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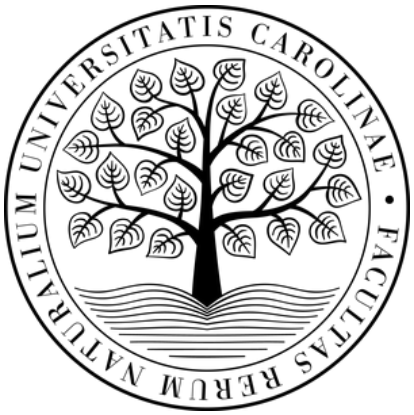

Zuzana Hollá

Synthesis of polycyclic lactones and lactams

Syntéza polycyklických laktonů a laktamů

Bachelor Thesis

Supervisor: PharmDr. Eliška Matoušová, Ph.D.

Prague, 2019

Declaration

I declare that I wrote my bachelor thesis by myself and that all sources used are listed in the bibliography. Neither this work, nor its parts were used to obtain other academic title. I agree that this work may be lent and published.

Prague, 27.5.2019 Zuzana Hollá

Acknowledgment

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Abstract

This bachelor thesis is focused on the synthesis of polycyclic lactones and lactams bearing all-carbon quaternary centres. Such quaternary centres can be found in numerous natural products, some of them having interesting biological activities. The two key steps of the synthesis were palladium-catalysed tandem cyclisation/Suzuki cross-coupling and halocarbocyclisation.

The first part of this thesis deals with the synthesis of ester starting materials and their use in the tandem reaction and halocyclisation. The preparation of a starting compound with an exocyclic ester group is described in the second part. The last part is focused on the synthesis of amide derivatives.

Keywords: synthesis, polycyclic compounds, lactones, lactams, all-carbon quaternary centres

Abstrakt

Tato bakalářská práce je zaměřena na syntézu polycyklických laktonů a laktamů obsahujících kvarterní uhlíková centra. Podobná kvarterní centra se nacházejí ve struktuře mnohých přírodních látek, z nichž některé vykazují zajímavou biologickou aktivitu. Klíčovými kroky zde popsané syntézy byly palladiem katalyzovaná tandemová cyklizace/Suzukiho coupling a halokarbocyklizace.

První část této práce je zaměřena na syntézu esterových výchozích látek a jejich použití v tandemové reakci a halokarbocyklizaci. Příprava výchozích látek obsahujících exocyklickou esterovou skupinu je popsána v druhé části. Poslední část této práce se věnuje syntéze amidových derivátů.

Klíčová slova: syntéza, polycyklické sloučeniny, laktony, laktamy, kvartérní uhlíková centra

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Abbreviations

Ar	aryl
Ac	acetyl
BDSB	bromodiethylsulfoniumromopentachloroantimonate
Bn	benzyl
CDSC	chlorodiethylsulfonium hexachloroantimonate
CuTC	copper(I)-thiophene-2-carboxylate
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
EDG	electron-donating group
Et	ethyl
EWG	electron-withdrawing group
eq.	equivalent
IDSI	bis(diethyliododulfonium) chlorideexachloroantimonate
IR	infrared spectroscopy
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
Me	methyl
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
Ph	phenyl
PIFA	phenyliodine bis(trifluoroacetate)

SEM	2-(trimethylsilyl)ethoxymethyl
TBAI	tetrabutylammonium bromide
TBCO	2,4,4,6-tetrabromocyclohexa-2,5-dienone
Tf	trifluoromethanesulfonate
THF	tetrahydrofuran
Ts	*p*-toluenesulfonyl
XPhos	2-dicyclohexylphosphino-2′,4′,6′- triisopropylbiphenyl

1. Introduction

One of the many challenges in organic chemistry is the elucidation of chemical structure and synthesis of natural products which are formed by living organisms. Among these compounds those having interesting biological activities have been particularly popular synthetic targets.[1] Many natural products, including those with significant biological properties, contain one or more all-carbon quaternary centres, which can be described as carbon atom bonded to four distinct carbon substituents.[2] It has been an ongoing goal of organic chemists to develop suitable methods for the synthesis of such compounds, however, it is a rather difficult task, because the creation of quaternary centres is complicated by a steric repulsion between their carbon substituents.[3, 4] Therefore, it is still beneficial to investigate new efficient methods for their synthesis.

1.1 Natural products containing all-carbon quaternary centres

As it was mentioned above, there is a lot of natural products which contain all-carbon quaternary centres. Several examples of such compounds are depicted in Figure 1. A lactone moiety can be seen in lingzhiol (**2**), which was isolated from a mushroom *Ganoderma lucidum* widely used in Chinese medicine[5] because of its various medical effects, such as antiaging properties, immunoregulation and anticancer effect. It was found to possess potent and selective inhibitory activity towards a transcription protein implicated in chronic kidney disease such as diabetic neprophaty.[6] A lactam moiety, on the other hand, can be seen in aknadilactam (**1**) and plicamine (**3**). Tazettine (**5**) and pretazeetine (**6**) belong to tazettine-type Amaryllidaceae alkaloids. Tazettine (**5**) was found to exhibit mild activity against certain tumor cell lines and pretazetine (**6**) is particularly known for its anticancer activity.[7] The above-mentioned plicamine (**3**) belongs to the same class of Amaryllidaceae alkaloids, the tazettine-type. The main difference between tazettine (**5**) and plicamine (**3**) is the presence of nitrogen atom instead of oxygen atom in the molecule of **3**.[8] It was isolated from a Chinese plant *Z. candida* alongside with other alkaloids and it was found that it exhibited significant inhibitory activities.[9] Galanthamine (**4**) is a compound that contains all-carbon quaternary centre and belongs to Amaryllidaceae family. It is used as a drug against Alzheimer's disease.[9]

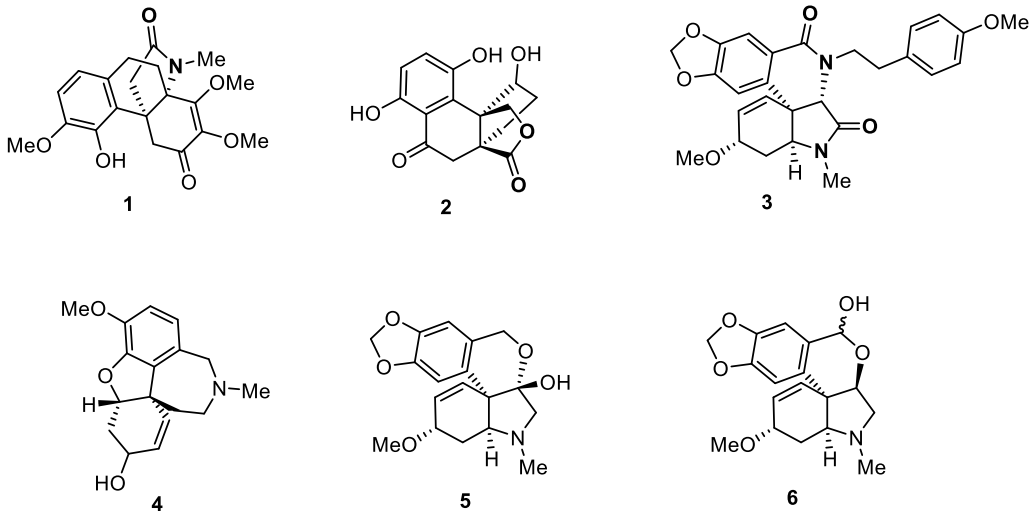


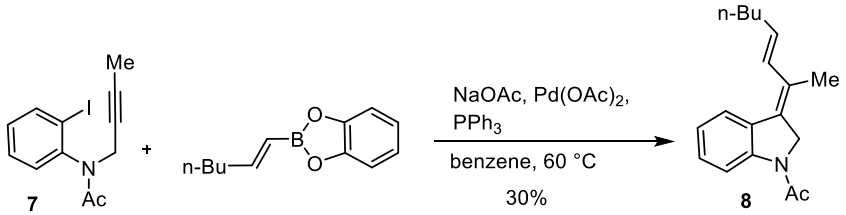
Figure 1: Examples of natural products containing all-carbon quaternary centres

1.2 Tandem cyclisation/Suzuki cross-coupling reactions

A tandem reaction, sometimes also called domino or cascade reaction, is a process in which two or more consecutive reactions are involved in a single synthetic operation. The subsequent reaction in this process is a result of the previous step – either fragmentation or formation of a bond. The product formed during the first transformation is not isolated.[10]

One of the two key reactions used in this project is a tandem cyclisation/Suzuki cross-coupling reaction. It is a combination of cyclic carbopalladation of a triple bond and subsequent Suzuki cross-coupling reaction with a boronic acid. This reaction is catalysed with palladium(0).[11]

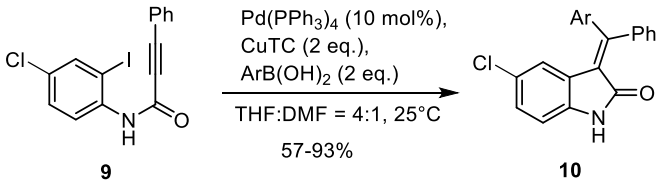
In 1989, the first example of a cyclic carbopalladation and subsequent Suzuki cross-coupling reaction was published by Grigg.[12] He carried out this reaction by reacting aryl iodide **7** with alkenyl borane as a transfer reagent in order to obtain product **8** (Scheme 1).



Scheme 1: Grigg's cyclic carbopalladation and subsequent Suzuki cross-coupling

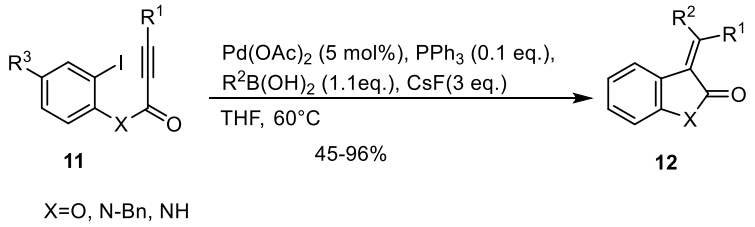
Since my work is focused on the synthesis of polycyclic lactones and lactams, the following text is dealing with tandem cyclisation/Suzuki cross-coupling reactions of ester an amide substrates.

The discussed tandem reaction was used in the synthesis of 3-(diarylidenyl)indolinones **10** reported by Cheung and his group.[13] After optimisation of the reaction conditions they developed a highly yielding process that proceeds at ambient temperature using a copper(I) catalyst (Scheme 2). A variety of nitrogen-containing heteroaryl boronic acids were used, since the presence of such heterocycles is a common feature of biologically important compounds.



