In the third step, the alkene group of **362** is transformed into a disubstituted alkane group as in compound **361**. In the fourth one-pot step, the ether group of **361** is subjected to a silyl deprotection reaction by fluoride ion to generate *o*-quinone methide **364** *in situ* by eliminating a good leaving group (X). Transient **364** will then undergo conjugate addition by a nearby nucleophile and the resulting transient adduct **366** will intramolecularly displace a good leaving group (X) to afford a 3-substituted- or a 2,3-disubstituted-2,3-dihydro-1-benzofurans **360**.

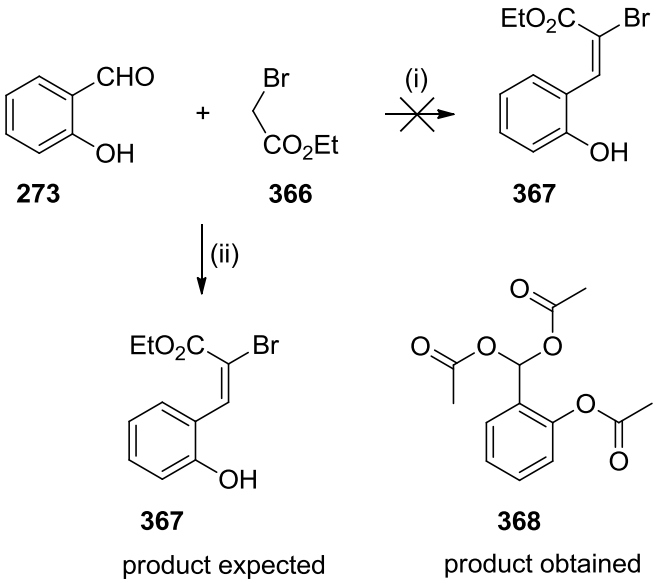


Scheme 2.37 *Proposed mechanism for the novel formation of mono- and disubstituted 2,3-dihydro-1-benzofurans. (i) Wittig olefination or Knoevenagel condensation, (ii) (i-Pr)$_3$SiCl, base, solvent, (iii) halogenations by X$_2$, (iv) nucleophile, TBAF, solvent.*

2.4.1 Preparation of ethyl (2*E*)-2-cyano-3-{2-[(triisopropylsilyl)oxy]phenyl}acrylate in the synthesis of substituted 2,3-dihydro-1-benzofurans

For preparation of the acrylate **363** required in the first step in the synthesis of substituted 2,3-dihydro-1-benzofurans **360** (Scheme 2.37), the first reaction of choice was the Knovenagel condensation. The reaction took place by treating salicylaldehyde **273** (Scheme 2.38) with ethyl bromoacetate in the presence of piperidine and acetic acid in

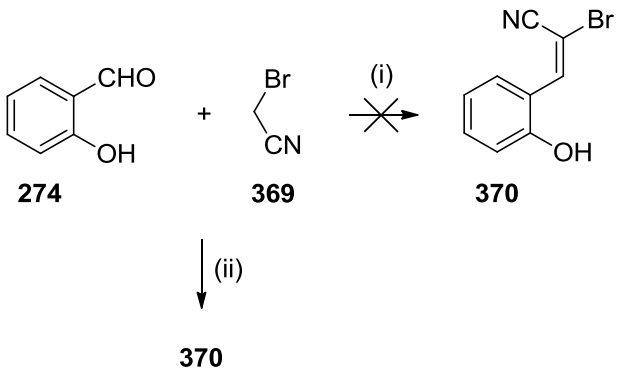
toluene, according to literature methods.[127,128] However, the reaction did not proceed to give compound **367** even after 24 hours of reflux. When the reaction was repeated using lithium bromide and acetic anhydride, again the desired product **367** was not formed and instead the unusual molecule of [2-(acetyloxy)phenyl]methylene diacetate **368** was isolated in 50% yield.



Scheme 2.38 *Attempted synthesis of ethyl (2E)-2-bromo-3-(2-hydroxyphenyl)acrylate. (i) piperidine, acetic acid, toluene, reflux, 24 h, (ii) LiBr, acetic anhydride, 80 °C.*

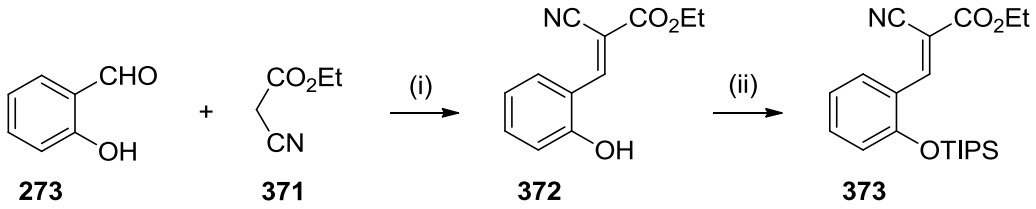
Mane and co-workers have reported[129] a Knovenagel condensation with bromoacetonitrile catalyzed by baker's yeast. The reaction did not proceed at all when dried yeast was used whereas when fresh baker's yeast was used the desired product **370** was isolated in 11% yield.

[127] Sylla, M.; Joseph, D.; Chevallier, E.; Camara, C.; Dumas, F. *Synthesis* **2006**, *6*, 1045-1049.
[128] Wang, T.; Liu, J.; Zhong, H.; Chen, H.; Lv, Z.; Zhang, Y.; Zhang, M.; Geng, D.; Niu, C.; Li, Y.; Li, K. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3381-3383.
[129] Pratap, U. R.; Jawale, D. V.; Waghmare, R. A.; Lingampalle, D. L.; Mane, R . A. *New J. Chem* **2011**, *35*, 49-51.



Scheme 2.39 *Synthesis of (2E)-2-bromo-3-(2-hydroxyphenyl)acrylonitrile. (i) dried baker's yeast, ethanol, rt (ii) fresh baker's yeast, ethanol.*

The low yield of acrylonitrile **370** in the above reaction using baker's yeast forced us to search for alternative reaction conditions. Yadav and co-workers[130] have reported the condensation of ethyl cyanoacetate with aromatic aldehydes in the presence of triphenylphosphine without solvent. Applying these reaction conditions to salicylaldehyde **273** (Scheme 2.40) acrylate **372** was isolated in 54% yield. The phenolic hydroxyl group of **372** was smoothly silylated with triisopropylsilyl chloride to give triisopropylsilyl ether **373** in 35% yield.



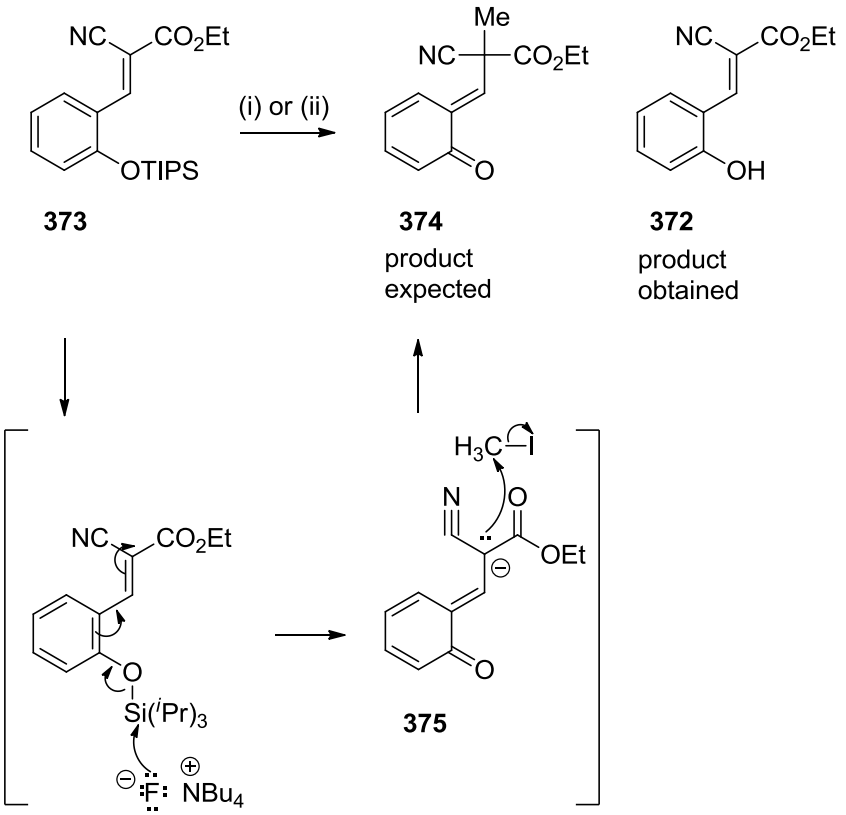
Scheme 2.40 *Synthesis of ethyl (2E)-2-cyano-3-(2-hydroxyphenyl)acrylate and transformation into the corresponding triisopropylsilyl ether. (i) PPh_3, 70-80 °C, (ii) $(i\text{-}Pr)_3SiCl$, $(i\text{-}Pr)_2NH$, DMAP, CH_2Cl_2.*

2.4.2 Reactivity of ethyl (2*E*)-2-cyano-3-{2-[(triisopropylsilyl)oxy]phenyl}acrylate as an *o*-quinone methide precursor

The initial plan for acrylate **373** was to investigate whether it can be used as a precursor to generate *o*-quinone methide **375** *in situ* which can be trapped by alkylation (Scheme

[130] Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Visali, B.; Narsaiah, A. V.; Nagaiah, K. *Eur. J. Org. Chem.* **2004**, 546-551.

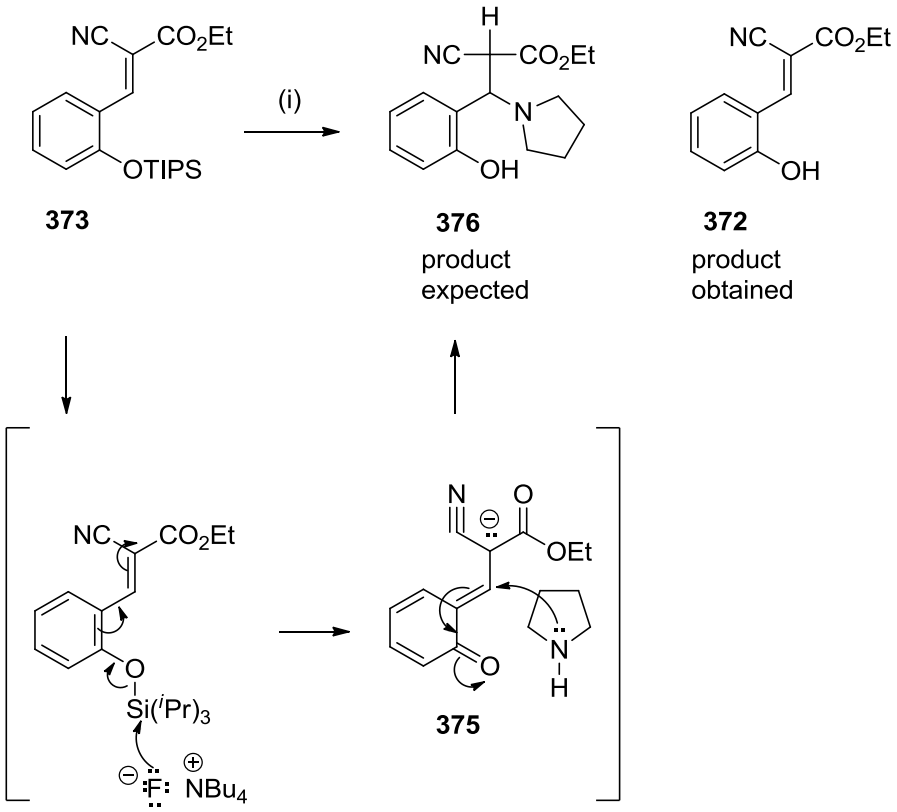
2.41). Fluoride ion cleavage of the Si–O bond of compound **373** leaves a negative charge on the oxygen atom so that an electron pair releases a +M effect along the conjugated system of the molecule to form the carbanionic *o*-quinone methide **375**. It was hoped that this stabilised carbanionic species would be methylated by methyl iodide by an S_N2 reaction that would "freeze" the *o*-quinone methide structure in molecule **374**. Unfortunately, the product obtained in this reaction is phenol **372**. The reaction was repeated by changing the solvent from THF to DMF using either TBAF or KF but again phenol **372** was retrieved in both cases.



Scheme 2.41 *Attempted methylation of the o-quinone methide carbanion resulting from fluoride ion deprotection of ethyl (2E)-2-cyano-3-{2-[(triisopropylsilyl)oxy]phenyl}acrylate. (i) MeI, TBAF, THF or DMF, -78 °C, (ii) MeI, KF, THF or DMF, -78 °C.*

In another attempt to meet the challenge of trapping the novel carbanionic *o*-quinone methide **375** (Scheme 2.42), to compound **373** in THF at -78 ^oC was added pyrrolidine followed by dropwise addition of TBAF to ensure that the generation of anionic *o*-quinone methide was controlled so that the Michael addition reaction would take place selectively on the heterodiene carbon atom. To our disappointment the product obtained was again

phenol **372**. Had this reaction succeeded it would have counted as a novel method of generating an *o*-quinone methide.



Scheme 2.42 *Attempted Michael addition on the o-quinone methide carbanion assumed to be formed during fluoride ion deprotection of ethyl (2E)-2-cyano-3-{2-[(triisopropylsilyl)oxy]phenyl}acrylate. (i) pyrrolidine, THF, -78 °C followed by TBAF in THF, -78 °C.*

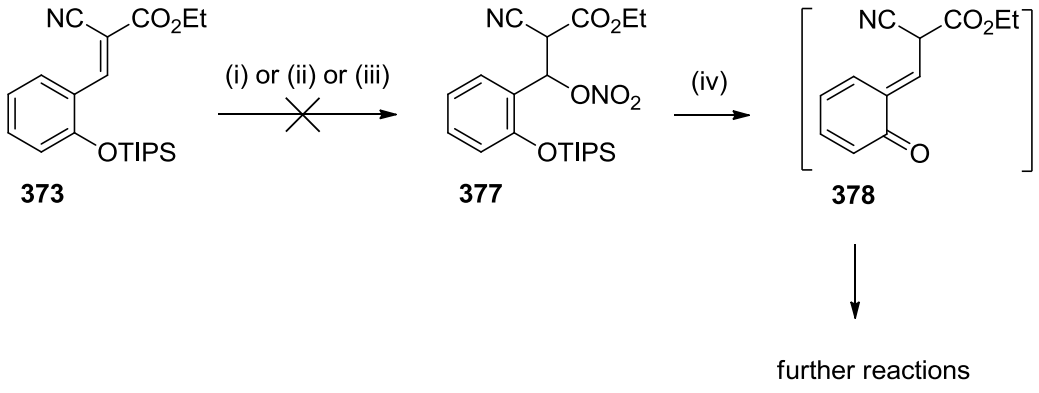
2.4.3 Addition and substitution reactions at the alkene group of ethyl (2*E*)-2-cyano-3-{2-[(triisopropylsilyl)oxy]phenyl}acrylate

Inoue and co-workers have reported[131] that C–H nitrooxylation at benzylic positions can be achieved by employing *N*-hydroxyphthalimide and cerium(IV) ammonium nitrate (CAN) as catalyst, in acetonitrile. Applying these reaction conditions to compound **373** we hoped to introduce a nitrate group at the β-carbon atom of the α,β-unsaturated cyanoester group of **373** and isolate compound **377**. The nitrate group in **377** would act as a good

[131] Kamijo, S.; Amaoka, Y.; Inoue, M. *Tetrahedron Lett.* **2011**, *52*, 4654-4657.

leaving group when the molecule is subjected to Si–O bond cleavage by fluoride ion in the process of generating the neutral *o*-quinone methide intermediate **378**. The reaction mixture of the reaction leading to **377**, when examined by TLC, revealed several spots with ΔR_f values ≤ 0.1. ESI mass spectrometry of a sample mixture after crude purification by column chromatography did not reveal any peaks in the mass spectrum whose m/z value corresponded to **377** or any other compound that could have formed from **377**. In another attempt to synthesise **377**, compound **373** was refluxed in ethanol with silver nitrate but in this case starting material was found to be unchanged.

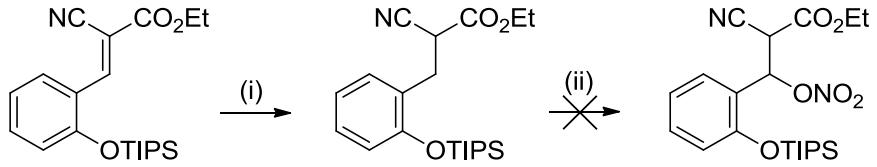
Sarker and co-workers[132] reacted 3-fluorophenylcyanoethylacrylate with sodium cyanide in ethanol under reflux for 1.5 hours and isolated 3-fluorophenyl α,β-dicyanoethylpropionate. Overall the reaction involves the Michael addition of cyanide ion to the acrylate resulting in the introduction of a cyano group at the benzylic position of the molecule. Similar reaction conditions were applied to compound **373** (Scheme 2.43) except that sodium cyanide was replaced with either silver nitrate or potassium nitrate but to our disappointment product **377** was not detected in the reaction mixture even after 24 hours of reflux.



Scheme 2.43 *Attempted nitrooxylation of ethyl (2E)-2-cyano-3-{2-[(triisopropylsilyl)oxy]phenyl}acrylate. (i) N-hydroxyphthalimide, cerium(IV) ammonium nitrate, CH_3CN, (ii) $AgNO_3$, ethanol, reflux, 1.5-24 h, (iii) KNO_3, ethanol, reflux, 1.5-24 h, (iv) TBAF in THF, -78 °C.*

[132] Das, S.; Yasmin, H.; Masud, M. M.; Roy, S. C.; Nahar, L.; Rahman, M. M.; Gibbons, S.; Bachar, S. C.; Sarker, S. D. *Tetrahedron* **2008**, *64*, 8642-8645.

Yet another approach to nitrate **377** was sought, this time the alkene group of **373** was reduced by sodium borohydride[133] in ethanol to yield the substituted benzyl derivative **379** (Scheme 2.44). The introduction of a nitrooxy group at the benzylic position of **379** was next attempted according to Inoue and co-workers[131] that is by reaction with *N*-hydroxyphthalimide and cerium(IV) ammonium nitrate in acetonitrile. The reaction unfortunately did not work.

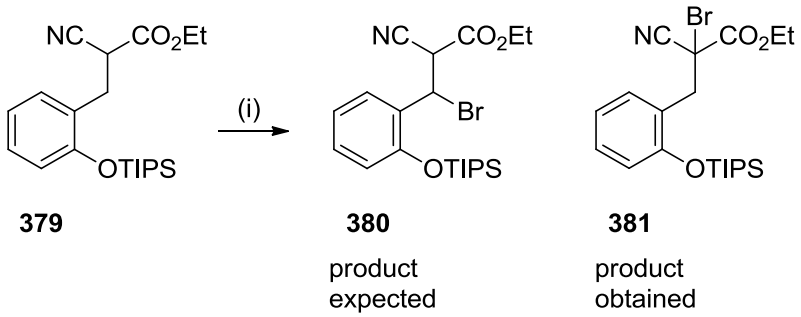


373 **379** **377**

Scheme 2.44 *Synthesis of ethyl 2-cyano-3-{2-[(triisopropylsilyl)oxy]phenyl}propanoate and attempted nitrooxylation. (i) sodium borohydride, ethanol, (ii) N-hydroxyphthalimide, cerium(IV) ammonium nitrate, CH_3CN.*

Jereb and co-workers[134] have reported the bromination at the benzylic position using *N*-bromosuccinimide under solvent free reaction conditions photochemically using a 40 W tungsten light bulb. We performed the bromination of compound **379** using similar conditions but surprisingly we got the product wherein bromination had occurred at the tertiary carbon atom and not the secondary carbon atom that is, compound **381**. The formation of this product can be logically supported as this reaction proceeds via radical formation and radicals are known to be stabilised for the same reasons as carbocations. Another reason supporting this result is that the proton at the tertiary carbon atom is more acidic than the protons of the secondary carbon atom due to the two electron attracting groups which contribute towards faster formation of the tertiary radical and hence radical bromination at this position.

[133] Gazit, A.; Yaish, P.; Gilon, C.; Levitzki, A. *J. Med. Chem.* **1989**, *32*, 2344-2352.
[134] Jereb, M.; Zupan, M.; Stavber, S. *Helv. Chim. Acta.* **2009**, *92*, 555-566.



Scheme 2.45 *Attempted bromination at the benzylic position of ethyl 2-cyano-3-{2-[(triisopropylsilyl)oxy]-phenyl}propanoate. (i) N-bromosuccinimide, 40 W lamp, 12 h.*

The ^{1}H NMR spectrum of compound **381** is shown in Figure 2.11. The four aromatic protons are found at 7.29-6.85 ppm. At 4.33 ppm the quartet signal belongs to the ester CH_2 while different chemical shifts of the doublets at 3.65 ppm and 3.86 ppm with a coupling constant of 14 Hz characterises them as geminal protons that are diastereotopic due to the adjacent quaternary carbon.

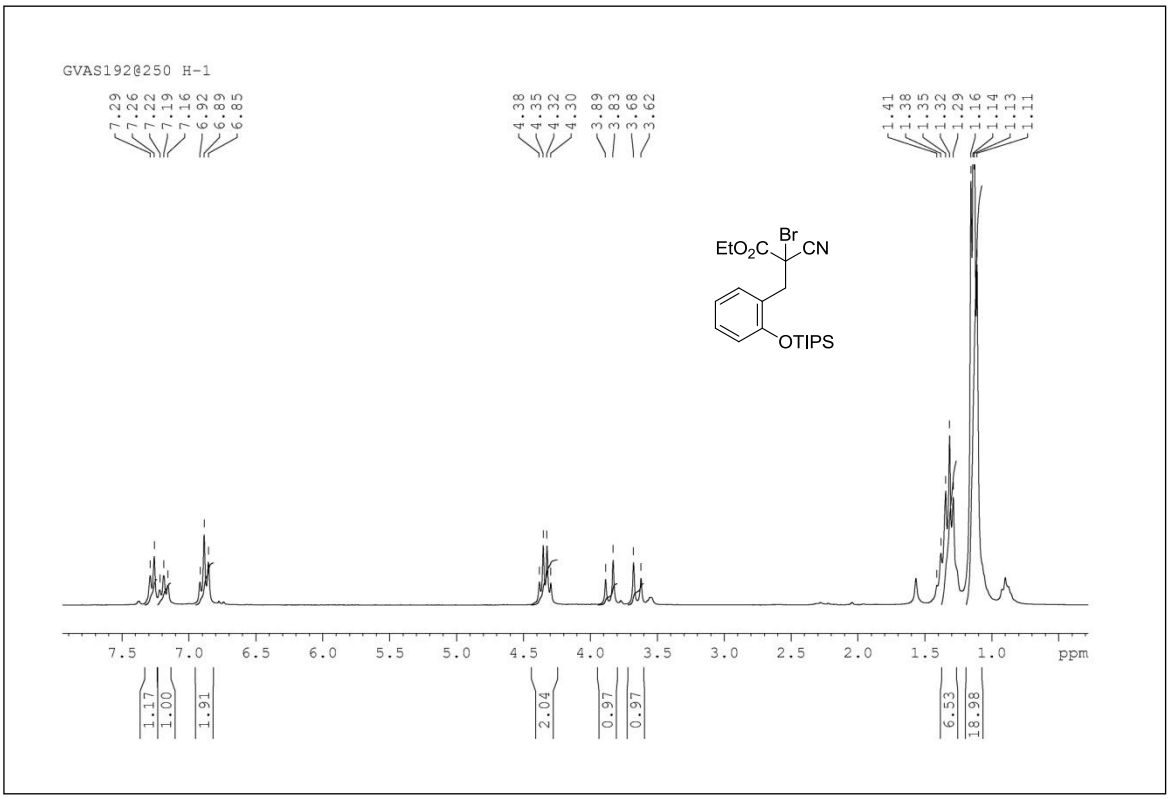


Figure 2.11 *^{1}H NMR (250 MHz, $CDCl_3$) spectrum of compound **381**.*

In order to rule out the possibility of having synthesised compound **380** instead of **381**, regardless of the above explanation, a ^{13}C NMR spectrum of compound **381** was taken

followed by a DEPT-135 measurement (Figure 2.12). These two spectra confirmed beyond doubt that there are geminal protons (benzylic) and the compound we obtained is compound **381** with the bromine attached to the tertiary carbon. From the DEPT-135 spectrum it can be seen that there are two peaks in the opposite phase *i.e.* at 38.61 ppm and at 64.48 ppm indicating the presence of two methylene groups out of which the one at 64.48 ppm is from the ethyl ester group and the other one at 38.61 must be the benzylic CH_2 group. Also the quaternary carbon in the aliphatic region is observed at 42.97 ppm which was confirmed by its absence in the DEPT-135. From the DEPT-135 it was seen that there is no tertiary carbon atom in the aliphatic region except the three tertiary carbons of the triisopropyl group at 13.12 ppm.

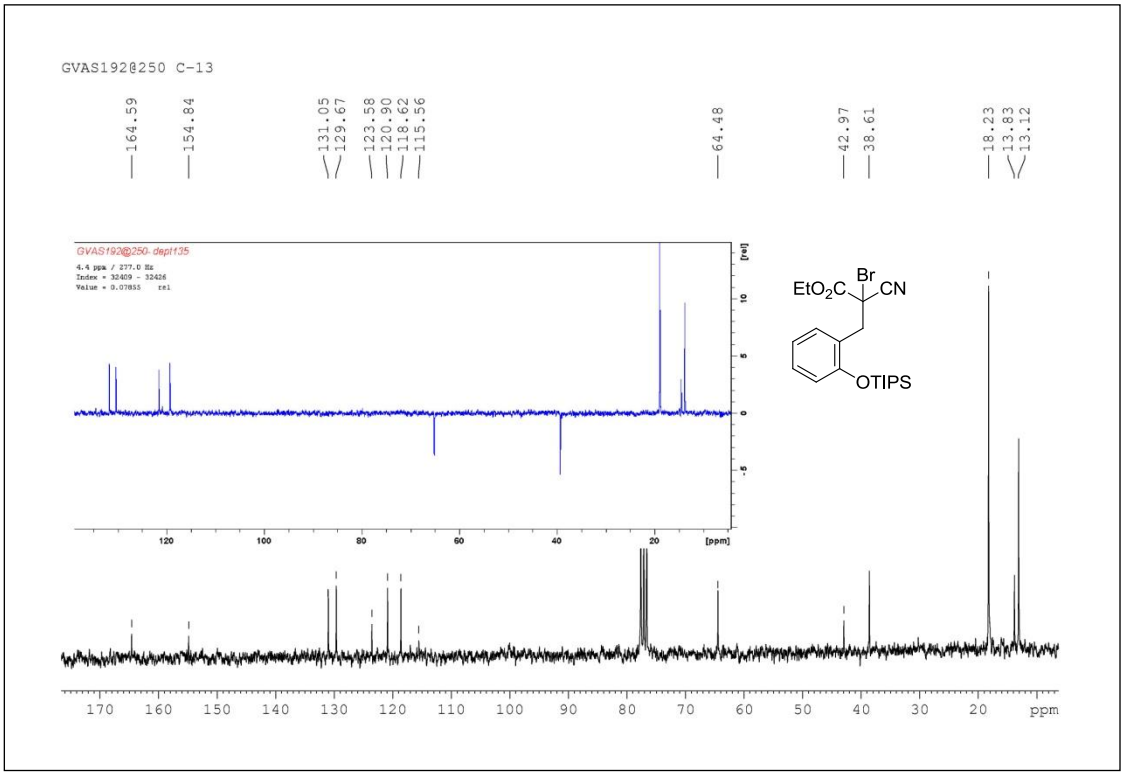


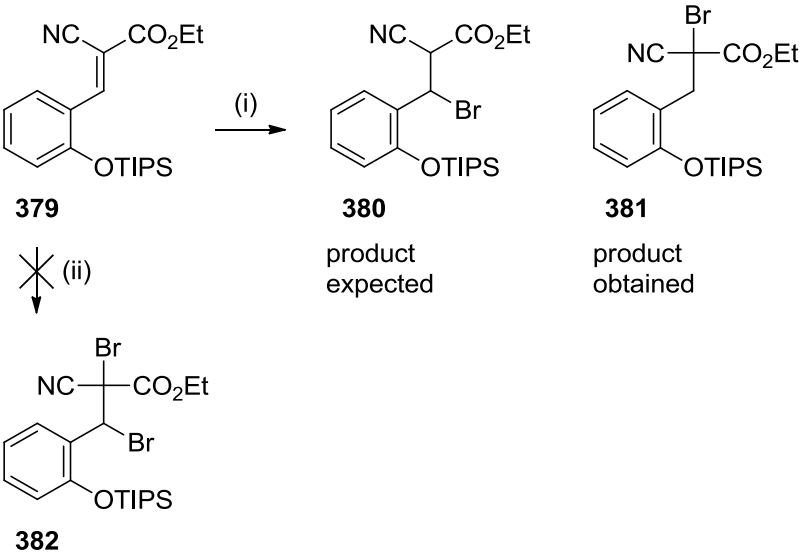
Figure 2.12 *^{13}C NMR and DEPT-135 (250 MHz, $CDCl_3$) spectra of compound **381**.*

Mattos and Sanseverino[135] have reported the addition of HBr across alkenes using phosphorus tribromide and silicon dioxide as reagents. Applying similar reaction conditions that are, adding a solution of phosphorus tribromide in dichloromethane to a well stirred suspension of **379** and silicon dioxide in dichloromethane, compound **381** was

[135] Sanseverino, A. M.; de Mattos, M. C. S. *J. Braz. Chem. Soc.* **2001**, *12*, 685-687.

isolated from the reaction mixture, formed according to Markovnikov's rule (Scheme 2.46). The same compound was isolated from the attempted dibromination reaction of **379** using bromine in chloroform, as reported by Reiser and co-workers.[136]

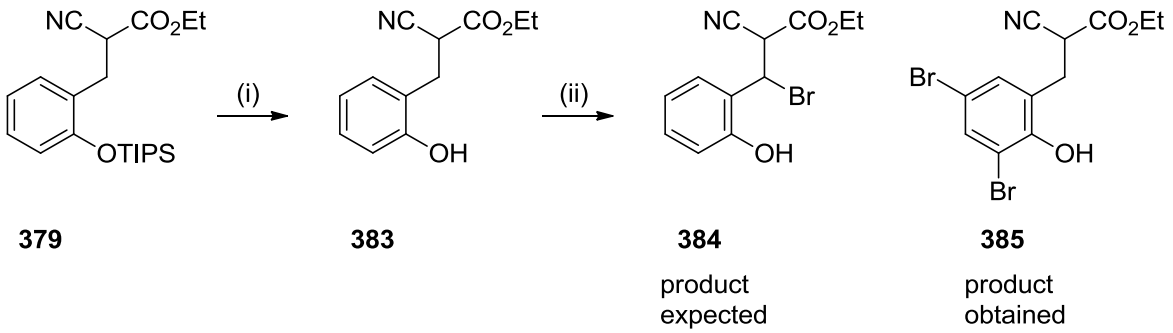
Das and co-workers[137] have reported the preparation of the dibromo alkanes from the corresponding alkenes using potassium bromide and iodobenzene diacetate in dichloromethane-water as solvents. This method was applied to acrylate **379** but the reaction did not proceed at all.



Scheme 2.46 *Attempted mono- and dibromination of ethyl (2E)-2-cyano-3-{2-[(triisopropylsilyl)oxy]-phenyl}acrylate. (i) PBr_3, SiO_2, CH_2Cl_2 or Br_2, $CHCl_3$, 0 °C, (ii) KBr, IBD, CH_2Cl_2-H_2O (1:1).*

Li and co-workers[138] have reported the bromination of alkanes using a manganese dioxide and bromine reagent system. Application of these reaction conditions to compound **383** did not produce the expected bromo derivative **384**, but instead bromination occurred at the aromatic ring to furnish the dibromo derivative **385** in 42% yield.

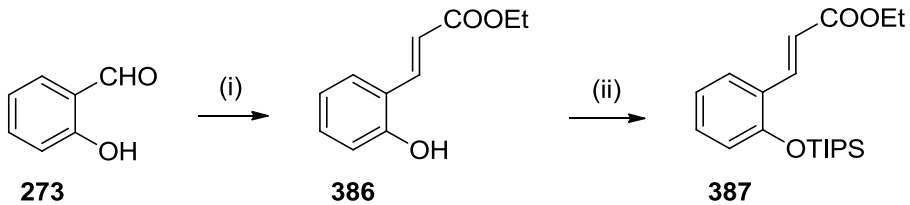
[136] Maji, T.; Karmakar, A.; Reiser, O. *J. Org. Chem.* **2011**, *76*, 736-739.
[137] Das, B.; Srinivas, Y.; Sudhakar, C.; Damodar, K.; Narender, R. *Syn. Comm.* **2009**, *39*, 220-227.
[138] Li, C.; Tang, Y.; Shen, M.; Jiang, X. *Tetrahedron Lett.* **2005**, *46*, 487-489.



Scheme 2.47 *Attempted bromination at the benzylic position of ethyl 2-cyano-3-(2-hydroxyphenyl) propanoate. (i) TBAF, THF, (ii) MnO_2, Br_2, CH_2Cl_2.*

2.4.4 Preparation of *anti*- and *syn*-ethyl-3-substituted 2,3-dihydro-1-benzofuran-2-carboxylate

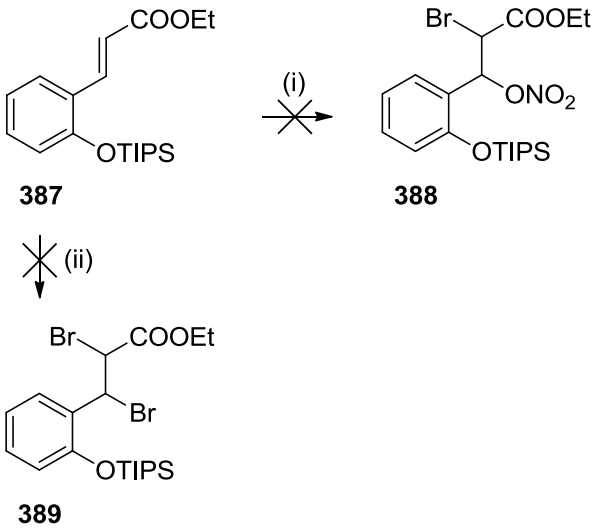
After several attempts, that did not lead to the synthesis of precursor **361** (Scheme 2.36), we decided to change the starting materials as well as the reaction conditions. For this reason we chose to synthesise acrylate **386** which was prepared through a Wittig condensation reported by Yue and Wu[139] by treating salicyaldehyde with triphenyl phosphine and ethyl bromoacetate in water. Acrylate **373** was isolated in 84% yield with high (*E*) isomer selectively (*E*/*Z* = 97/3), according to the published paper. The hydroxy group of **386** was then protected by introducing a triisopropylsilyl group as described earlier in this chapter. The yield of **387** is 90% yield. In the next step acrylate **387** was subjected to a nitrooxylation-bromination reaction as reported by Nair and co-workers.[140] In this reaction acrylate **387** (Scheme 2.49) was dissolved in dry, deoxygenated acetonitrile



Scheme 2.48 *Preparation of ethyl (2E)-3-{2-[(triisopropylsilyl)oxy]phenyl}acrylate. (i) PPh_3, ethyl bromoacetate, LiOH, LiCl, water, reflux, 15 min, (ii) TIPSCl, diisopropylamine, DMAP, CH_2Cl_2.*

[139] Wu, J.; Yue, C. *Syn. Comm.* **2006**, *36*, 2939-2947.
[140] Nair, V.; Panicker, S. B.; Augustine, A.; George, T. G.; Thomas, S.; Vairamani, M. *Tetrahedron* **2001**, *57*, 7417-7422.

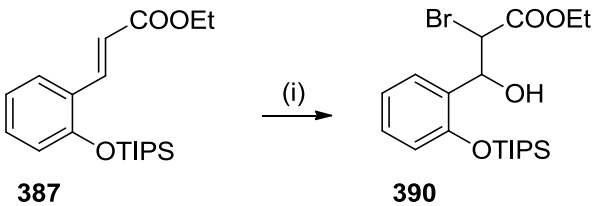
and stirred vigorously with lithium bromide and cerium(IV) ammonium nitrate (CAN). After several hours, TLC examination of the reaction mixture revealed that although starting material was consumed, several other spots had appeared with ΔR_f values ≤ 0.1. ESI mass spectrometry of a sample mixture, after crude purification by column chromatography, did not reveal any peaks in the mass spectrum whose m/z value was by any means even close to the molecular weight of compound **388**. Experimentally the situation was similar when acrylate **387** was reacted with bromine in chloroform at 0 °C, in order to synthesise dibromo derivative **389**.



387 **388** **389**

Scheme 2.49 *Attempted nitrooxylation-bromination and bromination of ethyl (2E)-3-{2-[(triisopropylsilyl)oxy]-phenyl}acrylate. (i) LiBr, CAN, CH_3CN, (ii) Br_2, $CHCl_3$, 0 °C.*

Another thought was to prepare bromohydrin derivative **390** as reported for similar α,β,-unsaturated esters.[141,142] The reaction was successful when acrylate **387** was reacted



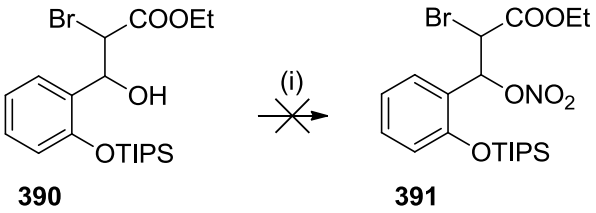
387 **390**

Scheme 2.50 *Preparation of ethyl 2-bromo-3-hydroxy-3-{2-[(triisopropylsilyl)oxy]phenyl}propanoate. (i) N-bromosuccinimide, THF-water (1:1).*

[141] Shin, C.; Yonezawa, Y.; Unoki, K.; Yoshimura, J. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1657-1660.
[142] Bar, S. *Can. J. Chem.* **2010**, *88*, 605-612.

with *N*-bromosuccinimide and water and gave bromohydrin derivative **390**, in 78% yield.

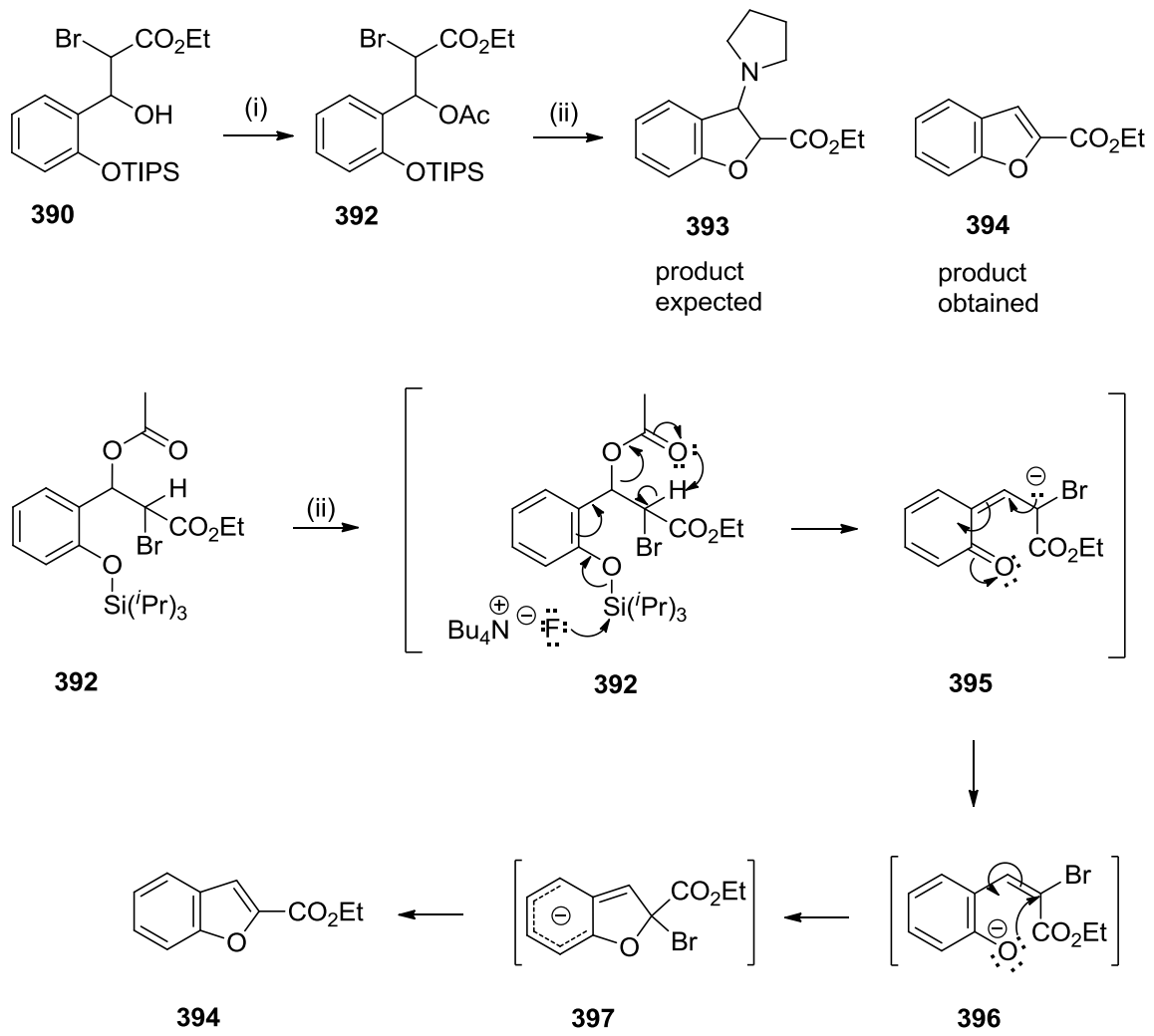
The reason of synthesising **390** was so that the hydroxyl group could be converted (Scheme 2.51) to a good leaving group such as nitrate. This therefore was a major step towards synthesising a precursor suitable for the preparation of 2,3-dihydrobenzo-1-furans. In our earlier work we have described the conversion of a primary alcohol to a nitrate ester (Scheme 2.2). Using our standard reaction conditions, which are reacting alcohol **390** with silver nitrate and thionyl chloride, did not furnish nitrate **391**.



390 **391**

Scheme 2.51 *Attempted conversion of hydroxyl group of ethyl 2-bromo-3-hydroxy-3-{2-[(triisopropylsilyl)oxy]-phenyl}propanoate to nitrate. (i) $AgNO_3$, $SOCl_2$, THF.*

Having failed to prepare nitrate ester **391** (Scheme 2.51) we turned to converting the hydroxy group to an acetoxy group in the hope that acetate ion would work as a good leaving group during the *o*-quinone methide generation step. In a simple reaction, alcohol **390** was reacted with acetic anhydride and a catalytic amount of 4-dimethylaminopyridine in dichloromethane to afford acetoxy derivative **392**, in 97% yield. Treatment of acetoxy derivative **392** in THF at -78 °C with pyrrolidine followed by dropwise addition of TBAF at -78 °C followed by standard work up, as described for the Michael addition of pyrrolidine to nitrate ester **270** in Scheme 2.4, did not yield the expected 2,3-dihydro-1-benzofuran **393** but instead the aromatic ethyl 1-benzofuran-2-carboxylate **394**, in 89% yield.

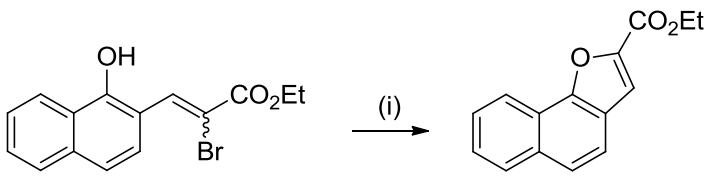


Scheme 2.52 *Synthesis of ethyl 1-benzofuran-2-carboxylate. (i) acetic anhydride, DMAP, CH_2Cl_2, (ii) TBAF, pyrrolidine, THF, -78 °C.*

The outcome of this reaction can be explained on the basis of the proposed mechanism depicted in Scheme 2.52. The first step of the reaction involves cleavage of the Si–O bond by fluoride ion and a positive mesomeric effect by a lone-pair of the negatively charged oxygen atom along the conjugated system of **392** which terminates by eliminating acetic acid. It is interesting to note that prior to elimination of acetic acid, the acetoxy group may be in strong hydrogen bonding with the acidic proton of the tertiary carbon atom that is bonded to a bromine atom and an ester group. The carbanion of the resulting intermediate **395** is stabilised by the aforementioned electron-withdrawing groups but more stability is offered to the molecule when it aromatises by resonance to give intermediate phenoxide **396**. The π-electrons of the α,β-unsaturated bond in **396** are displaced by resonance into the

aromatic benzene ring as the charged oxygen atom of the molecule approaches the α-carbon atom. The resulting intermediate carbanion **397** is stabilized by resonance but further stabilization is delivered by the elimination of bromine ion and the formation of the fully aromatic benzofuran **394**. Repeating the reaction in methanol (as solvent and nucleophile) instead of THF produced again compound **394**.

A similar type of cyclisation has been described by Mérour and co-workers[143] (Scheme 2.53), wherein **398** is heated in refluxing methyl isobutyl ketone (MIBK) in the presence of potassium carbonate, to give ethyl naphtho[1,2-*b*]furan-2-carboxylate **399**, in 54% yield. No mechanistic details have been given.



398 **399**

Scheme 2.53 *Synthesis of ethyl naphtho[1,2-b]furan-2-carboxylate. (i) K_2CO_3, MIBK, reflux.*

The ^{1}H NMR spectrum of compound **394** is shown in Figure 2.13, where the absence of the protons corresponding to the pyrrolidine group is evident. The five aromatic protons are in the region 7.70-7.27 ppm. The singlet signal at 7.53 ppm which can be singled out easily from the rest of the multiplets of aromatic protons corresponds to H-3 of benzofuran **394**. The ethyl ester protons are found at the expected chemical shifts with the usual characteristic coupling. Further evidence supporting this structure is from the peak at m/z = 191 in the ESI mass spectrum which corresponds to $[M + H]^+$.

[143] Arrault, A.; Merour, J.-Y.; Leger, J.-M.; Jarry, C.; Guillaumet, G. *Helv. Chim. Acta* **2001**, *84*, 2198-2211.

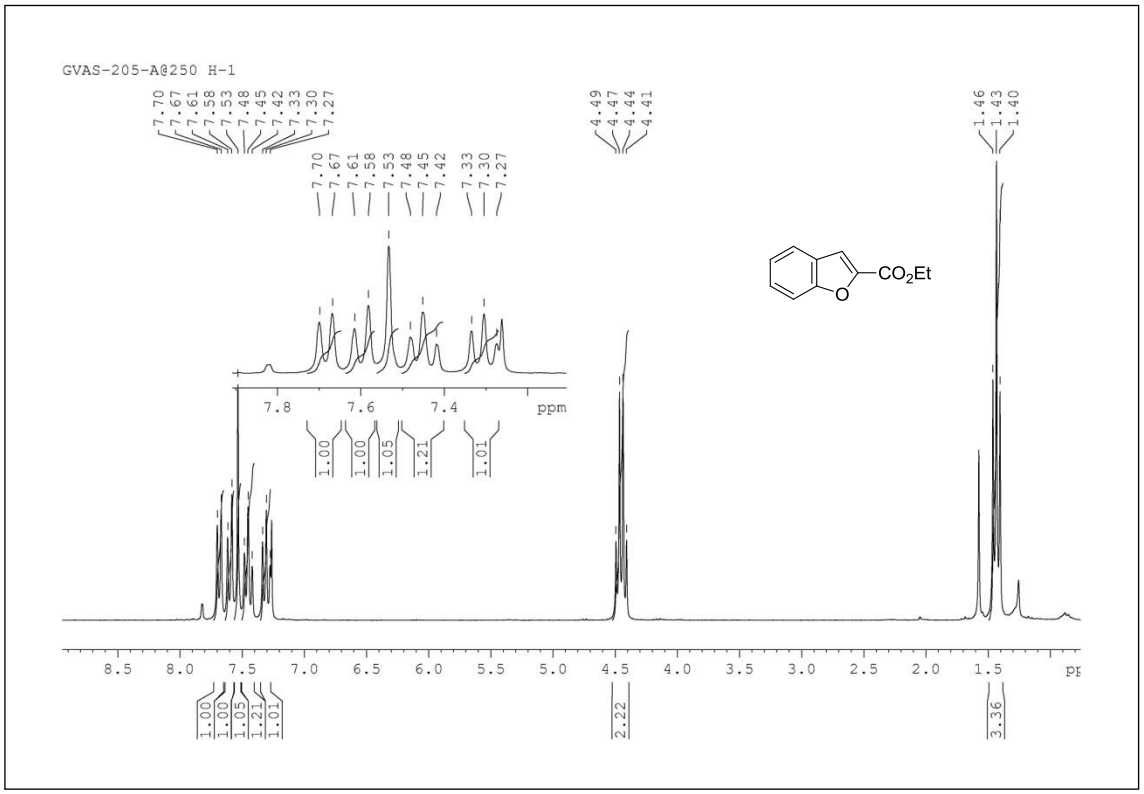
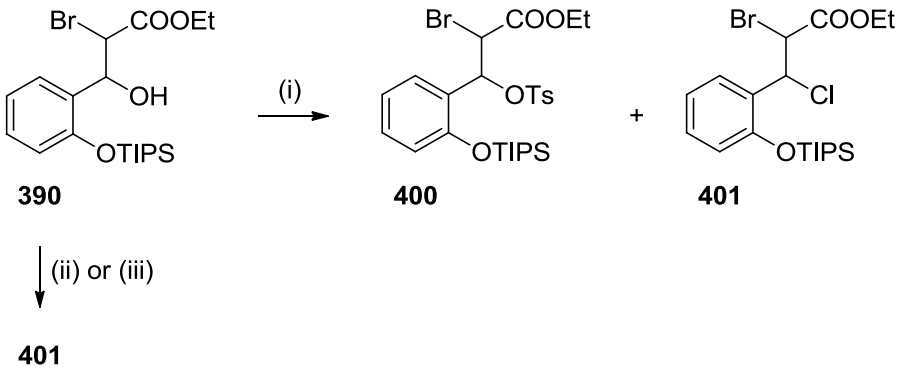


Figure 2.13 *^{1}H NMR (250 MHz, $CDCl_3$) spectrum of compound **394**.*

Since the acetoxy derivative **392** did not furnish 2,3-dihydro-1-benzofuran **393** (Scheme 2.52) as initially planned, an alternative leaving group was required in the place of the acetoxy group of **392**. Qi and co-workers[144] have reported the chlorination of alcohols to chloroalkanes via a tosylation reaction using tosyl chloride (TsCl) and triethylamine. In this reaction it was proposed that a tosyl ester intermediate is produced and that the chlorine ion from the formed triethylamine hydrochloride salt displaces the tosylate group to give the chloroalkane. Applying these reaction conditions to alcohol **390** produced tosyl ester **400** and the chloro derivative **401** in 29% and 30% yield, respectively. Because of the low yields of these two products we turned to the method reported by Kartika and co-workers[145] where it is reported that alcohols are converted to chloroalkanes using triphosgene and triethylamine in THF. In our case we treated bromohydrin **390** with triphosgene and diisopropylamine in the same solvent and obtained the chloro derivative

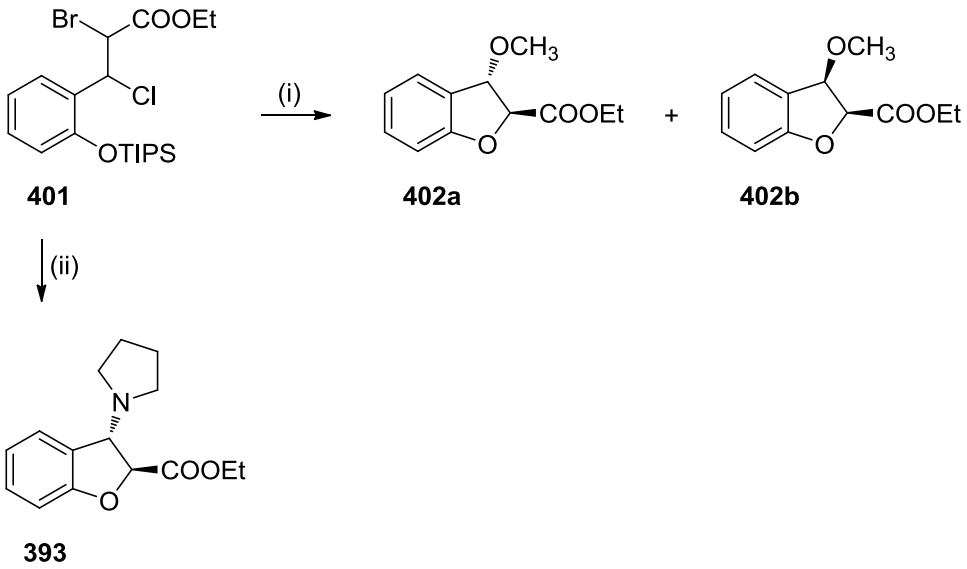
[144] Ding, R.; He, Y.; Wang, X.; Xu, J.; Chen, Y.; Feng, M.; Qi, C. *Molecules* **2011**, *16*, 5665-5673.
[145] Ayala, C. E.; Villalpando, A.; Nguyen, A. L.; McCandless,G. T.; Kartika, R. *Org. Lett.* **2012**, *14*, 3676-3679.

401, in 60% yield. The yield of **401** was pushed up to 90% when chlorination of the hydroxyl group of **390** took place in neat thionyl chloride at 65 ^{o}C.



Scheme 2.54 *Synthesis of ethyl 2-bromo-3-(2-{[tert-butyl(dimethyl)silyl]oxy}phenyl)-3-chloropropanoate. (i) tosyl chloride, NEt_3, DMAP, THF, (ii) triphosgene, $(i\text{-}Pr)_2NH$, THF, (iii) thionyl chloride, 65 °C.*

The dihalo substituted ester **401** was then subjected to the TBAF catalyzed generation of the *o*-quinone methide which was performed in methanol (Scheme 2.55). Two products were obtained the *anti* **402a** and *syn* **402b** stereoisomers of ethyl 3-methoxy-2,3-dihydro-1-benzofuran-2-carboxylate that were separated by column chromatography in 16% and 19% yield, respectively.



Scheme 2.55 *Synthesis of 2,3-dihydrobenzofuran. (i) methanol, TBAF, -78 °C, rt, (ii) pyrrolidine, THF, TBAF, -78 °C, rt.*

The ^{1}H NMR spectrum of compound **402a** is shown in Figure 2.14. The multiplet signal at 7.27-6.89 ppm corresponds to the four aromatic protons. The signals that appear as pair of doublets at 5.12 ppm and 5.08 ppm are derived from H-2 and H-3 and have a coupling constant of 5.0 Hz indicating their *anti* orientation. The presence of anti orientation is confirmed by comparing the coupling constants with the similar compounds reported by Zhou and co-workers[104] The signal at 4.35 ppm is a quartet corresponding to the CH_2 from the ester group. The three protons of the methoxy group appear as a singlet at 3.37 ppm and the three protons of the methyl ester group appear as a triplet at 1.35 ppm, as expected.

In Figure 2.15 the ^{1}H NMR spectrum of compound **402b** is shown. The multiplet signal at 7.27-6.89 ppm corresponds to the four aromatic protons. The two doublets at 4.73 ppm and 4.47 ppm integrating for one proton each correspond to the vicinal protons, H-2 and H-3, with a coupling constant of 9.9 Hz indicating their *syn* orientation. The multiplet at 4.35-4.25 ppm corresponds to the ester CH_2 group that seems to arise from coupling with the CH_3 group (J = 7.5 Hz) followed by long-range coupling with one or more protons in the vicinity. The three protons of the methoxy group and the three protons of the methyl group of the ester are in the vicinity of the corresponding signalsof the *anti*-isomer **402a**. In the 2D NOESY spectrum of **402b** (Figure 2.16) the two protons H-2 and H-3 were found to couple with each other through space confirming their syn orientation. The spectrum did not show any long range coupling for the ester CH_2 group. We therefore cannot explain the origin of the multiplet at 4.35-4.25 ppm. In the ESI mass spectra of compounds **402a** and **402b**, run in methanol solution, the peaks at m/z = 223 correspond to $[M + H]^+$ confirming further the correctness of the structures derived from the ^{1}H NMR spectra.

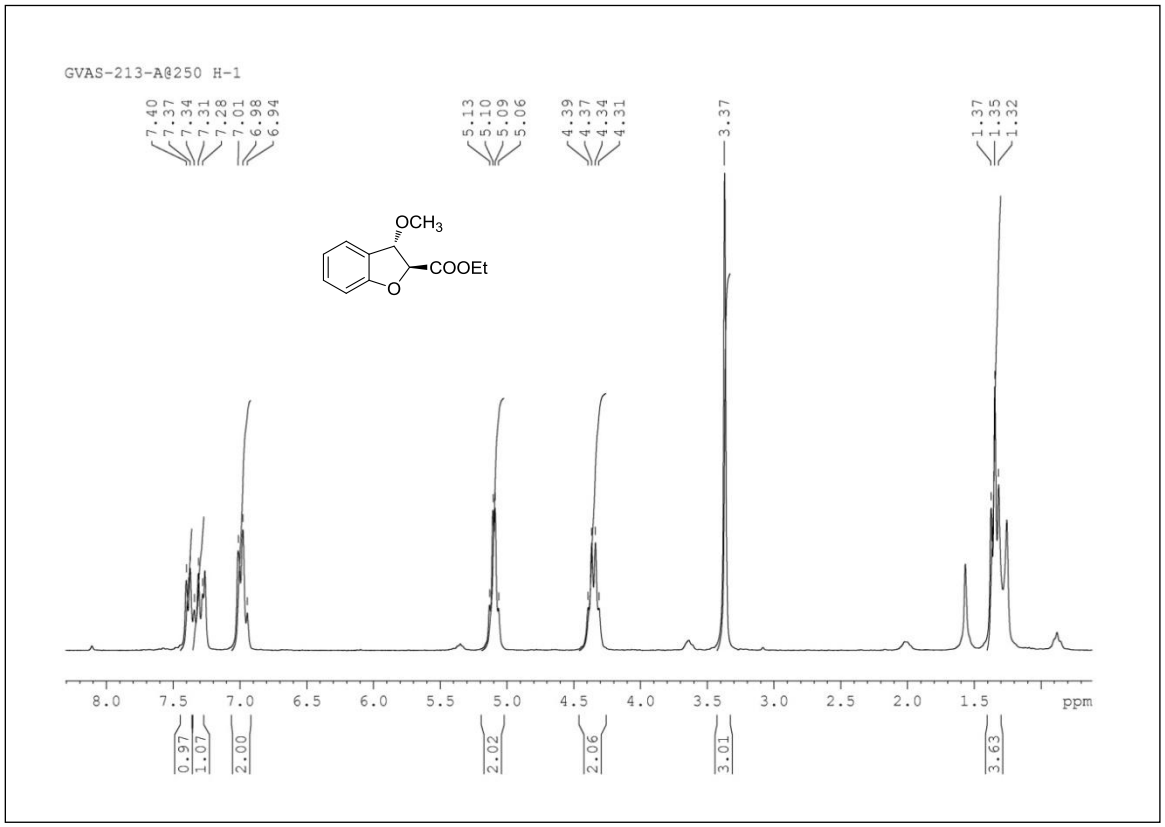


Figure 2.14 *^{1}H NMR (250 MHz, $CDCl_3$) spectrum of compound **402a**.*

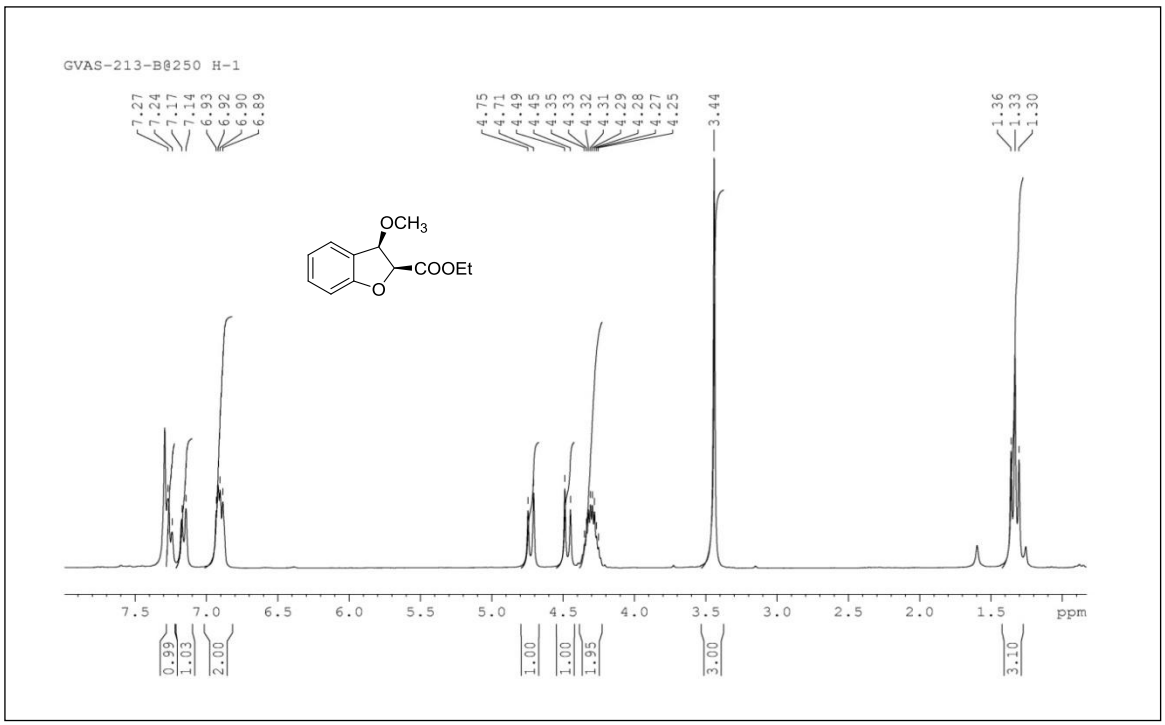


Figure 2.15 *^{1}H NMR (250 MHz, $CDCl_3$) spectrum of compound **402b**.*

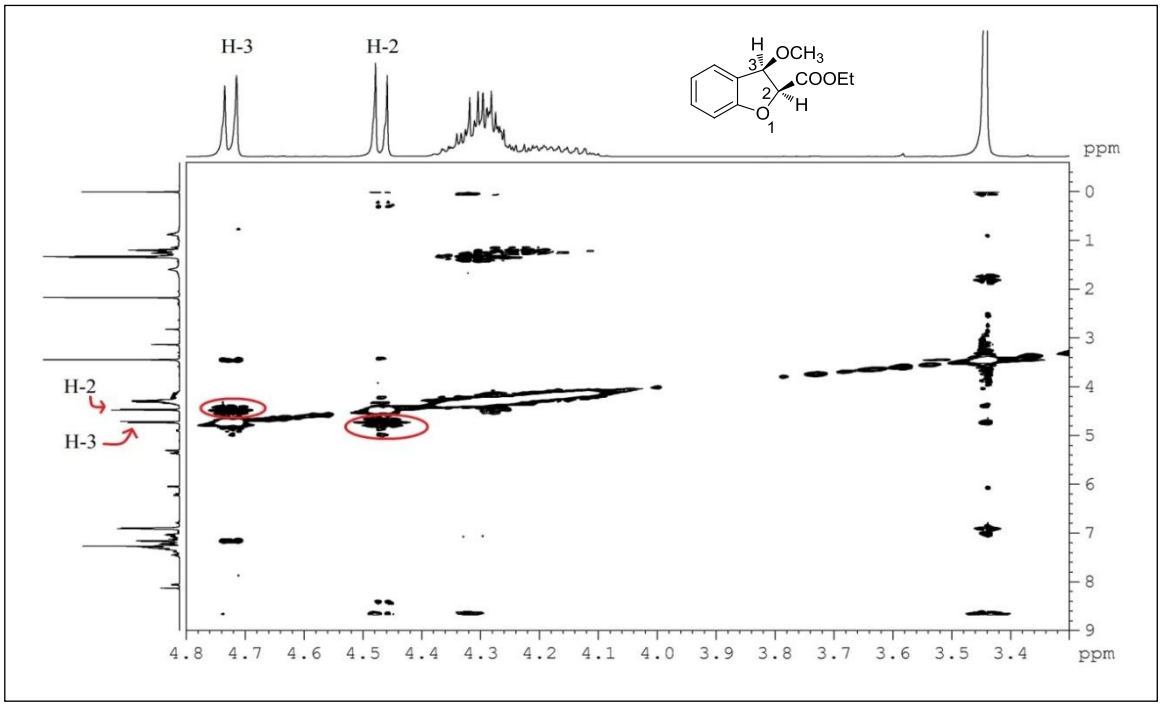
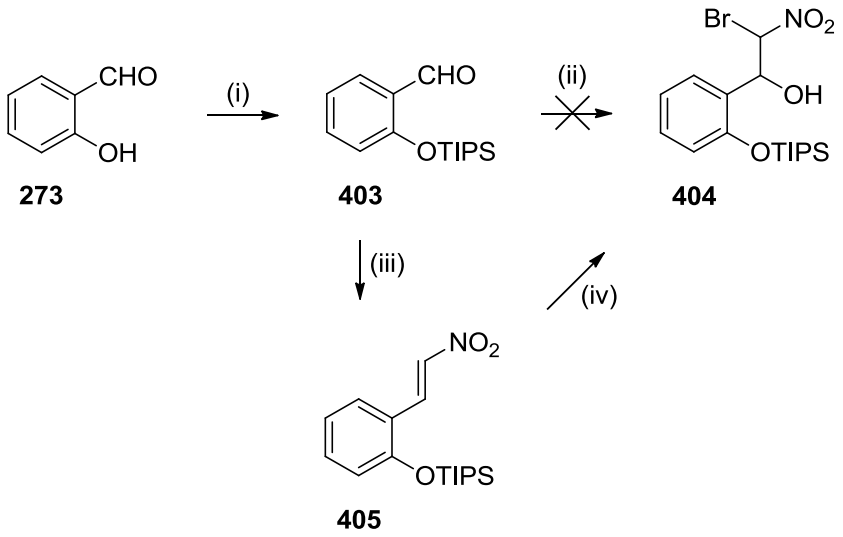


Figure 2.16 2D NOESY *(500 MHz, $CDCl_3$) spectrum of compound **402b***

The reaction of ester **401** with TBAF and pyrrolidine in THF produced the *anti* ethyl 3-pyrrolidin-1-yl-2,3-dihydro-1-benzofuran-2-carboxylate **393** stereoisomer, after purification by column chromatography. The characteristic feature in the ^{1}H NMR spectrum of this compound is the pair of doublets at 5.11 ppm and 6.66 ppm derived from H-2 and H-3 that have a coupling constant of 2.9 Hz, indicating their *anti* orientation. The rest of the signals of spectrum agree also with structure **393**. Further confirmation was derived from ESI HRMS mass spectrometry, run in methanol, from the peak at m/z 262.1437 that corresponds to $[M + H]^+$. Similar treatment of ester **392** with TBAF in THF in the presence of other nucleophiles such as thiophenol, 2-propanol or phenol and examination of their reaction mixtures with TLC, revealed several spots with ΔR_f values $\leq$ 0.1. ESI mass spectrometry of each reaction mixture, after crude purification by column chromatography, did not reveal any peaks in the mass spectrum whose m/z value corresponded to the ethyl 3-substituted-1-yl-2,3-dihydro-1-benzofuran-2-carboxylates or any other compounds derived from these products.

2.4.5. Preparation 2-bromo-2-nitro-1-{2-[(triisopropylsilyl)oxy]phenyl}ethanol and 2-(1-hydroxyethyl)phenol

The limited applicability of this reaction urged us to seek different precursors to *o*-quinone methides such as compound **404** (Scheme 2.56) and compounds **407** and **409** (Scheme 2.57). The main difference of these compounds compared to compound **401** (Scheme 2.55) is that the ester group in compound **401** has been replaced by either nitro or cyano groups. The preparation of nitro bromohydrin **404** took place by using the method reported by Concellon and co-workers.[146] Salicylaldehyde **273** is first protected at the hydroxyl group by TIPSCl to give aldehyde **403** which is then treated with bromonitromethane and a catalytic amount of sodium iodide but these reaction conditions turned out to be unsuitable since aldehyde **403** remained unchanged even after 48 hours of reflux. Following the method reported by Yao and Liu[147] that is heating aldehyde **403** with ammonium acetate and excess of nitromethane yielded alkene **405**, in 35%. This alkene was then subjected to the reaction conditions used to prepare bromohydrin **390** (Scheme 2.50) that is using *N*-bromosuccinimide in a THF-water solvent system, to afford

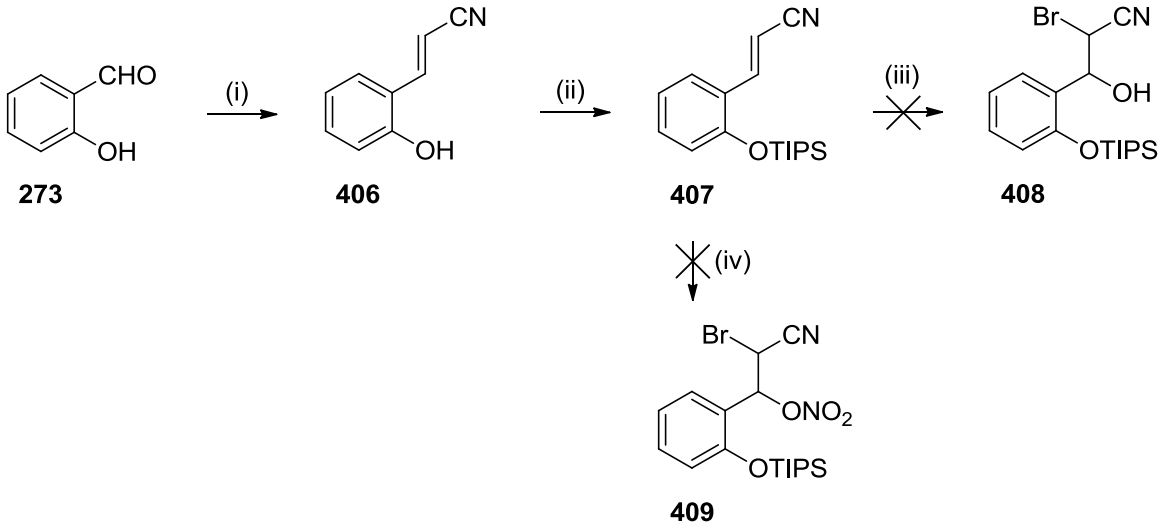


Scheme 2.56 *Synthesis of 2-bromo-2-nitro-1-{2-[(triisopropylsilyl)oxy]phenyl}ethanol. (i) TIPSCl, (i-Pr)$_2$NH, DMAP, CH_2Cl_2, (ii) bromonitromethane, NaI, THF, reflux, (iii) nitromethane, ammonium acetate, 90 °C, (iv) NBS, THF-water (1:1).*

[146] Concellon, J. M.; Rodriguez-Solla, H.; Concellon, C.; Garcia-Granda, S.; Diaz, M. R. *Org. Lett.* **2006**, *8*, 5979-5982.
[147] Liu, J. -T.; Yao, C. -F. *Tetrahedron Lett.* **2001**, *42*, 6147-6150.

nitrobromohydrin **404**, in less than 10% yield.

The low yield of nitrobromohydrin **404** persuaded us to pursue the synthesis of nitrilebromohydrin **408**. The first step required condensation of salicylaldehyde **273** with ethyl cyanoacetate in the presence of triphenylphosphine, lithium hydroxide and lithium chloride in water under reflux for 25 minutes to afford acrylonitrile **406**, in 28% yield. Protection of the hydroxyl group of **406** with TIPSCl yielded alkene **407**, in 97% yield. Unfortunately, reaction of **407** with *N*-bromosuccinimide in a THF-water solvent system did not proceed. Furthermore, the nitrooxylation-bromination reaction of α,β-unsaturated alkenes with lithium bromide and cerium(IV) ammonium nitrate (CAN), reported by Nair and co-workers,[140] did not work on alkene **407**.



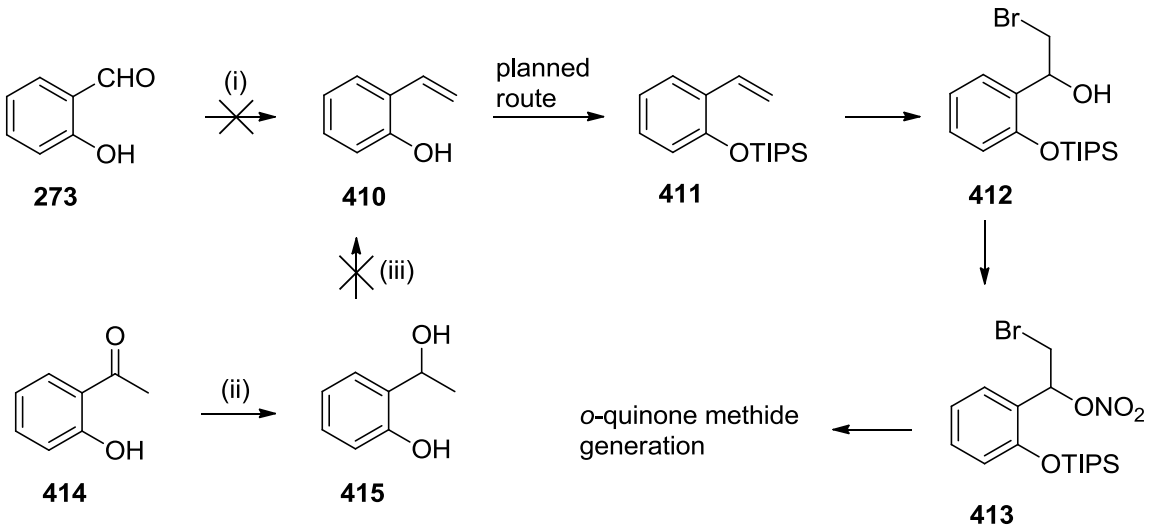
273 **406** **407** **408** **409**

Scheme 2.57 *Attempted synthesis of 2-bromo-3-hydroxy-3-(2-{[isobutyl(diisopropyl)silyl]oxy}phenyl-propanenitrile and its nitro ester derivative. (i) PPh_3, $NCCH_2CO_2Et$, LiOH, LiCl, water, reflux, 25 min., (ii) TIPSCl, diisopropylamine, DMAP, CH_2Cl_2, (iii) NBS, THF-water (1:1), (iv) LiBr, CAN, CH_3CN.*

Due to the difficulty in derivatising appropriately alkene **409** a new target was set to synthesise 2-vinylphenol **410** (Scheme 2.58) in order to follow the reaction sequence shown targeted at generating the *o*-quinone methide intermediate. The method of Manabe and co-workers[148] was applied wherein aldehydes are converted to alkenes by Wittig olefination using methyl(triphenyl)-phosphonium bromide in the presence of a strong base. The reaction however did not produce the required product **410**. Alternatively, 1-(2-

[148] Konishi, H.; Ueda, T.; Muto, T.; Manabe, K. *Org. Lett.* **2012**, *14*, 4722-4725.

hydroxy-phenyl)ethanone **412** was reduced with sodium borohydride to give 2-(1-hydroxyethyl)-phenol **415**in 60% yield but attempted copper sulphate catalyzed dehydration of **415**, using the methodology of Nishiguchi,[149] produced excessive polymerisation.



