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Enantioselective synthesis of cyclobutene compounds with potential pharmacological application

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TABLE OF CONTENTS

1. ABSTRACT 03

2. INDEX OF ACRONYMS AND ABBREVIATIONS 04

3. INTRODUCTION 05

3.1 CYCLOBUTANES IN NATURE 05

3.2 CYCLOBUTANES AS DRUGS 06

3.3 COMMON REACTIONS LEADING TO CYCLOBUTANES 08

3.3.1 Photochemical [2+2] Cycloaddition 08

3.3.2 Lewis Acid-Promoted Ficini Reaction 21

4. PURPOSE 29

5. RESULTS AND DISCUSSION 30

5.1 SYNTHESIS OF THE YNAMIDES 30

5.1.1 Synthesis of N-Benzyl-4-methyl-N-(phenylethynyl)benzenesulfonamide (50) 31

5.1.2 Synthesis of N-benzyl-N-{3-[(tert-butyldiphenylsilyl)oxy]prop-1-ynyl}-4-methylbenzenesulfonamide (52) 33

5.1.3 Attempted synthesis of 3-benzoyl-1-{3-[(tert-butyldiphenylsilyl)oxy] prop-1-yn-1-yl}-5-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione) (55) 34

5.2 SYNTHESIS OF THE CYCLO-OLEFINE 36

5.2.1 Synthesis of (2S)-2,2-Dimethyl-propionic acid 5-oxo-2,5-dihydro-furan-2-ylmethyl ester (37) 36

5.3 LEWIS ACID-MEDIATED CYCLOADDITIONS 38

5.3.1 Attempted synthesis of (1S,5R)- N-benzyl-N-tosyl-6-amino-7-phenyl-3-oxabicyclo[3.2.0]hept-6-ene-2,4-dione (61) 39

5.3.2 Attempted synthesis of [(1S,2S,5R)-N-benzyl-N-tosyl-6-amino-4-oxo-7-phenyl-3-oxabicyclo[3.2.0]hept-6-en-2-yl]methyl-2,2-[dimethylpropanoate] (46) 40

5.3.3 Attempted synthesis of (1S,5R)-N-benzyl-N-tosyl-6-amino-7-{[(tert-butyldiphenylsilyl)oxy]methyl}-3-oxabicyclo[3.2.0]hept-6-ene-2,4-dione (63) 42

5.3.4 Attempted synthesis of (1R,6S)-N-benzyl-N-tosyl-8-amino-7-{[(tert-butyldiphenylsilyl)oxy]methyl}bicyclo[4.2.0]oct-7-en-2-one] (65) 44

5.3.5 Synthesis of (1R,6S)-N-Benzyl-N-tosyl-8-amino-7-phenylbicyclo[4.2.0]oct-7-en-2-one (66) 45

6. CONCLUSION AND FUTURE PROSPECTS 46

7. EXPERIMENTAL SECTION 47

7.1 GENERAL METHODS 47

7.2 EXPERIMENTAL SECTION 47

8. ACKNOWLEDGMENTS 60

9. SPECTRA 61

10. BIBLIOGRAPHY 77

ABSTRACT

In the present project, we studied the design of an appropriate strategy for the preparation of cyclobutenes by means of Lewis acid catalysis. In particular the Ficini stepwise [2+2] cycloaddition of ynamides with lactones was taken under consideration as an excellent reaction for the preparation of substituted cyclobutene derivates.

The synthesis of a novel cyclobutene derivate has been carried out, with good yield. On the other hand, the synthesis of other derivates, such as a nucleoside analogue, will require further investigation.

2. INDEX OF ACRONYMS AND ABBREVATIONS

Ac	acetyl
AcOEt	ethyl acetate
AIBN	azobis(isobutyronitrile)
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
Bz	benzoyl
COD	1,5-cyclooctadiene
Cp	cyclopentadiene
DIBAL	diisobutylaluminium
DMAP	4-dimethylaminopyridine
EDG	electron donating groups
Et	ethyl
EWG	electron withdrawing group
GC	Gas Chromatography
hex	hexane
HSQC	Heteronuclear Single Quantum Coherence
Im	imidazole
LDA	lithium diisopropylamide
Me	methyl
Mnt	menthyloxy
MS	Mass Spectroscopy
MW	molecular weight
NMR	Nuclear Magnetic Resonance
Ph	phenyl
Piv	pivaloyl (trimethylacetyl)
Pr	propyl
Py	pyridine
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TEA	triethylamine
Tf	triflyl
TFA	trifluoroacetic acid
THF	tetrahydrofurane
TLC	Thin Layer Chromatography
Ts	tosyl

3. INTRODUCTION

3.1 CYCLOBUTANES IN NATURE

Cyclobutanes are found in many naturally occurring compounds with biological activities, which have important implications in the agriculture or pharmaceutical field (Figure 1). This important class of compounds is involved in several organic transformations, and the skeleton is common in many natural products.

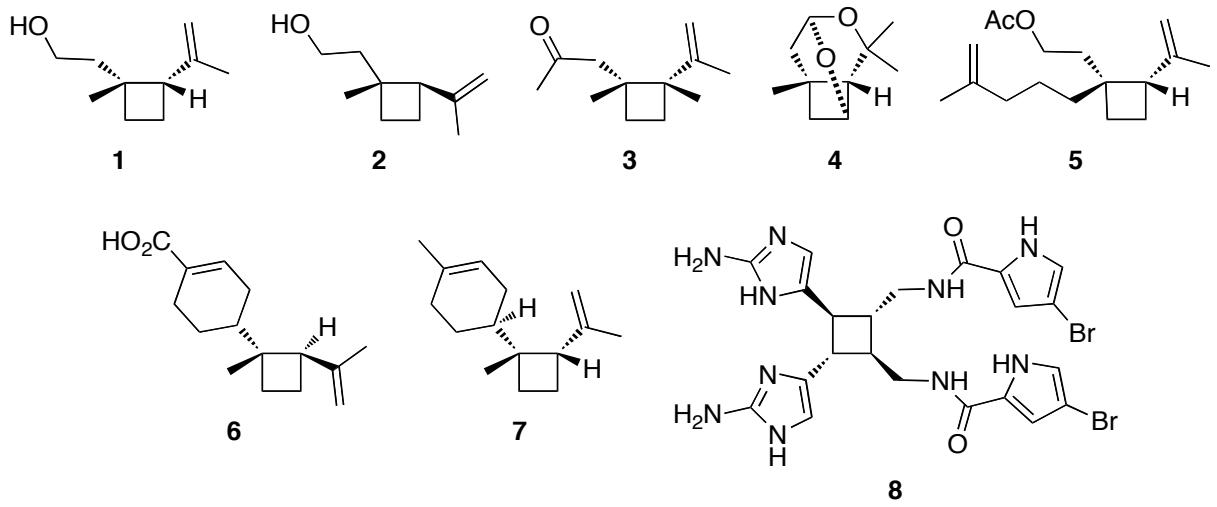


Figure 1. *Natural cyclobutane compounds.*

(+)-Grandisol (**1**) is the most important constituent of the aggregation pheromone produced by the male of the cotton boll weevil *Anthonomus grandis* and other beetles.[1] The trans isomer fragranol (**2**) has been found in some plants, such as *Artesia fragrans*,[2] and grandisal (**3**), the oxidation product of grandisol, can be identified as aggregation pheromone component of *Pissodes*. The female of ambrosia beetle *Tripodendron Lineatum* produces (+)-lineatin (**4**), and

the sesquiterpene (1*R*,2*S*)-*cis*-2-isopropenyl-1-(4'-methyl-4'-penten-1'-yl)cyclobutaneethanol (**5**) is found in the sex pheromone of females of the oleander scale *Aspidiotus nerii,* a lemon tree pest of tropical areas.[3] The sesquiterpene dunniane (**6**) and cumacrene (**7**) have been isolated from *Illicium dunnianum* Tutcher, a plant used in traditional medicine in Hong Kong,[4] and the Monterey Cypress *Cupressus macrocarpa* Hartw,[5] respectively. The alkaloid sceptrin (**8**), isolated from *Agelas sceptrum* in 1981, displays potent activity as an antiviral, antimuscarinic, antibacterial, and antihistaminic agent.[6] Therefore, these cyclobutane products and numerous other analogues are required and important in nature. Although several stereoselective syntheses, based on a [2+2] photochemical reaction of a chiral 2(5H)-furanone with different alkenes, have already been described, further refined syntheses are awaited to produce substantial amount of these compounds.

3.2 CYCLOBUTANES AS DRUGS

Cyclobutanes have been used and studied over the past thirty years for their biological activity. The largest part of the studies concerns nucleoside analogues, which have been the cornerstone of antiviral therapy (Figure 2).[7]

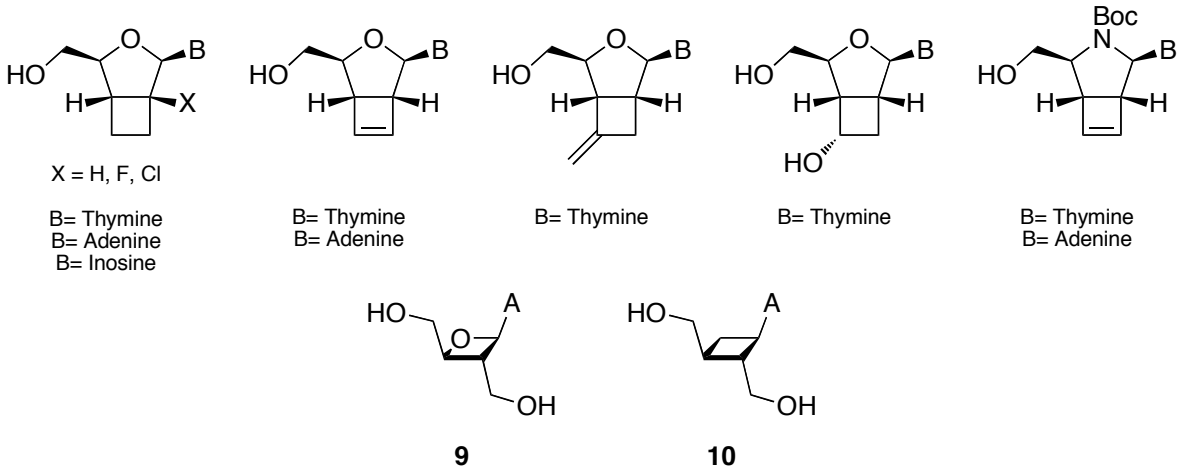


Figure 2. *Synthesized cyclobutane compounds.*

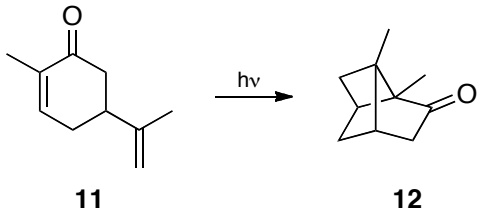
A nucleoside named oxetanocin (9-[(2*R*,3*R*4S)-3,4-bis(hydroxymethyl)-2-oxetanyl]adenine) (**9**), discovered in 1986 by the isolation from *Bacillus megaterium*, shows antiviral, antitumor and antibacterial activities.[8] At present, several nucleoside analogues of oxetanocin have been synthetized and investigated as antiviral agents. Cyclobut-A (**10**), for example, showed activity against HIV and herpes virus and possess greater enzymatic stability due to the absence of the *N-glycosidic* linkage.[9] During the past few years, a large number of bicyclic 2',3'-dideoxynucleoside analogues, which are conformationally restricted, have been prepared and the chemotherapeutical effects have been observed to be enhanced.[10] This activity, connected with the conformation, can be studied and helps to identify conformational preferences demanded by the target enzyme.[11] Anti-HIV studies with carbohydrate-modified nucleosides have culminated in various structural attributes which contribute to the observed activity.

3.3 COMMON REACTIONS LEADING TO CYCLOBUTANES

Most of the syntheses to prepare the described cyclobutanes are based on photochemical methodologies. Other options are quite limited as concerted [2+2] cycloaddition are forbidden by the Woodward-Hoffmann rules.

3.3.1 Photochemical [2+2] cycloaddition

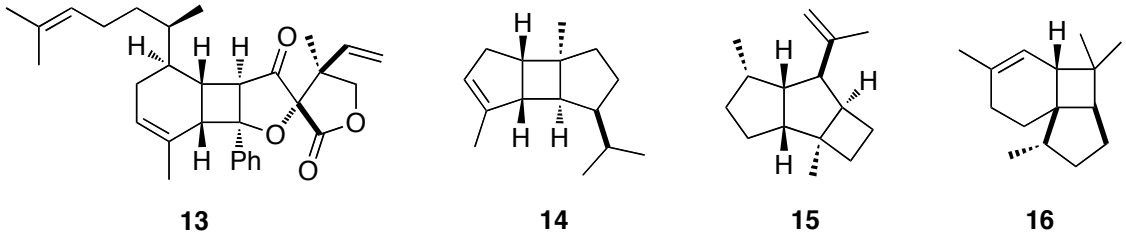
More than one hundred years ago, Ciamician and Silber performed what is considered the first [2+2] photocycloaddition of α,β-unsaturated compounds to unsaturated substrates using sunlight as energy source, which can be easily used for a synthesis of cyclobutane compounds.[12] Ciamician and Silber used organic compound such as carvone (**11**), although they were not able to deduce exactly the structure of the products. However, fifty years later, the reproduction of the experiment by Büchi and Goldman allowed the identification of the product as photocarvone (**12**) (Scheme 1).[13]



Scheme 1. *Intramolecular [2+2] photocycloaddition of carvone (11).*

Several complex natural product syntheses have been widely carried out since the aforementioned discovery (Figure 3). For instance, biyouyanagin-A (**13**),[14] α-bourbonene (**14**),[15]

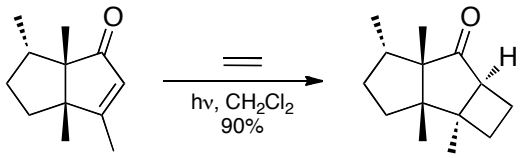
kelsoene (**15**) [16] and italicene (**16**),[17] have been synthetized using inter- or intramolecular versions of the reaction.



13 **14** **15** **16**

Figure 3. *Examples of cyclobutane-containing natural products.*

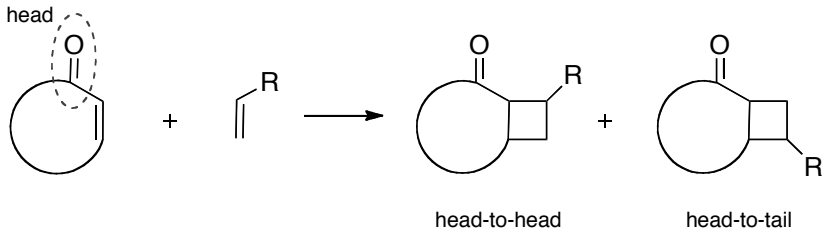
The synthesis of **18** is an example of a stereoselective synthesis with a facial discrimination controlled by the stereogenic centre within the cyclic enone. The ethylene approaches from the less hampered face of the enone (**17**) (Scheme 2).



17 **18**

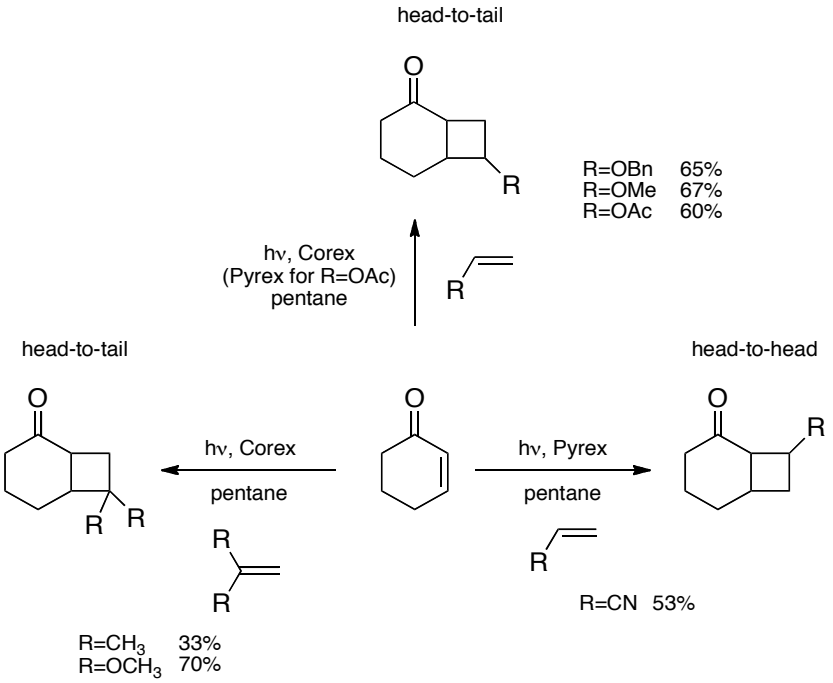
Scheme 2. *[2+2] Photocycloaddition of **17** to ethylene.*

The formation of regioisomers is unavoidable using asymmetric alkenes, which limit the synthetic applicability of the [2+2] photocycloadditions. A reaction involving a cyclic enone and a substituted alkene affords a mixture of head-to-head and head-to-tail compounds (the carbonyl group and the substituent of olefin are considered as heads) (Scheme 3).



Scheme 3. *Possible regioisomers obtained in the [2+2] photocycloaddition of cyclic enone to an asymmetric alkene.*

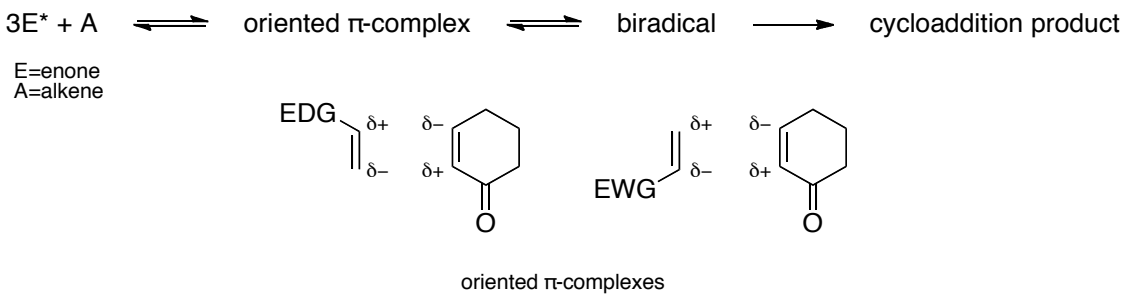
Corey reported for the first time in 1964 the use of an asymmetric alkene, 2-cyclohexenone and isobutene,[18] and later different mono- and di-substituted alkenes (Scheme 4).[19]



Scheme 4. *[2+2] Photocycloaddition of cyclohexene to substituted alkenes.*

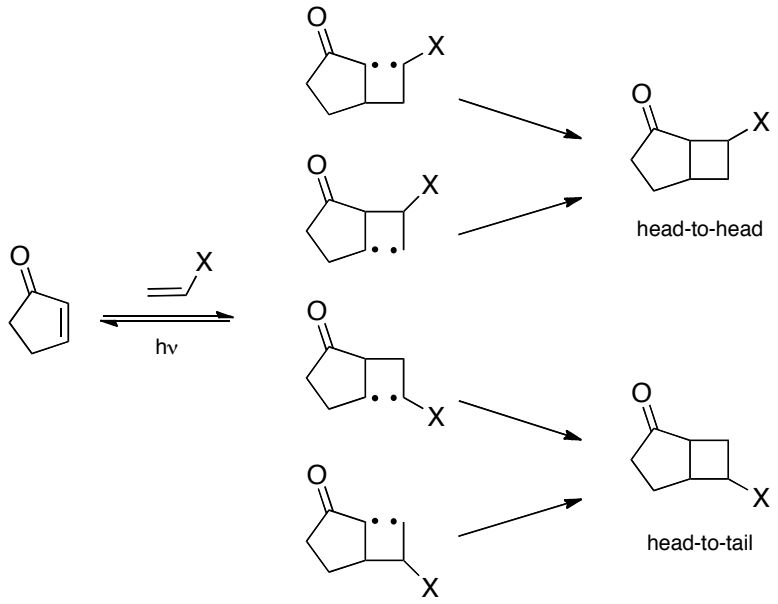
Corey was also able to propose a possible mechanism of the reaction, observing that electron-rich enones with electron-rich olefins afforded mainly head-to-tail regioisomers, while electron-

poor partners afforded head-to-head regioisomers. The first step involve the enone triplet state with the ground state of the alkene to give an oriented π-complex, which proceeds with the formation of 1,4-biradical and finally the final cycloadducts (Scheme 5).[19]



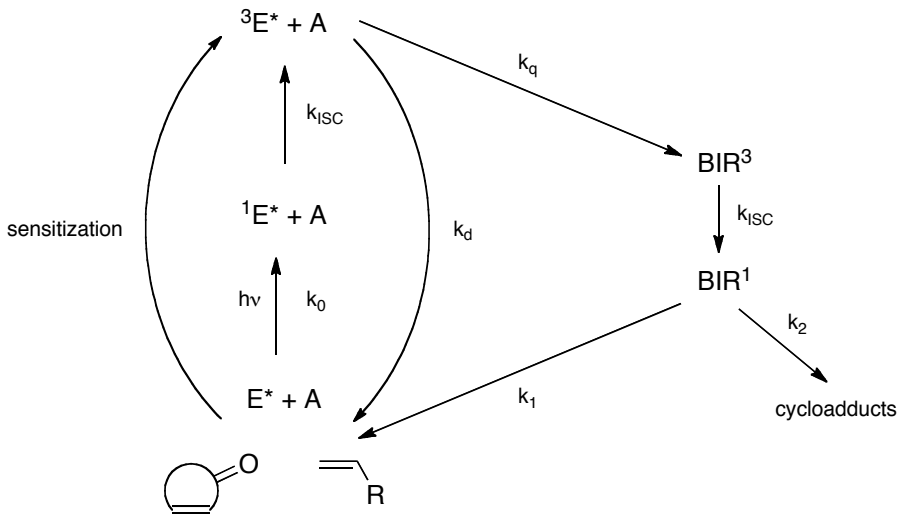
Scheme 5. *Corey's mechanistic proposal.*

Thanks to Corey's rule, the regioselectivity of the reaction can be predicted by the polarization of the olefin. However, not all the experiment can be justified, in particular when alkenes contain an electron-withdrawing group (EWG). An alternative mechanism was therefore proposed by Bauslugh (Scheme 6).[20] It was later confirmed by further studies by Schuster[21] and finally by Weedon and co-workers[22], who performed radical trapping experiments.