Scheme 2: Synthesis of 3-(diarylidenyl)indolinones

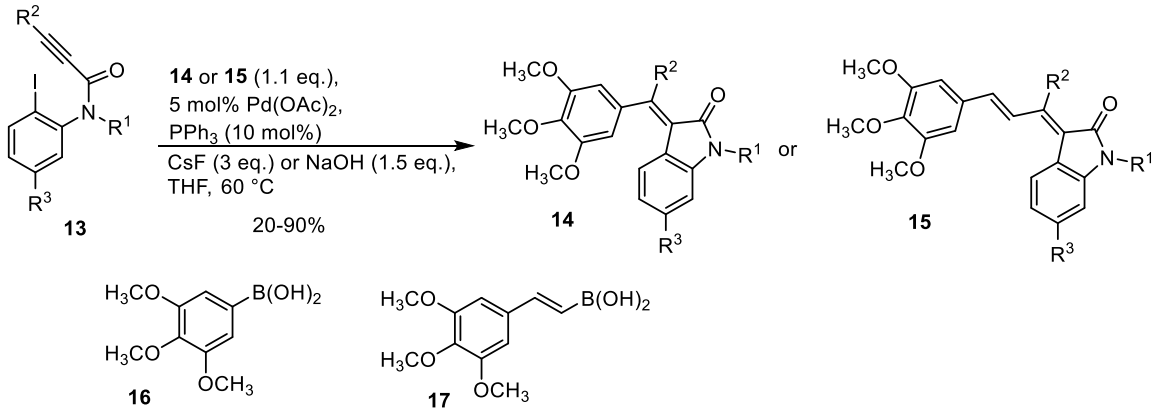
Yanada and his group performed tandem cyclisation/Suzuki cross-coupling reaction with alkyneamides and alkynesters in order to obtain disubstituted 3-alkylideneoxindoles **12** and 3-alkylidenebenzofuran-2-ones **12** (Scheme 3).[14] For most performed reactions the yields were high except for the case when aliphatic boronic acid (butyl boronic acid) was used, then the yield was only 45%. However that is a common observation in the Suzuki–Miyaura reactions.



Scheme 3: Tandem cyclisation/Suzuki cross-coupling reaction of alkyneamides and alkynesters

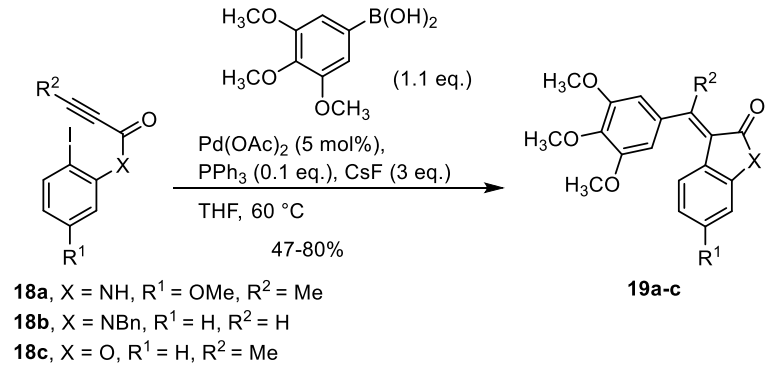
In 2007 Arthuis and his group reported the palladium-catalysed tandem reaction of *N*-alkynamides **13** (Scheme 4).[15] It was found that using a bulkier substituent on the amido group such as SEM or benzyl led to a more efficient carbopalladation step. In these reactions, two different bases were tried out – CsF and NaOH and after series of reactions CsF was confirmed to be a more suitable one out of the two. At first, there

were unsuccessful attempts to perform this reaction with *N*-free alkynamides however it was later observed that the reaction proceeds with internal alkynes.



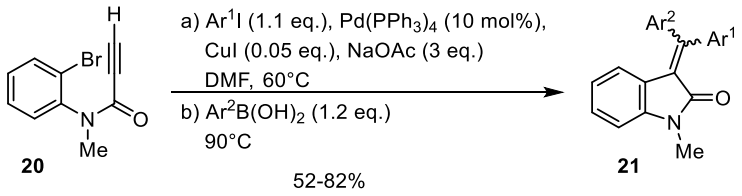
Scheme 4: Arthuis' approach to the palladium catalysed tandem reaction of N-alkynamides

Four years later the same research group came out with another publication, in which the scope of the reaction was extended to alkynesters as well (Scheme 5).[16]



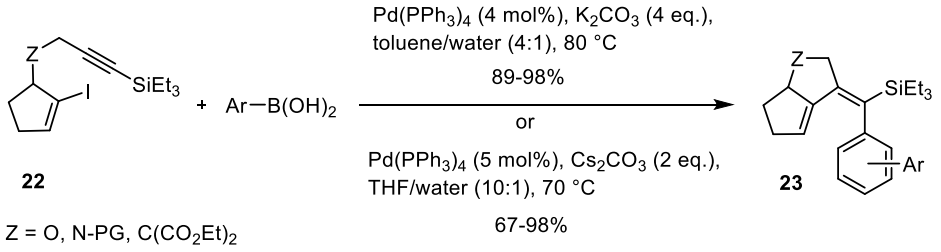
Scheme 5: Suzuki coupling reaction performed on alkkyneamides and alkynesters

Another example of lactam synthesis using palladium catalysed one-pot tandem cyclisation/Suzuki cross-coupling reaction was reported by Dong in 2013 (Scheme 6).[17] In this case bromide **20** was used as a starting material instead of iodide to ensure good selectivity (because bromide was expected to have lower reactivity towards palladium catalyst) between starting bromide and the added aryl iodide (Ar^1I). Synthesis of both symmetrically (Ar^1I = Ar^2I) and unsymmetrically substituted 3-(diarylmethylene)oxindoles **21** was performed.



Scheme 6: One-pot synthesis of unsymmetrically substituted 3-(diarylmethylene)oxindoles

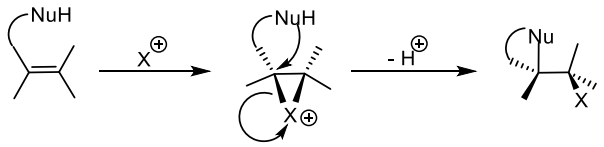
In our group we used the tandem cyclisation/Suzuki cross-coupling reaction as one of the key steps in the synthesis of polycyclic compounds with all-carbon quaternary centres (Scheme 7).[18] All the products **23** were obtained with high yields and considerably good *Z*:*E* ratios, which were generally better for nitrogen-containing products than for oxygen-containing ones. Importantly, the *Z*-isomers of the products, which only can undergo the following halocarbocyclisation reaction, were always formed in majority. As for these reported reactions triethylsilyl-protected alkynes were used as starting materials **22** and they were reacted with boronic acid, which regardless of their electronic properties, gave good yields in all cases. Notably, in this publication, ethers and amines **22** were used as starting materials, extending the scope to their amide and ester derivatives is the aim of this Bachelor thesis.



Scheme 7: Our group's use of the tandem cyclisation/Suzuki cross-coupling reaction

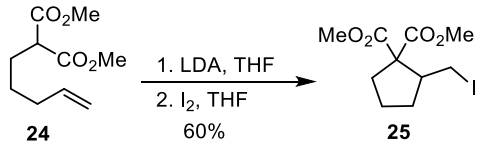
1.3 Halocarbocyclisation reactions

Halocarbocyclisation offers an access to variety of different cyclised products, including bioactive natural products as well. This process can be briefly described as electrophilic attack of double bond by the given halogenating reagent $\mathbf{X}^+$ (most of these reactions use either Br^+ or I^+) which leads to creation of cation intermediate. This intermediate is then approached by a carbon nucleophile $\mathbf{Nu}^-$ (in an intramolecular fashion) in order to form the desired C–C bond in a new cyclised product (Scheme 8).[19]



Scheme 8: Halocarbocyclisation reaction

One of the first halogen-induced cyclisation was published by Curran and Chang in 1989.[20] In this paper malonate was used as a nucleophile. This discovery was actually serendipitous since the anticipated reaction was α-iodination of dimethyl-4-pentenylmalonate **24** using LDA and I_2. However a cyclic product **25** was formed instead in 60% yield (Scheme 9).

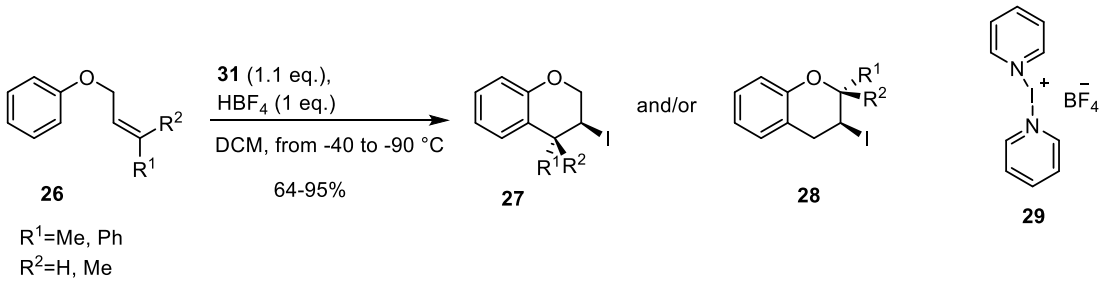


Scheme 9: Halocarbocyclisation reported by Curran and Chang

More examples of halocyclisations in general, and also halocarbocyclisation reactions with different carbon nucleophiles were extensively described in a review by Snyder. [19]

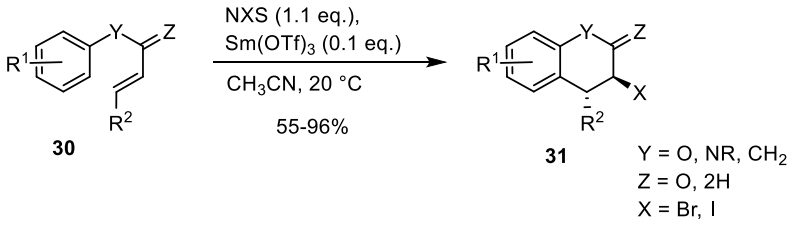
Aromatic ring as a nucleophile is also widely employed in halocarbocyclisation reactions and was present in substrates used in my work as well, hence the following text deals with different examples of halocarbocyclisation reactions where aromatic ring is present as nucleophile. Reagents capable to affect halocarbocyclisation are for example Barluenga's reagent combination (Scheme 10), as well as NIS or NBS are good enough candidates for these reactions.[19]

Barluenga and his group performed several halocarbocyclisation reactions using IPy_2BF_4 **29** as a source of iodonium ion.[21] A series of reactions using different allyphenyl ethers **26** were conducted in order to obtain chromans **27**. Interestingly, chromans **28** were formed at -90 °C through a selective rearrangement. All these reactions gave good yields of products when performed at low temperatures (Scheme 10).



