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Branch of study: Organic Chemistry

Bc. Tomáš Vašíček

Synthesis of polycyclic compounds containing quaternary carbon centers

Syntéza polycyklických sloučenin obsahujících kvartérní uhlíková centra

Diploma thesis

Supervisor: PharmDr. Eliška Matoušová, Ph.D.

Prague, 2018

Prohlášení:

Prohlašuji, že jsem závěrečnou práci zpracoval samostatně a že jsem uvedl všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

V Praze, 3.5.2018 Bc. Tomáš Vašíček

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Abstrakt

V rámci předložené diplomové práce byla vypracována metoda přípravy polykarbocyklických sloučenin obsahujících kvartérní uhlíková centra jako součást triquinanového skeletu. Klíčovou reakční sekvencí vedoucí k přípravě těchto karbocyklů byla Pd-katalyzovaná tandemová cyklizace/Suzuki cross-couplingová reakce následovaná halokarbocyklizací. V první části syntetického projektu byl připraven modelový kyslíkatý polycyklický derivát. V druhé části syntézy byly úspěšně připraveny 3 nové polykarbocyklické sloučeniny obsahující kvartérní uhlíková centra. K syntéze odpovídající výchozí látky pro klíčovou reakční sekvenci byl vyvinut postup založený na alkylaci diethyl-malonátu. Uvedená metoda může sloužit jako nový způsob přípravy polykarbocyklických přírodních látek.

Klíčová slova: syntéza, polycyklické sloučeniny, kvartérní centra, katalýza

Abstract

In this diploma Thesis, a method for the preparation of polycarbocyclic compounds containing all-carbon quaternary centers embedded in triquinane skeleton was prepared. The key reaction sequence leading towards the preparation of these carbocycles was Pd-catalyzed tandem cyclization/Suzuki cross-coupling reaction followed by halocarbocyclization. In the first part of synthetic project, a model oxygen-containing polycyclic derivative was prepared. In the second part, 3 novel polycarbocyclic compounds containing all-carbon quaternary centers were successfully prepared. Synthetic procedure for the starting material required for the key reaction sequence was developed. This approach represents another pathway for the synthesis of polycarbocyclic natural products.

Keywords: synthesis, polycyclic compounds, quaternary centers, catalys

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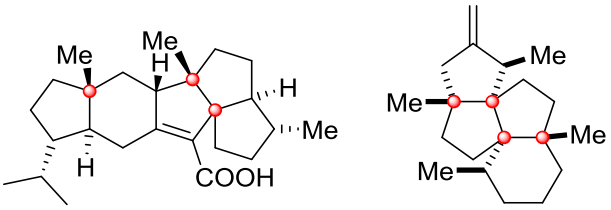
Abbreviations

BDSB	bromodiethylsulfonium bromopentachloroantimonate
CDSC	chlorodiethylsulfonium hexachloroantimonate
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
eq.	equivalent
FVP	flash vacuum pyrolysis
HRMS	high-resolution mass spectrometry
IDSI	bis(diethyliodosulfonium)chloride hexachloroantimonate
IR	infrared spectroscopy
LDA	lithium diisopropylamide
LG	leaving group
LiHMDS	lithium bis(trimethylsilyl)amide
Me	methyl
MMTPP chloride	(methoxymethyl)triphenylphosphonium chloride
MsCl	methanesulfonyl chloride
NIS	*N*-Iodosuccinimide
NMR	nuclear magnetic resonance
TES ($SiEt_3$)	triethylsilyl
THF	tetrahydrofyran
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethane-1,2-diamine
TMM	trimethylenemethane

1. Introduction

One of the most important areas in chemical research is the development of efficient synthetic methodologies leading towards natural compounds and their analogues. Natural products are substances produced by living organisms including plants, animals, or even microorganisms. Natural products and their analogues are often studied for their biological properties. Many of them have proven to have widespread benefits to humans.[1] They are used as modern drugs, life-saving medicines or agrochemicals.

Properties of organic molecules are in large dictated by the presence of various functional groups, as well as their stereochemistry. Countless natural products contain carbon atom bonded to four different carbon substituents, i.e. chiral all-carbon quaternary centers (in this Thesis they are depicted as grey spheres in the schemes). Formation of such carbon centers, especially in an enantioselective fashion, remains a challenging task in the field of organic synthesis (Scheme 1).[2,3]



retigeranic acid **1**

waihoensene **2**

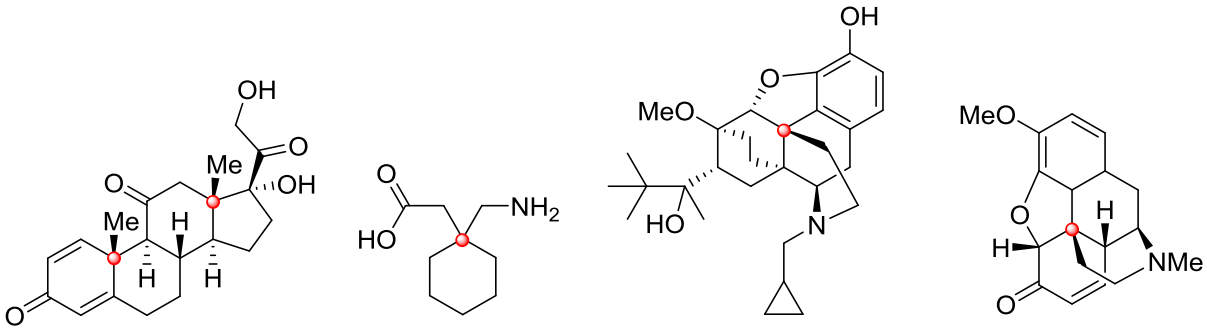
Scheme 1. Retigeranic acid **1**, waihoensene **2**

The reason for the difficulty in synthesizing all-carbon quaternary centers is that the presence of a tetra-substituted carbon atom in any given molecule causes great steric hindrance around this center. In addition, there is only a limited number of carbon-carbon bond-forming reactions that are suitable for construction of these centers.

Interestingly enough, among the top 200 prescription drugs sold in the USA in 2016, 19% contain at least one all-carbon quaternary center, while majority of these centers (87%) are asymmetric.[4] Most of these drugs are derived from opioid or estrone skeleton. (Scheme 2)

One example, prednisone **3**, a synthetic corticoid containing two all-carbon quaternary centers, is used to cure many autoimmune diseases and as an anti-inflammatory drug. Gabapentin **4**, a simple achiral molecule that is in fact a derivative of 4-aminobutanoic acid

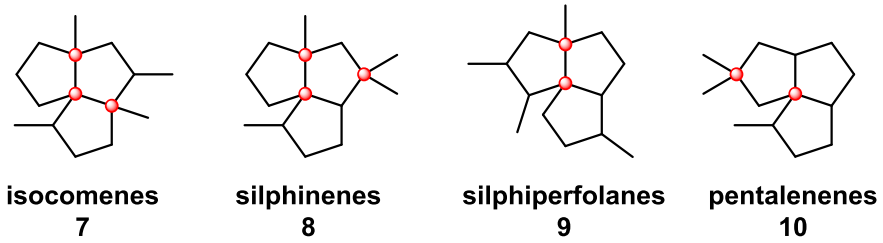
(GABA), is used as an anticonvulsant to treat epileptic seizures. A combination medication of buprenorphine **5** and naloxone **6**, both having one all-carbon quaternary center in its core, is sold under name Soboxone as an anti-narcotic.



Scheme 2. Selection of drugs containing all-carbon quaternary centers

1.1 Natural products with angular triquinane skeleton and their bioactivity

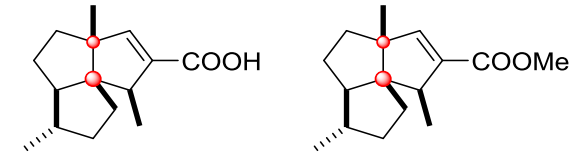
Angular tricarbocyclic and polycarbocyclic ring skeletons can be found in naturally occuring terpenoids, some of which show interesting biological properties. These 5/5/5 and 5/5/6 ring systems contain a sterically hindered all-carbon quaternary center, and therefore their synthesis is rather challenging. Our targeted carbocyclic molecules resemble their structure. Sesquiterpenes that contain this tricyclo[6.3.0.0$^{1.5}$] undecane core are isolated particularly often. They can be grouped into four subcategories, depending on the position of methyl substituents: isocomenes **7**, silphinenes **8**, silphiperfolanes **9**, and pentalenenes **10** (Scheme 3).[5]



Scheme 3. Subcategories of sesquiterpenes

Sometimes term [5.5.5] fenestrane is used for these structures, since they resemble window-like pattern, where three rings are joined at single point that represents an all-carbon quaternary center.

Subergorgic acid **11**,belonging to the silphiperfolane group, was isolated from gorgonian coral *Subergorgia suberosa* along with it´s methyl ester **12** (Scheme 4). Subergorgic acid shows cardiotoxic[6] and anticholinesterase activity[7]. Methyl subergorgate **12**, on the other hand, displays moderate cytotoxic activity against HeLa cancer cells.[8]

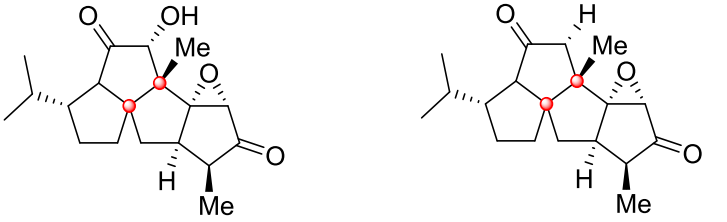


subergorgic acid
11

methyl subergorgate
12

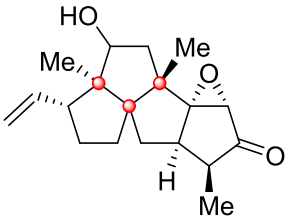
Scheme 4. The structures of subergorgic acid **11** and methyl subergorgate **12**

Recently, four new tetraquinane diterpenoids (crinipellin E-H, **13-16,** Scheme 5) were isolated from fermentations of *Crinipellis* species. These compounds have an anti-inflammatory effect by reducing the inducible expression of pro-inflammatory genes.[9]

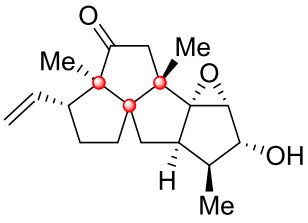


crinipellin E
13

crinipellin F
14



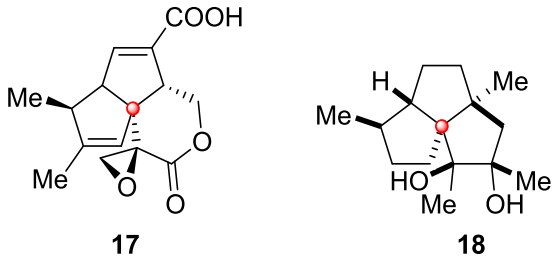
crinipellin G
15



crinipellin H
16

Scheme 5. The structures of crinipellins E-H

Pentalenolactone **17** (Scheme 6) exhibits variety of biological activity ranging from antibacterial (against both Gram-negative and Gram-positive bacteria), antifungal and antiprotozoal. This sesquiterpenoid inhibits the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GADPH) of procaryotic and eucaryotic organisms.[10]



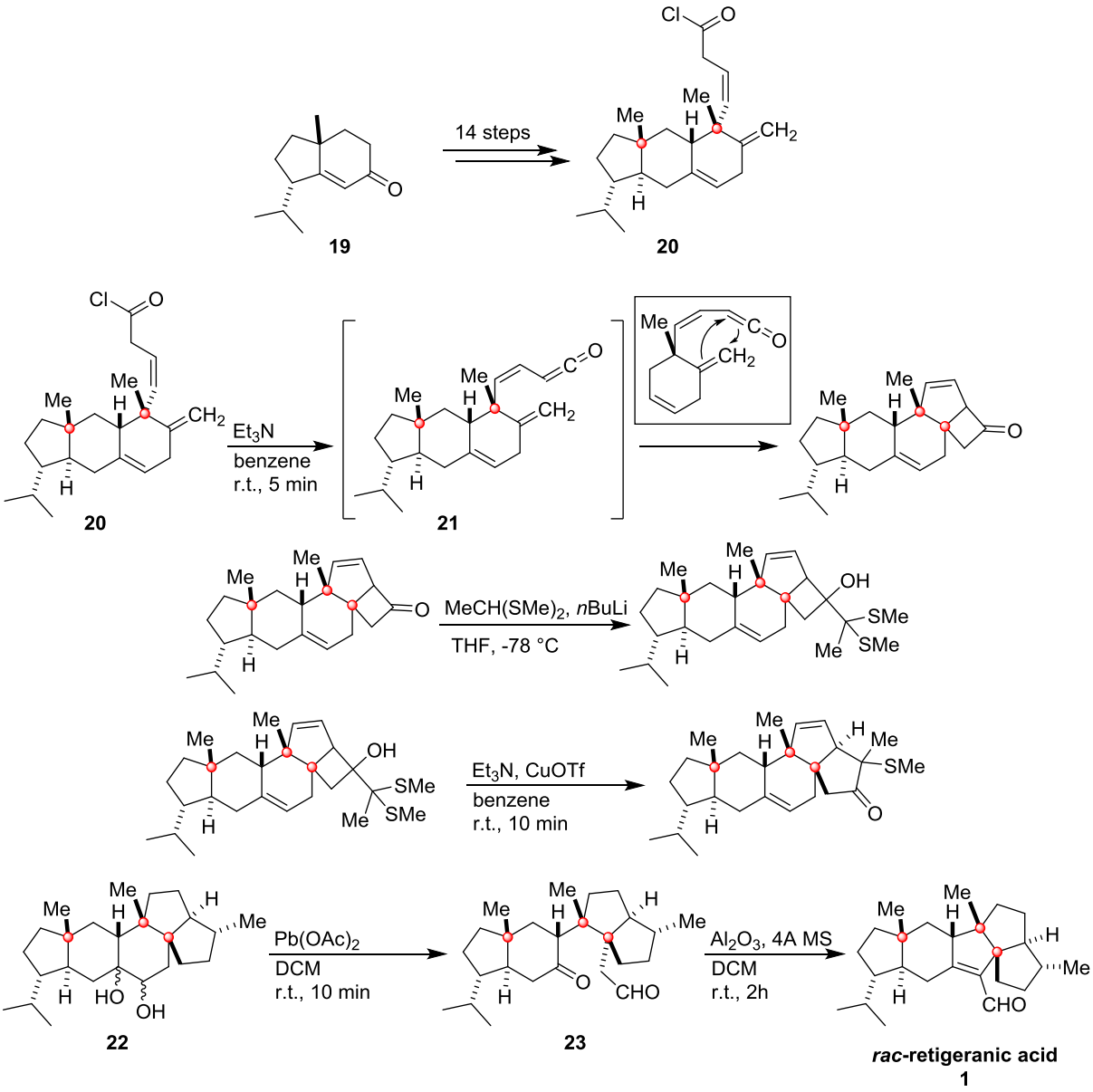
Scheme 6. Pentalenolactone **17** and structure **18**

Sesquiterpene **18** (Scheme 6) isolated from Brazilian red alga *Laurencia dondroidea* was found to show activity against *Leishmania amazonensis* promastigote and amastigote forms.[11] Additionally, it exhibits moderate antialgal activity against *Chlorella fusca*.

1.2 Reported syntheses of natural triquinanes

Retigeranic acid **1**, naturally-occuring sesterterpene was first isolated over 50 years ago from various lichens of *Lobaria retigera* group found in western Himalayas.[12] It contains two quaternary carbon centers, one of them is central to triquinane scaffold. In the following, selected syntheses leading to formation of an angular all-carbon quaternary center in retigeranic acid **1** as well as in waihoensene **2** are described.

In 1985 Corey and co-workers reported first total synthesis of retigeranic acid **1** (Scheme 7).[13] Hydrindenone **19** was used as a precursor that was in 14 steps transformed into tricyclic acyl chloride **20** featuring external double bond that under basic conditions (5 eq. Et_3N in benzene at room temperature) forms ketene intermediate **21** that undergoes intramolecular [2+2] cycloaddition between external double bond and ketene C=C double bond. In this process, two additional 5- and 4-membered rings are formed bearing a common quaternary center. This reaction step was reported to give 80% yield.