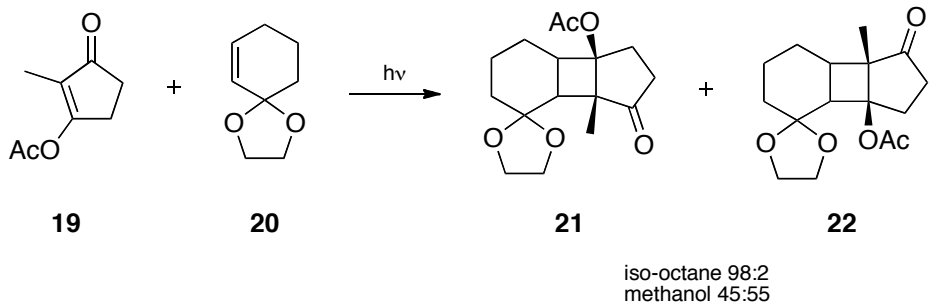
Scheme 6. *Bauslugh's mechanistic proposal based on postulated biradical intermediates for [2+2] photocycloaddition of enones to asymmetric alkenes.*

Scheme 7 shows the currently accepted mechanism.[23] The α,β-unsaturated carbonyl compound is excited by the light through a nπ* or ππ* single electron transition, generating the singlet state ^{1}E, which decays to the triplet state ^{3}E. Subsequently, this intermediate can add to the olefin to afford the triplet biradical BIR^3, which can yield the singlet state BIP^1 through a spin inversion. Finally BIR^1 can either afford the final cycloadducts or revert to initial substrates.



Scheme 7. *The currently accepted Bauslaugh-Schunster-Weedon mechanism.*

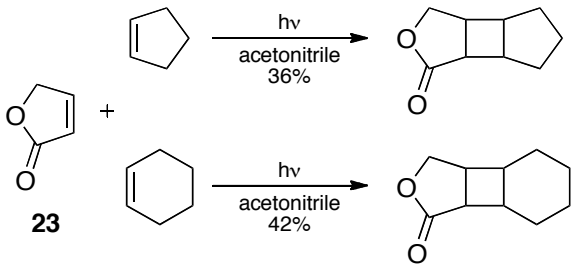
The solvent polarity can also be significant to influence the regioselectivity of the reaction. For instance, the photocycloaddition studied by Challand and Mayo between cyclopentenone (**19**) and alkene **20** is dramatically affected by the polarity of the solvent (Scheme 8).[24]



Scheme 8. *Effect of the solvent's polarity on the [2+2] photocycloaddition of 19 to 20.*

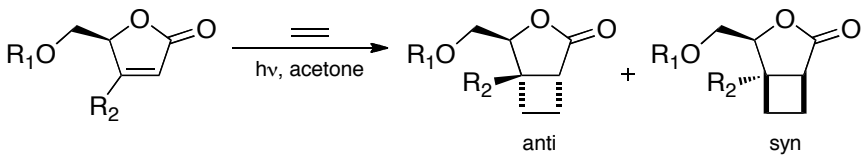
The effect of polarity has to be estimated in every single case, since the mechanistic proposals aforementioned do not predict it.

An important starting material, considered in this thesis, is 2(5H)-furanone. This substrate is considered the best starting material in order to synthetize natural cyclobutane compounds and nucleoside analogues. Tada and co-workers described the first reaction using this substrate in 1972: the [2+2]-photocycloaddition of the crotonolactone (**23**) to the cyclopentene and cyclohexene (Scheme 9).[25]



Scheme 9. *[2+2] Photocycloaddition of crotonolactone (82) to cyclopentene and cyclohexene.*

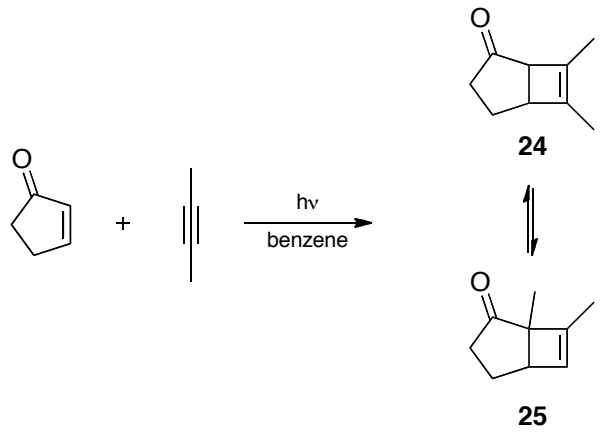
From 1991, the Font's research group of *Universitat Autonoma de Barcelona* have performed [2+2] photocycloaddition reactions of furanones.[26] The research clarified the factors, such as temperature and solvent, which control the facial diastereoselectivity of the reaction (Scheme 10). The alkene approaches to the less hindered face of the lactone affording mainly the *anti* adducts. Temperature does not influence the ratio, although low temperature affords best yields.



R_1	R_2	Yield (%)	*anti*:*syn* (%)
Ac	H	82	74:26
Piv	H	59	78:22
Ac	CH_3	65	54:46
Piv	CH_3	70	62:38

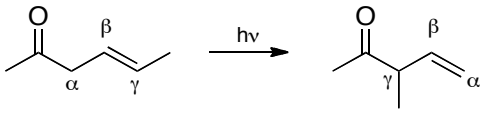
Scheme 10. *[2+2] Photocycloaddition of homochiral 2(5H)-furanones to ethylene.*

The [2+2] photocycloaddition of cyclic enones to alkynes presents some differences from the similarly substituted alkenes. In fact, the synthesis of natural product is somehow limited, as a consequence of the tendency of alkynes to produce polymeric material.[27] In fact, the formed cyclobutane can easily be excited and participate with another cycloaddition affording the polymer.[28] Eaton, in 1964, studied one of the first photochemical reaction,[29] between 2-cyclopentenone and 2-butyne (Scheme 11). The reaction afforded the expected cycloadduct **24** and the transposed derivate **25**.



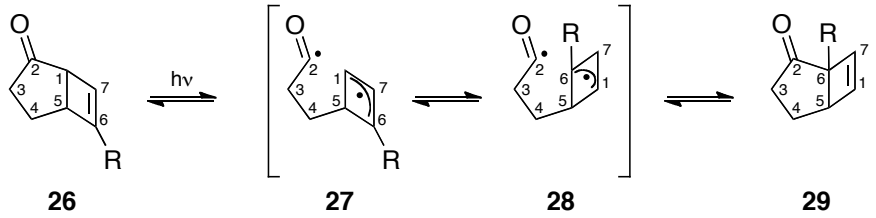
Scheme 11. *[2+2]Photocycloaddition of 2-cyclopentenone with 2-butyne.*

This 1,3-acyl shift rearrangement of β,γ-unsaturated ketones is often a competitive reaction for the cyclobutene derivatives (Scheme 12).



Scheme 12. *1,3-Acyl shift rearrangement of β,γ-unsaturated ketones.*

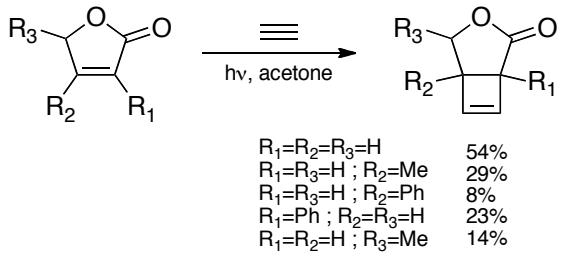
The mechanism of this rearrangement is shown in Scheme 13. The Norrish I type cleavage affords the acyl-ally biradical **27** which can rotate around the C_4-C_5 bond (**28**) and merge through the C_2-C_6 (**29**). In the reaction with mono and disubstituted alkyne, the 1,3-acyl shift can be noticed only in the head-to-tail regioisomers.[30]



Scheme 13. *1,3-Acyl shift rearrangement of β,γ-unsaturated ketones – mechanism.*

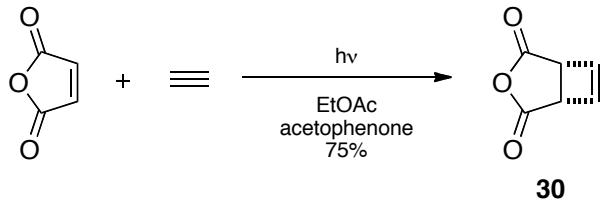
These types of reaction require long time and are characterized by low yields. [2+2]-Photocycloaddition reactions of 2(5H)-furanones must be carefully controlled and stopped at the appropriate time, in order to avoid the formation of large amounts of by-products deriving from

rearrangement. In 1976, Kosugi published the first work about this type of reaction, showing poor yields (Scheme 14).[31]



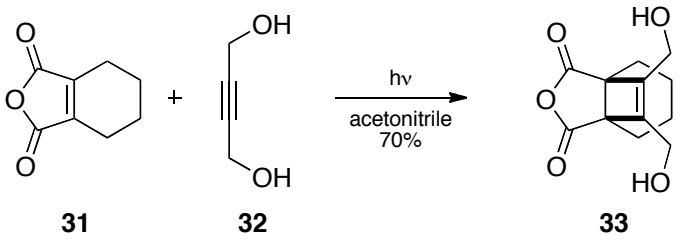
Scheme 14. *[2+2] Photocycloaddition of 2(5H)-furanones to acetylene.*

Bloomfield and Owsley[32] have studied the cycloaddition between maleic anhydride and acetylene, affording the bicyclic anhydride **30**, which has been adopted for the preparation of several carbocyclic nucleoside analogues (Scheme 15).[33]



Scheme 15. *[2+2] Photocycloaddition of maleic anhydride to acetylene.*

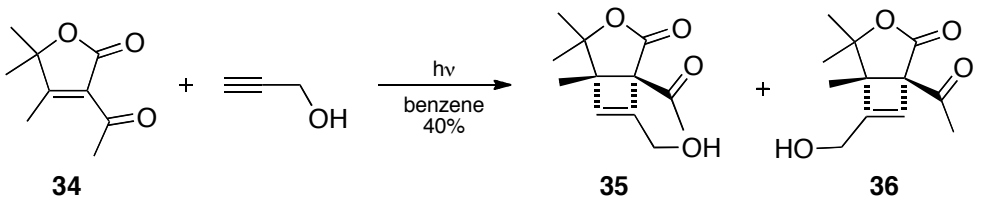
In 1999, a reaction involving a disubstituted alkyne was described (Scheme 16).[34] The reaction of the unsaturated bicyclic anhydride **31** to 2-butyne-1,4-diol (**32**) afforded the cyclobutene derivative **33**.



31 **32** **33**

Scheme 16. *[2+2] Photocycloaddition of the unsaturated bicyclic anhydride 99 to 2-butyne-1,4-diol (32).*

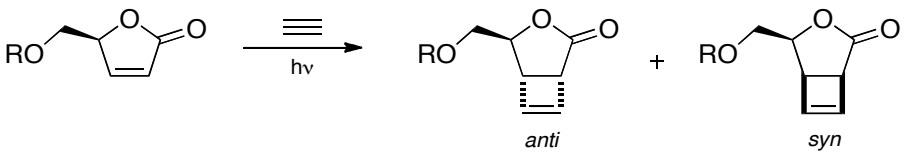
In 1989, another research group studied the reactivity of 2(5H)-furanones with 1-alkynes, wherein the [2+2] photocycloaddition of the 3,4,5,5-tetrasubstituted 2(5H)-furanones **34** afforded a mixture of head-to-head (**35**) and head-to-tail (**36**) cycloadducts (Scheme 17).[35]



34 **35** **36**

Scheme 17. *[2+2] Photocycloaddition of 3,4,5,5-tetrasubstituted 2(5H)-furanones 34 to propargyl alcohol.*

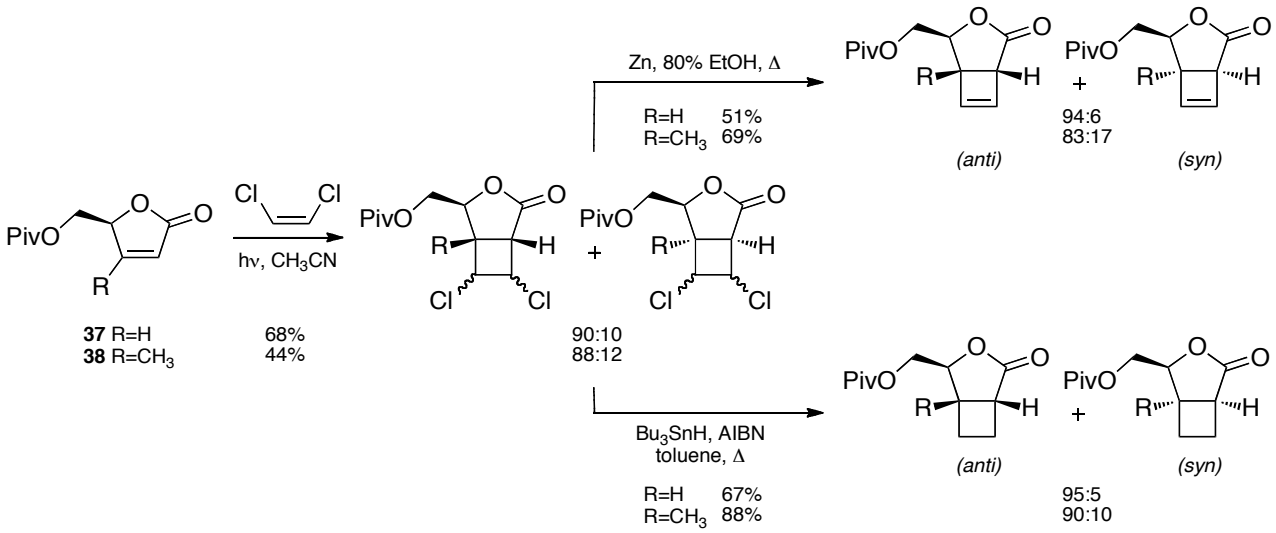
More recently Font and researchers reported a study regarding the influence different conditions on the facial diastereoselectivity between chiral 2(5H)-furanones and acetylene (Scheme 18).[26]



R_1	Solvent	Filter	Yield (%)	anti:syn (%)
Piv	acetonitrile	quartz	74	66:34
Piv	acetone	pyrex	53	70:30
CO_2Mnt	acetonitrile	quartz	57	59:41
CO_2Mnt	acetone	pyrex	51	66:34
Bz	acetonitrile	quartz	25	66:34
Bz	acetone	pyrex	26	68:32

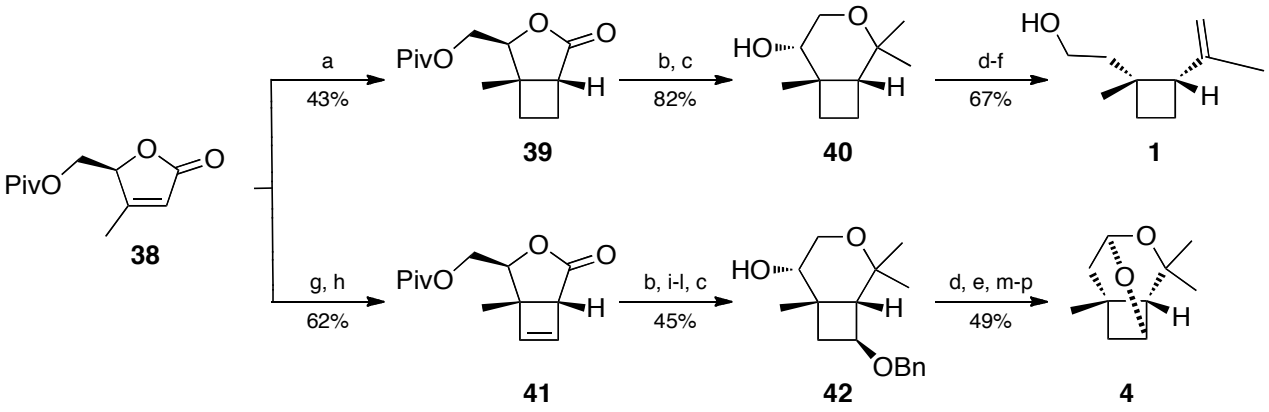
Scheme 18. *[2+2] Photocycloaddition of chiral 2(5H)-furanones to acetylene.*

Finally, in 2003, the same research group proposed a highly efficient and stereoselective approach to the cyclobutane and cyclobutene derivatives (Scheme 19).[36] This procedure consists in the [2+2] photocycloaddition of 2(5H)-furanone **37** and **38** with (*Z*)-1,2-dichloroethylene, followed by reductive substitution or reductive elimination.



Scheme 19. *Methodology for the synthesis of cyclobutane and cyclobutene derivatives from 2(5H)-furanones 37 and 38.*

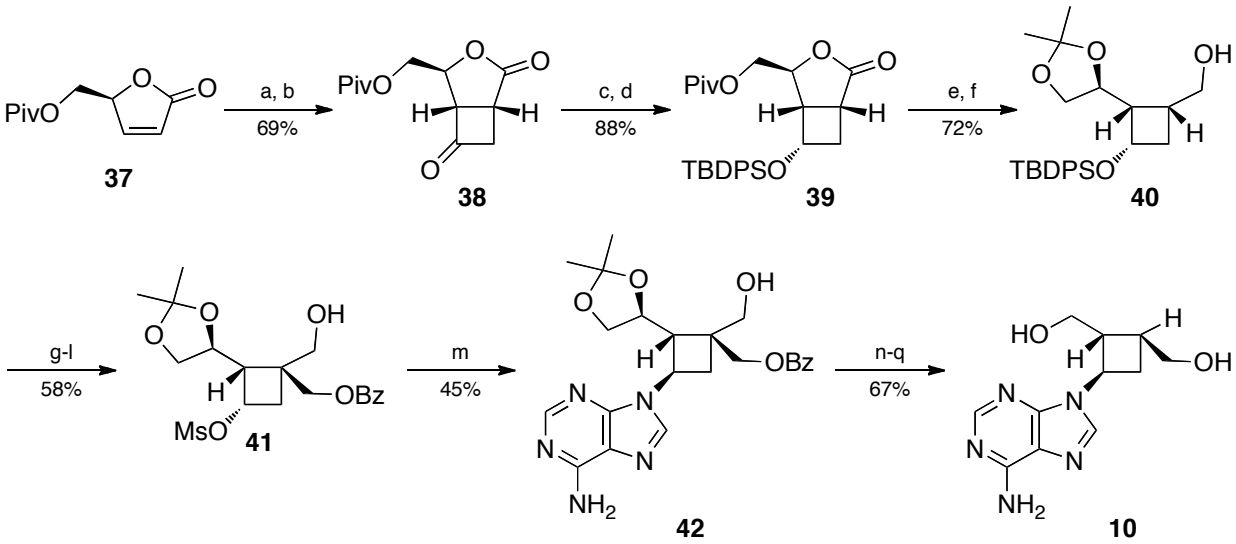
The naturally occurring pheromones so far described have been prepared through these methodologies. Grandisol (**1**) and Lineantin (**4**) were prepared with a [2+2] photocycloaddition of 2(5H)-furanone **37** to ethylene and (*Z*)-1,2-dichloroethylene respectively, which can be conveniently modified (Scheme 20).[37]



Reagents and conditions: (a) hν, athylene, acetone; (b) MeLi, THF; (c) TsCl, DMAP, py; (d) TCDI, THF; (e) Bu_3SnH, AIBN, toluene; (f) LDA, hexane; (g) hν, (Z)-1,2-dichloroethylene, CH_3CN; (h) Zn, 80% EtOH, MW; (i) p-TsOH, acetone; (j) I: $Hg(OAc)_2$, THF-H_2O, II: $NaBH_4$, NaOH; (k) NaH, BnBr, THF; (l) CF_3COOH, MeOH-H_2O; (m) H_2, Pd/C, EtOAc, AcOH; (n) Dess-Martin periodinane, CH_2Cl_2; (o) $RuCl_3$, $NaIO_4$, CCl_4-H_2O; (p) DIBAL-H, Et_2O, tartaric acid.

