TECHNISCHE UNIVERSITÄT WIEN
Vienna University of Technology

Dissertation

SYNTHESIS AND BIOLOGICAL EVALUATION OF NATURAL PRODUCTS AND DERIVATIVES AS POTENTIAL ANTI-INFLAMMATORY AGENTS AND $GABA_A$ RECEPTOR MODULATORS

Conducted for the purpose of obtaining the academic degree of
Doctor of Technical Sciences under the supervision of

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carried out at Vienna University of Technology

Faculty of Technical Chemistry

by

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Vienna, May 3rd,. 2015

No such a thing as spare time.

No such a thing as free time.

No such a thing as down time.

All you got is lifetime.

Go.

HENRY ROLLINS

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Acknowledgements

My first words of gratitude belong to my supervisor Marko D. Mihovilovic, who believed in me and provided me with the option to carry out my PhD studies in his research group. It was a great experience and I have learnt a lot.

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Next and enormous thanks go to my girlfriend Irena, for her patience and for her love, which makes me realize, where my real place is.

My great word of thanks belong to the members of Fiaker group, namely Lauril, Gerti, Nikolini, Finki, (Ban)Anna, Mitzi, Maxi, as well as some members of honor, who unfortunately graduated before this astonishing club was established, namely Navid, who was good support in the beginning of my studies. Of course, my great great thanks belong to el commandante Florian Untersteiner for all the support and valuable advices. Without them, my stay in Vienna, from both professional and personal point of view would have been not full-fledged.

Here, I would like to also thank to other members of the research group, the second cooking group and all the others for making the working atmosphere so easygoing.

My final words of thanks go to my parents, who were always supportive, not only during my work at this dissertation.

Abstract

The focus of this dissertation lies at the interface of organic and medicinal chemistry. With natural products Magnolol and Honokiol as starting point rational design of a compound library was achieved. Based on the known biological activity of the parent compounds, effects of non-natural derivatives on nuclear transcription factors (PPARγ, RXRα, LXRα and LXRβ) were investigated as a potential anti-inflammatory treatment. Compounds were also investigated with regard to their ability to modulate $GABA_A$ receptors.

Initially efforts were made to rapidly access novel derivatives. In a second round of compound design a hypothesis-driven approach based on the pharmacological data obtained from first-generation compounds was followed. Eventually, this approach led to the discovery of subtype-selective $GABA_A$ receptor modulators, a success en route to developing drugs with improved side-effect profiles. Moreover, compounds selectively acting on RXRα receptors were identified as well.

The second part of this work deals with the total synthesis of natural products Notoincisol A and B, which contain anunique polyenyne structure. Polyenyne-containing natural products, e.g. Falcarindiol, Falcarinol, Oploxynes or Oenanthotoxine, represent an important compound class due to their manifold biological activities. Notoincisol A and B were recently isolated from *Notopterygium incisum* and shown to possess potential anti-inflammatory activity *via* the interaction with peroxisome proliferator activated protein gamma (PPARγ).

The total synthesis of Notoincisol A containing two stereogenic centers was accomplished. Proof of the absolute configuration of the natural product was achieved by means of chemical synthesis. For medicinal chemistry purposes the remaining stereoisomers were synthesized and pharmacological evaluation of their anti-inflammatory potential is currently underway.

In the synthesis of Notoincisol B great advances toward the target molecule could be made. However, attempts to finalize the total synthesis were yet unsuccessful. Several alternative strategies were outlined to achieve the target structure.

Furthermore, Falcarindiol was synthesized for the purposes of an in-depth pharmacological characterization of the compound as $GABA_A$ receptor modulator.

Kurzfassung

Die vorliegende Dissertation ist an der Grenze zwischen organischer Chemie und Medizinalchemie angesiedelt. Ausgehend von den Naturstoffen Honokiol und Magnolol wurde mittels rationalem medizinalchemischen Design eine Bibliothek von Derivaten entworfen und synthetisiert. Basierend auf der bekannten biologischen Aktivität der Naturstoffe wurden die Wirkung der nicht-natürlichen Derivate auf nukleäre Transkriptionsfaktoren (PPARγ, RXRα, LXRα and LXRβ) als mögliche entzündungshemmende Wirkstoffe untersucht.

Anfangs wurde ein Hauptaugenmerk auf den schnellen Zugang zu neuen Derivaten gelegt. Für die zweite Verbindungsgeneration wurde basierend auf den zuvor am $GABA_A$-Rezeptor gewonnenen pharmakologischen Daten ein Hypothesen-geleiteter Ansatz verfolgt. Letzendlich führte dies zur Entdeckung von subtyp-selektive $GABA_A$-Rezeptor Modulatoren, ein Erfolg auf dem Weg zur Entwicklung nebenwirkungsarmer Wirkstoffe. Darüber hinaus wurden Verbindungen identifiziert, die selektiv auf RXRα Rezeptoren wirken.

Der zweite Teil dieser Arbeit beschäftigt sich mit der Totalsynthese der Naturstoffe Notoincisol A und B, die eine einzgartige Polyenin-Struktur aufweisen. Polyenin-haltige Naturstoffe, z.B. Falcarindiol, Falcarinol, Oploxyn oder Oenanthotoxin, sind aufgrund ihrer vielfältigen Bioaktivitäten eine bedeutende Substanzklasse. Notoincisol A und B, wurden unlängst aus *Notopterygium incisum* isoliert. Durch ihre Wechselwirkung mit Peroxisom-Proliferator-aktivierten Rezeptoren (PPARγ) wurden Notoincisol A und B als Wirkstoffe mit potentiell entzündungshemmender Wirkung identifiziert.

Die Totalsynthesis von Notoincisol A, mit zwei stereogenen Zentren, wurde erfolgreich abgeschlossen. Die Absolutkonfiguration des Naturstoffs wurde mithilfe der chemischen Synthese bewiesen. Mit dem Ziel der medizinalchemischen Untersuchung wurden die übrigen Steroisomere synthetisiert. Die pharamkologische Untersuchung ist gegenwärtig im Gang.

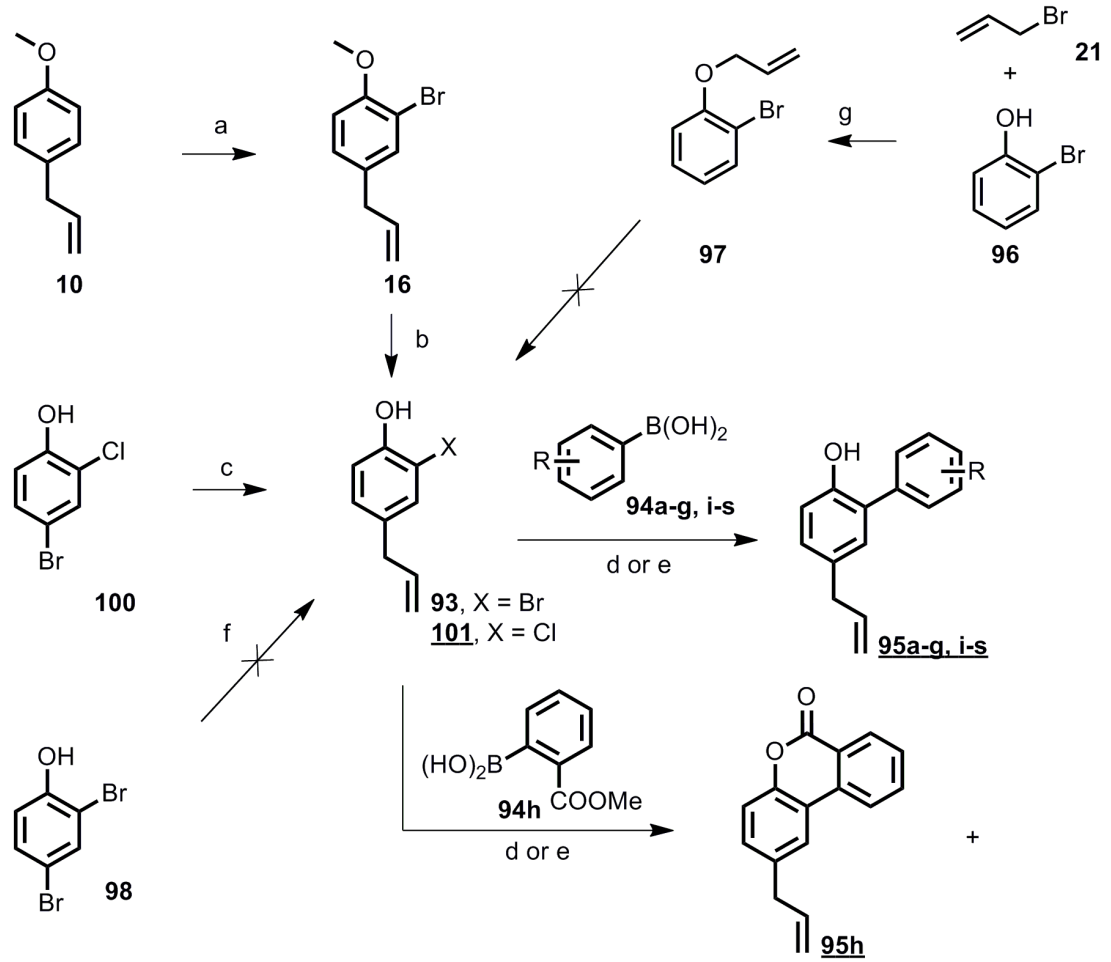
Bei der Totalsynthese von Notoincisol B wurden große Fortschritte in Richtung des Naturstoffs gemacht, allerdings konnte die Totalsynthese bisher nicht abgeschlossen werden. Mehrere Alternativstrategien für die Synthese der Zielverbindung wurden dargelegt.

Darüberhinaus wurde Falcarindiol für eine genauere pharmakologische Charakterisierung am $GABA_A$ Rezeptor hergestellt.

A Synthetic schemes

All compounds prepared or used as starting materials in this thesis are numbered in bold Arabic numerals. Compounds unknown to the literature are additionally underlined.

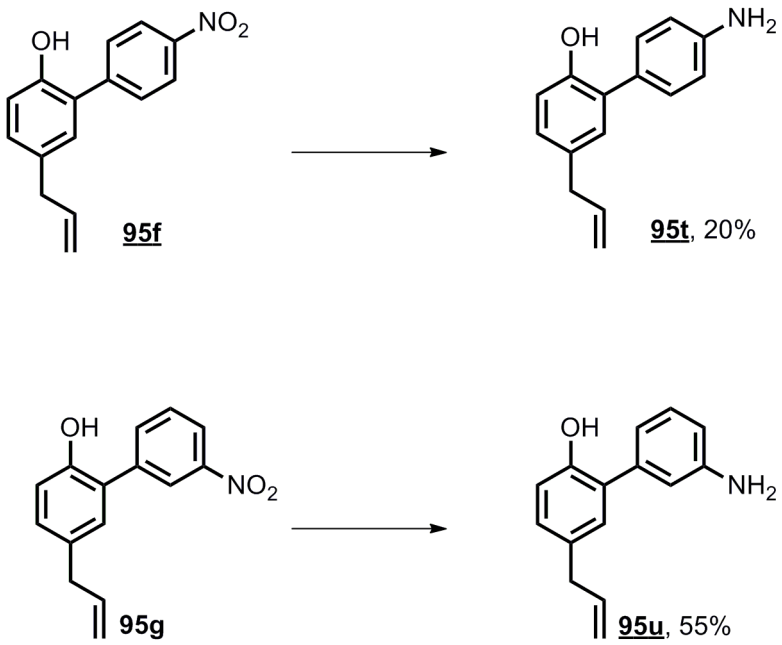
A I Synthesis of Magnolol and Honokiol derivatives



Compound	R	Yield [%] *Cond*. d	*Cond*. e	Compound	R	Yield [%] *Cond*.d	*Cond*. e
95a	H	56	58	**95k**	*o*-Me	nd	34
95b	*o*-OMe	31	54	**95l**	*m*-Me	nd	39
95c	*m*-OMe	35	48	**95m**	*p*-Me	nd	48
95d	*p*-OMe	46	34	**95n**	*m*-CN	nd	23
95e	*o*-NO_2	15	42	**95o**	*p*-CN	nd	37
95f	*m*-NO_2	55	86	**95p**	*m*-F	nd	46
95g	*p*-NO_2	20	60	**95q**	*p*-F	nd	16
95h	lactone	42	31	**95r**	*m*-NMe_2	nd	35
95i	*m*-COOMe	41	34	**95s**	*p*-NMe_2	nd	46
95j	*p*-COOMe	51	36				

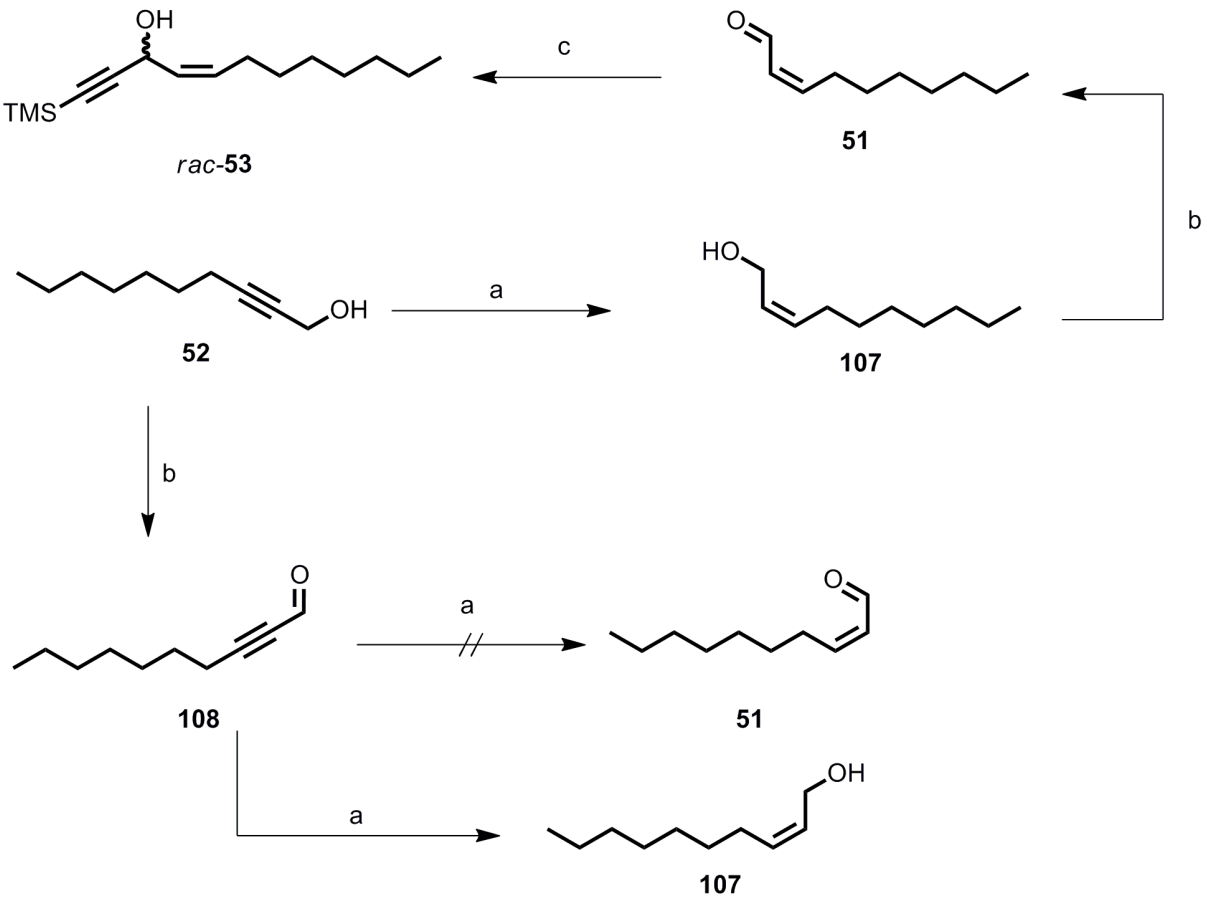
Scheme 1(**a**)1.Py.HBr_3, AcOH, reflux, overnight, 2. Zn dust, Et_2O, AcOH, reflux 4h then rt 18h, 53%; (**b**) BBr_3.SMe_2, DCM/DCE, reflux, overnight, 49% ; (**c**) potassium trifluoroallylborate, PdEn40®, K_2CO_3, dppf, dioxane/H_2O (9:1), 150°C, MW, 7 min, 80% (**d**) Pd_2dba_3, SPhos, KF, dioxane/H_2O (9:1), 120°C, MW, 30 min, X = Br; (**e**) Pd_2dba_3, SPhos, KF, dioxane/H_2O (9:1), 150°C, MW, 10 min, X = Cl; (**f**) various conditions; (**g**) K_2CO_3, acetone, reflux, 83%; various conditions