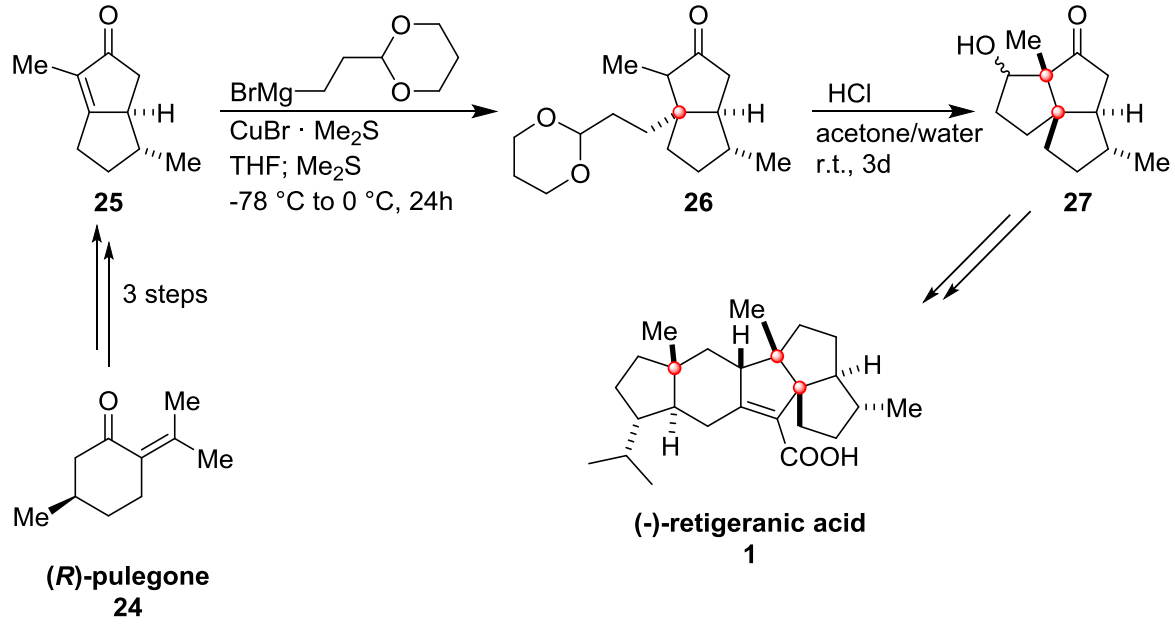


Scheme 7. Corey's synthesis of *rac*-retigeranic acid **1**

Subsequently, cyclobutanone ring was expanded to form 6/5/5 angular system. In later stage of this total synthesis, 1,2-diol **22** underwent Criegee reaction to form keto-aldehyde **23** that was then subjected to an aldol reaction to form 5/5/5 angular tricyclic system.

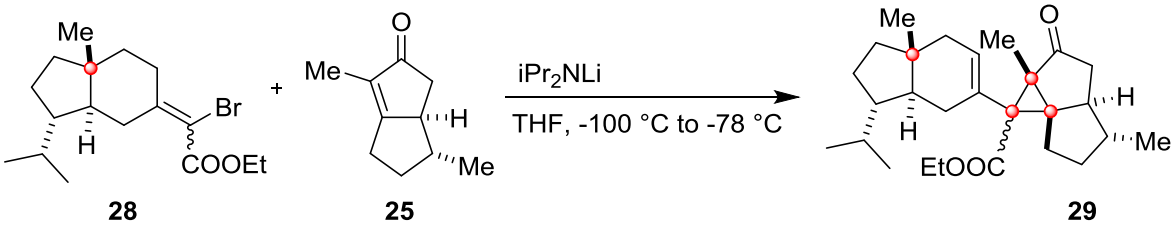
The first enantioselective synthesis of (−)-retigeranic acid **1** was accomplished by Paquette's group in overall 27 steps.[14] They combined Michael and aldol additions to create all-carbon quaternary center embedded in a triquinane moiety. Starting with (*R*)-pulegone **24**, the requisite diquinane enone **25** was obtained in 3 steps, then underwent Michael addition to

form **26** that was treated with HCl over 3 days at room temperature to give **27** in 72% yield (Scheme 8). Further transformations led to (−)- retigeranic acid **1**.

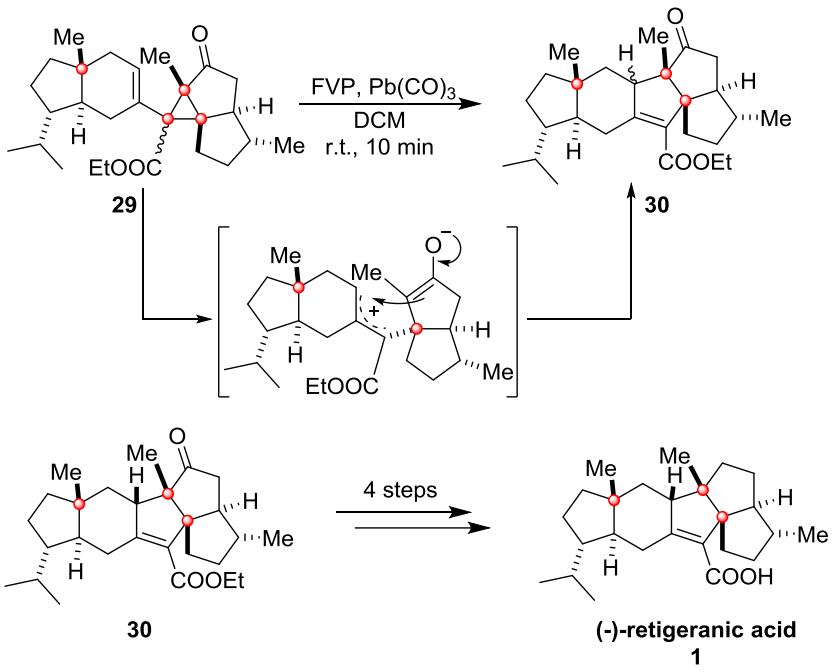


Scheme 8. The formation of carbon quaternary centers by Paquette

Hudlický's group approached the formation of this all-carbon quaternary center by formal [2+3] annulation methodology.[15] The very same diquinane **25** used by Paquette's group reacted with bromoacrylate **28** in cyclopropanation reaction to form precursor **29** for the flash vacuum pyrolysis (Scheme 9,10). This activation of cyclopropane ring gave desired α-isomer in 24% yield **30** as well as β-isomer in 27% yield that was further elaborated by deoxygenation and hydrolysis. Overall, this enantioselective synthesis of (−)-retigeranic acid was accomplished in 15 linear steps.



Scheme 9. Hudlický's formation of precursor **29** for the FVP



Scheme 10. Hudlický's approach towards (−)-retigeranic acid **1**

Wender and Singh accomplished the synthesis of (−)-retigeranic acid in 23 steps. Interestingly, they used arene-alkene [2+2] photocycloaddition as a crucial step (Scheme 11).

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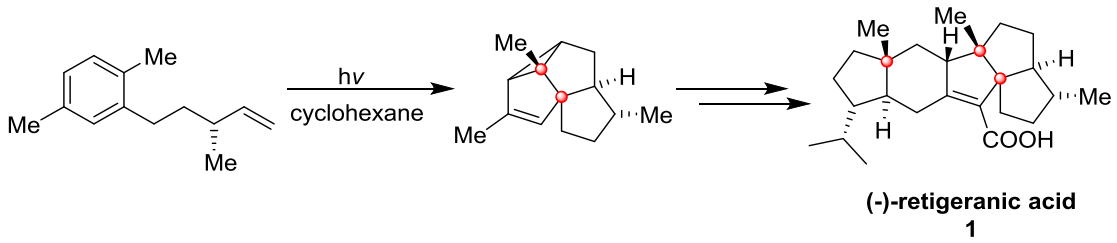
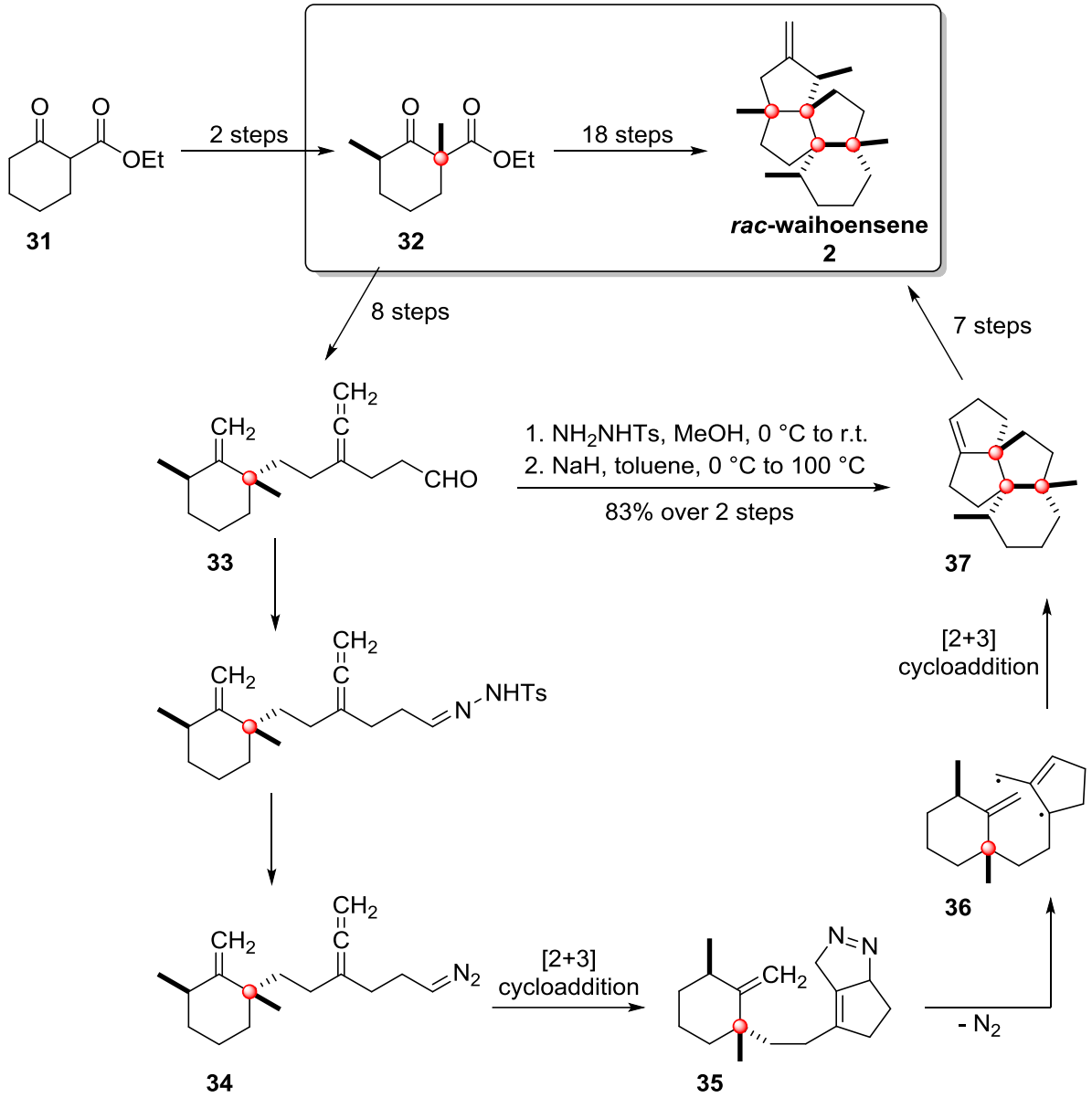


Scheme 11. Photocycloaddition approach by Wender

Waihoensene **2** is a tetracyclic terpene bearing four contiguous all-carbon quaternary centers and was just until recently considered as one of the ultimate challenges in total synthesis.[3]

Lee[16] and coworkers started the total synthesis of (±)-waihoensene originally with ethyl-2-cyclohexancarboxylate **31** that was in 2 steps converted to racemic ketoester **32** and within 8 steps turned to allenyl aldehyde **33**. Allenyl aldehyde was subjected to reaction with *p*-toluenesulfonehydrazide in methanol to yield hydrazine. Upon heating **33** formed allenyldiazo substrate **34** undergoing [2+3] cycloaddition reaction to form methylene pyrazole intermediate **35** that after N_2 extrusion gave TMM-diyl intermediate **36**. Following [2+3] cycloaddition, this radical species then formed tetracyclic structure **37** in 83% yield over these

two steps. Afterwards, few necessary modifications were accomplished in 7 steps to yield (±) waihoensene **2** (Scheme 12).



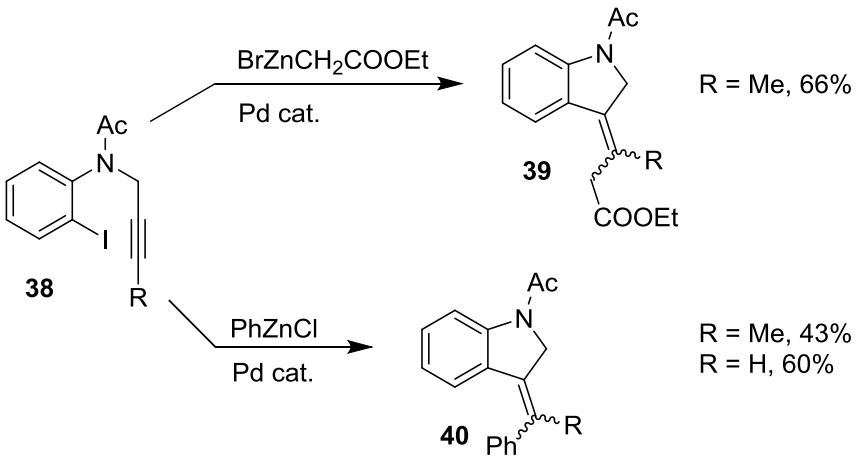
Scheme 12. Construction of waihoensene **2** framework by TMM diyl cyclization

1.3 Tandem cyclization/Suzuki cross coupling reactions

The efficiency of synthesis may certainly be enhanced by introducing tandem reactions. Tandem reactions, also known as domino or cascade reaction, basically combine two or more bond-forming reactions in a single synthetic operation. The use of tandem reactions satisfies the Hendrickson's postulate of ideal synthesis, where only skeleton forming reactions are the essential steps in the synthesis.[9]

The crucial reaction sequence of this project is based on tandem cyclization/Suzuki cross-coupling reaction. The combination of cyclic carbopalladation, that is intramolecular Heck reaction in principle, and subsequent Suzuki cross-coupling reaction was first published by Grigg in 1989 (Scheme 13).[17]

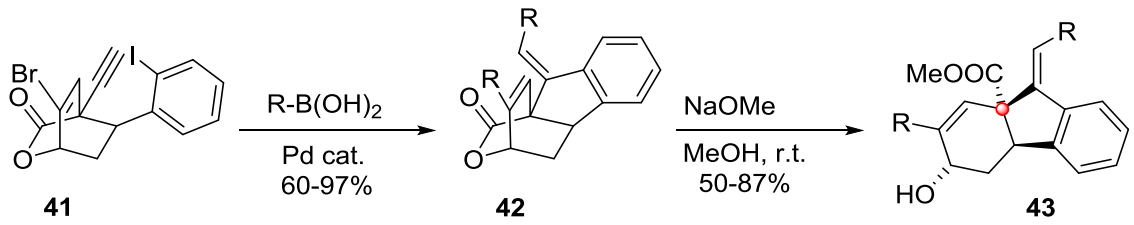
In Grigg's work, ortho-iodoaniline derivative **38** underwent initial 5-exo-dig cyclization to form vinyl palladium species that subsequently reacted with the Reformatsky reagent to give 1.4:1 mixture of indoline derivatives **39**.When reacted in the same Pd-catalyzed ($Pd(OAc)_2$, PPh_3) reaction conditions, but using phenylzinc chloride in a subsequent reaction provided **40** up to 60% yield.



Scheme 13. The first published combination of intramolecular Heck reaction and Suzuki cross-coupling reaction by Grigg

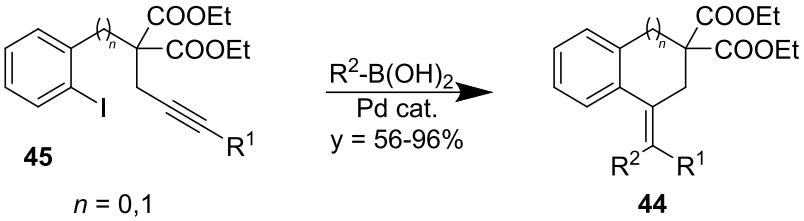
Based on this tandem reaction, several processes evolved allowing the formation isoindolinones, dihydroindene, dibenzofulvene, indoline and dihydro-benzofuran derivatives, as well as oxindoles, and recently even sulphur heterocycles. Because this Thesis deals primarily with carbocyclic compounds, the following text summarizes the previously published examples in which carbocycles were formed.

One of the first use of the discussed tandem reaction for the preparation of functionalized polycarbocycles was published by Min.[17] Reacting 2-iodoenyne **41** with various aryl and vinyl boronic acids (3 eq.) in sodium carbonate and a catalytic amount of $Pd(PPh_3)_4$ in acetonitrile at 100 °C gave the desired monosubstituted product **42** (Scheme 14). Final tetrahydrofluorenes **43** were obtained after reaction with NaOMe in methanol in up to 87% yields.