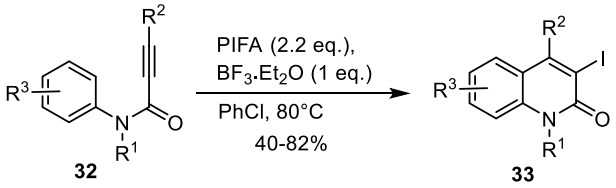
*Scheme 10: Berluenga's approach to synthesis of chroman **27** and/or **28** using IPy_2BF_4 **29***

Another example of an intramolecular haloarylation of alkenes **30** was performed using *N*-halosuccinimide (NXS) as a source of halogen while the reaction was catalysed by Lewis acid.[22] In order to find an effective method, a wide variety of Lewis acids were tried. Treating the substrate **30** with NXS and $Sm(OTf)_3$ proved to be the most suitable option to form the desired cyclised product **31** (Scheme 11).



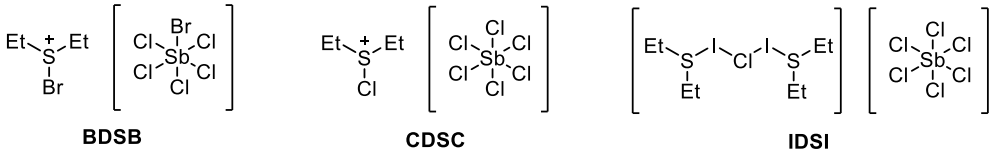
Scheme 11: Halocarbocyclisation reaction using NXS and $Sm(OTf)_3$ as Lewis base

In 2016 a new method for iodocyclication was published.[23] In this case PIFA, which contains iodine (III), was used as an iodination reagent to trigger iodocyclisation of *N*-arylpropynamides (Scheme 12). They found out that R^1 is limited to alkyl groups and as for R^2, aryls with EWG and EDG were submitted to these reaction conditions, and both EWG and EDG were tolerated. Besides aryl, alkyl and heteroaryl groups were also suitable for R^2. Various groups were tolerated for R^3 as well, including strongly EDG and EWG ones.



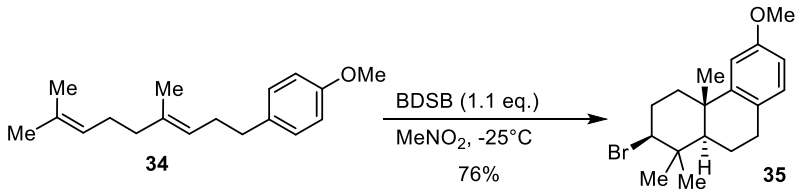
Scheme 12: PIFA-mediated iodocyclisation

In 2010 Snyder introduced three new crystalline solid reagents which are highly suitable to use in halocarbocyclisation in order to obtain wide range of chlorine-, bromine-, and iodine-containing polycycles.[24] Their advantages are high chemoselectivity as well as short reaction times of the given reactions. These reagents are BDSB, CDSI and IDSI (Scheme 13).



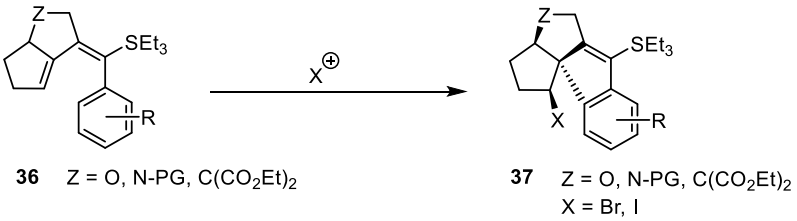
Scheme 13: Snyder's halogenating reagents

Regarding BDSB, it is a very effective reagent for halocarbocyclisation reactions even if electron-deficient alkenes are present. As for the chemoselectivity of the reactions, it is typical for BDSB to react faster with olefins than with aromatic systems, which applies even for electron-rich aromatics (Scheme 14).[24]



Scheme 14: Use of Snyder's BDSB in halocarbocyclisation

In our group halocarbocyclisation reactions were used to form all-carbon quaternary centres and BDSB turned out to be very effective reagent for a wide variety of these reactions (Scheme 15).[18] At first halocarbocyclisation was attempted with NBS, yet the results were unsatisfactory. As for the use of NIS, it gave good yields only for compounds with a methylenedioxy-substituted aromatic ring. Different substrates with both electron-donating and electron-withdrawing groups on the aromatic ring were submitted for halocarbocyclisation. Results showed, that while electron-donating groups were suitable for this reaction, electron-withdrawing group containing substrates did not get involved in halocarbocyclisation. The relative configuration of all products **37** was as drawn in Scheme 15.



36 Z = O, N-PG, $C(CO_2Et)_2$

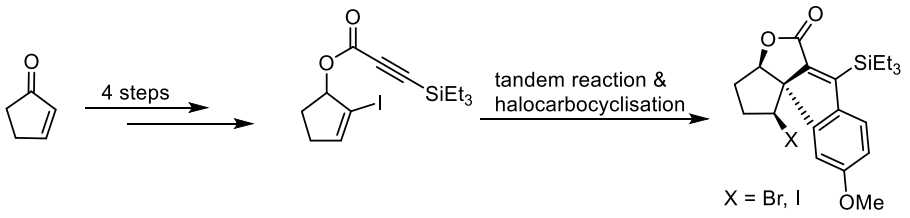
37 Z = O, N-PG, $C(CO_2Et)_2$
X = Br, I

Scheme 15: Our group's approach to halocarbocyclisation

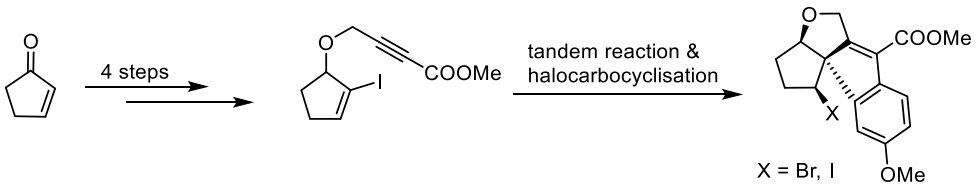
2. Aims of Work

The main aim of this thesis was to prepare compounds bearing all-carbon quaternary centres using tandem cyclisation/Suzuki cross-coupling followed by halocarbocyclisation. This work is a direct extension of a previous research performed in our group, where ether, protected amines and malonate derivatives were used in the key reaction sequence.[18] In this project, the goal was to synthesise three different derivatives containing either ester or amide group:

i) Synthesis of polycyclic lactones: In this part my aim was to prepare silylated alkyne with an ester linkage, which would then serve as a substrate for the key reaction sequence. By comparison of the results with those obtained for ether derivatives,[18] we should see what effect will the addition of extra carbonyl group have on the tandem reaction and halocarbocyclisation reactions.

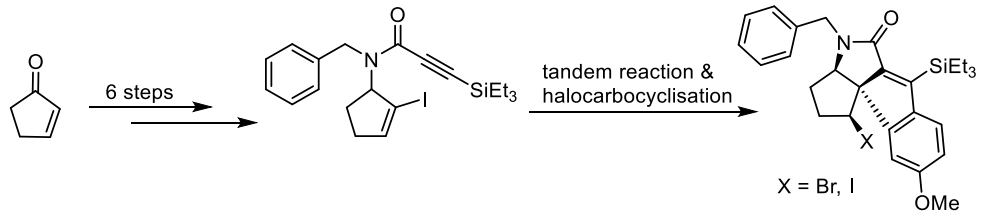


ii) Synthesis of an oxygen-containing polycyclic derivative with exocyclic ester group: In this case the substrate for the key reaction sequence should bear a methoxycarbonyl group instead of the silyl group used in the previous synthesis. It will give us an opportunity to compare the effect of this differently positioned on both yield and *Z*:*E* isomer ratio of the tandem reaction product, which is important in regards to halocarbocyclisation.



iii) Synthesis polycyclic lactams: To synthesise the corresponding alkyne substrate would require a new synthetic approach. The aim of this part was thus to test the feasibility of our synthetic plan, and then to compare the

reactivity of the prepared amide substrate in the tandem reaction and halocarbocyclisation with that of amine and ester derivatives

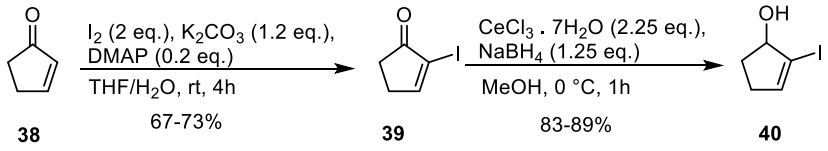


3. Results and Discussion

3.1 Synthesis polycyclic lactones

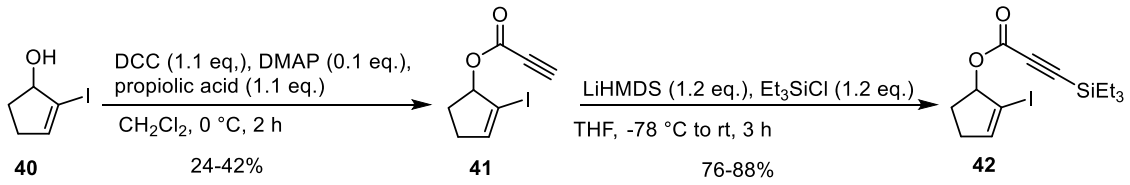
As mentioned above, prior to my work compounds **23** with tetrahydrofuran ring (Scheme 7, Z = O) were prepared in our research group by the tandem cyclisation/Suzuki cross-coupling in good to excellent yields (74–98%). The subsequent halocarbocyclisation of these compounds proceeded in moderate to good yields (32–82%).[18] My task was to prepare ester derivatives of these compounds (**45**, Table 2), i.e. containing a lactone ring in their structure. This method started with a commercially available cyclopent-2-en-1-one **38** which was then converted to iodinated alcohol **40** in two steps. This iodinated alcohol **40** was used as starting material for the following reactions reported by our group, however in my case instead of submitting it to alkylation, it underwent esterification in order to obtain alkyne **41** followed by capping it with $SiEt_3$ to give us a silyltaed starting material **42** for the tandem reaction.

First step of this sequence was iodination of the starting material **38** using a procedure which was published by Krafft with iodine in THF/water and DMAP at room temperature.[25] However, applying the published conditions yielded only 31–34% of product **39**. The yields could be improved to 67–73% by increasing the amount of iodine added into the reaction from 1.5 eq. to 2.0 eq. Afterwards reduction of **39** was performed in order to obtain iodinated alcohol **40** using Luche conditions in yields around 85% (Scheme 16).