A II Reduction of nitro to amino derivatives



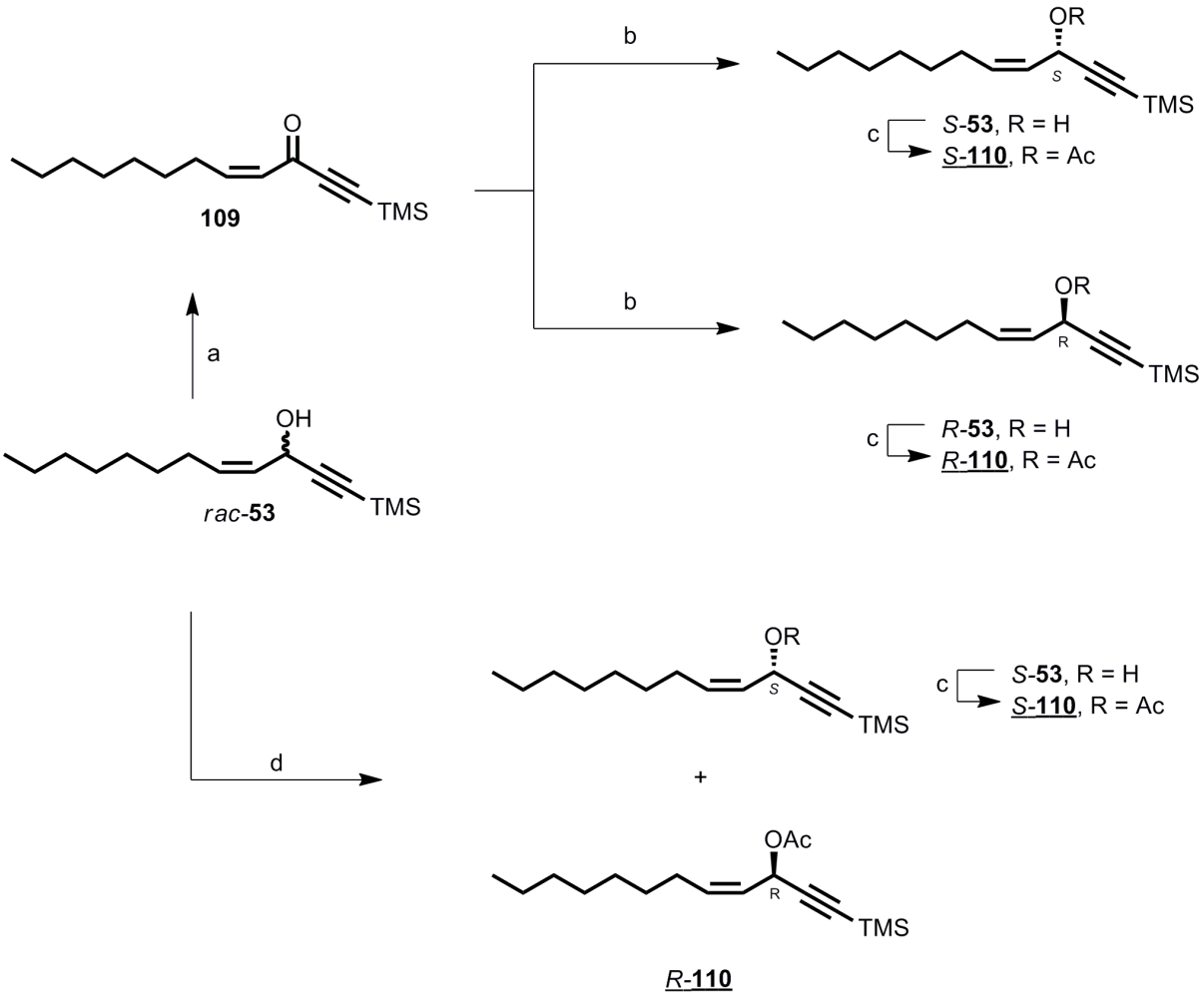
Scheme 2(a) Fe, NH_4Cl, $EtOH/H_2O$, 80°C, 4h

A III Synthesis of racemic (*Z*)-1-(trimethylsilyl)dodec-4-en-1-yn-3-ol



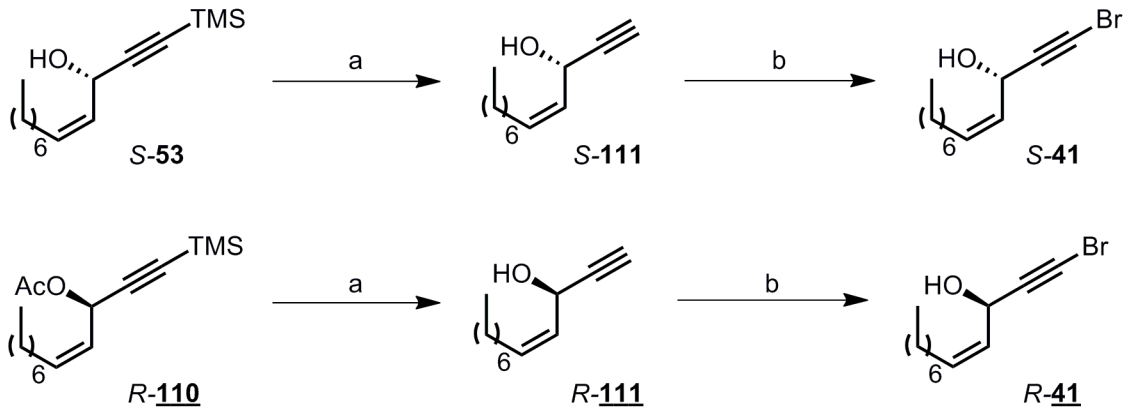
Scheme 3(**a**) $Ni(OAc)_2.4H_2O$, $NaBH_4$, $(CH_2NH_2)_2$, MeOH, rt, 3h, quantitative; (**b**) IBX, DMSO/DCM, rt; (**c**) 2h; n-BuLi, TMS-acetylene, -78°C to rt, 5h, 60% over three steps

A IV Stereoselective syntheses of (*Z*)-1-(trimethylsilyl)dodec-4-en-1-yn-3-ol



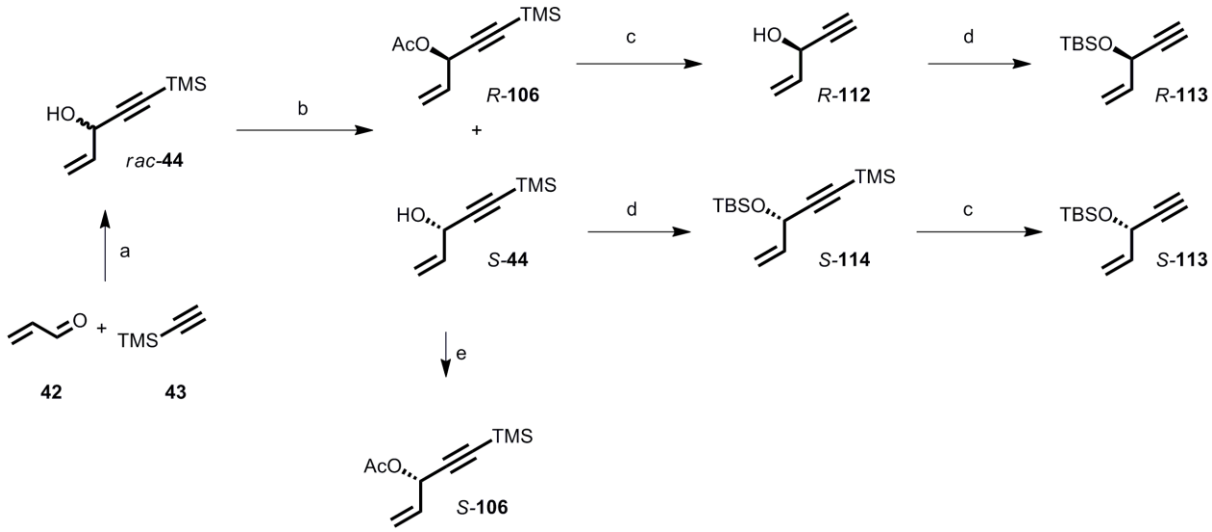
Scheme 4(**a**) DMP, TEMPO, DCM, rt or 0°C, 2h, 70%, *E/Z* 90:10; (**b**) (*S*)-methyl-CBS, $BH_3.SMe_2$, THF, -6°C, 62%; (**b**) (*R*)-methyl-CBS, $BH_3.SMe_2$, THF, 0°C, 50%; (**c**) Ac_2O, DMAP, DCM, Et_3N, rt, minutes, *S*-enantiomer – 98% *ee*, *R*-enantiomer – 88% *ee*; (**d**) Amano lipase PS, vinyl acetate, MTBE, rt, 36h,

A V Preparation of alkynyl bromides



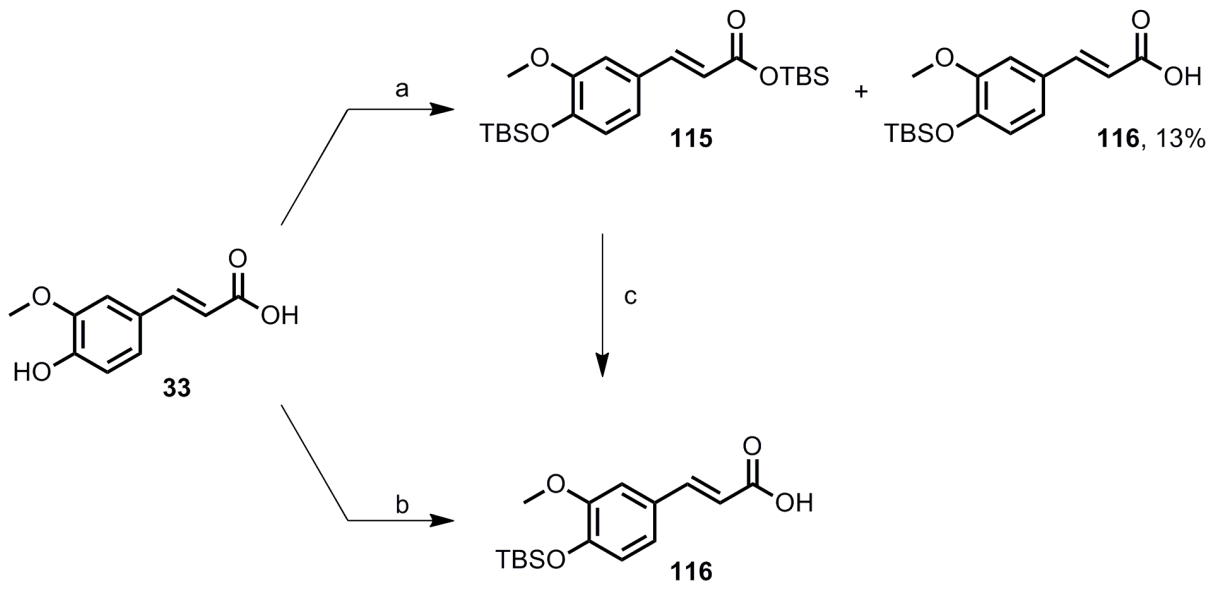
Scheme 5(**a**) K_2CO_3 K_2CO_3, MeOH, rt, 2h,81% for *S*-**111**, 85% for *R*-**111** ; (**b**) $AgNO_3$, NBS, Acetone, 2h, 77% for *S*-**41**, 81% for *R*-**41**

A VI Stereoselective synthesis of 5-TBS protected pent-1-en-4-yn-3-ol



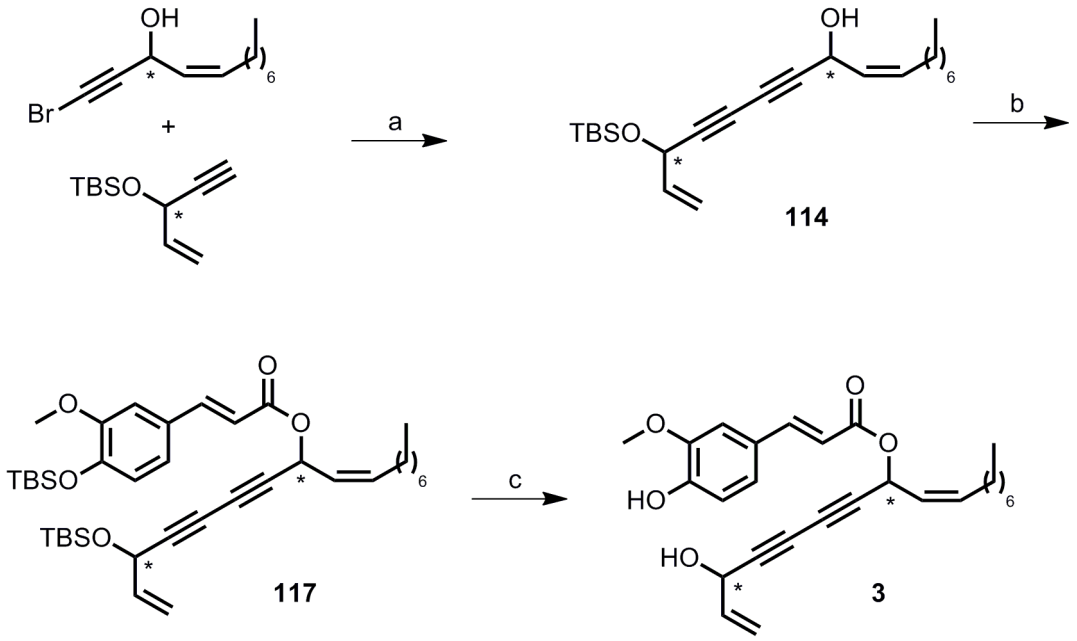
Scheme 6 (**a**) 1.*n*-BuLi, THF, 0°C; 2. THF acrolein, 0 °C to rt, 89% (**b**) Amano lipase PS, MTBE, rt, 4h, 48% for *R*-**106**, 33% for *S*-**44**, (**c**) K_2CO_3, MeOH, 2h, rt, 82% for *R*-**112**, 78% for *S*-**113**; (**d**) TBSCl, imidazole, DCM, rt, 2h, 91% for *R*-**113**, 93% for *S*-**114**; (**e**) Ac_2O, DMAP, Et_3N, DCM, rt, minutes

A VII TBS protection of ferulic acid



Scheme 7(**a**) TBSCl, imidazole, DCM, rt, 76% of **115**, 13% of **116**; (**b**) TBSCl, imidazole, DMF, 67%, rt, (**c**) K_2CO_3, THF/MeOH, H_2O, quantitative

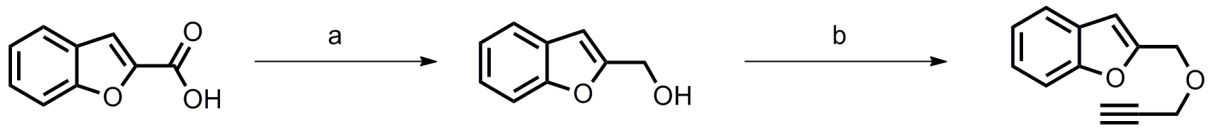
A VIII Final sequences towards Notoincisols A



Entry	Starting materials	Cadiot-Chodkiewitz (product, yield)	Esterification (product, yield)	Deprotection (product, yield)
1	*R*-**113**, *S*-**41**	*R,S*-**114**, 66%	*R,S*-**117**, 81%	*R,S*-**3**, 83%
2	*S*-**113**, *S*-**41**	*S,S*-**114**, 64%	*S,S*-**117**, 79%	*S,S*-**3**, 76%
3	*R*-**113**, *R*-**41**	*R,R*-**114**, 66%	*R,R*-**117**, 78%	*R,R*-**3**, 78%
4	*S*-**113**, *R*-**41**	*S,R*-**114**, 65%	*S,R*-**117**, 78%	*S,R*-**3**, 75%

Scheme 8 (**a**) $NH_2OH.HCl$, $EtNH_2$, CuCl, H_2O/MeOH,0°C to rt, 2h,; (**b**) ferulic acid **33**, EDCI, DMAP, rt, 2h; (**c**) HF/pyridine, THF, 0°C to rt, 2h

A IX Synthesis of Hashimi cyclization precursor



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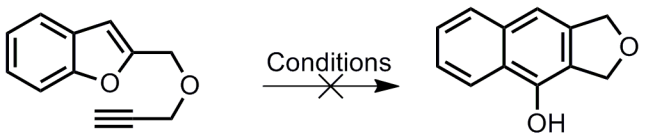
Scheme 9 (**a**) DIBAL-H, Et_2O, 0°C to rt, overnight, 63%; (**b**) NaH, propargyl bromide, DMF, 0°C to rt

A X Unsuccessful attempts of Hashimi cyclization



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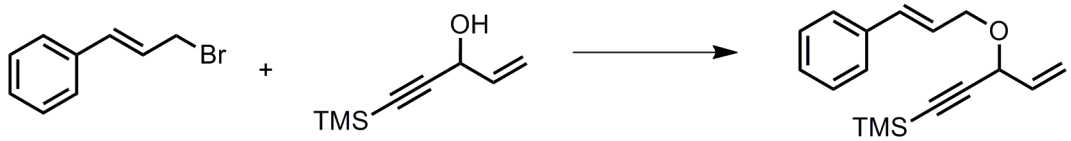
Entry	Solvent	Catalyst	T (°C)	Yield (%)
1	CH_3CN	$AuCl_3$	r.t.	0
2	CH_3CN	$AuCl_3$	50	0
3	CH_3CN	$AuCl_3$	100	0
4	CH_3CN	$AuCl_3$	120	0
5	DCM	$AuCl_3$	50	0
6	DMA	$AuCl_3$	180	0
7	Acetone	$PdCl_2$	50	0
8	DMA	$PdCl_2$	180	0