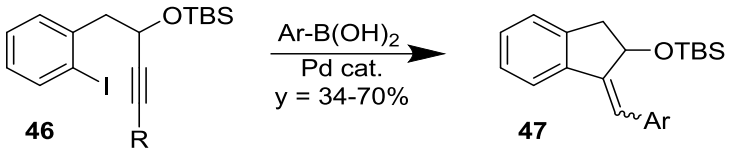
Scheme 14. Min's preparation of functionalized polycarbocycles

Synthesis of indene and naphthalene derivatives **44** was performed by reaction of both 2-iodo-en-6-ynes and 2-iodo-en-7-ynes **45** with variously substituted boronic acids (Scheme 15). Liang at al. used simple $Pd(PPh_3)_4$ as a catalyst, while the reaction was performed in DMF at 100 °C in the presence of K_2CO_3.[18]



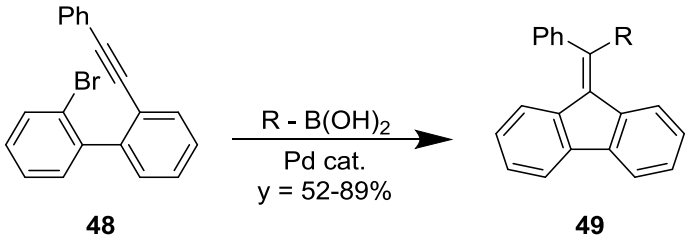
Scheme 15. Synthesis of indene and naphthalene derivatives by Liang

TBS-protected alcohols **46** underwent regio- and stereoselective tandem reactions to offer indenols **47**. Reaction used dry DMF as a solvent, $Pd(OAc)_2/PPh_3$ as a catalytic system and K_2CO_3 as a base (Scheme 16).[19]



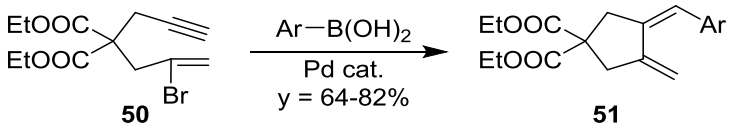
Scheme 16. Pd-catalyzed tandem cyclization offering indenols **47**

Palladium catalyzed reaction of 2,2'-disubstituted biphenyl **48** led to the formation of dibenzofulvane derivatives **49** (Scheme 17). Reactions were performed in ethanol at 70° C in the presence of $Pd(PPh_3)_4$ and Cs_2CO_3.[20]



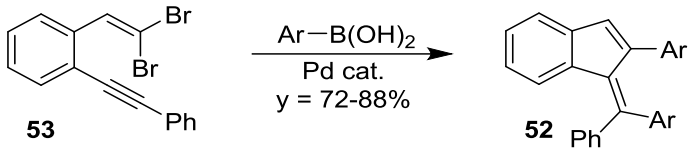
Scheme 17. Formation of dibenzofulvane derivatives **49**

In 2003 Oh and his group used 2-bromo-1,6-enynes **50** as starting material in the tandem Pd-catalyzed reaction with various boronic acids to form carbocyclic products **51** (Scheme 18).[21] Optimized reaction conditions used 3 mol % of $Pd(PPh_3)_4$ and Cs_2CO_3 (2 eq.) in ethanol. Reaction temperature varied with the substrate.



Scheme 18. Formation of carbocyclic products **49** from 2-bromo-1,6-enynes **50**

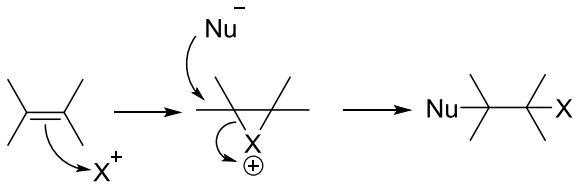
Later in 2010, Wu and his group reported on a novel synthesis of 1-methyleneindenes **52**.[23] Starting 1-(2,2-dibromovinyl)-alkynylbenzene **53** reacted in Pd-catalyzed reaction with various arylboronic acids to form a five-membered ring (Scheme 19). Compared to previously mentioned carbocyclizations, this procedure allows 1-(2,2-dibromovinyl)-alkynylbenzene **53** to undergo cross-coupling reaction twice to yield a disubstituted product **52**. Optimal reaction conditions used 5 mol % of $Pd(OAc)_2$, 20 mol % of simple PPh_3 as a ligand, K_3PO_4 as a base, while proceeding in THF/water solvent mixture at convenient room temperature.



Scheme 19. Novel synthesis of 1-methyleneindenes **52**

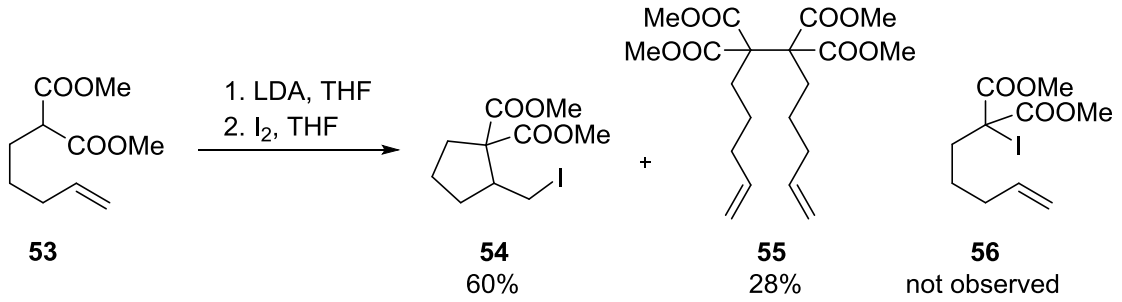
1.4 Halocarbocyclization reactions

Halocarbocyclization reactions represent a type of electrophilic additions of halogens to alkenes. First, double bond is attacked by electrophilic halogenating reagent $\mathbf{X^+}$ to form a tricyclic bromonium cation that is consequently approached by carbon nucleophile $\mathbf{Nu^-}$ to form a C-C bond (Scheme 20). Most of the halocarbocyclization reactions use iodine I^+ or bromine Br^+ as halogen inducing agent.



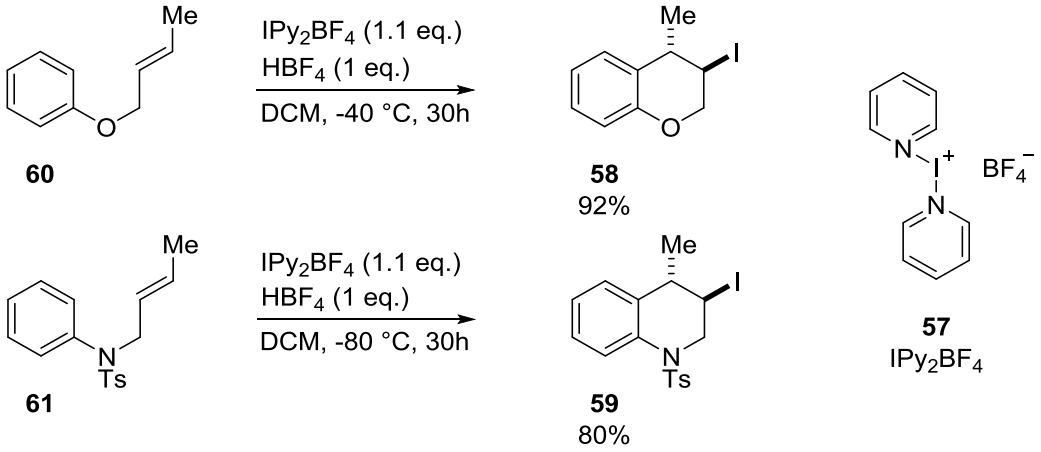
Scheme 20. Electrophilic addition of halogens to alkenes

Curran and Chuang investigated the formation of iodomalonates as they attempted the α-iodination of dimethyl 2-(pent-4-en-1-yl)malonate **53** using LDA as a base in THF followed by the addition of molecular iodine. To their surprise, carbocyclic product **54** was obtained in majority (60%) along with the oxidatively coupled product **55** in 28% yield. No desired product α-iodination dimethyl 2-iodo-2-(pent-4-en-1-yl)malonate **56** was formed (Scheme 21).



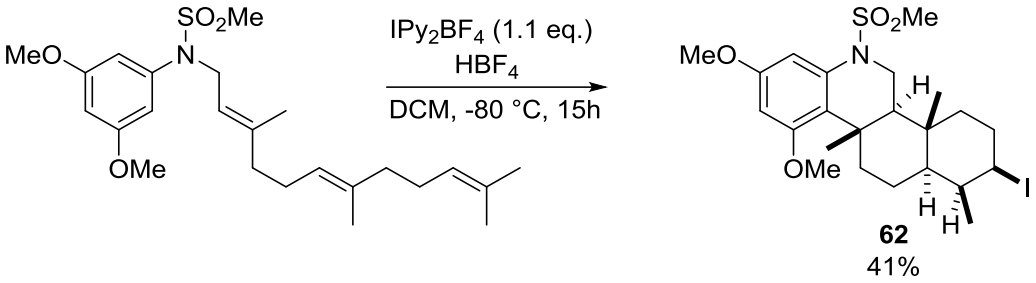
Scheme 21. Formation of carbocyclic product **54** by iodination

Burluenga and his team applied bis(pyridine)iodonium tetrafluoroborate IPy_2BF_4 **57** as the source of iodonium ion to the synthesis of chromans **58** and tetrahydroquinoline derivatives **59**.[22] Carbocyclizations of various allyl phenyl ethers **60** and *N*-protected allyl aniline derivatives **61** proceeded in DCM at low temperatures in the presence of etheral solution of HBF_4 in stereoselective way and good yields (Scheme 22).



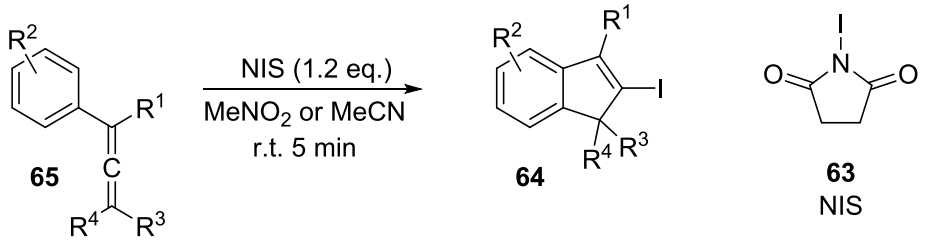
Scheme 22. Burluenga's IPy_2BF_4 **57** used for the synthesis of chromans **58** and tetrahydroquinoline derivatives **59**

This method was successfully used for the preparation of tetrasubstituted azahomosteroid **62** in 41% yield (Scheme 23).[22]



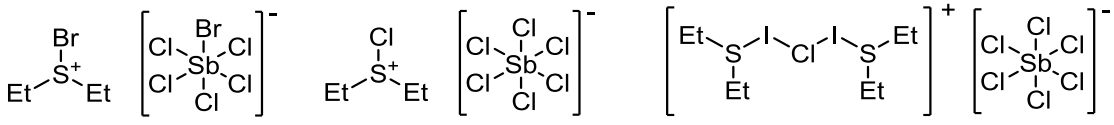
Scheme 23. IPy_2BF_4 **57** used in the synthesis of azahomosteroid **62**

N-Iodosuccinimide (NIS) **63** is often used as iodonium source and was recently used by Toullec to prepare polysubstituted 2-iodoindene structures **64** from arylallenes **65**.[23] Variously substituted allenyl arenes reacted in either nitromethane or acetonitrile at room temperature. (Scheme 24) Reported reactions proceeded within 5 minutes to give desired 2-iodoindene structures that could be further functionalized.



Scheme 24. Toullec's preparation of 2-iodoindenes **64** using NIS **63**

Snyder introduced the preparation of three halogenating agents BDSB, CDSI and IDSI (Scheme 25) for polyene cyclizations.[24] These **halogend**iethyl**s**ulfonium **halo**pentachloroantimonate reagents (**XDSX**) are capable of releasing halonium X^+ and thus initiating cyclization of polyenes.

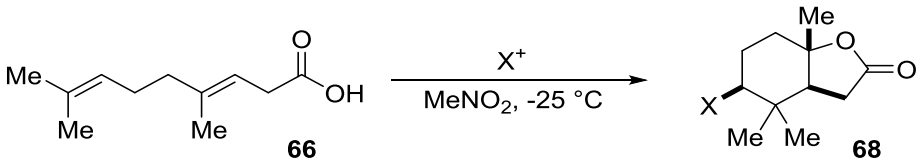


BDSB **CDSC** **IDSI**

Scheme 25. Snyder's **XDSX** halogenating agents

Halocyclizations using these halonium agents were performed in nitromethane at −25 °C reacting with geraniol substrates **66, 67** in moderate to excellent yields. It is important to note

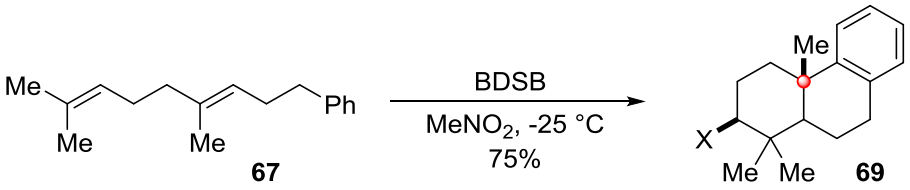
that even reagents with electron-withdrawing groups such as carboxylic acids **66** provided desired product **68** (Scheme 26).



Halonium source	yield
CDSC	38
BDSB	73
IDSI	79

Scheme 26. Formation of lactone **68** under XDSX halogenating agents

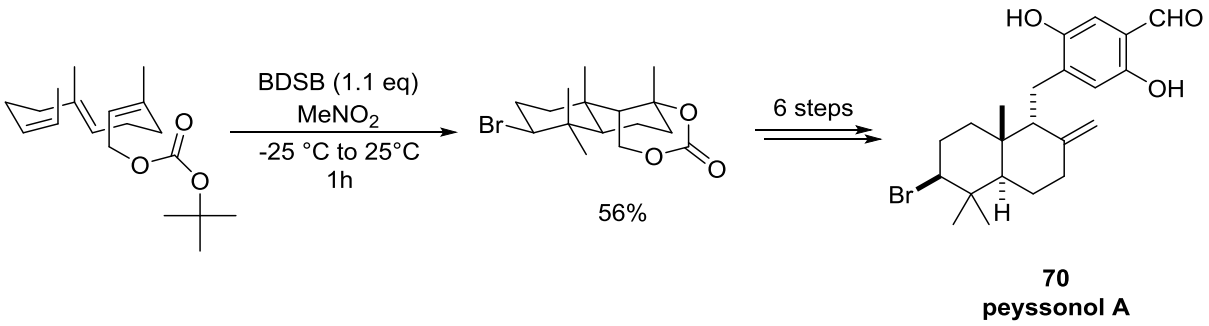
Homogeranylbenzene **67**, bearing electron rich phenyl substituent, gave under the same reaction conditions corresponding products **69** in comparable yields (Scheme 27).



Halonium source	yield
CDSC	46
BDSB	75
IDSI	93

Scheme 27. Formation of tricyclic product **69** from homogeranylbenzene **67**

Reactions were also performed on gram-scale and used in total synthesis of peyssonol A **70** (Scheme 28).

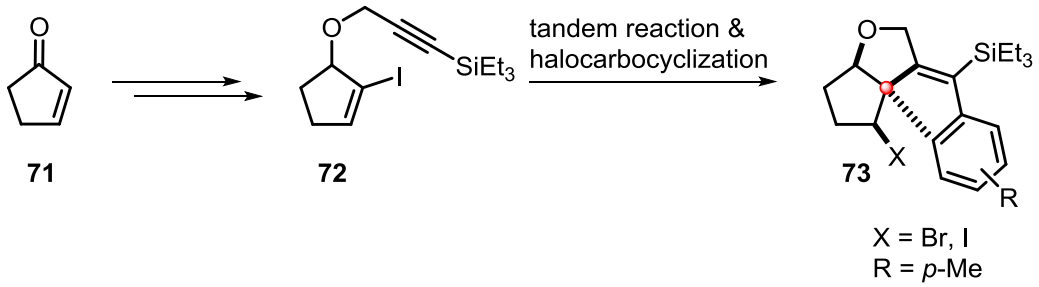


Scheme 28. BDSB applied in the total synthesis of peyssonol A **70**

2. Aims of the Thesis

The main aim of the Thesis was to prepare compounds containing an all-carbon quaternary center embedded in angular triquinane scaffold using tandem cyclization/Suzuki cross-coupling reaction followed by halocarbocyclization as a key reaction sequence. This involved:

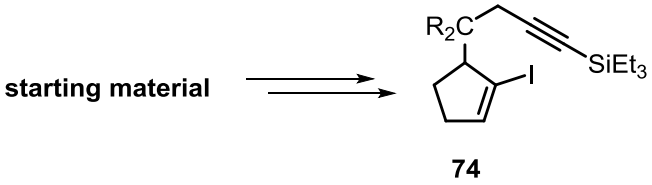
i) Synthesis of a model oxygen-containing compound



71 72 73

Starting with commercially available 2-cyclopentene-1-one **71**, iodide **72** could be prepared to undergo the key reaction sequence to form the desired product **73**.

