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Silver salts useful catalysts for the synthesis of cyclic and *O*-heterocyclic frameworks

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Abbreviation list

Ac	Acetyl
ACN	Acetonitrile
Ar	Aryl
BET	Back Electron Transfer
BHT	Butylated Hydroxytoluene
Bn	Benzyl
Boc	tert-butyloxycarbonyl
Bz	Benzoyl
Bu	Butyl
Cy	Cyclohexyl
d.r	Diastereomeric *ratio*
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCE	1,2-dichloroethane
DCM	Dichloromethane
DFT	Density Functional Theory
DIPA	Diisopropanolamine
DIPEA	N,N-Diisopropylethylamine
DMA	N,N-Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
DNP	2,4-Dinitrophenol
e.e.	Enantiomeric excess
e.r.	Enantiomeric *ratio*
E^+	Electrophile
eq.	Equivalent
Et	Ethyl
EWG	Electron withdrowing group
h	Hours
HMDS	Bis(trimethylsilyl)amine
HMPT	Hexamethylphosphorous triamide
*i*Pr	*iso*-propyl
L	Ligand
LAH	Lithium alluminium hydride
LDA	Lithium diisopropylamide
liq.	Liquid
M	Molar
Me	Methyl
min	Minutes

mol	mole
MS4Å	Molecular sieves 4 Ångstrom
MW	Microwaves
NBS	N-Bromosuccinimide
*n*Bu	*normal*-butyl
NMP	N-Methyl-2-pyrrolidone
NOE	Nuclear overhauser effect
NOESY	Nuclear overhauser effect spectrometry
Ns	Nitrobenzene-1-sulfonyl
n.r	No reaction
Nu^-	Nucleophile
o	ortho
p	para
Ph	Phenyl
Pr	*normal*-propyl
quant.	Quantitative
rt	Room temperature
TBAI	Tetra-*n*-butylammonium iodide
TBHP	Tert-butyl hydroperoxide
*t*Bu	*tert*-butyl
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
Tf	Trifluoromethanesulfonyl (Triflate)
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
tol	toluyl
Ts	*para*-toluylsulfonyl
TS	Transition state

I. Preamble

Our laboratory has a long lasting experience in the synthesis of complex natural compounds exhibiting relevant biological activities. For many years, our team has targeted several compounds having different potential therapeutic profiles such as anti-cancer agent, anti-diabetic, neurotrophic activities… Among the most recent molecules, of which the total synthesis have been surveyed in our laboratory, we can cite, hemicalide **1**,[1] thapsigargine **2**[2] or vibsatine **3** and **4**[3].(Figure 1)

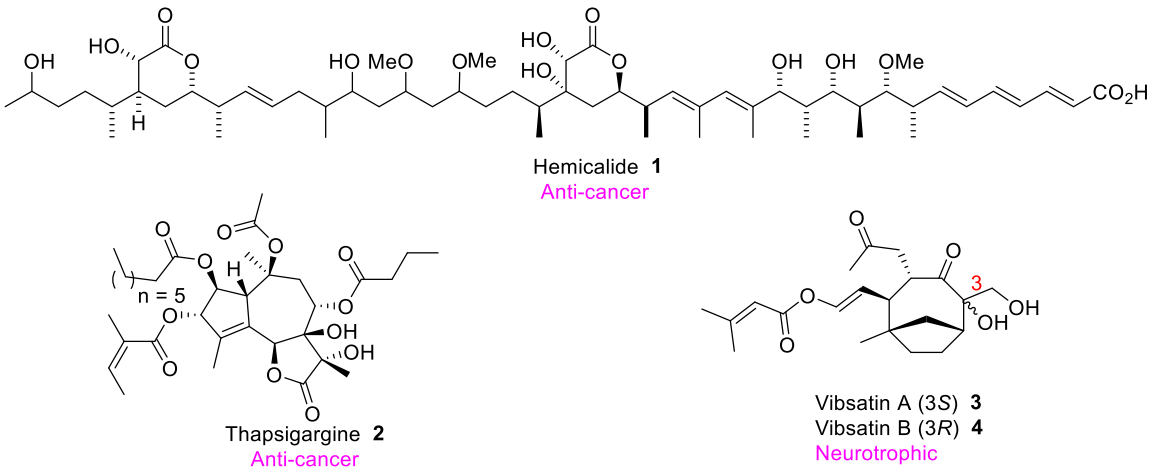
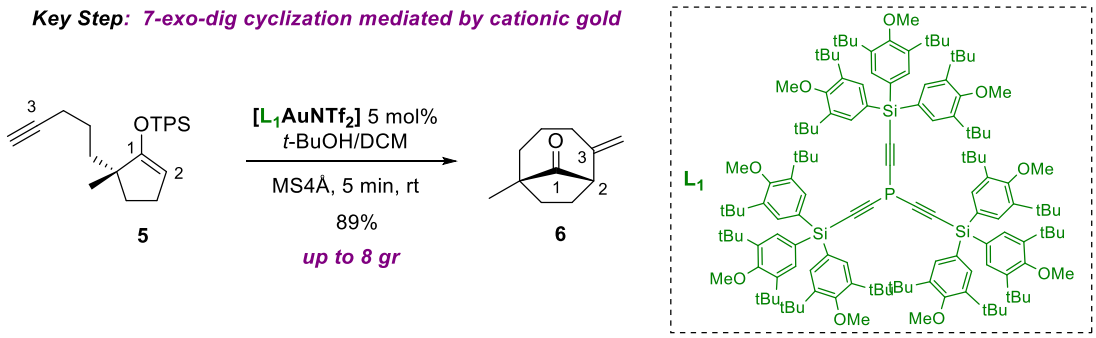


Figure 1

During our work on total synthesis of Vibsatin A **3** and B **4**, two diterpenoids isolated from *Viburnum tinus cv. Variegate* in 2014 by Zhao and co-workers,[4] we envisioned a intramolecular key cyclisation step mediated by gold catalysis involving a silyl enol ether and an alkyne **5** in order to build the [5-7] bicyclic core **6** of both vibsatins. After optimization of this crucial step, we were able to reach this bicyclic system in an efficient manner even in large scale (up to 8 gr). (Scheme 1)



Scheme 1

This kind of cyclization had previously been reported by Sawamura and coworkers for the synthesis of seven[5] or eight-membered rings.[6] Although this cyclization turned out to be very efficient, it suffers major drawbacks such as:

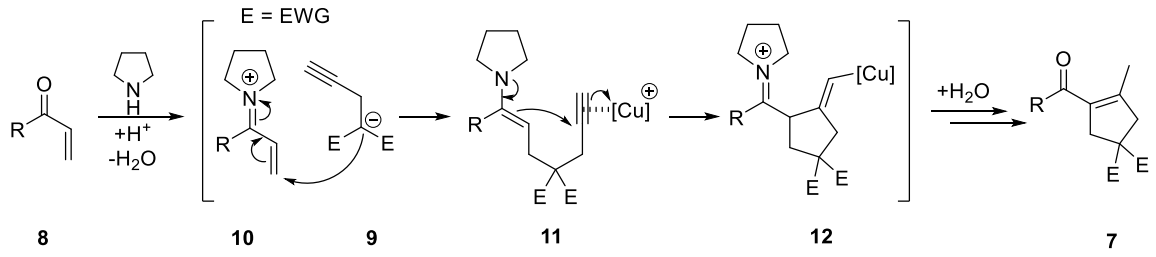
- Using a glove box

- High dilution, which can be restrictive in total synthesis when you need to perform a large scale reaction.

- The synthesis of a non-commercially available bulky phosphine, which required about 3 or 4 steps. Moreover, sometimes few steps were difficult to reproduce.

During his PhD work, Luca Allievi succeeded to overcome the issues concerning the glove-box and the high-dilution required for the cyclization reaction. However, despite the good results obtained for the 7-exo-dig-reaction, the catalyst remains expensive and the new conditions established by our group are not really easy to set up. To this purpose, we decided, in parallel of our total synthesis, to investigate a new way to access to the bicyclo[4.2.1]nonane skeleton of both vibsatins by another Conia-ene reaction.

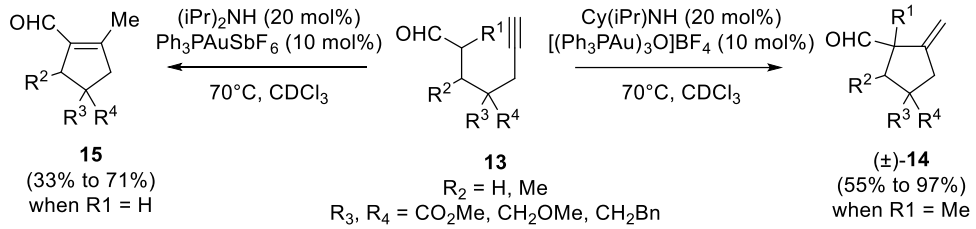
Since its discovery by Conia and Le Perchec in 1975, Conia-ène reaction has been intensively surveyed by several groups and numerous conditions have been reported like dual-activation, alkyne activation, and some other.[7] Among the myriad of published examples, two reports by Dixon[8] and Kirsche[9] have specially attracted our attention. In 2008, Dixon and co-workers reported a tandem reaction aiming to the synthesis of cyclopentenes featured with an exocyclic ketone **7** starting from an α,β-unsaturated ketone **8** and a homopropargylic malonate **9.** Pyrrolidine was elected as the organic catalyst and copper(II) triflate ($Cu(OTf)_2$) as the metallic counterpart. The authors also added PPh_3 since it was necessary to reduce Cu(II) into Cu(I) species. Thanks to these conditions, various linear and cyclic ketones were found suitable substrates for this reaction. In a mechanistic point of view, the pyrrolidine reacts with the ketone in order to generate a reactive iminium ion **10** which undergoes a Michael addition from the homopropargylic malonate, thus delivering the enamine **11.** Concomitantly, the metal activates the alkyne part allowing the cyclization to take place affording the vinyl copper **12**. Hydrolysis of the iminium restored the carbonyl whereas the protonation of the vinyl copper and subsequent isomerization delivered the cyclic σ,β-unsaturated ketone **7**. (Scheme 2)



Scheme 2

Although several five- and six-membered rings ketones were obtained by using these conditions, the access to seven membered rings were not reported by the authors.

The same year, Kirsch and co-workers reported the α-functionalization of aldehyde with unactivated alkyne by dual activation reaction involving Au(I) catalyst and a bulky secondary amine (Scheme 3). Hence, the authors described ε-alkynyl aldehydes and α-methyl ε-alkynyl aldehydes **13** reacting in 5-*exo*-dig cyclization in the presence of *N*-diisopropylamine or *N*-cyclohexylisopropylamine and a gold catalysts. α-Substituted aldehydes (R^1 = Me) afford exocyclic alkenes (±)-**14**, otherwise, α,β-unsaturated compounds **15** were delivered. Both $[(Ph_3PAu)_3O]BF_4$ and PPh_3AuSbF_6 are suitable catalysts but $[(Ph_3PAu)_3O]BF_4$ proved to be more resistant to decomposition and thus more appropriate than PPh_3AuSbF_6 when long time reaction were required such as the cyclization of α-substituted aldehydes. (Scheme 3)



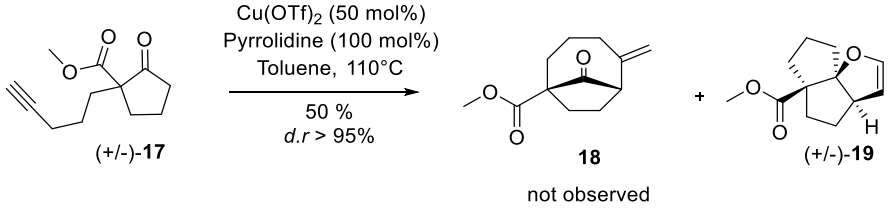
Scheme 3

Inspired by these two examples, we assumed that the cyclization to reach bicyclo[4.2.1]nonane skeleton of both vibsatins could also be possible by using a Conià-ene reaction involving a dual activation thanks to an amine and a copper salt. (Scheme 4)



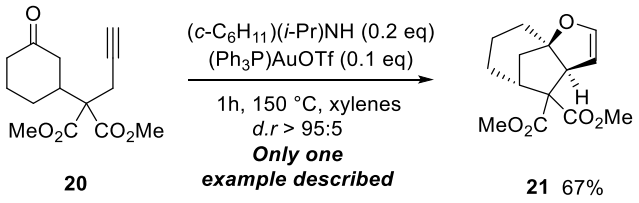
Scheme 4

In order to investigate the feasibility of such cyclization, we synthetized the simplified model **17**. Then, we performed a screening of several sources of copper and amine. Unfortunately, we never observed the expected bicyclic compound **18**. However, during our survey, we discovered a new compound **19**, which caught our attention.(Scheme 5)



Scheme 5

After careful NMR analysis, the structure proposed for **19** was a fused tricyclic core [5, 5, 5] including a 2,3-dihydrofuran part with three contiguous stereocenters. It is worth to mention that the reaction turned out to be highly diastereoselective since we observed only one isomer by ^{1}H and ^{13}C NMR. Regarding the literature, such transformation was, to the best of our knowledge, only reported once by Kirsch and co-workers in 2008 from the cyclohexanone derivative **20**.[9] (Scheme 6)



Scheme 6

This unexpected result was obtain by mixing cationic gold $(Ph_3P)AuOTf$ (0.1 eq) and bulky amine (*c*-C_6H_{11})(*i*-Pr)NH (0.2 eq) in xylene at 150°C for 1h! The authors mentioned only one example in their publication and no significant mechanism were provided to explain the synthesis of this congested tricyclic 2,3-dihydrofuran.

Intrigued by this transformation and the related mechanism, we decided to pursue our investigation. Unfortunately, these results were obtained at the end of the Luca's thesis. Hence, I was entrusted with the task of continuing this work in order to study this new reactivity in more depth.

II. Synthesis of 2,3-dihydrofuran units mediated by copper salts

2,3-Dihydrofurans subunits are, among the five-membered heterocycle derivatives, one of the most represented motifs which can be encountered in pharmaceuticals (for example: aflatoxin B1 **22** and clerodin **23**) as well as natural products (for example: azadirachtin **24** or austocystin A **25**). [10](Figure 2)

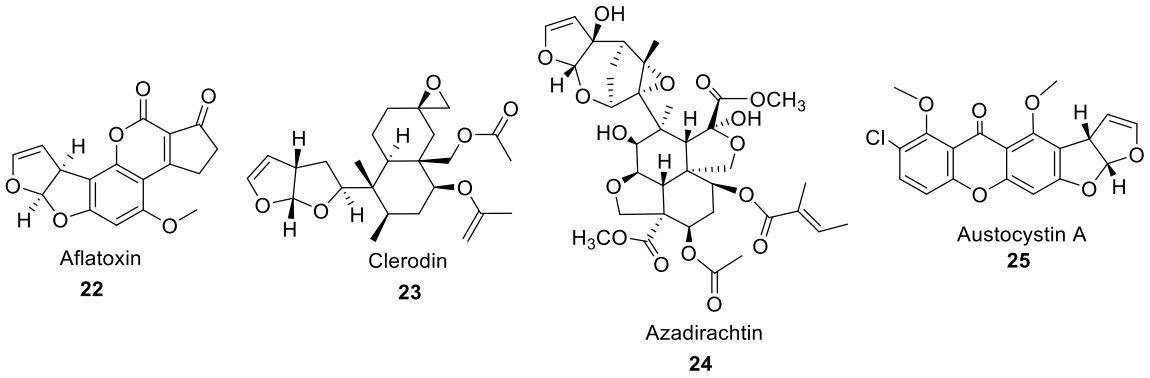


Figure 2

In addition, they can also be considered as useful synthetic intermediates, since they can be transformed into a broad array of functionalized tetrahydrofurans. Numerous methods have been developed and it will be fastidious to present all of them. In order to be concise, we will highlight in this chapter, a short and non-exhaustive overview of the cyclization methods reported to this date for the synthesis of 2,3-dihydrofurans using copper catalysis.

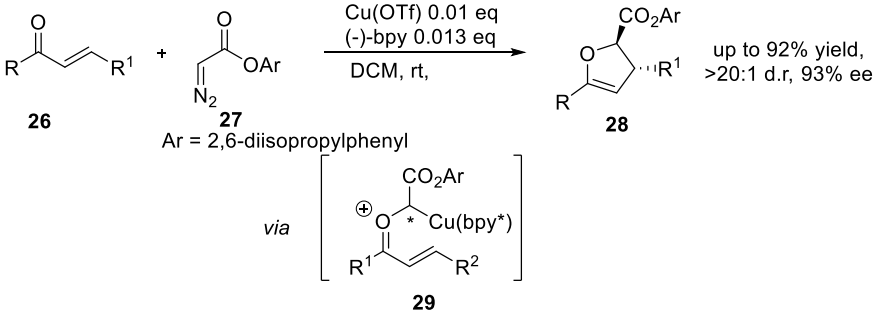
II.a State of art

Organic chemists have empowered their research field through the development and use of transition metals complexes in organic processes. [11] Transition metal-catalyzed reactions and specifically homogeneous catalysis have given a considerable impulse to the progress of the area of organometallic, organic and industrial chemistries. Homogeneous catalysis is fundamentally important and provides successful solutions to environmental and economic concerns. Indeed, in the area of pharmaceutical derivatives, the production of a high value compound generally results in the production of waste, several very costly purification steps that may reach 50% of the cost of the whole process.[12] Catalysis represents therefore one of the key points of sustainable chemistry. In this context, the use of coinage metals (copper, silver and gold) in organic synthesis is becoming particularly relevant, especially with the worldwide impact of green chemistry, since their use as catalysts is part of the 12 principles of "Green Chemistry" introduced by Paul Anastas and John Warner.[13]

Among the coinage metals, copper is far less expensive and it is present in large quantities in the earth crust avoiding its depletion. It's ability to react as a π-acid, oxidative reagent or Lewis acid makes it attractive for synthetic chemist. Copper salts has been used in myriad of chemical transformations including the synthesis of 2,3-dihydrofurans subunit. In the following chapter, we will briefly discuss about some transformations mediated by copper in the synthesis of 2,3-dihydrofuran motifs.

II.a.1 [4+1] Cyclization involving enones and dizao compounds

The first example of [4+1]-cycloaddition of β-methoxy-α,β-unsaturated ketones with ethyl diazoacetate, leading to furans has been published by Spencer in 1967 who reported that $CuSO_4$ catalyzes the upon elimination of methanol from the presumed 2,3-dihydrofuran intermediate.[14] In 2007, Fu and coworkers described an asymmetric version involving [4+1] cycloadditions of enones **26** with diazo compounds **27** catalyzed by a copper triflate and (-)-bpy as chiral inductor.[15] (Scheme 7)



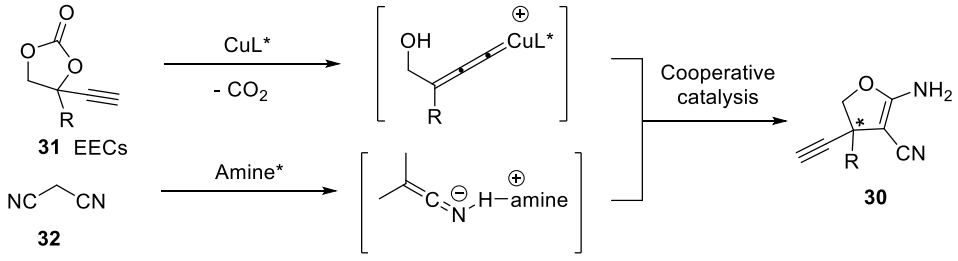
26 **27** **28** **29**

Scheme 7

The authors reported high yield (up to 92 yield and excellent diastereomeric ratio and enantiomeric excess.

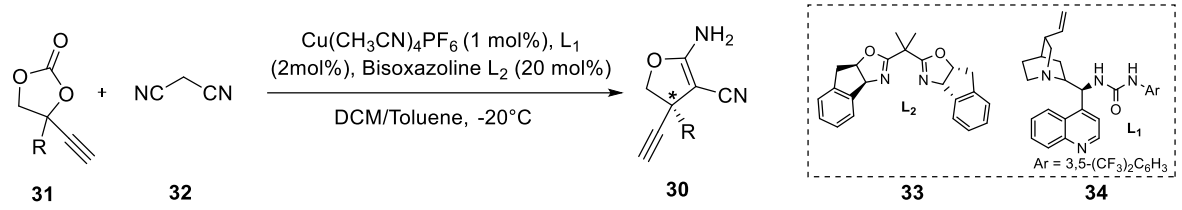
II.a.2 [3+2] Cyclization between Ethynylethylene carbonate (EECs) and malononitrile.

An elegant method has recently been described by Song and co-workers for the enantioselective construction of polysubstituted 2,3-dihydrofurans **30** utilizing various EECs **31** as 1,3-dipôle and malonitrile **32** as 1,2-dipôle surrogate.[16] Thanks to a cooperative catalysis, they generate both reactive partners in a same pot, which could react through a [3+2] cyclization.



Scheme 8

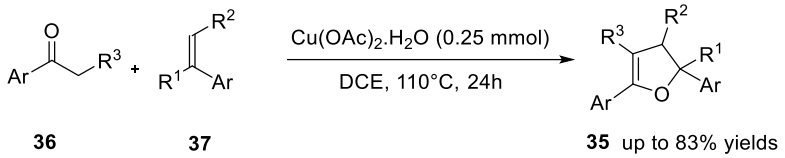
After a careful survey on chiral copper ligand and chiral amine catalyst, the best combination was the bis-oxazoline **L2 33** and urea-cinchona catalyst **L1 34**. Upon optimal condition, this strategy led to a broad range of enantiomerically pure 2,3-dihydrofurans **30** (up to 98% ee) in good yield (up to 98%).



Scheme 9

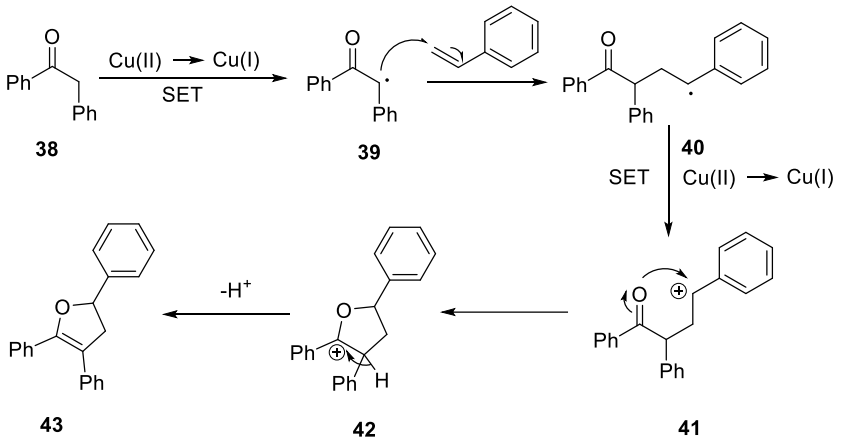
II.a.3 Copper mediated synthesis of 2,3-dihydrofuran by SET

Copper salts possess a versatile activity since they could also be employed in radical reaction. To this purpose, we can mention works reported by Maiti and collaborators in 2014 about the radical based strategy toward the synthesis of 2,3-dihydrofurans **35** from aryl ketones **36** and aromatic olefins **37** (Scheme 10).



Scheme 10

The mechanism proposed by the authors is based on successive single electron transfer (SET) where the copper (II) is reduced in copper (I) following the sequence below (Scheme 11).

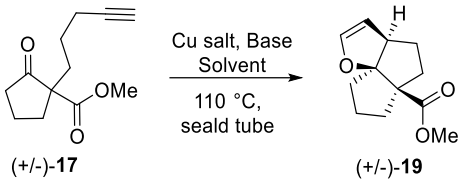


Scheme 11

II.b Copper mediated synthesis of 2,3-dihydrofuran by formal [3+2] cyclization

Despite the numerous method described in the literature for 2,3-dihydrofuran synthesis, developing new pathways remains attractive especially from readily available precursors and cheap reagent. Following the encouraging result obtained by Luca during his thesis, we decided to pursue this innovative work. We started to investigate the optimization of the reaction conditions, including Cu sources, bases and solvents. Numerous attempts have been performed during this survey. In order to lighten this manuscript, just a representative part of this work will be disclosed in the following table. All the reactions shown in the table were conducted at 110°C in a sealed tube.[17] The results are depicted in the Table 1

Table 1

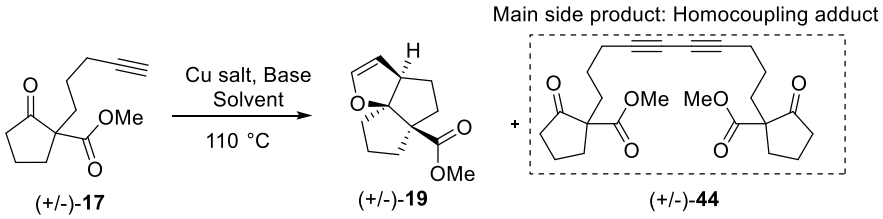


Entry	Cu salt (0.5 eq.)	Base[a]	Solvent	Time, Yield[b]%
1	$Cu(OTf)_2$	Pyrrolidine	Toluene	2h, 40%
2	$Cu(OTf)_2$	Dicyclohexylamine	Toluene	1h, 34%
3	$Cu(OTf)_2$	HMDS	Toluene	1h, n.r
4	$Cu(OTf)_2$	DIPEA	Toluene	1h, 38%
5	$Cu(OTf)_2$	Cyclohexylamine	Toluene	1h, 14%
6	$Cu(OTf)_2$	DIPA	Toluene	1h, 39%
7	$Cu(OTf)_2$	Morpholine	Toluene	1h, 9%
8	$Cu(OTf)_2$	DMAP	Toluene	1h, n.r
9	$Cu(OTf)_2$	DABCO	Toluene	1h, n.r
10	$Cu(OTf)_2$	NEt_3	Toluene	1h, 50%
11	$Cu(OTf)_2$	N-Methylmorpholine	Toluene	1h, n.r
12	$Cu(OTf)_2$	NEt_3	$(CH_3)_3CCN$	1h, 46%
13	$Cu(OTf)_2$	NEt_3	CH_3CN	1h, -[c]
14	$Cu(OTf)_2$	NEt_3	2-MeTHF	1h, 42%
15	$Cu(OTf)_2$	NEt_3	DMSO	1h, 32%
16	$Cu(OTf)_2$	NEt_3	DMF	1h, 51%
17	$Cu(OTf)_2$	NEt_3	1,4-Dioxane	1h, 24%
18	$Cu(OTf)_2$	NEt_3	*t*-BuOH	1h, 43%
19	$Cu(OTf)_2$	NEt_3	1,2-DCE	1h, 46%
20	**$Cu(OTf)_2$**	**NEt_3**	**NEt_3**	**1h, 60%**
21	CuCl	NEt_3	NEt_3	4h, 13%
22	$CuCl_2$	NEt_3	NEt_3	1h, -
23	$CuSO_4$	NEt_3	NEt_3	2h, 13%
24	$Cu(CH_3COO^-)_2.H_2O$	NEt_3	NEt_3	2h, 26%
25	**$[Cu(CH_3CN)_4]PF_6$**	**NEt_3**	**NEt_3**	**1h, 60%**
26	CuI	NEt_3	NEt_3	1h, n.r
27	CuSCN	NEt_3	NEt_3	1h, n.r
28	Copper Gluconate	NEt_3	NEt_3	1h, 10%
29	$Cu(CH_3COO^-)_2$	NEt_3	NEt_3	1h, 47%

[a] Each attempt was conducted with 1 eq. of base. [b] Yield calculated from ^{1}H-NMR. [c] Only traces of expected product were detected by ^{1}H-NMR.

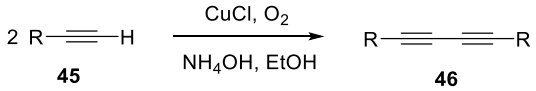
At the beginning of the optimization, we carried out a series of experiments using 1,3-keto ester **17** as a model substrate which was treated with different base. The reaction proceeded with primary amines (14%, Entry 5), secondary amines (40%, Entry 1 and 39%, Entry 6) and tertiary amines (50%, Entry 10 and 38%, Entry 4). However, DMAP, DABCO, *N*-methylmorpholine or HMDS were revealed not suitable for this transformation since no reaction was observed. The best result was obtained with NEt_3 (50%, Entry 10). A series of high boiling point solvents were next screened since this transformation needed to be conducted at high temperature (110 °C). A large range of solvents is well tolerated by the reaction giving the tricyclic dihydrofuran **19** in moderate to good yield (from 24% to 60% Entry 12 and Entry 14-19) but only traces of the cyclized product was detected after 1h by using CH_3CN (Entry 13). Surprisingly, the highest yield was obtained when NEt_3 was used as solvent (60%, Entry 20). Afterwards, different copper salts were used to conduct this reaction. As shown in the Table 1 (Entry 21-29), the source of copper salts is crucial and only $[Cu(CH_3CN)_4]PF_6$ (60%, Entry 25) and $Cu(CH_3COO^-)_2$ (47%, Entry 29), provided the dihydrofuran **19** in good yield. Considering the lower price of $Cu(OTf)_2$ compared with $[Cu(CH_3CN)_4]PF_6$, $Cu(OTf)_2$ in NEt_3 at 110 °C were selected as the best condition.

Through this optimization survey, we pinpointed the main issue to reach better yields. We often observed the formation of homocoupling product **44** as observed by Luca during his first trials (Scheme 12).



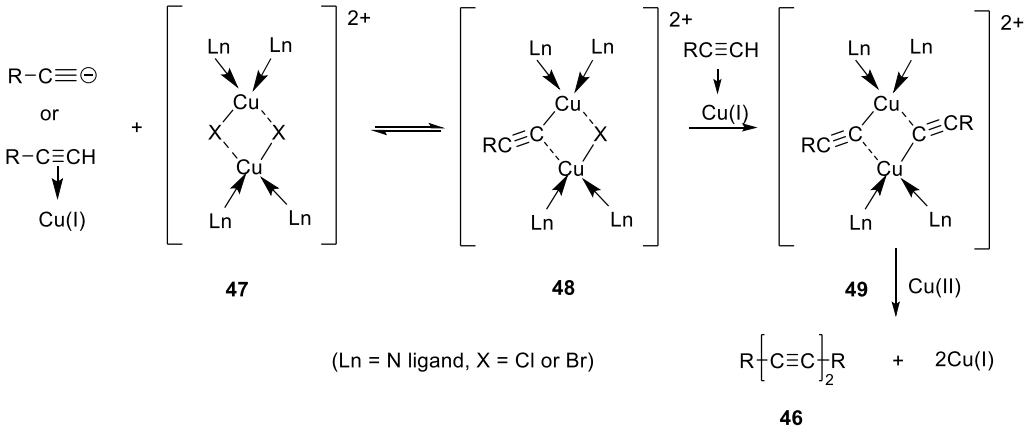
Scheme 12

This well-known homocoupling reaction is named Glaser-Hay coupling. The Glaser coupling is a strategy of oxidative homocoupling between terminal alkynes **45** based on copper salts and an additional oxidant like oxygen. This reaction was first reported by Carl Glaser in 1869 (Scheme 13).[18]



Scheme 13

Glaser coupling of alkynes is an important tool in organic synthesis,[19] and its widely accepted mechanism proposed by Bohlmann and co-workers, is shown in Scheme 14.[20]

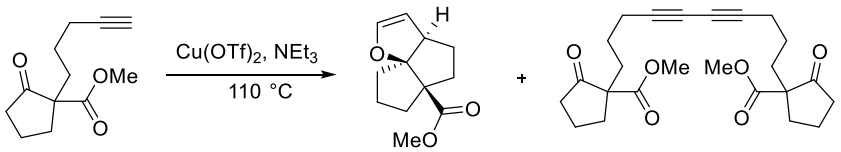


Scheme 14

In this mechanism, the coupling reaction begins with the π-coordination of the triple bond to a copper(I) species **47**, enhancing the acidity of the terminal proton that can be abstracted by an external base. The corresponding copper(II) dimers **49** is formed by oxidation from copper(I)-σ-acetylide **48**. At last, the homocoupling product **46** is obtained by a fast bimetallic reductive elimination regenerating copper(I).

In a recent report, Jeffrey T. Koberstein et al.[21] demonstrated that adding excess reducing agents can prevent Glaser coupling of alkynes. Inspired by their results, we screened different parameters such as adding antioxidant reagent, setting up the reaction on more diluted media or varying the temperature, the catalyst loading in order to reduce or to suppress the homo-coupling side reaction. These conditions are depicted in the Table 2.

Table 2



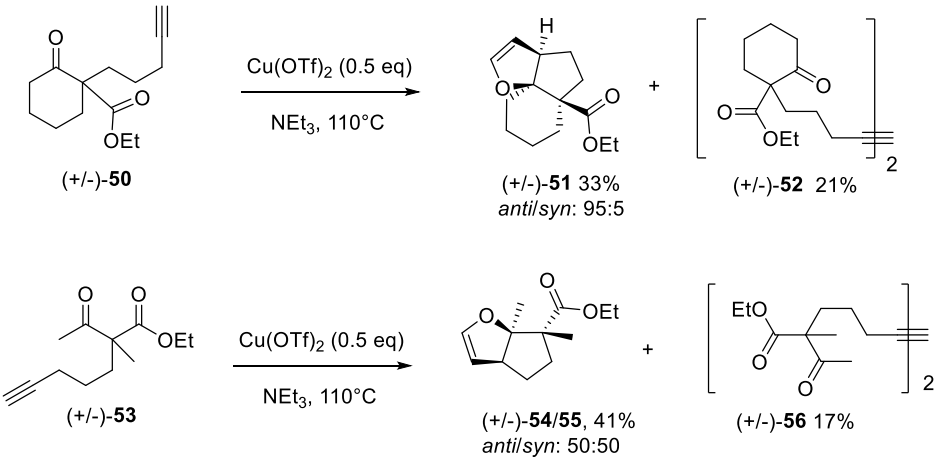
Entry	$Cu(OTf)_2$ (eq.)	Additional reagent	Time, Yield[a]%
1	0.25	-	1h, 55%
2	0.125	-	1h, 53%
3	0.05	-	16h, 20%
4	0.025	-	16h, 17%
5	0.5	-	1h, 57%[b]
6	0.5	BHT (2 eq)	2h, only **44**
7	0.5	L-Ascorbic acid sodium (2 eq)	2h, 48%
8	0.5	L-Ascorbic acid sodium (10 eq)	2h, 45%
9	0.5	L-Ascorbic acid sodium (20 eq)	5h, 54%
10	0.5	L-Ascorbic acid sodium (50 eq)	4h, 53%
11	0.5	50 °C	4h, only **44**
12	0.5	80 °C	4h, only **44**

13	0.5	-	1h, 52%[c]
14	0.5	Microwave (130 °C)	5 min,only **44**

[a] Yield calculated from ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard. [b] NEt_3 was freshly distilled and degassed prior to use. [c] Reaction carried out at 0.1M

No improvements were detected when we ran the reaction with different amount of copper(II) triflate (Entry 1-4). Besides, oxygen or other oxidants are also required for the Glaser coupling. Based on this mechanistic consideration, we tried to remove the oxygen in our media. Unfortunately, performed the reaction in a freshly distilled and degassed NEt_3 did not bring better results (Entry 5). Curiously, adding BHT to the reaction (2 eq) yielding only homo-coupling by-product **44** (Entry 6). Afterwards, L-ascorbic acid sodium salt was also tried but even with 50 equivalents, our different attempts did not afford satisfying results (Entry 7-10). In their paper, Koberstein and coworkers also proposed that the Glaser coupling reaction can be suppressed by maintaining the reaction at low temperature.[21] Accordingly, we conducted this reaction at 50 °C and 80 °C instead of 110 °C, yet only homo-coupling side product **44** was detected (Entry 11 and 12). Running the reaction in more diluted media was also ineffective (Entry 13). Finally, we ran the reaction under micro-wave activation. This kind of activation is known to considerably reduce the reaction time and maybe it was possible to discriminate one transformation (Glaser coupling) against the other one (cyclization reaction). However, this attempt was not conclusive too and only the homocoupling adduct **44** was obtained.

Finally, we tried other substrates to see if Glaser Coupling was still an issue for this transformation. We experimented six-membered ring substrates **50** and linear ketones **53**. As shown in Scheme 15, this side reaction still occurred, significantly undermined the success of expected cyclization reactions and therefore decreasing the conversion of starting materials in favour of expected product.



Scheme 15

All trials carried out for the optimization were not totally satisfying to pursue the screening of this reaction. In particular, we were not able to overcome the issue of Glaser coupling thus compromising

good yields for this transformation. In addition, during these works we met some trouble about the reproducibility and we were unfortunately unable to furnish good explanations about these issues. Despite the fact that the non-expensive copper makes this methodology very interesting and promising, we envisioned to move on and switch to another coinage metal to study this transformation in more depth. In this context, silver salt appeared to be a good alternative for us.

III. Synthesis of 2,3-dihydrofuran mediated by silver salts

III.a Introduction

In the last few decades, transition metals have emerged as powerful tools in organic chemistry. Among them copper, silver and gold named « coinage metals », and belonging to the last raw borderline between main elements and transition metals, have exhibited unique reactivity especially towards unsaturated systems having low-lying empty orbitals especially alkynes. This strong alkynophilicity, linked to their d^{10} electronic configuration, may furthermore be reinforced by the proximity of *f* orbitals and relastivistic effects.[22]

In this domain, due to its moderate Lewis acidity, silver has been neglected by organic chemists for a long time and its derivatives were, at the beginning, mainly considered for their halogenophilicity[23] and oxidizing capability.[24] It has broadly been used, for example, in stoichiometric amounts for oxidation of aldehydes to give carboxylic acids by the well-known Ag(I)-based Tollens' reaction.[25]

However, recently, a renewed interest has grown for silver salts especially thanks to their ability to activate alkynes and more generally π-systems, which has been highlighted.[26] Moreover, silver(I) salts have been extensively used for anion metathesis (anion exchange, halogen scavengers) in order to enhance the reactivity of transition metals such as Au, Pd, Cu, Rh, Ru and Pt.[27] Through numerous applications, silver salts have shown very interesting and promising activities in intriguing transformations.[27,28] In addition, silver is relatively inexpensive compared to other late transition metals (Rh, Ir, Au, Pt or Pd ..).

Finally, in an environmental point of view, the use of silver complexes is also interesting due to their relatively low toxicity.

Faced with the dimerization issues of copper salts (chapter II.b), we envisioned the use of silver salts. Several studies proved that silver salts are powerful π-activators for C-C multiple bond (Figure 3).[29,30,31]

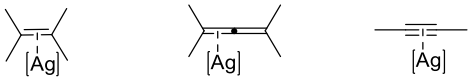


Figure 3

More specifically, as copper salts, silver salts are prone to activate triple bond rendering them electrophilic and capable to undergo a nucleophilic attack (Figure 4). In the presence of a terminal alkyne and a base, alkynyl silver can also be easily prepared via a concomitant activation of the triple bond and a deprotonation step.[32] In that case, the generated alkynyl silver can react either as a nucleophile or can be engage in cross-coupling reaction through a transmetalation process (Figure 4).[33] The reactivity of alkynyl silver is well-known and well documented. [34]

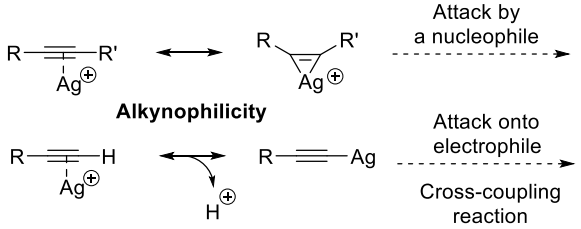


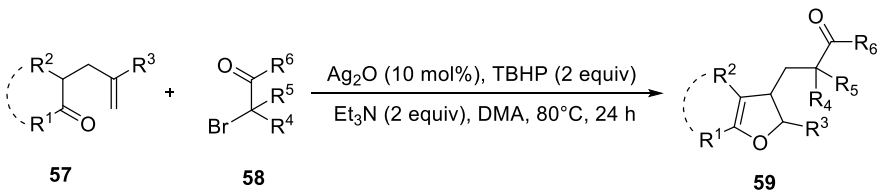
Figure 4

In addition, silver salts are capable to act either or both as a soft σ-Lewis acid (C-O or C-N bonds) or π-Lewis acid such as carbonyl or imine.[35,36] So silver salts can play many roles during a chemical transformation. Thanks to this versatile reactivity, silver salts have been employed in numerous synthesis of heterocycles and in particular in 2,3-dihydrofuran synthesis. A brief overview of the literature dealing with this topic will be presented below and more specifically with silver oxide(I) as catalyst.

III.b State of art

III.b.1 Silver oxide(I) catalyzed synthesis of 2,3-dihydrofurans via radical pathway

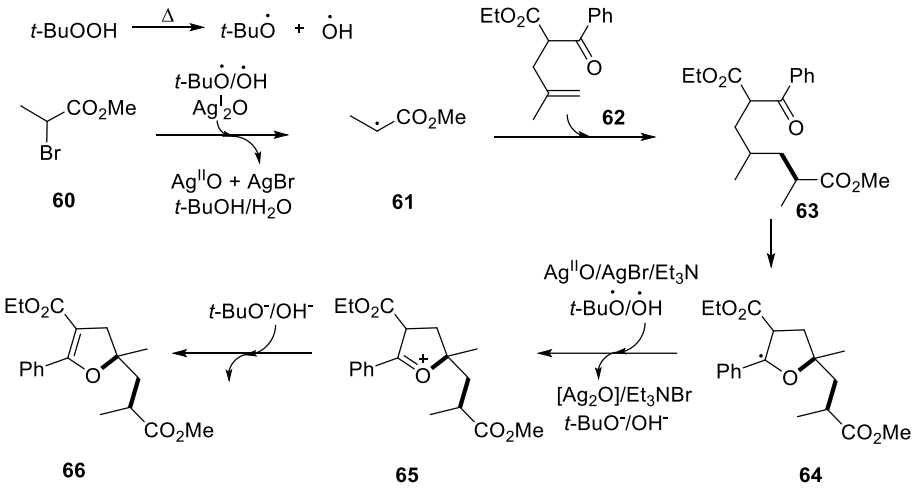
In 2019, Li and co-workers described a new and general silver-catalyzed 1,2-alkyletherification of olefinic carbonyls **57** with α-bromoalkyl carbonyls **58** for accessing a broad range of 2,3-dihydrofuran skeletons **59** (Scheme 16).[37]



57 **58** **59**

Scheme 16

The mechanism postulated by the authors relies on C–Br oxidative functionalization/annulative oxygenation process thanks to the radical pathway depicted below (Scheme 17).

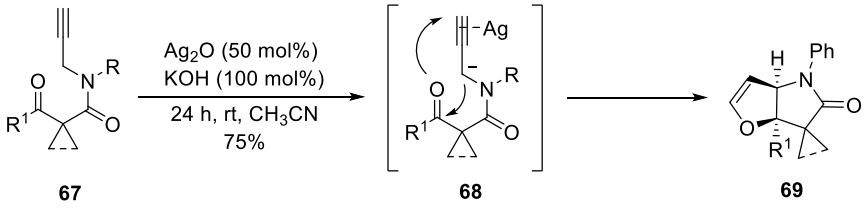


Scheme 17

These assumptions are supported by control experiments as running the reaction with a radical scavenger (TEMPO) which inhibits the production of 2,3-dihydrofurans frameworks. The authors mentioned excellent levels of selectivity as well as high functional group compatibility.

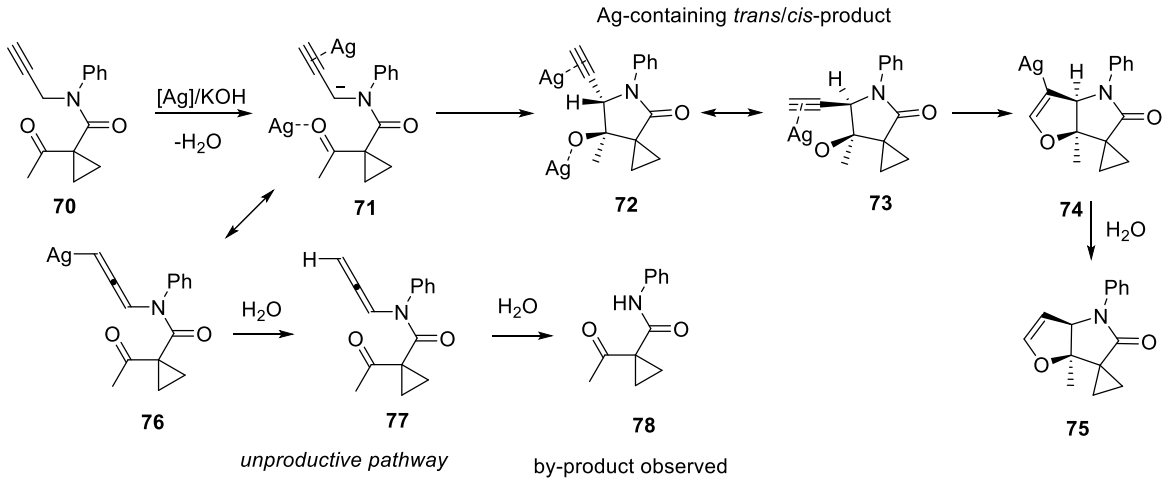
III.b.2 Silver oxide(I) catalyzed [3,2-b]-β/γ-lactams synthesis

In 2010, Zhang and coll. reported the synthesis of [3,2-b]-β/γ-lactams **69** by intramolecular formal cycloaddition between a *N*-propargylamide moiety and a ketone.[38] After a careful screening of silver salts, they were able to generate all-carbon 1,3-dipoles under basic conditions. (Scheme 18)



Scheme 18

Zhang obtained good yield (up to 81%) and excellent diastereoselectivities (up to 95/5 in favor of the *cis*-adduct) for this transformation. They suggested the following mechanism in order to explain the selectivity observed during the formation of the [3,2-b]-β/γ-lactams.(Scheme 19)

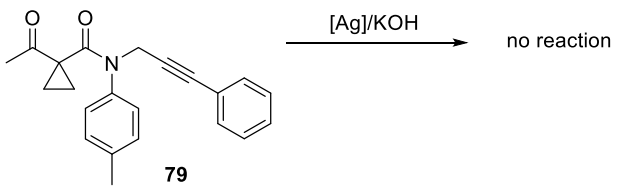


Scheme 19

The mechanism proposed by Zhang and coll., is a stepwise [3+2] cycloaddition mediated by silver(I) oxide, where silver(I) oxide act as a σ- and π-activator. After complexation of triple bond by the silver, the propargylic position is deprotonated by a strong base (KOH) thus generating the propargylic anion which is in equilibrium with the allenyl silver specie. Concomitantly, silver activates the ketone part thus facilitating the attack of the propargylic carbanion **71**. The attack by the carbonyl can happen on both sides leading to a mixture of the *cis*/*trans* isomers in equilibrium. At this stage, only the *cis* intermediate can cyclize pushing the equilibrium towards the formation of the *cis* adduct, thus delivering the corresponding 2,3-dihydrofuran derivative with excellent diastereoselectivity.

During the reaction, the authors observed the formation of **78**, a very minor side-product, which could result from the hydrolysis of the corresponding allenamide **77**. Based on this, they propose the allenyl silver intermediate **76** in equilibrium with the propargylic carbanion **71** as precursor of this unproductive pathway.

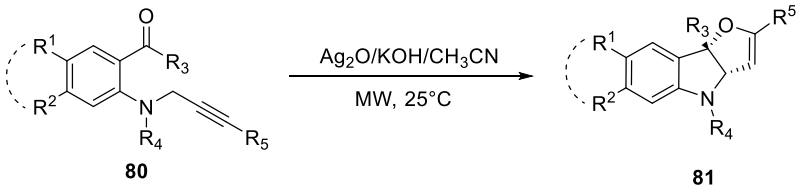
Interestingly, Zhang and coworkers described only one trial with a substituted alkyne **79** and no reaction was observed (Scheme 20).



Scheme 20

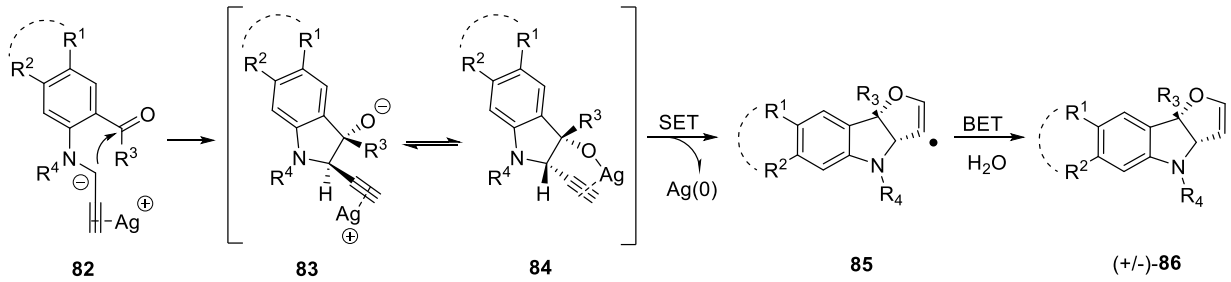
Moreover, we can underline that all cited cyclized compounds in the publication were obtained from terminal alkyne.

Two years later, Zhang et al. disclosed the synthesis of furo[3,2-b]indole **81** frameworks by silver(I)-mediated [3+2] cycloaddition under microwave assistance from various propargylamide derivatives **80** (Scheme 21).[39]



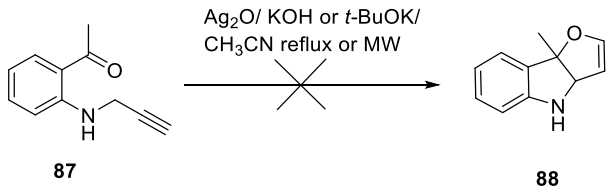
Scheme 21

Thanks to this activation mode, authors have considerably reduced the reaction time from 24 h (rt, without MW) to 1.5 h (25 °C, with MW). Regarding the mechanism, Zhang and coworkers postulated a similar mechanism as the first cyclization depicted in Scheme 19. Regarding the second ring closure reaction, authors envisioned a SET (Single Electron Transfer) and BET (Back Electron Transfer) sequence as shown below (Scheme 22).



Scheme 22

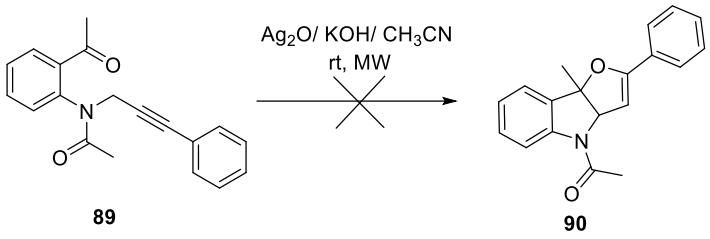
In their reported works, Zhang et al. pinpointed two important pieces of information. In one hand, the reaction doesn't work if the nitrogen is not substituted by an electro-withdrawing group. Several reaction conditions have been manage on 1-[2-(prop-2-yn-1-ylamino)-phenyl]ethanone **87** however no cyclized product has been detected (Scheme 23).



Scheme 23

According to the authors, the acidity of the methylene group was not strong enough thus prohibiting its deprotonation by KOH.

On the other hand, the authors reported only one reaction with the substituted alkyne **89**. However, under their optimized conditions, no reaction occurred (Scheme 24).



Scheme 24

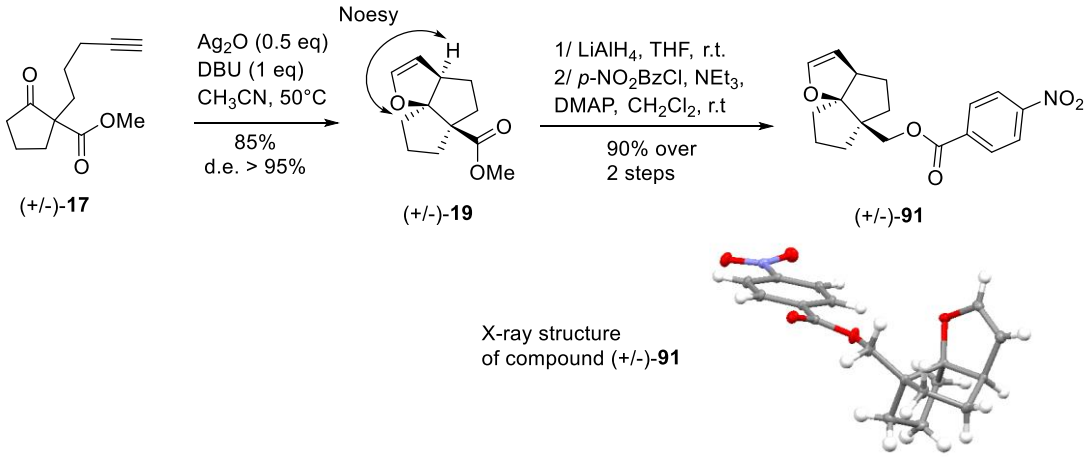
Unfortunately, in their two reports, Zhang *et al.* did not bring any explanations about the lack of reactivity of their system towards substituted alkynes.

III.c Ag_2O/DBU promoted synthesis of 2,3-dihydrofuran derivatives

III.c.1 Introduction

As seen in the previous chapter, during our work on total synthesis of Vibsatin, we discovered a new and unexpected bicyclic product. After an important optimization work, we were able to isolate the 2,3-dihydrofuran derivatives **19** in a good yield (see Table 1) by using $Cu(OTf)_2$ in NEt_3 in a sealed tube at high temperature. However, we encountered some difficulties about the reproducibility of the reactions and especially, we were not able to suppress the Glaser-coupling despite the addition of reductant in the media. In addition, the conditions developed were harsh and not suitable for sensitive reactants. For this reason, we looked for new conditions for this transformation. Silver salts appeared to us a good alternative since it possess similar activity to copper towards alkyne. Although some examples of Glaser couplings about alkynyl silver are described in the literature, their propensity to undergo such coupling is much less than their copper counterpart.

In a preliminary survey, we chose the combination of Ag_2O/DBU in acetonitrile and 1,3-keto ester **17** as substrate. To our delight, we were pleased to find a complete and clean conversion of **17** into the tricyclic compound **19** at 50°C after 2h (Scheme 25).



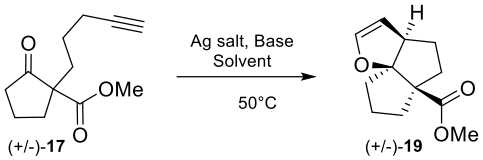
Scheme 25

The cyclized product was obtained in 82% yield with a total diastereoselectivity in favour of the *cis*-adduct without the detection of homo-coupling product. The stereochemistry was determined by nOe experiment and further confirmed by a single-cristal X-Ray diffraction analysis of *p*-nitrobenzoyl derivative **91** obtained after reduction of the ester **19** by $LiAlH_4$ and subsequent esterification of the resulting alcohol with the *p*-nitrobenzoyl chloride (90% yield over two steps) (Scheme 25).

III.c.2 Optimization of reactional conditions

Encouraged by this preliminary result, we focused on the optimization of the reaction conditions onto the β-keto-ester **17** (Table 3).

Table 3



Entry	Catalyst equiv.	Base[a]	Solvent	Time, Yield[b]%
1	Ag_2O 0.5	DBU	MeCN	2h, 85%
2	$AgNO_3$ 1.0	DBU	MeCN	2h, 64%
3	Ag_2SO_4 0.5	DBU	MeCN	3h, 32%
4	$AgSbF_6$ 1.0	DBU	MeCN	30h, 63%
5	Ag_2O 0.5	K_2CO_3	MeCN	12h, 80%
6	Ag_2O 0.5	NEt_3	MeCN	20h, -[c]
7	Ag_2O 0.5	Pyrrolidine	MeCN	20h, 80%
8	Ag_2O 0.5	DBU	DMF	2h, 76%
9	Ag_2O 0.5	DBU	Toluene	2h, 85%
10	Ag_2O 0.5	DBU	THF	2h, 84%
11	Ag_2O 0.5	DBU	NMP[d]	3h, 38%
12	Ag_2O 0.5	DBU	*t*-BuOH	28h, 75%
13	Ag_2O 0.5	-	MeCN	24h, n.r
14	-	DBU	MeCN	24h, n.r
15	Ag_2O 0.5	DBU	MeCN	24h, n.r[e]
16	Ag_2O 0.5	DBU	MeCN	3h, 85%[f]
17	$P(Ph)_3AuOTf$ 0.1	pyrrolidine	toluene	2h, n.r[g]

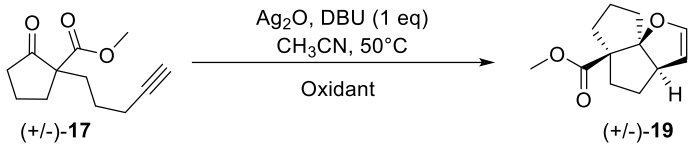
[a] Each attempt was conducted with 1 eq. of base. [b] Isolated Yield. [c] Only traces of expected product were detected by ^1H after 20h.[d] NMP = N-Methyl-2-pyrrolidone. [e] Reaction performed at r.t instead of 50°C. [f] Reaction performed with 0.1 eq of DBU [g] Reaction performed at 110°C.

A short screening of silver salts highlighted the ability of inexpensive silver(I) oxide to cleanly promote the cyclization after 2 h with a satisfying yield (85%, Entry 1). Silver nitrate and silver antimonate afforded **19** albeit in moderate yields, respectively 64% and 63% (Entry 2 and 4) whereas silver sulfate furnished only 32% of the desired product (Entry 3). The reaction proceeded smoothly with K_2CO_3 as a base (80%, Entry 5) and pyrrolidine (80%, Entry 6) but only traces of the cyclized product were detected after 20h by using NEt_3 (Entry 7). Interestingly, the reaction is able to proceed in a wide range of solvents, providing **19** in satisfying yields (Entry 8-10 and 12). However, NMP was

not suitable for the reaction even after a prolonged time (Entry 11). In order to underline the crucial role of the silver and DBU, we ran different test reaction. Thus, without DBU (Entry 13) or silver(I) oxide (Entry 14) no reaction was observed, establishing that the combination of silver reagent and base is mandatory to promote such cyclization. The optimized conditions were used at room temperature but no reaction was observed after 24h (Entry 15). A catalytic amount of DBU (0.1 eq) can also be used without lengthening the reaction time and good yield (85%) was obtain (Entry 16). Finally, we tried the gold catalyst used by kirsch et al. in a similar conditions that those reported by the authors ($P(Ph)_3AuOTf$ (0.1 eq), pyrrolidine and toluene at 110°C in sealed tube, Entry 17) but no product was detected after 2h.

We wanted to increase the efficiency of this transformation by reducing the silver(I) oxide loading. To this aim, we performed the cyclization reaction in the presence of different oxidants (Table 4).

Table 4



(+/-)-**17** (+/-)-**19**

Entry	Ag_2O equiv.	Oxidant	Yield %, time[a]
1	0.25	none	78%, 48h
2	0.25	Air Balloon	46%, 48h
3	0.25	O_2 Balloon	83%, 24h
4	0.25	O_2 bubbling and Balloon	79%, 70h
5	0.125	O_2 bubbling and Balloon	n.r after 70h
6	0.25	O_2 Balloon	25%, Not finished after 43h
7	0.125	O_2 Balloon	n.r after 43h
8	0.25	CeO_2 3 equiv.	35%, 48h messy
9	0.25	$K_2S_2O_8$ 3 equiv.	n.r after 48h
10	0.25	$PhI(OAc)_2$ 1 equiv.	n.r after 48h

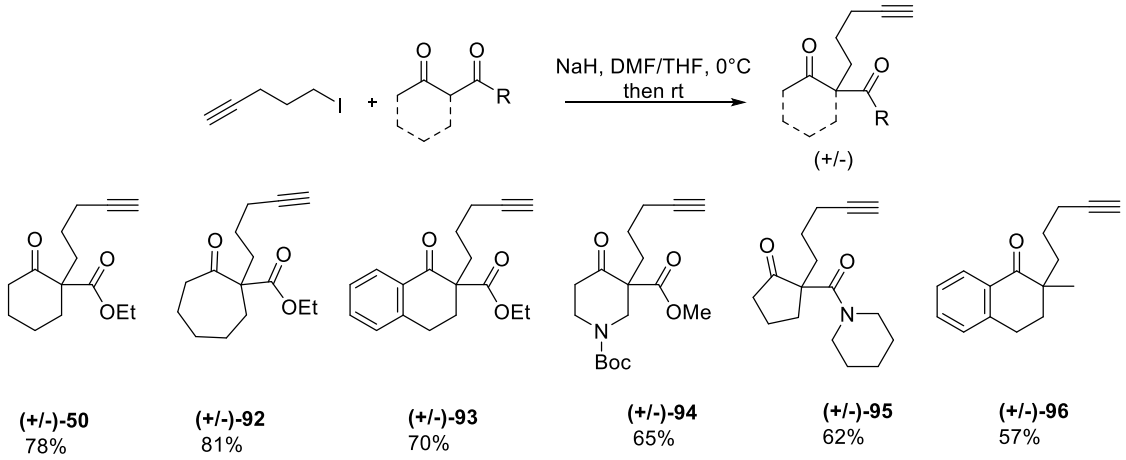
[a] Time was measured after TLC shows complete or sufficient disappearance

We tried the reaction with 0.25 equivalent of Ag_2O without oxidant and we obtained the tricyclic compound **19** in 78% yield after 48 hours reaction (Entry 1). Conducting the reaction under air balloon decreased the yield to 46 % (Entry 2) whereas using O_2 balloon (Entry 3) yielded 2,3-dihydrofuran derivatives in 83 %. However, this reaction has been conducted twice and was revealed not reproducible since the second time, compound **19** was obtained only with 25% yield (Entry 6).[40] Prior O_2 saturation of the solvent by a bubbling of O_2 followed by carried out the reaction under O_2 balloon afforded a similar yield (79%, Entry 4) but a longer reaction time (70 h). Using similar conditions and decreasing Ag_2O loading to (0.125 eq) had no reaction (Entry 5 and Entry 7). We performed the reaction with oxidative agents, respectively CeO_2, $K_2S_2O_8$ or $PhI(OAc)_2$ but messy crude (Entry 8) or no reaction were observed (Entry 9 and 10).

The condition developed herein appeared to be difficult to attain in a catalytic fashion since these reaction suffer a major reproducibility issue. However, the silver(I) oxide is one of the cheapest silver salts commercially available.[41] For this reason, we pursued our studies by using 0.5 eq of Ag_2O since the reaction is fast and provide very clean crude. In the same manner, the reaction can be conducted with a catalytic amount of DBU (Table 3, Entry 16) but for accuracy and reproducibility considerations, we performed the scope studies with 1 eq of DBU.

III.c.3 Scope investigations

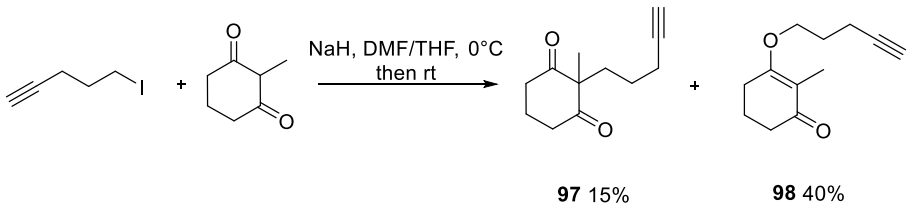
In order to get tricyclic compounds similar to **17,** we started by the synthesis of various cyclic ketone containing the right distance with the reactive alkyne function. To this aim, we performed the alkylation between malonate type cyclic ketone and freshly prepared 5-iodopent-1-yne following a standard procedure depicted Scheme 26.



Scheme 26

We chose malonate type cyclic ketones since some of them are commercially available and the reaction of alkylation is very easy to handle. However we don't think that the presence of the ester moiety is crucial for the cyclization reaction. Thanks to this sequence, we obtained six precursors in a good range of yield (between 57% and 81%).

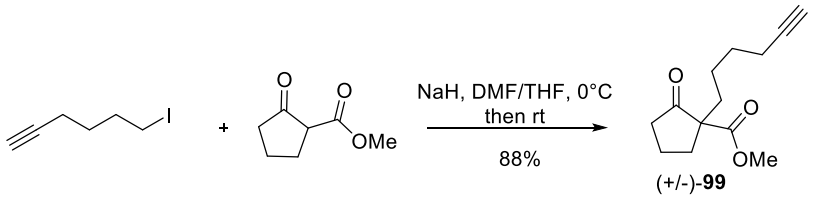
In the same way, we carried out this alkylation reaction on 2-methylcyclohexane-1,3-dione. However, we encountered some difficulties since this compound showed a strong propensity to undergo an *O*-alkylation (Scheme 27).



Scheme 27

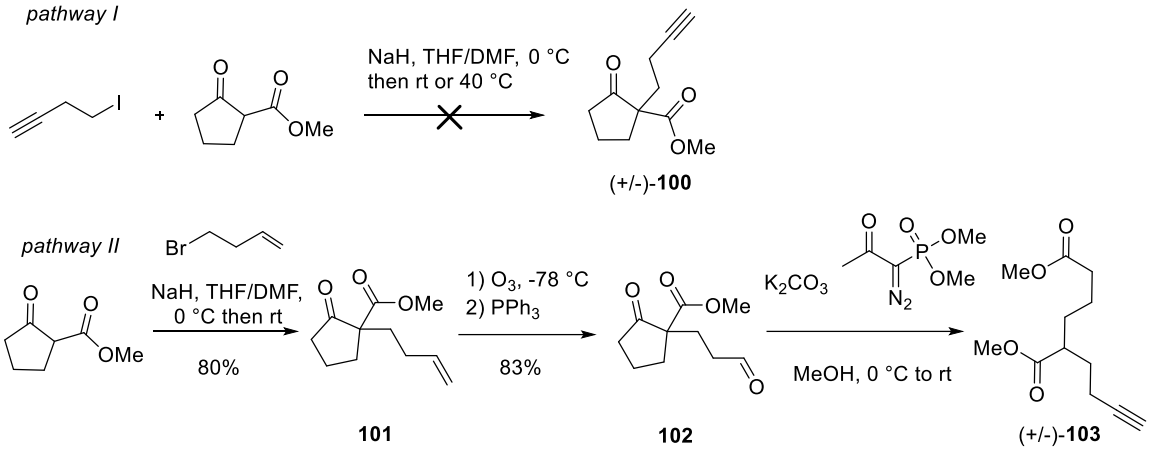
Thus, we isolated only 15% of the expected compound **97**. This reaction has not been optimized.

Similarly, we also prepared a cyclization precursor from 6-iodohex-1-yne and methyl 2-oxocyclopentane-1-carboxylate in order to get an analog with a longer chain (88% compound **99)** (Scheme 28).



Scheme 28

Unfortunately, access to shorter chain cyclization precursor was not productive despite several reactional conditions screened (Scheme 29).