Scheme 10

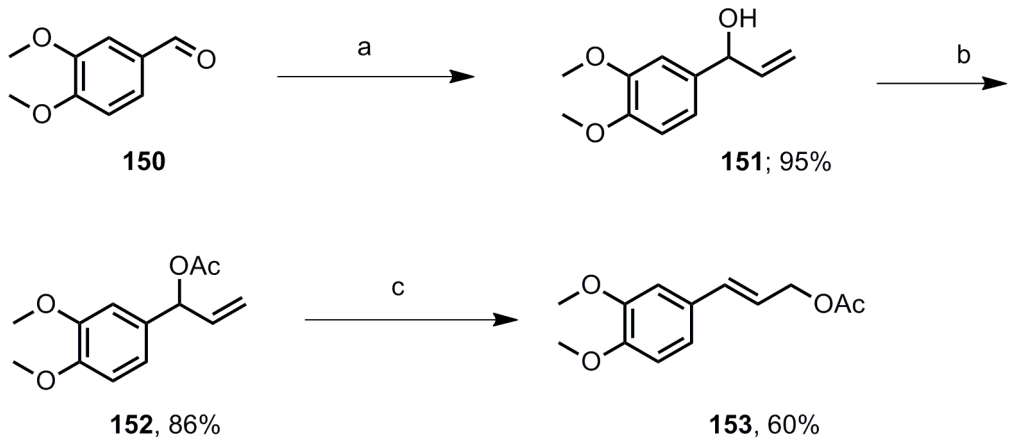
A XI Low yielding preparation of allylic ether, precursor for intramolecular Diels-Alder cyclization, *via* nucleophilic substitution



145 *rac*-**44** **146**

Scheme 11 *n*-BuLi, DMF, -78°C to rt, then reflux, 13%

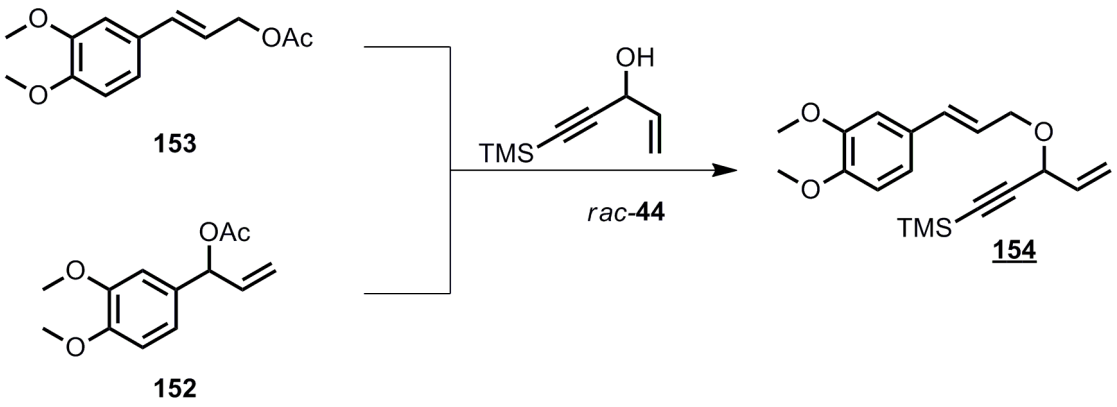
A XII Synthesis of acetates, precursors of C-O coupling



150 **151**; 95% **152**, 86% **153**, 60%

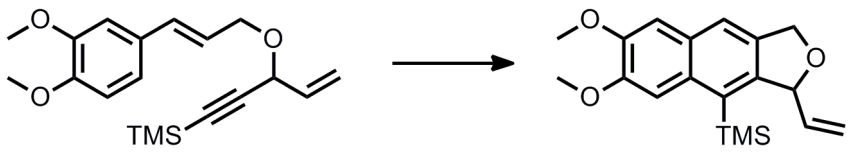
Scheme 12 (**a**) vinylmagnesium bromide, THF, 2h, 0°C 95%; (**b**] Ac_2O, pyridine, DMAP, Et_2O, 1.5h, rt, 86%; (**c**) DCM, 80°C, SiO_2, MW, 65 min, 60%

A XIII Palladium catalyzed C-O coupling for preparation of allylic ether, precursor for intramolecular Diels-Alder cyclization



Scheme 13 Et_2Zn, $Pd(OAc)_2$, DtBPB, NH_4OAc, THF, rt, 56% from **153**, 58% from **152**

A XIV Intramolecular Diels-Alder reaction



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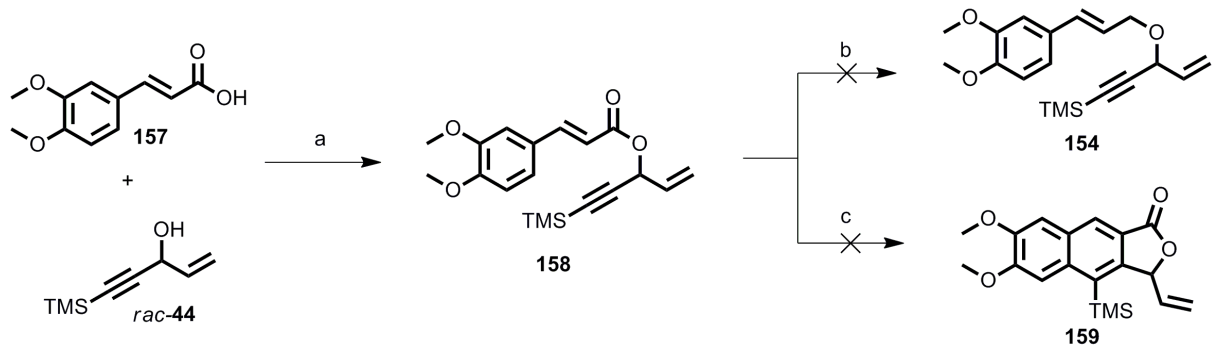
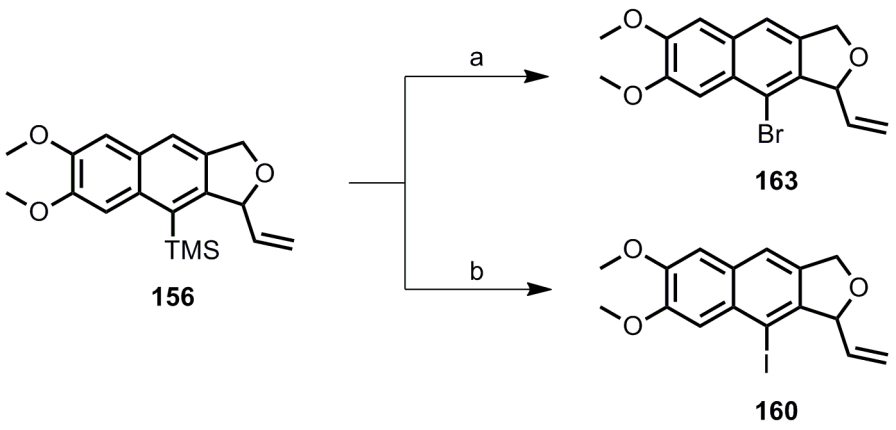
Scheme 14 Xylene, 180°C, overnight, 67%

A XV Attempts to achieve cyclic aromatic intermediate for Notoincisol B synthesis *via* ferulic ester



Scheme 15 (**a**) DCC, DMAP, DCM, reflux overnight, 86%; (**b**) TMDS, $Fe_3(CO)_{12}$, toluene, 100°C (**c**) 180°C, xylene; 140°C, Ac_2O

A XVI Halodesilylation



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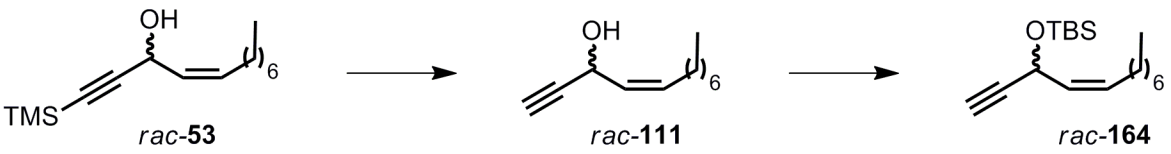
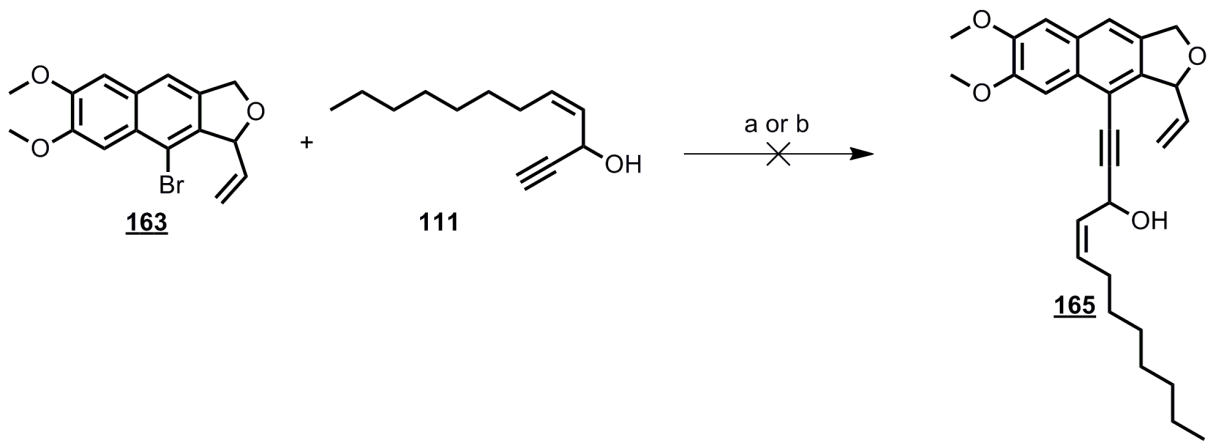
Scheme 16 (**a**) NBS, THF, °C, overnight, 60%; (**b**) NIS, AgF, THF, 0°C, overnight, 45%

A XVII Modifications of (*Z*)-1-(trimethylsilyl)dodec-4-en-1-yn-3-ol to corresponding ketone



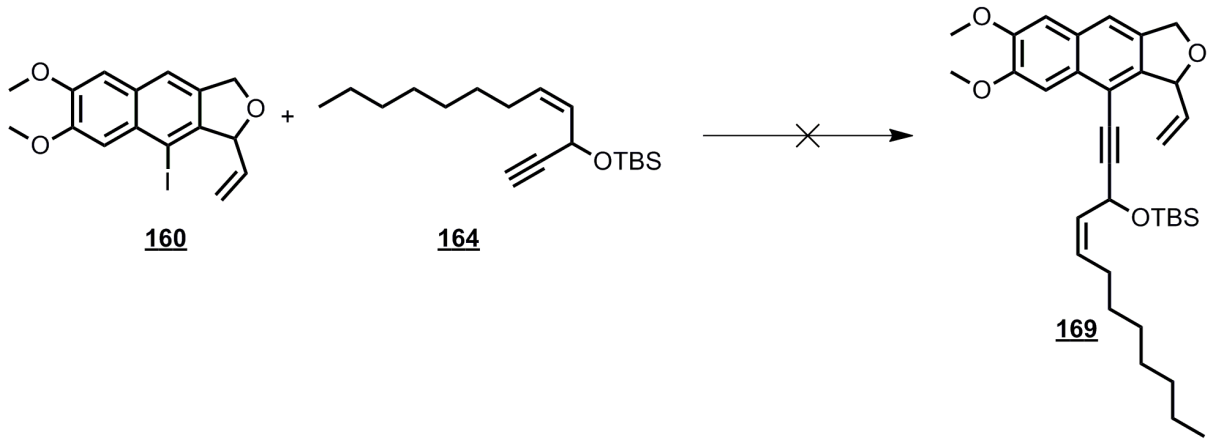
Scheme 17 K_2CO_3, MeOH, rt, 2h, 84%; (**b**) TBSCl, imidazole, DCM, rt, 2h, 91%

A XVIII Unsuccessful Sonogashira coupling with aryl bromide



Scheme 18 (**a**) $Pd(PPh_3)_2Cl_2$, Et_3N, CuI, DMF, 50°C or 80°C (**b**) $Pd(PPh_3)_2Cl_2$, Et_3N, CuI, 80°C

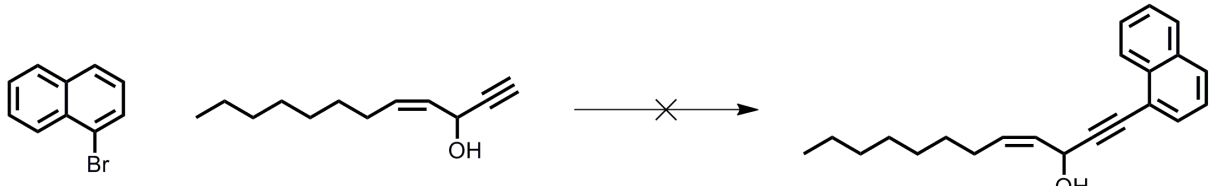
A XIX Unsuccessful Sonogashira coupling with aryl iodide



160 **164** **169**

Scheme 19 $Pd(PPh_3)_2Cl_2$, Et_3N, CuI, 50°C or 80°C

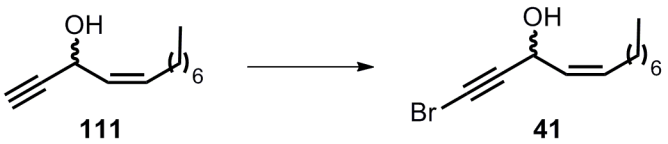
A XX Unsuccessful Sonogashira coupling on a model substrate at room temperature



166 **111** **170**

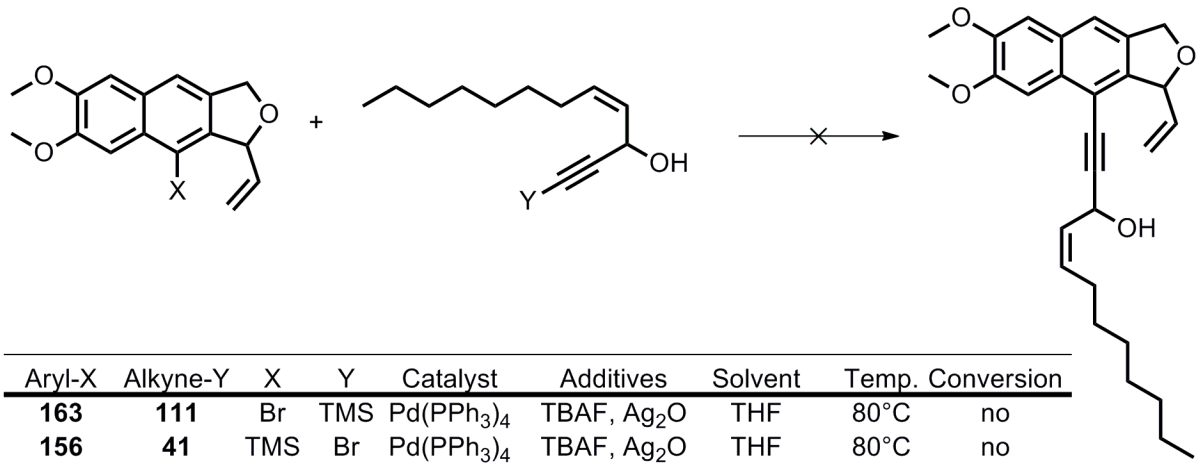
Scheme 20 Various conditions, room temperature

A XXI Bromination of racemic long alkyne



Scheme 21 $AgNO_3$, NBS, Acetone, 2h, 79%

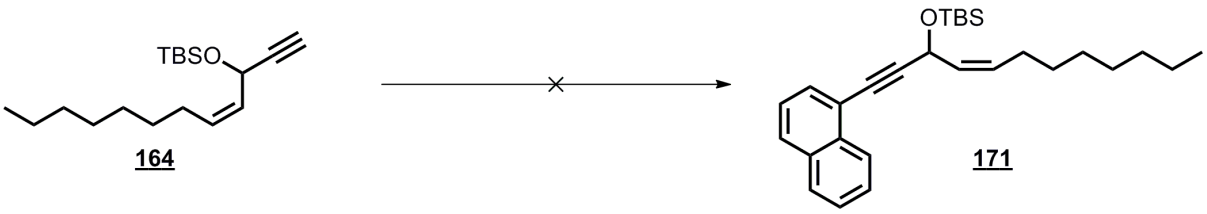
A XXII Unsuccessful Hiyama coupling



Aryl-X	Alkyne-Y	X	Y	Catalyst	Additives	Solvent	Temp.	Conversion
163	**111**	Br	TMS	$Pd(PPh_3)_4$	TBAF, Ag_2O	THF	80°C	no
156	**41**	TMS	Br	$Pd(PPh_3)_4$	TBAF, Ag_2O	THF	80°C	no