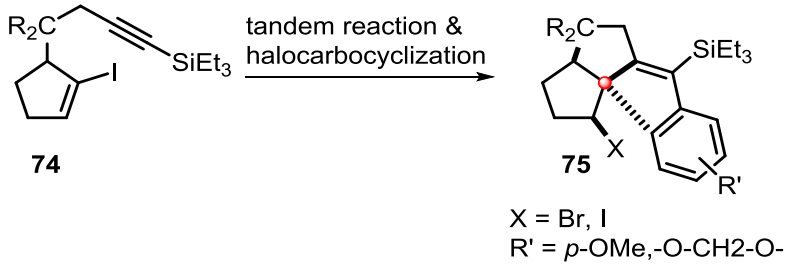
ii) Synthesis of corresponding carbon derivatives



74

The aim was to find a suitable method for the preparation of a substrate **74** which could be used for the synthesis of carbocyclic derivatives of compound **75**.

iii) Synthesis and characterization of target polycarbocyclic compounds **75**



74 **75**

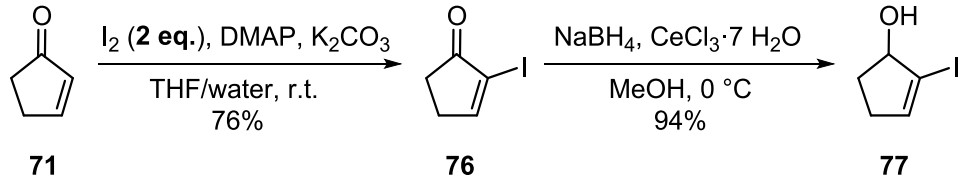
3. Results and discussion

3.1 Synthesis of a model oxygen-containing compound

In order to prepare an oxygen-containing polycyclic compound **73**, we planned to use the method developed previously in our group. Thus, we selected 2-cyclopentene-1-one **71** as a starting material which can be easily converted to silylated alkyne **72**, the substrate for the key tandem cyclization/Suzuki cross-coupling reaction followed by halocarbocyclization.

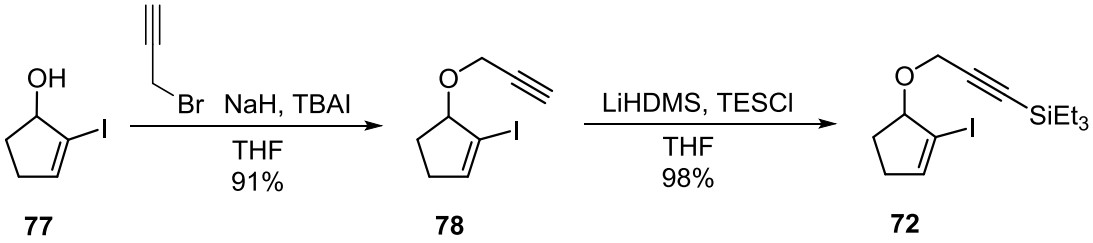
Commercially available 2-cyclopentene-1-one **71**, selected as a starting compound, was selectively iodinated in alpha position using iodine in THF/water medium in the presence of DMAP (4-dimethylaminopyridine) at room temperature.[25] Following the procedure Krafft published,[25] we were not able to prepare the desired iodinated enone **76** in reported yield (99%). Upon increasing the amount of iodine used (2.0 eq.) and prolonging the reaction time to 4 h, reaction proceeded with better yields. Nonetheless, the highest yield we were able to reach was 76%.

Following reduction performed under Luche conditions ($NaBH_4$ in methanol, $CeCl_3 \cdot 7H_2O$) gave the iodinated alcohol **77** in great 94% yield (Scheme 29).



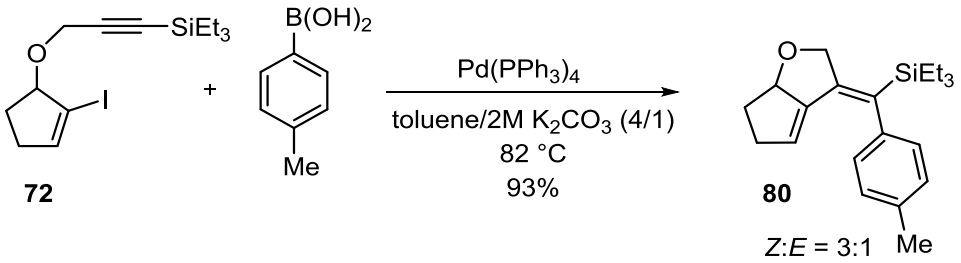
Scheme 29. Selective α-iodination of **71** followed by Luche reduction

Propargylation of iodinated alcohol **77** proceeded overnight at room temperature in THF to yield desired propargylated alcohol **78** that was simply capped with silyl using LiHMDS as a base followed by dropwise addition of TESCl at −78 °C to yield **72** in 82% yield (Scheme 30).



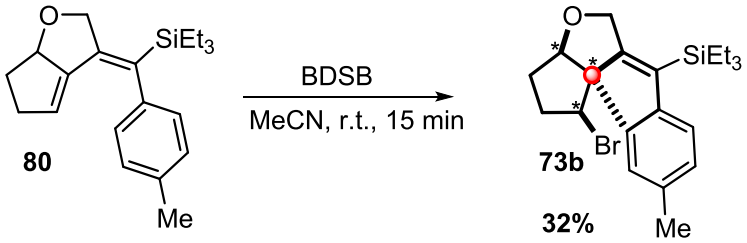
Scheme 30. Propargylation of alcohol **77** and subsequent silylation

This compound **72** was subjected to tandem cyclization/Suzuki cross-coupling reaction. Reaction was performed in toluene/2M aqueous solution K_2CO_3 (4/1 by volume) catalyzed by $Pd(PPh_3)_4$ (5 mol%) and gave **80** in 93% yield. We observed the formation of *Z*/*E* isomers in 3:1 ratio (Scheme 31).



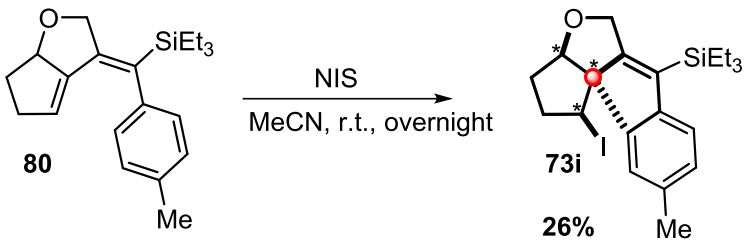
Scheme 31. Tandem cyclization/Suzuki cross coupling reaction forming **80** in 3:1 isomeric ratio

The mixture of isomers was first subjected to halocarbocyclization reaction using BDSB in anhydrous acetonitrile to yield the desired polycarbocyclic structure **73b** in 32% yield (Scheme 32).



Scheme 32. Halocarbocyclization reaction of **80** with BDSB

When NIS was used in halocarbocyclization reaction in anhydrous acetonitrile, longer reaction time was required for the full conversion of starting material. Desired final compound **73i** was isolated in 26% yield (Scheme 33).



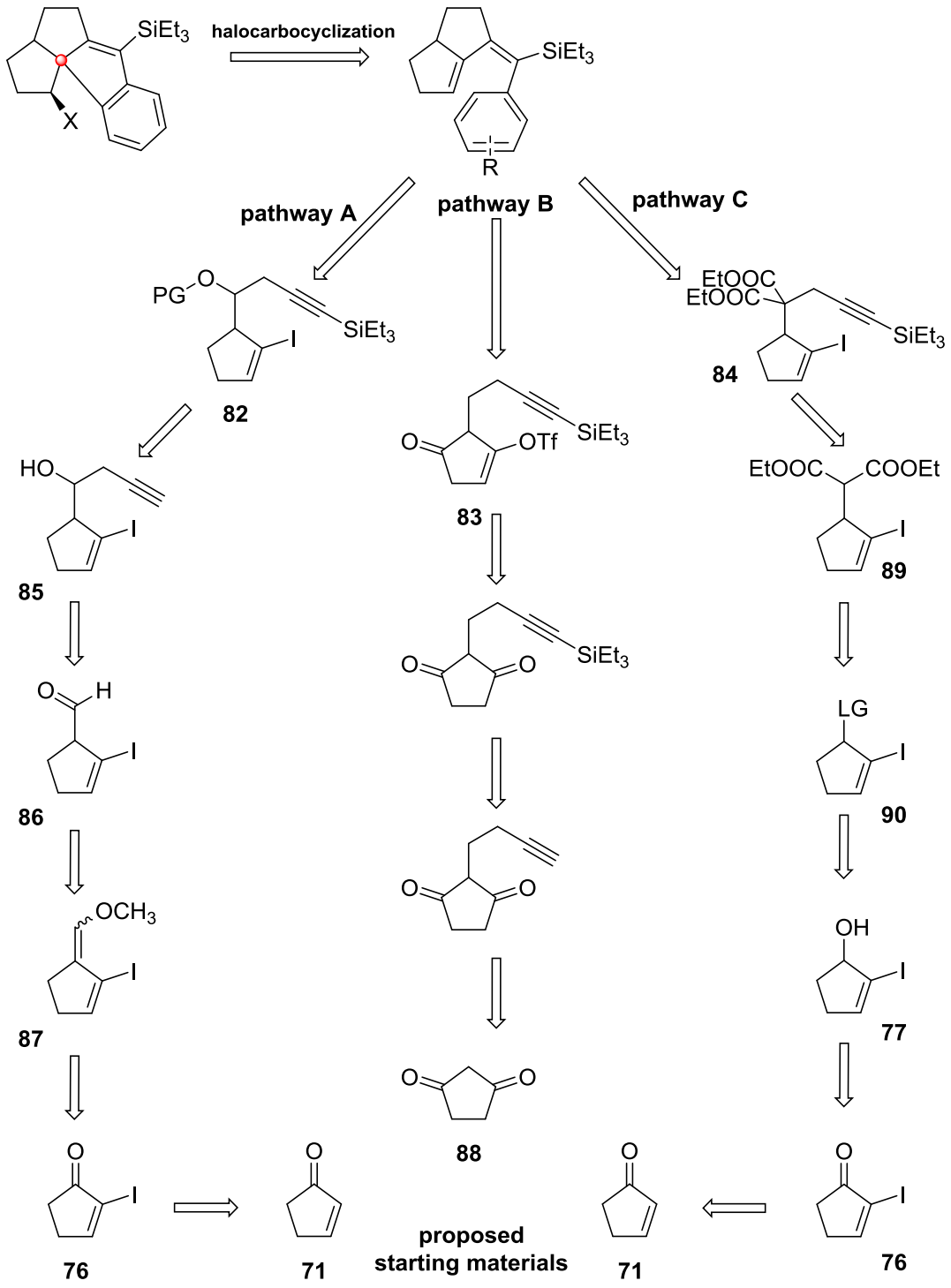
Scheme 33. Halocarbocyclization reaction of **80** with NIS

3.2 Synthetic plan for the preparation of carbocyclic compounds

Our synthesis of carbon derivatives bearing all-carbon quaternary center is based on the same key reaction sequence which was described above for oxygen-containing compounds.

In the course of this key sequence, two five-membered rings are formed. Tandem cyclization/Suzuki cross coupling allows the formation of first five-membered ring, while the halocarbocyclization reaction ensures the formation of latter one. At the same time all-carbon quaternary center is formed.

In order to accomplish this, starting materials **82**, **83**, **84** had to be prepared. We suggested three possible pathways leading to their preparation (Scheme 34).



Scheme 34. Retrosynthetic analysis of targeted polycarbocyclic structures

Pathway A – The first pathway suggests to perform tandem cyclization/Suzuki cross coupling reaction with a 2-iodoalkenyl substrate **82** with a protected hydroxyl group. This structure with protected alkynyl moiety and hydroxy group could be derived from **85** that could be attained by propargylation of aldehyde **86** prepared from ether **87** under acidic

conditions. Compound 87, in turn, can be prepared by Wittig reaction from the iodinated ketone **76**. Iodinated ketone is accessible from **71**.

Pathway B – Another suggested synthetic route involves a triflate bearing sililated enyne **83**. In that case, we could seek to perform direct alkynylation of commercially available 1,3-cyclopentanedione **88** using 4-bromobut-1-yne.

Pathway C – Alkynyl iodide capped with silyl **84** could be prepared from compound bearing diethylmalonate moiety **89**. This molecule could be prepared from 5-membered iodinated compound bearing a good leaving group **90** that could be traced back to starting 2-cyclopentene-1-one **71**.

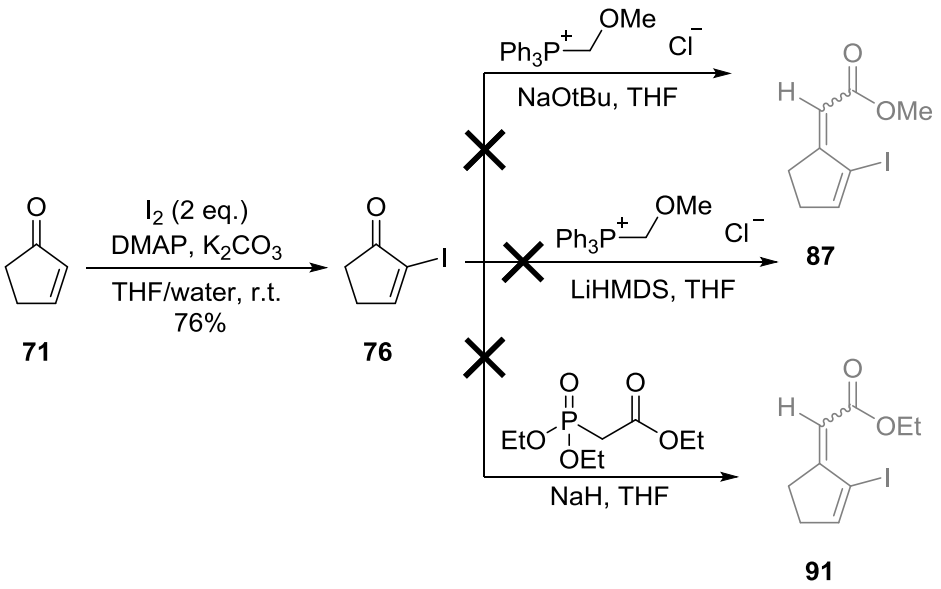
3.3 Synthesis of starting material for tandem cyclization

Pathway A

The first reaction in our pathway A was α-iodination that offered iodinated ketone **76**, which was reacted in Wittig reaction[26] with MMTPP in the presence of NaOtBu in THF, to form 1-iodo-5-(methoxymethylene)cyclopent-1-ene **87**. Although the formation of ylide was clearly observed by turning of the reaction mixture to deep purple, reaction did not yield the α,β-unsaturated methylester **87**.

The reaction was also tried with LiHMDS instead of tert-butoxide.[27] However, the outcome was the same, reaction did not proceed (Scheme 35).

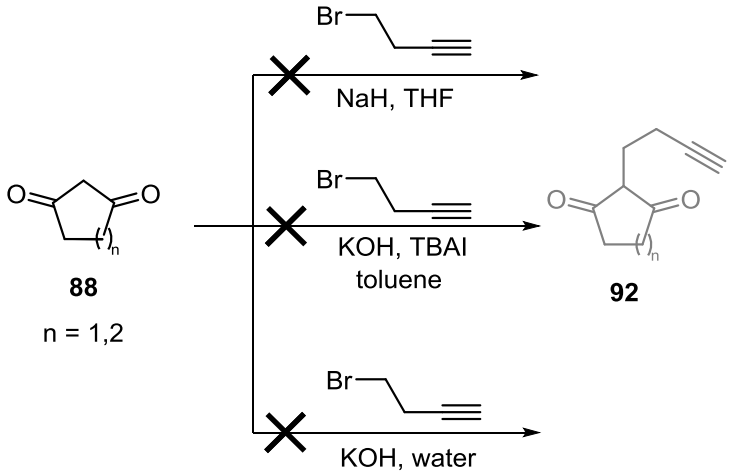
We then decided to submit iodinated ketone **76** to Horner-Emmons reaction conditions[26] instead, which should yield ethyl 2-(2-iodocyclopent-2-en-1-ylidene)acetate **91**. Triethyl phosphonoacetate reacted with NaH in dry THF at 0 °C as iodinated ketone was slowly dropwise added. Unfortunately, the reaction did not produce the desired α,β-unsaturated ethylester **91** (Scheme 35).



Scheme 35. Attempted synthesis of starting material for tandem cyclization (Pathway A)

Pathway B

As our previous reaction pathway did not work, we attempted a direct alkylation of cyclopentane-1,3-dione **88**. We made multiple attempts to carry out the butynylation of starting cyclopentane-1,3-dione. 4-Bromobutyne was used as an alkynylating agent in the presence of NaH as a base. Varying the temperature from 0 °C to 60 °C, did not yield the desired product **92** (Scheme 36).



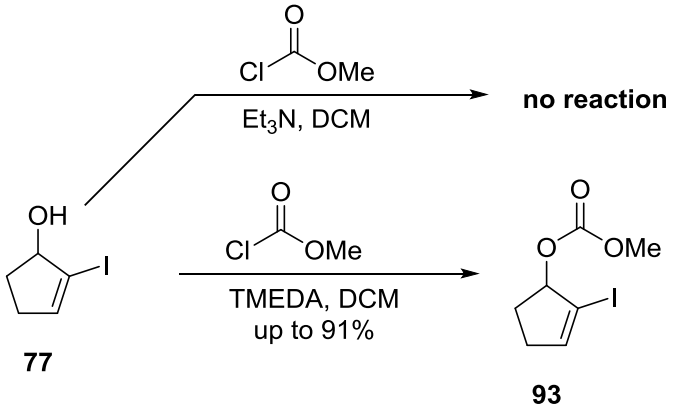
Scheme 36. Attempted synthesis of starting material for tandem cyclization (Pathway B)

Inspired by successful propargylation of cyclohexa-1,3-dione in basic aqueous environment (KOH), we tried to perform the butynylation of our starting cyclopentane-1,3-dione.[30] Unfortunately, we obtained a complex mixture instead.

