Curso 2012/13
CIENCIAS Y TECNOLOGÍAS/18
I.S.B.N.: 978-84-15910-81-7

GABRIELA MÉNDEZ ABT

Propargyl Vinyl Ethers: Synthetic Applications

Directores
FERNANDO GARCÍA TELLADO
DAVID TEJEDOR ARAGÓN

SERVICIO DE PUBLICACIONES
UNIVERSIDAD DE LA LAGUNA

SOPORTES AUDIOVISUALES E INFORMÁTICOS
Serie Tesis Doctorales

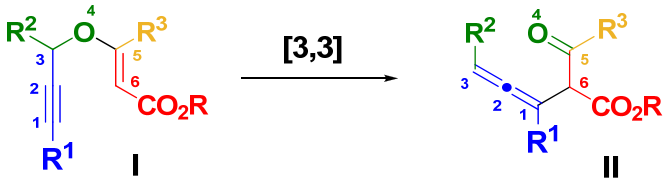
El trabajo que constituye la presente memoria ha sido realizado en el departamento de Química Biológica y Biotecnología del Instituto de Productos Naturales y Agrobiología del Consejo Superior de Investigaciones Científicas, bajo la dirección de los Doctores Fernando García Tellado y David Tejedor Aragón.

Contents

Resumen:

En esta memoria hemos diseñado e implementado una metodología dominó, asistida por microondas y en ausencia de metales, para la transformación de unidades de éteres propargílicos vinílicos **I** en productos más complejos y exhibiendo diversidad estructural. Estos procesos dominó se han diseñado para ser rápidos, eficientes, económicos (reactivos, tiempo), fáciles de procesar (no requieren especial cuidado en cuanto a purificación de disolventes ni atmósferas de reacción inertes) y respetuosos con el medio ambiente.

Hemos mostrado como los éteres propargílicos vinílicos constituyen un grupo privilegiado de bloques de construcción pequeños, densamente funcionalizados (máxima funcionalidad química soportada sobre la mínima conectividad atómica), simples desde un punto de vista estructural y fácilmente asequibles desde un punto de vista sintético. El agrupamiento espacial C_3-O-C_2 que define a estas unidades las convierte en candidatos excelentes para el desarrollo de reagrupamientos [3,3]-sigmatrópicos propargílicos. Estos reagrupamientos son la llave al patrón de reactividad química codificado en estas estructuras. Respecto a estos reagrupamientos, (también conocidos como reagrupaminetos [3,3]-Claisen propargílicos), igual que sucede con los otros reagrupamientos [3,3]-sigmatropicos relacionados, tienen lugar bajo control térmico para generar los correspondientes ésteres alénicos **II** de manera totalmente irreversible (de hecho, el reagrupamiento de retro-Claisen no ha sido nunca observado en estos procesos).



Hemos instrumentalizado el perfil de reactividad de estas plataformas propargílicas para obtener, a partir de ellas, colecciones (librerías) de moléculas de pequeño tamaño con interés biológico potencial, y lo hemos hecho de manera rápida y selectiva, mediante el diseño y desarrollo de nuevas metodologías basadas en la química dominó.

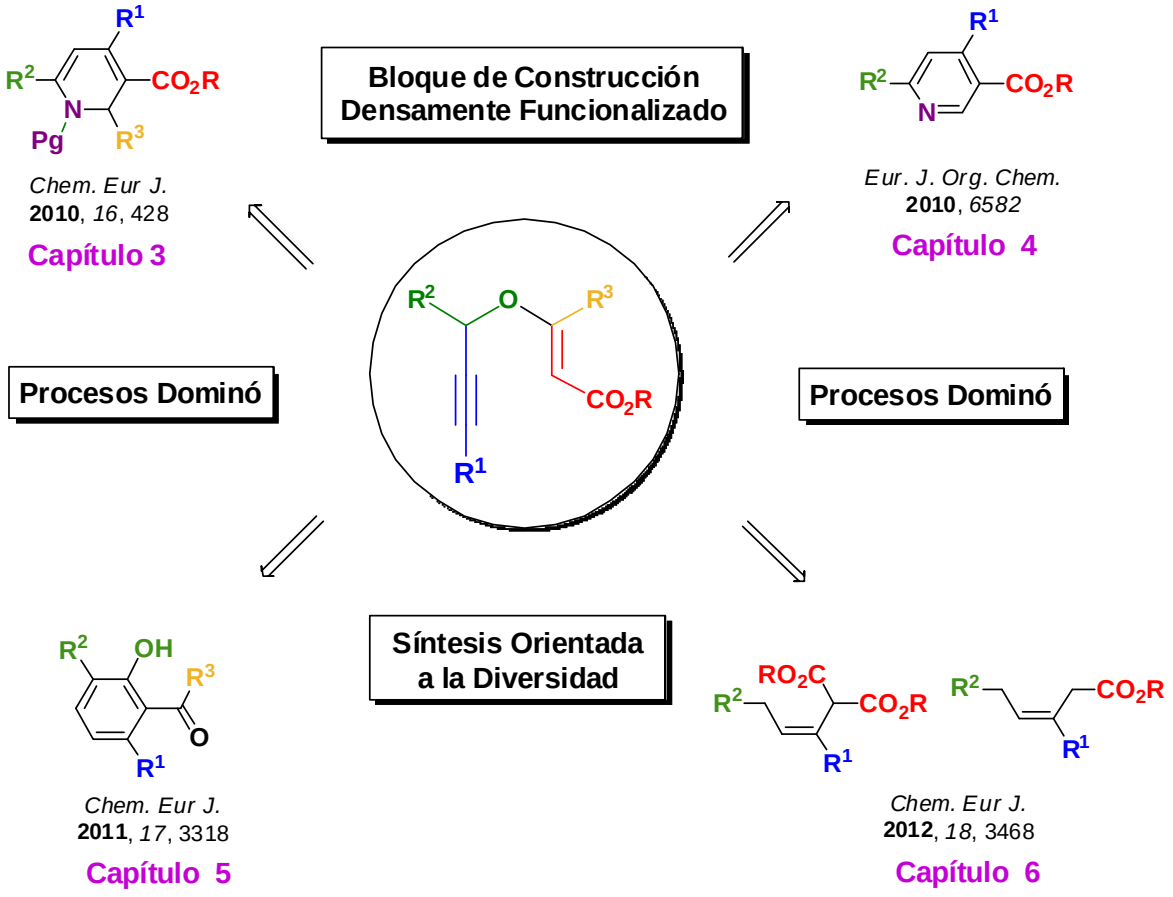
Las estructuras que hemos sintetizado en esta memoria incluyen:

- 1,2-Dihidropiridina-3-carboxilatos de alquilo trisustituidos (capítulo 3); 17 ejemplos han sido sintetizados con rendimientos del 17 al 100%.

- Piridina-3-carboxilatos de alquilo (capítulo 4); 14 productos han sido sintetizados con rendimientos del 13 al 77%.

- Fenoles trisustituidos llevando en su estructura un aldehído (salicilaldehídos) o una cetona en la posición orto al hidroxilo (capítulo 5); 18 ejemplos han sido sintetizados con rendimientos del 30 al 89%.

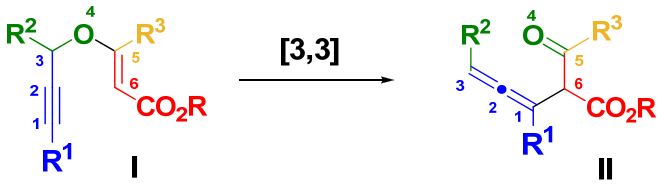
- Olefinas trisustituidas, estéreo-definidas, llevando uno o dos grupos ésteres en posición alílica (capítulo 6); 14 productos han sido sintetizados con rendimientos del 50 al 96%.



Summary:

Microwave-assisted metal-free domino methodologies have been designed to transform propargyl vinyl ethers (PVEs) **I** into products featuring structural diversity. Furthermore, these processes have been designed to be fast, economical, bench-friendly (they do not require special care with solvent and reaction atmospheres) and environmentally benign.

We have shown that the propargyl vinyl ether motives constitute a privileged group of small size, structurally simple, readily available, and densely functionalized building blocks (they support a maximum of functional density on a minimum of skeletal connectivity). The spatial clustering C_3-O-C_2 of a propargylic unit and a vinyl unit convert these structures in excellent candidates to participate in the [3,3] propargylic sigmatropic rearrangement. This is therefore the key to the chemical reactivity encoded in these structures. With regard to the propargyl Claisen rearrangement, as in any other [3,3]-sigmatropic rearrangement, it takes place under thermodynamic control to generate the corresponding allenic esters **II**. This reaction is by all means irreversible toward the formation of the carbonyl compounds as the retro-Claisen rearrangement of allenic substrates has never been observed.



The reactivity profile of these platforms has been therefore used to obtain collections of compounds with potential biological interest in a selective and efficient way, while developing new domino methodologies.

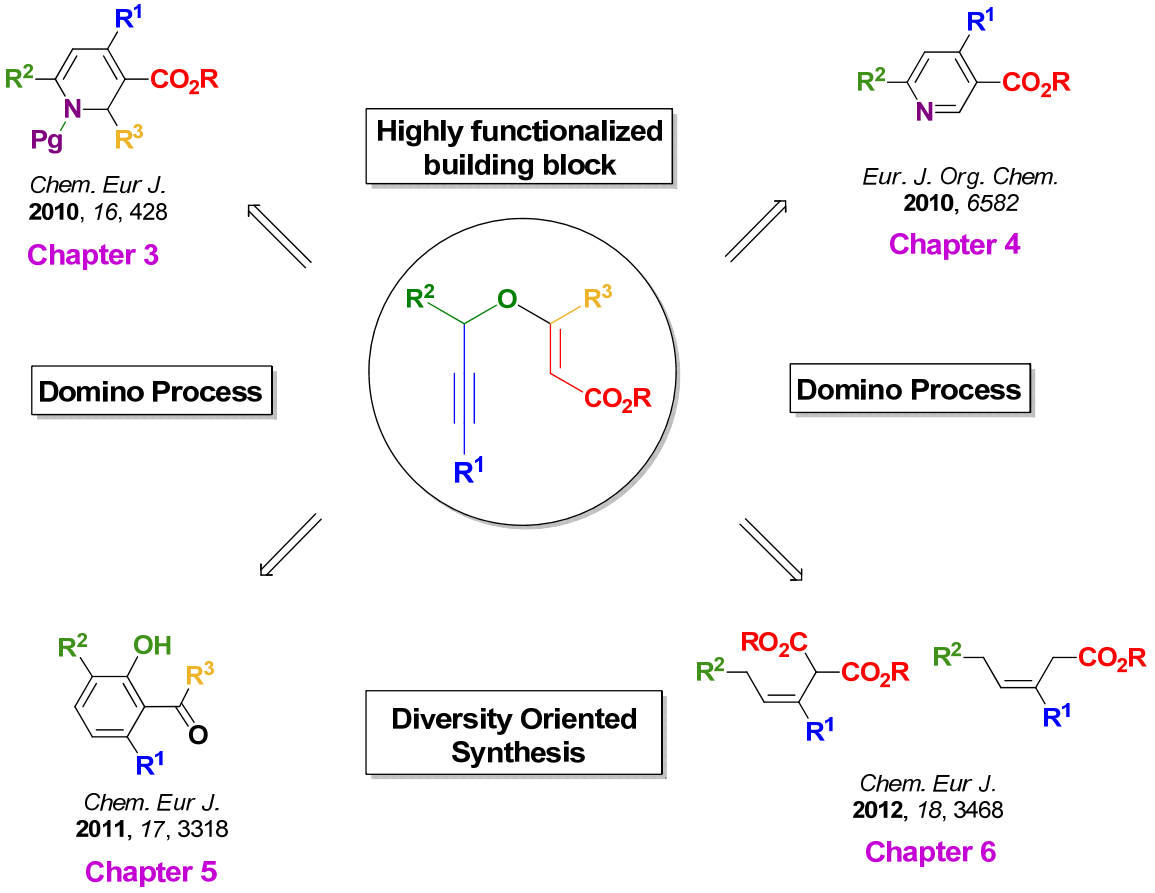
The structures obtained range from:

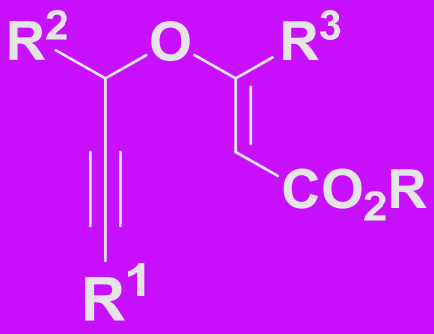
- Derivatives of trisubstituted alkyl 1,2-dihidropyridin-3-carboxylates (chapter 3), where 17 examples were synthesized with yields between 17-100%.

- Disubstituted alkyl pyridin-3-carboxylates (chapter 4), where 14 products were synthesized with yields between 13-77%.

- Trisubstituted phenols carrying an aldehyde functionality (salicilaldehydes) or ketone in the ortho position (chapter 5), where 18 examples were synthesized with yields between 30-89%.

- Stereodefined trisubstituted alkenes carrying one or two ester functionalities in the allylic position (chapter 6), where 21 products were synthesized with yields between 50-96%.



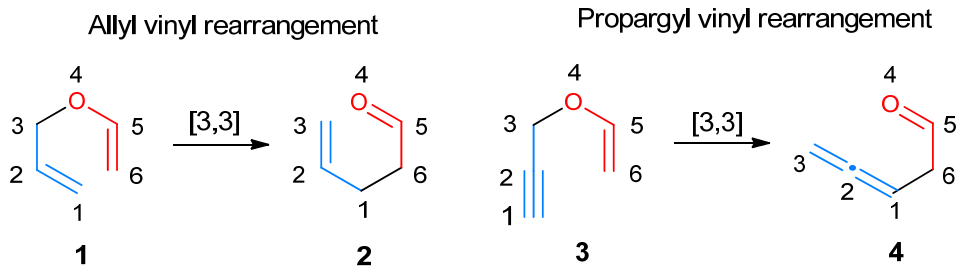


CHAPTER 1

Introduction

1. Introduction:

Classically, the Claisen rearrangement[1] can be described as the [3,3]-sigmatropic transformation of an allyl vinyl ether **1** into a γ,δ-unsaturated carbonyl compound **2** (Scheme 1). Many variations of this reaction are known regarding the substitution pattern of the vinyl group or the introduction of an aryl group, heteroatoms (most commonly nitrogen or sulphur) or a propargyl group. Due to its popularity, the Claisen rearrangement has received much attention, and it has been the subject of different comprehensive reviews.[2,3,4,5,6] At best, some of these reviews have incorporated the propargyl Claisen rearrangement as a minor component, always with the aim of studying the initial step involving the acetylenic bond, and never of exploring the potential that lies beyond.[7]



Scheme 1. Allyl vinyl rearrangement vs. propargyl vinyl rearrangement.

Since the first report by Claisen, and for the next fifty years, there was a general erroneous idea that a triple bond could not participate in such rearrengements. The fact that propargyl aryl ethers did not rearrange under the studied reaction conditions in the same way that allyl aryl ethers did, led to conclude that the triple bond could not participate in the reaction for geometrical reasons. It was not until the early 1960's, that the first successful attempts on the rearrangement of a propargyl aryl ether was reported.[8]

Consequently, the aliphatic propargylic Claisen rearrangement, which was first reported by Black and Landor in 1965,[9] nowadays is a known protocol to gain access to functionalized allenes **4** through the [3,3]-sigmatropic transformation of propargyl vinyl ethers

[1] L. Claisen, *Chem. Ber*. **1912**, *45*, 3157-3167.
[2] A. M. M. Castro, *Chem. Rev.* **2004**, *104*, 2939-3002.
[3] F. E. Ziegler, *Chem. Rev*. **1988**, *88*, 1423-1452.
[4] M. Hiersemann, U. Nubbemeyer, Eds. The Claisen Rearrangement; Wiley-VCH: Weinheim, Germany, **2007**.
[5] K. C. Majumdar, S. Alam and B. Chattopadhyay, *Tetrahedron* **2008**, *64*, 597-643.
[6] V. Michelet, P. Y. Toullec and J-P. Genêt, *Angew. Chem. Int. Ed.* **2008**, *47*, 4268-4315.
[7] For an older review on intramolecular pericyclic reactions of acetylenic compounds see: A. Viola, J. J. Collins, N. Filipp, *Tetrahedron* **1981**, *37*, 3765-3811.
[8] B. S. Thyagarajan, K. K. Balasubramanian, R. B. Rao, *Tetrahedron Lett.* **1963**, *21*, 1393-1398.
[9] D. K. Black, S. R. Landor, *J. Chem. Soc*. **1965**, 6784-6788.

3 (Scheme 1). Although allenes are themselves a sought after class of organic compounds,[10] they are in many cases excellent intermediates in route to other arrays of functional groups. As recent scientific literature reveals, this may be particularly the case for those allenes synthesized via the aliphatic acetylenic Claisen rearrangement of appropriate starting materials. Indeed, a wide range of important classes of organic compounds have been synthesized in this way. More importantly, they are often synthesized without the need to isolate the allene intermediates, via domino reactions[11,12] that always begin with the Claisen rearrangement.

Before new advances in this area can be made it would be important to understand how the correct use of appropriate propargyl vinyl ethers (or the propargyl alcohol precursors) and suitable reaction conditions are the key for the development of new methodologies in synthetic organic chemistry and for the design of new domino methodologies with marked applications in the area of diversity-oriented synthesis.

The majority of the reported propargyl Claisen rearrangements require high temperatures. As a result, they have been usually conducted in high boiling solvents. To transform this reaction into a more synthetically useful procedure, two key milestones in this field have been reported in the last decade: the transition metal catalyzed rearrangement and the microwave induced rearrangement of the propargyl vinyl ethers. The original work of Toste and co-workers deserves a special mention since it became the first example of a catalytic version of the Claisen rearrangement of propargyl vinyl ethers conducted at room temperature (Scheme 2).[13] Although the majority of the examples covered in this introduction are conducted at high temperatures, it will be observed that there is a definite trend in the recent literature for using more friendly reaction conditions with the use of metal catalysis or the replacement of conventional heating with laboratory microwave equipment.

It must be pointed out that although over the years different names have been used to refer to this process (i.e. acetylenic Claisen rearrangement, propargyl Claisen rearrangement or Saucy-Marbet rearrangement), in this introduction the term *propargyl Claisen rearrangement* will be used regardless of the substitution pattern present in the vinyl functionality.

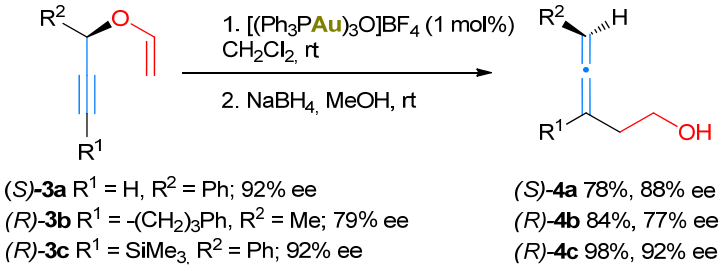
---

[10] S. Ma, *Chem. Rev*. **2005**, *105*, 2829-2871.

[11] The first definition of a domino process was given by Tiezte: "*A domino reaction is a process involving two or more bond-forming transformations (usually C-C bonds) which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step."*

[12] a) L. F. Tietze, U. Beifuss, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131. b) L. F. Tietze, G. Brasche and K. M. Gericke, Domino Reactions in Organic Synthesis, WILEY-VCH, Weinheim, **2006**. c) L. F. Tietze, Chem. Rev. **1996**, 96, 115 - 136. d) L. F. Tietze, A. Modi, Med. Res. Rev. **2000**, 20, 304-322. e) L. F. Tietze, M. E. Lieb, Curr. Opin. Chem. Biol. **1998**, *2*, 363-371.

[13] B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 15978-15979. The metal-catalysed rearrangement takes place with a deviation from a concerted mechanism. The PVE rearranges to a cyclic oxocarbenium ions which then opens to the allenic species (See Scheme 27).



Scheme 2. Au(I)-catalysed propargyl Claisen rearrangement.

1.1. Propargyl vinyl (aryl) ethers

The interest of the propargyl Claisen rearrangement justifies the importance of the availability of the starting materials. Thus, propargyl vinyl ethers (PVEs) constitute a privileged group of small size, structurally simple, readily available, and densely functionalized scaffolds. The key to the chemical reactivity encoded in these structures is the [3,3] propargylic sigmatropic rearrangement shown in Scheme 1, but nevertheless, there exists also the possibility to separately take advantage of each of the different functionalities. With regard to the propargyl Claisen rearrangement, as in any other [3,3]-sigmatropic rearrangement, it takes place under thermodynamic control. This reaction is by all means irreversible toward the formation of the carbonyl compounds as the retro-Claisen rearrangement of allenic substrates has never been observed.

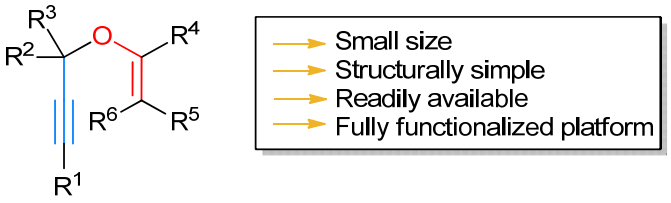
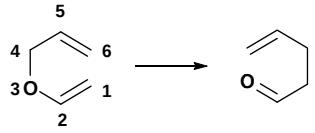


Figure 1. Propargyl vinyl ethers (PVEs): versatile synthetic platforms.

Another important aspect that will be observed throughout this introduction is that the degree and pattern of substitution in the PVEs will have a great impact on the outcome of the reactions. Although a systematic study on the influence of the different susbstituents in propargylic substrates has not been carried out, a recurrent observation made since the pioneer work of Black and Landor in 1965 is that increased substitution in the PVE leads to a more efficient rearrangement at lower temperatures. As it has already been pointed out, this shows that steric hindrance in the transition state is not the most relevant factor in terms of energy dependency.[9]

On the other hand, inductive or mesomeric effects of electron-withdrawing or electron-

donating substituents located at different positions of the carbon skeleton are expected to be similar to those observed for the better-studied Claisen rearrangement of allyl vinyl ethers (Figure 2).[2]



ELECTRON DONATING GROUP ACCELERATION

Position	Group
1	-O, $-NH_2$, -F, $-CH_3$
2	$-OSi(CH_3)_3$, $-CH_3$, $-CH^-SO_2Ph$, -F
4	$-CH_3$, $-OCH_3$
6	$-CH_3$, $-OCH_3$

ELECTRON DONATING GROUP DECELERATION

Position	Group
5	$-CH_3$, $-OCH_3$

ELECTRON WITHDRAWING GROUP ACCELERATION

Position	Group
2	-CN, $-CO_2^-$, $-CO_2CH_3$, $-CF_3$
4	-CN, $-CF_3$
5	-CN

ELECTRON WITHDRAWING GROUP DECELERATION

Position	Group
1	-CN, $-CO_2CF_3$
6	-CN

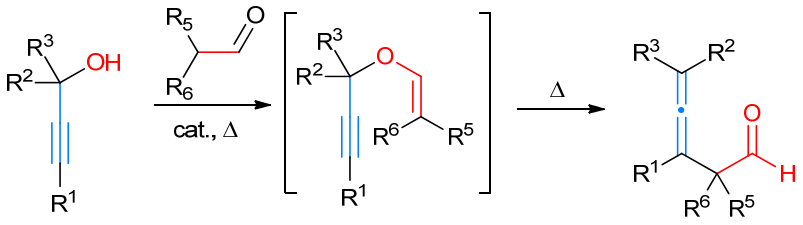
Figure 2. Influence of the substituents in Claisen rearrangement of allyl vinyl ethers.

The pace by which the propargyl Claisen rearrangement has progressed has been largely dictated by the availability of the PVEs, or even more importantly, by the availability of methodologies used to construct them. With regard to this fact, we now present the main advances in the synthesis of PVEs from a historical point of view (Schemes 3-7), and appropriate examples of how different research lines have taken advantage of the PVEs and the allene products derived from them.

1.1.1. Synthesis from propargyl alcohols and aldehydes

In their first report dealing with PVEs, Black and Landor, concluded that this rearrangement provided a new general method for the synthesis of allenic aldehydes. First, the desired starting materials were prepared following their own previously described methodology from propargyl alcohols and aldehydes with the aid of boron trichloride and trimethylamine. Thus, the PVEs (or the α-chloroalkyl ether precursors for the less substituted examples) were heated at temperatures ranging from 140-250 ºC to give the corresponding allenic aldehydes (Scheme 3).[7] This work served to determine that, although less favorable,

propargylic systems could be accommodated into the Claisen rearrangement with the use of higher temperatures.



Scheme 3. Synthesis from propargyl alcohol and aldehydes.

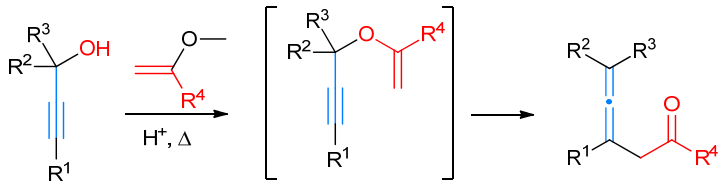
More recently, this procedure for the synthesis of PVEs has been used to prepare allenes via the propargyl Claisen rearrangement with slight changes in the experimental protocol. For instance, Tsuno and co-workers prepared an allenic aldehyde in multigram quantities from 2-methyl-4-phenyl-3-butyn-2-ol, and isobutyraldehyde in the presence of a catalytic amount of *p*-toluenesulfonic acid.[14] In addition, a series of allenic aldehydes were prepared by Potáček et al. using HCl and pyridine for the synthesis of the PVEs instead of the boron trichloride/ trimethylamine system.[15]

Although in general, there are few examples of the use of aldehydes in the synthesis of PVEs, it appears to be an appealing procedure when the desired allenic aldehyde is fully substituted in the α-position to the carbonyl group (R^5 and $R^6 \neq H$).

1.1.2. Synthesis from propargyl alcohols and isopropenyl ethers

The acid-catalysed reaction of isopropenyl ethers with acetylenic carbinols to give β-ketoallenes in high yields is the so called Saucy-Marbet rearrangement (Scheme 4) (R^4 = Me).[16] The main consequence from the employment of the isopropenyl ether is that a PVE is formed with a substituted vinyl functionality which, upon rearrangement, produces an allenic ketone instead of an allenic aldehyde. Furthemore, upon treatment with bases, these allenes readily undergo isomerization to conjugated dienones, leading to important intermediates in the production of flavors, fragances, pharmaceuticals and other fine chemicals. Since the reaction is known to take place under acid catalysis in volatile organic solvents, different research approaches are beeing envisaged to generate a greener and more sustainable process for industrial applications.[17]

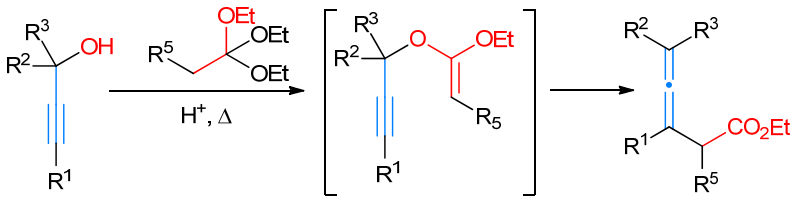
[14] T. Tsuno, H. Hoshino, R. Okuda, K. Sugiyama, *Tetrahedron* **2001**, *57*, 4831-4840.
[15] H. Zachova, S. Man, M. Necas, M. Potacek, *Eur. J. Org. Chem*. **2005**, 2548-2557.
[16] G. Saucy and R. Marbet, *Helv. Chim.Acta* **1967**, *50*, 1158-1167.
[17] C. Wang, W. Zhao, H. Li and L. Guo, *Green Chem*. **2009**, *11*, 843-847 and references cited therein.



Scheme 4. Synthesis from propargyl alcohol and isopropenyl ethers.

1.1.3. Synthesis from propargyl alcohols and orthoesters

Shortly after the disclosure of a version of the Claisen rearrangement by Johnson and co-workers involving allylic alcohols and excess ethyl orthoacetate in the presence of a trace amount of a weak acid (Johnson-Claisen rearrangement),[18] a similar report by Crandall and Tindell described the synthesis of β-allenic esters from propargyl alcohols (Scheme 5).[19] Without a doubt, these two reports constitute a landmark in the synthesis of functionalized allenes through the [3,3]-sigmatropic transformation of readily available starting materials. The new methodology called for the heating of appropriate propargyl alcohols, 4-7 equivalents of triethylorthoacetate and a catalytic amount of propionic acid with removal of ethanol by distillation. Furthermore, the methodology benefits from an increased tolerance in the substitution pattern of the starting materials and a higher stability (reduced reactivity) of the allenic esters with respect to the allenic aldehydes which translates in higher yields of the products.

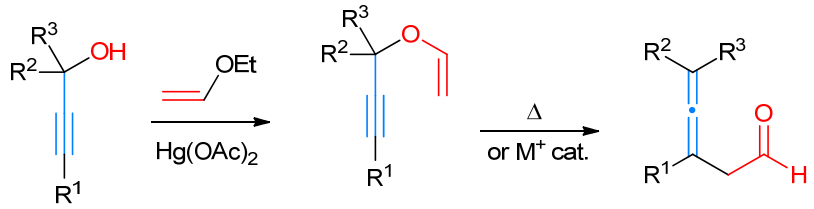


Scheme 5. Synthesis from propargyl alcohols and orthoesters.

In general, the Johnson orthoester Claisen rearrangement of substituted propargylic alcohols is therefore a robust and reliable methodology to construct β-allenic esters, or more complex compounds that can be accessed from these useful scaffolds, with high levels of enantiomeric excess. In this case, the PVEs are only convenient intermediates of the complete transformation because they can never be isolated under the reaction conditions required for their formation.

[18] W. S. Johnson, L. Werthermann, W. R. Bartlett, T. J. Brockson, T.-T. Li, D. J. Faulkner, and M. R. Petersen, *J. Am. Chem. Soc*. **1970**, *92*, 741-743.
[19] J. K. Crandall, G. L. Tindell, *J. Chem. Soc. Chem. Comm*. **1970**, 1411-1412.

1.1.4. Synthesis from propargyl alcohols and ethyl vinyl ether



Scheme 6. Synthesis from propargyl alcohols and ethyl vinyl ether.

In certain occasions, a line of research may require the use of an isolable PVE possessing the unsubstituted vinyl functionality ($R^4 = R^5 = R^6 = H$, Figure 1). In some earlier studies, the plain propargyl vinyl ether (additionally, $R^1 = R^2 = R^3 = H$) was prepared according to the method of Black and Landor,[9] although a different approach was also reported employing 2-propyn-1-ol and (trimethylsilyl) oxirane.[20] On the other hand, in the majority of occasions R^1 and R^2 or $R^3 \neq H$, and the method of choice to introduce the vinyl functionality has been the use of ethyl vinyl ether and propargyl alcohols in the presence of mercury (II) acetate (Scheme 6).[21,22] The [3,3]-sigmatropic rearrangement of these substrates gains therefore access to allenic aldehydes free of substituents in the α-position which can be engaged in further transformations.

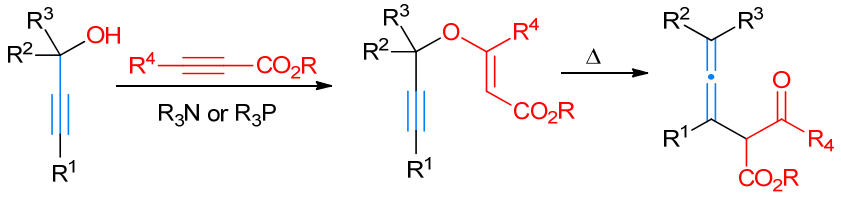
1.1.5. Synthesis from propargyl alcohols and conjugated alkynoates

Isolable PVEs possessing a substituted vinyl functionality are readily available from the trialkylamine or trialkylphosphine catalysed addition of propargylic alcohols to conjugated alkynoates (Scheme 7),[23,24,25] although obviously, $R^6 = H$ (Figure 1). It must be added at this point that PVEs with this type of vinyl substitution pattern can also be accessed directly from alkyl propiolates and aldehydes in a very straightforward manner if $R^1 = CO_2R$.[26]

When using a terminal alkyl propiolate, triethylamine seems to be the most convenient catalyst for the reaction, and the PVEs are synthesised in high yields and short periods of time

[20] M. C. Croudace, N. E. Schore, *J. Org. Chem*. **1981**, *46*, 5357-5363.
[21] K. Nonoshita, H. Banno, K. Maruoka, H. Yamamoto, *J. Am. Chem. Soc*. **1990,** *112*, 316-322.
[22] The vinylation of a terminal alkyne using this methodology has been reported to proceed in very poor yield (5%). K. Mori, *Tetrahedron* **2012**, *68*, 1936-1946.
[23] D. Tejedor, A. Santos-Expósito, G. Méndez-Abt, C. Ruiz-Pérez, F. García-Tellado, *Synlett* **2009**, 1223-1226.
[24] J. Inanaga, Y. Baba, T. Hanamoto, *Chem. Lett*. **1993**, 241-244.
[25] S. Inuki, S. Oishi, N. Fujii, H. Ohno, *Org. Lett*. **2008**, *10*, 5239-5242. Used in the total synthesis of indole alkaloids of the ergot family. Propargyl Claisen rearrangement under thermal, microwave and Au-catalysed conditions.
[26] P. de Armas, F. García-Tellado, J. J. Marrero-Tellado, D. Tejedor, M. A. Maestro, J. González-Platas, *Org. Lett*. **2001**, *3*, 1905-1908.

at room temperature (R^4 = H, Figure 1). In this case, a limitation of the reaction is that most tertiary alcohols do not afford the desired products in synthetically useful yields. Only tertiary alcohols having an electron withdrawing group are capable of participating as appropriate starting materials. When using internal alkynoates, trialkylphosphines must be used because the amine counterparts are not sufficiently nucleophilic to trigger the reaction.



Scheme 7. Synthesis from propargyl alcohols and conjugated alkynoates.

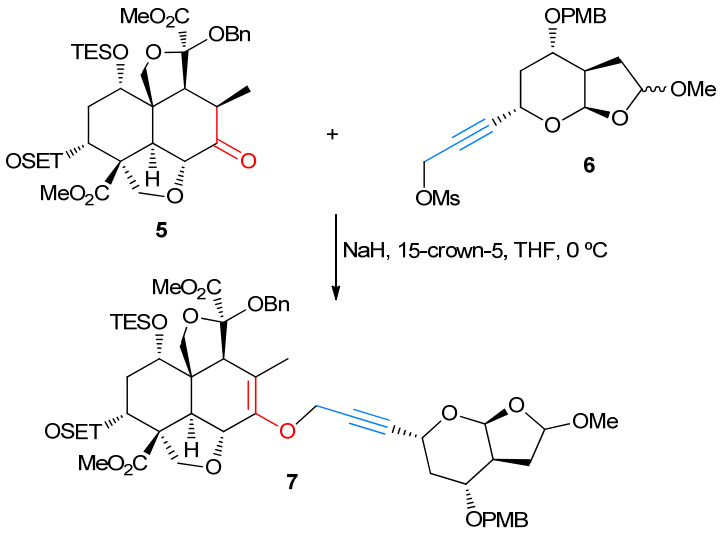
As it will be seen in some of the remaining parts of the introduction, this methodology is one of the most frequently used in the modern synthesis of PVEs. The [3,3]-sigmatropic rearrangement of this substrates affords allenic aldehydes or ketones, with an ester group in the α-position, that are often transformed into more complex structures.

1.1.6. Miscellaneous methods

The synthesis of PVEs is not limited to the methodologies shown in Schemes 3-7. Other methodologies have been used to prepare specific molecules or families of compounds that contain this **C_2-O-C_3** motive with or without the intention of performing the corresponding rearrangement. Nevertheless, the methodologies shown in Schemes 8-14 are representative examples of different types of reactivities directed to isolate PVEs.

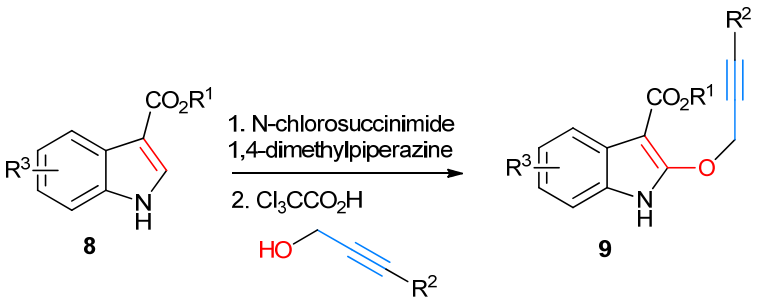
The landmark synthesis of azadirachtin complex naturalproduct by Ley's group called for the synthesis of n intermediate **7** (Scheme 8). Despite the observed mixtures of *O*- and *C*-alkylation products in experiments with simplified models of fragments **5** and **6**, the real system produced exclusively the desired *O*-alkylated product when the experimental protocol was carefully designed.[27]

[27] G. E. Veitch, E. Beckmann, B. J. Burke, A. Boyer, S. L. Maslen, S. V. Ley, *Angew. Chem. Int. Ed.* **2007**, *46*, 7629-7632.



Scheme 8. Synthesis from propargyl alcohol derivative **6** and ketone derivative **5**.

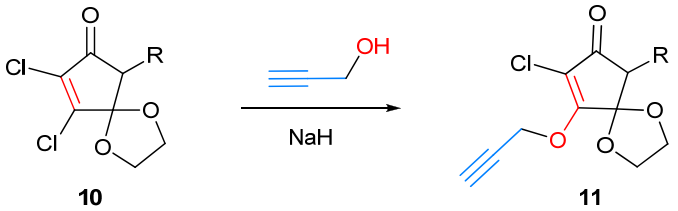
In a recent report dealing with the search for a catalytic enantioselective Claisen rearrangement of alkynyl vinyl ethers, functionalized indoles **8** were treated with N-chlorosuccinimide followed by substituted propargyl alcohols in the presence of an acid catalyst to afford a series of compounds **9** that contain the triple and the double bonds with the correct connectivity (Scheme 9).[28]



Scheme 9. Synthesis from propargyl alcohols and functionalized indoles.

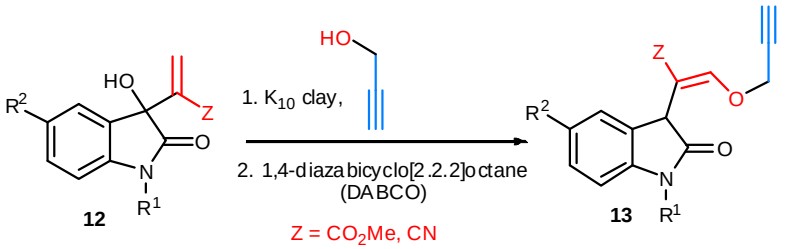
Another strategy employed is to use substrates which already possess the vinyl chloride functionality (or other halides) and which have a tendency to participate in substitution reactions with heteroatom-nucleophiles. Here, 2,3-dichlorocyclopentenones **10** react with the anion of propargyl alcohol to deliver the PVEs **11** (Scheme 10).[29]

[28] T. Cao, J. Deitch, E. C. Linton, M. C. Kozlowski, *Angew. Chem. Int. Ed.* **2012**, *51*, 2448-2451.
[29] R. R. Akhmetvaleev, L. R. Imaeva, T. A. Belogaeva, M. S. Miftakhov, *Russ. Chem. Bull.* **1997**, *46*, 1963-1964.



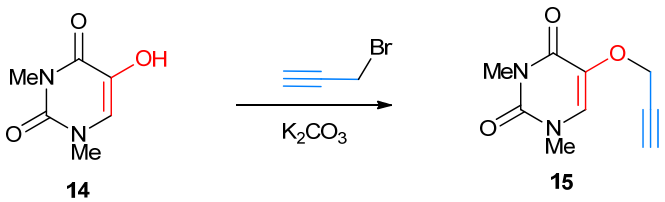
Scheme 10. Synthesis from propargyl alcohols and 2,3-dichlorocyclopentenones.

Morita-Baylis-Hillman adducts of isatin derivatives **12** have been transformed into propargyl ethers bearing a trisubstituted vinyl moiety **13** (Scheme 11)(Z = CO_2Me, CN).[30] The reaction takes place by nucleophilic addition of propargyl alcohol onto the Morita-Baylis-Hillman adduct, followed by a base-promoted isomerisation of the resulting allylic intermediate. In this same report, the highly functionalised PVEs are converted into the corresponding allenes via Claisen rearrangement in chlorobenzene at 135 ºC in good yields.



Scheme 11. Synthesis from propargyl alcohols and Morita-Baylis-Hillman adducts of isatin derivatives.

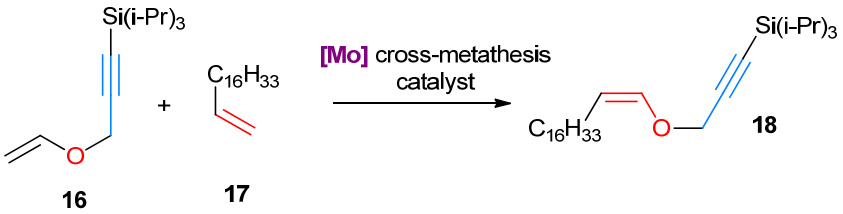
The reactivity of the reacting partners may also be changed as evidenced by the example shown in Scheme 12.[31] A vinyl alcohol, such as **14**, in the presence of a base can act as the nucleophilic species, while a propargyl bromide can act as the electrophilic counterpart. This methodology is reminiscent of the typical synthesis of propargyl aryl ethers. Furthermore, the [3,3]-sigmatropic rearrangement of substrate **15** affords an allene intermediate that gives 5- or 6-membered cyclisation products through a domino process.



Scheme 12. Synthesis from propargyl bromide and vinyl alcohol.

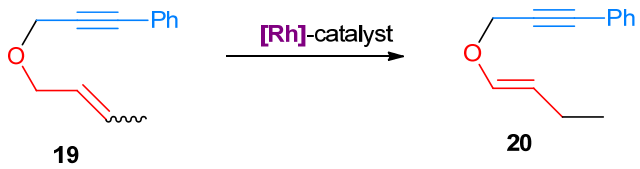
[30] V. Vaithiyanathan, K. Selvakumar, P. Shanmugam, *Synlett* **2009**, 1591-1596
[31] B. A. Otter, S. S. Saluja, J. J. Fox, *J. Org. Chem.* **1972**, *37*, 2858-2863.

Finally, reactions in Scheme 13 and Scheme 14 show two methods that have great potential applications. A novel approach to PVEs containing a substituted vinyl group has been recently reported (Scheme 13). Since the introduction of the plain vinyl group is well established (from propargyl alcohols and ethyl vinyl ether, see previous section), the desired vinyl group can be exchanged through a cross-metathesis reaction of an appropriate alkene.[32]



Scheme 13. Synthesis from propargyl vinyl ethers and substituted alkene.

On the other hand, the selective Rh-catalysed olefin isomerisation of 1,6-enynes instead of the better studied intramolecular cycloisomerisation provides PVEs (Scheme 14).[33]

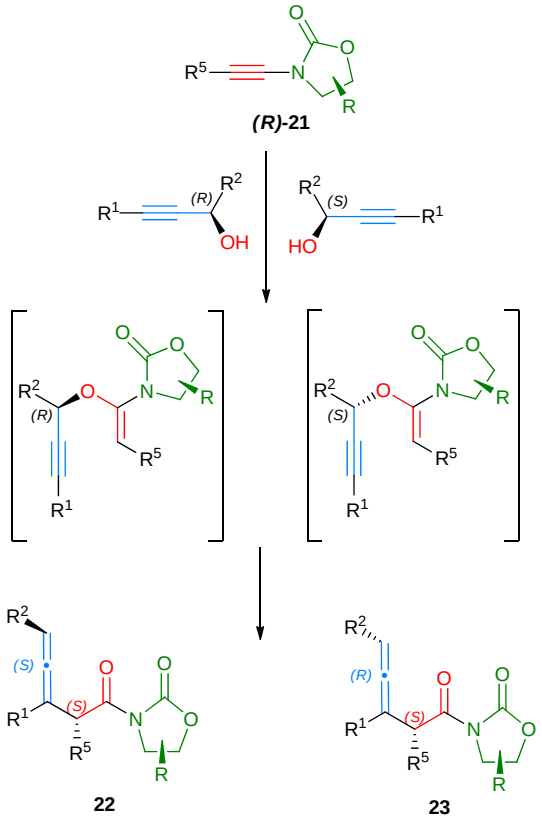


Scheme 14. Synthesis from propargyl homoallylic ethers catalyzed by Rh.

It is anticipated that these methodologies will be more regularly used in the future with applications that include a [3,3]-sigmatropic rearrangement.

It must also be added that there are other miscellaneous methodologies where, as in the case of the Johnson orthoester Claisen rearrangement, the PVEs are only reactive intermediates in way to the synthesis of allenic species. A good example may be the work done by Hsung and co-workers regarding the stereoselective synthesis of allenic amides from the acid-catalysed reaction of chiral ynamides *(R)*-**21** and propargyl alcohols (Scheme 15).[34] In the typical experimental conditions, the starting materials were heated at 100 ºC in sealed tubes for 24-48 h, where the PVEs were formed in situ and continued with the rearrangement to the corresponding allenes **22** and **23**.

[32] S. J. Meek, R. V. O'Brien, J. Llaveria, R. R. Schrock, A. Hoveyda, *Nature* **2011**, *471*, 461-466.
[33] P. Cao, B. Wang, X. Zhang, *J. Am. Chem. Soc.* **2000**, *122*, 6490-6491.
[34] K. C. M. Kurtz, M. O. Frederick, R. H. Lambeth, J. A. Mulder, M. R. Tracey, R. P. Hsung, *Tetrahedron* **2006**, *62*, 3928-3938.



Scheme 15. Stereoselective propargyl Claisen rearrangement using chiral ynamides.

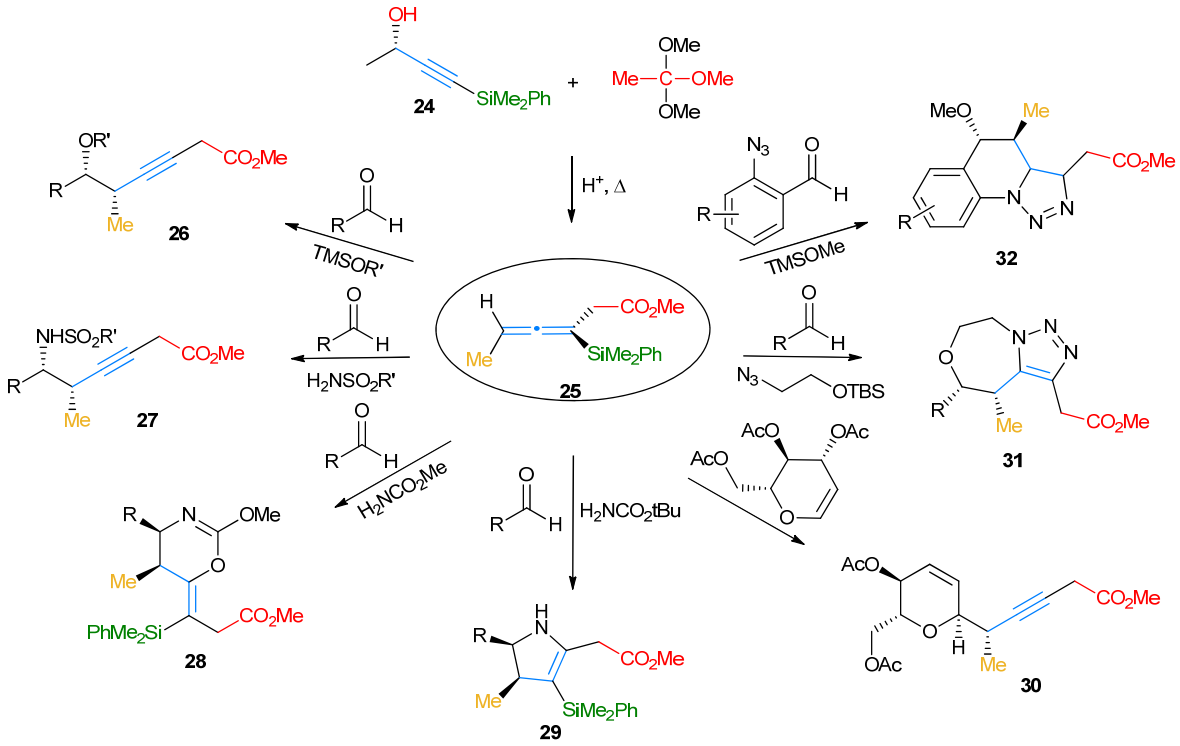
1.2. Allene synthesis and beyond

Although allenes are themselves a sought after class of organic compounds, they are in many cases excellent intermediates in route to other arrays of functional groups. In this section we will see how different strategies utilise the propargyl Claisen methodologies to gain access to more complex structures through functionalised allenes synthesised from PVEs.

1.2.1. Propargyl vinyl ethers as reactive intermediates

In many instances, the Johnson orthoester Claisen rearrangement of substituted propargylic alcohols is therefore the starting point for the development of a wide range of synthetic methodologies, being the PVE only a convenient intermediate of the reaction. For example, the group of Panek developed a suitable procedure for the synthesis of highly enantioenriched allenylsilane **25** from chiral propargylic alcohol **24**, which was further converted into functionalised alkynes (**26**, **27** and **30**), 4,5-dihydrooxazines **28**, 4,5-dihydropyrroles **29** and fused ring systems containing 1,2,3-triazoles (**31** and **32**, Scheme

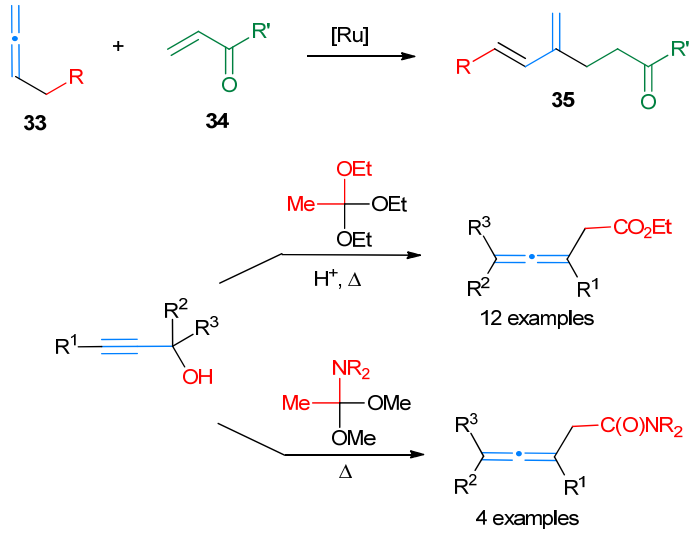
16).[35,36] It is worth mentioning that the key formation of the allenylsilanes were performed in refluxing xylenes with a catalytic amount of propionic acid in a 25 mmol scale. (R)-**24** afforded (S_a)-**25** in 79% yield and 98% ee while (S)-**24** afforded (R_a)-**25** in 81% yield and 98% ee.



Scheme 16. Synthesis and applications of highly enantioenriched allenylsilane **25**.

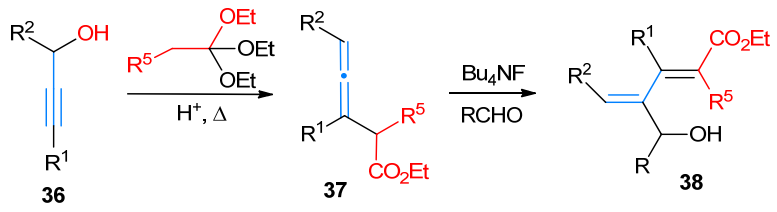
Trost et al. have developed a synthesis of 1,3-dienes via a ruthenium-catalysed reaction of allenes and activated olefins (Scheme 17).[37] To study the scope of the allenic component they utilised the propargyl orthoester Claisen rearrangement arguing that it is the most versatile and atom economic method for the preparation of allenic ester derivatives containing a full range of substitution patterns in the molecule. Interestingly, a set of tertiary allenic amides were also prepared with a modified procedure that employs dimethylacetamideacetals instead of triethylorthoacetate.[38] The work studies in detail the reactivity of mono-, di-, tri- and tetrasubstituted allenes towards activated olefins.

[35] R. A. Brawn, J. S. Panek, *Org. Lett*. **2007**, *9*, 2689-2692.
[36] R. A. Brawn, J. S. Panek, *Org. Lett*. **2010**, *12*, 4624-4627 and references cited therein.
[37] B. M. Trost, A. B. Pinkerton, M. Seidel, *J. Am. Chem. Soc*. **2001**, *123*, 12466-12476.
[38] K. A. Parker, J. J. Petraitis, R. W. Kosley, S. L. Buchwald, *J. Org. Chem*. **1982**, *47*, 389-398.



Scheme 17. Ruthenium-catalysed two-component formation of 1,3-dienes. Synthesis of starting allenic compounds.

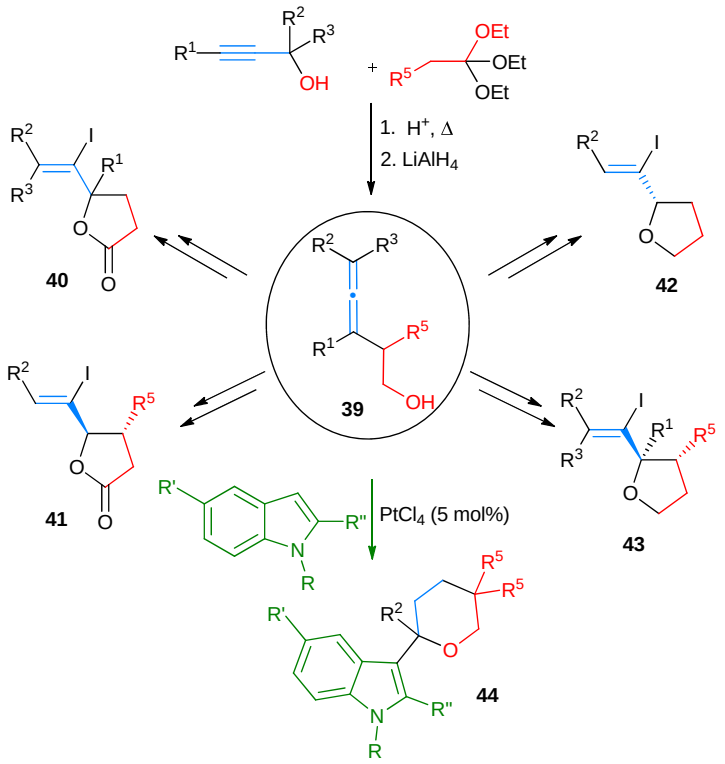
In another recent study, (2*E*,4*E*)-4-carbinol alkadienoates **38** have been synthesised stereoselectively in a two-step procedure from propargylic alcohols through a Claisen rearrangement – aldol reaction sequence (Scheme 18).[39] The β-allenyl ester intermediates **37** were functionalized through trapping of the allenylenolate with a carbon electrophile. Confirming that the rearrangement is a robust methodology, the β-allenyl esters were prepared in up to 70 mmol scale.



Scheme 18. Propargyl Claisen rearrangement – aldol reaction sequence.

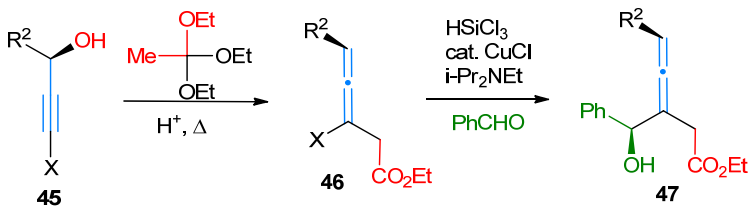
The group of Ma et al. has also been particularly active in the field of allenes. In many occasions, they have found the ortho Claisen rearrangement to be especially useful in the preparation of desired intermediates. Allenols **39** have been converted into lactones **40** and **41** through highly stereoselectiveiodolactonization,[40] tetrahydrofurans **42** and **43** through highly regio- and stereoselective cyclic iodoetherification,[41] or directly into compounds **44** through a $PtCl_4$-catalyzed cyclization reaction in the presence of indoles[42] (Scheme 19).

[39] J. C. Aponte, G. B. Hammond, B. Xu, *J. Org. Chem*. **2009**, *74*, 4623-4625.
[40] X. Jiang, C. Fu, S. Ma, *Chem. Eur. J*. **2008**, *14*, 9656-9664.
[41] B. Lu, X. Jiang, C. Fu, S. Ma, *J. Org. Chem*. **2009**, *74*, 438-441.
[42] W. Kong, J. Cui, Y. Yu, G. Chen, C. Fu, S. Ma, *Org. Lett*. **2009**, *11*, 1213-1216.



Scheme 19. Synthesis and applications of functionalized allenols **39**.

Alkynyl halides have also been used as functionalized starting units to synthesise valuable allenyl halides via the propargyl orthoester Claisen rearrangement. For example, Hsung and col. have studied the stereospecific conversion of alkynyl halides **45** into allenyl bromides or chlorides **46** and their subsequent coupling with aldehydes with transfer of chirality (Scheme 20).[43] With regard to the transformation **45**→**46**, the optimization of reaction conditions established that alkynyl bromides were more effective than the corresponding chlorides and iodides, while the reactions were conducted in toluene at 100 ºC with AcOH as the catalyst.

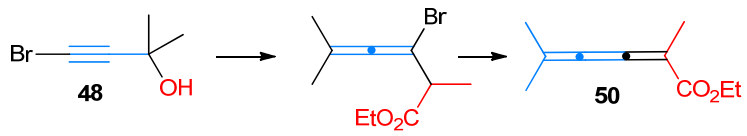


Scheme 20. Synthesis and reactivity of enantiomerically enriched allenyl halides.

In another attractive application, alkynyl bromide **48** was transformed into cumulene

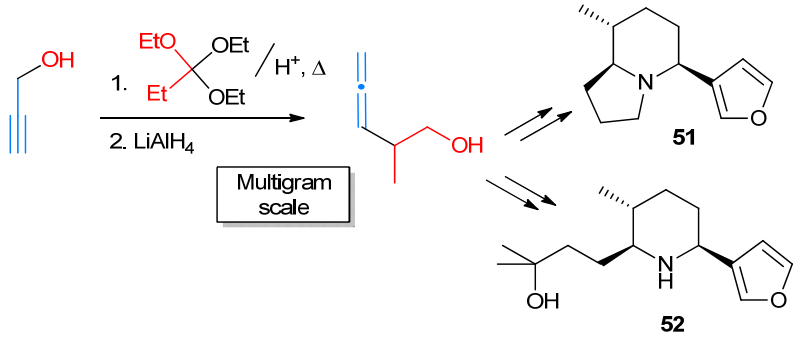
[43] Y. Tang, L. Shen, B. J. Dellaria, R. P. Hsung, *Tetrahedron Lett.* **2008**, *48*, 6404-6409.

50 through a rearrangement - hydrogen bromide elimination sequence (Scheme 21).[44]



Scheme 21. Two-step synthesis of cumulenes.

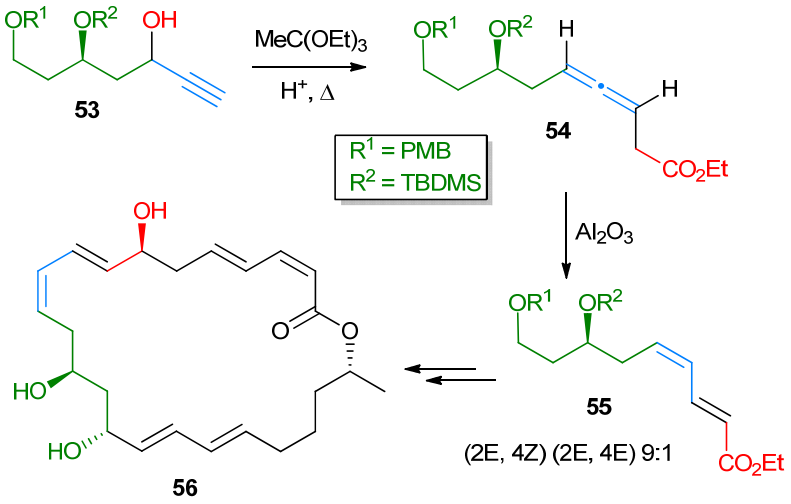
The field of natural product synthesis has also witnessed the use of the Johnson orthoester Claisen rearrangement of acetylenic compounds. For example, evidencing that this is an straightforward methodology, propargyl alcohol and triethylorthopropionate have been converted to an allenic alcohol in essentially quantitative yield in a multigram scale as the first step toward the synthesis of Nuphar alkaloids **51** and **52** (Scheme 22).[45]



Scheme 22. Allenic alcohol in route to alkaloids **51** and **52**.

A more elaborated propargylic alcohol **53** containing two protected hydroxyl groups has also been subjected to the [3,3]- sigmatropic transformation as one of the key steps during the synthesis of Macrolactin A **56** (Scheme 23).[46] The authors explain that some experimentation was required to improve the yield of allene **54**, with the best conditions being, 140 °C in the presence of 10% of propionic acid during 8 h, removing ethanol in vacuo and re-adding ethyl orthoacetate/propionic acid every 2 h. In this manner, **54** was found to be pure enough to be engaged in the alumina-mediated isomerization reaction to afford a conjugated diene **55** with good stereoselectivity in favour of the desired product (9:1 (2*E*,4*Z*)/(2*E*,4*E*) mixture). Notice that the original propargylic alcohol is easily transformed into a diene with an additional functionality (ester group) that in turn will gain access to a chiral hydroxyl group.

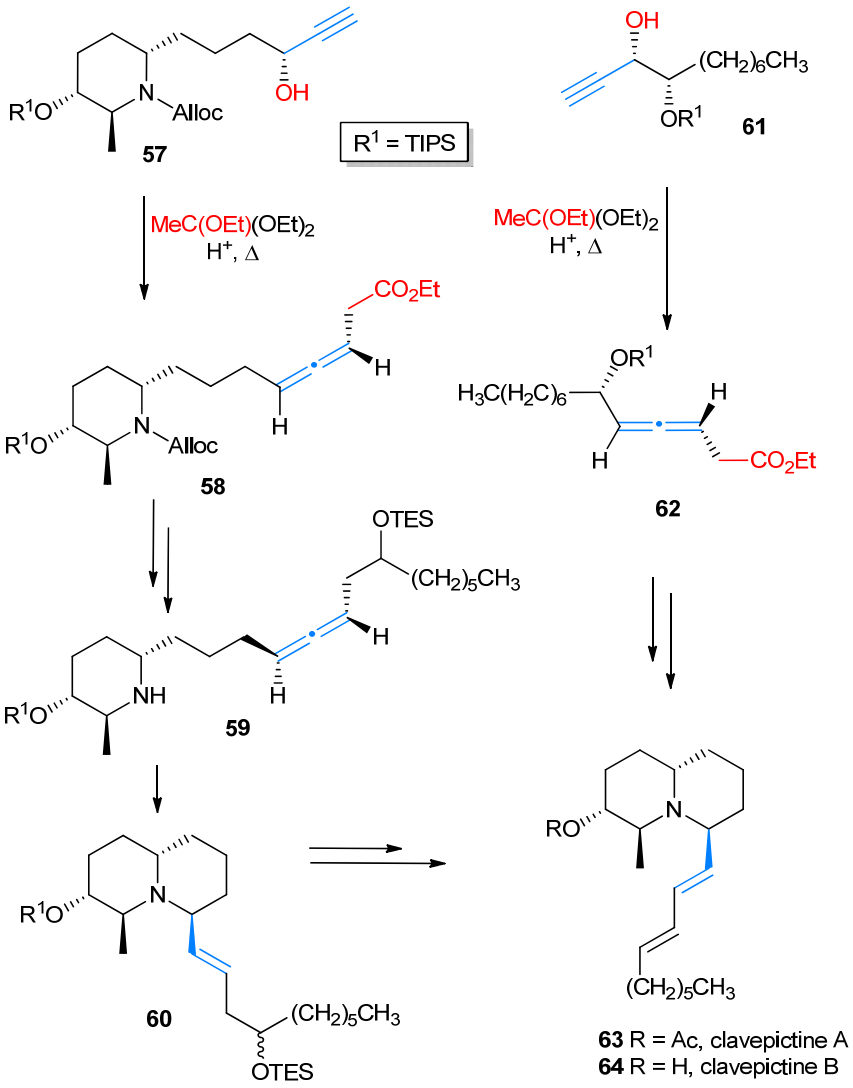
[44] R. W. Saalfrank, A. Welch, M. Haubner, *Angew. Chem. Int. Ed.* **1995**, *34*, 2709.
[45] R. W. Bates, C. J. Lim, *Synlett* **2010**, 866-868.
[46] M. Georgy, P. Lesot, J.-M. Campagne, *J. Org. Chem*. **2007**, *72*, 3543-3549.



Scheme 23. Johnson orthoester Claisen rearrangement – allene isomerization in the synthesis of Macrolactin A.

In a different study, an elegant stereocontrolled total synthesis of clavepictine A **63** and clavepictine B **64** was accomplished in which a key step was a rare diastereoselective silver(I)-promoted cyclisation of δ-amino allenes (**59**→**60** Scheme 24).[47] In a first-generation approach, the required allene **58** bearing a strategically placed piperidine ring was efficiently synthesised from a somewhat complex enantiopure propargyl alcohol **57** in a diastereoselective manner using the standard reaction conditions in 83% yield. In a second-generation approach, seeking to reduce the overall number of steps, a propargyl alcohol **61** bearing a silylated protecting group but with the absence of the piperidine ring was converted into the allenic ester **62** with excellent diastereocontrol in 71% yield (1.0 g scale). As in the previous approach, a key diastereoselective cyclisation of a δ-amino allene eventually lead to the synthesis of both clavepictine A and B.

[47] J. D. Ha, J. K. Cha, *J. Am. Chem. Soc*. **1999**, *121*, 10012-10020.



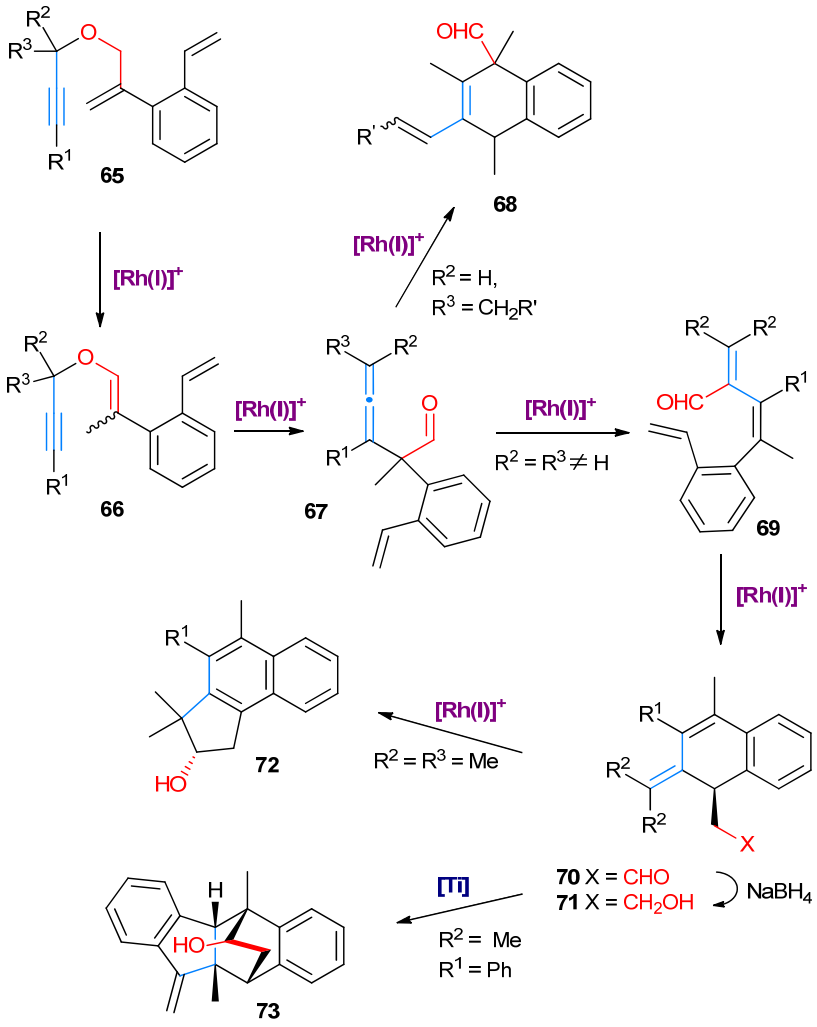
Scheme 24. Claisen rearrangement and cyclization of δ-aminoallenes in the synthesis of clavepictines A and B. Alloc = allyloxycarbonyl.

Finally, an impressive example of domino reactions that include the selective rhodium-catalysed olefin isomerisation of 1,6-enynes has been recently reported (see Scheme 14). The careful design of the starting 1,6-enyne (synthesised in two steps from commercially available compounds) places all the desired functionalities at strategically correct positions so that a set of rhodium catalysed reactions take place in a controlled manner (Scheme 25).[48]

Thus, 1,6-dienyne **65** isomerises to PVE **66** before rearranging to the allenic aldehyde **67** (40-80 ºC). When secondary propargyl ethers are formed (R^2 = H) and R^3 contains a methylene group, substituted 1,4-dihydronaphthalenes **68** form as mixtures of diastereomers

[48] E. Okazaki, R. Okamoto, Y. Shibata, K. Noguchi, K. Tanaka, *Angew. Chem. Int. Ed*. **2012**, *51*, 6722-6727.

through an enallene cycloisomerisation. On the other hand, when tertiary propargyl ethers are formed ($R^2 = R^3 \neq H$), allenic aldehyde **67** suffers a carbonyl migration reaction followed by a cyclisation reaction to afford substituted 1,2-dihydronaphthalenes **70**. If more elevated temperatures and prolonged reaction times are used, naphthalenes **72** are formed through a carbonyl ene reaction of product **70**.



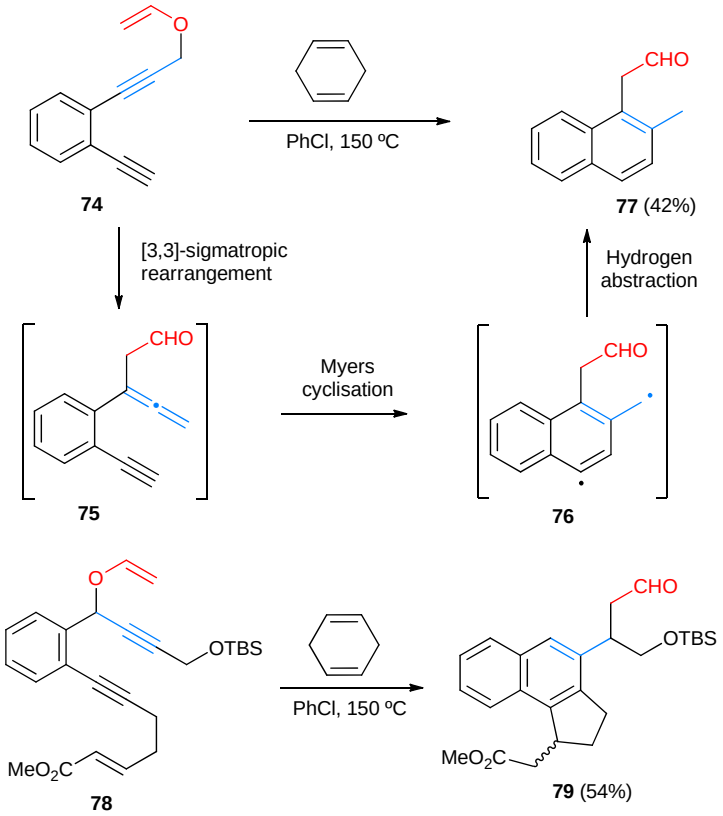
Scheme 25. Rhodium-catalysed domino reactions of 1,6-dienynes.

Interestingly, the product formation of **68**, **70** and **72** from 1,6-dienyne **65** are selective one-pot syntheses that take place through domino processes just by changing the reaction conditions or the nature of the substituents. Additionally, if chiral bisphosphine ligands are used in combination with the cationic rhodium catalyst, products **70**-**72** can be obtained with moderate to good enantioselectivities. Ultimately, pentacyclic product **73** can be obtained from **70** by the coupling of two domino processes which includes a new $TiCl_4$ mediated transformation.

1.2.2. Propargyl vinyl ethers as suitable platforms for domino chemistry

When the PVEs can be isolated, synthetic strategies may be designed so that the propargyl Claisen rearrangement is the first step of a domino process, and the corresponding allenes are only reaction intermediates. For example, Grissom and co-workers designed tandem enyneallene-radical cyclisation processes by strategically placing an aromatic ring into PVEs bearing an additional alkyne functionality (Scheme 26).[49]

In the first case, the aromatic ring is directly bonded to the alkyne which participates in the [3,3]- sigmatropic rearrangement. Thus, PVE **74** preferentially delivered allene **75** only as a reactive intermediate. This was followed by an enyne-allene cyclisation to form biradical **76** (Myers cyclisation) and a hydrogen abstraction from 1,4-cyclohexadiene to form the disubstituted naphthalene **77** as the major product. Furthermore, a more elaborated PVE **78** bearing the alkyne-functionalised aromatic ring at the propargylic position delivered the tricyclic product **79** as a mixture of diastereomers through a domino process that included an additional cyclisation reaction. Hence, the overall process entailed a [3,3]-sigmatropic rearrangement – Myers cyclisation – *5-exo* radical cyclisation – hydrogen abstraction in chlorobenzene at 150 ºC.

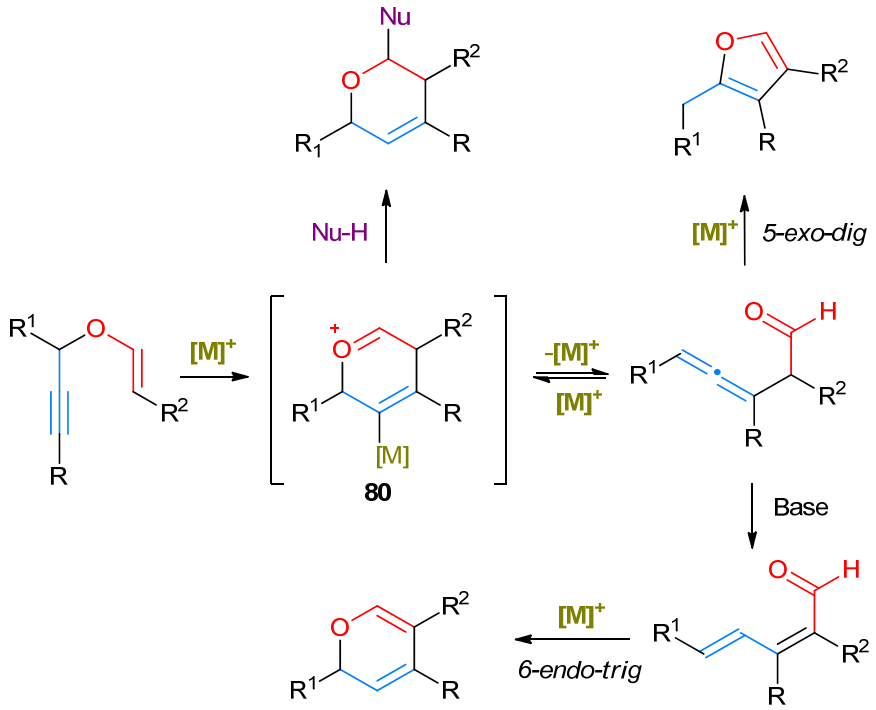


Scheme 26. An example of enyne-allene radical cyclisation.

[49] J. W. Grissom, D. Klingberg, D. Huang, B. J. Slattery, *J. Org. Chem*. **1997**, *72*, 603-626.

1.2.3. Metal-catalysed domino processes

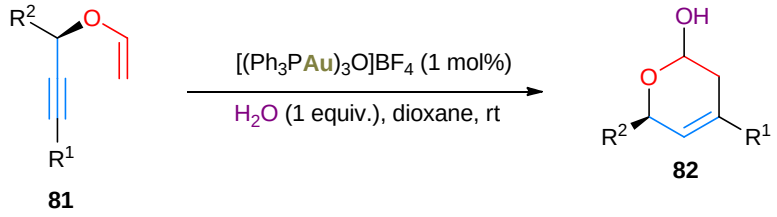
Gold catalysis has increased the synthetic potential of this chemistry allowing it to be performed under much milder reaction conditions and oriented to more structural diversity. Scheme 2 already showed how Toste and co-workers were able to carry out the [3,3]-sigmatropic transformation at room temperature with the gold (I) complex $[(Ph_3PAu)_3O]BF_4$. As a general reactivity principle, in the presence of a carbophilic metal catalyst (e.g., gold), PVEs rearrange into the intermediate oxonium derivatives **80**, which in turn can afford different products as a function of the reaction conditions (Scheme 27). In the absence of an external nucleophile, the *5-exo-dig* cyclization is the most favoured reaction pathway affording the corresponding furan derivatives. The base catalysed rearrangement of the allenal internediate into the corresponding α,β,γ,δ-dienal requires catalyst modulation in order to avoid the otherwise favoured formation of the furan derivative.



Scheme 27. Metal-catalysed rearrangements of PVEs.

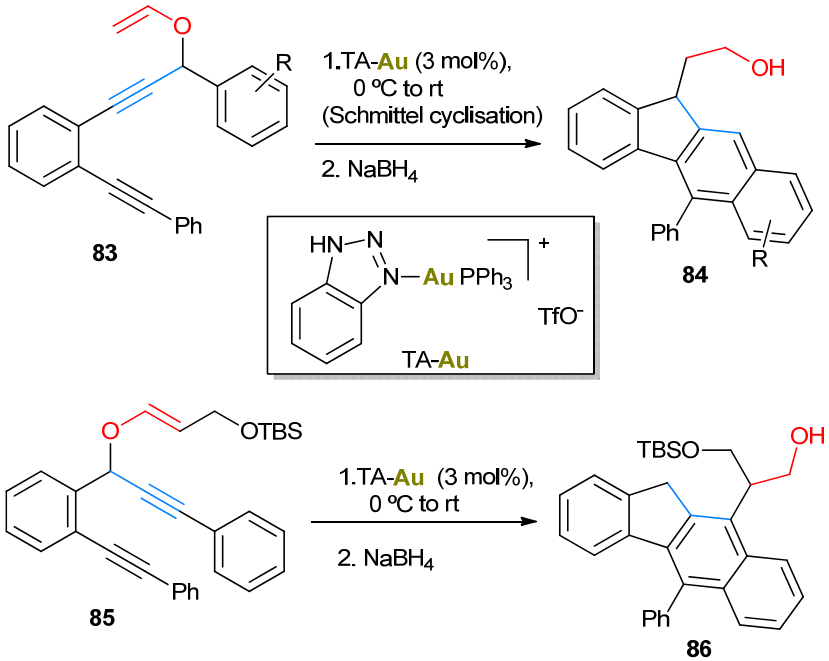
Following this reactivity guide, the same group developed a gold-cvatalysed domino methodology to construct 3,6-dihydro-2H-pyran-2-ol derivatives **82**.[50] The reaction entails a gold-catalysed *6-endo-trig* cyclisation followed by addition of water. Interestingly, the authors also demonstrated that the Claisen/heterocyclisation proceeded with excellent diastereocontrol and chirality transfer from the PVE stereocenter (Scheme 28).

[50] B. D. Sherry, L. Maus, B. N. Laforteza, F. D. Toste, *J. Am. Chem. Soc*. **2006**, *128*, 8132-8133.



Scheme 28. Au(I)-catalysed synthesis of 2-hydroxy dihydropyrans.

The work by Toste and co-workers sparked a great amount of research dealing with the metal-catalysed propargyl Claisen rearrangement. For instance, as part of a program directed to the search of novel and effective catalytic systems that selectively activate alkynes, Shi et al. studied triazole-gold catalysts in the rearrangement of PVEs bearing aromatic and alkyne substituents, reminiscent of the work previously described in Scheme 26. In this work, the substrates were devised so that a Schmittel cyclisation would be favoured in the course of the reaction. Therefore, PVEs **83** went through a propargyl Claisen rearrangement – radical cyclisation cascade process to afford the tetracyclic products **84**. Similarly, PVE **85** was converted into **86** containing a different substitution pattern (Scheme 29).[51] Both transformations proceeded with good chemoselectivity under mild reaction conditions (0 ºC to room temperature in CH_2Cl_2 as the solvent).

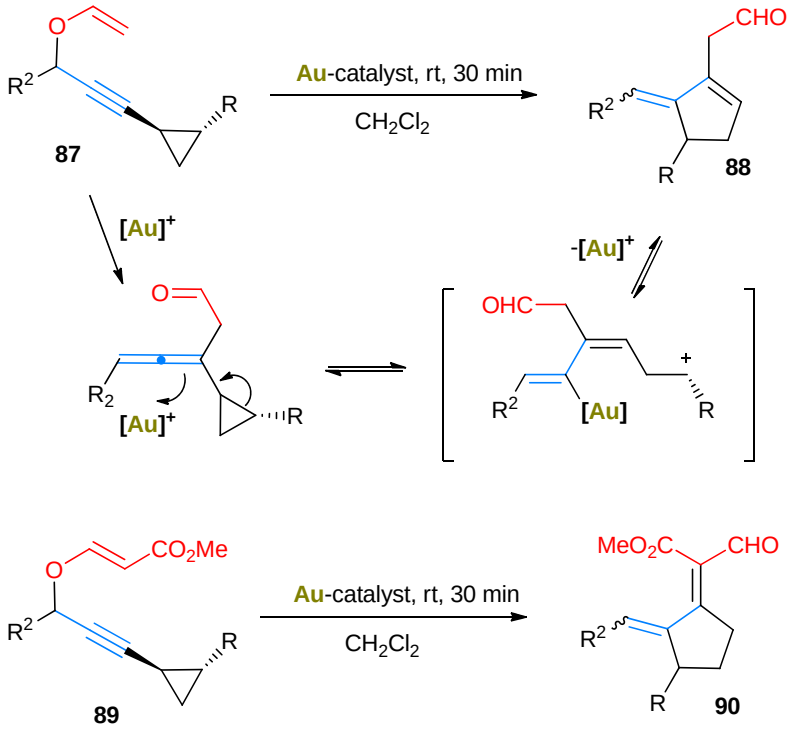


Scheme 29. Gold-catalysed propargyl Claisen rearrangement – Schmittel cyclisation.

[51] Q. Wang, S. Aparaj, N. G. Akhmedov, J. L. Petersen, X. Shi, *Org. Lett*. **2012**, *14*, 1334-1337.

The group of Nevado and co-workers envisioned a domino process in which a cyclopropyl group could participate once the propargyl Claisen rearrangement would have taken place. Hence, substrates **87** and **89** accommodating the small-size ring directly bonded to the alkyne moiety were stirred with catalytic amounts of a gold catalyst at ambient temperature to deliver substituted cyclopentenes **88** and **90** in good yields and short periods of time (Scheme 30).[52]

The domino process therefore included a [3,3]-sigmatropic rearrangement, a cyclopropyl ring opening and a cyclisation. Key to the success of the reaction was the presence of a substituent R that would aid in the delocalization of the δ^+ generated upon cyclopropyl ring opening.



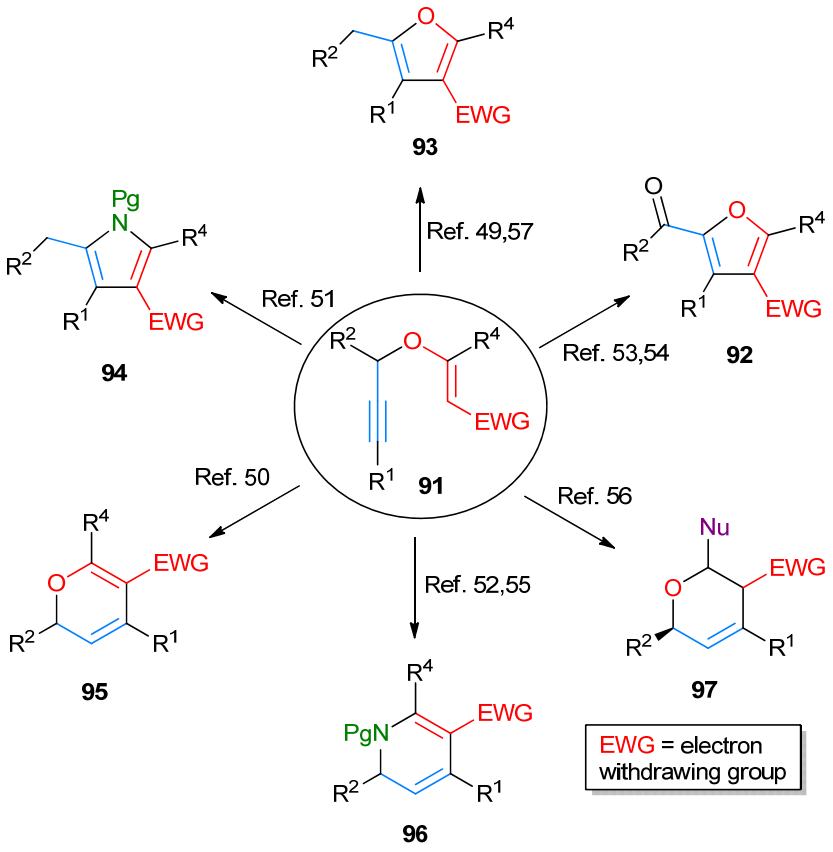
Scheme 30. Au(I)-catalysed Claisen rearrangement - cyclopropyl ring opening – cyclisation.

The ease of preparation of PVEs bearing an ester substituent at the vinyl functionality[23,24,25,26] in combination with metal catalysis has also been the source of inspiration for various research groups, especially those of Kirsch and co-workers[53,54,55,56] and Jiang and

[52] D. Garayalde, E. Gómez-Bengoa, X. Huang, A. Goeke, C. Nevado, *J. Am. Chem. Soc*. **2010**, *132*, 4720-4730.
[53] M. H. Suhre, M. Reif, S. F. Kirsch, *Org. Lett*. **2005**, *7*, 3925-3927.
[54] H. Menz, S. F. Kirsch, *Org. Lett*. **2006**, *8*, 4795-4797.
[55] J. T. Binder, S. F. Kirsch, *Org. Lett*. **2006**, *8*, 2151-2153.
[56] T. Harschneck, S. F. Kirsch, *J. Org. Chem*. **2011**, *76*, 2145-2156.

co-workers.[57,58] As Scheme 31 summarises, PVEs can be converted via domino processes into furans **92**[57,58]or **93**,[53,59] 2*H*-pyrans **95**[54] or 3,6-dihydro-2*H*-pyrans **97**.[60] Likewise, PVEs has been transformed into pyrroles **94**[55]and 1,2-dihydropyridines **96**[56,61] in one pot manner in the presence of an suitable base and a primary amine. Although in the majority of occasions gold complexes are used as catalysts, there have also been reports of the use of copper, silver, iron and palladium salts. Key to these transformations is the correct choice of the metal catalyst to selectively activate the different species present in the reaction pathway (PVE, oxocarbenium ion and allene, Scheme 27).

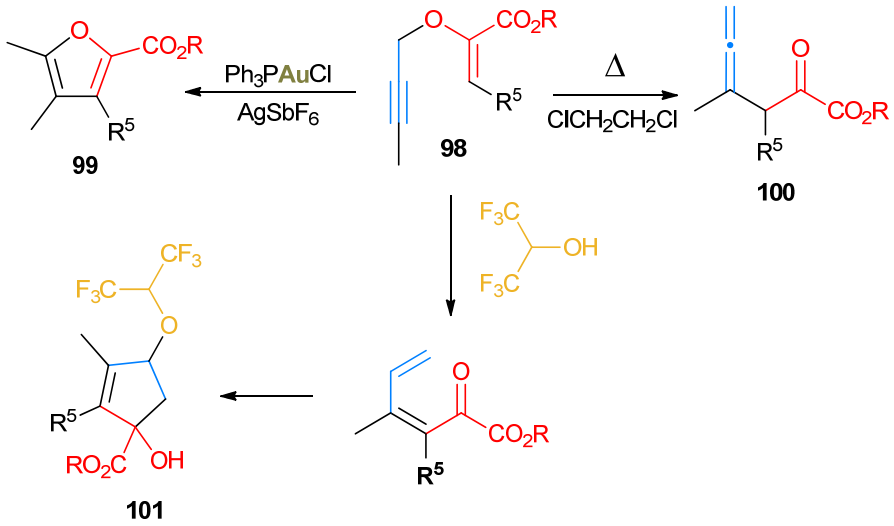
Another important aspect is that ingenious methodologies can be designed so that nucleophiles that are unreactive towards the PVE could trap one of the reaction intermediates to afford even more diversity in the product distribution (e.g., **94** and **96).**



Scheme 31. Metal-catalysed transformations from PVEs.

[57] H. Cao, H.-F. Jiang, H.-W. Huang, J.-W. Zhao, *Org. Biomol. Chem*. **2011**, *9*, 7313-7317 and references cited there in.
[58] H. Huang, H. Jiang, H. Cao, J. Zhao, D. Shi, *Tetrahedron* **2012**, *68*, 3135-3144 and references cited there in.
[59] A. Saito, T. Konishi, Y. Hanzawa, *Org. Lett*. **2010**, *12*, 372-374. This work also describes the amino-Claisen rearrangement of N-propargyl enaminone derivatives leading to polysubstituted pyrroles.
[60] E. Matoušová , A. Růžička, J. Kuneš, J. Králová, M. Pour, *Chem. Commun*. **2011**, *47*, 9390–9392.
[61] H. Wei, Y. Wang, B. Yue, P.-F. Xu, *Adv. Synth. Catal*. **2010**, *352*, 2450-2454.

A different scenario takes place if the electron withdrawing group of the vinyl group is located at the other carbon position. The synthesis of these PVEs is not as straightforward (4 steps are required staring from propargyl alcohols) but their [3,3]-sigmatropic rearrangement (sometimes referred as the Gosteli-Claisen rearrangement)[62] leads to new transformations that depend on the reaction conditions. Thus, Hiersemann and co-workers[63] have reported catalysed and uncatalysed domino molecular transformations from PVEs **98** (Scheme 32). Not surprisingly, in the presence of the $Ph_3PAuCl/AgSbF_6$ system, tetrasubstituted furans **99** were obtained following the reactivity principle described in Scheme 27. On the other hand, thermal rearrangement of PVEs **98** afforded the allenic α-ketoester **100** if performed in 1,2-dichloroethane, or an unexpected polysubstituted cyclopentene **101** if performed in fluorinated alcohols which act as nucleophiles.

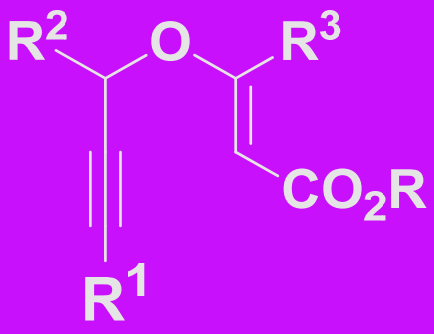


Scheme 32. Gosteli-Claisen rearrangement of propargyl vinyl ethers.

1.2.4. Microwave-driven domino processes

Redounding on the use of easily accessible PVEs synthesised from propargyl alcohols and conjugated alkynoates, our research group has studied the metal- free, microwave-induced rearrangement of these substrates in the presence or absence of external nucleophiles with very simple and bench friendly experimental protocols and the results obtained are going to be discussed in the following chapters.

[62] J. Rehbein, S. Leick and M. Hiersemann, *J. Org. Chem.* **2009**, *74*, 1531-1540.
[63] A. Gille, J. Rehbein, M. Hiersemann, *Org. Lett.* **2011**, *13*, 2122-2125.



CHAPTER 2

Aims

2. Aims:

2.1. General aims:

2.1.1. The development of new microwave-assisted domino processes and their application to the Diversity-Oriented Synthesis (DOS) of small molecules of chemical and/or biological interest.

2.1.2. The study of the reactivity profile of functionalized propargyl vinyl ether motives (platforms) and its instrumentalization in the development of novel metal-free domino processes.

2.1.3. To gain knowledge about the mechanistic insights of metal-free domino processes of relevant propargyl vinyl ethers which begin with the thermally-driven [3,3]-Claisen rearrangement.

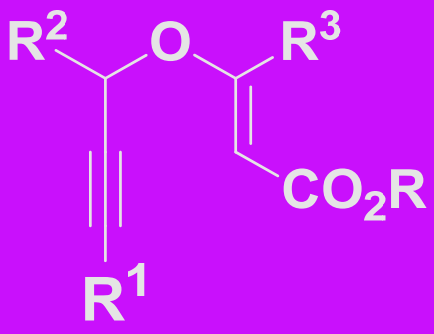
2.1.4. Synthesis of small libraries of compounds featuring functional and structural diversity from simple and readily available starting materials.

2.2. Specific aims:

2.2.1. The development of domino processes based on the thermally-driven [3,3]-Claisen rearrangement of propargyl vinyl ethers in the presence of nitrogen-containing nucleophiles.

2.2.2. The development of domino processes based on the thermally-driven [3,3]-Claisen rearrangement of propargyl vinyl ethers in the presence of oxygen-containing nucleophiles.

2.2.3. The development of domino processes based on the thermally-driven [3,3]-Claisen rearrangement of propargyl vinyl ethers in the absence of nucleophiles.



CHAPTER 3

A Convenient Domino Access to Substituted Alkyl 1,2-Dihydropyridine-3- carboxylates from Propargyl Enol Ethers and Primary Amines

CHEMISTRY
A EUROPEAN JOURNAL

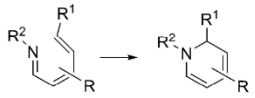
DOI: 10.1002/chem.200902140

A Convenient Domino Access to Substituted Alkyl 1,2-Dihydropyridine-3-carboxylates from Propargyl Enol Ethers and Primary Amines

David Tejedor,*[a, b] Gabriela Méndez-Abt,[a, b] and Fernando García-Tellado*[a, b]

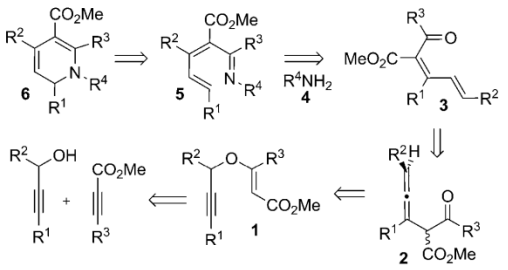
Dedicated to Professor José Barluenga Mur on the occasion of his 70th birthday

Azatrienes constitute important synthetic blocks for the synthesis of six-membered nitrogen heterocycles.[1] In particular, thermally driven 6π-electron electrocyclic ring closure (6π-aza-electrocyclization) of 1-azatrienes constitutes a main synthetic avenue to pyridines and 1,2-dihydropyridines [Eq. (1)].[2]



(1)

Pivotal to this strategy is the chemical access to the functionalized 1-azatriene unit. Currently, these units are assembled in situ and directly used to construct the nitrogen heterocycle. In particular, the Knoevenagel condensation of iminium ions with vinylogous amides has proved to be a successful strategy for the assembly of these units in route to chiral 1,2-dihydropyridines.[3] We envisioned that an alternative and more direct access to 1-azatrienes could rely on the reaction of primary amines **4** and 2,4-dienals **3** (Scheme 1),[4] which in turn could be obtained by a thermally driven [3,3] propargyl Claisen rearrangement of easily accessible propargyl vinyl ethers **1**. Precedents for the metal-catalyzed version of this rearrangement[5,6] have shown that the substitution pattern of the propargyl vinyl ether plays an important role on both the reaction conditions and the chemical outcome of the rearrangement. Under metallic catalysis, propargyl vinyl ethers **1** rearrange to allenes **2** that can reorganize to furans,[5c] 2*H*-pyrans,[5b] or dihydropyrans[5d] through selective 5-*exo*-dig or 6-*endo*-trig cyclizations, or they can afford substituted pyrroles[5a] by one-pot condensation with a primary amine and subsequent metal-catalyzed 5-*exo*-dig cyclization. We hypothesized that allenes **2**, in the absence of metals, would reorganize to 2,4-dienals **3** by means of a thermally allowed prototropic rearrangement biased by the ester group allocated at the α-position of both the allene and aldehyde functions (Scheme 1).[7] In the presence of a primary amine, 2,4-dienal **3** could form the corresponding functionalized 1-azatriene **5**, which in turn would rearrange to the 1,2-dihydropyridine derivative **6** through a 6π-aza-electrocyclization. Because the [3,3] propargyl enol ether rearrangement is expected to be compatible with the presence of a primary amine, we anticipated that the reaction could be carried out in a domino fashion.[8] Overall, the entire process would constitute a novel, modular, and metal-free domino synthesis of tetrasubstituted alkyl 1,2-dihydropyri-



Scheme 1. Proposed domino synthesis of 1,2-dihydropyridines from primary amines and propargyl vinyl ethers.

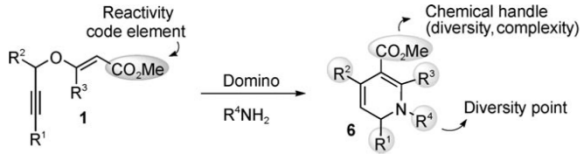
[a] Dr. D. Tejedor, G. Méndez-Abt, Dr. F. García-Tellado
Department of Química Biológica y Biotecnología
Instituto de Productos Naturales y Agrobiologia
Consejo Superior de Investigaciones Científicas
Avda. Astrofísico Francisco Sánchez 3
38206 La Laguna, Tenerife (Spain)
Fax: (+34) 922-260135
E-mail: fgarcia@ipna.csic.es
dtejedor@ipna.csic.es

[b] Dr. D. Tejedor, G. Méndez-Abt, Dr. F. García-Tellado
Instituto canario de Investigación del Cáncer (Spain)
Website: www.icic.es

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200902140.

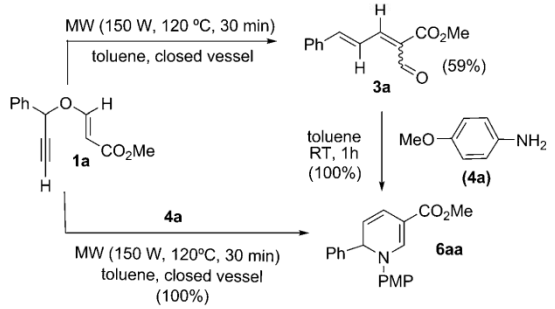
COMMUNICATION

dine-3-carboxylate derivatives from primary amines and propargyl enol ethers through a propargyl Claisen rearrangement/isomerization/amine condensation/6π-aza-electrocyclization process. Importantly, the ester group, which would be playing a vital role as a reactivity controlling element during the process, would be incorporated into the final 1,2-dihydropyridine unit as a convenient chemical handle for further generation of complexity and/or chemical diversity. Overall, in terms of diversity-oriented synthesis, 1,2-dihydropyridines **6** could be generated in a modular manner with four possible points for diversity generation (R^1–R^4) and a chemical handle for further elaboration (Scheme 2). In addition, propargyl enol ethers **1** are easily accessible starting materials spanning a wide substitution pattern.[9] In this communication we report on the proof of concept of this strategy and its extension to the synthesis of nicotinic acid derivatives.



Scheme 2. Modular and diversity oriented synthesis of substituted 1,2-dihydropyridines **6** featuring four possible diversity points and one chemical handle (carboxylic ester at C_3) for further complexity/diversity generation.

We started this work studying the reaction of *p*-anisidine (**4a**) and propargyl enol ether **1a** (Scheme 3). After some experimental work, we found that microwave irradiation[10] of a solution of **1a** in toluene (150 W, 120 °C, 30 min) afforded the corresponding dienal **3a**, which could be isolated as a mixture of *E*/*Z* (1:1) isomers in 59 % yield after flash-chromatographic purification (Scheme 3). This finding corroborates the advanced importance of the conjugated electron-withdrawing group at the terminus of the enol function (Scheme 2, reactivity-code element). Notably, after the rearrangement, this group is placed at the sp^3-position of intermediate allene **2** (Scheme 1), biasing the energetically

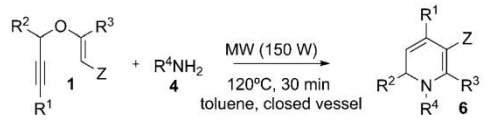


Scheme 3. Proof of concept: two-step versus domino reaction.

favored prototropic 1,3-rearrangement of allene **2** to the fully conjugated dienal **3a**.[11] Subsequent treatment of dienal **3a** with *p*-anisidine (**4a**; 1 equiv) at room temperature in toluene for 1 h delivered 1,2-dihydropyridine **6aa** in quantitative yield. It is remarkable that the double-bond geometries do not have a noticeable effect on the yield of this cyclization.[12] Once we proved that our synthetic concept could be conveniently carried out in a two-step manner, we next studied the domino version of this process by the direct reaction of the amine and the propargylic derivative **1a** under microwave irradiation. After some experimental efforts, we found that the microwave irradiation (150 W 120 °C, closed vessel, 30 min) of a solution of **4a** (1.1 mmol.) with **1a** (1 mmol) in toluene (5 mL) afforded 1,2-dihydropyridine **6aa** with an impressive efficiency (quantitative yield; Scheme 3).

Once the proof of concept was established, we next studied the scope of this reaction with regard to the propargylic component and the amine (Table 1). In general, the reaction presented a broad spectrum for the amine although aromatic amines gave better yields than aliphatic amines (compare entries 1, 15 and 16 with entries 10–14). The effect of diastereo induction by the amine component was studied with the commercial amine **4e**, which afforded chiral 1,2-dihydropyridine **6ae** with a significant 50 % de (entry 13). Presumably, other more sterically demanding chiral amines would introduce higher levels of stereo induction in this reaction.[13] The substitution pattern of the propargylic unit **1** was also

Table 1. Domino synthesis of 1,2-dihydropyridines **6** from propargyl enol ethers **1** and primary amines **4**.[a]

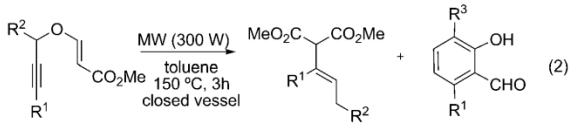


	R^1	R^2	R^3	**1**	R^4	**4**	**6**	Yield [%]
1	H	Ph	H	**a**	*p*MeOC_6H_4	**a**	**aa**	100
2	H	H	H	**b**	*p*MeOC_6H_4	**a**	**ba**	51[b]
3	H	Me	H	**c**	*p*MeOC_6H_4	**a**	**ca**	87
4	H	*n*Pent	H	**d**	*p*MeOC_6H_4	**a**	**da**	71
5	Ph	Ph	H	**e**	*p*MeOC_6H_4	**a**	**ea**	95
6	*c*Hex	Ph	H	**f**	*p*MeOC_6H_4	**a**	**fa**	55
7	H	Ph	Me	**g**	*p*MeOC_6H_4	**a**	**ga**	24[c]
8	H	Me	Me	**h**	*p*MeOC_6H_4	**a**	**ha**	17[c]
9	H	Ph	H	**i**	*p*MeOC_6H_4	**a**	**ia**	80[d]
10	H	Ph	H	**a**	Bn	**b**	**ab**	83
11	H	Ph	H	**a**	allyl	**c**	**ac**	72
12	H	Ph	H	**a**	Ad[e]	**d**	**ad**	87
13	H	Ph	H	**a**	(S)PhCHMe	**e**	**ae**	83[f]
14	H	Ph	H	**a**	PMB[g]	**f**	**af**	78
15	H	Ph	H	**a**	Ph	**g**	**ag**	93
16	H	Ph	H	**a**	4-Cl-C_6H_4	**h**	**ah**	88
17	H	Ph	H	**a**	*p*MeOC_6H_4	**a**	**aa**	100[h]

[a] Propargyl vinyl ether **1** (1 equiv), primary amine **4** (1.1 equiv) in toluene (5 mL). Z = CO_2Me. Yield of isolated product. [b] 300 W, 150 °C, 2 h. [c] 300 W, 150 °C, 3 h, Z = CO_2Et. [d] Z = SO_2Tol. [e] Ad = Adamantyl. [f] 50 % *de*. [g] PMB = p-Methoxybenzyl. [h] Commercial (*R*)-1-phenyl-prop-2-yn-1-ol was used to prepare enantiopure (*R*)-**1a**; product **6aa** obtained as a racemic mixture.

CHEMISTRY
A EUROPEAN JOURNAL

studied. Both aliphatic and aromatic substituents were tolerant in the terminal position of the triple bond (R^1; entries 1–6). It is remarkable that unsubstituted derivative **1b** gave the poorest yield even under forced conditions (entry 2). This result could be pointing out to the necessity of some conformational control in this kind of processes (a substituent-biased conformational control) or/and a certain degree of substitution at the terminal double bond. Propargylic derivatives **1g** and **1h** featuring a substituent at the O terminus of the enol function reacted with **4a** to give the corresponding pentasubstituted 1,2-dihydripyrines **6ga** and **6ha**, although in low yields and under vigorous conditions (300 W, 150 °C, 3 h) (entries 7 and 8).[14] This fact reflects the difficulty for ketimine formation under these conditions and its diminished reactivity for the 6π-aza-electrocyclization reaction. Substitution at the sp^3-propargylic position (R^2) was found to be dependent on the nature of substituent R^1. Whereas R^2 could be hydrogen, aliphatic, or aromatic for terminal alkynes (R^1 = H; entries 1–4) and aromatic for internal alkynes (R^1 = Ph or *c*Hex; entries 5 and 6), the combination of R^2 = Alk, and an internal alkyne [i.e., **7a** and **7b**, Eq. (2)] did not afford 1,2-dihydropyridines. Instead, mixtures of compounds **8** and **9** were systematically obtained. Importantly, the same mixtures were obtained when these reactions were performed in the absence of the amine. These results seem to point out to a new reaction pathway involving different thermally-driven rearrangements of the 2,4-dienal **3** intermediate. The study and synthetic utility of this interesting transformation are in progress in our lab.

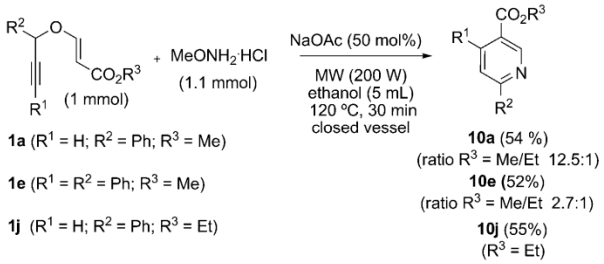


7a R^1= Ph, R^2 = *n*Pr
7b R^1= *n*Bu, R^2 = *n*Pr
8a (*E*/*Z* 9:1)(50%)
8b (≈ *E*/*Z* 9:1)(41%)
9a (R^3 = Et) (41%)
9b (R^3 = Et) (4%)

With regard to the vinyl functionality tolerance, propargyl enol ether **1i** bearing a SO_2Tol as the electron-withdrawing group afforded the corresponding 1,2-dihydropyridine **6ia** in very good yield (80%) (entry 9).

Finally, the domino reaction with enantiopure propargyl derivative (*R*)-**1a** (prepared from enantiopure (*R*)-1-phenyl-prop-2-yn-1-ol and methyl propiolate) and *p*-anisidine (**4a**) afforded the expected product **6aa** in racemic form (Table 1, entry 17). Observe that the chiral information present in the starting propargyl enol ether is completely lost in the rearrangement-isomerization process previous to the ketimine formation.

As a logical extension of this methodology, we attempted its application to the domino synthesis of pyridines **10**, featuring a biologically and chemically relevant nicotinic acid motive (Scheme 4).[15] Evidently, implementation of this methodology required an additional step to convert the 1,2-dihydropyridine intermediate into the corresponding pyridine by means of an elimination reaction. Methoxyamine has proved to be an excellent amine derivative for this kind of transformation.[4b] Accordingly, the microwave irradiation of an ethanolic mixture of propargyl enol ether **1a** (1 mmol) and $MeONH_2$·HCl (1.1 mmol) in the presence of NaOAc (50 mol%) yielded the methyl 2-phenyl-4-pyridinecarboxylate (**10a**) in a convenient 54% yield (4% of transesterification product; Scheme 4). A similar result was obtained with propargylic derivative **1e** (52% as a ≈3:1 mixture of methyl and ethyl esters). Derivative **1j** featuring an ethyl ester group at the enol position afforded, under the same conditions, the expected pyridine **10j** in 55% yield. To the best of our knowledge, this is the first example of a metal-free domino synthesis of nicotinic acid derivatives from propargyl enol ethers and amines involving this spectacular cascade of chemical processes. Although these preliminary results constitute an excellent proof of concept, more experimental work needs to be developed to increase the efficiency of this pyridine synthesis.[16]



1a (R^1 = H; R^2 = Ph; R^3 = Me)
1e (R^1 = R^2 = Ph; R^3 = Me)
1j (R^1 = H; R^2 = Ph; R^3 = Et)

10a (54 %) (ratio R^3 = Me/Et 12.5:1)
10e (52%) (ratio R^3 = Me/Et 2.7:1)
10j (55%) (R^3 = Et)

Scheme 4. Domino synthesis of substituted alkyl 3-pyridinecarboxylates (**10**) from propargyl enol ethers **1** and methoxyamine hydrochloride.

In summary, we have reported our preliminary results on the metal-free domino synthesis of substituted alkyl 1,2-dihydropyridine-3-carboxylates from propargyl enol ethers and primary amines by means of an unprecedented [3,3] propargyl Claisen rearrangement/isomerization/amine condensation/6π-aza-electrocyclization cascade reaction network. 1,2-Dihydropyridines **6** are obtained with remarkable high efficiency, good level of diversity (four possible diversity points), and bearing a convenient chemical handle for complexity-diversity generation (carboxylic ester at C_3-position). This methodology has been extended to the synthesis of substituted nicotinic acid derivatives **10**.

Experimental Section

Representative procedure for the microwave-assisted synthesis of 1,2-dihydropyridines 6: A solution of propargyl vinyl ether **1a** (1.0 mmol) and *p*-anisidine (**4a**) (1.1 mmol) in toluene (5 mL) was placed in a microwave-special closed vial and the solution was irradiated for 30 min in a single-mode microwave oven (150 W, 120 °C). The reaction mixture was dried over anhydrous sodium sulfate and filtrated using dichloromethane as solvent. After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 80:20) to yield **6aa** (100% yield).^{1}H NMR (400 MHz, $CDCl_3$,

25 °C): δ = 3.73 (s, 6H), 5.37 (ddd, ^3J(H,H) = 9.8, 5.3, 0.8 Hz, 1H), 5.51 (dpt, ^3J(H,H) = 5.3, 1.0 Hz, 1H), 6.49 (dpt, ^3J(H,H) = 9.8, 1.0 Hz, 1H), 6.77 (d, ^3J(H,H) = 9.0 Hz, 2H), 6.98 (d, ^3J(H,H) = 9.0 Hz, 2H), 7.23–7.31 (m, 5H), 7.79 ppm (dd, ^3J(H,H) = 1.0, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 50.8, 55.4, 63.3, 101.2, 144.4, 115.4, 119.5, 122.3, 125.5, 127.8, 128.9, 138.5, 142.2, 143.1, 157.1, 166.8 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3013.5, 1682.8, 1633.9, 1567.7, 1510.2, 1440.5, 1313.3, 1269.1, 1232.5, 1108.0 cm^{-1}; MS (70 eV): *m/z* (%): 321 (55) [M^+], 290 (14), 262 (28), 245 (46), 244 (100), 201 (15), 115 (14), 92 (14), 77 (20); elemental analysis calcd (%) for $C_{20}H_{19}NO_3$: C 74.75, H 5.96, N 4.36; found: C 74.76, H 5.85, N 4.55.

Acknowledgements

This research was supported by the Spanish Ministerio de Ciencia e Innovación, the European Regional Development Fund (CTQ2005-09074-C02-02 and CTQ2008-06806-C02-02) and the Spanish MSC ISCIII (RETICS, RD06/0020/1046, and RD06/0020/0041), CSIC (Proyecto Intramural Especial 200719), FUNCIS (REDESFAC PI01/06 and 35/06) and the Fundación Instituto Canario de Investigación del Cancer (FICI-G.I.N808/2007). G.M.-A. thanks Spanish MEC for a FPU grant.

Keywords: domino reactions · electrocyclic reactions · microwave chemistry · nitrogen heterocycles · rearrangement

[1] For recent reviews, see: a) J. P. A. Harrity, O. Provoost, *Org. Biomol. Chem.* **2005**, *3*, 1349–1358; b) R. P. Hsung, A. V. Kurdyumov, N. Sydorenko, *Eur. J. Org. Chem.* **2005**, 23–44.

[2] a) For recent progresses in this area, see: D. W. Hopper, K. M. K. Kutterer, J. J. Clemens in *Progress in Heterocyclic Chemistry, Part I, Vol 20* (Eds.: G. W. Gribble, J. A. Joule), Elsevier, New York, Chapter 6, p. 294; b) G.-D. Zhu, W. H. Okamura, *Chem. Rev.* **1995**, *95*, 1877–1952; c) W. H. Okamura, A. R. de Lera in *Comprehensive Organic Synthesis, Vol. 5* (Eds.: B. M. Trost, I. Fleming), Pergamon, London, **1991**, Chapter 6.2, pp. 699–750.

[3] a) N. Sydorenko, R. P. Hsung, E. L. Vera, *Org. Lett.* **2006**, *8*, 2611–2614; b) Z. Vincze, Z. Mucsi, P. Scheiber, P. Nemes, *Eur. J. Org. Chem.* **2008**, 1092–1100.

[4] For selected examples, see: a) T. Kobayashi, S. Hatano, H. Tsuchikawa, S. Katsumura, *Tetrahedron Lett.* **2008**, *49*, 4349–4351; b) B. M. Trost, A. C. Gutierrez, *Org. Lett.* **2007**, *9*, 1473–1476; c) K. Tanaka, H. Mori, M. Yamamoto, S. Katsumura, *J. Org. Chem.* **2001**, *66*, 3099–3110; d) D. F. Maynard, W. H. Okamura, *J. Org. Chem.* **1995**, *60*, 1763–1771.

[5] a) J. T. Binder, S. F. Kirsch, *Org. Lett.* **2006**, *8*, 2151–2153; b) H. Menz, S. F. Kirsch, *Org. Lett.* **2006**, *8*, 4795–4797; c) M. H. Suhre, M. Reif, S. F. Kirsch, *Org. Lett.* **2005**, *7*, 3925–3927; d) B. D. Sherry, L. Maus, B. N. Laforteza, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 8132–8133.

[6] S. F. Kirsch, *Synthesis* **2008**, 3183–3204.

[7] For a precedent, see: W. Peng, S. Zhu, *Tetrahedron* **2003**, *59*, 4641–4649.

[8] L. F. Tietze, G. Brasche, K. Gericke in *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim **2006**.

[9] a) D. Tejedor, A. Santos-Expósito, G. Méndez-Abt, C. Ruiz-Pérez, F. García-Tellado, *Synlett* **2009**, 1223–1226; b) J. Inanaga, Y. Baba, T. Hanamoto, *Chem. Lett.* **1993**, 241–244; c) for a seminal antecedent, see: E. Winterfeld, *Chem. Ber.* **1964**, *97*, 1952–1958.

[10] a) Although conventional heating is sufficient, microwave irtradation proved to be more efficient; b) the metal-free [3,3] propargyl Claisen rearrangement is a thermally driven process and it is usually performed at high temperatures: A. Viola, J. J. Collins, N. Filipp, *Tetrahedron* **1981**, *37*, 3765–3811; c) for a recent example, V. Vaithiyanathan, K. Selvakumar, P. Shanmugam, *Synlett* **2009**, 1591–1596;.

[11] a) In the absence of this EWG, allenes **2** are stable enough to be isolated; for a seminal example, see: M. A. Henderson, C. H. Heathcock, *J. Org. Chem.* **1988**, *53*, 4736–4745; b) N. Krause, A. S. K. Hashmi in *Modern Allene Chemistry*, Wiley-VCH, Weinheim, **2004**.

[12] A similar effect has been reported by Trost and co-workers in their ruthenium-catalyzed synthesis of pyridines (see ref. [4b]).

[13] For other examples of diastereoselective 6π-aza-electrocyclizations using chiral amines see: a) see references [4a,d] and refereneces therein; b) K. Tanaka, T. Kobayashi, H. Mori, S. Katsumura, *J. Org. Chem.* **2004**, *69*, 5906–5925.

[14] Kirsch and co-workers have described that the one-pot multimetal-catalyzed reaction of primary amines and trisubstituted propargyl enol ethers **1** (R^1 = Ph; R^2 = Ph, Et; R^3 = Me; Z = CO_2Et) affords 1,2-dihydropyridines in moderate yields (ref. [5a]).

[15] Nicotinic acid is a relevant member of the vitamin B complex family; for selected reviews, see; a) J. A. Farmer, *Curr. Atheroscler. Rep.* **2009**, *11*, 87–92; b) J. B. Kirkland in *Handbook of Vitamins*, 4th ed. (Eds.: J. Zempleni, R. B. Rucker, J. W. Suttie, D. B. McCormick), Taylor and Francis, Boca Raton, **2007**, pp. 191–232; c) C. Roderick, *Appl. Catal. A* **2005**, *280*, 75–82.

[16] Studies on the mechanism and synthetic improvement of these reactions are in progress in our group.

Received: July 31, 2009
Published online: November 17, 2009

Supporting Information

A Convenient Domino Access to Substituted Alkyl 1,2-Dihydropyridine-3-carboxylates from Propargyl Enol Ethers and Primary Amines

David Tejedor,* Gabriela Méndez-Abt and Fernando García-Tellado.*

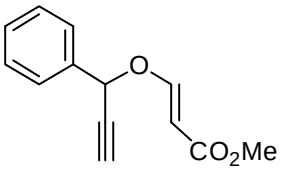
Instituto de Productos Naturales y Agrobiología, Consejo Superior de Investigaciones Científicas, Astrofísico Francisco Sánchez 3, E-38206 La Laguna, Tenerife, Spain, Instituto Canario de Investigación del Cáncer, Canary Islands, Spain.