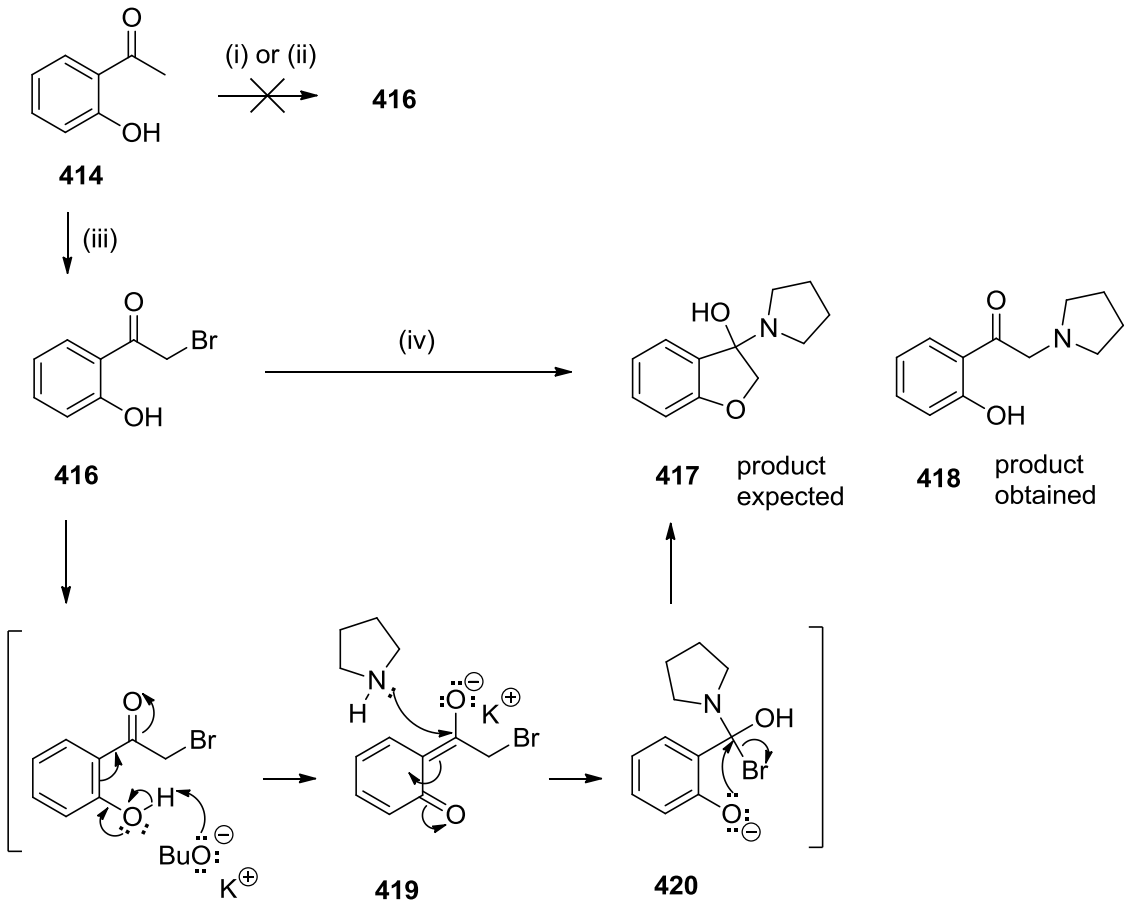
Scheme 2.58 *Attempted synthesis of 2-vinylphenol. (i) CH_3PPh_3Br, t-BuOK, THF, (ii) $NaBH_4$, methanol, (iii) $CuSO_4$ over SiO_2, CCl_4.*

2.4.6. Attempted synthesis of 3-pyrrolidin-1-yl-2,3-dihydro-1-benzofuran-3-ol from 2-bromo-1-(2-hydroxyphenyl)ethanone

The continued failure to synthesise an appropriate *o*-quinone methide precursor that would lead to 3-substituted 2,3-dihydro-1-benzofurans was the reason that we speculated on synthesising a different type of precursor. The idea was to synthesise a new precursor such as **416** (Scheme 2.59) which incorporates a new feature, the carbonyl group. The initial thought was that an appropriate base would abstract the phenolic hydrogen atom of **416** and the resulting phenoxide ion would then delocalise into the aromatic ring and give resonance form **419**, actually an *o*-quinone methide. The latter would then undergo Michael addition by a nucleophile to yield phenoxide addition product **420** which after cyclisation by intramolecular displacement of bromine ion could give 2,3-dihydro-1-

[149] Nishiguchi, T.; Machida,N.; Yamamoto, E. *Tetrahedron Lett.* **1987**, *28*, 4565-4568.

benzofuran-3-ol **417**. Direct preparation of **416** from 1-(2-hydroxyphenyl)ethanone **414** by reaction with sodium bromide and oxone[150] failed and so did reaction of **414** with *N*-bromosuccinimide and ammonium acetate. This reaction however did work when **414** was brominated by refluxing with copper bromide in chloroform[151] to afford **416**, in 65% yield. The carbonyl oxygen of **416** was expected to participate in the conjugation with the aromatic ring and the hydroxyl group, as explained above. However, using potassium *tert*-butoxide as base for generating the *o*-quinone methide did not give the expected 2,3-dihydro-1-benzofuran-3-ol **417** but instead nucleophilic substitution of the bromine atom by pyrrolidine occurred to give 1-(2-hydroxyphenyl)-2-pyrrolidin-1-ylethanone **418**, in 57% yield.

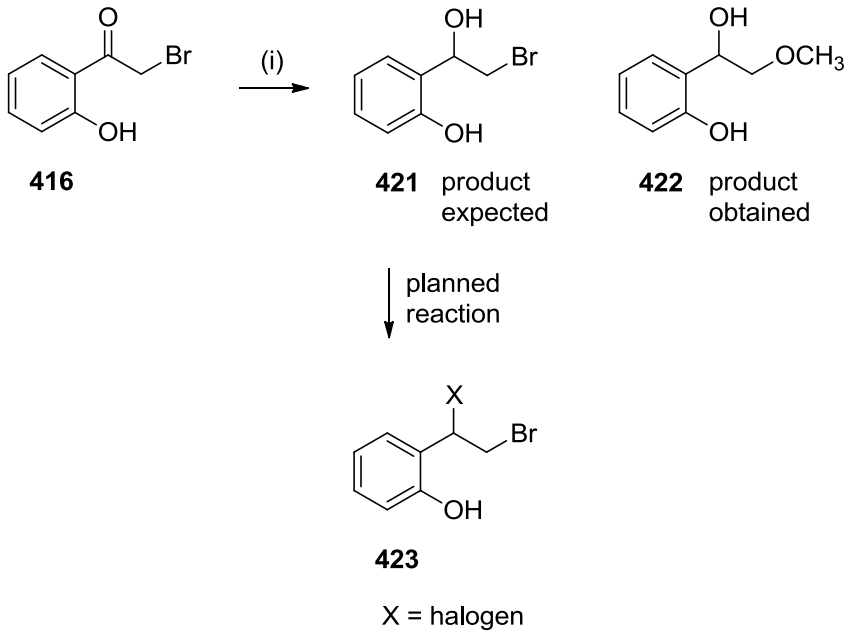


Scheme 2.59 *Attempted synthesis of 3-pyrrolidin-1-yl-2,3-dihydro-1-benzofuran-3-ol. (i) NaBr, oxone, methanol-water, (ii) NBS, NH_4Ac, CCl_4, (iii) $CuBr_2$, $CHCl_3$, reflux, (iv) t-BuOK, CH_2Cl_2.*

[150] Kim, E. -H.; Koo, B. -S.; Song, C. -E.; Lee, K. -J. *Syn. Comm.* **2001**, *31*, 3627-3632.
[151] Black, D. StC.; Kumar, N.; McConnell, D. B. *Tetrahedron* **2001**, *57*, 2203-2211.

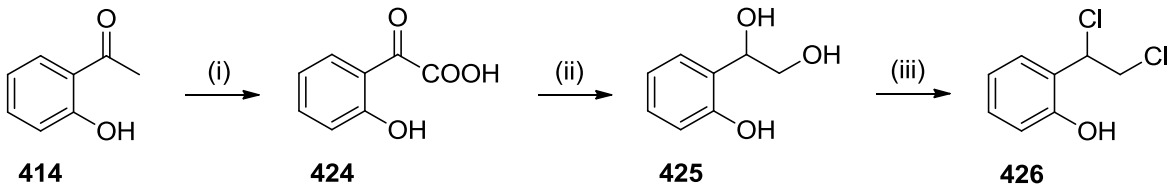
2.4.7. Synthesis of 3-substituted 2,3-dihydrobenzofurans from [2-(2-bromo-1-chloro ethyl)phenoxy](triisopropyl)silane and 2-bromo-1-{2-[(triisopropylsilyl)oxy]phenyl} ethyl nitrate

Having failed to synthesise **417** (Scheme 2.59) we thought of reducing the keto group of compound **416** to a hydroxyl group in order to convert the hydroxyl group to a good leaving group such as halogen. We treated ketone **416** with sodium borohydride in methanol but the expected bromoalcohol **421** was not obtained instead the reaction proceeded further by the displacement of bromine by a methoxy group to afford ether **422**, in 43% yield.



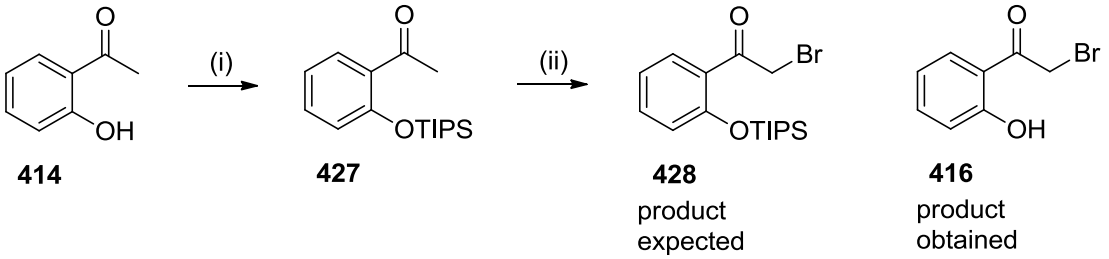
Scheme 2.60 *Attempted synthesis of 2-(1-hydroxy-2-methoxyethyl)phenol. (i) $NaBH_4$, methanol.*

Another approach to introduce a second halogen atom in compound **416** was to start again from 1-(2-hydroxyphenyl)ethanone **414** (Scheme 2.61) but this time in the next step to oxidise this compound to the corresponding carboxylic acid **424**. The oxidation of **414** proceeded smoothly with selenium dioxide in a mixture of dioxane and water under reflux to afford **424**, in 55%. In the second step keto acid **424** was reduced to the trihydroxy compound **425**, in 50% yield, using a strong reducing reagent such as lithium aluminium hydride in tetrahydrofuran. In the third step the dichloro compound **426** was prepared, in less than 10% yield, by heating under reflux **425** in thionyl chloride.



Scheme 2.61 *Preparation of 2-(1,2-dichloroethyl)phenol from 1-(2-hydroxyphenyl)ethanone. (i) SeO_2, dioxane-water (10:2), reflux, (ii) $LiAlH_4$, THF, (iii) $SOCl_2$, reflux.*

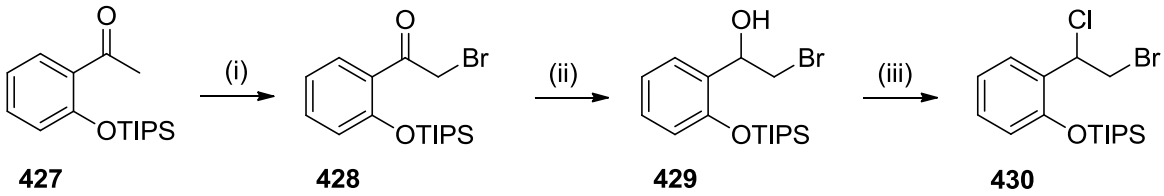
The low yield of dichloro derivative **426** might be due to the presence of free phenolic hydroxy group taking part in the reaction as a nucleophile. Returning to the philosophy of the synthetic approach of Scheme 2.60, the ability to brominate the acetyl group of silyl protected **427** (Scheme 2.62) was tested. Compound **427** was synthesised in 94% yield from **414** with triisopropylsilyl chloride, using standard conditions mentioned above, but bromination with copper bromide was found to give the deprotected bromo compound **416**, instead.



Scheme 2.62 *Attempted preparation of 2-bromo-1-{2-[(triisopropylsilyl)oxy]phenyl}ethanone. (i) TIPSCl, diisopropylamine, DMAP, CH_2Cl_2 (ii) $CuBr_2$, $CHCl_3$.*

In a second attempt, bromination of **427** (Scheme 2.63) was achieved by a solvent free reaction, as reported by Stavber and co-workers,[152] where *N*-bromosuccinimide and catalytic amount of *p*-toluene sulfonic acid were triturated with the ketone for about 3 hours to afford **428**, in 65% yield. In the second step of this reaction sequence, bromoketone **428** was reduced by sodium borohydride in tetrahydrofuran to afford alcohol **429**, in 59% yield. In the last step of this successful synthetic route, the hydroxy group of **429** was converted to a chloro atom by heating in thionyl chloride and this time the dihalo derivative **430** was isolated in 84% yield.

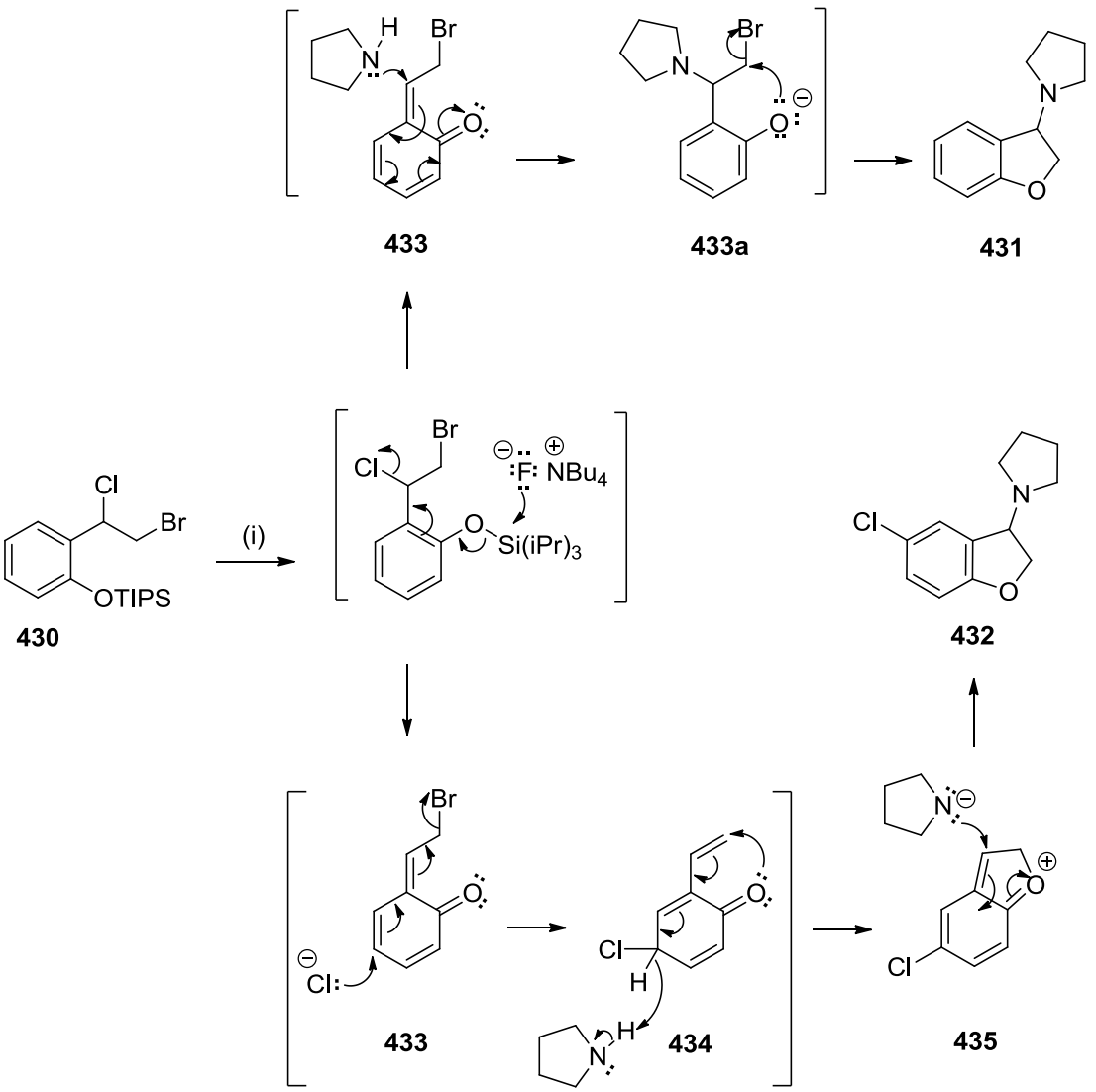
[152] Pravst, I.; Zupan, M.; Stavber, S. *Tetrahedron* **2008**, *64*, 5191-5199.



427 **428** **429** **430**

Scheme 2.63 *Preparation of [2-(2-bromo-1-chloroethyl)phenoxy](triisopropyl)silane. (i) NBS, PTSA, (ii) $NaBH_4$, THF, reflux (iii) $SOCl_2$, reflux.*

In the final step of this reaction sequence, ether **430** was subjected to our established method of *o*-quinone methide generation using TBAF in THF at -78 °C while pyrrolidine was present (Scheme 2.64). To our surprise, this reaction instead of giving solely 3-pyrrolidin-1-yl-2,3-dihydro-1-benzofuran **431**, a second product, 1-(5-chloro-2,3-dihydro-1-benzofuran-3-yl)pyrrolidine **432**, was isolated too. In the first experiment at -78 °C **431** and **432** were isolated by column chromatography in 5% and 2% yield, respectively. When the reaction was repeated at 0 °C followed by stirring the reaction mixture at room temperature for 1 hour, the two products **431** and **432** were isolated by column chromatography in 10% and 5% yield, respectively.



Scheme 2.64 *Preparation of 3-pyrrolidin-1-yl-2,3-dihydro-1-benzofuran via an o-quinone methide intermediate. (i) TBAF, pyrrolidine, THF.*

The proposed mechanism depicted in Scheme 2.64 involves the generation of *o*-quinone methide **433** *in situ* which follows two pathways. Transient species **433** undergoes Michael addition by pyrrolidine to give the intermediate phenoxide ion **433a** followed by intramolecular elimination of bromide ion by the phenoxide oxygen atom to afford benzofuran **431**. Alternatively **433** is nucleophilically attacked by chloride ion at the *para* position with respect to the carbonyl group that leads, due to the conjugation present between the π-electrons in the ring and the methylene of the *o*-quinone methide, to elimination of bromide ion and gives intermediate 4-chloro-2-vinylcyclohexa-2,5-dien-1-one **434**. This reaction can also be regarded as a *tele*-nucleophilic substitution by a similar

mechanism given for the loss of bromine ion of α-(benzotriazol-l-yl)alkyl aryl ketone as described by Katritzky and co-workers.[153] It is quite possible that **434** intramolecularly cyclises and in the process eliminates a hydride ion which abstracts the acidic proton of a pyrrolidine molecule to give highly electrophilic 5-chloro-2*H*-1-benzofuranium ion **435**. Benzofuran-1-ium ions have been reported as stable salts by Yamaguchi and Yamamoto as well as Tamm and co-workers.[154,155] The benzene ring of **435** acquires its aromatic character after pyrrolidine anion adds to position 3 of this intermediate species to afford benzofuran **432**.

The ^{1}H NMR spectrum of compound **432** is given in Figure 2.17. In the aromatic region at 7.30-6.74 ppm there are only three aromatic protons indicating that one of the benzene carbon atoms is substituted. In aliphatic region the peaks at 4.62 ppm and 4.45 ppm correspond to the two H-3 protons and the H-2 proton of the dihydrobenzofuran, respectively. The signals at 2.68 ppm, 2.51 ppm and 1.77 ppm correspond to the pyrrolidine ring. In the in the ESI mass spectrum of compound **432**, run in methanol solution, the peak at m/z = 224 corresponds to $[M + H]^{+}$ confirming further the correctness of the structure derived from the ^{1}H NMR spectra. However, in order to eliminate any doubts about this structure since there is the possibility of pyrrolidine being the substituent instead a chlorine atom, HSQC and HMBC of spectra this compound were obtained as shown in Figures 2.18-2.19. From these two spectra it is confirmed, beyond doubt, that the product obtained is compound **432**.

[153] Katritzky, A. R.; Wu, H.; Xie, L. *Tetrahedron Lett.* **1997**, *38*, 903-906.
[154] Yamaguchi, T.; Yamamoto, Y. *Chem. Lett.* **2007**, *36*, 1438-1439.
[155] Tamm, M.; Bannenberg, T.; Dressel, B. *Inorg. Chem.* **2002**, *41*, 47-59.

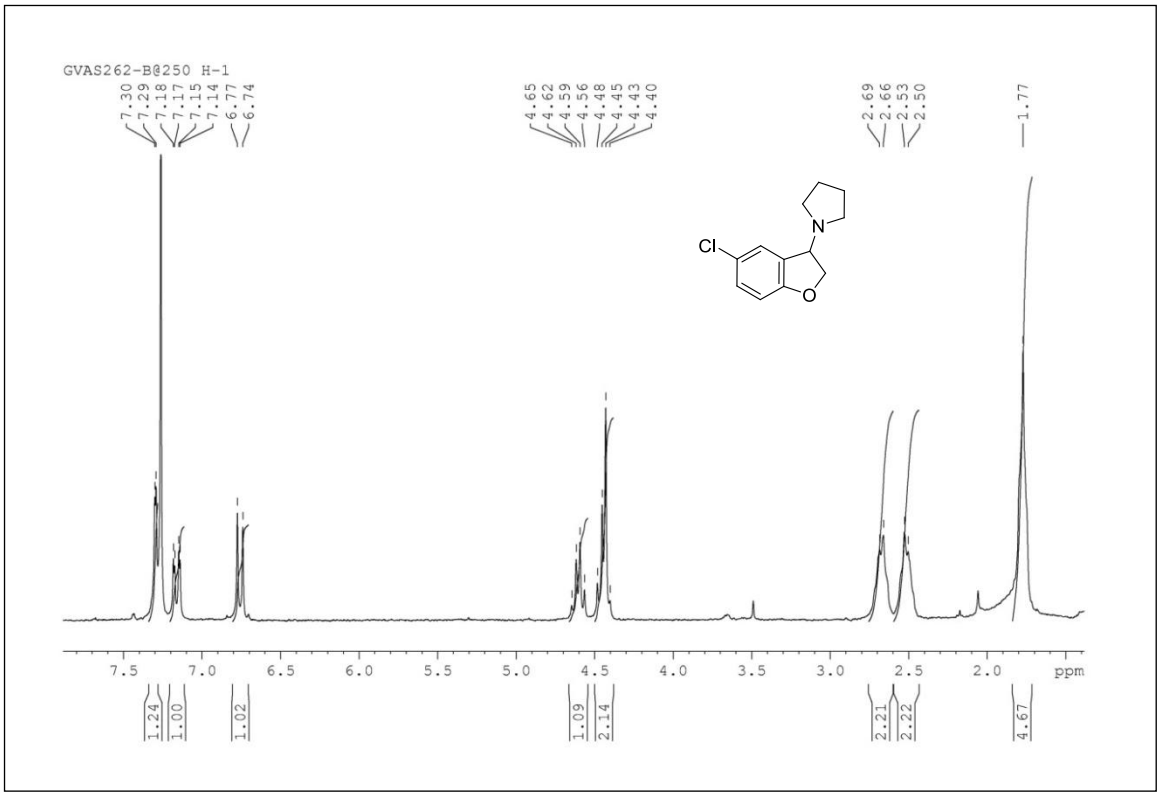


Figure 2.17 *^{1}H NMR (250 MHz, $CDCl_3$) spectrum of compound **432**.*

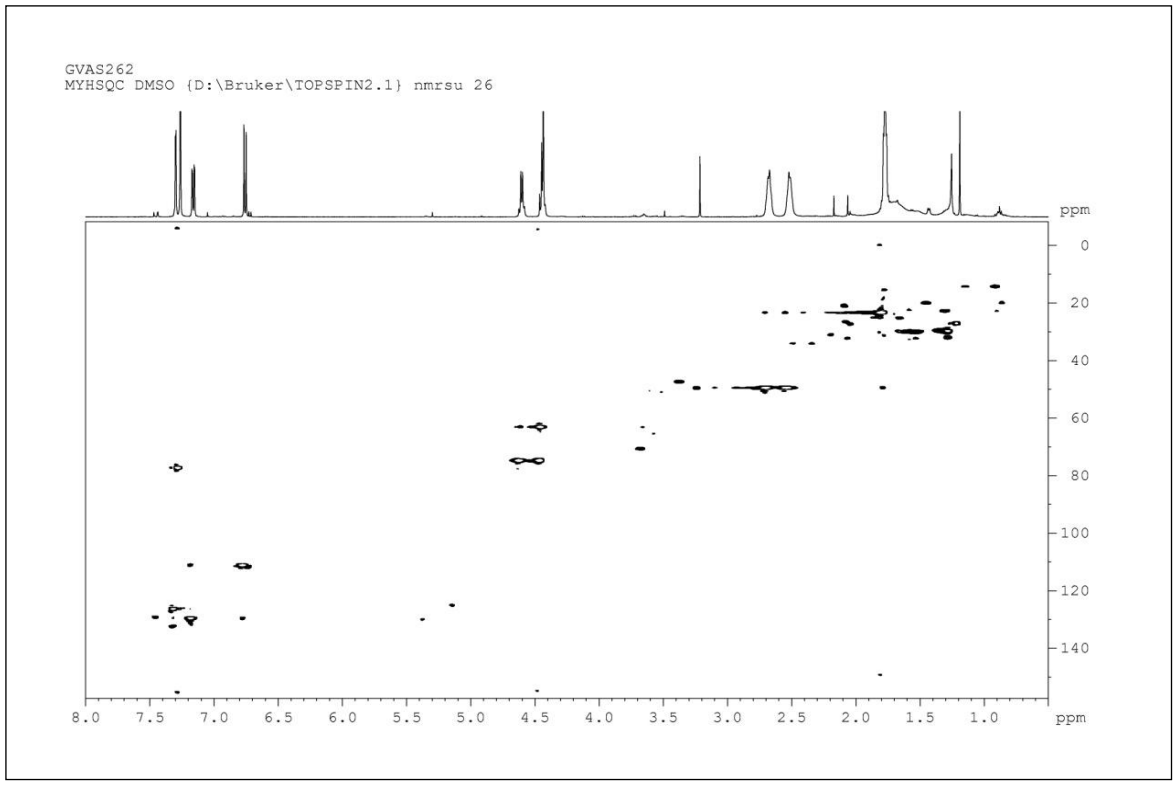


Figure 2.18 *HSQC (500 MHz, $CDCl_3$) spectrum of compound **432**.*

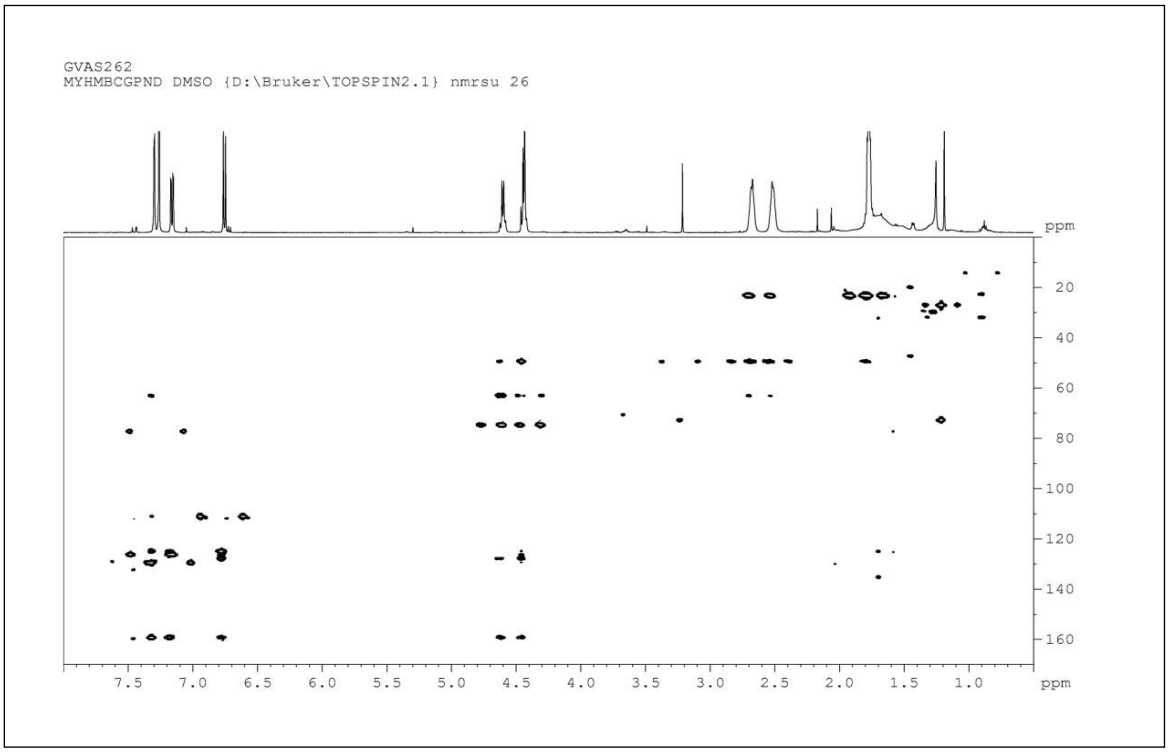
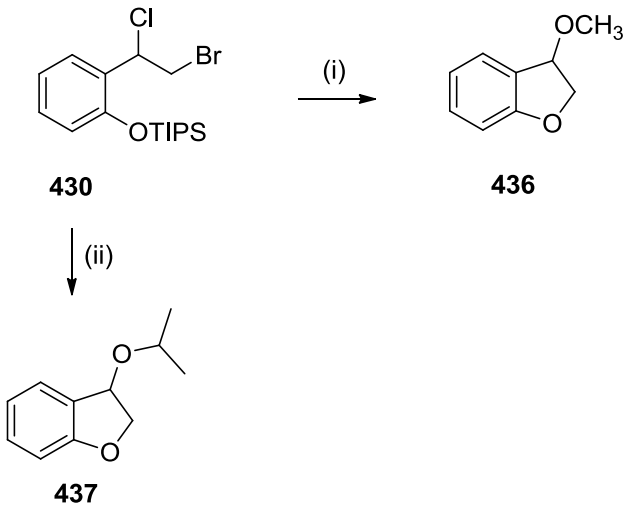


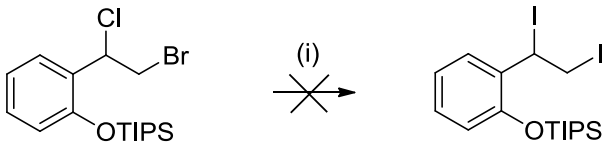
Figure 2.19 *HMBC (500 MHz, $CDCl_3$) spectrum of compound **432**.*

To see the applicability of this reaction with other nucleophiles, it was repeated using instead of pyrrolidine either methanol or 2-propanol to act both as solvent and nucleophile at 0 °C. Unfortunately the yields obtained for products **436** and **437** turned out to be very low *i.e.* 12% and 8%, respectively. Furthermore, to our surprise, no chlorination product was obtained in both of the reactions.



Scheme 2.65 *Preparation of 3-methoxy(or isopropoxy)-2,3-dihydrobenzofurans. (i) MeOH, TBAF, (ii) i-PrOH, TBAF.*

In order to increase the yield of the reactions leading to benzofurans **436** and **437**, a catalytic amount of sodium iodide was added to the reactions described above, with the hope that the Finkelstein reaction would work in favour of either or both of the elimination steps and give better yields of products. Unfortunately, after workup similar low yields of benzofurans **436** and **437** were obtained. Furthermore, the use of 1 equivalent of sodium iodide did not improve the situation. The replacement of the chlorine atom by an iodine atom in **430** by the Finkelstein reaction shown in Scheme 2.66 failed to work, even when compound **430** was boiled with 2 equivalents of sodium iodide in acetone.

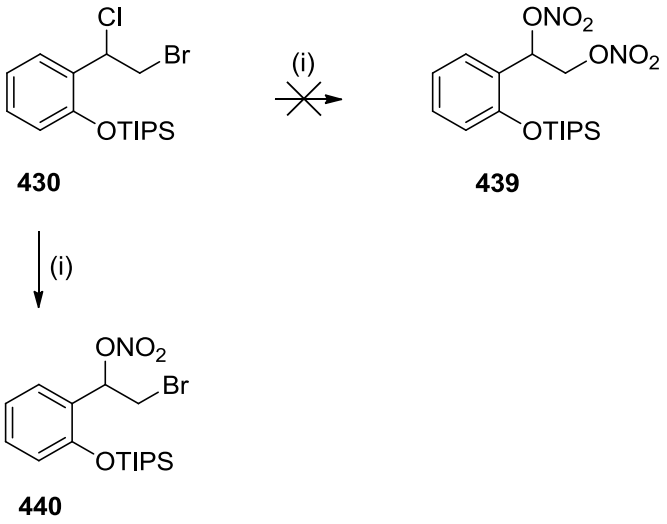


430 **438**

Scheme 2.66 *Attempted conversion of [2-(2-bromo-1-chloroethyl)phenoxy](triisopropyl)silane into [2-(1,2-di-iodoethyl)phenoxy](triisopropyl)silane. (i) NaI, acetone, reflux.*

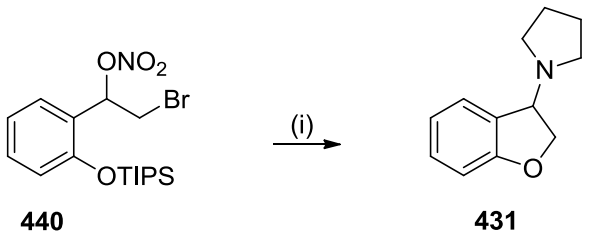
After the above mentioned failed attempts to synthesise diiodo derivative **438** which contains iodo atoms, potentially good leaving groups for both the generation of the *o*-quinone methide and the cyclisation following the Michael reaction, we decided to prepare the nitrate ester from the dihalo compound **430** using a method reported by Lehmann and co-workers.[156] Compound **430** was stirred overnight with 2 equivalents of silver nitrate in acetonitrile and to our pleasant surprise nitration occurred only at the benzylic carbon by displacement of the chloro atom to afford nitrate **440**, in 96% yield. This regioselective reaction has most probably occurred via an S_N1 mechanism whereby the benzylic carbocation has played a predominant role.

[156] Webler, C.; Homann, A.; Fricke, U.; Lehmann, J. *Eur. J. Med. Chem.* **2003**, *38*, 581-586.



Scheme 2.67 *Preparation of 2-bromo-1-{2-[(triisopropylsilyl)oxy]phenyl}ethyl nitrate. (i) $AgNO_3$, acetonitrile.*

The next step was preparation of 2,3-dihydrobenzofuran **431** by our established one-pot reaction sequence: generation of *o*-quinone methide *in situ*, Michael addition and intramolecular cyclization (Schemes 2.37 and 2.64). The reaction took place by dissolving compound **440** in THF, lowering the temperature to -78 °C and then adding slowly pyrrolidine followed by dropwise addition of TBAF at the same temperature. The crude material obtained after workup was purified by column chromatography using 20% ethyl acetate in hexane as eluent to afford **431** as colourless oil, in yield 82%. In comparison to the yield of 10% of **431** obtained from compound **440** (Scheme 2.64), the choice of starting material **440** is by far superior.



Scheme 2.68 *Preparation of 3-pyrrolidin-1-yl-2,3-dihydro-1-benzofuran via o-quinone methide. (i) TBAF, pyrrolidine, THF, -78 °C.*

The reaction was repeated using a variety of C, O, N and S nucleophiles and the results of these reactions is shown in Table 1.

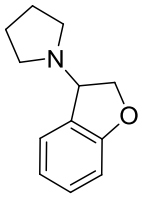
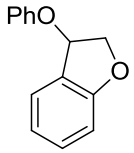
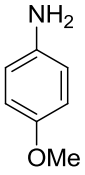
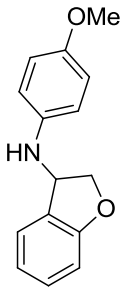
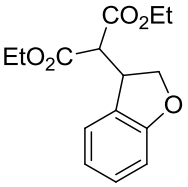
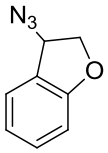
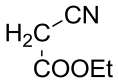
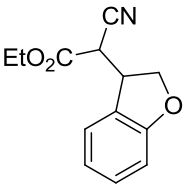
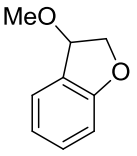
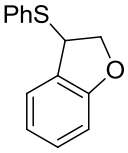
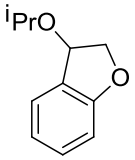
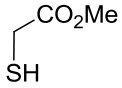
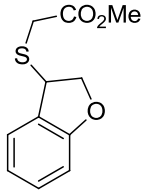
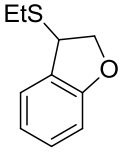
entry	RH	product	yield (%)	entry	RH	product	yield (%)
1		 **431**	82	6	PhOH	 **443**	59
2		 **441**	74	7	$CH_2(CO_2Et)_2$	 **444**	71
3	NaN_3	 **442**	79	8		 **445**	67
4	MeOH	 **436**	88	9	PhSH	 **446**	85
5	i-PrOH	 **437**	68	10		 **447**	80
				11	EtSH	 **448**	76

Table 2.2 *Synthesised 3-substituted 2,3-dihydro-1-benzofurans from 2-bromo-1-{2-[(triisopropylsilyl)oxy] phenyl}ethyl nitrate using C, O, N and S nucleophiles.*

Summary

- A novel method for *o*-quinone methide generation

In this research work we report a new method of generating *o*-quinone methide from 2-{[*tert*-butyl(dimethyl)-silyl]oxy}benzyl nitrate **270** and investigate the reactivity of an *o*-quinone methide generated *in situ*, with the nitrate ion as a leaving group. The method worked using fluoride ion as the trigger of the reaction and the *o*-quinone methide or *o*-naphthoquinone methide was trapped successfully by C, N, O and S nucleophiles via a Michael addition, to afford 2-substituted phenols **276a-m** or 1-substituted naphthols **294** and **295**. The *o*-quinone methide or *o*-naphthoquinone methide was also subjected to hetero-Diels-Alder reaction to obtain chromans **278**, **279**, **285**, **286**, **296** and **298**. This confirms the presence of *o*-quinone methide in the Michael reaction as well. From the yields obtained in the Diels-Alder reaction the stability and reactivity of substituted and unsubstituted *o*-quinone methide is compared and the substituted *o*-quinone methide is found to give better results.

- Application of this method to the synthesis of xyloketal H

Furthermore, we tried to apply this novel method of generating *o*-quinone methide to the synthesis of a recently reported natural product xyloketal H **303**. We prepared the *o*-quinone methide precursor 2-{[*tert*-butyl(dimethyl)silyl]oxy}-4,6-dimethoxybenzyl nitrate **299** which was then reacted with 3,5-dimethyl-2,3-dihydrofuran **300** in a Diels-Alder reaction in order to afford xyloketal H. Unfortunately the turnout of this reaction was only a polymer of *o*-quinone methide.

- A non-oxidative *in situ* generation *o*-naphthoquinone nitrosomethide

In previous reports *o*-naphthoquinone nitrosomethide was generated *in situ* using an oxidative method that gave variable results. In the present study the generation and trapping of this intermediate by a non-oxidative method was challenging. Although several attempts were undertaken to prepare the appropriate precursor for the generation of *o*-naphthoquinone nitrosomethide the outcome was disappointing.

When we tried the oxidative generation of *o*-naphthoquinone nitrosomethide intermediate from the oxime **114** using lead(IV) acetate as an oxidant and pyrrolidine as a nucleophile, to our surprise, three different products **346**, **347** and **348** in one reaction which was indirect proof of the presence of a *o*-naphthoquinone nitrosomethide intermediate.

- A novel method for the synthesis of 2,3-disubstituted or 3-substituted 2,3-dihydro-benzofurans via *o*-quinone methide generated *in situ*

In a simple approach we succeeded synthesising 2,3-disubstituted 2,3-dihydrobenzofurans in a one pot Michael addition followed by intramolecular cyclization step where the *in situ* generated *o*-quinone methides plays a major role. Two products were obtained from ethyl 2-bromo-3-(2-{[tert-butyl(dimethyl)silyl]oxy}phenyl)-3-chloropropan-oate **401**, *anti* **402a** and *syn* **402b**, stereoisomers of ethyl 3-methoxy-2,3-dihydro-1-benzofuran-2-carboxylate. On the other hand, the reaction of **401** with pyrrolidine gave only one stereoisomer, *anti* ethyl 3-pyrrolidin-1-yl-2,3-dihydro-1-benzofuran-2-carboxylate **393**.

By a similar approach starting from [2-(2-bromo-1-chloroethyl)phenoxy](triisopropyl) silane, 3-substituted 2,3-dihydrobenzofurans *i.e.* **431**, **436**, **437** and **441**-**448** were synthesized using C, N, O and S nucleophiles.

Conclusions

In conclusion, we have presented a new method of producing *o*-(naphtho)quinone methides from benzo and naphtho precursors bearing methylnitrate and tertbutyldimethylsilyloxy substituents at adjacent positions of the aromatic ring. The method of *o*-(naphtho)quinone methide generation involves fluoride anion nucleophilic cleavage of the silyloxy σ-bond by *n*-tetrabutylammonium fluoride followed by concomitant elimination of a nitrate anion. The intermediate *o*-(naphtho)quinone methides were trapped by nucleophiles and dienophiles showing the wide applicability of this method.

A new one-pot regioselective synthesis of 2,3-disubstituted 2,3-dihydrobenzofurans and 3-substituted 2,3-dihydrobenzofurans via *o*-quinone methide generated in situ and Michael addition of different C, N, O, and S nucleophiles to give a phenoxide anion intermediate which undergoes intramolecular 5-exo-tet elimination of a bromide anion. *o*-Quinone methide is formed from the dihalo substituted ester or the nitrate ester by a fluoride anion nucleophilic cleavage of the silyloxy σ-bond using n-tetrabutylammonium fluoride whereby the phenoxide anion intermediate undergoes conjugate elimination of a chloride anion or a nitrate anion.

The oxidative generation and trapping of *o*-naphthoquinone nitrosomethide intermediate is also presented.

3. General Experimental Procedures

Unless otherwise noted, reactions were carried out under argon atmosphere, in flame dried, three-neck, with magnetic stirring. Organic solutions were concentrated by rotary evaporation at 23–40 °C under 15 Torr. Melting points were taken on a Büchi 510 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ or DMSO-d_6 on a 250 or 400 MHz Brüker spectrometer. ^{1}H chemical shifts are reported in ppm from an internal standard TMS, residual chloroform (7.26 ppm) or DMSO-d_6 (2.50 ppm). ^{13}C NMR chemical shifts are reported in ppm from an internal standard TMS, residual chloroform (77.16 ppm) or DMSO-d_6 (39.43 ppm). High resolution ESI mass spectra were measured on a ThermoFisher Scientific Orbitrap XL system. Low resolution ESI spectra were measured with an Agilent 1100 LC-MS/MS spectrometer. IR spectra were acquired on a Perkin-Elmer GX FTIR spectrophotometer as liquids between sodium chloride discs or KBr discs and are reported in wave numbers (cm^{-1}). Elemental analyses were performed on a Carlo Erba 1106 elemental analyser. Analytical thin layer chromatography (TLC) was performed with TLC plates (Merck 70-230 mesh silica gel). TLC analysis was done under a 254 nm UV light source and generally by immersion in acidic aqueous-ethanolic vanillin solution, or in potassium permanganate ($KMnO_4$), followed by heating using a heat gun. Purification of reaction products was generally done by dry-column flash chromatography[157] using Merck silica gel 60 and/or flash chromatography[158] using Carlo Erba Reactifs-SDS silica gel 60.

Solvents, reagents and catalysts were used as received from the manufacturers (Aldrich, Acros, Fluka, and Alfa-Aesar) except for tetrahydrofuran, dichloromethane, ethanol, methanol, ethyl acetate, hexane and toluene that were purified and dried according to recommended procedures.[159,160]

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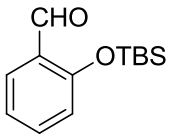
[157] Leonard, J.; Lygo, B.; Procter, G. Advanced Practical Organic Chemistry, Nelson Thornes Ltd. UK, 2001.
[158] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
[159] Furniss B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. Vogel's Textbook of Practical Organic Chemistry, 1996.
[160] Armarego, W. L. F.; Perrin, D. D. Purification of Laboratory Chemicals, 3. Aufl., Oxford Pergamon Press, 1988.

3.2. Experimental Procedures

2-{[*tert*-Butyl-(dimethyl)silyl]oxy}benzaldehyde 272



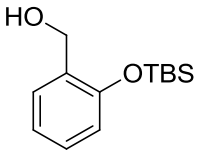
To a stirred solution of salicyaldehyde (690 mg, 10 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added DMAP (12 mg, 0.2 mmol), triethyl amine (1.1 g, 20 mmol) and *tert*-butyldimethylsilyl chloride (1.14 g, 12 mmol) in CH_2Cl_2 (5 mL) dropwise. The mixture was stirred at room temperature for 1 h. After TLC analysis had shown complete conversion of the starting material water (10 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 10 mL), the combined extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. Flash column chromatography (5% ethyl acetate in hexane) yielded **272** as colorless oil (1.15 g, 97%).

R_f = 0.54 (10% ethyl acetate in hexane). (Lit.[46])

^{1}H NMR (250 MHz, $CDCl_3$) δ: 10.47 (s, 1H), 7.83-7.80 (d, 1H, *J* = 7.8 Hz), 7.50-7.43 (t, 1H, *J* = 7.6 Hz), 7.07-7.0 (d, 1H, *J* = 7.5 Hz), 6.90-6.87 (t, 1H, *J* = 8.2 Hz), 1.03 (s, 9H) 0.28 (s, 6H).

ESI MS (m/z): 249.2 $[M+Na]^+$.

(2-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)methanol 271



To a stirred solution of $NaBH_4$ (200 mg, 12.5 mmol) in MeOH (10 mL) was added 2-{[*tert*-butyl-(dimethyl)silyl]oxy}benzaldehyde **272** (1.0 g, 10 mmol) in MeOH (10 mL). The mixture was stirred at room temperature for 6 h. MeOH was then removed and the resulting crude re-dissolved in EtOAc (30 mL) and washed with brine (10 mL). The organic layer was dried with sodium sulphate, filtered and the solvent was removed in

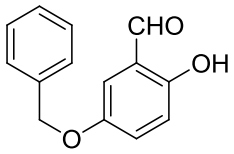
vacuo. The residue was purified by dry-column flash chromatography (5 % ethyl acetate in hexane) gave **271** (960 mg, 96%) as a colourless oil.

R_f = 0.27 (10% ethyl acetate in hexane). (Lit.[46])

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.32-7.29 (d, 1H, *J* = 7.4 Hz), 7.21-7.14 (t, 1H, *J* = 7.8 Hz), 6.98-6.92 (t, 1H, *J* = 7.5 Hz), 6.83-6.80 (d, 1H, *J* = 8.0 Hz), 4.69-4.67 (d, 1H, *J* = 5.4 Hz), 2.10-2.05 (t 1H, *J* = 5.8 Hz), 1.02 (s, 9H), 0.26 (s, 6H).

ESI MS (m/z): 239.1 $[M+H]^+$.

5-(Benzyloxy)-2-hydroxybenzaldehyde 281



To a stirred solution of 2,5-dihydroxybenzaldehyde (1.38 g, 10 mmol) in acetonitrile (15 mL) was added sodium bicarbonate (950 mg, 11.4 mmol), benzyl bromide (1.88 g, 11 mmol) and potassium iodide (166 mg, 1.0 mmol), and the mixture was stirred at 60 °C for 24 h. After TLC analysis had shown complete conversion of the starting material the solvent was removed in vacuo, 1N HCl (20 mL) was added to the residue, the mixture was extracted with EtOAc (3 × 10 mL), the combined extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. Flash column chromatography (10% ethyl acetate in hexane) yielded **281** as yellow solid (700 mg, 30%).

R_f = 0.35 (20% ethyl acetate in hexane).

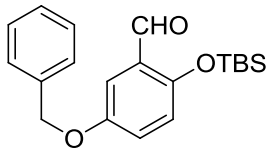
m.p. 93-95 °C (Lit.[161])

^{1}H NMR (250 MHz, $CDCl_3$) δ: 10.66 (s, 1H), 9.83 (s, 1H), 7.42-7.34 (m, 5H), 7.25-7.20 (dd, 1H, *J* = 3.0 Hz, 6.0 Hz), 7.08-7.07 (d, 1H, *J* = 3.0 Hz), 6.96-6.92 (d, 1H, *J* = 9.0 Hz), 5.07 (s, 2H).

ESI MS (m/z): 228.9 $[M+H]^+$.

[161] Haraldsson, G. G.; Baldwin, J. E. *Tetrahedron* **1997**, *53*, 215-224.

5-(Benzyloxy)-2-{[*tert*-butyl(dimethyl)silyl]oxy}benzaldehyde 282



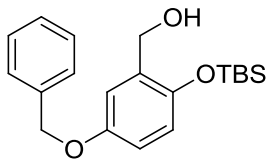
To a stirred solution of 5-(benzyloxy)-2-hydroxybenzaldehyde **281** (350 mg, 10 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added DMAP (3 mg, 0.2 mmol), triethyl amine (380 mg, 20 mmol) and *tert*-butyldimethylsilyl chloride (308 mg, 13 mmol) in CH_2Cl_2 (5 mL) dropwise. The mixture was stirred at room temperature for 1 h. After TLC analysis had shown complete conversion of the starting material water (10 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 10 mL), the combined extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. Flash column chromatography (20% ethyl acetate in hexane) yielded **282** as colorless oil becomes sticky solid on standing (430 mg, 82%).

R_f = 0.33 (40% ethyl acetate in hexane). (Lit.[46])

^{1}H NMR (250 MHz, $CDCl_3$) δ: 10.41 (s, 1H), 7.42-7.33 (m, 6H), 7.16-7.11 (dd, 1H, *J* = 3.1 Hz, 5.7 Hz), 6.85-6.81 (d, 1H, *J* = 8.9 Hz), 5.04 (s, 2H), 1.02 (s, 9H), 0.25 (s, 6H).

ESI MS (m/z): 365.7 $[M+Na]^+$.

(5-(Benzyloxy)-2-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)methanol 283



To a stirred solution of $NaBH_4$ (58 mg, 12.5 mmol) in MeOH (10 mL) was added 5-(benzyloxy)-2-{[*tert*-butyl(dimethyl)silyl]oxy}benzaldehyde **282** (425 mg, 10 mmol) in MeOH (10 mL). The mixture was stirred at room temperature for 12 h. MeOH was then removed and the resulting crude re-dissolved in EtOAc (30 mL) and washed with brine (10 mL). The organic layer was dried with sodium sulphate, filtered and the solvent was

removed in vacuo. The residue was purified by dry-column flash chromatography (10 % ethyl acetate in hexane) gave **283** (360 mg, 85%) as a colourless oil.

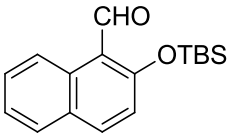
R_f = 0.38 (20% ethyl acetate in hexane). (Lit.[46])

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.44-7.31 (m, 5H), 6.98-6.97 (d, 1H, *J* = 2.4 Hz), 6.80-6.70 (m, 2H), 5.02 (s, 2H), 4.64 (s, 2H), 1.01 (s, 9H), 0.23 (s, 6H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 154.18, 148.25, 138.19, 133.19, 129.48, 128.82, 128.41, 119.97, 116.08, 115.46, 71.53, 62.94, 26.69, 19.08.

ESI MS (m/z): 345.5 $[M+H]^+$.

2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-naphthaldehyde 291



To a stirred solution of 2-hydroxy-1-naphthaldehyde (500 mg, 10 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added DMAP (7 mg, 0.2 mmol), triethyl amine (351 mg, 20 mmol) and *tert*-butyldimethylsilyl chloride (481 g, 12 mmol) in CH_2Cl_2 (5 mL) dropwise. The mixture was stirred at room temperature for 1 h. After TLC analysis had shown complete conversion of the starting material water (10 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 10 mL), the combined extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. Flash column chromatography (5% ethyl acetate in hexane) yielded **291** as colorless oil (800 mg, 96%).

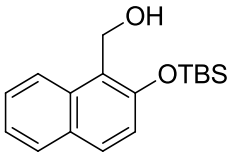
R_f = 0.41 (10% ethyl acetate in hexane). (Lit.[162])

^{1}H NMR (250 MHz, $CDCl_3$) δ: 10.87 (s, 1H), 9.29-9.26 (d, 1H, *J* = 8.6 Hz), 7.97-7.93 (d, 1H, *J* = 8.9 Hz), 7.78-7.74 (d, 1H, *J* = 8.0 Hz), 7.64-7.58 (t, 1H, *J* = 8.1 Hz), 7.45-7.40 (t, 1H, *J* = 7.1 Hz), 7.08-7.04 (d, 1H, *J* = 8.9 Hz), 1.05 (s, 9H) 0.32 (s, 6H).

ESI MS (m/z): 287.8 $[M+H]^+$.

[162] Fujita, Y.; Yonehara, M.; Tetsuhashi, M.; Noguchi-Yachide, T.; Hashimoto, Y.; Ishikawa, M. *Bioorg. Med. Chem.* **2010**, *18*, 1194-1203.

(2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-naphthyl)methanol 292



To a solution of $NaBH_4$ (317 mg, 12 mmol) in MeOH (20 mL) was added **2**-{[*tert*-butyl(dimethyl)silyl]oxy}-1-naphthaldehyde **291** (2.0 g,10 mmol) in MeOH (10 mL). The mixture was stirred at room temperature for 6 h. MeOH was then removed and the resulting crude re-dissolved in EtOAc (30 mL) and washed with brine (10 mL). The organic layer was dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by dry-column flash chromatography (5 % ethyl acetate in hexane) gave **292** (1.8 g, 89%) as a colourless oil.

R_f = 0.25 (10% ethyl acetate in hexane).

^{1}H NMR (250 MHz, DMSO-d_6) δ: 8.17-8.14 (d, 1H, *J* = 8.5 Hz), 7.84-7.75 (m, 2H), 7.52-7.46 (t, 1H, *J* = 7.2 Hz, 7.7 Hz), 7.39-7.33 (t, 1H, *J* = 7.5 Hz, 7.2 Hz), 7.11-7.08 (d, 1H, *J* = 7.5 Hz), 4.95-4.88 (m, 3H), 1.03 (s, 9H), 0.23 (s, 6H).

^{13}C NMR (63 MHz, DMSO-d_6) δ: 150.23, 133.55, 129.21, 129.00, 127.97, 126.12, 124.48, 124.10, 123.51, 120.81, 53.88, 25.69, 18.04.

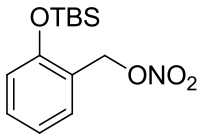
IR: 3350, 2958, 2858, 1626, 1580, 1468, 1358, 1248, 1014, 838, 780, 665 cm^{-1}

HRMS (ESI) Calcd for $C_{17}H_{23}OSi$: 271.1512. Found: 271.1519.

General procedure for the synthesis of nitrate esters

To a stirred solution of aryl methyl alcohols **271, 283** or **292** in THF at 25 °C silver nitrate was added followed by dropwise addition of thionyl chloride and the reaction mixture was left stirring overnight at 25 °C. After TLC analysis had shown complete conversion of the starting materials, water (20 mL) was added and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography with the indicated solvents to give the title products.

2-(*tert*-Butyldimethylsilyloxy)benzyl nitrate 270



According to the general procedure, {2-[(*tert*-butyldimethylsilyl)oxy]phenyl}-methanol **271** (2.4 g, 10 mmol), silver nitrate (1.7 g, 10 mmol) and thionyl chloride (1.2 g, 10 mmol) were reacted in THF (20 mL) at 25 °C overnight. Subsequent workup and flash column chromatography (5% ethyl acetate in hexane) gave **270** (1.57 g, 55%) as a colourless oil.

R_f = 0.75 (20% ethyl acetate in hexane).

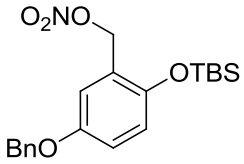
^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.36-7.33 (d, 1H, *J* = 7.5 Hz), 7.23-7.17 (t, 1H, *J* = 7.5 Hz), 6.97-6.91 (t, 1H, *J* = 7.5 Hz), 6.86-6.83 (d, 1H, *J* = 8 Hz), 4.62 (s, 2H), 1.07 (s, 9H), 0.29 (s, 6H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 154.74, 131.83, 130.71, 129.17, 122.24, 119.58, 42.72, 26.73, 19.21.

IR: 3284, 2958, 2860, 1914, 1602, 1492, 1456, 1284, 1258,1102, 928, 826, 670 cm^{-1}

HRMS (ESI) Calcd for $C_{14}H_{24}NaO_2Si$: 275.1438. Found: 275.1428.

{5-(Benzyloxy)-2-[(*tert*-butyldimethylsilyl)oxy]}benzyl nitrate 284



According to the general procedure, {5-(benzyloxy)-2-[(*tert*-butyldimethylsilyl)- oxy] phenyl}methanol **283** (3.5 g, 10 mmol), silver nitrate (1.7 g, 10 mmol) and thionyl chloride (1.2 g, 10 mmol) were reacted in THF (30 mL) at 25 °C overnight. Subsequent workup and flash column chromatography (5% ethyl acetate in hexane) afforded **284** (1.18 g, 55% yield as a brown oil.

R_f = 0.69 (20% ethyl acetate in hexane).

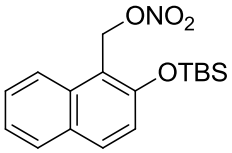
^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.44-7.32 (m, 5H) 7.01-7.00 (d, 1H, *J* = 2.9 Hz) 6.84-6.79 (dd, 1H, *J* = 5.8 Hz, 3 Hz) 6.75-6.72 (d, 1H, *J* = 8.8 Hz) 5.01 (s, 2H) 4.58 (s, 2H) 1.03 (s, 9H) 0.24 (s, 6H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 153.93, 148.59, 138.01, 129.60, 129.49, 128.87, 120.27, 117.72, 117.05, 71.56, 42.74, 26.69, 19.17.

IR: 3222, 2956, 1874, 1500, 1466, 1278, 1228, 1026, 922, 840, 696 cm^{-1}

HRMS (ESI) Calcd for $C_{20}H_{28}NaO_3Si$: 367.1700. Found: 367.1691.

{2-[(*tert*-Butyldimethylsilyl)oxy]-1-naphthyl}methyl nitrate 293



According to the general procedure, {2[(*tert*-butyldimethylsilyl)oxy]naphthalen-1-yl} methanol **292** (2.9 g, 10 mmol), silver nitrate (1.7 g, 10 mmol) and thionyl chloride (1.2 g, 10 mmol) were reacted in THF (25 mL) at 25 °C overnight. Subsequent workup and flash column chromatography (5% ethyl acetate in hexane) gave **293** (2.12 g, 63%) as a yellow oil. R_f = 0.70 (20% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.22-8.11 (q, 1H, *J* = 8.7 Hz, 9.2 Hz), 7.80-7.67 (m, 2H), 7.55-7.49 (t, 1H, *J* = 7.9 Hz, 7.0 Hz), 7.40-7.37 (d, 1H, *J* = 7.3 Hz), 7.14-7.06 (t, 1H, *J* = 8 Hz), 5.16 (s, 2H), 1.06 (s, 9H), 0.28 (s, 6H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 129.30, 127.98, 127.51, 126.70, 126.42, 123.36, 122.89, 120.18, 55.90, 29.29, 25.37.

IR: 3206, 2958, 2858, 1954, 1626, 1468, 1358, 1248, 1014, 838 cm^{-1}

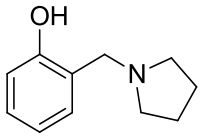
HRMS (ESI) Calcd for $C_{18}H_{26}NaO_2Si$: 325.1594. Found: 325.1589.

General procedure for the Michael addition reaction

The nitrate esters **270** or **293** were dissolved in THF, the reaction mixture was cooled to -78 °C, the appropriate nucleophile (Table 2.1, Scheme 2.13) was added followed by

TBAF (1M in THF) and the reaction was stirred at -78 °C for 2 min and then room temperature for 10 min. After TLC analysis had shown complete conversion of the starting materials, water (10 mL) was added, the mixture was extracted with EtOAc (3 × 10 mL), the combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. Flash column chromatography using the stated solvent mixtures yielded the corresponding products **276a-m**, **294, 295**.

2-(Pyrrolidin-1-ylmethyl)phenol 276a



According to the general procedure, 2-(*tert*-butyldimethylsilyloxy)benzyl nitrate **270** (200 mg, 0.7 mmol) and pyrrolidine (55 mg, 0.77 mmol) were reacted with TBAF (0.7 mL, 0.7 mmol) in THF (8 mL) at -78 °C. Subsequent workup and flash column chromatography (10% ethyl acetate in hexane) afforded **276a** as a pale yellow oil (100 mg, 80%).

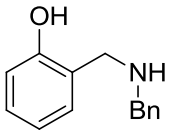
R_f = 0.53 (40% ethyl acetate in hexane). (Lit.[163])

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.18-7.12 (t, 1H, *J* = 7.7 Hz), 6.98-6.95 (d, 1H, *J* = 7.3 Hz), 6.82-6.73 (m, 2H), 3.81 (s, 2H), 2.67-2.59 (m, 4H), 1.87-1.82 (s, 4H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 158.85, 129.46, 128.72, 123.25, 119.70, 116.84, 59.81, 54.44, 24.68.

ESI MS (m/z): 178.2 $[M+H]^+$.

2-[(Benzylamino)methyl]phenol 276b



According to the general procedure, 2-(*tert*-butyldimethylsilyloxy)benzyl nitrate **270** (200 mg, 0.7 mmol) and benzylamine (83 mg, 0.77 mmol) were reacted with TBAF (0.7

[163] Dilman, A. D.; Arkhipov, D. E.; Belyakov, P.A.; Struchkova, M. I.; Tartakovsky, V. A. *Russ. Chem. Bull.* **2006**, *55*, 517-522.

mL, 0.7 mmol) in THF (8 mL) at -78 °C. Subsequent workup and flash column chromatography (10% ethyl acetate in hexane) afforded **276b** as colourless oil (20 mg, 13% yield)

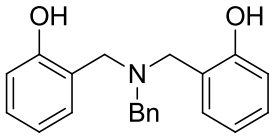
R_f = 0.45 (40% ethyl acetate in hexane). (Lit.[164])

^{1}H NMR (250 MHz, DMSO-d_6) δ: 7.33-7.23 (m, 7H), 7.08-7.04 (m, 2H), 6.75-6.70 (m, 2H), 3.78 (s, 2H), 3.69 (s, 2H).

^{13}C NMR (63 MHz, DMSO-d_6) δ: 157.22, 139.58, 128.63, 128.28, 128.13, 127.86, 126.88, 124.12, 118.54, 115.33, 51.74, 49.59.

ESI MS (m/z): 214.3 $[M+H]^+$.

2,2'-[(Benzylazanediyl)bis(methylene)]diphenol 276c



Another product obtained from the same flash column chromatography was recrystallized from hexane to afford **276c** as colourless microcrystals (45 mg, 20%).

R_f = 0.62 (40% ethyl acetate in hexane).

m.p. 129-131 °C.

^{1}H NMR (250 MHz, DMSO-d_6) δ: 10.07 (s, 2H), 7.26-7.35 (m, 5H), 7.18-7.16 (d, 2H, J = 6.6Hz), 7.11-7.05 (t, 2H, J = 7.6 Hz), 6.79-6.74 (t, 4H, J = 7.9 Hz, 5.6 Hz), 3.58 (s, 6H).

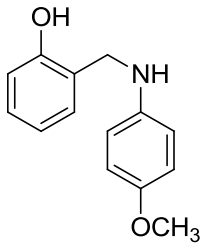
^{13}C NMR (63 MHz, DMSO-d_6) δ: 156.39, 137.46, 129.89, 129.14, 128.35, 127.25, 123.18, 118.94, 115.33, 57.19, 53.16.

IR: 3234, 2240, 1702, 1460, 1274, 1252, 1098, 922, 762 cm^{-1}

HRMS (ESI) Calcd for $C_{21}H_{22}NO_2$: 320.1645. Found: 320.1647.

[164] Andreu, R. and Ronda, J. C. *Synth. Commun.* **2008**, 38, 2316-2329.

2-{[(4-Methoxyphenyl)amino]methyl}phenol 276d



According to the general procedure, 2-(*tert*-butyldimethylsilyloxy)benzyl nitrate **270** (200 mg, 0.7 mmol) and *p*-anisidine (95 mg, 0.77 mmol) were reacted with TBAF (0.7 mL, 0.7 mmol) in THF (8 mL) at -78 °C. Subsequent workup and flash column chromatography (5% ethyl acetate in hexane) yielded **276d** as an off white solid which was recrystallized from hexane to afford **276d** as off white microcrystals (50 mg, 30% yield).

R_f = 0.52 (40% ethyl acetate in hexane).

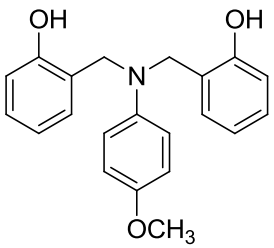
m.p. 129-131 °C. (Lit.[165])

^{1}H NMR (250 MHz, DMSO-d_6) δ: 8.92 (s, 1H), 7.21-7.18 (t, 1H, *J* = 8.0 Hz, 10 Hz), 7.14-7.11 (d, 1H, *J* = 7.0 Hz), 6.90-6.86 (m, 2H), 6.82 (s, 4H), 4.38 (s, 2H), 3.76 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 158.12, 155.56, 141.40, 130.08, 129.49, 123.75, 120.79, 118.77, 117.61, 115.73, 56.59, 51.18.

ESI MS (m/z): 230.4 $[M+H]^+$.

2, 2'-{[(4-Methoxyphenyl)azanediyl]bis(methylene)}diphenol 276e



[165] Davion, Y.; Guillaumet, G.; Leger, J. M.; Jarry, C.; Lesur, B.; and Merour J. Y. *Heterocycles* **2003**, *60*, 1793-1804.

Another product obtained from the same flash column chromatography was recrystallized from toluene-hexane to afford **276e** as colourless microcrystals (46 mg, 20% yield).

R_f = 0.44 (40% ethyl acetate in hexane).

m.p. 163-165 °C.

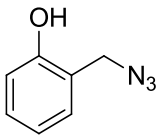
^{1}H NMR (250 MHz, DMSO-d_6) δ: 9.59 (s, 2H), 7.06-6.98 (q, 4H, *J* = 7.6 Hz, 6.4 Hz), 6.82-6.79 (d, 2H, *J* = 7.7 Hz), 6.72-6.70 (d, 4H, *J* = 6.6 Hz), 6.57-6.53 (d, 2H, *J* = 8.9 Hz), 4.44 (s, 4H), 3.60 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 157.67, 156.99, 142.61, 131.30, 130.13, 129.54, 124.97, 120.73, 118.83, 116.92, 115.72, 58.19, 56.28.

IR: 3308, 2986, 1588, 1512, 1462, 1378, 1246, 1188, 1038, 928, 832, 760 cm^{-1}

HRMS (ESI) Calcd for $C_{21}H_{22}NO_3$: 336.1594. Found: 336.1591.

2-(Azidomethyl)phenol 276f



According to the general procedure, 2-(*tert*-butyldimethylsilyloxy)benzyl nitrate **270** (200 mg, 0.7 mmol), sodium azide (55 mg, 0.84 mmol) and 18-crown-6 (5 mg) were reacted with TBAF (0.7 mL, 0.7 mmol) in THF (8 mL) at -78 °C. Subsequent workup and flash column chromatography (10% ethyl acetate in hexane) yielded **276f** as pale yellow oil (66 mg, 63%).

R_f = 0.53 (40% ethyl acetate in hexane). (Lit.[166])

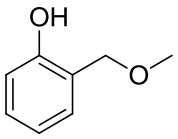
^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.22-7.12 (m, 2H), 6.98-6.91 (m, 1H), 6.85-6.82 (d, 1H, *J* = 7.6 Hz), 5.23 (s, 1H), 4.17 (s, 2H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 154.54, 130.49, 129.04, 121.76, 120.08, 115.58, 55.39.

ESI MS (m/z): 150.2 $[M+H]^+$.

[166] Zhang, Q.; Takacs, J. M. *Org. Lett.* **2008**, *10*, 545-548.

2-(Methoxymethyl)phenol 276g



According to the general procedure, 2-(*tert*-butyldimethylsilyloxy)benzyl nitrate **270** (200 mg, 0.7 mmol) was reacted with TBAF (0.7 mL, 0.7 mmol) in MeOH (8 mL) instead of THF at -78 °C. Methanol was then evaporated under reduced pressure, subsequent workup and flash column chromatography (5% ethyl acetate in hexane) yielded **276g** as colorless oil (45 mg, 94%).

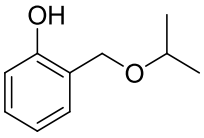
R_f = 0.52 (40% ethyl acetate in hexane). (Lit.[167])

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.01-6.95 (t, 1H, *J* = 8.0 Hz), 6.80-6.77 (d, 1H, *J* = 7.2 Hz), 6.67-6.58 (m, 2H), 4.43 (s, 2H), 3.21 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 157.12, 130.45, 129.15, 122.95, 120.80, 117.39, 75.01, 59.15.

ESI MS (m/z): 139.3 $[M+H]^+$.

2-(*iso*-Propoxymethyl)phenol 276h



According to the general procedure, 2-(*tert*-butyldimethylsilyloxy)benzyl nitrate **270** (200 mg, 0.7 mmol) was reacted with TBAF (0.7 mL, 0.7 mmol) in *i*-PrOH (8 mL) at -78 °C. The solvent was then evaporated under reduced pressure, subsequent workup and flash column chromatography (5% ethyl acetate in hexane) yielded **276h** as a colorless oil (76 mg, 65%).

R_f = 0.58 (40% ethyl acetate in hexane).

[167] Kawada, A.; Yasuda, K.; Abe, H.; Harayama, T. *Chem. Pharm. Bull.* **2002**, *50*, 380-383.

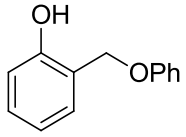
^{1}H NMR (250 MHz, DMSO-d_6) δ: 9.36 (s, 1H), 7.23-7.20 (d, 1H, *J* = 7.4 Hz), 7.08-7.03 (t, 1H, *J* = 8.4 Hz), 6.79-6.73 (t, 2H, *J* = 7.6 Hz, 8 Hz), 4.41 (s, 2H), 3.70-3.56 (m, 1H), 1.14-1.12 (d, 6H)

^{13}C NMR (63 MHz, $CDCl_3$) δ: 157.41, 130.16, 128.67, 123.49, 120.64, 117.46, 72.79, 70.72, 22.77.

IR**:** 3258, 2974, 1898, 1590, 1490, 1458, 1382, 1242, 1122, 1034, 754 cm^{-1}

Elemental Analysis: Found: C, 72.22; H, 8.47. $C_{10}H_{14}O_2$ requires C, 72.26; H, 8.49.

2-(Phenoxymethyl)phenol 276i



According to the general procedure, 2-(*tert*-butyldimethylsilyloxy)benzyl nitrate **270** (200 mg, 0.7 mmol) and phenol (132 mg, 1.4 mmol) were reacted with TBAF (0.7 mL, 0.7 mmol) in THF (8 mL) at -78 °C. Subsequent workup and flash column chromatography (5% ethyl Acetate in hexane) yielded **276i** as a colorless oil (73 mg, 52%).

R_f = 0.57 (40% ethyl acetate in hexane). (Lit.[168])

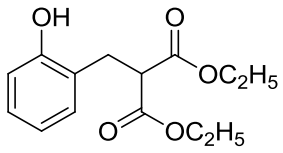
^{1}H NMR (250 MHz, DMSO-d_6) δ: 7.00-6.91 (m, 5H), 6.78-6.61 (m, 4H), 4.94 (s, 1H), 3.72 (s, 2H)

^{13}C NMR (63 MHz, $CDCl_3$) δ: 153.42, 131.74, 130.65, 128.99, 127.86, 122.47, 121.76, 117.11, 116.74, 116.28, 36.48.

ESI MS (m/z): 201.1 $[M+H]^+$.

[168] Latowski, T.; Latowska, E.; Poplawska, B.; Przytarska, M.; Walczak, M.; Zelent, B. *Pol. J. Chem.* **1980**, *54*, 1073.

Diethyl 2-(2-hydroxybenzyl)malonate 276j



According to the general procedure, 2-(*tert*-butyldimethylsilyloxy)benzyl nitrate **270** (200 mg, 0.7 mmol) and diethyl malonate (124 mg, 0.77 mmol) [it was reacted first with sodium hydride (20 mg) in THF (8 mL) to generate the carbanion] were reacted with TBAF (0.7 mL, 0.7 mmol) at -78 °C. Subsequent workup and flash column chromatography (5% ethyl acetate in hexane) yielded **276j** as a colorless oil (112 mg, 60%).

R_f = 0.47 (40% ethyl acetate in hexane).

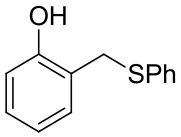
^{1}H NMR (250 MHz, DMSO-d_6) δ: 9.51 (s, 1H), 7.05-6.97 (q, 2H, *J* = 7.4 Hz), 6.78-6.75 (d, 1H, *J* = 7.9 Hz), 6.70-6.64 (t, 1H, *J* = 7.4 Hz), 4.09-4.01 (q, 4H), 3.82-3.75 (t, 1H), 3.01-2.98 (d, 2H), 1.12-1.06 (m, 6H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 170.90, 155.42, 132.00, 129.36, 125.11, 121.51, 117.68, 62.84, 53.69, 30.32, 14.87.

IR: 3228, 1952, 1732, 1458, 1372, 1232, 1154, 1102, 1032, 860, 754 cm^{-1}

HRMS (ESI) Calcd for $C_{14}H_{18}NaO_5$: 289.1046. Found: 280.1046.

2-[(Phenylthio)methyl]phenol 276k



According to the general procedure, 2-(*tert*-butyldimethylsilyloxy)benzyl nitrate **270** (200 mg, 0.7 mmol) and thiophenol (93 mg, 0.84 mmol) were reacted with TBAF (0.7 mL, 0.7 mmol) in THF (8 mL) at -78 °C. Subsequent workup and flash column chromatography (5% ethyl acetate in hexane) yielded **276k** as colorless oil (103 mg, 68%).

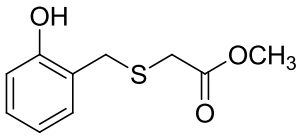
R_f = 0.67 (40% ethyl acetate in hexane). (Lit.[169])

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.29 (s, 1H), 7.22-7.11 (m, 4H), 7.08-7.05 (d, 1H, *J* = 8.0 Hz), 6.98-6.96 (d, 1H, *J* = 7.0 Hz), 6.80-6.71 (m, 2H), 5.84 (s, 1H), 4.09 (s, 2H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 155.55, 135.56, 131.75, 129.90, 128.03, 123.58, 121.77, 117.68, 36.49.

ESI MS (m/z): 217.4 $[M+H]^+$.

Methyl 2-[(2-hydroxybenzyl)thio]acetate 276l



According to the general procedure, 2-(*tert*-butyldimethylsilyloxy)benzyl nitrate **270** (200 mg, 0.7 mmol) and methyl thioglycolate (82 mg, 0.77 mmol) were reacted with TBAF (0.7 mL, 0.7 mmol) in THF (8 mL) at -78 °C. Subsequent workup and flash column chromatography (5% ethyl acetate in hexane) yielded **276l** as a colorless oil (84 mg, 56% yield.

R_f = 0.43 (40% ethyl acetate in hexane).

^{1}H NMR (250 MHz, DMSO-d_6) δ: 9.54 (s, 1H), 7.14-7.11 (d, 1H, *J* = 7.4 Hz), 7.07-7.04 (d, 1H, *J* = 7.5 Hz), 6.81-6.78 (d, 1H, *J* = 7.7 Hz), 6.76-6.70 (t, 1H, *J* = 7.4 Hz), 3.72 (s, 2H), 3.62 (s, 3H), 3.26 (s, 2H).

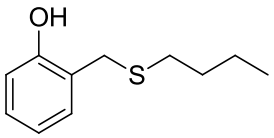
^{13}C NMR (63 MHz, $CDCl_3$) δ: 72.66, 155.88, 131.77, 130.19, 123.28, 121.53, 117.91, 53.74, 32.96, 32.77.

IR: 3322, 1954, 1954, 1726, 1712, 1634, 1456, 1300, 1170, 1006, 850, 756 cm^{-1}

HRMS (ESI): Calcd for $C_{10}H_{12}NaO_3S$: 235.0399. Found: 235.0395.

[169] Sato, K.; Inoue, S.; Ozawa, K.; Kobayashi, T.; Ota, T.; Tazaki, M. *J. Chem. Soc. Perkin Trans. I* **1987**, 1753-1756.

2-[(Butylthio)methyl]phenol 276m



According to the general procedure, 2-(*tert*-butyldimethylsilyloxy)benzyl nitrate **270** (200 mg, 0.7 mmol) and methyl 1-butylmercaptan (70 mg, 0.77 mmol) were reacted with TBAF (0.7 mL, 0.7 mmol) in THF (8 mL) at -78 °C. Subsequent workup and flash column chromato-graphy (5% ethyl acetate in hexane) yielded **276m** as a colorless oil (91 mg, 66%).

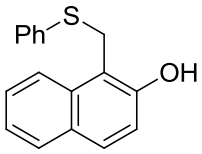
R_f = 0.56 (40% ethyl acetate in hexane). (Lit.[170])

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.23-7.17 (t, 1H, *J* = 7.3 Hz), 7.10-7.07 (d, 1H, *J* = 7.0 Hz), 6.92-6.83 (m, 2H), 3.81 (s, 2H), 2.44-2.38 (t, 2H, *J* = 7.4 Hz, 7.1 Hz), 1.60-1.49 (m, 2H), 1.40-1.31 (m, 2H), 0.91-0.85 (t, 3H, J = 7.3 Hz, 7.1 Hz)

^{13}C NMR (63 MHz, $CDCl_3$) δ: 156.34, 131.39, 129.98, 123.50, 121.41, 118.04, 33.60, 31.99, 31.36, 22.77, 14.54.

ESI MS (m/z): 197.4 $[M+H]^+$.

1-[(Phenylthio)methyl]naphthalen-2-ol 294



According to the general procedure, {2-[(*tert*-Butyldimethylsilyl)oxy]-1-naphthyl}methyl nitrate **293** (200 mg, 0.59 mmol) and thiophenol (72 mg, 0.65 mmol) were reacted with TBAF (0.59 mL, 0.59 mmol) in THF (8 mL) at -78 °C. Subsequent workup and flash column chromatography (5% ethyl acetate in hexane) yielded a brown solid which was recrystallized from ethanol to afford **294** as colorless microcrystals (120 mg, 75%).

[170] Tsay, S. C.; Lin, L. C.; Furth, P. A.; Shum, C. C.; King, D. B.; Yu, S. F.; Chen, B. L.; Hwu, J. R. *Synthesis* **1993**, 329-333.

R_f = 0.52 (40% ethyl acetate in hexane). (Lit.[171])

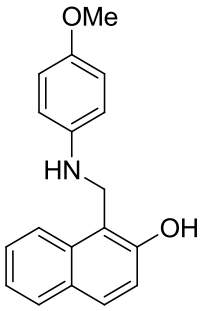
m.p. 123-125 °C.

^{1}H NMR (250 MHz, DMSO-d_6) δ: 10.12 (s, 1H), 7.94-7.91 (d, 1H, *J* = 8.5 Hz), 7.80-7.77 (d, 1H, *J* = 8.1 Hz), 7.73-7.70 (d, 1H, *J* = 8.8 Hz), 7.49-7.42 (m, 3H), 7.36-7.26 (m, 3H), 7.22-7.16 (m, 2H), 4.62 (s, 2H)

^{13}C NMR (63 MHz, $CDCl_3$) δ: 152.97, 136.90, 133.83, 131.36, 130.57, 130.33, 129.88, 129.54, 127.84, 127.74, 124.43, 123.61, 119.08, 115.33, 30.80.

HRMS (ESI) Calcd for $C_{17}H_{15}OS$: 267.0838. Found: 267.0838.

