Cascade Reactions Initiated by π-Activation. A Flexible Way to Heterocycles

&

Studies toward the Total Synthesis of Melohenine B

DISSERTATION

Zur Erlangung des Grades Dr. rer. nat.

angefertigt im Fachbereich C, Mathematik und Naturwissenschaften

der Bergischen Universität Wuppertal

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geb. am 12.04.1985 in Saint Vallier sur Rhône

The work reported in this dissertation was conducted at the Technische Universität München, from November 2009 to September 2011 and at the Bergische Universität Wuppertal, from October 2011 to January 2013 under the guidance of Prof. Dr. Stefan Kirsch.

Parts of this study have been published:

Umland, K.-D.; Palisse, A.; Haug, T. T.; Kirsch, S. F. *Angew. Chem. Int. Ed*. **2011**, *50*, 9965-9968.

The present dissertation is divided in two parts. The first one concerns the investigations on cascade reactions initiated by π-activation to synthesize heterocycles and the second one describes the studies toward the total synthesis of melohenine B.

In this thesis, distinction between racemates and enantiomers will be applied according to the convention shown below:

« Il faut toujours se réserver le droit de rire le lendemain de ses idées de la veille. »

N. Bonaparte

A mes parents

Acknowledgements

First, I would like to thank Prof. Dr. Stefan Kirsch for giving me the opportunity to conduct my PhD work in his research group at the Technische Universität München, and then at the Bergische Universität Wuppertal. Thank you for the everyday support, the interest in my work, the numerous interesting discussions on various topics and for the advice on my future career.

From my time in Munich, I would also like to thank Prof. Dr. Thorsten Bach for establishing the nice collaboration of his working group with ours, the possibility to use apparatus and materials and also to participate in research seminars, as well as his kind invitation to the Christmas parties. At the same time, I would like to thank Mrs Kerstin Voigt for her help in all the Kafkaesque administrative matters.

Thank you to all the permanent coworkers at the Bergische Universität Wuppertal for their cordial welcome and everyday support. In particular, I would like to thank Mrs Christine Schneidereit for always being enthusiastic to help and find quickly a response at our problematics.

Since without analytic data, this work would have never seen the light, I would like to thank Mrs Simone Bettinger, Mrs Ilka Polanz and Mr Jürgen Dönecke for the measurement of numerous MS-spectra, and Mr Andreas Siebert for the NMR-spectra.

Furthermore, I would like to thank the DAAD for their financial support over two years on my research projects.

Special thanks go to my lab colleagues, the old generation, Bene, Helge, Alex, Timm and Tobi, who helped my integration into the group and in Bavaria. Of course my generation, KD and Philipp for the great working atmosphere and comprehensive behaviour when faced with my German skills and finally the last generation, Michi, Flo, Angela, Sara, Andy, and the

postdoctoral researcher, Zhi-Bin, who accompanied me through this last year. Thank you, both past and present for all the great moments we shared.

Additionally, I would like to thank Sara, Philipp, KD, Michi, Angela, Flo and Andy for taking the time to correct my PhD thesis as well as their interesting comments.

Now, I would like to thank all my friends from Munich, Antoine, Typhène, Fred, Ariane, Manoj, Vinc, Kirzstina, Christopher, Lazlo and Shao-wei for their support and for all the nice moments we shared. Thank you Diana, Aude, Fabien and Stella for the beyond boundaries support.

Finally, big thanks go to my family for their presence and support since the beginning.

Part I:

Cascade Reactions Initiated by π-Activation. A Flexible Way to Heterocycles.

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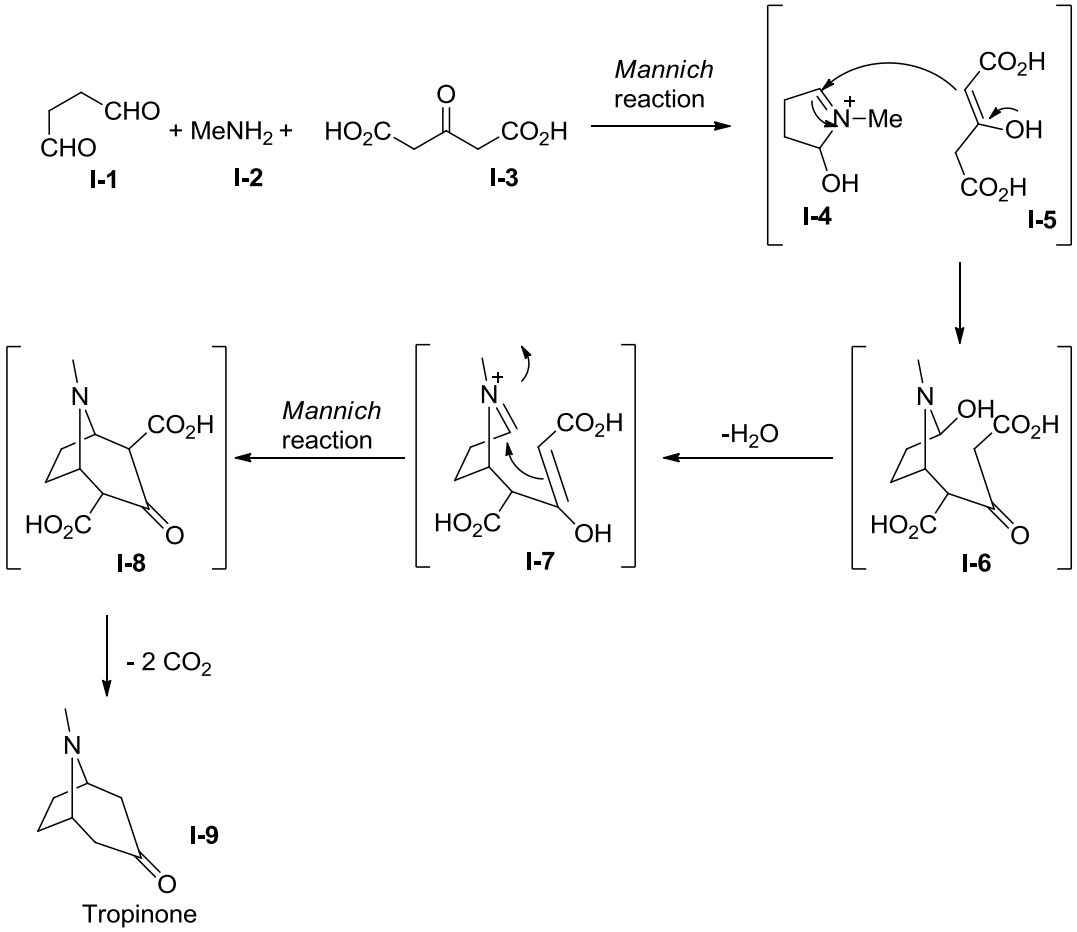
I) The cascade way to heterocycles

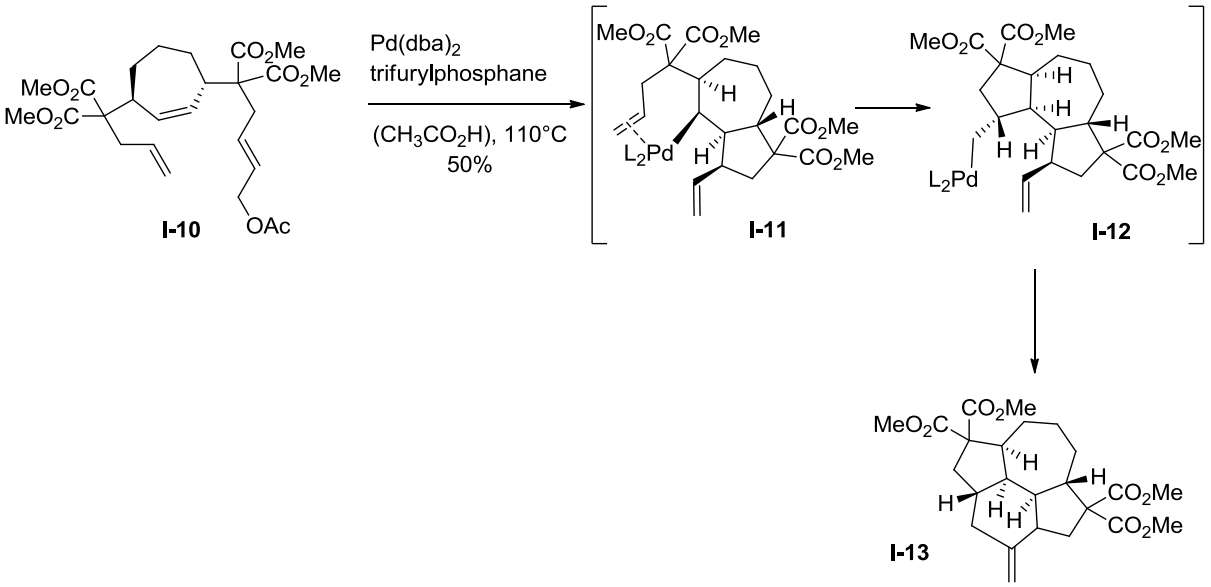
A cascade reaction, also named a *domino reaction* is, following the definition given by Tietze, "a process involving two or more consecutive reactions in which subsequent reactions results as a consequence of the functionality formed by bond formation or fragmentation in the previous step".[1] As such, the cascade reactions have an excellent economical and ecological advantage over the traditional multistep processes, as they perform several steps in one pot without isolating the reaction intermediates. Because one of the most important challenges of modern chemistry is to face the increase in complexity of the target molecules, in the meantime reduce the environmental impact related to the waste disposal, and the conservation of natural resources,[2] the domino process has been the subject of intense investigations in the past few years.[3]

However, long before public awareness regarding the necessity to reduce the human impact on the environment, cascade reactions have been recognized as an efficient method to synthesize natural products. Indeed, in 1917, after analysis of the biogenesis of the bicyclic tropane structure, *Schöpf* and *Robinson* described the first domino reaction, leading from succindialdehyde **I-1**, methylamine **I-2** and acetonedicarboxylic acid **I-3** to tropinone **I-9** via a double *Mannich* reaction (Scheme 1).[4] More recently, inspired by the biosynthesis of lanosterol, the precursor of steroids,[5] W. S. Johnson devised, in 1971, the synthesis of progesterone through a cationic polyolefin cyclization.[6]



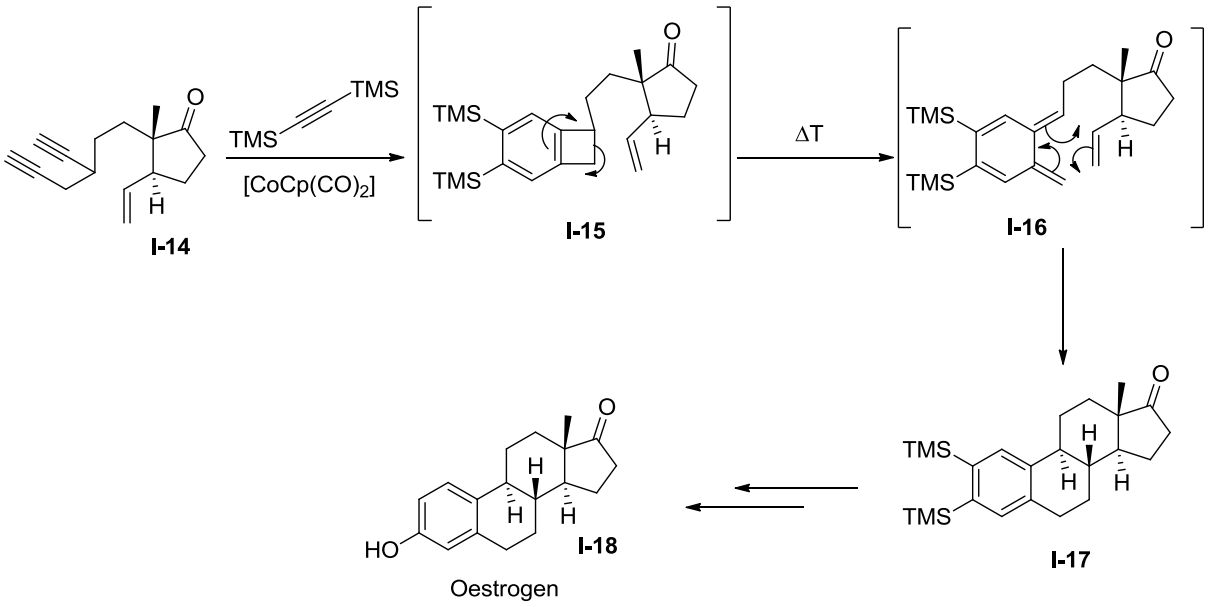
Scheme 1. The *Robinson* and *Schöpf* cascade reaction to tropinone synthesis.

Different reviews on the subject have tried to classify the domino reactions. The method employed by *Tietze et al.* can be singled out.[3b] The arrangement is based on the reaction type of the first two steps of the cascade. Cationic, anionic, radical, pericyclic, redox and transition-metal-catalyzed transformations are thus distinguished. The last category, the transition-metal-catalyzed reactions, has only recently offered new perspectives for generating complex molecules.[7] The great potential of this tool lies in the catalytic amounts necessary for the reaction and the novel processes for bond formation with no direct parallel in nature. In an impressive example, *Oppolzer* and coworkers described the synthesis of tetracyclic compound **I-13** via the palladium-catalyzed reaction of the cycloheptene **I-10** (Scheme 2).[8]



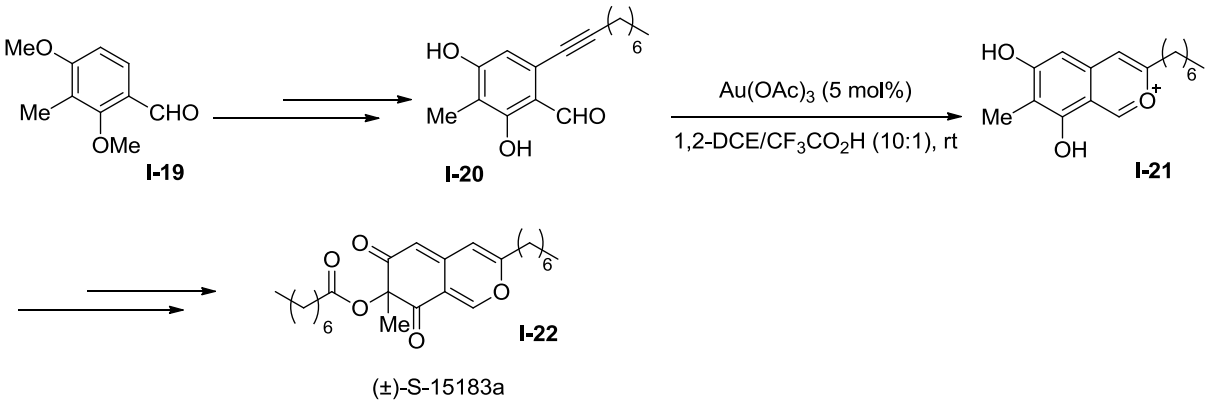
Scheme 2. Palladium-catalyzed cascade reaction (*Oppolzer et al.,* 1991*).*[8]

In addition, an early example of transition-metal-catalyzed domino process to construct natural product was described by *Vollhardt et al.* described in 1979, in the total synthesis of (±)-oestrogen using a cobalt-catalyzed cycloaddition, followed by an intramolecular *Diels-Alder* reaction (Scheme 3).[9]



Scheme 3. Cobalt-catalyzed total synthesis of (±)-oestrogen (*Vollhardt et al.*, 1979).[9]

Over the last years, a large number of synthetic routes to obtain heterocyclic compounds have applied transition-metal-catalyzed cascade reactions.[10] Due to their ability to activate π-systems,[11] especially alkynes,[12] strategies using soft metal cations, such as Au^{I}, Au^{III}, Ag^{I} or Pt^{II} have been found to be excellent for constructing complex scaffolds. Moreover, it appears that these catalysts can be employed easily in simple reaction conditions and show a remarkable functional group tolerance.[13] For example, *Porco et al* described in 2004 the synthesis of (±)-azaphilone S-15183a, where the key step is a gold-catalyzed cycloisomerization of *o*-alkynylbenzaldehyde **I-20** (Scheme 4).[14]



Scheme 4. Synthesis of (±)-azaphilone S-15183a (*Porco et al.*, 2004).[14]

II) Catalyzed cascade reactions, a way toward furan compounds

1) Furans, an important class of heterocycles

Furans correspond to a significant class of five-membered heterocycles. They are present as key structural units in a variety of natural products,[15] for example in the teubrevin G **(I-23)** and in pharmaceutical substances like the anti gastric ulcer drug ranitidine **(I-24)** (Zantac®).[16]

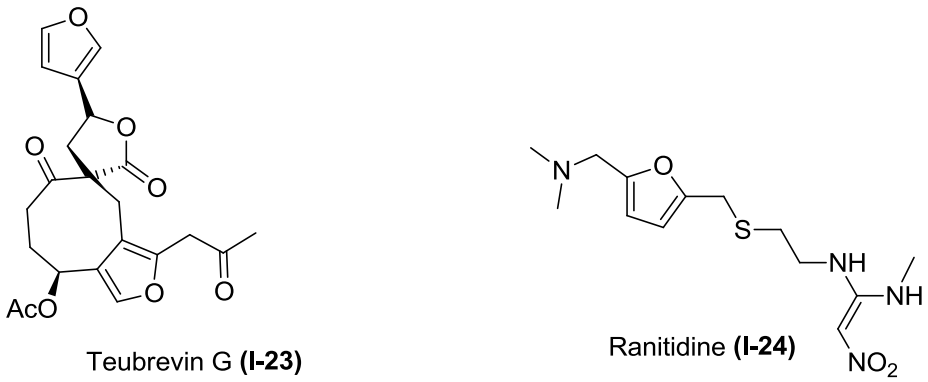
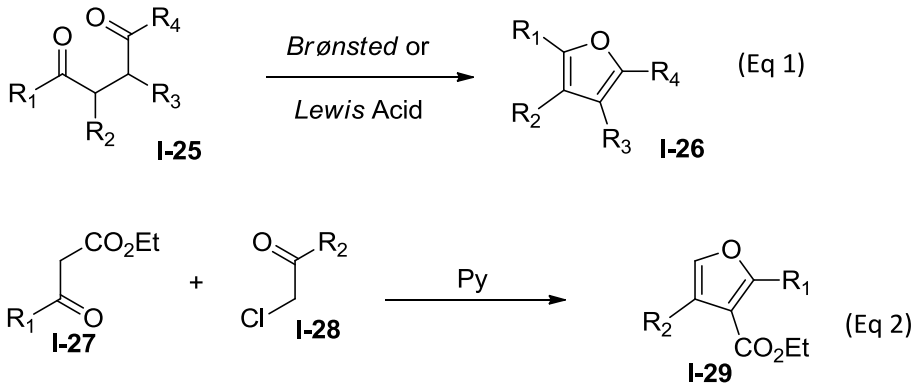


Figure 1. Presentation of selected furan-containing compounds.

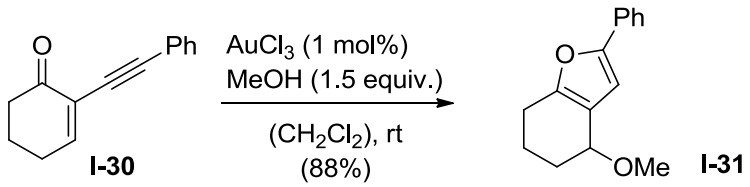
Moreover, they play a useful synthetic role in total syntheses as intermediates ready to be further oxidized, reduced or to undergo a cycloaddition.[17] Therefore, their value has pressed chemists to develop methods for their syntheses. Classical ways, such as the *Paal-Knorr* synthesis[18] (Scheme 5, Eq 1) or the *Feist-Benary*[19] synthesis (Scheme 5, Eq 2) are frequently employed.



Scheme 5. Classical methods for furan synthesis.

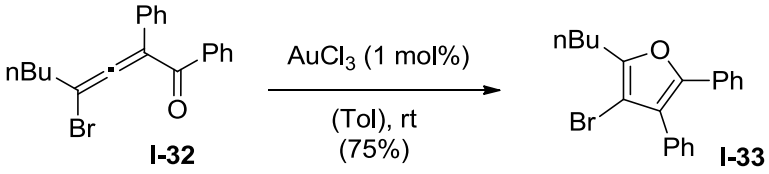
Although these reactions have shown to be useful, the development of new routes stays a current issue, in particular efficient methods giving access to highly functionalized furans under mild conditions.

Amongst various examples, methods employing cascade reactions to synthesize furans are also depicted. They mostly involve a 5-*endo* cyclization of an alkynyl or allenyl ketone.[20] Thus, *Larock* and coworkers have introduced a gold-catalyzed process where the oxonium ion intermediate is trapped with different nucleophiles to produce trisubstituted furans (Scheme 6).[21]



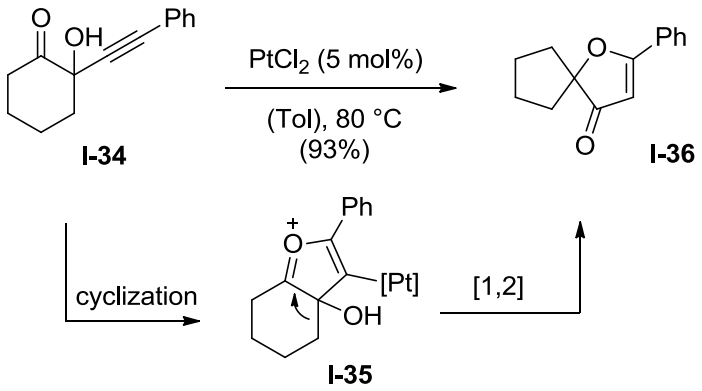
Scheme 6. Catalyzed synthesis of trisubstituted furans (*Larock et al*., 2004).[21]

Copper catalysts are also efficient in catalyzing the cyclization, as shown by *Yamamoto et al.* with the formation of trisubstituted furans employing alkynyl enones and copper(I) bromide.[22] *Gevorgyan* and coworkers have made use of haloallenyl ketones to construct di-, tri-, and tetrasubstituted furans.[23] In this case, the cascade reaction was triggered by gold(III) chloride (Scheme 7).



Scheme 7. Gold-catalyzed synthesis of tetrasubstituted furans (*Gevorgyan et al*, 2005).[23]

In addition to the above examples, *Kirsch* and coworkers have developed a domino reaction that combines a 5-*endo* heterocyclization and a pinacol-type rearrangement to construct 3(*2H*)-furanones **I-36** (Scheme 8).[24]

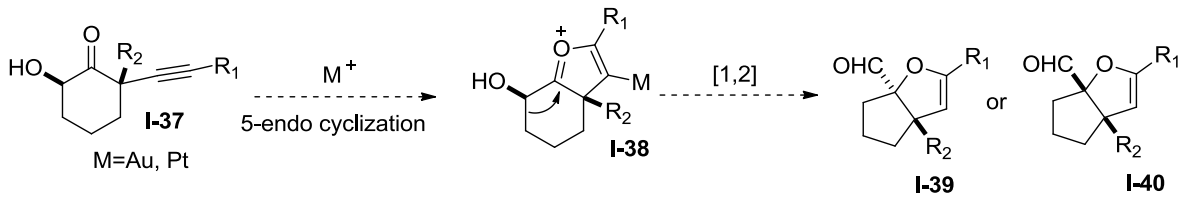


Scheme 8. Synthesis of 3(*2H*)-furanones via a cyclization/pinacol-type 1,2-alkyl shift sequence (*Kirsch et al.,* 2006).[24]

2) Cyclization/1,2-migration sequence, new development

2.1) The planned process

The encouraging results on the 3(*2H*)-furanone syntheses have inspired us to explore further the possibilities of the cascade process heterocyclization/1,2-migration.[25] We planned that the designed alkynone **I-37**, following a similar pathway, could be the right substrate to generate 2,3-dihydrofurans **I-39**. After π-activation, **I-37** should thus form an oxonium ion intermediate, in which the hydroxyl group outside the newly established cycle could induce a 1,2-alkyl migration (Scheme 9).

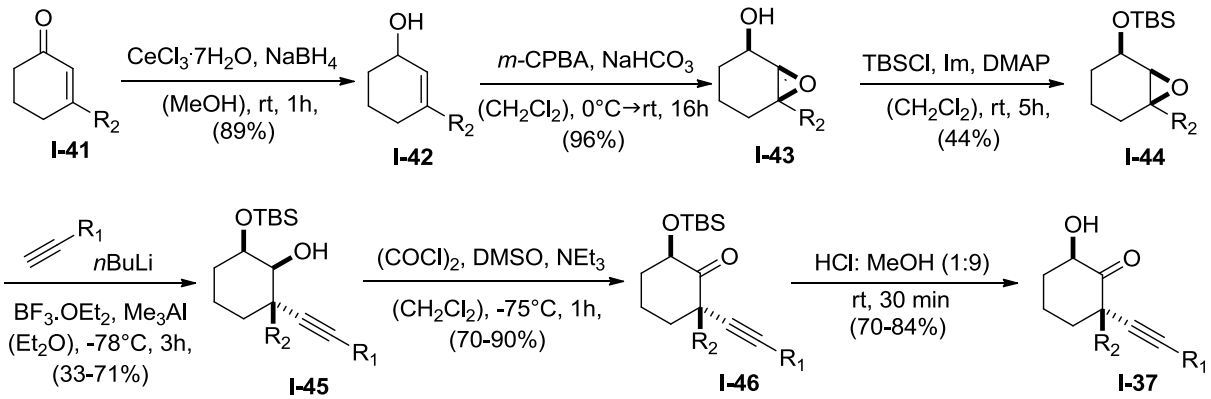


Scheme 9. Planned sequence to 2,3-dihydrofurans.

2.2) Results and discussion

2.2.1) Substrate synthesis

Starting substrates **I-37** were prepared as shown in Scheme 10. Reduction of 3-methylcyclohex-2-enone under Luche conditions[26] followed by diastereoselective epoxidation with *m*-CPBA gave epoxide **I-43**, which was treated with *tert*-BuMe_2SiCl (TBSCl), imidazole, and DMAP in CH_2Cl_2 to afford silyl ether **I-44**. By use of the conditions developed by *Pagenkopf* and co-workers,[27] alkynylation of the epoxide at the more hindered carbon was possible in varying yields with a range of terminal alkynes. Swern oxidation[28] and removal of the silyl group under acidic conditions gave cyclohexanone derivatives **I-37**. As confirmed by NOE signals, the alkynyl side chain and hydroxyl group are *trans* in the six-membered ring.[1]

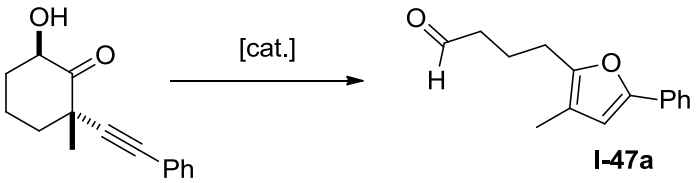


Scheme 10. Synthesis of substrates I-37.

2.2.2) An unexpected furan

When the first experiments with substrate **I-37a** were conducted to test the possibility of the cyclization/1,2-alkyl migration cascade with carbophilic *Lewis* acids, traces of an unexpected furan (**I-47a**) were detected (Entry 1, Table 1).

[1] Haug. T. T *Die Totalsynthese von (+)-Chloriolide*, Technische Universität München, **2010**.



I-37a **I-47a**

Entry	**Catalyst** (5 mol%)	**Solvent** (0.05 M)	**Time**	**Temperature (°C)**	**Yield[a] (%) I-47a**
1	$AuCl(PPh_3)/AgSbF_6$	CH_2Cl_2	1h	rt	traces
2	$AuCl(PMe_3)/AgSbF_6$	CH_2Cl_2	15 min	rt	54
3	$AuCl(PMe_3)/AgSbF_6$	Toluene	1h	100	68
4	$AuCl(PPh_3)/AgSbF_6$	Toluene	20 min	100	35
5	$AuCl(PMe_3)/AgOTf$	Toluene	30 min	100	23
6	$AuCl(PMe_3)/AgBF_4$	Toluene	24h	100	22
7	$PtCl_2$	Toluene	5h	100	74
8	$PtCl_4$	Toluene	2h	100	77
9	$PtCl_4$	*i*PrOH[b]/Toluene	45 min	100	83
10	HBF_4	CH_2Cl_2	5h	rt	0

a: Yield of isolated product after complete consumption of **I-37a**; b: 1.5 equiv.

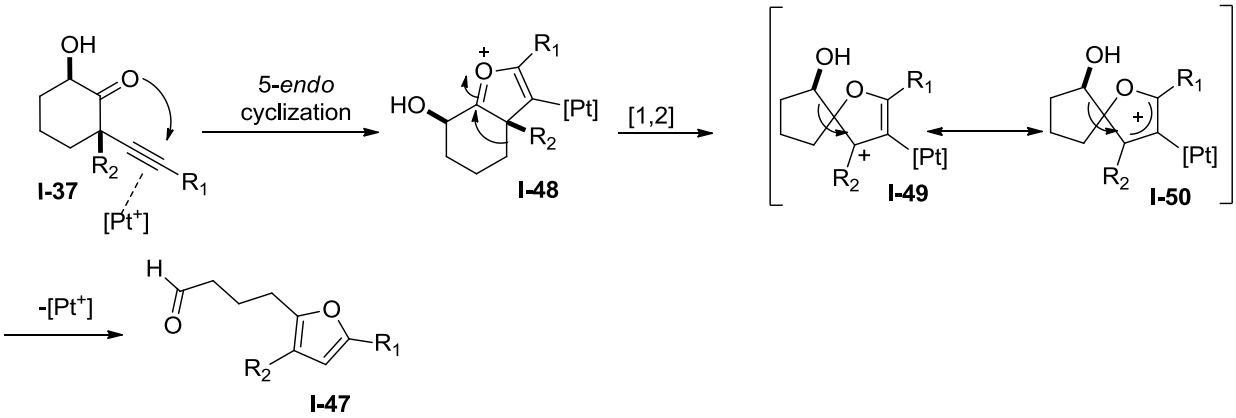
Table 1. Screening of conditions.

Changing the ligand PPh_3 to PMe_3 led to the formation of the furan **I-47a** (Entry 1-2, Table 1), or switching to other silver salts gave the same result in various yields: no trace of the desired dihydro-furan (**I-39** or **I-40**) was observed (Entry 5-6, Table 1).

As previously described, polysubstituted furans are interesting target structures, it appeared to us that this catalyzed route from the cyclohexanones **I-37** can be a new and convenient way to access trisubstituted furans with an aldehyde-containing side chain. Subsequently several conditions were examined to improve the yield of the domino sequence. Changing from gold catalysts to platinium proved to be successful, $PtCl_4$ (5 mol%) catalyzed the formation of furan **I-47a** in toluene at 100°C in 77% (Entry 8, Table 1). The

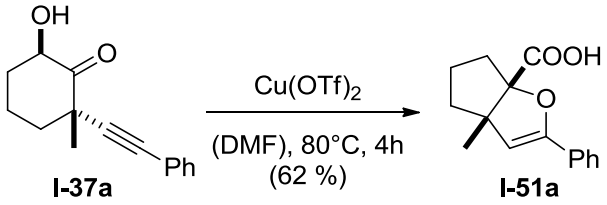
addition of *i*PrOH remarkably decreased the time needed for complete conversion (Entry 9, Table 1).

To explain the furan formation, a mechanism was proposed (Scheme 11). The cascade reaction starts as planned for the formation of the 2,3-dihydrofuran, with the activation of the alkyne moiety via coordination of the π-acid. The nucleophilic attack of the carbonyl group gives the oxonium ion **I-48**, which after 1,2 shift, rearranges to the spirocyclic intermediate **I-50**.[25b] Grob-type fragmentation[29] of the cation **I-50** produces the furan **I-47** with the aldehyde containing side chain. The protodemetalation, necessary for regeneration of the catalyst, is probably facilitated by the presence of isopropanol as external proton source.



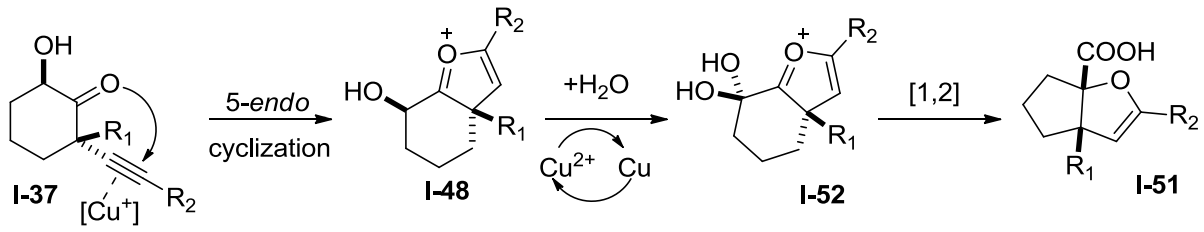
Scheme 11. Proposed mechanism for the formation of I-47.

The bicyclic dihydrofuran **I-39** was not isolated, instead a bicyclic dihydrofuran with acid functionality (**I-51a**) was found by *T. T. Haug*, using 10 mol% $Cu(OTf)_2$ in wet DMF at 80°C (Scheme 12). *Klaus-Daniel Umland*, a coworker on the project, improved the condition for the synthesis of the methyl ester of **I-51**. He found that the reaction of **I-37** with 10 mol% CuCl in wet DMPU at 80°C, directly followed by methylation, delivered the bicyclic ester in 82% yield.



Scheme 12. Copper-catalyzed cascade reaction.

The mechanistic investigations by *Klaus-Daniel Umland* have shown that contrary to the redox neutral platinum catalyst, the oxidative copper catalyst leads to heterocyclization and oxidation as described in Scheme 13.



Scheme 13. Plausible mechanism for the formation of I-51.

2.2.3) Scope of the platinum-catalyzed cascade reaction

The optimized reaction conditions were applied to a scope of substrates (Table 2). Various trisubstituted furans were obtained in good to excellent yields. The domino process proved to be efficient with alkyl- (**I-47h**), aryl- (**I-47a, I-47c, I-47d**) and heteroaryl- (**I-47b**) substituted alkynes. It appeared that electron donating groups have a positive effect on the yield, perhaps due to a better coordination of the π-system to the platinum catalyst. Substrates with trimethylsilylethinyl-, silyloxypropinyl- and silyloxybutinyl-moieties were also tested. Unfortunately, the cascade reactions failed in these cases. Furans with methyl substituted alkyl-chains were also performed in excellent yields (**I-47i and I-47j**).

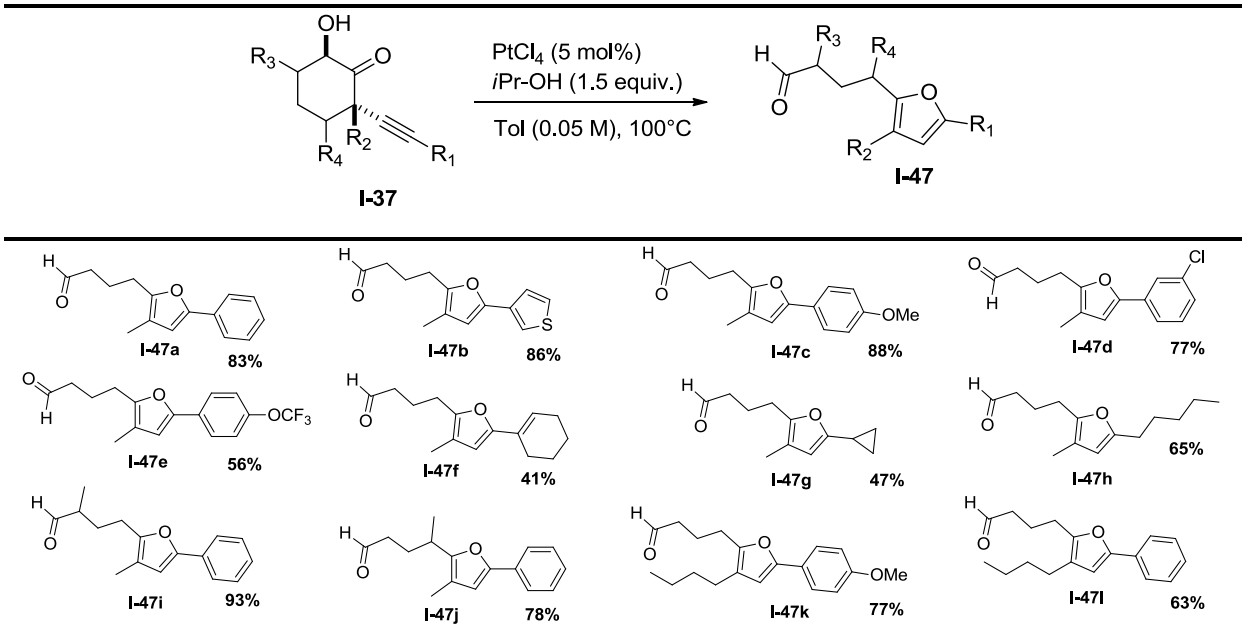
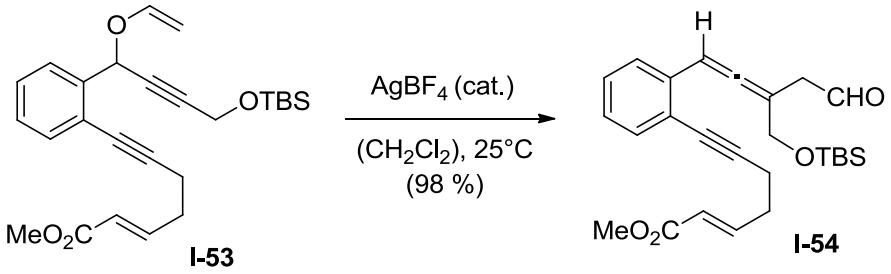


Table 2. Substrate scope.

In conclusion, a novel and highly practical route to access a library of trisubstituted furans with an aldehyde-containing side chain was developed thanks to a platinum-catalyzed sequence consisting of heterocyclization/1,2-migration.

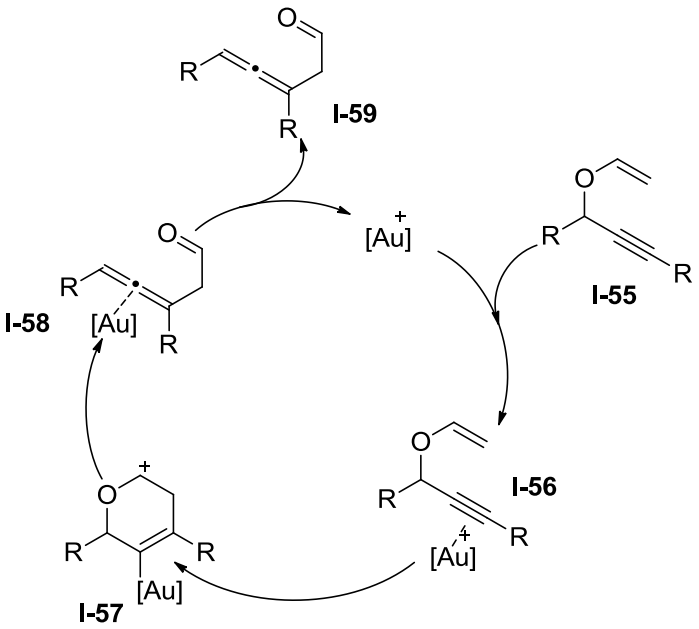
3) The catalyzed propargyl-*Claisen* rearrangement in cascade reactions

Since the first discovery of [3,3]-sigmatropic rearrangements in 1912 by *L. Claisen,*[30] the method has been a widespread tool for synthetic chemists.[31] The interest generated by the *Claisen* rearrangement gave birth to a plethora of different versions of [3,3]-sigmatropic rearrangements, as the *Carroll* rearrangement,[32] the *Eschenmoser* rearrangement[33] or the *Ireland-Claisen* rearrangement[34]. More recently, transition-metal catalyzed reactions also entered into the game.[35] To name some examples, *Overman et al.* devised the rearrangement of allyltrichloroacetimidate to the corresponding trichloroacetamide using mercury salt as the catalyst,[36] or even the palladium-catalyzed *Claisen* rearrangement developed by V*an der Baan* and *Bickelhaupt*.[37] A catalyzed propargyl-type-*Claisen* rearrangement was first reported in 1997 by *Grissom et al.*. They described the reaction of propargyl-vinyl-ethers to their resultant allenyl-carbonyl products, employing a silver salt (Scheme 14).[38]



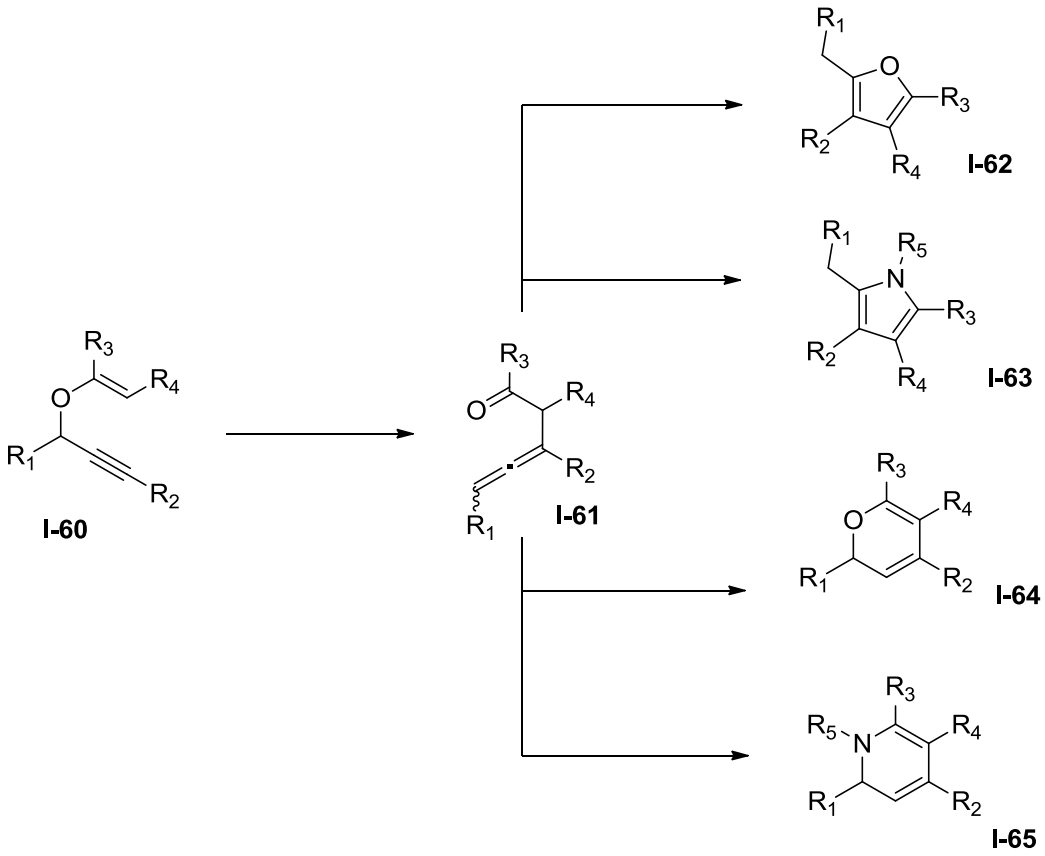
Scheme 14. First propargyl-*Claisen* rearrangement (*Grissom et al.,* 1997).[38]

Toste and coworkers further developed this process by broadening the substrate scope and by providing a mechanism to explain the gold-catalyzed rearrangement for propargylic vinyl ethers and propargylic vinyl esters.[39] In the case of propargylic vinyl ethers, they showed that the [3,3]-rearrangement is irreversible and proceeds via a concerted pathway (Scheme 15). After activation of the starting material **I-55** through the π-complex **I-56** the rearrangement is induced, assisted by the formation of a cyclic carbocation (cyclization-induced rearrangement). A *Grob*-type fragmentation of **I-57** provides the allene complex **I-58**. Finally, the gold cation is released giving the free allene **I-59**.



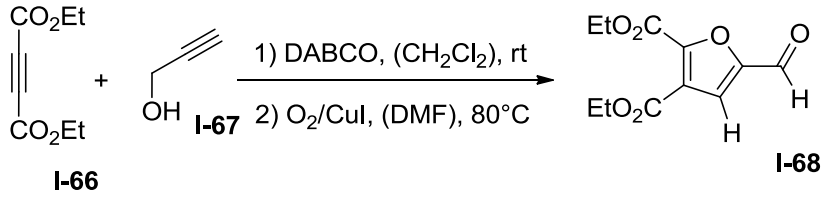
Scheme 15. Gold-catalyzed [3,3]-rearrangements of propargyl vinyl ethers (*Toste et al*., 2004).[39]

In 2005, *Kirsch* and coworkers performed a domino process where the propargyl-*Claisen* rearrangement occurs prior to a cyclization reaction. With this approach available, they have converted easily accessible propargyl vinyl ether[40] into furans,[41] pyrans,[42] pyrroles[43] and 1,2-dihydropyridines[44] (Scheme 16).



Scheme 16. Scope of syntheses with propargyl vinyl ether (*Kirsch et al*.).

Moreover, propargyl-vinyl-ethers were also used as a powerful starting material by *Jiang et al.*, who demonstrated that the propargyl-Claisen rearrangement can also be catalyzed by copper,[45] iron,[46] silver[47] and palladium[48] catalysts to deliver, after a domino sequence, tri- and tetra-substituted furans. Interestingly, the propargyl-vinyl-ethers were prepared *in situ* with acceptor activated alkynes and propargylic alcohols under basic conditions (Scheme 17).

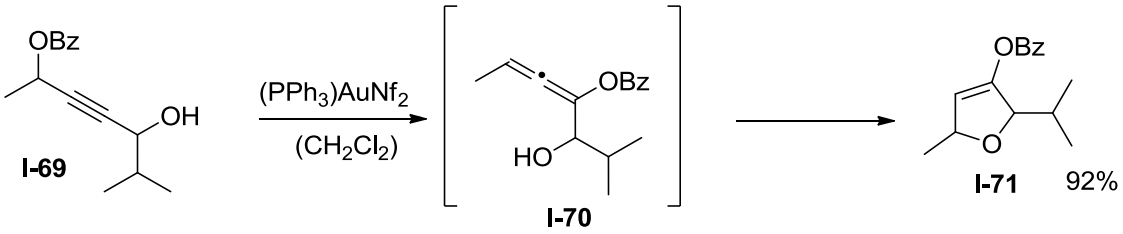


Scheme 17. One-pot Synthesis of polysubstituted furans (*Jiang et al.,* 2009).[45]

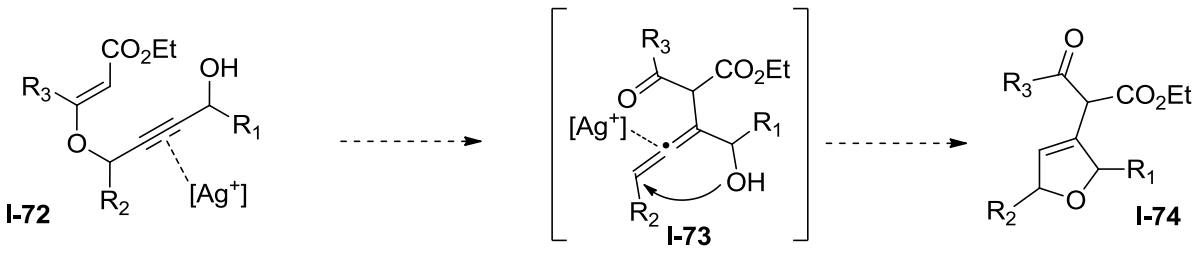
Tejedor and coworkers showed in a series of works that microwave-assisted cascade reactions are also great tools to obtain heterocycles from propargyl-vinyl-ethers.[49]

3.1) The new sequence

Bearing in mind that the propargyl-*Claisen* rearrangement[50] can still play an important role in building novel cascade reactions, new propargyl vinyl ethers **I-72** were designed. On the basis of previous work of *Kirsch et al.* on propargyl-*Claisen* rearrangements and the published work of *Gagosz et al*[51] (Scheme 18), the catalyzed sequence depicted in Scheme 19 was expected to occur to give compound **I-74**. We planned that the cascade reaction starts with activation of the alkyne group of **I-72** through coordination with the silver-catalyst, which triggers a silver-catalyzed propargyl-*Claisen* rearrangement. The newly formed allene in **I-73** should also be activated by the catalyst, which induces a 5-*endo* heterocyclization of the hydroxy group into the allene delivering the desired product **I-74** (Scheme 19).



Scheme 18. Cascade reaction including a propargyl-*Claisen* rearrangement (*Gagosz et al.*, 2006).[51]

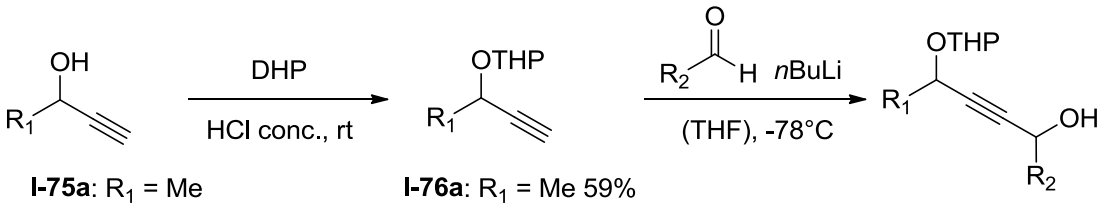


Scheme 19. Proposal of a novel cascade reaction.

3.2) Results and Discussion

3.2.1) Synthesis of the propargyl vinyl ethers

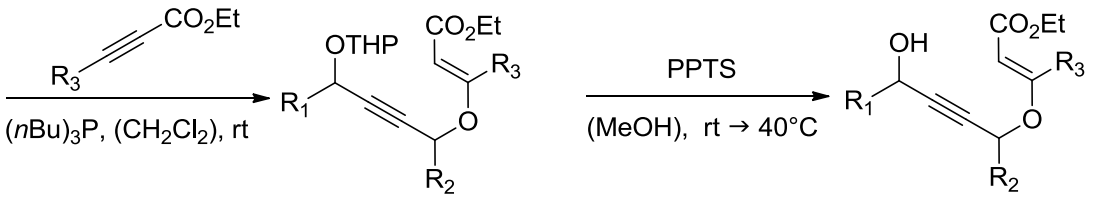
To test this idea, the substrates were synthesized in a four-step synthesis as described in Scheme 20.



I-75a: R_1 = Me
I-75b: R_1 = *i*Bu
I-75c: R_1 = Ph
I-75d: R_1 = H

I-76a: R_1 = Me 59%
I-76b: R_1 = *i*Bu 58%
I-76c: R_1 = Ph 69%
I-76d: R_1 = H 88%

I-77a: R_1 = Me; R_2 = Et 86%
I-77b: R_1 = Me; R_2 = *n*Pr 65%
I-77c: R_1 = Me; R_2 = *t*Bu 31%
I-77d: R_1 = Me; R_2 = Ph 85%
I-77e: R_1 = *i*Bu; R_2 = Et 78%
I-77f: R_1 = *i*Bu; R_2 = Ph 86%
I-77g: R_1 = Ph; R_2 = Et 72%
I-77h: R_1 = Ph; R_2 = Ph 74%
I-77q: R_1 = H; R_2 = Et 80%
I-77r: R_1 = H; R_2 = Ph 65%



I-78a: R_1 = Me; R_2 = Et; R_3 = Me 95%
I-78b: R_1 = Me; R_2 = *n*Pr; R_3 = Me 61%
I-78c: R_1 = Me; R_2 = *t*Bu; R_3 = Me 96%
I-78d: R_1 = Me; R_2 = Ph; R_3 = Me 72%
I-78e: R_1 = *i*Bu; R_2 = Et; R_3 = Me 78%
I-78f: R_1 = *i*Bu; R_2 = Ph; R_3 = Me 72%
I-78g: R_1 = Ph; R_2 = Et; R_3 = Me 67%
I-78h: R_1 = Ph; R_2 = Ph; R_3 = Me 67%
I-78i: R_1 = Me; R_2 = Et; R_3 = H 93%
I-78j: R_1 = Me; R_2 = Et; R_3 = Ph 98%
I-78q: R_1 = H; R_2 = Et; R_3 = Me 82%
I-78r: R_1 = H; R_2 = Ph; R_3 = Me 50%

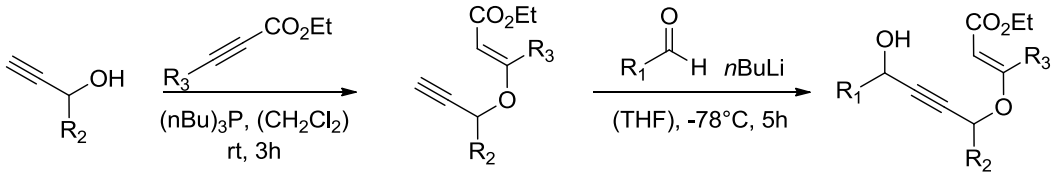
I-72a: R_1 = Me; R_2 = Et; R_3 = Me 45%
I-72b: R_1 = Me; R_2 = *n*Pr; R_3 = Me 35%
I-72c: R_1 = Me; R_2 = *t*Bu; R_3 = Me 57%
I-72d: R_1 = Me; R_2 = Ph; R_3 = Me 44%
I-72e: R_1 = *i*Bu; R_2 = Et; R_3 = Me 67%
I-72f: R_1 = *i*Bu; R_2 = Ph; R_3 = Me 72%
I-72g: R_1 = Ph; R_2 = Et; R_3 = Me 62%
I-72h: R_1 = Ph; R_2 = Ph; R_3 = Me 39%
I-72i: R_1 = Me; R_2 = Et; R_3 = H 80%
I-72j: R_1 = Me; R_2 = Et; R_3 = Ph 27%
I-72q: R_1 = H; R_2 = Et; R_3 = Me 61%
I-72r: R_1 = H; R_2 = Ph; R_3 = Me 66%

Scheme 20. Synthesis of substrates for the catalyzed cascade reaction.

Propargylic alcohol **I-75** was protected as a THP ether followed by the addition to an aldehyde, after which the phosphine catalyzed *Michael*-type addition to an acetylene[52]

gave the propargylic vinyl ether **I-78**, which was deprotected under mild acidic conditions with PPTS to produce the starting material (**I-72**) requisite for the catalyzed domino reaction.

To broaden the scope of substrates and to shorten their access, a two-step synthesis was implemented. The propargyl alcohol **I-79** was directly added to the acetylene via the phosphine catalyzed *Michael*-type addition, the final addition to an aldehyde gave the desired substrate for the catalysis (Scheme 21).



I-79a: R_2 = Me
I-79b: R_2 = H

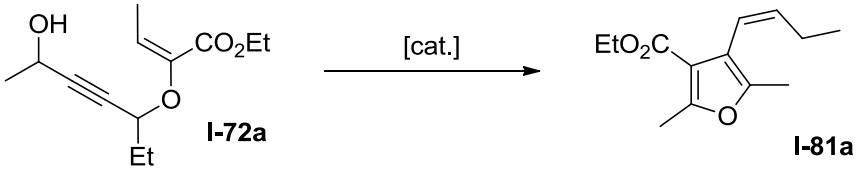
I-80a: R_2 = Me; R_3 = Me 71%
I-80b: R_2 = H; R_3 = Me 80%

I-72k: R_1 = Et; R_2 = Me; R_3 = Me 37%
I-72l: R_1 = Ph; R_2 = Me; R_3 = Me 44%
I-72m: R_1 = 4-F-C_6H_4; R_2 = Me; R_3 = Me 34%
I-72n: R_1 = 4-MeO-C_6H_4; R_2 = Me; R_3 = Me 25%
I-72o: R_1 = Et; R_2 = H; R_3 = Me 38%
I-72p: R_1 = Ph; R_2 = H; R_3 = Me 32%

Scheme 21. Shorter approach to the substrates.

3.2.2) Propargyl-*Claisen* Rearrangement and Condensation

With regard to the previous results published in the group, the standard substrate (R_1 = Me, R_2 = Et) was first subjected to silver and gold salts as catalysts. To our surprise, an unexpected furan appeared to be formed in a good yield, particularly with the silver salts (Table 3).

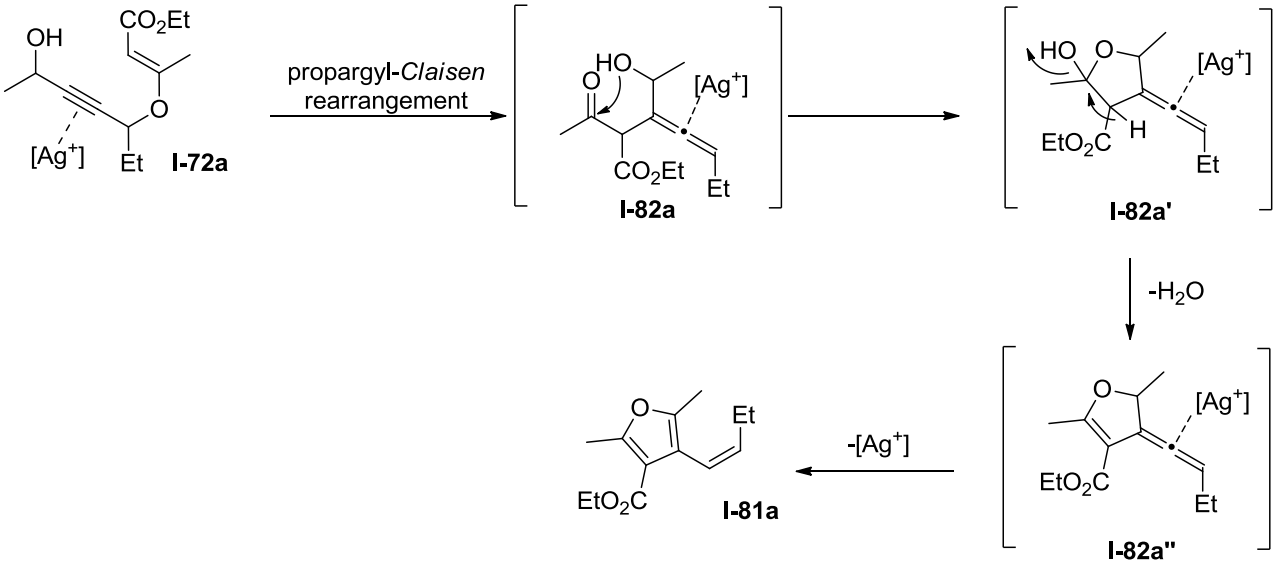


Entry	Cat. (10 mol%)	Acid (mol%)	Solvent (0.1 M)	Temp. (°C)	Time (h)	Yield[a] (%)	*Z/E*
1	$AgSbF_4$		CH_2Cl_2	rt	24	74	7/2
2	AuCl		CH_2Cl_2	rt	3	23	7/2
3	$(PPh_3)AuNTf_2$		CH_2Cl_2[b]	rt	24	32	5/1
4	$AgBF_4(CN)_2$		CH_2Cl_2	rt	24	32	7/2
5	AgOTf		CH_2Cl_2	rt	24	76	4/1
6	AgOTf	$SnCl_4$ (10)	CH_2Cl_2	rt	3	0	
7	AgOTf	$ZnCl_2$ (10)	CH_2Cl_2	rt	48	traces	
8	AgOTf	*t*BuCl (20)	CH_2Cl_2	rt	3	9	
9	$AgBF_4$		CH_2Cl_2	rt	48	88	4/1
10	$AgBF_4$[c]		CH_2Cl_2	35	24	87	4/1
11	$AgBF_4$		CH_2Cl_2	35	1	91	3/1
12			DCE	60	24	0	
13			DCE	90	48	12	7/1
14			Toluene	120 (Mw)	5	24, P_2	

a: Isolated yield after flash chromatography; b: 0.5 M; c: 2 mol%.

Table 3. Screening of conditions.

A possible explanation for the formation of the tetra-substituted furan could reside in a sequence propargyl-*Claisen* rearrangement/condensation. After activation of the alkyne moiety in **I-72a** by coordination with the silver-catalyst, which triggers the propargyl-Claisen rearrangement, a condensation of the alcohol into the newly formed ketone probably occurs instead of the planned 5-*endo* heterocyclization. Final protodemetalation and aromatization give the tetra-substituted furan **I-81a** (Scheme 22).



Scheme 22. A surprising result.

As in most cases, only the condensation product was isolated, it appears that the condensation is quicker than a possible catalyzed heterocyclization. *Lewis* acids ($SnCl_4$, $ZnCl_2$), or hidden *Brønsted* acid[53] were thought to help the condensation of the alcohol into the ketone (Entry 6-8, Table 3). Instead, other products were isolated: unfortunately, a proper characterization was not completed due to the difficulty of obtaining pure samples. Thermic conditions were also tested, and formation of the furan was observed at 90°C. However, after 48h at this temperature, only 12% of the product was isolated (Entry 13, Table 3). Using microwave and heating the propargylic vinyl ether at 120°C for 5h also gave the tetrasubstituted furan in mixture with another product, **P_2** (Figure 2). The latter probably arises from a lactonization subsequent to the propargyl-*Claisen* rearrangement.

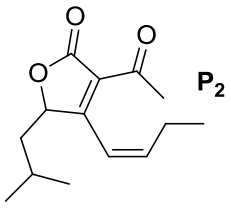


Figure 2. Propargyl-*Claisen* rearrangement and lactonization.