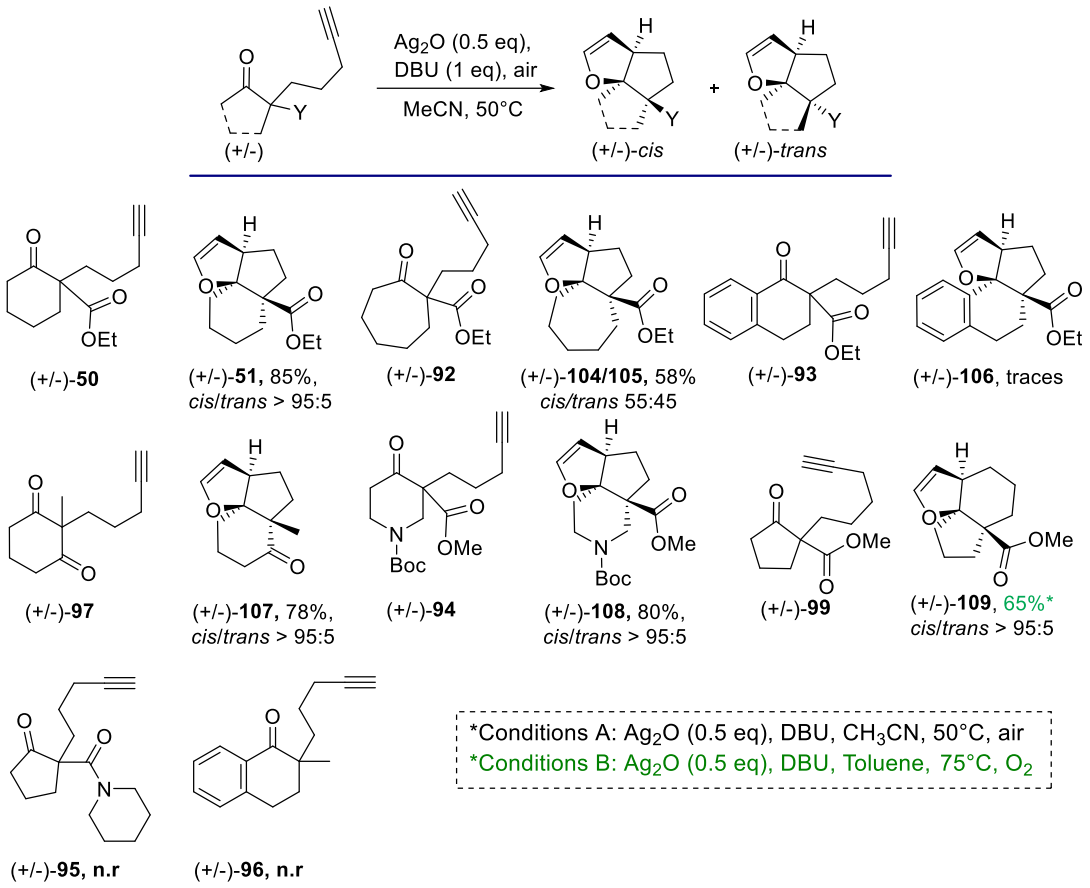
Scheme 29

By alkylation reaction involving 4-iodo-but-1-yne or and methyl 2-oxocyclopentanecarboxylate at low temperature or at 40 °C, no reaction happened (pathway I). We hypothesized that the nucleophilic center was too hindered and couldn't approach the electrophilic center. Thus only a reaction of deprotonation then elimination of the 4-iodobut-1-yne happened, prohibiting the reaction.

To circumvent this issue, a multi-reactional sequence described in the literature on a closer example was attempted (Scheme 29, pathway II). [42] In the first place, we alkylated methyl 2-oxocyclopentanecarboxylate with commercially available 4-bromobut-1-ene (80 % yield). The double bond was then submitted to oxidative cleavage by ozonolysis, delivering the corresponding aldehyde **102** in 83% yield. Unfortunately, subsequent introduction of the triple bond by using Ohira-Bestmann reagent was not effective since a concomitant ring opening side-reaction afforded the diester **103** as a major product. This kind of reaction has already been described in the literature under similar conditions.[43]

Faced with these problems, we decided to give up the synthesis of a shorter chain analog.

With different cyclization precursors in hand, we next investigated the scope of the reaction under our optimized conditions (Ag_2O: 0.5 eq., DBU: 1 eq. in MeCN, [C] = 0.24 M). We first investigated the behavior of various cyclic ketones (Scheme 30):



Scheme 30

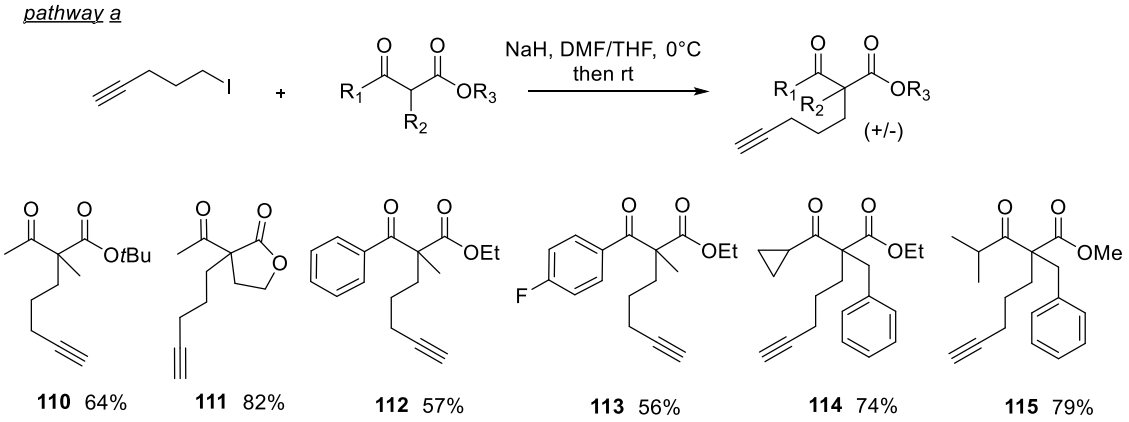
The cyclization of five **17** or six-membered ring substrates **50** occured under mild conditions and good yields were obtained (up to 85%) with a total diastereoselectivity in favour of the *cis*-adduct. We assumed that the selectivity is imposed by the configuration at the spiro carbon. Hence, for geometry and distance considerations, the ketone can only be attacked in a *syn*-periplanar fashion leading to the (+/-)-*cis*-isomer. Surprisingly, seven-membered ring analog **92** was reluctant to cyclize and two equivalents of silver were necessary to attain a good conversion. Additionally, the cyclized products **104/105** were obtained as a mixture of two diastereoisomers (55:45 by ^{1}H NMR) probably due to a higher conformational flexibility. Starting from the naphtalenone derivative **93**, no cyclization occurred even under heating in a sealed tube at 100 °C.[18] Tricyclic ketone **107** was obtained in 78% yield from the corresponding symmetrical diketone **97**. Noteworthy, these cyclization conditions were also suitable to heterocyclic compounds and piperidine derivative **108** could be isolated in satisfying yield (80%). To our delight, using conditions B (see Scheme

33) allowed the extension to substrate with longer chain **99** in order to reach six-membered-ring analog with good yield and high selectivity for the *cis*-isomer **109**. Bulkier compound **95** or **96** did not work with conditions A or B, even under micro-wave assistance.

Thanks to this methodology, we were able to access to complex and congested tricyclic compounds having a 2,3-dihydrofuran subunit in an easy way from readily accessible cyclic ketones. High yields and diastereomeric ratio were obtained in a general manner.

In a second time, we wanted to investigate the behaviour of linear ketones addressing, among other things, interesting questions about diastereoselective issues. To this aim, we synthetized various β-keto-ester derivatives by two standard methods:

In the first way, the pathway a, 5-iodopent-1-yne and different malonate containing methyl or benzylic groups between both carbonyls were employed (Scheme 31).

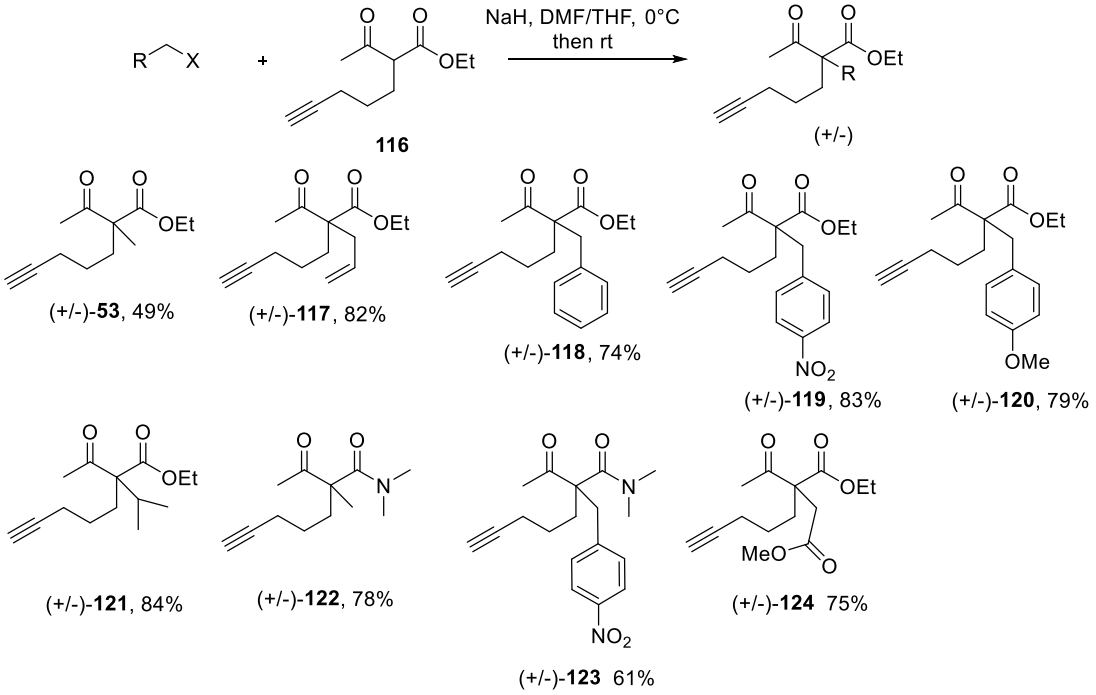


Scheme 31

By this way, we synthesized six precursors of cyclization with different steric hindrance in α position of the ketone and/or size of ester. All compounds were obtained in good yields (56% to 82%).

In the second way, the alkylation reaction between the ethyl 2-acetylhept-6-ynoate **116** and various electrophiles was applied (pathway b, Scheme 32).

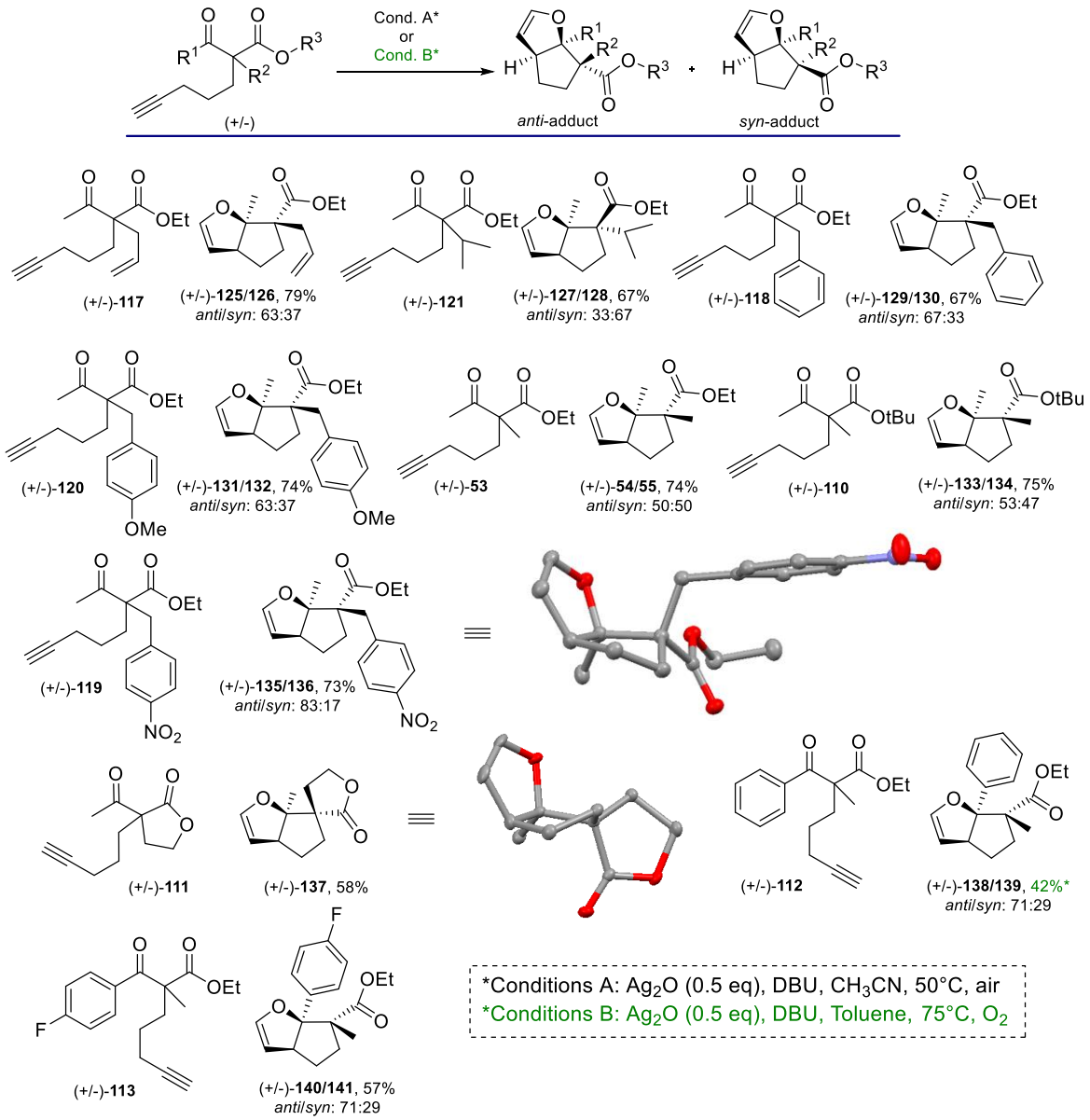
pathway b



Scheme 32

Thanks to this reaction sequence, we modulated the functional groups between the two carbonyls. In addition, we prepared two amide analogs. All the precursors were obtained in satisfying yield (49% to 84%) and were next subjected to our optimized conditions.

The reactivity of linear ketones was surveyed by varying the substitution of the malonate, the nature of the ketone and/or the influence of the functional group in β-position.

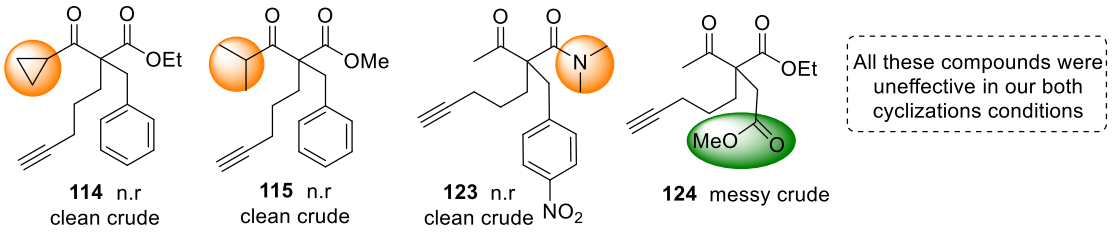


Scheme 33

We first studied the behavior of different linear compounds towards the optimized cyclization conditions by tuning the nature of the substituent in α position to the ketone (R^2). Substitution by an allylic chain (compound **117**) as well as neutral- (**118**) or enriched- (**120**) benzylic chains was not deleterious to the reaction and good reactivities were observed along with modest selectivities in favor of the *anti*-adduct (63:37, 67:33 and 63:37, respectively). Astonishingly, the diastereomeric ratio raised to 83:17 when the aromatic moiety was substituted by a *p*-nitro group (**119**). A bulkier isopropyl chain **121** delivered the corresponding bicyclic compound in 67% yield with inversion of the diastereomeric ratio in favour of the *syn*-adduct (**128**), evidencing that the steric hindrance at this position is not detrimental to the reaction but strongly influences the selectivity. Modification of the size of the ester provided the expected 2,3-dihydrofurans in good yields, however without notable improvement of the diastereoselectivity. On the contrary, the *anti*-isomer **137** was exclusively

obtained with 58% yield when the lactone **111** was used. Unlike benzylic ketone **113**, ketone **112** was reluctant to cyclize under conditions A while applying conditions B afforded good conversion, providing bicyclic compounds **140/141** and **138/139** (in 57 and 42% yield, respectively) with a similar selectivity towards the *anti*-isomer, along with degradation products.

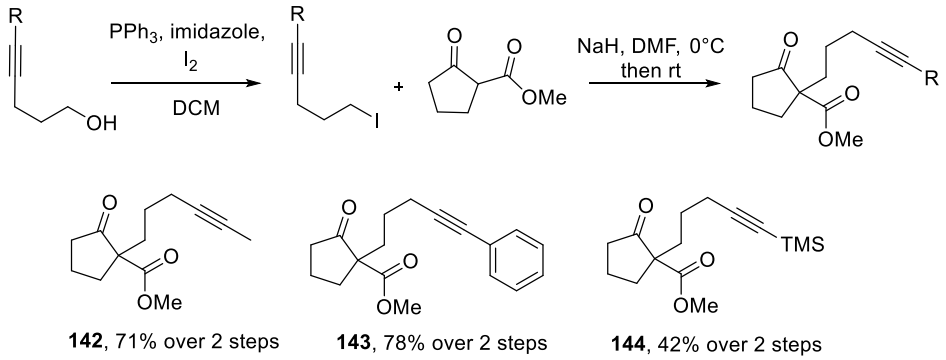
However, some starting materials were reluctant to cyclize in both conditions even after a prolonged time.



Scheme 34

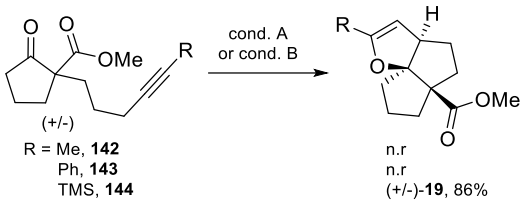
In regards to the results obtained during our cyclization reactions, some limitations have emerged (see Scheme 30, Scheme 33, Scheme 34). Firstly, compounds having a strong steric hindrance close to the ketone part (compounds **114**, **115**) turned out unproductive. Secondly, compounds having amide moiety seems more difficult to cyclize and sometimes are unable to cyclize **123** whereas the compound **124** having a methoxyester turned out to be very (or maybe too) reactive in both conditions (even at rt) since we observed the disappearance of the starting material but always leading to a complex mixture of products.

Finally, the substitution pattern of the triple bond was next examined. To this aim, three precursors bearing either methyl (**142**), phenyl (**143**) or TMS (**144**) groups have been synthetized following the sequence depicted below (Scheme 35).



Scheme 35

All these compounds were submitted to conditions A (or B) (Scheme 36).



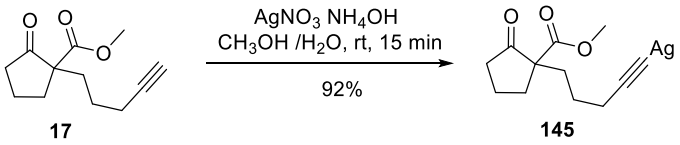
Scheme 36

Reactions onto **142** or **143** were ineffective under both conditions (A or B). On the contrary, when trimethylsilylalkyne **144** was submitted to conditions A, it was smoothly converted into the cyclized product **19** (R = H). This result suggests a preliminary insertion of silver into the C-Si bond, which is consistent with the well-known propensity of terminal alkynes and TMS alkynes to undergo a metalation step under similar conditions.[44],[45],[46],[47].

III.d Mechanistic studies

III.d.1 Synthetic pathway

In order to get insight into the mechanism, we synthetized and isolated the alkynyl silver **145**. Alkynyl silver can be easily obtained by mixing silver nitrate and terminal alkynes or TMS alkynes in a mixture of MeOH and water. We managed the reaction onto the alkynyl compound **17**. After filtration, the residue was quickly washed with cold MeOH and dried under high vacuum yielding the expected alkynyl silver as a white solid (92%) (Scheme 37). Unlike the alkylsilver, which are notoriously unstable, alkynyl silver are quite stable against moisture and air (sometimes). Indeed, they can be stored over weeks but they must be protected from the light. Thus, they can be prepared and stored before to perform a reaction.



Scheme 37

In 2005, Pale and coworkers evidenced the formation of hexyn-1-yl silver by recording ^{1}H, ^{13}C and ^{109}Ag NMR. Inspired by these works, we performed numerous NMR studies on compound X but unfortunately, we were unable to properly observe the alkynyl silver. Nevertheless, we could confirm the presence of the alkynyl silver by mass spectroscopy (two isotopes: ^{107}Ag and ^{109}Ag) (Figure 5).

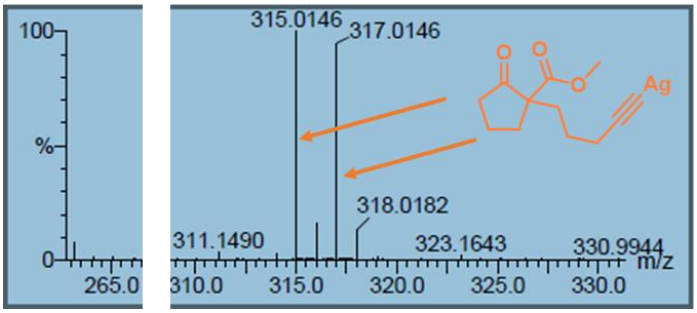
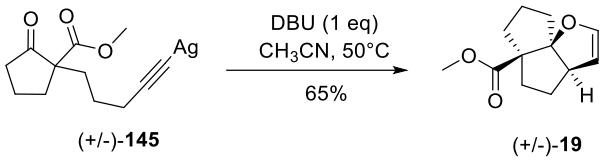


Figure 5

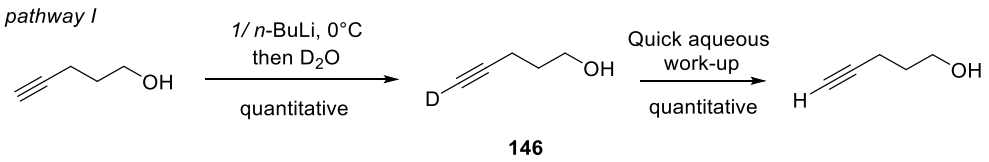
In order to evidence the primary insertion of the silver into the C-H bond of the alkyne moiety, we performed the cyclization reaction directly from the alkynyl silver **145**. To this aim, we only added DBU (1 eq) and CH_3CN (same concentration as usual) and heating at 50°C (Scheme 38).



Scheme 38

We obtained the corresponding tricyclic compounds **19** in a good yield 65%. Thus, we confirmed that the first step of the reaction was the formation of the alkynyl silver or more precisely, alkynyl silver **145** could be an intermediate of the reaction.

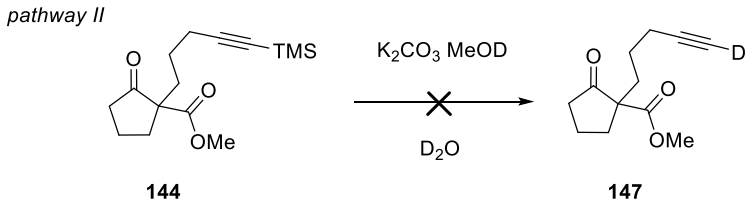
We also envisioned the deuteration of the alkyne in order to follow the displacement of the deuterium on the triple bond. So, we started by the synthesis of the 5-iodopent-1-yne-1-d **146** following the sequence described by Borhan and coworkers (Scheme 39).[48]



Scheme 39

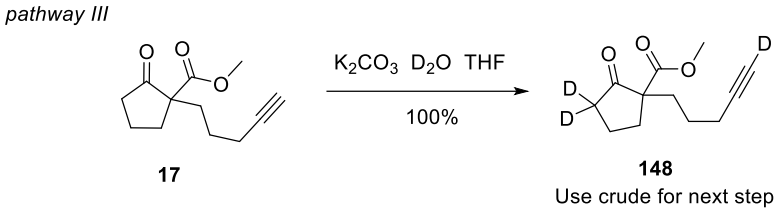
We observed a complete deuteration by crude ^1H NMR, however, in our hand, we lose the deuterium during the work-up with brine.

A straightforward access consisted in the deprotection of the TMS alkyne **144** in deuterated media following the procedure depicted by Chen and coworkers.[49] We submitted the β-keto ester **17** to a mixture of K_2CO_3/MeOD/D_2O, but we didn't observe the expected product. The crude was messy and showed, among other products, the compound corresponding to the ring opening (see Scheme 29) (Scheme 40).



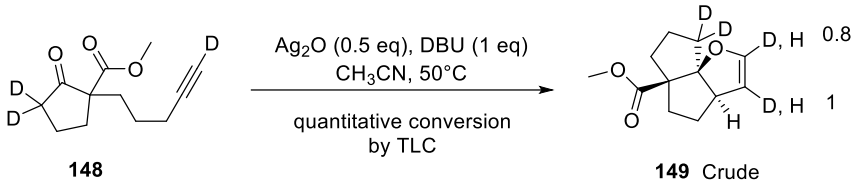
Scheme 40

Finally, the easiest way to attain the deuterated compound was the use of K_2CO_3 in a mixture of THF/D_2O delivering the product **148** in a quantitative yield (Scheme 41). However, we observed an over deuteration reaction since one or two deuterium were also integrated in α position of the ketone.



Scheme 41

The crude product **148** was directly used under our cyclized conditions for the next step (Scheme 42).



Scheme 42

The crude ^1H NMR showed a ratio 0.8 to 1 between the ethylenic protons (Figure 6).

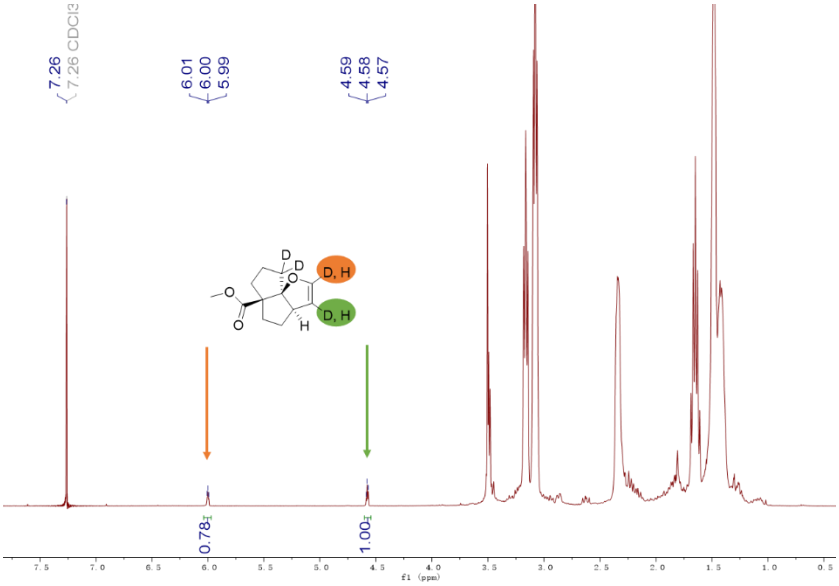
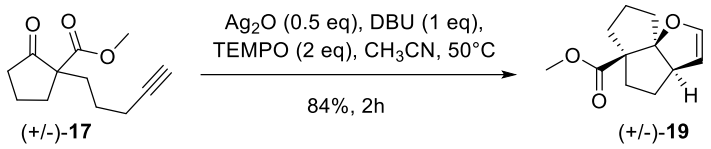


Figure 6

This result suggests that the H carried by the triple bond moves during the reaction and can be trap latter in the reaction by both ethylenic carbons in almost equal manner. In addition, this result confirms the formation of the alkynyl silver intermediate during the reaction.

In order to exclude any radical mechanism, we performed the reaction in the presence of a large amount of TEMPO (2 equivalents) as a scavenger of radical species (Scheme 43).

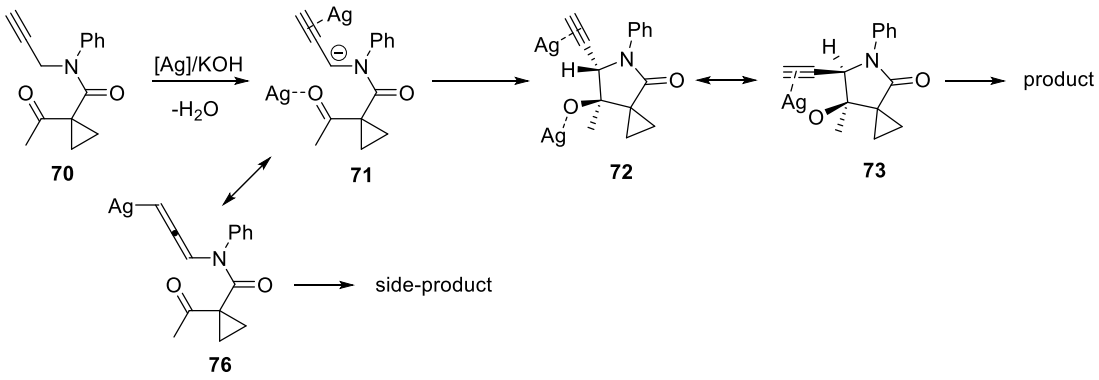


Scheme 43

Although the reaction became slightly slower (2h instead of 1h), we got the cyclized product in a similar yield, evidencing that the reaction did not include any formation of a radical intermediates during the reaction.

With all these mechanistic investigations in hand, we could affirm that the first reaction was the formation of the alkynyl silver (see Scheme 36, Scheme 38 and Scheme 42). However, we cannot obtain the first five membered ring by this way. The mechanism proposed by Zhang and coworkers is unclear regarding the first cyclization. Indeed, in the meantime, there is a complexation of the silver onto the alkyne moiety and a deprotonation leading to a carbanionic specie. Then, the propargylic anion attack the carbonyl delivering the first cycle whereas the allenyl specie which is in equilibrium with the propargylic carbanion, lead to the side-product (Scheme 44).

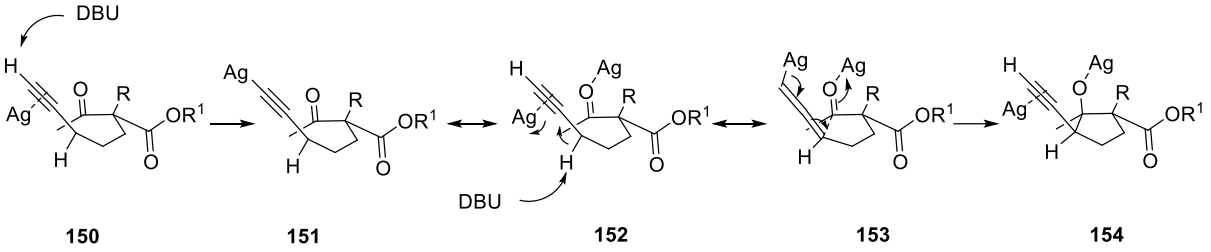
First steps of the cyclization proposed by Zhang et al.



Scheme 44

However, in their both papers, Zhang et al. mentioned that the reaction doesn't take place when the alkyne is substituted (see Scheme 20 and Scheme 24) which would suggest the preliminary formation of the silver alkyne as we also observed during our mechanistic studies. Based on these considerations, we postulated the mechanism displayed below (Scheme 45).

first part of the postulated mechanism



Scheme 45

In order to clarify the mechanistic pathway as well as the nature of the nucleophile attacking the ketone during the first cyclization, we managed DFT calculations. A collaboration was initiated with our partners from the Chemical Theory and Modeling group at Chimie Paris, Dr Ilaria Ciofini and Anna Perfetto.

They studied the first five steps of the Ag(I) mediated cycloaddition reaction mechanism by means of Density Functional Theory (DFT) approaches.[50] The computed reaction path together is presented in Figure 7. Several conformers/approaches have been computed for **B** and **BH**$^+$ species. The data reported here correspond to the arrangements of the **B/BH**$^+$ and reactants providing the lowest energies.

A multistep pathway is proposed to explain the reaction mechanism up to the first cyclization process involving the carbonyl group and carbons of alkynyl residue (Figure 7).

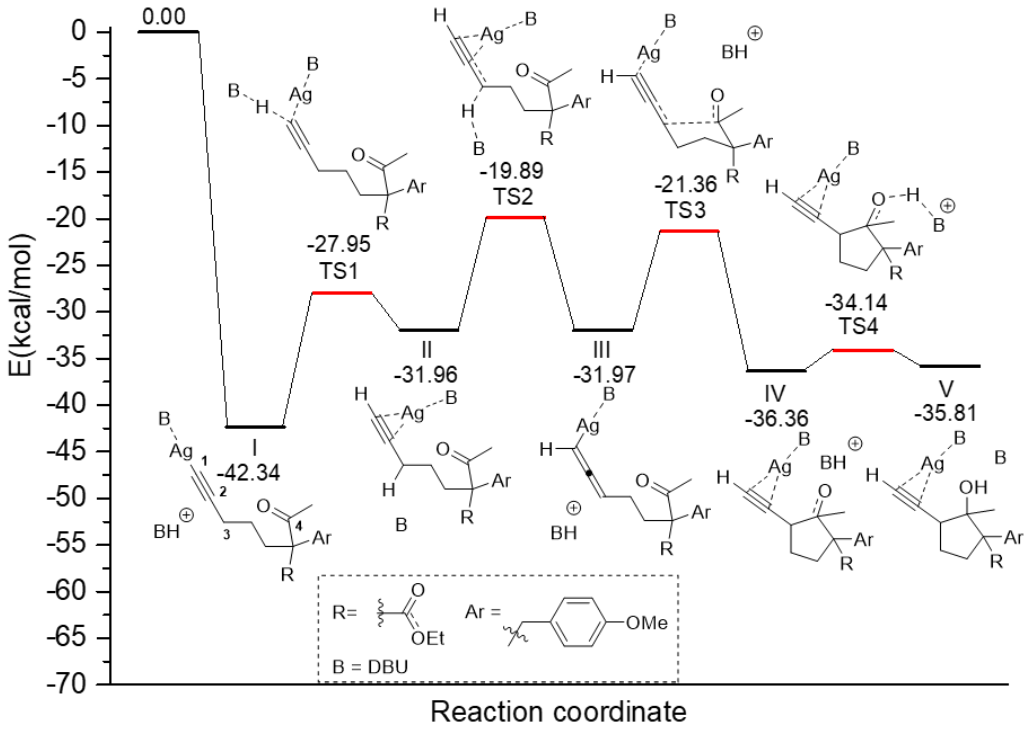
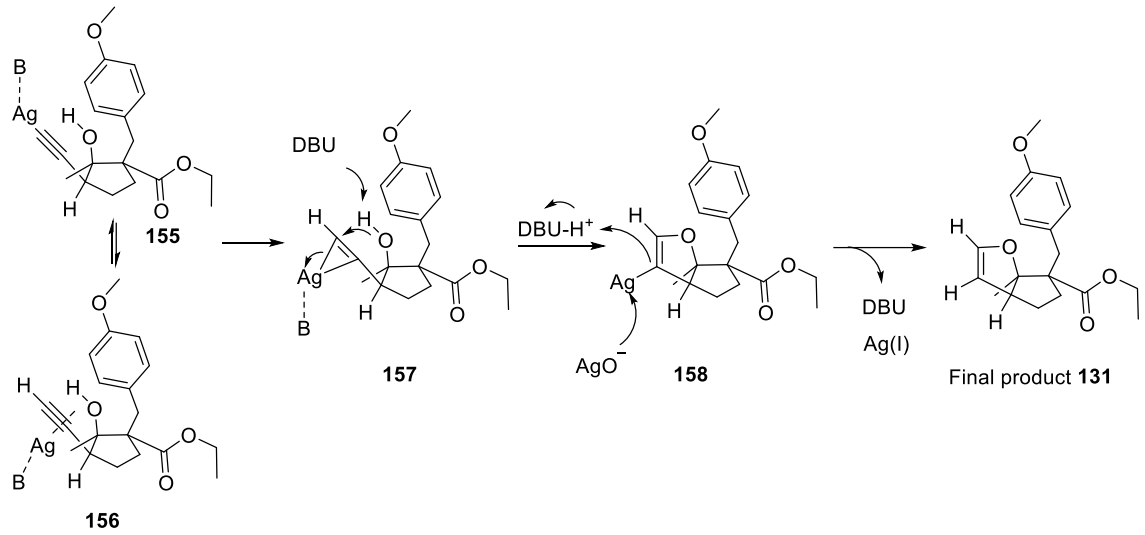


Figure 7

The analyzed reaction mechanism proceeds through five steps. Starting from the very stable silver alkynyl intermediate (**I**), the initial step corresponds to the proton transfer from conjugated acid of DBU (BH^+ in Figure 7) to **I** leading to the formation of intermediate **II**. This step proceeds with a barrier of 14.40 kcal/mol and leads to the formation of stable intermediate **II**. A subsequent proton transfer from **II** to DBU (B in Figure 7) generates the silver allenyl intermediate (**III**). The energetic barrier to overcome for its formation is found to be 12.07 kcal/mol (Figure 7). Of note the back reaction from **II** to **I** is characterized by a very small barrier so that we can assume that **I** is easily reformed. Following the energetic span model,[51] we can therefore assume that the energy span is related to the difference between the energy of **I** and **TS2**, leading to an effective barrier of 22.45 kcal/mol determining the reaction turnover. The **III** allenyl intermediate is characterized by practically equivalent C_1-C_2 and C_2-C_3 bonds (1.30 Å). From this intermediate, a first cyclization occurs *via* the **TS3** transition state: the C_3-C_4 bond decrease achieving a value of 2.20 Å and suggesting the closure of the cycle. **TS3** lies at 10.61 kcal/mol higher in energy with respect to the **III** and leads to the formation of intermediate **IV**, characterized by a C_3-C_4 bond of 1.57 Å and thus by a fully formed 5-carbon cycle. Of note in **IV** the silver atom approaches the oxygen (Ag-O bond of 2.15 Å), while C_1-Ag and C_2-Ag are elongating up to 2.70 Å. Comparing the atomic (Mulliken) charges computed for the **TS3** and the **IV**, it is found that C_4 becomes more electrophilic (from -1.91 |e-| to -0.22 |e-|), while the oxygen becomes more nucleophilic (from -0.34 |e-| and -0.49 |e-|). This makes possible to envisage a proton transfer from the conjugated acid BH^+ of DBU to the oxygen atom of **IV**. The very low energy barrier (2.23 kcal/mol) computed for this reaction confirmed this hypothesis. In the corresponding transition state (**TS4**), the Ag atom is found to bridge the oxygen and the alkynyl lateral group (C_1-Ag, C_2-Ag, Ag-O bonds in the 2.30-2.40 Å range), while the C_4-O bond is elongated up to 1.41 Å and the O-H bond is forming (1.21 Å). Indeed, the **V** intermediate shows a proton bonded to the oxygen (O-H bond 1.02 Å) and the silver atom coordinated to the carbons of alkynyl residue (C_1-Ag, C_2-Ag around 2.30-2.35 Å).

At this stage, the reaction proceeds *via* a second cyclization process involving the alkynyl lateral group and the oxygen to form the 2,3-dihydrofuran cycle (Scheme 46).[52] This reaction is found to be catalytic in silver by the authors.

second part of the postulated mechanism



Scheme 46

As the first step, we could envision an equilibrium between the alkynyl silver **155** and the silver complexation onto the triple bond **156**. At this stage, a deprotonation by DBU and subsequent cyclization onto the alkyne would deliver the silver alkene **157**. Silver counter-ion would displace the silver(I), then the resulting carbanion **158** could be protonated by the conjugated acid of DBU. Finally, DBU and Ag(I) would be release at the end of the mechanism and be available for another run.

However, we are not totally convinced by this mechanism since we were not able to properly run the reaction with a catalytic amount of silver(I) oxide. In addition, at the end of the reaction, we always observed a silver mirror (Ag(0)) and a dark grey insoluble powder which could be silver nanoparticules prohibiting a catalytic pathway.

Zhang and coworkers postulated for the second ring closure a SET (Single Electron Transfer) and BET (Back Electron Transfer) process (see Scheme 22) delivering the 2,3-dihydrofuran and releasing Ag(0) at the end of the mechanism. The authors mentioned in their report[39] the formation of a grey powder which is elemental silver. Regarding this observation, Zhang et al assumed that Ag would plays an oxidative role explaining the formation of the elemental silver. Nevertheless, we ran a reaction with TEMPO as radical scavenger (Scheme 43) and we obtained cyclized compound X in a good yield (84%) which is inconsistent with a radical pathway such as SET and BET sequence.

In addition, as mentioned above, the counter ion AgO^- was not taken into account in the calculation. However, we presume that AgO^- act as a base like DBU in the whole mechanism.

III.d.2 Diastereoselectivity of the reaction

In order to disclose the origin of the diastereoselectivity, our collaborators computed the first three steps of the reaction mechanism following two approaches leading to *anti or syn* diasteroisomers depicted in Figure 8.

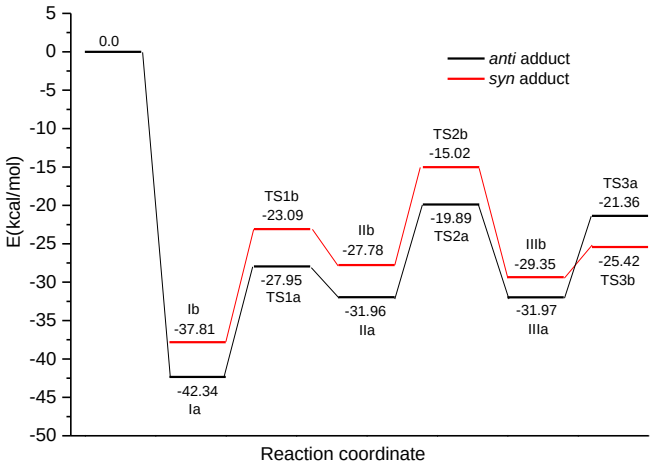


Figure 8

We can notice that the first intermediate is more stable in the case leading to an *anti*-product. Indeed, **Ia** is more stable of about 4.5 kcal/mol with respect to **Ib**, since the destabilizing interaction between the oxygen lone pairs of both carbonyls (O-O bond 2.80 Å) disfavors the *syn* adduct (Figure 9).

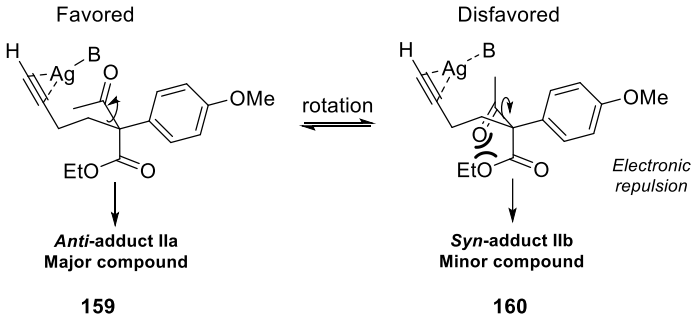


Figure 9

The reaction then proceeds with similar barriers both along with the pathway a and b, suggesting that the final product depends on the most favorable initial intermediate. Indeed, with the aim of further validating our hypothesis, we extended the study of the reaction steps of compound **120**. In this case, comparing the two optimized diasteroisomers, it is worth to notice that while the energy difference between the *anti/syn* adducts for the first step is similar to the value observed for compound **53** (3.43 kcal/mol), it decreases down to 1.39 kcal/mol at step **II**. Since such energy difference is very low, we can assume that this is the origin of the absence of diastereoselectivity. Indeed, for this compound, the destabilizing interaction is substantially decreased upon substitution

with less sterically-hindered methyl group, since the oxygen lone pairs of both carbonyls are located further apart in this case (O-O bond 3.00 Å) (Figure 10).

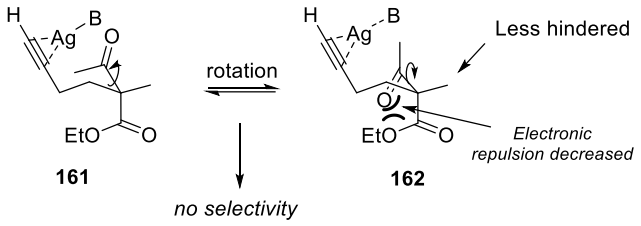
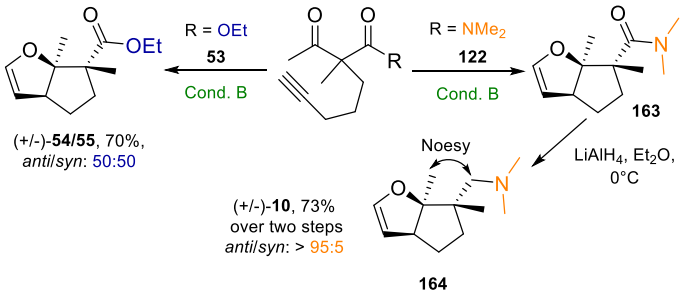


Figure 10

These two examples highlight the crucial role of the steric hindrance between the two carbonyls on the selectivity.

In addition, we next examined two close starting materials where the ester moiety (compound **53**) is substituted by an amide moiety (compound **122**). Experimentally, we ran the reaction on bulkier amide **122** moiety leading to a drastic enhancement of the diastereomeric ratio (*anti*/*syn:* > 95:5) (Scheme 47).



Scheme 47

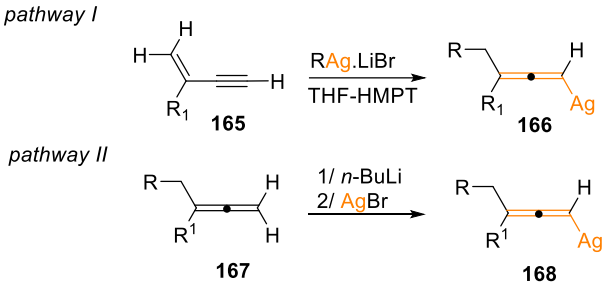
However, we were unable to confirm the stereochemistry at this stage. In order to determine the relative configuration of the cyclized product, the amide **163** was subsequently reduced into the corresponding amine **164** in 73% yield over two steps. A NOE experiment unambiguously evidenced *anti* adduct **164** as the major compound. In parallel, performing the reaction on ethyl ester **53** under conditions B did not allow any improvement of the diastereomeric ratio (50:50), underlining the primary importance of the nature of the electron withdrawing group on the diastereoselectivity outcome. Noteworthy, conditions B led to a better conversion without influencing the *anti/syn* ratio.

III.e Allenyl silver in the literature

In regards to the mechanism supported by DFT calculations (Figure 7) and our mechanistic investigations (see above), we can affirm that the reaction operates through the formation of an allenyl silver intermediate. Zhang and coworkers has briefly reported its presence as a silver

allenamide in their first work, explaining the formation of their side-product by this way.[38] Allenyl silver has, to the best of our knowledge, only been studied by Vermeer groups concerning their syntheses and behaviors towards various electrophiles.[53]

Vermeer and coworkers reported two different ways for the synthesis of allenyl silver (Scheme 48).

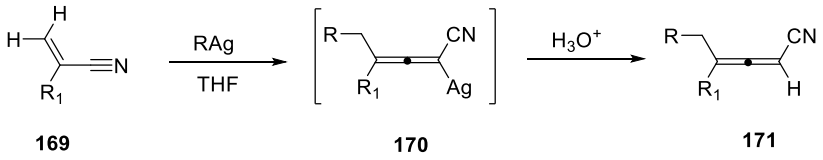


Scheme 48

In pathway I, allenylsilver(I) are obtained by 1,4-addition of organosilver(I) species on an ene-yne system. This approach is quite tedious since alkylsilver(I) species are highly unstable. To this aim, Vermeer et al. described the beneficial effect of the addition of lithium salt in order to stabilize organosilvers.

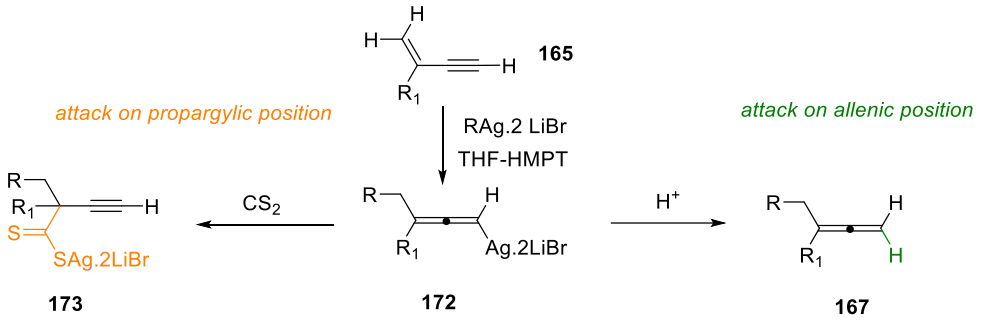
In the second pathway, Vermeer *et al.* use a transmetallation process by deprotonation of an allene with *n*-BuLi and a subsequent trapping of the resulting carbanion by a silver bromide.

It is worth to mention that as the pathway I, the 1,4-addition of alkylsilver(I) can also be extended to enynenitriles **169** leading to the allenylsilver intermediate **170** (Scheme 49).[54]



Scheme 49

Concerning their reactivity, Vermeer and coworkers tried to rationalize their behavior towards different electrophile. So, it appears that allenylsilver(I) could react by their both allenyl or propargylic position as depicted in the Scheme 50 below.

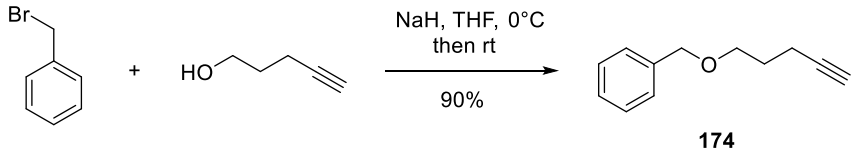


Scheme 50

In a general manner, allenylsilver(I) show a higher propensity to attack on its allenic position than its propargylic counterpart. However, Vermeer and coworkers could not rationalize their behavior towards electrophile because many parameters seems to be taken into account (HSAB, steric hindrance, stability of the final product…) which played a large part in determining the acetylene-allene ratios.

III.f Intermolecular attempts

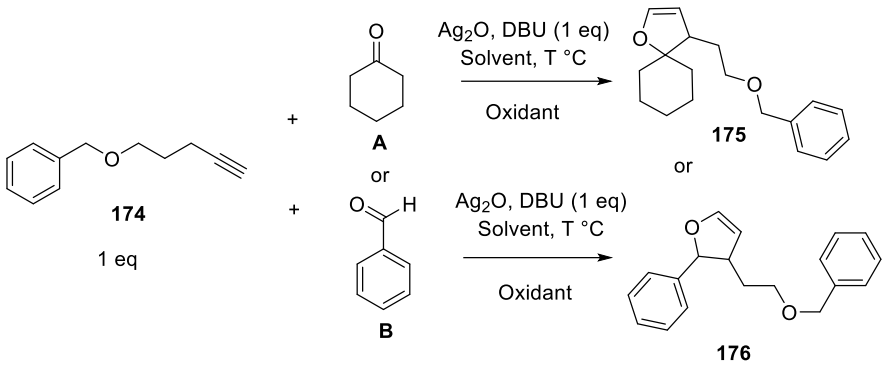
After studying the intramolecular cyclization, we envisioned a more challenging access to 2,3-dihydrofuran by extending the reaction to an intermolecular fashion. To this aim, we selected the ((pent-4-yn-1-yloxy)methyl)benzene **174** as the alkyne, which can be obtained by simple substitution reaction between pent-4-yn-1-ol and benzyl bromide (Scheme 51).



Scheme 51

From the alkyne **174**, we tried several intermolecular reactions with cyclohexanone or benzaldehyde following conditions depicted in (Table 5)[55].

Table 5



Entry	Substrate	Ag_2O (eq)	[c][a]	Solvent	T (°C)	Oxidant	Time, Yield[a]%
1	A (2 eq)	0.5	0.2 M	MeCN	50	-	2h, n.r
2	A (2 eq)	0.5	1.0 M	MeCN	50	O_2	12h, n.r
3	A (2 eq)	1	1.0 M	Toluene	80	O_2	12h, n.r
4	A (2 eq)	1	1.0 M	Toluene	110	-	12h, n.r
5	B (2 eq)	0.5	1.0 M	MeCN	50	-	12h, n.r
6	B (2 eq)	1	1.0 M	MeCN	50	O_2	12h, n.r
7	B (2 eq)	1	1.0 M	MeCN	80	-	20h, n.r
8	B (2 eq)	2	2.0 M	Toluene	80	O_2	24h, n.r
9	B (2 eq)	2	2.0 M	Toluene	110	-	12h, n.r

[a] ^1H NMR yield was calculated from 1,3,5-trimethoxybenzene as internal standard.

We first started from the reaction between cyclohexanone and alkyne **174**. Using our optimized conditions A (Entry 1), we have never observed the formation of the 2,3-dihydrofuran. Leading the reaction in more concentrated media, with 1 equivalent of silver oxide(I) and/or at higher temperature (80 or 110 °C) could not afford the expected product (Entry 2-4). Suspecting a lack of reactivity of the allenyl silver, we shifted to a more reactive electrophile. Unfortunately, conducting the reaction on benzaldehyde, even with a large excess of silver, at high temperature and more concentrated media, never allowed us to observe traces of the expected product by ^1H NMR.

To explain this lack of reactivity, we hypothesized several reasons:

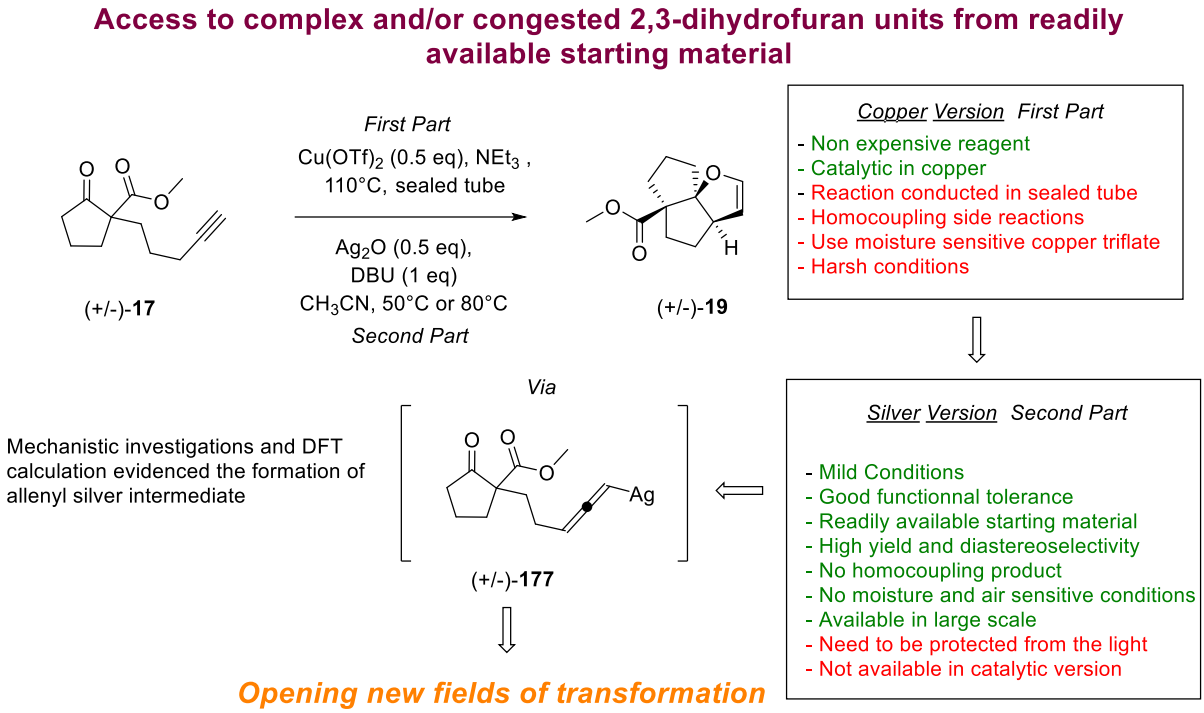
- On the one hand, the transitory allenyl silver formation needs to be close to the electrophilic center. However, this specie is probably not the major organosilver form in the reaction thus lowering its probability to react with the ketone.
- On the other hand, reactions must be very fast in order to avoid the degradation of the silver oxide(I) or organo-silver species into unreactive metallic silver precipitates. Indeed, during our studies on intramolecular reactions, we always observed that conducting the reaction for prolonged time has never improved the yield. This observation could be attributed to the formation of both silver mirror and metallic silver precipitates thus limiting or prohibiting any reaction.

For these two reasons, we presumed that the formation of the allenyl silver close to the reactive center and a quick reaction are mandatory pre-requisite which can't be reached in intermolecular reactions thus circumventing this transformation to intramolecular fashion.

III.g Conclusion on Ag_2O/DBU promoted synthesis of 2,3-dihydrofuran derivatives

In conclusion, during our work on total synthesis of Vibsatine A and B, we discovered an unprecedented cyclization promoted by a mixture of copper(II)/pyrrolidine in toluene from ketone containing terminal alkyne moiety. Although we obtained good yield, we were unable to exceed 60 % yield due to Glaser homo-coupling side reaction. We could not find a way to overcome this major drawback despite numerous optimization attempts. In addition, the reaction required high temperature (110°C), rendering it not suitable for sensitive substrates. At last, reproducibility issues were also encountered during our optimization works and were not solved. To this aim, we elected silver salt as new catalyst for this reaction since it possess quite similar properties to copper and it is less prone to promote Glaser coupling reaction.

After a short survey, we found two optimized conditions (conditions A and B) which would allow the access to complex (and sometimes highly congested) 2,3-dihydrofurans derivatives through a formal [3+2] cyclization. The reaction showed good functionality tolerance, yielding the product in moderate to very good yield with good selectivity (up to 95/5). More than 15 examples of cyclization have thus been described.[56] However, this reaction seems to circumvent to intramolecular fashion (Scheme 52).



Scheme 52

This unprecedented formal silver mediated [3+2] cyclization appears to be a valuable tool for the synthesis of complex and/or congested polycyclic dihydrofurans. For example, the approach developed herein would permit a straightforward access to precursor natural compounds, which possess an angularly fused tricyclic lactone backbone like alliacol **179** or teucrolivin **180**, under smooth conditions (Figure 11).

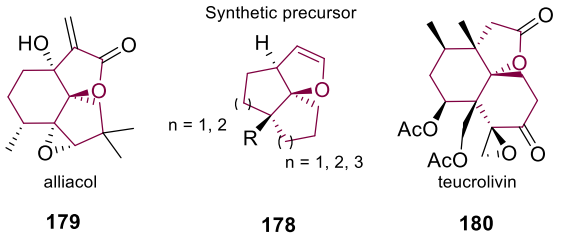


Figure 11

In addition, mechanistic investigations supported by DFT calculations provided by our collaborators Dr. I. Ciofini and A. Perfetto unambiguously showed the formation of an unprecedented allenyl silver specie. Allenylsilver(I) have been scarcely studied in the literature and this novel reaction could open new fields in silver chemistry.

IV. EXPERIMENTAL PART I

Usual procedures

Unless otherwise stated, all commercially available reagents and solvents were used without further purification.

All reactions were carried out in oven or flame-dried glassware under an argon atmosphere employing standard techniques in handling air-sensitive materials. For reactions requiring anhydrous conditions, dry solvents were freshly distillated prior to use (THF, diethyl ether and toluene over sodium/benzophenone system, CH_2Cl_2 and DMSO over calcium hydride and MeOH and EtOH over magnesium turnings).

Reactions were magnetically stirred and monitored by thin layer chromatography with 0.20 mm Merck $60F_{254}$ pre-coated silica gel plates. Visualization was accomplished with UV light and subsequent treatment with a 10% ethanolic phosphomolybdic acid solution followed by heating at 100-110 °C.

Flash chromatography was performed with silica gel 60 (particle size 0.040-0.063 µm) supplied by SDS Carlo Erba. Yield refers to chromatography and spectroscopically pure compounds, unless otherwise noted.

Whenever "deactivated silica gel" is mentioned, the corresponding flash chromatography was performed using solvents containing 3% of triethylamine.

Physical data and spectroscopic measurements

NMR Spectra were recorded on Bruker Avance 300 MHz, 400 MHz or 600 MHz spectrometers.

^{1}H NMR spectra were recorded using an internal deuterium lock at ambient temperature. Internals references of δ_H 7.26 and 3.35 were used respectively for CDCl3 and methanol-*d*$_4$ (MeOD). Data are represented as follows: chemical shift (in ppm), multiplicity (s = single, d = doublet, t = triplet, q = quartet and *br.* = broad), integration, coupling constant (*J*), expressed in Hz, attribution. ^{13}C-NMR spectra were recorded at 75 MHz, 100 MHz or 125 MHz. Internals references of δ_C 77.00 and 49.8 were used respectively for $CDCl_3$ and methanol-*d*$_4$ (MeOD). ^{13}C NMR assignments were confirmed by 2D COSY, HSQC and HMBC spectra.

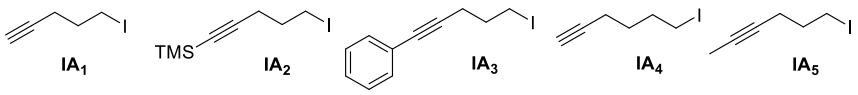
Mass spectra were recorded on a GC/MS coupling unit with a MSD 5973 spectrometer and a Hewlett-Packard HP-GC 6890 chromatograph. Ionization was obtained either by electronic impact (EI) or chemical ionization with methane (CI, CH_4). Mass spectral data are reported as m/z.

High-resolution mass-spectra were obtained on a Thermo-Electron MAT-95 or Q-TOF1 spectrometer (Waters). Ionization was obtained by electrospray (ES) using Na, K or Li. Mass spectral data are reported as *m/z*.

Optical rotations were recorded on a Perkin Elmer Model 341 polarimeter at 589 nm and reported as follows: $[\alpha]_D$, concentration (c in g/100 mL) and solvent.

Nomenclature

IUPAC nomenclature was used for all the compounds.

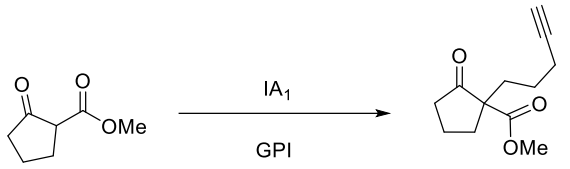


Iodo-alkynes IA_1[57], IA_2[58], IA_3[59], IA_4[60] and IA_5[61] were synthetized following standard procedure described in the literature.

General procedure for the alkylation reaction from malonate (GPI):

To a suspension of NaH (60% in oil) (11.4 mmol, 1.14 equiv.) in dry DMF (5 mL) at 0 °C, was slowly added a solution of corresponding malonate (10 mmol, 1 equiv.). The reaction was stirred at 0°C until the gas evolution ceased then allowed to warm to room temperature and stirred for 15 additional min. A solution of the corresponding iodoalkyne (**IA_x**) (12 mmol, 1.2 equiv.) in THF (5 mL) was added dropwise. The mixture was stirred until TLC showed complete disappearance of the starting material. The reaction was quenched by a saturated solution of NH_4Cl and the aqueous layer was extracted twice by EtOAc. The combined organics extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash chromatography over silica gel affording the expected compound in a pure form.

(+/-)-methyl 2-oxo-1-(pent-4-yn-1-yl)cyclopentane-1-carboxylate **17**

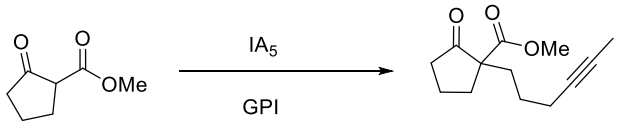


17
$C_{12}H_{16}O_3$
208.26 g/mol

The compound **17** was obtained from methyl 2-oxocyclopentane-1-carboxylate and **IA_1** following the **GPI** on 47.5 mmol scale (6.7 g). Purification by flash chromatography (EtOAc/Cyclohexane: 6 /94) afforded **17** as a colorless oil (m= 8.5 g, 86% yield).

All spectroscopic data are in accordance with those described in the literature.[62]

(+/-)-methyl 1-(hex-4-yn-1-yl)-2-oxocyclopentane-1-carboxylate **142**



142
$C_{13}H_{18}O_3$
222.28 g/mol

The compound **142** was obtained from methyl 2-oxocyclopentane-1-carboxylate and **IA_5** following the **GPI** on 2.4 mmol scale (341 mg). Purification by flash chromatography (EtOAc/Cyclohexane: 5/95) afforded **142** as a colorless oil (m= 379 mg, 71% yield).

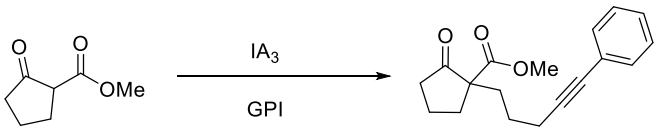
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 2.55 – 2.48 (m, 1H), 2.43 – 2.34 (m, 1H), 2.28 – 2.19 (m, 1H), 2.13 - 2.07 (m, 2H), 2.03 – 1.83 (m, 4H), 1.73 (t, *J* = 2.5 Hz, 3H), 1.65 – 1.58 (m, 1H), 1.52-1.45 (m, 1H), 1.42 – 1.31 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 214.7, 171.4, 78.4, 76.1, 60.4, 52.6, 38.0, 33.3, 32.8, 24.6, 19.6, 19.1, 3.5.

FTIR (neat): ν = 2954, 2257, 1749, 1723, 1435, 1260, 1148, 908, 727 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{13}H_1O_3Na^+$: $[M+Na]^+$: 245.1154; found: 245.1152.

(+/-)-methyl 2-oxo-1-(5-phenylpent-4-yn-1-yl)cyclopentane-1-carboxylate **143**



143
$C_{18}H_{20}O_3$
284.36 g/mol

The compound **143** was obtained from methyl 2-oxocyclopentane-1-carboxylate and **IA_3** following the **GPI** on 5.5 mmol scale (0.8 g). Purification by flash chromatography (EtOAc/Cyclohexane: 8/92 to 12/88) afforded **143** as a pale yellow oil (m= 1.2 g, 78% yield).

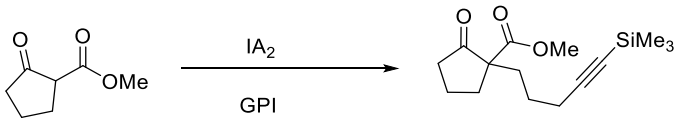
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.37 (m, 2H), 7.29 – 7.26 (m, 3H), 3.71 (s, 3H), 2.58 – 2.55 (m, 1H), 2.45 – 2.38 (m, 3H), 2.32 – 2.25 (m, 1H), 2.13 – 2.06 (m, 1H), 2.04 – 1.89 (m, 3H), 1.77 – 1.61 (m, 2H), 1.58 – 1.50 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 214.7, 171.5, 131.6 (2 C), 128.3 (2 C), 127.7, 123.9, 89.4, 81.2, 60.4, 52.7, 38.0, 33.3, 33.0, 24.5, 19.8, 19.7.

FTIR (neat): ν = 2953, 1750, 1725, 1490, 1434, 1259, 1148, 910, 758, 693 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{18}H_{20}O_3Na^+$: $[M+Na]^+$: 307.1310; found: 307.1302.

(+/-)-methyl 2-oxo-1-(5-(trimethylsilyl)pent-4-yn-1-yl)cyclopentane-1-carboxylate **144**



144
$C_{15}H_{24}O_3Si$
280.44 g/mol

The compound **144** was obtained from methyl 2-oxocyclopentane-1-carboxylate and **IA_2** following the **GPI** on 10.5 mmol scale (1.5 g). Purification by flash chromatography (EtOAc/Cyclohexane: 4/96) afforded **144** as a colorless oil (m= 1.23 g, 42% yield).