Scheme 20. *Synthesis of grandisol (1) and lineantin (4).*

Cyclobut-A (**10**) was also prepared starting with a regio- and diastereoselective [2+2] photocycloaddition of ketene diethyl acetal to 2(5H)-furanone **37** (Scheme 21).[38] The synthesis continues with the hydrolysis of the acetal moiety to afford **38** and, after further modifications, **39** is obtained. Next, **39** is reduced and protected as an acetonide, affording **40**. Subsequently, the primary hydroxyl group is protected and the epimerization, followed by the conversion of secondary hydroxyl group providing **41**. The nucleobase is introduced by a nucleophilic substitution of the mesylate group, affording **42**. The removal of the protecting groups followed by the oxidative cleavage of the vicinal diol and reduction of the aldehyde leads to the final product **10**.



Reagents and conditions: (a) hν, ketene diethyl acetal, Et_2O; (b) p-TsOH, acetone, reflux; (c) L-Selectride, THF, -78 °C; (d) TBDPSCl, imidazole, THF; (e) $LiAlH_4$, THF, 0 °C; (f) acetone, $CuSO_4$, HCl (catalytic); (g) Dess-Martin periodinane, CH_2Cl_2; (h) Na_2CO_3, MeOH; (i) $NaBH_4$, MeOH; (j) BzCl, py, CH_2Cl_2; (k) TBAF, THF; (l) MsCl, Et_3N, Ch_2Cl_2; (m) adenine, K_2CO_2, 18-C-6, DMF, 120 °C; (n) Na_2CO_3, MeOH, rt; (o) TFA-H_2O, rt; (p) $NaIO_4$, THF-H_2O, rt; (q) $NaBH_4$, MeOH, 0 °C.

Scheme 21. *Synthesis of cyclobut-A (10).*

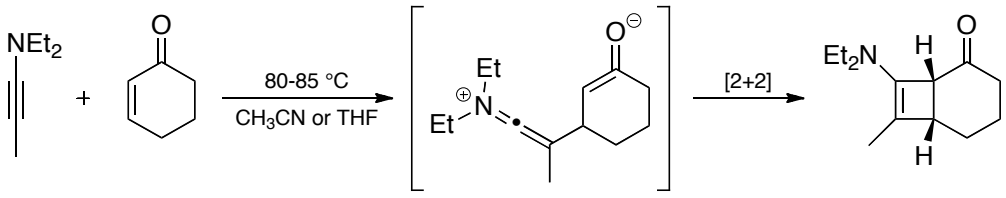
3.3.2 Lewis acid-promoted Ficini reactions

[2+2] Cycloadditions are forbidden by the Woodward-Hoffmann rules, therefore thermally or Lewis acid activated reactions must proceed through a stepwise mechanism.[39]

The first example of [2+2] cycloaddition in the presence of Lewis acids described is based on the use of enantiopure Ti(IV) species. The asymmetric [2+2] cycloaddition reaction between 3-(2-acryloyl)-1,3-oxazolidin-2-one derivatives and 1,1-bis(methylthio)ethylene gave the corresponding cyclobutanes with high enantioselectivity.[40] Meyers and co-workers investigated the nature of the Lewis acid and similar reactants few years later, claiming that certain Al(III) species were capable to favour the [2+2] process, though in stoichiometric amounts.[41] Five years later, modest results were obtained in the presence of some aromatic Al(III) complexes as Lewis acid in catalytic loadings.[42] The same year, Takasu's group obtained excellent selectivity and yields in a [2+2] reaction of enantiopure α,β-unsaturated carbonyl compounds and enol ethers,

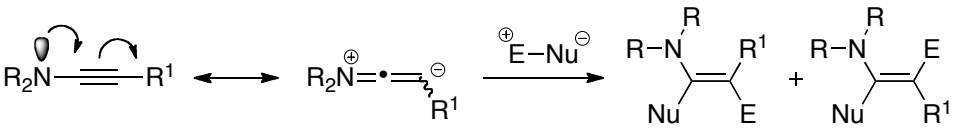
with sub-stoichiometric amounts of Lewis acid.[43] Another example was also published, in order to obtain aza-cyclobutanes, with stoichiometric amounts of Al(III).[44] Later, Yamamoto and Boxer used a highly electron-donating group (tris(trimethylsilyl)silyl) with acrylates, to obtain excellent results concerning both yield and selectivity.[45] Finally, Ihara and co-workers operated with Tf_2NH as catalyst to achieve selectivity in the range of 70-90% and high yields, although only in the case of cyclic enol ethers.[46] The methodologies so far described are not general, and a delicate balance between the electronic nature of reactants and the catalyst acidity seems to exist.

More than 40 years ago, Ficini reported a useful methodology for a C-C bond forming. The reaction involves ynamines in a thermally [2+2]-cycloaddition, leading to the formation of cyclobutenamine (Scheme 22).[47]

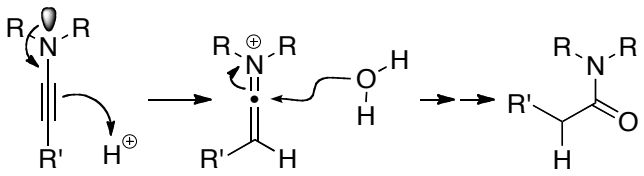


Scheme 22. *Ficini's ynamine-[2+2] cycloaddition.*

More recently, the use of ynamines increased in organic and organometallic synthesis. Many researchers, such as Pitacco and Valentin[48] in 1979, Himbert[49] in 1993 and Katritzky[50] have taken into consideration the use of ynamines. Thanks to the electron donating nature of the nitrogen atom, ynamines are high reactive and regioselective (Scheme 23). On the other hand, due to the sensitivity toward hydrolysis, and the difficult preparation, the synthetic use remained relatively limited (Scheme 24).



Scheme 23. *Electronic bias imposed by the nitrogen atom.*



Scheme 24. *Hydrolytic instability.*

To solve the problem of the stability, some advances have been recently made exploring ynamides. By placing an electron-withdrawing carbonyl group on the nitrogen atom, the electrodonating ability of the nitrogen atom decrease, offering a good balance between stability and reactivity. The electron-withdrawing group can also acts as an efficient directing group (Figure 4).

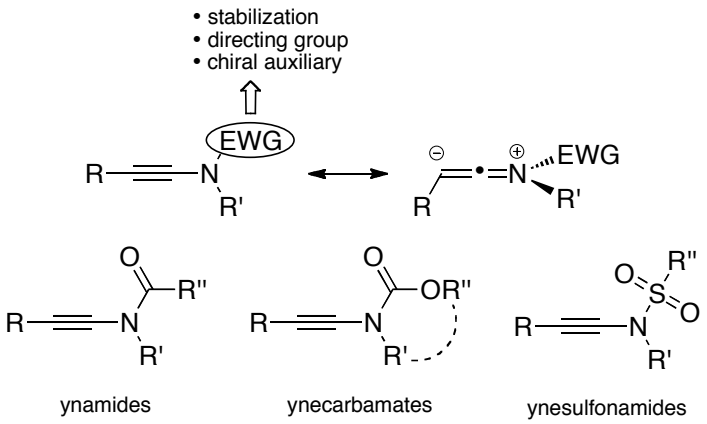
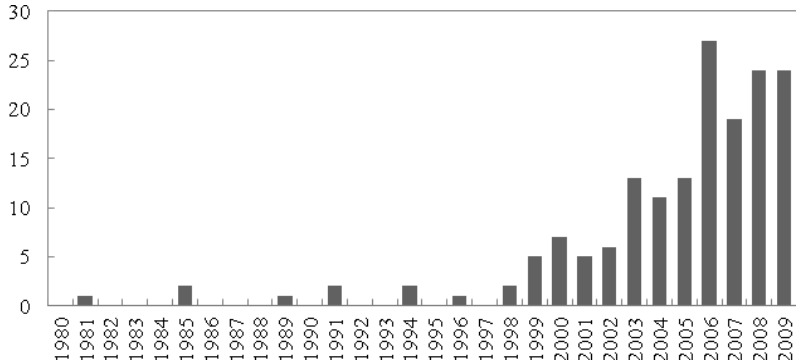


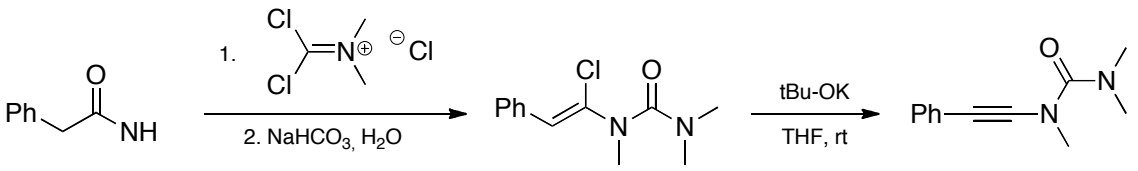
Figure 4. *The most common classes of ynamides.*

All these reasons have allowed the chemistry of ynamides to explode (Graphic 1).[51]



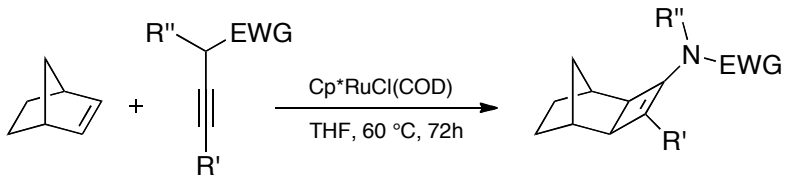
Graphic 1. *Increasing of the publication concerning ynamides.*

The very first ynamide has been synthetized by Viehe and co-workers in 1972 by elimination of HCl from the α-chloroenamide (Scheme 25).[52]



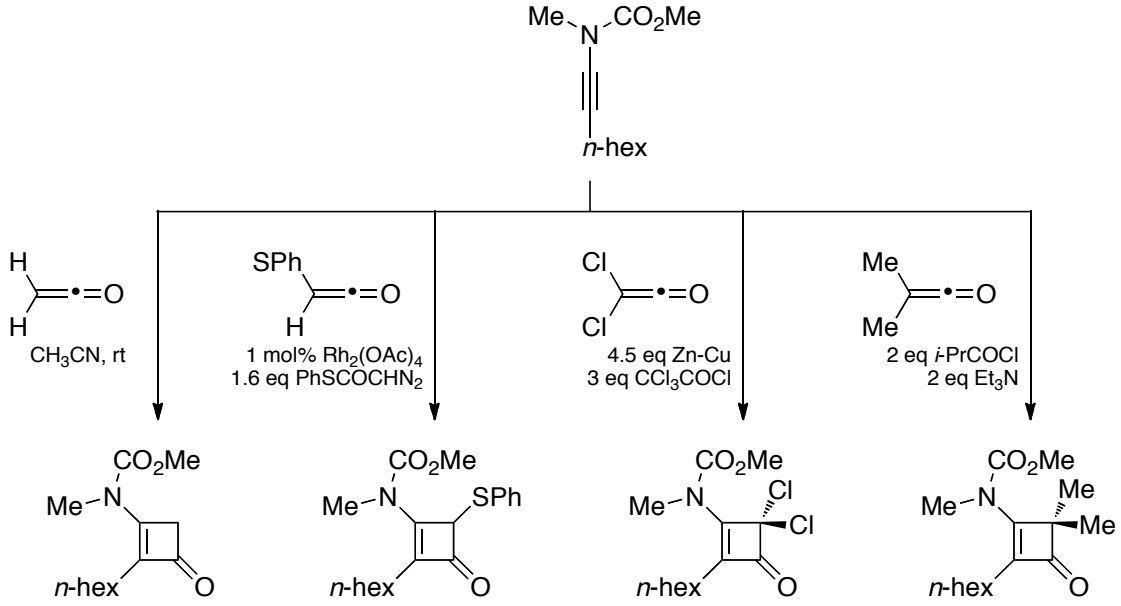
Scheme 25. *The first ynamide synthesis.*

The synthetic use of ynamides is extended to a great number of reactions, such as additions, reduction, oxidation, etc.[51] However this thesis is focused on the [2+2] cycloadditions. Highly efficient reactions in this area have been developed by Tam, who used a Ru catalyst to obtain a [2+2] cycloaddition on norbornene (Scheme 26).[53]



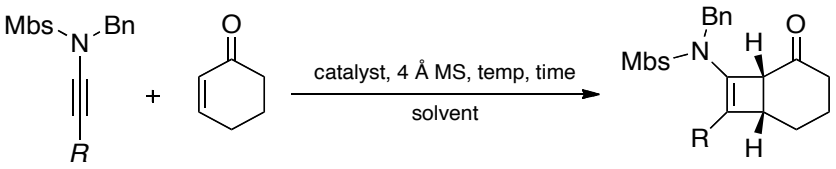
Scheme 26. *Ru-catalysed [2+2] cycloaddition of norbornene.*

Danhesiers used ketenes to obtain thermal cycloadditions with ynamides, providing substituted 3-amidocyclobutenones in good yields (Scheme 27).[54]



Scheme 27. *Thermal cycloaddition of ketenes.*

The first successful [2+2] Ficini reaction was reported for the first time by Hsung and co-workers in 2010.[55] The research was focused on the best Lewis acid and reaction conditions to obtain the best yields (Scheme 28).

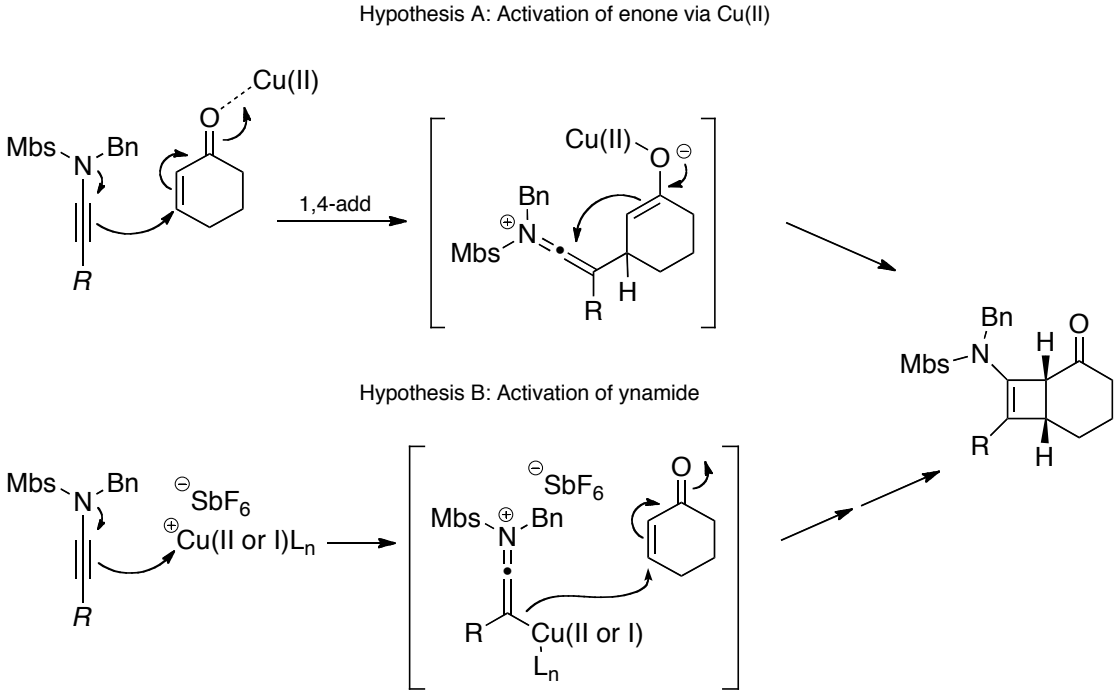


R	Solvent	Catalyst (mol%)	Temp (°C)	Time (h)	Yield (%)
H	CH_3CN	$In(OTf)_2$ (30)	-15	1	--
H	CH_3CN	$Sc(OTf)_3$ (30)	-15	1	--
H	CH_3CN	$Cu(OTf)_2$ (10)	25-80	4	--
H	CH_3CN	$AgSbF_6$ (10)	0-80	5	--
H	CH_3CN	$AgSbF_6$ (10)	50-120	3	--
H	CH_2Cl_2	$CuCl_2/AgSbF_6$ (20/42)	-78-25	10	<5
Me	CH_2Cl_2	$CuCl_2/AgSbF_6$ (20/60)	-40	1	7
Me	CH_2Cl_2	$CuCl_2/AgSbF_6$ (20/60)	-15	1	77
Me	CH_2Cl_2	$CuCl_2/AgSbF_6$ (20/60)	0	1	76

Scheme 28. *Cu(II)-catalysed ynamide-[2+2] cycloaddition.*

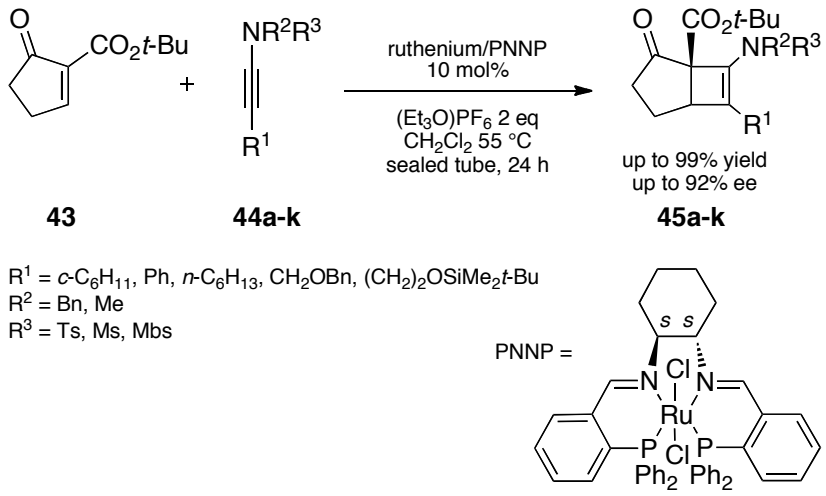
From the scheme we can easily conclude that the reaction can be carried out using $CuCl_2$ and $AgSbF_6$ as the best catalysts.

The two possible mechanistic paths are shown in Scheme 29. In the first hypothesis, the first step is the coordination of the ketone moiety with the Lewis acid ($CuCl^+$ generated from $CuCl_2$ and naked silver ion), leading to an electron-deficient olefin, which is prone to nucleophilic attack by the electron-rich alkyne. In the second hypothesis, the first step is the coordination of the alkyne with the Lewis acid ($CuCl^+$ generated from $CuCl_2$ and naked silver ion), leading to a cuprated ynamidium ion, capable of nucleophilic attack on the β-position of the carbonyl.[55]



Scheme 29. *Mechanistic considerations.*

Recently, Mezzetti and Schotes, reported the first enantioselective Ficini reaction between ynamides **44** and the unsaturated β-keto ester **43** to give the corresponding aminidocyclobutenes (Scheme 30).[56] The protocol tolerates several functional groups and high enantioselectivity is achieved when R^1 is a efficient electron donor.



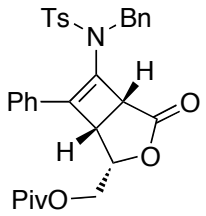
Scheme 30. *Enantioselective Ficini reaction of ynamides 44 to unsaturated β-keto ester 43.*

The reaction proceeds stepwise by nucleophilic attack of the β-carbon atom of the ynamide to the electrophilic position of the enone as the mechanistic considerations in Scheme 29.

4. PURPOSE

The aim of this research work is to implement the already known Lewis acid-catalysed Ficini [2+2] cycloaddition from several publications, operated with ynamides, in order to synthetize novel cyclobutene compounds, which could present biological and pharmaceutical activity.

The final intent would be the synthesis, in a satisfying yield, of the new compound **46**. We projected to synthetize the chiral 2(5H)-furanone as the starting material, though the step-wise mechanism common in literature. The use of the ynamides is essential to achieve the objective and they will be synthetized with the simple protocol acknowledged in publications.



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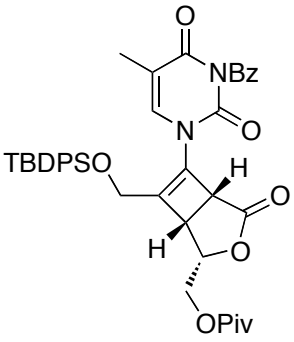


47

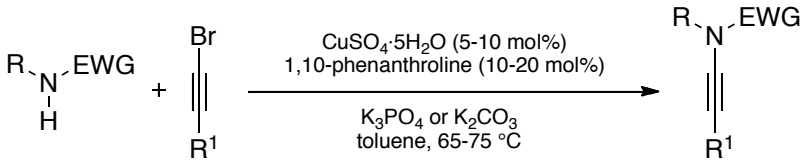
The present thesis is also focused on the development of a novel nucleoside cyclobutene analogue (**47**) by the same protocol. In order to proceed, the synthesis of the corresponding new ynamides will have to be implemented (from benzoyl thymine), adopting the protocol used for the synthesis of the other ynamides.