Scheme 22

A XXIII Unsuccessful Suzuki coupling



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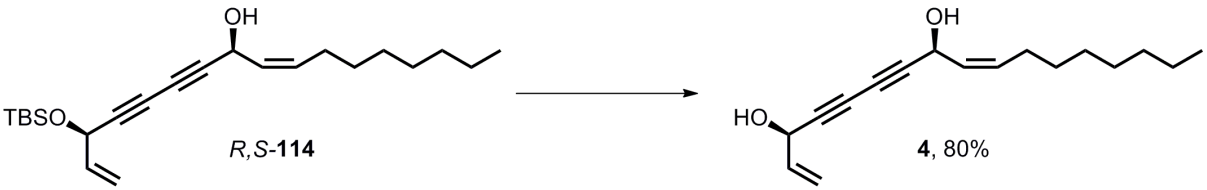
Scheme 23 1. *n*-BuLi, DME, -78°C, 1h, 2. $(i\text{PrO})_3\text{B}$, -78°C, 2h, then rt, 3. THF, 4. Bromonaphthalene, DME, $\text{Pd}(\text{PPh}_3)_4$

A XXIV Synthesis of Falcarindiol

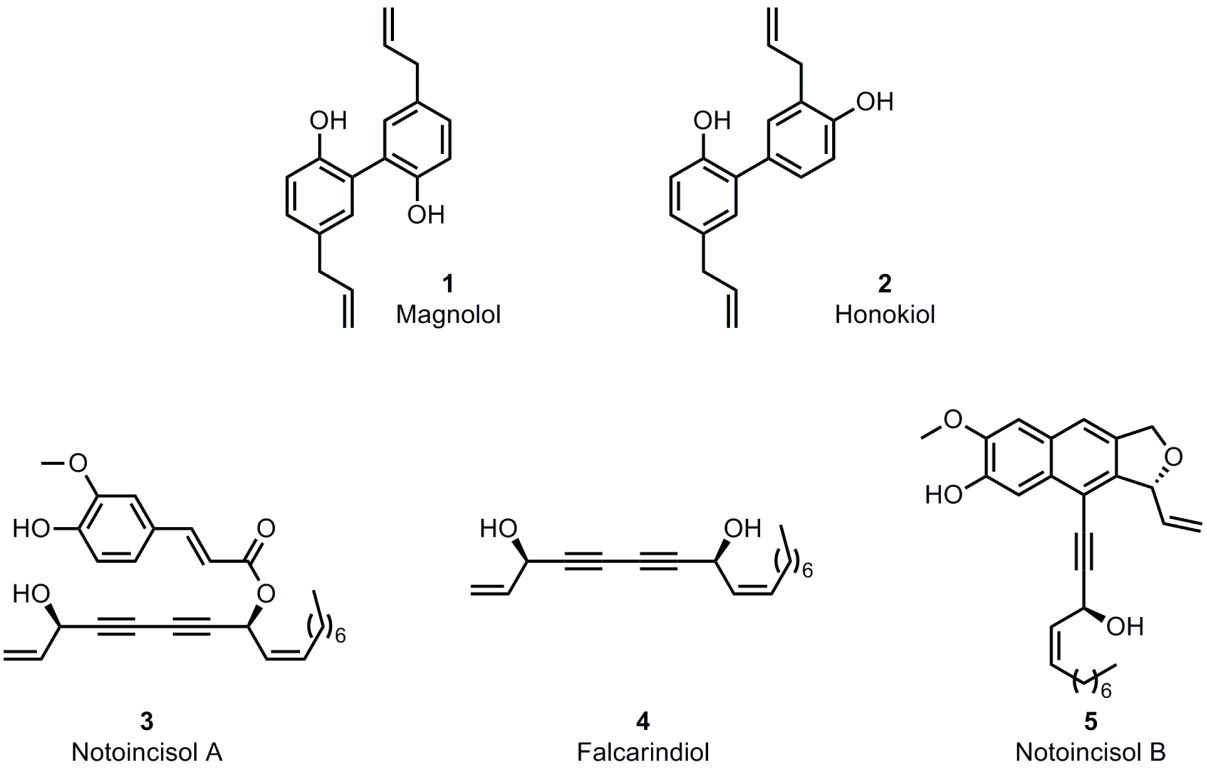


Scheme 24 HF.pyridine, THF, 0°C to rt

B Introduction

This thesis describes the synthesis of natural products and/or their derivatives with established biological activity. Several natural products were in the center of attention (Scheme 1). In the first part, synthesis of the derivatives of the neolignans Magnolol (**1**) and Honokiol (**2**), natural products originating from *magnolia officinalis*[1] is described. In the second part, synthesis of Notoincisol A (**3**) and Notoincisol B (**5)**, or achieved progress within, is discussed. Notoincisol A and B belong to the class of polyenynes, recently isolated from *Notopterygium incisum*.[2] In addition, Falcarindiol (**4**), another member of polyenyne family, of which the synthesis was already described[3-7], is prepared as well with the purpose of further in-depth biological evaluation of the natural product on $GABA_A$ receptors.

There is a long term interest in the development of compounds active at the $GABA_A$ receptors as well as the interest in the development of agents potentially active against inflammation in the research group, where this PhD thesis was conducted. Therefore, synthesized natural products were evaluated for their effects on $GABA_A$ receptors, with the attention on the subtype selectivity of the derivatives as well as the interaction with nuclear transcription factors playing the role in the regulation of inflammation.



Scheme 25

B I Goals of this thesis

This thesis aimed at the following goals:

(A) Development of a simple synthetic approach to new derivatives of natural products Magnolol **1** and Honokiol **2** and subsequent synthesis of a library of these derivatives. New derivatives were aimed to be evaluated as a $GABA_A$ modulators and agonist of PPARγ, RXRα, LXRα and LXRβ as targets associated to inflammatory effects. It was planned to develop ligands with functional selectivity towards $GAGA_A$ receptors and the above transcription factor family. In such a case, natural product would serve as an inspiration for the development of derived ligands with distinct biological activity.

(B) Development of the first total synthesis of the natural product Notoincisol A **3**, all possible stereoisomers of the natural product and confirmation of the absolute stereochemistry by the comparison of the physical data of the isolated and synthesized molecules. Biological evaluation of the synthetic molecules as potential anti-inflammatory agents and $GABA_A$ modulators.

(C) Synthesis of the natural product Falcarindiol **4**, for in-depth evaluation as the $GABA_A$ modulator

(D) Development of the first total synthesis of the natural product Notoincisol B **5**.

Following goals were fulfilled:

(A) New synthetic strategy towards novel Magnolol and Honokiol derivatives was developed. A library of 21 compounds was evaluated on the $GABA_A$ receptor and library of 13 compounds was evaluated on PPARγ. RXRα and LXRα and LXRβ receptors.

(B) Synthesis of the Notoincisol A as well as the stereoisomers of the natural product was successfully accomplished. Absolute stereochemistry of the natural product was confirmed by means of optical rotation. At the time of finishing this thesis, all compounds were under investigation for their ability to modulate $GABA_A$ receptors and PPARγ receptors with cooperation partners.

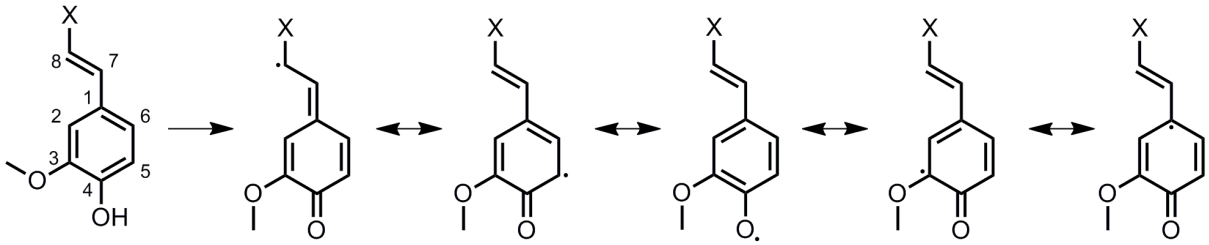
(C) Synthesis of the natural product Falcarindiol was accomplished and at the time of writing this thesis, biological evaluation of Falcarindiol on $GABA_A$ receptors is underway.

(D) Total synthesis of Notoincisol B was not finalized within the timeframe of this thesis. Several approaches were investigated. Synthesis was developed to the advanced stage of the molecule, however several problems were encountered with the final steps and so far, key steps in the total synthesis could not be implemented

successfully. New possibilities and suggestions to circumvent the problems are outlined for prospective follow-up projects.

B IINeolignans

Lignans and neolignans represent a large class of structurally diverse natural products. The common property of the (neo)lignan compound family lies in the origin. The mechanism of formation was initially suggested by Erdtman already in 1933 and nowadays it is generally accepted.[8, 9] Lignans are formed *via* oxidative connection of two phenylpropens as for instance ferulic acid, coniferyl alcohol or isoeugenol.

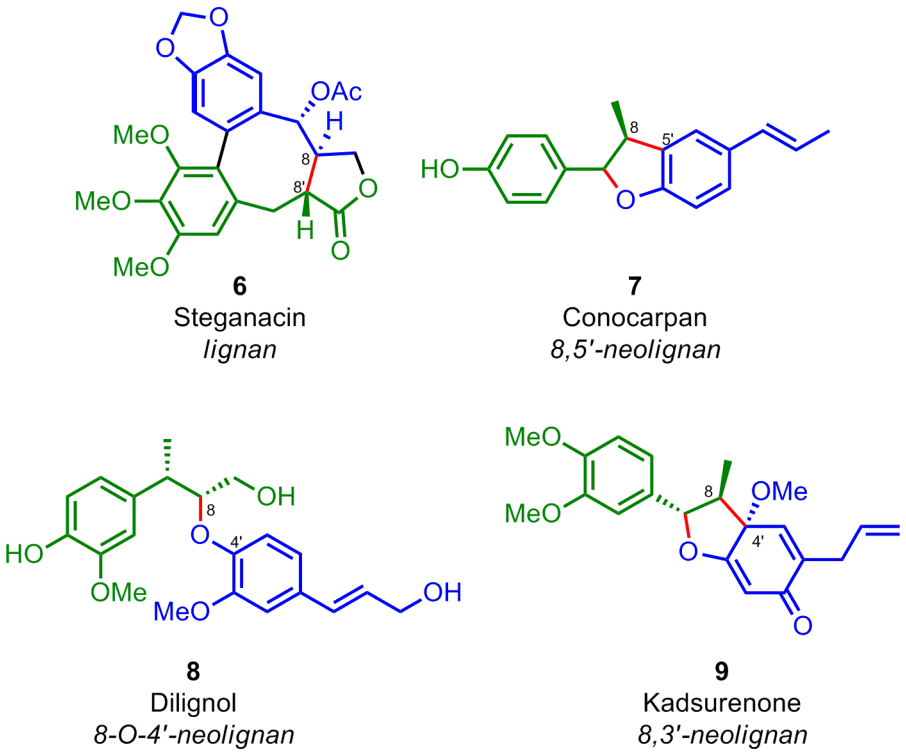


X = COOH, Ferulic acid
OH - Coniferyl alcohol
CH_3 - Isoeugenol

Scheme 26

Connection *via* 8-8' carbons leads to the formation of lignans. Any other connection leads to the formation of neolignans (see Scheme 27). (Neo)lignans are formed *via* radical reactions. In the first step, abstraction of hydrogen and formation of the radical species takes place. The obtained radical is highly stabilized by resonance. Several resonance structures can be drawn, as depicted at the Scheme 26.[10] In the next step, the monomeric radical reacts with a second monomeric unit. Attack of the radical can occur at various positions, which is a reason of the broad structural diversity of neolignans.

Naturally, with such structural diversity, (neo)lignans display a broad spectrum of biological effects. Several representatives of the (neo)lignans with known biological activity are depicted in the scheme below.



6
Steganacin
lignan

7
Conocarpan
8,5'-neolignan

8
Dilignol
8-O-4'-neolignan

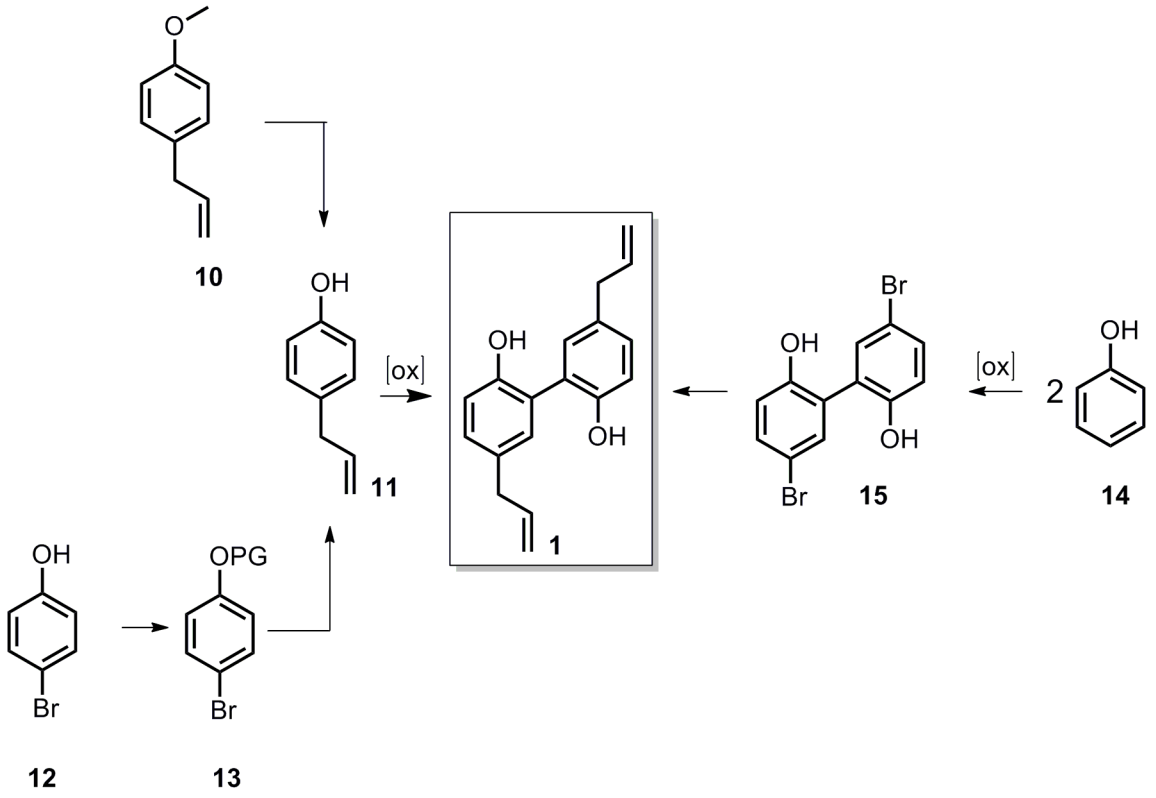
9
Kadsurenone
8,3'-neolignan

Scheme 27

B II.1 Magnolol and Honokiol

The natural product Magnolol **1** has been known for a long time; together with its structural isomer Honokiol **2** they are constituents of the plants from *Magnolia* family. First scientific reference mentioning Magnolol originates from Japanese literature from the year 1930.[11]However, *magnolia* has widely been used in Eastern traditional medicine for treatment of psychical and gastrointestinal diseases since long time[1].