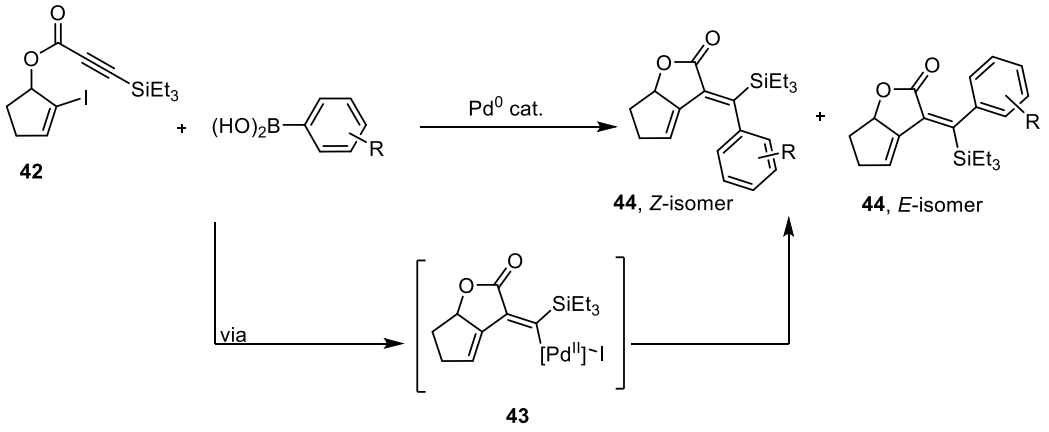
*Scheme 16: Iodinatiom of starting material **38** followed by Luche reduction*

With iodinated alcohol **40** in hand esterification was performed to introduce propiolate into the structure of product **41**. We found out that the product **41** was not stable for too long when stored in a fridge since after one week a TLC experiment showed partial decomposition. Therefore the compound had to be repurified. In order to prepare a starting material **42** for the key tandem cyclisation/Suzuki cross-coupling reaction, compound **41** needed to be capped with silyl group which was done with LiHMDS as a base followed up by adding of Et_3SiCl dropwise (Scheme 17).



*Scheme 17: Preparation of silylated starting material **42** for the tandem reaction*

The prepared silylated compound **44** was subjected to tandem cyclisation/Suzuki cross-coupling. The product of this tandem reaction was always formed as a mixture of two isomers, *Z*- and *E*-isomer, but only the *Z*-isomer can undergo the following halocarbocyclisation and therefore is a desired one. From the previous experiments we reasoned that the formation of the undesired *E*-isomer takes place during the reaction via isomerisation of the intermediate **43** (Scheme 18).



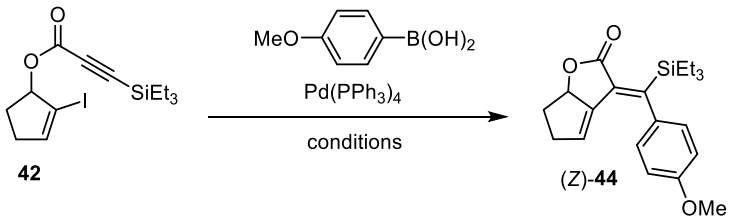
Scheme 18: Tandem cyclisation/Suzuki cross-coupling reaction sequence

For the tandem reaction, we first tested the condition, which were previously optimised in our group for the ether and amine compounds.[18] These were two different sets of conditions, both using Pd(PPh3)4 as a catalyst but differed in base (Cs_2CO_3 or K_2CO_3), solvents (THF or toluene) and temperature (80 °C or 70 °C). In both cases silylated iodoalkyne **42** reacted with *p*-methoxyphenyl boronic acid (1.6 eq.) this was because using this boronic acid gave good results in the previous project.[18]

The obtained results are depicted in Table 1. The first reaction was performed using Cs_2CO_3 in THF/water (10:1) and $Pd(PPh_3)_4$ (5 mol%) as catalyst, which gave us the product **44** in 32% yield. The main isomer which was present was the desired *Z*-isomer (*Z*:*E* = 6:1).

Second reaction conditions used K_2CO_3 (4 eq.) in toluene/water (4:1), the catalyst remained the same but 4 mol% were used. Through this approach the desired product **44** was obtained in 31–54% isolated yield. In entry 2 (Table 1) is listened the best yield out of all the reactions performed under these conditions. In all attempted reactions under these conditions second reaction conditions was the *Z*-isomer formed in majority.

*Table 1: Tandem cyclisation/Suzuki cross-coupling performed on **42***



Entry	Base	Solvent	Reaction conditions	Isolated yield [%]	Isomer ratio (Z:E)
1	Cs_2CO_3	THF/water	70 °C, 3 h	32	6:1
2	K_2CO_3	toluene/water	80 °C, 2 h	54	11:1

With the tandem product **44** in hand, we moved to explore halocarbocyclisation reaction. Four different reaction conditions were attempted, but unfortunately only one of them gave us the desired product (Table 2).

As a first attempt, the starting material **44** was reacted with NIS (1.2 eq.) in CH_3CN, nut and inseparable mixture of several compounds was formed under these conditions. From the NMR analysis of the mixture we assume that the desired cyclised product **45** could have been among the formed compounds, but only in a very low yield.

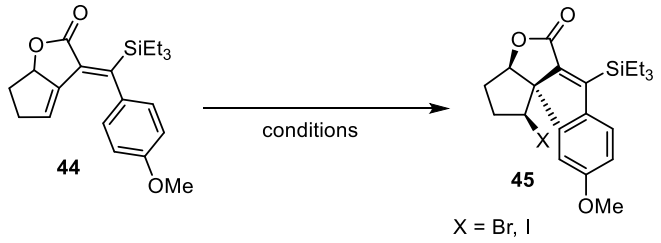
The second reagent we used for halocarbocyclisation was BDSB in CH_3CN. In this reaction the cyclised product **45** was isolated in 14% yield. Initially 1.2 eq. of BDSB was added into the reaction mixture. Then because the TLC analysis showed that the starting material was not fully consumed, additional 0.3 eq. of BDSB were added after two hours. Besides the desired product **45,** an unknown side product was isolated from the reaction mixture, in a bigger amount than compound **45**. At first, we believed that it could be starting material **44** since TLC analysis showed it had the same R_f as **44**. When examining the NMR spectra of this side product, all the signals belonging to starting material were observed but were slightly shifted, with the exception of the signals of the double bond in the 5-membered ring, which were missing. Even though we are not

completely sure about the structure of this side product, we can say that it did not cyclise.

The third reaction conditions used TBCO (1.1 eq.) in DCM. In this reaction two different products were isolated. The first one was the same unknown side product as in the previous reaction, and the second one was still another side product with a different structure. But according to NMR analysis, neither of these compounds was desired product **45**.

In the last reaction pyridinium tribromide (1.2 eq.) was used as a reagent. The only isolated product from this reaction was yet again the unknown side product which was already observed in the previous two reactions.

*Table 2: Halocarbocyclisation of compound **44***



Entry	Reagent	Solvent	Reaction conditions	Isolated yield [%]
1	NIS	CH_3CN	rt, 3 h	–
2	BDSB	CH_3CN	rt, 1 h	14 [a]
3	TBCO	DCM	0 °C to rt, 2 h	– [a]
4	pyridinium trubromide	CH_3CN	rt, 3 h	– [a]

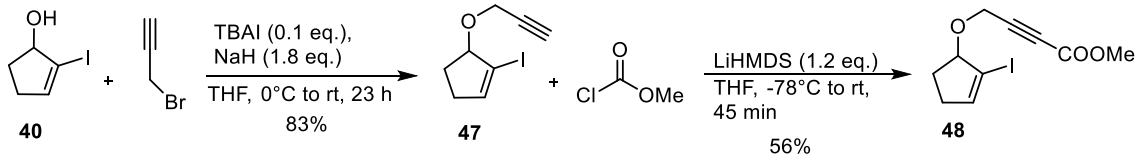
[a] unknown side product was isolated

From these results it can be seen that the tandem reaction proceeded in moderate yields whereas halocarbocyclisation provided the desired product in only one of the four performed experiment, and that in a low yield. When comparing these results with those of ether derivatives performed previously in our group, we can conclude that there is an apparent negative effect of the carbonyl group on this reaction.

3.2 Synthesis of polycyclic compounds with an exocyclic ester group

After completing the synthesis of polycyclic ester derivatives, we moved to the synthesis of oxygen-containing polycyclic compounds with an exocyclic ester group. The tandem reaction with such an ester-containing compound was performed once before in our group and the undesired *E*-isomer appeared to be the only product formed in this reaction. Performing this reaction sequence should also give us an opportunity to compare the results with the ones obtained for ester derivatives to see the effect of the differently positioned carbonyl group on our key reaction sequence.

At the beginning the same method as the one in Scheme 16 was used in order to prepare the iodinated alcohol **40** which was then treated with NaH and propargyl bromide (1.8 eq.) in THF. Thus formed ether **47** the underwent reaction with methyl chloroformate (1.2 eq.) in order to introduce a methoxycarbonyl group (Scheme 19). Product **48** could be then used as the substrate for the tandem reaction.



40 **47** **48**

*Scheme 19: Propargylation of **40** followed by capping of **47** with a methoxycarbonyl group*

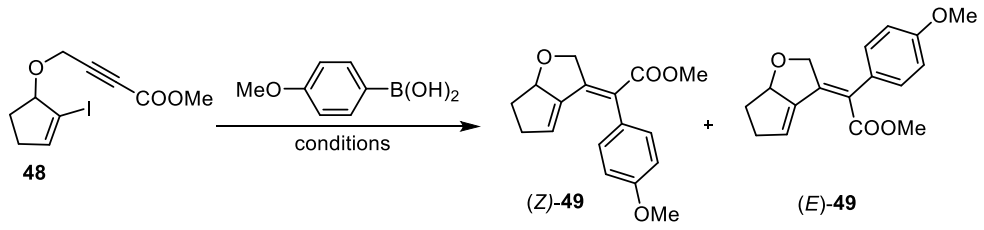
As for the tandem cyclisation/Suzuki cross-coupling reaction of compound **48**, three different reaction conditions were applied (Table 3). For better comparison with previously obtained results, *p*-methoxyphenyl boronic acid (1.6 eq.) was used in all cases.

At first, the same reaction conditions which were already used for ester derivatives were tested. Thus compound **48** was treated with $Pd(PPh_3)_4$ (5 mol%) as a catalyst and Cs_2CO_3 (2 eq.) in THF/water (10:1). The desired product **49** was obtained under these reaction conditions in 11% yield and the isomer ratio was in favour of the undesired *E*-isomer (*Z*:*E* = 4:94) which cannot undergo following halocarbocyclisation.

Second reaction conditions were the same as the ones used previously by our colleague. Compound 49 was treated with K_2CO_3 (4 eq.) in toluene/water (4:1) and $Pd(PPh_3)_4$ (4 mol%) as catalyst. Product **49** was obtained 31% yield as a pure *E*-isomer.

Lastly, we tried to change the ligand for XPhos (0.1 eq.) using $Pd_2(dba)_3$ (5 mol%) as a pre-catalyst and K_2CO_3 (4 eq.) as a base in toluene/water (4:1). Product **49** was obtained in 21% yield, however again the only isolated isomer was the *E*-isomer.