Finally, the following discussion will display the successful synthesis of a new cyclobutene derivate and will explain the problems found during the preparation of some of these compounds and, in particular, one collateral reaction which must be avoid in order to succeed in the syntheses.

5. RESULTS AND DISCUSSION

5.1 SYNTHESIS OF THE YNAMIDES

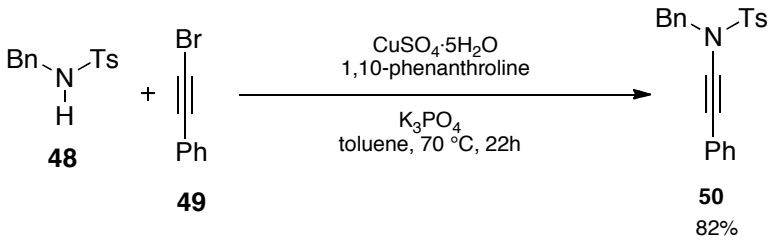
This project aims to prepare cyclobutene compounds using ynamides as an important and versatile reagent. In order to synthetize this requested functionalized alkynes, the second-generation protocol of Hung was adopted (Scheme 31).[57]



Scheme 31. *Copper-catalysed ynamide synthesis.*

The reaction proceeds with a Cu(I)-catalysed cross-coupling of alkyl bromide with the appropriate amide in the presence of either anhydrous K_3PO_4 or K_2CO_3 as the base and 1,10-phenanthroline.

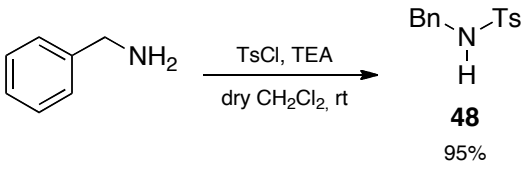
5.1.1 Synthesis of N-Benzyl-4-methyl-N-(phenylethynyl)benzenesulfonamide (50)



Scheme 32. *Synthesis of N-Benzyl-4-methyl-N-(phenylethynyl)benzenesulfonamide (50).*

N-benzyl-4-methylbenzenesulfonamide (**48**) is the starting amide to prepare *N*-benzyl-4-methyl-*N*-(phenylethynyl)benzenesulfonamide (**50**). The amount of the solvent was estimated in order to have a final 1M concentration based on **48**. The reaction was monitored by TLC and afforded the desired product in good yield (82%), after purification by column chromatography (eluent hexane-EtOAc 8:1).

The synthesis of the amide **48** was carried out as illustrated in Scheme 33.[58]

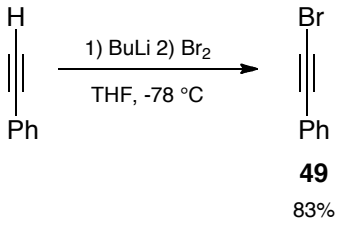


Scheme 33. *Synthesis of N-benzyl-4-methylbenzenesulfonamide (48).*

The use of the commercially available triethylamine benzylamine and tosyl chloride in dry dichloromethane at room temperature furnished **48** in good spectroscopic yields. The original

protocol[58] describes the purification of the desired compounds by crystallization from ethyl acetate and hexane to obtain the white solid, but in our hands the procedure failed to afford any crystalline material. For this reason, we decided to purify the crude by column chromatography (eluent hexane-diethyl ether 3:2), which afforded the desired product in excellent yield.[59]

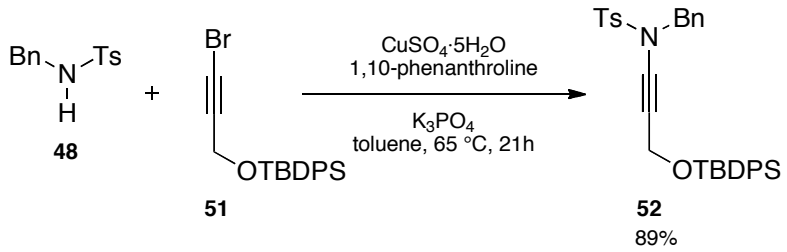
The (bromoethynyl)benzene (**49**) was obtained from the commercial available phenylacetylene with *n*-BuLi and Br_2 at -78 °C in THF (Scheme 34).[60]



Scheme 34. *Synthesis of (bromoethynyl)benzene (49).*

The purification of this product required a simple extractive aqueous work-up, furnishing the product in high grade of purity in 83% yield.

5.1.2 Synthesis of N-benzyl-N-{3-[(tert-butyldiphenylsilyl)oxy]prop-1-ynyl}-4-methylbenzenesulfonamide (52)

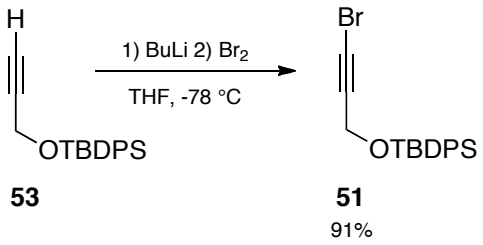


Scheme 35. *Synthesis of N-benzyl-N-{3-[(tert-butyldiphenylsilyl)oxy]prop-1-ynyl}-4-methylbenzenesulfonamide (52).*

The preparation of substrate **52** was accomplished according to the general procedure employed previously with **50,** although a lower concentration (0.66M) was indicated by the authors.[57] The reaction was checked by TLC to afford the product after purification by column chromatography (eluent hexane-EtOAc 8:1) in 89% yield.

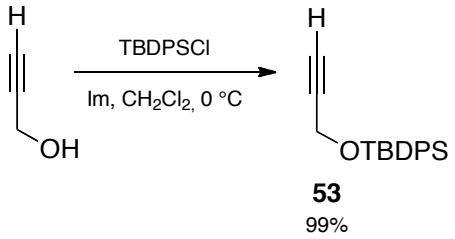
The amide **48** was synthetized through the same protocol mentioned in 5.1.1 (Scheme 33).

The bromoalkyne in this case is [(3-bromoprop-2-yn-1-yl)oxy](*tert*-butyl)diphenylsilane (**51**) synthetized as the previous (bromoethynyl)benzene (**49**) (Scheme 36) in 91% yield.[60]



Scheme 36. *Synthesis of [(3-bromoprop-2-yn-1-yl)oxy](tert-butyl)diphenylsilane (51).*

The protected propargyl alcohol **53** was obtained as reported in Scheme 37,[61] from *tert*-butyldiphenylchlorosilane and propargyl alcohol, with imidazole in dry dichloromethane.

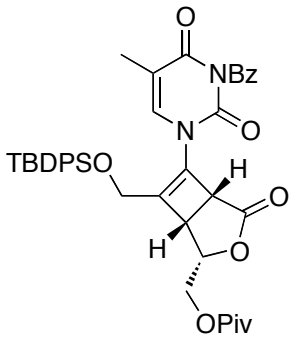


Scheme 37. *Synthesis of 3-tert-butyldiphenylsilyloxy-1-propyne (53).*

The reaction is nearly quantitative and the product does not require any further purification after usual work-up.

5.1.3 Attempted synthesis of 3-benzoyl-1-{3-[(tert-butyldiphenylsilyl)oxy]prop-1-yn-1-yl}-5-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione) (55)

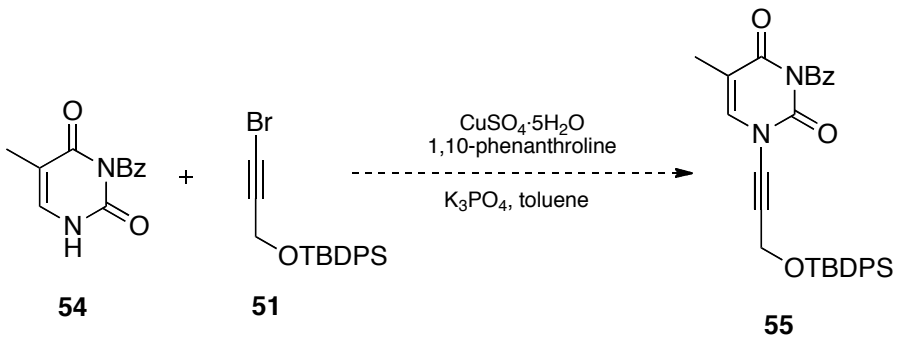
Another particular type of ynamide (**55**) was taken under consideration in order to try to synthetize the new cyclobutene nucleoside analogue **47** (Figure 5)



47

Figure 5. *Cyclobutene nucleoside analogue 47.*

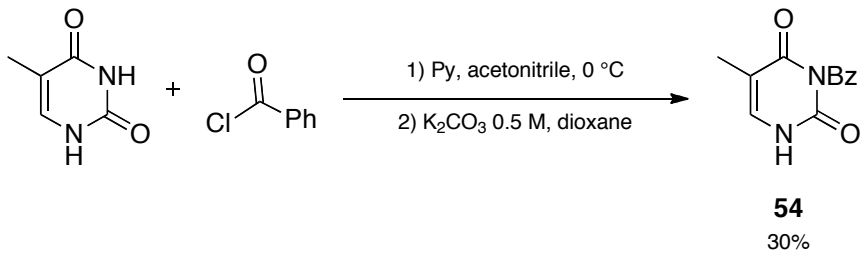
The same protocol aforementioned was followed for the preparation of the ynamide **55** from the bromoalkyne **51** with N^3-benzoylthymine (**54**) (Scheme 38).



54 **51** **55**

Scheme 38. *Synthesis of N^3-benzoylthymine (55).*

The required **54** was prepared by dibenzoylation of thymine at N^1 and N^3 positions, followed by selective deprotonation with a weak base (Scheme 39).[62]



Scheme 39. *Synthesis of N^3-benzoylthymine (54).*

The compound was obtained in 30% yield after crystallization from aqueous CH_3CN.

The synthesis of the new ynamides **55** was attempted with either 1M or 0.33M N^3-benzoylthymine (**54**) solutions. Unfortunately, all the crudes of reaction showed complex mixture of unknown products by NMR analysis.

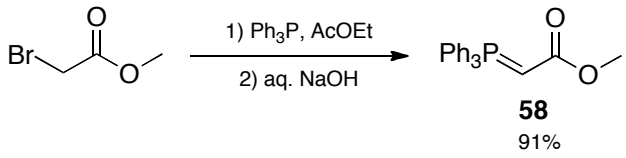
5.2 SYNTHESIS OF THE CYCLO-OLEFINE

As specified in the introduction, the project focuses on the 2(5H)-furanone substrate since it is an excellent starting material for diastereoselective synthesis of many biological and natural compounds.

5.2.1 Synthesis of (2S)-2,2-Dimethyl-propionic acid 5-oxo-2,5-dihydro-furan-2-yl methyl ester (37)

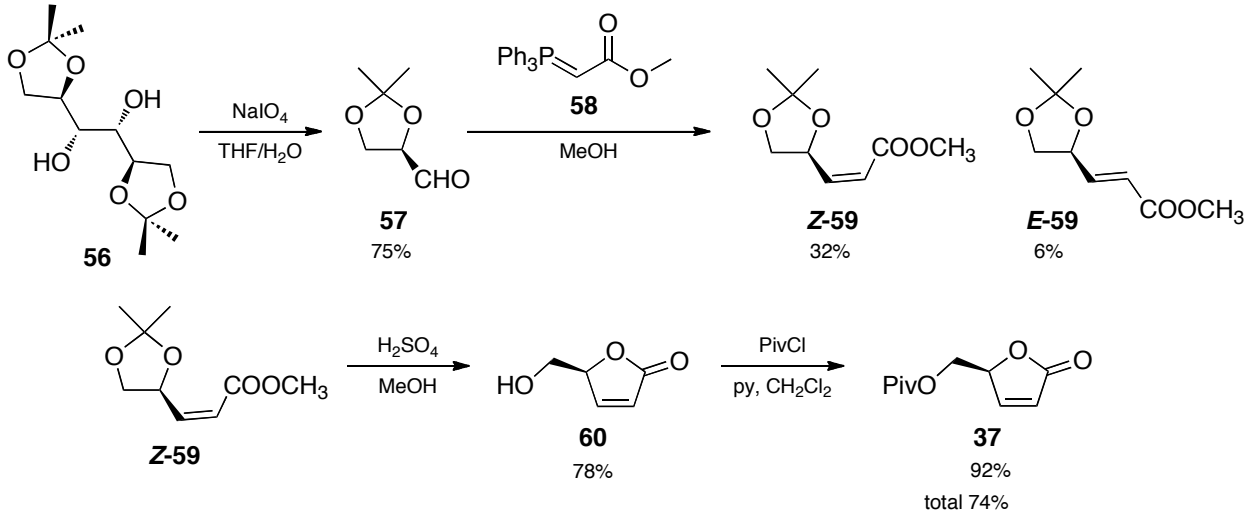
Phosphorane **58**, necessary for the synthesis of **37**, was synthetized by the treatment of methylbromoacetate in ethyl acetate to furnish the solid triphenylphosphonium bromide, which,

after filtration, was deprotonated with sodium hydroxide to give the desired **58** (Scheme 41) with 91% yield in a grade of purity sufficient for the next steps.[63]



Scheme 40. *Synthesis of [(methoxycarbonyl)methylene]triphenylphosphorane (58).*

The *O*-substituted 2(5H)-furanone **37** was synthesised from the commercial 1,2:5,6-di-*O*-isopropylidiene-D-mannitol (**56**) as described by Mann and co-workers (Scheme 40).[64]



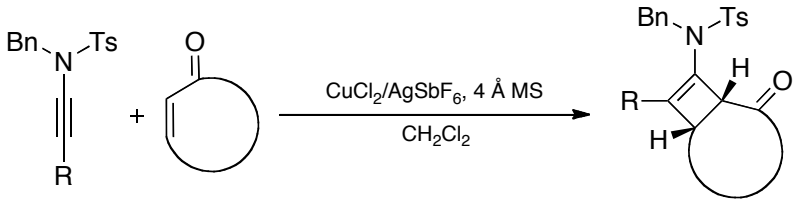
Scheme 41. *Synthesis of (2S)-2,2-dimethyl-propionic acid 5-oxo-2,5-dihydro-furan-2-ylmethyl ester (6).*

The synthesis starts with a periodate cleavage of **56** at room temperature in a 10:1 THF/H_2O mixture as the solvent. The afforded **57** reacts – through Wittig conditions – with

[(methoxycarbonyl)methylene]triphenylphosphorane (**58**) in methanol at 0 °C, to yield 84:16 mixture of ***Z*-59** and ***E*-59**, which can be easily separated by column chromatography (hexane-diethyl ether 3:1). Subsequently, the (*Z*)-isomer is treated with sulphuric acid in methanol producing (5*S*)-5-hydroxymethyl-5*H*-furan-2-one (**60**). The final protection with the pivaloyl group affords the final product with 74% overall yield (from **56**).

5.3 LEWIS ACID-MEDIATED CYCLOADDITIONS

[2+2] Cycloadditions require a stepwise mechanism in order to proceed correctly, since a concerted pathway is forbidden by the Woodward-Hoffmann rules. The Ficini [2+2] cycloadditions is an excellent reaction in order to synthetize the cyclobutene compounds. The synthesis of the desired cyclobutenes was carried out following the protocol of Hsung and co-workers (Scheme 42).[55]



Scheme 42. *Lewis acid-catalysed Ficini reaction.*

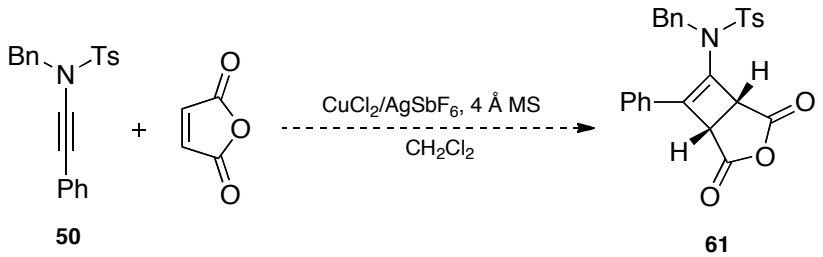
The Lewis acid must not contain metals such as Sn, Mg, Al, In, B, Ti and Si, as well as OTf as the counteranion, in order to eliminate the possibility of the hydro-halogenations of the ynamide as the competitive reaction.[55, 65] $CuCl_2$ and $AgSbF_6$ are considered, from previous studies, the

most suitable catalysts (Scheme 28), which minimize the hydro-halogenation side-reaction. [55] Ficini has also reported the modest *syn*-selectivity of the reaction.[66]

The replacement of ynamines with ynamides, decrease the reactivity of the triple bond, according to the lowered electron density of the alkyne operated by the electron-withdrawing group. In such circumstance, a thermal reaction is inhibited, in favour of a catalytic one.[56]

The tosyl group has been the selected electron-withdrawing group. Thus, the nitrogen pair is less delocalized into the alkyne and the nucleophilicity is increased over simple ymines (according to what stated by Hsung).[55, 67]

5.3.1 Attempted synthesis of (1S,5R)- N-benzyl-N-tosyl-6-amino-7-phenyl-3-oxabicyclo [3.2.0]hept-6-ene-2,4-dione (61)

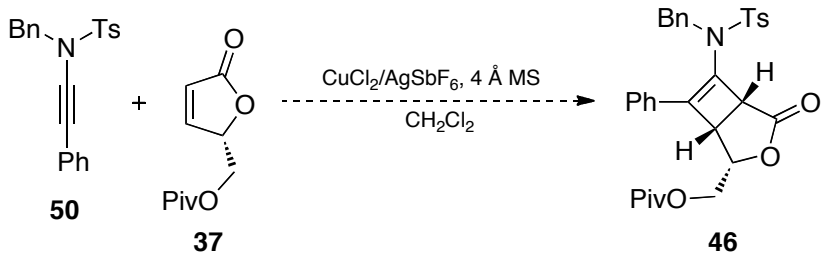


Scheme 43. *Synthesis of (1S,5R)- N-benzyl-N-tosyl-6-amino-7-phenyl-3-oxabicyclo[3.2.0]hept-6-ene-2,4-dione (61)*

The reaction starts with the activation of the bimetallic catalysts (1 h) and proceeds with the addition via a syringe pump during one hour of the reagents mixture. Subsequently the reaction is monitored by TLC, which finally displayed complete consumption of the ynamide. On the other hand, the major compound purified by chromatography displayed no diagnostic ^{1}H NMR resonance of the desired product. Further investigation by GC-MS showed an *m/z* =379, which correspond to the hydrated alkyne.

5.3.2 Attempted synthesis of [(1S,2S,5R)-N-benzyl-N-tosyl-6-amino-4-oxo-7-phenyl-3-oxabicyclo [3.2.0]hept-6-en-2-yl]methyl-2,2-dimethylpropanoate] (46)

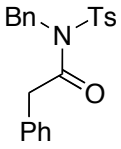
After the unsuccessful aforementioned synthesis, we tested the reactivity of ynamide **50** with a slightly less electron poor alkene: the chiral *O*-substituted 2(5H)-furanone **37** (Scheme 44).



Scheme 44. *Synthesis of [(1S,2S,5R)-N-benzyl-N-tosyl-6-amino-4-oxo-7-phenyl-3-oxabicyclo[3.2.0]hept-6-en-2-yl] methyl-2,2-dimethylpropanoate] (46)*

Even in this case, no diagnostic resonances of the desired product were displayed, concomitantly with the presence in ^{1}H NMR spectra of the same diagnostic resonances of the aforementioned hydrated compound. This evidence suggests a competitive reaction concerning only the common ynamide **50**.

Further investigation enabled us to attribute the synthetized product as *N*-benzyl-*N*-[(4-methylbenzene)sulfonyl]-2-phenylacetamide (**62**) (Figure 6), resulting from the hydration of ynamide **50**.

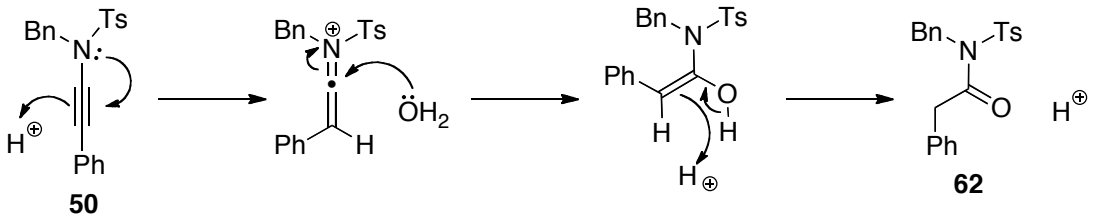


62

Figure 6. *N-benzyl-N-[(4-methylbenzene)sulfonyl]-2-phenylacetamide (62).*

The enamide **62** matches the molecular weight of the GC-MS executed for the compound **61**, confirming the first hypothesis. Moreover, this structure easily explains the singlet resonating at 3.9 ppm, attributable to the methylen group in alpha to the carbonyl group of the amide moiety. The presence of this functional group is confirmed by the resonance at 171.2 ppm in ^{13}C NMR spectrum.