Magnolol can be efficiently synthesized *via* oxidative homocoupling (Scheme 28). First reports of the synthesis of Magnolol reach back to late 1950's. Chavicol **11** was oxidatively coupled in the presence of $FeCl_3$ and air to give Magnolol by Erdtman and Runeberg.[12]Alternatively, Runeberg synthesized Magnolol *via* oxidative coupling of phenol **14**, *para* bromination of the biphenol, formation of Grignard reagent with magnesium and subsequent treatment with allyl bromide.[13] Several variations were published over the time. Iron trichloride can be substituted with $AlCl_3$ and DDQ, leading to 77% of Magnolol.[14] Oxidative homocoupling can be also mediated by enzyme horseradish peroxidase in the presence of H_2O_2, nevertheless with rather low yields (27% of isolated yield, 40% determined by HPLC).[15, 16]

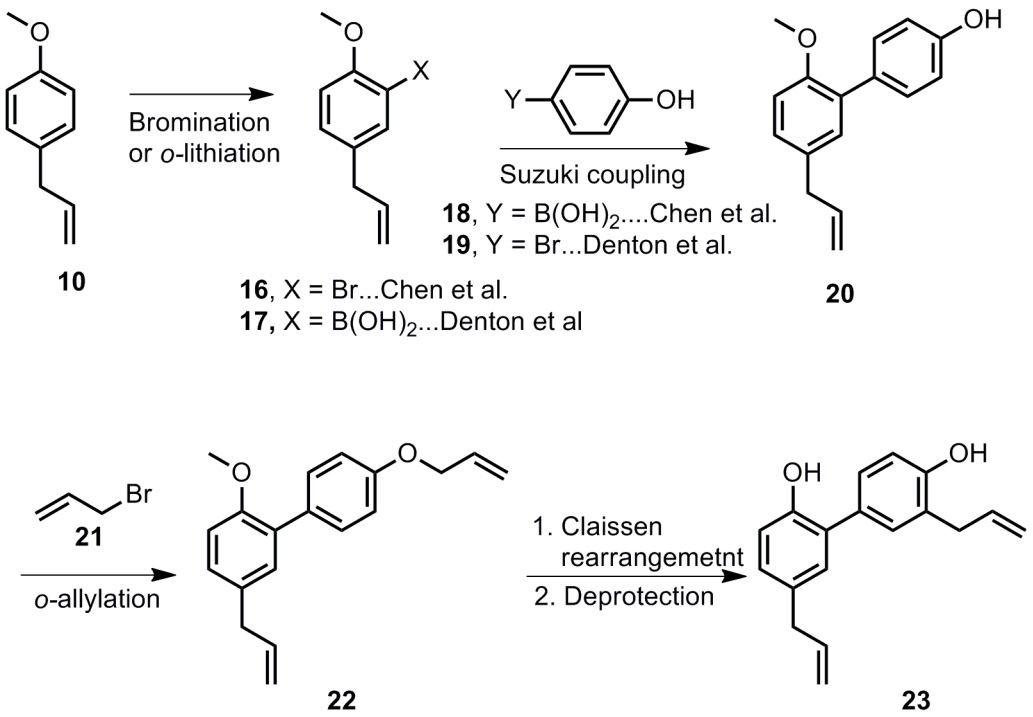


Scheme 28

Oxidative homocoupling however leads inevitably to symmetrical molecules. Honokiol, which lacks symmetry, cannot be accessed *via* this way. In 2009 and 2010 Chen[17] and Denton[18], respectively, reported the synthesis of Honokiol. According to Chen, 4-allylanisole **10** was firstly brominated, yielding 2-bromo-4-allylanisol **16**. Subsequent Suzuki coupling with 4-hydroxyboronic acid **18** provided intermediate **20**. *O*-Allylation, Claissen rearrangement and demethylation provided Honokiol. In the report of Denton[18], *o*-lithiation of 4-bromoanisol **10** and subsequent introduction of boronic acid led to the formation of arylboronic acid **17**. In the next step, 4-bromophenol **19** was coupled in a Suzuki reaction, providing intermediate **20**, identical to intermediate of Chen. The same subsequent modifications provided Honokiol.

Magnolol and Honokiol were described to have diverse biological effects, which was comprehensively covered in the literature.[1] Recently, several studies have revealed additional pharmaceutical effects of Magnolol or Honokiol as anti-angiogenetic[19], antiepileptic[20], neuroprotective,[21] or antimicrobial and antiproliferative activity[22]. Honokiol has been shown to have somnogenic effects in mice.[23] Furthermore, interaction with the PPARγ receptor, involved in treatment of type 2 diabetes, metabolic syndrome, and potential anti-inflammatory target, was shown as well.[24] In the central nervous system, neolignans interact with $GABA_A$ receptors and modulate their GABA-induced activity leading to the assumption that their antiepileptic and somnogenic *in vivo* effects are mediated by

these receptors.[25, 26] Anti-inflammatory activity and interaction with $GABA_A$ receptors are discussed separately.

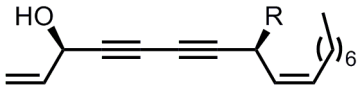


Scheme 29

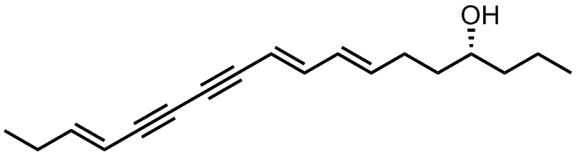
B III Polyenynes

B III.1 Abundance and biological properties

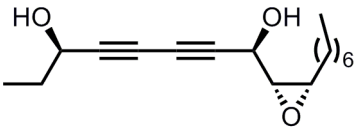
The class of polyenyne natural products shares poly-unsaturated functionalities and functional groups derived thereof as common structural feature (Scheme 30). Most of the compounds have two adjacent triple bonds and double bond either again in the neighborhood or in the close proximity. Amongst the known polyenynes Falcarindiol, Falcarinol, Oenanthotoxine or Opoxynes are well known; they are found in many *Apiaceae* and *Araliaceae* species[27]. Polyenynes often occur in common vegetables from the family of *Apiaceae* as carrot, celery or parsley. They had been considered as unwanted constituents of the food plants for long time, due to their negative impact on the organism as they are neurotoxic and allergenic. However, some discussion has arisen, pointing out the beneficial aspects of polyenynes, as they display antifungal, anti-inflammatorial or anticancer effect. It has been hypothesized that these compounds can be classified as so called toxicants. Toxicants are compounds which at higher intake and increased concentrations can cause undesired effects, however, regulated daily intake can be in fact beneficial and play a protective role for the organism[28].



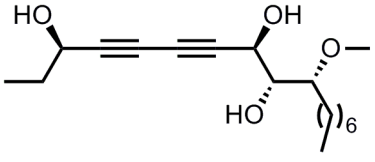
R = H, falcarinol, **24**
OH, falcarindiol, **4**



25, Oenanthotoxine



26, Oploxyne A



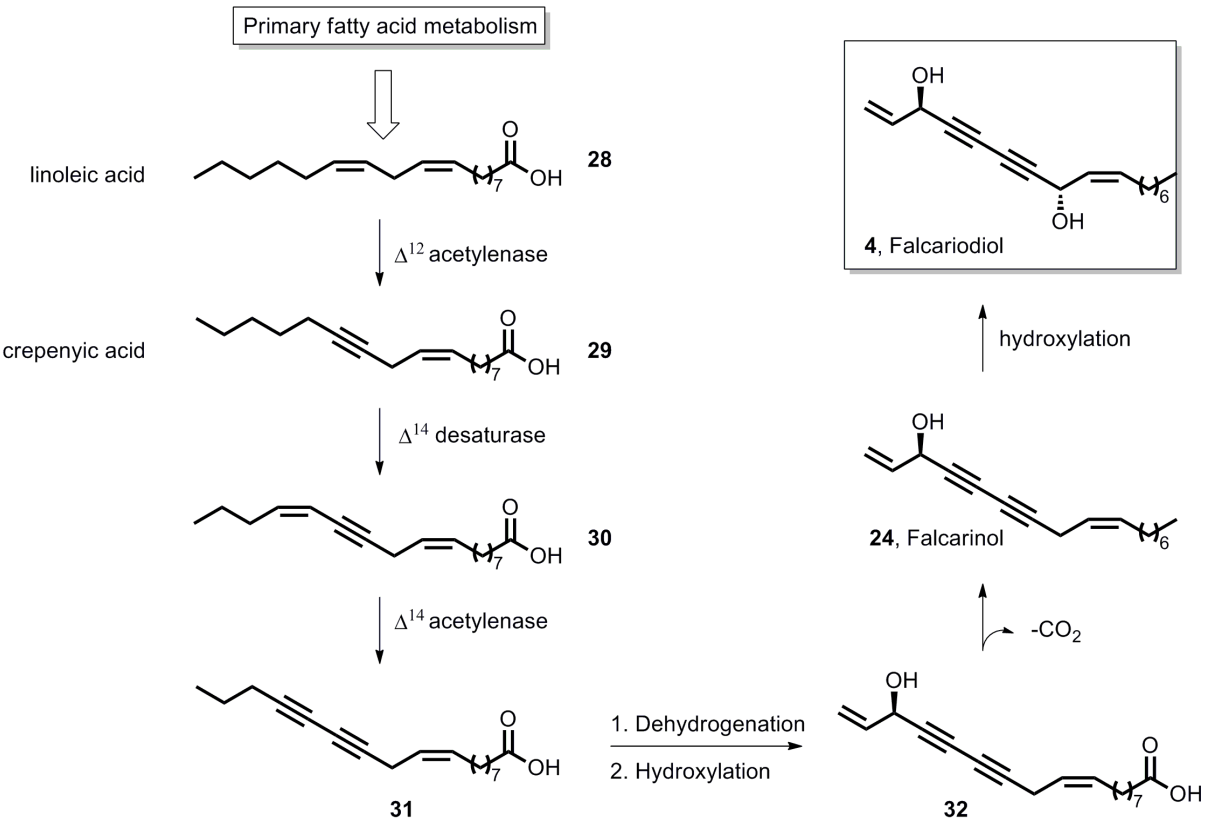
27, Oploxyne B

Scheme 30

B III.2 Biosynthesis of Falcarindiol, Notoincisol A and Notoincisol B

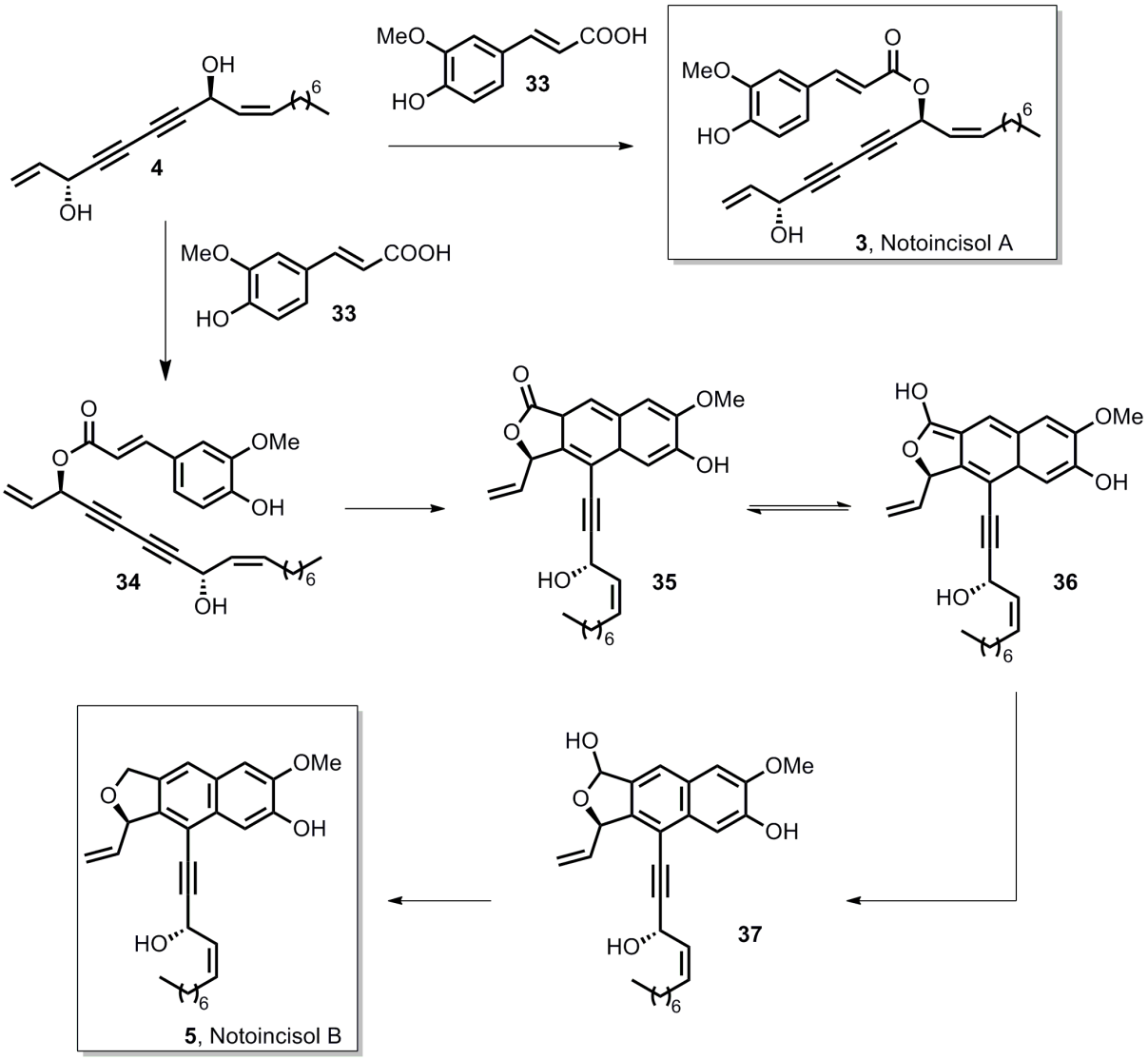
Biosynthesis of the polyenynes starts from oleic acid. There is a specific class of enzymes called desaturase and acetylenase which stepwise oxidize the saturated chain of oleic acid. In the case of Falcarindiol, initially, oleic acid is converted to linoleic acid with the utilization of Δ^{12} desaturase. In the next step, Δ^{12} acetylenase is employed to form the first triple bond. This sequence is repeated once more with the replacement of Δ^{12} desaturase

and Δ^{12} acetylenase byΔ^{14} desaturase and Δ^{14} acetylenase, enzymes with an analogous function – dehydrogenation and acetylanation, but this time at position 14.Several subsequent transformations such as dehydrogenation, hydroxylation, decarboxylation and further hydroxylation eventually lead to Falcarindiol (Scheme 31).[29]



Scheme 31

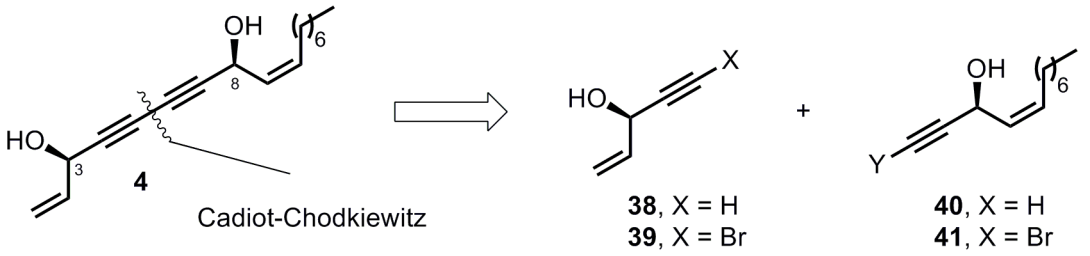
It was proposed that Notoincisol A and Notoincisol B originate from Falcarindiol. Direct esterification of the hydroxyl group in position 8 of Falcarindiol with ferulic acid leads to Notoincisol A. For synthesis of Notoincisol B, the other hydroxyl group must be esterified. Subsequent intramolecular Diels-Alder reaction would lead to formation of the tricyclic ring contained in Notoincisol B. Eventually, tautomerization and reduction would yield Notoincisol B (Scheme 32).[2]



Scheme 32

B III.3 Total synthesis of Falcarindiol

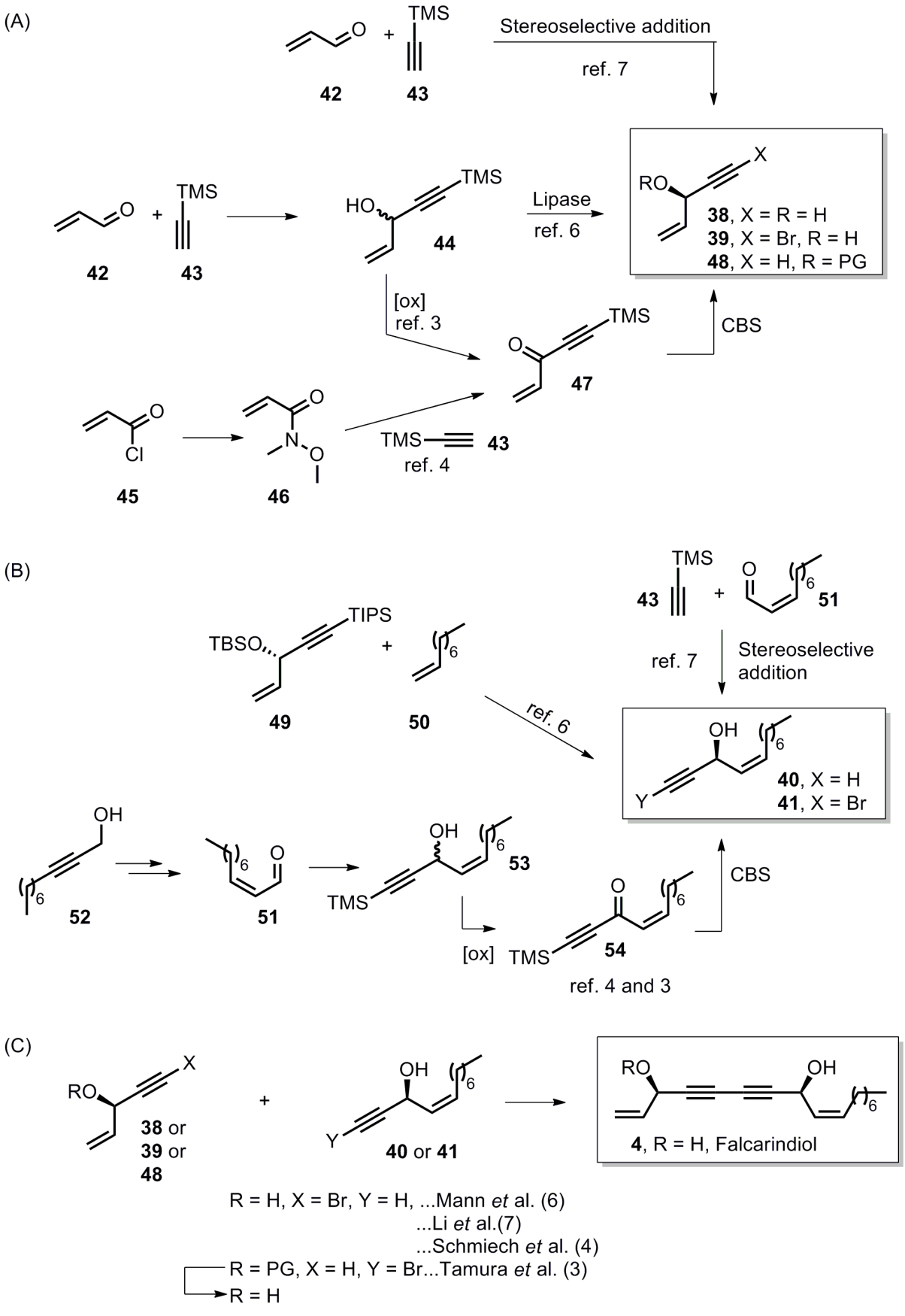
Inspiration for the total synthesis of Notoincisol A **3** comes from the total synthesis of Falcarindiol **4**, since the compounds are structurally closely related. Several total syntheses of Falcarindiol were achieved.[3, 4, 6, 7]The key step of the syntheses is the formation of alkyne-alkyne bond. Such transformation can be mediated by copper catalysts, starting from terminal alkyne and alkynylbromide and is called Cadiot-Chodkiewitz coupling.[30] Another crucial point is the introduction of the chirality at carbons 3 and 8. After the initial retrosynthetic disconnection of two alkynes, two enantiomeric secondary alcohols are obtained (Scheme 33). There are several methods available, for synthesis of enantiomerically enriched alcohols of such type.