1-{[(4-Methoxyphenyl)amino]methyl}naphthalen-2-ol 295



According to the general procedure, {2-[(*tert*-butyldimethylsilyl)oxy]-1-naphthyl}methyl nitrate **293**(200 mg, 0.59 mmol) and *p*-anisidine (81 mg, 0.65 mmol) were reacted with TBAF (0.59 mL, 0.59 mmol) in THF (8 mL) at -78 °C. Subsequent workup and flash column chromatography (10% ethyl acetate in hexane) yielded a yellow solid which was recrystallized from chloroform-hexane to afford **295** colorless microcrystals (126 mg, 75%).

R_f = 0.55 (40% ethyl acetate in hexane).

m.p. 125-127 °C. (Lit.[172])

^{1}H NMR (250 MHz, DMSO-d_6) δ: 9.93(s, 1H), 7.95-7.91 (d, 1H, *J* = 8.3 Hz), 7.79-7.76 (d, 1H, *J* = 8.0 Hz), 7.73-7.69 (d, 1H, *J* = 8.8 Hz), 7.46-7.40 (t, 1H, *J* = 7.6 Hz, 7.0 Hz), 7.30-

[171] Katritzky, A. R.; Zhang, Z.; Lan, X.; Lang, H. *J. Org. Chem.* **1994**, *59*, 1900-1903.
[172] Bilgic, S.; Bilgic, O.; Bilgic, M.O.; Gunduz, M.; Karakoc, N. *Arkivoc* **2009**, *xiii*, 185-192.

7.24 (t, 1H, *J* = 7.5 Hz, 7.1 Hz), 7.20-7.17 (d, 1H, *J* = 8.8 Hz), 6.71 (s, 4H), 5.21 (s, 1H), 4.48 (s, 2H), 3.63 (s, 3H)

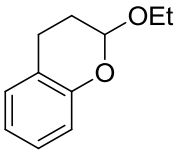
^{13}C NMR (63 MHz, DMSO-d_6) δ: 153.07, 150.67, 143.61, 133.63, 128.72, 128.15, 126.26, 123.30, 122.41, 118.19, 115.93, 114.51, 113.10, 55.35.

HRMS (ESI) Calcd for $C_{18}H_{18}NO_2$: 280.1332. Found: 280.1328.

General procedure for hetero Diels-Alder reaction of the nitrate ester

2-(*tert*-Butyldimethylsilyloxy)benzyl nitrate **270** was dissolved in toluene (20 mL) and the reaction mixture was cooled to -78 °C. Ethyl vinyl ether or ethyl vinyl sulfide was added followed by dropwise addition of TBAF (1M in THF) for a period of about 4 h. After TLC analysis had shown complete conversion of the starting material the precipitated solid was filtered off, washed with hexane and recrystallized from acetone to give the trimer of *o*-quinone methide as colourless needles m.p. 188-190 °C. The filtrate was evaporated under reduced pressure and the residue was purified using preparative TLC (5% ethyl acetate in hexane) to yield the corresponding products **278, 279**.

2-Ethoxychroman 278



According to the general procedure, 2-(*tert*-butyldimethylsilyloxy)benzyl nitrate **270** (200 mg, 0.7 mmol) and ethyl vinyl ether (5 g, 70 mmol) were reacted with TBAF (0.7 mL, 0.7 mmol) in toluene (20 mL) at -78 °C. Subsequent workup and purification yielded **278** as colorless oil (20 mg, 16%).

R_f = 0.68 (40% ethyl acetate in hexane). (Lit.[173])

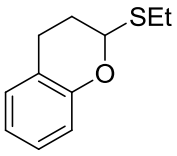
^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.14-7.03 (m, 2H), 6.89-6.81 (m, 2H), 5.26-5.24 (t, *J* = 2.7 Hz, 1H), 3.96-3.83 (m, 1H), 3.70-3.58 (m,1H), 3.05-2.91 (m, 1H), 2.69-2.59 (m, 1H), 2.09-1.89 (m, 2H), 1.22-1.16 (t, 3H, *J* = 7.0 Hz).

[173] Bray, C. D. *Org. Biomol. Chem.* **2008**, *6*, 2815-2819.

^{13}C NMR (63 MHz, $CDCl_3$) δ: 153.15, 130.19, 128.17, 123.57, 121.49, 117.86, 97.85, 64.62, 27.48, 21.48, 16.08.

ESI MS (m/z): 179.3 $[M+H]^+$.

2-(Ethylthio)chroman 279



According to the general procedure, the 2-(*tert*-butyldimethylsilyloxy)benzyl nitrate **270** (200 mg, 0.7 mmol) and ethyl vinyl sulfide (6.2 g, 70 mmol) were reacted with TBAF (0.7 mL, 0.7 mmol) in toluene (20 mL) at -78 °C. Subsequent workup and purification yielded **279** as pale yellow oil (28 mg, 23%).

R_f = 0.60 (40% ethyl acetate in hexane). (Lit.[173])

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.16–7.05 (m, 2H), 6.91–6.83 (m, 2H), 5.56-5.53 (t, 1H, J = 4.0 Hz, 3.7 Hz), 3.04–2.59 (m, 4H), 2.37–2.23 (m, 1H), 2.18–2.06 (m, 1H), 1.37-1.31 (t, 3H, *J* = 7.4 Hz).

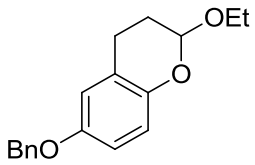
^{13}C NMR (63 MHz, $CDCl_3$) δ: 152.64, 129.69, 127.67, 123.07, 120.99, 117.36, 80.30, 27.55, 24.81, 23.02, 15.30.

ESI MS (m/z): 195.5 $[M+H]^+$.

General procedure for the Diels-Alder reaction of the nitrate esters

The nitrate ester **284** or **293** was dissolved in the designated solvent, the reaction mixture was cooled to -78 °C and the appropriate dienophile was added followed by dropwise addition of TBAF (1M in THF) for a period of about 4 h. After TLC analysis had shown complete conversion of the starting materials, water (10 mL) was added, the mixture was extracted with EtOAc (3 × 10 mL), the combined extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. Flash column chromatography using the stated solvent mixtures yielded the corresponding products.

6-(Benzyloxy)-2-ethoxychroman 285



According to the general procedure, 5-(benzyloxy)-2-[(*tert*-butyldimethylsilyl) oxy]}benzyl nitrate **284** (200 mg, 0.5 mmol) and ethyl vinyl ether (3.69 g, 50 mmol) were reacted with TBAF (0.24 mL, 0.5 mmol) in toluene (20 mL) at -78 °C. Subsequent workup and flash column chromatography (5% ethyl acetate in hexane) yielded **285** as a colorless oil (168 mg, 84%).

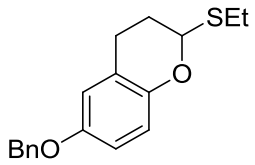
R_f = 0.55 (20% ethyl acetate in hexane). (Lit.[46])

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.43–7.31 (m, 5H), 6.75 (s, 2H), 6.69 (s, 1H), 5.22-5.20 (t, 1H, J = 2.7 Hz), 4.99 (s, 2H), 3.93-3.80 (m, 1H), 3.68-3.56 (m, 1H), 3.02-2.89 (m, 1H), 2.65-2.55 (m, 1H), 2.05-1.91 (m, 2H), 1.21-1.16 (t, 3H, *J* = 7.1 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 153.61, 147.15, 138.28, 129.38, 128.68, 128.31, 124.10, 118.27, 115.93, 115.03, 97.62, 71.47, 64.41, 27.37, 21.72, 15.95.

ESI MS (m/z): 285.5 $[M+H]^+$.

6-(Benzyloxy)-2-(ethylthio)chroman 286



According to the general procedure, 5-(benzyloxy)-2-[(*tert*-butyldimethylsilyl)oxy]} benzyl nitrate **284** (200 mg, 0.5 mmol) and ethyl vinyl sulfide (4.5 g, 50 mmol) were reacted with TBAF (0.24 mL, 0.5 mmol) in Toluene (20 mL) at -78 °C. Subsequent workup and flash column chromatography (2% ethyl Acetate in hexane) yielded **286** as a colorless oil (158 mg, 74%).

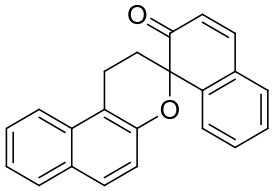
R_f = 0.53 (20% ethyl acetate in hexane). (Lit.[46])

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.43–7.31 (m, 5H), 6.75 (s, 2H), 6.69 (s, 1H), 5.54-5.51 (t, 1H, J = 3.9 Hz), 4.99 (s, 2H), 3.02-2.88 (m, 1H), 2.84-2.54 (m, 3H), 2.35-2.21 (m, 1H), 2.15-2.04 (m, 1H), 1.35-1.29 (t, 3H, *J* = 7.4 Hz)

^{13}C NMR (63 MHz, $CDCl_3$) δ: 153.98, 147.32, 138.24, 129.40, 128.72, 128.33, 123.39, 118.93, 116.08, 115.30, 80.96, 71.44, 28.20, 25.47, 23.68, 15.96.

ESI MS (m/z): 301.5 $[M+H]^+$.

1,2-Dihydro-2'H-spiro(benzo[*f*]chromene-3,1'-naphthalen)-2'-one 296



According to the general procedure, {2-[(*tert*-Butyldimethylsilyl)oxy]-1-naphthyl} methyl nitrate **293** (200 mg, 0.59 mmol) was reacted with TBAF (0.59 mL, 0.59 mmol) in THF (10 mL) at -78 °C. Subsequent workup and flash column chromatography (5% ethyl Acetate in hexane) yielded yellow viscous oil that crystallized on standing to give **296** (75 mg, 40%).

R_f = 0.65 (20% ethyl acetate in hexane).

m.p. 143-145 °C. (Lit.[174])

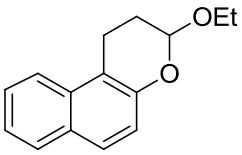
^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.83-7.72 (m, 3H), 7.65-7.62 (d, 1H, *J* = 7.0 Hz), 7.52-7.46 (t, 1H, *J* = 7.0 Hz, 8.0 Hz), 7.43-7.34 (m, 6H), 6.17-6.13 (d, 1H, *J* = 9.0 Hz), 3.16-3.06 (m, 1H), 2.92-2.79 (m, 1H), 2.55-2.46 (m, 1H), 2.24-2.12 (m, 1H)

^{13}C NMR (63 MHz, $CDCl_3$) δ: 201.62, 153.56, 145.14, 144.82, 133.53, 131.41, 130.49, 130.04, 129.52, 129.38, 129.10, 127.34, 126.97, 124.53, 122.93, 119.55, 113.27, 83.59, 34.49, 19.27.

HRMS (ESI) Calcd for $C_{22}H_{17}O_2$: 313.1223. Found: 313.1223.

[174] Belyanin, M. L.; Filimonov, V. D.; Raldugin, V. A.; Krasnov, E. A. *Russ. Chem. Bull.* **2001**, *50*, 914-916.

3-Ethoxy-2,3-dihydro-1H-benzo[*f*]chromene 298



According to the general procedure, {2-[(*tert*-Butyldimethylsilyl)oxy]-1-naphthyl} methyl nitrate **293** (200 mg, 0.59 mmol) and ethyl vinyl ether (216 mg, 2.9 mmol) were reacted with TBAF (0.59 mL, 0.59 mmol) in THF (8 mL) at -78 °C. Subsequent workup and flash column chromatography (5% ethyl acetate in hexane) yielded **298** as colorless oil (32 mg, 23% yield.

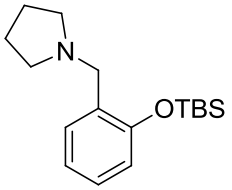
R_f = 0.51 (20% ethyl acetate in hexane). (Lit.[175])

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.86-7.83 (d, 1H, *J* = 8.3 Hz), 7.78-7.75 (d, 1H, *J* =8.0 Hz), 7.65-7.62 (d, 1H, *J* = 8.8 Hz), 7.51-7.46 (t, 1H, *J* = 7.0 Hz), 7.37-7.31 (t, 1H, *J* = 7.0 Hz), 7.08–7.05 (d, 1H, *J* = 8.8 Hz), 5.33-5.31 (t, 1H, J = 3.0 Hz), 3.94–3.84 (m, 1H), 3.74–3.65 (m, 1H), 3.14–3.06 (m, 2H), 2.28–2.19 (m, 1H), 2.17–2.07 (m, 1H), 1.22-1.16 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 150.34, 133.76, 130.09, 129.35, 128.68, 127.23, 124.30, 122.97, 120.06, 115.40, 97.83, 64.78, 27.39, 18.46, 16.14.

HRMS (ESI) Calcd for $C_{15}H_{15}O_2$: 227.1066. Found: 227.1065.

1-{2-[(*tert*-Butyldimethylsilyl)oxy]benzyl}pyrrolidine 277



2-(*tert*-Butyldimethylsilyloxy)benzyl nitrate **270** (200 mg, 0.7 mmol) and pyrrolidine (60 mg, 0.84 mmol) were dissolved in THF (10 mL) at -78 °C and stirred for 6 h from -78 °C to 0 °C then at rt for 1 h as there was no major change in starting material it was

[175] Matsumoto, J.; Ishizu, M.; Kawano, R.; Hesaka, D.; Shiragami, T.; Hayashi, Y.; Yamashita, T.; Yasuda, M. *Tetrahedron*, **2005**, *61*, 5735-5740.

refluxed for 24 h. After TLC analysis had shown complete conversion of the starting material water (10 mL) was added, the mixture was extracted with EtOAc (3 × 10 mL), the combined extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. Flash column chromatography (50% ethyl acetate in hexane) yielded **277** as colorless oil (94 mg, 45%).

R_f = 0.26 (10% ethyl acetate in hexane).

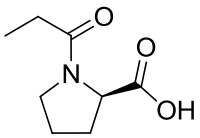
^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.38-7.35 (d, 1H, *J* = 7.4 Hz), 7.14-7.08 (t, 1H, *J* = 7.8 Hz), 6.96-6.90 (t, 1H, *J* = 7.2 Hz), 6.81-6.78 (d, 1H, *J* = 7.9 Hz), 3.65 (s, 2H), 2.55 (s, 4H), 1.77 (s, 4H) 1.03 (s, 9H), 0.23 (s, 6H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 153.69, 130.64, 129.99, 127.55, 121.05, 118.74, 54.20, 26.01, 23.61, 18.45.

IR: 2929, 1591, 1471, 1409, 1255, 1102, 913, 835, 751 cm^{-1}

HRMS (ESI) Calcd for $C_{17}H_{30}ONSi$: 292.2091. Found: 292.2077.

1-Propionyl-D-proline 305



Water (2.3 mL) was heated to 50 °C, proline (5 g, 10 mmol) was added to it slowly under stirring followed by dropwise addition of propionic anhydride (8.47 g, 15 mmol), the mixture was stirred at 70 °C for 1 h. After TLC analysis had shown complete conversion of the starting material water and propionic anhydride were removed in vacuo, the residue was purified by flash column chromatography (10% to 50% ethyl acetate in hexane then 30% dichloromethane in ethyl acetate) to yield **305** as colorless oil which became solid on standing (3 g, 40%).

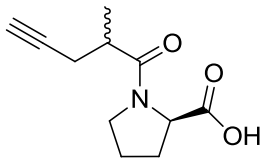
R_f = 0.21 (70% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 10 (s, 1H), 4.56 (d, 1H, *J* = 5.7 Hz), 3.62 (m, 1H), 3.50 (m, 1H), 2.41 (m, 3H) 2.10 (m, 3H), 1.18 (t, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 175.49, 173.42, 59.77, 47.65, 27.94, 27.81, 24.83, 8.72.

ESI MS (m/z): 172.3 $[M+H]^+$.

1-(2-Methylpent-4-ynoyl)-D-proline 306



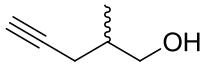
To a solution of diisopropyl amine (440 mg, 15 mmol) in THF (20 mL) at 0 °C was added *tert*-butyl lithium (222 mg, 12 mmol) dropwise. The mixture was stirred at 0 °C for 30 min then **1**-propionyl-D-proline **305** (500 mg, 10 mmol) and hexamethylphosphoramide (514 mg, 9.9 mmol) were added. The mixture was stirred at room temperature for 1 h and then cooled to 0 °C, propargyl bromide (500 mg, 15 mmol) was then added to it dropwise. The mixture was stirred at room temperature for 16 h. After TLC analysis had shown complete conversion of the starting material the reaction mixture was acidified to pH 2-3 using 2M hydrochloric acid the mixture was extracted with EtOAc (3 × 20 mL), the combined extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. Flash column chromatography (90% ethyl acetate in hexane) yielded **306** as colorless oil (300 mg, 50%).

R_f = 0.02 (70% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 9.85 (s, 1H), 4.59 (m, 1H), 3.74 (m, 2H), 2.85 (m, 1H), 2.55 (m, 2H), 2.34 (m, 3H), 2.05 (m, 3H), 1.99 (m, 2H).

ESI MS (m/z): 172.3 $[M+H]^+$.

2-Methylpent-4-yn-1-ol 307



To a suspension of lithium aluminium hydride (169 mg, 20 mmol) in THF (10 mL) at 0 °C was added 2-Methylpent-4-ynoic acid **310** (250 mg, 10 mmol) in THF (2 mL) dropwise. The mixture was stirred at room temperature for 2 h. After TLC analysis had

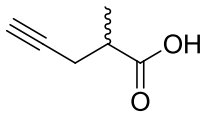
shown complete conversion of the starting material water (1 mL) was added to the reaction mixture followed by 15% NaOH (1 mL) the salt obtained was filtered and washed with EtOAc (5 mL) filtrate was extracted with EtOAc (3 × 10 mL), the combined extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. Flash column chromatography (40% ethyl acetate in hexane) yielded **307** as colorless oil (230 mg, 88%).

R_f = 0.65 (70% ethyl acetate in hexane). (Lit.[63])

^{1}H NMR (250 MHz, $CDCl_3$) δ: 3.58 (d, 2H), 2.30 (m, 2H), 1.99 (t, 1H), 1.93 (m, 1H), 1.62 (d, 1H), 2.34 (m, 3H), 1.02 (d, 3H).

ESI MS (m/z): 99.2 $[M+H]^+$.

2-Methylpent-4-ynoic acid 310



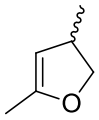
To a solution of diisopropyl amine (6.34 g, 23 mmol) in THF (50 mL) at 0 °C was added *tert*-butyl lithium (1.92 g, 11 mmol) dropwise. The mixture was stirred at 0 °C for 30 min then propionic acid (2 g, 10 mmol) and hexamethylphosphoramide (4.83 g, 9.9 mmol) were added. The mixture was stirred at room temperature for 1 h and then cooled to 0 °C, propargyl bromide (3.89 g, 12 mmol) was then added to it dropwise. The mixture was stirred at room temperature for 16 h. After TLC analysis had shown complete conversion of the starting material the reaction mixture was acidified to pH 2-3 using 2M hydrochloric acid the mixture was extracted with EtOAc (3 × 20 mL), the combined extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. Flash column chromatography (10% ethyl acetate in hexane) yielded **310** as colorless oil (750 mg, 25%).

R_f = 0.47 (70% ethyl acetate in hexane). (Lit.[63])

^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.75 (m, 1H), 2.61 (m, 1H), 2.44 (m, 1H) 2.03 (t, 1H), 1.33 (d, 3H).

ESI MS (m/z): 113.2 $[M+H]^+$.

3,5-Dimethyl-2,3-dihydrofuran 300



Sodium amide (55 mg, 1.4 mmol) was added to 2-methylpent-4-yn-1-ol **307** (1 g, 10 mmol). The mixture was refluxed for 4h. The mixture was distilled at atmospheric pressure and it was refluxed for 16 h to yield **300** as colorless oil (580 mg, 58%).

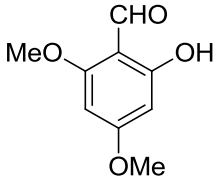
R_f = 0.22 (70% ethyl acetate in hexane). (Lit.[63])

^{1}H NMR (250 MHz, $CDCl_3$) δ: 3.54 (dd, 1H, *J* = 5.1 Hz, 5.4 Hz), 3.39 (dd, 1H, *J* = 3.6 Hz, 6.9 Hz), 2.61 (dd, 1H, *J* = 6.35 Hz, 10.0 Hz), 2.34 (dd, 1H, *J* = 6.5 Hz, 10.0 Hz), 2.13 (s, 3H), 0.90 (d, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 209.65, 67.76, 48.04, 32.00, 30.54, 16.91

ESI MS (m/z): 99.2 $[M+H]^+$.

2-Hydroxy-4,6-dimethoxybenzaldehyde 313



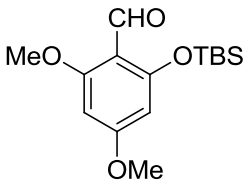
To a solution of 2,4,6-trimethoxybenzaldehyde (2 g, 10 mmol) in CH_2Cl_2 (30 mL) at -78 °C was added boron tribromide (1.5 g, 5.9 mmol) dropwise. The mixture was stirred at room temperature for 16 h. After TLC analysis had shown complete conversion of the starting material the reaction mixture was poured on ice-water (~30 mL) the mixture was extracted with CH_2Cl_2 (3 × 10 mL), the combined extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. Flash column chromatography (10% ethyl acetate in hexane) yielded **313** as white solid (1.27 g, 64%).

R_f = 0.39 (30% ethyl acetate in hexane). (Lit.[121])

^{1}H NMR (250 MHz, $CDCl_3$) δ: 12.51 (s, 1H), 10.09 (s, 1H), 6.01 (d, 1H, *J* = 1.44 Hz), 5.90 (d, 1H, *J* = 1.8 Hz), 3.84 (s, 3H), 3.83 (s, 1H).

ESI MS (m/z): 183.3 $[M+H]^+$.

2-{[*tert*-Butyl(dimethyl)silyl]oxy}-4,6-dimethoxybenzaldehyde 314



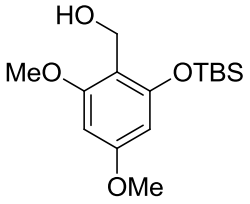
To a solution of 2-hydroxy-4,6-dimethoxybenzaldehyde **313** (690 mg, 10 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added DMAP (9 mg, 0.2 mmol), diisopropyl amine (765 mg, 20 mmol) and *tert*-butyldimethylsilyl chloride (685 mg, 12 mmol) in CH_2Cl_2 dropwise. The mixture was stirred at room temperature for 4 h. After TLC analysis had shown complete conversion of the starting material water (10 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 10 mL), the combined extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. Flash column chromatography (10% ethyl acetate in hexane) yielded **314** as yellow oil (1.03 g, 92%).

R_f = 0.20 (20% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 10.33 (s, 1H), 6.09 (d, 1H, *J* = 1.9 Hz), 5.98 (d, 1H, *J* = 2.1 Hz), 3.87 (s, 3H), 3.82 (s, 1H), 1.00 (s, 9H) 0.26 (s, 6H).

ESI MS (m/z): 297.5 $[M+H]^+$.

(2-{[*tert*-Butyl(dimethyl)silyl]oxy}-4,6-dimethoxyphenyl)methanol 315



To a solution of $NaBH_4$ (50 mg, 12 mmol) in MeOH (10 mL) was added 2-{[*tert*-butyl(dimethyl)silyl]oxy}-4,6-dimethoxybenzaldehyde **314** (330 mg, 10 mmol) in MeOH (5 mL). The mixture was stirred at room temperature for 6 h. MeOH was then removed and the resulting crude re-dissolved in EtOAc (30 mL) and washed with brine (10 mL). The

organic layer was dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by dry-column flash chromatography (20 % ethyl acetate in hexane) gave **315** (260 mg, 78%) as a colorless oil.

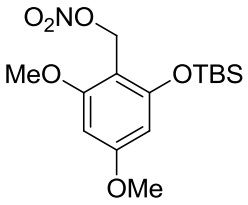
R_f = 0.20 (20% ethyl acetate in hexane).

^{1}H NMR (250 MHz, DMSO-d_6) δ: 6.13 (d, 1H, *J* = 2.11 Hz), 6.03 (d, 1H, *J* = 2.11 Hz), 4.68 (d, 2H, *J* = 6.17 Hz), 3.82 (s, 3H), 3.76 (s, 3H), 2.21 (q, 1H, *J* = 3.55 Hz, *J* = 6.48 Hz), 1.01 (s, 9H), 0.24 (s, 6H).

^{13}C NMR (63 MHz, DMSO-d_6) δ: 159.83, 159.67, 154.87, 112.98, 97.04, 91.72, 55.46, 55.01, 51.89, 25.64, 17.96.

ESI MS (m/z): 299.6 $[M+H]^+$.

2-{[*tert*-Butyl(dimethyl)silyl]oxy}-4,6-dimethoxybenzyl nitrate 299



To a stirred solution of (2-{[*tert*-butyl(dimethyl)silyl]oxy}-4,6-dimethoxyphenyl) methanol **315** (260 mg, 10 mmol) in THF (10 mL), silver nitrate (148 mg, 10 mmol) was added, followed by dropwise addition of thionyl chloride (103 mg, 10 mmol) in THF (5 mL) and the reaction mixture was left stirring overnight at 25 °C. After TLC analysis had shown complete conversion of the starting materials, water (20 mL) was added and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (5% ethyl acetate in hexane) gave **299** (49 mg, 16%) as a pale yellow oil.

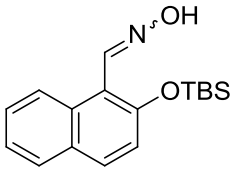
R_f = 0.42 (20% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 6.14-6.13 (d, 1H, *J* = 2.5 Hz), 6.02-6.03 (d, 1H, *J* = 2.5 Hz), 3.82 (s, 3H), 3.50 (s, 3H), 1.07 (s, 9H), 0.24 (s, 6H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 157.50, 153.99, 151.17, 115.79, 97.05, 90.89, 56.25, 55.67, 51.05, 26.17, 18.95.

ESI MS (m/z): 344.4 $[M+H]^+$.

2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-naphthaldehyde oxime 317



To a stirred solution of 2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-naphthaldehyde **291**(400 mg, 10 mmol) in IPA (10 mL), hydroxyl amine hydrochloride (194 mg, 20 mmol) was added, followed by the addition of sodium acetate (229 mg, 20 mmol) and the reaction mixture was left stirring overnight at 25 °C. After TLC analysis had shown complete conversion of the starting materials, solvent was removed in vacuo, water (20 mL) was added to the residue and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (10% ethyl acetate in hexane) gave **317** (330 mg, 78% yield) as a colorless oil which became sticky solid on standing.

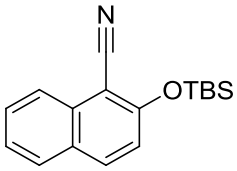
R_f = 0.46 (20% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.83-8.80 (d, 2H, *J* = 6.9 Hz), 7.78-7.48 (d, 2H, *J* = 9.0 Hz), 7.55-7.49 (t, 1H, *J* = 7.4 Hz), 7.45 (s, 1H), 7.41-7.35 (t, 1H, *J* = 7.3 Hz), 7.08-7.04 (d, 1H, *J* = 8.9 Hz), 1.06 (s, 9H), 0.26 (s, 6H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 154.79, 149.62, 132.82, 132.65, 130.54, 129.25, 128.61, 126.83, 125.23, 121.56, 117.11, 26.79, 19.41.

ESI MS (m/z): 302.4 $[M+H]^+$.

2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-naphthonitrile 319



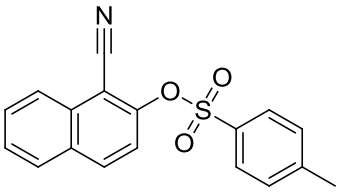
To a stirred solution of 2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-naphthaldehyde oxime **317** (50 mg, 10 mmol) in THF (5 mL) at 0 °C, tosyl chloride (31 mg, 10 mmol) was added followed by dropwise addition of triethyl amine (18 mg, 11 mmol) and stirred it for 12 h at room temperature. After TLC analysis had shown complete conversion of the starting materials water (10 mL) was added, the mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (10% ethyl acetate in hexane) gave **319** (15 mg, 32% yield) as a colorless sticky solid.

R_f = 0.46 (20% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.11-8.08 (d, 1H, *J* = 8.32 Hz), 7.94-7.90 (d, 1H, *J* = 8.9 Hz), 7.83-7.80 (d, 1H, *J* = 8.1 Hz), 7.66-7.60 (t, 1H, *J* = 7.7 Hz), 7.49-7.42 (t, 1H, *J* = 7.7 Hz), 7.10-7.06 (d, 1H, *J* = 9.0 Hz), 1.09 (s, 9H), 0.33 (s, 6H).

ESI MS (m/z): 284.5 $[M+H]^+$.

1-Cyano-2-naphthyl 4-methylbenzenesulfonate 320



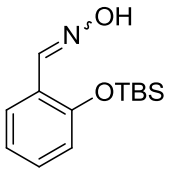
The second product obtained from flash column chromatography was **320** colorless sticky solid (25 mg, 60% yield).

R_f = 0.18 (20% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.11-8.07 (d, 2H, *J* = 8.7 Hz), 7.94-7.84 (m, 3H), 7.72-7.59 (m, 3H), 7.37-7.33 (d, 2H, *J* = 8.2 Hz), 2.45 (s, 3H).

ESI MS (m/z): 324.4 $[M+H]^+$.

2-{[*tert*-Butyl(dimethyl)silyl]oxy}benzaldehyde oxime 322



To a stirred solution of 2-{[*tert*-butyl-(dimethyl)silyl]oxy}benzaldehyde **272** (4 g, 10 mmol) in IPA (30 mL), hydroxyl amine hydrochloride (2.35 g, 20 mmol) was added, followed by the addition of sodium acetate (2.78 g, 20 mmol) and the reaction mixture was left stirring overnight at 25 °C. After TLC analysis had shown complete conversion of the starting materials, solvent was removed in vacuo, water (20 mL) was added to the residue and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (10% ethyl acetate in hexane) gave **322** (3.7 g, 88% yield) as a colorless sticky solid.

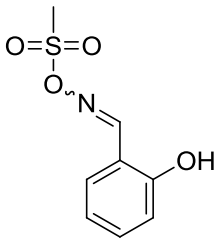
R_f = 0.28 (10% ethyl acetate in hexane).

^{1}H NMR (250 MHz, DMSO-d_6) δ: 11.22 (s, 1H), 8.26 (s, 1H), 7.68 (d, 1H, *J* = 7.43 Hz), 7.31 (t, 1H, *J* = 7.0 Hz, 7.5 Hz), 7.00 (t, 1H, *J* = 7.5 Hz), 6.91 (d, 1H, *J* = 8.15 Hz), 0.97 (s, 9H), 0.21 (s, 6H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 154.34, 146.68, 131.22, 126.55, 123.14, 121.70, 119.77, 25.88, 18.45.

ESI MS (m/z): 252.3 $[M+H]^+$.

2-((*E*)-{[(Methylsulfonyl)oxy]imino}methyl)phenol 324



Method A

To a stirred solution of 2-{[*tert*-butyl(dimethyl)silyl]oxy}benzaldehyde oxime **322** (100 mg, 10 mmol) in pyridine (5 mL), mesityl chloride (54 mg, 12 mmol) was added, and the reaction mixture was left stirring for 12 h at room temperature. After TLC analysis had shown complete conversion of the starting materials, the solvent was removed in vacuo the residue was purified by recrystalization (dichloromethane : hexane) to obtain **324** (60 mg, 70%) as a colorless solid.

R_f = 0.13 (20% ethyl acetate in hexane).

Method B

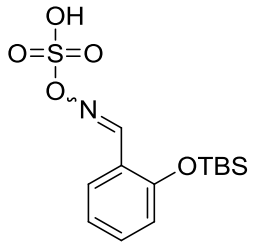
To a stirred solution of 2-{[*tert*-butyl(dimethyl)silyl]oxy}benzaldehyde oxime **322** (100 mg, 10 mmol) in THF (5 mL), sodium hydride (10 mg, 11.5 mmol) was added and stirred it for 10 min then mesityl chloride (52 mg, 11.5 mmol) was added, and the reaction mixture was left stirring for 12 h at room temperature. After TLC analysis had shown complete conversion of the starting materials water (20 mL) was added, the mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by recrystalization (dichloromethane : hexane) (25 mg, 29%) as a colorless solid.

R_f = 0.13 (20% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.98 (d, 2H, *J* = 5.4 Hz), 8.47 (t, 1H, *J* = 7.8 Hz), 8.00 (t, 2H, *J* = 6.8 Hz), 2.89 (s, 3H).

ESI MS (m/z): 254.3 $[M+K]^+$.

(*E*)-1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-*N*-[(methylsulfonyl)oxy]methanimine 325



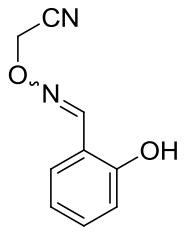
To a stirred solution of 2-{[*tert*-butyl(dimethyl)silyl]oxy}benzaldehyde oxime **322** (320 mg, 10 mmol) in 2-propanol (10 mL), sulfonic acid hydroxyl amine (192 mg, 12.5 mmol) was added followed by sodium acetate (222 mg, 20 mmol) was added, and the reaction mixture was left stirring for 12 h at room temperature. After TLC analysis had shown complete conversion of the starting materials the solvent was removed in vacuo, water (20 mL) was added to the residue, the mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo to obtain the pure product **325** (250 mg, 55%) as colorless oil.

R_f = 0.31 (10% ethyl acetate in hexane).

^{1}H NMR (250 MHz, DMSO-d_6) δ: 11.23 (s, 1H), 8.26 (s, 1H), 7.68 (d, 1H, *J* = 6.8 Hz), 7.31 (t, 1H, *J* = 6.8 Hz), 7.00 (t, 1H, *J* = 6.8 Hz), 6.91 (d, 1H, *J* = 6.8 Hz) 0.97 (s, 9H), 0.21 (s, 6H).

ESI MS (m/z): 354.3 $[M+Na]^+$.

({[(1*E*)-(2-Hydroxyphenyl)methylene]amino}oxy)acetonitrile 326



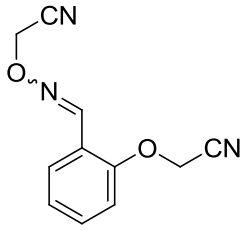
To a stirred solution of 2-{[*tert*-butyl(dimethyl)silyl]oxy}benzaldehyde oxime **322** (266 mg, 10 mmol) in THF (10 mL) at room temperature, bromo acetonitrile (139 mg, 11 mmol) followed by potassium *tert*-butoxide (236 mg, 10.5 mmol) was added, and the reaction mixture was left stirring at 25 °C for 12 h. After TLC analysis had shown complete conversion of the starting materials, water (20 mL) was added, the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (10% ethyl acetate in hexane) gave **326** (30 mg, 16%) as an off white sticky solid.

R_f = 0.25 (10% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 9.08 (s, 1H), 8.26 (s, 1H), 7.38 (t, 1H, *J* = 7.8 Hz), 7.21 (d, 1H, *J* = 7.3 Hz), 7.03 (d, 1H, *J* = 8.3 Hz), 6.97 (t, 1H, *J* = 7.4 Hz), 4.81 (s, 2H).

ESI MS (m/z): 177.2 $[M+H]^+$.

(2-{(*E*)-[(Cyanomethoxy)imino]methyl}phenoxy)acetonitrile 327



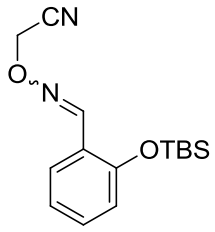
Another product obtained from flash column chromatography was **327** as yellow sticky solid (35 mg, 15%).

R_f = 0.12 (10% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.48 (s, 1H), 7.88 (d, 1H, *J* = 7.76 Hz), 7.49 (t, 1H, *J* = 8.0 Hz), 7.16 (t, 1H, *J* = 7.6 Hz), 7.01 (d, 1H, *J* = 8.4 Hz), 4.83 (s, 2H), 4.80 (s, 2H).

ESI MS (m/z): 216.3 $[M+H]^+$.

({[(1*E*)-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)methylene]amino}oxy)acetonitrile 328



To a stirred solution of 2-{[*tert*-butyl(dimethyl)silyl]oxy}benzaldehyde oxime **322** (350 mg, 10 mmol) in THF (10 mL) at 0 °C, sodium hydride (36 mg, 11 mmol) was added, and after 10 minutes bromo acetonitrile (334 mg, 20 mmol) was added and the reaction

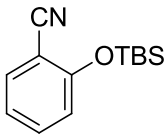
mixture was left stirring at 25 °C for 3 h. After TLC analysis had shown complete conversion of the starting materials, water (20 mL) was added, the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (10% ethyl acetate in hexane) gave **328** (148 mg, 37%) as a colorless sticky solid.

R_f = 0.46 (20% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.47 (s, 1H), 7.80 (d, 1H, *J* = 7.80 Hz), 7.31 (s, 1H), 6.99 (t, 1H, *J* = 7.5 Hz), 6.84 (d, 1H, *J* = 7.9 Hz), 4.78 (s, 2H), 1.01 (s, 9H), 0.23 (s, 6H).

ESI MS (m/z): 313.4 $[M+Na]^+$.

2-{[*tert*-Butyl(dimethyl)silyl]oxy}benzonitrile 331



To a stirred solution of 2-{[*tert*-butyl(dimethyl)silyl]oxy}benzaldehyde oxime **322** (200 mg, 10 mmol) in THF (10 mL) at 0 °C, cyanogen bromide (168 mg, 20 mmol) was added, followed by sodium hydride (21 mg, 11 mmol) and the reaction mixture was left stirring at 25 °C for 12 h. After TLC analysis had shown complete conversion of the starting materials, water (20 mL) was added, the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (10% ethyl acetate in hexane) gave **331** (150 mg, 81%) as a colorless oil.

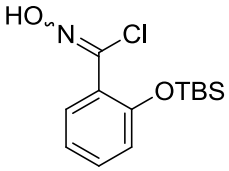
R_f = 0.42 (20% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.52 (d, 1H, *J* = 7.80 Hz), 7.45 (t, 1H, *J* = 7.11 Hz), 7.02 (t, 1H, *J* = 7.5 Hz), 6.90 (d, 1H, *J* = 8.3 Hz), 1.04 (s, 9H), 0.27 (s, 6H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 158.13, 134.11, 133.64, 121.53, 119.94, 117.05, 105.47, 25.61, 18.25.

ESI MS (m/z): 234.5 $[M+H]^+$.

2-{[*tert*-Butyl(dimethyl)silyl]oxy}-*N*-hydroxybenzenecarboximidoyl chloride 333



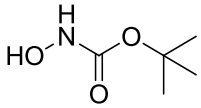
To a stirred solution of 2-{[*tert*-butyl(dimethyl)silyl]oxy}benzaldehyde oxime **322** (330 mg, 10 mmol) in $CHCl_3$ (10 mL), NCS (195 mg, 10 mmol) was added, followed by the addition of pyridine (1 drop, catalytic) and the reaction mixture was left stirring for 2 h at 40 °C. After TLC analysis had shown complete conversion of the starting materials, water (20 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (5% ethyl acetate in hexane) gave **333** (300 mg, 81%) as a pale yellow sticky solid.

R_f = 0.62 (20% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.94 (s, 1H-disappeared in D_2O), 7.38 (t, 2H, *J* = 8.5 Hz), 7.01 (t, 1H, *J* = 7.0 Hz, 7.4 Hz), 6.89 (d, 1H, *J* = 8.2 Hz), 0.98 (s, 9H), 0.21 (s, 6H).

ESI MS (m/z): 286.9 $[M+H]^+$.

***tert*-Butyl hydroxycarbamate 342**



To a stirred solution of hydroxyl amine hydrochloride (1 g, 10 mmol) in THF + water (5 mL + 5 mL) at 0 °C, boc anhydride (3.16 g, 10 mmol) was added followed by sodium bicarbonate (2.43 g, 20 mmol) and stirred it for 2 h at 0 °C. After TLC analysis had shown complete conversion of the starting materials water (30 mL) was added, the mixture was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried with sodium

sulphate, filtered and the solvent was removed in vacuo to obtain the pure product **342** (1.54 g, 80%) as colorless solid.

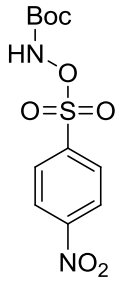
R_f = 0.87 (ethyl acetate).

m.p. 55-57 °C (Lit.[125])

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.06 (s, 1H), 6.83 (s, 1H), 1.47 (s, 9H).

ESI MS (m/z): 134.2 $[M+H]^+$.

***tert*-Butyl {[(4-nitrophenyl)sulfonyl]oxy}carbamate 343**



To a stirred solution of *tert*-butyl hydroxycarbamate **342** (1.54 g, 10 mmol) in THF (5 mL + 5 mL) at 0 °C, 4-nitrosulfonyl chloride (2.57 g, 10 mmol) was added followed by dropwise addition of triethyl amine (1.3 g, 11 mmol) and stirred it for 2 h at 0 °C. After TLC analysis had shown complete conversion of the starting materials water (30 mL) was added, the mixture was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (25% ethyl acetate in hexane) gave **343** (1 g, 28%) as a colorless solid.

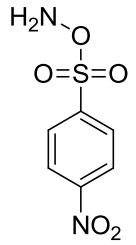
R_f = 0.6 (50% ethyl acetate in hexane).

m.p. 88-92 °C.

^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.42-8.38 (d, 2H, *J* = 8.74 Hz), 8.23-8.19 (d, 2H, *J* = 8.74 Hz), 7.77 (s, 1H), 1.31 (s, 9H).

ESI MS (m/z): 341.2 $[M+Na]^+$.

1-[(Aminooxy)sulfonyl]-4-nitrobenzene 344



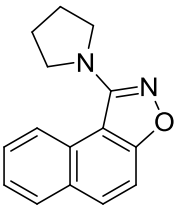
tert-Butyl {[(4-nitrophenyl)sulfonyl]oxy}carbamate **343** (310 mg, 10 mmol) is placed in trifluoroacetic acid (5 mL) at 0 °C and the reaction mixture was left stirring for 0.5h at 0 °C. After TLC analysis had shown complete conversion of the starting material trifluoroacetic acid was removed in vacuo and water (10 mL) was added to the residue, the precipitate was filtered and washed with hexane, dried it to get the pure product **344** as colorless solid (180 mg, 85%).

^{1}H NMR (250 MHz, DMSO-d_6) δ: 8.21 (d, 2H, J = 8.5 Hz), 7.85 (d, 2H, J = 8.5 Hz), 6.21 (s, 2H).

m.p. 143-145 °C. (Lit.[124])

ESI MS (m/z): 241.2 $[M+Na]^+$.

1-Pyrrolidin-1-ylnaphtho[1,2-*d*]isoxazole 346



To a stirred solution of 2-hydroxy-1-naphthaldehyde oxime (200 mg, 10 mmol) in THF (10 mL) at 0 °C, pyrrolidine (113 mg, 15 mmol) was added followed by slow addition of $Pb(OAc)_4$ (940 mg, 20 mmol). The reaction was stirred at 0 °C for 30 min and then room temperature for 12 h. When TLC analysis had shown complete conversion of the starting materials, water (10 mL) was added, the mixture was extracted with EtOAc (3 × 10 mL), the combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (20%

ethyl acetate in hexane) gave **346** as a brown solid that was recrystalised from CH_2Cl_2-hexane to give the pure product as a yellow solid (43 mg, 18%).

R_f = 0.2 (10% ethyl acetate in hexane).

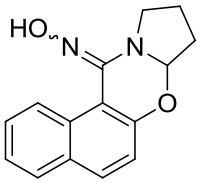
m.p. 65-67 °C.

^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.38-8.35 (d, 1H, *J* = 8.01 Hz), 7.89-7.86 (d, 1H, *J* = 8.2 Hz), 7.54-7.39 (m, 4H), 3.76-3.71 (quin, 4H), 2.09-2.04 (quin, 4H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 161.33, 145.12, 138.70, 131.22, 128.46, 125.66, 125.01, 124.57, 122.46, 120.42, 109.83, 47.75, 25.81.

ESI MS (m/z): 239.5 $[M+H]^+$.

(12*E/Z*)-7a,8,9,10-Tetrahydro-12*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazin-12-one oxime 347



Another product obtained from flash column chromatography was **347** as brown solid recrystalised from CH_2Cl_2-hexane to obtain the pure product as beige solid (42 mg, 15% yield).

R_f = 0.35 (20% ethyl acetate in hexane).

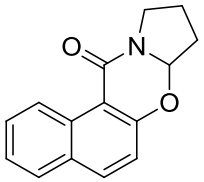
m.p. 91-93 °C.

^{1}H NMR (250 MHz, $CDCl_3$) δ: 10.01 (s, 1H), 8.64-8.61 (d, 1H, *J* = 8.5 Hz), 7.83-7.75 (m, 4H), 7.53-7.47 (t, 1H, *J* = 7.2 Hz), 7.38-7.32 (t, 1H, *J* = 7.5 Hz), 7.24-7.20 (d, 1H, *J* = 9.0 Hz), 5.99-5.96 (dd, 1H, *J* = 1.4 Hz, 3.0 Hz), 3.14-2.96 (m, 2H), 2.32-2.17 (m, 2H), 1.85-1.65 (m, 2H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 157.43, 133.51, 131.84, 128.92, 128.77, 127.73, 126.04, 124.66, 123.78, 118.71, 102.49, 98.55, 52.75, 33.71, 23.37.

ESI MS (m/z): 255.2 $[M+H]^+$.

7a,8,9,10-Tetrahydro-12*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazin-12-one 348



Another product obtained from flash column chromatography was **348** as a brown oil (26 mg, 10% yield).

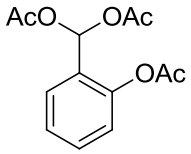
R_f = 0.1 (20% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 9.14-9.11 (d, 1H, *J* = 8.7 Hz), 7.90-7.87 (d, 1H, , *J* = 8.9 Hz), 7.79-7.76 (d, 1H, *J* = 8.0 Hz), 7.63-7.58 (t, 1H, *J* = 7.15 Hz), 7.46-7.40 (t, 1H, *J* = 7.5 Hz), 7.14-7.10 (d, 1H, *J* = 9.0 Hz), 5.55-5.51 (dd, 1H, *J* = 1.3 Hz, 4.5 Hz), 4.17-3.95 (m, 2H), 3.69-3.56 (m, 2H), 2.55-2.29 (m, 2H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 161.53, 157.75, 134.94, 131.85, 130.16, 128.42, 128.22, 126.14, 125.03, 124.91, 123.11, 117.02, 88.18, 45.14, 32.20, 22.07.

ESI MS (m/z): 240.3 $[M+H]^+$.

[2-(Acetyloxy)phenyl]methylene diacetate 368



A mixture of acetic anhydride (910 mg, 22 mmol), lithium bromide (77 mg, 2.2 mmol) and ethyl bromoacetate (820 mg, 12 mmol) was stirred at 80 °C for 3 h. Salicyaldehyde (500 mg, 10 mmol) was added and the reaction mixture was left stirring for 15 h at 80 °C. When TLC analysis had shown complete conversion of the starting materials, water (30 mL) was added, the mixture was extracted with EtOAc (3 × 15 mL), the organic layer was separated and washed with saturated Na_2CO_3 solution (10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (20% ethyl acetate in hexane) gave **368** (506 mg, 50%) as a colorless solid.

R_f = 0.7 (40% ethyl acetate in hexane).

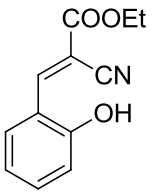
m.p. 102-104 °C (Lit.[176])

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.89 (s, 1H), 7.64-7.61 (d, 1H, *J* = 7.7 Hz), 7.46-7.39 (t, 1H, *J* = 7.8 Hz), 7.32-7.26 (t, 1H, *J* = 7.6 Hz), 7.13-7.10 (d, 1H, *J* = 8.1 Hz), 2.33 (s, 3H), 2.09 (s, 6H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 169.48, 168.50, 148.35, 130.86, 127.93, 126.34, 123.33, 85.44, 20.98, 20.83.

ESI MS (m/z): 305.2 $[M+K]^+$.

Ethyl (2*E*)-2-cyano-3-(2-hydroxyphenyl)acrylate 372



Method A

To a stirred solution of salicyaldehyde (1 g, 10 mmol) in EtOH (20 mL), ethyl cyanoacetate (972 mg, 10.5 mmol) was added, followed by the addition of baker's yeast (2 g) and the reaction mixture was left stirring for 5h at 25 °C. After TLC analysis had shown complete conversion of the starting materials, the reaction mixture was filtered through celite bed the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (10% ethyl acetate in hexane) gave **372** (200 mg, 11%) as a yellow solid.

Method B

To a stirred solution of salicyaldehyde (2 g, 10 mmol) in ethyl cyanoacetate (2.22 g, 12 mmol), PPh_3 (catalytic) was added, and the reaction mixture was left stirring for 5h at 80 °C. After TLC analysis had shown complete conversion of the starting materials, water (20

[176] Li, T.-S.; Zhang, Z.-H.; Gao, Y.-J. *Syn. Comm.* **1998**, *28*, 4665-4671.

mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (10% ethyl acetate in hexane) gave **372** (1.92 g, 54%) as a yellow solid.

R_f = 0.14 (20% ethyl acetate in hexane).

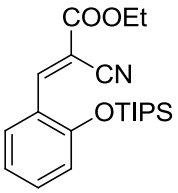
m.p. 128-130 °C (Lit.[130])

^{1}H NMR (250 MHz, DMSO-d_6) δ: 8.71 (s, 1H), 7.90 (d, 1H, *J* = 7.8 Hz), 7.75 (t, 1H, *J* = 7.8 Hz), 7.42 (t, 2H, *J* = 7.8 Hz, 8.2 Hz), 4.33 (q, 2H, *J* = 7.06 Hz), 1.33 (t, 3H, *J* = 7.06 Hz).

^{13}C NMR (63 MHz, DMSO-d_6) δ: 162.52, 155.88, 154.46, 148.52, 134.38, 130.19, 124.75, 117.73, 117.65, 116.06, 61.17, 13.99.

ESI MS (m/z): 218.3 $[M+H]^+$.

Ethyl (2*E*)-2-cyano-3-{2-[(triisopropylsilyl)oxy]phenyl}acrylate 373



To a stirred solution of ethyl (2*E*)-2-cyano-3-(2-hydroxyphenyl)acrylate **372** (600 mg, 10 mmol) in CH_2Cl_2 (20 mL) diisopropylamine (614 mg, 22 mmol), DMAP (catalytic) was added, followed by the dropwise addition of triisipropylsilyl chloride (640 mg, 12 mmol) and the reaction mixture was left stirring for 2h at 25 °C. After TLC analysis had shown complete conversion of the starting materials, water (20 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (5% ethyl acetate in hexane) gave **373** (350 mg, 35%) as a yellow oil.

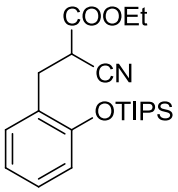
R_f = 0.57 (20% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.84 (s, 1H), 8.35 (d, 1H, *J* = 8.0 Hz), 7.43 (t, 1H, *J* = 7.5 Hz), 7.07 (t, 1H, *J* = 7.6 Hz), 6.91 (d, 1H, *J* = 8.3 Hz), 4.40 (q, 2H, *J* = 7.12 Hz), 1.40 (m, 6H) 1.13 (d, 18H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 171.00, 159.29, 157.02, 150.12, 134.91, 129.46, 122.92, 121.61, 119.33, 119.25, 62.51, 18.05, 13.04, 12.45.

ESI MS (m/z): 396.5 $[M+Na]^+$.

Ethyl 2-cyano-3-{2-[(triisopropylsilyl)oxy]phenyl}propanoate 379



To a solution of $NaBH_4$ (24 mg, 12 mmol) in EtOH (5 mL) was added ethyl (2*E*)-2-cyano-3-{2-[(triisopropylsilyl)oxy]phenyl}acrylate **373** (200 mg, 10 mmol) in EtOH (5 mL). The mixture was stirred at room temperature for 10 minutes. EtOH was then removed and the resulting crude re-dissolved in EtOAc (30 mL) and washed with brine (10 mL). The organic layer was dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by dry-column flash chromatography (10 % ethyl acetate in hexane) gave **379** (110 mg, 54%) as a colorless oil.

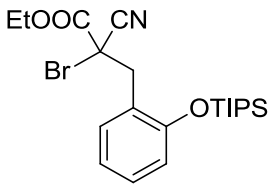
R_f = 0.50 (20% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.21 (m, 2H), 6.92 (t, 1H, *J* = 7.4 Hz), 6.83 (d, 1H, *J* = 8.0 Hz), 4.27 (q, 2H, *J* = 7.14 Hz), 3.93 (q, 1H, *J* = 2.8 Hz, 6.5 Hz) 3.43 (q, 1H, *J* = 6.5 Hz, 6.8 Hz) 3.11 (q, 1H, *J* = 3.8 Hz, 9.4 Hz) 1.37 (m, 6H), 1.13 (m, 18H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 166.06, 154.25, 131.55, 129.15, 125.58, 121.28, 118.13, 116.56, 62.81, 37.73, 32.19, 18.22, 14.09, 13.25.

ESI MS (m/z): 376.5 $[M+Na]^+$.

Ethyl 2-bromo-2-cyano-3-{2-[(triisopropylsilyl)oxy]phenyl}propanoate 381



To NBS (26 mg, 11 mmol) was added ethyl 2-cyano-3-{2-[(triisopropylsilyl)oxy] phenyl}propanoate **379** (50 mg, 10 mmol) and the mixture was irradiated by a 60W lamp at 40 °C under stirring for 12h. After TLC analysis had shown complete conversion of the starting materials, water (5 mL) was added, the mixture was extracted with EtOAc (10 mL) and washed with brine (10 mL). The organic layer was dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by dry-column flash chromatography (5 % ethyl acetate in hexane) gave **381** (30 mg, 50%) as a pale yellow oil.

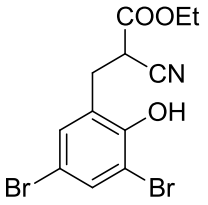
R_f = 0.58 (20% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.28 (d, 1H, *J* = 7.5 Hz), 7.21 (t, 1H, *J* = 7.3 Hz), 6.91 (t, 2H, *J* = 7.8 Hz), 4.38 (q, 2H, *J* = 7.18 Hz), 3.88 (d, 1H, *J* = 14.0 Hz), 3.67 (d, 1H, *J* = 14.0 Hz), 1.41 (m, 6H), 1.15 (m, 18H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 164.56, 154.85, 131.04, 129.67, 123.60, 120.90, 118.62, 115.57, 64.51, 42.99, 38.60, 18.32, 13.83, 13.16.

ESI MS (m/z): 455.5 $[M+H]^+$.

Ethyl 2-cyano-3-(3,5-dibromo-2-hydroxyphenyl)propanoate 385



To a solution of ethyl 2-cyano-3-{2-[(triisopropylsilyl)oxy]phenyl} propanoate **379** (50 mg, 10 mmol) in CH_2Cl_2 (5 mL) at room temperature was added MnO_2 (20 mg, 10 mmol) followed by dropwise addition of bromine (18 mg, 5 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at room temperature for 12 h. After TLC analysis had shown complete

conversion of the starting materials water (10 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (20% ethyl acetate in hexane) gave **385** (35 mg, 42%) as a yellow oil.

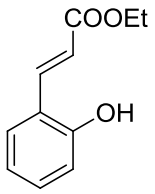
R_f = 0.35 (20% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.56-7.55 (d, 1H, *J* = 2.2 Hz), 7.29-7.28 (d, 1H, *J* = 2.2 Hz), 5.89 (s, 1H), 4.30-4.21 (q, 2H, *J* = 7.18 Hz), 3.97-3.91 (dd, 1H, *J* = 1.8 Hz, 6.7 Hz), 3.40-3.32 (dd, 1H, *J* = 6.6 Hz, 7.0 Hz), 3.16-3.07 (dd, 1H, *J* = 5.0 Hz, 8.7 Hz), 1.32-1.26 (t, 3H, *J* = 7.08 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 165.52, 149.87, 133.86, 133.65, 125.00, 115.99, 112.81, 111.29, 63.24, 36.87, 31.44, 14.07.

ESI MS (m/z): 378.3 $[M+H]^+$.

Ethyl (2*E*)-3-(2-hydroxyphenyl)acrylate 386



To a solution of salicyaldehyde (1 g, 10 mmol) in water (15 mL) at room temperature was added triphenyl phosphine (3.86 g, 18 mmol), bromoethyl acetate (2.46 g, 18 mmol), lithium hydroxide (721 mg, 21 mmol) and lithium chloride (2g, 60 mmol) were added and the mixture was refluxed for 15 min. After TLC analysis had shown complete conversion of the starting materials water (10 mL) was added, the mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (20% ethyl acetate in hexane) gave **386** (1.32 g, 84%) as colorless solid.

R_f = 0.27 (20% ethyl acetate in hexane).

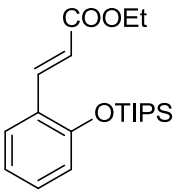
m.p. 83-85 °C (Lit.[139])

^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.11-8.04 (d, 1H, *J* = 16.4 Hz), 8.03 (s, 1H), 7.44-7.41 (d, 1H, *J* = 7.16 Hz), 7.22-7.17 (t, 1H, *J* = 7.16 Hz), 6.92-6.83 (m, 2H), 6.68-6.61 (d, 1H, *J* = 16.4 Hz), 4.32-4.23 (q, 2H, *J* = 7.02 Hz), 1.35-1.30 (t, 3H, *J* = 7.08 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 168.98, 156.17, 141.34, 131.55, 129.24, 121.66, 120.33, 117.93, 116.51, 60.86, 14.31.

ESI MS (m/z): 193.2 $[M+H]^+$.

Ethyl (2*E*)-3-{2-[(triisopropylsilyl)oxy]phenyl}acrylate 387



To a stirred solution of ethyl (2*E*)-3-(2-hydroxyphenyl)acrylate **386** (6.5 g, 10 mmol) in CH_2Cl_2 (50 mL) diisopropylamine (7.52 g, 22 mmol), DMAP (catalytic) was added, followed by the dropwise addition of triisipropylsilyl chloride (7.83 g, 12 mmol) and the reaction mixture was left stirring for 2h at 25 °C. After TLC analysis had shown complete conversion of the starting materials, water (20 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (2% ethyl acetate in hexane) gave **387** (10.71 g, 90%) as a colorless oil.

R_f = 0.62 (20% ethyl acetate in hexane).

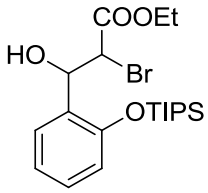
^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.20 (d, 1H, *J* = 16.4 Hz), 7.55 (d, 1H, *J* = 7.6 Hz), 7.25 (t, 1H, *J* = 7.5 Hz), 6.96 (t, 1H, *J* = 7.6 Hz), 6.86 (d, 1H, *J* = 8.0 Hz), 6.41 (d, 1H, *J* = 16.4 Hz), 4.29 (q, 2H, *J* = 7.12 Hz), 1.39 (m, 6H), 1.14 (d, 18H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 167.25, 155.03, 139.96, 131.26, 127.29, 125.56, 121.18, 119.35, 117.69, 60.27, 18.00, 14.33, 12.97.

IR: 2950, 2870, 1688, 1598, 1480, 1266, 904, 738 cm^{-1}.

HRMS (ESI) Calcd for $C_{20}H_{33}O_3Si$: 349.2193. Found: 349.2190.

Ethyl 2-bromo-3-hydroxy-3-{2-[(triisopropylsilyl)oxy]phenyl}propanoate 390



To a stirred solution of ethyl (2*E*)-3-{2-[(triisopropylsilyl)oxy]phenyl}acrylate **387** (100 mg, 10 mmol) in THF:H_2O (5 mL : 5 mL), NBS (61 mg, 12 mmol) was added and the reaction mixture was left stirring for 12 h at 25 °C. After TLC analysis had shown complete conversion of the starting materials, the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (5% ethyl acetate in hexane) gave **390** (90 mg, 78%) as a colorless oil becomes solid on standing.

R_f = 0.42 (20% ethyl acetate in hexane).

m.p. 52-54 °C.

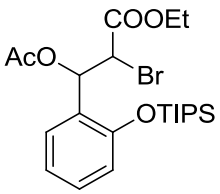
^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.35 (d, 1H, *J* = 7.5 Hz), 7.21 (t, 1H, *J* = 7.5 Hz), 6.97 (t, 1H, *J* = 7.45 Hz), 6.83 (d, 1H, *J* = 8.0 Hz), 5.31 (dd, 1H, *J* = 2.2 Hz, 6.4 Hz), 4.67 (d, 1H, *J* = 6.3 Hz), 4.19 (q, 2H, *J* = 7.12 Hz), 3.90 (d, 1H, *J* = 8.6 Hz), 1.43 (m, 6H), 1.16 (m, 18H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 169.42, 153.28, 129.38, 128.45, 128.37, 121.09, 117.90, 72.40 62.09, 46.25, 18.21, 13.88, 13.24.

IR: 3438, 2868, 2342, 1746, 1642, 1492, 1374, 1272, 876, 754, 664 cm^{-1}.

HRMS (ESI) Calcd for $C_{20}H_{33}NaBrO_4Si$: 469.1206. Found: 469.1199.

Ethyl 3-(acetyloxy)-2-bromo-3-{2-[(triisopropylsilyl)oxy]phenyl}propanoate 392



To a stirred solution of ethyl 2-bromo-3-hydroxy-3-{2-[(triisopropylsilyl)oxy]phenyl} propanoate **390** (164 mg, 10 mmol) in CH_2Cl_2 (10 mL) acetic anhydride (45 mg, 22 mmol) was added, followed by the addition of DMAP (catalytic) and the reaction mixture was left stirring for 12h at 25 °C. After TLC analysis had shown complete conversion of the starting materials, water (20 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (5% ethyl acetate in hexane) gave **392** (174 mg, 97%) as a colorless oil.

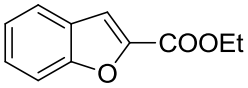
R_f = 0.29 (10% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.30 (d, 1H, *J* = 7.5 Hz), 7.21 (t, 1H, *J* = 7.6 Hz), 6.94 (t, 1H, *J* = 7.36 Hz), 6.82 (d, 1H, *J* = 8.12 Hz), 6.55 (s, 1H), 4.75 (s, 1H), 4.23 (q, 2H, *J* = 7.12 Hz), 2.04 (s, 3H), 1.41 (m, 6H), 1.17 (d, 18H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 168.98, 167.84, 154.12, 129.94, 126.05, 120.69, 117.96, 62.09, 20.89, 18.22, 14.00, 13.25.

HRMS (ESI) Calcd for $C_{22}H_{35}NaBrO_5Si$: 509.1329. Found: 509.1315.

Ethyl 1-benzofuran-2-carboxylate 394



To a stirred solution of ethyl 3-(acetyloxy)-2-bromo-3-{2-[(triisopropylsilyl)oxy] phenyl}propanoate **392** (20 mg, 10 mmol) in THF at -78 °C, pyrrolidine (4 mg, 12 mmol) was added followed by dropwise addition of TBAF (12 mg, 11 mmol) and the reaction was stirred at -78 °C for 30 min and then room temperature for 10 min. After TLC analysis had shown complete conversion of the starting materials, water (10 mL) was added, the mixture was extracted with EtOAc (3 × 10 mL), the combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (5% ethyl acetate in hexane) gave **394** (250 mg, 39%) as a colorless oil.

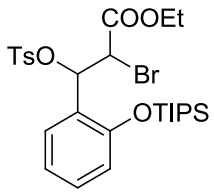
R_f = 0.42 (10% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.69-7.66 (d, 1H, *J* = 7.7 Hz), 7.61-7.58 (d, 1H, *J* = 8.4 Hz), 7.53 (s, 1H), 7.48-7.41 (t, 1H, *J* = 7.2 Hz, 8.4 Hz), 7.33-7.27 (t, 1H, , *J* = 7.5 Hz), 4.49-4.40 (q, 2H, *J* = 7.12 Hz), 1.46-1.40 (t, 3H, *J* = 7.1 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 159.76, 155.85, 145.88, 127.70, 127.12, 123.90, 122.93, 113.92, 112.52, 61.66, 14.48.

ESI MS (m/z): 191.2 $[M+H]^+$.

Ethyl 2-bromo-3-{[(4-methylphenyl)sulfonyl]oxy}-3-{2-[(triisopropylsilyl)oxy]phenyl} propanoate 400



To a stirred solution of ethyl 2-bromo-3-hydroxy-3-{2-[(triisopropylsilyl)oxy]phenyl} propanoate **390** (50 mg, 10 mmol) in CH_2Cl_2 (5 mL) at 0 °C, DMAP (2 mg, catalytic) and triethyl amine (22 mg, 20 mmol) were added followed by dropwise addition of tosyl chloride (34 mg, 15 mmol) in CH_2Cl_2 (1 mL) and the reaction was stirred at room temperature for 12 h. After TLC analysis had shown complete conversion of the starting materials, water (10 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (5% ethyl acetate in hexane) gave **400** (20 mg, 29%) as a colorless oil.

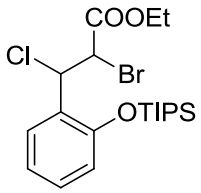
R_f = 0.43 (10% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.93-7.90 (d, 2H, *J* = 8.3 Hz), 7.42-7.38 (d, 2H, *J* = 8.2 Hz), 7.20-7.11 (m, 2H), 6.94-6.89 (t, 1H, *J* = 7.5 Hz), 6.83-6.80 (d, 1H, , *J* = 8.0 Hz), 4.45-4.44 (d, 1H, *J* = 1.5 Hz), 4.27-4.23 (q, 2H, *J* = 2.0 Hz, 5 Hz), 3.35-3.34 (d, 1H, *J* = 1.5 Hz), 2.48 (s, 3H), 1.33-1.28 (t, 6H, , *J* = 7.05 Hz), 1.11-1.08 (d, 18H, 7.05 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 168.55, 155.00, 146.92, 130.36, 129.45, 128.03, 127.18, 125.79, 125.31, 121.23, 118.22, 61.70, 56.54, 54.84, 21.94, 18.08, 14.25, 13.03.

ESI MS (m/z): 622.3 $[M+Na]^+$.

Ethyl 2-bromo-3-chloro-3-{2-[(triisopropylsilyl)oxy]phenyl}propanoate 401



Method A

To a stirred solution of ethyl 2-bromo-3-hydroxy-3-{2-[(triisopropylsilyl)oxy]phenyl} propanoate **390** (35 mg, 10 mmol) in THF (5 mL), diisopropyl amine (22 mg, 20 mmol) was added followed by triphosgene (11 mg, 3.3 mmol) and the reaction was stirred at 25 °C for 12 h. After TLC analysis had shown complete conversion of the starting materials, water (10 mL) was added, the mixture was extracted with EtOAc (3 × 10 mL), the combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (5% ethyl acetate in hexane) gave **401** (24 mg, 60%) as a colorless oil becomes solid on standing.

Method B

The stirred solution of ethyl 2-bromo-3-hydroxy-3-{2-[(triisopropylsilyl)oxy]phenyl} propanoate **390** (100 mg, 10 mmol) in thionyl chloride left stirring for 4h at 60 °C. After TLC analysis had shown complete conversion of the starting materials, thionyl chloride was distilled off and the residue was dissolved in water (20 mL), the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (5% ethyl acetate in hexane) gave **401** (94 mg, 90%) as a colorless oil becomes solid on standing.

R_f = 0.56 (10% ethyl acetate in hexane).

m.p. 38-40 °C.

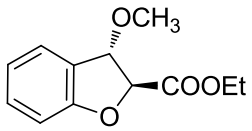
^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.34 (d, 1H, *J* = 6.7 Hz), 7.25 (t, 1H, *J* = 7.5 Hz), 7.0 (t, 1H, *J* = 7.3 Hz), 6.86 (d, 1H, *J* = 8.1 Hz), 6.02 (s, 1H), 4.67 (s, 1H), 4.37 (q, 2H, *J* = 7.1 Hz), 1.41 (m, 6H), 1.17 (d, 18H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 167.97, 154.04, 130.32, 127.66, 121.30, 118.44, 62.49, 53.78, 46.85, 18.22, 14.02, 13.20.

IR: 2868, 2362, 1746, 1642, 1492, 1374, 1272, 920, 754 cm^{-1}.

HRMS (ESI) Calcd for $C_{20}H_{32}NaBrClO_3Si$: 487.0864. Found: 487.0862.

Ethyl (2*S*,3*S*)-3-methoxy-2,3-dihydro-1-benzofuran-2-carboxylate 402a



To a stirred solution of ethyl 2-bromo-3-chloro-3-{2-[(triisopropylsilyl)oxy]phenyl} propanoate **401** (200 mg, 10 mmol) in MeOH (10 mL) at -78 °C, TBAF (118 mg, 11 mmol) was added and the reaction was stirred at -78 °C for 30 min and then room temperature for 10 min. After TLC analysis had shown complete conversion of the starting materials, the solvent was removed in vacuo water (10 mL) was added to the residue, the mixture was extracted with EtOAc (3 × 10 mL), the combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (5% acetone in hexane) gave **402a** (15 mg, 16%) as a colorless oil.

R_f = 0.23 (10% acetone in hexane).

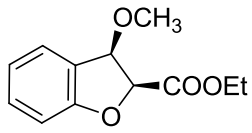
^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.40-7.37 (d, 1H, *J* = 7.28 Hz), 7.34-7.27 (t, 1H, *J* = 7.9 Hz), 7.01-6.94 (t, 2H, *J* = 8.2 Hz, 8.9 Hz), 5.12-5.06 (q, 2H, *J* = 4.0 Hz, 6.5 Hz), 4.39-4.31 (q, 2H, *J* = 6.9 Hz), 3.37 (s, 3H), 1.37-1.31 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 167.46, 159.81, 131.24, 125.98, 124.80, 121.44, 111.33, 84.16, 80.89, 61.64, 56.76, 14.38.

IR: 3056, 2988, 1758, 1738, 1610, 1478, 1466, 1376, 1266, 1204, 1092, 1054, 968, 738 cm^{-1}.

HRMS (ESI) Calcd for $C_{20}H_{14}NaO_4$: 245.0784. Found: 245.0777.

Ethyl (2*S*,3*R*)-3-methoxy-2,3-dihydro-1-benzofuran-2-carboxylate 402b



Another product obtained from the same flash column chromatography was **402b** colorless oil (18 mg, 19% yield).

R_f = 0.13 (10% acetone in hexane).

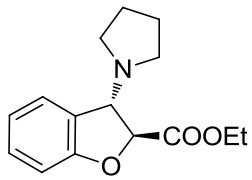
^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.26-7.23 (d, 1H, *J* = 7.35 Hz), 7.17-7.14 (d, 1H, *J* = 7.17 Hz), 6.93-6.88 (m, 2H), 4.74-4.70 (d, 1H, *J* = 9.9 Hz), 4.48-4.44 (d, 1H, *J* = 9.9 Hz), 4.34-4.25 (dq, 2H, *J* = 3.4 Hz, 3.6 Hz, 7.0 Hz), 3.44 (s, 3H), 1.35-1.30 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 168.73, 155.67, 131.49, 130.63, 120.16, 119.89, 117.49, 85.35, 62.38, 58.81, 44.91, 14.10.

IR: 3056, 2988, 1758, 1738, 1610, 1478, 1466, 1376, 1266, 1204, 1092, 1054, 968, 738 cm^{-1}.

HRMS (ESI) Calcd for $C_{20}H_{14}NaO_4$: 245.0784. Found: 245.0777.

Ethyl (2*S*,3*S*)-3-pyrrolidin-1-yl-2,3-dihydro-1-benzofuran-2-carboxylate 393



To a stirred solution of ethyl 2-bromo-3-chloro-3-{2-[(triisopropylsilyl)oxy]phenyl} propanoate **401** (200 mg, 10 mmol) in THF at -78 °C, pyrrolidine (34 mg, 11 mmol) was added followed by dropwise addition of TBAF (118 mg, 12 mmol) and the reaction was stirred at -78 °C for 30 min and then room temperature for 10 min. After TLC analysis had shown complete conversion of the starting materials, water (10 mL) was added, the mixture was extracted with EtOAc (3 × 10 mL), the combined organic extracts were dried

with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (5% ethyl acetate in hexane) gave **393** (60 mg, 54%) as a yellow oil.

R_f = 0.17 (10% acetone in hexane).

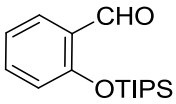
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33-7.31 (d, 1H, *J* = 7.6 Hz), 7.24-7.22 (d, 1H, *J* = 8.2 Hz), 6.96-6.91 (m, 2H), 5.11-5.10 (d, 1H, *J* = 2.9 Hz), 4.67-4.66 (d, 1H, , *J* = 2.9 Hz), 4.27-4.19 (m, 2H), 2.69-2.64 (m, 2H), 2.59-2.54 (m, 2H),1.81-1.75 (m, 4H), 1.30-1.26(t, 3H, *J* = 7.06 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 171.29, 159.90, 130.09, 126.20, 125.07, 121.29, 110.51, 80.47, 67.95, 61.73, 49.12, 23.44, 14.33.

IR: 3056, 2934, 1758, 1738, 1610, 1452, 1466, 1376, 1266, 1190, 1092, 1054, 968, 704 cm^{-1}.

HRMS (ESI) Calcd for $C_{15}H_{20}NO_3$: 262.1438. Found: 262.1437.

2-[(Triisopropylsilyl)oxy]benzaldehyde 403



To a stirred solution of salicyaldehyde (1 g, 10 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added DMAP (10 mg, catalytic), diisopropyl amine (1.65 g, 20 mmol) and triisopropylsilyl chloride (1.89 g, 12 mmol) in CH_2Cl_2 dropwise. The mixture was stirred at room temperature for 2 h. After TLC analysis had shown complete conversion of the starting material water (20 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 10 mL), the combined extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. Flash column chromatography (5% ethyl acetate in hexane) yielded **403** as colorless oil (2 g, 90%).

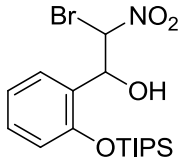
R_f = 0.52 (10% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 10.55 (s, 1H), 7.82-7.79 (d, 1H, *J* = 7.6 Hz), 7.47-7.41 (t, 1H, *J* = 7.8 Hz), 7.03-6.88 (m, 2H), 1.41-1.27 (m, 3H), 1.14-1.11 (d, 18H, *J* = 7.1 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 190.40, 159.55, 135.84, 128.42, 126.94, 121.26, 119.87, 18.07, 13.13.

ESI MS (m/z): 279.5 $[M+H]^+$.

2-Bromo-2-nitro-1-{2-[(triisopropylsilyl)oxy]phenyl}ethanol 404



To a stirred solution of triisopropyl{2-[(*E*)-2-nitrovinyl]phenoxy}silane **405** (350 mg, 10 mmol) in THF : H_2O (5 mL : 5 mL), NBS (582 mg, 30 mmol) was added and the reaction mixture was left stirring for 12h at 25 °C. After TLC analysis had shown complete conversion of the starting materials, the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (10% ethyl acetate in hexane) gave **404** (32 mg, 07%) as a colorless oil.

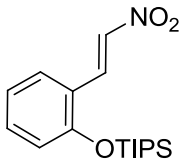
R_f = 0.50 (20% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.32-7.29 (d, 1H, *J* = 7.8 Hz), 7.26-7.23 (d, 1H, *J* = 7.8 Hz), 7.02-6.96 (t, 1H, *J* = 7.45 Hz), 6.89-6.85 (d, 1H, *J* = 8.1 Hz), 6.30-6.27 (d, 1H, *J* = 8.2 Hz), 5.42-5.36 (t, 1H, *J* = 8.3 Hz), 3.65-3.61 (d, 1H, *J* = 8.6 Hz), 1.43-1.25 (m, 3H), 1.17-1.14 (d, 18H, *J* = 7.0 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 153.72, 130.59, 130.11, 125.10, 121.58, 118.21, 79.83, 74.87, 18.19, 13.28.

ESI MS (m/z): 441.4 $[M+Na]^+$.

Triisopropyl{2-[(*E*)-2-nitrovinyl]phenoxy}silane 405



To a stirred solution of 2-[(triisopropylsilyl)oxy]benzaldehyde **403** (1 g, 10 mmol) in nitromethane (5 mL) was added ammonium acetate (70 mg, 2.5 mmol) and stirred it at 90 °C for 5 h. After TLC analysis had shown complete conversion of the starting material water (10 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 10 mL), the combined extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. Flash column chromatography (5% ethyl acetate in hexane) yielded **405** as yellow oil (400 mg, 35%).

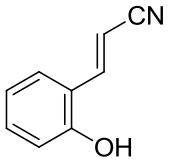
R_f = 0.50 (10% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.41-8.35 (d, 1H, *J* = 13.7 Hz), 7.73-7.67 (d, 1H, *J* = 13.7 Hz), 7.48-7.45 (d, 1H, *J* = 7.6 Hz), 7.38-7.31 (t, 1H, *J* = 7.4 Hz), 7.01-6.95 (t, 1H, *J* = 7.6 Hz), 6.93-6.90 (d, 1H, *J* = 8.3 Hz), 1.43-1.24 (m, 3H), 1.16-1.13(d, 18H, *J* = 7.2 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 156.46, 137.15, 135.17, 133.42, 129.69, 121.60, 121.25, 119.62, 17.98, 13.12.

ESI MS (m/z): 322.3 $[M+H]^+$.

(2*E*)-3-(2-Hydroxyphenyl)acrylonitrile 406



To a solution of salicyaldehyde (1 g, 10 mmol) in water (15 mL) at room temperature was added triphenyl phosphine (3.86 g, 18 mmol), bromoacetonitrile (1.76 g, 18 mmol), lithium hydroxide (721 mg, 21 mmol) and lithium chloride (2g, 60 mmol) were added and the mixture was refluxed for 25 min. After TLC analysis had shown complete conversion of the starting materials water (10 mL) was added, the mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (30% ethyl acetate in hexane) gave **406** (330 mg, 28%) as colorless solid.

R_f = 0.12 (20% ethyl acetate in hexane).