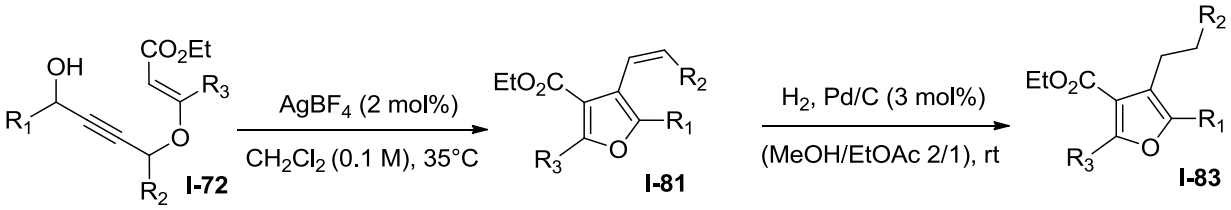
To our knowledge, no other work has reported this sequence of reaction and since polysubstituted furans represent an important building block, further investigations were

carried out. Silver(I) tetrafluoroborate (Entry 9, Table 3) emerges to be the best catalyst for this reaction. After optimization of the conditions, the polysubstituted furan was produced in 87% yield in 24h in dichloromethane at 35°C, with 2 mol% silver(I) tetrafluoroborate (Entry 10, Table 3). However, the product can only be isolated as a mixture of *E* and *Z* isomers. To facilitate the analytical analysis, it was decided to reduce the double bond.[2] Moreover, it is worth noticing that a 10 mol% loading in silver salt delivered the product in 91% yield in 1h at 35°C (Entry 11, Table 3). However, since the yields are similar, a low catalyst loading was favoured over the reaction time.

3.2.3) Scope of the domino sequence

The selected reaction conditions were applied to test the scope of substrates. A library of tri- and tetra-substituted furans was easily synthesized. Alkyl (Entry 1-2-3, Table 4) and aryl (Entry 4-7-8, Table 4) substituted furans were obtained in good yields. Nevertheless, a more crowded alkyl substituent reduces the performance of the reaction (Entry 5- 6, Table 4). Moreover, it seems that the presence of a phenyl moiety in R_1 is a drawback for the reaction, contrary to its presence in R_2. The presence of a donor substituent at the vinyl position seems to be of prime importance. Indeed when R_3 = H (Entry 9, Table 4) the reaction occured very slowly (72 hours) with 6 mol% $AgBF_4$ instead of 2 mol%. Gold (I) chloride was also tested with substrate **I-72i**. Although the complete conversion was accelerated (24 hours), the yield stayed at 31%.

[2] 2D-NMR studies on p. 149.

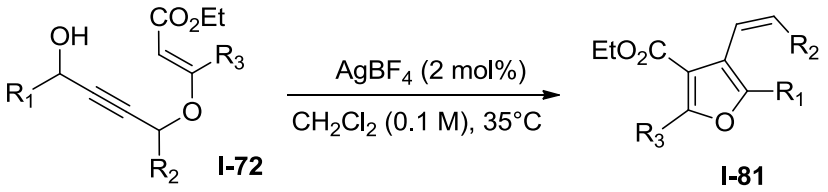


Entry	Substrate	R_1	R_2	R_3	Time (h)	Yield[a] (%)
1	I-72a	Me	Et	Me	14	72
2	I-72b	Me	*n*Pr	Me	14	68
3	I-72c	Me	*t*Bu	Me	14	66
4	I-72d	Me	Ph	Me	14	78
5	I-72e	*i*Bu	Et	Me	14	64
6	I-72f	*i*Bu	Ph	Me	14	60
7	I-72g	Ph	Et	Me	14	30
8	I-72h	Ph	Ph	Me	14	65
9	I-72i	Me	Et	H	72	33[b]
10	I-72j	Me	Et	Ph	22	68
11	I-72k	Et	Me	Me	18	49
12	I-72l	Ph	Me	Me	5	25
13	I-72m	4-F-C_6H_4	Me	Me	21	decomposition
14	I-72n	4-MeO-C_6H_4	Me	Me	2	decomposition
15	I-72o	Et	H	Me	21	43[c]
16	I-72p	Ph	H	Me	19	36[c]
17	I-72q	H	Et	Me	18	53
18	I-72r	H	Ph	Me	14	60

a: Isolated yield after flash chromatography; b: 6 mol% $AgBF_4$; c: The hydrogenation of the double bond was not performed.

Table 4. Substrate scope.

In some cases of poor yields, the products were isolated directly after cyclization, in order to define if the hydrogenation of the double bond or the sequence of rearrangement-condensation was responsible for the result. As illustrated in Table 5, with the exception of the entries 1 and 6, the yields were already low after the domino sequence.



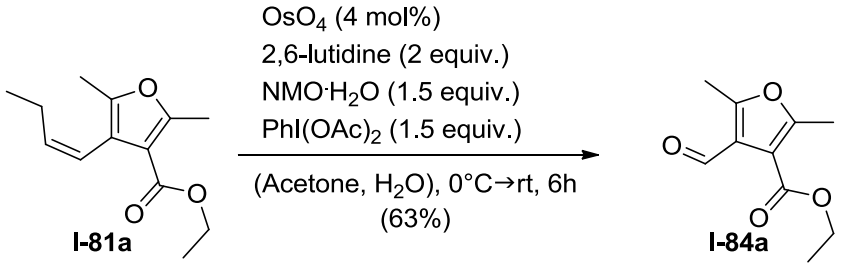
Entry	Subtrate	R_1	R_2	R_3	Time (h)	Yield[a] (%)
1	I-72f	*i*Bu	Ph	Me	15	75 (*Z*/*E* 2 :1)
2	I-72g	Ph	Et	Me	15	34 (*Z*/*E* 3 :1)
3	I-72k	Et	Me	Me	16	56 (*Z*/*E* 2.5 :1)
4	I-72l	Ph	Me	Me	22	31 (*Z*/*E* 3 :1)
5	I-72q	H	Et	Me	16	45 (*Z*/*E* 6 :1)
6	I-72r	H	Ph	Me	15	70 (*Z*/*E* 100 :1)

a: Isolated yield after flash chromatography.

Table 5. Scope limitation.

3.2.4) Further developments

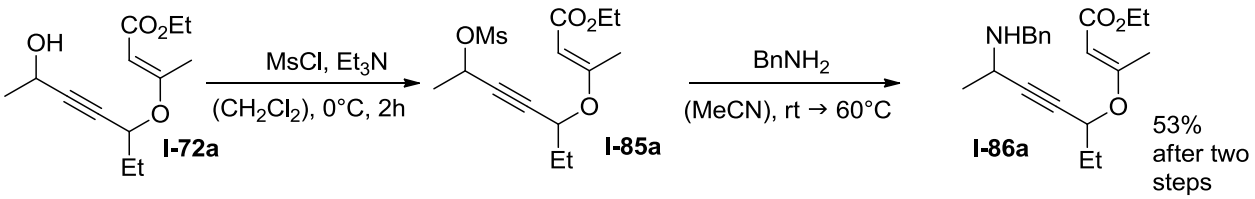
To further explore the functionalization of the furan, an oxidative cleavage was performed on the double bond. Using conditions developed by Nicolaou *et al.*,[54] the aldehyde functionalized tetra-substituted furan was introduced (Scheme 23).



Schema 23. Oxidative cleavage.

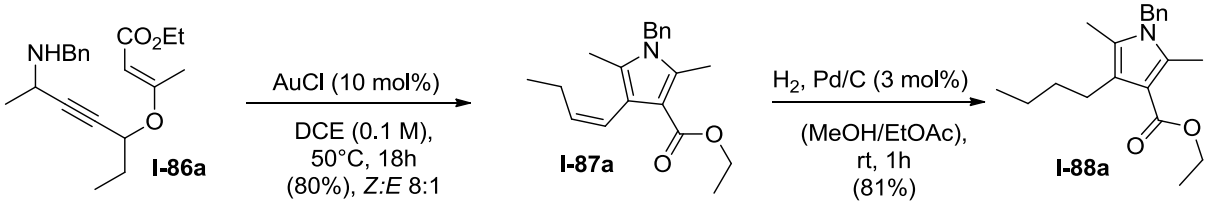
With these encouraging results, pyrrole synthesis was envisioned using the same process. With regard to the mechanism described for the furan formation, a new substrate containing a nitrogen moiety was formed. Starting from substrate **I-72a**, the novel nitrogen

building block was produced in two steps: the secondary alcohol was transformed into a mesylate, which was then easily substituted by benzylamine (Scheme 24).



Scheme 24. Substrate production for pyrrole synthesis.

The amino compound was intended to react under the same conditions to give the corresponding pyrrole derivative. However, only traces were observed. By submitting **I-86a** to gold(I) chloride in DCE at 50°C, we were able to isolate desired pyrrole **I-87a** in a good yield (80%). The hydrogenation of the double bond delivered **I-88a** in 81% yield (Scheme 25).



Scheme 25. Synthesis of tetrasubstituted pyrrole.

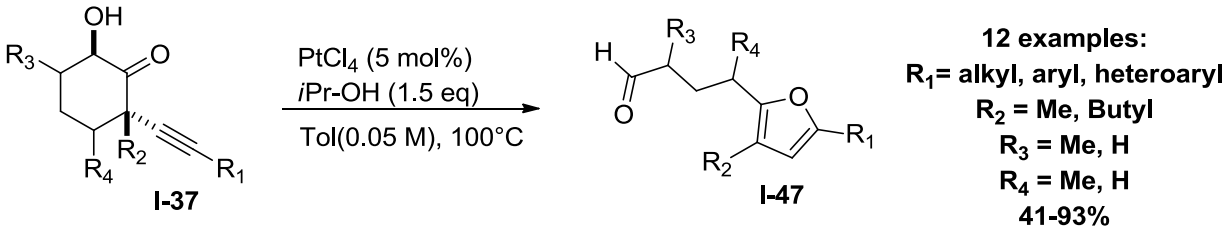
However, it seems that the benzyl substituent is essential for a good yield. Switching from a benzyl to a butyl group, the yield was reduced dramatically to 29%.

To conclude, a silver-catalyzed cascade reaction was developed and implemented as a convenient process to deliver tri- and tetra-substituted furans with the side chain available for further functionalization. In addition to the furans, the sequence also gave access to polysubstituted pyrroles.

4) Summary

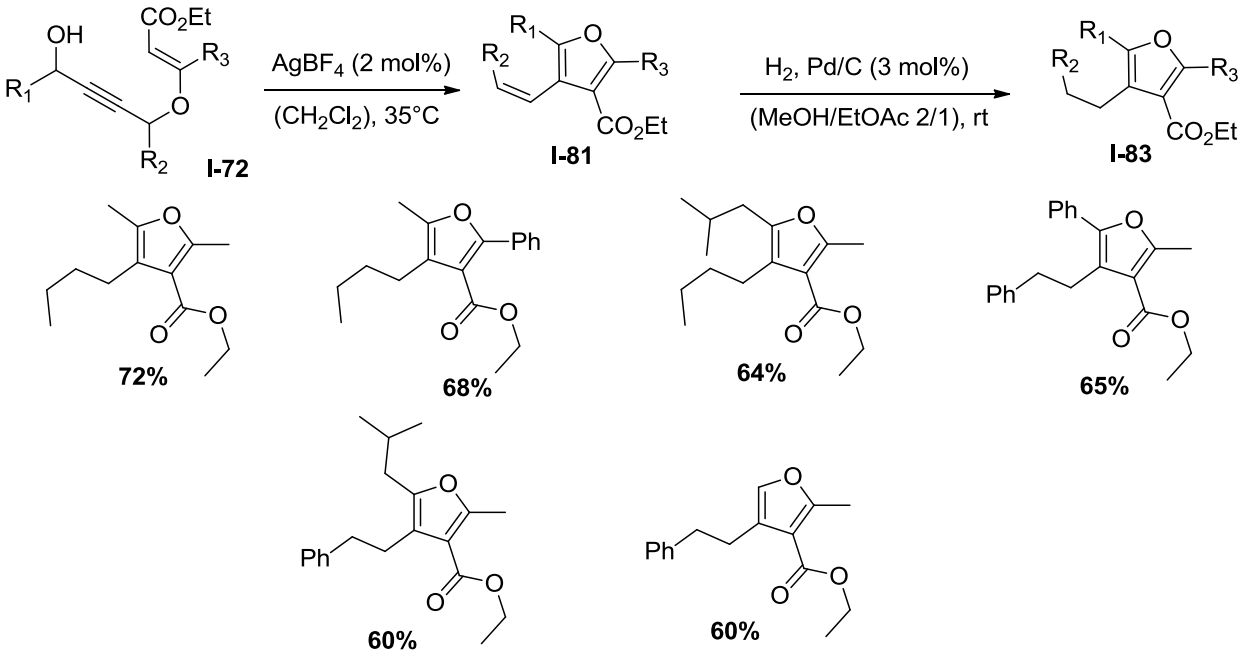
As part of the project on the cascade reactions initiated by π-activation, two sequences were developed to produce tri- and tetra-substituted furans.

On one hand, by exploring the cascade process of heterocyclization/1,2-migration to provide 2,3-dihydrofurans, an unexpected furan was isolated. Nevertheless, as poly-substituted furans are interesting target structures, the catalyzed route from the cyclohexanones **I-37** was investigated and a new and convenient way to access tri-substituted furans with an aldehyde-containing side chain was developed (Scheme 26). The sequence is catalyzed by $PtCl_4$ and probably proceeds via a heterocyclization followed by 1,2-shift ring-contraction and a *Grob*-type fragmentation.[55]



Scheme 26. Platinum-catalyzed cascade reaction, heterocyclization /1,2-migration.

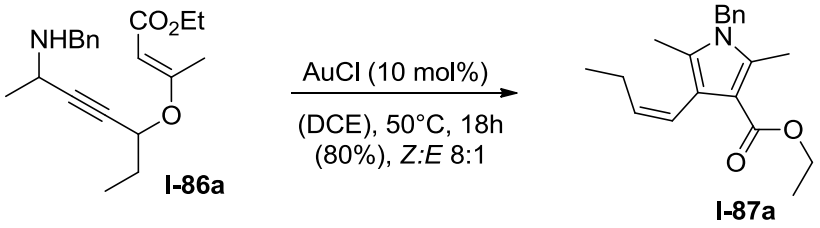
On the other hand, in the realm of the study on catalyzed propargyl-*Claisen* rearrangements launched in the *Kirsch* group, a sequence of propargyl-*Claisen* rearrangement/condensation on propargylic vinyl ethers has generated tri- and tetra-substituted furans. The domino reaction was effectively catalyzed by $AgBF_4$, and to facilitate the analytical analysis, the process was terminated by hydrogenation of the double bond (Scheme 27).



Scheme 27. Silver-catalyzed propargyl-*Claisen* rearrangement.

However, the method presents some limitations in the case of phenyl moiety in R_1 or in the case of a terminal double bond, where the yields drop dramatically to 30-40%.

In addition to the furan formation, a pyrrole synthesis was envisioned using the same process. Nevertheless, it required 10 mol% AuCl in DCE at 50°C to be effective (Scheme 28). *N*-benzyl pyrrole was isolated in an excellent 80% yield. Unfortunately replacing the benzyl group by a butyl group, the yield was reduced to 29%.

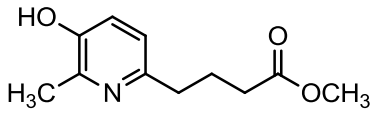


Scheme 28. Synthesis of tetrasubstituted pyrrole.

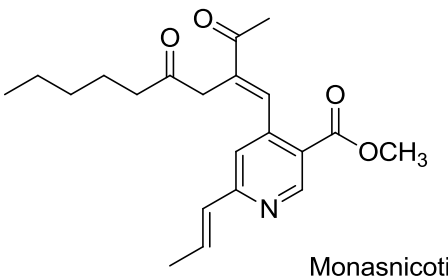
III) Catalyzed cascade reactions, a way toward pyridine derivatives

1) Introduction

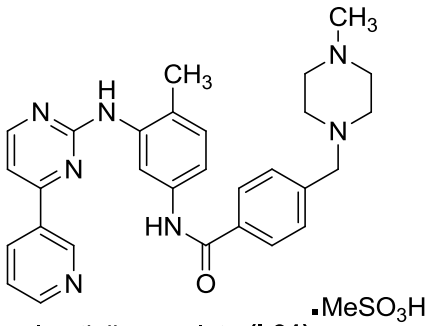
Like furans, pyridines are also a significant class of heterocycles. They are present in numerous natural products, active pharmaceuticals and functional materials.[56] To name some examples, the alkaloids methyl multijuguinate[57] (**I-89**) and monasnicotinate A[58] (**I-90**), were recently isolated from a Brazilian tree and fermented rice respectively. Pyridine derivatives for pharmaceutical uses include, for example, imatinib mesylate (Gleevec)[59] (**I-91**) prescribed for chronic myelogenous leukemia or the asthma treatment drug, tripelennamine (Pyribenzamine)[60] (**I-92**).



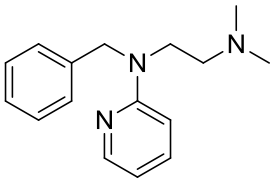
Methyl multijuguinate **(I-89)**



Monasnicotinate A **(I-90)**



Imatinib mesylate **(I-91)**

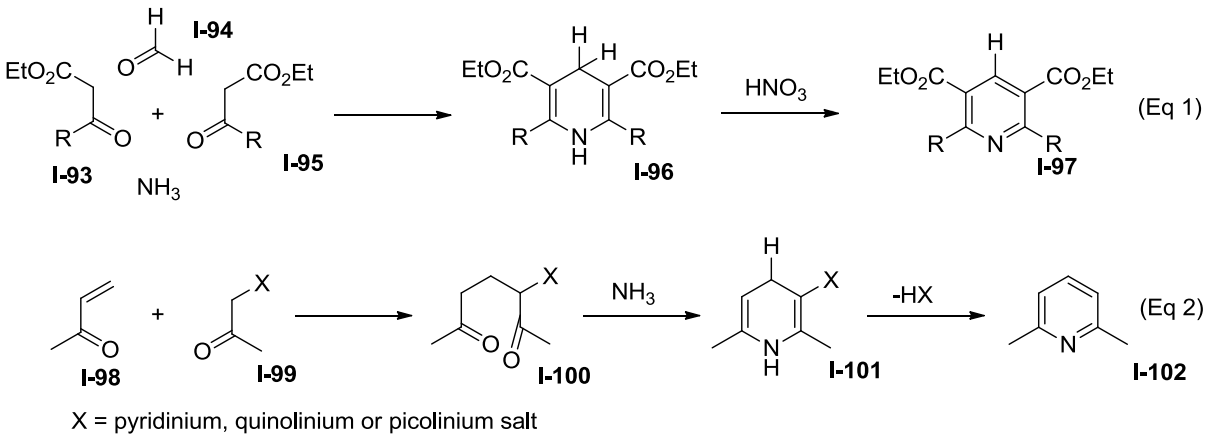


Tripelennamine **(I-92)**

Figure 3. Presentation of selected pyridine-containing compounds.

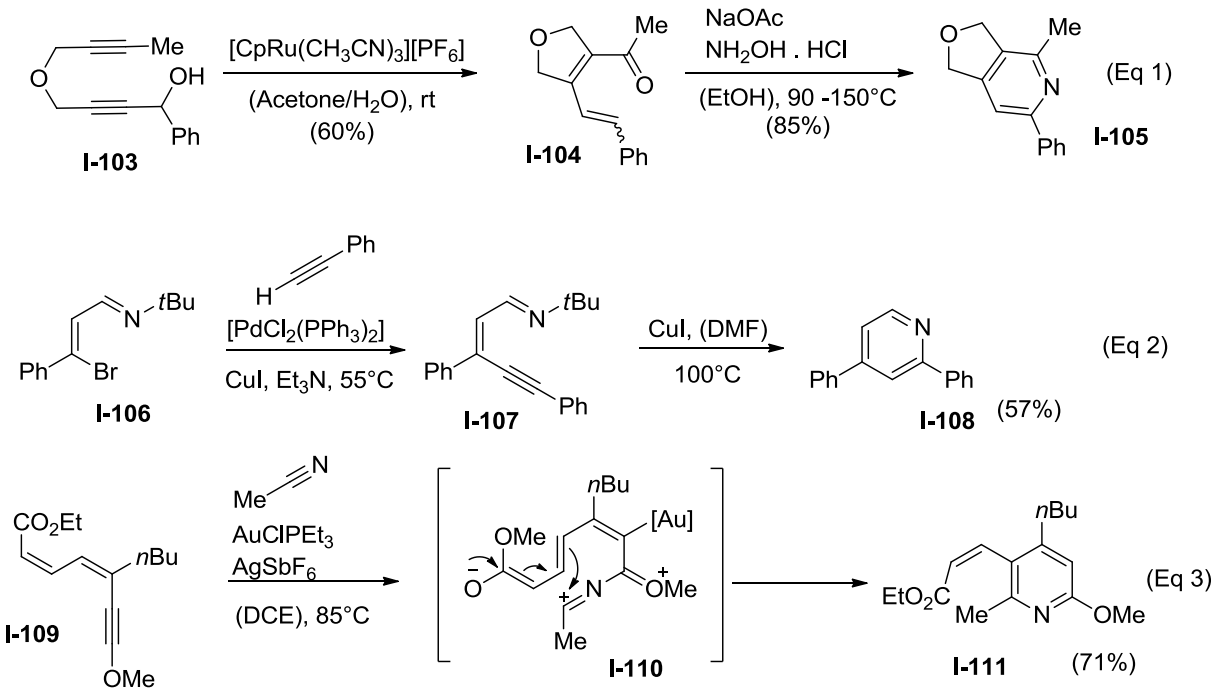
Since the first isolation of the pyridine base picoline by *Anderson* from bone oil in 1846,[61] and the structure elucidation by *Körner*[62] (1869) and Dewar[63] (1871), the pyridine derivatives have gained in commercial importance. The production by coal tar distillation

was no longer adequate and synthetic methods were implemented. Most of them were condensation reactions between an amine and a carbonyl compound as the *Hantzsch* pyridine synthesis[64] (Scheme 29, Eq 1) or the [3 + 2+ 1] *Kröhnke* synthesis[65] (Scheme 29, Eq 2).



Scheme 29. Condensation methods.

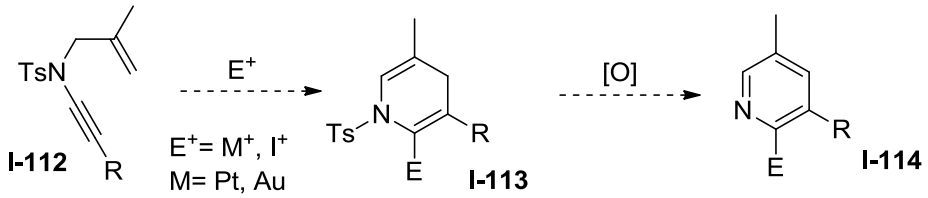
Modern routes do not banish condensation approaches: nevertheless, the current trend is the transition-metal-catalyzed process.[66] Amongst several groups, *Trost* and coworkers make use of a ruthenium-catalyzed cascade reaction (Scheme 30, Eq 1).[67] The strategy is based on a metal-catalyzed cycloisomerization followed by a 6π–electro-cyclization. This last stage is a rather common approach to terminate the cascade sequence and to provide the pyridine derivatives.[68] For his part, *Larock et al.* have developed a two-step synthesis via palladium/copper catalyzed procedure (Scheme 30, Eq 2),[69] and *Barluenga* and coworkers have devised a [4 + 2] route through a gold-catalyzed dehydro-aza-*Diels-Alder* reaction (Scheme 30, Eq 3).[70]



Scheme 30. Transition-metal catalyzed methods.

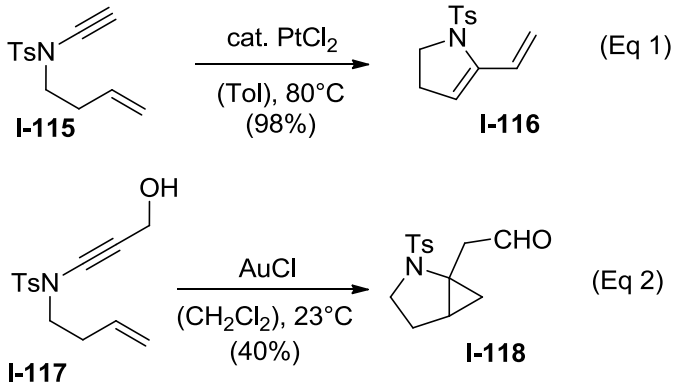
2) Pyridine synthesis, a novel approach

Despite the large development of transition-metal-catalyzed or electrophilically induced cascade reactions to synthesize *N*-heterocycles,[71] their application to the pyridine synthesis is rather rare. With the desire to rectify this tendency, we decided to launch a study on the activity of ene-ynamides toward π-acids to access pyridine derivatives. Keeping in mind the previous works achieved in the *Kirsch* group on enynes,[72] and in particular the one, demonstrating that 1,5-enynes can undergo a 6-*endo* cyclization to reach a large scope of polysubstituted benzenes,[73] we believed that *N*-allyl-ynamides should be the elements of choice to produce pyridines. The envisaged cascade sequence is similar to the one applied for the polysubstituted benzenes, namely a 6-*endo* carbocyclization and subsequent oxidative aromatization (Scheme 31).



Scheme 31. Planned sequence for pyridine synthesis.

Although methods using ene-ynamides are sparse,[74] two processes based on the activation of ene-ynamide π-system have convinced us of the power of this entity.[75] *Malacria* and coworkers demonstrated that 1,6- and 1,7-ene-ynamides can undergo platinum-catalyzed cycloisomerization (Scheme 32, Eq 1) via activation of the alkyne and [2+2] cycloaddition. In addition, *Cossy et al*. reported a 1,6-ene-ynamide gold-catalyzed cycloisomerization (Scheme 32, Eq 2).

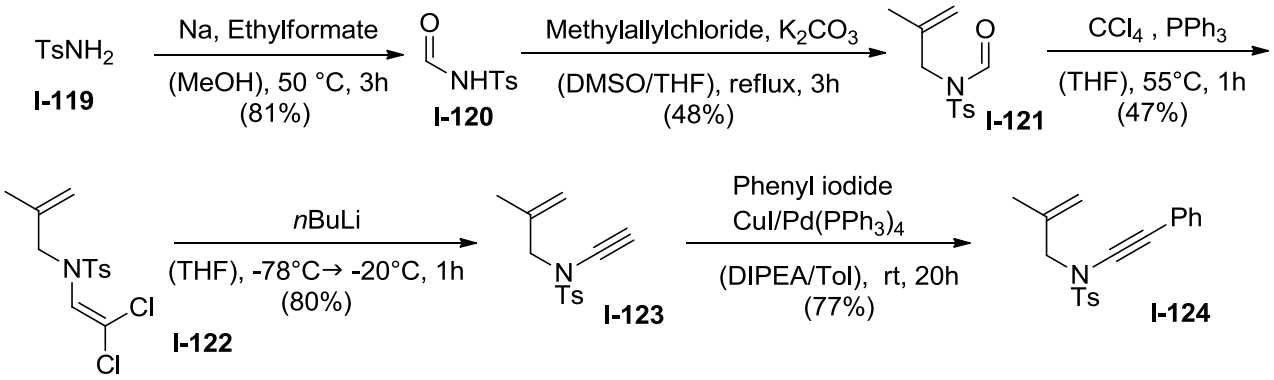


Scheme 32. Examples of ene-ynamide applications.

3) Results and Discussion

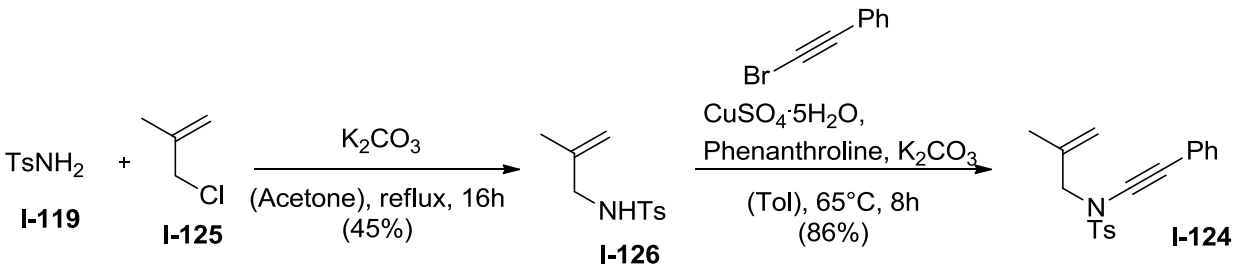
3.1) Substrate synthesis

Various routes for the synthesis of ene-ynamides are known.[76] *Brückner*'s procedure[76b] was first chosen due to it's flexibility in obtaining a large variety of substrates (Scheme 33). The commercially available tosylamide is formylated, followed by alkylation to obtain *N*-allyl formamide **I-121**. One must note that the inverse process, *i.e*. alkylation followed by formylation, failed in case of tosyl protection of the amine. Compound **I-121** was then converted to *N*-allyl ynamide via a *Corey-Fuchs* protocol.[77] A final *Sonogashira* cross-coupling reaction allowed us to functionalize the terminal acetylene carbon.[78]



Scheme 33. Synthesis of the starting material I-124.

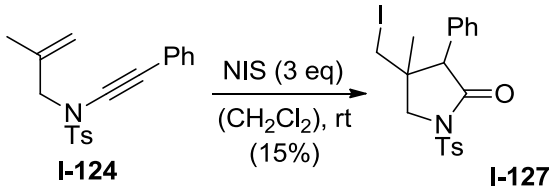
We also used *Hsung*'s alternative.[76a] The substrate production was reduced to a two-step synthesis (Scheme 34). After alkylation, amide **I-126** was converted to ynamide via a cross-coupling reaction of the amide with bromo-phenylacetylene using a Cu(II) catalyst.



Scheme 34. Alternative route for the subtrate synthesis.

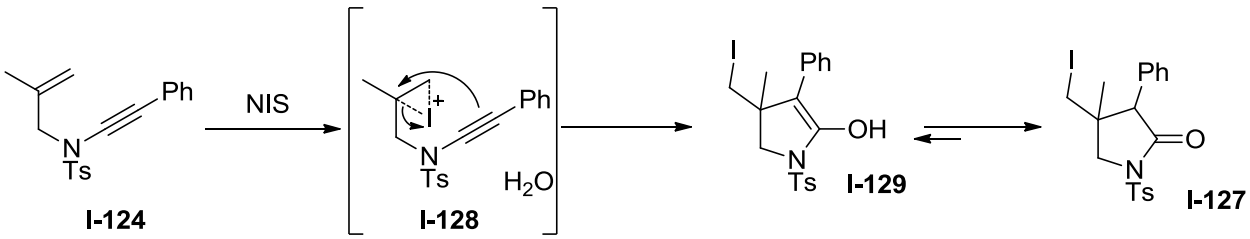
3.2) Studies on the pyridine synthesis

Based on the previous work on 1,5-enynes to access benzene derivatives using metal-free conditions[73] and the attraction for simple reaction conditions, we started our journey by testing iodocarbocyclization protocols.[79] Treatment of ene-ynamide **I-124** with NIS in dichloromethane did not produce the desired pyridine, but a lactam compound **I-127** (Scheme 35).



Scheme 35. An unexpected result.

As shown in Scheme 36, contrary to the anticipated mechanism, NIS seems to activate the olefin rather than the alkynyl moiety. The iodonium ion triggered then the 5-*exo* cyclization and the newly formed cationic species was trapped by a nucleophile, here a water molecule, and tautomerisation delivered finally **I-127**.



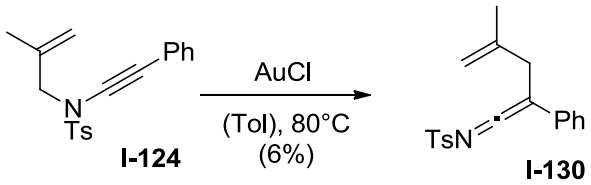
Scheme 36. A proposed mechanism for the formation of lactam I-127.

Although this result was not the anticipated one, it could be an interesting road into the production of lactam derivatives. However, further investigations in this path revealed that the route is not robust since the isolation of **I-127** was not reproduced. As the metal-free pathway was fruitless, transition-metal catalysts were tested (Table 6).

Entry	**Catalyst** (5 mol%)	**Solvent** (0.1 M)	**Temp. (°C)**	**Results**
1	AuCl	CH_2Cl_2	rt → 50	SM
2	AuCl	Toluene	80	**I-130**
3	$(PPh_3)AuCl/AgSbF_6$	CH_2Cl_2	rt → 50	SM
4	$(PPh_3)AuCl/AgSbF_6$	Toluene	80	Decomposition
5	$PtCl_2$	Toluene	80	Decomposition

Table 6. Screening of transition-metal catalysts.

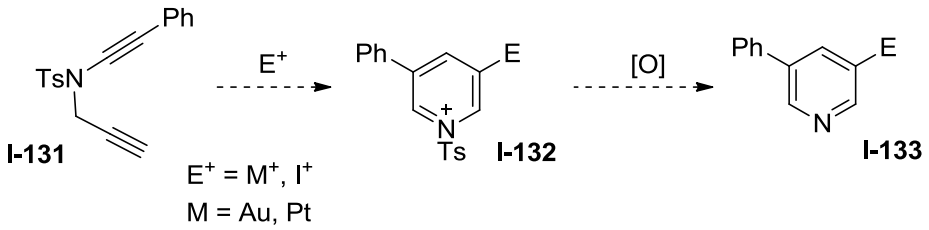
Standard conditions for "π-acids" were employed without significant results. At room temperature and slightly higher temperature (50°C), no reactivity was observed. However, treatment of *N*-allyl ynamide **I-124** with gold(I) chloride in hot toluene allowed us to isolate a new product, ketenimine **I-130** (Scheme 37).



Scheme 37. Formation of an unwished ketenime.

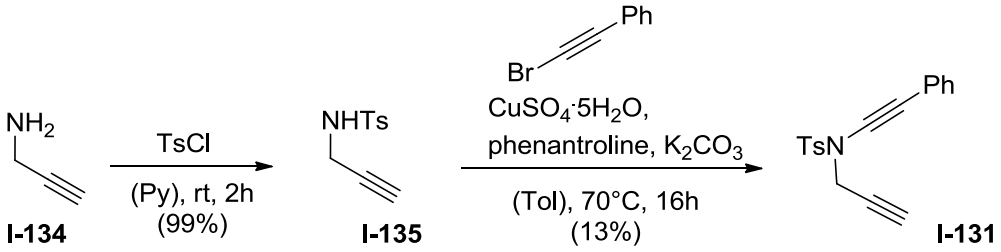
An aza-*Claisen* rearrangement[80] is most likely responsible for this result. The formation of ketenimines[81] via a 3-aza-*Claisen* rearrangement of *N*-allyl ynamides has already been demonstrated by *Hsung et al*. in the case of thermal or palladium-catalyzed conditions.[82] Recognizing this, no further investigation was continued in this direction.

At this point, substrate **I-124** appeared to be unsuitable for the planned pyridine synthesis. It was then decided to change the orientation and to start over with a new kind of substrate. The novel strategy was based on a propargyl ynamide building block, where activation of one of the alkyne moieties should trigger a 6-*endo* cyclization and oxidative aromatization should deliver the pyridine derivative (Scheme 38).



Scheme 38. Novel strategy for pyridine synthesis.

As illustrated in Scheme 39, the synthesis of substrate **I-131** proceeded by using *Hsung*'s protocol, which was less effective with a propargyl amide than with an allyl amide.



Scheme 39. Synthesis of substrate I-131.

Various conditions were screened (Table 7), transition-metal-catalyzed as well as metal free conditions. In both cases, the results were clearly unsatisfactory. With transition-metal catalysts, no reaction occurred at room temperature or at slightly higher temperatures (50°C), and heating up to 80°C resulted in decomposition of the starting material. For gold(I) chloride (Entry 2, Table 7), a new compound was isolated without complete identification. Nevertheless it appeared that the primary alkyne moiety did not react. In the case of metal-free conditions (Entry 8, Table 7), the diacetylene was reactive toward NIS, unfortunately none of the isolated compounds corresponded to a pyridine derivative.

Entry	**Catalyst** (5 mol%)	**Solvent** (0.1 M)	**Temp. (°C)**	**Results**
1	AuCl	CH_2Cl_2	rt →50	SM
2	AuCl	Toluene	80	Primary alkyne still present
3	$PtCl_2$	Toluene[a]	80	Decomposition
4	$PtCl_4$	Toluene[a]	80	Decomposition
5	$(PPh_3)AuCl/AgSbF_6$	CH_2Cl_2	rt	SM
6	$(PPh_3)AuCl/AgSbF_6$	Toluene	80	Decomposition
7	CuI	DMF	80	-
8	NIS[b]	CH_2Cl_2[a]	rt	-

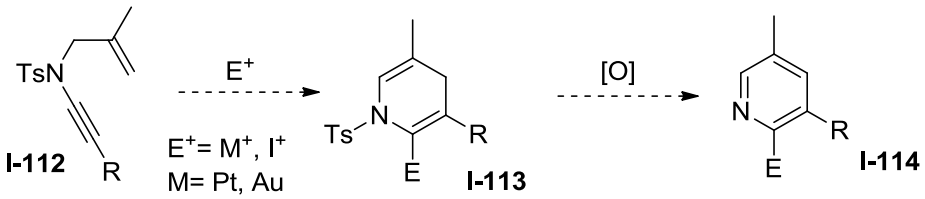
a: 0.07 M; b: 2 equiv.

Table 7. Tests on I-131 for pyridine construction.

In light of these results, the investigations on the subject were stopped. Both imagined substrates seemed to be powerless to reach pyridine derivatives. A new modeling of the substrate appears necessary, for example new protecting groups for the amine or other substituents attached to the π-system. However, the latter also means a reduction of the reaction scope.

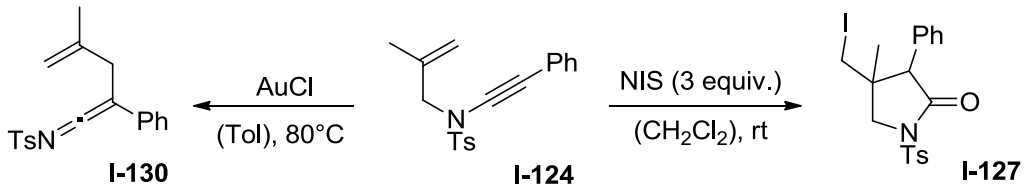
4) Summary

In our effort to develop new strategies for heterocycle synthesis, a cascade sequence to access pyridine derivatives was planned. Based on previous works achieved in the *Kirsch* group on enynes,[72] and in particular on the one demonstrating that 1,5-enynes can undergo a 6-*endo* cyclization to reach a large scope of polysubstituted benzenes,[73] *N*-allyl ynamides were formed to provide a library of pyridine backbones (Scheme 40).



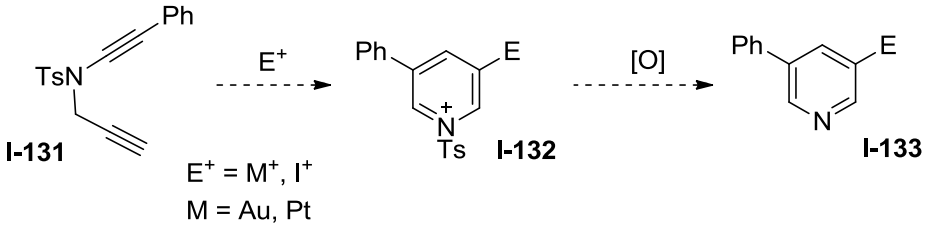
Scheme 40. Planned sequence for pyridine synthesis.

Unfortunately, as the first tests were carried out, it appeared that substrate **I-124** was not well conceived to produce pyridines. Indeed, the screened conditions did not give significant results. They either led to complete recovery of the starting material or complete decomposition. In two different cases, products were isolated, nevertheless none of them were the expected pyridine derivative. In the first case, contrary to the anticipated mechanism, NIS seemed to activate the olefin rather than the alkynyl moiety. Then, as planned, the iodonium ion probably triggered the 5-*exo* cyclization and the newly formed cationic species was trapped by a water molecule, tautomerization delivered finally lactam **I-127** (Scheme 41). In the second case, the substrate **I-124** with a catalytic presence of gold(I) chloride in hot toluene provided a new product, ketenimine **I-130**, most likely due to an aza-*Claisen* rearrangement of the *N*-allyl-ynamide (Scheme 41).



Scheme 41. Formation of undesired products.

At this point, a novel strategy was envisioned based on a propargyl ynamide substrate. Similarly, activation of one of the alkyne moieties should trigger a 6-*endo* cyclization and oxidative aromatization should deliver the pyridine derivative (Scheme 42).



Scheme 42. Novel strategy for pyridine synthesis.

Various conditions were tried: transition-metal-catalyzed as well as metal free conditions. In both cases, no positive result emerged.

Together, tested substrates and conditions seemed to be powerless to reach pyridine derivatives. A new modeling of the substrate appears necessary, like a new protecting group for the amine or other substituents attached to the π-system. However, the latter also means a reduction of the reaction scope. Consequently, no further investigation has been conducted on this project.

IV) Experimental part

1) General procedures

Air and water sensitive reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere. Air and moisture sensitive reagents were introduced via argon or nitrogen pre-filled plastic syringes, dry glass syringes or cannula.

At low temperature, the reactions were carried out in a *dewar* filled with ice-water (0°C) or acetone/dry ice (-78°C). Under 0°C, reactions were accomplished with a cryostat (Thermo Haake, EK90).

1.1) Solvents and reagents

Dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), tetrahydrofuran (THF) were dried using a solvent purification system SPS-800 from M.Braun GmbH:

- CH_2Cl_2: *Merck* Emsure®, p. a., 99.8%, <0.03% H_2O, Column 2 × MB-KOL-A.
- Et_2O: *Merck* Emsure®, p. a., 99.7%, <0.03% H_2O, Column 1 × MB-KOL-A, 1 × MB-KOL-M Typ 2.
- THF: *Merck* Emsure®, p. a., 99.8%, <0.03% H_2O, Column 2 × MB-KOL-M Typ 2.

Other solvents and reagents were purchased dry:

- Acetonitrile: *Acros Organics*, Extra Dry, 99.9% over molecular sieves, < 0.005% H_2O.
- Dimethylsulfoxide: *Sigma-Aldrich*, puriss., 99.5% over molecular sieves, < 0.01% H_2O or *Acros Organics*, Extra Dry, 99.9% over molecular sieves, < 0.005% H_2O.
- Methanol: *Acros Organics*, Extra Dry, 99.8% over molecular sieves, < 0.005% H_2O.

- *N,N*-Dimethylformamide: *Sigma-Aldrich*, puriss., 99.5% over molecular sieves, < 0.01% H_2O or *Acros Organics*, Extra Dry, 99.9% over molecular sieves, < 0.005% H_2O.
- Toluene: *Acros Organics*, Extra Dry, 99.8% over molecular sieves, < 0.005% H_2O.
- 1,2-dichloroethane: *Acros Organics*, Extra Dry, 99.8% over molecular sieves, < 0.005% H_2O.
- N,N-Diisopropylethylamine: *Sigma-Aldrich*, puriss., 99.5% over molecular sieves, < 0.05% H_2O.
- Pyridine: *Acros Organics*, Extra Dry, 99.8% over molecular sieves, < 0.005% H_2O or *Sigma-Aldrich*, puriss., 99.8% over molecular sieves, < 0.005% H_2O
- Triethylamine: Distillated from molecular sieves and used immediately after distillation.

Solvents used for thin layer chromatography (TLC), flash chromatography or work up (CH_2Cl_2, Et_2O, THF, ethyl acetate, acetone, ethanol, methanol, pentanes, cyclohexane, petroleum ethers) were simply distilled. All other solvents and reagents were purchased from *Aldrich, Acros*, *Fluka* and *Merck* and used without further purification.

1.2) Analytical techniques and apparatus

Analytical thin-layer chromatography (TLC)

TLC was performed with *Merck* Kieselgel 60 F_{254}, 0.25 mm precoated glass-backed TLC plates. TLC plates were visualized using UV_{254}, cerium ammonium molybdate (CAM) solution, or potassium permanganate ($KMnO_4$) solution. CAM solution was prepared using 2.0 g cerium (IV) sulfate, 25.0 g ammonium heptamolybdate, 50 mL H_2SO_4 and 300 mL water. KMnO4 was prepared using 3 g potassium permanganate, 20.0 g potassium carbonate and 5 mL 5% sodium hydroxide in 300 mL water.

Flash Chromatography

Flash chromatography was carried out using 60 silica gel (40-63 µm, 230-400 mesh ASTM) available from *Merck*.

Gas chromatography (GC and GC-MS)

GC-MS spectra were recorded on an Agilent gas chromatography, Agilent Technologies 7890 A equipped with column HP-5MS (30 m x 250 µm x 0.25 µm), an Agilent Technologies 5975C inert MSD with triple-axis detector and helium as the carrier gas.

Infrared spectroscopy (IR)

Infrared spectra were recorded on a JASCO IR-4100 spectrometer. Samples were analysed neat with attenuated total reflection (ATR). Characteristic bands are reported in wave length (cm-1).

Mass Spectroscopy (MS)

Mass spectroscopic data were recorded using Finnigan MAT 8200 and an Agilent Technologies 5975C (electron ionization, EI 70 eV), or using a MAT 95S and a Bruker micrOTOF Agilent 1100 Series (high resolution mass spectroscopy, HRMS).

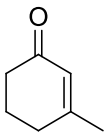
Nuclear Magnetic Resonance Spectroscopy (NMR)

^{1}H NMR spectra were obtained on Bruker 600 MHz FT-NMR, 400 Mhz FT-NMR, 500 MHz FT-NMR, 360 MHz FT-NMR and 250 MHz FT-NMR spectrometers. ^{13}C NMR spectra were recorded at 151.1 Mhz, 100.7 MHz, 90.6 MHz or 62.9 Mhz. Chemical shifts are reported in ppm relative to solvent signal. Multiplicity is indicated as follows: s (singlet); d (doublet); t (triplet); m (multiplet); dd (doublet of doublets).

2) Catalyzed cascade reactions, a way toward furan compounds

2.1) Cyclization/1,2-migration sequence, new development

3-Methylcyclohex-2-enone (I-41)



$C_7H_{10}O$
110,15

To a solution of ethylacetoacetate (9.20 g, 71.0 mmol) in *t*BuOH (71 mL) methyl vinyl ketone (5.00 g, 71.0 mmol) was added. The solution was cooled to 0°C and *t*BuOK (599 mg, 5.34 mmol) was added.The resulting mixture was stirred for 30 minutes, then another portion of *t*BuOK (1.59 g, 14.2 mmol) was incorporated. The reaction mixture was heated to reflux. After 20 hours, it was quenched with a 1M solution of HCl and extracted three times with EtOAc. The combined organic phase was washed with NaOH (1M) and sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. After distillation, **I-41** (5.73 g, 52.0 mmol, 67%) was obtained as a clear colorless liquid.

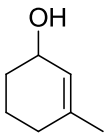
TLC: Rf = 0.43 (Pentanes/EtOAc = 8/2) [CAM/UV]

^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 5.87 (s, 1H), 2.39-2.21 (m, 4H), 2.07-1.89 (m, 5H).

^{13}C NMR(63 MHz, $CDCl_3$) δ [ppm] 199.7, 162.7, 126.7, 37.0, 30.9, 24.4, 22.5.

The analytic data are identical to the literature data.[83]

3-Methylcyclohex-2-enol (I-42a)



$C_7H_{12}O$
112,17

To a solution of $CeCl_3 \cdot 7H_2O$ (1.68 g, 45.0 mmol) in dry methanol (82 mL) 3-methylcyclohex-2-enone **I-41** (5.0 g, 45.0 mmol) was added. Under ice bath cooling, $NaBH_4$ (1.70 g, 45.0 mmol) was slowly introduced. The reaction mixture was allowed to stir at room temperature for 1 h. Then, it was quenched with water and extracted three times with Et_2O. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product **I-42a** (4.74 g, 42.5 mmol, 94%) was obtained as colourless oil. It was directly used for the next step without further purification.

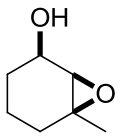
TLC: Rf = 0.43 (Pentanes/EtOAc= 8/2) [CAM]

^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 5.46 (d, *J* =1.3 Hz, 1H), 4.14 (s, 1H), 1.87 (d, *J* = 5.7 Hz, 2H), 1.80-1.69 (m, 2H), 1.65 (d, *J* = 0.7 Hz, 3H), 1.59-1.48, m, 2H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] 139.1, 124.6, 66.2, 32.0, 30.4, 24.0, 19.3.

The analytical data are identical to the literature data.[84]

6-Methyl-7-oxabicyclo[4.1.0]heptan-2-ol(I-43a)



$C_7H_{12}O_2$
128,17

To a solution of **I-42a** (7.75 g, 69.1 mmol) in dry CH_2Cl_2 (461 mL), $NaHCO_3$ (14.5 g, 172 mmol) was added. The resulting mixture was cooled to 0°C and *m*-CPBA (17.9 g, 103 mmol) was slowly introduced. The mixture was allowed to warm to room temperature and was stirred overnight. The reaction was then quenched with sat. Na_2SO_3-solution, and extracted three times with EtOAc. The combined organic phase was washed with sat. $NaHCO_3$ solution and sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product **I-43a** (8.53 g, 66.55 mmol, 96%) was obtained as colourless oil. It was directly used for the next step without further purification.

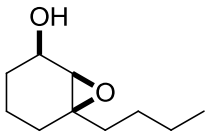
TLC: Rf = 0.11 (Pentanes/EA = 8/2) [CAM]

^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 4.02 (td, *J* = 5.3, 3.5 Hz, 1H), 3.16 (d, *J* = 3.3 Hz, 1H), 1.94-1.80 (m, 1H), 1.73-1.55 (m, 1H), 1.55-1.42 (m, 3H), 1.35 (s, 3H), 1.31-1.20 (m, 1H).

^{13}C NMR(91 MHz, $CDCl_3$) δ [ppm] 66.9, 62.7, 62.1, 29.4, 29.1, 24.1, 18.1.

The analytical data are identical to the literature data.[84]

6-butyl-7-oxabicyclo[4.1.0]heptan-2-ol (I-43b)



$C_{10}H_{18}O_2$
170,25

Following the same procedure as for **I-43a**, 3-butyl-2-cyclohexen-1-ol (1.5 g, 9.72 mmol) was epoxidized with *m*-CPBA (2.30 g, 14.6 mmol) giving the product **I-43b** (1.59 g, 9.03 mmol, 93%).

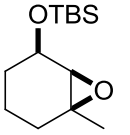
TLC: Rf = 0.17 (Pentanes/Et_2O = 7/3) [CAM]

^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 4.04-3.91 (m, 1H), 3.13 (d, *J* = 3.0 Hz, 1H), 2.01-1.80 (m, 1H), 1.78 (dd, *J* = 8.4, 4.9 Hz, 1H), 1.74-1.64 (m, 1H), 1.54 (ddd, *J* = 12.6, 6.4, 3.7 Hz, 5H), 1.42-1.18 (m, 5H), 0.90 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] 66.96, 64.40, 61.43, 37.15, 29.06, 26.87, 26.65, 22.70, 18.25, 13.97.

The analytical data are conformed to the literature.[85]

***t*-Butyldimethyl((-6-methyl-7-oxabicyclo[4.1.0]heptan-2-yl)oxy)silane(I-44a)**



$C_{13}H_{26}O_2Si$
242,43

To a solution of 6-methyl-7-oxabicyclo[4.1.0]heptan-2-ol **I-43a** (1.00 g, 7.80 mmol) in abs. CH_2Cl_2 (49 mL) at 0°C, were added imidazole (637 mg, 9.36 mmol), TBS-chloride (1.41 g, 9.36

mmol) and DMAP (47.6 mg, 390 µmol). The reaction mixture was allowed to warm to room temperature and stirred for 5 h. Then the reaction was quenched with water and extracted with Et_2O, the combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (Pentanes/Et_2O = 9/1) to obtain the product **I-44a** (1.64 g, 6.77 mmol, 87%).

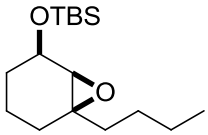
TLC: Rf = 0.27 (Pentanes/EtOAc = 99/1) [CAM]

^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 4.01 (ddd, *J* = 8.3, 6.1, 2.0 Hz, 1H), 2.96 (d, *J* = 1.8 Hz, 1H), 1.85–1.36 (m, 6H), 1.30 (s, 3H), 0.92(s, 9H), 0.11 (s, 3H), 0.09 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 69.7, 63.4, 60.5, 28.2, 27.9, 26.0, 24.3, 20.1, 18.4, -4.37, -4.41.

The analytical data are identical to the literature data.[86]

***t*-Butyl((-6-butyl-7-oxabicyclo[4.1.0]heptan-2-yl)oxy)dimethylsilane (I-44b)**



$C_{16}H_{32}O_2Si$
284,51

Following the same procedure as for **I-44a**, **I-43b** (1.40 g, 8.22 mmol) was protected with TBS-chloride (1.49 g, 9.87 mmol). After flash chromatography (Pentanes/Et_2O = 99/1), the product **I-44b** (1.74 g, 6.12 mmol, 75%) was obtained.

TLC: Rf = 0.24 (Pentanes/Et_2O = 99/1) [CAM]

^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 4.03-3.92 (m, 1H), 2.94 (d, *J* = 1.9 Hz, 1H), 1.70 (dd, *J* = 8.8, 4.1 Hz, 2H), 1.64-1.14 (m, 10H), 0.91 (s, 12H), 0.11 (s, 3H), 0.09 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 69.8, 63.4, 62.4, 37.7, 26.9, 28.0, 26.0, 25.9, 22.7, 20.4, 18.2, 14.0, -4.48, -4.52.

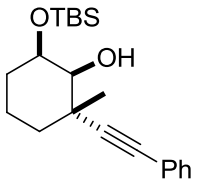
MS (EI, 70 eV) *m/z* (%): 227.17 (100) [M^+- *t*Bu], 185 (11), 171 (72), 157 (72), 141 (56), 129 (31), 115 (20), 105 (17), 93 (36), 75 (100), 67 (27), 41 (26).

HRMS (EI, 70 eV) *m/z* 227.14585, [227.14619 calcd. for $C_{12}H_{23}O_2Si$ (M^+- *t*Bu)].

General procedure for the epoxide opening(A) [27]

To a solution of alkyne (1.2 equiv.) in abs. Et_2O (0.20 M) at 0°C, were slowly added to *n*BuLi (1.2 eq) and $AlMe_3$ (1.1 equiv.), the resulting mixture was allowed to warm to room temperature, and then the epoxide (1 equiv.) was introduced. The solution was cooled to -78°C and $BF_3.OEt_2$ (2 equiv.) was slowly added. After 3 h at -78°C, methanol was added; the reaction was stirred for 15 minutes, quenched with aq. 20% Na-/K-tartrate-solution and glycerine. The resulting mixture was extracted three times with Et_2O. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography.

6-((*t*-Butyldimethylsilyl)oxy)-2-methyl-2-(phenylethynyl)cyclohexanol(S5a) (I-45a)



$C_{21}H_{32}O_2Si$
344,56

Following procedure A, the epoxide **I-44a** (750 mg, 3.31 mmol) was reacted with phenylacetylene (440 mg, 4.30 mmol). After flash chromatography (Pentanes/Et_2O = 99/1), the product **I-45a** (888 mg, 2.57 mmol, 78%) was obtained.

TLC: Rf = 0.27 (Pentanes/EtOAc = 99/1) [CAM/UV]

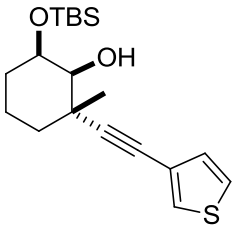
^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 7.41-7.27 (m, 5H), 4.26-4.14 (m, 1H), 3.67 (d, *J* = 2.7 Hz, 1H), 2.45 (s, 1H), 1.75-1.32 (m, 9H), 0.91 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 131.4, 128.2, 127.7, 123.7, 94.2, 83.2, 75.9, 71.1, 37.4, 31.3, 28.1, 25.8, 20.9, 18.1, -4.53, -4.83.

MS (EI, 70 eV) *m/z* (%): 287 (61) [M^+- *t*Bu], 269 (10) [M^+- *i*Pr-H_2O], 195 (40), 180 (20), 167 (30), 141 (22), 115 (25), 75 (100).

The analytical data are conformed to the literature.[27]

6-((*t*-Butyldimethylsilyl)oxy)-2-methyl-2-(thiophen-3-ylethynyl)cyclohexanol (I-45b)



$C_{19}H_{30}O_2SSi$
350,59

Following procedure A, the epoxide **I-44a** (500 mg, 2.06 mmol) was reacted with 3-ethynylthiophene (267mg, 2.47 mmol). After flash chromatography (Pentanes/Et_2O = 99/1), the product **I-45b** (374 mg, 1.07 mmol, 52%) was obtained.

TLC: Rf = 0.50 (Pentanes/Et_2O = 99/1) [CAM/UV]

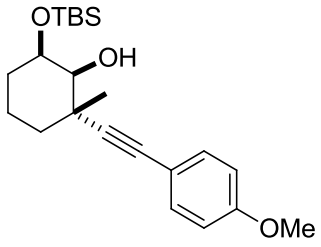
^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 7.35 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.27-7.25 (m, 1H), 7.07 (dd, *J* = 5.0, 1.2 Hz, 1H), 4.21-4.14 (m, 1H), 3.67 (d, *J* = 2.6 Hz, 1H), 2.45 (s, 1H), 1.75-1.45 (m, 8H), 1.39 (s, 3H), 0.93 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] 129.9, 127.6, 125.1, 122.6, 93.7, 78.1, 75.8, 71.0, 37.4, 31.3, 28.1, 25.9, 25.8, 20.9, 18.1, -4.50, -4.79.

MS (EI, 70 eV) *m/z* (%): 293 (100) [M^+- *t*Bu], 275 (8), 247 (14), 201 (55), 186 (16), 167 (16), 161 (14), 147 (10), 131 (15), 121 (10), 93 (11), 75 (97), 44 (10).

HRMS (EI, 70 eV) *m/z* 293.1022, [293.1026 calcd. for $C_{15}H_{21}O_2SSi$ (M^+- *t*Bu)].

6-((*t*-Butyldimethylsilyl)oxy)-2-((4-methoxyphenyl)ethynyl)-2-methylcyclohexanol (I-45c)



$C_{22}H_{34}O_3Si$
374,59

Following procedure A, the epoxide **I-44a** (495 mg, 2.06 mmol) was reacted with 4-ethynylanisole (323 mg, 2.47 mmol). After flash chromatography (Pentanes/Et_2O = 99/1), the product **I-45c** (458 mg, 1.22 mmol, 60%) was obtained.

TLC: Rf = 0.63 (Pentanes/Et_2O = 95/5) [UV/CAM]

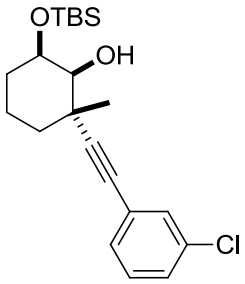
^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 7.35-7.31 (m, 2H), 6.87-6.82 (m, 2H), 4.23-4.16 (m, 1H), 3.83 (s, 3H), 3.67 (d, *J* = 2.7 Hz, 1H), 2.45 (s, 1H), 1.70-1.44 (m, 7H), 1.39 (s, 3H), 0.93 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] 159.2, 132.8, 115.8, 113.8, 92.6, 82.9, 76.0, 71.0, 55.3, 37.4, 31.4, 28.2, 25.9, 21.0, 18.1, -4.51, -4.78.

MS (EI, 70 eV) *m/z* (%): 317 (100) [M^+- *t*Bu], 298 (5), 224 (32), 209 (8), 185 (13), 159 (5), 131 (8), 121 (10), 75 (41), 43 (18).

HRMS (EI, 70 eV) *m/z* 374.2273, [374.2272 calcd. for $C_{22}H_{34}O_3Si$].

6-((*t*-Butyldimethylsilyl)oxy)-2-((3-chlorophenyl)ethynyl)-2-methylcyclohexanol (I-45d)



$C_{21}H_{31}ClO_2Si$
379,01

Following procedure A, the epoxide **I-44a** (700 mg, 2.89 mmol) was reacted with 3-chloro-1-ethynyl-benzene (474 mg, 3.47 mmol). After flash chromatography (Pentanes/Et_2O = 99/1), the product **I-45d** (362 mg, 0.95 mmol, 33%) was obtained.

TLC: Rf = 0.60 (Pentanes/Et_2O = 99/1) [UV/CAM]

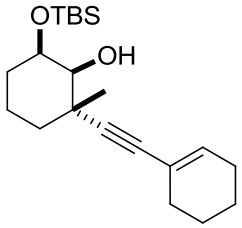
^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 7.39 (d, *J* = 1.8 Hz, 1H), 7.30-7.25 (m, 3H), 4.25-4.07 (m, 1H), 3.68 (d, *J* = 2.7 Hz, 1H), 2.47 (s, 1H), 1.66-1.57 (m, 6H), 1.41 (s, 3H), 0.94 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 134.1, 131.4, 129.6, 129.4, 128.0, 125.4, 95.6, 81.9, 75.7, 71.1, 37.5, 31.3, 28.1, 25.8, 20.9, 18.1, -4.49, -4.79.

MS (EI, 70 eV). *m/z* (%): 323 (17), 321 (60) [M^+- *t*Bu], 303 (6), 286 (8), 239 (6), 229 (40), 194 (20), 179 (10), 165 (8), 131 (12), 93 (11), 75 (100).

HRMS (EI, 70 eV) *m/z* 321.1076, [321.1072 calcd. for $C_{17}H_{22}O_2ClSi$ (M^+- *t*Bu)].

6-((*t*-Butyldimethylsilyl)oxy)-2-(cyclohex-1-en-1-ylethynyl)-2-methylcyclohexanol (I-45f)



$C_{21}H_{36}O_2Si$
348,59

Following procedure A, the epoxide **I-44a** (500 mg, 2.06 mmol) was reacted with 1-ethynylcyclohexene (268 mg, 2.47 mmol). After flash chromatography (Pentanes/Et_2O = 99/1), the product **I-45f** (512 mg, 1.47 mmol, 71%) was obtained.

TLC: Rf = 0.63 (Pentanes/Et_2O = 99/1) [CAM/UV]

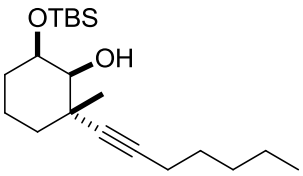
^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 6.04-5.97 (m, 1H), 4.16-4.04 (m, 1H), 3.56 (d, *J* = 2.8Hz, 1H), 2.39 (s, 1H), 2.09 (t, *J* = 5.3 Hz, 4H), 1.67-1.43 (m, 10H), 1.30 (s, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 133.3, 120.7, 91.3, 84.9, 76.0, 71.0, 37.1, 31.3, 29.6, 28.1, 25.9, 25.8, 25.5, 22.3, 21.5, 20.9, 18.1, -4.57, -4.83.