Scheme 33

Short secondary alcohols can be synthesized in several ways (Scheme 34, A). A stereoselective addition of TMS-acetylene to acrolein represents one option[7]. This straight forward method however suffers from rather poor *ee's* and ligands used for the introduction of the chirality are not commercially available, thus the synthesis is required. Second approach is based on the synthesis of racemic secondary alcohol and further modifications. Chirality can be introduced either by stereoselective CBS reduction[3, 4] or lipase mediated kinetic resolution[6]. Last approach consists of direct synthesis of the ketone **47** from Weinreb amid and subsequent stereoselective CBS reduction.

Synthesis of long secondary alcohol (Scheme 34, B) can be achieved *via* reoxidation of the secondary alcohol, obtained from *cis* reduction of decynol, oxidation to α,β-unsaturated aldehyde and TMS-acetylene addition. Subsequently, the same reaction sequence as discussed for the short secondary alcohol – reoxidation/CBS reduction – can be applied. Alternatively, in the report of Mann[6], *Z*-selective cross metathesis between decen and protected alcohol **49** was reported. In this way, the stereogenic center is introduced into the short alcohol **49**. That can be achieved as discussed above, however since the other enantiomer of the alcohol **49** is required, either employing lipase mediated kinetic resolution or stereoselective synthesis by using the antipode of the CBS catalyst is an option (short secondary alcohol has *S* configuration, whereas, long secondary alcohol has *R* configuration). Long secondary alcohol can be also synthesized *via* stereoselective addition of TMS acetylene to α,β-unsaturated aldehyde, with the same disadvantages as discussed above.

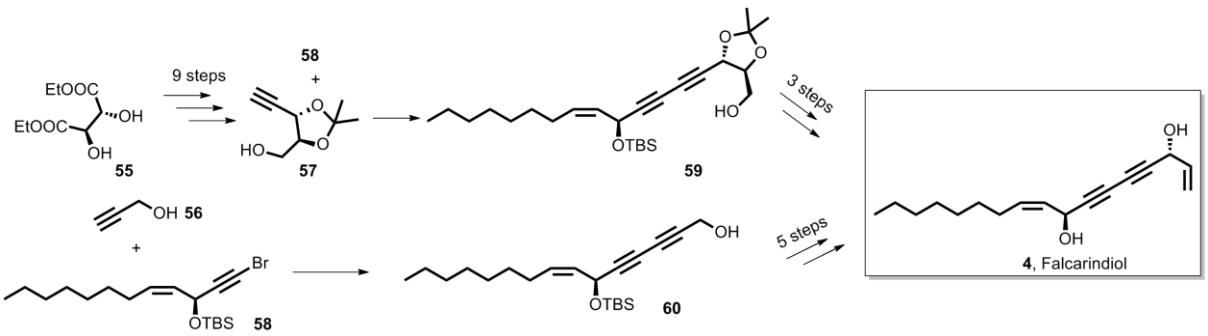

(A)
Stereoselective addition
ref. 7
42
43
Lipase
ref. 6
44
38, X = R = H
39, X = Br, R = H
48, X = H, R = PG
[ox]
ref. 3
CBS
47
45
46
ref. 4
(B)
49
50
ref. 6
40, X = H
41, X = Br
ref. 7
Stereoselective addition
51
52
53
54
[ox]
CBS
ref. 4 and 3
(C)
38 or
39 or
48
40 or 41
4, R = H, Falcarindiol
R = H, X = Br, Y = H, ...Mann et al. (6)
...Li et al.(7)
...Schmiech et al. (4)
R = PG, X = H, Y = Br...Tamura et al. (3)
R = H

Scheme 34

The Cadiot-Chodkiewitz coupling represents another critical step in the total synthesis. Here, both possibilities were described: (i) bromine introduction on short alcohol **39** and use substituent free long alkyne **40** or (ii) vice versa, both providing satisfactory results. If necessary, deprotection of the hydroxyl group is carried out.

Other two synthetic routes towards Falcarindiol were described (Scheme 35).[5] The main step, Cadiot-Chodkiwitz coupling and the long alcohol remained the same. However, synthesis of the short coupling partner with the proper stereochemistry was based on chiral starting material, L-(+)-DET **55**. L-(+)-DET was transformed *via* 7 steps to the coupling partner **57**, which was then coupled with alkynylbromide **58**. Further modifications including nucleophilic substitution of primary alcohol with iodine, zinc induced elimination and deprotection led to the Falcarindiol.

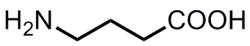
Alternatively, **58** can be coupled with propargyl alcohol and elaborately converted to the final product *via* a number of steps where resulting propargylic alcohol is oxidized to corresponding aldehyde, subjected to Wittig olefination with ethyl acrylate, reduction of the ester to allylic alcohol, Sharpless epoxidation of the allylic double bond and similarly as in the previous case zinc promoted elimination towards protected Falcarindiol. Deprotection provided the desired product. The length of these synthetic routes is significantly longer than in the synthetic pathways depicted in the Scheme 34 and makes these pathways unattractive.



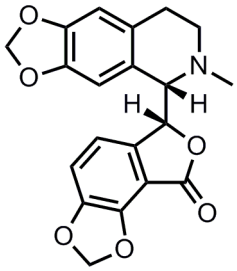
Scheme 35

B IV GABA receptors

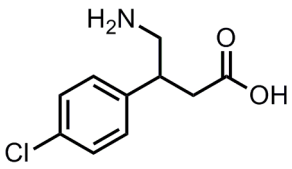
GABA receptors are protein receptors located at the neuronal surface in the whole CNS, whose activity is mediated by γ-amminobutyric acid **61** (GABA). GABA is a main inhibitory transmitter present in the vertebrate brain. Early research of GABA receptors led to the discovery of two main types of GABA receptors. First type, of which the activity was blocked by application of bicuculline (**62**) was designated $GABA_A$. Second type, $GABA_B$ was discovered later as bicuculline insensitive but simulated by baclofen (**63**). Subsequently, a third type of GABA receptor, $GABA_C$, was found to be insensitive for both bicuculline and baclofen. However, it was later reclassified as $GABA_A$ receptor containing ρ subunit, responsible for the insensitivity to the mentioned drugs. There is a major difference between $GABA_A$ and $GABA_B$ mode of action: $GABA_A$ receptor is a chloride gated ion channel, where opening of the channel and thus its conductivity is directly linked to the binding of the endogenous agonist GABA. On the other hand, $GABA_B$ receptor is linked with G proteins.[31]



61
γ-aminobutyric acid
(GABA)



62
Bicuculine



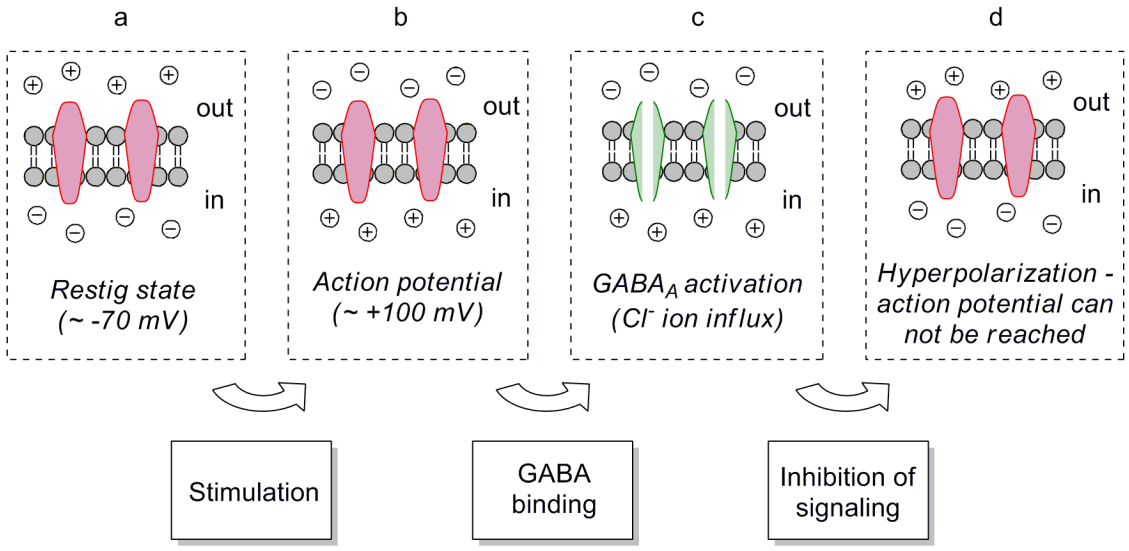
63
Baclofen

Scheme 36

B IV.1 Function of $GABA_A$

Main function of $GABA_A$ receptors consists of the inhibition of the neuronal signal. Under normal circumstances, when the neuron is in the resting state (does not participate in transmission of any signal), there is a potential built across the cell membrane. Positive charge is cumulated inside the cell and negative is located outside the cell membrane. Potential at the membrane reaches the value of -70 mV (Picture 1, a). Once the neuron is stimulated, situation at the cell membrane changes drastically due to the inward flow of

sodium cations. As a consequence, an action potential is formed with the potential up to +100 mV (Picture 2, b).Upon the binding of GABA to its binding site, GABA receptor undergoes a conformational change resulting in the opening of the ion channel and chloride ions can pass through the membrane (Picture 1, c). As a consequence, hyperpolarization is reached, due to the accumulation of the negative Cl^- ions inside the cell. In such a state, action potential cannot be reached, thus, neuronal signaling is inhibited (Picture 1, d).



Picture 1

There is an exception, when GABA can act as excitatory neurotransmitter as well. In such a case, chloride flux takes place in the reversed direction. Such an action leads to neuropathic pain.

B IV.2 GABA$_A$ receptor classification

There are several approaches to the classification of $GABA_A$ receptors. First of them is transductional criteria. According to the transductional criteria $GABA_A$ receptors are sorted according to the kinetics of the opening or closing step of the channel. However, such classification never gained significant importance. Second way to categorize $GABA_A$ receptor is according to the operational criteria. An operational criterion is linked with selective modulation of subtypes with specific drugs. In other receptor classes, selective agonists are most powerful tools for discriminating between subtypes. However, agonists at GABA site usually lead to convulsions *in vivo*. Therefore, developing and systematic exploration of the subtype antagonists is limited. On the other hand the large number of modulatory binding sites present at the $GABA_A$ receptor opens the possibility for a development of a recognition system (some of the most important binding sites will be discussed later in this chapter). So

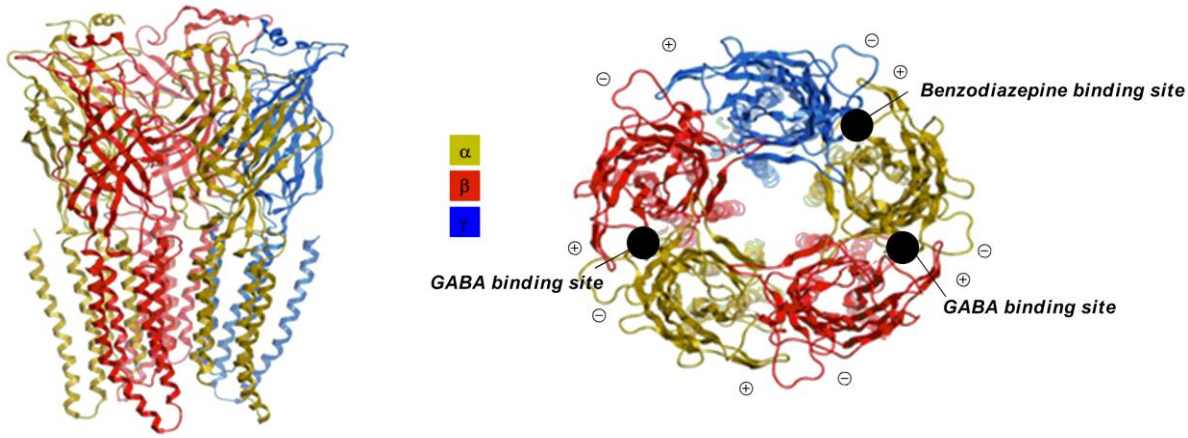
far, to a certain extend such system has been realized with a site at which benzodiazepines or structurally related molecules bind.[31]

By far the most important criteria is the structure of the receptor. $GABA_A$ receptors are composed of five protein subunits. So far, there have been 19 genes identified, encoding $GABA_A$ receptor subunits. There are six α, three β, γ and ρ each, and one δ, π, ε and θ subunit. Given the fact that each $GABA_A$ receptor consists of 5 subunits, there is a large number of possible combinations, leading to the many possible subtypes of $GABA_A$ receptors. However, so far, observations suggest that for instance γ or δ subunits do not tolerate the presence of the same subunit in one receptor, consequently decreasing the number of possible $GABA_A$ receptor types. Nevertheless, there is an estimation that about 800 receptors can actually exist in the brain. The vast majority of them has not been discovered yet, since there can be expressed heterologously. There have been 26 subunits described by now. [32]

It has been noticed that distinct subtypes are localized differently in the CNS. In addition, some of the subtypes are localized at synaptic regions and some at extrasynaptic regions. For details see review from Olsen and Sieghard.[32]

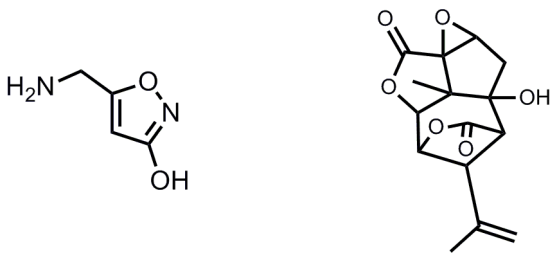
In the nineties of the last century, immunocytochemical studies as well as electron microscopic studies suggested that $\alpha 1 \beta 2 \gamma 2$ represents the most abundant composition of $GABA_A$ receptors.[33-35] This indication was confirmed later by studies using subunit specific ligands.[36]

B IV.3 Structure and pharmacology of $GABA_A$ receptors



Structure wise, $GABA_A$ receptor is a member of the Cys-loop pentameric LGIC superfamily. As mentioned above, it is mostly heteropentamer. Five subunits are composed around the central pore, through which the chloride ions pass when channel is opened (Picture 2).[37] Binding of GABA takes place at the interface of α and β subunit and triggers the opening of the channel. Nowadays, X-ray structure of homopentameric β3 receptor is available.[38] Several molecules are known to bind to the GABA binding site as for instance above mentioned bicuculline, muscimol **64** or picrotoxin **65** (Scheme 37).[39] Most of the drugs, targeting $GABA_A$ receptors, however bind allosterically and act as modulators, consequently displaying no effect in the absence of GABA.