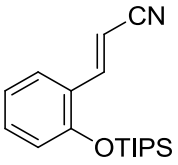
m.p. 62-64 °C (Lit.[139])

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.66-7.59 (d, 1H, *J* = 16.7 Hz), 7.33-7.24 (m, 2H), 7.09 (s, 1H), 6.95-6.87 (m, 2H), 6.21-6.14 (d, 1H, *J* = 16.7 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 155.87, 147.68, 132.39, 129.56, 120.96, 120.81, 119.29, 116.62, 96.34.

ESI MS (m/z): 168.2 $[M+Na]^+$.

(2*E*)-3-{2-[(Triisopropylsilyl)oxy]phenyl}acrylonitrile 407



To a stirred solution of (2*E*)-3-(2-hydroxyphenyl)acrylonitrile **406** (410 mg, 10 mmol) in CH_2Cl_2 (10 mL) diisopropylamine (571 mg, 20 mmol), DMAP (catalytic) was added, followed by the dropwise addition of triisipropylsilyl chloride (654 mg, 12 mmol) and the reaction mixture was left stirring for 1 h at 25 °C. After TLC analysis had shown complete conversion of the starting materials, water (10 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (10% ethyl acetate in hexane) gave **407** (830 mg, 97%) as a colorless oil.

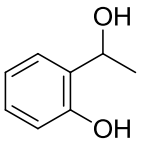
R_f = 0.52 (20% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.82-7.75 (d, 1H, *J* = 16.8 Hz), 7.42-7.39 (d, 1H, *J* = 7.7 Hz), 7.30-7.24 (t, 1H, *J* = 7.4 Hz), 6.97-6.91 (t, 1H, *J* = 7.4 Hz), 6.88-6.85 (d, 1H, *J* = 8.3 Hz), 5.92-5.85 (d, 1H, *J* = 16.8 Hz), 1.39-1.25 (m, 3H), 1.13-1.10 (d, 18H, *J* = 7.1 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 154.76, 146.28, 132.28, 127.11, 124.59, 121.33, 119.38, 118.79, 95.64, 17.92, 13.02.

ESI MS (m/z): 302.5 $[M+H]^+$.

2-(1-Hydroxyethyl)phenol 415



To a solution of $NaBH_4$ (330 mg, 12 mmol) in MeOH (25 mL) was added 2-hydroxyacetophenone (2 g,10 mmol) in MeOH (5 mL). The mixture was stirred at room temperature for 15 min. MeOH was then removed in vacuo and the resulting crude re-dissolved in EtOAc (30 mL) and washed with brine (10 mL). The organic layer was dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash chromatography (20 % ethyl acetate in hexane) gave **415** (1.2 g, 60%) as brown oil.

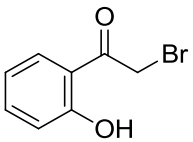
R_f = 0.22 (10% ethyl acetate in hexane after 4 runs).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.05 (bs, 1H), 7.18-7.12 (t, 1H, *J* = 8.1 Hz), 6.98-6.96 (d, 1H, *J* = 6.7 Hz), 6.86-6.80 (t, 2H, *J* = 8.2 Hz), 5.07-4.99 (dd, 1H, *J* = 6.7 Hz), 2.89 (bs, 1H), 1.57-1.54 (d, 3H, *J* = 6.5 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 155.35, 129.01, 128.59, 126.60, 120.06, 117.12, 71.53, 23.48.

ESI MS (m/z): 139.2 $[M+H]^+$.

2-Bromo-1-(2-hydroxyphenyl)ethanone 416



To a boiling solution of copper(II) bromide (558 mg, 17 mmol) in $CHCl_3$ (10 mL) 2-hydroxyacetophenone (200 mg, 10 mmol) was added, and the reaction mixture was refluxed for 12 h. After TLC analysis had shown complete conversion of the starting materials, the reaction mixture was filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (1% ethyl acetate in hexane) gave **416** (205 mg, 65%) as off white solid.

R_f = 0.17 (5% ethyl acetate in hexane).

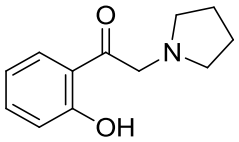
m.p. 42-44 °C (Lit.[151])

^{1}H NMR (250 MHz, $CDCl_3$) δ: 11.73 (s, 1H), 7.77-7.74 (d, 1H, *J* = 7.0 Hz), 7.56-7.50 (t, 1H, *J* = 7.3 Hz), 7.04-7.01 (d, 1H, *J* = 8.4 Hz), 6.97-6.91 (t, 1H, *J* = 7.5 Hz), 4.45 (s, 2H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 197.16, 163.38, 137.59, 130.49, 119.43, 119.10, 117.20, 30.05.

ESI MS (m/z): 238.1 $[M+Na]^+$.

1-(2-Hydroxyphenyl)-2-pyrrolidin-1-ylethanone 418



To a stirred solution of 2-bromo-1-(2-hydroxyphenyl)ethanone **416** (200 mg, 10 mmol) in CH_2Cl_2 (10 mL) at 0 °C, pyrrolidine (100 mg, 15 mmol) was added, followed by the portionwise addition of potassium *tert*-butoxide (109 mg, 10.5 mmol) and the reaction mixture was left stirring for 12 h at 25 °C. After TLC analysis had shown complete conversion of the starting materials, water (10 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (40% ethyl acetate in hexane) gave **416** (110 mg, 57%) as a colorless oil.

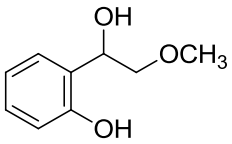
R_f = 0.10 (10% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 10.85 (s, 1H), 7.85-7.82 (d, 1H, *J* = 7.0 Hz), 7.44-7.38 (t, 1H, *J* = 7.3 Hz), 6.95-6.91 (d, 1H, *J* = 7.5 Hz), 6.87-6.81 (t, 1H, *J* = 8.4 Hz), 3.84 (s, 2H), 2.73 (bs, 4H), 1.87 (bs, 4H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 198.81, 162.18, 136.15, 130.22, 120.84, 119.44, 118.87, 63.19, 53.62, 23.74.

ESI MS (m/z): 244.1 $[M+K]^+$.

2-(1-Hydroxy-2-methoxyethyl)phenol 422



To a solution of $NaBH_4$ (38 mg, 11 mmol) in MeOH (5 mL) was added 2-bromo-1-(2-hydroxyphenyl)ethanone **416** (200 mg,10 mmol) in MeOH (5 mL). The mixture was stirred at room temperature for 6 h. MeOH was then removed in vacuo and the resulting crude re-dissolved in EtOAc (30 mL) and washed with brine (10 mL). The organic layer was dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash chromatography (20 % ethyl acetate in hexane) gave **422** (67 mg, 43%) as a colourless oil.

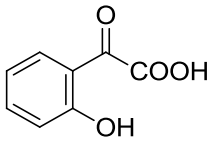
R_f = 0.45 (40% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.33 (s, 1H), 7.21-7.15 (t, 1H, *J* = 7.1 Hz), 7.01-6.99 (d, 1H, *J* = 6.9 Hz), 6.89-6.80 (m, 2H), 5.04-5.00 (dd, 1H, *J* = 3.0 Hz, 5.5 Hz), 3.60 (s, 1H), 3.58-3.53 (m, 2H), 3.45 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 156.14, 129.48, 127.71, 123.08, 119.94, 117.52, 76.24, 74.25, 59.14.

ESI MS (m/z): 169.3 $[M+H]^+$.

(2-Hydroxyphenyl)(oxo)acetic acid 424



To a boiling solution of selenium dioxide (1.63 g, 20 mmol) in dioxane : water (10 mL : 2 mL) 2-hydroxyacetophenone (1 g, 10 mmol) was added, and the reaction mixture was refluxed for 12 h. After TLC analysis had shown complete conversion of the starting materials, the reaction mixture was filtered and the solvent was removed in vacuo the resulting crude re-dissolved in EtOAc (30 mL) and washed with brine (10 mL). The organic layer was dried with sodium sulphate, filtered and the solvent was removed in

vacuo. The residue was purified by flash column chromatography (ethyl acetate) gave **424** (680 mg, 55%) as yellow oil.

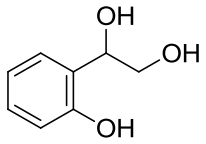
R_f = 0.05 (30% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 10.44 (bs, 2H), 7.99-7.96 (d, 1H, *J* = 7.0 Hz), 7.61-7.55 (t, 1H, *J* = 7.3 Hz), 7.05-6.93 (m, 2H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 189.71, 163.96, 163.88, 138.79, 132.64, 120.03, 118.56, 115.95.

ESI MS (m/z): 189.3 $[M+Na]^+$.

1-(2-Hydroxyphenyl)ethane-1,2-diol 425



To a stirred solution of (2-hydroxyphenyl)(oxo)acetic acid **424** (680 mg, 10 mmol) in THF at 0 °C, lithium aluminium hydride (466 mg, 30 mmol) was added portion wise and the reaction was stirred at room temperature for 2 h. After TLC analysis had shown complete conversion of the starting materials, ice-cold water (10 mL) was added to the reaction at 0 °C, the mixture was extracted with EtOAc (3 × 10 mL), the combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (20% ethyl acetate in hexane) gave **425** (320 mg, 50%) as colorless oil.

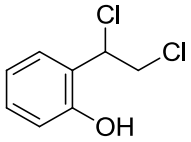
R_f = 0.15 (50% ethyl acetate in hexane).

^{1}H NMR (250 MHz, DMSO-d_6) δ: 9.32 (s, 1H), 7.30-7.27 (d, 1H, *J* = 7.0 Hz), 7.05-6.99 (t, 1H, *J* = 7.2 Hz), 6.78-6.72 (t, 2H, *J* = 7.0 Hz, 7.7 Hz), 5.11-5.09 (d, 1H, *J* = 3.5 Hz), 4.86-4.82 (t, 1H, *J* = 4.1 Hz), 4.71-4.67 (t, 1H, *J* = 5.5 Hz), 3.53-3.45 (m, 1H), 3.29-3.20 (m, 1H).

^{13}C NMR (63 MHz, DMSO-d_6) δ: 154.41, 129.41, 127.89, 127.46, 119.14, 115.21, 69.62, 66.62.

ESI MS (m/z): 177.1 $[M+Na]^+$.

2-(1,2-Dichloroethyl)phenol 426



To a stirred solution of 1-(2-hydroxyphenyl)ethane-1,2-diol **425** (100 mg, 10 mmol) in CH_2Cl_2 (2 mL), thionyl chloride (5 mL) was added, and the reaction mixture was refluxed for 12 h. After TLC analysis had shown complete conversion of the starting materials, thionyl chloride was removed by distillation and water (10 mL) was added to the residue, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (20% ethyl acetate in hexane) gave **426** (5 mg, 4%) as colorless oil.

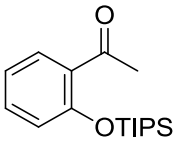
R_f = 0.30 (50% ethyl acetate in hexane).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.43-7.32 (m, 2H), 7.24-7.21 (d, 1H, *J* = 7.5 Hz), 7.13-7.10 (d, 1H, *J* = 7.9 Hz), 5.11-5.05 (dd, 2H, *J* = 1.6 Hz, 2.5 Hz), 4.22-4.15 (d, 1H, *J* = 4.9 Hz, 8.2 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 146.65, 132.83, 131.13, 129.93, 126.76, 124.96, 61.63, 60.98.

ESI MS (m/z): 192.1 $[M+H]^+$.

1-{2-[(Triisopropylsilyl)oxy]phenyl}ethanone 427



To a stirred solution of 2-hydroxy acetophenone (500 mg, 10 mmol) in CH_2Cl_2 (10 mL) diisopropylamine (816 mg, 22 mmol), DMAP (catalytic) was added, followed by the dropwise addition of triisipropylsilyl chloride (850 mg, 12 mmol) and the reaction mixture

was left stirring for 1 h at 25 °C. After TLC analysis had shown complete conversion of the starting materials, water (10 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (5% ethyl acetate in hexane) gave **427** (1.1 g, 94%) as a yellow oil.

R_f = 0.42 (10% ethyl acetate in hexane).

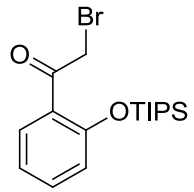
^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.62-7.59 (d, 1H, *J* = 7.7 Hz), 7.35-7.29 (t, 1H, *J* = 7.3 Hz), 6.99-6.93 (t, 1H, *J* = 7.4 Hz), 6.89-6.85 (d, 1H, *J* = 8.2 Hz), 2.63 (s, 3H), 1.42-1.27 (m, 3H), 1.14-1.11 (d, 18H, *J* = 7.2 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 201.01, 155.30, 132.98, 131.04, 130.14, 120.95, 119.59, 31.43, 18.02, 13.41.

IR: 2950, 2870, 1688, 1598, 1480, 1266, 904, 738 cm^{-1}.

HRMS (ESI) Calcd for $C_{17}H_{29}O_2Si$: 293.1931. Found: 293.1929.

2-Bromo-1-{2-[(triisopropylsilyl)oxy]phenyl}ethanone 428



The suspension of 1-{2-[(triisopropylsilyl)oxy]phenyl}ethanone **427** (500 mg, 10 mmol), NBS (304 mg, 10 mmol) and 4-toluenesulfonic acid (32 mg, 1 mmol) is triturated for about 3 h in a mortar and pestle. After TLC analysis had shown complete conversion of the starting materials, water (10 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (5% ethyl acetate in hexane) gave **428** (415 mg, 65%) as colorless oil.

R_f = 0.58 (5% *tert*-butylmethyl ether in hexane two runs)

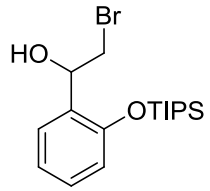
^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.67-7.64 (d, 1H, *J* = 7.7 Hz), 7.41-7.35 (t, 1H, *J* = 8.0 Hz), 7.03-6.97 (t, 1H, *J* = 7.46 Hz), 6.91-6.87 (d, 1H, *J* = 8.3 Hz), 4.62 (s, 2H), 1.43-1.28 (m, 3H), 1.14-1.11 (d, 18H, 7.2 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 193.84, 155.20, 133.93, 131.14, 127.64, 121.35, 119.37, 36.73, 18.02, 13.39.

IR: 2948, 2868, 1690, 1596, 1480, 1298, 1260, 1158, 996, 906, 758, 680 cm^{-1}.

HRMS (ESI) Calcd for $C_{17}H_{28}BrO_2Si$: 371.1036. Found: 371.1035.

2-Bromo-1-{2-[(triisopropylsilyl)oxy]phenyl}ethanol 429



To a solution of $NaBH_4$ (122 mg, 12 mmol) in THF (25 mL) was added 2-bromo-1-{2-[(triisopropylsilyl)oxy]phenyl}ethanone **428** (1 g,10 mmol) and the mixture was refluxed for 4 h. After TLC analysis had shown complete conversion of the starting materials, water (10 mL) was added, the mixture was extracted with EtOAc (3 × 10 mL). The organic layer was dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash chromatography (10 % ethyl acetate in hexane) gave **429** (730 mg, 73%) as colorless oil.

R_f = 0.24 (10% ethyl acetate in hexane).

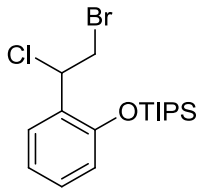
^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.50-7.47 (d, 1H, *J* = 6.7 Hz), 7.21-7.14 (t, 1H, *J* = 7.8 Hz), 7.01-6.95 (t, 1H, *J* = 7.4 Hz), 6.82-6.79 (d, 1H, *J* = 8.0 Hz), 5.30-5.24 (ddd, 1H, *J* = 1.9 Hz, 3.0 Hz, 3.5 Hz), 3.80-3.75 (dd, 1H, *J* = 2.7 Hz, 7.4 Hz), 3.49-3.41 (t, 1H, *J* = 10.0 Hz), 2.77-2.75 (d, 1H, *J* = 3.9 Hz), 1.41-1.26 (m, 3H), 1.15-1.11 (dd, 18H, *J* = 3.0 Hz, 4.2 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 152.77, 130.08, 129.02, 126.83, 121.22, 117.91, 69.64, 39.62, 18.22, 13.18.

IR: 3438, 2868, 1746, 1642, 1492, 1272, 1260, 1144, 920, 876, 754, 664 cm^{-1}.

HRMS (ESI) Calcd for C_{17} H_{28}OBr Si = 355.1087. Found: 355.1083.

[2-(2-Bromo-1-chloroethyl)phenoxy](triisopropyl)silane 430



A solution of 2-bromo-1-{2-[(triisopropylsilyl)oxy]phenyl}ethanol **429** (6 g, 10 mmol) in thionyl chloride (20 mL) was refluxed for 6 h. After TLC analysis had shown complete conversion of the starting materials, thionyl chloride was removed by distillation and water (20 mL) was added to the residue, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (10% ethyl acetate in hexane) gave **430** (5.3 g, 84%) as colorless oil.

R_f = 0.64 (10% ethyl acetate in hexane).

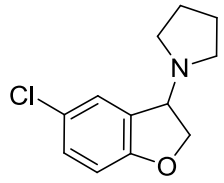
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45-7.43 (d, 1H, *J* = 7.5 Hz), 7.22-7.18 (t, 1H, *J* = 7.5 Hz), 7.00-6.96 (t, 1H, *J* = 7.9 Hz), 6.84-6.82 (d, 1H, *J* = 1.6 Hz, 2.5 Hz), 5.64-5.61 (t, 1H, *J* = 4.9 Hz, 8.2 Hz), 3.93-3.89 (dd, 1H, *J* = 4.9 Hz, 8.2 Hz), 3.84-3.80 (dd, 1H, *J* = 4.9 Hz, 8.2 Hz), 1.40-1.30 (m, 3H), 1.15-1.13 (dd, 18H, *J* = 3.0 Hz, 4.2 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 153.39, 129.97, 127.98, 121.25, 119.38, 118.26, 56.15, 35.66, 18.20, 13.18.

IR: 2948, 2870, 1690, 1596, 1480, 1298, 1260, 1158, 906, 758, 680, 610 cm^{-1}.

HRMS (ESI) Calcd for $C_{17}H_{29}$OBrSi: 356.1165. Found: 356.1165.

1-(5-Chloro-2,3-dihydro-1-benzofuran-3-yl)pyrrolidine 432



To a stirred solution of [2-(2-bromo-1-chloroethyl)phenoxy](triisopropyl)silane **430** (200 mg, 10 mmol) in THF (10 mL) at 0 °C, pyrrolidine (43 mg, 12 mmol) was added followed by dropwise addition of TBAF (267 mg, 20 mmol) and the reaction was stirred at 0 °C for 10 min and then room temperature for 1 h. After TLC analysis had shown complete conversion of the starting materials, water (10 mL) was added, the mixture was extracted with EtOAc (3 × 10 mL), the combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (20% methanol in dichloromethane) gave **432** (6 mg, 5%) as a colorless oil.

R_f = 0.18 (10% methanol in dichloromethane).

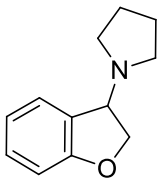
^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.30-7.29 (d, 1H, *J* = 2.0 Hz), 7.18-7.13 (dd, 1H, *J* = 2.1 Hz, 6.4 Hz), 6.77-6.74 (d, 1H, *J* = 8.6 Hz), 4.64-4.55 (dd, 1H, *J* = 6.2 Hz, 7.1 Hz), 4.48-4.38 (dd, 2H, , *J* = 5.7 Hz, 7.5Hz), 2.70-2.46 (m, 4H), 1.77 (bs, 4H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 159.30, 129.59, 126.37, 125.01, 111.19, 74.76, 63.09, 49.46, 23.29.

IR: 2990, 2974, 1642, 1478, 1366, 1266, 1224, 896, 738, 704, 666 cm^{-1}.

HRMS (ESI) Calcd for $C_{12}H_{15}ClNO$: 224.0837. Found: 224.0832.

1-(2,3-Dihydro-1-benzofuran-3-yl)pyrrolidine 431



Another product obtained from the same flash column chromatography was **431** as brown oil (9 mg, 10% yield).

Method B

To a stirred solution of 2-bromo-1-{2-[(triisopropylsilyl)oxy]phenyl}ethyl nitrate **440** (200 mg, 10 mmol) in THF (10 mL) at -78 °C, pyrrolidine (41 mg, 12 mmol) was added followed by dropwise addition of TBAF (249 mg, 20 mmol) and the reaction was stirred at -78 °C for 30 min and then room temperature for 30 min. After TLC analysis had shown complete conversion of the starting materials, water (10 mL) was added, the mixture was extracted with EtOAc (3 × 10 mL), the combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (40% ethyl acetate in hexane) gave **431** (73 mg, 82%) as brown oil.

R_f = 0.29 (20% ethyl acetate in hexane).

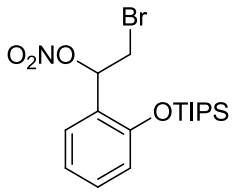
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35-7.33 (d, 1H, *J* = 7.3 Hz), 7.23-7.19 (t, 1H, *J* = 7.5 Hz), 6.90-6.86 (t, 1H, *J* = 7.4 Hz), 6.85-6.83 (d, 1H, *J* = 8.0 Hz), 4.63-4.57 (dd, 1H, *J* = 7.5 Hz, 9.0 Hz), 4.46-4.40 (dd, 2H, , *J* = 7.6 Hz, 8.5 Hz, 9.0 Hz), 2.73-2.69 (m, 2H), 2.57-2.52 (m, 2H), 1.80-1.73 (m, 4H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 160.70, 129.73, 126.50, 126.04, 120.31, 110.28, 74.29, 63.31, 49.59, 23.33.

IR: 2966, 2940, 1636, 1696, 1480, 1320, 1232, 982, 824, 754 cm^{-1}.

HRMS (ESI) Calcd for $C_{12}H_{16}NO$: 190.1226. Found: 190.1222.

2-Bromo-1-{2-[(triisopropylsilyl)oxy]phenyl}ethyl nitrate 440



To a solution of [2-(2-bromo-1-chloroethyl)phenoxy](triisopropyl)silane **430** (100 mg, 10 mmol) in acetonitrile (10 mL) was added $AgNO_3$ (86 mg, 10 mmol) and the reaction mixture was stirred for 12 h. After TLC analysis had shown complete conversion of the starting materials, the solvent was removed in vacuo and water (20 mL) was added to the residue, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (10% ethyl acetate in hexane) gave **440** (100 g, 94%) as yellow oil.

R_f = 0.16 (hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32-7.30 (d, 1H, *J* = 7.7 Hz), 7.25-7.21 (t, 1H, *J* = 7.8 Hz), 6.98-6.94 (t, 1H, *J* = 7.5 Hz), 6.87-6.84 (d, 1H, *J* = 8.2 Hz), 6.53-6.50 (dd, 1H, *J* = 3.8 Hz, 5.0 Hz), 3.68-3.64 (dd, 1H, *J* = 3.9 Hz, 7.4 Hz), 3.59-3.54 (dd, 1H, *J* = 2.3 Hz, 9.0 Hz), 1.41-1.32 (m, 3H), 1.16-1.13 (dd, 18H, *J* = 3.4 Hz, 4.0 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 153.29, 130.51, 126.33, 125.62, 121.36, 118.27, 79.47, 30.09, 18.17, 13.18.

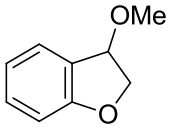
IR: 2984, 2918, 1732, 1596, 1484, 1370, 1234, 1260, 1154, 1022, 978, 802, 754 cm^{-1}.

HRMS (ESI) Calcd for $C_{17}H_{30}BrO_2Si$: 373.1193. Found: 373.1196.

General procedure for the Michael addition reaction

2-Bromo-1-{2-[(triisopropylsilyl)oxy]phenyl}ethyl nitrate **440** was dissolved in THF, the reaction mixture was cooled to -78 °C, the appropriate nucleophile (Table 2.1) was added followed by dropwise addition of TBAF (1M in THF) and the reaction was stirred at -78 °C for 30 min and then room temperature for 30 min. After TLC analysis had shown complete conversion of the starting materials, water (10 mL) was added, the mixture was extracted with EtOAc (3 × 10 mL), the combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. Flash column chromatography using the stated solvent mixtures yielded the corresponding products.

3-Methoxy-2,3-dihydro-1-benzofuran 436



To a stirred solution of [2-(2-bromo-1-chloroethyl)phenoxy](triisopropyl)silane **430** (200 mg, 10 mmol) in MeOH (10 mL) at 0 °C, TBAF (267 mg, 20 mmol) was added and the reaction was stirred at 0 °C for 10 min and then room temperature for 1 h. After TLC analysis had shown complete conversion of the starting materials, solvent was removed in vacuo water (10 mL) was added to the residue, the mixture was extracted with EtOAc (3 × 10 mL), the combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (ethyl acetate in hexane) afforded **436** as colorless oil (9 mg, 12%).

Method B

According to the general procedure, 2-bromo-1-{2-[(triisopropylsilyl)oxy]phenyl}ethyl nitrate **440** (100 mg, 10 mmol) is reacted with TBAF (124 mg, 20 mmol) in MeOH (10 mL) at -78 °C. Subsequent workup and flash column chromatography (20% ethyl acetate in hexane) afforded **436** as colorless oil (31 mg, 88%).

R_f = 0.36 (20% ethyl acetate in hexane).

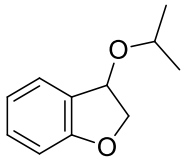
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42-7.40 (d, 1H, *J* = 7.3 Hz), 7.29-7.25 (t, 1H, *J* = 7.7 Hz), 6.95-6.91 (t, 1H, *J* = 7.4 Hz), 6.90-6.88 (d, 1H, *J* = 8.0 Hz), 5.01-4.99 (dd, 1H, *J* = 2.0 Hz, 4.3 Hz), 4.56-4.53 (dd, 1H, , *J* = 2.2 Hz, 8.5 Hz), 4.46-4.42 (dd, 1H, , *J* = 4.2 Hz, 6.4 Hz), 3.34 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 160.88, 130.86, 126.24, 125.67, 120.63, 110.72, 80.03, 76.11, 55.09.

IR: 2986, 2940, 1612, 1480, 1364, 1232, 1168, 1090, 1016, 950, 880, 754 cm^{-1}.

HRMS (ESI) Calcd for $C_9H_{10}NaO_2$: 173.0573. Found: 173.0577.

3-Isopropoxy-2,3-dihydro-1-benzofuran



To a stirred solution of [2-(2-bromo-1-chloroethyl)phenoxy](triisopropyl)silane **430** (200 mg, 10 mmol) in 2-propanol (10 mL) at 0 °C, TBAF (267 mg, 20 mmol) was added and the reaction was stirred at 0 °C for 10 min and then room temperature for 1 h. After TLC analysis had shown complete conversion of the starting materials, solvent was removed in vacuo water (10 mL) was added to the residue, the mixture was extracted with EtOAc (3 × 10 mL), the combined organic extracts were dried with sodium sulphate, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (20% ethyl acetate in hexane) afforded **437** as colorless oil (7.5 mg, 8%).

Method B

According to the general procedure, 2-bromo-1-{2-[(triisopropylsilyl)oxy]phenyl}ethyl nitrate **440** (100 mg, 10 mmol) is reacted with TBAF (124 mg, 20 mmol) in 2-propanol (10 mL) at -78 °C. Subsequent workup and flash column chromatography (20% ethyl acetate in hexane) afforded **437** as colorless oil (29 mg, 68%).

R_f = 0.57 (20% ethyl acetate in hexane).

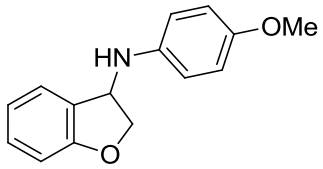
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37-7.35 (d, 1H, *J* = 7.3 Hz), 7.25-7.21 (t, 1H, *J* = 7.8 Hz), 6.93-6.89 (t, 1H, *J* = 7.5 Hz), 6.87-6.85 (d, 1H, *J* = 8.1 Hz), 5.17-5.15 (dd, 1H, *J* = 3.1 Hz), 4.52-4.48 (dd, 1H, , *J* = 3.9 Hz, 6.3 Hz), 4.47-4.43 (dd, 1H, , *J* = 3.1 Hz, 7.1 Hz), 3.88-3.78 (sep, 1H, *J* = 6.1 Hz), 1.22-1.20 (d, 6H, *J* = 6.1 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 160.60, 130.47, 126.88, 126.02, 120.73, 110.65, 77.49, 76.54, 70.22, 22.84, 22.76.

IR: 2972, 2928, 1600, 1482, 1466, 1378, 1232, 1078, 980, 752, 618 cm^{-1}.

HRMS (ESI) Calcd for $C_{11}H_{14}NaO_2$: 201.0886. Found: 201.877.

2,3-Dihydro-1-benzofuran-3-yl(4-methoxyphenyl)amine 441



According to the general procedure, 2-bromo-1-{2-[(triisopropylsilyl)oxy]phenyl}ethyl nitrate **440** (100 mg, 10 mmol) and 4-methoxy aniline (35 mg, 12 mmol) were reacted with TBAF (124 mg, 20 mmol) in THF (10 mL) at -78 °C. Subsequent workup and flash column chromatography (10% ethyl acetate in hexane) afforded **441** as yellow solid (43 mg, 74%).

m.p. 37-39 °C.

R_f = 0.44 (20% ethyl acetate in hexane)

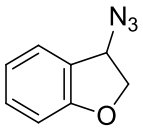
^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.32-7.31 (d, 1H, *J* = 7.3 Hz), 7.23-7.19 (t, 1H, *J* = 7.3 Hz), 6.89-6.83 (m, 2H), 6.75-6.73 (d, 2H, *J* = 8.9 Hz), 6.67-6.65 (d, 2H, *J* = 9.0 Hz), 5.66-5.64 (d, 1H, *J* = 8.2 Hz), 5.22-5.16 (ddd, 1H, , *J* = 2.9 Hz, 5.0 Hz, 7.9 Hz), 4.74-4.70 (dd, 1H, *J* = 1.4 Hz, 7.8 Hz), 4.20-4.17 (dd, 1H, *J* = 4.6 Hz, 4.8 Hz), 3.65 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 160.27, 152.86, 140.67, 130.17, 127.78, 125.41, 120.99, 115.18, 115.01, 110.44, 77.66, 56.49, 55.87.

IR: 2942, 2928, 2362, 1638, 1512, 1480, 1290, 1236, 1036, 970, 752, 668 cm^{-1}.

HRMS (ESI) Calcd for $C_{15}H_{14}NO_2$: 240.1030. Found: 240.1024.

2,3-Dihydro-1-benzofuran-3-yl azide 442



According to the general procedure, 2-bromo-1-{2-[(triisopropylsilyl)oxy]phenyl}ethyl nitrate **440** (100 mg, 10 mmol) and sodium azide (19 mg, 12 mmol) were reacted with TBAF (124 mg, 20 mmol) in THF (10 mL) at -78 °C. Subsequent workup and flash

column chromatography (10% ethyl acetate in hexane) afforded **442** as pale yellow oil (30 mg, 79%).

R_f = 0.50 (20% ethyl acetate in hexane).

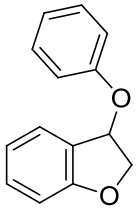
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43-7.41 (d, 1H, *J* = 7.5 Hz), 7.34-7.30 (t, 1H, *J* = 7.8 Hz), 7.01-6.98 (t, 1H, *J* = 7.4 Hz), 6.94-6.92 (d, 1H, *J* = 8.2 Hz), 5.04-5.01 (dd, 1H, *J* = 2.3 Hz, 4.3 Hz), 4.58-4.54 (dd, 1H, , *J* = 3.4 Hz, 7.0 Hz, 9.0 Hz), 4.51-4.48 (dd, 1H, , *J* = 2.9 Hz, 7.6 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 160.33, 131.31, 125.46, 123.95, 121.34, 110.87, 76.39, 62.10.

IR: 2956, 2920, 2360, 2096, 1644, 1478, 1234, 1164, 934, 750, 668 cm^{-1}.

HRMS (ESI) Calcd for C_8H_8O: 120.0570. Found: 120.0567.

3-Phenoxy-2,3-dihydro-1-benzofuran 443



According to the general procedure, 2-bromo-1-{2-[(triisopropylsilyl)oxy]phenyl}ethyl nitrate **440** (100 mg, 10 mmol) and phenol (27 mg, 12 mmol) were reacted with TBAF (124 mg, 20 mmol) in THF (10 mL) at -78 °C. Subsequent workup and flash column chromatography (10% ethyl acetate in hexane) afforded **443** as colorless oil (29 mg, 59%).

R_f = 0.63 (20% ethyl acetate in hexane).

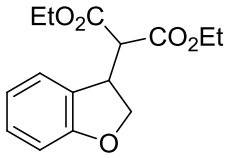
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41-7.39 (d, 1H, *J* = 7.6 Hz), 7.33-7.28 (m, 3H), 7.02-6.98 (t, 1H, *J* = 7.4 Hz), 6.95-6.89 (m, 4H), 5.90-5.88 (dd, 1H, *J* = 2.7 Hz, 3.5 Hz), 4.69-4.65 (dd, 1H, , *J* = 3.0 Hz, 4.5 Hz, 6.4 Hz), 4.63-4.60 (dd, 1H, , *J* = 2.9 Hz, 7.9 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 161.02, 157.22, 131.23, 129.84, 128.41, 126.39, 121.67, 121.04, 115.91, 110.75, 77.22, 76.17.

IR: 2928, 2892, 1710, 1614, 1482, 1228, 1174, 1062, 968, 750, 692 cm^{-1}.

HRMS (ESI) Calcd for $C_{14}H_{12}NaO_2$: 235.0730. Found: 235.0727.

Diethyl 2,3-dihydro-1-benzofuran-3-ylmalonate 444



According to the general procedure, 2-bromo-1-{2-[(triisopropylsilyl)oxy]phenyl}ethyl nitrate **440** (100 mg, 10 mmol) and diethyl malonate (45 mg, 12 mmol) [it was reacted first with sodium hydride (8 mg, 13 mmol) in THF (8 mL) to generate the anion] were reacted with TBAF (124 mg, 20 mmol) in THF (10 mL) at -78 °C. Subsequent workup and flash column chromatography (10% ethyl acetate in hexane) afforded **444** as colorless oil (32 mg, 76%).

R_f = 0.38 (20% ethyl acetate in hexane).

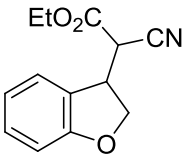
^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.17-7.14 (t, 2H, *J* = 7.5 Hz), 6.85-6.76 (m, 2H), 4.74-4.66 (t, 1H, *J* = 9.4 Hz), 4.53-4.47 (dd, 1H, *J* = 4.7 Hz, 5.0 Hz), 4.25-4.16 (dd, 5H, *J* = 7.1 Hz), 3.68-3.65 (d, 1H, *J* = 8.6Hz), 1.22-1.16 (t, 6H, *J* = 7.1 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 167.91, 167.77, 160.23, 129.11, 126.39, 125.05, 120.39, 109.76, 74.56, 61.64, 55.93, 41.33, 13.87.

IR: 2984, 2918, 1732, 1596, 1484, 1370, 1234, 1180, 1096, 1022, 978, 864, 754 cm^{-1}.

HRMS (ESI) Calcd for $C_{15}H_{18}NaO_5$: 301.1046. Found: 301.1042.

Ethyl cyano(2,3-dihydro-1-benzofuran-3-yl)acetate 445



According to the general procedure, 2-bromo-1-{2-[(triisopropylsilyl)oxy]phenyl}ethyl nitrate **440** (100 mg, 10 mmol) and ethyl cyanoacetate (32 mg, 12 mmol) [it was reacted first with sodium hydride (8 mg, 13 mmol) in THF (8 mL) to generate the anion] were reacted with TBAF (124 mg, 20 mmol) in THF (10 mL) at -78 °C. Subsequent workup and flash column chromatography (10% ethyl acetate in hexane) afforded **445** as brown oil (37 mg, 67%).

R_f = 0.36 (20% ethyl acetate in hexane).

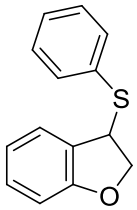
^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.21-7.14 (t, 2H, *J* = 7.5 Hz), 6.89-6.81 (m, 2H), 4.49-4.43 (dd, 1H), 4.23-4.05 (m, 4H), 3.63-3.60 (d, 1H), 1.24-1.19 (t, 3H, *J* = 7.1 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 165.19, 157.63, 126.55, 123.79, 122.45, 117.83, 115.06, 107.21, 71.99, 59.09, 42.10, 38.75, 11.38.

IR: 2984, 2918, 2360, 1742, 1598, 1484, 1370, 1234, 1180, 1096, 1022, 978, 864, 802, 754 cm^{-1}.

HRMS (ESI) Calcd for $C_{13}H_{13}NNaO_3$: 254.0788. Found: 254.0785.

3-(Phenylthio)-2,3-dihydro-1-benzofuran 446



According to the general procedure, 2-bromo-1-{2-[(triisopropylsilyl)oxy]phenyl}ethyl nitrate **440** (100 mg, 10 mmol) and thiophenol (32 mg, 12 mmol) were reacted with TBAF (124 mg, 20 mmol) in THF (10 mL) at -78 °C. Subsequent workup and flash column chromatography (10% ethyl acetate in hexane) afforded **446** as colorless oil (46 mg, 85%).

R_f = 0.56 (20% ethyl acetate in hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35-7.23 (m, 6H), 7.17-7.13 (t, 1H, *J* = 7.5 Hz), 6.89-6.85 (t, 1H, *J* = 7.48 Hz), 6.78-6.76 (d, 1H, *J* = 8.0 Hz), 4.90-4.87 (dd, 1H, *J* = 3.8 Hz, 4.0 Hz), 4.75-4.71 (dd, 1H, , *J* = 1.7 Hz, 8.1 Hz), 4.57-4.53 (dd, 1H, , *J* = 4.0 Hz, 5.6 Hz).

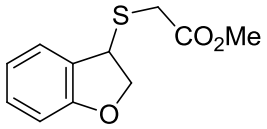
^{13}C NMR (63 MHz, $CDCl_3$) δ: 159.91, 133.87, 132.40, 129.75, 129.14, 127.74, 126.46, 125.44, 121.0, 110.14, 77.55, 48.85.

ESI MS (m/z): 251.3 $[M+Na]^+$.

IR: 2998, 2884, 2098, 1642, 1478, 1320, 1332, 1162, 1088, 988, 808, 736, 682 cm^{-1}.

HRMS (ESI) Calcd for $C_{14}H_{12}NaOS$: 251.0501. Found: 251.0499.

Methyl (2,3-dihydro-1-benzofuran-3-ylthio)acetate 447



According to the general procedure, 2-bromo-1-{2-[(triisopropylsilyl)oxy]phenyl}ethyl nitrate **440** (100 mg, 10 mmol) and methyl thioglycolate (30 mg, 12 mmol) were reacted with TBAF (124 mg, 20 mmol) in THF (10 mL) at -78 °C. Subsequent workup and flash column chromatography (10% ethyl acetate in hexane) afforded **447** as colorless oil (43 mg, 80%).

R_f = 0.41 (20% ethyl acetate in hexane).

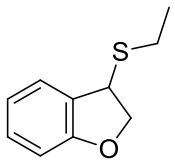
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32-7.30 (d, 1H, *J* = 7.5 Hz), 7.20-7.16 (t, 1H, *J* = 7.7 Hz), 6.92-6.89 (t, 1H, *J* = 7.5 Hz), 6.83-6.81 (d, 1H, *J* = 8.0 Hz), 4.80-4.76 (dd, 1H, *J* = 1.5 Hz, 8.2 Hz), 4.67-4.64 (dd, 1H, *J* = 4.0 Hz), 4.58-4.55 (dd, 1H, , *J* = 4.0 Hz, 5.6 Hz) 3.70 (s, 3H), 3.22-3.21(d, 2H, *J* = 2.0 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 170.70, 159.88, 129.80, 125.81, 125.46, 121.09, 110.14, 77.86, 52.55, 45.99, 32.13.

IR: 2964, 2854, 2104, 1644, 1478, 1434, 1276, 1230, 1140, 1008, 918, 734 cm^{-1}.

HRMS (ESI) Calcd for $C_{11}H_{12}NaO_3S$: 247.0399. Found: 247.0390.

3-(Ethylthio)-2,3-dihydro-1-benzofuran 448



According to the general procedure, 2-bromo-1-{2-[(triisopropylsilyl)oxy]phenyl}ethyl nitrate **440** (100 mg, 10 mmol) and ethyl mercaptan (18 mg, 12 mmol) [it was reacted first with sodium hydride (8 mg, 13 mmol) in THF (8 mL) to generate the anion] were reacted with TBAF (124 mg, 20 mmol) in THF (10 mL) at -78 °C. Subsequent workup and flash column chromatography (10% ethyl acetate in hexane) afforded **448** as colorless oil (32 mg, 76%).

R_f = 0.48 (20% ethyl acetate in hexane).

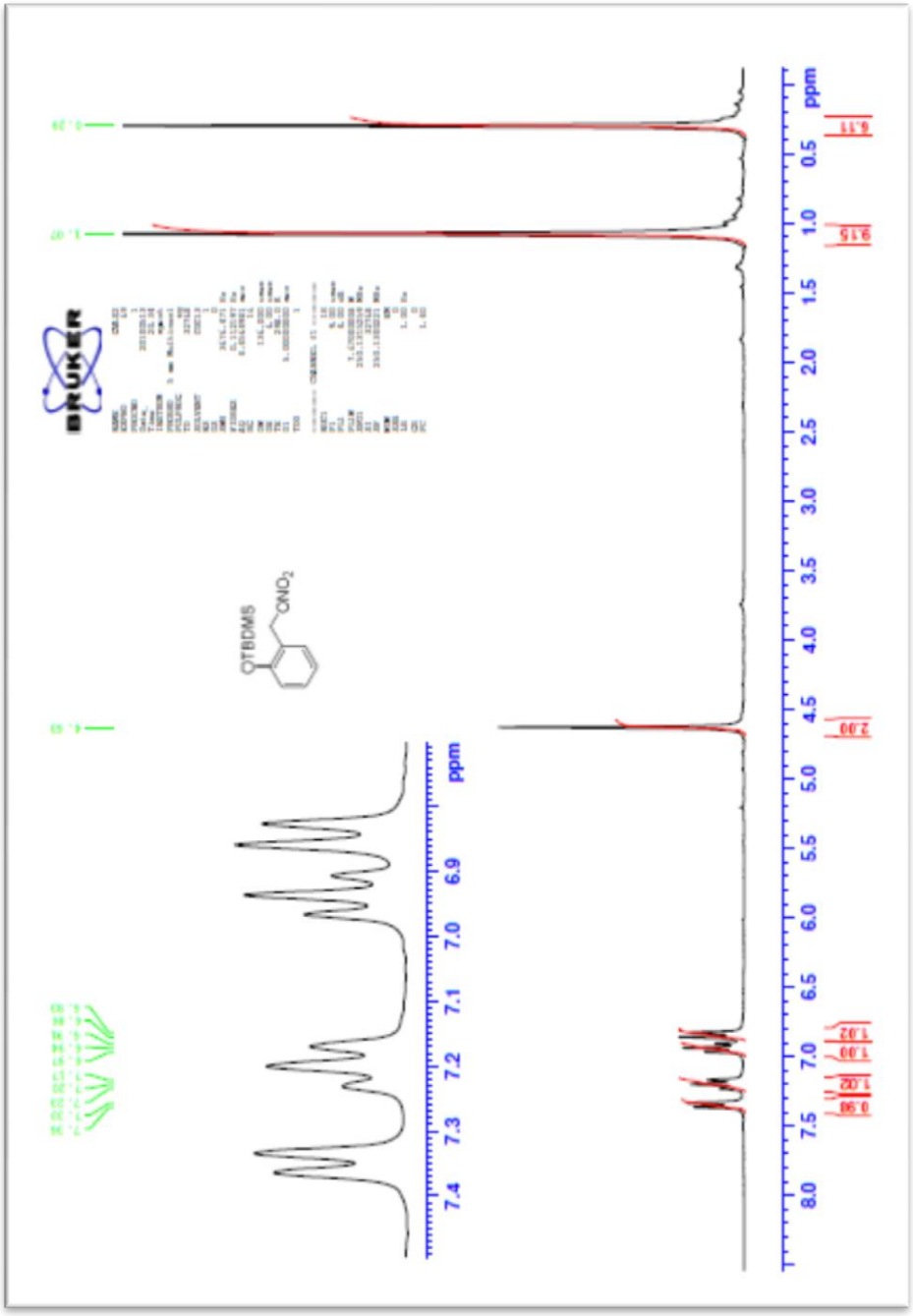
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31-7.29 (d, 1H, *J* = 7.0 Hz), 7.19-7.15 (t, 1H, *J* = 7.5 Hz), 6.86-6.82 (t, 1H, *J* = 7.2 Hz), 6.81-6.79 (d, 1H, *J* = 7.8 Hz), 4.85-4.81 (dd, 1H, *J* = 2.5 Hz, 6.0 Hz), 4.72-4.69 (dd, 1H, *J* = 1.5 Hz, 5.0 Hz), 4.63-4.60 (dd, 1H, *J* = 3.0 Hz, 6.0 Hz), 2.65-2.56 (q, 2H, *J* = 7.5 Hz), 1.37-1.31 (t, 3H, *J* = 7.5 Hz).

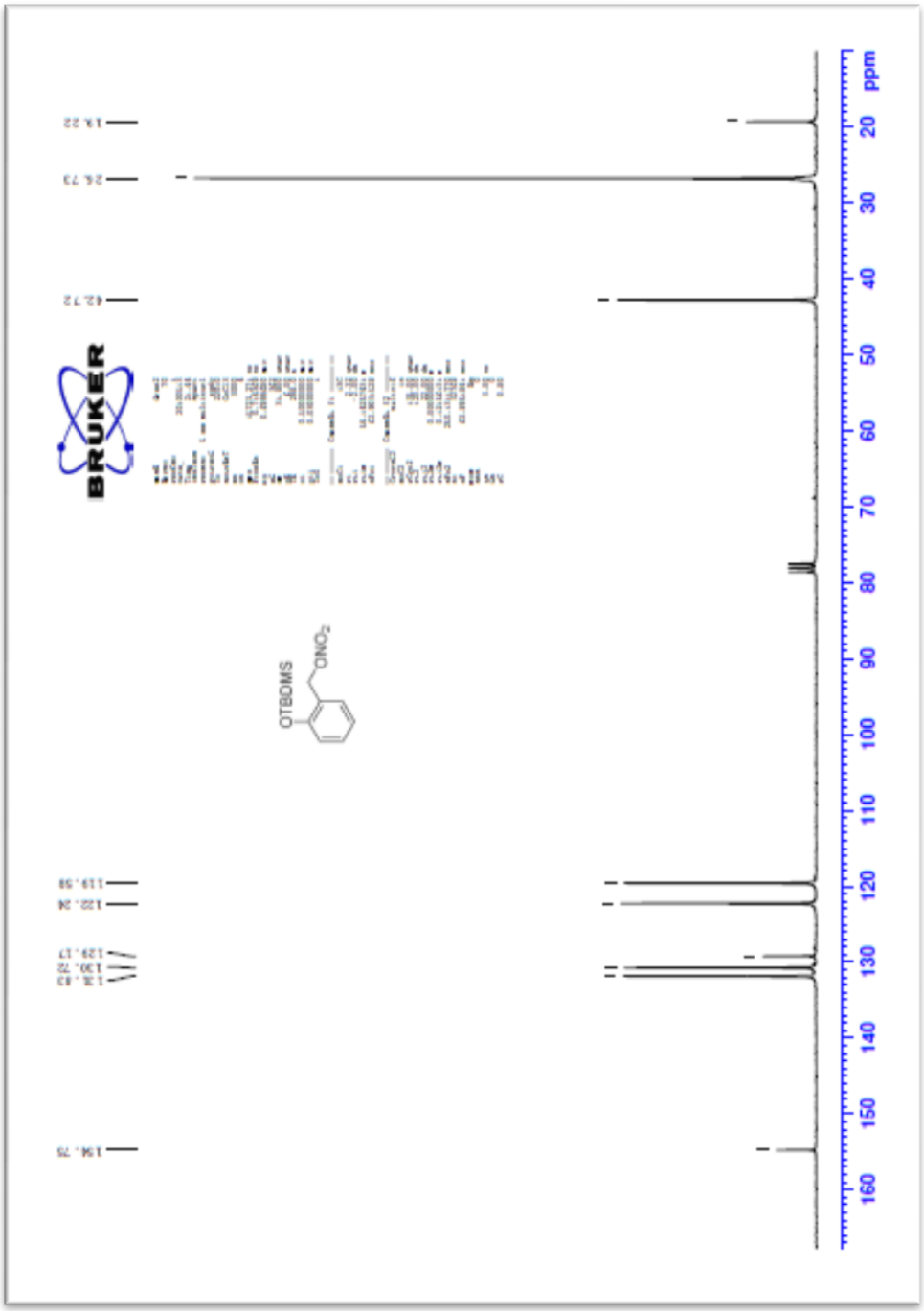
^{13}C NMR (63 MHz, $CDCl_3$) δ: 161.03, 130.95, 126.96, 126.61, 122.24, 111.29, 78.11, 53.69, 33.27, 17.58.

IR: 2956, 2854, 2108, 1650, 1478, 1436, 1276, 1230, 1128, 1098, 988, 744 cm^{-1}.

HRMS (ESI) Calcd for $C_{10}H_{13}OS$: 181.0682. Found: 181.0677.