General remarks. ^{1}H NMR and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded either at 400 and 100 MHz or at 500 and 125 MHz (Bruker Ac 200 and AMX2-500), respectively. Microwave reactions were conducted in sealed glass vessels (capacity 10 mL) using a CEM Discover microwave reactor. FT-IR spectra were measured in chloroform solutions using a Perkin Elmer FT-IR Spectrum BX spectrophotometer. Mass spectra (low resolution) (EI/CI) were obtained with a Hewlett-Packard 5995 gas chromatograph/mass spectrometer. High-resolution mass spectra were recorded with a Micromass Autospec mass spectrometer. Microanalyses were performed with a Fisons Instruments EA 1108 carbon, hydrogen, and nitrogen analyzer. Analytical thin-layer chromatography plates used were E. Merck Brinkman UV-active silica gel (Kieselgel 60 F254) on aluminum. Flash column chromatography was carried out with E. Merck silica gel 60 (particle size less than 0.020 mm) using appropriate mixtures of ethyl acetate and hexanes as eluent. All reactions were performed in oven-dried glassware under nitrogen unless otherwise stated. Dichloromethane was distilled from CaH_2. All other materials were obtained from commercial suppliers and used as received. The propargylic alcohols are commercially available or readily synthesized according to literature references (P. G. Cozzi, J. Rudolph, C. Bolm, P.-O. Norrby, C. Tomasini, *J. Org. Chem.* **2005**, *70*, 5733-6). Products **1b**, **10a** and **10j** have been previously reported.

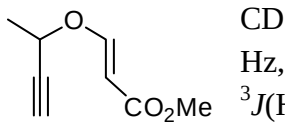
Experimental section.

Representative procedure for the synthesis of propargyl vinyl ethers (1a-1f, 1i-1j and 7a-7b). Triethylamine (0.30 mmol) was added to a solution of methyl propiolate (3.0 mmol) and 1-phenylprop-2-yn-1-ol (3.0 mmol) in dry CH_2Cl_2 (10 ml). The reaction mixture was stirred for 2 h. After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, n-hexane/EtOAc 90/10) to yield **1a** (95%).

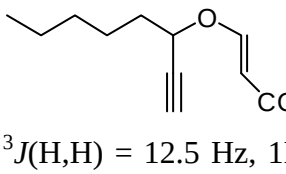
(±) (E)-methyl 3-(1-phenylprop-2-ynyloxy)acrylate (1a): ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 2.81 (d, ^{3}J(H,H) = 2.1 Hz, 1H), 3.69 (s, 3H), 5.47 (d, ^{3}J(H,H) = 12.5 Hz, 1H), 5.63 (d, ^{3}J(H,H) = 2.1 Hz, 1H), 7.38-7.41 (m, 3H), 7.50-7.52 (m, 2H), 7.67 (d, ^{3}J(H,H) = 12.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ = 51.2, 72.8, 78.2, 79.0, 99.5, 127.4, 128.8, 129.4, 135.7, 159.7, 167.7; IR ($CHCl_3$) ν bar = 3305.6, 3026.1, 2126.0, 1706.9, 1645.6, 1625.5, 1438.2, 1334.0, 1289.6, 1191.3, 1136.2 cm^{-1}; MS (70 eV): *m/z* (%): 216 (15) [M^+], 184 (30), 157 (24), 128 (55), 116 (95), 115 (100), 89 (63), 65 (39), 63 (50); elemental analysis calcd (%) for $C_{13}H_{12}O_3$: C 72.21, H 5.59; found: C 72.19, H 5.57.



(±) (E)-methyl 3-(but-3-yn-2-yloxy)acrylate (1c): (98% yield) ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ =1.56 (d, ^{3}J(H,H) = 6.6 Hz, 3H), 2.57 (d, ^{3}J(H,H) = 2.1 Hz, 1H), 3.69 (s, 3H), 4.66 (dq, ^{3}J(H,H) = 6.6 and 2.1 Hz, 1H), 5.37 (d, ^{3}J(H,H) = 12.5 Hz, 1H), 7.59 (d, ^{3}J(H,H) = 12.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ = 21.6, 51.2, 67.0, 75.4, 80.9, 98.8, 160.0, 167.9; IR ($CHCl_3$) ν bar = 3306.9, 3024.2, 2952.9, 2122.0, 1706.4, 1645.7, 1625.6, 1438.4, 1333.4, 1293.9, 1224.5, 1194.1, 1145.3, 1120.8, 1035.2 cm^{-1}; MS (70 eV): *m/z* (%): 154 (3.8) [M^+], 123 (20), 111 (16), 102 (13), 95 (30), 71 (76), 53 (100); elemental analysis calcd (%) for $C_8H_{10}O_3$: C 62.33, H 6.54; found: C 62.20, H 6.56.



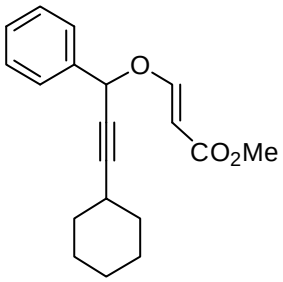
(±) (E)-methyl 3-(oct-1-yn-3-yloxy)acrylate (1d): (87% yield) ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 0.88 (t, ^{3}J(H,H) = 6.9 Hz, 3H), 1.27-1.35 (m, 4H), 1.42-1.50 (m, 2H), 1.75-1.89 (m, 2H), 2.57 (d, ^{3}J(H,H) = 2.1 Hz, 1H), 3.69 (s, 3H), 4.52 (dt, ^{3}J(H,H) = 6.6 and 2.1 Hz, 1H), 5.38 (d, ^{3}J(H,H) = 12.5 Hz, 1H), 7.60 (d, ^{3}J(H,H) = 12.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ = 13.9, 22.4, 24.4, 31.2, 35.1, 51.1, 71.3, 76.0, 80.2, 98.6, 160.3, 168.0; IR ($CHCl_3$) ν bar = 3306.3, 2955.2, 2122.4, 1705.0, 1644.3, 1624.8, 1438.3, 1333.1, 1294.4, 1232.1, 1191.6, 1144.8 cm^{-1}; MS (70 eV): *m/z* (%): 210 (2.0) [M^+], 115 (43), 103 (36), 93 (37), 79 (45), 69 (40), 67 (100), 55 (55); elemental analysis calcd (%) for $C_{12}H_{18}O_3$: C 68.54, H 8.63; found: C 68.57, H 8.34.



(±)(E)-methyl 3-(1,3-diphenylprop-2-ynyloxy)acrylate (1e): (89% yield) ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 3.70 (s, 3H), 5.53 (d, ^{3}J(H,H) = 12.5 Hz, 1H), 5.87 (s, 1H), 7.30-7.46 (m, 6H), 7.48-7.50 (m, 2H), 7.57-7.60 (m, 2H), 7.77 (d, ^{3}J(H,H) = 12.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ = 51.1, 73.8, 84.3, 89.9, 99.4, 127.5, 128.4, 128.8, 129.1, 129.3, 130.1, 131.9, 136.4, 160.0, 167.9; IR ($CHCl_3$) ν bar = 3026.3, 2228.7, 1706.2, 1643.6, 1623.8, 1492.0, 1439.3, 1334.9, 1291.9, 1220.3, 1190.8, 1135.9 cm^{-1}; MS (70 eV): *m/z* (%): 292

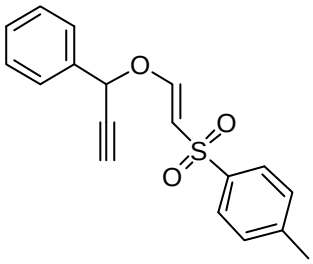
(9.4) [M^+], 260 (18), 232 (17), 231 (21), 192 (21), 191 (100), 181 (25), 180 (28), 105 (19), 77 (40); elemental analysis calcd (%) for $C_{19}H_{16}O_3$: C 78.06, H 5.52; found: C 78.28, H 5.46.

(±)(E)-methyl 3-(3-cyclohexyl-1-phenylprop-2-ynyloxy)acrylate (1f): (80% yield) ^{1}H



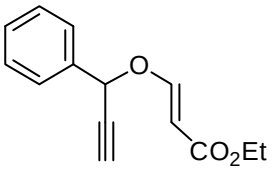
NMR (400 MHz, $CDCl_3$,25ºC): δ = 1.28-1.41 (m, 3H), 1.46-1.59 (m, 3H), 1.67-1.78 (m, 2H), 1.80-1.89 (m, 2H), 2.49-2.57(m, 1H), 3.72 (s, 3H), 5.48 (d, ^3J(H,H) = 12.5 Hz, 1H), 5.69 (s, 1H), 7.39-7.45 (m, 3H), 7.52-7.55 (m, 2H), 7.75 (d, ^3J(H,H) = 12.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ = 24.7, 25.8, 29.1, 32.3, 51.1, 73.8, 75.6, 95.5, 99.0, 127.5, 128.7, 129.0, 137.0, 160.1, 168.1; IR ($CHCl_3$) ν bar = 2935.3, 2857.0, 2231.9, 1704.7, 1642.3, 1622.9, 1451.3, 1439.9, 1190.3, 1135.7 cm^{-1}; MS (70 eV): *m/z* (%): 298 (2.2) [M^+], 198 (27), 197 (100), 155 (28), 141 (30), 129 (23), 117 (31), 115 (50), 91 (59); elemental analysis calcd (%) for $C_{19}H_{22}O_3$: C 76.48, H 7.43; found: C 76.44, H 7.35.

(±) (E)-1-methyl-4-(2-(1-phenylprop-2-ynyloxy)vinylsulfonyl)benzene (1i): (98% yield)



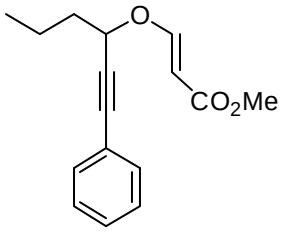
^{1}H NMR (400 MHz, $CDCl_3$,25ºC): δ = 2.41 (s, 3H), 2.83 (d, ^3J(H,H) = 2.4 Hz, 1H), 5.63 (d, ^3J(H,H) = 2.4 Hz, 1H), 5.96 (d, ^3J(H,H) = 12.1 Hz, 1H), 7.29 (d, ^3J(H,H) = 8.2 Hz, 2H), 7.39-7.41 (m, 3H), 7.47-7.50 (m, 2H), 7.67 (d, ^3J(H,H) = 12.1 Hz, 1H), 7.73 (d, ^3J(H,H) = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ = 21.5, 73.7, 78.4, 79.0, 110.2, 127.0, 127.4, 128.9, 129.65, 129.70, 135.1, 139.4, 143.7, 157.6; IR ($CHCl_3$) ν bar = 3304.8, 3028.3, 2126.4, 1629.1, 1609.1, 1313.7, 1303.0, 1195.2, 1141.9 cm^{-1}; MS (70 eV): *m/z* (%): 312 (22) [M^+], 248 (13), 157 (18), 156 (31), 155 (33), 129 (18), 128 (100), 127 (21), 91 (26).

(±) (E)- ethyl 3-(1-phenylprop-2-ynyloxy)acrylate (1j): (95% yield) ^{1}H NMR (400 MHz,

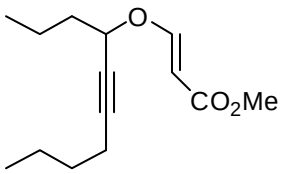


$CDCl_3$,25ºC): δ = 1.26 (t, ^3J(H,H) = 7.2 Hz, 3H), 2.81 (d, ^3J(H,H) = 2.1 Hz, 1H), 4.16 (q, ^3J(H,H) = 7.2 Hz, 2H), 5.47 (d, ^3J(H,H) = 12.5 Hz, 1H), 5.63 (d, ^3J(H,H) = 2.1 Hz, 1H), 7.38-7.43 (m, 3H), 7.50-7.52 (m, 2H), 7.66 (d, ^3J(H,H) = 12.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ = 14.3, 59.9, 72.6, 78.1, 79.1, 99.9, 127.4, 128.8, 129.4, 135.8, 159.5, 167.3; IR ($CHCl_3$) ν bar = 3304.9, 3020.5, 2125.8, 1703.2, 1643.0, 1323.7, 1287.3, 1171.1, 1132.6 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{14}O_3$: C 73.03, H 6.13; found: C 73.38, H, 6.13.

(±) (E)-methyl 3-(1-phenylhex-1-yn-3-yloxy)acrylate (7a): (86% yield) ^{1}H NMR (400 MHz, $CDCl_3$,25ºC): δ = 0.97 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.50-1.60 (m, 2H), 1.82-1.97 (m, 2H), 3.69 (s, 3H), 4.77 (t, ^3J(H,H) = 6.6 Hz, 1H), 5.43 (d, ^3J(H,H) = 12.5 Hz, 1H), 7.27-7.33 (m, 3H), 7.41-7.44 (m, 2H), 7.69 (d, ^3J(H,H) = 12.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ = 13.5, 18.3, 37.4, 51.0, 71.9, 85.4, 87.8, 98.4, 121.9, 128.3, 128.8, 131.8, 160.6, 168.1; IR ($CHCl_3$) ν bar = 3019.9, 2963.2, 2876.7, 2233.4, 1705.5, 1642.9, 1440.1, 1336.0, 1294.1, 1194.8, 1142.9 cm^{-1}; MS (70 eV): *m/z* (%): 258 (0.7) [M^+], 199 (10), 157 (79), 142 (14), 129 (26), 128 (21), 115 (100), 91 (22); elemental analysis calcd (%) for $C_{16}H_{18}O_3$: C 74.39, H 7.02; found: C 74.45, H 6.95.

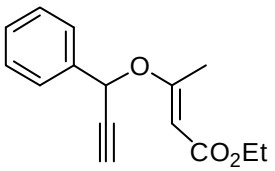


(±) (E)-methyl 3-(dec-5-yn-4-yloxy)acrylate (7b): (79% yield) ^{1}H NMR (400 MHz, $CDCl_3$,25ºC): δ = 0.87 (t, ^3J(H,H) = 7.2 Hz, 3H), 0.91 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.32-1.49 (m, 6H), 1.66-1.81 (m, 2H), 2.19 (dt, ^3J(H,H) = 6.9 and 2.1 Hz, 2H), 3.67 (s, 3H), 4.51 (tt, ^3J(H,H) = 6.6 and 2.1 Hz, 1H), 5.33 (d, ^3J(H,H) = 12.5 Hz, 1H), 7.61 (d, ^3J(H,H) = 12.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ = 13.4, 13.5, 18.2, 18.3, 21.8, 30.4, 37.6, 50.9, 72.0, 76.6, 89.0, 98.0, 160.7, 168.2; IR ($CHCl_3$) ν bar = 2961.5, 2236.6, 1704.2, 1641.6, 1439.0, 1335.6, 1197.7, 1137.9 cm^{-1}; MS (70 eV): *m/z* (%): 238 (0.5) [M^+], 137 (9.3), 95 (100), 81 (91), 79 (22), 67 (50), 55 (36); elemental analysis calcd (%) for $C_{14}H_{22}O_3$: C 70.56, H 9.30; found: C 70.29, H 9.42.

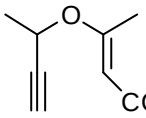


Representative procedure for the synthesis of propargyl vinyl ethers (1g-1h). Tributylphosphine (0.60 mmol) was added to a solution of ethyl but-2-ynoate (3.0 mmol) and but-3-yn-2-ol (3.0 mmol) in dry CH_2Cl_2 (10 ml). The reaction mixture was stirred for 2 h. After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, n-hexane/EtOAc 90/10) to yield **1h** (80%) as a mixture of *E* (69%) and *Z* (11%) isomers.

(±) Ethyl 3-(1-phenylprop-2-ynyloxy)but-2-enoate (1g): (52% yield of major isomer, *E*) ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 1.28 (t, ^3J(H,H) = 7.2 Hz, 3H), 2.35 (s, 3H) 2.75 (d, ^3J(H,H) = 2.1 Hz, 1H), 4.12-4.18 (m, 2H), 5.38 (s, 1H), 5.63 (d, ^3J(H,H) = 2.1 Hz, 1H), 7.35-7.43 (m, 3H), 7.50-7.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ = 14.4, 19.0, 59.5, 69.2, 77.3, 79.5, 94.0, 127.2, 128.7, 129.0, 136.4, 167.5, 170.0; IR ($CHCl_3$) ν bar = 3305.9, 3028.7, 2124.9, 1705.1, 1625.7, 1261.5, 1144.1, 1038.9 cm^{-1}; MS (70 eV): *m/z* (%): 244 (10) [M^+], 215 (25), 171 (27), 128 (19), 115 (100); elemental analysis calcd (%) for $C_{15}H_{16}O_3$: C 73.75, H 6.60; found: C 73.55, H 6.54.



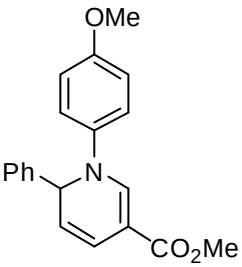
(±) Ethyl 3-(but-3-yn-2-yloxy)but-2-enoate (1h): ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC) (*E*



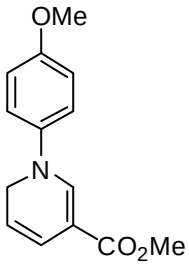
isomer, major): δ = 1.24 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.56 (t, ^3J(H,H) = 6.6 Hz, 3H), 2.27 (s, 3H) 2.51 (d, ^3J(H,H) = 2.1 Hz, 1H), 4.08-4.15 (m, 2H), 4.65 (dq, ^3J(H,H) = 6.6 and 2.1 Hz, 1H), 5.19 (s, 1H); (*Z* isomer, minor) δ = 1.21 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.59 (t, ^3J(H,H) = 6.6 Hz, 3H), 2.06 (s, 3H) 2.49 (d, ^3J(H,H) = 2.1 Hz, 1H), 4.08 (q, ^3J(H,H) = 7.2 Hz, 2H), 4.94 (dq, ^3J(H,H) = 6.6 and 2.1 Hz, 1H), 4.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC) (*E* isomer): δ = 14.4, 19.0, 21.7, 59.4, 63.1, 74.5, 81.4, 93.3, 167.7, 170.0; (*Z* isomer) δ = 14.3, 20.2, 22.0, 59.2, 64.5, 74.1, 82.5, 99.2, 165.0, 165.7; IR ($CHCl_3$) (*E* isomer) ν bar = 3307.1, 2122.8, 2993.1, 1704.2, 1624.1, 1267.1, 1152.8, 1090.6, 1047.3 cm^{-1}; MS (70 eV): *m/z* (%): 182 (29) [M^+], 180 (100), 167 (94); elemental analysis calcd (%) for $C_{10}H_{14}O_3$: C 65.91, H 7.74; found: C 66.01, H 7.67.

Representative procedure for the microwave-assisted synthesis of 1,2-dihydropyridines (6). A solution of propargyl vinyl ether **1a** (1.0 mmol) and *p*-anisidine **4a** (1.1 mmol) in toluene (5 mL) was placed in a microwave-special closed vial and the solution was irradiated for 30 min in a single-mode microwave oven (150 Watt, 120 ºC). The reaction mixture was dried over anhydrous sodium sulfate and filtrated using dichloromethane as solvent. After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, n-hexane/EtOAc 80/20) to yield **6aa** (100%). Check Table 1 for specific reaction conditions for other derivatives.

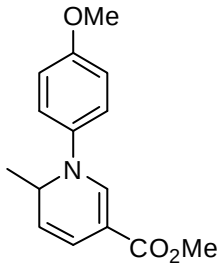
(±) Methyl 1-(4-methoxyphenyl)-6-phenyl-1,6-dihydropyridine-3-carboxylate (6aa):



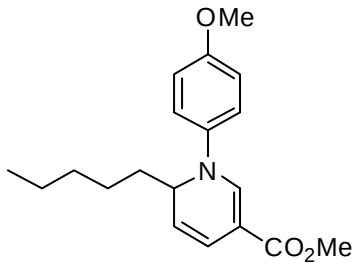
^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 3.73 (s, 6H), 5.37 (ddd, ^3J(H,H) = 9.8, 5.3 and 0.8 Hz, 1H), 5.51 (dpt, ^3J(H,H) = 5.3 and 1.0 Hz, 1H), 6.49 (dpt, ^3J(H,H) = 9.8 and 1.0 Hz, 1H), 6.77 (d, ^3J(H,H) = 9.0 Hz, 2H), 6.98 (d, ^3J(H,H) = 9.0 Hz, 2H), 7.23-7.31 (m, 5H), 7.79 (dd, ^3J(H,H) = 1.0 and 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ = 50.8, 55.4, 63.3, 101.2, 144.4, 115.4, 119.5, 122.3, 125.5, 127.8, 128.9, 138.5, 142.2, 143.1, 157.1, 166.8; IR ($CHCl_3$) ν bar = 3013.5, 1682.8, 1633.9, 1567.7, 1510.2, 1440.5, 1313.3, 1269.1, 1232.5, 1108.0 cm^{-1}; MS (70 eV): *m/z* (%): 321 (55) [M^+], 290 (14), 262 (28), 245 (46), 244 (100), 201 (15), 115 (14), 92 (14), 77 (20); elemental analysis calcd (%) for $C_{20}H_{19}NO_3$: C 74.75, H 5.96, N 4.36; Found: C 74.76, H 5.85, N 4.55.

(±) Methyl 1-(4-methoxyphenyl)-1,6-dihydropyridine-3-carboxylate (6ba): 

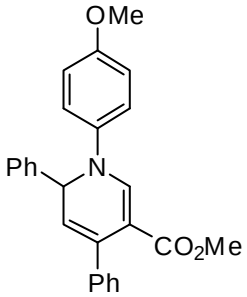
^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 3.70 (s, 3H), 3.78 (s, 3H), 4.47 (dd, ^3J(H,H) = 3.4 and 1.6 Hz, 2H), 5.20 (dtd, ^3J(H,H) = 10.1, 3.4 and 0.8 Hz, 1H), 6.43 (dtd, ^3J(H,H) = 10.1, 1.3 and 0.8 Hz, 1H), 6.88 (d, ^3J(H,H) = 9.3 Hz, 2H), 7.02 (d, ^3J(H,H) = 9.3 Hz, 2H), 7.60 (dd, ^3J(H,H) = 1.0 and 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ = 48.5, 50.8, 55.5, 101.4, 110.9, 114.5, 119.4, 122.1, 138.4, 142.4, 156.6, 166.9; IR ($CHCl_3$) ν bar = 3015.5, 1684.4, 1638.7, 1574.6, 1512.2, 1440.0, 1237.5, 1220.4, 1109.8 cm^{-1}; MS (70 eV): *m/z* (%): 245 (41) [M^+], 244 (100), 230 (13), 214 (7.9), 201 (6.0), 175 (5.6), 105 (8.2), 77 (6.8); elemental analysis calcd (%) for $C_{14}H_{15}NO_3$: C 68.56, H 6.16, N 5.71; found: C 68.56, H 6.24, N 5.91.

(±) Methyl 1-(4-methoxyphenyl)-6-methyl-1,6-dihydropyridine-3-carboxylate (6ca): 

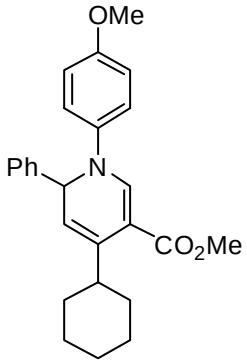
^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 1.16 (d, ^3J(H,H) = 6.4 Hz, 3H), 3.65 (s, 3H), 3.72 (s, 3H), 4.52-4.58 (m, 1H), 5.15 (dd, ^3J(H,H) = 9.8 and 5.3 Hz, 1H), 6.40 (d, ^3J(H,H) = 9.8 Hz, 1H), 6.81 (d, ^3J(H,H) = 9.0 Hz, 2H), 7.13 (d, ^3J(H,H) = 9.0 Hz, 2H), 7.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ = 20.4, 50.8, 54.2, 55.5, 101.8, 114.6, 115.4, 120.6, 121.6, 138.1, 141.1, 156.9, 167.0; IR ($CHCl_3$) ν bar = 3013.3, 1682.0, 1630.2, 1565.7, 1511.7, 1441.3, 1323.2, 1233.4, 1109.9, 1036.2 cm^{-1}; MS (70 eV): *m/z* (%): 259 (38) [M^+], 245 (24), 244 (100), 230 (31), 201 (10), 77 (9.0), 53 (8.2); elemental analysis calcd (%) for $C_{15}H_{17}NO_3$: C 69.48, H 6.61, N 5.40; found: C 69.29, H 6.56, N 5.43.

(±) Methyl 1-(4-methoxyphenyl)-6-pentyl-1,6-dihydropyridine-3-carboxylate (6da): 

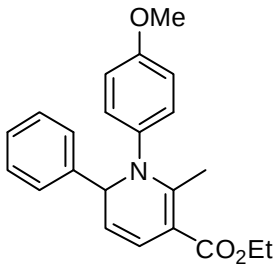
^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 0.84 (t, ^3J(H,H) = 6.9 Hz, 3H), 1.16-1.28 (m, 4H), 1.32-1.47 (m, 3H), 1.71-1.79 (m, 1H), 3.70 (s, 3H), 3.78 (s, 3H), 4.54-4.58 (m, 1H), 5.21 (dd, ^3J(H,H) = 9.8 and 5.0 Hz, 1H), 6.49 (d, ^3J(H,H) = 9.8 Hz, 1H), 6.87 (d, ^3J(H,H) = 9.0 Hz, 2H), 7.10 (d, ^3J(H,H) = 9.0 Hz, 2H), 7.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ = 13.9, 22.5, 23.3, 31.7, 34.5, 50.8, 55.5, 58.5, 101.7, 113.8, 114.6, 121.4, 121.9, 138.3, 142.3, 156.9, 167.0; IR ($CHCl_3$) ν bar = 2934.0, 1678.1, 1630.0, 1565.7, 1510.9, 1441.2, 1233.7, 1106.1, 1036.8 cm^{-1}; MS (70 eV): *m/z* (%): 315 (4.4) [M^+], 245 (40), 244 (100), 229 (6.4), 201 (15), 122 (7.8), 77 (6.4); elemental analysis calcd (%) for $C_{19}H_{25}NO_3$: C 72.35, H 7.99, N 4.44; found: C 72.12, H 8.02, N 4.71.

(±) Methyl 1-(4-methoxyphenyl)-4,6-diphenyl-1,6-dihydropyridine-3-carboxylate (6ea): 

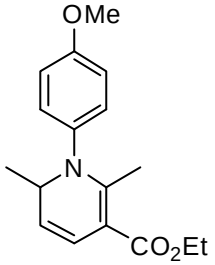
^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 3.56 (s, 3H), 3.78 (s, 3H), 5.39 (d, ^3J(H,H) = 6.4 Hz, 1H), 5.63 (dd, ^3J(H,H) = 6.4 and 1.3 Hz, 1H), 6.84 (d, ^3J(H,H) = 9.0 Hz, 2H), 7.07 (d, ^3J(H,H) = 9.0 Hz, 2H), 7.21-7.40 (m, 10H), 8.05 (d, ^3J(H,H) = 1.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ = 50.5, 54.4, 63.0, 103.2, 114.5, 115.7, 121.7, 125.6, 126.7, 127.4, 127.5, 127.8, 128.9, 134.7, 138.3, 140.7, 142.3, 143.5, 157.1, 166.4; IR ($CHCl_3$) ν bar = 3013.8, 1687.6, 1625.1, 1561.3, 1511.0, 1437.9, 1220.5, 1107.3 cm^{-1}; MS (70 eV): *m/z* (%): 397 (22) [M^+], 338 (8.4), 321 (32), 320 (100), 277 (6.5), 121 (4.7); elemental analysis calcd (%) for $C_{26}H_{23}NO_3$: C 78.57, H 5.83, N 3.52, found: C 78.66, H 5.96, N, 3.50.

(±) Methyl 4-cyclohexyl-1-(4-methoxyphenyl)-6-phenyl-1,6-dihydropyridine-3-carboxylate (6fa): 

^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 0.96-1.17 (m, 3H), 1.30-1.42 (m, 2H), 1.66-1.82 (m, 5H), 3.03 (tt, ^3J(H,H) = 11.7 and 2.4 Hz, 1H), 3.70 (s, 3H), 3.73 (s, 3H), 5.19 (d, ^3J(H,H) = 5.8 Hz, 1H), 5.47 (d, ^3J(H,H) = 5.8 Hz, 1H), 6.78 (d, ^3J(H,H) = 9.0 Hz, 2H), 6.96 (d, ^3J(H,H) = 9.0 Hz, 2H), 7.22-7.28 (m, 5H), 7.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ = 26.6, 26.9, 27.1, 32.7, 33.9, 38.4, 50.5, 55.4, 63.1, 102.2, 110.9, 114.4, 121.8, 125.7, 127.5, 128.7, 138.5, 138.6, 143.2, 143.9, 156.9, 166.8; IR ($CHCl_3$) ν bar = 3013.1, 2930.9, 2852.8, 1686.1, 1636.8, 1561.4, 1511.2, 1437.2, 1229.5, 1101.2, 1038.4 cm^{-1}; MS (70 eV): *m/z* (%): 403 (12) [M^+], 389 (5.2), 327 (24), 326 (100), 320 (34), 105 (4.8), 77 (4.6); elemental analysis calcd (%) for $C_{26}H_{29}NO_3$: C 77.39, H 7.24, N 3.47; found: C 77.19, H 7.45, N 3.47.



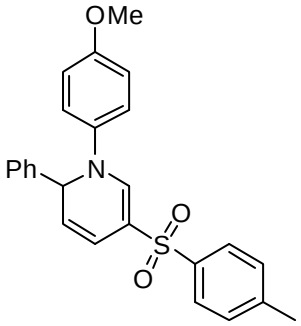
(±) Ethyl 1-(4-methoxyphenyl)-2-methyl-6-phenyl-1,6-dihydropyridine-3-carboxylate (6ga): ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC) Representative signals: δ = 1.30 (t, ^3J(H,H) = 7.2 Hz, 3H), 2.22 (s, 3H), 3.76 (s, 3H), 4.14-4.21 (m, 2H), 5.15 (d, ^3J(H,H) = 5.3 Hz, 1H), 5.296 (dd, ^3J(H,H) = 9.8 and 5.3 Hz, 1H), 6.71 (d, ^3J(H,H) = 9.8 Hz, 1H).

(±) Ethyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,6-dihydropyridine-3-carboxylate (6ha): 

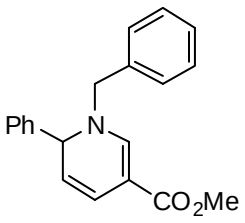
^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 1.17 (d, ^3J(H,H) = 6.4 Hz, 3H), 1.27 (t, ^3J(H,H) = 7.2 Hz, 3H), 2.13 (s, 3H), 3.79 (s, 3H), 4.18-4.11 (m, 3H), 5.11 (dd, ^3J(H,H) = 9.5 and 5.3 Hz, 1H), 6.58 (d, ^3J(H,H) = 9.5 Hz, 1H), 6.86 (d, ^3J(H,H) = 9.0 Hz, 2H), 7.07 (d, ^3J(H,H) = 9.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ = 14.5, 19.2, 20.5, 55.4, 58.0, 58.9, 99.6, 112.9, 114.4, 123.1, 129.0, 137.5, 154.0, 158.4, 167.4; IR ($CHCl_3$) ν bar = 3011.8, 1671.3, 1630.7, 1509.0, 1288.1, 1222.8, 1116.0 cm^{-1}; MS

(70 eV): *m/z* (%): 287 (11) [M^+], 273 (20), 272 (100), 244 (47), 242 (12), 148 (11); elemental analysis calcd (%) for $C_{17}H_{21}NO_3$: C 71.06, H 7.37, N, 4.87; found: C 70.96, H 7.19, N 5.01.

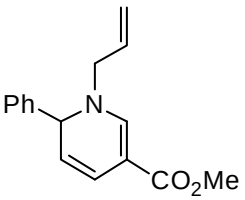
(±)1-(4-Methoxyphenyl)-2-phenyl-5-tosyl-1,2-dihydropyridine (6ia): ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 2.40 (s, 3H), 3.75 (s, 3H), 5.36 (dd, ^3J(H,H) = 9.8 and 5.3 Hz, 1H), 5.46 (d, ^3J(H,H) = 5.3 Hz, 1H), 6.20 (d, ^3J(H,H) = 9.8 Hz, 1H), 6.78 (d, ^3J(H,H) = 9.0 Hz, 2H), 6.96 (d, ^3J(H,H) = 9.0 Hz, 2H), 7.17-7-28 (m, 7H), 7.67 (s, 1H), 7.74 (d, ^3J(H,H) = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ = 21.4, 55.5, 63.6, 110.3, 114.5, 116.8, 117.1, 122.8, 125.7, 126.6, 128.2, 128.9, 129.6, 138.1, 140.4, 140.5, 142.5, 142.7, 157.6; IR ($CHCl_3$) ν bar = 3023.4, 1628.4, 1571.2, 1511.2, 1280.0, 1249.6, 1216.0, 1146.0, 1107.5 cm^{-1}; MS (70 eV): *m/z* (%): 417 (41) [M^+], 341 (34), 340 (100), 262 (26). HRMS (m/z): [M]+ calcd for $C_{25}H_{23}NO_3S$, 417.1399; found, 417.1399.



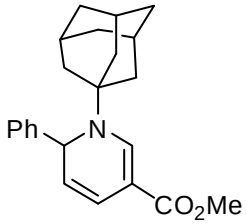
(±) Methyl 1-benzyl-6-phenyl-1,6-dihydropyridine-3-carboxylate (6ab): ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 3.72 (s, 3H), 4.10 (d, ^3J(H,H) = 15.1 Hz, 1H), 4.24 (d, ^3J(H,H) = 15.1 Hz, 1H), 5.01-5.05 (m, 2H), 6.42-6.46 (m, 1H), 7.22-7.24 (m, 2H), 7.31-7.39 (m, 8H), 7.55 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 50.7, 57.5, 61.2, 96.0, 114.6, 120.1, 127.1, 127.9, 128.1, 128.3, 128.86, 128.91, 135.2, 142.2, 147.0, 167.0. IR ($CHCl_3$) ν bar = 3017.0, 2950.9, 1672.6, 1635.9, 1573.4, 1436.8, 1310.7 cm^{-1}; MS (70 eV): *m/z* (%):305 (9.1) [M^+], 228 (54), 213 (13), 182 (13), 91 (100); elemental analysis calcd (%) for $C_{20}H_{19}NO_2$: C 78.66, H 6.26, N 4.59; found: C 78.49, H 6.44, N 4.51.



(±) Methyl 1-allyl-6-phenyl-1,6-dihydropyridine-3-carboxylate (6ac): ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 3.53-3-56 (m, 2H), 3.65 (s, 3H), 5.01 (dd, ^3J(H,H) = 10.0 and 4.3 Hz, 1H), 5.12 (d, ^3J(H,H) = 4.3 Hz, 1H), 5.16-5.24 (m, 2H), 5.60-5.70 (m, 1H), 6.38 (dt, ^3J(H,H) = 10.0 and 1.3 Hz, 1H), 7.24-7.30 (m, 5H), 7.35 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 50.6, 56.1, 61.6, 95.9, 114.4, 119.3, 120.1, 127.0, 128.2, 128.8, 131.9, 142.4, 146.4, 166.9; IR ($CHCl_3$) ν bar = 3013.4, 1672.9, 1633.8, 1573.1, 1438.2, 1311.8, 1220.5, 1211.7, 1189.7, 1172.3, 1150.0 cm^{-1}; MS (70 eV): *m/z* (%): 255 (14) [M^+], 179 (13), 178 (100), 154 (11), 86 (12), 84 (19); elemental analysis calcd (%) for $C_{16}H_{17}NO_2$: C 75.27, H 6.71, N 5.49; found: C 75.28, H 6.71, N 5.61.

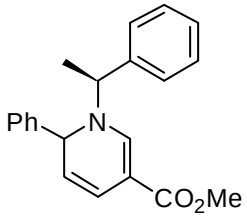


(±) Methyl 1-adamantyl-6-phenyl-1,6-dihydropyridine-3-carboxylate (6ad): ^{1}H NMR



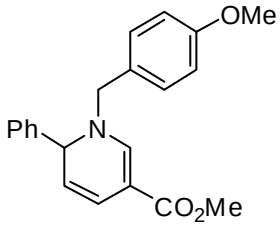
(400 MHz, $CDCl_3$, 25ºC): δ = 1.54-1.67 (m, 6H), 1.75 (ddd, ^3J(H,H) = 11.7, 5.0 and 2.7 Hz, 3H), 1.95 (ddd, ^3J(H,H) = 11.7, 5.0 and 2.7 Hz, 3H), 2.09 (m, 3H), 3.70 (s, 3H), 5.18 (dd, ^3J(H,H) = 9.4 and 5.8 Hz, 1H), 5.34 (dd, ^3J(H,H) = 5.8 and 1.3 Hz, 1H), 6.34 (dd, ^3J(H,H) = 9.4 and 1.3 Hz, 1H), 7.20-7.28 (m, 5H), 7.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 29.6, 35.8, 42.1, 50.6, 56.5, 59.2, 98.6, 113.7, 120.3, 124.8, 127.3, 128.7, 143.1, 146.0, 167.3; IR ($CHCl_3$) ν bar = 3010.9, 2914.2, 2855.8, 1672.6, 1625.6, 1599.4, 1557.3, 1442.1, 1297.4, 1252.4, 1131.4 cm^{-1}; MS (70 eV): *m/z* (%): 349 (10) [M^+], 272 (56), 135 (100), 79 (12); elemental analysis calcd (%) for $C_{23}H_{27}NO_2$: C 79.05, H 7.79, N 4.01; found: C 78.94, H 8.07, N 3.83.

(±) Methyl 6-phenyl-1-((S)-1-phenylethyl)-1,6-dihydropyridine-3-carboxylate (6ae):



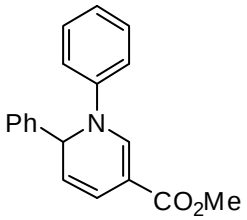
^{1}H NMR (400 MHz, $CDCl_3$, 25ºC) major isomer: δ = 1.49 (d, ^3J(H,H) = 6.9 Hz, 3H), 3.73 (s, 3H), 4.23 (q, ^3J(H,H) = 6.9 Hz, 1H), 4.95-4.99 (m, 2H), 6.41 (d, ^3J(H,H) = 9.8 Hz, 1H), 7.23-7.38 (m, 10H), 7.86 (s, 1H); minor isomer: δ = 1.49 (d, ^3J(H,H) = 6.9 Hz, 3H), 3.65 (s, 3H), 4.44 (q, ^3J(H,H) = 6.9 Hz, 1H), 5.07 (dd, ^3J(H,H) = 9.8 and 4.5 Hz, 1H), 5.16 (d, ^3J(H,H) = 4.5 Hz, 1H), 6.41 (d, ^3J(H,H) = 9.8 Hz, 1H), 7.03-7.06 (m, 2H), 7.23-7.38 (m, 8H), 7.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): (major isomer) δ= 21.4, 50.6, 59.8, 62.8, 95.8, 114.4, 120.1, 126.3, 126.8, 127.9, 128.2, 128.9, 129.0, 141.7, 142.0, 143.2, 167.2; IR ($CHCl_3$) ν bar = 3013.8, 1672.3, 1634.3, 1568.6, 1440.4, 1262.8, 1144.8 cm^{-1}; MS (70 eV): *m/z* (%): 319 (10) [M^+], 242 (22), 213 (88), 182 (69), 138 (42), 127 (28), 105 (100), 104 (42), 77 (28); elemental analysis calcd (%) for $C_{21}H_{21}NO_2$: C 78.97, H 6.63, N 4.39; found: C 78.87, H 6.72, N 4.70.

(±) Methyl 1-(4-methoxybenzyl)-6-phenyl-1,6-dihydropyridine-3-carboxylate (6af):

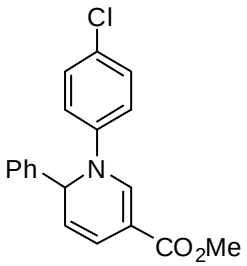


^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 3.71 (s, 3H), 3.81 (s, 3H), 4.03 (d, ^3J(H,H) = 14.8 Hz, 1H), 4.17 (d, ^3J(H,H) = 14.8 Hz, 1H), 4.90-5.01 (m, 2H), 6.41 (ddd, ^3J(H,H) = 10.1, 2.9 and 1.3 Hz, 1H), 6.89 (d, ^3J(H,H) = 8.8 Hz, 2H), 7.13 (d, ^3J(H,H) = 8.8 Hz, 2H), 7.30-7.38 (m, 5H), 7.53 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 50.6, 55.3, 57.0, 61.0, 95.7, 114.3, 114.5, 120.0, 126.9, 127.1, 128.3, 128.8, 129.3, 142.3, 146.9, 159.6, 167.0; IR ($CHCl_3$) ν bar = 3013.1, 2951.1, 1672.9, 1634.6, 1572.1, 1512.7, 1438.2, 1311.3, 1250.2, 1171.3, 1146.6 cm^{-1}; MS (70 eV): *m/z* (%): 335 (22) [M^+], 304 (5.3), 258 (31), 122 (25), 121 (100), 77(11); elemental analysis calcd (%) for $C_{21}H_{21}NO_3$: C 75.20, H 6.31, N 4.18; found: C 75.06, H 6.47, N 4.05.

(±) Methyl 1,6-diphenyl-1,6-dihydropyridine-3-carboxylate (6ag): ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 3.75 (s, 3H), 5.47 (dd, ^3J(H,H) = 9.8 and 5.6 Hz, 1H), 5.57 (d, ^3J(H,H) = 5.6 Hz, 1H), 6.49 (d, ^3J(H,H) = 9.8 Hz, 1H), 7.06-7.12 (m, 3H), 7.24-7.32 (m, 7H), 7.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 51.0, 62.4, 103.1, 116.4, 119.4, 119.8, 124.7, 125.1, 127.8, 129.0, 129.3, 141.0, 142.9, 144.9, 166.8; IR ($CHCl_3$) ν bar = 3011.7, 1687.2, 1636.0, 1568.3, 1487.5, 1441.0, 1314.4, 1232.5, 1210.4, 1108.6 cm^{-1}; MS (70 eV): *m/z* (%): 291 (38) [M^+], 290 (18), 260 (15), 232 (25), 215 (43), 214 (100), 154 (18), 77 (41); elemental analysis calcd (%) for $C_{19}H_{17}NO_2$: C 78.33, H 5.88, N 4.81; found: C 78.23, H 6.09, N 4.92.

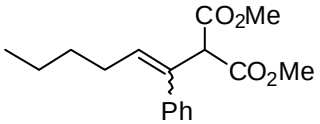


(±) Methyl 1-(4-chlorophenyl)-6-phenyl-1,6-dihydropyridine-3-carboxylate (6ah): ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 3.75 (s, 3H), 5.44 (dd, ^3J(H,H) = 9.5 and 5.5 Hz, 1H), 5.53 (d, ^3J(H,H) = 5.5 Hz, 1H), 6.47 (dt, ^3J(H,H) = 9.5 and 1.0 Hz, 1H), 6.99 (d, ^3J(H,H) = 9.0 Hz, 2H), 7.22 (d, ^3J(H,H) = 9.0 Hz, 2H), 7.26-7.34 (m, 5H), 7.86 (d, ^3J(H,H) = 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 51.0, 62.4, 103.6, 116.8, 119.2, 120.8, 125.1, 128.0, 129.0, 129.3, 129.9, 140.2, 142.4, 143.4, 166.5; IR ($CHCl_3$) ν bar = 3013.5, 1691.7, 1635.6, 1569.4, 1440.8, 1312.3, 1234.8, 1109.0, 1096.1 cm^{-1}; MS (70 eV): *m/z* (%): 325 (17) [M^+], 294 (5.1), 266 (10), 250 (32), 249 (15), 248 (100), 115 (13); elemental analysis calcd (%) for $C_{19}H_{16}ClNO_2$: C 70.05, H 4.95, N 4.30; found: C 69.91, H 5.21, N 4.18.

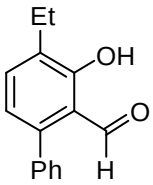


Representative procedure for the microwave-assisted reaction of propargyl vinyl ether 7a or 7b. A solution of propargyl vinyl ether **7a** (0.565mmol) in toluene (5 mL) was placed in a microwave-special closed vial and the solution was irradiated for 3 hours in a single-mode microwave oven (300 Watt, 150 ºC). The reaction mixture was dried over anhydrous sodium sulfate and filtrated using dichloromethane as solvent. After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, n-hexane/EtOAc 80/20) to yield **8a** as a mixture of two isomers ~9:1 (50%) and **9a** (41%).

Dimethyl 2-(1-phenylhex-1-enyl)malonate (8a): major isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 0.92 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.34-1.46 (m, 4H), 2.17 (q, ^3J(H,H) = 7.4 Hz, 2H), 3.67 (s, 6H), 4.75 (s, 1H), 5.90 (d, ^3J(H,H) = 7.4 Hz, 1H), 7.22-7.30 (m, 3H), 7.36-7.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 22.4, 28.7, 31.2, 52.5, 54.1, 127.1, 128.0, 132.5, 136.3, 141.8, 168.8. One carbon signal buried under the aromatic region; IR ($CHCl_3$) ν bar = 3022.8, 2931.0, 2863.3, 1741.1, 1438.9, 1312.3, 1216.9, 1154.1 cm^{-1}; MS (70 eV): *m/z* (%): 290 (19) [M^+], 231 (95), 198 (31), 187 (100), 129 (47), 128 (45), 115 (45), 91(36).

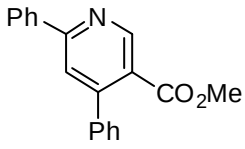


4-Ethyl-3-hydroxybiphenyl-2-carbaldehyde (9a): ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 1.28 (t, ^{3}J(H,H) = 7.2 Hz, 3H), 2.74 (q, ^{3}J(H,H) = 7.2 Hz, 2H), 6.83 (d, ^{3}J(H,H) = 7.6 Hz, 1H), 7.34-7.36 (m, 2H), 7.40-7.45 (m, 3H), 7.43 (d, ^{3}J(H,H) = 7.6 Hz, 1H), 9.84 (s, 1H), 12.24 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.6, 22.3, 117.4, 121.0, 128.0, 128.3, 130.1, 132.0, 135.7, 137.7, 145.0, 160.8, 197.4; IR ($CHCl_3$) ν bar = 3021.7, 1641.7, 1426.1, 1398.1, 1316.5, 1222.2 cm^{-1}

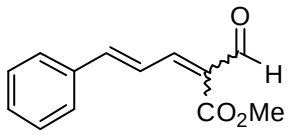


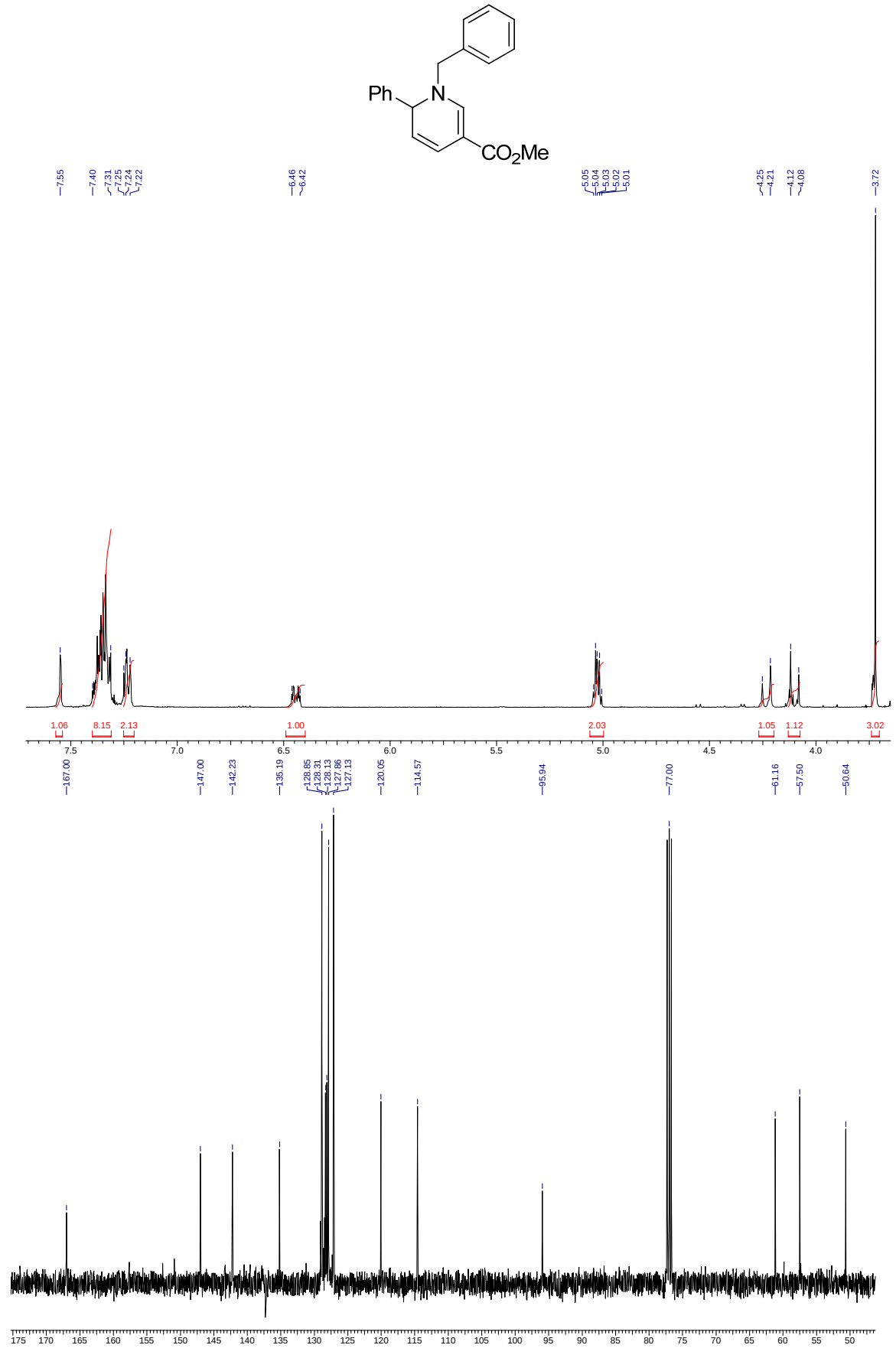
Representative procedure for the microwave-assisted synthesis of pyridines (10). A solution of propargyl vinyl ether **1j** (1.0 mmol), methoxyamine hydrochloride (1.1 mmol) and NaOAc (0.55 mmol) in ethanol (5 mL) was placed in a microwave-special closed vial and the solution was irradiated for 30 min in a single-mode microwave oven (150 Watt, 120 ºC). The reaction mixture was dried over anhydrous sodium sulfate and filtrated using dichloromethane as solvent. After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, n-hexane/EtOAc 80/20) to yield **10j** (57%).

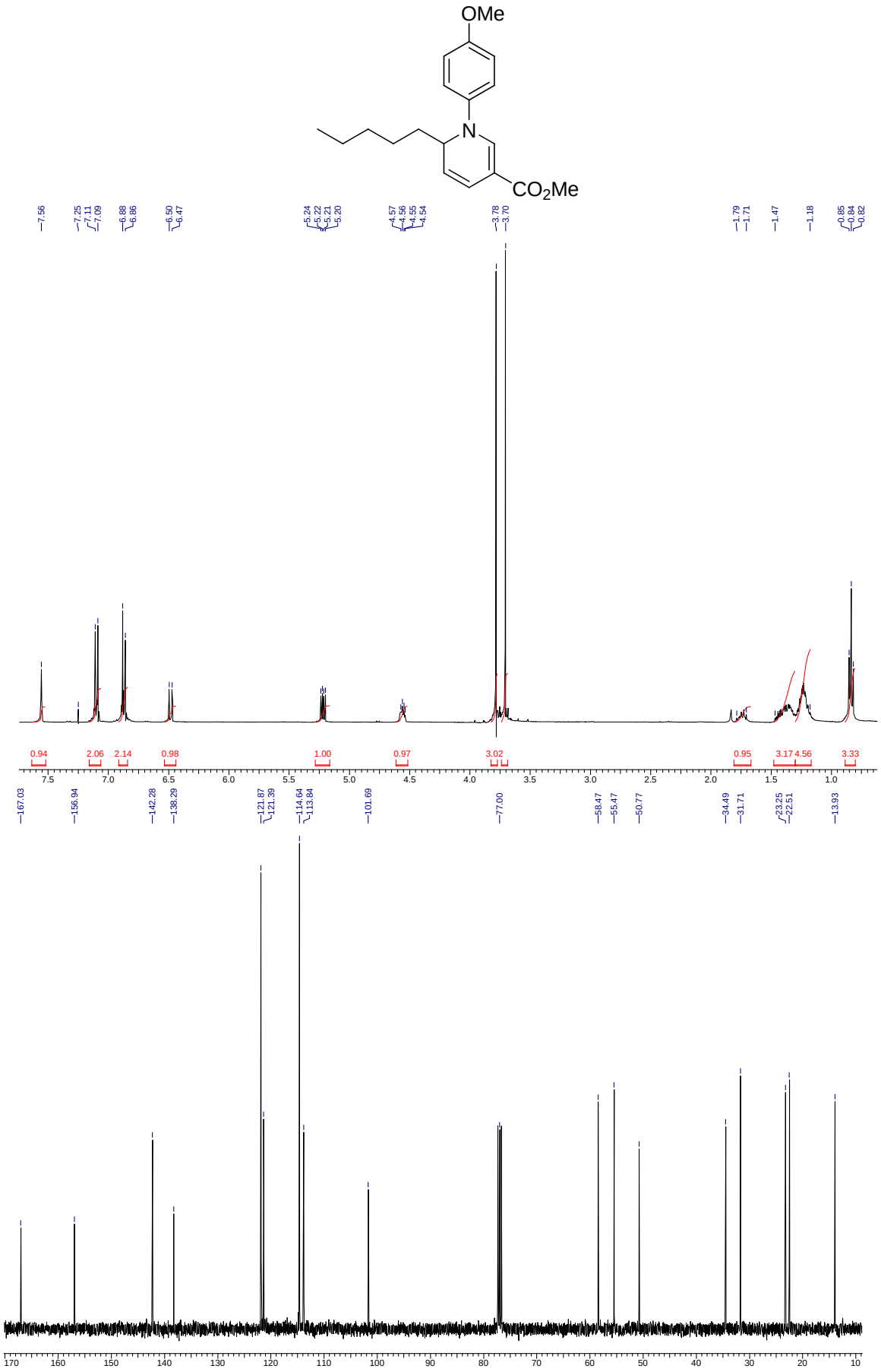
Methyl 4,6-diphenylnicotinate (10e): ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 3.72 (s, 3H), 7.36-7.38 (m, 2H), 7.44-7.51 (m, 6H), 7.72 (d, ^{3}J(H,H) = 0.8 Hz, 1H), 8.05-8.08 (m, 2H), 9.13 (d, ^{3}J(H,H) = 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 55.1, 121.8, 124.4, 127.3, 128.0, 128.3, 128.5, 128.9, 129.9, 138.2, 139.0, 151.2, 151.3, 159.6, 167.1; IR ($CHCl_3$) ν bar = 3018.3, 2928.0, 2361.3, 1724.2, 1591.2, 1438.8, 1295.0, 1222.2, 1120.1 cm^{-1}; MS (70 eV): *m/z* (%): 289 (100) [M^+], 274 (66), 258 (75), 230 (11), 202 (31), 129 (6.0), 77 (10). HRMS (m/z): [M]+ calcd for $C_{19}H_{15}NO_2$, 289.1098; found, 289.1103.

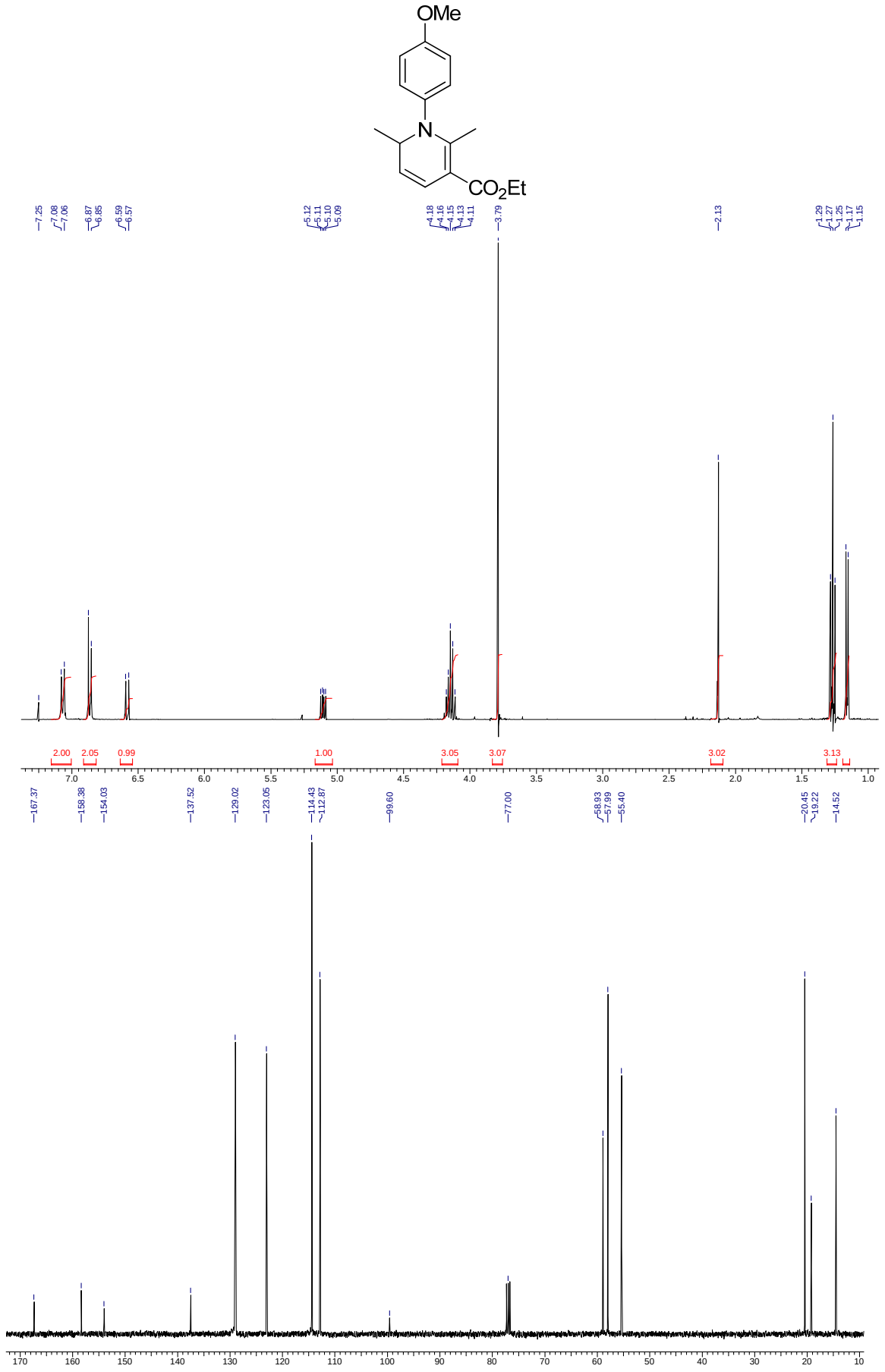


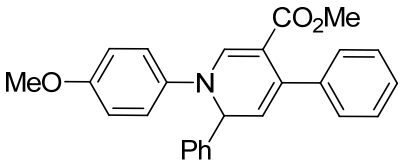
(4E)-methyl 2-formyl-5-phenylpenta-2,4-dienoate (3a): mixture of 2 isomers. Major isomer after chromatography: ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 3.92 (s, 3H), 7.24 (d, ^{3}J(H,H) = 15.6 Hz, 1H), 7.37-7.39 (m, 3H), 7,58-7.60 (m, 2H), 7.66 (d, ^{3}J(H,H) = 11.9 Hz, 1H), 7.93 (dd, ^{3}J(H,H) = 15.6 and 11.9 Hz, 1H), 9.93 (s, 1H). Minor isomer δ = 3.86 (s, 3H), 7.24 (d, ^{3}J(H,H) = 15.6 Hz, 1H), 7.37-7.39 (m, 3H), 7,58-7.60 (m, 2H), 7.74 (dd, ^{3}J(H,H) = 11.9 and 2.9 Hz, 1H), 8.30 (dd, ^{3}J(H,H) = 15.6 and 11.9 Hz, 1H), 10.2 (d, ^{3}J(H,H) = 2.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): major isomer: δ = 51.9, 124.2, 126.4, 128.5, 129.0, 130.8, 135.4, 150.3, 151.4, 165.4, 189.7; minor isomer δ = 52.1, 123.6, 124.2, 128.6, 129.0, 130.8, 135.3, 151.4, 151.5, 166.7, 191.2.

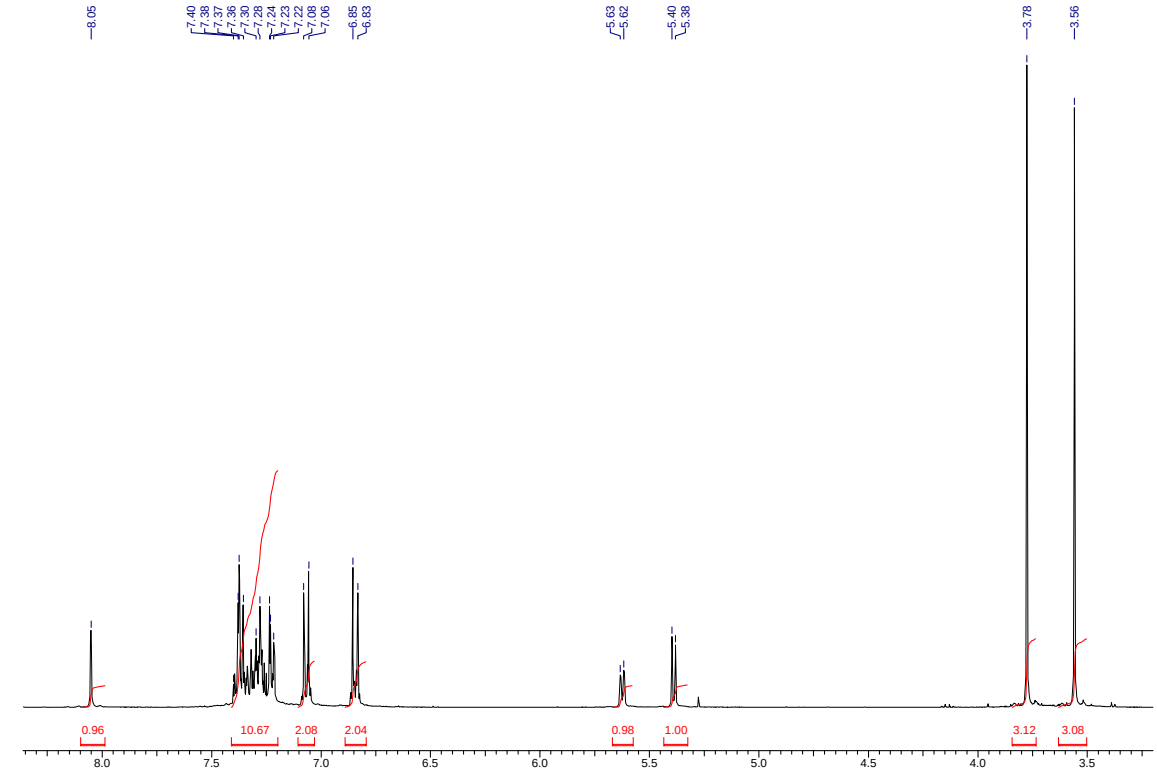


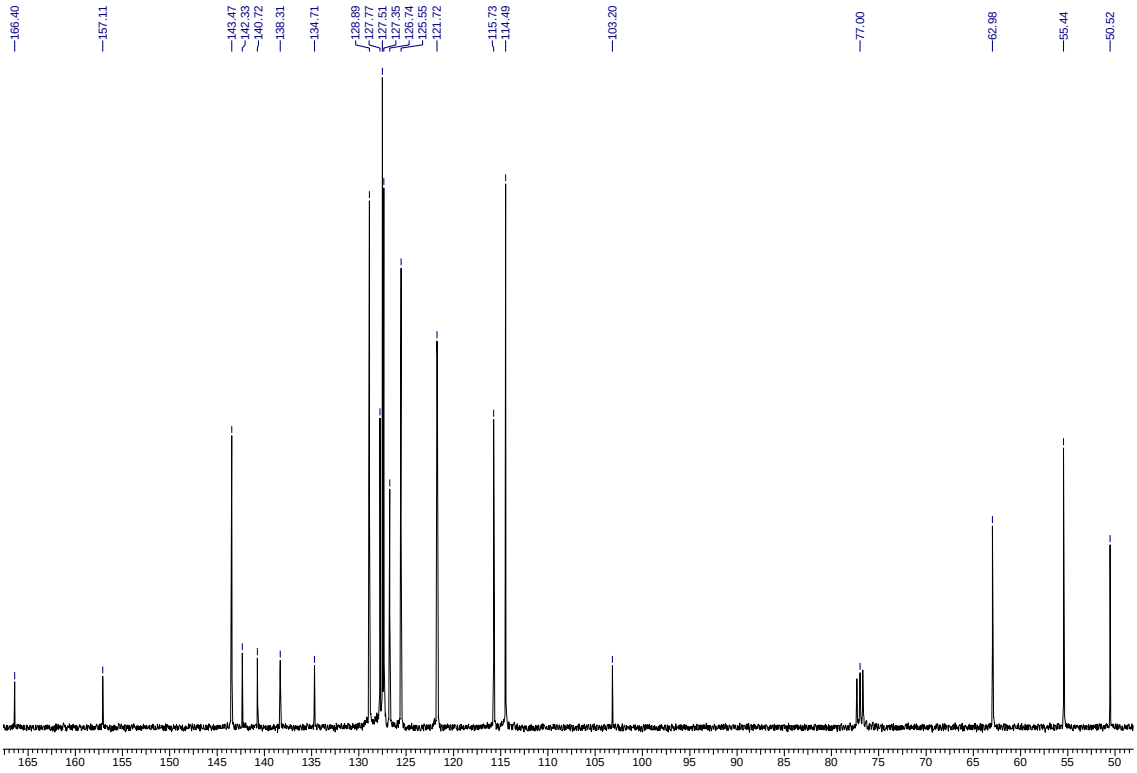

Ph
N
CO2Me
7.55
7.40
7.31
7.25
7.24
7.22
6.46
6.42
5.05
5.04
5.03
5.02
5.01
4.25
4.21
4.12
4.08
3.72
1.06
8.15
2.13
1.00
2.03
1.05
1.12
3.02
167.00
147.00
142.23
135.19
128.85
128.31
128.13
127.86
127.13
120.05
114.57
95.94
77.00
61.16
57.50
50.64

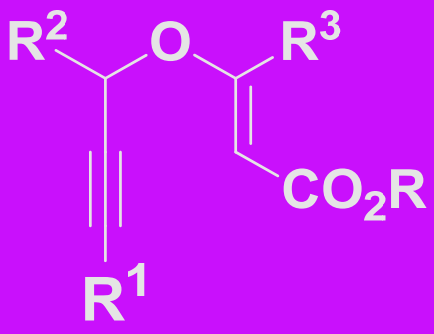

OMe
N
CO2Me
7.56
7.25
7.11
7.09
6.88
6.86
6.50
6.47
5.24
5.22
5.21
5.20
4.57
4.56
4.55
4.54
3.78
3.70
1.79
1.71
1.47
1.18
0.85
0.84
0.82
0.94
2.06
2.14
0.98
1.00
0.97
3.02
0.95
3.17
4.56
3.33
167.03
156.94
142.28
138.29
121.87
121.39
114.64
113.84
101.69
77.00
58.47
55.47
50.77
34.49
31.71
23.25
22.51
13.93


OMe
N
CO2Et
7.25
7.08
7.06
6.87
6.85
6.59
6.57
5.12
5.11
5.10
5.09
4.18
4.16
4.15
4.13
4.11
3.79
2.13
1.29
1.27
1.25
1.17
1.15
2.00
2.05
0.99
1.00
3.05
3.07
3.02
3.13
167.37
158.38
154.03
137.52
129.02
123.05
114.43
112.87
99.60
77.00
59.93
57.99
55.40
20.45
19.22
14.52


CO2Me
MeO
N
Ph


8.05
7.40
7.38
7.37
7.36
7.28
7.24
7.23
7.22
7.08
7.06
6.85
6.83
5.63
5.62
5.40
5.38
3.78
3.56
0.96
10.67
2.08
2.04
0.98
1.00
3.12
3.08


166.40
157.11
143.47
142.33
140.72
138.31
134.71
128.89
127.77
127.51
127.35
126.74
125.55
121.72
115.73
114.49
103.20
77.00
62.98
55.44
50.52



CHAPTER 4

Microwave-Assisted Diversity-Oriented Domino Synthesis of Functionalized Nicotinic Acid Derivatives

FULL PAPER

DOI: 10.1002/ejoc.201001067

Microwave-Assisted Diversity-Oriented Domino Synthesis of Functionalized Nicotinic Acid Derivatives

David Tejedor,*[a,b] Gabriela Méndez-Abt,[a,b] and Fernando García-Tellado*[a,b]

Dedicated to Professor Carmen Nájera on the occasion of her 60th birthday

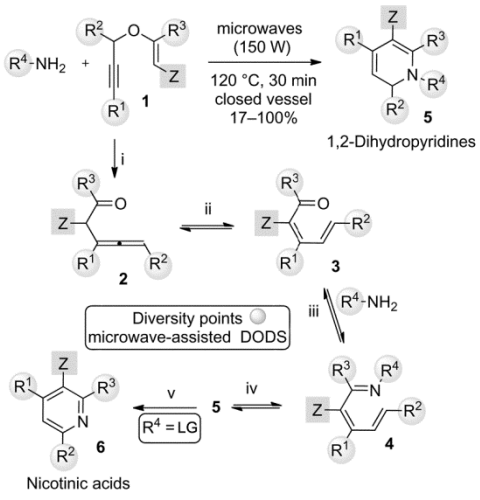
Keywords: Domino reactions / Electrocyclic reactions / Microwave chemistry / Nitrogen heterocycles / Nicotinic acid

The microwave-assisted diversity-oriented domino synthesis of functionalized alkyl nicotinates from propargyl vinyl ethers is described. The domino manifold comprises a complex network of reactions involving at least five distinct chemical steps. The obtained alkyl nicotinates incorporate two diversity points at the ring and one ester functionality as convenient handles for further elaboration.

Introduction

Functionalized pyridines with one carboxylic acid derived function (e.g., amide, ester, oxazoline) at the C-3 position (nicotinic acid derivatives), constitute an important group of biologically and pharmaceutically relevant molecules.[1] A survey of the methodologies for general access to functionalized pyridine rings has been published.[2] Among the approaches described, modern (catalyzed) versions of the Bohlmann–Rahtz heteroannulation reaction[3] with combinatorial[4] and multicomponent[4a,5] extensions, involving β-amino acrylates (conjugated enamines) and conjugated alkynes, have proven to be synthetically convenient and general processes for the construction of substituted nicotinic derivatives.[2c] Recently, Rodriguez and co-workers have reported a regioselective, multicomponent synthesis of functionalized nicotinic acid derivatives through the H^+-catalyzed reaction of 1,3-dicarbonyl compounds with β,γ-unsaturated α-oxo carbonyl compounds and ammonium acetate under oxidative conditions.[6] In spite of these advances, there is still a need for synthetic methodologies that enable controlled access to these heterocycles with structural (functional) diversity and a wide range of ring substitution patterns.[7] The use of commercially available or readily accessible, simple starting materials, together with bench-friendly and environmentally benign reaction conditions are important factors that should be taken into account in these strategies.[8]

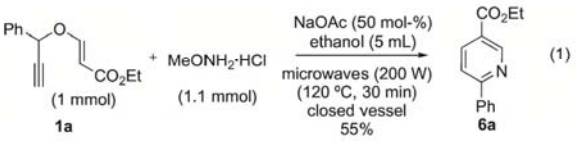
In a recent communication,[9] we reported the formation of substituted alkyl 1,2-dihydropyridine-3-carboxylates **5** from propargyl enol ethers **1** and primary amines through a microwave-assisted domino reaction (Scheme 1). Therein, we proposed that azatrienes **4** could be conveniently transformed into substituted alkyl nicotinates **6** if a primary amine armed with a good leaving group was used in this



Scheme 1. Microwave-assisted diversity-oriented domino synthesis (DODS) of 1,2-dihydropyridines **5** and nicotinic acid derivatives **6** from propargyl vinyl ethers **1**. Domino sequence: (i) [3,3] propargyl enol ether rearrangement; (ii) 1,3-protropic isomerization; (iii) condensation; (iv) 6π-aza-electrocyclization; (v) elimination. Z = CO_2R; LG = leaving group.

[a] Instituto de Productos Naturales y Agrobiología, Consejo Superior de Investigaciones Científicas,
Astrofísico Francisco Sánchez 3, 38206 La Laguna, Tenerife, Canary Islands, Spain
Fax: +34-922-260135
E-mail: fgarcia@ipna.csic.es
dtejedor@ipna.csic.es
http://www.ipna.csic.es/departamentos/qbb/qb/
[b] Instituto Canario de Investigación del Cáncer, Canary Islands, Spain

manifold [R^4 = leaving group (LG); Scheme 1]. In this scenario, the 1,2-dihydropyridine intermediate **5**, which would be formed from the corresponding azatriene **4** through a thermally allowed 6π-aza electrocyclization reaction,[10] would generate the corresponding pyridine derivative **6** by elimination of a neutral molecule (H-LG). As a proof of concept, we reported therein the microwave-assisted domino synthesis of ethyl 6-phenylnicotinate (**6a**) from the propargyl derivative **1a** and methoxyamine hydrochloride [Equation (1)]. In this paper, we have extended this protocol to the diversity-oriented domino synthesis (DODS) of functionalized alkyl nicotinates **6** from propargyl vinyl ethers **1** and methoxyamine hydrochloride under microwave irradiation. Nicotinates **6** are obtained in good yields, incorporating three points for diversity and a wide range of aryl-based substitution patterns on the ring.[11]



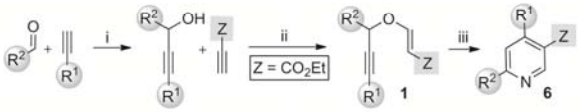
(1)

Results and Discussion

Propargyl vinyl ethers **1** (Scheme 1) constitute densely functionalized platforms with three diversity points and a reactivity-directing carboxylic ester group.[9] These scaffolds can be conveniently assembled from commercial sources (aldehydes, alkynes, and alkyl propiolates) in one or two straightforward synthetic steps (some propargyl alcohols are commercially available) (Table 1).[12] Because libraries of these scaffolds can be prepared in a very simple and direct way with a certain degree of functional (structural) diversity, they constitute versatile building blocks for use in DODS. We started our study by optimizing the previously reported reaction of propargyl vinyl ether **1a** and methoxyamine hydrochloride to generate ethyl nicotinate **6a** [Equation (1)]; the reaction was assessed by careful variation of the reaction conditions (microwave potency, temperature, time, solvent, stoichiometry, and buffer). It was found that performing the reaction in ethanol, in the presence of sodium acetate (0.55 equiv.), under microwave irradiation (200 W, 100 °C, closed vessel)[13] for 60 min, increased the initially reported 55% yield for product **6a**[9] to 65%. The use of 2-propanol instead of ethanol as the reaction solvent allowed the yield to be further increased to 77% (Table 1, Entry 1). Once a set of optimized conditions was established, we next studied the scope of this process by using the set of propargyl vinyl ethers **1a–n** outlined in Table 1. Under the standardized conditions, the majority of propargyl vinyl ethers assayed afforded the corresponding alkyl nicotinates **6** in good yields, although we observed that changing the solvent from ethanol to 2-propanol was not beneficial in all cases (small differences were observed). Therefore, we routinely performed the reactions in both solvents to determine the optimal solvent for each entry.

With regard to the functionalities decorating the propargylic platform **1**, the reaction tolerated a diverse range of alkyl/aryl substitution patterns. As a general tendency, aromatic substituents at the propargylic sp^3-position (R^2) and the sp^3-alkyne position (R^1) were more productive than alkyl substituents (compare Table 1, Entries 1 and 9 with Entries 2–4). A bulky *tert*-butyl group located at the pro-

Table 1. Microwave-assisted diversity-oriented domino synthesis of functionalized alkyl nicotinates **6** from propargyl vinyl ethers **1**.[a]



Entry	R^1	R^2	**1** (yield [%])[b]	Solvent	Microwave power [W][c]	Temperature [°C]	Time [min]	**6**	Yield [%][d]
1	H	Ph	**1a** (95)	*i*PrOH	200	100	60	**6a**	77
2	H	*n*Pent	**1b** (87)	EtOH	300	150	180	**6b**	54
3	H	Me	**1c** (98)[e]	EtOH	300	150	180	**6c**	14
4	*n*Bu	Ph	**1d** (96)	EtOH	200	100	60	**6d**	45
5	*p*-$MeOC_6H_4$	Ph	**1e** (78)[f]	*i*PrOH	200	100	60	**6e**	78
6	3,4-$Cl_2C_6H_3$	Ph	**1f** (79)	EtOH	200	100	60	**6f**	61
7	*p*-ClC_6H_4	Ph	**1g** (84)	EtOH	200	100	60	**6g**	60
8	*p*-MeC_6H_4	Ph	**1h** (81)[f]	EtOH	200	100	60	**6h**	61
9	Ph	Ph	**1i** (89)	EtOH	200	100	60	**6i**	67
10	Ph	*t*Bu	**1j** (99)	*i*PrOH	300	150	180	**6j**	13
11	Ph	*p*-ClC_6H_4	**1k** (79)[f]	EtOH	200	100	60	**6k**	62
12	Ph	*p*-$MeOC_6H_4$	**1l** (76)[f]	*i*PrOH	200	100	60	**6l**	72
13	Ph	2-furyl	**1m** (48)	*i*PrOH	200	100	60	**6m**	60
14	Me_3Si	Ph	**1n** (77)	*i*PrOH	200	100	60	**6n**	35

[a] Reagents and conditions: (i) BuLi, THF, –78 °C (30 min), then –30 °C (30 min), then –78 °C, R^2CHO, 1 h; (ii) Et_3N (10 mol-%), CH_2Cl_2, room temp., 2 h; (iii) propargyl vinyl ether **1** (1 mmol), $MeONH_2$·HCl (1.1 mmol), NaOAc (0.55 mmol), EtOH or *i*PrOH (5 mL), microwave irradiation. [b] Yields of isolated compounds **1** from the corresponding propargyl alcohols. [c] Microwave irradiation of specialized closed vessels. [d] Yield of isolated compounds **6**. [e] Methyl propiolate was used as alkynoate. [f] These substrates spontaneously rearranged partially to the corresponding dienals **3** (combined yield of **1** and **3**).

pargylic sp^3-position (**1j**; R^2 = *t*Bu) reduced the efficiency of the reaction significantly (Table 1, Entry 10). Release of steric congestion at this position (**1b**; R^2 = *n*Pent) increased the yield to 54% (Table 1, Entry 2). Intriguingly, methyl-substituted **1c** (R^2 = Me) afforded nicotinate **6c** in very low yield (14%; Table 1, Entry 3). Remarkably, when no substituents were present in the propargylic scaffold (R^1 = R^2 = H), none of the desired product was formed (data not shown). These results could point to the existence of a certain degree of conformational control (a substituent-biased conformational control) in the intermediate azatriene **4**, which drives the process toward pyridine ring formation. Substitution at the sp^3-propargylic position (R^2) was found to be dependent on the nature of substituent R^1.[9] Whereas R^2 could be aliphatic or aromatic for terminal alkynes (R^1 = H) (Table 1, Entries 1, 2, and 3) and aromatic for internal alkynes (R^1 = *n*Bu, Ar, or Me_3Si) (Entries 4–9 and Entries 11–14), the combination of R^2 = alkyl and an internal alkyne, was detrimental for the transformation of these propargyl derivatives into the corresponding functionalized pyridines (data not shown). The electronic nature of the aryl substituents at either the propargylic sp^3-position or at the alkyne sp-position did not significantly influence the global efficiency of the reaction (compare Table 1, Entries 5–8 and 11–13 with Entry 9), although the *para*-methoxy group proved to be the most convenient (compare Table 1, Entries 5 and 12 with Entries 6–8 and 11). Propargylic scaffold **1m**, bearing a furan ring at the propargylic sp^3-position, was efficiently converted into the corresponding nicotinate derivative **6m**, which is a very interesting biheterocyclic scaffold (Table 1, Entry 13). Remarkably, even the silyl-containing propargylic vinyl ether **1n** was able to give, in reasonable yield (35%), the corresponding alkyl nicotinate **6n**, which bears an important trimethylsilyl group at the ring.

Conclusions

We have described the microwave-assisted diversity-oriented synthesis of functionalized alkyl nicotinates **6** from propargyl vinyl ethers **1** through a complex and efficient domino manifold involving at least five discrete chemical steps. The propargylic platforms **1** are rapidly and easily assembled from commercially available or readily available materials. The obtained alkyl nicotinates **6** feature a maximum of two diversity points at the ring and one appended chemical handle for further elaboration (ester functionality). The reaction is fast, economical, bench-friendly (it does not require special care with solvent and protective reaction atmospheres) and environmentally benign. These practical advantages make this approach a good alternative to other well-known methods, and can be used to rapidly generate libraries of functionalized nicotinate derivatives **6** for use in drug discovery programs.[11]

Experimental Section

General Remarks: ^1H and ^{13}C NMR spectra of the samples as $CDCl_3$ solutions were recorded either at 400 and 100 MHz or at 500 and 125 MHz (Bruker AC200 or AMX2-500), respectively. Microwave reactions were conducted in sealed glass vessels (capacity 10 mL) with a CEM Discover microwave reactor. FTIR spectra were measured in chloroform solutions with a Perkin–Elmer FTIR Spectrum BX spectrophotometer. Mass spectra (low-resolution) (EI/CI) were obtained with a Hewlett–Packard 5995 gas chromatograph/mass spectrometer. High-resolution mass spectra (HRMS) were recorded with a Micromass Autospec mass spectrometer. Microanalyses were performed with a Fisons Instruments EA 1108 carbon, hydrogen, and nitrogen analyzer. Analytical thin-layer chromatography (TLC) plates used were E. Merck Brinkman UV-active silica gel (Kieselgel 60 F254) on aluminum. Flash column chromatography was carried out with E. Merck silica gel 60 (particle size less than 0.020 mm) by using appropriate mixtures of ethyl acetate and hexanes as eluent. All reactions were performed in oven-dried glassware under nitrogen unless otherwise stated. Dichloromethane was distilled from CaH_2. All other materials were obtained from commercial suppliers and used as received. Products **1a**,[9] **6a**,[14] and **6c**[15] have been previously reported, and all data are in accordance with those reported in the literature.

Representative Procedure for the Synthesis of Propargyl Vinyl Ethers 1a–n: Triethylamine (0.30 mmol) was added to a solution of ethyl propiolate (3.0 mmol) and 1-phenylprop-2-yn-1-ol (3.0 mmol) in anhydrous CH_2Cl_2 (10 mL). The reaction mixture was stirred for 2 h; then, after removing the solvent under reduced pressure, the products were purified by flash column chromatography (silica gel; *n*-hexane/EtOAc, 90:10) to yield **1a** (656 mg, 95%).[9]

(±)-Ethyl (*E*)-3-(Oct-1-yn-3-yloxy)acrylate (1b): Yield: 584.6 mg (2.61 mmol, 87%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.89 (t, $^3J_{H,H}$ = 6.9 Hz, 3 H, Me), 1.26 (t, $^3J_{H,H}$ = 6.9 Hz, 3 H, Me), 1.29–1.33 (m, 4 H, 2 × 5′-H and 2 × 6′-H), 1.42–1.50 (m, 2 H, 2 × 7′-H), 1.76–1.90 (m, 2 H, 2 × 4′-H), 2.57 (d, $^3J_{H,H}$ = 2.1 Hz, 1 H, 1′-H), 4.12–4.20 (q, $^3J_{H,H}$ = 6.9 Hz, 2 H, OCH_2Me), 4.52 (dt, $^3J_{H,H}$ = 6.6, 2.1 Hz, 1 H, 3′-H), 5.37 (d, $^3J_{H,H}$ = 12.5 Hz, 1 H, 2-H), 7.59 (d, $^3J_{H,H}$ = 12.5 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 14.3, 22.4, 24.4, 31.2, 35.1, 59.8, 71.2, 75.9, 80.2, 99.0, 160.1, 167.5 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3305.6, 2957.8, 2122.7, 1701.0, 1640.3, 1464.7, 1371.3, 1289.6, 1222.8, 1191.7, 1136.5 cm^{-1}. MS (70 eV): *m/z* (%) = 225 (22) [M^+ + 1], 195 (12.7), 179 (22), 151 (9.4), 139 (9.1), 125 (8.5), 117 (40), 109 (35), 93 (49), 89 (22), 81 (54), 79 (56), 71 (66), 67 (100), 55 (75). $C_{13}H_{20}O_3$ (224.14): calcd. C 69.61, H 8.99; found C 69.52, H 8.69.

(±)-Methyl (*E*)-3-(But-3-yn-2-yloxy)acrylate (1c): Yield: 452.8 mg (2.94 mmol, 98%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.56 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, Me), 2.57 (d, $^3J_{H,H}$ = 2.1 Hz, 1 H, 4′-H), 3.69 (s, 3 H, OMe), 4.66 (dq, $^3J_{H,H}$ = 6.6, 2.1 Hz, 1 H, 2′-H), 5.37 (d, $^3J_{H,H}$ = 12.5 Hz, 1 H, 2-H), 7.59 (d, $^3J_{H,H}$ = 12.5 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.6, 51.2, 67.0, 75.4, 80.9, 98.8, 160.0, 167.9 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3306.9, 3024.2, 2952.9, 2122.0, 1706.4, 1645.7, 1625.6, 1438.4, 1333.4, 1293.9, 1224.5, 1194.1, 1145.3, 1120.8, 1035.2 cm^{-1}. MS (70 eV): *m/z* (%) = 154 (3.8) $[M]^+$, 123 (20), 111 (16), 102 (13), 95 (30), 71 (76), 53 (100). $C_8H_{10}O_3$ (154.06): calcd. C 62.33, H 6.54; found C 62.20, H 6.56.

(±)-Ethyl (*E*)-3-(1-Phenylhept-2-ynyloxy)acrylate (1d): Yield: 823.7 mg (2.88 mmol, 96%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.91 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 1.26 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 1.37–1.46 (m, 2 H, 2 × 6′-H), 1.50–1.57 (m, 2 H, 2 × 5′-H), 2.30 (dt, $^3J_{H,H}$ = 6.9, 2.1 Hz, 2 H, 2 × 4′-H), 4.16 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, OCH_2Me), 5.43 (d, $^3J_{H,H}$ = 12.5 Hz, 1 H, 2-H), 5.62 (t, $^3J_{H,H}$ = 2.1 Hz, 1 H, 1′-H), 7.35–7.41 (m, 3 H, Ph), 7.48–7.51 (m, 2 H, Ph), 7.69 (d, $^3J_{H,H}$ = 12.5 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.5, 14.3, 18.5, 21.9, 30.4, 59.7, 73.7, 75.7, 91.4,

99.4, 127.4, 128.7, 129.0, 137.0, 159.9, 167.6 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3018.8, 2936.1, 2871.1, 2232.5, 1701.2, 1641.4, 1324.4, 1289.0, 1216.8, 1179.0, 1131.5 cm^{-1}. MS (70 eV): *m/z* (%) = 286 (1.4) $[M]^+$, 257 (1.7), 229 (2.9), 213 (4.8), 171 (100), 141 (9.9), 128 (30), 115 (23), 91 (36), 77 (10). $C_{18}H_{22}O_3$ (286.16): calcd. C 75.50, H 7.74; found C 75.15, H 7.39.

Ethyl (2*Z*,4*E*)-2-Formyl-3-(4-methoxyphenyl)-5-phenylpenta-2,4-dienoate (1e): Yield: 786.2 mg (2.34 mmol, 78%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.42 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 3.88 (s, 3 H, OMe), 4.44 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, OCH_2Me), 6.68 (d, $^3J_{H,H}$ = 15.9 Hz, 1 H, 5-H), 6.98–7.02 (m, 2 H, ArH), 7.26–7.41 (m, 8 H, 4-H and ArH), 9.33 (s, 1 H, CHO) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.3, 55.3, 61.6, 113.9, 125.6, 127.2, 127.8, 128.8, 129.9, 131.8, 132.8, 135.6, 143.3, 157.7, 160.7, 166.4, 189.6 ppm. MS (70 eV): *m/z* (%) = 336 (32) $[M]^+$, 318 (25), 290 (100), 262 (81), 247 (33), 234 (29), 231 (32), 219 (42), 202 (32), 191 (37), 165 (22), 159 (11), 135 (17), 115 (19), 105 (16), 91 (28), 77 (20). HRMS: calcd. for $C_{21}H_{20}O_4$ $[M]^+$ 336.1362; found 336.1354.

(±)-Ethyl (*E*)-3-[3-(3,4-Dichlorophenyl)-1-phenylprop-2-ynyloxy]-acrylate (1f): Yield: 886.4 mg (2.37 mmol, 79% yield). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.23–1.28 (m, 3 H, Me), 4.08–4.19 (m, 2 H, OCH_2Me), 5.48 (d, $^3J_{H,H}$ = 12.7 Hz, 1 H, 2-H), 5.82 (s, 1 H, 1′-H), 7.29 (dd, $^3J_{H,H}$ = 8.5 and 2.1 Hz, 1 H, ArH), 7.38–7.43 (m, 4 H, ArH), 7.53–7.55 (m, 3 H, ArH), 7.69 (d, $^3J_{H,H}$ = 12.7 Hz, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.3, 59.9, 73.4, 86.4, 87.2, 99.9, 121.5, 127.4, 128.9, 129.4, 130.4, 131.0, 132.7, 133.5, 133.7, 136.0, 159.6, 167.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3025.1, 2231.8, 1703.3, 1653.0, 1466.9, 1288.3, 1177.1, 1131.9 cm^{-1}. MS (70 eV): *m/z* (%) = 374 (8.0) $[M]^+$, 328 (16), 301 (13), 259 (100), 236 (10), 202 (26), 189 (20), 105 (13), 91 (13), 77 (11). $C_{20}H_{16}O_3Cl_2$ (374.05): calcd. C 64.02, H 4.30; found C 63.90, H 4.51.

(±)-Ethyl (*E*)-3-[3-(4-Chlorophenyl)-1-phenylprop-2-ynyloxy]acrylate (1g): Yield: 856.8 mg (2.52 mmol, 84%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.26 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 4.16 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, OCH_2Me), 5.51 (d, $^3J_{H,H}$ = 12.5 Hz, 1 H, 2-H), 5.84 (s, 1 H, 1′-H), 7.28–7.31 (m, 2 H, ArH), 7.39–7.45 (m, 5 H, ArH), 7.55–7.58 (m, 2 H, ArH), 7.74 (d, $^3J_{H,H}$ = 12.5 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.3, 59.8, 73.5, 85.3, 88.5, 99.7, 120.1, 127.4, 128.7, 128.8, 129.3, 133.1, 135.2, 136.2, 159.7, 167.6 ppm. MS (70 eV): *m/z* (%) = 340 (3.0) $[M]^+$, 225 (56), 188 (4.9), 138 (9.2), 105 (13), 91 (100), 65 (9.2). HRMS: calcd. for $C_{20}H_{17}ClO_3$ $[M]^+$ 340.0866; found 340.0854.

(±)-Ethyl (*E*)-3-[1-Phenyl-3-(*p*-tolyl)prop-2-ynyloxy]acrylate (1h): Yield: 777.6 mg (2.43 mmol, 81%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.27 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 2.35 (s, 3 H, Me), 4.17 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, OCH_2Me), 5.50 (d, $^3J_{H,H}$ = 12.5 Hz, 1 H, 2-H), 5.86 (s, 1 H, 1′-H), 7.13 (d, $^3J_{H,H}$ = 7.9 Hz, 2 H, ArH), 7.36–7.45 (m, 5 H, ArH), 7.57–7.60 (m, 2 H, ArH), 7.76 (d, $^3J_{H,H}$ = 12.5 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.3, 21.5, 59.9, 73.8, 83.6, 90.0, 99.6, 118.6, 127.5, 128.8, 129.1, 129.2, 131.8, 136.6, 139.4, 159.9, 167.6 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3027.0, 2227.6, 1701.9, 1642.7, 1511.6, 1287.8, 1177.8, 1131.6 cm^{-1}. MS (70 eV): *m/z* (%) = 320 (3.5) $[M]^+$, 247 (7.7), 205 (100), 143 (6.8), 119 (8.1), 77 (5.1). $C_{21}H_{20}O_3$ (320.38): calcd. C 78.73, H 6.29; found C 78.83, H 6.25.

(±)-Ethyl (*E*)-3-(1,3-Diphenylprop-2-ynyloxy)acrylate (1i): Yield: 817.0 mg (2.67 mmol, 89%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.27 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 4.17 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, OCH_2Me), 5.51 (d, $^3J_{H,H}$ = 12.5 Hz, 1 H, 2-H), 5.86 (s, 1 H, 1′-H), 7.30–7.38 (m, 3 H, PhH), 7.39–7.45 (m, 3 H, PhH), 7.48–7.50 (m, 2 H, PhH), 7.57–7.59 (m, 2 H, PhH), 7.75 (d, $^3J_{H,H}$ = 12.5 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.3, 59.9, 73.7, 84.3, 89.8, 99.7, 121.7, 127.5, 128.4, 128.8, 129.1, 129.3, 131.9, 136.5, 159.9, 167.5 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3020.2, 2228.4, 1701.8, 1642.4, 1323.7, 1289.5, 1177.1, 1132.3 cm^{-1}. MS (70 eV): *m/z* (%) = 306 (2.9) $[M]^+$, 260 (3.9), 231 (4.4), 202 (4.5), 191 (100), 189 (14.7), 165 (5.4), 129 (3.0), 105 (5.2), 89 (2.7), 77 (4.8). $C_{20}H_{18}O_3$ (306.13): calcd. C 78.41, H 5.92; found C 78.23, H 6.00.

(±)-Ethyl (*E*)-3-(4,4-Dimethyl-1-phenylpent-1-yn-3-yloxy)acrylate (1j): Yield: 849.4 mg (2.97 mmol, 99%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.08 (s, 9 H, *t*Bu), 1.26 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 4.16 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, OCH_2Me), 4.38 (s, 1 H, 3′-H), 5.42 (d, $^3J_{H,H}$ = 12.5 Hz, 1 H, 2-H), 7.28–7.34 (m, 3 H, PhH), 7.42–7.45 (m, 2 H, PhH), 7.69 (d, $^3J_{H,H}$ = 12.5 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.3, 25.6, 36.0, 59.7, 80.8, 84.3, 88.5, 98.4, 122.1, 128.3, 128.7, 131.8, 161.2, 167.8 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3017.7, 2976.7, 2226.7, 1699.4, 1626.0, 1323.4, 1221.9, 1186.5, 1135.6 cm^{-1}. MS (70 eV): *m/z* (%) = 286 (0.8) $[M]^+$, 229 (6.4), 213 (8.7), 171 (100), 156 (54), 143 (25), 129 (21), 115 (26), 102 (3.6), 91 (18), 77 (8.6), 57 (12). $C_{18}H_{22}O_3$ (286.16): calcd. C 75.50, H 7.74; found C 75.66, H 7.45.

(±)-Ethyl (*E*)-3-[1-(4-Chlorophenyl)-3-phenylprop-2-ynyloxy]acrylate (1k): Yield: 805.8 mg (2.37 mmol, 79%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.26 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 4.16 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, OCH_2Me), 5.49 (d, $^3J_{H,H}$ = 12.5 Hz, 1 H, 2-H), 5.82 (s, 1 H, 1′-H), 7.30–7.36 (m, 3 H, ArH), 7.37–7.40 (m, 2 H, ArH), 7.46–7.48 (m, 2 H, ArH), 7.49–7.52 (m, 2 H, ArH), 7.72 (d, $^3J_{H,H}$ = 12.5 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.3, 59.9, 72.9, 83.8, 90.1, 99.9, 121.4, 128.4, 128.8, 129.0, 129.2, 131.9, 135.0, 135.2, 159.6, 167.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3017.6, 2228.9, 1703.8, 1643.6, 1491.3, 1131.8, 1044.6 cm^{-1}. MS (70 eV): *m/z* (%) = 294 (11) $[M^+ - EtOH]$, 240 (11), 225 (100), 202 (15), 139 (13), 129 (19), 105 (19), 77 (12). $C_{20}H_{17}ClO_3$ (340.09): calcd. C 70.49, H 5.03; found C 70.25, H 5.00.

Ethyl (2*Z*,4*E*)-2-Formyl-5-(4-methoxyphenyl)-3-phenylpenta-2,4-dienoate (3l): Yield: 766.1 mg (2.28 mmol, 76%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.42 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 3.81 (s, 3 H, OMe), 4.44 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, OCH_2Me), 6.55 (d, $^3J_{H,H}$ = 15.6 Hz, 1 H, 5-H), 6.83–6.87 (m, 2 H, ArH), 7.21 (d, $^3J_{H,H}$ = 15.6 Hz, 1 H, 4-H), 7.33–7.35 (m, 4 H, ArH), 7.46–7.48 (m, 3 H, ArH), 9.25 (s, 1 H, CHO) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.3, 55.4, 61.6, 114.4, 124.7, 128.0, 128.4, 129.2, 129.6, 130.1, 132.1, 133.8, 143.5, 158.4, 161.3, 166.4, 189.6 ppm. MS (70 eV): *m/z* (%) = 336 (48) $[M]^+$, 290 (100), 245 (12), 234 (68), 219 (24), 202 (21), 191 (46), 165 (17), 135 (22), 121 (20), 105 (11), 77 (15). HRMS: calcd. for $C_{21}H_{20}O_4$ $[M]^+$ 336.1362; found 336.1358.

Ethyl (2*Z*,4*E*)-2-Formyl-5-(furan-2-yl)-3-phenylpenta-2,4-dienoate (3m): Yield: 426.2 mg (1.44 mmol, 48%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.42 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 4.44 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, OCH_2Me), 6.33 (d, $^3J_{H,H}$ = 15.4 Hz, 1 H, 5-H), 6.42 (m, 2 H, furan 3-H and 4-H), 7.22 (d, $^3J_{H,H}$ = 15.4 Hz, 1 H, 4-H), 7.31–7.33 (m, 2 H, PhH), 7.46–7.48 (m, 4 H, PhH and furan 5-H), 9.20 (s, 1 H, CHO) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.2, 61.6, 112.5, 114.5, 124.9, 128.1, 128.4, 129.3, 129.5, 130.0, 133.3, 144.8, 152.0, 157.4, 166.1, 189.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3019.7, 1724.7, 1661.8, 1567.1, 1333.0, 1266.8, 1146.4, 1019.3 cm^{-1}. MS (70 eV): *m/z* (%) = 296 (32) $[M]^+$, 250 (65), 221 (28), 194 (83), 165 (100), 152 (27), 139 (16), 115 (27), 105 (14), 94 (12), 77 (19), 63 (14). $C_{18}H_{16}O_4$ (296.10): calcd. C 72.96, H 5.44; found C 73.09, H 5.48.

(±)-Ethyl (*E*)-3-[1-Phenyl-3-(trimethylsilyl)prop-2-ynyloxy]acrylate (1n): Yield: 697.6 mg (2.31 mmol, 77%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.09 (s, 9 H, $SiMe_3$), 1.13 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 4.03 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, OCH_2Me), 5.33 (d, $^3J_{H,H}$ =

12.5 Hz, 1 H, 2-H), 5.50 (s, 1 H, 1′-H), 7.23–7.29 (m, 3 H, PhH), 7.36–7.39 (m, 2 H, PhH), 7.57 (d, $^3J_{H,H}$ = 12.5 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = –0.45, 14.2, 59.7, 73.5, 95.7, 99.6, 100.0, 127.4, 128.7, 129.1, 136.1, 159.6, 167.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3019.7, 2178.5, 1701.7, 1642.0, 1454.0, 1248.9, 1176.8, 1133.0, 849.9 cm^{-1}. MS (70 eV): *m/z* (%) = 302 (0.5) $[M]^+$, 213 (12), 187 (100), 172 (11), 83 (15). $C_{17}H_{22}O_3Si$ (302.13): calcd. C 67.51, H 7.33; found C 67.70, H 7.15.

Representative Procedure for the Microwave-Assisted Synthesis of Pyridines 6a–n: A solution of propargyl vinyl ether **1a** (1.0 mmol), methoxyamine hydrochloride (1.1 mmol), and NaOAc (0.55 mmol) in 2-propanol (5 mL) was placed in a microwave-specific closed vial, and the solution was irradiated in a single-mode microwave oven (200 W, 100 °C) for 60 min. The reaction mixture was filtered through Celite by using dichloromethane as solvent. After removing the solvent under reduced pressure, the products were purified by flash column chromatography (silica gel; *n*-hexane/EtOAc, 90:10, 1% Et_3N) to yield **6a** (175.0 mg, 77%).[14]

Ethyl 6-Pentylnicotinate (6b): Yield: 119.34 mg (0.54 mmol, 54%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.86 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 1.22–1.33 (m, 4 H, 2×3′-H and 2×4′-H), 1.37 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 1.69–1.73 (m, 2 H, 2×2′-H), 2.82 (pseudo t, $^3J_{H,H}$ = 7.7 Hz, 2 H, 2×1′-H), 4.36 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, OCH_2Me), 7.20 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, 5-H), 8.16 (dd, $^3J_{H,H}$ = 8.0, 2.4 Hz, 1 H, 4-H), 9.10 (d, $^3J_{H,H}$ = 2.4 Hz, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 14.2, 22.4, 29.3, 31.5, 38.4, 61.1, 122.3, 123.8, 137.3, 150.3, 165.4, 167.0 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2933.2, 1715.8, 1600.8, 1377.7, 1289.9, 1121.9, 1030.7 cm^{-1}. MS (70 eV): *m/z* (%) = 221 (7.4) $[M]^+$, 192 (56), 178 (65), 165 (100), 150 (27), 137 (90), 92 (15), 65 (16). $C_{13}H_{19}NO_2$ (221.14): calcd. C 70.56, H 8.65, N 6.33; found C 70.19, H 8.61, N 5.92.

Ethyl 4-Butyl-6-phenylnicotinate (6d): Yield: 127.4 mg (0.45 mmol, 45%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.95 (t, $^3J_{H,H}$ = 7.4 Hz, 3 H, Me), 1.41 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 1.38–1.48 (m, 2 H, 2×3′-H), 1.59–1.67 (m, 2 H, 2×2′-H), 3.03 (pseudo t, $^3J_{H,H}$ = 8.0 Hz, 2 H, 2×1′-H), 4.40 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, OCH_2Me), 7.41–7.50 (m, 3 H, PhH), 7.58 (s, 1 H, 5-H), 8.01–8.03 (m, 2 H, PhH), 9.12 (s, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 14.2, 22.8, 33.1, 33.9, 61.0, 121.9, 124.1, 127.2, 128.8, 129.6, 138.5, 152.0, 154.4, 159.6, 166.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2964.3, 1713.2, 1596.9, 1371.6, 1282.4, 1102.4 cm^{-1}. MS (70 eV): *m/z* (%) = 283 (100) $[M]^+$, 241 (33), 28 (72), 226 (45), 208 (36), 194 (13), 167 (17), 153 (14), 115 (10), 77 (13). $C_{18}H_{21}NO_2$ (283.16): calcd. C 76.29, H 7.47, N 4.94; found C 76.24, H 7.42, N 5.00.

Ethyl 4-(4-Methoxyphenyl)-6-phenylnicotinate (6e): Yield: 259.7 mg (0.78 mmol, 78%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.15 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 3.84 (s, 3 H, OMe), 4.21 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, OCH_2Me), 6.95–6.99 (m, 2 H, *p*-$MeOC_6H_4$, 3-H and 5 H), 7.31–7.33 (m, 2 H, *p*-$MeOC_6H_4$, 2-H and 6 H), 7.41–7.50 (m, 3 H, PhH), 7.69 (d, $^3J_{H,H}$ = 0.8 Hz, 1 H, 5-H), 8.04–8.07 (m, 2 H, PhH), 9.08 (d, $^3J_{H,H}$ = 0.8 Hz, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.8, 55.2, 61.1, 113.7, 121.5, 124.7, 127.2, 128.7, 129.4, 129.6, 131.2, 138.2, 150.6, 151.0, 159.3, 159.9, 166.9 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2984.6, 2840.6, 1715.9, 1598.1, 1513.7, 1291.7, 1246.1, 1111.6 cm^{-1}. MS (70 eV): *m/z* (%) = 333 (100) $[M]^+$, 304 (29), 288 (75), 233 (15), 189 (13), 77 (4.2). $C_{21}H_{19}NO_3$ (333.14): calcd. C 75.66, H 5.74, N 4.20; found C 75.62, H 5.80, N 3.92.

Ethyl 4-(3,4-Dichlorophenyl)-6-phenylnicotinate (6f): Yield: 226.3 mg (0.61 mmol, 61%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.17 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 4.22 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, OCH_2Me), 7.19 (dd, $^3J_{H,H}$ = 8.2, 2.1 Hz, 1 H, 3,4-Cl_2Ph 5-H), 7.46–7.52 (m, 5 H, ArH), 7.64 (s, 1 H, 5-H), 8.04–8.06 (m, 2 H, PhH), 9.18 (s, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 61.4, 121.3, 123.9, 127.3, 127.5, 128.9, 130.0, 130.1, 130.2, 132.5, 132.7, 137.8, 139.1, 148.8, 151.6, 159.9, 165.9 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2986.7, 1717.2, 1591.7, 1466.4, 1290.3, 1120.1, 1038.2 cm^{-1}. MS (70 eV): *m/z* (%) = 371 (100) $[M]^+$, 342 (65), 326 (99), 273 (20), 236 (35), 200 (15), 160 (8.9), 77 (12). $C_{20}H_{15}Cl_2NO_2$ (371.05): calcd. C 64.53, H 4.06, N 3.76; found C 64.47, H 4.18, N 3.51.

Ethyl 4-(4-Chlorophenyl)-6-phenylnicotinate (6g): Yield: 202.2 mg (0.60 mmol, 60%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.14 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 4.20 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, OCH_2Me), 7.29–7.31 (m, 2 H, *p*-ClC_6H_4, 3-H and 5-H), 7.41–7.44 (m, 2 H, ArH), 7.45–7.50 (m, 3 H, ArH), 7.66 (d, $^3J_{H,H}$ = 0.8 Hz, 1 H, 5-H), 8.04–8.07 (m, 2 H, PhH), 9.15 (d, $^3J_{H,H}$ = 0.8 Hz, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.8, 61.3, 121.5, 124.3, 127.3, 128.4, 128.9, 129.4, 129.9, 134.6, 137.6, 138.0, 150.1, 151.4, 159.7, 166.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3021.2, 2084.1, 1715.6, 1641.2, 1473.0, 1285.0, 1218.7, 1115.3 cm^{-1}. MS (70 eV): *m/z* (%) = 337 (100) $[M]^+$, 308 (57), 292 (94), 237 (31), 202 (39), 126 (9.1), 77 (11). HRMS: calcd. for $C_{20}H_{16}ClNO_2$ $[M]^+$ 337.0870; found 337.0859.

Ethyl 6-Phenyl-4-*p*-tolylnicotinate (6h): Yield: 193.4 mg (0.61 mmol, 61%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.99 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 2.28 (s, 3 H, Me), 4.06 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, OCH_2Me), 7.10–7.15 (m, 4 H, tolyl), 7.29–7.36 (m, 3 H, PhH), 7.56 (s, 1 H, 5-H), 7.90–7.93 (m, 2 H, PhH), 8.97 (s, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.8, 21.2, 61.2, 121.7, 124.9, 127.3, 128.0, 128.8, 129.0, 129.8, 136.1, 138.2, 138.4, 150.9, 151.2, 159.3, 166.8 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2985.8, 1716.2, 1593.6, 1472.5, 1292.6, 1222.5, 1113.0 cm^{-1}. MS (70 eV): *m/z* (%) = 317 (90) $[M]^+$, 272 (100), 244 (15), 217 (16), 202 (18), 115 (10), 59 (17). $C_{21}H_{19}NO_2$ (317.14): calcd. C 79.47, H 6.03, N 4.41; found C 79.39, H 6.06, N 4.34.

Ethyl 4,6-Diphenylnicotinate (6i): Yield: 203.0 mg (0.67 mmol, 67%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.07 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 4.17 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, OCH_2Me), 7.36–7.51 (m, 8 H, PhH), 7.71 (d, $^3J_{H,H}$ = 0.5 Hz, 1 H, 5-H), 8.05–8.07 (m, 2 H, PhH), 9.13 (d, $^3J_{H,H}$ = 0.5 Hz, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.7, 61.2, 121.7, 124.8, 127.3, 128.1, 128.2, 128.3, 128.9, 129.8, 138.3, 139.2, 151.13, 151.16, 159.5, 166.8 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2987.6, 1716.1, 1590.7, 1296.3, 1221.3, 1115.8 cm^{-1}. MS (70 eV): *m/z* (%) = 303 (90) $[M]^+$, 274 (58), 258 (100), 230 (18), 202 (41), 77 (15). HRMS: calcd. for $C_{20}H_{17}NO_2$ $[M]^+$ 303.1260; found 303.1259.

Ethyl 6-*tert*-Butyl-4-phenylnicotinate (6j): Yield: 36.8 mg (0.13 mmol, 13%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.04 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 1.40 (s, 9 H, *t*Bu), 4.13 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, OCH_2Me), 7.30–7.33 (m, 3 H, PhH), 7.41–7.44 (m, 3 H, PhH and 5-H), 9.00 (s, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.7, 30.0, 37.8, 61.1, 120.6, 123.9, 128.1, 128.2, 128.3, 131.9, 139.4, 149.7, 149.8, 166.8 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2970.4, 1717.2, 1592.4, 1370.2, 1294.3, 1142.1 cm^{-1}. MS (70 eV): *m/z* (%) = 283 (69) $[M]^+$, 268 (100), 254 (17), 241 (62), 238 (18), 227 (13), 194 (14), 154 (12), 127 (12), 86 (15), 84 (21), 57 (23). HRMS: calcd. for $C_{18}H_{21}NO_2$ $[M]^+$ 283.1572; found 283.1570.

Ethyl 6-(4-Chlorophenyl)-4-phenylnicotinate (6k): Yield: 208.9 mg (0.62 mmol, 62%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.06 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 4.16 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, OCH_2Me), 7.34–7.37 (m, 2 H, PhH), 7.36–7.46 (m, 5 H, ArH), 7.67 (s, 1 H, 5-H), 8.00–8.02 (m, 2 H, *p*-ClC_6H_4, 2-H and 6-H), 9.10 (s, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.7, 61.3, 121.4, 125.1, 128.0, 128.3, 128.5, 128.6, 129.1, 136.1, 136.6, 139.0, 151.1, 151.3, 158.2, 166.6 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2979.8, 1717.8, 1592.9, 1469.7,

1296.5, 1220.6, 1100.1 cm^{-1}. MS (70 eV): *m/z* (%) = 337 (100) [M]$^+$, 292 (99), 265 (25), 237 (28), 202 (41), 127 (10), 105 (13), 77 (17). $C_{20}H_{16}ClNO_2$ (337.09): calcd. C 71.11, H 4.77, N 4.15; found C 71.00, H 5.09, N 4.11.

Ethyl 6-(4-Methoxyphenyl)-4-phenylnicotinate (6l): Yield: 239.8 mg (0.72 mmol, 72%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.06 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 3.87 (s, 3 H, OMe), 4.15 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, OCH_2Me), 6.98–7.02 (m, 2 H, *p*-$MeOC_6H_4$, 3-H and 5-H), 7.35–7.37 (m, 2 H, PhH), 7.43–7.45 (m, 3 H, PhH), 7.64 (s, 1 H, 5-H), 8.02–8.06 (m, 2 H, *p*-$MeOC_6H_4$, 2-H and 6-H), 9.09 (s, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.7, 55.4, 61.1, 114.3, 120.9, 124.0, 128.0, 128.2, 128.3, 128.5, 128.8, 139.4, 151.0 (2 signals), 159.0, 161.3, 166.7 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2978.9, 2841.7, 1714.0, 1590.9, 1470.1, 1369.3, 1228.7, 1176.6, 1113.8 cm^{-1}. MS (70 eV): *m/z* (%) = 333 (100) [M]$^+$, 304 (16), 288 (43), 233 (15), 189 (11). $C_{21}H_{19}NO_3$ (333.14): calcd. C 75.66, H 5.74, N 4.20; found C 75.82, H 5.93, N 3.86.

Ethyl 6-(Furan-2-yl)-4-phenylnicotinate (6m): Yield: 175.8 mg (0.60 mmol, 60%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.04 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 4.14 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, OCH_2Me), 6.55 (dd, $^3J_{H,H}$ = 3.5, 1.9 Hz, 1 H, furan 4-H), 7.19 (dd, $^3J_{H,H}$ = 3.5, 0.8 Hz, 1 H, furan 3-H), 7.33–7.35 (m, 2 H, PhH), 7.40–7.44 (m, 3 H, Ph and furan 5-H), 7.54 (dd, $^3J_{H,H}$ = 1.9, 0.8 Hz, 1 H, 5-H), 7.65 (d, $^3J_{H,H}$ = 0.8 Hz, 1 H, 2-H), 9.02 (s, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.6, 61.1, 110.9, 112.4, 119.5, 124.3, 128.0, 128.2, 128.3, 139.0, 144.3, 151.0, 151.2, 151.3, 152.8, 166.5 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2979.0, 1713.7, 1602.6, 1493.1, 1372.1, 1290.1, 1224.6, 1162.8, 1113.3, 1044.7 cm^{-1}. MS (70 eV): *m/z* (%) = 293 (96) [M]$^+$, 248 (100), 193 (15), 165 (36), 139 (10), 77 (5.0). $C_{18}H_{13}NO_3$ (293.11): calcd. C 73.71, H 5.15, N 4.78; found C 73.86, H 5.33, N 4.35.

Ethyl 4-(Trimethylsilyl)-6-phenylnicotinate (6n): Yield: 104.7 mg (0.35 mmol, 35%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.39 (s, 9 H, $SiMe_3$), 1.42 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 4.42 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, OCH_2Me), 7.43–7.52 (m, 3 H, PhH), 7.98 (d, $^3J_{H,H}$ = 0.8 Hz, 1 H, 5-H), 8.02–8.04 (m, 2 H, PhH), 9.24 (d, $^3J_{H,H}$ = 0.8 Hz, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = –0.37, 14.3, 61.3, 126.4, 127.4, 128.9, 129.5, 129.7, 138.7, 150.5, 153.3, 158.8, 167.0 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2984.9, 1714.9, 1513.9, 1286.1, 1137.7 cm^{-1}. MS (70 eV): *m/z* (%) = 284 (18) [M$^+$ – CH_3], 256 (61), 203 (19), 187 (27), 159 (33), 128 (17), 115 (13), 99 (28), 77 (18), 73 (100), 59 (11). HRMS: calcd. for $C_{17}H_{21}NO_2Si$ [M – 15]$^+$ 284.1107; found 284.1111.

Acknowledgments

This research was supported by the Spanish Ministerio de Ciencia e Innovación (MICINN), the European Regional Development Fund (CTQ2008-06806-C02-02), the Spanish Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III (MSC ISCIII) (RETICS RD06/0020/1046), the Fundación Canaria de Investigación y Salud (FUNCIS) (REDESFAC PI01/06) and the Fundación Instituto Canario de Investigación del Cancer (FICI-G.I.N808/2007). G. M.-A. thanks the Spanish Ministerio de Educación y Ciencia (MEC) for a Beca del Programa de Formación del Profesorado Universitario (FPU) grant. The authors thank technician Ms. Anna Jurado Varona for her assistance with the experiments.

[1] For selected reviews, see: a) H. Vosper, *Br. J. Pharmacol.* **2009**, *158*, 429–441; b) J. A. Farmer, *Curr. Atheroscler. Rep.* **2009**, *11*, 87–92; c) E. T. Bodor, S. Offermanns, *Br. J. Pharmacol.* **2008**, *153*, S68–S75; d) R. Raja, J. M. Thomas, M. Greenhill-Hooper, S. V. Ley, A. A. F. Paz, *Chem. Eur. J.* **2008**, *14*, 2340–2348; e) V. M. Kopelevich, V. I. Gunar, *Pharm. Chem. J.* **1999**, *33*, 177–187.

[2] For selected reviews, see: a) P. A. Keller, "Pyridines and their Benzo Derivatives: Synthesis" in *Comprehensive Heterocyclic Chemistry III* (Eds.: A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor), Elsevier Science, Ltd., Oxford, **2008**, vol. 7, pp. 217–308; b) J. A. Varela, C. Saa, *Synlett* **2008**, 2571–2578; c) M. C. Bagley, C. Glover, E. A. Merritt, *Synlett* **2007**, 2459–2482; d) B. Heller, M. Hapke, *Chem. Soc. Rev.* **2007**, *36*, 1085–1094; e) G. D. Henry, *Tetrahedron* **2004**, *60*, 6043–6061; f) J. A. Varela, C. Saa, *Chem. Rev.* **2003**, *103*, 3787–3801; g) T. L. Gilchrist, *J. Chem. Soc. Perkin Trans. 1* **2001**, 2491–2515.

[3] F. Bohlmann, D. Rahtz, *Chem. Ber.* **1957**, *90*, 2265–2272.

[4] For selected examples, see: a) A.-L. Blayo, S. L. Meur, D. Grée, R. Grée, *Adv. Synth. Catal.* **2008**, *350*, 471–476; b) M. C. Bagley, J. W. Dale, M. Ohnesorge, X. Xiong, J. Bower, *J. Comb. Chem.* **2003**, *5*, 41–44.

[5] M. C. Bagley, J. W. Dale, J. Bower, *Chem. Commun.* **2002**, 1682–1683.

[6] a) C. Allais, T. Constantieux, J. Rodriguez, *Chem. Eur. J.* **2009**, *15*, 12945–12948;b) F. Liéby-Muller, C. Allais, T. Constantieux, J. Rodriguez, *Chem. Commun.* **2008**, 4207–4209.

[7] For selected recent examples of controlled ring substitution of simple nicotinic acid derivatives, see: a) M. Wasa, B. T. Worrell, J.-Q. Yu, *Angew. Chem.* **2010**, *122*, 1297–1299; *Angew. Chem. Int. Ed.* **2010**, *49*, 1275–1277; b) N. Robert, A.-L. Bonneau, C. Hoarau, F. Marsais, *Org. Lett.* **2006**, *8*, 6071–6074; for an excellent review on this topic, see: c) M. Schlosser, F. Mongin, *Chem. Soc. Rev.* **2007**, *36*, 1161–1172.