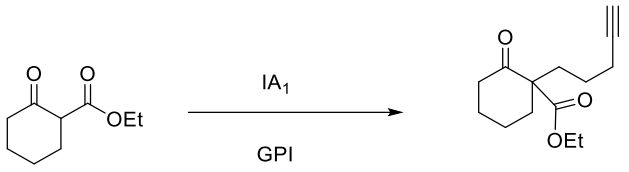
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 2.55 – 2.49 (m, 1H), 2.43 –2.35 (m, 1H), 2.29 – 2.17 (m, 3H), 2.02 –1.84 (m, 4H), 1.66-1.49 (m, 2H), 1.46 – 1.36 (m, 1H), 0.11 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 214.6, 171.4, 106.6, 85.0, 60.3, 52.6, 37.9, 33.1, 32.9, 24.3, 20.2, 19.6, 0.2.

FTIR (neat): *v* = 2957, 2174, 1752, 1724, 1435, 1249, 840, 760 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{15}H_{24}O_3SiNa^+$: $[M+Na]^+$: 303.1392; found: 303.1378.

(+/-)-ethyl 2-oxo-1-(pent-4-yn-1-yl)cyclohexane-1-carboxylate **50**

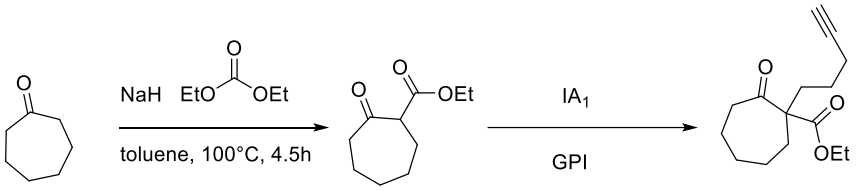


50
$C_{14}H_{20}O_3$
236.31 g/mol

The compound **50** was obtained from ethyl 2-oxocyclohexane-1-carboxylate and **IA_1** following the **GPI** on 5.8 mmol scale (1 g). Purification by flash chromatography (EtOAc/Cyclohexane: 5/95 to 10/90) afforded **50** as a pale yellow oil (m= 1.07 g, 78% yield).

All the spectroscopic data are in accordance with those described in the literature.[63]

(+/-)-ethyl 2-oxo-1-(pent-4-yn-1-yl)cycloheptane-1-carboxylate 9**2**



426
$C_{10}H_{16}O_3$
184.24 g/mol

92
$C_{15}H_{22}O_3$
250.34 g/mol

Step I

Diethyl carbonate (6.48 mL, 53.5 mmol) was added to a degassed flask containing NaH (60% dispersion in mineral oil, 3 g, 74.9 mmol) and toluene (60 mL). The mixture was heated at 100 °C then cycloheptanone (3.16 mL, 26.75 mmol) was added over 2 h using a syringe pump. After 2.5h, the yellow suspension was cooled to room temperature then 20 mL of water followed by aqueous HCl (3 M) (100 mL) to dissolve the salt. The aqueous layer was extracted twice by EtOAc. The combined organics extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash chromatography over silica gel (EtOAc/Cyclohexane: 5/95 to 10/90) affording **426** as a colorless oil (m= 4.53g, 92% yield).

All the spectroscopic data are in accordance with those described in the literature.[64]

Step II

The compound **92** was obtained from **426** and **IA_1** following the **GPI** on 8.1 mmol scale (1.5 g). Purification by flash chromatography (EtOAc/Cyclohexane: 5/95) afforded **92** as a pale yellow oil (m= 1.6 g, 81% yield).

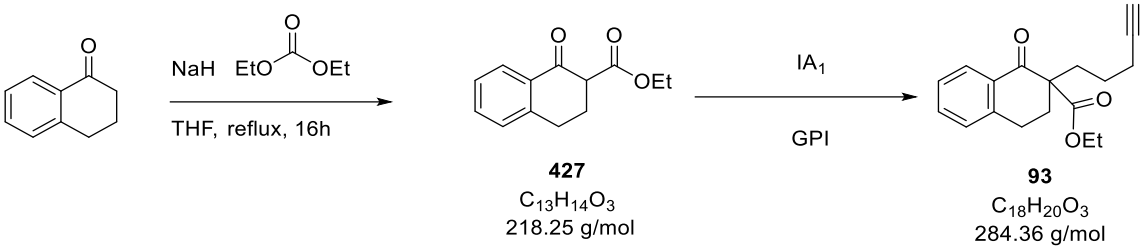
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 – 4.14 (m, 2H), 2.64 – 2.58 (m, 1H), 2.48 – 2.42 (m, 1H), 2.18 – 2.09 (m, 3H), 2.06 – 1.98 (m, 1H), 1.93-1.91 (m, 1H), 1.75 – 1.38 (m, 10H), 1.23 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 172.4, 83.9, 68.7, 62.6, 61.2, 42.1, 34.6, 32.9, 29.9, 25.6, 24.9, 23.8, 18.9, 14.2.

FTIR (neat): ν = 2934, 1704, 1456, 1221, 1177, 1023, 907, 728 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{15}H_{22}O_3Na^+$: $[M+Na]^+$: 273.1467; found: 273.1458.

(+/-)-ethyl 1-oxo-2-(pent-4-yn-1-yl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate **93**



Step I

α-tetralone (2.92 g, 20 mmol) was added dropwise to a stirred suspension of NaH (60%, 1.68 g, 42 mmol) in THF (50 mL) containing diethyl carbonate (4.73 g, 40 mmol). The mixture was heated at reflux overnight. The reaction was quenched by aqueous HCl (1 M) (25 mL) then the aqueous layer was extracted twice by Et_2O. The combined organics extracts were washed with $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash chromatography over silica gel (EtOAc/Cyclohexane: 10/90) affording **427** as a light brown oil (m= 3.93g, 90% yield).

All the spectroscopic data are in accordance with those described in the literature.[65]

Step II

The compound **93** was obtained from **427** and IA_1 following the **GPI** on 4.6 mmol scale (1 g). Purification by flash chromatography (EtOAc/Cyclohexane: 6/94) afforded **93** as a yellow oil (m= 0.9 g, 70% yield).

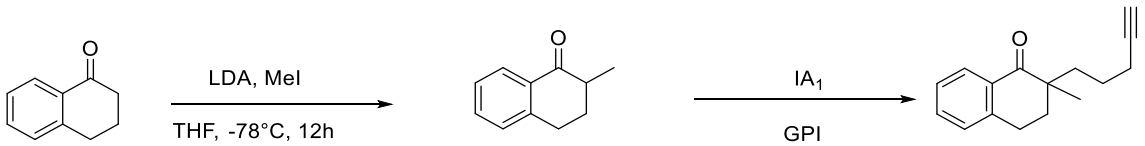
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.8 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 7.8 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.11 – 3.03 (dq, *J* = 17.4, 4.7 Hz, 1H), 2.92 (dt, *J* = 17.4, 5.0 Hz, 1H), 2.57 (dt, *J* = 13.4, 5.0 Hz, 1H), 2.25 – 2.20 (m, 2H), 2.17 – 2.08 (dq, *J* = 13.4, 4.8 Hz, 1H), 2.07-1.97 (m, 2H), 1.95 – 1.93 (m, 1H), 1.73 – 1.53 (m, 2H), 1.15 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 171.8, 143.0, 133.5, 132.1, 128.7, 128.1, 126.8, 83.9, 68.7, 61.4, 57.3, 33.2, 30.7, 25.9, 23.9, 18.9, 14.1.

FTIR (neat): ν = 3291, 2937, 1726, 1686, 1455, 1293, 1179, 1095, 911, 742 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{18}H_{20}O_3Na^+$: $[M+Na]^+$: 307.1310; found: 307.1309.

2-methyl-2-(pent-4-yn-1-yl)-3,4-dihydronaphthalen-1(2H)-one **96**



428
$C_{11}H_{12}O$
160.22 g/mol

96
$C_{16}H_{18}O$
226.32 g/mol

Step I

α-tetralone (4 g, 27.4 mmol) was added dropwise to THF (100 mL) containing LDA (18 mL, 1.5 M in THF, 27.4 mmol) at -78 °C and stirred for 20 min. Then Iodomethane (3.9 g, 27.4 mmol) was added slowly. After stirring for 12 h, the reaction was quenched by aqueous NH_4Cl (20 mL) then the aqueous layer was extracted twice by Et_2O. The combined organics extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash chromatography over silica gel (EtOAc/Cyclohexane: 5/95) affording **428** as a colorless oil (m= 3.1 g, 71% yield).

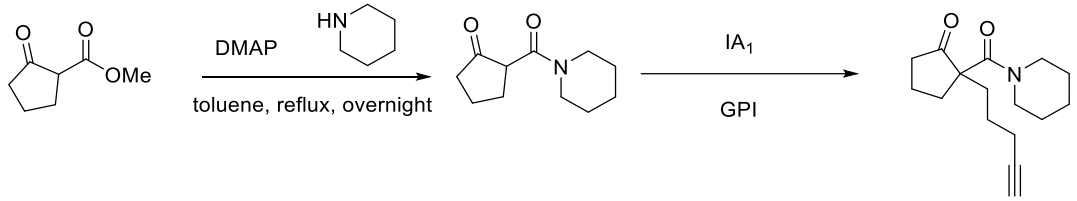
All the spectroscopic data are in accordance with those described in the literature.[66]

Step II

The compound **96** was obtained from **428** and IA_1 following the **GPI** on 3.1 mmol scale (500 mg). Purification by flash chromatography (EtOAc/Cyclohexane: 5/95) afforded **96** as a pale yellow oil (m= 399 mg, 57% yield).

All the spectroscopic data are in accordance with those described in the literature.[67]

2-(pent-4-yn-1-yl)-2-(piperidine-1-carbonyl)cyclopentan-1-one **95**



429
$C_{11}H_{17}NO_2$
195.26 g/mol

95
$C_{16}H_{23}NO_2$
261.37 g/mol

Step I

methyl 2-oxocyclopentane-1-carboxylate (2 g, 14.1 mmol) and piperidine (2.4 g, 28.2 mmol) were added to DMAP(513 mg, 4.2 mmol) in toluene (30 mL). The mixture was heated at reflux overnight. After removing the solvent, the crude mixture was purified by flash chromatography directly over silica gel (EtOAc/Cyclohexane: 25/75 to 40/60) affording **429** as a colorless oil (m= 1.8 g, 66% yield).

All the spectroscopic data are in accordance with those described in the literature.[68]

Step II

The compound **95** was obtained from **429** and **IA_1** following the **GPI** on 5.1 mmol scale (1 g). Purification by flash chromatography (EtOAc/Cyclohexane : 25/75 to 50/50) afforded **95** as a colorless oil (m= 826 mg, 62% yield).

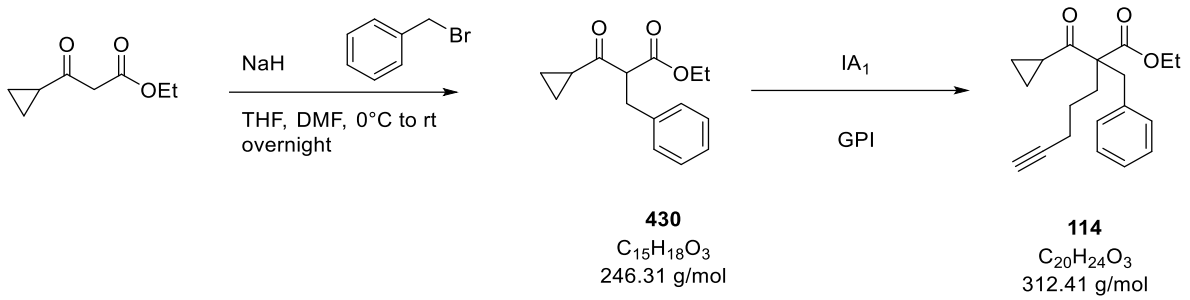
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 - 3.37 (m, 4H), 2.59 – 2.53 (m, 1H), 2.41 – 2.33 (m, 1H), 2.21 – 2.10 (m, 3H), 1.93 – 1.79 (m, 4H), 1.74 – 1.60 (m, 2H), 1.59 – 1.51 (m, 2H), 1.50 – 1.37 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 215.5, 167.6, 83.8, 68.8, 60.9, 36.8, 34.4, 32.8, 25.9, 24.5, 24.0, 18.7, 18.5.

FTIR (neat): ν = 1622, 904, 723 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{16}H_{23}NO_2Na^+$: $[M+Na]^+$: 284.1626; found: 284.1620.

ethyl 2-benzyl-2-(cyclopropanecarbonyl)hept-6-ynoate **114**



430
$C_{15}H_{18}O_3$
246.31 g/mol

114
$C_{20}H_{24}O_3$
312.41 g/mol

Step I

To a suspension of NaH (60% in oil) (438 mg, 10.9 mmo) in dry THF/DMF (1:1, 20 mL) at 0 °C, was slowly added ethyl 3-cyclopropyl-3-oxopropanoate (1.5 g, 9.6 mmol). The reaction was stirred at 0°C until the gas evolution ceased then allowed to warm to room temperature and stirred for 15 additional min. A solution of benzyl bromide (2.0 g, 11.5 mmol) was added dropwise. The reaction was stirred overnight and quenched by a saturated solution of NH_4Cl and the aqueous layer was extracted twice by EtOAc. The combined organics extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash chromatography over silica gel (EtOAc/Cyclohexane : 5/95) afforded **430** as a pale yellow oil (m= 1.8 g, 78% yield).

All the spectroscopic data are in accordance with those described in the literature.[69]

Step II

The compound **114** was obtained from **430** and **IA_1** following the **GPI** on 6.5 mmol scale (1.6 g). Purification by flash chromatography (EtOAc/Cyclohexane : 5/95 to 10/90) afforded **114** as a colorless oil (m= 1.5 g, 74% yield).

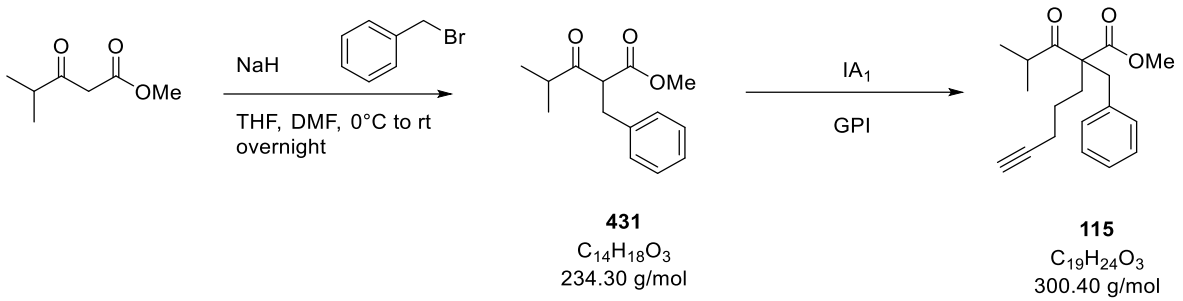
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.12 (m, 3H), 7.07 (d, *J* = 8.2 Hz, 2H), 4.27 – 4.04 (m, 2H), 3.28-3.11 (m, 2H), 2.21 – 2.05 (m, 2H), 2.02 – 1.79 (m, 4H), 1.59 – 1.32 (m, 2H), 1.27 – 1.14 (m, 3H), 1.11 – 0.96 (m, 2H), 0.92-0.82 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 206.6, 172.0, 136.3, 129.9 (2C), 128.2 (2C), 126.8, 83.6, 68.9, 64.6, 61.2, 37.0, 30.2, 23.3, 18.7, 18.6, 14.1, 12.3, 11.9.

FTIR (neat): ν = 1733, 1698, 1381, 1181, 906, 730, 701 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{20}H_{24}O_3Na^+$: $[M+Na]^+$: 335.1623; found: 335.1613.

methyl 2-benzyl-2-isobutyrylhept-6-ynoate **115**



431
$C_{14}H_{18}O_3$
234.30 g/mol

115
$C_{19}H_{24}O_3$
300.40 g/mol

Step I

To a suspension of NaH (60% in oil) (474mg, 11.9 mmo) in dry THF/DMF (1:1, 20 mL) at 0 °C, was slowly added methyl Isobutyrylacetate (1.5 g, 10.4 mmol). The reaction was stirred at 0°C until the gas evolution ceased then allowed to warm to room temperature and stirred for 15 additional min. A solution of benzyl bromide (2.2 g, 12.5 mmol) was added dropwise. The reaction was stirred overnight and quenched by a saturated solution of NH_4Cl and the aqueous layer was extracted twice by EtOAc. The combined organics extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash chromatography over silica gel (EtOAc/Cyclohexane : 5/95) afforded **431** as a pale yellow oil (m= 1.8 g, 74% yield).

All the spectroscopic data are in accordance with those described in the literature.[70]

Step II

The compound **115** was obtained from **431** and **IA_1** following the **GPI** on 7.3 mmol scale (1.7 g). Purification by flash chromatography (EtOAc/Cyclohexane : 5/95) afforded **115** as a colorless oil (m= 1.7 g, 79% yield).

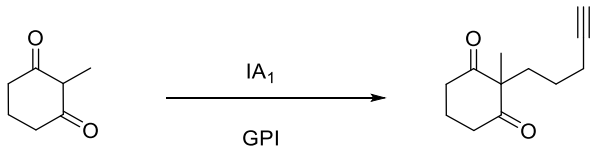
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.27 – 7.14 (m, 3H), 7.06 – 6.99 (m, 2H), 3.67 (s, 3H), 3.17 (dd, *J* = 54.0, 14.3 Hz, 2H), 2.86-2.74 (m, 1H), 2.16 (td, *J* = 9.1, 4.9 Hz, 2H), 2.02 – 1.85 (m, 3H), 1.66-1.53 (m, 1H), 1.36 – 1.22 (m, 1H), 1.05 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 211.5, 172.3, 136.4, 129.8, 128.3, 126.9, 83.4, 69.2, 65.0, 52.0, 37.5, 36.7, 29.6, 23.1, 20.6, 20.1, 18.6.

FTIR (neat): *ν* = 1708, 1176, 907, 728, 701 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{19}H_{24}O_3Na^+$: $[M+Na]^+$: 323.1623; found: 323.1610.

(+/-)-2-methyl-2-(pent-4-yn-1-yl)cyclohexane-1,3-dione **97**



97
$C_{12}H_{16}O_2$
192.26 g/mol

The compound **97** was obtained from 2-methylcyclohexane-1,3-dione and **IA_1** following the **GPI** on 6.4 mmol scale (812 mg). Purification by flash chromatography (EtOAc/Cyclohexane : 15/85 to 25/75) afforded **97** as a colorless oil (m= 191 mg, 15% yield).

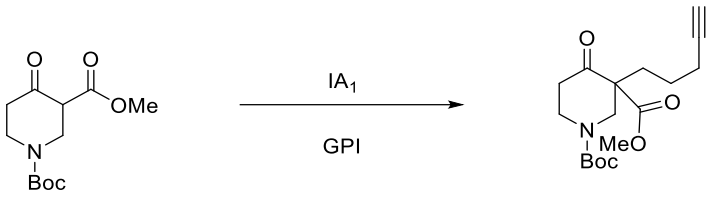
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (ddd, 15.9, 9.7, 5.8 Hz, 2H), 2.61 (ddd, 15.9, 7.0, 5.2 Hz, 2H), 2.14 (td, *J* = 6.9, 2.6 Hz, 2H), 2.04 – 1.96 (m, 1H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.89 – 1.81 (m, 3H), 1.37 – 1.30 (m, 2H), 1.21 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 210.1, 83.5, 69.0, 65.6, 37.9, 36.2, 23.7, 19.1, 18.6, 17.8.

FTIR (neat): ν = 3284, 2959, 2116, 1725, 1692, 1459, 1428, 1274, 1027 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{12}H_{16}O_2Na^+$: $[M+Na]^+$: 215.1048; found: 215.1039.

(+/-)-1-(*tert*-butyl) 3-methyl 4-oxo-3-(pent-4-yn-1-yl)piperidine-1,3-dicarboxylate **94**



94
$C_{17}H_{25}NO_5$
323.39 g/mol

The compound **94** was obtained from 1-(*tert*-butyl) 3-ethyl 4-oxopiperidine-1,3-dicarboxylate and **IA_1** following the **GPI** on 1.9 mmol scale (0.5 g). Purification by flash chromatography (EtOAc/Cyclohexane : 15/85) afforded **94** as a pale yellow solid (m= 408 mg, 65% yield).

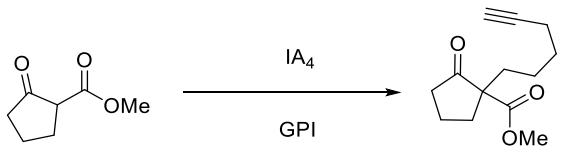
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.37 (brd, *J* = 13.7 Hz, 1H), 4.03 – 3.88 (m, 1H), 3.71 (s, 3H), 3.41 (ddd, *J* = 13.7, 9.0, 4.8 Hz, 1H), 3.24 (d, *J* = 13.7 Hz, 1H), 2.70 – 2.60 (m, 1H), 2.52 – 2.41 (m, 1H), 2.18 (td, *J* = 6.9, 2.6 Hz, 2H), 1.96 – 1.86 (m, 1H), 1.93 (t, *J* = 2.6 Hz, 1H), 1.75 – 1.65 (m, 1H), 1.56 – 1.48 (m, 2H), 1.46 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 170.7, 154.2, 83.5, 80.7, 69.0, 61.4, 52.5, 50.3, 43.4, 39.7, 30.9, 28.3 (3C), 23.6, 18.8.

FTIR (neat): ν = 3292, 2976, 1692, 1423, 1366, 1242, 1162, 732 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{17}H_{25}NO_5Na^+$: $[M+Na]^+$: 346.1630; found: 346.1625.

(+/-)-methyl 1-(hex-5-yn-1-yl)-2-oxocyclopentane-1-carboxylate **99**

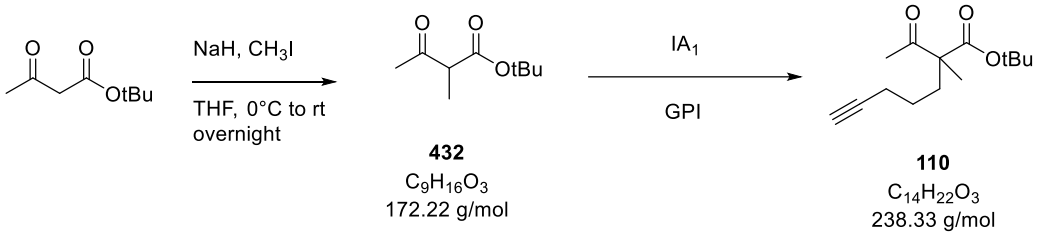


99
$C_{13}H_{18}O_3$
222.28 g/mol

The compound **99** was obtained from methyl 2-oxocyclopentane-1-carboxylate and **IA_4** following the **GPI** on 10.5 mmol scale (1.5 g). Purification by flash chromatography (EtOAc/Cyclohexane : 5/95 to 8/92) afforded **99** as a colorless oil (m= 2.1 g, 88% yield).

All spectroscopic data are in accordance with those described in the literature.[71]

(+/-)-*tert*-butyl 2-acetyl-2-methylhept-6-ynoate **110**



432
$C_9H_{16}O_3$
172.22 g/mol

110
$C_{14}H_{22}O_3$
238.33 g/mol

Step I

3-oxo-butyric acid tert-butyl ester (5.1 mL, 31.6 mmol) was added to a stirred suspension of NaH (1.3 g, 33.2 mmol) in THF (120 mL) at 0 °C. Then MeI (3.94 mL, 63.2 mmol) was added slowly to the reaction mixture. The reaction was stirred at room temperature overnight. The reaction was quenched by a saturated solution of NH_4Cl and the aqueous layer was extracted twice by EtOAc. The combined organics extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash chromatography over silica gel (EtOAc/Cyclohexane : 10/90) afforded **432** as a colorless oil (m= 5.1 g, 94% yield).

All spectroscopic data are in accordance with those described in the literature.[72]

Step II

The compound **110** was obtained from **432** and **IA_1** following the **GPI** on 31.6 mmol scale (5.4 g). Purification by flash chromatography (EtOAc/Cyclohexane : 5/95) afforded **110** as a yellow oil (m= 4.8 g, 64% yield).

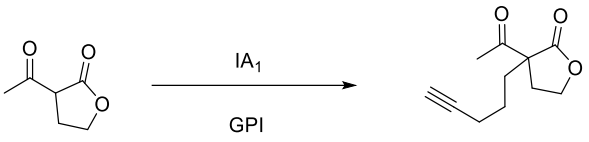
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 2.18 (td, *J* = 6.9, 2.7 Hz, 2H), 2.12 (s, 3H), 1.97 – 1.89 (m, 1H), 1.93 (t, *J* = 2.7 Hz, 1H), 1.84 – 1.76 (m, 1H), 1.43 (s, 9H), 1.41 – 1.33 (m, 2H), 1.26 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 205.7, 172.0, 83.8, 81.8, 68.8, 60.1, 33.9, 27.9 (3C), 26.1, 23.4, 18.9, 18.8.

FTIR (neat): *ν* = 3291, 2979, 1708, 1458, 1369, 1257, 1150, 1118, 845 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{14}H_{22}O_3Na^+$: $[M+Na]^+$: 261.1467; found: 261.1460.

(+/-)-3-acetyl-3-(pent-4-yn-1-yl)dihydrofuran-2(*3H*)-one **111**



111
$C_{11}H_{14}O_3$
194.23 g/mol

The compound **111** was obtained from 3-acetyldihydrofuran-2(*3H*)-one and **IA₁** following the **GPI** on 11.7 mmol scale (1.5 g). Purification by flash chromatography (EtOAc/Cyclohexane : 5/95 to 10/90) afforded **111** as a pale yellow oil (m= 1.86 g, 82% yield).

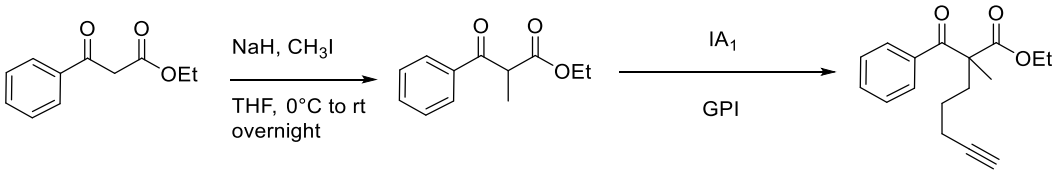
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 4.23 (td, *J* = 9.0, 3.0 Hz, 1H), 4.08 (td, *J* = 9.0, 7.0 Hz, 1H), 2.84 (ddd, *J* = 12.9, 7.0, 3.0 Hz, 1H), 2.25 (s, 3H), 2.23 – 2.13 (m, 3H), 2.02 – 1.93 (m, 2H), 1.81 (ddd, *J* = 14.5, 11.9, 4.9 Hz, 1H), 1.41 – 1.27 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 202.2, 175.2, 82.9, 69.4, 66.2, 61.1, 33.7, 29.1, 25.4, 23.7, 18.3.

FTIR (neat): *ν* = 3287, 2925, 1757, 1709, 1360, 1220, 1150, 1023, 910, 729 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{11}H_{14}O_3Na^+$: $[M+Na]^+$: 217.0841; found: 217.0847.

(+/-)-ethyl 2-benzoyl-2-methylhept-6-ynoate **112**



433
$C_{12}H_{14}O_3$
206.24 g/mol

112
$C_{17}H_{20}O_3$
272.34 g/mol

Step I

Ethyl benzoylacetate (5 g, 26.0 mmol) was added to a stirred suspension of NaH (1.2 g, 28.6 mmol) in THF (30 mL) at 0 °C. Then MeI (1.78 mL, 28.6 mmol) was added slowly to the reaction mixture. The reaction was stirred at room temperature overnight. The reaction was quenched by a saturated solution of NH_4Cl and the aqueous layer was extracted twice by EtOAc. The combined organics extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash chromatography over silica gel (EtOAc/Cyclohexane : 10/90) afforded **433** as a yellow oil (m= 4.7 g, 89% yield).

All spectroscopic data are in accordance with those described in the literature.[73]

Step II

The compound **112** was obtained from **433** and **IA₁** following the **GPI** on 14.6 mmol scale (3 g). Purification by flash chromatography (EtOAc/Cyclohexane: 5/95) afforded **112** as a pale yellow oil (m= 2.3 g, 57% yield).

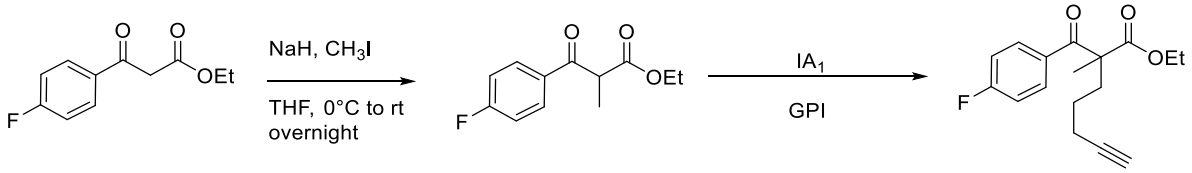
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.82 – 7.80 (m, 2H), 7.52 – 7.47 (m, 1H), 7.41 – 7.37 (m, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 2.16 (td, *J* = 7.1, 2.6 Hz, 2H), 2.14 – 2.09 (m, 2H), 1.89 (t, *J* = 2.6 Hz, 1H), 1.52 (s, 3H), 1.48 – 1.37 (m, 2H), 1.05 – 1.02 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 174.2, 135.6, 132.7, 128.5 (4C), 83.7, 68.8, 61.4, 56.8, 35.6, 23.2, 21.1, 18.8, 13.8.

FTIR (neat): ν = 3295, 2940, 1732, 1682, 1447, 1377, 1259, 1182, 1110, 972, 705 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{17}H_{20}O_3Na^+$: $[M+Na]^+$: 295.1310; found: 295.1306.

(+/-)-ethyl 2-(4-fluorobenzoyl)-2-methylhept-6-ynoate **113**



434
$C_{12}H_{13}FO_3$
224.23 g/mol

113
$C_{17}H_{19}FO_3$
290.33 g/mol

Step I

Ethyl 4-fluorobenzoylacetate (2 g, 9.5 mmol) was added to a stirred suspension of NaH (418.4 g, 10.5 mmol) in THF (10 mL) at 0 °C. Then MeI (0.7 mL, 10.5 mmol) was added slowly to the reaction mixture. The reaction was stirred at room temperature overnight. The reaction was quenched by a saturated solution of NH_4Cl and the aqueous layer was extracted twice by EtOAc. The combined organics extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash chromatography over silica gel (EtOAc/Cyclohexane : 10/90 to 15/85) afforded **434** as a pale yellow oil (m= 1.8 g, 85% yield).

All spectroscopic data are in accordance with those described in the literature.[74]

Step II

The compound **113** was obtained from **434** and **IA_1** following the **GPI** on 4.5 mmol scale (1 g). Purification by flash chromatography (EtOAc/Cyclohexane: 5/95) afforded **113** as a yellow oil (m= 722 mg, 56% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.6 Hz, 2H), 7.03 (dd, *J* = 8.6 Hz, 2H), 4.07 (q, *J* = 7.1 Hz, 2H), 2.12 (td, *J* = 7.1, 2.6 Hz, 2H), 2.09 – 2.03 (m, 2H), 1.87 (t, *J* = 2.6 Hz, 1H), 1.50 (s, 3H), 1.47 – 1.34 (m, 2H), 1.05 (t, *J* = 7.1 Hz, 3H).

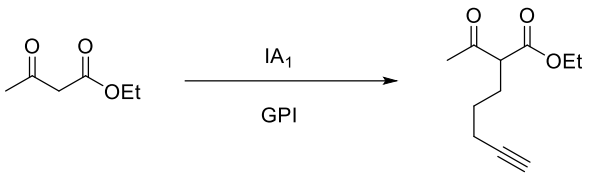
^{13}C NMR (100 MHz, $CDCl_3$) δ 195.8, 174.1, 165.4 (d, *J* = 254.9 Hz), 131.9 (d, *J* = 3.2 Hz), 131.2 (d, *J* = 9.2 Hz, 2C), 115.6 (d, *J* = 21.7 Hz, 2C), 83.6, 68.8, 61.5, 56.7, 35.6, 23.1, 21.1, 18.8, 13.9.

^{19}F NMR (280 MHz, $CDCl_3$) δ -105.5.

FTIR (neat): ν = 3303, 2940, 1732, 1682, 1598, 1507, 1235, 1159, 1110, 1025, 974, 849 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{17}H_{19}O_3FNa^+$: $[M+Na]^+$: 313.1216; found: 313.1203.

(+/-)-ethyl 2-acetylhept-6-ynoate **116**



116
$C_{11}H_{16}O_3$
196.25 g/mol

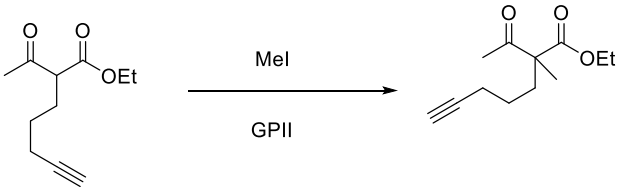
116 was obtained from ethyl 3-oxobutanoate and **IA_1** following the **GPI** on 30.7 mmol scale (4 g). Purification by flash chromatography (EtOAc/Cyclohexane : 5/95 to 8/92) afforded **116** as a colorless oil (m= 4.8 g, 79% yield).

All spectroscopic data are in accordance with those described in the literature.[75]

General procedure for the alkylation reaction from ethyl 2-acetylhept-6-ynoate (GPII):

To a suspension of NaH (60% in oil) (11.4 mmol, 1.14 equiv.) in dry DMF (5 mL) at 0 °C, was slowly added a solution of corresponding malonate (10 mmol, 1 equiv.). The reaction was stirred at 0°C until the gas evolution ceased then allowed to warm to room temperature and stirred for 15 additional min. A solution of the corresponding alkyl bromide or iodide (12 mmol, 1.2 equiv.) in THF (5 mL) was added dropwise. The mixture was stirred until TLC showed complete disappearance of the starting material. The reaction was quenched by a saturated solution of NH_4Cl and the aqueous layer extracted twice by EtOAc. The combined organics extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel affording the expected compound in a pure form.

(+/-)-ethyl 2-acetyl-2-methylhept-6-ynoate **53**



116

53
$C_{12}H_{18}O_3$
210.27 g/mol

The compound **53** was obtained from **116** and methyl iodide following the **GPII** on 8.0 mmol scale (1.2 g). Purification by flash chromatography (EtOAc/Cyclohexane : 5/95 to 15/85) afforded **53** as a colorless oil (m= 816 mg, 49% yield).

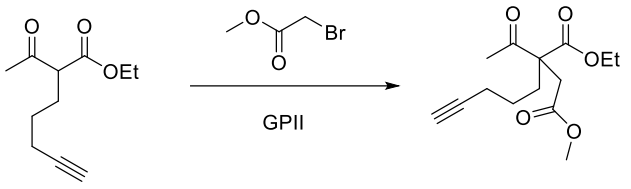
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (q, *J* = 7.1 Hz, 2H), 2.20 – 2.15 (m, 2H), 2.12 (s, 3H), 1.98 – 1.92 (m, 1H), 1.93 (t, *J* = 2.6 Hz, 1H), 1.88 – 1.80 (m, 1H), 1.44 – 1.34 (m, 2H), 1.31 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 205.4, 172.9, 83.7, 68.9, 61.4, 59.4, 33.9, 26.1, 23.5, 18.9, 18.8, 14.1.

FTIR (neat): ν = 3289, 2984, 1709, 1357, 1258, 1180, 1100, 1026, 860 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{12}H_{18}O_3Na^+$: $[M+Na]^+$: 233.1154; found: 233.1143.

1-ethyl 4-methyl 2-acetyl-2-(pent-4-yn-1-yl)succinate **124**



116

124
$C_{14}H_{20}O_5$
268.31 g/mol

The compound **124** was obtained from **116** and methyl bromoacetate following the **GPII** on 5.1 mmol scale (1 g). Purification by flash chromatography (EtOAc/Cyclohexane : 5/95 to 10/90) afforded **124** as a colorless oil (m=1.0 g, 75% yield).

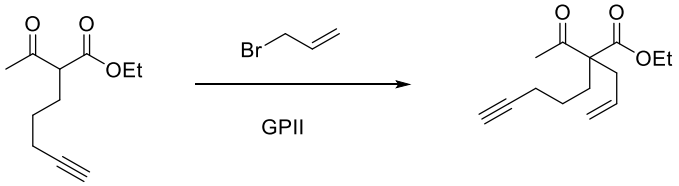
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 4.19 (q, *J* = 7.2 Hz, 2H), 3.61 (s, 3H), 2.95 – 2.83 (m, 2H), 2.24 (s, 3H), 2.21 – 2.12 (m, 2H), 2.10 – 1.99 (m, 2H), 1.93 (t, *J* = 2.6 Hz, 1H), 1.43 – 1.27 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 204.2, 171.4, 171.2, 83.3, 69.1, 61.8, 61.3, 51.8, 36.8, 32.3, 26.9, 23.4, 18.6, 14.0.

FTIR (neat): *ν* = 1732, 1712, 1356, 1165, 1017 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{14}H_{20}O_5Na^+$: $[M+Na]^+$: 291.1208; found: 291.1195.

(+/-)-ethyl 2-acetyl-2-allylhept-6-ynoate **117**



116

117
$C_{14}H_{20}O_3$
236.31 g/mol

The compound **117** was obtained from **116** and allyl bromide following the **GPII** on 5.9 mmol scale (1 g). Purification by flash chromatography (EtOAc/Cyclohexane : 7/93) afforded **117** as a pale yellow oil (m= 1.1 g, 82% yield).

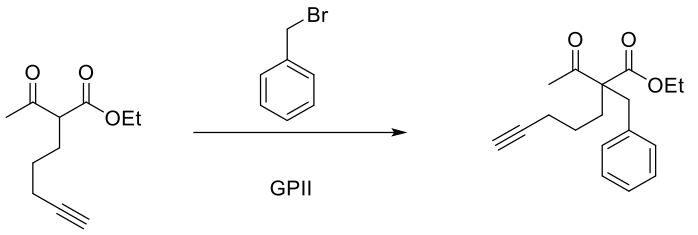
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 5.61 – 5.50 (m, 1H), 5.09 – 5.03 (m, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.64 – 2.52 (m, 2H), 2.20 – 2.14 (m, 2H), 2.11 (s, 3H), 2.00 – 1.87 (m, 3H), 1.43 – 1.28 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 204.4, 171.8, 132.3, 119.0, 83.6, 68.9, 63.1, 61.4, 35.9, 30.5, 26.8, 23.0, 18.7, 14.1.

FTIR (neat): *ν* = 3291, 2981, 1738, 1708, 1269, 1217, 1197, 1175, 920 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{14}H_{20}O_3Na^+$: $[M+Na]^+$: 259.1310; found: 259.1314.

(+/-)-ethyl 2-acetyl-2-benzylhept-6-ynoate **118**



116

118
$C_{18}H_{22}O_3$
286.37 g/mol

The compound **118** was obtained from **116** and benzyl bromide following the **GPII** on 6.4 mmol scale (1.4 g). Purification by flash chromatography (EtOAc/Cyclohexane : 5/95 to 8/92) afforded **118** as a yellow oil (m= 1.4 g, 74% yield).

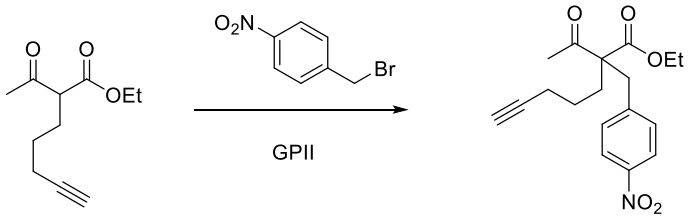
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.20 (m, 3H), 7.07 – 7.05 (m, 2H), 4.22 (ddd, *J* = 14.1, 10.8, 7.0 Hz, 1H), 4.18 (ddd, *J* = 14.1, 10.7, 7.0 Hz, 1H), 3.26 (d, *J* = 14.2 Hz, 1H), 3.16 (d, *J* = 14.2 Hz, 1H), 2.27 – 2.19 (m, 2H), 2.16 (s, 3H), 2.00 (t, *J* = 2.7 Hz, 1H), 1.98 – 1.92 (m, 2H), 1.63 – 1.50 (m, 1H), 1.48 – 1.35 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 171.9, 136.3, 129.9 (2C), 128.4 (2C), 127.0, 83.6, 69.1, 64.6, 61.4, 37.4, 30.6, 27.3, 23.2, 18.7, 14.1.

FTIR (neat): *v* = 3290, 3030, 2940, 1708, 1496,1455, 1358, 1259, 1181, 1153, 701 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{18}H_{22}O_3Na^+$: $[M+Na]^+$: 309.1467; found: 309.1462.

(+/-)-ethyl 2-acetyl-2-(4-nitrobenzyl)hept-6-ynoate **119**



116

119
$C_{18}H_{21}NO_5$
331.37 g/mol

The compound **119** was obtained from **116** and *p*-nitrobenzyl bromide following the **GPII** on 5.1 mmol scale (1 g). Purification by flash chromatography (EtOAc/Cyclohexane : 5/95 to 10/90) afforded **119** as a yellow solid (m= 1.4 g, 83% yield).

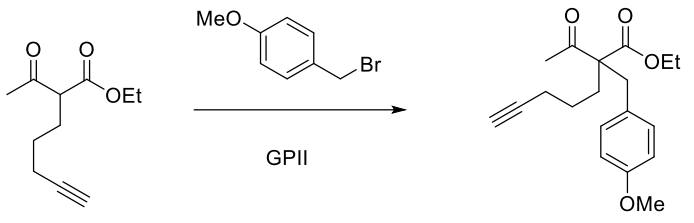
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 8.8 Hz, 2H), 4.19 (ddd, *J* = 14.1, 10.7, 7.0 Hz, 1H), 4.12 (ddd, *J* = 14.1, 10.7, 7.0 Hz, 1H), 3.34 (d, *J* = 14.0 Hz, 1H), 3.15 (d, *J* = 14.0 Hz, 1H), 2.23 – 2.19 (m, 2H), 2.14 (s, 3H), 2.01 – 1.86 (m, 3H), 1.58 – 1.47 (m, 1H), 1.39 – 1.28 (m, 1H), 1.22 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 171.3, 147.1, 144.5, 130.9 (2C), 123.5 (2C), 83.2, 69.4, 64.5, 61.8, 37.2, 30.9, 27.2, 23.0, 18.6, 14.0.

FTIR (neat): *ν* = 3292, 2940, 1708, 1519, 1345, 1259, 1181, 1153, 853, 700 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{18}H_{21}NO_5Na^+$: $[M+Na]^+$: 354.1317; found: 354.1312.

(+/-)-ethyl 2-acetyl-2-(4-methoxybenzyl)hept-6-ynoate **120**



116

120
$C_{19}H_{24}O_4$
316.40 g/mol

The compound **120** was obtained from **116** and *p*-methoxybenzyl bromide following the **GPII** on 5.1 mmol scale (1 g). Purification by flash chromatography (EtOAc/Cyclohexane : 7/93 to 10/90) afforded **120** as a colorless oil (m= 1.3 g, 79% yield).

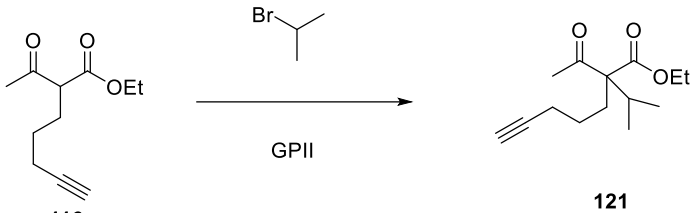
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.96 (d, *J* = 8.9 Hz, 2H), 6.75 (d, *J* = 8.9 Hz, 2H), 4.18 (ddd, *J* = 14.2, 10.8, 6.9 Hz, 1H), 4.12 (ddd, *J* = 14.2, 10.8, 6.9 Hz, 1H), 3.73 (s, 3H), 3.14 (d, *J* = 14.3 Hz, 1H), 3.05 (d, *J* = 14.3 Hz, 1H), 2.19 – 2.14 (m, 2H), 2.09 (s, 3H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.90 – 1.85 (m, 2H), 1.53 – 1.43 (m, 1H), 1.40 – 1.31 (m, 1H), 1.22 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 205.0, 171.8, 158.5, 130.8 (2C), 128.0, 113.7 (2C), 83.5, 69.0, 64.6, 61.3, 55.1, 36.5, 30.5, 27.3, 23.1, 18.6, 14.0.

FTIR (neat): *ν* = 3305, 2937, 2837, 2254, 1708, 1611, 1513, 1247, 1177, 1034, 729 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{19}H_{24}O_4Na^+$: $[M+Na]^+$: 339.1572; found: 339.1569.

(+/-)-ethyl 2-acetyl-2-isopropylhept-6-ynoate **121**



116

121
$C_{14}H_{22}O_3$
238.33 g/mol

The compound **121** was obtained from **116** and isopropyl bromide following the **GPII** on 2.6 mmol scale (500 mg). Purification by flash chromatography (EtOAc/Cyclohexane : 5/95 to 7/93) afforded **121** as a pale yellow oil (m= 510 mg, 84% yield).

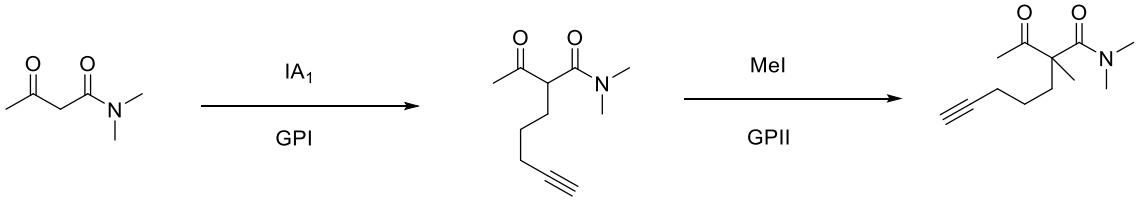
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 4.13 (2q, *J* = 7.1 Hz, 2H), 2.27 (hept, *J* = 7.0 Hz, 1H), 2.12 – 2.09 (m, 2H), 2.08 (s, 3H), 1.96 – 1.79 (m, 3H), 1.33 – 1.13 (m, 2H), 1.20 (t, *J* = 7.1 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 205.4, 171.6, 83.5, 68.8, 66.6, 60.7, 31.3, 30.5, 28.7, 23.3, 18.9, 18.7, 18.0, 14.1.

FTIR (neat): ν = 3309, 2969, 1703, 1464, 1355, 1229, 1128, 910, 730 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{14}H_{22}O_3Na^+$: $[M+Na]^+$: 261.1461; found: 261.1462.

(+/-)-2-acetyl-*N,N*,2-trimethylhept-6-ynamide **122**



435
$C_{11}H_{17}NO_2$
195.26 g/mol

122
$C_{12}H_{19}NO_2$
209.29 g/mol

The compound **122** was obtained in a two-step sequence from *N*,*N*-dimethyl-3-oxobutanamide and **IA_1** following the **GPI** on 23.2 mmol scale (3 g). Purification by flash chromatography (EtOAc/Cyclohexane: 1/9 to 1/1) afforded **435** as a pale yellow oil (m= 1.2 g, 26 % yield) which was submitted to the **GPII** on 3.1 mmol scale (600 mg) using methyl iodide as electrophile. Purification by flash chromatography (EtOAc/Cyclohexane : 10/90 to 25/75) afforded **122** as a colorless solid (m= 501 mg, 78% yield).

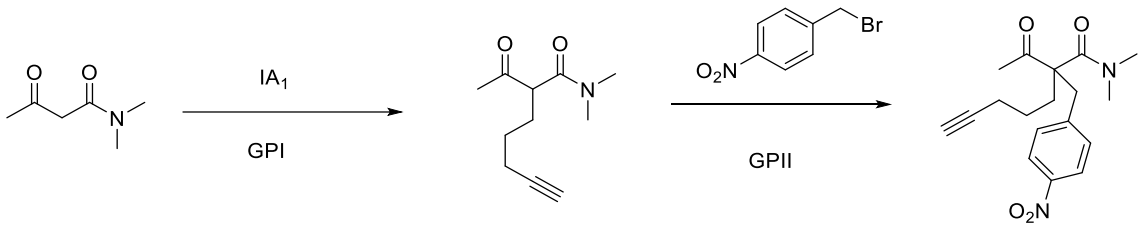
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.92 (brs, 3H), 2.81 (brs, 3H), 2.16 (td, *J* = 7.0, 2.5 Hz, 2H), 2.09 (s, 3H), 2.00 (ddd, *J* = 14.4, 12.1, 5.0 Hz, 1H), 1.90 (t, *J* = 2.6 Hz, 1H), 1.82(ddd, *J* = 14.4, 12.5, 4.6 Hz, 1H), 1.42 – 1.24 (m, 2H), 1.30 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4, 171.3, 83.8, 68.8, 59.5, 37.0 (2C), 34.0, 26.1, 23.2, 20.4, 18.7.

FTIR (neat): ν = 3308, 2941, 2249, 1707,1630, 1390, 1093, 907, 726 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{12}H_{19}NO_2Na^+$: $[M+Na]^+$: 232.1313; found: 232.1306.

2-acetyl-N,N-dimethyl-2-(4-nitrobenzyl)hept-6-ynamide **123**



435

123
$C_{18}H_{22}N_2O_4$
330.38 g/mol

The compound **123** was obtained in a two-step sequence from *N*,*N*-dimethyl-3-oxobutanamide and **IA_1** following the **GPI** on 23.2 mmol scale (3 g). Purification by flash chromatography (EtOAc/Cyclohexane: 1/9 to 1/1) afforded **435** as a pale yellow oil (m= 1.2 g, 26 % yield) which was

submitted to the **GPII** on 2 mmol scale (391 mg) using 4-nitrobenzyl bromide as electrophile. Purification by flash chromatography (EtOAc/Cyclohexane : 20/80 to 30/70) afforded **123** as a yellow solid (m= 403 mg, 61% yield).

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.16 – 8.06 (m, 2H), 7.25 – 7.19 (m, 2H), 3.28 (s, 2H), 3.05 – 2.79 (m, 6H), 2.26 – 2.18 (m, 2H), 2.17 (s, 3H), 1.99 – 1.90 (m, 3H), 1.49 – 1.33 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 207.1, 169.8, 147.2, 144.5, 131.1(2C), 123.5(2C), 83.5, 69.4, 64.3, 37.3(2C), 37.2, 30.9, 27.4, 22.9, 18.7.

FTIR (neat): *ν* = 1634, 1519, 1346, 908, 729 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{18}H_{22}N_2O_4Na^+$: $[M+Na]^+$: 353.1477; found: 353.1464.

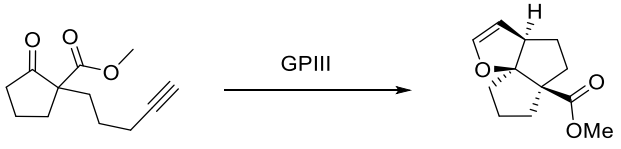
General procedure for the cyclization reaction GPIII (conditions A):

In a vial protected from the light was placed a suspension of Ag_2O (0.12 mmol, 0.5 equiv.) in acetonitrile (0.5 mL), DBU (0.24 mmol, 1 equiv.) was added, then a solution of corresponding precursors (0.24 mmol, 1 equiv.) in acetonitrile (0.5 mL) was added dropwise. The mixture was heated to 50 °C under air atmosphere and stirred until TLC showed complete disappearance of the starting material. The reaction mixture was quenched by water and extracted twice with Et_2O. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude mixture was purified by flash chromatography over silica gel affording the expected compound in a pure form.

General procedure for the cyclization reaction GP IV (conditions B):

In a vial protected from the light was placed a suspension of Ag_2O (0.12 mmol, 0.5 equiv.) in toluene (0.5 mL), protected from the light, was added DBU (0.24 mmol, 1 equiv.). Then a solution of corresponding precursors (0.24 mmol, 1 equiv.) in toluene (0.5 mL) was added dropwise. The mixture was heated to 75 °C under O_2 atmosphere (by O_2 balloon) and stirred until TLC showed complete disappearance of the starting material. The reaction mixture was quenched by water and extracted twice with Et_2O. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash chromatography over silica gel affording the expected compound in a pure form.

(+/-)-methyl (3a*R*,5a*R*,8a*S*)-3a,4,7,8-tetrahydro-5*H*-pentaleno[6a,1-b]furan-5a(6*H*)-carboxylate **19**



17

19

$C_{12}H_{16}O_3$

208.26 g/mol

The cyclization reaction was performed following the **GPIII** starting from **17** (67 mg, 0.24 mmol). Purification by flash chromatography (EtOAc/Cyclohexane : 5/95) afforded **19** as a colorless oil (m= 43 mg, 86% yield).

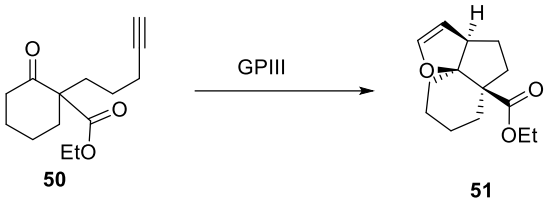
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (t, *J* = 3.0 Hz, 1H), 4.74 (t, *J* = 3.0 Hz, 1H), 3.68 (s, 3H), 3.04 – 3.02 (m, 1H), 2.48 (dt, *J* = 13.4, 8.9 Hz, 1H), 2.38 (td, *J* = 12.1, 7.0 Hz, 1H), 2.29 – 2.21 (m, 1H), 1.92 – 1.79 (m, 3H), 1.72 – 1.66 (m, 1H), 1.60 – 1.54 (m, 2H), 1.47 – 1.40 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 145.0, 106.1, 103.7, 63.3, 53.8, 51.9, 37.6, 35.9, 33.9, 31.5, 23.1.

FTIR (neat): *v* = 2951, 2255, 1725, 1621, 1434, 1271, 1148, 1070, 1012, 909, 728 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{12}H_{16}O_3Na^+$: $[M+Na]^+$: 231.0997; found: 231.0993.

(+/-)-ethyl (3a*R*,5a*R*,9a*S*)-4,5,6,7,8,9-hexahydroindeno[7a,1-b]furan-5a(3a*H*)-carboxylate **51**



50

51
$C_{14}H_{20}O_3$
236.31 g/mol

The cyclization reaction was performed following the **GPIII** starting from **50** (57 mg, 0.24 mmol). Purification by flash chromatography (EtOAc/Cyclohexane : 2/98 to 5/95) afforded **51** as a colorless oil (m= 48 mg, 85% yield).

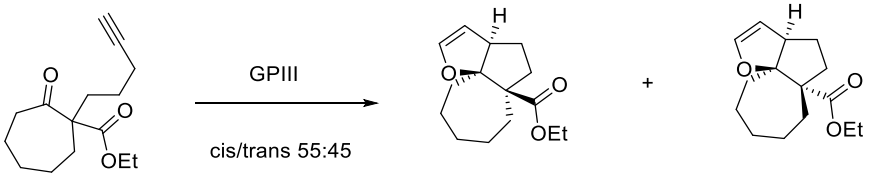
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (dd, *J* = 2.8, 1.6 Hz, 1H), 4.78 – 4.75 (t_{app}. *J* = 2.8 Hz, 1H), 4.21 (dq, *J* = 11.0, 7.1 Hz, 1H), 4.17 (dq, *J* = 11.0, 7.1 Hz, 1H), 3.00 – 2.97 (m, 1H), 2.24 (td, *J* = 12.9, 7.6 Hz, 1H), 2.03 (td, *J* = 13.5, 4.0 Hz, 1H), 1.93 – 1.70 (m, 5H), 1.58 – 1.50 (m, 2H), 1.43 – 1.37 (m, 2H), 1.29 – 1.24 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 144.4, 103.4, 96.9, 60.2, 55.8, 49.4, 33.3, 33.1, 30.6, 29.6, 22.5, 21.8, 14.3.

FTIR (neat): *v* = 2948, 2861, 1728, 1622, 1275, 1238, 1138, 1062, 1024, 727 cm^{-1}.

HRMS (ESI): *m/z* calcd for C14H20O3Na+: [M+Na]+: 259.1305; found: 259.1307.

(+/-)-ethyl (3a*R*,5a*R*,10a*S*)-3a,4,7,8,9,10-hexahydro-5*H*-azuleno[8a,1-b]furan-5a(6*H*)-carboxylate **104** and (+/-)-ethyl (3a*R*,5a*S*,10a*S*)-3a,4,7,8,9,10-hexahydro-5*H*-azuleno[8a,1-b]furan-5a(6*H*)-carboxylate **105**



92

104
5a(R)

105
5a(S)

$C_{15}H_{22}O_3$
250.34 g/mol

The cyclization reaction was performed following a modified **GP III** (2 eq of silver oxide was used instead of 0.5 eq) starting from **92** (120 mg, 0.48 mmol) affording the expected product as a diastereomeric mixture (*cis*/*trans*: 55/45). Purification by flash chromatography (EtOAc/Cyclohexane : 1/99 to 5/95) afforded **104** as a pale yellow oil (m= 39 mg, 33% yield) and **105** as a pale yellow oil (m= 30 mg, 25% yield).

104

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.21 (dd, *J* = 2.8, 1.5 Hz, 1H), 4.88 (t, *J* = 2.8 Hz, 1H), 4.20 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.15 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.02 – 2.99 (m, 1H), 2.14 (ddd, *J* = 14.3, 6.2, 5.0 Hz, 1H), 2.10 (ddd, *J* = 14.3, 6.2, 3.1 Hz, 1H), 1.94 – 1.62 (m, 8H), 1.50 – 1.41 (m, 2H), 1.37 – 1.32 (m, 1H), 1.30 – 1.24 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 175.3, 143.2, 105.1, 100.5, 61.1, 60.3, 53.4, 38.0, 34.9, 31.6, 30.3, 27.9, 26.1, 25.3, 14.3.

FTIR (neat): *ν* = 2930, 2862, 1722, 1620, 1452, 1270, 1239, 1179, 1095, 908, 732 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{15}H_{23}O_3^+$: $[M+H]^+$: 251.1642; found: 251.1639.

105

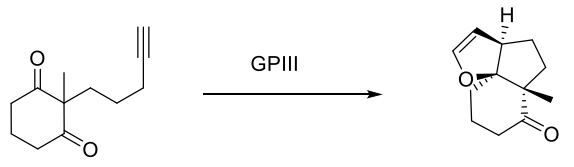
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.16 (dd, *J* = 2.8, 1.7 Hz, 1H), 4.77 (t, *J* = 2.8 Hz, 1H), 4.17 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.12 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.10 (ddd, *J* = 8.8, 4.7, 2.4 Hz, 1H), 2.31 – 2.21 (m, 2H), 1.93 – 1.83 (m, 3H), 1.77 – 1.49 (m, 9H), 1.26 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 174.5, 143.9, 103.6, 100.6, 61.5, 60.1, 51.3, 35.7, 34.9, 34.5, 30.5, 28.4, 22.8, 20.9, 14.3.

FTIR (neat): *ν* = 2926, 2864, 1725, 1623, 1461, 1257, 1183, 1149, 1069, 911, 730 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{15}H_{23}O_3^+$: $[M+H]^+$: 251.1642; found: 251.1641.

(+/-)-(3a*R*,5a*S*,9a*S*)-5a-methyl-3a,4,5,5a,8,9-hexahydroindeno[7a,1-b]furan-6(7*H*)-one **107**



97

107
$C_{12}H_{16}O_2$
192.26 g/mol

The cyclization reaction was performed following the **GPIII** starting from **97** (46 mg, 0.24 mmol). Purification by flash chromatography (EtOAc/Cyclohexane : 10/90) afforded **107** as a colorless oil (m= 36 mg, 78% yield).

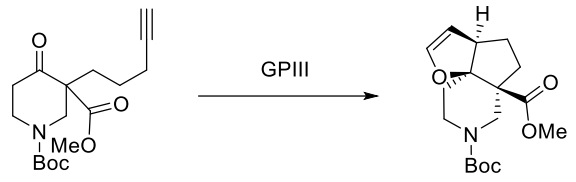
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.27 (dd, *J* = 1.8, 2.9 Hz, 1H), 4.77 (t, *J* = 2.9 Hz, 1H), 2.95 (ddd, *J* = 8.7, 3.8, 2.3 Hz, 1H), 2.49 (td, *J* = 5.7, 14.4Hz, 1H), 2.39 – 2.35 (m, 1H), 2.31 – 2.26 (m, 1H), 2.03 – 1.95 (m, 2H), 1.94 – 1.84 (m, 1H), 1.60 – 1.26 (m, 4H), 1.20 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 213.7, 144.3, 103.8, 98.7, 61.8, 49.9, 38.3, 32.6, 30.9, 29.9, 19.5, 18.7.

FTIR (neat): *v* = 2936, 2872, 2254, 1708, 1621, 1458, 1148, 1068, 997, 909, 728 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{12}H_{16}O_2Na^+$: $[M+Na]^+$: 215.1043; found: 215.1044.

(+/-)-7-(*tert*-butyl) 5a-methyl (3a*R*,5a*S*,9a*S*)-4,5,8,9-tetrahydrofuro[2',3':2,3]cyclopenta[1,2-c]pyridine-5a,7(3a*H*,6*H*)-dicarboxylate **108**



94

108
$C_{17}H_{25}NO_5$
323.39 g/mol

The cyclization reaction was performed following the **GPIII** starting from **94** (78 mg, 0.24 mmol). Purification by flash chromatography (EtOAc/Cyclohexane : 10/90 to 20/80) afforded **108** as a colorless oil (m= 62 mg, 80% yield).

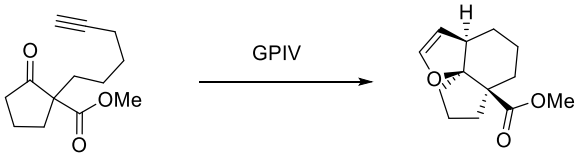
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.23 – 6.22 (m, 1H), 4.82 (t, *J* = 2.8 Hz, 1H), 4.29 – 4.26 (m, 1H), 4.13 – 4.07 (m, 1H), 3.70 – 3.66 (m, 3H), 3.07 – 3.06 (m, 1H), 2.83 – 2.59 (m, 2H), 2.29 – 2.21 (m, 2H), 1.93 – 1.85 (m, 1H), 1.78 – 1.73 (m, 1H), 1.65 – 1.58 (m, 1H), 1.54 – 1.48 (m, 1H), 1.46 – 1.42 (m, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 173.2, 154.6, 144.5, 103.5, 79.7, 56.0, 52.0, 49.6, 49.5, 48.5, 47.7, 30.6, 29.7, 29.5, 28.5 (3C).

FTIR (neat): *v* = 2971, 1733, 1693, 1427, 1250, 1169, 1139, 1066, 1018 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{17}H_{25}NO_5Na^+$: $[M+Na]^+$: 346.1630; found: 346.1613.

(+/-)-methyl (3a*R*,6a*S*,9a*S*)-3a,4,5,6,8,9-hexahydroindeno[3a,4-b]furan-6a(7*H*)-carboxylate **109**



99

109
$C_{13}H_{18}O_3$
222.28 g/mol

The cyclization reaction was performed following the **GPIV** starting from **99** (53 mg, 0.24 mmol). Purification by flash chromatography (EtOAc/Cyclohexane : 5/95 to 6/94) afforded **109** as a colourless oil (m= 35 mg, 65% yield).

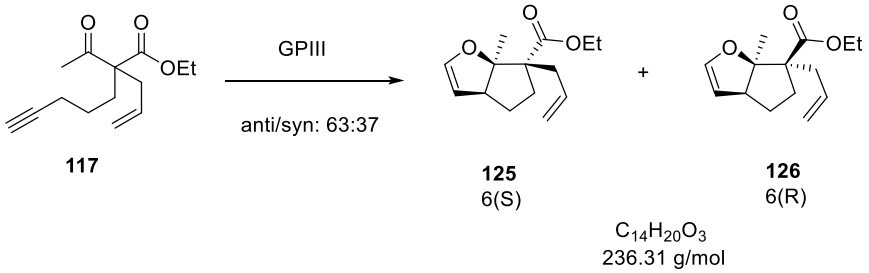
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.26 (dd, *J* = 2.8, 1.6 Hz, 1H), 4.98 (t, *J* = 2.8 Hz, 1H), 3.69 (s, 3H), 2.35-2.26 (m, 2H), 2.10 – 1.97 (m, 2H), 1.92 – 1.78 (m, 2H), 1.78 – 1.52 (m, 5H), 1.28 -1.18 (m, 1H), 1.15 – 1.05 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 176.7, 144.9, 107.0, 93.3, 52.5, 51.9, 45.9, 37.4, 34.2, 30.4, 30.1, 20.3, 18.6.

FTIR (neat): *v* = 2949, 2862, 1724, 1612, 1270, 1173, 1145, 1051, 908, 728 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{13}H_{18}O_3Na^+$: $[M+Na]^+$: 245.1154; found: 245.1146.

(+/-)-ethyl (3a*S*,6*S*,6a*R*)-6-allyl-6a-methyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*b*]furan-6-carboxylate **125** and (+/-)-ethyl (3a*S*,6*R*,6a*R*)-6-allyl-6a-methyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*b*]furan-6-carboxylate **126**



The cyclization reaction was performed following the **GPIII** starting from **117** (113.3 mg, 0.48 mmol) affording the expected product as a diastereomeric mixture (*anti*/*syn*: 63/37). Purification by flash chromatography (EtOAc/Cyclohexane: 2/98) afforded **125** as a colorless oil (m= 49.4 mg, 44% yield) and **126** as a colorless oil (m= 40 mg, 35% yield).

125

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.21 (dd, *J* = 2.8, 1.8 Hz, 1H), 5.67 (dddd, *J* = 17.2, 10.0, 7.6, 6.7 Hz, 1H), 5.06 (dddd, *J* = 17.2, 2.3, 1.6, 1.3 Hz, 1H), 5.00 (dddd, *J* = 10.0, 2.3, 1.3, 0.9 Hz, 1H), 4.86 (t, *J* = 2.8 Hz, 1H), 4.19 (ddd, *J* = 10.9, 7.1, 6.8 Hz, 1H), 4.13 (ddd, *J* = 10.9, 7.1, 6.8 Hz, 1H), 2.94 – 2.90 (m, 1H), 2.76 (qt, *J* = 7.0, 1.3, 1H), 2.26 – 2.18 (m, 1H), 2.14 – 2.07 (m, 1H), 2.05 – 1.97 (m, 1H), 1.70 – 1.63 (m, 1H), 1.44 – 1.36 (m, 1H), 1.30 (s, 3H), 1.32 – 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 174.4, 143.8, 135.1, 117.6, 104.8, 96.7, 61.5, 60.5, 53.6, 36.6, 32.6, 30.7, 23.3, 14.3.

FTIR (neat): *v* = 3078, 2978, 1723, 1618, 1446, 1217, 1144, 1072, 1020, 915, 722 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{14}H_{20}O_3Na^+$: $[M+Na]^+$: 259.1310; found: 259.1302.

126

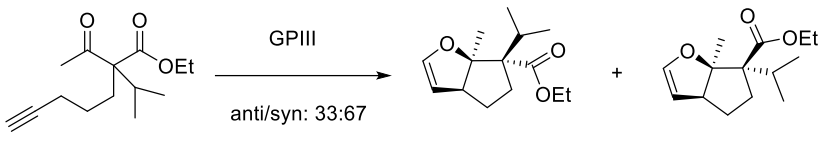
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.19 (dd, *J* = 2.7, 1.7 Hz, 1H), 5.64 – 5.53 (m, 1H), 5.07 (m, 1H), 5.05 – 5.03 (m, 1H), 4.77 (t, *J* = 2.8 Hz, 1H), 4.20 (dq, *J* = 10.3, 3.3 Hz, 1H), 4.16 (dq, *J* = 10.3, 3.3 Hz, 1H), 2.90 – 2.86 (m, 1H), 2.67 (ddq, *J* = 13.5, 6.1, 1.5 Hz, 1H), 2.20 – 2.11 (m, 1H), 1.95 (ddt, *J* = 13.4, 8.1, 1 Hz, 1H), 1.81 – 1.69 (m, 2H), 1.45 (s, 3H), 1.43 – 1.39 (m, 1H), 1.29 – 1.25 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 173.4, 144.4, 133.5, 118.2, 103.5, 97.5, 60.5, 60.5, 52.3, 37.0, 29.2, 28.2, 20.4, 14.4.