^{1}H and ^{13}C NMR Spectra

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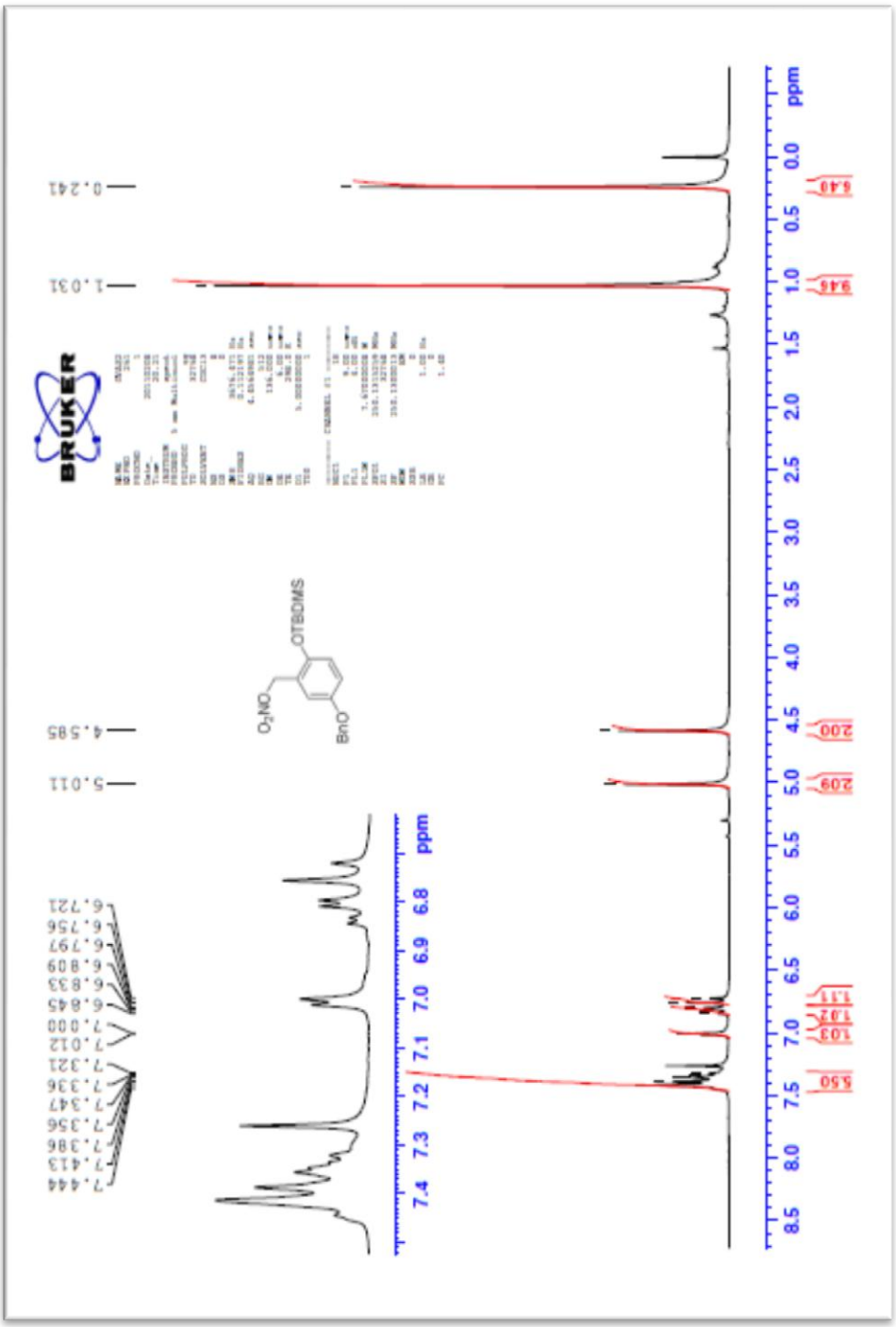
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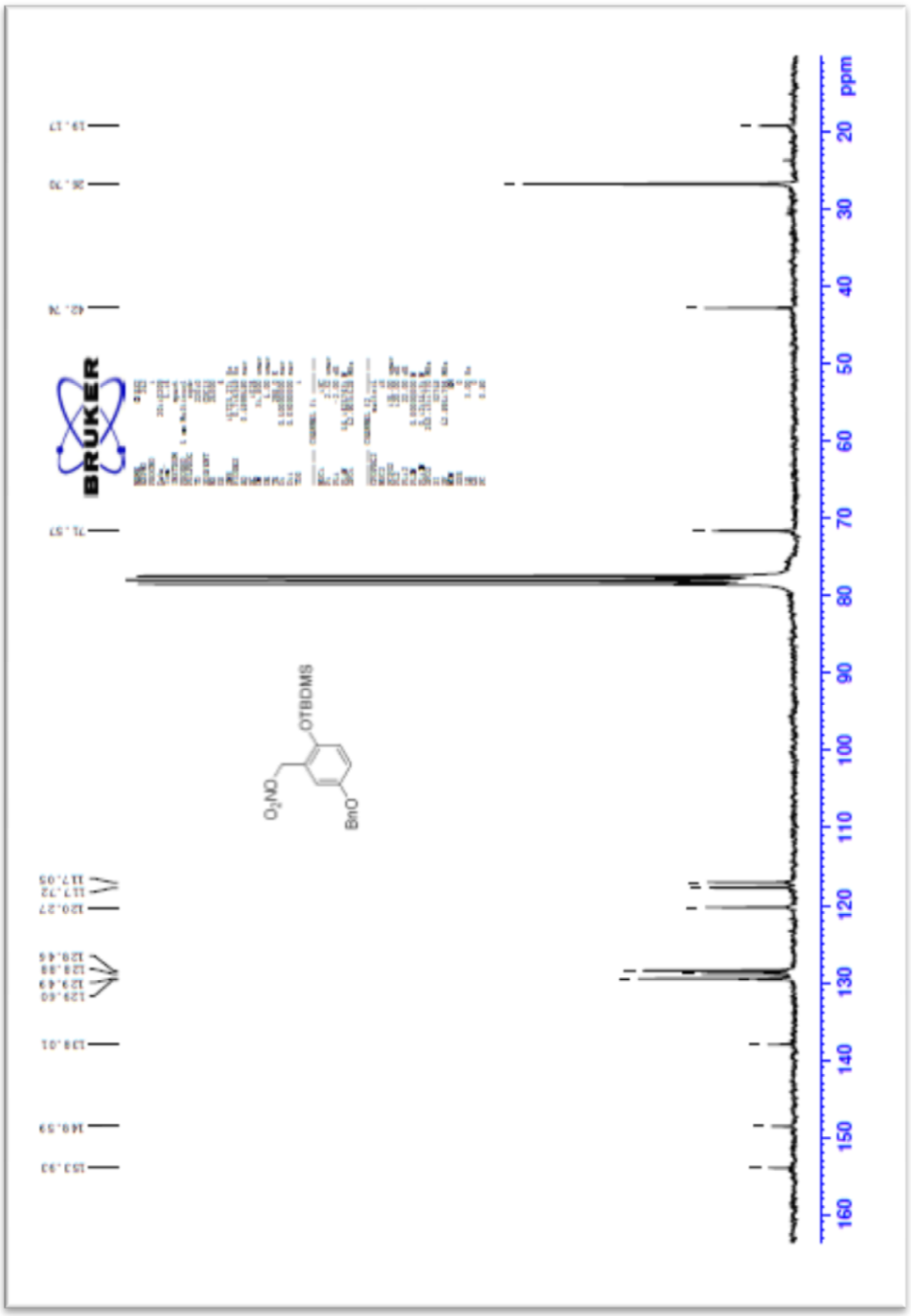
7.336
7.321
7.012
7.000
6.845
6.833
6.809
6.797
6.756
6.721
OTBDMS
BnO
O2NO
BRUKER
ppm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BnO
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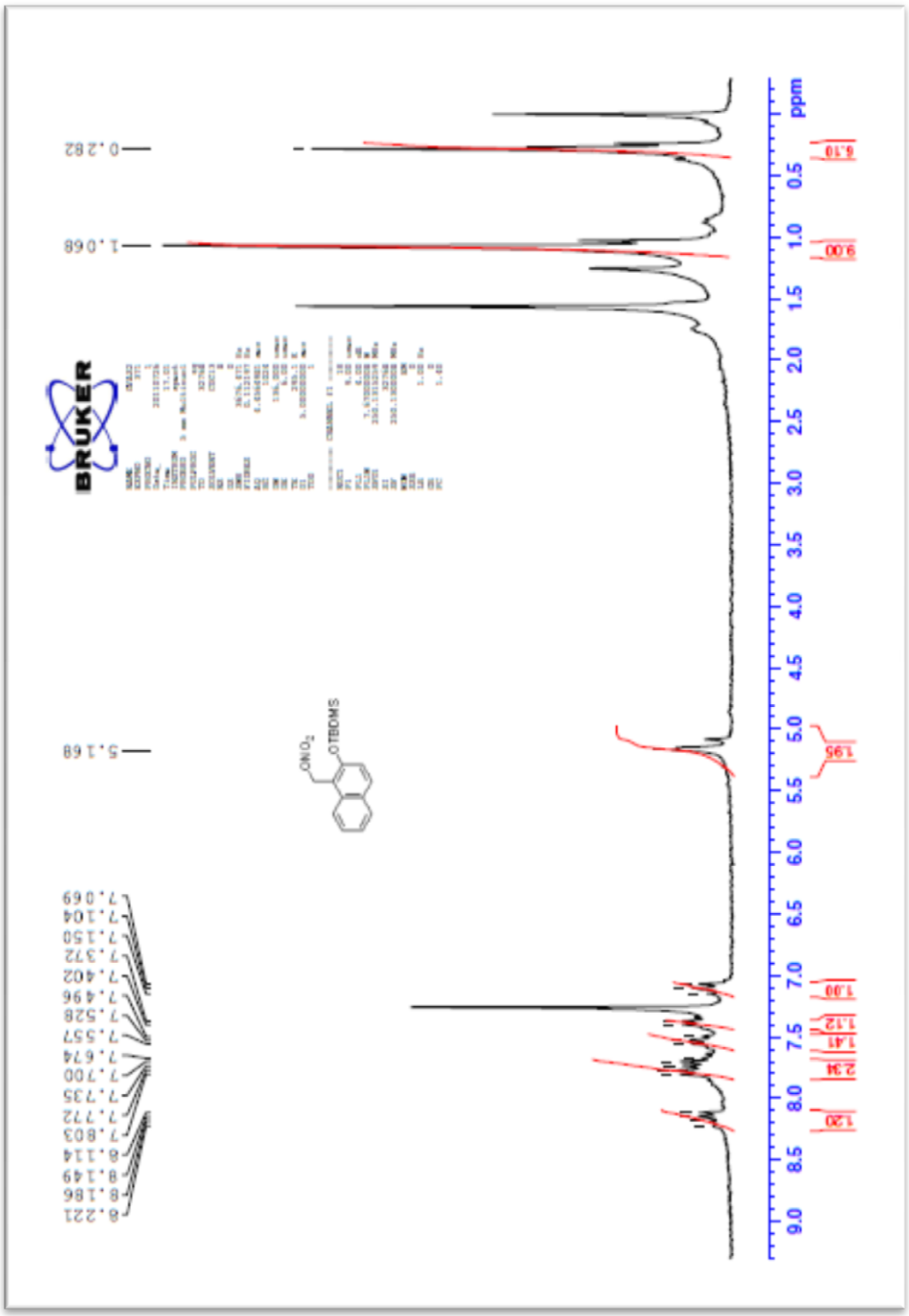
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7.700
7.674
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7.496
7.402
7.372
7.150
7.104
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ONO2
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BRUKER
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1.00
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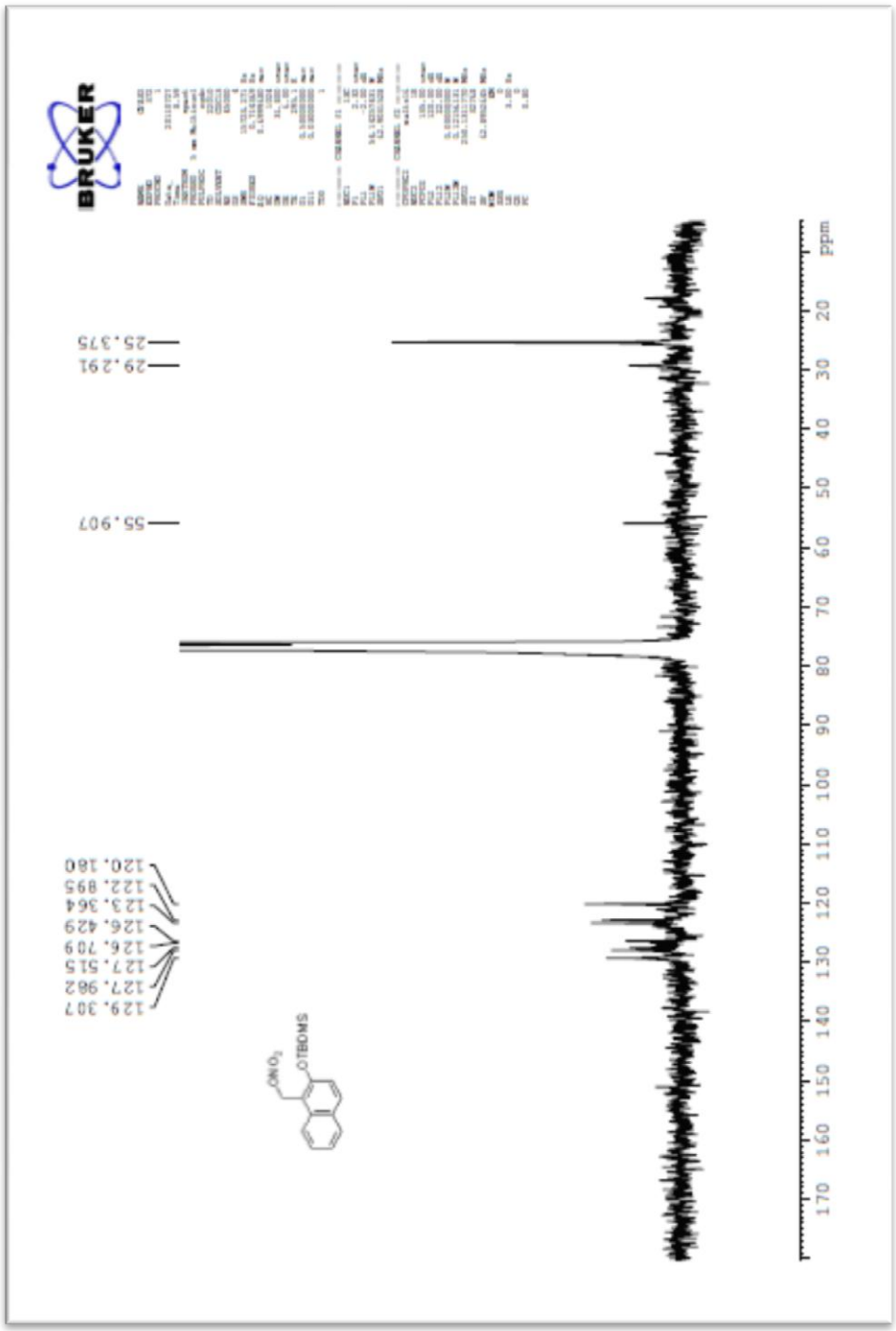
2.34
1.20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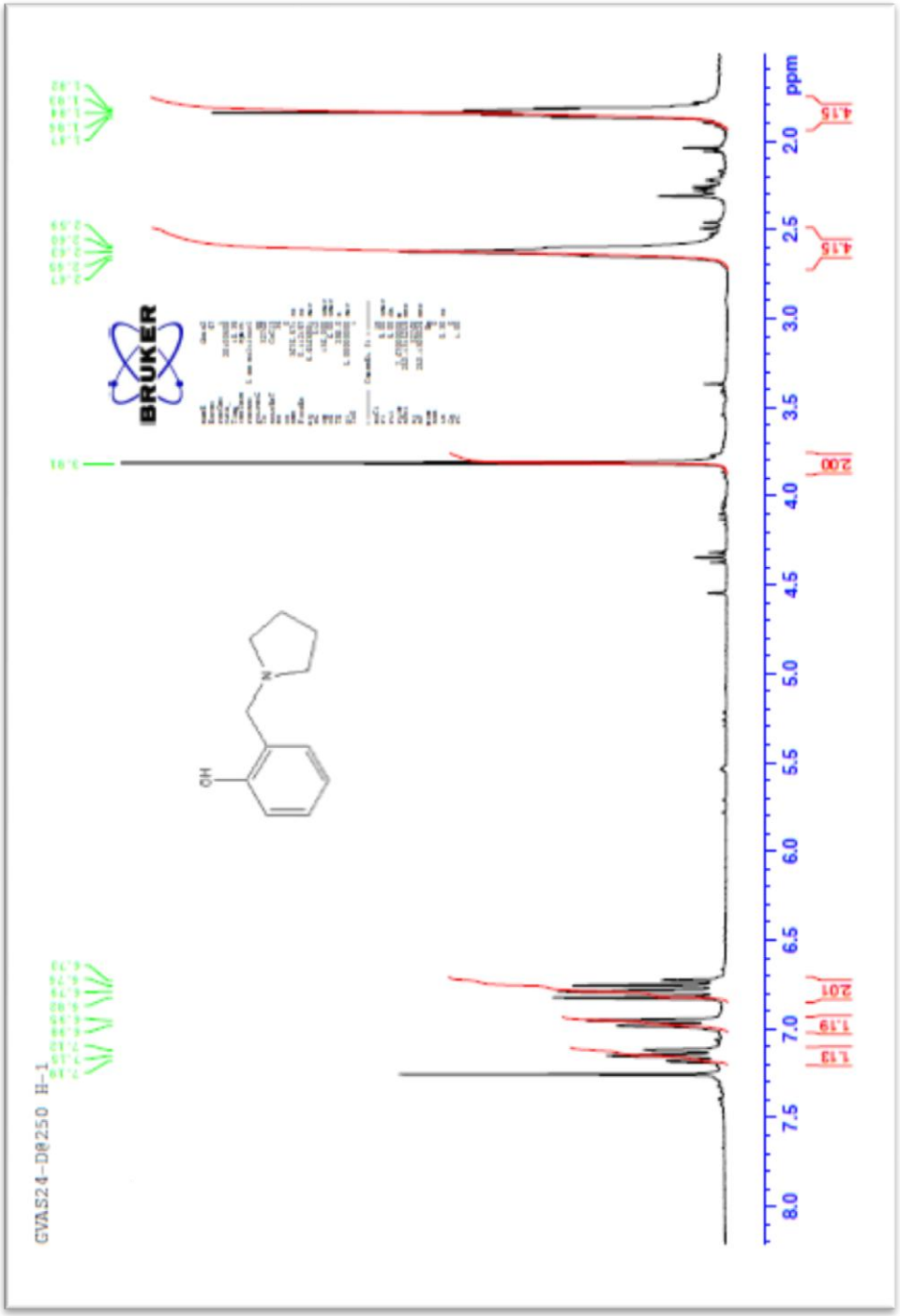
OTBDMS
ppm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4.15
4.15
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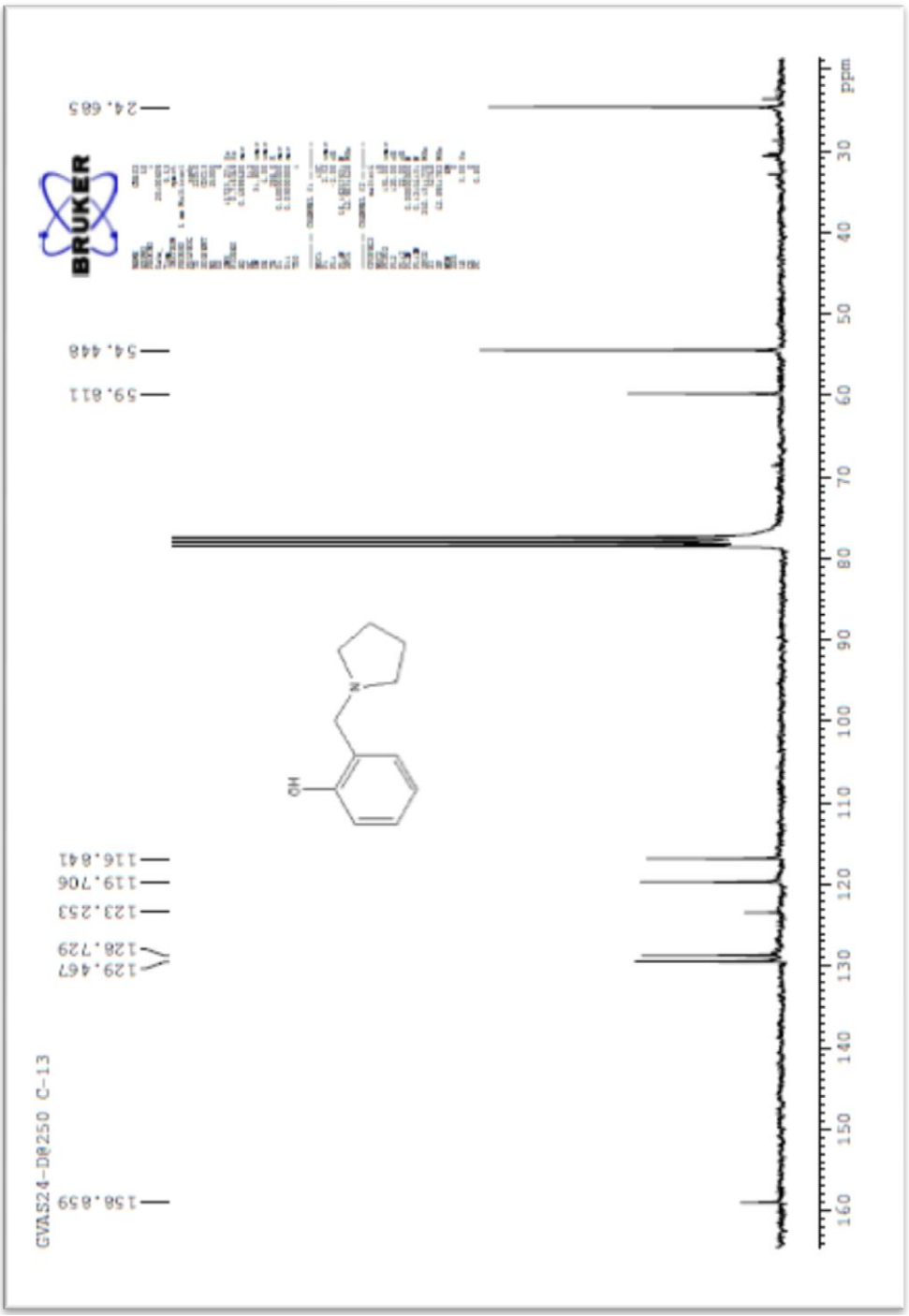
2.01
1.19
1.13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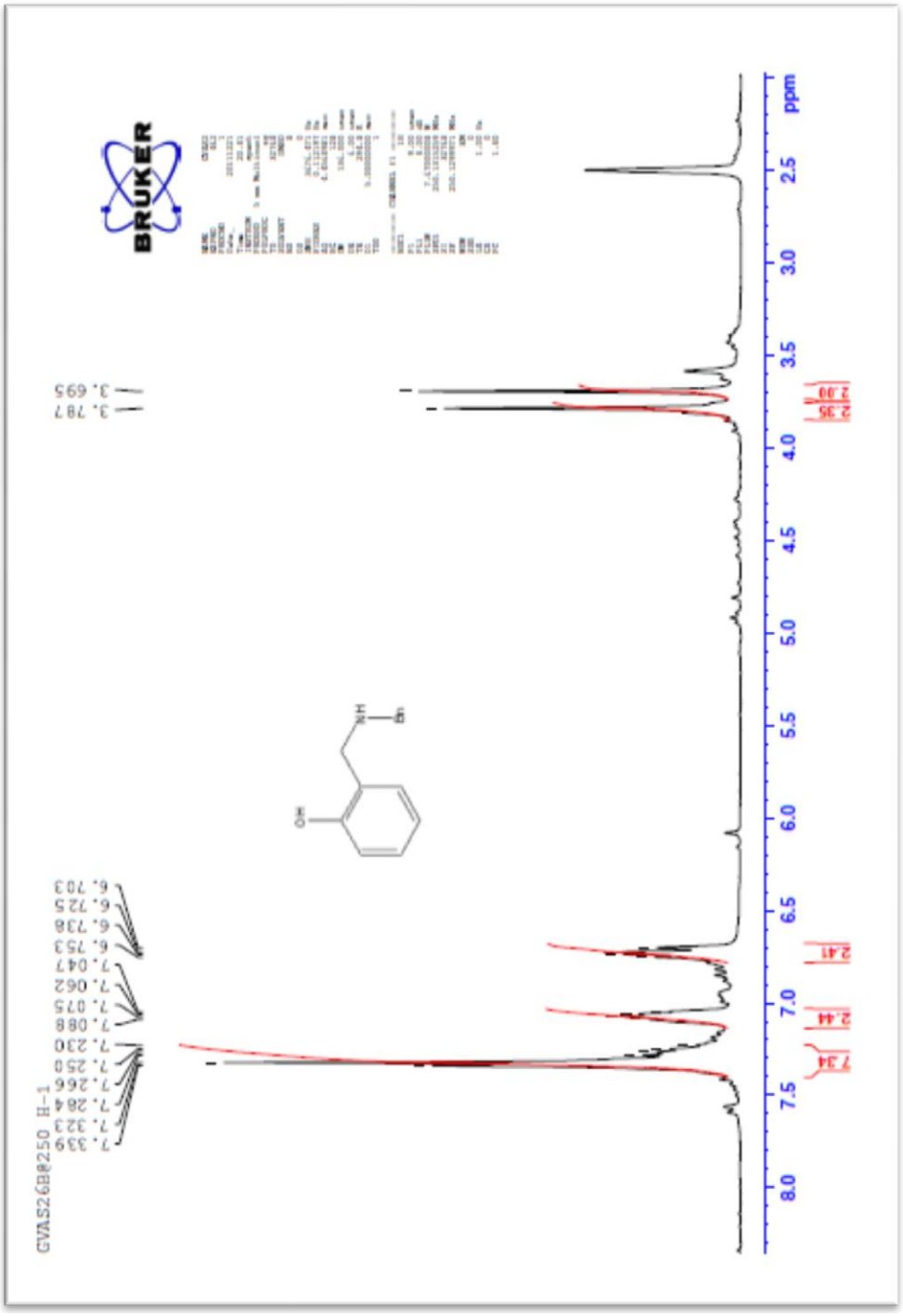
N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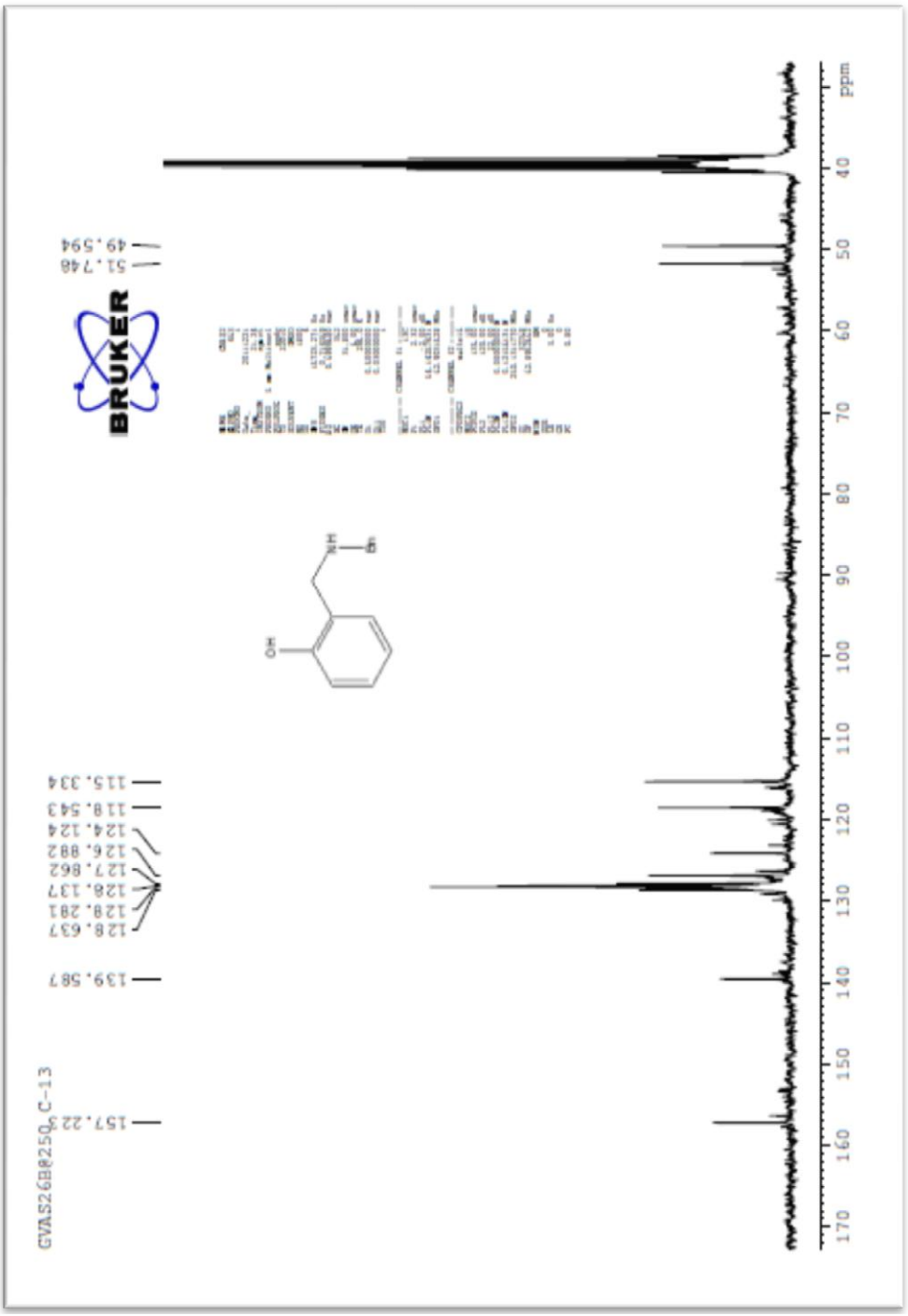
ppm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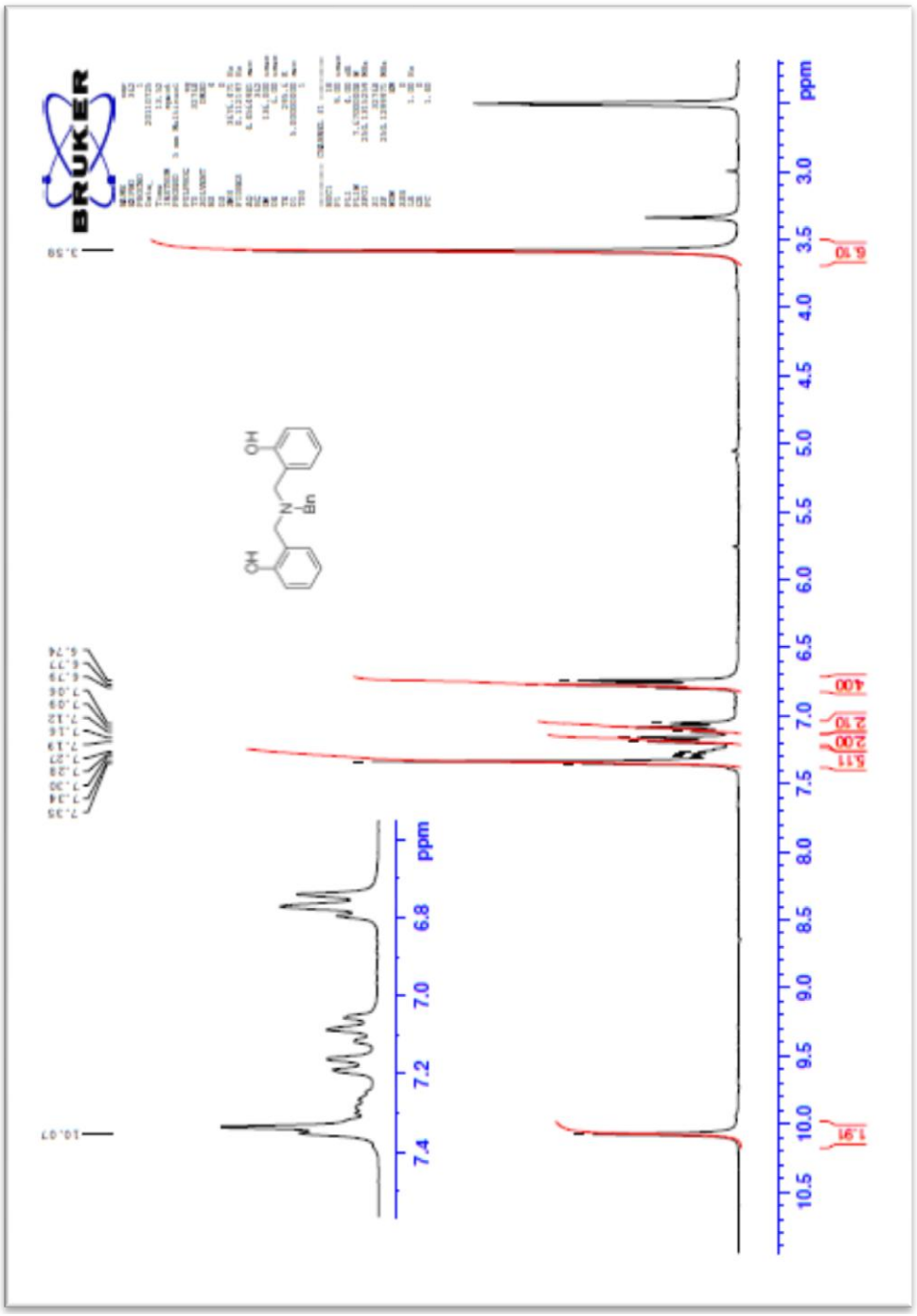
NH
Bn
BRUKER
ppm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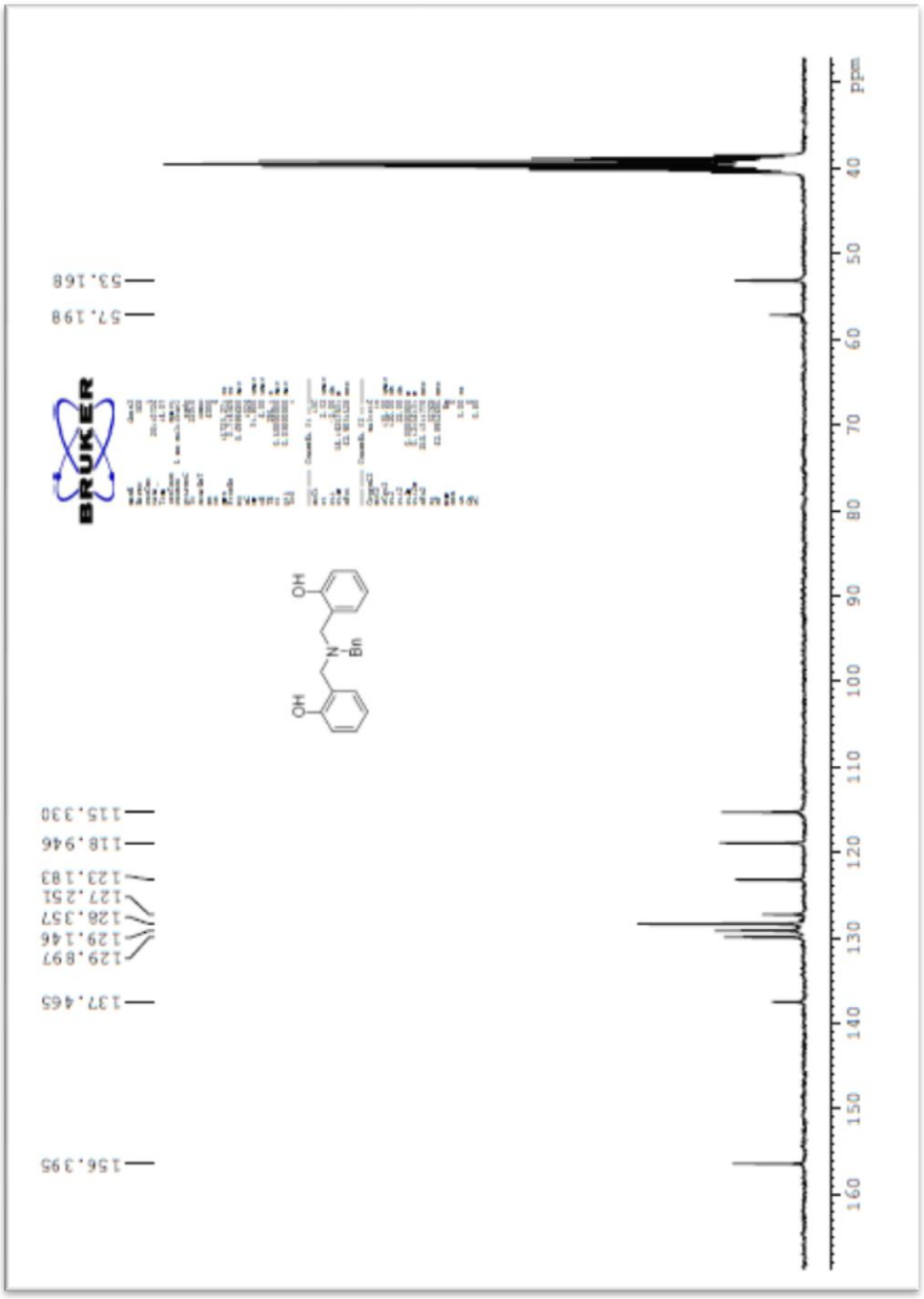
7.0
6.8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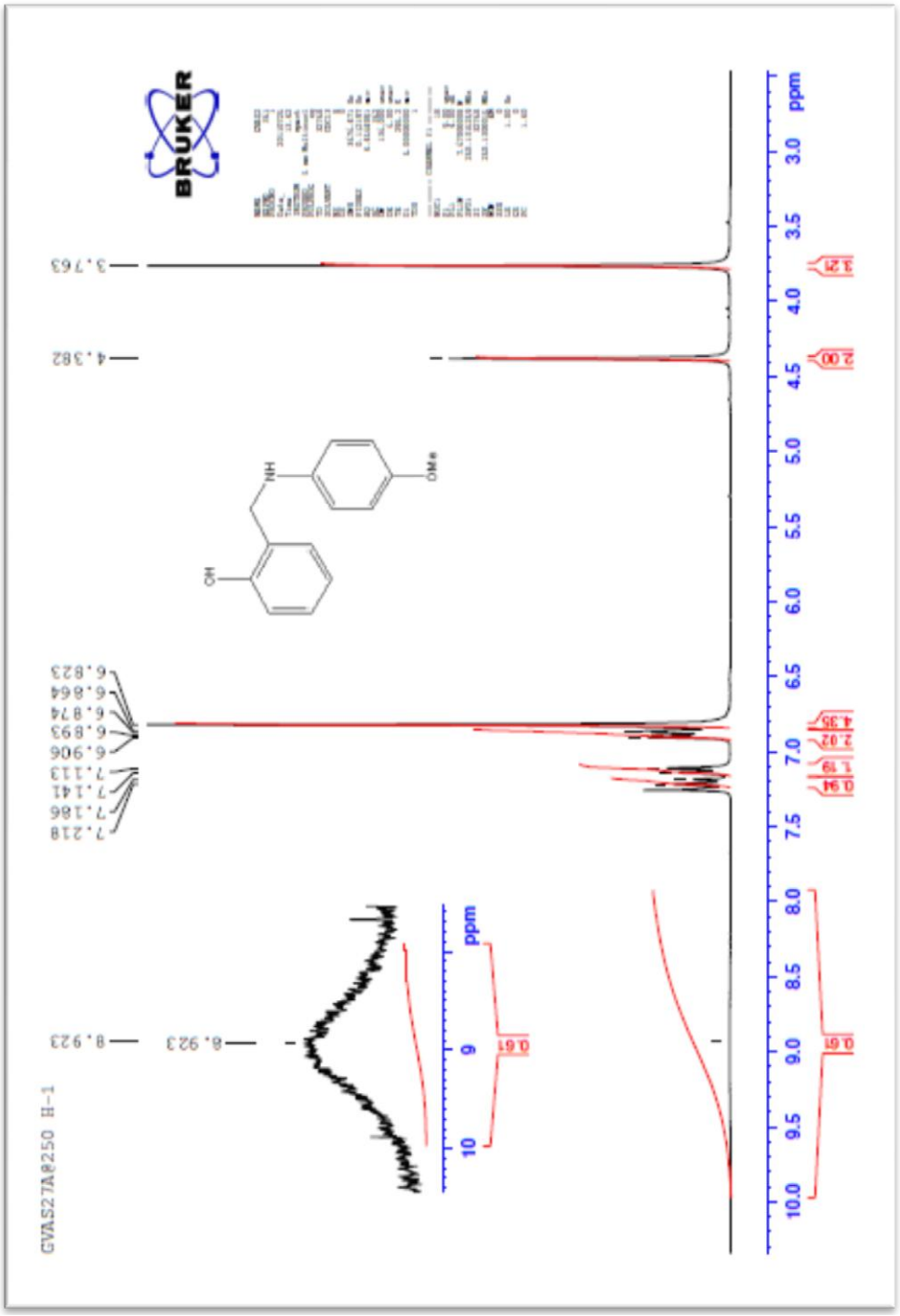
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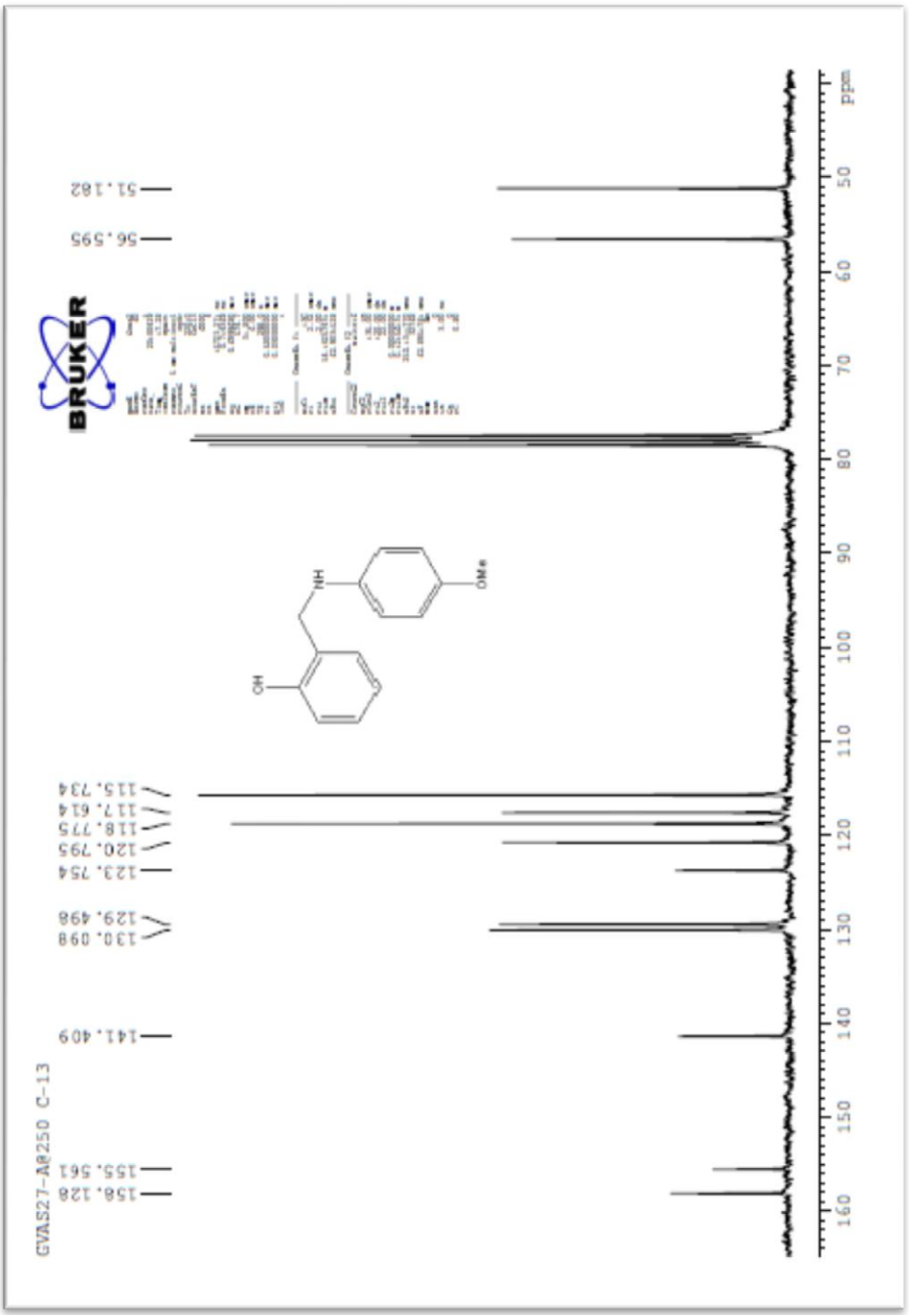
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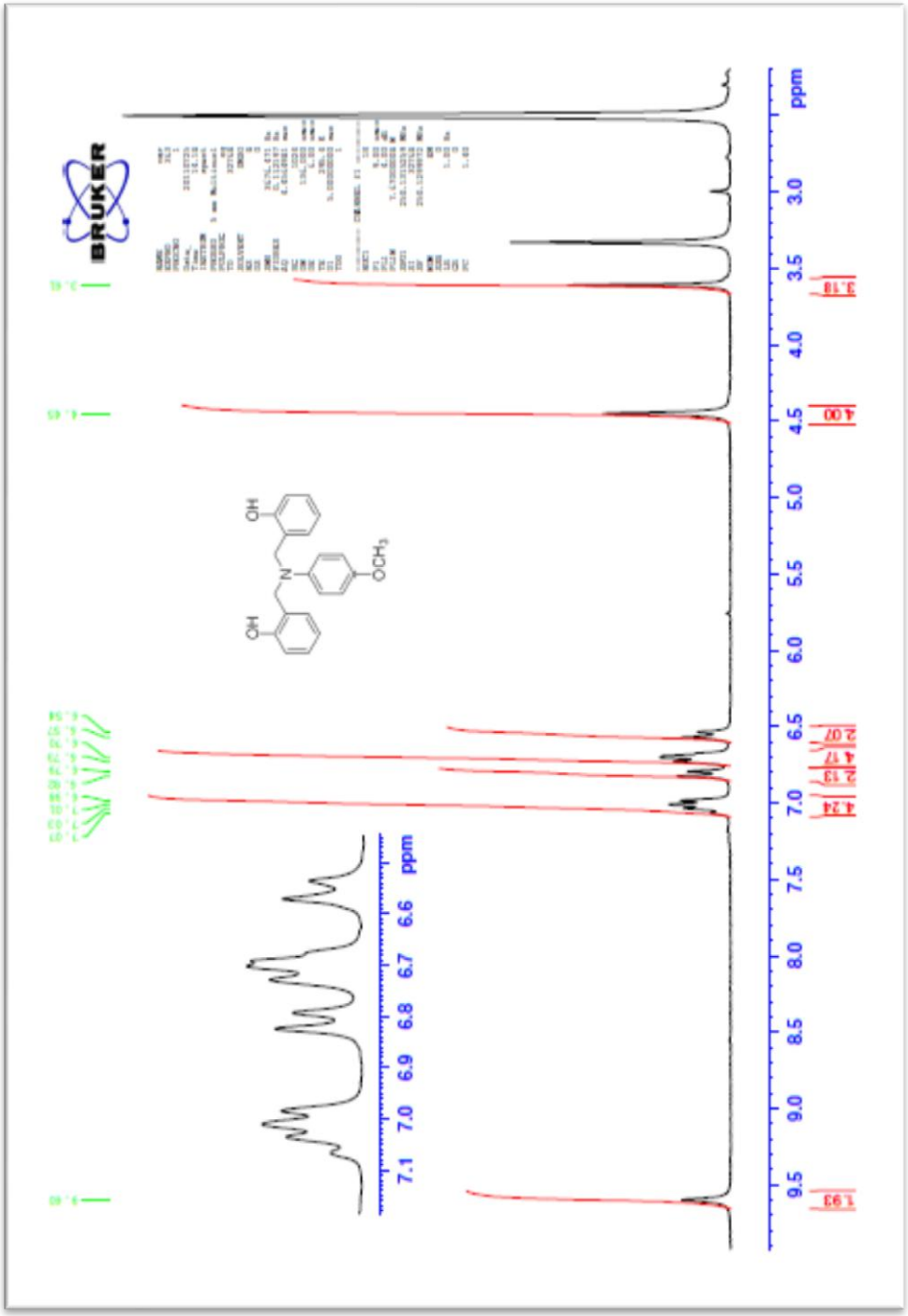
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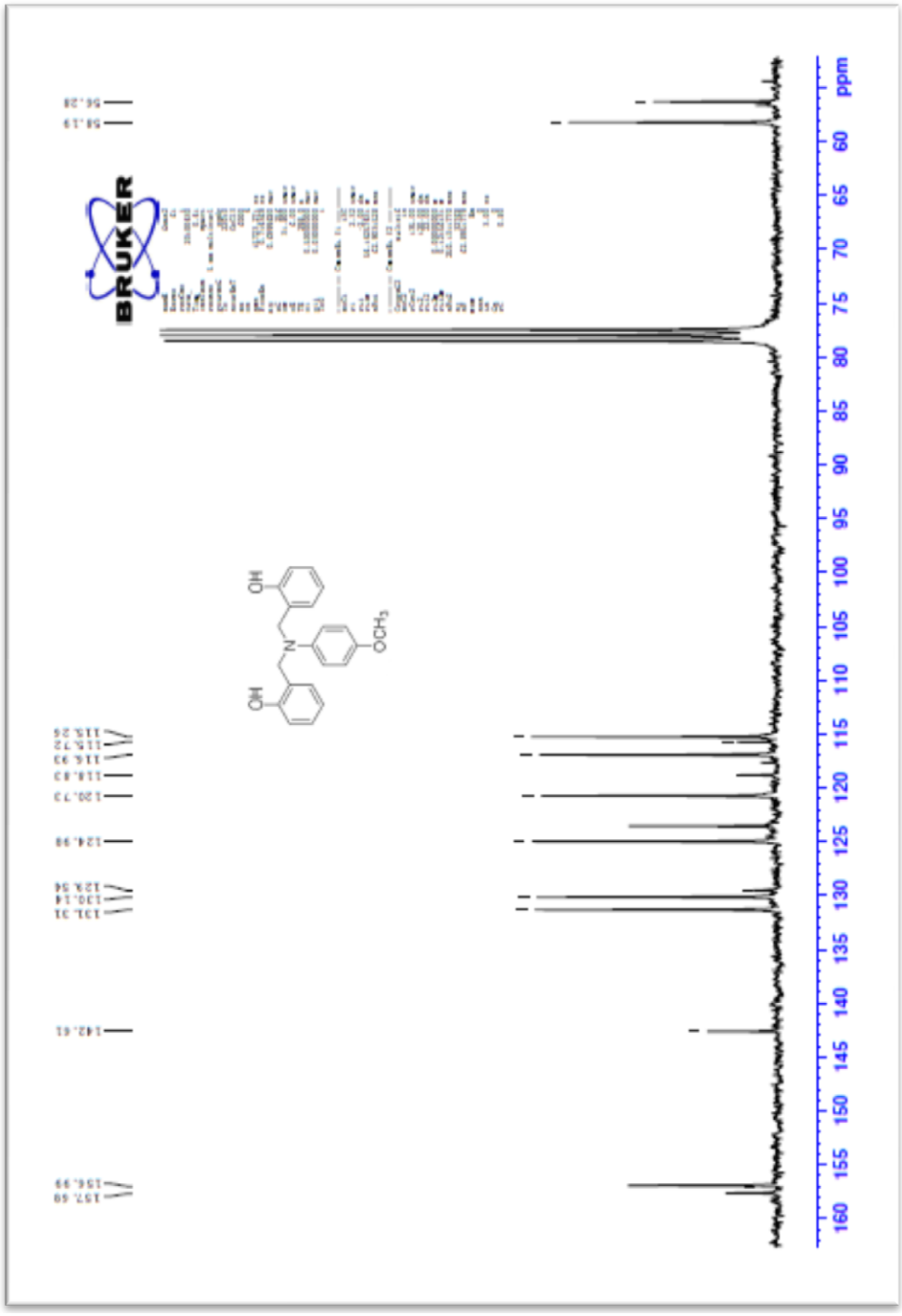
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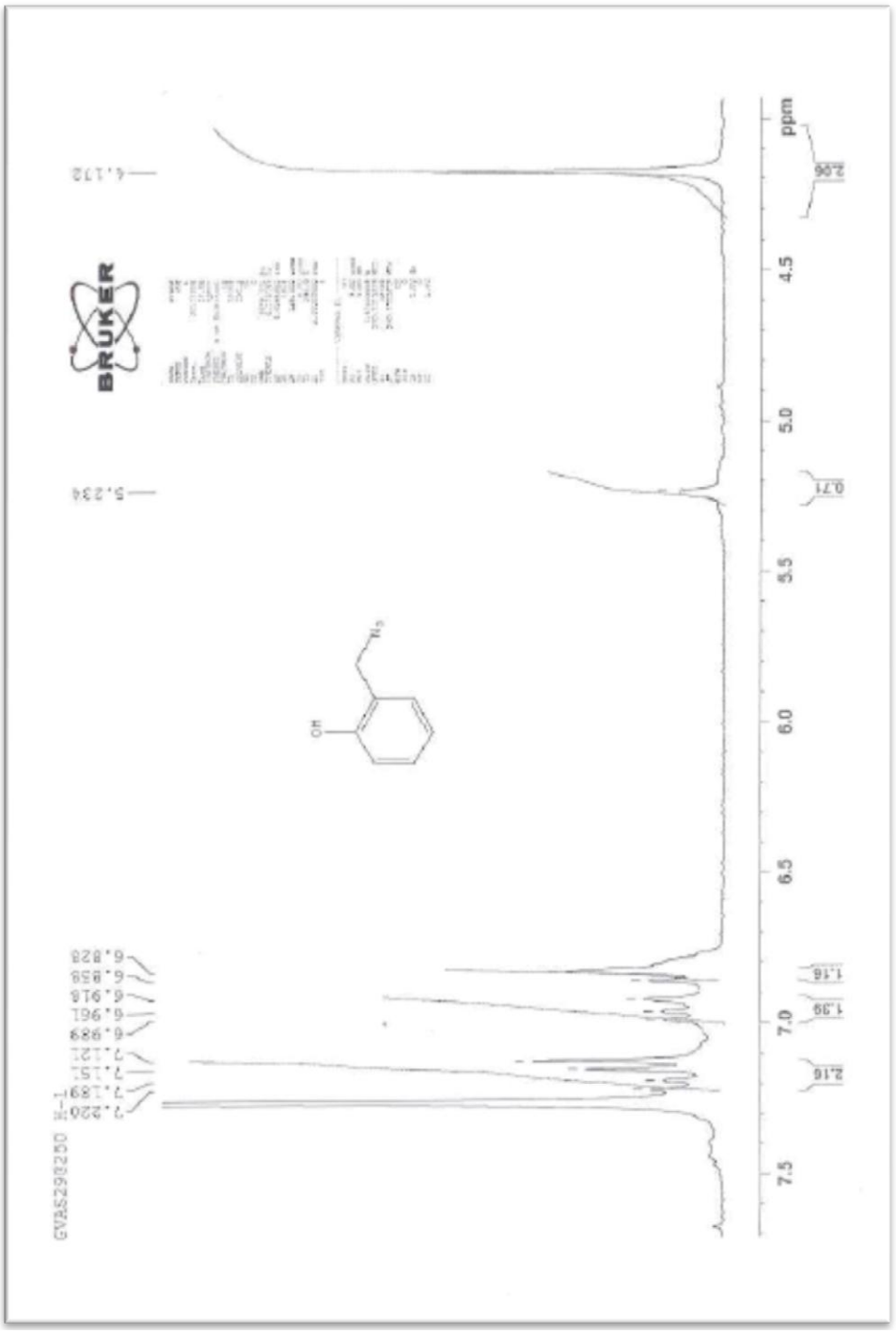
N
OCH3
ppm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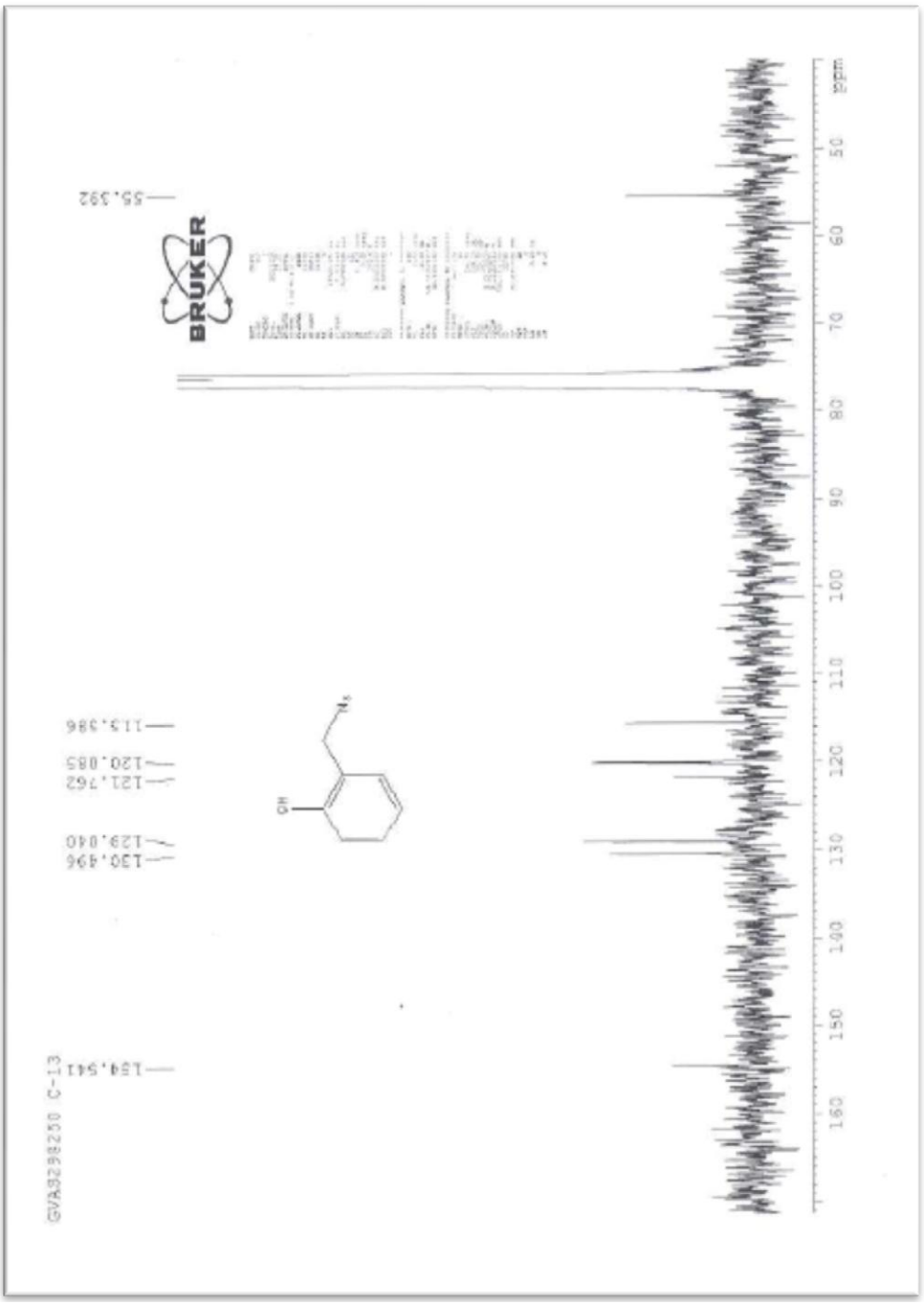
2.16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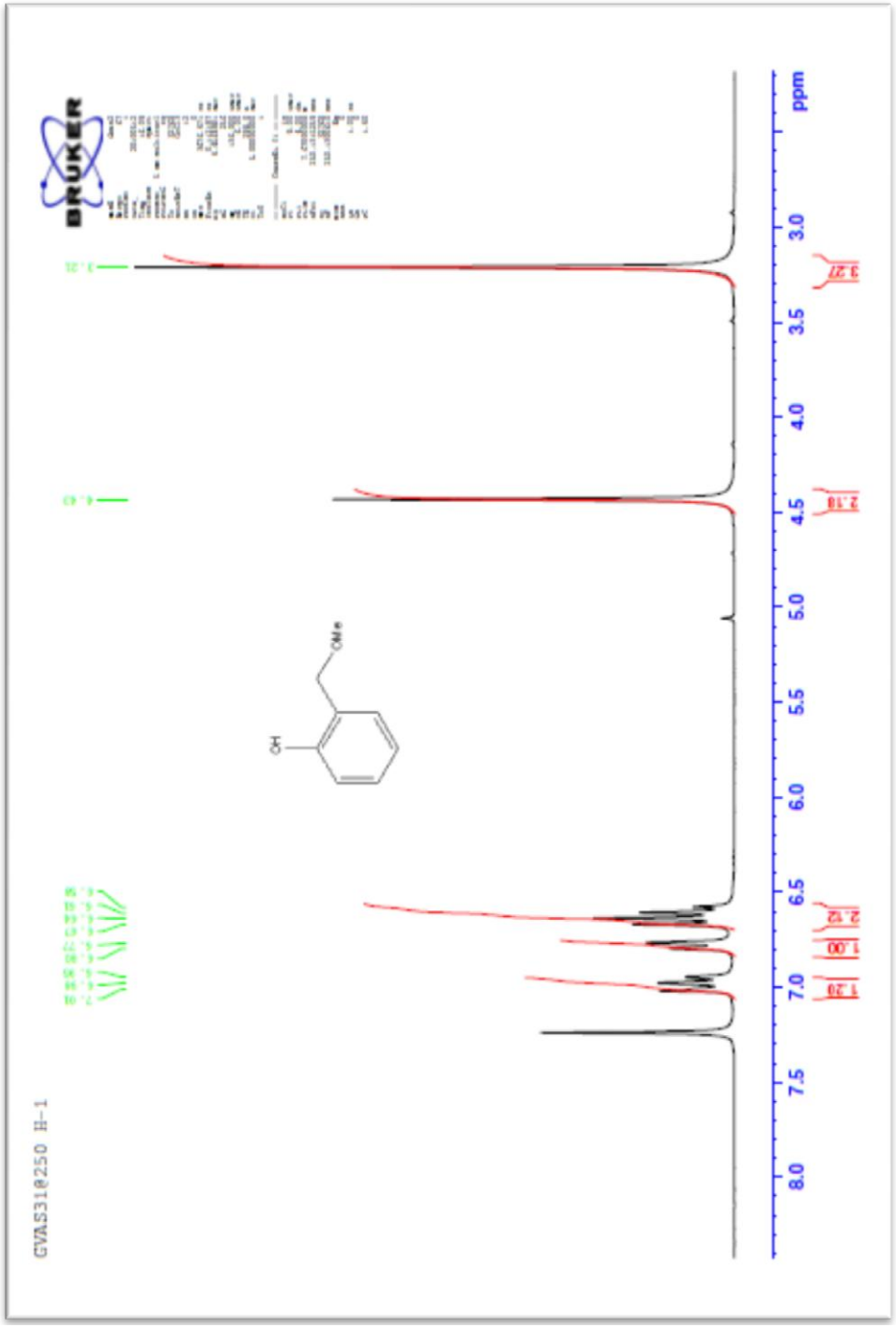
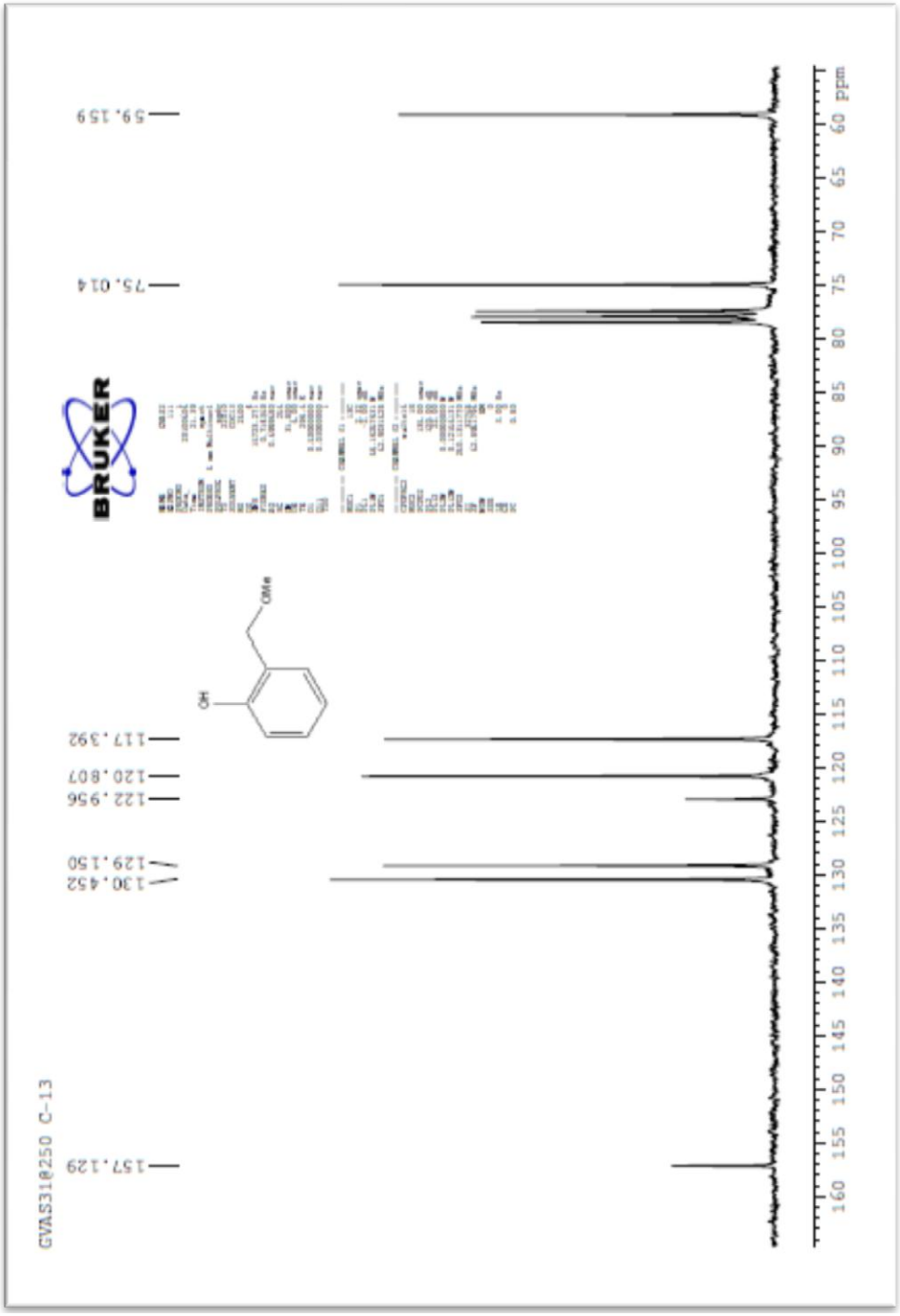
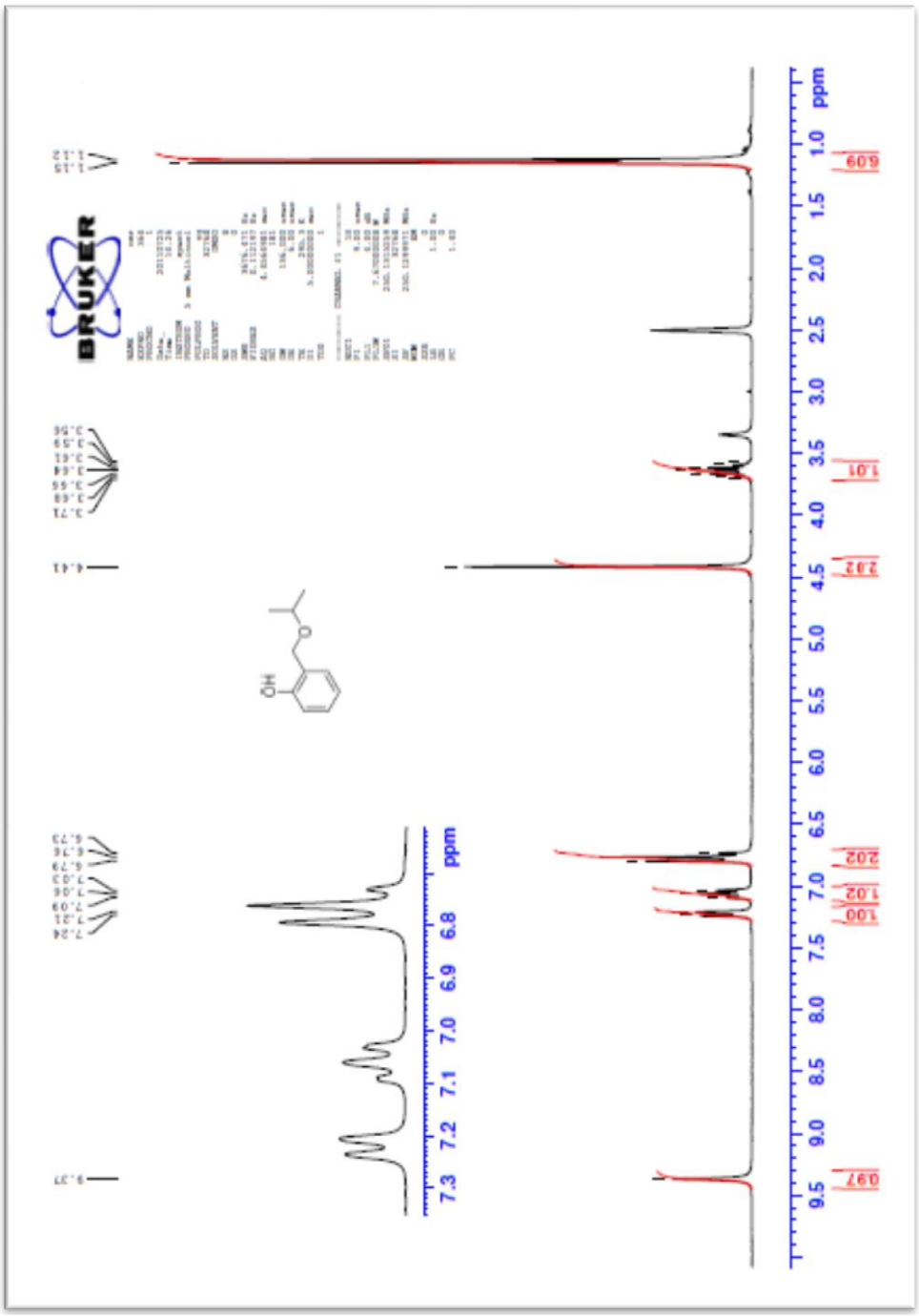
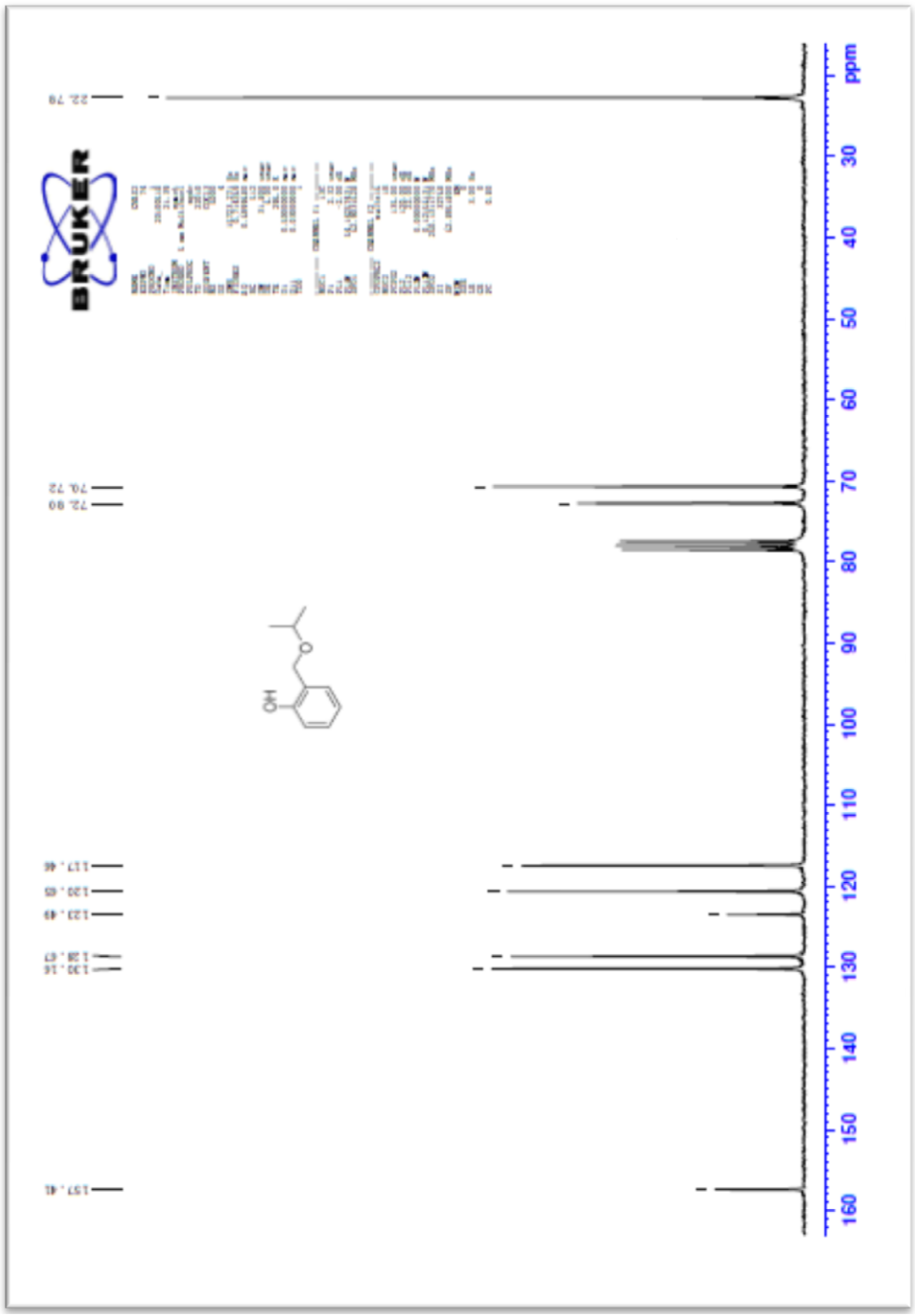
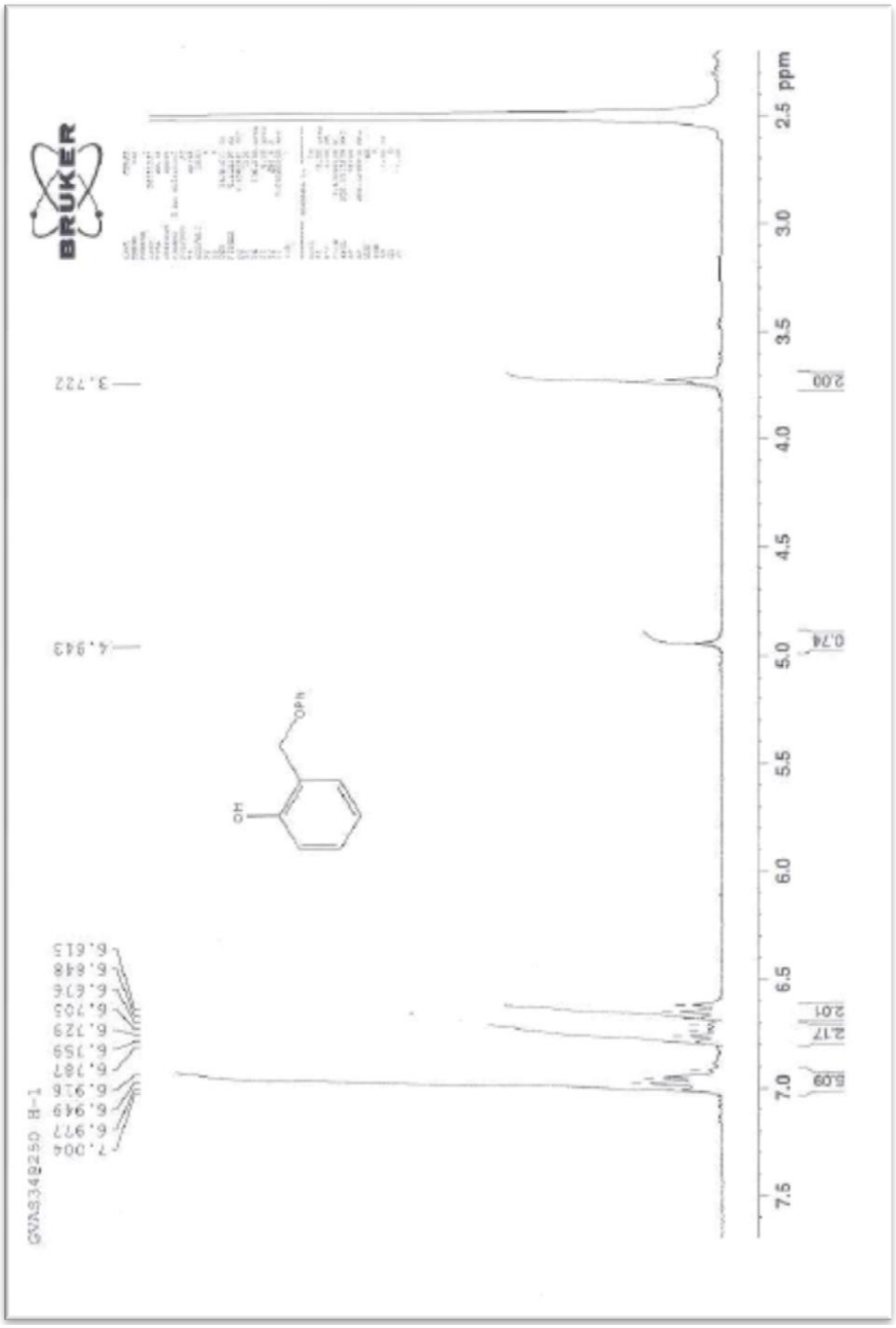
55.392
ppm

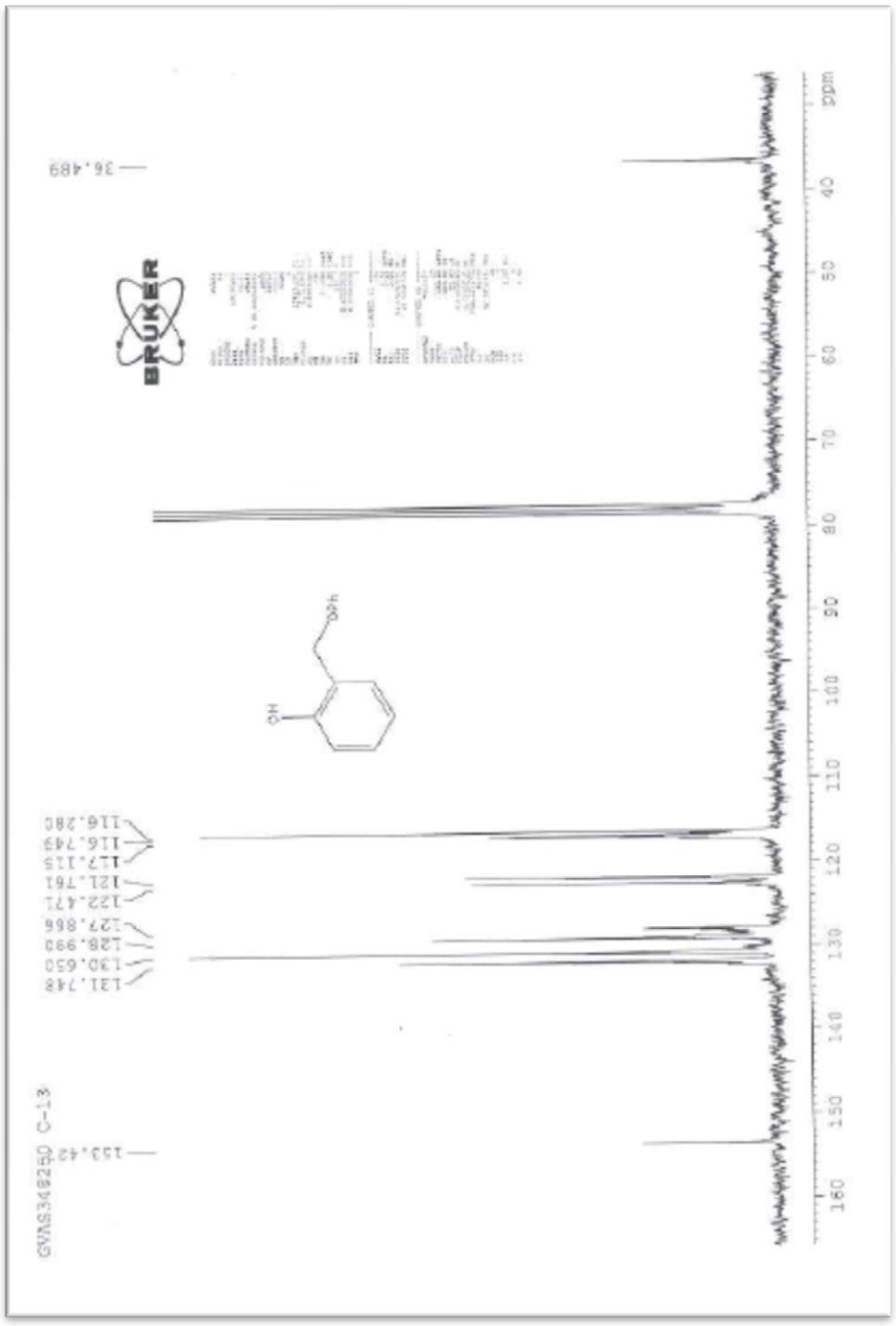

GVAS310250 H-1
ppm
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
3.27
2.18
2.52
1.00
1.20

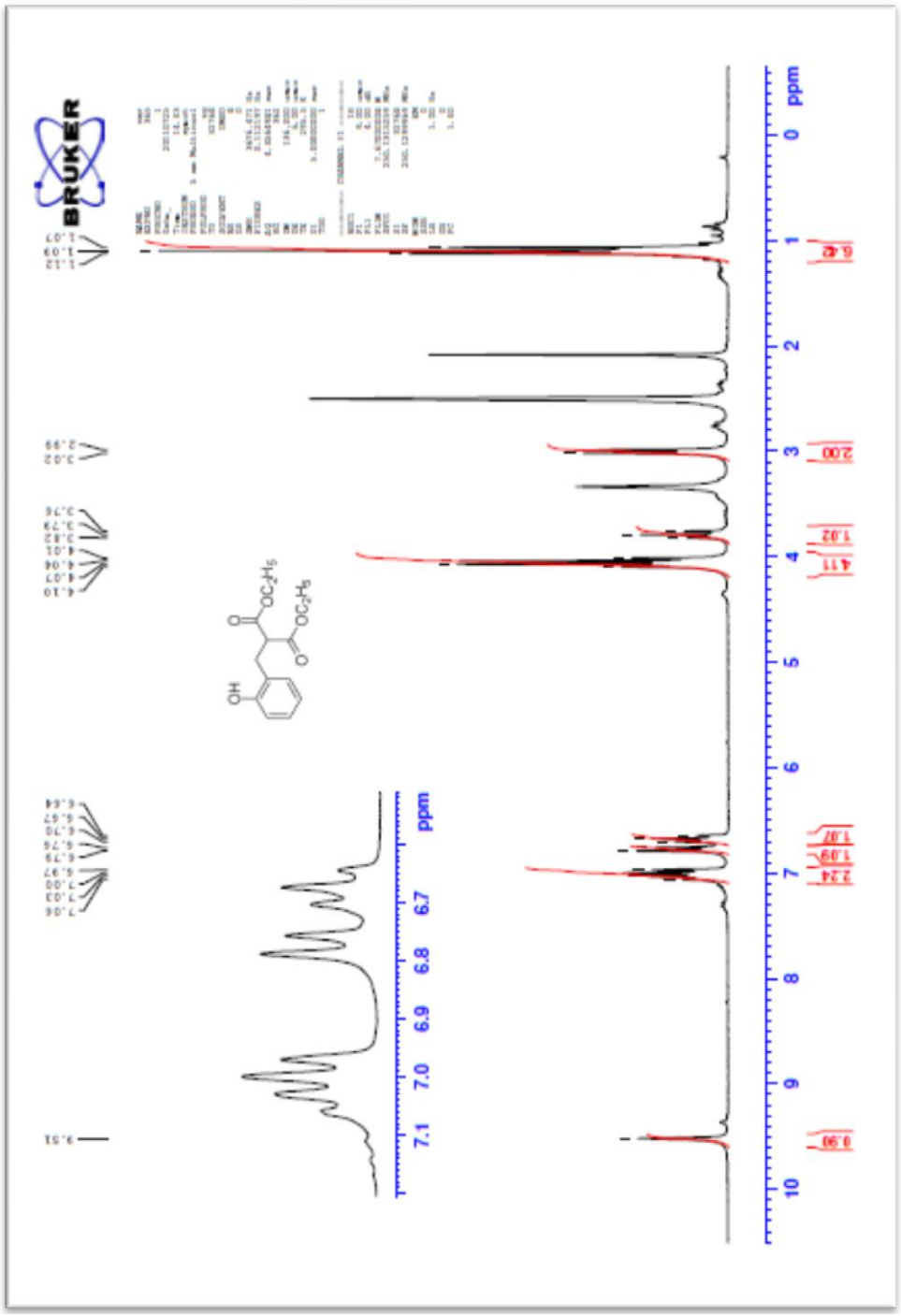

GVAS310250 C-13
157.129
130.452
129.150
122.956
120.807
117.392
75.014
59.159
OMe
OH
BRUKER
ppm

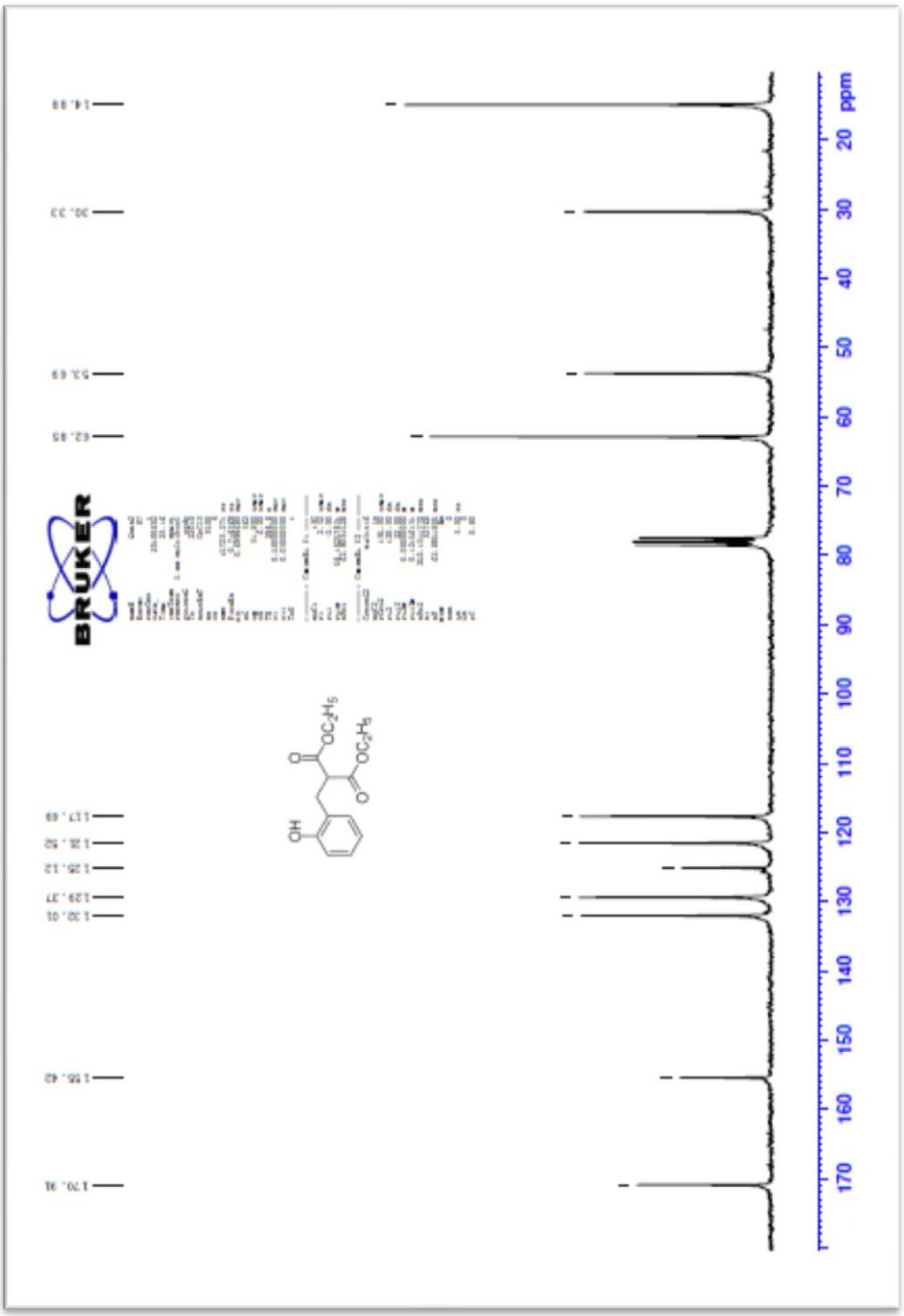

BRUKER
OH
ppm
7.3 7.2 7.1 7.0 6.9 6.8
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
0.97
2.02
1.00
1.02
2.02
1.01
2.02
6.09

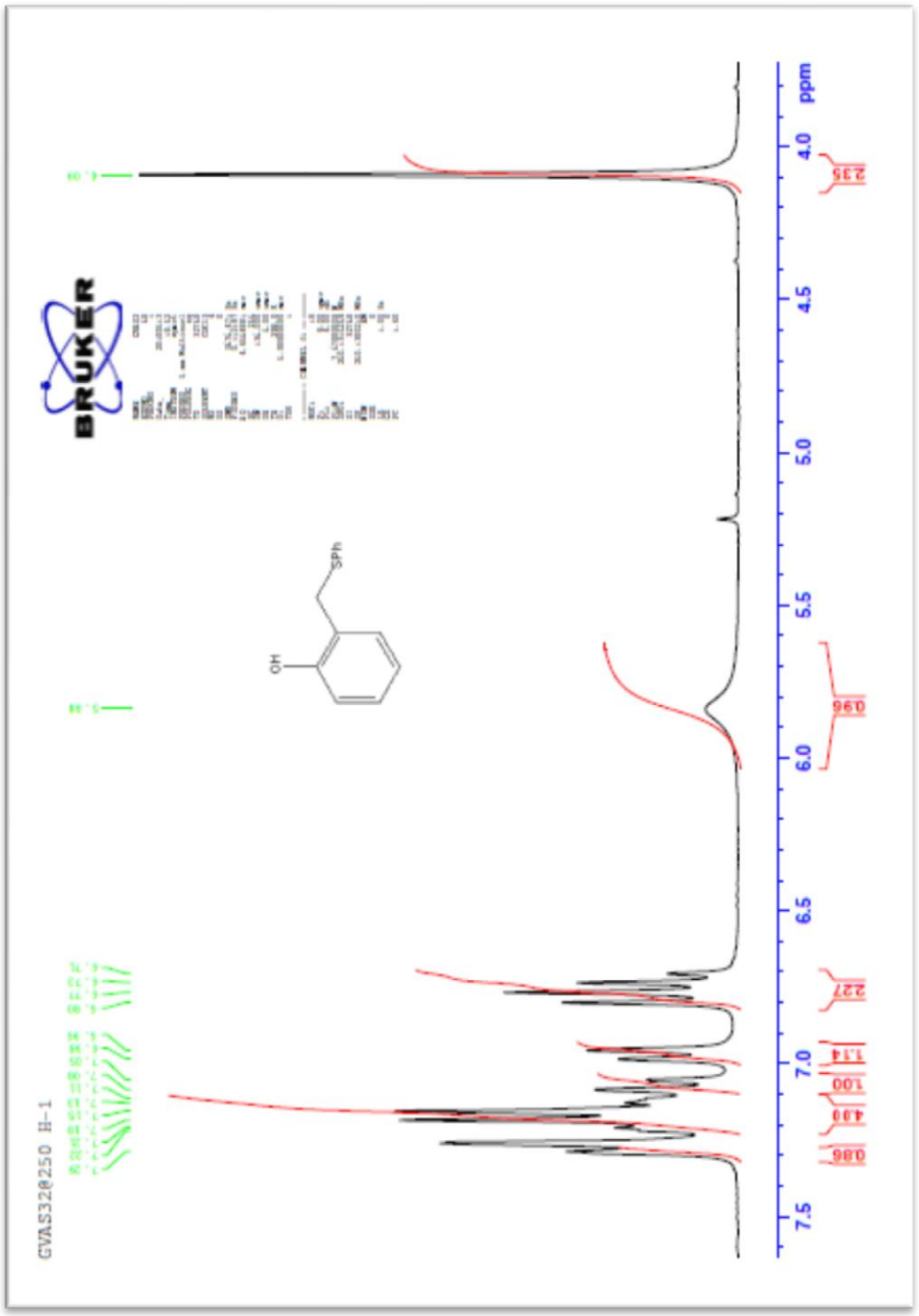

22.78
70.72
72.80
117.46
120.65
123.49
128.67
130.16
157.41
ppm
30
40
50
60
70
80
90
100
110
120
130
140
150
160
OH

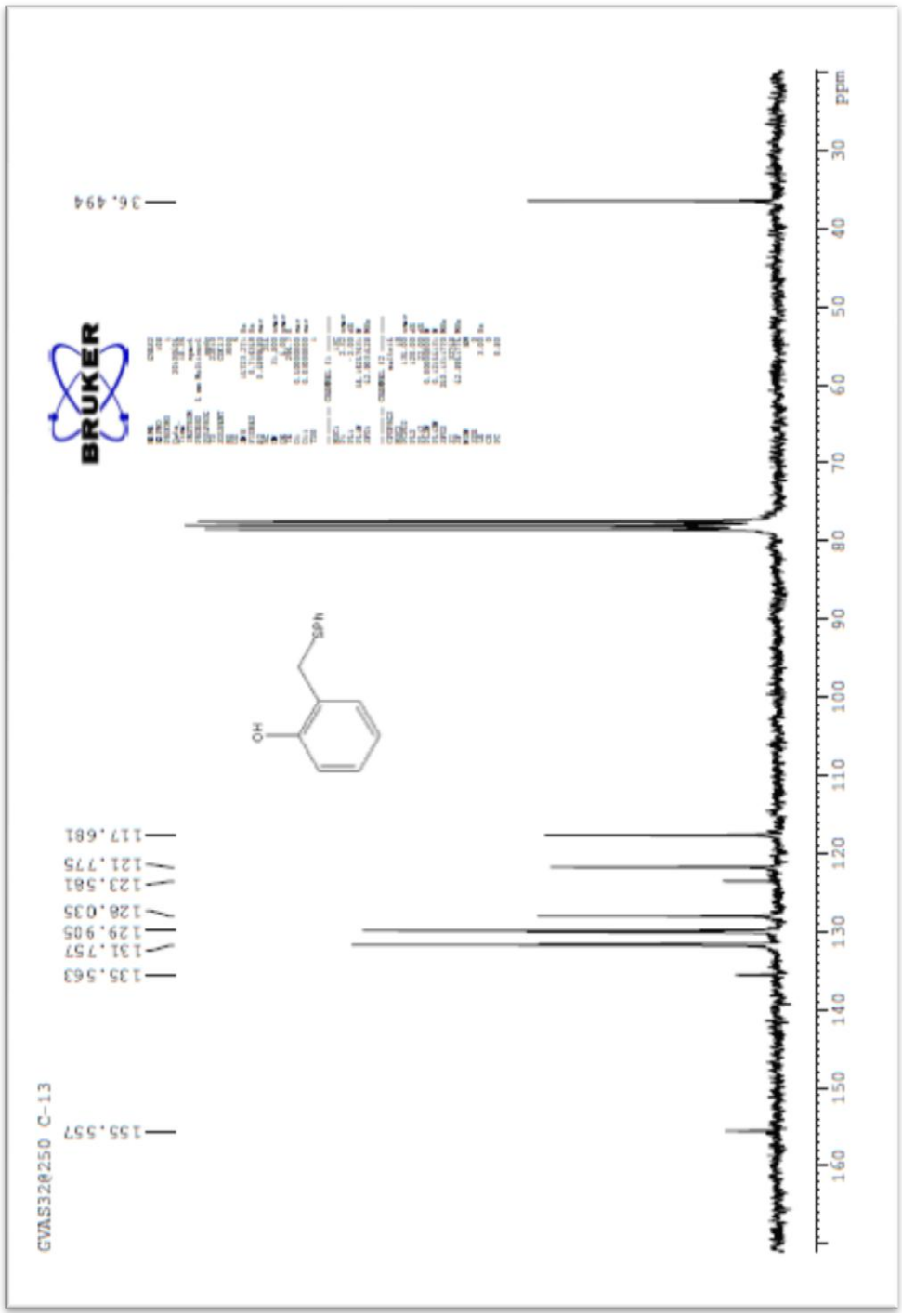

BRUKER
GVA8349250 H-1
7.004
6.977
6.949
6.916
6.887
6.759
6.729
6.705
6.676
6.648
6.615
4.943
3.722
2.00
0.74
2.01
2.17
5.09
OH
OPh
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5 ppm

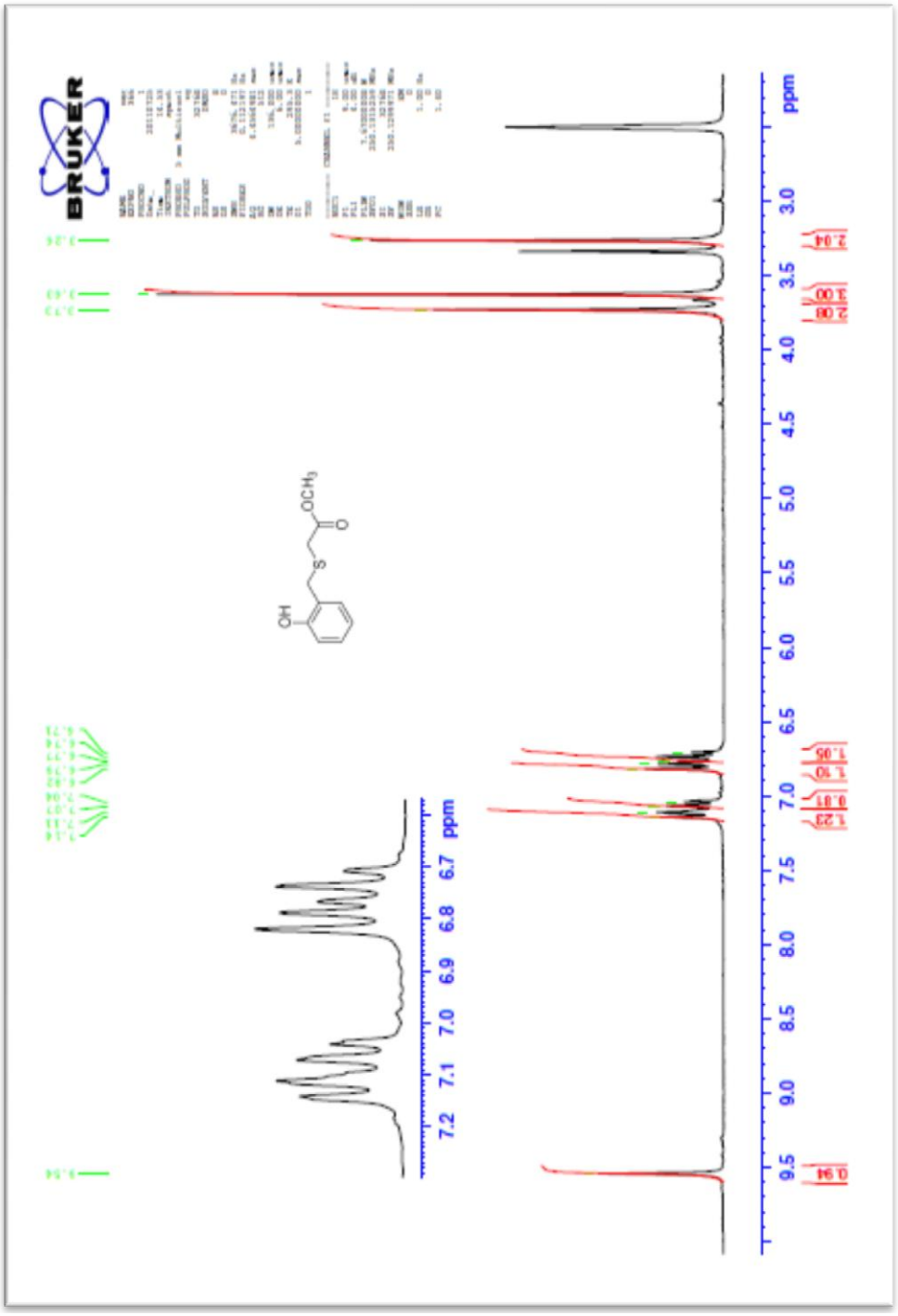

GVNS346250 C-13
153.420
131.748
130.650
128.990
127.866
122.471
121.761
117.115
116.749
116.280
36.489
OH
OH
BRUKER
ppm

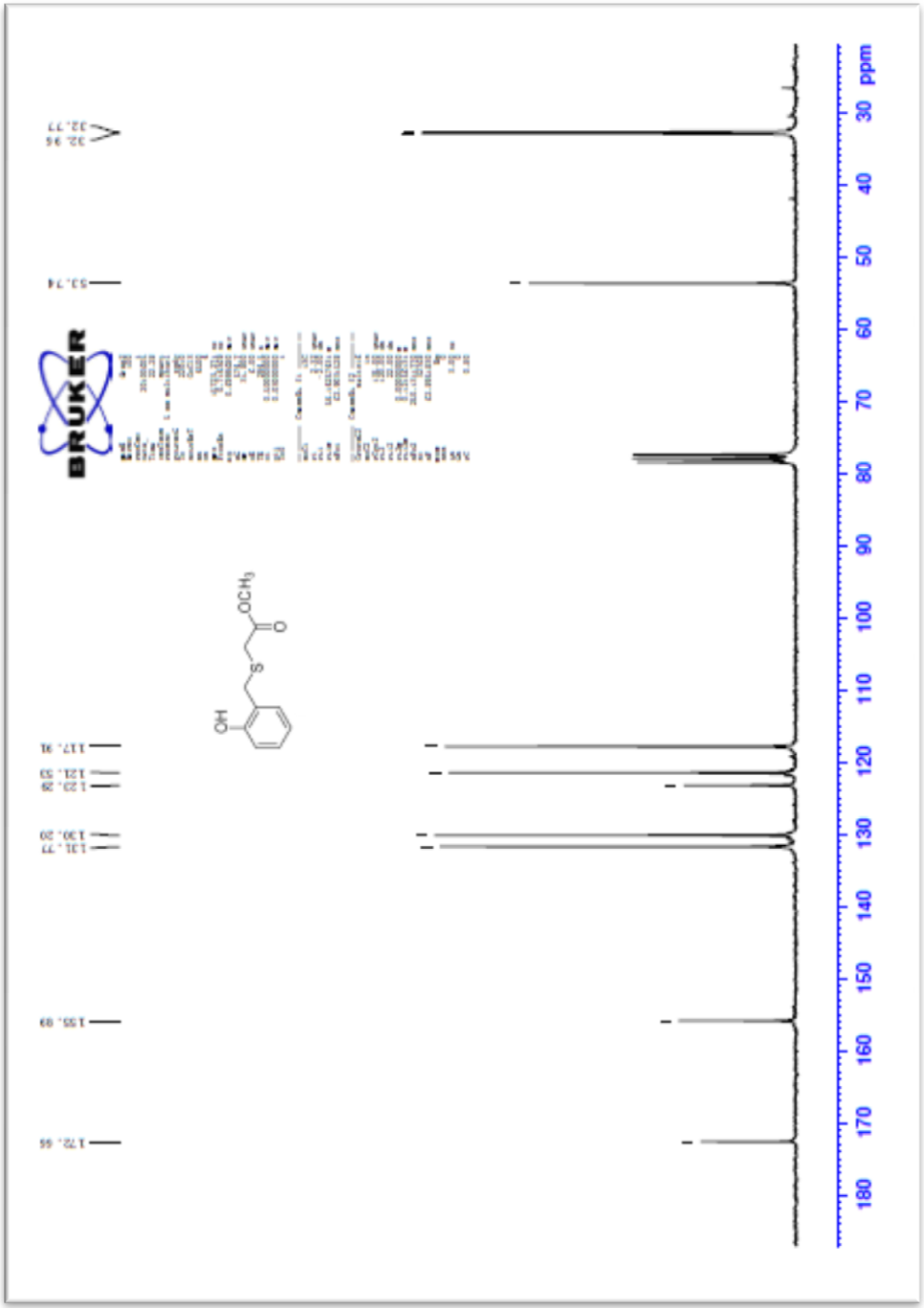

BRUKER
ppm
0
1
2
3
4
5
6
7
8
9
10
6.42
2.00
1.02
4.11
1.07
1.09
2.24
0.90
OC2H5
OC2H5
O
O
OH

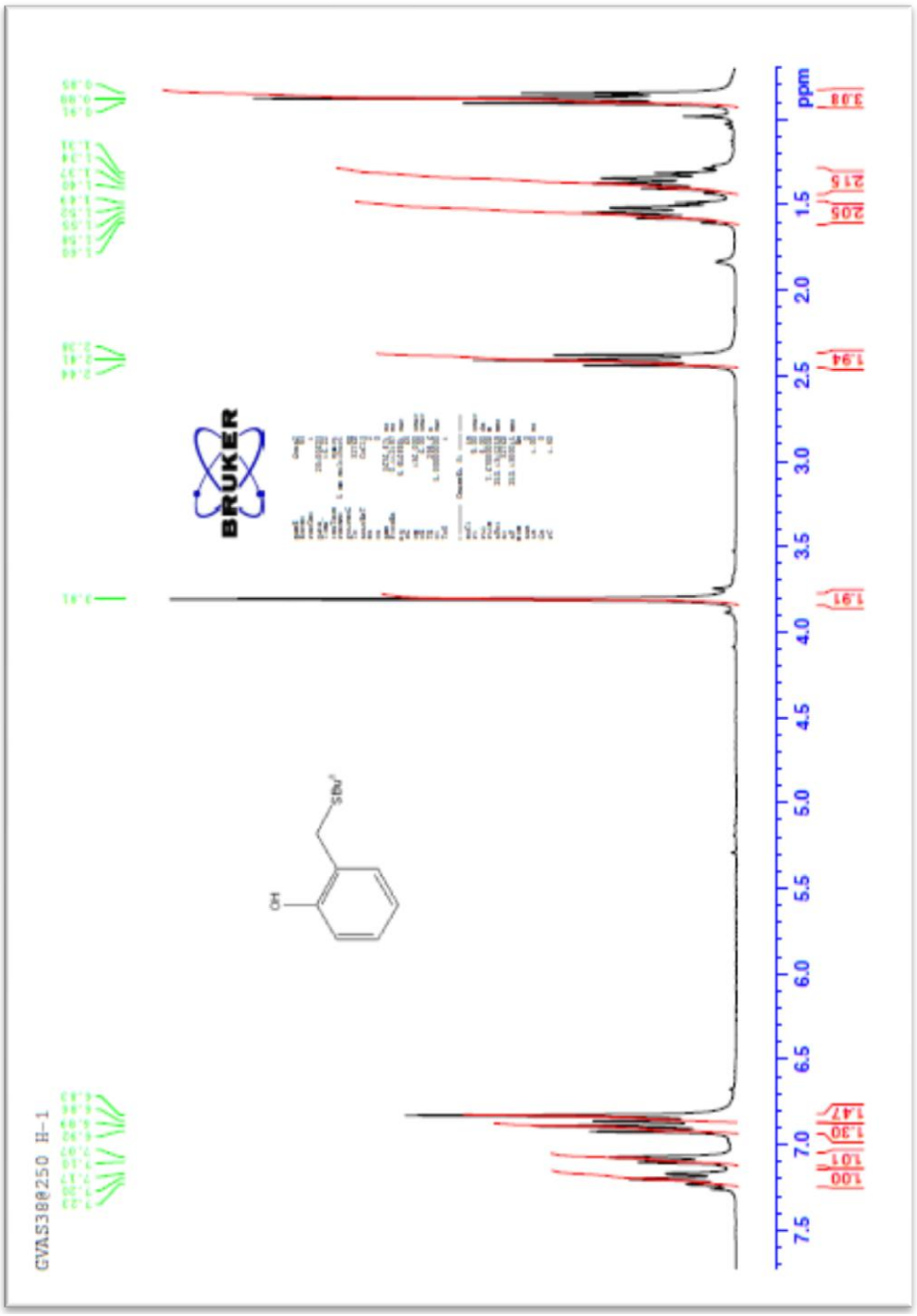

14.08
30.33
53.69
62.85
117.69
121.42
126.12
129.37
130.01
155.42
170.31
ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
BRUKER
OC2H5
OC2H5
O
O
OH