Picture 2



64
Muscimol

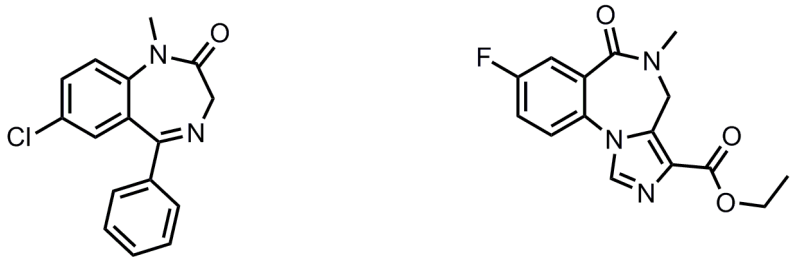
65
Picrotoxinin

Scheme 37

B IV.3.1 Benzodiazepine binding site

Several binding sites have been known for decades. Amongst them the benzodiazepine binding site was subject to the most extensive investigation and broad knowledge was gained. First benzodiazepine drugs were introduced to the market in 1960 and there are still nowadays drugs available in clinical practice. In the early stage of research, GABA receptors were even nomeclatured GABA/BZ receptors, but it was desisted from, as benzodiazepines were also found to bind to other types of receptors as well, unrelated to the GABA receptors.[31] A large number of papers and several reviews were published up to date dealing with benzodiazepine binding sites and ligands associated with it. Benzodiazepine binding site is located at the interface of α+/γ- subunit interface. Application of benzodiazepines or ligands binding at this site leads to an enhanced frequency of the channel opening. Effect on the conductance or opening time of the channel is little. The classical benzodiazepines such as diazepam (**66**) are not subtype selective. Paradoxically, this property of diazepam and smart experimental design led to the disclosure of responsibility of certain $GAGA_A$ receptor subtypes for particular pharmacological effect. Point mutations were introduced to the genes of the individual subunits in mice, leaving the subtype containing this receptor insensitive for diazepam. Comparison of behavioral responses on the drug administration to the wild type and mutated mice led to the recognition of the particular effect of the corresponding subtype. In such a way $\alpha1\beta2\gamma$ receptor subtypes were found to mediate the sedative, anterograde and partly anticonvulsant effect of diazepam. Anxiolytic effect of diazepam is mediated primarily by $\alpha2\beta2\gamma$ receptors and to certain extent also by $\alpha3$ containing subtype. $\alpha2\beta\gamma2$ Receptors are also responsible for muscle relaxant effect of diazepam. Receptors containing $\alpha3$ subunit are responsible for anti-absence effect of benzodiazepines. Modulation of$\alpha5\beta\gamma2$ receptors seem to have an effect on learning and memory. Overview of the major $GABA_A$ receptor subunits and their function is summarized by Michels and Moss.[40]

Besides diazepam, flumazenil (**67**), another member of the benzodiazepine family is able to block all the receptors containing $\alpha1$, $\alpha2$, $\alpha3$ or $\alpha5$ subunits. Therefore, it is often used to mask the receptors with such subunit components.



66
Diazepam

67
Flumazenil

Scheme 38

B IV.3.2 Barbiturate binding site[39, 41]

Barbiturates came into the market way long before benzodiazepines. Phenobarbital (**68**) and pentobarbital (**69**) were introduced as antiepileptic agents in the beginning of twentieth century. But it is not surprising that with the discovery of benzodiazepines, barbiturates were replaced by benzodiazepines due to their relative safety, compared to barbiturates. Barbiturates can lead to physical dependence, addiction or at overdose, consequences can be lethal due to respiratory depression (some studies indicate that respiratory depression is not caused by the interaction with $GABA_A$ receptors).

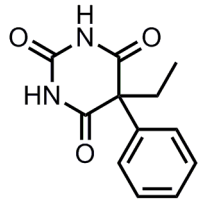
Action of barbiturates differs significantly from the action of benzodiazepines. Three distinct effects of barbiturates have been described on $GABA_A$ receptors:

(A) At lower concentrations (low micromolar), barbiturates bind to the receptors and act as modulators (they show no activity in the absence of GABA). Effect is mediated by extending the opening time of the channel. Frequency of opening and/or conductivity is influenced minimally. Although the specific binding site is still unknown for barbiturates, it was demonstrated that β subunit is crucial for the modulatory action of barbiturates.

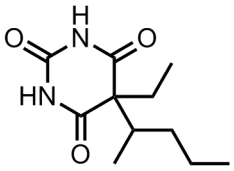
(B) At higher concentrations (low milimolar, <3 mM), barbiturates can act as $GABA_A$ agonists and can activate the $GABA_A$ receptor in the absence of GABA. Herein, α subunit seems to play a crucial role, unlike in the previous case.

(C) At even higher concentrations (>3 mM), barbiturates block GABA receptors.

Barbiturates can also interact with some extrasynaptic $GABA_A$ receptors and cause tonic inhibition. In addition to their complex effect on $GABA_A$ receptors, barbiturates interact with several other receptors as for instance voltage gated Ca^+ channels or non-NMDA receptors.



68
Phenobarbital

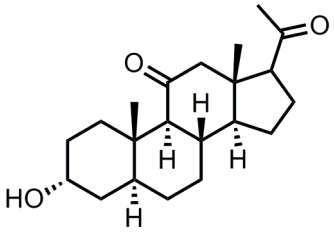


69
Pentobarbital

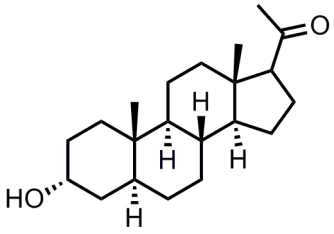
Scheme 39

B IV.3.3 Other $GABA_A$ ligands

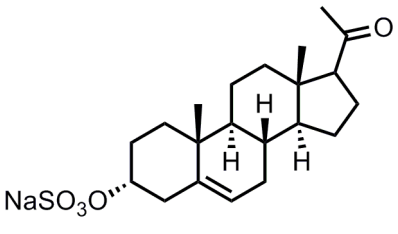
Besides benzodiazepines and barbiturates several other ligands or classes of ligands are known. Several steroids such as alphaxalone **70** (having anesthetic effect) or progesterone **71** and deoxycorticosterone **72** derived ligands display sedative hypnotic, anxiolitic, and anticonvulsant effects (Scheme 40). At lower concentrations, GABA induced chloride conductance is enhanced. At higher concentrations, similarly to barbiturates, steroids act as $GABA_A$ agonists and open the channel even without GABA. That indicates, as in the case of barbiturates, interaction of steroids on more than one site of the receptor.[39]



70
Alphaxalone



71
3α-OH-5α-pregnan-20-one



72
Pregnenolon sulfate

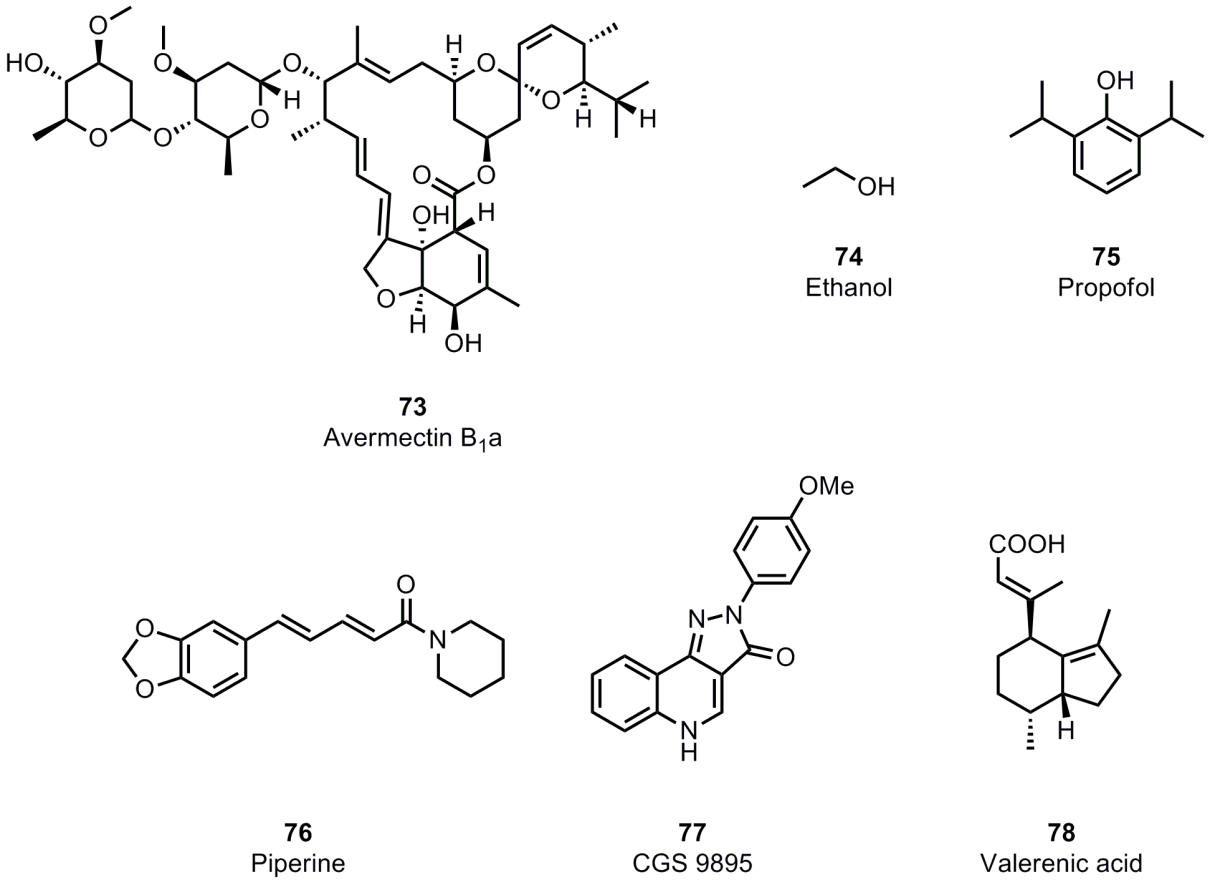
Scheme 40

Several lines of evidence indicate that ethanol is able to potentiate the GABAerig transmission. Anticonvulsant, anxiolytic and sedative effect of alcohol are mediated *via* $GABA_A$ receptors. However, the entire effect of alcohol does not result only from the interaction with $GABA_A$ receptors, but as a consequence of a promiscuity of the ethanol molecule to interact with other receptors as well. In addition effects on the fluidity of the cell membrane plays a role.[39]

Several other ligands interact with $GABA_A$ receptors as depicted in the Scheme 41: avermectine B_1a **73**, propofol **74**, compounds containing pyrazoloquinolinone motif like GSC9895 **75**. Recently, some natural products were found to interact with the $GABA_A$

receptors e.g. valerenic acid **78**[42-44]or piperine **76**[45-48]displayed interesting subtype selectivity profiles and are subjected to further investigation in-house.

After the construction of a homology model by Ernst et al in 2005[49], it was noticed that besides known binding site for GABA or benzodiazepines, located in the binding pockets at the interface between α and β respectively α and γ, there are several other binding pockets. In total five subunits offer five binding pockets at five subunit interfaces. Besides that several other cavities were found, which may be necessary for the conformational change, but can also serve as a potential binding site for drugs. Such an observation can be an explanation for very complicated pharmacological behavior of $GABA_A$ receptors. Recently, the group of Ernst described the α+/β- interface as a binding site for several subtype selective ligands.[50-53]



73
Avermectin B_1a

74
Ethanol

75
Propofol

76
Piperine

77
CGS 9895

78
Valerenic acid

Scheme 41

B IV.4 $GABA_A$ receptor and neolignans

First evidence of an interaction of Magnolol and Honokiol with CNS was reported by Watanbe et al in 1983.[54]Magnolol and Honokiol induced sedation, ataxia, muscle relaxation and a loss of the righting reflex. Fifteen years latter Maruyama et al described the anxiolitic properties of Magnolol and Honokiol.[55] Interaction of Magnolol and Honokiol with $GABA_A$ receptors was proven one year later by Squires et al. Both neolignans increased binding of labeled $GABA_A$ agonists [^{3}H]muscimol and [^{3}H]flunitrazepam.[56]

Several papers were then published, showing that flumazenil can suppress the anti-epileptic effect or other effects, mediated by of neolignans *via* their interaction with $GABA_A$ receptors.[20, 23] Such observation indicates that Magnolol and Honokiol binds to benzodiazepine binding site. However, contrary to that, Teferner *et* al. report concentration depended effects of Magnolol and Honokiol at the receptors lacking γ subunit, which in fact represents an integral structural component of the benzodiazepine binding site.[25] This might indicate multiple binding sites for Magnolol and Honokiol.

Teferner et al[25] have synthesized an extended library of Magnolol and Honokiol analogs and evaluated them at various $GABA_A\alpha\beta$ receptors. Several compounds were found to have potency much higher than lead the compounds as well as efficacies were significantly improved in many cases. The identified hits were evaluated for their subtype selectivity and displayed preference of binding to $\alpha2$ or $\alpha3$ subunit containing subtypes over $\alpha1$. Such behavior is a good prerequisite for anxiolitic and anticonvulsive properties and elimination of sedative effects.

B IV.5 $GABA_A$ receptors and polyenynes

Up to date polyenynes were investigated as $GABA_A$ modulators, having very distinct effects. While oenanthotoxine and several derivatives were described as inhibitors of $GABA_A$ receptors[57, 58], Falcarindiol and falcarinol were described as positive modulators[59, 60].

Investigation of subtype selectivity of falcarinol was performed by Czyzewska *et* al.[60] Three subtypes were investigated: the most abundant$\alpha1\beta2\gamma2$, then $\alpha1\beta2$ and $\alpha1\beta2\delta$, of which last two are thought to mediate the tonic current inhibition. Results indicated that falcarinol enhances the $GABA_A\alpha1\beta2\gamma2$ subtype activity with the signs of use dependant block. In contrast, inhibition of the current through $\alpha1\beta2$ subtype is observed without sign of an open channel block.

The report of Wyrembek *et* al.[59] deals with interaction and modulatory properties of Falcarindiol. It was found that Falcarindiol behaves differently when co-applied with 3 μM

and with saturation level of GABA (10 mM). At 3 μM Falcarindiol significantly increases the amplitude of miniature inhibitory postsynaptic current and has an enhancing effect on the kinetics of the onset as well as accelerate the fading of the current. On the other hand, when receptor is fully saturated with GABA (10 mM), Falcarindiol decreases the current and slowed the current onset and deactivation.

B V Inflammation

B V.1 Physiology and pathology of inflammation[61]

Inflammation is a complex biological operation. The word inflammation origins from Latin *inflammare* – to set on fire. It is a non-specific response of the innate immune system to injury initiated by physical (burn, radiation, etc.), biological (infection by pathogen) or chemical (irritants, toxins) cause. The opinions about the benefits of inflammation varied over history. Some authors saw inflammation as fully beneficial while other fully pathogenic. Nowadays, the scientific understanding of inflammation is more complex. Indeed, lack of inflammatory response can result in survival of the pathogen and all related consequences. But on the other hand, extensive inflammation can have a severe impact on the organism and can lead to numerous diseases. There are two types of inflammation: acute and chronic.

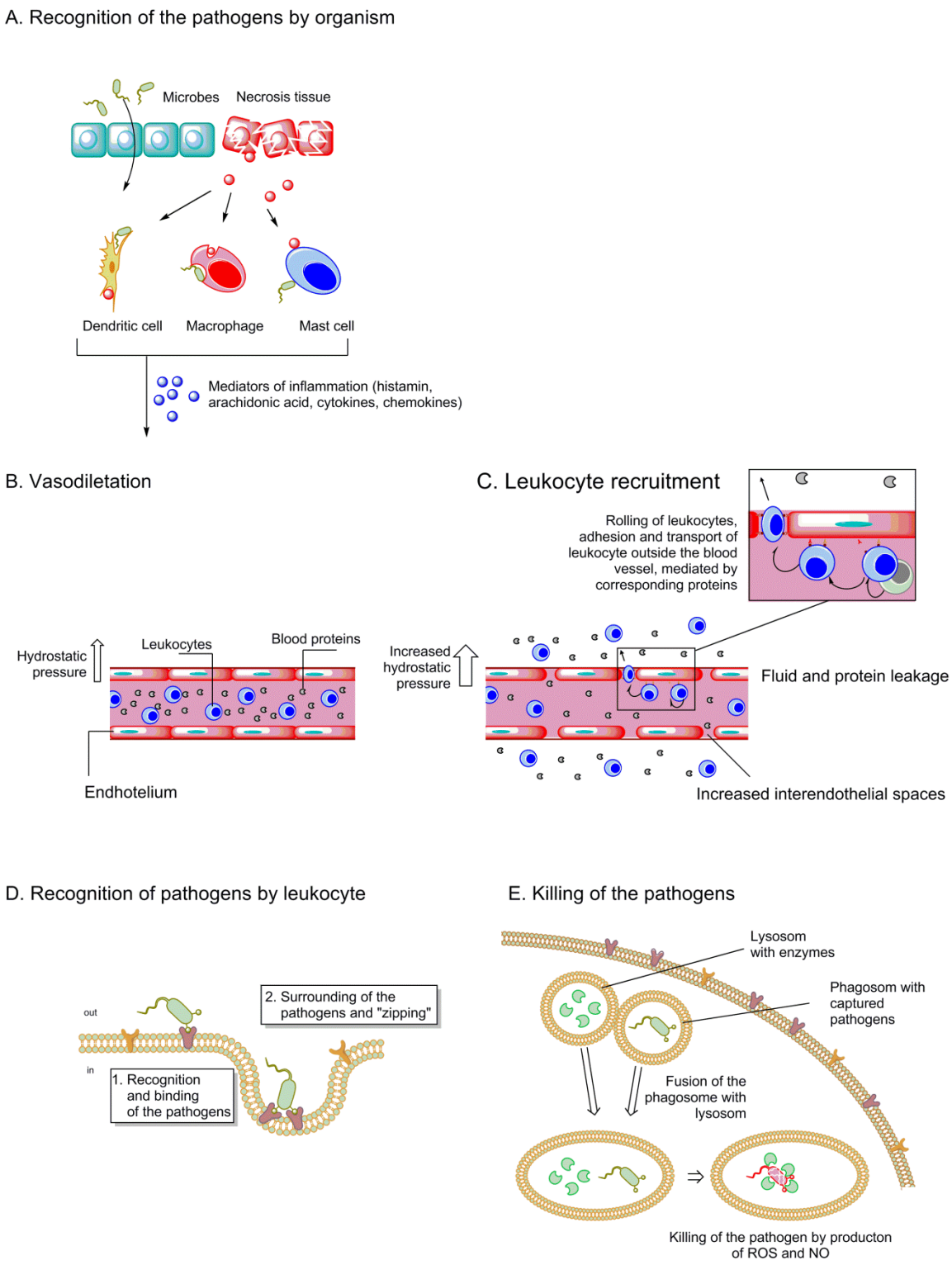
Acute inflammation occurs shortly after a contact with pathogen. It has five typical signs: dolor – pain, calor – heat, rubor – redness, tumor – swelling, functio laesa – loss of function. The process can be divided in several parts: recognition of the pathogen, vasodilatation, recruitment of lymphocytes, phagocytosis and clearance of the offending agent and termination. Process is then completed by the repair of the damaged tissue.