FTIR (neat): *v* = 3426, 2922, 2853, 1730, 1457, 1259, 1219, 1093, 1014, 799 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{14}H_{20}O_3Na^+$: $[M+Na]^+$: 259.1310; found:259.1310.

(+/-)-ethyl (3a*R*,6*R*,6a*S*)-6-isopropyl-6a-methyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*b*]furan-6-carboxylate **127** and (+/-)-ethyl (3a*R*,6*S*,6a*S*)-6-isopropyl-6a-methyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*b*]furan-6-carboxylate **128**



121 **127** 6(R) **128** 6(S)

$C_{14}H_{22}O_3$
238.33 g/mol

The cyclization reaction was performed following the **GPIII** starting from **121** (114 mg, 0.48 mmol) affording the expected product as a diastereomeric mixture (*anti*/*syn*: 33/67). Purification by flash chromatography (EtOAc/Cyclohexane : 2/98) afforded **127** as a colorless oil (m= 25 mg, 22% yield) and **128** as a colorless oil (m= 51 mg, 45% yield).

127

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.24 (dd, *J* = 2.6, 1.8 Hz, 1H), 4.82 (t, *J* = 2.8, 1H), 4.19 – 4.11 (m, 2H), 2.88 – 2.85 (brd, *J* = 9.2 Hz, 1H), 2.25 (ddd, *J* = 12.6, 6.6, 1.2 Hz, 1H), 2.10 – 2.02 (m, 1H), 2.00 – 1.90 (m, 1H), 1.58 – 1.53 (m, 1H), 1.46 (s, 3H), 1.39 – 1.33 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.29 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 174.0, 143.5, 104.3, 97.9, 64.9, 60.1, 54.9, 35.8, 34.4, 31.0, 24.8, 20.0, 19.5, 14.3.

FTIR (neat): *ν* = 2976, 2256, 1717, 1240, 1150, 908, 732 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{14}H_{22}O_3Na^+$: $[M+Na]^+$: 261.1467; found: 261.1461.

128

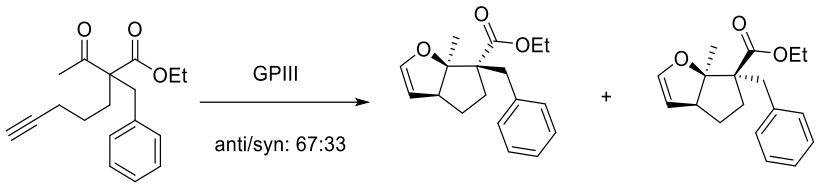
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.14 (dd, *J* = 2.8, 1.5 Hz, 1H), 4.85 – 4.83 (m, 1H), 4.17 – 4.11 (m, 2H), 2.85 – 2.82 (m, 1H), 2.35 – 2.24 (m, 2H), 1.85 – 1.75 (m, 2H), 1.48 (s, 3H), 1.42 – 1.36 (m, 1H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 174.3, 143.2, 104.9, 99.3, 64.8, 60.3, 53.1, 31.9, 30.7, 26.7, 20.3, 19.5, 19.3, 14.2.

FTIR (neat): *ν* = 2973, 1726, 1622, 1247, 1224, 1028, 910, 732 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{14}H_{22}O_3Na^+$: $[M+Na]^+$: 261.1467; found: 261.1480.

(+/-)-ethyl (3a*S*,6*S*,6a*R*)-6-benzyl-6a-methyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*b*]furan-6-carboxylate **129** and (+/-)-ethyl (3a*S*,6*R*,6a*R*)-6-benzyl-6a-methyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*b*]furan-6-carboxylate **130**



118 **129** 6(S) **130** 6(R)

$C_{18}H_{22}O_3$
286.37 g/mol

The cyclization reaction was performed following the **GPIII** starting from **118** (137 mg, 0.48 mmol) affording the expected product as a diastereomeric mixture (*anti*/*syn*: 67/33). Purification by flash chromatography (EtOAc/Cyclohexane : 2/98) afforded **129** as a colorless oil (m= 67 mg, 49% yield) and **130** as a colorless oil (m=25 mg, 18% yield).

129

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.19 (m, 3H), 7.18 – 7.14 (m, 2H), 6.30 (dd, *J* = 2.8, 1.9 Hz, 1H), 4.94 (t, *J* = 2.8 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.38 (d, *J* = 13.8 Hz, 1H), 2.97 – 2.93 (m, 1H), 2.83 (d, *J* = 13.8 Hz, 1H), 2.12 – 2.03 (m, 1H), 1.98 – 1.92 (m, 1H), 1.76 – 1.69 (m, 1H), 1.55 – 1.48 (m, 1H), 1.35 (s, 3H), 1.29 (t, *J* = 7,1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 144.1, 138.7, 130.0 (2C), 128.1 (2C), 126.3, 104.9, 97.0, 63.0, 60.5, 53.6, 37.4, 32.2, 30.7, 23.5, 14.2.

FTIR (neat): ν = 3030, 2976, 1721, 1618, 1453, 1183, 1141, 1076, 1021, 700 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{18}H_{22}O_3Na^+$: $[M+Na]^+$: 309.1467; found: 309.1452.

130

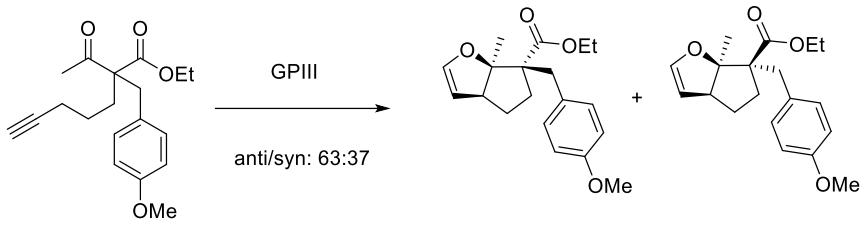
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.20 (m, 3H), 7.06 – 7.04 (m, 2H), 6.21 (dd, *J* = 2.7, 1.6 Hz, 1H), 4.81 (t, *J* = 2.7 Hz, 1H), 4.21 (ddd, *J* = 7.9, 4.2, 3.5 Hz, 1H), 4.17 (ddd, *J* = 7.9, 4.2, 3.5 Hz, 1H), 3.34 (d, *J* = 13.3 Hz, 1H), 3.01 – 2.98 (m, 1H), 2.44 (d, *J* = 13.3 Hz, 1H), 2.11 – 2.02 (m, 1H), 1.98 – 1.88 (m, 1H), 1.61 – 1.60 (m, 1H), 1.58 (s, 3H), 1.48 – 1.42 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 144.5, 137.5, 129.5 (2C), 128.4 (2C), 126.7, 103.6, 98.0, 61.9, 60.5, 52.2, 38.1, 29.5, 27.7, 20.3, 14.3.

FTIR (neat): ν = 3029, 2934, 2872, 1733, 1720, 1452, 1261, 1184, 1072, 1020, 723, 700 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{18}H_{22}O_3Na^+$: $[M+Na]^+$: 309.1467; found:309.1462.

(+/-)-ethyl (3a*S*,6*S*,6a*R*)-6-(4-methoxybenzyl)-6a-methyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*b*]furan-6-carboxylate **131** and (+/-)-ethyl (3a*S*,6*R*,6a*R*)-6-(4-methoxybenzyl)-6a-methyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*b*]furan-6-carboxylate **132**



120

131
6(S)

132
6(R)

$C_{19}H_{24}O_4$
316.40 g/mol

The cyclization reaction was performed following the **GPIII** starting from **120** (152 mg, 0.48 mmol) affording the expected product as a diastereomeric mixture (*anti*/*syn*: 63/37). Purification by flash chromatography (EtOAc/Cyclohexane : 4/96) afforded **131** as a colorless oil (m= 71 mg, 47% yield) and **132** as a colorless oil (m= 42 mg, 27% yield).

131

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 6.29 (dd, *J* = 2.8, 1.8 Hz, 1H), 4.93 (t, *J* = 2.8 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.76 (s, 3H), 3.31 (d, *J* = 13.9 Hz, 1H), 2.96 – 2.91 (m, 1H), 2,76 (d, *J* = 13.9 Hz, 1H), 2.05 (t, *J* = 12.5, 8.9, 7.2 Hz, 1H), 1.93 ($dt_{app.}$, *J* = 13.2, 6.8 Hz, 1H, 1H), 1.70 ($dt_{app.}$, *J* = 13.2, 6.8 Hz, 1H), 1.53 – 1.45 (m, 1H), 1.33 (s, 3H), 1.29 (t, *J* = 7,1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 158.2, 144.1, 130.9 (2C), 130.7, 113.5 (2C), 104.8, 96.9, 63.1, 60.5, 55.2, 53.7, 36.5, 32.2, 30.6, 23.6, 14.3.

FTIR (neat): *v* = 2936, 2835, 1720, 1611, 1511, 1445, 1245, 1176, 1021, 720 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{19}H_{24}O_4Na^+$: $[M+Na]^+$: 339.1572; found: 339.1582.

132

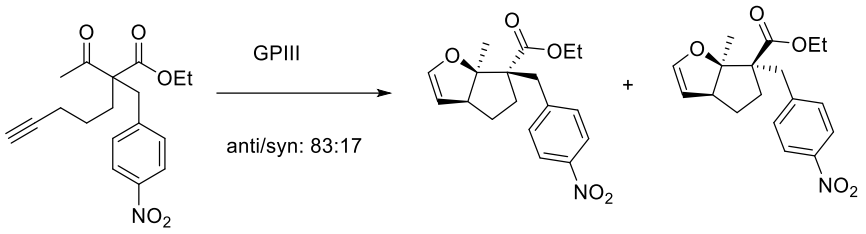
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 6.21 (dd, *J* = 2.7, 1.6 Hz, 1H), 4.80 (t, *J* = 2.8 Hz, 1H), 4.19 (2q, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 3.27 (dd, *J* = 13.5, 1.5 Hz, 1H), 2.99 – 2.97 (m, 1H), 2,38 (d, *J* = 13.5 Hz, 1H), 2.05 (tdd, *J* = 13.5, 7.1, 1.5 Hz, 1H), 1.95 – 1.85 (m, 1H), 1.62 – 1.58 (m, 1H), 1.56 (s, 3H), 1.46 – 1.41 (m, 1H), 1.28 (t, *J* = 7,1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 158.5, 144.5, 130.5 (2C), 129.5, 113.8 (2C), 103.6, 97.9, 62.0, 60.4, 55.3, 52.2, 37.3, 29.5, 27.6, 20.3, 14.3.

FTIR (neat): *v* = 2955, 2255, 1725, 1613, 1513, 1248, 1178, 1022, 909, 730 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{19}H_{24}O_4Na^+$: $[M+Na]^+$: 339.1566; found: 339.1566.

(+/-)-ethyl (3a*S*,6*S*,6a*R*)-6a-methyl-6-(4-nitrobenzyl)-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*b*]furan-6-carboxylate **135** and (+/-)-ethyl (3a*S*,6*R*,6a*R*)-6a-methyl-6-(4-nitrobenzyl)-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*b*]furan-6-carboxylate **136**



119 **135** 6(S) **136** 6(R)

$C_{18}H_{21}NO_5$
331.37 g/mol

The cyclization reaction was performed following the **GPIII** starting from **119** (80 mg, 0.24 mmol) affording the expected product as a diastereomeric mixture (*anti*/*syn*: 83/17). Purification by flash chromatography (EtOAc/Cyclohexane : 3/97) afforded **135** as a yellow solid (m= 49 mg, 62% yield) and **136** as a yellow oil (m= 9 mg, 11% yield) (**136** is contaminated by 10-15% of unseparable unknown byproduct).

135

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.11 (d, *J* = 8.7 Hz, 2H), 7.34 (d, *J* = 8.7 Hz, 2H), 6.28 (dd, *J* = 2.8, 1.8 Hz, 1H), 4.94 (t, *J* = 2.8 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.44 (d, *J* = 13.7 Hz, 1H), 2.97 – 2.93 (m, 1H), 2.95 (d, *J* = 13.7 Hz, 1H), 2.16 – 2.06 (m, 1H), 1.94 (ddd, *J* = 13.1, 6.7, 5.6 Hz, 1H), 1.70 (ddd, *J* = 13.1, 8.8, 6.7 Hz, 1H), 1.53 – 1.46 (m, 1H), 1.31 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 173.6, 147.0, 146.7, 143.9, 131.0 (2C), 123.3 (2C), 105.0, 97.2, 62.9, 60.9, 53.5, 37.7, 32.9, 30.9, 23.2, 14.2.

FTIR (neat): *ν* = 2977, 1722, 1605, 1520, 1347, 1187, 1022, 909, 731 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{18}H_{21}NO_5Na^+$: $[M+Na]^+$: 354.1317; found: 354.1302.

136

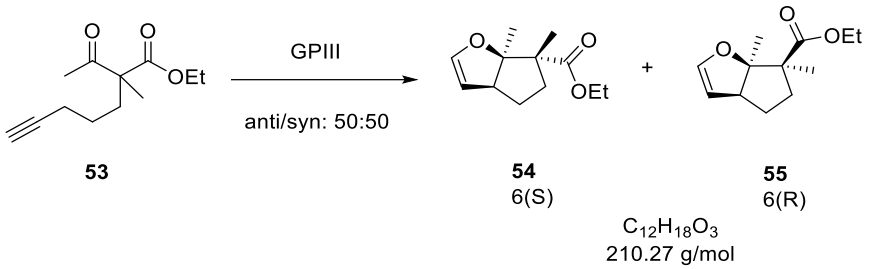
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.13 – 8.10 (m, 2H), 7.23 – 7.20 (m, 2H), 6.21 (dd, *J* = 2.8, 1.7 Hz, 1H), 4.82 (t, *J* = 2.8 Hz, 1H), 4.22 – 4.16 (m, 2H), 3.43 (d, *J* = 13.2 Hz, 1H), 3.02 – 3.00 (m, 1H), 2.55 (d, *J* = 13.2 Hz, 1H), 2.15 – 2.07 (m, 1H), 1.96 – 1.85 (m, 1H), 1.57 (s, 3H), 1.52 – 1.45 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 172.9, 145.4, 144.6, 130.4 (2C), 123.6 (2C), 103.6, 97.8, 61.7, 60.8, 52.1, 37.9, 29.5, 27.7, 27.0, 20.3, 14.3.

FTIR (neat): *ν* = 2928, 1727, 1606, 1521, 1346, 1188, 1074, 1020, 908, 858, 728 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{18}H_{21}NO_5Na^+$: $[M+Na]^+$: 354.1317; found: 354.1304.

(+/-)-ethyl (3a*R*,6*S*,6a*S*)-6,6a-dimethyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*b*]furan-6-carboxylate **54** and (+/-)-ethyl (3a*R*,6*R*,6a*S*)-6,6a-dimethyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*b*]furan-6-carboxylate **55**



53 **54** 6(S) **55** 6(R)

$C_{12}H_{18}O_3$
210.27 g/mol

The cyclization reaction was performed following the **GPIII** starting from **53** (50 mg, 0.24 mmol) affording the expected product as a diastereomeric mixture (*anti*/*syn*: 50/50). Purification by flash chromatography (EtOAc/Cyclohexane : 2/98) afforded **54** as a colorless oil (m= 19 mg, 38% yield) and **55** as a colorless oil (m= 18 mg, 36% yield).

54

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (dd, *J* = 2.8, 1.7 Hz, 1H), 4.87 (t, *J* = 2.8 Hz, 1H), 4.16 – 4.11 (m, 2H), 2.97 – 2.93 (m, 1H), 2.17 – 2.08 (m, 1H), 1.98 (ddd, *J* = 12.8, 7.4, 3.9 Hz, 1H), 1.68 – 1.62 (m, 1H), 1.43 – 1.37 (m, 1H), 1.28 – 1.25 (m, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 143.6, 104.9, 97.1, 60.5, 57.6, 52.9, 36.2, 31.4, 21.7, 18.3, 14.2.

FTIR (neat): ν = 2976, 2940, 1723, 1618, 1450, 1259, 1175, 1085, 1027, 725 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{12}H_{18}O_3Na^+$: $[M+Na]^+$: 233.1154; found: 233.1146.

55

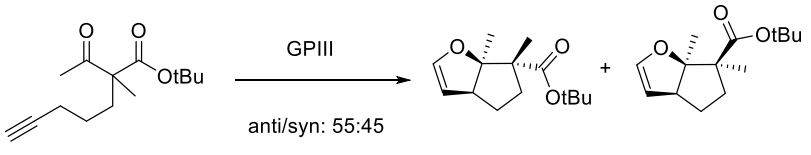
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (dd, *J* = 2.7, 1.7 Hz, 1H), 4.75 (t, *J* = 2.8 Hz, 1H), 4.19 (dq, *J* = 7.4, 3.6 Hz, 1H), 4.16 (dq, *J* = 7.4, 3.6 Hz, 1H), 2.91 – 2.87 (m, 1H), 2.37 – 2.26 (m, 1H), 1.86 – 1.72 (m, 1H), 1.59 – 1.52 (m, 1H), 1.45 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.28 – 1.22 (m, 1H), 1.19 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 144.5, 103.4, 97.4, 60.4, 56.5, 52.4, 33.1, 29.6, 21.1, 20.7, 14.3.

FTIR (neat): ν = 2971, 2255, 1729, 1621, 1372, 1261, 1156, 1021, 909, 730 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{12}H_{18}O_3Na^+$: $[M+Na]^+$: 233.1154; found: 233.1153.

(+/-)-*tert*-butyl (3a*S*,6*R*,6a*R*)-6,6a-dimethyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*b*]furan-6-carboxylate **133** and (+/-)-*tert*-butyl (3a*S*,6*S*,6a*R*)-6,6a-dimethyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*b*]furan-6-carboxylate **134**



110 **133** 6(R) **134** 6(S)

$C_{14}H_{22}O_3$
238.33 g/mol

The cyclization reaction was performed following the **GPIII** starting from **110** (114 mg, 0.24 mmol) affording the expected product as a diastereomeric mixture (*anti*/*syn*: 55/45). Purification by flash

chromatography (EtOAc/Cyclohexane : 2/98) afforded **133** as a colorless oil (m= 44.2 mg, 39 % yield) and **134** as a colorless oil (m= 41.6 mg, 36 % yield).

Only ^{1}H NMR are available due to the high unstability of the product and its rapid decomposition occurring even during storage neat at -20°C.

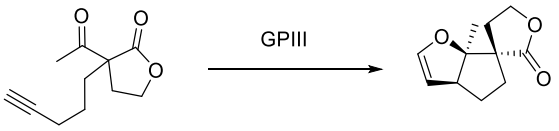
133

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 (dd, *J* = 2.8, 1.6 Hz, 1H), 4.87 (t, *J* = 2.8 Hz, 1H), 2.96 – 2.93 (m, 1H), 2.16 – 2.06 (m, 1H), 1.98 – 1.90 (m, 1H), 1.67 – 1.59 (m, 1H), 1.45 (s, 9H), 1.31 (s, 3H), 1.23-1.20 (m, 1H), 1.22 (s, 3H).

134

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 (dd, *J* = 2.8, 1.7 Hz, 1H), 4.77 (t, *J* = 2.8 Hz, 1H), 2.90 – 2.87 (m, 1H), 2.19 – 2.11 (m, 1H), 1.82-1.69 (m, 3H), 1.45 (m, 9H), 1.29 – 1.26 (m, 6H).

(+/-)-(3a*R*,6*R*,6a*S*)-6a-methyl-3a,4,4',5,5',6a-hexahydro-2'*H*-spiro[cyclopenta[*b*]furan-6,3'-furan]-2'-one **137**



111

137
$C_{11}H_{14}O_3$
194.23 g/mol

The cyclization reaction was performed following the **GPIII** starting from **111** (47 mg, 0.24 mmol). Purification by flash chromatography (EtOAc/Cyclohexane : 10/90) afforded **137** as a pale yellow solid (m= 27 mg, 58% yield).

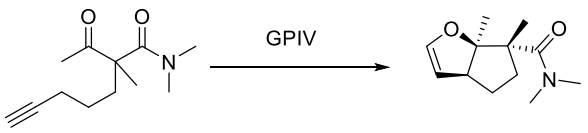
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (dd, *J* = 2.9, 1.5 Hz, 1H), 4.88 (t, *J* = 2.9 Hz, 1H), 4.34 – 4.29 (m, 1H), 4.26 – 4.20 (m, 1H), 3.09 – 3.06 (m, 1H), 2.63 – 2.56 (m, 1H), 2.30 – 2.21 (m, 1H), 2.06 – 2.00 (m, 2H), 1.83 – 1.75 (m, 1H), 1.46 – 1.41 (m, 1H), 1.36 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 143.9, 104.7, 96.3, 66.2, 57.5, 52.2, 34.5, 31.1, 30.5, 20.5.

FTIR (neat): ν = 2935, 2255, 1757, 1153, 1068, 1030, 907, 726 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{11}H_{14}O_3Na^+$: $[M+Na]^+$: 217.0841; found: 217.0839.

(3a*R*,6*R*,6a*S*)-*N*,*N*,6,6a-tetramethyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*b*]furan-6-carboxamide **163**



122

163
$C_{12}H_{19}NO_2$
209.29 g/mol

The cyclization reaction was performed following the **GPIV** starting from **122** (50 mg, 0.24 mmol). Purification by flash chromatography (EtOAc/Cyclohexane : 10/90 to 14/86) afforded **163** as a colorless oil (m= 37 mg, 73% yield).

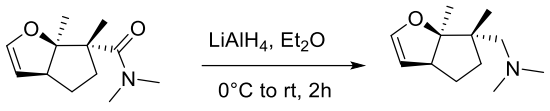
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.19 (m, 1H), 4.92 (m, 1H), 3.20 (brs, 3H), 2.94 – 2.89 (m, 4H), 2.32 (td, *J* = 13.7, 7.0 Hz, 1H), 2.00 – 1.93 (m, 1H), 1.60 (dd, *J* = 13.4, 6.1 Hz, 1H), 1.45 – 1.33 (m, 1H), 1.23 (s, 3H), 1.19 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 175.3, 143.3, 105.0, 94.8, 58.4, 55.6, 37.8, 37.5, 37.2, 29.4, 25.2, 18.7.

FTIR (neat): *ν* = 2965, 2241, 1618, 1376, 1080, 1080, 1022, 908, 728 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{12}H_{19}NO_2Na^+$: $[M+Na]^+$: 232.1313; found: 232.1251.

1-((3a*S*,6*S*,6a*R*)-6,6a-dimethyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*b*]furan-6-yl)-*N*,*N*-dimethylmethanamine **164**



163 **164**
$C_{12}H_{21}NO$
195.31 g/mol

To a cooled solution of amide **163** (40 mg, 0.19 mmol) in Et_2O (5mL) at 0°C was added $LiAlH_4$ (28.8 mg, 0.76 mmol) in one portion. The reaction mixture was allowed to warm to r.t and stirred for 2h. The solution was quenched by a saturated solution of $NaHCO_3$ and extracted three times by CH_2Cl_2. The organics combined were washed with brine, dried over $MgSO_4$ and reduced under pressure to afford the pure amine **164** as a yellow oil (m = 38 mg, quantitative yield).

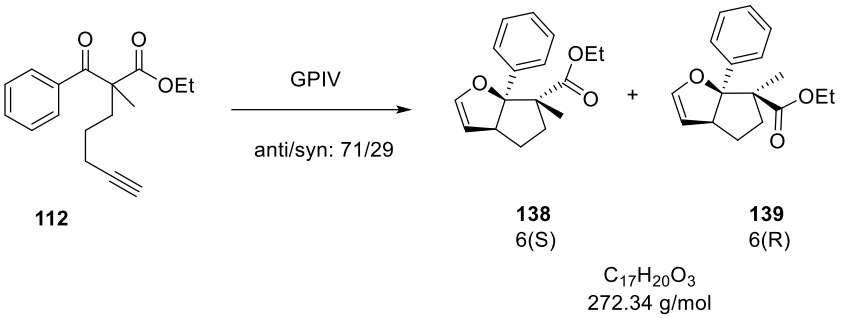
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.18 (brs, 1H), 4;78 (t, *J* = 2.4 Hz, 1H), 2.77 (brd, *J* = 8.4 Hz, 1H), 2.29 (s, 6H), 2.13 (d, *J* = 13.6 Hz, 1H), 2.02 (d, *J* = 13.6 Hz, 1H), 1.85 (dd, *J* = 6.4, 12.4 Hz, 1H), 1.78-1.68 (m, 1H), 1.45 (dt, *J* = 7.2, 12.4 Hz, 1H), 1.31-1.24 (m, 1H), 1.10 (s, 3H), 1.05 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 143.9, 104.18, 98.0, 64.0, 51.5, 50.7, 49.2, 33.0, 30.5, 29.8, 18.9, 18.7.

FTIR (neat): *ν* = 2926, 2855, 2766, 1618, 1456, 1369, 1276, 1147, 1067, 1067, 1035, 861, 720 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{12}H_{20}NO_2^+$: $[M+H]^+$: 196.1701; found: 196.1697.

(+/-)-ethyl (3a*R*,6*S*,6a*R*)-6-methyl-6a-phenyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*b*]furan-6-carboxylate **138** and (+/-)-ethyl (3a*R*,6*R*,6a*R*)-6-methyl-6a-phenyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*b*]furan-6-carboxylate **139**



112 **138** 6(S) **139** 6(R)

$C_{17}H_{20}O_3$
272.34 g/mol

The cyclization reaction was performed following the **GPIV** starting from **112** (131 mg, 0.48 mmol) affording the expected product as a diastereomeric mixture (*anti*/*syn*: 71/29). Purification by flash chromatography (EtOAc/Cyclohexane : 1/99 to 5/95) afforded **138** as a colourless oil (m= 38 mg, 29% yield) and **139** as a colourless oil (m= 17 mg, 13% yield).

138

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.39 (m, 2H), 7.28 – 7.26 (m, 2H), 7.22 - 7.18 (m, 1H), 6.33 (dd, *J* = 2.8, 1.8 Hz, 1H), 4.94 (t, *J* = 2.8 Hz, 1H), 3.69 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.67 – 3.62 (m, 1H), 3.50 (dq, *J* = 10.7, 7.1 Hz, 1H), 2.54 – 2.44 (m, 1H), 2.31 (ddd, *J* = 12.6, 7.2, 5.1 Hz, 1H), 1.82 – 1.74 (m, 1H), 1.67 – 1.60 (m, 1H), 1.34 (s, 3H), 0.82 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 143.5, 143.1, 127.7 (2C), 127.3, 125.6 (2C), 105.2, 100.0, 60.8, 60.3, 54.3, 37.0, 32.1, 19.5, 13.6.

FTIR (neat): *v* = 2938, 1720, 1624, 1447, 1148, 1029, 763, 700 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{17}H_{20}O_3Na^+$: $[M+Na]^+$: 295.1305; found: 295.1301.

139

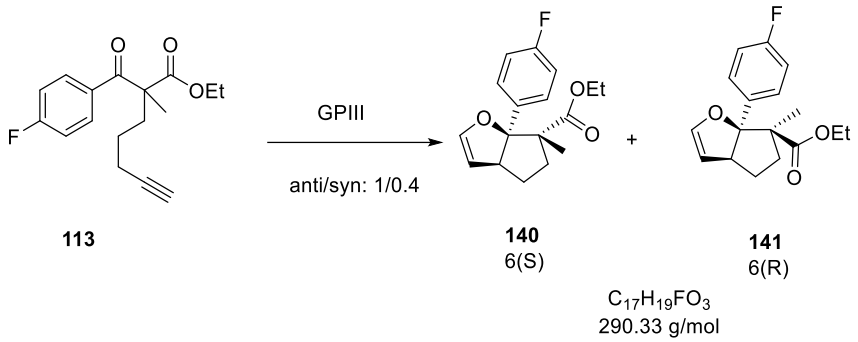
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.46 (m, 2H), 7.34 –7.26 (m, 3H), 6.33 (dd, *J* = 2.8, 1.8 Hz, 1H), 4.81 (t, *J* = 2.8 Hz, 1H), 4.19 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.09 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.57 (m, 1H), 2.60 (td, *J* = 13.2, 6.8, 1H), 2.13 – 2.02 (m, 1H), 1.68 (td, *J* = 12.4, 6.8 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, 3H), 0.96 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 144.3, 141.5, 127.4, 127.1 (2C), 127.0 (2C), 103.8, 100.0, 60.4, 58.8, 54.8, 33.7, 30.3, 22.4, 14.2

FTIR (neat): *v* = 2928, 1730, 1627, 1465, 1259, 1153, 908, 731 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{17}H_{20}O_3Na^+$: $[M+Na]^+$: 295.1305; found: 295.1303.

(+/-)-ethyl (3a*R*,6*S*,6a*R*)-6a-(4-fluorophenyl)-6-methyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*b*]furan-6-carboxylate **140** and (+/-)-ethyl (3a*R*,6*R*,6a*R*)-6a-(4-fluorophenyl)-6-methyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*b*]furan-6-carboxylate **141**



The cyclization reaction was performed following the **GPIII** starting from **113** (140 mg, 0.48 mmol) affording the expected product as a diastereomeric mixture (*anti*/*syn*: 1/0.4). Purification by flash chromatography (EtOAc/Cyclohexane : 1/99 to 5/95) afforded **140** as a colourless oil (m= 53 mg, 38% yield) and **141** as a colourless oil (m= 27 mg, 19% yield). (Product **7j** is contaminated by unseparable and unknown side products).

140

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.42 – 7.36 (m, 2H), 6.99 – 6.93 (m, 2H), 6.32 (dd, *J* = 2.8, 1.7 Hz, 1H), 4.95 (t, *J* = 2.8 Hz, 1H), 3.74 (dq, *J* = 10.7, 7.2 Hz, 1H), 3.64 – 3.58 (m, 1H), 3.57 (dq, *J* = 10.7, 7.2 Hz, 1H), 2.53 – 2.44 (m, 1H), 2.28 (ddd, *J* = 12.9, 7.2, 4.9 Hz, 1H), 1.79 (ddd, *J* = 12.9, 9.0, 7.3 Hz, 1H), 1.67 – 1.60 (m, 1H), 1.33 (s, 3H), 0.90 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 174.9, 162.1 (d, *J* = 245.6 Hz), 143.4, 138.7 (d, *J* = 3.3 Hz), 127.5 (d, *J* = 8.0 Hz, 2C), 114.4 (d, *J* = 21.3 Hz, 2C), 105.2, 99.7, 60.7, 60.4, 54.3, 37.0, 32.0, 19.3, 13.7.

^{19}F NMR (280 MHz, $CDCl_3$) *δ* -115.7.

FTIR (neat): *ν* = 2980, 1718, 1509, 1147, 1032, 907, 829, 728 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{17}H_{19}FO_3Na^+$: $[M+Na]^+$: 313.1210; found: 313.1207.

141

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.40 (m, 2H), 7.02-6.98 (m, 2H), 6.31 (dd, *J* = 2.8, 2.0 Hz, 1H), 4.81 (t, *J* = 2.8 Hz, 1H), 4,19 (dq, *J* = 10.9, 7.0 Hz, 1H), 4.12 (dq, *J* = 10.9, 7.0 Hz, 1H), 3.55-3.49 (m, 1H), 2.57 (td, *J* = 7.2, 13.6 Hz, 1H), 2.09-2.02 (m, 1H), 1.72-1.62 (m, 2H), 1.22 (t, *J* = 7.2 Hz, 3H), 0.94 (s, 3H).

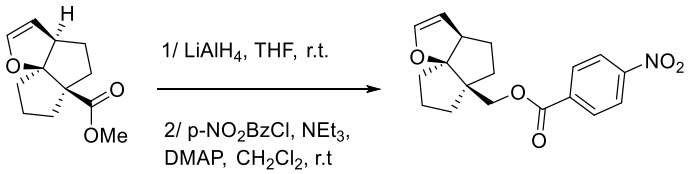
^{13}C NMR (100 MHz, $CDCl_3$) *δ* 174.3, 162.3 (d, *J* = 245.6 Hz), 144.3, 137.2 (d, *J* = 3.3 Hz), 128.7 (d, *J* = 8.0 Hz, 2C), 114.1 (d, *J* = 21.3 Hz, 2C), 103.9, 99.8, 60.5, 58.7, 54.9, 33.7, 30.3, 22.4, 14.3.

^{19}F NMR (280 MHz, $CDCl_3$) *δ* -115.7.

FTIR (neat): *ν* = 2954, 1727, 1509, 1153, 1038, 907, 830, 728 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{17}H_{19}FO_3Na^+$: $[M+Na]^+$: 313.1210; found: 313.1208.

(+/-)- ((3a*R*,5a*S*,8a*S*)-3a,4,7,8-tetrahydro-5*H*-pentaleno[6a,1-b]furan-5a(6*H*)-yl)methyl 4-nitrobenzoate **91**



(+/-)-**19**

91
$C_{18}H_{19}NO_5$
329.35 g/mol

To a suspension of $LiAlH_4$ (170.8 mg, 4.5 mmol) in THF (3 mL), cooled to 0 °C, was slowly added at 0 °C a solution **19** (100 mg, 0.48 mmol) in THF (3 mL) over 20 minutes. After completion of addition, the mixture was stirred at room temperature for 1 h. EtOAc (3 mL) was carefully added at 0 °C followed by slow addition of water (1 mL). The reaction mixture was filtered, dried over $MgSO_4$ and concentrated under reduced pressure affording the corresponding alcohol in a pure form. The crude was dissolved in dry DCM (5 mL) then NEt_3 (84 µL, 0.6 mmol), DMAP (2.5 mg, 0.02 mmol) and 4-nitrobenzoyl chloride (94 mg, 0.5 mmol) were successively added. The reaction was stirred for 24 h at room temperature. The reaction mixture was diluted with DCM (20 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 8/92 to 10/90) afforded **91** as colorless needles (m= 142 mg, 90% over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.30 – 8.27 (m, 2H), 8.21 – 8.18 (m, 2H), 6.24 (dd, *J* = 2.8, 2.0 Hz, 1H), 4.78 (t, *J* = 2.5 Hz, 1H), 4.33 (d, *J* = 14.4 Hz, 1H), 4.28 (d, *J* = 14.4 Hz, 1H), 3.10 (dq, *J* = 7.5, 2.6 Hz, 1H), 2.13 – 2.04 (m, 1H), 1.99 – 1.89 (m, 3H), 1.85 – 1.75 (m, 2H), 1.68 – 1.54 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 164.9, 150.5, 145.0, 136.1, 130.7 (2C), 123.6 (2C), 103.8, 70.4, 55.5, 54.7, 53.5, 38.5, 35.3 (2C), 31.4, 22.5.

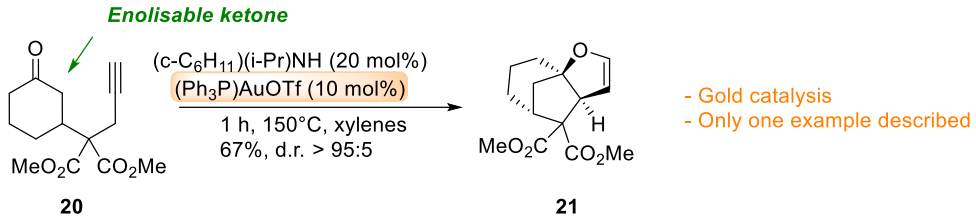
FTIR (neat): *ν* = 2951, 2898, 1723, 1608, 1527, 1348, 1273, 1119, 1102, 1014, 718 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{18}H_{19}NO_5Na^+$: $[M+Na]^+$: 352.1161; found: 352.1169.

V Silver oxide(I)/DBU promoted synthesis of furan frameworks

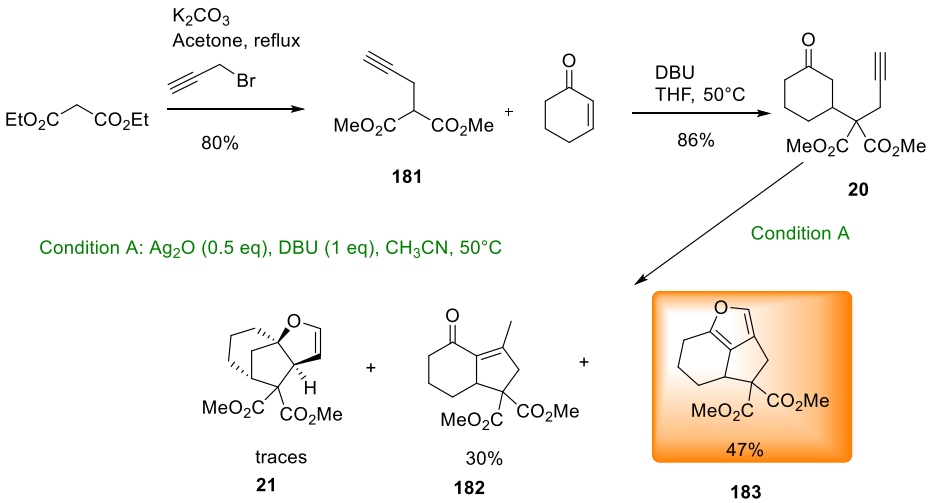
V.a Preamble

In the course of their work on dual organocatalysis combining gold and aminocatalysis, Kirsch *et al*. unexpectedly obtained a tricyclic *cis*-fused dihydrofuran adduct by using a co-catalytic amount of (Ph_3P)AuOTf (10 mol%) and (*c*-C_6H_{11})(*i*-Pr)NH (20 mol%) in xylenes at 150°C for 1h (Scheme 53).[9] Surprisingly, this transformation has only been underlined in a single case by the authors and, to the best of our knowledge, has not been reported again in literature.



Scheme 53

During our study on 2,3-dihydrofuran synthesis,[56] we took care to avoid enolisable position between the two carbonyls since the pka is low which could be deleterious for our reaction. However, we did not try simple enolizable ketone like Kirsch and coworkers (Scheme 53). We decided, in parallel to our work on intermolecular reaction (chapter III.f), to reproduce their result by submitting the same ketone **20** to our conditions for the synthesis of 2,3-dihydrofuran derivatives. To this aim, we previously synthetized the same ketone precursor **20** and we applied conditions A for the cyclization (Scheme 54).

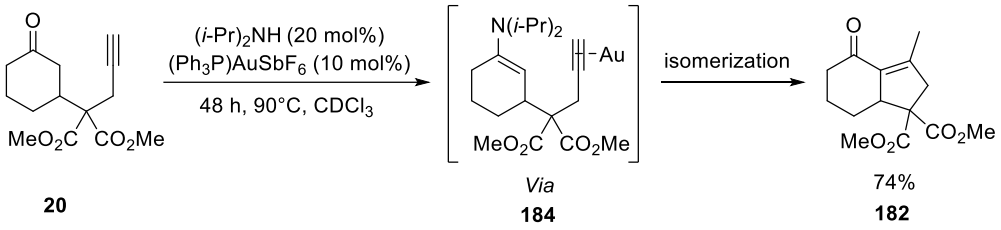


Scheme 54

To our surprise, we detected only traces of 2,3-dihydrofuran **21** (product already obtained and described by Kirsch and collaborators) whereas two new products were isolated. After investigations,

we could unambiguously confirm the structure of the newly formed compounds: We got the bicyclic enone **182** in 30 % yield and the furan derivatives **183** in 47 % yield.

Enone **182** would probably come from a conià-ene reaction and subsequent isomerization of the resultant external double bond. We can notice that this enone **182** has already been described, among other, by Kirsch and collaborators during their study on dual activation (Scheme 55).[9]

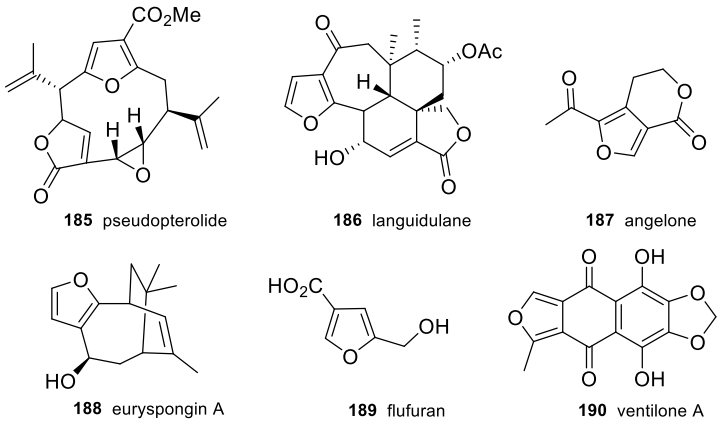


Scheme 55

In our opinion, the most relevant result was getting the highly strained furan derivative **183**. Indeed, if we go through the literature, we can find that access to similar congested furans requires harsh conditions, expensive catalyst and/or multistep sequence for the elaboration of the precursor (we will discuss some representative examples later in this chapter). In a more general view, we did not find any similar reaction in the literature for the synthesis of furan cores. Access to such units is highly important since they are very useful from a synthetic point of view as well as their various biological properties. For this purpose, we decided to pursue our investigation on this new transformation more deeply.

V.b Introduction

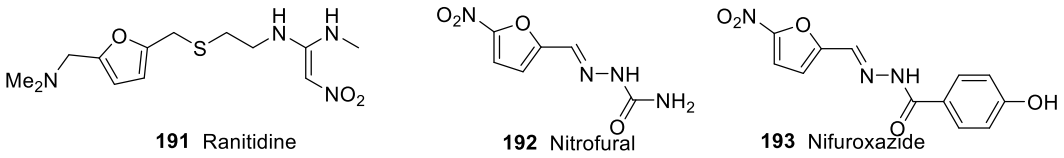
Furan-based molecules are among the most commonly found heterocyclic compounds encountered in a broad array of natural products but also in pharmaceuticals and polymers (Scheme 56).



Scheme 56

Due to their biological activities, considerable efforts have been devoted to drugs discovery in the synthesis of molecules containing furan moiety. For example, we can mention Ranitidine **191** which is

receptor antagonist inhibiting stomach acid production or Nitrofural **192** and Nifuroxaxide **193** two bactericides used against infectious disease (Scheme 57).

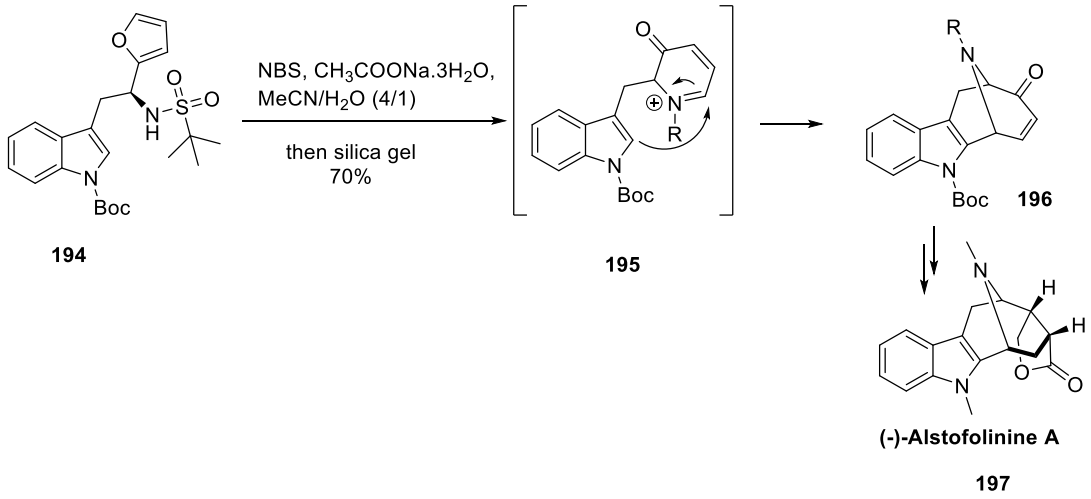


191 Ranitidine **192** Nitrofural **193** Nifuroxazide

Scheme 57

In addition, furan derivatives represent a valuable intermediate in organic chemistry as they participate, for example, in total synthesis of complex molecules.[76] As a significant and recent example, we can mention the elegant synthesis of Astofolinine A **197** by Qi and coworkers in 2019.[77] The authors used a cascade reaction involving an aza-Achmatowics rearrangement followed by indole nucleophilic cyclization in the building of indole-fuzed azabicyclo[3.3.1]nonane framework **196** of Astofoline A (Scheme 58).

Qi *et al.*: *key step in the total synthesis of (-)-Alstofolinine A*



194 **195** **197**

Scheme 58

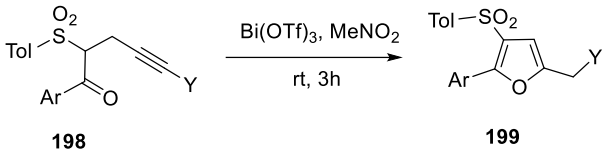
Consequently substantial consideration has been paid to the advance of effective methods to build furan cores after the discovery of traditional and well-known sequences such as Paal-Knorr synthesis[78] or Feist-Benary reaction.[79] Over the last decades, numerous alternatives approach have been reported and reviewed.[80]

V.c Furan synthesis catalyzed by silver salts.

Due to its highly important properties in biological and synthetic point of view, numerous synthetic pathways has been developed and reported by chemists.[80] In this chapter, we will expose few selected examples without silver and then we will examine some examples involving silver catalysis (obviously in both cases this list will not be exhaustive).

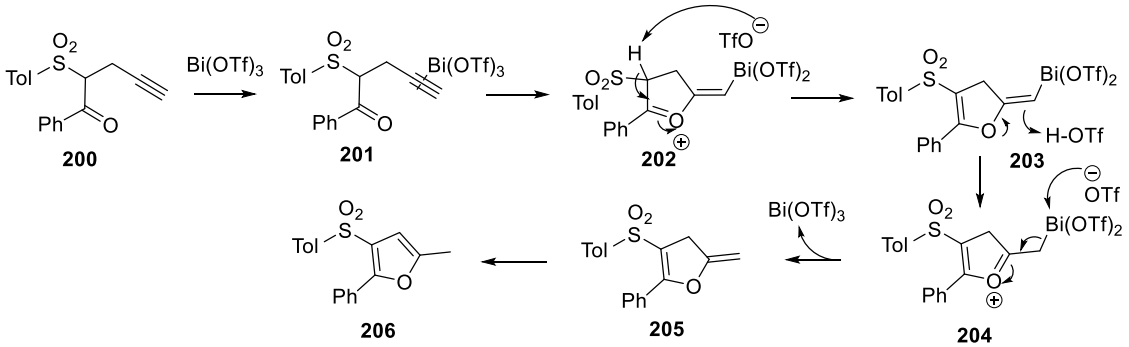
V.c.1 Furan synthesis by Chang and coworkers

Metal transitions have been extensively studied in the synthesis of polysubstituted furan units. In this filed, we can mention the recent work made by Chang and coworkers on the $Bi(OTf)_3$ mediated cycloisomerisation of γ-alkynyl arylketones **198** leading to tri-substituted furan cores **199**. In their report, the author described the first use of $Bi(OTf)_3$ applied to the furan synthesis (Scheme 59).



Scheme 59

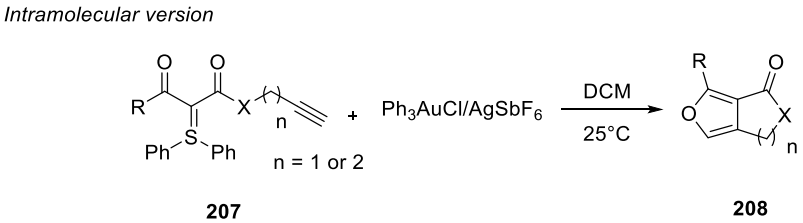
The mechanism postulated by the authors involves a first complexation of the $Bi(OTf)_3$ onto the triple bond followed by a 5 *exo-dig* intramolecular annulation (Scheme 60).



Scheme 60

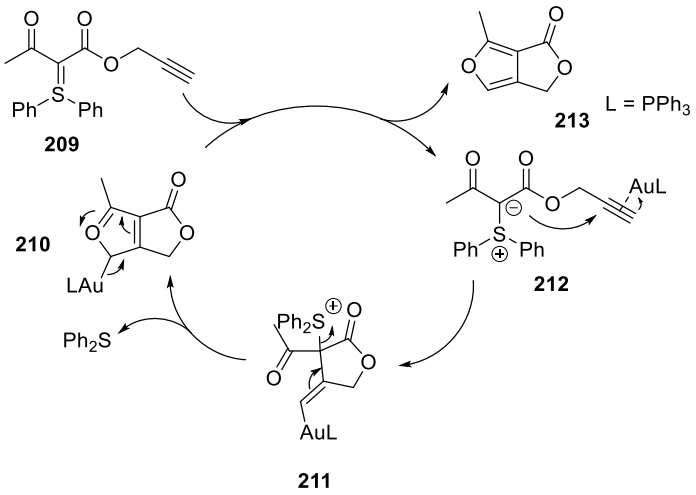
V.c.2 Furan synthesis by Maulide *et al.*

For recent example, we can also highlight the work reported by Maulide and collaborators on gold-catalyzed synthesis of furans and furanones from sulfur ylides.[81] This methodology has proved its efficiency by delivering polysubstituted furans in inter- or intramolecular fashion in good yield with excellent regioselectivity. The intramolecular version is gathered in Scheme 61.



Scheme 61

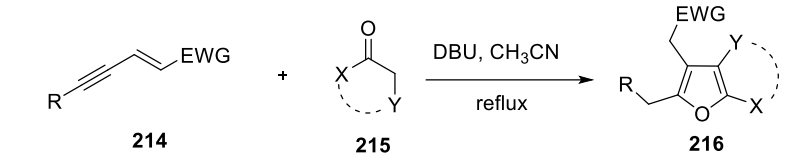
The mechanism postulated by Maulide and coworkers is the following (Scheme 62):



Scheme 62

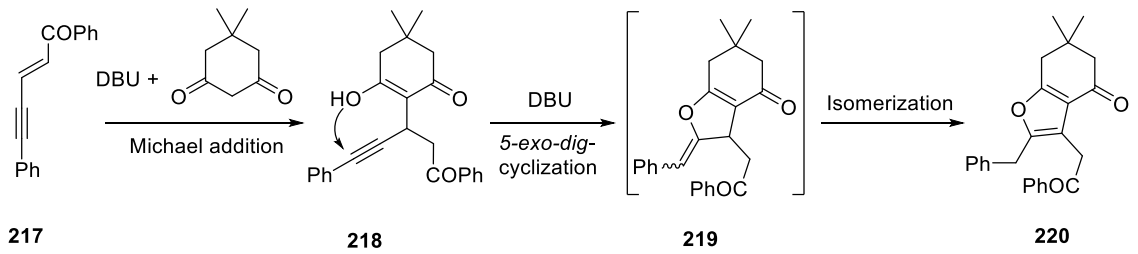
V.c.3 Furan synthesis by Reddy's group

Although transition metals are useful and widely described in the furan synthesis, some developed routes towards furan synthesis occur without metal. For example, we can cite the work reported by Reddy's group on metal free tandem C–C/C–O Bond formation for the access to diversely functionalized tetra-substituted furans. Authors depicted herein a method where DBU-mediated tandem Michael addition/5-exo-dig-cycloisomerization of enynes and keto-methylenes. This [3 + 2]-cyclization operates simply under metal-free reaction conditions with perfect atom economy (Scheme 63).[82]



Scheme 63

The mechanism proposed by Reddy *et al*. is a one-pot cascade reaction depicted below (Scheme 64).



Scheme 64

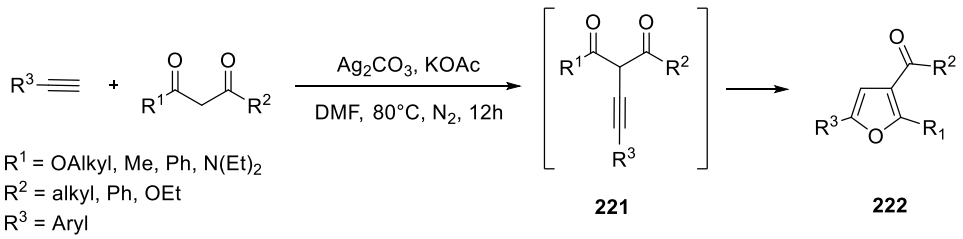
V.d Silver catalyzes furan synthesis

Among transition metals, silver salts have shown its usefulness in the synthesis of furan derivatives through numerous and various chemical transformations.[83] In 2016, Pale and coworkers dedicated a review to this topic.[84]

Due to the myriad methods published, we cannot present all of them so we will expose few representatives' synthetic developments in this chapter, highlighting the versatile activity of silver salts.

V.d.1 Lei's furan synthesis

In most cases, the synthesis of furan units can require tedious multi-step synthesis and purification. Additionally, some of these transformations require a transitory leaving group for their promotion, which is, in an eco-compatibility and carbon footprint point of view, less attractive. In 2012, Lei's group solved this problem through an elegant strategy using silver mediated oxidative C-H/C-H coupling between an alkyne and 1,3-dicarbonyl compounds, allowing the synthesis of furan derivatives **222** with perfect atom economy (Scheme 65).[85]

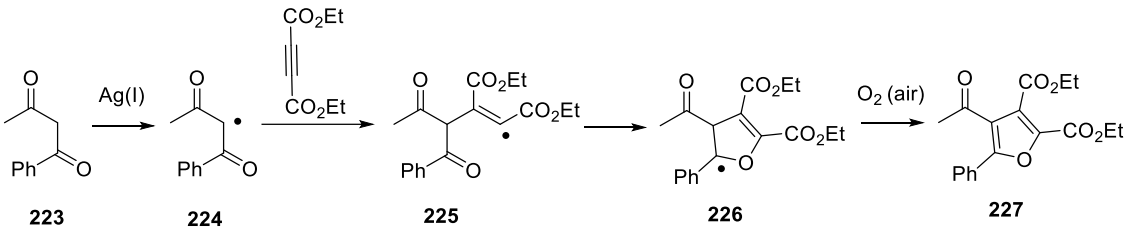


Scheme 65

While no mechanism was proposed in this publication, control experiments would suggest a dual role of silver carbonate. So, Ag_2CO_3 would serve to the formation of the alkynyl silver whereas additional silver carbonate would act as oxidizing agent initiating a radical process necessary to promote the coupling reaction. In addition, while Ag_2CO_3 is used in a sub-stoichiometric amount (2 eq), it is worth to mention authors described a process to recycle Ag_2CO_3 at the end of the reaction.

V.d.2 Furan synthesis by Zhang et al.

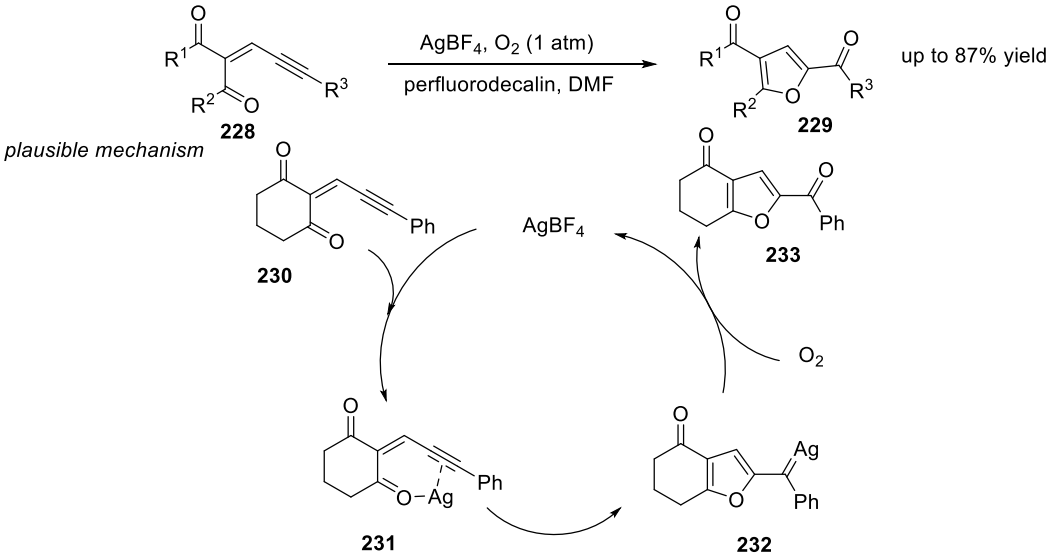
In a similar manner Zhang et al reported addition/oxidative cyclization of 1,3-dicarbonyl compounds and alkynoates promoted by Ag_2CO_3 highlighting the propensity of silver salts to initiate radical reaction.[86] The mechanism is depicted in Scheme 66.



Scheme 66

V.d.3 Furan synthesis by Liu and coworkers

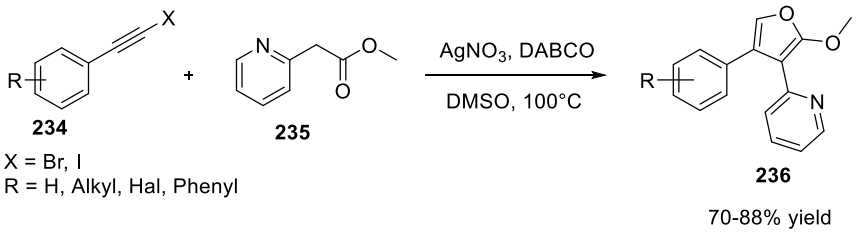
Unsaturated systems such as enynol, allenylketone or enynone are useful precursors for the synthesis of furans. In this field we could cite the work reported by Liu *et al.*[87] where $AgBF_4$ initiates the transformation of the unsaturated system thanks to a π-Lewis activation of the alkyne part. The mechanism proposed by Liu and coworkers is depicted below (Scheme 67).



Scheme 67

V.d.4 Furan synthesis by Jiang and coworkers

Another interesting example is the synthesis of 2,3,4-trisubstituted furans *via* silver-catalyzed sequential nucleophilic addition and cyclization reactions of haloalkynes reported by Jiang and coworkers (Scheme 68).[88]



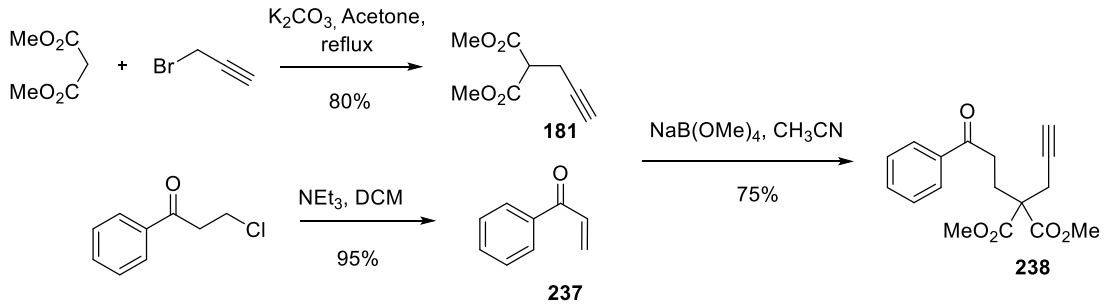
Scheme 68

Although isolated yields ranged from 70% to 88%, this approach seems to be restricted to pyridinylacetate since the authors described all their examples with this substrate.

V.e Silver oxide(I)/DBU promoted synthesis of furans derivatives

V.e.1 Optimization of reactional conditions

Enthusiastic by the discovering of a new containing furan unit product 183 (see Scheme 54), we wished to pursue our investigations about the reactivity of silver salts towards such alkynone systems. We clearly identified that the key point to promote this unprecedented cyclization lay in the use of enolizable ketone. So firstly, in order to confirm this result, we ran a similar reaction on simpler substrate **238**. This precursor was easily accessible by the following sequence depicted below (Scheme 69).



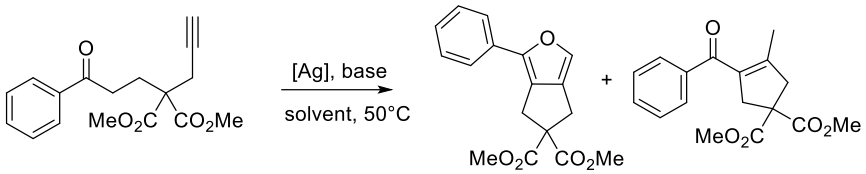
Scheme 69

Malonate **181** was obtained by using classical alkylation conditions between both commercially available dimethyl malonate and propargyl bromide. In parallel, 3-chloropropiophenone was subjected to NEt_3 in DCM, delivering the α-β unsaturated ketone **237**. Both partners **181** and **237** were submitted to the conditions developed by Gottbrath et al. using $NaB(OMe)_4$ as catalyst for Michael addition. [89] The ynone precursor **238** was obtained in 75 % yield.

It is worth to mention that $NaB(OMe)_4$ was prepared by mixing $NaBH_4$ in MeOH according the procedure reported by Gottbrath and coworkers. The white powder obtained can be stored over several months without specific precautions.

With the ynone precursor **238** in hand, we performed the optimization of the reaction conditions (Table 6).

Table 6



238 **239** **240**

Entry	[Ag]	Base	Solvent	Time[a]	^{1}H NMR yield[b] **239**/**240**
1	$AgNO_3$ 1 eq	DBU	CH_3CN	24h[c]	24% / 4%
2	Ag_2CO_3 0.5 eq	DBU	CH_3CN	2h	53% / 5 %
3	AgOTf 1 eq	DBU	CH_3CN	2h	44% / 4%
4	$AgNTf_2$ 1 eq	DBU	CH_3CN	2h	70% / 7%
5	$AgSbF_6$ 1 eq	DBU	CH_3CN	4h	54% / 3%
6	Ag_3PO_4 0.33 eq	DBU	CH_3CN	4h	47% / 12%
7	Ag_2O 0.5 eq	DBU	CH_3CN	2h	75% / -[d]
8	Ag_2O 0.5 eq	K_2CO_3	CH_3CN	24h[c]	40% / 8%
9	Ag_2O 0.5 eq	NEt_3	CH_3CN	24h[c]	66% / 3%
10	Ag_2O 0.5 eq	Pyrrolidine	CH_3CN	4h	73% / 4%
11	Ag_2O 0.5 eq	*i*Pr_2NEt	CH_3CN	24h[c]	45% 5%
12	Ag_2O 0.5 eq	DBU	DMF	2h	62% / 3%
13	Ag_2O 0.5 eq	DBU	CH_2Cl_2	24h[c]	14% / 2%
14	Ag_2O 0.5 eq	DBU	THF	3h	66% / 3%
15	Ag_2O 0.5 eq	DBU	MeOH	3h	20% / 2%
16	Ag_2O 0.5 eq	DBU	Toluene	3h	54% / 5%
17	Ag_2O 0.5 eq	-	CH_3CN	24h[c]	19% / 2%
18	-	DBU	CH_3CN	24h	n.r

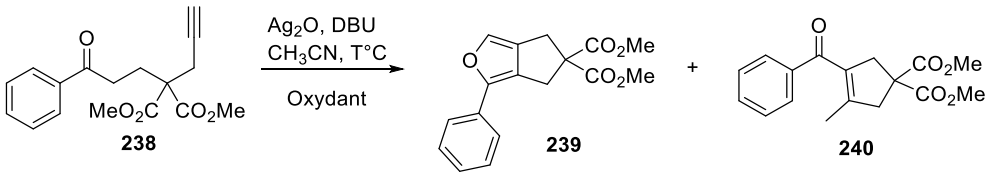
[a] The reaction was monitored by TLC. [b] ^{1}H NMR yield was determined from 1,3,5-trimethoxybenzene as internal standard. [c] Not complete after 24h. [d] Only traces of expected product were detected by ^{1}H NMR

As shown in Table 6, using the couple $AgNO_3$/DBU in CH_3CN at 50°C allowed the low conversion of ketone **238** into the desired furan derivative **239** after 24h (Entry 1, 24% by ^{1}H NMR). Traces of the ketone **240** (Entry 1, 4%), probably deriving from a Conia-ene reaction and subsequent isomerisation was also detected. Ag_2CO_3 and AgOTf provided **239** in similar yield (respectively 53 % and 44 %, Entry 2 and 3) whereas $AgNTf_2$ improved significantly the yield in favour of **239** (70 %, Entry 4). $AgSbF_6$ and Ag_3PO_4 afforded **239** in moderate yields after 4h, respectively 54% and 47% (Entry 5 and 6). Finally, the best catalyst has proved to be Ag_2O, affording the expected furan **239** in 75 % yield without traces of Conia-ene product (Entry 7). Using other organic or inorganic bases like K_2CO_3 or NEt_3 or *i*Pr_2NEt turned out to be effective while with a very slow conversion (Entry 8, 9 and 11). Pyrrolidine afforded **239** in good yield after 4h (Entry 10, 73%). A short screening of solvent highlighted the propensity of DMF (Entry 12) and THF (Entry 14) to promote cleanly the reaction with similar yield in contrast to protic solvent such as MeOH (Entry 15). DCM was not suitable for the reaction even after a prolonged time (Entry 13), while toluene could afford **239** in moderate yields after 3h (Entry 16, 54%). Finally, CH_3CN has been revealed to be the most suitable solvent for this reaction. Without base, we obtained only 19% conversion after 24 h (Entry 17), whereas without silver, no reaction

occurred after a prolonged time (Entry 18). These two last experiments underlined the need to combine Ag_2O/DBU for a clean and complete conversion of ketone **238** into the furan **239**.

To increase the efficiency of this transformation, we tried to reduce the amount of Ag_2O and DBU. Different oxidants were also added when silver(I) oxide loading was lowered (Table 7).

Table 7



Entry	Ag_2O	Oxidant	DBU	Time	^{1}H NMR yield[b] **239/240**
1	0.5 eq	-	0.5 eq	2h	68% / -
2	0.5 eq	-	0.2 eq	2h	70% / 3 %
3	0.25 eq	-	0.2 eq	24h[a]	49% / 3%
4	0.25 eq	O_2	0.2 eq	18h	67% / 3%
5	0.25 eq	O_2	1 eq	3h	56% / 6%
6	0.25 eq	CeO_2 1 eq	1 eq	8h	45% / 13%
7	0.25 eq	$K_2S_2O_8$ 1 eq	1 eq	4h	16% / 25%
8	0.25 eq	$PhI(OAc)_2$ 1 eq	1 eq	24h[a]	44% / 3%

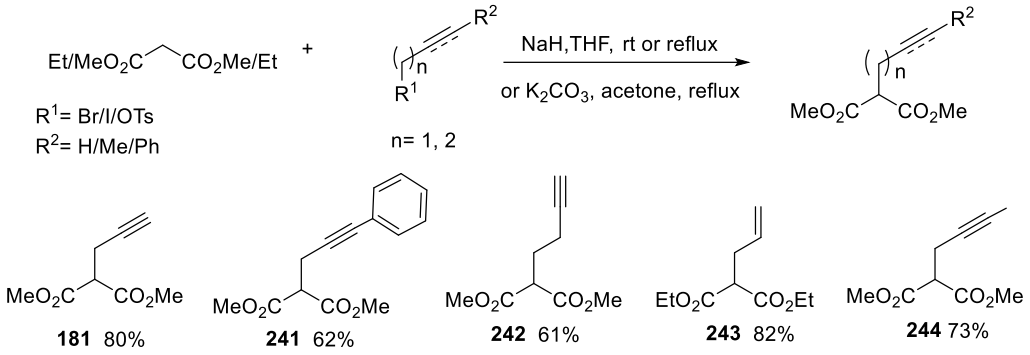
[a] Not complete after 24h. [b] ^{1}H NMR yield was determined from internal standard 1,3,5-trimethoxybenzene

To our delight, reactions can be conducted with a catalytic amount of DBU (0.2 eq) without significantly changing the yield and reaction time (Entry 2). However, for accuracy and reproducibility considerations, we chose to perform the reactions with 1 equivalent of DBU instead of 0.2. We tried the reaction with 0.25 equivalent of Ag_2O without oxidant and we obtained the expected compound **239** in 49% yield after 24 hours reaction (Entry 3). Conducting the reaction under O_2 balloon increased the yield to 67 % (Entry 4). We also performed the reaction with oxidative agents, respectively CeO_2, $K_2S_2O_8$ or $PhI(OAc)_2$ but only poor yield were observed, ranging from 16-45% (Entry 6-8).