*Table 3: Tandem cyclisation/Suzuki cross-coupling of compound **48***



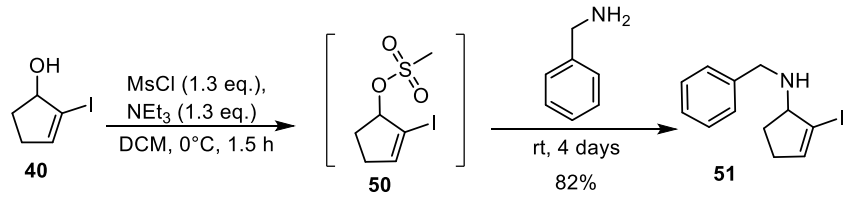
Entry	Catalyst	Base	Solvent	Reaction conditions	Isolated yield [%]	Isomer ratio (*Z*:*E*)
1	$Pd(PPh_3)_4$	Cs_2CO_3	THF/water	70 °C, 3 h	11	4:94
2	$Pd(PPh_3)_4$	K_2CO_3	toluene/water	80 °C, 2h	31	0:1
3	$Pd_2(dba)_3$, Xphos	K_2CO_3	toluene/water	80 °C, 2h	21	0:1

Ending up with *E*-isomer in all three cases, the next halocarbocyclisation step could not be performed. This confirmed the previously made assumption, that only the undesired isomer is created in the tandem reaction where the substrate contains an electron-withdrawing carbonyl group instead of the electron-donating silyl group. The carbonyl group present in the exocyclic ester group had even more negative effect on the tandem reaction than in case of lactone derivatives.

3.3 Synthesis of polycyclic lactams

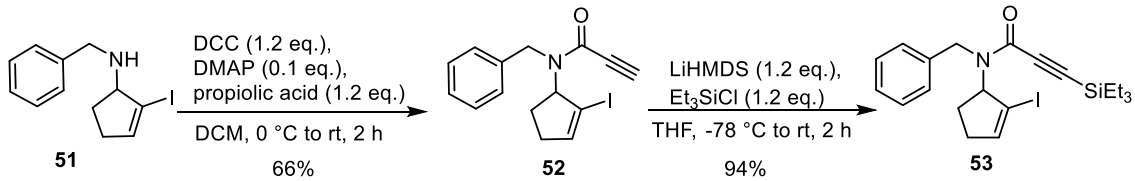
After performing reactions on ester derivatives, we decided to try to synthesise amide derivatives of polycyclic compounds. Reaction on protected amines were already performed in our group where tandem cyclisation/Suzuki cross-coupling proceeded in excellent yields (90–98%) and halocarbocyclisation gave the products in good to excellent yields (59–98%).[18] The synthesis of polycyclic lactams was planned to start from the same starting material, a commercially available cyclopent-2-en-1-one **38**, which can be converted to silylated amide **53** in several steps. These reactions were tried for the first time on this substrate. Compound **55** was then subjected as a substrate for the key reaction sequence.

Iodinated alcohol **40** was reacted with mesyl chloride (1.3 eq.) in DCM. The crude mesylate **50** was used directly after work-up for a nucleophilic substitution with benzylamine. This reaction was solvent-free and it was left to stir for 4 days. The amine **51** was obtained in 82% yield. (Scheme 20).



*Scheme 20: Mesylation of **40** followed by reaction with benzylamine*

In order to synthesise amide **52**, the obtained amine **51** was treated with propiolic acid under previously reported reaction conditions.[26] Specifically propiolic acid (1.2 eq.), DCC (1.2 eq.) and DMAP (0.1 eq.) in CH_2Cl_2 were used and the product **52** was obtained in 66% yield. Characterisation of compound **52** and the following products in this reaction sequence was complicated by the appearance of rotamers in the NMR spectra, all the signals in both ^1H NMR and ^{13}C NMR were doubled. In the next step, alkyne 53 was capped with triethylsilyl group by a treatment with LiHMDS (1.2 eq.) as a base followed by dropwise addition of Et_3SiCl (1.2 eq.). The silylated product **52** was isolated in 94% yield (Scheme 21).



*Scheme 21: Introduction of propiolic acid to **51** followed by silylation of **52***

Silylated compound **53** became a starting material for tandem cyclisation/Suzuki cross-coupling reaction. Three different reaction conditions were applied and in all *p*-methoxyphenyl boronic acid (1.6 eq.) was used (Table 4).

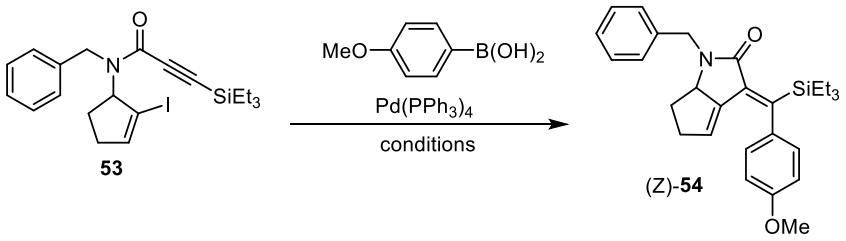
Firstly, we performed the reaction under the conditions that gave us the best yields for ester derivatives K_2CO_3 (4 eq.) in toluene/water (4:1) and $Pd(PPh_3)_4$ (4 mol%) as catalyst. Surprisingly, we could isolate neither the desired product nor starting material. The reaction process was monitored by TLC which after three hours showed only the spot of starting material. The reaction was thus let to stir overnight before another series of TLC experiments was performed. Even after performing TLC analysis in different

mobile phases, we were not able to tell, whether the spot that was observed was starting material **53** or product **54**. However after performing a column chromatography it was to our disappointment that neither product nor starting material were isolated.

Second reaction conditions used Cs_2CO_3 (2.1 eq.) in THF/water (10:1) while $Pd(PPh_3)_4$ (5 mol%) was used as catalyst. In this case the product **54** was in 20% yield and the major isomer present was the desired, *Z*-isomer (*Z*:*E* = 5:1).

Lastly, third reaction conditions were applied, which were the same as the ones used in the previous attempt except for the solvent, which was here swapped for toluene/water (10:1). This procedure turned out to be the most effective out of the three since the product **54** was obtained in 46% yield. The isomer ratio was in favour of *Z*-isomer (*Z*:*E* = 8.5:1).

*Table 4: Tandem cyclisation/Suzuki cross-coupling of **53***



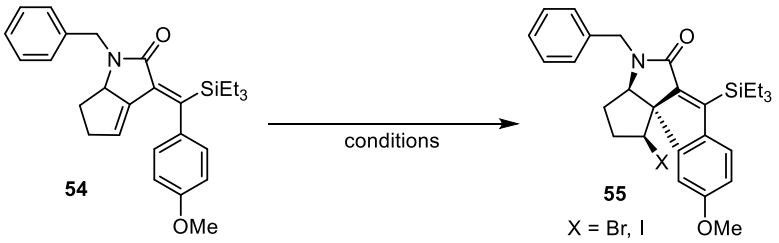
Entry	Base	Solvent	Reaction conditions	Isolated yield [%]	Isomer ratio (*Z*:*E*)
1	K_2CO_3	toluene/water	80 °C, 2h	–	–
2	Cs_2CO_3	THF/water	70 °C, 3 h	20	5:1
3	Cs_2CO_3	toluene/water	70 °C, 3 h	45	8.5:1

The last step in this reaction sequence was halocarbocyclisation of compound **54**, where two different reaction conditions were applied (Table 5).

In the first reaction compound **54** was treated with NIS (1.2 eq.) in CH_3CN. The TLC analysis of the reaction mixture showed a creation of a new spot, however, after performing column chromatography, no product was isolated.

Second reaction conditions used BDSB (1.03 eq.) in CH_3CN. By this procedure the final product **55** which contains an all-carbon quaternary centre was obtained in 36% yield.

*Table 5: Halocarbocyclisation performed on **54***



Entry	Reagent	Solvent	Reaction conditions	Isolated yield [%]
1	NIS	CH_3CN	rt, 2 h	–
2	BDSB	CH_3CN	0 °C to rt, 1 h	36

The above-described results show that both tandem reaction and halocarbocyclisation proceeded in better yields for amide derivatives compared to ester-containing compounds. It could be due to a lower electron-withdrawing effect of the amide carbonyl.

4. Experimental section

4.1 General

All commercially available chemicals which were in the synthesis were purchased and used without further purification. Some reactions required the use of unhydrous solvents which were dried as follows: (DCM) from calcium hydride, tetrahydrofuran (THF) from sodium/benzophenone. Ethyl acetate, hexane and methanol were distilled prior to their use.

Nuclear magnetic resonance spectra ^{1}H and ^{13}C NMR were measured with a Bruker AVANCE III 400 spectrometer in $CDCl_3$ at 298 K. Chemical shifts (δ/ppm) are referenced to a residual $CDCl_3$ signal (^{1}H, δ = 7.26; ^{13}C, δ = 77.16). Multiplicity is defined as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and coupling constants *J* are given in Hz.

Infrared spectra were recorded with Thermo Nicolet AVATAR 370 FT-IR spectrometer on KBr tablets of the compounds via DRIFT method or ATR method and are reported in wave numbers (cm^{-1}) within the mid-infrared (4000 – 400 cm^{-1}) region.

Mass spectra were recorded on LTQ Orbitrap XL (Thermo Fisher Scientific), Shimadzu QP 2010 and VG-Analytical ZAB-SEQ instruments.

The reactions were monitored using analytical thin layer chromatography (TLC) which was performed on Merck Silica gel 60-F254 coated aluminium plates. To visualise eluted plates, UV light (254 nm) was used. These plates were then treated with a suitable dip and subsequent heating. Dips which were used:

a) Anisaldehyde dip: CH_3COOH (99%, 6 ml), anisaldehyde (8 ml), EtOH (400 mL), H_2SO_4 (20 ml)

b) Ceric ammonium molybdate dip: $Ce(SO_4)_2$ (2 g), $H_3PMo_{12}O_{40}$ (4 g), conc. H_2SO_4 (10 ml), 200 ml distilled water

c) $KMnO_4$ dip: $KMnO_4$ (3 g), K_2CO_3 (20 g), 10% NaOH (2.5 ml), 300 ml distilled water

The column chromatography was performed using silica gel 60 A (0.035 – 0.070 mm) purchased from Acros Organics.