We can assume that adventitious water is the responsible for the hydration of the alkyne. The proposed mechanism of this reaction is showed in Scheme 45.[68]

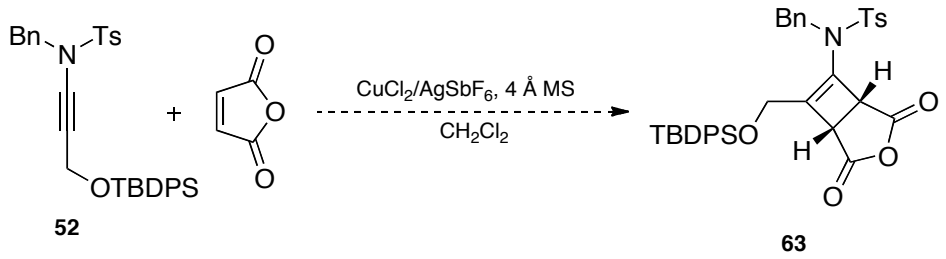


Scheme 45. *Proposal mechanism.*

The ynamide might be either protonated or coordinated with a Lewis acid in order to be attacked by the water to form the undesired amide **62**.

The presence of water in the solvent used or from reagents may have been the cause of the antagonistic reaction.

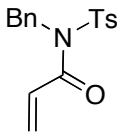
5.3.3 Attempted synthesis of (1S,5R)-N-benzyl-N-tosyl-6-amino-7-{[(tert-butyldiphenylsilyl)oxy] methyl}-3-oxabicyclo[3.2.0]hept-6-ene-2,4-dione (63)



Scheme 46. *Synthesis of (1S,5R)-N-benzyl-N-tosyl-6-amino-7-{[(tert-butyldiphenylsilyl)oxy]methyl}-3-oxabicyclo[3.2.0]hept-6-ene-2,4-dione (63).*

Concurrently with the aforementioned reactions, the reaction between ynamide **52** and maleic anhydride was tested. The outcome of the reaction was possibly more surprising than the previous cases. Indeed, ^{1}H-NMR of the purified main compound displayed no diagnostic resonances of the desired product, concomitantly with the presence of three resonances attributable to a vinyl moiety, and the absence of the *t*-Bu resonance of the TBDPS group.

Full NMR characterisation assigned the structure as *N*-benzyl-*N*-[(4-methylbenzene)sulfonyl]prop-2-enamide (**64**) (Figure 7).

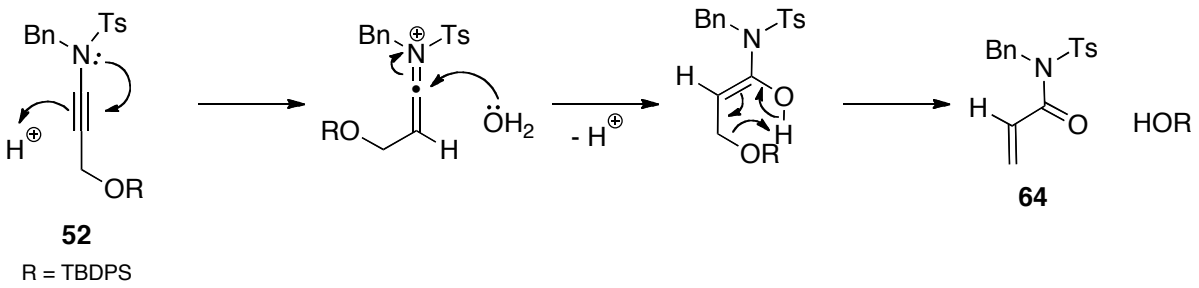


64

Figure 7. *N-benzyl-N-[(4-methylbenzene)sulfonyl]prop-2-enamide (64).*

This compound is nearly related to the aforementioned undesired product (**62**), except for the absence of the phenyl group.

In this case the mechanism of hydration results more complicated, indeed the substituent OTBDPS is not present in the final product. A possible similar reaction was reported by other authors.[69] The more likely mechanism is outlined in Scheme 47.



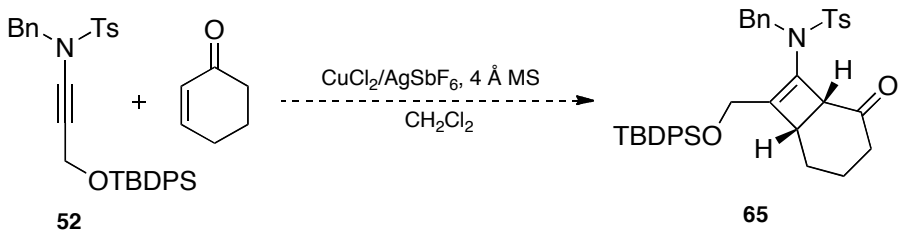
52
R = TBDPS

Scheme 47. *Proposal mechanism.*

In our hypothesis the proton (or a Lewis acid) coordinates the ynamide affording the ethenylidenazanium, which is suitable for a nucleophilic attack by the water. The intramolecular transposition of the hydrogen of the enol to the silyl ether causes the elimination of the silanol, concomitantly with the tautomerization of the enol.

In order to better understand the limit of the reaction, we tried it with cyclohexenone, which is less electron poor (compared to maleic anhydride) and less hindered (compared to (2*S*)-2,2-dimethyl-propionic acid 5-oxo-2,5-dihydro-furan-2-ylmethyl ester (**37**)).

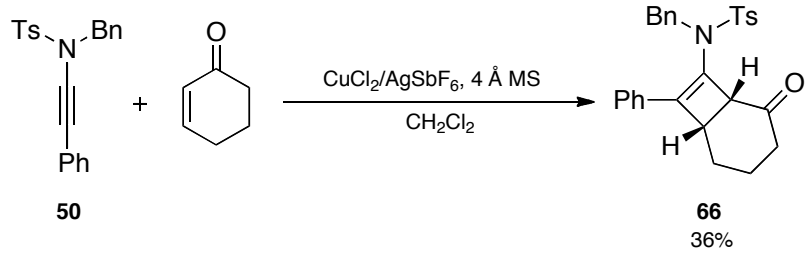
5.3.4 Attempted synthesis of (1R,6S)-N-benzyl-N-tosyl-8-amino-7-{[(tert-butyldiphenylsilyl)oxy] methyl}bicyclo[4.2.0]oct-7-en-2-one] (65)



Scheme 48. *Synthesis of (1R,6S)-N-benzyl-N-tosyl-8-amino-7-{[(tert-butyldiphenylsilyl)oxy]methyl}bicyclo[4.2.0]oct-7-en-2-one] (65)*

The reaction did not afford the desired compound. In fact, one more time ^{1}H-NMR analysis showed resonances attributed to the hydrated compound **64**, as mentioned before.

5.3.5 Synthesis of (1R,6S)-N-Benzyl-N-tosyl-8-amino-7-phenylbicyclo[4.2.0]oct-7-en-2-one (66)



50 **66** 36%

Scheme 49. *Synthesis of (1R,6S)-N-Benzyl-N-tosyl-8-amino-7-phenylbicyclo[4.2.0]oct-7-en-2-one (66).*

The Ficini reaction between ynamide **50** and cyclohexenone furnished a crude displaying the expected signals for the 2+2-cycloadduct, concomitantly with minor amounts of hydrated by-product **62**. After column chromatography purification (gradient eluent EtOAc in hexane), the desired cyclobutene **66** was obtained in a satisfying 36% yield.

The novel compound has been fully characterized by ^{1}H and ^{13}C-NMR as well as HSQC. Proton NMR displayed a number of signals in accordance with a 1:1 adduct between the two substrates, as confirmed by the number of carbon resonances. The two signals of the vinyl hydrogens of cyclohexenone were replaced by two isochronous (as proved by HSQC) resonances of the two hydrogens of the cyclobutene moiety, which can be observed as a singlet resonating at 3.32 ppm. The two carbons of the starting alkyne were replaced by two signals resonating at lower field.

6. CONCLUSIONS AND FUTURE PROSPECTS

A new type of ynamide, with a nucleoside substituent, has been considered in order to try to synthetize a new nucleoside analogue. This ynamide had not been produced before and we tried to synthetize it implementing the protocol previously adopted. The next step could be to try to prepare this novel ynamide following other procedure from the literature. For instance, a new protocol, designed by Jiao and co workers, has already been successfully applied with similar substrate.[70] The protocol consists in a Cu-catalysed aerobic oxidative amidation of propiolic acids via decarboxylation under air. The study of the reaction in different condition and with different catalysts can also be useful to achieve the objective.

The synthesis of novel cyclobutene derivates was investigated. It was possible to establish that electron-poor (maleic anhydride) or hindered ((2*S*)-2,2-Dimethyl-propionic acid 5-oxo-2,5-dihydro-furan-2-ylmethyl ester (**37**)) alkenes are not fast enough to react with electron poor ynamides. Under these conditions the competitive degradation of the alkyne via hydration is much more efficient. The failure in the procedure for the synthesis of these cyclobutenes brought us to investigate the nature of the common undesirable products. We discovered and characterized these by-products and we also proposed the mechanism, which cause the collateral reaction. On the contrary, when scarcely hindered and less electron poor substrates were employed it was possible to obtain the desired cycloadduct. A possible breakthrough in this research could be the use of more stringent protocols in the drying of the reagents and the use of the latter in a glove-box.

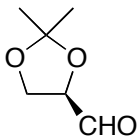
7. EXPERIMENTAL SECTION

7.1 GENERAL METHODS

Solvents were purified according standard methods before use. All the reagents were of commercial quality and used without any further purification. Reactions, when necessary, were carried out under argon atmosphere and monitored by TLC analysis. Flash chromatography was performed on silica according to methodologies and instrumentations described by W. C. Still, M. Kahn, A. Mitra *J. Org. Chem.* **1978**, *43*, 2923. ^{1}H NMR and ^{13}C NMR spectra were recorded on a BRUKER 250 or BRUKER 400 operating at 250 MHz and 400 MHz respectively. Chemical shifts (δ) are reported in parts per million downfield from TMS, coupling constants (*J*) are reported in Hertz and refer to apparent peak multiplicity. Mass spectra were obtained using gas chromatograph 6890, Agilent Technologies and mass spectrometer 5973, Hewlett-Packard.

7.2 EXPERIMENTAL SECTION

2,3-*O*-Isopropylidene-D-gliceraldehyde (57)



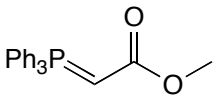
57

To a solution of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**1**) (12.02 g, 45.8 mmol) in THF (100 ml), was slowly added a suspension of sodium periodate (10.78 g, 50.41 mmol) in a mixture of THF (37 ml) and H_2O (17 ml). The resulting suspension was stirred for 2 hrs at room temperature. Afterwards, diethyl ether (170 ml) was added and the mixture was stirred for 15 min before the filtration of the white solid formed. The solvents were removed under reduced pressure and the resulting aqueous solution was extracted with dichloromethane (2x25 ml). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was carefully removed under reduced pressure avoiding the loss of the

highly volatile aldehyde, to obtain a colourless oil (9.75 g, 74.9 mmol, 75% yield) pure enough for the next step.

^{1}H NMR (250 MHz, $CDCl_3$) δ: 9.70 (d, *J*=1.8 Hz, 1H), 4.37 (ddd, *J*=7.4, 4.8 and1.8 Hz, 1H), 4.15 (dd, *J*=8.9 and 7.4 Hz, 1H), 4.08 (dd, *J*=8.9 and 4.8 Hz, 1H), 1.46 (s, 3H), 1.39 (s, 3H).

[(Methoxycarbonyl)methylene]triphenylphosphorane (58)



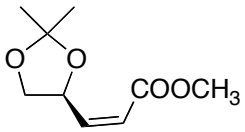
58

A solution of methylbromoacetate (10.88 ml, 114.9 mmol) in ethyl acetate (50 ml) was added to a solution of triphenylphosphane (30.14 g, 114.9 mmol) in ethyl acetate (200 ml). The solution was stirred overnight. The white precipitate was filtered through a fritted filter funnel, washed with diethyl ether (2x25 ml) and dried under reduced pressure.

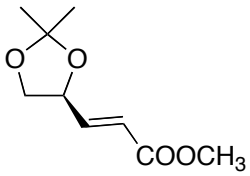
In a separation funnel, the so-far obtained solid was suspended in a two-layer system of dichloromethane (300 ml) and aqueous 1M NaOH (182.5 ml, 187.5 mmol) and it was vigorously shaken until all the solid was vanished. Organic layer was separated and the aqueous layer was extracted twice with dichloromethane (50 ml). The combined organic layers were washed with a saturated solution of NaCl (50 ml) and dried over $MgSO_4$. The solvent was evaporated to yield 34.95 g (104.53 mmol, 91% yield) of a white solid.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.40-7.80 (m, 15H), 3.52 (75%) (3H), 2.90 (25%).

_Z_-Methyl-3-[(4_S_)-(2',2'-dimethyl-1',3'-dioxolan-4'yl)]-2-propenoate (_Z_ -59) and _E_-Methyl-3-[(4_S_)-(2',2'-dimethyl-1',3'-dioxolan-4'yl)]-2-propenoate (_E_-59)



Z-59

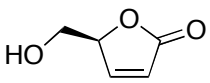


E-59

To an ice-cooled solution of 2,3-*O*-isopropylidene-D-gliceraldehyde (**57**) (9.74 g, 74.9 mmol) in 75 ml of methanol, solid [(methoxycarbonyl)methylene]-triphenylphosphorane (**58**) (25.04 g, 74.9 mmol) was added in small portions. The mixture was stirred for 2 hours, allowing to warm to room temperature. The solvent was removed under reduced pressure and the resulting white solid was extracted with dichloromethane. The excess of triphenylphosphine oxide was removed eluting the mixture through a short pad of silica-gel (eluent hexane-diethyl ether 3:1). Purification by column chromatography (hexane-diethyl ether 3:1) afforded *Z*-**59** (4.03 g, 23.68 mmol, 32% yield) and *E*-**59** (0.78 g, 4.58 mmol, 6% yield) as oils.

Z-59 ^{1}H NMR (250 MHz, $CDCl_3$) δ: 6.37 (dd, *J*=11.5 and 6.8 Hz, 1H), 5.85 (dd, *J*=11.6 and 1.9 Hz, 1H), 5.49 (dddd, *J*=13.5, 6.8 and 1.8 Hz, 1H), 4.37 (dd, *J*=9.0 and 7.0 Hz, 1H), 3.72 (s, 3H), 3.62 (dd, *J*=9.0 and 7.0 Hz, 1H), 1.45 (s, 3H), 1.39 (s, 3H).

(5_S_)-5-Hydroxymethyl-5_H_-furan-2-one (60)

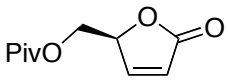


60

A 30% aqueous solution of H_2SO_4 (0.11 ml) was added to a solution of (2*Z*)-3-[(4*S*)-(2',2'-dimethyl-1',3'-dioxolan-4'yl)]-2-propenoate (*Z*-**59**) (4.34 g, 25.4 mmol) in methanol (13 ml). The reaction mixture was stirred for 3 hours at room temperature. After TLC had proved the end of the reaction, the solvent was removed under reduced pressure. The crude was purified by column chromatography (eluent hexane-ethyl acetate 1:30) to afford the title compound as a white solid (2.27 g, 19.9 mmol, 78% yield).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.46 (dd, *J*=5.80 and 1.5 Hz, 1H), 6.19 (dd, *J*=5.8 and 2.2 Hz, 1H), 5.13 (dddd, *J*=5.1, 3.6, 2.2 and 1.5 Hz, 1H), 3.98 (ddd, *J*=12.4, 6.9 and 3.6 Hz), 3.77 (ddd, *J*=12.4, 6.9 and 5.1 Hz, 1H), 2.13 (dd, *J*=6.9 and 6.9 Hz, 1H).

(2*S*)-2,2-Dimethyl-propionic acid 5-oxo-2,5-dihydro-furan-2-ylmethyl ester (37)

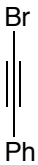


37

To a solution of (5*S*)-5-hydroxymethyl-5*H*-furan-2-one (**60**) (2.27 g, 19.9 mmol) and pyridine (3.22 ml, 39.86 mmol) in dry dichloromethane (40 ml) cooled to 0 °C, pivaloyl chloride (4.90 ml, 39.9 mmol) was added dropwise and the mixture was stirred overnight at room temperature. Water (10 ml) was added and the two phases were separated. The organic layer was washed with 5% aq. HCl (2x28 ml), saturated aq. $NaHCO_3$ (2x28 ml), brine (1x28 ml) and it was dried over Na_2SO_4 to afford **37** (3.67, 18.4 mmol, 92% yield) as a colourless oil.

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.44 (dd, *J*=5.8 and 2.0 Hz, 1H), 6.22 (dd, *J*=5.8 and 2.0 Hz, 1H), 5.28-5.23 (m, 1H), 4.40 (d, *J*=4.5 Hz, 2H) 1.20 (s, 9H).

(Bromoethynyl)benzene (49)



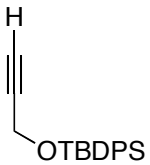
49

A solution of phenylacetylene (5.5 ml, 50.0 mmol) in dry THF (150 ml) was cooled to -78 °C in inert atmosphere and a solution 2.5 M of *n*-BuLi in hexane (21.0 ml, 52.2 mmol) was added. The mixture was stirred for 45 minutes and Br_2 (3.0 ml, 55 mmol) was added dropwise. The mixture was stirred at the same temperature for 45 minutes, and it was left to rise to rt. Water was added, the two phases were separated, and the aqueous layer was further extracted with hexane. Combined organic layers were washed with 10% aqueous $Na_2S_2O_3$, dried

over Na_2SO_4 and concentrated, to afford a crude material, which was purified by column chromatography (eluent hexane) to afford **49** (7.53 g,41.6 mmol, 83% yield) as an oil.

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.50-7.33 (m, 5H).

3-*tert*-Butyldiphenylsilyloxy-1-propyne (53)

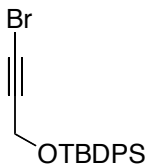


53

A solution of propargyl alcohol (5.20 ml, 89.2 mmol), *t*-$BuPh_2SiCl$ (25.16 ml, 98.1 mmol) and imidazole (6.68 g, 98.11 mmol) in dry dichloromethane (50 ml) was stirred at room temperature for 14 h. The mixture was diluted in diethyl ether (50 ml) and washed with brine (2x50 ml). The organic layer was dried over Na_2SO_4, and evaporated under reduced pressure to afford **53** (26.12 g, 88.7, 99% yield) as a yellow single crystal.

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.74-7.71 (m, 4H), 7.46-7.39 (m, 6H), 4.32 (s, 2H), 2.41 (s, 1H), 1.09 (s, 9H).

[(3-bromoprop-2-yn-1-yl)oxy](*tert*-butyl)diphenylsilane (51)



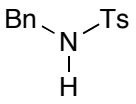
51

To a solution of 3-*tert*-butyldimethylsilyloxy-1-propyne (**53**) (10.00 g, 34.0 mmol) in dry THF (150 ml), cooled to -78 °C in inert atmosphere a 2.5M solution of *n*-BuLi in hexane (14.3 ml, 35.7 mmol) was added. After stirring for 45 minutes, Br_2 (2.0 ml, 37.4 mmol) was added dropwise followed by stirring for further 45 minutes. The reaction was left to rise to room temperature and it was poured into water. The two phases were separated, the aqueous layer was extracted with hexane and the combined organic phases were washed with 10% aq. $Na_2S_2O_3$, dried over Na_2SO_4 and filtered. The solvent was removed under

reduced pressure and the product was purified by column chromatography (eluent hexane) to afford **51** (11.54 g, 30.9 mmol, 91% yield) as an oil.

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.74-7.70 (m, 4H), 7.47-7.40 (m, 6H), 4.32 (2, 2H), 1.09 (s, 9H).

***N*-Benzyl-4-methylbenzenesulfonamide (48)**

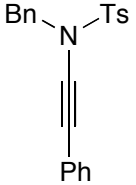


48

To a solution of benzylamine (13.1 ml, 119.6 mmol) and triethylamine (16.67 ml, 79.7 mmol) in dry dichloromethane (120 ml) cooled 0 °C was slowly added a solution of tosyl chloride (15.2 g, 79.7 mmol) in dry dichloromethane (80 ml). The resulting mixture was stirred at room temperature overnight. The solvent was removed and the resulting residue was taken-up with ethyl acetate. The mixture was washed with an aq. 1M HCl (2x25ml), brine (2x25ml) and it was dried over Na_2SO_4. The solvent was evaporated at reduced pressure affording a white solid, which was purified by column chromatography (eluent hexane-diethyl ether 3:2) to afford the desired compounds as a colourless solid (19.88 g, 76.1 mmol, 95% yield).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.78 (d, *J*=8.5 Hz, 2H), 7.36-7.20 (m, 7H), 4.61 (br s, 1H), 4.14 (d, *J*=6.3 Hz, 2H), 2.47 (s, 3H).