At this stage, we were unfortunately unable to find efficient catalytic conditions. Nonetheless, the use of substochiometric amount of Ag_2O is not deleterious because silver oxide(I) is one of the cheapest silver salts commercially available.[90] So, we pursued our studies by using 0.5 eq of Ag_2O since the reaction is fast and provide very clean crude.

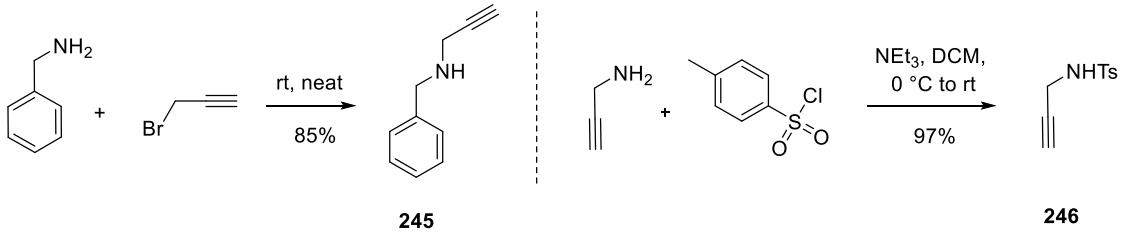
V.e.2 Limitations and scope

In order to investigate the scope of this reaction, we synthesized various linear or aromatic alkynones systems. First of all, we prepared different kind of malonates, which were obtained by using classical alkylation conditions (Scheme 70).



Scheme 70

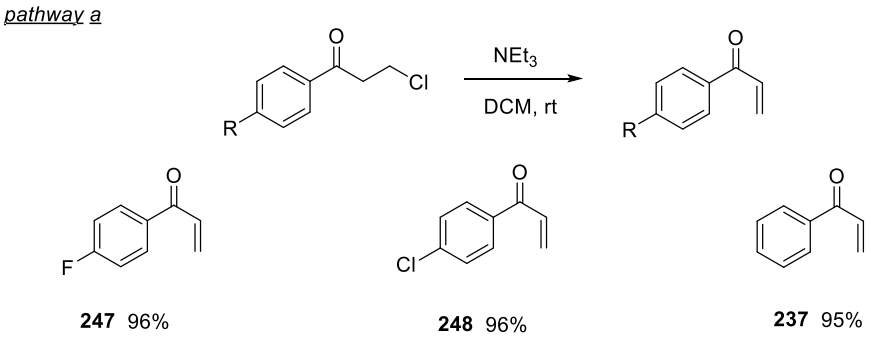
Besides, *N*-Bn and *N*-Ts counterparts were also introduced in the framework using traditional synthetic pathways (Scheme 71).



Scheme 71

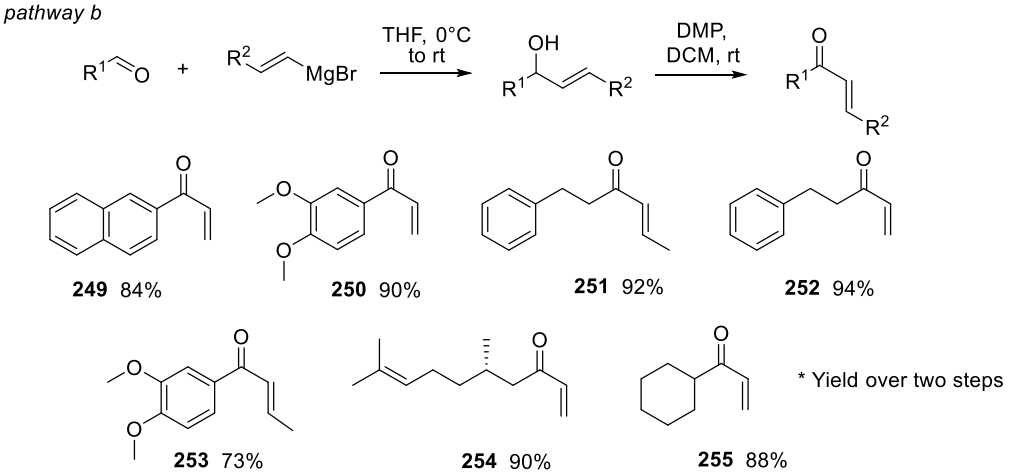
In parallel, vinyl ketones were synthesized by two standard procedures:

By the first way, vinyl ketones were obtained by elimination reaction from the commercially available 3-chloropropiophenone or its para-substituted analogs (Scheme 72).



Scheme 72

By the second way, aldehydes were submitted to vinyl magnesium bromide or 1-propenylmagnesium bromide and the resulting alcohol was oxidized by Dess-Martin Periodinane (DMP) delivering the α-β unsaturated ketone (Scheme 73).

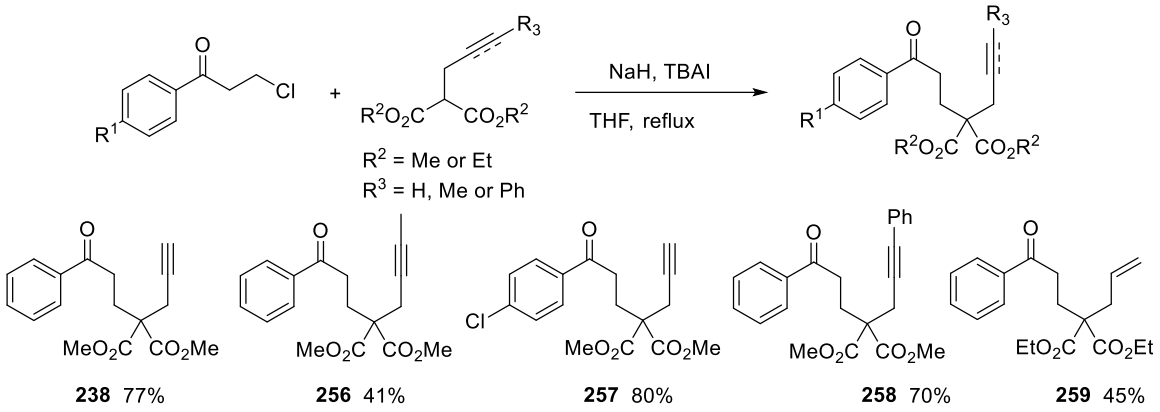


Scheme 73

Due to their instability, α-β-unsaturated ketones were freshly prepared before to be directly engaged in the next step without purification on column chromatography.

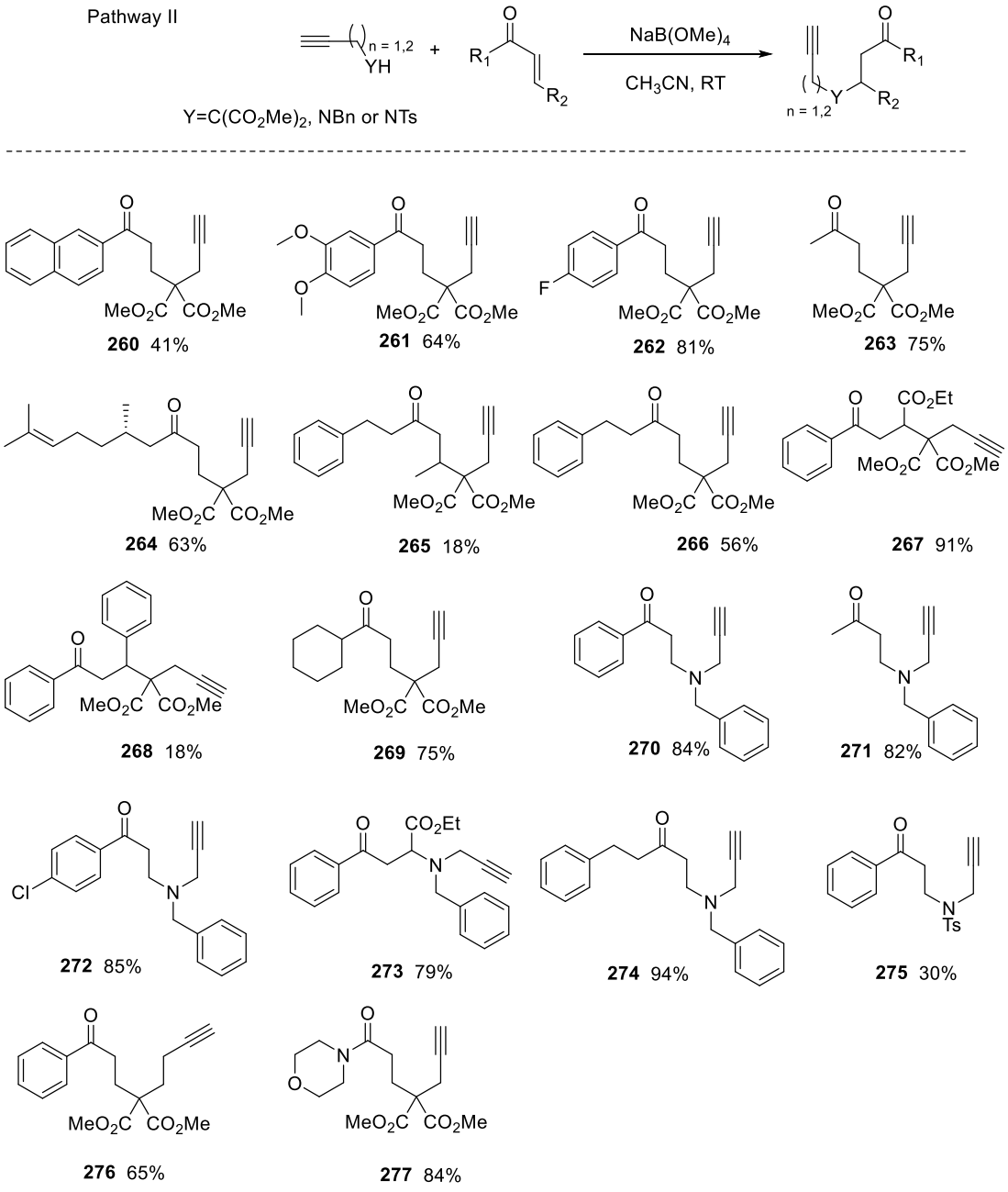
Cyclization precursors were synthesized by three different pathways:

First pathway consisted in an alkylation reaction between 3-chloropropiophenone or 3,4'-dichloropropiophenone and different malonates previously deprotonated by NaH (Scheme 74). Five precursors of cyclization were obtained with moderate to good yields, ranging from 41% to 80%.



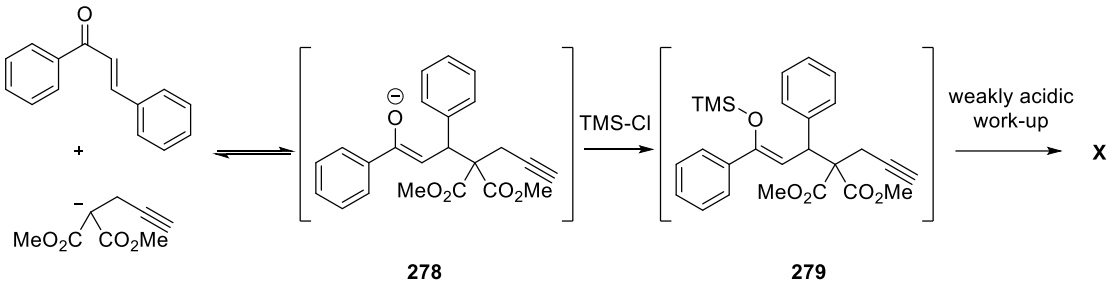
Scheme 74

In the second pathway, both alkyne and vinyl ketones were submitted to the Michael addition using $NaB(OMe)_4$ as catalyst and CH_3CN as solvent. Thanks to this sequence, we synthesized eighteen precursors of cyclization and most of them were obtained in good yield (18% to 94%) (Scheme 75).



Scheme 75

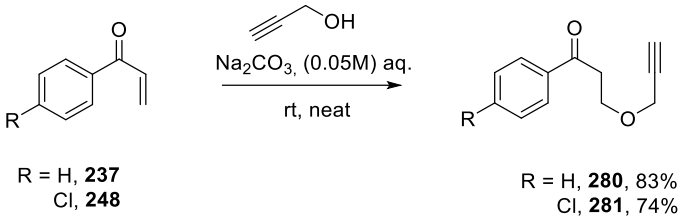
Although the yield are generally good for this second pathway, some precursors turned out to be quite tedious to obtain (especially **265** and **268**). These low yields could be explained by the fact that Michael addition is tougher when the double bond is substituted rendering the approach of the nucleophile more difficult. In addition, these types of ketones seem to be more prone to undergo a retro-Michael addition. One possibility to enhance the yield of such addition consists in the addition of TMSCl in the same pot in order to trap the intermediate enolate (Scheme 76).



Scheme 76

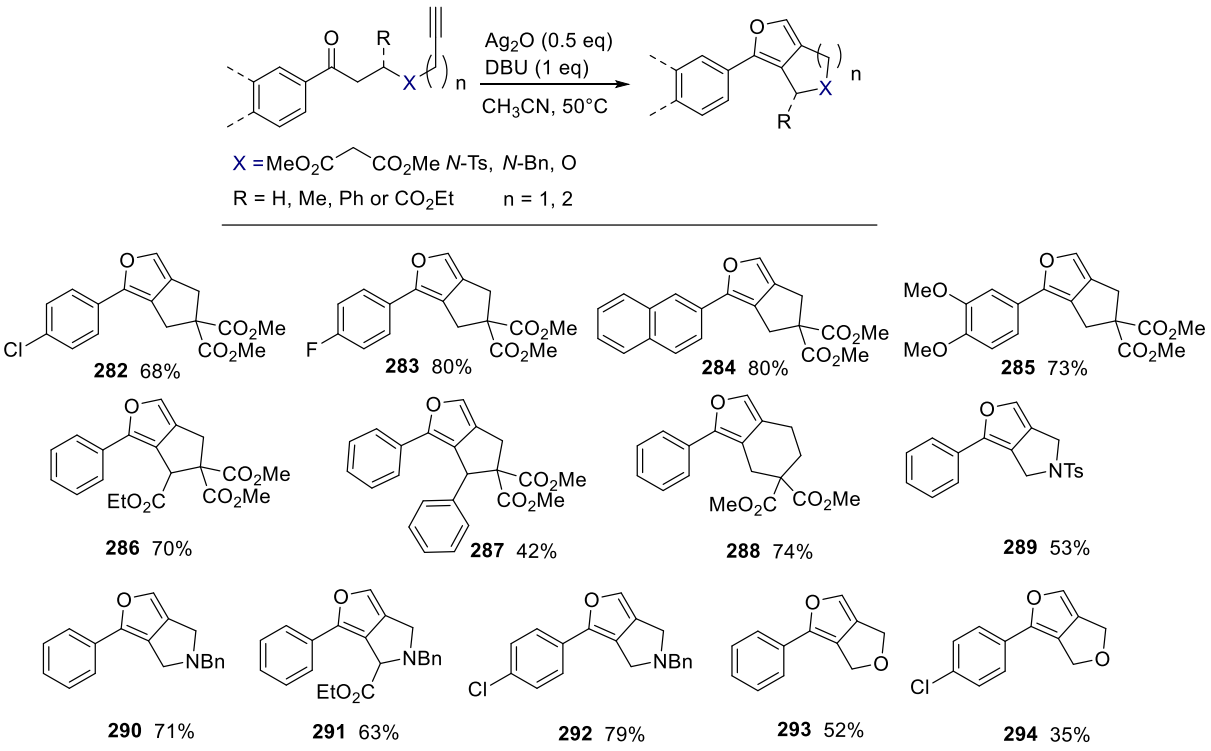
In such procedure, TMSCl plays a dual role since it acts as Lewis acid thus facilitating the attack onto the unsaturated ketone.

Finally, *O*-containing precursors were also obtained by hetero-Michael addition in weak basic condition (Scheme 77).



Scheme 77

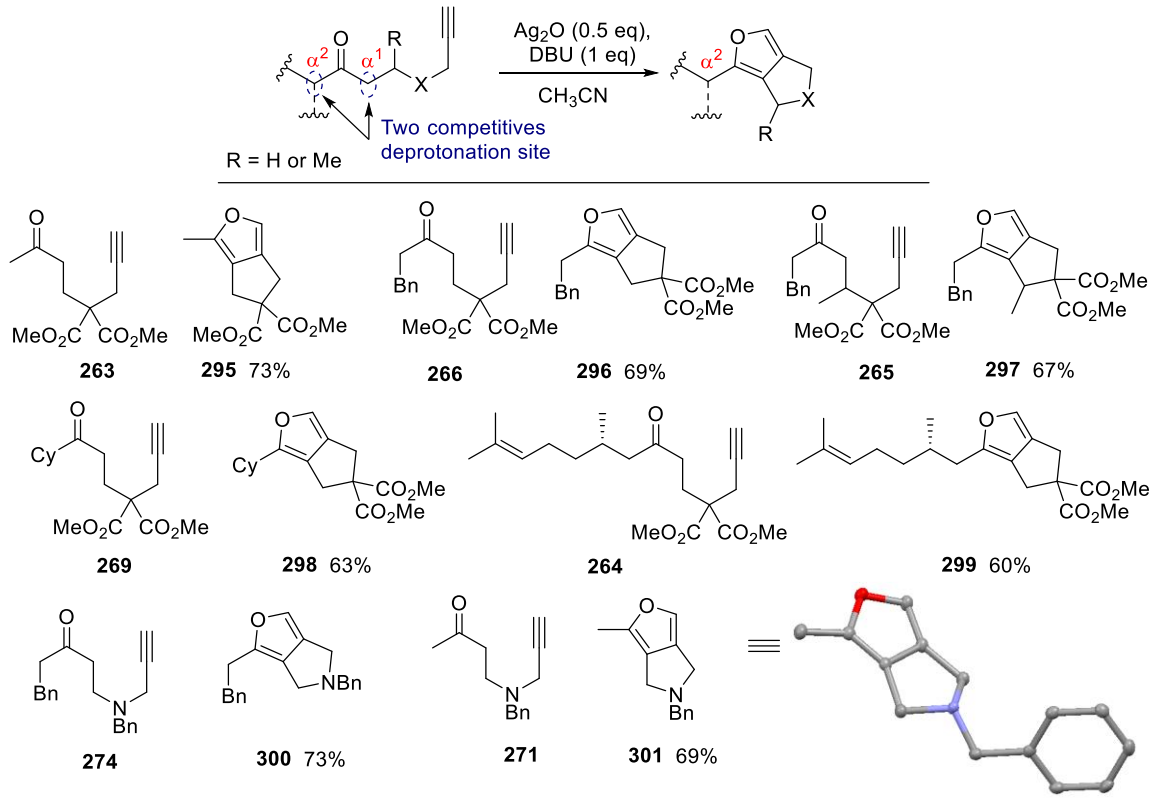
Thanks to these different pathways we prepared 25 precursors of cyclization. With the optimised conditions and various precursors in hands, we firstly screened different aromatic alkynones (Scheme 78).



Scheme 78

Substituted or polysubstituted aromatic ketones afforded the corresponding furans (**282**, **283**, **284** and **285**) with roughly similar yield (68 to 80%). A slight decrease of yield was observed when the ketone was substituted in β position (**286** and **287**) especially for the compound **287** having a phenyl ring. This drop could be attributed to a retro-Michael addition side reaction[91] but also to a steric clash between the two aromatic parts during the first cyclization, which are very close in the final structure. Introducing a nitrogen instead of dimethyl ester turned out to be effective and poly-heteroaromatic structure has been achieved with very good yield (from 53 to 78%). The reaction was found more efficient when it was conducted on the *N*-benzyl protected nitrogen (compound **290**, 71 %) than its *N*-tosyl counterpart (**289**, 53 %). Indeed, the crude of *N*-tosyl was much less cleaner than the *N*-benzyl compound and showed multiple side products. This is probably due to the higher acidity of the proton in the α-position of the *N*-tosyl group which could be snatch by the DBU, allowing some side reactions. This transformation has also been successfully extended to oxygenated propargyl derivatives affording dehydrofurofuran core **293** and **294** with moderate yields (respectively 52 and 35 %). To our delight, the optimized condition allowed the extension to substrate with longer chain **276** in order to reach six-membered-ring analogs with good yield (**288**, 74%).

After this survey, we decided to turn our attention to more challenging ketone having less acidic proton in α-position[92] and being enolisable on both sides (α^1 and α^2) (Scheme 79).



Scheme 79

Using the same conditions, we were pleased to find similar yields on aliphatic ketones. Thus, ketone **265** and **266** afforded the corresponding furan with similar yield (respectively 67% and 69%). More accessible **263** or bulkier carbonyl **269** and **264** afforded satisfying yield (73%, 63% and 60%) without significant difference. In a similar way, *N*-Bn compounds **274** and **271** provided furans derivatives with good yield. We managed to get X-ray structure of the compound **301**, showing the flat structure of such compounds. All these results highlighted that sterically hindered ketones and/or enolizable on both sides (α^1 and α^2) are not deleterious for the reaction. Attack of the α^1-enolate onto the alkyne is obviously favoured since it leads to the five membered ring whereas attack of α^2-enolate would provide the corresponding 7-membered ring.[93]

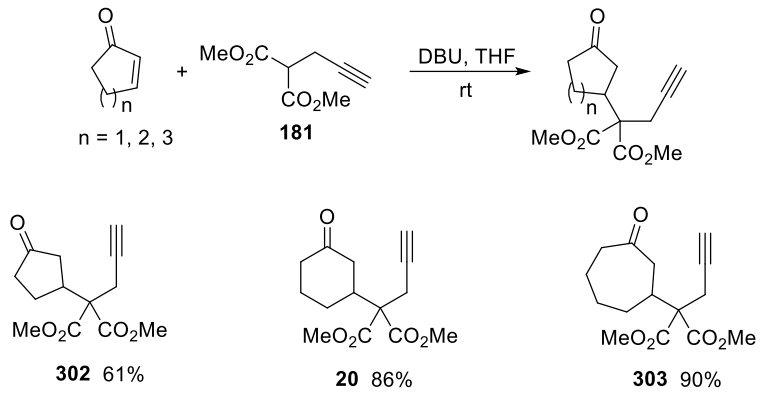
In the meantime, we investigated the cyclization of more challenging substrate such as the alkene **259** and the amide **277**. (Figure 12)



Figure 12

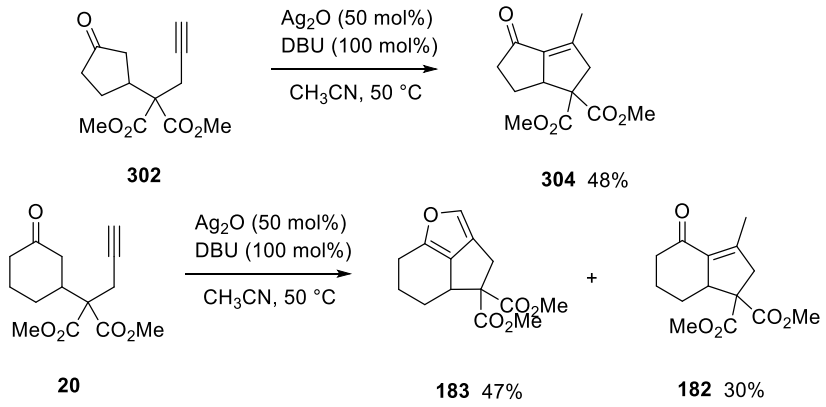
Not surprisingly, no furan derivatives were detected and only starting material were recovered when ketone **259** and amide **277** were used under optimized conditions. These two results could be explained by two different reasons. Concerning the alkene precursors **259,** silver oxide(I) is not enough lewis acidic to activate the double bond preventing any attack from the enolate. About the amide, this lack of reactivity is certainly due to lower acidity of the proton in the α-position thus prohibiting the preliminary enolisation required for the Conia-ene reaction.

We also subjected our cyclization conditions to cyclic ketones. To this aim, we previously synthesized the respective five, six and seven membered ring alkynones (**302**, **20** and **303**) by Michael addition from commercially available corresponding cyclic vinyl ketone and propargyl malonate **181** with DBU as the base.[94] Thanks to this easy method, the three cyclic precursors were obtained in satisfying yield. (61% to 90%) (Scheme 80).



Scheme 80

These three cyclic alkynones were next submitted to our conditions in order to obtain tricyclic complex furan derivatives (Scheme 81).

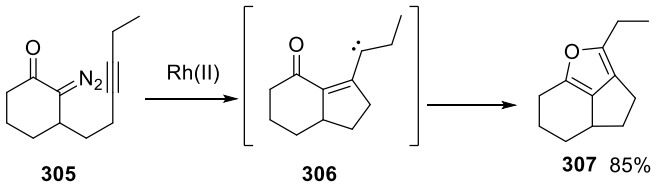


Scheme 81

These attempts turned out to be very instructive in a mechanistic point of view. This part will be discussed later in this chapter.

As expected, performing the reaction on the five membered ketone **302** did not provide the furan derivatives and only the α-β unsaturated ketone **304** was recovered (48 %). The latter probably come from a conia-ene/isomerization reaction affording exclusively the bicyclic enone **304** in 48% yield. This conia-ene adduct was also observed from cyclohexanone **20** (30%) but we were please to find the highly strained tricyclic furan **183** in a good yield (47%).[95]

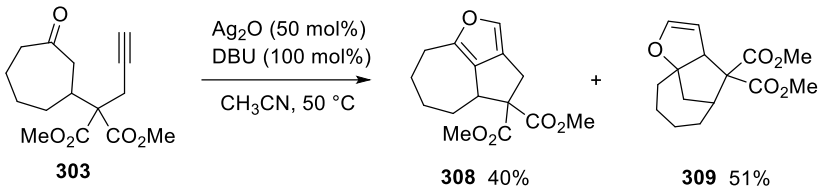
The synthesis of such strained furan has already been described in the literature. To this date, this type of furan core was only accessible by using Rh/carbene chemistry [96] or radical chemistry. [97] We can cite for example the work reported by Padwa and coworkers involving Rh(II) carboxylate and diazoketone **305** (Scheme 82).



Scheme 82

Padwa and coworkers obtained the furan **307** in 85% through the formation of the vinylcarbene intermediate **306**.

We also carried out the reaction on cycloheptanone **303** (Scheme 83).

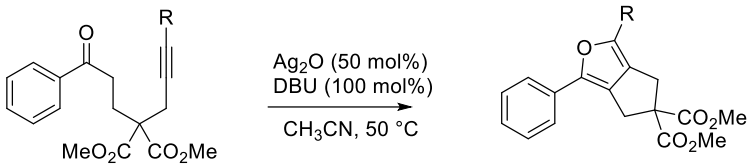


Scheme 83

Under our optimized conditions, the seven membered ring analog **308** was also obtained in a similar yield (40%) from the ketone **303**. Nevertheless, the major compound was the tricyclic dihydrofuran **309** (51%). Obtaining this adduct would result from the reactivity described in our previous methodology (chapter III) and especially the formation of a silver allenyl intermediate.

In order to confirm this assumption, we have previously synthetized two ynone precursors containing a substituent on the triple bond, respectively a methyl (compound **256**) and a phenyl (compound **258**) pattern (see Scheme 74).

Applying our conditions to substituted alkynes **256** and **258** did not afford the cyclized product. Actually, either we observed no reaction, or messy crude without detecting the expected furan derivative (Scheme 84).



R= Me, **256** — n.r
Ph, **258** — n.r

Scheme 84

Indeed, trying more π-acidic silver salt like $AgNTf_2$ or higher temperature on **256** and **258** has never led to the corresponding furan derivatives (Table 8).

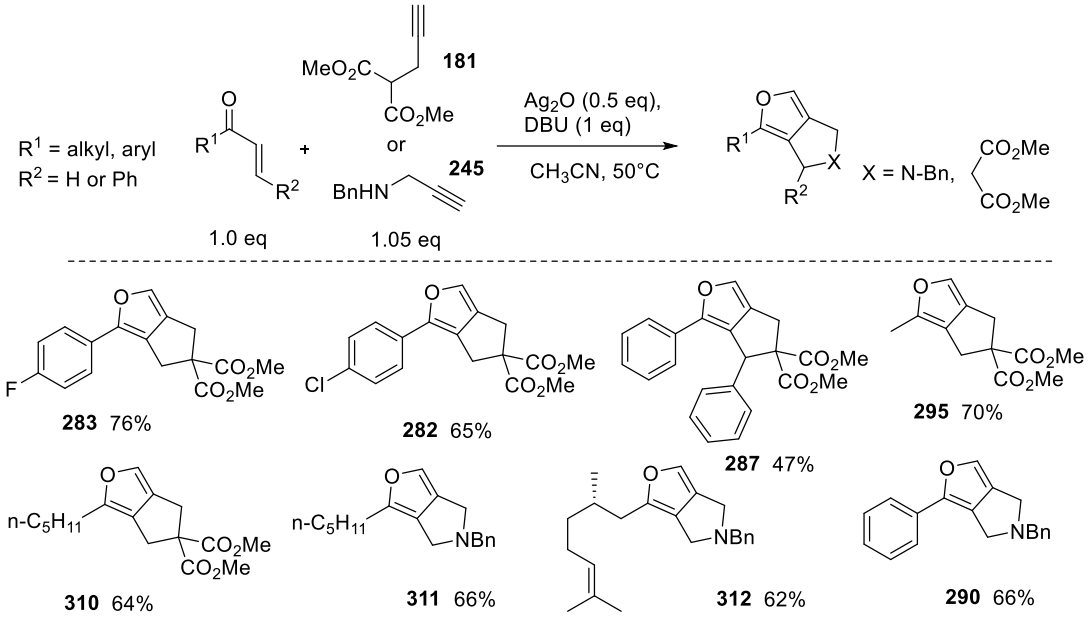
Table 8

Entry	R	[Ag]	T °C	Results
1	Me	Ag_2O, 0.5 eq	50	n.r.
2	Me	$AgNTf_2$, 1eq	50	n.r.
3	Me	Ag_2O, 0.5 eq	90	messy, degradation
4	Ph	Ag_2O, 0.5 eq	50	n.r.
5	Ph	$AgNTf_2$, 1eq	50	n.r.
6	Ph	Ag_2O, 0.5 eq	90	messy, degradation

As the first methodology, these results could suggest that the formation of the allenyl silver for this reaction is a pre-requisite to allow this cyclization.

V.e.3 One-pot reactions

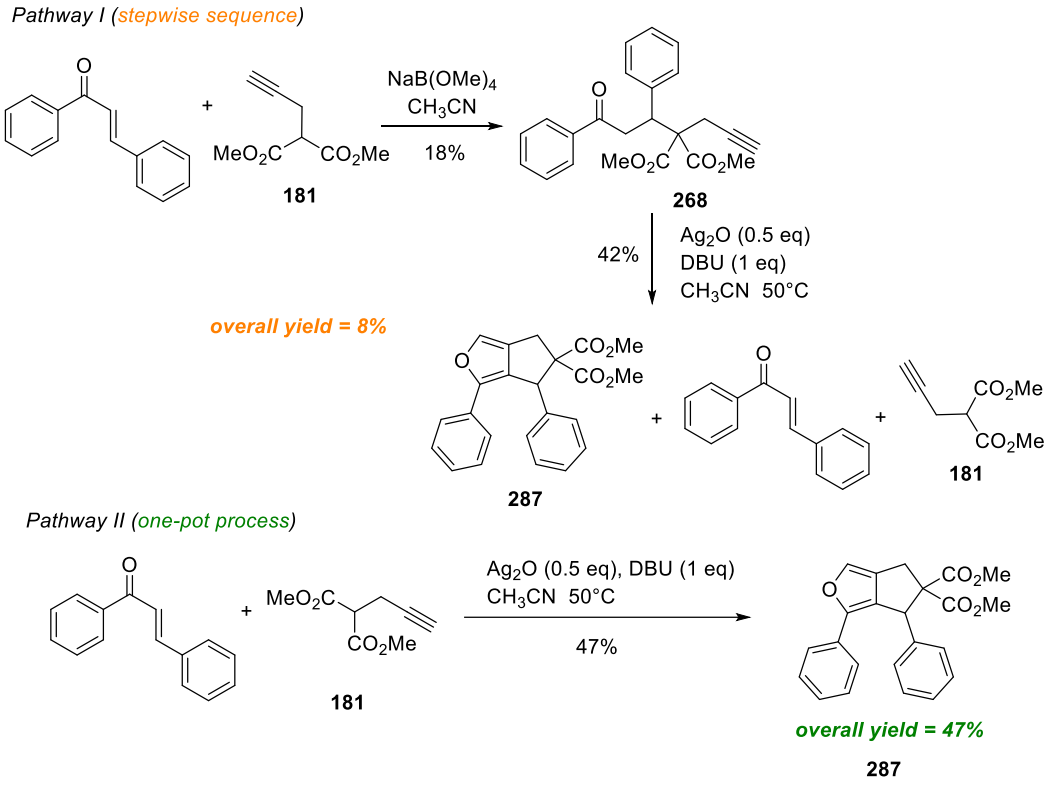
In order to set up a flexible and more environmentally friendly process, we focused on a one-pot reaction since DBU has been identified by Kim and co-workers as an efficient base for promoting Michael addition reaction.[98] Thus, the base could previously allow the 1,4-addition onto α-β unsaturated ketone before to be engaged in the cyclization. To this aim, we applied our optimized condition onto various Michael acceptors in the presence of malonate or amine derivatives (Scheme 85).



Scheme 85

To our delight, the cyclization conditions were found suitable for one-pot process and similar yields were obtained for **283**, **282**, **287**, **295** and **290** than reported in Scheme 78 and Scheme 79. Additionally, three others new furans (**310**, **311** and **312**) were provided with a satisfying yield (respectively 64 %, 66 %, 62 %).

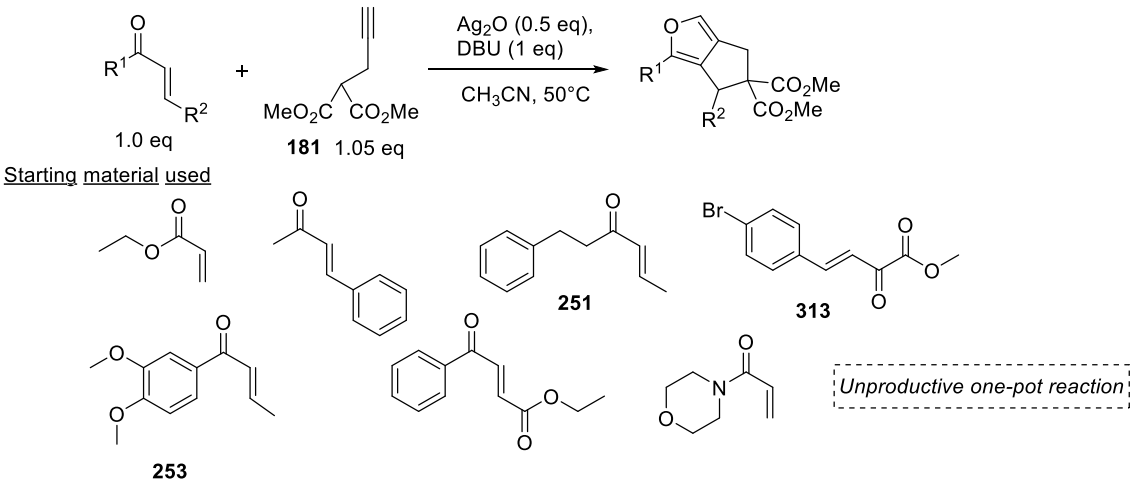
It is worth to mention that we synthetized the furan derivatives **287** according two different pathways from chalcone and dimethyl 2-(prop-2-yn-1-yl)malonate. As shown in the Scheme 86 below, one pot process turned out to be more efficient than the stepwise method since the overall yield for pathway I is 8% whereas for the pathway II is 47% (Scheme 86).



Scheme 86

The first route (pathway I) is conventional Michael addition followed by cyclization. The yields of these two steps were 18% and 42%, respectively. The yield over two steps was only 7.6 %, which could be attributed to a retro-Michael addition since chalcone and dimethyl 2-(prop-2-yn-1-yl)malonate could be detected even in the second cyclization step. However, the yield could reach as much as 47% when one-pot reaction was applied. This is certainly due to the cyclization step, which is probably irreversible thus preventing any retro-Michael addition. Besides, not only the one-pot process is more efficient, but also it is more interesting in an environmentally point of view since only one column purification is required.

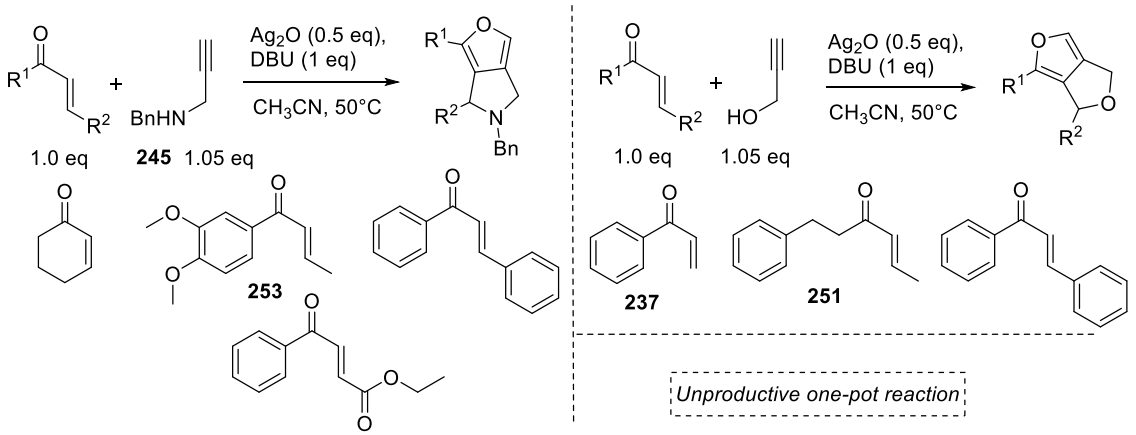
Unfortunately, the one-pot process could not be extended to a wide variety of substrate. Indeed, we also tried different commercially available vinyl ketones with dimethyl 2-(prop-2-yn-1-yl)malonate **181** by one-pot process without success (Scheme 87).



Scheme 87

In most of case, we observed the starting material by ^{1}H NMR and a small proportion of Michael adduct (less than 30% in most cases) whereas only traces of furan derivatives were detected. A plausible explanation for these unsuccessful transformations is the slow rate of the Michael addition, the reaction becomes very sluggish and a significant degradation of silver salts occurred, prohibiting the cyclization reaction. Additionally, this failure can also be explained by the intrinsic reactivity of some α-β unsaturated ketones such as **313**, which turned out to be very (maybe too) reactive in the optimized conditions (even at rt) since we always observed the disappearance of the starting material but leading to a complex mixture of products.

Furthermore, we also applied one-pot process in the cyclization between different vinyl ketones and *N*-benzylprop-2-yn-1-amine **245** or prop-2-yn-1-ol (Scheme 88).



Scheme 88

Unfortunately, only starting material and traces of Michael addition products were observed.

V.f Mechanistic investigations

We have previously depicted methods dealing with the furan synthesis mediated by silver salts in the state of art few. There are plenty of other methods described in the literature especially in intramolecular fashion. In their recent review on “silver and gold catalyzed routes to furans”,[84] Pale and collaborators have classified different substrate types allowing the synthesis of furan derivatives thanks to the activation by silver salts (Figure 13).

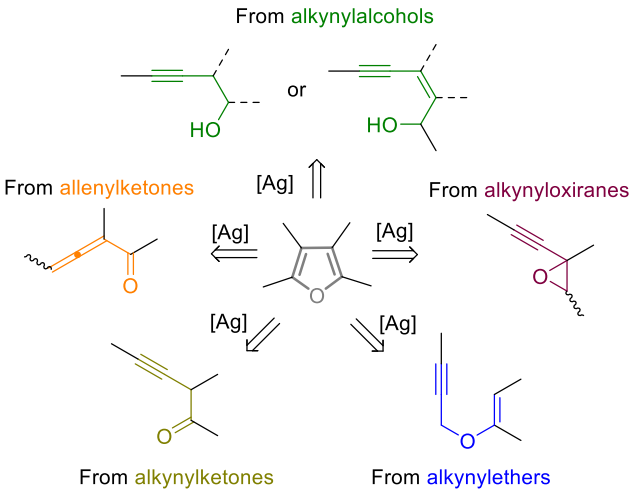


Figure 13

In their classification depicted in Figure 13, the closest system of ours is the alkynylketone type. However, the spacing between both reactive functions is totally different implying another mechanism than those reported for such systems. A brief survey of the literature showed that our system type has, to the best of our knowledge, never been described. However, some close examples have been reported and are depicted in the Figure 14.

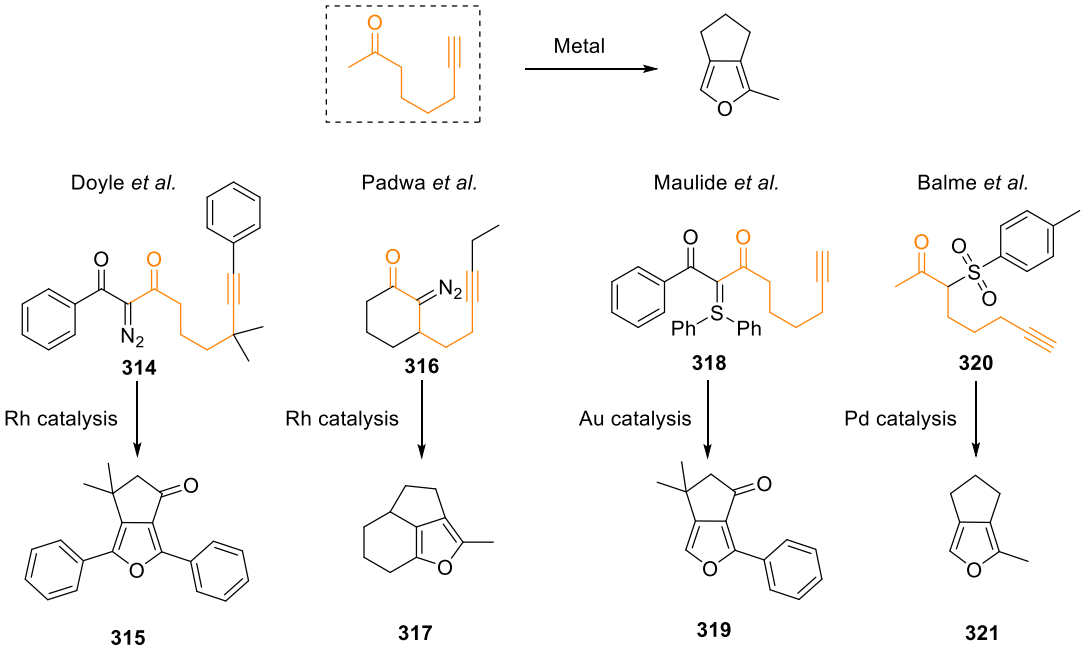
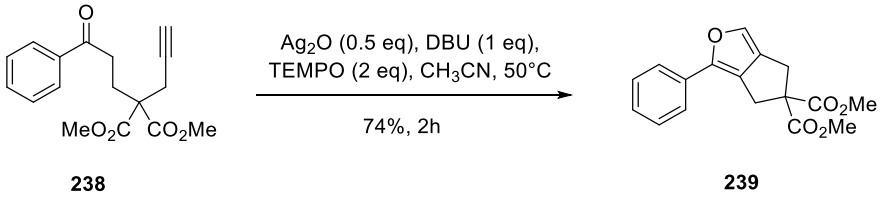


Figure 14

Boyle[99] and Padwa[100] both reported the reaction of alkynone system for their synthesis of furan derivatives by rhodium catalysis. However, these two methodologies previously necessitate the incorporation of diazo function in α-position of the ketone. In 2012, Maulide and coworkers described the synthesis of furane adducts from alkynone comporting a sulfur ylides in the presence of gold catalyst (see Scheme 62 for the mechanism).[81] Finally, Balme and coll. described the synthesis of furane core catalyzed by palladium (Pd(dppe)) from alkynone having a sulfone moiety in α position of the ketone.[101]

In our case, we used another metal and the ketone is not substituted by N_2, sulfur ylides or a sulphonyl groups thus implying another type of mechanism. Since this transformation appeared to be unprecedented, we decided to investigate on it.

First, we performed the reaction in the presence of a large amount of TEMPO (2 equivalents) as a scavenger of radical species (Scheme 89).



Scheme 89

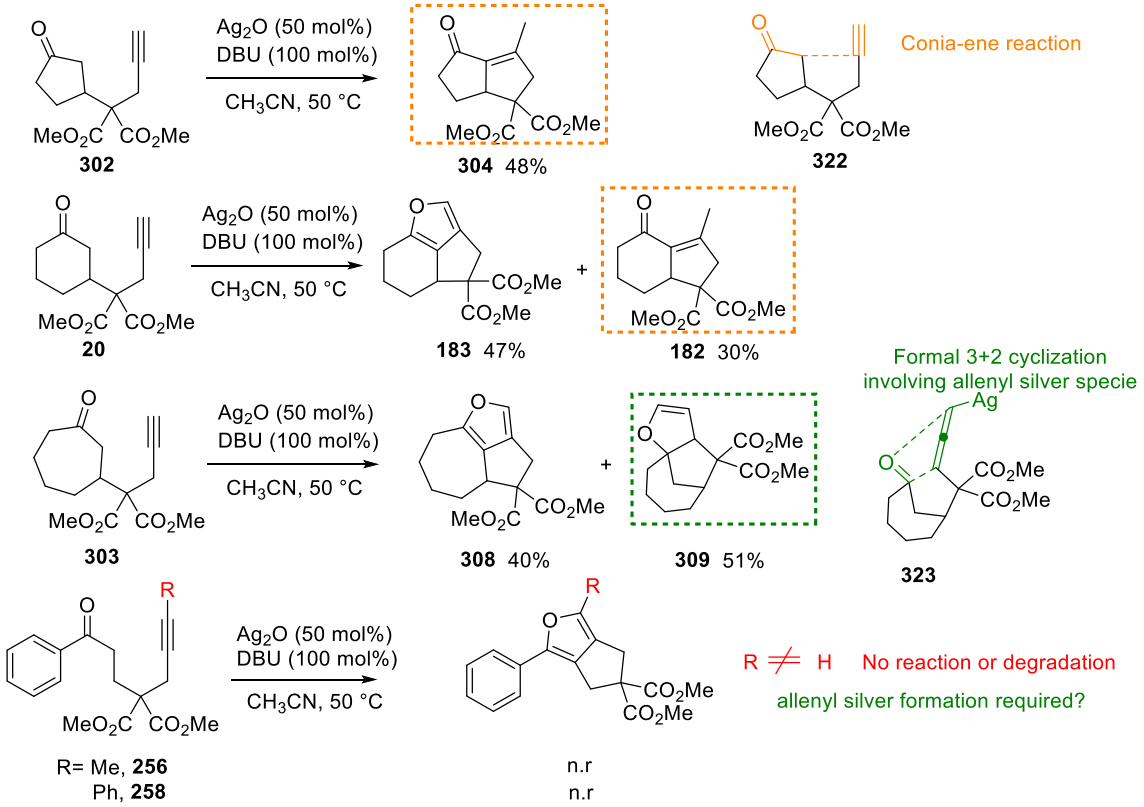
However, we got the cyclized product in a similar yield within same time, evidencing that the reaction did not include any formation of a radical intermediates during the reaction.

Our cyclization managed on cyclic ketone **302**, **20** and **303** (Scheme 81 and Scheme 83) turned out to be very instructive concerning the mechanism.

As previously seen in chapter 1, in the presence of terminal alkynes, the combination of Ag_2O and DBU lead to an equilibrium between the allenyl- and the alkynyl silver. So, firstly, we presumed that this equilibrium takes place as demonstrated by previous DFT calculations. This assumption is also supported by other two points:

- Leading the reaction onto substituted alkynes has turned out to be fruitless (Scheme 84)
- The formation of the dihydrofuran derivatives **309** from the cycloheptanone **303** (Scheme 83).

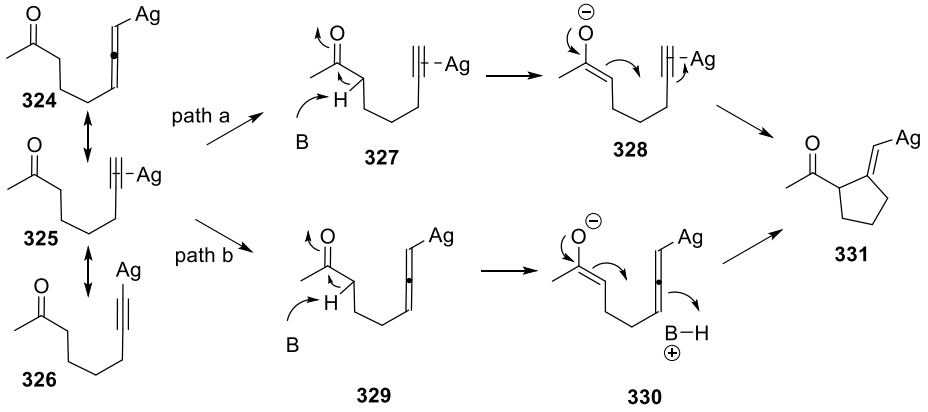
Secondly, we observed the formation of the enone adduct during the cyclization of the cyclopentanone **302** and cyclohexanone **20**, suggesting a conia-ene type reaction. All the interesting results previously obtained concerning the mechanism are summarized in the Scheme 90.



Scheme 90

To the best of our knowledge, conia-ene reactions using simple ketone as starting material without organocatalysis are really scarce[102] and have never been reported for the synthesis of furan or dihydrofuran cores from unactivated alkyne.

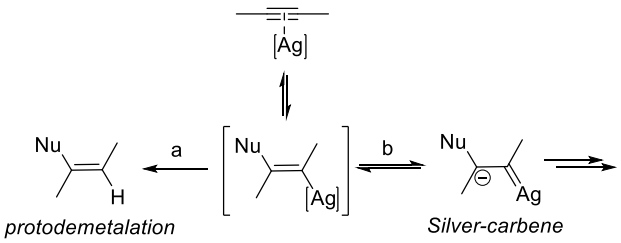
We assumed that the first reaction is a conia-ene cyclization but several pathways can be envisioned. Indeed, we cannot clearly identify on which unsaturated system the attack of the enolate occurs. Since the dihydrofuran obtained from the cycloheptanone **303** shows also the formation of the allenyl silver during the reaction, we can considered two routes (path a and path b) leading to the formation of a mutual vinyl silver intermediate. The first part of the mechanism is outlined in Scheme 91.



Scheme 91

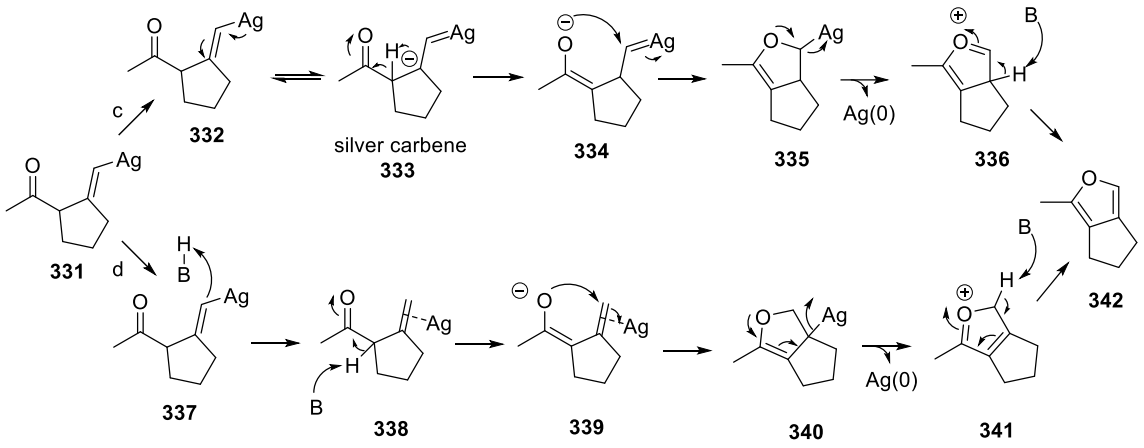
From the equilibrium between alkynyl- and allenyl silver, DBU would generate the enolate by deprotonation on α-position of the ketone. After subsequent attack onto activated alkyne (route a) or allenyl silver followed by concomitant reprotonation (route b), we would obtain the terminal silver alkene **331**.

At this stage, we can envision two other possibilities. Indeed, as π-activators of the carbon-carbon triple bond, silver catalyzed transformations of alkynes mainly fall into two important types: the protodemetalation pathway (a) or the silver carbene pathway (b) as depicted below (Scheme 92).



Scheme 92

Thus, from the alkenyl silver intermediate **331,** we can consider two other pathways (path c and path d) to reach the furan core **342** (Scheme 93).

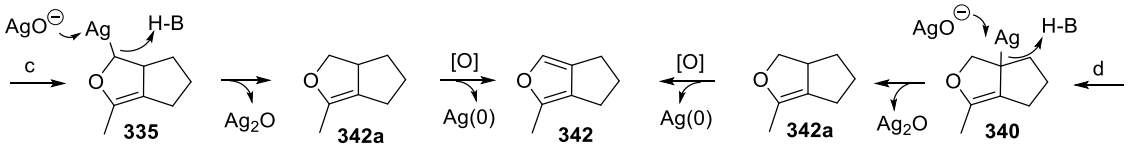


Scheme 93

According to the pathway c, silver would be in equilibrium with the silver carbene **333**. Silver carbene commonly exists in diazo chemistry,[103] but few examples are also described from carbon-carbon triple bonds.[104]In our case, a 1,2-shift of the proton would lead to an enolate which could cyclize onto the silver carbene. Releasing of silver(0) through the oxonium formation and subsequent deprotonation would lead to the furan **342**. We can notice that silver mirror and silver particles were observed after each reaction supporting the formation of silver(0) during the reaction.

According to the pathway d, a protodemetalation step of vinyl silver followed by the attack of the enolate onto silver activated alkene would conduct to dihydrofuran **341**. Removal of the silver(0) through the formation of the oxonium and subsequent isomerization would achieve the formation of the furan framework **342**.

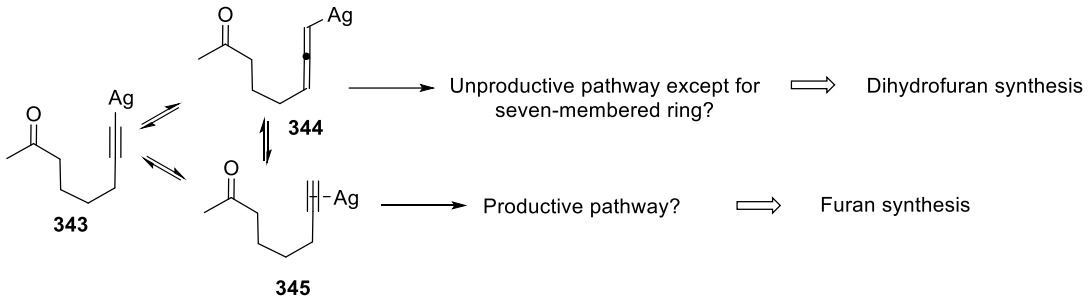
Another plausible outcome would be the protonation of intermediates **335** or **340** releasing Ag_2O and leading to the corresponding 2,3-dihydrofuran adduct **342a**. A subsequent oxidation by Ag_2O would deliver furan **342** since Ag_2O could also act as an oxidant (Scheme 94).[38,39]



Scheme 94

Meanwhile, another reasonable theory could be that allenyl silver is formed during the reaction but can react only with cycloheptanone **303** leading to dihydrofuran **309**. However, it could be an unproductive route with other substrates whereas the silver complexed to the C-C triple bond would achieve the synthesis of furan. There would be a competitive reaction with allenyl silver which only could happen with cycloheptanone explaining the mixture of furan and dihydrofuran obtained (see

Scheme 90). Nonetheless, the formation of the allenyl silver could not also be required in the furan synthesis (Scheme 95).



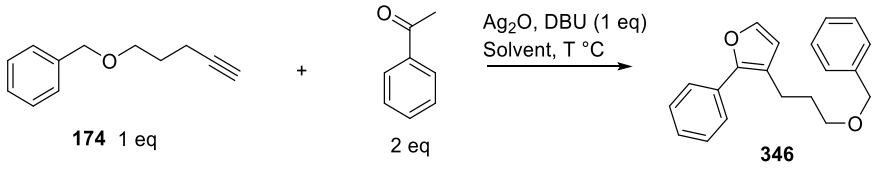
Scheme 95

In conclusion, the mechanism associated to this transformation will not appear to be clear to us since many routes can be envisioned. In order to shine light on the plausible mechanism, we started a second collaboration with Dr. Ilaria Ciofini and Anna Perfetto. DFT calculations are in progress.

V.h Intermolecular attempts

After studied intramolecular cyclization, we envisioned a more challenging access to furan units by extending the reaction to an intermolecular fashion. To this aim, we selected ((pent-4-yn-1-yloxy)methyl)benzene **174** as alkyne and 4'-methoxyacetophenone as ketone. These two partners were reacted under different conditions (Table 9).

Table 9



Entry	Ag_2O (eq)	[**174**][a]	Solvent	T (°C)	Time, Yield%
1	0.5	0.2 M	MeCN	50	12h, n.r
2	0.5	1.0 M	MeCN	50	12h, n.r [b]
3	0.5	1.0 M	MeCN	80	12h, n.r
4	0.5	1.0 M	DMF	130	12h, n.r
5	0.5	1.0 M	Toluene	110	12h, n.r
6	1	1.0 M	Toluene	110	12h, n.r

[a] concentration of ((pent-4-yn-1-yloxy)methyl)benzene **174**. [b] reaction performed with O_2 balloon

At first, we tried our optimized condition (Entry 1) but only starting materials were detected. After that, we use O_2 balloon and increase the concentration of ((pent-4-yn-1-yloxy)methyl)benzene **174** from 0.2 M to 1 M to promote intermolecular reaction while no changes were observed (Entry 2). Besides, higher temperature (80 °C, 110 °C and 130 °C), different solvents (DMF and toluene) and higher silver loading (1 eq instead of 0.5 eq) were applied, unfortunately, still no reaction. So at present, this transformation can't be made by intermolecular fashion. We presumed that the allenyl formation is too transitory, and need to be done near to the electrophile part. The inherent intramolecular loss of order combined with the weak nucleophilicity of the allenyl silver specie make this reaction impossible to do in intermolecular manner.

V.i Conia-ene attempts

V.i.1 Introduction

Based on our first observation regarding the mechanism, we assumed that the access to furan derivatives would first involve a conia-ene cyclization. In the postulated mechanism, the second hydrogen in α position of the ketone is required for the second cyclization since it authorized the C-O bond formation through a second enolisation. We envisioned to apply our conditions to α-mono-substituted ketone which would interrupt the process after the cycloisomerisation. By this way, we hoped to attain cyclic ketones having α quaternary center (Figure 15).

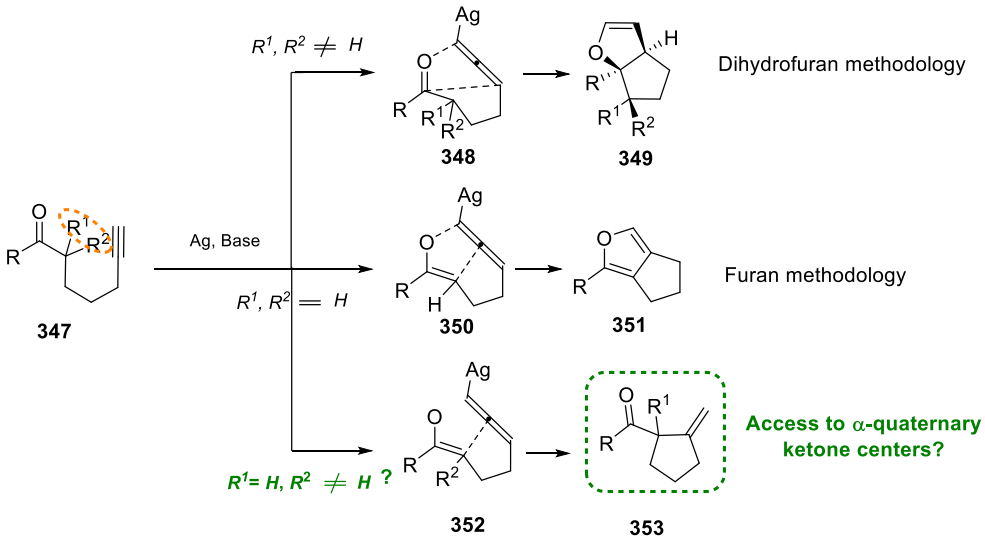


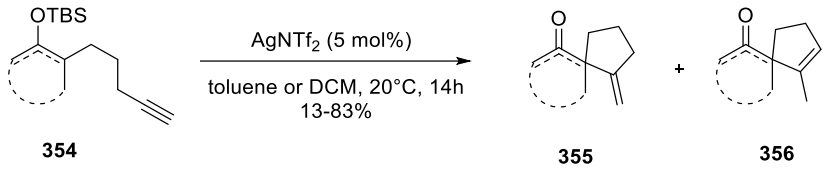
Figure 15

Before to continue, we will briefly present the Conia-ene cyclization which is a powerful tool for the creation of C-C bond. This pericyclic reaction has been discovered by Conia and Le Perchec. During this process, an enolizable carbonyl group reacts with an alkyne, leading to the formation of a quarternary center. Initially, this reaction required high temperatures thus strongly limiting its application field. So, several groups brought important improvement in order to avoid the harsh

reaction conditions needed for this cyclization. In this context, transition metals have addressed an interesting and powerful answer through various activation modes thus dramatically lowering the temperature.[105]

However, the main limitation of the Conia-ene reaction is the use of malonate or malonate-type systems in order to favorise the enolization step, which is a pre-requisite for this cyclization. Transition metal- combined with organo-catalysis or enolate surrogate, typically as a sylil enol ether, both permitted to extend the scope of this reaction to aldehydes[106] and ketones.[107,108]

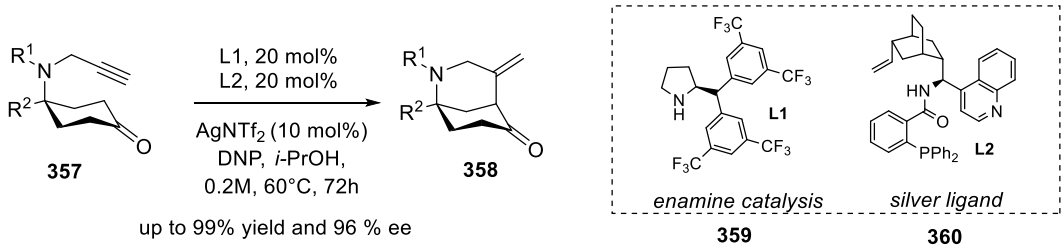
Few effective silver catalyzed protocols have been developed from unactivated alkyne. In 2012, Miesch and coworkers reported an efficient $AgNTf_2$ catalyzed cycloisomerization reaction from alkynylsilyl enol ethers leading to various spirocycles in moderate to good yield.[109]



Scheme 96

Interestingly, in most cases DCM lead to the exo adduct whereas the toluene mainly afford the endo compound.

In 2017, Dixon and coworkers reported the synthesis of 6,6-bicyclic morphan skeletons by enantioselective desymmetrizing cycloisomerization of prochiral scaffold using co-operative metal and amine co-catalyst system (Scheme 97).[110]



Scheme 97

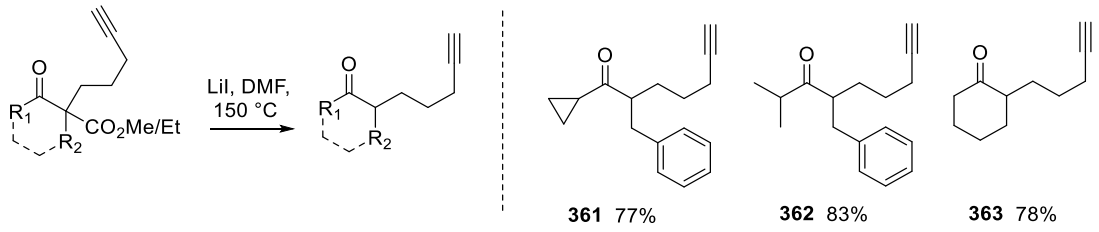
The combination of two chiral catalysts addressed a match/mismatch issues. After investigation, proline derivative L1 and cinchonine derivative L2 were found to be the best combination yielding the morphane cores with high yield (up to 99%) and enantiomeric excess (up to 96%).

However, conia-ene reactions using ketone without organocatalysis onto unactivated alkyne catalyzed by silver salts has, to the best of our knowledge, never been reported.

V.i.2 Preliminary attempts on conia-ene cyclization

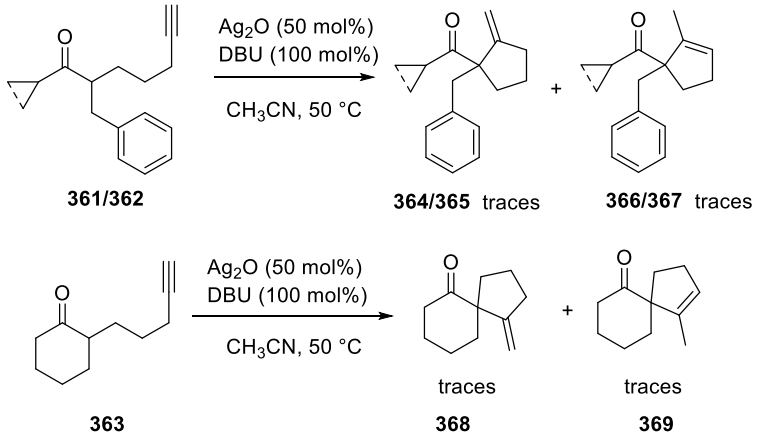
Since our postulated mechanism for the furan synthesis involved conia-ene and because we had already synthesized many alkylated β-ketoesters in the first methodology, we could easily obtain monosubstituted α-keto-alkynes by Krapcho decarboxylation. We had the opportunity to quickly try our conditions in a challenging conia-ene reaction.

We submitted the malonate **50**, **114** and **115** to decarbethoxylation reaction in the presence of LiI at 150°C. Thanks to this method, we synthesized three precursors with a satisfying yield, from 77% to 83% (Scheme 98).



Scheme 98

After that, these three precursors were submitted to the optimised conditions. Results are depicted in Scheme 82.



Scheme 99

Unfortunately, these reactions were not finished after 12h and apart from the starting material, only a mixture of β,γ-unsaturated ketones traces were detected by ^{1}H NMR. Internal double bond adducts may come from a sequence conia-ene/isomerization reaction in accordance with previous literature.[111]

Few assays have been realized on these substrates since in the meantime another interesting result have emerged during our cyclization attempts on furan synthesis. Nonetheless, this methodology would deserve to spend more time and will constitute an overview in a near future.