Pathway C

In our continual attempt to prepare a carbocyclic derivative, we tried to transform the free hydroxy group of the starting iodinated alcohol **77** into a good leaving group so that substitution reaction could take place and the propargyl moiety could be in fact succesfully incorporated (Scheme 34).

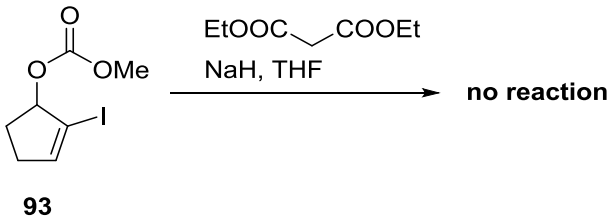
Firstly, iodinated alcohol **77** was treated with methylchloroformate (1.2 eq.) in excess of Et_3N (1.5 eq.) in dry DCM. Reaction proceeded at 0 °C, but no consuption of starting material was observed even after overnight stirring at room temperature. Heating up to 40 °C, or even 50 °C did not yield any detectable amount of the desired product.



Scheme 37. Formation of **93** from iodinated alcohol **77** using methylchloroformate and TMEDA

Following the procedure of Fukuda,[32] we decided to use TMEDA (1.5 eq.) as a base. Iodinated alcohol **77** was dissolved in dry DCM and accompanied with methylchloroformate (1.2 eq.) and TMEDA at 0 °C. Within 1 h, all starting material reacted and gave pale yellow liquid **93** in 81% yield. The same procedure was later repeated to offer 91% yield (Scheme 37).

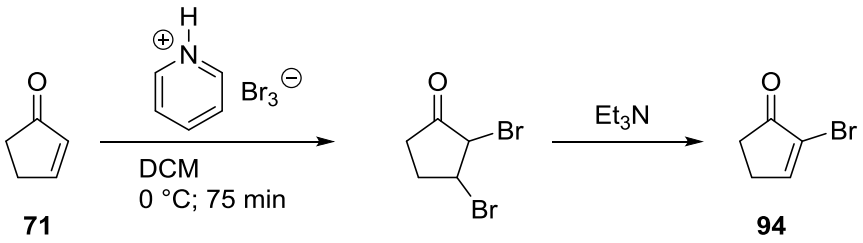
In the subsequent reaction, freshly prepared carbonate **93** was submitted to reaction with diethyl malonate (1.6 eq.) in the presence of NaH (1.6 eq.). Unfortunately, the reaction gave no desired product of substitution (Scheme 38). Replacing NaH with LiHMDS did not give any better result.



Scheme 38. Attempted substitution of **93**

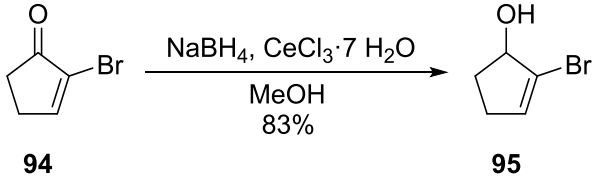
We then decided to prepare a brominated derivative and see whether this substitution reaction could proceed under Pd-catalyzed conditions. We reasoned that the presence of bromine in molecule could permit allylation to happen before the insertion of palladium into C-X bond occurs.[30]

Cyclopent-2-en-1-one **71** reacted with pyridinium tribromide (1.0 eq.) as a brominating reagent at 0 °C for the period of 75 min. When TLC analysis showed consumption of starting material, triethylamine (1.5 eq.) was added and reaction mixture turned from strong orange to pale gray and was let to react for additional 75 min. Brominated enone **94** was furnished in 67% yield as pale yellow liquid (Scheme 39).



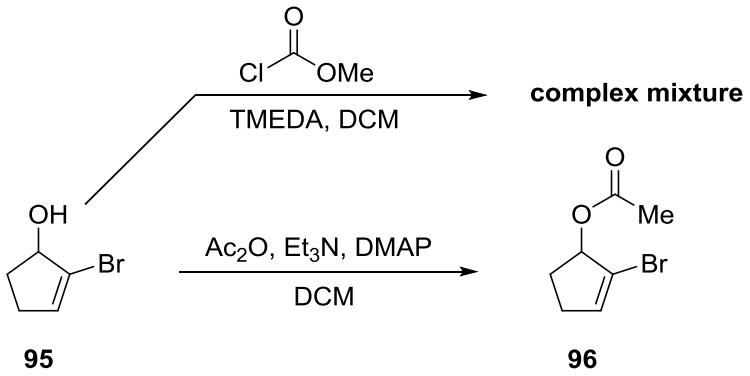
Scheme 39. Preparation of α-brominated enone **94**

The prepared 2-bromocyclopent-2-en-1-one **94** reacted in Luche reduction conditions to selectively give monobrominated 2-bromocyclopent-2-en-1-ol **95** as yellowish liquid in 83% yield (Scheme 40).



Scheme 40. Luche reduction of **94** offering alcohol **95**

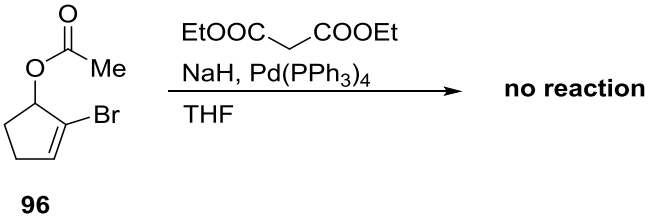
2-Bromocyclopent-2-en-1-ol **95** was reacted with methylchloroformate in dry DCM at 0 °C. TMEDA (1.5 eq.) was used as a base. Reaction proceeded overnight to give a complex mixture of products.



Scheme 41. Preparation of 2-bromocyclopent-2-en-1-yl acetate **96**

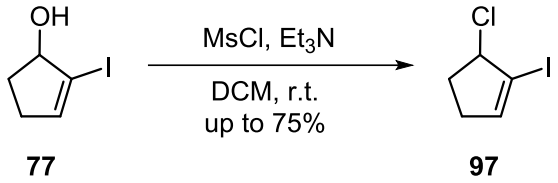
Next option was to use acetic anhydride to form acylated five-membered ring that could undergo the desired Pd-catalyzed substitution with diethylmalonate. With this in mind, 2-bromocyclopent-2-en-1-ol **95** was dissolved in DCM and subjected to reaction with Ac_2O (1.2 eq.) in the presence of Et_3N (1.3 eq.) along with the addition of catalytic amount of DMAP. Reaction was observed to proceed swiftly as the majority of starting material was reacted within 30 min at 0 °C. This procedure afforded 2-bromocyclopent-2-en-1-yl acetate **96** as white powder in 77% yield (Scheme 41).

Following the procedure[32] used for the substitution of 6-membered allylic acetate with dimethylmalonate in the presence of catalytic ammounts of $Pd(PPh_3)_4$ (0.04 eq.) and triphenylphosphine (0.12 eq.), we decided to subject 2-bromocyclopent-2-en-1-yl acetate **96** to the same reaction conditions as reported. Reaction temperature was continually raised to 40 °C, but did not yield the substituted product. Applying the refluxing conditions in THF, as suggested by Cossy did not lead to full conversion, neither to the formation of desired product (Scheme 42).



Scheme 42. Attempted substitution of **96**

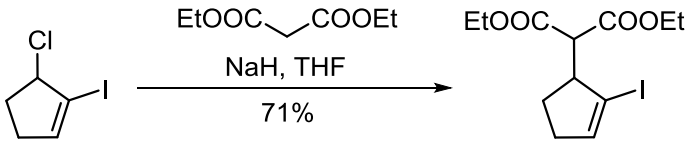
Because the applied conditions did not work, we returned to our efforts to form a better leaving group from starting iodinated alcohol **77**. Therefore **77** was treated with mesylchloride (1.3 eq.) in the presence of Et_3N (1.3 eq.) at room temperature. To our surprise, chloride **97** was formed under these conditions (Scheme 43). This compound tended to form starting alcohol back as soon as the column chromatography separation on silica was performed.



77 **97**

Scheme 43. Formation of chloride **97**

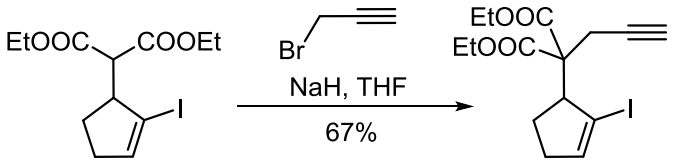
Freshly prepared 5-chloro-1-iodocyclopent-1-ene **97** was thought to swiftly react with diethylmalonate in THF. Indeed, when diethylmalonate was treated with NaH, the enolate was formed and underwent the following substitution that formed **89** (Scheme 44).[31]



97 **89**

Scheme 44. Reaction of chloride **97** with formed enolate gave **89**

Following propargylation performed in THF at reflux[31] gave the desired product **98** in 67%. yield (Scheme 45).

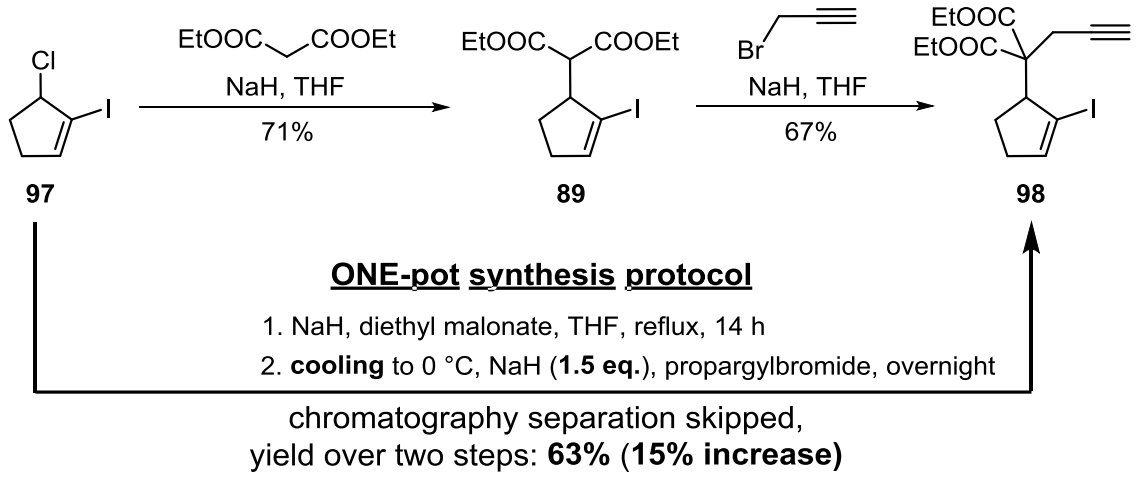


89 **98**

Scheme 45. Propargylation of **89**

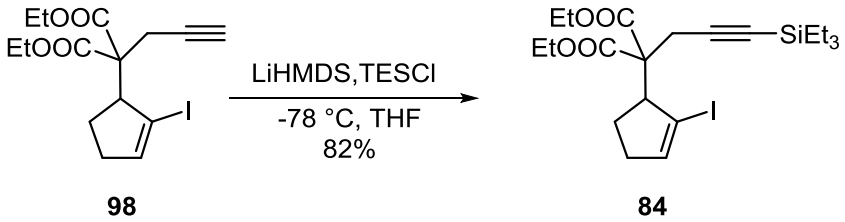
Upon realizing the nature of reaction conditions used in these two steps, we suspected that one-pot reaction procedure could be easily applied. Therefore 5-chloro-1-iodocyclopent-1-ene **97** was first reacted with activated diethylmalonate in THF refluxing conditions, then the reaction mixture was cooled down to 0 °C as the hydride was put in excess (1.5 eq.) along with the propargyl bromide. 2-Iodo-1,6-enyne **98** was isolated in 63% yield and therefore

saved us from tedious chromatographic separation, while at the same time offered an increased yield (Scheme 46).



Scheme 46. One-pot synthesis protocol leading to **98** from chloride **97** in an increased yield

Before subjecting this 2-iodo-1,6-enyne to tandem Heck-Suzuki reaction, free alkynyl bond was capped with silyl. In order to do so, LiHMDS was used as a base to cleave the acidic alkynyl proton and TESCl was used as sililating agent. Silylated product was isolated in 82% yield (Scheme 47).

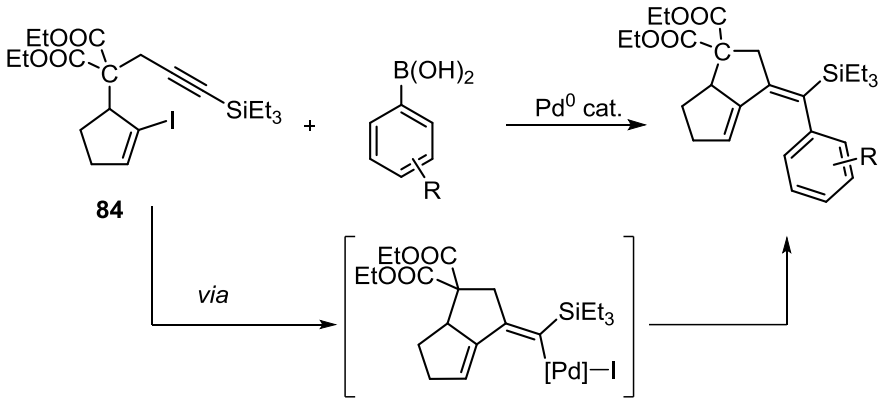


Scheme 47. Silylation of alkyne gave **84** in 82% yield

This starting material **84** for tandem cyclization/Suzuki cross coupling reaction was used for the following set of reactions.

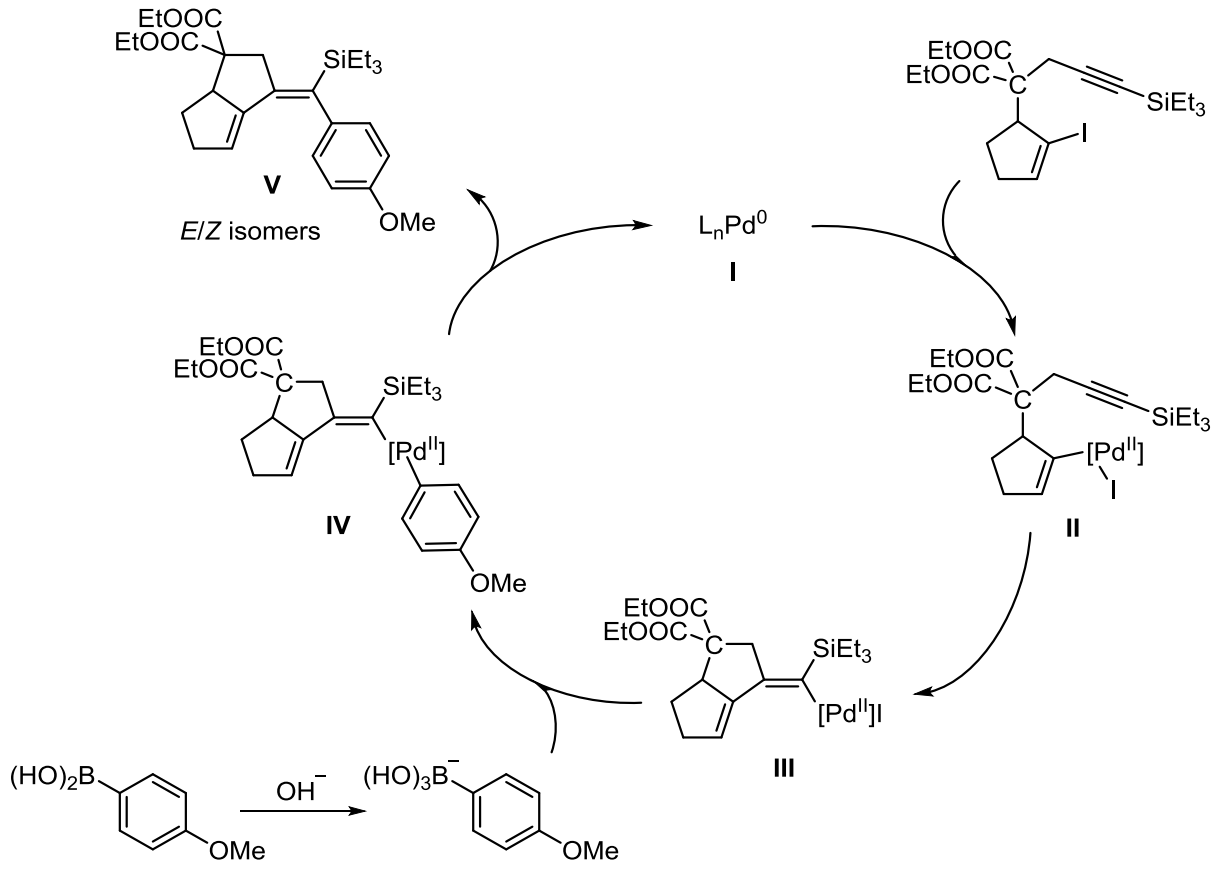
3.4 Tandem cyclization/Suzuki cross coupling reaction

Having corresponding silylated substrate **84** in hand, we could move to the planned tandem cyclization/Suzuki cross-coupling reaction (Scheme 48).