***N*-Benzyl-4-methyl-*N*-(phenylethynyl)benzenesulfonamide (50)**



50

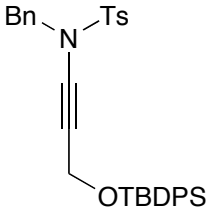
N-benzyl-4-methylbenzenesulfonamide **(48)** (0.30 g, 1.2 mmol), $CuSO_4 \cdot 5H_2O$ (0.03 g, 0.1 mmol), 1,10-phenanthroline (41.37 mg, 0.3 mmol) and K_3PO_4 (0.49 g, 2.3 mmol) were mixed together under an atmosphere of argon and heated to 70 °C in dry toluene* (some 1 ml). A solution of (bromoethynyl)benzene **(49)** (0.29 g, 1.3

mmol) in dry toluene* (some 0.15 ml) was added followed by stirring for 22 hours. The reaction mixture was successively cooled to room temperature, diluted with ethyl acetate and filtered through a pad of celite and concentrated under reduced pressure. After column chromatography (eluent hexane-EtOAc 8:1) the title compound was obtained as a yellow solid (0.34 g, 0.94 mmol, 82% yield).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.82 (d, *J*=8.3 Hz, 2H), 7.36-7.34 (m, 7H), 4.61 (s, 2H), 2.47 (s, 3H).

(*) – 1 M final solution based on **49**.

***N*-benzyl-*N*-{3-[(tert-butyldiphenylsilyl)oxy]prop-1-ynyl}-4-methylbenzenesulfonamide (52)**



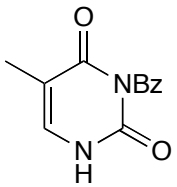
52

N-benzyl-4-methylbenzenesulfonamide **(48)** (0.30 g, 1.2 mmol), $CuSO_4 \cdot 5H_2O$ (0.03 g, 0.1 mmol), 1,10-phenanthroline (41.37 mg, 0.3 mmol) and K_3PO_4 (0.49 g, 2.3 mmol) were mixed together under an atmosphere of argon and heated to 65 °C in dry toluene* (some 1 ml). A solution of (3-bromoprop-2-ynyloxy)(*tert*-butyl)diphenylsilane **(51)** (0.29 g, 2 mmol) in in dry toluene* (some 0.5 ml) was added followed by stirring for 21 hours. The reaction mixture was successively cooled to room temperature, diluted with chloroform and filtered through a pad of celite and concentrated under reduced pressure. After column chromatography (eluent hexane-EtOAc 95:5) the title compound was obtained as a colourless oil (0.57 g, 1.0 mmol, 89% yield).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.77-7.72 (d, *J*=8.3 Hz, 2H), 7.67-7.64 (m, 4H), 7.44-7.40 (m, 2H), 7.38-7.35 (m, 4H), 7.28-7.20 (m, 7H), 4.42 (s, 2H), 4.39 (s, 2H), 2.44 (s, 3H), 1.03 (s, 9H).

(*) – 0.66 M final solution based on **51**.

3-Benzoyl-5-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (N^3-benzoylthymine) (54)

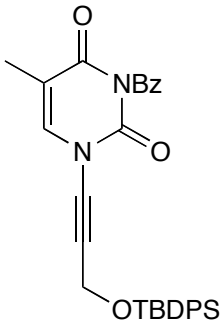


54

To a solution of thymine (3.00 g, 23.8 mmol) in dry acetonitrile (24 ml), anhydrous pyridine (9.5 ml, 117.8 mmol) was added, and the mixture was cooled to 0 °C. Subsequently, benzoyl chloride (6.2 ml, 52.6 mmol) was added dropwise and the solution was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was partitioned between dichloromethane (120 ml) and water (120 ml). The organic phase was evaporated and the products was dissolved in a mixture of dioxane (50 ml) and a 0.5 M solution of K_2CO_3 (25 ml), and stirred for 30 minutes at room temperature. After the suspension was acidified to pH 5 by glacial acetic acid, the products were rotary concentrated and stirred with a saturated aq. $NaHCO_3$ solution. After 1 hour, the compound was filtered and washed with cold H_2O (2x12 ml) and, finally, crystallized from aqueous CH_3CN to afford **13** (1.67 g, 7.2 mmol, 30% yield).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.96 (dd, *J*=7.6 and 1.3 Hz, 2H), 7.72-7.66 (m, 1H), 7.57-7.50 (m, 2H), 1.96 (d, *J*=1.0 Hz, 3H).

3-benzoyl-1-{3-[(*tert*-butyldiphenylsilyl)oxy]prop-1-yn-1-yl}-5-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (55)



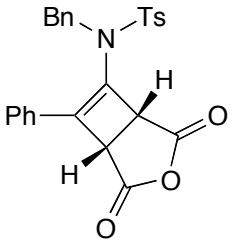
55

N^3-benzoylthymine, **(54)** (1.75 g, 4.7 mmol), $CuSO_4 \cdot 5H_2O$ (0.10 g, 0.40 mmol), 1,10-phenanthroline (0.14 g, 0.78 mmol) and K_3PO_4 (1.66 g, 7.8 mmol) were mixed together under an atmosphere of argon and heated to 65 °C in dry toluene* (some 1 ml). A solution of (3-bromoprop-2-ynyloxy)(*tert*-butyl)diphenylsilane **(51)** (1.75 g, 4.7 mmol) in in dry toluene* (some 0.35 ml) was added followed by stirring for 36 hours. The reaction mixture was successively cooled to room temperature, diluted with chloroform and filtered through a pad of

celite and concentrated under reduced pressure. ^{1}H NMR of the crude displayed no diagnostic resonances of the desired product. The reaction was tested also in more diluted conditions (0.33M final concentration), with similar results.

(*) – 1 M final solution based on **51**

(1*S*,5*R*)- *N*-benzyl-*N*-tosyl-6-amino-7-phenyl-3-oxabicyclo[3.2.0]hept-6-ene-2,4-dione (61)

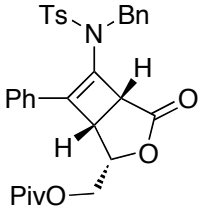


61

To a stirring suspension of $CuCl_2$ (3.72 mg, 0.28mmol) and 4Å MS (50.0 mg) in 4.6 ml of dry dichloromethane, AgSbF6 (28.6 mg, 0.83 mmol) was added, under an atmosphere of argon and in the dark at room temperature. After stirring for 1 hour, the catalyst mixture was cooled to -20 °C and a solution of *N*-benzyl-4-methyl-*N*-(phenylethynyl)benzenesulfonamide **(50)** (0.50 g, 1.4 mmol) and maleic anhydride (16.3 mg, 1.66 mmol) in dichloromethane (3.6 ml) was added over 1 hour via a syringe pump. The reaction was allowed to stirring for an additional hour post addition, phosphate buffer (pH 7, 1 ml) was added and the resulting mixture was extracted with ethyl acetate. The organic phase was washed with brine and dried by $MgSO_4$. Filtration and concentration under reduced pressure afforded the crude product, which was purified by column chromatography (eluent hexane-EtOAc 3:1) to afford 0.183 g (0.48 mmol, 35% yield) of *N*-benzyl-*N*-[(4-methylbenzene)sulfonyl]-2-phenylacetamide (**62**), resulting from the hydration of the starting material.

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.66 (d, *J*=8.5 Hz, 2H), 7.38-7.25 (m, 10H), 7.01 (dd, *J*=5.0 and 1.8 Hz, 2H), 5.10 (s, 2H), 3.90 (s, 2H), 2.46 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 171.2, 136.5, 136.4, 133.1, 129.65, 129.63, 129.62, 129.23, 129.22, 129.20, 128.65, 128.63, 128.61, 128.50, 128.48, 127.91, 127.90, 127.88, 127.7, 127.6, 127.1, 49.8, 42.8, 21.5.

[(1*S*,2*S*,5*R*)-*N*-benzyl-*N*-tosyl-6-amino-4-oxo-7-phenyl-3-oxabicyclo[3.2.0]hept-6-en-2-yl]methyl-2,2-dimethylpropanoate] (46)

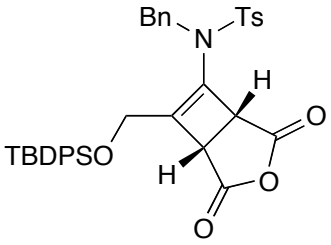


46

To a stirring suspension of $CuCl_2$ (3.72 mg, 0.28 mmol) and 4Å MS (50.0 mg) in 4.6 ml of dry dichloromethane, $AgSbF_6$ (28.7 mg, 0.83 mmol) was added, under an atmosphere of argon and in the dark at room temperature. After stirring for 1 hour, the catalyst mixture was cooled to -20 °C and a solution of *N*-benzyl-4-methyl-*N*-(phenylethynyl)benzenesulfonamide **(50)** (0.50 g, 1.38 mmol) and (*S*)-5-pivaloyloxymethyl-2(5H)-furanone **(37)** (0.33 g, 1.66 mmol) in dichloromethane (3.6 ml) was added over 1 hour via a syringe pump. The reaction was stirred for 30 minutes post addition, and, subsequently, phosphate buffer (pH 7, 1 ml) was added and the resulting mixture was extracted with ethyl acetate. The organic phase was washed with saturated NaCl solution and dried by $MgSO_4$. Filtration and concentration under reduced pressure afforded the crude product, which was purified by column chromatography (eluent hexane-EtOAc 3:1) to afford of *N*-benzyl-*N*-[(4-methylbenzene)sulfonyl]-2-phenylacetamide (**62**), resulting from the hydration of starting material.

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.66 (d, *J*=8.2 Hz, 2H), 7.42-7.23 (m, 10H), 6.98 (dd, 2H), 5.08 (s, 2H), 3.87 (s, 2H), 2.42 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 171.2, 136.5, 136.4, 133.1, 129.65, 129.63, 129.62, 129.23, 129.22, 129.20, 128.65, 128.63, 128.61, 128.50, 128.48, 127.91, 127.90, 127.88, 127.7, 127.6, 127.1, 49.8, 42.8, 21.5.

(1*S*,5*R*)-*N*-benzyl-*N*-tosyl-6-amino-7-{[(*tert*-butyldiphenylsilyl)oxy]methyl}-3-oxabicyclo[3.2.0]hept-6-ene-2,4-dione] (63)

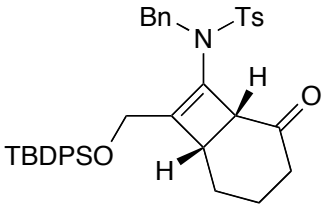


63

To a stirring suspension of $CuCl_2$ (0.75 mg, 0.06 mmol) and 4Å MS (10.0 mg) in 1 ml of dry dichloromethane, $AgSbF_6$ (5.8 mg, 0.83 mmol) was added, under an atmosphere of argon and in the dark at room temperature. After stirring for 1 hour, the catalyst mixture was cooled to 0 °C and a solution of *N*-benzyl-*N*-{3-[(tert-butyldiphenylsilyl)oxy]prop-1-ynyl}-4-methylbenzenesulfonamide **(52)** (15.4 Mg, 0.28 mmol) and maleic anhydride (3.3 Mg, 0.33 mmol) in dichloromethane (0.8 ml) was added over 1 hour via a syringe pump. The reaction was stirred for 30 minutes post addition, and, subsequently, phosphate buffer (pH 7, 0.2 ml) was added and the resulting mixture was extracted with ethyl acetate. The organic phase was washed with saturated NaCl solution and dried by $MgSO_4$. Filtration and concentration under reduced pressure afforded the crude product, which was purified by column chromatography (eluent hexane-EtOAc 3:1) to afford 0.071 g (0.22 mmol, 80% yield) of *N*-benzyl-*N*-[(4-methylbenzene)sulfonyl]prop-2-enamide (**64**), resulting from the hydration of starting material.

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.66 (d, *J*=8.3 Hz, 2H), 7.38-7.21 (m, 7H), 6.38 (dd, *J*=1.8 and 14.2 Hz, 1H), 5.74 (dd, *J*=1.8 and 10.5 Hz, 1H), 5.12 (s, 2H), 2.44 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 165.8, 144.9, 136.6, 136.5, 131.8, 129.7, 128.6 128.4, 127.9, 127.7, 49.4, 21.6.

(1*R*,6*S*)-*N*-benzyl-*N*-tosyl-8-amino-7-{[(*tert*-butyldiphenylsilyl)oxy]methyl}bicyclo[4.2.0] oct-7-en-2-one (65)

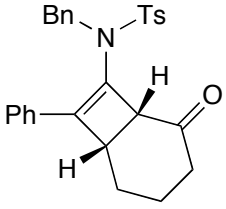


65

To a stirring suspension of $CuCl_2$ (0.71 mg, 0.28mmol) and 4Å MS (10.0 mg) in 1 ml of dry dichloromethane, AgSbF6 (5.5 mg, 0.16 mmol) was added, under an inert atmosphere and in the dark at room temperature. After stirring for 1 hour, the catalyst mixture was cooled to 0 °C and a solution of *N*-benzyl-*N*-{3-[(*tert*-butyldiphenylsilyl)oxy]prop-1-ynyl}-4-methylbenzenesulfonamide **(52)** (14.6 mg, 0.26 mmol) and 2-cyclohexen-1-one (3.0 mg, 0.32 mmol) in dichloromethane (0.8 ml) was added over 1 hour via a syringe pump. The reaction was allowed to stirring for an additional hour post addition and, afterwards, phosphate buffer (pH 7, 0.2 ml) was added and the resulting mixture was extracted with ethyl acetate. The organic phase was washed with brine and dried by $MgSO_4$. Filtration and concentration under reduced pressure afforded the crude product, which was purified by column chromatography (eluent hexane-EtOAc 3:1) to afford 0.054 g (0.14 mmol, 54% yield) of *N*-benzyl-*N*-[(4-methylbenzene)sulfonyl]prop-2-enamide (**64**), resulting from the hydration of starting material.

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.66 (d, *J*=8.5 Hz, 2H), 7.41-7.29 (m, 7H), 6.38 (dd, *J*=1.8 and 14.0 Hz, 1H), 5.74 (dd, *J*=1.8 and 10.5 Hz, 1H), 5.12 (s, 2H), 2.43 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 165.8, 144.9, 136.6, 136.5, 131.8, 129.7, 128.6 128.4, 127.9, 127.7, 49.4, 21.6.

(1*R*,6*S*)-*N*-Benzyl-*N*-tosyl-8-amino-7-phenylbicyclo[4.2.0]oct-7-en-2-one (66)



66

To a stirring suspension of $CuCl_2$ (4.06 mg, 0.30 mmol) and 4Å MS (50.0 mg) in 5 ml of dry dichloromethane, $AgSbF_6$ (31.2 mg, 0.91 mmol) was added under an atmosphere of argon and in the dark at room temperature.

After stirring for 1 hour, the catalyst mixture was cooled to -20 °C and a solution of *N*-benzyl-4-methyl-*N*-(phenylethynyl)benzenesulfonamide **(50)** (0.54 g, 1.5 mmol) and 2-cyclohexen-1-one (17.4 mg, 1.81 mmol) in dichloromethane (4 ml) was added over 1 hour via a syringe pump. The reaction was allowed to stirring for an additional 30 minutes post addition, phosphate buffer (pH 7, 1 ml) was added and the resulting mixture was extracted with ethyl acetate. The organic phase was washed with brine and dried by $MgSO_4$. Filtration and concentration under reduced pressure afforded the crude product, which was purified by column chromatography (gradient eluent EtOAc in hexane). 24.6 mg (0.58 mmol) of **14** were obtained, corresponding to 36% yield.

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.86 (d, *J*=8.5, 2H), 7.39-7.34 (m, 7H), 7.20-7.17 (m, 5H), 7.05-7.01 (m, 2H), 4.50 (dd, *J*=14.25 and 32.5 Hz, 2H), 3.32 (s, 2H), 2.48 (s, 3H), 2.26-1.93 (m, 3H), 1.67-1.48 (m, 4H). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 210.5, 144.5, 144.2, 136.2, 135.3, 132.0, 129.9, 128.8, 128.39, 128.34, 128.3, 127.9, 127.8, 127.2, 126.7, 55.3, 51.1, 40.4, 37.3, 24.8, 21.7, 17.3.

8. ACKNOWLEDGMENTS

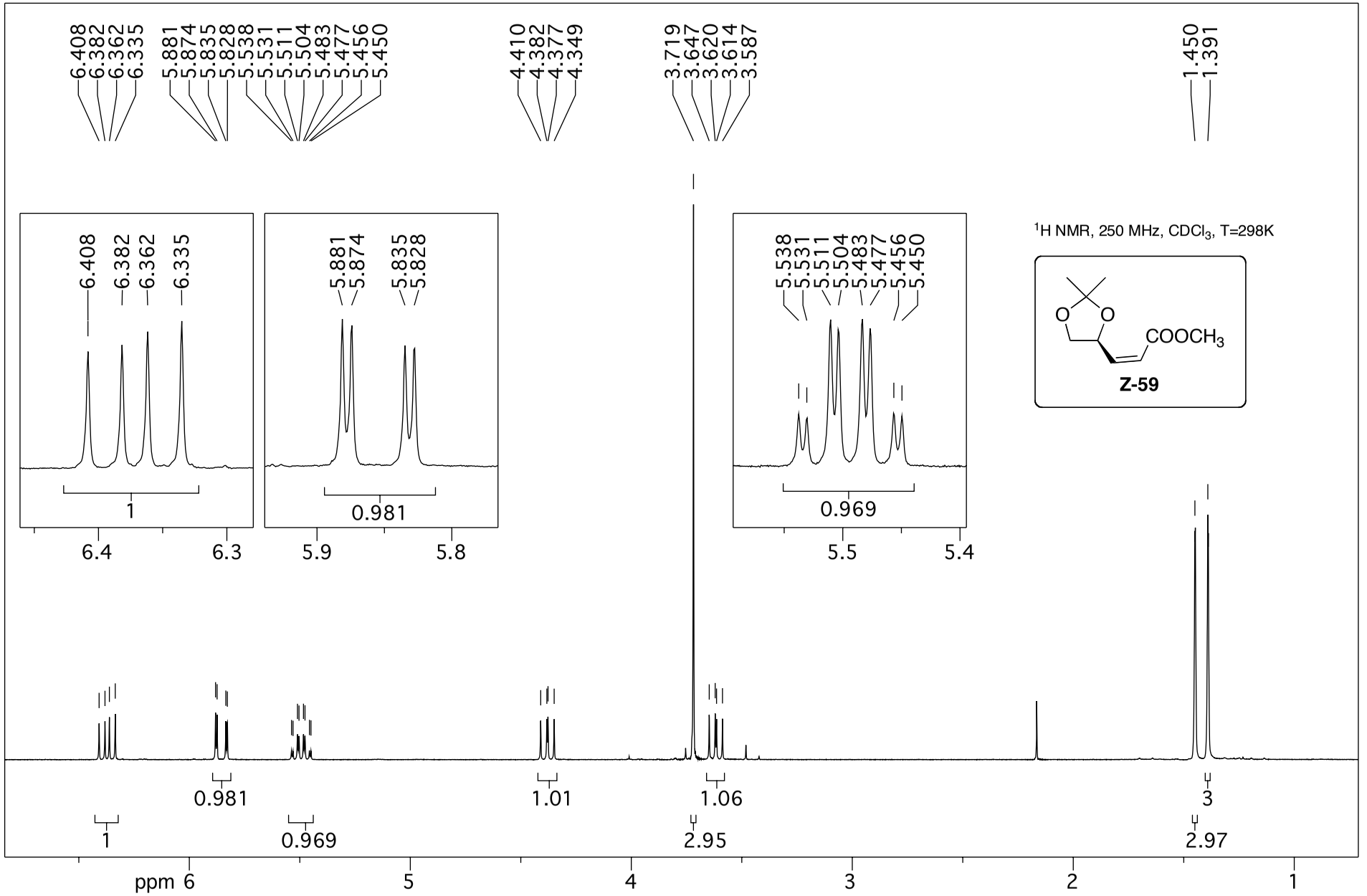
First, I would like to thank my supervisor, Prof. Ramon Alibés Arqués and the research chief Prof. Marta Figueredo Galimany, to let me attend my internship by the research group. I also would like to express my deepest appreciation to Prof. Pau Bayón Rueda, to Yangchun Xin and to all the other members of the laboratory; I am grateful for their constant support and help.

In addition, a thank to Prof. Fabrizio Fabris; without his assistance and involvement, this manuscipt would have never been accomplished.

Getting through my dissertation required more than academic support, and I have many people to thank for listening to and, at times, having to tolerate me over the past three years. I cannot begin to express my gratitude and appreciation for their friendship.

Last but not the least, I would like to thank my family and my parents to supporting me spiritually and economically throughout my life.