V.j Conclusion on silver oxide(I)/DBU promoted synthesis of furan frameworks

In conclusion, we developed herein a new route for the synthesis of furan derivatives. The procedure is easy to set-up and uses mild conditions. From readily available substrates, we synthetized more than thirty furans in good to moderate yields. Despite several attempts, we were unfortunately unable to make the reaction catalytic in silver. However, silver oxide(I) being inexpensive, it less penalizes the process set-up. Interestingly, we succeed to extend the condition to a one-pot process but the latter is not suitable for all substrates. Thanks to this methodology, we attained several furans derivatives which can be potentially interesting in medicinal chemistry. In addition, we also attained highly complex and strained furan frameworks which normally required tedious synthesis and/or expensive metal catalysts (Figure 16).

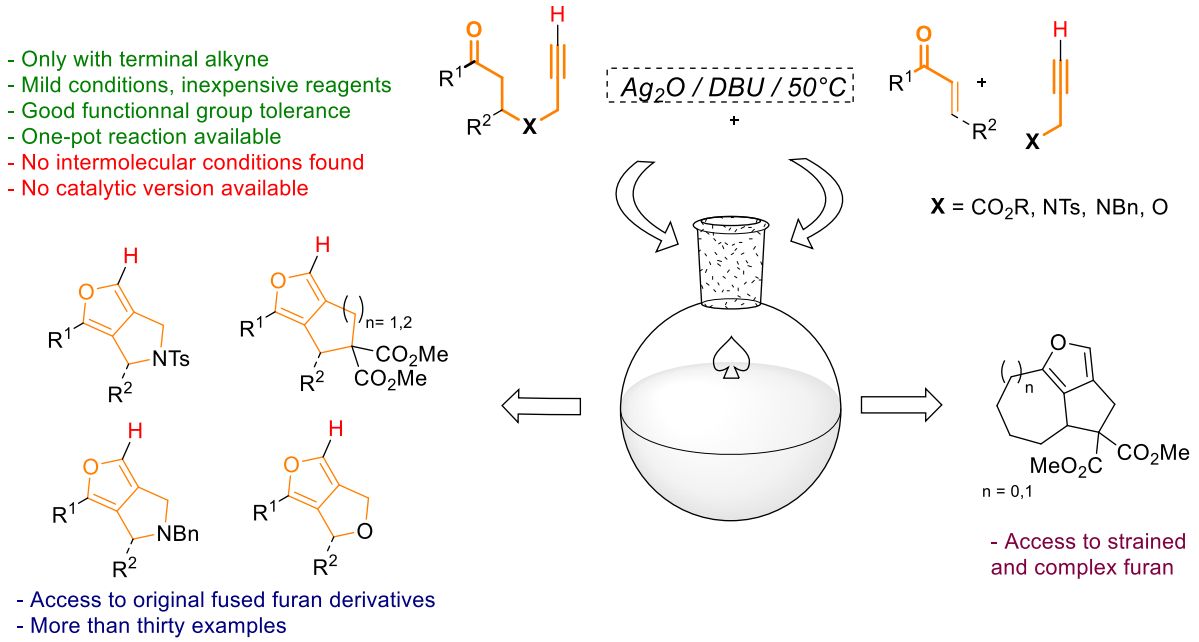


Figure 16

Several attempts have been carried out to make this reaction possible in an intramolecular manner. Unfortunately, no product was observed restricting, to this date, the field of this transformation to intramolecular fashion. Deeper studies will be required in order to attain this goal.

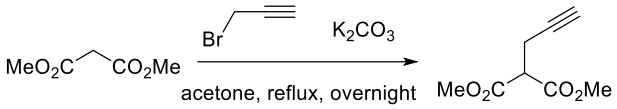
In parallel, we also submitted our conditions to α-substituted ketones in the aim to reach α-tetrasubstituted ketones from unactivated ketone and alkyne. Traces of conia-ene adducts were found in the crude which constitute a promising sign for the future but this study will deserve more investigations.

We tried to rationalize our results in order to find a plausible mechanism for this unique transformation. In view of the results obtained, the mechanism doesn't appear obvious to us. Indeed, several routes can be considered and at this moment we cannot select one route against another one. For this purpose, we have extended our collaboration with Dr. Ilaria Ciofini and Anna Perfetto from the Chemical Theory and Modeling group at Chimie Paris. DFT calculations are in progress and should help to determine the right synthetic pathway.

VI. EXPERIMENTAL PART II

Preparation of the cyclization precursors

dimethyl 2-(prop-2-yn-1-yl)malonate **181**

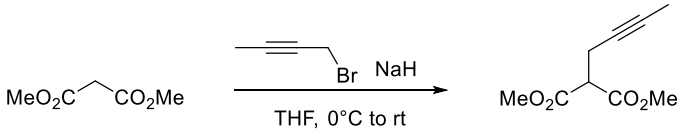


181
$C_8H_{10}O_4$
170.16 g/mol

A flask containing powdered potassium carbonate (20.05 g, 145 mmol) was charged with dry acetone (125 mL) and dimethyl malonate (17.5 mL, 140 mmol). The suspension was warmed to reflux and propargyl bromide (80% in toluene, 6.25 mL, 56 mmol) was slowly added over 30 minutes. The mixture was stirred overnight at reflux. The reaction was cooled to room temperature and filtered over sand. The solution was concentrated under reduced pressure then purified by flash chromatography on silica gel (EtOAc/Cyclohexane : 5/95 to 10/90) to afford **181** as a colorless oil (m= 7.6 g, 80% yield).

All the spectroscopic data are in accordance with those described in the literature.[112]

dimethyl 2-(but-2-yn-1-yl)malonate **244**

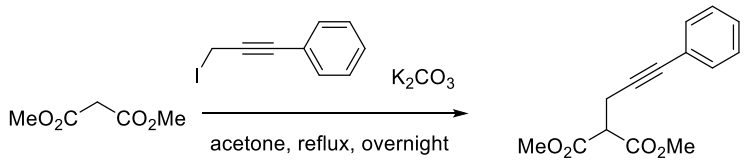


244
$C_9H_{12}O_4$
184.19 g/mol

To a dry flask containing dimethyl malonate (9.0 mL, 78.9 mmol) and THF (245 mL) was slowly added NaH (60% w/w in mineral oil, 28.93 mmol) at 0 °C. 1-Bromo-2-butyne (2.3 mL, 26.3 mmol) was then slowly added then the solution was stirred for 30 min at 0 °C at which time a white precipitated formed. The mixture was then warmed to room temperature and stirred for 5h. The reaction was quenched by a saturated solution of NH_4Cl and the aqueous layer was extracted twice by EtOAc. The combined organics extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel (EtOAc/Cyclohexane : 5/95) affording **244** as a colorless oil (m= 3.5 g, 73% yield).

All the spectroscopic data are in accordance with those described in the literature.[113]

dimethyl 2-(3-phenylprop-2-yn-1-yl)malonate **241**

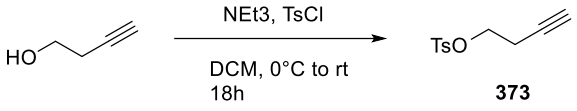


241
$C_{14}H_{14}O_4$
246.26 g/mol

A flask containing powdered potassium carbonate (4 g, 29.3 mmol) was charged with dry acetone (25 mL) and dimethyl malonate (3.2 mL, 28.4 mmol). The suspension was warmed to reflux and (3-iodoprop-1-yn-1-yl)benzene (11.3 mmol) was slowly added over 30 minutes. The mixture was stirred overnight at reflux. The reaction was cooled to room temperature and filtered over sand. The solution was concentrated under vacuum then purified by flash chromatography on silica gel (EtOAc/Cyclohexane : 5/95) affording **241** as yellow oil (m= 1.7 g, 62% yield).

All the spectroscopic data are in accordance with those described in the literature.[114]

but-3-yn-1-yl 4-methylbenzenesulfonate **373**

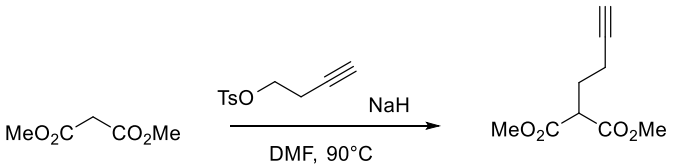


373
$C_{11}H_{12}O_3S$
224.27 g/mol

To a solution of but-3-yn-1-ol (701 mg, 10 mmol) in CH_2Cl_2 (15 mL) were added NEt_3 (2.7 mL, 20 mmol) and TsCl (1.9 g, 10 mmol) at 0 °C. The solution was stirred for 18 h at r.t. and then quenched with sat. NH_4Cl. The mixture was extracted with CH_2Cl_2 (3x), the combined organic layers were neutralized with sat. $NaHCO_3$, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel (EtOAc/Cyclohexane : 2/98 to 10/90) affording **373** as a colorless oil (m= 2.1 g, 90% yield).

All the spectroscopic data are in accordance with those described in the literature.[115]

dimethyl 2-(but-3-yn-1-yl)malonate **242**



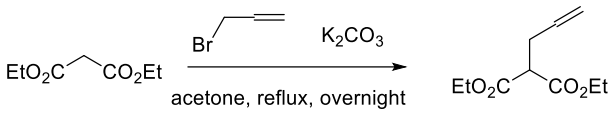
242
$C_9H_{12}O_4$
184.19 g/mol

To a dry flask containing NaH (60% in mineral oil, 396 mg, 9.90 mmol) and anhydrous DMF (16 ml) was slowly added dimethylmalonate (3.56 g, 26.9 mmol) at 0 °C. The solution was stirred for 15 min at r.t. After this, but-3-yn-1-yl 4-methylbenzenesulfonate (2.01 g, 8.97 mmol) was added and the resulting mixture was stirred at 90 °C for 21 h. The reaction was quenched by water and the aqueous layer was extracted twice by Et_2O. The combined organics extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash

chromatography on silica gel (EtOAc/Cyclohexane : 5/95 to 10/90) affording **242** as a colorless oil (m= 1 g, 61% yield).

All the spectroscopic data are in accordance with those described in the literature.[116]

diethyl 2-allylmalonate **243**

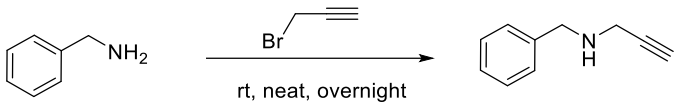


243
$C_{10}H_{16}O_4$
200.23 g/mol

A flask containing powdered potassium carbonate (10.4 g, 75 mol) was charged with dry acetone (1.24 L) and diethyl malonate (5.7 mL, 37.5 mol). The suspension was warmed to reflux and allyl bromide (2.16 mL, 25 mol) was slowly added over 30 minutes. The mixture was stirred overnight at reflux. The reaction was cooled to room temperature and filtered over sand. The solution was concentrated under vacuum then purified by flash chromatography on silica gel (EtOAc/Cyclohexane : 5/95) affording **243** as colorless oil (m= 4.1 g, 82% yield).

All the spectroscopic data are in accordance with those described in the literature.[117]

N-benzylprop-2-yn-1-amine **245**

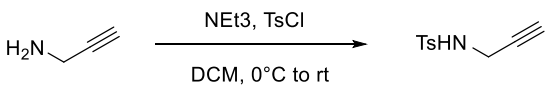


245
$C_{10}H_{11}N$
145.21 g/mol

Propargyl bromide (4.3 mL, 38 mmol) was added to benzyl amine (25 mL, 228 mmol) over 30 min *via* addition funnel and allowed to stir overnight. The resulting mixture was diluted in Et_2O and extracted with saturated aq. $NaHCO_3$ and dried over $MgSO_4$. The reaction mixture was concentrated under reduced pressure then purified by flash chromatography on silica gel (EtOAc/Cyclohexane : 10/90 to 15/85) affording **245** as pale yellow oil (m= 4.7 g, 85% yield).

All the spectroscopic data are in accordance with those described in the literature.[112]

4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide **246**



246
$C_{10}H_{11}NO_2S$
209.26 g/mol

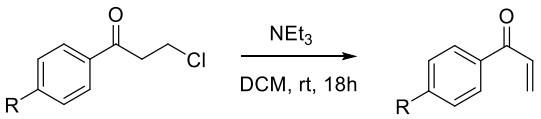
p-toluenesulfonyl chloride (4.8 g, 25 mmol) was added dropwise to a solution of propargylamine (1.9 mL, 30 mmol) and Et_3N (4.7 mL, 35 mmol) in DCM (25 mL) at 0 °C under argon. Then the resulting

mixture was warmed up to room temperature and stirred overnight. The reaction was quenched by H_2O, extracted twice with DCM, dried over $MgSO_4$ and concentrated under reduced pressutre. The residue was purified by flash chromatography on silica gel (EtOAc/Cyclohexane : 10/90) to afford **246** as white solid (m= 5.1 g, 97% yield).

All the spectroscopic data are in accordance with those described in the literature.[118]

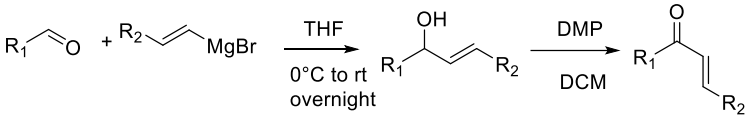
General procedure for the synthesis of vinyl ketones (GPI and GPII) :

GPI



To a pre-stirred solution of 3-chloropropionyl aryl ketone (5.0 mmol, 1.0 eq.) in CH_2Cl_2 (10 mL), triethylamine (10.0 mmol, 2 eq.) was added dropwise over 5 min under argon atmosphere. The reaction mixture was stirred for 18 h at room temperature followed by washing with 0.1 N HCl aq., distilled water, saturated $NaHCO_3$ aq., and brine. The organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel yielding the α,β-unsaturated ketone.

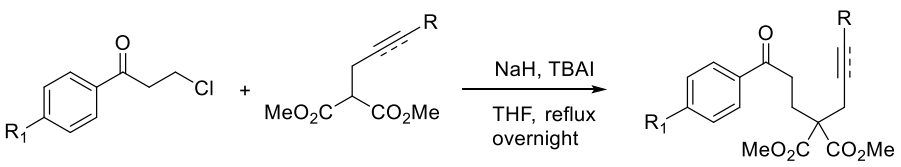
GPII



A solution of aldehyde (3 mmol, 1 eq.) in dry THF (5 mL) was cooled to 0 °C in an ice –water bath and Grignard reagent (3.6 mmol, 1.2 eq.) was added dropwise. The mixture was warmed to room temperature and stirred for overnight. Saturated NH_4Cl solution (20 mL) was added to quench the reaction and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL) and Dess-Martin periodinane (4.0 mmol, 1.3 eq.) was added. The mixture was stirred at room temperature until TLC showed complete disappearance of the starting alcohol. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel affording the expected compound in a pure form.

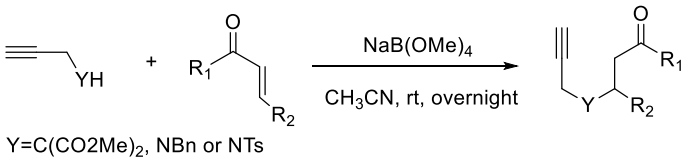
General procedure for the synthesis of cyclization precursors (GPIII, GPIV, GPV and GPVI) :

GPIII



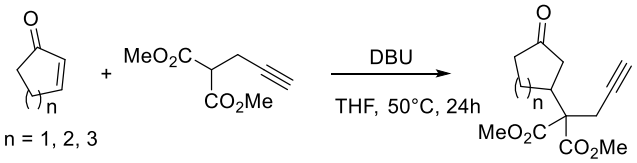
The alkyne or alkene (2.0 mmol, 1 eq.) was dissolved in THF (5 mL) and cooled to 0 °C. NaH (60% w/w in mineral oil, 2.6 mmol, 1.3 eq.) was added in one portion. The reaction mixture was stirred for 30 min at 0 °C. The 3-chloropropiophenone or derivatives (4.0 mmol, 2 eq.) was dissolved in THF (8 mL) and transferred slowly to the reaction mixture. Tetrabutylammonium iodide (0.2 mmol, 0.1 eq.) was added in one portion. The reaction was warmed to room temperature and then stirred at reflux overnight. The suspension was cooled to room temperature, quenched by a saturated solution of NH_4Cl and the aqueous layer was extracted twice by EtOAc. The combined organics extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel affording the expected compound in a pure form.

GPIV



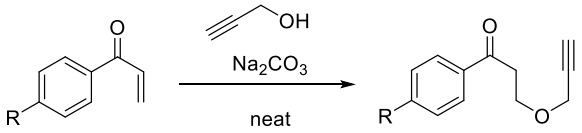
To a solution of Michael donor (1.2 mmol, 1.2 eq.) and $NaB(OMe)_4$ (0.2 mmol, 0.2 eq.) in CH_3CN (3 mL) was added α-β-unsaturated ketone (1.0 mmol, 1 eq.) at room temperature. The resulting solution was stirred at room temperature under air atmosphere and monitored by TLC. Upon completion, solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel to give the desired product in a pure form.

GPV



A solution of cyclic vinyl ketone (10 mmol, 1 eq.), dimethylpropargyl-malonate (13 mmol, 1.3 eq.) and DBU (13 mmol, 1.3 eq.) in THF (15 mL) was stirred for 24 h under argon at 50 °C. The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography on silica gel to give the desired product in a pure form.

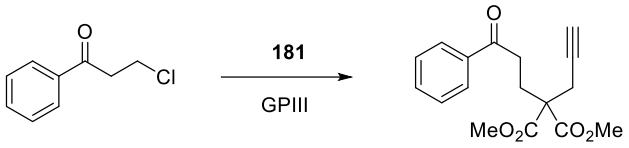
GPVI



To a solution of activated alkene (0.5 mmol, 1 eq.) in propargyl alcohol (2.0 mmol, 4 eq.) was added Na_2CO_3 (0.2 mL, 0.05M aq.), and the solution was stirred until alkene was completely consumed (monitored by TLC). The reaction mixture was extracted with ethyl acetate (3 × 5 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and

concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to give the expected product in a pure form.

dimethyl 2-(3-oxo-3-phenylpropyl)-2-(prop-2-yn-1-yl)malonate **238**



238
$C_{17}H_{18}O_5$
302.33 g/mol

The compound **238** was obtained from 3-chloropropiophenone and compound **181** following the **GPIII** on 47 mmol scale (8 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 10/90) afforded **238** as a pale yellow solid (m= 10.9 g, 77% yield).

All the spectroscopic data are in accordance with those described in the literature.[119]

dimethyl 2-(but-2-yn-1-yl)-2-(3-oxo-3-phenylpropyl)malonate **256**

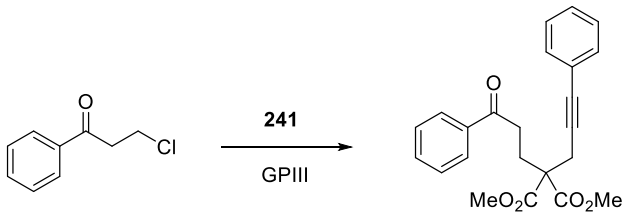


256
$C_{18}H_{20}O_5$
316.35 g/mol

The compound **256** was obtained from 3-chloropropiophenone and compound **244** following the **GPIII** on 8.1 mmol scale (1.5 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95 to 8/92) afforded **256** as a white solid (m= 1.0 g, 41% yield).

All the spectroscopic data are in accordance with those described in the literature.[120]

dimethyl 2-(3-oxo-3-phenylpropyl)-2-(3-phenylprop-2-yn-1-yl)malonate **258**



258
$C_{23}H_{22}O_5$
378.42 g/mol

The compound **258** was obtained from 3-chloropropiophenone and compound **241** following the **GPIII** on 4.9 mmol scale (1.2 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95 to 8/92) afforded **258** as a yellow solid (m= 1.3 g, 70% yield).

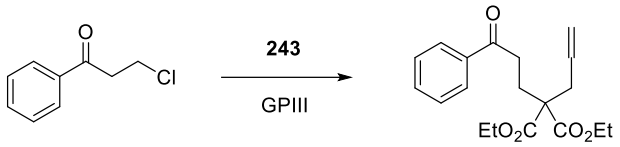
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.98 – 7.96 (m, 2H), 7.54 (tt, *J* = 6.8, 1.2 Hz, 1H), 7.38 - 7.32 (m, 2H), 7.38 – 7.32 (m, 2H), 7.29-7.23 (m, 3H), 3.76 (s, 6H), 3;13 (s, 2H), 3.13 – 3.09 (m, 2H), 2.61 – 2.57 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 198.8, 170.7, 136.7, 133.2, 131.8, 128.7, 128.3, 128.2, 123.1, 84.1, 56.8, 53.0, 34.0, 27.6, 25.0

FTIR (neat): *ν* = 2954, 2255, 1732, 1204, 906, 725, 690 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{23}H_{22}O_5Na^+$: $[M+Na]^+$: 401.1365; found: 401.1367

diethyl 2-allyl-2-(3-oxo-3-phenylpropyl)malonate **259**

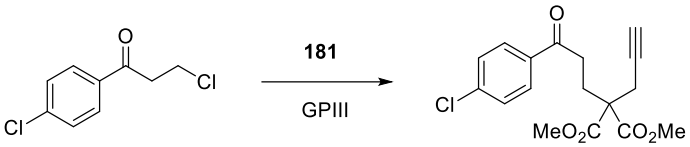


259
$C_{19}H_{24}O_5$
332.40 g/mol

The compound **259** was obtained from 3-chloropropiophenone and compound **243** following the **GPIII** on 7.5 mmol scale (1.5 g). Purification by flash chromatography (EtOAc/Cyclohexane: 3/97 to 4/96) afforded **259** as a pale yellow solid (m= 1.1 g, 45% yield).

All the spectroscopic data are in accordance with those described in the literature.[121]

dimethyl 2-(3-(4-chlorophenyl)-3-oxopropyl)-2-(prop-2-yn-1-yl)malonate **257**

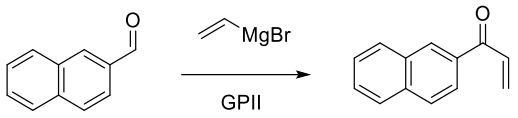


257
$C_{17}H_{17}ClO_5$
336.77 g/mol

The compound **257** was obtained from 3,4'-dichloropropiophenone and compound **181** following the **GPIII** on 2.9 mmol scale (500 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95 to 10/90) afforded **257** as a white solid (m= 781 mg, 80% yield).

All the spectroscopic data are in accordance with those described in the literature.[119]

1-(naphthalen-2-yl)prop-2-en-1-one **249**

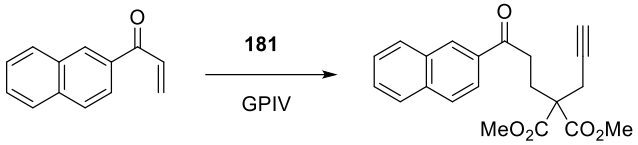


249
$C_{13}H_{10}O$
182.22 g/mol

The compound **249** was obtained from 2-naphthaldehyde and vinylmagnesium bromide following the **GPII** on 20 mmol scale (3.2 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 6/94) afforded **249** as a colorless oil (m= 3 g, 84% yield over 2 steps).

All the spectroscopic data are in accordance with those described in the literature.[122]

dimethyl 2-(3-(naphthalen-2-yl)-3-oxopropyl)-2-(prop-2-yn-1-yl)malonate **260**



249

260
$C_{21}H_{20}O_5$
352.39 g/mol

The compound **260** was obtained from compound **249** and **181** following the **GPIV** on 10 mmol scale (1.8 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95) afforded **260** as a pale yellow solid (m= 1.4 g, 41% yield).

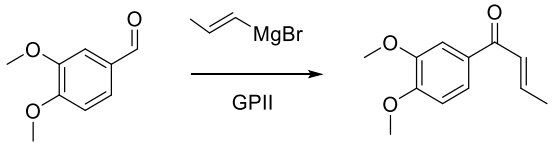
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.03 (dd, *J* = 8.8, 1.8 Hz, 1H), 7.97 (brd, *J* = 8.0 Hz, 1H), 7.93 – 7.84 (m, 2H), 7.64 – 7.51 (m, 2H), 3.76 (s, 6H), 3.19 (t, *J* = 7.6 Hz, 2H), 2.95 (d, *J* = 2.8 Hz, 2H), 2.58 (t, *J* = 7.6 Hz, 2H), 2.07 (t, *J* = 2.7 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 170.6, 135.8, 134.1, 132.6, 129.9, 129.7, 128.7, 128.6, 127.9, 126.9, 124.0, 78.7, 72.1, 56.4, 53.1, 33.9, 27.4, 24.2

FTIR (neat): ν = 3291, 2954, 1731, 1679, 1436, 1203, 1125, 909, 732 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{21}H_{20}O_5Na^+$: $[M+Na]^+$: 375.1208; found: 375.1209

(*E*)-1-(3,4-dimethoxyphenyl)but-2-en-1-one **253**

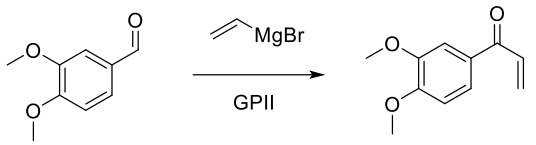


253
$C_{12}H_{14}O_3$
206.24 g/mol

The compound **253** was obtained from 3,4-dimethoxybenzaldehyde and 1-propenylmagnesium bromide following the GPII on 8 mmol scale (1.3 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 10/90 to 15/85) afforded **253** as a yellow solid (m= 1.2 g, 73% yield over 2 steps).

All the spectroscopic data are in accordance with those described in the literature.[123]

1-(3,4-dimethoxyphenyl)prop-2-en-1-one **250**

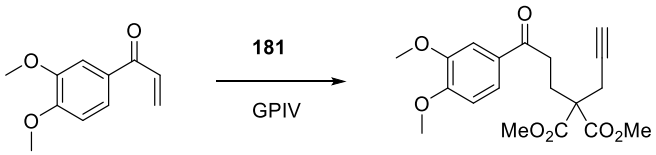


250
$C_{11}H_{12}O_3$
192.21 g/mol

The compound **250** was obtained from 3,4-dimethoxybenzaldehyde and vinylmagnesium bromide following the **GPII** on 20 mmol scale (3.4 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 10/90) afforded **250** as a pale yellow solid (m= 3.4 g, 90% yield over 2 steps).

All the spectroscopic data are in accordance with those described in the literature.[124]

dimethyl 2-(3-(3,4-dimethoxyphenyl)-3-oxopropyl)-2-(prop-2-yn-1-yl)malonate **261**



250

261
$C_{19}H_{22}O_7$
362.38 g/mol

The compound **261** was obtained from compound **250** and **181** following the **GPIV** on 10 mmol scale (1.9 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 10/90 to 20/80) afforded **261** as a yellow solid (m= 2.3 g, 64% yield).

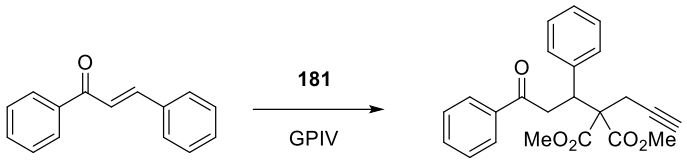
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.49 (d, *J* = 8.4 Hz, 1H), 7.41 (s, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 3.82 (d, *J* = 4.8 Hz, 6H), 3.64 (s, 6H), 2.89 (t, *J* = 7.6 Hz, 2H), 2.78 (d, *J* = 2.6 Hz, 2H), 2.38 (t, *J* = 7.6 Hz, 2H), 1.99 (t, *J* = 2.6 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 197.0, 170.2 (2C), 153.2, 148.9, 129.6, 122.6, 110.0, 109.9, 78.4, 71.8, 56.1, 55.9, 55.8, 52.7 (2C), 33.1, 27.4, 23.8

FTIR (neat): *ν* = 2256, 1733, 1515, 1265, 1023, 905, 724 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{19}H_{22}O_7Na^+$: $[M+Na]^+$: 385.1263; found: 385.1253

dimethyl 2-(3-oxo-1,3-diphenylpropyl)-2-(prop-2-yn-1-yl)malonate **268**



268
$C_{23}H_{22}O_5$
378.42 g/mol

The compound **268** was obtained from chalcone and compound **181** following the **GPIV** on 10 mmol scale (2.1 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 10/90 to 20/80) afforded **268** as a white solid (m= 710 mg, 18% yield).

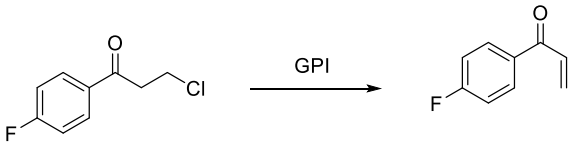
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.91 (m, 2H), 7.50 (tt, *J* = 1.2, 7.6 Hz, 1H), 7.43 – 7.39 (m, 2H), 7.26 – 7.19 (m, 5H), 4.43 (dd, *J* = 10.6, 2.8 Hz, 1H), 3.84 (d, *J* = 2.8 Hz, 1H), 3.82 (s, 3H), 3.79 (d, *J* = 10.6 Hz, 1H), 3.75 (s, 3H), 2.77 (dd, *J* = 17.2, 2.7 Hz, 1H), 2.52 (dd, *J* = 17.2, 2.8 Hz, 1H), 2.18 (t, *J* = 2.8 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 170.1, 170.0, 138.6, 137.1, 133.0, 129.0, 128.5, 128.4, 128.1, 127.7, 79.3, 72.5, 61.0, 52.9, 52.7, 43.6, 41.5, 24.3

FTIR (neat): ν = 3308, 2251, 1734, 1214, 905, 725 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{23}H_{23}O_5$: $[M+H]^+$: 379.1545; found: 379.1536

1-(4-fluorophenyl)prop-2-en-1-one **247**

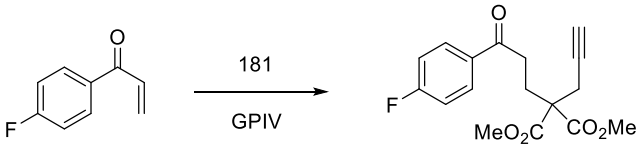


247
C_9H_7FO
150.15 g/mol

The compound **247** was obtained from 3-chloro-4'-fluoropropiophenone following the **GPI** on 16 mmol scale (3 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 10/90) afforded **247** as a colorless oil (m= 2.3 g, 96% yield).

All the spectroscopic data are in accordance with those described in the literature.[125]

dimethyl 2-(3-(4-fluorophenyl)-3-oxopropyl)-2-(prop-2-yn-1-yl)malonate **262**



262
$C_{17}H_{17}FO_5$
320.32 g/mol

The compound **262** was obtained from compound **247** and **181** following the **GPIV** on 10 mmol scale (1.5 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 10/90) afforded **262** as a white solid (m= 2.6 g, 81% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 - 7.95 (m, 2H), 7.11 (t_{app}, J= 8.7 Hz, 2H), 3.72 (s, 6H), 3.01 (t_{app}, *J* = 7.5 Hz, 2H), 2.88 (d, *J* = 2.6 Hz, 2H), 2.47 (t, *J* = 7.5 Hz, 2H), 2.03 (t, *J* = 2.6 Hz, 1H

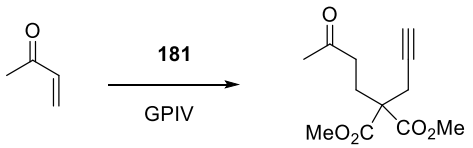
^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 170.5 (2C), 165.8 (d, *J* = 253 Hz), 133.1 (d, *J* = 3 Hz), 130.8 (d, *J* = 3 Hz, 2C), 115.7 (d, *J* = 21 Hz, 2C), 78.6, 72.0, 56.3, 52.9 (2C), 33.7, 27.3, 24.1

^{19}F NMR (280 MHz, $CDCl_3$) δ -105.15

FTIR (neat): ν = 3308, 2257, 1733, 1686, 1599, 1206, 1157, 906, 726 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{17}H_{18}O_5F$: $[M+H]^+$: 321.1138; found: 321.1137

dimethyl 2-(3-oxobutyl)-2-(prop-2-yn-1-yl)malonate **263**

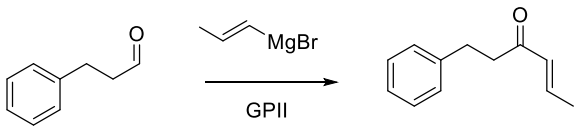


263
$C_{12}H_{16}O_5$
240.26 g/mol

The compound **263** was obtained from methyl vinyl ketone and compound **181** following the **GPIV** on 10 mmol scale (0.7 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 10/90 to 15/85) afforded **263** as a white solid (m= 1.8 g, 75% yield).

All the spectroscopic data are in accordance with those described in the literature.[126]

(*E*)-1-phenylhex-4-en-3-one **251**

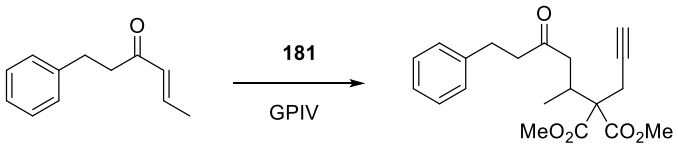


251
$C_{12}H_{14}O$
174.24 g/mol

The compound **251** was obtained from 3-phenylpropionaldehyde and 1-propenylmagnesium bromide following the **GPII** on 6 mmol scale (0.8 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 10/90 to 15/85) afforded **251** as a colorless oil (m= 966 mg, 92% yield over 2 steps).

All the spectroscopic data are in accordance with those described in the literature.[127]

dimethyl 2-(4-oxo-6-phenylhexan-2-yl)-2-(prop-2-yn-1-yl)malonate **265**



251

265
$C_{20}H_{24}O_5$
344.41 g/mol

The compound **265** was obtained from compound **251** and **181** following the **GPIV** on 2.3 mmol scale (401 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 10/90 to 15/85) afforded **265** as a yellow solid (m= 142 mg, 18% yield).

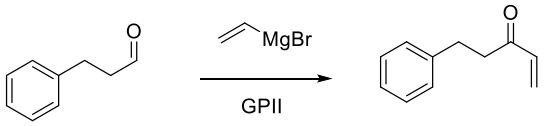
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.28 - 7.24 (m, 2H), 7.20 – 7.16 (m, 3H), 3.73 (s, 6H), 3.05 – 2.95 (m, 1H), 2.92 – 2.83 (m, 4H), 2.82 – 2.67 (m, 3H), 2.23 (dd, *J* = 16.8, 10.4 Hz, 1H), 2.03 (t, *J* = 2.8 Hz, 1H), 0.89 (d, *J* = 6.8 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 208.4, 170.3, 167.0, 141.1, 128.6, 128.4, 126.2, 79.1, 71.8, 60.3, 52.8, 52.6, 46.7, 44.5, 31.9, 29.9, 23.04, 15.7

FTIR (neat): *ν* = 2954, 1730, 1435, 1202, 1049, 908, 728, 700 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{20}H_{25}O_5$: $[M+H]^+$: 345.1702; found: 345.1695

5-phenylpent-1-en-3-one **252**

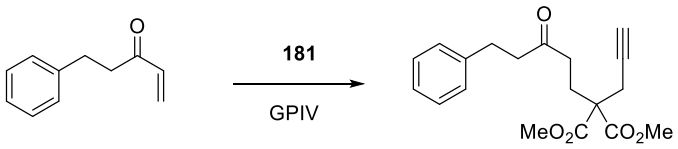


252
$C_{11}H_{12}O$
160.22 g/mol

The compound **252** was obtained from 3-phenylpropionaldehyde and vinylmagnesium bromide following the **GPII** on 14.9 mmol scale (2 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 20/80) afforded **252** as a yellow oil (m= 2.2 g, 94% yield over 2 steps).

All the spectroscopic data are in accordance with those described in the literature.[128]

dimethyl 2-(3-oxo-5-phenylpentyl)-2-(prop-2-yn-1-yl)malonate **266**



252

266
$C_{19}H_{22}O_5$
330.38 g/mol

The compound **266** was obtained from compound **252** and **181** following the **GPIV** on 2.2 mmol scale (350 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95) afforded **266** as a white solid (m= 405 mg, 56% yield).

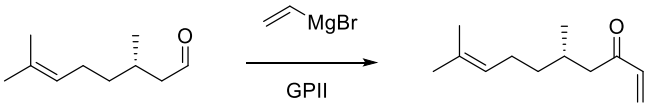
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.25 (m, 2H), 7.20-7.15 (m, 3H), 3.71 (s, 6H), 2.89 (t, *J* = 7.6 Hz, 2H), 2.79 (d, *J* = 2.7 Hz, 2H), 2.73 (t, *J* = 7.6 Hz, 2H), 2.44 (t, *J* = 8.0 Hz, 2H), 2.32 (t, *J* = 8.0 Hz, 2H), 2.02 (t, *J* = 2.7 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 208.3, 170.5 (2C), 141.0, 128.6 (2C), 128.4 (2C), 126.2, 78.5, 71.9, 56.1, 52.9 (2C), 44.3, 37.9, 29.8, 26.5, 23.9

FTIR (neat): ν = 3308, 2254, 1733, 1204, 905, 725 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{19}H_{23}O_5$: $[M+H]^+$: 331.1545; found: 331.1540

(*S*)-5,9-dimethyldeca-1,8-dien-3-one **254**

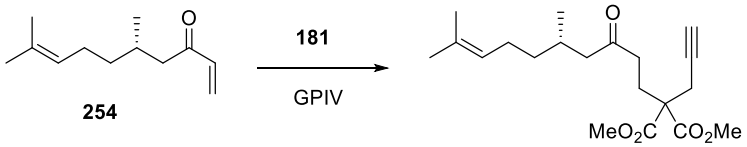


254
$C_{12}H_{20}O$
180.29 g/mol

The compound **254** was obtained from (*S*)-(−)-citronellal and vinylmagnesium bromide following the **GPII** on 13.3 mmol scale (2.1 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95) afforded **254** as a pale yellow oil (m= 2.2 g, 90% yield for 2 steps).

All the spectroscopic data are in accordance with those described in the literature.[129]

dimethyl (S)-2-(5,9-dimethyl-3-oxodec-8-en-1-yl)-2-(prop-2-yn-1-yl)malonate **264**



254

264
$C_{20}H_{30}O_5$
350.46 g/mol

The compound **264** was obtained from compound **254** and **181** following the **GPIV** on 1.7 mmol scale (300 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 10/90) afforded **264** as a colorless oil (m= 367 mg, 63% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09-5.04 (m, 1H), 3.72 (s, 6H), 2.80 (d, *J* = 2.8 Hz, 2H), 2.45-2.39 (m, 2H), 2.39 – 2.28 (m, 3H), 2.20 (dd, *J* = 15.8, 8.2 Hz, 1H), 2.01 (t, J = 2.8 Hz, 1H), 1.99 – 1.90 (m, 3H), 1.66 (s, 3H), 1.58 (s, 3H), 1.40 – 1.12 (m, 2H), 0.88 (d, *J* = 6.4 Hz, 3H)

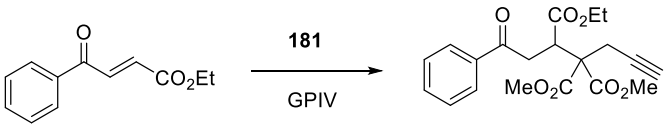
^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2, 170.5 (2C), 131.6, 124.4, 78.6, 71.9, 56.2, 53.0, 50.3, 38.2, 37.1, 29.1, 26.5, 25.8, 25.6, 23.9, 19.8, 17.8

FTIR (neat): ν = 3310, 2956, 2256, 1734, 1437, 1205, 906, 727 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{20}H_{30}O_5Na^+$: $[M+Na]^+$: 373.1991; found: 373.1996

$[\alpha]_D^{25}$ = -1.8 (c = 0.5, $CHCl_3$)

(+/-)-3-ethyl 4,4-dimethyl 1-oxo-1-phenylhept-6-yne-3,4,4-tricarboxylate **267**



267
$C_{20}H_{22}O_7$
374.39 g/mol

The compound **267** was obtained from ethyl 3-benzoylacrylate and compound **181** following the **GPIV** on 2.45 mmol scale (500 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 20/80) afforded **267** as a yellow solid (m= 830 mg, 91% yield).

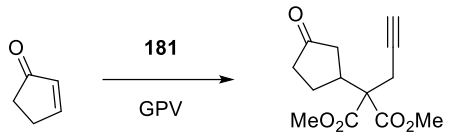
^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.96 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.11 (dd, *J* = 10.6, 3.0 Hz, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.77 (dd, *J* = 18.0, 10.6 Hz, 1H) 3.52 (dd, *J* = 18.0, 3.0 Hz, 1H), 3.03 (dd, *J* = 17.4, 2.7 Hz, 1H), 2.92 (dd, *J* = 17.4, 2.7 Hz, 1H) (m, 2H), 2.12 (t, *J* = 2.7 Hz, 1H), 1.21 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 197.8, 171.9, 169.5, 169.2, 136.6, 133.3, 128.7 (2C), 128.2 (2C), 79.5, 72.1, 61.5, 58.5, 53.2, 53.1, 44.5, 37.9, 23.2, 14.1

FTIR (neat): *ν* = 2955, 1734, 1689, 1436, 1207, 1027, 908, 730, 690 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{20}H_{23}O_7$: $[M+H]^+$: 375.1444; found: 375.1441

dimethyl 2-(3-oxocyclopentyl)-2-(prop-2-yn-1-yl)malonate **302**

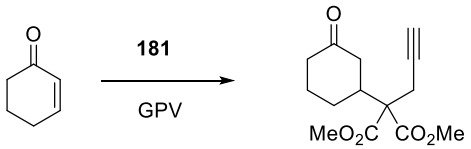


302
$C_{13}H_{16}O_5$
252.27 g/mol

The compound **302** was obtained from 2-cyclopentenone following the **GPV** on 5.9 mmol scale (482 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 30/70 to 50/50) afforded **302** as a white solid (m= 900 mg, 61% yield).

All the spectroscopic data are in accordance with those described in the literature.[130]

dimethyl 2-(3-oxocyclohexyl)-2-(prop-2-yn-1-yl)malonate **20**

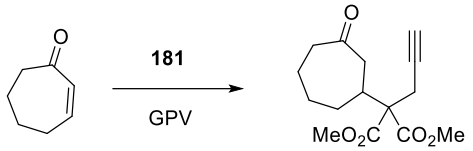


20
$C_{14}H_{18}O_5$
266.29 g/mol

The compound **20** was obtained from 2-cyclohexen-1-one following the **GPV** on 5.9 mmol scale (564 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 30/70 to 50/50) afforded **20** as a colorless oil (m= 1.35 g, 86% yield).

All the spectroscopic data are in accordance with those described in the literature.[130]

dimethyl 2-(3-oxocycloheptyl)-2-(prop-2-yn-1-yl)malonate **303**

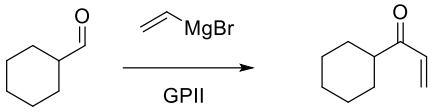


303
$C_{15}H_{20}O_5$
280.32 g/mol

The compound **303** was obtained from cyclohept-2-en-1-one following the **GPV** on 3.8 mmol scale (419 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 20/80 to 30/70) afforded **303** as a yellow oil (m= 959 mg, 90% yield).

All the spectroscopic data are in accordance with those described in the literature.[131]

1-cyclohexylprop-2-en-1-one **255**

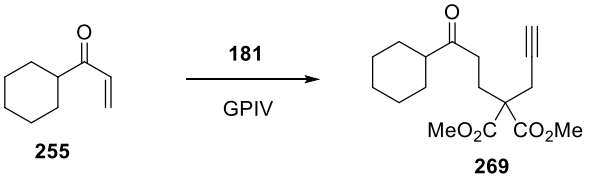


255
$C_9H_{14}O$
138.21 g/mol

The compound **255** was obtained from cyclohexanecarboxaldehyde and vinylmagnesium bromide following the **GPII** on 20 mmol scale (2.2 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95) afforded **255** as a yellow oil (m= 2.4 g, 88% yield for 2 steps).

All the spectroscopic data are in accordance with those described in the literature.[132]

dimethyl 2-(3-cyclohexyl-3-oxopropyl)-2-(prop-2-yn-1-yl)malonate **269**



269
$C_{17}H_{24}O_5$
308.37 g/mol

The compound **269** was obtained from compound **255** and **181** following the **GPIV** on 10 mmol scale (1.38 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 10/90) afforded **269** as a white solid (m= 2.3 g, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 6H), 2.78 (d, *J* = 2.6 Hz, 2H), 2.53 – 2.42 (m, 2H), 2.37 – 2.23 (m, 3H), 2.01 (t, *J* = 2.6 Hz, 1H), 1.86 – 1.68 (m, 4H), 1.65 – 1.61 (m, 1H), 1.35 – 1.09 (m, 5H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3, 170.5 (2C), 78.5, 71.8, 56.2, 52.9 (2C), 50.8, 35.4, 28.6, 26.5, 25.9, 25.7, 23.9

FTIR (neat): ν = 2931, 1732, 1437, 1200, 910, 729 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{17}H_{25}O_5$: $[M+H]^+$: 309.1702; found: 309.1702

1-(4-chlorophenyl)prop-2-en-1-one **248**

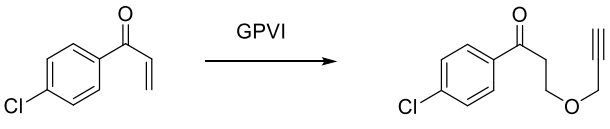


248
C_9H_7ClO
166.60 g/mol

The compound **248** was obtained from 3,4'-dichloropropiophenone following the **GPI** on 14.8 mmol scale (3 g). Purification by flash chromatography (EtOAc/Cyclohexane: 10/90) afforded **248** as a colorless oil (m= 2.4 g, 96% yield).

All the spectroscopic data are in accordance with those described in the literature.[122]

1-(4-chlorophenyl)-3-(prop-2-yn-1-yloxy)propan-1-one **281**



248

281
$C_{12}H_{11}ClO_2$
222.67 g/mol

The compound **281** was obtained from compound **248** following the **GPVI** on 7.4 mmol scale (1.2 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95) afforded **281** as a white solid (m= 1.2 g, 74% yield).

All the spectroscopic data are in accordance with those described in the literature.[119]

1-phenylprop-2-en-1-one **237**

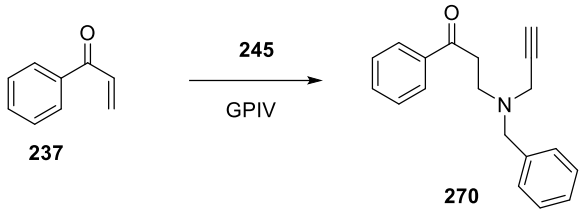


237
C_9H_8O
132.16 g/mol

The compound **237** was obtained from 3-chloropropiophenone following the **GPI** on 20 mmol scale (3.4 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95 to 10/90) afforded **237** as a yellow oil (m= 2.5 g, 95% yield).

All the spectroscopic data are in accordance with those described in the literature.[132]

3-(benzyl(prop-2-yn-1-yl)amino)-1-phenylpropan-1-one **270**



237

270
$C_{19}H_{19}NO$
277.37 g/mol

The compound **270** was obtained from compound **237** and **245** following the **GPIV** on 17.8 mmol scale (2.3 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95) afforded **270** as a colorless oil (m= 3.4 g, 84% yield).

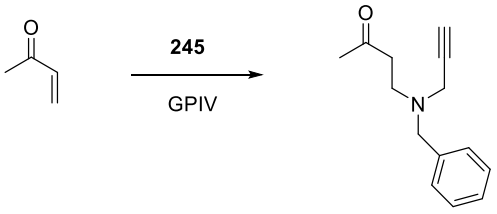
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.97 (m, 2H), 7.57 (brt, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.37 – 7.25 (m, 5H), 3.74 (s, 2H), 3.41 (d, *J* = 2.4 Hz, 2H), 3.21 (t_{app}, *J* = 7.2 Hz, 2H), 3.10 (t_{app}, *J* = 7.2 Hz, 2H), 2.32 (t, *J* = 2.4 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0, 138.4, 136.9, 132.9, 128.9 (2C), 128.5 (2C), 128.2 (2C), 128.0 (2C), 127.1, 78.3, 73.5, 58.0, 48.8, 41.6, 37.2

FTIR (neat): ν = 3295, 1682, 1448, 1212, 1120, 909, 735, 689 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{19}H_{20}NO$: $[M+H]^+$: 278.1545; found: 278.1529

4-(benzyl(prop-2-yn-1-yl)amino)butan-2-one **271**



271
$C_{14}H_{17}NO$
215.30 g/mol

The compound **271** was obtained from methyl vinyl ketone and compound **245** following the **GPIV** on 2.1 mmol scale (145 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 7/93 to 10/90) afforded **271** as a colorless oil (m= 365 mg, 82% yield).

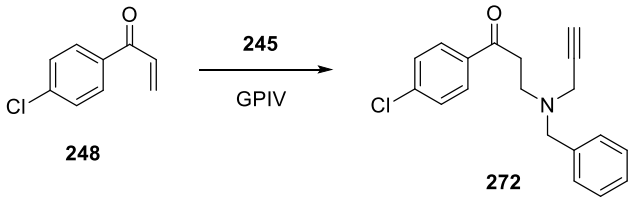
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.21 (m, 5H), 3.62 (s, 2H), 3.29 (d, *J* = 2.4 Hz, 2H), 2.88 (t, *J* = 7.0 Hz, 2H), 2.60 (t, *J* = 7.0 Hz, 2H), 2.24 (t, *J* = 2.4 Hz, 1H), 2.12 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8, 138.3, 129.0 (2C), 128.3 (2C), 127.2, 78.1, 73.5, 57.8, 48.2, 42.1, 41.3, 29.8

FTIR (neat): *v* = 3287, 2834, 1710, 1454, 1358, 1123, 1028, 738, 699 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{14}H_{18}NO$: $[M+H]^+$: 216.1388; found: 216.1379

3-(benzyl(prop-2-yn-1-yl)amino)-1-(4-chlorophenyl)propan-1-one **272**



248

272
$C_{19}H_{18}ClNO$
311.81 g/mol

The compound **272** was obtained from compound **245** and **248** following the **GPIV** on 2.7 mmol scale (458 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95) afforded **272** as a colorless oil (m= 729 mg, 85% yield).

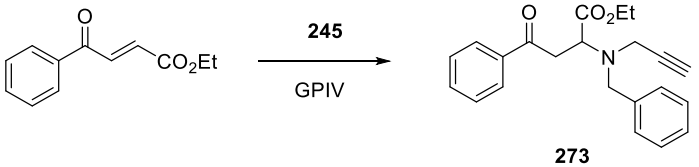
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.85 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.30 – 7.23 (m, 6H), 3.69 (s, 2H), 3.38 (d, *J* = 2.4 Hz, 2H), 3.13 (t, *J* = 6.4 Hz, 2H), 3.04 (t, *J* = 6.4 Hz, 2H), 2.29 (t, *J* = 2.4 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 197.8, 139.3, 138.3, 135.2, 129.4 (2C), 129.0 (2C), 128.8 (2C), 128.3 (2C), 127.2, 78.3, 73.6, 58.0, 48.6, 41.7, 37.2

FTIR (neat): *v* = 3302, 1683, 1588, 1400, 1092, 906, 729, 698 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{19}H_{19}NOCl$: $[M+H]^+$: 312.1155; found: 312.1144

(+/-)-ethyl 2-(benzyl(prop-2-yn-1-yl)amino)-4-oxo-4-phenylbutanoate **273**



273
$C_{22}H_{23}NO_3$
349.43 g/mol

The compound **273** was obtained from ethyl 3-benzoylacrylate and compound **245** following the **GPIV** on 2.4 mmol scale (500 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 3/97) afforded **273** as a pale yellow solid (m= 663 mg, 79% yield).

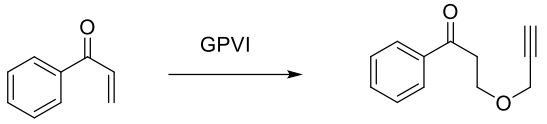
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.95 (d, *J* = 8.0 Hz, 2H), 7.60 – 7.52 (tt, *J* = 8.0, 1.2, 1H), 7.46 (t, *J* = 8.0 Hz, 2H), 7.37 – 7.22 (m, 5H), 4.30 (dd, *J* = 9.4, 4.8 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 4.02 (d, *J* = 13.6 Hz, 1H), 3.80 (d, *J* = 13.6 Hz, 1H), 3.70 (dd, *J* = 17.2, 9.4 Hz, 1H), 3.47 (d, *J* = 2.4 Hz, 2H), 3.33 (dd, *J* = 17.2, 4.8 Hz, 1H), 2.22 (t, *J* = 2.4 Hz, 1H), 1.33 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 197.8, 171.7, 138.5, 136.8, 133.3, 128.9 (2C), 128.7 (2C), 128.5 (2C), 128.2 (2C), 127.4, 80.2, 73.0, 60.9, 60.2, 54.8, 40.4, 39.1, 14.4

FTIR (neat): *v* = 1724, 1683, 1449, 1207, 1174, 907, 735, 689 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{22}H_{24}NO_3$: $[M+H]^+$: 350.1756; found: 350.1749

1-phenyl-3-(prop-2-yn-1-yloxy)propan-1-one **280**



237

280
$C_{12}H_{12}O_2$
188.23 g/mol

The compound **280** was obtained from compound **237** following the **GPVI** on 17.8 mmol scale (2.4 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 4/96) afforded **280** as a colorless oil (m= 2.8 g, 83% yield).

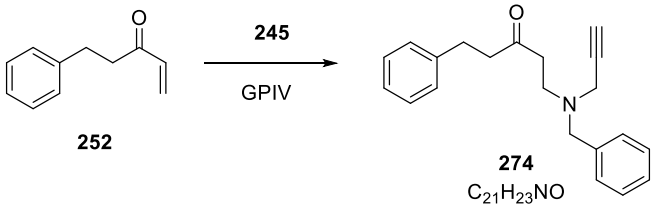
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.94 (m, 2H), 7.60 – 7.52 (m, 1H), 7.51 – 7.42 (m, 2H), 4.18 (d, *J* = 2.4 Hz, 2H), 3.97 (t, *J* = 6.5 Hz, 2H), 3.27 (t, *J* = 6.5 Hz, 2H), 2.44 (t, *J* = 2.4 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 137.0, 133.3, 128.7 (2C), 128.2 (2C), 79.7, 74.6, 65.4, 58.5, 38.7

FTIR (neat): ν = 3298, 1680, 1449, 1216, 1099, 908, 728, 688 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{12}H_{12}O_2Na^+$: $[M+Na]^+$: 211.0735; found: 211.0734

1-(benzyl(prop-2-yn-1-yl)amino)-5-phenylpentan-3-one **274**



252

274
$C_{21}H_{23}NO$
305.42 g/mol

The compound **274** was obtained from compound **252** and **245** following the **GPIV** on 1.6 mmol scale (256 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95) afforded **274** as a yellow oil (m= 460 mg, 94% yield).

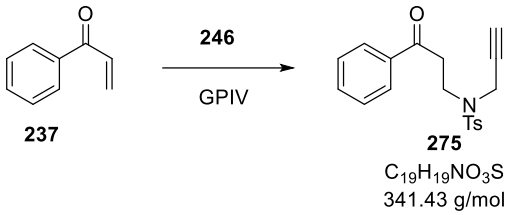
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.21 (m, 10H), 3.67 (s, 2H), 3.34 (d, *J* = 2.4 Hz, 2H), 2.94 (t, *J* = 7,4 Hz, 2H), 2.93 (t, *J* = 7,0 Hz, 2H), 2.77 (t, *J* = 7.4 Hz, 2H), 2.62 (t, *J* = 7.0 Hz, 2H), 2.29 (t, *J* = 2.4 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8, 141.1, 138.4, 129.1 (2C), 128.5 (2C), 128.4 (2C), 128.3 (2C), 127.3, 126.1, 78.2, 73.5, 57.9, 48.3, 44.1, 41.5, 41.4, 29.6

FTIR (neat): ν = 1710, 1454, 906, 729, 698 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{21}H_{24}NO$: $[M+H]^+$: 306.1858; found: 306.1848

4-methyl-*N*-(3-oxo-3-phenylpropyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide **275**



237 **275**

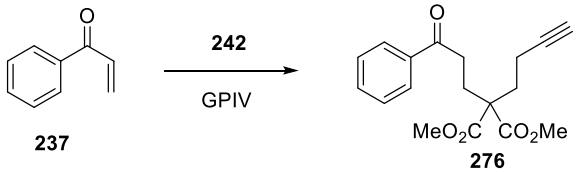
$C_{19}H_{19}NO_3S$

341.43 g/mol

The compound **275** was obtained from compound **237** and **246** following the **GPIV** on 12 mmol scale (1.6 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95 to 15/85) provided **275** as a white solid (m=1.2 g, 30% yield).

All the spectroscopic data are in accordance with those described in the literature.[133]

dimethyl 2-(but-3-yn-1-yl)-2-(3-oxo-3-phenylpropyl)malonate **276**



237 **276**

$C_{18}H_{20}O_5$

316.35 g/mol

The compound **276** was obtained from compound **237** and **242** following the **GPIV** on 4 mmol scale (528.6 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95 to 7/93) provided **276** as a white solid (m=822.5 mg, 65% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 – 7.91 (m, 2H), 7.57 – 7.52 (m, 1H), 7.47 - 7.42 (m, 2H), 3.72 (s, 6H), 2.98 (t, *J* = 7.8 Hz, 2H), 2.33 (t, *J* = 7.8 Hz, 2H), 2.21 (s, 4H), 1.96 – 1.95 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 171.3 (2C), 136.7, 133.3, 128.7 (2C), 128.1 (2C), 83.1, 69.1, 56.6, 52.7 (2C), 33.8, 32.9, 27.5, 14.2

FTIR (neat): ν = 3292, 2954, 1728, 1686, 1449, 1202, 906, 732 cm^{-1}

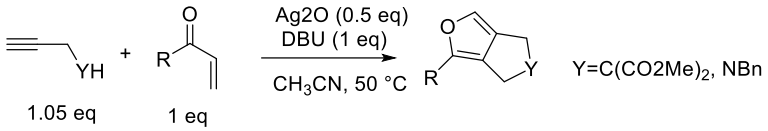
HRMS (ESI): *m/z* calcd for $C_{18}H_{21}O_5$: $[M+H]^+$: 317.1389; found: 317.1386

Cyclized Products

General procedure for the cyclization reaction GPVII:

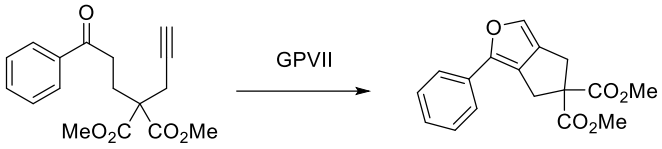
In a vial protected from the light was placed a suspension of Ag_2O (0.1 mmol, 0.5 eq.) in CH_3CN (0.5 mL). DBU (0.2 mmol, 1 eq.) was added, then a solution of corresponding precursors (0.2 mmol, 1 eq.) in CH_3CN (0.5 mL) was added dropwise. The mixture was heated to 50 °C under air atmosphere and stirred until TLC showed complete disappearance of the starting material. The reaction mixture was quenched by water and extracted twice with Et_2O. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel affording the expected compound in a pure form.

General procedure for the one-pot reaction GPVIII:



A vial protected from the light was charged with the alkyne (0.21 mmol, 1. 05 eq.) and the α-β unsaturated ketone (0.2 mmol, 1 eq.). The mixture was solubilized in CH_3CN (1 mL) then Ag_2O (0.1 mmol, 0.5 eq.) and DBU (0.2 mmol, 1 eq.) was successively introduced. The reaction was heated to 50 °C under air atmosphere and stirred until TLC showed complete disappearance of the starting materials. The reaction was quenched by water and extracted twice with Et_2O. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel affording the expected compound in a pure form.

dimethyl 1-phenyl-4*H*-cyclopenta[*c*]furan-5,5(6*H*)-dicarboxylate **239**



238

239
$C_{17}H_{16}O_5$
300.31 g/mol

The compound **239** was obtained from compound **238** following the **GPVII** on 0.2 mmol scale (60.5 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95 to 10/90) afforded **239** as a pale yellow solid (m= 45 mg, 75% yield).

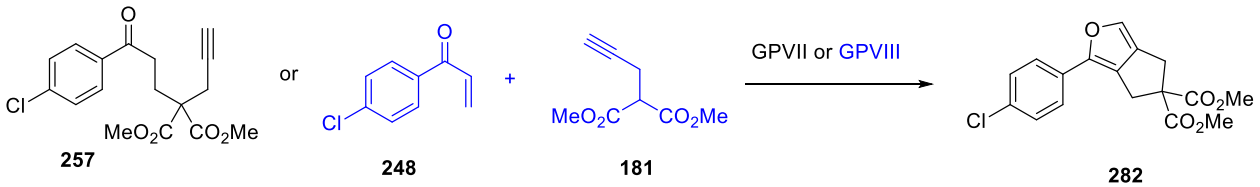
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.56 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.12 (s, 1H), 3.77 (s, 6H), 3.56 (s, 2H), 3.35 (d, *J* = 1.4 Hz, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 171.6 (2C), 144.3, 132.5, 131.1, 130.9, 128.8 (2C), 126.8, 125.1, 123.9 (2C), 67.5, 53.2 (2C), 33.5, 31.8

FTIR (neat): *ν* = 2954, 1732, 1435, 1248, 1199, 963, 906, 728, 692 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{17}H_{16}O_5Na^+$: $[M+Na]^+$: 323.0895; found: 323.0889

dimethyl 1-(4-chlorophenyl)-4*H*-cyclopenta[*c*]furan-5,5(6*H*)-dicarboxylate **282**



257

248

181

282
$C_{17}H_{15}ClO_5$
334.75 g/mol

The compound **282** was obtained from compound **257** following the **GPVII** on 0.2 mmol scale (67.4 mg). Purification by flash chromatography (EtOAc/Cyclohexane: 5/95) afforded **282** as white solid (m= 45.5 mg, 68% yield).

The compound **282** was obtained from compound **248** and **181** following the **GPVIII** on 0.2 mmol scale (33.3 mg). Purification by flash chromatography (EtOAc/Cyclohexane: 5/95) afforded **282** as a white solid (m= 43.5 mg, 65% yield).

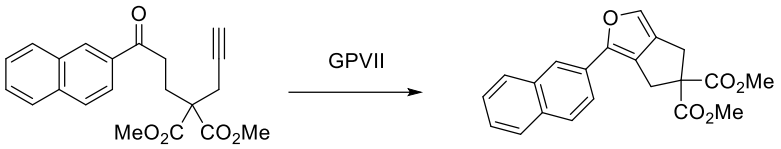
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.46 (d, *J* = 8.6 Hz, 2H), 7.33 (d, *J* = 8.6 Hz, 2H), 7.10 (s, 1H), 3.77 (s, 6H), 3.52 (s, 2H), 3.34 (d, *J* = 1.4 Hz, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 171.5 (2C), 143.4, 132.8, 132.4, 131.1, 129.6, 129.0 (2C), 125.6, 125.1 (2C), 67.5, 53.3 (2C), 33.4, 31.8

FTIR (neat): *ν* = 2955, 1733, 1489, 1435, 1250, 1092, 908, 830, 730 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{17}H_{16}ClO_5$: $[M+H]^+$: 335.0686; found: 335.0677

dimethyl 1-(naphthalen-2-yl)-4*H*-cyclopenta[*c*]furan-5,5(6*H*)-dicarboxylate **284**



260

284
$C_{21}H_{18}O_5$
350.37 g/mol

The compound **284** was obtained from compound **260** following the **GPVII** on 0.2 mmol scale (70.5 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 10/90 to 15/85) afforded **284** as a white solid (m= 56.3 mg, 80% yield).

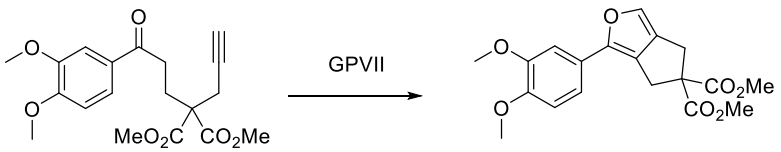
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.00 (s, 1H), 7.90 - 7.77 (m, 3H), 7.75 - 7.66 (m, 1H), 7.52 – 7.40 (m, 2H), 7.18 (s, 1H), 3.80 (s, 6H), 3.66 (s, 2H), 3.39 (d, *J* = 1.4 Hz, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 171.6 (2C), 144.5, 133.6, 132.7, 132.3, 131.1, 128.5, 128.4, 128.1, 127.8, 126.5, 125.9, 125.6, 122.4, 122.2, 67.5, 53.2 (2C), 33.6, 31.8

FTIR (neat): *ν* = 2954, 1732, 1435, 1250, 1199, 1066, 905, 816, 725 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{21}H_{19}O_5$: $[M+H]^+$: 351.1232; found: 351.1237

dimethyl 1-(3,4-dimethoxyphenyl)-4*H*-cyclopenta[*c*]furan-5,5(6*H*)-dicarboxylate **285**



261

285
$C_{19}H_{20}O_7$
360.36 g/mol

The compound **285** was obtained from compound **261** following the **GPVII** on 0.2 mmol scale (72.5 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 20/80 to 30/70) afforded **285** as a yellow solid (m= 52.6 mg, 73% yield).

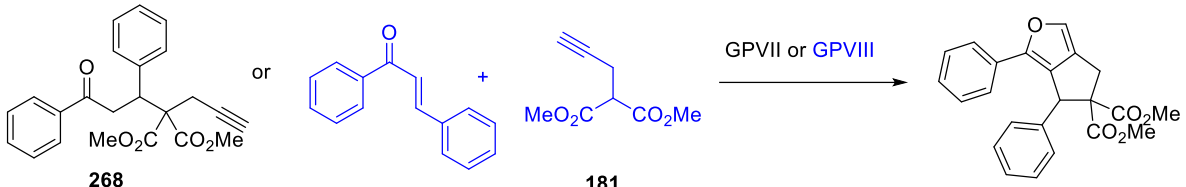
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 2.0 Hz, 1H), 7.08 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.07 (t, *J* = 1.4 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.76 (s, 6H), 3.51 (s, 2H), 3.33 (d, *J* = 1.4 Hz, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6 (2C), 149.3, 148.2, 144.3, 131.8, 130.9, 124.5, 123.5, 116.7, 111.5, 107.2, 67.5, 56.0, 55.9, 53.2, 33.3, 31.8

FTIR (neat): ν = 2256, 1733, 1512, 1247, 1025, 906, 730 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{19}H_{21}O_7$: $[M+H]^+$: 361.1287; found: 361.1289

dimethyl 1,6-diphenyl-4*H*-cyclopenta[*c*]furan-5,5(6*H*)-dicarboxylate **287**



268 **181** **287**

$C_{23}H_{20}O_5$

376.41 g/mol

The compound **287** was obtained from compound **268** following the **GPVII** on 0.2 mmol scale (75.7 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95) afforded **287** as a white solid (m= 31.6 mg, 42% yield).

The compound **287** was obtained from chalcone and compound **181** following the **GPVIII** on 0.2 mmol scale (41.6 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95) afforded **287** as a white solid (m= 35.4 mg, 47% yield).