4.2 Synthesis of ester derivatives

2-Iodocyclopent-2-en-1-one (39)

Starting cyclopent-2-en-1-one **38** (3.030 g, 36.9 mmol) was added into reaction flask and was then dissolved in THF (90 ml). Afterwards K_2CO_3 (6.121 g, 44.3 mmol), iodine (18.733 g, 73.8 mmol) and distilled water (90 ml) were added. Lastly DMAP (0.902 g, 7.38 mmol) was added to the mixture and the reaction proceeded at room temperature for 4 hours and 15 minutes. The reaction was quenched by addition of a saturated aqueous solution of $Na_2S_2O_3$ (180 ml) into the reaction mixture and this action was followed by extraction into EtOAc. The combined organic layers were dried using Na_2SO_4, filtered and concentrated under reduced pressure. Obtained dark brown oil was then purified by column chromatography on silica gel (80/20 hexane/EtOAc). Via this procedure compound **39** was obtained as yellowish powder (5.273g, 67%). The reaction was repeated several times and the isolated yields were in the range of 67–73%. The recorded spectral data were in agreement with previously reported values.[27]

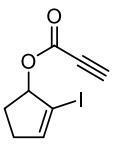
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (t, *J* = 2.9 Hz, 1H), 2.80–2.75 (m, 2H), 2.52–2.48 (m, 2H).

2-Iodocyclopent-2-en-1-ol (40)

Ketone **39** (5.273 g, 25.4 mmol) was transferred to a reaction flask and then dissolved in MeOH (245 ml) followed up by adding $CeCl_3 \cdot 7H_2O$ (21.248 g, 57.0 mmol). The reaction was cooled down to 0 °C in an ice cooling bath, then $NaBH_4$ (1.199 g, 31.7 mmol) was added slowly and the reaction mixture was let to stir for an hour at 0 °C. The reaction was diluted with distilled water (56 ml) and was let to stir for another 10 minutes at room temperature. Afterwards the methanol was evaporated and remaining reaction mixture was extracted into EtOAc. The combined organic layers were dried using $MgSO_4$, filtered and concentrated under reduced pressure. The obtained crude alcohol was used in the next step without purification. Via this procedure compound **40** (4.748 g, 89%) was obtained as a yellowish oil. The reaction was repeated several times and the isolated yields were in the range of 83–89%. The recorded spectral data were in agreement with previously reported values.[28]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (td, *J* = 2.5, 1.0 Hz, 1H), 4.75–4.65 (m, 1H), 2.55–2.43 (m, 1H), 2.39–2.24 (m, 2H), 1.91–1.81 (m, 2H).

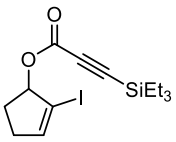
2-Iodocyclopent-2-en-1-yl propiolate (41)



Under an argon atmosphere the alcohol **40** (2.370 g, 11.3 mmol) was added into a reaction flask alongside with DCC (2.561 g; 12.4 mmol) and DMAP (0.138 g; 1.13 mmol) which were dissolved in dry DCM (34 ml). This reaction mixture was then cooled to 0 °C in an ice cooling bath. Then the solution of propiolic acid (0.870 g; 12.4 mmol), in dry DCM (11 ml) was slowly added. The reaction mixture was left to stir for 2 hours 10 minutes at room temperature. The reaction was diluted with ether, filtered celite and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (95/5 hexane/EtOAc). Via this procedure compound **41** (1.123 g, 42%) was obtained as yellow oil. The reaction was repeated several times and the isolated yields were in the range of 24–42%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (td, *J* = 2.5, 0.9 Hz, 1H), 5.81 – 5.76 (m, 1H), 2.92 (s, 1H), 2.59 – 2.50 (m, 1H), 2.48 – 2.32 (m, 2H), 1.99 – 1.91 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.4, 147.2, 90.8, 86.3, 75.3, 74.7, 33.2, 30.0; **IR** (KBr) ν_{max} 3378, 3216, 2929, 2110, 1697, 1242, 1024, 934 cm^{-1}; **MS** molecular peak was not found.

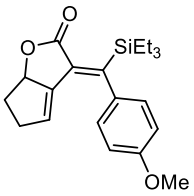
2-Iodocyclopent-2-en-1-yl 3-(triethylsilyl)popiolate (42)



Under an argon atmosphere the ester **41** (0.349 g; 1.33 mmol) was dissolved in dry THF (2 ml) and this solution was cooled to -78 °C in a dry ice/acetone cooling bath. Then LiHMDS (1 M solution in THF; 1.60 mmol) was added dropwise and the resulting mixture was let to stir for an hour. Afterwards Et_3SiCl (0.241 g; 1.60 mmol) was added, and the cooling bath was removed and the reaction mixture was stirred at room temperature for another 90 minures. The reaction was quenched by adding a saturated aqueous solution of NH_4Cl (4 ml) followed up by extraction into EtOAc. The combined organic layers were dried using Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (98/2 hexane/EtOAc). Using this procedure compound **42** (0.440 g, 88%) was obtained as yellow oil. The reaction was repeated several times and the isolated yields were in the range of 76 – 88 %.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (td, *J* = 2.5, 0.9 Hz, 1H), 5.79 – 5.74 (m, 1H), 2.59 – 2.48 (m, 1H), 2.47 – 2.29 (m, 2H), 1.99 – 1.90 (m, 1H), 1.01 (t, *J* = 7.9 Hz, 9H), 0.68 (q, *J* = 7.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.7, 146.9, 95.7, 92.9, 91.3, 85.9, 33.2, 30.0, 7.4, 3.9; **IR** (KBr) ν_{max} 2956, 2178, 1712, 1222, 1024, 737 cm^{-1}; **MS** (EI) *m/z* % 399.2 (100, $[M+Na]^+$), 207.2 (9); **HRMS** (ESI) *m/z* calcd for $C_{14}H_{21}O_2INaSi$ 399.0248, found 399.0247.

(*Z*)-3-((4-Methoxyphenyl)(triethylsilyl)methylene)-3,5,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one (44)

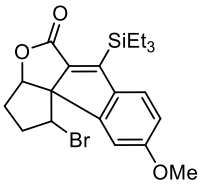


Under an argon atmosphere silylated ester **42** (0.094 g, 0.25 mmol) was added into a reaction flask alongside with *p*-methoxyphenyl boronic acid (0.061 g; 0.40 mmol), Cs_2CO_3 (0.171 g; 0.53 mmol), dry THF (4 ml) and distilled water (0.4 ml). After degassing the reaction (the flask was evacuated and then the atmosphere was switched for argon; this process was repeated thrice), $Pd(PPh_3)_4$ (0.014 g; 0.01 mmol) was added followed up by another degassing. The reaction mixture was heated at 70 °C for 2 hours. Then the reaction was diluted with ether, filtered through celite and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (98/2 hexane/EtOAc). Using this procedure compound **44** was obtained as yellow oil (0.027 g, 32%).

Under an argon atmosphere **42** (0.094 g, 0.25 mmol) was added into a reaction flask alongside with *p*-methoxyphenyl boronic acid (0.061 g; 0.40 mmol), toluene (3 ml) and a 2 M aqueous solution of K_2CO_3 (0.4 ml). After degassing the reaction (the flask was evacuated and then the atmosphere was switched for argon; this process was repeated thrice), $Pd(PPh_3)_4$ (0.012 g; 0.01 mmol) was added into the mixture followed up by another degassing. The reaction mixture was heated at 80 °C for 2 hours. The reaction was diluted with ether and filtrated through celite followed by concentration under reduced pressure. The crude product was purified by column chromatography on silica gel (98/2 hexane/EtOAc). Using this procedure compound **44** (0.094 g, 31%) was obtained as yellow oil. The reaction was repeated several times and the isolated yields were in the range of 31–54%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 – 6.81 (m, 4H), 5.17 – 5.09 (m, 1H), 4.9 (dt, *J* = 3.5, 2.4 Hz, 1H), 3.82 (s, 3H), 2.43 – 2.32 (m, 3H), 1.84 – 1.71 (m, 1H), 0.92 – 0.85 (m, 9H), 0.78 – 0.70 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.8, 159.9, 158.3, 142.8, 136.6, 133. 0, 128.0, 126.8, 113.7, 86.4, 55.4, 33.9, 33.2, 8.0, 3.8; **IR** (KBr) ν_{max} 2956, 1766, 1512, 1242, 1126, 1063, 725 cm^{-1}; **MS** (EI) *m/z* % 356.2 (8, $M^{+\cdot}$), 338.2 (30), 327.1 (100), 268.1 (49), 225.1 (35), 197.1 (23), 161.1 (38), 87.1 (58); **HRMS** (ESI) *m/z* calcd for $C_{21}H_{28}O_3Si$ 356.1808, found 356.1811.

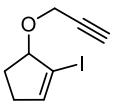
1-Bromo-9-methoxy-6-(triethylsilyl)-1,2,3,3a-tetrahydro-5*H*-cyclopenta[*b*]indeno[1,2-*c*]furan-5-one (45)



Under an argon atmosphere compound **44** (0.025 g, 0.07 mmol) was added into a reaction flask and was dissolved in dry CH_3CN (1.4 ml). The reaction mixture was cooled down to 0 °Cin an ice cooling bath, then BDSB (0.046 g; 0.08 mmol) was added slowly and the mixture was let to stir at 0 °C for 90 minutes. Afterwards the cooling bath was removed and the reaction mixture was left to stir at room temperature for 40 min. Then additional BDSB (11.5 mg; 0.03 mmol) was added to the reaction mixture which was then left to stir for another 35 minutes. The reaction was quenched by adding saturated aqueous solution of $Na_2S_2O_3$ (3 ml) and filtrating it though celite followed up by extraction into EtOAc. The combined organic layers were dried using Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (98/2 later on changed to 90/10 hexane/EtOAc). Via this procedure compound **45** was obtained as yellow oil (0.0044 g, 14%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.6 Hz, 1H), 6.87 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.76 (d, *J* = 2.4 Hz, 1H), 4.67 (d, *J* = 3.2 Hz, 1H), 4.46 (dd, *J* = 10.8, 7.3 Hz, 1H), 3.84 (s, 3H), 2.68 – 2.52 (m, 2H), 2.44 – 2.36 (m, 1H), 2.04 – 1.94 (m, 1H), 1.04 – 0.96 (m, 15H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.4, 160.1, 154.9, 150.7, 149.3, 143.0, 126.9, 113.3, 110.0, 84.6, 71.4, 55.8, 54.8, 35.5, 33.6, 7.7, 3.8.

1-Iodo-5-(prop-2-yn-1-yloxy)cyclopent-1-ene (47)

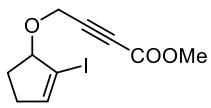


Under an argon atmosphere alcohol **40** (0.983 g; 4.68 mmol) was added into a reaction flask alongside with propargyl bromide (1.252 g; 8.42 mmol), TBAI (0.173 g; 0.47 mmol) and dry THF (18 ml). The reaction mixture was cooled down to 0 °C in an ice cooling bath, then NaH (0.337 g; 8.421 mmol) was added.

After stirring the mixture at 0 °C for 10 minutes, the cooling bath was removed and the mixture was left to stir at room temperature for 23 hours. The reaction was quenched by adding a saturated aqueous solution of NH_4Cl (20 ml) followed up by extraction into EtOAc. The combined organic layers were dried using Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (90/10 hexane/EtOAc). Using this procedure compound **47** was obtained as yellow oil (0.958 g, 83%).