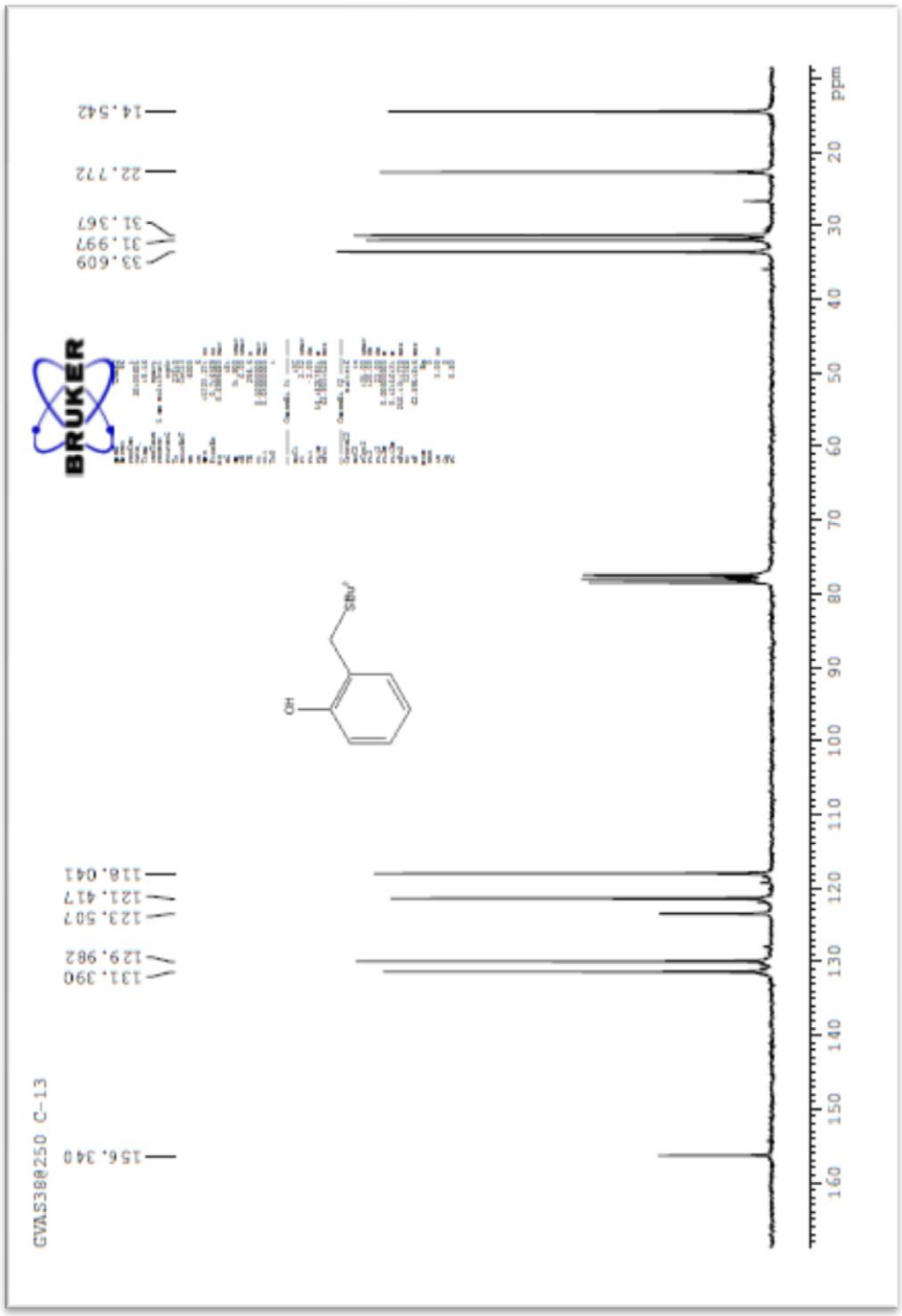

GVA532@250 H-1
BRUKER
SPh
OH
ppm
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
2.35
0.96
2.27
1.14
1.00
4.00
0.86

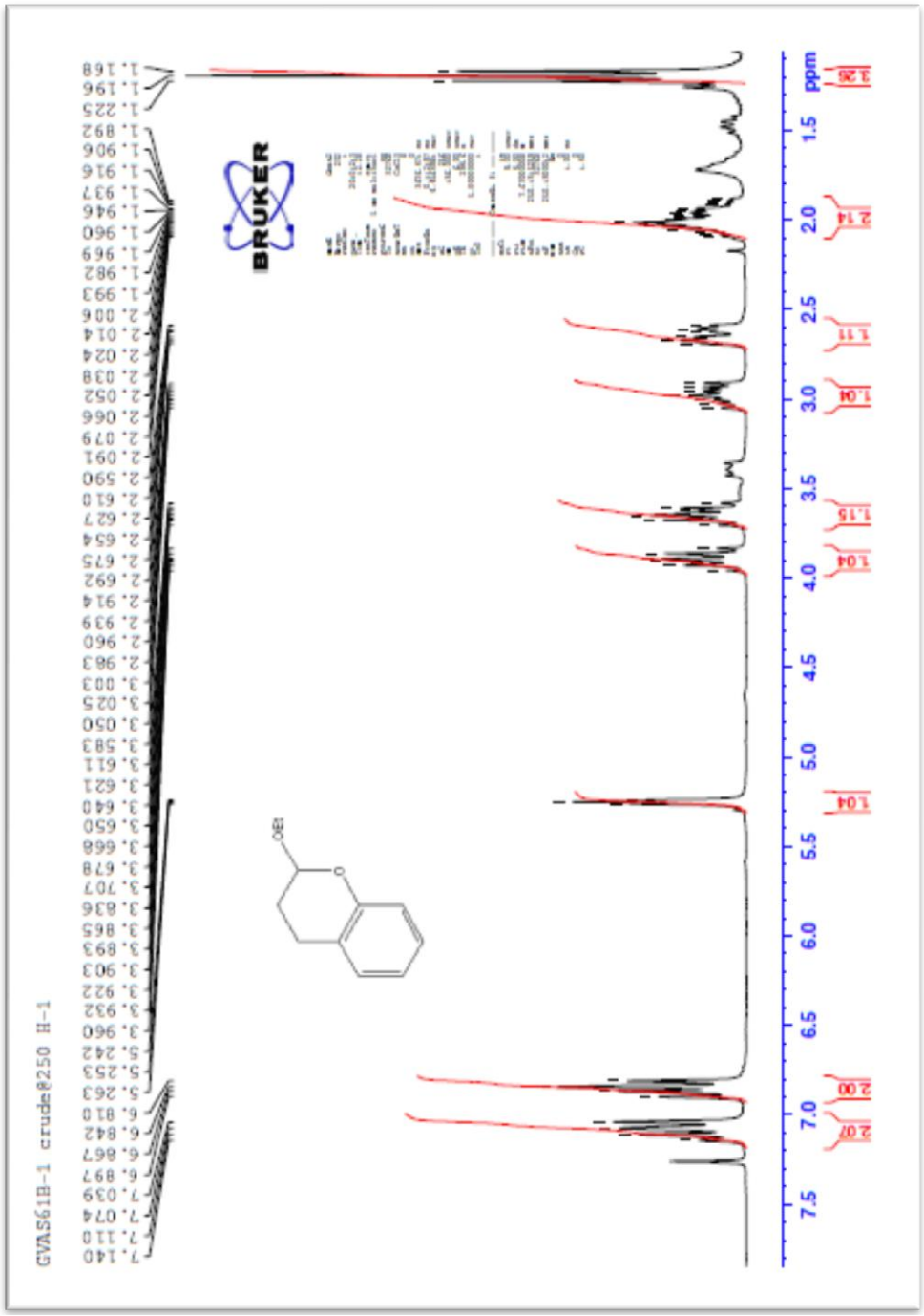

GVAS320250 C-13
155.557
135.563
131.757
129.905
128.035
123.581
121.775
117.681
36.494
OH
ppm

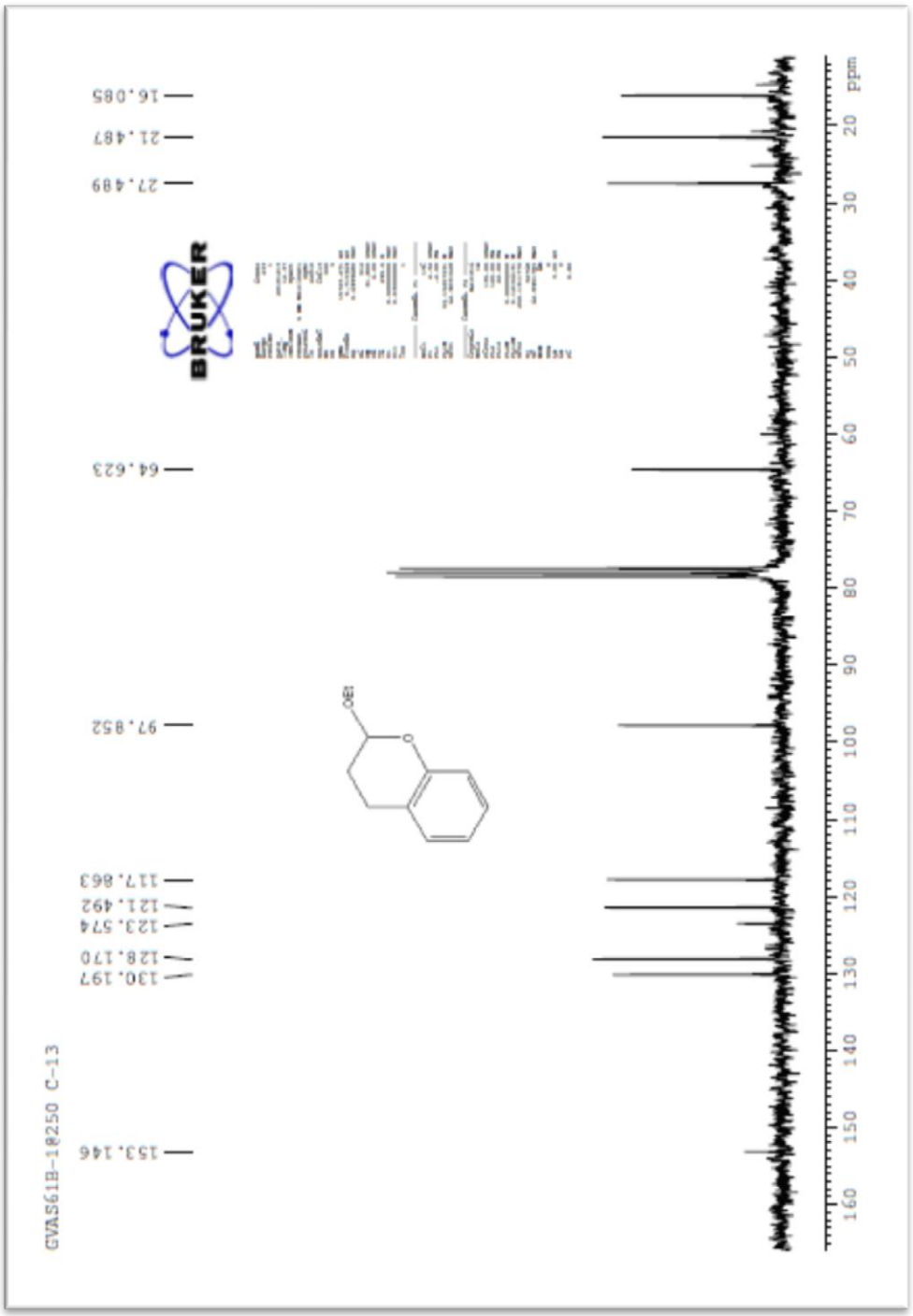

BRUKER
OCH3
O
S
OH
ppm
7.2
7.1
7.0
6.9
6.8
6.7
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.04
3.00
2.08
1.05
1.10
0.81
1.23
0.94

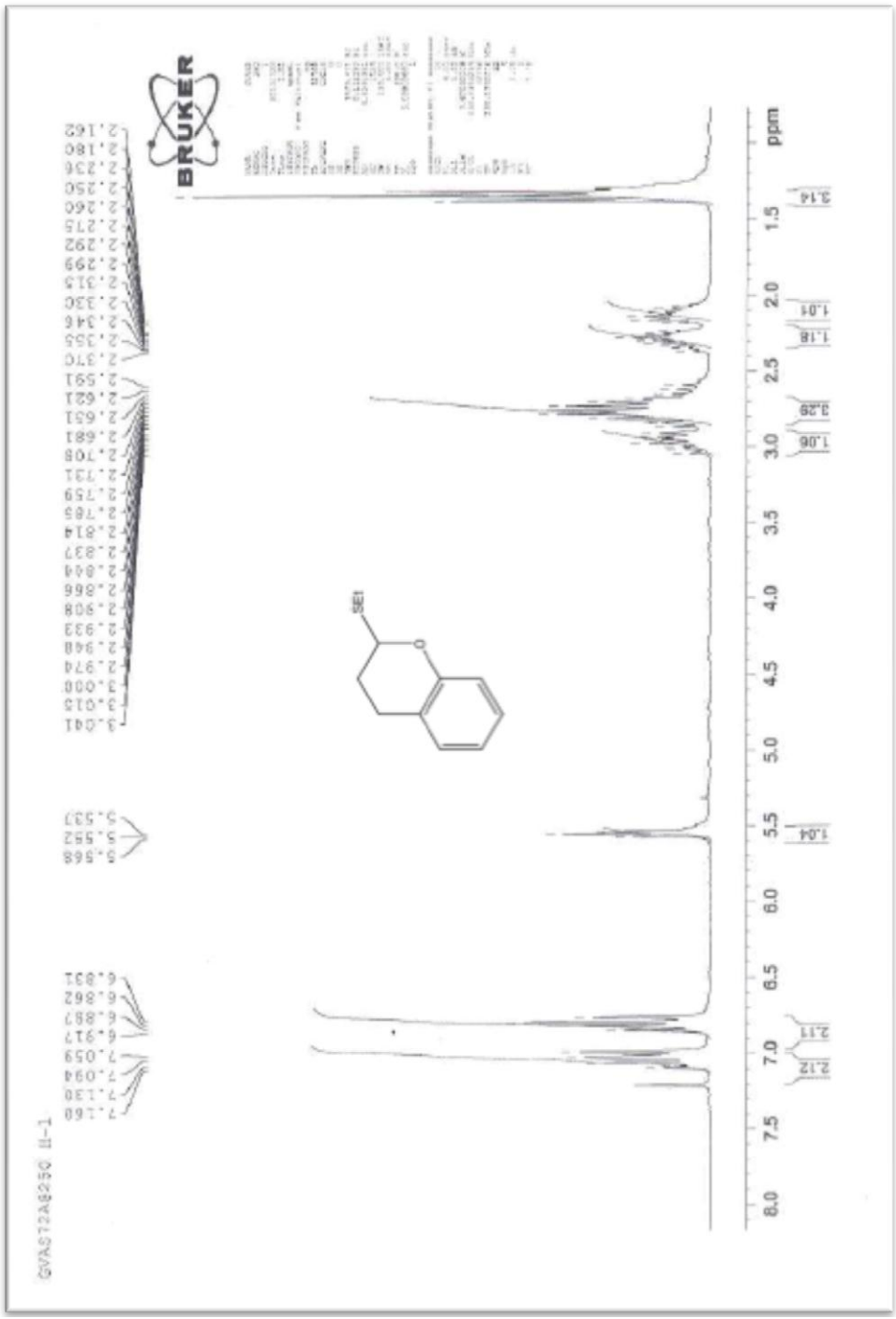

BRUKER
OCH3
O
S
OH
32.95
32.77
53.74
117.91
121.53
123.29
130.20
131.77
155.09
172.65
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
ppm

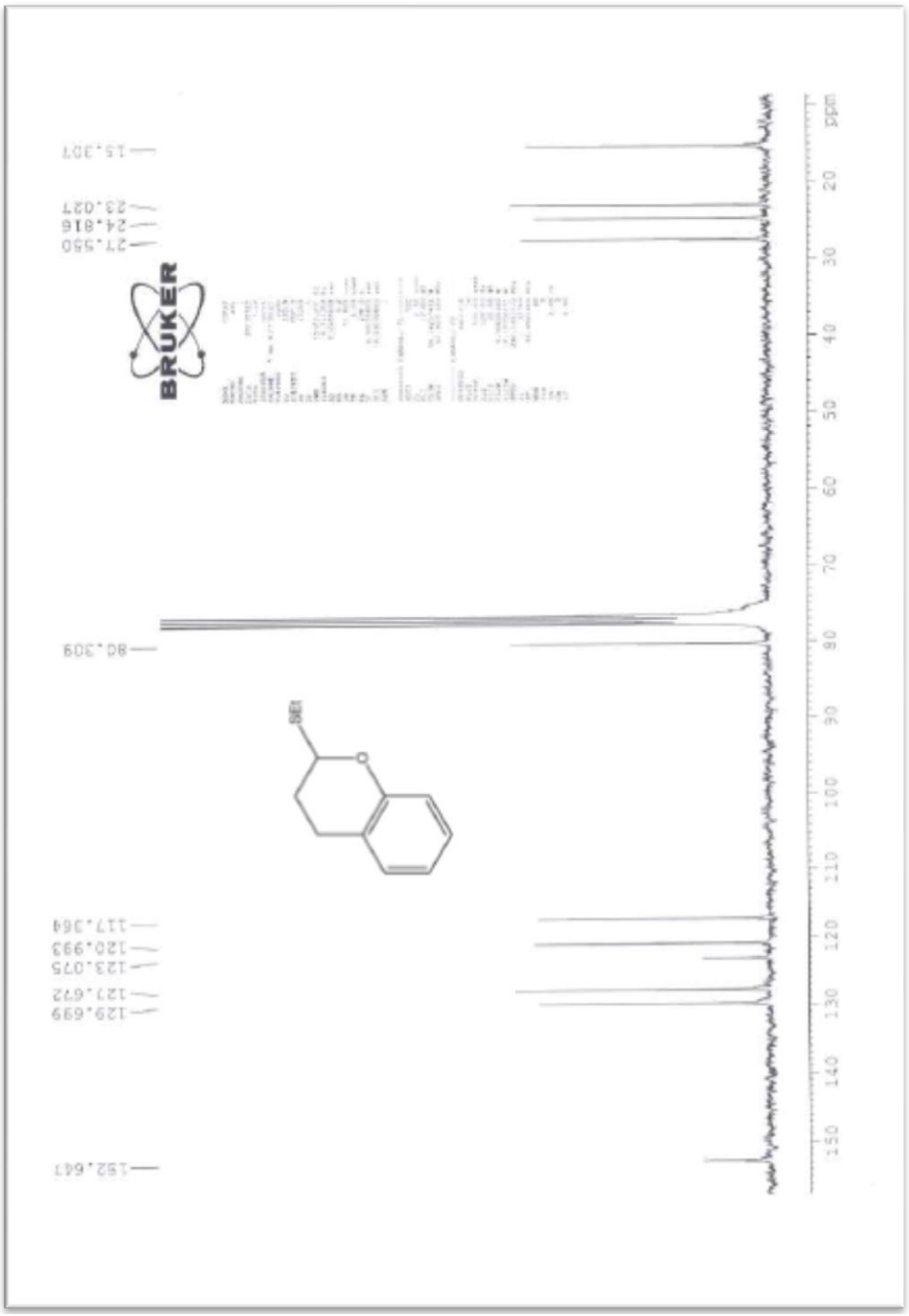

GVAS380250 H-1
BRUKER
OH
SBu
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
3.08
2.15
2.05
1.94
1.91
1.47
1.30
1.01
1.00

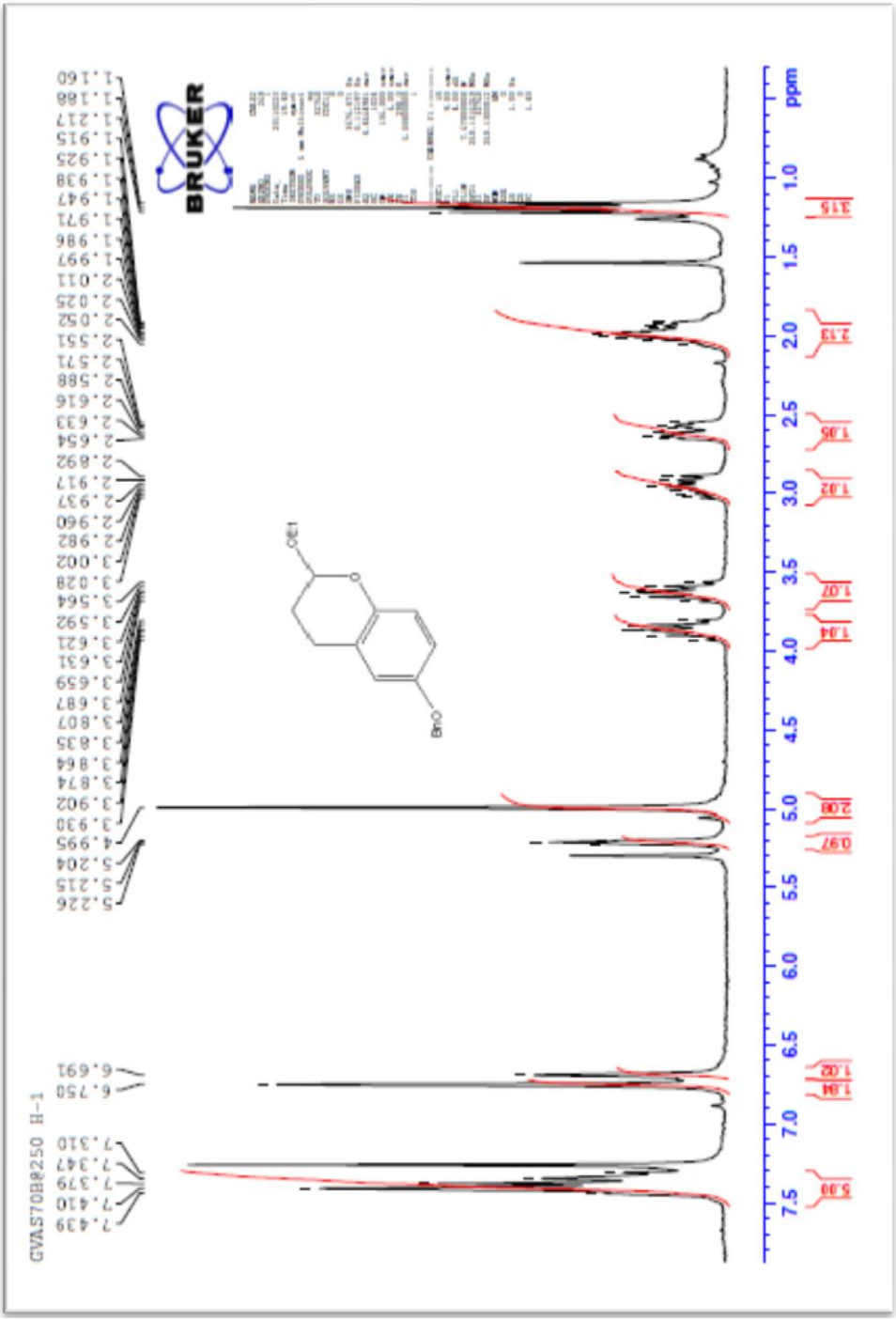

GVA530@250 C-13
156.340
131.390
129.982
123.507
121.417
118.041
33.609
31.997
31.367
22.772
14.542
OH
ppm

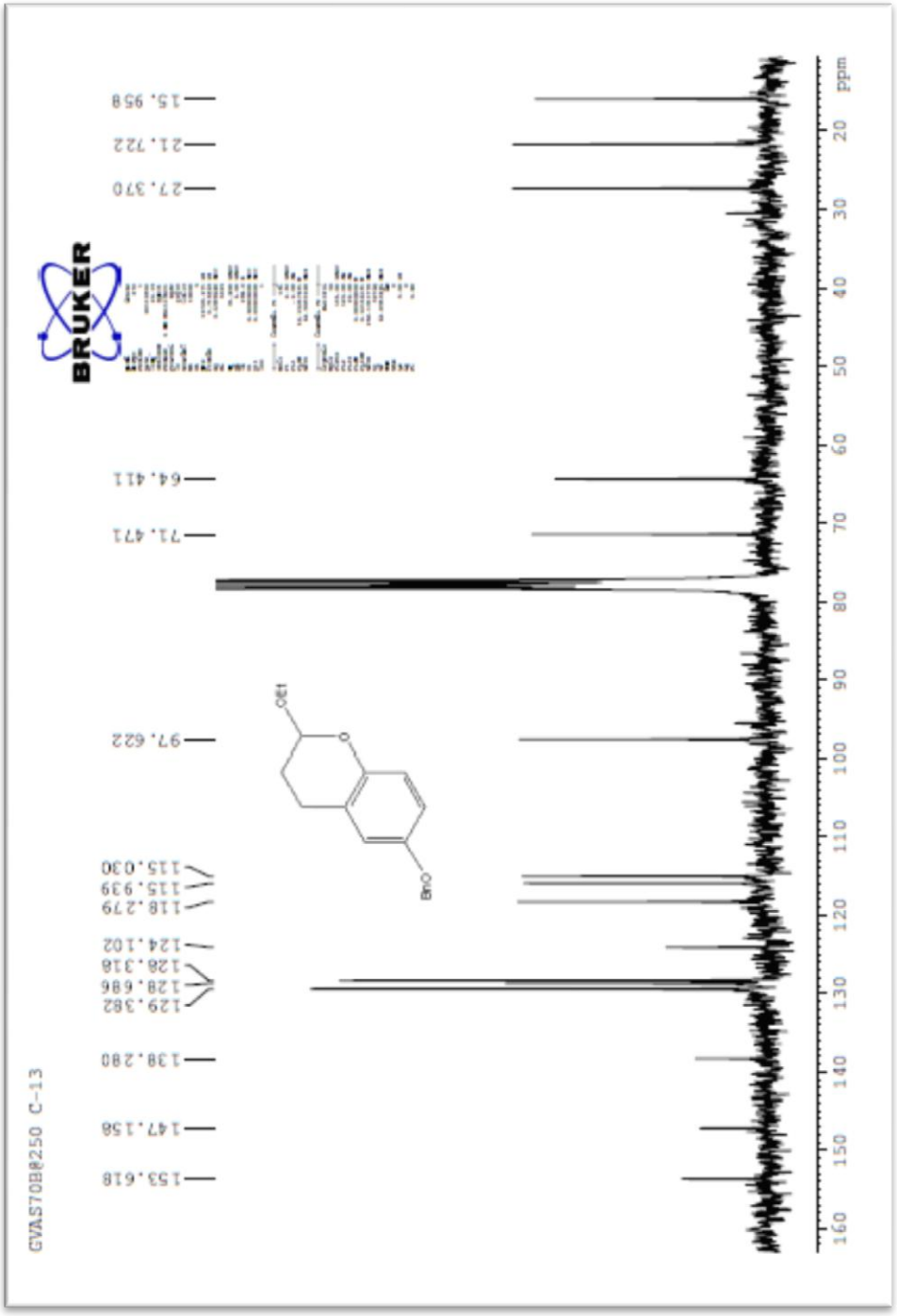

GVAS61B-1 crude@250 H-1
BRUKER
ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
1.26
2.14
1.11
1.04
1.15
1.04
1.04
2.00
2.07

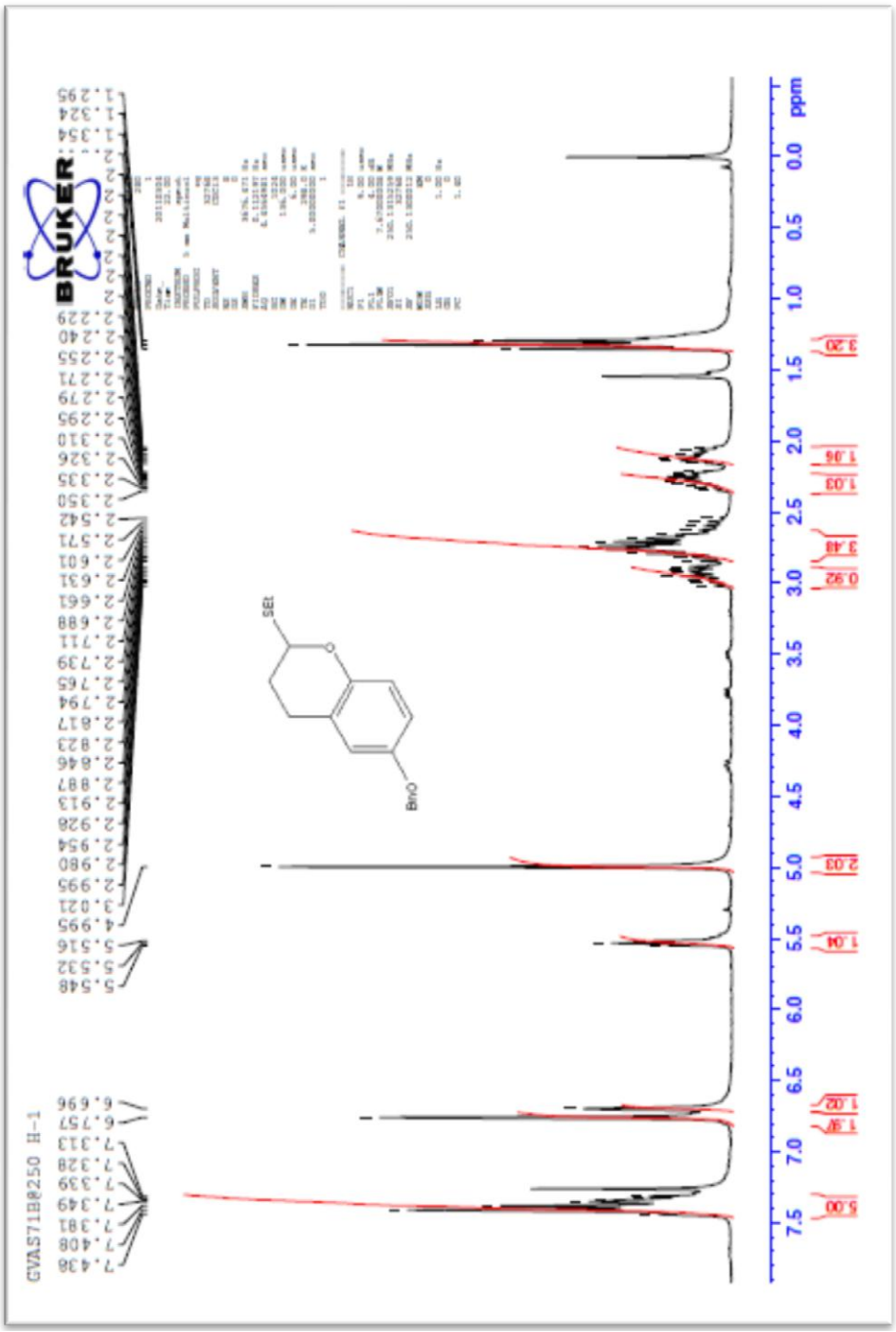

GVAS61B-10250 C-13
153.146
130.197
128.170
123.574
121.492
117.863
97.852
64.623
27.489
21.487
16.085
OEt
BRUKER
ppm

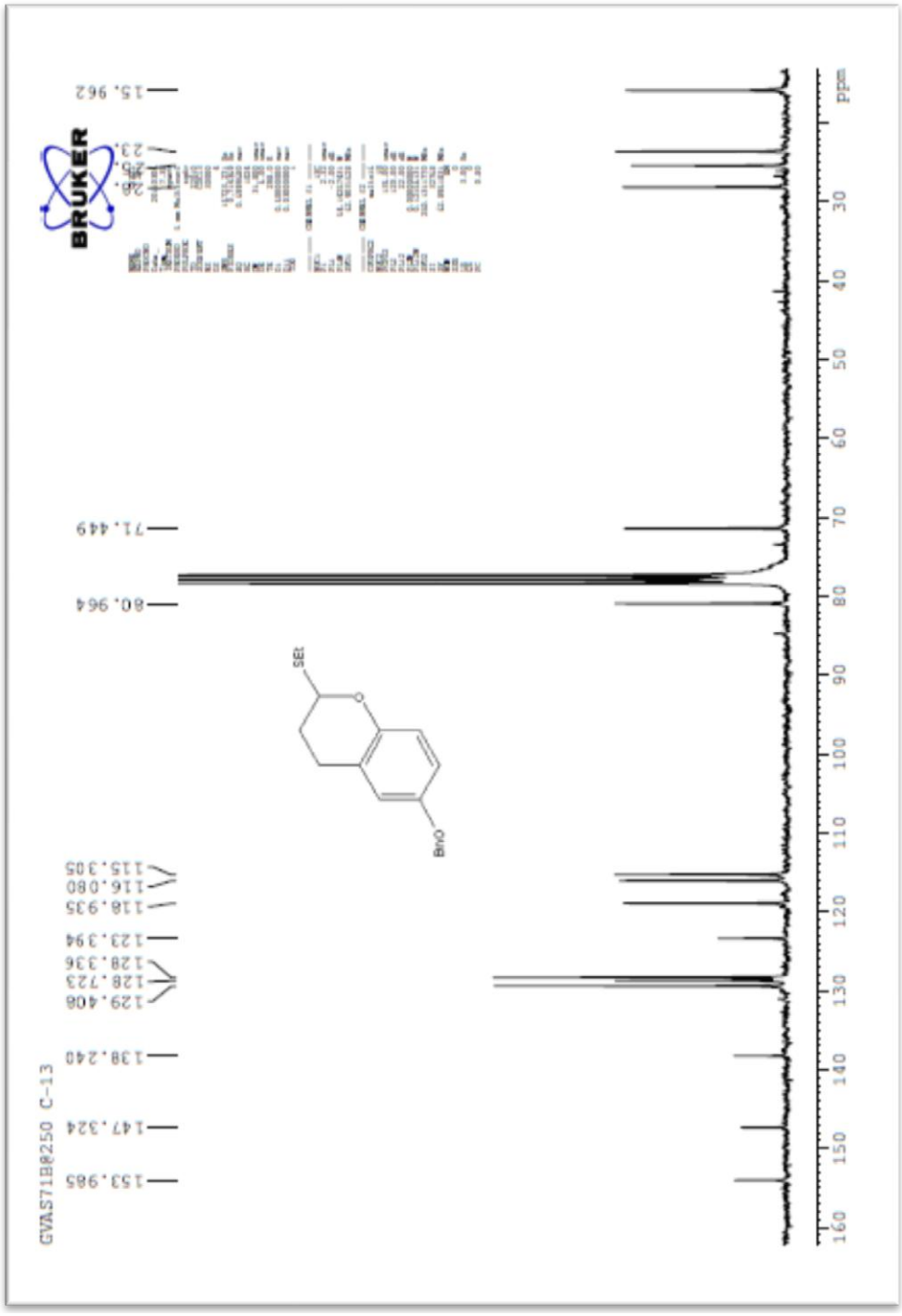

BRUKER
SEt
ppm
GVA572A8250 H-1

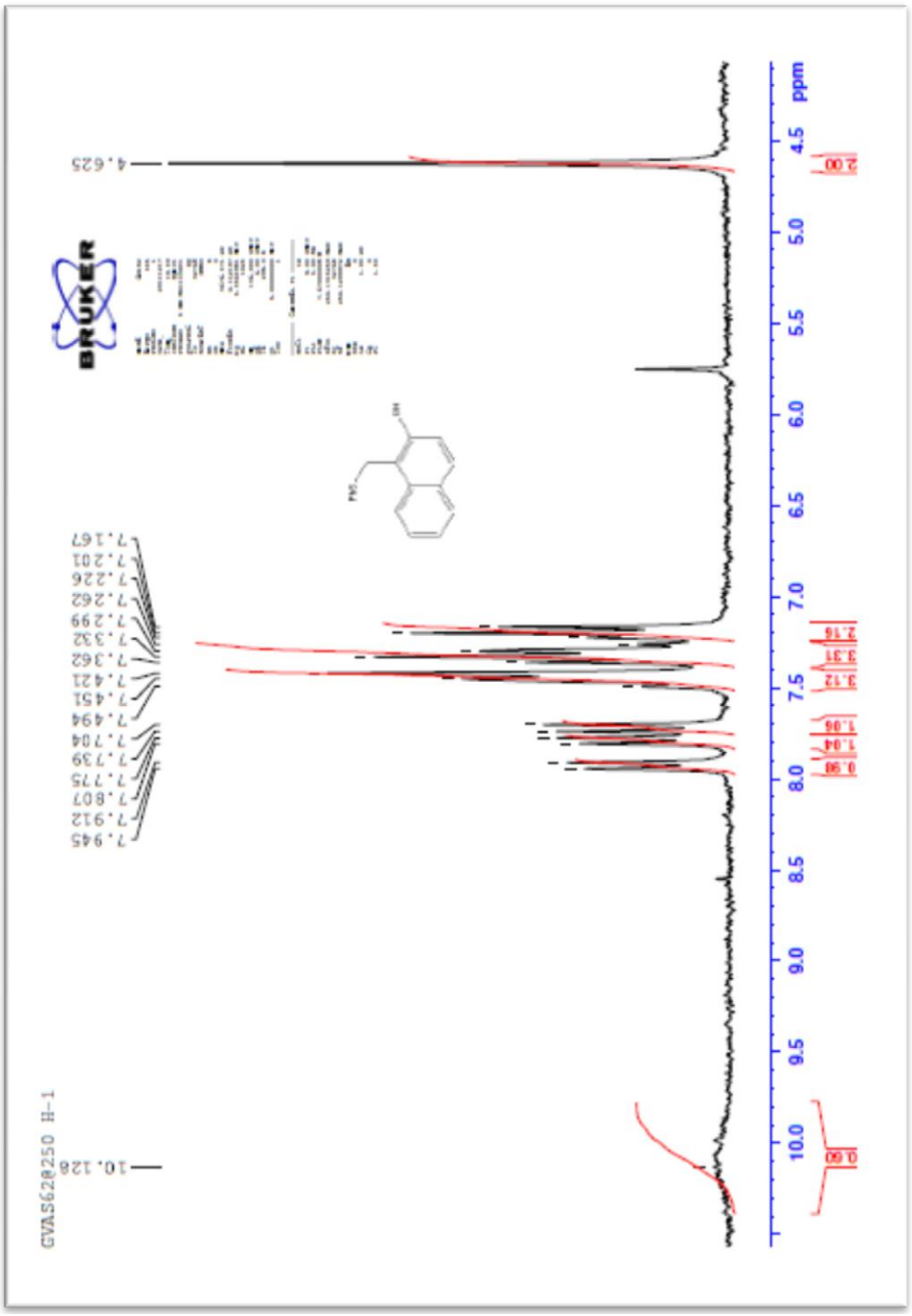

15.307
23.027
24.816
27.550
80.309
117.364
120.993
123.075
127.672
129.699
152.647
ppm
BRUKER

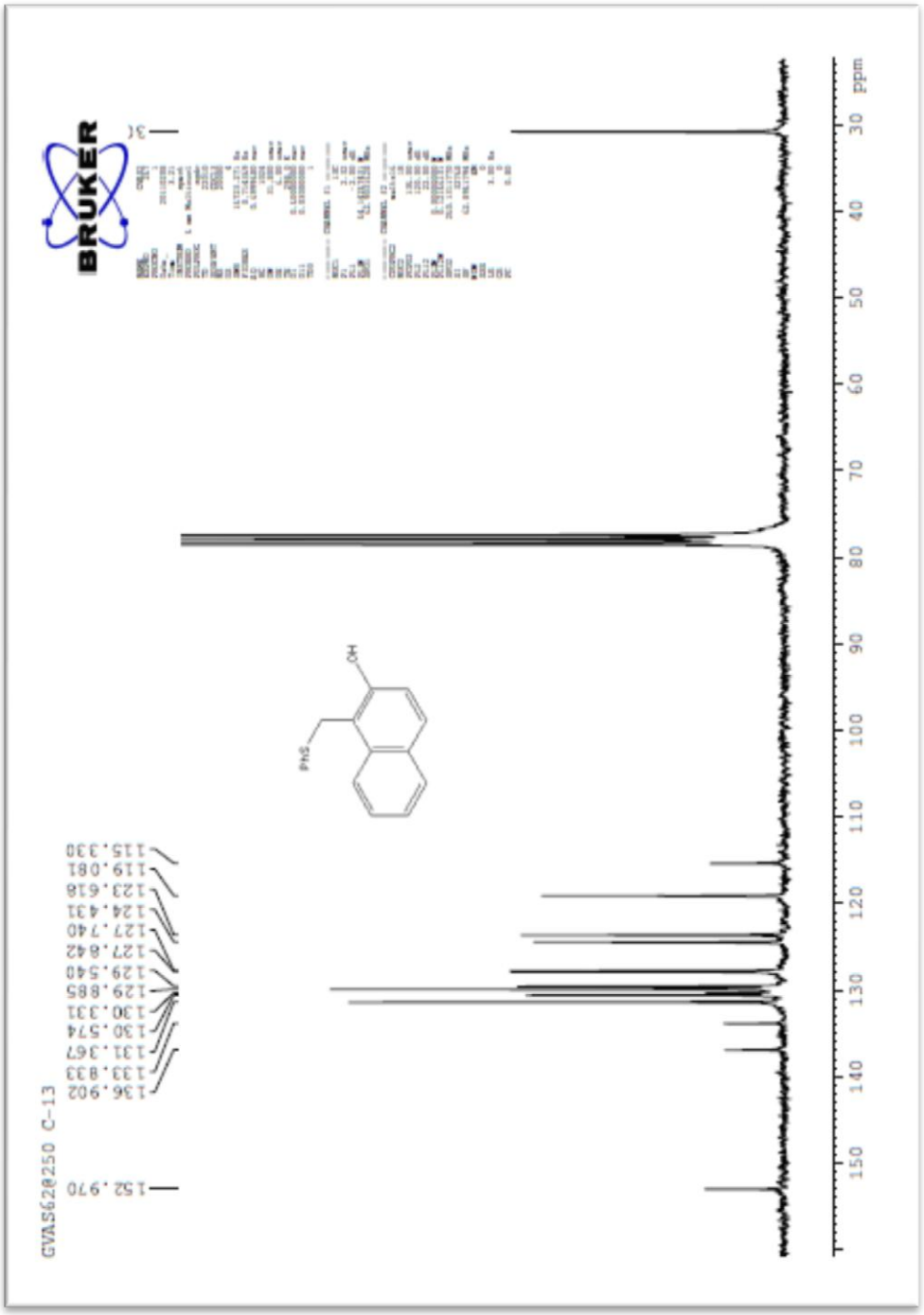

GVAS70B@250 H-1
BRUKER
OEt
BnO
ppm

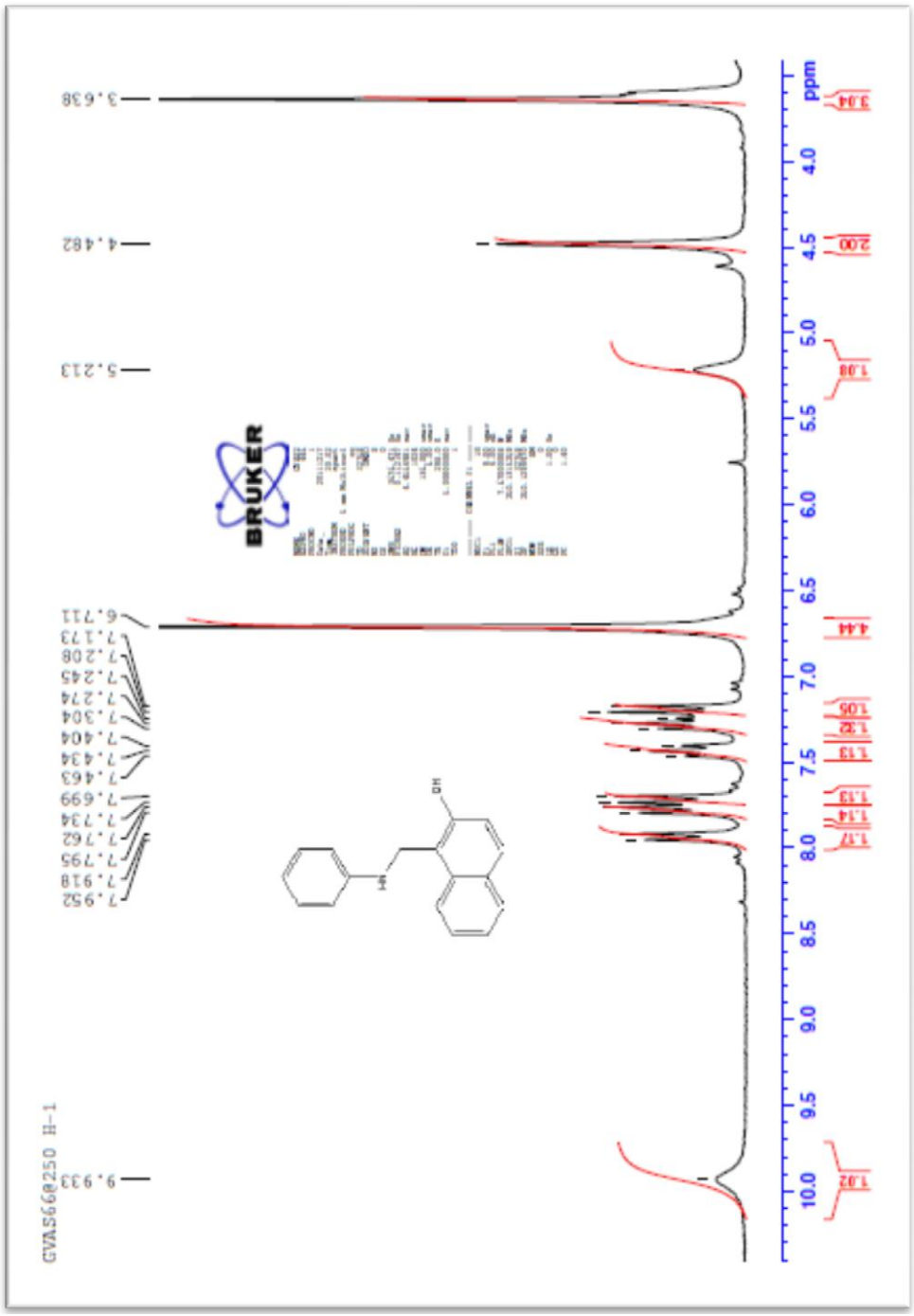

GVAS70B@250 C-13
15.958
21.722
27.370
64.411
71.471
97.622
115.030
115.939
118.279
124.102
128.318
128.686
129.382
138.280
147.158
153.618
ppm

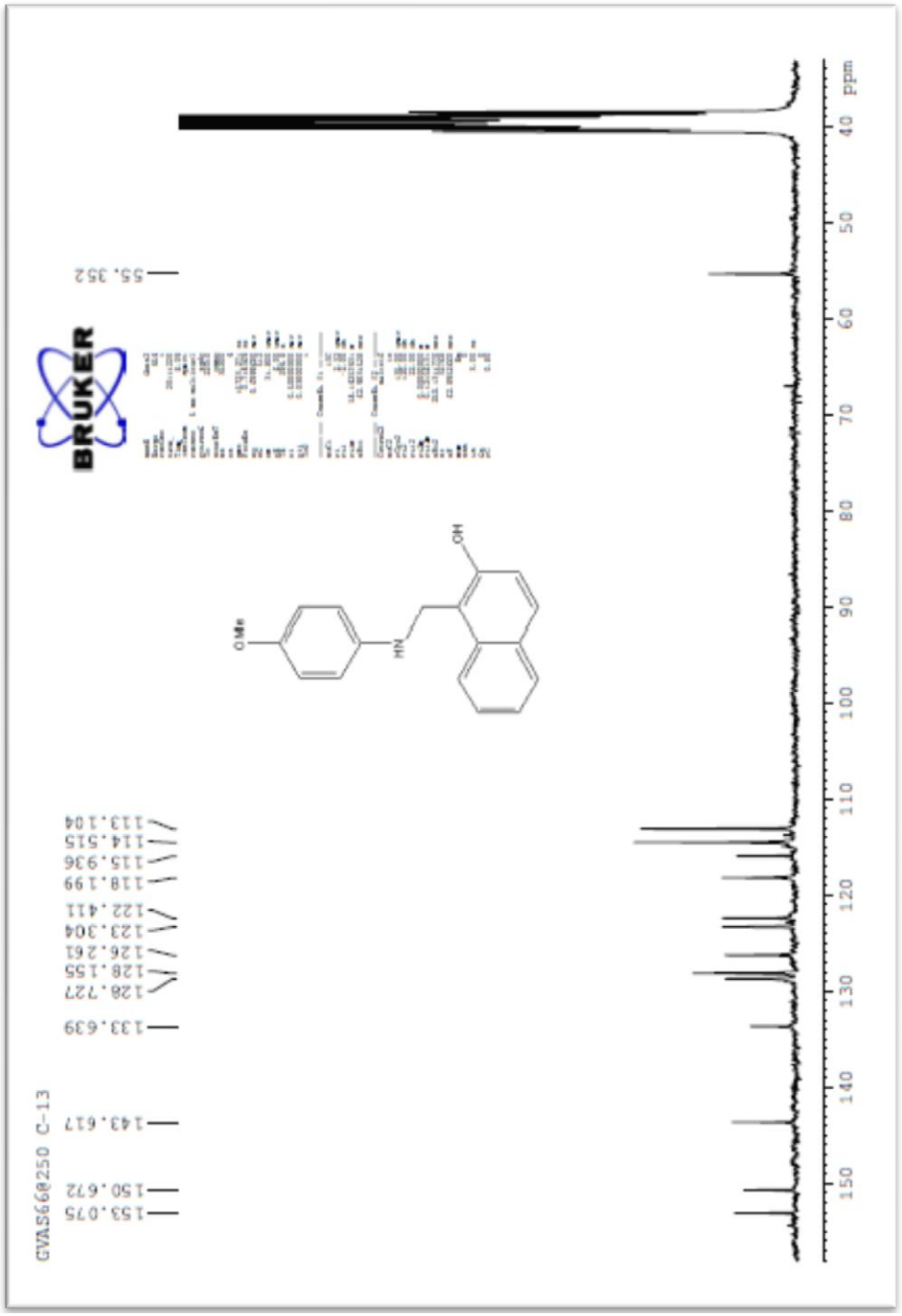

BRUKER
GVA571B@250 H-1
SEt
BnO
ppm

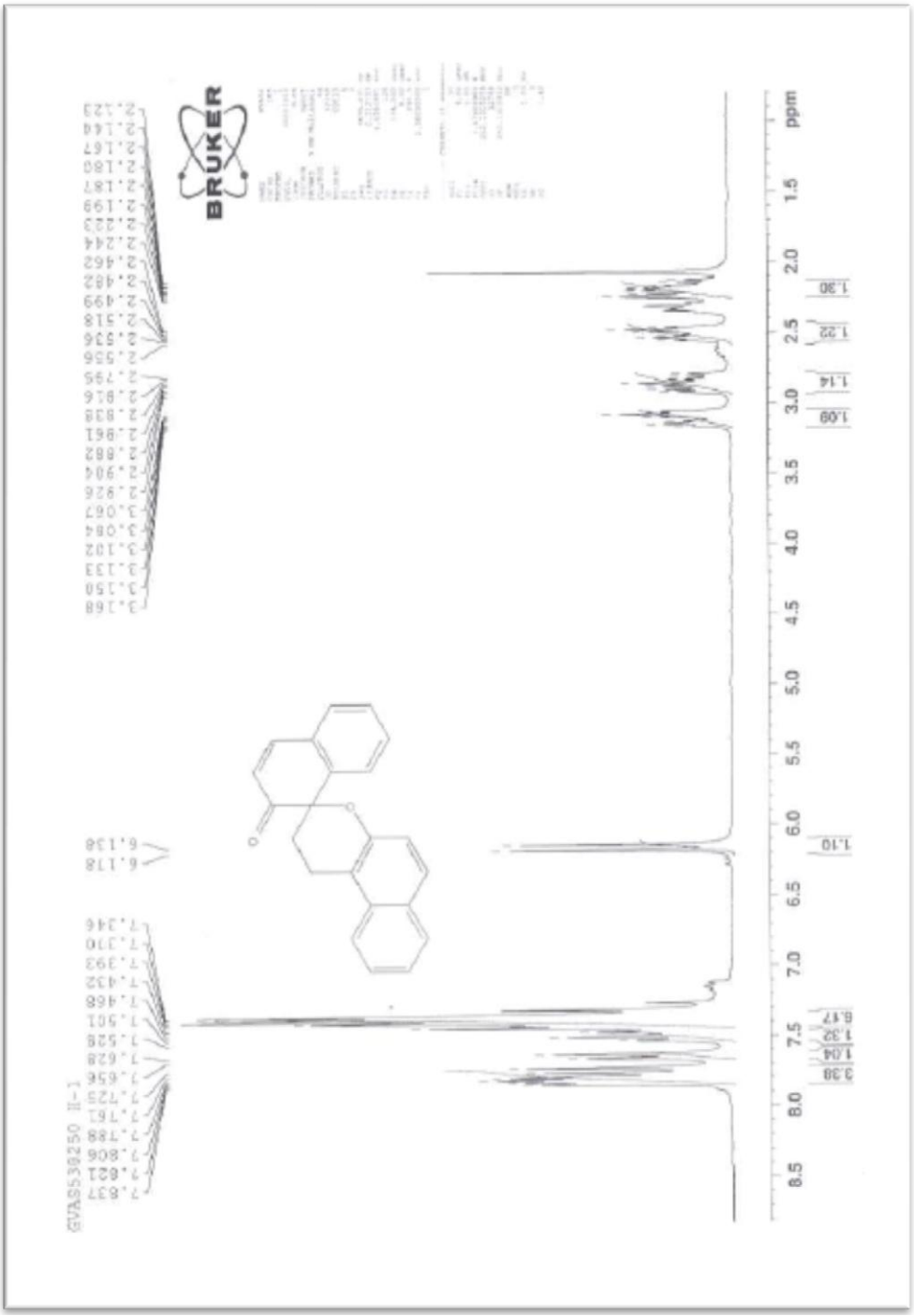

GVAL71B0250 C-13
153.985
147.324
138.240
129.408
128.723
128.336
123.394
118.935
116.080
115.305
80.964
71.449
15.962
SEt
BnO
ppm

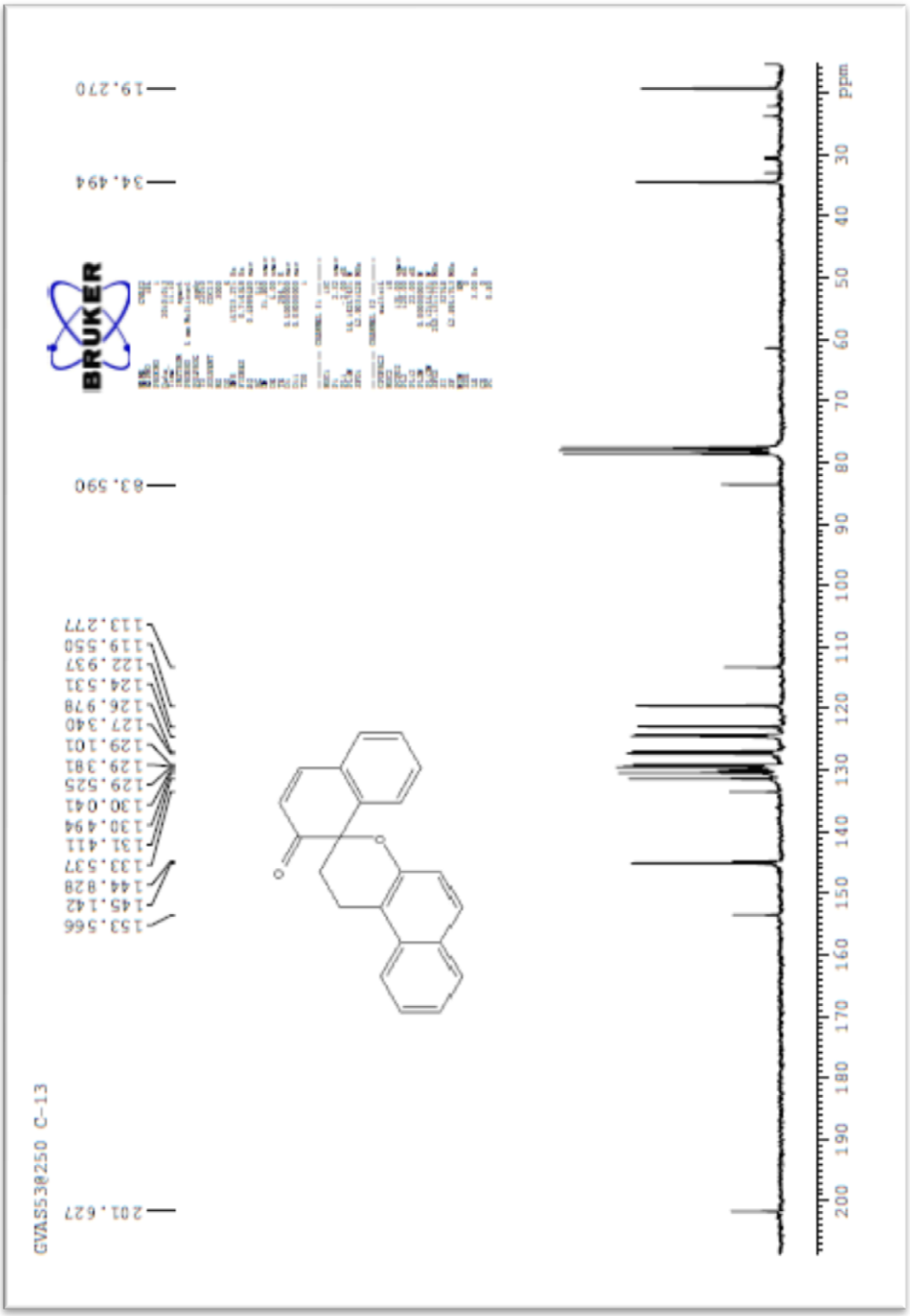

GVA562@250 H-1
10.128
7.945
7.912
7.807
7.775
7.739
7.704
7.494
7.451
7.421
7.362
7.332
7.299
7.262
7.226
7.201
7.167
4.625
BRUKER
ppm

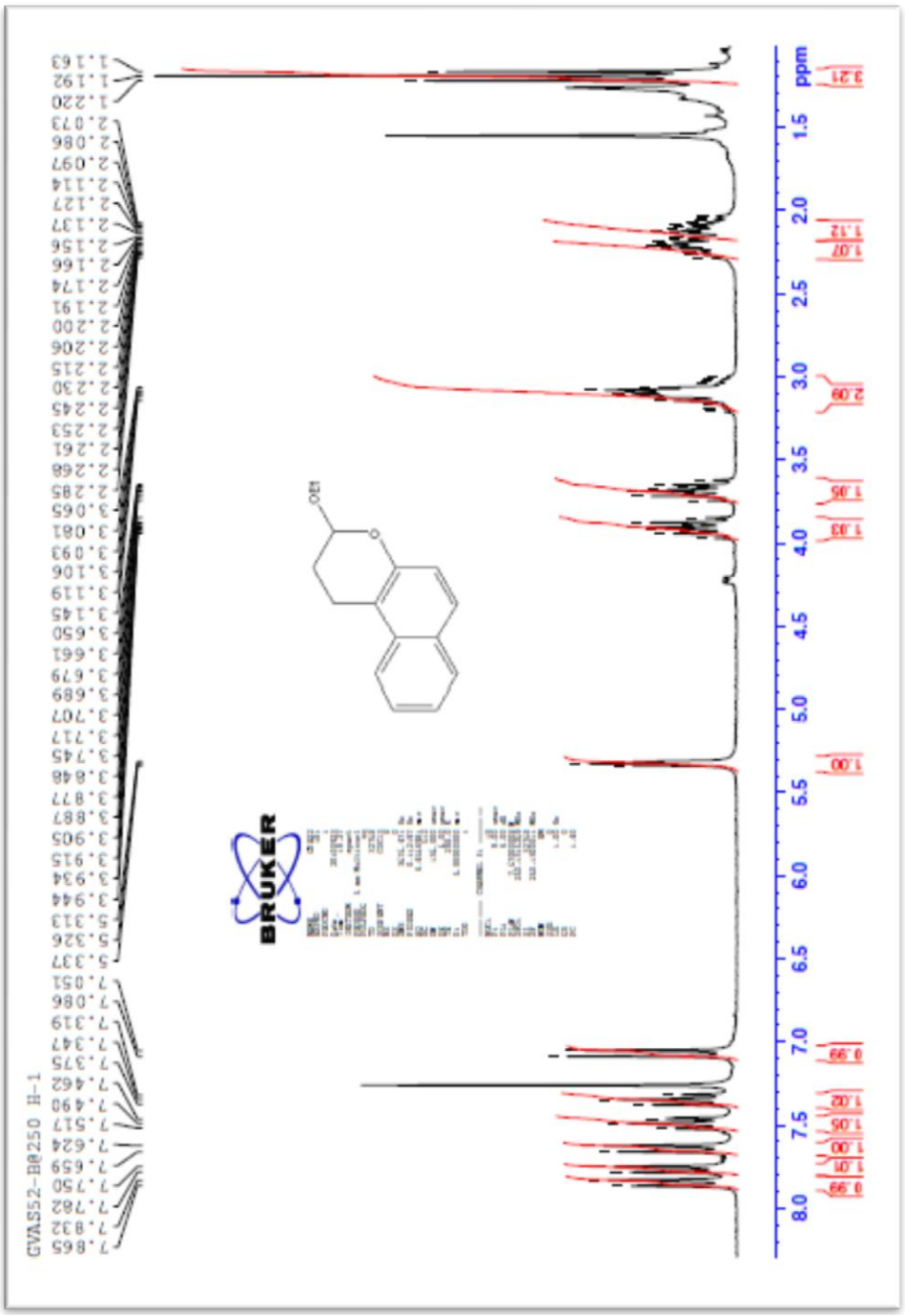

GVALS620250 C-13
152.970
136.902
133.833
131.367
130.574
130.331
129.885
129.540
127.842
127.740
124.431
123.618
119.081
115.330
OH
PhS
ppm

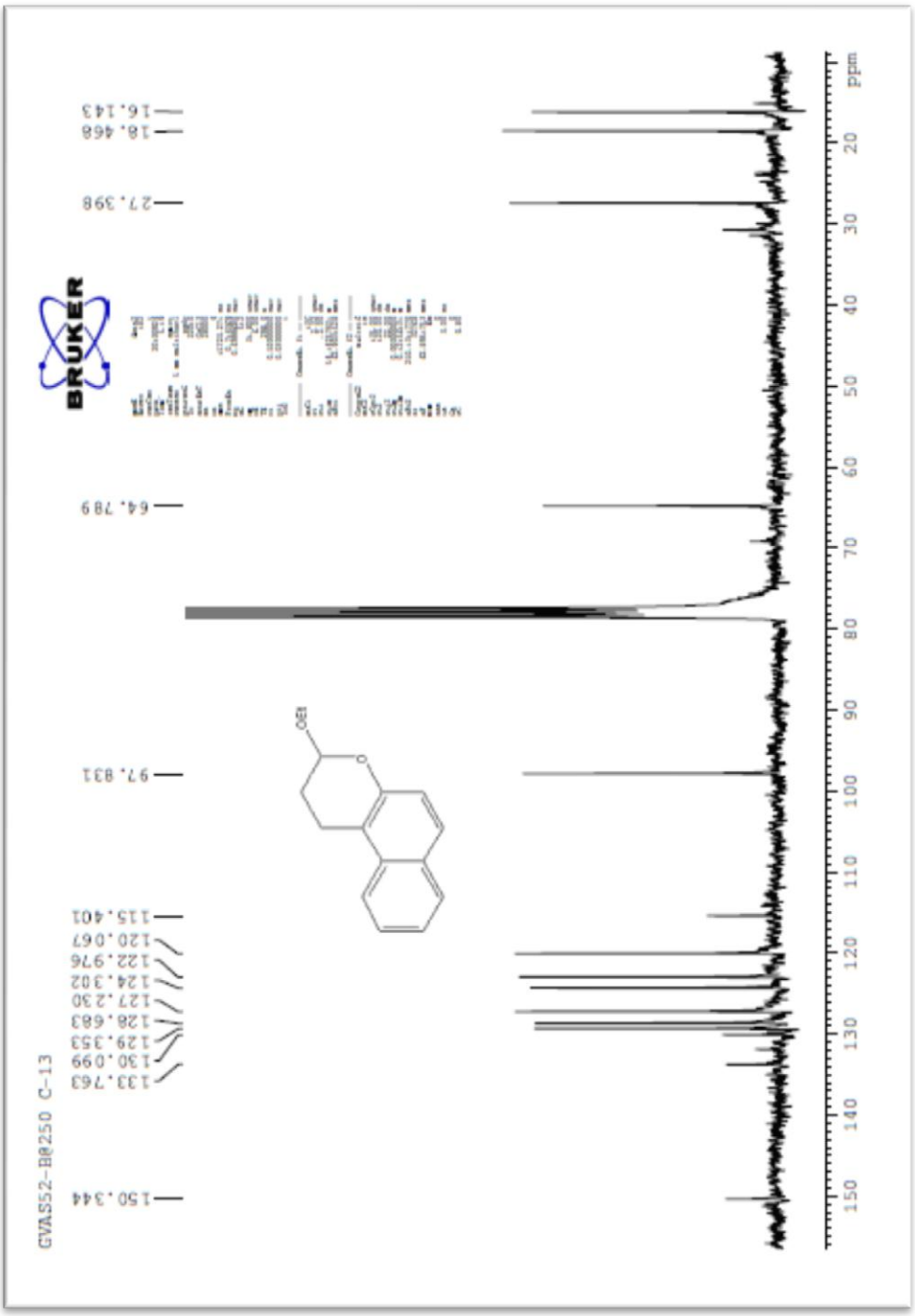

GVA566@250 H-1
9.933
7.952
7.918
7.795
7.762
7.734
7.699
7.463
7.434
7.404
7.304
7.274
7.245
7.208
7.173
6.711
5.213
4.482
3.638
BRUKER
NH
OH
ppm
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
1.02
1.17
1.14
1.13
1.13
1.05
1.00
4.44
1.08
2.00
3.04

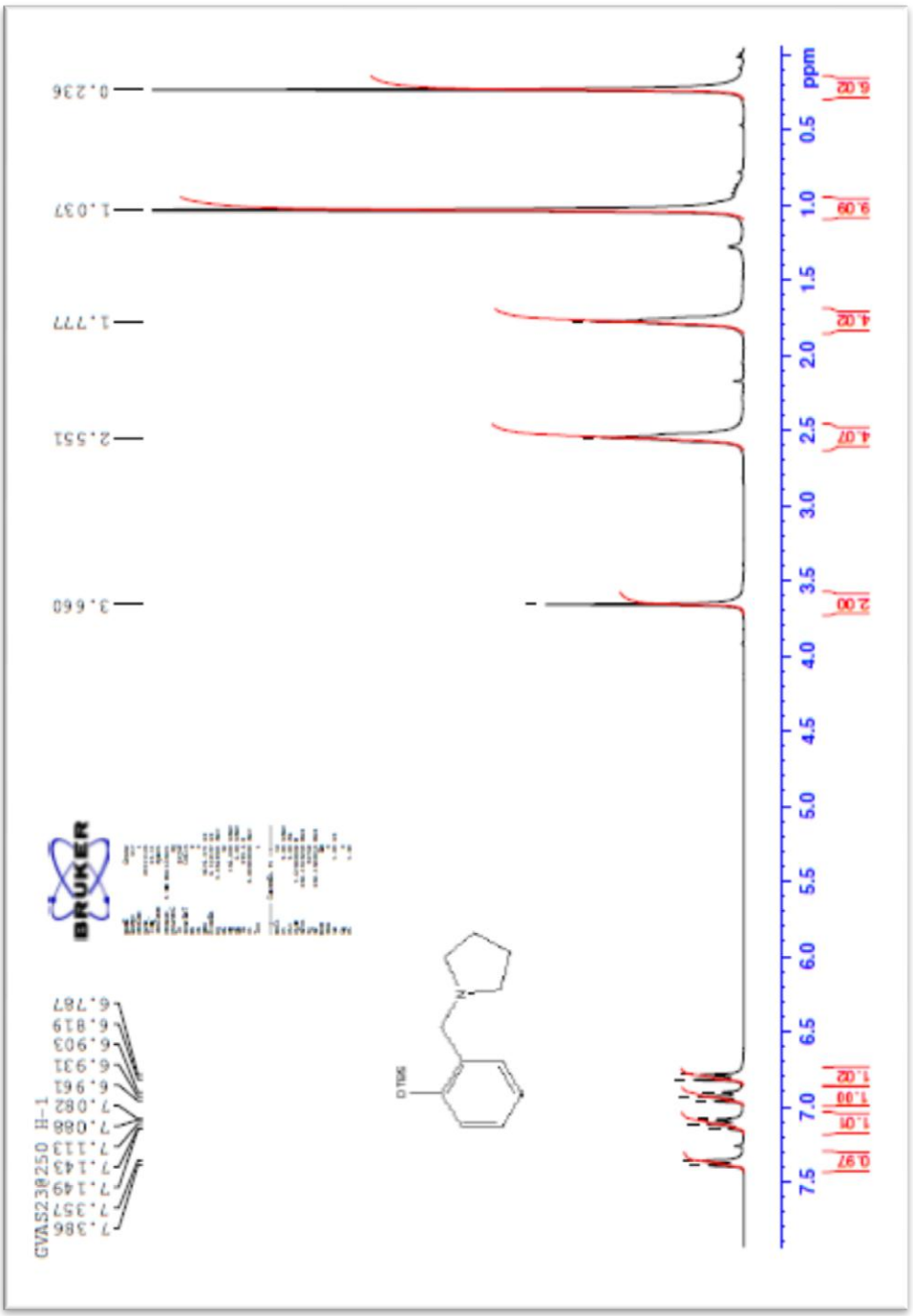

GVA566@250 C-13
153.075
150.672
143.617
133.639
128.727
128.155
126.261
123.304
122.411
118.199
115.936
114.515
113.104
55.352
OMe
HN
OH
ppm

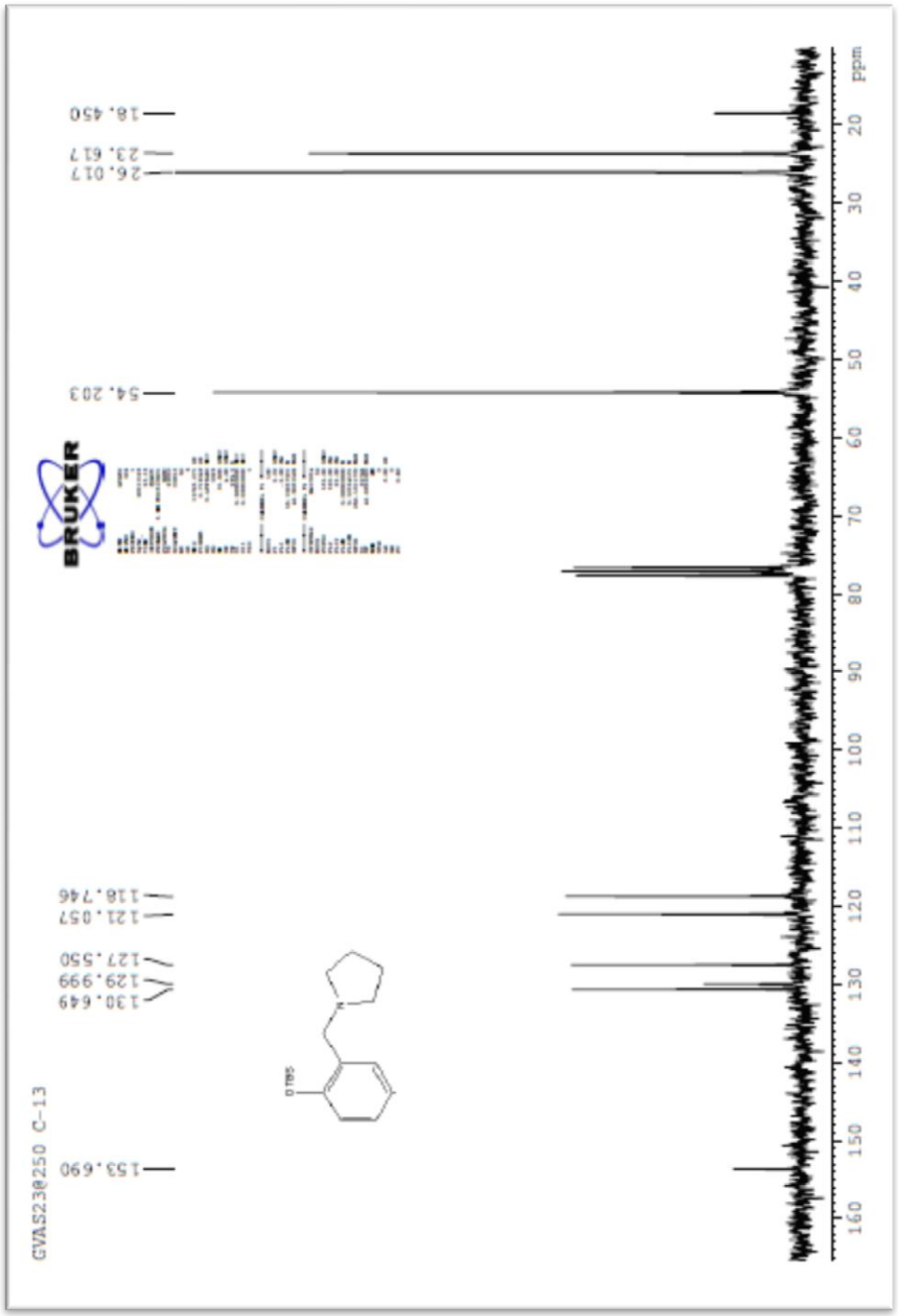


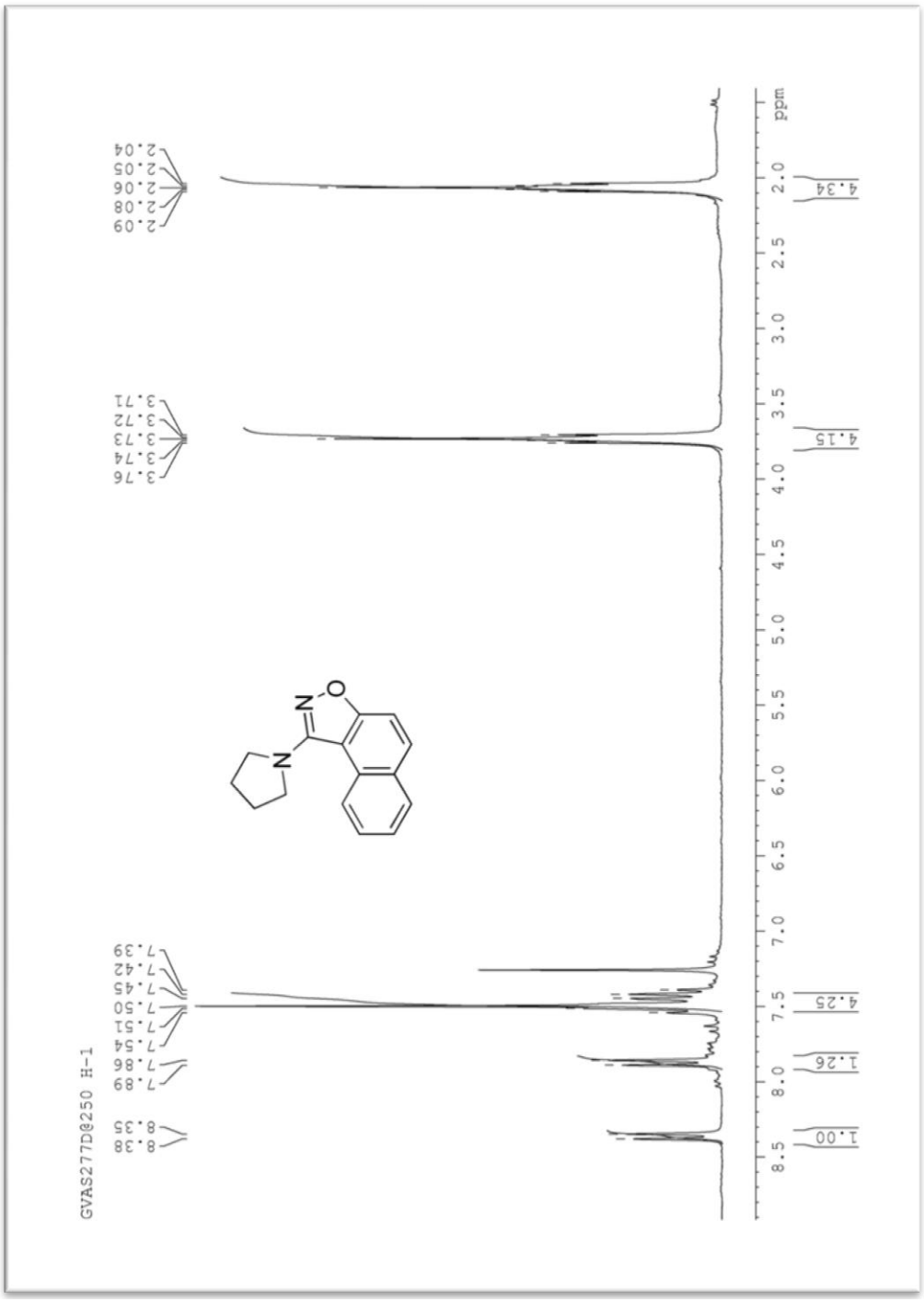

GVA553@250 C-13
201.627
153.566
145.142
144.828
133.537
131.411
130.494
130.041
129.525
129.381
129.101
127.340
126.978
124.531
122.937
119.550
113.277
83.590
34.494
19.270
ppm