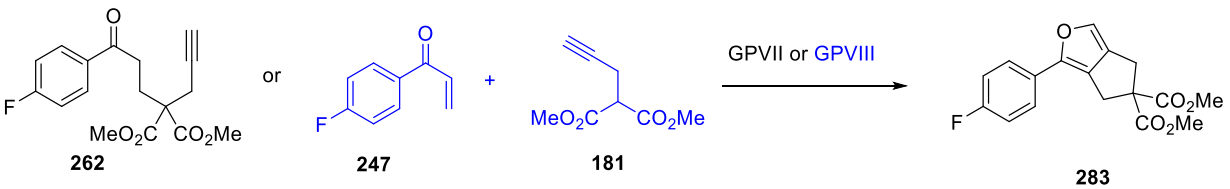
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 2H), 7.29 – 7.17 (m, 8H), 7.16 – 7.09 (m, 1H), 5.30 (s, 1H), 3.79 (dd, *J* = 16.4, 1.8 Hz, 1H), 3.77 (s, 3H), 3.31 (s, 3H), 3.24 (dd, *J* = 16.4, 1.1 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 168.8, 145.1, 138.1, 132.6, 130.7, 130.6, 129.0 (2C), 128.8, 128.5 (2C), 128.4 (2C), 127.7, 126.9, 124.3 (2C), 73.8, 53.3, 52.3, 50.0, 30.6

FTIR (neat): ν = 2952, 1733, 1435, 1259, 1160, 907, 729 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{23}H_{21}O_5$: $[M+H]^+$: 377.1389; found: 377.1393

dimethyl 1-(4-fluorophenyl)-4*H*-cyclopenta[*c*]furan-5,5(6*H*)-dicarboxylate **283**



262 **247** **181** **283**

$C_{17}H_{15}FO_5$

318.30 g/mol

The compound **283** was obtained from compound **262** following the **GPVII** on 0.2 mmol scale (64.1 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95) afforded **283** as a white solid (m= 50.9 mg, 80% yield).

The compound **283** was obtained from compound **247** and **181** following the **GPVIII** on 0.2 mmol scale (30 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95) afforded **283** as a white solid (m= 48.4 mg, 76% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.49 (m, 2H), 7.09 – 7.04 (m, 3H), 3.77 (s, 6H), 3.51 (s, 2H), 3.34 (d, *J* = 1.4 Hz, 2H)

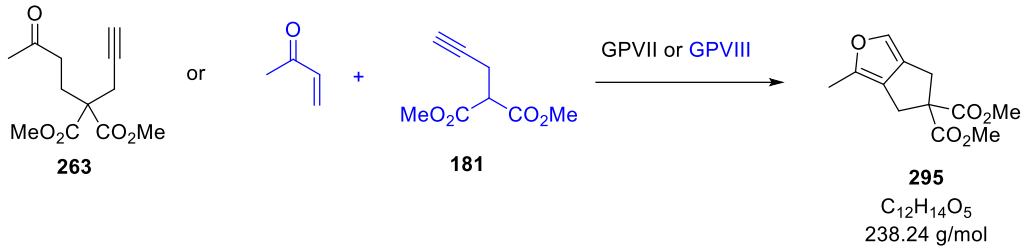
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5 (2C), 161.7 (d, *J* = 291.8), 143.6, 132.4 (d, *J* = 1.0 Hz), 131.0, 127.5 (d, *J* = 3.0 Hz), 125.6 (d, *J* = 8.0 Hz), 124.6 (d, *J* = 2.0 Hz), 115.9 (d, *J* = 21.0 Hz), 67.5, 53.2 (2C), 33.3, 31.9

^{19}F NMR (280 MHz, $CDCl_3$) δ -114.8

FTIR (neat): ν = 2955, 1732, 1506, 1435, 1232, 1157, 1064, 907, 835, 731 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{17}H_{16}O_5F$: $[M+H]^+$: 319.0982; found: 319.0983

dimethyl 1-methyl-4*H*-cyclopenta[*c*]furan-5,5(6*H*)-dicarboxylate **295**



The compound **295** was obtained from compound **263** following the **GPVII** on 0.2 mmol scale (48.1 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95) afforded **295** as a yellow solid (m= 34.7 mg, 73% yield).

The compound **295** was obtained from methyl vinyl ketone and compound **181** following the **GPVIII** on 0.2 mmol scale (14 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95) afforded **295** as a yellow solid (m= 33.4 mg, 70% yield).

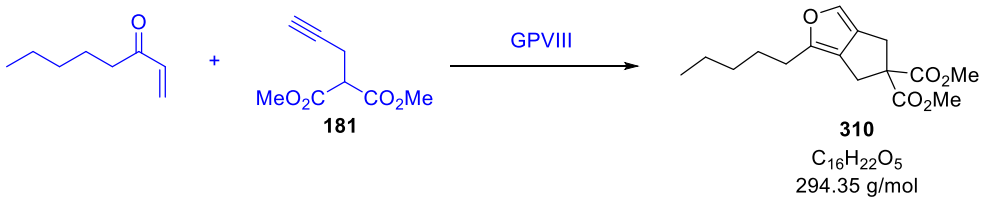
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (t, *J* = 1.6 Hz, 1H), 3.74 (brs, 6H), 3.26 (d, *J* = 1.6 Hz, 2H), 3.19 (q, *J* = 1.2 Hz, 2H), 2.18 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (2C), 142.5, 131.3, 129.2, 123.8, 67.3, 53.1 (2C), 32.2, 31.6, 12.7

FTIR (neat): ν = 2955, 2258, 1732, 1435, 1257, 1199, 1066, 908, 727 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{12}H_{14}O_5Na^+$: $[M+Na]^+$: 261.0739; found: 261.0732

dimethyl 1-pentyl-4*H*-cyclopenta[*c*]furan-5,5(6*H*)-dicarboxylate **310**



The compound **310** was obtained from oct-1-en-3-one and compound **181** following the **GPVIII** on 0.2 mmol scale (25.2 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95) afforded **310** as a yellow solid (m= 37.7 mg, 64% yield).

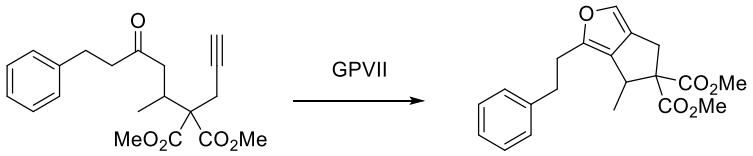
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (t_{app}, *J* = 1.5 Hz, 1H), 3.75 (s, 6H), 3.25 (d, *J* = 1.5 Hz, 2H), 3.22 (s, 2H), 2.53 (t, *J* = 7.5 Hz, 2H), 1.65 - 1.56 (m, 2H), 1.34 - 1.25 (m, 4H), 0.89 (t, *J* = 6.9 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (2C), 146.8, 131.2, 129.1, 123.3, 67.3, 53.1 (2C), 32.0, 31.9, 31.5, 27.4, 27.3, 22.5, 14.1

FTIR (neat): *v* = 2955, 1735, 1435, 1254, 1198, 1159, 1066, 731 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{16}H_{23}O_5$: $[M+H]^+$: 295.1545; found: 295.1536

dimethyl 6-methyl-1-phenethyl-4*H*-cyclopenta[*c*]furan-5,5(6*H*)-dicarboxylate **297**



265

297
$C_{20}H_{22}O_5$
342.39 g/mol

The compound **297** was obtained from compound **265** following the **GPVII** on 0.2 mmol scale (68.8 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 3/97 to 7/93) afforded **297** as a yellow solid (m= 45.8 mg, 67% yield).

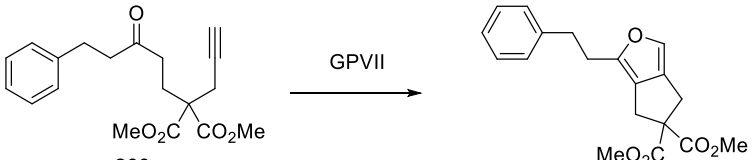
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.25 (m, 2H), 7.20 – 7.16 (m, 1H), 7.14 – 7.12 (m, 2H), 6.95 (t, *J* = 1.6 Hz, 1H), 3.76-3.68 (m, 7H), 3.43 (dd, *J* = 16.2, 1.6 Hz, 1H), 3.03 (dd, *J* = 16.2, 1.6 Hz, 1H), 2.98 – 2.90 (m, 2H), 2.90 – 2.78 (m, 2H), 0.96 (d, *J* = 7.2 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 170.2, 145.4, 141.4, 131.4, 129.4, 128.5 (2C), 128.4 (2C), 127.7, 126.1, 71.2, 52.9, 52.4, 37.6, 34.7, 30.6, 29.5, 16.2

FTIR (neat): *v* = 2953, 1733, 1434, 1252, 1159, 1084, 1042, 738, 700 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{20}H_{23}O_5$: $[M+H]^+$: 343.1545; found: 343.1545

dimethyl 1-phenethyl-4*H*-cyclopenta[*c*]furan-5,5(6*H*)-dicarboxylate **296**



266

296
$C_{19}H_{20}O_5$
328.36 g/mol

The compound **296** was obtained from compound **266** following the **GPVII** on 0.2 mmol scale (66.1 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 8/92) afforded **296** as a white solid (m= 45.3 mg, 69% yield).

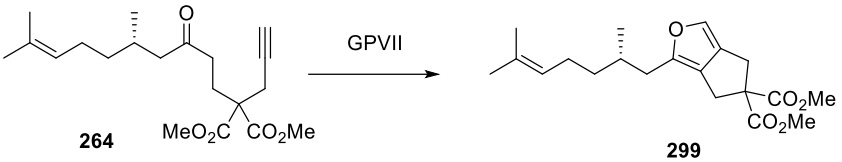
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.25 (m, 2H), 7.21 – 7.12 (m, 3H), 6.96 (t, *J* = 1.6 Hz, 1H), 3.73 (s, 6H), 3.24 (d, *J* = 1.6 Hz, 2H), 3.07 (s, 2H), 2.96 – 2.89 (m, 2H), 2.89 – 2.80 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7 (2C), 145.4, 141.2, 131.4, 129.2, 128.4 (2C), 128.3 (2C), 126.0, 124.0, 67.2, 53.0 (2C), 34.0, 31.9, 31.7, 29.3

FTIR (neat): ν = 2953, 1733, 1434, 1253, 1198, 1065, 909, 729, 699 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{19}H_{21}O_5$: $[M+H]^+$: 329.1389; found: 329.1383

dimethyl (*S*)-1-(2,6-dimethylhept-5-en-1-yl)-4*H*-cyclopenta[*c*]furan-5,5(6*H*)-dicarboxylate **299**



264 **299**

$C_{20}H_{28}O_5$

348.44 g/mol

The compound **299** was obtained from compound **264** following the **GPVII** on 0.2 mmol scale (70.1 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95) afforded **299** as a pale yellow oil (m= 41.8 mg, 60% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (t, *J* = 1.6 Hz, 1H), 5.08 (m, 1H), 3.74 (s, 6H), 3.26 (d, *J* = 1.6 Hz, 2H), 3.19 (s, 2H), 2.53 (dd, *J* = 14.8, 5.8 Hz, 1H), 2.35 (dd, *J* = 14.8, 7.6 Hz, 1H), 2.09 – 1.89 (m , 2H), 1.84-1.72 (m, 1H), 1.67 (s, 3H), 1.60 (s, 3H), 1.43 – 1.06 (m, 2H), 0.88 (d, *J* = 6.6 Hz, 3H)

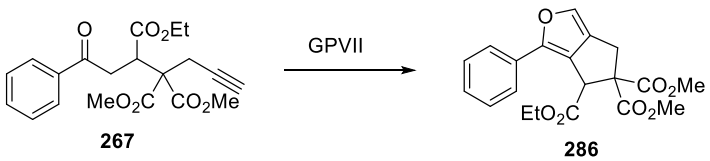
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7 (2C), 145.9, 131.4, 131.3, 128.9, 124.8, 124.1, 67.3, 53.0 (2C), 36.8, 34.8, 32.4, 32.1, 32.0, 25.8, 25.7, 19.7, 17.7

FTIR (neat): ν = 2955, 1734, 1435, 1255, 1199, 1066, 908, 729 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{20}H_{29}O_5$: $[M+H]^+$: 349.2015; found: 349.2013

$[\alpha]_D^{25}$ = -1.6 (c = 0.5, $CHCl_3$)

4-ethyl 5,5-dimethyl 3-phenyl-4H-cyclopenta[c]furan-4,5,5(6H)-tricarboxylate **286**



267 **286**

$C_{20}H_{20}O_7$

372.37 g/mol

The compound **286** was obtained from compound **267** following the **GPVII** on 0.2 mmol scale (74.9 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 8/92 to 13/87) afforded **286** as a white solid (m= 52.1 mg, 70% yield).

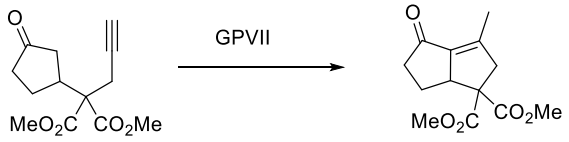
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.75 (brd, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.15 (s, 1H), 4.84 (s, 1H), 4.14 (dq, *J* = 10.8, 6.8, 1H), 4.05 (dq, *J* = 10.8, 6.8, 1H), 3.77 (s, 3H), 3.71 (s, 3H), 3.70 (dd, J = 3.0, 15.6 Hz), 3.36 (d, *J* = 15.6 Hz, 1H), 1.16 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 170.2, 169.1, 146.0, 133.1, 130.3, 130.2, 128.6 (2C), 127.5, 124.6 (2C), 123.6, 71.2, 61.6, 53.7, 53.0, 49.9, 30.9, 14.0

FTIR (neat): ν = 2955, 2259, 1735, 1239, 1163, 1025, 905, 725, 691 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{20}H_{21}O_7$: $[M+H]^+$: 373.1287; found: 373.1283

dimethyl 3-methyl-4-oxo-4,5,6,6a-tetrahydropentalene-1,1(2*H*)-dicarboxylate **304**



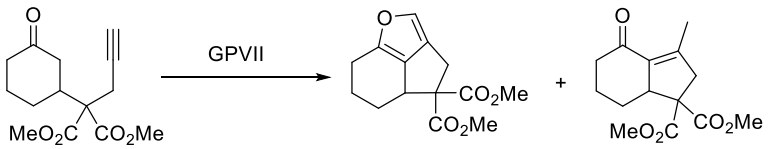
302

304
$C_{13}H_{16}O_5$
252.27 g/mol

The compound **304** was obtained from compound **302** following the **GPVII** on 0.2 mmol scale (50.5 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 15/85 to 20/80) afforded **304** as a colorless oil (m= 24.2 mg, 48% yield).

All the spectroscopic datas are in accordance with those described in the literature.[134]

dimethyl 3,4,5,5a-tetrahydroindeno[7,1-*bc*]furan-6,6(7*H*)-dicarboxylate **183** and dimethyl 3-methyl-4-oxo-2,4,5,6,7,7a-hexahydro-1H-indene-1,1-dicarboxylate **182**



20

183
$C_{14}H_{16}O_5$
264.28 g/mol

182
$C_{14}H_{18}O_5$
266.29 g/mol

The cyclization reaction was performed following the **GPVII** starting from **20** on 0.4 mmol scale (106.5 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95) afforded **183** as a yellow solid (m= 50 mg, 47% yield) and **182** as a white solid (m= 32 mg, 30% yield).

183

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (brd, *J* = 0.9 Hz,1H), 3.78 (s, 3H), 3.70 – 3.64 (m, 1H), 3.63 (s, 3H), 3.36 (d, *J* = 15.4 Hz, 1H), 3.11 (dd, *J* = 15.4, 1.8 Hz, 1H), 2.65 – 2.58 (m, 1H), 2.44 – 2.32 (m, 1H), 2.15 – 2.07 (m, 2H), 1.94 – 1.80 (m, 1H), 0.72 – 0.59 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 170.4, 147.8, 134.8, 133.4, 126.5, 73.1, 52.8, 52.1, 40.6, 35.6, 27.6, 25.2, 23.8

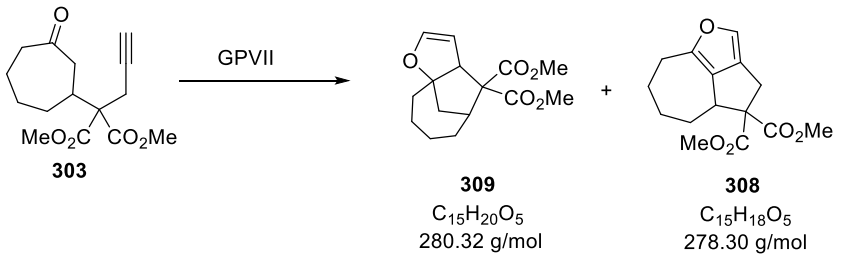
FTIR (neat): ν = 2951, 1731, 1435, 1269, 1242, 1081, 1037, 933 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{14}H_{17}O_5$: $[M+H]^+$: 265.1076; found: 265.1077

182

All the spectroscopic datas are in accordance with those described in the literature.[134]

dimethyl 6,7,8,9-tetrahydro-5*H*-5,9a-methanocycloocta[*b*]furan-4,4(3a*H*)-dicarboxylate **309** and dimethyl 5,6,7,8-tetrahydro-3*H*-azuleno[8,1-bc]furan-4,4(4a*H*)-dicarboxylate **308**



309
$C_{15}H_{20}O_5$
280.32 g/mol

308
$C_{15}H_{18}O_5$
278.30 g/mol

The cyclization reaction was performed following the **GPVII** starting from **303** on 0.2 mmol scale (56.1 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 2/98 to 5/95) afforded **309** as a yellow solid (m= 28.2 mg, 51% yield) and **308** as a yellow solid (m= 22.3 mg, 40% yield).

309

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.15 (t, *J* = 2.4 Hz, 1H), 4.72 (t, *J* = 2.4 Hz, 1H), 3.95 (t_{app}, *J* = 2.4 Hz, 1H), 3.72 (brs, 3H), 3.65 (s, 3H), 2.83 (dt, *J* = 7.2, 3.2 Hz, 1H), 2.35 (dd, *J* = 12.8, 7.2 Hz, 1H), 2.21 (d, *J* = 12.8 Hz, 1H), 1.95 (ddd, J = 13.6, 6.8, 4.0 Hz, 1H), 1.85 – 1.77 (m, 1H), 1.75 – 1.67 (m, 1H), 1.58 - 1.48 (m, 2H), 1.46 – 1.31 (m, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 171.0, 170.9, 144.6, 99.2, 96.4, 69.5, 59.3, 52.4, 51.9, 42.3, 42.2, 37.5, 31.3, 24.0, 23.7

FTIR (neat): *ν* = 2950, 1729, 1615, 1434, 1262, 1195, 1155, 1073, 909, 727 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{15}H_{21}O_5$: $[M+H]^+$: 281.1389; found: 281.1383

308

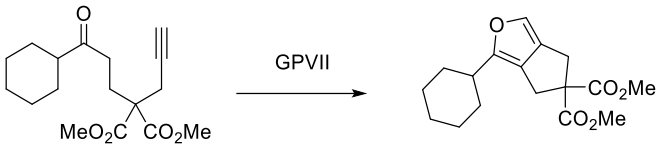
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.89 (t, *J* = 1.0 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 3.66 – 3.59 (m, 1H), 3.37 (dd, *J* = 16.0, 0.9 Hz, 1H), 2.96 (dd, *J* = 16.0, 2.0 Hz, 1H), 2.71 (dt, *J* = 16.2, 3.8 Hz, 1H), 2.59 (m, 1H), 2.27 – 2.17 (m, 1H), 2.17-2.08 (m, 1H), 2.06-1.95 (m, 1H), 1.51 – 1.36 (m, 2H), 1.00 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 171.8, 171.1, 148.0, 130.8, 129.5, 128.1, 70.4, 52.8, 52.2, 44.5, 33.5, 31.6, 28.1, 27.7, 27.6

FTIR (neat): *ν* = 2925, 1730, 1435, 1264, 1219, 1173, 1071, 910, 728 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{15}H_{19}O_5$: $[M+H]^+$: 279.1232; found: 279.1225

dimethyl 1-cyclohexyl-4*H*-cyclopenta[*c*]furan-5,5(6*H*)-dicarboxylate **298**



269

298
$C_{17}H_{22}O_5$
306.36 g/mol

The compound **298** was obtained from compound **269** following the **GPVII** on 0.2 mmol scale (61.7 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 10/90 to 20/80) afforded **298** as a colorless oil (m= 38.3 mg, 63% yield).

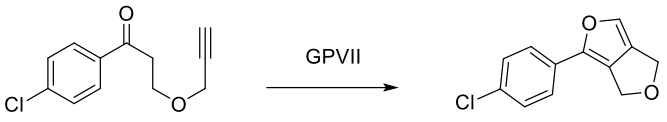
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.92 (t_{app}, *J* = 1.6 Hz, 1H), 3.74 (s, 6H), 3.26 (dd, *J* = 13.8, 1.2 Hz, 4H), 2.60 – 2.55 (m, 1H), 2.00 – 1.96 (m, 2H), 1.77 – 1.72 (m, 2H), 1.69 – 1.65 (m, 1H), 1.48 – 1.17 (m, 5H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 171.8 (2C), 150.5, 130.8, 129.2, 121.9, 67.3, 53.1 (2C), 37.3, 32.6, 31.7, 31.2, 26.2, 26.0

FTIR (neat): *ν* = 2928, 2854, 1734, 1435, 1256, 1199, 1066, 909, 730 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{17}H_{23}O_5$: $[M+H]^+$: 307.1545; found: 307.1541

4-(4-chlorophenyl)-1*H*,3*H*-furo[3,4-*c*]furan **294**



281

294
$C_{12}H_9ClO_2$
220.65 g/mol

The compound **294** was obtained from compound **281** following the **GPVII** on 0.2 mmol scale (44.5 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95) afforded **294** as a yellow solid (m= 15.4 mg, 35% yield).

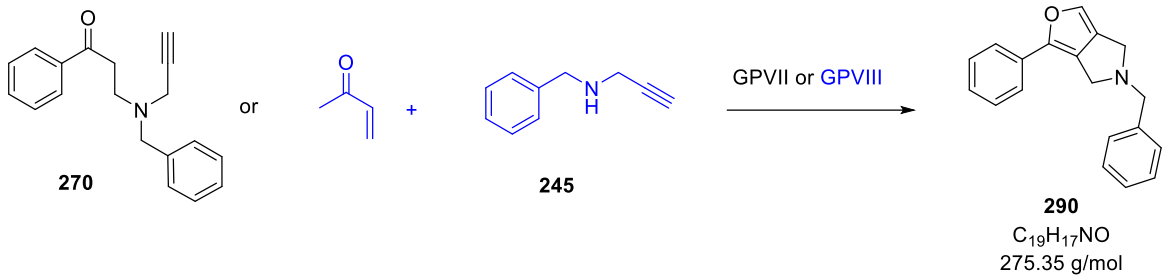
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.35 (s, 4H), 7.15 (dd, *J* = 1.6, 1.2 Hz, 1H), 4.99 (s, 2H), 4.86 (dd, *J* = 1.2, 1.6 Hz, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 141.8, 132.9, 132.7, 130.5, 129.2 (2C), 129.1, 127.1, 125.2 (2C), 66.4, 65.6

FTIR (neat): *ν* = 2925, 1490, 1092, 1015, 908, 732 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{12}H_{10}ClO_2$: $[M+H]^+$: 221.0369; found: 221.0368

5-benzyl-1-phenyl-5,6-dihydro-4*H*-furo[3,4-*c*]pyrrole **290**



270 **245** **290**

$C_{19}H_{17}NO$
275.35 g/mol

The compound **290** was obtained from compound **270** following the **GPVII** on 0.4 mmol scale (110.9 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95 to 10/90) afforded **290** as a white solid (m= 78.2 mg, 71% yield).

The compound **290** was obtained from methyl vinyl ketone and compound **245** following the **GPVIII** on 0.4 mmol scale (28 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95 to 10/90) afforded **290** as a white solid (m= 72.7 mg, 66% yield).

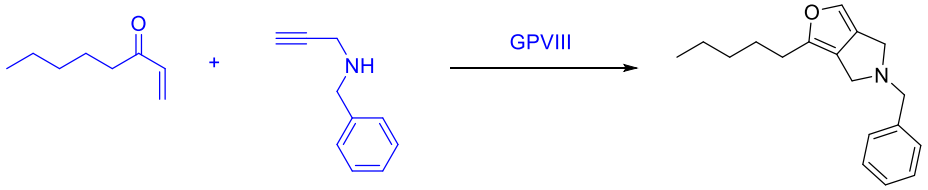
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.50 (m, 2H), 7.48 – 7.44 (m, 2H), 7.43 – 7.30 (m, 5H), 7.23 (tt, *J* = 7.6, 1.2 Hz, 1H), 7.15 (t_{app}, *J* = 1.2 Hz, 1H), 3.98 (s, 2H), 3.93 (s, 2H), 3.78 (d, *J* = 1.2 Hz, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 139.1, 131.2, 131.1, 131.0, 128.8 (2C), 128.7 (2C), 128.6 (2C), 127.3, 126.8, 125.5, 123.9 (2C), 60.4, 52.2, 51.1

FTIR (neat): *ν* = 2789, 1494, 1044, 966, 906, 841, 762, 731, 689 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{19}H_{18}NO$: $[M+H]^+$: 276.1388; found: 276.1378

5-benzyl-1-pentyl-5,6-dihydro-4*H*-furo[3,4-*c*]pyrrole **311**



245 **311**

$C_{18}H_{23}NO$
269.39 g/mol

The compound **311** was obtained from oct-1-en-3-one and compound **245** following the **GPVIII** on 0.4 mmol scale (50.5 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95 to 7/93) afforded **311** as a colorless oil (m= 71.1 mg, 66% yield).

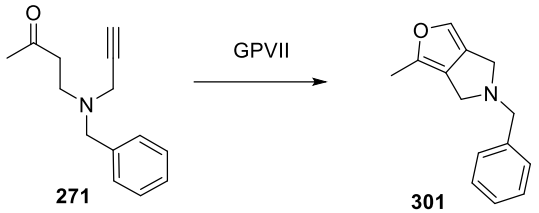
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.39 (m, 2H), 7.38 – 7.31 (m, 2H), 7.31 – 7.25 (m, 1H), 6.96 (t_{app}, *J* = 1.2 Hz, 1H), 3.90 (s, 2H), 3.66 (s, 2H), 3.62 (d, *J* = 1.2 Hz, 2H), 2.54 (t, *J* = 7.6 Hz, 2H), 1.67 – 1.54 (m, 2H), 1.38-1.24 (m, 4H), 0.90 (m, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 139.1, 129.8, 129.4, 128.8 (2C), 128.5 (2C), 127.2, 123.6, 60.5, 51.2, 51.1, 31.6, 27.5, 27.3, 22.5, 14.1

FTIR (neat): *ν* = 2929, 2788, 1592, 1454, 1139, 908, 784, 732, 698 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{18}H_{24}NO$: $[M+H]^+$: 270.1858; found: 270.1848

5-benzyl-1-methyl-5,6-dihydro-4*H*-furo[3,4-*c*]pyrrole **301**



The compound **301** was obtained from compound **271** following the **GPVII** on 0.2 mmol scale (43.1 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 7/93) afforded **301** as a colorless oil (m= 29.4 mg, 69% yield).

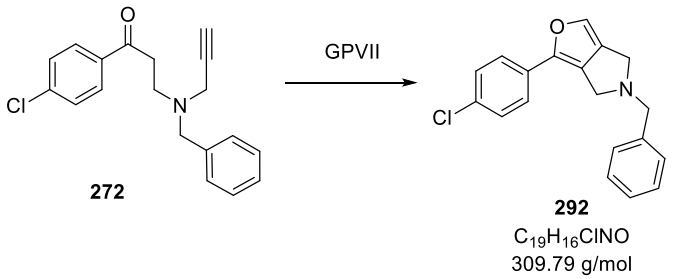
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.43 (dd, *J* = 8.0 Hz, 2H), 7.36 (t, *J* = 8.0 Hz, 2H), 7.33 – 7.25 (m, 1H), 6.97 (t, *J* = 8.0 Hz, 1H), 3.91 (s, 2H), 3.68 (s, 2H), 3.59 (d, *J* = 1.4 Hz, 2H), 2.22 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 141.1, 139.1, 130.0, 129.6, 128.8 (2C), 128.4 (2C), 127.2, 124.1, 60.4, 51.4, 50.8, 12.7

FTIR (neat): *ν* = 2787, 1594, 1453, 1367, 1254, 1087, 926, 841, 732, 697 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{14}H_{16}NO$: $[M+H]^+$: 214.1232; found: 214.1223

5-benzyl-1-(4-chlorophenyl)-5,6-dihydro-4*H*-furo[3,4-*c*]pyrrole **292**



The compound **292** was obtained from compound **272** following the **GPVII** on 0.4 mmol scale (124.7 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95 to 10/90) afforded **292** as a yellow solid (m= 97.8 mg, 79% yield).

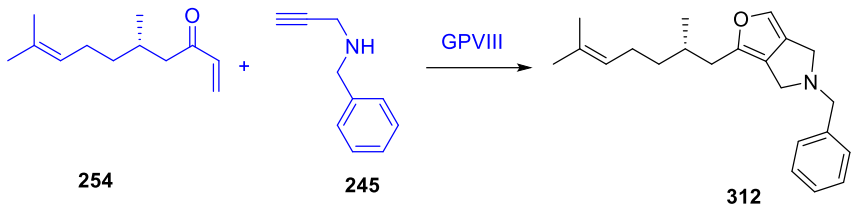
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.46 – 7.44 (m, 2H), 7.43 – 7.36 (m, 4H), 7.36 – 7.29 (m, 3H), 7.13 (s 1H), 3.97 (s, 2H), 3.88 (s, 2H), 3.76 (s, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 142.4, 138.9, 132.3, 131.4, 131.3, 129.5, 128.9 (2C), 128.8 (2C), 128.6 (2C), 127.3, 126.0, 125.1 (2C), 60.3, 52.1, 51.0

FTIR (neat): *ν* = 2792, 1489, 1091, 968, 905, 828, 733, 698 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{19}H_{17}NOCl$: $[M+H]^+$: 310.0999; found: 310.0988

(*S*)-5-benzyl-1-(2,6-dimethylhept-5-en-1-yl)-5,6-dihydro-4*H*-furo[3,4-*c*]pyrrole **312**



254 **245** **312**

$C_{22}H_{29}NO$

323.48 g/mol

The compound **312** was obtained from compound **254** and **245** following the **GPVIII** on 0.4 mmol scale (72.1 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95) afforded **312** as a colorless oil (m= 80.2 mg, 62% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (brd, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.6, 2.4 Hz, 1H), 7.00 (t_{app}, *J* = 1.6 Hz, 1H), 5.13 (m, 1H), 3.93 (s, 2H), 3.71 (s, 2H), 3.64 (s, 2H), 2.58 (dd, *J* = 15.0, 6.0 Hz, 1H), 2.41 (dd, *J* = 15.0, 7.6 Hz, 1H), 2.12 – 1.95 (m, 2H), 1.88 – 1.79 (m, 1H), 1.73 (s, 3H), 1.64 (s, 3H), 1.46 – 1.36 (m, 1H), 1.26-1.19 (m, 1H), 0.94 (d, *J* = 6.8 Hz, 3H)

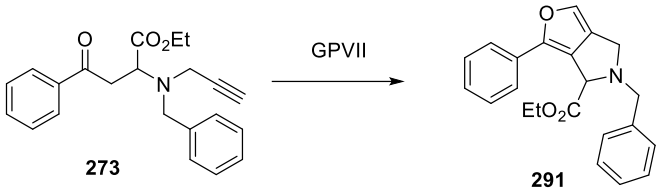
^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 139.0, 131.2, 129.9, 129.3, 128.8 (2C), 128.4 (2C), 127.1, 124.7, 124.4, 60.4, 51.3, 51.1, 36.7, 34.8, 32.3, 25.8, 25.6, 19.8, 17.7

FTIR (neat): *v* = 2913, 1454, 1376, 906, 728, 698 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{22}H_{30}NO$: $[M+H]^+$: 324.2327; found: 324.2326

$[\alpha]_D^{25}$ = -0.83 (c = 0.48, $CHCl_3$)

ethyl 5-benzyl-3-phenyl-5,6-dihydro-4*H*-furo[3,4-*c*]pyrrole-4-carboxylate **291**



273 **291**

$C_{22}H_{21}NO_3$

347.41 g/mol

The compound **291** was obtained from compound **273** following the **GPVII** on 0.4 mmol scale (139.8 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95 to 7/93) afforded **291** as a yellow solid (m= 87.5 mg, 63% yield).

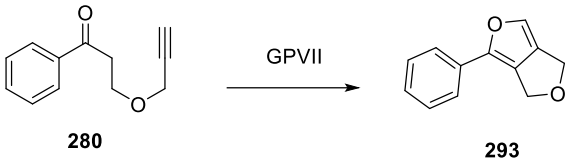
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.6 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H),7.39 – 7.34 (m, 4H), 7.33 – 7.28 (m, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.17 (s, 1H), 4.85 (s, 1H), 4.20 (dq, J = 7.2, 10.8 Hz, 1H), 4.24 – 4.06 (m, 4H), 3.88 (d, *J* = 11.8 Hz, 1H), 1.18 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 144.8, 138.5, 131.4, 131.1, 130.3, 128.8 (2C), 128.6 (2C), 128.5 (2C), 127.4, 127.3, 124.6 (2C), 124.5, 63.6, 61.0, 56.3, 49.5, 14.3

FTIR (neat): *v* = 1728, 1495, 1179, 1027, 906, 727, 692 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{22}H_{22}NO_3$: $[M+H]^+$: 348.1600; found: 348.1589

4-phenyl-1*H*,3*H*-furo[3,4-*c*]furan **293**



280

293
$C_{12}H_{10}O_2$
186.21 g/mol

The compound **293** was obtained from compound **280** following the **GPVII** on 0.4 mmol scale (75.3 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95 to 7/93) afforded **293** as a yellow solid (m= 38.4 mg, 52% yield).

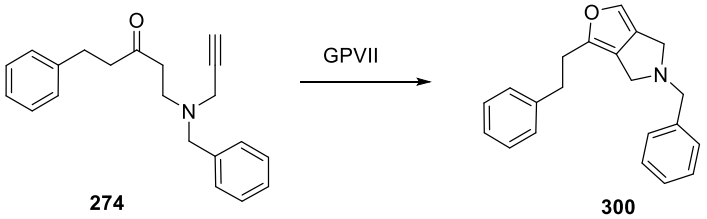
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.46 – 7.36 (m, 4H), 7.28 – 7.22 (m, 1H), 7.15 (s, 1H), 5.02 (s, 2H), 4.86 (s, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 142.7, 132.5, 130.6, 130.2, 128.9 (2C), 127.1, 126.6, 123.9 (2C), 66.5, 65.5

FTIR (neat): *ν* = 2863, 2251, 1495, 1049, 905, 725, 690 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{12}H_{10}O_2Na^+$: $[M+Na]^+$: 209.0578; found: 209.0570

5-benzyl-1-phenethyl-5,6-dihydro-4*H*-furo[3,4-*c*]pyrrole **300**



274

300
$C_{21}H_{21}NO$
303.41 g/mol

The compound **300** was obtained from compound **274** following the **GPVII** on 0.4 mmol scale (122.2 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95) afforded **300** as a yellow solid (m= 88.6 mg, 73% yield).

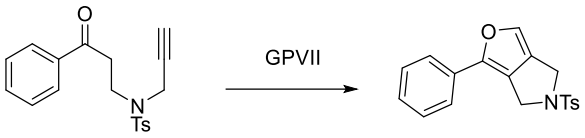
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.41 – 7.33 (m, 4H), 7.31 – 7.27 (m, 3H), 7.23 – 7.15 (m, 3H), 7.00 (s, 1H), 3.87 (s, 2H), 3.66 (s, 2H), 3.48 (s, 2H), 2.96 – 2.85 (m, 4H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 144.3, 141.3, 139.1, 130.1, 129.5, 128.9, 128.5, 128.5, 128.4, 127.2, 126.2, 124.3, 60.4, 51.2, 50.9, 34.1, 29.4

FTIR (neat): *ν* = 2925, 2792, 1454, 908, 731, 699 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{21}H_{22}NO$: $[M+H]^+$: 304.1701; found: 304.1697

1-phenyl-5-tosyl-5,6-dihydro-4*H*-furo[3,4-*c*]pyrrole **289**



275 **289**

$C_{19}H_{17}NO_3S$

339.41 g/mol

The compound **289** was obtained from compound **275** following the **GPVII** on 0.2 mmol scale (68.3 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95 to 15/85) afforded **289** as a white solid (m= 35.9 mg, 53% yield).

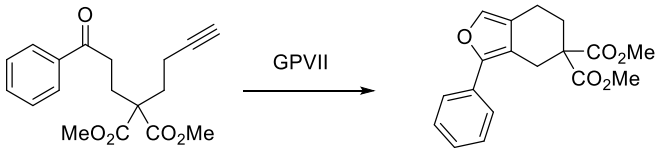
^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.79 (d, *J* = 8.1 Hz, 2H), 7.45 – 7.32 (m, 6H), 7.28 – 7.22 (m, 1H), 7.14 (s, 1H), 4.58 (s, 2H), 4.41 (s, 2H), 2.41 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 144.3, 144.0, 134.2, 131.9, 130.1 (2C), 129.0 (2C), 127.7, 127.6 (2C), 127.5, 124.0 (2C), 121.6

FTIR (neat): *ν* = 1343, 1160, 907, 814, 728, 659 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{19}H_{18}NO_3S$: $[M+H]^+$: 340.1007; found: 340.0998

dimethyl 3-phenyl-6,7-dihydroisobenzofuran-5,5(4H)-dicarboxylate **288**



276 **288**

$C_{18}H_{18}O_5$

314.34 g/mol

The compound **288** was obtained from compound **276** following the **GPVII** on 0.4 mmol scale (126.5 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 2/98 to 4/96) afforded **288** as a white solid (m= 93.0 mg, 74% yield).

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.63 – 7.61 (m, 2H), 7.42 – 7.38 (m, 2H), 7.27 – 7.22 (m, 1H), 7.20 (t, *J* = 1.4 Hz, 1H), 3.75 (s, 6H), 3.35 (s, 2H), 2.66 (td, *J* = 6.6, 1.4 Hz, 2H), 2.31 (t, *J* = 6.6 Hz, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 171.8 (2C), 147.5, 136.5, 131.8, 128.7 (2C), 126.8, 124.7 (2C), 121.4, 115.2, 54.2, 53.0 (2C), 28.6, 28.5, 17.0

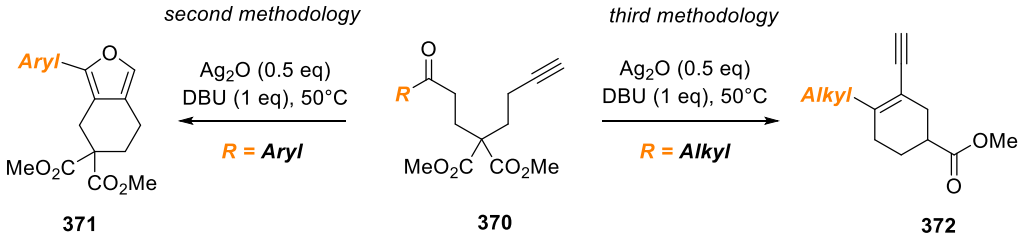
FTIR (neat): *ν* = 2954, 1733, 1248, 905, 728, 692 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{18}H_{19}O_5$: $[M+H]^+$: 315.1232; found: 315.1226

VII. Silver carbonate/DBU catalyzed addition/ fragmentation/ decarboxylation reaction

VII.a Introduction

During our works on polysubstituted furan synthesis, we screened different length of chain bearing alkyne moiety in order to reach 6-membered ring analogs (see Scheme 78). Astonishingly, depending on the substitution pattern of the ketone, we observed different behaviors concerning the cyclization. Indeed, with aromatic ketones, the expected bicyclic furans **371** was obtained as the major product whereas alkyl chain mainly led to cyclohexenyne adduct **372** (Scheme 100).



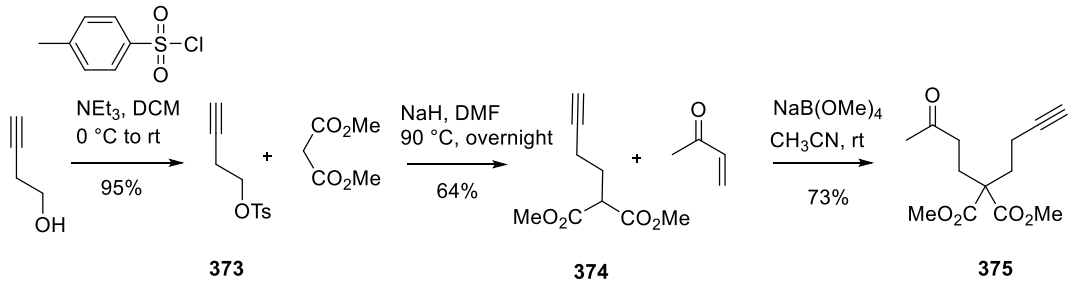
Scheme 100

Intrigued by this versatile behavior, we wanted to pursue our investigations on this new transformation. Indeed, from a readily available malonate, we could reach complex structures in a single step with smooth conditions. Derivatives compound **372** obtained could constitute interesting building blocks. Additionally, it would appear to us very interesting to understand this new reactivity and to explore the scope of such reaction. Finally, to the best of our knowledge, nothing was described in the literature mentioning this type of reaction.

VII.b Optimization of reactional conditions

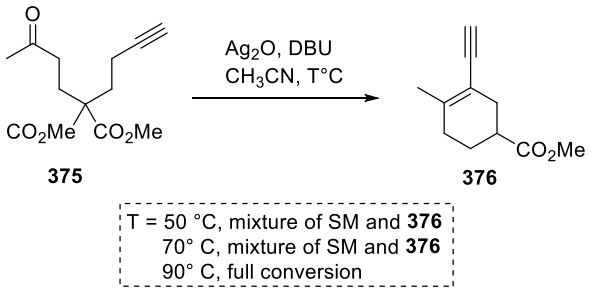
Assuming that the reaction involves an allenylsilver intermediate, we decided to circumvent the scope to terminal alkyne. Our screening would imply different malonate system, substitution patterns on α position of the ketone, length and substitution on the chain.

First, we set up optimal conditions by varying different reaction parameters. We selected the malonate type compound **375** as a precursor of cyclization. This diester was readily obtained following the sequence depicted below (Scheme 101):



Scheme 101

It should be noted that previously, during our cyclization attempts on furan synthesis, we screened three different temperatures (respectively 50, 70 and 90°C) (Scheme 102).

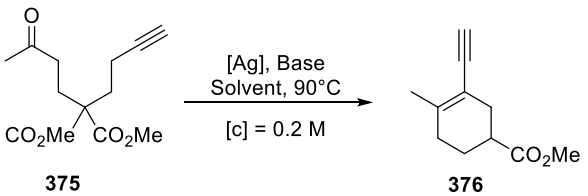


Scheme 102

At 50°C or 70°C, a mixture of starting material and cyclized compound **376** was observed. Increasing the temperature to 90°C allowed a full conversion into enyne **376.**

So for the determination of the optimized conditions, we performed the reaction in a sealed tube and we set the temperature at 90 °C over 12 h (Table 10).

Table 10



Entry	Silver	Base	Solvent	^{1}H NMR Yield [a]

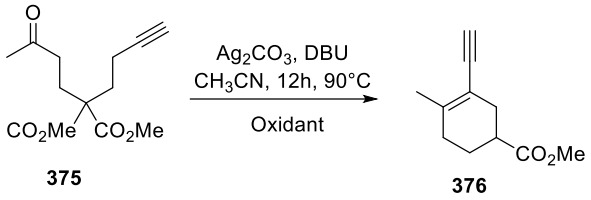
1	Ag_2O (0.5 eq)	DBU	CH_3CN	67.0% BY853
2	Ag_2CO_3(0.5 eq)	DBU	CH_3CN	87.2% BY852[b]
3	$AgNO_3$ (1 eq)	DBU	CH_3CN	8.9% BY851
4	AgOTf (1 eq)	DBU	CH_3CN	7.5% BY854
5	$AgNTf_2$ (1 eq)	DBU	CH_3CN	22.8% BY858
6	$AgSbF_6$(1 eq)	DBU	CH_3CN	29.3% BY857
7	Ag_3PO_4(0.33 eq)	DBU	CH_3CN	60.2% BY856
8	Ag_2CO_3 (0.5 eq)	K_2CO_3	CH_3CN	36.4% BY862
9	Ag_2CO_3 (0.5 eq)	Pyrrolidine	CH_3CN	13.5% BY860
10	Ag_2CO_3 (0.5 eq)	NEt_3	CH_3CN	30.6% BY861
11	Ag_2CO_3 (0.5 eq)	i-Pr_2NEt	CH_3CN	29.7% BY863
12	Ag_2CO_3 (0.5 eq)	DBU	THF	84.7% BY869
13	Ag_2CO_3 (0.5 eq)	DBU	MeTHF	68.4% BY866
14	Ag_2CO_3 (0.5 eq)	DBU	MeOH	43.5% BY870
15	Ag_2CO_3 (0.5 eq)	DBU	DMF	66.6% BY867
16	Ag_2CO_3 (0.5 eq)	DBU	Toluene	68.0% BY868
17	--	DBU	CH_3CN	0% BY874
18	Ag_2CO_3 (0.5 eq)	--	CH_3CN	9.4% BY875
19	Ag_2CO_3 (0.5 eq)	DBU	CH_3CN	84.2% BY876[c]
20	Ag_2CO_3 (0.5eq)	DBU	CH_3CN	83.0% BY877[d]

[a] ^1H NMR yield was calculated by using 1,3,5-trimethoxybenzene as internal standard. [b] the reaction has been performed twice more with an respectively 85.0% (BY896, isolated yield) and 86.4% (BY855). [c] reaction performed at 0.1 M. [d] reaction performed at 0.4 M.

A rapid survey of silver catalysts demonstrated that silver carbonate(I) was the best option for this transformation (86 % yield average over three reactions, Entry 2). Silver oxide(I) provided the compound **376** in 67 % yield (Entry 1) whereas using silver phosphonate led to 60 % yield (Entry 7). Other silver salts gave poor conversions in favor of product **376**, $AgNTf_2$ (23%, Entry 5), $AgSbF_6$ (29%, Entry 6) or sometimes almost no conversion $AgNO_3$ (9%, Entry 3), AgOTf (8%, Entry 4). The role of the base appears crucial since K_2CO_3 (Entry 8), pyrrolidine (Entry 9), NEt_3 (Entry 10) and *i*-Pr_2NEt (Entry 11) afforded poor conversions (respectively 36%, 13%, 30% and 30%). Various solvent are well tolerated THF (85%, Entry 12), MeTHF (68%, Entry 13), DMF (67%, Entry 15) and Toluene (68%, Entry 16). However, we noticed a slight decreasing of the yield by using protic solvent like MeOH (43%, Entry 14). Finally, test reactions highlighted the mandatory combination of both reagents since without silver carbonate no reaction takes place (Entry 17, 0%) and a dramatic drop of yield is observed when the reaction is conducted without DBU (9%, Entry 18). Leading the reaction on more diluted (Entry 19) or more concentrated media (Entry 20) has no significant effect on the yield (respectively 84% and 83%).

Finally, we surveyed the feasibility of a catalytic version of this transformation in silver and base (Table 11).

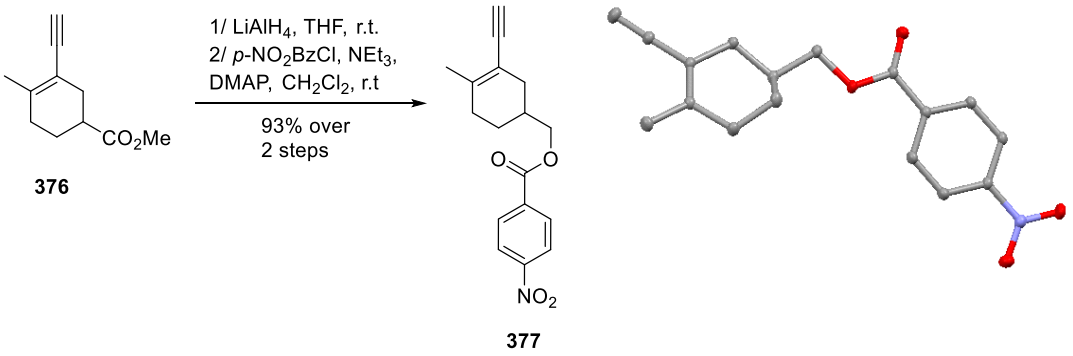
Table 11



Entry	Ag_2CO_3	DBU	Oxidant	CH_3CN	Time	Yield (NMR)
1	0.25 eq	1 eq	--	1 mL	12h	86.2% BY878
2	0.125 eq	1 eq	--	1 mL	12h	86.5% BY879
3	0.0625 eq	1 eq	--	1 mL	12h	47.2% BY880
4	0.0625 eq	1 eq	O_2	1 mL	12h	45.4% BY885
5	0.0625 eq	1 eq	$PhI(OAc)_2$ (3 eq)	1 mL	12h	0% BY886
6	0.0625 eq	1 eq	CeO_2 (3 eq)	1 mL	12h	33.7% BY884
7	0.0625 eq	1 eq	$K_2S_2O_8$ (3 eq)	1 mL	12h	0% BY883
8	0.5 eq	0.5 eq	--	1 mL	12h	57.3% BY881

To our delight, we obtained same good yields by diminishing the loading of Ag_2CO_3 to 0.25 equivalent (Entry 1, 86%) or to 0.125 equivalent (Entry 2, 86%). However, we observed a collapse of yield when 0.0625 equivalent of silver carbonate(I) were employed (Entry 3, 47%). At this stage, we tried to add oxidative agent in order to restore the catalytic specie. Unfortunately, by using O_2 (Entry 4), $PhI(OAc)_2$ (Entry 5), CeO_2(Entry 6) or $K_2S_2O_8$ (Entry 7), we never succeed to improve the yield. We also tried to render the reaction catalytic in base by decreasing the amount of DBU by two (0.5 equivalent, Entry 8) but a significative drop of yield was observed (57 %). In conclusion, best parameters for this reaction were: Ag_2CO_3 (0.125 eq), DBU (1 eq), CH_3CN, reflux over 12h.

In the meantime, in order to confirm the structure of the compound **376** by X-ray diffraction, we synthetized the ester **377** following the sequence depicted below (Scheme 103).

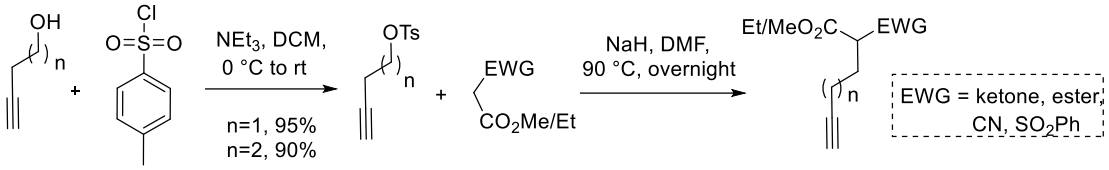


Scheme 103

A reduction of the methyl ester by $LiAlH_4$ followed by the concomitant esterification reaction with *p*-nitrobenzoyl chloride delivered the crystalline product **377** in 93 % yield over 2 steps. X-ray diffraction confirmed the structure of **376** obtained.

VII.c Scope and limitations

With the optimized conditions in hand, first we started the synthesis of different cyclization precursors.



Scheme 104

A tosylation reaction of the but-3-yn-1-ol or its homologue pent-4-yn-1-ol afforded the electrophile necessary to introduce the alkyne part on the malonate. Thanks to this sequence, we synthetized nine malonate derivatives with moderate to good yield.

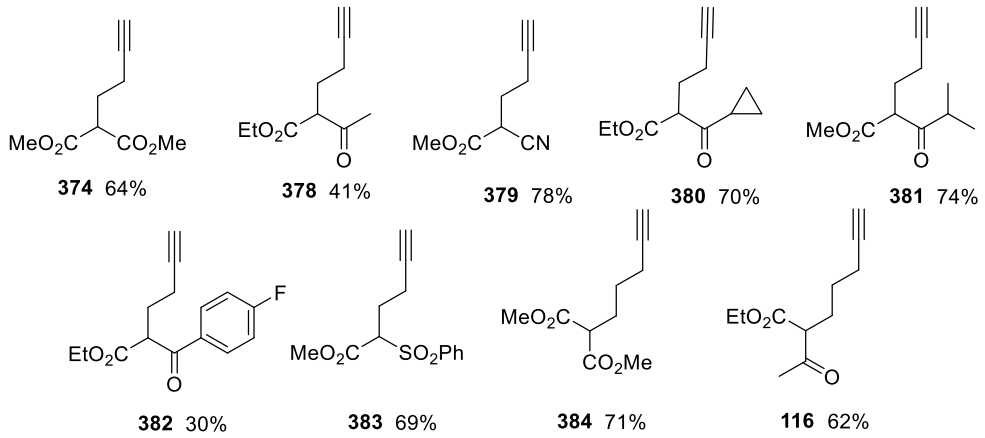
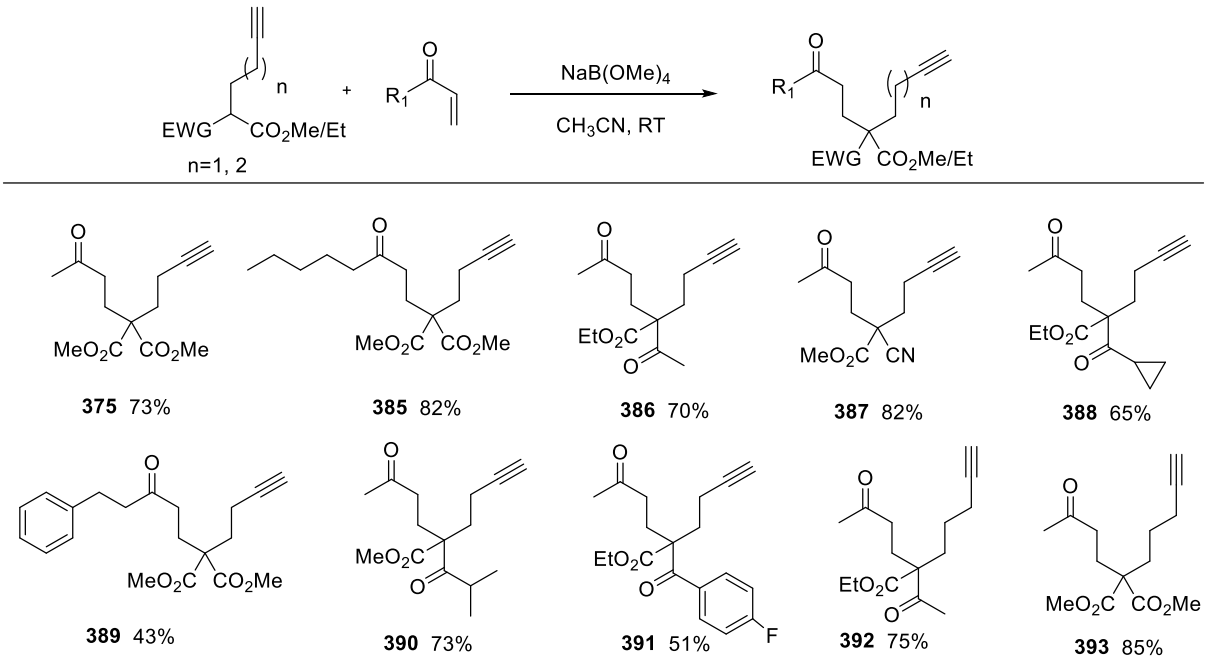


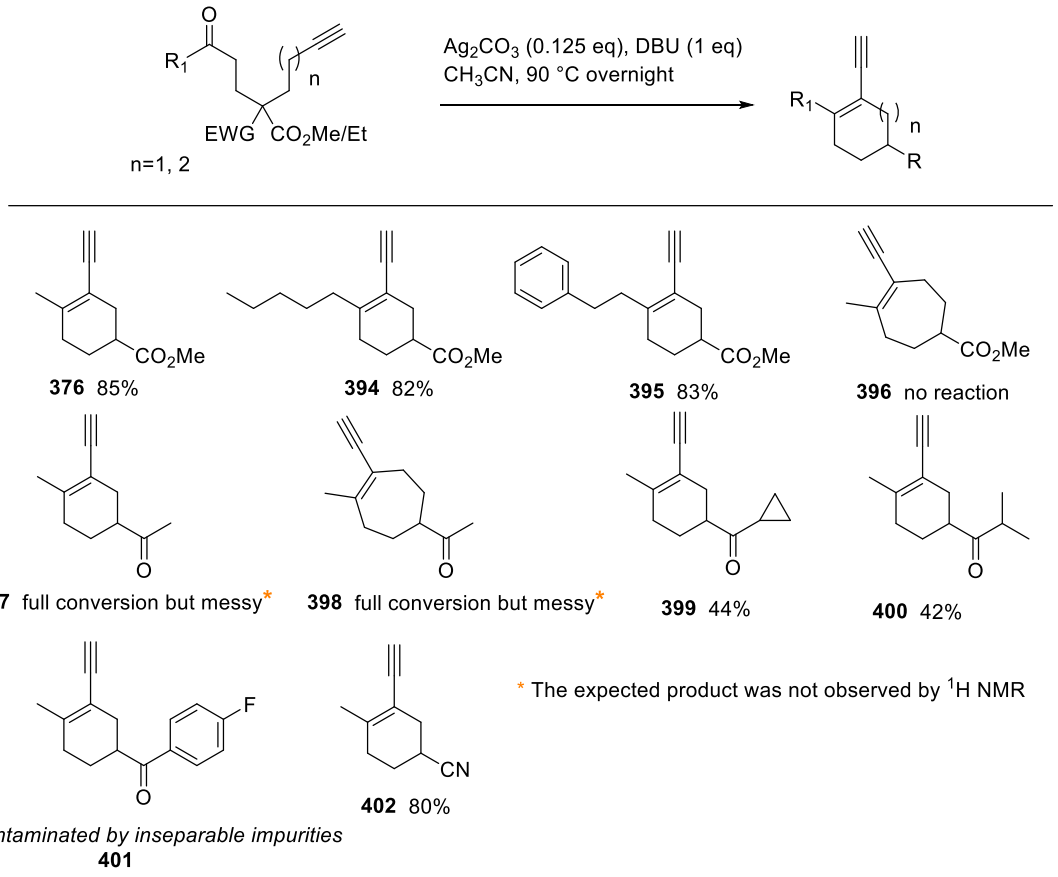
Figure 17

We incorporated the ketone part through a Michael addition between a malonate and an α,β-unsaturated ketones by using $NaB(OMe)_4$ in CH_3CN. We obtained ten cyclization precursors in a range of (43% to 85% yield) (Scheme 105).



Scheme 105

Then, we submitted these precursors to our optimized conditions. Results are listed in the Scheme 106 below.



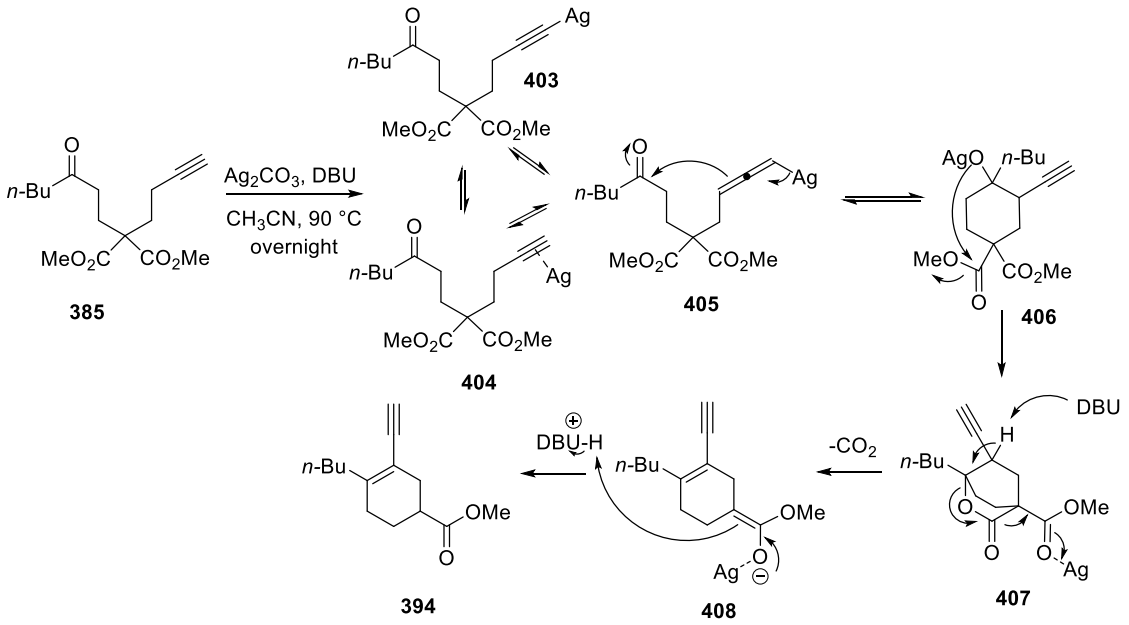
Scheme 106

From the diester **375**, we obtained 85% yield and *n*-pentyl or *n*-ethylbenzene analogs led to similar yields (respectively 82 % and 83%). With malonate **393** having a longer chain, no reaction was observed even by increasing the loading of Ag_2CO_3 to 2 equivalent. When the reaction is performed on methyl ketone **386**, crudes of the reaction are always messy and we have never detected any trace of the expected product by ^1H NMR. Unfortunately, similar behavior was observed with the analog containing a longer chain. However, when the more hindered cyclopropyl or isopropyl ketone **388** and **390** were submitted to the same conditions, we were pleased to find the cyclized products **399** and **400** in respectively moderate yield 44% and 42%. These results suggest that with precursors **397** and **398**, the ketone in the malonate system is easily reachable and we have probably a competitive reaction with the other ketone. The reactions works also in the presence of benzylic ketone even if the crude was quite messy suggesting one or several side reactions too. The relatively low yield can be explained by difficulties encountered during the purification step. Finally, we were pleased to find that the reaction can be conducted in the presence of cyanide with very good yield (80%).

Due to a lack of time, we couldn't finish this survey before to write this thesis however the screening of this new transformation is currently ongoing in our laboratory.

VII.d Mechanism

For this transformation, we postulated the mechanism depicted in Scheme 107.



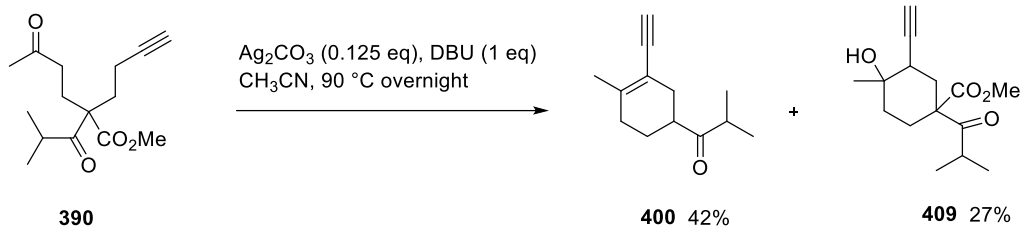
Scheme 107

As the first and second methodology, we used a combination of DBU and silver salt in the presence of terminal alkyne. Hence, we presumed that the first step is the formation of the alkynyl silver **403**.

By the support of DFT calculation made for the dihydrofuran part (see chapter III.d), we could assume that the specie **403** is in equilibrium with the allenyl silver **405** through the transitory formation of the silver alkyne complex **404**. Due to the very weak nucleophilicity of the intermediate **405**, alkynyl silver cannot react in intra- or intermolecular fashion. In contrast, the allenyl silver could attack the ketone leading to the hydroxylate **406**. A retro-addition can be reasonably envisioned rendering this cyclization step reversible too. The hydroxylate thus generated would attack one of the ester to form the highly strained lactone **407**. A releasing of the tricyclic adduct **407** would be achieved by deprotonation in α-position of the alkyne and subsequent fragmentation/decarboxylation step. This irreversible transformation would push the equilibrium towards the formation of the six-membered ring **408**. This fragmentation step could constitute the driving force of the reaction. The newly formed silver enolate could be reprotonated by the conjugated acid of the DBU yielding the final compound **394**.

In the mechanism proposed herein, we could also add the effect of the lewis acidity of silver salt towards carbonyl functions enhancing their electrophilicity.

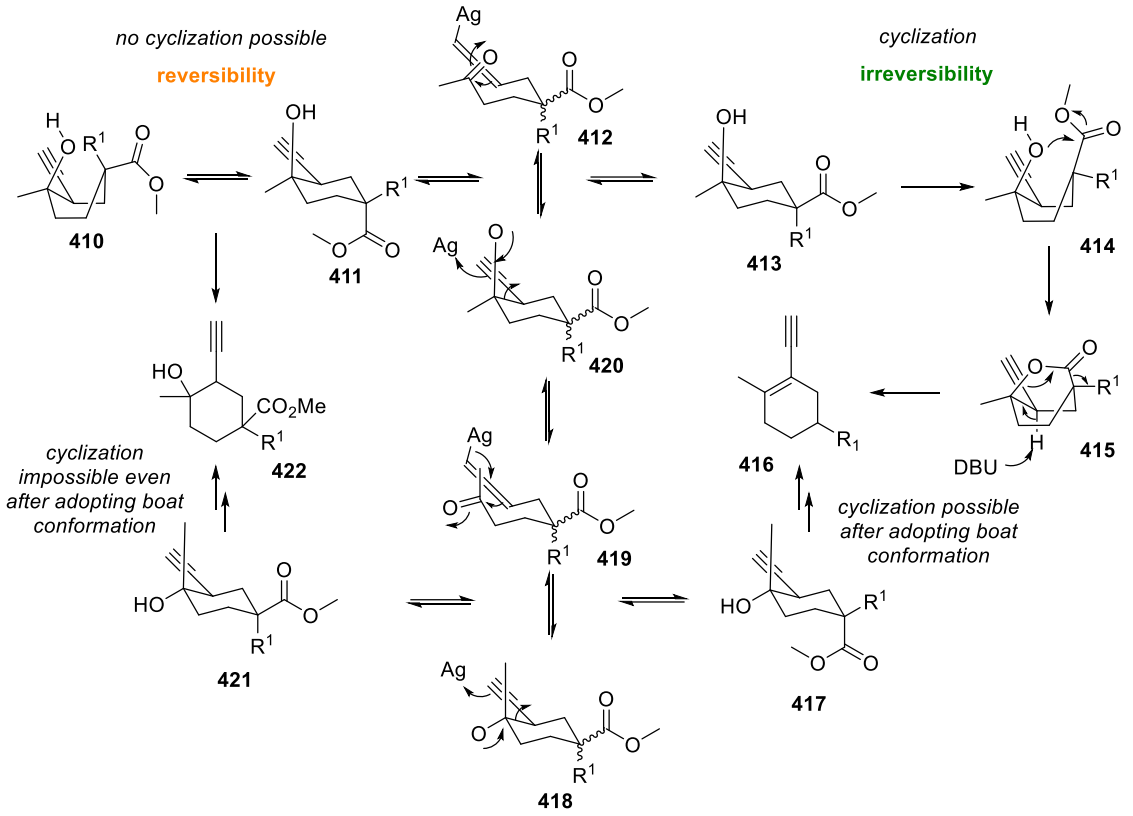
Interestingly, during our scope investigation, we isolated the intermediate **409** in 27 % from the isopropyl ketone **390** (Scheme 108).



390 **400** 42% **409** 27%

Scheme 108

This result would suggest the preliminary attack of the allenylsilver onto the ketone. However, at this stage, we presumed that the newly formed alcohol was not able to reach the ester for the second cyclization interrupting the mechanism pathway. This observation reinforced the mechanism proposed regarding the first part. In order to explain these results, we proposed the synthetic pathway below (Scheme 109).