^{1}H NMR (400 MHz, CDCl3) δ 6.35 (td, *J* = 2.5, 1.0 Hz, 1H), 4.65–4.56 (m, 1H), 4.25 (dd, *J* = 9.0, 2.4 Hz, 2H), 2.53–2.42 (m, 1H), 2.43 (t, *J* = 2.4 Hz, 1H), 2.33–2.16 (m, 2H), 2.00–1.91 (m, 1H); **^{13}C NMR** (100 MHz, CDCl3) δ 144.2, 95.3, 88.3, 80.0, 74.3, 56.5, 32.9, 29.1.

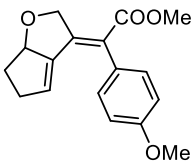
Methyl 4-((2-iodocyclopent-2-en-1-yl)oxy)but-2-ynoate (48)



Under an argon atmosphere terminal alkyne **47** (0.150 g; 0.60 mmol) was added into a reaction flask and dissolved in dry THF (2 ml). The mixture was then cooled down to -78 °C in dry ice/acetone cooling bath, then LiHMDS (1 M; 0.723 mmol) was added dropwise and the resulting mixture was let to sir at -78 °C for 30 minutes. Afterwards, methyl chloroformate (0.069 g; 0.073 mmol) was added. The cooling bath was removed and the reaction mixture was left to stir at room temperature for another 45 minutes. The reaction was quenched by adding a saturated aqueous solution of NH_4Cl (3 ml) followed up by extraction into EtOAc. The combined organic layers were dried using Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (98/2 hexane/EtOAc). Using this procedure compound **48** was obtained as yellow oil (0.103 g, 56%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (td, *J* = 2.5, 1.1 Hz, 1H), 4.61 – 4.55 (m, 1H), 4.38 (d, *J* = 6.8 Hz, 2H), 3.78 (s, 3H), 2.53 – 2.42 (m, 1H), 2.35 – 2.20 (m, 2H), 2.02 – 1.92 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.7, 144.9, 94.8, 89.2, 84.0, 77.6, 56.4, 53.0, 33.1, 29.2.

Methyl(Z)-2-(6,6a-dihydro-2H-cyclopenta[*b*]furan-3(5*H*)-ylidene)-2-(4-methoxyphenyl)acetate (49)



Under an argon atmosphere **48** (0.069 g; 0.23 mmol) was added into a reaction flask alongside with *p*-methoxyphenyl boronic acid (0.055 g; 0.36 mmol), Cs_2CO_3 (0.147 g; 0.45 mmol), THF (4 ml) and distilled water (0.4 ml). After degassing the reaction (the flask was evacuated and then the atmosphere was switched for argon; this process was repeated thrice), $Pd(PPh_3)_4$ (0.013 g; 0.01 mmol) was added into the mixture followed up by another degassing. The reaction mixture was heated at 70 °C for 3 hours. The reaction was quenched by adding HCl (2 M solution in water, 4 ml) followed up by extraction into EtOAc. The combined organic layers were dried using Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (90/10 hexane/EtOAc). Using this procedure compound **49** was obtained as yellow oil (0.007 g, 11%).

Under an argon atmosphere **48** (0.150 g; 0.49 mmol) was added into a reaction flask alongside with *p*-methoxyphenyl boronic acid (0.119 g; 0.78 mmol), toluene (4 ml) and 2 M aqueous solution of K_2CO_3 (1 ml). After degassing the reaction (the flask was evacuated and then the atmosphere was switched for argon; this process was repeated thrice), $Pd(PPh_3)_4$ (0.023 g; 0.02 mmol) was added into the mixture followed up by another degassing. The reaction mixture was heated at 80 °C for 2 hours. The reaction was quenched by adding HCl (2 M solution in water, 3 ml) followed up by extraction into EtOAc. The combined organic layers were dried using Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (95/5 hexane/EtOAc). Using this procedure compound **49** was obtained as yellow oil (0.043 g, 31%).

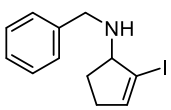
Under an argon atmosphere XPhos (0.016 g; 0.03 mmol), $Pd_2(dba)_3$ (0.015 g; 0.02 mmol) and toluene (3 ml) were added into a reaction flask and were left to stir for 5 minutes. Afterwards compound **48** (0.100 g; 0.33 mmol), *p*-methoxyphenyl boronic acid (0.079 g; 0.52 mmol) and 2 M aqueous solution of K_2CO_3 (1 ml) were added into the mixture which was then heated at 80 °C for 2 hours. The reaction was quenched by

adding HCl (2 M solution in water, 2 ml) followed up by extraction into EtOAc. The combined organic layers were dried using Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (95/5 hexane/EtOAc). Using this procedure compound **49** was obtained as yellow oil (0.020 g, 21%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.11 (m, 2H), 6.95 – 6.88 (m, 2H), 5.38 (d, *J* = 16.5 Hz, 1H), 5.09 – 5.02 (m, 1H), 4.99 (dt, *J* = 4.2, 2.2 Hz, 1H), 4.94 – 4.87 (m, 1H), 3.83 (s, 3H), 3.70 (s, 3H), 2.70 – 2.44 (m, 2H), 2.29 – 2.20 (m, 1H), 1.80 – 1.67 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.3, 159.2, 147.5, 147.0, 130.5, 130.5, 129.4, 124.7, 114.0, 89.4, 78.8, 55.4, 52.1, 37.3, 33.2; **IR** (KBr) ν_{max} 2953, 1709, 1509, 1299, 1242, 1033, 833 cm^{-1}.

4.3 Synthesis of amide derivatives

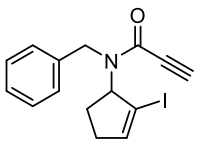
N-Benzyl-2-iodocyclopent-2-en-1-amine (51)



The iodinated alcohol **40** (1.200 g; 5.71 mmol) was added into a reaction flask alongside with triethylamine (0.752 g; 7.43 mmol) and DCM (5 ml) . The reaction mixture was cooled down to 0 °C in an ice cooling bath, then mesyl chloride (0.851 g; 7.43 mmol) was added and the mixture was left to stir for 80 minutes at 0 °C. The reaction was quenched by adding distilled water and saturated aqueous solution of $NaHCO_3$ (6 ml) followed up by extraction into EtOAc. The combined organic layers were dried using saturated aqueous solution of Na_2SO_4, filtered and concentrated under reduced pressure. The crude mesylated product was then immediately treated with benzylamine (3.671 g; 34.26 mmol) and the mixture (without solvent) was left to stir at room temperature for 4 days. The crude product was purified by column chromatography on silica gel (95/5 hexane/EtOAc). Using this two-step procedure compound **51** was obtained as dark yellow oil (1.403 g, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.22 (m, 5H), 6.29 (td, *J* = 2.5, 1.5 Hz, 1H), 3.91 – 3.85 (m, 1H), 3.78 (d, *J* = 12.8 Hz, 1H), 3.69 (d, *J* = 12.8 Hz, 1H), 2.50 – 2.27 (m, 2H), 2.24 – 2.13 (m, 1H), 1.92 – 1.83 (m, 1H), 1.68 (bs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141.7, 140.5, 128.5, 128.4, 127.1, 101.0, 69.1, 49.4, 33.4, 28.3.

***N*-Benzyl-*N*-(2-iodocyclopent-2-en-1-yl)propiolamide (52)**

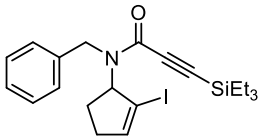


Under an argon atmosphere amine **51** (1.403 g; 4.69 mmol) was added into a reaction flask and diluted in dry DCM (6 ml). Afterwards DCC (1.162 g; 5.63 mmol) and DMAP (0.057 g; 0.47 mmol) were added. The resulting mixture was cooled down to 0 °C in an ice cooling bath, then propiolic acid (0.394 g; 5.63 mmol) was slowly added. Afterwards, the cooling bath was removed and the reaction was left to stir at room temperature for 2 hours. The reaction was diluted with distilled water and DCM followed up by an extraction into EtOAc, where HCl (2 M solution in water) was added as well. The combined organic layers were dried using Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (gradient elution 98/2 → 92/8 → 90/10 hexane/EtOAc). Using this procedure compound **52** was obtained as yellow oil (1.088 g, 66%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 3H, 3H$^{\#}$), 7.25 – 7.20 (m, 2H, 2H$^{\#}$), 6.43 (q, *J* = 2.4 Hz, 1H), 6.37 (q, J = 2.4 Hz, 1H$^{\#}$), 5.69 (s, 1H), 5.56 (s, 1H$^{\#}$), 5.09 (s, 1H$^{\#}$), 5.05 (s, 1H), 4.41 (d, *J* = 14.9 Hz, 1H$^{\#}$), 3.85 (d, *J* = 15.9 Hz, 1H), 3.24 (s, 1H), 3.06 (s, 1H$^{\#}$), 2.34 – 2.25 (m, 1H, 1H$^{\#}$), 2.24 – 2.01 (m, 2H, 2H$^{\#}$), 1.76 – 1.65 (m, 1H), 1.64 – 1.53 (m, 1H$^{\#}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.5, 145.3, 145.0, 141.8, 137.9, 128.8, 128.6, 128.4, 127.7, 127.3, 127.0, 101.1, 95.8, 80.6, 79.1, 76.4, 76.0, 71.9, 69.1, 49.4, 44.7, 33.5, 33.4, 27.1, 26.8. (second signal of a carbonyl group – the rotamer – is missing)