[8] For a review, see: T. E. Nielsen, S. L. Schreiber, *Angew. Chem.* **2008**, *120*, 52–61; *Angew. Chem. Int. Ed.* **2008**, *47*, 48–56.

[9] D. Tejedor, G. Méndez-Abt, F. García-Tellado, *Chem. Eur. J.* **2010**, *16*, 428–431.

[10] For a mechanistic discussion of this process, see ref.[9] and references cited therein.

[11] Arylated derivatives of nicotinic acids are widely used as building blocks for pharmaceuticals, see: a) Y. S. Babu, R. S. Rowland, P. Chand, P. L. Kotian, Y. El-Kattan, S. Niwas, U. S. Patent No. 6699994, **2004**; b) K. H. Donaldson, B. G. Shearer, D. E. Uehling, WO Patent No. 01/42217, **2001**; c) R. C. Bernotas, R. R. Singhaus, J. W. Ullrich, D. H. Kaufman, R. L. Morris, J. E. Wrobel, B. Hu, J. W. Jetter, M. D. Collini, J. M. Travins, R. L. Magolda, WO Patent No. **2008**/049047, **2008**.

[12] a) Propargylic alcohols were either commercially available or prepared from the corresponding aldehydes and lithiated acetylenes according to a standard procedure, see: T. E. Nielsen, D. Tanner, *J. Org. Chem.* **2002**, *67*, 6366–6371; b) propargyl vinyl ethers **1** were assembled from alkyl propiolates and the corresponding propargylic alcohols according to published protocols, see: D. Tejedor, A. Santos-Expósito, G. Méndez-Abt, C. Ruiz-Pérez, F. García-Tellado, *Synlett* **2009**, 1223–1226 and references cited therein.

[13] Microwave reactions were conducted in microwave-specific closed vials (capacity 10 mL) by using a CEM Discover microwave reactor.

[14] P. Molina, A. Pastor, M. J. Vilaplana, *J. Org. Chem.* **1996**, *61*, 8094–8098.

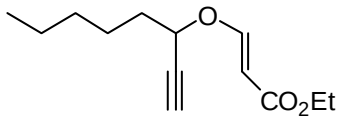
[15] F. Palacios, E. Herran, G. Rubiales, C. Alonso, *Tetrahedron* **2007**, *63*, 5669–5676.

Received: July 27, 2010
Published Online: October 22, 2010

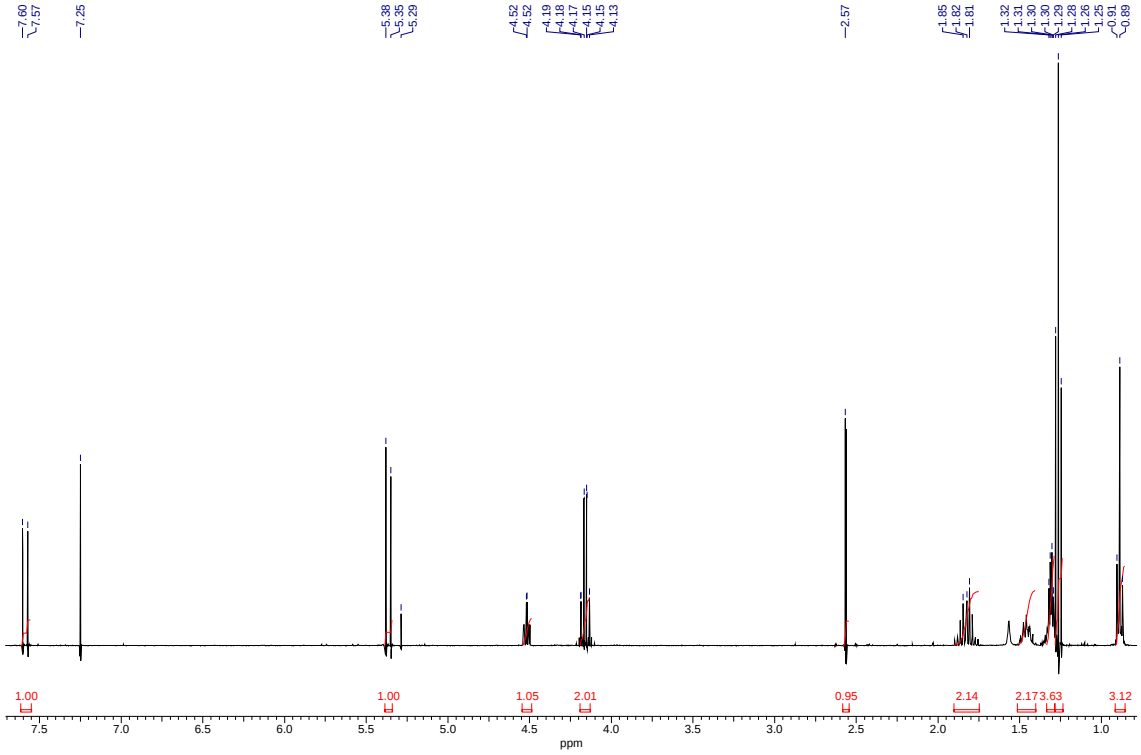
Supporting Information

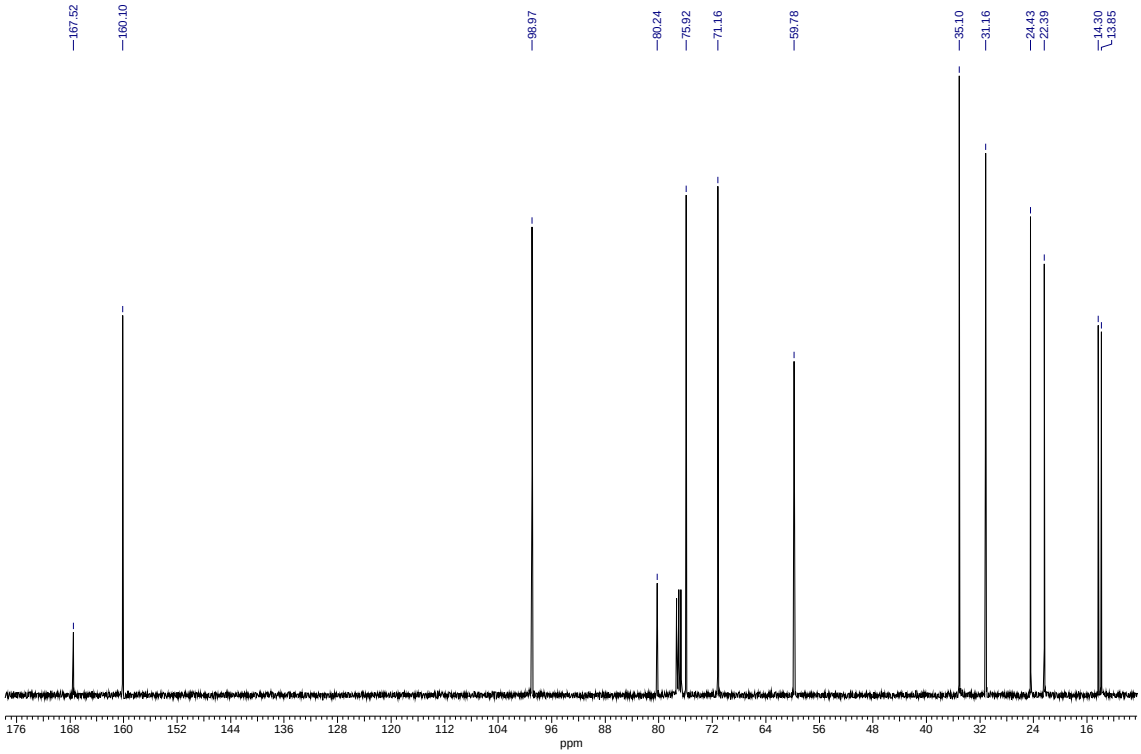
Microwave-assisted Diversity-oriented Domino Synthesis of Functionalized Nicotinic Acid Derivatives

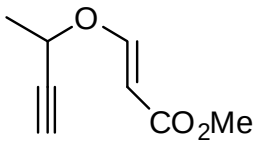
David Tejedor*, Gabriela Méndez-Abt and Fernando García-Tellado*
Instituto de Productos Naturales y Agrobiología, Consejo Superior de Investigaciones Científicas, Astrofísico Francisco Sánchez 3, E-38206 La Laguna, Tenerife, Spain, Instituto Canario de Investigación del Cáncer, Canary Islands, Spain.


O
CO2Et

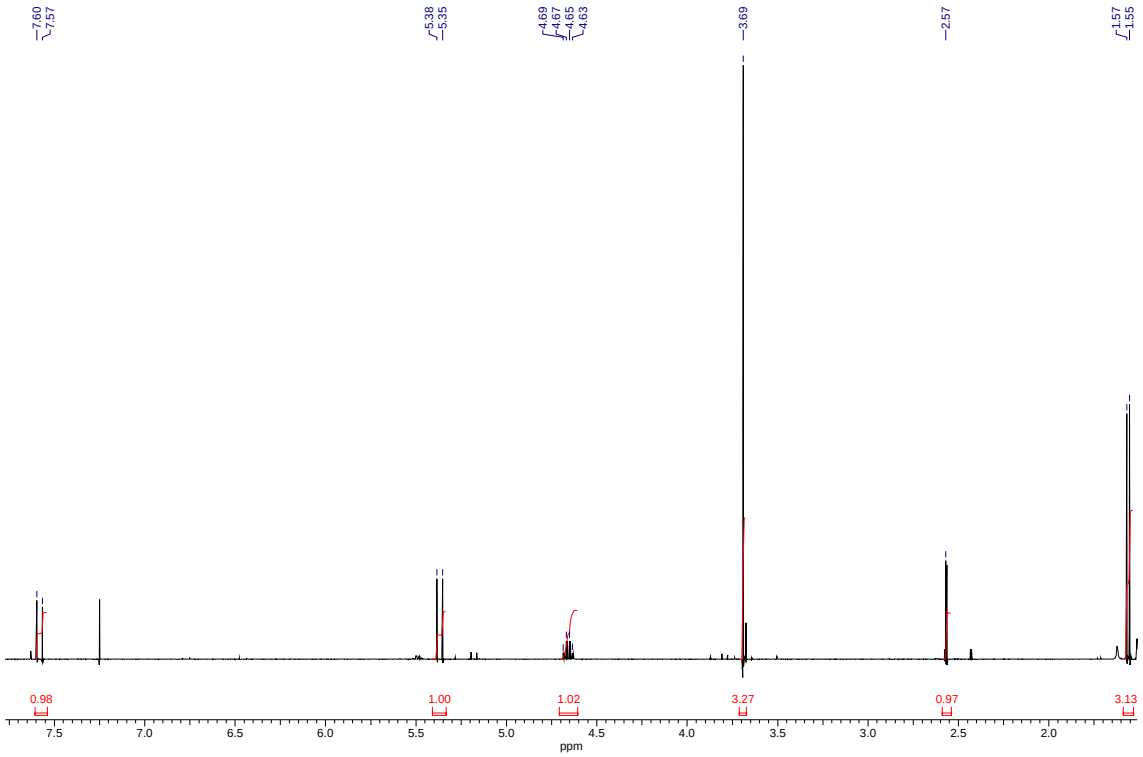
1b

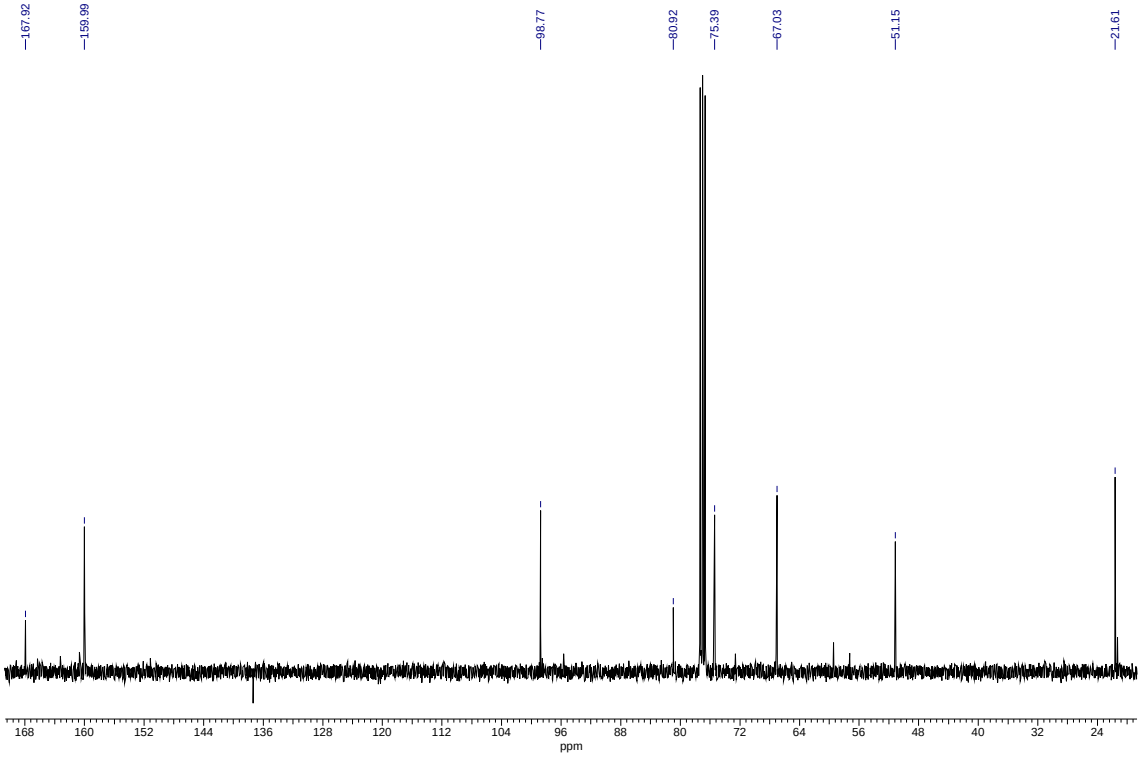

7.60
7.57
7.25
5.38
5.35
5.29
4.52
4.52
4.19
4.18
4.17
4.15
4.15
4.13
2.57
1.85
1.82
1.81
1.32
1.31
1.30
1.30
1.29
1.28
1.26
1.25
0.91
0.89
1.00
1.00
1.05
2.01
0.95
2.14
2.17
3.63
3.12
ppm

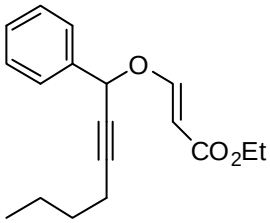

167.52
160.10
98.97
80.24
75.92
71.16
59.78
35.10
31.16
24.43
22.39
14.30
13.85
ppm


O
CO2Me

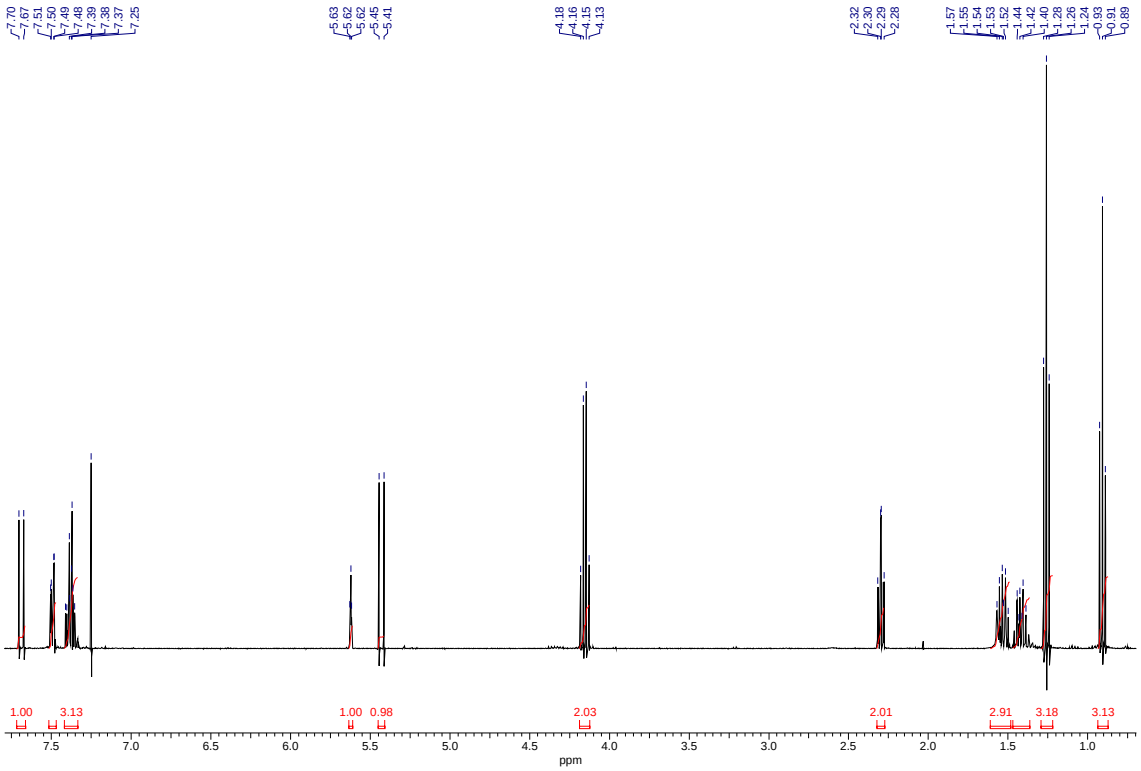
1c

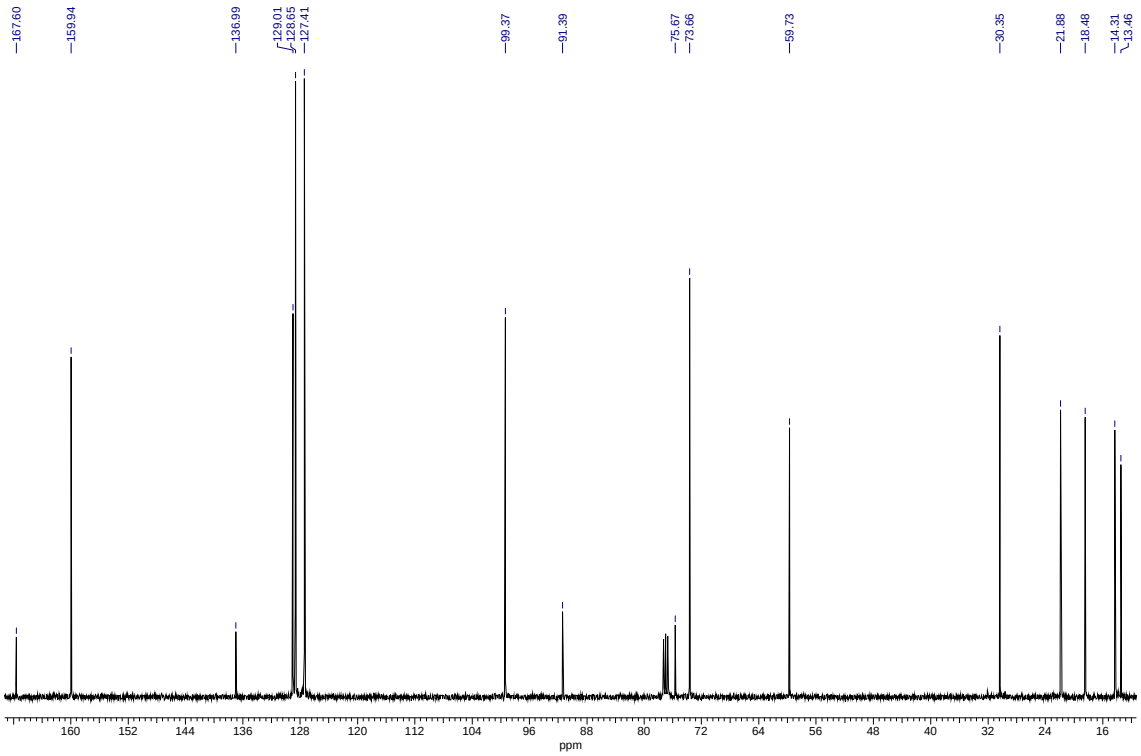

7.60
7.57
5.38
5.35
4.69
4.67
4.65
4.63
3.69
2.57
1.57
1.55
0.98
1.00
1.02
3.27
0.97
3.13
ppm

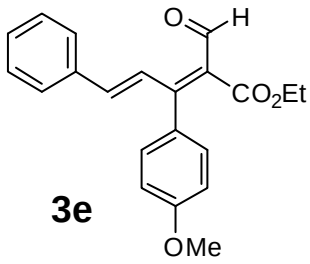

167.92
159.99
98.77
80.92
75.39
67.03
51.15
21.61
ppm


O
CO2Et

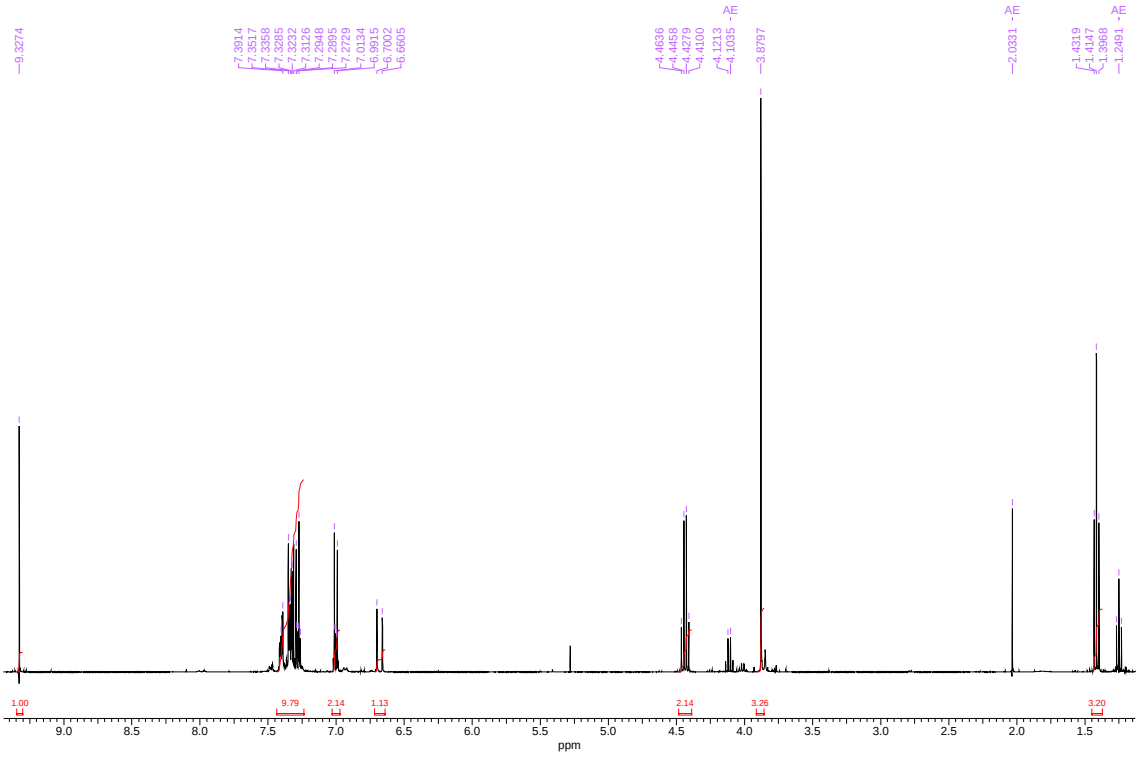
1d

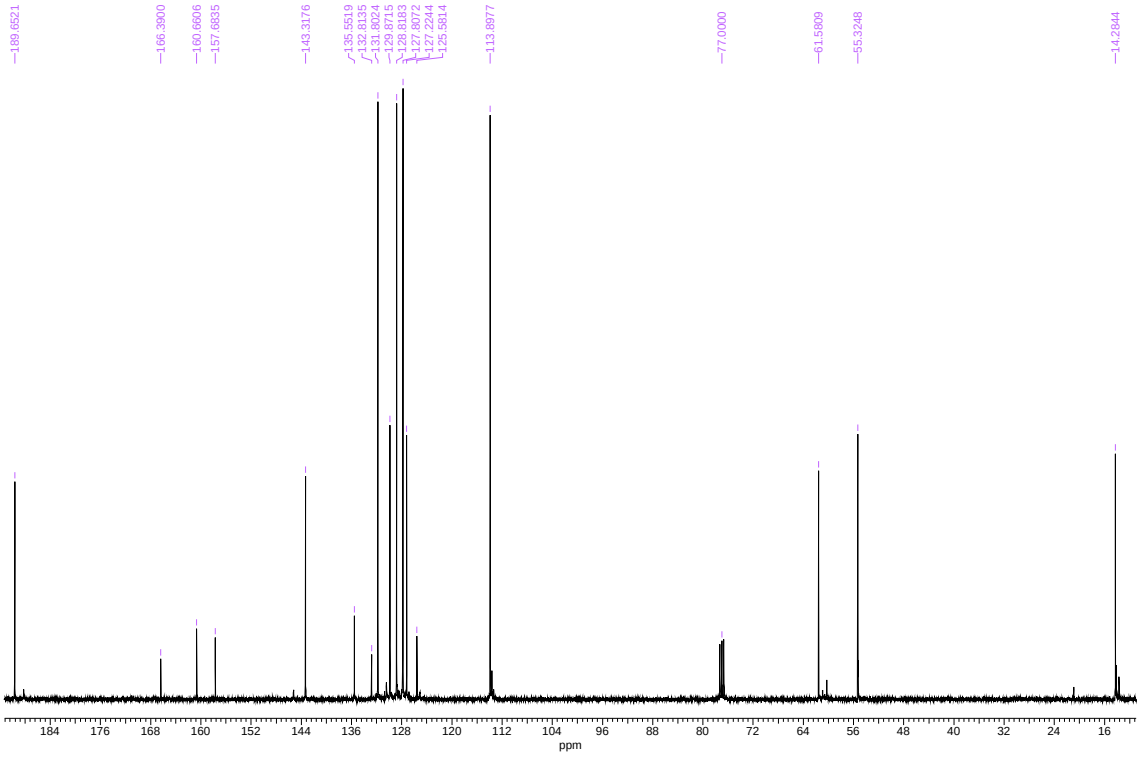

7.70
7.67
7.51
7.50
7.49
7.48
7.39
7.38
7.37
7.25
5.63
5.62
5.62
5.45
5.41
4.18
4.16
4.15
4.13
2.32
2.30
2.29
2.28
1.57
1.55
1.54
1.53
1.52
1.44
1.42
1.40
1.28
1.26
1.24
0.93
0.91
0.89
1.00
3.13
1.00
0.98
2.03
2.01
2.91
3.18
3.13
ppm

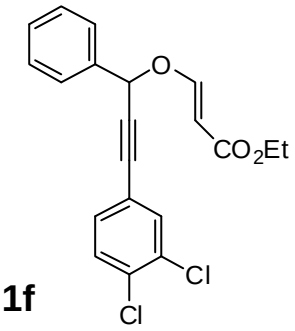

167.60
159.94
136.99
129.01
128.65
127.41
99.37
91.39
75.67
73.66
59.73
30.35
21.88
18.48
14.31
13.46
ppm


O
H
CO2Et
OMe

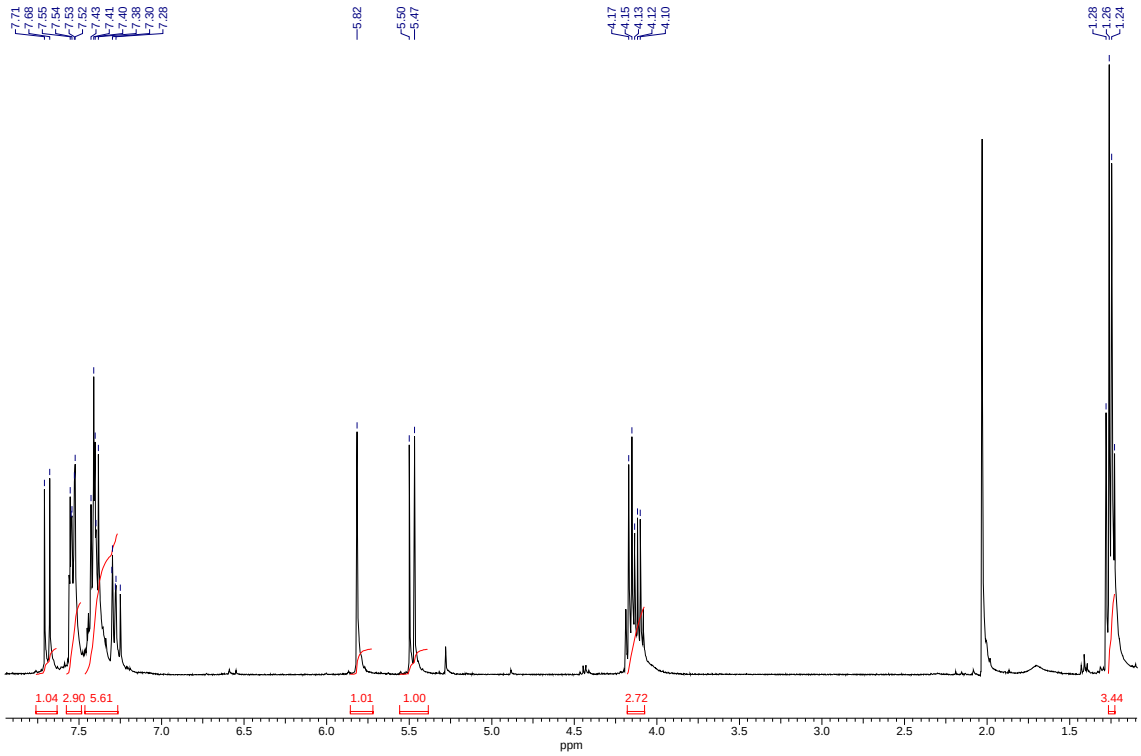
3e

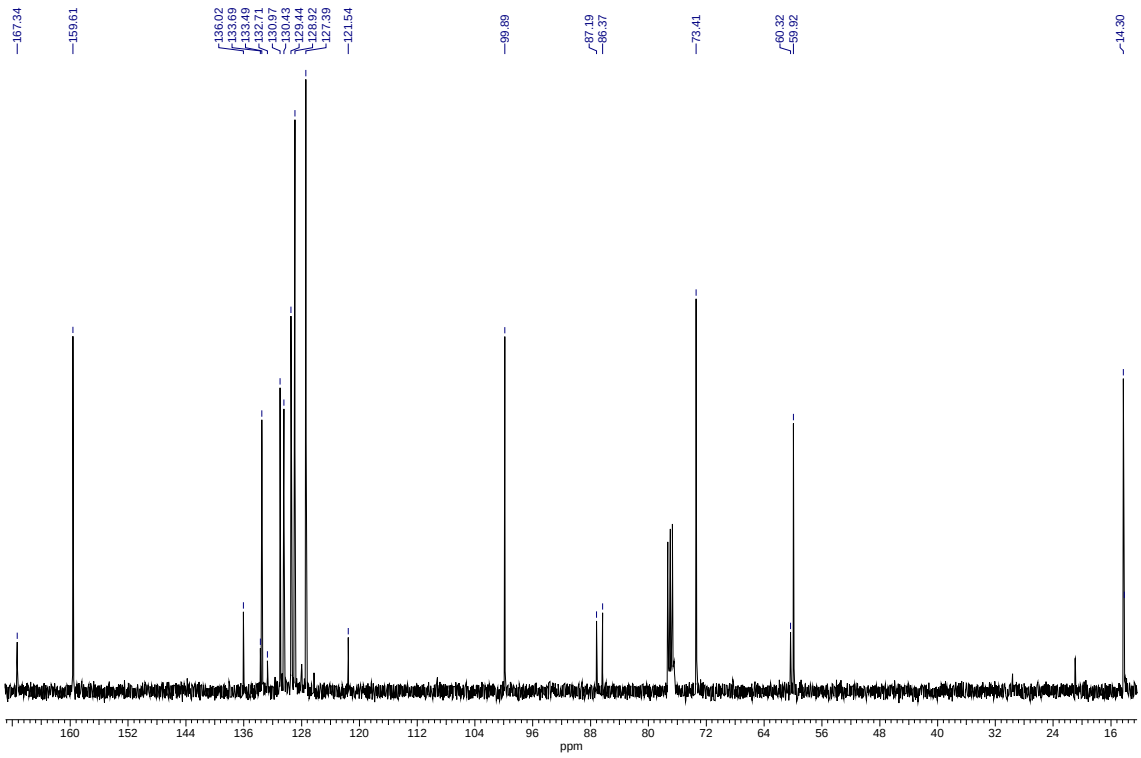

9.3274
7.3914
7.3517
7.3368
7.3285
7.3232
7.3126
7.2948
7.2895
7.2729
7.0134
6.9915
6.7002
6.6605
4.4636
4.4458
4.4279
4.4100
4.1213
4.1035
3.8797
2.0331
1.4319
1.4147
1.3968
1.2491
1.00
9.79
2.14
1.13
2.14
3.26
3.20
ppm

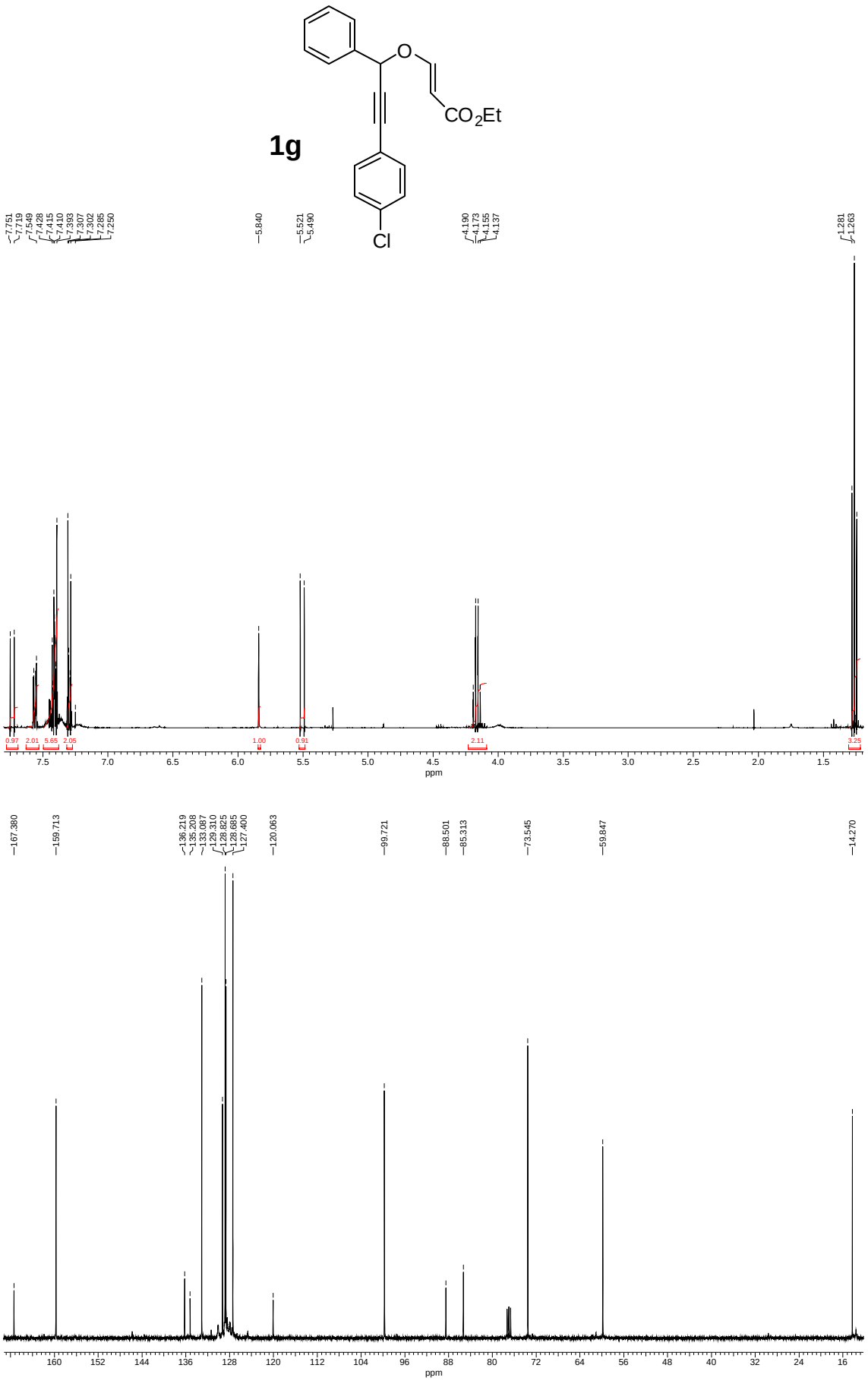

189.6521
166.3900
160.6606
157.6835
143.3176
135.5519
132.8135
131.8024
129.8715
128.8183
127.8072
127.2244
125.5814
113.8977
77.0000
61.5809
55.3248
14.2844
ppm

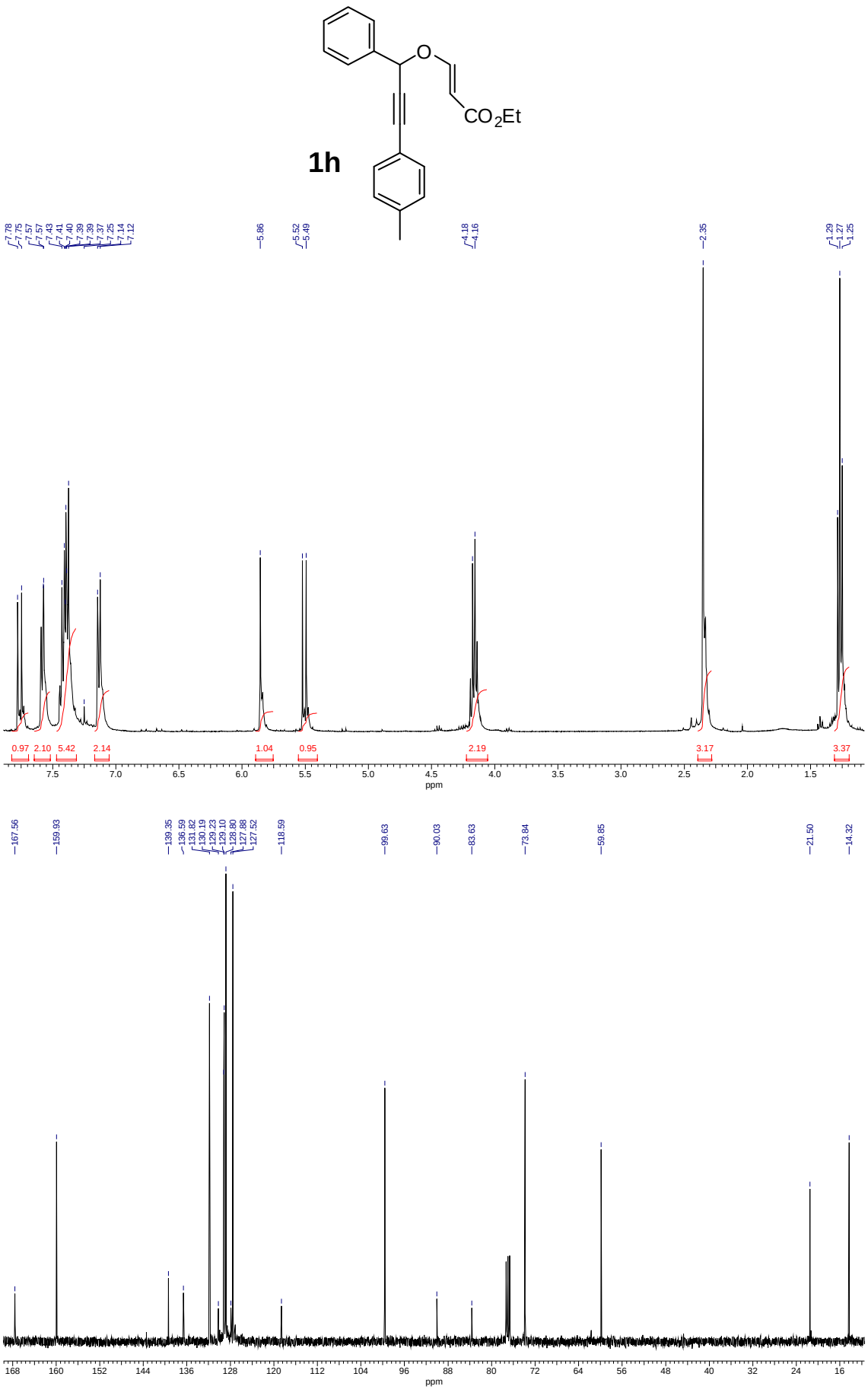

O
CO2Et
Cl
Cl

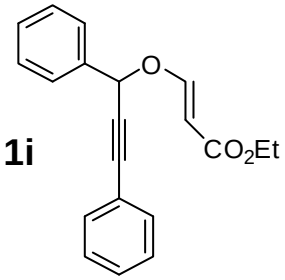
1f

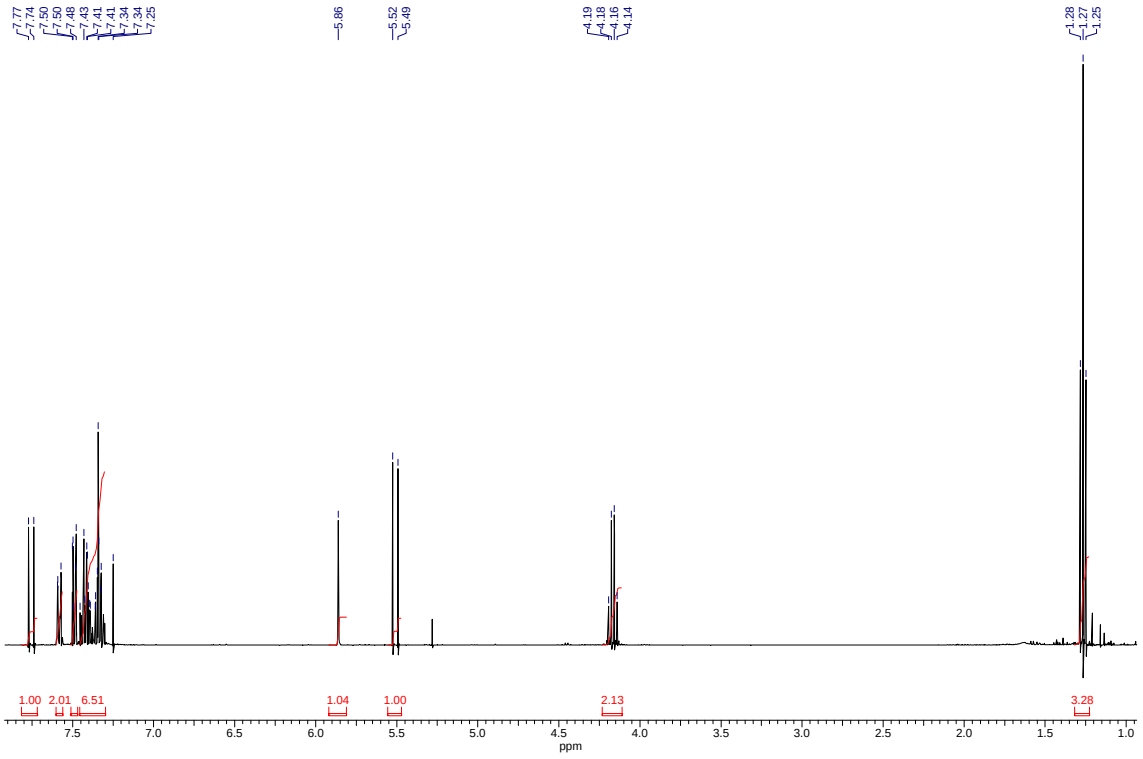

7.71
7.68
7.55
7.54
7.53
7.52
7.43
7.41
7.40
7.38
7.30
7.28
5.82
5.50
5.47
4.17
4.15
4.13
4.12
4.10
1.28
1.26
1.24
1.04
2.90
5.61
1.01
1.00
2.72
3.44
ppm

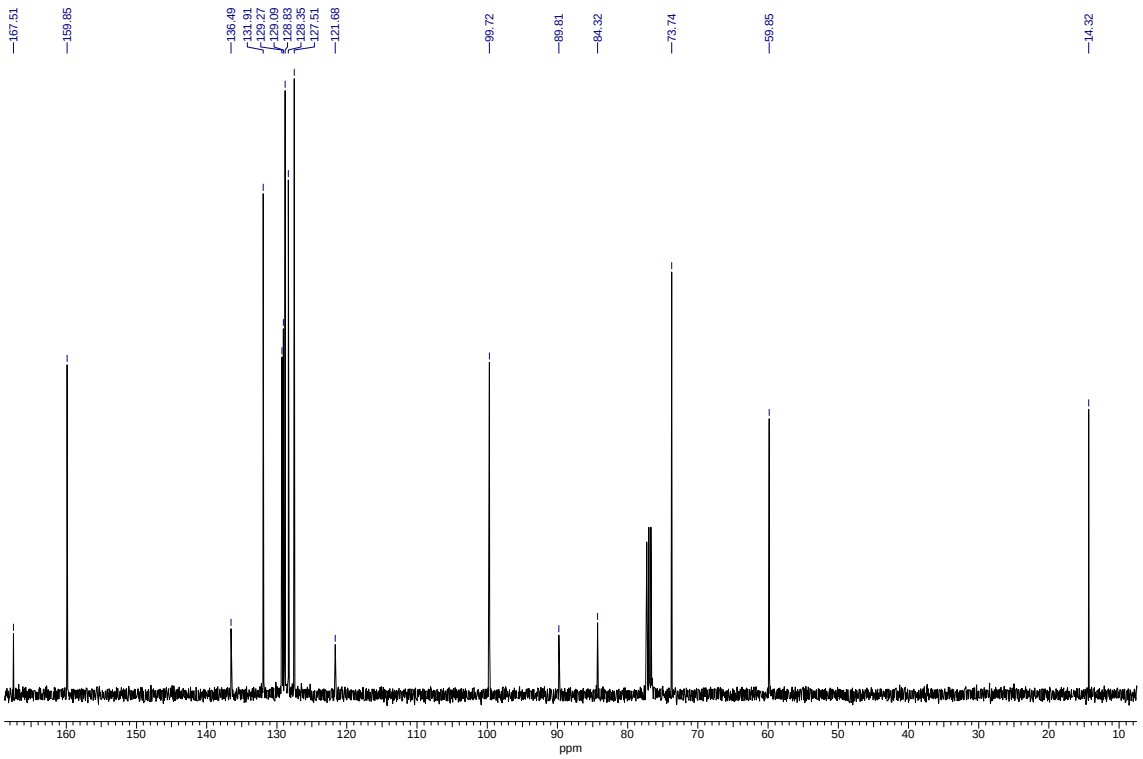

167.34
159.61
136.02
133.69
133.49
132.71
130.97
130.43
129.44
128.92
127.39
121.54
99.89
87.19
86.37
73.41
60.32
59.92
14.30
ppm

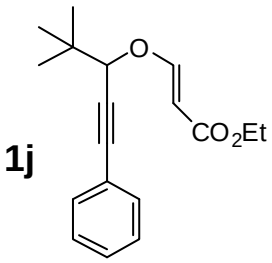

1g
O
CO2Et
Cl
7.751
7.719
7.549
7.428
7.415
7.410
7.393
7.307
7.302
7.285
7.250
5.840
5.521
5.490
4.190
4.173
4.155
4.137
1.281
1.263
0.97
2.01
5.65
2.05
1.00
0.91
2.11
3.25
ppm
167.380
159.713
136.219
135.208
133.087
129.310
128.825
128.685
127.400
120.063
99.721
88.501
85.313
73.545
59.847
14.270
ppm


O
CO2Et
1h
7.78
7.75
7.57
7.57
7.43
7.41
7.40
7.39
7.39
7.37
7.25
7.14
7.12
5.86
5.52
5.49
4.18
4.16
2.35
1.29
1.27
1.25
0.97
2.10
5.42
2.14
1.04
0.95
2.19
3.17
3.37
ppm
167.56
159.93
139.35
136.59
131.82
130.19
129.23
129.10
128.80
127.88
127.52
118.59
99.63
90.03
83.63
73.84
59.85
21.50
14.32
ppm

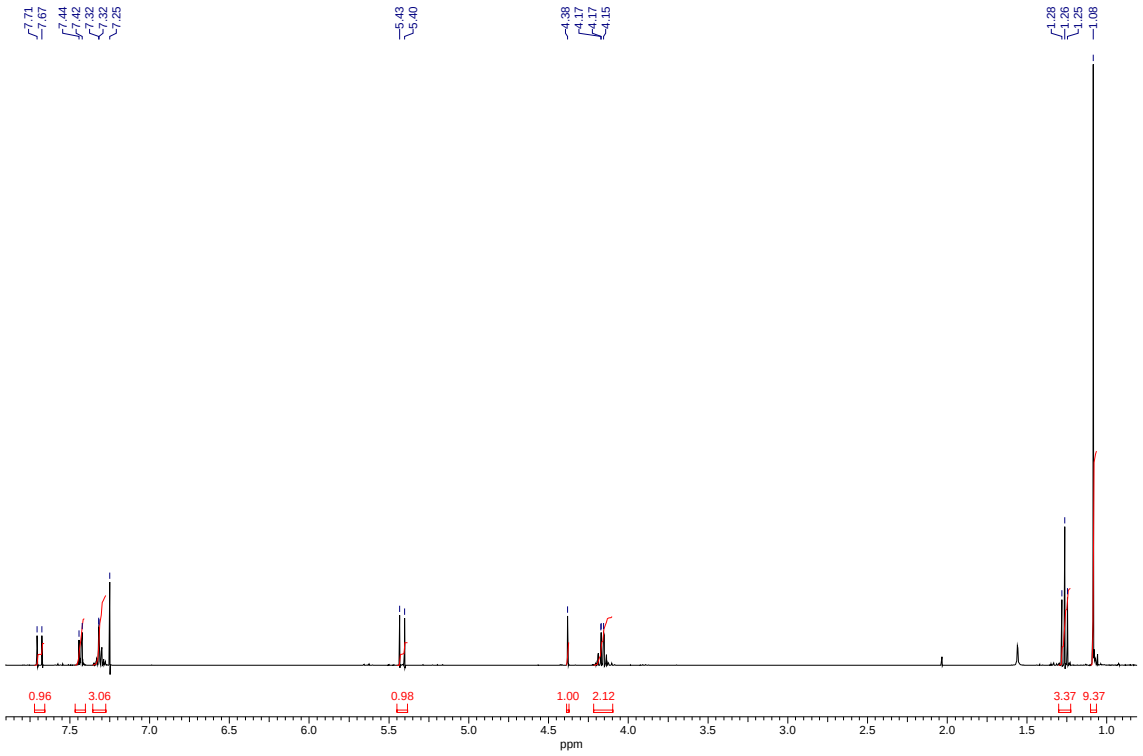

1i
O
CO2Et

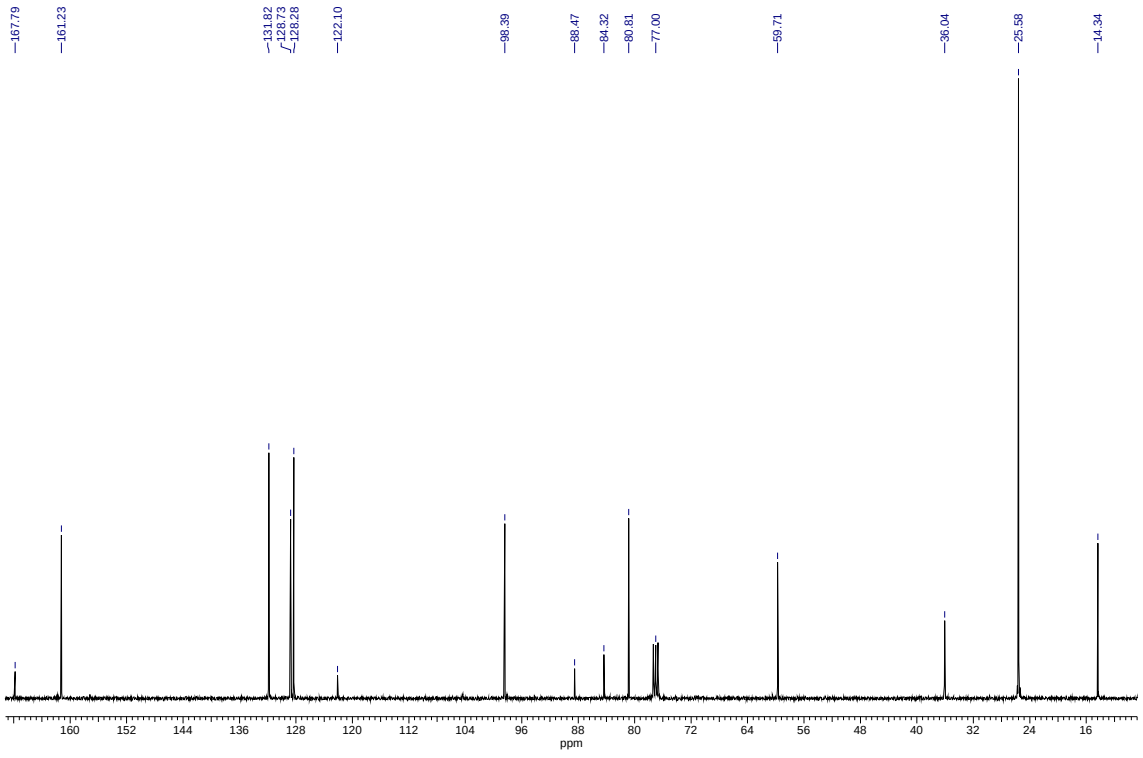

7.77
7.74
7.50
7.50
7.48
7.43
7.41
7.41
7.34
7.34
7.25
5.86
5.52
5.49
4.19
4.18
4.16
4.14
1.28
1.27
1.25
1.00
2.01
6.51
1.04
1.00
2.13
3.28
ppm

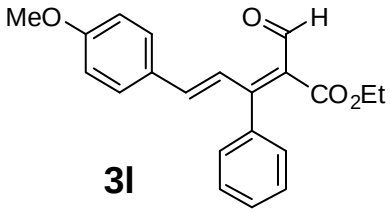

167.51
159.85
136.49
131.91
129.27
129.09
128.83
128.35
127.51
121.68
99.72
89.81
84.32
73.74
59.85
14.32
ppm


O
CO2Et

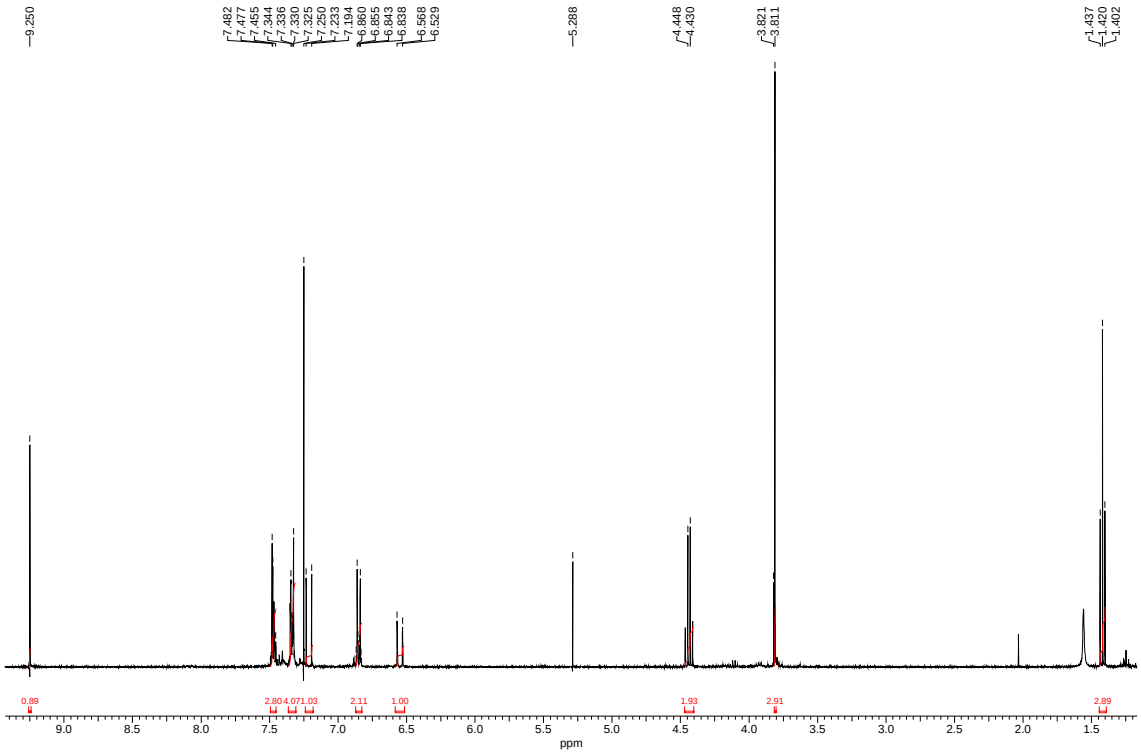
1j

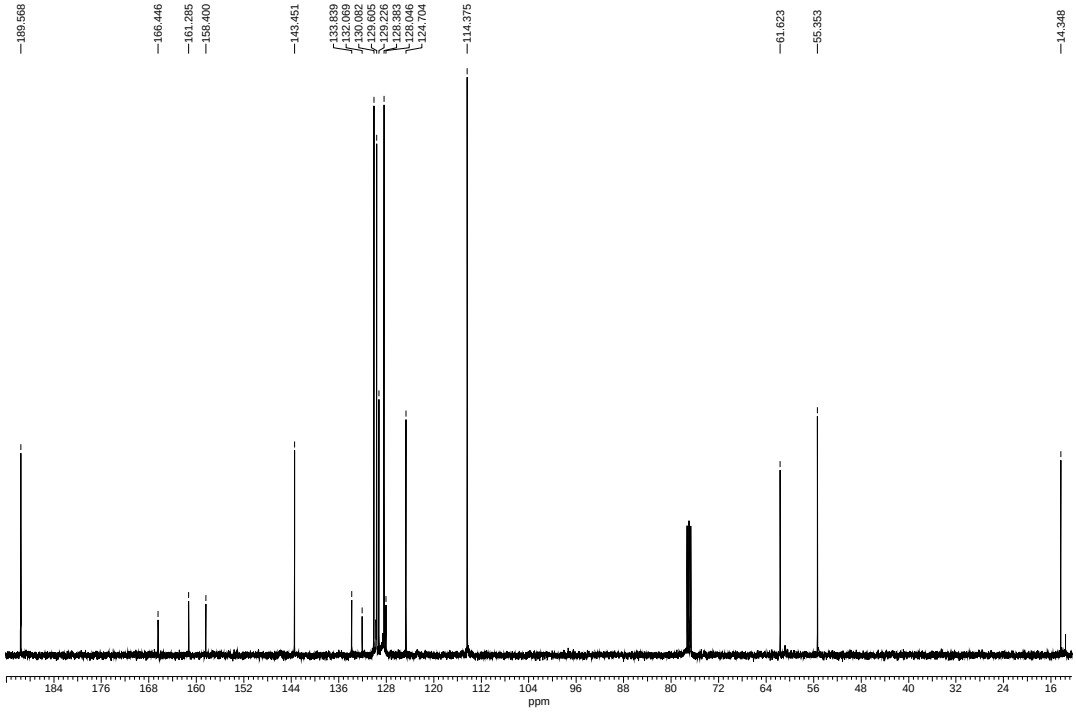

7.71
7.67
7.44
7.42
7.32
7.32
7.25
5.43
5.40
4.38
4.17
4.17
4.15
1.28
1.26
1.25
1.08
0.96
3.06
0.98
1.00
2.12
3.37
9.37
ppm

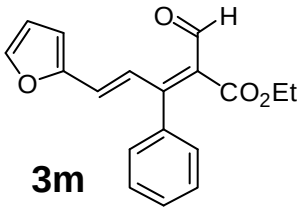

167.79
161.23
131.82
128.73
128.28
122.10
98.39
88.47
84.32
80.81
77.00
59.71
36.04
25.58
14.34
ppm


MeO
O
H
CO2Et

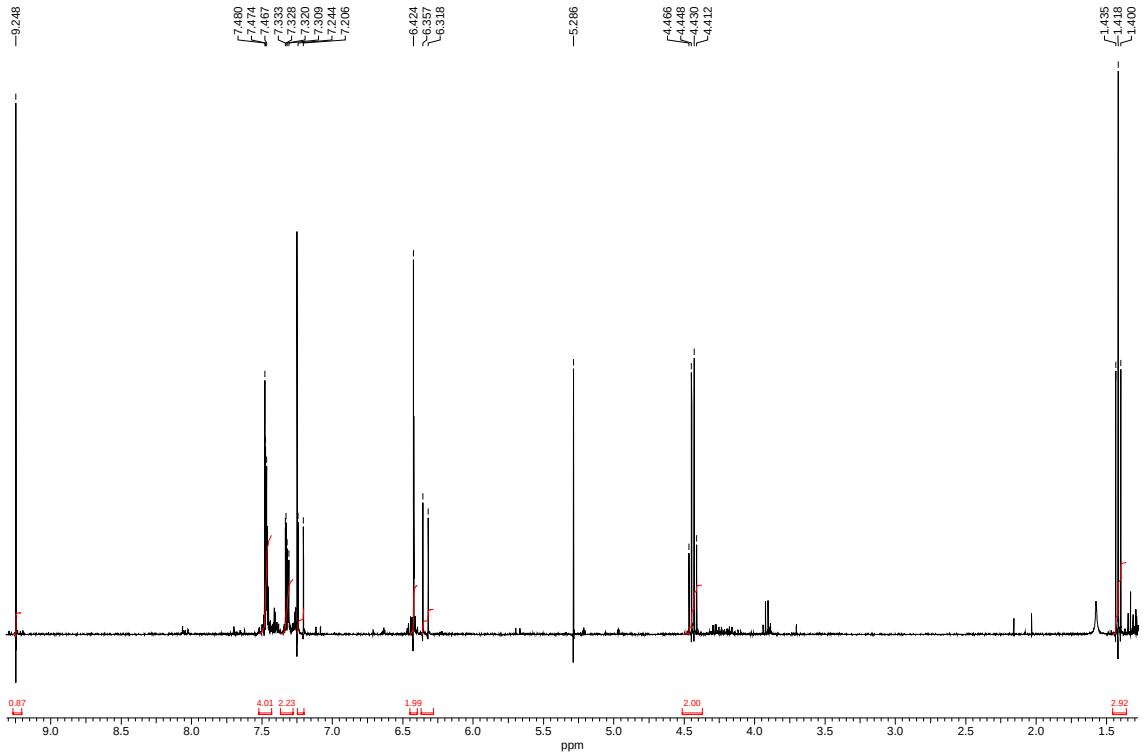
3l

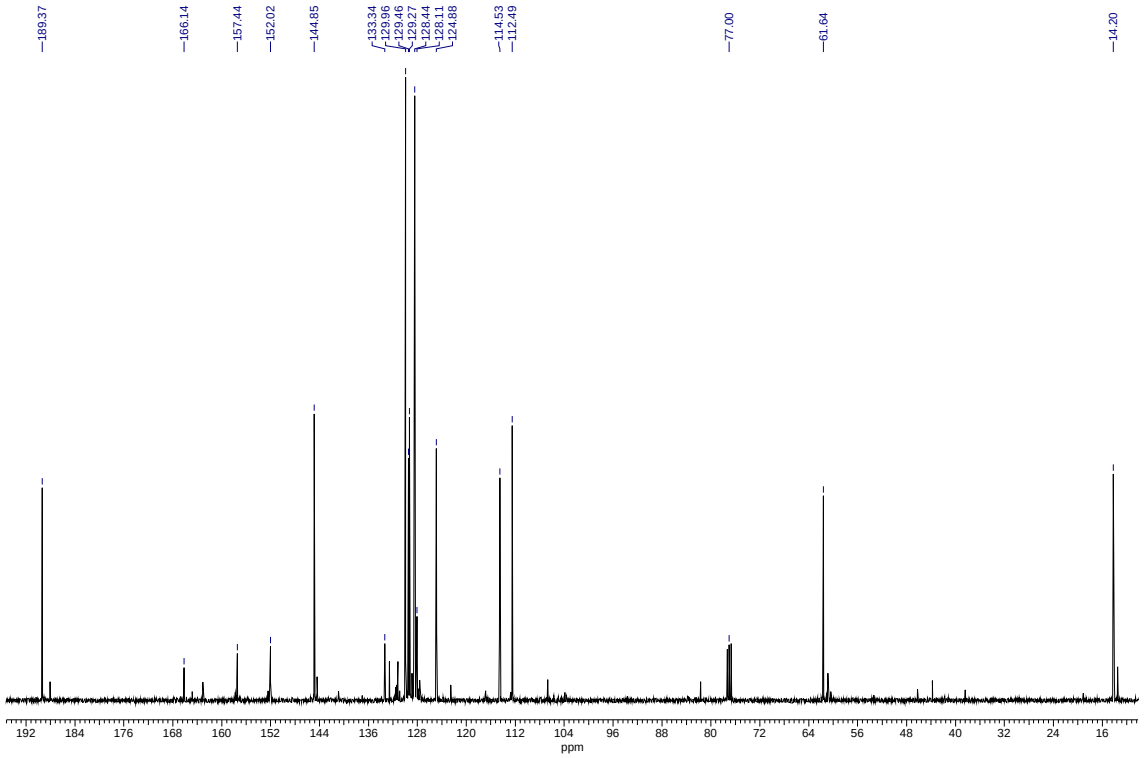

9.250
7.482
7.477
7.455
7.344
7.336
7.330
7.325
7.250
7.233
7.194
6.860
6.855
6.843
6.838
6.568
6.529
5.288
4.448
4.430
3.821
3.811
1.437
1.420
1.402
0.89
2.80
4.07
1.03
2.11
1.00
1.93
2.91
2.89
ppm

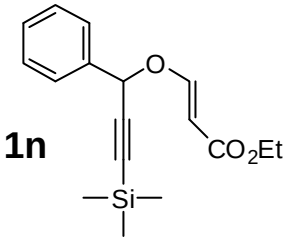

189.568
166.446
161.285
158.400
143.451
133.839
132.069
130.082
129.605
129.226
128.383
128.046
124.704
114.375
61.623
55.353
14.348
ppm

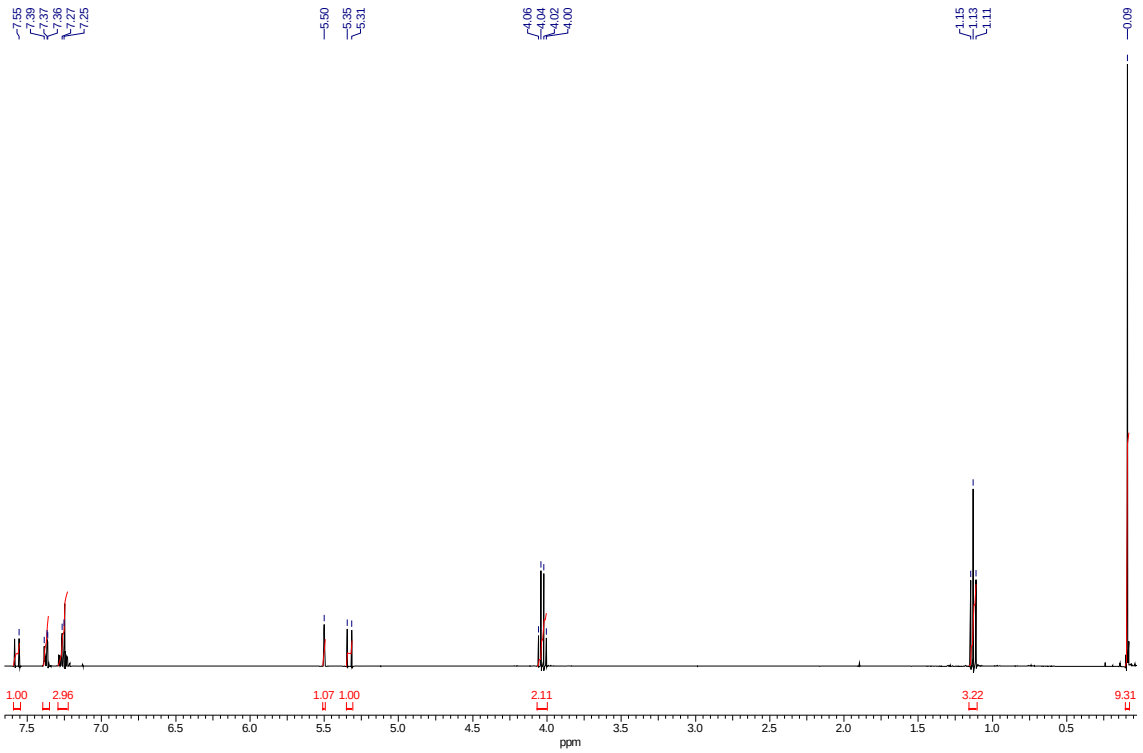

O
H
O
CO2Et

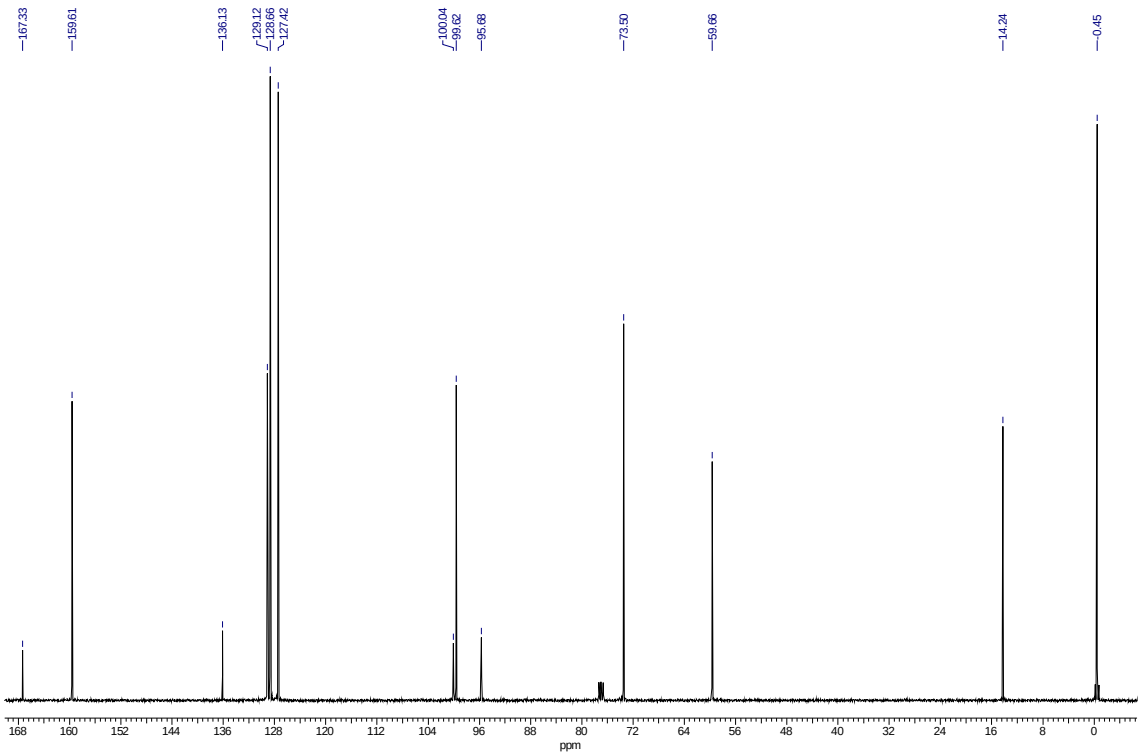
3m

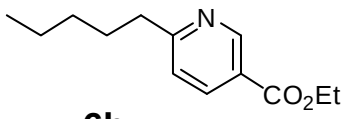

9.248
7.480
7.474
7.467
7.333
7.328
7.320
7.309
7.244
7.206
6.424
6.357
6.318
5.286
4.466
4.448
4.430
4.412
1.435
1.418
1.400
0.87
4.01
2.23
1.99
2.00
2.92
ppm


189.37
166.14
157.44
152.02
144.85
133.34
129.96
129.46
129.27
128.44
128.11
124.88
114.53
112.49
77.00
61.64
14.20
ppm

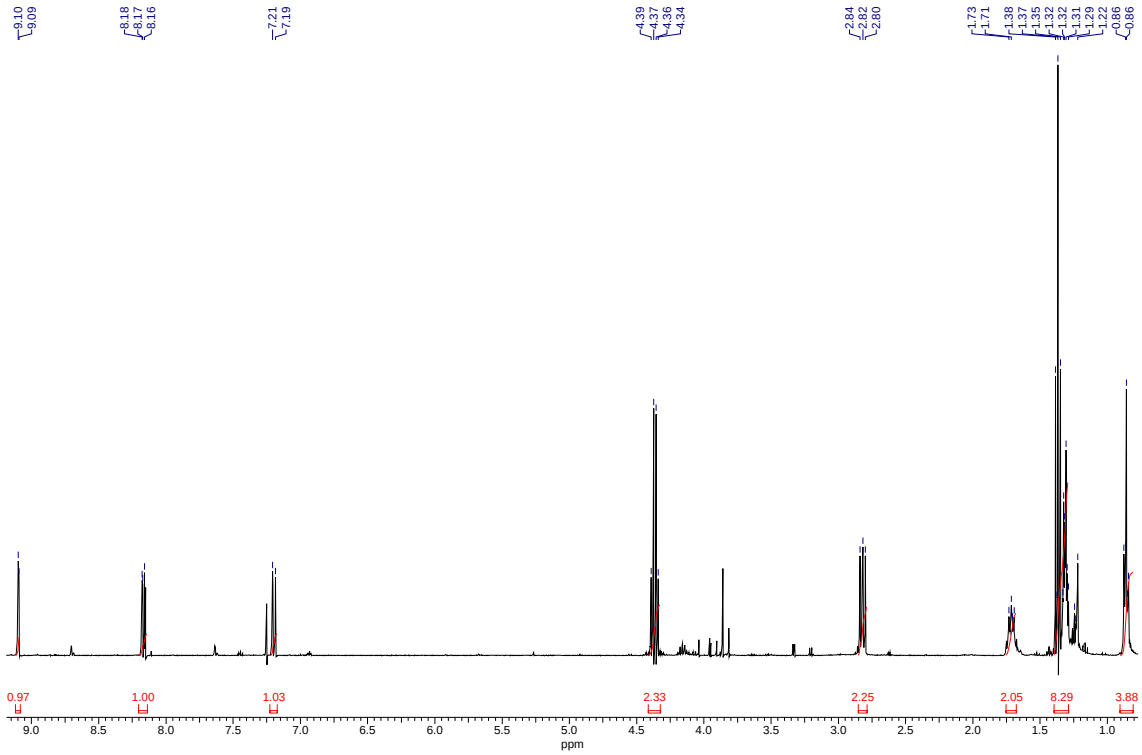

1n
O
CO2Et
Si

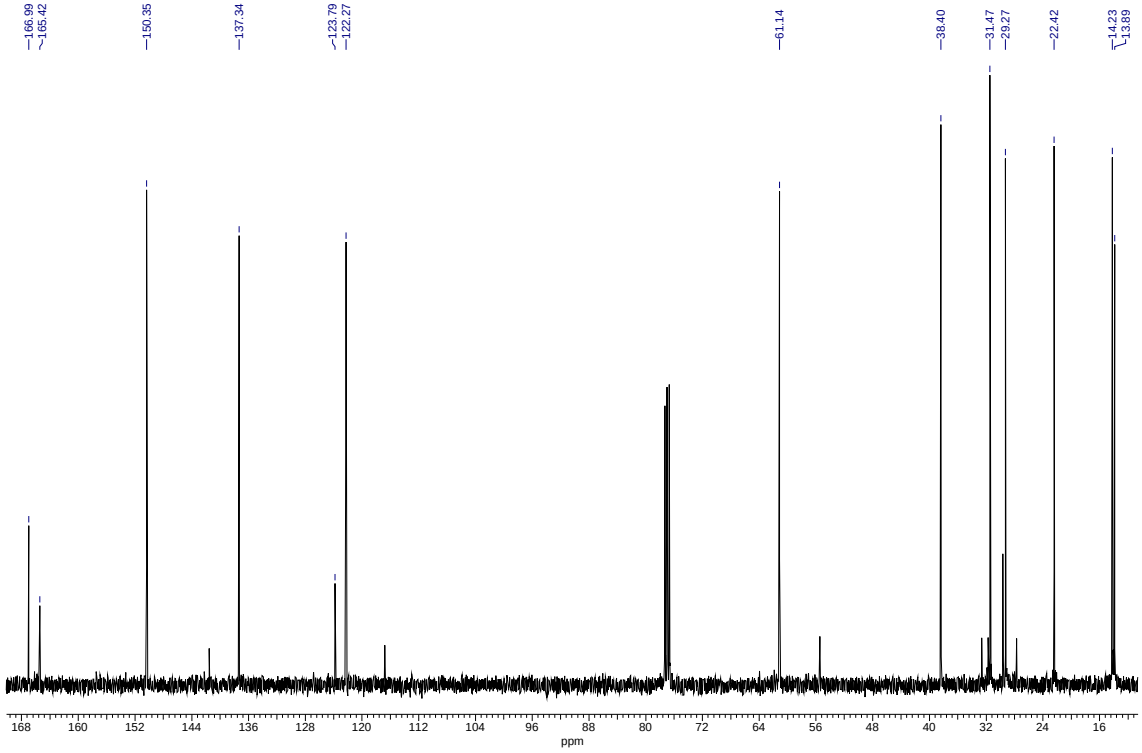

7.55
7.39
7.37
7.36
7.27
7.25
5.50
5.35
5.31
4.06
4.04
4.02
4.00
1.15
1.13
1.11
0.09
1.00
2.96
1.07
1.00
2.11
3.22
9.31
ppm

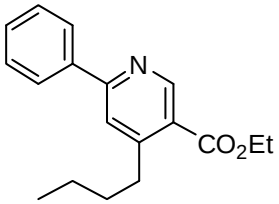

167.33
159.61
136.13
129.12
128.66
127.42
100.04
99.62
95.68
73.50
59.66
14.24
0.45
ppm


N
CO2Et

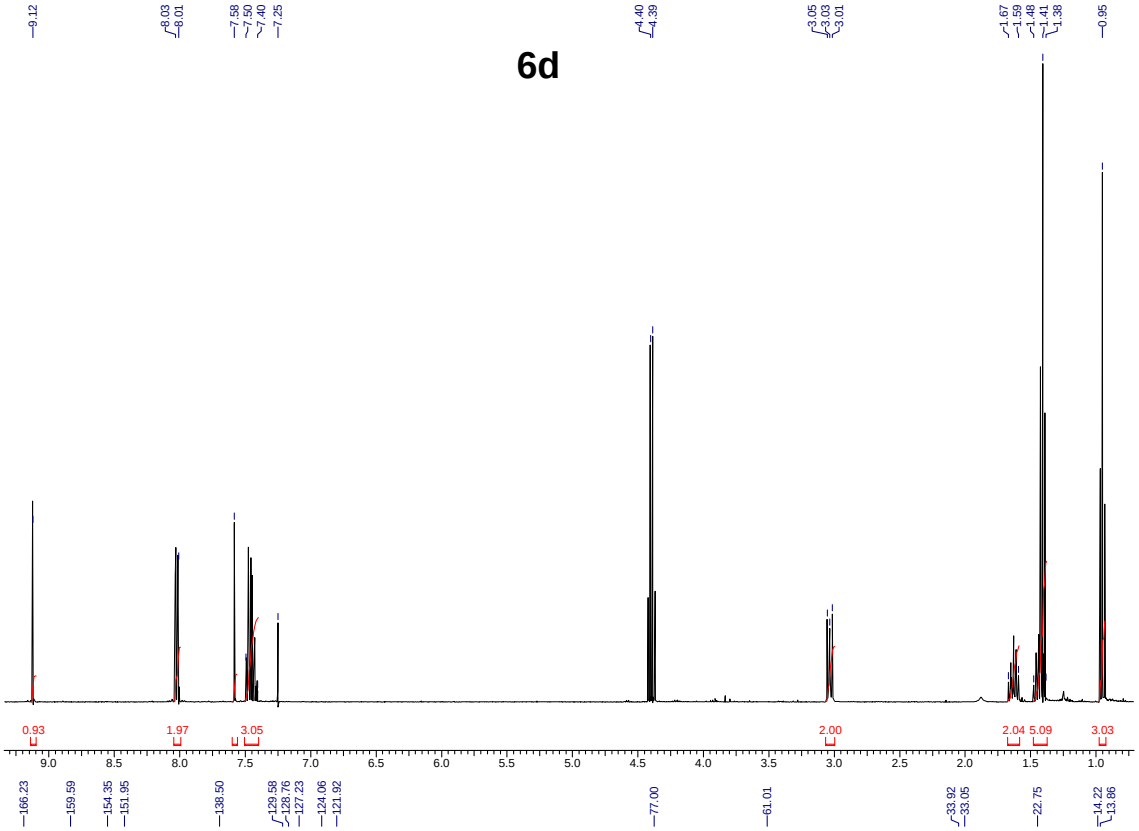
6b

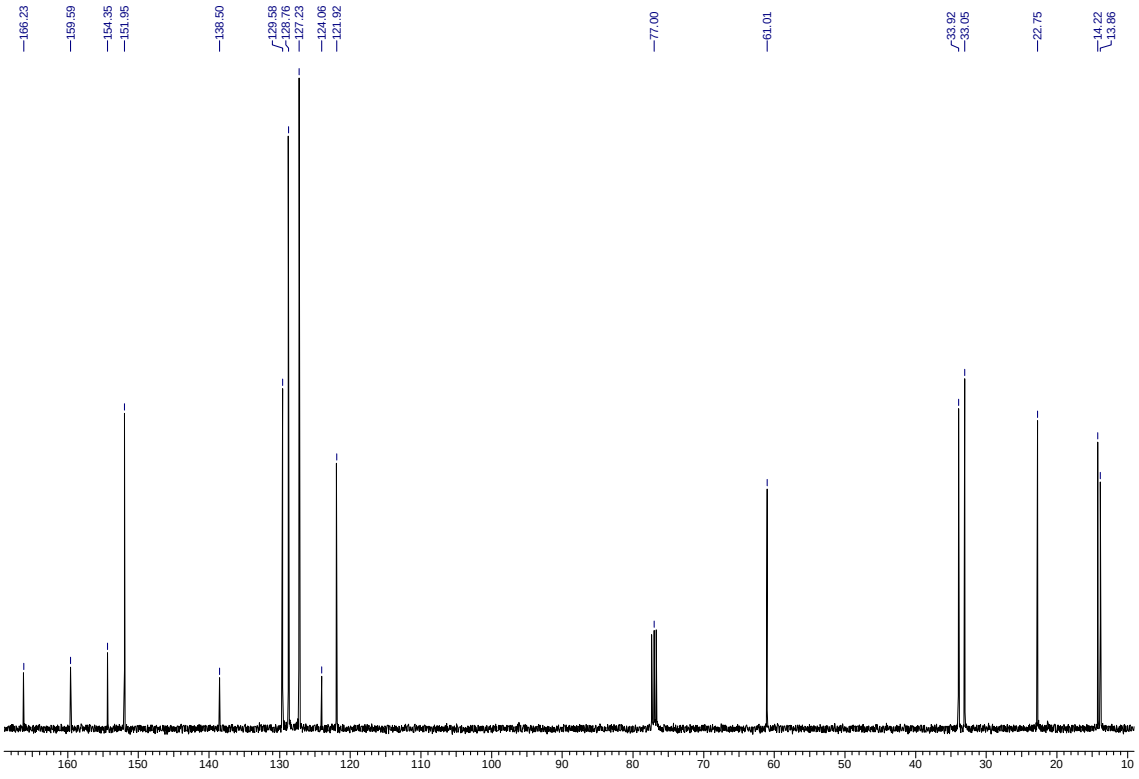

9.10
9.09
8.18
8.17
8.16
7.21
7.19
4.39
4.37
4.36
4.34
2.84
2.82
2.80
1.73
1.71
1.38
1.37
1.35
1.32
1.32
1.31
1.29
1.22
0.86
0.86
0.97
1.00
1.03
2.33
2.25
2.05
8.29
3.88
ppm

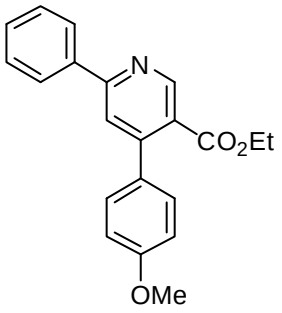

166.99
165.42
150.35
137.34
123.79
122.27
61.14
38.40
31.47
29.27
22.42
14.23
13.89
ppm


N
CO2Et

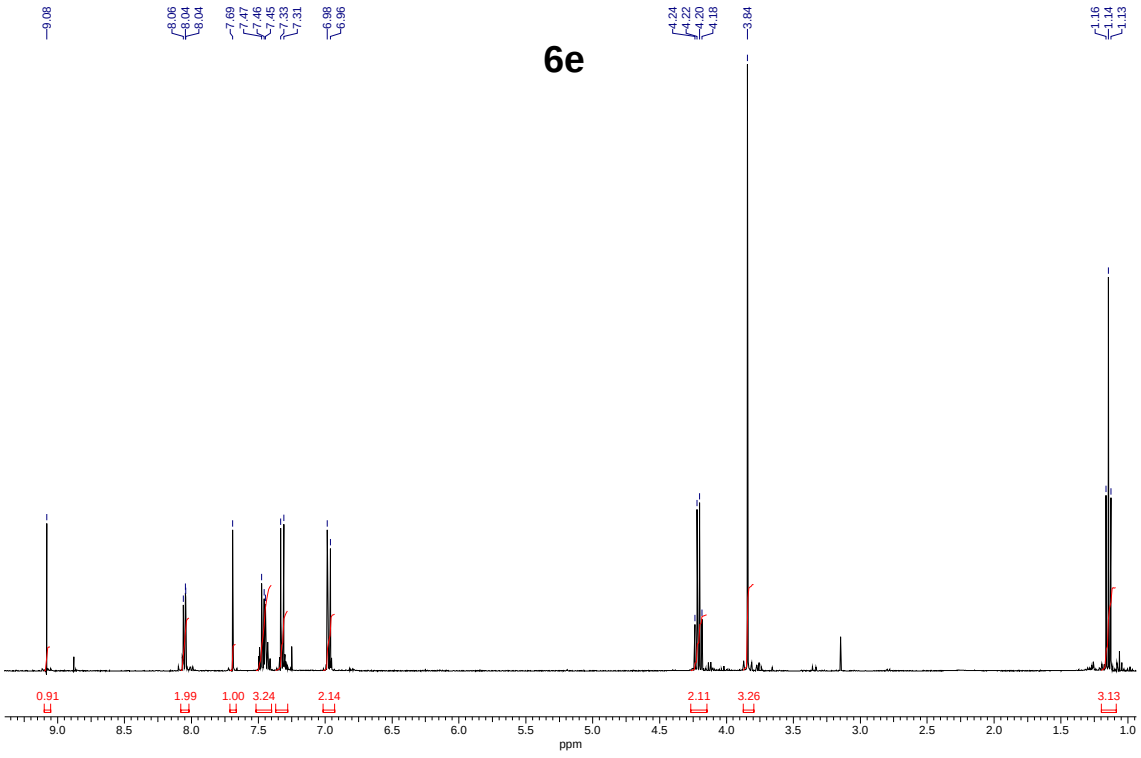
6d

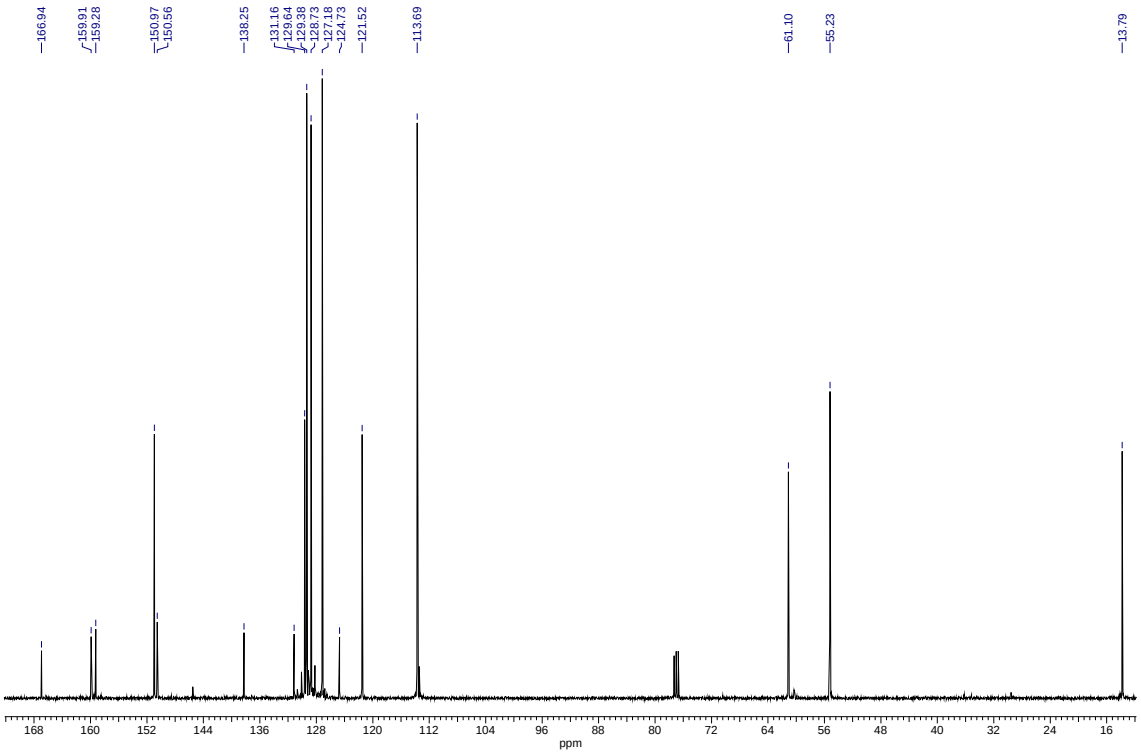

9.12
8.03
8.01
7.58
7.50
7.40
7.25
4.40
4.39
3.05
3.03
3.01
1.67
1.59
1.48
1.41
1.38
0.95
0.93
1.97
3.05
2.00
2.04
5.09
3.03

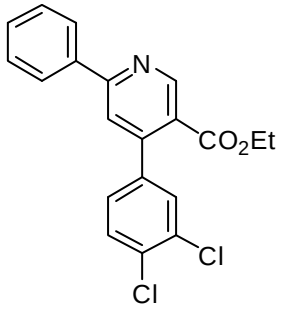

166.23
159.59
154.35
151.95
138.50
129.58
128.76
127.23
124.06
121.92
77.00
61.01
33.92
33.05
22.75
14.22
13.86


N
CO2Et
OMe

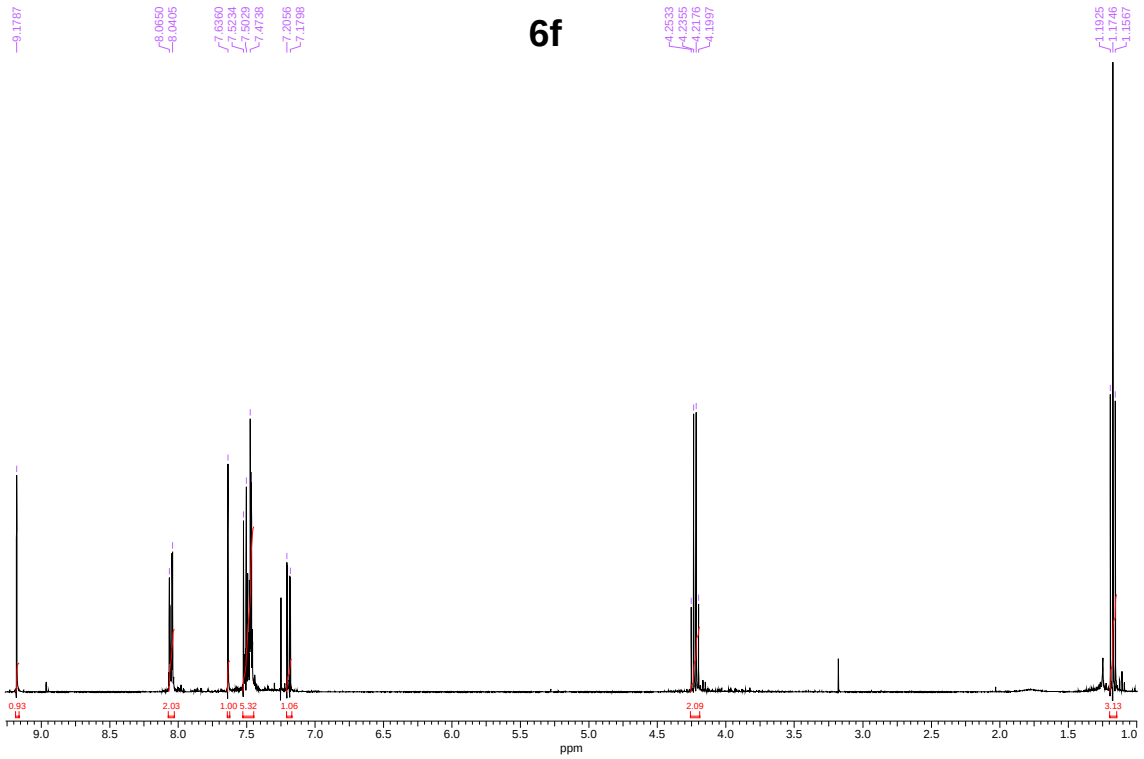
6e

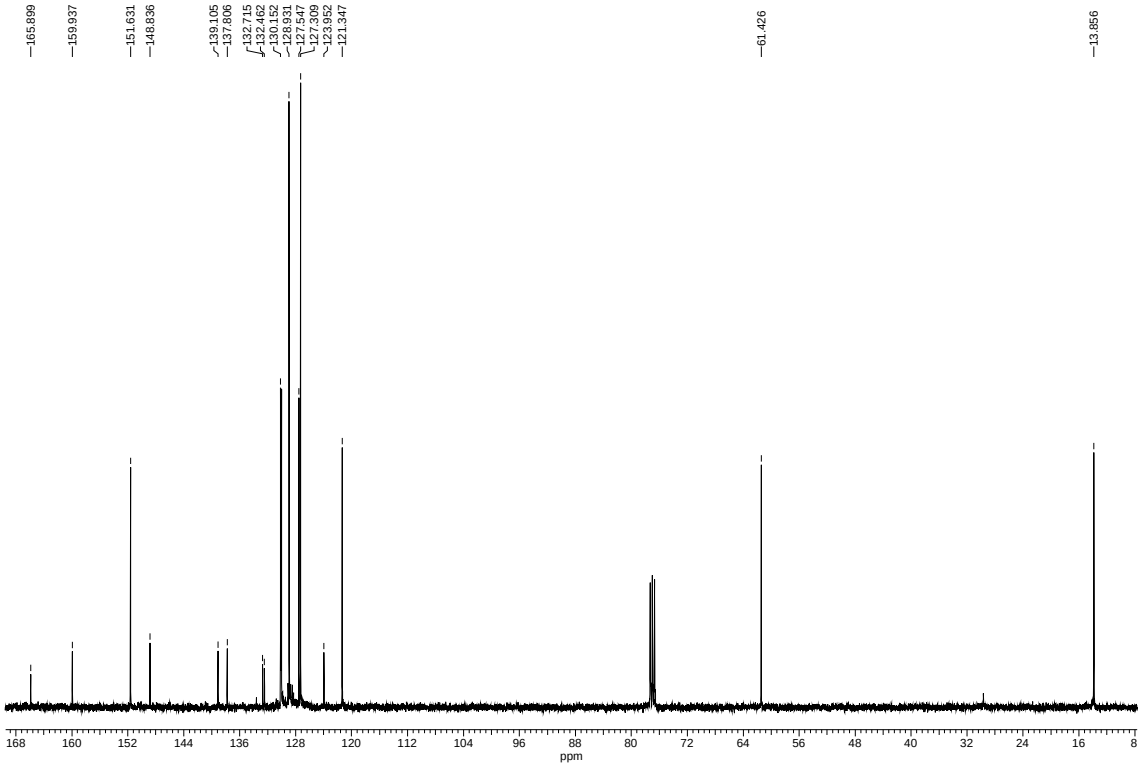

9.08
8.06
8.04
8.04
7.69
7.47
7.46
7.45
7.33
7.31
6.98
6.96
4.24
4.22
4.20
4.18
3.84
1.16
1.14
1.13
0.91
1.99
1.00
3.24
2.14
2.11
3.26
3.13
ppm

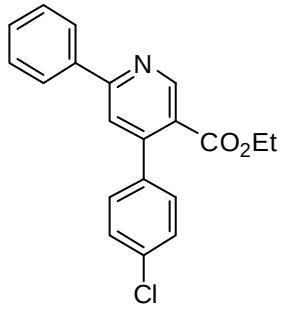

166.94
159.91
159.28
150.97
150.56
138.25
131.16
129.64
129.38
128.73
127.18
124.73
121.52
113.69
61.10
55.23
13.79
ppm


N
CO2Et
Cl
Cl

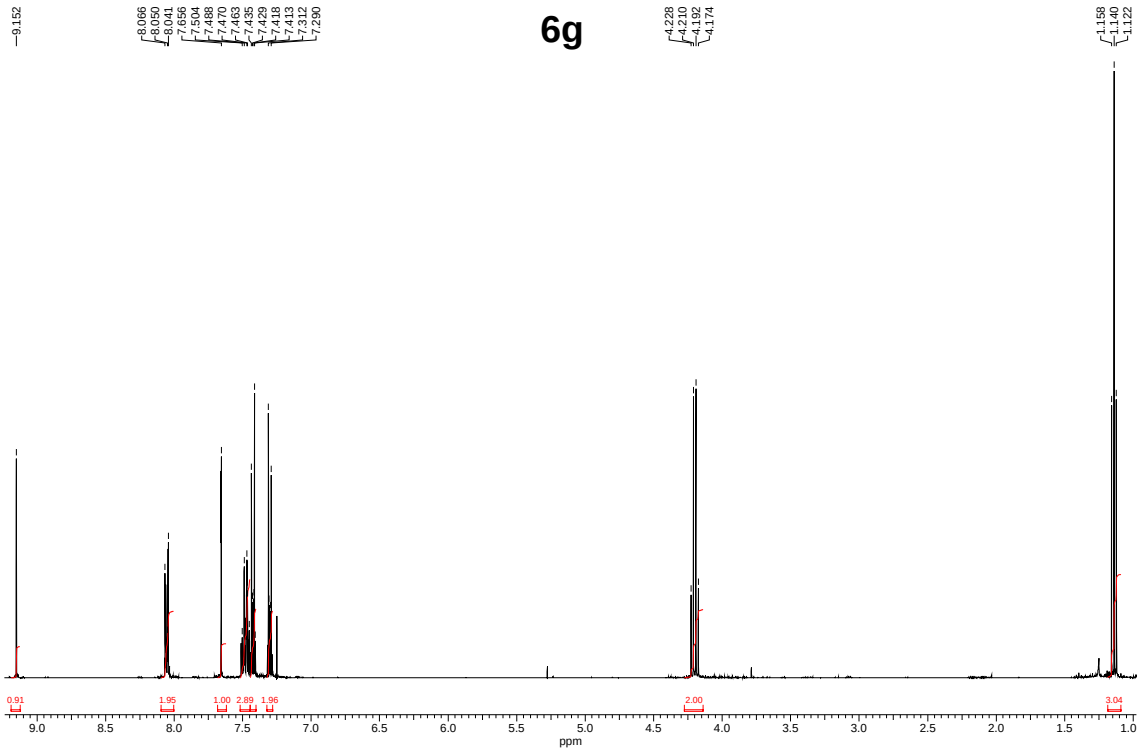
6f

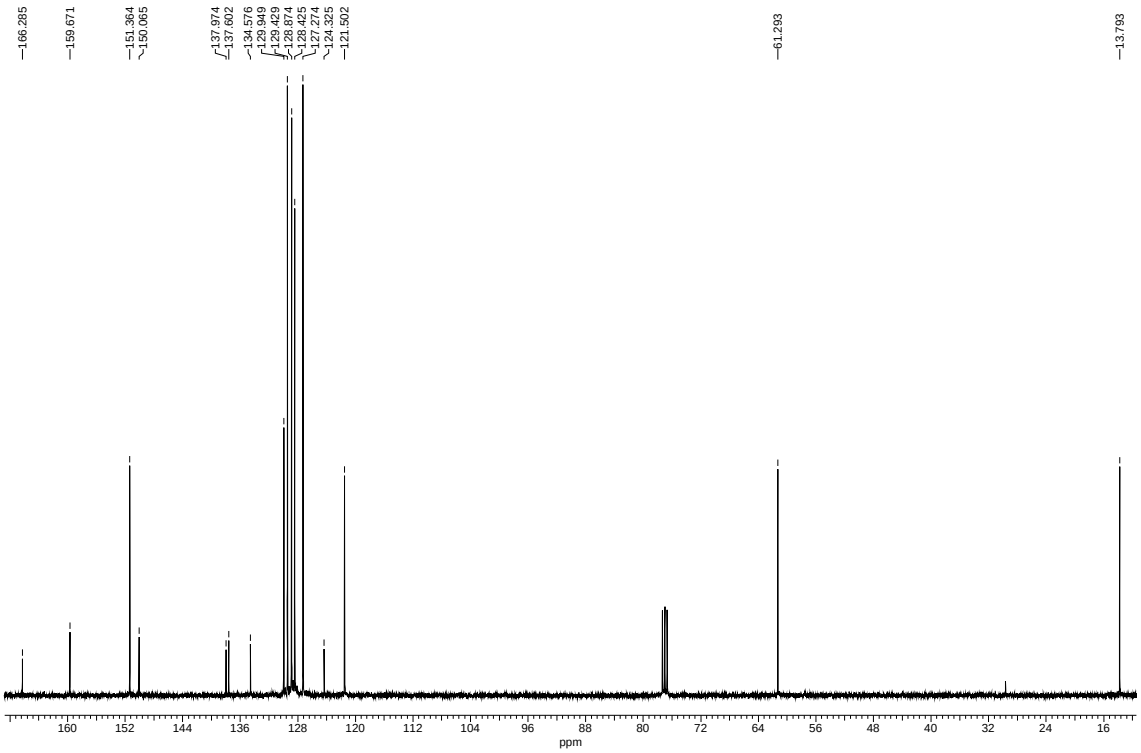

9.1787
8.0650
8.0405
7.6360
7.5234
7.5029
7.4738
7.2056
7.1798
4.2533
4.2355
4.2176
4.1997
1.1925
1.1746
1.1567
0.93
2.03
1.00
5.32
1.06
2.09
3.13
ppm

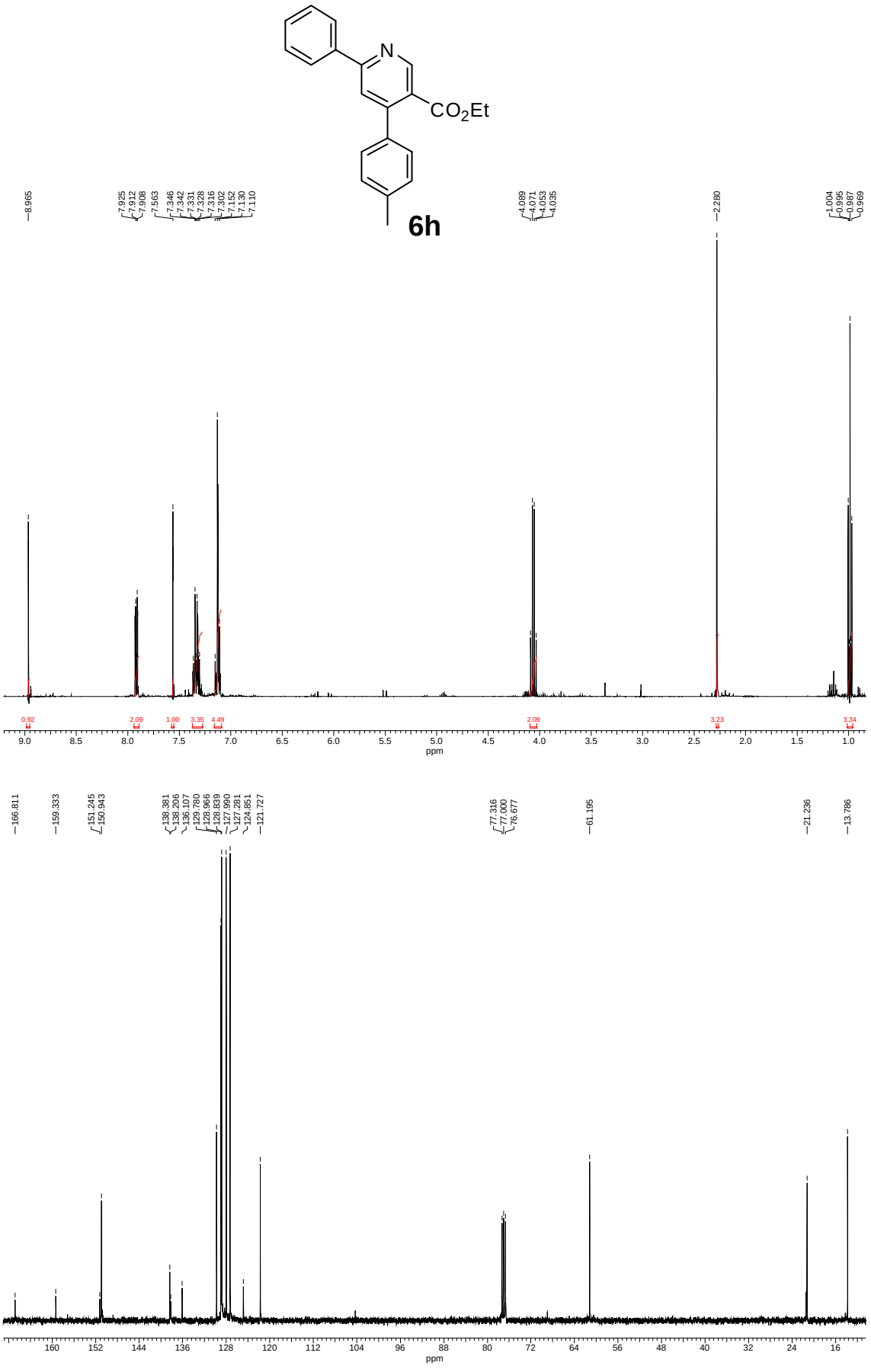

165.899
159.937
151.631
148.836
139.105
137.806
132.715
132.462
130.152
128.931
127.547
127.309
123.952
121.347
61.426
13.956
ppm

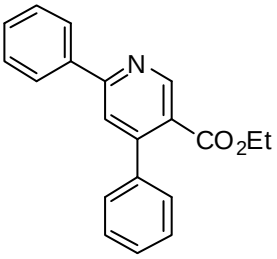

N
CO2Et
Cl

6g

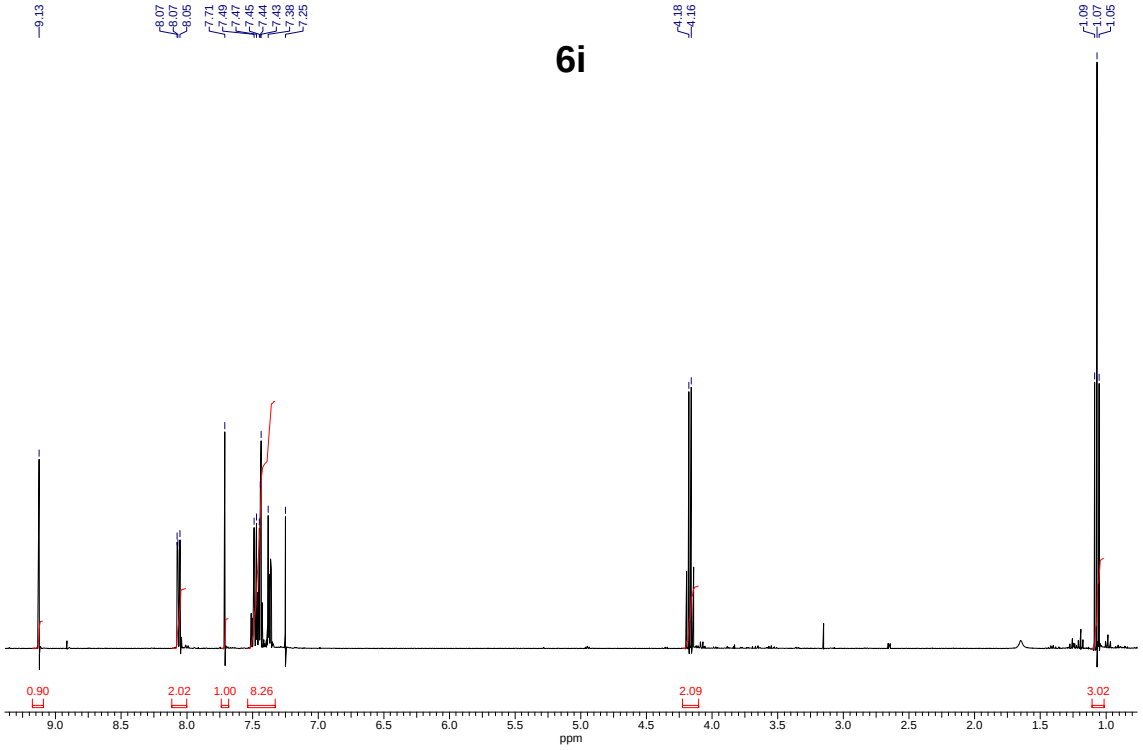

9.152
8.066
8.050
8.041
7.656
7.504
7.488
7.470
7.463
7.435
7.429
7.418
7.413
7.312
7.290
4.228
4.210
4.192
4.174
1.158
1.140
1.122
0.91
1.95
1.00
2.89
1.96
2.00
3.04
ppm

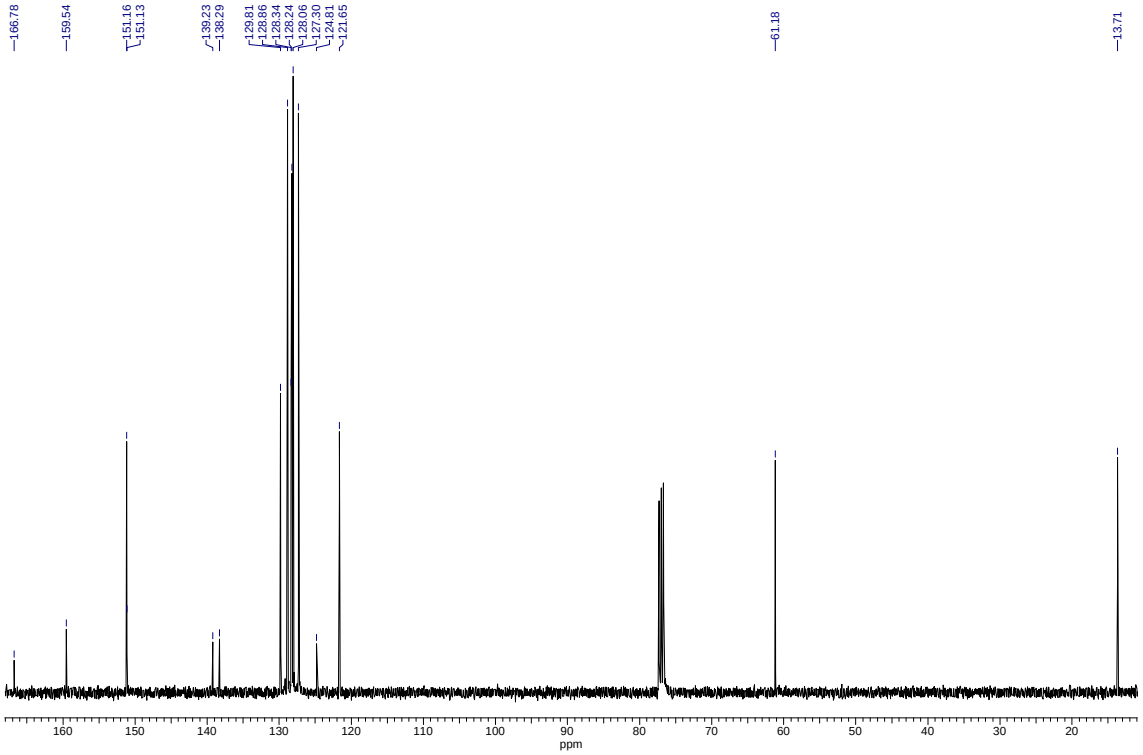

166.285
159.671
151.364
150.065
137.974
137.602
134.576
129.949
129.429
128.874
128.425
127.274
124.325
121.502
61.293
13.793
ppm

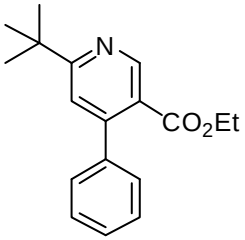

N
CO2Et
6h
8.965
7.925
7.912
7.908
7.563
7.346
7.342
7.331
7.328
7.316
7.302
7.152
7.130
7.110
4.089
4.071
4.053
4.035
2.280
1.004
0.995
0.987
0.969
0.92
2.09
1.00
3.35
4.49
2.09
3.23
3.34
ppm
166.811
159.333
151.245
150.943
138.381
138.206
136.107
129.780
128.966
128.839
127.990
127.281
124.851
121.727
77.316
77.000
76.677
61.195
21.236
13.786
ppm


N
CO2Et

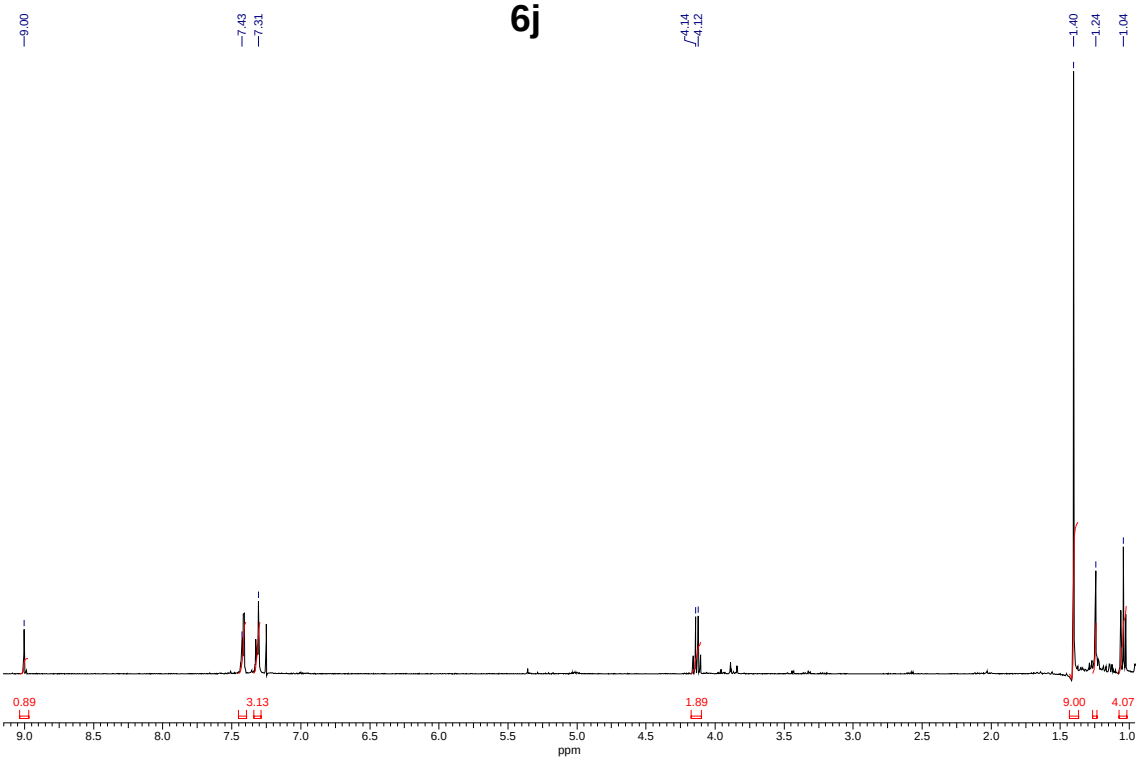
6i

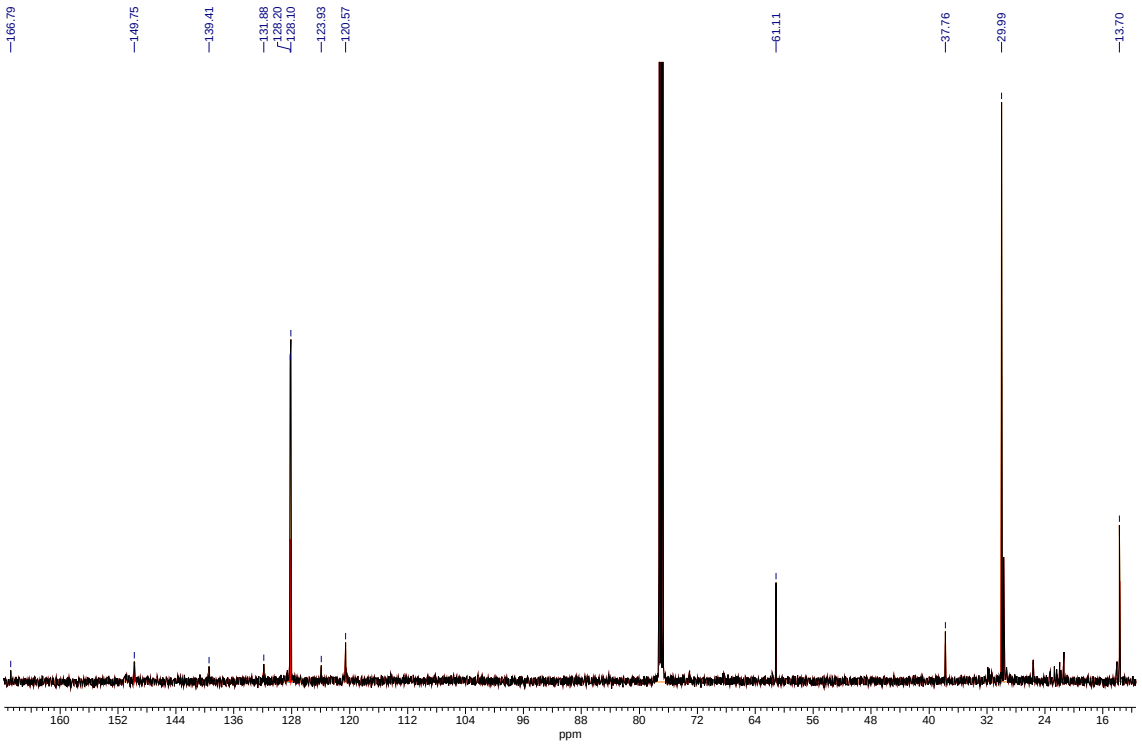

9.13
8.07
8.07
8.05
7.71
7.49
7.47
7.45
7.44
7.43
7.38
7.25
4.18
4.16
1.09
1.07
1.05
0.90
2.02
1.00
8.26
2.09
3.02
ppm