MS (EI, 70 eV) *m/z* (%): 305 (16) [M^+- *iPr*], 291 (4) [M^+- *t*Bu], 215 (22), 201 (8), 185 (20), 131 (22), 109 (28), 93 (16), 75 (100), 55 (23), 43 (23).

HRMS (EI, 70 eV) *m/z* 305.15710, [305.17804 calcd. for $C_{17}H_{27}O_2Si$ (M^+-*i*Pr)].

6-((*t*-Butyldimethylsilyl)oxy)-2-(hept-1-yn-1-yl)-2-methylcyclohexanol (I-45h)



$C_{20}H_{38}O_2Si$
338,60

Following procedure A, the epoxide **I-44a** (500 mg, 2.06 mmol) was reacted with heptyne (237 mg, 2.47 mmol). After flash chromatography (Pentanes/Et_2O = 99/1), the product **I-45h** (430 mg, 1.27 mmol, 62%) was obtained.

TLC: Rf = 0.44 (Pentanes/Et_2O = 99/1) [CAM/UV]

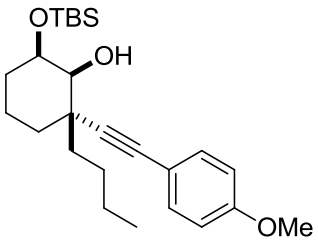
^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 4.11 (ddd, *J* = 8.9, 5.7, 2.8 Hz, 1H), 3.52 (d, *J* = 2.7 Hz, 1H), 2.38 (s, 1H), 2.16 (t, *J* = 6.8 Hz, 2H), 1.68- 1.20 (m, 15H), 0.95- 0.85 (m, 12H), 0.09 (s, 3H), 0.08 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 84.6, 82.9, 76.1, 70.9, 36.7, 31.4, 31.0, 28.8, 28.2, 26.2, 25.8, 22.2, 20.8, 18.6, 18.1, 14.0, -4.60, -4.85.

MS (EI, 70 eV), *m/z* (%): 281 (28) [M^+- *t*Bu], 263 (5), 199 (26), 189 (87), 133 (31), 119 (40), 95 (41), 81 (38), 75 (100), 55 (26).

HMRS (EI, 70 eV) *m/z* 281.19379, [281.19370 calcd. for $C_{16}H_{29}O_2Si$ (M^+- *t*Bu)].

2-butyl-6-((*t*-Butyldimethylsilyl)oxy)-2-((4-methoxyphenyl)ethynyl)cyclohexanol(I-45k)



$C_{25}H_{40}O_3Si$
416,67

Following procedure A, the epoxide **I-44b** (500 mg, 1.76 mmol) was reacted with 4-ethynylanisole (278.7 mg, 2.11 mmol). After flash chromatography (Pentanes/Et_2O = 99/1), the product **I-45k** (306 mg, 0.734 mmol, 42%) was obtained.

TLC: Rf = 0.79 (Pentanes/Et_2O = 95/5) [UV/CAM]

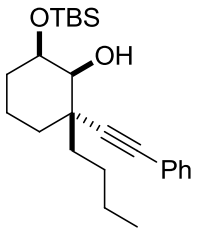
^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 7.32 (d, *J* = 8.9 Hz, 2H), 6.3 (d, *J* = 8.9 Hz, 2H), 4.17 (td, *J* = 8.1, 2.7 Hz, 1H), 3.81 (s, 3H), 3.70 (d, *J* = 2.8 Hz, 1H), 1.76-1.28 (m, 12H), 1.01-0.86 (m, 11H), 0.10 (s, 3H), 0.10 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 132.8, 116.0, 113.8, 91.4, 84.1, 74.2, 71.2, 55.3, 41.4, 37.9, 30.4, 28.6, 26.3, 25.8, 23.2, 20.8, 18.1, 14.1, -4.52, -4.77.

MS (EI, 70 eV). *m/z* (%): 359 (6) [M^+- *t*Bu], 237 (7), 227 (93), 209 (8), 171 (81), 135 (46), 107 (19), 93 (41), 75 (100), 67 (16), 57 (12).

HRMS (EI, 70 eV) *m/z* 359.20258, [359.20370 calcd. for $C_{21}H_{31}O_3Si$ (M^+- *t*Bu)].

2-butyl-6-((*t*-Butyldimethylsilyl)oxy)-2-(phenylethynyl)cyclohexanol (I-45l)



$C_{24}H_{38}O_2Si$
386,64

Following procedure A, the epoxide **I-44b** (1.0 g, 3.51 mmol) was reacted with phenylacetylene (430 mg, 4.21 mmol). After flash chromatography (Pentanes/Et_2O = 99/1), the product **I-45l** (643.5 mg, 1.66 mmol, 47%) was obtained.

TLC: Rf = 0.24 (Pentanes/Et_2O = 99/1) [UV/CAM]

^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 7.43-7.34 (m, 2H), 7.34-7.28 (m, 3H), 4.17 (td, *J* = 8.0, 2.8 Hz, 1H), 4.02-3.94 (m, 1H), 3.71 (d, *J* = 2.7 Hz, 1H), 2.41 (s, 1H), 1.79-1.46 (m, 8H), 1.44-1.25 (m, 4H), 0.98-0.90 (m, 12H), 0.11 (s, 3H), 0.10 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 147.3, 131.4, 128.2, 127.6, 93.1, 84.4, 74.1, 71.2, 41.5, 37.8, 30.3, 28.6, 26.3, 25.8, 23.2, 20.8, 18.1, 14.1, -4.51, -4.77.

MS (EI, 70 eV). *m/z* (%): 329 (13) [M^+-*t*Bu], 243 (28), 227 (93), 185 (8), 171 (43), 157 (47), 151 (67), 141 (33), 131 (27), 109 (60), 95 (83), 75 (100), 69 (61), 55 (41).

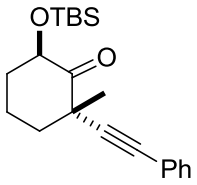
HRMS (EI, 70 eV) *m/z* 329.19, [329.26 calcd. for $C_{20}H_{29}O_2Si$ (M^+-*t*Bu)].

General procedure for Swern oxidation (B)[28]

To a solution of oxalyl chloride (1.1 equiv.) in abs. CH_2Cl_2 (5 M) at -78°C, was slowly added a solution of DMSO (2.2 equiv.) in abs. CH_2Cl_2 (12.5 M). The solution was stirred for 30

minutes, and then the alcohol (1 equiv.) in abs. CH_2Cl_2 (3 M) was slowly added dropwise. The reaction mixture was stirred for 30 minutes. Finally Et_3N (5 equiv.) was slowly added. The resulting mixture was allowed to warm to room temperature. After 1 hour, it was quenched with water and extracted three times with Et_2O. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography.

6-((*t*-Butyldimethylsilyl)oxy)-2-methyl-2-(phenylethynyl)cyclohexanone (I-46a)



$C_{21}H_{30}O_2Si$
342,55

Following procedure B, substrat **I-45a** (920 mg, 2.67 mmol) was oxidized. After flash chromatography (Pentanes/Et_2O = 99/1), the product **I-46a** (897 mg, 2.62 mmol, 98%) was obtained.

TLC: Rf = 0.27 (Pentanes/EA = 99/1) [CAM/UV]

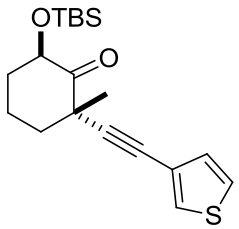
^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 7.45-7.28 (m, 5H), 5.02 (dd, *J* = 12, 6.4 Hz, 1H), 2.22 (dqd, *J* = 8.8, 5.9, 3.2 Hz, 3H), 1.86-1.46 (m, 3H), 1.41 (s, 3H), 0.92 (s, 9H), 0.16 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 206.9, 128.4, 122.8, 91.0, 84.8, 74.3, 46.2, 41.7, 37.8, 25.8, 23.1, 21.3, 18.6, -4.72, -5.67.

MS (EI, 70 eV) *m/z* (%): 285 (100) [M^+- *t*Bu], 257 (7), 199 (20), 183 (13), 155 (22), 115 (20), 75 (55).

HRMS (EI, 70 eV) *m/z* 285.1310, [285.1311 calcd. for $C_{17}H_{21}O_2Si$ (M^+- *i*Pr)].

6-((*t*-Butyldimethylsilyl)oxy)-2-methyl-2-(thiophen-3-ylethynyl)cyclohexanone (I-46b)



$C_{19}H_{28}O_2SSi$
348,57

Following procedure B, substrat **I-45b** (298 mg, 0.85 mmol) was oxidized. After flash chromatography (Pentanes/Et_2O = 99/1), the product **I-46b** (232 mg, 0.67 mmol, 78%) was obtained.

TLC: Rf = 0.50 (Pentanes/Et_2O = 99/1) [CAM/UV]

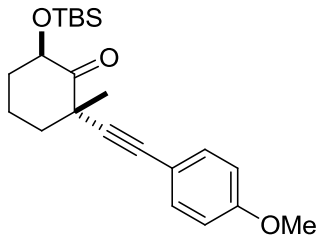
^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 7.40 (dd, *J* = 3.0, 1.1 Hz, 1H), 7.31-7.28 (m, 1H), 7.08 (dd, *J* = 5.0, 1.1 Hz, 1H), 5.01 (dd, *J* = 12.1, 6.4 Hz, 1H), 2.33-2.13 (m, 3H), 1.88-1.15 (m, 5H), 1.41 (s, 3H), 0.93 (s, 9H), 0.17 (s, 3H), 0.07 (s, 3H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] 206.9, 129.7, 128.4, 125.4, 121.8, 90.5, 79.9, 74.4, 46.2, 41.7, 37.8, 25.8, 23.1, 21.1, 18.5, -4.69, -5.51.

MS (EI, 70 EV) *m/z* (%): 291 (74) [M^+-*t*Bu], 276 (13), 231 (20), 217 (10), 199 (27), 183 (100), 161 (15), 141 (10), 115 (14), 75 (55), 61 (11).

HRMS (EI, 70 eV) *m/z* 333.13480, [333.13391 calcd. for $C_{18}H_{25}O_2SSi$ (M^+- Me)].

6-((*t*-Butyldimethylsilyl)oxy)-2-((4-methoxyphenyl)ethynyl)-2-methylcyclohexanone (I-46c)



$C_{22}H_{32}O_3Si$
372,57

Following procedure B, substrat **I-45c** (340 mg, 0.93 mmol) was oxidized. After flash chromatography (Pentanes/Et_2O = 99/1), the product **I-46c** (247 mg, 0.66 mmol, 73%) was obtained.

TLC: Rf = 0.63 (Pentanes/Et_2O = 95/5) [UV/CAM]

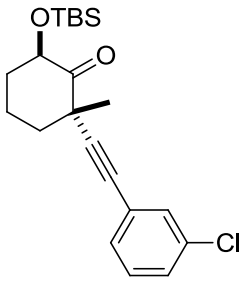
^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 7.38-7.31 (m, 2H), 6.92-6.82 (m, 2H), 5.03 (dd, *J* = 12.1, 6.4 Hz, 1H), 3.83 (s, 3H), 2.34-2.10 (m, 3H), 1.66 (ddd, *J* = 29.3, 13.3, 5.9, 3.1 Hz, 4H), 1.41 (s, 3H), 0.93 (s, 9H), 0.17 (s, 3H), 0.07 (s, 3H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] 207.2, 159.5, 132.9, 115.0, 114.0, 89.5, 84.6, 74.4, 55.3, 46.1, 41.8, 37.8, 25.8, 23.1, 21.1, 18.6, -4.69, -5.53.

MS (EI, 70 EV) *m/z* (%): 315 (100) [M^+- *t*Bu], 300 (9), 287 (30), 269 (7), 241 (10), 213 (11), 185 (21), 145 (6), 129 (7), 75 (19).

HRMS (EI, 70 eV) *m/z* 315.1408, [315.1411 calcd. for $C_{18}H_{23}O_3Si$ (M^+- *t*Bu)].

6-((*t*-butyldimethylsilyl)oxy)-2-((3-chlorophenyl)ethynyl)-2-methylcyclohexanone (I-46d)



$C_{21}H_{29}ClO_2Si$
376,99

Following procedure B, substrat **I-45d** (349 mg, 0.92 mmol) was oxidized. After flash chromatography (Pentanes/Et_2O = 99/1), the product **I-46d** (281 mg, 0.75 mmol, 81%) was obtained.

TLC: Rf = 0.60 (Pentanes/Et_2O = 99/1) [UV/CAM]

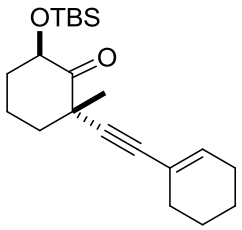
^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 7.43-7.37 (m, 1H), 7.37-7.26 (m, 3H), 4.99 (dd, *J* = 12.0, 6.4 Hz, 1H), 2.36-2.08 (m, 3H), 1.89-1.59 (m, 3H), 1.43 (s, 3H), 0.94 (s, 9H), 0.18 (s, 3H), 0.08 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 206.5, 134.2, 131.4, 129.6, 129.6, 128.6, 124.5, 92.3, 83.4, 74.5, 46.2, 41.8, 37.8, 25.8, 23.0, 21.1, 18.5, -4.68, -5.48.

MS (EI, 70 eV) m/z (%): 322 (32), 319 (100) [M^+- *t*Bu], 269 (12), 245 (6), 189 (15), 75 (28), 59 (6).

HRMS (EI, 70 eV) *m/z* 319.0912, [319.0912 calcd. for $C_{17}H_{20}O_2ClSi$ (M^+- *t*Bu)].

6-((*t*-Butyldimethylsilyl)oxy)-2-(cyclohex-1-en-1-ylethynyl)-2-methylcyclohexanone (I-46f)



$C_{21}H_{34}O_2Si$
346,58

Following procedure B, substrat **I-45f** (444 mg, 1.27 mmol) was oxidized. After flash chromatography (Pentanes/Et_2O = 99/1), the product **I-46f** (365 mg, 1.05 mmol, 83%) was obtained.

TLC: Rf = 0.50 (Pentanes/Et_2O = 99/1) [CAM/UV]

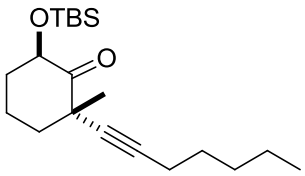
^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 6.05 (dd, *J* = 4.0, 2.0 Hz, 1H), 4.95 (dd, *J* = 11.2, 6.4 Hz, 1H), 2.28-1.99 (m, 6H), 1.80-1.40 (m, 8H), 1.32 (s, 3H), 1.04-0.83 (m, 9H), 0.14 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δppm] 207.2, 134.5, 120.3, 88.2, 85.6, 74.2, 46.0, 41.8, 31.8, 29.3, 25.8, 25.6, 23.2, 22.3, 21.4, 21.0, 18.5, -4.73, -5.57.

MS (EI, 70 EV) *m/z* (%): 289 (100) [M^+- *t*Bu], 239 (6), 215 (6), 187 (8), 159 (8), 143 (5), 129 (8), 105 (12), 91 (12), 75 (28), 59 (8), 41 (8).

HRMS (EI, 70 eV) *m/z* 289.16232, [289.16238 calcd. for $C_{17}H_{25}O_2Si$ (M^+- *t*Bu)].

6-((*t*-Butyldimethylsilyl)oxy)-2-(hept-1-yn-1-yl)-2-methylcyclohexanone (I-46h)



$C_{20}H_{36}O_2Si$
336,58

Following procedure B, substrat **I-45h** (397.6 mg, 1.17 mmol) was oxidized. After flash chromatography (Pentanes/Et_2O = 99/1), the product **I-46h** (274.6 mg, 0.816 mmol, 70%) was obtained.

TLC: Rf = 0.44 (Pentanes/Et_2O = 99/1) [CAM/UV]

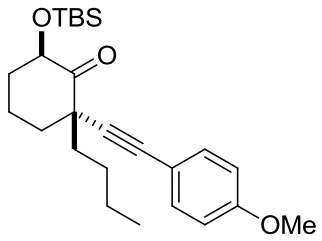
^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 4.96 (dd, *J* =12.1, 6.5Hz, 1H), 2.28 -1.98 (m, 5H), 1.77-1.27 (m, 12H), 0.96 -0.88 (m, 12H), 0.16 (s, 3H), 0.05 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 207.7, 85.1, 81.9, 74.1, 45.5, 41.8, 37.8, 31.1, 28.5, 25.8, 23.4, 22.2, 21.0, 18.7, 18.5, 14.0, -4.75, -5.61.

MS (EI, 70 eV), *m/z* (%): 279 (100) [M^+- *t*Bu], 222 (13), 205 (16), 187 (9), 105 (11), 75 (40), 55 (10).

HMRS (EI, 70 eV) *m/z* 279.17819, [279.17858 calcd. for $C_{16}H_{27}O_2Si$ (M^+- *t*Bu)].

2-butyl-6-((*t*-Butyldimethylsilyl)oxy)-2-((4-methoxyphenyl)ethynyl)cyclohexanone (I-46k)



$C_{25}H_{38}O_3Si$
414,65

Following procedure B, substrat **I-45k** (214 mg, 0.490 mmol) was oxidized. After flash chromatography (Pentanes/Et_2O = 99/1), the product **I-46k** (132.6 mg, 0.305 mmol, 62%) was obtained.

TLC: Rf = 0.79 (Pentanes/Et_2O = 95/5) [UV/CAM]

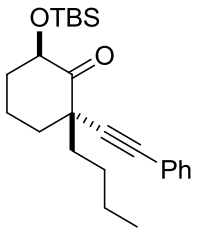
^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 7.33 (d, *J* = 8.9 Hz, 2H), 6.85 (d, *J* = 8.9 Hz, 2H), 5.04 (dd, *J* = 12.0, 6.2 Hz, 1H), 3.82 (s, 3H), 2.33-2.07 (m, 3H), 2.00-1.59 (m, 3H), 1.00-1.30 (m, 6H), 0.97-0.83 (m, 12H), 0.15 (s, 3H), 0.05 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 207.2, 159.5, 132.8, 115.2, 113.9, 88.6, 85.8, 74.6, 55.3, 50.3, 39.7, 37.9, 35.5, 26.8, 25.8, 23.2, 20.9, 18.5, 14.0, -4.69, -5.53.

MS (EI, 70 eV). *m/z* (%): 357 (100) [M^+- *t*Bu], 329 (25), 300 (16), 225 (29), 183 (14), 171 (12), 121 (14), 95 (12), 75 (76), 57 (18).

HRMS (EI, 70 eV) *m/z* 399.23480, [399.23500 calcd.for $C_{24}H_{35}O_3Si$ (M^+- Me)].

2-butyl-6-((*t*-Butyldimethylsilyl)oxy)-2-(phenylethynyl)cyclohexanone (I-46l)



$C_{24}H_{36}O_2Si$
384,63

Following procedure B, substrat **I-45l** (580 mg, 1.50 mmol) was oxidized. After flash chromatography (Pentanes/Et_2O = 99/1), the product **I-46l** (372.8 mg, 0.969 mmol, 65%) was obtained.

TLC: Rf = 0.24 (Pentanes/Et_2O = 99/1) [UV/CAM]

^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 7.44-7.39 (m, 2H), 7.37-7.31 (m, 3H), 5.05 (dd, *J* = 12.1, 6.3 Hz, 1H), 2.32-2.15 (m, 3H), 2.00-1.87 (m, 1H), 1.80 (ddd, *J* = 16.7, 8.9, 5.3 Hz, 1H), 1.72 (d, *J* = 3.6 Hz, 1H), 1.60-1.51 (m, 2H), 1.50-1.33 (m, 4H), 0.99-0.90 (m, 12H), 0.17 (s, 3H), 0.07 (s, 3H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] 207.1, 131.5, 128.3, 128.2, 123.0, 90.1, 85.0, 74.6, 50.4, 39.7, 37.9, 35.4, 26.8, 25.8, 23.2, 20.9, 18.5, 14.0, -4.68, -5.51.

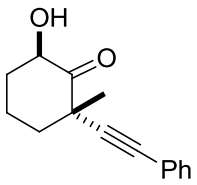
MS (EI, 70 eV) *m/z* (%): 327 (100) [M^+-*t*Bu], 271 (10), 225 (8), 197 (8), 141 (7), 129 (6), 91 (7), 75 (23), 43 (8).

HRMS (EI, 70 eV) *m/z* 327.17719, [327.17749 calcd. for $C_{20}H_{27}O_2Si$ (M^+-*t*Bu)].

General prodecure for deprotection(C)

To a solution of MeOH:conc. HCl (9:1; 0.1 M), the ketone was added. After 1h, the reaction mixture was quenched with sat. $NaHCO_3$ solution and extracted three times with Et_2O. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography.

6-hydroxy-2-methyl-2-(phenylethynyl)cyclohexanone (I-37a)



$C_{15}H_{16}O_2$
228,29

Following procedure C, substrat **I-46a** (1.23 g, 3.58 mmol) was deprotected. After flash chromato-graphy(Pentanes/EtOAc = 9/1), product **I-37a** (743 mg, 3.25 mmol, 91%) was obtained.

TLC: Rf = 0.58 (Pentanes/EtOAc = 9/1) [CAM/UV]

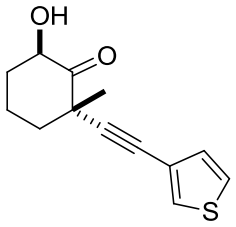
^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 7.45-7.28 (m, 5H), 4.96-4.81 (m, 1H), 3.45 (d, *J* = 4.4Hz, 1H), 2.49 (ddt, *J* = 13.1, 6.4, 3.2 Hz, 1H), 2.24 (tt, *J* = 12.1, 6.0 Hz, 2H), 1.85-1.71 (m, 1H), 1.68-1.52 (m, 2H), 1.47 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 209.4, 131.6, 128.3, 122.5, 89.9, 84.9, 72.6, 45.5, 42.5, 37.6, 22.9, 20.3.

MS (EI, 70 eV) *m/z* (%): 228 (53) [M^+], 213 (82), 199 (41), 183 (44), 141 (51), 129 (100), 115 (46).

HRMS (EI, 70 eV) *m/z* 228.1147, [228.1150 calcd. for $C_{15}H_{16}O_2$].

6-hydroxy-2-methyl-2-(thiophen-3-ylethynyl)cyclohexanone (I-37b)



$C_{13}H_{14}O_2S$
234,31

Following procedure C, substrat **I-46b** (200 mg, 0.57 mmol) was deprotected. After flash chromatography (Pentanes/Et_2O = 9/1), the product **I-37b** (113 mg, 0.48 mmol, 84%) was obtained.

TLC: Rf = 0.14 (Pentanes/Et_2O = 99/1) [CAM/UV]

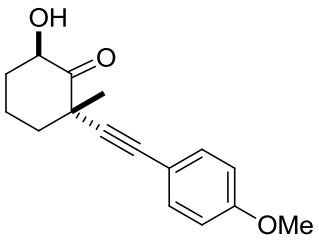
^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 7.40-7.35 (m, 1H), 7.27 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.08 (d, *J* = 5.0 Hz, 1H), 4.93-4.78 (m, 1H), 3.45 (d, *J* = 4.2 Hz, 1H), 2.48 (ddd, *J* = 12.8, 6.7, 3.3 Hz, 1H), 2.23 (dd, *J* = 13.2, 5.3 Hz, 2H),1.85-1.71 (m, 1H), 1.57 (ddd, *J* = 12.7, 10.5, 3.7 Hz, 2H), 1.45 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 209.4, 155.9, 129.8, 128.8, 125.4, 89.6, 80.1, 72.6, 45.5, 42.4, 37.6, 22.9, 20.3.

MS (EI, 70 EV) *m/z* (%): 234 (29) [M^+], 219 (68) [M^+- Me], 216 (14) [M^+- H_2O], 205 (24), 189 (28), 173 (36), 161 (86), 147 (54), 135 (100), 121 (26), 115 (17), 97 (33), 91 (22), 77(12), 40 (37).

HRMS (EI, 70 eV) *m/z* 234.0709, [234.0709 calcd. for $C_{13}H_{14}O_2S$ (M^+)].

6-hydroxy-2-((4-methoxyphenyl)ethynyl)-2-methylcyclohexanone (I-37c)



$C_{16}H_{18}O_3$
258,31

Following procedure C, substrat **I-46c** (180 mg, 0.48 mmol) was deprotected. After flash chromatography (Pentanes/Et_2O = 9/1), product **I-37c** (93 mg, 0.36 mmol, 75%) was obtained.

TLC: Rf = 0.25 (Pentanes/EtOAc = 9/1) [CAM/UV]

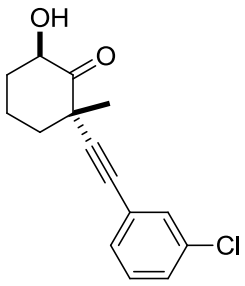
^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 7.38–7.32 (m, 2H), 6.88–6.82 (m, 2H), 4.94–4.86 (m, 1H), 3.83 (s, 3H), 3.47 (d, *J* = 4.4 Hz, 1H), 2.54–2.44 (m, 1H), 2.30–2.17 (m, 2H), 1.84–1.75 (m, 1H), 1.64–1.54 (m, 2H), 1.47 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 209.6, 159.7, 133.0, 114.6, 113.9, 88.6, 84.9, 72.5, 55.3, 45.4, 42.5, 37.6, 25.8, 22.9.

MS (EI, 70 EV) *m/z* (%): 258 (92) [M^+], 243 (100), 229 (29), 213 (22), 199 (34), 185 (72), 171 (34), 159 (100), 145 (32), 135 (48), 121 (51), 115 (33).

HRMS (EI, 70 eV) *m/z* 258.1250, [258.1256 calcd. for $C_{16}H_{18}O_3$].

2-((3-chlorophenyl)ethynyl)-6-hydroxy-2-methylcyclohexanone (I-37d)



$C_{15}H_{15}ClO_2$
262,73

Following procedure C, substrat **I-46d** (261 mg, 0.69 mmol) was deprotected. After flash chromatography (Pentanes/EA = 9/1), the product **I-37d** (146 mg, 0.56 mmol, 80%) was obtained.

TLC: Rf = 0.28 (Pentanes/EtOAc = 9/1) [UV/CAM]

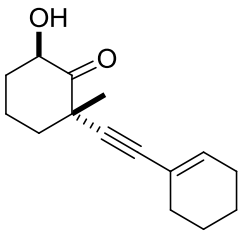
^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 7.41 (d, *J* = 1.6 Hz, 1H), 7.33 (t, J = 1.9 Hz, 1H), 7.31 (t, *J* = 1.9 Hz, 1H), 7.30-7.27 (m, 1H), 4.93-4.80 (m, 1H), 3.45 (d, *J* = 4.4 Hz, 1H), 2.51 (ddd, *J* = 12.7, 6.8, 3.3 Hz, 1H), 2.34-2.14 (m, 2H), 1.87-1.77 (m, 1H), 1.67-1.60 (m, 1H), 1.53 (dd, *J* = 12.5, 4.1 Hz, 1H), 1.48 (s, 3H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] 209.1, 134.2, 131.5, 129.7, 129.6, 128.7, 124.2, 91.3, 83.7, 72.7, 45.5, 42.4, 37.6, 22.8, 20.4.

MS (EI, 70 eV) *m/z* (%): 262 (26) [M^+], 247 (45), 233 (22), 227 (20), 205 (27), 199 (37), 189 (37), 177 (26), 163 (44), 155 (38), 143 (100), 139 (55), 128 (47), 125 (39), 115 (30), 111 (17), 101 (13), 77 (19), 55 (27), 43 (29).

HRMS (EI, 70 eV) *m/z* 262.0744, [262.0755 calcd. for $C_{15}H_{15}O_2Cl$].

2-(cyclohex-1-en-1-ylethynyl)-6-hydroxy-2-methylcyclohexanone (I-37f)



$C_{15}H_{20}O_2$
232,32

Following procedure C, substrat **I-46f** (300 mg, 0.87 mmol) was deprotected. After flash chromatography (Pentanes/Et_2O = 9/1), the product **I-37f** (161 mg, 0.69 mmol, 80%) was obtained.

TLC: Rf = 0.14 (Pentanes/Et_2O = 9/1) [UV/CAM]

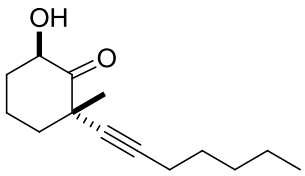
^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 6.09 (d, *J* = 1.8Hz, 1H), 4.92-4.74 (m, 1H), 3.47 (dd, *J* = 17.2, 5.4 Hz, 1H), 2.45 (ddt, *J* = 9.8, 6.3, 2.9 Hz, 1H), 2.24-2.05 (m, 6H), 1.74 (ddd, *J* = 16.4, 7.6, 4.6 Hz, 1H), 1.61 (ddd, *J* = 14.0, 8.1, 2.9 Hz, 5H), 1.54-1.34 (m, 4H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] 209.8, 135.2, 120.1, 87.3, 86.9, 72.4, 45.3, 42.5, 37.6, 29.2, 25.6, 23.0, 22.2, 21.4, 20.3.

MS (EI, 70 EV) *m/z* (%): 232 (55) [M^+], 216 (90), 203 (24), 189 (35) [M^+-*i*Pr], 175 (41) [M^+-*t*Bu], 159 (38), 145 (44), 131 (43), 117 (39), 105 (92), 91 (100), 75 (67), 57 (40), 42 (92).

HMRS (EI, 70 eV) *m/z* 232.1458, [232.1458 calcd. for $C_{15}H_{20}O_2$].

2-(hept-1-yn-1-yl)-6-hydroxy-2-methylcyclohexanone (I-37h)



$C_{14}H_{22}O_2$
222,32

Following procedure C, substrat **I-46h** (200 mg, 0.59 mmol) was deprotected. After flash chromatography (Pentanes/Et_2O = 9/1), the product **I-37h** (92 mg, 0.41 mmol, 69%) was obtained.

TLC: Rf = 0.24 (Pentanes/Et_2O = 99/1) [CAM/UV]

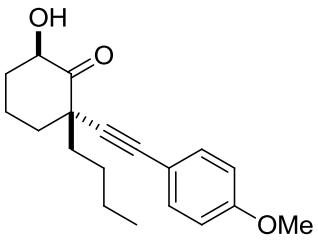
^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 4.87-4.72 (m, 1H), 3.44 (d, *J* = 4.4 Hz, 1H), 2.52-2.33 (m, 1H), 2.24-1.99 (m, 4H), 1.77-1.64 (m, 1H), 1.60-1.20 (m, 11H), 0.90 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 210.2, 85.6, 80.9, 72.3, 44.8, 42.5, 37.6, 31.0, 28.4, 23.2, 22.1, 20.2, 18.7, 14.0.

MS (EI, 70 eV) *m/z* (%): 222 (14) [M^+], 207 (8), 176 (15), 166 (48) [M^+- *t*Bu], 147 (30), 137 (30), 121 (50), 105 (80), 94 (84), 79 (100), 67 (53), 55 (85), 53 (37), 41 (86).

HMRS (EI, 70 eV) *m/z* 222.1622, [222.1620 calcd. for $C_{14}H_{22}O_2$].

2-butyl-6-hydroxy-2-((4-methoxyphenyl)ethynyl)cyclohexanone (I-37k)



$C_{19}H_{24}O_3$
300,39

Following procedure C, substrat **I-46k** (161 mg, 0.388 mmol) was deprotected. After flash chromatography (Pentanes/Et_2O = 9/1), product **I-37ka** (90.2 mg, 0.300 mmol, 77%) was obtained.

TLC: Rf = 0.17 (Pentanes/Et_2O = 9/1) [UV/CAM]

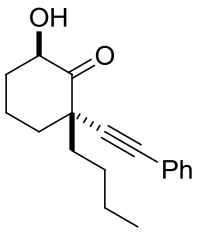
^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 7.41-7.28 (m, 2H), 6.89-6.79 (m, 2H), 4.89 (ddd, J = 11.8, 6.9, 4.5 Hz, 1H), 3.82 (s, 3H), 3.48-3.43 (m, 1H), 2.47 (ddd, *J* = 12.6, 6.7, 3.2 Hz, 1H), 2.35-2.14 (m, 2H), 2.05-1.88 (m, 1H), 1.87-1.70 (m, 1H), 1.66-1.32 (m, 6H), 1.23 (dd, *J* = 13.0, 6.0 Hz, 1H), 0.95 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 209.9, 159.7, 133.0, 114.8, 113.9, 87.6, 86.2, 72.7, 55.3, 49.7, 40.6, 37.9, 35.4, 26.8, 23.1, 20.2, 14.0.

MS (EI, 70 eV) *m/z* (%): 300 (34) [M^+], 265 (7), 258 (17), 243 (50) [M^+- *n*Bu], 227 (32), 213 (16), 205 (42), 201 (26), 185 (23), 171 (25), 159 (34), 145 (21), 135 (44), 121 (100), 108 (25), 91 (15), 69 (15), 57 (35), 43 (32).

HRMS (EI, 70 eV) *m/z* 300.1720, [300.1720 calcd. for $C_{19}H_{24}O_3$].

2-butyl-6-hydroxy-2-(phenylethynyl)cyclohexanone (I-37l)



$C_{18}H_{22}O_2$
270,37

Following procedure C, substrat **I-46l** (344 g, 0.894 mmol) was deprotected. After flash chromatography (Pentanes/Et_2O = 9/1), product **I-37l** (186.4 mg, 0.689 mmol, 77%) was obtained.

TLC: Rf = 0.14 (Pentanes/Et_2O = 9/1) [UV/CAM]

^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 7.47-7.37 (m, 2H), 7.37-7.28 (m, 3H), 4.97-4.81 (m, 1H), 3.45 (s, 1H), 2,48 (ddd, *J* = 12.6, 6.7, 3.3 Hz, 1H), 2.38-2.16 (m, 2H), 2.13-1.86 (m, 1H), 1.79 (ddd, *J* = 8.0, 6.5, 3.6 Hz, 1H), 1.67-1.25 (m, 7H), 0.95 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 209.7, 131.6, 128.3, 122.7, 89.1, 86.3, 72.8, 49.7, 40.6, 37.9, 35.3, 26.8, 23.1, 20.2, 14.0.

MS (EI, 70 eV) *m/z* (%): 270 (8) [M^+], 228 (15), 213 (34) [M^+- *t*Bu], 200 (21), 197 (15), 167 (21), 155 (27), 148 (85), 128 (81), 115 (53), 96 (81), 81 (91), 70 (60), 55 (100).

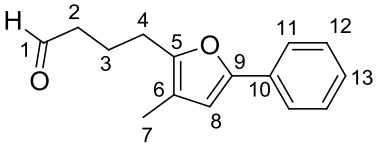
HRMS (EI, 70 eV) *m/z* 270.1614, [270.1614 calcd. for $C_{18}H_{22}O_2$].

General procedure for the furan synthesis.(D)

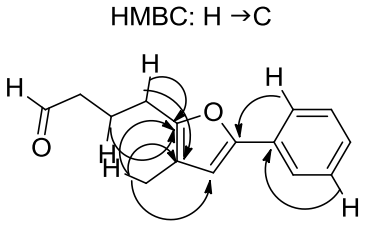
To 1-hydroxy-2-alkynyl carbonyl substrate in toluene (0.05 M), $PtCl_4$ (5 mol%) and isopropanol (1.5 equiv.) were added. The solution was stirred at 100°C. The reaction advancement was controlled by TLC. Finally it was quenched with water and extracted three

times with Et_2O. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography.

4-(3-methyl-5-phenylfuran-2-yl)butanal (I-47a)



$C_{15}H_{16}O_2$
228,29



Following procedure D, substrate **I-37a** (40 mg, 0.18 mmol) gave after flash chromatography (Pentanes/Et_2O = 9/1), the furan **I-47a** (33 mg, 0.14 mmol, 83%).

TLC: Rf = 0.40 (Pentanes/Et_2O = 8/2) [CAM/UV]

^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 9.75 (s, 1H), 7.62 (dd, *J* = 5.2, 3.3 Hz, 2H), 7.41-7.30 (m, 2H), 7.23 (ddd, *J* = 9.3, 6.0, 4.4 Hz, 1H), 6.45 (s, 1H), 2.70 (t, *J* = 7.1Hz, 2H), 2.49 (td, *J* = 7.2, 1.4 Hz, 2H), 2.10-1.96 (m, 5H).

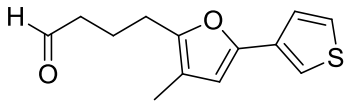
^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 202.1, 151.3, 149.8, 131.1, 128.6, 126.8, 123.3, 116.9, 108.3, 43.0, 25.1, 21.1, 9.9.

MS (EI, 70 eV) *m/z* (%): 228 (25) [M^+], 200 (20) [M^+-CO], 184 (36) [M^+- C_2H_4O], 171 (100) [M^+-C_3H_5O], 158 (8), 128 (18), 105 (25).

HMRS (EI, 70 eV) *m/z* 228.1149, [228.1150 calc. for $C_{15}H_{16}O$].

Entry	δ_H	δ_C	COSY (^{1}H-^{1}H)	HMBC (^{1}H-^{13}C)
1	9.75 (s, 1H)	202.1	2	2, 3
2	2.49 (td, 2H)	42.9	1, 3	1, 3, 4
3	2.10-1.96 (m, 2H)	21.1	2, 4	1, 2, 4, 5
4	2.70 (t, 2H)	25.0	3	2, 3, 5, 6, 8
5		149.8		
6		116.9		
7	2.00 (s, 3H)	9.9		5, 6, 8
8	6.45 (s, 1H)	108.3		4, 5, 6, 7, 9
9		151.3		
10		131.1		
11	7.62 (dd, 2H)	123.3	12	9, 12, 13
12	7.41-7.30 (m, 2H)	128.6	11, 13	9, 10, 11, 13
13	7.23 (ddd, 1H)	126.8	12	10, 11, 12

4-(3-methyl-5-(thiophen-3-yl)furan-2-yl)butanal (I-47b)



$C_{13}H_{14}O_2S$
234,31

Following procedure D, substrate **I-37b** (41 mg, 0.18 mmol) gave after flash chromatography (Pentanes/Et_2O = 9/1), the furan **I-47b** (36 mg, 0.15 mmol, 86%).

TLC: Rf = 0.14 (Pentanes/Et_2O = 99/1) [CAM/UV]

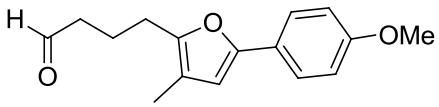
^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 9.76 (s, 1H), 7.39-7.21 (m, 3H), 6.27 (s, 1H), 2.67 (t, *J* = 7.1 Hz, 2H), 2.48 (td, *J* = 7.2, 1.5 Hz, 2H), 2.07-1.93 (m, 5H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] 202.1, 149.0, 148.6, 132.8, 126.0, 124.5, 117.8, 116.5, 108.0, 43.0, 25.0, 21.2, 9.8.

MS (EI, 70 EV) *m/z* (%): 234 (17) [M^+], 206 (12) [M^+-CO], 190 (26) [M^+- C_2H_4O], 177 (100) [M^+- C_3H_5O].

HRMS (EI, 70 eV) *m/z* 234.07054, [234.07018 calc. for $C_{13}H_{14}O_2S$].

4-(5-(4-methoxyphenyl)-3-methylfuran-2-yl)butanal (I-47c)



$C_{16}H_{18}O_3$
258,31

Following procedure D, substrate **I-37c** (40 mg, 0.16 mmol) gave after flash chromatography (Pentanes/Et_2O = 9/1), the furan **I-47c** (36 mg, 0.14 mmol, 88%).

TLC: Rf = 0.47 (Pentanes/EtOAc = 9/1) [CAM/UV]

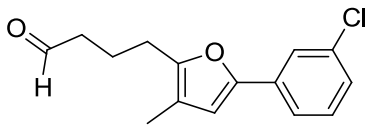
^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 9.76 (s, 1H), 7.65-7.48 (m, 2H), 6.96-6.87 (m, 2H), 6.32 (s, 1H), 3.84 (s, 3H), 2.69 (t, *J* = 7.1 Hz, 2H), 2.50 (td, *J* = 7.2, 1.6 Hz, 2H), 2.07-2.00 (m, 2H), 1.99 (s, 3H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] 202.2, 158.7, 151.4, 149.0, 124.7, 124.3, 116.8, 114.1, 106.7, 55.3, 43.0, 25.1, 21.2, 9.9.

MS (EI, 70 EV) *m/z* (%): 258 (16) [M^+], 214 (13) [M^+- C_2H_4O], 201 (100) [M^+- C_3H_5O], 135 (11).

HRMS (EI, 70 eV) *m/z* 258.12527, [258.12505 calc. for $C_{16}H_{18}O_3$].

4-(5-(3-chlorophenyl)-3-methylfuran-2-yl)butanal (I-47d)



$C_{15}H_{15}ClO_2$
262,73

Following procedure D, substrate **I-37d** (40 mg, 0.15 mmol) gave after flash chromatography (Pentanes/Et_2O = 9/1), the furan **I-47d** (31 mg, 0.12 mmol,77%).

TLC: Rf = 0.26 (Pentanes/Et_2O = 9/1) [UV/CAM]

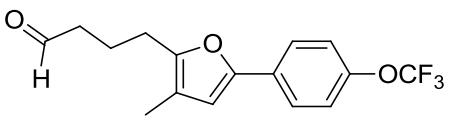
^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 9.77 (s, 1H), 7.59 (t, *J* = 1.8 Hz, 1H), 7.51-7.45 (m, 1H), 7.35-7.24 (m, 1H), 7.19 (ddd, *J* = 8.0, 2.0, 1.1 Hz, 1H), 6.49 (s, 1H), 2.70 (t, *J* = 7.2 Hz, 2H), 2.51 (td, *J* = 2.2, 1.5 Hz, 2H), 2.09-1.95 (m, 5H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] 202.0, 150.5, 149.9, 134.6, 132.7, 129.9, 126.6, 123.2, 121.3, 117.2, 109.5, 43.0, 25.1, 21.1, 9.9.

MS (EI, 70 eV) *m/z* (%): 262 (23) [M^+], 234 (15) [M^+-CO], 218 (54) [M^+- C_2H_4O], 205 (100) [M^+-C_3H_5O], 191 (7), 149 (9), 141 (12), 111 (10), 57 (8), 44 (34).

HRMS (EI, 70 eV) *m/z* 262.0748, [262.0755 calc. for $C_{15}H_{15}O_2Cl$].

4-(3-methyl-5-(4-(trifluoromethoxy)phenyl)furan-2-yl)butanal (I-47e)



$C_{16}H_{15}F_3O_3$
312,28

Following procedure D, substrate **I-37e** (41 mg, 0.13 mmol) gave after flash chromatography (Pentanes/Et_2O = 9/1), the furan **I-47e** (23 mg, 0.07 mmol, 56%).

TLC: Rf = 0.30 (Pentanes/Et_2O = 9/1) [UV/CAM]

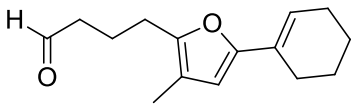
^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 9.77 (s, 1H), 7.65-7.58 (m, 2H), 7.26-7.18 (m, 2H), 6.46 (s, 1H), 2.71 (t, *J* = 7.1 Hz, 2H), 2.51 (td, *J* = 7.2, 1.5 Hz, 2H), 2.09-1.99 (m, 5H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] 202.0, 150.4, 150.1, 147.8, 129.9, 124.5? 121.3, 117.2, 109.0, 43.0, 25.1, 21.1, 9.9.

MS (EI, 70 eV) *m/z* (%): 312 (16) [M^+], 284 (12) [M^+-CO], 268 (38) [M^+- C_2H_4O], 255 (100) [M^+-C_3H_5O], 189 (5).

HRMS (EI, 70 eV) *m/z* 312.0967, [312.0968 calc. for $C_{16}H_{15}O_3F_3$].

4-(5-(cyclohex-1-en-1-yl)-3-methylfuran-2-yl)butanal (I-47f)



$C_{15}H_{20}O_2$
232,32

Following procedure D, substrate **I-37f** (40 mg, 0.17 mmol) gave after flash chromatography (Pentanes/Et_2O = 9/1), the furan **I-47f** (17 mg, 0.07 mmol, 41%).

TLC: Rf = 0.68 (Pentanes/EtOAc = 9/1) [CAM/UV]

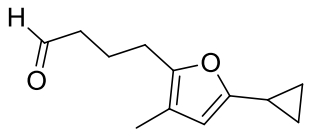
^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 9.72 (s, 1H), 6.28-6.09 (m, 1H), 5.94 (s, 1H), 2.61 (t, *J* = 7.1 Hz, 2H), 2.45 (td, *J* = 7.3, 1.6 Hz, 2H), 2.29-2.12 (m, 4H), 2.03-1.92 (m, 2H), 1.91 (s, 3H), 1.76-1.58 (m, 4H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] 202.2, 153.0, 148.4, 127.2, 121.1, 116.0, 106.9, 43.0, 25.1, 25.0, 24.8, 22.4, 22.3, 21.2, 9.8.

MS (EI, 70 EV) *m/z* (%): 248 (12), 232 (16) [M^+], 205 (34), 191 (18), 175 (63) [M^+- C_3H_5O], 163 (36), 149 (26), 137 (28), 125 (40), 109 (50), 91 (43), 81 (46), 71 (47), 55 (64), 43 (100)

HRMS (EI, 70 eV) *m/z* 232.14581, [232.14578 calc. for $C_{15}H_{20}O_2$].

4-(5-cyclopropyl-3-methylfuran-2-yl)butanal (I-47g)



$C_{12}H_{16}O_2$
192,25

Following procedure D, substrate **I-37g** (49 mg, 0.26 mmol) gave after flash chromatography (Pentanes/Et_2O = 9/1), the furan **I-47g** (23 mg, 0.12 mmol, 47%).

TLC: Rf = 0.59 (Pentanes/EtOAc = 9/1) [CAM/UV]

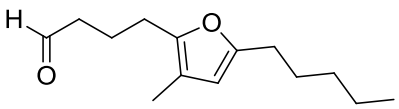
^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 9.70 (s, 1H), 5.72 (s, 1H), 2.56 (t, *J* = 7.1 Hz, 2H), 2.42 (td, *J* = 7.2, 1.6 Hz, 2H), 1.94 (dd, *J* = 14.4, 7.3 Hz, 2H), 1.87 (s, 3H), 1.78 (ddd, *J* = 13.3, 6.6, 4.2 Hz, 1H), 0.82 (ddd, *J* = 12.0, 5.2, 3.3 Hz, 2H), 0.73-0.59 (m, 2H).

^{3}C NMR (63 MHz, $CDCl_3$) δ [ppm] 202.2, 154.9, 147.5, 115.2, 106.6, 43.0, 25.0, 21.3, 9.8, 8.6, 6.4.

MS (EI, 70 eV) *m/z* (%): 192 (20) [M^+], 164 (5) [M^+-CO], 148 (27) [M^+- C_2H_4O], 135 (100) [M^+-C_3H_5O], 91 (10), 55 (6).

HRMS (EI, 70 eV) *m/z* 192.1140, [192.1145 calc. for $C_{12}H_{16}O_2$].

4-(3-methyl-5-pentylfuran-2-yl)butanal (I-47h)



$C_{14}H_{22}O_2$
222,32

Following procedure D, substrate **I-37h** (37 mg, 0.16 mmol) gave after flash chromatography (Pentanes/Et_2O = 9/1), the furan **I-47h** (24 mg, 0.11 mmol, 65%).

TLC: Rf = 0.59 (Pentanes/EtOAc = 9/1) [CAM/UV]

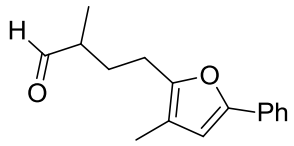
^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 9.72 (s, 1H), 5.76 (s, 1H), 2.59 (t, *J* = 7.1 Hz, 2H), 2.53 (t, *J* = 7.6 Hz, 2H), 2.44 (t, *J* = 7.2 Hz, 2H), 1.96 (dd, *J* = 14.4, 7.2 Hz, 2H), 1.90 (s, 3H), 1.67-1.58 (m, 2H), 1.45-1.26 (m, 4H), 0.91 (t, *J* = 6.7Hz, 3H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] 202.4, 154.1, 147.6, 115.0, 107.8, 43.0, 31.4, 28.0, 27.8, 25.0, 22.4, 21.3, 14.0, 9.8.

MS (EI, 70 eV) *m/z* (%): 222 (18) [M^+], 178 (27) [M^+- C_2H_4O], 165 (100) [M^+- C_3H_5O], 137 (13), 121 (66), 109 (10).

HRMS (EI, 70 eV) *m/z* 222.16129, [222.16143 calc. for $C_{14}H_{22}O_2$].

2-methyl-4-(3-methyl-5-phenylfuran-2-yl)butanal (I-47i)



$C_{16}H_{18}O_2$
242,31

Following procedure D, substrate **I-37i** (27 mg, 0.11 mmol) gave after flash chromatography (Pentanes/Et_2O = 9/1), the furan **I-47i** (22 mg, 0.09 mmol, 93%).

TLC: Rf = 0.48 (Pentanes/Et_2O = 9/1) [UV/CAM]

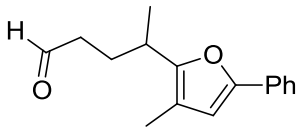
^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 9.61 (s, 1H), 7.70-7.56 (m, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.30-7.16 (m, 1H), 6.45 (s, 1H), 2.71 (t, *J* = 13.1, 6.1 Hz, 1H), 2.27-2.06 (m, 2H), 1.99 (s, 3H), 1.75 (td, *J* = 14.1, 7.1Hz, 1H), 1.29-1.08 (m, 4H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 204.5, 151.3, 149.8, 131.1, 128.6, 126.7, 123.3, 116.8, 108.3, 45.6, 29.8, 23.3, 13.3, 9.9.

MS (EI, 70 eV) *m/z* (%): 242 (15) [M^+], 214 (19) [M^+-CO], 184 (33) [M^+- C_3H_6O], 171 (100) [M^+-C_4H_7O], 128 (12), 105 (7), 77 (8), 44 (36).

HRMS (EI, 70 eV) *m/z* 242.13006, [242.13013 calc. for $C_{16}H_{18}O_2$].

4-(3-methyl-5-phenylfuran-2-yl)pentanal (I-47j)



$C_{16}H_{18}O_2$
242,31

Following procedure D, substrate **I-37j** (19 mg, 0.08 mmol) gave after flash chromatography (Pentanes/Et_2O = 9/1), the furan **I-47j** (15 mg, 0.06 mmol, 78%).

TLC: Rf = 0.66 (Pentanes/EA = 9/1) [UV/CAM]

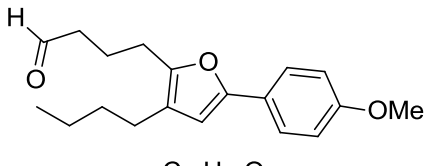
^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 9.69 (s, 1H), 7.69-7.54 (m, 2H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.24 (t, *J* = 7.3 Hz, 1H), 6.46 (s, 1H), 2.95 (dq, *J* = 13.8, 6.9 Hz, 1H), 2.47-2.35 (m, 2H), 2.10-1.90 (m, 5H), 1.36 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 202.2, 152.7, 151.2, 131.1, 128.6, 126.8, 123.3, 116.4, 108.3, 42.1, 30.9, 28.4, 19.7, 9.8.

MS (EI, 70 eV) *m/z* (%): 242 (17) [M^+], 214 (7) [M^+- CO], 198 (19) [M^+- C_2H_4O], 185 (100) [M^+- C_3H_5O], 171 (6) [M^+- C_4H_7O], 158 (6), 141 (7), 128 (8), 105 (13), 77 (12), 55 (7), 44 (62).

HRMS (EI, 70 eV) *m/z* 242.1299, [242.1301 calc. for $C_{16}H_{18}O_2$].

4-(3-butyl-5-(4-methoxyphenyl)furan-2-yl)butanal (I-47k)



$C_{19}H_{24}O_3$
300,39

Following procedure D, substrate **I-37k** (40 mg, 0.14 mmol) gave after flash chromatography (Pentanes/Et_2O = 9/1), the furan **I-47k** (31 mg, 0.10 mmol, 77%).

TLC: Rf = 0.27 (Pentanes/Et_2O = 9/1) [UV/CAM]

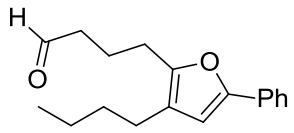
^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 9.78 (d, *J* = 1.4 Hz, 1H), 7.57-7.53 (m, 2H), 6.94-6.90 (m, 2H), 6.36 (s, 1H), 3.85 (s, 3H), 2.70 (t, *J* = 7.2 Hz, 2H), 2.52 (td, *J* = 7.3, 1.5 Hz, 2H), 2.37- 2.32 (m, 2H), 2.03 (p, *J* = 7.2 Hz, 2H), 1.54 (ddd, *J* = 12.6, 8.7, 6.4 Hz, 2H), 1.38 (dd, *J* = 15.0, 7.4 Hz, 2H), 0.95 (t, J = 7.3 Hz, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 202.2, 158.6, 151.5, 148.7, 124.7, 124.3, 122.1, 114.0, 105.5, 55.3, 43.0, 32.7, 25.1, 24.4, 22.4, 21.3, 13.9.

MS (EI, 70 eV) *m/z* (%): 300 (43) [M^+], 272 (16) [M^+-CO], 256 (15)[M^+- C_2H_4O], 243 (100) [M^+-C_3H_5O], 227 (11), 215 (19), 201 (33), 135 (18), 57 (9), 43 (15).

HRMS (EI, 70 eV) *m/z* 300.17142, [300.17200 calc. for $C_{19}H_{24}O_3$].

4-(3-butyl-5-phenylfuran-2-yl)butanal (I-47l)



$C_{18}H_{22}O_2$
270,37

Following procedure D, substrate **I-37l** (40 mg, 0.15 mmol) gave after flash chromatography (Pentanes/Et_2O = 9/1), the furan **I-47l** (25 mg, 0.09 mmol, 63%).

TLC: Rf = 0.30 (Pentanes/Et_2O = 9/1) [UV/CAM]

^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 9.77 (s, 1H), 7.61 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.49-7.30 (m, 2H), 7.30-7.12 (m, 1H), 6.48 (s, 1H), 2.69 (t, *J* = 7.2 Hz, 2H), 2.51 (td, *J* = 7.3, 1.5 Hz, 2H), 2.34 (t, *J* = 7.4 Hz, 2H), 2.02 (p, *J* = 7.3 Hz, 2H), 1.61-1.45 (m, 2H), 1.45-1.25 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H).

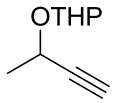
^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 202.1, 151.4, 149.5, 131.1, 128.5, 126.7, 123.2, 122.2, 107.0, 43.0, 32.7, 25.1, 24.4, 22.3, 21.3, 13.9.

MS (EI, 70 eV) *m/z* (%): 270 (20) [M^+], 242 (18) [M^+-CO], 226 (25) [M^+- C_2H_4O], 213 (100) [M^+-C_3H_5O], 197 (18), 185 (20), 171 (54), 158 (9), 141 (9), 105 (20), 77 (10), 43 (14).

HRMS (EI, 70 eV) *m/z* 270.16126, [270.16143 calc.for $C_{18}H_{22}O_2$].

2.2) Propargyl-Claisen Rearrangement

2-(but-3-yn-2-yloxy)tetrahydro-2H-pyran (I-76a)



$C_9H_{14}O_2$
154,21

(Procedure A)[87]

At rt, a few drops of concentrated hydrochloric acid were added to a mixture of 3-butyn-2-ol (5.00 g, 71.3 mmol) and dihydropyran (6.60 g, 78.5 mmol), the mixture was stirred at rt for 1.5 h. It was dried with $MgSO_4$, and after filtration the crude product was purified by distillation (Bp: 65-70°C (15 mbar)) to give the product (6.01 g, 42.2 mmol, 59%) as a diastereoisomeric mixture.

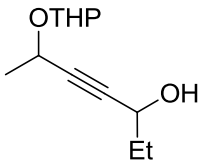
TLC: Rf = 0.83 (Cyclohexane/EtOAc = 1/1) [CAM]

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] 4.97 – 4.91 (m, 0.85H), 4.77 (t, *J* = 3.4 Hz, 0.15H), 4.55 (qd, *J* = 6.7, 1.9 Hz, 0.85H), 4.46 (qd, *J* = 6.6, 2.1 Hz, 0.15H), 4.03 – 3.96 (m, 0.15H), 3.82 (ddd, *J* = 11.3, 8.5, 3.1 Hz, 0.85H), 3.53 (dt, *J* = 6.5, 4.7 Hz, 1.10H), 2.42 (d, *J* = 2.1 Hz, 0.15H), 2.37 (d, *J* = 2.0 Hz, 0.80H), 1.89 – 1.79 (m, 1.15H), 1.75 (ddt, *J* = 12.2, 9.0, 3.0 Hz, 1.0H), 1.65 – 1.50 (m, 3.80H), 1.48 (d, *J* = 6.7 Hz, 2.65H), 1.44 (d, *J* = 6.6 Hz, 0.50H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] (97.3, 96.1), (84.7, 83.9), (72.6, 72.0), (62.7, 62.42, 62.37), 60.8, (30.71, 30.67), (25.6, 25.5), (22.2, 22.0), (19.6, 19.3).

The analytical data are identical to the literature data.[87]

6-((tetrahydro-2H-pyran-2-yl)oxy)hept-4-yn-3-ol (I-77a)



$C_{12}H_{20}O_3$
212,29

(Procedure B)[87]

At -78°C, *n*BuLi (9.3 mL, 23.2 mmol, 2.5 M in hexanes) was slowly added to a solution of 2-(but-3-yn-2-yloxy)tetrahydro-2H-pyran **I-76a** (3.0 g, 21.1 mmol) in dry THF (21.1 mL, 1 M). The mixture was stirred at -78°C for 2 h and then propanal (1.40 g, 24.0 mmol) was added dropwise, the solution was stirred for 2h. After allowing the mixture to warm to room temperature, it was quenched with sat. NH_4Cl-solution and extracted three times with Et_2O. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Cyclohexane/EtOAc = 4/1) to obtain the product (3.83 g, 18.0 mmol, 86%) as a diastereoisomeric mixture.

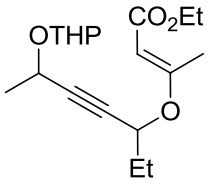
TLC: Rf = 0.26 (Cyclohexane/EtOAc = 4/1) [CAM].

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] 4.90 (t, *J* = 3.5 Hz, 0.80H), 4.75 (t, *J* = 3.4 Hz, 0.20H), 4.56 (qd, *J* = 6.7, 1.4 Hz, 0.80H), 4.47 (qd, *J* = 6.6, 1.5 Hz, 0.20H), 4.33 (dd, *J* = 11.0, 5.5 Hz, 1H), 3.96 (ddd, *J* = 12.8, 7.8, 3.1 Hz, 0.20H), 3.79 (ddd, *J* = 11.3, 8.5, 3.2 Hz, 0.80H), 3.49 (ddt, *J* = 10.2, 6.9, 5.2 Hz, 1.0H), 1.87 – 1.47 (m, 9H), 1.43 (d, *J* = 6.7 Hz, 2.45H), 1.40 (d, *J* = 6.6 Hz, 0.60H), 0.98 (td, *J* = 7.4, 3.0 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] (97.4, 96.05), (85.71, 85.68), (84.92, 84.88), (63.92, 62.91), (62.68, 62.67), 61.0, (31.12, 31.09) (30.82, 30.75), (25.7, 25.6), (22.4, 22.2), (19.7, 19.4), (9.60, 9.59).

The analytical data are identical to the literature data.[87]

(*E*)-ethyl 3-((6-((tetrahydro-2H-pyran-2-yl)oxy)hept-4-yn-3-yl)oxy)but-2-enoate (I-78a)



$C_{18}H_{28}O_5$
324,41

(Procedure C)[88]

At rt, P(*n*Bu)$_3$ (191 mg, 0.942 mmol) was added dropwise to the solution of propargyl alcohol **I-77a** (1.0 g, 4.71 mmol) and ethyl 2-butynoate (581.0 mg, 5.18 mmol) in dry CH_2Cl_2 (15.7 mL, 0.3 M). The mixture was stirred at room temperature for 24 h, and then concentrated under reduced pressure. The residue was purified by flash chromatography (Cyclohexane/EtOAc = 9/1) to obtain the product (1.48 g, 4.50 mmol, 95%) as a diastereoisomeric mixture.

TLC: Rf = 0.42 (Cyclohexane/EtOAc = 4/1) [CAM]

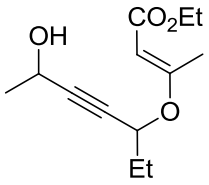
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 5.23 (d, *J* = 1.9 Hz, 0.15H), 5.22 (d, *J* = 3.0 Hz, 0.85H), 4.90 – 4.84 (m, 0.85H), 4.77 (t, *J* = 3.2 Hz, 0.15H), 4.63 – 4.55 (m, 1H), 4.55 – 4.48 (m, 1H), 4.18 – 4.09 (m, 2H), 3.96 (dd, *J* = 14.2, 6.2 Hz, 0.20H), 3.82 (ddd, *J* = 10.9, 7.3, 3.4 Hz, 0.80H), 3.49 (td, *J* = 10.9, 4.6 Hz, 1H), 2.29 (d, *J* = 1.5 Hz, 3H), 1.90 – 1.80 (m, 3H), 1.63 – 1.49 (m, 5H), 1.45 (d, *J* = 6.7 Hz, 2.30H), 1.42 (dd, *J* = 6.7, 1.4 Hz, 0.70H), 1.26 (td, *J* = 7.1, 1.4 Hz, 3H), 1.03 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] (170.60, 170.56), 168.1, (96.3, 96.2), 93.3, (87.4, 87.2), (81.5, 81.3), (69.0, 68.9), (62.9, 62.8), (60.92, 60.88), 59.5, 30.7, (28.74, 28.71), (25.59, 25.58), (22.05, 21.98), (19.8, 19.7), 19.2, 14.6, (9.63, 9.59).