$^{\#}$ = rotamer

***N*-Benzyl-*N*-(2-iodocyclopent-2-en-1-yl)-3-(triethylsilyl)propiolamide (53)**



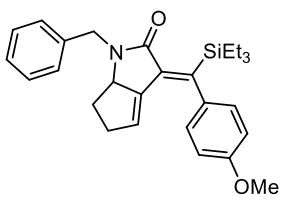
Under an argon atmosphere amide **52** (0.506 g; 1.44 mmol) was added into a reaction flask and diluted in dry THF (7 ml). This mixture was then cooled down to -78 °C in a dry ice/acetone cooling bath followed by a dropwise addition of LiHMDS (1 M solution in THF, 1.73 mmol) and the reaction mixture was left to stir for an hour at this temeprature. Afterwards Et_3SiCl (0.261 g; 1.73 mmol) was added and the reaction was left to stir at room temperature for 2 hours. The reaction was quenched by adding a saturated aqueous solution of NH_4Cl (10 ml) followed up by extraction into EtOAc. The combined organic layers were dried using Na_2SO_4, filtered and concentrated under

reduced pressure. The crude product was purified by column chromatography on silica gel (90/10 hexane/EtOAc). Using this procedure compound **53** was obtained as yellow oil (0.631 g, 94 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.19 (m, 5H, 5H$^{\#}$), 6.46 – 6.39 (m, 1H), 6.36 (q, *J* = 2.4 Hz, 1H$^{\#}$), 5.77 (s, 1H), 5.63 (s, 1H$^{\#}$), 5.16 – 4.96 (m, 1H, 1H$^{\#}$), 4.38 (d, *J* = 16.9 Hz, 1H$^{\#}$), 3.83 (d, *J* = 15.7 Hz, 1H), 2.34 – 2.23 (m, 1H, 1H$^{\#}$), 2.24 – 2.02 (m, 2H, 2H$^{\#}$), 1.78 – 1.63 (m, 1H), 1.53 – 1.37 (m, 1H$^{\#}$), 1.07 – 0.84 (m, 9H, 9H$^{\#}$), 0.74 – 0.50 (m, 6H, 6H$^{\#}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.3, 155.0, 145.0, 144.8, 138.3, 138.0, 128.6, 128.5, 127.5, 127.4, 127.2, 126.9, 97.8, 97.4, 97.2, 96.0, 95.9, 94.7, 71.9, 66.4, 49.7, 44.5, 33.5, 33.5, 27.1, 26.8, 7.6, 7.3, 4.1, 3.9; **IR** (KBr) ν_{max} 2953, 2872, 1637, 1413, 1296, 1237, 1018, 737 cm^{-1}; **MS** (EI) *m/z* % 465.1 (8, $M^{+\cdot}$), 436.1 (90), 374.0 (95), 338.2 (100), 310.2 (22), 272.1 (25), 167.1 (20); **HRMS** (ESI) *m/z* calcd for $C_{21}H_{28}NOISi$ 465.0985, found 465.0987.

$^{\#}$ = rotamer

(Z)-1-Benzyl-3-((4-methoxyphenyl)(triethylsilyl)methylene)-3,5,6,6a-tetrahydrocyclopenta[*b*]pyrrol-2(1*H*)-one (54)



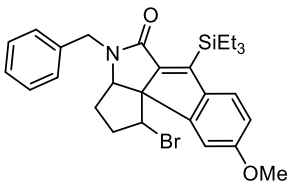
Under an argon atmosphere compound **53** (0.100 g; 0.215 mmol) was added into a reaction flask alongside with *p*-methoxyphenyl boronic acid (0.052 g; 0.34 mmol), Cs_2CO_3 (0.147 g; 0.451 mmol), THF (4 ml) and distilled water (0.3 ml). After degassing the reaction (the flask was evacuated and then the atmosphere was switched for argon; this process was repeated thrice), $Pd(PPh_3)_4$ (0.012 g; 0.01 mmol) was added into the reaction flask followed up by another degassing. The reaction mixture was heated at 70 °C for 5 hours. The reaction was diluted with ether, filtered through celite and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (98/2 hexane/EtOAc). Using this procedure compound **54** was obtained as yellow oil (0.019 g, 20%).

Under an argon atmosphere compound **53** (0.100 g; 0.215 mmol) was added into a reaction flask alongside with *p*-methoxyphenyl boronic acid (0.052 g; 0.34 mmol), Cs_2CO_3 (0.147 g; 0.451 mmol), toluene (3.3 ml) and distilled water (0.3 ml). After

degassing the reaction (the flask was evacuated and then the atmosphere was switched for argon; this process was repeated thrice), $Pd(PPh_3)_4$ (0.012 g; 0.01 mmol) was added into the reaction flask followed up by another degassing. The reaction mixture was heated up to 70 °C and was left to stir for 23 hours. The reaction was diluted with ether and filtrated through celite followed by concentration under reduced pressure. The crude product was purified by column chromatography on silica gel (98/2 hexane/EtOAc). Using this procedure compound **54** was obtained in form of yellow oil (0.044 g, 46%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 5H), 6.94 – 6.80 (m, 4H), 4.86 (d, *J* = 14.6 Hz, 1H), 4.73 (dt, *J* = 3.7, 2.4 Hz, 1H), 4.29 (d, *J* = 14.6 Hz, 1H), 4.11 – 4.03 (m, 1H), 3.81 (s, 3H), 2.33 – 2.17 (m, 2H), 2.02 – 1.93 (m, 1H), 1.45 – 1.31 (m, 1H), 0.94 – 0.85 (m, 9H), 0.81 – 0.71 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.4, 157.8, 151.9, 142.0, 137.6, 137.3, 137.1, 128.7, 128.7, 127.6, 127.3, 126.7, 114.3, 65.4, 55.3, 45.9, 33.8, 33.4, 8.2, 4.5; **IR** (KBr) ν_{max} 2936, 2863, 1685, 1505, 1249, 1046, 913, 739 cm^{-1}; **MS** (EI) *m/z* % 445.2 (1, $M^{+\cdot}$), 417,2 (35), 416.2 (100); **HRMS** (ESI) *m/z* calcd for $C_{28}H_{35}NO_2Si$ 445.2437, found 445.2436.

4-Benzyl-1-bromo-9-methoxy-6-(triethylsilyl)-2,3,3a,4-tetrahydrocyclopenta[*b*]indeno[1,2-*c*]pyrrol-5(1H)-one (55)



Under an argon atmosphere compound **54** (0.014 g; 0.03 mmol) was added into a reaction flask and was dissolved in CH_3CN (1 ml). The reaction mixture was then cooled down to 0 °C in an ice cooling bath, then BDSB (0.018 g; 0.03 mmol) was added and the mixture was left to stir at 0 °C for an hour. The reaction was quenched by adding a saturated aqueous solution of $Na_2S_2O_3$ (1 ml) and a saturated aqueous solution of $NaHCO_3$ (1 ml) followed by filtration through celite and concentrating it under reduced pressure. The crude product was purified by column chromatography on silica gel (gradual elution 95/5 → 90/10 hexane/EtOAc). Using this procedure compound **55** was obtained as yellow oil (0.006 g, 36%).

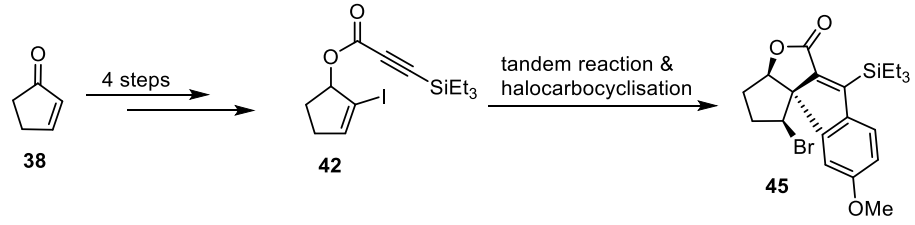
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.5 Hz, 1H), 7.28 – 7.19 (m, 3H), 7.19 – 7.13 (m, 2H), 6.79 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.69 (d, *J* = 2.4 Hz, 1H), 5.17 (d, *J* = 15.2 Hz, 1H), 4.42 (dd, *J* = 10.5, 7.1 Hz, 1H), 3.90 (d, *J* = 15.2 Hz, 1H), 3.79 (s, 3H), 3.67 (d, *J* = 3.8 Hz, 1H), 2.56 – 2.47 (m, 1H), 2.43 – 2.33 (m, 1H), 2.33 – 2.25 (m, 1H), 1.80

(tdd, J = 13.5, 6.1, 3.8 Hz, 1H), 1.11 – 0.99 (m, 15H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.5, 159.3, 156.2, 151.5, 147.0, 143.5, 136.6, 128.8, 128.2, 127.6, 125.9, 112.6, 110.1, 67.8, 63.2, 55.7, 55.2, 44.1, 35.3, 29.7, 7.8, 4.1; **IR** (KBr) ν_{max} 2933, 2873, 2249, 1679, 1606, 1467, 1394, 1287, 1033, 729 cm^{-1}; **MS** (EI) *m/z* % 548,9 (95, $[M+Na]^+$), 546,9 (100, $[M+Na]^+$), 524.9 (18, $[M+H]^+$), 494.8 (12), 466.8 (10); **HRMS** (ESI) *m/z* calcd for $C_{28}H_{35}O_2NBrSi$ 524.1618, found 524.1615.

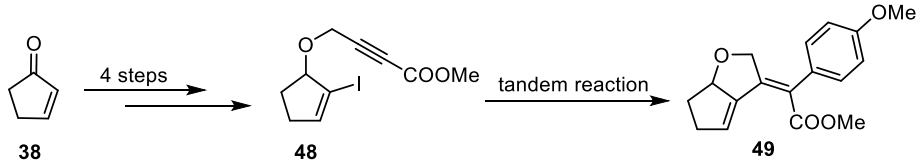
5. Conclusion

In conclusion, all the desired substrates for tandem reaction were successfully prepared. As for the final products, they were obtained for both amide and ester derivative of polycyclic compounds, however we were not able to obtain the final product in case of exocyclic ester compounds. Reactions with amide derivatives proceeded in better yields compared to ester-containing compounds.

i) For ester derivative of polycyclic compounds tandem reaction proceeded in moderate yields (highest obtained yield was 54%) whereas halocarbocyclisation proceeded in low yield (product was obtained in 14%) through which we were able to obtain the desired product containing an all-carbon quaternary centre. In comparison to ether-containing compounds which were reported by our group, ester derivative performed in this work proceeded in worse yields, which proves the negative effect of the carbonyl group on the key reaction sequence.[18]

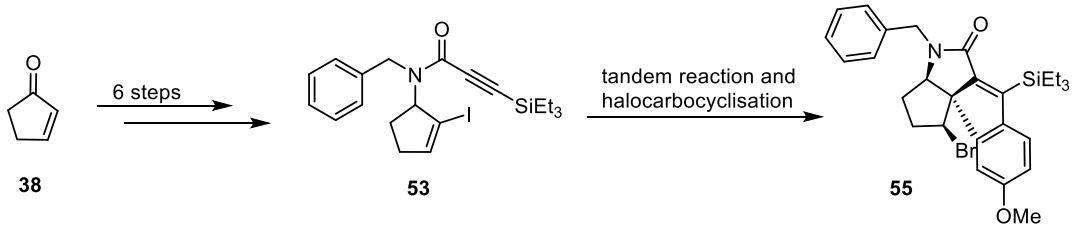


ii) For exocyclic ester derivative only the undesired E-isomer was obtained through tandem reaction, hence we were not able to perform the halocarbocyclisation, since this isomer is not able to undergo this reaction. This result was surprising, since complete isomerisation of either palladium intermediate **45** or product must have happened under the reaction conditions which were used. However, we still don't know the exact mechanism of this reaction.



iii) For amide derivative of polycyclic compounds both tandem cyclisation/Suzuki cross-coupling reaction (the highest obtained yield was 45%) and halocarbocyclisation (product was obtained in 36%) were

performed giving us the desired product containing an all-carbon quaternary centre. In comparison to ester derivative, reactions with amide derivatives proceeded in better yields.



38 53 55

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