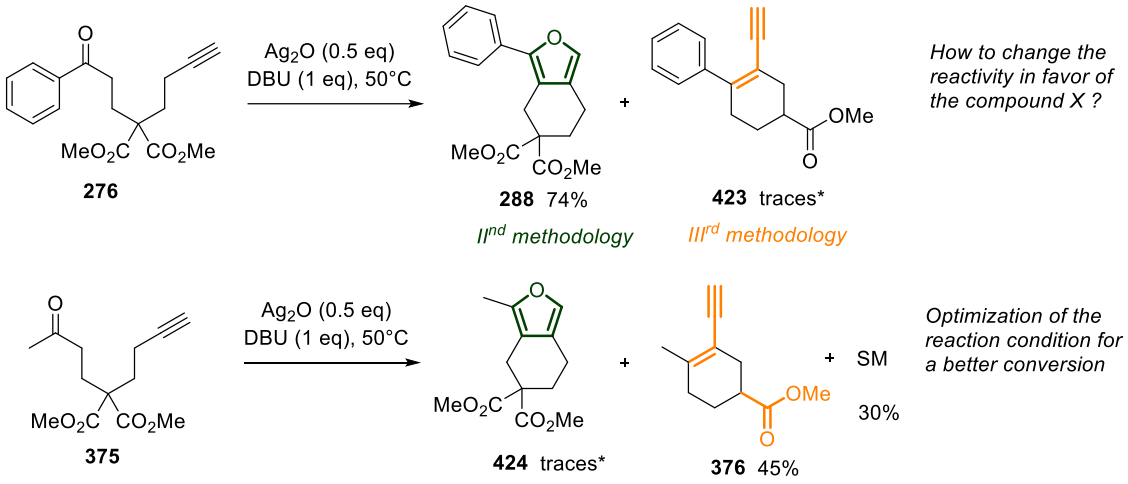


Scheme 109

The outcome of this transformation is probably based on the capacity of the alcohol to attack the ester part. At the beginning, we certainly have an equilibrium between cyclic and acyclic forms until the cyclization of the allenyl silver onto the ketone. At this stage, we presumed that the cyclohexane adopts a chair conformation. However, in this conformation, the resulting alcohol cannot reach the ester part and the molecule must adopt a boat conformation in order to cyclize. In one case, this cyclization is still not possible leading to the formation of the intermediate **414**. In the second case, the cyclization is possible leading to the tricyclic intermediate **415**. The hydrogen is in an *anti*-position compared with the leaving group which is a perfect condition to undergo a deprotonation by DBU. The subsequent decarboxylation and reprotonation step of the resulting stabilized anion yielded the expected ene-yne compound **416**.

VII.e Summary of part VII

During our work on synthesis of furan derivatives, we observed the formation of a new product when the tethered bearing the alkyne moiety is longer. Our first results showed a correlation between the type of the ketone involved and the product obtained. Indeed, employing an aromatic ketone mainly lead to a furan derivative (second methodology) whereas an aliphatic ketone conduct to the ene-yne adduct (third methodology). Scheme 110 summarizes the reactivity observed.



** conversion observed in crude 1H NMR and calculated from 1,3,5-trimethoxybenzene as internal standard*

Scheme 110

These results addressed two important questions:

- How to efficiently switch the reactivity towards ene-yne cycloadducts from aromatic ketones.
- How to improve the conversion from aliphatic ketones.

After investigation, a combination of Ag_2CO_3 (0.125 eq), DBU (1 eq) in CH_3CN at 90°C were found to be the optimized conditions. Thanks to this reactional condition, we obtained several six membered ring containing enyne systems in moderate to good yields. However, due to a lack of time, this survey has not been finished and we are currently working on the scope of this reaction in our laboratory.

Switching the reactivity towards ene-yne cycloadducts from aromatic ketones is really tough and we are investigating new conditions to fix it.

Nonetheless, we managed to find an unprecedented transformation allowing access to various enyne cycloadducts. This new transformation requires a combination of catalytic amount of silver carbonate/DBU in CH_3CN at 90°C. Thus, from readily available starting materials, we were able to achieve a complex molecule in one step. A full investigation into the potential of this powerful process has not yet been established and is currently underway in the laboratory.

VIII. Summarize and outlooks

VIII.a Summarize

Total synthesis is an inexhaustible source of inspiration to develop new synthetic pathway. Numerous methodologies have been initiated in the goal to find a shorter and/or a more efficient way to attain a key intermediate or the final product. Considerable progress has been made by scientific community, contributing to an even sharper knowledge of this science. However, if sometimes we have the right intuition, chemistry remains full of resources and surprises. Our preliminary work on the total synthesis of Vibsatin A and B, initiated in 2014 in our laboratory, is a representative example. According to the cyclization conditions reported by Sawamura et al, we succeeded to reach the [5,7] bicyclic core of Vibsatin thanks to a reaction involving gold catalyst. Nevertheless, we wished to develop a new way to attain this framework by using cheaper metal than gold and less restrictive set-up. Hence, in parallel of our total synthesis, we surveyed a new possibility to synthetize the [5,7] bicyclic core of Vibsatins. Based on preliminary works described in the literature, we envisioned to perform a challenging 7 exo-dig cyclization mediated by dual activation

combining organo- and copper catalysis from the ketone **17**. After few trials, we didn't observe the expected product, but we were please to discover the formation of a complex molecule containing 2,3-dihydrofuran unit during these reactions. This new compound turned out to be very interesting due to its complexity as well as the mechanism associated to its transformation. During this thesis, we were interested by developing this new transformation and to shine a light on the associated mechanism.

Preliminary works on copper catalysis delivered mixed results since we were not able to curb the Glaser coupling reaction thus restricting the yield around 60%. Furthermore, the condition of the reaction was rather harsh and sometimes difficult to reproduce. At this stage, silver salts appeared to be a good alternative to pursue our studies.

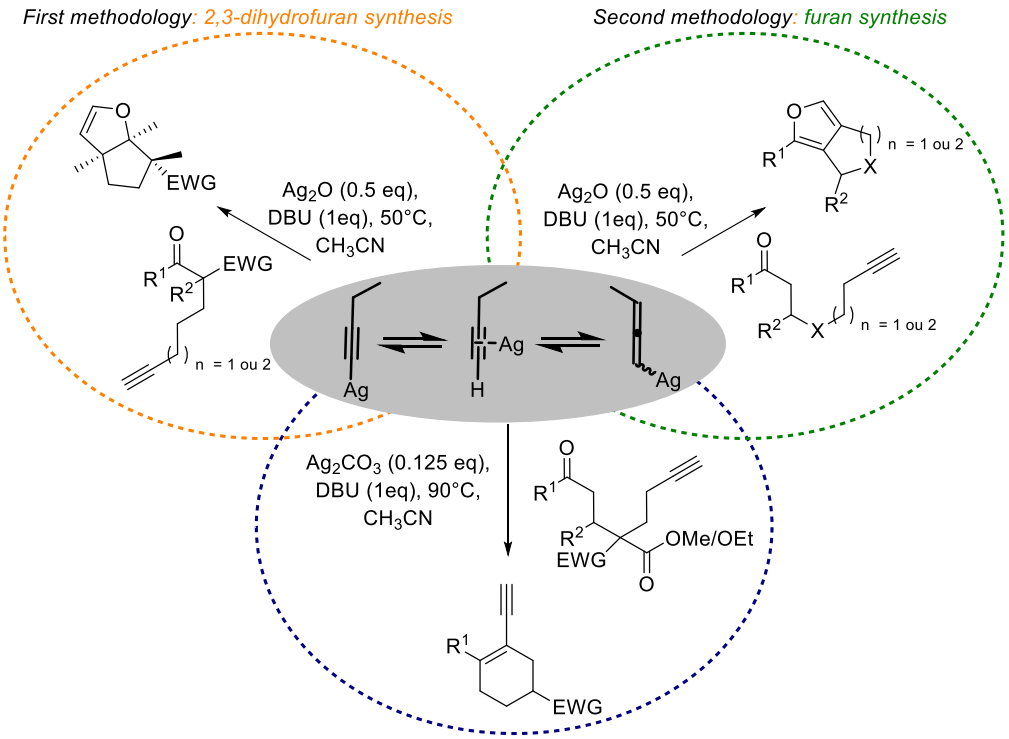
Very quickly, silver has revealed superior to copper in this transformation since milder conditions and higher yields (up to 85%) were obtained without formation of any Glaser homo-coupling side-products. Best results were attain with a combination of Ag_2O (0.5 eq) and DBU (1 eq) in CH_3CN at 50°C. Also, this reaction has shown a good diastereoselectivity (up to 95/5). Thanks to this methodology, more than twenty complex and/or congested 2,3-dihydrofuran derivatives were synthetized from readily available precursors. Obtaining such dihydrofuran by another way would certainly be fastidious. Thanks to DFT calculations performed by our collaborators Dr. Ilaria Ciofini and A. Perfetto and some test reactions, we have unambiguously highlighted the formation of an allenyl silver intermediate. This represents a key point in the methodologies developed and described all along this manuscript.

In a second time, we tried to extend our first methodology to enolizable ketone in order to reproduce the unexpected result depicted by Kirsch and collaborators with gold catalyst. However, submitting our reactional conditions to enolizable ketone led to furan cores. This heterocycle is broadly represented in pharmaceuticals and biologically relevant natural products. Thus, despite the numerous reactions described in the literature evoking the synthesis of furans core, this approach seemed to us important, innovative and complementary to those already described in the literature. To this aim, we investigated this reaction on various ynone system with success yielding bicyclic furans derivatives in a range of 42% to 80% in mild conditions. It is worth to mention that we obtained fused furan/-tetrahydropyran of -tetrahydrofuran cores which are quite scarce in the literature. Challenging synthesis of highly tricyclic strained furan frameworks were found possible too. We were also able to promote the reaction in a one-pot fashion delivering the furan adducts sometimes in better yield than the stepwise sequence from malonate and Michael acceptors. Unfortunately, the one-pot sequence was not suitable for some starting materials. Based on several

results, notably obtained from cyclic enone system, we presumed that the mechanism implied a conia-ene reaction onto an allenyl silver intermediate. However, this assumption needs to be support by other experiments or DFT calculations. In order to shine light on the mechanistic pathway, our collaboration has been pursued with our partners from the chemical theory and modelling group at Chimie Paris Tech, Dr. Ilaria Ciofini and Dr. Anna Perfetto. Concerning this methodology, we assume that the formation of a transitory allenyl silver is a mandatory pre-requisite for the success of this cyclization. Unfortunately, we didn't succeed in transposing our conditions to an intermolecular reaction to this date. Nevertheless, we hope to be able to study this component in a near future. In a similar manner, we failed to find suitable conditions in order to extend the conia-ene reaction from ynone system having a substituent in α-position of the ketone.

To our surprise, when we performed the reaction on a ketone having a longer tethered containing the alkyne part, we observed the formation of a new product. More precisely, it appeared that the type of ketone (aromatic vs aliphatic) as well as the longer of the tether seems crucial for the outcome of the reaction. Indeed, aromatic ketone looks more prone to furnish the furan derivatives whereas aliphatic ketone leads to the formation of the cyclic enyne system. After a short survey of reactional conditions, we found that the combination of silver carbonate(I)/ DBU is the best catalytic system in the promotion of such reaction. Different from the other methodologies cited above, this transformation can be run with a catalytic amount of silver carbonate. The study of the scope and limitations of this unprecedented transformation is ongoing in our laboratory.

Through these three methodologies, we developed new transformations implying terminal alkyne/silver chemistry and pinpointed the powerfulness of this unique combination for the creation of multiple C-C and C-O bonds in a single step.



The crucial point for these three methodologies is based on the isomerization of the alkynyl silver into allenyl silver. Thanks to this phenomenon, nucleophilic and electrophilic centers are different conferring to this system a chameleon activities (Figure 18).

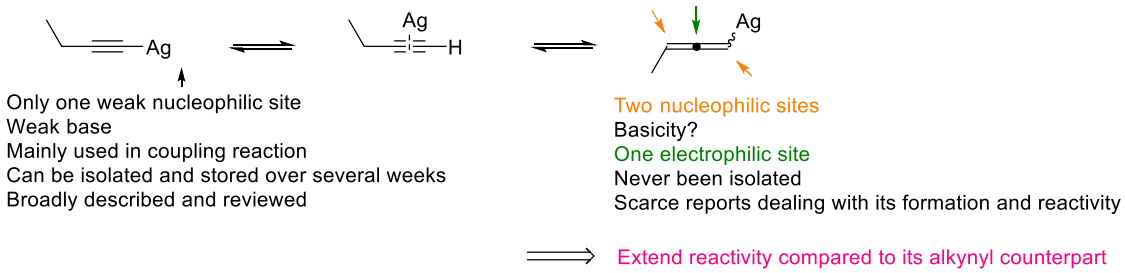


Figure 18

IX.b. Outlooks

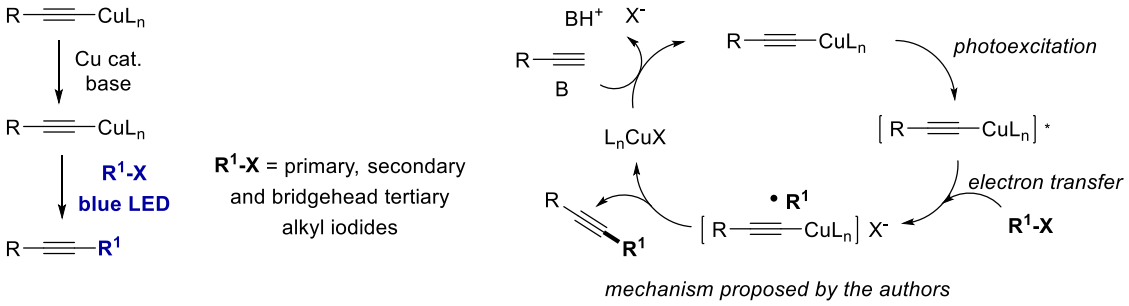
First, we can envisage in a near future to render the dihydrofuran and furan strategy suitable in intermolecular reaction. To do this, we could explore different reaction parameters as well as the addition of ligands such as phosphine. For example, it has been demonstrated that phosphine enhanced the reactivity organo-silvers.

All along this manuscript, we highlighted that the unique combination of silver salts and base with terminal alkyne opened a way to new chemical transformations. In this context, we wish in a near future, to extend this chemical reactivity of the alkynyl- and allenyl silver to other substrates. Find suitable conditions for intermolecular reactions either by stabilizing or reinforcing the nucleophilicity of allenyl silver would be also highly desirable. To this aim, we could envision to add ligands like

phosphines or NHC. For example, it has been demonstrated that the addition of phosphine ligand would enhance the nucleophilic character of the alkyne center allowing the attack of alkynyl silver onto unactivated aldehyde .[135]

In addition, we also could envision to find new reactivities. In this field, we were interested by developing photochemical chemistry from alkynyl silver. Some recent papers mentioned photo-induced reactions such as Ulmann or Sonogashira types coupling from copper or gold acetylides.[136]

In this context, we can mention the recent work reported by Lalic group in the photoinduced copper-catalyzed coupling of terminal alkynes and alkyl iodides (Scheme 111).[137]



Scheme 111

In a similar manner, it would be very interesting to explore similar transformations from alkynyl silver (Figure 19).

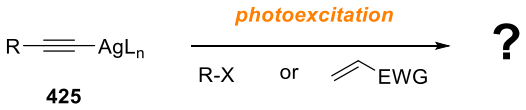


Figure 19

Moreover, these species are easily obtained, they possess a high stability and can be stored over months. The electronic properties of silver actetylides as well as their solubility could be finely tuned by adding ligands. Additionally, in this kind of transformations, the halogenophilicity of silver would play a crucial role in the outcome of the reaction.

IX. Final conclusion

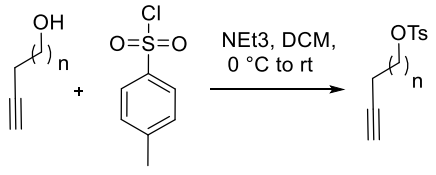
The reactivity of silver salts has been underestimated over several decades and their use was mainly circumvent to their oxidation and halogenophilicity properties. Silver, such as gold and copper, belongs to coinage metals and exhibited interesting catalytic activities in organic chemistry. During a long time, silver reactivity's suffered from the comparison with gold and copper. Generally, compared with Ag(I), Au(I) exhibits stronger σ-and/or π-Lewis acidity, which renders the Au(I)

catalyst acceptable and feasible for diverse types of transformations such as cycloisomerization. Ag salts were mainly employed for anion methathesis (counterion exchange) enhancing the gold reactivity. Whereas copper salts were preferred for their oxidative properties through single electron transfer process. However, a renewed interest has emerged in silver chemistry and especially towards alkyne chemistry. The field of silver catalyzed reactions of alkynes has been intensively studied and extended through numerous novel transformations allowing C-C, C-N or C-O bonds. Our works are part of this approach, since we showed that silver salt could promote the synthesis of 2,3-dihydrofuran derivatives in an very efficient manner. Silver salts have found to be superior and more selective than copper for this transformation even if a substoechiometric amount were required. More interestingly, we highlighted the formation of allenyl silver intermediate from terminal and unactivated alkynes. Thanks to this isomerization reaction, we were able to efficiently create C-C and C-O bond for a straightforward access to 2,3-dihydrofuran, furans derivatives as well as ethynylcyclohexene units. These first results constitute a promising development of the silver alkyne chemistry and would contribute to the emerging “silver rush” towards alkyne.

X. EXPERIMENTAL PART III

Preparation of the cyclization precursors

General procedure for the synthesis of sulfonate (GPI)

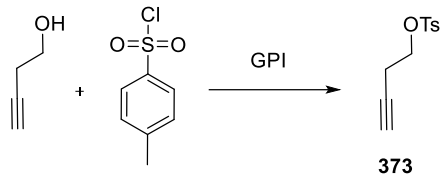


n=1,2

To a solution of alcohol (10 mmol) in CH_2Cl_2 (15 mL) were added NEt_3 (2.7 mL, 20 mmol) and TsCl (1.9 g, 10 mmol) at 0 °C. The solution was stirred for 18 h at r.t. and then quenched with sat. NH_4Cl. The mixture was extracted with CH_2Cl_2 (3x), the combined organic layers were neutralized with sat.

$NaHCO_3$, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel to give the desired product in a pure form.

but-3-yn-1-yl 4-methylbenzenesulfonate **373**

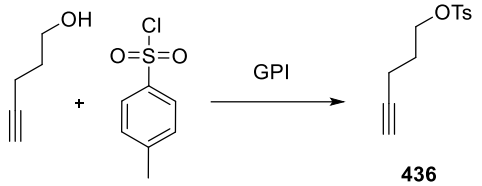


373
$C_{11}H_{12}O_3S$
224.27 g/mol

The compound **373** was obtained from 3-butyn-1-ol following the **GPI** on 10 mmol scale (700 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 2/98 to 10/90) afforded **373** as a colorless oil (m= 2.0 g, 90% yield).

All the spectroscopic data are in accordance with those described in the literature.[138]

pent-4-yn-1-yl 4-methylbenzenesulfonate **436**

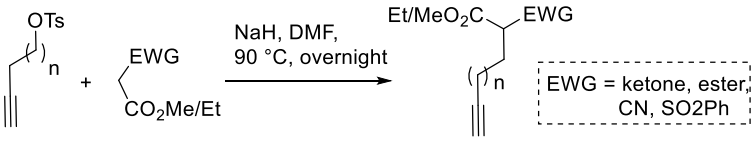


436
$C_{12}H_{14}O_3S$
238.30 g/mol

The compound **436** was obtained from 4-pentyn-1-ol following the **GPI** on 10 mmol scale (841 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95 to 10/90) afforded **436** as a colorless oil (m= 2.3 g, 95% yield).

All the spectroscopic data are in accordance with those described in the literature.[139]

General procedure for the synthesis of malonate derivatives (GPII)



n=1,2

To a dry flask containing NaH (60% in mineral oil, 396 mg, 9.90 mmol) and anhydrous DMF (16 ml) was slowly added malonate (26.9 mmol) at 0 °C. The solution was stirred for 15 min at r.t. After this, sulfonate (8.97 mmol) was added and the resulting mixture was stirred at 90 °C overnight. The reaction was diluted with water and Et_2O and the aqueous layer was extracted twice by Et_2O. The combined organics extracts were washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel to give the desired product in a pure form.

dimethyl 2-(but-3-yn-1-yl)malonate **374**



373 **374**
$C_9H_{12}O_4$
184.19 g/mol

The compound **374** was obtained from **373** and dimethylmalonate following the **GPII** on 9 mmol scale (2.0 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95 to 10/90) afforded **374** as a colorless oil (m= 1.0 g, 61% yield).

All the spectroscopic data are in accordance with those described in the literature.[140]

methyl 2-cyanohex-5-ynoate **379**



373 **379**
$C_8H_9NO_2$
151.17 g/mol

The compound **379** was obtained from **373** and methyl cyanoacetate following the **GPII** on 5 mmol scale (1.1 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 10/90 to 20/80) afforded **379** as a pale yellow oil (m= 589 mg, 78% yield).

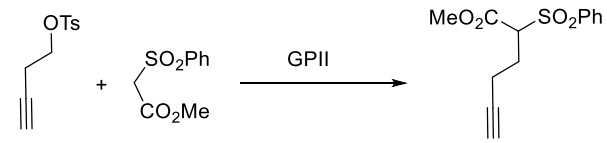
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.76 (dd, *J* = 8.8, 6.0 Hz, 1H), 2.47 – 2.42 (m, 2H), 2.24 – 2.08 (m, 2H), 2.05 (t, *J* = 2.6 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 115.9, 80.9, 71.0, 53.7, 36.0, 28.5, 16.2

FTIR (neat): ν = 3303, 1747, 1437, 907, 728 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_8H_{10}NO_2$: $[M+H]^+$: 152.0712; found: 152.0706

methyl 2-(phenylsulfonyl)hex-5-ynoate **383**



373 **383**
$C_{13}H_{14}O_4S$
266.31 g/mol

The compound **383** was obtained from **373** and methyl phenylsulfonylacetate following the **GPII** on 6 mmol scale (1.4 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95 to 13/87) afforded **383** as a yellow oil (m= 1.1 g, 69% yield).

^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.88 – 7.85 (m, 2H), 7.72 – 7.66 (m, 1H), 7.60 – 7.54 (m, 2H), 4.22 – 4.17 (m, 1H), 3.66 (s, 3H), 2.44 – 2.30 (m, 1H), 2.29 – 2.13 (m, 3H), 1.99 (t, *J* = 2.5 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 165.8, 137.0, 134.4, 129.1 (4C), 81.1, 70.7, 69.3, 53.0, 25.4, 16.1

FTIR (neat): *ν* = 1739, 1323, 1148, 906, 724 cm^{-1}

ethyl 2-acetylhex-5-ynoate **378**



373

378
$C_{10}H_{14}O_3$
182.22 g/mol

The compound **378** was obtained from **373** and ethyl acetoacetate following the **GPII** on 10 mmol scale (2.2 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95 to 7/93) afforded **378** as a colorless oil (m= 747 mg, 41% yield).

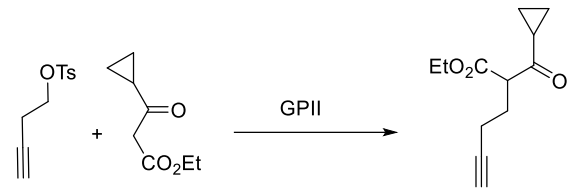
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 4.18 (qd, *J* = 7.2, 0.8 Hz, 2H), 3.69 (t, *J* = 7.2 Hz, 1H), 2.25 (s, 3H), 2.25 – 2.21 (m, 2H), 2.06 – 2.02 (m, 2H), 1.98 (t, *J* = 2.8 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 202.7, 169.3, 82.6, 69.9, 61.6, 58.0, 29.5, 26.4, 16.4, 14.2

FTIR (neat): *ν* = 1738, 1713, 1151, 909, 729 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{10}H_{15}O_3$: $[M+H]^+$: 183.1021; found: 183.1022

ethyl 2-(cyclopropanecarbonyl)hex-5-ynoate **380**



373

380
$C_{12}H_{16}O_3$
208.26 g/mol

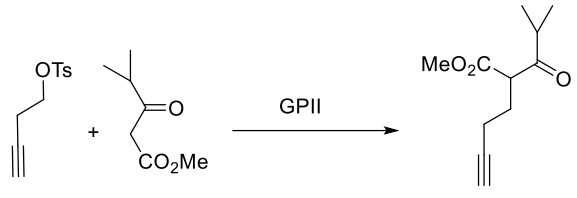
The compound **380** was obtained from **373** and ethyl 3-cyclopropyl-3-oxopropanoate following the **GPII** on 5 mmol scale (1.1 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95) afforded **380** as a colorless oil (m= 729 mg, 70% yield).

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 4.16 (qd, *J* = 7.2, 2.0 Hz, 2H), 3.79 (t, *J* = 7.2 Hz, 1H), 2.22 – 2.18 (m, 2H), 2.08 – 2.01 (m, 3H), 1.96 (t,2.8 Hz, 1H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.05 – 1.01 (m, 2H), 0.92 – 0.87 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 204.8, 169.3, 82.7, 69.7, 61.4, 58.0, 26.6, 20.2, 16.4, 14.1, 11.9, 11.7

FTIR (neat): *ν* = 1735, 1699, 1383, 907, 728 cm^{-1}

methyl 2-isobutyrylhex-5-ynoate **381**



373

381
$C_{11}H_{16}O_3$
196.25 g/mol

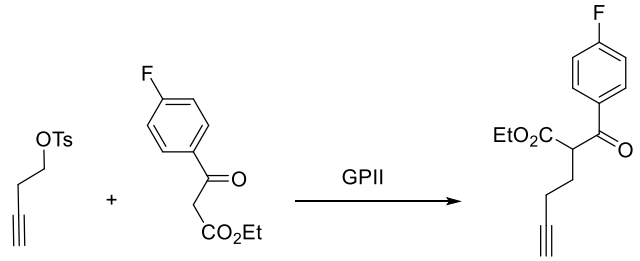
The compound **381** was obtained from **373** and methyl 4-methyl-3-oxopentanoate following the **GPII** on 5 mmol scale (1.1 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 2/98 to 3/97) afforded **381** as a colorless oil (m= 726 mg, 74% yield).

^{1}H NMR (300 MHz, $CDCl_3$) *δ* 3.94 (t, *J* = 7.2 Hz, 1H), 3.71 (s, 3H), 2.83 (p, *J* = 6.9 Hz, 1H), 2.26 – 2.18 (m, 2H), 2.06 – 1.98 (m, 3H), 1.11 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 208.7, 169.9, 82.7, 69.9, 54.8, 52.5, 41.0, 26.7, 18.3, 18.0, 16.5

FTIR (neat): *ν* = 1743, 1713, 1162, 911, 730 cm^{-1}

ethyl 2-(4-fluorobenzoyl)hex-5-ynoate **382**



373

382
$C_{15}H_{15}FO_3$
262.28 g/mol

The compound **382** was obtained from **373** and ethyl 4-fluorobenzoylacetate following the **GPII** on 5 mmol scale (1.1 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95 to 10/90) afforded **382** as a colorless oil (m= 393 mg, 30% yield).

^{1}H NMR (300 MHz, $CDCl_3$) *δ* 8.10 – 8.04 (m, 2H), 7.20 – 7.12 (m, 2H), 4.58 (t, *J* = 6.9 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.36 – 2.29 (m, 2H), 2.24 – 2.17 (m, 2H), 2.03 (t, *J* = 2.6 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H)

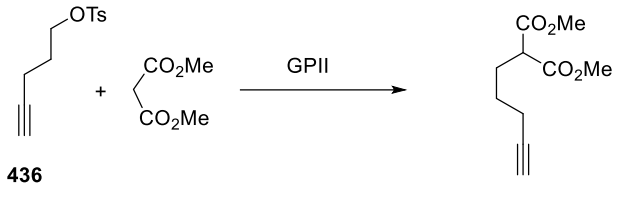
^{13}C NMR (100 MHz, $CDCl_3$) *δ* 193.4, 169.4, 166.2, 132.6, 131.6, 131.5, 116.1, 115.9, 82.9, 70.1, 61.7, 52.4, 27.4, 16.6, 14.1

^{19}F NMR (280 MHz, $CDCl_3$) *δ* -104.04

FTIR (neat): *ν* = 1734, 1685, 1598, 1235, 1157, 907, 845, 728 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{15}H_{16}FO_3$: $[M+H]^+$: 263.1083; found: 263.1077

dimethyl 2-(pent-4-yn-1-yl)malonate **384**



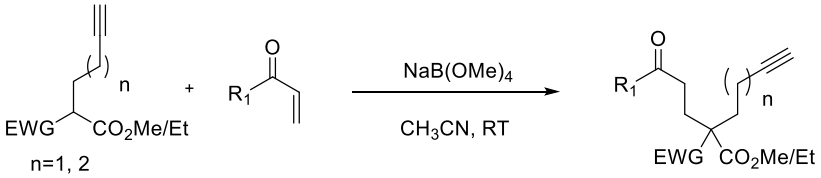
436

384
$C_{10}H_{14}O_4$
198.22 g/mol

The compound **384** was obtained from **436** and dimethylmalonate following the **GPII** on 20 mmol scale (4.8 g). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 10/90 to 20/80) afforded **384** as a colorless oil (m= 2.8 g, 71% yield).

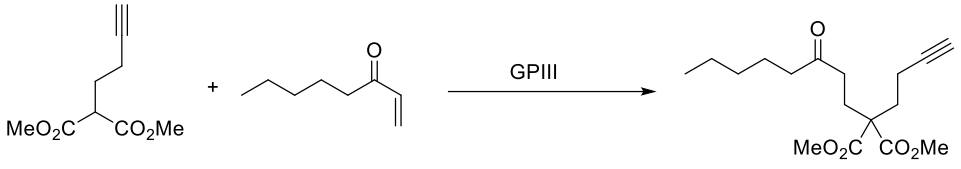
All the spectroscopic data are in accordance with those described in the literature.[141]

General procedure for the Michael addition (GPIII)



To a solution of Michael donor (1.2 mmol, 1.2 eq.) and $NaB(OMe)_4$ (0.2 mmol, 0.2 eq.) in CH_3CN (3 mL) was added α-β-unsaturated ketone (1.0 mmol, 1 eq.) at room temperature. The resulting solution was stirred at room temperature under air atmosphere and monitored by TLC. Upon completion, solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel to give the desired product in a pure form.

dimethyl 2-(but-3-yn-1-yl)-2-(3-oxooctyl)malonate **385**



374

385
$C_{17}H_{26}O_5$
310.39 g/mol

The compound **385** was obtained from **374** and oct-1-en-3-one following the **GPIII** on 1.7 mmol scale (219 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95 to 7/93) afforded **385** as a colorless oil (m= 440 mg, 82% yield).

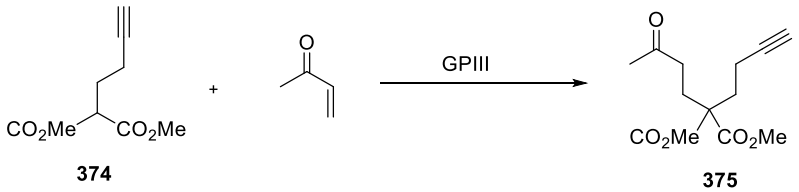
^{1}H NMR (300 MHz, $CDCl_3$) *δ* 3.68 (s, 6H), 2.36 (q, *J* = 7.3 Hz, 4H), 2.15 – 2.10 (m, 6H), 1.94 – 1.92 (m, 1H), 1.51 (p, *J* = 7.4 Hz, 2H), 1.30 – 1.18 (m, 4H), 0.84 (t, *J* = 6.8 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 171.2 (2C), 83.0, 68.9, 56.3, 52.6 (2C), 42.8, 37.6, 32.5, 31.4, 26.7, 23.5, 22.4, 14.0, 13.9

FTIR (neat): ν = 1729, 1199, 906, 727 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{17}H_{27}O_5$: $[M+H]^+$: 311.1858; found: 311.1860

dimethyl 2-(but-3-yn-1-yl)-2-(3-oxobutyl)malonate **375**



374 | **375** $C_{13}H_{18}O_5$ 254.28 g/mol

The compound **375** was obtained from **374** and methyl vinyl ketone following the **GPIII** on 5 mmol scale (350 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 10/90 to 25/75) afforded **375** as a white solid (m= 927 mg, 73% yield).

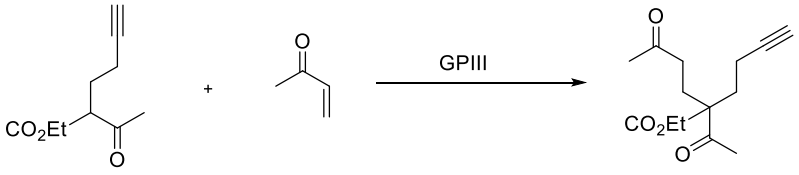
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 6H), 2.41 (t, *J* = 7.8 Hz, 2H), 2.16 – 2.06 (m, 9H), 1.92 (t, *J* = 2.4 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 206.9, 171.2 (2C), 83.0, 69.0, 56.3, 52.6 (2C), 38.6, 32.5, 30.0, 26.7, 14.1

FTIR (neat): ν = 1728, 1199, 907, 727 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{13}H_{18}O_5Na^+$: $[M+Na]^+$: 277.1052; found: 277.1044

ethyl 2-acetyl-2-(3-oxobutyl)hex-5-ynoate **386**



378 | **386** $C_{14}H_{20}O_4$ 252.31 g/mol

The compound **386** was obtained from **378** and methyl vinyl ketone following the **GPIII** on 0.55 mmol scale (39 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 20/80 to 30/70) afforded **386** as a yellow solid (m= 100 mg, 70% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (q, *J* = 7.1 Hz, 2H), 2.39 – 2.22 (m, 2H), 2.17 – 1.97 (m, 12H), 1.93 – 1.92 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 206.9, 204.5, 171.6, 83.0, 69.2, 62.0, 61.7, 38.1, 30.9, 30.0, 26.8, 25.0, 14.1, 13.7

FTIR (neat): ν = 1708, 1189, 1098, 909, 728 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{14}H_{20}O_4Na^+$: $[M+Na]^+$: 275.1259; found: 275.1250

methyl 2-cyano-2-(3-oxobutyl)hex-5-ynoate **387**



379

387
$C_{12}H_{15}NO_3$
221.26 g/mol

The compound **387** was obtained from **379** and methyl vinyl ketone following the **GPIII** on 3.2 mmol scale (224 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 25/75 to 40/60) afforded **387** as a colorless oil (m= 572 mg, 82% yield).

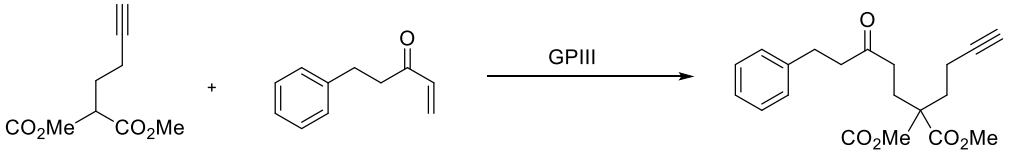
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 3.78 (s, 3H), 2.72 – 2.63 (m, 1H), 2.55 – 2.39 (m, 2H), 2.33 – 2.15 (m, 3H), 2.14 (s, 3H), 2.09 – 1.97 (m, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 205.5, 168.4, 118.0, 81.2, 70.0, 53.6, 48.2, 38.9, 35.7, 30.8, 29.9, 15.1

FTIR (neat): *ν* = 3288, 1742, 1716, 1227, 1098 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{12}H_{15}NO_3Na^+$: $[M+Na]^+$: 244.0950; found: 244.0941

dimethyl 2-(but-3-yn-1-yl)-2-(3-oxo-5-phenylpentyl)malonate **389**



374

252

389
$C_{20}H_{24}O_5$
344.41 g/mol

The compound **389** was obtained from **374** and **252** following the **GPIII** on 5 mmol scale (801 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95 to 8/92) afforded **389** as a yellow oil (m= 740 mg, 43% yield).

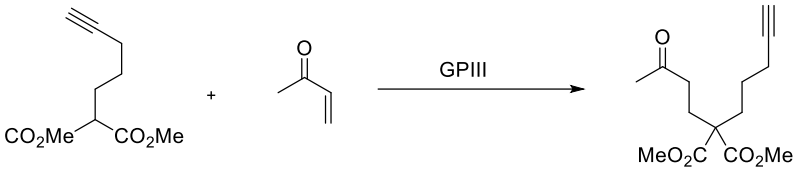
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.29 – 7.26 (m, 2H), 7.21 – 7.16 (m, 3H), 3.70 (s, 6H), 2.89 (t, *J* = 7.6 Hz, 2H), 2.72 (t, *J* = 7.6 Hz, 2H), 2.41 – 2.37 (m, 2H), 2.18 – 2.10 (m, 6H), 1.94 (t, 2.4 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 208.2, 171.2, 140.9, 128.5, 128.3, 126.2, 83.0, 69.0, 56.3, 52.6, 44.3, 37.9, 32.5, 29.8, 26.6, 14.0

FTIR (neat): *ν* = 1728, 1199, 907, 727 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{20}H_{24}O_5Na^+$: $[M+Na]^+$: 367.1521; found: 367.1512

dimethyl 2-(3-oxobutyl)-2-(pent-4-yn-1-yl)malonate **393**



393
$C_{14}H_{20}O_5$
268.31 g/mol

The compound **393** was obtained from **384** and methyl vinyl ketone following the **GPIII** on 3 mmol scale (210 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 10/90 to 15/85) afforded **393** as a colorless oil (m= 684 mg, 85% yield).

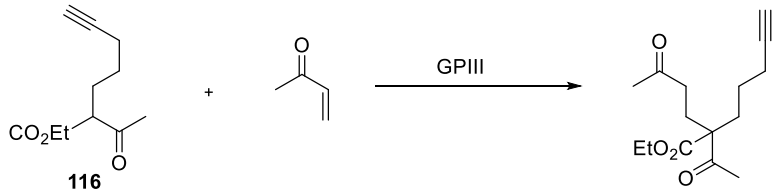
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 3.67 (s, 6H), 2.42 – 2.38 (m, 2H), 2.17 – 2.11 (m, 3H), 2.10 – 2.08 (m, 4H), 1.94 – 1.90 (m, 3H), 1.41 – 1.34 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 207.1, 171.7, 83.5, 69.0, 56.6, 52.5, 38.6, 32.7, 30.0, 26.7, 23.4, 18.6

FTIR (neat): *ν* = 1727, 1171, 908, 728 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{14}H_{20}O_5Na^+$: $[M+Na]^+$: 291.1208; found: 291.1196

ethyl 2-acetyl-2-(3-oxobutyl)hept-6-ynoate **392**



392
$C_{15}H_{22}O_4$
266.34 g/mol

The compound **392** was obtained from **116** and methyl vinyl ketone following the **GPIII** on 2 mmol scale (140 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 8/92 to 10/90) afforded **392** as a colorless oil (m= 405 mg, 75% yield).

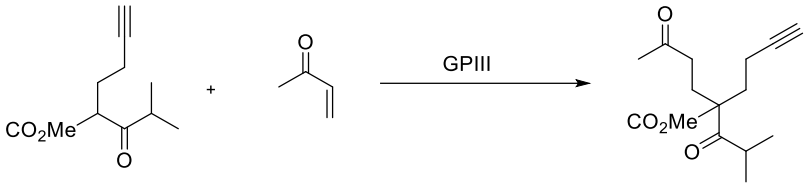
^{1}H NMR (300 MHz, $CDCl_3$) *δ* 4.17 (qd, *J* = 7.2, 1.6 Hz, 2H), 2.41 – 2.27 (m, 2H), 2.21 – 2.04 (m, 10H), 1.97 – 1.89 (m, 3H), 1.39 – 1.21 (m, 5H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 207.2, 205.0, 172.0, 83.5, 69.1, 62.3, 61.5, 38.2, 31.1, 30.0, 26.8, 25.1, 23.0, 18.7, 14.1

FTIR (neat): *ν* = 1706, 1359, 1167, 1020 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{15}H_{22}O_4Na^+$: $[M+Na]^+$: 289.1416; found: 289.1406

methyl 2-isobutyryl-2-(3-oxobutyl)hex-5-ynoate **390**



381 **390**

$C_{15}H_{22}O_4$

266.34 g/mol

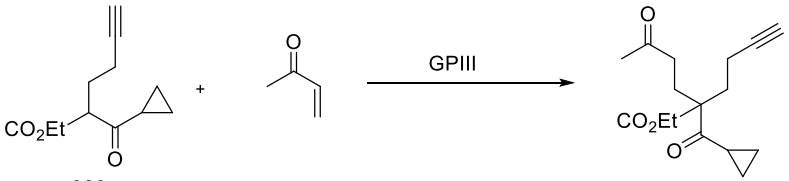
The compound **390** was obtained from **381** and methyl vinyl ketone following the **GPIII** on 2.7 mmol scale (189 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95 to 10/90) afforded **390** as a colorless oil (m= 525 mg, 73% yield).

^{1}H NMR (300 MHz, $CDCl_3$) *δ* 3.68 (s, 3H), 2.77 (hept, *J* = 6.6 Hz, 1H), 2.38 – 1.98 (m, 11H), 1.92 (t, *J* = 2.0 Hz, 1H), 1.00 (dd, *J* = 6.6, 5.4 Hz, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 211.1, 206.8, 172.1, 83.0, 69.1, 62.5, 52.3, 38.1, 37.3, 30.2, 30.0, 24.3, 20.4, 20.3, 13.7

FTIR (neat): *ν* = 1705, 903, 727 cm^{-1}

ethyl 2-(cyclopropanecarbonyl)-2-(3-oxobutyl)hex-5-ynoate **388**



380 **388**

$C_{16}H_{22}O_4$

278.35 g/mol

The compound **388** was obtained from **380** and methyl vinyl ketone following the **GPIII** on 3.4 mmol scale (238 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 10/90 to 20/80) afforded **388** as a colorless oil (m= 608 mg, 65% yield).

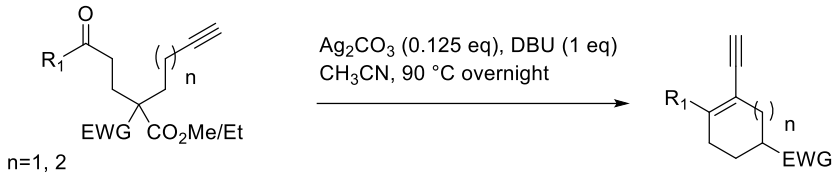
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 4.19 (q, *J* = 7.2 Hz, 2H), 2.40 – 2.03 (m, 11H), 1.94 – 1.88 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.04 – 0.95 (m, 2H), 0.93 – 0.81 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 207.1, 206.5, 171.9, 83.3, 69.0, 62.1, 61.6, 38.4, 31.0, 30.1, 25.2, 18.4, 14.2, 13.9, 12.1, 12.0

FTIR (neat): *ν* = 1717, 1698, 1189, 908, 726 cm^{-1}

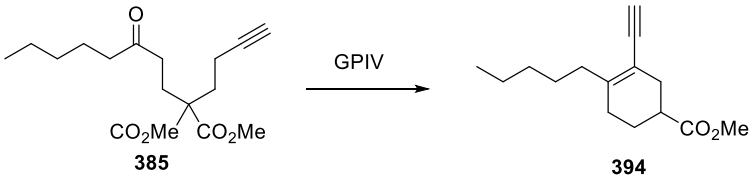
Cyclized Products

General procedure for the cyclization reaction GPIV:



In a vial protected from the light was placed a suspension of Ag_2CO_3 (0.025 mmol, 0.125 eq.) in CH_3CN (0.5 mL). DBU (0.2 mmol, 1 eq.) was added, then a solution of corresponding precursors (0.2 mmol, 1 eq.) in CH_3CN (0.5 mL) was added dropwise. The mixture was heated to 90 °C and stirred overnight. The reaction mixture was quenched by water and extracted twice with Et_2O. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel affording the expected compound in a pure form.

methyl 3-ethynyl-4-pentylcyclohex-3-ene-1-carboxylate **394**



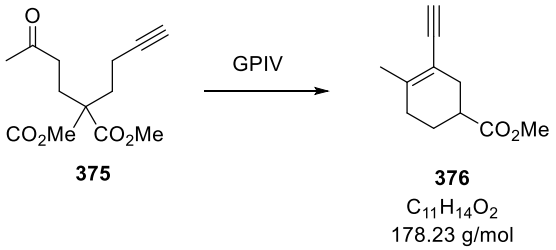
The compound **394** was obtained from **385** following the **GPIV** on 0.4 mmol scale (124 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 1/99 to 2/98) afforded **394** as a colorless oil (m= 77 mg, 82% yield).

^{1}H NMR (300 MHz, $CDCl_3$) *δ* 3.67 (s, 3H), 3.02 (s, 1H), 2.58 – 2.48 (m, 1H), 2.39 (d, *J* = 8.4 Hz, 2H), 2.27 (t, *J* = 7.6 Hz, 2H), 2.16 – 2.10 (m, 2H), 2.03 – 1.95 (m, 1H), 1.71 – 1.58 (m, 1H), 1.46 – 1.36 (m, 2H), 1.32 – 1.20 (m, 4H), 0.87 (t, *J* = 6.9 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) *δ* 175.6, 147.2, 112.0, 83.7, 79.3, 51.9, 39.2, 35.6, 31.9, 31.7, 28.4, 27.5, 25.1, 22.6, 14.2

FTIR (neat): *ν* = 1733, 1436, 1170, 907, 730 cm^{-1}

methyl 3-ethynyl-4-methylcyclohex-3-ene-1-carboxylate **376**



The compound **376** was obtained from **375** following the **GPIV** on 0.4 mmol scale (102 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 1/99) afforded **376** as a colorless oil (m= 61 mg, 85% yield).

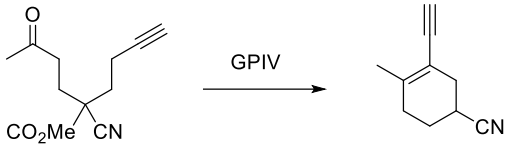
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 3.66 (s, 3H), 3.03 (s, 1H), 2.56 – 2.48 (m, 1H), 2.39 – 2.36 (m, 2H), 2.15 – 2.10 (m, 2H), 2.00 – 1.94 (m, 1H), 1.87 (s, 3H), 1.69 – 1.60 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 175.5, 142.8, 112.0, 83.7, 79.3, 51.8, 39.1, 31.7, 30.6, 25.0, 21.8

FTIR (neat): *ν* = 1732, 1437, 1198, 1174, 913, 732 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{11}H_{14}O_2Na^+$: $[M+Na]^+$: 201.0891; found: 201.0890

3-ethynyl-4-methylcyclohex-3-ene-1-carbonitrile **402**



387

402

$C_{10}H_{11}N$

145.21 g/mol

The compound **402** was obtained from **387** following the **GPIV** on 0.4 mmol scale (88 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 1/99 to 2/98) afforded **402** as a colorless oil (m= 46 mg, 80% yield).

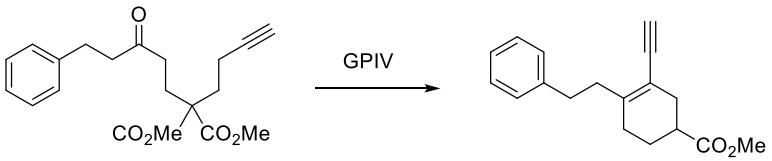
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 3.08 (s, 1H), 2.85 – 2.79 (m, 1H), 2.55 – 2.40 (m, 2H), 2.36 – 2.25 (m, 1H), 2.19 – 2.10 (m, 1H), 2.01 – 1.85 (m, 5H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 143.0, 121.8, 110.6, 82.8, 80.2, 32.2, 29.1, 25.4, 24.8, 21.9

FTIR (neat): *ν* = 2926, 909, 732 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{10}H_{11}NNa^+$: $[M+Na]^+$: 168.0789; found: 168.0790

methyl 3-ethynyl-4-phenethylcyclohex-3-ene-1-carboxylate **395**



389

395

$C_{18}H_{20}O_2$

268.36 g/mol

The compound **395** was obtained from **389** following the **GPIV** on 0.4 mmol scale (138 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 1/99 to 2/98) afforded **395** as a yellow oil (m= 89 mg, 83% yield).

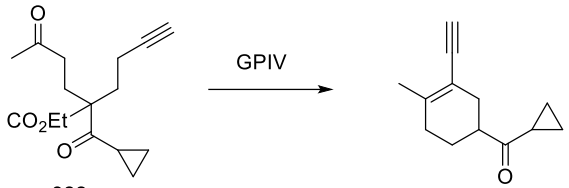
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.31 – 7.28 (m, 2H), 7.23 – 7.18 (m, 3H), 3.70 (s, 3H), 3.10 (s, 1H), 2.82 – 2.70 (m, 2H), 2.62 – 2.51 (m, 3H), 2.45 – 2.43 (m, 2H), 2.20 – 2.06 (m, 2H), 2.04 – 1.97 (m, 1H), 1.72 – 1.62 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 175.4, 146.2, 141.8, 128.5 (2C), 128.4 (2C), 125.9, 113.0, 83.3, 79.8, 51.8, 39.0, 37.7, 34.3, 31.8, 28.8, 25.0

FTIR (neat): *v* = 1731, 1170, 907, 728 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{18}H_{21}O_2$: $[M+H]^+$: 269.1542; found: 269.1538

cyclopropyl(3-ethynyl-4-methylcyclohex-3-en-1-yl)methanone **399**



388 **399**

$C_{13}H_{16}O$

188.27 g/mol

The compound **399** was obtained from **388** following the **GPIV** on 0.4 mmol scale (111 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 1/99) afforded **399** as a pale yellow oil (m= 33 mg, 44% yield).

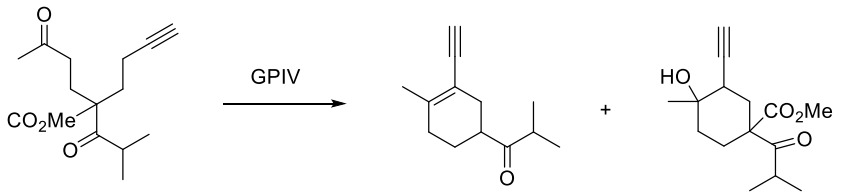
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 3.04 (s, 1H), 2.76 – 2.68 (m, 1H), 2.37 – 2.33 (m, 2H), 2.16 – 2.11 (m, 2H), 2.03 – 1.95 (m, 2H), 1.88 (s, 3H), 1.64 – 1.53 (m, 1H), 1.00 – 0.96 (m, 2H), 0.87 – 0.82 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 212.4, 143.0, 112.2, 83.9, 79.3, 47.1, 31.2, 30.9, 24.6, 21.8, 19.0, 11.0, 10.9

FTIR (neat): *v* = 1691, 1391, 1067, 907, 727 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{13}H_{16}ONa^+$: $[M+Na]^+$: 211.1099; found: 211.1090

1-(3-ethynyl-4-methylcyclohex-3-en-1-yl)-2-methylpropan-1-one **400** and methyl 3-ethynyl-4-hydroxy-1-isobutyryl-4-methylcyclohexane-1-carboxylate **409**



390 **400** **409**

$C_{13}H_{18}O$

190.29 g/mol

$C_{15}H_{22}O_4$

266.34 g/mol

The compound **400** and **409** was obtained from **390** following the **GPIV** on 0.4 mmol scale (107 mg). Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 1/99) afforded **400** as a colorless oil (m= 32 mg, 42% yield) and **409** as a colorless oil (m= 29 mg, 27% yield).

400

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 3.03 (s, 1H), 2.81 – 2.67 (m, 2H), 2.34 – 2.18 (m, 2H), 2.14 – 2.09 (m, 2H), 1.87 (s, 3H), 1.84 – 1.81 (m, 1H), 1.58 – 1.48 (m, 1H), 1.06 (d, *J* = 6.9 Hz, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 216.5, 142.7, 112.3, 83.8, 79.4, 44.6, 39.2, 31.6, 31.0, 24.9, 21.7, 18.5, 18.4

FTIR (neat): *v* = 1705, 1383, 910, 730 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{13}H_{18}ONa^+$: $[M+Na]^+$: 213.1255; found: 213.1251

409

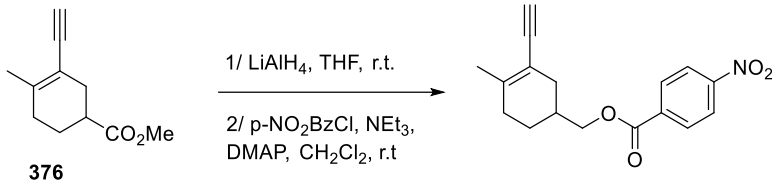
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 3.71 (s, 3H), 2.94 (hept, *J* = 6.6 Hz, 1H), 2.52 – 2.47 (m, 1H), 2.36 – 2.30 (m, 1H), 2.19 (d, *J* = 2.5 Hz, 1H), 2.09 – 1.94 (m, 3H), 1.81 – 1.75 (m, 2H), 1.41 – 1.31 (m, 1H), 1.29 (s, 3H), 1.00 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 210.9, 172.1, 83.9, 72.3, 68.5, 61.2, 52.5, 37.4, 35.9, 34.3, 31.5, 29.4, 25.1, 20.2, 20.1

FTIR (neat): *v* = 1709, 1227, 906, 726 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{15}H_{23}O_4$: $[M+H]^+$: 267.1596; found: 267.1590

(3-ethynyl-4-methylcyclohex-3-en-1-yl)methyl 4-nitrobenzoate **377**



376

377
$C_{17}H_{17}NO_4$
299.33 g/mol

To a suspension of $LiAlH_4$ (341.6 mg, 9 mmol) in THF (5 mL), cooled to 0 °C, was slowly added at 0 °C a solution **376** (178 mg, 1 mmol) in THF (5 mL) over 20 minutes. After completion of addition, the mixture was stirred at room temperature for 1 h. EtOAc (5 mL) was carefully added at 0 °C followed by slow addition of water (2 mL). The reaction mixture was filtered, dried over $MgSO_4$ and concentrated under reduced pressure affording the corresponding alcohol in a pure form. The crude was dissolved in dry DCM (10 mL) then NEt_3 (175 µL, 1.3 mmol), DMAP (5 mg, 0.04 mmol) and 4-nitrobenzoyl chloride (186 mg, 1 mmol) were successively added. The reaction was stirred for 24 h at room temperature. The reaction mixture was diluted with DCM (20 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/Cyclohexane: 5/95) afforded **377** as a pale yellow solid. (m= 278 mg, 93% over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.29 – 8.25 (m, 2H), 8.21 – 8.17 (m, 2H), 4.26 (qd, *J* = 10.9, 6.3 Hz, 2H), 3.05 (s, 1H), 2.37 – 2.30 (m, 1H), 2.18 – 1.99 (m, 4H), 1.90 (s, 3H), 1.88 – 1.82 (m, 1H), 1.46 – 1.36 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 164.7, 150.6, 143.4, 135.7, 130.8, 123.6, 112.0, 84.1, 79.2, 69.6, 33.1, 32.7, 30.6, 25.2, 21.9

FTIR (neat): *v* = 1722, 1527, 1270, 1103, 907, 719 cm^{-1}

HRMS (ESI): *m/z* calcd for $C_{17}H_{18}NO_4$: $[M+H]^+$: 300.1236; found: 300.1230

XI. Résumé

Au cours de précédents travaux de thèse effectués au sein de notre laboratoire, portant sur la synthèse totale de la vibsatine A, nous avons mis en lumière une nouvelle réaction de cyclisation intramoléculaire mettant en jeu le $Cu(OTf)_2$ et un système yne-one. Nous avons, à la suite de cette réaction, pu isoler et caractériser le nouveau produit formé, celui-ci possédant une structure complexe contenant notamment un motif 2,3-dihydrofurane. Faute de temps, cette réaction n'avait pas pu être étudié plus assidument. Les molécules comportant un dihydrofurane au sein de leur structure sont largement représentés parmi les composés naturels d'intérêt biologiques. De même, ceux-ci présentent également un intérêt synthétique certains, car ils peuvent constituer des briques élémentaires de choix en synthèse organique. Ainsi, il nous a apparu opportun de réétudier cette transformation de façon plus approfondie. L'objectif de cette thèse était donc de s'appuyer sur ce le résultat préliminaire obtenu précédemment pour améliorer, étudier et exemplifier cette nouvelle réaction de cyclisation intramoléculaire inédite.

Nous avons, dans un premier temps, déterminer les conditions réactionnelles optimales pour cette réaction en faisant varier plusieurs paramètres tels que la source de cuivre, la température, la base ou encore le solvant. Les meilleurs résultats ont été atteint en conduisant la réaction en tube scellé avec du $Cu(OTf)_2$ en présence de NEt_3 comme solvant. Cependant, les meilleurs rendements n'ont jamais pu excéder 60% ceci étant dû à une réaction compétitive d'homocouplage de type Glaser-Haye. Malgré plusieurs tentatives pour déjouer cette réaction secondaire, nous ne sommes jamais parvenus à annihiler cette réaction parasite compromettant dès lors l'utilisation des sels de cuivre comme catalyseur pour cette réaction.

Les sels d'argent, appartenant à la famille des « coinage metals », possèdent des caractéristiques physico-chimiques proches de ceux leurs homologues à base de cuivre. Nous avons ainsi envisagé leur utilisation en lieu et place du cuivre dans cette réaction de cyclisation. Les premiers essais ont rapidement démontré que les sels d'argent surpassaient les résultats obtenus avec le triflate de cuivre(I). La combinaison oxyde d'argent(I)/DBU s'est avérée optimale pour cette transformation et deux conditions réactionnelles complémentaires, utilisant cette combinaison, ont pu être établies. De même, la structure complexe du dérivé dihydrofuranique a pu être identifier sans ambiguïté grâce à l'obtention de clichés aux rayons-X. Cette réaction s'est avérée facile à mettre en œuvre et les bruts de réaction obtenus se sont révélés être très souvent très propres facilitant ainsi l'étape de purification. Nous avons, dès lors, pu accéder rapidement à une grande variété de dihydrofurane (plus d'une vingtaine d'exemples a pu être décrit) avec de très bon rendements et une excellente diastéréosélectivité. Notons que la synthèse des précurseurs est facilement accessible facilitant ainsi l'accès à ces motifs dihydrofuraniques complexe. D'un point de vue mécanistique, des études préliminaires associées à des calculs DFT effectués par nos collaborateurs de l'école de chimie Paris-Tech, le Dr. Ilariar Ciofini et le Dr. Anna Perfetto, ont permis de mettre en lumière la formation d'un intermédiaire allenyl argent, espèce très peu décrite dans la littérature. De même, nous avons également pu expliquer la très bonne sélectivité observée au cours de ces réactions de cyclisations intramoléculaires par le biais de réactions tests et grâce au support des calculs DFT. Ces travaux ont fait l'objet d'une publication.

Dans un second temps, nous avons cherché à reproduire un résultat de la littérature rapporté par l'équipe de Kirshe, utilisant un catalyseur d'or pour la synthèse de dihydrofuranes. L'entité réactionnelle utilisée par les auteurs, un système yne-one possédant un bras espaceur similaire et structurellement proche de celles que nous avions employées lors de la synthèse des dihydrofuranes, comportait, cette fois-ci, une cétone énolisable. En appliquant nos conditions optimisées, nous avons obtenu un nouveau composé comportant cette-fois ci un motif furanique et non 2,3-

dihydrofuranique comme précédemment. Après des recherches dans la littérature, cette réaction s'est avérée sans précédent. Les furanes se retrouvent dans de nombreux composés biologiquement actifs, mais également dans les polymères, dans l'industrie du parfum ou encore dans les aliments. En outre, les furanes représentent également un outil synthétique extrêmement intéressant et sont largement utilisés comme intermédiaire dans la synthèse de produits d'intérêts. Même si la littérature regorge de synthèse décrivant l'accès de furanes, il nous est apparu important d'étudier cette transformation avec plus de soin. Après un travail important d'optimisation des conditions réactionnelles, la combinaison Ag_2O/DBU dans l'acétonitrile à 50°C s'est révélée, à nouveau, être la plus efficace, délivrant différents motifs furaniques avec de très bons rendements. Nous avons pu accéder par ce biais à des motifs bicycliques contenant une unité furane fusionné à un cyclopentane, un tetrahydrofurane ou encore une pyrrolidine en peu d'étapes et avec une grande efficacité. Des motifs furaniques complexes et extrêmement tendu ont également été obtenu avec de bons rendements. Une version en un pot a également été initiée à partir de dérivés de malonate et de cétones α-β insaturées correctement fonctionnalisés utilisant les mêmes conditions réactionnelles. Cette approche s'est révélée être, dans certains cas, plus performante que celle consistant à effectuer la synthèse en deux étapes avec respectivement une réaction d'addition de Michael suivie d'une réaction de cyclisation. Nous avons également cherché à rendre cette réaction catalytique en sels d'argent, cependant sans succès malgré de nombreuses tentatives dont notamment l'adjonction d'oxydant afin de recycler les sels d'argent durant la réaction. Toutefois, l'oxyde d'argent(I) étant relativement bon marché, cet aspect n'est pas rédhibitoire vis-à-vis des conditions mises au point et n'interdit aucunement d'effectuer cette réaction à large échelle.

Afin de déterminer le mécanisme réactionnel de cette transformation, des réactions tests ont été menées impliquant par exemple l'adjonction dans le milieu réactionnel d'un piège à radicaux tel que le TEMPO, excluant, dès lors tout mécanisme radicalaire. De même, la substitution de la triple liaison par un groupement phényle ou méthyle semble inappropriée pour cette réaction puisque aucun produit de cyclisation n'a pu être observé même en durcissant les conditions opératoires. Ainsi, pareillement à la méthodologie avec les 2,3-dihydrofuranes, seul les alcynes terminaux semblent en mesure de délivrer les produits escomptés. De surcroit, des résultats obtenus sur des cétones cycliques nous ont également permis d'identifier de potentiels intermédiaires de synthèse. Cependant, malgré de nombreux indices nous n'avons pas été en mesure, à l'heure actuelle, de discriminer un chemin réactionnel par rapport à un autre. Ainsi, nous avons fait appel à nos partenaires de Chimie Paris-Tech pour effectuer des calculs DFT, qui nous l'espérons, pourront nous aider à sélectionner la voie de synthèse la plus probable parmi celles que nous avons envisagées.

En marge de ces travaux, nous avons aussi entrepris de trouver un nouvel accès à des cétones α-tétra-substituée. En effet, nous supposons que le mécanisme menant à la synthèse des furanes fait intervenir en premier lieu une réaction de Conia-ène. Ainsi, en bloquant la seconde cyclisation menant à la formation du motif furanique par adjonction d'un groupement en positions α de la cétone, nous espérions atteindre de tels produits. Des premiers résultats encourageants ont montré la faisabilité d'un tel procédé, cependant, par manque de temps et dû à la découverte d'une nouvelle réactivité durant ces recherches, nous n'avons pas poursuivi ces investigations.

Au cours de nos travaux sur la synthèse des dérivés furaniques, nous avons étudier, entre autre, l'influence de la longueur du bras espaceur entre la fonction alcyne terminale et la cétone. Si nous avons pu accéder à des homologues bicycliques comportant un cycle à 6 chaînons fusionnés à un noyau furane, nous avons également observé la formation d'un nouveau composé. Après investigation, nous avons pu déterminer que ce nouveau composé se formait de manière préférentielle lorsque la cétone mise en jeu possédait un groupement alkyle en α. Inversement, ce

nouveau composé était minoritaire lorsque la cétone impliquée était en position benzylique. La structure du nouveau composé formé présentait un système de type cyclohexène-yne. Une confirmation du squelette de la molécule a pu être établie après quelques étapes d'aménagements fonctionnels. Nous avons pu obtenir une structure cristalline dont nous avons eu les clichés aux rayons X. Nous avons dans un premier temps cherché à améliorer la conversion vers ce composé en modifiant les conditions réactionnelles. Après une étude d'optimisation, le couple Ag_2CO_3/DBU s'est avéré être la meilleure combinaison. De surcroît, nous avons pu accéder à un système catalytique en carbonate d'argent (0.125 eq) sans que cela soit délétère envers la conversion et le temps de réaction. Le mécanisme réactionnel de cette transformation a également été élucidé et impliquerait une série de réaction en cascade. Tout d'abord, nous aurions une isomérisation de la double liaison en allényl argent. Celui-ci viendrait attaquer la cétone pour former le cylcohexane correspondant. L'alcoolate ainsi formé viendrait à son tour attaquer un des esters du système malonique conduisant à la formation d'une lactone tricyclique extrêmement tendue. Une étape de déprotonation au pied de l'alcyne provoquerait alors une décarboxylation permettant un relâchement de la tension de cycle. L'enolate résultant serait alors reprotonné pour conduire au produit désiré. Ce mécanisme a été corroboré par la présence d'un sous-produit, observé dans le cas où le système malonique ne contient qu'un seul ester. Ce sous-produit semblerait provenir d'un intermédiaire de synthèse. En effet, les premières étapes menant jusqu'à la formation du cyclohexane seraient réversibles, autorisant ou non l'attaque de l'alcoolate sur l'ester conduisant à la lactone. Ainsi, selon la conformation adoptée par la molécule, les fonctions réactives peuvent soit se retrouver suffisamment proche pour réagir soit trop distante interrompant dès lors la cascade réactionnelle. Il est intéressant de noter que si le malonate doit comporter un ester, il n'est pas obligatoire que la fonction en position en β de l'ester soit également un autre ester. Ainsi, cette réaction a pu être soumise indifféremment à des β-cétoesters, des β-cyanoesters ou encore des β-sulfoesters. De même, l'encombrement stérique au niveau de la cétone a également été étudiée et ne semble pas délétère pour l'issue de la réaction. Cette transformation s'est montrée chimiosélective et nous sommes ainsi parvenu à une grande diversité moléculaire. Par le biais de cette nouvelle méthodologie, nous avons pu accéder à des composés complexes à partir de précurseur facilement disponible en une seule étape en employant des conditions douces. Les produits obtenus pourront constituer des briques élémentaires particulièrement intéressante dans le cadre de la synthèse totale de molécules complexes. Notons qu'une version en un seul pot consistant à utiliser des cétones α-β insaturées et différents systèmes comportant un malonate correctement fonctionnalisé est en cours d'étude au laboratoire.

En conclusion, au cours de ces travaux de thèse, nous avons pu élargir et développer la réactivité des sels d'argent vis-à-vis des alcynes terminaux. Nous avons pu, en outre, démontrer grâce à notre collaboration avec nos partenaires de Chimie Paris-Tech, que nous pouvions facilement accéder à des intermédiaires allenyl argent réactif vis-à-vis de cétones afin d'atteindre rapidement et sélectivement des systèmes 2,3-dihydrofuranes, furanes et cyclohexène-ynes complexes avec de bons rendements. Une analyse fine de cette réactivité nous a permis de sélectionner les précurseurs ainsi que les conditions réactionnelles adéquates pour atteindre de manière sélective l'un des trois systèmes vus plus haut. Pour les trois méthodologies décrites dans ce manuscrit, la synthèse des précurseurs réactionnels nécessitent très peu d'étape, les catalyseurs utilisés sont peu couteux et les réactions sont sont facile à mettre en place, ce qui rend ces méthodologies particulièrement attrayantes comparé à d'autres dont la synthèse des précurseurs est fastidieuse. Enfin, à partir de structure simple, nous arrivons à une diversité et complexité moléculaire importante en une seule étape, ce qui constitue également un atout majeur pour l'emploi de ces trois méthodologies décrites ici. D'un point de vue plus globale, ces avancées dans la chimie de l'argent et des alcynes constitue de

nouveaux outils de synthèse mais devraient également ouvrir de nouveaux champs d'applications et d'investigations dans un futur proche pour les chimistes organiciens.

XII. Bibliography

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