MS (EI) *m/z* (%): 281.1 (20), 222.1 (78) [M^+-*n*Pr], 161.0 (42), 151.0 (59), 85.1 (100).

HRMS (ESI) *m/z* 347.1829 [347.1829 calcd. for $C_{18}H_{28}O_5Na$ (M^++Na^+)].

(*E*)-ethyl 3-((6-hydroxyhept-4-yn-3-yl)oxy)but-2-enoate (I-72a)



$C_{13}H_{20}O_4$
240,30

(Procedure D)[89]

At rt, PPTS (466 mg, 1.86 mmol) was added to a solution of THP-protected alcohol **I-78a** (3.05 g, 9.28 mmol) in dry MeOH (37 mL, 0.25 M). The mixture was heated to 40°C and stirred for 24 h. It was quenched with sat. $NaHCO_3$-solution and extracted three times with Et_2O. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Cyclohexane/EtOAc = 4/1) to obtain the product (1.01 g, 4.20 mmol, 45%).

TLC: Rf = 0.27 (Cyclohexane/EtOAc = 4/1) [CAM]

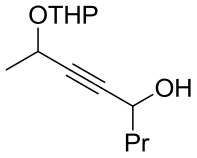
^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] 5.22 (s, 1H), 4.59 (q, *J* = 6.4 Hz, 1H), 4.55 (t, *J* = 6.3 Hz, 1H), 4.22 – 4.12 (m, 2H), 2.32 (s, 3H), 1.88 (dtd, *J* = 14.0, 7.2, 2.6 Hz, 3H), 1.48 (d, *J* = 6.6 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.06 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 170.4, 167.9, 93.2, 89.0, 80.7, 68.7, 59.4, 58.3, 28.6, 24.2, 19.0, 14.4, 9.5.

MS (EI) *m/z* (%): 240.0 (5) [M^+], 222.1 (54) [M^+-H_2O], 165.0 (100) [M^+-$EtCH_2O_2$], 161.0 (85), 151.1 (75), 123 (60), 107 (51), 91.1 (58), 79 (58).

HRMS (ESI) *m/z* 263.1255 [263.1254 calcd. for $C_{13}H_{20}O_4Na$ (M^++Na^+)].

7-((tetrahydro-2H-pyran-2-yl)oxy)oct-5-yn-4-ol (I-77b)



$C_{13}H_{22}O_3$
226,31

Following procedure B, propargyl alcohol **I-76a** (500 mg, 3.51 mmol) was added to butanal (288.9 mg, 4.01 mmol). After flash chromatography (Cyclohexane/EtOAc = 4/1), the product (513.1 mg, 2.27 mmol, 65%) was obtained as a diastereoisomeric mixture.

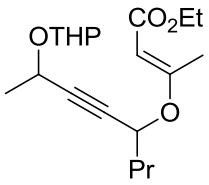
TLC: Rf = 0.29 (Cyclohexane/EtOAc = 4/1) [CAM]

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 4.91 (t, *J* = 3.4 Hz, 0.85H), 4.77 (t, *J* = 3.4 Hz, 0.15H), 4.62 – 4.54 (m, 0.85H), 4.53 – 4.45 (m, 0.25H), 4.40 (dd, *J* = 11.5, 5.9 Hz, 1H), 3.97 (dd, *J* = 14.4, 6.1 Hz, 0.20H), 3.86 – 3.77 (m, 0.80H), 3.56 – 3.48 (m, 1H), 1.88 – 1.41 (m, 14H), 0.97 – 0.91 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 96.0, 85.9, 84.7, 62.6, 62.4, 60.9, (40.09, 40.05), 30.7, 25.6, 22.3, 19.6, 18.6, 13.9.

The analytical data are identical to the literature data.[87]

(*E*)-ethyl 3-((7-((tetrahydro-2H-pyran-2-yl)oxy)oct-5-yn-4-yl)oxy)but-2-enoate (I-78b)



$C_{19}H_{30}O_5$
338,44

Following procedure C, propargyl alcohol **I-77b** (316.1 mg, 1.40 mmol) was added to ethyl 2-butynoate (156.0 mg, 1.40 mmol). After flash chromatography (Cyclohexane/EtOAc = 9/1), the product (287.0 mg, 0.85 mmol, 61%) was obtained as a diastereoisomeric mixture.

TLC: Rf = 0.4 (Cyclohexane/EtOAc= 4/1) [CAM]

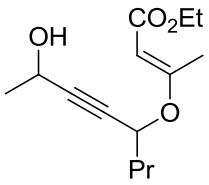
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 5.23 (d, *J* = 2.1 Hz, 0.15H), 5.22 (d, *J* = 3.1 Hz, 0.85H), 4.90 – 4.83 (m, 0.15H), 4.77 (t, *J* = 3.3 Hz, 0.85H), 4.61 – 4.53 (m, 1.90H), 4.50 – 4.44 (m, 0.10H), 4.18 – 4.07 (m, 2H), 3.82 (ddd, *J* = 10.9, 7.4, 3.3 Hz, 1H), 3.55 – 3.44 (m, 1H), 2.28 (d, *J* = 1.6 Hz, 3H), 1.89 – 1.66 (m, 4H), 1.63 – 1.46 (m, 6H), 1.44 (d, *J* = 6.7 Hz, 3H), 1.26 (td, *J* = 7.1, 1.4 Hz, 3H), 0.99 – 0.91 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] (170.63, 170.57), 168.1, (96.3, 96.2), 93.3, (87.3, 87.1), (81.7, 81.5), 67.5, (62.95, 62.81), (60.93, 60.89), 59.5, (37.48, 37.45), 30.7, (25.60, 25.58), (22.1, 22.0), (19.8, 19.7), 19.2, (18.54, 18.56), 14.6, 13.8.

MS (EI) *m/z* (%): 236.0 (59) [M^+-THPOH], 165.0 (67), 161.0 (41), 85.0 (100), 55.0 (53).

HRMS (ESI) *m/z* 361.1986 [361.1985 calcd. for $C_{19}H_{30}O_5Na$ (M^++Na^+)].

(*E*)-ethyl 3-((7-hydroxyoct-5-yn-4-yl)oxy)but-2-enoate (I-72b)



$C_{14}H_{22}O_4$
254,32

Following procedure D, THP-protected alcohol **I-78b** (227.3 mg, 0.680 mmol) was deprotected. After flash chromatography (Cyclohexane/EtOAc = 9/1), the product (60 mg, 0.236 mmol, 35%) was obtained.

TLC: Rf = 0.13 (Cyclohexane/EtOAc = 9/1) [CAM]

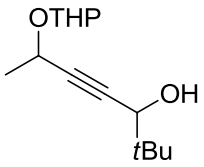
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 5.20 (s, 1H), 4.56 (q, *J* = 6.3 Hz, 2H), 4.19 – 4.09 (m, 2H), 2.28 (s, 3H), 1.95 – 1.74 (m, 3H), 1.54 – 1.46 (m,2H), 1.44 (d, *J* = 6.6 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 170.6, 168.1, 93.3, 89.1, 81.1, 67.5, 59.6, 58.5, 37.5, 24.3, 19.2, 18.5, 14.6, 13.7.

MS (EI) *m/z* (%): 254.1 (2) [M^+], 236.1 (35) [M^+-H_2O], 211.1 (51) [M^+-C_2H_3O], 181.1 (36) [M^+-CO_2Et], 165.0 (100) [M^+- $PrCH_2O_2$], 137.0 (46), 91.0 (46).

HRMS (ESI) *m/z* 277.1410 [277.1410 calcd. for $C_{14}H_{22}O_4Na$ (M^++Na^+)].

2,2-dimethyl-6-((tetrahydro-2H-pyran-2-yl)oxy)hept-4-yn-3-ol (I-77c)



$C_{14}H_{24}O_3$
240,34

Following procedure B, propargyl alcohol **I-76a** (500 mg, 3.51 mmol) was added to pivaldehyde (345.4 mg, 4.01 mmol). After flash chromatography (Cyclohexane/EtOAc = 4/1), the product (265.0 mg, 1.10 mmol, 31%) was obtained as a diastereoisomeric mixture.

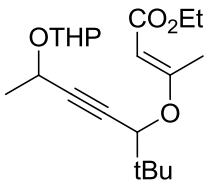
TLC: Rf = 0.32 (Cyclohexane/EtOAc = 4/1) [CAM]

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] 4.92 (t, *J* = 3.4 Hz, 0.85H), 4.78 (s, 0.15H), 4.59 (qd, *J* = 6.7, 1.4 Hz, 0.85H), 4.51 (qd, *J* = 6.6, 4.5 Hz, 0.15H), 4.03 (d, *J* = 6.0 Hz, 1H), 3.98 (ddd, *J* = 11.8, 9.1, 2.9 Hz, 0.15H), 3.82 (ddd, *J* = 11.1, 8.3, 3.1 Hz, 0.85H), 3.55 – 3.48 (m, 1H), 1.87 – 1.80 (m, 1H), 1.73 (ddd, *J* = 15.7, 13.5, 8.8 Hz, 2H), 1.63 – 1.50 (m, 4H), 1.46 (dd, *J* = 6.7, 1.2 Hz, 2.70H), 1.43 (d, *J* = 6.6 Hz, 0.50H), 0.99 (d, *J* = 3.7 Hz, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] (95.91, 95.88), 85.5, 84.2, 71.3, 71.3, 62.5, 60.8, 35.8, 30.5, 25.4, 25.2, 25.2, 22.1, 19.5.

The analytical data are identical to the literature data.[90]

(*E*)-ethyl 3-((2,2-dimethyl-6-((tetrahydro-2H-pyran-2-yl)oxy)hept-4-yn-3-yl)oxy)but-2-enoate (I-78c)



$C_{20}H_{32}O_5$
352,47

Following procedure C, propargyl alcohol **I-77c** (255.6 mg, 1.06 mmol) was added to ethyl 2-butynoate (118.9 mg, 1.06 mmol). After flash chromatography (Cyclohexane/EtOAc = 9/1), the product (359.9 mg, 1.02 mmol, 96%) was obtained as a diastereoisomeric mixture.

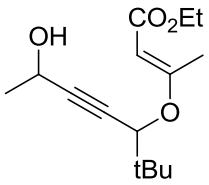
TLC: Rf = 0.51 (Cyclohexane/EtOAc = 4/1) [CAM]

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 5.26 (s, 0.15H), 5.24 (d, *J* = 1.6 Hz, 0.85H), 4.87 (td, *J* = 4.9, 2.9 Hz, 0.85H), 4.78 (t, *J* = 3.3 Hz, 0.15H), 4.62 – 4.56 (m, 0.90H), 4.48 (qd, *J* = 6.7, 1.5 Hz, 0.15H), 4.19 (d, *J* = 1.2 Hz, 1H), 4.18 – 4.06 (m, 2H), 3.86 – 3.78 (m, 1H), 3.54 – 3.44 (m, 1H), 2.30 (d, *J* = 1.7 Hz, 3H), 1.82 (dt, *J* = 9.6, 5.6 Hz, 1H), 1.77 – 1.65 (m, 1H), 1.63 – 1.48 (m, 4H), 1.45 (d, *J* = 6.7 Hz, 3H), 1.29 – 1.23 (m, 3H), 1.02 (d, *J* = 0.9 Hz, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] (171.00, 171.95), 168.1, (96.4, 96.3), 93.3, (88.1, 87.9), (80.3, 80.1), 76.3, (63.0, 62.9), (61.00, 60.96), 59.4, 35.7, 30.7, (25.76, 25.73), (25.61, 25.59), (22.1, 22.0), (19.9, 19.8), 19.0, 14.6.

HRMS (ESI) *m/z* 375.2140 [375.2142 calcd. for $C_{20}H_{32}O_5Na$ (M^++Na^+)].

(*E*)-ethyl 3-((6-hydroxy-2,2-dimethylhept-4-yn-3-yl)oxy)but-2-enoate (I-72c)



$C_{15}H_{24}O_4$
268,35

Following procedure D, THP-protected alcohol **I-78c** (302 mg, 0.851 mmol) was deprotected. After flash chromatography (Cyclohexane/EtOAc = 9/1), the product (132 mg, 0.492 mmol, 57 %) was obtained.

TLC: Rf = 0.1 (Cyclohexane/EtOAc = 9/1) [CAM]

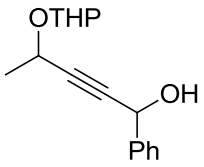
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 5.22 (s, 1H), 4.57 (p, *J* = 6.2 Hz, 1H), 4.21 – 4.19 (m, 1H), 4.17 – 4.11 (m, 2H), 2.30 (s, 3H), 1.89 (s, 1H), 1.46 (d, *J* = 6.6 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.02 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 170.9, 168.1, 93.3, 89.8, 79.7, 76.2, 59.5, 58.5, 35.7, 25.7, 24.4, 19.0, 14.6.

MS (EI) *m/z* (%): 250.1 (36) [M^+-H_2O], 189.1 (86), 179.0 (36), 165.0 (100) [M^+-*t*BuCH_2O_2], 137.1 (58), 91.0 (43).

HRMS (ESI) *m/z* 291.1572 [291.1567 calcd. for $C_{15}H_{24}O_4Na$ (M^++Na^+)].

1-phenyl-4-((tetrahydro-2H-pyran-2-yl)oxy)pent-2-yn-1-ol (I-77d)



$C_{16}H_{20}O_3$
260,33

Following procedure B, propargyl alcohol **I-76a** (500 mg, 3.51 mmol) was added to benzaldehyde (425.6 mg, 4.01 mmol). After flash chromatography (Cyclohexane/EtOAc = 4/1), the product (779.4 mg, 2.99 mmol, 85%) was obtained as a diastereoisomeric mixture.

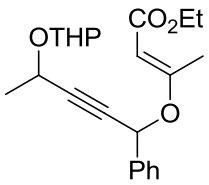
TLC: Rf = 0.27 (Cyclohexane/EtOAc = 4/1) [CAM]

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] 7.56 (d, *J* = 7.5 Hz, 2H), 7.41 (dd, *J* = 10.5, 4.3 Hz, 2H), 7.36 (t, *J* = 7.3 Hz, 1H), 5.53 (d, *J* = 6.0 Hz, 1H), 4.97 (dd, *J* = 4.5, 2.5 Hz, 0.85H), 4.82 (t, *J* = 3.4 Hz, 0.15H), 4.68 (qd, *J* = 6.7, 1.3 Hz, 0.85H), 4.60 – 4.55 (m, 0.15H), 4.02 – 3.96 (m, 0.15H), 3.89 – 3.79 (m, 0.85H), 3.57 – 3.51 (m, 1H), 2.25-2.19 (m, 1H), 1.90 – 1.82 (m, 1H), 1.80 – 1.73 (m, 1H), 1.64-1.55 (m, 4H), 1.53 (dd, *J* = 6.7, 1.2 Hz, 2.65H), 1.49 (dd, *J* = 6.6, 1.7 Hz, 0.45H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 140.7, 128.8, 128.7, 128.6, 126.8, 126.8, 96.1, 86.9, 84.4, 64.8, 62.7, 61.0, 30.7, 25.6, 22.2, 19.6.

The analytical data are identical to the literature data.[87]

(*E*)-ethyl 3-((1-phenyl-4-((tetrahydro-2H-pyran-2-yl)oxy)pent-2-yn-1-yl)oxy)but-2-enoate (I-78d)



$C_{22}H_{28}O_5$
372,45

Following procedure C, propargyl alcohol **I-77d** (300 mg, 1.15 mmol) was added to ethyl 2-butynoate (128.9 mg, 1.15 mmol). After flash chromatography (Cyclohexane/EtOAc = 9/1), the product (310.2 mg, 0.83 mmol, 72%) was obtained as a diastereoisomeric mixture.

TLC: Rf = 0.51 (Cyclohexane/EtOAc = 4/1) [CAM]

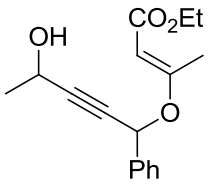
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.46 (dd, *J* = 7.7, 1.7 Hz, 2H), 7.40 – 7.32 (m, 3H), 5.64 (s, 0.15H), 5.62 (s, 0.85H), 5.34 (d, *J* = 4.4 Hz, 1H), 4.85 (td, *J* = 5.0, 2.8 Hz, 0.85H), 4.75 (dd, *J* = 6.0, 3.2 Hz, 0.15H), 4.67 – 4.57 (m, 0.85H), 4.50 – 4.47 (m, 0.15H), 4.17 – 4.07 (m, 2H), 3.84 – 3.75 (m, 1H), 3.46 (tt, *J* = 17.3, 5.8 Hz, 1H), 2.30 (d, *J* = 2.0 Hz, 3H), 1.84 – 1.74 (m, 1H), 1.73 – 1.62 (m, 1H), 1.53 – 1.41 (m, 7H), 1.25 (q, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] (170.4, 170.3), 167.9, 137.0, 129.1, 128.8, (128.55, 128.53), (127.52, 127.49), (96.4, 96.3), 94.0, (89.6, 89.5), (80.6, 80.4), (69.8, 69.7), (63.0, 62.8), (61.02, 60.97), 59.6, 30.7, (25.57, 25.56), (22.0, 21.9), (19.8, 19.7), 19.3, 14.6.

MS (EI) *m/z* (%): 270.1 (100) [M^+-THPOH], 181.0 (29), 153.0 (41).

HRMS (ESI) *m/z* 395.1827 [395.1829 calcd. for $C_{22}H_{28}O_5Na$ (M^++Na^+)].

(*E*)-ethyl 3-((4-hydroxy-1-phenylpent-2-yn-1-yl)oxy)but-2-enoate (I-72d)



$C_{17}H_{20}O_4$
288,34

Following procedure D, THP-protected alcohol **I-78d** (200 mg, 0.537 mmol) was deprotected. After flash chromatography (Cyclohexane/EtOAc = 9/1), the product (67.5 mg, 0.234 mmol, 44%) was obtained.

TLC: Rf = 0.10 (Cyclohexane/EtOAc = 9/1) [CAM]

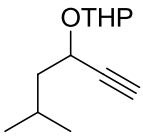
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.49 (dd, *J* = 7.9, 1.7 Hz, 2H), 7.42 – 7.38 (m, 3H), 5.66 (d, *J* = 0.8 Hz, 1H), 5.34 (s, 1H), 4.65 – 4.57 (m, 1H), 4.16 (tdd, *J* = 7.1, 3.5, 2.0 Hz, 2H), 2.34 (s, 3H), 1.90 (s, 1H), 1.50 – 1.46 (m, 3H), 1.32 – 1.25 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 170.3, 167.9, 136.9, 129.2, 128.9, 128.8, 127.4, 94.1, 80.1, 69.7, 59.7, 58.6, 24.2, 19.3, 14.6.

MS (EI) *m/z* (%): 270.1 (100) [M^+-H_2O], 181.0 (27) [M^+-PhCO], 153.0 (44).

HRMS (ESI) *m/z* 311.1254 [311.1254 calcd. for $C_{17}H_{20}O_4Na$ (M^++Na^+)].

2-((5-methylhex-1-yn-3-yl)oxy)tetrahydro-2H-pyran (I-76b)



$C_{12}H_{20}O_2$
196,29

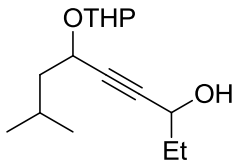
Following procedure A, 5-Methyl-1-hexyn-3-ol (1.0 g, 8.92 mmol) was protected with dihydropyran (0.825 g, 9.81 mmol). After distillation (T = 65-75°C, 1 mmHg), the product (1.02 g, 5.19 mmol, 58%) was obtained as a diastereoisomeric mixture.

TLC: Rf = 0.51 (Cyclohexane/EtOAc = 4/1) [CAM]

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 4.99 (t, *J* = 3.3 Hz, 0.85H), 4.95 (dd, *J* = 4.8, 2.8 Hz, 0.15H), 4.48 (ddd, *J* = 7.7, 6.8, 2.0 Hz, 0.85H), 4.31 (td, *J* = 7.2, 2.1 Hz, 0.15H), 4.03 (qd, *J* = 8.7, 4.2 Hz, 0.15H), 3.81 (ddd, *J* = 11.7, 8.7, 3.2 Hz, 0.90H), 3.57 – 3.49 (m, 1H), 2.43 (d, *J* = 2.1 Hz, 0.15H), 2.36 (d, *J* = 2.0 Hz, 0.85H), 1.91 (dd, *J* = 13.5, 6.8 Hz, 1H), 1.79 – 1.67 (m, 2H), 1.59 (dt, *J* = 20.7, 6.8 Hz, 6H), 0.94 (dt, *J* = 7.9, 3.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 95.6, 83.3, 73.2, 63.5, 62.5, 44.8, 30.7, 25.6, 24.8, 22.8, 22.6, 19.5.

8-methyl-6-((tetrahydro-2H-pyran-2-yl)oxy)non-4-yn-3-ol (I-77e)



$C_{15}H_{26}O_3$
254,37

Following procedure B, propargyl alcohol **I-76b** (500 mg, 2.55 mmol) was added to propanal (168.7 mg, 2.90 mmol). After flash chromatography (Cyclohexane/EtOAc = 4/1), the product (503.6 mg, 1.98 mmol, 78%) was obtained as a diastereoisomeric mixture.

TLC: Rf = 0.50 (Cyclohexane/EtOAc = 4/1) [CAM]

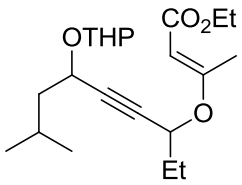
^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] 5.09 (s, 0.15H), 4.97 (s, 0.85H), 4.55 (q, *J* = 5.4 Hz, 0.10H), 4.53 – 4.49 (m, 0.90H), 4.35 (d, *J* = 5.9 Hz, 1H), 4.04 – 3.99 (m, 0.10H), 3.80 (ddd, *J* = 11.8, 9.1, 3.0 Hz, 0.85H), 3.56 – 3.50 (m, 1H), 1.89 (dd, *J* = 13.5, 6.7 Hz, 1H), 1.80 (d, *J* = 5.6 Hz, 1H), 1.77 – 1.65 (m, 4H), 1.65 – 1.49 (m, 6H), 1.00 (t, *J* = 7.4 Hz, 3H), 0.94 (dd, *J* = 9.2, 6.7 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] (95.51, 95.49), (86.3, 86.2), (84.30, 84.25), (63.90, 63.88), (63.65, 63.64), (62.40, 62.38), (44.95, 44.94), (31.09, 31.06), 30.7, 25.6, (24.88, 24.87), 22.9, 22.6, 19.4, (9.52, 9.50).

MS (EI) *m/z* (%): 152.1 (3) [M^+-THPOH], 95.1 (15), 85.0 (100) [THP], 84.0 (17), 57.0 (32), 55.0 (31).

HRMS (ESI) *m/z* 277.1777 [277.1774 calcd. for $C_{15}H_{26}O_3Na$ (M^++Na^+)].

(*E*)-ethyl 3-((8-methyl-6-((tetrahydro-2H-pyran-2-yl)oxy)non-4-yn-3-yl)oxy)but-2-enoate (I-78e)



$C_{21}H_{34}O_5$
366,49

Following procedure C, propargyl alcohol **I-77e** (490 mg, 1.93 mmol) was added to ethyl 2-butynoate (237.7 mg, 2.12 mmol). After flash chromatography (Cyclohexane/EtOAc = 9:1), the product (549.9 mg, 1.50 mmol, 78%) was obtained as a diastereoisomeric mixture.

TLC: Rf = 0.63 (Cyclohexane/EtOAc = 4/1) [CAM]

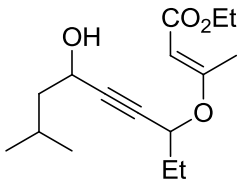
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 5.24 (s, 0.10H), 5.22 (s, 0.90H), 4.92 (dt, *J* = 6.9, 3.6 Hz, 0.90H), 4.82 – 4.75 (m, 0.20H), 4.61 (t, *J* = 5.3 Hz, 0.10H), 4.52 (td, *J* = 6.6, 3.1 Hz, 1.90H), 4.17 – 4.07 (m, 2H), 3.80 (dd, *J* = 13.6, 6.3 Hz, 1H), 3.57 – 3.46 (m, 1H), 2.32 (t, *J* = 2.3 Hz, 0.5H), 2.29 (d, *J* = 1.7 Hz, 2.5H), 1.92 – 1.47 (m, 11H), 1.26 (td, *J* = 7.1, 1.4 Hz, 3H), 1.03 (t, *J* = 7.4 Hz, 3H), 0.96 – 0.90 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 170.4, 167.9, (95.73, 95.65), 93.2, (86.7, 86.5), (82.0, 81.8), 68.8, 63.7, (62.5, 62.4), 59.3, 44.4, 30.5, 28.6, 25.5, 24.8, 22.6, (19.5, 19.4), 19.0, 14.4, (9.5, 9.4).

MS (EI) *m/z* (%): 264.1 (22) [M^+-THPOH], 221.1 (51) [M^+-THPOH-*n*Pr], 207.0 (25), 175.0 (26), 85.0 (100).

HRMS (ESI) *m/z* 389.2303 [389.2298 calcd. for $C_{21}H_{34}O_5Na$ (M^++Na^+)].

(*E*)-ethyl 3-((6-hydroxy-8-methylnon-4-yn-3-yl)oxy)but-2-enoate (I-72e)



$C_{16}H_{26}O_4$
282,38

Following procedure D, THP-protected alcohol **I-78e** (450 mg, 1.23 mmol) was deprotected. After flash chromatography (Cyclohexane/EtOAc = 9/1), the product (239.6 mg, 0.849 mmol, 67%) was obtained.

TLC: Rf = 0.16 (Cyclohexane/EtOAc = 9/1) [CAM]

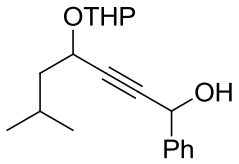
^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] 5.20 (s, 1H), 4.52 (t, *J* = 6.3 Hz, 1H), 4.45 (t, *J* = 6.7 Hz, 1H), 4.19 – 4.09 (m, 2H), 2.29 (d, *J* = 2.1 Hz, 3H), 1.91 – 1.79 (m, 3H), 1.73 (s, 1H), 1.66 – 1.60 (m, 1H), 1.59 – 1.52 (m, 1H), 1.27 (td, *J* = 7.1, 1.8 Hz, 3H), 1.03 (t, *J* = 7.4 Hz, 3H), 0.99 – 0.88 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 170.5, 168.0, 93.4, 88.7, 81.6, 68.9, 61.2, 59.5, (46.83, 46.80), 28.8, 25.0, (22.68, 22.66), 22.6, 19.1, 14.6, 9.6.

MS (EI) *m/z* (%): 282.1 (4) [M^+], 264.2 (36) [M^+-H_2O], 221.1 (100) [M^+-H_2O-*n*Pr], 207.0 (65) [M^+-$EtCH_2O_2$], 179.0 (86), 151.0 (71).

HRMS (ESI) *m/z* 305.1721 [305.1723 calcd. for $C_{16}H_{26}O_4Na$ (M^++Na^+)].

6-methyl-1-phenyl-4-((tetrahydro-2H-pyran-2-yl)oxy)hept-2-yn-1-ol (I-77f)



$C_{19}H_{26}O_3$
302,41

Following procedure B, propargyl alcohol **I-76b** (500 mg, 2.55 mmol) was added to benzaldehyde (308.2 mg, 2.90 mmol). After flash chromatography (Cyclohexane/EtOAc = 4/1), the product (558.8 mg, 2.20 mmol, 86%) was obtained.

TLC: Rf = 0.25 (Cyclohexane/EtOAc = 4/1) [CAM]

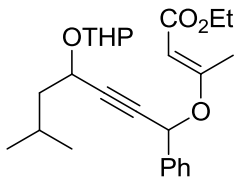
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.54 (dd, *J* = 8.2, 6.8 Hz, 2H), 7.43 – 7.31 (m, 3H), 5.50 (s, 1H), 4.99 (d, *J* = 2.6 Hz, 1H), 4.66 – 4.54 (m, 1H), 3.92 – 3.75 (m, 1H), 3.62 – 3.45 (m, 1H), 2.20 (s, 1H), 1.99 – 1.48 (m, 9H), 1.05 – 0.90 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 134.4, 128.6, 128.4, 126.7, (95.50, 95.48), 86.2, 84.9, 64.7, 63.6, (62.30, 62.29), 44.7, 30.5, 25.5, 24.7, 22.7, 22.4, 19.3.

MS (EI) *m/z* (%): 199.1 (70), 157.0 (47), 105.0 (86) [PhCO], 85 (100), 55 (52).

HRMS (ESI) *m/z* 325.1771 [325.1774 calcd. for $C_{19}H_{26}O_3Na$ (M^++Na^+)].

(*E*)-ethyl 3-((6-methyl-1-phenyl-4-((tetrahydro-2H-pyran-2-yl)oxy)hept-2-yn-1-yl)oxy)but-2-enoate (I-78f)



$C_{25}H_{34}O_5$
414,53

Following procedure C, propargyl alcohol **I-77f** (565 mg, 2.22 mmol) was added to ethyl 2-butynoate (273.6 mg, 2.44 mmol). After flash chromatography (Cyclohexane/EtOAc = 9/1), the product (667.0 mg, 1.61 mmol, 72%) was obtained as a diastereoisomeric mixture.

TLC: Rf = 0.39 (Cyclohexane/EtOAc = 4/1) [CAM]

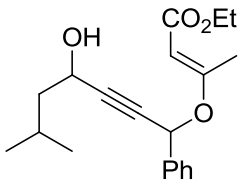
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.49 (dd, *J* = 7.7, 1.6 Hz, 2H), 7.40 – 7.36 (m, 3H), 5.65 (s, 1H), 5.39 (d, *J* = 2.6 Hz, 1H), 4.96 – 4.88 (m, 1H), 4.58 (tdd, *J* = 7.3, 3.5, 1.6 Hz, 1H), 4.15 (ddd, *J* = 10.2, 7.0, 3.4 Hz, 2H), 3.81 (t, *J* = 9.4 Hz, 1H), 3.56 – 3.45 (m, 1H), 2.33 (s, 3H), 1.93 – 1.85 (m, 1H), 1.75 – 1.47 (m, 8H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.97 – 0.88 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 170.4, 167.9, 137.0, 129.1, 128.8, (127.6, 127.5), (96.0, 95.9), 94.1, (89.2, 89.1), (81.2, 81.0), (69.8, 69.8), (63.9, 63.9), (62.7, 62.6), 59.6, (44.5, 44.5), 30.7, 25.6, 24.9, 22.8, 22.6, 19.2, 14.6, 13.8.

MS (EI) *m/z* (%): 199.0 (84), 157.0 (53), 105.0 (86) [PhCO], 85 (100), 55 (54).

HRMS (ESI) *m/z* 437.2299 [437.2298 calcd. for $C_{25}H_{34}O_5Na$ (M^++Na^+)].

(*E*)-ethyl 3-((4-hydroxy-6-methyl-1-phenylhept-2-yn-1-yl)oxy)but-2-enoate (I-72f)



$C_{20}H_{26}O_4$
330,42

Following procedure D, THP-protected alcohol **I-78f** (565 mg, 2.22 mmol) was deprotected. After flash chromatography (Cyclohexane/EtOAc = 9/1), the product (667 mg, 1.61 mmol, 72%) was obtained.

TLC: Rf = 0.16 (Cyclohexane/EtOAc = 9/1) [CAM]

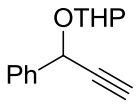
^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] 7.52 (d, *J* = 7.1 Hz, 2H), 7.46 – 7.38 (m, 3H), 5.69 (s, 1H), 5.39 (s, 1H), 4.53 (t, *J* = 7.1 Hz, 1H), 4.18 (qd, *J* = 7.1, 2.7 Hz, 2H), 2.37 (s, 3H), 1.87 (td, *J* = 13.6, 6.8 Hz, 1H), 1.81 (s, 1H), 1.69 (dtd, *J* = 10.6, 7.3, 3.3 Hz, 1H), 1.65 – 1.59 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.96 (dd, *J* = 11.9, 6.2 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 170.1, 167.7, 136.8, 129.0, 128.7, 127.3, 94.0, 90.5, 80.6, 69.6, 61.1, 59.5, 46.5, 24.8, 22.5, 19.1, 14.4.

MS (EI) *m/z* (%): 312.1 (8) [M^+-H_2O], 273.0 (45), 251.0 (22), 227.0 (100) [M^+-C_8H_7], 91.0 (19).

HRMS (ESI) *m/z* 353.1723 [353.1723 calcd. for $C_{20}H_{26}O_4Na$ (M^++Na^+)].

2-((1-phenylprop-2-yn-1-yl)oxy)tetrahydro-2H-pyran (I-76c)



$C_{14}H_{16}O_2$
216,28

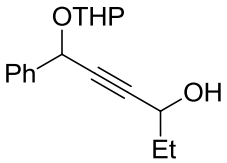
Following procedure A, 1-Phenyl-2-propyn-1-ol (1.0 g, 7.57 mmol) was protected with dihydropyran (0.700 g, 8.32 mmol). After flash chromatography (Cyclohexane/EtOAc = 9/1), the product (1.14 g, 5.26 mmol, 69%) was obtained as a diastereoisomeric mixture.

TLC: Rf = 0.55 (Cyclohexane/EtOAc = 9/1) [CAM]

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.61 – 7.55 (m, 1H), 7.52 – 7.46 (m, 1H), 7.41 – 7.30 (m, 3H), 5.52 (d, *J* = 2.1 Hz, 0.70H), 5.43 (d, *J* = 2.3 Hz, 0.30H), 5.20 (t, *J* = 3.1 Hz, 0.70H), 4.57 (t, *J* = 3.4 Hz, 0.30H), 4.06 – 3.98 (m, 0.30H), 3.90 – 3.81 (m, 0.70H), 3.63 – 3.53 (m, 1H), 2.60 (d, *J* = 2.3 Hz, 0.30H), 2.58 (d, *J* = 2.2 Hz, 0.70H), 1.96 – 1.46 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 138.6, 128.8, 128.6, 128.4, 127.7, 127.5, (96.0, 95.8), (83.1, 81.8), (75.3, 74.3), (67.3, 66.7), (62.3, 62.2), (30.4, 30.3), (25.6, 25.5), (19.2, 19.0).

6-phenyl-6-((tetrahydro-2H-pyran-2-yl)oxy)hex-4-yn-3-ol (I-77g)



$C_{17}H_{22}O_3$
274,35

Following procedure B, propargyl alcohol **I-76c** (500 mg, 2.31 mmol) was added to propanal (152.9 mg, 2.64 mmol). After flash chromatography (Cyclohexane/EtOAc = 4/1), the product (458.3 mg, 1.67 mmol, 72%) was obtained as a diastereoisomeric mixture.

TLC: Rf = 0.24 (Cyclohexane/EtOAc = 4/1) [CAM]

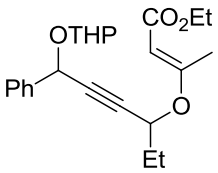
^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] 7.55 (d, *J* = 7.3 Hz, 1H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.37 (q, *J* = 6.8 Hz, 2H), 7.32 (dd, *J* = 8.4, 6.2 Hz, 1H), 5.55 (s, 0.65H), 5.46 (s, 0.25H), 5.30 (s, 0.25H), 5.17 (s, 0.65H), 4.56 (t, *J* = 3.4 Hz, 0.30H), 4.41 (t, *J* = 6.4 Hz, 0.70H), 4.04 – 3.98 (m, 0.30H), 3.88 – 3.81 (m, 0.70H), 3.61 – 3.57 (m, 0.70H), 3.57 – 3.52 (m, 0.30H), 1.93 – 1.47 (m, 9H), 1.02 (td, *J* = 7.4, 1.8 Hz, 2.20H), 1.00 – 0.97 (m, 0.80H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 138.9 128.7, 128.6, 128.3, 127.7, 127.5, 95.6, (88.30, 88.27), 82.8, 66.8, 64.0, (62.3, 62.2), (31.04, 31.01), 30.5, (25.60, 25.55), 19.2, 9.6.

MS (EI) *m/z* (%): 172.0 (73) [M^+-THPOH], 114.9 (66), 85.1 (63), 57.0 (100).

HRMS (ESI) *m/z* 297.1461 [297.1461 calcd. for $C_{17}H_{22}O_3Na$ (M^++Na^+)].

(*E*)-ethyl 3-((6-phenyl-6-((tetrahydro-2H-pyran-2-yl)oxy)hex-4-yn-3-yl)oxy)but-2-enoate (I-78g)



$C_{23}H_{30}O_5$
386,48

Following procedure C, propargyl alcohol **I-77g** (448 mg, 1.63 mmol) was added to ethyl 2-butynoate (200.7 mg, 1.80 mmol). After flash chromatography (Cyclohexane/EtOAc = 9/1), the product (425.7 mg, 1.10 mmol, 67%) was obtained as a diastereoisomeric mixture.

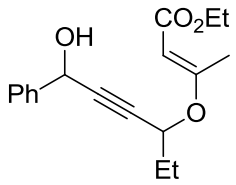
TLC: Rf = 0.33 (Cyclohexane/EtOAc = 9/1) [CAM]

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.57 – 7.51 (m, 1H), 7.47 – 7.43 (m, 1H), 7.39 – 7.28 (m, 3H), 5.56 (s, 0.70H), 5.45 (s, 0.30H), 5.30 – 5.24 (m, 1H), 5.14 – 5.10 (m, 0.70H), 4.64 – 4.54 (m, 1.20H), 4.24 – 4.06 (m, 2H), 4.03 – 3.95 (m, 0.30H), 3.91 – 3.83 (m, 0.70H), 3.63 – 3.51 (m, 1H), 2.30 (d, *J* = 3.9 Hz, 2.20H), 2.28 (d, *J* = 5.8 Hz, 0.70H), 1.94 – 1.47 (m, 8H), 1.31 – 1.23 (m, 3H), 1.04 (ddd, *J* = 7.6, 7.0, 1.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] (170.44, 170.39) 167.8, 138.3, (128.48, 128.41), 128.2, (127.5, 127.4), (95.8, 95.7), 93.3, (85.1, 84.9), (84.0, 83.8), 68.8, (66.72, 66.70), (62.3, 62.2), 59.3, 30.3, 28.6, 25.4, 19.1, 19.0, 14.4, 9.5.

HRMS (ESI) *m/z* 409.1987 [409.1985 calcd. for $C_{23}H_{30}O_5Na$ (M^++Na^+)].

(*E*)-ethyl 3-((6-hydroxy-6-phenylhex-4-yn-3-yl)oxy)but-2-enoate (I-72g)



$C_{18}H_{22}O_4$
302,36

Following procedure D, THP-protected alcohol **I-78g** (370 mg, 0.957 mmol) was deprotected. After flash chromatography (Cyclohexane/EtOAc = 9/1), the product (180.2 mg, 0.596 mmol, 62%) was obtained.

TLC: Rf = 0.11 (Cyclohexane/EtOAc = 9/1) [CAM]

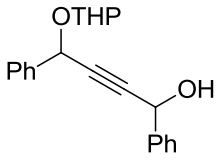
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.52 (dd, *J* = 8.1, 1.2 Hz, 2H), 7.40 – 7.30 (m, 3H), 5.50 (s, 1H), 5.26 (s, 1H), 4.59 (td, *J* = 6.3, 1.1 Hz, 1H), 4.21 – 4.07 (m, 2H), 2.30 (d, *J* = 2.3 Hz, 4H), 1.91 (p, *J* = 7.2 Hz, 2H), 1.27 (td, *J* = 7.1, 1.3 Hz, 3H), 1.05 (td, *J* = 7.4, 1.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 170.5, 168.0, 140.3, 128.8, 128.6, 126.8, 126.8, 93.5, 87.0, 83.6, 68.9, 64.7, 59.6, 28.7, 19.1, 14.6, 9.7.

MS (EI) *m/z* (%): 280.9 (38), 227.0 (26) [M^+-$EtCH_2O_2$], 207.0 (100), 105 (43) [PhCO], 73 (41).

HRMS (ESI) *m/z* 325.1411 [325.1410 calcd. for $C_{18}H_{22}O_4Na$ (M^++Na^+)].

1,4-diphenyl-4-((tetrahydro-2H-pyran-2-yl)oxy)but-2-yn-1-ol (I-77h)



$C_{21}H_{22}O_3$
322,40

Following procedure B, propargyl alcohol **I-76c** (500 mg, 2.31 m mol) was added to benzaldehyde (279.7 mg, 2.64 mmol). After flash chromatography (Cyclohexane/EtOAc = 4/1), the product (553.0 mg, 1.72 mmol, 74%) was obtained as a diastereoisomeric mixture.

TLC: Rf = 0.29 (Cyclohexane/EtOAc = 4/1) [CAM]

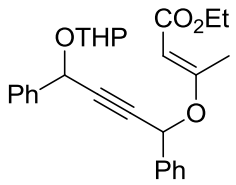
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.66 – 7.46 (m, 4H), 7.46 – 7.30 (m, 6H), 5.62 (s, 1H), 5.56 (s, 1H), 5.19 (d, *J* = 3.0 Hz, 1H), 3.96 – 3.79 (m, 1H), 3.70 – 3.39 (m, 1H), 2.34 (s, 1H), 1.95 – 1.73 (m, 2H), 1.73 – 1.49 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 140.6, 138.7, 128.8, 128.6, 128.4, 127.7, 127.5, (126.84, 126.82), 95.8, 87.0, 84.7, 66.9, 64.9, 62.3, (30.44, 30.39), (25.6, 25.5), 19.2.

MS (EI) *m/z* (%): 222.0 (50) [M^+-THPOH], 191.1 (50), 105.0 (100) [PhCO], 77.0 (84) [Ph].

HRMS (ESI) *m/z* 345.1457 [345.1461 calcd. for $C_{21}H_{22}O_3Na$ (M^++Na^+)].

(*E*)-ethyl 3-((1,4-diphenyl-4-((tetrahydro-2H-pyran-2-yl)oxy)but-2-yn-1-yl)oxy)but-2-enoate (I-78h)



$C_{27}H_{30}O_5$
434,52

Following procedure C, propargyl alcohol **I-77h** (550 mg, 1.71 mmol) was added to ethyl 2-butynoate (210.8 mg, 1.88 mmol). After flash chromatography (Cyclohexane/EtOAc = 9/1), the product (498.5 mg, 1.15 mmol, 67%) was obtained as a diastereoisomeric mixture.

TLC: Rf = 0.49 (Cyclohexane/EtOAc = 4/1) [CAM]

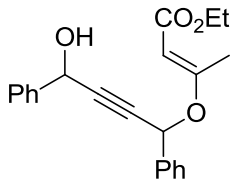
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.58 – 7.44 (m, 4H), 7.43 – 7.30 (m, 6H), 5.72 (s, 1H), 5.62 (s, 0.75H), 5.50 (s, 0.25H), 5.44 (d, *J* = 3.0 Hz, 0.75H), 5.41 (d, *J* = 1.3 Hz, 0.25H), 5.13 (dd, *J* = 6.5, 3.2 Hz, 1H), 4.23 – 4.14 (m, 2H), 3.90 – 3.81 (m, 1H), 3.61 – 3.52 (m, 1H), 2.35 (d, *J* = 4.4 Hz, 2H), 2.33 (d, *J* = 6.1 Hz, 1H), 1.89 – 1.48 (m, 6H), 1.31 – 1.27 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 170.3, 167.8, 138.3, 136.8, 129.2, 128.9, 128.6, 128.5, 127.6, (127.58, 127.56), (96.1, 96.0), 94.2, (87.5, 87.4), (83.2, 83.0), 69.8, 66.9, (62.5, 62.4), 59.6, (31.0, 30.5), 25.6, 21.2, (19.3, 19.2), (14.6, 14.3).

MS (EI) *m/z* (%): 332.1 (100) [M^+-THPOH], 285.1 (38), 215.1 (46), 105.0 (23) [PhCO], 77.0 (14) [Ph].

HRMS (ESI) *m/z* 457.1990 [457.1985 calcd. for $C_{27}H_{30}O_5Na$ (M^++Na^+)].

(*E*)-ethyl-3-((4-hydroxy-1,4-diphenylbut-2-yn-1-yl)oxy)but-2-enoate (I-72h)



$C_{22}H_{22}O_4$
350,41

Following procedure D, THP-protected alcohol **I-78h** (486 mg, 1.12 mmol) was deprotected. After flash chromatography (Cyclohexane/EtOAc = 9/1), the product (153.9 mg, 0.440 mmol, 39%) was obtained.

TLC: Rf = 0.24 (Cyclohexane/EtOAc = 4/1) [CAM]

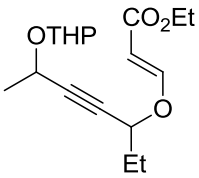
^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] 7.52 (dd, *J* = 9.0, 4.2 Hz, 4H), 7.44 – 7.31 (m, 6H), 5.73 (s, 1H), 5.55 (s, 1H), 5.41 (s, 1H), 4.20 – 4.12 (m, 2H), 2.35 (d, *J* = 3.6 Hz, 3H), 2.26 (s, 1H), 1.28 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.3, 167.8, 140.1, 136.8, 129.2, 128.9, 128.8, 128.7,127.48, 127.47, 126.89, 126.88, 94.3, 89.0, 82.7, 69.7, 64.8, 59.7, 19.2, 14.6.

MS (EI) *m/z* (%): 332.1 (12) [M^+-H_2O], 303.1 (31.3), 281.0 (39), 207 (100) [M^+-C_8H_7].

HRMS (ESI) *m/z* 373.1413 [373.1410 calcd. for $C_{22}H_{22}O_4Na$ (M^++Na^+)].

(*E*)-ethyl 3-((6-((tetrahydro-2H-pyran-2-yl)oxy)hept-4-yn-3-yl)oxy)acrylate (I-78i)



$C_{17}H_{26}O_5$
310,39

Following procedure C, propargyl alcohol **I-77a** (200 mg, 0.94 mmol) was added to ethyl propiolate (101.4 mg, 1.03 mmol). After flash chromatography (Cyclohexane/EtOAc = 9/1), the product (271.6 mg, 0.88 mmol, 93%) was obtained as a diastereoisomeric mixture.

TLC: Rf = 0.44 (Cyclohexane/EtOAc = 4/1) [CAM]

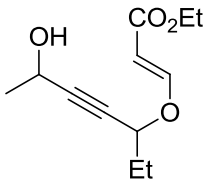
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.59 (dd, *J* = 12.5, 0.7 Hz, 1H), 5.34 (d, *J* = 12.5 Hz, 1H), 4.86 (d, *J* = 2.0 Hz, 1H), 4.59 (q, *J* = 6.7 Hz, 1H), 4.51 (t, *J* = 6.3 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.81 (ddd, *J* = 10.9, 7.8, 3.2 Hz, 1H), 3.50 (dd, *J* = 10.1, 5.0 Hz, 1H), 1.89 – 1.78 (m, 3H), 1.74 (d, *J* = 13.0 Hz, 1H), 1.66 – 1.49 (m, 4H), 1.45 (d, *J* = 6.7 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.01 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 167.6, (160.4, 160.3), (98.72, 98.69), (96.14, 96.06), (88.1, 87.9), (80.8, 80.7), (72.6, 72.5), (62.7, 62.6), 60.7, 59.8, (30.52, 30.50), (28.6, 28.5), 25.4, (21.90, 21.87), (19.54, 19.49), 14.3, (9.28, 9.26).

MS (EI) *m/z* (%): 281.0 (61) [M^+-Et], 252.9 (40), 207.0 (100) [M^+-THPOH], 134.9 (45), 85.0 (59), 73.0 (54).

HRMS (ESI) *m/z* 333.1674 [333.1672 calcd. for $C_{17}H_{26}O_5Na$ (M^++Na^+)].

(*E*)-ethyl 3-((6-hydroxyhept-4-yn-3-yl)oxy)acrylate (I-72i)



$C_{12}H_{18}O_4$
226,27

Following procedure D, THP-protected alcohol **I-78i** (1 g, 3.22 mmol) was deprotected. After flash chromatography (Cyclohexane/EtOAc = 9/1), the product (585.6 mg, 2.59 mmol, 80%) was obtained.

TLC: Rf = 0.22 (Cyclohexane/EtOAc = 4/1) [CAM]

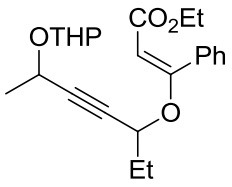
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.59 (d, *J* = 12.5 Hz, 1H), 5.35 (d, *J* = 12.5 Hz, 1H), 4.58 (dd, *J* = 9.3, 3.9 Hz, 1H), 4.52 (t, *J* = 6.4 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 1.90 (s, 1H), 1.89 – 1.80 (m, 2H), 1.46 (d, *J* = 6.6 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.02 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 167.9, 160.5, 98.9, 90.1, 80.4, 72.8, 60.0, 58.4, 28.7, 24.3, 14.5, 9.5.

MS (EI) *m/z* (%): 208.0 (16) [M^+-H_2O], 180.1 (37) [M^+-C_2H_6O], 151.0 (100) [M^+-$EtCH_2O_2$], 91.0 (47), 79.0 (38).

HRMS (ESI) *m/z* 249.1097 [249.1097 calcd. for $C_{12}H_{18}O_4Na$ (M^++Na^+)].

(*E*)-ethyl 3-phenyl-3-((6-((tetrahydro-2H-pyran-2-yl)oxy)hept-4-yn-3-yl)oxy)acrylate (I-78j)



$C_{23}H_{30}O_5$
386,48

Following procedure C, propargyl alcohol **I-77a** (200 mg, 0.94 mmol) was added to ethyl phenylpropiolate (181.1 mg, 1.03 mmol). After flash chromatography (Cyclohexane/EtOAc = 9/1), the product (356.3 mg, 0.92 mmol, 98%) was obtained as a diastereoisomeric mixture.

TLC: Rf = 0.44 (Cyclohexane/EtOAc= 4/1) [CAM]

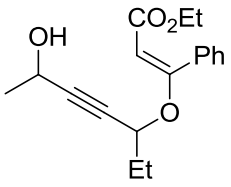
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.64 – 7.57 (m, 2H), 7.45 – 7.37 (m, 3H), 5.71 (d, *J* = 2.3 Hz, 1H), 4.97 (td, *J* = 6.2, 1.5 Hz, 1H), 4.76 (dt, *J* = 6.7, 4.1 Hz, 1H), 4.52 (qd, *J* = 6.7, 1.5 Hz, 1H), 4.23 (qd, *J* = 7.2, 0.5 Hz, 2H), 3.85 – 3.77 (m, 1H), 3.58 – 3.43 (m, 1H), 2.04 – 1.93 (m, 2H), 1.81 (dt, *J* = 15.2, 10.9 Hz, 2H), 1.60 – 1.48 (m, 4H), 1.37 (d, *J* = 6.7 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.12 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 165.9, 165.3, 135.8, 130.4, 128.6, 127.8, (103.4, 103.3), (96.1, 96.0), (87.3, 87.2), (81.0, 80.9), 73.0, (62.75, 62.69), (60.85, 60.82), 60.0, (30.70, 30.66), 28.9, 25.6, (22.1, 22.0), (19.8, 19.7), 14.5, 9.6.

MS (EI) *m/z* (%): 284.1 (82) [M^+-THPOH], 213.1 (48), 105 (100) [PhCO], 77 (52).

HRMS (ESI) *m/z* 409.1988 [409.1985 calcd. for $C_{23}H_{30}O_5Na$ (M^++Na^+)].

(*E*)-ethyl 3-((6-hydroxyhept-4-yn-3-yl)oxy)-3-phenylacrylate (I-72j)



$C_{18}H_{22}O_4$
302,36

Following procedure D, THP-protected alcohol **I-78j** (666.8 mg, 1.73 mmol) was deprotected. After flash chromatography (Cyclohexane/EtOAc = 9/1), the product (138.6 mg, 0.458 mmol, 27%) was obtained.

TLC: Rf = 0.10 (Cyclohexane/EtOAc = 4/1) [CAM]

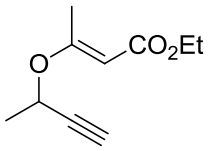
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.61 – 7.57 (m, 2H), 7.43 – 7.36 (m, 3H), 5.73 (s, 1H), 4.87 (tdd, *J* = 6.1, 3.0, 1.6 Hz, 1H), 4.44 (q, *J* = 6.6 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 1.99 – 1.91 (m, 2H), 1.60 (s, 1H), 1.35 – 1.30 (m, 6H), 1.10 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 165.6, 165.5, 135.7, 130.4, 128.6, 127.7, 104.0, 89.7, 81.6, 73.0, 60.1, 58.3, 28.9, 24.3, 14.5, 9.5.

MS (EI) *m/z* (%): 284.0 (100) [M^+-H_2O], 237.1 (35), 222.9 (34), 207.1 (44), 105.0 (69) [PhCO].

HRMS (ESI) *m/z* 325.1407 [325.1410 calcd. for $C_{18}H_{22}O_4Na$ (M^++Na^+)].

(*E*)-ethyl 3-(but-3-yn-2-yloxy)but-2-enoate (I-80a)



$C_{10}H_{14}O_3$
182,22

Following procedure C, 3-butyn-2-ol (500 mg, 7.13 mmol) was added to ethyl 2-butynoate (288.7 mg, 1.43 mmol). After flash chromatography (Cyclohexane/EtOAc = 9/1), the E product (918 mg, 5.03 mmol, 71%) and Z product (139.2 mg, 11%) were isolated.

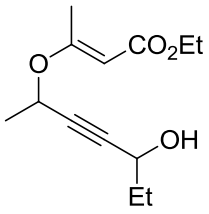
TLC: Rf = 0.63 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 5.21 (s, 1H), 4.70 – 4.64 (m, 1H), 4.19 – 4.09 (m, 2H), 2.52 (d, *J* = 2.0 Hz, 1H), 2.29 (s, 3H), 1.58 (d, *J* = 6.6 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 170.2, 167.9, 93.5, 81.6, 74.7, 63.3, 59.6, 21.9, 19.2, 14.6.

The analytical data are identical to the literature data.[91]

(*E*)-ethyl 3-((5-hydroxyhept-3-yn-2-yl)oxy)but-2-enoate (I-72k)



$C_{13}H_{20}O_4$
240,30

Following procedure B, vinyl propargyl alcohol **I-80a** (207.4 mg, 1.14 mmol) was added to propanal (79.3 mg, 1.37 mmol). After flash chromatography (Cyclohexane/EtOAc = 4/1), the product (101.3 mg, 0.42 mmol, 37%) was obtained as a diastereoisomeric mixture.

TLC: Rf = 0.25 (Cyclohexane/EtOAc= 4/1) [UV/CAM]

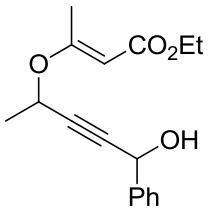
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 5.20 (s, 1H), 4.71 (qd, *J* = 6.6, 1.3 Hz, 1H), 4.35 (dd, *J* = 11.3, 5.5 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.29 (s, 3H), 1.79 (d, *J* = 5.6 Hz, 1H), 1.75 – 1.67 (m, 2H), 1.56 (d, *J* = 6.6 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.99 (td, *J* = 7.4, 0.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 170.3, 168.0, 93.5, 87.5, 82.8, 63.8, 63.6, 59.5, 30.9, 22.0, 19.2, 14.6, 9.4.

MS (EI) *m/z* (%): 222.0 (44) [M^+-H_2O], 179.0 (73), 165.0 (76) [M^+-$EtCH_2O_2$], 153.1 (76), 152.0 (73), 137.0 (100), 57.0 (70) [EtCHO].

HRMS (ESI) *m/z* 263.1254 [263.1254 calcd. for $C_{13}H_{20}O_4Na$ (M^++Na^+)].

(*E*)-ethyl 3-((5-hydroxy-5-phenylpent-3-yn-2-yl)oxy)but-2-enoate (I-72l)



$C_{17}H_{20}O_4$
288,34

Following procedure B, vinyl propargyl alcohol **I-80a** (200 mg, 1.10 mmol) was added to benzaldehyde (140.1 mg, 1.32 mmol). After flash chromatography (Cyclohexane/EtOAc = 4/1), the product (139.6 mg, 0.48 mmol, 44%) was obtained as a diastereoisomeric mixture.

TLC: Rf = 0.23 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

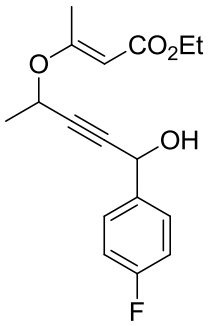
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.52 (ddd, *J* = 5.8, 1.7, 0.7 Hz, 2H), 7.40 – 7.32 (m, 3H), 5.50 (d, *J* = 6.3 Hz, 1H), 5.24 (d, *J* = 1.8 Hz, 1H), 4.81 – 4.74 (m, 1H), 4.19 – 4.09 (m, 2H), 2.31 – 2.28 (m, 3H), 2.25 (d, *J* = 6.2 Hz, 1H), 1.60 (d, *J* = 6.6 Hz, 3H), 1.27 (td, *J* = 7.1, 1.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 170.3, 168.0, 140.2, 128.8, 128.7, 126.9, 126.8, 93.6, 86.2, 84.5, 64.7, 63.6, 59.6, 21.9, 19.2, 14.6.

MS (EI) *m/z* (%): 227.0 (21), 115.0 (16), 105.9 (20), 104.9 (100) [PhCO], 77.0 (54) [Ph].

HRMS (ESI) *m/z* 311.1256 [311.1254 calcd. for $C_{17}H_{20}O_4Na$ (M^++Na^+)].

(*E*)-ethyl 3-((5-(4-fluorophenyl)-5-hydroxypent-3-yn-2-yl)oxy)but-2-enoate (I-72m)



$C_{17}H_{19}FO_4$
306,33

Following procedure B, vinyl propargyl alcohol **I-80a** (200 mg, 1.10 mmol) was added to 4-fluorobenzaldehyde (163.5 mg, 1.32 mmol). After flash chromatography (Cyclohexane/ EtOAc = 4/1), the product (115.3 mg, 0.376 mmol, 34%) was obtained as a diastereoisomeric mixture.

TLC: Rf = 0.25 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

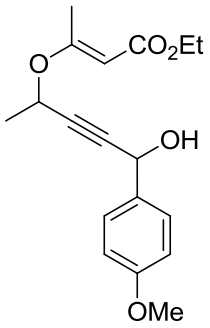
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.52 – 7.45 (m, 2H), 7.04 (td, *J* = 8.7, 0.9 Hz, 2H), 5.47 (s, 1H), 5.22 (d, *J* = 2.7 Hz, 1H), 4.76 (q, *J* = 6.6 Hz, 1H), 4.21 – 4.08 (m, 2H), 2.31 (s, 1H), 2.29 (d, *J* = 2.5 Hz, 3H), 1.59 (d, *J* = 6.6 Hz, 3H), 1.27 (td, *J* = 7.1, 1.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 170.3, 167.9, 164.1, 161.7, 136.2, 128.7, 115.7, 115.5, 93.6, 86.1, 84.7, 64.0, 63.6, 59.7, 21.9, 19.2, 14.6.

MS (EI) *m/z* (%): 149.0 (100), 123.0 (79) [*p*F-PhCHO], 120.0 (79), 95.0 (55) [*p*F-Ph], 75.0 (28), 53.0 (31).

HRMS (ESI) *m/z* 329.1156 [329.1160 calcd. for $C_{17}H_{19}FO_4Na$ (M^++Na^+)].

(*E*)-ethyl 3-((5-hydroxy-5-(4-methoxyphenyl)pent-3-yn-2-yl)oxy)but-2-enoate (I-72n)



$C_{18}H_{22}O_5$
318,36

Following procedure B, vinyl propargyl alcohol **I-80a** (200 mg, 1.10 mmol) was added to anisaldehyde (170.4 mg, 1.25 mmol). After flash chromatography (Cyclohexane/EtOAc = 4/1), the product (88.1 mg, 0.277 mmol, 25%) was obtained as a diastereoisomeric mixture.

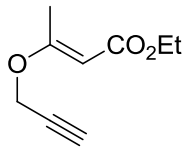
TLC: Rf = 0.15 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

^{1}H NMR (400 MHz, $CDCl_3$) 7.44 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.44 (s, 1H), 5.24 (d, *J* = 3.1 Hz, 1H), 4.77 (q, *J* = 6.6 Hz, 1H), 4.20 – 4.09 (m, 2H), 3.81 (s, 3H), 2.30 (d, *J* = 3.3 Hz, 3H), 2.15 (s, 1H), 1.60 (d, *J* = 6.6 Hz, 3H), 1.30 – 1.24 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 170.3, 168.0, 159.9, 132.6, 128.3, 114.1, 93.6, 86.4, 84.3, 64.3, 63.6, 59.6, 55.5, 21.9, 19.2, 14.6.

HRMS (ESI) *m/z* 341.1351 [341.1359 calcd. for $C_{18}H_{22}O_5Na$ (M^++Na^+)].

(*E*)-ethyl 3-(prop-2-yn-1-yloxy)but-2-enoate (I-80b)



$C_9H_{12}O_3$
168,19

Following procedure C, 2-propyn-1-ol (500 mg, 8.92 mmol) was added to ethyl 2-butynoate (360.9 mg, 1.78 mmol). After flash chromatography (Cyclohexane/EtOAc = 9/1), the E product (1.20 g, 7.14 mmol, 80 %) and Z product (217.2 mg, 1.29 mmol, 14%) were isolated.

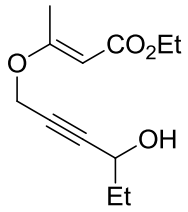
TLC: Rf = 0.8 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 5.10 (s, 1H), 4.49 (d, *J* = 2.4 Hz, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.55 (t, *J* = 2.4 Hz, 1H), 2.31 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 170.8, 167.6, 92.8, 91.8, 76.3, 59.7, 55.8, 18.9, 14.5.