9. SPECTRA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5.4
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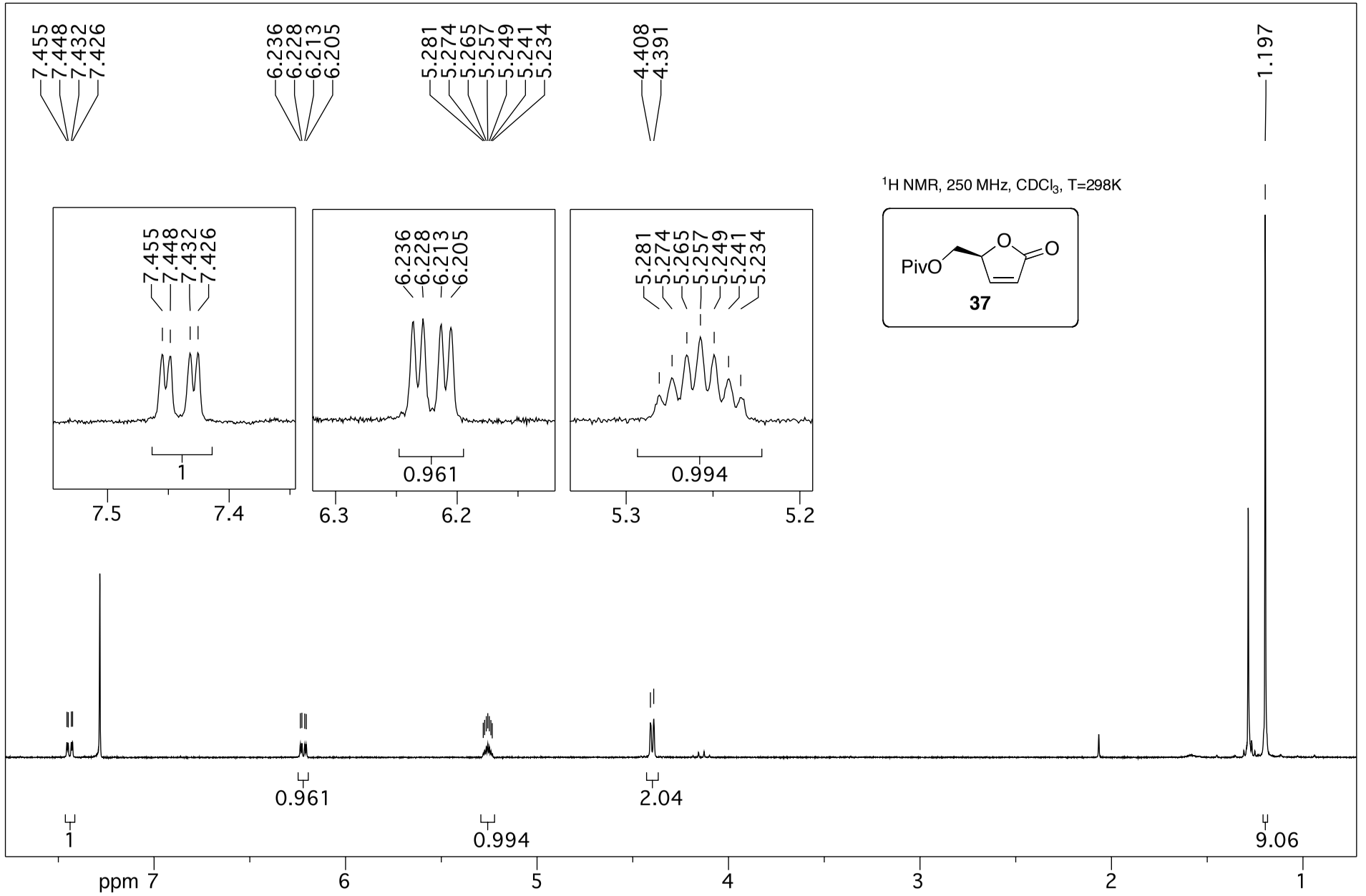
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7.4
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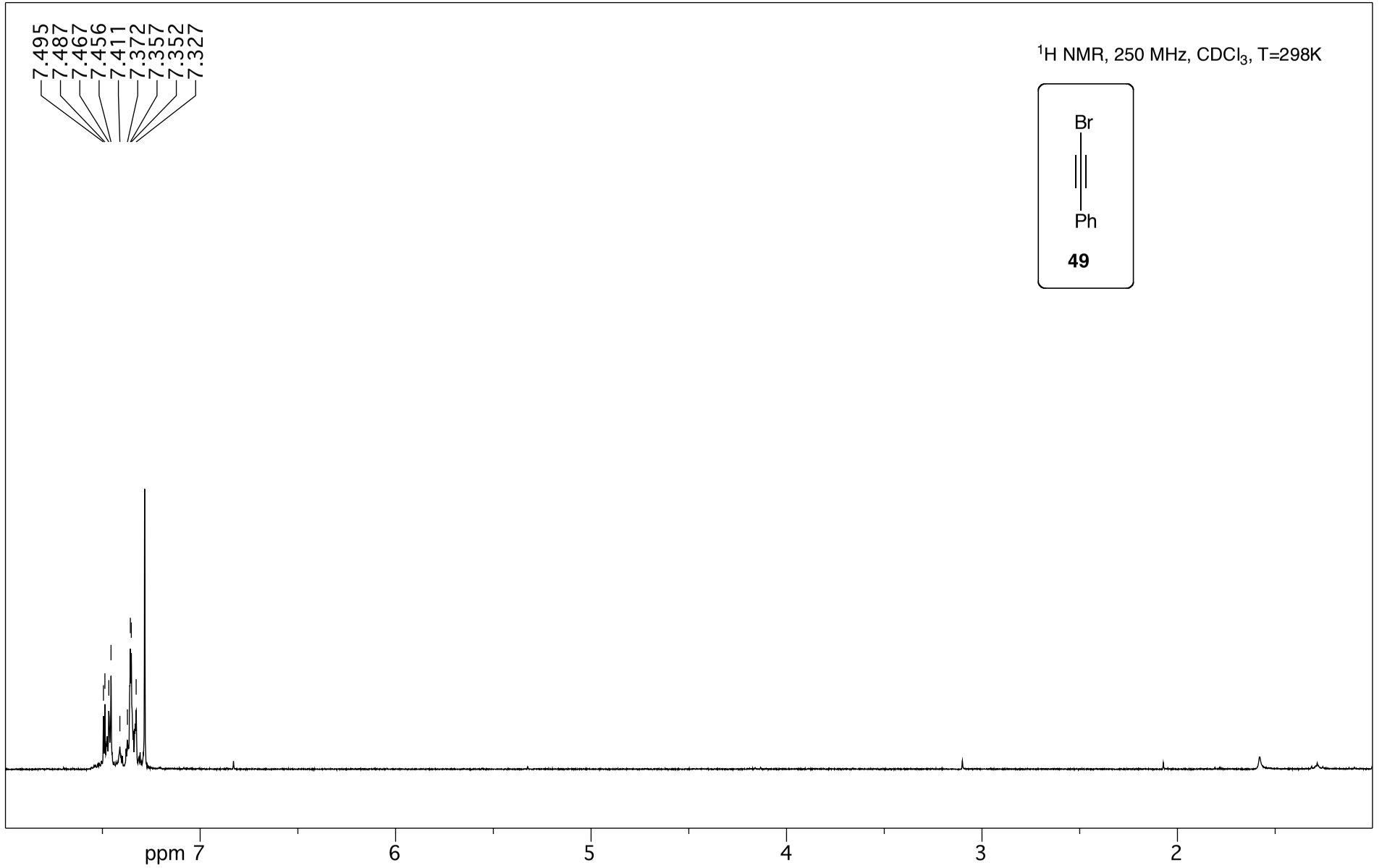
2
1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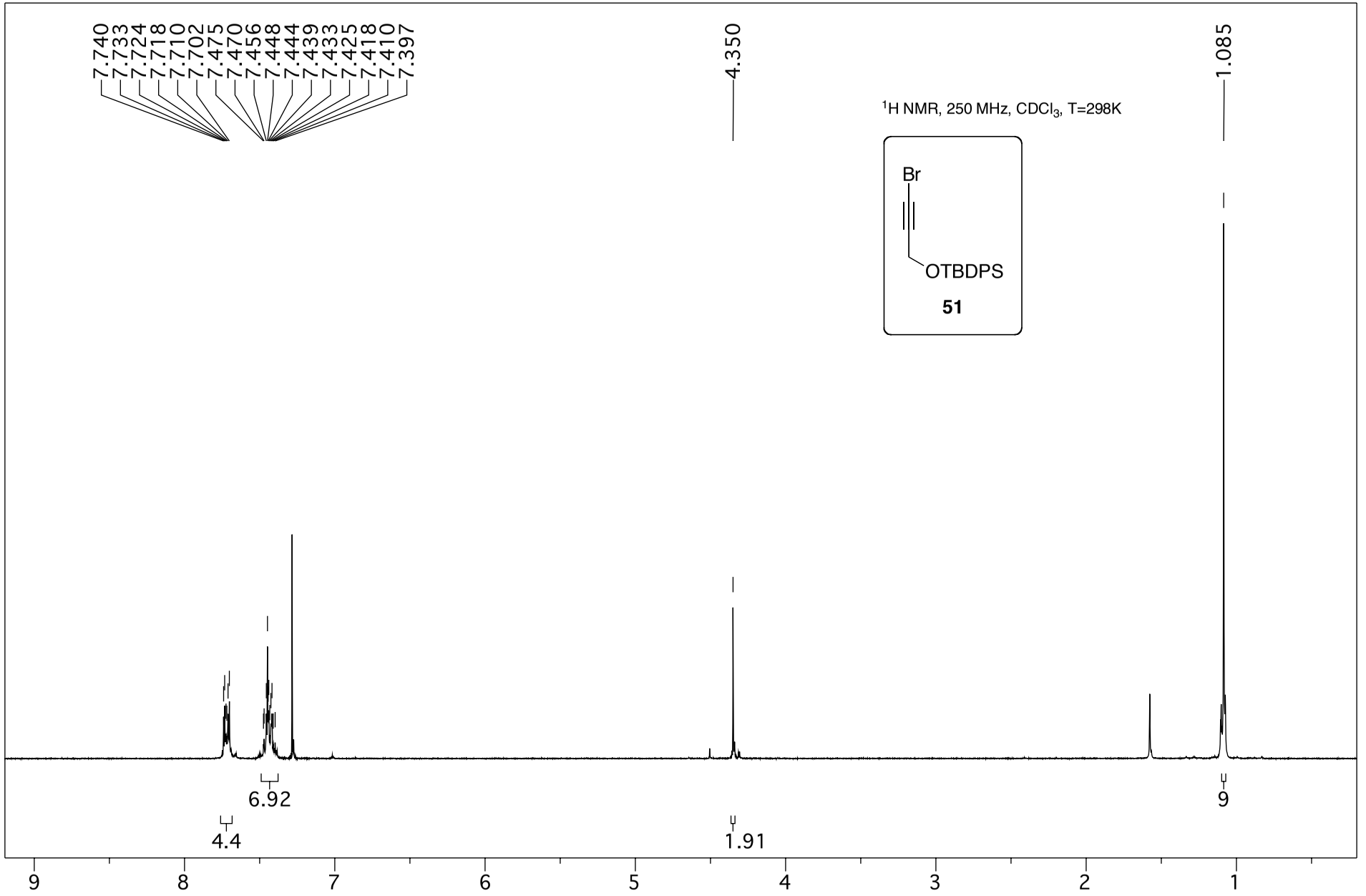
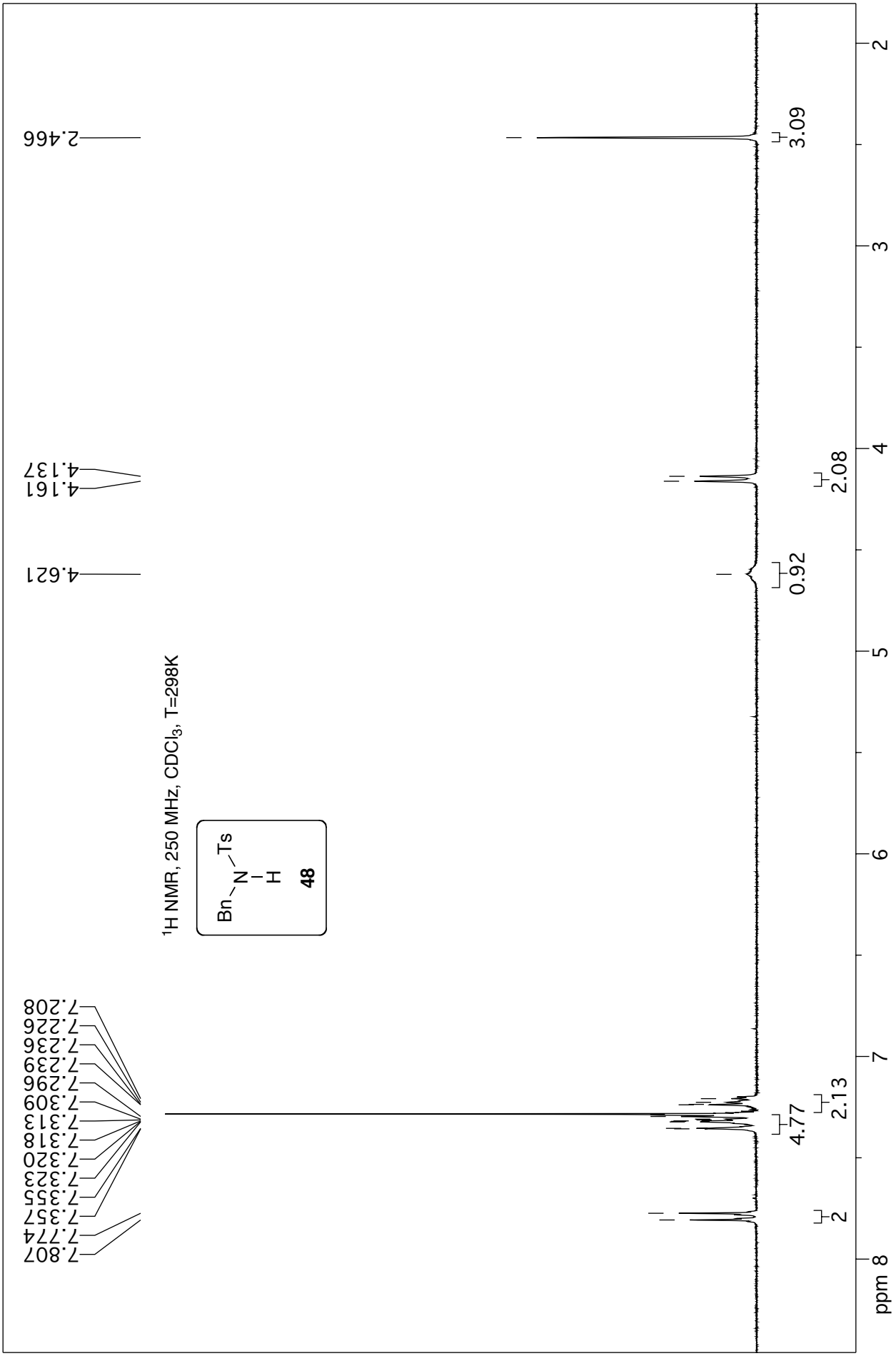
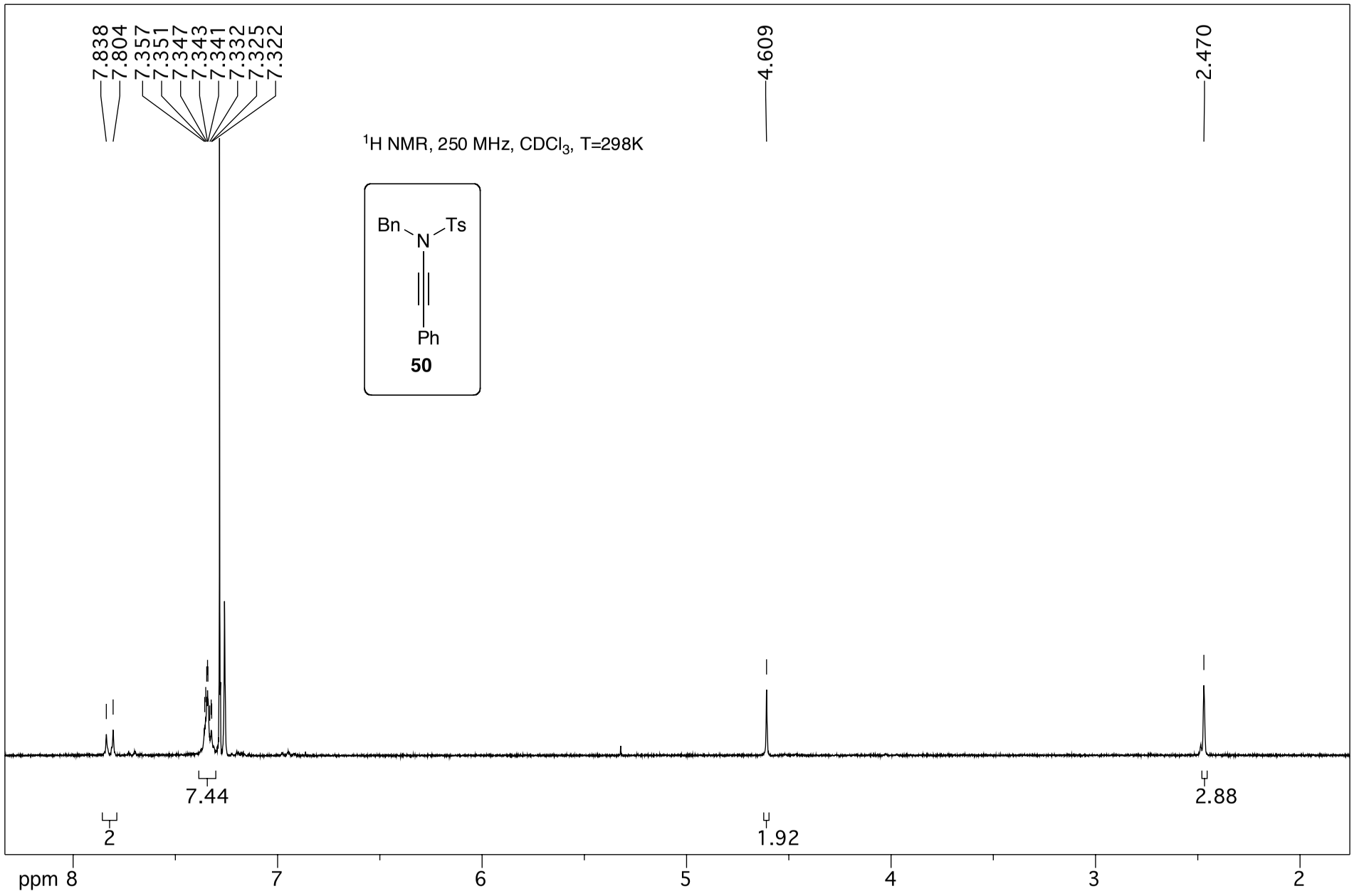
7.487
7.467
7.456
7.411
7.372
7.357
7.352
7.327
^{1}H NMR, 250 MHz, $CDCl_3$, T=298K
Br
Ph
49
ppm 7
6
5
4
3
2

1H NMR, 250 MHz, CDCl3, T=298K
H
OTBDPS
53
7.736
7.735
7.718
7.714
7.461
7.442
7.432
7.413
7.412
7.395
4.320
2.406
1.078
3.91
6.03
1.77
0.841
9
ppm 8
7
6
5
4
3
2
1


7.740
7.733
7.724
7.718
7.710
7.702
7.475
7.470
7.456
7.448
7.444
7.439
7.433
7.425
7.418
7.410
7.397
4.350
1.085
^{1}H NMR, 250 MHz, $CDCl_3$, T=298K
Br
OTBDPS
51
6.92
4.4
1.91
9
9
8
7
6
5
4
3
2
1