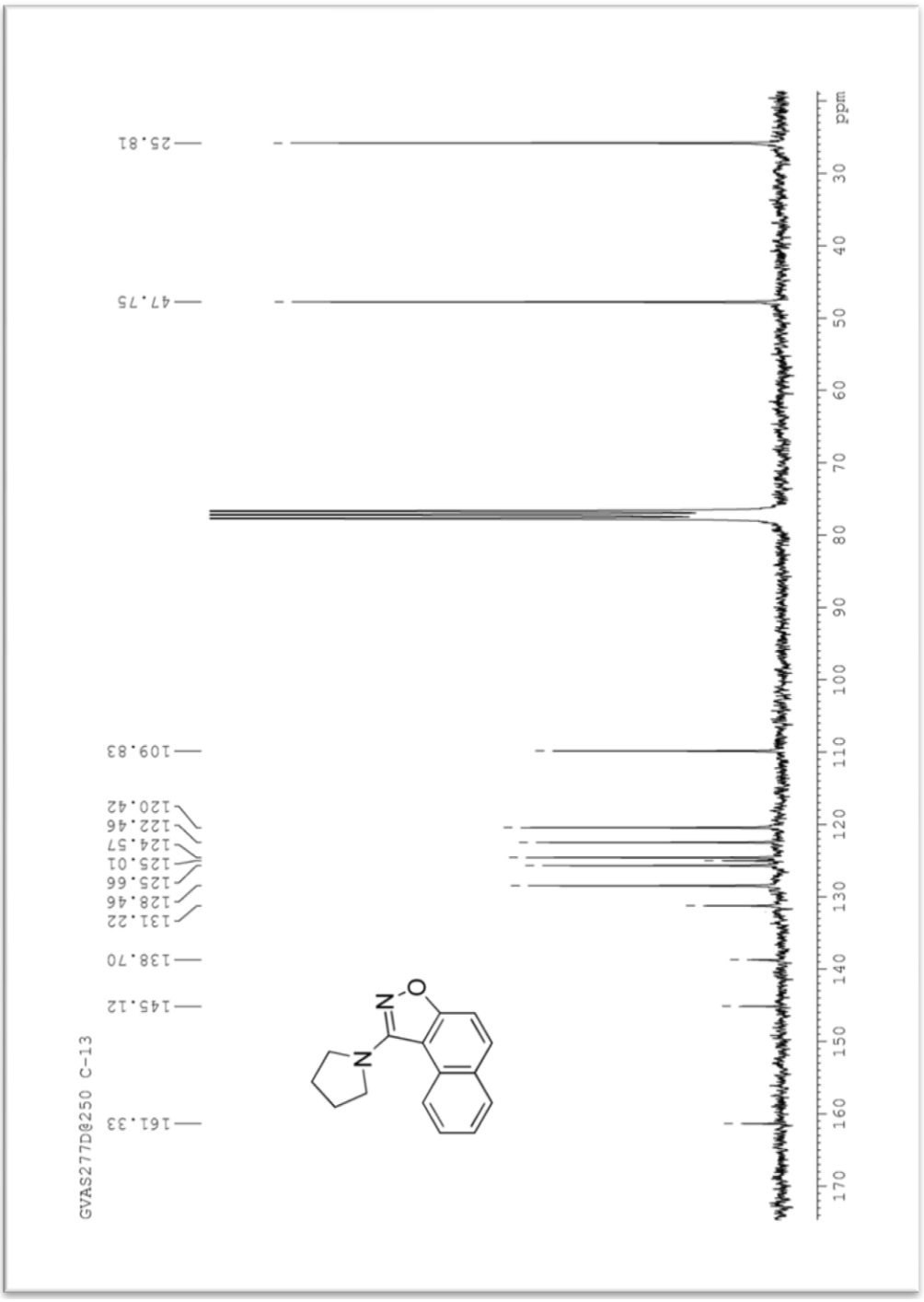

GVA552-B0250 H-1
1.163
1.192
1.220
2.073
2.086
2.097
2.114
2.127
2.137
2.156
2.166
2.174
2.191
2.200
2.206
2.215
2.230
2.245
2.253
2.261
2.268
2.285
3.065
3.081
3.093
3.106
3.119
3.145
3.650
3.661
3.679
3.689
3.707
3.717
3.745
3.846
3.877
3.887
3.905
3.915
3.934
3.944
5.313
5.326
5.337
7.051
7.086
7.319
7.347
7.375
7.462
7.490
7.517
7.624
7.659
7.750
7.782
7.832
7.865
BRUKER
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
3.21
1.07
1.12
2.09
1.05
1.03
1.00
0.99
1.01
1.00
1.05
1.02
0.99

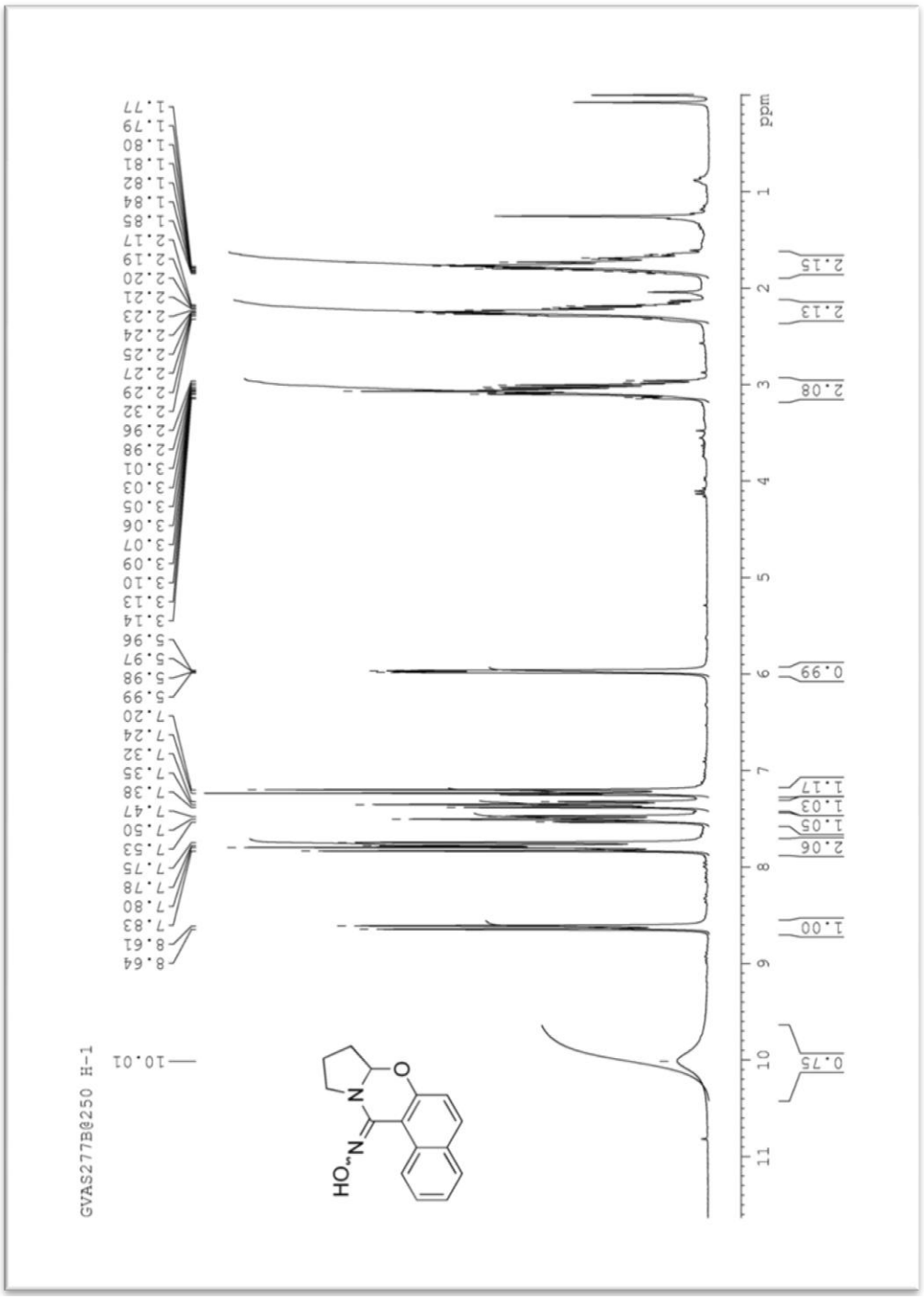

GVAS52-B@250 C-13
150.344
133.763
130.099
129.353
128.683
127.230
124.302
122.976
120.067
115.401
97.831
64.789
27.398
18.468
16.143
OEt
ppm

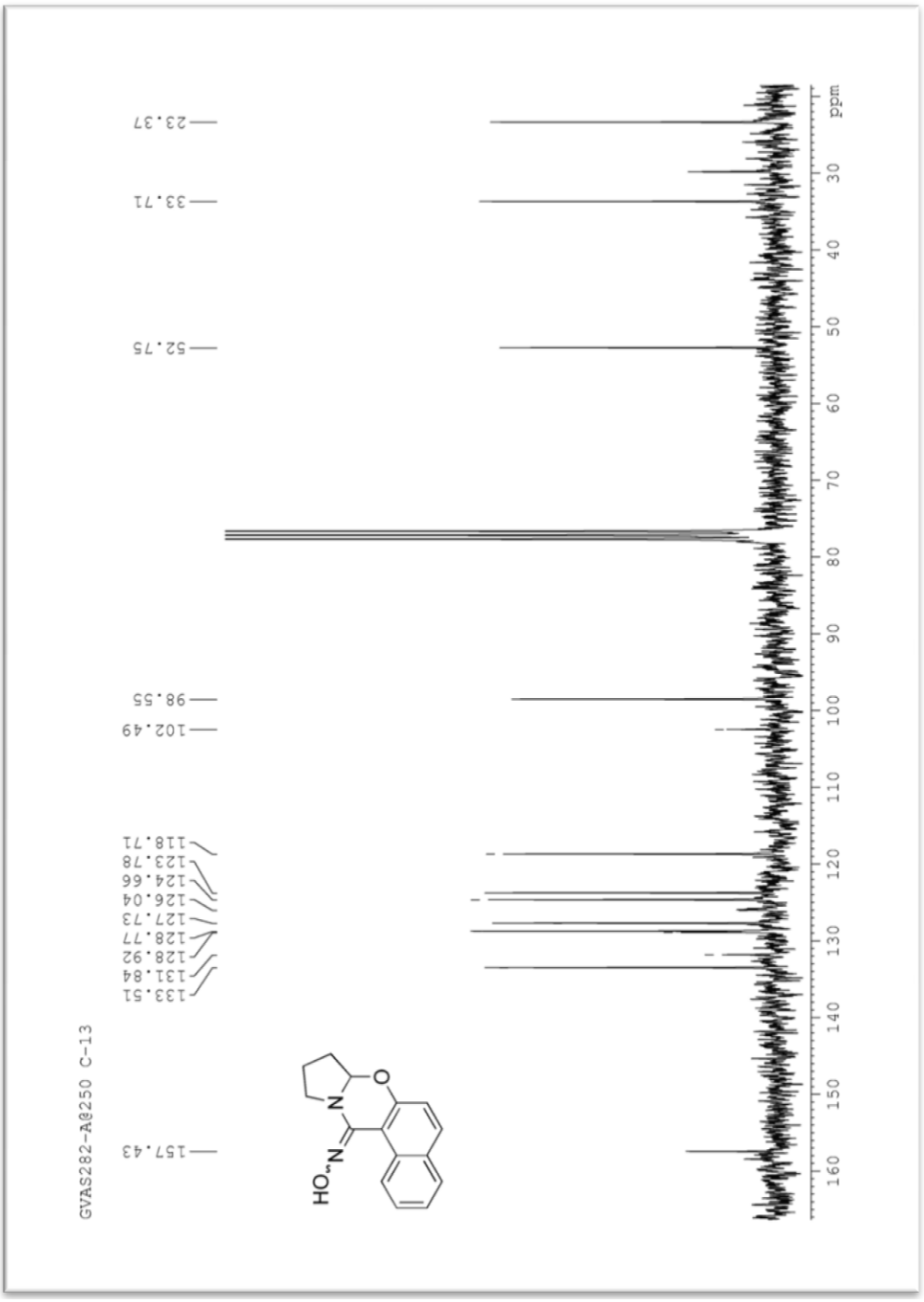

GVAS230250 H-1
0.236
1.037
1.777
2.551
3.660
6.787
6.819
6.903
6.931
6.961
7.082
7.088
7.113
7.143
7.149
7.357
7.386
ppm
BRUKER

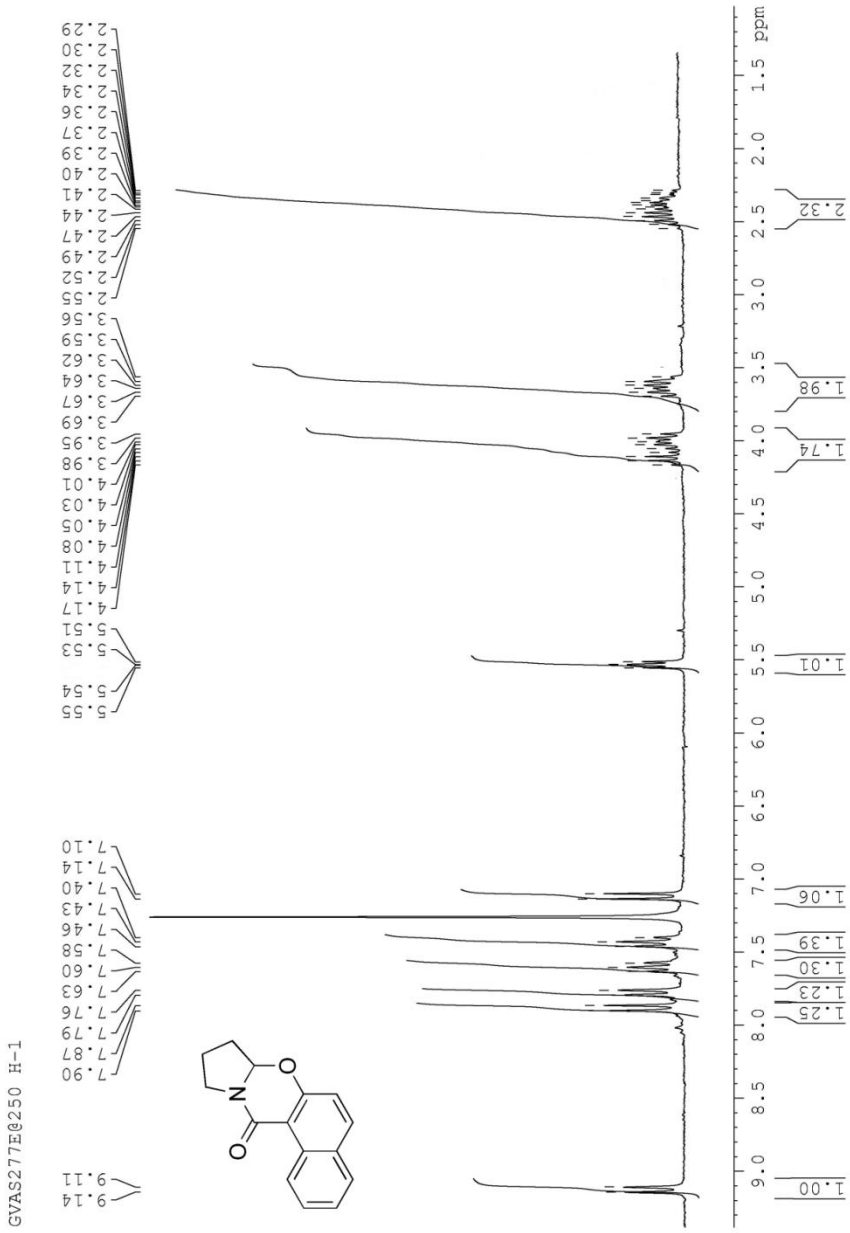

GVAS230250 C-13
153.690
130.649
129.999
127.550
121.057
118.746
54.203
26.017
23.617
18.450
ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
BRUKER


GVAS277D8250 H-1
8.38
8.35
7.89
7.86
7.54
7.51
7.50
7.45
7.42
7.39
3.76
3.74
3.73
3.72
3.71
2.09
2.08
2.06
2.05
2.04
ppm
1.00
1.26
4.25
4.15
4.34

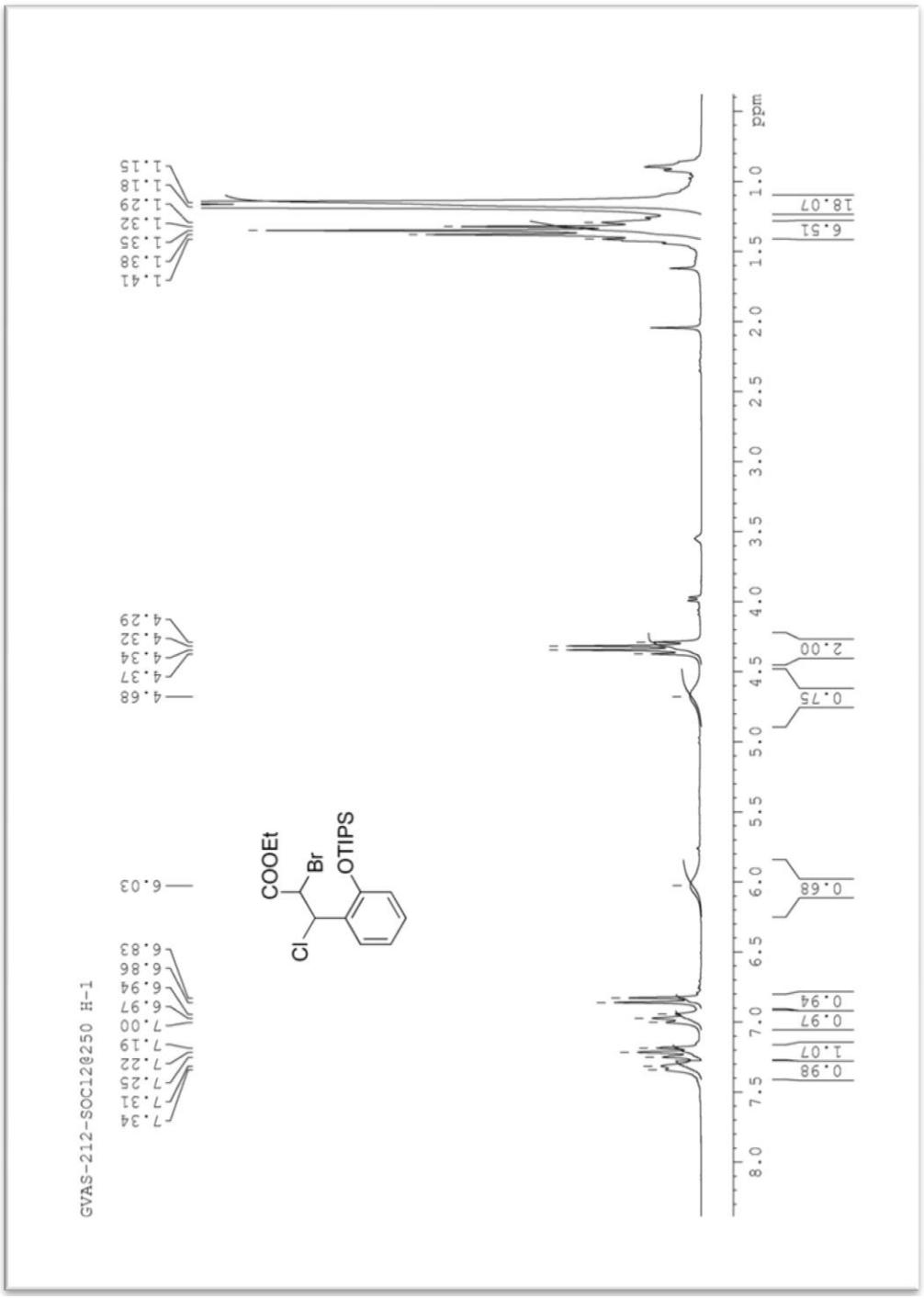

GVAS277D8250 C-13
161.33
145.12
138.70
131.22
128.46
125.66
125.01
124.57
122.46
120.42
109.83
47.75
25.81
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
N
O
N

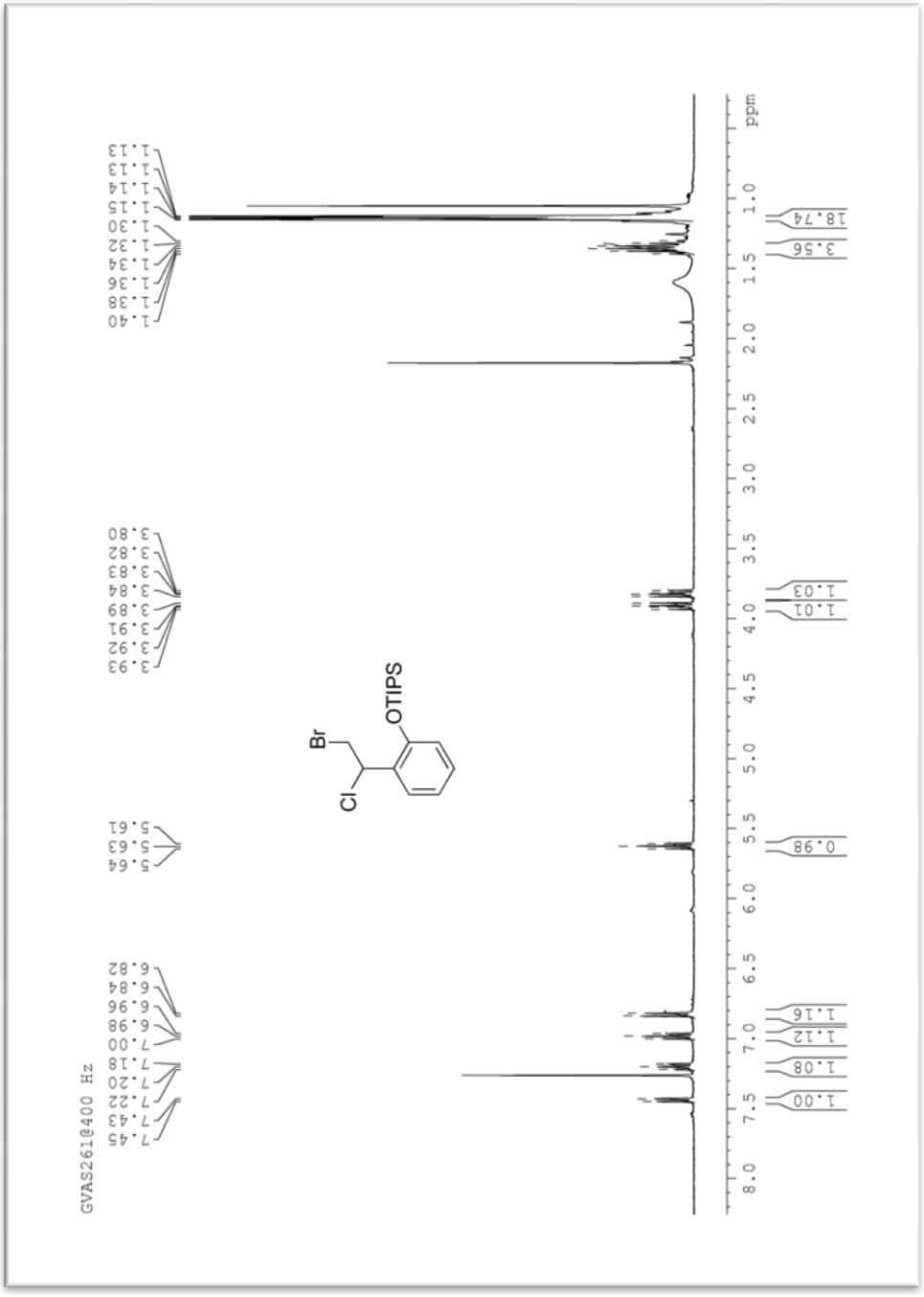

GVAS277B0250 H-1
10.01
8.64
8.61
7.83
7.80
7.78
7.75
7.53
7.50
7.47
7.38
7.35
7.32
7.24
7.20
5.99
5.98
5.97
5.96
3.14
3.13
3.10
3.09
3.07
3.06
3.05
3.03
3.01
2.98
2.96
2.32
2.29
2.27
2.25
2.24
2.23
2.21
2.20
2.19
2.17
1.85
1.84
1.82
1.81
1.80
1.79
1.77
HO
N
N
O
ppm
0.75
1.00
2.06
1.05
1.03
1.17
0.99
2.08
2.13
2.15


GVAS282-A@250 C-13
157.43
133.51
131.84
128.92
128.77
127.73
126.04
124.66
123.78
118.71
102.49
98.55
52.75
33.71
23.37
ppm
HO
N
N
O

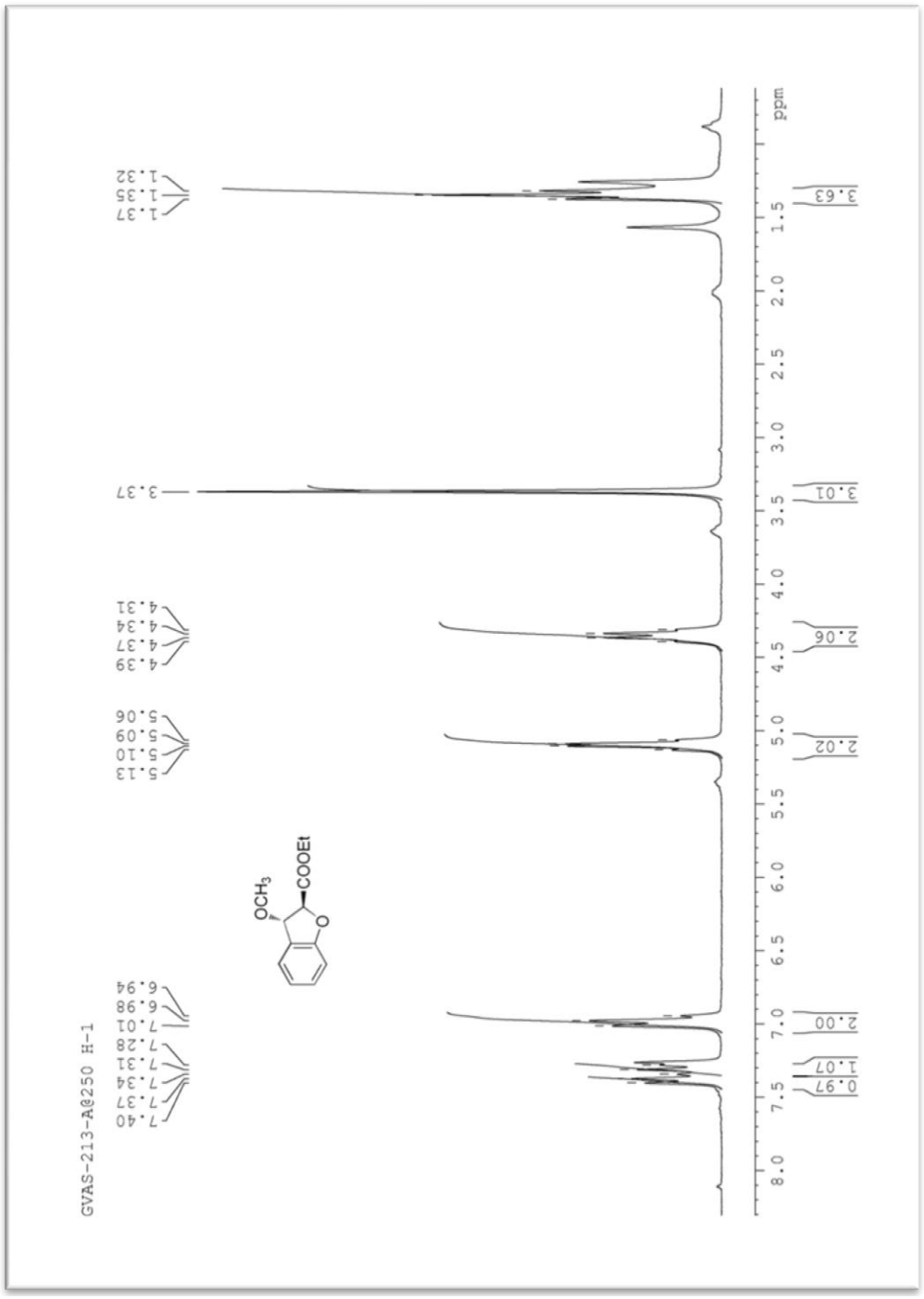

GVAS277E@250 H-1
9.14
9.11
7.90
7.87
7.79
7.76
7.63
7.60
7.58
7.46
7.43
7.40
7.14
7.10
5.55
5.54
5.53
5.51
4.17
4.14
4.11
4.08
4.05
4.03
4.01
3.98
3.95
3.69
3.67
3.64
3.62
3.59
3.56
2.55
2.52
2.49
2.47
2.44
2.41
2.40
2.39
2.37
2.36
2.34
2.32
2.30
2.29
O
N
O
1.00
1.25
1.23
1.30
1.39
1.06
1.01
1.74
1.98
2.32
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

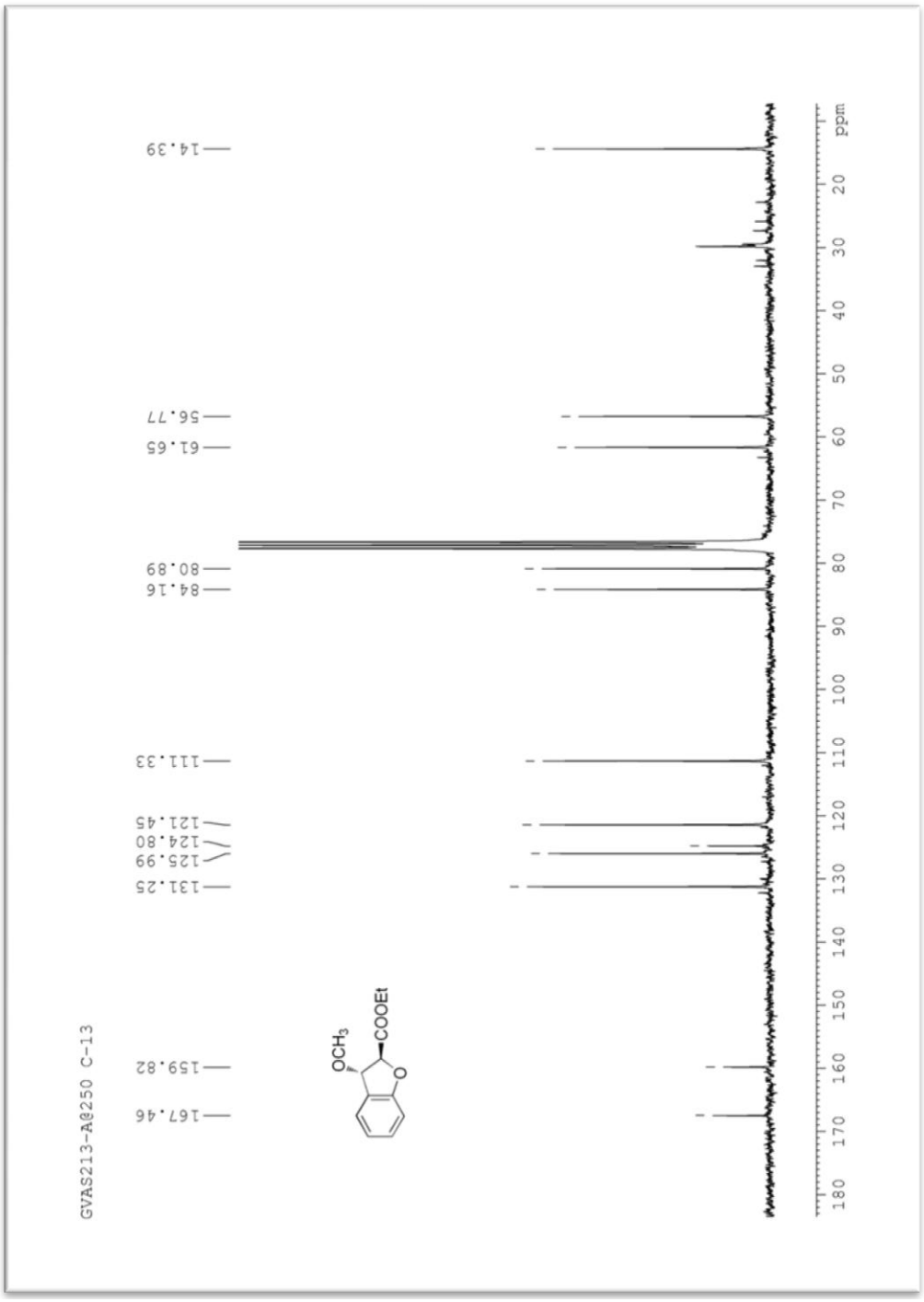
GVAS277E@250 C-13
161.53
157.75
134.94
131.85
130.16
128.42
128.22
126.14
125.03
124.91
123.11
117.02
88.18
45.14
32.20
22.07
ppm

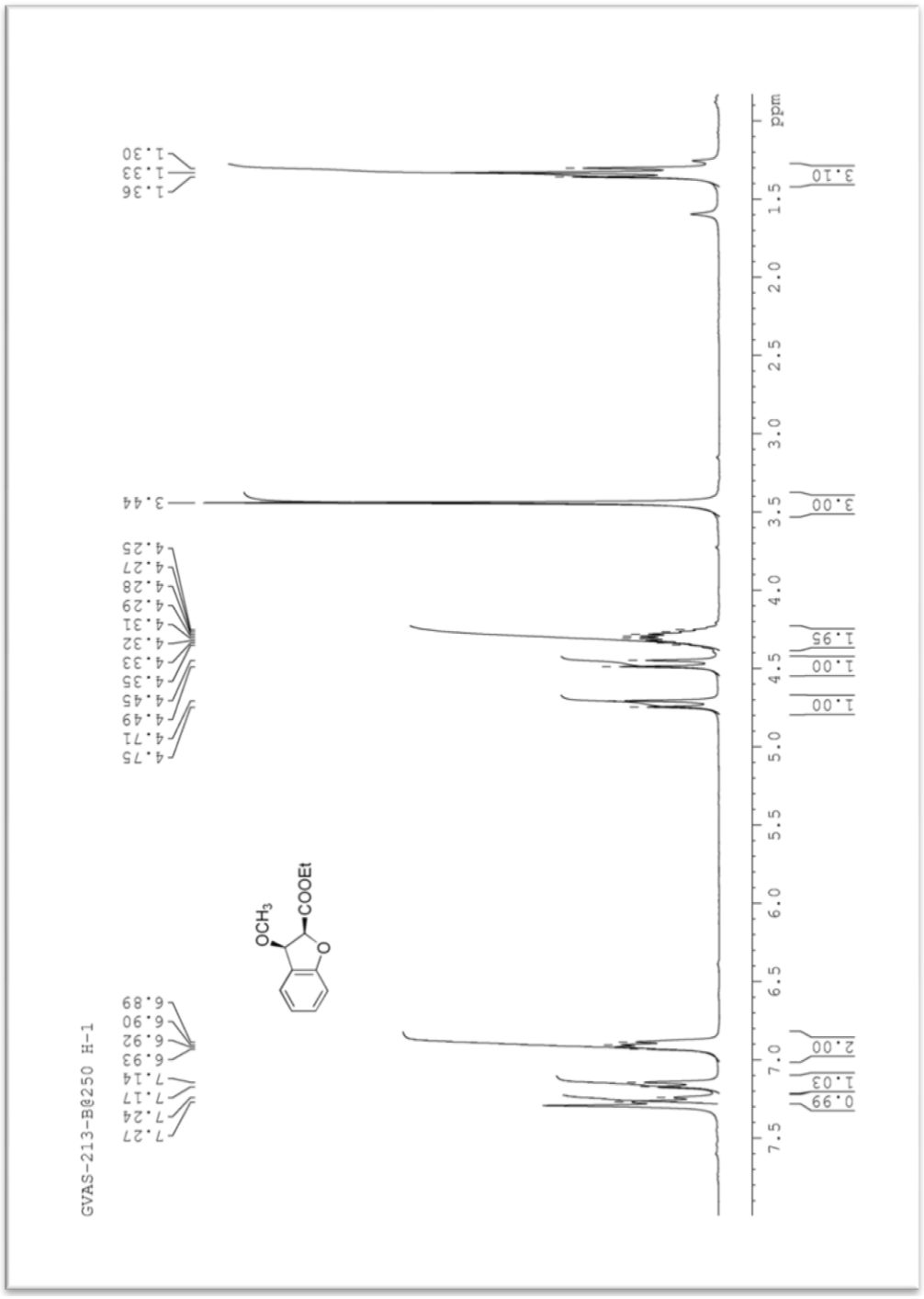

GVAS-212-SOC120250 H-1
COOEt
Br
OTIPS
Cl
ppm

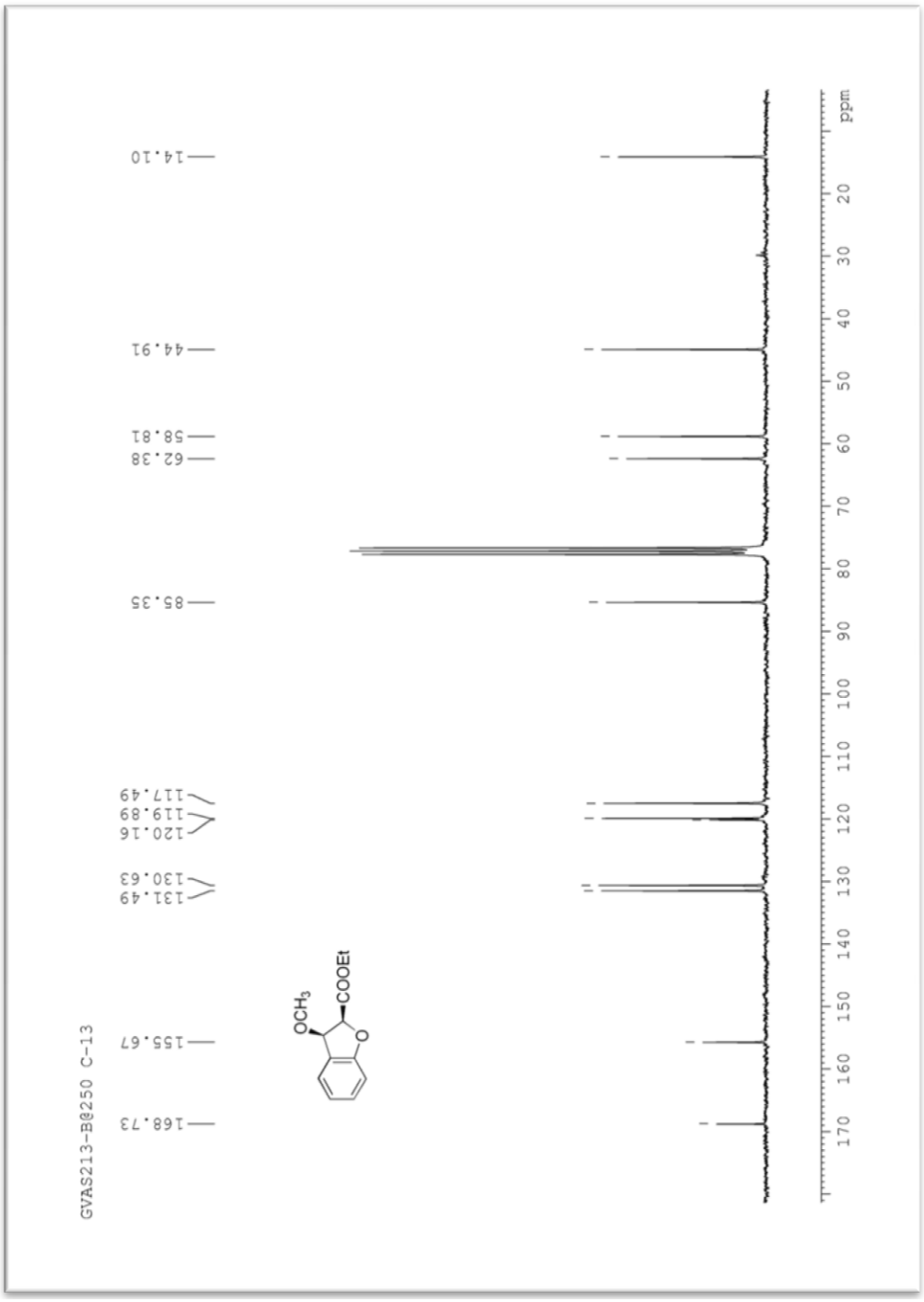

GVAS261@400 Hz
7.45
7.43
7.22
7.20
7.18
7.00
6.98
6.96
6.84
6.82
5.64
5.63
5.61
3.93
3.92
3.91
3.89
3.84
3.83
3.82
3.80
1.40
1.38
1.36
1.34
1.32
1.30
1.15
1.14
1.13
1.13
Br
Cl
OTIPS
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
1.00
1.08
1.12
1.16
0.98
1.03
1.01
3.56
18.74

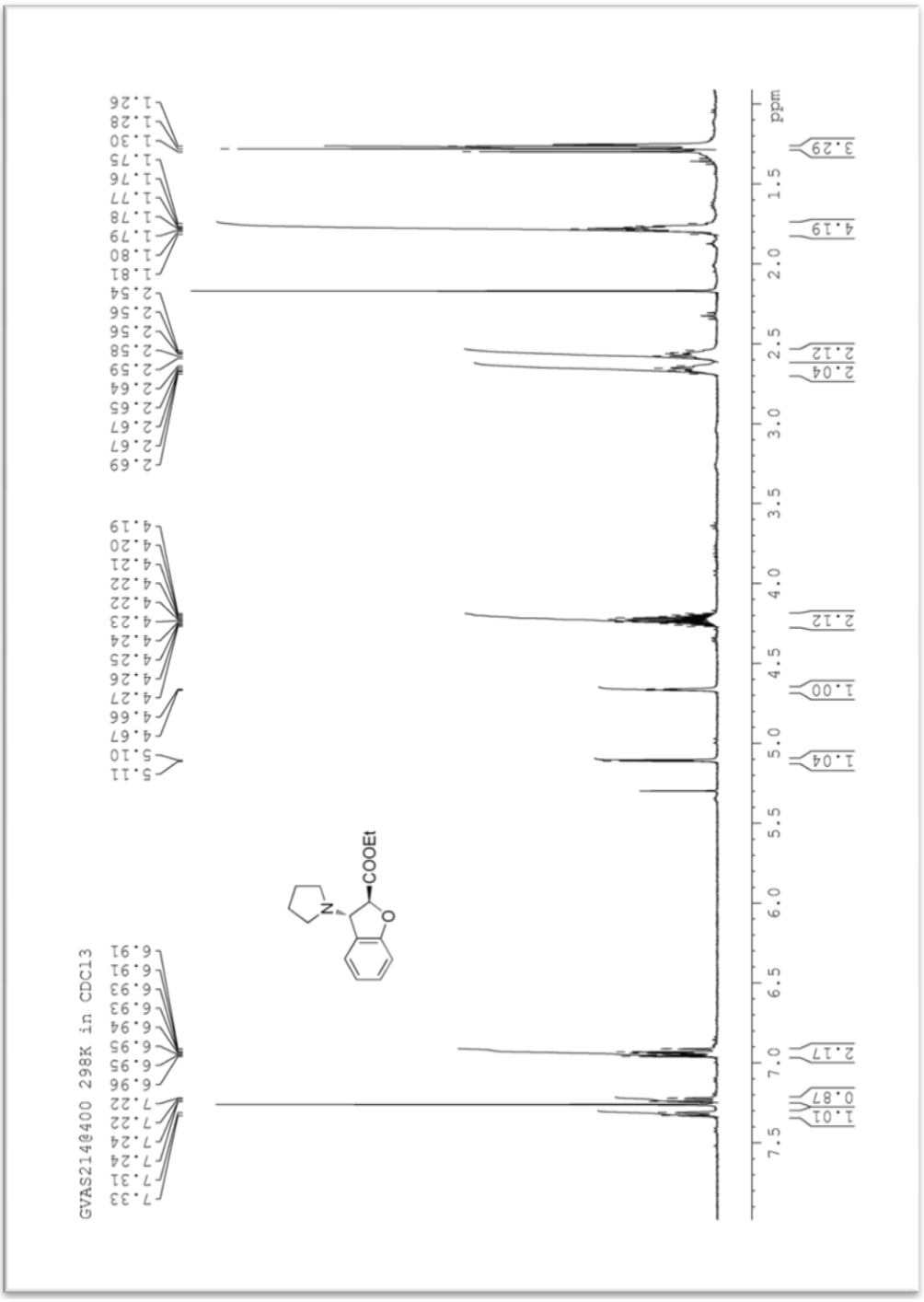
GVAS2120250_C-13
167.98
154.04
130.32
127.66
121.31
118.45
62.49
53.78
18.23
14.03
13.20
COOEt
Br
OTIPS
Cl

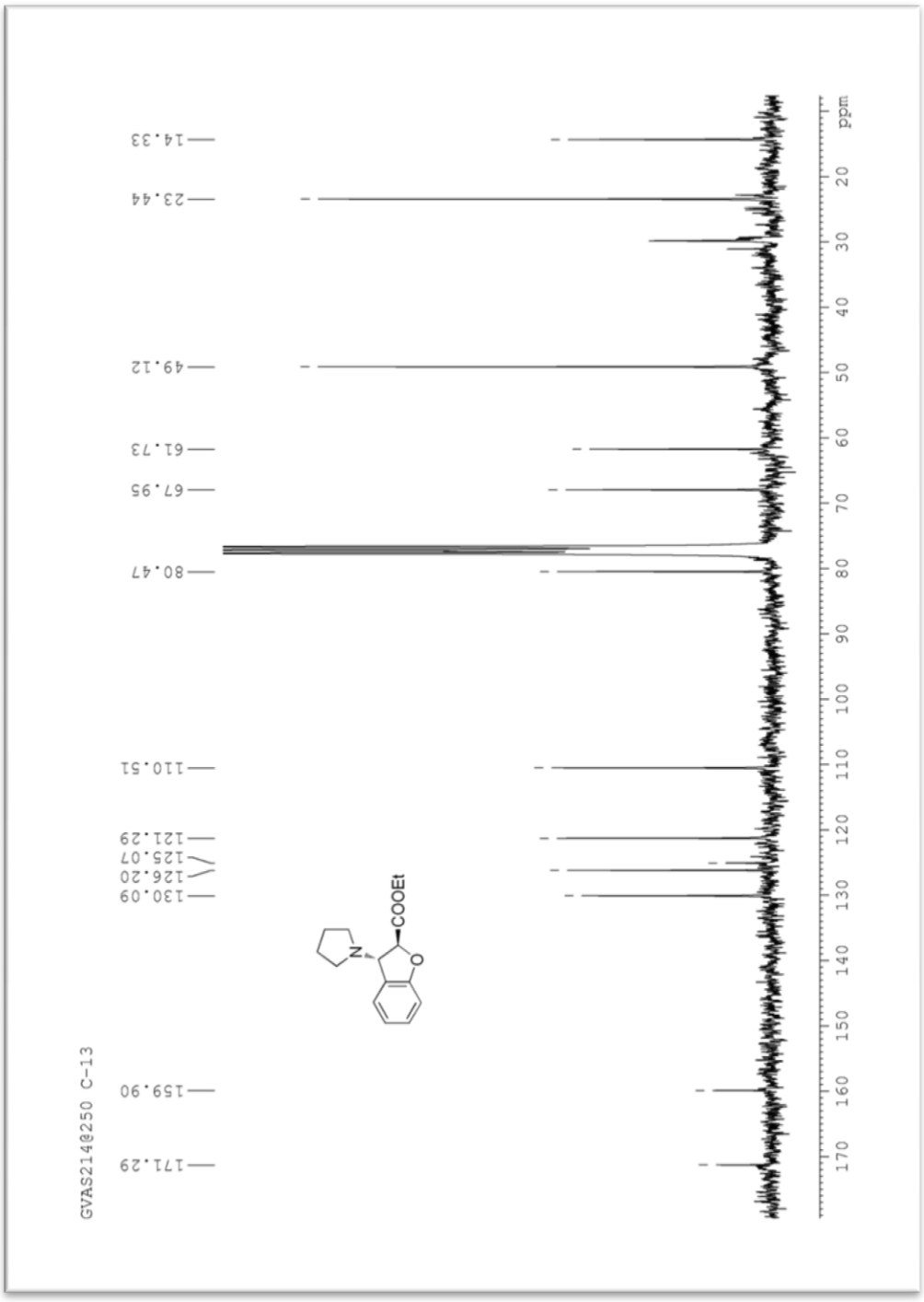

GVAS-213-A@250 H-1
OCH3
COOEt
O
ppm

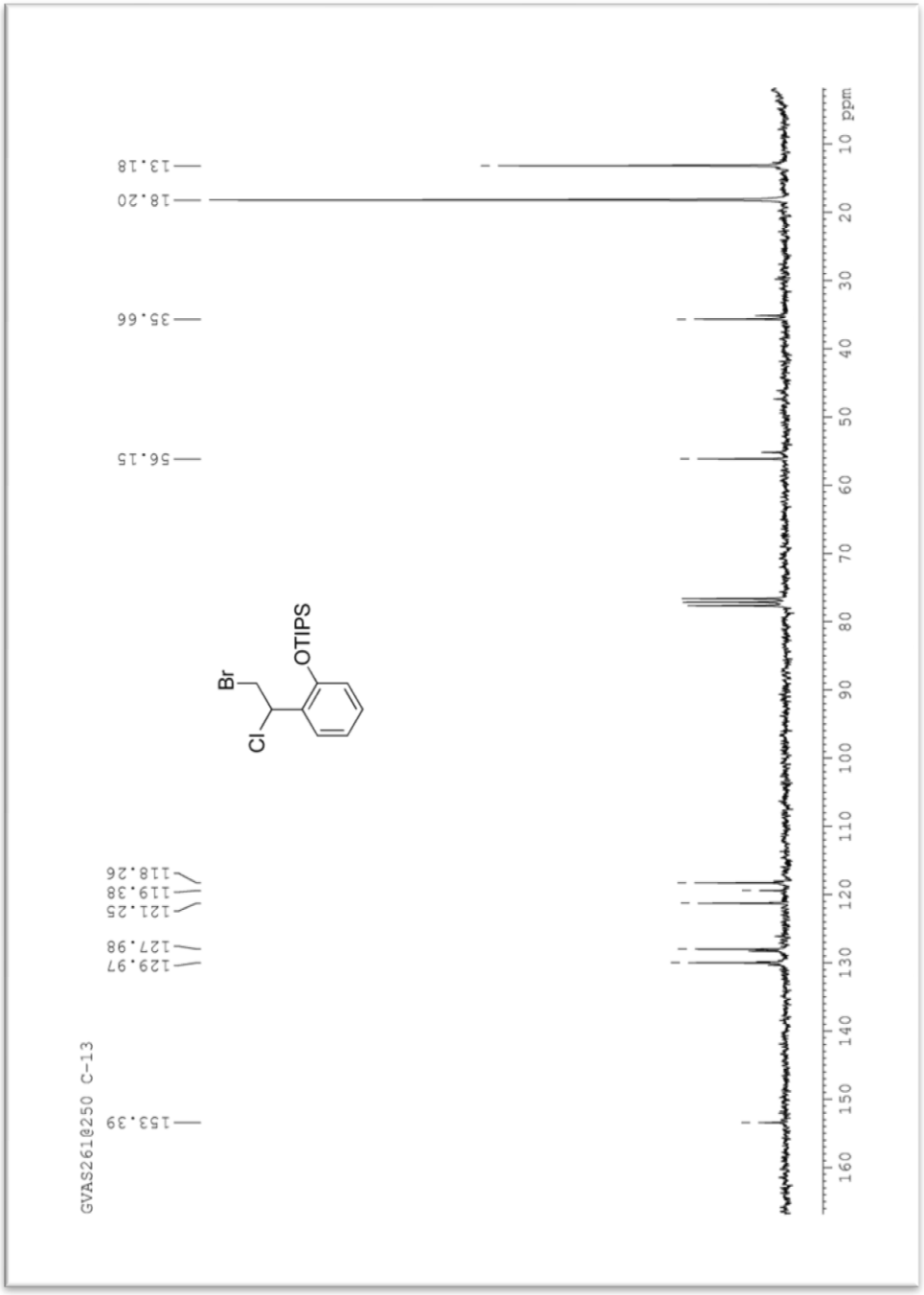

GVAS213-A@250 C-13
14.39
56.77
61.65
80.89
84.16
111.33
121.45
124.80
125.99
131.25
159.82
167.46
OCH3
COOEt
O
ppm

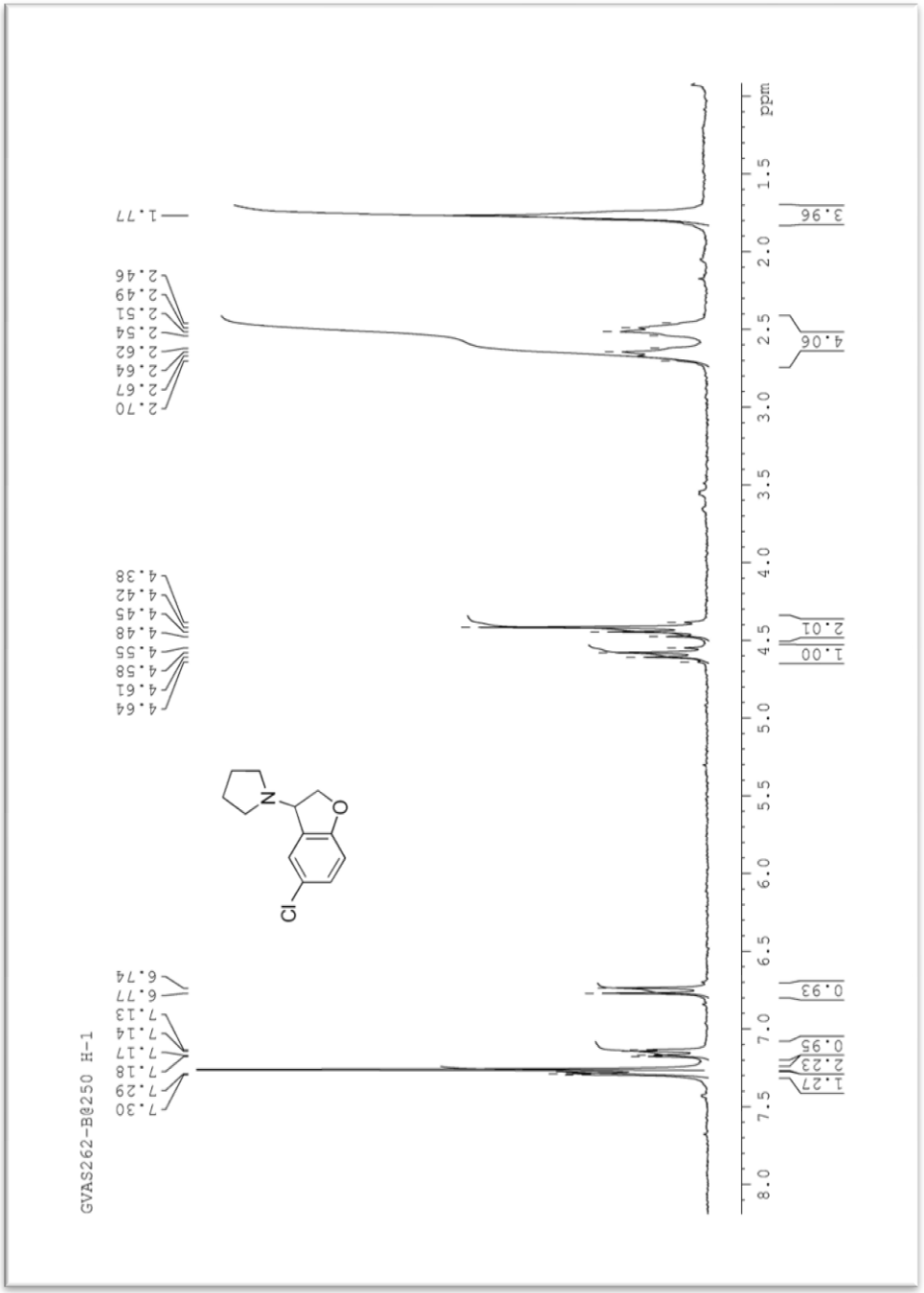

GVAS-213-B@250 H-1
OCH3
COOEt
ppm

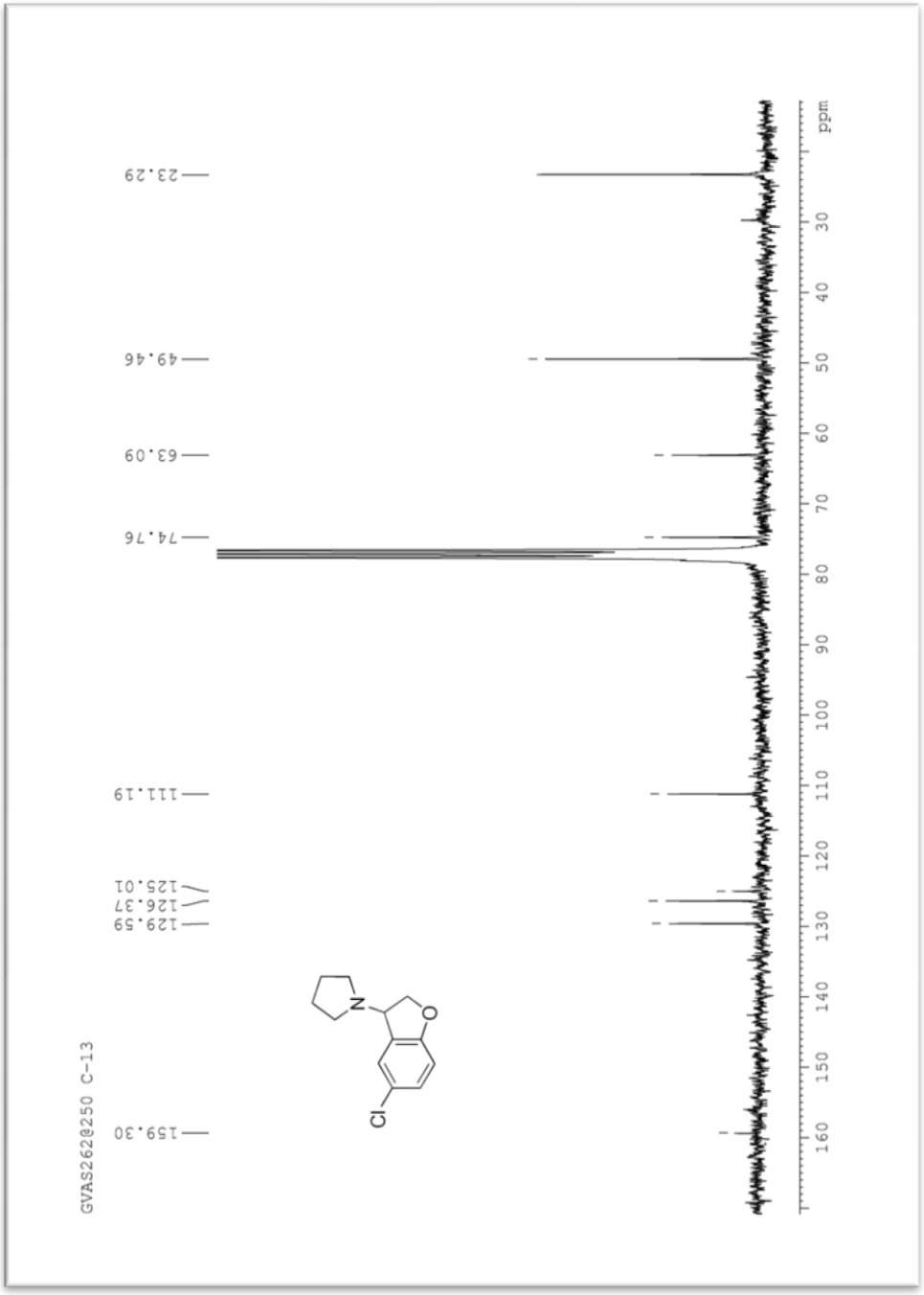

GVAS213-B@250 C-13
168.73
155.67
131.49
130.63
120.16
119.89
117.49
85.35
62.38
58.81
44.91
14.10
OCH3
COOEt
ppm

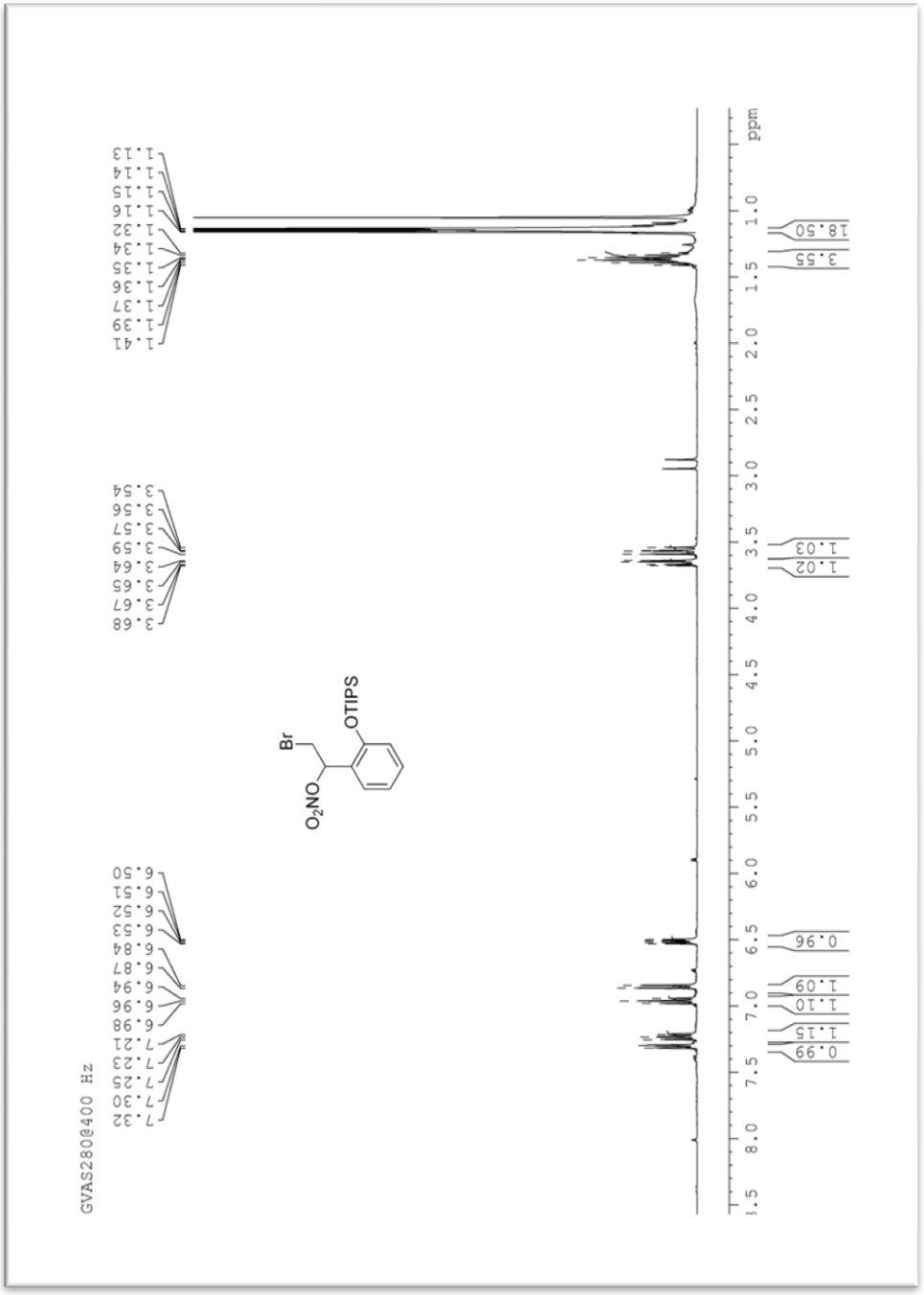

GVAS2140400 298K in CDCl3
COOEt
N
O
ppm

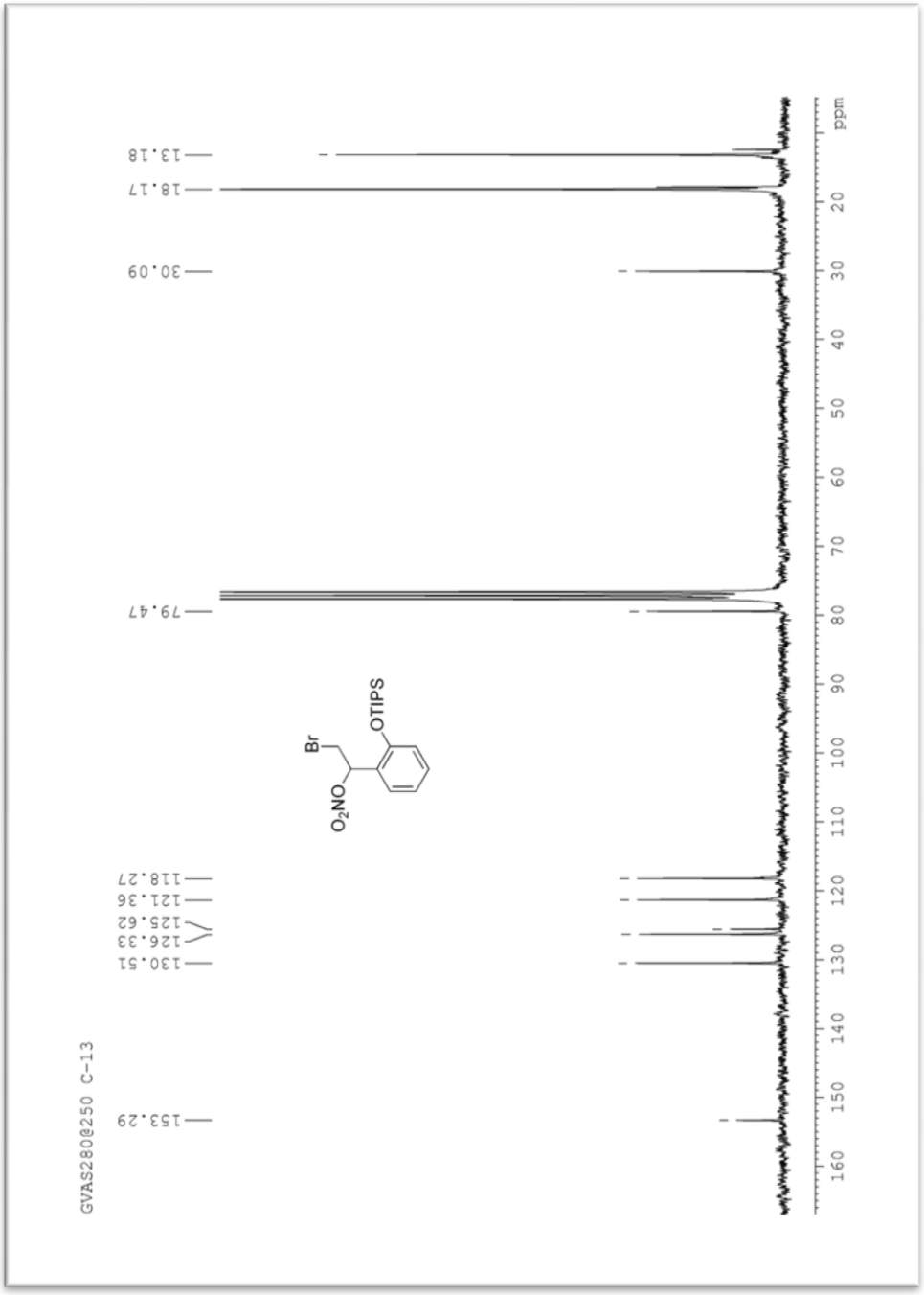

GVAS2140250 C-13
14.33
23.44
49.12
61.73
67.95
80.47
110.51
121.29
125.07
126.20
130.09
159.90
171.29
COOEt
ppm

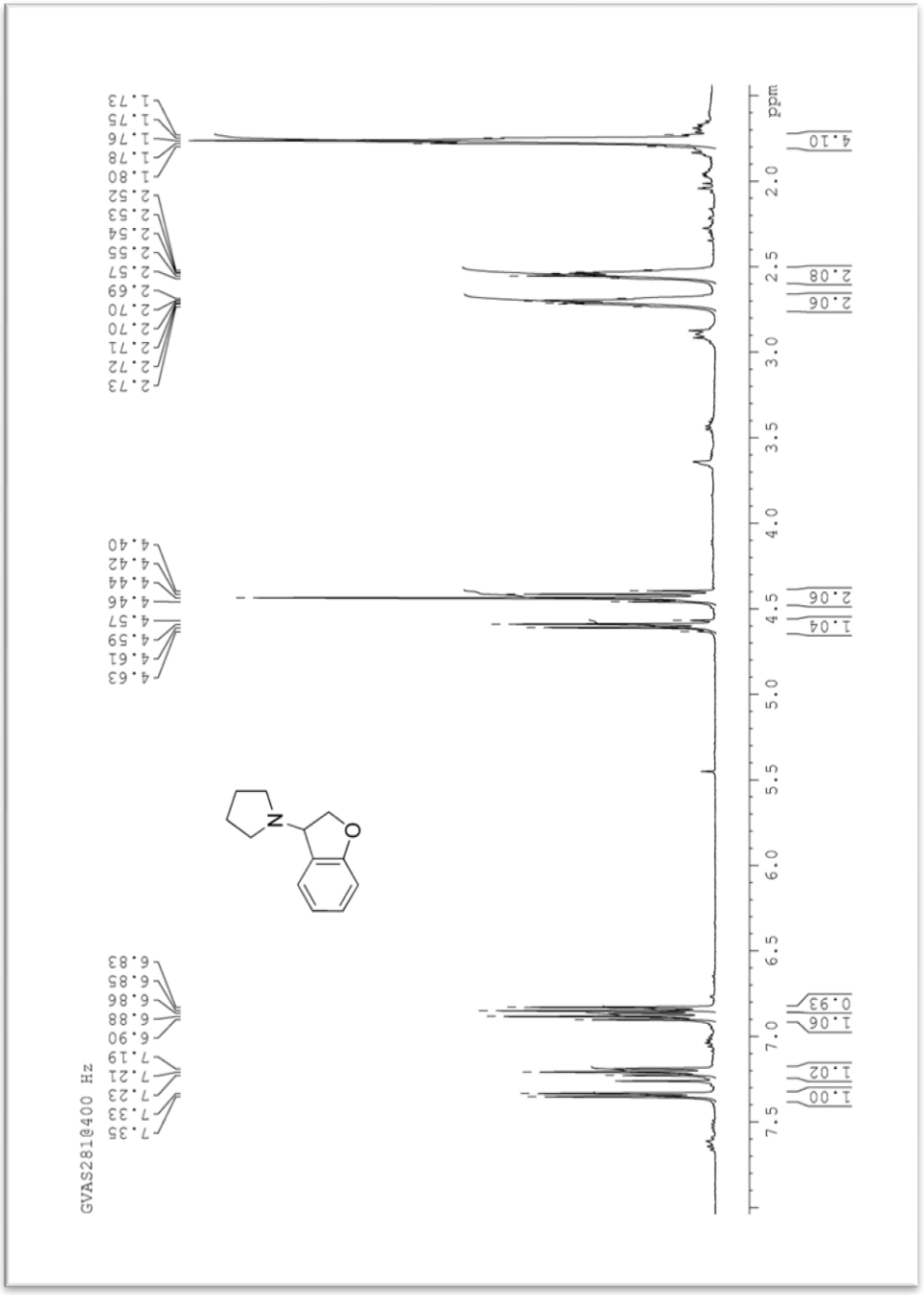

GVAS2610250 C-13
153.39
129.97
127.98
121.25
119.38
118.26
56.15
35.66
18.20
13.18
Br
Cl
OTIPS
ppm

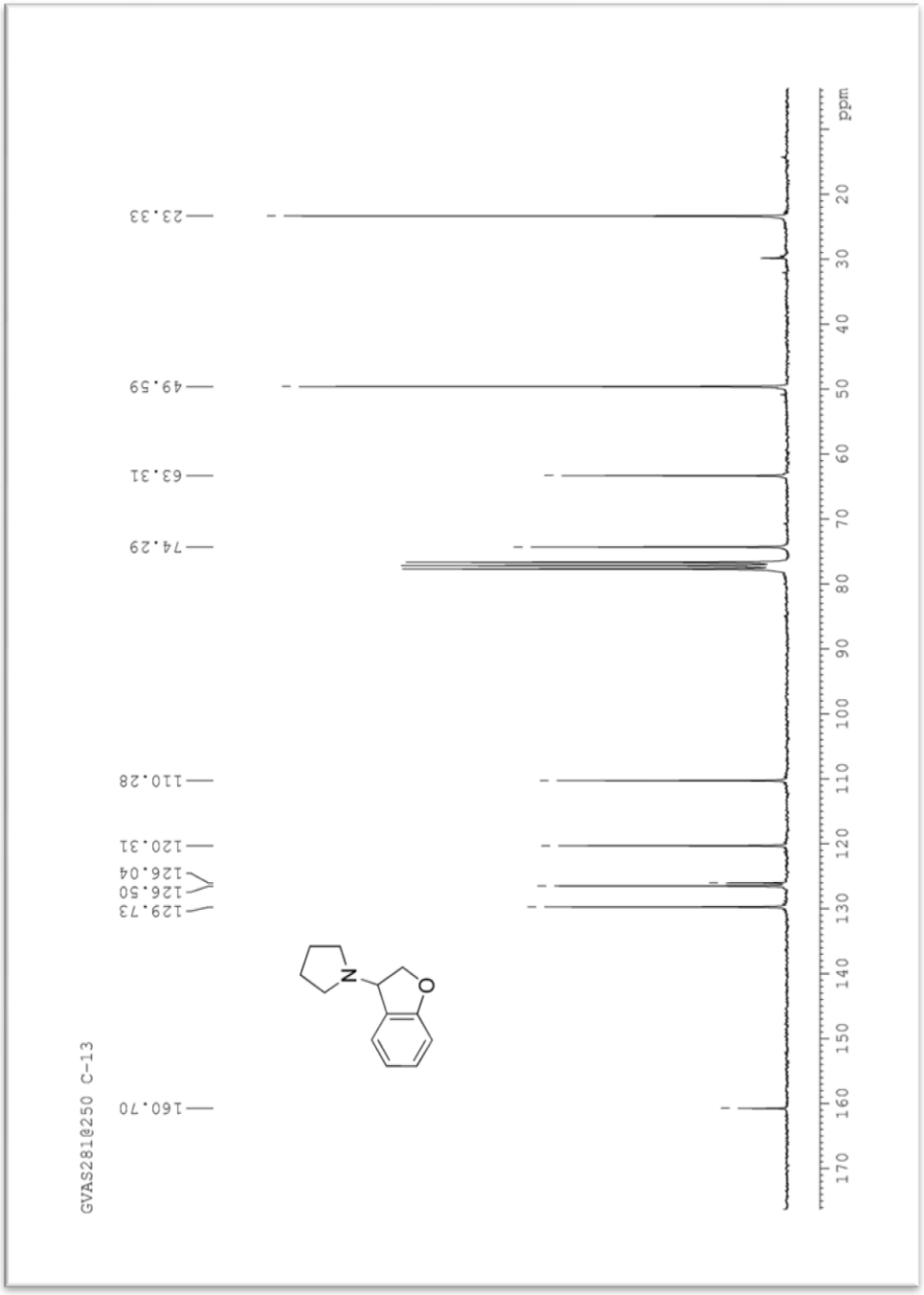

GVAS262-B@250 H-1
7.30
7.29
7.18
7.17
7.14
7.13
6.77
6.74
4.64
4.61
4.58
4.55
4.48
4.45
4.42
4.38
2.70
2.67
2.64
2.62
2.54
2.51
2.49
2.46
1.77
Cl
N
O
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.27
2.23
0.95
0.93
1.00
2.01
4.06
3.96