The analytical data are identical to the literature data.[92]

(*E*)-ethyl 3-((4-hydroxyhex-2-yn-1-yl)oxy)but-2-enoate (I-72o)



$C_{12}H_{18}O_4$
226,27

Following procedure B, vinyl propargyl alcohol **I-80b** (200 mg, 1.19 mmol) was added to propanal (83.1 mg, 1.43 mmol). After flash chromatography (Cyclohexane/EtOAc = 4/1), the product (101.6 mg, 0.449 mmol, 38%) was obtained as a diastereoisomeric mixture.

TLC: Rf = 0.17 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

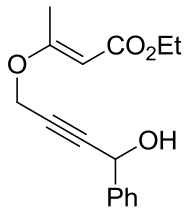
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 5.08 (s, 1H), 4.52 (d, *J* = 1.6 Hz, 2H), 4.38 (t, *J* = 6.3 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.31 (s, 3H), 1.88 (s, 1H), 1.79 – 1.69 (m, 2H), 1.29 – 1.24 (m, 3H), 1.01 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 170.9, 167.7, 92.8, 89.0, 78.4, 63.8, 59.7, 56.2, 30.8, 19.0, 14.5, 9.5.

MS (EI) *m/z* (%): 208.1 (16) [M^+-H_2O], 180.0 (16) [M^+-EtOH], 151.0 (100) [M^+-$EtCH_2O_2$], 138.0 (21), 123.0 (25), 57.0 (23) [EtCHO].

HRMS (ESI) *m/z* 249.1104 [249.1097 calcd. for $C_{12}H_{18}O_4Na$ (M^++Na^+)].

(*E*)-ethyl 3-((4-hydroxy-4-phenylbut-2-yn-1-yl)oxy)but-2-enoate (I-72p)



$C_{16}H_{18}O_4$
274,31

Following procedure B, vinyl propargyl alcohol **I-80b** (200 mg, 1.19 mmol) was added to benzaldehyde (153.8 mg, 1.43 mmol). After flash chromatography (Cyclohexane/EtOAc = 4/1), the product (105.8 mg, 0.386 mmol, 32%) was obtained as a diastereoisomeric mixture.

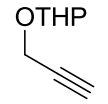
TLC: Rf = 0.17 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.53 (dd, *J* = 8.1, 1.3 Hz, 2H), 7.37 (tdd, *J* = 8.7, 4.6, 2.3 Hz, 3H), 5.52 (s, 1H), 5.11 (s, 1H), 4.57 (d, *J* = 1.7 Hz, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.31 (s, 3H), 1.61 (s, 1H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 170.9, 167.7, 140.1, 128.8, 128.7, 126.8, 92.8, 87.8, 80.2, 64.7, 59.7, 56.2, 19.0, 14.5.

HRMS (ESI) *m/z* 297.1099 [297.1097 calcd. for $C_{16}H_{18}O_4Na$ (M^++Na^+)].

2-(prop-2-yn-1-yloxy)tetrahydro-2H-pyran (I-76d)



$C_8H_{12}O_2$
140,18

Following procedure A, 2-propyn-1-ol (3.0 g, 53.5 mmol) was protected with dihydropyran (4.95 g, 58.9 mmol). After distillation, the product (6.62 g, 47.2 mmol, 88%) was obtained as a diastereoisomeric mixture.

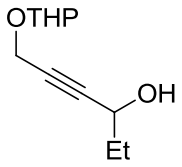
TLC: Rf = 0.70 (Cyclohexane/EtOAc = 4/1) [CAM]

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 4.82 (t, *J* = 3.4 Hz, 1H), 4.26 (qd, *J* = 15.7, 2.4 Hz, 2H), 3.88 – 3.79 (m, 1H), 3.57 – 3.49 (m, 1H), 2.40 (t, *J* = 2.4 Hz, 1H), 1.90 – 1.69 (m, 2H), 1.68 – 1.49 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 97.0, 79.9, 74.1, 62.2, 54.1, 30.4, 25.5, 19.2.

The analytical data are identical to the literature data.[93]

6-((tetrahydro-2H-pyran-2-yl)oxy)hex-4-yn-3-ol (I-77q)



$C_{11}H_{18}O_3$
198,26

Following procedure B, propargyl alcohol **I-76d** (1.0 g, 7.13 mmol) was added to propanal (497.0 mg, 8.56 mmol). After flash chromatography (Cyclohexane/EtOAc = 4/1), the product (1.14 g, 5.73 mmol, 80%) was obtained.

TLC: Rf = 0.12 (Cyclohexane/EtOAc = 4/1) [CAM]

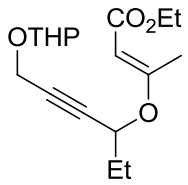
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 4.81 (t, *J* = 3.3 Hz, 1H), 4.39 – 4.33 (m, 1H), 4.31 (d, *J* = 1.7 Hz, 1H), 4.29 – 4.23 (m, 1H), 3.88 – 3.79 (m, 1H), 3.56 – 3.49 (m, 1H), 1.93 (s, 1H), 1.78 – 1.68 (m, 3H), 1.68 – 1.49 (m, 5H), 1.01 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 96.9, 87.0, 81.0, 63.9, 62.2, 54.4, 30.9, 30.4, 25.5, 19.2, 9.6.

MS (EI) *m/z* (%): 140.1 (1) [M^+-EtCHO], 85 (60) [THP], 84 (71), 83.0 (45), 55 (100).

HRMS (ESI) *m/z* 221.1153 [221.1148 calcd. for $C_{11}H_{18}O_3Na$ (M^++Na^+)].

(E)-ethyl 3-((6-((tetrahydro-2H-pyran-2-yl)oxy)hex-4-yn-3-yl)oxy)but-2-enoate (I-78q)



$C_{17}H_{26}O_5$
310,39

Following procedure C, propargyl alcohol **I-77q** (400 mg, 2.02 mmol) was added to ethyl 2-butynoate (249.5 mg, 2.22 mmol). After flash chromatography (Cyclohexane/EtOAc = 9/1), the product (516.4 mg, 1.66 mmol, 82%) was obtained as a diastereoisomeric mixture.

TLC: Rf = 0.45 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

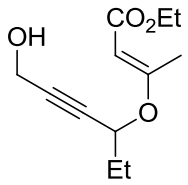
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 5.21 (d, *J* = 2.0 Hz, 1H), 4.80 (dd, *J* = 6.0, 2.8 Hz, 1H), 4.52 (td, *J* = 6.3, 1.3 Hz, 1H), 4.30 (s, 2H), 4.19 – 4.07 (m, 2H), 3.84 (ddd, *J* = 11.3, 7.2, 3.1 Hz, 1H), 3.58 – 3.47 (m, 1H), 2.29 (d, *J* = 0.8 Hz, 3H), 1.96 – 1.82 (m, 2H), 1.67 – 1.49 (m, 6H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.03 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] (170.63, 170.59), 168.1, (96.91, 96.86), 93.3, (83.4, 83.3), (82.8, 82.7), 68.9, (62.3, 62.2), 59.5, (54.26, 54.18), (30.42, 30.41), 28.7, 25.5, 19.3, (19.21, 19.16), 14.6, 9.7.

MS (EI) *m/z* (%): 208.1 (100) [M^+-THPOH], 179.0 (71), 137.0 (38), 85 (88) [THP], 55 (29).

HRMS (ESI) *m/z* 333.1676 [333.1672 calcd. for $C_{17}H_{26}O_5Na$ (M^++Na^+)].

(*E*)-ethyl 3-((6-hydroxyhex-4-yn-3-yl)oxy)but-2-enoate (I-72q)



$C_{12}H_{18}O_4$
226,27

Following procedure D, THP-protected alcohol **I-78q** (300 mg, 0.97 mmol) was deprotected. After flash chromatography (Cyclohexane/EtOAc = 9/1), the product (132.9 mg, 0.59 mmol, 61 %) was obtained.

TLC: Rf = 0.24 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

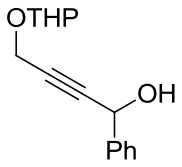
^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] 5.19 (s, 1H), 4.53 (t, *J* = 6.3 Hz, 1H), 4.31 (dd, *J* = 6.3, 1.5 Hz, 2H), 4.14 (tdd, *J* = 10.9, 7.1, 3.8 Hz, 2H), 2.29 (s, 3H), 1.91 – 1.83 (m, 2H), 1.61 (t, *J* = 6.3 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.04 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 170.6, 168.0, 93.3, 85.3, 82.7, 68.8, 59.6, 51.2, 28.8, 19.2, 14.6, 9.6.

MS (EI) *m/z* (%): 150.9 (92) [M^+-$EtCH_2O_2$], 91.0 (93), 79.0 (91), 76.9 (100), 52.9 (92).

HRMS (ESI) *m/z* 249.1105 [249.1097 calcd. for $C_{12}H_{18}O_4Na$ (M^++Na^+)].

1-phenyl-4-((tetrahydro-2H-pyran-2-yl)oxy)but-2-yn-1-ol (I-77r)



$C_{15}H_{18}O_3$
246,30

Following procedure B, propargyl alcohol **I-76d** (1.0 g, 7.13 mmol) was added to benzaldehyde (909.0 mg, 8.56 mmol). After flash chromatography (Cyclohexane/EtOAc = 4/1), the product (1.15 mg, 4.67 mmol, 65%) was obtained.

TLC: Rf = 0.16 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

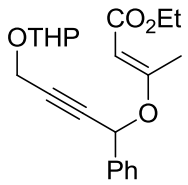
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.58 – 7.50 (m, 2H), 7.42 – 7.29 (m, 3H), 5.52 (d, *J* = 5.5 Hz, 1H), 4.82 (t, *J* = 3.4 Hz, 1H), 4.42 – 4.27 (m, 2H), 3.88 – 3.79 (m, 1H), 3.57 – 3.47 (m, 1H), 2.28 (d, *J* = 23.0 Hz, 1H), 1.90 – 1.68 (m, 2H), 1.67 – 1.51 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 140.6, 128.8, 128.6, 126.8, 97.1, 85.8, 83.0, 64.8, 62.2, 54.5, 30.4, 25.5, 19.2.

MS (EI) *m/z* (%): 143.9 (24) [M^+-THPOH], 115.0 (69) [CH_2OTHP], 105.0 (97) [PhCO], 84.0 (83), 77.0 (100) [Ph], 55.0 (100).

HRMS (ESI) *m/z* 269.1148 [269.1148 calcd. for $C_{15}H_{18}O_3Na$ (M^++Na^+)].

(*E*)-ethyl 3-((1-phenyl-4-((tetrahydro-2H-pyran-2-yl)oxy)but-2-yn-1-yl)oxy)but-2-enoate (I-78r)



$C_{21}H_{26}O_5$
358,43

Following procedure C, propargyl alcohol **I-77r** (400 mg, 1.62 mmol) was added to ethyl 2-butynoate (200.6 mg, 1.79 mmol). After flash chromatography (Cyclohexane/EtOAc = 9/1), the product (291.7 mg, 0.81 mmol, 50%) was obtained as a diastereoisomeric mixture.

TLC: Rf = 0.47 (Cyclohexane/EtOAc = 9/1) [UV/CAM]

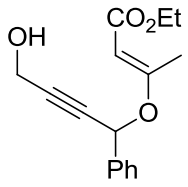
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.50 (dd, *J* = 7.8, 1.7 Hz, 2H), 7.43 – 7.36 (m, 3H), 5.67 (s, 1H), 5.36 (d, *J* = 2.7 Hz, 1H), 4.80 (q, *J* = 3.4 Hz, 1H), 4.35 (t, *J* = 1.4 Hz, 2H), 4.20 – 4.10 (m, 2H), 3.88 – 3.79 (m, 1H), 3.54 – 3.47 (m, 1H), 2.34 (d, *J* = 0.6 Hz, 3H), 1.87 – 1.77 (m, 1H), 1.76 – 1.67 (m, 1H), 1.65 – 1.57 (m, 2H), 1.55 – 1.48 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 170.4, 167.9, 137.0, 129.1, 128.9, 127.5, (97.05, 97.02), 94.0, 85.6, 82.0, 69.8, (62.3, 62.2), 59.6, (54.4, 54.3), 30.4, 25.5, 19.3, 19.2, 14.6.

MS (EI) *m/z* (%): 144.0 (100), 115.0 (82) [CH_2OTHP], 105.0 (41) [PhCO], 85.0 (33), 55.0 (27).

HRMS (ESI) *m/z* 381.1671 [381.1672 calcd. for $C_{21}H_{26}O_5Na$ (M^++Na^+)].

(*E*)-ethyl 3-((4-hydroxy-1-phenylbut-2-yn-1-yl)oxy)but-2-enoate (I-72r)



$C_{16}H_{18}O_4$
274,31

Following procedure D, THP-protected alcohol **I-78r** (282.9 mg, 0.789 mmol) was deprotected. After flash chromatography (Cyclohexane/EtOAc = 9/1), the product (142.9 mg, 0.52 mmol, 66%) was obtained.

TLC: Rf = 0.17 (Cyclohexane/EtOAc = 9/1) [UV/CAM]

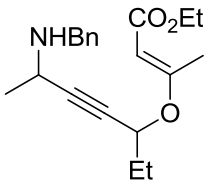
^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] 7.54 – 7.48 (m, 2H), 7.45 – 7.35 (m, 3H), 5.67 (s, 1H), 5.33 (s, 1H), 4.36 (s, 2H), 4.16 (tdd, *J* = 11.0, 7.1, 3.7 Hz, 2H), 2.34 (s, 3H), 1.66 (s, 1H), 1.29 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 170.3, 167.9, 136.9, 129.2, 128.9, 127.3, 94.1, 87.4, 81.9, 69.6, 59.7, 51.3, 19.3, 14.5.

MS (EI) *m/z* (%): 151.8 (38) [M^+-PhCHO-H_2O], 105.0 (100) [PhCO], 77.0 (100) [Ph].

HRMS (ESI) *m/z* 297.1109 [297.1097 calcd. for $C_{16}H_{18}O_4Na$ (M^++Na^+)].

(*E*)-ethyl 3-((6-(benzylamino)hept-4-yn-3-yl)oxy)but-2-enoate (I-86a)



$C_{20}H_{27}NO_3$
329,43

At 0°C, Et_3N (98.39 mg, 1.665 mmol) and MsCl (142.97 mg, 1.248 mmol, 4 M in CH_2Cl_2) were added to vinyl propargyl alcohol **I-72a** (200 mg, 0.832 mmol) in CH_2Cl_2 (1.66 mL, 0.5 M). The reaction mixture was stirred at 0°C for 2 h. CH_2Cl_2 was added and the organic phase was washed with sat. $NaHCO_3$-solution and sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. At rt, the crude product was dissolved in MeCN (0.8 mL, 1 M) and benzylamine (178.3 mg, 1.66 mmol) was added. The reaction mixture was stirred at 60°C for 3 h. Finally, it was quenched with H_2O and extracted three times with EtOAc. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH = 95/5) to obtain the product (145.6 mg, 0.442 mmol, 53%).

TLC: Rf = 0.45 (CH_2Cl_2/MeOH = 95/5) [UV/CAM]

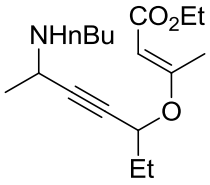
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.36 – 7.28 (m, 4H), 7.25 – 7.21 (m, 1H), 5.31 (d, *J* = 2.9 Hz, 1H), 4.54 (dd, *J* = 7.0, 5.6 Hz, 1H), 4.16 – 4.04 (m, 2H), 3.98 (dd, *J* = 12.8, 1.9 Hz, 1H), 3.78 (dd, *J* = 12.8, 1.1 Hz, 1H), 3.56 – 3.49 (m, 1H), 2.32 (s, 3H), 1.92 – 1.82 (m, 2H), 1.49 (s, 1H), 1.35 (dd, *J* = 6.8, 0.9 Hz, 3H), 1.21 (td, *J* = 7.1, 4.4 Hz, 3H), 1.06 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 170.6, 168.1, 140.0, 128.6, 127.2, 93.4, 89.8, 79.8, 69.14, 59.5, 51.6, 44.6, 29.0, 22.4, 19.2, 14.5, 9.7.

MS (EI) *m/z* (%): 254.1 (100) [M^+-$C_3H_7O_2$], 163.0 (18), 106 (10) [BnNH], 91.1 (73) [Bn].

HRMS (ESI) *m/z* 330.2064 [330.2064 calcd. for $C_{20}H_{28}NO_3$ (M^++H^+)].

(*E*)-ethyl 3-((6-(butylamino)hept-4-yn-3-yl)oxy)but-2-enoate (I-86b)



$C_{17}H_{29}NO_3$
295,42

At 0°C, Et_3N (49.2 mg, 0.832 mmol) and MsCl (71.5 mg, 0.624 mmol, 4 M in CH_2Cl_2) were added to vinyl propargyl alcohol **I-72a** (100 mg, 0.416 mmol) in CH_2Cl_2 (0.83 mL, 0.5 M). The reaction mixture was stirred at 0°C for 4 h. CH_2Cl_2 was added and the organic phase was washed with sat. $NaHCO_3$-solution and sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. At rt, the crude product was then dissolved in MeCN (0.47 mL, 1 M) and *n*Butylamine (68.4 mg, 0.935 mmol) was added. The reaction mixture was then stirred at 60°C for 6 h. Finally, it was quenched with H_2O and extracted three times with Et_2O. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (Petroleum ether/EtOAc = 4/1 → 3/2) to obtain the product (71.6 mg, 0.242 mmol, 58%).

TLC: Rf = 0.07 (Petroleum ether/ EtOAc = 4/1) [UV]

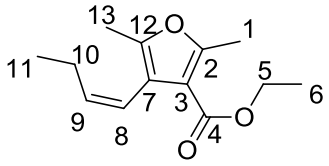
^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] 5.24 (d, *J* = 2.4 Hz, 1H), 4.53 – 4.46 (m, 1H), 4.20 – 4.06 (m, 2H), 3.52 (qdd, *J* = 6.8, 3.0, 1.6 Hz, 1H), 2.80 (dddd, *J* = 10.7, 8.4, 6.4, 4.0 Hz, 1H), 2.61 – 2.52 (m, 1H), 2.29 (s, 3H), 1.88 – 1.79 (m, 2H), 1.52 – 1.39 (m, 4H), 1.33 (d, *J* = 6.8 Hz, 4H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.03 (t, *J* = 7.4 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 170.6, 168.1, 93.3, 90.2, 79.4, 69.1, 59.4, 47.3, 45.4, 32.3, 28.9, 22.4, 20.6, 19.2, 14.6, 14.1, 9.7.

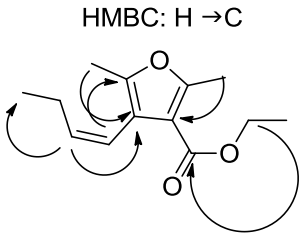
MS (EI) *m/z* (%): 249.1 (16), 220.1 (100) [M^+-$C_3H_7O_2$], 206.1 (17), 135.1 (12), 56.0 (4) [C_4H_8].

HRMS (ESI) *m/z* 296.2219 [296.2220 calcd. for $C_{17}H_{30}NO_3$ (M^++H^+)].

ethyl 4-(but-1-en-1-yl)-2,5-dimethylfuran-3-carboxylate (I-81a)



$C_{13}H_{18}O_3$
222,28



(Procedure E)

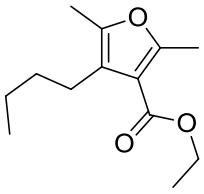
Under N_2, $AgBF_4$ (0.8 mg, 4.16 μmol) was added to a solution of propargyl vinyl ether **I-72a** (50.5 mg, 0.208 mmol) in dry CH_2Cl_2 (2.1 mL, 0.1 M), then reaction mixture was heated to 35°C for 12 h. After filtration over celite and concentration, the crude product was purified by flash chromatography (Cyclohexane/EtOAc= 95/5) to obtain the product (40.9 mg, 0.184 mmol, 87%) as a *E/Z* mixture.

TLC: Rf = 0.64 (Cyclohexane/EtOAc = 4/1) [UV/CAM];

For the major isomer:

Entry	δ_H	δ_C	COSY (^{1}H-^{1}H)	HMBC (^{1}H-^{13}C)
1	2.51 (s, 3H)	14.2		3, 2
2		157.5		
3		113.8		
4		164.7		
5	4.25 (q, *J* = 7.1 Hz, 2H)	59.9	6	4, 6
6	1.32 (t, *J* = 7.1 Hz, 3H)	14.4	5	5
7		117.2		
8	6.20 (dd, *J* = 11.2, 0.9 Hz, 1H)	119.6	9	10, 12
9	5.60 (dt, *J* = 11.2, 7.2 Hz, 1H)	134.6	8, 10	11, 10, 7
10	2.00 - 1.90 (m, 2H)	22.4	9, 11	11, 9, 8
11	0.96 (t, *J* = 7.5 Hz, 3H)	14.1	10	10, 9
12		146.3		
13	2.11 (s, 3H)	12.6		7, 12

ethyl 4-butyl-2,5-dimethylfuran-3-carboxylate (I-83a)



$C_{13}H_{20}O_3$
224,30

(Procedure F)

Under N_2, $AgBF_4$ (0.6 mg, 3.32 μmol) was added to a solution of propargyl vinyl ether **I-72a** (40 mg, 0.166 mmol) in dry CH_2Cl_2 (1.6 mL, 0.1 M), then reaction mixture was heated to 35°C for 12 h. After filtration over celite and concentration, the residue was dissolved in dry MeOH/ EtOAc (2/1, 1.1 mL, 0.15 M) and 5 mol% Pd/C (10.6 mg, 4.98 μmol) was added. The

mixture was stirred at rt for 1 h under H_2 atmosphere. It was filtered over celite and the crude product was purified by flash chromatography (Cyclohexane/EtOAc = 95/5) to obtain the product (26.8 mg, 0.120 mmol, 72%).

TLC: Rf = 0.74 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

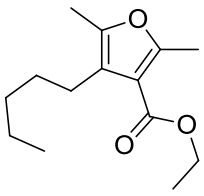
^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] 4.27 (q, *J* = 7.1 Hz, 2H), 2.53 – 2.45 (m, 5H), 2.16 (s, 3H), 1.48 – 1.41 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.33 – 1.28 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 165.0, 157.6, 146.0, 119.6, 113.3, 59.7, 33.0, 24.2, 22.7, 14.4, 14.3, 14.1, 11.2.

MS (EI) *m/z* (%): 224.1 (53) [M^+], 195.1 (16) [M^+-Et], 182.0 (100) [M^+-*n*Pr], 167.0 (18) [M^+-*n*Bu], 153.0 (88), 137.0 (58).

HRMS (ESI) *m/z* 225.1485 [225.1485 calcd. for $C_{13}H_{21}O_3$ (M^++H^+)].

ethyl 2,5-dimethyl-4-pentylfuran-3-carboxylate (I-83b)



$C_{14}H_{22}O_3$
238,32

Following procedure F, substrat **I-72b** (30.1 mg, 0.118 mmol) gave after flash chromatography (Cyclohexane/EtOAc = 95/5) the furan **I-83b** (19.0 mg, 79.7 μmol, 68%).

TLC: Rf = 0.8 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

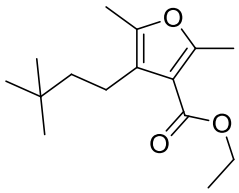
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 4.27 (q, *J* = 7.1 Hz, 2H), 2.53 – 2.45 (m, 5H), 2.16 (s, 3H), 1.53 – 1.41 (m, 2H), 1.40 – 1.23 (m, 7H), 0.88 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 165.0, 157.6, 146.0, 119.7, 113.3, 59.8, 31.9, 30.5, 24.5, 22.8, 14.5, 14.4, 14.3, 11.3.

MS (EI) *m/z* (%): 238.1 (43) [M^+], 182.1 (100) [M^+-C_5H_9], 153.0 (68), 137.0 (46).

HRMS (ESI) *m/z* 239.1644 [239.1642 calcd. for $C_{14}H_{23}O_3$ (M^++H^+)].

ethyl 4-(3,3-dimethylbutyl)-2,5-dimethylfuran-3-carboxylate (I-83c)



$C_{15}H_{24}O_3$
252,35

Following procedure F, substrat **I-72c** (40.0 mg, 0.149 mmol) gave after flash chromatography (Cyclohexane/EtOAc = 95/5) the furan **I-83c** (24.9 mg, 98.7 μmol, 66%).

TLC: Rf = 0.8 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

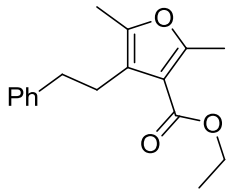
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 4.28 (q, *J* = 7.1 Hz, 2H), 2.49 (s, 3H), 2.48 – 2.44 (m, 2H), 2.16 (s, 3H), 1.36 – 1.29 (m, 5H), 0.95 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 165.0, 157.7, 145.7, 120.1, 113.3, 59.8, 45.2, 30.6, 29.4, 19.6, 14.6, 14.4, 11.1.

MS (EI) *m/z* (%): 252.1 (86) [M^+], 181.0 (80) [M^+-C_5H_{11}], 149.0 (100), 137.0 (65).

HRMS (ESI) *m/z* 253.1804 [253.1798 calcd. for $C_{15}H_{25}O_3$ (M^++H^+)].

ethyl 2,5-dimethyl-4-phenethylfuran-3-carboxylate (I-83d)



$C_{17}H_{20}O_3$
272,34

Following procedure F, substrat **I-72d** (30.4 mg, 0.104 mmol) gave after flash chromatography (Cyclohexane/EtOAc = 95/5) the furan **I-83d** (22.4 mg, 82.3 μmol, 78%).

TLC: Rf = 0.72 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

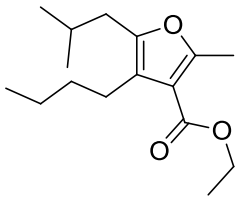
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.26 (dd, *J* = 8.1, 6.4 Hz, 2H), 7.23 – 7.11 (m, 3H), 4.32 (q, *J* = 7.1 Hz, 2H), 2.78 (s, 4H), 2.52 (s, 3H), 1.89 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 165.0, 157.8, 146.8, 142.3, 128.8, 128.3, 125.9, 118.4, 113.1, 59.9, 36.9, 26.9, 14.6, 14.5, 10.9.

MS (EI) *m/z* (%): 272.1 (67) [M^+], 227.1 (14) [M^+-EtO], 181.0 (100) [M^+-Bn], 153.0 (75), 137.0 (61), 91.0 (19).

HRMS (ESI) *m/z* 295.1299 [295.1305 calcd. for $C_{17}H_{20}O_3Na$ (M^++Na^+)].

ethyl 4-butyl-5-isobutyl-2-methylfuran-3-carboxylate (I-83e)



$C_{16}H_{26}O_3$
266,38

Following procedure F, substrat **I-72e** (39.7 mg, 0.142 mmol) gave after flash chromatography (Cyclohexane/EtOAc = 95/5) the furan **I-83e** (24.0 mg, 90.1 μmol, 64%).

TLC: Rf = 0.8 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

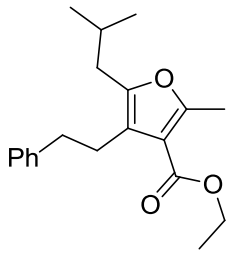
^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] 4.27 (q, *J* = 7.1 Hz, 2H), 2.50 (s, 3H), 2.49 – 2.46 (m, 2H), 2.37 (d, *J* = 7.2 Hz, 2H), 1.93 (dt, *J* = 13.6, 6.8 Hz, 1H), 1.44 (tt, *J* = 7.7, 6.3 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 5H), 0.94 – 0.89 (m, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 165.1, 157.8, 149.5, 120.4, 113.2, 59.8, 34.9, 33.3, 28.3, 24.3, 23.0, 22.5, 14.5, 14.2.

MS (EI) *m/z* (%): 266.2 (31) [M^+], 223.1 (100) [M^+-*n*Pr], 181.0 (43), 153.0 (33), 137.0 (21).

HRMS (ESI) *m/z* 267.1955 [267.1955 calcd. for $C_{16}H_{27}O_3$ (M^++H^+)].

ethyl 5-isobutyl-2-methyl-4-phenethylfuran-3-carboxylate (I-83f)



$C_{20}H_{26}O_3$
314,42

Following procedure F, substrat **I-72f** (47.5 mg, 0.144 mmol) gave after flash chromatography (Petroleum Ether/EtOAc = 95/5) the furan **I-83f** (27.0 mg, 85.8 μmol, 60%).

TLC: Rf = 0.74 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

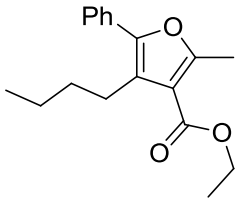
^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] 7.29 – 7.26 (m, 2H), 7.18 (dd, *J* = 11.8, 4.3 Hz, 3H), 4.32 (q, *J* = 7.1 Hz, 2H), 2.81 – 2.75 (m, 4H), 2.53 (s, 3H), 2.22 (d, *J* = 7.2 Hz, 2H), 1.84 (dt, *J* = 13.6, 6.8 Hz, 1H), 1.37 (t, *J* = 7.1 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 165.0, 158.0, 150.0, 142.5, 128.7, 128.4, 125.9, 119.4, 113.1, 59.9, 37.3, 34.6, 28.2, 26.9, 22.5, 14.6, 14.6.

MS (EI) *m/z* (%): 314.2 (31) [M^+], 223.1 (100) [M^+-Bn], 91.0 (31).

HRMS (ESI) *m/z* 337.1774 [337.1774 calcd. for $C_{20}H_{26}O_3Na$ (M^++Na^+)].

ethyl 4-butyl-2-methyl-5-phenylfuran-3-carboxylate (I-83g)



$C_{18}H_{22}O_3$
286,37

Following procedure F, substrat **I-72g** (30.0 mg, 0.099 mmol) gave after flash chromatography (Cyclohexane/EtOAc = 95/5) the furan **I-83g** (8.5 mg, 29.6 μmol, 30%).

TLC: Rf = 0.64 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

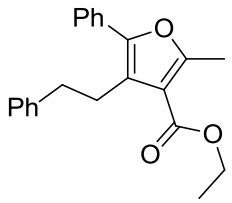
^{1}H NMR (600 MHz, $CDCl_3$) 7.57 (dd, *J* = 8.3, 1.0 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.32 – 7.27 (m, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.81 (dd, *J* = 8.8, 7.3 Hz, 2H), 2.61 (s, 3H), 1.62 (tt, *J* = 7.9, 6.4 Hz, 2H), 1.43 (dd, *J* = 14.9, 7.4 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 164.8, 158.9, 147.6, 131.2, 128.7, 127.4, 126.2, 122.3, 114.9, 60.0, 32.9, 24.6, 23.1, 14.7, 14.5, 14.1.

MS (EI) *m/z* (%): 286.1 (100) [M^+], 243.1 (47) [M^+-*n*Pr], 215.0 (23), 199.0 (25), 105.0 (20) [PhCO].

HRMS (ESI) *m/z* 309.1462 [309.1461 calcd. for $C_{18}H_{22}O_3Na$ (M^++Na^+)].

ethyl 2-methyl-4-phenethyl-5-phenylfuran-3-carboxylate (I-83h)



$C_{22}H_{22}O_3$
334,41

Following procedure F, the substrat **I-72h** (40.0 mg, 0.114 mmol) gave after flash chromatography (Cyclohexane/EtOAc = 95/5) the furan **I-83h** (24.7 mg, 73.9 mmol, 65%).

TLC: Rf = 0.7 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

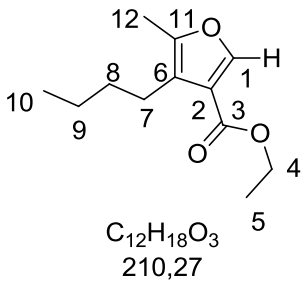
^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] 7.51 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.31 – 7.26 (m, 3H), 7.26 – 7.24 (m, 2H), 7.21 – 7.17 (m, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.14 – 3.08 (m, 2H), 2.98 – 2.92 (m, 2H), 2.64 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 164.7, 159.1, 148.2, 142.1, 131.0, 128.7, 128.6, 128.5, 127.6, 126.2, 126.1, 121.2, 114.8, 60.2, 36.8, 27.0, 14.8, 14.6.

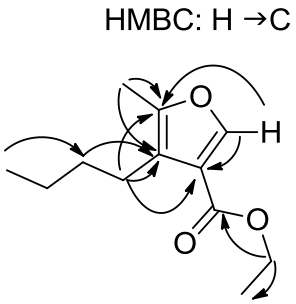
MS (EI) *m/z* (%): 334.1 (46) [M^+], 243.1 (100) [M^+-Bn], 199.0 (21), 105.0 (20) [PhCO].

HRMS (ESI) *m/z* 357.1459 [357.1461 calcd. for $C_{22}H_{22}O_3Na$ (M^++Na^+)].

3-butyl-4-(ethoxymethyl)-2-methylfuran (I-83i)



$C_{12}H_{18}O_3$
210,27



Following procedure F, substrat **I-72i** (30.5 mg, 0.135 mmol) gave after flash chromatography (Cyclohexane/EtOAc = 95/5) the furan **I-83i** (8.9 mg, 42.3 μmol, 31%).

TLC: Rf = 0.76 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] 7.83 (s, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 2.56 – 2.52 (m, 2H), 2.22 (s, 3H), 1.48 (ddd, *J* = 15.2, 11.0, 7.5 Hz, 2H), 1.35 – 1.30 (m, 5H), 0.91 (t, *J* = 7.3 Hz, 3H).

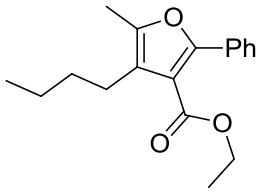
^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 164.0, 149.7, 146.5, 119.4, 119.0, 60.0, 32.8, 23.6, 22.7, 14.5, 14.1, 11.6.

MS (EI) *m/z* (%): 210.1 (26) [M^+], 168.0 (59) [M^+-C_3H_6], 139.0 (100), 123.0 (25).

HRMS (ESI) *m/z* 211.1329 [211.1329 calcd. for $C_{12}H_{19}O_3$ (M^++H^+)].

Entry	δ_H	δ_C	COSY (^{1}H-^{1}H)	HMBC (^{1}H-^{13}C)
1	7.83 (s, 1H)	146.5		2, 11
2		119.0		
3		164.0		
4	4.27 (q, *J* = 7.1 Hz, 2H)	60.0	5	3, 5
5	1.35-1.30 (m, 5H)	14.5	4	
6		119.4		
7	2.56 – 2.52 (m, 2H)	23.6	8	2, 6, 8, 9, 11
8	1.48 (ddd, *J* = 15.2, 11.0, 7.5 Hz, 2H)	32.8	7, 9	6, 7, 9, 10
9	1.35-1.30 (m, 5H)	22.7	8, 10	
10	0.91 (t, *J* = 7.3 Hz, 3H)	14.1	9	8, 9
11		149.7		
12	2.22 (s, 3H)	11.6		6, 11

ethyl 4-butyl-5-methyl-2-phenylfuran-3-carboxylate (I-83j)



$C_{18}H_{22}O_3$
286,37

Following procedure F, substrat **I-72j** (37.0 mg, 0.125 mmol) gave after flash chromatography (Cyclohexane/EtOAc = 95/5) the furan **I-83j** (20.5 mg, 71.6 μmol, 59%).

TLC: Rf = 0.71 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

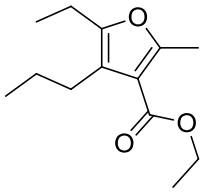
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.75 – 7.71 (m, 2H), 7.41 – 7.30 (m, 3H), 4.27 (q, *J* = 7.1 Hz, 2H), 2.59 – 2.52 (m, 2H), 2.28 (s, 3H), 1.49 (ddd, *J* = 8.7, 7.7, 3.9 Hz, 2H), 1.36 (dq, *J* = 14.2, 7.1 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.93 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 165.0, 155.1, 147.9, 130.8, 128.7, 128.3, 128.0, 121.3, 114.4, 60.4, 33.0, 24.3, 22.7, 14.2, 14.1, 11.6.

MS (EI) *m/z* (%): 286.1 (100) [M^+], 244.1 (40) [M^+-C_3H_6], 215.0 (47), 199.0 (20).

HRMS (ESI) *m/z* 309.1462 [309.1461 calcd. for $C_{28}H_{22}O_3Na$ (M^++Na^+)].

ethyl 5-ethyl-2-methyl-4-propylfuran-3-carboxylate (I-83k)



$C_{13}H_{20}O_3$
224,30

Following procedure F, substrat **I-72k** (30.0 mg, 0.125 mmol) gave after flash chromatography (Cyclohexane/EtOAc = 95/5) the furan **I-83k** (13.7 mg, 61.1 μmol, 49%).

TLC: Rf = 0.74 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

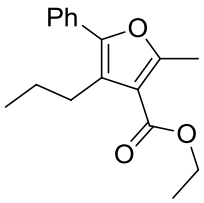
^{1}H NMR (400 MHz, $CDCl_3$) 4.27 (q, *J* = 7.1 Hz, 2H), 2.57 – 2.44 (m, 7H), 1.54 – 1.43 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.5 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 165.1, 157.7, 151.5, 118.6, 113.2, 59.7, 26.3, 24.2, 19.2, 14.5, 14.4, 14.1, 13.4.

MS (EI) *m/z* (%): 224.1 (100) [M^+], 209.1 (79) [M^+-Me], 195.1 (93) [M^+-Et], 167.0 (65) [M^+-C_2H_5-C_2H_4], 151.0 (51) [M^+-CO_2Et].

HRMS (APCI) *m/z* 225.1510 [225.1485 calcd. for $C_{13}H_{21}O_3$ (M^++H^+)].

ethyl 2-methyl-5-phenyl-4-propylfuran-3-carboxylate (I-83l)



$C_{17}H_{20}O_3$
272,34

Following procedure F, substrat **I-72l** (30.0 mg, 0.104 mmol) gave after flash chromatography (Cyclohexane/EtOAc = 95/5) the furan **I-83l** (7.2 mg, 26.4 μmol, 25%).

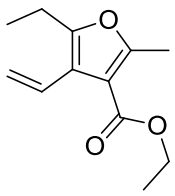
TLC: Rf = 0.67 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

^{1}H NMR (400 MHz, $CDCl_3$) 7.59 – 7.54 (m, 2H), 7.41 (dd, *J* = 10.9, 4.5 Hz, 2H), 7.32 – 7.27 (m, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 2.83 – 2.74 (m, 2H), 2.61 (s, 3H), 1.71 – 1.60 (m, 2H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.00 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 164.8, 158.9, 147.7, 131.2, 128.7, 127.4, 126.2, 122.2, 114.9, 60.0, 26.9, 24.0, 14.7, 14.5, 14.4.

HRMS (ESI) *m/z* 273.1484 [273.1485 calcd. for $C_{17}H_{21}O_3$ (M^++H^+)].

ethyl 5-ethyl-2-methyl-4-vinylfuran-3-carboxylate (I-83o)



$C_{12}H_{16}O_3$
208,25

Following procedure E, substrat **I-72o** (30.0 mg, 0.132 mmol) gave after flash chromatography (Cyclohexane/EtOAc = 95/5) the furan **I-83o** (11.8 mg, 56.7 μmol, 43%).

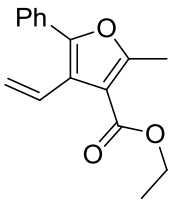
TLC: Rf = 0.71 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

^{1}H NMR (400 MHz, $CDCl_3$) 6.86 – 6.76 (m, 1H), 5.29 (q, *J* = 1.9 Hz, 1H), 5.25 (dd, *J* = 4.2, 1.9 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 2.69 (q, *J* = 7.5 Hz, 2H), 2.51 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 164.8, 157.4, 152.5, 128.6, 118.2, 116.0, 112.9, 60.1, 20.2, 14.5, 14.3, 12.9.

HRMS (APCI) *m/z* 209.0849 [209.1172 calcd. for $C_{12}H_{17}O_3$ (M^++H^+)].

ethyl 2-methyl-5-phenyl-4-vinylfuran-3-carboxylate (I-83p)



$C_{16}H_{16}O_3$
256,30

Following procedure E, substrat **I-72p** (30.0 mg, 0.109 mmol) gave after flash chromatography (Cyclohexane/EtOAc = 95/5) the furan **I-83p** (10.1 mg, 39.4 μmol, 36%).

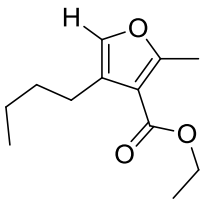
TLC: Rf = 0.6 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

^{1}H NMR (400 MHz, $CDCl_3$) 7.74 – 7.66 (m, 2H), 7.37 (tq, *J* = 3.5, 1.1 Hz, 2H), 7.32 – 7.28 (m, 1H), 6.86 (dd, *J* = 17.8, 11.4 Hz, 1H), 5.53 (dd, *J* = 17.8, 1.9 Hz, 1H), 5.35 (dd, *J* = 11.4, 1.9 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 2.60 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 164.6, 158.5, 148.3, 130.9, 128.6, 128.1, 127.9, 127.0, 119.8, 119.3, 114.6, 60.3, 14.4, 14.4.

HRMS (ESI) *m/z* 257.1172 [257.1172 calcd. for $C_{16}H_{16}O_3$ $(M)^+$].

ethyl 4-butyl-2-methylfuran-3-carboxylate (I-83q)



$C_{12}H_{18}O_3$
210,27

Following procedure F, substrat **I-72q** (30.0 mg, 0.133 mmol) gave after flash chromatography (Cyclohexane/EtOAc = 95/5) the furan **I-83q** (14.9 mg, 70.9 μmol, 53%).

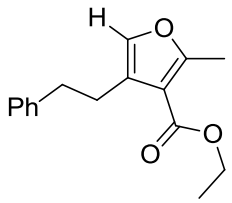
TLC: Rf = 0.73 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

^{1}H NMR (400 MHz, $CDCl_3$) 7.02 (s, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 2.60 – 2.55 (m, 2H), 2.53 (s, 3H), 1.57 – 1.48 (m, 2H), 1.40 – 1.31 (m, 5H), 0.92 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 164.9, 160.9, 137.5, 126.5, 113.1, 59.9, 31.9, 24.6, 22.7, 14.6, 14.5, 14.1.

MS (EI) *m/z* (%): 181.9 (100) [M^+-C_2H_4], 153.9 (62) [M^+-C_4H_8], 135.9 (84) [M^+-$C_3H_6O_2$], 109.0 (55), 79.0 (55).

ethyl 2-methyl-4-phenethylfuran-3-carboxylate (I-83r)



$C_{16}H_{18}O_3$
258,31

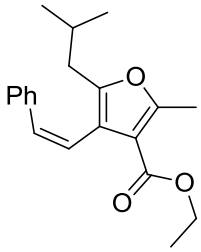
Following procedure F, substrat **I-72r** (30.0 mg, 0.109 mmol) gave after flash chromatography (Petroleum ether/EtOAc = 95/5) the furan **I-83r** (17.0 mg, 65.8 μmol, 60%).

TLC: Rf = 0.69 (Petroleum ether /EtOAc = 4/1) [UV/CAM]

^{1}H NMR (600 MHz, $CDCl_3$) 7.28 (t, *J* = 7.6 Hz, 2H), 7.19 (dd, *J* = 13.9, 7.2 Hz, 3H), 6.98 (s, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 2.93 – 2.88 (m, 2H), 2.88 – 2.84 (m, 2H), 2.55 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 164.8, 160.4, 142.1, 137.8, 128.6, 128.4, 126.0, 125.6, 113.0, 60.0, 36.2, 26.8, 14.6, 14.6.

ethyl 5-isobutyl-2-methyl-4-styrylfuran-3-carboxylate (I-81f)



$C_{20}H_{24}O_3$
312,40

Following procedure E, substrat **I-72f** (50.0 mg, 0.151 mmol) gave after flash chromatography (Petroleum ether/EtOAc = 95/5) a diastereoisomeric mixture of furans **I-81f** (35.3 mg, 113.0 μmol, 75%, *Z: E* 2:1).

TLC: Rf = 0.78 (Petroleum ether/EtOAc = 4/1) [UV/CAM]

For the major isomer:

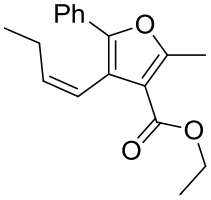
^{1}H NMR (400 MHz, $CDCl_3$) 7.21 – 7.17 (m, 4H), 7.13 (ddd, *J* = 9.6, 5.2, 3.0 Hz, 1H), 6.56 (d, *J* = 12.0 Hz, 1H), 6.43 (d, *J* = 12.0 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.55 (s, 3H), 1.97 (d, *J* = 7.1 Hz, 2H), 1.76 (td, *J* = 13.5, 6.7 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.74 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 164.73, 157.9, 149.8, 137.9, 131.0, 128.5, 128.3, 126.9, 121.7, 117.4, 113.6, 60.1, 35.5, 27.4, 22.4, 14.4, 14.3.

MS (EI) *m/z* (%): 312.1 (28) [M^+], 223.0 (79), 181.0 (100), 152 (46), 77 (24) [Ph].

HRMS (ESI) *m/z* 335.1619 [335.1618 calcd. for $C_{20}H_{24}O_3Na$ (M^++Na^+)].

ethyl 4-(but-1-en-1-yl)-2-methyl-5-phenylfuran-3-carboxylate (I-81g)



$C_{18}H_{20}O_3$
284,35

Following procedure E, substrat **I-72g** (50.0 mg, 0.165 mmol) gave after flash chromatography (Petroleum ether/EtOAc = 95/5) a diastereoisomeric mixture of furans **I-81g** (16.0 mg, 56.3 µmol, 34 %, *Z: E* 3:1).

TLC: Rf = 0.78 (Petroleum ether/EtOAc = 4/1) [UV/CAM]

^{1}H NMR (600 MHz, $CDCl_3$) 7.73 (d, *J* = 7.6 Hz, 1.50H), 7.70 (d, *J* = 7.5 Hz, 0.50H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 6.48 (d, *J* = 16.1 Hz, 0.25H), 6.42 (d, *J* = 11.2 Hz, 0.75H),

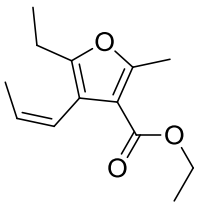
5.96 (dt, *J* = 16.1, 6.5 Hz, 0.25H), 5.69 (dt, *J* = 11.2, 7.2 Hz, 0.75H), 4.30 (dq, *J* = 11.5, 7.1 Hz, 2H), 2.62 (s, 2.30H), 2.59 (s, 0.70H), 2.18 (qd, *J* = 7.5, 1.5 Hz, 0.50H), 1.79 (pd, *J* = 7.4, 1.5 Hz, 1.50H), 1.36 (dt, *J* = 10.1, 7.1 Hz, 3H), 1.05 (t, *J* = 7.4 Hz, 1H), 0.79 (t, *J* = 7.5 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] (164.5, 158.3), 147.2, (137.4, 136.5), 131.3, 128.5, 127.6, (127.4, 126.7), 125.5, (119.7, 119.2), 117.8, 115.6, (60.21, 60.15), 22.4, 14.5, 14.4, (13.4, 13.3).

MS (EI) *m/z* (%): 284.1 (100) [M^+], 255.1 (34) [M^+-Et], 223.0 (87), 199.0 (100), 105.0 (26) [PhCO], 77.0 (24) [Ph].

HRMS (APCI) *m/z* 285.1485 [285.1485 calcd. for $C_{18}H_{21}O_3$ (M^++H^+)].

ethyl 5-ethyl-2-methyl-4-(prop-1-en-1-yl)furan-3-carboxylate (I-81k)



$C_{13}H_{18}O_3$
222,28

Following procedure E, substrat **I-72k** (29.8 mg, 0.125 mmol) gave after flash chromatography (Petroleum ether/EtOAc = 95/5) a diastereoisomeric mixture of furans **I-81k** (15.6 mg, 70.2 μmol, 56 %, *Z: E* 2.5:1).

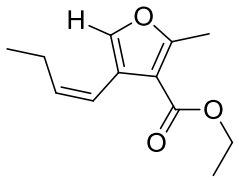
TLC: Rf = 0.68 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

^{1}H NMR (600 MHz, $CDCl_3$) 6.46 (dd, *J* = 15.9, 1.7 Hz, 0.30H), 6.27 (dd, *J* = 11.2, 1.0 Hz, 0.70H), 5.76 – 5.69 (m, 1H), 4.26 (dq, *J* = 14.3, 7.1 Hz, 2H), 2.65 (q, *J* = 7.5 Hz, 0.70H), 2.52 (s, 2.10H), 2.49 (s, 0.90H), 2.45 (q, *J* = 7.5 Hz, 1.50H), 1.85 (dd, *J* = 6.5, 1.7 Hz, 1H), 1.59 (dd, *J* = 6.9, 1.8 Hz, 2H), 1.33 (dt, *J* = 14.2, 7.1 Hz, 3H), 1.19 (dt, *J* = 12.5, 7.5 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] (164.9, 164.8), (157.7, 157.2), (151.8, 151.1), (127.7, 127.1), (122.2, 121.5), (117.9, 115.7), (113.6, 112.8), (60.0, 59.9), (20.3, 20.2), (19.0, 14.9), (14.47, 14.45), 14.3, (13.1, 12.1).

HRMS (ESI) *m/z* 245.1127 [245.1148 calcd. for $C_{13}H_{18}O_3Na$ (M^++Na^+)].

ethyl 4-(but-1-en-1-yl)-2-methylfuran-3-carboxylate (I-81q)



$C_{12}H_{16}O_3$
208,25

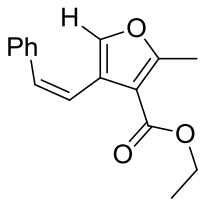
Following procedure E, substrat **I-72q** (29.7 mg, 0.124 mmol) gave after flash chromatography (Petroleum ether/EtOAc = 95/5) a diastereoisomeric mixture of furans **I-81q** (12.4 mg, 59.5 µmol, 45 %, *Z: E* 6:1).

TLC: Rf = 0.69 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

^{1}H NMR (600 MHz, $CDCl_3$) 7.30 (s, 0.15H), 7.22 (s, 0.80H), 6.53 (dd, *J* = 13.8, 8.5 Hz, 1H), 6.00 (dt, *J* = 16.0, 6.4 Hz, 0.10H), 5.68 (dt, *J* = 11.5, 7.0 Hz, 0.90H), 4.30 (q, *J* = 7.1 Hz, 2H), 2.55 (s, 2.70H), 2.53 (s, 0.40H), 2.20 (dqd, *J* = 15.1, 7.5, 1.5 Hz, 2H), 1.36 (dd, *J* = 13.7, 6.6 Hz, 3H), 1.06 (dt, *J* = 15.1, 7.6 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 164.6, 159.7, 138.6, 134.8, 122.2, 118.1, 112.8, 60.2, 22.7, 14.5, 14.5, 14.3.

(*Z*)-ethyl 2-methyl-4-styrylfuran-3-carboxylate (I-81r)



$C_{16}H_{16}O_3$
256,30

Following procedure E, substrat **I-72r** (30.0 mg, 0.109 mmol) gave after flash chromatography (Petroleum ether/EtOAc = 95/5) the furan **I-81r** (19.5 mg, 76.1 μmol, 70 %).

TLC: Rf = 0.66 (Petroleum ether/EtOAc = 4/1) [UV/CAM]

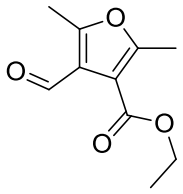
^{1}H NMR (600 MHz, $CDCl_3$) 7.30 – 7.26 (m, 4H), 7.22 – 7.18 (m, 1H), 6.88 (d, *J* = 0.8 Hz, 1H), 6.67 (dd, *J* = 12.2, 1.0 Hz, 1H), 6.61 (d, *J* = 12.2 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 2.54 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 164.5, 159.6, 139.0, 138.0, 131.0, 128.6, 128.5, 127.2, 121.7, 120.4, 113.0, 60.3, 14.5, 14.4.

MS (EI) *m/z* (%): 155.0 (56), 106.0 (77), 105.0 (84) [PhCO], 90.9 (77) [Bn], 77 (100) [Ph].

HRMS (APCI) *m/z* 257.0926 [257.1172 calcd. for $C_{16}H_{17}O_3$ (M^++H^+)].

ethyl 4-formyl-2,5-dimethylfuran-3-carboxylate (I-84a)



$C_{10}H_{12}O_4$
196,20

At 0°C, NMO monohydrate (34.4 mg, 0.254 mmol), 2,6-lutidine (36.3 mg, 0.339 mmol) and OsO_4 (43.1 mg, 6.78 μmol, 4% in H_2O) were added to furan **I-81a** (37.7 mg, 0.170 mmol) in acetone/H_2O (1.7 mL, 0.1 M, 4/1). The reaction mixture was allowed to warm to room temperature and stirred for 1 h, then $PhI(OAc)_2$ (81.9 mg, 0.254 mmol) was added. The mixture was stirred for 2h, quenched with H_2O and extracted three times with EtOAc. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (Petroleum ether/EtOAc = 9/1) to obtain the product (20.8 mg, 106.0 μmol, 63%).

TLC: Rf = 0.71 (Cyclohexane/EtOAc = 7/3) [UV/$KMnO_4$]

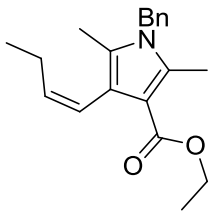
^{1}H NMR (600 MHz, $CDCl_3$) 10.36 (s, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 2.55 (s, 3H), 2.55 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 189.2, 163.7, 158.3, 158.1, 120.1, 112.7, 60.8, 14.5, 14.1, 13.9.

MS (EI) *m/z* (%): 196.0 (62) [M^+], 167.0 (49) [M^+-Et], 150.0 (100) [M^+-EtOH], 139.0 (47), 122.0 (44) [M^+-HC(O)OEt].

HRMS (ESI) *m/z* 219.0621 [219.0628 calcd. for $C_{10}H_{12}O_4Na$ (M^++Na^+)].

ethyl 1-benzyl-4-(but-1-en-1-yl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (I-87a)



$C_{20}H_{25}NO_2$
311,42

Under N_2, AuCl (1.4 mg, 6.07 μmol) was added to a solution of propargyl vinyl ether **I-86a** (20.0 mg, 60.7 μmol) in dry DCE (0.6 mL, 0.1 M), the reaction mixture was heated to 50°C for 18 h. After filtration over celite and concentration, the crude product was purified by flash chromatography (Cyclohexane/EtOAc = 98/2) to obtain a diastereoisomeric mixture of pyrroles (15.1 mg, 48.5 μmol, 80%, *Z: E* 8:1).

TLC: Rf = 0.54 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

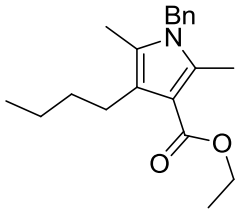
^{1}H NMR (400 MHz, $CDCl_3$) 7.34 – 7.28 (m, 2H), 7.28 – 7.24 (m, 1H), 6.90 (d, *J* = 7.0 Hz, 2H), 6.68 (d, *J* = 16.5 Hz, 0.10H), 6.42 (dd, *J* = 11.1, 0.7 Hz, 0.90H), 5.66 (dt, *J* = 16.0, 6.4 Hz, 0.10H), 5.54 (dt, *J* = 11.1, 7.1 Hz, 0.90H), 5.06 (s, 2H), 4.30 – 4.22 (m, 2H), 2.44 (s, 3H), 1.97 (s, 3H), 1.93 (ddd, *J* = 14.8, 7.4, 1.7 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.4 Hz, 0.30H), 0.96 (t, *J* = 7.5 Hz, 2.70H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 166.3, 137.3, 135.2, 132.8, 129.0, 127.5, 125.7, 125.5, 122.9, 118.4, 110.8, 59.3, 47.1, 22.4, 14.6, 14.2, 11.7, 11.1.

MS (EI) *m/z* (%): 311.1 (68) [M^+], 282.1 (14) [M^+-Et], 250.1 (36), 238.1 (25) [M^+-CO_2Et], 91.0 (100) [Bn].

HRMS (ESI) *m/z* 334.1772 [334.1778 calcd. for $C_{20}H_{25}NO_2Na$ (M^++Na^+)].

ethyl 1-benzyl-4-butyl-2,5-dimethyl-1H-pyrrole-3-carboxylate (I-88a)



$C_{20}H_{27}NO_2$
313,43

Under H_2, 5% Pd/C (5.4 mg, 2.53 μmol) was added to a solution of pyrrole **I-87a** (24.9 mg, 80.0 μmol) in dry MeOH/EtOAc (2/1, 0.56 mL, 0.15 M), then reaction mixture was stirred at rt for 2 h. After filtration over celite and concentration, the crude product was purified by flash chromatography (Cyclohexane/EtOAc = 95/5) to obtain the product (20.3 mg, 64.7 μmol, 81%).

TLC: Rf = 0.57 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

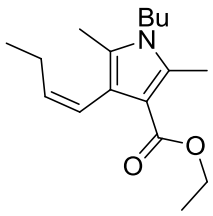
^{1}H NMR (600 MHz, $CDCl_3$) 7.30 (t, *J* = 7.5 Hz, 2H), 7.24 (t, *J* = 7.3 Hz, 1H), 6.88 (d, *J* = 7.4 Hz, 2H), 5.03 (s, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 2.69 – 2.64 (m, 2H), 2.44 (s, 3H), 2.04 (s, 3H), 1.48 (ddd, *J* = 12.3, 8.6, 6.5 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 5H), 0.92 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 166.6, 137.5, 135.2, 129.0, 127.4, 125.7, 124.9, 121.5, 110.2, 59.1, 47.0, 34.2, 25.7, 22.9, 14.6, 14.3, 11.8, 9.8.

MS (EI) *m/z* (%): 313.2 (7) [M^+], 270.0 (13) [M^+-*n*Pr], 91.0 (100) [Bn].

HRMS (ESI) *m/z* 336.1934 [336.1934 calcd. for $C_{20}H_{27}NO_2Na$ (M^++Na^+)].

ethyl 4-(but-1-en-1-yl)-1-butyl-2,5-dimethyl-1H-pyrrole-3-carboxylate (I-87b)



$C_{17}H_{27}NO_2$
277,40

Under N_2, AuCl (3.1 mg, 1.35 μmol) was added to a solution of propargyl vinyl ether **I-86a** (20.0 mg, 67.7 μmol) in dry DCE (0.7 mL, 0.1 M), the reaction mixture was heated to 70°C for 18 h. After filtration over celite and concentration, the crude product was purified by flash chromatography (Cyclohexane/EtOAc = 98/2) to obtain a diastereoisomeric mixture of pyrroles (5.5 mg, 19.8 μmol, 29%, *Z: E* 1:2).

Rf = 0.54 (Cyclohexane/EtOAc = 4/1) [UV/CAM]

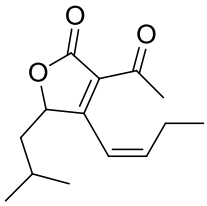
^{1}H NMR (400 MHz, $CDCl_3$) 6.36 (d, *J* = 11.1 Hz, 1H), 5.50 (dt, *J* = 11.1, 7.1 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.79 – 3.72 (m, 2H), 2.50 (s, 3H), 2.04 (s, 3H), 1.96 – 1.87 (m, 2H), 1.60 (ddd, *J* = 15.3, 10.9, 7.6 Hz, 2H), 1.44 – 1.27 (m, 5H), 0.95 (dd, *J* = 14.0, 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 166.3, 134.6, 132.5, 124.8, 123.0, 118.1, 110.3, 59.2, 43.8, 32.9, 22.4, 20.3, 14.6, 14.2, 13.9, 11.7, 11.2.

MS (EI) *m/z* (%): 277.1 (99) [M^+], 248.0 (28) [M^+-Et], 216.0 (100), 204.1 (93) [M^+-CO_2Et], 162.0 (43), 91.0 (40), 57.0 (36) [*n*Bu].

HRMS (ESI) *m/z* 300.1934 [300.1934 calcd. for $C_{17}H_{27}NO_2Na$ (M^++Na^+)].

(*Z*)-3-acetyl-4-(but-1-en-1-yl)-5-isobutylfuran-2(5H)-one (P2)



$C_{14}H_{20}O_3$
236,31

I-72e (30.0 mg, 0.106 mmol) in dry toluene (1 mL, 0.1 M) was heated to 120°C in microwave for 5.5h. Toluene was evaporated and the residue was purified by flash chromatography (Petroleum ether/EtOAc = 9/1) to obtain the product (11.4 mg, 48.2 µmol, 46%).

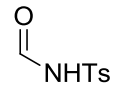
^{1}H NMR (600 MHz, $CDCl_3$) 7.33 (d, *J* = 16.5 Hz, 1H), 6.43 (dt, *J* = 16.5, 6.5 Hz, 1H), 5.25 (dd, *J* = 10.4, 1.9 Hz, 1H), 2.60 (s, 3H), 2.38 (qd, *J* = 7.5, 1.3 Hz, 2H), 2.11 – 2.01 (m, 2H), 1.75 (ddd, *J* = 14.4, 9.6, 2.2 Hz, 1H), 1.15 (t, *J* = 7.4 Hz, 3H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 195.7, 170.9, 170.6, 150.3, 121.5, 120.8, 78.6, 45.4, 30.5, 27.3, 25.6, 23.6, 21.6, 12.6.

MS (EI) *m/z* (%): 236.2 (2) [M^+], 207.1 (100) [M^+-Et], 151.0 (13), 79.0 (6), 77.0 (7).