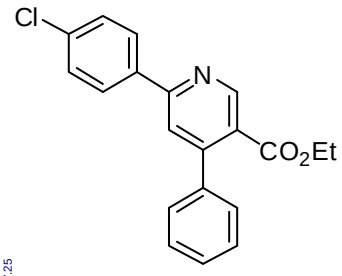

166.78
159.54
151.16
151.13
139.23
138.29
129.81
128.86
128.34
128.24
128.06
127.30
124.81
121.65
61.18
13.71
ppm


N
CO2Et

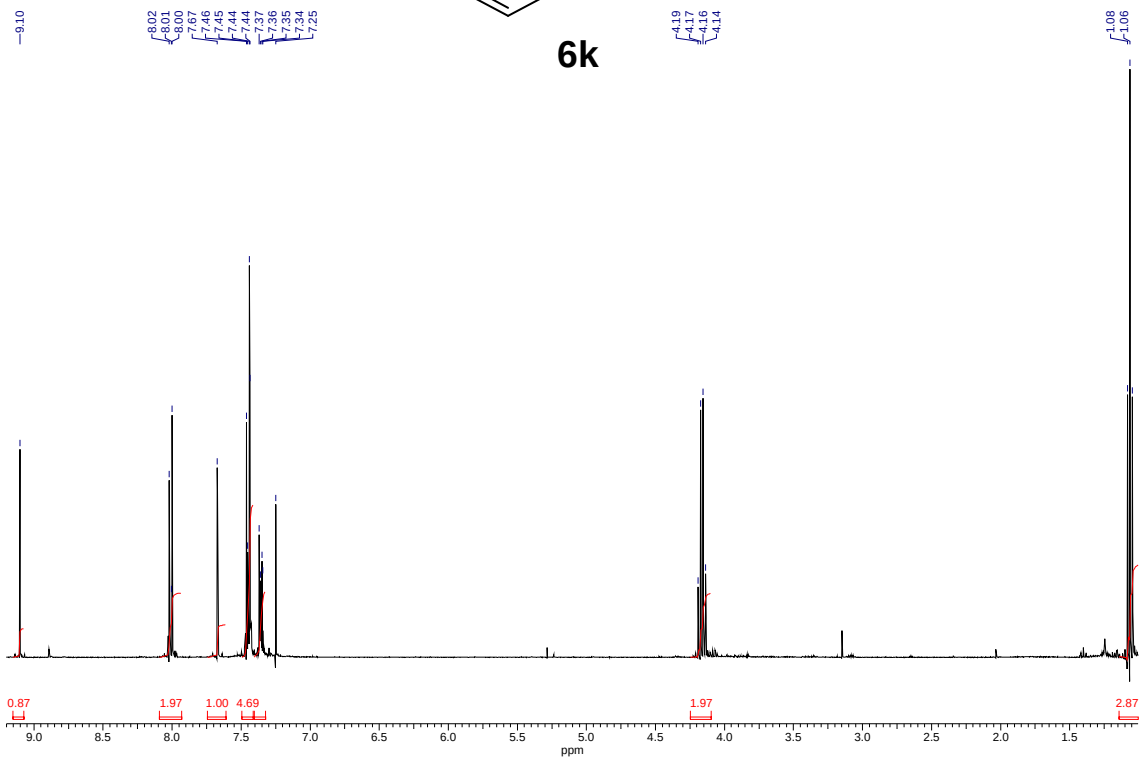
6j

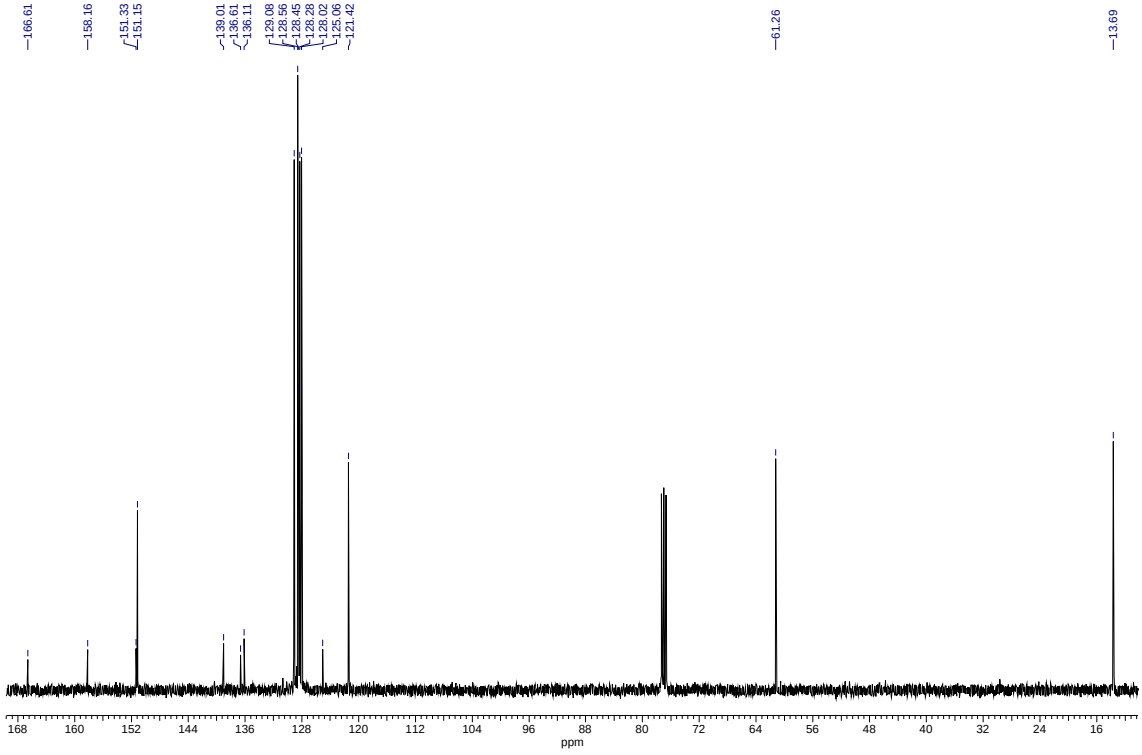

9.00
7.43
7.31
4.14
4.12
1.40
1.24
1.04
0.89
3.13
1.89
9.00
4.07
ppm

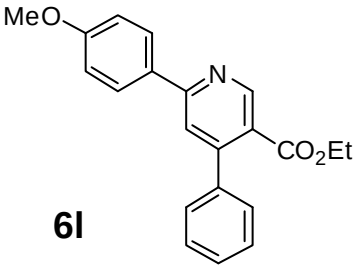

166.79
149.75
139.41
131.88
128.20
128.10
123.93
120.57
61.11
37.76
29.99
13.70
ppm


Cl
N
CO2Et

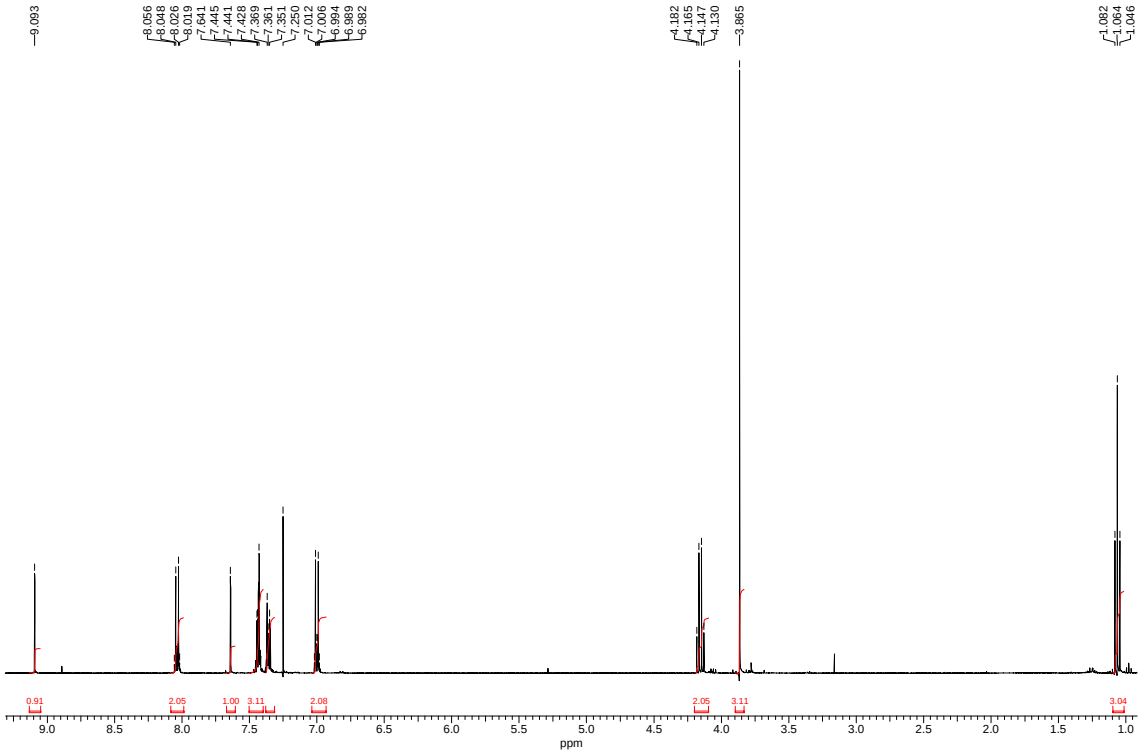
6k

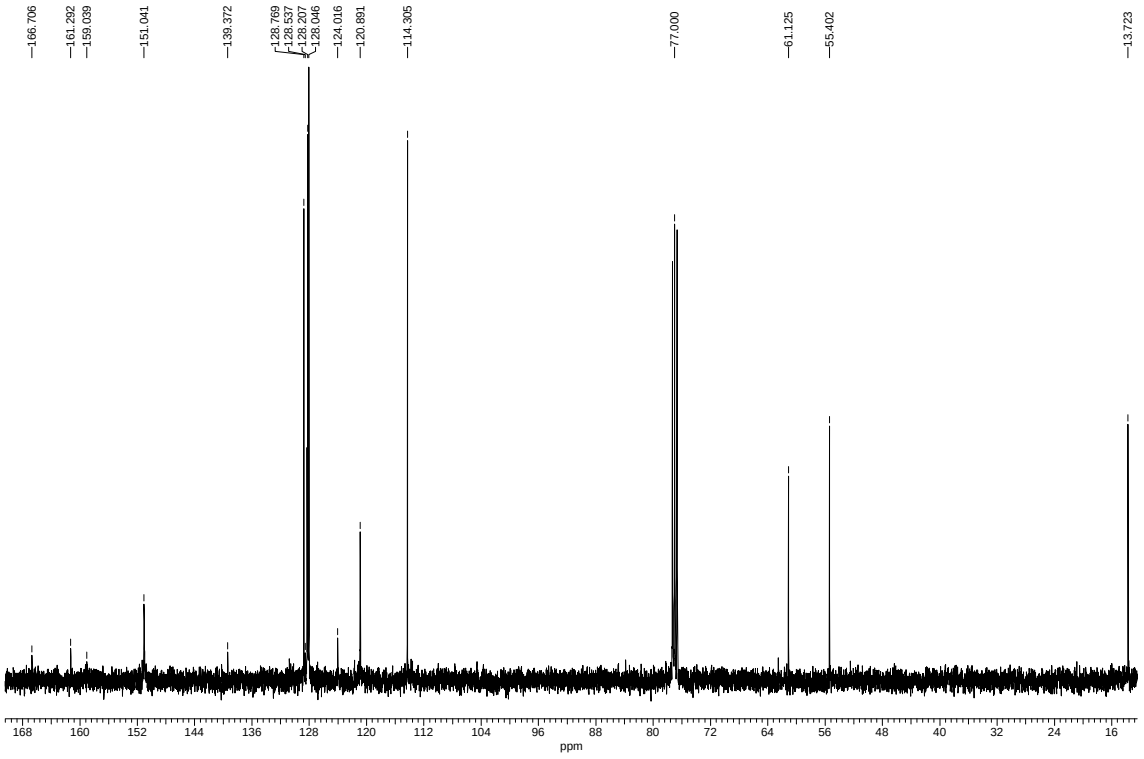

9.10
8.02
8.01
8.00
7.67
7.46
7.45
7.44
7.37
7.36
7.35
7.34
7.25
4.19
4.17
4.16
4.14
1.08
1.06
0.87
1.97
1.00
4.69
1.97
2.87
ppm

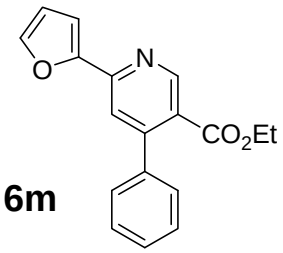

166.61
158.16
151.33
151.15
139.01
136.61
136.11
129.08
128.56
128.45
128.28
128.02
125.06
121.42
61.26
13.69
ppm


MeO
N
CO2Et

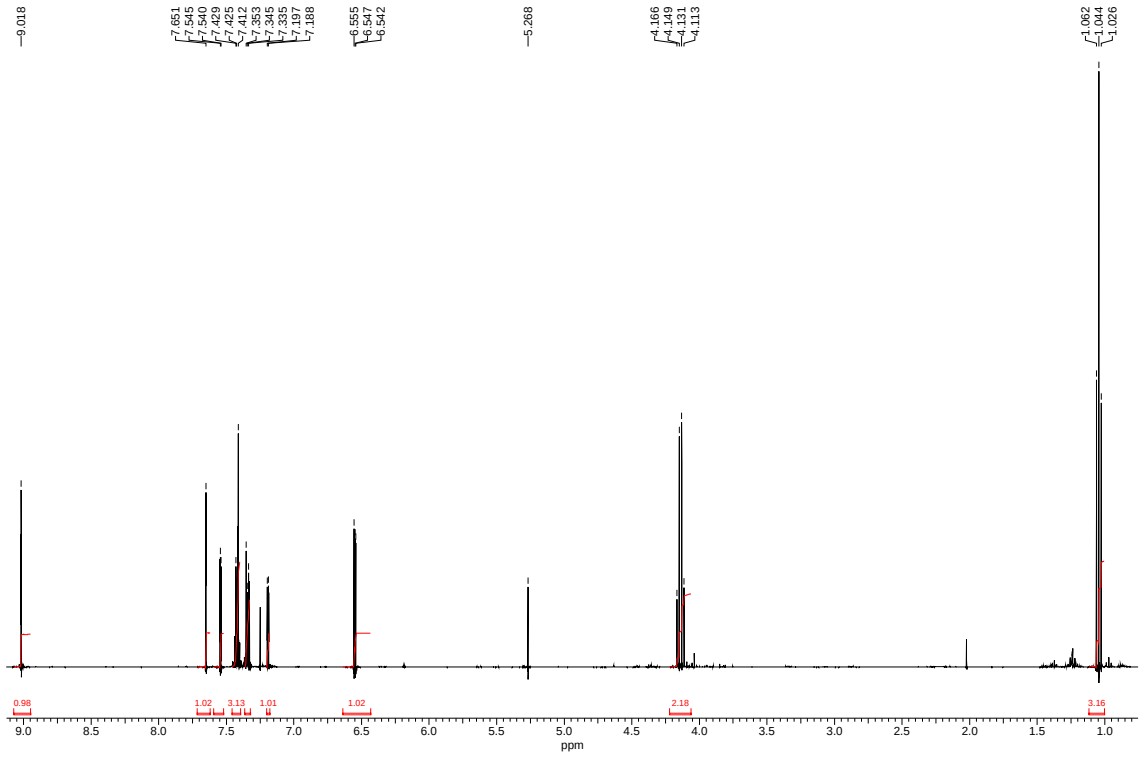
6l

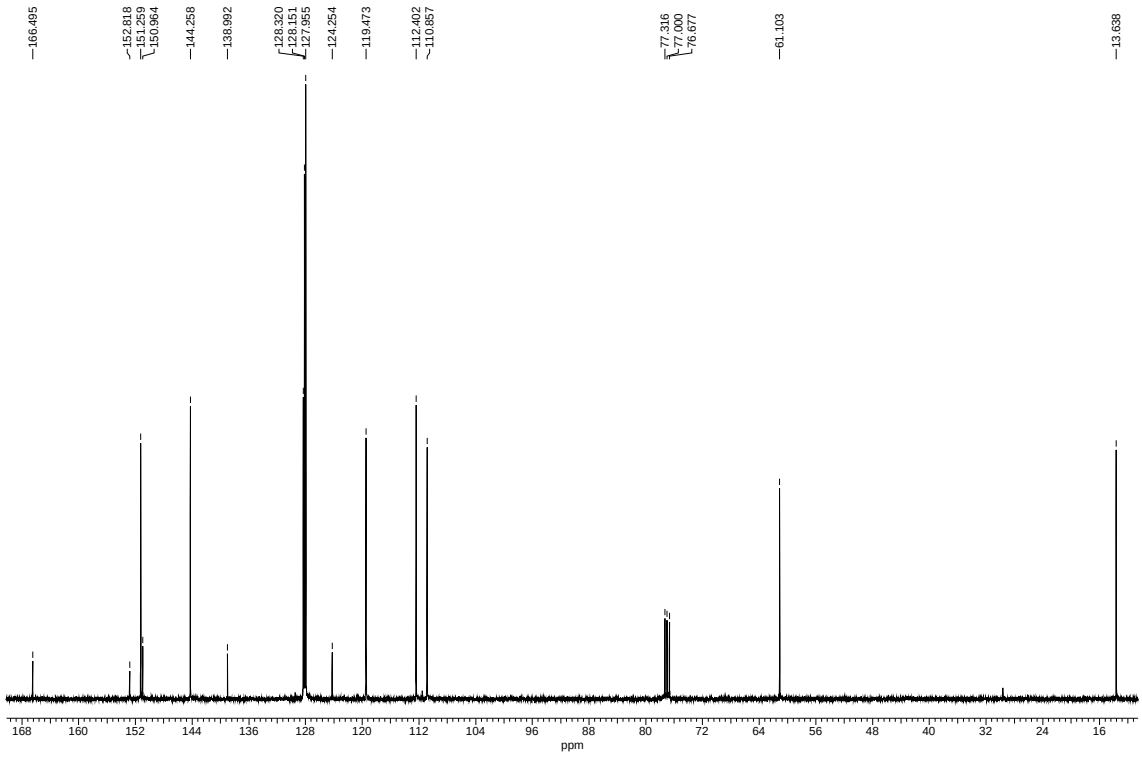

9.093
8.056
8.048
8.026
8.019
7.641
7.445
7.441
7.428
7.389
7.381
7.351
7.250
7.012
7.006
6.994
6.989
6.982
4.182
4.165
4.147
4.130
3.865
1.082
1.064
1.046
0.91
2.05
1.00
3.11
2.08
2.05
3.11
3.04
ppm

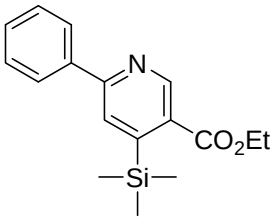

166.706
161.292
159.039
151.041
139.372
128.769
128.537
128.207
128.046
124.016
120.891
114.305
77.000
61.125
55.402
13.723
ppm


O
N
CO2Et

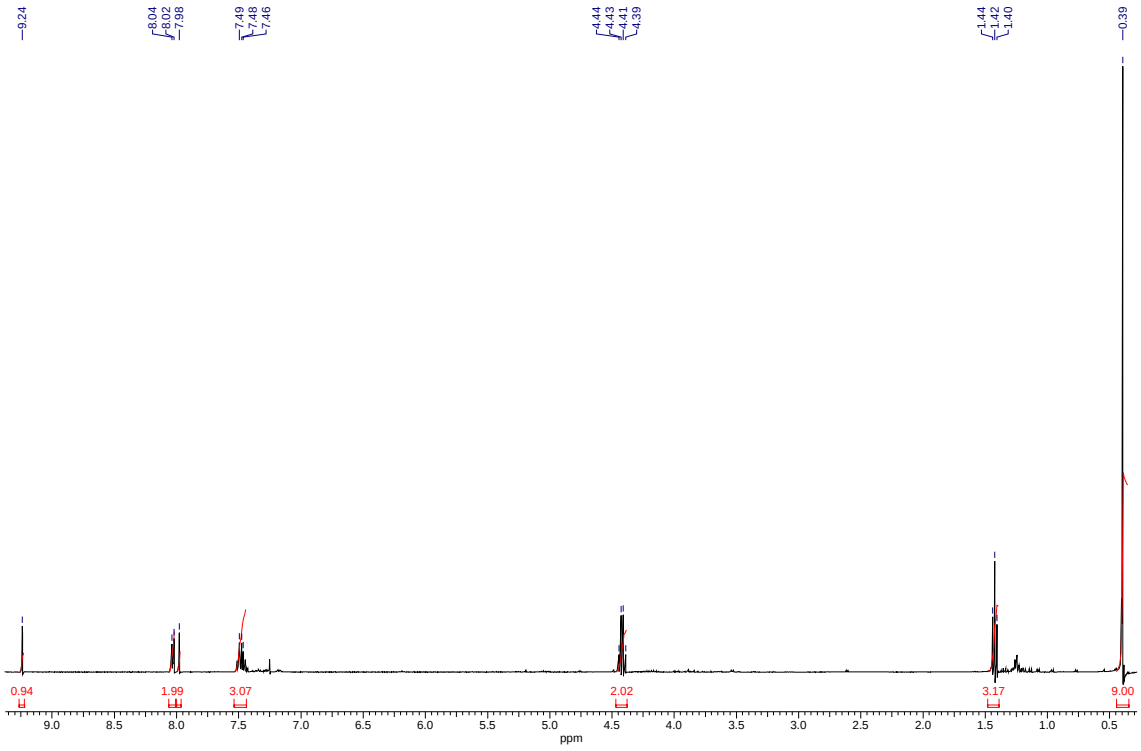
6m

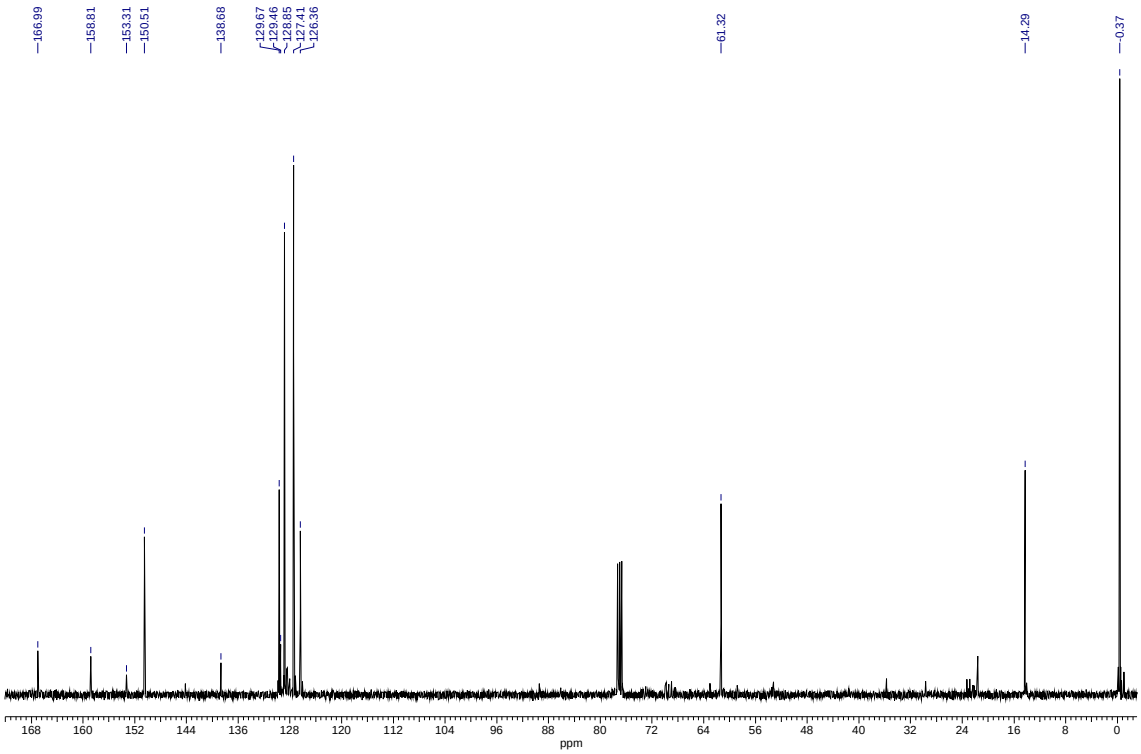

9.018
7.651
7.645
7.640
7.429
7.425
7.412
7.353
7.345
7.335
7.197
7.188
6.555
6.547
6.542
5.268
4.166
4.149
4.131
4.113
1.062
1.044
1.026
0.98
1.02
3.13
1.01
1.02
2.18
3.16
ppm

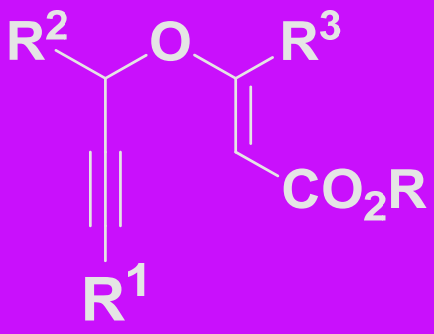

166.495
152.818
151.259
150.964
144.258
138.992
128.320
128.151
127.955
124.254
119.473
112.402
110.857
77.316
77.000
76.677
61.103
13.638
ppm


N
CO2Et
Si

6n


9.24
8.04
8.02
7.98
7.49
7.48
7.46
4.44
4.43
4.41
4.39
1.44
1.42
1.40
0.39
0.94
1.99
3.07
2.02
3.17
9.00
ppm


166.99
158.81
153.31
150.51
138.68
129.67
129.46
128.85
127.41
126.36
61.32
14.29
0.37
ppm



CHAPTER 5

A Microwave-Assisted Domino Rearrangement of Propargyl Vinyl Ethers to Multifunctionalized Aromatic Platforms

CHEMISTRY
A EUROPEAN JOURNAL

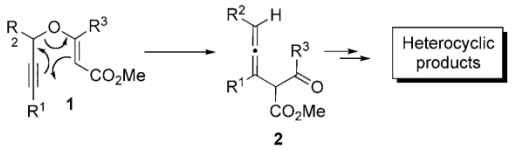
DOI: 10.1002/chem.201003532

A Microwave-Assisted Domino Rearrangement of Propargyl Vinyl Ethers to Multifunctionalized Aromatic Platforms

David Tejedor,*[a, b] Gabriela Méndez-Abt,[a, b] Leandro Cotos,[a, b] Miguel A. Ramirez,[c] and Fernando García-Tellado*[a, b]

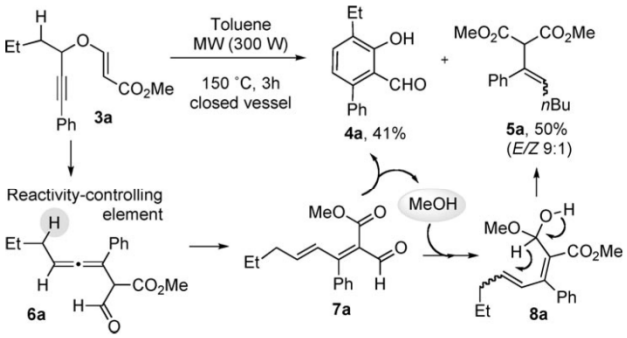
In memory of Professor Rafael Suau

Propargyl vinyl ethers (PVEs) **1** constitute a privileged group of small size, structurally simple, readily available, and densely functionalized scaffolds.[1–4] Efforts from our group,[2] and others,[3] have revealed the synthetic potential of these platforms in accessing important heterocyclic cores. The key to the chemical reactivity encoded in these structures is the [3,3] propargylic sigmatropic rearrangement[5] shown in Scheme 1. The allenyl compounds **2**, thus obtained,



Scheme 1. [3,3] Propargylic sigmatropic rearrangement of PVEs.

are reactive units and well suited to participate in a wide array of chemical transformations. Thus, in the presence of metallic catalysts, they have been selectively transformed into furans,[3a–d] 2*H*-pyrans,[3e] dihydropyrans,[3f] 1,2-dihydropyridines,[3g] or pyrroles.[3h] Recently, we have described a metal-free, microwave-assisted domino synthesis of substituted 1,2-dihydropyridines[2c] and pyridines,[2d] from PVEs **1** and primary amines, via the thermally-assisted formation of a homoallenyl ester intermediate **2**. During the course of these studies, we discovered a new chemical reactivity of these platforms when a solution of PVE **3a** in toluene was submitted to microwave (MW) irradiation in a sealed vial (Scheme 2). The reaction cleanly afforded the unexpected



Scheme 2. Unexpected new chemical reactivity of **3a**, after microwave (MW) irradiation.

mixture of compounds **4a** and **5a** in 91% overall yield. These structures featured an unprecedented chemical outcome for this domino process, which is enabled by the presence of a hydrogen atom at the homopropargylic position. Fascinated by these unexpected results, we undertook the study and scope of this novel domino reaction. Overall, this reaction should provide an expedient route to useful multifunctionalized phenolic platforms,[6] such as **4**, which constitute key structural motifs for the preparation of numerous pharmacologically important natural products (e.g., coumarins,[7a] flavones,[7b] and several mycotoxins[7c]) and catalysts.[8] In addition, PVEs **3** are easily accessible starting materials, spanning a wide substitution pattern. They are conveniently assembled from commercial sources (aldehydes, alkynes, and alkyl propiolates) in one or two straightforward synthetic steps.[2]

We hypothesized that the formation of products **4a** and **5a** should result from a domino process triggered by the expected microwave-assisted rearrangement of PVE **3a** to the corresponding dienic ester **7a**, via the formation of a transi-

[a] Dr. D. Tejedor, G. Méndez-Abt, L. Cotos, Dr. F. García-Tellado
Química Biológica y Biotecnología
Instituto de Productos Naturales y Agrobiología
Consejo Superior de Investigaciones Científicas
Avda. Astrofísico Francisco Sánchez 3
38206 La Laguna, Tenerife (Spain)
Fax: (+34) 922-2260135
E-mail: fgarcia@ipna.csic.es
dtejedor@ipna.csic.es

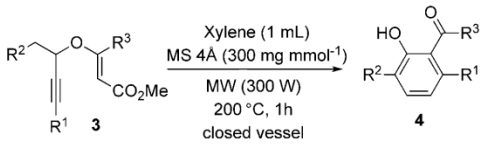
[b] Dr. D. Tejedor, G. Méndez-Abt, L. Cotos, Dr. F. García-Tellado
Instituto Canario de Investigación del Cáncer (Spain)

[c] Dr. M. A. Ramirez
Instituto Universitario de Bioorgánica Antonio González
Universidad de La Laguna
Avda. Astrofísico Francisco Sánchez 2
38206 La Laguna, Tenerife (Spain)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201003532.

ent homoallenyl ester **6a**.[9] A subsequent tandem cyclization–aromatization reaction should afford the corresponding phenolic derivatives **4a** with the concomitant elimination of one equivalent of methanol. Addition of this liberated methanol to the intermediate **7a** should trigger a second reaction path affording the product **5a** via the formation of hemiacetal **8a**. In this scenario, it was expected that the removal of the generated methanol should funnel the whole transformation towards the exclusive formation of **4a**. With this idea, we designed an experimental protocol that included molecular sieves (4 Å) in the reaction mixture, to act as a methanol scavenger. Under these new conditions, the formation of the malonate derivative **5a** was totally suppressed. After several experiments, the reaction was standardized, and scaffold **3a** was conveniently converted into the salicylaldehyde **4a** in 76% yield (Table 1, entry 1). Salicyladehyde

Table 1. Substitution of R groups on **3** to test the scope of the domino reaction.



3 **4**

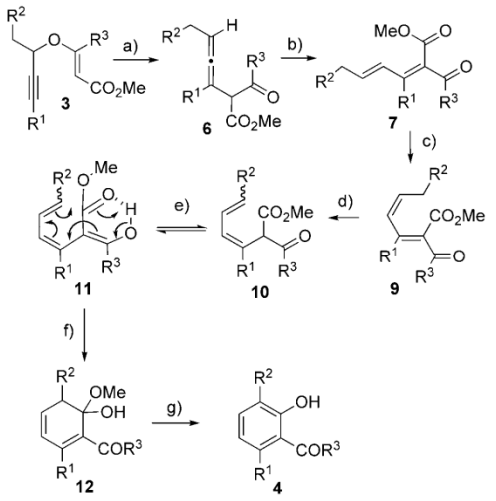
Entry	R^1	R^2	R^3	**4**	Yield [%][a]
1	Ph	Et	H	**4a**	76
2	Ph	*i*Pr	H	**4b**	72
3	Ph	*t*Bu	H	**4c**	67
4	Ph	H	H	**4d**	27
5	Ph	Ph	H	**4e**	89
6	Ph	$PhCH_2$	H	**4f**	61
7	Ph	F	H	**4g**	63
8	*p*-$MeOC_6H_4$	Et	H	**4h**	72
9	3,4-$Cl_2C_6H_3$	Et	H	**4i**	77
10	*p*-MeC_6H_4	Et	H	**4j**	81
11	Ph	Et	Me	**4k**	65[b]
12	Ph	Et	*n*Pen	**4l**	72[b]
13	Ph	Et	Ph	**4m**	75[b]
14	*n*Bu	Et	H	**4n**	43[c]
15	CO_2Me	*n*Pr	H	**4o**	70
16	CO_2Me	Ph	H	**4p**	56
17	CO_2Me	H	H	**4q**	29
18	Me_3Si	Et	H	**4r**	30

[a] Yield of isolated product. [b] Generally, the reaction gave the same yields in the absence of molecular sieves 4 Å. [c] Diester **5n** was also obtained (see the Supporting Information for details).

4a, incorporating a phenyl substituent at the C6 position of the ring, can be regarded as a functionalized biphenyl derivative, and therefore, a pharmacologically privileged structural motif.[10] The common synthetic approach to salicylaldehydes relies mainly on the direct electrophilic substitution of a suitable phenol derivative. From a preparative point of view, this transformation suffers from regioselective drawbacks when the positions *ortho* and *para* with respect to the hydroxyl functionality are not conveniently blocked.[11] From this perspective, the direct generation of a 3,6-disubstituted salicylaldehyde derivative is notable.

With the standardized protocol in place, we next studied the scope of this domino reaction (Table 1). In general, the reaction was tolerant to substitution of the starting PVE; the reaction accommodated different aromatic substituents at the terminal position of the alkyne, regardless of their electronic nature (Table 1, entries 1–10). However, substitution of the aromatic substituent with an aliphatic substituent at this position, resulted in a lower yield of the corresponding salicylaldehyde derivative (Table 1, entry 14). Derivative **3e**, with a benzyl substituent at the propargylic position and a phenyl group at the terminal alkyne position, generated the *p*-terphenyl derivative **4e** in an excellent yield of 89% (Table 1, entry 5). Fully substituted propargylic platforms **3k**–**3m** afforded the corresponding phenolic ketones **4k**–**4m** in good yields (Table 1, entries 11–13). In these cases, the use of a methanol scavenger is unnecessary because the corresponding intermediate ketals **8k**–**8m** (Scheme 2) cannot rearrange and they remain in equilibrium with their dienic precursors **7k**–**7m**. Conjugated alkynes **3o**–**3q** were also convenient substrates for this reaction, affording the corresponding methyl 2-formyl-3-hydroxybenzoate derivatives **4o**–**4q** (Table 1, entries 15–17). Interestingly, the substitution at the homopropargylic position increased the chemical efficiency of the reaction from 29% (**4q**) to 70% (**4o**) and 56% (**4p**). A silicon substituent at the alkyne position was also tolerated (Table 1, entry 18), although with diminished efficiency (30%). Finally, the reaction delivered valuable *o*-fluorophenol derivatives in an easy and efficient manner (Table 1, entry 7).

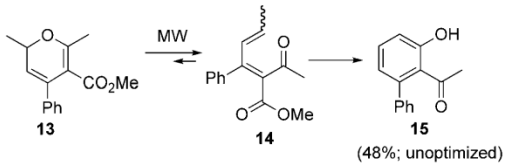
With regard to the mechanism of this domino reaction, a working proposal is outlined in Scheme 3. The reaction manifold is launched by the microwave-assisted propargyl Claisen rearrangement of the starting PVE **3** to generate the



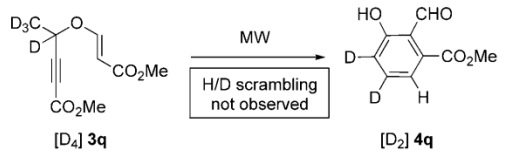
Scheme 3. A mechanistic proposal for the domino process. Microwave-assisted reactions: a) propargyl Claisen rearrangement; b) pseudo-pericyclic [1,3] hydride shift; c) 4*E*–4*Z* isomerization; d) [1,5] hydride shift; e) enolization; f) electrocyclization; g) aromatization.

CHEMISTRY
A EUROPEAN JOURNAL

allenic intermediate **6**, which rearranges to the corresponding dienyl intermediate **7** by a thermally allowed pseudopericyclic [1,3] hydride shift.[12] A tandem 4*E*/4*Z* isomerization–[1,5] hydride shift–enolization reaction affords the key dienyl enol intermediate **11**. Finally, electrocyclization and aromatization deliver the phenolic derivative **4**. Three experimental observations reinforced this mechanistic picture (see the Supporting Information for further details): 1) MW irradiation of the 2*H*-pyran derivative **13**[3b] afforded phenol **15** by the well-established reversible electrocyclic ring opening to 1-oxatriene derivative **14** (Scheme 4)[13]; 2) MW irradiation of tetradeuterated PVE derivative **3q** delivered exclusively dideuterated salicylate **4q** (Scheme 5), excluding any hydrogen/deuterium (H/D) scrambling during the process; 3) (*E*)-dimethyl 2-(pent-2-en-1-ylidene)malonate did not react under the standardized conditions.[14] This finding highlights the importance of the acyl group, which modulates the acidity of the allylic hydrogen involved in the double-bond isomerization, to provide the required enol **11**. Preliminary calculations support this mechanistic picture (see the Supporting Information for details).

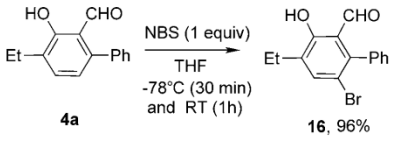


Scheme 4. Reversible electrocyclic ring opening of 2*H*-pyran derivative **13** to 1-oxatriene derivative **14**, to give phenol **15**.



Scheme 5. MW irradiation of tetradeuterated PVE derivative **3q** to give exclusive formation of dideuterated salicylate **4q**.

Finally, functionalization of the phenolic products can be easily carried out as exemplified by bromination of **4a** by treatment with *N*-bromosuccinimide (Scheme 6).



Scheme 6. Bromination of salicylaldehyde derivative **4a** with *N*-bromosuccinimide.

In summary, we have shown how readily available PVEs **3**, can be efficiently converted into convenient multifunctionalized aromatic products by using a microwave-assisted, novel domino process involving a key electrocyclization reaction. Efforts directed towards the application of this methodology in natural product synthesis are ongoing in our laboratory and will be reported in due course.

Experimental Section

Representative procedure: Propargyl vinyl ether **3a** (0.700 mmol), activated molecular sieves 4 Å (250 mg) and dry xylene (1 mL) were placed in a sealed microwave vial and the mixture was irradiated for 1 h in a single-mode microwave oven (300 W, 200 °C). The reaction mixture was filtered through a pad of celite using dichloromethane as a solvent. After removing the solvent at reduced pressure, the products were purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 95:5) to yield **4a** (76 %). M.p. 38.8–39.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.28 (t, ^3J(H,H) = 7.2 Hz, 3H), 2.74 (q, ^3J(H,H) = 7.2 Hz, 2H), 6.83 (d, ^3J(H,H) = 7.6 Hz, 1H), 7.34–7.36 (m, 2H), 7.43–7.46 (m, 4H), 9.84 (s, 1H), 12.22 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.6, 22.3, 117.4, 121.0, 128.0, 128.3, 130.1, 132.0, 135.7, 137.7, 145.0, 160.8, 197.4 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3021.7, 2974.3, 2933.3, 2880.2, 1641.7, 1426.1, 1316.5, 1222.2 cm^{-1}; MS (70 eV): *m*/*z* (%): 226 (100) $[M+H]^+$, 225 (27), 211 (62), 208 (22), 197 (20), 165 (14), 152 (14).; elemental analysis calcd (%) for $C_{15}H_{14}O_2$: C 79.62, H 6.24; found: C 79.68, H 6.22.

Acknowledgements

This research was supported by the Spanish MICINN and the European RDF (CTQ2008-06806-C02-01 and CTQ2008-06806-C02-02), the Spanish MSC ISCIII (RETICS RD06/0020/1046), FUNCIS (REDESFAC PI01/06). G.M.A. and L.C. thank the Spanish MEC for FPU and FPI grants, respectively. The authors thank Dr. T. Martín and Professor V. S. Martín for insightful discussions, Professor F. Cossío for mechanistic advice, and Anna Jurado for technical assistance.

Keywords: allenes · domino reactions · electrocyclic reactions · heterocycles · propargyl vinyl ethers

[1] B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 15978–15979.
[2] a) D. Tejedor, A. Santos-Expósito, D. González-Cruz, J. J. Marrero-Tellado, F. García-Tellado, *J. Org. Chem.* **2005**, *70*, 1042–1045; b) D. Tejedor, D. González-Cruz, F. García-Tellado, J. J. Marrero-Tellado, M. L. Rodríguez, *J. Am. Chem. Soc.* **2004**, *126*, 8390–8391; c) D. Tejedor, G. Méndez-Abt, F. García-Tellado, *Chem. Eur. J.* **2010**, *16*, 428–431; d) D. Tejedor, G. Méndez-Abt, F. García-Tellado, *Eur. J. Org. Chem.* **2010**, 6582–6587.
[3] a) M. H. Suhre, M. Reif, S. F. Kirsch, *Org. Lett.* **2005**, *7*, 3925–3927; b) H. Jiang, W. Yao, H. Cao, H. Huang, D. Cao, *J. Org. Chem.* **2010**, *75*, 5347–5350; c) H. Cao, H. Jiang, R. Mai, S. Zhu, C. Qi, *Adv. Synth. Catal.* **2010**, *352*, 143–152; d) H. Cao, H. Jiang, W Yao, X. Liu, *Org. Lett.* **2009**, *11*, 1931–1933; e) H. Menz, S. F. Kirsch, *Org. Lett.* **2006**, *8*, 4795–4797; f) D. Sherry, L. Maus, B. N. Laforteza, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 8132–8133; g) H. Wei, Y. Wang, B. Yue, P.-F. Xu, *Adv. Synth. Catal.* **2010**, *352*, 2450–2454; h) J. T. Binder, S. F. Kirsch, *Org. Lett.* **2006**, *8*, 2151–2153.
[4] PVEs with an ester group at the alkyne terminal position behave as catalytic inhibitors of the enzyme DNA topoisomerase II: L. León, C. Ríos-Luci, D. Tejedor, E. Pérez-Roth, J. C. Montero, A. Pandiel-

la, F. Garcia-Tellado, J. M. Padrón, *J. Med. Chem.* **2010**, *53*, 3835–3839.
[5] A. S. K. Hashmi, *Synthesis of Allenes by Isomerisation Reactions in Modern Allene Chemistry, Vol. 1* (Eds.: N. Krause, A. S. K. Hashmi), Wiley-VCH, Weinheim, **2004**.
[6] For a review on the synthesis of hydroxylated arenes, see: D. A. Alonso, C. Najera, I. M. Pastor, M. Yus, *Chem. Eur. J.* **2010**, *16*, 5274–5284.
[7] a) *Coumarins: Biology, Applications and Mode of Action* (Eds.: R. O'Kennedy, R. D. Thornes), Wiley, New York, **1997**; b) *Flavonoids: Chemistry, Biochemistry and Applications* (Eds.: O. M. Andersen, K. R. Markham), CRC Press, Boca Raton, **2006**; c) S. Bräse, A. Encinas, J. Keck, C. F. Ni, *Chem. Rev.* **2009**, *109*, 3903–3990.
[8] For selected reviews, see: a) K. C. Gupta, A. K. Sutar, *Coord. Chem. Rev.* **2008**, *252*, 1420–1450; b) J. F. Larrow, E. N. Jacobsen, *Top. Organomet. Chem.* **2004**, *6*, 123–152; c) T. Katsuki, *Chem. Soc. Rev.* **2004**, *33*, 410–421.
[9] For a precedent for this transformation, see the two-step synthesis of 1,2-dihydropyridines described in reference [2c].
[10] D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893–930.
[11] For an interesting discussion, see: G. Cozzi, *Chem. Soc. Rev.* **2004**, *33*, 410–421.
[12] For a theoretical study of the allene effect in [1,3] hydride shifts, see: F. Jensen, *J. Am. Chem. Soc.* **1995**, *117*, 7487–7492.
[13] a) A. F. Kluge, C. P. Lillya, *J. Am. Chem. Soc.* **1971**, *93*, 4458–4463; b) A. F. Kluge, C. P. Lillya, *J. Org. Chem.* **1971**, *36*, 1977–1988; c) Y. Zhu, S. Ganapathy, R. S. H. Liu, *J. Org. Chem.* **1992**, *57*, 1110–1113.
[14] For an earlier precedent for this type of experiment, see: W. Fischetti, R. F. Heck, *J. Organomet. Chem.* **1985**, *293*, 391–405.

Received: December 7, 2010
Published online: February 15, 2011

Supporting Information

A Microwave-assisted Domino Rearrangement of Propargyl Vinyl Ethers to Multifunctionalized Aromatic Platforms.

David Tejedor,*†§ Gabriela Méndez-Abt,†§ Leandro Cotos,†§ Miguel A. Ramírez‡ and Fernando García-Tellado*†§

Instituto de Productos Naturales y Agrobiología, CSIC, Astrofísico Francisco Sánchez 3, 38206 La Laguna, Tenerife, Spain, Instituto Canario de Investigación del Cáncer, and Instituto Universitario de Bio-Orgánica Antonio González, Universidad de La Laguna, Astrofísico Francisco Sánchez 2, 38204 La Laguna, Tenerife, Spain.

Contents:

General remarks. ^{1}H NMR and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded either at 400 and 100 MHz or at 500 and 125 MHz, respectively. Microwave reactions were conducted in sealed glass vessels (capacity 10 mL) using a CEM Discover microwave reactor. FT-IR spectra were measured in chloroform solutions. Flash column chromatography was carried out with silica gel 60 (particle size less than 0.020 mm) using appropriate mixtures of ethyl acetate and hexanes as eluent. All reactions were performed in oven-dried glassware under nitrogen unless otherwise stated. Dichloromethane was distilled from CaH_2. Xylene was dried with sodium/benzophenone prior to distillation. Molecular sieves (4Å, powder, activated, 2.5μm) were heated with a heat gun under high vacuum before used. Propargyl vinyl ethers (PVEs) were synthesized according to literature procedures (**3a**-**3n**, **3p**, **3r**),[1] and (**3o**, **3q**)[2]. When not commercially available, the propargyl alcohols were prepared by addition of the lithium acetylides onto the appropriate aldehydes following the literature procedure[3,4] with the exception of **3f** which was prepared by a modified procedure (reduction with $NaBH_4$).[5] All other materials were obtained from commercial suppliers and used as received. Products **3a**[6], **3n**[6], **3o**[7], **3q**[2], **4d**[9], **4q**[8]and **5a**[6] have been previously reported and all data are in accordance with those of the literature. Melting points are uncorrected.

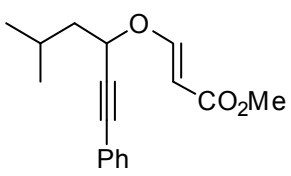
Experimental section.

Representative procedure for the synthesis of propargyl vinyl ethers (3a-3j, 3n, **3p, 3r)**. Triethylamine (0.30 mmol) was added to a solution of methyl propiolate (3.0 mmol) and 1-phenylhex-1-yn-3-ol (3.0 mmol) in dry CH_2Cl_2 (10 ml). The reaction mixture was stirred for 2 h. After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, n-hexane/EtOAc 90/10) to yield **3a** (95%).

Representative procedure for the ABB' 3CR synthesis of propargyl vinyl ethers (3o, 3q).[2] To a solution of methyl propiolate (3.90 mmol) and pentanal (2.34 mmol) in dry DCM (10 mL) cooled to 0 °C was added triethylamine (1.95 mmol). The reaction mixture was stirred for 2 h. After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, n-hexane/EtOAc 90/10) to yield **3o** (89%).

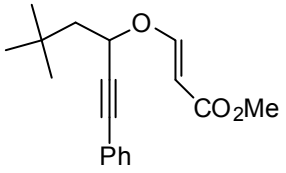
Representative procedure for the synthesis of propargyl vinyl ethers (3k-3m). Tributylphosphine (0.60 mmol) was added to a solution of ethyl 2-butynoate (3.0 mmol) and 1-phenylhex-1-yn-3-ol (3.0 mmol) in dry CH_2Cl_2 (10 ml). The reaction mixture was stirred for 2 h. After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, n-hexane/EtOAc 90/10) to yield **3k** (80%; 69%E isomer, 11% Z isomer). These PVEs are more difficult to characterize since they tend to isomerizes readily, especially in $CDCl_3$ and they have been used directly. Nevertheless, characterization and NMR spectra in C_6D_6 for **3m** are shown below.

(±) ((*E*)-methyl 3-((5-methyl-1-phenylhex-1-yn-3-yl)oxy)acrylate (3b): ^{1}H NMR ($CDCl_3$, 400 MHz):

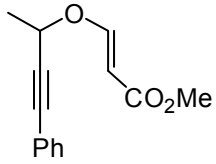


δ= 0.97 (d, ^{3}J(H,H) = 6.6, 6H), 1.72-1.79 (m, 1H), 1.84-1.94 (m, 2H), 3.69 (s, 3H), 4.81 (t, ^{3}J(H,H) = 6.9 Hz, 1H), 5.44 (d, ^{3}J(H,H) = 12.5, 1H), 7.29-7.32 (m, 3H), 7.41-7.44 (m, 2H), 7.70 (d, ^{3}J(H,H) = 12.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 22.3, 22.4, 24.6, 44.2, 51.0, 70.8, 85.5, 87.7, 98.5, 121.9, 128.3, 128.8, 131.8, 160.5, 168.0. IR ($CHCl_3$, cm^{-1}) 2957.2, 2870.0, 2234.2, 1705.4, 1641.8, 1625.2, 1333.8, 1294.4, 1215.9, 1195.8, 1132.0. Elemental analysis calcd. (%) for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.87; H, 7.56. MS (70 eV): *m/z* (%): 272 (0.6) [M^+], 171 (93), 143 (24), 129 (52), 128 (59), 115 (100), 91 (44).

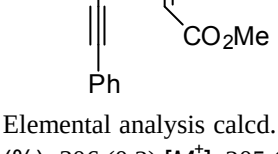
(±) (E)-methyl 3-(5,5-dimethyl-1-phenylhex-1-yn-3-yloxy)acrylate (3c): ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.00 (s, 9H), 1.85 (dd, ^3J(H,H) = 5.3 and 14.3 Hz, 1H), 1.96 (dd, ^3J(H,H) = 7.4 and 14.3 Hz, 1H), 3.70 (s, 3H), 4.84 (dd, ^3J(H,H) = 5.3 and 7.4 Hz, 1H), 5.43 (d, ^3J(H,H) = 12.5, 1H), 7.30-7.32 (m, 3H), 7.40-7.42 (m, 2H), 7.69 (d, ^3J(H,H) = 12.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 29.8, 30.2, 48.9, 51.1, 70.0, 86.5, 87.6, 98.6, 122.0, 128.3, 128.8, 131.7, 160.3, 168.1. IR ($CHCl_3$, cm^{-1}) 3017.4, 2958.7, 2235.0, 1703.2, 1622.9, 1439.2, 1211.8, 1191.9, 1138.0, 1049.6. Elemental analysis calcd. (%) for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.48; H, 7.81. MS (70 eV): *m/z* (%): 286 (0.6) [M^+], 215 (17), 185 (100), 128 (48), 115 (17), 57 (79).



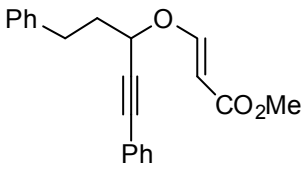
(±) (*E*)-methyl 3-((4-phenylbut-3-yn-2-yl)oxy)acrylate (3d): ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.64 (d, ^3J(H,H) = 6.6 Hz, 3H), 3.69 (s, 3H), 4.89 (q, ^3J(H,H) = 6.6 Hz, 1H), 5.43 (d, ^3J(H,H) = 12.5, 1H), 7.27-7.33 (m, 3H), 7.41-7.44 (m, 2H), 7.68 (d, ^3J(H,H) = 12.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 21.8, 51.1, 68.0, 86.1, 87.1, 98.6, 121.8, 128.3, 128.9, 131.8, 160.3, 168.0. IR ($CHCl_3$, cm^{-1}) 2992.6, 2121.6, 1704.1, 1624.8, 1375.8, 1266.6, 1152.8, 1090.3, 1047.8. Elemental analysis calcd. (%) for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 72.93; H, 6.01. MS (70 eV): *m/z* (%): 230 (0.24) [M^+], 171 (10), 130 (14), 129 (100), 128 (41), 127 (17), 77 (8.0).



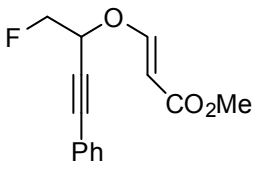
(±) (*E*)-methyl 3-((1,4-diphenylbut-3-yn-2-yl)oxy)acrylate (3e): ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 3.21-3.24 (m, 2H), 3.69 (s, 3H), 4.94 (t, ^3J(H,H) = 6.8 Hz, 1H), 5.43 (d, ^3J(H,H) = 12.6, 1H), 7.27-7.34 (m, 8H), 7.39-7.41 (m, 2H), 7.66 (d, ^3J(H,H) = 12.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 41.8, 51.1, 72.7, 84.8, 88.8, 98.8, 121.7, 127.1, 128.3, 128.4, 128.9, 129.7, 131.8, 135.7, 160.3, 168.0. IR ($CHCl_3$, cm^{-1}) 3016.1, 2233.9, 1704.4, 1642.9, 1492.3, 1439.1, 1190.6, 1138.2, 1050.0. Elemental analysis calcd. (%) for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.34; H, 5.87. MS (70 eV): *m/z* (%): 306 (0.2) [M^+], 205 (100), 178 (11), 127 (13), 91 (17), 77 (11).



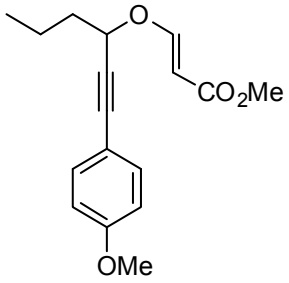
(±) (*E*)-methyl 3-((1,5-diphenylpent-1-yn-3-yl)oxy)acrylate (3f): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.17-2.33 (m, 2H), 2.80-2.92 (m, 2H), 3.70 (s, 3H), 4.72 (t, ^3J(H,H) = 6.5 Hz, 1H), 5.43 (d, ^3J(H,H) = 12.5 Hz, 1H), 7.20-7.23 (m, 3H), 7.28-7.35 (m, 5H), 7.43-7.46 (m, 2H), 7.69 (d, ^3J(H,H) = 12.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 31.1, 36.9, 51.1, 71.1, 85.1, 88.2, 98.7, 121.8, 126.3, 128.3, 128.3, 128.5, 128.6, 128.9, 131.9, 140.4, 160.5, 168.0. IR ($CHCl_3$, cm^{-1}) 3024.7, 2953.3, 2231.2, 1705.9, 1641.8, 1493.2, 1441.4, 1335.2, 1294.7, 1196.5, 1138.4. Elemental analysis calcd. (%) for $C_{21}H_{20}O_3$: C, 78.73; H, 6.29. Found: C, 78.55; H, 6.50. MS (70 eV): *m/z* (%):320 (0.14) [M^+], 219(24), 128(17), 117 (12), 115 (15), 91 (100).



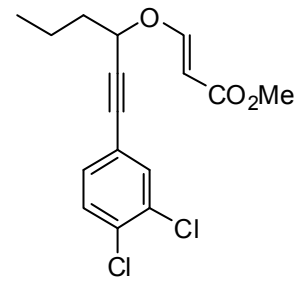
(±) (*E*)-methyl 3-((1-fluoro-4-phenylbut-3-yn-2-yl)oxy)acrylate (3g): ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 3.71 (s, 3H), 4.60-4.73 (m, 2H), 5.02-5.08 (m, 1H), 5.50 (d, ^3J(H,H) = 12.5, 1H), 7.32-7.37 (m, 3H), 7.43-7.45 (m, 2H), 7.68 (d, ^3J(H,H) = 12.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 51.2, 70.8 (d, J_{CF} = 24.7 Hz), 79.9 (d, J_{CF} = 12.7 Hz), 83.1 (d, J_{CF} = 181.6 Hz), 89.9 (d, J_{CF} = 1.4 Hz), 99.4, 120.9, 128.4, 129.4, 132.0, 159.9, 167.7. IR ($CHCl_3$, cm^{-1}) 3028.1, 2203.9, 1687.7, 1646.3, 1627.1, 1490.5, 1294.6, 1142.0, 1045.4. Elemental analysis calcd. (%) for $C_{14}H_{13}FO_3$: C, 67.73; H, 5.28. Found: C, 67.88; H, 4.87. MS (70 eV): *m/z* (%): 248 (0.34) [M^+], 189 (14), 147 (100), 127 (40), 105 (5.8), 77 (8.6), 51 (5.7).



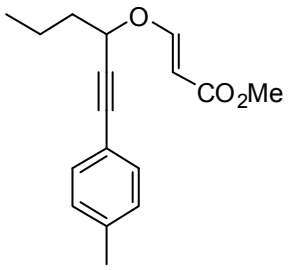
(±) (*E*)-methyl 3-((1-(4-methoxyphenyl)hex-1-yn-3-yl)oxy)acrylate (3h): ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 0.97 (t, ^{3}J(H,H) = 7.3, 3H), 1.53-1.55 (m, 2H), 1.86-1.90 (m, 2H), 3.69 (s, 3H), 3.79 (s, 3H), 4.76 (t, ^{3}J(H,H) = 6.6 Hz, 1H), 5.41 (d, ^{3}J(H,H) = 12.4, 1H), 6.82 (d, ^{3}J(H,H) = 9.1 Hz, 2H), 7.36 (d, ^{3}J(H,H) = 8.8 Hz, 2H), 7.68 (d, ^{3}J(H,H) = 12.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 13.6, 18.3, 37.5, 51.1, 55.3, 72.2, 84.0, 87.8, 98.3, 113.8, 113.9, 133.4, 160.0, 160.7, 168.2. IR ($CHCl_3$, cm^{-1}) 3017.3, 2963.3, 2876.0, 2229.7, 1702.6, 1642.9, 1510.3, 1292.5, 1250.0, 1192.1, 1143.8, 1033.9. Elemental analysis calcd. (%) for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.92; H, 6.71. MS (70 eV): *m/z* (%): 288 (1.1) [M^+], 229 (27), 187 (87), 172 (10), 158 (15), 145 (100), 143 (7.7), 121 (8.1), 115 (13).



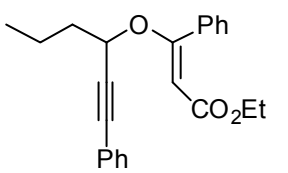
(±) (*E*)-methyl 3-((1-(3,4-dichlorophenyl)hex-1-yn-3-yl)oxy)acrylate (3i): ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 0.97 (t, ^{3}J(H,H) = 7.3, 3H), 1.51-1.56 (m, 2H), 1.86-1.91 (m, 2H), 3.70 (s, 3H), 4.74 (t, ^{3}J(H,H) = 6.6 Hz, 1H), 5.40 (d, ^{3}J(H,H) = 12.5, 1H), 7.24 (dd, ^{3}J(H,H) = 1.8 and 8.3 Hz, 1H), 7.38 (d, ^{3}J(H,H) = 8.3 Hz, 1H), 7.51 (d, ^{3}J(H,H) = 1.8 Hz, 1H), 7.64 (d, ^{3}J(H,H) = 12.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 14.0, 18.7, 37.6, 51.6, 72.0, 85.7, 87.8, 99.1, 122.2, 130.8, 131.4, 133.1, 133.8, 133.9, 160.8, 168.4. IR ($CHCl_3$, cm^{-1}) 2963.8, 2234.1, 1704.2, 1644.2, 1624.2, 1464.5, 1334.6, 1218.9, 1211.7, 1192.3, 1144.4, 1033.6. Elemental analysis calcd. (%) for $C_{16}H_{16}Cl_2O_3$: C, 58.73; H, 4.93. Found: C, 58.72; H, 5.06. MS (70 eV): *m/z* (%): 327 (0.5) [M^+], 225 (91), 196 (21), 190 (40), 183 (100), 159 (48), 148 (15), 126 (45), 103 (54), 79 (23), 71 (17), 69 (14).



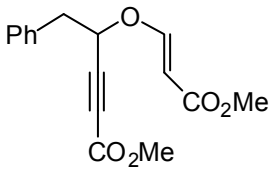
(±) (*E*)-methyl 3-((1-(p-tolyl)hex-1-yn-3-yl)oxy)acrylate (3j): ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 0.97 (t, ^{3}J(H,H) = 7.6, 3H), 1.54-1.57 (m, 2H), 1.87-1.91 (m, 2H), 3.26 (s, 3H), 4.76 (t, ^{3}J(H,H) = 6.6 Hz, 1H), 5.42 (d, ^{3}J(H,H) = 12.4, 1H), 7.10 (d, ^{3}J(H,H) = 7.8 Hz, 2H), 7.31 (d, ^{3}J(H,H) = 8.1 Hz, 2H), 7.68 (d, ^{3}J(H,H) = 12.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 13.6, 18.3, 21.4, 37.5, 51.0, 72.1, 84.7, 88.0, 98.4, 118.8, 129.0, 131.7, 139.0, 160.7, 168.1. IR ($CHCl_3$, cm^{-1}) 3017.7, 2963.3, 2875.8, 2231.5, 1907.7, 1703.2, 1643.2, 1623.1, 1510.2, 1438.4, 1334.6, 1211.7, 1192.4, 1143.9, 1051.6. Elemental analysis calcd. (%) for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.94; H, 7.34. MS (70 eV): *m/z* (%): 272 (1.5) [M^+], 213 (40), 171 (100), 156 (52), 143 (60), 129 (100), 115 (45), 105 (57), 79 (17).



(±) (*E*)-ethyl 3-phenyl-3-(1-phenylhex-1-yn-3-yloxy)acrylate (3m): major isomer, ^{1}H NMR (C_6D_6, 400 MHz): δ= 0.99 (t, ^{3}J(H,H) = 7.4 Hz, 3H), 1.12 (t, ^{3}J(H,H) = 7.1 Hz, 3H), 1.71-1.89 (m, 2H), 2.09-2.27 (m, 2H), 4.18 (q, ^{3}J(H,H) = 7.1 Hz, 2H), 5.77 (t, ^{3}J(H,H) = 6.4, 1H), 6.02 (s, 1H), 6.97-7.01 (m, 3H), 7.09-7.14 (m, 3H), 7.36-7.38 (m, 2H), 7.65-7.68 (m, 2H). ^{13}C NMR (C_6D_6, 100 MHz): δ= 14.0, 14.4, 18.8, 38.3, 59.7, 72.7, 87.7, 87.9, 103.0, 123.1, 127.9, 128.4, 128.5, 128.6, 130.2, 131.9, 136.9, 164.9, 165.7. MS (70 eV): *m/z* (%): 348 (4.6) [M^+], 305 (18), 275 (90), 243 (38), 233 (35), 157 (41), 115 (100), 105 (85), 91 (33), 77(53).

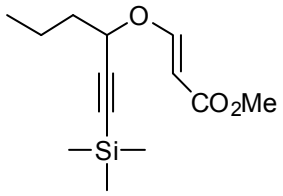


(±) (*E*)-methyl 4-(3-methoxy-3-oxoprop-1-enyloxy)-5-phenylpent-2-ynoate (3p): ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 3.16 (dd, ^{3}J(H,H) = 14.0, 6.1 Hz, 1H), 3.21 (dd, ^{3}J(H,H) = 14.0, 7.2 Hz, 1H), 3.68 (s, 3H), 3.77 (s, 3H), 4.78 (dd, ^{3}J(H,H) = 7.2, 6.1 Hz, 1H), 5.36 (d, ^{3}J(H,H) = 12.5, 1H), 7.22-7.34 (m, 5H), 7.49 (d, ^{3}J(H,H) = 12.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 40.9, 51.2, 52.9, 71.2, 79.2, 82.3, 99.5, 127.5, 128.6, 129.5, 134.6, 153.0, 159.6, 167.5. IR ($CHCl_3$, cm^{-1}) 3026.4, 2955.0, 2244.8, 1715.2, 1645.5, 1627.0, 1437.6, 1264.0, 1218.1, 1139.1. HRMS (m/z):



$[M]^+$ calcd for $C_{16}H_{16}O_5$, 288.0998; found, 288.0988. MS (70 eV): *m/z* (%): 288 (5.0) [M^+], 187 (43), 159 (60), 155 (42), 128 (100), 127 (51), 91(67).

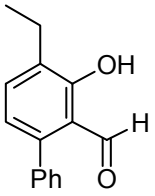
(±) (E)-methyl 3-((1-(trimethylsilyl)hex-1-yn-3-yl)oxy)acrylate (3r): ^{1}H NMR ($CDCl_3$, 400 MHz): δ



0.14 (s, 9H), 0.92 (t, ^3J(H,H) = 7.4 Hz, 3H), 1.40-1.48 (m, 2H), 1.72-1.82 (m, 2H), 3.67 (s, 3H), 4.51 (t, ^3J(H,H) = 6.6 Hz, 1H), 5.33 (d, ^3J(H,H) = 12.5 Hz, 1H), 7.60 (d, ^3J(H,H) = 12.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ -0.36, 13.5, 18.2, 37.3, 51.0, 71.9, 93.3, 98.4, 101.5, 160.5, 168.1. IR ($CHCl_3$, cm^{-1}) 3022.4, 2962.9, 1707.7, 1643.4, 1438.0, 1252.9, 1214.0, 1128.0, 1048.8. Elemental analysis calcd. (%) for $C_{13}H_{22}O_3Si$: C, 61.38; H, 8.72. Found: C, 61.17; H, 8.57. MS (70 eV): *m/z* (%): 254 (2.5) [M^+], 239 (11), 225 (10), 195 (33), 159 (10), 153 (44), 137 (67), 125 (30), 109 (58), 97 (99), 93 (12), 89 (25), 83 (39), 73 (100).

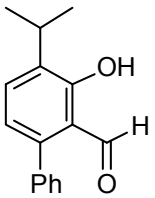
Representative procedure for the microwave-assisted reaction of propargyl vinyl ether 3a-r. Propargyl vinyl ether **3a** (0.700 mmol) and activated molecular sieves 4Å (250mg) in dry xylene (1 mL) were placed in a microwave-special closed vial and the solution was irradiated for 1 hour in a single-mode microwave oven (300 Watt, 200 ºC). The reaction mixture was filtrated through a pad of celite using dichloromethane as solvent. After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, n-hexane/EtOAc 95/5) to yield **4a** (76%).

4-ethyl-3-hydroxybiphenyl-2-carbaldehyde (4a): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.28 (t, ^3J(H,H) =



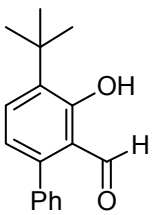
7.2 Hz, 3H), 2.74 (q, ^3J(H,H) = 7.2 Hz, 2H), 6.83 (d, ^3J(H,H) = 7.6 Hz, 1H), 7.34-7.36 (m, 2H), 7.43-7.46 (m, 4H), 9.84 (s, 1H), 12.22 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.6, 22.3, 117.4, 121.0, 128.0, 128.3, 130.1, 132.0, 135.7, 137.7, 145.0, 160.8, 197.4. IR ($CHCl_3$, cm^{-1}) 3021.7, 2974.3, 2933.3, 2880.2, 1641.7, 1426.1, 1316.5, 1222.2. Elemental analysis calcd. (%) for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.68; H, 6.22. MS (70 eV): *m/z* (%): 226 (100) [M^+], 225 (27), 211 (62), 208 (22), 197 (20), 165 (14), 152 (14). Mp = 38.8-39.4 ºC.

3-hydroxy-4-isopropylbiphenyl-2-carbaldehyde (4b): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.28 (d,

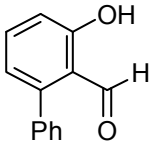


^3J(H,H) = 6.8 Hz, 6H), 3.37-3.47 (m, 1H), 6.85(d, ^3J(H,H) = 7.6 Hz, 1H), 7.34-7.38 (m, 2H), 7.41-7.48 (m, 4H), 9.83 (s, 1H), 12.29 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.3, 26.3, 117.5, 121.1, 128.0, 128.3, 130.1, 133.2, 136.4, 137.8, 144.9, 160.4, 197.5. IR ($CHCl_3$, cm^{-1}) 3026.9, 2965.6, 2878.5, 1638.8, 1465.8, 1425.1, 1397.5, 1317.3, 1253.8, 1218.1. Elemental analysis calcd. (%) for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.95; H, 6.93. MS (70 eV): *m/z* (%): 240 (74) [M^+], 225 (100), 207 (58), 179 (14), 178 (18), 152 (12).

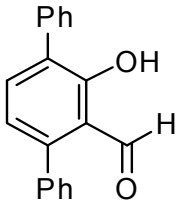
4-tert-butyl-3-hydroxybiphenyl-2-carbaldehyde (4c): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.48 (s, 9H),



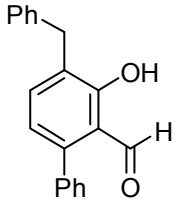
6.83(d, ^3J(H,H) = 8.1 Hz, 1H), 7.36 (dd, ^3J(H,H) = 2.0 and 7.6 Hz, 2H), 7.44 (m, 3H), 7.55 (d, ^3J(H,H) = 8.1 Hz, 1H), 9.85 (s, 1H), 12.74 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 29.2, 34.8, 117.8, 120.7, 128.0, 128.3, 130.1, 133.7, 137.4, 137.6, 145.3, 162.3, 197.7. IR ($CHCl_3$, cm^{-1}) 3012.9, 2962.7, 2910.2, 1636.1, 1484.0, 1423.6, 1393.3, 1259.0, 1214.3, 1195.9, 1143.0, 1110.1, 913.2. Elemental analysis calcd. (%) for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.49; H, 7.00. MS (70 eV): *m/z* (%): 254 (47) [M^+], 239 (100), 221 (45), 178 (12), 165 (12), 115 (8.0). Mp = 53.3-53.9 ºC.

3-hydroxybiphenyl-2-carbaldehyde (4d)[9]: 

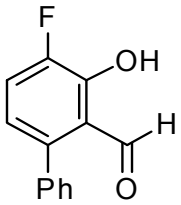
^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.88(dd, ^3J(H,H) = 7.3, 1.0 Hz, 1H), 6.99 (d, ^3J(H,H) = 8.6 Hz, 1H), 7.35-7.37 (m, 2H), 7.41-7.48 (m, 3H), 7.52 (pseudot, ^3J(H,H) = 8.0 Hz, 1H), 9.83 (s, 1H), 11.91 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 116.9, 118.0, 121.5, 128.3, 128.4, 130.0, 136.6, 137.5, 147.5, 162.8, 197.1.

3-hydroxy-4-phenylbiphenyl-2-carbaldehyde (4e): 

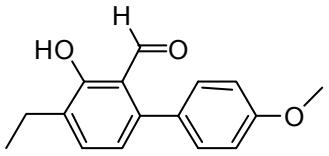
^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.98 (d, ^3J(H,H) = 7.6 Hz, 1H), 7.38-7.49 (m, 8H), 7.61-7.65 (m, 3H), 9.90 (s, 1H), 12.50 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 118.1, 121.5, 127.6, 128.29, 128.34, 128.5, 129.3, 129.7, 130.1, 136.4, 137.3, 137.4, 146.8, 160.1, 197.5. IR ($CHCl_3$, cm^{-1}) 3026.6, 2889.8, 1640.4, 1394.0, 1262.0, 1214.1, 1086.3. Elemental analysis calcd. (%) for $C_{19}H_{14}O_2$: C, 83.19; H, 5.14. Found: C, 83.39; H, 5.07. MS (70 eV): *m/z* (%): 274 (100) [M^+], 255 (11), 215 (12), 128 (8.1), 101 (3.5).

4-benzyl-3-hydroxybiphenyl-2-carbaldehyde (4f): 

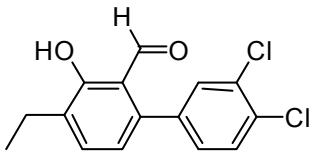
^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.08 (s, 2H), 6.82 (d, ^3J(H,H) = 7.6 Hz, 1H), 7.22-7.27 (m, 1H), 7.31-7.37 (m, 7H), 7.42-7.48 (m, 3H), 9.85 (s, 1H), 12.30 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 34.9, 117.6, 121.1, 126.2, 128.1, 128.3, 128.5, 129.0, 129.2, 130.1, 136.9, 137.5, 139.9, 145.6, 160.6, 197.3. IR ($CHCl_3$, cm^{-1}) 3027.0, 2889.3, 1641.1, 1493.7, 1424.5, 1316.2, 1252.3. Elemental analysis calcd. (%) for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found: C, 83.46; H, 5.51. MS (70 eV): *m/z* (%): 288 (100) [M^+], 287 (18), 270 (22), 269 (61), 91 (24).

4-fluoro-3-hydroxybiphenyl-2-carbaldehyde (4g): 

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.83 (dd, ^3J(H,H) = 8.3 Hz, ^3J(H,F) = 4.3 Hz, 1H), 7.32-7.37 (m, 3H), 7.44-7.46 (m, 3H), 9.80 (s, 1H), 11.90 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 119.4 (d, J_{CF} = 3.5 Hz), 120.7 (d, J_{CF} = 5.7 Hz), 122.2 (d, J_{CF} = 17.0 Hz), 128.4, 128.5, 130.1, 136.7, 142.7 (d, J_{CF} = 4.2 Hz), 150.3 (d, J_{CF} = 248.7 Hz), 150.9 (d, J_{CF} = 12.7 Hz), 197.3. IR ($CHCl_3$, cm^{-1}) 3030.1, 1715.9, 1654.5, 1478.8, 1448.2, 1434.8, 1392.6, 1248.1, 1222.2, 1209.7. Elemental analysis calcd. (%) for $C_{13}H_9FO_2$: C, 72.22; H, 4.20. Found: C, 72.28; H, 4.34. MS (70 eV): *m/z* (%): 216 (100) [M^+], 215 (86), 188 (16), 170 (9.5), 139 15), 133 (4.8), 63 (1.5). Mp = 65.8-66.4 ºC.

4-ethyl-3-hydroxy-4'-methoxybiphenyl-2-carbaldehyde (4h): 

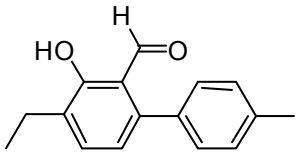
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.26 (t, ^3J(H,H) = 7.5 Hz, 3H), 2.72 (q, ^3J(H,H) = 7.5 Hz, 2H), 3.85 (s, 3H), 6.80 (d, ^3J(H,H) = 7.6 Hz, 1H), 6.97 (d, ^3J(H,H) = 8.8 Hz, 2H), 7.27 (d, ^3J(H,H) = 8.8 Hz, 2H), 7.39 (d, ^3J(H,H) = 8.8 Hz, 1H), 9.85 (s, 1H), 12.20 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.6, 22.2, 55.3, 113.8, 117.5, 121.0, 130.0, 131.2, 131.5, 135.7, 144.7, 159.6, 160.8, 197.5. IR ($CHCl_3$, cm^{-1}) 3016.1, 2968.3, 1638.4, 1517.1, 1429.5, 1246.2, 1211.2, 1033.7. Elemental analysis calcd. (%) for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.99; H, 6.36. MS (70 eV): *m/z* (%): 256 (100) [M^+], 241 (48), 213 (12), 115 (7.6), 89 (2.7), 77 (4.2).

3',4'-dichloro-4-ethyl-3-hydroxybiphenyl-2-carbaldehyde (4i): 

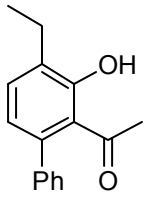
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25 (t, ^3J(H,H) = 7.6 Hz, 3H), 2.72 (q, ^3J(H,H) = 7.6 Hz, 2H), 6.77 (d, ^3J(H,H) = 7.6 Hz, 1H), 7.18 (dd, ^3J(H,H) = 8.1, 2.0 Hz, 1H), 7.41 (d, ^3J(H,H) = 7.6 Hz, 1H), 7.46 (d, ^3J(H,H) = 2.0 Hz, 1H), 7.51 (d, ^3J(H,H) = 8.1 Hz, 1H), 9.80 (s, 1H), 12.16 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.5, 22.3, 117.1, 120.9, 129.3, 130.3, 131.6, 132.6, 132.7, 133.1, 135.8,

137.7, 142.0, 161.0, 196.3. IR ($CHCl_3$, cm^{-1}) 3017.9, 2974.1, 2880.3, 1644.0, 1544.2, 1460.7, 1398.0, 1254.3, 1218.1, 1213.4, 1134.3, 1032.8. Elemental analysis calcd. (%) for $C_{15}H_{12}Cl_2O_2$: C, 61.04; H, 4.10. Found: C, 61.09; H, 4.29. MS (70 eV): *m/z* (%): 294 (100) [M^+], 279 (70), 259 (18), 241 (29), 215 (6.0), 186 (4.9), 152 (19), 105 (2.9), 77 (2.2), 63 (2.9). Mp = 107.8-108.6 ºC.

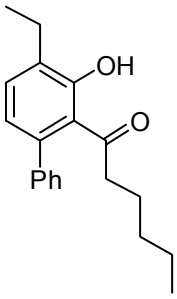
4-ethyl-3-hydroxy-4'-methylbiphenyl-2-carbaldehyde (4j): ^1H NMR ($CDCl_3$, 400 MHz): δ 1.25 (t, $^3J(H,H)$ = 7.6 Hz, 3H), 2.40 (s, 3H), 2.71 (q, $^3J(H,H)$ = 7.6 Hz, 2H), 6.80 (d, $^3J(H,H)$ = 7.6 Hz, 1H), 7.23 (pseudo s, 4H), 7.39 (d, $^3J(H,H)$ = 7.6 Hz, 1H), 9.83 (s, 1H), 12.20 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.6, 21.1, 22.3, 117.5, 121.0, 129.0, 130.0, 131.7, 134.8, 135.7, 137.9, 145,.1, 160.8, 197.5. IR ($CHCl_3$, cm^{-1}) 3026.3, 2969.2, 1638.5, 1517.0, 1428.3, 1397.5, 1317.5, 1215.4, 1071.1. Elemental analysis calcd. (%) for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.05; H, 6.63. MS (70 eV): *m/z* (%): 240 (100) [M^+], 225 (67), 207 (22), 165 (12), 152 (11), 115 (8.4), 105 (4.8), 77 (4.4), 63 (4.3).



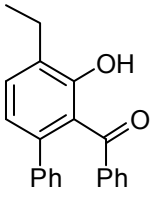
1-(4-ethyl-3-hydroxybiphenyl-2-yl)ethanone (4k): ^1H NMR ($CDCl_3$, 400 MHz): δ= 1.26 (t, $^3J(H,H)$ = 7.6 Hz, 3H), 1.85 (s, 3H), 2.73 (q, $^3J(H,H)$ = 7.6 Hz, 2H), 6.79 (d, $^3J(H,H)$ = 7.6, 1H), 7.30-7.33 (m, 3H), 7.37-7.44 (m, 3H), 11.91 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 13.7, 22.9, 31.8, 120.7, 121.6, 127.9, 128.6, 129.0, 132.0, 133.1, 142.2, 142.3, 159.0, 207.5. IR ($CHCl_3$, cm^{-1}) 3018.8, 2972.0, 1624.5, 1417.4, 1360.9, 1312.2, 1266.1, 1231.0. Elemental analysis calcd. (%) for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.04; H, 6.63. MS (70 eV): *m/z* (%): 240 (100) [M^+], 239 (50), 225 (58), 207 (15), 197 (29), 178 (14), 152 (15).



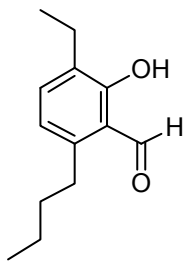
1-(4-ethyl-3-hydroxybiphenyl-2-yl)hexan-1-one (4l): ^1H NMR ($CDCl_3$, 400 MHz): δ= 0.74 (t, $^3J(H,H)$ = 7.2 Hz, 3H), 0.86-0.94 (m, 2H), 1.01-1.10 (m, 2H), 1.25 (t, $^3J(H,H)$ = 7.4, 3H), 1.33-1.40 (m, 2H), 2.01-2.05 (m, 2H), 2.72 (q, $^3J(H,H)$ = 7.4, 2H), 6.80 (d, $^3J(H,H)$ = 7.4 Hz, 1H), 7.28-7.32 (m, 3H), 7.37-7.43 (m, 3H), 11.28 (s,1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 13.7, 13.8, 22.1, 22.9, 22.5, 31.1, 43.5, 121.3, 121.6, 127.8, 128.6, 129.0, 131.9, 132.6, 141.4, 142.2, 158.0, 211.1. IR ($CHCl_3$, cm^{-1}) 2963.3, 2933.7, 1626.8, 1413.9, 1232.6. Elemental analysis calcd. (%) for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.11; H, 8.13. MS (70 eV): *m/z* (%): 296 (29) [M^+], 239 (18), 225 (100), 197 (19), 152 (10).



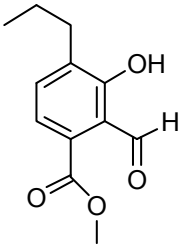
(4-ethyl-3-hydroxybiphenyl-2-yl)(phenyl)methanone (4m): ^1H NMR ($CDCl_3$, 400 MHz): δ= 1.32 (t, $^3J(H,H)$ = 7.4 Hz, 3H), 2.79 (q, $^3J(H,H)$ = 7.4 Hz, 2H), 6.94 (d, $^3J(H,H)$ = 7.7, 1H), 6.97 (tt,, $^3J(H,H)$ = 6.6, 1.3 Hz, 1H), 7.01-7.07 (m, 4H), 7.10-7.13 (m, 2H), 7.18 (tt, $^3J(H,H)$ = 6.6, 1.3 Hz, 1H), 7.36-7.40 (m, 3H), 9.84 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 13.8, 23.0, 120.5, 121.4, 127.0, 127.5, 128.0, 129.4, 129.6, 131.5, 131.9, 132.8, 139.3, 141.0, 141.8, 157.4, 202.1. IR ($CHCl_3$, cm^{-1}) 3028.1, 1613.9, 1449.2, 1410.7, 1329.3, 1279.2, 1216.5. Elemental analysis calcd. (%) for $C_{21}H_{18}O_2$: C, 83.42; H, 6.00. Found: C, 83.40; H, 6.01. MS (70 eV): *m/z* (%): 302 (100) [M^+], 301 (96), 225 (21), 209 (14), 105 (24), 77 (30). Mp = 103.9-104.8 ºC.



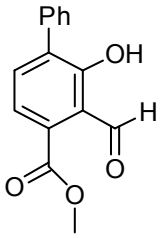
6-butyl-3-ethyl-2-hydroxybenzaldehyde (4n): ^1H NMR ($CDCl_3$, 400 MHz): δ 0.93 (t, $^3J(H,H)$ = 7.6 Hz, 3H), 1.20 (t, $^3J(H,H)$ = 7.6 Hz, 3H), 1.34-1.43 (m, 2H), 1.56-1.64 (m, 2H), 2.63 (q, $^3J(H,H)$ = 7.6 Hz, 2H), 2.85-2.89 (m, 2H), 6.63 (d, $^3J(H,H)$ = 7.6 Hz, 1H), 7.27 (d, $^3J(H,H)$ = 7.6 Hz, 1H), 10.28 (s, 1H), 12.21 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.6, 13.8, 22.1, 22.5, 31.4, 35.4, 117.3, 120.6, 130.7, 136.5, 144.7, 161.4, 195.4. IR ($CHCl_3$, cm^{-1}) 2962.9, 2934.0, 1638.5, 1428.0, 1312.5, 1287.9. Elemental analysis calcd. (%) for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.60; H, 8.94. MS (70 eV): *m/z* (%): 206 (84) [M^+], 177 (59), 173 (53), 163 (20), 159 (100), 135 (22), 91 (34).



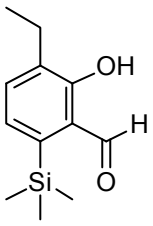
methyl 2-formyl-3-hydroxy-4-propylbenzoate (4o): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.94 (t, ^3J(H,H) = 7.4 Hz, 3H), 1.59-1.64 (m, 2H), 2.63-2.67 (m, 2H), 3.92 (s, 3H), 7.36 (d, ^3J(H,H) = 8.0 Hz, 1H), 7.41 (d, ^3J(H,H) = 8.0 Hz, 1H), 10.65 (s, 1H), 12.53 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.8, 22.1, 31.6, 52.6, 117.7, 121.9, 130.9, 135.5, 136.9, 161.5, 166.4, 197.9. IR ($CHCl_3$, cm^{-1}) 3024.8, 2961.7, 2873.1, 1715.1, 1643.8, 1432.0, 1296.9, 1222.8, 1209.8. Elemental analysis calcd. (%) for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.99; H, 6.17. MS (70 eV): *m/z* (%): 222 (47) [M^+], 207 (84), 190 (22), 165 (100), 161 (22), 77 (25). Mp = 30.5-32.3 ºC.



methyl 3-formyl-2-hydroxybiphenyl-4-carboxylate (4p): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.97 (s, 3H), 7.37-7.47 (m, 3H), 7.55-7.62 (m, 4H), 10.71 (s, 1H), 12.79 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 52.8, 118.5, 122.2, 128.2, 128.3, 129.3, 132.4, 135.2, 135.8, 136.4, 160.6, 166.2, 197.9. IR ($CHCl_3$, cm^{-1}) 3017.7, 2955.5, 1717.3, 1645.8, 1449.6, 1435.8, 1423.1, 1303.2, 1284.3, 1255.1, 1209.4, 1151.4. Elemental analysis calcd. (%) for $C_{15}H_{12}O_4$: C, 70.31; H, 4.72. Found: C, 70.40; H, 4.66. MS (70 eV): *m/z* (%): 256 (74) [M^+], 241 (100), 228 (25), 197 (68), 168 (24), 141 (41), 139 (56), 115 (37). Mp = 100.9-101.8 ºC.

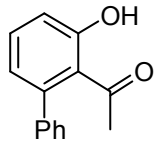


3-ethyl-2-hydroxy-6-(trimethylsilyl)benzaldehyde (4r): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.38 (s, 9H), 1.22 (t, ^3J(H,H) = 7.6 Hz, 3H), 2.68 (q, ^3J(H,H) = 7.6 Hz, 2H), 7.06 (d, ^3J(H,H) = 7.3 Hz, 1H), 7.34 (d, ^3J(H,H) = 7.3 Hz, 1H), 10.28 (s, 1H), 12.12 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 1.06, 13.5, 22.3, 123.4, 126.1, 134.4, 135.1, 143.4, 161.8, 197.0. IR ($CHCl_3$, cm^{-1}) 2966.8, 2882.3, 1716.4, 1639.0, 1419.2, 1306.8, 1256.5, 1132.4. Elemental analysis calcd. (%) for $C_{12}H_{18}O_2Si$: C, 64.82; H, 8.16. Found: C, 64.70; H, 8.11. MS (70 eV): *m/z* (%): 222 (14) [M^+], 208 (28), 207 (100), 192 (10), 177 (3.7), 149 (3.7), 91 (4.6).



Synthesis of 15 from product 13. 2*H*-pyran **13**[10] (0.700 mmol) and activated molecular sieves 4Å (250mg) in dry xylene (5 mL) were placed in a microwave-special closed vial and the solution was irradiated for 1 hour in a single-mode microwave oven (300 Watt, 200 ºC). The reaction mixture was filtrated through a pad of celite using dichloromethane as solvent. After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, n-hexane/EtOAc 95/5) to yield **15** (48%).

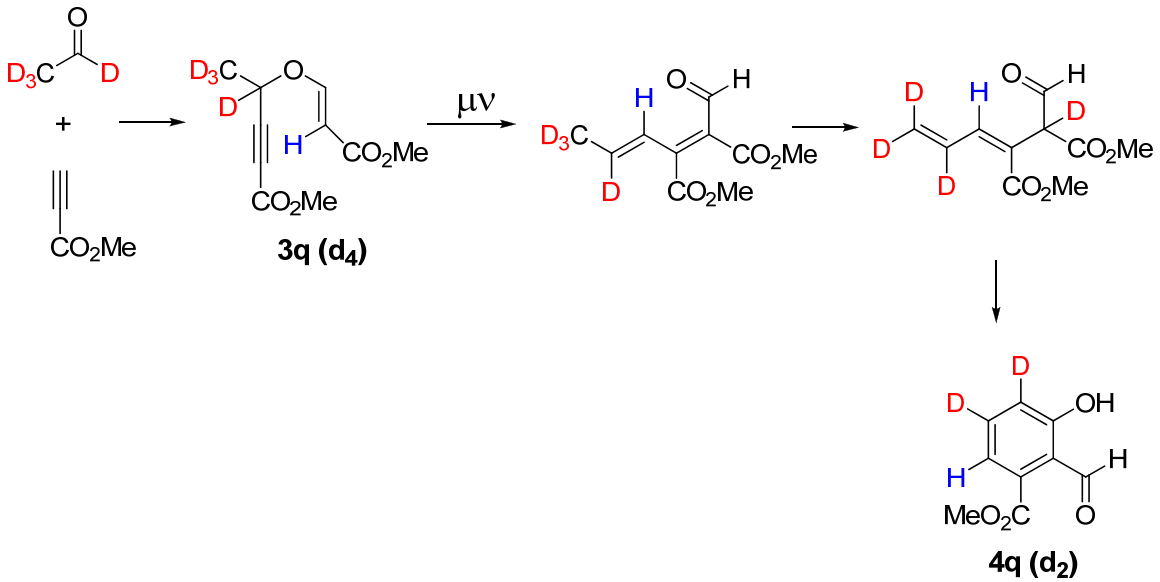
1-(3-hydroxybiphenyl-2-yl)ethanone (15)[11]: ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.84 (s, 3H), 6.84 (dd, ^3J(H,H) = 7.6, 1.1 Hz, 1H), 6.99 (dd, ^3J(H,H) = 8.4, 1.1 Hz, 1H), 7.31-7.34 (m, 2H), 7.38-7.44 (m, 4H), 11.60 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 31.6, 117.2, 121.3, 122.2, 128.2, 128.7, 129.0, 133.9, 142.0, 144.7, 161.0, 207.1. IR ($CHCl_3$, cm^{-1}) 3396.0, 3022.2, 1632. 5, 1441.5. Elemental analysis calcd. (%) for $C_{14}H_{12}O_2$: C, 79.22 H, 5.70. Found: C, 79.35; H, 5.98. MS (70 eV): *m/z* (%): 212. (98) [M^+], 198 (14), 197 (100), 141 (20), 115 (23).

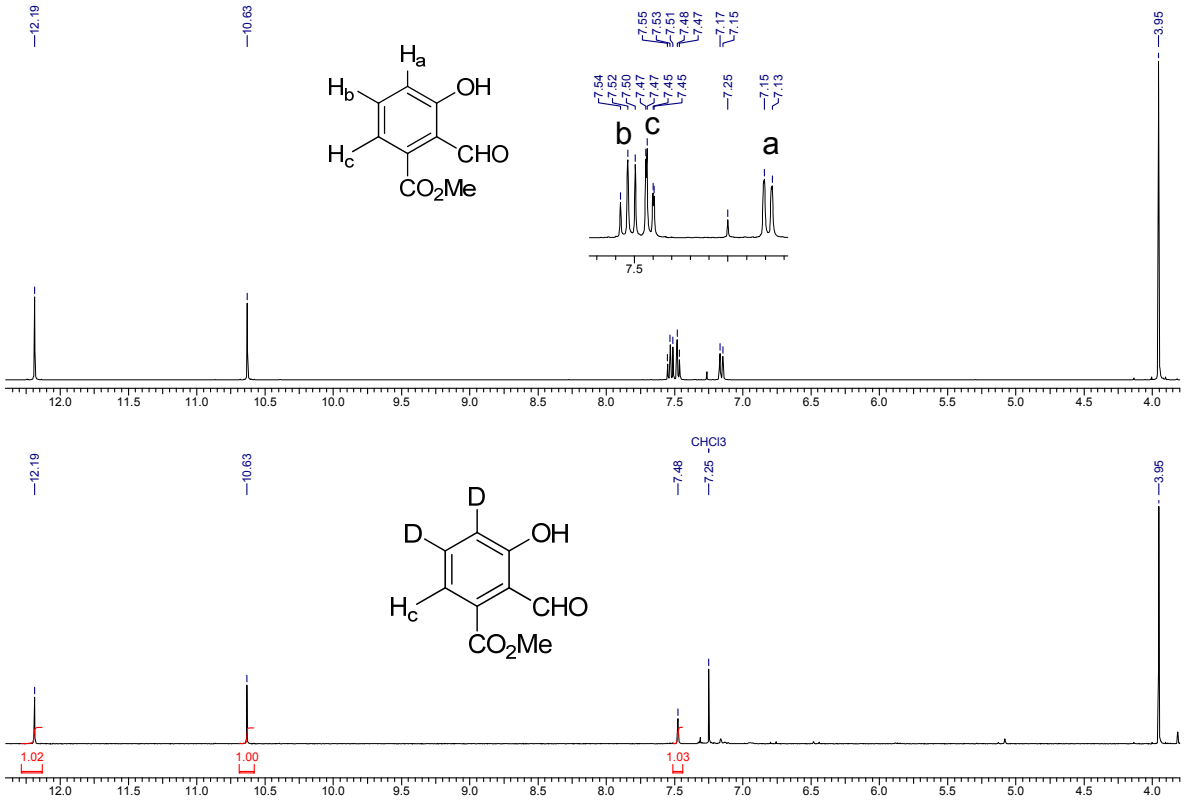


Bromination of 4a; synthesis of 16. NBS (185.0 mg, 1.04 mmol) in 2 mL of THF was added slowly to a solution of **4a** (235.2 mg, 1.04 mmol) in 5 ml of THF at -78ºC. The reaction was stirred at -78ºC for 30 min and then 1 hr at room temperature. After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, n-hexane/EtOAc 97/3) to yield **16** (305.7 mg, 96%).

6-bromo-4-ethyl-3-hydroxybiphenyl-2-carbaldehyde (16): (96% yield) ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.26 (t, ^{3}J(H,H) = 7.5 Hz, 3H), 2.71 (q, ^{3}J(H,H) = 7.5 Hz, 2H), 7.24-7.26 (m, 2H), 7.43-7.48 (m, 3H), 7.62 (s,1H) 9.50 (s, 1H), 12.19 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 13.4, 22.1, 113.1, 119.6, 128.3, 128.5, 130.2, 134.6, 136.4, 139.5, 143.7, 160.1, 197.4. IR ($CHCl_3$, cm^{-1}) 3027.8, 3013.3, 2974.3, 2935.6, 2892.0, 1641.1, 1607.1, 1541.5, 1498.3, 1446.3, 1415.1, 1300.4, 1279.5, 1237.7, 1222.8, 1072.2. Elemental analysis calcd. (%) for $C_{15}H_{13}BrO_2$: C, 59.04; H, 4.44. Found: C, 59.03; H, 4.29. MS (70 eV): *m/z* (%): 307 (16), 306 (97), 304 (100) [M^+], 291 (23), 289 (27), 225 (34), 209 (21), 207 (51), 181 (21), 165 (21), 153 (29), 152 (47), 139(20). Mp = 53.9-54.6 ºC.

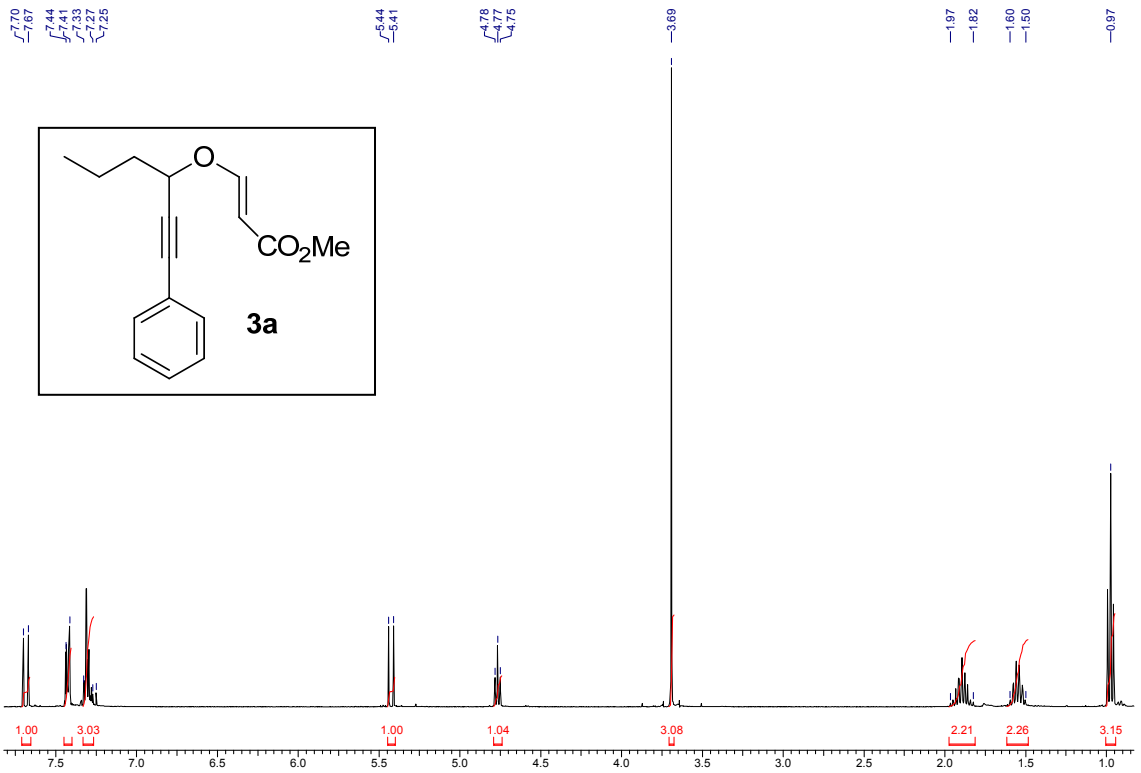
Synthesis of partially deuterated product 4q. 3q (d_4) was synthesized accordingly[2] from methyl propiolate and acetaldehyde-d_4. **3q (d_4)** (20 mg) and activated molecular sieves 4Å (100mg) in dry xylene (1 mL) were placed in a microwave-special closed vial and the solution was irradiated for 1 hour in a single-mode microwave oven (300 Watt, 200 ºC). The reaction mixture was filtrated through a pad of celite using dichloromethane as solvent. After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, n-hexane/EtOAc 95/5) to yield **4q (d_4)**.

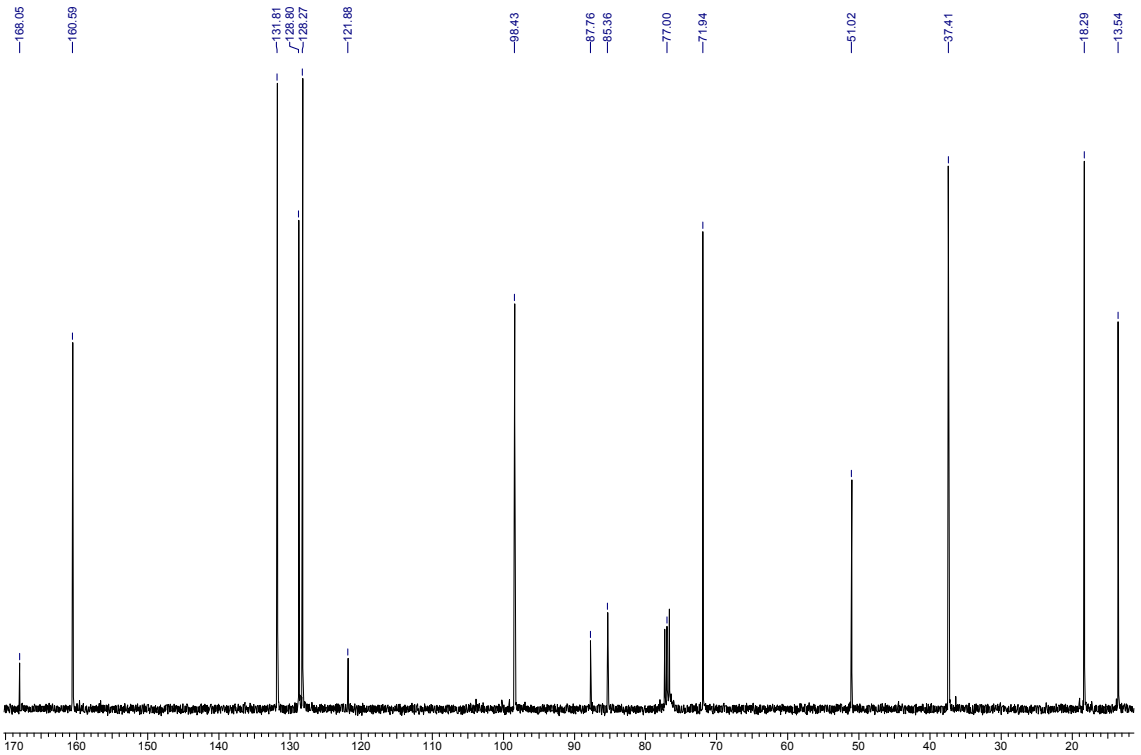


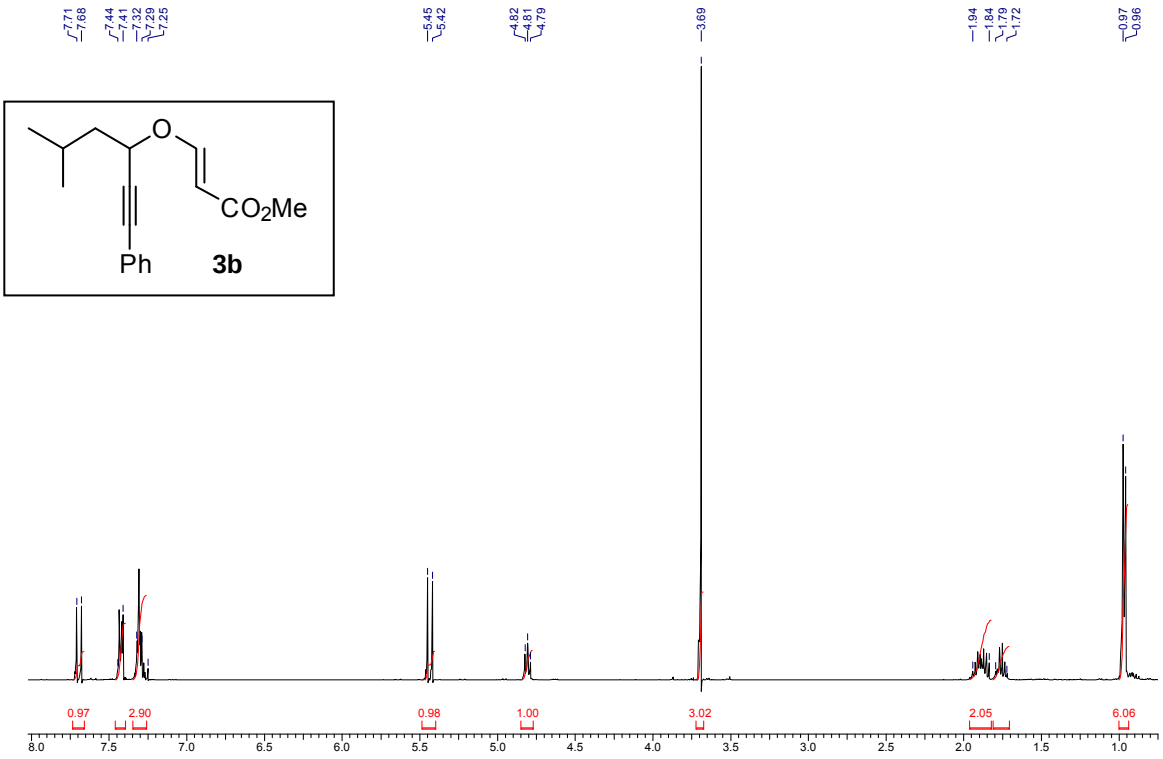


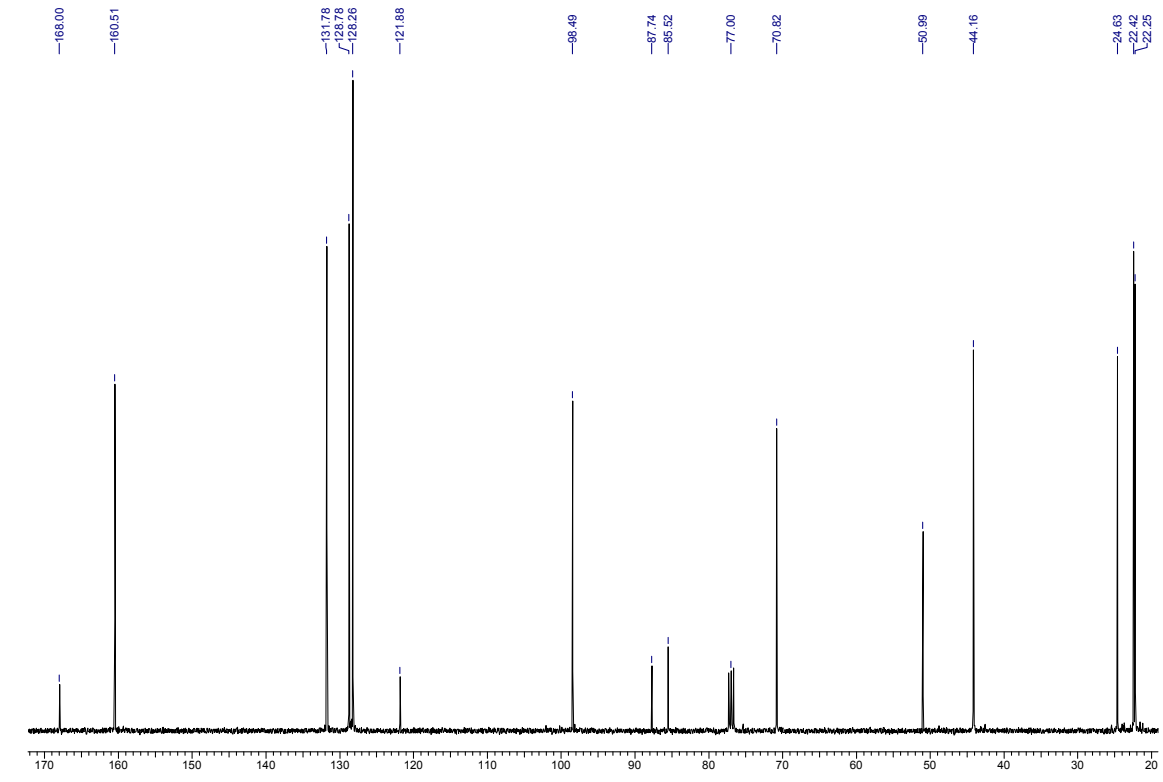
References

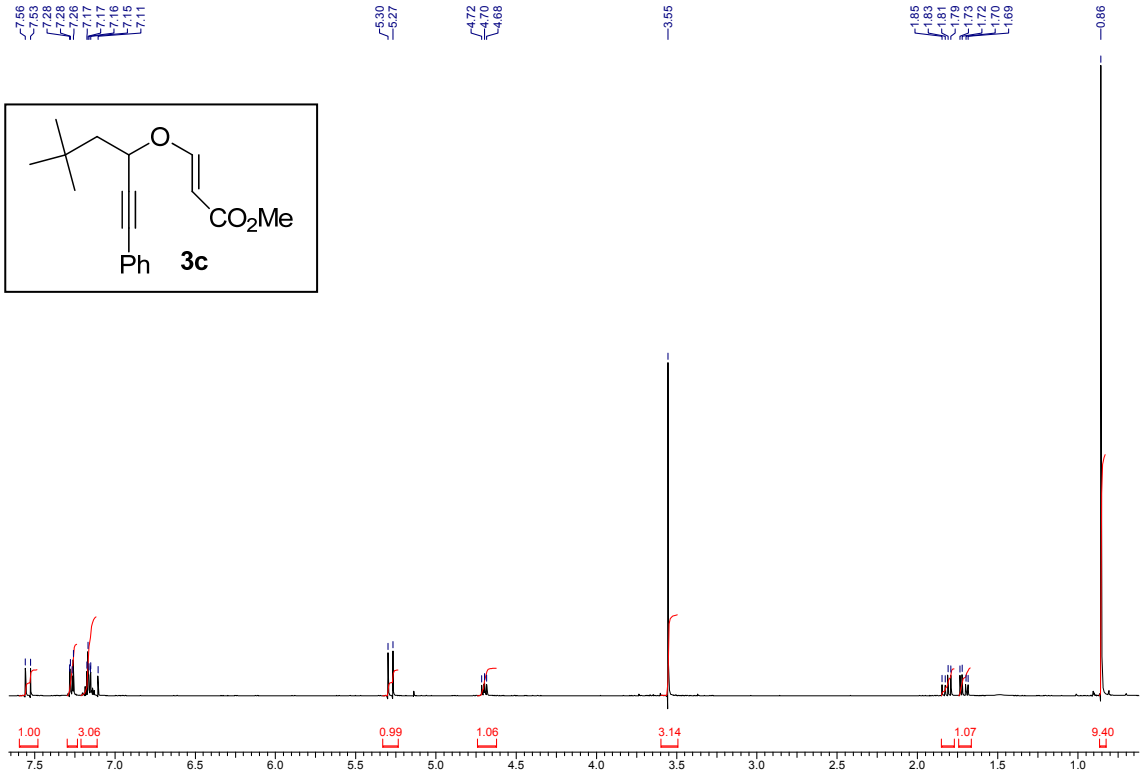
1. (a) D. Tejedor, A. Santos-Expósito, G. Méndez-Abt, C. Ruiz-Pérez, F. García-Tellado, *Synlett* **2009**, 1223-6; (b) J. Inanaga, Y. Baba, T. Hanamoto, *Chem. Lett*. **1993**, 241-4; (c) for a seminal antecedent, see: E. Winterfield, *Chem. Ber*. **1964**, *97*, 1952-8.
2. P. de Armas, F. García-Tellado, J. J. Marrero-Tellado, D. Tejedor, M. A. Maestro, J. González-Platas, *Org. Lett.* **2001**, *3*, 1905-8.
3. P. G. Cozzi, J. Rudolph, C. Bolm, P.-O Norrby, C. Tomasini, *J. Org. Chem.* **2005**, *70*, 5733-6.
4. M. M. Midland, A. Tramontano, J. R. Cable, *J. Org Chem.* **1980**, *45*, 28-9.
5. P. V. Ramachandran, B. G. Aleksandar, V. Teodorovic, H. C. Brown, *Tetrahedron*: *Asymmetry*, **1994**, *6*, 1061-74.
6. D. Tejedor, G. Méndez-Abt, F. García-Tellado, *Chem. Eur. J.* **2010**, *16*, 428-431.
7. L. G. León, C. Ríos-Luci, D. Tejedor, E. Pérez-Roth, J. C. Montero, A. Pandiella, F García-Tellado, J. M. Padrón, *J. Med. Chem.* **2010**, *53*, 3835–3839.
8. T. Harayama, K. Nakatsuka, H. Nishioka, K. Murakami, N. Hayashida, H. Ishii, *Chem. Pharm. Bull.* **1994**, *42*, 2170-2173.
9. S. G. Das, J. M. Doshi, D. Tian, S. N. Addo, B. Srinivasan, D. L. Hermanson, C Xing, *J. Med. Chem.* **2009**, *52*, 5937-5949.
10. H. Menz, S. F. Kirsch, *Org. Lett.* **2006**, *8*, 4795-4797.
11. Takeuchi, N.; Handa, S.; Koyama, K.; Kamata, K.; Goto, K.; Tobinaga, S. *Chem. Pharm. Bull.* **1991**, *39*, 1655-1658.