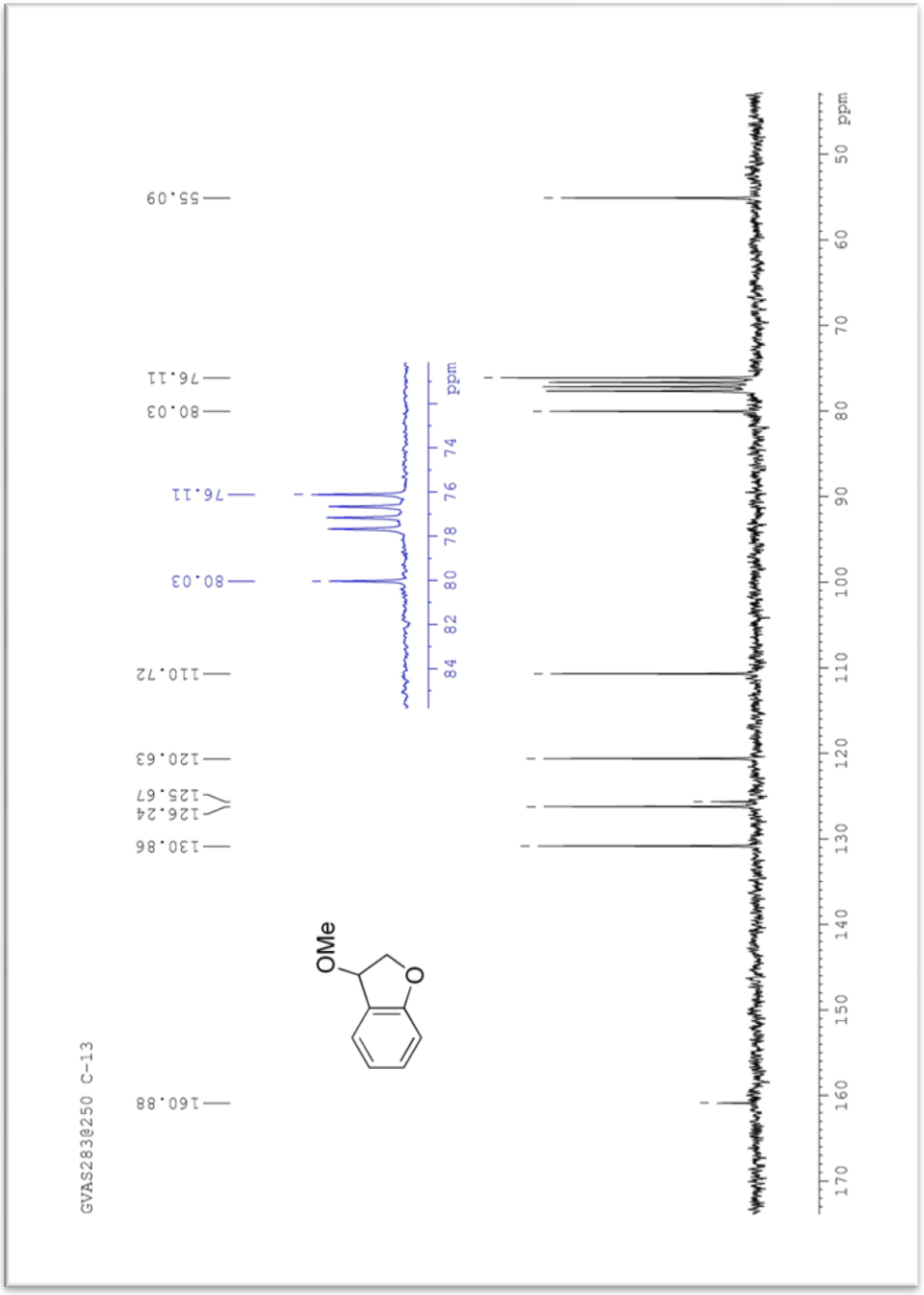

GVAS262@250 C-13
159.30
129.59
126.37
125.01
111.19
74.76
63.09
49.46
23.29
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
N
O
Cl

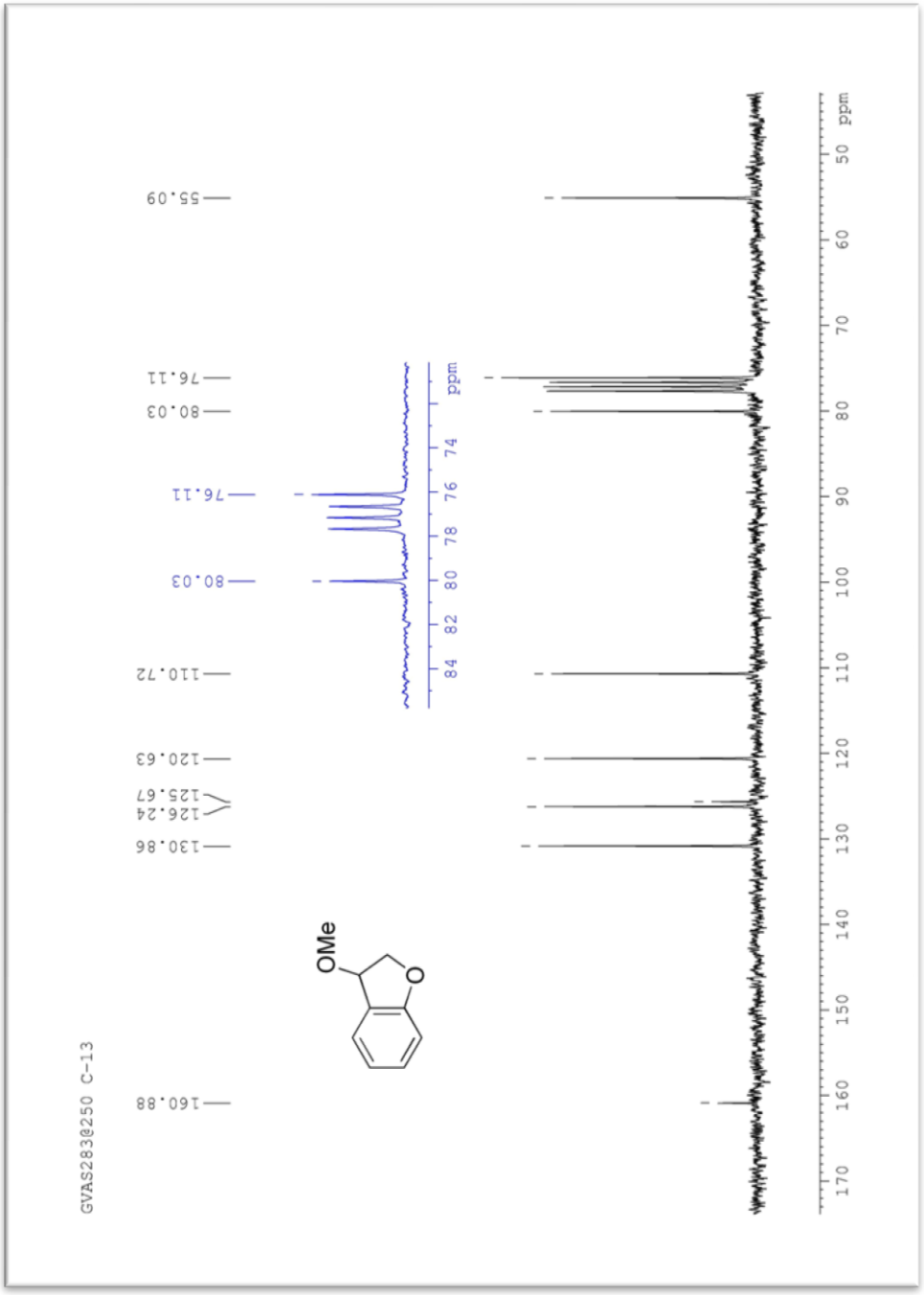

GVAS280@400 Hz
7.32
7.30
7.25
7.23
7.21
6.98
6.96
6.94
6.87
6.84
6.53
6.52
6.51
6.50
3.68
3.67
3.65
3.64
3.59
3.57
3.56
3.54
1.41
1.39
1.37
1.36
1.35
1.34
1.32
1.16
1.15
1.14
1.13
Br
OTIPS
O2NO
0.99
1.15
1.10
1.09
0.96
1.02
1.03
3.55
18.50
ppm

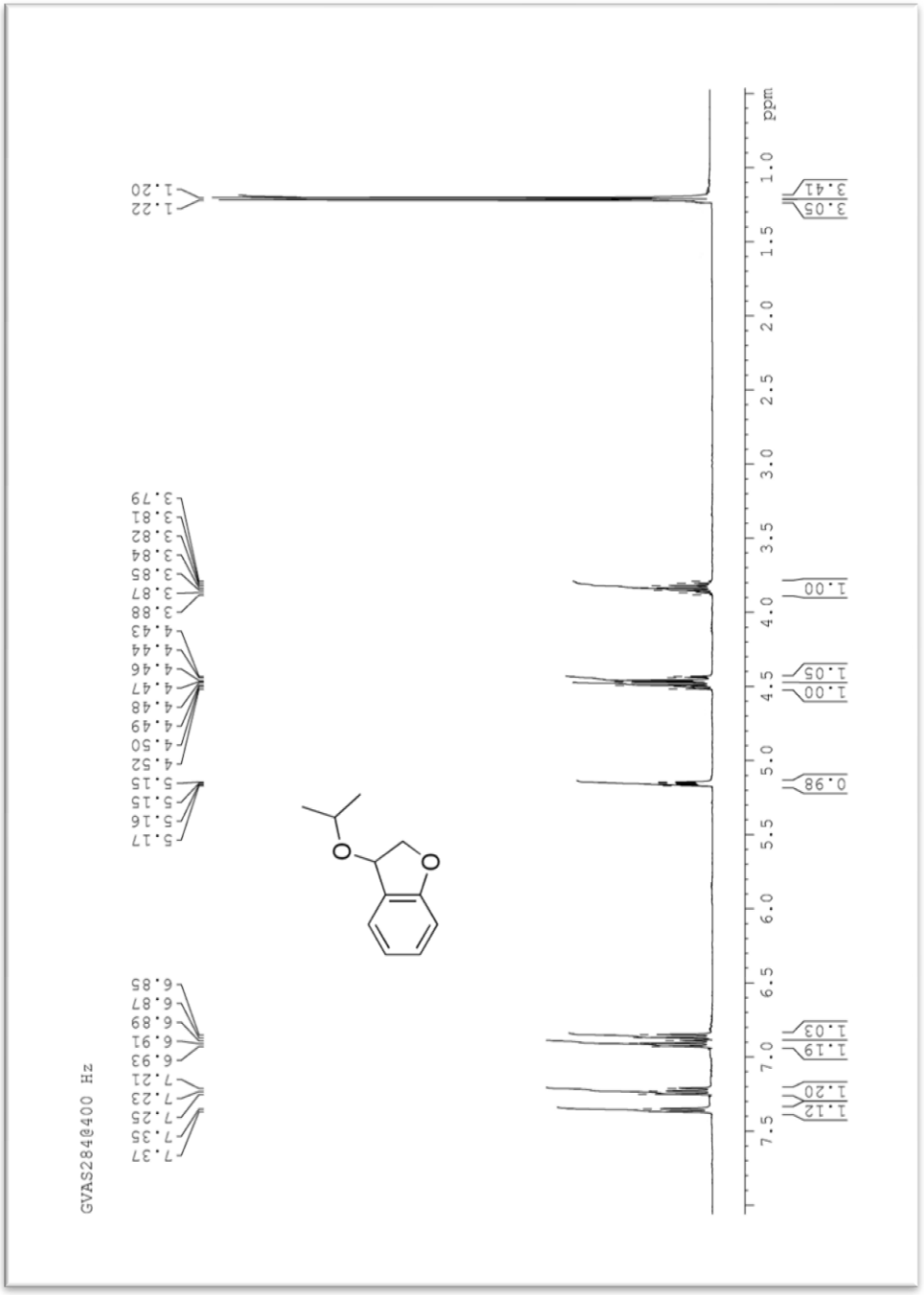

GVAS280@250 C-13
153.29
130.51
126.33
125.62
121.36
118.27
79.47
30.09
18.17
13.18
ppm
Br
OTIPS
O2NO

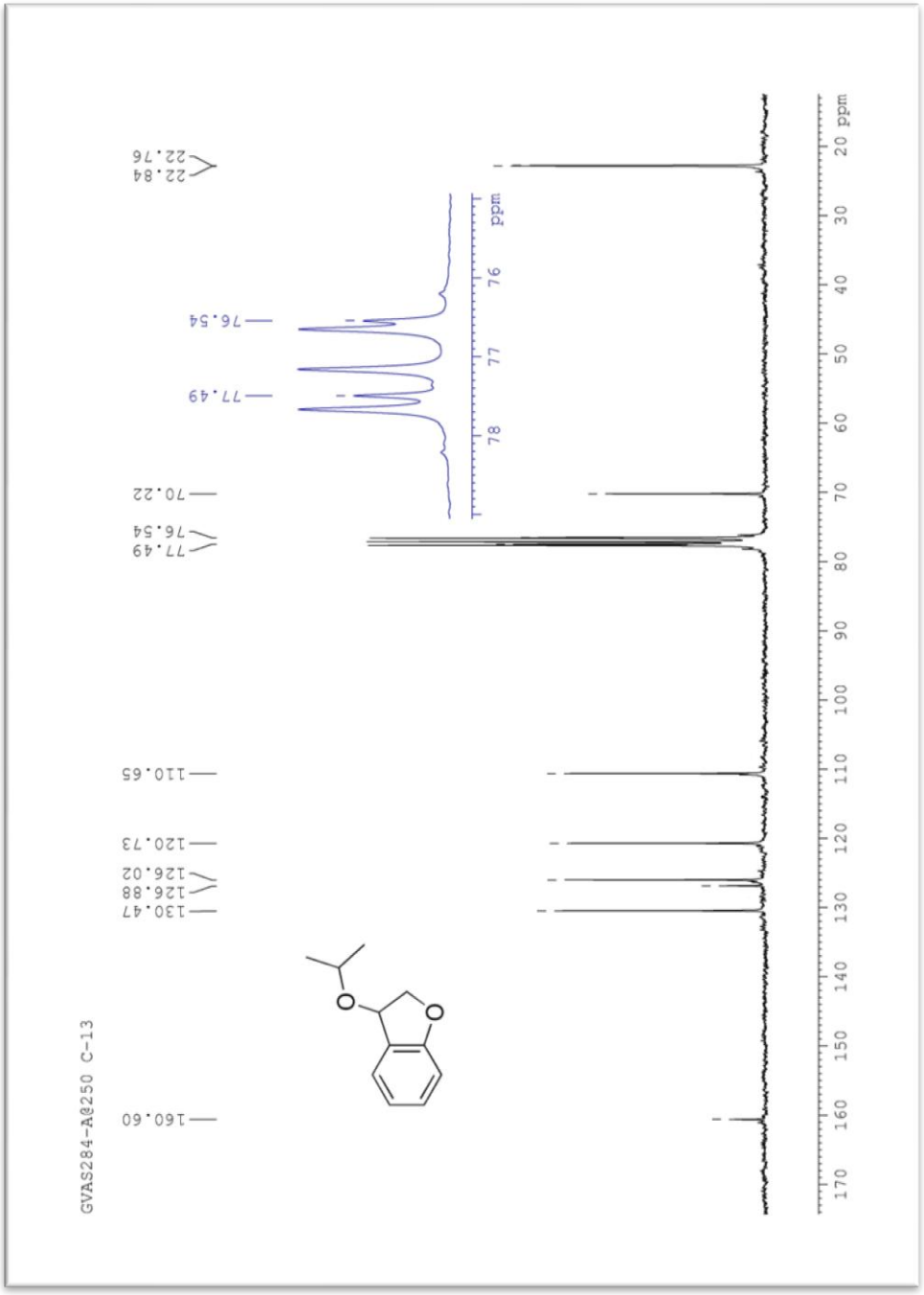

GVAS281@400 Hz
7.35
7.33
7.23
7.21
7.19
6.90
6.88
6.86
6.85
6.83
4.63
4.61
4.59
4.57
4.46
4.44
4.42
4.40
2.73
2.72
2.71
2.70
2.70
2.69
2.57
2.55
2.54
2.53
2.52
1.80
1.78
1.76
1.75
1.73
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.00
1.02
1.06
0.93
2.06
1.04
2.06
2.08
4.10
N
O

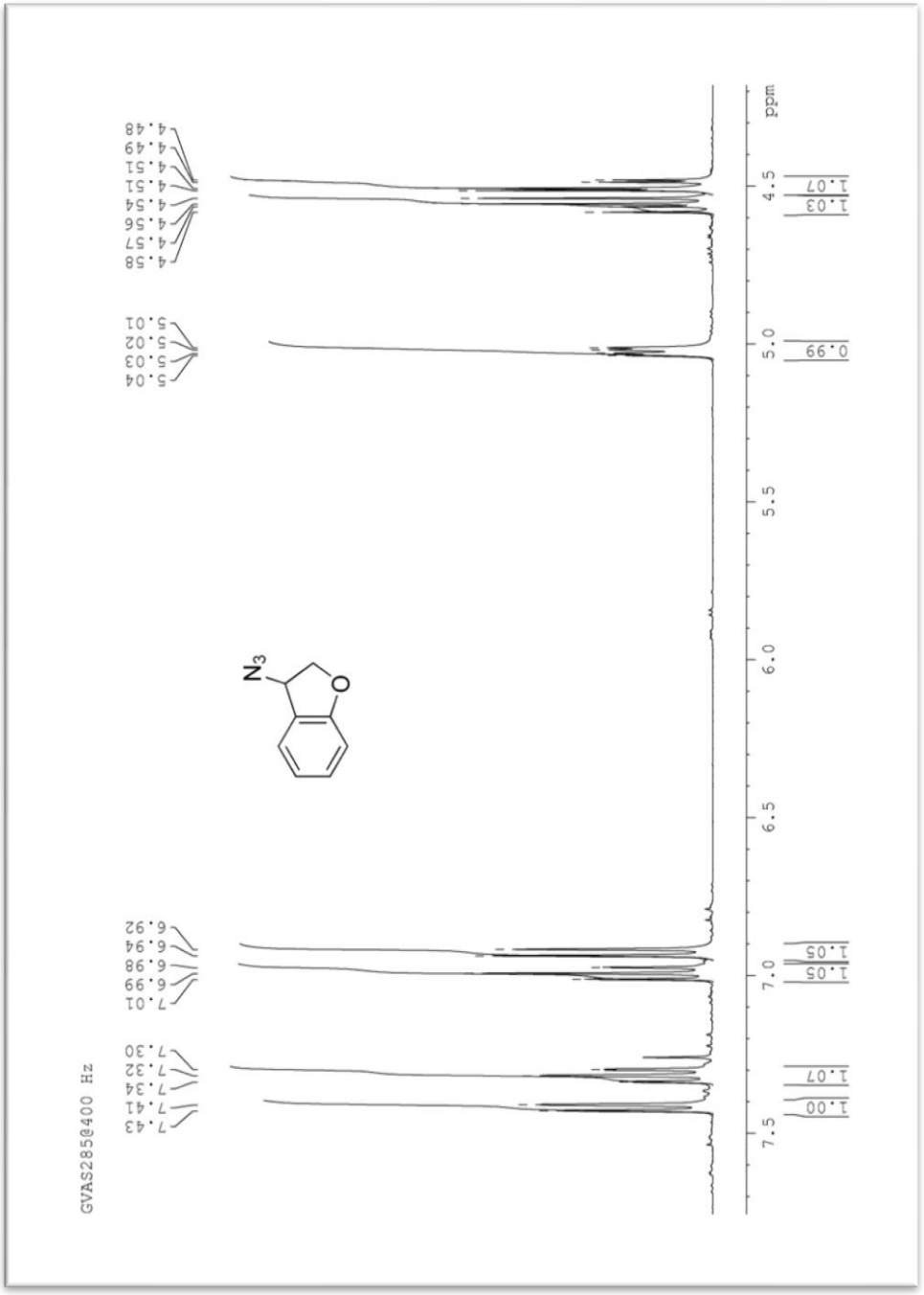

GVAS2810250 C-13
160.70
129.73
126.50
126.04
120.31
110.28
74.29
63.31
49.59
23.33
ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
N
O

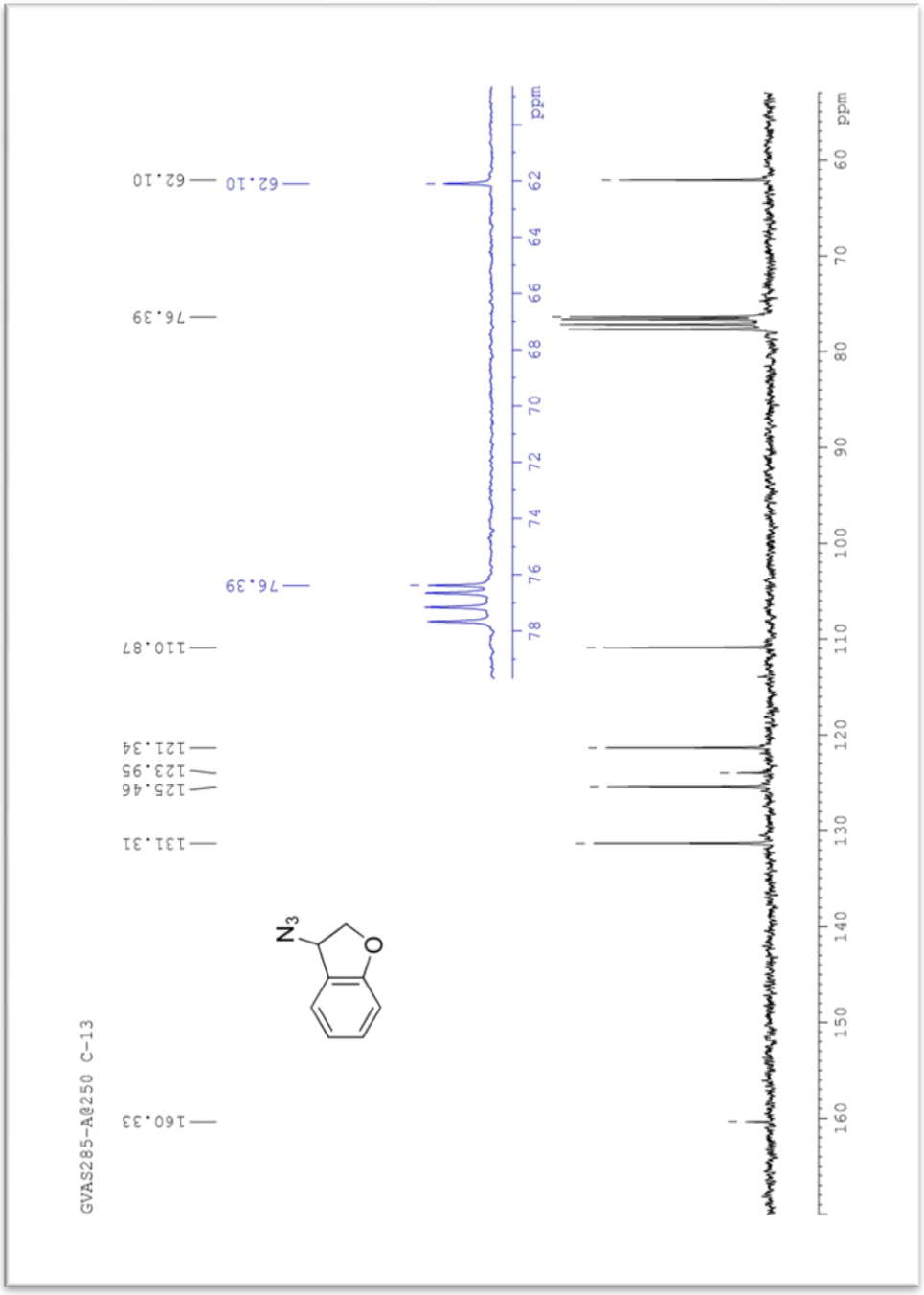

GVAS283@250 C-13
160.88
130.86
126.24
125.67
120.63
110.72
80.03
76.11
55.09
OMe
O
ppm

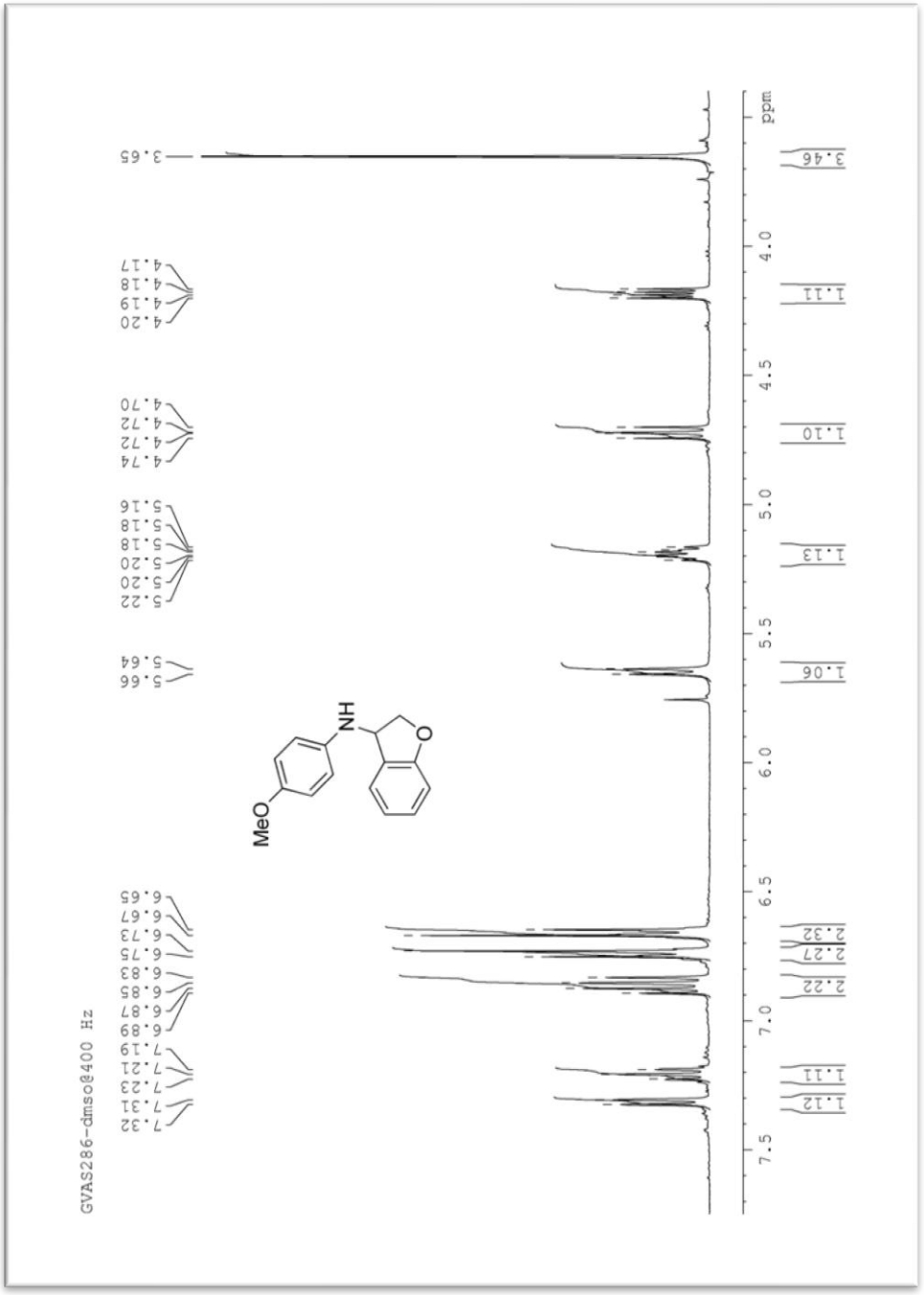

GVAS2830250 C-13
160.88
130.86
126.24
125.67
120.63
110.72
80.03
76.11
80.03
76.11
55.09
OMe
O
ppm

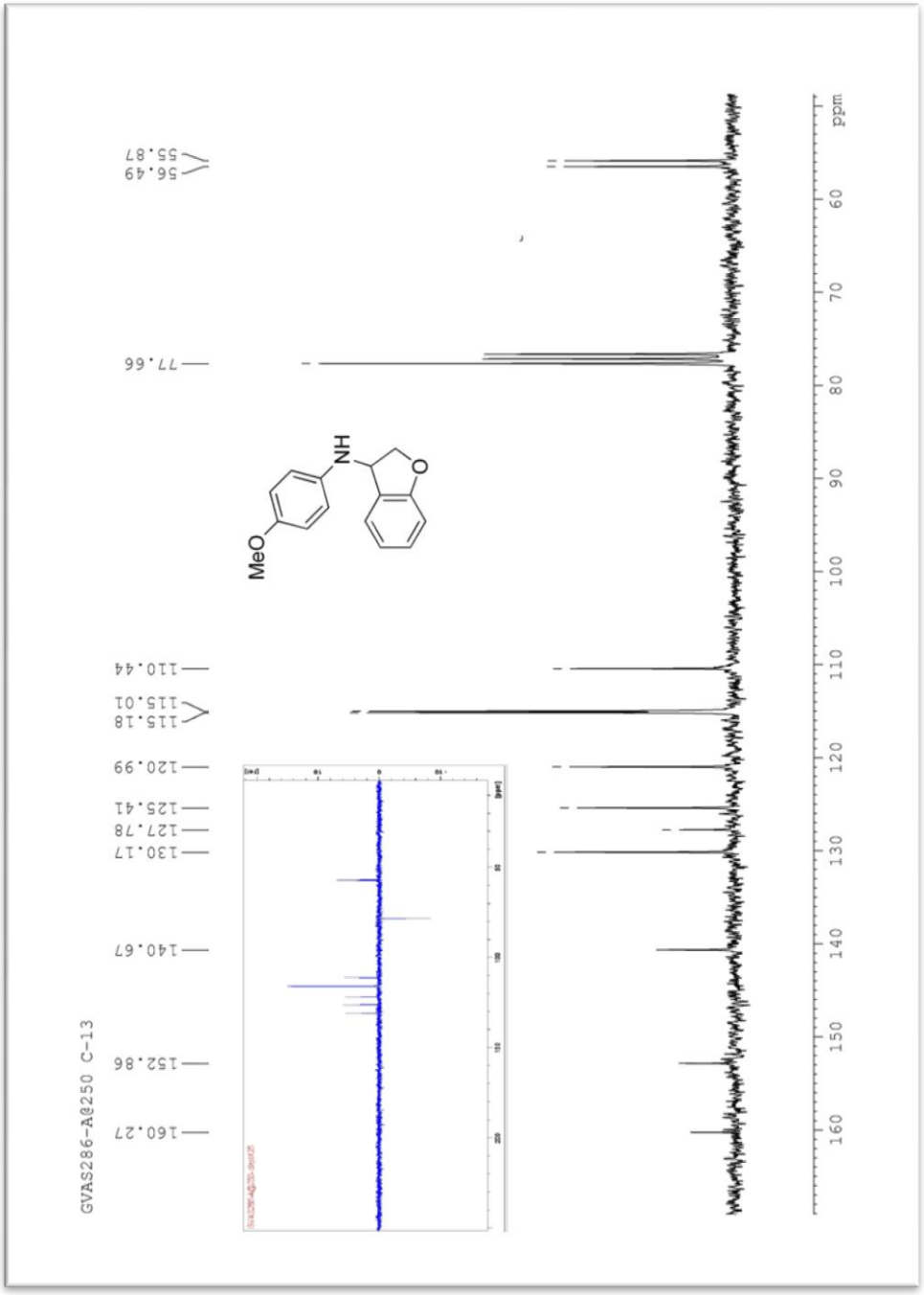

GVAS284@400 Hz
7.37
7.35
7.25
7.23
7.21
6.93
6.91
6.89
6.87
6.85
5.17
5.16
5.15
5.15
4.52
4.50
4.49
4.48
4.47
4.46
4.44
4.43
3.88
3.87
3.85
3.84
3.82
3.81
3.79
1.22
1.20
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.12
1.20
1.19
1.03
0.98
1.00
1.05
1.00
3.05
3.41

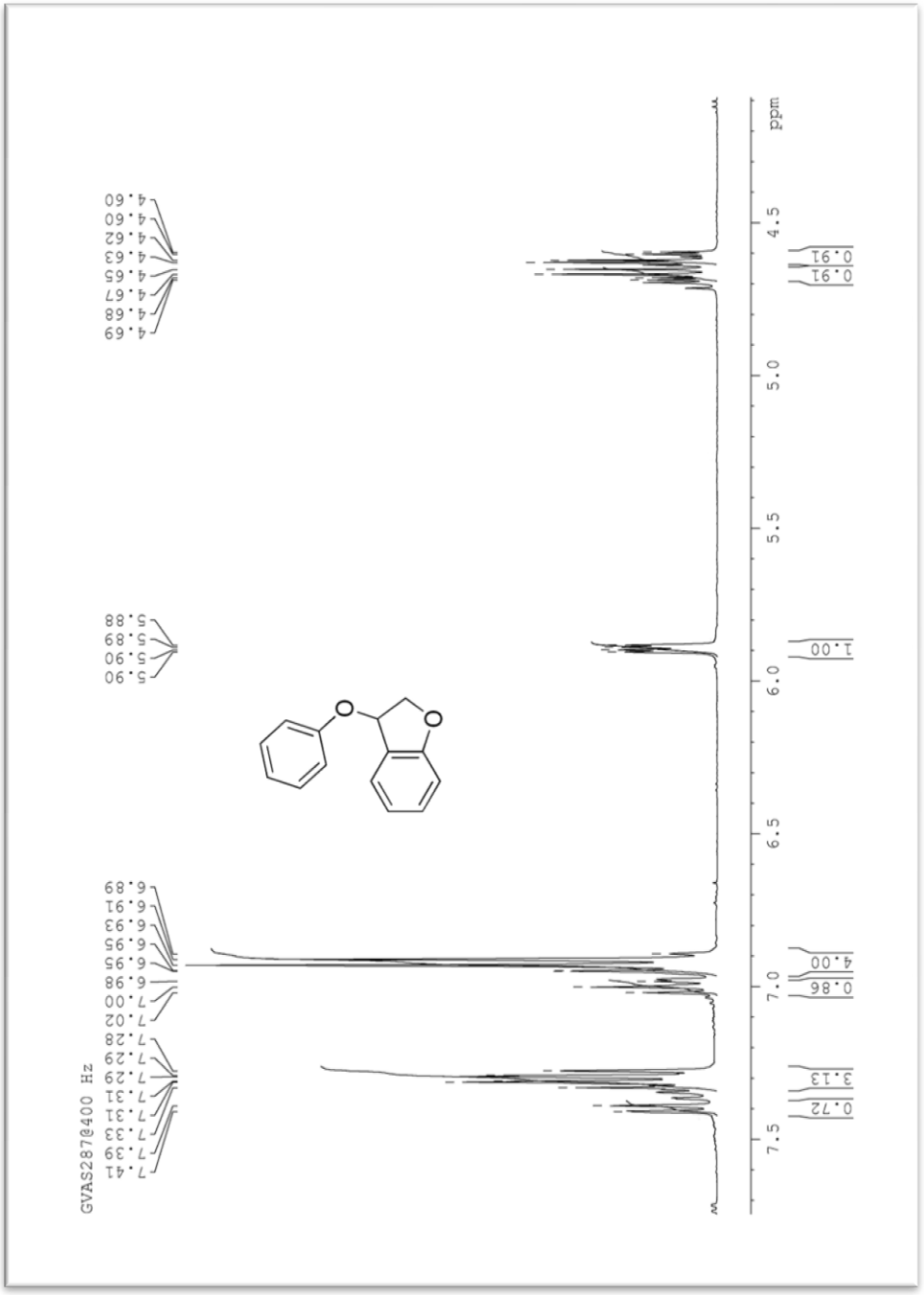

GVAS284-A@250 C-13
160.60
130.47
126.88
126.02
120.73
110.65
77.49
76.54
70.22
77.49
76.54
22.84
22.76
ppm
20 ppm

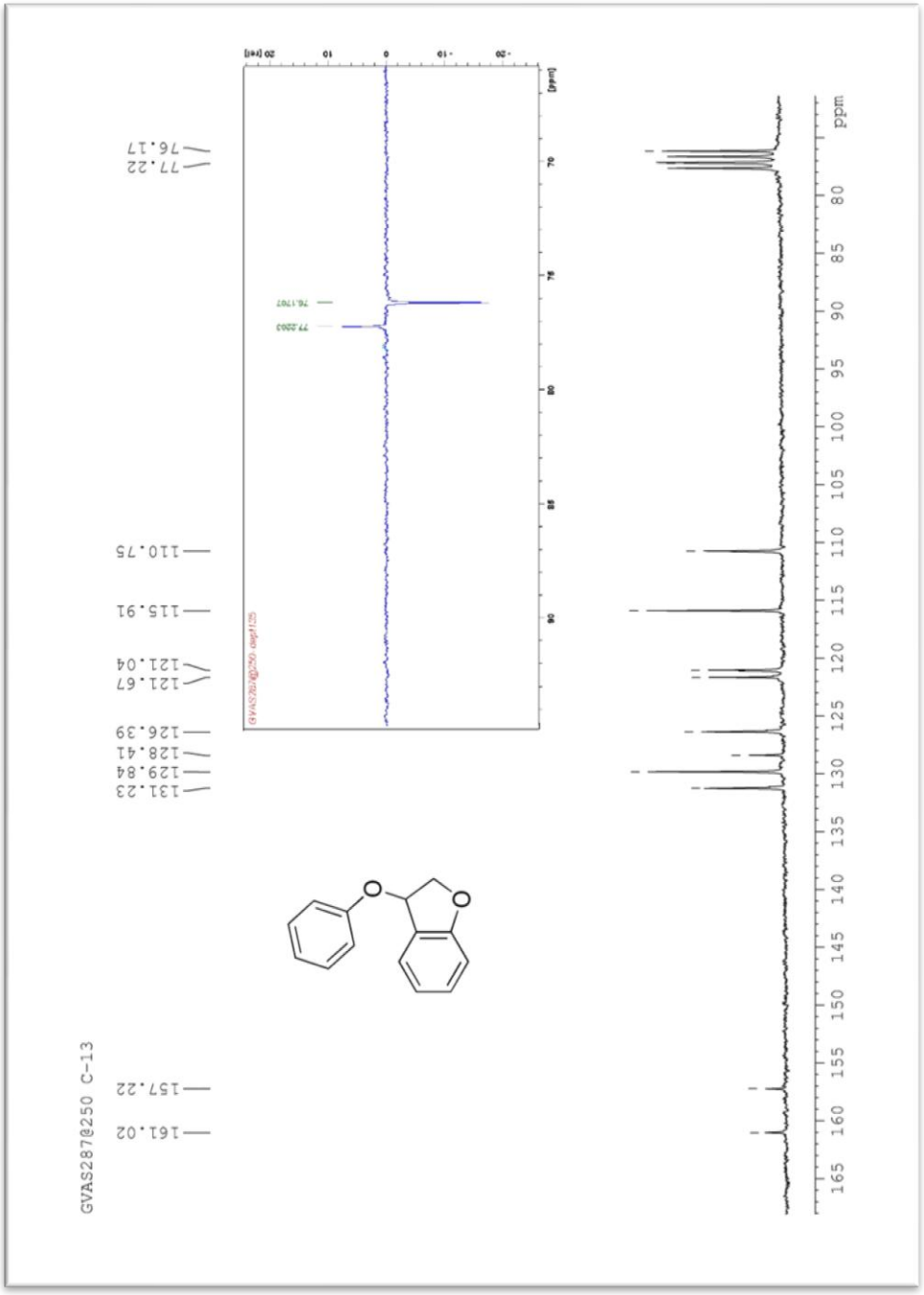

GVAS285@400 Hz
7.43
7.41
7.34
7.32
7.30
7.01
6.99
6.98
6.94
6.92
5.04
5.03
5.02
5.01
4.58
4.57
4.56
4.54
4.51
4.51
4.49
4.48
N3
O
ppm
1.00
1.07
1.05
1.05
0.99
1.03
1.07

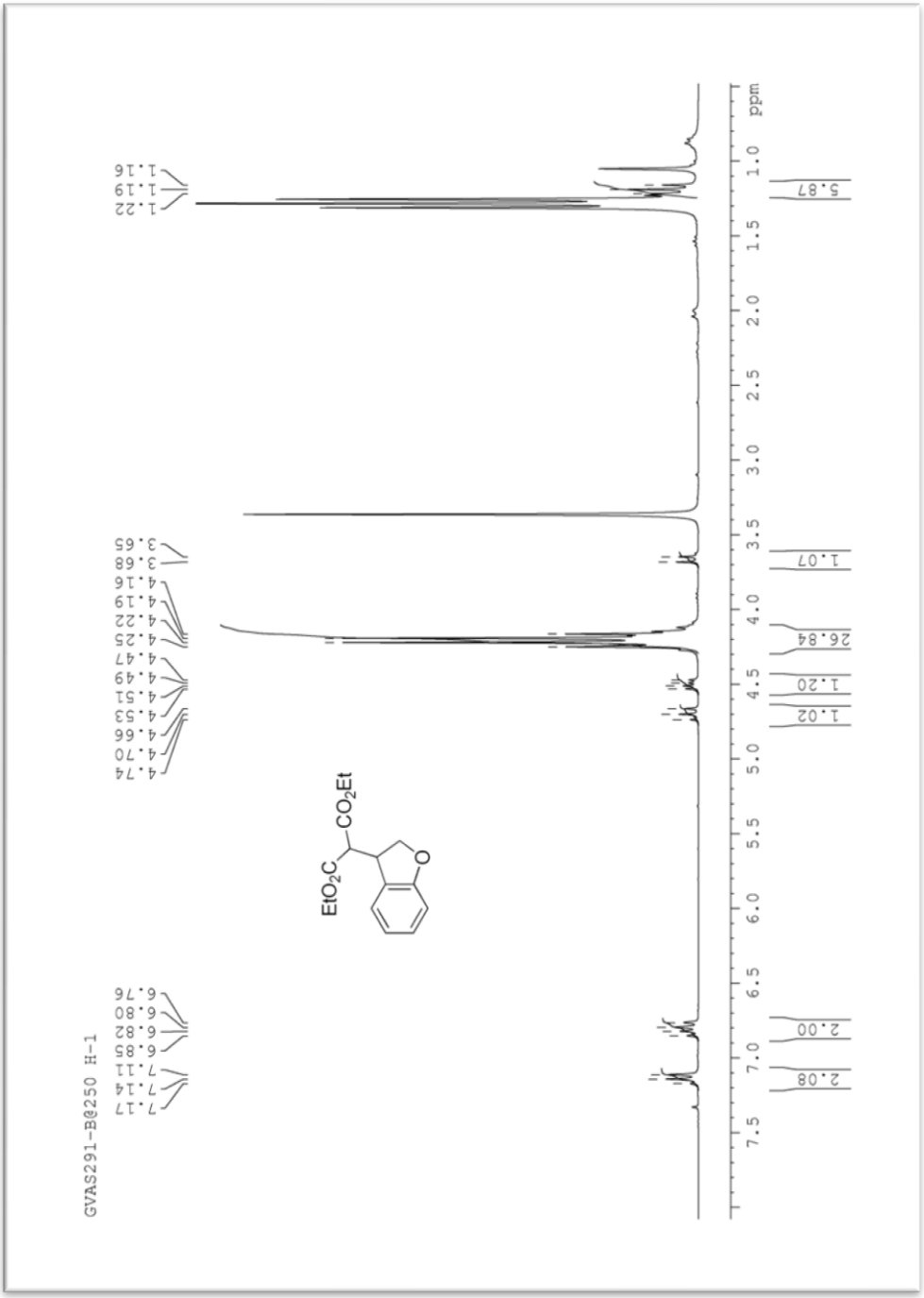

GVAS285-A@250 C-13
160.33
131.31
125.46
123.95
121.34
110.87
76.39
62.10
62.10
76.39
ppm
ppm

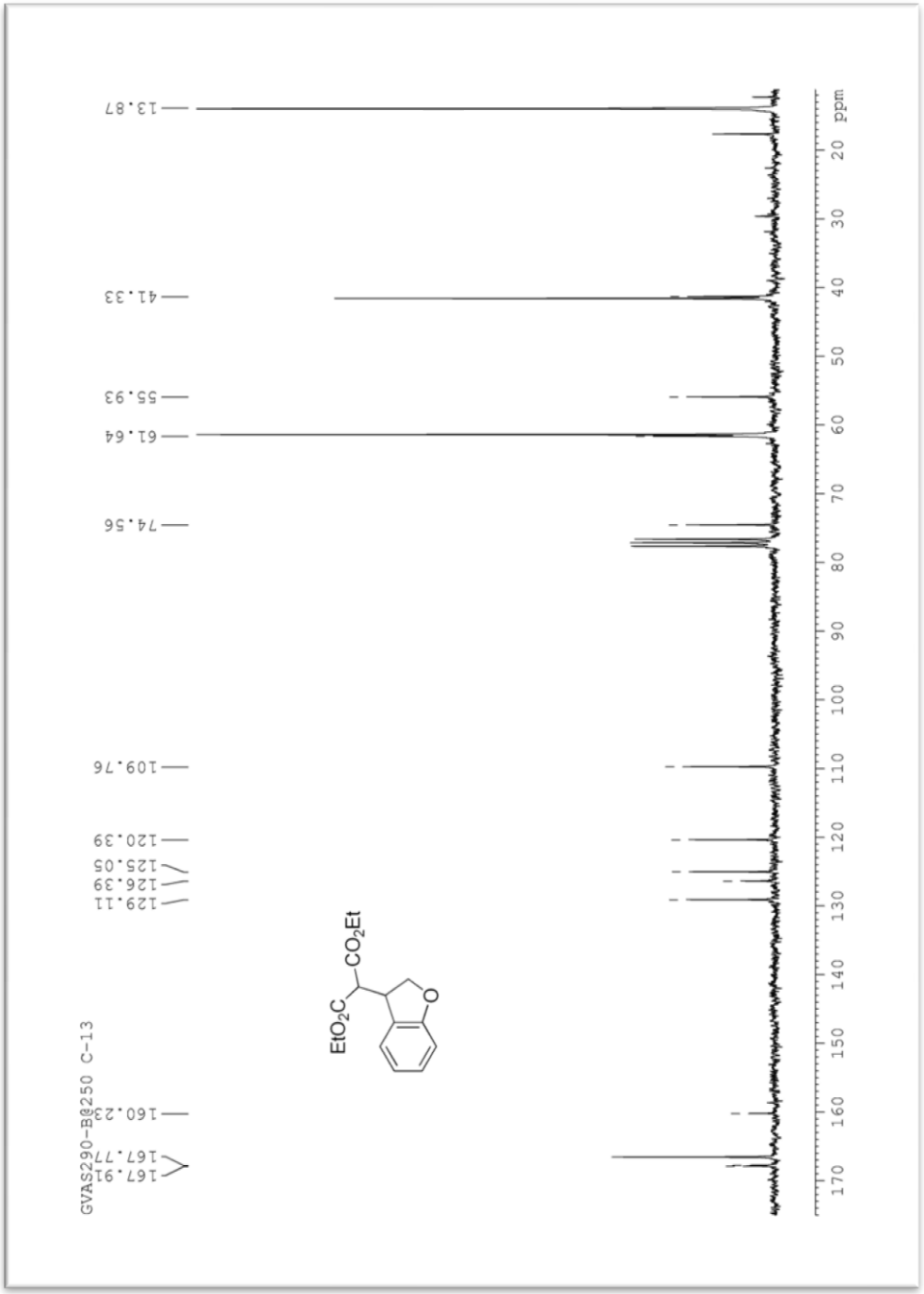

GVAS286-dmso@400 Hz
7.32
7.31
7.23
7.21
7.19
6.89
6.87
6.85
6.83
6.75
6.73
6.67
6.65
5.66
5.64
5.22
5.20
5.20
5.18
5.18
5.16
4.74
4.72
4.72
4.70
4.20
4.19
4.18
4.17
3.65
MeO
NH
O
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
1.12
1.11
2.22
2.27
2.32
1.06
1.13
1.10
1.11
3.46

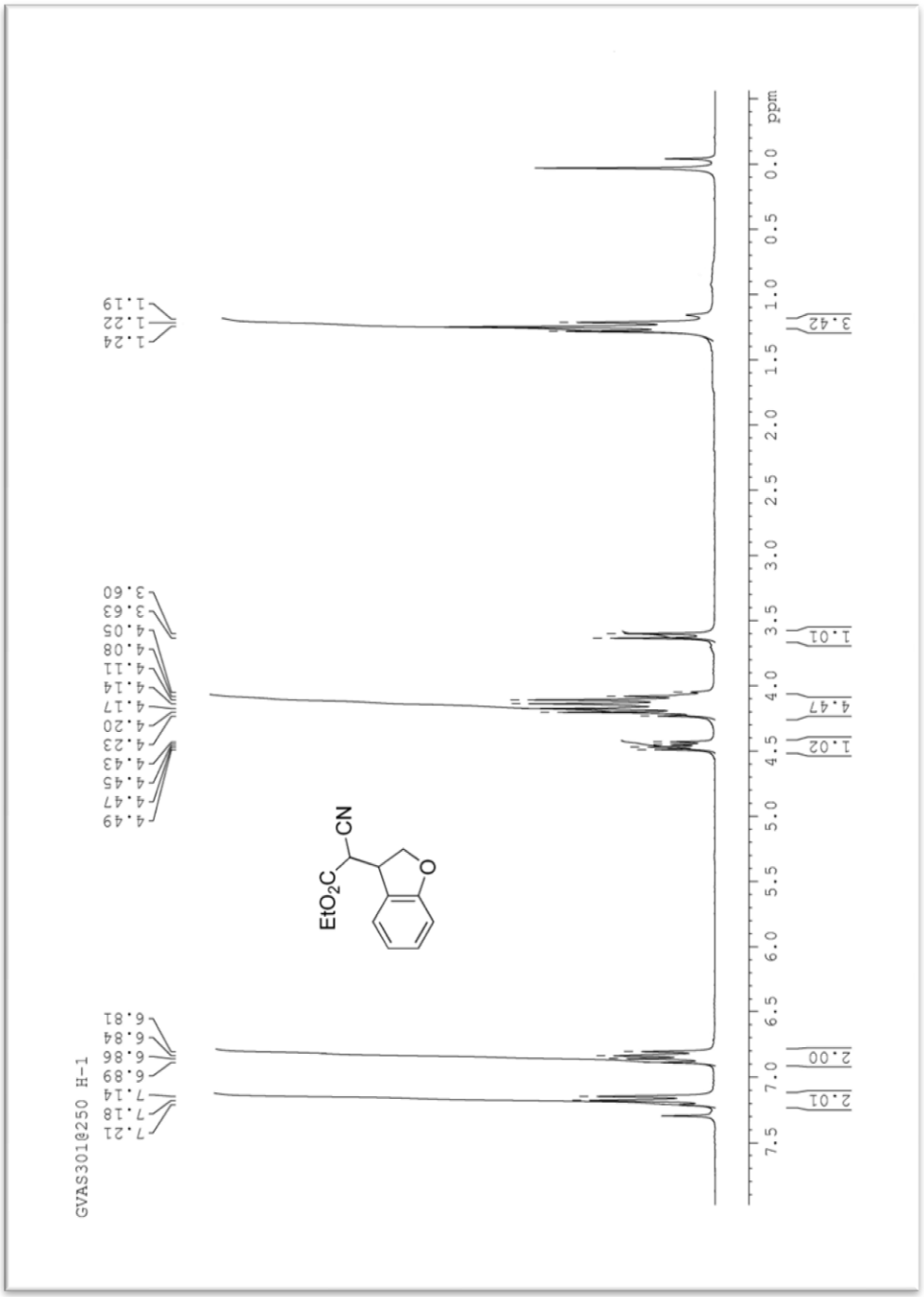

GVAS286-A@250 C-13
160.27
152.86
140.67
130.17
127.78
125.41
120.99
115.18
115.01
110.44
77.66
56.49
55.87
MeO
NH
O
ppm

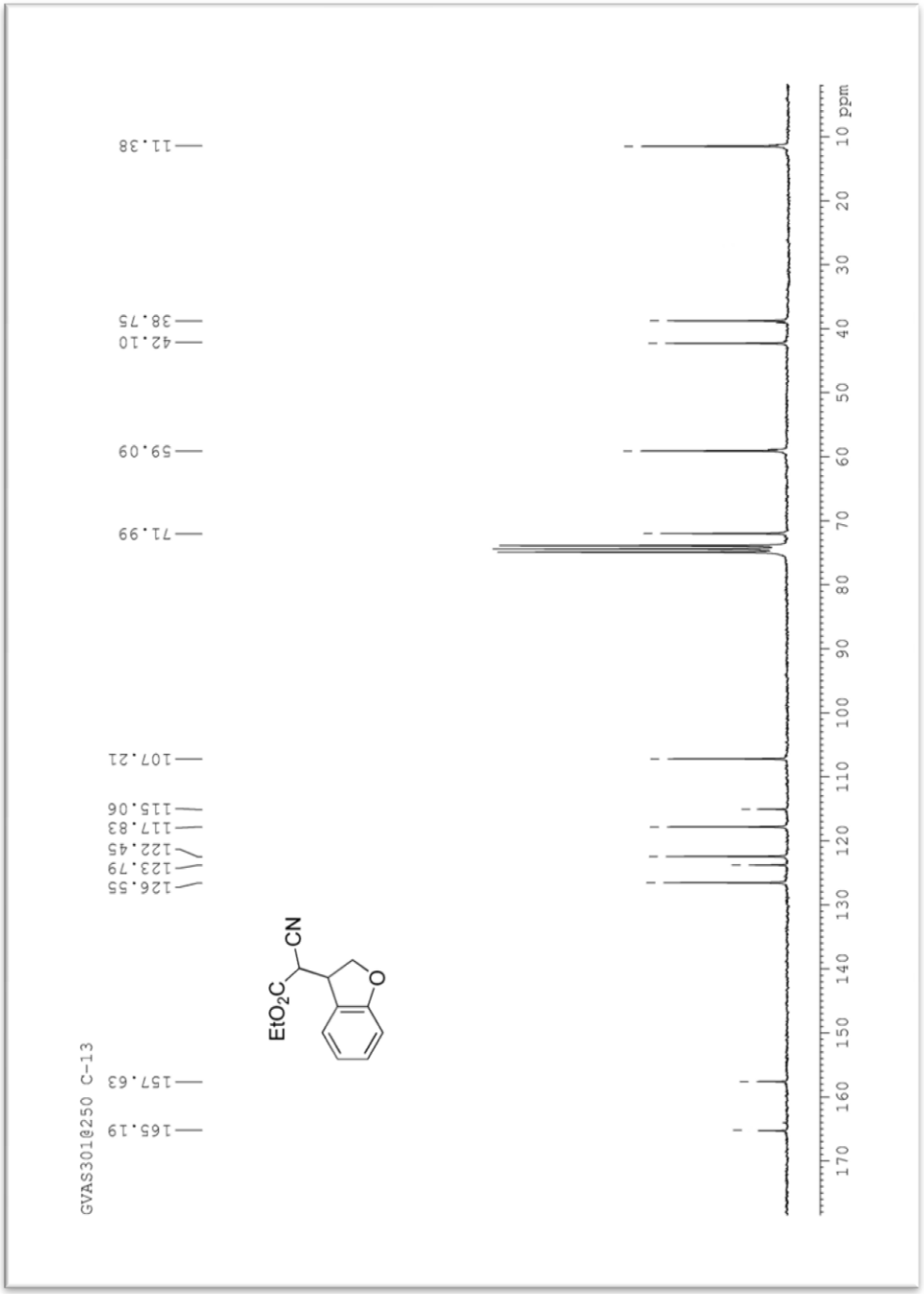

GVAS287@400 Hz
7.41
7.39
7.33
7.31
7.31
7.29
7.29
7.28
7.02
7.00
6.98
6.95
6.95
6.93
6.91
6.89
5.90
5.89
5.90
5.88
4.69
4.68
4.67
4.65
4.63
4.62
4.60
4.60
0.72
3.13
0.86
4.00
1.00
0.91
0.91
7.5
7.0
6.5
6.0
5.5
5.0
4.5
ppm


GVAS2870250 C-13
157.22
161.02
126.39
128.41
129.84
131.23
121.04
121.67
115.91
110.75
76.17
77.22
77.2003
76.1787
ppm

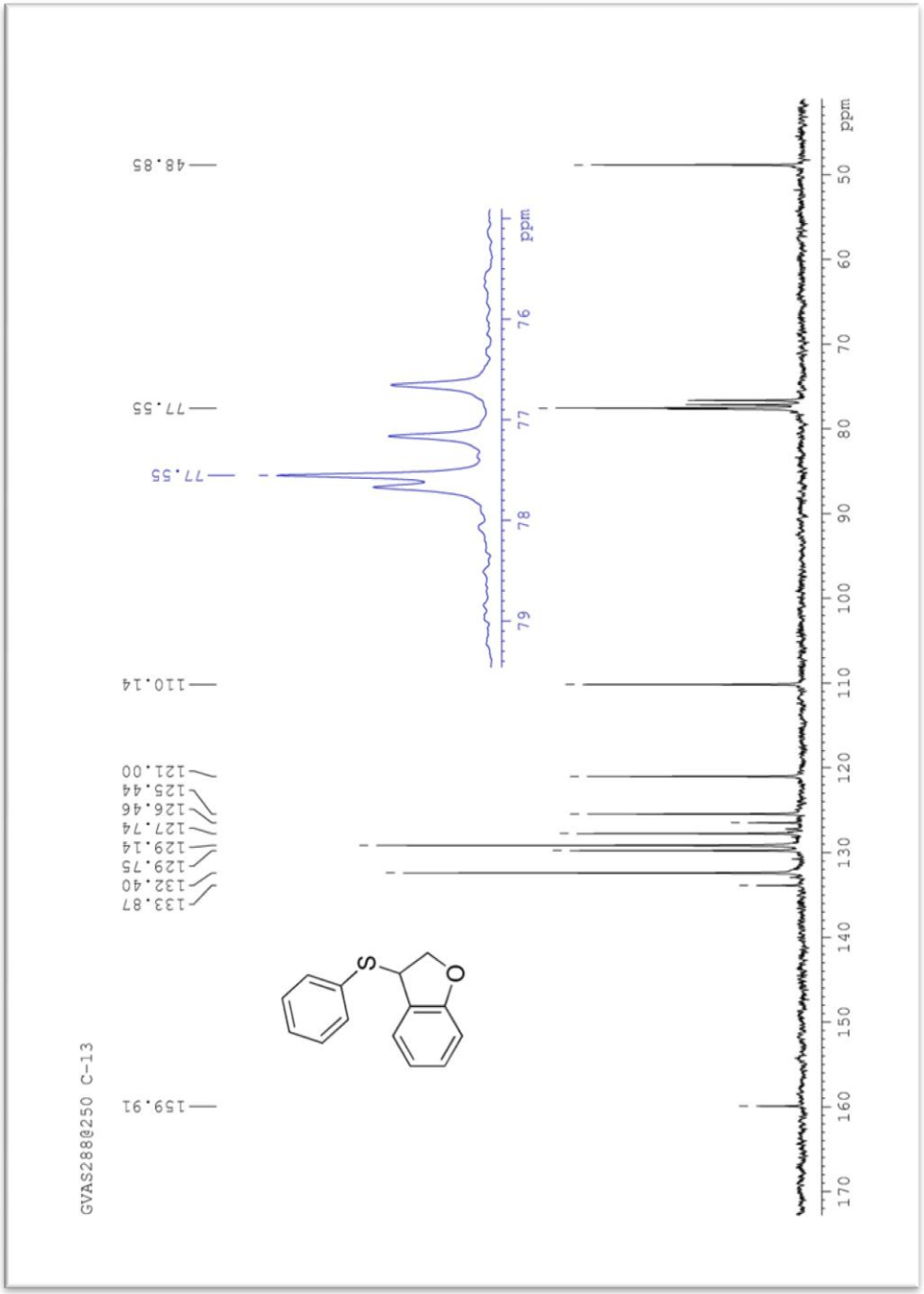

GVAS291-B@250 H-1
7.17
7.14
7.11
6.85
6.82
6.80
6.76
4.74
4.70
4.66
4.53
4.51
4.49
4.47
4.25
4.22
4.19
4.16
3.68
3.65
1.22
1.19
1.16
EtO2C
CO2Et
O
2.08
2.00
1.02
1.20
26.84
1.07
5.87
ppm

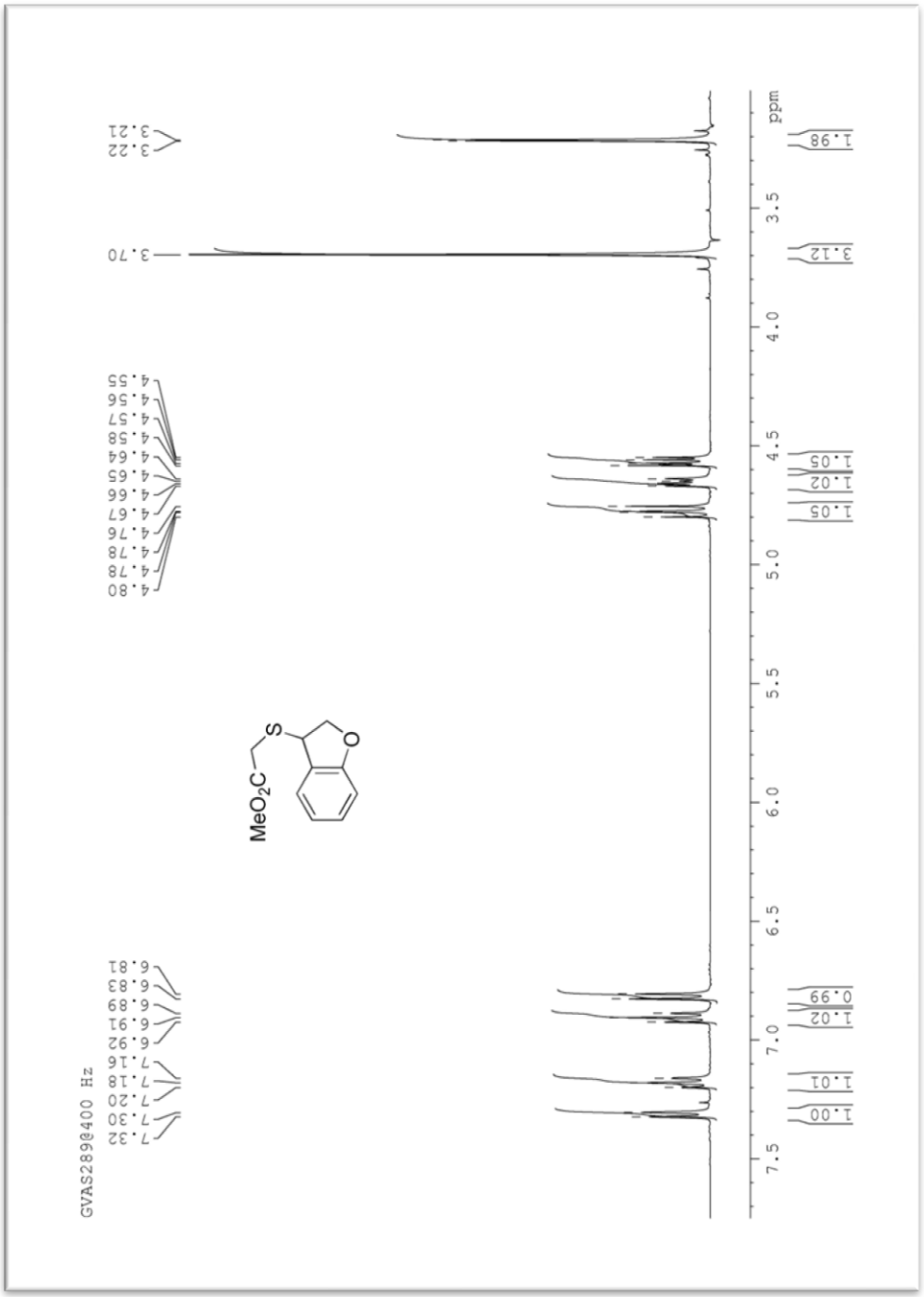

GVAS290-B@250 C-13
13.87
41.33
55.93
61.64
74.56
109.76
120.39
125.05
126.39
129.11
160.23
167.77
167.91
EtO2C
CO2Et
O
ppm

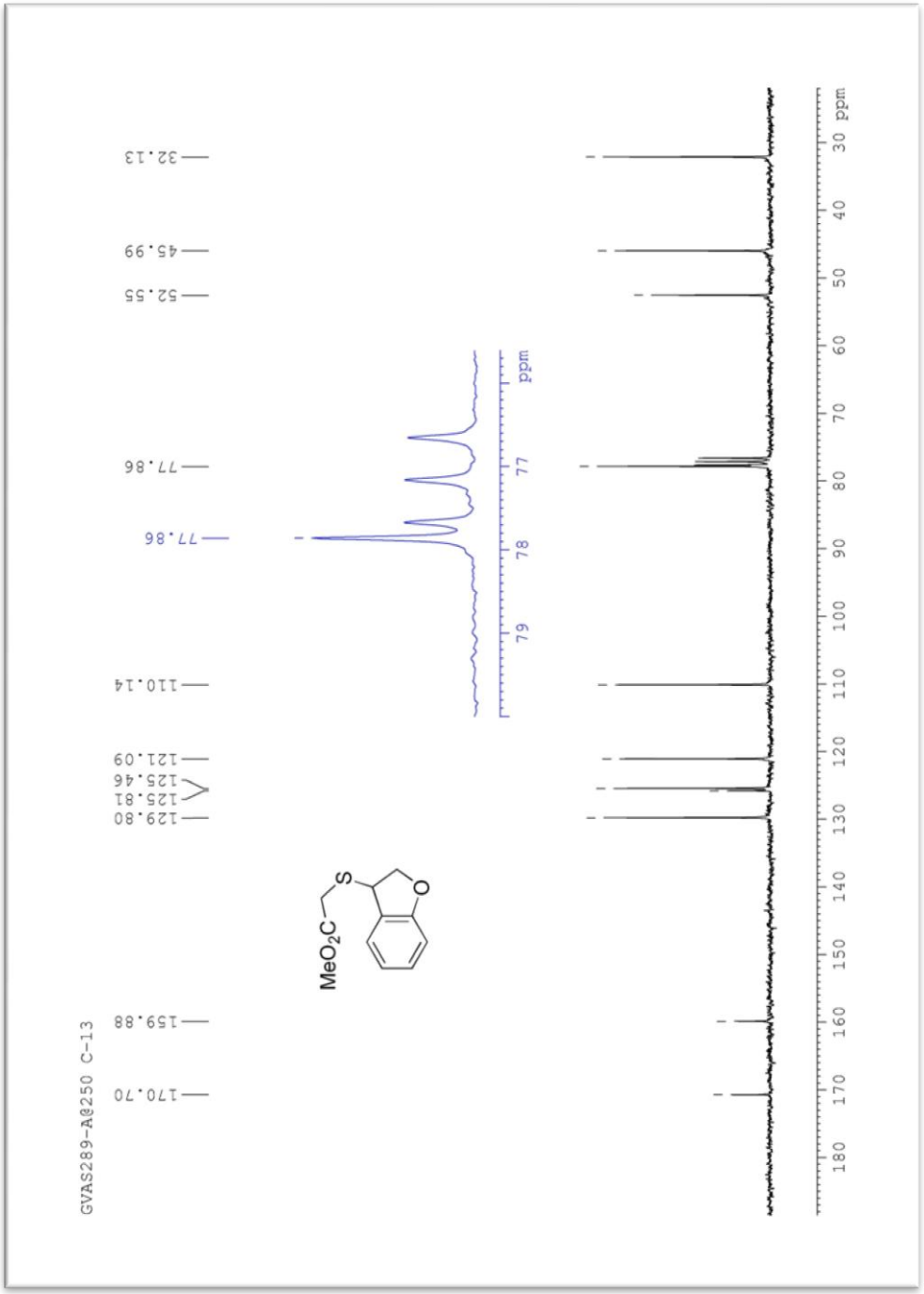

GVAS301@250 H-1
7.21
7.18
7.14
6.89
6.86
6.84
6.81
4.49
4.47
4.45
4.43
4.23
4.20
4.17
4.14
4.11
4.08
4.05
3.63
3.60
1.24
1.22
1.19
EtO2C
CN
O
2.01
2.00
1.02
4.47
1.01
3.42
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

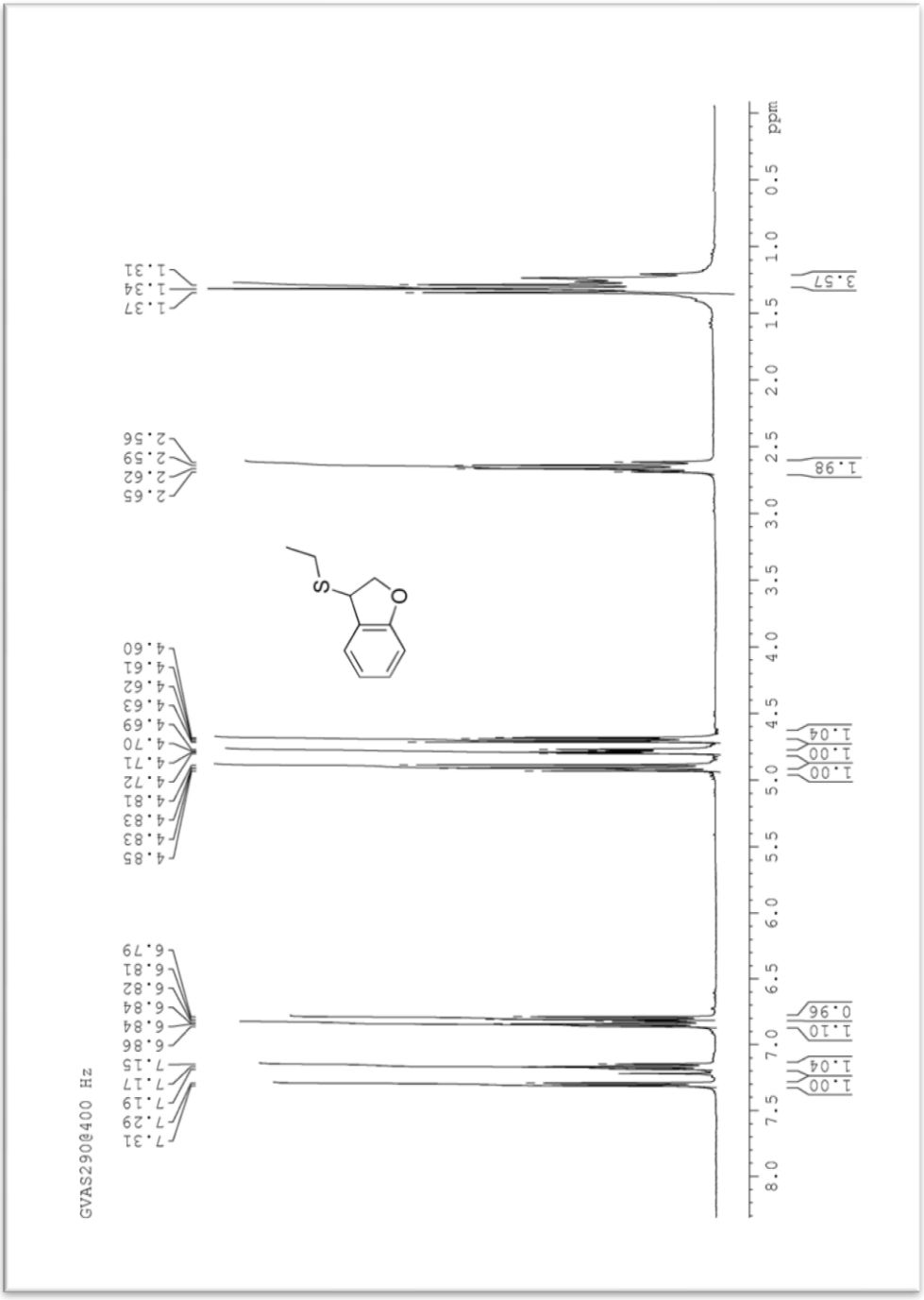

GVAS3O1@250 C-13
11.38
38.75
42.10
59.09
71.99
107.21
115.06
117.83
122.45
123.79
126.55
157.63
165.19
EtO2C
CN
O
10 ppm

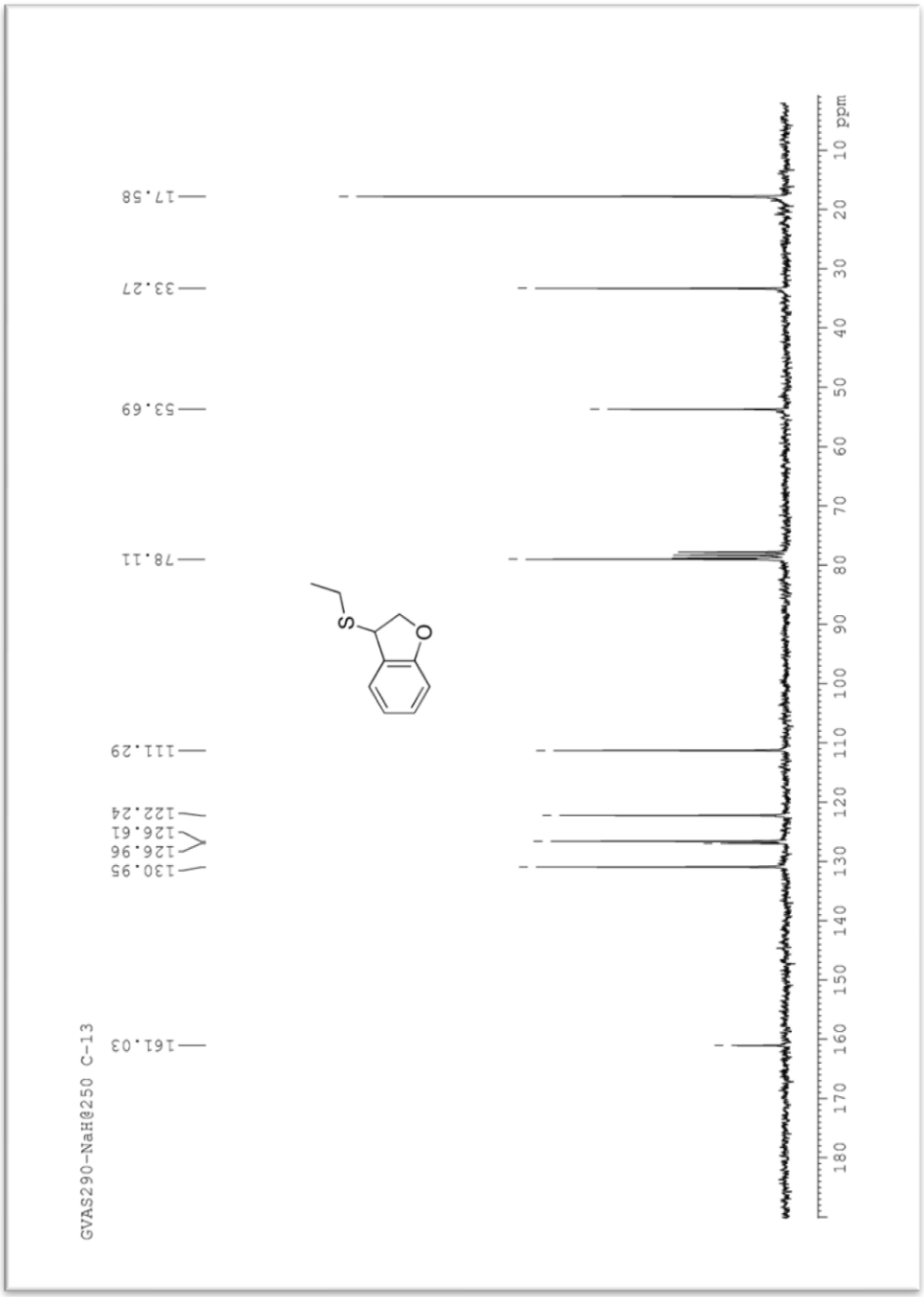
GVAS288-B@400 Hz
7.35
7.34
7.34
7.34
7.33
7.33
7.33
7.28
7.28
7.28
7.27
7.26
7.26
7.25
7.25
7.24
7.23
7.23
7.17
7.15
7.13
6.89
6.87
6.85
6.78
6.76
4.90
4.89
4.88
4.87
4.75
4.73
4.73
4.71
4.57
4.56
4.54
4.53
S
O
1.87
4.20
1.08
1.00
0.99
1.00
1.07
1.05
7.5
7.0
6.5
6.0
5.5
5.0
4.5
ppm


GVAS2880250 C-13
159.91
133.87
132.40
129.75
129.14
127.74
126.46
125.44
121.00
110.14
77.55
77.55
48.85
ppm
S
O


GVAS289@400 Hz
7.32
7.30
7.20
7.18
7.16
6.92
6.91
6.89
6.83
6.81
4.80
4.78
4.78
4.76
4.67
4.66
4.65
4.64
4.58
4.57
4.56
4.55
3.70
3.22
3.21
MeO2C
S
O
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
1.00
1.01
1.02
0.99
1.05
1.02
1.05
3.12
1.98


GVAS289-A@250 C-13
170.70
159.88
129.80
125.81
125.46
121.09
110.14
77.86
77.86
52.55
45.99
32.13
MeO2C
S
O
ppm
30 ppm


GVAS2904400 Hz
7.31
7.29
7.19
7.17
7.15
6.86
6.84
6.84
6.82
6.81
6.79
4.85
4.83
4.83
4.81
4.72
4.71
4.70
4.69
4.63
4.62
4.61
4.60
2.65
2.62
2.59
2.56
1.37
1.34
1.31
S
O
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.04
0.96
1.10
1.00
1.04
1.00
1.00
1.98
3.57


GVAS290-NaH@250 C-13
17.58
33.27
53.69
78.11
111.29
122.24
126.61
126.96
130.95
161.03
S
O
10 ppm