3) Catalyzed cascade reactions, a way toward pyridine derivatives

_N_-tosylformamide (I-120)



$C_8H_9NO_3S$
199,23

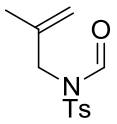
N-tosylamine (1 g, 5.84 mmol) was added to a freshly prepared NaOMe solution (12 mL, 0.73 M). The reaction mixture was heated to 40°C for 30 min, ethylformate (2.35 mL, 29.2 mmol) was introduced. The reaction mixture was heated to 50°C for 3 h. Finally, it was quenched with a 1M HCl-solution and methanol was evaporated. After concentration, the residue was dissolved in MTBE and water, the solution was acidified to pH = 2, and the aqueous phase was extracted three times with MTBE. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by recristallisation with MTBE (5 mL) to the product (942.0 mg, 4.73 mmol, 81%) as a white solid.

TLC: Rf = 0.27 (CH_2Cl_2/Et_2O = 5/1) [UV]

^{1}H NMR (250 MHz, $CDCl_3$) δ[ppm] 8.65 (s, 1H), 8.06 (s, 1H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 2.46 (s, 3H).

The analytical data are identical to the literature data.[76b]

_N_-(2-methylallyl)-N-tosylformamide (I-121)



$C_{12}H_{15}NO_3S$
253,32

N-tosylformamide (100 mg, 0.502 mmol) and K_2CO_3 (104.1 mg, 0.753 mmol) were added to a solution of methylallychloride (45.2 mg, 0.502 mmol) in dry THF/DMSO (2/1) (0.7 mL, 0.7 M). The reaction mixture was stirred at reflux for 2 h. Finally, it was quenched with water and extracted three times with Et_2O. The combined organic phase was washed with sat. $NaHCO_3$-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Pentanes/Et_2O = 9/1) to obtain the product (61.2 mg, 0.242 mmol, 48%) as a white solid.

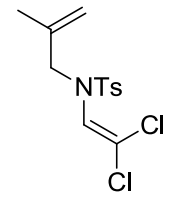
TLC: Rf = 0.46 (Pentanes/Et_2O = 9/1) [UV/$KMnO_4$]

^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 9.16 (s, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 4.80 (d, *J* = 8.8 Hz, 2H), 4.08 (s, 2H), 2.46 (s, 3H), 1.55 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 161.4, 145.6, 138.4, 135.5, 130.3, 127.7, 113.7, 47.7, 21.8, 19.9.

The analytical data are identical to the literature data.[76b]

_N_-(2,2-dichlorovinyl)-4-methyl-_N_-(2-methylallyl)benzenesulfonamide (I-122)



$C_{13}H_{15}Cl_2NO_2S$
320,23

At 55°C, CCl_4 (1.54 mL, 15.8 mmol) was added to the *N*-methylallyl-*N*-tosylformamide **I-121** (400 mg, 1.58 mmol) and PPh_3 (1.24 g, 4.74 mmol) in dry THF (16 mL, 0.1 M), over a period of 3 h. The reaction mixture was stirred at 55°C for an additional hour. Finally it was quenched with sat. $NaHCO_3$-solution and extracted three times with Et_2O. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Pentanes/Et_2O = 99/1) to obtain the product (235.5 mg, 0.735 mmol, 47%) as a white solid.

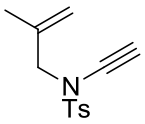
TLC: Rf = 0.74 (Pentanes/Et_2O = 9/1) [UV/$KMnO_4$]

^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 7.70 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 6.21 (s, 1H), 4.88 (d, *J* = 14.5 Hz, 2H), 3.88 (s, 2H), 2.44 (s, 3H), 1.75 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 144.3, 139.6, 135.8, 130.0, 127.5, 124.9, 115.2, 55.3, 21.8, 20.0.

The analytical data are identical to the literature data.[76b]

_N_-ethynyl-4-methyl-_N_-(2-methylallyl)benzenesulfonamide (I-123)



$C_{13}H_{15}NO_2S$
249,33

At -78°C, *n*BuLi (1.37 mL, 3.44 mmol, 2.5 M in hexanes) was slowly added to a solution of dichlorovinyl compound **I-122** (500 mg, 1.56 mmol) in dry THF (7.8 mL, 0.2 M). The reaction mixture was allowed to warm to -20°C and stirred for 1 h. Then MeOH (0.30 mL) was added. Finally the reaction mixture was diluted with Et_2O and washed with sat. $NaHCO_3$-solution. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Pentanes/Et_2O = 9/1) to obtain the product (311 mg, 1.25 mmol, 80%) as a white solid.

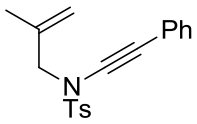
TLC: Rf = 0.38 (Pentanes/Et_2O = 9/1) [UV]

^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 7.81 (d, *J* = 8.3 Hz, 2H), 7.42 – 7.31 (m, 2H), 4.94 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 2H), 2.70 (s, 1H), 2.46 (s, 3H), 1.72 (s, 3H)

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 144.9, 138.6, 134.8, 129.9, 127.9, 115.9, 76.1, 59.2, 57.7, 21.8, 19.8.

The analytical data are identical to the literature data.[76b]

4-methyl-N-(2-methylallyl)-*N*-(phenylethynyl)benzenesulfonamide (I-124)



$C_{19}H_{19}NO_2S$
325,42

Phenyl iodide (47.9 mg, 0.235 mmol) was dissolved in a degassed solution of DIPEA (2.8 mL) and toluene (1.2 mL). The mixture was in turn degassed. Then $Pd(PPh_3)_4$ (20.8 mg, 18.0 µmol), CuI (2.4 mg, 18.0 µmol) and **I-123** (45 mg, 0.180 mmol) were added. After stirring at rt for 2.5h, the reaction mixture was diluted with CH_2Cl_2 and filtered through celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (Pentanes/Et_2O = 95/5) to obtain the product (45.5 mg, 0.140 mmol, 77%).

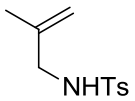
TLC: Rf = 0.38 (Pentanes/Et_2O = 9/1) [UV]

^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 7.85 (d, *J* = 8.3 Hz, 2H), 7.39 – 7.25 (m, 7H), 4.98 (s, 2H), 3.95 (s, 2H), 2.45 (s, 3H), 1.76 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 144.8, 138.9, 131.4, 129.9, 128.4, 129.9, 128.4, 116.0, 82.5, 71.0, 58.1, 21.8, 19.9.

The analytical data are identical to the literature data.[94]

4-methyl-*N*-(2-methylallyl)benzenesulfonamide (I-126)



$C_{11}H_{15}NO_2S$
225,31

Methylallyl chloride (2.38 g, 26.3 mmol) and K_2CO_3 (3.63 g, 26.3 mmol) were added to tosylamide (3 g, 17.5 mmol) in acetone (88 mL, 0.2 M). The reaction mixture was stirred at 70°C (reflux) for 24 h. It was diluted with water and CH_2Cl_2 and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Pentanes/Et_2O = 4/1) to obtain the product (1.76 g, 7.81 mmol, 45%).

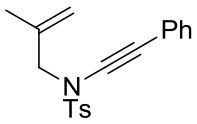
TLC: Rf = 0.40 (Pentanes/Et_2O = 9/1) [$KMnO_4$]

^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 7.75 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.95 – 4.76 (m, 2H), 4.40 (s, 1H), 3.49 (d, *J* = 6.4 Hz, 2H), 2.43 (s, 3H), 1.68 (d, *J* = 0.4 Hz, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 143.6, 140.7, 137.2, 129.8, 127.3, 112.9, 49.2, 21.7, 20.3.

The analytical data are identical to the literature data.[95]

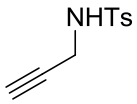
4-methyl-*N*-(2-methylallyl)-*N*-(phenylethynyl)benzenesulfonamide (I-124)



$C_{19}H_{19}NO_2S$
325,42

Bromophenyl acetylene (441.9 mg, 2.44 mmol) was dissolved in dry toluene (2.4 mL, 1 M), *N*-methylallyl-*N*-tosylamide **I-126** (500 mg, 2.22 mmol), K_2CO_3 (613.4 mg, 4.44 mmol), $CuSO_4 \cdot 5H_2O$ (54.9 mg, 0.22 mmol) and phenanthroline (80.0 mg, 0.44 mmol) were added. The reaction mixture was sonicated at 60°C for 7 h. It was diluted with CH_2Cl_2 and filtered through celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (Pentanes/Et_2O = 99/1) to obtain the product (562.5 mg, 1.42 mmol, 86%).

4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (I-135)



$C_{10}H_{11}NO_2S$
209,26

At rt, propargyl amine (100 mg, 1.82 mmol) was stirred in pyridine for 30 min, then TsCl (519.2 mg, 2.72 mmol) was added portionwise. The reaction mixture was stirred at rt for 2.5 h. It was quenched with a 1M HCl-solution and extracted three times with EtOAc. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Pentanes/Et_2O = 9/1) to obtain the product (394.9 mg, 1.89 mmol, 99%).

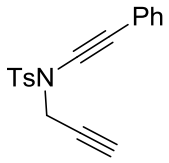
TLC: Rf = 0.35 (Pentanes/Et_2O = 9/1) [UV]

^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 7.77 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 4.57 (s, 1H), 3.83 (dd, *J* = 6.1, 2.5 Hz, 2H), 2.43 (s, 3H), 2.11 (t, *J* = 2.5 Hz, 1H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] 144.0, 136.7, 129.9, 127.6, 78.1, 73.2, 33.0, 21.7.

The analytical data are identical to the literature data.[96]

4-methyl-N-(phenylethynyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (I-131)



$C_{18}H_{15}NO_2S$
309,38

Bromophenyl acetylene (324.6 mg, 1.79 mmol) was dissolved in dry toluene (2.4 mL, 0.5 M), propargyl tosylamide **I-135** (250 mg, 1.20 mmol), K_2CO_3 (330.2 mg, 2.39 mmol), $CuSO_4 \cdot 5H_2O$ (29.8 mg, 0.12 mmol) and phenanthroline (43.1 mg, 0.24 mmol) were added. The reaction mixture was sonicated at 65°C for 20 h. It was diluted with CH_2Cl_2 and filtered through celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (Pentanes/Et_2O = 9/1) to obtain the product (48.4 mg, 0.156 mmol, 13%).

TLC: Rf = 0.78 (Pentanes/Et_2O = 9/1) [UV]

^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 7.88 (d, *J* = 8.3 Hz, 2H), 7.45 – 7.27 (m, 7H), 4.34 (d, *J* = 2.5 Hz, 2H), 2.46 (s, 3H), 2.22 (t, *J* = 2.5 Hz, 1H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 145.1, 134.3, 131.7, 129.8, 128.4, 128.2, 122.7, 81.7, 76.0, 74.8, 42.0.

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Part II:

Studies toward the Total Synthesis of Melohenine B

Table of contents

I) Introduction

1) A definition with a long history

The term alkaloids was first employed in 1819 by *Carl Friedrich Wihelm Messner* to qualify natural products contained in plants, that showed alkaline properties.[1] It derives from the Arabic word, "*al qali"*, which is the plant from which the soda was first extracted. The suffix "*oid"* refers to the resemblance of it's structure and activity. As no clear definition was given, the term was used during the whole 19th century to characterize several molecule types.[2]

Almost one century after *Messner*, *Winterstein* and *Trier* attempted to define the term. They used the expression "*true alkaloids*" to name natural products that have a nitrogen atom included in a heterocyclic system, present a complex structure, possess potent pharmaceutical activities, and belong to the plant kingdom. In spite of the remarkable effort in precision, this definition proved to be too restrictive. Compounds commonly recognized as alkaloids were not presenting all the necessary characteristics.[3]

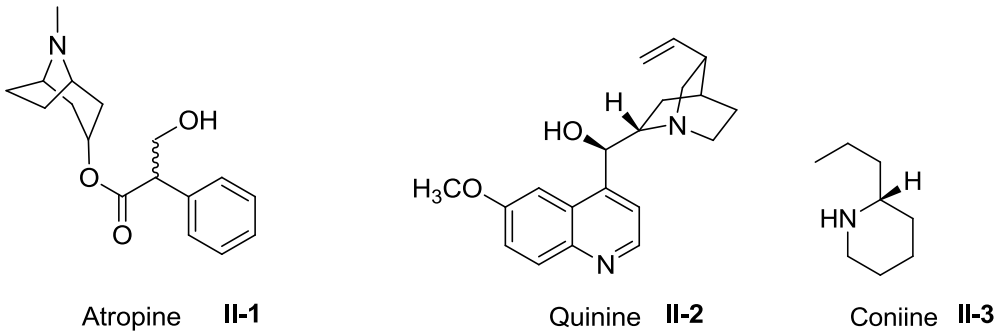
In the 1960s, *Hegnauer* divided alkaloids into three classes: the true alkaloids; the pseudoalkaloids; and the protoalkaloids. The first category described the compounds arising from the condensation between a decarboxylate amino acid and a non-nitrogenous partner. The pseudoalkaloids are products without a link to amino acids, and the last class, the protoalkaloids, concerns amino-acid related compounds, where the nitrogen atom is not part of a heterocyclic system.[4]

However, the distinction between the different types is often difficult to apply, and in 1983, *Pelletier* suggested a simple and suitable definition: "An alkaloid is a cyclic compound containing nitrogen in a negative oxidation state which is of limited distribution on living organisms".[5]

2) Natural products of prime interest

Alkaloids belong to an important type of secondary metabolites mainly produced by plants. They are essential for their defense against herbivores and predators. They are also applied as herbicides against competing plants. Often one alkaloid is multifunctional, showing more than one biological activity. Furthermore, it never occurs alone, but in a mixture of alkaloids deriving from a specific biosynthetic unit.

Alkaloids are as central in the plant kingdom, as in human history: for early civilizations, they were recognized to be useful medicines, stimulants, or poisons. *Cleopatra*'s consumption of atropine **(II-1)** containing henbane to dilate her pupils is one example.[6] Or the preparation from the bark *Cinchona officinalis* that holds the antimalarial drug quinine **(II-2)** and helped European exploration and inhabitation of the tropics.[7] Approximately 13 000 plant species have been used around the world as drugs, and nowadays about 25% of medicines have a plant source.[8]



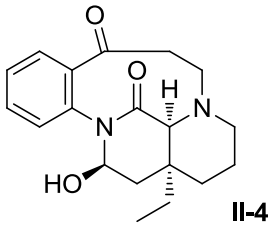
Atropine **II-1** Quinine **II-2** Coniine **II-3**

Figure 1. Presentation of selected alkaloids.

Since the first alkaloid synthesis with the poisonous (+)-coniine **(II-3)** by *Ladenburg* in 1886,[9] other chemists have been encouraged by this wealth of pharmacologically active compounds amongst alkaloids to synthesize this group of natural products.[10]

3) Melohenine B, a unique alkaloid from *Melodinus Henryi*

Melodinus plants have shown to be good sources of indole and quinoline alkaloids, which exhibit interesting pharmaceutical properties.[11] They are also used in Chinese and Thai traditional medicine to cure meningitis in children and rheumatic heart diseases.[11a] These advantages have attracted the attention of several groups, among them the *Luo* group, who investigated the *Melodinus Henryi* plant.[12] In 2009, the group isolated and characterized two novel alkaloids, melohenine A and B.[12] Both were tested for cytotoxycity against five human cell cancers. Unfortunately they showed inactivity with IC_{50} values superior to 40 μM.[13] However, melohenine B **(Figure 2)** presents an interesting ketolactam derivative, with an unprecedented 6/9/6/6 tetracyclic ring system.



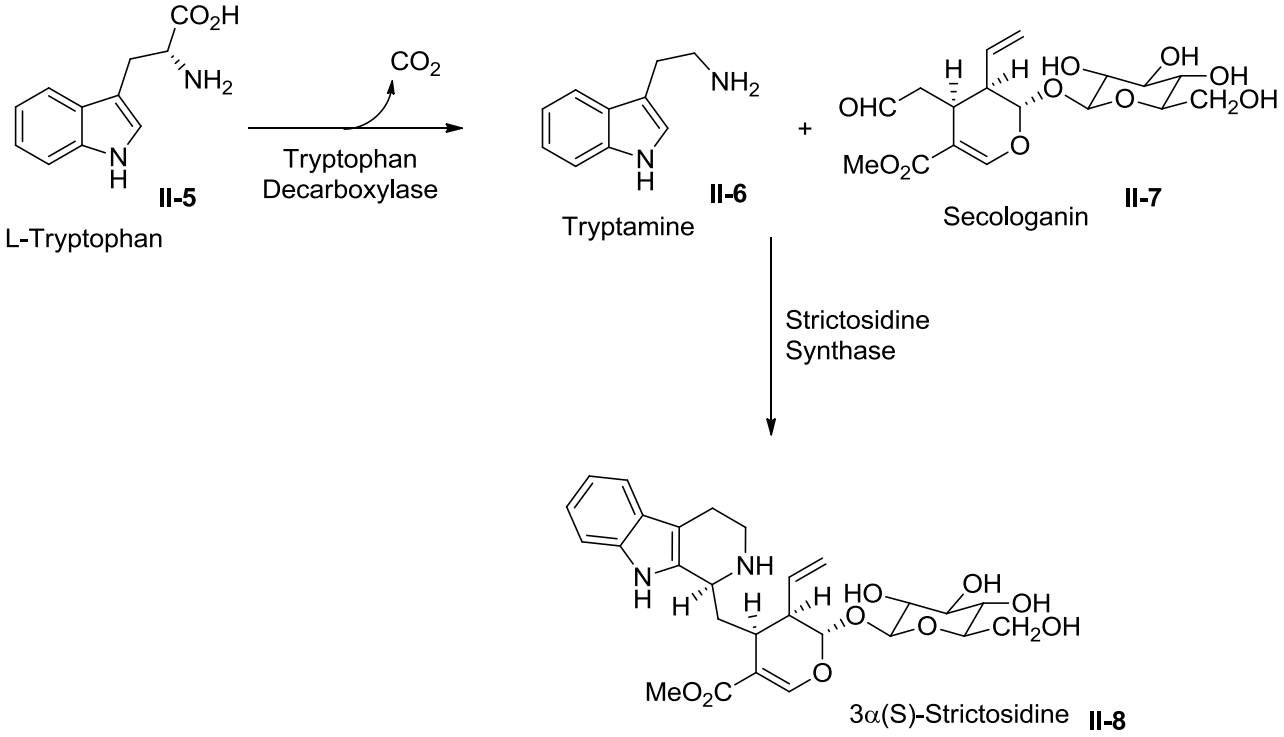
II-4

Figure 2. The melohenine B.

4) The biosynthesis: from monoterpenoid indole alkaloids to quinoline alkaloids

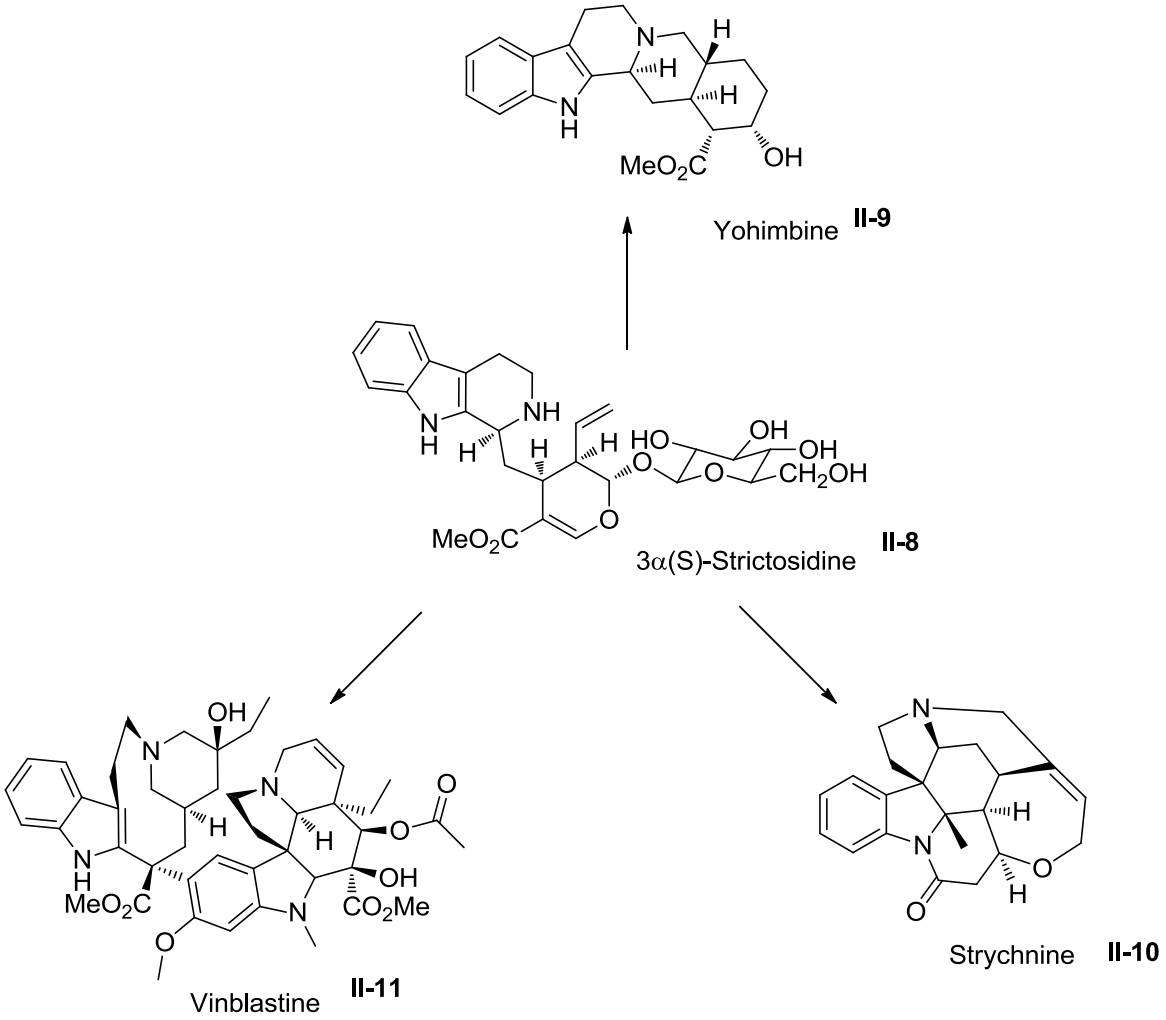
As the alkaloids encompass a considerable class of secondary metabolites with several structural families, their biosyntheses differ from one to another. Here, I choose to report the biosynthesis of monoterpenoid indole alkaloids and quinoline alkaloids, with regard to melohenine B. Both can be seen as true alkaloids, following the definition of *Hegnauer*, they find their origins in the condensation of a decarboxylate amino acid and a non-nitrogenous partner. The monoterpenoid indole alkaloids are a large family of alkaloids, with a great number of various structures. However, only two enzymes catalyze the early steps in the biosynthesis of all these alkaloids, the tryptophan decarboxylase and the strictosidine synthase.[14]

As its name informs us, the tryptophan decarboxylase catalyzes the decarboxylation of the amino acid L-tryptophan to give the tryptamine, which in turn acts as a substrate for the enzyme strictosidine synthase. The latter catalyzes the stereospecific condensation of the amino moiety from tryptamine and the aldehyde group of the monoterpene secologanin to produce the 3α(S)-strictosidine (Scheme 1).



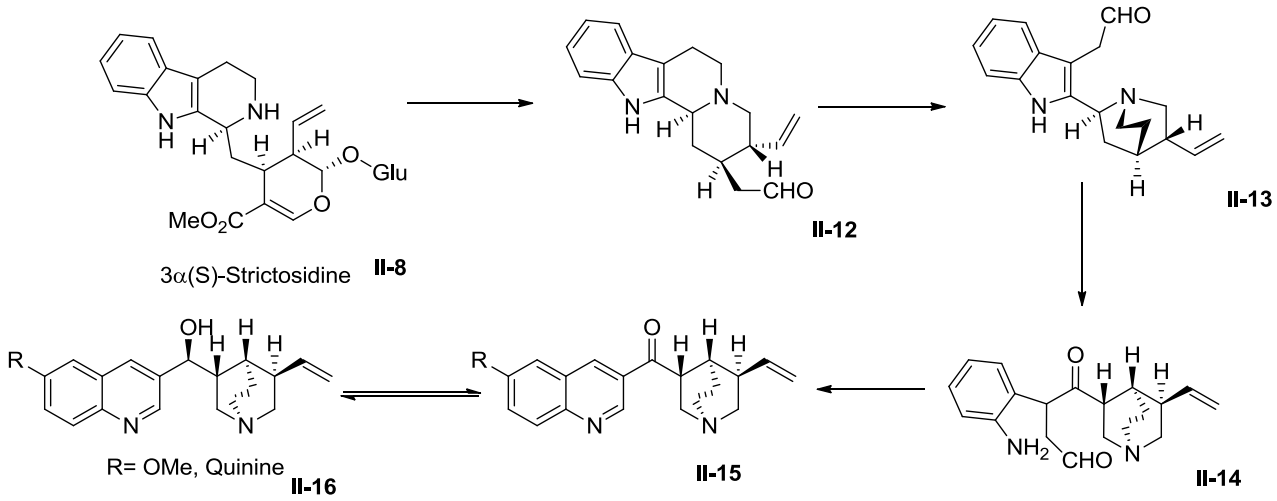
Scheme 1. The early steps of the biosynthesis of monoterpenoid indole alkaloids.

From the 3α(S)-strictosidine, a rich diversity of monoterpenoid indole alkaloids is accessible. Among them, we can name the antineoplastic chemotherapeutic agents vincristine and vinblastine,[15] the rat poison and homeopathic drug strychnine,[16] or the aphrodisiac yohimbine[17] (Scheme 2).



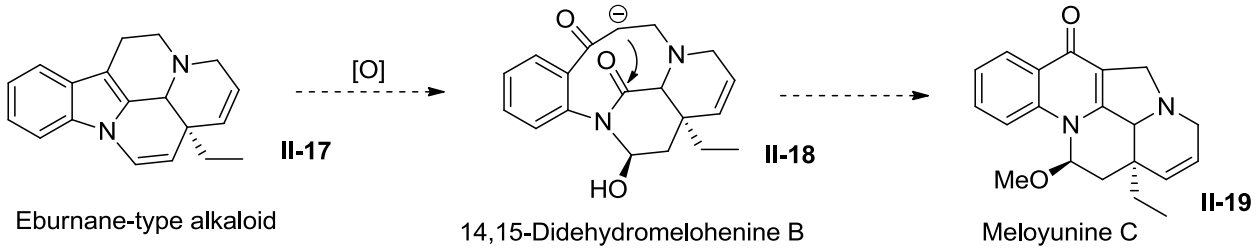
Scheme 2. From the 3α(S)-strictosidine, a gain in diversity.

On the side of the quinoline alkaloids, some, such as quinine, have been found to derive from the rearrangement of monoterpenoid indole alkaloids (Scheme 3).[18]



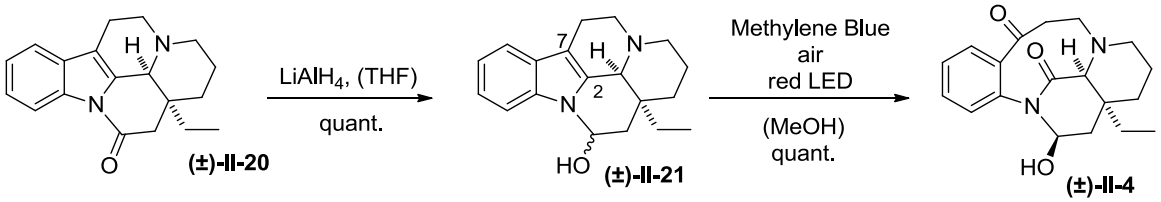
Scheme 3. An access to quinoline alkaloids.

In 2009, when *Luo* and coworkers isolated melohenine B, they suggested that the molecule could be seen as a key intermediate from indole to quinoline alkaloids.[12] More recently, various novel alkaloids were isolated from the *Melodinus yunnanensis*, a plant of the genus *Melodinus*. Among them is a quinolone alkaloid, Meloyunine C, in presence of its biosynthetic precursors, the keto-lactam **II-18** and the eburnane-type alkaloid **II-17** (Scheme 4).[19]



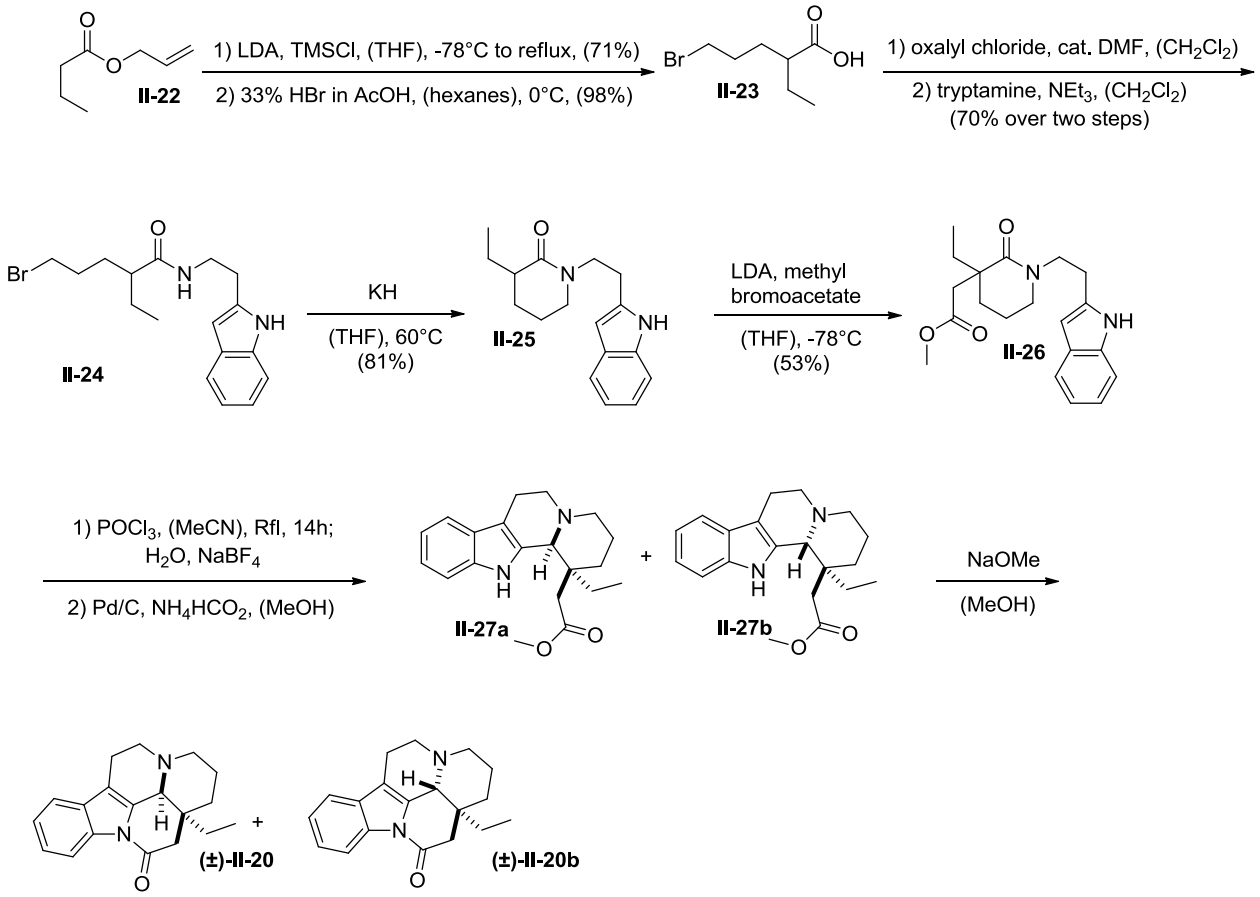
Scheme 4. Proposed biosynthesis from indole to quinolone alkaloids in *Melodinus* plant.

Furthermore, as illustrated in Scheme 5, the first total synthesis of melohenine B **(II-4)** was designed by *Westwood et al.* on the basis of this biogenetic relationship. As eburnamine **(II-21)** is an indole alkaloid also present in *Melodinus Henryi*,[20] they have developed a method to oxidatively cleave the C_2-C_7 indole bond and therefore obtain **II-4** as a single diastereoisomer in quantitative yield.[21]



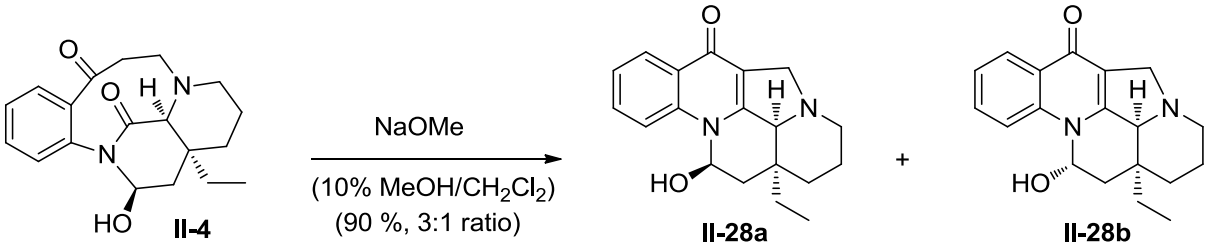
Scheme 5. The synthesis of melohenine B (*Westwood et al.*, 2012).[21]

The racemic eburnamonine **(±)-II-20** was prepared following a modified version of the *Sclessinger* approach (Scheme 6).[22]



Scheme 6. Synthesis of eburnamonine (±)-II-20 (*Westwood et al.*, 2012).[21]

In addition to the synthesis of melohenine B, *Westwood* and coworkers investigated the intramolecular aldol reaction to the quinolone alkaloid (Scheme 7).



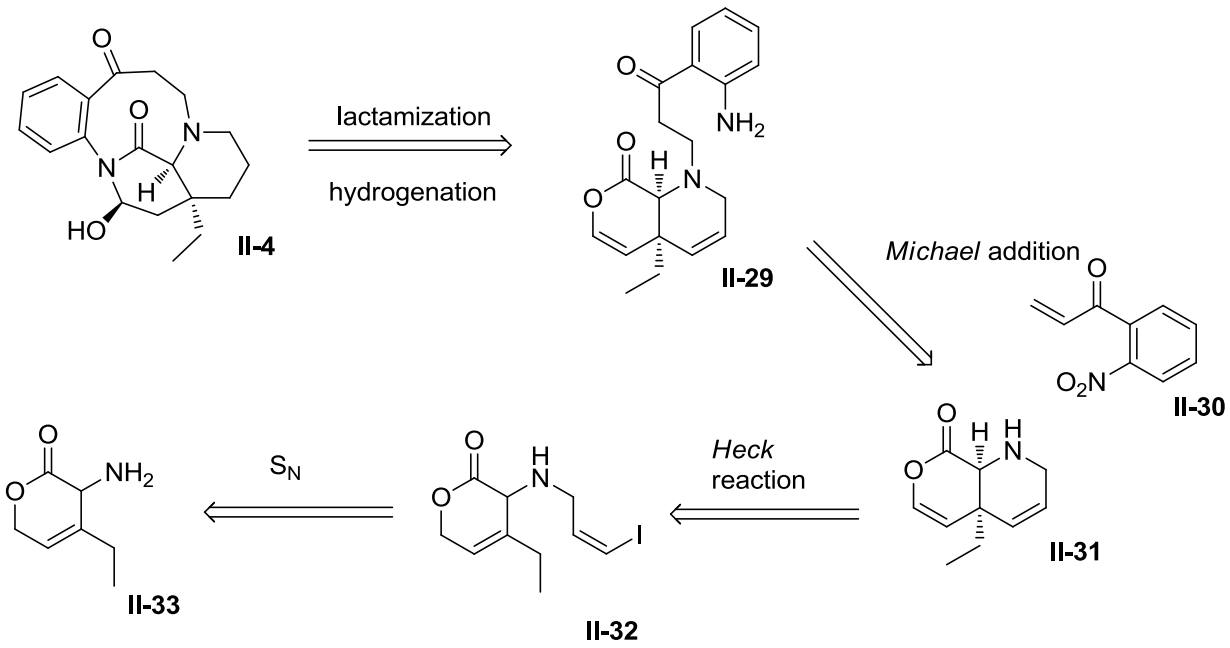
Scheme 7. Synthesis of quinolone from melohenine B (*Westwood et al.*, 2012).[21]

Using sodium methoxide, they were able to isolate the desired condensation product as a 3:1 mixture of diastereoisomers.

II) Results and Discussion

1) The retrosynthesis

In 2009, intrigued by this unprecedented 6/9/6/6 tetracyclic ketolactam derivative we decided to launch a study toward the total synthesis of melohenine B. Although the first investigations have not demonstrated any biological effects,[12,19,20] a concise synthesis of this molecule is nevertheless an interesting challenge from a synthetic chemist's point of view and could be a road to improve its pharmacological properties via the synthesis of analogues and to test its activity against other targets. The retrosynthesis analysis for **II-4** is outlined in Scheme 8.



Scheme 8. Retrosynthesis of melohenine B.

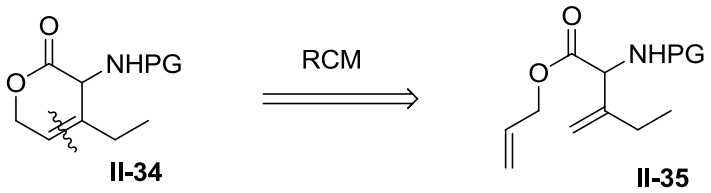
Melohenine B was expected to arise from an intramolecular lactamization of the lacton with primary amine **II-29**. The latter should be formed by *Michael* addition[23] of the *Heck* reaction product **II-31** to the α,β-unsaturated carbonyl compound **II-30**, directly followed by reduction of the nitro group to the amine. The intramolecular *Heck* cross-coupling[24] on the iodoallyl aminodihydro-*2H*-pyranone would be the key step as the

emergence of two stereogenic centers will occur at this stage. Finally, the five-step synthesis to melohenine B should start with the simple building block **II-33**. In fact, the road to this goal was demanding and at this point in the investigations, several strategies have been tested. The first plan was to use a ring-closing metathesis to produce the lacton ring (Strategy A), then our attention was steered toward carbohydrate chemistry as they can provide a direct access to the dihydropyranone structure (Strategy B). Two other alternatives were also proposed, one ending with a lactonization, the second with an enyne metathesis.

2) Studies toward the synthesis of building block II-33

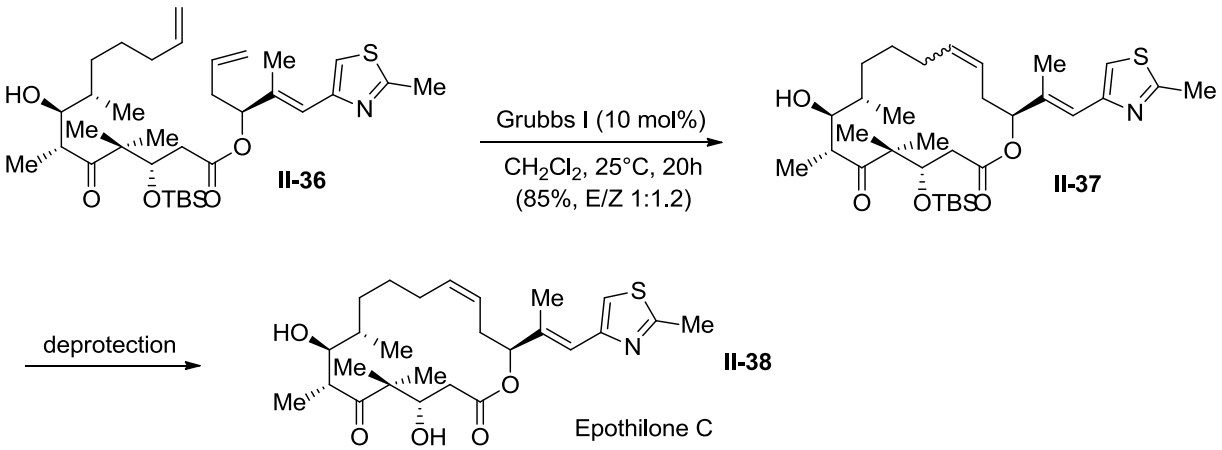
2.1) Ring closing metathesis strategy (Strategy A)

Our first plan was to obtain molecule **II-34** via a ring-closing metathesis (RCM) (Scheme 9).



Scheme 9. Ring-closing metathesis strategy to access the building block.

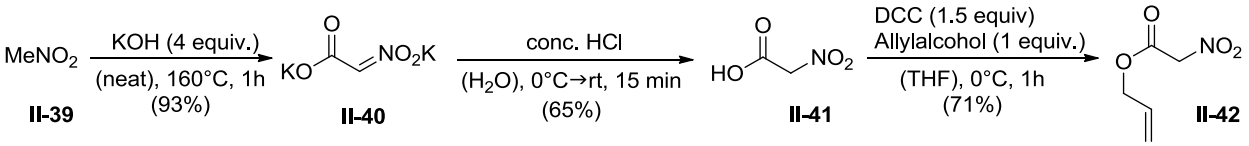
In recent years, this method has been commonly involved in total synthesis to fashion complex rings.[25] A case in point is the total synthesis of epothilone C by *Nicolaou* and coworkers,[26] where a macrocylization was performed in 85% yield, despite the presence of an unprotected hydroxyl group and a thiazole unit (Scheme 10).



Scheme 10. Ring-closing metathesis reaction in the total synthesis of epothilone C (*Nicolaou et al.,* 1997).[26]

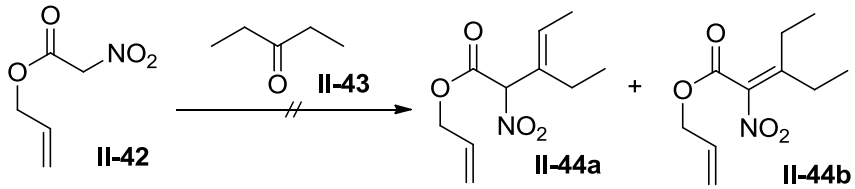
2.1.1) The *Michael*-type reaction.

Our first approach was to reach the metathesis substrate **II-35** using a *Michael*-type reaction between nitro allylester **II-42** and pentanone (Scheme 12). As featured in Scheme 11, **II-42** was synthesized in three steps with an overall yield of 43%. The process was initiated with the cheap starting material nitromethane, which after self-condensation[27] and esterification,[28] gave the desired nitro allylester.



Scheme 11. The synthetic route to nitro allyl ester II-42.

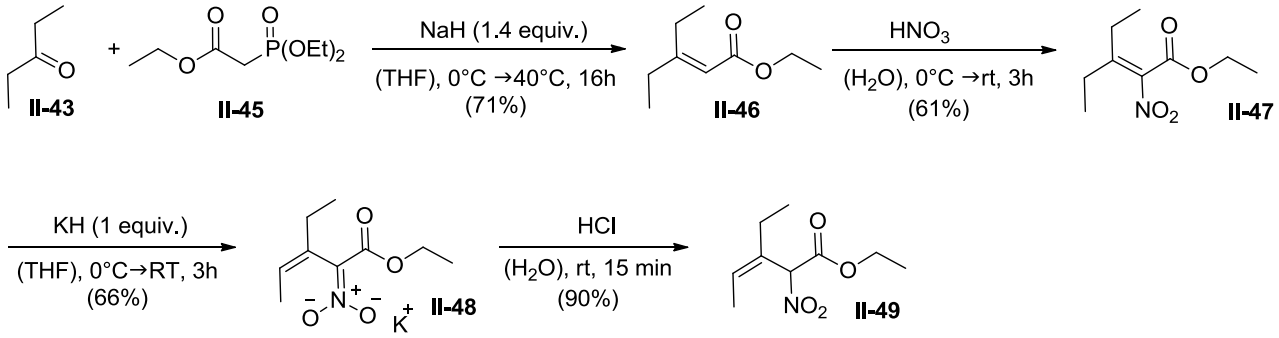
Nevertheless, after initial experiments, no trace of the expected product **II-44** was found and this route was investigated no further.



Scheme 12. The unsuccessful *Michael*-type reaction.

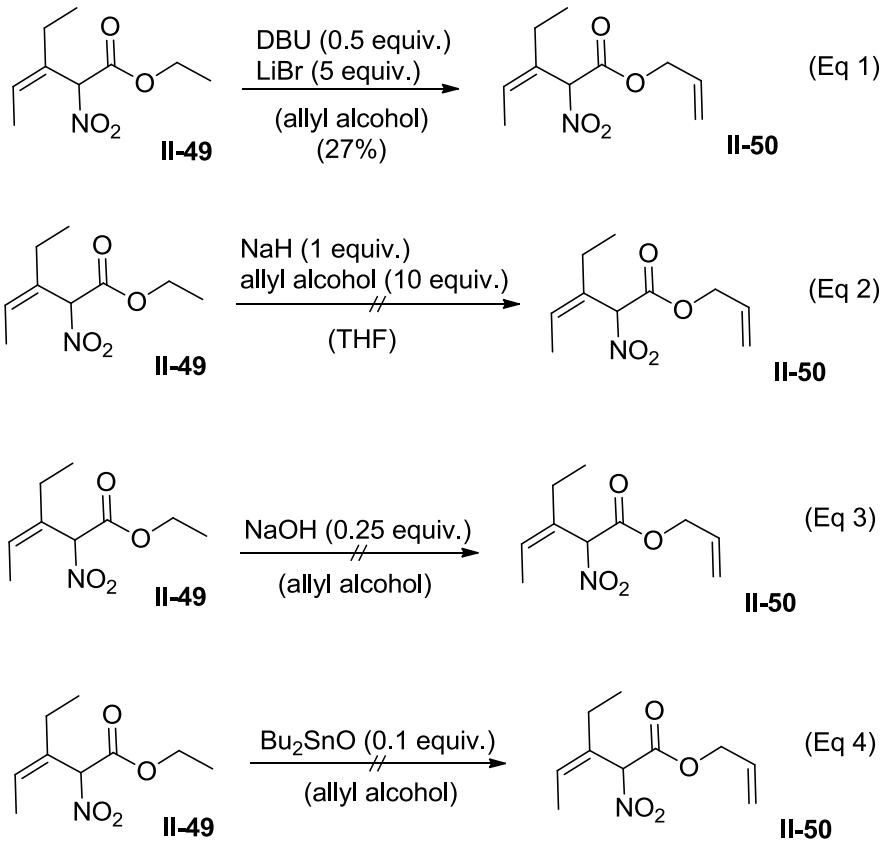
2.1.2) The transesterification

As the first method, described above, was aborted, another angle of attack was to reverse the synthesis and terminate with the introduction of the allyl ester via a transesterification[29] from nitro ethyl ester **II-49** to nitro allyl ester **II-50**. Compound **II-49** was formed in four steps starting with pentanone and ethyl-2-(diethoxyphosphoryl)acetate. A *Horner-Wadsworth-Emmons* reaction,[30] followed by nitration[31] gave **II-47** in good yield. After deconjugation,[32] this latter produced nitro ethyl ester **II-49** in excellent yield (Scheme 13).



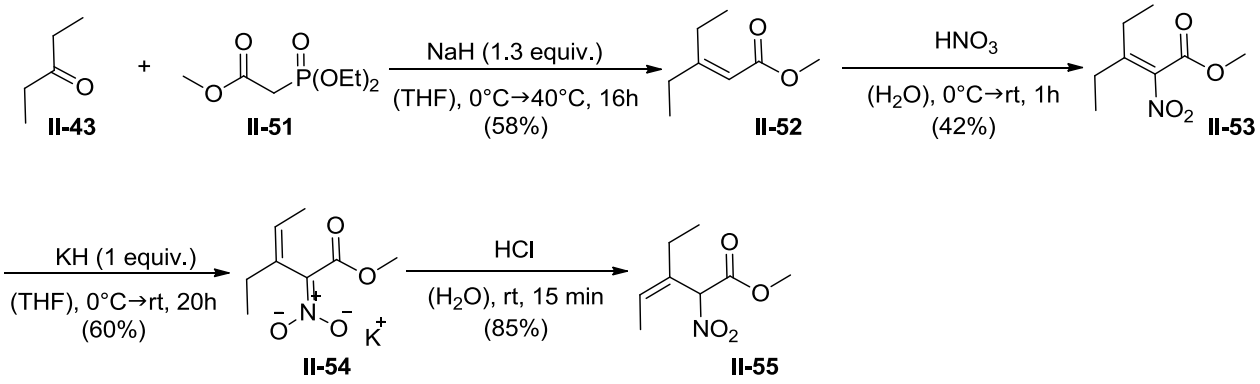
Scheme 13. Synthesis of the nitro compound II-49.

To eventually produce the allylic ester, the transesterification was investigated. As shown in Scheme 14, this convenient method to prepare esters was tested using different conditions.[33] With the exception of the Conditions 1**,** which gave us the product in a 27% unreproducible yield, they were, to our disappointment, all fruitless. Another member of the group, M. Sc. Chem. *P. Klahn* tried the same conditions on the amino starting material without improving on previous results.



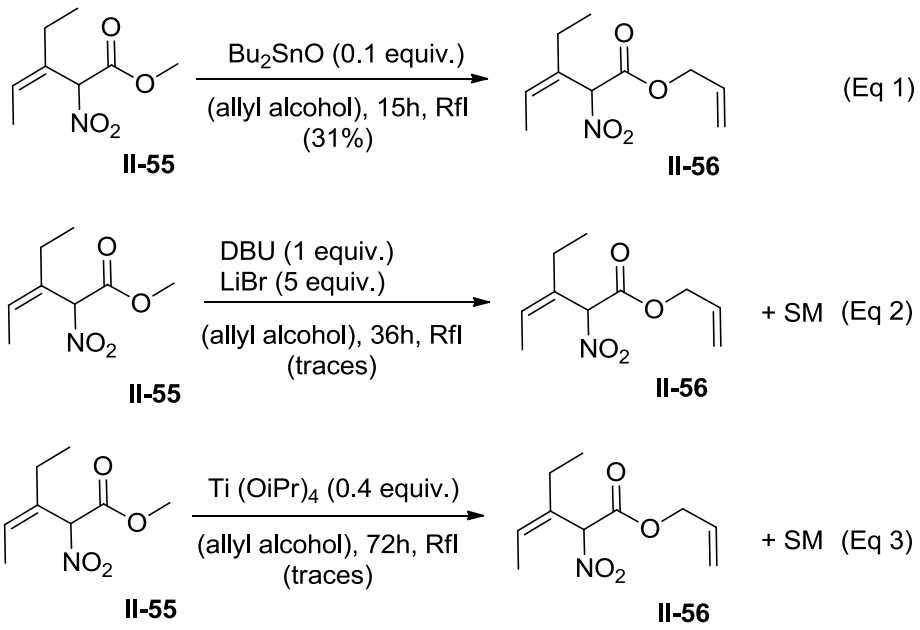
Scheme 14. A problematic transesterification.

We reasoned that the methyl ester may have a better reactivity than the ethyl ester. The nitro methyl ester **II-55** was synthesized employing the same reaction conditions as for the nitro ethyl ester **II-49** (Scheme 15).



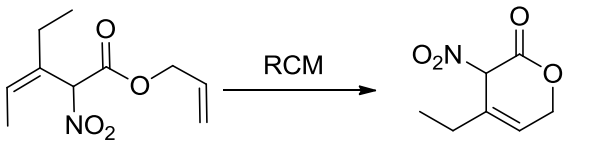
Scheme 15. Change of plan, from nitro ethyl ester II-49 to nitro methyl ester II-55.

We subsequently examined different conditions for the transesterification (Scheme 16) and were pleased to obtain the nitro allylic ester **II-56** using Bu_2SnO as a catalyst,[34] albeit in low yield (Eq 1).



Scheme 16. Transesterification of the nitro methyl ester II-55 into the nitro allyl ester II-56

However, having compound **II-56** in hand, RCM could be tested. Attempting to avoid an unconvenient protecting group, the metathesis was first tested on the compound containing the nitro group[35] in presence of various ruthenium catalysts: Grubbs I,[36] Grubbs II,[37] with or without the additive Ti(O*i*Pr)$_4$,[38] or Grubbs-Hoveyda II[39].



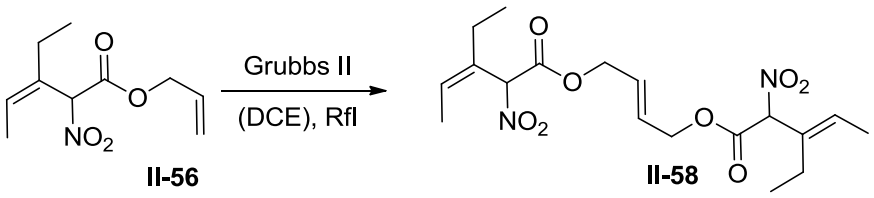
II-56 **II-57**

Entry	**Catalyst** (10 mol%)	**Solvent** (0.01M)	**Temperature (°C)**	**Result**
1	Grubbs II	CH_2Cl_2	Rfl	-
2	Grubbs II/ Ti(OiPr)$_4$	CH_2Cl_2	Rfl	SM + CM
3	Grubbs II	DCE	60 to Rfl	SM + CM
4	Grubbs II	Benzene	70	-
5	Grubbs I	CH_2Cl_2	Rfl	SM
6	Grubbs-Hoveyda II	CH_2Cl_2	Rfl	-

CM: cross-metathesis compound, SM: recovery of the starting material.

Table 1. Attempts at ring-closing metathesis on II-56.

As shown in Table 1, the only significant isolated compound was the cross-metathesis (CM) product when using the Grubbs II catalyst (Scheme 17).

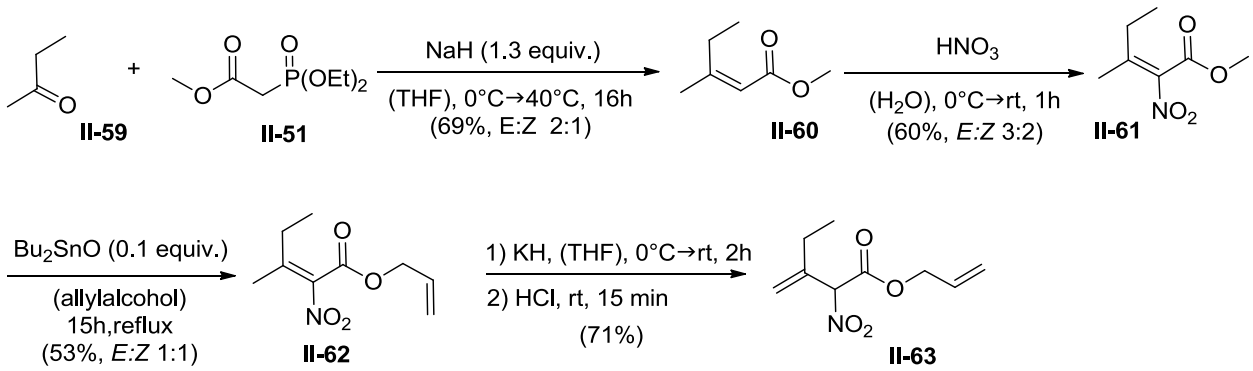


II-56 **II-58**

Scheme 17. The cross-metathesis product.

From previous results, we deduced that we may need two terminal olefins. A new nitro methyl ester was synthesized employing the reactions conditions as previously

described (Scheme 18). However, here the transesterification was performed prior to the isomerization to avoid the presence of the acidic proton alpha to the nitro group. Indeed, when the previous order was maintained, **II-61** underwent an isomerization of the double bond in tandem with the transesterification.



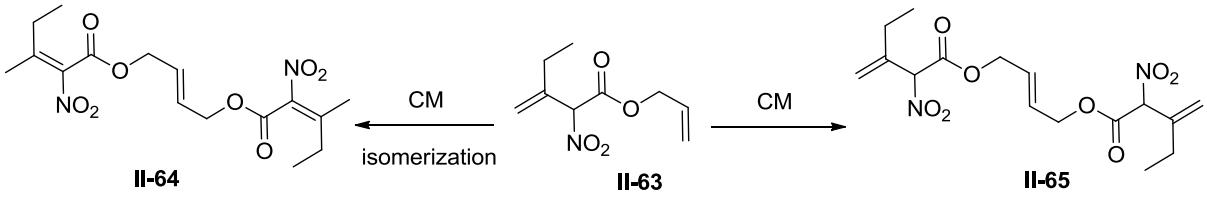
Scheme 18. Synthesis of compound II-63.

Compound **II-63** was then available to be tested with typical metathesis conditions. As for compound **II-56**, only the cross-metathesis product was found, sometimes with observed isomerization of the double bond (Table 2, Scheme 19).

Entry	**Catalyst** (10 mol%)	**Solvent** (0.01M)	**Temperature**	**Result**
1	Grubbs II	CH_2Cl_2	Rfl	CM+ isomerisation
2	Grubbs II/ $Ti(OiPr)_4$	CH_2Cl_2	Rfl	CM+ isomerisation
3	Grubbs-Hoveyda II	CH_2Cl_2	Rfl	CM
4	Grubbs I	CH_2Cl_2	Rfl	SM
5	Grubbs II	Toluene	Rfl	CM+ isomerisation
6	Grubbs- Hoveyda II	Toluene	Rfl	CM+ isomerisation

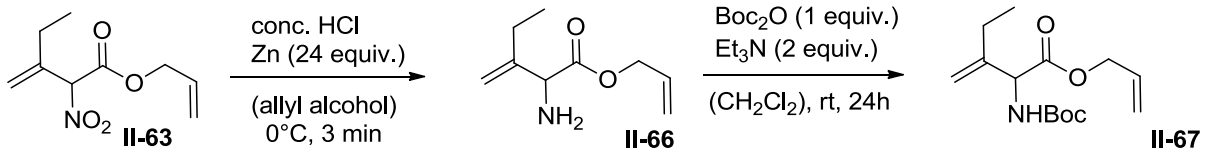
CM: cross-metathesis compound, SM: recovery of the starting material.

Table 2. Attempts at ring-closing metathesis on II-63.



Scheme 19. The cross-metathesis products.

We concluded that the nitro-moiety could be the reason for the unsuccessful metathesis and decided to make other attempts on the amine protected compound **II-67**. From intermediate **II-63**, product **II-67** was produced in two steps through reduction with zinc[40] and *tert*-butyloxycarbonyl protection of the amine, with 32% overall yield (Scheme 20).



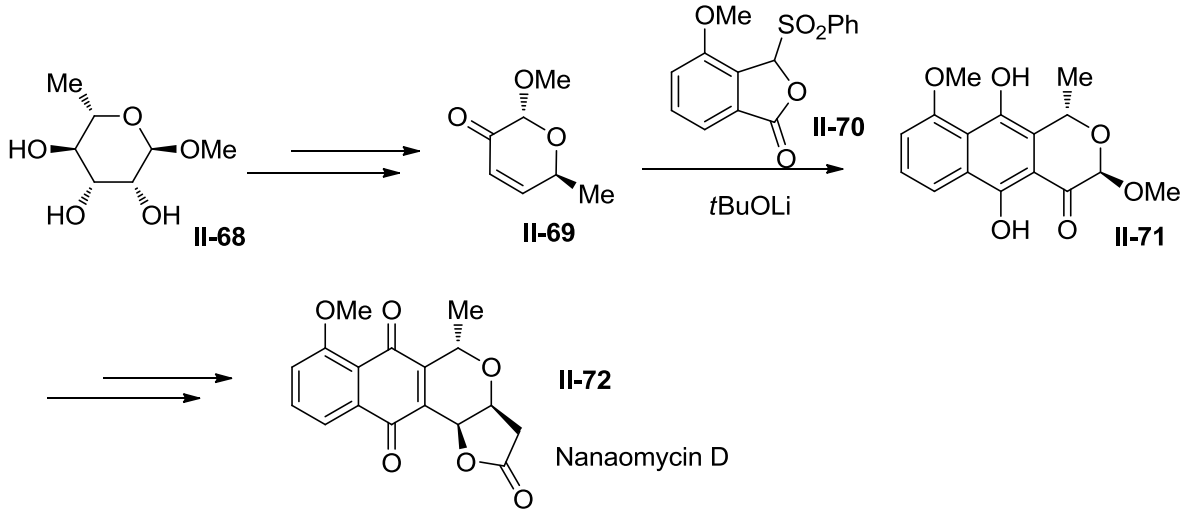
Scheme 20. Synthetic approach to Boc-amino allylic ester II-67.

To our delight, the RCM product was detected and isolated in 16 % yield (22% brsm). The yield was low and during the reaction, the cross-metathesis compound was also produced in a rather short time, even at extremely low concentration (0.005 M). The RCM might fail due to the sterically-hindered or electronically deactivated alkene moiety.[41] Some other groups have also had trouble closing dihydropyranone derivatives and have employed a relay RCM to overcome the problem.[42] However, at this point, we considered changing our initial plan, and to start with a completely new approach to synthesize the building block **II-33**.

2.2) The carbohydrate strategy (Strategy B)

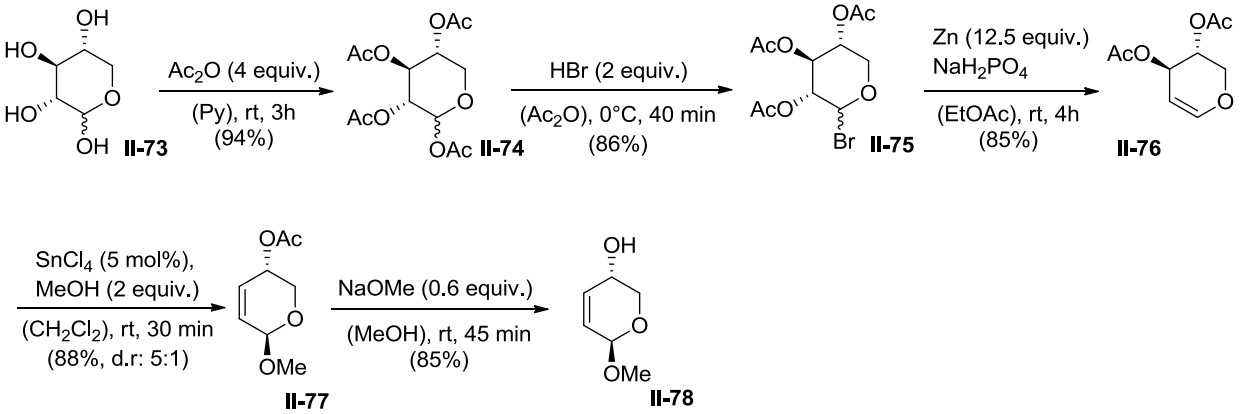
2.2.1) Starting with D-(+)-xylose

Carbohydrate chemistry has been successfully applied to several total syntheses. As carbohydrates are rich in stereochemistry and functionality, they represent an excellent class of starting materials for total synthesis.[43] To name one example, *Tatsuta et al.* have reported the stereoselective construction of the pyranonaphthoquinone antibiotic, nanaomycin D, starting with the carbohydrate methyl L-rhamnoside (Scheme 21).[44]



Scheme 21. Total synthesis of nanaomycin D from methyl L-rhamnoside (*Tatsuta et al.,* 1985*).*[44]

Recognizing that carbohydrate chemistry can be an excellent chiral pool for a stereoselective synthesis of melohenine B, a new strategy was launched, starting with the natural sugar, D-(+)-xylose.