Scheme 48. Tandem cyclization/Suzuki cross-coupling reaction sequence

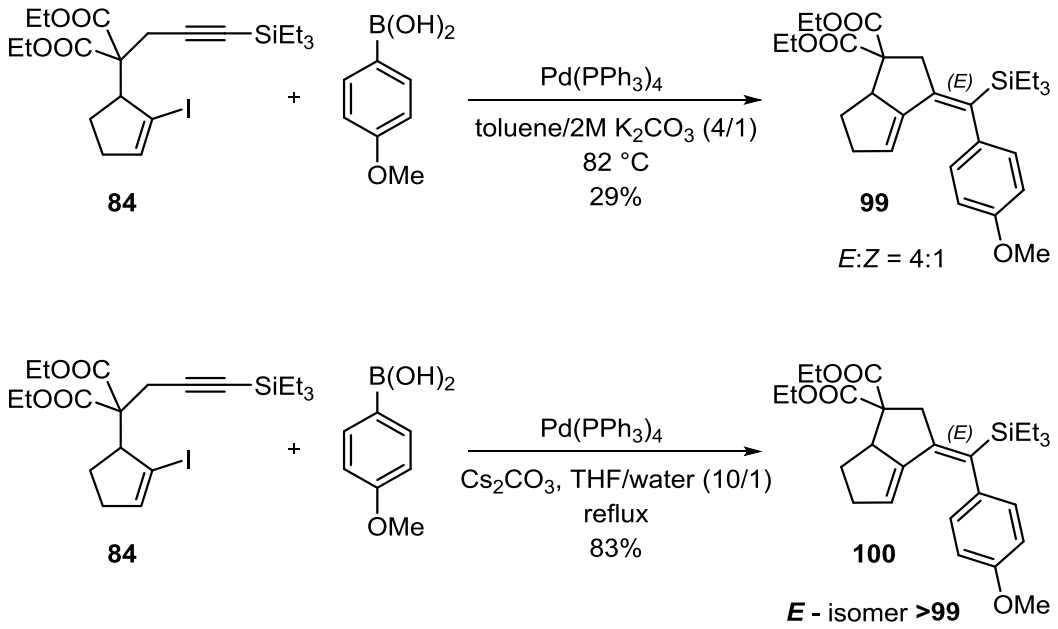
It is proposed,[19,32] that tandem cyclization/Suzuki cross-coupling reaction proceeds via following mechanism (Scheme 49): zero-valent palladium (L_nPd^0) **I** inserts to C-I bond in the process of oxidative addition to form a Pd^{II} intermediate **II** that readily accepts the electron density from the triple bond. As a result a new C-C bond is formed along with a 5-membered ring with an external double bond. The Pd^{II} intermediate **III** reacts further in Suzuki cross-coupling reaction, with an activated arylboronic acid to form intermediate **IV**. Lastly, reductive elimination leads to the formation of coupling product **V** and Pd^0 is further reused in a catalytic cycle.



Scheme 49. Proposed mechanism for tandem cyclization/Suzuki cross-coupling reaction sequence

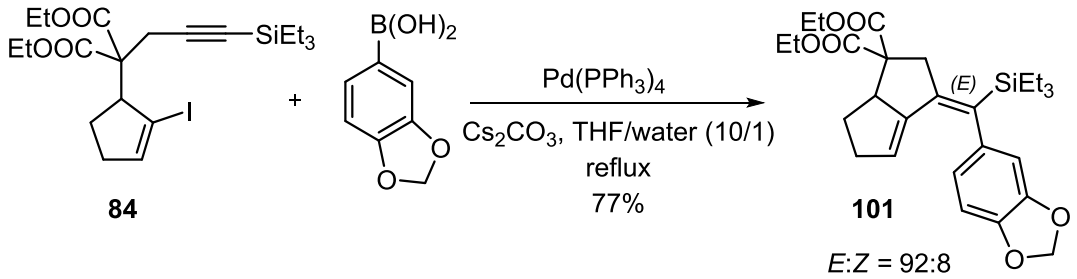
First, we performed tandem cyclization/Suzuki cross coupling reaction between silylated iodo-alkyne **84** and 4-methoxyphenylboronic acid (1.6 eq.) in the presence of K_2CO_3 as a base in toluene at 82 °C. Simple $Pd(PPh_3)_4$ (5 mol%) was used as a catalyst. Reaction proceeded overnight (16 h) to offer **99** in a rather low 29% yield. We observed the formation of isomers in 4:1 ratio (*E*:*Z*) (Scheme 50).

We decided to apply Cs_2CO_3 as a base in THF/water (10/1) while leaving $Pd(PPh_3)_4$ (5 mol%) as a catalyst. Reaction proceeded overnight to offer **100** in much increased yield (83%). Interestingly enough, we observed the selective formation of *E*-isomer at these conditions (Scheme 50).



Scheme 50. Products of tandem cyclization/Suzuki cross-coupling reaction **99**,**100** differing by the base used in reaction sequence.

Additionally, we subjected the silylated iodo-alkyne **84** to react with 3,4-(methylenedioxy)phenylboronic acid (1.6 eq.) in the presence of Cs_2CO_3 as a base in THF/water (10/1). Simple $Pd(PPh_3)_4$ (5 mol%) was used as a catalyst. Reaction proceeded overnight to give **101** in a lower 77% yield (Scheme 51). We observed the formation of isomers in 92:8 ratio (*E*:*Z*)

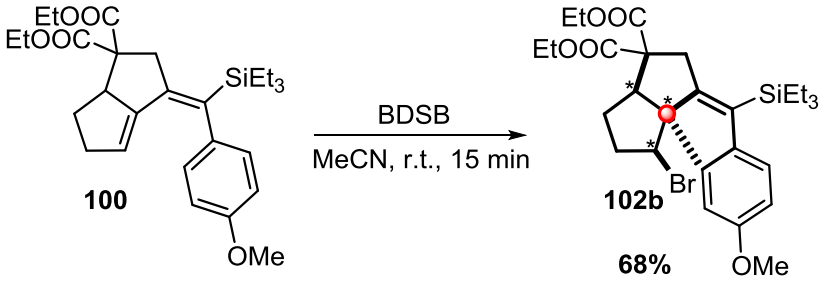


Scheme 51. Tandem cyclization/Suzuki cross-coupling reaction of **84** with 3,4-(methylenedioxy)phenylboronic acid gave **101**.

3.5 Halocarbocyclization reactions

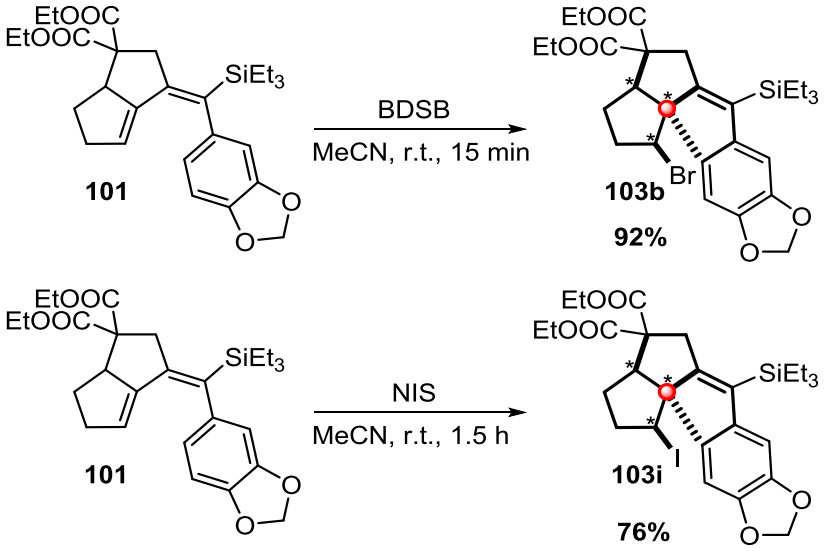
Having successfully accomplished tandem cyclization/Suzuki cross-coupling reaction step, we approached the terminal halocarbocyclization step and thus creating all-carbon quaternary centers.

Carbocyclic derivative bearing electron donating *p*-methoxy group **100** was transformed to the desired product **102b** in 68% yield. Reaction was performed in anhydrous acetonitrile, using BDSB as the source of Br^+ and was terminated after 15 min (Scheme 52).



Scheme 52. Halocarbocyclization of **100** using BDSB gave **102b** in 68% yield

Another two carbocyclic derivatives containing all-carbon quaternary center were successfully prepared. Reaction of **101** with BDSB gave the desired product **103b** in 92% yield, whereas reaction with NIS furnished **103i** in 75% yield (Scheme 53), but required longer reaction time (1.5 h).



Scheme 53. Halocarbocyclization of **101** using BDSB gave **103b** in 92% yield, whereas using NIS gave **103i** in 76% yield.

4. Experimental section

4.1 General Comments

All commercially available chemicals were purchased and used without further purification. Solvents were purified and dried by distillation as follows: tetrahydrofuran (THF) from sodium/benzophenone, dichloromethane (DCM) from calcium hydride. Anhydrous acetonitrile was purchased from VWR Chemicals and used without further purification. Ethyl acetate and hexane used for chromatography separation were distilled prior to their use.

Nuclear magnetic resonance spectra

^{1}H, ^{13}C NMRspectra were measured with a Bruker AVANCE III HD 400 spectrometer or VARIAN VNMR 300 spectrometer at 298 K in $CDCl_3$. Chemical shifts (δ/ppm) are referenced to residual CDCl3 signal. (^{1}H, δ = 7.26; ^{13}C, δ = 77.0). Coupling constants *J* are given in Hz, multiplicity is defined as s = singlet, d = doublet, t = triplet, q = quartet, m= multiplet.

Infrared sprectra

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-infrered (4000-400 cm^{-1}) region.

Mass spectra

Low-resolution electrospray ionization (ESI) mass spectra were obtained with LTQ Orbitrap XL or Shimadzu QP 2010 instruments. High resolution mass spectra were recorded on VG-Analytical ZAB-SEQ.

The course of the reactions was monitored by analytical thin layer chromatography (TLC) performed on Merck Slica gel 60-F254 coated aluminum plates. Eluated plates were then visualized under UV light (254 nm, 365 nm) and subsequently treated with a suitable dip followed by heating. Following dips were most often used:

a) Anisaldehyde dip: CH_3COOH (99%, 6 mL), anisaldehyde (8 mL), CH_3CH_2OH (400 mL), H_2SO_4 (20 mL)

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

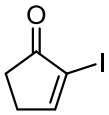
c) $KMnO_4$ dip: $KMnO_4$ (3 g), K_2CO_3 (20 g), 10% NaOH (2.5 mL) and 300 mL distilled water

d) Vanillin dip: vanillin (15g), ethanol (250 mL), conc. H_2SO_4 (2.5 ml)

Flash column chromatography was performed using Acros Organics silica gel 60A, (0.035 – 0.070 mm).

4.2 Synthetic procedures

2-Iodocyclopent-2-en-1-one (76)

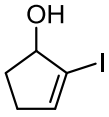


76

Starting 2-cyclopentene-1-one **71** (1.001 g) was dropwise introduced to 100mL reaction flask and dissolved in 25 mL THF. Then K_2CO_3 (2.02 g, 14.6 mmol) was added at once followed by iodine (6.20 g, 24.4 mmol) added in parts over 2 min. Addition of DMAP (295 mg, 2.4 mmol) was followed and reaction proceeded at room temperature for 3.5 hours. Reaction was quenched by adding 25 mL of a saturated aqueous solution of $Na_2S_2O_3$ (125 mL) and extracted between brine (20 mL) and EtOAc (2 × 50mL, 3 × 25mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Obtained purple liquid was was purified by column chromatography (90/10 hexanes/EtOAc) to obtain transparent oily liquid, that almost immediately turns to white crystalline powder after cooling it down and placing it under vacuum to dry. This procedure afforded 2-iodocyclopent-2-en-1-one **76** as white crystalline powder (1.923 g, 76%). The recorded spectral data were in agreement with previously reported values.[33]

^{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); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.9, 169.5, 102.9, 31.2, 30.9.

Iodocyclopent-2-en-1-ol (77)



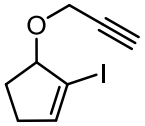
77

Freshly prepared 2-iodocyclopent-2-en-1-one **76** (1.001 g, 4.81 mmol) was kept in a 100mL reaction flask and dissolved in distilled MeOH (50 mL). Then $CeCl_3 \cdot 7H_2O$ (4.03 g, 10.83 mmol) was added in parts over 1 min, When dissolved (2 min), $NaBH_4$ (228 mg, 6.02 mmol) was added carefully while immersed into pre-cooled ice-cold bath. Reaction first proceeded for 10 min at 0°C, then was allowed to warm to ambient temperature. Reaction was quenched with distilled water (10 mL) and let it

stir for additional 10 min. Methanol was evaporated and remaining reaction mixture was then extracted with EtOAc (20mL, 3 × 15mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Crude was not further purified to yield desired iodocyclopent-2-en-1-ol **77** as yellowish oil of sweet-flower smell (956 mg, 94%). The recorded spectral data were in agreement with previously reported values.[34]

^{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); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.6, 100.2, 82.3, 32.8, 31.5.

1-Iodo-5-(prop-2-yn-1-yloxy)cyclopent-1-ene (78)

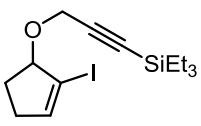


78

Alcohol **77** was dissloved in dry THF (44 mL) under an argon atmosphere, then propargylbromide (3.69 g, 24.8 mmol) and tetrabutylammonium iodide (0.51 g, 1.4 mmol) were added. The reaction mixture was cooled to 0 °C before NaH (0.99 g of a 60% dispersion in mineral oil, 24.8 mmol) was added portionwise, stirred for 10 min at 0 °C, then warmed to room temperature and stirred for additional 24 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (60 mL) and extracted into EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (9/1 hexanes/EtOAc) to provide the title compound **78** as a light yellow amorphous solid (3.12 g, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) 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, $CDCl_3$) δ 144.2, 95.3, 88.3, 80.0, 74.3, 56.5, 32.9, 29.1; **IR** (KBr) ν_{max} 3294, 2935, 2848, 1601, 1449, 1350, 1078, 922, 815, 671, 641 cm^{-1}; **MS** (EI) *m/z* (%) 248.0 (100, $M^{+\bullet}$), 208.9 (51), 193.0 (30), 126.9 (28), 121.1 (52), 91.1 (53); **HRMS** (EI) *m/z* calcd for C_8H_9IO 247.9698, found 247.9691.

1-Iodo-5-[3-(triethylsilyl)prop-2-yn-1-yloxy]cyclopent-1-ene (79)



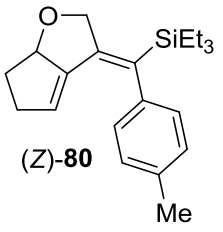
79

Compound **78** (2.98 g, 12.0 mmol) was dissolved in dry THF (11 mL) under an argon atmosphere and cooled to -78°C. LiHMDS (14.4 mL of a 1 M solution in THF, 14.4 mmol) was added, and the mixture was stirred at -78 °C for 1 h before chlorotriethylsilane (2.17 g, 14.4 mmol) was added at the

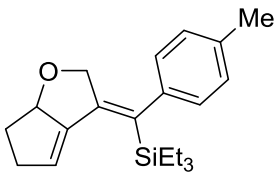
same temperature. The reaction mixture was warmed to room temperature and stirred for 1 h, then it was quenched with a saturated aqueous solution of NH_4Cl (15 mL), and extracted between brine (20 mL) and EtOAc (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (95/5 hexanes/EtOAc) to provide the title compound **79** as a brownish oil (4.33 g, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (td, *J* = 2.5, 1.0 Hz, 1H), 4.67–4.61 (m, 1H), 4.30 (d, *J* = 16.2 Hz, 1H), 4.23 (d, *J* = 16.2 Hz, 1H), 2.52–2.42 (m, 1H), 2.33–2.15 (m, 2H), 2.02–1.92 (m, 1H), 0.99 (t, *J* = 7.9 Hz, 9H), 0.61 (q, *J* = 7.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.0, 102.9, 95.7, 88.7, 88.1, 57.4, 32.9, 29.2, 7.4, 4.2; **IR** (KBr) ν_{max} 2954, 2910, 2874, 2172, 1458, 1348, 1236, 1081, 1018, 990, 738, 727 cm^{-1}; **MS** (EI) *m/z* (%) 362.1 (2, $M^{+\bullet}$), 333.0 (95), 303.0 (94), 275.0 (88), 205.1 (100), 192.9 (100), 139.1 (58), 113.0 (57), 66.0 (55); **HRMS** (EI) *m/z* calcd for $C_{14}H_{23}IOSi$ 362.0563, found 362.0562.