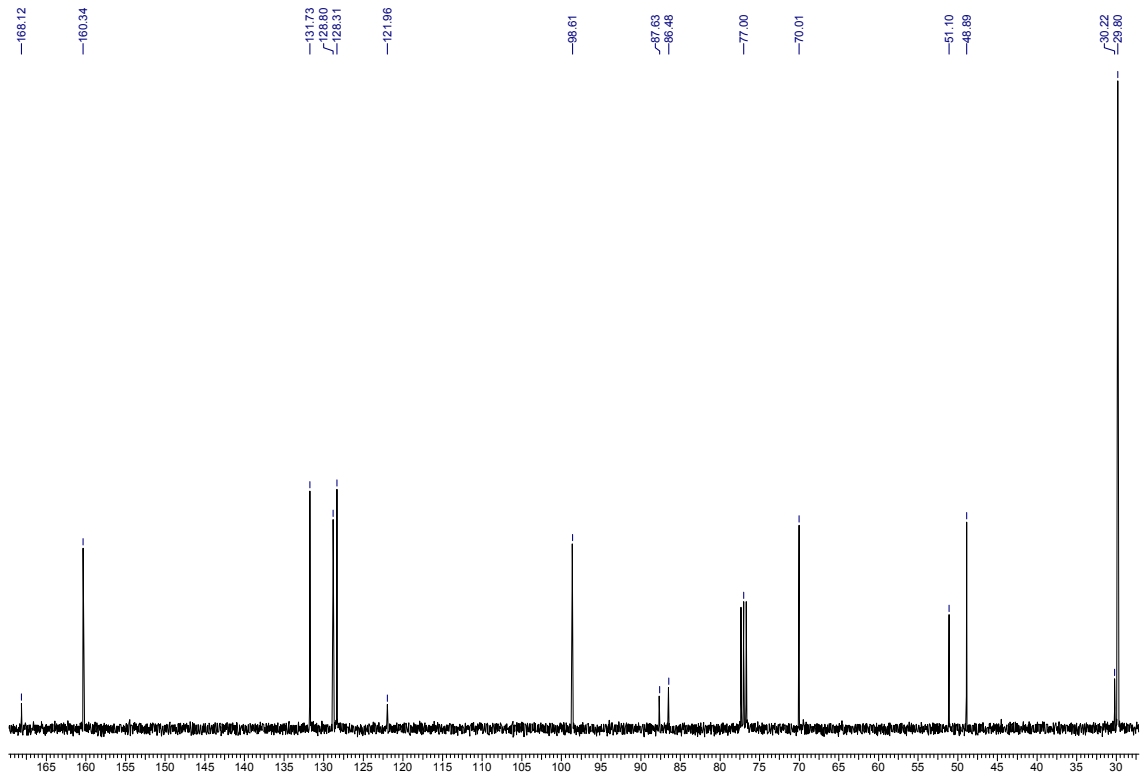

7.70
7.67
7.44
7.41
7.33
7.27
7.25
5.44
5.41
4.78
4.77
4.75
3.69
1.97
1.82
1.60
1.50
0.97
O
CO2Me
3a
1.00
3.03
1.00
1.04
3.08
2.21
2.26
3.15

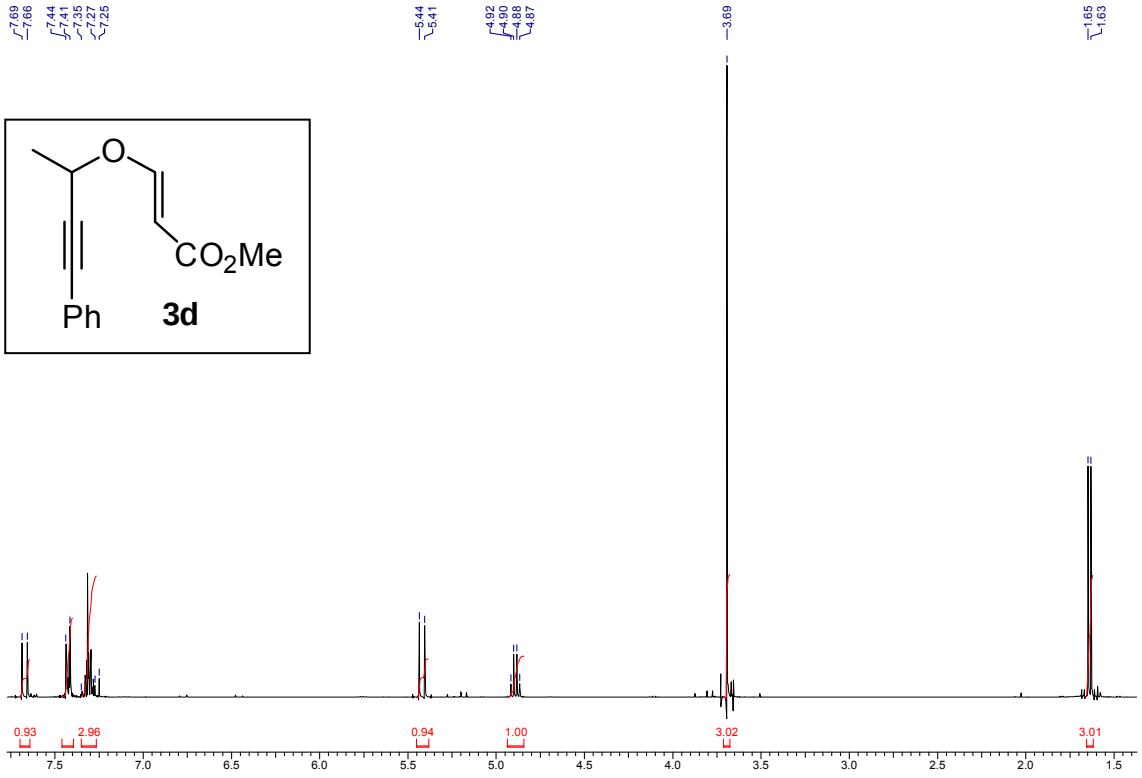

168.05
160.59
131.81
128.80
128.27
121.88
98.43
87.76
85.36
77.00
71.94
51.02
37.41
18.29
13.54

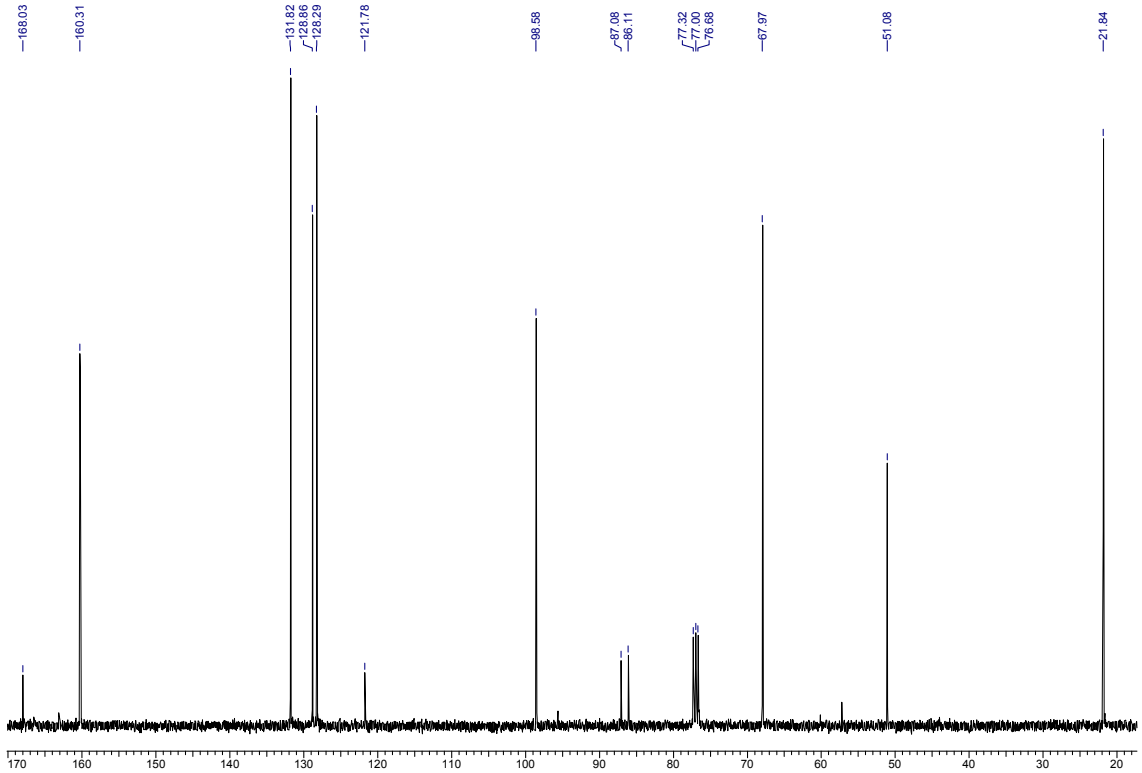

7.71
7.68
7.44
7.41
7.32
7.29
7.25
5.45
5.42
4.82
4.81
4.79
3.69
1.94
1.84
1.79
1.72
0.97
0.96
O
CO2Me
Ph
3b
0.97
2.90
0.98
1.00
3.02
2.05
6.06

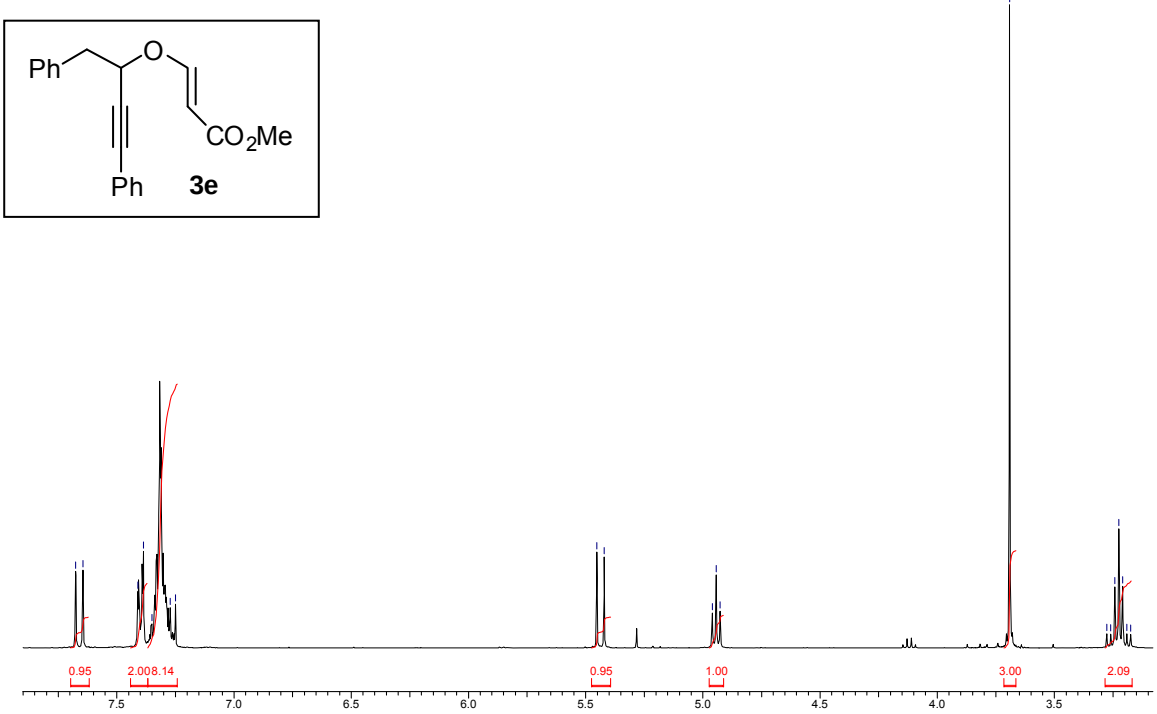

168.00
160.51
131.78
128.78
128.26
121.88
98.49
87.74
85.52
77.00
70.82
50.99
44.16
24.63
22.42
22.25

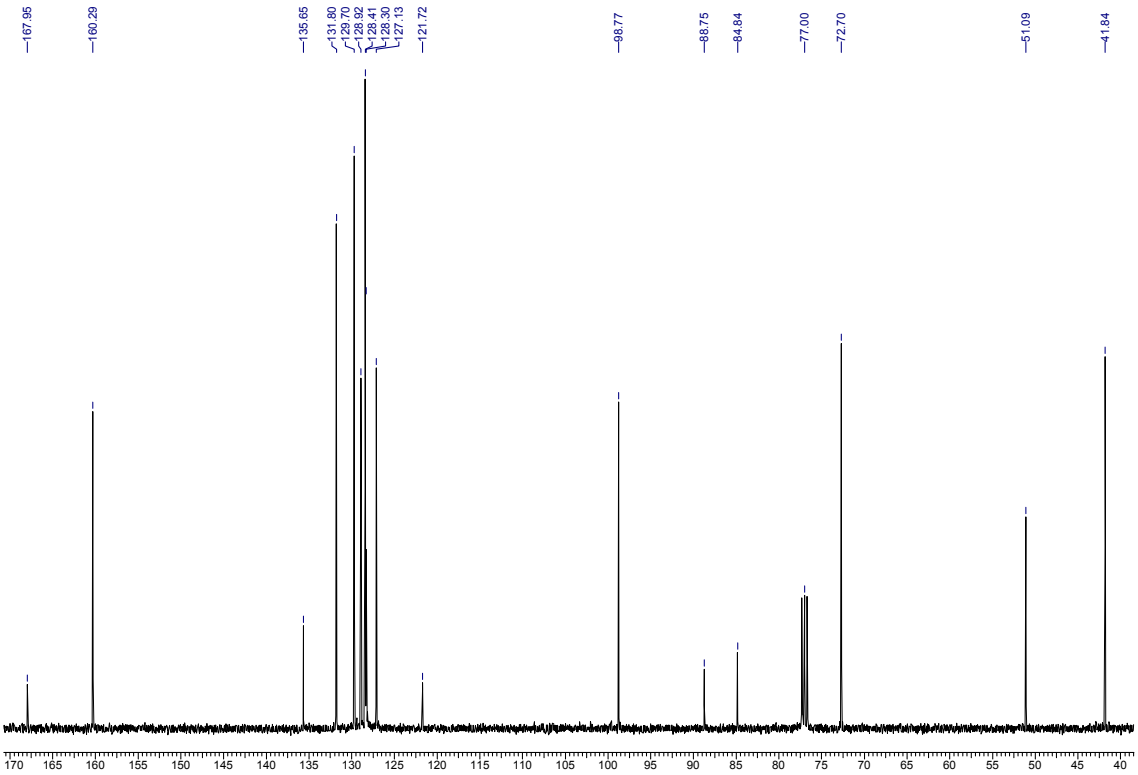

7.56
7.53
7.28
7.28
7.26
7.17
7.17
7.16
7.15
7.11
5.30
5.27
4.72
4.70
4.68
3.55
1.85
1.83
1.81
1.79
1.73
1.72
1.70
1.69
0.86
O
CO2Me
Ph
3c
1.00
3.06
0.99
1.06
3.14
1.07
9.40

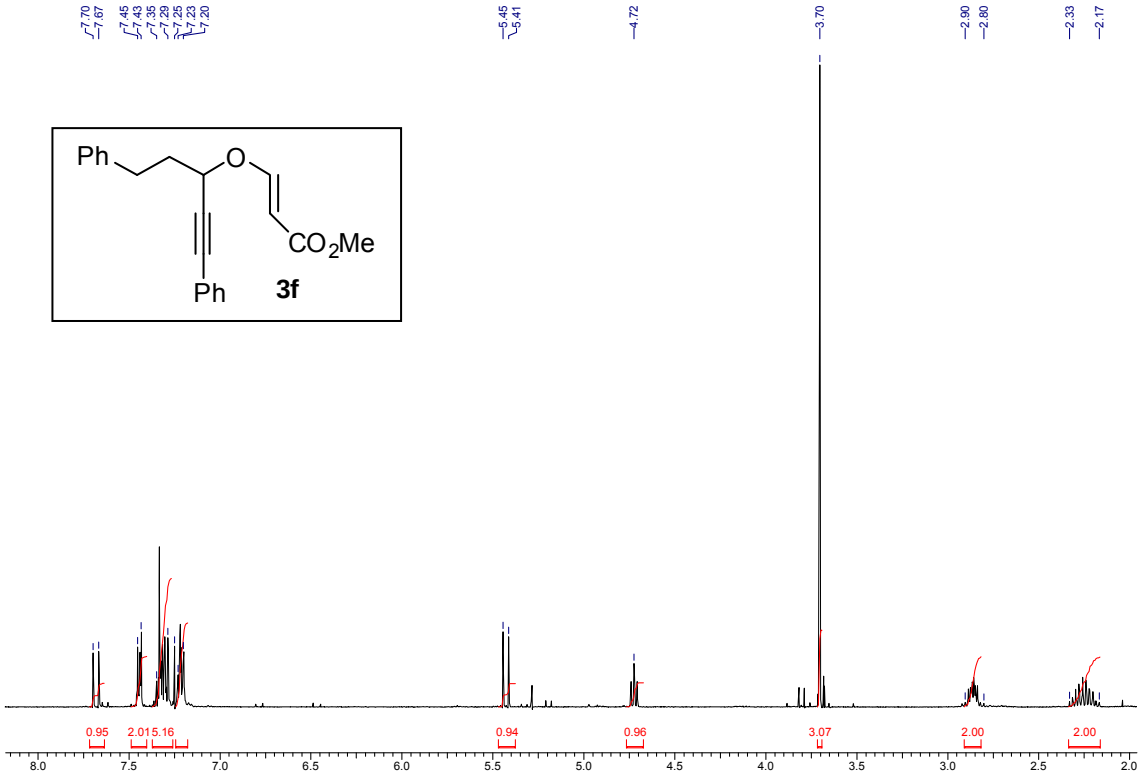

168.12
160.34
131.73
128.80
128.31
121.96
98.61
87.63
86.48
77.00
70.01
51.10
48.89
30.22
29.80

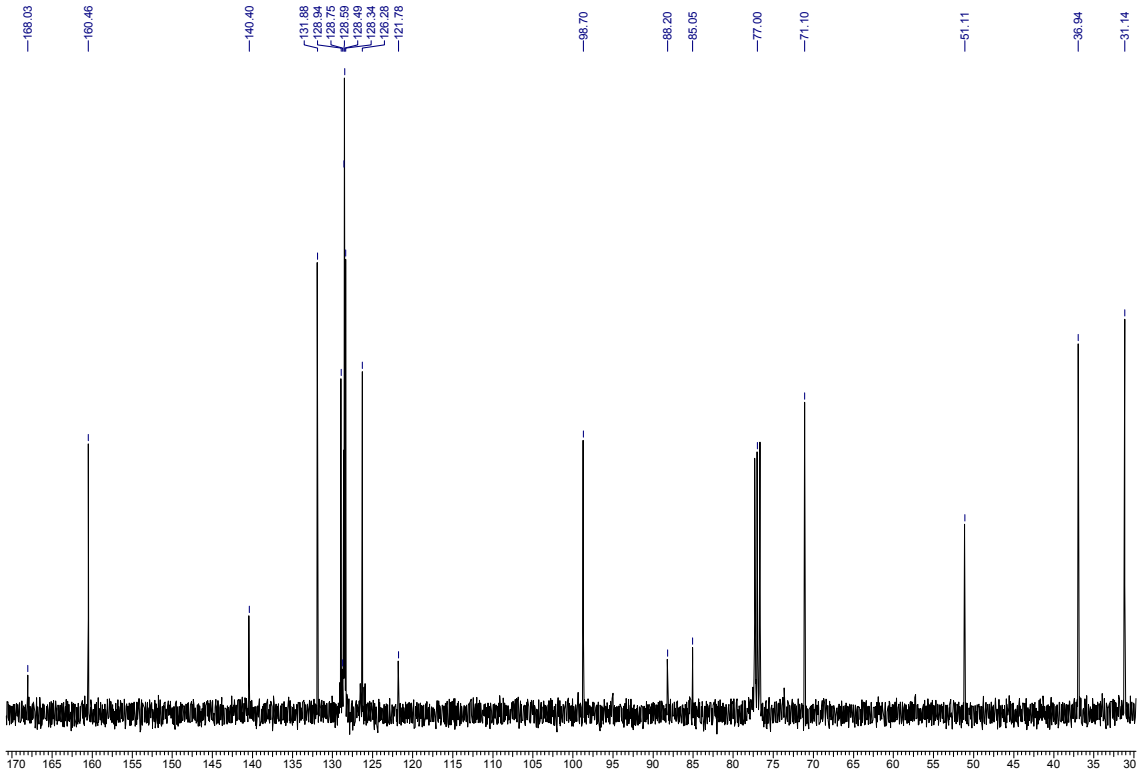

7.69
7.66
7.44
7.41
7.35
7.27
7.25
5.44
5.41
4.92
4.90
4.88
4.87
3.69
1.65
1.63
O
CO2Me
Ph
3d
0.93
2.96
0.94
1.00
3.02
3.01
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5

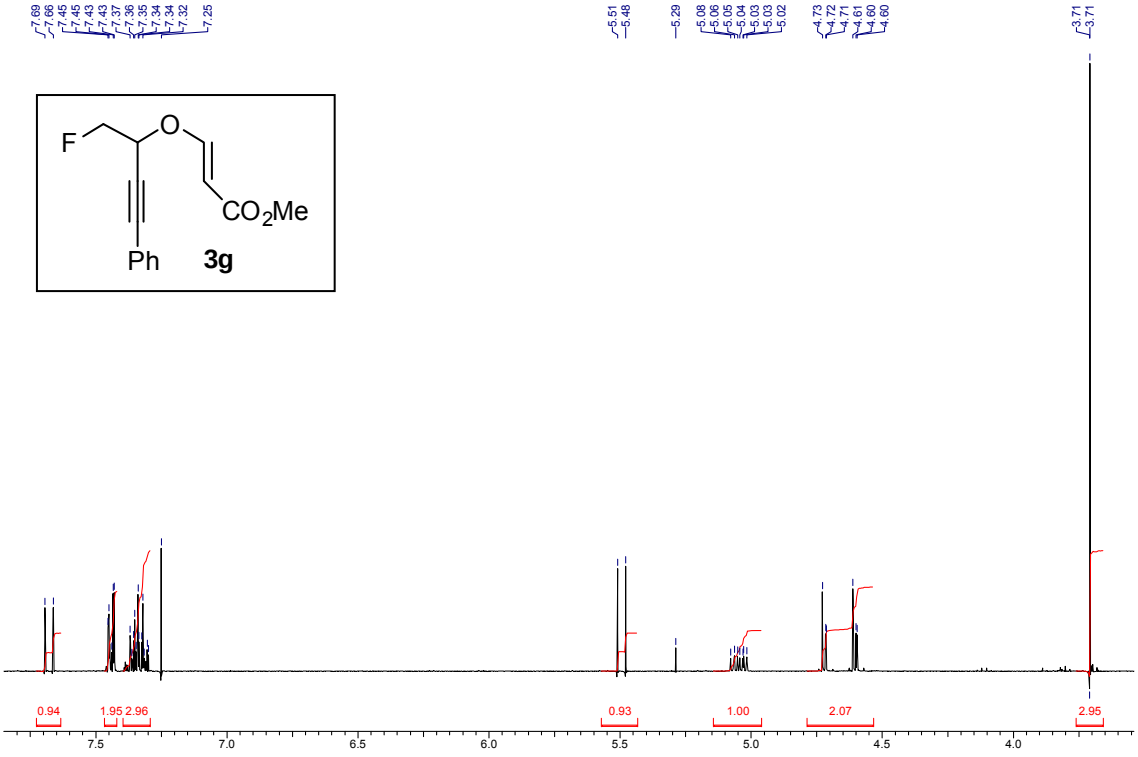

168.03
160.31
131.82
128.86
128.29
121.78
98.58
87.08
86.11
77.32
77.00
76.68
67.97
51.08
21.84
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

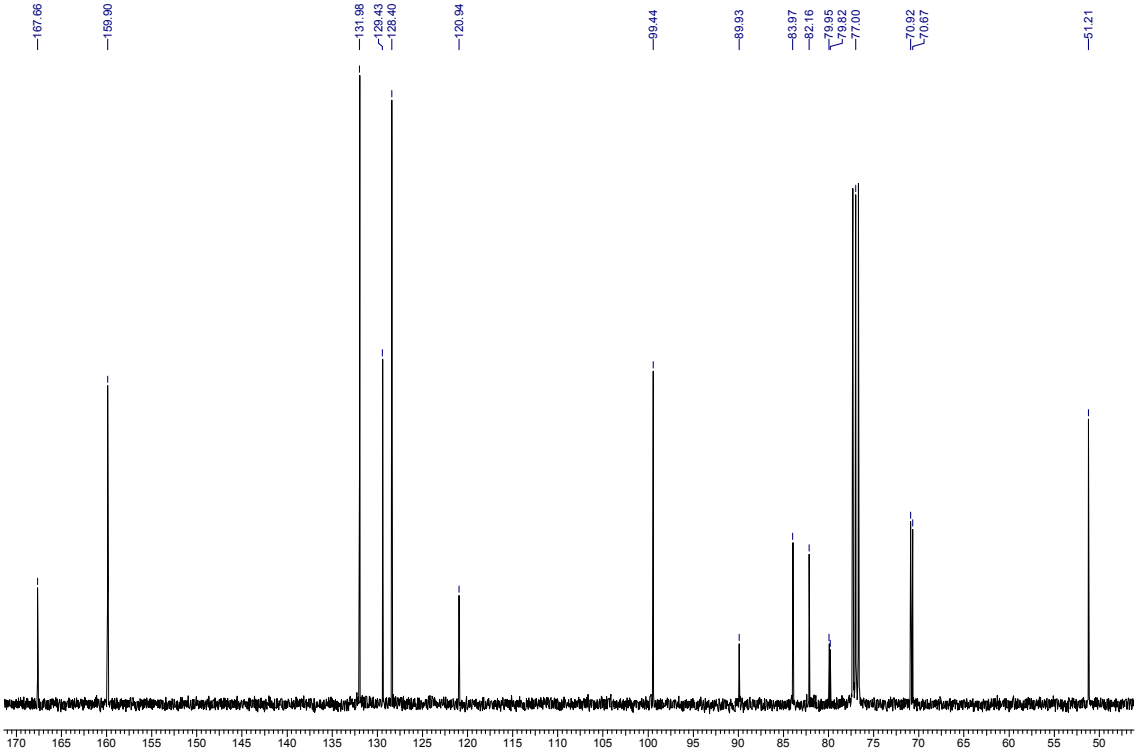

7.68
7.64
7.41
7.39
7.35
7.27
7.25
5.45
5.42
4.96
4.94
4.93
3.69
3.28
3.24
3.23
3.21
3.19
Ph
O
CO2Me
Ph
3e
0.95
2.00
8.14
0.95
1.00
3.00
2.09

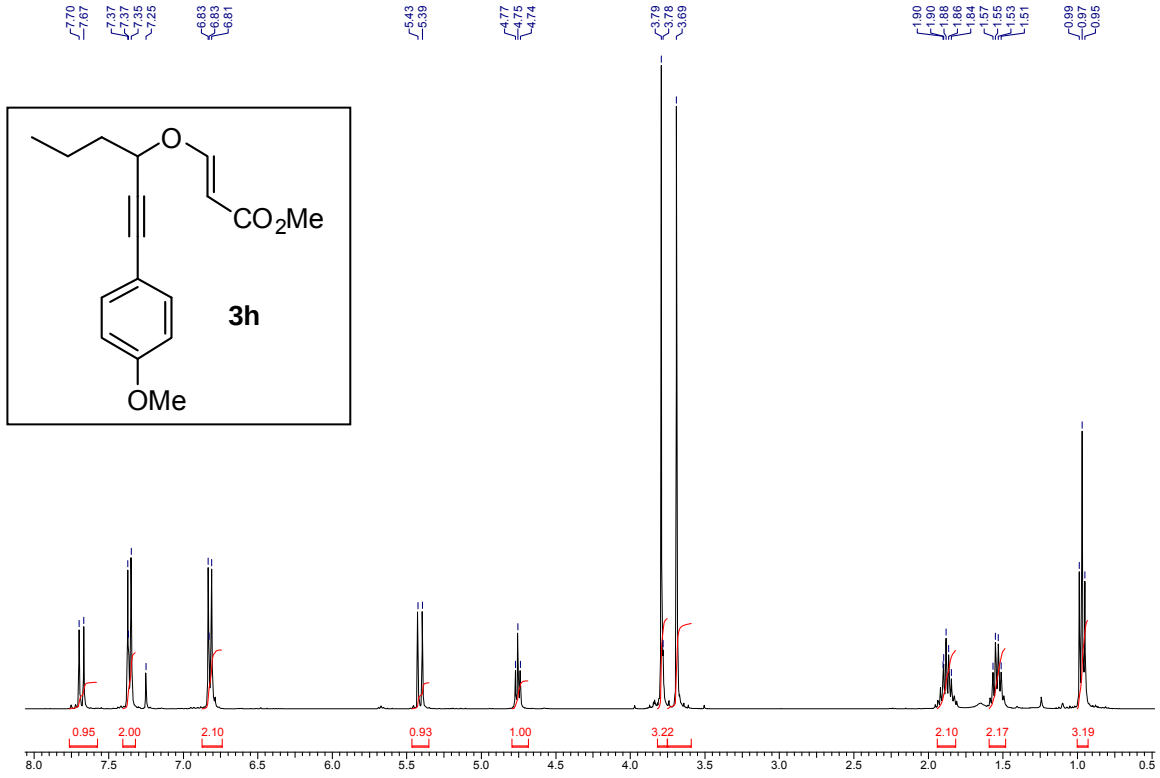

167.95
160.29
135.65
131.80
129.70
128.92
128.41
128.30
127.13
121.72
98.77
88.75
84.84
77.00
72.70
51.09
41.84

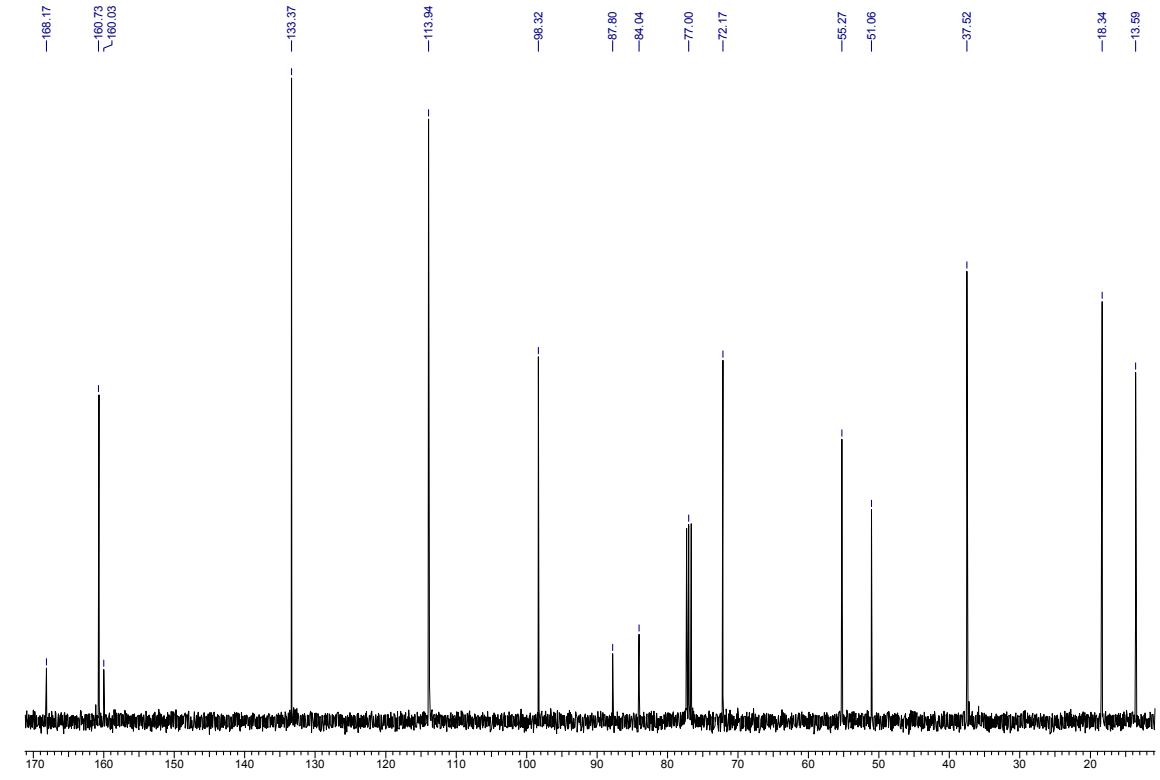

7.70
7.67
7.45
7.43
7.35
7.29
7.25
7.23
7.20
5.45
5.41
4.72
3.70
2.90
2.80
2.33
2.17
Ph
O
CO2Me
Ph
3f
0.95
2.01
5.16
0.94
0.96
3.07
2.00
2.00

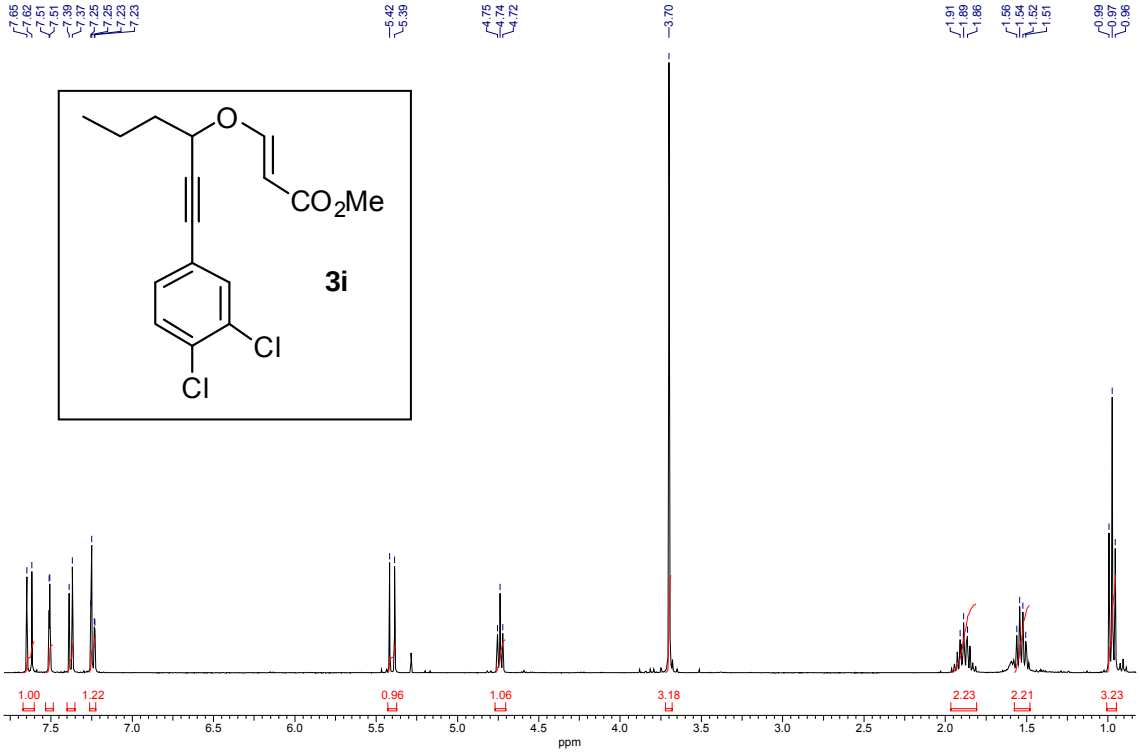

168.03
160.46
140.40
131.88
128.94
128.75
128.59
128.49
128.34
126.28
121.78
98.70
88.20
85.05
77.00
71.10
51.11
36.94
31.14

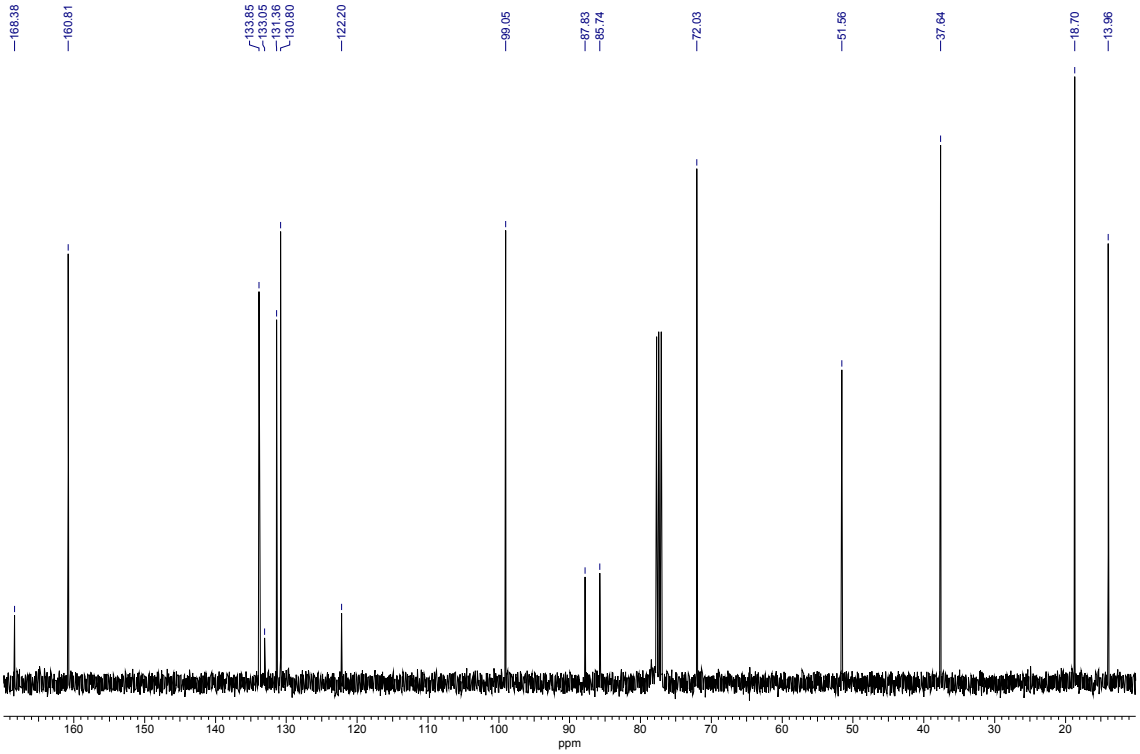

7.69
7.66
7.45
7.45
7.43
7.43
7.37
7.36
7.35
7.34
7.34
7.32
7.25
5.51
5.48
5.29
5.08
5.06
5.05
5.04
5.03
5.03
5.02
4.73
4.72
4.71
4.61
4.60
4.60
3.71
3.71
F
O
CO2Me
Ph
3g
0.94
1.95
2.96
0.93
1.00
2.07
2.95
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0

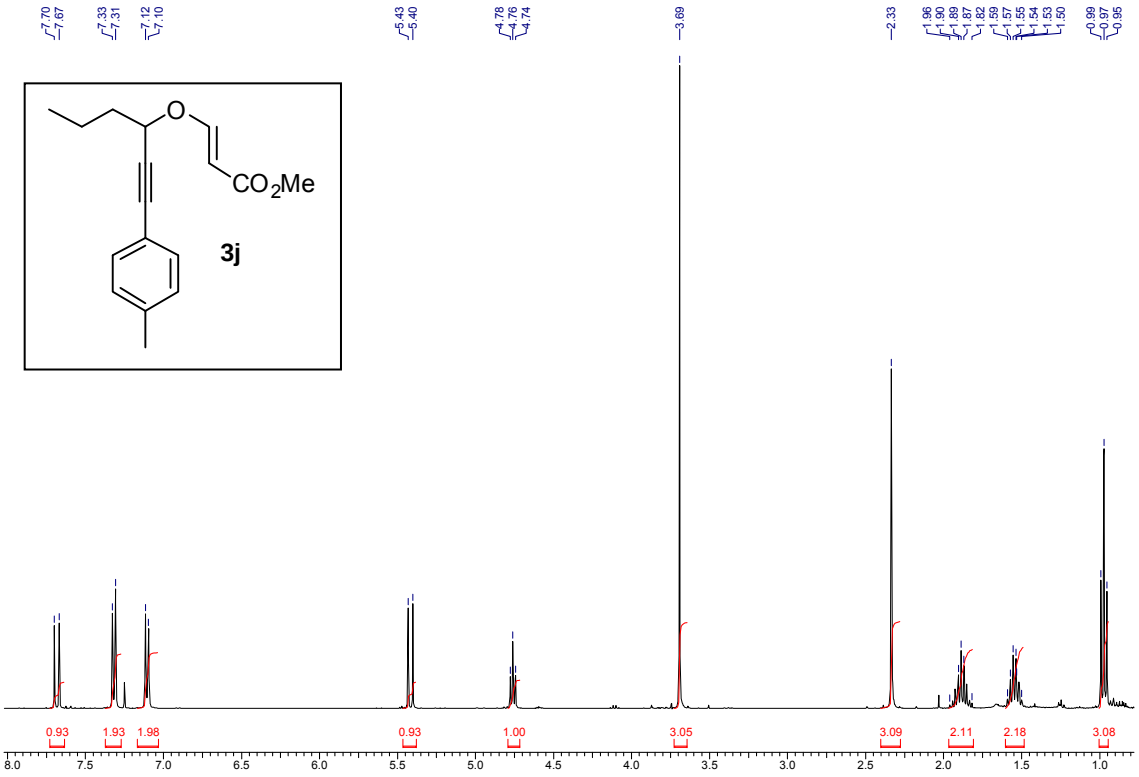

167.66
159.90
131.98
129.43
128.40
120.94
99.44
89.93
83.97
82.16
79.95
79.82
77.00
70.92
70.67
51.21
170
165
160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50

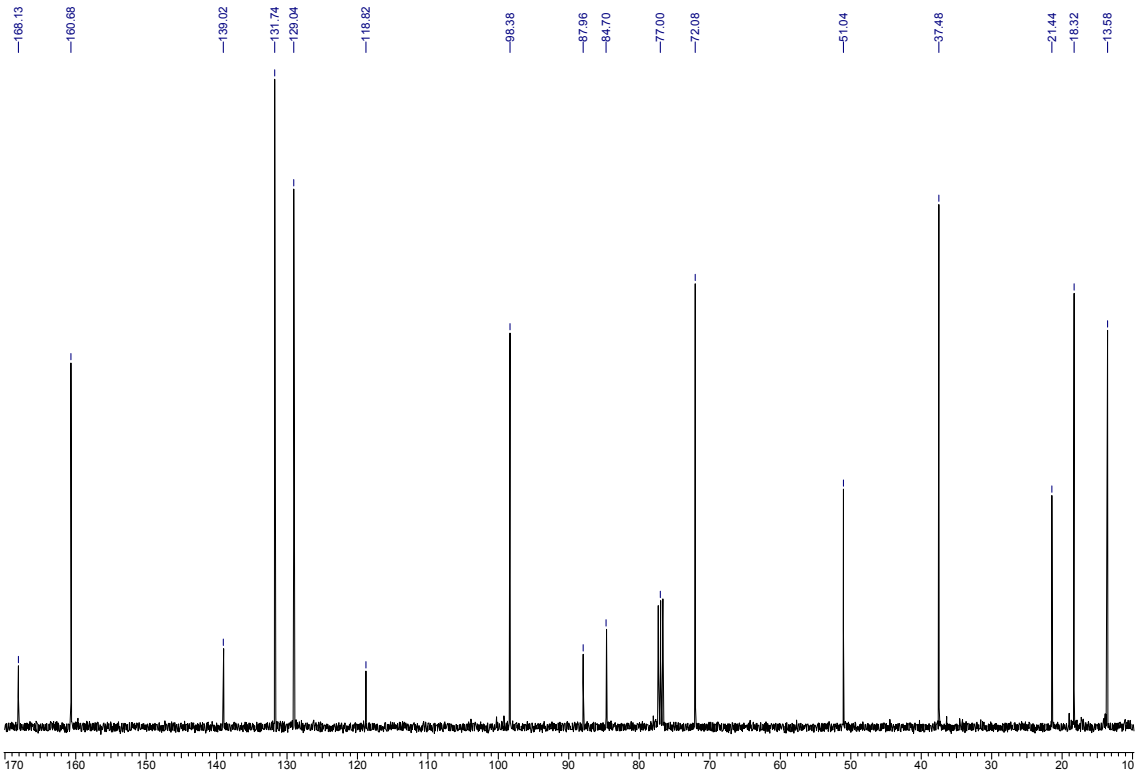

7.70
7.67
7.37
7.37
7.35
7.25
6.83
6.83
6.81
5.43
5.39
4.77
4.75
4.74
3.79
3.78
3.69
1.90
1.90
1.88
1.86
1.84
1.57
1.55
1.53
1.51
0.99
0.97
0.95
O
CO2Me
3h
OMe
0.95
2.00
2.10
0.93
1.00
3.22
2.10
2.17
3.19
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

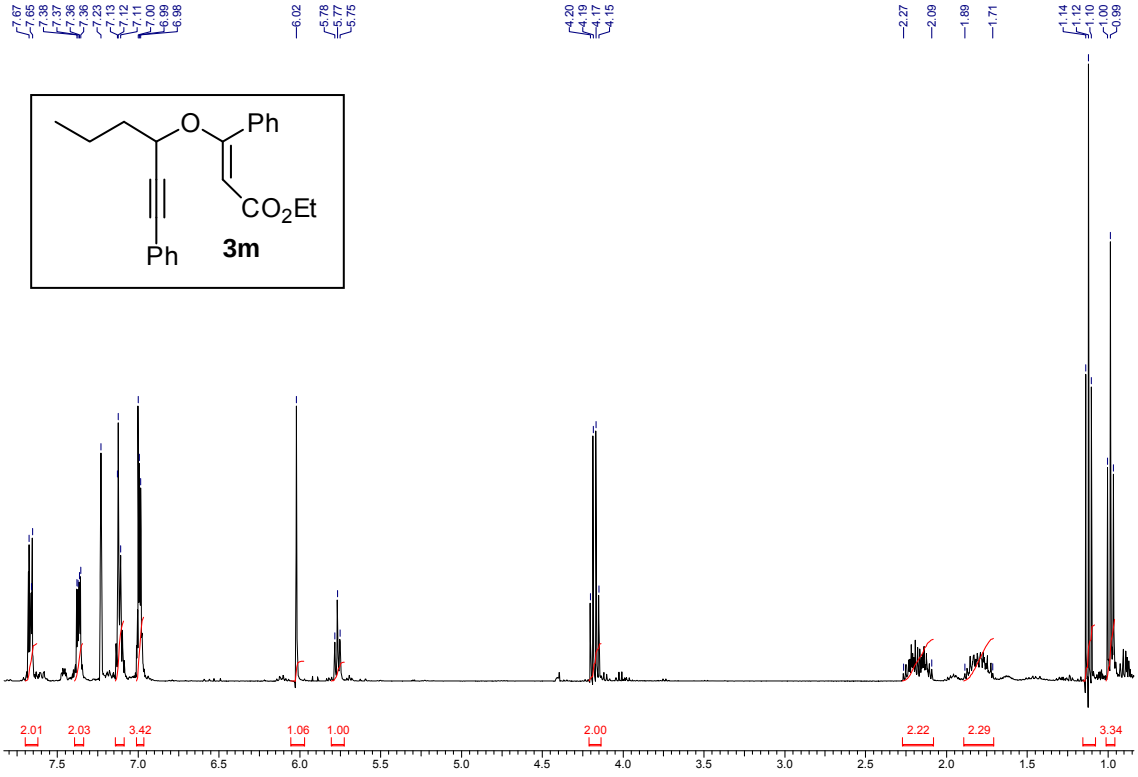

168.17
160.73
160.03
133.37
113.94
98.32
87.80
84.04
77.00
72.17
55.27
51.06
37.52
18.34
13.59
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

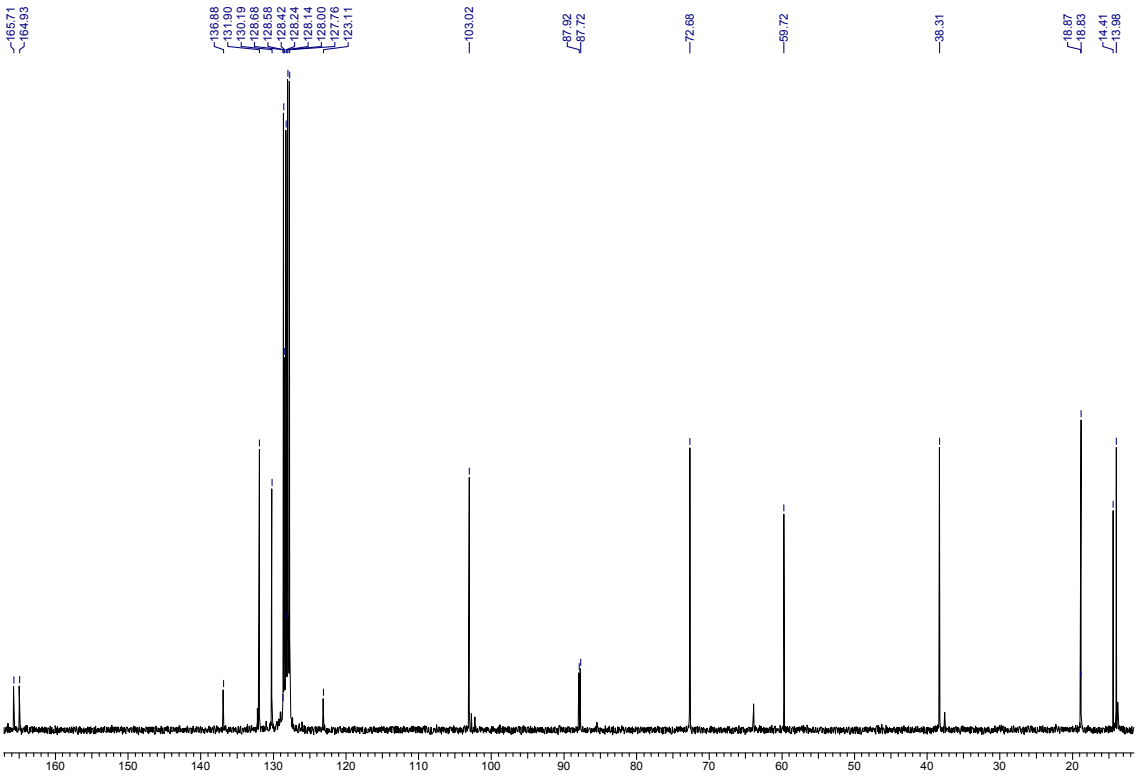

7.65
7.62
7.51
7.51
7.39
7.37
7.25
7.25
7.23
7.23
5.42
5.39
4.75
4.74
4.72
3.70
1.91
1.89
1.86
1.56
1.54
1.52
1.51
0.99
0.97
0.96
O
CO2Me
3i
Cl
Cl
1.00
1.22
0.96
1.06
3.18
2.23
2.21
3.23
ppm

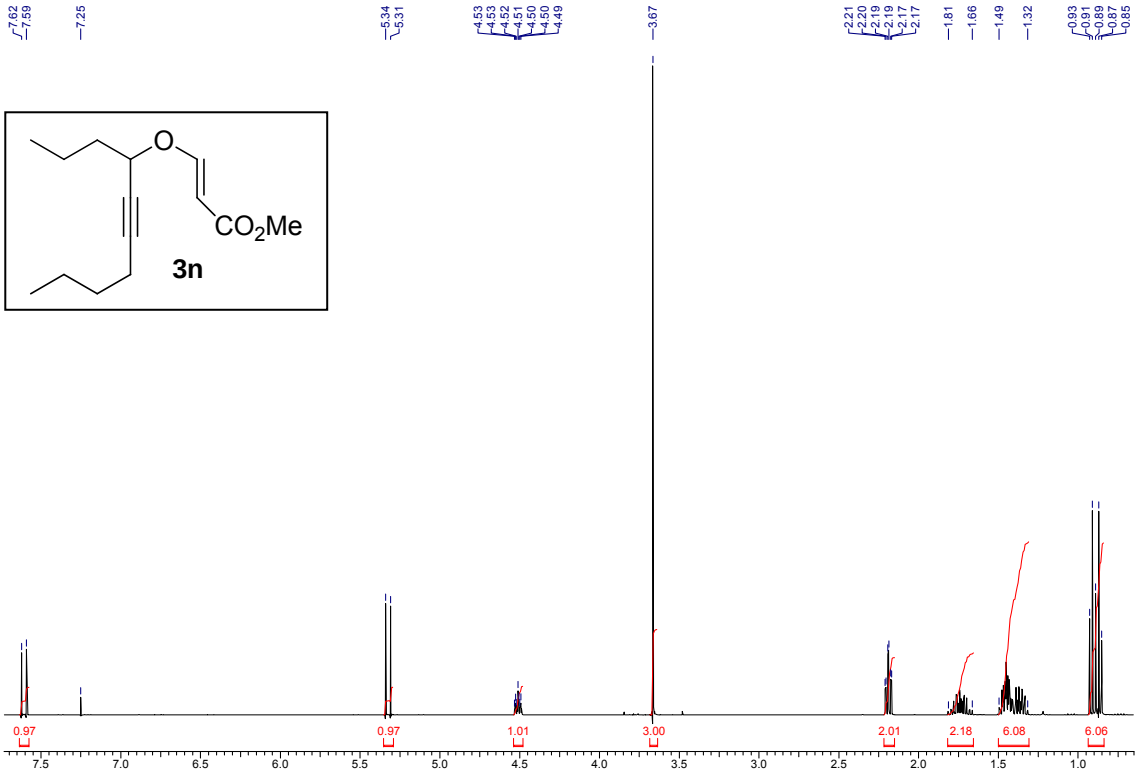

168.38
160.81
133.85
133.05
131.36
130.80
122.20
99.05
87.83
85.74
72.03
51.56
37.64
18.70
13.96
ppm

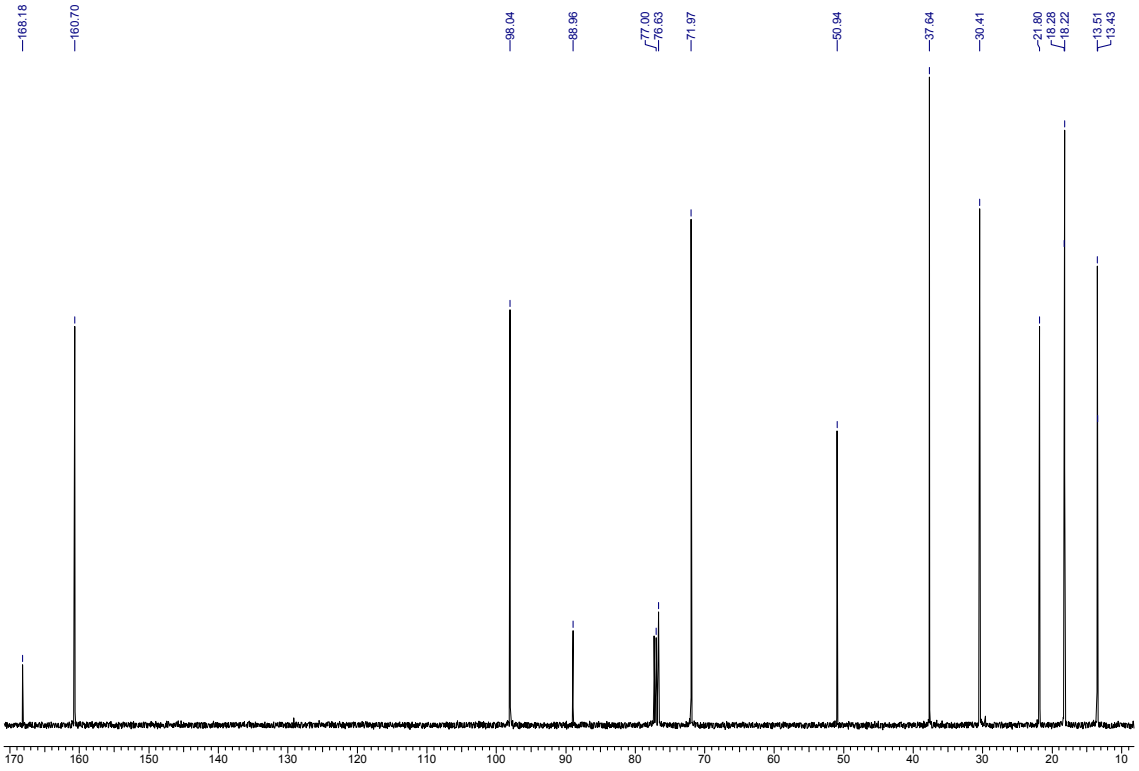

7.70
7.67
7.33
7.31
7.12
7.10
5.43
5.40
4.78
4.76
4.74
3.69
2.33
1.96
1.90
1.89
1.87
1.82
1.59
1.57
1.55
1.54
1.53
1.50
0.99
0.97
0.95
O
CO2Me
3j
0.93
1.93
1.98
0.93
1.00
3.05
3.09
2.11
2.18
3.08

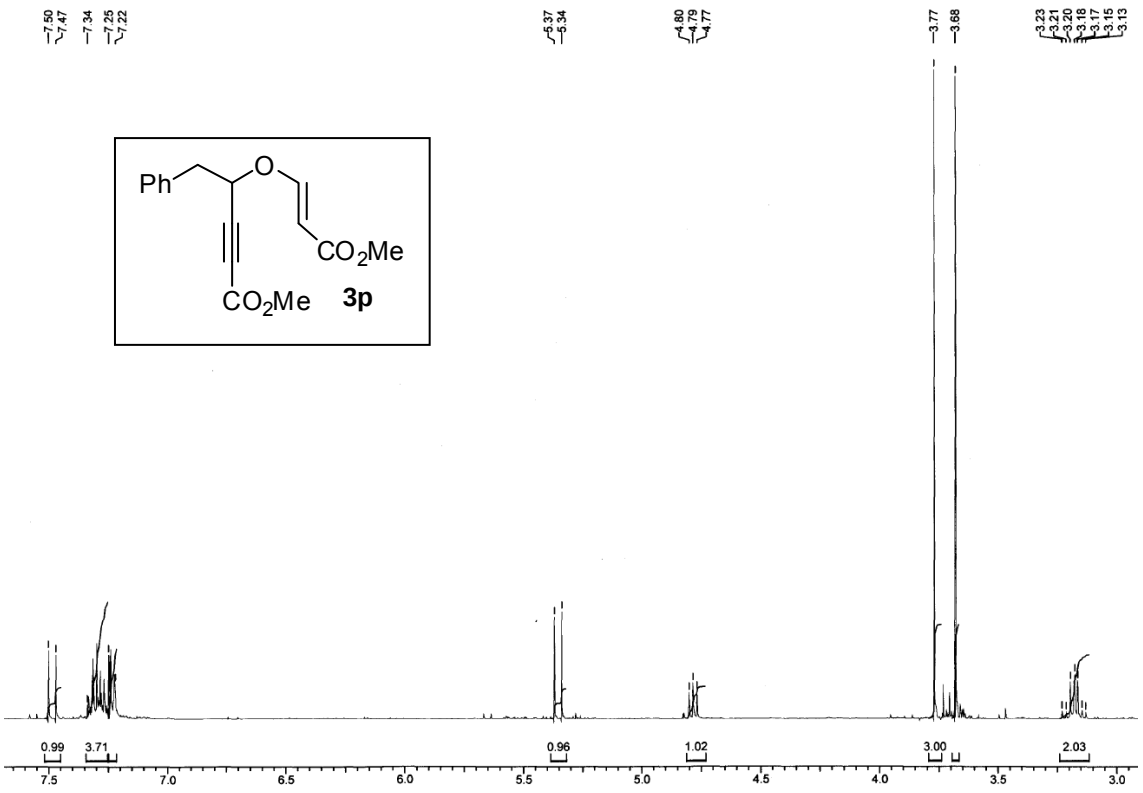

168.13
160.68
139.02
131.74
129.04
118.82
98.38
87.96
84.70
77.00
72.08
51.04
37.48
21.44
18.32
13.58

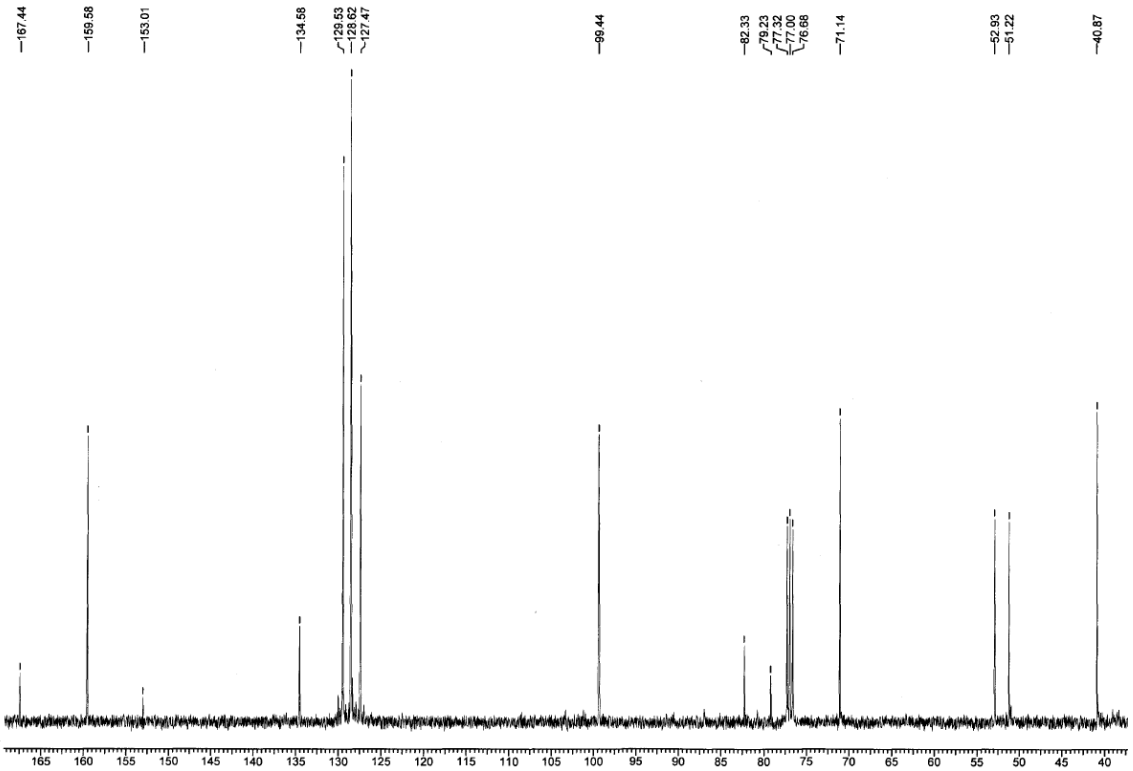

7.67
7.65
7.38
7.37
7.36
7.36
7.23
7.13
7.12
7.11
7.00
6.99
6.98
6.02
5.78
5.77
5.75
4.20
4.19
4.17
4.15
2.27
2.09
1.89
1.71
1.14
1.12
1.10
1.00
0.99
O
Ph
CO2Et
Ph
3m
2.01
2.03
3.42
1.06
1.00
2.00
2.22
2.29
3.34
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

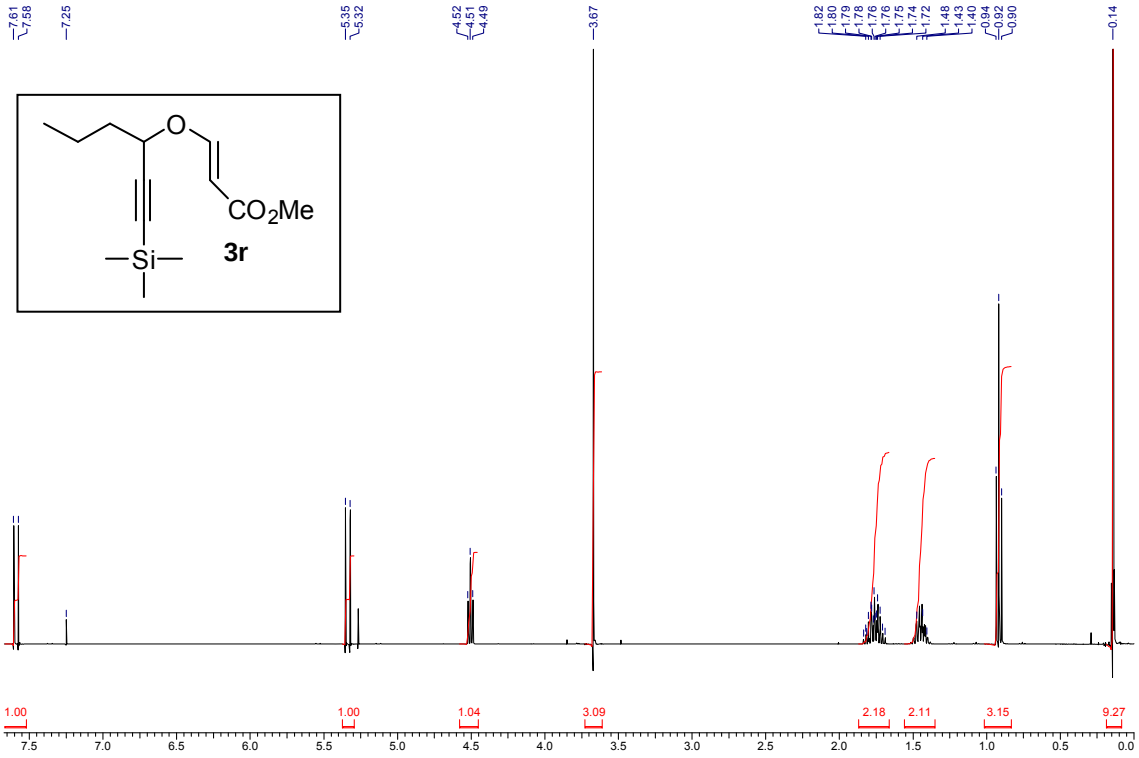

165.71
164.93
136.88
131.90
130.19
128.68
128.58
128.42
128.24
128.14
128.00
127.76
123.11
103.02
87.92
87.72
72.68
59.72
38.31
18.87
18.83
14.41
13.98
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

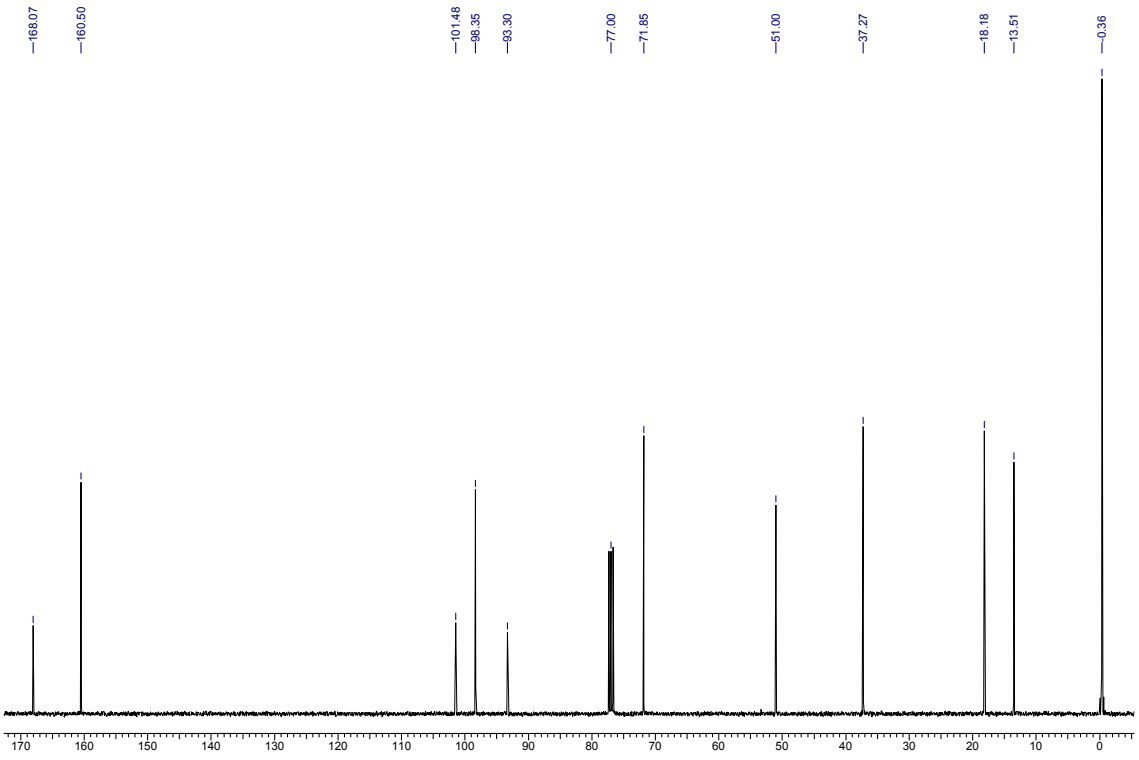

7.62
7.59
7.25
5.34
5.31
4.53
4.53
4.52
4.51
4.50
4.50
4.49
3.67
2.21
2.20
2.19
2.19
2.17
2.17
1.81
1.66
1.49
1.32
0.93
0.91
0.89
0.87
0.85
O
CO2Me
3n
0.97
0.97
1.01
3.00
2.01
2.18
6.08
6.06

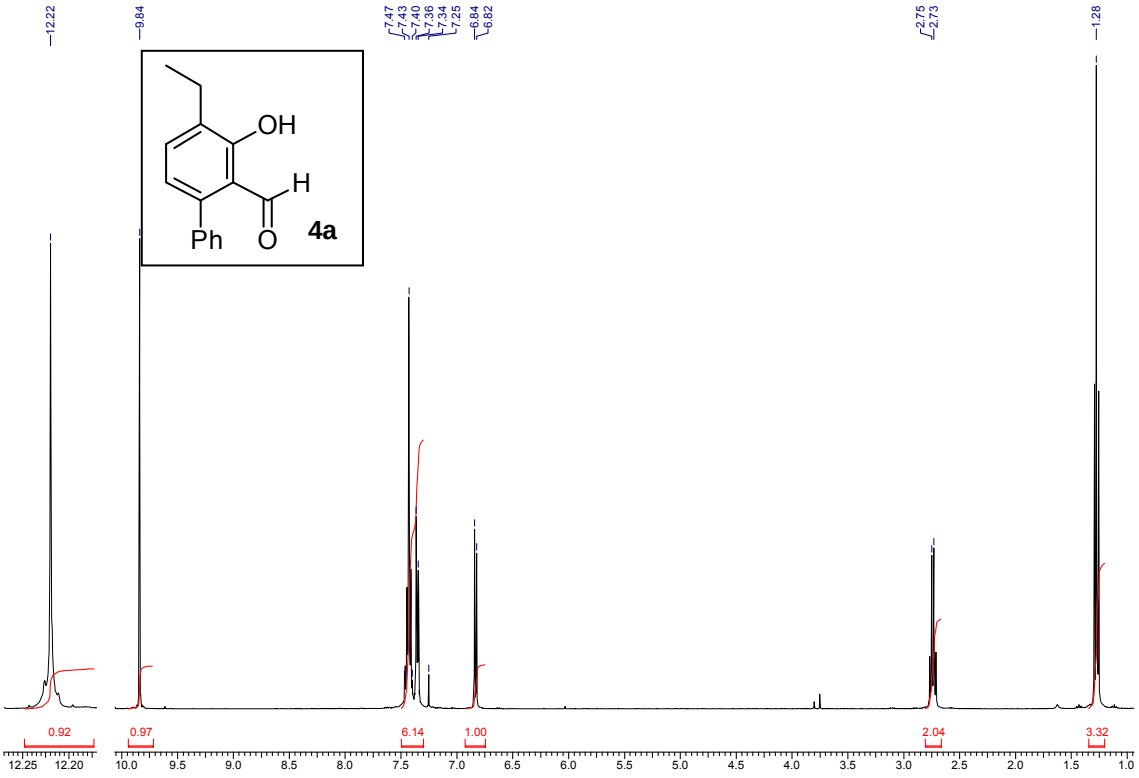

168.18
160.70
98.04
88.96
77.00
76.63
71.97
50.94
37.64
30.41
21.80
18.28
18.22
13.51
13.43

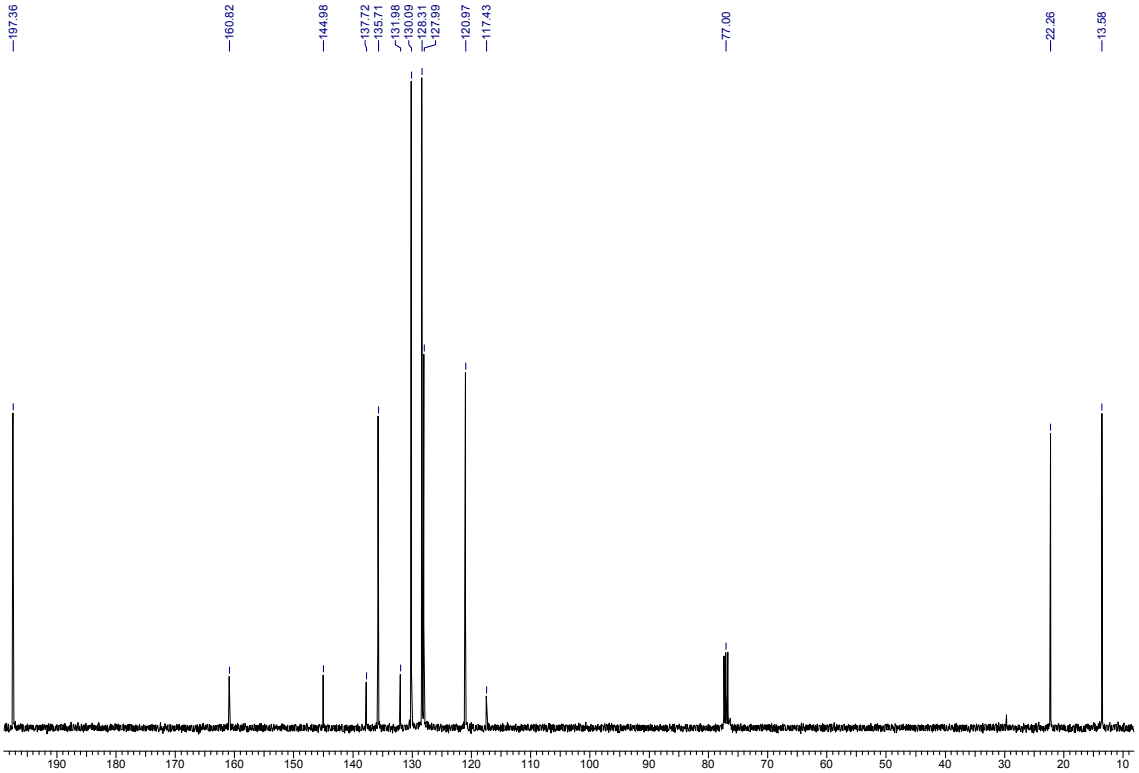

7.50
7.47
7.34
7.25
7.22
5.37
5.34
4.80
4.79
4.77
3.77
3.68
3.23
3.21
3.20
3.18
3.17
3.15
3.13
Ph
O
CO2Me
CO2Me
3p
0.99
3.71
0.96
1.02
3.00
2.03

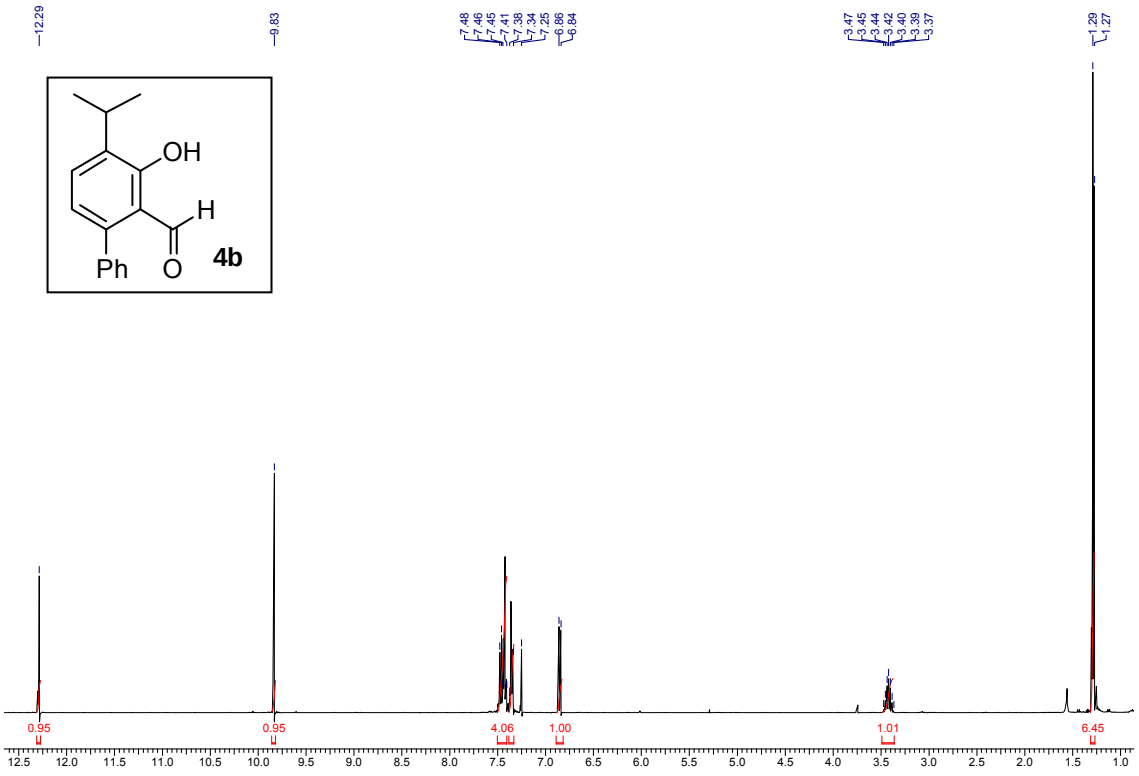

167.44
159.58
153.01
134.58
129.53
128.62
127.47
99.44
82.33
79.23
77.32
77.00
76.68
71.14
52.93
51.22
40.87

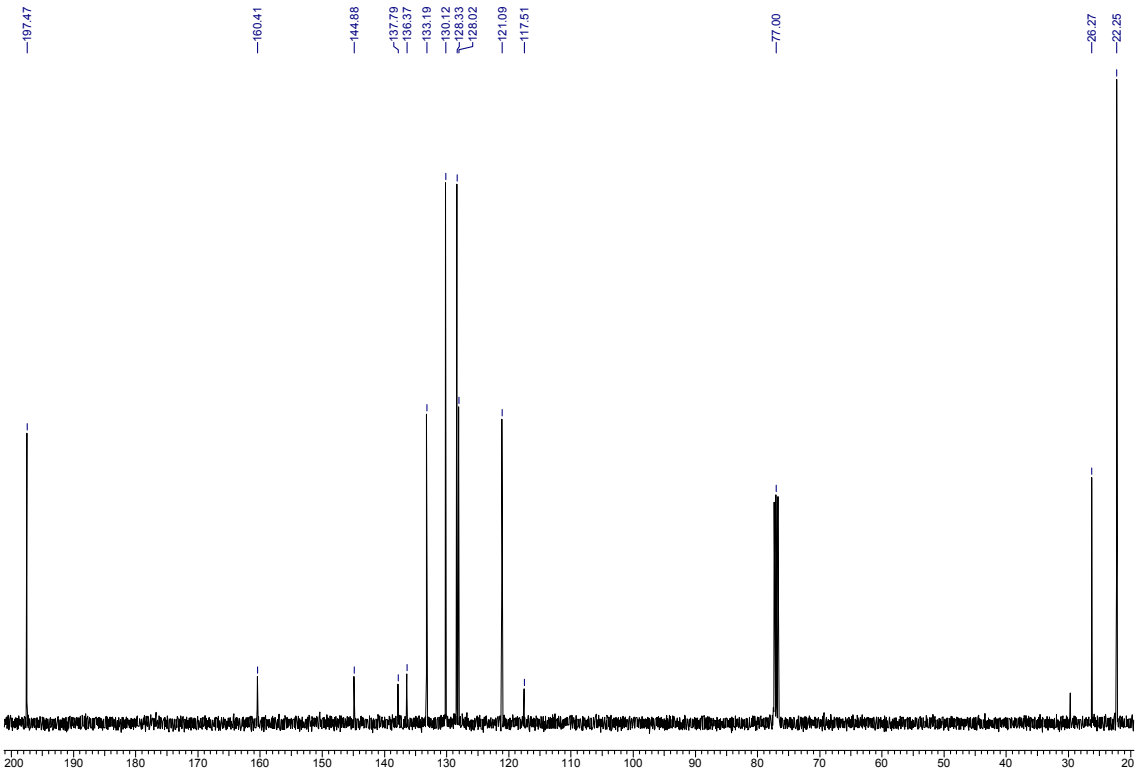

7.61
7.58
7.25
5.35
5.32
4.52
4.51
4.49
3.67
1.82
1.80
1.79
1.78
1.76
1.75
1.74
1.72
1.48
1.43
1.40
0.94
0.92
0.90
0.14
O
CO2Me
Si
3r
1.00
1.00
1.04
3.09
2.18
2.11
3.15
9.27

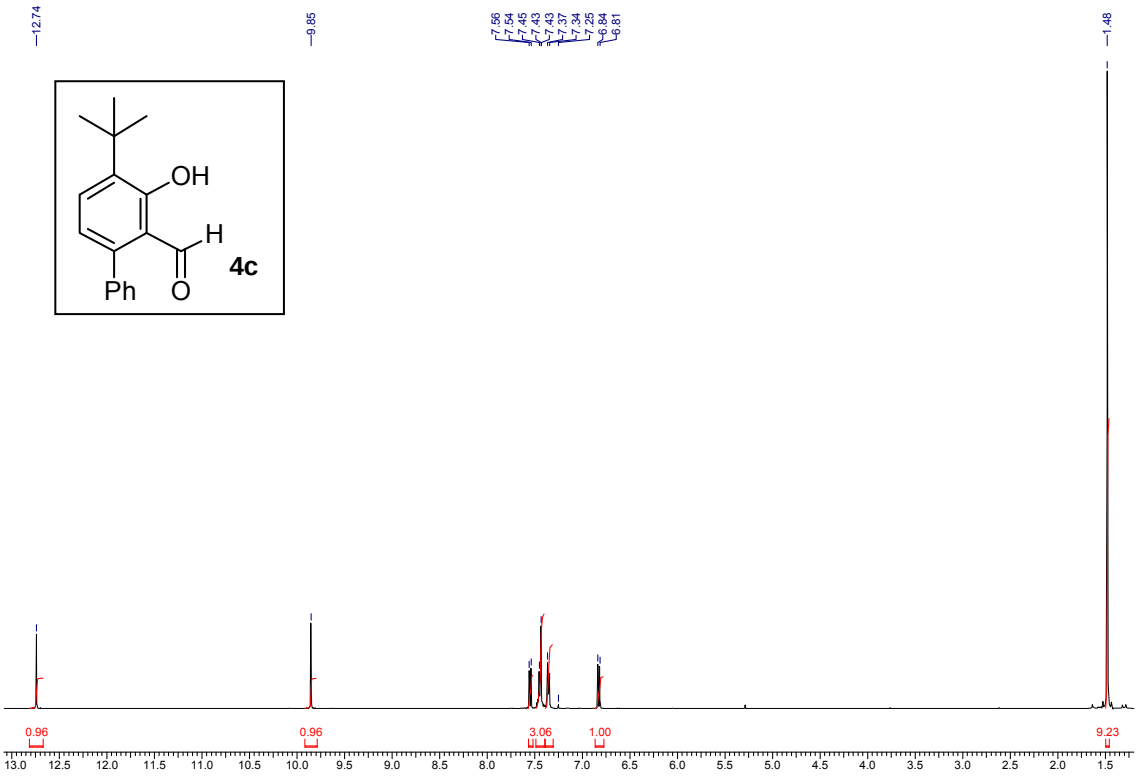

168.07
160.50
101.48
98.35
93.30
77.00
71.85
51.00
37.27
18.18
13.51
0.36

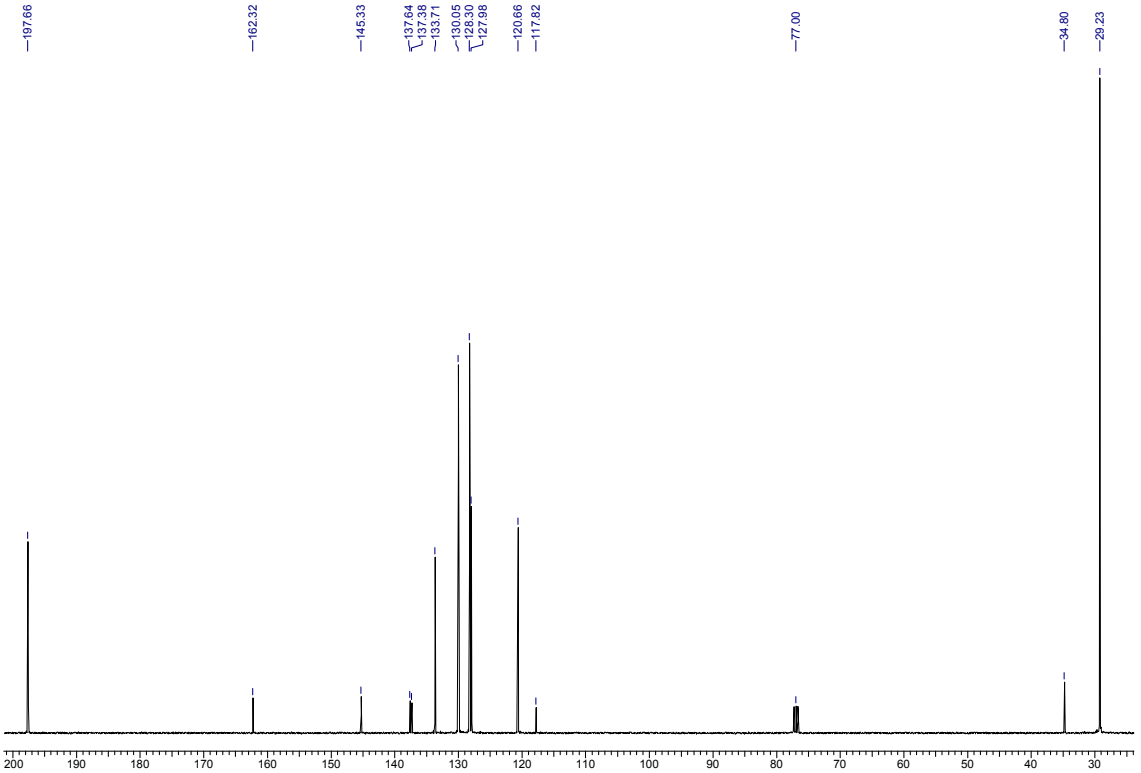

12.22
9.84
7.47
7.43
7.40
7.36
7.34
7.25
6.84
6.82
2.75
2.73
1.28
OH
H
Ph
O
4a
0.92
0.97
6.14
1.00
2.04
3.32

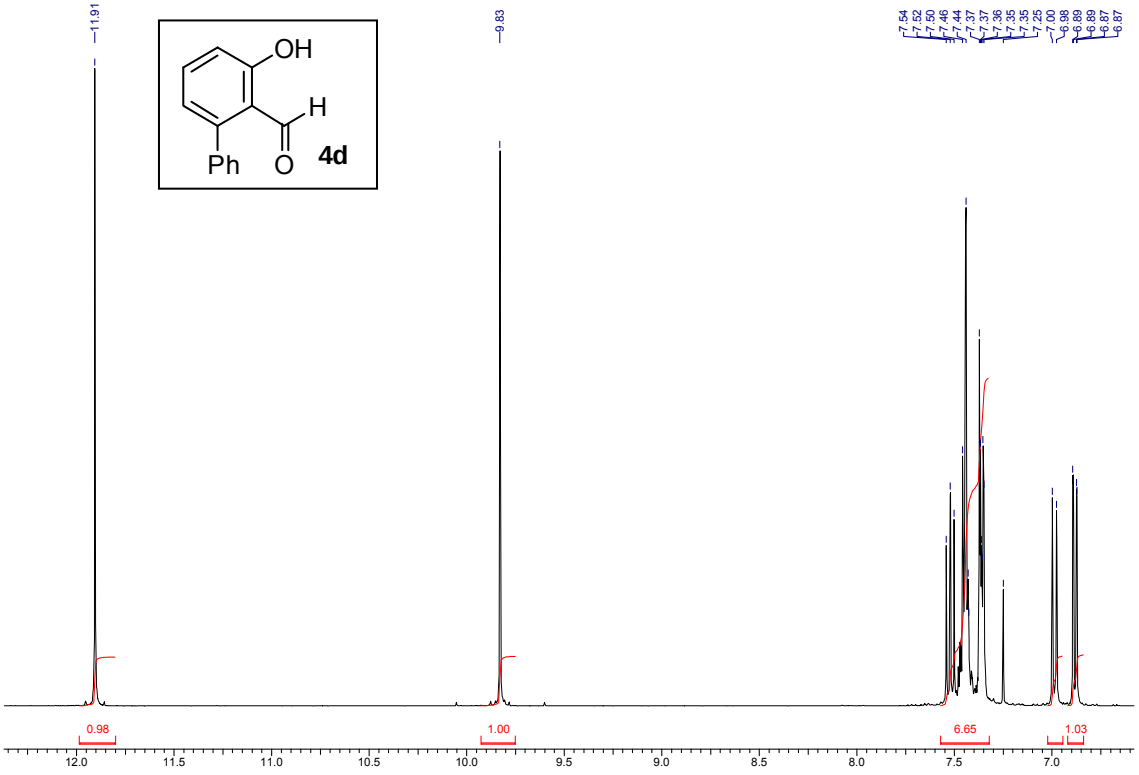

197.36
160.82
144.98
137.72
135.71
131.98
130.09
128.31
127.99
120.97
117.43
77.00
22.26
13.58

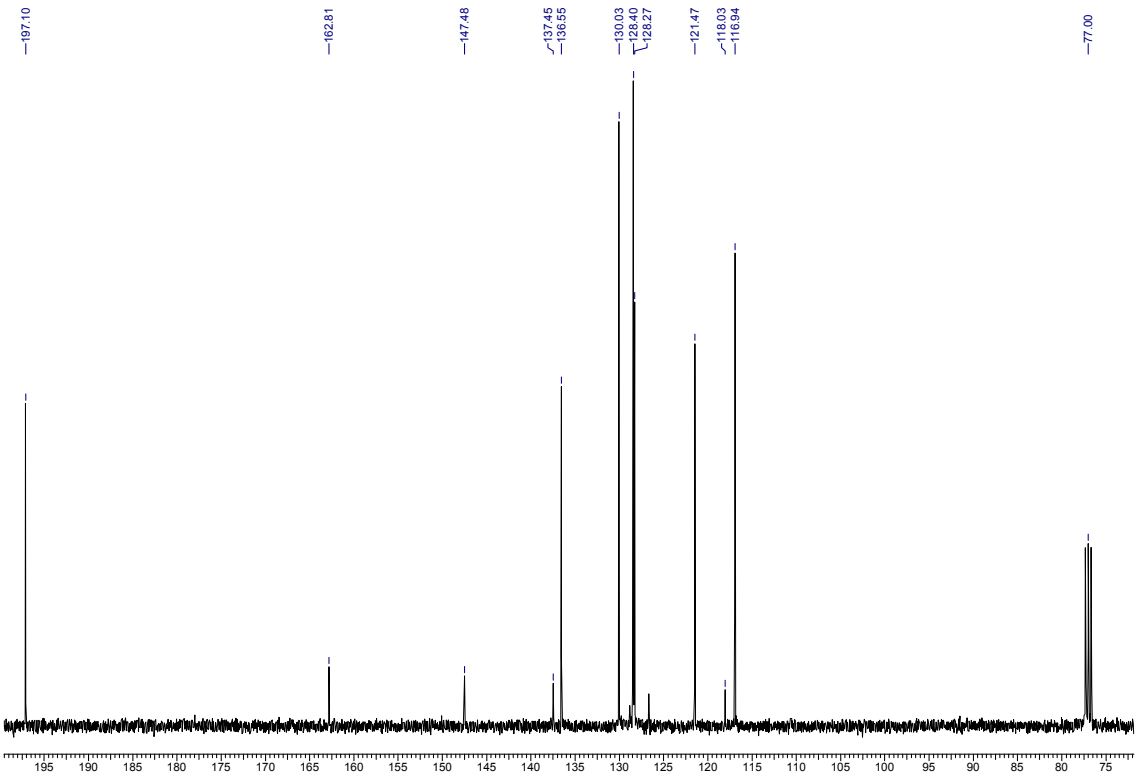

12.29
9.83
7.48
7.46
7.45
7.41
7.38
7.34
7.25
6.86
6.84
3.47
3.45
3.44
3.42
3.40
3.39
3.37
1.29
1.27
OH
H
Ph
O
4b
0.95
0.95
4.06
1.00
1.01
6.45

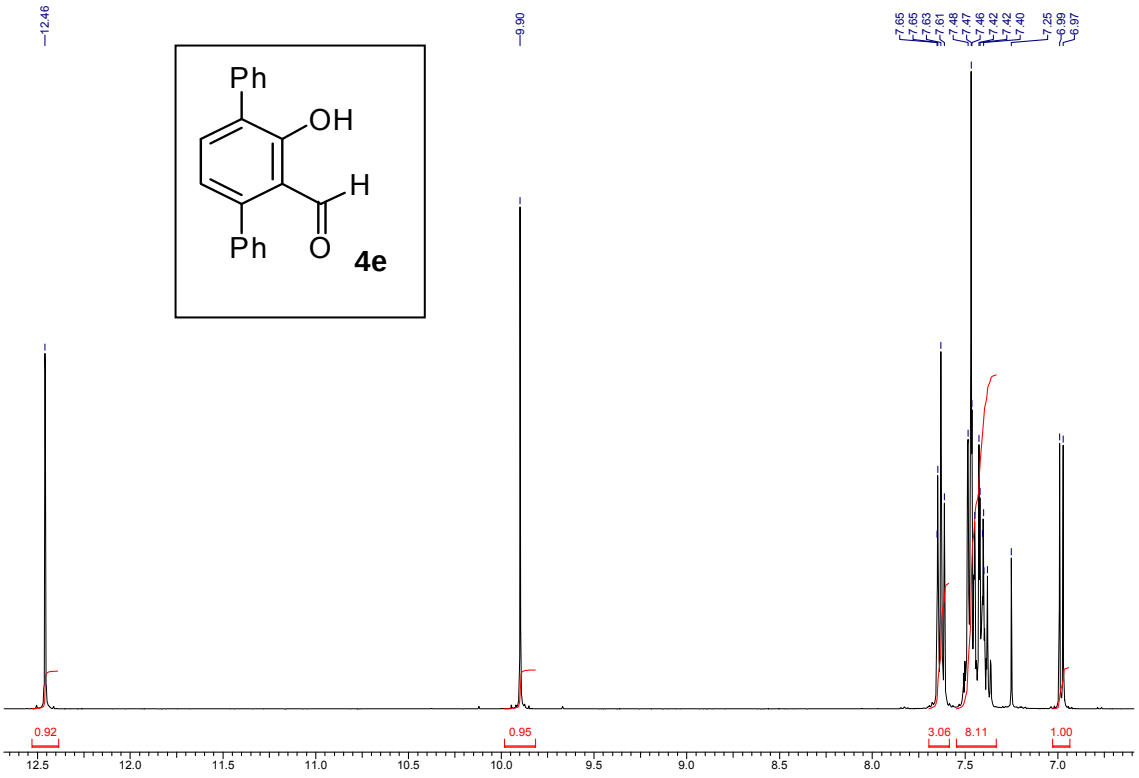

197.47
160.41
144.88
137.79
136.37
133.19
130.12
128.33
128.02
121.09
117.51
77.00
26.27
22.25

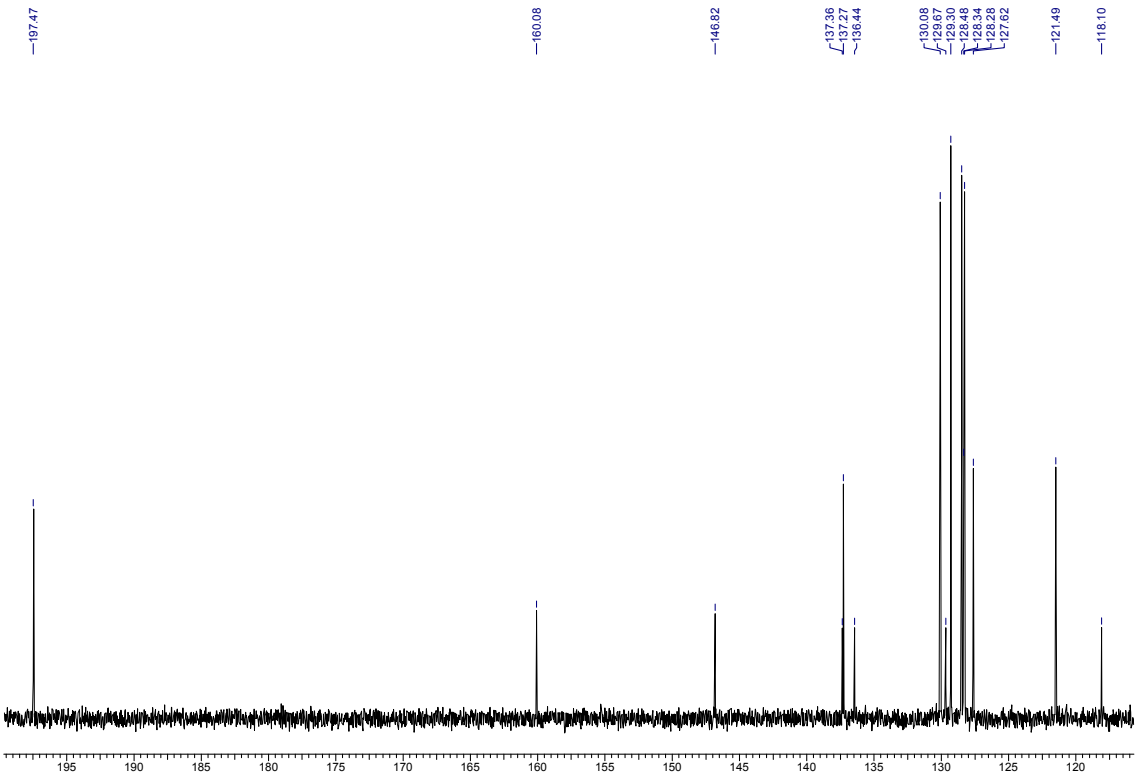

12.74
9.85
7.56
7.54
7.45
7.43
7.43
7.37
7.34
7.25
6.84
6.81
1.48
OH
H
Ph
O
4c
0.96
0.96
3.06
1.00
9.23

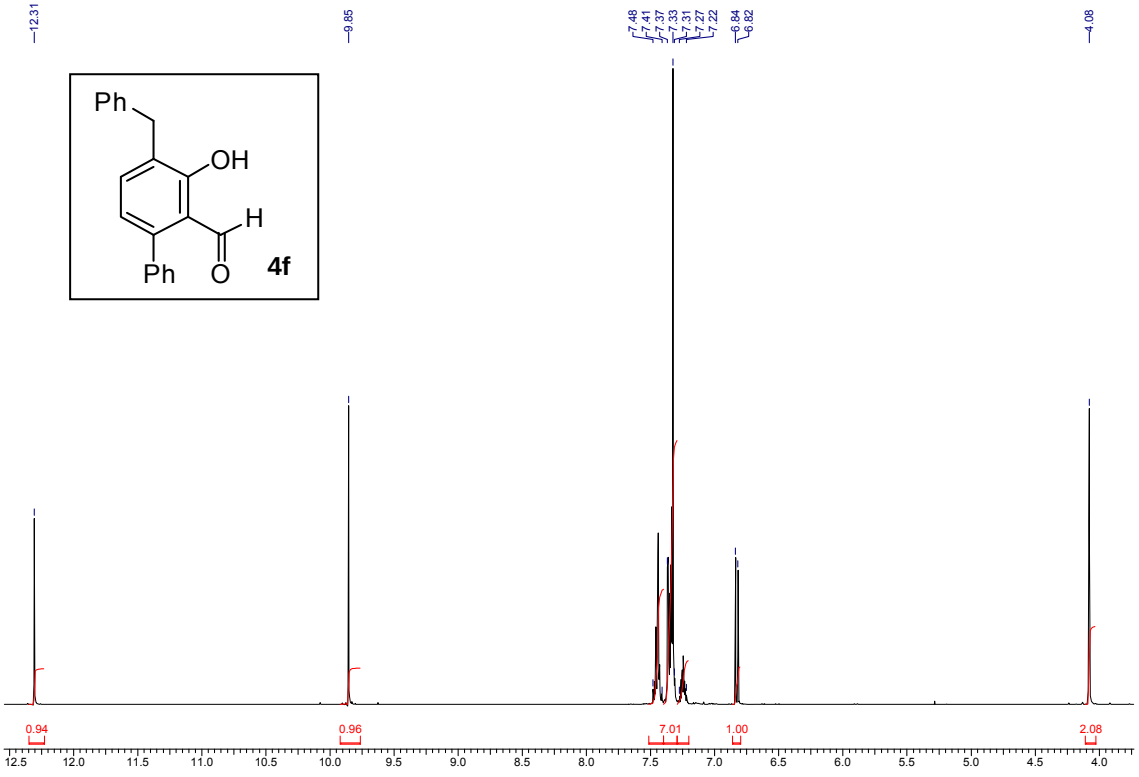

197.66
162.32
145.33
137.64
137.38
133.71
130.05
128.30
127.98
120.66
117.82
77.00
34.80
29.23

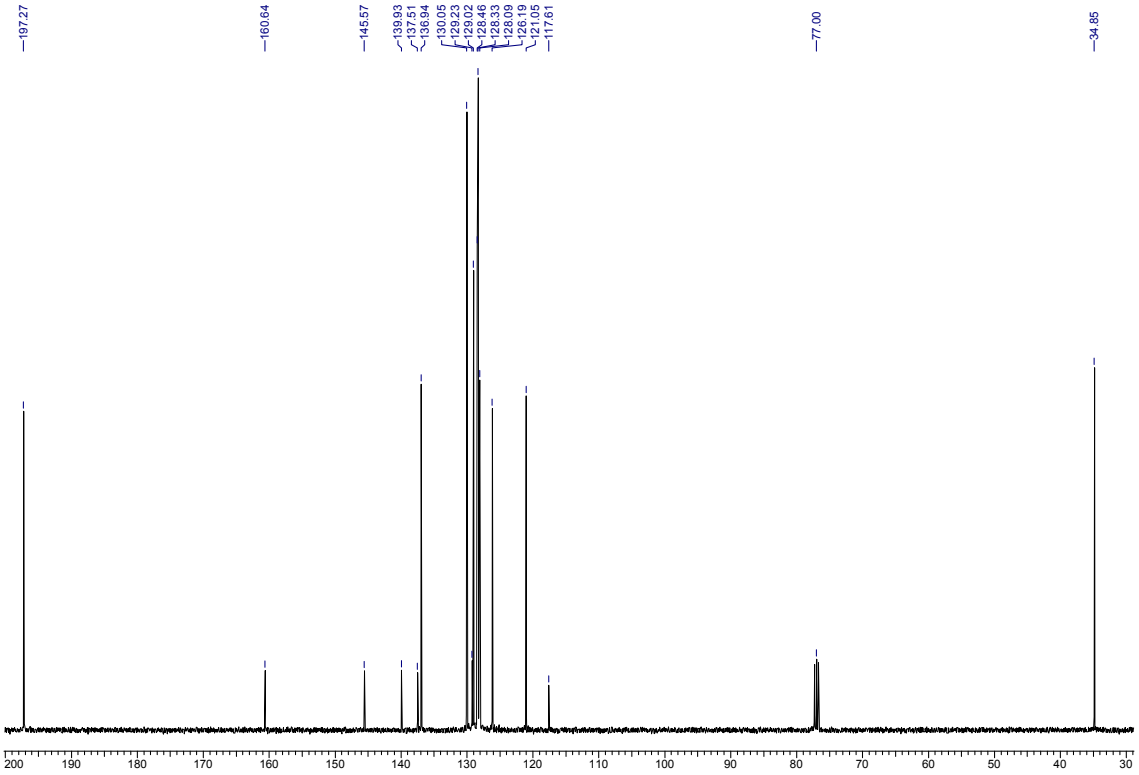

11.91
9.83
7.54
7.52
7.50
7.46
7.44
7.37
7.37
7.36
7.36
7.35
7.25
7.00
6.98
6.89
6.89
6.87
6.87
OH
H
Ph
O
4d
0.98
1.00
6.65
1.03
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0

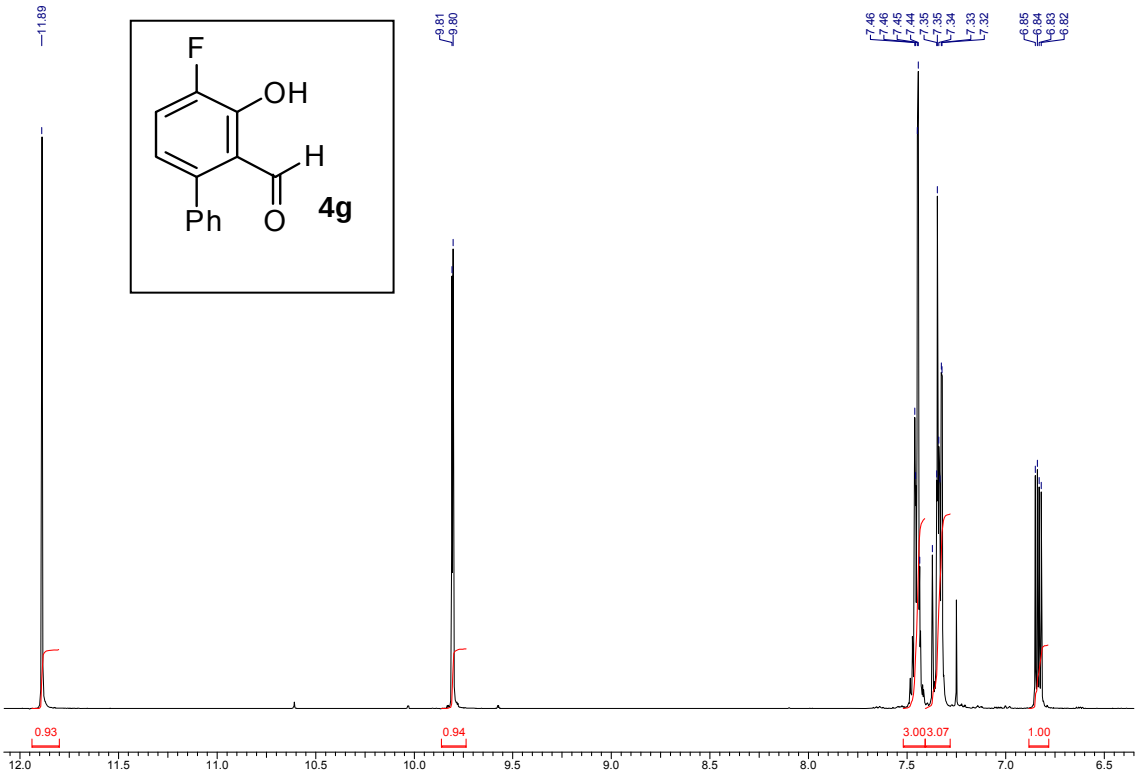

197.10
162.81
147.48
137.45
136.55
130.03
128.40
128.27
121.47
118.03
116.94
77.00
195
190
185
180
175
170
165
160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75

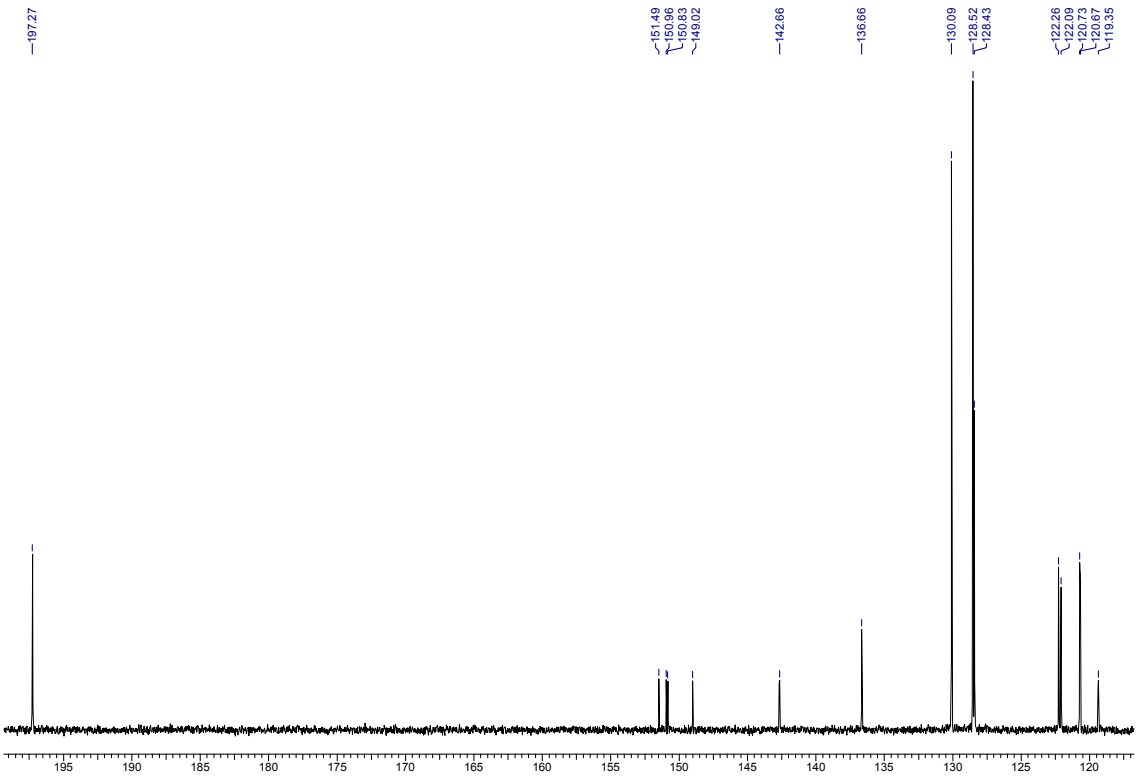

12.46
9.90
7.65
7.65
7.63
7.61
7.48
7.47
7.46
7.42
7.42
7.40
7.25
6.99
6.97
Ph
OH
H
Ph
O
4e
0.92
0.95
3.06
8.11
1.00
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0

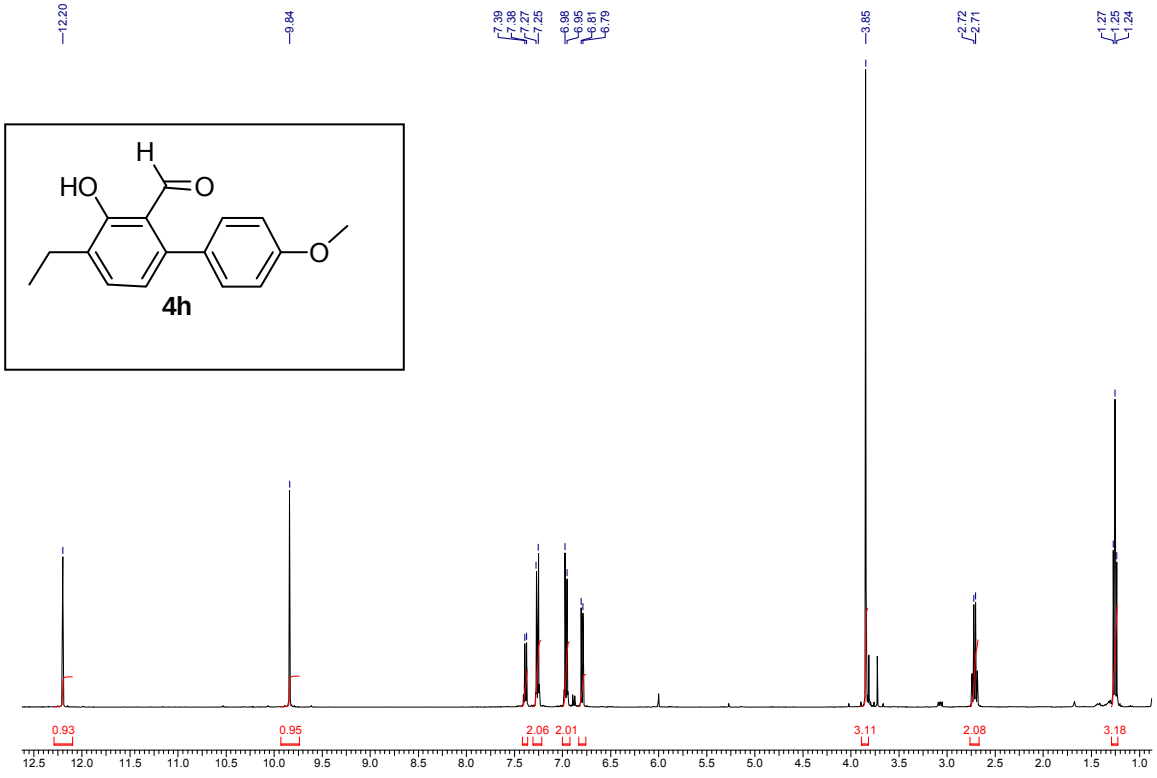

197.47
160.08
146.82
137.36
137.27
136.44
130.08
129.67
129.30
128.48
128.34
128.28
127.62
121.49
118.10
195
190
185
180
175
170
165
160
155
150
145
140
135
130
125
120

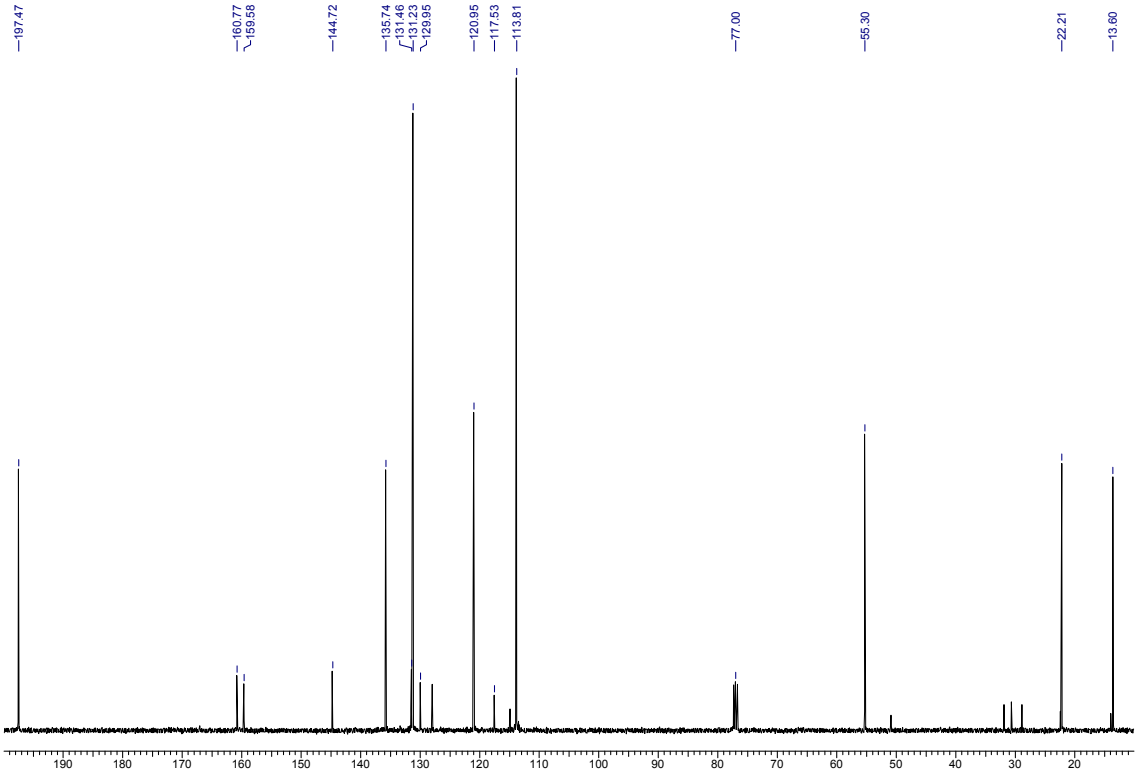

12.31
9.85
7.48
7.41
7.37
7.33
7.31
7.27
7.22
6.84
6.82
4.08
Ph
OH
H
Ph
O
4f
0.94
0.96
7.01
1.00
2.08

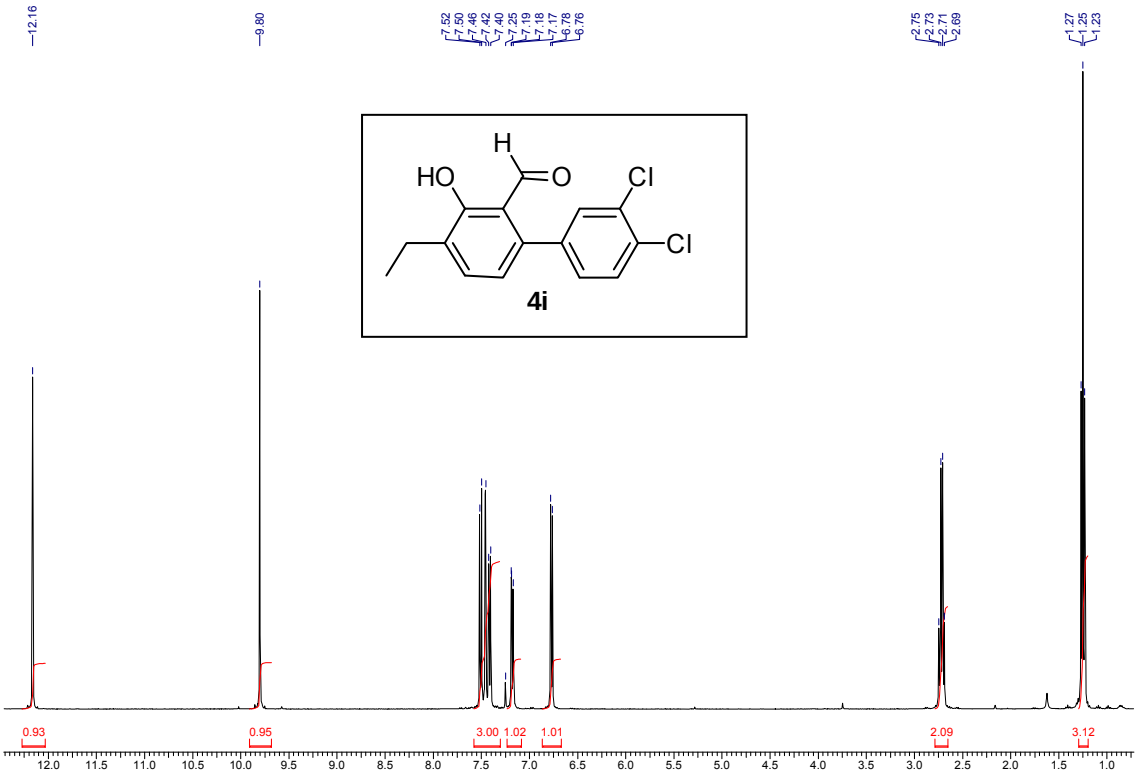

197.27
160.64
145.57
139.93
137.51
136.94
130.05
129.23
129.02
128.46
128.33
128.09
126.19
121.05
117.61
77.00
34.85

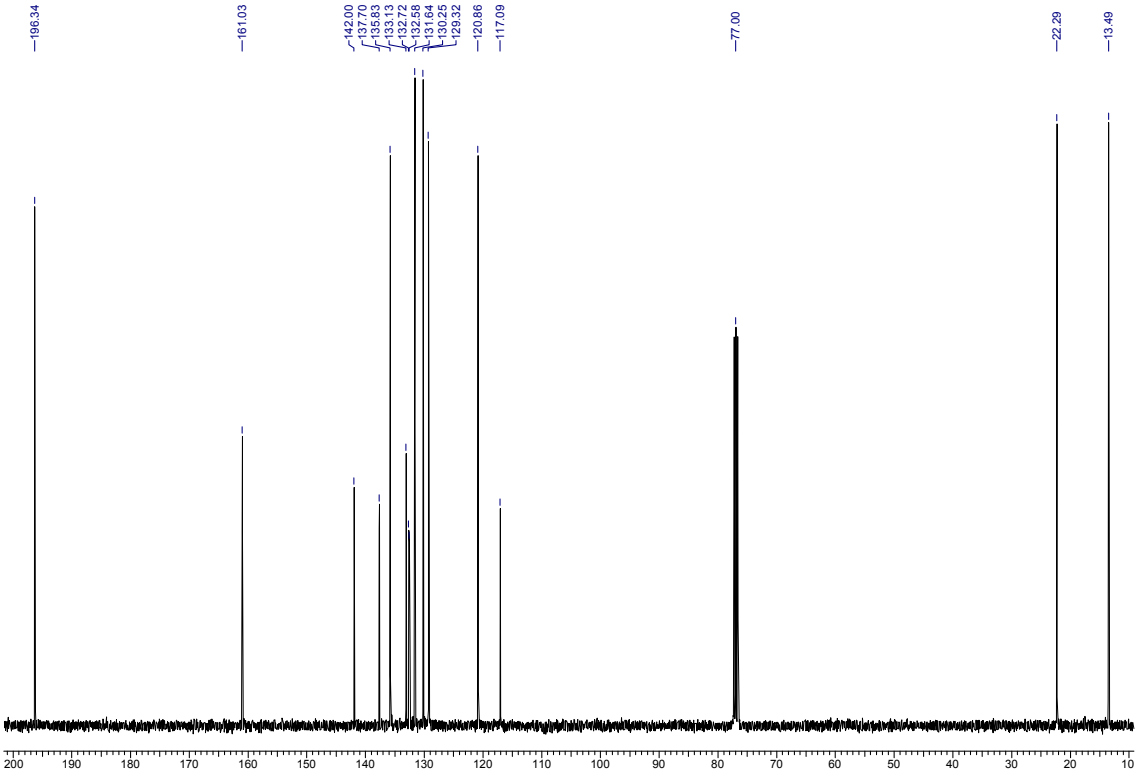

11.89
9.81
9.80
7.46
7.46
7.45
7.44
7.35
7.35
7.34
7.33
7.32
6.85
6.84
6.83
6.82
F
OH
H
Ph
O
4g
0.93
0.94
3.00
3.07
1.00
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5