Scheme 22. An enantioselective synthesis of the methoxy dihydropyranol II-78.

The already well-known reactions on monosaccharides allow us to have an easy access to the methoxy dihydropyranol product (**II-78**). As shown in Scheme 22, acetyl protection of the D-(+)-xylose, substitution with a bromine on the anomeric position[45] and elimination with zinc gave the diacetate dihydropyran in good yield. The standard procedure to obtain glycal **II-76** involves treating bromide **II-75** with zinc in acetic acid,[46] but in this case high yield was not reproducible. Instead, a mild and efficient reaction developed by *Zhao et al*. was employed, using NaH_2PO_4 and zinc dust in ethyl acetate at room temperature.[47] Finally, *Ferrier* rearrangement[48] and acetate deprotection afforded product **II-78**. However, it is worth noting that the rearrangement did not provide a pure diastereoisomer, but instead a diastereoisomeric mixture with a ratio of 5 to 1. Nevertheless, both diastereoisomers were easily separated.

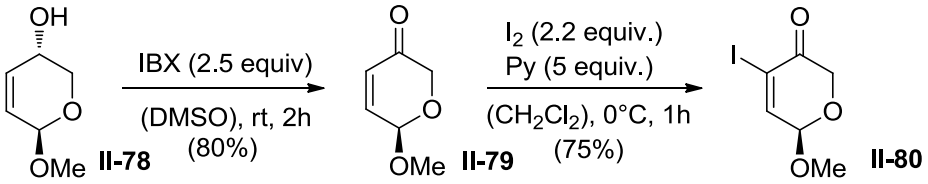
The next step, oxidation of alcohol **II-78**, was more demanding. It required the screening of different oxidation methods (Table 3). Finally, IBX was found to be the best oxidant for this reaction (Entry 5). Thus, by stirring **II-78** in DMSO in the presence of 2.5 equivalents of IBX, **II-79** was isolated in 80% yield.

Entry	Oxidant	Solvent	Temp. (°C)	Yield[a] (%)
1	$Py^{\cdot}SO_3$, Et_3N	DMSO	rt	-
2	Swern	CH_2Cl_2	-78	21
4	IBX (1 equiv.)	DMSO (0.3 M)	rt	28
5	IBX (2.5 equiv.)	DMSO (0.3 M)	rt	80
6	Ac_2O (35 equiv.)	DMSO (0.2 M)	rt	56
7	NMO (2 equiv.)/TPAP (5 mol%)	CH_2Cl_2 (0.1 M)	rt	25

a: Isolated yield after flash chromatography.

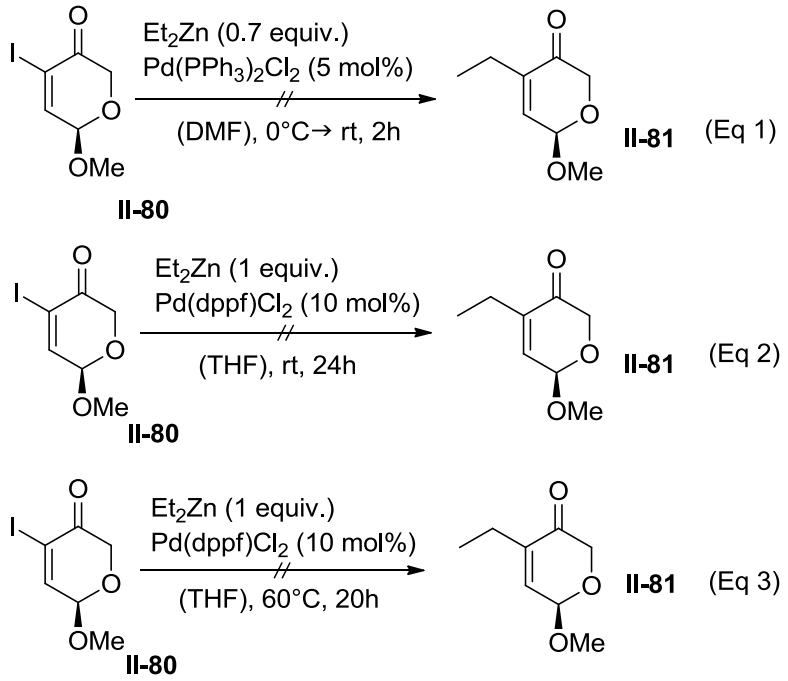
Table 3. Oxidation of the alcohol II-78.

In order to introduce the ethyl group, the *Negishi* reaction[49] was tested on molecule **II-80**, obtained by α-iodination[50] of the methoxy dihydropyranone (Scheme 23).



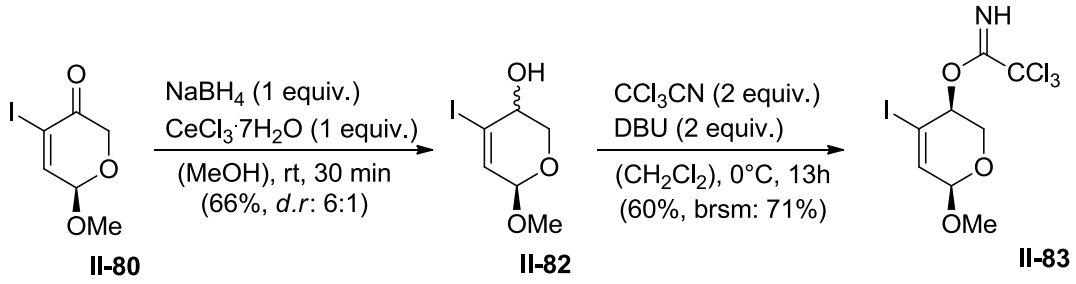
Scheme 23. Synthesis of iodo compound II-80.

Regrettably, several attempts led us to believe that the *Negishi* cross coupling does not work on substrate **II-80** (Scheme 24).



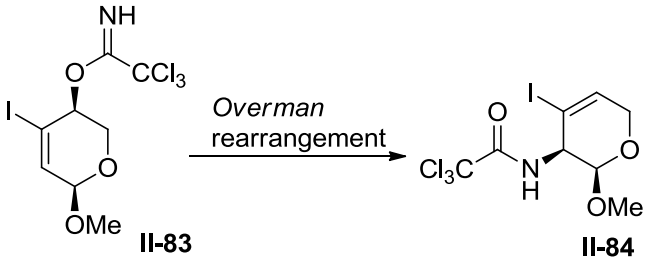
Scheme 24. Unsuccessful *Negishi* cross-coupling on II-80.

α-Iodoenone **II-80** was then reduced under *Luche* conditions[51] and the alcohol moiety was protected with trichloroacetonitrile (Scheme 25), in order to proceed to the *Overman* rearrangement.[52] With the reduction step, two diastereoisomers were formed (*cf.* experimental part 3., p 244), both were separated by flash chromatography and the major isomer was used for the next step.



Scheme 25. Formation of the trichloroacetimidate II-83.

Trichloroacetimidate **II-83** was tested with the *Overman* rearrangement. Despite the optimization phase, the yield remained moderate (51%, 58% brsm). The presence of the bulky iodine moiety and the methoxy group[53] could be one explanation of this result.



II-83 **II-84**

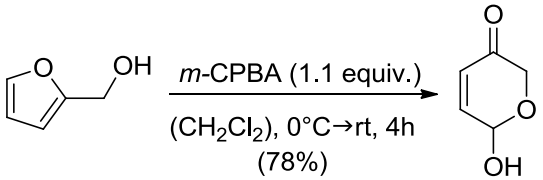
Entry	**Solvent** (0.1 M)	**Additive** (equiv.)	**Mode**	**Temperature (°C)**	**Time (h)**	**Yield[a] (%)**
1	*o*-dichlorobenzene	K_2CO_3 (0.2)	Mw	200	8	5
2	*o*-dichlorobenzene	K_2CO_3 (0.2)	Mw	180	12	19
3	*o*-dichlorobenzene	K_2CO_3 (0.2)	Thermal	180	2	23
4	*o*-dichlorobenzene[b]	/	Thermal	170	3	11
5	xylene	K_2CO_3 (0.2)	Thermal	135	48	35
6	xylene	K_2CO_3 (1)	Thermal	135	48	51 (58% brsm)
7	xylene	K_2CO_3 (2)	Thermal	135	48	34 (39 % brsm)

a: Isolated yield after flash chromatography; b: 0.08 M.

Table 4. *Overman* rearrangement.

2.2.2) A shortcut

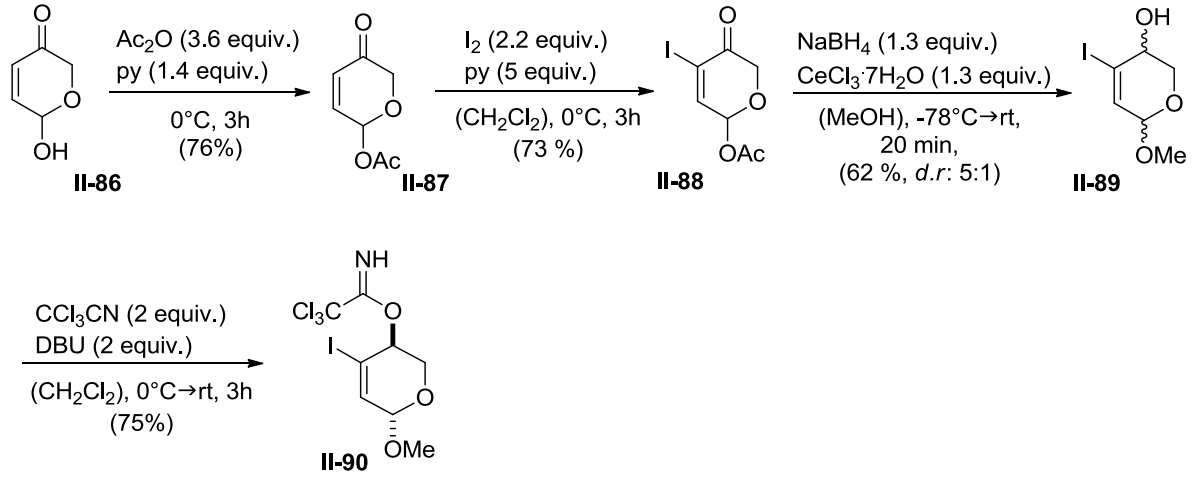
Parallel to the work on the [3,3]-sigmatropic rearrangement, a shorter, but racemic approach to **II-79** was investigated. *Lefebvre et al.* have further developed an interesting rearrangement found by *Achmatowicz* and coworkers,[54] using 2-furfuryl alcohol with *m*-CPBA to afford hydroxyl-pyranone.[55] As depicted in Scheme 26, with the same conditions as *Lefebvre* we were able to isolate product **II-86** in 78% yield, saving 5 steps in comparison to the previous route.



II-85 **II-86**

Scheme 26. The oxidative rearrangement of 2-furfuryl alcohol.

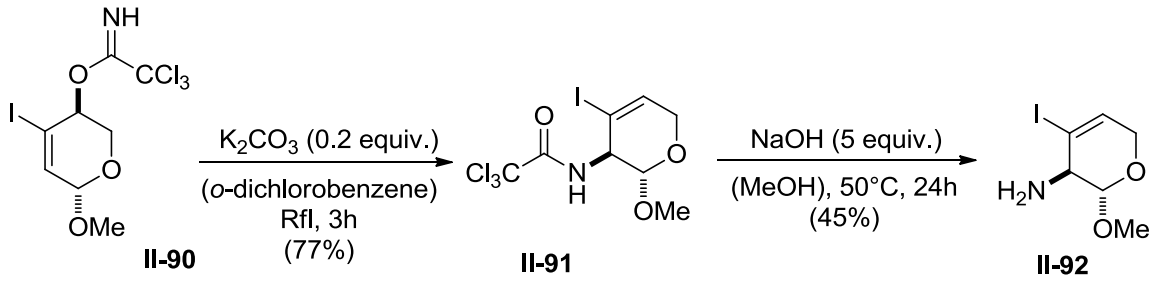
The next step was the glycosidation of the obtained hydroxypyranone **II-86** into methyl glycoside. Unfortunately, the reaction with trimethyl formate and *Lewis* or *Brønsted* acids gave the desired compound only in a poor yield. However, the treatment with acetic anhydride and pyridine at 0°C delivered, to our delight, *o*-acetyl derivative **II-87**[51] in high yield. Iodination and reduction of the ketone moiety provided compound **II-90** after formation of the trichloroacetimidate, ready for the *Overman* rearrangement. It should be noted that the acetyl group was substituted by a methoxy group[56] during the course of the reduction, giving the *trans*-product as the major isomer.



Scheme 27. Formation of the trichloroacetimidate II-90.

The conditions applied on **II-83** were reproduced on **II-90**, and the *Overman* rearrangement gave *trans*-trichloroacetamide[3] **II-91** in 77% yield by refluxing **II-90** in *o*-dichlorobenzene for 1h in presence of 0.2 equivalents K_2CO_3 (Scheme 28). Eventually, a procedure[57] was employed to cleave away the trichloroacetamide group and to provide the primary amine compound **II-92**.

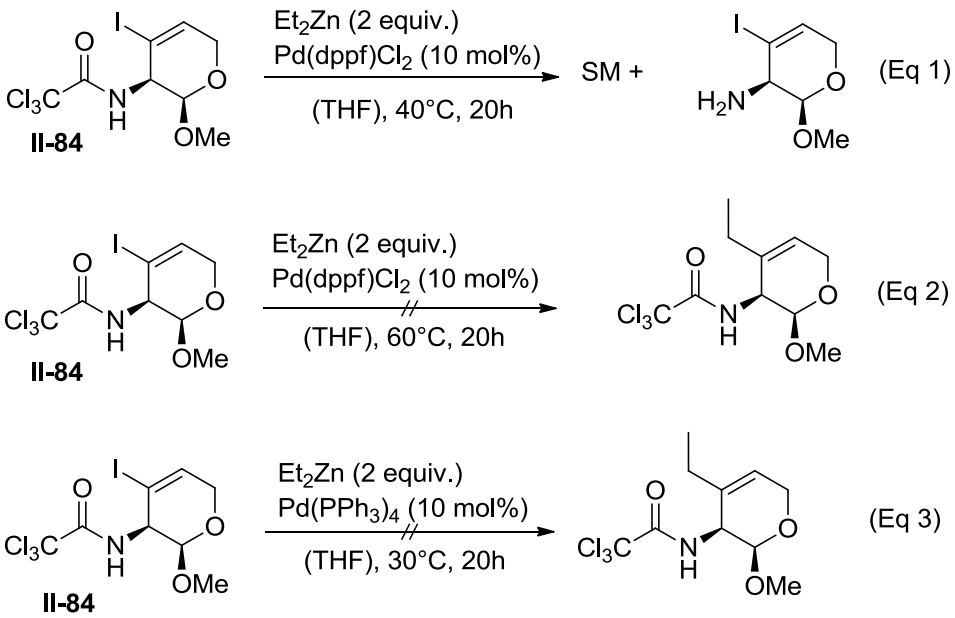
[3] The thermal *Overman* rearrangement occurs suprafacially.[52a,d]



Scheme 28. The *Overman* rearrangement of II-90.

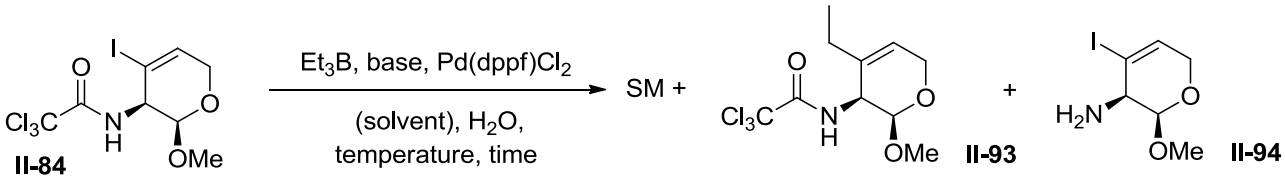
2.2.3) Cross-coupling reaction to introduce the ethyl chain

At this point, the ethyl group was the only remaining motif necessary for completion of building block **II-33**. As previously described, the introduction of this alkyl chain had first been attempted on the reactant **II-80** via a *Negishi* cross-coupling reaction without success (Scheme 22). Since this attempt, several experiments have been undertaken on various stages of the synthesis. Thus the *Negishi* reaction was also investigated on the substrate **II-84**, two different palladium catalysts have been employed in THF at diverse temperatures without significant results (Scheme 29). Either starting material **II-84**, was reisolated or decomposition products were found, but no trace of an ethyl group was detected.



Scheme 29. The unsuccessful *Negishi* cross-coupling reactions on II-84.

As the *Negishi* cross-coupling reaction seemed to be inefficient in bringing the desired alkyl moiety, the *Suzuki* cross-coupling[58] was carried out on **II-84**. To our delight, the *Suzuki* reaction delivered the right product. However, as illustrated in Table 5, the yield stayed low due to a poor conversion or the hydrolysis of the trichloroacetamide group (Entries 2 and 3).



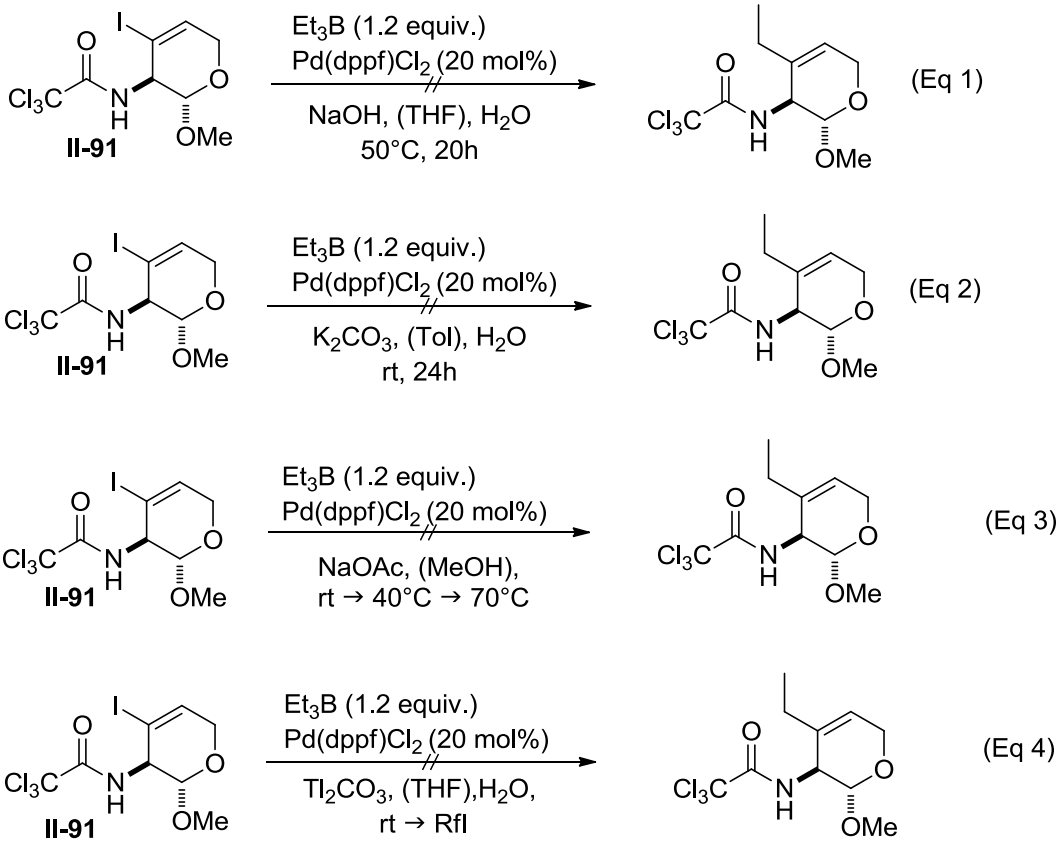
Entry	Cat. Loading (mol%)	Base (1.8 equiv.)	Solvent (0.3 M)	Temp. (°C)	Time (h)	Result[a]
1	5	NaOH[b]	THF[c]	30	20	SM + **II-93** (15%)
2	20	NaOH[b]	THF[c]	50	20	SM + **II-93** (11%) + **II-94** (13%)
3	10	Cs_2CO_3	DMF	30	20	**II-94** (17%)
4	10	K_2CO_3	DMF	80	2	decomposition
5	10	K_2CO_3	Tol	rt	24	**II-93** (41% not pure)
6	10	Et_3N	THF	50	24	SM

a: Isolated yield after flash chromatography; b: 2.2 equiv.; c: 0.5 M.

Table 5. The *Suzuki* cross-coupling reactions on II-84.

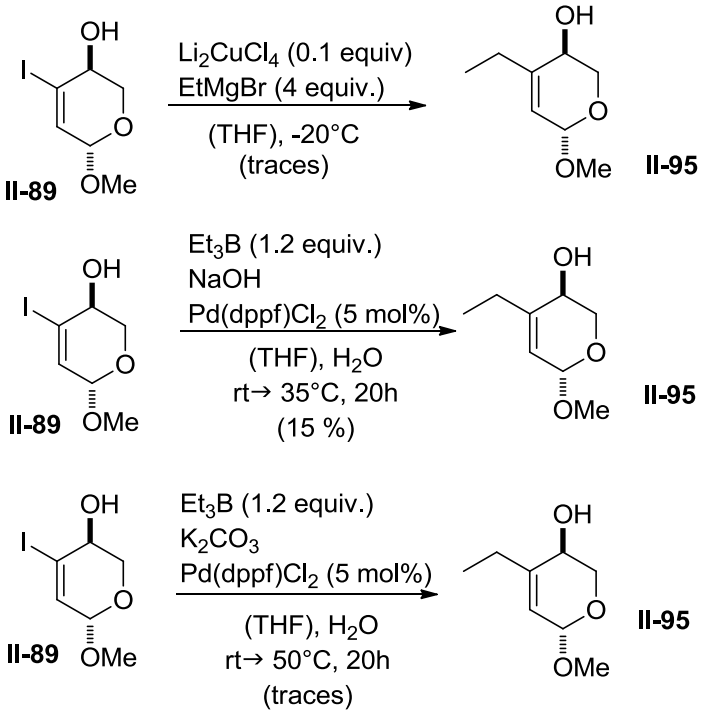
Despite this, the result was encouraging and further experiments could be explored. In particular at room temperature or employing KF[59] to avoid the product of hydrolysis. Regrettably, batch **II-84** (*cis*-isomer) was no longer available and **II-91** (*trans*-isomer) was used instead, and surprisingly, when the working *Suzuki* conditions were applied on **II-91**, no trace of the required product was found (Scheme 30, Eq 1 and Eq 2). As the route to **II-91** was much shorter than the one to **II-84**, some additional efforts were made on this diastereoisomer, in particular using other bases. However, neither sodium acetate nor the booster-base Tl_2CO_3[60] were appropriate to promote the coupling of the ethyl group to **II-91**

(Scheme 30, Eq 3 and Eq 4). It appears that the *trans*-isomer does not favour the cross-coupling reaction, for which the steric hindrance of the bulky trichloroacetamide group may be responsible.



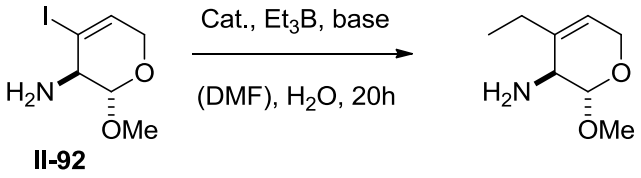
Scheme 30. *Suzuki* cross-coupling reactions on II-91.

At this time, two other possibilities remained viable: indeed, cross-coupling reactions were still practicable on **II-89** and **II-92**. In the case of iodo-dihydropyranol, a copper(I) catalyzed cross-coupling between the ethyl *Grignard* reagent and the vinyl iodide was carried out at -20°C in tetrahydrofuran,[61] producing traces of the desired ethyl-dihydropyranol **II-95** (Scheme 31, Eq 1). Changing from *Grignard* cross-coupling to a *Suzuki* reaction with the palladium-catalyzed cross-coupling between the triethylborane and the alcohol **II-89** in the presence of NaOH or K_2CO_3 as base in THF proved to be encouraging, as **II-95** was isolated in 15% yield when using NaOH (Scheme 31, Eq 2).



Scheme 31. Cross-coupling reactions on II-89.

In parallel, the *Suzuki* cross-coupling was investigated on the stage of **II-92**. Various bases (NaOH, K_2CO_3, Cs_2CO_3) were tested in the presence of $Pd(dppf)Cl_2$ or $Pd(PPh_3)_4$ in DMF at room temperature or higher (Table 6). Unfortunately, none of these conditions led to the desired product.

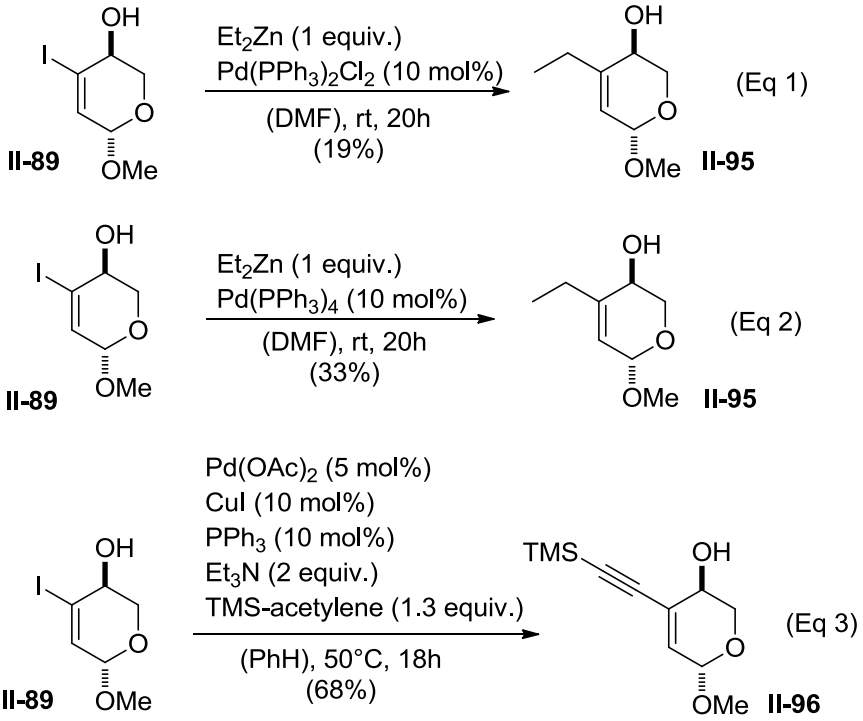


Entry	**Catalyst** (5 mol%)	**Base** (2.2 equiv.)	**Temperature (°C)**	**Result**
1	$Pd(dppf)Cl_2$	NaOH	rt →60	-
2	$Pd(PPh_3)_4$	NaOH	rt →60	-
3	$Pd(PPh_3)_4$	K_2CO_3	rt →60	-
4	$Pd(PPh_3)_4$	Cs_2CO_3	rt →60	-

Table 6. *Suzuki* cross-coupling reactions on II-92.

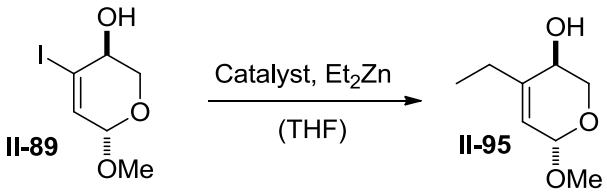
Based on these findings, the iododihydropyranol **II-89** seemed to be the most appropriate subject for an efficient cross-coupling reaction. Consequently, *Negishi* cross-

coupling and even a *Sonogashira* reaction[62] were tested, yielding the best results so far. Particularly with the *Sonogashira* reaction as shown in Scheme 32.



Scheme 32. Further cross-coupling on II-89.

However, in the case of the *Sonogashira* product, two additional steps were required to access the alkyl chain. Although TBAF was sufficient to remove the TMS-protecting group, efforts were required for the selective reduction of the triple bond, leaving the double bond unchanged.[63] Therefore, the conditions of the *Negishi* cross-coupling were further optimized. As depicted in Table 7, the yield was remarkably improved when **II-89** was reacted in the presence of 10 mol% $Pd(dppf)Cl_2$ in THF at room temperature. At 50°C, the reaction time was accelerated considerably (Entry 4-5, Table 7). However, the yield was reduced and thus improvement must be done in this direction.

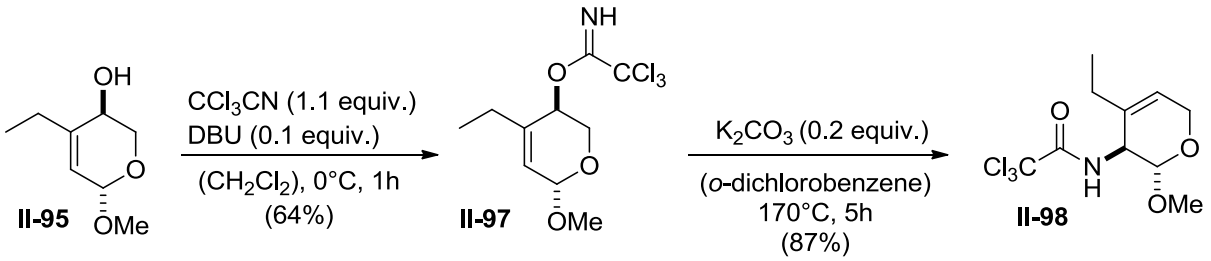


Entry	Catalyst (mol%)	Temperature (°C)	Time (h)	Yield[a] (%)
1	$Pd(PPh_3)Cl_2$ (10)	rt	18	32
2	$Pd(dppf)Cl_2$ (10)	rt	18	61
3	$Pd(PPh_3)_4$ (20)	rt → 50	24	66
4	$Pd(PPh_3)_4$ (10)	50	1	55
5	$Pd(dppf)Cl_2$ (10)	50	3	46

a: Isolated yield after flash chromatography.

Table 7. Condition screening for *Negishi* reaction on II-89.

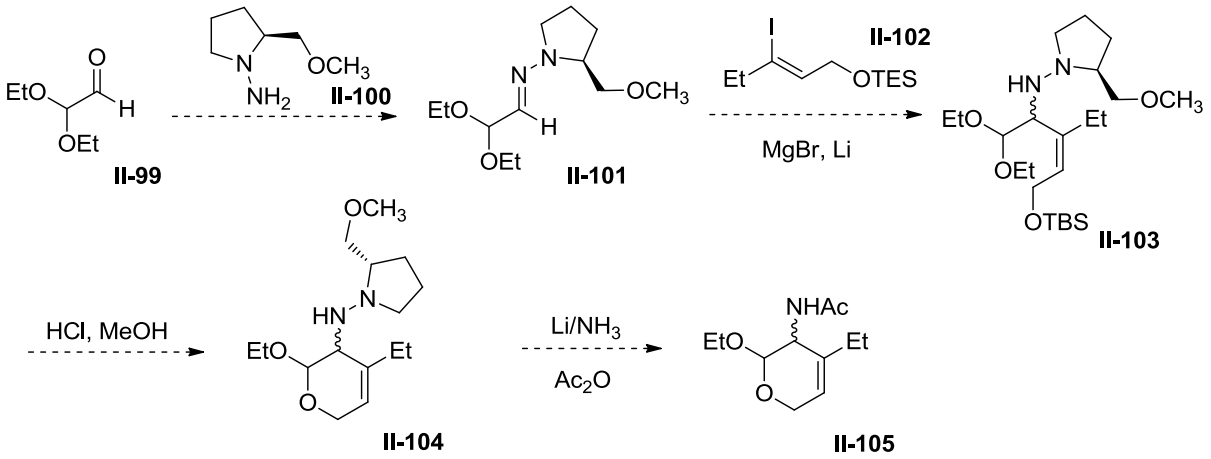
As the ethyl group was finally introduced on **II-89**, *Overman* rearrangement had to be repeated on structure **II-95.** As featured in Scheme 33, formation of the trichloroacetimidate and *Overman* rearrangement gave the desired building block **II-98**, albeit in a low overall yield. Optimization is still left to be conducted, but with **II-98** in hand, only six steps remain until the natural product, melohenine B.



Scheme 33. Formation of the building block.

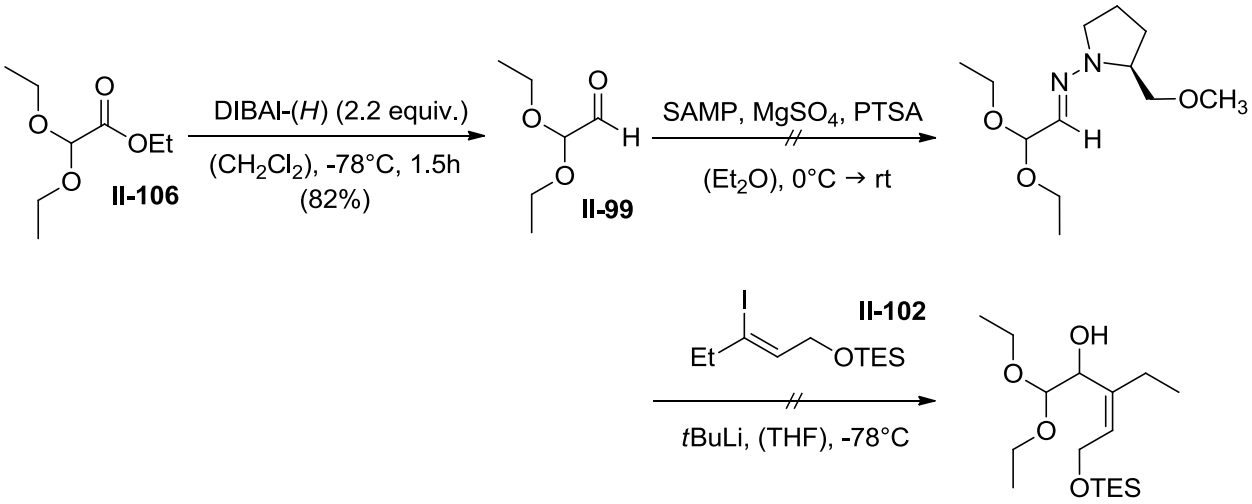
2.3) Two other approaches to the building block

Two alternative routes to the building block (**II-33**) were envisaged. One relied on a lactonization reaction to deliver lactone ring product **II-33**. In addition, the use of chiral auxiliary, (S)-1-amino-2-methoxymethylpyrrolidine (SAMP),[64] should lead to **II-33** asymmetrically (Scheme 34).



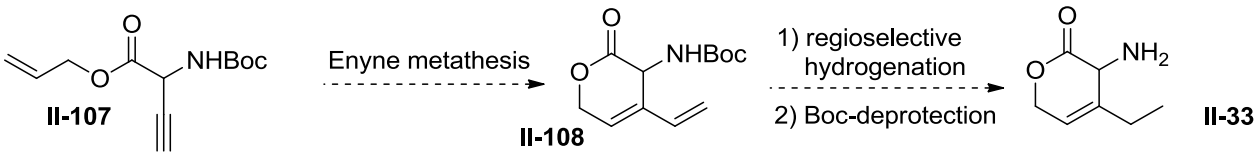
Scheme 34. The lactonization approach to II-33.

Unfortunately, this strategy quickly turned out to be in vain. The poor stability of the aldehyde **II-99** did not allow the condensation of the *Enders* auxiliary, the organomagnesium-, or lithium reaction (Scheme 35).



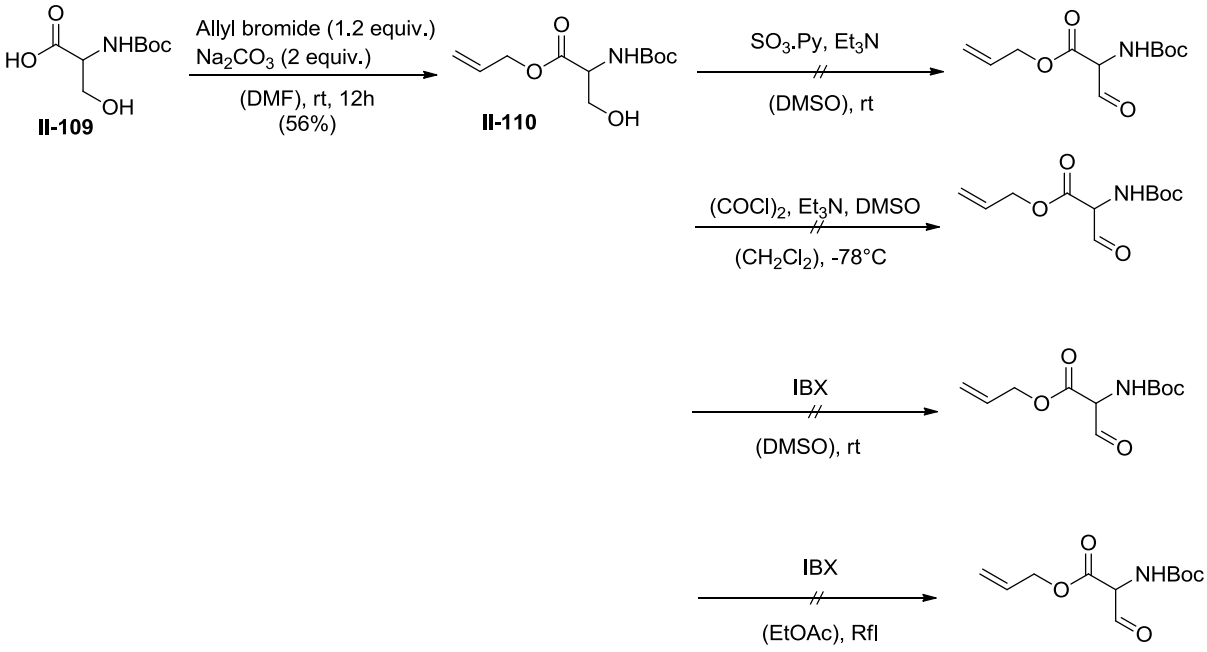
Scheme 35. A dead-end road.

The second approach employed an enyne metathesis as the key step to form the ring.[65] With regard to the difficulty of introducing the ethyl group, the enyne metathesis may be a response to this problem, while delivering the lactone ring. Nevertheless, a regioselective alkene reduction must be performed (Scheme 36).[66]



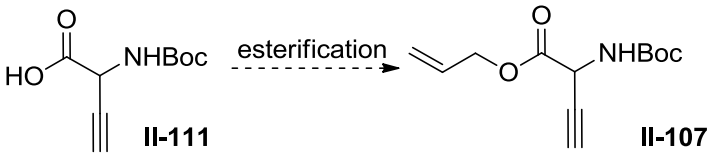
Scheme 36. Enyne metathesis plan.

We anticipated that the synthesis of compound **II-107** would be straightforward starting from the amino acid, Boc-serine. However, the oxidation of the *N*-Boc-O-allyl-serine to the corresponding aldehyde failed (Scheme 37).



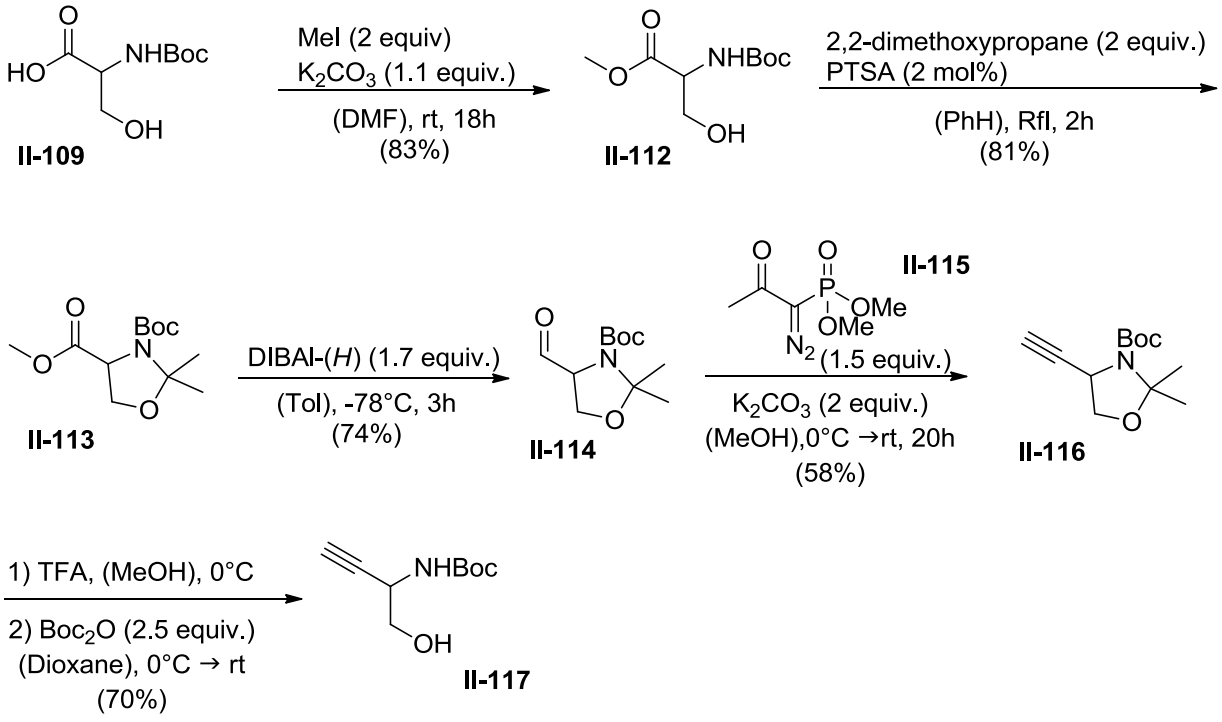
Scheme 37. Difficulties to oxidize the alcohol.

Thereafter, a literature precedent from *Meffre et al.* regarding the synthesis of β,γ--alkynylglycine derivatives was found,[67] and from *N*-Boc-β,γ-alkynylglycine a simple esterification should give the desired substrate for the enyne metathesis (Scheme 38).



Scheme 38. Access to the enyne metathesis substrate.

The group devised the synthesis starting from L-serine. As illustrated in Scheme 39, methylation of the Boc-protected amino acid followed by protection of both the alcohol and secondary amine, via formation of an oxazolidine ring, gave the product **II-113** in good overall yield. Then, reduction of the ester with DIBAl-(*H*) produced the aldehyde **II-114**, which was subject to a *Seyfert-Gilbert* homologation[68] in the presence of the *Bestmann-Ohira* reagent and potassium carbonate.[69] A final deprotection sequence delivered the alcohol **II-117** in good yield.

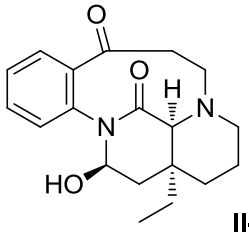


Scheme 39. Formation of II-117 via *Meffre's* route.

Finally, a Jones oxidation[70] of the alcohol to form the corresponding acid was performed employing the conditions described by *Meffre* and coworkers. However, in our hands the reaction did not work.

III) Summary

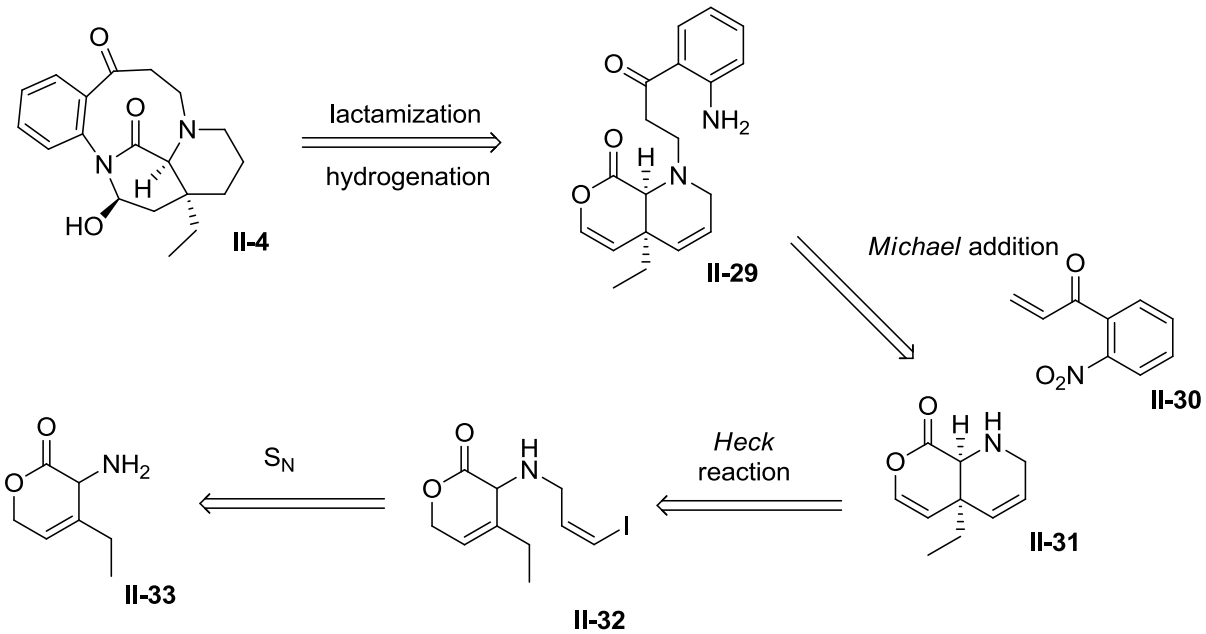
In 2009, the *Luo* group isolated and characterized two novel alkaloids from the *Melodinus Henryi* plant,[12] the melohenines A and B. The same year, intrigued by the unprecedented 6/9/6/6 tetracyclic ketolactam structure of the melohenine B (Figure 3), we decided to launch a study toward the total synthesis of this alkaloid.



II-4

Figure 3. Melohenine B.

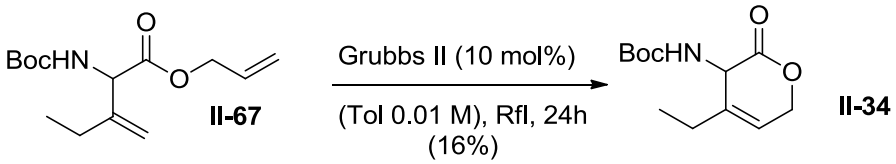
The retrosynthesis plan to reach **II-4** is outlined in Scheme 40. Nevertheless, the investigations up to this point, have focused on the production of the aminolactone building block **II-33**.



II-4 **II-29** **II-30** **II-31** **II-32** **II-33**

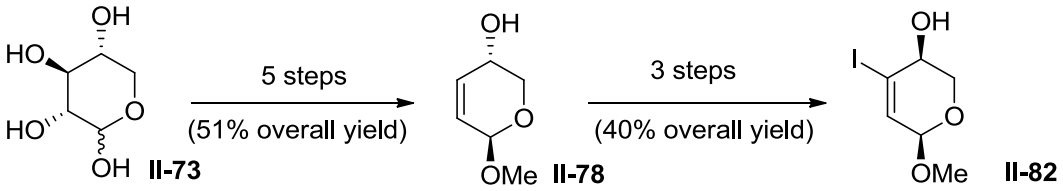
Scheme 40. Retrosynthesis of melohenine B.

Our initial strategy was to close the lacton ring through a ring-closing metathesis. Regrettably the reaction on **II-67** delivered the desired product in poor yield (Scheme 41).



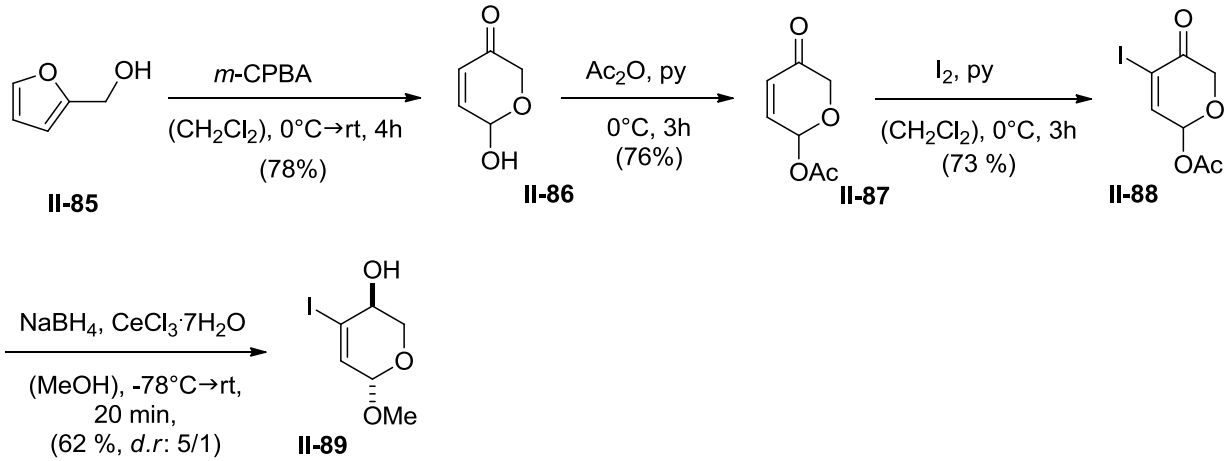
Scheme 41. Ring-closing metathesis to synthesize the building block.

The alternative solution was to start with a preformed lactone and to functionalize the ring. To this end, D-(+)-xylose was employed as the starting material and after five known steps, methoxy dihydropyranol **II-78** was isolated in an overall good yield, as featured in Scheme 42. Then **II-78** was functionalized with iodine in three additional steps in order to proceed to a cross-coupling reaction to introduce the ethyl group.



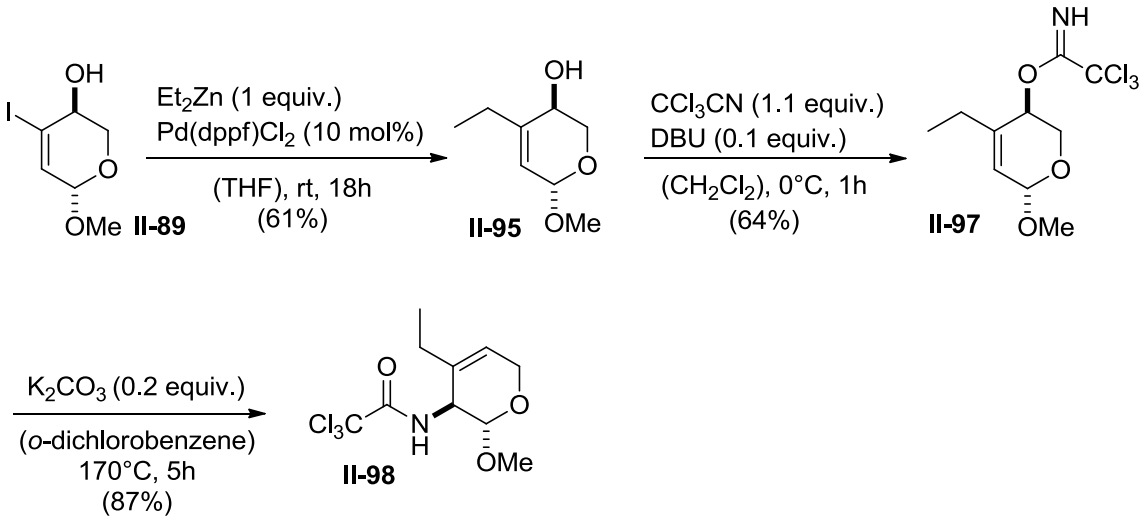
Scheme 42. Carbohydrate chemistry to form the ring structure.

A shorter, but racemic route to **II-82** was also developed starting with furfuryl alcohol to form the *trans*-isomer **II-89** in only four reactions (Scheme 43).



Scheme 43. A shorter alternative.

Then, in order to install the amine functionality, an *Overman* rearrangement was examined after formation of the trichloroacetimidate on **II-82** or **II-89**. For the ethyl moiety, cross-coupling reactions on vinyl iodide compounds were explored. After various experiments on diverse stages of the synthesis, we finally found that the ethyl chain was best introduced via a *Negishi* reaction on **II-89**. Thus, *Overman* rearrangement was repeated on structure **II-95.** As featured in Scheme 44, formation of the trichloroacetimidate and the *Overman* rearrangement gave the desired building block **II-98**. Eventually, only six more steps are remaining until melohenine B.



Scheme 44. The final steps for the building block synthesis.

IV) Experimental part

1) General procedures

Air and water sensitive reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere. Air and moisture sensitive reagents were introduced via argon or nitrogen pre-filled plastic syringes, dry glass syringes or cannula.

At low temperature, the reactions were carried out in a *dewar* filled with ice-water (0°C) or acetone/dry ice (-78°C). Under 0°C, reactions were accomplished with a cryostat (Thermo Haake, EK90).

1.1) Solvents and reagents

Dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), tetrahydrofuran (THF) were dried using a solvent purification system SPS-800 from M.Braun GmbH:

- CH_2Cl_2: *Merck* Emsure®, p. a., 99.8%, <0.03% H_2O, Column 2 × MB-KOL-A.
- Et_2O: *Merck* Emsure®, p. a., 99.7%, <0.03% H_2O, Column 1 × MB-KOL-A, 1 × MB-KOL-M Typ 2.
- THF: *Merck* Emsure®, p. a., 99.8%, <0.03% H_2O, Column 2 × MB-KOL-M Typ 2.

Other solvents and reagents were purchased dry:

- Acetonitrile: *Acros Organics*, Extra Dry, 99.9% over molecular sieves, < 0.005% H_2O.
- Dimethylsulfoxide: *Sigma-Aldrich*, puriss., 99.5% over molecular sieves, < 0.01% H_2O or *Acros Organics*, Extra Dry, 99.9% over molecular sieves, < 0.005% H_2O.
- Methanol: *Acros Organics*, Extra Dry, 99.8% over molecular sieves, < 0.005% H_2O.

- *N,N*-Dimethylformamide: *Sigma-Aldrich*, puriss., 99.5% over molecular sieves, < 0.01% H_2O or *Acros Organics*, Extra Dry, 99.9% over molecular sieves, < 0.005% H_2O.
- Toluene: *Acros Organics*, Extra Dry, 99.8% over molecular sieves, < 0.005% H_2O.
- 1,2-dichloroethane: *Acros Organics*, Extra Dry, 99.8% over molecular sieves, < 0.005% H_2O.
- N,N-Diisopropylethylamine: *Sigma-Aldrich*, puriss., 99.5% over molecular sieves, < 0.05% H_2O.
- Pyridine: *Acros Organics*, Extra Dry, 99.8% over molecular sieves, < 0.005% H_2O or *Sigma-Aldrich*, puriss., 99.8% over molecular sieves, < 0.005% H_2O
- Triethylamine: Distillated from molecular sieves and used immediately after distillation.

Solvents used for thin layer chromatography (TLC), flash chromatography or work up (CH_2Cl_2, Et_2O, THF, ethyl acetate, acetone, ethanol, methanol, pentanes, cyclohexane, petroleum ethers) were simply distilled. All other solvents and reagents were purchased from *Aldrich, Acros*, *Fluka* and *Merck* and used without further purification.

1.2) Analytical techniques and apparatus

Analytical thin-layer chromatography (TLC)

TLC was performed with *Merck* Kieselgel 60 F_{254}, 0.25 mm precoated glass-backed TLC plates. TLC plates were visualized using UV_{254}, cerium ammonium molybdate (CAM) solution, or potassium permanganate ($KMnO_4$) solution. CAM solution was prepared using 2.0 g cerium (IV) sulfate, 25.0 g ammonium heptamolybdate, 50 mL H_2SO_4 and 300 mL water. KMnO4 was prepared using 3 g potassium permanganate, 20.0 g potassium carbonate and 5 mL 5% sodium hydroxide in 300 mL water.

Flash Chromatography

Flash chromatography was carried out using 60 silica gel (40-63 µm, 230-400 mesh ASTM) available from *Merck*.

Gas chromatography (GC and GC-MS)

GC-MS spectra were recorded on an Agilent gas chromatography, Agilent Technologies 7890 A equipped with column HP-5MS (30 m x 250 µm x 0.25 µm), an Agilent Technologies 5975C inert MSD with triple-axis detector and helium as the carrier gas.

Infrared spectroscopy (IR)

Infrared spectra were recorded on a JASCO IR-4100 spectrometer. Samples were analysed neat with attenuated total reflection (ATR). Characteristic bands are reported in wave length (cm-1).

Mass Spectroscopy (MS)

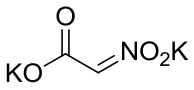
Mass spectroscopic data were recorded using Finnigan MAT 8200 and an Agilent Technologies 5975C (electron ionization, EI 70 eV), or using a MAT 95S and a Bruker micrOTOF Agilent 1100 Series (high resolution mass spectroscopy, HRMS).

Nuclear Magnetic Resonance Spectroscopy (NMR)

^{1}H NMR spectra were obtained on Bruker 600 MHz FT-NMR, 400 Mhz FT-NMR, 500 MHz FT-NMR, 360 MHz FT-NMR and 250 MHz FT-NMR spectrometers. ^{13}C NMR spectra were recorded at 151.1 Mhz, 100.7 MHz, 90.6 MHz or 62.9 Mhz. Chemical shifts are reported in ppm relative to solvent signal. Multiplicity is indicated as follows: s (singlet); d (doublet); t (triplet); m (multiplet); dd (doublet of doublets).

2) Ring closing metathesis strategy (Strategy A)

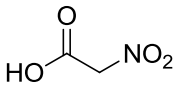
Dipotassium salt of nitroacetic acid (II-40)



$C_2HK_2NO_4$
181,23

Nitromethane (10 g, 163.8 mmol) was added dropwise to a solution of potassium hydroxide (36.7 g, 654.8 mmol) in water (20 mL, 8 M). The solution turned yellow to brown and a precipitate was suddenly formed. The reaction mixture was heated to reflux for 1h. After cooling to room temperature, the precipitate was filtered, washed with methanol and dried under vacuum to give a brown solid (13.95 g, 77.0 mmol, 93%). It was directly used for the next step without further purification.

2-nitroacetic acid (II-41)



$C_2H_3NO_4$
105,05

At 0°C, a 37% HCl-solution (11.1 mL, 135.4 mmol) was slowly added to a solution of dipotassium nitro acetate (5.0 g, 27.6 mmol) in water (7 mL, 4 M), so that the temperature of the reaction mixture did not exceed 0°C. After complete addition, the reaction mixture was allowed to warm to room temperature. The precipitate was filtered and the filtrate was extracted three times with Et_2O. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure, to give a brown solid (1.85 g, 17.6 mmol, 65%). It was directly used for the next step without further purification.

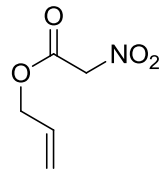
IR (neat) cm^{-1}: 1719, 1550, 1387.

m.p. 94 °C

^{13}C NMR (63 MHz, $(CD_3)_2SO$) δ [ppm] 123.84, 62.99.

The analytical data are identical to the literature data.[71]

Allyl 2-nitroacetate (II-42)



$C_5H_7NO_4$
145,11

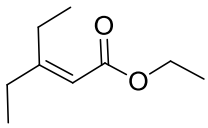
Allyl alcohol (1.46 mL, 21.4 mmol) was added to a solution of nitroacetic acid **II-41** (2.25 g, 21.4 mmol) in THF (110 mL, 0.2 M). After cooling to 0°C, a solution of DCC (4.42 g, 21.4 mmol) in THF (40 mL, 0.5 M) was slowly added, so that the temperature did not exceed 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 20 h. It was then extracted three times with CH_2Cl_2. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Pentanes/EtOAc = 9/1) to obtain the product (2.21 g, 15.2 mmol, 71%).

^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 6.00 – 5.79 (m, 1H), 5.38 (dd, *J* = 2.7, 1.4 Hz, 1H), 5.33 – 5.25 (m, 1H), 5.16 (s, 2H), 4.72 (d, *J* = 5.9 Hz, 2H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] 161.6, 130.4, 120.4, 76.4, 67.6.

The analytical data are identical to the literature data.[72]

Ethyl 3-ethylpent-2-enoate (II-46)



$C_9H_{16}O_2$
156,22

At 0°C, triethyl phosphonoacetate (2.99 mL, 15.1 mmol) was slowly added to a suspension of NaH (60% in paraffin oil) (0.604 g, 15.1 mmol) in dry THF (30 mL, 0.5 M). After stirring for 30 min, pentan-3-one (1.23 mL, 11.6 mmol) was added dropwise. The reaction mixture was heated to 40 °C. After 20 h, it was quenched with sat. NH_4Cl-solution and extracted three times with Et_2O. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromato-graphy (Pentanes/EtOAc = 99/1) to obtain the product (1.30 g, 8.31 mmol, 71%) as an oil.

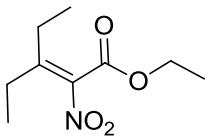
Rf = 0.26 (Pentanes/EtOAc = 99/1) [UV]

^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 5.60 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.61 (q, *J* = 7.5 Hz, 2H), 2.19 (qd, *J* = 7.4, 1.3 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.07 (td, *J* = 7.5, 1.4 Hz, 6H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] 167.4, 166.8, 113.8, 59.6, 30.9, 25.6, 14.5, 13.2, 12.2.