((6,6a-Dihydro-2*H*-cyclopenta[*b*]furan-3(5*H*)-ylidene)(p-tolyl)methyl)triethylsilane (80)



(*Z*)-**80**



(*E*)-**80**

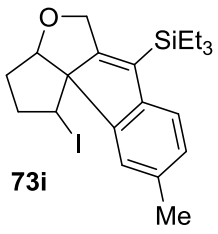
Reaction flask charged with sililated alkyne **79** (190 mg, 0.52 mmol), *p*-tolylboronic acid (106 mg, 0.78 mmol) was dissolved in toluene/2M K_2CO_3 (16 mL/4 mL). Reaction mixture was then immediately degassed and backfilled with the argon. $Pd(PPh_3)_4$ (23.1 mg, 0.02 mmol) was carefully added to the reaction mixture, degassed twice and backfilled with argon. Reaction mixture was heated at 82°C overnight (16h), then was allowed to cool to ambient temperature and quenched with 1M HCl (12 mL). Extracted with EtOAc (4 × 25 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure, crude was then purified by flash chromatography on silica gel (95/5 hexanes/EtOAc) and gave yellowish oil **80** (158.8 mg, 93%).

(*Z*)**-80: ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.12–7.08 (m, 2H), 6.92–6.80 (m, 2H), 4.89 (d, *J* = 13.0 Hz, 1H), 4.87–4.80 (m, 1H), 4.75 (d, *J* = 13.0 Hz, 1H), 4.54 (dt, *J* = 4.1, 2.2 Hz, 1H), 2.59–2.48 (m, 1H), 2.45– 2.36 (m, 1H), 2.34 (s, 3H), 2.20–2.12 (m, 1H), 1.66 (ddt, *J* = 11.9, 10.3, 8.7 Hz, 1H), 0.92 (t, *J* = 7.9 Hz, 9H), 0.60–0.52 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 147.1, 143.4, 141.7, 135.8, 134.9, 129.4, 128.6, 126.9, 124.9, 89.9, 77.2, 36.7, 32.6, 21.1, 7.44, 3.5.

(*E*)-**80:** **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.10–7.06 (m, 2H), 6.82–6.78 (m, 2H), 5.99 (dt, *J* = 3.9, 2.1 Hz, 1H), 5.01–4.95 (m, 1H), 4.40 (d, *J* = 14.0 Hz, 1H), 4.32 (d, *J* = 14.0 Hz, 1H), 2.88–2.69 (m, 2H), 2.34 – 2.25 (m, 1H), 2.32 (s, 3H), 1.86–1.75 (m, 1H), 0.88 (t, *J* = 7.9 Hz, 9H), 0.68–0.56 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 146.3, 143.7, 141.3, 136.5, 134.8, 128.9, 126.6, 125.4, 91.2, 77.6, 36.8, 33.0, 21.1, 7.6, 3.3.

(*Z*)-**80**+(*E*)-**80: IR** (KBr) ν 2958, 2870, 1505, 1458, 1318, 1074, 1005, 964, 910, 729, 808 cm^{-1}; **MS** (EI) *m/z* (%) 327.2 (25, $[M+H]^+$), 326.2 (92, $M^{+\bullet}$), 311.2 (21), 308.2 (41), 298.2 (100, $[M-Et]^{+\bullet}$), 297.2 (51), 295.2 (44), 279.2 (63), 267.1 (34), 195.1 (73), 115.1 (15), 87.1 (14); **HRMS** (EI) *m/z* calcd for $C_{21}H_{30}OSi$ 326.2066, found 326.2063.

Triethyl(1-iodo-1,2,3,3a-tetrahydro-5*H*-cyclopenta[2',3']furo[3',4':1,2]indeno[5,6-*d*][1,3]dioxol-6-yl)silane (73i)

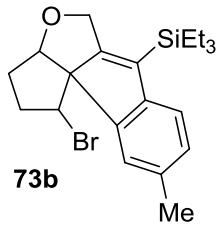


73i

25mL reaction flask containing **80** (81.0 mg, 0.25 mmol) was wrapped in aluminum foil and NIS (69.2 mg, 0.30 mmol) was carefully added. Reaction vial was backfilled with argon, then dissolved in dry acetonitrile (3 mL) at room temperature. Reaction was quenched with $Na_2S_2O_3$ (1.5 mL). Dark purple reaction mixture was allowed to stir for 10 min, organic phase was washed with brine (2 × 2.5 mL) and water phase washed with EtOAc (2 × 1.5 mL). Combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure giving orange liquid that was purified by flash chromatography on silica gel (90/10 hexanes/EtOAc) and gave transparent oil of the desired product **73i** (21.5 mg, 26%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 1H), 6.65 (s, 1H), 5.96–5.94 (m, 2H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.40 (dd, *J* = 11.5, 7.3 Hz, 1H), 4.29 (d, *J* = 11.5 Hz, 1H), 4.02 (d, *J* = 2.7 Hz, 1H), 2.67–2.49 (m, 2H), 2.10 (dd, *J* = 13.4, 5.8 Hz, 1H), 1.84–1.73 (m, 1H), 1.00 (t, *J* = 7.8 Hz, 9H), 0.85–0.78 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.5, 147.4, 145.3, 144.2, 140.4, 134.1, 103.8, 103.6, 101.2, 83.2, 72.8, 67.1, 38.2, 36.6, 30.2, 7.5, 3.8; **IR** (KBr) νmax 2953, 2911, 2875, 1473, 1335, 1299, 1153, 1033, 1003, 943, 857, 716 cm^{-1}; **MS** (EI) *m/z* (%) 483.1 (12, $[M+H]^+$), 482.1 (91, $M^{+\bullet}$), 355.2 (100), 338.2 (36), 253.1 (21), 222.1 (51), 165.1 (28), 115.1 (26), 87.1 (40); **HRMS** (EI) *m/z* calcd for $C_{21}H_{27}O_3SiI$ 482.0774, found 482.0760.

(1-Bromo-1,2,3,3a-tetrahydro-5*H*-cyclopenta[2',3']furo[3',4':1,2]indeno[5,6-*d*][1,3]dioxol-6-yl)triethylsilane (81b)

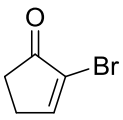


73b

Freshly prepared **80** (51.2 mg, 0.16 mmol), BDSB (90.4 mg, 0.17 mmol) were put under argon, then dissolved in dry acetonitrile (2 mL) at ambient temperature. After 10 min (TLC run after 5 min, detected as azure blue spot under CPM), reaction was quenched with $Na_2S_2O_3$ (2.5 mL). Reaction mixture was extracted with EtOAc (4 × 2 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Crude was then purified by flash chromatography on silica gel (95/5 hexanes/EtOAc) and gave transparent oil of the desired product **73b** (45.7 mg, 32%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 1H), 6.66 (s, 1H), 5.95 (s, 2H), 4.61 (d, *J* = 11.5 Hz, 1H), 4.44 (dd, *J* = 9.7, 8.5 Hz, 1H), 4.38 (d, *J* = 11.5 Hz, 1H), 4.08 (d, *J* = 2.3 Hz, 1H), 2.59–2.49 (m, 2H), 2.22–2.14 (m, 1H), 1.81 (dtd, *J* = 13.2, 10.0, 9.1, 2.9 Hz, 1H), 0.98 (t, *J* = 7.6 Hz, 9H), 0.84–0.76 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.3, 147.4, 145.3, 144.5, 140.9, 134.0, 103.8, 103.7, 101.2, 84.1, 72.5, 67.0, 54.7, 36.2, 34.8, 7.4, 3.7; **IR** (KBr) νmax 2956, 2911, 2869, 1473, 1305, 1153, 1036, 1021, 1006, 943, 860, 728 cm^{-1}; **MS** (EI) *m/z* (%) 436.1 (21, $M^{+\bullet}$), 434.1 (20, $M^{+\bullet}$), 355.1 (100), 354.2 (85), 325.1 (43), 281.1 (43), 252.1 (34), 224.1 (55), 165.1 (51), 115.1 (50), 87.1 (58); **HRMS** (EI) *m/z* calcd for $C_{21}H_{27}O_3SiBr$ 434.0913, found 434.0911.

2-Bromocyclopent-2-en-1-one (94)



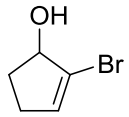
94

2-cyclopentene-1-one **71** (86 μL, 1 mmol) was dissolved in dry DCM (4 mL) and immersed to ice-cold bath. Tribromopyridinium (355 mg, 90% purity, 1 mmol) was carefully added over the course of 5 min. Complete consumption of starting material was observed after 75 min. Reaction was allowed to warm to room temperature and Et_3N (0.21 mL, mmmol) was dropwise added over 2 min. Reaction was quenched after 1.5h by adding 10 mL 10% HCl. Additional DCM (10 mL) was added and reaction mixture was washed with brine (2 × 8 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Obtained yellowish powder was then purified by column chromatography (1/1 hexanes/EtOAc, short layer) to obtain transparent oily liquid. This procedure afforded 2-bromocyclopent-2-en-1-one **94** as white crystalline powder (108 mg, 67%). The recorded spectral data were in agreement with

previously reported values.[35]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (m, 1H), 2.72–2.68 (m, 2H), 2.55–2.52 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 201.7, 161.7, 126.3, 32.4, 28.0.

2-Bromocyclopent-2-en-1-ol (95)

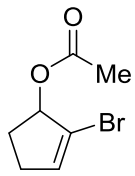


95

Freshly prepared 2-bromocyclopent-2-en-1-one **94** (1.061 g, 6.59 mmol) was kept in a 100mL reaction flask and dissolved in distilled MeOH (25 mL). Then $CeCl_3 \cdot 7H_2O$ (5.524 g, 14.83 mmol) was added in parts over 2 min. When dissolved, $NaBH_4$ (318 mg, 8.24 mmol) was added carefully while immersed into pre-cooled ice-cold bath. Reaction first proceeded for 10 min at 0°C, then was allowed to warm to ambient temperature. Reaction was quenched after 45 min with distilled water (15 mL), then stirred for additional 30 min. Methanol was evaporated and remaining reaction mixture was then extracted with EtOAc (2 × 25mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Crude was not further purified to yield desired 2-bromocyclopent-2-en-1-ol **95** as yellowish liquid (893 mg, 83%). The recorded spectral data were in agreement with previously reported values.[36]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (m, 1H), 4.73–4.68 (m, 1H), 2.48–2.34 (m, 2H), 2.32–2.25 (m, 1H), 1.97 (s, 1H), 1.91–1.87 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 134.2, 124.9, 79.4, 31.9, 30.3.

2-Bromocyclopent-2-en-1-yl acetate (96)

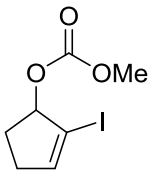


96

2-bromocyclopent-2-en-1-ol **95** (52 mg, 0.318 mmol) was introduced to 10mL reaction flask, immersed to ice-cold bath and dissolved in DCM (2 mL). Et_3N (58µL, 0.416 mmol) was added along Ac_2O (36µL, 0.382 mmol) followed by addition of catalytic amount of DMAP. After 30 min, reaction mixture was transferred to separatory funnel, quenched with saturated NH_4Cl (10 ml). Additional DCM (5 mL) was added. Organic phase was then washed with saturated NH_4Cl (2 × 6 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Crude was not further purified to yield desired 2-bromocyclopent-2-en-1-yl acetate **96** as white crystalline powder (50 mg, 77%). The recorded spectral data were in agreement with previously reported values.[36]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21–6.18 (m, 1H), 5.72–5.67 (m, 1H), 2.51–2. 40 (m, 2H), 2.37–2.29 (m, 1H), 2.10 (s, 3H), 1.92–1.85 (m, 1H).

2-Iodocyclopent-2-en-1-yl methyl carbonate (93)

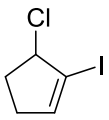


93

2-iodocyclopent-2-en-1-ol **77** (211 mg, 1.00 mmol) was introduced to 25mL reaction flask under argon and dissolved in dry DCM (6 mL). Reaction flask was immersed to ice-cold bath, TMEDA (225µL, 1.50 mmol) was added along methylchloroformate (93µL, 1.20 mmol). After 30 min, reaction mixture was quenched with saturated NH_4Cl (10 mL) and diluted with EtOAc (2 × 15mL). Organic phase was then washed with brine (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Crude was not further purified to yield 2-iodocyclopent-2-en-1-yl methyl carbonate **93** as yellowish liquid (242.6 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46–6.44 (m, 1H), 5.61–5.57 (m, 1H), 3.81 (s, 3H), 2.56–2. 47 (m, 1H), 2.45–2.30 (m, 2H), 2.01–1.94 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.3, 146.4, 91.5, 87.7, 54.9, 32.9, 29.8.

5-Chloro-1-iodocyclopent-1-ene (97)

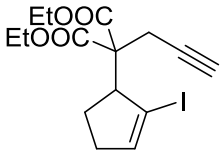


97

Starting iodinated alcohol **77** (573 mg, 2.73 mmol) kept in a 100mL reaction flask was dissolved in CH_2Cl_2 (20 mL) at ambient temperature, stirred and then immersed to ice-cold bath. Et_3N (570 µL, 4.09 mmol) was added dropwise, followed by the dropwise addition of MsCl (320 µL, 4.13 mmol) at 0 °C. After 30min ice-cold bath was removed and reaction mixture was kept stirring at ambient temperature for additional 4 hours as the continual color change from transparent to slight yellow was observed. The reaction was quenched by the addition of saturated aqueous solution of NH_4Cl (20 mL). The reaction mixture was then extracted between brine (20 mL) and EtOAc (3 × 15mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Strongly red liquid of mustard smell was purified by column chromatography (90/10 hexanes/EtOAc) providing the titled compound **97** as yellowish oily liquid (386 mg, 62%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (m, 1H), 4.88 (dt, J = 7.3, 2.2 Hz, 1H), 2.69–2.56 (m, 1H), 2.55–2.42 (m, 1H), 2.40–2.26 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 145.3, 72.4, 34.1, 33.0; **IR** (KBr) ν 2968, 2939, 2879, 1594, 1312, 1264, 1230, 1014, 913, 793, 710 cm^{-1};

Diethyl 2-(2-iodocyclopent-2-en-1-yl)-2-(prop-2-yn-1-yl)malonate (98)

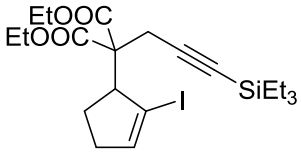


98

Pre-heated reaction flask was charged with 218 mg NaH (5.46 mmol, 60% in mineral oil), flushed with argon and dissolved in freshly dried THF (15 mL) and stirred at room temperature, then immersed into an ice-cold bath. Meanwhile 5-chloro-1-iodocyclopent-1-ene **97** (830 mg, 3.64 mmol) was kept ready under argon. Diethylmalonate (660 μL, 4.37 mmol) was added dropwise over 1.5 min, while vigorous bubling persisted. Immediately the addition of 5-chloro-1-iodocyclopent-1-ene [CODE] followed. Over the course of 10 min, reaction mixture turned dark purple and was refluxed at 76 °C for 16 h. Reaction mixture was then once again flushed with argon, immersed into ice-cold bath as the addition of NaH (218 mg, 5.46 mmol, 60% in mineral oil), was followed by the dropwise addition of propargyl bromide (608 μL, 5.46 mmol, 80% in toluene). Reaction was kept at room temperature for 5 h, then quenched with brine (15 mL) and taken up with EtOAc (4 × 15 mL). Dark-orange crude was purified by flash chromatography on silica gel (95/5 hexanes/EtOAc) and gave yellowish crystalline product **98** of spicy smell. (898 mg, 63%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37–6.32 (m, 1H), 4.28–4.19 (m, 4H), 3.88–3.80 (m, 1H), 3.23 (dd, *J* = 17.3, 2.8 Hz, 1H), 2.77 (dd, *J* = 17.3, 2.7 Hz, 1H), 2.42–2.19 (m, 4H), 2.02 (t, *J* = 2.7 Hz, 1H), 1.31–1.26 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.3, 169.0, 145.9, 91.6, 80.1, 71.0, 61.9, 61.7, 60.4, 54.4, 33.2, 26.9, 22.6, 14.0, 13.9; **IR** (KBr) *v* 3288, 3276, 2980, 2941, 2902, 2851, 1736, 1464, 1446, 1425, 1389, 1368, 1278, 1228, 1189, 1096, 1072, 1027, 866 cm^{-1}; **MS** (ESI) *m/z* (%) 413.0 (100, $[M+Na]^+$), 414.1 (16); **HRMS** (ESI) *m/z* calcd for $C_{15}H_{19}IO_4Na$ $[M+Na]^+$ 413.0220, found 413.0221

Diethyl 2-(2-iodocyclopent-2-en-1-yl)-2-(3-(triethylsilyl)prop-2-yn-1-yl)malonate (84)