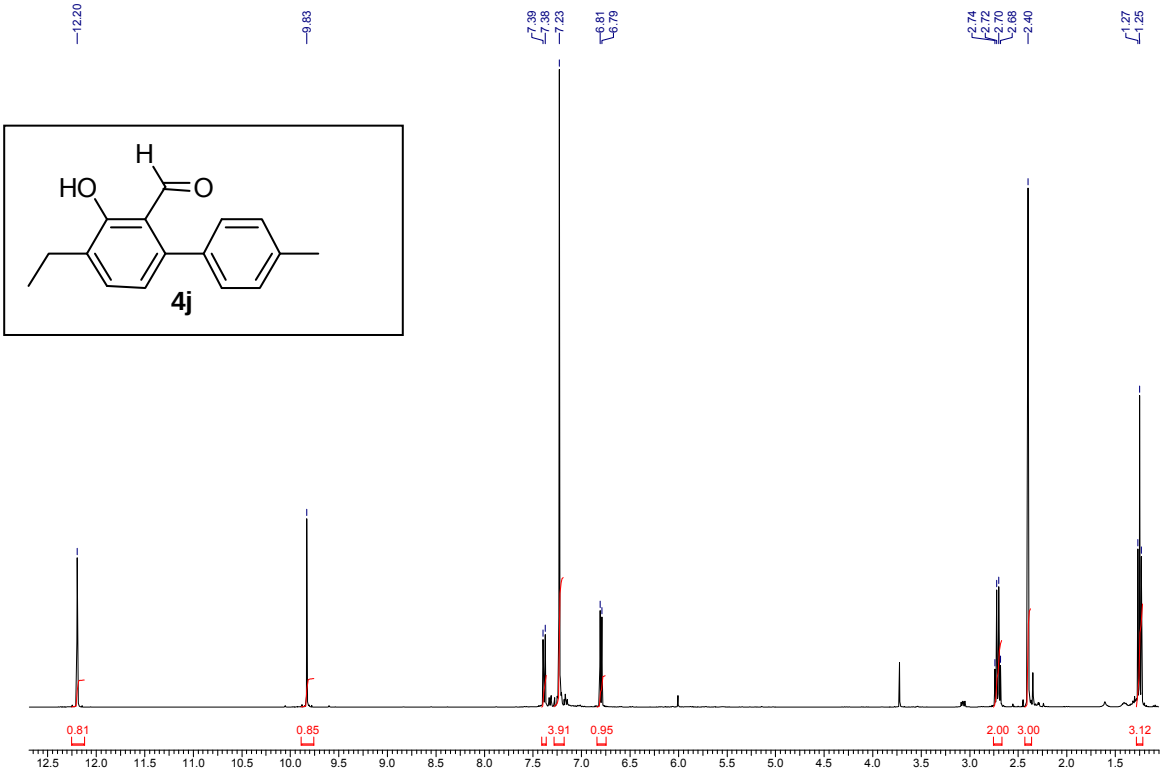

197.27
151.49
150.96
150.83
149.02
142.66
136.66
130.09
128.52
128.43
122.26
122.09
120.73
120.67
119.35
195
190
185
180
175
170
165
160
155
150
145
140
135
130
125
120

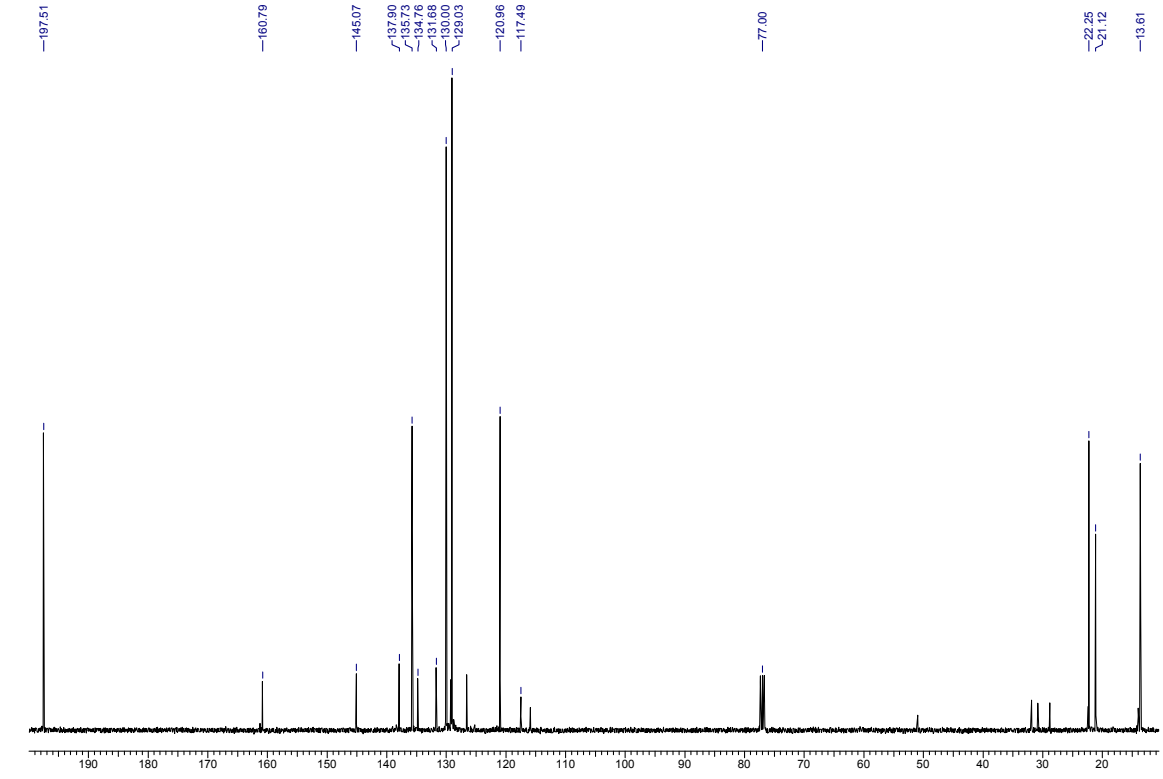

12.20
9.84
7.39
7.38
7.27
7.25
6.98
6.95
6.81
6.79
3.85
2.72
2.71
1.27
1.25
1.24
HO
H
O
O
4h
0.93
0.95
2.06
2.01
3.11
2.08
3.18

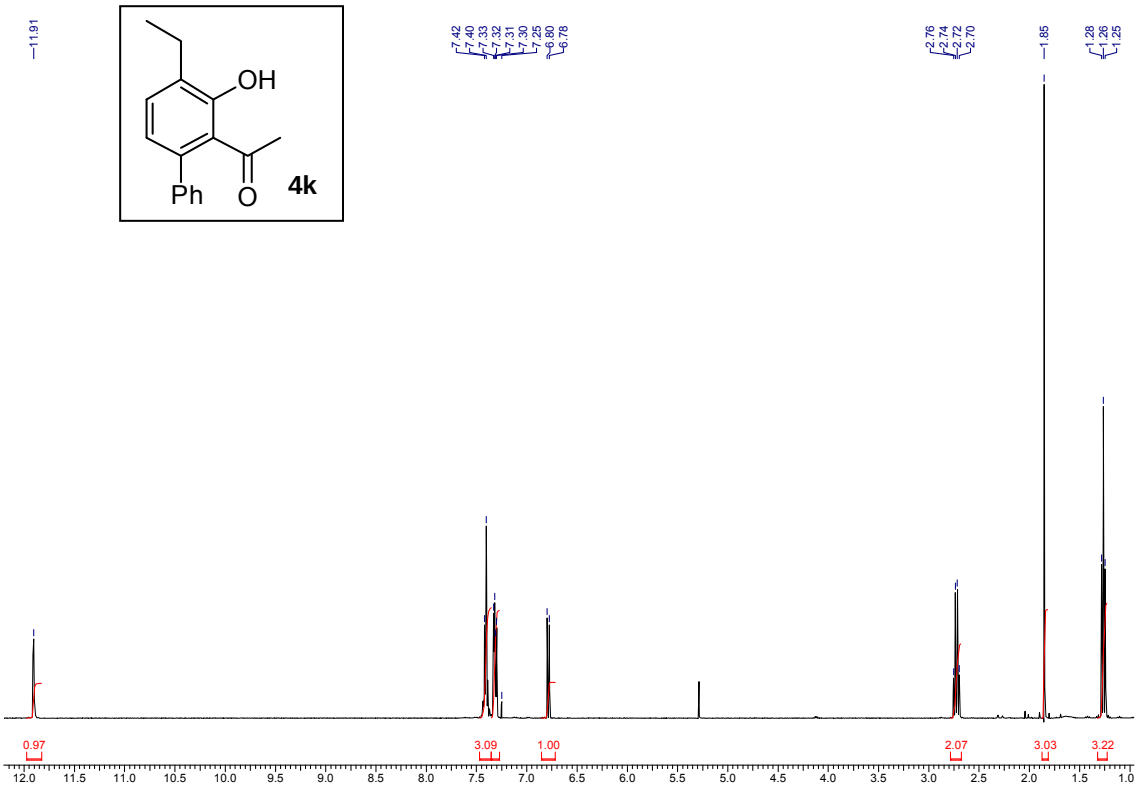

197.47
160.77
159.58
144.72
135.74
131.46
131.23
129.95
120.95
117.53
113.81
77.00
55.30
22.21
13.60

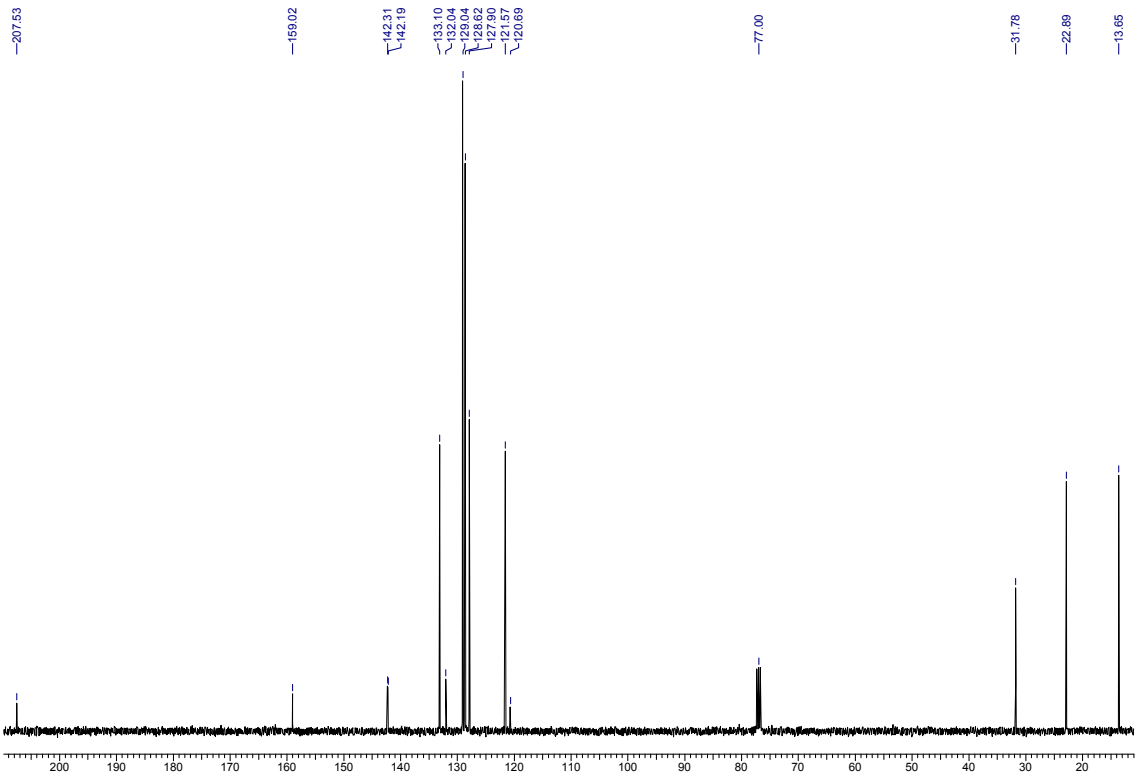

12.16
9.80
7.52
7.50
7.46
7.42
7.40
7.25
7.19
7.18
7.17
6.78
6.76
2.75
2.73
2.71
2.69
1.27
1.25
1.23
H
HO
O
Cl
Cl
4i
0.93
0.95
3.00
1.02
1.01
2.09
3.12

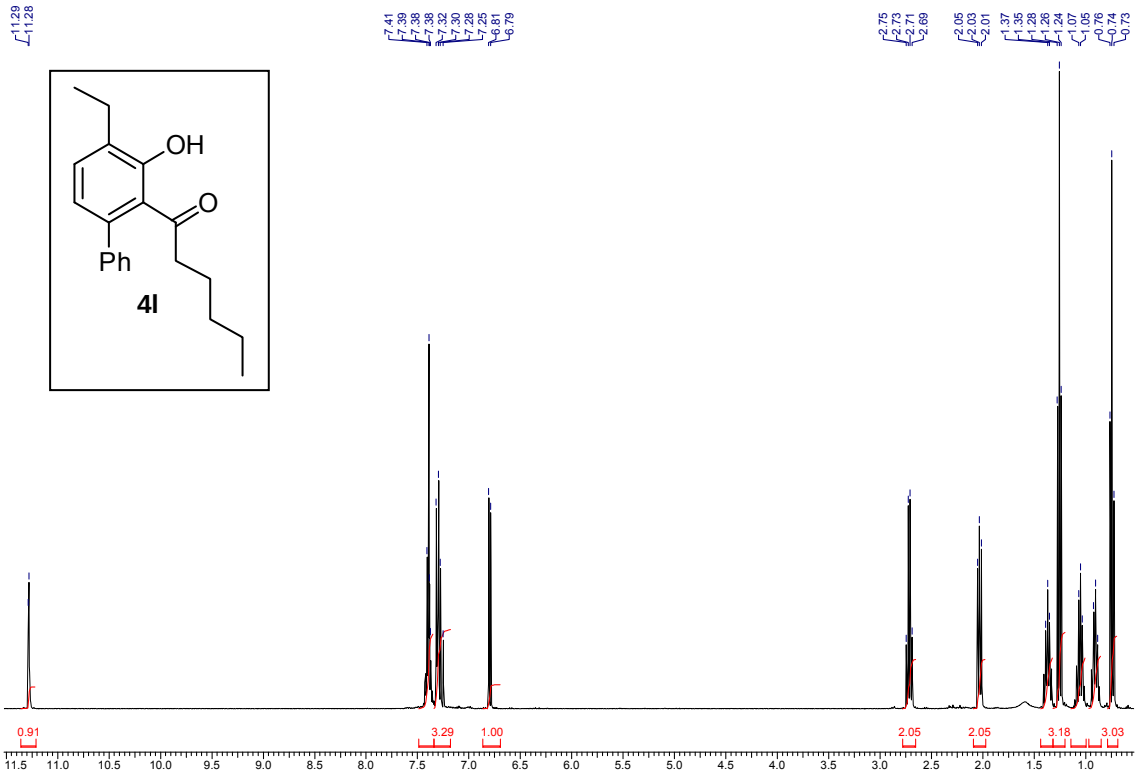

196.34
161.03
142.00
137.70
135.83
133.13
132.72
132.58
131.64
130.25
129.32
120.86
117.09
77.00
22.29
13.49

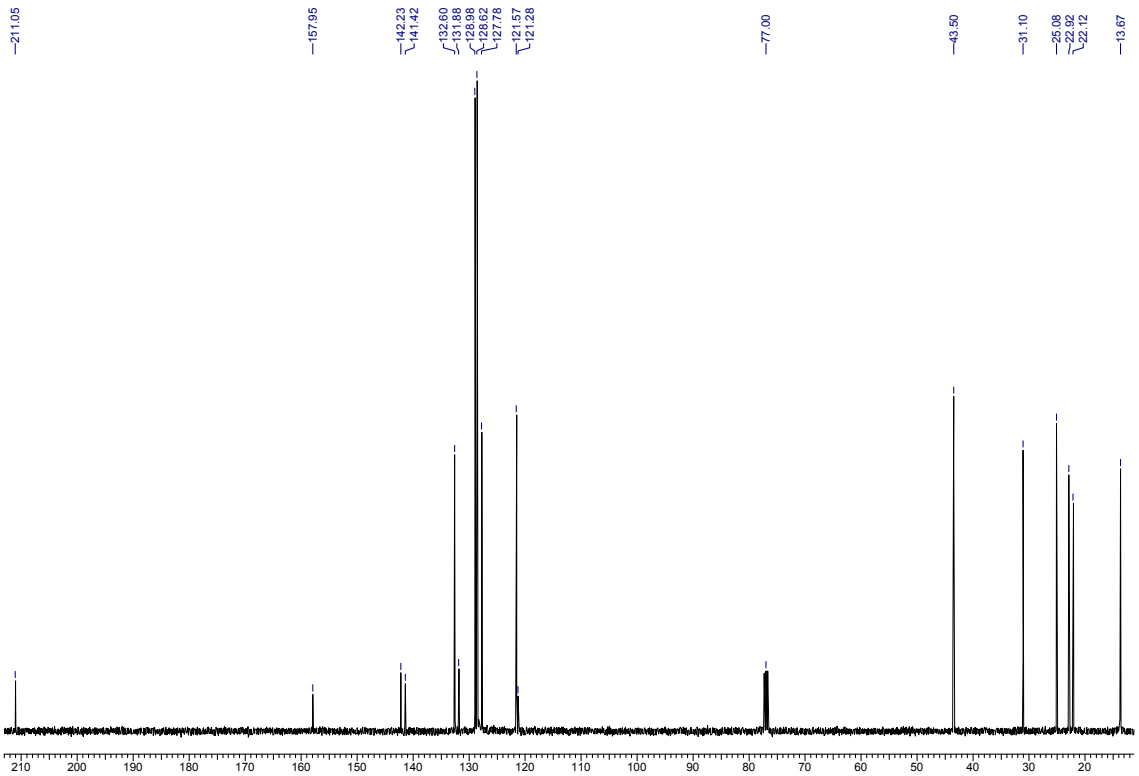

12.20
9.83
7.39
7.38
7.23
6.81
6.79
2.74
2.72
2.70
2.68
2.40
1.27
1.25
H
HO
O
4j
0.81
0.85
3.91
0.95
2.00
3.00
3.12

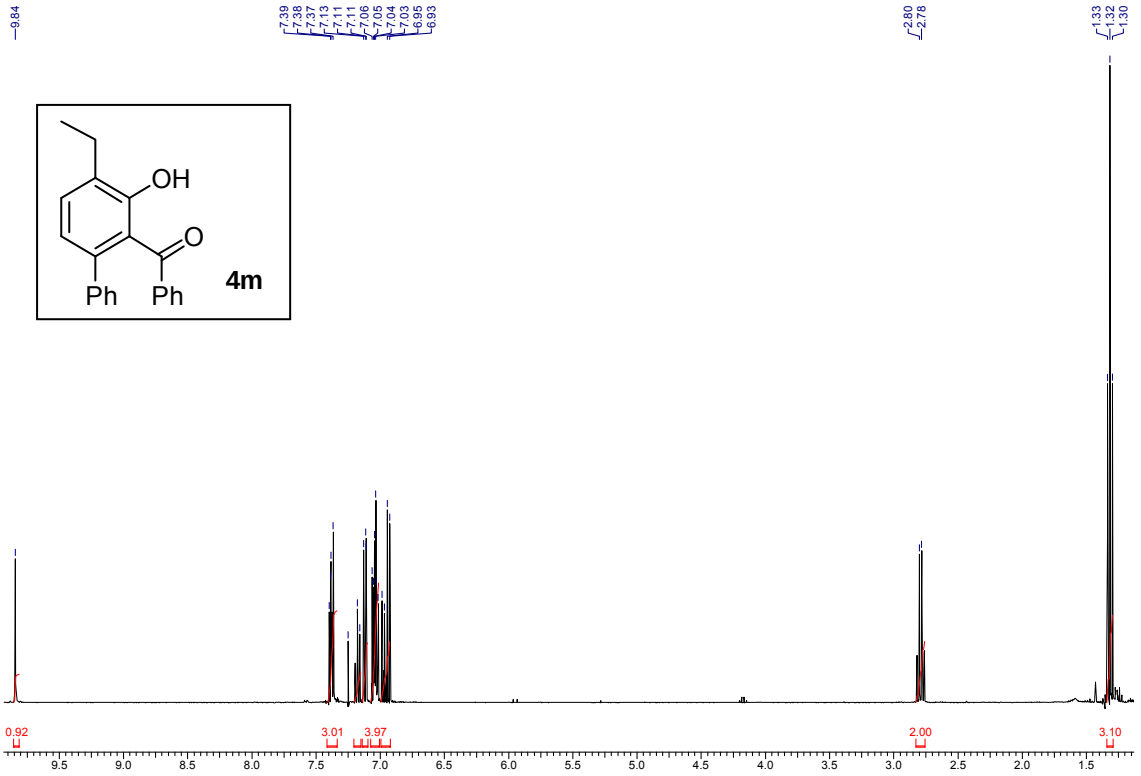

197.51
160.79
145.07
137.90
135.73
134.76
131.68
130.00
129.03
120.96
117.49
77.00
22.25
21.12
13.61

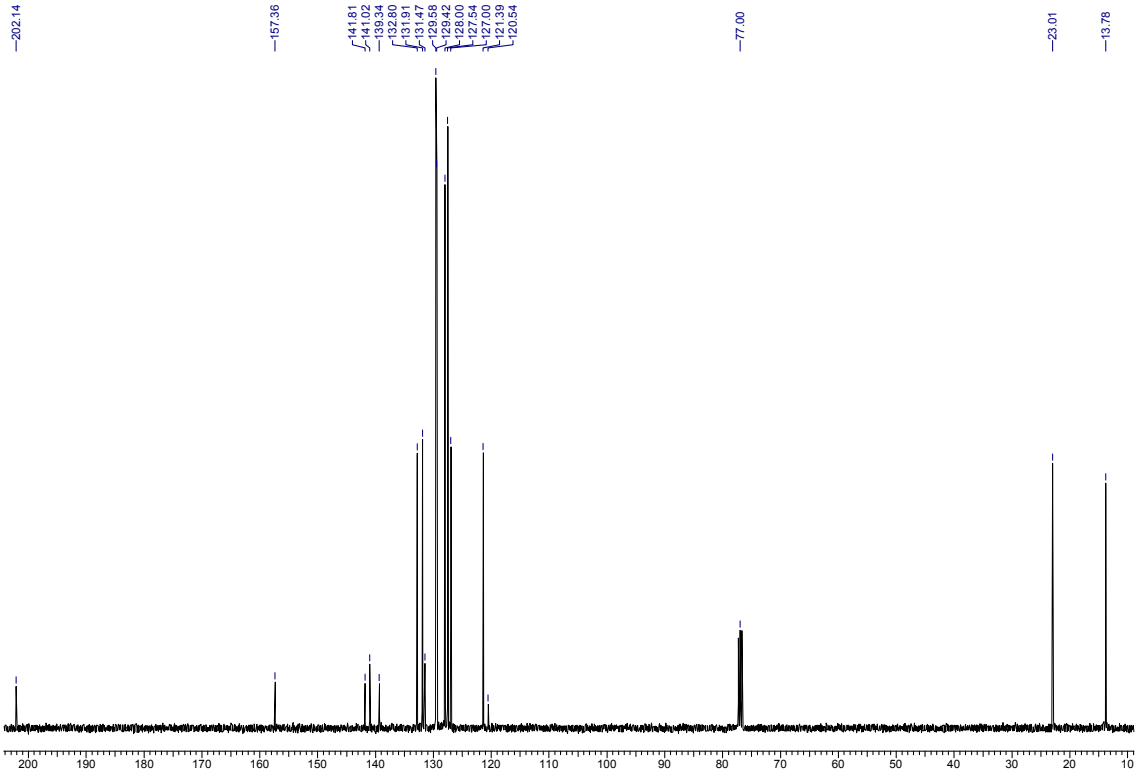

11.91
7.42
7.40
7.33
7.32
7.31
7.30
7.25
6.80
6.78
2.76
2.74
2.72
2.70
1.85
1.28
1.26
1.25
OH
Ph
O
4k
0.97
3.09
1.00
2.07
3.03
3.22

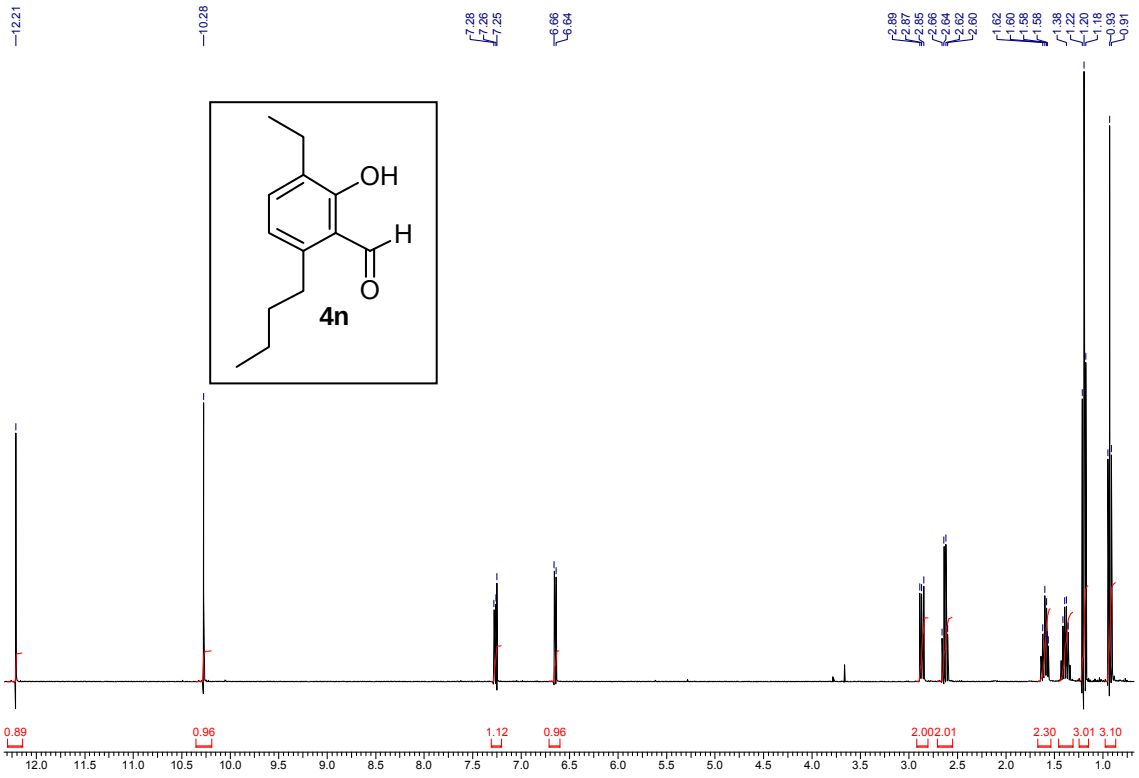

207.53
159.02
142.31
142.19
133.10
132.04
129.04
128.62
127.90
121.57
120.69
77.00
31.78
22.89
13.65

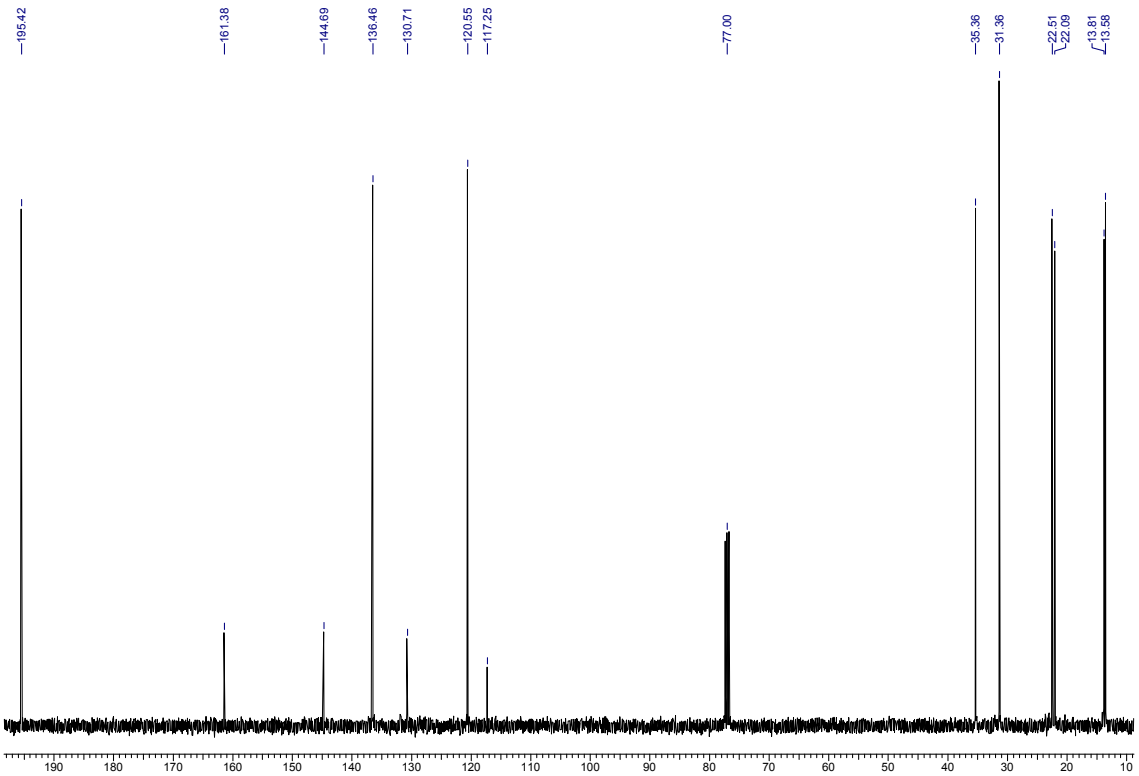

11.29
11.28
7.41
7.39
7.38
7.38
7.32
7.30
7.28
7.25
6.81
6.79
2.75
2.73
2.71
2.69
2.05
2.03
2.01
1.37
1.35
1.28
1.26
1.24
1.07
1.05
0.76
0.74
0.73
OH
O
Ph
4l
0.91
3.29
1.00
2.05
2.05
3.18
3.03

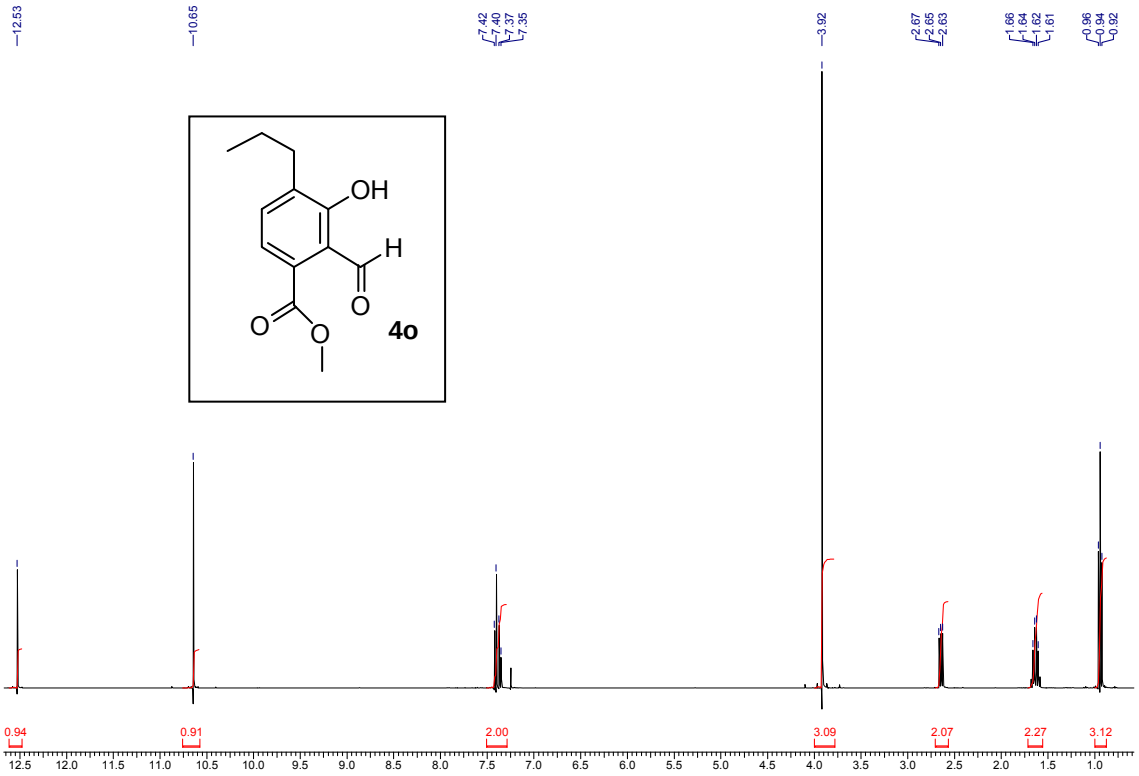

211.05
157.95
142.23
141.42
132.60
131.88
128.98
128.62
127.78
121.57
121.28
77.00
43.50
31.10
25.08
22.92
22.12
13.67

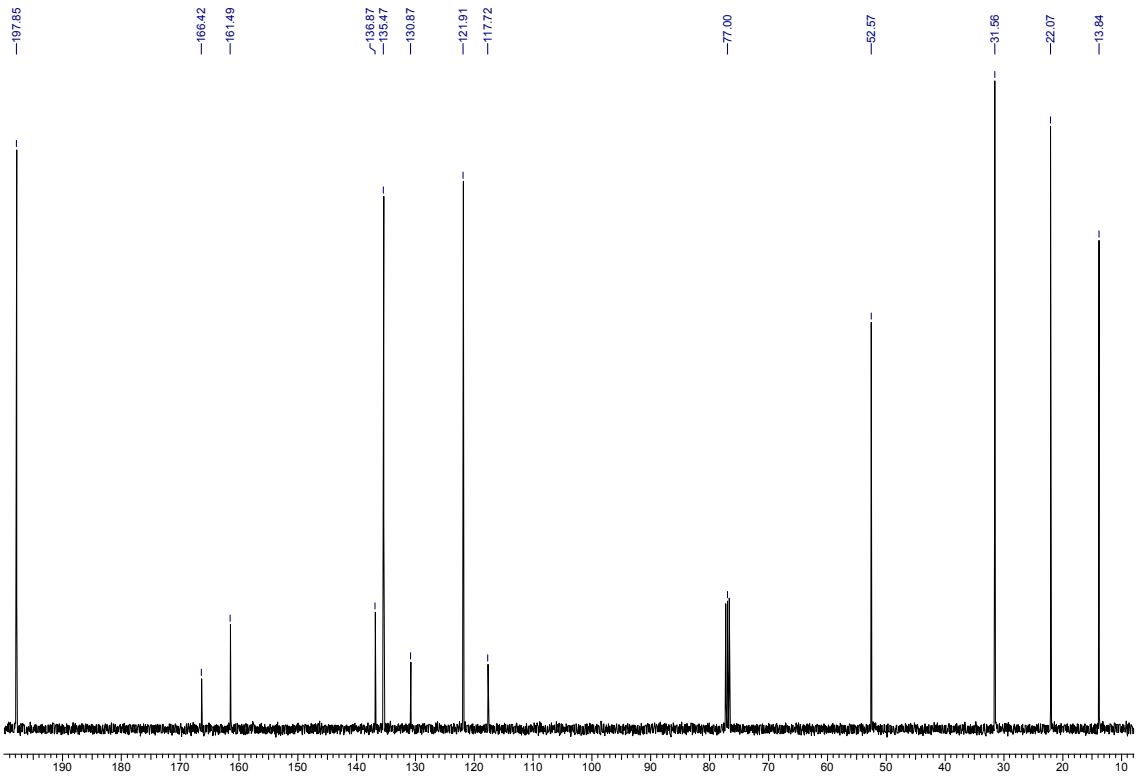

9.84
7.39
7.38
7.37
7.13
7.11
7.11
7.06
7.05
7.04
7.03
6.95
6.93
2.80
2.78
1.33
1.32
1.30
OH
O
Ph
Ph
4m
0.92
3.01
3.97
2.00
3.10

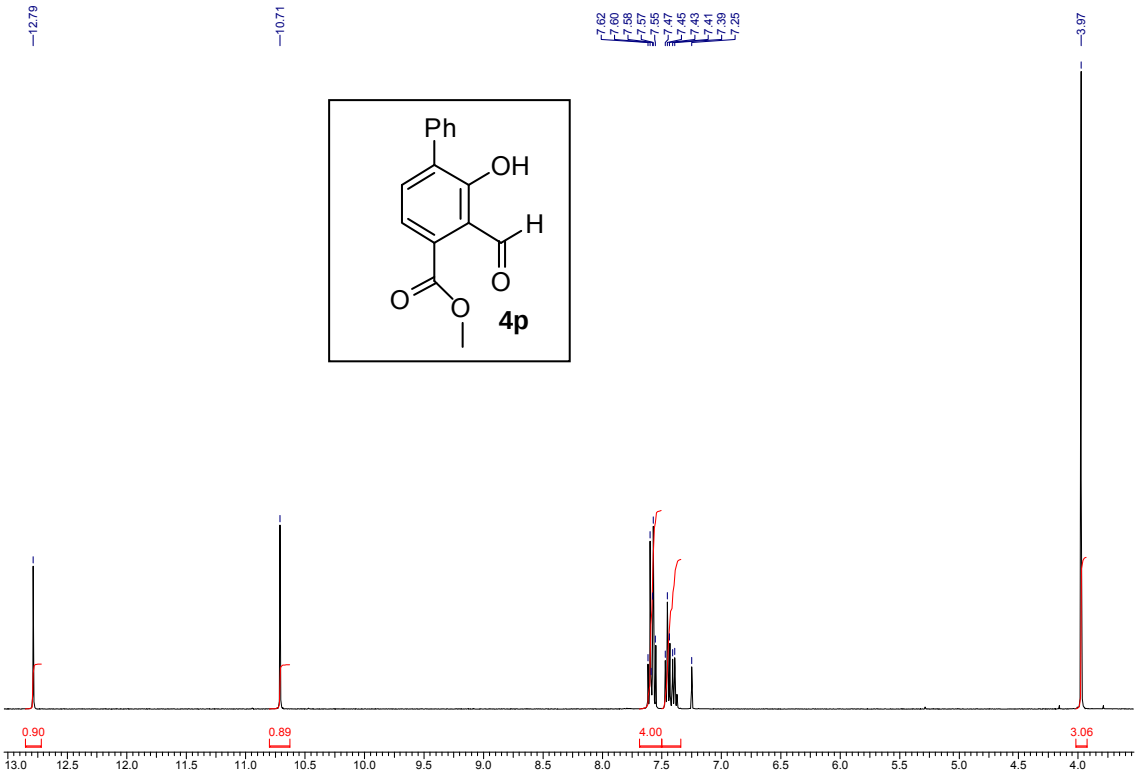

202.14
157.36
141.81
141.02
139.34
132.80
131.91
131.47
129.58
129.42
128.00
127.54
127.00
121.39
120.54
77.00
23.01
13.78

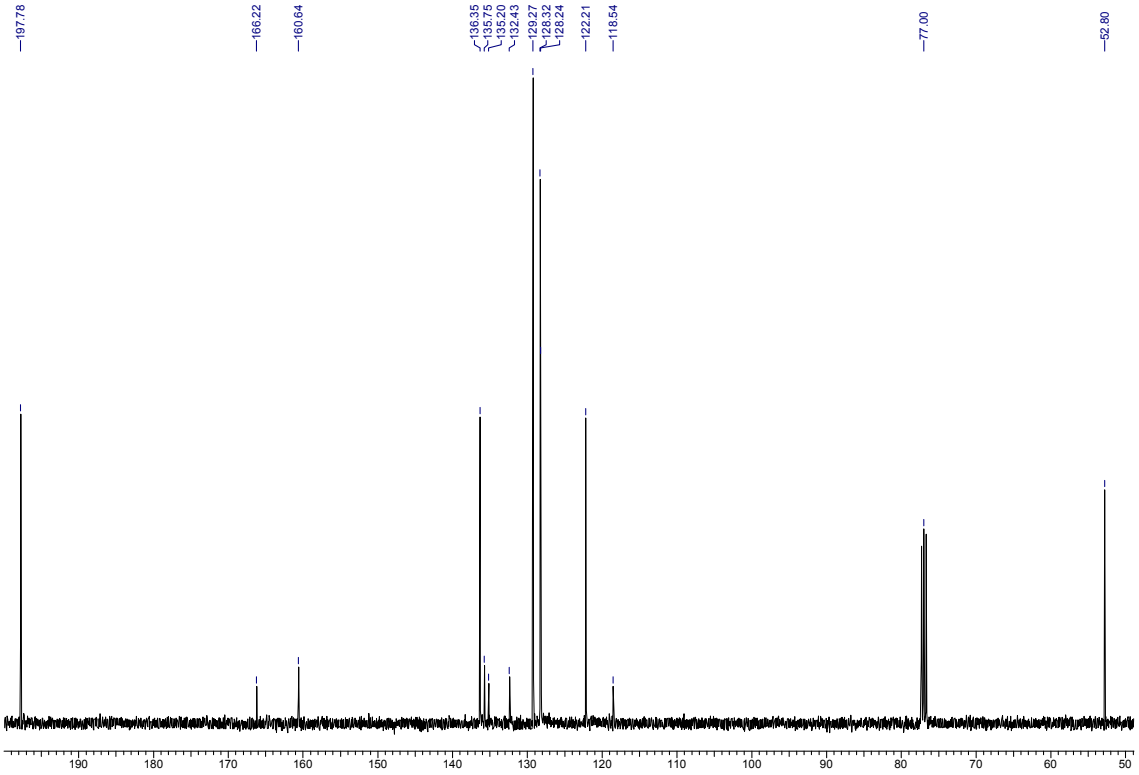

12.21
10.28
7.28
7.26
7.25
6.66
6.64
2.89
2.87
2.85
2.66
2.64
2.62
2.60
1.62
1.60
1.58
1.58
1.38
1.22
1.20
1.18
0.93
0.91
OH
H
O
4n
0.89
0.96
1.12
0.96
2.00
2.01
2.30
3.01
3.10

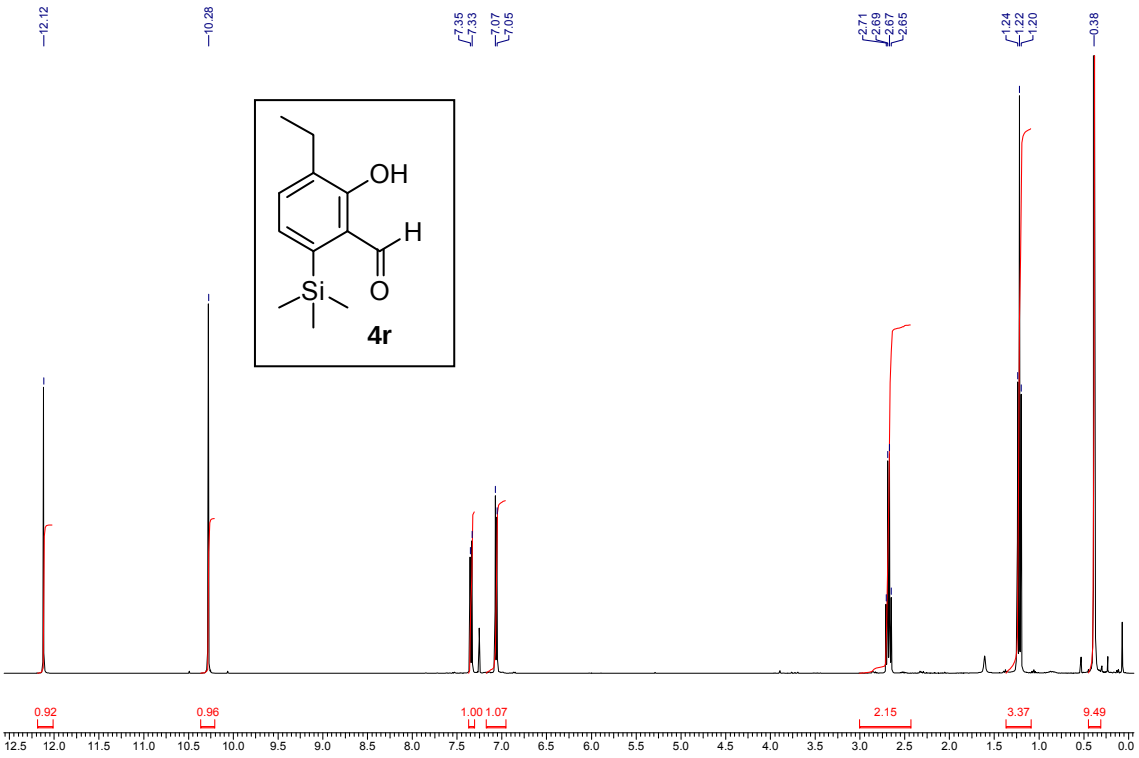

195.42
161.38
144.69
136.46
130.71
120.55
117.25
77.00
35.36
31.36
22.51
22.09
13.81
13.58

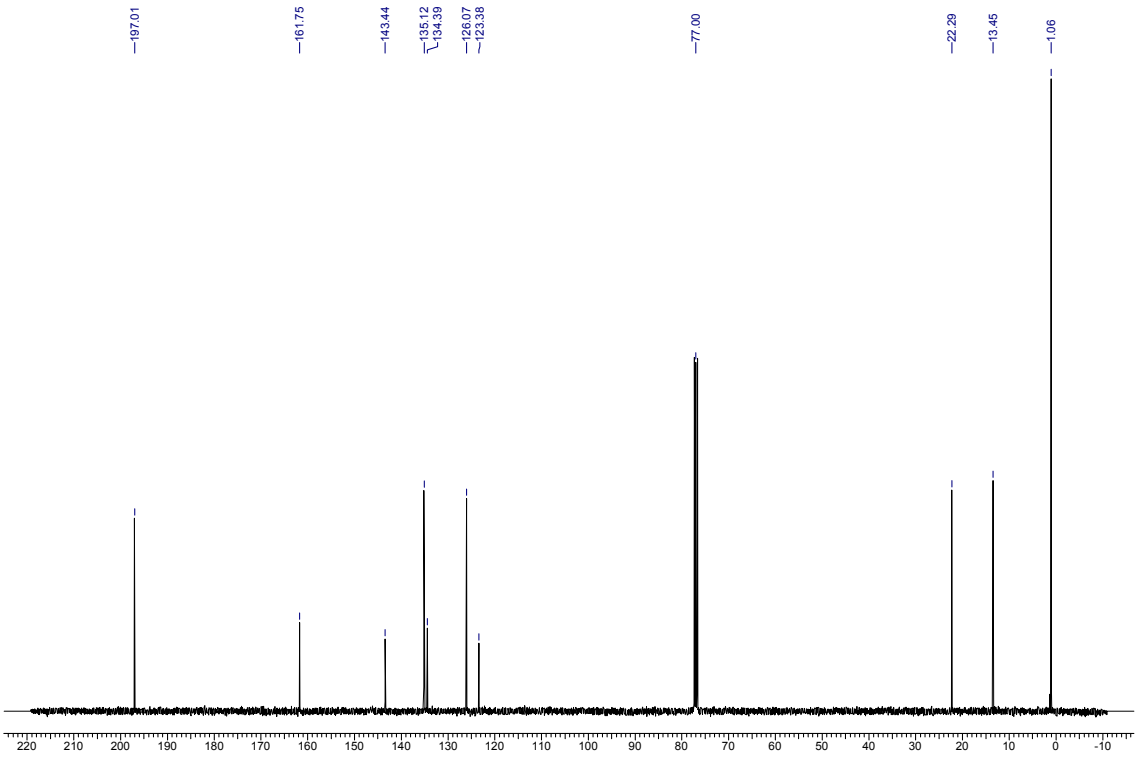

12.53
10.65
7.42
7.40
7.37
7.35
3.92
2.67
2.65
2.63
1.66
1.64
1.62
1.61
0.96
0.94
0.92
OH
H
O
O
O
4o
0.94
0.91
2.00
3.09
2.07
2.27
3.12

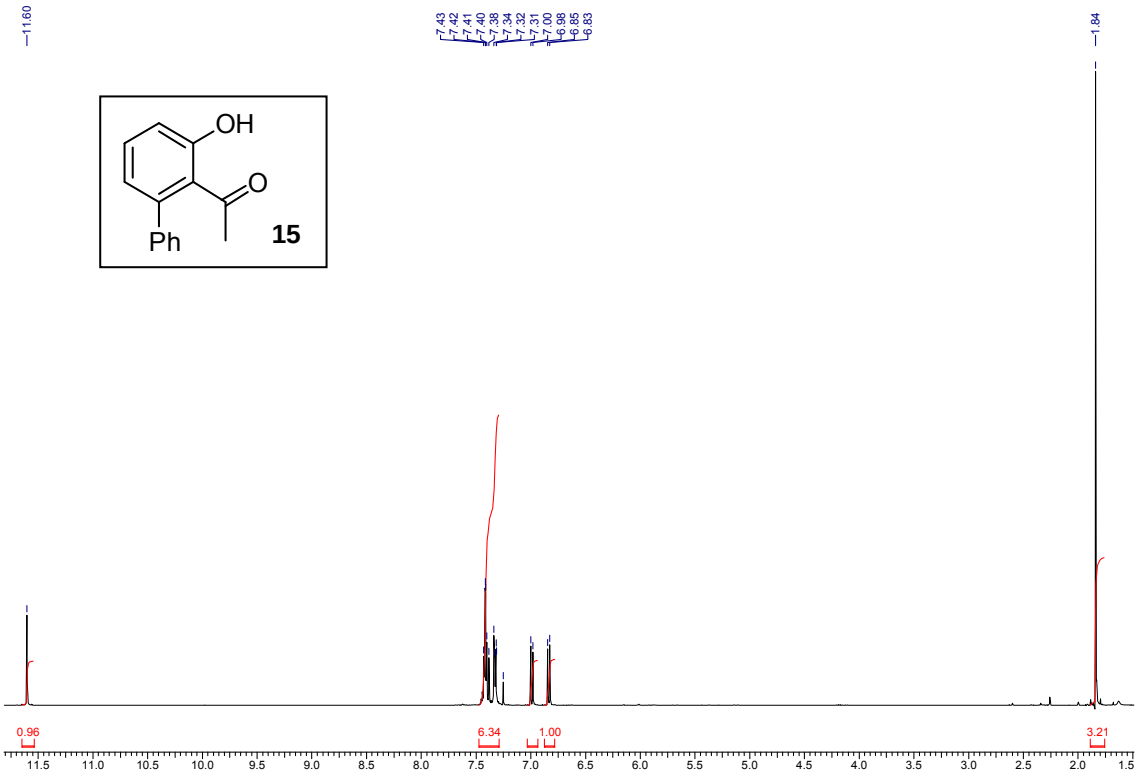

197.85
166.42
161.49
136.87
135.47
130.87
121.91
117.72
77.00
52.57
31.56
22.07
13.84

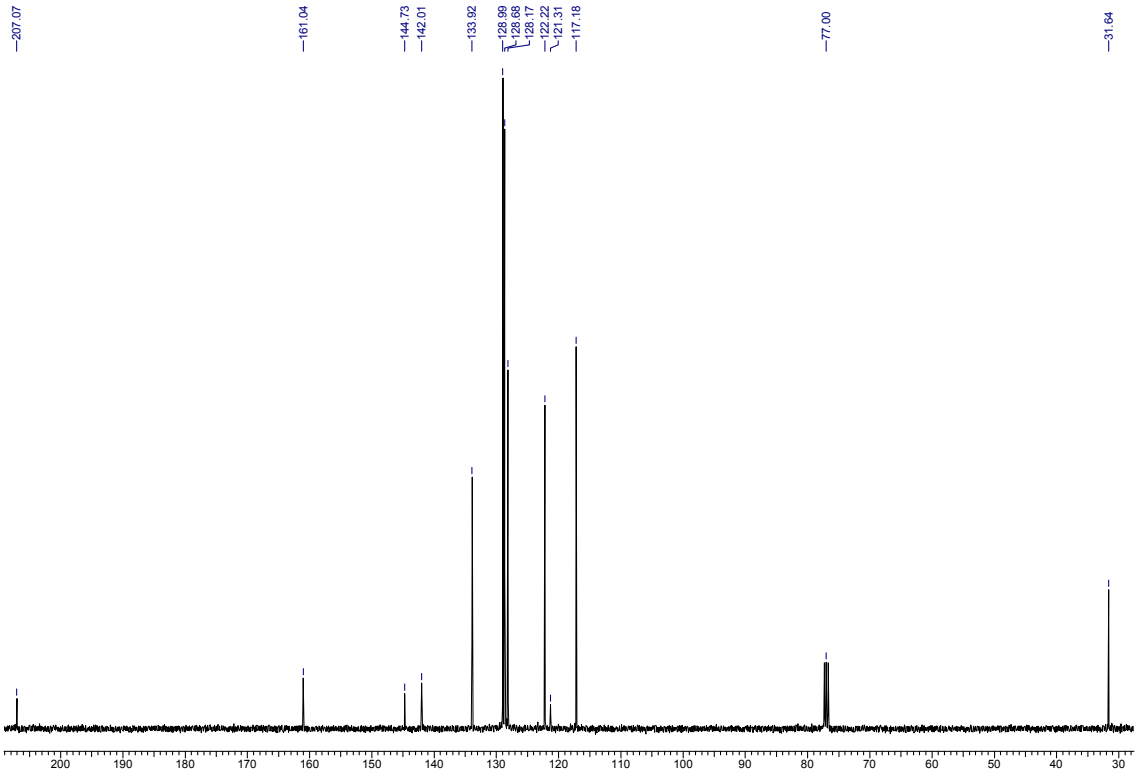

12.79
10.71
7.62
7.60
7.58
7.57
7.55
7.47
7.45
7.43
7.41
7.39
7.25
3.97
Ph
OH
H
O
O
O
4p
0.90
0.89
4.00
3.06

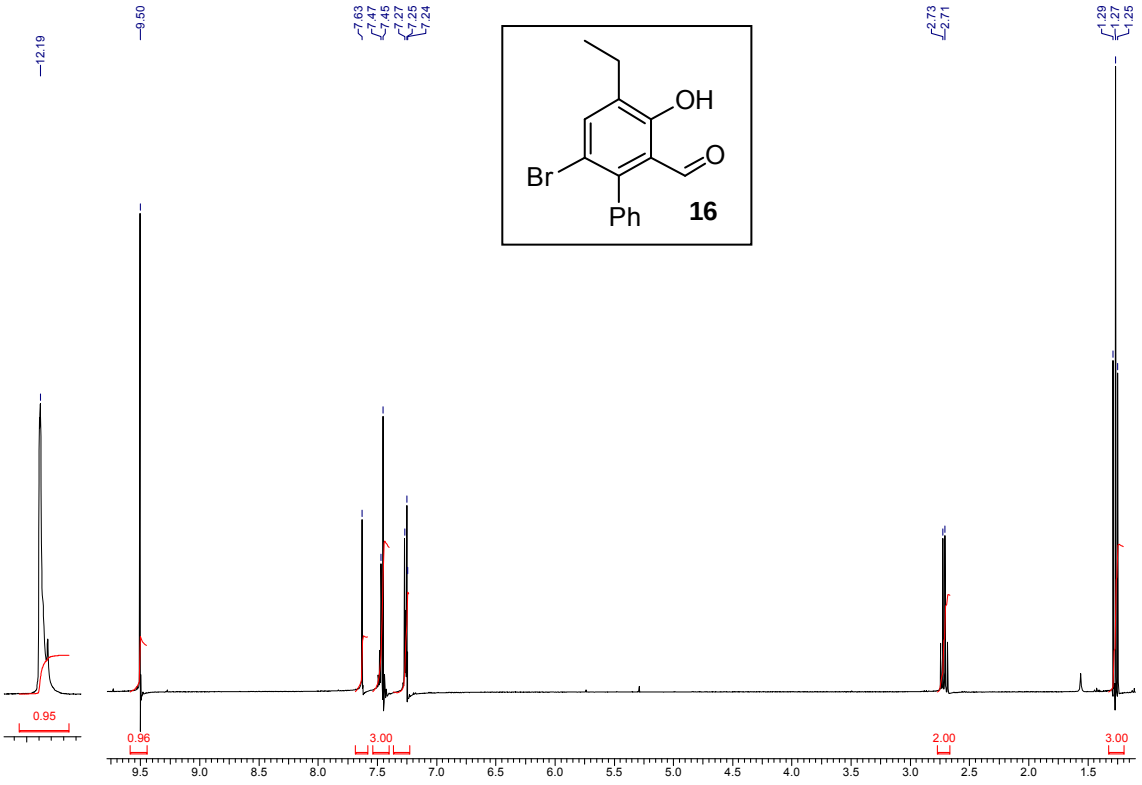

197.78
166.22
160.64
136.35
135.75
135.20
132.43
129.27
128.32
128.24
122.21
118.54
77.00
52.80

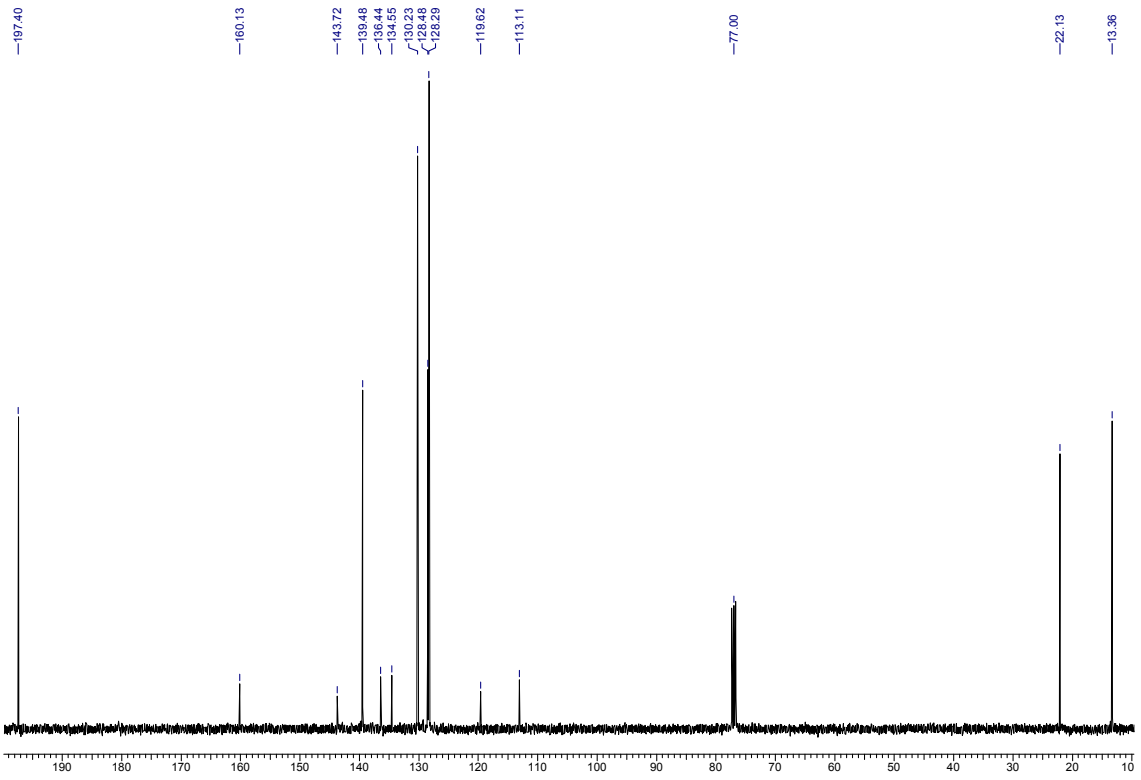

12.12
10.28
7.35
7.33
7.07
7.05
2.71
2.69
2.67
2.65
1.24
1.22
1.20
0.38
OH
H
O
Si
4r
0.92
0.96
1.00
1.07
2.15
3.37
9.49


197.01
161.75
143.44
135.12
134.39
126.07
123.38
77.00
22.29
13.45
1.06

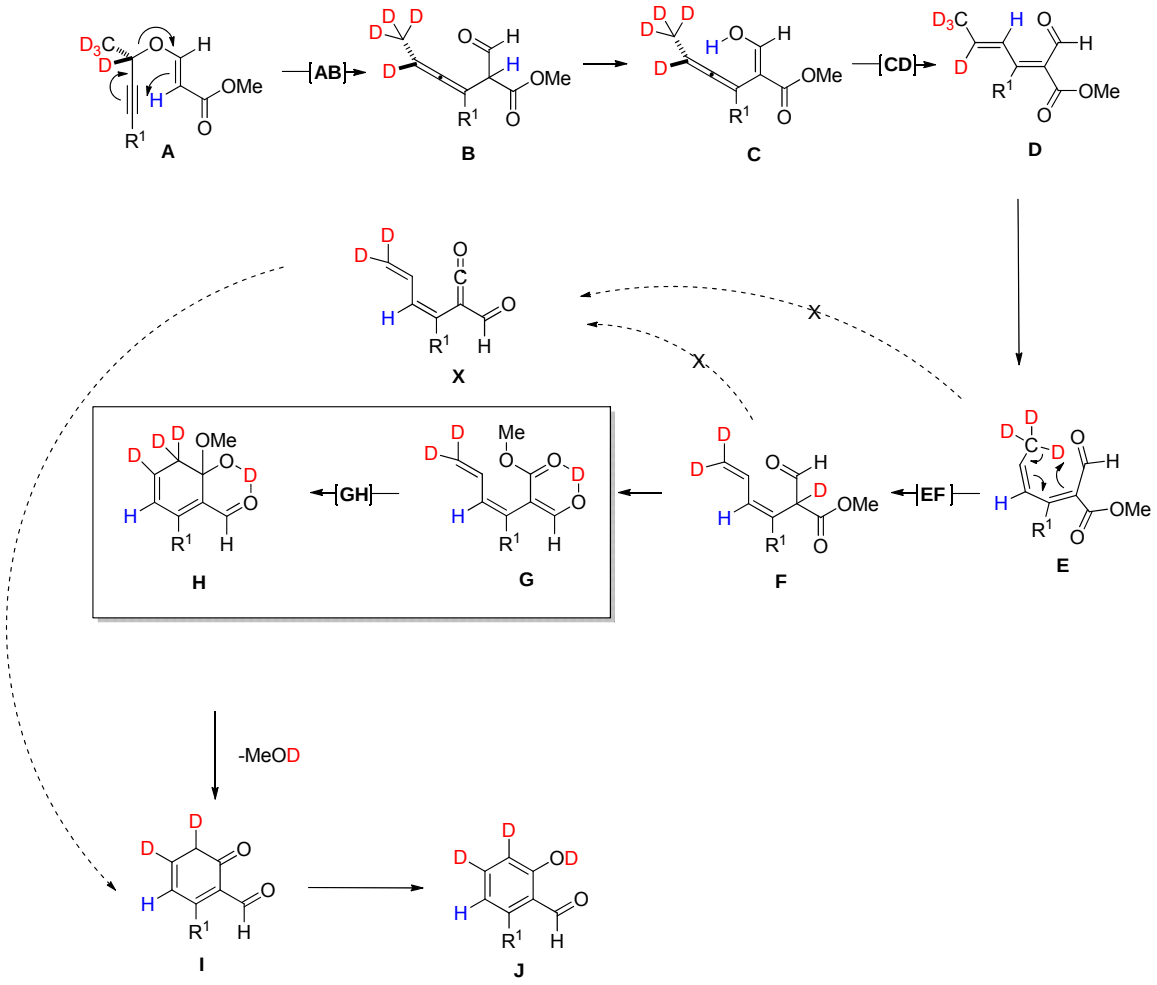

11.60
7.43
7.42
7.41
7.40
7.38
7.34
7.32
7.31
7.00
6.98
6.85
6.83
1.84
OH
O
Ph
15
0.96
6.34
1.00
3.21


207.07
161.04
144.73
142.01
133.92
128.99
128.68
128.17
122.22
121.31
117.18
77.00
31.64


12.19
9.50
7.63
7.47
7.45
7.27
7.25
7.24
2.73
2.71
1.29
1.27
1.25
OH
O
Br
Ph
16
0.95
0.96
3.00
2.00
3.00


197.40
160.13
143.72
139.48
136.44
134.55
130.23
128.48
128.29
119.62
113.11
77.00
22.13
13.36

Computational section. To provide further evidence of the proposed mechanism, DFT theoretical calculations at B3LYP/6-31+G (d,p) level were performed in Gaussian 09W.[12] In the expected intramolecular process, the transition states (TS) on the reaction coordinate were evaluated using QST3 method, with an initial semiempirical (PM6) tentative TS. The results are summarized in Scheme 1 (Table 1). They agree with the deuteration studies (See main text, [Eq. (4)] and page S10). Thermochemical studies were conducted in gas phase and at 200ºC. We have evaluated the TS corresponding to the intramolecular steps of this process. We have assumed that the intermolecular enolization processes are not relevant to this study; in any case, they will never be the rate determining steps of this reaction.



Scheme 1: Possible paths to the aromatic product (in brackets evaluated transition states shown in Fig. 1)

Table 1. Energy values are given in Kcal/mol

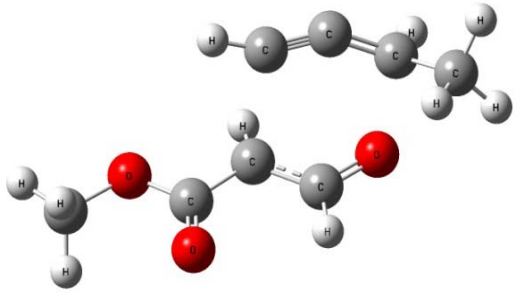
Paths	R_1	ΔH	ΔH^*	ΔG_{200^oC}	$\Delta G^*_{200^oC}$
A→B	H	-16.1	29.2	-18.8	28.0
B→C	H	-4.9		-1.5	
C→D	H	-18.8	16.8	-19.1	34.0
D→E	H	2.2		2.0	
E→F	H	12.3	41.2	10.1	41.7
	Ph	1.1	29.5	1.7	30.5
	TMS	1.2	38.4	0.0	29.5
F→G	H	-7.0		2.5	
G→H	H	5.1	40.4	9.1	42.7
	Ph	8.2	39.1	12.2	41.8
	TMS	10.0	43.2	14.8	46.3
H→I	H	2.0		-5.2	
I→J	H	-27.0		-20.3	

Overall, the enthalpy and entropy change are strongly negative (for $R^1=R^2=R^3=H$, ΔH= -52.1 kcal/mol, ΔG=-41.2 kcal/mol), and the proposed mechanism involves: 1) an initial exothermic [3,3]-propargylic sigmatropic rearrangement to the allenyl intermediate **B**, 2) the isomerization to the conjugated dienes **D** (*E*,*E*-isomer) and **E** (*E*,*Z*-isomer), 3) a key [1,5]H-shift to intermediate **F**, 4) a key cyclization that forms the 6-membered ring **H**, 5) elimination of methanol, and 6) the final aromatization step.

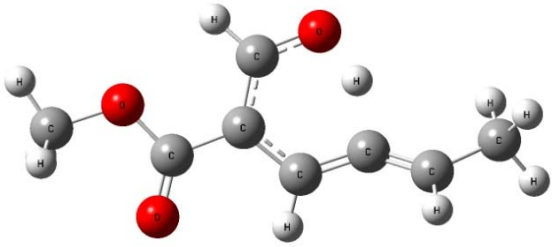
The formation of aromatic precursor (**I**) via 6π-electrocyclization of a ketene intermediate (**X**) was also evaluated. However, the formation of this intermediate from **E** leads to transition states which are extremely high in energy (86.5 kcal / mol for R^1=H). On the other hand, we could not even find a suitable reaction path from the intermediate **F**. We have therefore ruled out the involvement of the ketene intermediate in the process.

In the first step, previous semiempirical (PM6 Hamiltonian) calculations show that the energies involved in the rearrangement to both allenyl stereoisomers are similar. Since the chirality is completely lost in the subsequent steps we believe that it is only necessary to show the ab initio results for one of the stereoisomers.

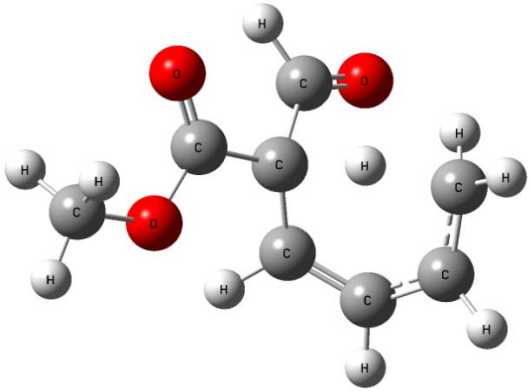
In the absence of a broader study on the influence of substituents, DFT/"ab initio" calculations allow a general understanding of the mechanistic steps involved.



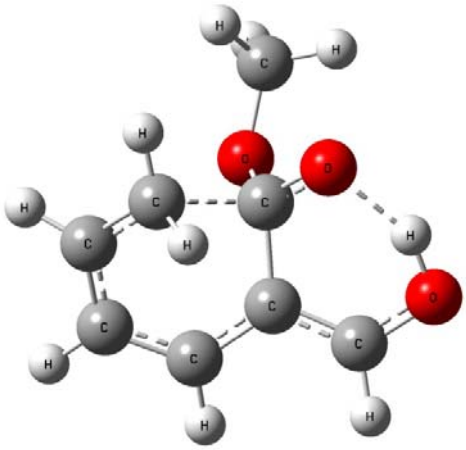
AB. Imaginary frequency: -424.72 cm^{-1}



CD. Imaginary frequency: -1521.41 cm^{-1}



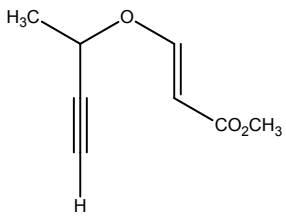
EF. Imaginary frequency: -1409.50 cm^{-1}

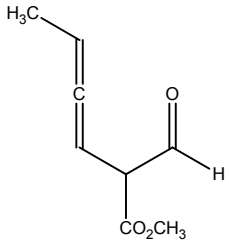


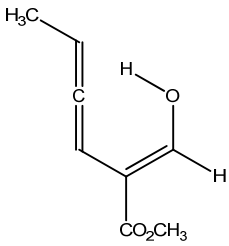
GH. Imaginary frequency: -665.56 cm^{-1}

Fig. 1: Significant transition states shown in Scheme 1, with characteristic imaginary frequency (R=H).

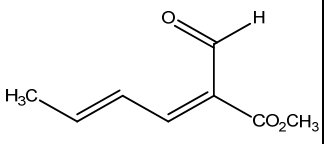
Summary of “log” Gaussian files of stable structures on Scheme 1:

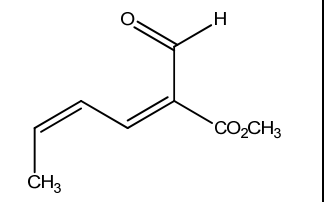
	N-N= 5.707116477917D+02 E-N=-2.391910195839D+03 KE= 5.314854864176D+02 1|1|UNPC-LUCAS|FOpt|RB3LYP|6-31+G(d,p)|C8H10O3|USER1|29-Jun-2010|0||# opt b3lyp/6-31+g (d,p) geom =connectivity||Title Card Required||0,1|C,-1 .4556707666,3.0899290188,1.9770187008|H,-1.035725224,3.2193798592,2.97 75287502|H,-1.1728729462,3.9445075098,1.3567884605|H,-2.5452153331,3.0 478677551,2.0542627711|C,-0.930084615,1.8009323587,1.3459731626|H,-1.3 216506236,1.7020561464,0.3245333907|O,0.5081149505,1.9531240269,1.2560 302105|C,-1.292962094,0.6095383796,2.1226474287|C,-1.6205409681,-0.356 1116333,2.7723033444|H,-1.8964457831,-1.2139821694,3.3430771712|C,1.20 72801529,1.1518335383,0.4314770882|C,0.7608961767,0.1331208434,-0.3296 9534|H,2.2583560896,1.4245519854,0.4256717593|H,-0.2657961897,-0.20839 74803,-0.338007433|C,1.7232995506,-0.5852898473,-1.1761667926|O,2.9174 422236,-0.3530891431,-1.2780061764|O,1.1064603467,-1.5822962308,-1.864 6579272|C,1.9528252929,-2.3592964544,-2.7290415687|H,1.2962832827,-3.0 959616252,-3.1919273736|H,2.4136365904,-1.7223437725,-3.4882925286|H,2 .7396408869,-2.8525570654,-2.1527300982||Version=IA32W-G09RevA.02|Stat e=1-A|HF=-536.4898787|RMSD=3.694e-009|RMSF=1.087e-005|Dipole=-1.195274 8,-0.0004955,0.1941441|Quadrupole=-5.1356959,4.0831715,1.0525244,-2.23 2729,-1.388922,1.6960134|PG=C01 [X(C8H10O3)]||@

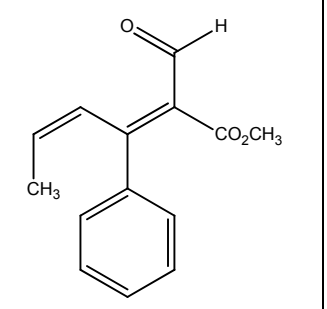
	N-N= 5.688117316429D+02 E-N=-2.387864208181D+03 KE= 5.314877560050D+02 1|1|UNPC-MIGUEL2|FOpt|RB3LYP|6- 31+G(d,p)|C8H10O3|MIGUEL|29-Jun-2010|0| |# opt b3lyp/6-31+g(d,p) geom=connectivity||Title Card Required||0,1|C ,0.8200942408,-0.7009363764,-0.3597143462|H,1.3195834972,-0.9003075696 ,-1.3070493883|C,-0.0502677755,-1.5500893856,0.1312922605|C,-0.9272515 504,-2.39481953,0.6147853509|H,-1.9734437261,-2.2625039208,0.333042817 7|C,-0.6100435759,-3.5481385336,1.5366923588|H,0.4579098681,-3.5988731 564,1.7608822951|H,-1.1586060994,-3.4467815713,2.4806037099|H,-0.91726 05243,-4.4978857651,1.082931336|C,1.2176677517,0.5931184267,0.34644113 66|H,0.5305051647,0.8245038452,1.1607914703|C,2.6183355658,0.391630682 1,0.9405366141|O,2.8367706481,0.3696554246,2.1306167582|H,3.4250763929 ,0.2373171523,0.1964324699|C,1.2684924227,1.732620222,-0.6613560578|O, 1.9537966103,1.7181586969,-1.6650744474|O,0.4811535929,2.7596313246,-0 .2969311663|C,0.4731920998,3.8970564734,-1.1878863005|H,0.125765969,3. 5970225058,-2.1789062931|H,-0.2137052253,4.6107229324,-0.7351945511|H, 1.4767386529,4.3205121225,-1.2681820273||Version=IA32W-G09RevA.02|Stat e=1-A|HF=-536.5155695|RMSD=4.171e-009|RMSF=5.432e-006|Dipole=- 1.012542 5,0.0664374,-0.4317364|Quadrupole=-1.6100991,9.5423333,- 7.9322342,0.5400259,-1.927601,-2.9696264|PG=C01 [X(C8H10O3)]||@

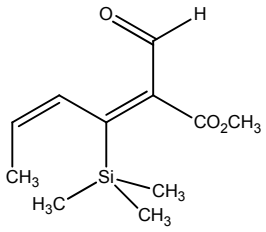
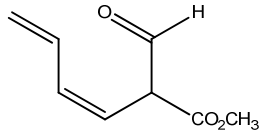
	N-N= 5.755909675208D+02 E-N=-2.401666555724D+03 KE= 5.315081713743D+02 1|1|UNPC-LUCAS|FOpt|RB3LYP|6-31+G(d,p)|C8H10O3|USER1|02-Jul- 2010|0||# opt b3lyp/6-31+g(d,p) geom=connectivity||Untitled||0,1|C,0.5857184199, 0.6683107011,0.7400391027|C,1.8906768828,0.535730851,0.8915822786|C,3. 1916409897,0.4470325062,1.0604663079|C,4.2356577954,0.7869421734,0.020 2268007|C,-0.3614094279,-0.3498238762,0.2659574181|C,-0.0184680422,-1. 6223627697,-0.0747202743|C,-1.773278331,0.0823644845,0.1719316071|O,1. 2172038261,-2.1381589334,-0.0323387521|O,-2.6091958438,-0.8945170848,- 0.2652279481|C,-3.9957020674,-0.5265257865,-0.3754104321|H,0.131780197 ,1.627711824,0.9856596639|H,3.5671038158,0.1199326147,2.0334561139|H,4 .8758963262,1.6017115402,0.3793753314|H,3.7753202287,1.0974917901,-0.9 207011119|H,4.8881574936,-0.0726817671,-0.1746642966|H,-0.7539932738,- 2.338934406,-0.4192886443|H,1.8548024048,-1.4697303914,0.2886191062|O, -2.1668418095,1.2019281179,0.4552591189|H,-4.5036905651,-1.4224623119, -0.7320376995|H,-4.1189281631,0.2946911336,-1.0856030241|H,-4.38945685 62,-0.2214404097,0.5970823336||Version=IA32W-G09RevA.02|State=1-A|HF=-

	536.5232853|RMSD=5.608e-009|RMSF=3.044e-006|Dipole=0.464121,-0.4027624 ,-0.1479434|Quadrupole=9.2233592,-6.7436259,-2.4797332,5.4393003,3.000 3578,-0.7154456|PG=C01 [X(C8H10O3)]||@

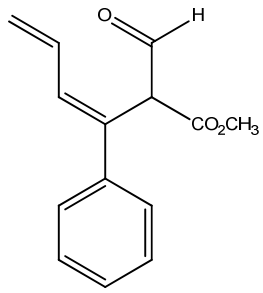
	N-N= 5.713799554170D+02 E-N=-2.393478427636D+03 KE= 5.315244771934D+02 1|1|UNPC-LUCAS|FOpt|RB3LYP|6-31+G(d,p)|C8H10O3|USER1|06-Jul-2010|0||# opt b3lyp/6-31+g(d,p) geom=connectivity||Title Card Required||0,1|O,0.5361590009,2.9546625179,-0.1946918384|C,3.1862200429,-0.3597859477,0.0491508719|C,2.1396781817,0.4954749191,-0.0182549276|C,0.7849923527,0.0034084908,-0.0033063029|C,-0.3725218541,0.7313066712,-0.0640181696|C,-0.4346950426,2.2095736755,-0.1592913193|C,-1.6968544274,0.0525525982,-0.0372687178|O,-1.6103839577,-1.2972556823,0.0528785981|C,-2.8653967071,-2.0030208314,0.0819552535|O,-2.766646577,0.63641745,-0.0902568634|H,2.2992798428,1.5661159644,-0.0847446298|H,0.6747350344,-1.0770647899,0.0644032542|H,-1.4582012502,2.6191401009,-0.1983545452|H,-2.6009599034,-3.0576074841,0.1556458875|H,-3.4581455361,-1.691759701,0.94526745|H,-3.4330245778,-1.8096184355,-0.8312571023|H,2.9813786942,-1.4300586119,0.1150601069|C,4.6251656716,0.0414375254,0.0408928128|H,5.1306342805,-0.310037854,0.949982321|H,5.1518640047,-0.4226285982,-0.8033385235|H,4.7452269569,1.1258408923,-0.0273348461||Version=IA32W-G09RevA.02|State=1-A|HF=-536.5531647|RMSD=5.457e-009|RMSF=6.752e-006|Dipole=0.936988 6,-1.8014788,0.1277264|Quadrupole=5.1859114,-3.6007115,-1.5852,1.738951,-0.0438815,0.153502|PG=C01 [X(C8H10O3)]||@

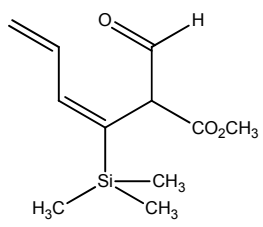
	N-N= 5.768901711987D+02 E-N=-2.404425384735D+03 KE= 5.315206893445D+02 1|1|UNPC-LUCAS|FOpt|RB3LYP|6-31+G(d,p)|C8H10O3|USER1|01-Jul-2010|0||# opt b3lyp/6-31+g(d,p) geom=connectivity||Title Card Required||0,1|O,-2.5173627759,-2.5603877552,0.1153550078|C,1.7210191541,-2.5597043509,0.1052879499|C,0.4075461511,-2.2198272782,0.0997092287|C,-0.0715339711,-0.8602212671,0.0648816498|C,-1.3752216486,-0.4419536737,0.0569197765|C,-2.5581567225,-1.3375646279,0.0833926572|C,-1.7016767163,1.0107793302,0.0193525994|O,-0.6077782795,1.8111127675,-0.0045380101|C,-0.8709815214,3.2267628779,-0.0412164237|O,-2.8369765948,1.457003954,0.010493746|C,2.9241545255,-1.6691543321,0.0782425714|H,1.9452300552,-3.6258243782,0.1329320782|H,-0.3371619195,-3.0060157619,0.1224760714|H,0.6758602119,-0.0732952825,0.042281716|H,-3.5260714967,-0.808711791,0.0718895969|H,0.1096345347,3.7017789848,-0.0560125361|H,-1.4396211633,3.4858182801,-0.9373548251|H,-1.4354986837,3.5327173682,0.8426560139|H,2.6869125134,-0.6039902211,0.0535802998|H,3.5522478499,-1.8589167505,0.9581566836|H,3.5440994976,-1.9013070922,-0.7973268514||Version=IA32W-G09RevA.02|State=1-A|HF=-536.5495047|RMSD=5.911e-009|RMSF=2.848e-005|Dipole=2.017 9049,0.663107,-0.0226711|Quadrupole=-0.7519637,1.6659141,-0.9139503,-4.0240083,0.1034439,-0.0586204|PG=C01 [X(C8H10O3)]||@

	N-N= 1.160409918622D+03 E-N=-4.106082080825D+03 KE= 7.603214357975D+02 1|1|UNPC-LUCAS|FOpt|RB3LYP|6-31+G(d,p)|C14H14O3|USER1|07-Jul-2010|0||# opt b3lyp/6-31+g(d,p) geom=connectivity||Title Card Required||0,1|C,-0.4552753045,-1.2437206575,0.6143104395|C,0.5017466725,-0.4031497447,0.0222193973|C,1.1126918681,0.7492561281,0.7532886598|C,2.5749501298,0.7830088085,0.8678407567|C,0.3515259307,1.8162489924,1.1853486254|C,0.8857159047,3.0055903434,1.8910472883|C,-1.1218937496,1.9095486966,0.9179090054|C,0.9239642429,-0.676442691,-1.2915192837|O,-1.4071031188,3.0520299688,0.2478304774|C,-2.8049331169,3.3030247281,-0.0058547165|C,0.3911449135,-1.752785786,-2.0008975887|C,-0.9671029535,-2.3359598625,-0.

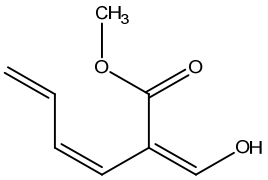
	0893106956|C,-0.5512554768,-2.5917250474,-1.3982362174|C,3.4438113622,-0.2527787486,0.9222159126|O,2.0141653987,3.141412903,2.3434764945|O,-1.978210487,1.1232426398,1.2720949866|C,3.2175950876,-1.7332612056,0.9879507678|H,-0.792446077,-1.0437975228,1.623699858|H,3.0056280828,1.772670287,0.9632639039|H,0.1487405419,3.8220855423,2.0115127297|H,1.667295079,-0.0359524539,-1.7566087498|H,-2.8356582857,4.2599800251,-0.5257185878|H,-3.3593664266,3.3532337643,0.9343475455|H,-3.2240916193,2.5099527042,-0.6290631124|H,0.7164600571,-1.9396348993,-3.0202837108|H,-1.6986473628,-2.9821800596,0.386827142|H,-0.958602819,-3.4369374238,-1.9455099402|H,4.4937481333,0.0362268849,0.9766252485|H,2.1737000718,-2.0157802025,1.1148462288|H,3.5934085072,-2.2174225345,0.0763982081|H,3.7969058138,-2.1505965766,1.8209829273||Version=IA32W-G09RevA.02|State=1 -A|HF=-767.5993694|RMSD=6.354e-009|RMSF=2.759e-006|Dipole=-0.3057554,- 0.6772639,-1.0294387|Quadrupole=1.4910998,1.7313446,-3.2224444,-8.7743271,-1.5903283,-2.2901733|PG=C01 [X(C14H14O3)]||@
	N-N= 1.155365483113D+03 E-N=-4.525610119447D+03 KE= 9.377987115320D+02 1|1|UNPC-MIGUEL2|FOpt|RB3LYP|6-31+G(d,p)|C11H18O3Si1|MIGUEL|18-Jul-201 0|0||# opt b3lyp/6-31+g(d,p) geom=connectivity||Title Card Required||0,1|C,-0.185476288,0.6743378063,0.2950784734|C,-0.8421929127,1.9179472809,0.7600037622|C,1.1821175802,0.650683752,0.1697606522|C,2.0484093379,1.8482735524,0.3927029867|C,1.8827766034,-0.5910109377,-0.2699504368|O,3.2221102925,-0.5265528415,-0.0851149069|C,3.9751679952,-1.6811282525,-0.5053420024|C,-1.736761149,2.6676992987,0.0943894305|O,1.6811537994,2.8958627561,0.9006454792|O,1.342452826,-1.5737322164,-0.7475051842|C,-2.2087508266,2.4826508614,-1.3182246072|H,-0.5258961949,2.2675016342,1.7406043845|H,3.0921822169,1.7391126226,0.052217495|H,5.0165202392,-1.4339967654,-0.3017743663|H,3.8212275009,-1.8689281112,-1.570407963|H,3.6685616303,-2.5617971765,0.063614343|H,-2.1127148261,3.5529522195,0.6050792481|H,-1.8308697185,1.562699483,-1.77102757|H,-3.3046309413,2.4750386199,-1.3733787207|H,-1.8703859065,3.3184122019,-1.944848292|Si,-1.3662384434,-0.8868312694,0.1445851563|C,-3.0646000331,-0.3619225667,0.8050344036|H,-3.0112399567,0.0043981304,1.8357294829|H,-3.5436688871,0.4144296273,0.2023720075|H,-3.7215176488,-1.2409975348,0.7986907624|C,-1.6196250699,-1.4847929653,-1.6317171657|H,-0.6819204444,-1.7899888257,-2.098249753|H,-2.2959481662,-2.3488233785,-1.6150913511|H,-2.0924388093,-0.7160249307,-2.2521370874|C,-0.7853999369,-2.2531700394,1.3215510996|H,0.1170835139,-2.7598459191,0.9771423168|H,-0.6037404346,-1.8515126161,2.3251719756|H,-1.5865871218,-2.9973745699,1.4098447771||Version=IA32W-G09RevA.02|State=1-A|HF=-945.2211015|RMSD=3.151e-009|RMSF=6.188e-006|Dipole=0.1006812,-0.7109605,-0.3432|Quadrupole=7.2982492,-6.0222869,-1.2759623,-7.4169195,-1.6127989,-3.5949848|PG=C01 [X(C11H18O3Si1)]||@ 980475,-3.7954339844,-1.2095984645|H,0.9336201957,-4.0870261824,-2.2407768554|H,1.4665587192,-4.2506675161,-0.533438118|H,-0.2683401521,-4.0888490402,-0.9061889798||Version=IA32W-G09RevA.02|State=1-A|HF=-764.4161026|RMSD=5.816e-009|RMSF=5.641e-006|Dipole=0.5332287,-1.8783893,-1.0808621|Quadrupole=8.4486508,-3.4739477,-4.9747031,0.6755154,2.8483322,1.9891642|PG=C01 [X(C10H12O5)]||@
	N-N= 5.824397411898D+02 E-N=-2.415081604790D+03 KE= 5.314893726250D+02 1|1|UNPC-MIGUEL-PC|FOpt|RB3LYP|6-31+G(d,p)|C8H10O3|MIGUEL|17-Sep-2010| 0||# opt b3lyp/6-31+g(d,p) geom=connectivityscf=tight||Title Card Required

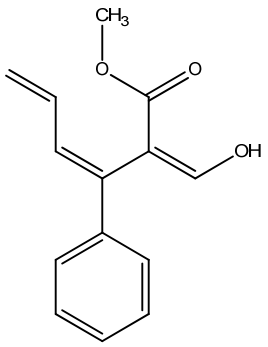
	||0,1|O,0.3410865383,2.3065937509,-1.7135527709|C,2.4517845401,-1 .4681337853,0.5849920552|C,1.8142617344,-1.2533994457,-0.7088786645|C, 0.819789049,-0.3930955856,-1.00017533|C,0.164310969,0.5528556832,-0.03 35273671|C,-0.0218163628,1.9675771716,-0.6117100819|C,-1.2104570516,0. 1176008869,0.4943660768|O,-1.8861235074,-0.6259984882,-0.395981449|C,- 3.205982333,-1.053716294,0.0053767426|O,-1.6484245658,0.4586810702,1.5 740041844|C,3.4493726286,-2.3466756016,0.7832897148|H,2.0955483933,-0. 8894738864,1.4354315653|H,2.1958884726,-1.8680434895,-1.5234145408|H,0 .4481633215,-0.3503934624,-2.0188999116|H,-0.5224041939,2.6784321576,0 .0771184795|H,-3.5861967239,-1.6340500744,-0.8340923728|H,-3.144433132 6,-1.6682625411,0.9061007426|H,-3.841685143,-0.1870834159,0.1995399921 |H,0.7627296647,0.699241426,0.8734169118|H,3.9015080441,-2.4822562331, 1.7603349032|H,3.8401555582,-2.9543463433,-0.0294040596||Version=IA32W -G09RevA.02|State=1-A|HF=-536.5298851|RMSD=4.634e-009|RMSF=3.487e- 006| Dipole=-0.3583485,-0.8456389,0.2346174|Quadrupole=6.1904363,-1.208436, -4.9820003,-0.4127525,4.031409,3.480295|PG=C01 [X(C8H10O3)]||@

	N-N= 1.149452994242D+03 E-N=-4.084083726184D+03 KE= 7.603457703491D+02 1|1|UNPC-LUCAS|FOpt|RB3LYP|6-31+G(d,p)|C14H14O3|USER1|13-Sep- 2010|0||# opt b3lyp/6-31+g(d,p) geom=connectivityscf=tight||Title Card Required ||0,1|O,-2.5680422659,-1.2117095769,-1.277087956|C,1.8348802313,-1.30 44423274,0.3708785938|C,0.5541949231,-1.5408808787,0.7601367344|C,-0.6 043090806,-0.890494738,0.0710388863|C,-1.5014595775,-1.6557813068,-0.6 243450951|C,-0.8633926499,0.547851276,0.1300444369|O,-0.0087208201,1.2 466550763,0.8909949923|C,-0.2363044274,2.6670956857,0.9726304369|O,-1. 8102415057,1.097095041,-0.4588320658|H,-1.3823000145,-2.7348906482,-0. 683661069|H,0.5519768965,3.0438655964,1.6231756171|H,-0.169472236,3.12 10943952,-0.0187443861|H,-1.2213772975,2.8725494953,1.3979034132|H,-2. 5764137103,-0.2207844142,-1.1594081577|H,2.6396224511,-1.7341590864,0. 9645389333|C,2.2537764383,-0.5120535894,-0.7700423322|H,1.4748955642,- 0.1178385788,-1.4195255585|C,3.5411743261,-0.2604742196,-1.073181812|H ,4.3547424603,-0.633919328,-0.4556509318|H,3.8150530218,0.3241388237,- 1.9454269404|C,0.2600796236,-2.4471474386,1.901401362|C,-0.8582944848, -2.2283540413,2.7293099354|C,1.0867207373,-3.5506553964,2.1937388859|C ,-1.1202818789,-3.0557377442,3.8217984556|H,-1.5197598386,-1.393330810 7,2.5220019396|C,0.8228487166,-4.3803824289,3.2832197047|H,1.927298035 3,-3.7758414834,1.5446693422|C,-0.2803153573,-4.1356369909,4.106649702 7|H,-1.9832144197,-2.8560198304,4.450842842|H,1.4714834269,-5.22942387 2,3.4801138106|H,-0.4886445577,-4.7849056305,4.9519530497||Version=IA3 2W-G09RevA.02|State=1-A|HF=-767.6121489|RMSD=4.977e- 009|RMSF=3.016e-00 6|Dipole=0.5756124,0.1723433,0.5377318|Quadrupole=-3.158636,5.6174984, -2.4588624,-0.0007688,-5.0144818,-1.394254|PG=C01 [X(C14H14O3)]||@

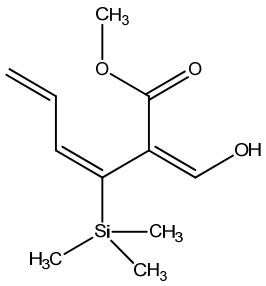
	N-N= 1.146543005259D+03 E-N=-4.507858595926D+03 KE= 9.378207282031D+02 1|1|UNPC-LUCAS|FOpt|RB3LYP|6-31+G(d,p)|C11H18O3Si1|USER1|04-Oct- 2010|0 ||# opt b3lyp/6-31+g(d,p) geom=connectivityscf=tight||Title Card Required ||0,1|O,-2.3751742603,0.0006334686,2.1988216401|C,1.7740839883,-1. 4271258534,0.9051230501|C,0.5124052624,-1.6919020095,0.484241104|C,-0. 6060992554,-0.7236244759,0.7348781585|C,-1.3424098746,-0.7803138185,1. 8858963036|C,-0.9836843378,0.2950044585,-0.2448962275|O,-0.2085359452, 0.3270754437,-1.3417991017|C,-0.5389908298,1.3239578195,-2.3278763508| O,-1.9298566238,1.0850841825,-0.0939162755|H,-1.1107539356,-1.50828732 7,2.6591730592|H,0.1970002993,1.1957799224,-3.1208930573|H,-1.55032168 3,1.164176907,-2.7089916059|H,-0.4707598281,2.3248194742,-1.8955472476 |H,-2.5015584557,0.6216294344,1.431092885|H,2.5534266179,-2.1648669997

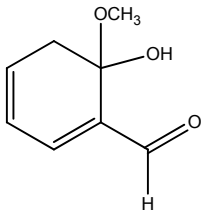
	,0.7115005137|C,2.2303804357,-0.2273239566,1.5978296409|H,1.4901676019 ,0.5435310402,1.8008875285|C,3.5027914813,-0.0353051821,1.9876441873|H ,4.272045566,-0.7827215595,1.8064222652|H,3.8110294644,0.8717001813,2. 4979581115|Si,0.0862458355,-3.3270263295,-0.3864466162|C,1.665894818,- 4.2844765629,-0.8021474212|H,1.4096013912,-5.2144367611,-1.3234565978| H,2.3296691356,-3.7097345098,-1.4576975085|H,2.2305998403,-4.558900828 ,0.095994534|C,-0.8867567383,-2.9887134189,-1.9749346009|H,-1.15929807 78,-3.9322463532,-2.4628181674|H,-1.8150578088,-2.4437933175,-1.770156 7707|H,-0.3001673019,-2.3964763323,-2.684790928|C,-0.989836626,-4.3739 443267,0.7725903035|H,-1.9188195429,-3.8578417014,1.039542195|H,-1.265 7241119,-5.3195592264,0.290434843|H,-0.459150871,-4.6149504124,1.70072 7764||Version=IA32W-G09RevA.02|State=1-A|HF=- 945.2350383|RMSD=8.269e-0 09|RMSF=2.297e-006|Dipole=0.6877513,-0.2498225,-0.6190566|Quadrupole=- 3.0825242,1.5988828,1.4836413,2.7929008,3.2165731,-3.1067515|PG=C01 [X (C11H18O3Si1)]]|@

	N-N= 5.975039102584D+02 E-N=-2.445553970620D+03 KE= 5.315166579782D+02 1|1|UNPC-LUCAS|FOpt|RB3LYP|6-31+G(d,p)|C8H10O3|USER1|13-Sep- 2010|0||# opt b3lyp/6-31+g(d,p) geom=connectivityscf=tight||Title Card Required ||0,1|O,-2.9205374695,-1.0608914075,-0.8448325044|C,1.7676528388,-1.33 35506409,0.4340200597|C,0.4480889877,-1.5265472731,0.65545699|C,-0.708 7016712,-0.8087541567,0.0776595134|C,-1.7945204289,-1.5404266268,-0.33 50035743|C,-0.8481232487,0.6491613422,0.0160809643|O,0.1441827812,1.34 42277158,0.5873537822|C,0.0108236988,2.7792499425,0.5799444662|O,-1.82 87654044,1.2187392291,-0.4920160774|H,0.1843421383,-2.339086337,1.3313 141732|H,-1.7902327742,-2.6256861369,-0.2608159397|H,0.9046290696,3.14 92215749,1.0806282872|H,-0.0422669316,3.1529002162,-0.4452134286|H,-0. 8894866082,3.0802499027,1.12036593|H,-2.8140109578,-0.0682869589,-0.87 31429625|H,2.4563700252,-1.9725499528,0.985702988|C,2.3880829039,-0.40 07208974,-0.493861312|H,1.7318708342,0.1929925561,-1.1247391082|C,3.71 89325795,-0.2623454911,-0.6289791176|H,4.4148744049,-0.833662751,-0.01 89600949|H,4.1488382326,0.4240281506,-1.3513871202||Version=IA32W- G09R evA.02|State=1-A|HF=-536.5409684|RMSD=8.744e-009|RMSF=6.704e- 006|Dipol e=0.6021193,0.2119514,0.3831166|Quadrupole=-4.1091708,5.5603786,-1.451 2078,1.2628575,-1.7500269,-1.0494342|PG=C01 [X(C8H10O3)]||@

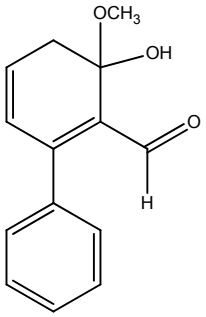
	N-N= 1.182071983914D+03 E-N=-4.149643526857D+03 KE= 7.603690703135D+02 1|1|UNPC-MIGUEL2|FOpt|RB3LYP|6-31+G(d,p)|C14H14O3|MIGUEL|14-Sep- 2010|0 ||# opt b3lyp/6-31+g(d,p) geom=connectivityscf=tight||Title Card Required ||0,1|O,2.7905197623,-0.5499299725,-0.1400478954|C,-1.9660530224,- 1.4431091364,-0.3072705901|C,-0.5665810123,-1.8473324954,-0.4574736211 |C,0.4388813902,-0.9652098078,-0.1569902503|C,1.8395394941,-1.27408161 01,-0.4449885088|C,0.1004625031,0.4628054304,0.2938486245|O,0.10436394 83,1.1858888301,-0.9460607184|C,-0.0371400914,2.6035778249,-0.86812907 46|O,1.0412966177,0.9793570205,1.1980013753|H,2.0322863527,-2.21220505 13,-0.9903926342|H,0.2774465451,2.9898036665,-1.8399980571|H,-1.080848 0639,2.9008400634,-0.6954872087|H,0.598950926,3.026015881,-0.084100418 1|H,1.9245483053,0.7217747892,0.8600273162|H,-2.7298945775,-2.10862665 2,-0.6973693367|C,-2.3038090214,-0.3274828393,0.3655547385|H,-3.351505 9641,-0.0793275694,0.5165387541|C,-1.2618193725,0.5405176199,0.9983167 422|H,-1.1160988205,0.2194294707,2.0401934002|H,-1.5851260156,1.583896 435,1.0517252685|C,-0.3288904002,-3.2442956197,-0.9185260107|C,-0.9217 248234,-3.7019460173,-2.1090530725|C,0.4398462212,-4.143509585,-0.1599 255626|C,-0.7251697309,-5.0132112178,-2.5428487769|H,-1.5167767492,-3. 0194618748,-2.7093643979|C,0.6250141702,-5.4597153948,-0.5890408525|H,

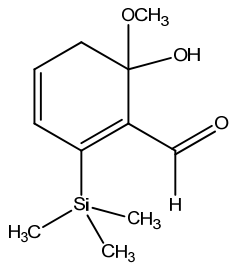
	0.8739292349,-3.8137576831,0.7792472889|C,0.0473091587,-5.8971993611,-1.7830809516|H,-1.1748556945,-5.344615107,-3.4742533094|H,1.2180933265,-6.1421029606,0.0126412172|H,0.1936169132,-6.9198749462,-2.117772668||Version=IA32W-G09RevA.02|State=1-A|HF=-767.5991173|RMSD=5.708e-009|RM SF=6.960e-006|Dipole=-1.4533504,-0.9401966,-0.2913798|Quadrupole=-4.7483536,6.7125629,-1.9642093,-6.2448228,-0.4590446,1.2035812|PG=C01 [X(C14H14O3)]||@

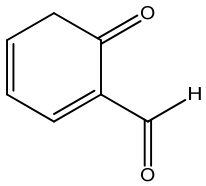
	N-N= 1.174906274053D+03 E-N=-4.564779151286D+03 KE= 9.378526332780D+02 1|1|UNPC-MIGUEL-PC|FOpt|RB3LYP|6-31+G(d,p)|C11H18O3Si1|MIGUEL|05-Oct-2 010|0||# opt b3lyp/6-31+g(d,p) geom=connectivity scf=tight||Title Card Required||0,1|O,2.798981237,-0.6197322995,0.1349066433|C,-1.9470912789,-1.3821459584,-0.3602844864|C,-0.5542043862,-1.8345379037,-0.4423041656|C,0.4364489439,-0.960579598,-0.067614882|C,1.8431099037,-1.3425895505,-0.1525696771|C,0.1093956098,0.4902116233,0.3279729376|O,0.1726369865,1.1724086826,-0.9319356243|C,0.0304590511,2.5919825761,-0.9043100297|O,1.014634229,1.0296478459,1.2542181396|H,2.0457177566,-2.369546149,-0.501015865|H,0.3756422272,2.9461533626,-1.8779488174|H,-1.0177281463,2.8948688562,-0.7737633343|H,0.6422037512,3.0394514354,-0.1147382875|H,1.9100088253,0.7534477098,0.9702852686|H,-2.7207745613,-1.9967123316,-0.8073345967|C,-2.2992324206,-0.2569673824,0.2943232692|H,-3.3481444836,0.0184076414,0.3774321135|C,-1.2772407427,0.5935777702,0.9771445494|H,-1.1768373386,0.266658833,2.0228994802|H,-1.5857392509,1.6419684327,1.0217300517|Si,-0.2816253813,-3.6426251977,-1.0739369534|C,0.5351911092,-4.7004209217,0.2674949879|H,0.5798839291,-5.7460829985,-0.0601666455|H,1.5551550243,-4.382968536,0.5049697144|H,-0.0467587955,-4.6686131181,1.1955301394|C,0.7232526837,-3.6513635115,-2.6786460975|H,1.7588252039,-3.3249429651,-2.5438777739|H,0.7453724893,-4.6658319888,-3.0947947916|H,0.264797999,-2.9952076705,-3.4270357562|C,-1.9729010422,-4.4027516239,-1.4556227411|H,-1.8261866783,-5.4351311188,-1.794896186|H,-2.6265032502,-4.4369095034,-0.5771715999|H,-2.5015795031,-3.8705875721,-2.2541504035||Version=IA32W-G09RevA.02|State=1-A|HF=-945.2191054|RM SD=2.445e-009|RMSF=3.598e-006|Dipole=-1.4339221,-0.8402955,-0.3371101|Quadrupole=-3.05258,5.5657141,-2.513134,-4.3123914,-2.7302307,0.049893|PG=C01 [X(C11H18O3Si1)]||@

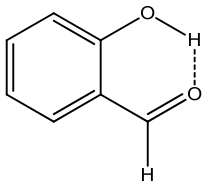
	N-N= 6.364207970673D+02 E-N=-2.523887192726D+03 KE= 5.315509790949D+02 1|1|UNPC-LUCAS|FOpt|RB3LYP|6-31+G(d,p)|C8H10O3|USER1|13-Sep-2010|0||# opt b3lyp/6-31+g(d,p) geom=connectivity scf=tight||Title Card Required ||0,1|O,2.7220209573,-0.8297505532,0.0973700115|C,-2.0641594727,-1.4084985572,-0.3443991592|C,-0.6759112789,-1.8192541102,-0.4329303149|C,0.3478905937,-0.9966403796,-0.0887025666|C,1.7205517796,-1.4779819366,-0.2009892935|C,0.0654464744,0.4531476369,0.3072086984|O,0.1652936319,1.1429280252,-0.9444685938|C,0.0918616311,2.5679708598,-0.9041552446|O,0.9827801593,0.9477909526,1.2470804987|H,-0.4504846017,-2.8245777655,-0.786617021|H,1.8272521338,-2.5164439686,-0.5755190874|H,0.4302434942,2.9108472688,-1.8839349082|H,-0.9367779515,2.9200335154,-0.7462886294|H,0.742861738,2.9793318463,-0.1267019461|H,1.8688036375,0.637516651,0.9724959091|H,-2.8320637607,-2.050934357,-0.7641226232|C,-2.3830731443,-0.2600131641,0.2879829878|H,-3.4236874294,0.0368855451,0.3927525432|C,-1.3325281795,0.5920525511,0.9383334472|H,-1.246783783,0.2949635186,1.9941992379|H,-1.6254036292,1.6456914212,0.9499980541||Version=IA32W-G0 9RevA.02|State=1-A|HF=-536.5328743|RMSD=8.413e-009|RMSF=3.437e-006|Dip ole=-1.5224303,-0.386875,-0.1931903|Quadrupole=-2.6084926,5.9354322,-3

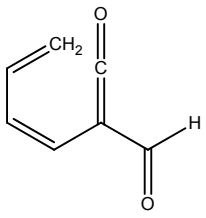
	.3269396,0.3454596,-1.4862184,0.6697947|PG=C01 [X(C8H10O3)]||@

	N-N= 1.182071983914D+03 E-N=-4.149643526857D+03 KE= 7.603690703135D+02 1|1|UNPC-MIGUEL2|FOpt|RB3LYP|6-31+G(d,p)|C14H14O3|MIGUEL|14-Sep-2010|0 ||# opt b3lyp/6-31+g(d,p) geom=connectivity scf=tight||Title Card Required ||0,1|O,2.7905197623,-0.5499299725,-0.1400478954|C,-1.9660530224,-1.4431091364,-0.3072705901|C,-0.5665810123,-1.8473324954,-0.4574736211|C,0.4388813902,-0.9652098078,-0.1569902503|C,1.8395394941,-1.2740816101,-0.4449885088|C,0.1004625031,0.4628054304,0.2938486245|O,0.1043639483,1.1858888301,-0.9460607184|C,-0.0371400914,2.6035778249,-0.8681290746|O,1.0412966177,0.9793570205,1.1980013753|H,2.0322863527,-2.2122050513,-0.9903926342|H,0.2774465451,2.9898036665,-1.8399980571|H,-1.0808480639,2.9008400634,-0.6954872087|H,0.598950926,3.026015881,-0.0841004181|H,1.9245483053,0.7217747892,0.8600273162|H,-2.7298945775,-2.108626652,-0.6973693367|C,-2.3038090214,-0.3274828393,0.3655547385|H,-3.3515059641,-0.0793275694,0.5165387541|C,-1.2618193725,0.5405176199,0.9983167422|H,-1.1160988205,0.2194294707,2.0401934002|H,-1.5851260156,1.583896435,1.0517252685|C,-0.3288904002,-3.2442956197,-0.9185260107|C,-0.9217248234,-3.7019460173,-2.1090530725|C,0.4398462212,-4.143509585,-0.1599255626|C,-0.7251697309,-5.0132112178,-2.5428487769|H,-1.5167767492,-3.0194618748,-2.7093643979|C,0.6250141702,-5.4597153948,-0.5890408525|H,0.8739292349,-3.8137576831,0.7792472889|C,0.0473091587,-5.8971993611,-1.7830809516|H,-1.1748556945,-5.344615107,-3.4742533094|H,1.2180933265,-6.1421029606,0.0126412172|H,0.1936169132,-6.9198749462,-2.117772668||Version=IA32W-G09RevA.02|State=1-A|HF=-767.5991173|RMSD=5.708e-009|RM SF=6.960e-006|Dipole=-1.4533504,-0.9401966,-0.2913798|Quadrupole=-4.7483536,6.7125629,-1.9642093,-6.2448228,-0.4590446,1.2035812|PG=C01 [X(C14H14O3)]||@

	N-N= 1.174906274053D+03 E-N=-4.564779151286D+03 KE= 9.378526332780D+02 1|1|UNPC-MIGUEL-PC|FOpt|RB3LYP|6-31+G(d,p)|C11H18O3Si1|MIGUEL|05-Oct-2 010|0||# opt b3lyp/6-31+g(d,p) geom=connectivity scf=tight||Title Card Required||0,1|O,2.798981237,-0.6197322995,0.1349066433|C,-1.9470912789,-1.3821459584,-0.3602844864|C,-0.5542043862,-1.8345379037,-0.4423041656|C,0.4364489439,-0.960579598,-0.067614882|C,1.8431099037,-1.3425895505,-0.1525696771|C,0.1093956098,0.4902116233,0.3279729376|O,0.1726369865,1.1724086826,-0.9319356243|C,0.0304590511,2.5919825761,-0.9043100297|O,1.014634229,1.0296478459,1.2542181396|H,2.0457177566,-2.369546149,-0.501015865|H,0.3756422272,2.9461533626,-1.8779488174|H,-1.0177281463,2.8948688562,-0.7737633343|H,0.6422037512,3.0394514354,-0.1147382875|H,1.9100088253,0.7534477098,0.9702852686|H,-2.7207745613,-1.9967123316,-0.8073345967|C,-2.2992324206,-0.2569673824,0.2943232692|H,-3.3481444836,0.0184076414,0.3774321135|C,-1.2772407427,0.5935777702,0.9771445494|H,-1.1768373386,0.266658833,2.0228994802|H,-1.5857392509,1.6419684327,1.0217300517|Si,-0.2816253813,-3.6426251977,-1.0739369534|C,0.5351911092,-4.7004209217,0.2674949879|H,0.5798839291,-5.7460829985,-0.0601666455|H,1.5551550243,-4.382968536,0.5049697144|H,-0.0467587955,-4.6686131181,1.1955301394|C,0.7232526837,-3.6513635115,-2.6786460975|H,1.7588252039,-3.3249429651,-2.5438777739|H,0.7453724893,-4.6658319888,-3.0947947916|H,0.264797999,-2.9952076705,-3.4270357562|C,-1.9729010422,-4.4027516239,-1.4556227411|H,-1.8261866783,-5.4351311188,-1.794896186|H,-2.6265032502,-4.4369095034,-0.5771715999|H,-2.5015795031,-3.8705875721,-2.2541504035||Version=IA32W-G09RevA.02|State=1-A|HF=-945.2191054|RM SD=2.445e-009|RMSF=3.598e-006|Dipole=-1.4339221,-0.8402955,-0.3371101|Quadrupole=-3.05258,5.5657141,-2.513134,-4.3123914,-2.7302307,0.049893|PG=C01 [X(C11H18O3Si1)]||@

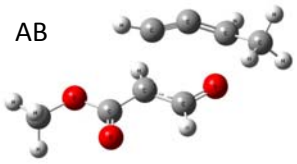
	N-N= 4.013095052991D+02 E-N=-1.782456802872D+03 KE= 4.168335803713D+02 1|1|UNPC-MIGUEL2|FOpt|RB3LYP|6-31+G(d,p)|C7H6O2|MIGUEL|05-Jul-2010|0|| # B3LYP/6-31+G(d,p) Opt||Untitled||0,1|C,-1.3155100704,-1.0443149487,0.5775552973|C,0.2138365198,-1.0628612466,0.6059212107|C,0.9150811843,0.0714969077,-0.0300789541|C,0.2049736842,1.081617969,-0.6123384154|C,2.3997338129,0.1002691531,-0.0287958121|C,-1.2408548411,1.1185046265,-0.6504217535|C,-1.9646996018,0.1240170576,-0.0939438878|H,-1.6468662295,-1.9825780186,0.1087939826|H,-1.6644476081,-1.1251348239,1.6175529075|O,0.8088938745,-1.9926308058,1.1412829456|H,0.7691734805,1.8936840705,-1.0669838685|O,3.0558665443,0.9996851243,-0.5318988938|H,2.8873777307,-0.7575451477,0.4642836064|H,-3.0515559132,0.1501253105,-0.1216066976|H,-1.7283135594,1.9593384089,-1.1339043065||Version=IA32W-G09RevA.02|State=1-A|HF=-420.7931333|RMSD=1.449e-009|RMSF=1.573e-005|Dipole=-2.047396,0.3523157,-0.224388|Quadrupole=0.7734171,-1.5037137,0.7302966,-2.0003244,1.1240962,1.8268072|PG=C01 [X(C7H6O2)]||@

	N-N= 4.102890023416D+02 E-N=-1.800409317655D+03 KE= 4.168876194907D+02 1|1|UNPC-LUCAS|FOpt|RB3LYP|6-31+G(d,p)|C7H6O2|USER1|06-Jul-2010|0||# opt b3lyp/6-31+g(d,p) geom=connectivity||Title Card Required||0,1|C,-0.3679224251,-0.3801439867,0.0006880191|C,1.04283778,-0.3945952966,0.0002667229|C,1.753776194,0.8364263388,-0.0011660482|C,1.0401668039,2.0452145457,-0.0020619449|C,-0.3496861903,2.0268500299,-0.0016223335|C,-1.0675632752,0.8161697228,-0.0002753875|H,-0.8984186682,-1.3296039797,0.0017881255|H,1.5963026504,2.9766622851,-0.0030922092|H,-0.8902887522,2.9691410773,-0.0023519928|H,-2.1523197435,0.8226786331,0.0000178667|C,1.762843176,-1.6570030857,0.0014053326|O,2.9951683099,-1.7544481699,0.0015317014|H,1.144506783,-2.5744382597,0.0022076338|O,3.0957918208,0.8770111902,-0.0016486984|H,3.4265182464,-0.0541572146,-0.0009517576||Version=IA32W-G09RevA.02|State=1-A|HF=-420.8360994|RMSD=8.065e-009|RMSF=8.784e-005|Dipole=-1.3192431,0.1661719,-0.0001382|Quadrupole=-1.0125222,2.6521941,-1.6396719,1.6948924,-0.0035101,-0.0029883|PG=C01 [X(C7H6O2)]||@

	N-N= 3.742440009006D+02 E-N=-1.727372744537D+03 KE= 4.167577973307D+02 1|1|UNPC-LUCAS|FOpt|RB3LYP|6-31+G(d,p)|C7H6O2|USER1|05-Jul-2010|0||# opt b3lyp/6-31+g(d,p) geom=connectivity||Untitled||0,1|C,-0.8240151424,-0.5461846801,1.2359415152|C,-1.3986761518,0.0999623382,0.2152630489|C,-0.8188056264,1.1897301294,-0.5787682991|C,-2.768295797,-0.3781067138,-0.1035874719|C,0.3870485399,1.7947818646,-0.4918281518|C,1.4651750338,1.5180799284,0.4412318551|C,2.6367206535,2.1796269499,0.4489457062|H,2.8418175273,2.9764145557,-0.2617098431|H,3.4181426944,1.9426928601,1.1632258451|H,1.3224678816,0.7306420044,1.1793648313|H,0.5786820449,2.5902768907,-1.2096500494|H,-1.5171501595,1.520554219,-1.3419974685|O,-0.4036168824,-1.1607559765,2.131221806|O,-3.440569477,0.0951001903,-1.0012935891|H,-3.154742139,-1.2011105603,0.5270002651||Version=IA32W-G09RevA.02|State=1-A|HF=-420.7558659|RMSD=5.349e-009|RMSF=4.142e-006|Dipole=0.7803107,-0.0411899,0.5099458|Quadrupole=-1.8612655,2.9089769,-1.0477115,2.9554387,-4.0288046,-1.5956546|PG=C01 [X(C7H6O2)]||@

Summary of “log” Gaussian files of transition states structures of Scheme 1:

AB

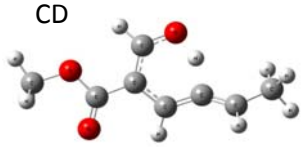


1|1|UNPC-MIGUEL-PC|Freq|RB3LYP|6-31+G(d,p)|C8H10O3|MIGUEL|30-Jun-2010|
0||#N Geom=AllCheckGuess=TCheck SCRF=CheckGenChk RB3LYP/6-31+G(d,p) Freq||TitleCardRequired||0,1|C,3.7608497334,-0.1610893343,0.6922134212|H,3.2617815824,-0.4219228105,1.6284157759|H,4.1989218941,-1.0581385215,0.25002721|H,4.5697206978,0.5452451676,0.9177523617|C,2.8014237814,0.4738781492,-0.2786121953|H,3.1909749722,0.6358475129,-1.2818468203|O,1.7599068631,-1.0550710187,-0.7995911382|C,1.824123842,1.3588143722,0.1436336634|C,0.6182573112,1.5908685517,0.3418066669|H,-0.2244937283,2.1727812287,0.6533231638|C,0.5938626437,-1.1178694477,-0.2639382675|C,-0.4286555661,-0.2311512341,-0.5869872005|H,0.4304676528,-1.8155306073,0.5672762526|H,-0.3852284212,0.3319837872,-1.511228383|C,-1.7432842489,-0.3605323749,0.0705431944|O,-2.0056916048,-1.0765318915,1.0221558889|O,-2.6609614651,0.4543803599,-0.5149163699|C,-3.987650459,0.4029356701,0.0409202824|H,-4.5705758422,1.1230899536,-0.5327958384|H,-4.4058686589,-0.6012801434,-0.0634046187|H,-3.9712769797,0.6732716307,1.0997169507||Version=IA32W-G09RevA.02|State=1-A|HF=-536.4433442|RMSD=6.170e- 009|RMSF=4.832e-006|ZeroPoint=0.1627262|Thermal=0.1748196|Dipole=0.2313211,0.8671942,-0.0595195|…

Harmonic frequencies (cm**-1), IR intensities (KM/Mole), Raman scattering activities (A**4/AMU), depolarization ratios for plane and unpolarized incident light, reduced masses (AMU), force constants (mDyne/A), and normal coordinates:

	1	2	3
	A	AA	…..
Frequencies --	-424.7176	43.5089	56.0434
Red. masses --	10.1338	4.4441	4.0952
Frc consts --	1.0770	0.0050	0.0076
IR Inten --	17.7425	2.3022	1.8108