The analytical data are identical to the literature data.[73]

Ethyl 3-ethyl-2-nitropent-2-enoate (II-47)



$C_9H_{15}NO_4$
201,22

At 0°C, a 90 % nitric acid solution (2.41 mL) was carefully added to water (330 µL). After slow addition of ethyl 3-ethylpent-2-enoate **II-46** (1.0 g, 6.40 mmol) over a period of 90 min, the green solution was stirred for 1 h at 0°C and at room temperature for 2 h. The yellow reaction mixture was quenched with ice-water and extracted three times with CH_2Cl_2. The combined organic phase was washed with sat. $NaHCO_3$-solution and sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Pentanes/EtOAc = 9/1) to obtain the product (791.0 g, 3.93 mmol, 61%) as a yellow oil.

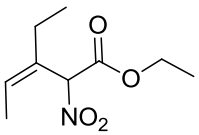
Rf = 0.58 (Pentanes/Et_2O = 95/5) [UV/$KMnO_4$]

^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 4.28 (q, *J* = 7.1 Hz, 2H), 2.61 (q, *J* = 7.5 Hz, 2H), 2.21 (q, *J* = 7.5 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.16 (td, *J* = 7.5, 3.5 Hz, 6H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] 163.9, 159.4, 158.4, 62.3, 27.1, 24.7, 14.1, 12.6, 12.3.

MS (EI) *m/z* (%): 156.1 (52) [M^+-EtO], 127.1 (32) [M^+-$EtCHO_2$], 110.0 (20) [M^+-EtO-NO_2], 94.1 (68), 81.0 (79), 70.1 (65), 67.0 (100).

Ethyl 3-ethyl-2-nitropent-3-enoate (II-49)



$C_9H_{15}NO_4$
201,22

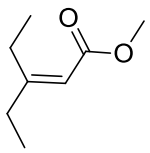
II-47 (700.0 mg, 3.48 mmol) dissolved in dry THF (0.88 mL, 4 M) was slowly added to a suspension of potassium hydride (140.0 mg, 3.48 mmol) in dry THF (1.74 mL, 2 M) at 0°C. After stirring for 30 min, THF was added, and after 1 h at 0°C, the reaction mixture was stirred at rt for 2 h. The formed precipitate was filtered, washed with Et_2O and dried under vacuum to give a brown solid (552 mg, 2.31 mmol, 66%).

The potassium salt (500 mg, 2.09 mmol) was dissolved in water (6.33 mL) and a 1M HCl-solution was added. After stirring at rt for 10 min, the reaction mixture was extracted three times with Et_2O. The combined organic phase was washed with sat. $NaHCO_3$-solution and sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure to give the product (376 mg, 1.87 mmol, 90%). It was directly used for the next step without further purification.

^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 5.79 (q, *J* = 6.9 Hz, 1H), 5.56 (s, 1H), 4.36 – 4.21 (m, 2H), 2.41 – 2.11 (m, 2H), 1.78 (d, *J* = 6.9 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.00 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (91 MHz, $CDCl_3$): δ [ppm] 163.8, 133.6, 132.1, 92.9, 63.1, 22.1, 14.2, 14.1, 12.9.

Methyl 3-ethylpent-2-enoate (II-52)



$C_8H_{14}O_2$
142,20

Following the same procedure as for **II-46**, pentan-3-one (2.0 g, 23.2 mmol) was reacted with methyl diethyl phosphonoacetate (6.34 g, 30.2 mmol) in the presence of NaH (1.25 g, 31.1 mmol). After flash chromatography (Pentanes/Et_2O = 99/1), the product (1.93 g, 13.5 mmol, 58%) was obtained.

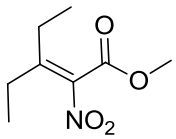
Rf = 0.55 (Cyclohexane/EtOAc = 95/5) [UV/$KMnO_4$].

^{1}H NMR (250 MHz, $CDCl_3$) δ[ppm] 5.61 (s, 1H), 3.68 (s, 3H), 2.62 (q, *J* = 7.5 Hz, 2H), 2.19 (dt, *J* = 8.7, 6.8 Hz, 2H), 1.07 (td, *J* = 7.5, 0.9 Hz, 6H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 167.8, 167.2, 113.4, 50.9, 30.9, 25.6, 13.2, 12.2.

The analytical data are identical to the literature data.[74]

Methyl 3-ethyl-2-nitropent-2-enoate (II-53)



$C_8H_{13}NO_4$
187,19

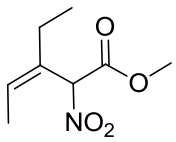
Following the same procedure as for **II-47**, **II-52** (4.7 g, 33.1 mmol) was nitrated with a 90 % nitric acid solution (12.6 mL). After flash chromatography (Pentanes/Et_2O = 99/1) the product (2.62 g, 14.0 mmol, 42%) was obtained.

Rf = 0.53 (Pentanes/Et_2O= 95/5) [UV/$KMnO_4$]

^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 3.81 (s, 3H), 2.62 (q, *J* = 7.5 Hz, 2H), 2.22 (q, *J* = 7.5 Hz, 2H), 1.16 (td, *J* = 7.5, 3.7 Hz, 6H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 165.1, 159.7, 159.0, 52.9, 27.1, 24.7, 12.6, 12.3.

Methyl 3-ethyl-2-nitropent-3-enoate (II-55)



$C_8H_{13}NO_4$
187,19

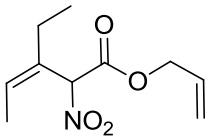
Following the same procedure as for **II-49**, **II-53** (1.07 g, 5.71 mmol) was reacted with potassium hydride (236.0 mg, 5.88 mmol). After acidic work up, the product (509.3 mg, 2.72 mmol, 48%) was isolated.

Rf = 0.71 (Cyclohexane/EtOAc = 95/5) [UV/$KMnO_4$]

^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 5.79 (q, *J* = 6.9 Hz, 1H), 5.58 (s, 1H), 3.84 (s, 3H), 2.38 – 2.14 (m, 2H), 1.78 (d, *J* = 6.9 Hz, 3H), 1.00 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] 165.0, 133.6, 132.0, 92.6, 53.5, 22.0, 14.0, 12.7.

Allyl 3-ethyl-2-nitropent-3-enoate (II-56)



$C_{10}H_{15}NO_4$
213,23

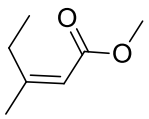
Bu_2SnO (6.65 mg, 26.7 μmol) was added to a solution of methyl 3-ethyl-2-nitropent-3-enoate **II-55** (49.0 mg, 267 μmol) in allyl alcohol (2.3 mL, 0.01 M). The reaction mixture was heated to reflux for 15 h. It was quenched with sat. $NaHCO_3$-solution and extracted three times with EtOAc. The combined organic phase was filtered through celite and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (Pentanes/Et_2O = 95/5) to obtain the product (17.5 mg, 82.0 μmol, 31%).

Rf= 0.48 (Pentanes/Et_2O = 95/5) [UV/$KMnO_4$]

^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 6.00 – 5.73 (m, 2H), 5.84 – 5.75 (m, 1H), 5.59 (s, 1H), 5.43 – 5.25 (m, 1H), 4.72 (d, *J* = 5.9 Hz, 2H), 2.44 – 2.10 (m, 2H), 1.78 (d, *J* = 6.9 Hz, 3H), 1.00 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 164.2, 133.6, 131.9, 130.8, 112.0, 92.7, 67.3, 22.0, 14.0, 12.8.

Methyl 3-methylpent-2-enoate (II-60)



$C_7H_{12}O_2$
128,17

Following the same procedure as for **II-46**, butanone (8.0 g, 0.110 mol) was reacted with methyl diethyl phosphonoacetate (26.3 g, 0.114 mol) in the presence of NaH (5.32 g, 0.144 mol). After flash chromatography (Pentanes/Et_2O = 95/5), the product (9.85 g, 76.9 mmol, 69%) was obtained as a mixture of *E* and *Z* isomers.

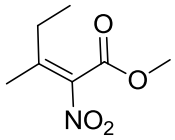
Rf = 0.69 (Pentanes/Et_2O = 95/5) [UV/$KMnO_4$].

^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 5.66 (d, *J* = 1.2 Hz, 0.7H), 5.63 (s, 0.3H), 3.68 (s, 2H), 3.67 (s, 1H), 2.63 (q, *J* = 7.5 Hz, 0.6H), 1.21 – 1.10 (m, 3.4H), 1.88 (d, *J* = 1.3 Hz, 1H), 1.07 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 167.5, 166.9, 162.6, 162.0, 115.2, 114.2, 50.9, 33.9, 31.0, 26.7, 24.7, 18.9, 12.7, 12.1.

The analytical data are identical to the literature data.[75]

Methyl 3-methyl-2-nitropent-2-enoate (II-61)



$C_7H_{11}NO_4$
173,17

Following the same procedure as for **II-47**, **II-60** (9.0 g, 70.3 mmol) was nitrated with a 90 % nitric acid solution (24.5 mL). After flash chromatography (Pentanes/EtOAc = 95/5) the product (7.35 g, 42.4 mmol, 60%) was obtained as a mixture of *E* and *Z* isomers.

Rf = 0.43 (Pentanes/Et_2O = 9/1) [UV/$KMnO_4$]

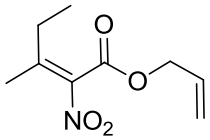
^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 3.82 (s, 3H), 2.63 (q, *J* = 7.5 Hz, 1H), 2.25 (s, 1.3H), 2.20 (q, *J* = 7.6 Hz, 1H), 1.97 (s, 1.7H), 1.21 – 1.10 (m, 3H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] (160.0, 159.7), (154.3, 154.0), 141.6, (52.9, 52.9), (29.7, 27.4), (20.2, 18.3), (12.1, 12.0).

MS (EI) *m/z* (%): 173.0 (2) [M^+], 156.1 (41) [M^+-OH], 142.0 (30) [M^+-MeO], 67.0 (70), 59.0 (100).

IR (neat) cm^{-1}: 2981, 2958, 2883, 1732, 1530, 1270, 1214, 1120, 1053, 769.

Allyl 3-methyl-2-nitropent-2-enoate (II-62)



$C_9H_{13}NO_4$
199,20

Following the same procedure as for **II-56**, **II-60** (2.0 g, 11.5 mmol) was transesterificated in presence of Bu_2SnO (287.0 mg, 1.15 mmol) in allylic alcohol (115 mL). After flash chromatography (Pentanes/Et_2O = 95/5) the product (1.24 g, 6.22 mmol, 53%) was obtained as a mixture of *E* and *Z* isomers.

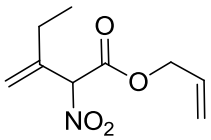
Rf = 0.31 (Cyclohexane/EtOAc= 95/5) [UV/$KMnO_4$]

^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 5.98 – 5.80 (m, 1H), 5.41 – 5.21 (m, 2H), 4.71 (ddd, *J* = 5.6, 2.2, 1.3 Hz, 2H), 2.63 (q, *J* = 7.5 Hz, 1H), 2.28 – 2.14 (m, 2.5H), 1.98 (s, 1.5H), 1.16 (td, *J* = 7.5, 3.5 Hz, 3H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] (159.2, 158.9), (154.4, 154.1), (130.98, 130.96), (119.3, 119.2), 100.1, (66.5, 66.4), (29.7, 27.5), (20.2, 18.3), (12.1, 12.0).

MS (EI) *m/z* (%): 199.0 (4) [M^+], 158.0 (36) [M^+-Allyl], 142.0 (42) [M^+-CH_2CHCH_2O], 81.0 (64), 67.1 (77), 57.1 (100) [CH_2CHCH_2O].

Allyl 3-methylene-2-nitropentanoate (II-63)



$C_9H_{13}NO_4$
199,20

Following the same procedure as for **II-49**, **II-62** (1.0 g, 5.02 mmol) was reacted with potassium hydride (302.0 mg, 7.53 mmol). After acidic work up and flash chromatography (Pentanes/Et_2O = 95/5) the product (708.7 mg, 3.56 mmol, 71%) was obtained.

Rf = 0.31 (Cyclohexane/EtOAc = 95/5) [UV/$KMnO_4$]

^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 5.98 – 5.81 (m, 1H), 5.67 (s, 1H), 5.44 – 5.26 (m, 4H), 4.74 (dt, *J* = 5.9, 1.2 Hz, 2H), 2.24 (ddd, *J* = 8.6, 5.4, 1.3 Hz, 2H), 1.12 (t, *J* = 7.4 Hz, 3H).

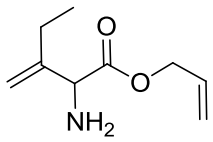
^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 163.5, 140.0, 130.6, 120.5, 120.2, 91.9, 67.4, 26.1, 11.9.

MS (EI) *m/z* (%): 158.0 (26) [M^+-Allyl], 142.0 (28) [M^+-CH_2CHCH_2OH], 81.0 (51), 67.0 (70), 57.0 (100) [CH_2CHCH_2O].

HRMS (ESI) *m/z* 222.0738 [222.0737 calcd. for $C_9H_{13}NO_4Na$ (M^++Na^+)].

IR (neat) cm^{-1}: 3090, 2974, 2883, 1751, 1561, 1534, 1360, 1266, 1210, 990, 930, 748.

Allyl 2-amino-3-methylenepentanoate (II-66)



$C_9H_{15}NO_2$
169,22

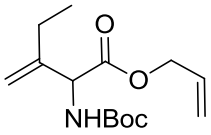
At 0°C, a conc. HCl-solution (11.5 mL, 0.5 M) was slowly added to a solution of allyl 3-methylene-2-nitropentanoate **II-63** (1.14 g, 5.75 mmol) in allyl alcohol (57.5 mL, 0.1 M). Then zinc powder (3.76 g, 57.5 mmol) was added portionwise to the reaction mixture under strong stirring. At the end of the addition, the suspension was filtered over celite and the filtrate was quenched with sat. $NaHCO_3$-solution and extracted three times with EtOAc. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure to give the product (874.4 mg, 5.17 mmol, 90%). It was directly used for the next step without further purification.

Rf = 0.25 (Pentanes/EtOAc = 6/4) [UV/$KMnO_4$]

^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 5.90 (ddt, *J* = 17.1, 10.4, 5.7 Hz, 1H), 5.39 – 5.19 (m, 2H), 5.06 (s, 1H), 4.96 (d, *J* = 1.4 Hz, 1H), 4.62 (dd, *J* = 5.7, 1.3 Hz, 2H), 4.05 (s, 1H), 2.21 – 2.01 (m, 2H), 1.69 (s, 2H), 1.07 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 173.5, 149.4, 131.9, 118.7, 111.5, 65.9, 59.7, 25.8, 12.2.

Allyl 2-((tert-butoxycarbonyl)amino)-3-methylenepentanoate (II-67)



$C_{14}H_{23}NO_4$
269,34

At rt, triethylamine (271.1 mg, 2.68 mmol) and Boc anhydride (438.7 mg, 2.01 mmol) were added to a solution of allyl 2-amino-3-methylenepentanoate (226.7 mg, 1.34 mmol) in CH_2Cl_2 (2.68 mL, 0.5 M). After stirring for 21 h, the reaction mixture was quenched with sat. $NaHCO_3$-solution and extracted three times with EtOAc. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Pentanes/EtOAc = 9/1) to obtain the product (166.3 mg, 617.4 μmol, 46%) as an oil.

Rf = 0.31 (Cyclohexane/EtOAc = 95/5) [UV/$KMnO_4$]

^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 5.89 (ddt, *J* = 17.1, 10.5, 5.7 Hz, 1H), 5.37 – 5.22 (m, 3H), 5.08 (s, 1H), 5.01 (t, *J* = 1.6 Hz, 1H), 4.78 (d, *J* = 7.8 Hz, 1H), 4.64 (dd, *J* = 7.5, 3.3 Hz, 2H), 2.11 (ddd, *J* = 20.6, 13.9, 5.9 Hz, 2H), 1.44 (s, 9H), 1.07 (t, *J* = 7.4 Hz, 3H).

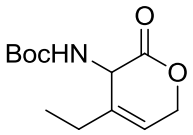
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 171.0, 159.0, 132.7, 131.7, 118.8, 112.4, 73.3, 66.1, 39.3, 28.5, 26.3, 12.0.

MS (EI) *m/z* (%): 269.1 (1) [M^+], 196.1 (4) [M^+-*t*BuO], 154.0 (18) [M^+-*t*BuOC(O)N], 128.1 (100), 84.1 (62), 57.1 (56) [CH_2CHCH_2O].

HRMS (ESI) *m/z* 292.1520 [292.1519 calcd. for $C_{14}H_{23}O_4NNa$ (M^++Na^+)].

IR (neat) cm^{-1}: 3382, 3090, 2974, 2935, 1713, 1492, 1366, 1246, 1154, 1050, 988, 907.

Tert-butyl (4-ethyl-2-oxo-3,6-dihydro-2H-pyran-3-yl)carbamate (II-33)



$C_{12}H_{19}NO_4$
241,28

Grubbs II catalyst (31.3 mg, 36.9 μmol) was added to **II-67** (99.3 mg, 368.7 μmol) dissolved in degassed toluene (37 mL, 0.01M). The reaction mixture was heated to reflux and stirred for 24 h. After cooling to rt, the solution was filtered through celite. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (Pentanes/EtOAc = 8/2) to obtain the product (13.9 mg, 57.6 μmol, 16%, 22% brsm) as an oil.

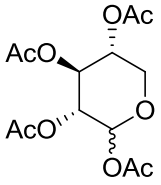
Rf = 0.26 (Pentanes/EtOAc = 8/2) [UV/$KMnO_4$]

^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 5.78 – 5.70 (m, 1H), 5.30 (s, 1H), 4.90 – 4.75 (m, 3H), 2.23 – 2.11 (m, 2H), 1.46 (s, 9H), 1.06 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] 170.7, 156.2, 142.6, 116.2, 80.6, 66.9, 53.2, 28.4, 23.6, 11.5.

3) The carbohydrate strategy (Strategy B)

(3R,4S,5R)-tetrahydro-2H-pyran-2,3,4,5-tetrayl tetraacetate (II-74)



$C_{13}H_{18}O_9$
318,28

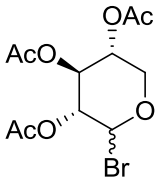
At 0°C, acetic acid (12.6 mL, 133.2 mmol) was added dropwise to a solution of D-(+)-xylose (5.0 g, 33.3 mmol) in pyridine (16 mL, 2 M). After the addition, the reaction mixture was allowed to warm to rt and stirred for 18 h. It was quenched with water and extracted three times with CH_2Cl_2. The combined organic phase was washed with sat. $NaHCO_3$-solution and sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/EtOH = 100/3) to obtain the product (9.98 g, 31.4 mmol, 94%) as a colorless syrup.

Rf = 0.56 (Pentanes/EtOAc = 1/1) [CAM]

^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 6.26 (d, *J* = 3.7 Hz, 1H), 5.72 (d, *J* = 6.9 Hz, 1H), 5.47 (t, *J* = 9.8 Hz, 1H), 5.21 (t, *J* = 8.3 Hz, 1H), 5.01 (tdd, *J* = 8.2, 6.8, 4.0 Hz, 4H), 4.15 (dd, *J* = 12.1, 5.0 Hz, 1H), 3.94 (dd, *J* = 11.2, 5.9 Hz, 1H), 3.71 (t, *J* = 11.0 Hz, 1H), 3.52 (dd, *J* = 12.0, 8.4 Hz, 1H), 2.17 (s, 13H), 2.11 (s, 3H), 2.05 (d, *J* = 0.5 Hz, 12H), 2.02 (s, 3H).

The analytical data are identical to the literature data.[76]

(3R,4S,5R)-2-bromotetrahydro-2H-pyran-3,4,5-triyl triacetate (II-75)



$C_{11}H_{15}BrO_7$
339,14

At 0°C, HBr (10 mL, 62.8 mmol, 33% solution in acetic acid) was added dropwise to tetrahydro-2H-pyran-2,3,4,5-tetrayl tetraacetate **II-74** (10 g, 31.4 mmol) in solution in CH_2Cl_2 (52 mL, 0.6 M). After stirring at 0°C for 30 min, the reaction mixture was quenched with ice water and extracted three times with CH_2Cl_2. The combined organic phase was washed with sat. $NaHCO_3$-solution and sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. Diethyl ether was added at 0°C to precipitate the product, which was dried under vacuum to give white crystals (16.75 g, 49.4 mmol, 86%).

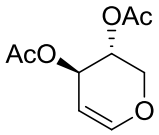
Rf = 0.75 (Pentanes/EtOAc = 2/3) [CAM]

^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 6.15 (d, *J* = 3.7 Hz, 1H), 5.25 (t, *J* = 9.5 Hz, 1H), 5.04 – 4.92 (m, 1H), 3.90 (dd, *J* = 11.2, 5.7 Hz, 1H), 3.85 – 3.76 (m, 1H), 3.62 (t, *J* = 10.8 Hz, 1H), 2.19 (s, 3H), 2.12 (s, 3H), 2.05 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 171.6, 169.9, 169.5, 91.8, 72.8, 70.2, 68.3, 60.9, 21.1, 21.0, 20.8.

The analytical data are identical to the literature data.[76]

(3R,4R)-3,4-dihydro-2H-pyran-3,4-diyl diacetate (II-76)



$C_9H_{12}O_5$
200,19

Pyranose bromide **II-75** (50.7 mg, 149.5 μmol) was dissolved in EtOAc (0.3 mL, 0.5 M). Sat. NaH_2PO_4 solution (0.6 mL, 0.25 M) and zinc dust (120 mg, 1.83 mmol) were added. The reaction mixture was stirred at room temperature for 3 h. The solution was extracted three times with EtOAc. The combined organic phase was washed with water, sat. $NaHCO_3$-solution and sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Pentanes/EtOAc = 8/2) to obtain the product (25.3 mg, 126.4 μmol, 85%) as colorless syrup.

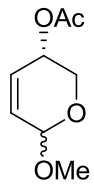
Rf = 0.33 (Pentanes/EtOAc = 9/1) [CAM]

^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 6.60 (d, *J* = 5.8 Hz, 1H), 4.98 (tdd, *J* = 9.2, 5.4, 3.4 Hz, 3H), 4.20 (ddd, *J* = 12.0, 3.1, 1.5 Hz, 1H), 3.98 (dd, *J* = 12.2, 1.8 Hz, 1H), 2.10 (s, 3H), 2.07 (s, 3H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] 170.1, 170.0, 148.2, 97.6, 67.4, 63.8, 63.6, 21.3, 21.1.

The analytical data are identical to the literature data.[77]

6-methoxy-3,6-dihydro-2H-pyran-3-yl acetate (II-77)



$C_8H_{12}O_4$
172,18

At rt, abs. methanol (1.09 mL, 33.9 mmol) and tin (IV) chloride (0.85 mL, 0.847 mmol, 1M in CH_2Cl_2) were added to 3,4-dihydro-2H-pyran-3,4-diyl diacetate **II-76** (3.39 g, 16.9 mmol) dissolved in dry CH_2Cl_2 (85 mL, 0.2 M). After 45 min, the purple reaction was quenched with sat. $NaHCO_3$-solution and extracted three times with CH_2Cl_2. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Pentanes/EtOAc = 8/2) to obtain the product (2.56 g, 14.8 mmol, 88%) as a mixture of both diastereoisomers.

***Cis*-diastereoisomer (minor) (II-77a)**

Rf = 0.43 (Pentanes/EtOAc= 4/1) [CAM]

^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 6.01 – 5.80 (m, 2H), 5.33 – 5.22 (m, 1H), 4.85 (s, 1H), 3.92 – 3.72 (m, 2H), 3.45 (s, 3H), 2.07 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 170.7, 129.2, 129.1, 95.5, 65.1, 60.4, 56.0, 21.1.

***Trans*-diastereoisomer (major) (II-77b)**

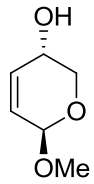
Rf = 0.32 (Pentanes/EtOAc = 4/1) [CAM]

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 6.04 (qd, *J* = 10.1, 3.9 Hz, 2H), 4.98 – 4.92 (m, 1H), 4.89 (d, *J* = 2.6 Hz, 1H), 4.13 (dd, *J* = 13.0, 2.8 Hz, 1H), 3.83 (d, *J* = 13.0 Hz, 1H), 3.43 (s, 3H), 2.09 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 170.7, 130.9, 125.2, 94.2, 63.5, 61.4, 55.9, 21.2.

The analytical data are identical to the literature data.[77]

(*3S,6R*)-6-methoxy-3,6-dihydro-2H-pyran-3-ol (II-78)



$C_6H_{10}O_3$
130,14

At rt, *trans* methoxy-3,6-dihydro-2H-pyran-3-yl acetate **II-77b** (451.0 mg, 2.62 mmol) was added to a fresh solution of sodium methoxide (1.75 mmol) in methanol (17.5 mL, 0.1 M). After 45 min, acetic acid (1.5 mL) was added dropwise and the reaction mixture was concentrated under reduce pressure. The residue was purified by flash chromatography (Pentanes/EtOAc = 1/1) to obtain the product (291.0 mg, 2.24 mmol, 85%) as a white solid.

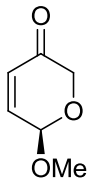
Rf = 0.09 (Pentanes/EtOAc = 4/1) [$KMnO_4$]

^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 6.17 – 6.10 (m, 1H), 5.92 – 5.86 (m, 1H), 4.86 – 4.81 (m, 1H), 4.09 (dd, *J* = 12.2, 2.5 Hz, 1H), 3.85 – 3.76 (m, 2H), 3.43 (s, 3H), 1.93 (s, 1H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] 129.4, 128.6, 94.4, 64.4, 61.7, 55.8.

The analytical data are identical to the literature data.[78]

(*R*)-6-methoxy-2H-pyran-3(6H)-one (II-79)



$C_6H_8O_3$
128,13

At rt, IBX (3.81 g, 13.6 mmol) was added to 6-methoxy-3,6-dihydro-2H-pyran-3-ol **II-78** (709.2 mg, 5.45 mmol) in DMSO (18 mL, 0.3 M). After 2 h, CH_2Cl_2 (10 × 18 mL) was added to the solution, which was then stirred for 15 min. The precipitate was filtered and the filtrate was quenched with sat. $NaHCO_3$-solution and extracted three times with CH_2Cl_2. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Pentanes/EtOAc = 9/1) to obtain the product (560.2 mg, 4.37 mmol, 80%) as a white solid.

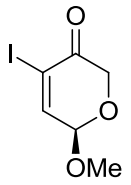
Rf = 0.71 (Pentanes/EtOAc = 3/2) [$KMnO_4$]

^{1}H NMR (250 MHz, $CDCl_3$) δ [ppm] 6.89 (dd, *J* = 10.4, 3.3 Hz, 1H), 6.14 (d, *J* = 10.4 Hz, 1H), 5.11 (d, *J* = 3.3 Hz, 1H), 4.45 (d, *J* = 16.9 Hz, 1H), 4.11 (d, *J* = 16.9 Hz, 1H), 3.53 (s, 3H).

^{13}C NMR (63 MHz, $CDCl_3$) δ [ppm] 194.7, 144.3, 128.0, 94.4, 66.4, 56.8.

The analytical data are identical to the literature data.[79]

(*R*)-4-iodo-6-methoxy-2H-pyran-3(6H)-one (II-80)



$C_6H_7IO_3$
254,02

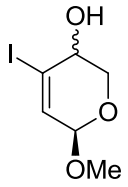
I_2 (87.2 mg, 0.343 mmol) was added to 6-methoxy-*2H*-pyran-3(6H)-one **II-79** (20 mg, 0.156 mmol) dissolved in dry pyridine (61.7 mg, 0.780 mmol) and dry CH_2Cl_2 (0.78 mL, 0.2 M) at 0°C. The reaction mixture was stirred at 0°C. After 1 h, it was quenched with sat. $Na_2S_2O_3$-solution and sat. NH_4Cl-solution. The solution was extracted three times with Et_2O and the combined organic phase was washed with sat. NH_4Cl-solution and with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Pentanes/EtOAc = 9/1) to obtain the product (29.6 mg, 0.117 mmol, 75%) as a yellow liquid.

Rf = 0.67 (Pentanes/EtOAc = 4/1) [$KMnO_4$]

^{1}H NMR (360 MHz, $CDCl_3$) δ [ppm] 7.62 (d, *J* = 3.7 Hz, 1H), 4.99 (d, *J* = 3.6 Hz, 1H), 4.64 (d, *J* = 16.7 Hz, 1H), 4.34 (d, *J* = 16.7 Hz, 1H), 3.51 (s, 3H).

^{13}C NMR (91 MHz, $CDCl_3$) δ [ppm] 188.2, 153.0, 103.1, 96.3, 65.8, 56.8.

4-iodo-6-methoxy-3,6-dihydro-2H-pyran-3-ol (II-82)

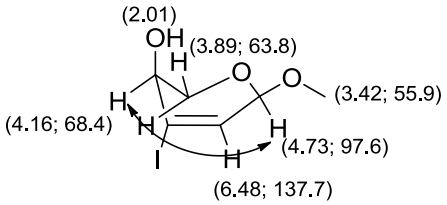


$C_6H_9IO_3$
256,04

At 0°C, cerium (III) chloride heptahydrate (147.3 mg, 0.395 mmol) and $NaBH_4$ (14.95 mg, 0.395 mmol) were added to iodopyranone **II-80** (99.8 mg, 0.394 mmol) in dry methanol (0.7 mL, 0.6 M). The reaction mixture was allowed to warm to rt. After stirring for 1 h, the reaction was quenched with water and extracted three times with Et_2O. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Pentanes/EtOAc 9/1) to obtain the product (66.5 mg, 0.260 mmol, 66%) as a diastereoisomeric mixture.

***Cis*- diastereoisomer (Major) (II-82a)**

NOESY contact:



Rf = 0.23 (Cyclohexane/EtOAc= 4/1) [$KMnO_4$]

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 6.48 (dd, *J* = 2.8, 1.4 Hz, 1H), 4.73 (dd, *J* = 2.8, 1.2 Hz, 1H), 4.16 (dt, *J* = 6.8, 5.6 Hz, 1H), 3.89 (qd, *J* = 11.2, 6.7 Hz, 2H), 3.42 (s, 3H), 2.01 (d, *J* = 7.1 Hz, 1H).

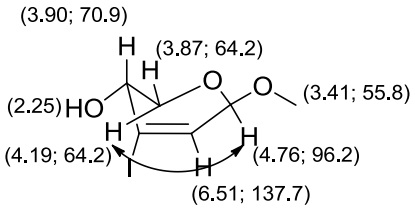
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 137.7, 108.6, 97.4, 68.4, 63.8, 55.9.

MS (EI) *m/z* (%): 238.9 (65) [M^+-OH], 224.9 (64) [M^+-MeO], 129.0 (81) [M^+-H-HI], 97.0 (100).

IR (neat) cm^{-1}: 3426, 2978, 2925, 2830, 1637, 1355, 1328, 1232, 1121, 1058, 946, 891, 640, 550.

***Trans*-diastereoisomer (minor) (II-82b)**

NOESY contact:

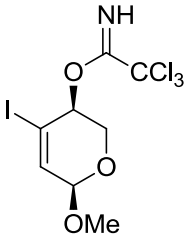


Rf = 0.19 (Cyclohexane/EtOAc = 4/1) [CAM]

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 6.51 (d, *J* = 3.3 Hz, 1H), 4.76 (d, *J* = 3.1 Hz, 1H), 4.22 – 4.16 (m, 1H), 3.93 – 3.89 (m, 1H), 3.87 (dd, *J* = 12.1, 1.4 Hz, 1H), 3.41 (s, 3H), 2.25 (d, *J* = 8.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 137.7, 102.3, 96.2, 70.9, 64.2, 55.8.

(*3S,6R*)-4-iodo-6-methoxy-3,6-dihydro-2H-pyran-3-yl 2,2,2-trichloroacetimidate (II-83)



$C_8H_9Cl_3INO_3$
400,43

At 0°C, DBU (59.4 mg, 0.390 mmol), 4Å molecular sieves (cat.) and trichloroacetonitrile (50.7 mg, 0.351 mmol) were added into a solution of *cis* iodopyranol **II-82a** (50 mg, 0.195 mmol) in dry CH_2Cl_2 (1.0 mL, 0.2 M). The reaction mixture was stirred at rt. After 12 h, it was

quenched with sat. NH_4Cl-solution and extracted three times with CH_2Cl_2. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Pentanes/EtOAc = 9/1) to obtain the product (73.7 mg, 0.184 mmol, 94%) as a white solid.

Rf = 0.46 (Cyclohexane/EtOAc = 4/1) [$KMnO_4$]

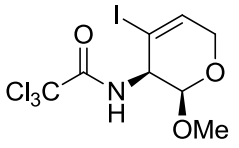
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 8.45 (s, 1H), 6.59 (dd, *J* = 2.9, 1.6 Hz, 1H), 5.47 (ddt, *J* = 7.0, 5.4, 1.4 Hz, 1H), 4.74 (dd, *J* = 2.8, 1.3 Hz, 1H), 3.97 (dtd, *J* = 9.4, 7.6, 2.9 Hz, 2H), 3.37 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 162.0, 140.2, 98.9, 97.2, 91.0, 73.2, 60.6, 55.8.

MS (EI) *m/z* (%): 238.9 (64) [M^+-$CCl_3C(NH)O$], 178.0 (32) [M^+-$CCl_3C(NH)O$-$MeOCH_2O$], 129.0 (69), 107.9 (100), 97.0 (95).

IR (neat) cm^{-1}: 3340, 2932, 2887, 2831, 1663, 1281, 1056, 966, 835, 795, 645.

2,2,2-trichloro-N-((*2R,3R*)-4-iodo-2-methoxy-3,6-dihydro-2H-pyran-3-yl)acetamide (II-84)



$C_8H_9Cl_3INO_3$
400,43

Trichloroacetimidate **II-83** (499 mg, 1.25 mmol) and K_2CO_3 (172.2 mg, 1.25 mmol) were heated to reflux in dry xylene (12,5 mL, 0.1 M) for 60 h. The solution was cooled to rt and filtered. The filtrate was concentrated and the residue was purified by flash chromatography (Cyclohexane/EtOAc = 9/1) to obtain the product (256.7 mg, 0.641 mmol, 51%, 58% brsm) as a white solid.

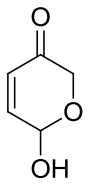
Rf = 0.46 (Cyclohexane/EtOAc = 4/1) [CAM]

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 6.93 (d, *J* = 8.0 Hz, 1H), 6.62 (dt, *J* = 4.0, 2.1 Hz, 1H), 4.89 (d, *J* = 4.1 Hz, 1H), 4.81 (tdd, *J* = 6.2, 4.3, 2.5 Hz, 1H), 4.19 (ddd, *J* = 17.0, 3.6, 2.1 Hz, 1H), 4.04 (ddd, *J* = 16.7, 3.6, 2.6 Hz, 1H), 3.50 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 161.7, 138.9, 99.5, 96.9, 91.8, 62.2, 56.4, 53.2.

IR (neat) cm^{-1}: 3329, 2959, 2933, 2853, 2839, 1712, 1522, 1382, 1299, 1093, 1047, 836, 816, 721, 674, 602, 561.

6-hydroxy-2H-pyran-3(6H)-one (II-86)



$C_5H_6O_3$
114,10

At 0°C, *m*-CPBA (26.9 g, 112.1 mmol) was added portionwise to a solution of furfuryl alcohol (10 g, 101.9 mmol) in dry CH_2Cl_2 (204 mL, 0.5 M). The reaction mixture was allowed to warm to room temperature and was stirred for 4 h. The precipitate was filtered at -10°C, the filtrate was concentrated to 1/3 of its volume and cooled to -10°C, the formed solid was filtered. Finally, hexane was added to the filtrate to give the product as a white precipitate (9.11 g, 79.8 mmol, 78%).

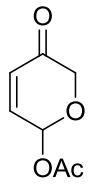
Rf = 0.08 (Cyclohexane/EtOAc = 4/1) [CAM]

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] 6.95 (dd, *J* = 10.4, 3.1 Hz, 1H), 6.17 (d, *J* = 10.4 Hz, 1H), 5.65 (dd, *J* = 3.0, 0.6 Hz, 1H), 4.58 (d, *J* = 16.8 Hz, 1H), 4.14 (d, *J* = 16.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 195.0, 146.2, 127.9, 88.3, 66.7.

The analytical data are identical to the literature data.[80]

5-oxo-5,6-dihydro-2H-pyran-2-yl acetate (II-87)



$C_7H_8O_4$
156,14

At 0°C, pyridine (3 mL, 37.2 mmol) was added to **II-86** (3 g, 26.3 mmol) in acetic anhydride (9 mL, 95.4 mmol). The reaction mixture was stirred at 0°C. After 3 h, it was concentrated under reduced pressure and the residue was purified by flash chromatography (Cyclohexane/EtOAc = 4/1) to obtain the product (3.12 g, 20.0 mmol, 76%) as a yellow liquid.

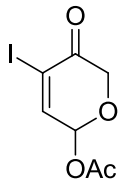
Rf = 0.22 (Cyclohexane/EtOAc = 4/1) [CAM]

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] 6.92 (dd, *J* = 10.4, 3.6 Hz, 1H), 6.49 (d, *J* = 3.6 Hz, 1H), 6.27 (d, *J* = 10.4 Hz, 1H), 4.51 (d, *J* = 17.0 Hz, 1H), 4.22 (d, *J* = 17.0 Hz, 1H), 2.14 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 193.4, 169.6, 142.4, 128.9, 86.8, 67.6, 21.0.

The analytical data are identical to the literature data.[54]

4-iodo-5-oxo-5,6-dihydro-2H-pyran-2-yl acetate (II-88)



$C_7H_7IO_4$
282,03

I_2 (17.9 g, 70.5 mmol) was added portionwise to **II-87** (5 g, 32.0 mmol) in solution in dry CH_2Cl_2 (160 mL, 0.2 M) and dry pyridine (12.9 mL, 160.1 mmol) at 0°C. The reaction mixture was stirred at 0°C for 3 h. Finally, it was quenched with sat. NH_4Cl-solution and sat. $Na_2S_2O_3$-solution and extracted three times with Et_2O. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Cyclohexane/EtOAc = 4/1) to obtain the product (6.57 g, 23.3 mmol, 73%) as a white solid.

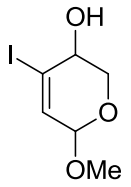
Rf = 0.4 (Cyclohexane/EtOAc = 4/1) [CAM]

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] 7.68 (d, *J* = 3.9 Hz, 1H), 6.36 (d, *J* = 3.9 Hz, 1H), 4.73 (d, *J* = 16.8 Hz, 1H), 4.49 (d, *J* = 16.8 Hz, 1H), 2.18 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 187.1, 169.3, 150.9, 103.9, 88.6, 67.1, 20.9.

IR (neat) cm^{-1}: 3074, 3004, 1749, 1699, 1604, 1368, 1328, 1312, 1209, 1153, 997, 929, 906, 895, 591, 524, 503.

4-iodo-6-methoxy-3,6-dihydro-2H-pyran-3-ol (II-89)



$C_6H_9IO_3$
256,04

At -78°C, cerium (III) chloride heptahydrate (687.0 mg, 1.84 mmol) and $NaBH_4$ (69.8 mg, 1.84 mmol) were added to α-iodoketon **II-88** (400 mg, 1.42 mmol) dissolved in dry methanol (2.36 mL, 0.6 M). The reaction mixture was then allowed to warm to rt and was stirred for 10 min. Finally, it was quenched with water and extracted three times with EtOAc. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Cyclohexane/EtOAc = 4/1) to obtain two diastereoisomers as a white solid, **II-89a** (186.7 mg, 0.729 mmol, 51%) and **II-89b** (38.2 mg, 0.149 mmol, 11%).

***Trans*-diastereoisomer (major) (II-89a)**

Rf = 0.19 (Cyclohexane/EtOAc = 4/1) [CAM]

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] 6.51 (d, *J* = 3.3 Hz, 1H), 4.76 (d, *J* = 3.3 Hz, 1H), 4.19 (dd, *J* = 12.2, 2.7 Hz, 1H), 3.93 – 3.89 (m, 1H), 3.87 (dd, *J* = 12.2, 1.4 Hz, 1H), 3.41 (s, 3H), 2.19 (d, *J* = 8.6 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 137.7, 102.2, 96.3, 70.9, 64.2, 55.8.

MS (EI) *m/z* (%): 238.9 (68) [M^+-H_3O], 224.9 (72) [M^+-MeO], 129.0 (90) [M^+-I], 97 (100) [M^+-I-MeOH].

IR (neat) cm^{-1}: 3427, 2977, 2965, 2935, 2829, 1744, 1629, 1346, 1248, 1048, 934, 821, 571.

***Cis*-diastereoisomer (minor) (II-89b)**

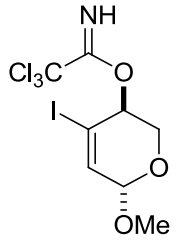
Rf = 0.24 (Cyclohexane/EtOAc = 4/1) [CAM]

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 6.48 (dd, *J* = 2.8, 1.4 Hz, 1H), 4.74 (dd, *J* = 2.7, 1.1 Hz, 1H), 4.21 – 4.12 (m, 1H), 3.89 (qd, *J* = 11.2, 6.7 Hz, 2H), 3.42 (s, 3H), 1.96 (d, *J* = 7.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 137.7, 108.7, 97.4, 68.3, 63.8, 55.9.

MS (EI) *m/z* (%): 238.9 (60) [M^+-H_3O], 224.9 (60) [M^+-MeO], 129.0 (78) [M^+-I], 97 (100) [M^+-I-MeOH].

(±)-4-iodo-6-methoxy-3,6-dihydro-2H-pyran-3-yl 2,2,2-trichloroacetimidate (II-90)



$C_8H_9Cl_3INO_3$
400,43

At 0°C, DBU (213.7 mg, 1.37 mmol), 4Å molecular sieves (cat.) and trichloroacetonitrile (197.4 mg, 1.37 mmol) were added to a solution of **II-89a** (175.1 mg, 0.684 mmol) in dry CH_2Cl_2 (3.4 mL, 0.2 M). The reaction mixture was stirred at 0°C. After 3 h, it was quenched with sat. NH_4Cl-solution and extracted three times with CH_2Cl_2. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Cyclohexane/EtOAc = 9/1) to obtain the product (206.3 mg, 0.515 mmol, 75%).

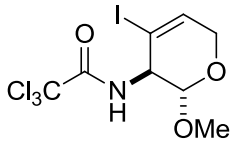
Rf = 0.58 (Cyclohexane/EtOAc = 4/1) [CAM/$KMnO_4$]

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] 8.49 (s, 1H), 6.73 (d, *J* = 3.4 Hz, 1H), 5.30 (d, *J* = 2.3 Hz, 1H), 4.87 (d, *J* = 3.4 Hz, 1H), 4.26 (dd, *J* = 13.2, 2.8 Hz, 1H), 4.06 (dd, *J* = 13.2, 1.0 Hz, 1H), 3.42 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 162.1, 140.8, 100.4, 96.2, 94.0, 75.2, 61.1, 55.9.

MS (EI) *m/z* (%): 254.9 (6) [M^+-$CCl_3C(NH)$], 238.9 (82) [M^+-$CCl_3C(NH)O$], 224.9 (81), 129.0 (84), 96.9 (100).

(±)-2,2,2-trichloro-N-(-4-iodo-2-methoxy-3,6-dihydro-2H-pyran-3-yl)acetamide (II-91)



$C_8H_9Cl_3INO_3$
400,43

Trichloroacetimidate **II-90** (105.3 mg, 0.263 mmol) and K_2CO_3 (7.3 mg, 52.6 µmol) were heated to 170°C in dry *o*-dichlorobenzene (2.6 mL, 0.1 M) for 3h. The solution was cooled to rt and filtered. The filtrate was purified by flash chromatography (Cyclohexane/EtOAc = 9/1) to obtain the product (81.4 mg, 0.203 mmol, 77%) as a white solid.

Rf = 0.42 (Cyclohexane/EtOAc= 4/1) [CAM/$KMnO_4$]

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] 6.69 – 6.66 (m, 2H), 4.77 (d, *J* = 0.9 Hz, 1H), 4.48 – 4.43 (m, 1H), 4.26 (dt, *J* = 16.9, 2.2 Hz, 1H), 4.08 (ddd, *J* = 16.8, 3.8, 0.6 Hz, 1H), 3.48 (s, 3H).

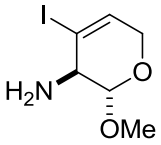
^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 161.8, 140.0, 100.1, 99.5, 86.5, 61.7, 57.0, 56.3.

MS (EI) *m/z* (%): 338.9 (22) [M^+-$MeOCH_2O$], 271.9 (18) [M^+-HI], 237.9 (4) [M^+-$Cl_3C(O)NH_2$], 211.9 (100), 177.9 (47), 176.9 (46), 78.0 (47).

HRMS (ESI) *m/z* 421.8585 [421.8585 calcd. for $C_8H_9Cl_3INNaO_3$ (M^++Na^+)].

IR (neat) cm^{-1}: 3268, 2957, 2935, 2906, 2839, 1694, 1520, 1343, 1308, 1250, 1136, 1100, 818, 654, 590, 547.

(±)-4-iodo-2-methoxy-3,6-dihydro-2H-pyran-3-amine (II-92)



$C_6H_{10}INO_2$
255,05

A 3M NaOH-solution (2.1 mL, 6.24 mmol) was added to **II-91** (500 mg, 1.25 mmol) in MeOH (12.5 mL, 0.1 M), and the solution was heated to reflux. After 24 h, a 1M HCl-solution was added dropwise into the reaction mixture until pH = 1-2, and the mixture was extracted three times with CH_2Cl_2. The aqueous phase was basified with NaOH-solution and extracted with three times Et_2O. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (Petroleum ether/EtOAc 1/1) to obtain the product (144.2 mg, 0.565 mmol, 45%) as oil.

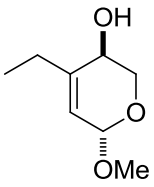
Rf = 0.11 (Cyclohexane/EtOAc= 4/1) [$KMnO_4$]

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 6.39 (dd, *J* = 3.4, 2.3 Hz, 1H), 4.73 (d, *J* = 1.7 Hz, 1H), 4.20 (dt, *J* = 16.5, 2.1 Hz, 1H), 4.02 (ddd, *J* = 16.5, 3.5, 1.0 Hz, 1H), 3.46 (s, 3H), 3.19 (s, 1H), 1.56 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 135.4, 102.5, 98.3, 62.3, 58.4, 56.1.

MS (EI) *m/z* (%): 195.9 (6), 194.9 (100), 126.9 (2), 68.0 (27), 67.0 (6).

(±)-4-ethyl-6-methoxy-3,6-dihydro-2H-pyran-3-ol (II-95)



$C_8H_{14}O_3$
158,20

At rt, Pd(dppf)Cl_2 (6.4 mg, 7.81 µmol) was added to a degassed solution of **II-89a** (20 mg, 78.1 µmol) in dry THF (0.31 mL, 0.25 M) The reaction mixture was cooled to 0°C and Et_2Zn (78.1 µL, 78.1 µmol, 1 M in hexanes) was added dropwise. The reaction mixture was then allowed to warm to rt and was stirred for 16 h. Finally, it was quenched with sat. NH_4Cl-solution and extracted three times with Et_2O. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Cyclohexane/EtOAc = 4/1) to obtain the product (7.5 mg, 47.4 µmol, 61%).

Rf = 0.15 (Petroleum ether/EtOAc = 4/1) [$KMnO_4$]

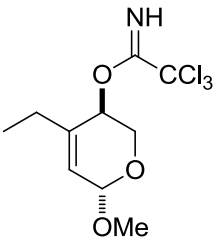
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 5.53 (dt, *J* = 3.2, 1.7 Hz, 1H), 4.85 (dt, *J* = 2.7, 1.2 Hz, 1H), 4.03 (dd, *J* = 12.2, 2.1 Hz, 1H), 3.79 (dd, *J* = 12.1, 1.2 Hz, 1H), 3.64 (d, *J* = 9.7 Hz, 1H), 3.43 (s, 3H), 2.36 – 2.23 (m, 1H), 2.21 – 2.10 (m, 1H), 1.84 (d, *J* = 10.2 Hz, 1H), 1.08 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 143.4, 120.7, 95.2, 64.9, 64.5, 55.7, 26.7, 11.6.

MS (EI) *m/z* (%): 157.1 (6) [M^+-H], 141.1 (71) [M^+-OH], 128.1 (66), 127.1 (100) [M^+-MeO], 97.1 (44) [M^+-$MeOCH_2O$], 81.1 (50), 69.1 (45).

HRMS (APCI) *m/z* 157.0861 [157.0859 calcd. for $C_8H_{13}O_3$ $(M-H)^+$].

(±)-4-ethyl-6-methoxy-3,6-dihydro-2H-pyran-3-yl 2,2,2-trichloroacetimidate (II-96)



$C_{10}H_{14}Cl_3NO_3$
302,58

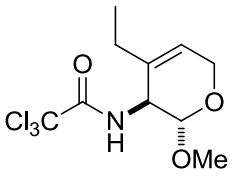
At 0°C, DBU (6.1 mg, 40.3 µmol) and trichloroacetonitrile (64.0 mg, 443.8 µmol) were added to a solution of **II-95** (63.8 mg, 403.3 µmol) in dry CH_2Cl_2 (1.6 mL, 0.25 M). The reaction mixture was stirred at 0°C. After 1 h, it was quenched with H_2O and extracted three times with CH_2Cl_2. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Cyclohexane/EtOAc = 9/1) to obtain the product (77.6 mg, 256.5 µmol, 64%).

Rf = 0.59 (Cyclohexane/EtOAc = 4/1) [$KMnO_4$]

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 8.39 (s, 1H), 5.79 (dt, *J* = 3.2, 1.6 Hz, 1H), 5.12 (d, *J* = 2.3 Hz, 1H), 4.98 – 4.95 (m, 1H), 4.12 (dd, *J* = 13.3, 2.7 Hz, 1H), 4.03 (dd, *J* = 13.3, 1.0 Hz, 1H), 3.44 (s, 3H), 2.29 – 2.08 (m, 2H), 1.09 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 162.7, 138.6, 124.1, 95.1, 91.6, 70.7, 60.5, 55.8, 26.6, 11.4.

(±)-2,2,2-trichloro-N-(4-ethyl-2-methoxy-3,6-dihydro-2H-pyran-3-yl)acetamide (II-97)



$C_{10}H_{14}Cl_3NO_3$
302,58

Trichloroacetimidate **II-96** (20 mg, 66.1 µmol) and K_2CO_3 (1.8 mg, 13.2 µmol) were heated to 170°C in dry *o*-dichlorobenzene (0.70 mL, 0.1 M) for 5 h. The solution was cooled to rt and filtered. The filtrate was purified by flash chromatography (Cyclohexane/EtOAc = 9/1) to obtain the product (17.4 mg, 57.5 µmol, 87%).

Rf = 0.40 (Cyclohexane/EtOAc= 4/1) [$KMnO_4$]

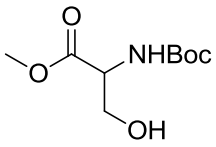
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 6.58 (d, *J* = 7.6 Hz, 1H), 5.69 (dd, *J* = 3.3, 1.6 Hz, 1H), 4.72 (s, 1H), 4.25 – 4.08 (m, 3H), 3.48 (s, 3H), 2.14 – 2.01 (m, 2H), 1.07 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 161.9, 133.4, 122.5, 100.2, 99.3, 59.4, 56.2, 50.0, 27.1, 11.6.

HRMS (ESI) *m/z* 323.9929 [323.9931 calcd. for $C_{10}H_{14}Cl_3NNaO_3$ (M^++Na^+)].

4) Enyne metathesis strategy (Strategy C)

methyl 2-((tert-butoxycarbonyl)amino)-3-hydroxypropanoate (II-112)



$C_9H_{17}NO_5$
219,23

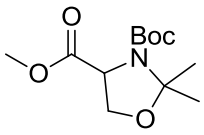
At 0°C, K_2CO_3 (1.48 g, 10.7 mmol) and methyl iodide (2.77 g, 19.5 mmol) were added to Boc-serine (2.0 g, 9.75 mmol) in dry DMF (16.0 mL, 0.6 M). The reaction mixture was stirred at rt. After 18 h, it was concentrated, quenched with H_2O and extracted three times with EtOAc. The combined organic phase was washed with H_2O and with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product (1.78 g, 8.11 mmol, 83%) was used for the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 5.43 (br s, 1H), 4.38 (br s, 1H), 3.93 (qd, *J* = 11.2, 4.1 Hz, 2H), 3.79 (s, 3H), 2.29 (br s, 1H), 1.45 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] 171.4, 162.7, 80.4, 63.7, 55.9, 52.8, 28.4.

The analytical data are identical to the literature data.[81]

3-tert-butyl 4-methyl 2,2-dimethyloxazolidine-3,4-dicarboxylate (II-113)



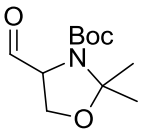
$C_{12}H_{21}NO_5$
259,30

A solution of *O*-methyl-*N*-Boc serine **II-112** (1.74 g, 8.48 mmol), 2,2-dimethoxypropane (2.21 g, 21.2 mmol) and PTSA (32.3 mg, 0.170 mmol) in dry benzene (14.1 mL, 0.6 M) was heated to reflux. After 2h, the reaction mixture was allowed to cool to rt then it was quenched with sat. $NaHCO_3$-solution and extracted three times with EtOAc. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product (1.77 g, 6.82 mmol, 81%) was used for the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 4.49 (dd, *J* = 6.7, 2.6 Hz, 0.4H), 4.38 (dd, *J* = 7.0, 3.1 Hz, 0.6H), 4.14 (td, *J* = 9.0, 7.0 Hz, 1H), 4.04 (td, *J* = 9.4, 2.9 Hz, 1H), 3.76 (s, 3H), 1.67 (s, 1.7H), 1.64 (s, 1.3H), 1.57 (s, 1H), 1.54 (s, 2H), 1.50 (s, 4H), 1.41 (s, 5H).

The analytical data are identical to the literature data.[81]

***tert*-butyl 4-formyl-2,2-dimethyloxazolidine-3-carboxylate (II-114)**



$C_{11}H_{19}NO_4$
229,27

At -78°C, DIBAl-(*H*) (5.46 mL, 6.56 mmol, 1.2 M in toluene) was slowly added to **II-113** (1 g, 3.86 mmol) in dry toluene (7.7 mL, 0.5 M). The reaction mixture was stirred at -78°C for 3 h. Then MeOH (1.5 mL) was added, after 15 minutes the suspension was poured in a 1M HCl-

solution and extracted three times with EtOAc. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Cyclohexane/EtOAc = 4/1) to obtain the product (657.3 mg, 2.87 mmol, 74%) as a rotameric mixture.

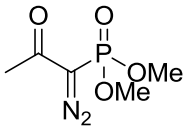
Rf = 0.31 (Cyclohexane/EtOAc = 4/1) [$KMnO_4$]

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 9.61 (br s, 0.4H), 9.55 (d, *J* = 2.1 Hz, 0.6H), 4.33 (br s, 0.4H), 4.19 (br s, 0.6H), 4.14 – 4.02 (m, 2H), 1.68 – 1.40 (m, 15H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 199.6, 160.8, 95.2, 81.3, 64.9, 64.1, 28.4, (26.9, 26.0), (24.9, 24.0).

The analytical data are identical to the literature data.[81]

dimethyl (1-diazo-2-oxopropyl)phosphonate (II-115)



$C_5H_9N_2O_4P$
192,11

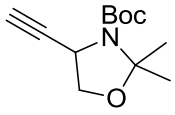
At 0°C, the solution of dimethyl (2-oxopropyl)phosphonate (3.0 g, 18.1 mmol) in benzene (14 mL, 1.3 M) was slowly added to the suspension of NaH (455.1 mg, 19.0 mmol) in benzene (63 mL, 0.3 M) and THF (11.1 mL, 1.7 M), the reaction mixture was stirred for 1 h, before tosyl azide (3.9 g, 19.9 mmol, 1.4 M in benzene) was added. After stirring at rt for 15 h; the suspension was filtered through celite and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (Cyclohexane/EtOAc 2/3) to obtain the product (2.38 g, 12.3 mmol, 69%).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 3.85 (s, 3H), 3.82 (s, 3H), 2.26 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 190.1, 189.9, 53.7, 53.7, 27.3.

The analytical data are identical to the literature data.[82]

***tert*-butyl 4-ethynyl-2,2-dimethyloxazolidine-3-carboxylate (II-116)**



$C_{12}H_{19}NO_3$
225,28

At 0°C, K_2CO_3 (2.17 g, 15.7 mmol) was added to a solution of **II-114** (1.8 g, 7.85 mmol) and dimethyl (1-diazo-2-oxopropyl)phosphonate **II-115** (2.26 g, 11.8 mmol) in dry MeOH (26 mL, 0.3 M). After 1 h at 0°C, the reaction mixture was stirred at rt for 20 h. It was quenched with sat. NH_4Cl-solution, MeOH was evaporated and the residue was extracted three times with EtOAc. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (Cyclohexane/EtOAc 95/5) to obtain the product (1.03 g, 4.58 mmol, 58%) as a rotameric mixture.

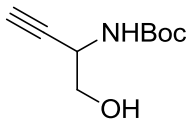
Rf = 0.52 (Cyclohexane/EtOAc= 4/1) [$KMnO_4$]

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 4.61 (br s, 0.5H), 4.49 (br s, 0.5H), 4.08 – 3.99 (m, 2H), 2.26 (s, 1H), 1.63 (s, 3H), 1.49 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 160.8, 94.6, 81.1, 80.6, 70.3, 68.9, 48.5, 28.6.

The analytical data are identical to the literature data.[67]

***tert*-butyl (1-hydroxybut-3-yn-2-yl)carbamate (II-117)**



$C_9H_{15}NO_3$
185,22

At 0°C, **II-116** (1.03 g, 4.56 mmol) in MeOH (4 mL, 1.1 M) was added to TFA (41 mL, 0.1 M), the reaction mixture was stirred at room temperature for 1 h. Et_2O was added and the solution was concentrated under reduced pressure, this operation was repeated three times, before dioxane (23 mL, 0.2 M) was introduced and sat. $NaHCO_3$-solution was added until pH = 7-8. The solution was cooled to 0°C, then Na_2CO_3 (1.21 g, 11.4 mmol) and Boc anhydride (2.49 g, 11.4 mmol) were added. After 1 h at 0°C and 1 h at room temperature, the reaction mixture was filtered and the filtrate was extracted three times with EtOAc. The combined organic phase was washed with sat. NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Cyclohexane/EtOAc = 7/3 → 6/4) to obtain the product (592 mg, 3.19 mmol, 70%) as a white solid.

Rf = 0.38 (Cyclohexane/EtOAc = 1/1) [$KMnO_4$]

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 5.01 (br s, 1H), 4.53 (br s, 1H), 3.77 – 3.69 (m, 2H), 2.33 (d, *J* = 2.4 Hz, 1H), 1.46 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 146.9, 85.3, 80.6, 72.7, 65.8, 45.4, 28.5.

The analytical data are identical to the literature data.[67]

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Abbreviations

Ac	Acetyl
Ac_2O	Acetic anhydride
Aq.	Aqueous
Ar	Aryl
b. p.	Boiling point
Bn	Benzyl
Boc_2O	Di-*t*butyl dicarbonate
n-BuLi	*n*-Butyllithium
brsm	Based on recovering starting material
Bu	Butyl
Bz	Benzoyl
calcd.	Calculated
CAM	Cerium ammonium molybdate
Cat.	Catalyst, catalytic
COD	1,5-cyclooctadiene
Conc.	Concentrated
COSY	Correlated spectroscopy
m-CPBA	*meta*-Chloroperoxybenzoic acid
δ	Chemical shift
D	Doublet (NMR)
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCE	Dichloroethane
DIBAL(*H*)	Diisobutylaluminium hydride
DIPEA	Diisopropylamine
DHP	2,3-Dihydropyran
DMAP	4-Dimethylaminopyridine
DMF	*N,N'*-dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone

DMSO	Dimethyl sulfoxide
Dppf	1,1'-Bis(diphenylphosphino)ferrocene
d.r.	Diastereomeric ratio
EI	Electron ionization
Eq	Equation
Equiv.	Equivalent
ESI	Electrospray ionization
Et	Ethyl
EtOAc	Ethyl acetate
Et_2O	Diethyl ether
GC	Gas chromatography
G	Gram
h	Hour(s)
HMBC	Heteronuclear multiple-bond-coherence
HMQC	Heteronuclear multiple-quantum-coherence
HRMS	High resolution mass spectroscopy
Hz	Herz
IBX	2-Iodoxybenzoic acid
Im	Imidazole
*i*Pr	*Iso*-propyl
*i*PrOH	Isopropanol
J	Coupling constant
M	Molar
m	Multiplet
m/z	Ratio mass/charge
Me	Methyl
MeOH	Methanol
mg	Milligram
MHz	Megaherz
Min	Minute(s)
mL	Milliliter

mmol	Millimole
m.p	Melting point
MS	Mass spectroscopy
Mw	Microwave
*n*Bu	*n*Butyl
NIS	*N*-Iodosuccinimide
NMO	*N*-Methylmorpholine-*N*-oxide
*n*Pr	*n*Propyl
Pd/C	Palladium on charcoal
Pent	Pentyl
Ph	Phenyl
PhH	Benzene
Ppm	parts-per-million
PPTS	Pyridinium *p*-toluenesulfonate
PTSA	*para*-Toluenesulfonic acid
Py	Pyridine
$Py.SO_3$	Sulfur trioxide pyridine complex
Q	quadruplet
Quant.	Quantitative
RCM	Ring closing metathesis
Rf	Retention factor
Rfl	Reflux
rt	Room temperature
s	Singlet
Sat.	Saturated
SM	Starting material
t	Triplet
TBSCl	*tert*-Butyldimethylsilyl chloride
*t*Bu	*tert*-Butyl
Temp.	Temperature
TFA	Trifluoroacetic acid

THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin layer chromatography
Tol	Toluene
TPAP	Tetrapropylammonium perruthenate
UV	Ultra violet