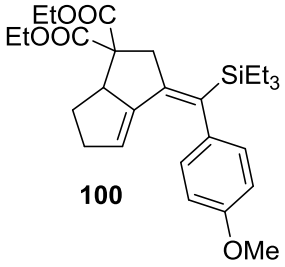
84

Freshly prepared terminal alkyne **98** (898 mg, 2.301 mmol) was dissolved in dry THF (25 mL), flushed with argon and then immersed to −78 °C bath while LiHMDS (2.90 mL, 2.9 mmol) was carefully added dropwise over 1.5 min and allowed to react for 1 h. Neatly purified TESCl (490 μL, 2.86 mmol) was added dropwise over 1 min. Inert atmosphere was ensured while the reaction mixture was allowed to be warmed up to room temperature and stirred for 1 h. Reaction was finally quenched with saturated aqueous solution of NH_4Cl (25 mL), stirred and then extracted with EtOAc (4 × 15

mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Desired compound **84** was further purified by flash chromatography on silica gel (95/5 hexanes/EtOAc) and gave yellowish oil with a strong mint odor. (1.087 g, 94%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (m, 1H), 4.26–4.15 (m, 4H), 3.86–3.79 (m, 1H), 3.29 (d, *J* = 17.5 Hz, 1H), 2.75 (d, *J* = 17.5 Hz, 1H), 2.43–2.13 (m, 4H), 1.31–1.25 (m, 6H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.53 (q, *J* = 7.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.3, 169.0, 146.2, 103.6, 91.6, 84.6, 61.8, 61.5, 60.4, 54.6, 33.2, 27.1, 23.3, 13.9, 13.8, 7.4, 4.3; **IR** (KBr) *v* 2986, 2953, 2914, 2872, 2175, 1736, 1598, 1464, 1443, 1413, 1386, 1365, 1338, 1269, 1228, 1189, 1159, 1093, 1066, 1033, 982, 917, 860, 797, 743, 725, 623 cm^{-1}; **MS** (ESI) *m/z* (%) 543.1 (12, $[M+K]^+$), 528.1 (38), 527.1 (100, $[M+Na]^+$); **HRMS** (ESI) *m/z* calcd for $C_{21}H_{33}IO_4NaSi$ $[M+Na]^+$ 527.1085, found 527.1091

Diethyl (*E*)-3-((4-methoxyphenyl)(triethylsilyl)methylene)-3,5,6,6a-tetrahydropentalene-1,1(2H)-dicarboxylate (100)



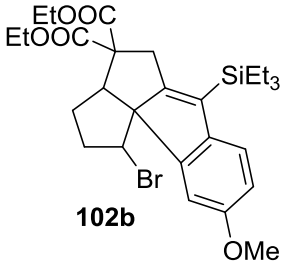
100

Reaction flask charged with sililated alkyne **84** (52 mg, 103 mmol), 4-methoxyphenylboronic acid (26 mg, 163 mmol), cesium carbonate (68 mg, 203 mmol) was dissolved in THF/water mixture (5 mL/0.5 mL). Reaction mixture was then immediately degassed and backfilled with the argon. $Pd(PPh_3)_4$ (6.0 mg, 5 mmol) was carefully added to the reaction mixture, degassed twice and backfilled with argon. Reaction mixture was allowed to reflux at 82°C over 16h, then was allowed to cool to ambient temperature and quenched with EtOAc (5 mL). Extracted with EtOAc (4 × 5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure, crude was then purified by flash chromatography on silica gel (98/2 hexanes/EtOAc) and gave yellowish oil **100** (41.6 mg, 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92–6.76 (m, 4H), 4.32–4.17 (m, 4H), 4.17–4.10 (m, 1H), 3.80 (s, 3H), 3.68–3.60 (m, *J* = 6.4 Hz, 1H), 3.47 (d, *J* = 16.4 Hz, 1H), 3.02 (d, *J* = 16.4 Hz, 1H), 2.49–2.37 (m, 1H), 2.35–2.25 (m, 1H), 2.04–1.96 (dt, *J* = 13.5, 7.0 Hz, 1H), 1.43 (m, 1H), 1.31–1.25 (t, *J* = 7.1 Hz, 3H), 1.25–1.20 (t, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 7.9 Hz, 9H), 0.58 (q, *J* = 8.1, 7.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.7, 170.1, 157.4, 147.4, 142.8, 138.0, 137.0, 128.2, 124.9, 114.1, 113.3, 61.2, 60.9, 57.5, 55.1, 45.6, 37.2, 27.4, 14.2,

14.1, 7.5, 3.7; **IR** (KBr) *v* 2954, 2873, 2171, 1598, 1329, 1301, 1262, 1157, 1098, 1021, 878, 728, 581 cm^{-1}; **MS** (ESI) *m/z* (%) 555.2 (48), 539.2 (100), 523.2.1 (52)

Diethyl 1-bromo-9-methoxy-6-(triethylsilyl)-1,2,3,3a-tetrahydropentaleno[6a,1-a]indene-4,4(5H)-dicarboxylate (102b)

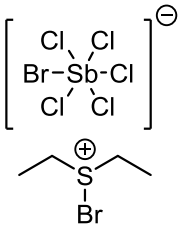


102b

Freshly prepared **99** (21.1 mg, 44 mmol), BDSB (25.1 mg, 46 mmol) were put under argon, then dissolved in dry acetonitrile (2.5 mL) at ambient temperature. After 10 min (TLC run after 5 min, detected as azure blue spot under CPM), reaction was quenched with $Na_2S_2O_3$ (2.5 mL). Reaction mixture was extracted with EtOAc (4 × 2 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Crude was then purified by flash chromatography on silica gel (98/2 hexanes/EtOAc) and gave transparent oil of the desired product **102b** (17 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.1 Hz, 1H), 6.75 (m, 1H), 6.68 (m, 1H), 4.40–4.08 (m, 4H), 3.96–3.88 (m, 1H), 3.79 (s, 3H), 3.49 (d, *J* = 12.0 Hz, 1H), 3.39 (d, *J* = 12.0 Hz, 1H), 3.04 (d, *J* = 14.5 Hz, 1H), 2.45–2.32 (m, 1H), 2.32–2.17 (m, 1H), 2.08–1.96 (m, 1H), 1.84–1.72 (m, 1H), 1.29–1.24 (m, 3H), 1.11 (m, 3H), 0.96 (m, 9H), 0.78 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.6, 168.7, 163.6, 157.4, 152.3, 143.0, 133.3, 121.9, 111.2, 109.1, 72.0, 69.2, 61.6, 61.5, 55.5, 37.8, 37.6, 30.3, 14.1, 13.7, 7.5, 4.0; **IR** (KBr) *v* 2980, 2956, 2935, 2911, 2875, 2830, 1736, 1607, 1577, 1470, 1431, 1389, 1365, 1329, 1281, 1257, 1201, 1180, 1147, 1099, 1084, 1054, 1036, 1000, 973, 931, 863, 833, 809, 791, 737, 674, 594 cm^{-1}; **MS** (ESI) *m/z* (%) 603.1 (15), 588.2 (34), 587.2 (100, $[M+Na]^+$), 532.1 (5), 419.0 (4), 341.1 (9), 340.1 (34); **HRMS** (ESI) *m/z* calcd for $C_{28}H_{40}O_5BrSi$ $[M+H]^+$ 563.1823, found 563.1815 (100), 565.1795 (82)

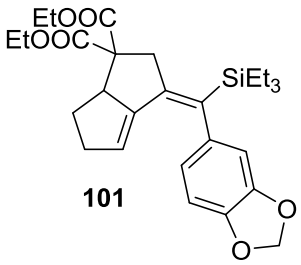
Bromodiethylsulfonium bromopentachloroantimonate (BDSB)



Under argon atmosphere, bromine (270 μL, 5.24 mmol) was carefully dissolved in a 50 mL reaction flask containing dry dichloroethane (15 mL). Reaction flask was immersed into −30 °C bath (set by cryocooler), then Et_2S (560 μL, 5.20 mmol) was cautionary added dropwise along with $SbCl_5$ (760 μL, 5.24 mmol). Reaction was kept at −30 °C for 50 min as dark orange precipitate was being formed. Reaction mixture was heated until the precipitate dissappeared

and was kept at 36°C water bath for additional 1h. Clear orange solution was then placed for 2h to fridge (4 °C) and then to fridge (−20 °C) over 72 h. Shiny range crystals (1.972 g, 69%) were collected, washed with hexane and evacuated. Following recrystalization was performed by heating the remainder of reaction solution to 40°C, then allowing it cool down, placing it to freezer. After washing it with hexane, additional (152 mg, 5.3%) of bromodiethylsulfonium bromopentachloroantimonate we collected.

Diethyl (E)-3-(benzo[d][1,3]dioxol-5-yl(triethylsilyl)methylene)-3,5,6,6a-tetrahydropentalene-1,1(2H)-dicarboxylate (101)

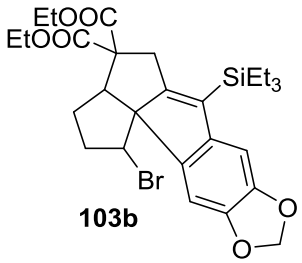


101

Preheated 25mL reaction flask was charged with sililated alkyne **84** (53 mg, 106 mmol), 3,4-(methylenedioxy)phenylboronic acid (27.8 mg, 168 mmol), Cs_2CO_3 (70.2 mg, 215 mmol) was dissolved in THF/water mixture (5 mL/0.5 mL). Reaction mixture was then immediately degassed and backfilled with the argon. After degassing and argon backfilling two more times, $Pd(PPh_3)_4$ (6.2 mg, 5.4 mmol) was carefully added to the reaction mixture, degassed twice and backfilled with argon. Reaction mixture was allowed to reflux at 80°C over 12h, then was allowed to cool to ambient temperature and diluted with EtOAc (5 mL). Reaction mixture was extracted between EtOAc (4 × 5 mL) and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Crude was then purified by flash chromatography on silica gel (98/2 hexanes/EtOAc) and gave yellowish oil of pleasant minty odor **101** (41 mg, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, *J* = 7.9 Hz, 1H), 6.50–6.32 (m, 2H), 5.92 (d, *J* = 1.9 Hz, 2H), 4.47–4.43 (m, 1H), 4.28–4.10 (m, 4H), 3.67–3.59 (m, 1H), 3.79 (s, 3H), 3.45 (d, *J* = 16.4 Hz, 1H), 3.00 (d, *J* = 16.4 Hz, 1H), 2.52–2.40 (m, 1H), 2.38–2.28 (m, 1H), 2.03–1.99 (m, 1H), 1.49–1.38 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 0.92 (m, *J* = 7.9 Hz, 9H), 0.58 (q, *J* = 8.1 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.6, 170.1, 145.1, 143.0, 137.0, 125.4, 125.1, 119.9, 100.6, 61.3, 60.9, 60.0, 57.4, 45.6, 37.3, 27.4, 21.0, 14.2, 14.1, 7.5, 3.7; **IR** (KBr) *v* 2987, 2908, 2873, 1736, 1375, 1233, 1040, 938, 843, 783 cm^{-1}.

Diethyl 1-bromo-6-(triethylsilyl)-1,2,3,3a-tetrahydropentaleno[6a',1':1,2]indeno[5,6-d][1,3]dioxole-4,4(5H)-dicarboxylate (103b)

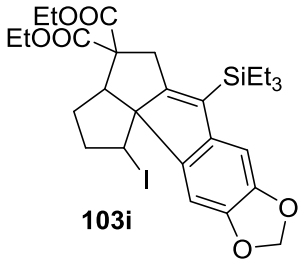


103b

BDSB (9.9 mg, 0.020 mmol) was carefully introduced to 4mL reaction vial with already present starting material **101** (11.4 mg, 0.021 mmol). Reaction vial was backfilled with argon, then dissolved in dry acetonitrile (1.5 mL) at room temperature. After 15 min of stirring at room temperature (TLC run after 5 min, detected as azure blue spot under CPM), reaction was quenched with $Na_2S_2O_3$ (2 mL) and allow to stir for 10 min. Brownish solution was filtered through celite layer, rinsed with additional EtOAc. Organic phase was washed with brine (2 × 2.5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Crude was then purified by flash chromatography on silica gel (95/5 hexanes/EtOAc) and gave transparent oil of the desired product **103b** (11 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (s, 1H), 6.69 (s, 1H), 5.92 (d, *J* = 1.9 Hz, 2H), 4.37–4.24 (m, 2H), 4.21–4.12 (m, 2H) 3.49 (d, *J* = 16.4 Hz, 1H), 3.35 (d, *J* = 16.4 Hz, 1H), 3.07–3.00 (m, 1H), 2.40–2.21 (m, 1H), 2.05–1.95 (m, 1H), 1.80–1.73 (m, 1H), 1.57 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H), 0.98–0.92 (m, 9H), 0.81–0.73 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.6, 168.6, 164.9, 146.9, 145.0, 143.9, 143.5, 133.4, 103.3, 103.2, 101.0, 71.7, 69.6, 61.7, 61.5, 58.2, 46.6, 37.6, 37.5, 30.4, 14.1, 13.8, 7.5, 4.0; **IR** (KBr) *ν* 2961, 2911, 2876, 1730, 1473, 1302, 1258, 1147, 1043, 913, 856, 729 cm^{-1}.

Diethyl 1-iodo-6-(triethylsilyl)-1,2,3,3a-tetrahydropentaleno[6a',1':1,2]indeno[5,6-d][1,3]dioxole-4,4(5H)-dicarboxylate (103i)



103i

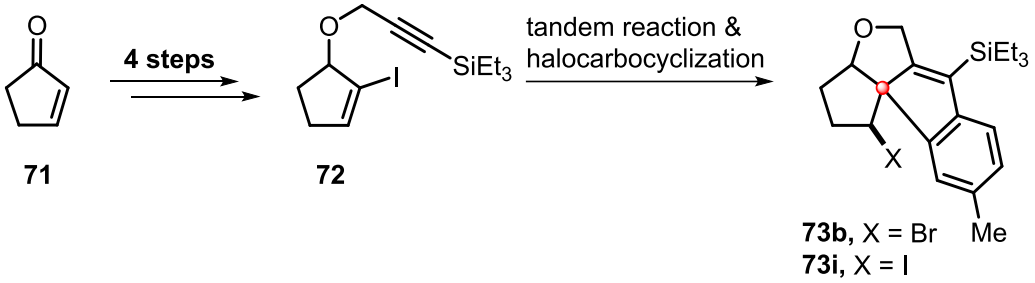
A 4mL reaction vial containing fresh **101** (18.3 mg, 0.037 mmol) was wrapped in aluminum foil and NIS (9.9 mg, 0.044 mmol) was carefully added. Reaction vial was backfilled with argon, then dissolved in dry acetonitrile (1.5 mL) at room temperature for 90 min. Reaction was quenched with $Na_2S_2O_3$ (1.5 mL). Dark purple reaction mixture was allowed to stir for 10 min, organic phase was washed with brine (2 × 2.5 mL) and water phase washed with EtOAc (2 × 1.5 mL). Combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure

giving orange liquid that was purified by flash chromatography on silica gel (90/10 hexanes/EtOAc) and gave transparent oil of the desired product **103i** (17 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (s, 1H), 6.67 (s, 1H), 5.93 (s, 2H), 4.36–4.26 (m, 2H), 4.20–4.12 (m, 2H), 3.98–3.91 (m, 1H), 3.39 (d, *J* = 14.5 Hz, 1H), 3.34 (d, 1H), 3.01 (d, *J* = 14.6 Hz, 1H), 2.41–2.28 (m, 2H), 2.00–1.90 (m, 1H), 1.73–1.66 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H), 1.00–0.94 (m, 9H), 0.82–0.74 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.6, 168.6, 164.9, 146.9, 145.0, 143.9, 143.5, 133.4, 103.3, 103.2, 101.0, 71.7, 69.6, 61.7, 61.5, 58.2, 46.6, 37.6, 37.5, 30.4, 14.1, 13.8, 7.5, 4.0; **IR** (KBr) *v* 2955, 2908, 2876, 1730, 1470, 1306, 1258, 1140, 910, 850 cm^{-1}.

5. Conclusion

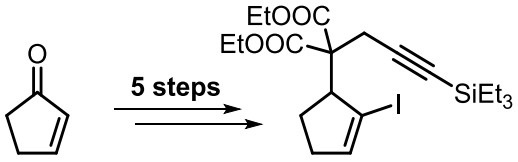
i) Synthesis of a model oxygen-containing compound was successfully accomplished



71 **72**

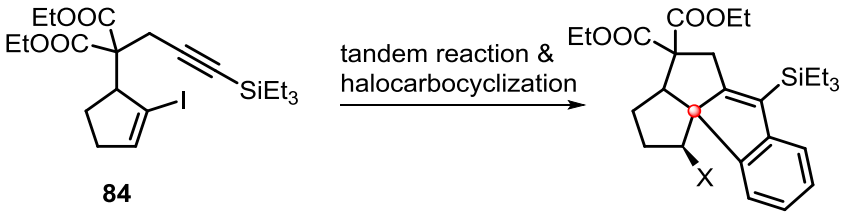
73b, X = Br
73i, X = I

ii) Suitable reaction pathway was found for the synthesis of corresponding carbon derivative. Synthesis was accomplished from commercially available 2-cyclopentene-1-one in 5 steps.



71 **84**

iii) Three new polycarbocyclic compounds bearing all-carbon quaternary centers were successfully prepared and characterized by available spectroscopic methods.



84

102b, R = *p*-OMe, X = Br
103b, R = -O-CH_2-O-, X = Br
103i, R = -O-CH_2-O-, X = I

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