CD

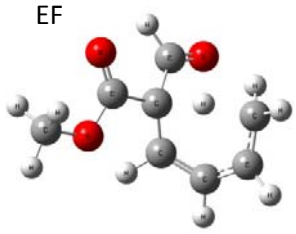


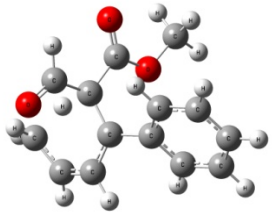
1|1|UNPC-LUCAS|Freq|RB3LYP|6-31+G(d,p)|C8H10O3|USER1|06-Jul-2010|0||#N Geom=AllCheckGuess=TCheck SCRF=CheckGenChk RB3LYP/6-31+G(d,p) Freq||TitleCardRequired||0,1|C,0.9421993572,0.0496705341,0.3838429219|C,1.1477607598,-1.2768344497,0.6937672245|C,2.1102139455,-2.2108303158,0.7017299764|C,2.0550246279,-3.4968318367,1.4713890713|C,-0.290002519,0.5082269745,-0.1593051182|C,-1.3759911755,-0.3771724228,-0.177872816|C,-0.4515208317,1.9472175484,-0.4380160499|O,-1.2573409797,-1.6260657455,0.1126478065|O,-1.7004562353,2.263085634,-0.8672366842|C,-1.9224082444,3.6501605849,-1.1805946227|H,1.6374301894,0.8180512424,0.7260867571|H,2.9760247758,-2.0914301081,0.0429192113|H,2.0424844993,-4.3609422851,0.7939024794|H,1.1741370877,-3.544577873,2.1165490258|H,2.9535071585,-3.6025676376,2.0932139554|H,-2.3870484518,-0.0053631188,-0.3474328373|H,-0.1613326163,-1.7297154267,0.6079727437|O,0.4351666832,2.7765952094,-0.3200359197|H,-2.9582989138,3.7081793917,-1.5141015595|H,-1.2430999219,3.9764592766,-1.9716828345|H,-1.7668171948,4.2715818241,-0.2954447314||Version=IA32W-G09RevA.02|State=1-A|HF=-536.4964388|RMSD=1.305e-0 09|RMSF=1.285e-005|ZeroPoint=0.1610887|Thermal=0.1726357|Dipole=-0.0164901,-0.2716281,0.0044271|…

Harmonic frequencies (cm**-1), IR intensities (KM/Mole), Raman scattering activities (A**4/AMU), depolarization ratios for plane and unpolarized incident light, reduced masses (AMU), force constants (mDyne/A), and normal coordinates:

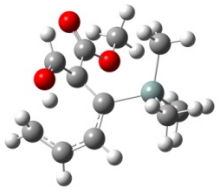
	1	2	3

	A AA …….. Frequencies -- -1521.4108 52.8161 86.0045 Red. masses -- 1.2007 4.5527 3.3088 Frc consts -- 1.6375 0.0075 0.0144 IR Inten -- 272.8534 3.3299 0.7402

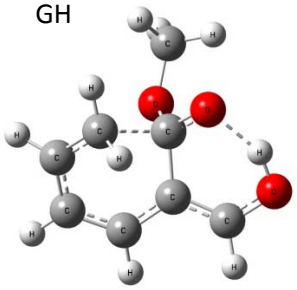
EF 	1|1|UNPC-MIGUEL-PC|Freq|RB3LYP|6-31+G(d,p)|C8H10O3|MIGUEL|17-Sep-2010| 0||#N Geom=AllCheckGuess=TCheck SCRF=CheckGenChk RB3LYP/6-31+G(d,p) Freq||TitleCardRequired||0,1|O,1.8156160359,1.9274112891,-0.6927963303|C,2.4111990061,-1.3255339812,0.5797186823|C,1.7778240736,-1.4704491866,-0.6795138942|C,0.6007183295,-0.8025559767,-0.9412055925|C,0.1009758944,0.3164986442,-0.1633619873|C,0.6560296481,1.6892130699,-0.3977583414|C,-1.3741069893,0.3560023331,0.1185145943|O,-1.993901252,-0.8118787384,-0.1649136806|C,-3.4066653806,-0.8581621502,0.1175954992|O,-1.9532841224,1.3138293028,0.6001600051|C,2.2408421659,-0.197877415,1.3887186915|H,2.8495005361,-2.2305881502,1.0009044452|H,2.0234241452,-2.3350970824,-1.2894791134|H,-0.0779237132,-1.2502790195,-1.6622221581|H,-0.0789168648,2.5004276019,-0.2529613645|H,-3.722285519,-1.8643518636,-0.156492087|H,-3.5868142992,-0.6706814365,1.1785346481|H,-3.9393451051,-0.1105023848,-0.474723761|H,0.9024036664,0.0881705036,1.0049636392|H,2.4659952689,-0.2920067358,2.4497632002|H,2.4975194755,0.7726153764,0.9602939053||Version=IA32W-G09RevA.02|State=1-A|HF=-536.4839072|RMSD=4.351e-009|RMSF=7.470e-006|ZeroPoint=0.16195|Thermal=0.1728357|Dipole=-0.4813223,-1.5728972,0.1821549| _____ Harmonic frequencies (cm**-1), IR intensities (KM/Mole), Raman scattering activities (A**4/AMU), depolarization ratios for plane and unpolarized incident light, reduced masses (AMU), force constants (mDyne/A), and normal coordinates: 1 2 3 A AA Frequencies -- -1409.5012 47.2700 102.5927 Red. masses -- 1.2050 5.6059 2.8439 Frc consts -- 1.4105 0.0074 0.0176 IR Inten -- 470.0389 0.7289 0.9874 …

EF 	1|1|UNPC-LUCAS|Freq|RB3LYP|6-31+G(d,p)|C14H14O3|USER1|23-Sep-2010|0||#N Geom=AllCheckGuess=TCheck SCRF=CheckGenChk RB3LYP/6-31+G(d,p) Freq||TitleCardRequired||0,1|O,-2.4302322013,-0.9505447165,2.0618206956|C,-2.182759385,-1.9923989548,-1.3128216945|C,-0.8917746594,-1.9888979884,-0.7408105482|C,-0.3757975443,-0.8656680155,-0.1081286813|C,-1.2453992998,0.2331295082,0.3334329677|C,-1.9800171211,0.0981549299,1.6231479668|C,-0.8072908017,1.642513284,0.0557928946|O,-0.1543693959,1.7376948085,-1.1240318507|C,0.290370833,3.0569855719,-1.4915825503|O,-1.0778667459,2.6132532168,0.7426885517|C,-3.2147926071,-1.1607747905,-0.859553737|H,-2.2914239495,-2.5283160856,-2.2563767473|H,-0.1944248067,-2.7645688377,-1.0429140922|H,-2.1255031128,1.0531798294,2.1584155495|H,0.7773881036,2.9379489192,-2.459000621|H,-0.5595904281,3.7393481892,-1.5662675111|H,0.9954696707,3.4405962655,-0.7500685088|H,-2.3969877797,-0.0997188735,-0.4772755742|H,-4.0519002253,-0.9740553267,-1.530439034|H,-3.49769619,-1.2457225026,0.1919861704|C,1.0941687014,-0.726899366,0.0434064456|C,1.6300224188,-0.1195022338,1.1948303885|C,1.9901125218,-1.2145129721,-0.9275911759|C,3.0099089555,-0.0103175606,1.3731255599|H,0.962149847,0.2441565175,1.9695656155|C,3.3682193034,-1.1059098592,-0.7492847362|H,1.6028895806,-1.6465795652,-1.8448528769|C,3.8849277913,-0.04163245,0.4029146806|H,3.3993213008,0.4529887666,2.2749332869|H,4.040467702,-1.479054951,-1.5166367551|H,4.9588785237,-0.4197699667,0.5407

	599211||Version=IA32W-G09RevA.02|State=1-A|HF=-767.5522926|RMSD=2.535e-009|RMSF=6.941e-006|ZeroPoint=0.2424908|Thermal=0.258122|Dipole=0.9568121,-0.0514245,-1.55644| _____ Harmonic frequencies (cm**-1), IR intensities (KM/Mole), Raman scattering activities (A**4/AMU), depolarization ratios for plane and unpolarized incident light, reduced masses (AMU), force constants (mDyne/A), and normal coordinates: 1 2 3 A AA Frequencies -- -1396.3959 49.2401 52.7130 Red. masses -- 1.2065 4.1612 4.4140 Frcconsts -- 1.3861 0.0059 0.0072 IR Inten -- 463.6800 0.5307 0.6881

EF 	1|1|UNPC-LUCAS|Freq|RB3LYP|6-31+G(d,p)|C11H18O3Si1|USER1|09-Oct-2010|0 ||#N Geom=AllCheckGuess=TCheck SCRF=CheckGenChk RB3LYP/6-31+G(d,p) Freq||TitleCardRequired||0,1|O,-2.3607233039,-1.1877303577,1.7698192722|C,-1.7768397696,-1.8595455704,-1.6341241639|C,-0.5447827733,-1.8686087737,-0.9320687008|C,-0.1309149794,-0.7803041227,-0.1763561174|C,-1.0968016661,0.2221758667,0.2787724759|C,-1.9266810591,-0.0817537419,1.4839534148|C,-0.7516918926,1.6763645167,0.1824252521|O,0.1816050203,1.9159190876,-0.7715325337|C,0.5191258899,3.3007244199,-0.9822717354|O,-1.2941357303,2.5705738013,0.8083846333|C,-2.8848825326,-1.1198551818,-1.2061150527|H,-1.7554467179,-2.2669596237,-2.6456706145|H,0.202193322,-2.5913836026,-1.2524925726|H,-2.1528014868,0.8010663681,2.1076016254|H,1.2540165214,3.3014242118,-1.7869975748|H,-0.369391595,3.8672118124,-1.2699219482|H,0.9413610268,3.7361650436,-0.0730854187|H,-2.163976625,-0.0686422382,-0.652489604|H,-3.6594176177,-0.8882182295,-1.9357285648|H,-3.2619362216,-1.3222307358,-0.2013221953|Si,1.7536393373,-0.6639803552,0.1771239005|C,2.122860704,0.5584210019,1.5714371234|H,3.1788767094,0.4741572074,1.8550050102|H,1.9404580528,1.5994398068,1.2907094776|H,1.5272853895,0.3384670394,2.4646079029|C,2.7289159672,-0.2338872845,-1.3852958133|H,3.8059593007,-0.2388924956,-1.1789011689|H,2.5394791521,-0.9637000595,-2.1805304204|H,2.4556797033,0.7543981738,-1.7657832669|C,2.2795759208,-2.3874399261,0.7684310356|H,2.151158535,-3.1556073734,-0.0016093059|H,3.341162544,-2.3757500656,1.0440341979|H,1.7076768745,-2.6989396196,1.6491284505||Version=IA32W-G09RevA.02|State=1-A|HF=-945.1739066|RMSD=3.357e-009|RMSF=2.698e-006|ZeroPoint=0.2629458|Therma l=0.2818662|Dipole=1.0357215,0.1768208,-1.3786148| _____ Harmonic frequencies (cm**-1), IR intensities (KM/Mole), Raman scattering activities (A**4/AMU), depolarization ratios for plane and unpolarized incident light, reduced masses (AMU), force constants (mDyne/A), and normal coordinates: 1 2 3 A AA Frequencies -- -1348.4512 37.7671 55.8629 Red. masses -- 1.2268 3.2239 4.3831 Frc consts -- 1.3143 0.0027 0.0081 IR Inten -- 396.8096 0.2712 1.4802…

GH

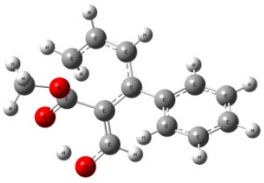


1|1|UNPC-LUCAS|Freq|RB3LYP|6-31+G(d,p)|C8H10O3|USER1|13-Sep-2010|0||#N Geom=AllCheckGuess=TCheck SCRF=CheckGenChk RB3LYP/6-31+G(d,p) Freq||TitleCardRequired||0,1|O,2.8310232857,0.0498563886,0.0144095504|C,-1.5748020646,-1.9283146663,-0.2940267845|C,-0.2096465595,-1.9066706719,-0.5720049086|C,0.6354255132,-0.827445237,-0.2394952681|C,2.0062852941,-0.9235486998,-0.3183732053|C,0.0647289645,0.5343894935,0.2405717924|O,-0.5206595398,1.1426676189,-0.8790890948|C,-0.7216645105,2.5541205466,-0.7833149499|O,0.8226198626,1.2492069387,0.9805175126|H,0.2176257419,-2.7263248825,-1.1491563993|H,2.4987055721,-1.8600441998,-0.5795493944|H,-1.105805514,2.8645127366,-1.7563581198|H,-1.4575012354,2.7932569621,-0.0048294373|H,0.2130221676,3.0726929342,-0.5557579797|H,2.2466588395,0.7595332234,0.4591666634|H,-2.2051340303,-2.6673543889,-0.7789943396|C,-2.1457645965,-0.9167370719,0.4900069067|H,-3.2104073349,-0.7121282441,0.3741575918|C,-1.3468004639,-0.0786248356,1.3067496913|H,-0.6463910158,-0.587446978,1.9662959532|H,-1.8335023762,0.7677690331,1.7869952197||Version=IA32W-G09RevA.02|State=1-A|HF=-536.4765687|RMSD=1.837e-009|RMSF=8.104e-006|ZeroPoint=0.165592|Thermal=0.175764|Dipole=-1.0452356,-0.9200891,-0.4158617

Harmonic frequencies (cm**-1), IR intensities (KM/Mole), Raman scattering activities (A**4/AMU), depolarization ratios for plane and unpolarized incident light, reduced masses (AMU), force constants (mDyne/A), and normal coordinates:

	1	2	3
	A	AA	
Frequencies --	-665.5632	72.0815	102.4937
Red. masses --	4.8738	3.1608	2.2206
Frc consts --	1.2720	0.0097	0.0137
IR Inten --	463.9750	2.6204	0.1491…

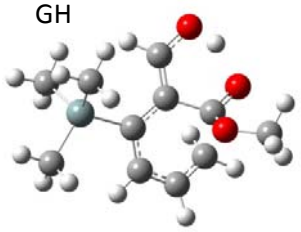
GH



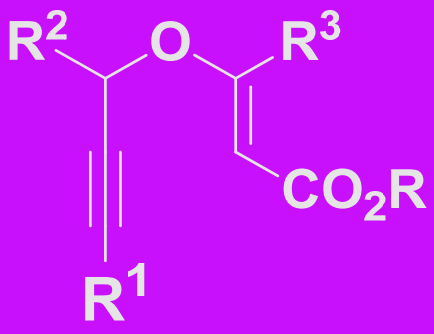
_ 1|1|UNPC-LUCAS|Freq|RB3LYP|6-31+G(d,p)|C14H14O3|USER1|24-Sep-2010|0||# N Geom=AllCheckGuess=TCheck SCRF=CheckGenChk RB3LYP/6-31+G(d,p) Freq||TitleCardRequired||0,1|O,-1.2022021769,-2.6158618431,-1.1417422208|C,-0.0384980571,1.955829382,-0.1151917256|C,0.3457414447,0.6068452027,-0.2076824037|C,-0.632283262,-0.417122017,-0.4047168491|C,-0.3258367438,-1.6480799601,-0.9312679692|C,-2.1364413655,-0.1522700503,-0.0919086581|O,-2.2352558063,0.0793416476,1.2861095426|C,-3.5499830405,-0.0205701374,1.8354087211|O,-2.9932530107,-0.9315594911,-0.6264455725|H,0.6758853047,-1.8742145607,-1.2908586315|H,-3.4318484661,0.1056975188,2.9129288484|H,-4.1988025642,0.7733375804,1.442752351|H,-4.000812351,-0.9900208262,1.6091124749|H,-2.1140274374,-2.1951288372,-0.969642555|H,0.6732487526,2.6691517427,0.2874487354|C,-1.3601045811,2.3541260136,-0.3291851631|H,-1.6837401093,3.2903569788,0.1264556105|C,-2.31138437,1.5101425626,-0.9499235238|H,-2.0216459728,1.0649061954,-1.8990291301|H,-3.3513392526,1.8306722616,-0.9382060355|C,1.7701440052,0.2621492461,0.01255606|C,2.782652481,1.0548191757,-0.5642091582|C,2.1474154333,-0.8335312347,0.8112082996|C,4.1279370901,0.7534138233,-0.3574107897|H,2.5069484858,1.8930129574,-1.1971357351|C,3.4945976265,-1.1232295771,1.0300785541|H,1.3788882947,-1.434577631,1.2855412971|C,4.4885537443,-0.3351906136,0.4433701117|H,4.8949722045,1.3647112889,-0.8237693693|H,3.7674328224,-1.9626635275,1.6627725977|H,5.5367178774,-0.5662642706,0.6091657401||Version=IA32W-G09RevA.02|State=1-A|HF=-767.5498612|RMSD=4.840e-009|RMSF=1.010e-05|ZeroPoint=0.2467093|Thermal=0.2615|Dipole=1.2985775,1.1301024,0.4211423|

Harmonic frequencies (cm**-1), IR intensities (KM/Mole), Raman scattering activities (A**4/AMU), depolarization ratios for plane and unpolarized incident light, reduced masses (AMU), force constants (mDyne/A),

	and normal coordinates: 1 2 3 A AA Frequencies -- -650.1980 46.7060 60.3292 Red. masses -- 5.3207 4.7995 3.6409 Frc consts -- 1.3253 0.0062 0.0078 IR Inten -- 719.3717 0.4963 0.6252…

GH 	1|1|UNPC-LUCAS|Freq|RB3LYP|6-31+G(d,p)|C11H18O3Si1|USER1|06-Oct-2010|0 ||#N Geom=AllCheckGuess=TCheck SCRF=CheckGenChk RB3LYP/6-31+G(d,p) Freq||TitleCardRequired||0,1|O,1.1889452032,2.7912267026,-0.3620390183|C,-0.2842498913,-1.8050295669,-0.5201009885|C,-0.5890873603,-0.4543053257,-0.2870553012|C,0.4591276252,0.5153028707,-0.2793845393|C,0.2405036625,1.8700334081,-0.3800287052|C,1.9613348144,0.0907492973,-0.1481585446|O,2.1145738342,-0.4473695387,1.138851471|C,3.4572790327,-0.5356677846,1.6174779733|O,2.8455941439,0.9224345823,-0.5483018422|H,-0.7473672888,2.2745743464,-0.586041652|H,3.3823720467,-0.8891948723,2.6472886796|H,4.037993678,-1.2552753529,1.0253298685|H,3.9566148926,0.4357015319,1.5806216739|H,2.0683055919,2.2747451888,-0.4110051718|H,-1.0299726836,-2.5634347829,-0.3043270103|C,1.0010646543,-2.228256204,-0.8818559948|H,1.2767102083,-3.2623404424,-0.6710106141|C,1.9786881257,-1.3187264129,-1.3490252966|H,1.6726841695,-0.6599742495,-2.1595376204|H,2.9943042733,-1.6896468862,-1.4737221297|Si,-2.4024618931,-0.0216093258,0.1960148371|C,-3.2341731861,0.9157714054,-1.2272988268|H,-4.2988851916,1.0521863166,-1.0021149589|H,-2.8073824254,1.9077329802,-1.4047314631|H,-3.1624994484,0.3507112742,-2.1633085978|C,-2.4244498136,1.0007186405,1.7845459482|H,-3.4585603286,1.1876774657,2.0974418161|H,-1.9183510014,0.4686569713,2.5975589467|H,-1.9292437632,1.9693554838,1.6669150475|C,-3.3684595015,-1.6235637031,0.4780695726|H,-4.3974817549,-1.3756368354,0.7646093344|H,-3.4225509392,-2.2440077544,-0.4231753302|H,-2.9406094853,-2.2285474281,1.2848904368||Version=IA32W-G09RevA.02|State=1-A|HF=-945.1661463|RMSD=4.335e-009|RMSF=2.250e-006|ZeroPoint=0.2669823|Thermal=0.2850747|Dipole=-1.1993913,-1.2030423,0.1460236| _____ Harmonic frequencies (cm**-1), IR intensities (KM/Mole), Raman scattering activities (A**4/AMU), depolarization ratios for plane and unpolarized incident light, reduced masses (AMU), force constants (mDyne/A), and normal coordinates: 1 2 3 A AA Frequencies -- -662.6615 36.3938 46.6487 Red. masses -- 4.9731 3.0737 4.1309 Frc consts -- 1.2866 0.0024 0.0053 IR Inten -- 559.0400 0.2585 0.1683…

[12] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, *Gaussian 03*, Revision C.02,Gaussian, Inc., Wallingford CT, 2004.



CHAPTER 6

Merging Domino and Redox Chemistry: Stereoselective Access to Di- and Trisubstituted β,γ-Unsaturated Acids and Esters

CHEMISTRY
A EUROPEAN JOURNAL

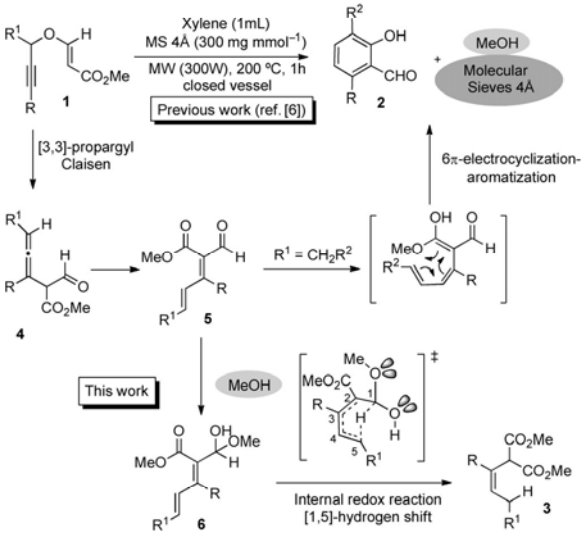
DOI: 10.1002/chem.201103763

Merging Domino and Redox Chemistry: Stereoselective Access to Di- and Trisubstituted β,γ-Unsaturated Acids and Esters

David Tejedor,* Gabriela Méndez-Abt, Leandro Cotos, and Fernando García-Tellado*[a]

The regio- and stereocontrolled access to multisubstituted alkenes bearing reactive functionalities constitutes a current topic in organic synthesis. These alkenes are appreciated building blocks for molecular construction and versatile platforms for diversity-oriented synthesis.[1] The most developed and used synthetic approaches to these structural motifs comprise the olefination of suitable carbonyl derivatives (carbonyl olefination)[2] and the transition-metal-catalyzed cross-coupling reactions of stereodefined alkenyl derivatives.[3] Whereas carbonyl olefination methodologies present stereochemical limitations and often stereocontrol problems,[4] the transition-metal-catalyzed cross-coupling approach requires the previous access to stereodefined alkenyl derivatives, which adds to the process an extra number of synthetic transformations and a second synthetic challenge, the synthesis of the precursor itself. Modern tendencies in synthetic chemistry demand efficient protocols able to achieve the molecular construction in a fast manner with atom and step economy, in a simple and bench-friendly process.[5] In this sense, the discovery of metal-free, domino manifolds for the regio- and stereocontrolled access to multisubstituted alkenes from easily accessible starting materials constitutes an important challenge.[5] We report herein the discovery and development of a novel approach to this challenge, which is based on the microwave-assisted (MWA) rearrangement of propargyl vinyl ethers (PVEs) **1** and utilizes a [3,3]-propargyl Claisen rearrangement and a [1,5]-hydrogen shift as key chemical transformations.

The chemical foundation for this domino manifold was discovered while exploring the microwave-assisted rearrangement of PVEs **1** leading to salicylaldehydes **2** (Scheme 1).[6] We found that the microwave irradiation of



Scheme 1. Microwave (MW)-assisted rearrangement of PVEs 1.

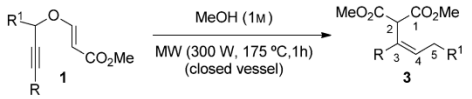
PVE **1a** (R = Ph; R^1 = *n*Pr) in the presence of molecular sieves (MS 4 Å) directly afforded the corresponding salicylaldehyde derivative **2a** (R = Ph, R^2 = Et; 76%), through a complex domino process involving a sequential [3,3]-propargyl Claisen rearrangement/pseudo-pericyclic [1,3]-H/enolization/6π-electrocyclization and aromatization set of discrete reactions. Overall, the process generated one equivalent of methanol per equivalent of salicylaldehyde produced. In the absence of MS 4 Å (an efficient methanol scavenger), the domino process delivered the corresponding salicylaldehyde **2a** (41%) and the β,γ-unsaturated malonate ester **3a** (50%). We envisioned that the formation of **3a** could be mediated by the formation of the redox active hemiacetal **6a** through a [1,5]-hydrogen shift from the hemiacetal center to the terminus of the conjugated diene with the concomitant rearrangement of the dienic chain. Although examples of formation of activated carboxylates by direct internal redox reactions from α,β,γ,δ-unsaturated aldehydes have been described,[7,8] in only a few cases have they shown some preparative value.[8] Evidently, this is not the case of dienal **5a** whose hydricity[9] is not enough to launch a direct internal redox reaction in the presence of a methanol scavenger (MS 4 Å). Thus, the productive formation of the internal redox reaction product **3a** seems to be strongly related

[a] Dr. D. Tejedor, G. Méndez-Abt,[+] L. Cotos,[+] Dr. F. García-Tellado
Departamento de Química Biológica y Biotecnología
Instituto de Productos Naturales y Agrobiología
Consejo Superior de Investigaciones Científicas
Astrofísico Francisco Sánchez 3
38206 La Laguna, Tenerife (Spain)
Fax: (+34) 922-210-635
E-mail: dtejedor@ipna.csic.es
fgarcia@ipna.csic.es
Homepage: http://www.ipna.csic.es/dept/qbb/qb/
[+] These authors have contributed equally to this work

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201103763.

with the capacity of the system to selectively produce hemiacetal **6a**. This issue was experimentally corroborated by performing the microwave-assisted reaction in methanol, a solvent unable to react with the starting PVE but highly reactive toward the intermediate α,β,γ,δ-unsaturated aldehyde **5**. When irradiated in methanol (300 W, 175 °C, 1 h, closed vessel), PVE **1a** cleanly afforded the corresponding β,γ-unsaturated malonate **3a** in 83 % yield with complete regio- and stereoselectivity (**3a** was obtained as the unique isomer; Table 1, entry 1). It deserves to be highlighted how the chemical efficiency of this reaction involves a complete rebuilding of the original carbon–carbon connectivity pattern. The generality and scope of this redox domino reaction was studied using the set of PVEs shown in Table 1.[10] In general, the reaction was tolerant with a broad functional diversity at the propargylic and sp-terminal positions of the PVE units. Different combinations of alkyl/aryl/hydrogen substituents at the propargyl position and ester/alkyl/aromatic/hydrogen at the sp-terminal position uniformly afforded the corresponding di- or trisubstituted β,γ-unsaturated esters **3b–h** in good to excellent yields and with the same stereochemical pattern than **3a** (only the isomers bearing the R and R^1 substituents in a *trans* relationship were observed). Even the PVE **1j** bearing a hydrogen atom at the homopropargylic position and an ester group at the sp-terminal position afforded the corresponding triester **3j** in a convenient 50 % yield (Table 1, entry 10). The combination of these two substituents generates a particular reactivity profile in the intermediate α,β,γ,δ-unsaturated aldehyde **5j** (R = CO_2Me; R^1 = *c*Hex), which allows the formation of other redox inactive intermediates,[6] and consequently, it reduces the efficiency of the internal redox reaction (Scheme 1).

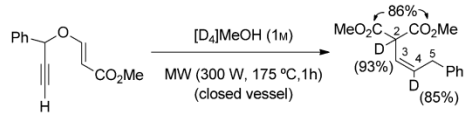
Table 1. Stereoselective synthesis of β,γ-unsaturated malonates **3** from PVEs **1**.[a]



Entry	R	R^1	**3** [%][b]	
1	Ph	*n*Pr	**a**	83
2	H	*n*Pent	**b**	86
3	H	Ph	**c**	90
4	Ph	Ph	**d**	85
5	*n*Bu	Ph	**e**	70
6	*n*Bu	*n*Pr	**f**	91
7	Ph	H	**g**	75[c]
8	CO_2Me	*t*Bu	**h**	93
9	CO_2Me	*m*Xylyl	**i**	94
10	CO_2Me	*c*Hex	**j**	50

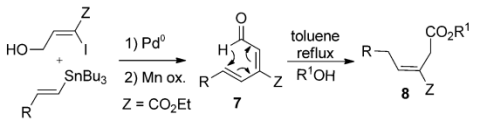
[a] See the Experimental Section for details. [b] Isolated material. [c] 3 h.

The intermediacy of a [1,5]-hydrogen shift in these reactions was established by isotopic labeling experiments (Scheme 2). Deuterium incorporation from the solvent resulted in the expected labile positions (esters, C2 and C4). Therefore, the deuterium label was not incorporated at the allylic (C5) position. This fact proved that the hydride migrated directly from the hemiacetalic position (C1) onto the conjugated diene (C5). The high acidic methine of the malonate function (C2), which largely incorporated deuterium in the reaction (93 % of D incorporation), suffered a large D/H exchange in the chromatography process, giving an overall 11 % of total deuterium incorporation (see the Supporting Information for details).



Scheme 2. Isotopic labeling experiment.

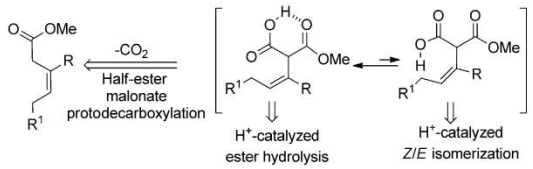
From a preparative point of view, the reaction offers the following advantages: 1) the substituted PVEs **1** are readily available;[10] 2) the substituted (*E,E*)-dienals **5** are assembled directly from the corresponding PVEs in a regiocontrolled manner,[11] and 3) the experimental protocol is operationally simple and bench-friendly. These advantages are highlighted when this reaction is compared with the recently described direct oxidation of the dienals **7** to carboxylic esters **8** (Scheme 3),[8b] which requires the previous formation of these dienals by a sequential Pd-catalyzed cross-coupling reaction of stereodefined vinyl iodide derivatives and (*E*)-vinyl stannanes, and the corresponding allylic oxidation to the aldehyde level.



Scheme 3. Direct oxidation of dienal **7** to carboxylic ester **8**.

With these results in hand, we envisioned the feasibility to perform this reaction under aqueous conditions to access these valuable synthetic building blocks in a more benign and sustainable manner.[12] It was expected that the dienal molecule **5** should express in water the same reactivity pattern as it exhibits in MeOH, affording the corresponding hydrates,[13] which should oxidize to the corresponding carboxylic acids. In Nature, aldehyde oxidations to carboxylates are performed by the NAD^+-dependent aldehyde dehydrogenases (ALDHs) enzymes. The mechanism of these oxidations involves the transformation of the aldehyde in a more oxidizable thiohemiacetal derivative (ALDHs use cysteine residues to perform this task) and a hydride transfer to the NAD^+ unit, which plays the role of an activated reducible functional group.[14] Although we have not found precedents for the [1,5]-H shift-mediated oxidation of dienals under aqueous conditions, which gives an added value to this study,[15] we were concerned with the possibility that the free carboxylic acid would act as an internal acid catalyst for the

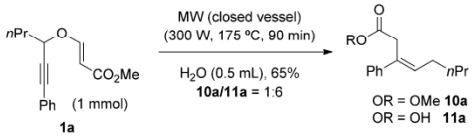
CHEMISTRY
A EUROPEAN JOURNAL



Scheme 4. Acid-catalyzed transformations of the half-ester malonate intermediate.

hydrolysis of the geminal ester and for the *Z*/*E* isomerization of the distal double bond, introducing a certain grade of instability to the redox product (Scheme 4). However, the characteristic protodecarboxylation reaction of the half-ester malonates was also expected to occur under microwave irradiation in water. If this reaction were fast enough, then the side H^+-catalyzed reactions could be inhibited and the expected monoester derivative could be accumulated in the reaction medium without suffering chemical deterioration.

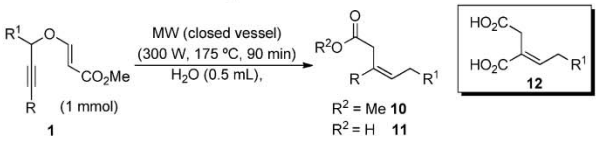
With these concerns in mind, we undertook the study of these reactions under aqueous conditions[16] by using the hydrophobic PVE **1a** as a model. After some trials, a set of reaction conditions were selected for the heterogeneous reaction (Scheme 5). Under these conditions, **1a** was transformed into the 1:6 mixture of trisubstituted β,γ-unsaturated methyl ester **10a** and carboxylic acid **11a** in a combined yield of 65%. Three main characteristics of this reaction deserve to be highlighted: Firstly, the stereoselectivity of the process is good (90% of the *E* isomer); secondly, the expected H^+-catalyzed ester hydrolysis is achieved with a low erosion of the alkene stereochemistry (10%), and thirdly, the expected protodecarboxylation of the half-ester malonate function takes place without significant alkene reordering.



Scheme 5. Microwave-assisted rearrangement of PVE **1a** under aqueous conditions.

Once a proof of concept was established, we studied the scope of this reaction with regard to the nature of the PVE (Table 2). Three conclusions could be extracted from the data of Table 2: 1) the reaction showed good tolerance with regard to the substituents, affording the desired products as mixtures of the carboxylic acids or esters; 2) the stereoselectivity of the reaction is governed by the nature of the alkyne substituent R, which is optimal for R = H or CO_2Me (up to 90%; Table 2, entries 2, 3, and 7–10); and 3) the isolated product yields of the products range from good to excellent. Furthermore, it is worth mentioning that under these reaction conditions, there is no significant double-bond migration to give the corresponding α,β-unsaturated esters/acids. Consequently, this procedure becomes a simple, metal-free stereoselective access to di- and trisubstituted β,γ-unsaturated esters/acids, which are valuable synthetic building blocks.

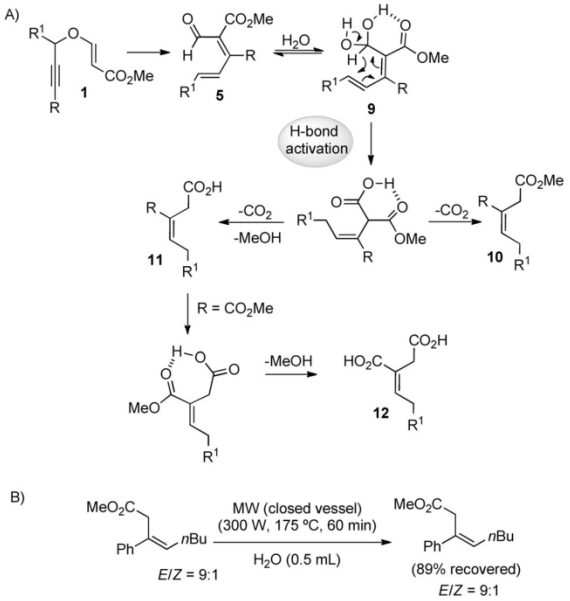
Table 2. Stereoselective synthesis of di- and trisubstituted β,γ-unsaturated esters/acids **10**:**11** under aqueous conditions.[a]



Entry	R	R^1		[%][b]	**10**:**11**	Stereoselectivity
1	Ph	*n*Pr	**a**	65[c]	1:6	9:1
2	H	*n*Pent	**b**	58	3:1	15:1
3	H	Ph	**c**	82	2.6:1	19:1
4	Ph	Ph	**d**	92	1:2.1	3.2:1
5	*n*Bu	Ph	**e**	69	1:1.6	6:1
6	*n*Bu	*n*Pr	**f**	56[d]	1:5.2	3.1:1
7	CO_2Me	*t*Bu	**h**	96	2:1	≥19:1
8	CO_2Me	*m*Xyl	**i**	96	2.4:1	≥19:1
9	CO_2Me	*c*Hex	**j**	68[e]	1:1.7	≥19:1
10	CO_2Me	*n*Bu	**k**	66[f]	1:12	≥19:1
11	*c*Hex	Ph	**l**	57	1:2	6.3:1

[a] See the Experimental Section for details. [b] Isolated material. [c] H_2O (1 mL), **2a** (10%). [d] **2f** (12%). [e] **12j** (8%). [f] **12k** (7%).

A mechanistic proposal for this reaction is outlined in Scheme 6A. Three experimental evidences confirm this mechanistic picture. Firstly, the intermediacy of a [1,5]-H migration in these reactions was again established by isotopic labeling experiments when the reaction was carried out in

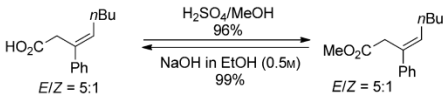


Scheme 6. Microwave-assisted domino-redox rearrangement of PVE **1** under aqueous conditions.

D_2O (see the Supporting Information for details). Secondly, the allylic ester functionality is stable to hydrolysis in the absence of a geminal carboxylic acid (Scheme 6B). Lastly, the isolation of diacids **12j** and **12k** (Table 2, entries 9 and 10) establishes that the allylic ester needs to be hydrolyzed before the protodecarboxylation reaction of the geminal carboxylic acid takes place to give the monoacid **11** (H^+-catalyzed ester hydrolysis). The free carboxylic acid in **11** could catalyze the hydrolysis of the vinylic ester to render the diacid **12**.

The efficiency of this transformation is highlighted when we take into account that it enables a domino process consisting of a [3,3]-propargyl Claisen rearrangement/pseudopericyclic [1,3]-H shift reaction/diene *E*/*E* to *E*/*Z* isomerization/water addition/redox [1,5]-H shift/ester hydrolysis and protodecarboxylation.

Finally, the ester–acid mixture (**10**/**11**) can be selectively converted in just one of the two derivatives by the chemical transformation shown in Scheme 7.



Scheme 7. Controlled acid–ester interconversion of the acid–ester mixture **10**/**11**.

In summary, we have shown how the coupling of a MWA domino reaction and an internal neutral redox reaction constitutes an excellent manifold for the stereoselective synthesis of di- and trisubstituted olefins featuring a malonate unit, an ester, or a free carboxylic acid at the allylic position. These reactive functionalities can be used as convenient chemical handles for the development of enantioselective transformations at the double bond or for the chemical homologation of these unsaturated platforms. The reaction utilizes simple starting materials (propargyl vinyl ethers), methanol or water as solvents, and a very simple and bench-friendly experimental protocol. The reaction in methanol is highly efficient, rendering the β,γ-unsaturated malonate with complete stereoselectivity. The use of water as the reaction medium changes the chemical outcome of the reaction to give the corresponding trisubstituted β,γ-unsaturated acid (ester) with high stereoselectivity (up to 19/1).

Experimental Section

Representative procedure for the microwave-assisted reaction of propargyl vinyl ether in methanol: Synthesis of β,γ-unsaturated malonates **3**: Propargyl vinyl ether **1a** (1.00 mmol) and methanol (1 mL) were placed in a microwave-special closed vial and the solution was irradiated for 1 hour in a single-mode microwave oven (300 Watt, 175 °C). After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, appropriate mixtures of *n*-hexane/EtOAc) to yield **3a** (83 %).

Representative procedure for the microwave-assisted reaction of propargyl vinyl ether in water. Synthesis of β,γ-unsaturated carboxylic esters/acids (**10**/**11**): Propargyl vinyl ether **6i** (1.00 mmol) and water (0.5 mL) were placed in a microwave-special closed vial and the solution was irradiated for 90 min in a single-mode microwave oven (300 Watt, 175 °C). The products were extracted with CH_2Cl_2 and the solvent was removed at reduced pressure. The products were purified by flash column chromatography (silica gel, appropriate mixtures of *n*-hexane/EtOAc) to yield **10i**/**11i** (2.4:1) (96 %).

(E)-dimethyl 2-(2-(2,6-dimethylphenyl)ethylidene)succinate (***10i***): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) : δ = 2.28 (s, 6H), 3.52 (d, ^3J(H,H) = 6.8, 2H), 3.52 (s, 2H), 3.71 (s, 3H), 3.72 (s, 3H), 6.82 (t, ^3J(H,H) = 6.8, 1H), 7.01–7.08 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 20.0, 29.5, 32.4, 51.9, 52.0, 125.8, 126.6, 128.3, 135.2, 136.4, 143.5, 167.1, 171.0 ppm; IR ($CHCl_3$) $\tilde{\nu}$ = 3027.6, 2952.7, 1736.8, 1710.9, 1469.1, 1332.5, 1306.7, 1267.4 cm^{-1}; MS (70 eV): *m*/*z* (%): 244 (8.6) [$M^+ - CH_3OH$], 230 (49), 201 (18), 184 (30), 157 (100), 143 (54), 142 (35), 141 (24), 128 (24), 115 (17), 91 (16); elemental analysis calcd (%) for $C_{16}H_{20}O_4$: C 69.54, H 7.30; found: C 69.35, H 7.10.

(E)-5-(2,6-dimethylphenyl)-3-(methoxycarbonyl)pent-3-enoic acid (***11i***): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.27 (s, 6H), 3.54 (d, ^3J(H,H) = 6.8, 2H), 3.56 (s, 2H), 3.72 (s, 3H), 6.84 (t, ^3J(H,H) = 6.8, 1H), 7.01–7.08 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 20.1, 29.6, 32.6, 52.1, 125.3, 126.7, 128.4, 135.1, 136.5, 144.0, 167.4, 175.9 ppm; IR ($CHCl_3$) $\tilde{\nu}$ = 3024.0, 2952.2, 1712.9, 1437.5, 1296.9, 1266.8, 1200.8 cm^{-1}. MS (70 eV): *m*/*z* (%): 262 (5.6) [M^+], 230 (37), 201 (25), 184 (31), 157 (100), 143 (56), 142 (49), 141 (30), 128 (30), 115 (28), 91 (26); HRMS calcd for $C_{15}H_{18}O_4$: 262.1205; found: 262.1205.

Acknowledgements

This research was supported by the Spanish MICINN and the European RDF (CTQ2008–06806-C02–02), the Spanish MSC ISCIII (RETICS RD06/0020/1046), FUNCIS (REDESFAC PI01/06). G. M.-A. and L. C. thank Spanish MEC for FPU and FPI grants, respectively.

Keywords: alkenes · domino reactions · redox chemistry · stereoselectivity · water

[1] For a concept article, see: K. Itami, J.-I Yoshida, *Chem. Eur. J.* **2006**, *12*, 3966–3974.
[2] *Modern Carbonyl Olefination. Methods and Applications* (Ed.: T. Takeda), Wiley-VCH, Weinheim, **2004**.
[3] a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd completely revised and enlarged edition, Vol.1 and 2 (Eds.: A. de Meijere, F. Diederich), Wiley-VCH: Weinheim, **2004**; for recent and selected reviews, see: b) W. Shi, C. Liu, A. Lei, *Chem. Soc. Rev.* **2011**, *40*, 2761–2776; c) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780–1824; d) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417–1492.
[4] L. Kürti, B. Czakó in *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier Academic Press, Amsterdam, **2005**.
[5] For selected reviews, see: a) N. Z. Burns, P. S. Baran, R. W. Hoffmann, *Angew. Chem.* **2009**, *121*, 2896–2910; *Angew. Chem. Int. Ed.* **2009**, *48*, 2854–2867; b) P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40–49.
[6] D. Tejedor, G. Méndez-Abt, L. Cotos, M. A. Ramirez, F. García-Tellado, *Chem. Eur. J.* **2011**, *17*, 3318–3321.
[7] a) P. Schiess, P. Radimerski, *Angew. Chem.* **1972**, *84*, 345–346; *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 288–289 and references cited therein; b) A. Smit, J. G. J. Kok, H. W. Geluk, *Chem. Commun.* **1975**, 513–514.

[8] a) S. E. Steinhardt, J. S. Silverston, C. D. Vanderwal, *J. Am. Chem. Soc.* **2008**, *130*, 7560–7561; b) T. Sakaguchi, Y. Okuno, Y. Tsutsumi, H. Tsuchikawa, S. Katsumura, *Org. Lett.* **2011**, *13*, 4292–4295.

[9] a) M. Alajarin, B. Bonillo, M.-M. Ortin, P. Sanchez-Andrada, A. Vidal, *Eur. J. Org. Chem.* **2011**, 1896–1913 and references cited therein; for a theoretical study of the rearrangement of (5-(dialkylamino)-2,4-pentadienals, see: b) R. S. Paton, S. E. Steinhardt, C. D. Vanderwal, K. N. Houk, *J. Am. Chem. Soc.* **2011**, *133*, 3895–3905.

[10] PVEs **1a–g** were synthesized from the corresponding propargylic alcohols:D. Tejedor, G. Méndez-Abt, F. García-Tellado, *Chem. Eur. J.* **2010**, *16*, 428–431. PVEs **1h–j** were synthesized by the ABB′ three-component reaction of aldehydes and methyl propiolate in the presence of triethylamine, see: D. Tejedor, F. García-Tellado, J. J. Marrero-Tellado, P. de Armas, *Chem. Eur. J.* **2003**, *9*, 3122–3131. For a definition of the ABB′ 3CR notation, see: D. Tejedor, F. García-Tellado, *Chem. Soc. Rev.* **2007**, *36*, 484–491.

[11] We have shown that under controlled conditions, these dienals can be isolated in good yields from the corresponding PVEs (see Ref. [6])

[12] For selected reviews on this topic, see: a) V. Polshettiwar, R. S. Varma, *Acc. Chem. Res.* **2008**, *41*, 629–639; b) D. Dallinger, C. O. Kappe, *Chem. Rev.* **2007**, *107*, 2563–2591.

[13] For a discussion of formation of hydrates in water, see: a) E. T. Urbansky, *J. Chem. Educ.* **2000**, *77*, 1644–1647 and references cited therein; for selected theoretical studies, see: b) B. Wang, Z. Cao, *Angew. Chem.* **2011**, *123*, 3324–3328; *Angew. Chem. Int. Ed.* **2011**, *50*, 3266–3270; c) R. Gómez-Bombarelli, M. González-Pérez, M. T. Pérez-Prior, E. Calle, Julio Casado, *J. Phys. Chem. A* **2009**, *113*, 11423–11428; d) S. H. Hilal, *QSAR Comb. Sci.* **2005**, 24,631–638; e) P. Guthrie, *J. Am. Chem. Soc.* **2000**, *122*, 5529–5538; f) J. P. Guthrie, V. Pitchko, *J. Am. Chem. Soc.* **2000**, *122*, 5520–5528.

[14] For a discussion on this topic, see: S. Marchal, S. Rahuel-Clermont, G. Branlant, *Biochemistry* **2000**, *39*, 3327–3335.

[15] For an example of aerobic oxidation of aldehydes in aqueous conditions, see: N. Shapiro, A. Vigalok, *Angew. Chem.* **2008**, *120*, 2891–2894; *Angew. Chem. Int. Ed.* **2008**, *47*, 2849–2852.

[16] Although the PVEs are not soluble in water and we observed two phases in the reaction vessel at the end of the reaction, we think that "under aqueous conditions" is the best description for these reaction conditions (closed vessel, microwave irradiation (300 W) and high temperature (150 °C)) because it includes a wide range of processes spanning from "in water" (one homogeneous phase) to "on water" processes (aqueous emulsion).

Received: November 30, 2011
Published online: February 22, 2012

Supporting Information

Merging Domino and Redox Chemistry. Stereoselective Access to Di- and Trisubstituted β,γ-Unsaturated Acids and Esters.

David Tejedor,* Gabriela Méndez-Abt, Leandro Cotos, and Fernando García-Tellado*
Instituto de Productos Naturales y Agrobiología, CSIC,
Astrofísico Francisco Sánchez 3, 38206 La Laguna, Tenerife, Spain

Contents: Page

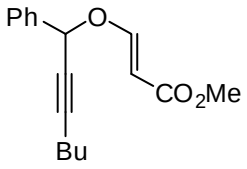
General remarks. ^{1}H NMR and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded either at 400 and 100 MHz or at 500 and 125 MHz, respectively. Microwave reactions were conducted in sealed glass vessels (capacity 10 mL) using a CEM Discover microwave reactor. FT-IR spectra were measured in chloroform solutions. Flash column chromatography was carried out with silica gel 60 (particle size less than 0.020 mm) using appropriate mixtures of dichloromethyl and methanol or ethyl acetate and hexanes as eluents. All reactions were performed in oven-dried glassware. Dichloromethane was distilled from CaH_2. Propargyl vinyl ethers (PVEs) were synthesized according to literature procedures (**1a**-**1g, 1l**),[1] and (**1h-k**)[2]. When not commercially available, the propargyl alcohols were prepared by addition of the lithium acetylides onto the appropriate aldehydes following the literature procedure.[3] All other materials were obtained from commercial suppliers and used as received. Products **1a-d**[4], **1f**[4], **1h**[2], **1j**[5], **3a**[4], **10b/11b**[6], **10c**[7], **11c**[8], **10k**[9], **11k**[10] have been previously reported and all data are in accordance with those of the literature.

Experimental section.

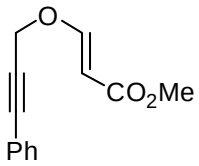
Representative procedure for the synthesis of propargyl vinyl ethers (1a-g, 1l).[1] Triethylamine (0.30 mmol) was added to a solution of methyl propiolate (3.0 mmol) and 1-phenylhex-1-yn-3-ol (3.0 mmol) in dry CH_2Cl_2 (10 ml). The reaction mixture was stirred for 2 h. After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, n-hexane/EtOAc 90/10) to yield **1a** (95%).

Representative procedure for the ABB' 3CR synthesis of propargyl vinyl ethers (1h-k).[2] To a solution of methyl propiolate (3.90 mmol) and cyclohexanecarbaldehyde (1.95 mmol) in dry DCM (10 mL) cooled to 0 °C was added triethylamine (1.95 mmol). The reaction mixture was stirred for 2 h. After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, n-hexane/EtOAc 90/10) to yield **6j** (68%).

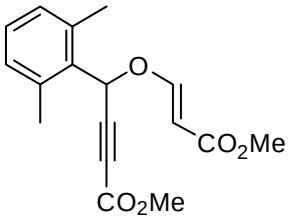
(E)-methyl 3-(1-phenylhept-2-ynyloxy)acrylate (1e): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.91 (t, ^3J(H,H) = 7.1, 3H), 1.37-1.46 (m, 2H), 1.50-1.57 (m, 2H), 2.30 (dt, ^3J(H,H) = 6.8, 2.0 Hz, 2H), 3.69 (s, 3H), 5.43 (d, ^3J(H,H) = 12.4, 1H), 5.63 (t, ^3J(H,H) = 1.8, 1H), 7.36-7.41 (m, 3H), 7.48-7.51 (m, 2H), 7.70 (d, ^3J(H,H) = 12.4, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.5, 18.5, 21.9, 30.4, 51.1, 73.8, 75.6, 91.5, 99.1, 127.5, 128.7, 129.1, 137.0, 160.1, 168.1. IR ($CHCl_3$, cm^{-1}) 3028.0, 2959.7, 2874.7, 2232.2, 1705.9, 1642.9, 1623.8, 1438.3, 1334.4, 1290.1, 1191.3, 1134.1. Elemental analysis calcd. (%) for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.77; H, 7.28. MS (70 eV): *m/z* (%): 272 (7.4) [M^+], 243 (6.1), 215 (20), 171 (100), 141 (22), 128 (43), 91 (68), 77 (20).



(E)-methyl 3-(3-phenylprop-2-ynyloxy)acrylate (1g): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.70 (s, 3H), 4.73 (s, 2H), 5.39 (d, ^3J(H,H) = 12.4, 1H), 7.28-7.33 (m, 3H), 7.42-7.45 (m, 2H), 7.63 (d, ^3J(H,H) = 12.4, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 51.1, 59.1, 81.9, 88.4, 98.0, 121.7, 128.3, 128.9, 131.8, 160.8, 167.7. IR ($CHCl_3$, cm^{-1}) 3026.7, 2953.7, 2232.2, 1706.9, 1649.3, 1627.1, 1491.9, 1439.9, 1375.2, 1331.2, 1214.4, 1134.2. Elemental analysis calcd. (%) for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.17; H, 5.88. MS (70 eV): *m/z* (%): 216 (0.3) [M^+], 13 (6.1), 15 (20), 115 (100), 89 (10).



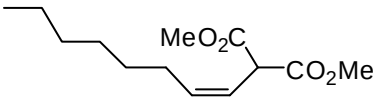
(E)-methyl 4-(2,6-dimethylphenyl)-4-(3-methoxy-3-oxoprop-1-enyloxy)but-2-ynoate (1i): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.46 (s, 6H), 3.68 (s, 3H), 3.76 (s, 3H), 5.43 (d, ^3J(H,H) = 12.7, 1H), 6.06 (s, 1H), 7.04 (d, ^3J(H,H) = 7.7, 2H), 7.15-7.18 (m, 1H), 7.54 (d, ^3J(H,H) = 12.7, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.3, 51.2, 52.9, 68.4, 79.4, 81.6, 99.5, 129.4, 129.6, 130.9, 137.1, 153.1, 159.4, 167.4. IR ($CHCl_3$, cm^{-1}) 3025.6, 2929.0, 2240.8, 1715.4, 1646.7, 1624.7, 1436.7, 1271.7, 1136.2. Elemental analysis calcd. (%) for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.60; H, 6.06. MS (70 eV): *m/z* (%): 302 (3.2) [M^+], 202 (50), 201 (100),



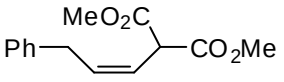
155 (42), 142 (70), 141 (100), 129 (37) 128 (50), 115 (86).

Representative procedure for the microwave-assisted reaction of propargyl vinyl ether in methanol. Synthesis of β,γ-unsaturated malonates 3. Propargyl vinyl ether **1a** (1.00 mmol) and methanol (1 mL) were placed in a microwave-special closed vial and the solution was irradiated for 1 hour in a single-mode microwave oven (300 Watt, 175 ºC). After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, appropriate mixtures of *n*-hexane/EtOAc) to yield **3a** (83%).

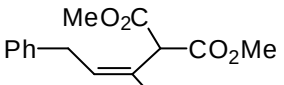
(Z)-Dimethyl 2-(oct-1-enyl)malonate (3b): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.83 (t, ^3J(H,H) = 6.8, 3H), 1.20-1.34 (m, 8H), 2.01-2.06 (m, 2H), 3.69 (s, 6H), 4.32 (d, ^3J(H,H) = 8.8, 1H), 5.60-5.71 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 22.5, 27.6, 28.8, 29.0, 31.6, 50.3, 52.5, 120.5, 135.7, 168.6. IR ($CHCl_3$, cm^{-1}) 3029.6, 2956.5, 2930.1, 2858.1, 1734.1, 1436.5, 1310.4, 1263.3, 1220.5, 1153.0. MS (70 eV): *m/z* (%): 242 (8.9) [M^+], 183 (57), 182 (41), 133 (44), 132 (100), 127 (44), 123 (46) 111 (85), 110 (30), 81 (39), 67 (36), 59 (48). HRMS calculated for $C_{13}H_{22}O_4$ 242.1518, found 242.1511.



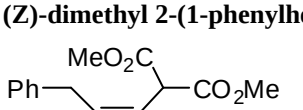
(Z)-dimethyl 2-(3-phenylprop-1-enyl)malonate (3c): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.46 (d, ^3J(H,H) = 6.8, 2H), 3.75 (s, 6H), 4.48 (d, ^3J(H,H) = 8.8, 1H), 5.81-5.94 (m, 2H), 7.16-7.21 (m, 3H), 7.27-7.30 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 33.8, 50.4, 52.7, 121.5, 126.2, 128.3, 128.5, 133.8, 139.3, 168.4. IR ($CHCl_3$, cm^{-1}) 3026.5, 2955.7, 2927.6, 1735.8, 1602.7, 1495.4, 1455.1, 1436.5, 1313.2, 1153.4. Elemental analysis calcd. (%) for $C_{13}H_{22}O_4$: C, 67.73; H, 6.50. Found: C, 67.45; H, 6.41. MS (70 eV): *m/z* (%): 248 (23) [M^+], 188 (30), 157 (16), 129 (100), 128 (39), 115 (22), 91 (22).



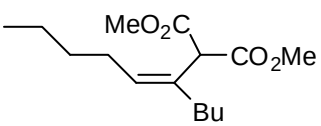
(E)-dimethyl 2-(1,3-diphenylprop-1-enyl)malonate (3d): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.55 (d, ^3J(H,H) = 7.6, 2H), 3.66 (s, 6H), 4.82 (s, 1H), 6.09 (t, ^3J(H,H) = 7.6, 1H), 7.19-7.24 (m, 4H), 7.26-7.30 (m, 4H), 7.38-7.40 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 35.2, 52.6, 54.3, 126.3, 127.1, 127.3, 128.2, 128.5, 128.6, 133.4, 134.3, 139.6, 141.7, 168.6. IR ($CHCl_3$, cm^{-1}) 3027.5, 2955.1, 1736.6, 1601.7, 1494.7, 1436.5, 1312.3, 1212.0, 1155.1. Elemental analysis calcd. (%) for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21. Found: C, 74.46; H, 6.21. MS (70 eV): *m/z* (%): 324 (15) [M^+], 292 (14), 266 (15), 233 (18), 205 (100), 193 (99), 178 (19), 128 (33), 115 (72), 103 (20), 91 (55), 84 (25), 77 (21).



(Z)-dimethyl 2-(1-phenylhept-2-en-3-yl)malonate (3e): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.99 (t, ^3J(H,H) = 7.3, 3H), 1.27-1.36 (m, 2H), 1.39-1.46 (m, 2H), 2.10 (dt, ^3J(H,H) = 7.3 and 1.3, 2H), 3.41 (d, ^3J(H,H) = 7.6, 2H), 3.73 (s, 6H), 4.53 (s, 1H), 5.66 (dt, ^3J(H,H) = 7.6 and 1.5, 1H), 7.16-7.20 (m, 3H), 7.26-7.30 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 22.4, 30.2, 34.36, 34.39, 52.5, 53.5, 126.1, 128.39, 128.44, 129.1, 132.4, 140.2, 168.7. IR ($CHCl_3$, cm^{-1}) 3029.3, 2956.7, 2871.8, 1736.3, 1495.1, 1454.7, 1436.3, 1312.7, 1229.8, 1152.6. MS (70 eV): *m/z* (%): 304 (14) [M^+], 272 (29), 244 (22), 240 (28), 213 (26), 185 (32), 173 (19), 142 (53), 129 (81), 115 (45), 91 (100), 77 (14), 59 (20). HRMS calculated for $C_{18}H_{24}O_4$ 304.1675, found 304.1668.

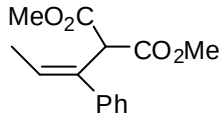


(Z)-dimethyl 2-(dec-5-en-5-yl)malonate (3f): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.86-0.89 (m, 6H), 1.26-1.42 (m, 8H), 2.01 (q, ^3J(H,H) = 7.1, 2H), 2.09 (t, ^3J(H,H) = 7.1, 2H), 3.72 (s, 6H), 4.44 (s, 1H), 5.45 (t, ^3J(H,H) = 7.3, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.88, 13.95, 22.3, 22.4, 27.9, 30.3, 31.6, 33.9, 52.3, 53.3, 130.9, 131.1, 168.9. IR ($CHCl_3$, cm^{-1}) 3029.3, 2957.6, 2871.6, 1735.6, 1458.1,

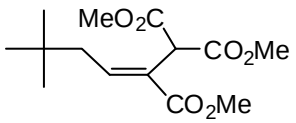


1436.3, 1314.7, 1277.7, 1150.5. MS (70 eV): *m/z* (%): 270 (18) [M^+], 211 (100), 181 (33), 167 (97), 154 (10), 138 (3312), 84 (31), 55 (15). HRMS calculated for $C_{15}H_{26}O_4$ 270.1831, found 270.1837.

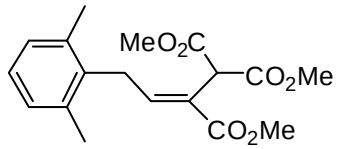
(E)-dimethyl 2-(1-phenylprop-1-enyl)malonate (3g): The solution was irradiated for 3 hours (300 Watt, 190 ºC) ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.81 (d, ^3J(H,H) = 7.1, 3H), 3.68 (s, 6H), 4.75 (s, 1H), 6.01 (q, ^3J(H,H) = 7.1, 1H), 7.26-7.30 (m, 3H), 7.35-7.37 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.5, 52.5, 53.9, 126.9, 127.0, 128.1, 130.2, 133.7, 141.8, 168.6. IR ($CHCl_3$, cm^{-1}) 3029.6, 2955.4, 1736.5, 1493.1, 1436.4, 1313.4, 1263.1, 1230.9, 1154.0. MS (70 eV): *m/z* (%): 248 (4.0) [M^+], 190 (14), 189 (100), 185 (12), 184 (12), 157 (40), 156 (16), 129 (65), 128 (36), 115 (26). HRMS calculated for $C_{14}H_{16}O_4$ 248.1049, found 248.1055.



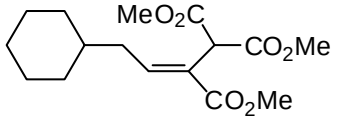
(E)-trimethyl 5,5-dimethylhex-2-ene-1,1,2-tricarboxylate (3h): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.93 (s, 9H), 2.09 (d, ^3J(H,H) = 7.8, 2H), 3.73 (s, 6H), 3.75 (s, 3H), 4.59 (s, 1H), 7.12 (t, ^3J(H,H) = 7.8, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 29.3, 31.7, 42.8, 49.8, 52.1, 52.6, 126.8, 145.1, 166.4, 168.0. IR ($CHCl_3$, cm^{-1}) 3028.3, 2957.1, 1736.6, 1437.3, 1314.6, 1234.6, 1159.1. MS (70 eV): *m/z* (%): 286 (0.4) [MH^+], 254 (19), 230 (18), 223 (12), 198 (100), 166 (82), 139 (40), 91 (11), 57 (79). HRMS calculated for $C_{14}H_{23}O_6$ 287.1495, found 287.1502.



(E)-trimethyl 4-(2,6-dimethylphenyl)but-2-ene-1,1,2-tricarboxylate (3i): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.26 (s, 6H), 3.54 (d, ^3J(H,H) = 6.8, 2H), 3.72 (s, 3H), 3.78 (s, 6H), 4.74 (s, 1H), 6.89 (d, ^3J(H,H) = 6.8, 1H), 7.01-7.08 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.1, 29.4, 50.0, 52.2, 52.8, 126.2, 126.8, 128.4, 134.9, 136.5, 145.4, 166.2, 167.8. IR ($CHCl_3$, cm^{-1}) 3018.9, 2956.1, 1735.9, 1515.6, 1438.1, 1311.3, 1261.0. MS (70 eV): *m/z* (%): 334 (8.0) [M^+], 302 (100), 271 (21), 255 (21), 238 (27), 214 (88), 183 (79), 155 (67), 141 (42), 128 (26), 119 (27), 115 (32), 91 (24), 59 (49). HRMS calculated for $C_{18}H_{22}O_6$ 334.1416, found 334.1429.

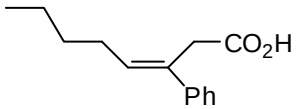


(E)-trimethyl 4-cyclohexylbut-2-ene-1,1,2-tricarboxylate (3j): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.88-0.96 (m, 2H), 1.11-1.26 (m, 4H), 1.67-1.70 (m, 5H), 2.10 (t, ^3J(H,H) = 7.6, 2H), 3.74 (s, 6H), 3.74 (s, 3H), 4.61 (s, 1H), 7.07 (t, ^3J(H,H) = 7.6, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.19, 26.22, 33.1, 36.8, 37.7, 49.9, 52.1, 52.7, 126.1, 146.9, 166.4, 168.1. IR ($CHCl_3$, cm^{-1}) 3027.9, 2937.0, 2857.1, 1737.6, 1714.4, 1437.3, 1279.2, 1255.41193.5, 1116.9, 1073.8. Elemental analysis calcd. (%) for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.31; H, 7.68. MS (70 eV): *m/z* (%): 313 (4.6) [MH^+], 280 (71), 249 (20), 220 (23), 198 (65), 166 (100), 139 (41), 91 (22), 55 (78).



Representative procedure for the microwave-assisted reaction of propargyl vinyl ether in water. Synthesis of β,γ-unsaturated carboxylic esters/acids (10/11). Propargyl vinyl ether **6i** (1.00 mmol) and water (0.5 mL) were placed in a microwave-special closed vial and the solution was irradiated for 90 minnutes in a single-mode microwave oven (300 Watt, 175 ºC). The products were extracted with CH_2Cl_2 and the solvent was removed at reduced pressure. The products were purified by flash column chromatography (silica gel, appropriate mixtures of *n*-hexane/EtOAc) to yield **15i/16i** (96%).

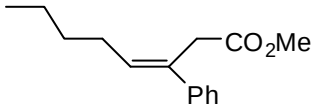
(*E*)-3-Phenyloct-3-enoic acid (11a). (9:1 *E*/*Z* ratio). 1 mL of water used to increase the yield of **10**/**11** and to decrease the amount of byproduct **2a**. When the reaction was carried out with 0.5 mL of water the yield of **10**/**11** was 58% (1:3.8 ratio) and the yield of byproduct **2a** was 24%: Major isomer. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.92 (t, ^3J(H,H) = 7.3, 3H), 1.31-1.49 (m, 4H), 2.23 (q, ^3J(H,H) = 7.1 Hz, 2H), 3.55



(s, 2H), 5.99 (t, ^3J(H,H) = 7.1, 1H), 7.18-7.38 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 22.4, 28.8, 31.5, 35.7, 125.9, 126.9, 128.3, 131.5, 133.4, 142.1, 177.8. IR ($CHCl_3$, cm^{-1}) 3513.0, 2961.3, 2931.9, 1710.5, 1494.4, 1445.3, 1409.9, 1261.5. Elemental analysis calcd. (%) for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.31; H, 7.97. MS (70 eV): *m/z* (%): 218 (63) [M^+], 162 (37), 159 (29), 134 (26), 133 (27), 129 (100), 128 (29), 117 (37), 115 (49), 91 (34).

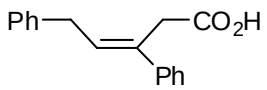
Representative data of the minor isomer (*Z*): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.82 (t, ^3J(H,H) = 7.3, 3H), 1.22-1.39 (m, 4H), 2.01 (q, ^3J(H,H) = 7.1 Hz, 2H), 3.36 (s, 2H), 5.63 (t, ^3J(H,H) = 7.1, 1H), 7.18-7.38 (m, 5H).

(*E*)-methyl 3-phenyloct-3-enoate (10a) (5:1 *E*/*Z* ratio): Major isomer ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.93 (t, ^3J(H,H) = 7.3, 3H), 1.33-1.50 (m, 4H), 2.23 (q, ^3J(H,H) = 7.1 Hz, 2H), 3.53 (s, 2H), 3.64 (s, 3H), 5.96 (t, ^3J(H,H) = 7.1, 1H), 7.21-7.24 (m, 1H), 7.28-7.32 (m 2H), 7.36-7.39 (m 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 22.4, 28.7, 31.5, 35.8, 51.8, 125.9, 126.8, 128.3, 132.1, 132.9, 142.4, 171.9. IR ($CHCl_3$, cm^{-1}) 3023.6, 2956.6, 2930.1, 1732.6, 1600.4, 1494.7, 1436.5, 1327.8, 1164.0. Elemental analysis calcd. (%) for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.47; H, 8.77. MS (70 eV): *m/z* (%): 232 (23) [M^+], 176 (10), 172 (23), 158 (19), 143 (19), 130 (17), 129 (100), 118 (19), 115 (27), 91 (21).



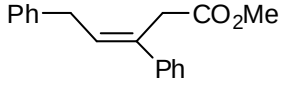
Representative data of the minor isomer (*Z*): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.83 (t, ^3J(H,H) = 7.3, 3H), 1.23-1.40 (m, 4H), 2.00 (q, ^3J(H,H) = 7.1 Hz, 2H), 3.35 (s, 2H), 3.60 (s, 3H), 5.61 (t, ^3J(H,H) = 7.1, 1H), 7.17-7.39 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.8, 22.2, 28.7, 31.9, 44.4, 51.6, 128.0, 128.4, 132.4, 142.1, 172.1.

(E)-3,5-diphenylpent-3-enoic acid (11d): Major isomer (3.2:1 *E*/*Z* ratio) ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.63 (d, ^3J(H,H) = 7.3, 2H), 3.68 (s, 2H), 6.20 (t, ^3J(H,H) = 7.3, 1H), 7.16-7.45 (m, 10H), 10.5 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 35.2, 35.8, 126.0, 126.2, 127.2, 128.3, 128.39, 128.43, 128.46, 128.6, 131.4, 132.5, 139.9, 141.7, 175.5. IR ($CHCl_3$, cm^{-1}) 3601.4, 3064.2, 3028.9, 3014.2, 2927.9, 1711.9, 1602.0, 1495.1, 1454.8, 1410.1, 1225.1, 1177.8. Elemental analysis calcd. (%) for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.67; H, 6.43. MS (70 eV): *m/z* (%): 252 (30) [M^+], 206 (20), 193 (100), 192 (75), 178 (23), 128 (20), 115 (74), 91 (52), 77 (21).



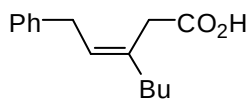
Representative data of the minor isomer (*Z*): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.39 (d, ^3J(H,H) = 7.6, 2H), 3.46 (s, 2H), 5.86 (t, ^3J(H,H) = 7.3, 1H), 7.16-7.38 (m, 10H), 10.5 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 35.2, 44.2, 130.9, 133.9, 139.39, 140.5, 175.7.

(E)-methyl 3,5-diphenylpent-3-enoate (10d): Major isomer. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.61 (d, ^3J(H,H) = 7.3, 2H), 3.63 (s, 2H), 3.66 (s, 3H), 6.14 (t, ^3J(H,H) = 7.3, 1H), 7.14-7.42 (m, 10H).



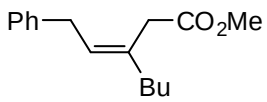
Representative data of the minor isomer (*Z*): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.36 (d, ^3J(H,H) = 7.6, 2H), 3.41 (s, 2H), 3.61 (s, 3H), 5.81 (t, ^3J(H,H) = 7.3, 1H), 7.14-7.42 (m, 10H).

(Z)-3-(2-phenylethylidene)heptanoic acid (11e). (6:1 *Z*/*E* ratio). Major isomer. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.89 (t, ^3J(H,H) = 7.3, 3H), 1.26-1.36 (m, 2H), 1.36-1.46 (m, 2H), 2.16 (t, ^3J(H,H) = 7.3 Hz, 2H), 3.19 (s, 2H), 3.41 (d, ^3J(H,H) = 7.3, 2H), 5.63 (t, ^3J(H,H) = 7.3, 1H), 7.17-7.20 (m, 3H), 7.26-7.29 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 22.3, 29.9, 34.4, 35.7, 37.3, 126.0, 127.6, 128.38, 128.44, 132.7, 140.7, 177.0. IR ($CHCl_3$, cm^{-1}) 3509.6, 2960.6, 2932.1, 1709.1, 1494.8, 1454.6, 1410.3, 1293.7, 1176.0. Elemental analysis calcd. (%) for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.44; H, 8.41. MS (70 eV): *m/z* (%): 232 (33) [M^+], 173 (15), 157 (11), 129 (80), 117 (31), 104 (54), 91 (100), 81 (17), 65 (14).



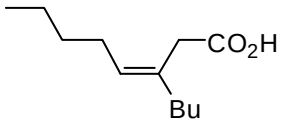
Representative data of the minor isomer (*E*): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.89 (t, ^3J(H,H) = 7.3, 3H), 1.26-1.36 (m, 2H), 1.36-1.46 (m, 2H), 2.24 (t, ^3J(H,H) = 7.3 Hz, 2H), 3.09 (s, 2H), 3.41 (d, ^3J(H,H) = 7.3, 2H), 5.52 (t, ^3J(H,H) = 7.3, 1H), 7.17-7.20 (m, 3H), 7.26-7.29 (m, 2H).

(Z)-methyl 3-(2-phenylethylidene)heptanoate (10e) (3:1 *E*/*Z* ratio): Major isomer ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.89 (t, ^3J(H,H) = 7.1, 3H), 1.25-1.33 (m, 2H), 1.35-1.43 (m, 2H), 2.11 (t, ^3J(H,H) = 7.1 Hz, 2H), 3.15 (s, 2H), 3.40 (d, ^3J(H,H) = 7.3, 2H), 3.67 (s, 3H), 5.53 (t, ^3J(H,H) = 7.3, 1H), 7.17-7.19 (m, 3H), 7.26-7.29 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 22.3, 30.0, 34.3, 35.9, 37.3, 51.7, 125.9, 127.0, 128.31, 128.39, 133.2, 140.9, 171.9.



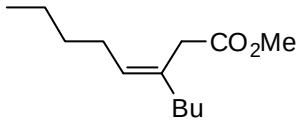
Representative data of the minor isomer (*E*): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.91 (t, ^3J(H,H) = 7.1, 3H), 1.25-1.33 (m, 2H), 1.35-1.43 (m, 2H), 2.20 (t, ^3J(H,H) = 7.1 Hz, 2H), 3.05 (s, 2H), 3.40 (d, ^3J(H,H) = 7.3, 2H), 3.68 (s, 3H), 5.47 (t, ^3J(H,H) = 7.3, 1H), 7.17-7.19 (m, 3H), 7.26-7.29 (m, 2H).

(Z)-3-butyloct-3-enoic acid (11f) (3.1:1 *Z*/*E* ratio). Major isomer. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.88 (t, ^3J(H,H) = 7.3, 3H), 0.88 (t, ^3J(H,H) = 7.3, 3H), 1.23-1.40 (m, 8H), 1.99-2.12 (m, 4H), 3.07 (s, 2H), 5.37 (t, ^3J(H,H) = 7.1, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.93, 13.93, 22.30, 22.33, 27.9, 30.0, 31.8, 35.6, 37.2, 129.4, 131.4, 182.1. IR ($CHCl_3$, cm^{-1}) 3510.8, 3029.2, 2960.0, 2931.0, 1707.4, 1460.3, 1409.7, 1379.7. MS (70 eV): *m/z* (%): 198 (23) [M^+], 138 (100), 109 (23), 95 (48), 81 (47), 69 (32), 55 (65). HRMS calculated for $C_{12}H_{22}O_2$ 198.1620, found 198.1616.



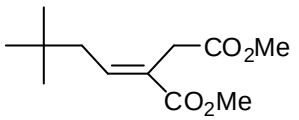
Representative data of the minor isomer (*E*): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.88 (t, ^3J(H,H) = 7.3, 3H), 0.88 (t, ^3J(H,H) = 7.3, 3H), 1.23-1.40 (m, 8H), 1.99-2.12 (m, 4H), 3.01 (s, 2H), 5.30 (t, ^3J(H,H) = 7.1, 1H).

(Z)-methyl 3-butyloct-3-enoate (10f) Representative data of the minor isomer (*Z*): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.88 (t, ^3J(H,H) = 7.3, 3H), 0.88 (t, ^3J(H,H) = 7.3, 3H), 1.23-1.40 (m, 8H), 1.99-2.12 (m, 4H), 3.04 (s, 2H), 3.65 (s, 3H), 5.33 (t, ^3J(H,H) = 7.1, 1H).

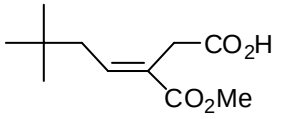


Representative data of the minor isomer (*E*): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.88 (t, ^3J(H,H) = 7.3, 3H), 0.88 (t, ^3J(H,H) = 7.3, 3H), 1.23-1.40 (m, 8H), 1.99-2.12 (m, 4H), 2.98 (s, 2H), 3.66 (s, 3H), 5.26 (t, ^3J(H,H) = 7.1, 1H).

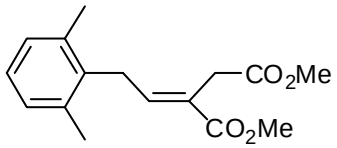
(E)-dimethyl 2-(3,3-dimethylbutylidene)succinate (10h): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.93 (s, 9H), 2.07 (d, ^3J(H,H) = 7.6, 2H), 3.35 (s, 2H), 3.66 (s, 3H), 3.74 (s, 3H), 7.04 (t, ^3J(H,H) = 7.6, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 29.4, 31.6, 32.2, 42.8, 51.9, 51.9, 126.5, 143.3, 167.3, 169.5. IR ($CHCl_3$, cm^{-1}) 3024.1, 2955.3, 1735.9, 1709.9, 1437.1, 1272.7, 1170.0. Elemental analysis calcd. (%) for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.21; H, 8.52. MS (70 eV): *m/z* (%): 228 (0.3) [M^+], 197 (16), 172 (19), 140 (100), 112 (48), 93 (20), 57 (55).



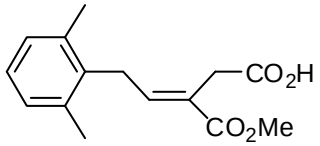
(E)-3-(methoxycarbonyl)-6,6-dimethylhept-3-enoic acid (11h): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.93 (s, 9H), 2.08 (d, ^3J(H,H) = 8.1, 2H), 3.38 (s, 2H), 3.74 (s, 3H), 7.05 (t, ^3J(H,H) = 8.1, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 29.4, 31.6, 32.2, 42.8, 52.0, 125.9, 143.8, 167.5, 176.4.



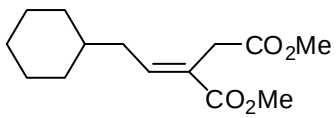
(E)-dimethyl 2-(2-(2,6-dimethylphenyl)ethylidene)succinate (10i): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.28 (s, 6H), 3.52 (d, ^3J(H,H) = 6.8, 2H), 3.52 (s, 2H), 3.71 (s, 3H), 3.72 (s, 3H), 6.82 (t, ^3J(H,H) = 6.8, 1H), 7.01-7.08 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.0, 29.5, 32.4, 51.9, 52.0, 125.8, 126.6, 128.3, 135.2, 136.4, 143.5, 167.1, 171.0. IR ($CHCl_3$, cm^{-1}) 3027.6, 2952.7, 1736.8, 1710.9, 1469.1, 1332.5, 1306.7, 1267.4. Elemental analysis calcd. (%) for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.35; H, 7.10. MS (70 eV): *m/z* (%): 244 (8.6) [M^+-CH_3OH], 230 (49), 201 (18), 184 (30), 157 (100), 143 (54), 142 (35), 141 (24), 128 (24), 115 (17), 91 (16).



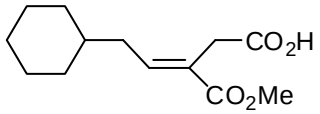
(E)-5-(2,6-dimethylphenyl)-3-(methoxycarbonyl)pent-3-enoic acid (11i): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.27 (s, 6H), 3.54 (d, ^3J(H,H) = 6.8, 2H), 3.56 (s, 2H), 3.72 (s, 3H), 6.84 (t, ^3J(H,H) = 6.8, 1H), 7.01-7.08 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.1, 29.6, 32.6, 52.1, 125.3, 126.7, 128.4, 135.1, 136.5, 144.0, 167.4, 175.9. IR ($CHCl_3$, cm^{-1}) 3024.0, 2952.2, 1712.9, 1437.5, 1296.9, 1266.8, 1200.8. MS (70 eV): *m/z* (%): 262 (5.6) [M^+], 230 (37), 201 (25), 184 (31), 157 (100), 143 (56), 142 (49), 141 (30), 128 (30), 115 (28), 91 (26). HRMS calculated for $C_{15}H_{18}O_4$ 262.1205, found 262.1205.



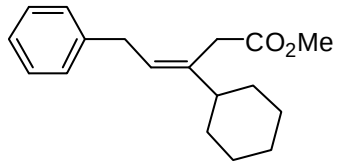
(E)-dimethyl 2-(2-cyclohexylethylidene)succinate (10j): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.07-1.26 (m, 4H), 1.36-1.47 (m, 1H), 1.59-1.70 (m, 6H), 2.06 (t, ^3J(H,H) = 7.2, 2H), 3.33 (s, 2H), 3.76 (s, 3H), 3.72 (s, 3H), 6.98 (t, ^3J(H,H) = 7.2, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.2, 26.3, 32.2, 33.2, 36.6, 37.7, 51.86, 51.88, 125.8, 145.0, 167.4, 171.3. IR ($CHCl_3$, cm^{-1}) 3027.2, 2928.3, 2854.9, 1736.8, 1710.5, 1438.5, 1294.6, 1270.6, 1174.6. Elemental analysis calcd. (%) for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.32; H, 8.34. MS (70 eV): *m/z* (%): 222 (47) [M^+-CH_3OH], 139 (100), 135 (14), 134 (13), 112 (58), 83 (17), 67 (15), 55 (43).



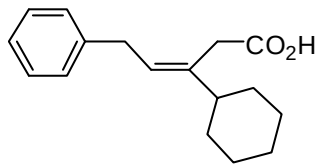
(E)-5-cyclohexyl-3-(methoxycarbonyl)pent-3-enoic acid (11j): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.87-0.96 (m, 2H), 1.10-1.26 (m, 3H), 1.40-1.45 (m, 1H), 1.61-1.70 (m, 5H), 2.07 (t, ^3J(H,H) = 7.2, 2H), 3.37 (s, 2H), 3.74 (s, 3H), 7.00 (t, ^3J(H,H) = 7.2, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.15, 26.24, 32.3, 33.2, 36.7, 37.6, 52.0, 125.3, 145.5, 167.5, 176.4.



(E)-methyl 3-cyclohexyl-5-phenylpent-3-enoate (10l): Major isomer ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.11-1.79 (m, 10H), 1.95-2.00 (m, 1H), 3.15 (s, 2H), 3.39 (d, ^3J(H,H) = 7.3, 2H), 3.66 (s, 3H), 5.53 (t, ^3J(H,H) = 7.3, 1H), 7.16-7.19 (m, 3H), 7.25-7.28 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.7, 29.7, 32.2, 34.3, 35.1, 45.8, 51.8, 125.7, 125.9, 128.37, 128.38, 138.4, 141.1, 172.3. MS (70 eV): *m/z* (%): 272 (9.3) [M^+], 190 (21), 181 (20), 168 (28), 157 (29), 144 (22), 129 (87), 104 (44), 91 (100), 83 (51), 77 (39), 67 (36), 55 (63). HRMS calculated for $C_{18}H_{24}O_2$ 272.1776, found 272.1777.



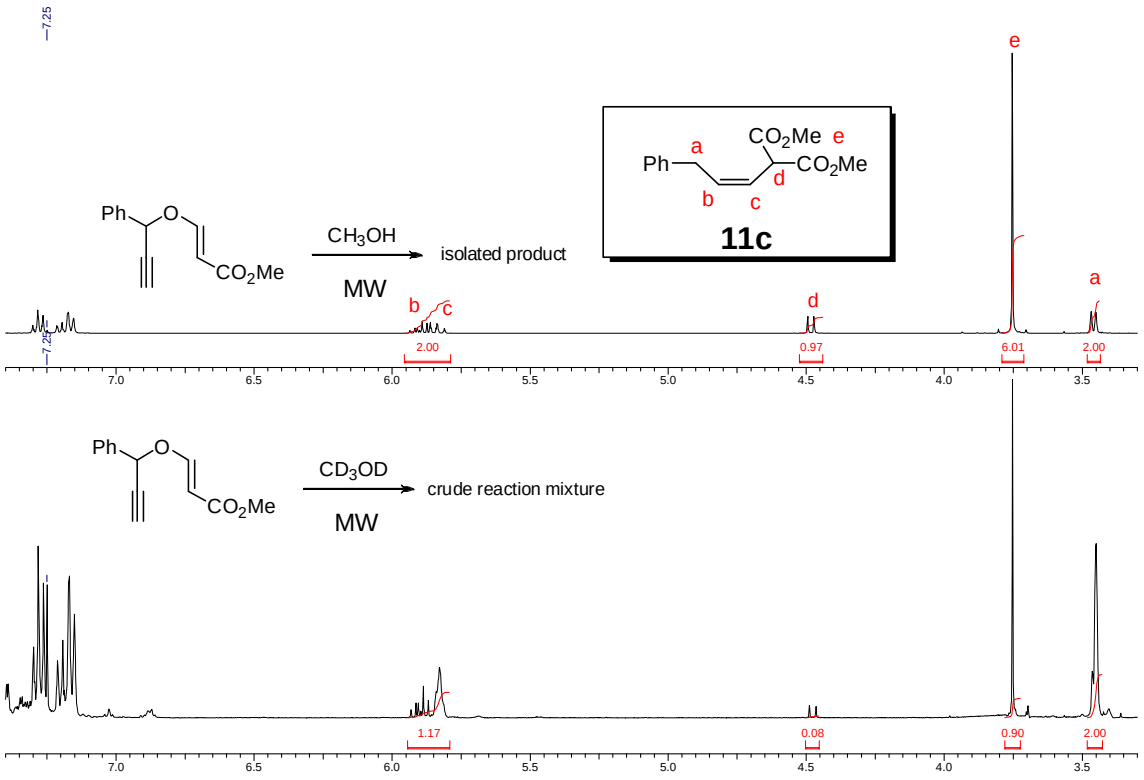
(E)-3-cyclohexyl-5-phenylpent-3-enoic acid (11l). (6.3:1 *Z*/*E* ratio). Major isomer. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.11-1.79 (m, 10H), 1.95-2.00 (m, 1H), 3.19 (s, 2H), 3.40 (d, ^3J(H,H) = 7.3, 2H), 5.57 (t, ^3J(H,H) = 7.3, 1H), 7.16-7.19 (m, 3H), 7.25-7.28 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.2, 26.7, 29.7, 32.1, 34.3, 45.8, 125.9, 126.1, 128.36, 128.38, 138.0, 140.9, 180.3. IR ($CHCl_3$, cm^{-1}) 3027.3, 2960.4, 2928.8, 2855.5, 1715.6, 1603.5, 1453.2, 1261.6, 1097.5. MS (70 eV): *m/z* (%): 258 (10) [M^+], 176 (48), 167 (24), 129 (73), 104 (81), 91 (100), 83 (67), 67 (55), 55 (78). HRMS calculated for $C_{17}H_{22}O_2$ 258.1620, found 258.1613.



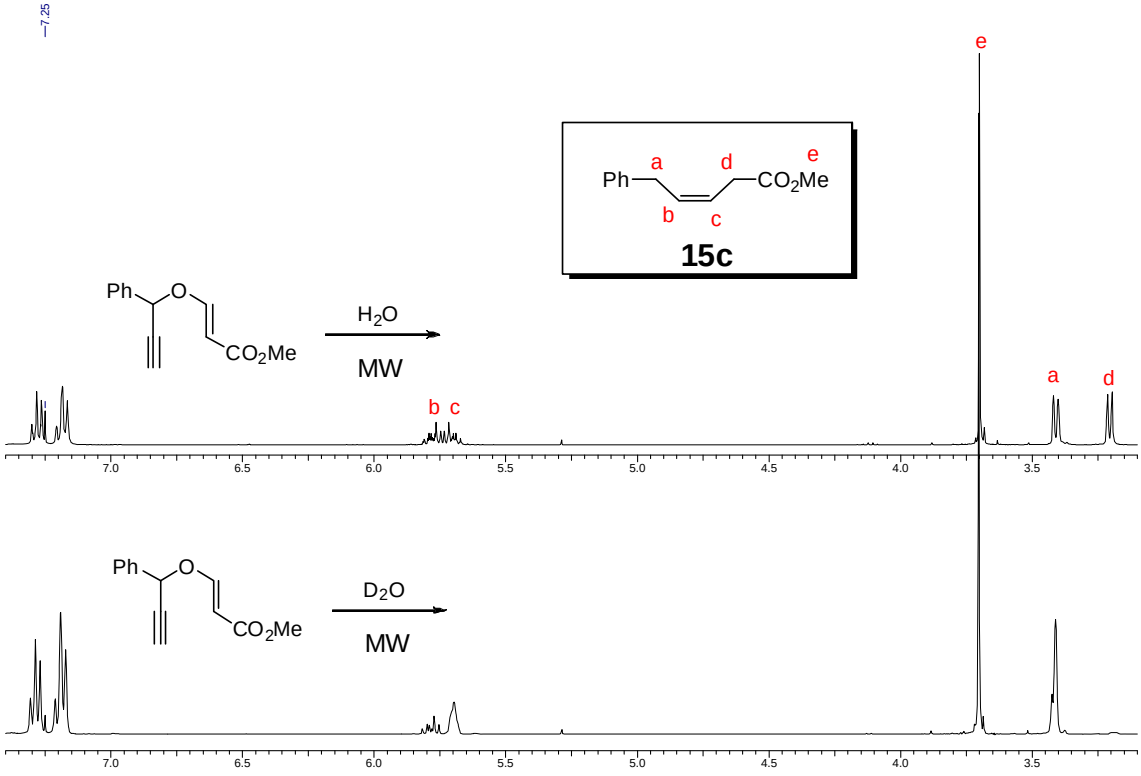
Representative data of the minor isomer (*Z*): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.11-1.79 (m, 10H), 1.95-2.00 (m, 1H), 3.10 (s, 2H), 3.40 (d, ^3J(H,H) = 7.3, 2H), 5.34 (t, ^3J(H,H) = 7.3, 1H), 7.16-7.19 (m, 3H), 7.25-7.28 (m, 2H).

Reactions in deuterated solvents

Reaction of propargyl vinyl ether 1c in CH_3OH and CD_3OD, to afford the corresponding product 3c. From the ^1H NMR data of product **3c** and the crude reaction mixture from the experiment in CD_3OD, it can be observed that there is deuterium incorporation in the most acidic positions (**d** and **b**). There is also a large amount of deuterium incorporation in the methyl esters evidencing a transesterification process. The delta-position (a) does not incorporate the deuterium, which suggests that there is indeed an intramolecular migration of the H from the hemiacetal position to the terminus of the dienic chain (see main text). It should be noted the after isolation of the deuterated product there is further H/D exchange in the most acidic positions (**d** and **b**).



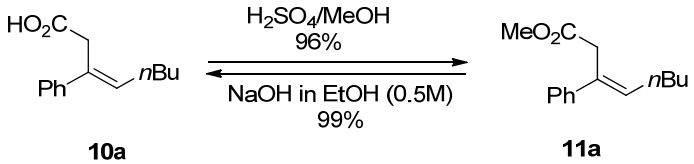
Reaction of propargyl vinyl ether 1c in H_2O and D_2O, followed by the isolation of the corresponding ester product 10c. From the ^1H NMR data it can be observed that there is only deuterium incorporation in the most acidic positions (**d** and **b**). The delta-position (a) does not incorporate the deuterium, which suggests that there is indeed an intramolecular migration of the H from the hemiacetal position to the terminus of the dienic chain (see main text) (see main text, Scheme 2).



β,γ-Unsaturated acid/ester interconversion. The β,γ-unsaturated acids and esters can be interconverted without affecting the stereochemistry of the double bond.

Transformation of acid 10a into ester 11a: β,γ-unsaturated acid **10a** (1.5 mmol), two drops of concentrated H_2SO_4 and methanol (10 mL) were refluxed overnight. After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, 10% of EtOAc/*n*-hexane) to yield **11a** (96%).

Transformation of ester 11a into acid 10a:[11] β,γ-unsaturated ester **11a** (1.5 mmol) was dissolved in EtOH (6 mL) and 2% NaOH (30 mL) was added. The solution was refluxed for 5 h. After removing 1/3 of the volume at reduced pressure, the solution was washed with EtOAc. The aqueous solution was acidified to pH 1. Extraction with EtOAc (three times) followed by evaporation of the solvent at reduced pressure and purification by flash column chromatography (silica gel, 2% of MeOH/CH_2Cl_2) afforded **10a** (99%).



10a **11a**

References

[1] a) D. Tejedor, A. Santos-Expósito, G. Méndez-Abt, C. Ruiz-Pérez, F. García-Tellado, *Synlett* **2009**, 1223; b) J. Inanaga, Y. Baba, T. Hanamoto, *Chem. Lett*. **1993**, 241.

[2] P. de Armas, F. García-Tellado, J. J. Marrero-Tellado, D. Tejedor, M. A. Maestro, J. González-Platas, *Org. Lett.* **2001**, *3*, 1905.

[3] M. M. Midland, A. Tramontano, J. R. Cable, *J. Org. Chem.* **1980**, *45*, 28.

[4] D. Tejedor, G. Méndez-Abt, F. García-Tellado, *Chem. Eur. J.* **2010**, *16*, 428.

[5] L. G. León, C. Ríos-Luci, D. Tejedor, E. Pérez-Roth, J. C. Montero, A. Pandiella, F. García-Tellado, J. M. Padrón *J. Med. Chem.* **2010**, *53*, 3835.

[6] A. A.Vasil'ev, A. L. Vlasyuk, G. D. Gamalevich, E. P. Serebryakov, *Bioorg. Med. Chem.* **1996**, *4*, 389.

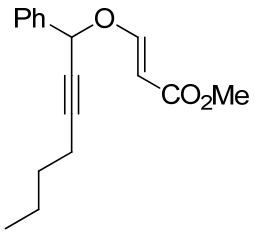
[7] C. S. Pak, E. Lee, G. Lee, *J. Org. Chem.* **1993**, *58*, 1523.

[8] The *E*-isomer is described and it matches the signals of the minor isomer: J. Thibonnet, M. Abarbri, J.-L Parrain, A. Duchêne, *Tetrahedron*, **2003**, *59*, 4433.

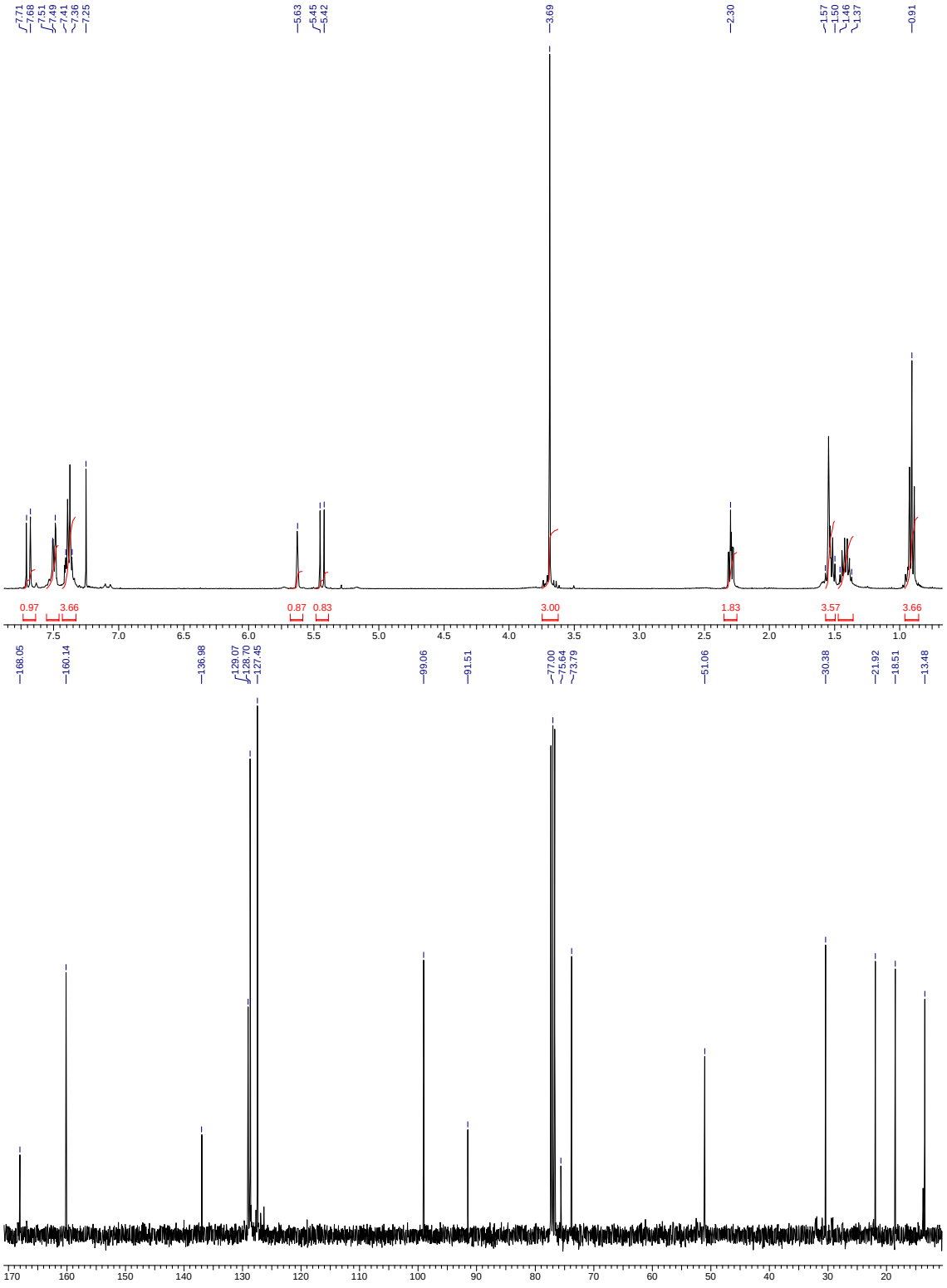
[9] R. Ballini, G. Bosica, A. Mase, M. Petrini, *Eur. J. Org. Chem.* **2000**, 2927.

[10] R. Ballini, G. Bosica, A. Palmieri, M. Petrini, C. Pierantozzi, *Tetrahedron*, **2003**, *59*, 7283.

[11] R. Ballini, G. Bosica, D. Fiorini, P. Righi, *Synthesis*, **2002**, 681.

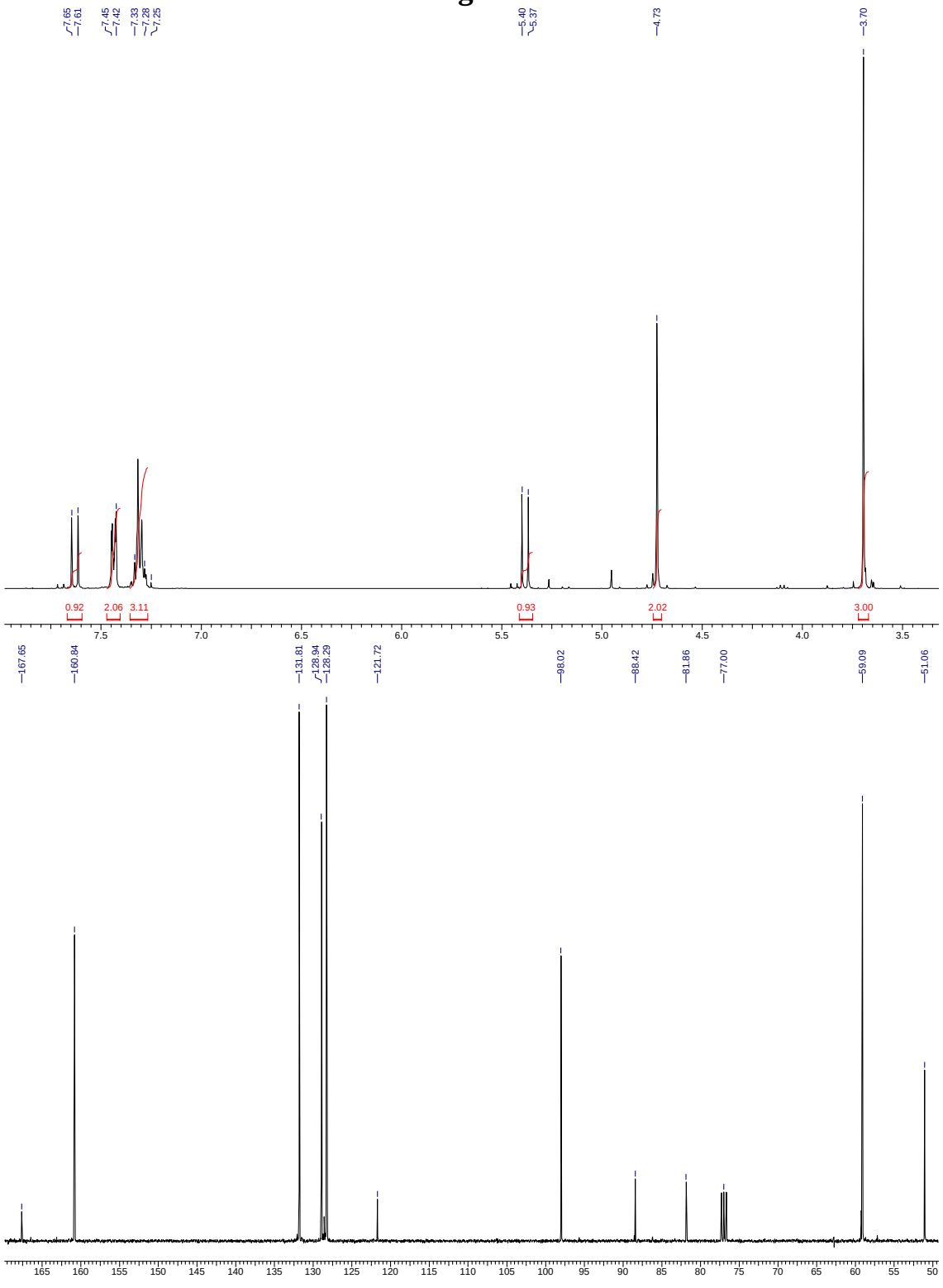

Ph
O
CO2Me

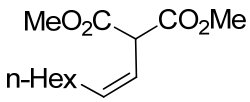
1e


7.71
7.68
7.51
7.49
7.41
7.36
7.25
5.63
5.45
5.42
3.69
2.30
1.57
1.50
1.46
1.37
0.91
0.97
3.66
0.87
0.83
3.00
1.83
3.57
3.66
168.05
160.14
136.98
129.07
128.70
127.45
99.06
91.51
77.00
75.64
73.79
51.06
30.38
21.92
18.51
13.48

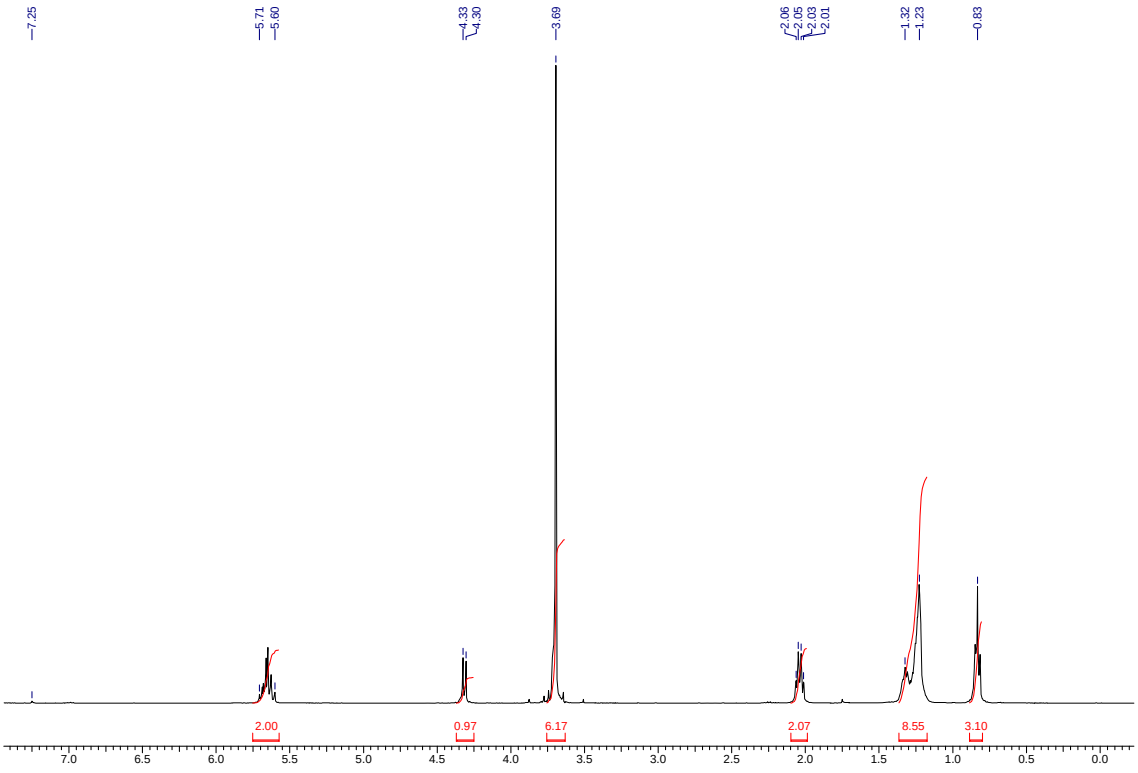

O
CO2Me
Ph

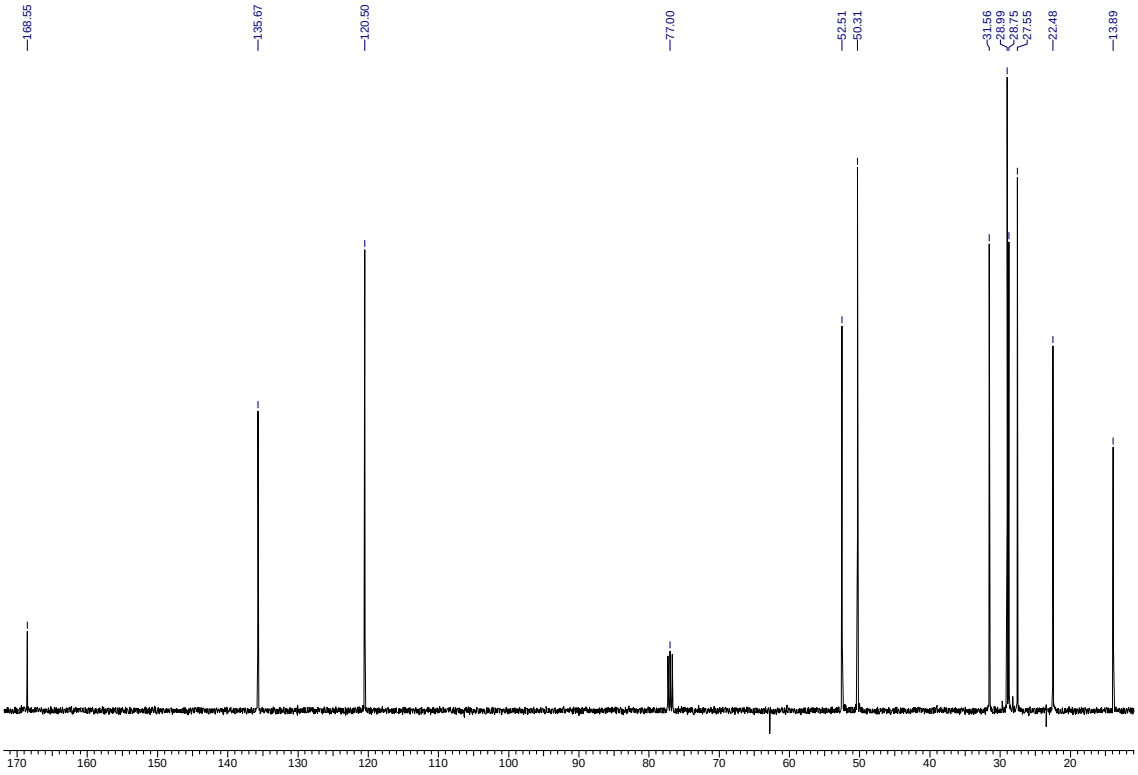
1g

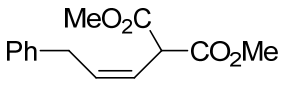

7.65
7.61
7.45
7.42
7.33
7.28
7.25
5.40
5.37
4.73
3.70
0.92
2.06
3.11
0.93
2.02
3.00
167.65
160.84
131.81
128.94
128.29
121.72
98.02
88.42
81.86
77.00
59.09
51.06


MeO2C
CO2Me
n-Hex

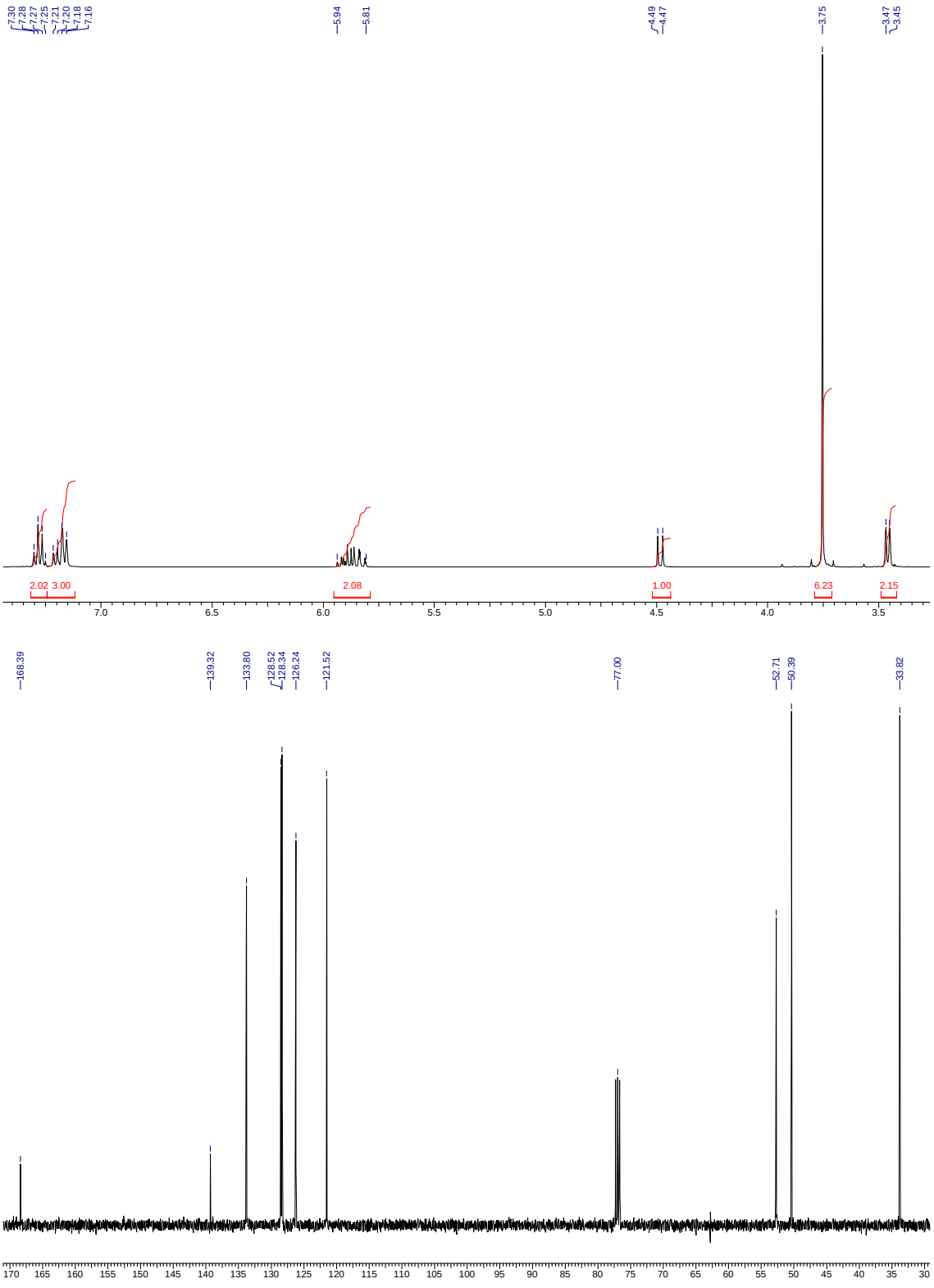
3b

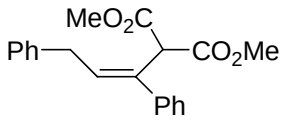

7.25
5.71
5.60
4.33
4.30
3.69
2.06
2.05
2.03
2.01
1.32
1.23
0.83
2.00
0.97
6.17
2.07
8.55
3.10


168.55
135.67
120.50
77.00
52.51
50.31
31.56
28.99
28.75
27.55
22.48
13.89

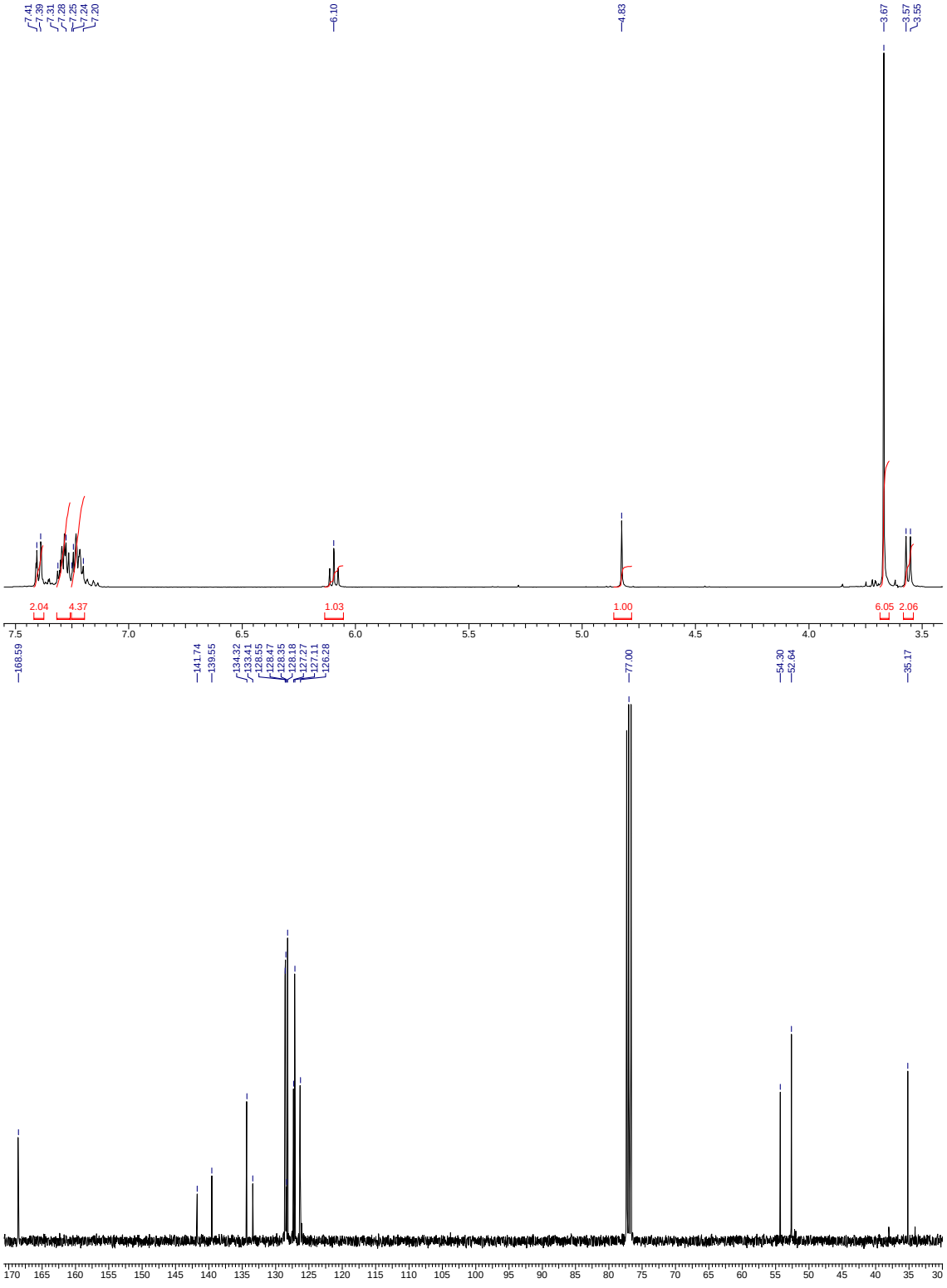

MeO2C
Ph
CO2Me

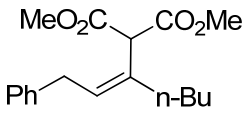
3c


7.30
7.28
7.27
7.25
7.21
7.20
7.18
7.16
5.94
5.81
4.49
4.47
3.75
3.47
3.45
2.02 3.00
2.08
1.00
6.23
2.15
168.39
139.32
133.80
128.52
128.34
126.24
121.52
77.00
52.71
50.39
33.82

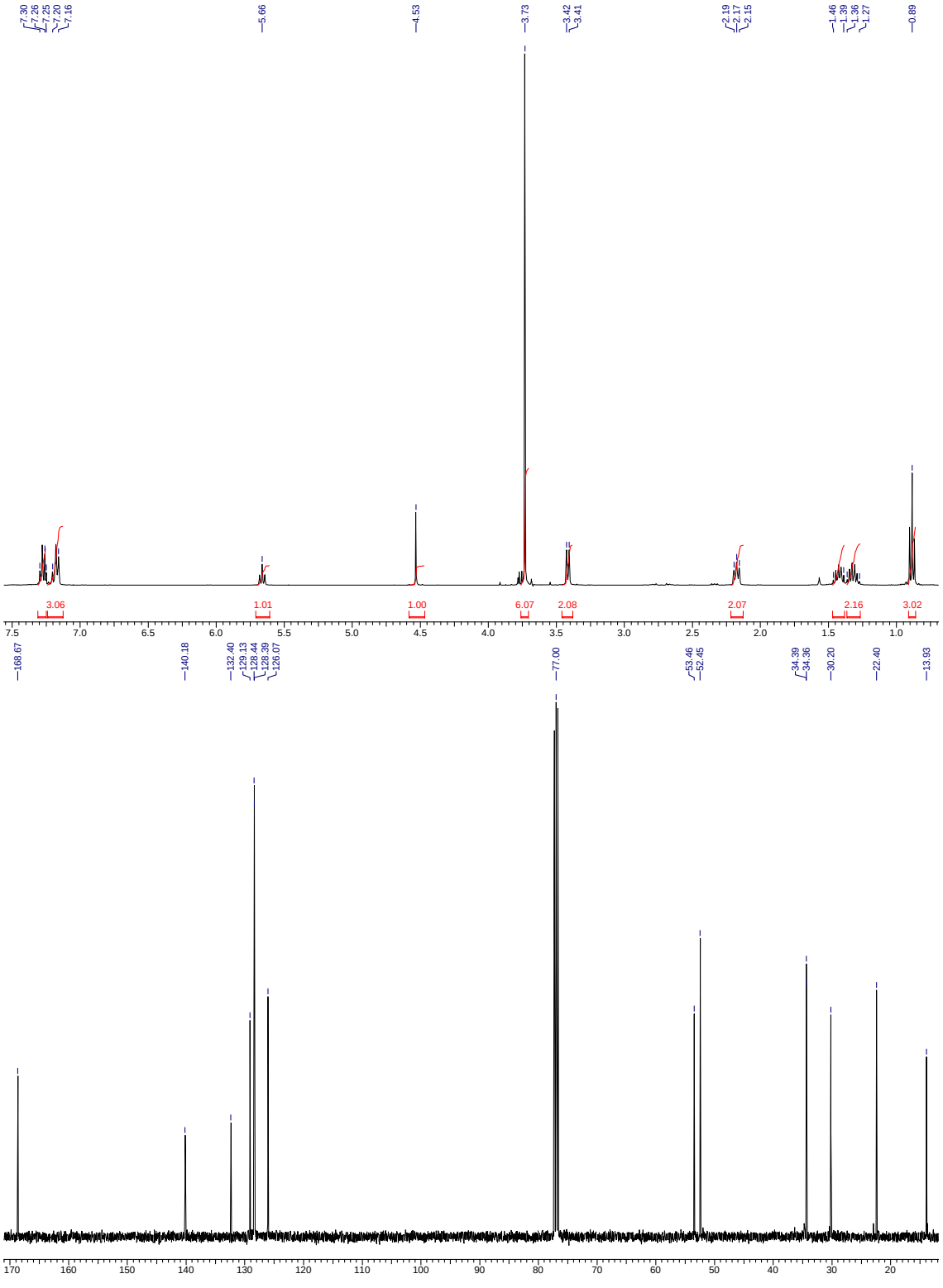

MeO2C
Ph
CO2Me
Ph

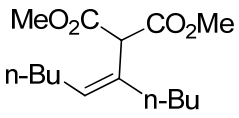
3d


7.41
7.39
7.31
7.28
7.25
7.24
7.20
6.10
4.83
3.67
3.57
3.55
2.04
4.37
1.03
1.00
6.05
2.06
168.59
141.74
139.55
134.32
133.41
128.55
128.47
128.35
128.18
127.27
127.11
126.28
77.00
54.30
52.64
35.17