^{1}H NMR, 250 MHz, $CDCl_3$, T=298K
Bn
N
H
Ts
48
7.807
7.774
7.357
7.355
7.323
7.320
7.318
7.313
7.309
7.296
7.239
7.236
7.226
7.208
4.621
4.161
4.137
2.466
2
4.77
2.13
0.92
2.08
3.09
ppm 8
7
6
5
4
3
2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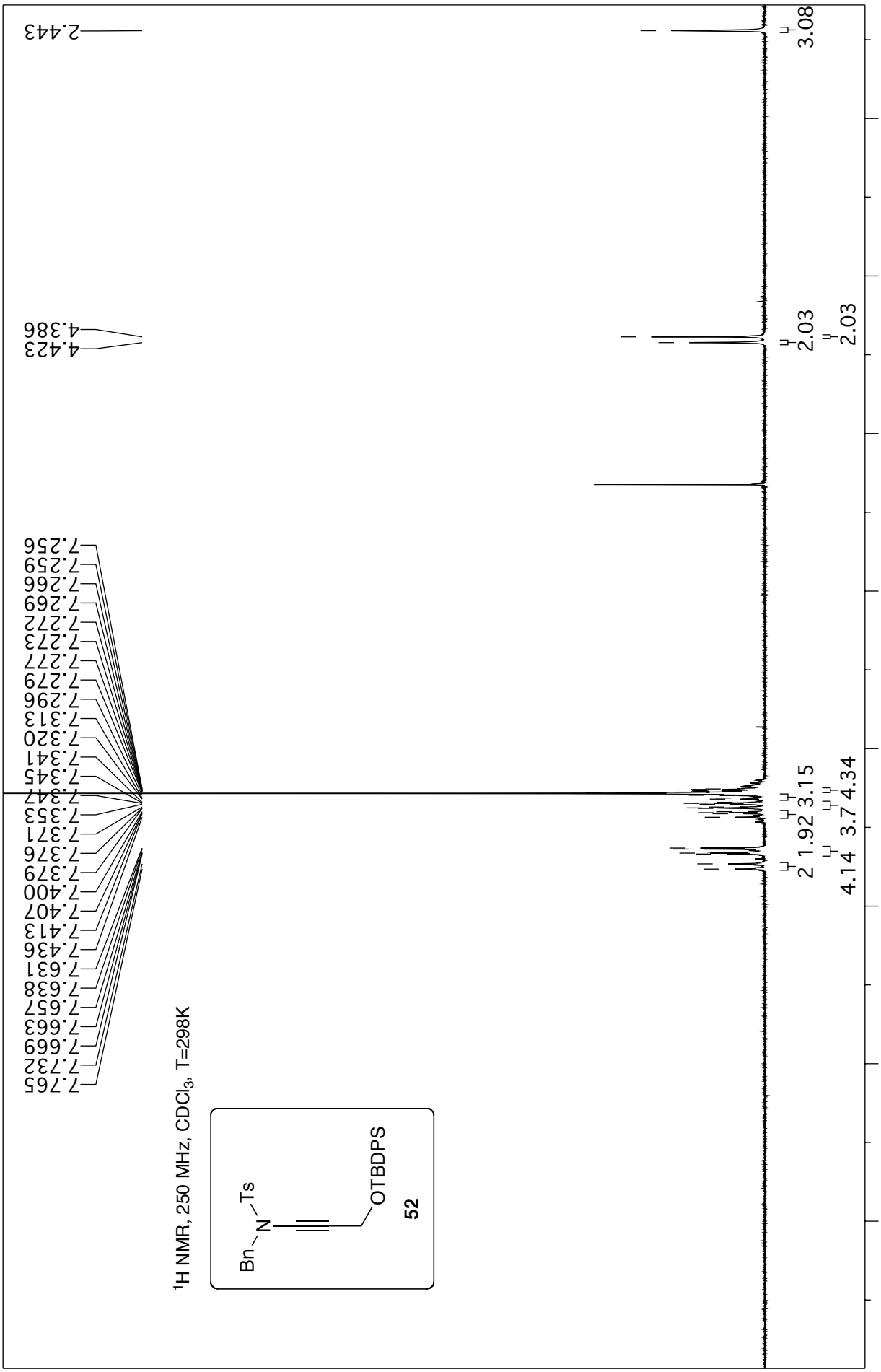
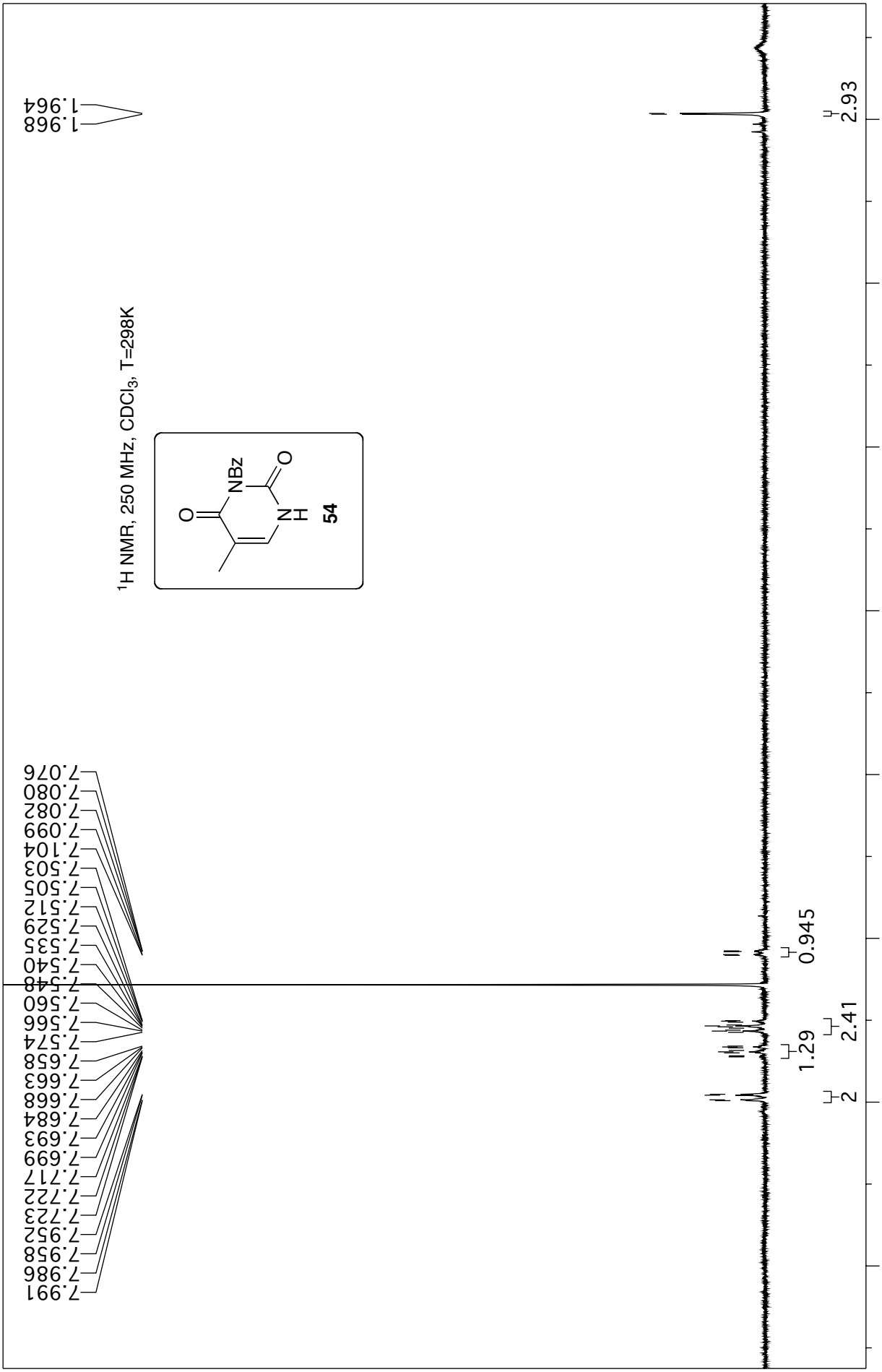
7.804
7.357
7.351
7.347
7.343
7.341
7.332
7.325
7.322
4.609
2.470
^{1}H NMR, 250 MHz, $CDCl_3$, T=298K
Bn
N
Ts
Ph
50
2
7.44
1.92
2.88
ppm 8
7
6
5
4
3
2


2.443
4.423
4.386
7.765
7.732
7.669
7.663
7.657
7.638
7.631
7.436
7.413
7.407
7.400
7.379
7.376
7.371
7.353
7.347
7.345
7.341
7.320
7.313
7.296
7.279
7.277
7.273
7.272
7.269
7.266
7.259
7.256
3.08
2.03
2.03
2 1.92 3.15
4.14 3.7 4.34
ppm 10
9
8
7
6
5
4
3
^{1}H NMR, 250 MHz, CDCl$_3$, T=298K
Bn
N
Ts
OTBDPS
52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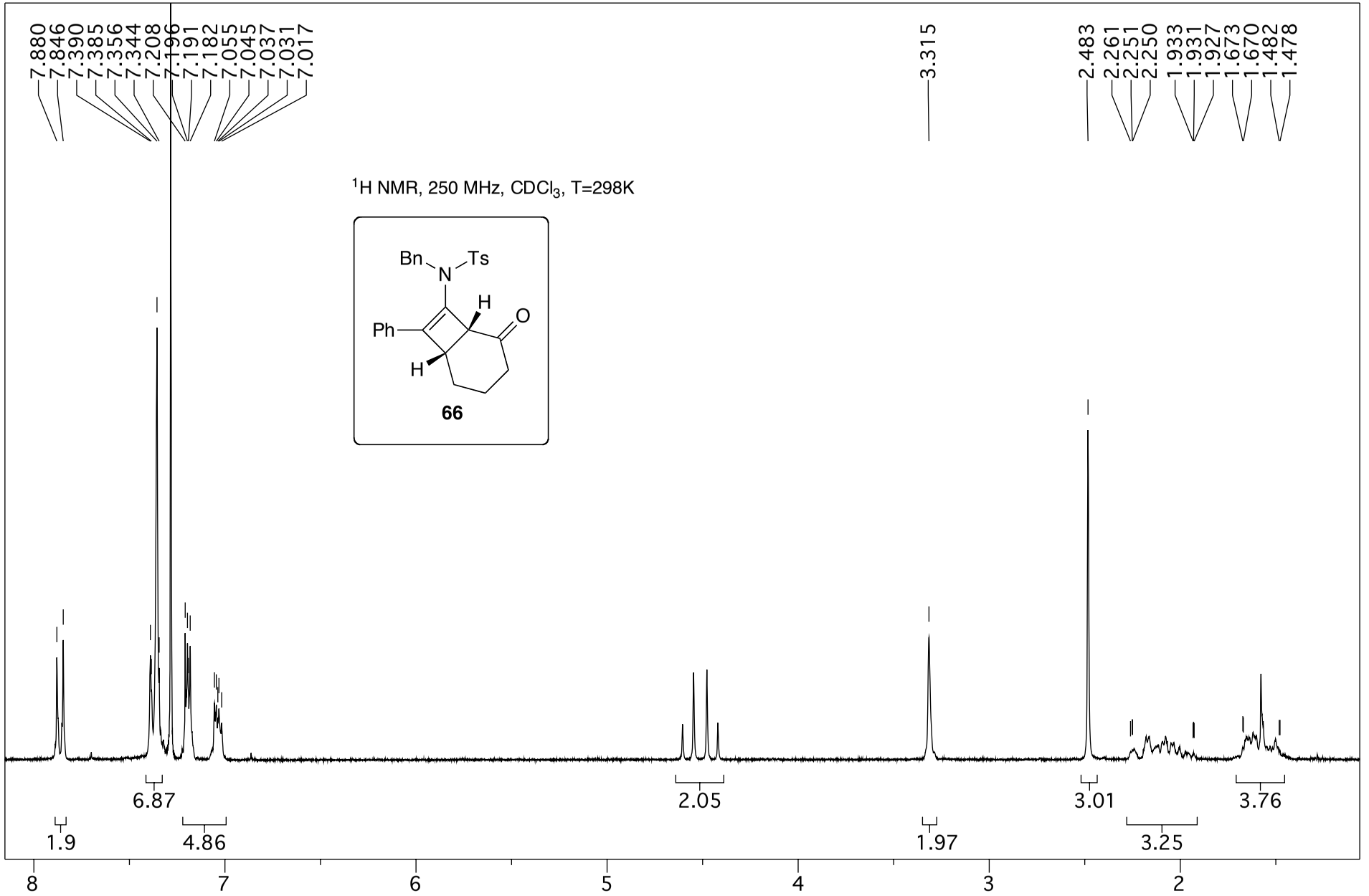
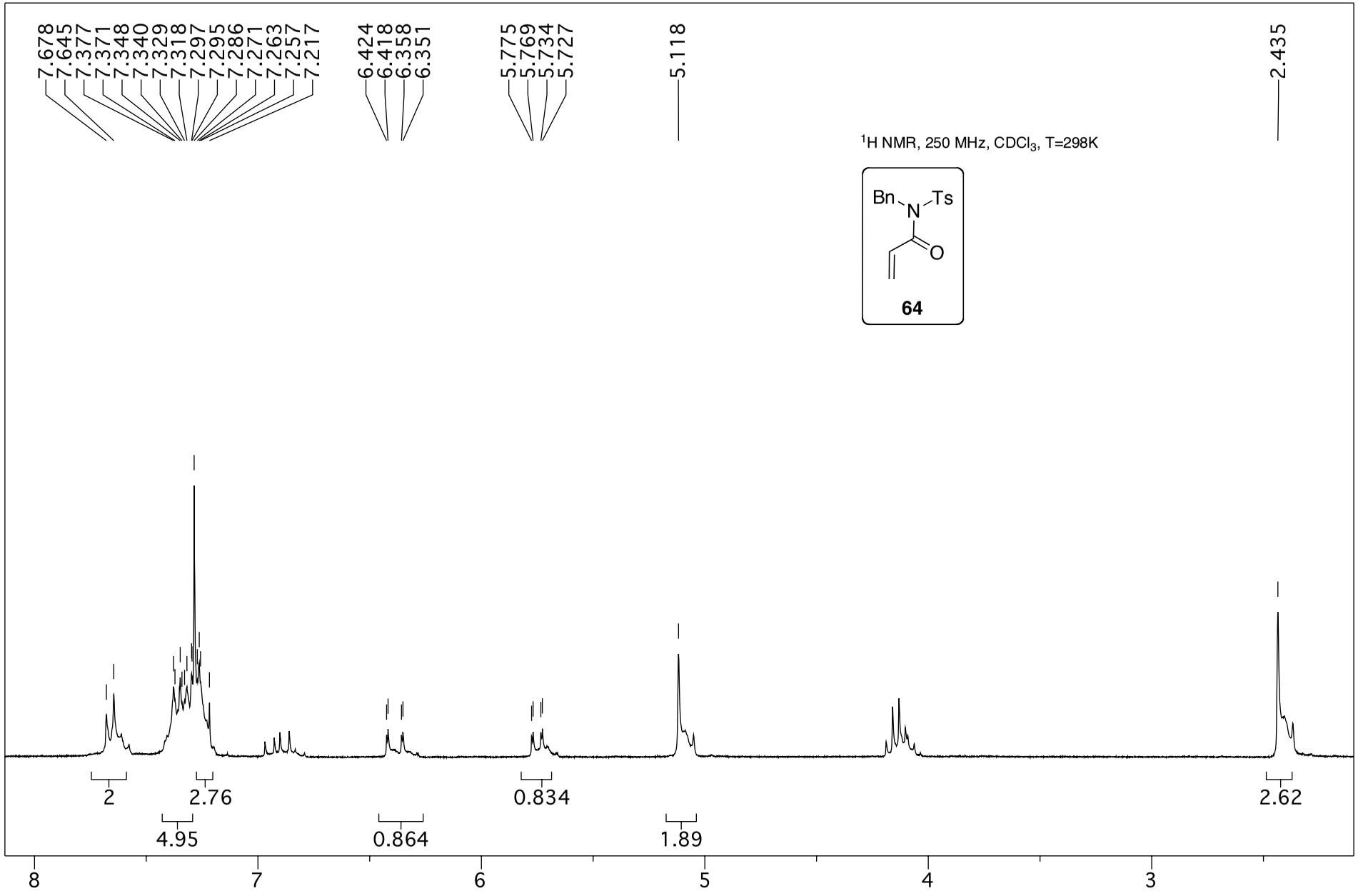
1.968
7.076
7.080
7.082
7.099
7.104
7.503
7.505
7.512
7.529
7.535
7.540
7.548
7.560
7.566
7.574
7.658
7.663
7.668
7.684
7.693
7.699
7.717
7.722
7.723
7.952
7.958
7.986
7.991
^{1}H NMR, 250 MHz, CDCl$_3$, T=298K
NBz
O
O
N
H
54
2.93
0.945
2.41
1.29
2
ppm 9
8
7
6
5
4
3
2

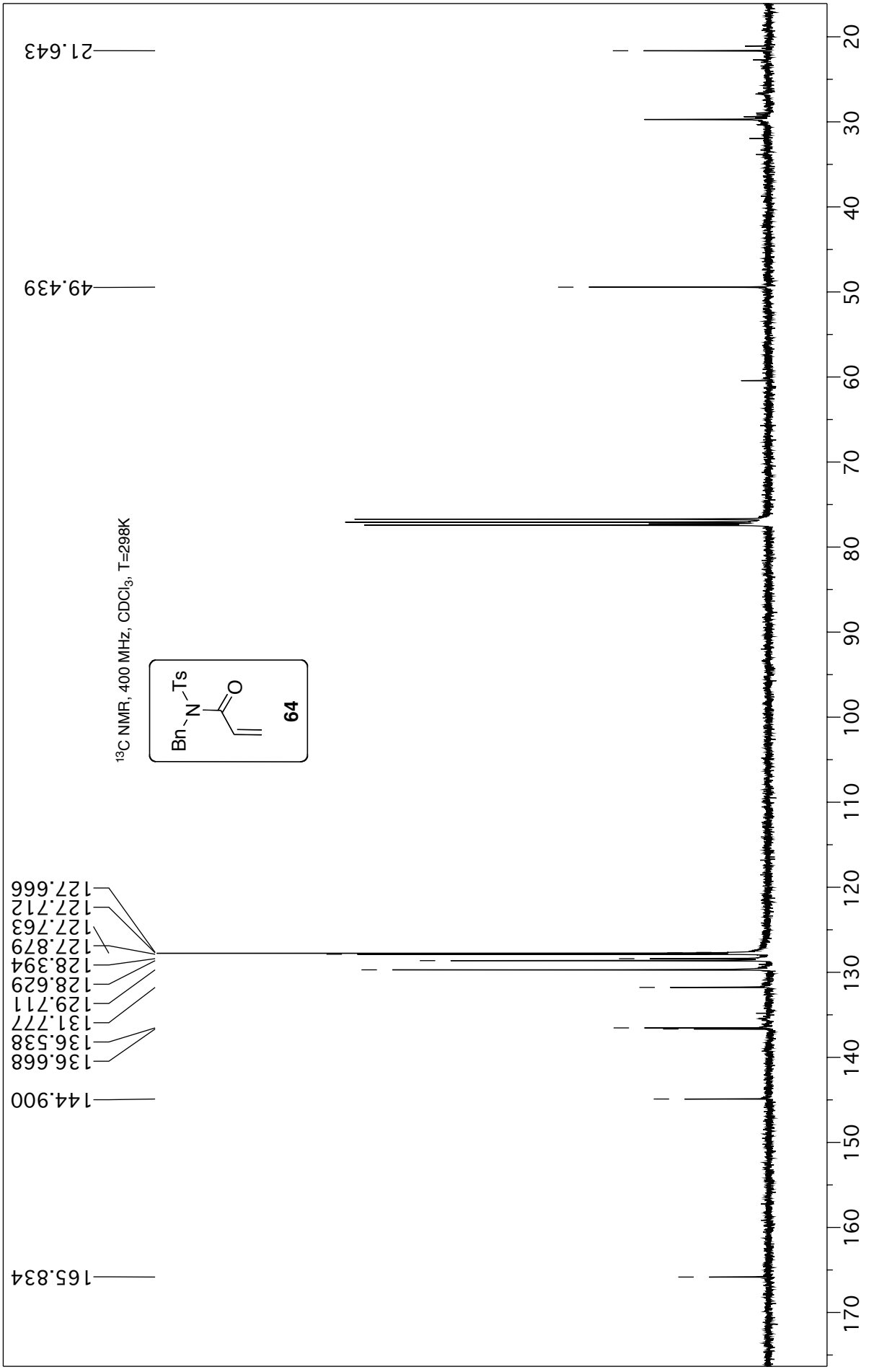

7.880
7.846
7.390
7.385
7.356
7.344
7.208
7.196
7.191
7.182
7.055
7.045
7.037
7.031
7.017
3.315
2.483
2.261
2.251
2.250
1.933
1.931
1.927
1.673
1.670
1.482
1.478
^{1}H NMR, 250 MHz, $CDCl_3$, T=298K
Bn
N
Ts
H
O
Ph
H
66
6.87
2.05
3.01
3.76
1.9
4.86
1.97
3.25
8
7
6
5
4
3
2

210.511
144.505
144.174
136.171
135.353
132.000
129.902
128.767
128.407
128.353
127.938
127.847
127.262
126.752
55.340
51.108
40.456
37.275
24.796
21.676
17.353
ppm 200
180
160
140
120
100
80
60
40
20
^{13}C NMR, 400 MHz, CDCl$_3$, T=298K
Bn
N
Ts
H
O
Ph
H
66

7.683
7.649
7.385
7.377
7.371
7.365
7.359
7.355
7.343
7.330
7.304
7.303
7.302
7.300
7.299
7.285
7.278
7.272
7.270
7.258
7.250
7.035
7.022
7.006
6.999
5.097
3.902
2.456
6.53
4.17
2.04
2.11
2.15
3.18
2
3
4
5
6
7
8
ppm
62
Bn
N
Ts
O
Ph
^{1}H NMR, 250 MHz, $CDCl_3$, T=298K

196.555
175.312
46.939
81.562
81.685
84.969
88.473
88.895
89.478
89.628
90.211
90.412
90.506
90.996
^{13}C NMR, 400 MHz, CDCl$_3$, T=298K
Bn
N
Ts
O
Ph
62
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200


7.678
7.645
7.377
7.371
7.348
7.340
7.329
7.318
7.297
7.295
7.286
7.271
7.263
7.257
7.217
6.424
6.418
6.358
6.351
5.775
5.769
5.734
5.727
5.118
2.435
^{1}H NMR, 250 MHz, $CDCl_3$, T=298K
Bn
N
Ts
O
64
2
2.76
4.95
0.864
0.834
1.89
2.62
8
7
6
5
4
3


21.643
49.439
165.834
144.900
136.668
136.538
131.777
129.711
128.629
128.394
127.879
127.763
127.712
127.666
^{13}C NMR, 400 MHz, $CDCl_3$, T=298K
Bn
N
Ts
O
64
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170

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