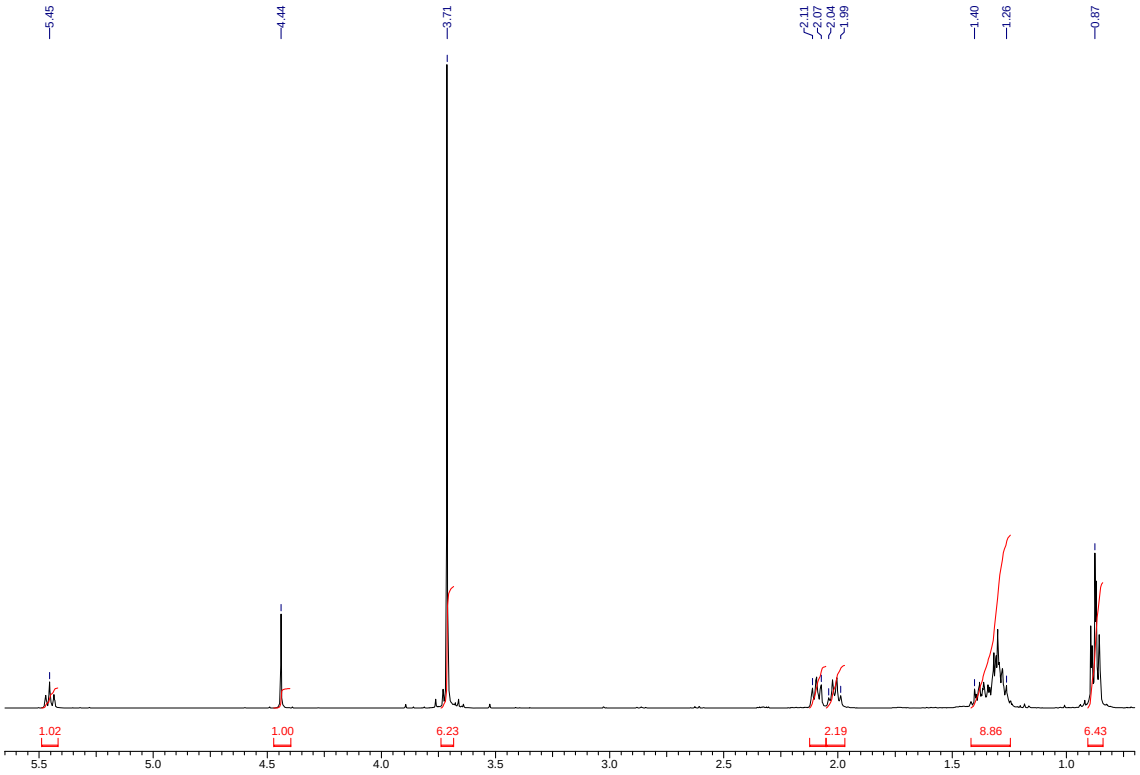

MeO2C
CO2Me
Ph
n-Bu

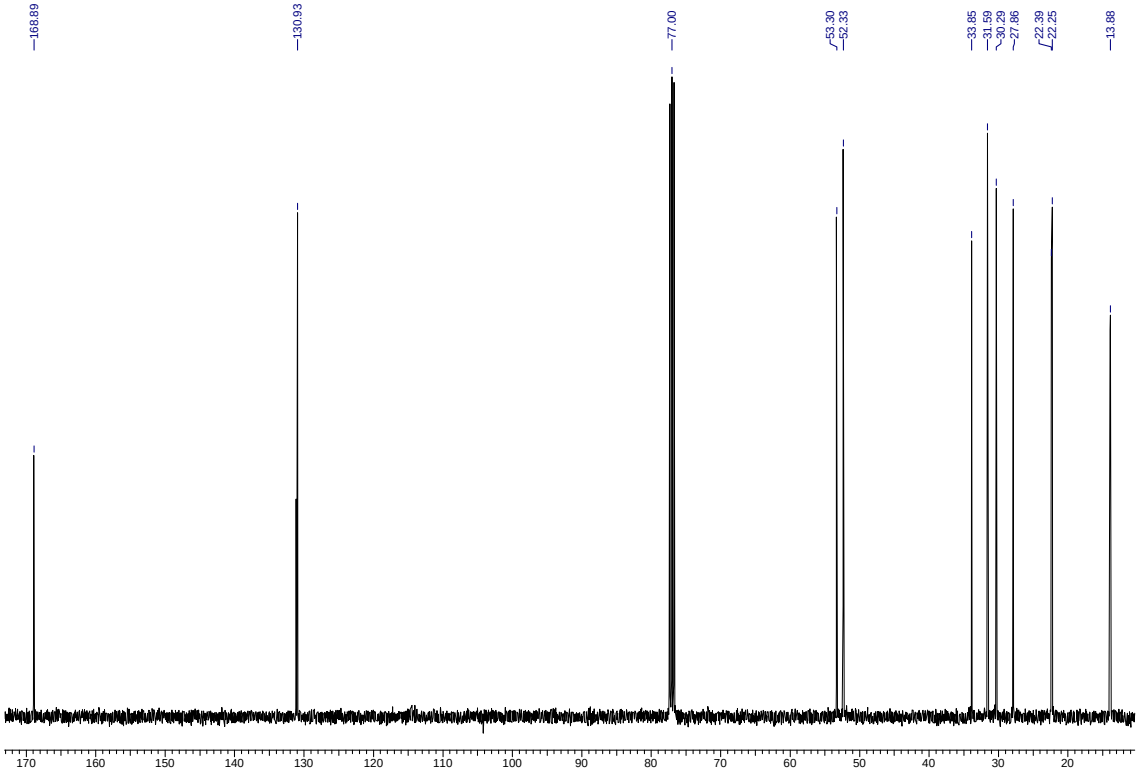
3e

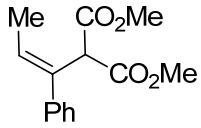

7.30
7.26
7.25
7.20
7.16
5.66
4.53
3.73
3.42
3.41
2.19
2.17
2.15
1.46
1.39
1.36
1.27
0.89
3.06
1.01
1.00
6.07
2.08
2.07
2.16
3.02
168.67
140.18
132.40
129.13
128.44
128.39
126.07
77.00
53.46
52.45
34.39
34.36
30.20
22.40
13.93


MeO2C
CO2Me
n-Bu
n-Bu

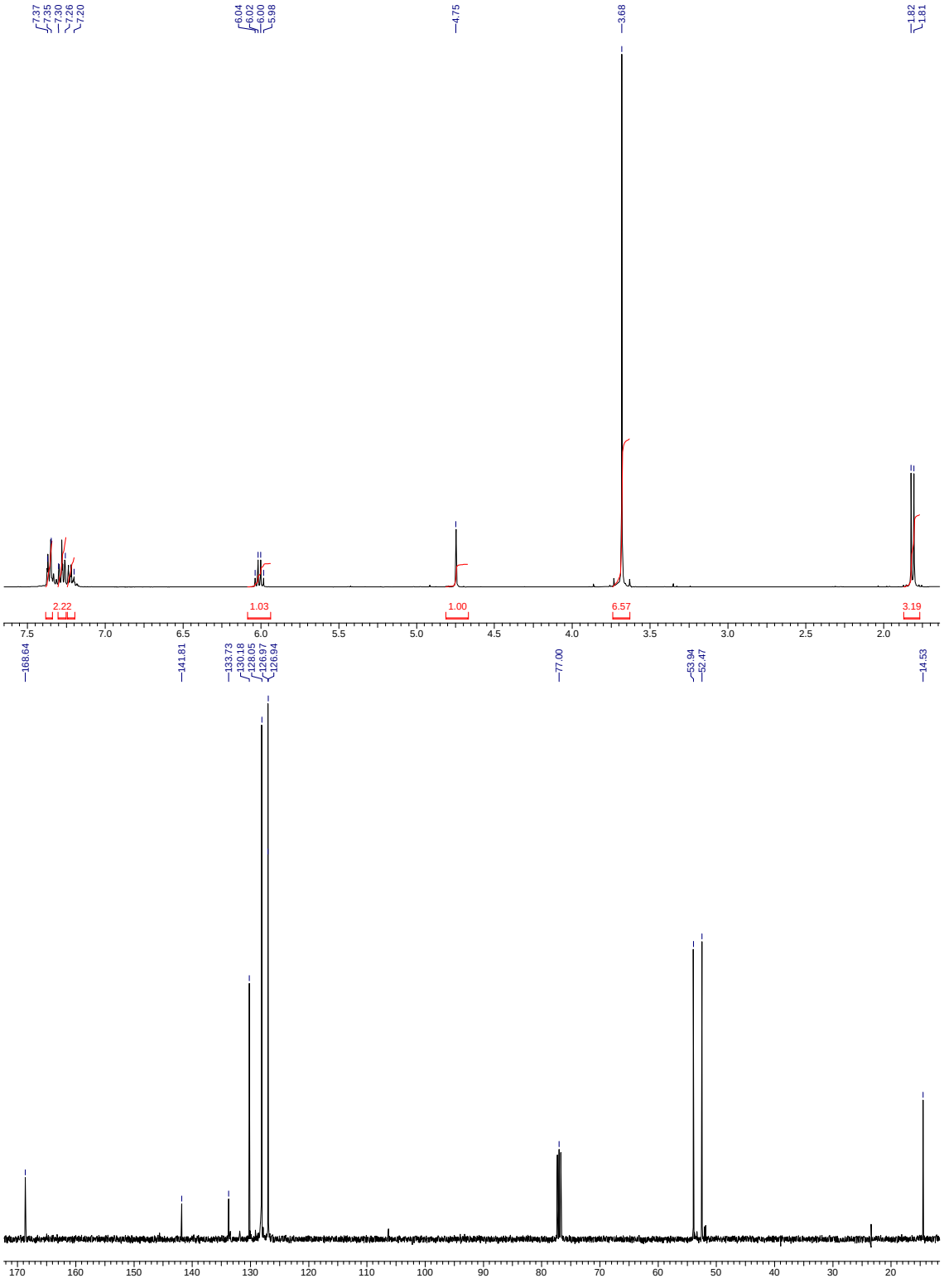
3f

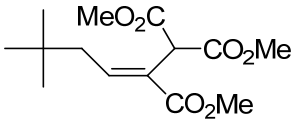

5.45
4.44
3.71
2.11
2.07
2.04
1.99
1.40
1.26
0.87
1.02
1.00
6.23
2.19
8.86
6.43
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0


168.89
130.93
77.00
53.30
52.33
33.85
31.59
30.29
27.86
22.39
22.25
13.88
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

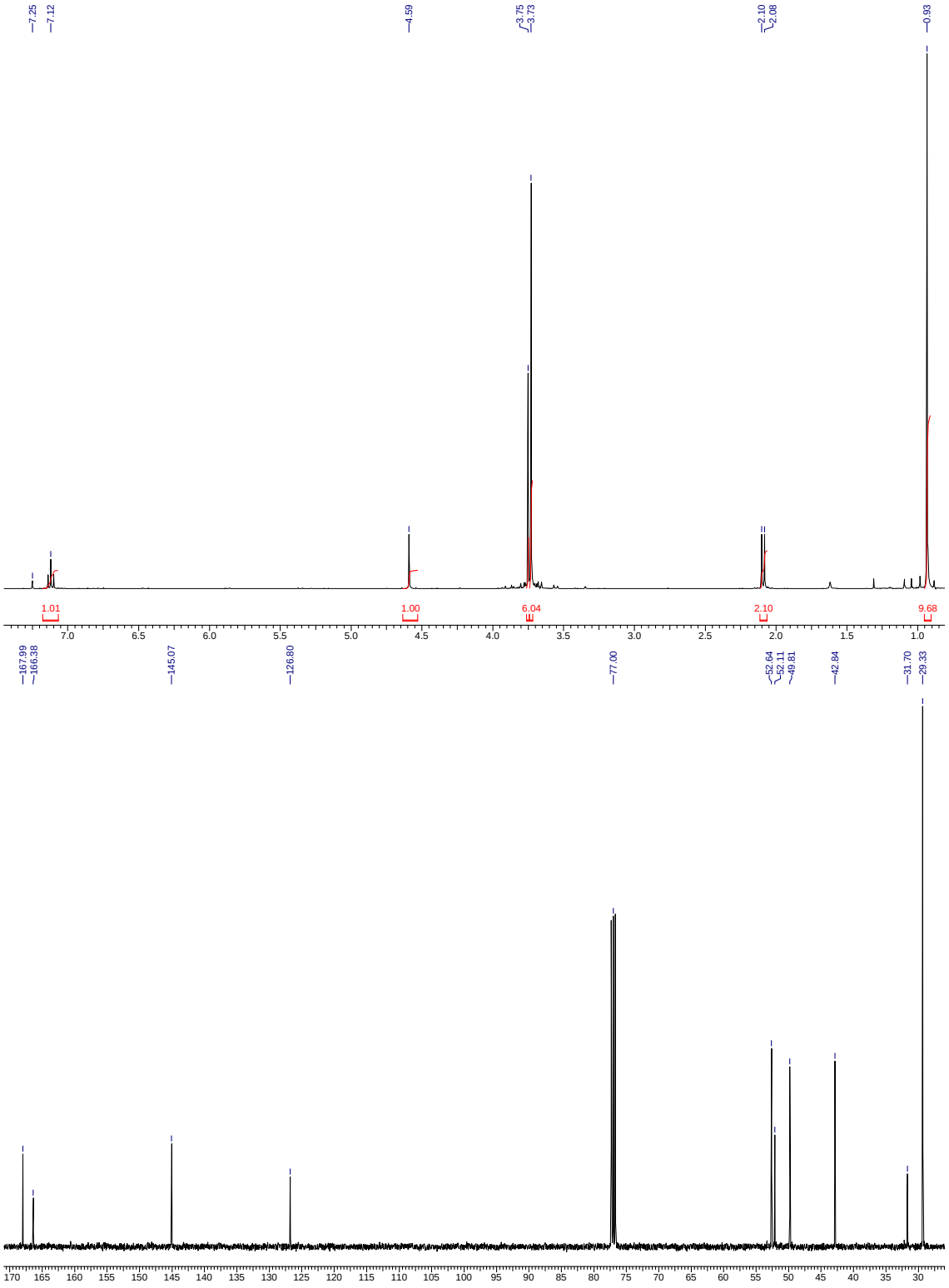

Me
CO2Me
CO2Me
Ph

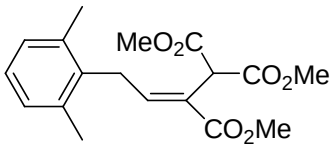
3g


7.37
7.35
7.30
7.26
7.20
6.04
6.02
6.00
5.98
4.75
3.68
1.82
1.81
2.22
1.03
1.00
6.57
3.19
168.64
141.81
133.73
130.18
128.05
126.97
126.94
77.00
53.94
52.47
14.53

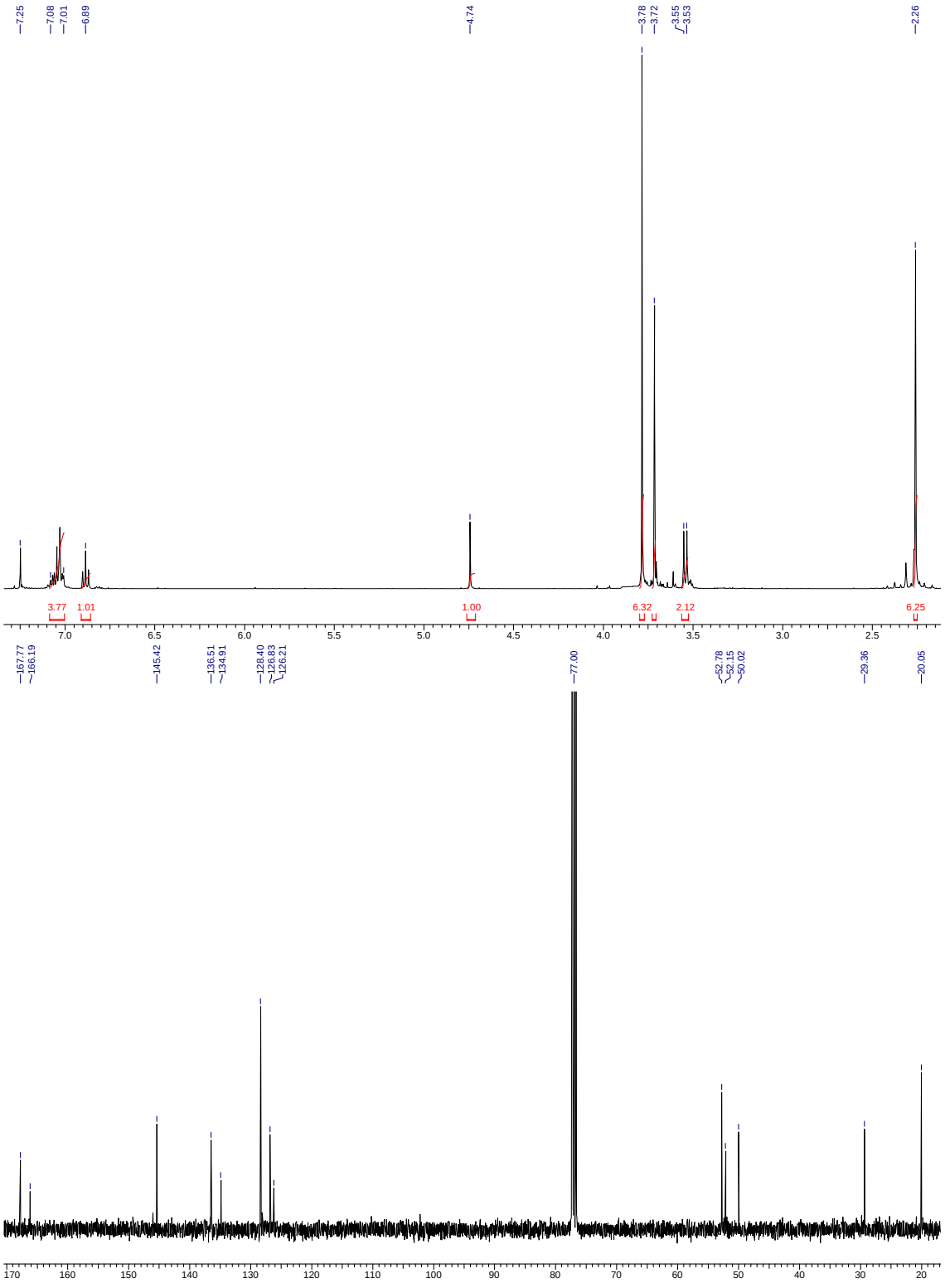

MeO2C
CO2Me
CO2Me

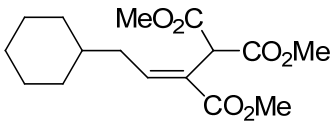
3h


7.25
7.12
4.59
3.75
3.73
2.10
2.08
0.93
1.01
1.00
6.04
2.10
9.68
167.99
166.38
145.07
126.80
77.00
52.64
52.11
49.81
42.84
31.70
29.33

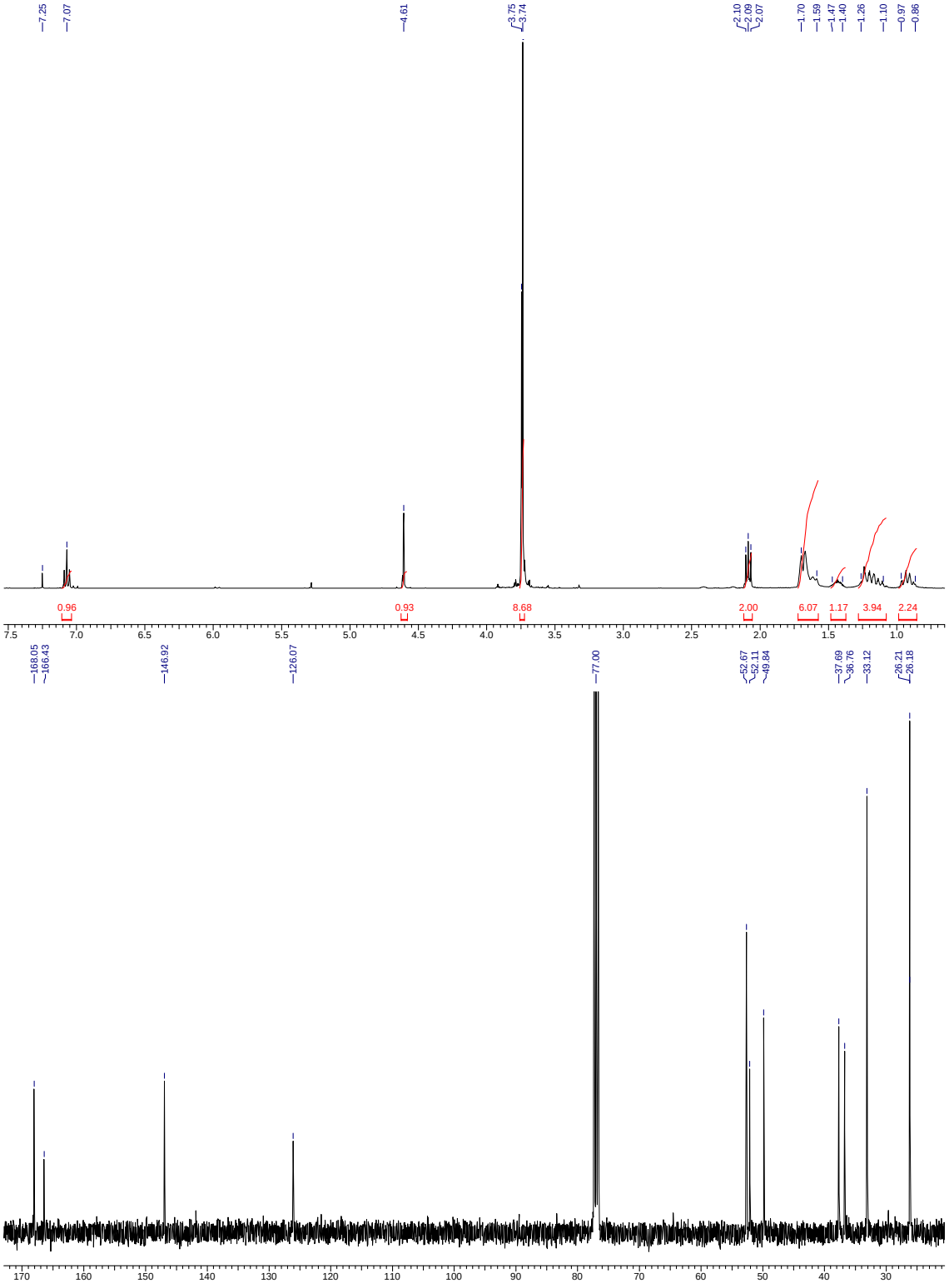

MeO2C
CO2Me
CO2Me

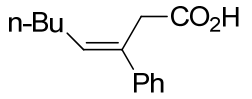
3i


7.25
7.08
7.01
6.89
4.74
3.78
3.72
3.55
3.53
2.26
3.77
1.01
1.00
6.32
2.12
6.25
167.77
166.19
145.42
136.51
134.91
128.40
126.83
126.21
77.00
52.78
52.15
50.02
29.36
20.05


MeO2C
CO2Me
CO2Me

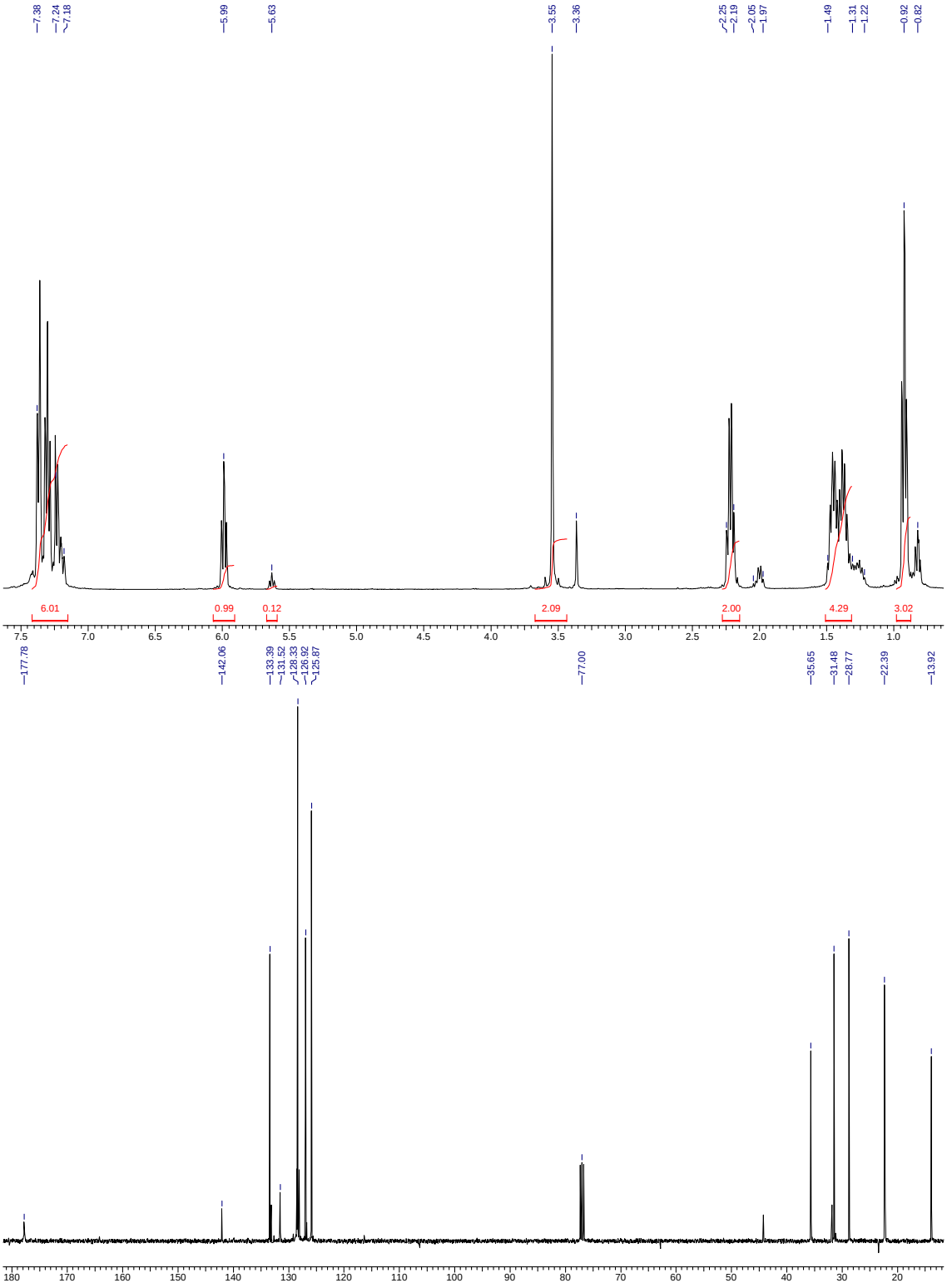
3j

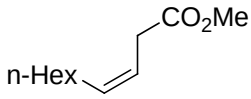

7.25
7.07
4.61
3.75
3.74
2.10
2.09
2.07
1.70
1.59
1.47
1.40
1.26
1.10
0.97
0.86
0.96
0.93
8.68
2.00
6.07
1.17
3.94
2.24
168.05
166.43
146.92
126.07
77.00
52.67
52.11
49.84
37.69
36.76
33.12
26.21
26.18


n-Bu
CO2H
Ph

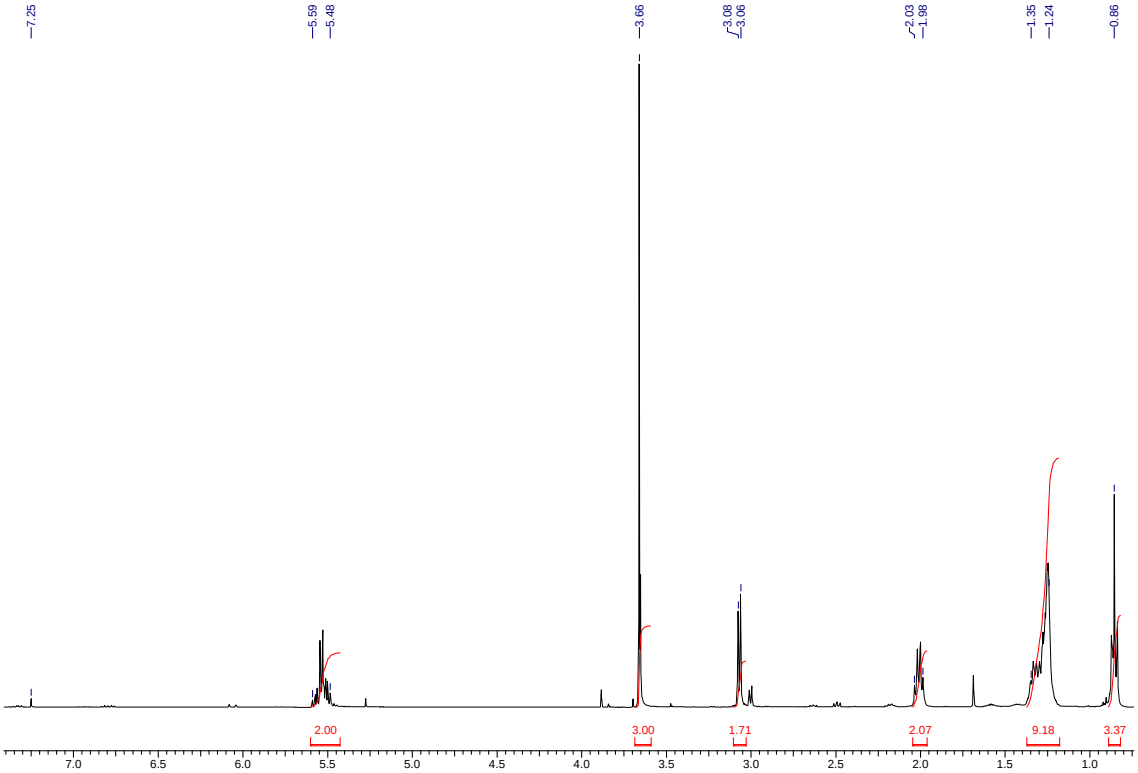
E/Z = 9:1

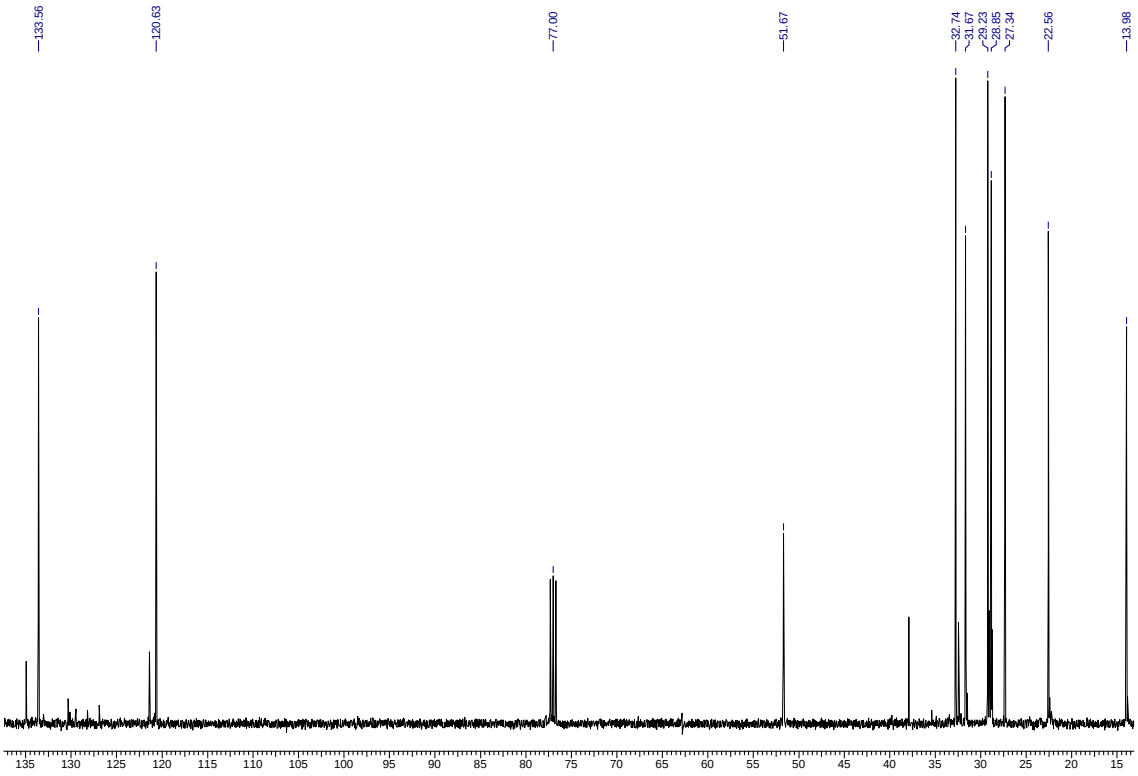
11a

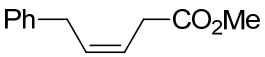

7.38
7.24
7.18
5.99
5.63
3.55
3.36
2.25
2.19
2.05
1.97
1.49
1.31
1.22
0.92
0.82
6.01
0.99
0.12
2.09
2.00
4.29
3.02
177.78
142.06
133.39
131.52
128.33
126.92
125.87
77.00
35.65
31.48
28.77
22.39
13.92


CO2Me
n-Hex

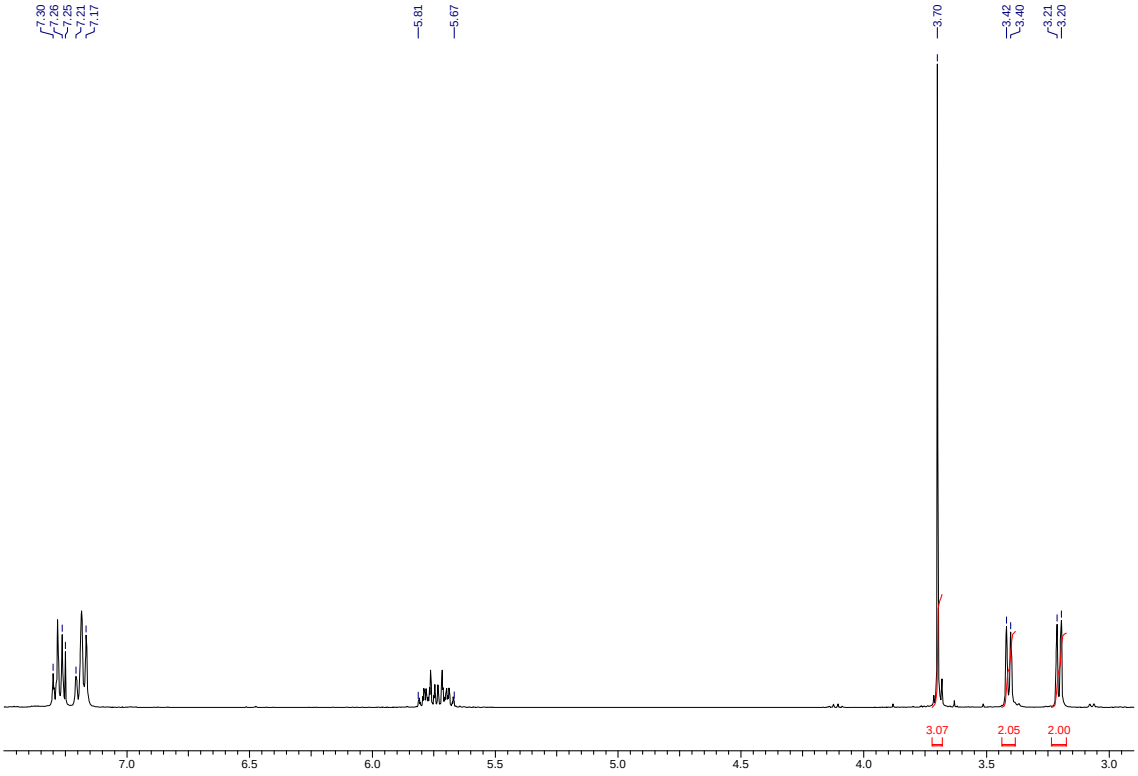
10b

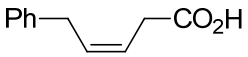

7.25
5.59
5.48
3.66
3.08
3.06
2.03
1.98
1.35
1.24
0.86
2.00
3.00
1.71
2.07
9.18
3.37


133.56
120.63
77.00
51.67
32.74
31.67
29.23
28.85
27.34
22.56
13.98

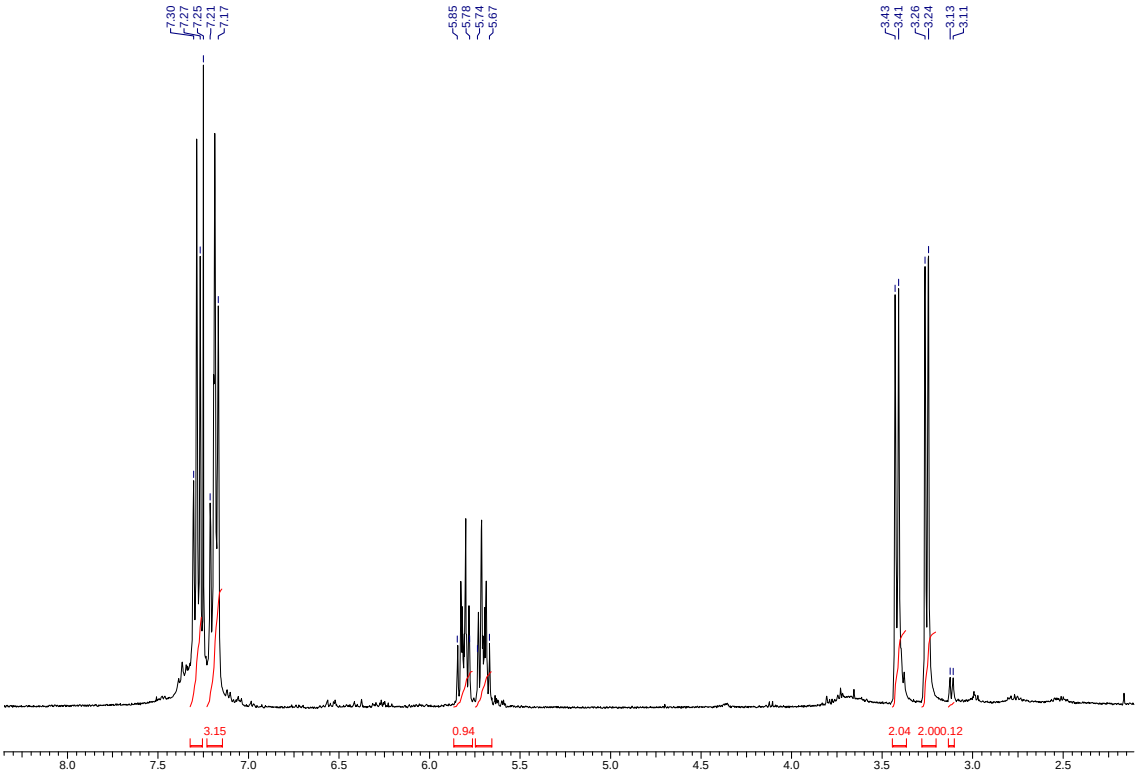

Ph
CO2Me

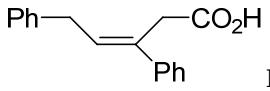
10c


7.30
7.26
7.25
7.21
7.17
5.81
5.67
3.70
3.42
3.40
3.21
3.20
3.07
2.05
2.00
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0


Ph
CO2H

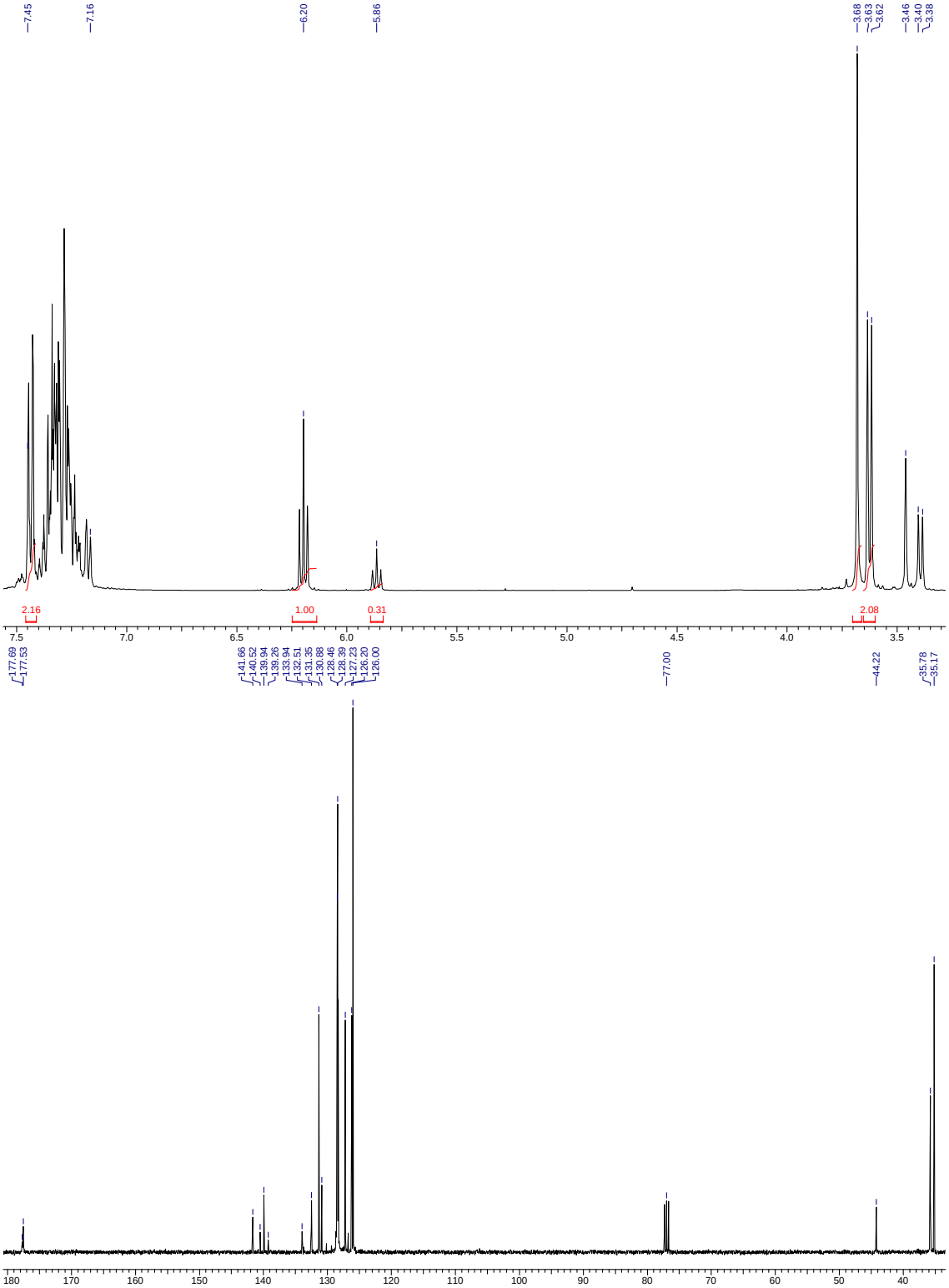
11c

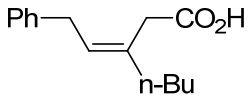

7.30
7.27
7.25
7.21
7.17
5.85
5.78
5.74
5.67
3.43
3.41
3.26
3.24
3.13
3.11
3.15
0.94
2.04
2.00
0.12
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5


Ph
CO2H
Ph

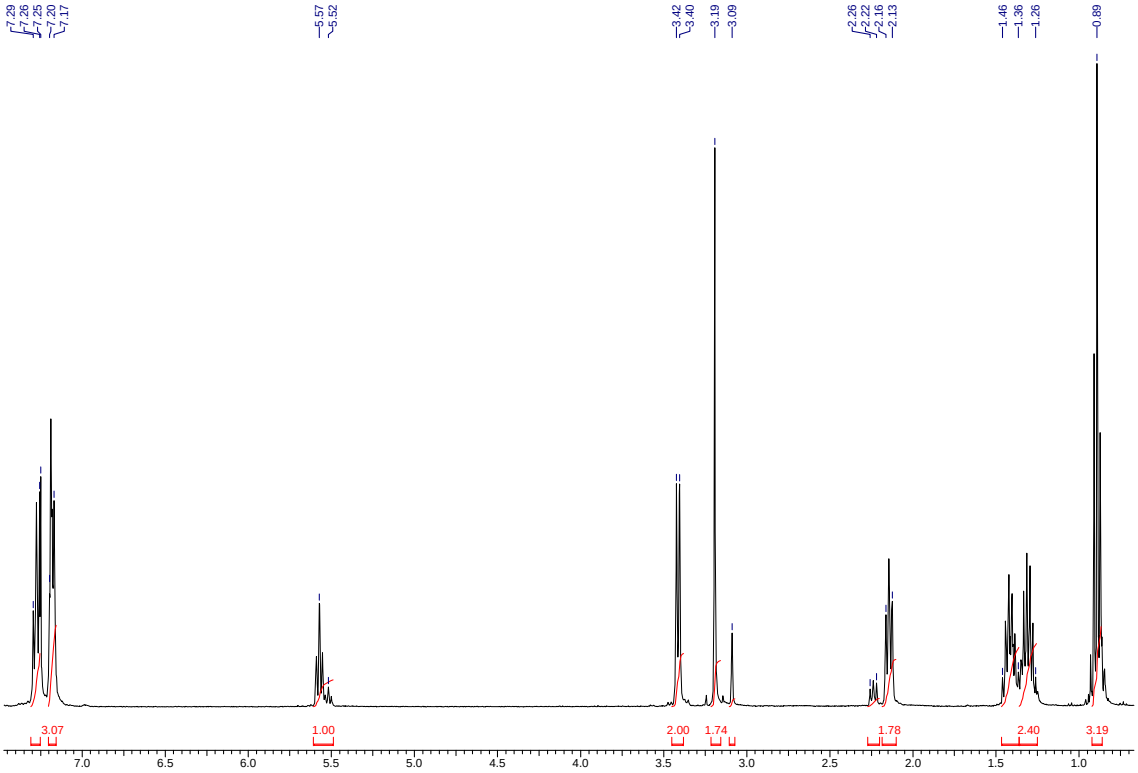
E/Z = 3.2/1

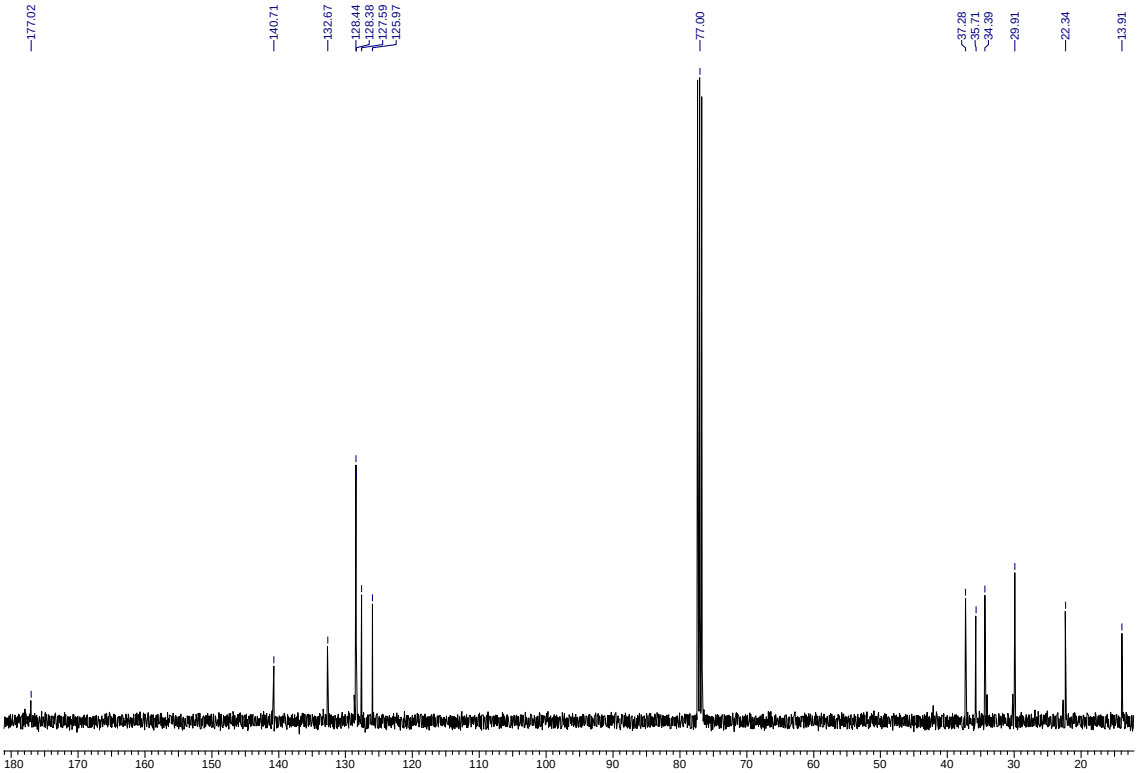
11d

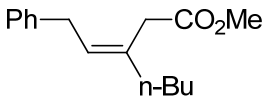

7.45
7.16
6.20
5.86
3.68
3.63
3.62
3.46
3.40
3.38
2.16
1.00
0.31
2.08
177.69
177.53
141.66
140.52
139.94
139.36
139.04
132.51
131.35
130.88
128.46
128.39
127.23
126.20
126.00
77.00
44.22
35.78
35.17


Ph
CO2H
n-Bu

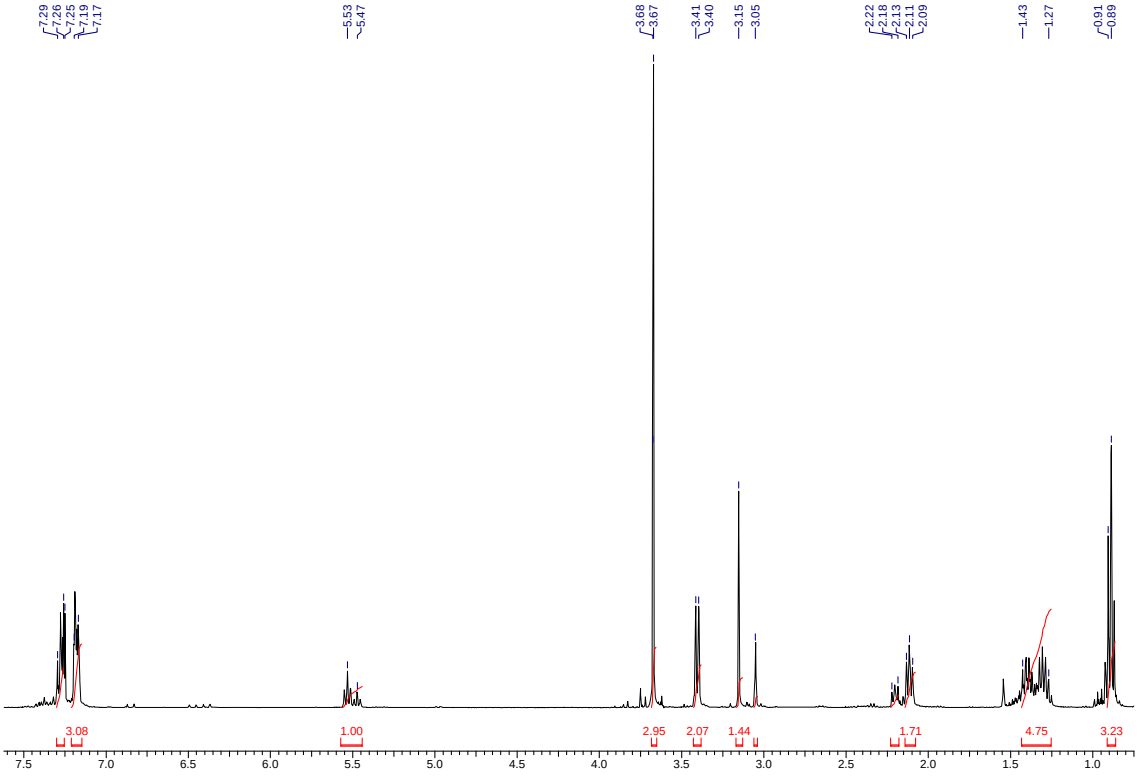
11e

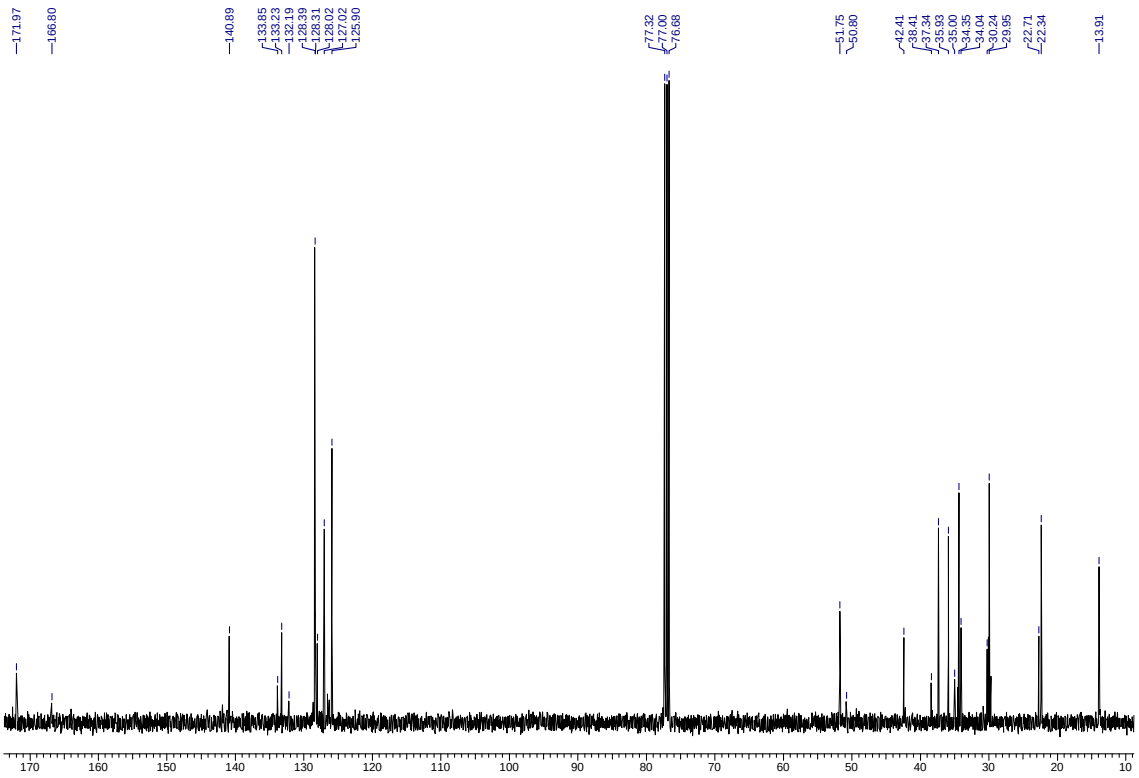

7.29
7.26
7.25
7.20
7.17
5.57
5.52
3.42
3.40
3.19
3.09
2.26
2.22
2.16
2.13
1.46
1.36
1.26
0.89
3.07
1.00
2.00
1.74
1.78
2.40
3.19

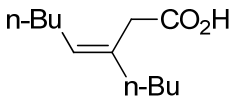

177.02
140.71
132.67
128.44
128.38
127.59
125.97
77.00
37.28
35.71
34.39
29.91
22.34
13.91


Ph
CO2Me
n-Bu

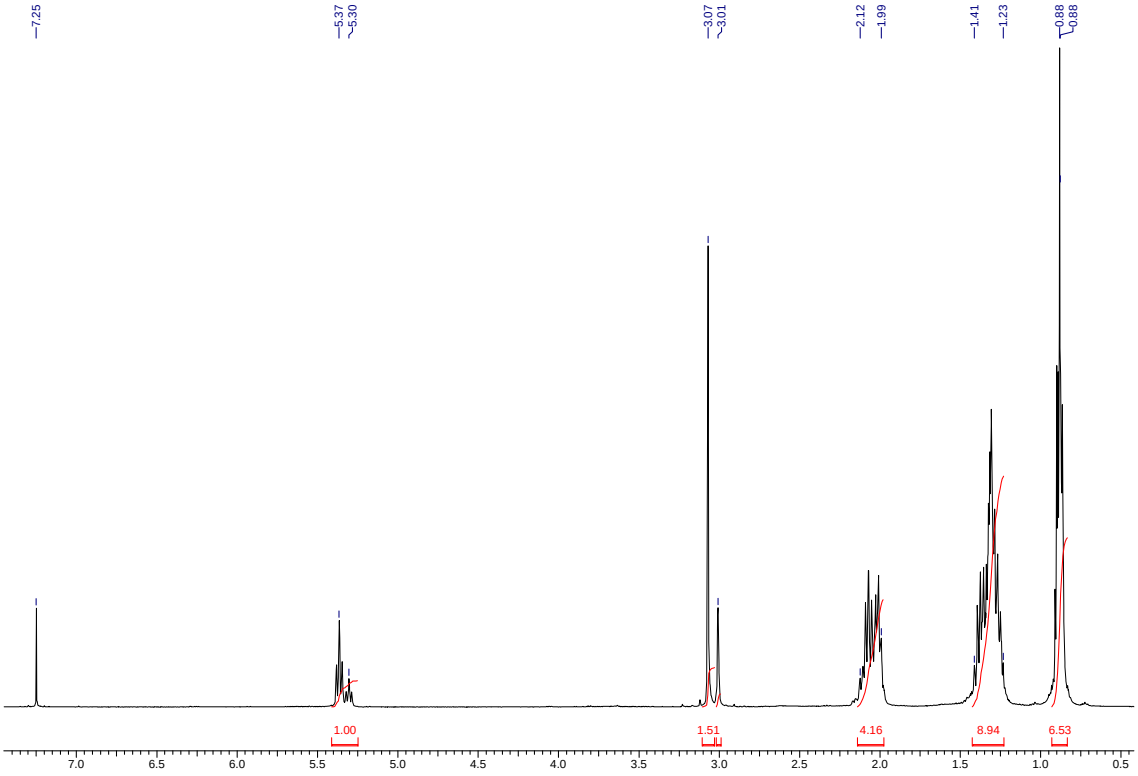
10e

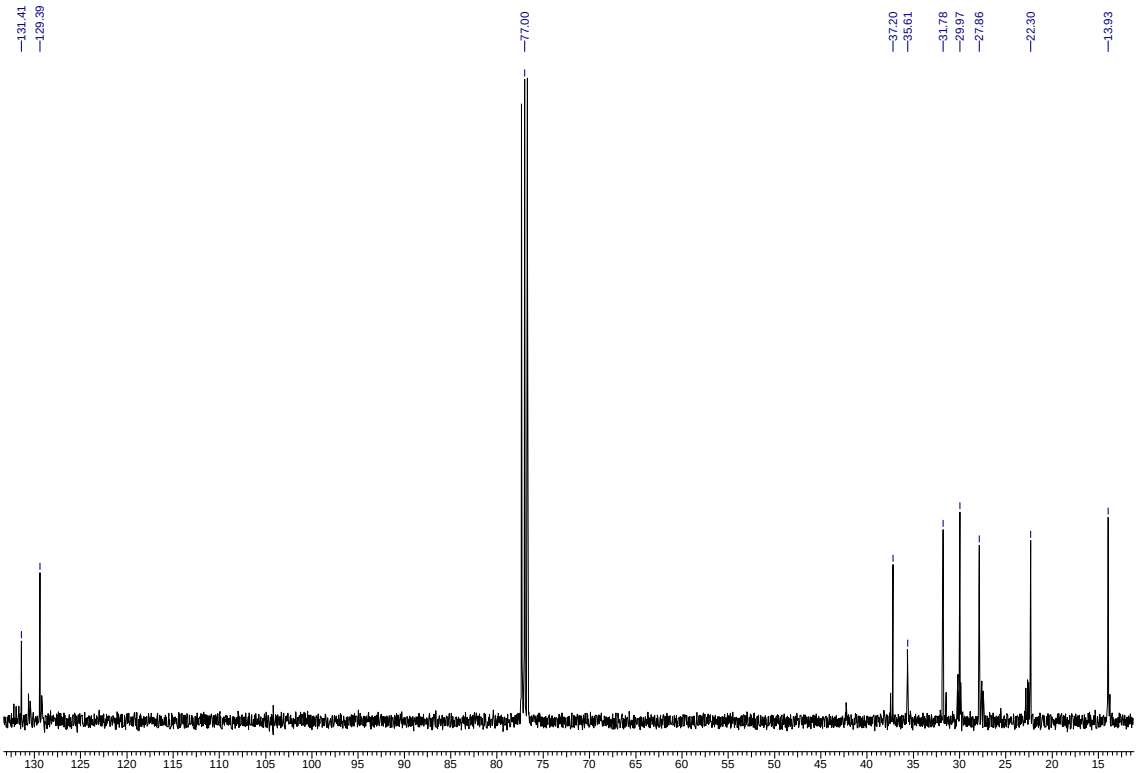

7.29
7.26
7.25
7.19
7.17
5.53
5.47
3.68
3.67
3.41
3.40
3.15
3.05
2.22
2.18
2.13
2.11
2.09
1.43
1.27
0.91
0.89
3.08
1.00
2.95
2.07
1.44
1.71
4.75
3.23

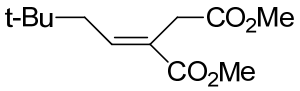

171.97
166.80
140.89
133.85
133.23
132.19
128.39
128.31
128.02
127.02
125.90
77.32
77.00
76.68
51.75
50.80
42.41
38.41
37.34
35.93
35.00
34.35
34.04
30.24
29.95
22.71
22.34
13.91


n-Bu
CO2H
n-Bu

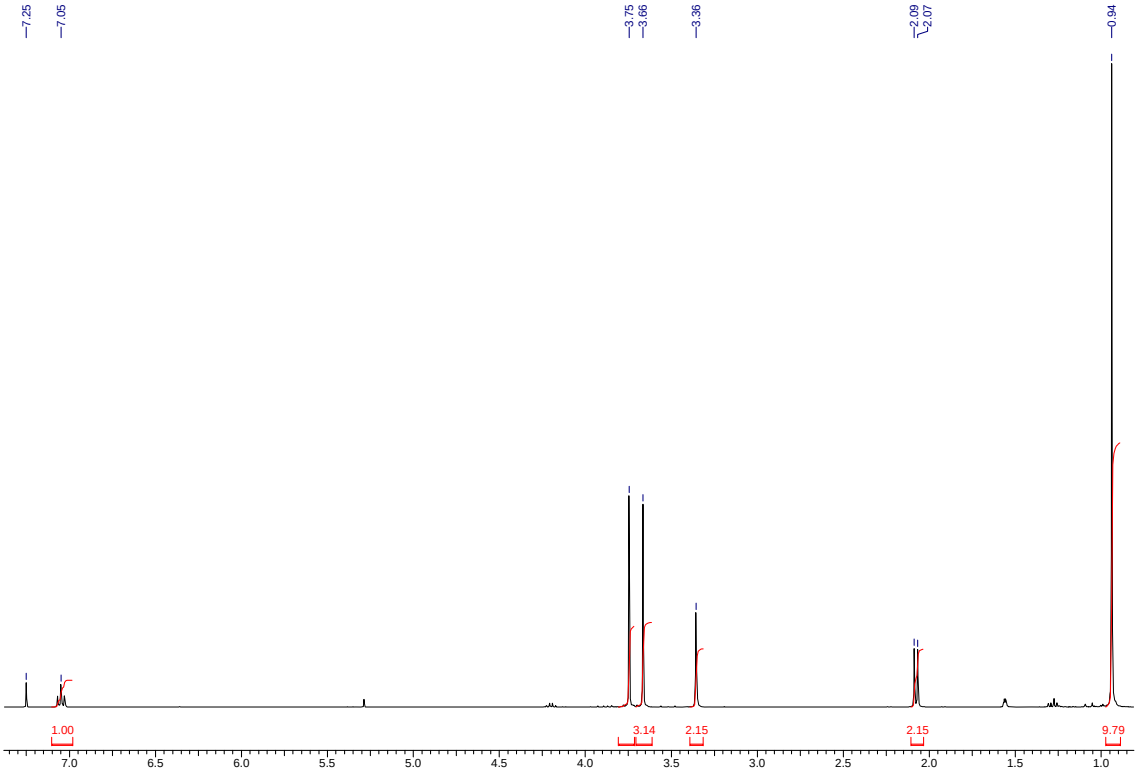
11f

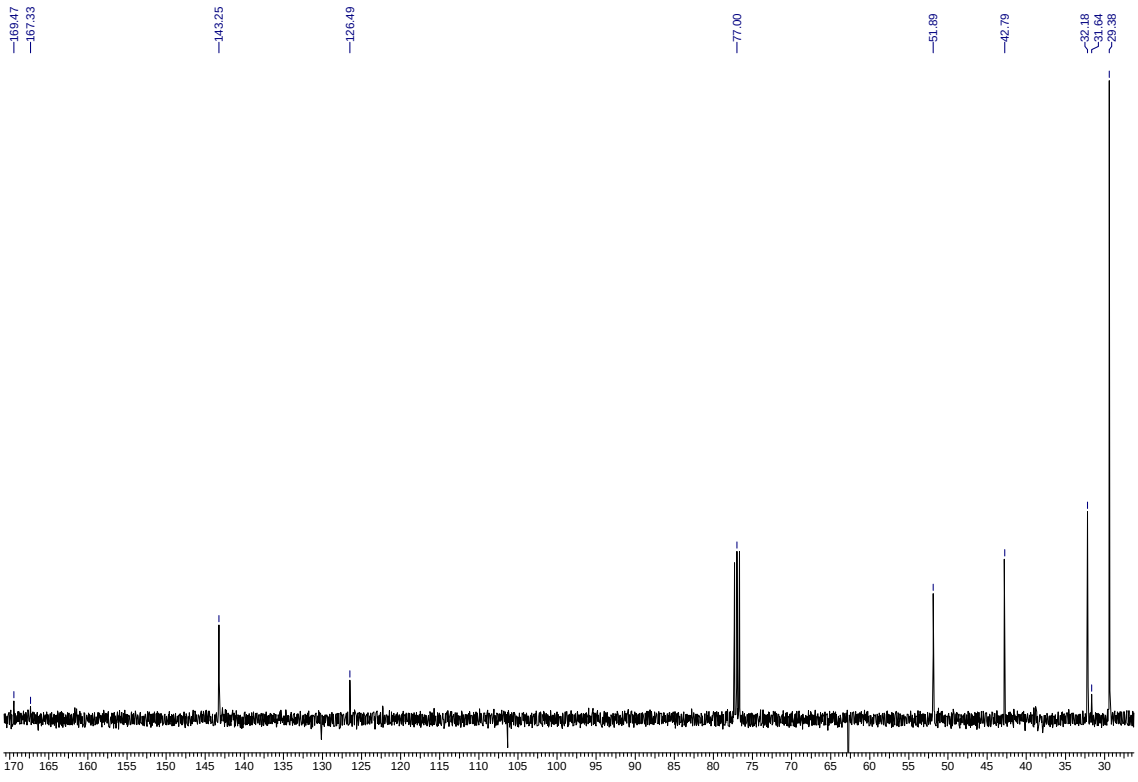

7.25
5.37
5.30
3.07
3.01
2.12
1.99
1.41
1.23
0.88
0.88
1.00
1.51
4.16
8.94
6.53

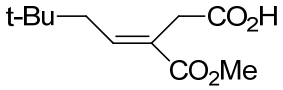

131.41
129.39
77.00
37.20
35.61
31.78
29.97
27.86
22.30
13.93


t-Bu
CO2Me
CO2Me

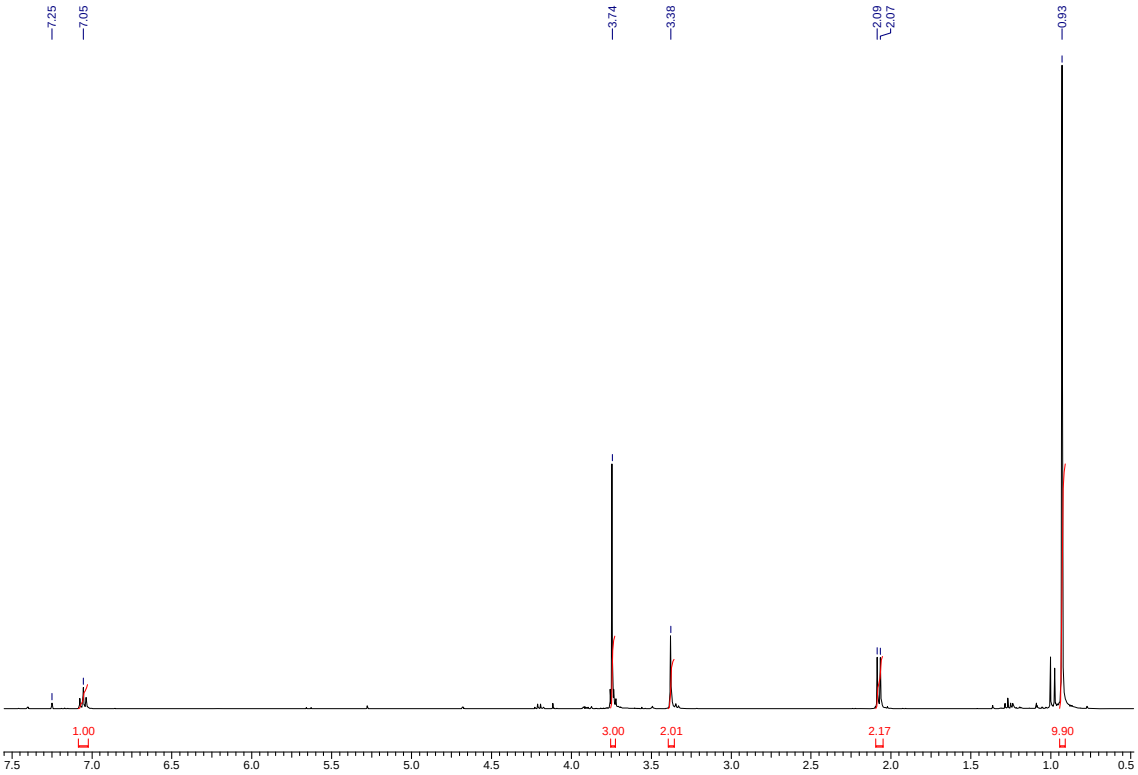
10h

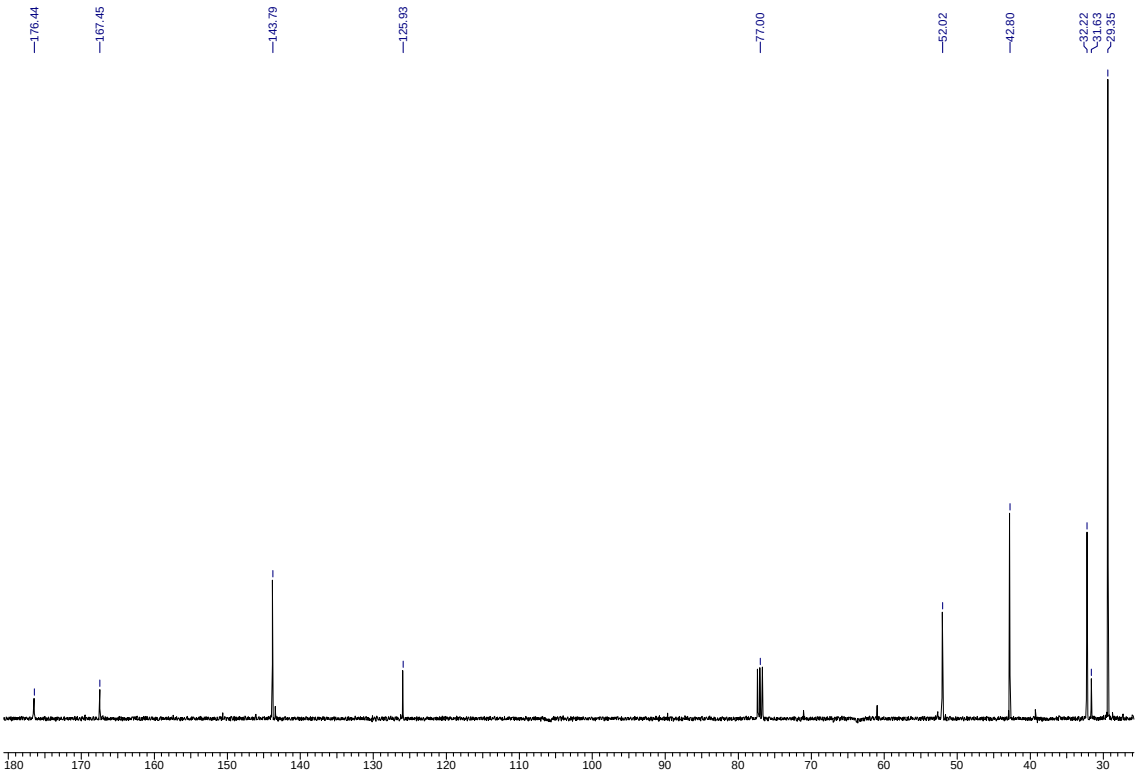

7.25
7.05
3.75
3.66
3.36
2.09
2.07
0.94
1.00
3.14
2.15
2.15
9.79

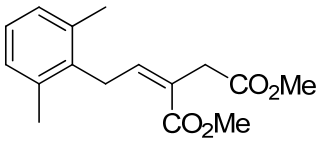

169.47
167.33
143.25
126.49
77.00
51.89
42.79
32.18
31.64
29.38


t-Bu
CO2H
CO2Me

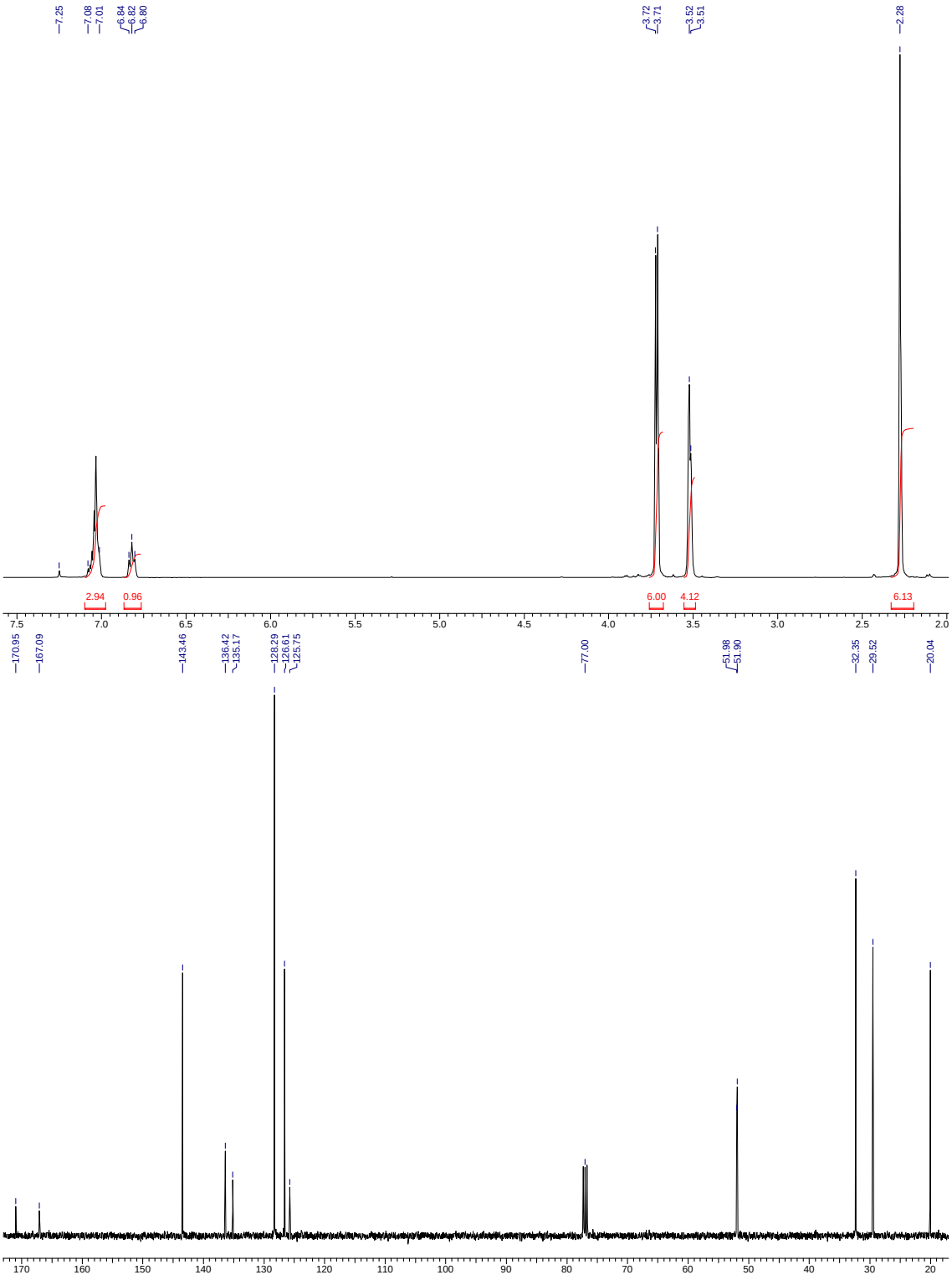
11h

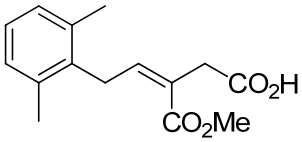

7.25
7.05
3.74
3.38
2.09
2.07
0.93
1.00
3.00
2.01
2.17
9.90


176.44
167.45
143.79
125.93
77.00
52.02
42.80
32.22
31.63
29.35

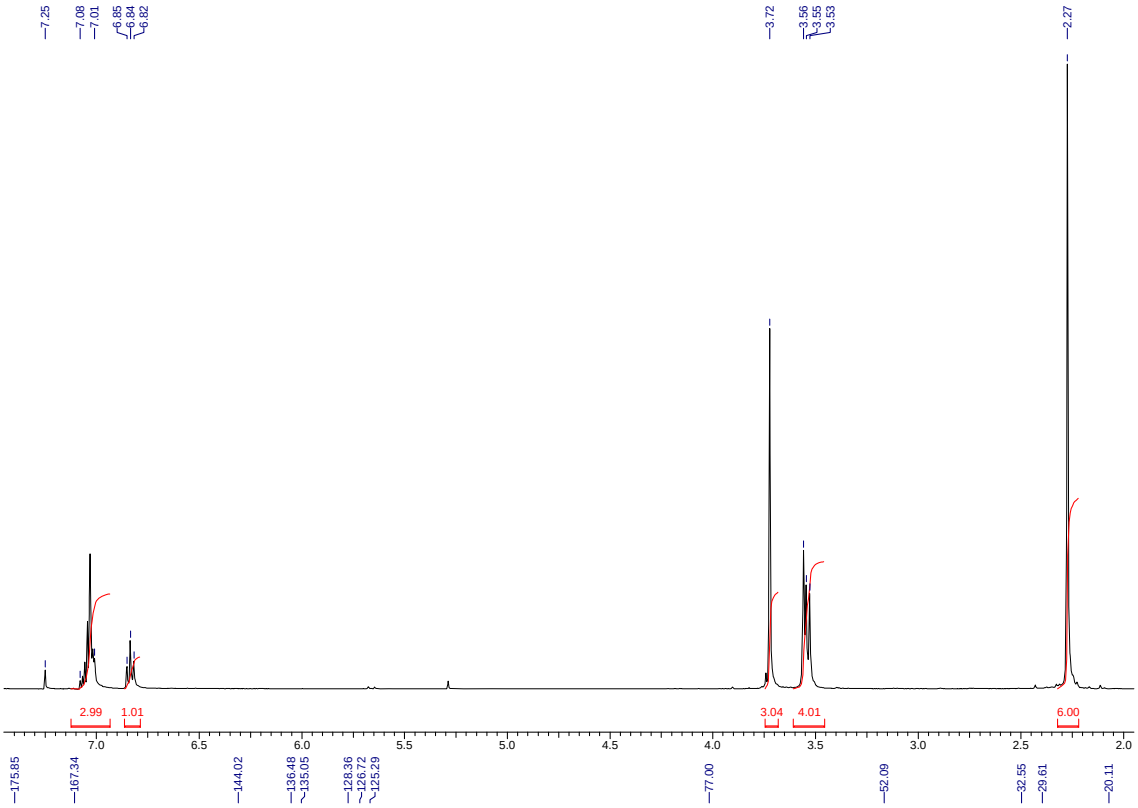

CO2Me
CO2Me

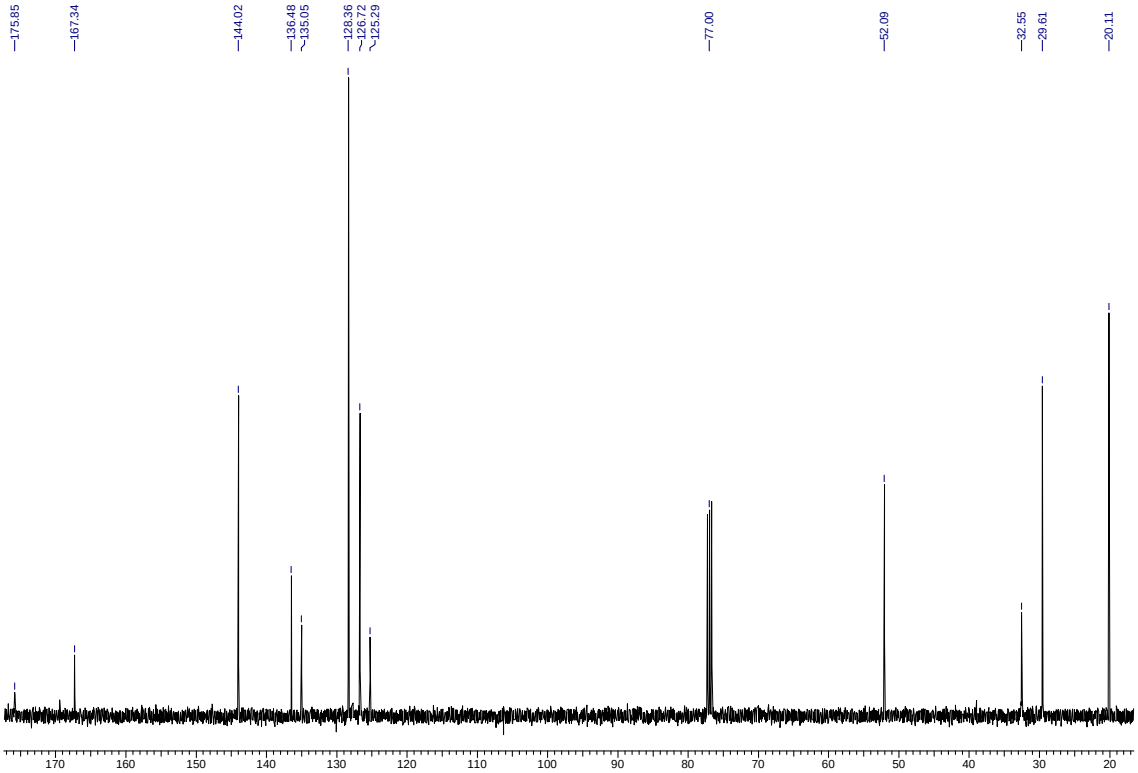
10i

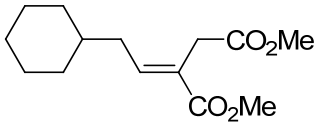

7.25
7.08
7.01
6.84
6.82
6.80
3.72
3.71
3.52
3.51
2.28
2.94
0.96
6.00
4.12
6.13
170.95
167.09
143.46
136.42
135.17
128.29
126.61
125.75
77.00
51.98
51.90
32.35
29.52
20.04


CO2H
CO2Me

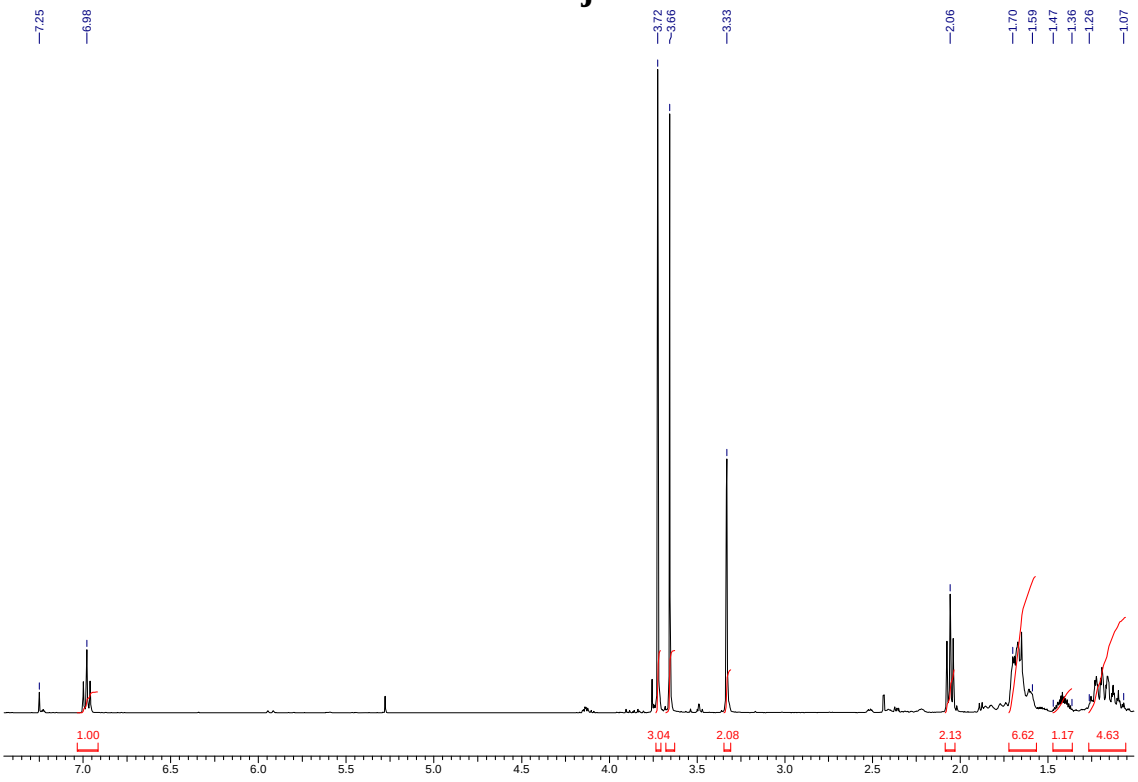
11i

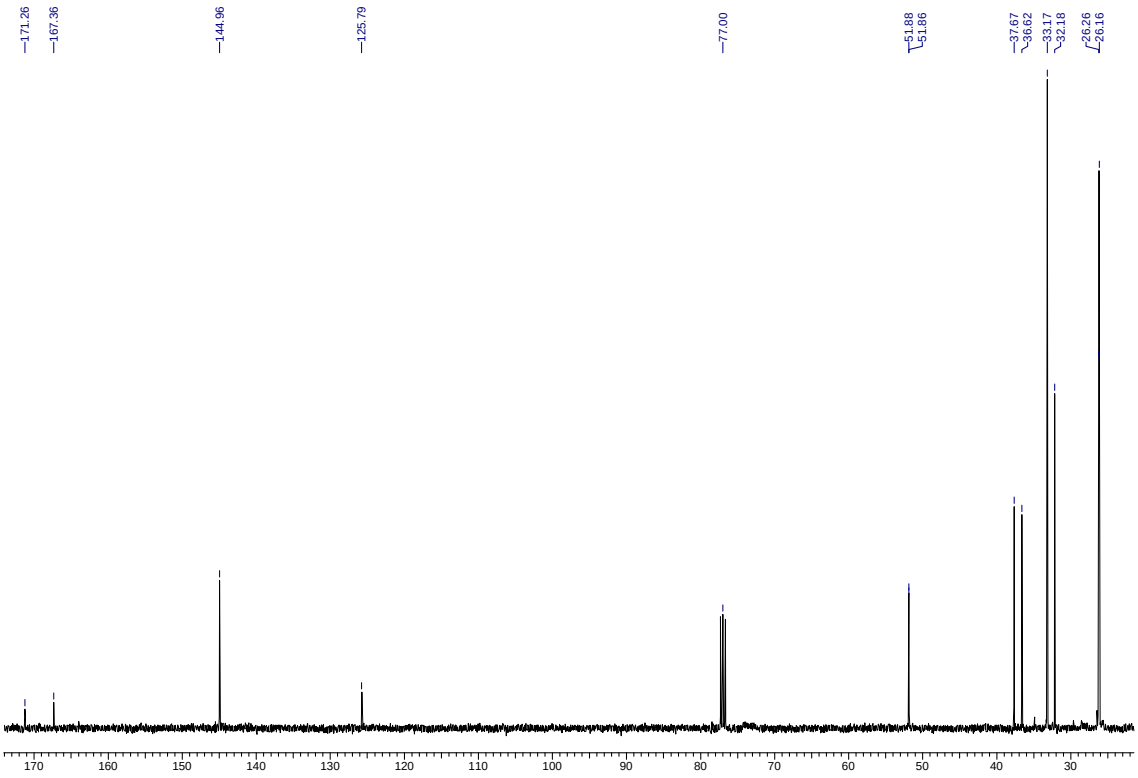

7.25
7.08
7.01
6.85
6.84
6.82
3.72
3.56
3.55
3.53
2.27
2.99
1.01
3.04
4.01
6.00

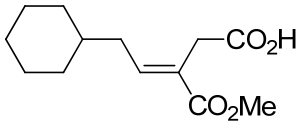

175.85
167.34
144.02
136.48
135.05
128.36
126.72
125.29
77.00
52.09
32.55
29.61
20.11


CO2Me
CO2Me

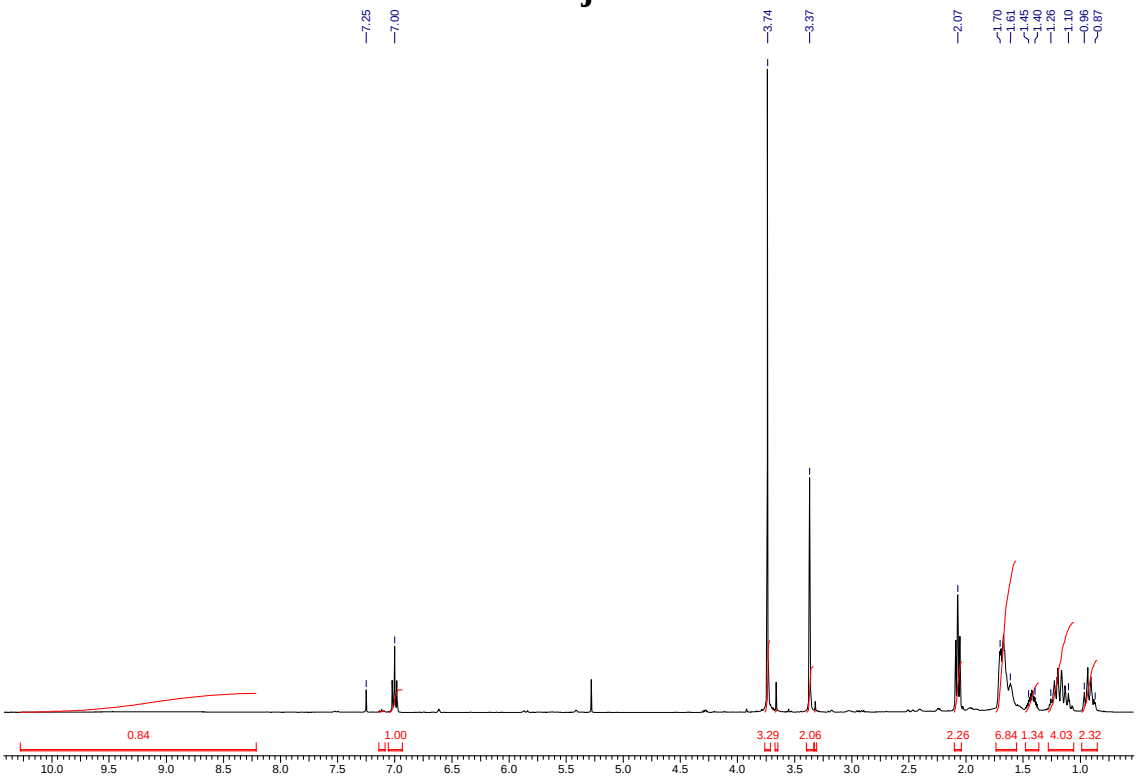
10j

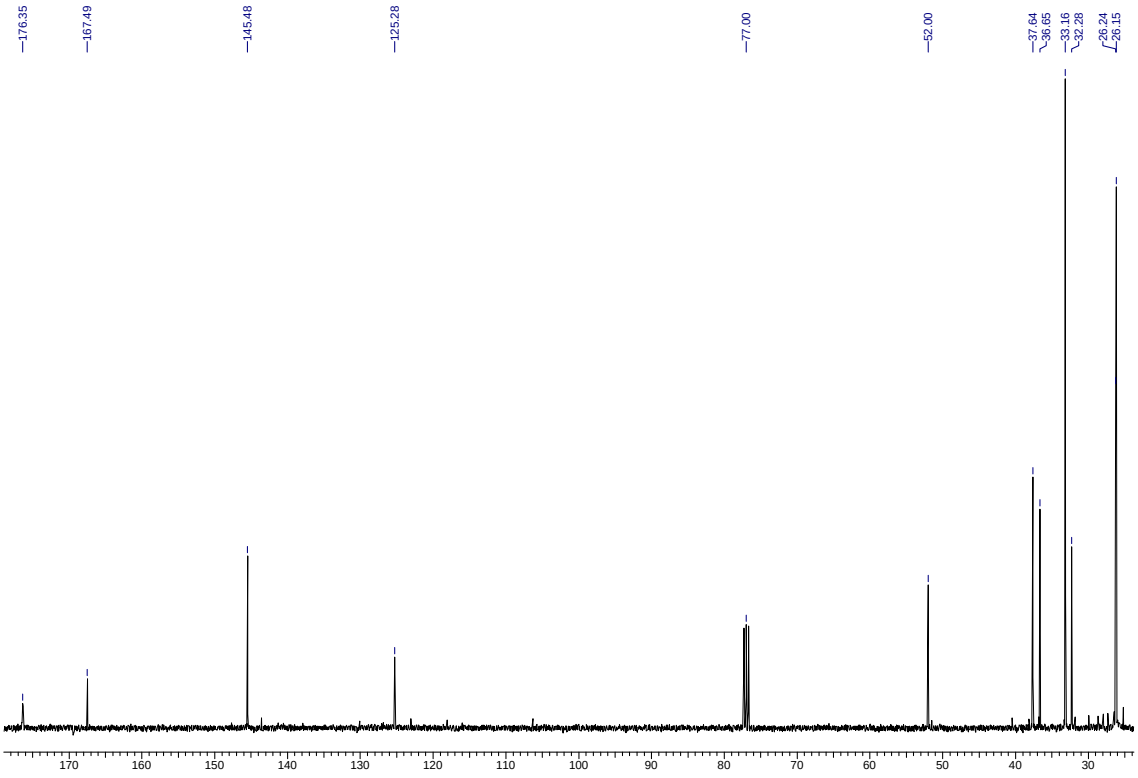

7.25
6.98
3.72
3.66
3.33
2.06
1.70
1.59
1.47
1.36
1.26
1.07
1.00
3.04
2.08
2.13
6.62
1.17
4.63
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5

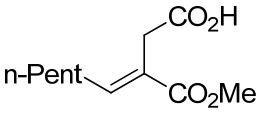

171.26
167.36
144.96
125.79
77.00
51.88
51.86
37.67
36.62
33.17
32.18
26.26
26.16
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30


CO2H
CO2Me

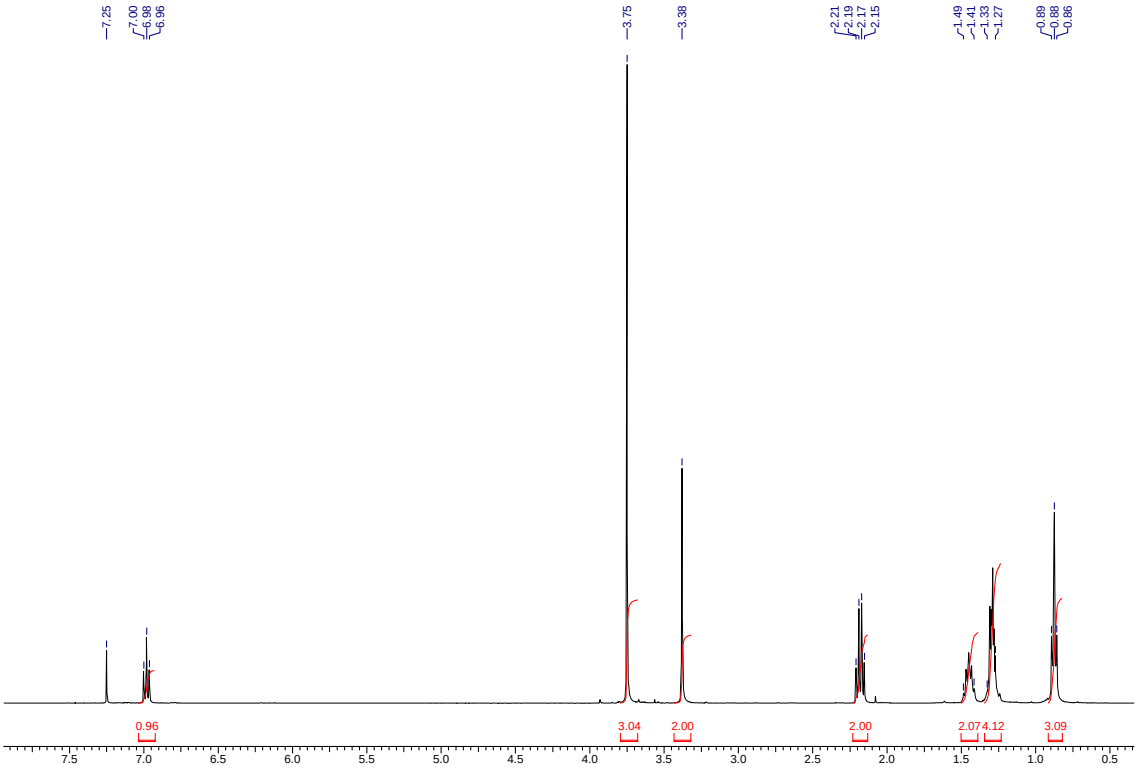
11j

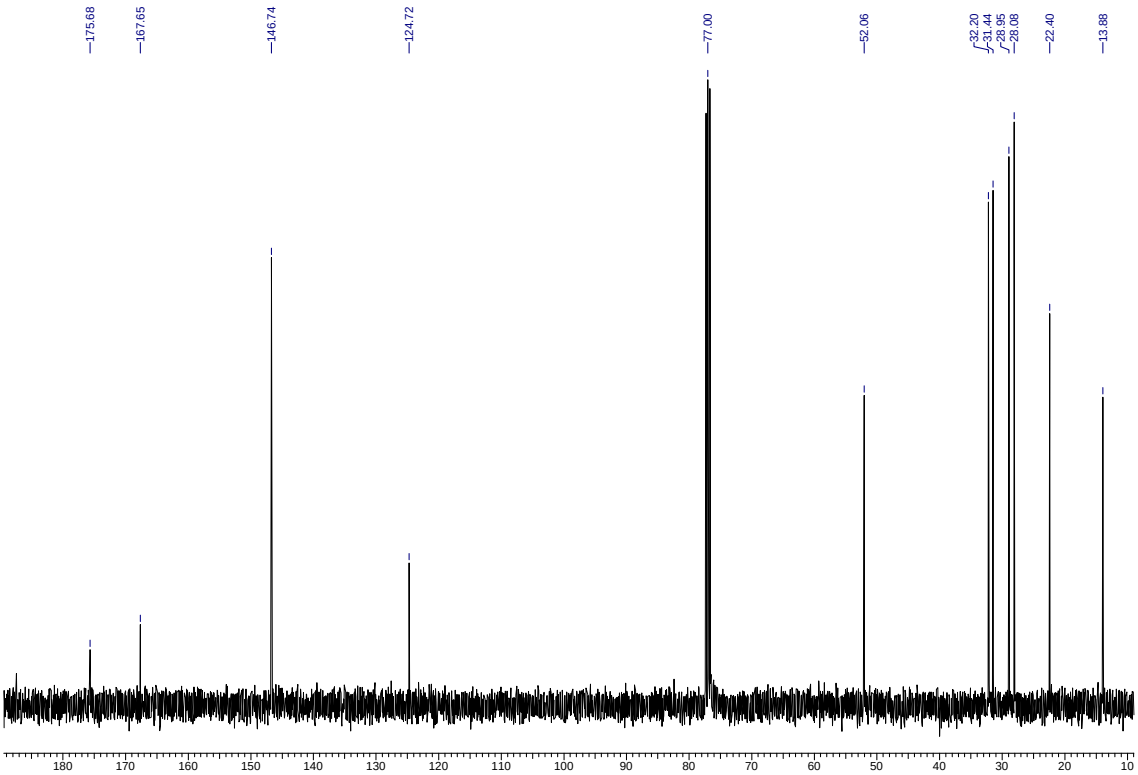

7.25
7.00
3.74
3.37
2.07
1.70
1.61
1.45
1.40
1.26
1.10
0.96
0.87
0.84
1.00
3.29
2.06
2.26
6.84
1.34
4.03
2.32

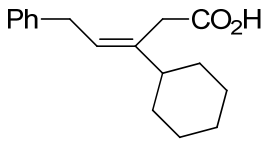

176.35
167.49
145.48
125.28
77.00
52.00
37.64
36.65
33.16
32.28
26.24
26.15


CO2H
n-Pent
CO2Me

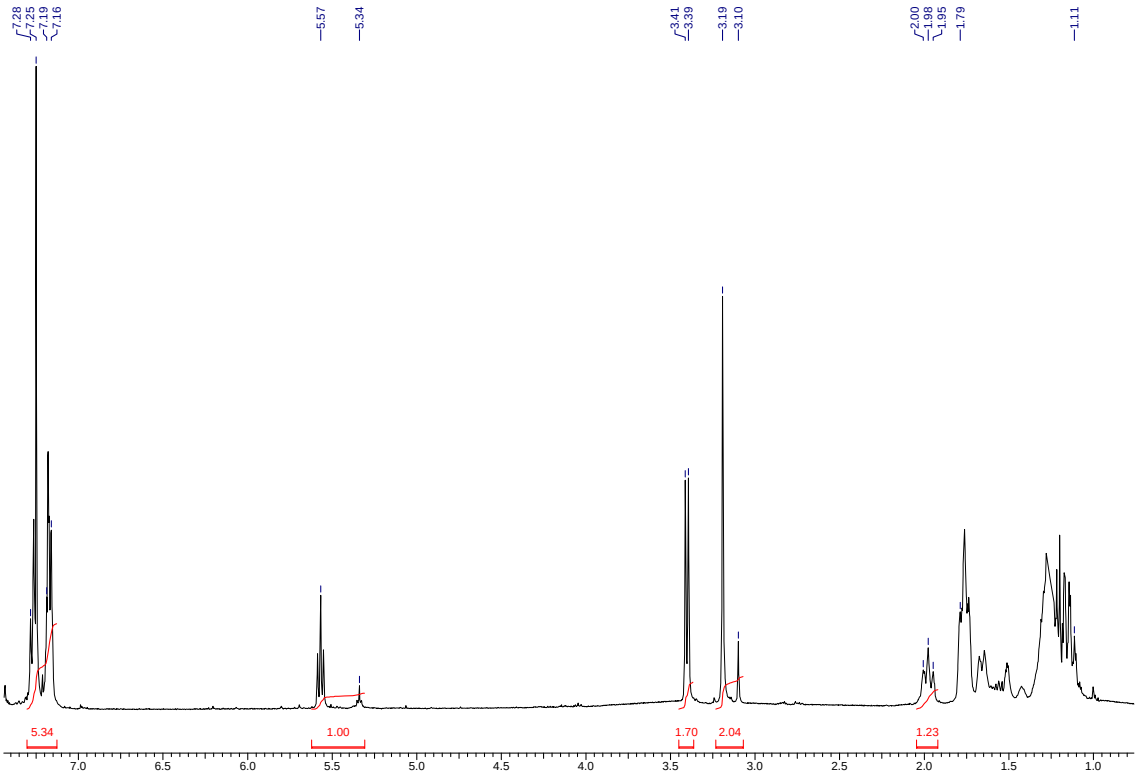
11k

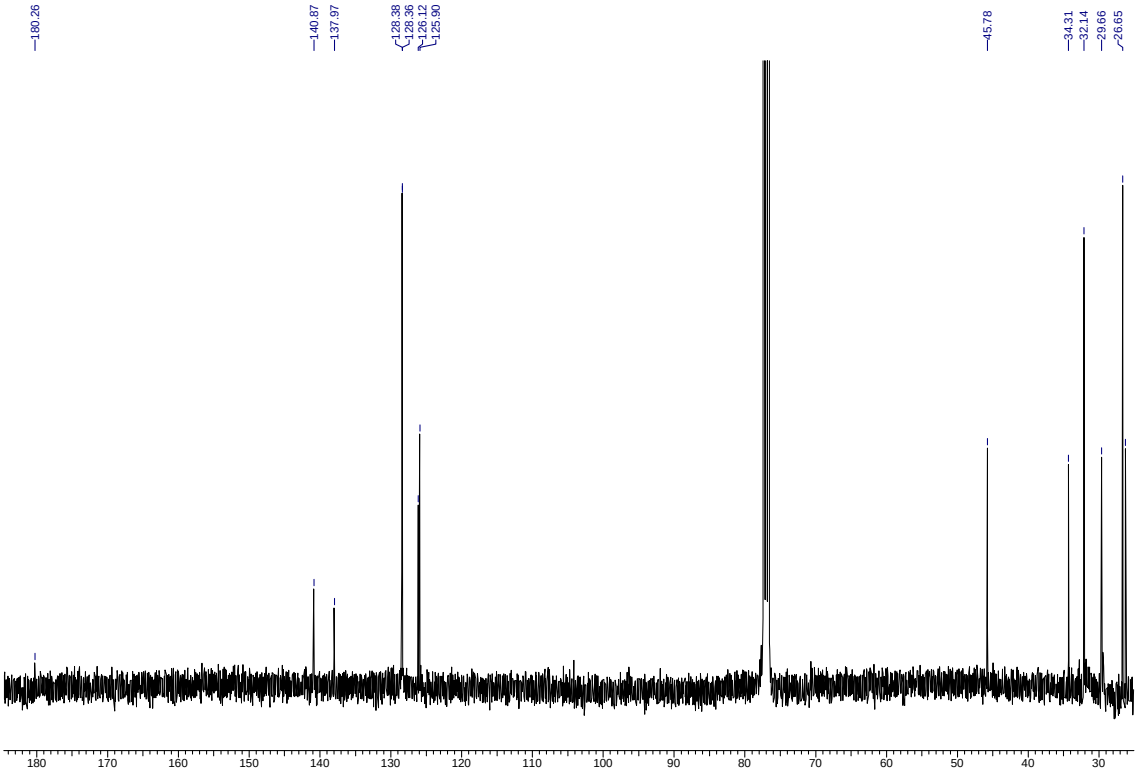

7.25
7.00
6.98
6.96
3.75
3.38
2.21
2.19
2.17
2.15
1.49
1.41
1.33
1.27
0.89
0.88
0.86
0.96
3.04
2.00
2.00
2.07
4.12
3.09

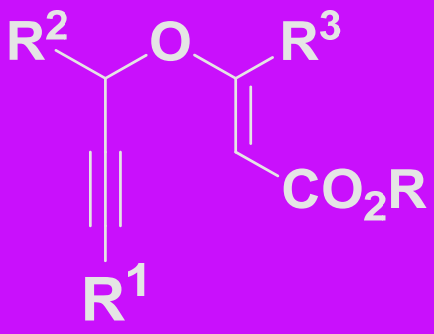

175.68
167.65
146.74
124.72
77.00
52.06
32.20
31.44
28.95
28.08
22.40
13.88


Ph
CO2H

11l


7.28
7.25
7.19
7.16
5.57
5.34
3.41
3.39
3.19
3.10
2.00
1.98
1.95
1.79
1.11
5.34
1.00
1.70
2.04
1.23


180.26
140.87
137.97
128.38
128.36
126.12
125.90
45.78
34.31
32.14
29.66
26.65



CHAPTER 7

Conclusions

7. Conclusions:

7.1. General conclusions:

7.1.1. The [3,3]-sigmatropic rearrangement of propargyl vinyl ethers is more than just the acetylenic version of the Claisen rearrangement. As we have seen, it may be combined with other known reactivities to gain access to much more complex compounds, often in a very elegant manner.

7.1.2. The availability of the propargyl vinyl ethers along with novel metal-catalysed and microwave-induced strategies have sparked a great interest in the development of new domino processes. It is anticipated that the future will bring the design of new strategies that will combine the propargyl Claisen rearrangement with other reactivities in yet more innovating domino processes. Furthermore, new methodologies will be designed for the synthesis of propargyl vinyl ethers which will aid in the broadening of this powerful organic synthetic tool.

7.1.3. It has been demonstrated that it is possible to use propargyl vinyl ethers as pluripotent platforms in order to obtain as much scaffold diversity as possible leading to a wide range of different skeletons. They are rapidly and easily assembled from commercial or readily available simple starting materials.

7.1.4. The newly design methodologies have been carried out under metal-free conditions assisted by microwave irradiation. Therefore, these processes are fast, economical, bench-friendly (they do not require special care with solvent and reaction atmospheres) and environmentally benign.

7.2. Specific conclusions:

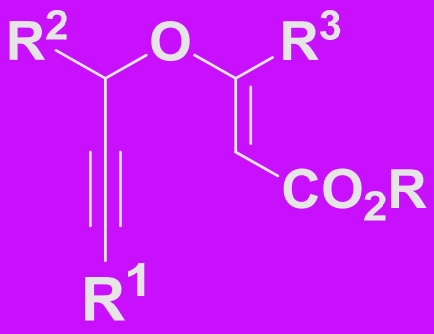
7.2.1. A metal-free domino synthesis of substituted alkyl 1,2-dihydropyridine-3-carboxylates has been developed from propargyl vinyl ethers and primary amines via an unprecedented [3,3] propargyl-Claisen rearrangement - isomerization - amine condensation and 6π-aza-electrocyclization cascade reaction network. 1,2-Dihydropyridines are obtained with remarkable high efficiency, good level of diversity (four possible diversity points) and bearing a convenient chemical handle for complexity-diversity generation (carboxylic ester at C3-position).

7.2.2. A microwave-assisted diversity-oriented synthesis of functionalized alkyl nicotinates has been developed from propargyl vinyl ethers, via a complex and efficient

domino manifold involving at least five distinct and discrete chemical steps ([3,3] propargyl-Claisen rearrangement - isomerization - amine condensation and 6π-aza-electrocyclization – elimination). The obtained alkyl nicotinates feature a maximum of two diversity points at the ring and one appended chemical handle for further elaboration (ester functionality). Taking into account that this is an efficient method that relies on readily accessible starting materials, this approach could be a good alternative to other well-known methods to rapidly generate libraries of functionalized nicotinate derivatives to use in drug discovery programs.

7.2.3. Readily available propargyl vinyl ethers have been efficiently converted into convenient multi-functionalized aromatic products via a microwave-assisted and novel domino process involving: [3,3] propargyl-Claisen rearrangement, pseudo-pericyclic [1,3] hydride shift, 4*E*–4*Z* isomerization, [1,5] hydride shift, enolization, electrocyclization and aromatization, where the electrocyclization is the key step of the process.

7.2.4. It has been shown that the coupling of a microwave assisted domino reaction and an internal neutral redox reaction constitutes an excellent manifold for the stereoselective synthesis of di- and trisubstituted olefins featuring a malonate unit, an ester, or a free carboxylic acid at the allylic position. The efficiency of these transformations is highlighted when we take into account that they entitle domino processes consisting of at least, a [3,3]-propargyl Claisen rearrangement, a pseudo-pericyclic [1,3]-H shift reaction, a diene E/E to E/Z isomerization, a nucleophilic addition and a [1,5]-H shift.



CAPÍTULO 8

Conclusiones

8. Conclusiones:

8.1. Conclusiones generales:

8.1.1 El reagrupamiento [3,3]-sigmatrópico de éteres propargílicos vinílicos constituye algo más que la simple versión acetilénica del reagrupamiento de Claisen. Como hemos visto en esta memoria, cuando éste se acopla con otras reactividades compatibles, el proceso resultante permite generar complejidad química, y hacerlo además de manera muy elegante.

8.1.2 El desarrollo de nuevas estrategias catalíticas basadas en metales o inducidas por microondas, junto a la disponibilidad de estas unidades propargílicas, ha despertado gran interés tanto en el diseño como en el desarrollo e implementación de nuevos procesos dominó basados en estas estructuras. La combinación de este tipo de reagrupamiento sigmatrópico con otras reactividades presentes en la molécula y compatibles con él, permitirá generar procesos dominó nuevos y más potentes, que abrirán aún más el alcance y el poder sintético que esta herramienta ofrece para la generación de complejidad química.

8.1.3 Se ha demostrado que es posible el uso de éteres propargílicos vinílicos como plataformas pluripotentes con el fin de generar la máxima diversidad estructural (máximo número de diferentes esqueletos) a partir de una única plataforma de construcción molecular. Además, hemos demostrado que estas plataformas se pueden generan de manera inmediata (una o dos etapas sintéticas), eficiente y a cualquier escala.

8.1.4 La metodología dominó presentada en esta memoria reúne, entre otras virtudes, rapidez (las reacciones se llevan a cabo en tiempos razonablemente cortos), economía (tanto de átomo como de procesado), sencillez experimental (no se requiere un especial cuidado con los disolventes ni con la atmósfera de reacción) y respeto al medio ambiente.

8.2. Conclusiones específicas:

8.2.1. Se ha desarrollado una síntesis orientada a la diversidad de unidades de 1,2-dihidropiridina-3-carboxilato de alquilo trisustituidos a partir de éteres propargílicos vinílicos y aminas primarias, vía un proceso dominó nuevo y complejo, que incluye las siguientes reacciones: reagrupamiento [3,3]-Claisen propargílico – isomerización - condensación (formación de imina) y 6π-aza-electrociclación. Las unidades de 1,2-

dihidropiridina se obtienen con eficiencia y buen nivel de diversidad (cuatro posibles puntos de diversidad). La presencia de un grupo éster carboxílico en posición C_3 del anillo permite la creación de más complejidad y/o diversidad en la molécula.

8.2.2. Se ha desarrollado una síntesis orientada a la diversidad y asistida por microondas de unidades de piridina-3-carboxilato de alquilo disustituidas a partir de éteres propargílicos vinílicos, vía un proceso dominó complejo y muy eficiente que involucra al menos cinco pasos sintéticos diferenciados; éstos son: reagrupamiento [3,3]-Claisen propargílico - isomerización – condensación (formación de imina) - 6π-aza-electrociclación - eliminación. Los nicotinatos de alquilo obtenidos presentan un máximo de dos puntos de diversidad en el anillo y un grupo éster como punto de creación de complejidad y/o diversidad en la molécula. La metodología es eficiente, instrumentalmente sencilla y utiliza materiales de partida fácilmente accesibles, lo que la convierte en una buena alternativa a otros métodos descritos para la generación de colecciones moleculares focalizadas a estas unidades estructurales y con aplicación en programas de descubrimiento y desarrollo de fármacos/sondas.

8.2.3. Unidades de éteres propargílicos vinílicos han sido convertidas de manera eficiente en productos aromáticos multifuncionalizados de alto valor añadido, vía un proceso dominó que involucra las siguientes reacciones consecutivas: reagrupamiento [3,3]-Claisen propargílico, migración de hidruro [1,3]-pseudo-pericíclica, isomerización 4*E*-4*Z*, migración de hidruro [1,5]-pseudo-pericíclica, enolización, 6π-electrociclación y aromatización, donde la electrociclación es el paso clave del proceso.

8.2.4. Se ha demostrado que el acoplamiento de una reacción domino asistida por microondas y una reacción redox neutra e intramolecular es una excelente combinación para la síntesis estereoselectiva de olefinas di- y tri-sustituidas, adornadas con una unidad de dialquil malonato, un éster alquílico o un ácido carboxílico libre en posición alílica. El proceso es muy eficiente e incluye las siguientes reacciones: un reagrupamiento [3,3]-Claisen propargílico, una migración de hidruro [1,3]-pseudo pericíclica, una isomerización diénica E/E a E/Z, una adición nucleofílica y una migración de hidruro [1,5] -pseudo pericíclica.