Recognition of the pathogen is mediated by many receptors, both soluble or membrane receptors. They can by classified into *cellular receptors for microbes*, amongst which the toll-like receptor (TLR) is the most studied. Next important class is the *cell damage sensors*; these are a specific set of cytosolic receptors, capable of recognition of molecules which accompany the decomposition of the cell (uric acid – product of DNA breakdown – and DNA from damaged mitochondria, decreased K^+ concentration due to efflux from the cell, etc.). There are some other recognition machineries as for instance *circulating proteins*, which can also recognize microbial pathogens and initiate inflammation and pathogen destruction. Upon pathogen recognition, mediators of inflammation are released, mainly from macrophages and mast cells (Picture 3, A)

After the recognition of the pathogen, blood vessels at the affected location undergo vasodilatation. That leads to increased vascular permeability and blood flow which allows the plasma proteins and leucocytes to enter the affected tissue. Such a vascular leakage of the protein rich fluid into the tissue, together with the increased hydrostatic pressure leads typically to the signs of the inflammation (Picture 3, B).

Recruitment of leukocytes is a multistep process, which includes leukocytes binding to and rolling on endothelium (thin cell layer in the interior of a blood vessel) passing of the leukocytes through the membrane. This process is mediated by several proteins like

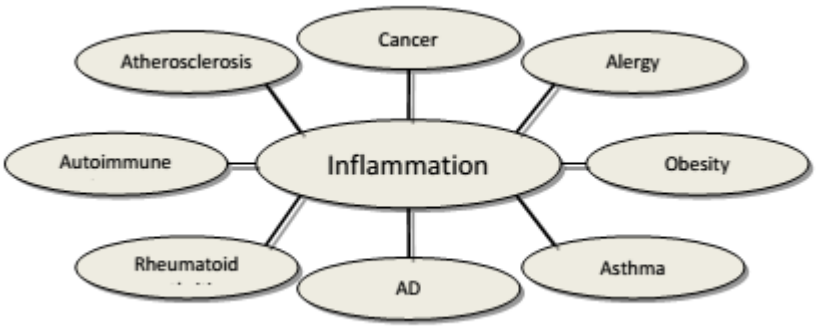
selectins or integrins, ensuring the adhesion, rolling and releasing of the leucocytes outside of the vessel (Picture3, C).



Picture 3

In the affected tissue, leukocyte recognizes the pathogen and attaches it to the surface. Surface will subsequently surround the offending agent and will form the vacuole with the pathogen inside. Once ingested in the cell, vacuole with undesired content fuses with the vacuole containing the enzymes mediating the killing of the offender. Killing is executed by enzymes like iNOS, which produce reactive oxygen species or NO, capable of killing the pathogen (Picture 3, D).

If the termination of the inflammation does not occur, acute inflammation can turn into chronic inflammation. That can happen from several reasons: (a) resistance of the pathogen, (b) inflammation agents start to affect a healthy tissue of the host or (c) prolonged exposure to the potentially toxic agent either exo- or endogenous.

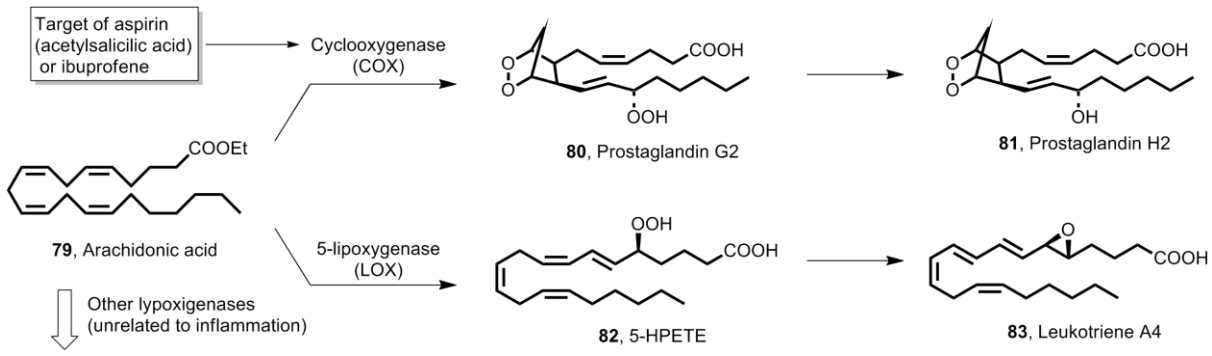


Picture 4

Many diseases can be connected to inflammation (Picture 4), amongst them also some which were not considered of the inflammatory origin but rather some other origin e.g. metabolic or genetic. Some of the diseases which are nowadays thought to originate or be linked to inflammatory dysfunction are depicted in the following picture and are for instance: Alzheimer disease, obesity or certain types of cancer, allergies, asthma, atherosclerosis or autoimmune disease can be in fact linked to inflammation.

B V.2 Inflammation on biochemical level – involvement of NF-κB, PPARγ, RXR and other related receptors

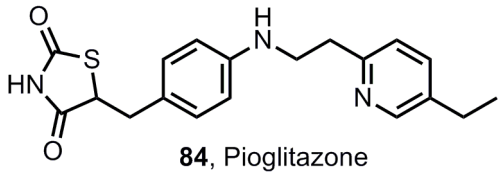
On the biochemical level, recognition of the pathogen triggers release of inflammatory mediators. Various entities belong to this group, including organic molecules such as histamine, arachidonic acid (**79**) and compounds derived from it called prostaglandins (**80**, **81**) and leukotrienes (**82**, **83** – synthesis of both classes is mediated by enzymes called cyclooxigenase – COX – and 5-lipoxygenase – 5-LOX – Scheme 42) then proteins like chemokines and cytokines (TNF, IL-4, IL-6). Inflammatory mediators have various origins, but most of them come from mast cells or macrophages but can come from leucocytes as well. They have diverse function. Histamine and prostaglandins are responsible for vasodilatation; prostaglandins, in addition, are causing pain and fever. Therefore, COX enzyme is a target for many anti-inflammatory drugs and painkillers such as aspirin (acetylsalicylic acid) or ibuprofen. Leukotrienes play a crucial role in the recruitment of leukocytes but are also important for inhibition of the inflammation. Cytokines influence several processes on both local and systemic level. They are involved in the transpassing of leukocytes from blood vessels to the affected tissue but have an impact on fever, hypertension or metabolic abnormalities as well.



Scheme 42

Involvement of NF-κB in inflammation has been recognized for long time. NF-κB belongs to the nuclear transcription factor protein family, responsible for expression of genes essential in the inflammatory process. It also amplifies the inflammatory signal. NF-κB is directly activated by TNF and some cytokines (IL-1β). Upon the activation, it forms either homo or heterodimers and subsequently binds to the DNA binding domain and triggers gene transcription. Gene expressed upon the NF-κB stimuli encode proteins (COX, iNOS), cytokines (IL-2, IL-4, IL-5, IL-6, TNF) and other chemokines and adhesion proteins, all involved in inflammatory processes.[62]

In 1998 it was shown that activation of peroxisome proliferator activated receptor γ (PPARγ) can inhibit function of NF-κB.[63-65] PPARγ is a nuclear transcription factor and belongs to the nuclear receptor superfamily with the main function on regulation of the genes involved in glucose and lipid metabolism. PPARγ is mostly expressed in adipose tissue and its activation leads to adiptogenesis and to increased insulin sensitivity. Therefore, PPARγ activators such as thiazolidinediones (e.g. pioglitazone), are clinically used to combat type II diabetes. Pioglitazone, however possesses several severe side effect such as weight gain, fluid retention, increased bone fracture or even heart failure.[24]



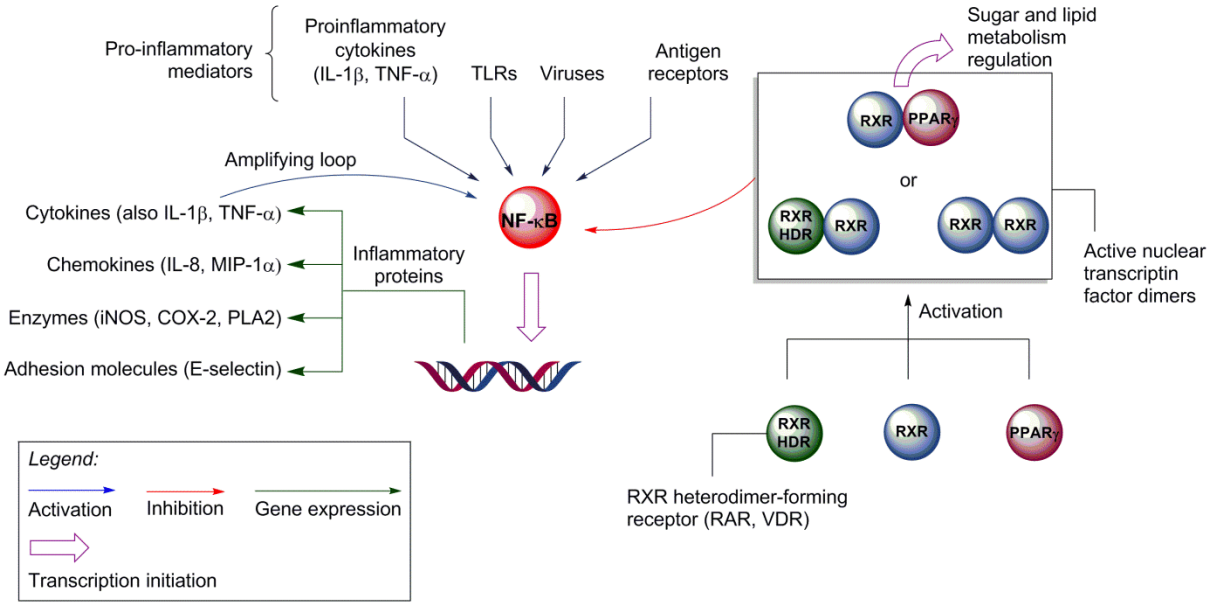
84, Pioglitazone

Scheme 43

Upon activation, PPARγ forms a heterodimer with another nuclear transcription factor, retinoid X factor (RXR), recruits certain co-activators and then binds to the DNA binding domain to initiate transcription. Two years after the discovery of PPARγ ability to inhibit NF-κB, some evidence indicated the possible involvement of RXR in inflammation as well. [66, 67] Latter, the involvement of the PPARγ/RXR dimer was shown.[68] Moreover, recently it was demonstrated that anti-inflammatory properties of RXR agonists again come from inhibition of NF-κB by activated form of RXR[69, 70]. The whole process, including the role of NF-κB and nuclear transcription factors is depicted in the Picture 5.

In addition, it was demonstrated that anti-inflammatory properties of vitamin D are partially mediated by RXR as well. Vitamin D binds to the vitamin D receptor (VDR), which in turn forms a dimer with RXR. It was shown that only binding of vitamin B to the VDR does not have desired anti-inflammatory effect in the absence of RXR.[71]

Besides PPARγ, RXR can form heterodimers with several other proteins such as liver X factor (LRX) and as such can regulate levels of inflammation mediators. Retinoid X receptor can also form homodimer with itself.[72]

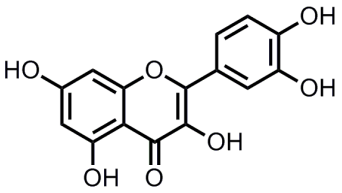


Picture 5

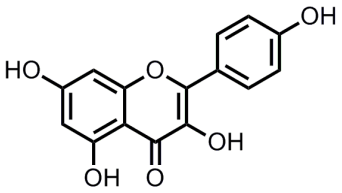
B V.3 PPARγ and natural product agonists[73]

From the above mentioned nuclear receptors, PPARγ has been studied most extensively. A number of natural product classes has been described to modify the activity of the receptor. Several flavenoids were found to be partial agonists of PPARγ. Interestingly, some of the compounds as for instance querecetin **85** or kaempferol **86** were described to modify glucose metabolism, while having no effect on adiptogenesis, while several other compounds from the same class, like (-)-catechin **87**, affect the lipid metabolism as well. Several flavenoids were shown to inhibit TNF-α induced adhesion of the monocytes to HUVEC, indicating their potential anti-inflammatory activity.

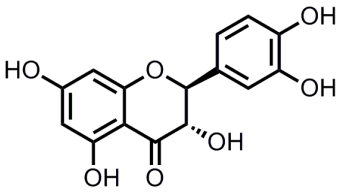
From other natural product classes, stilbens were found to effect glucose and lipid metabolism; amorfrutines or some terpen derived natural products were described as PPARγ partial agonists as well (Scheme 44). Neolignans and polyenynes will be discussed separately.



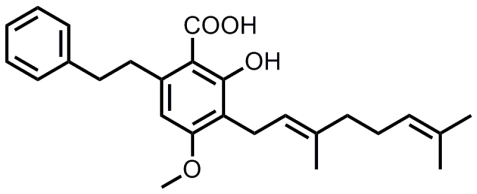
85, Querecitin



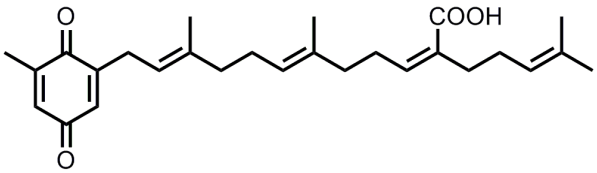
86, Kaempferol



87, (-)-Catechin



88, Amorfrutin B



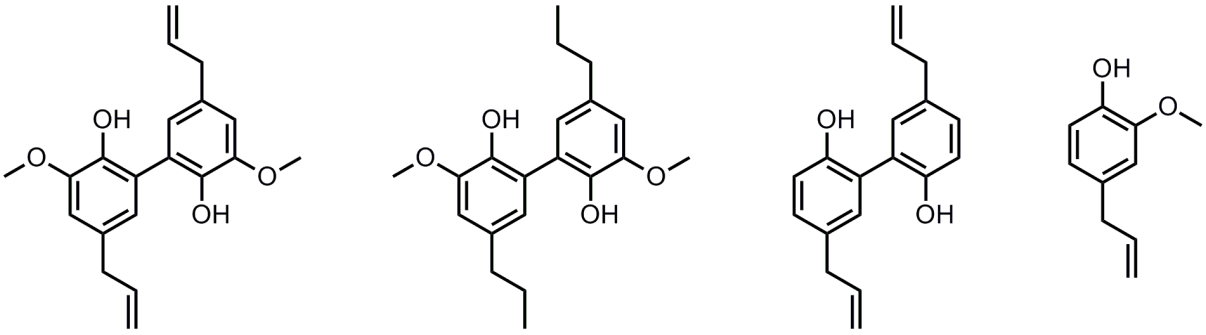
89, Sergaquinoic acid

Scheme 44

The existence of PPARγ partial agonists with distinct biological effect, as can be seen for instance in the case of flavenoids, leads to the assumption, that activation of the receptor can lead to diverse biological effects. It was hypothesized that partial agonism or activation with various ligands can result in different conformational changes of the protein. Such differences are then decisive for the recruitments of co-activators required for expression of particular genes.

B V.4 Inflammation and neolignans

In silico library screening has predicted a binding of several neolignans to the ligand binding domain of PPARg.[24] Prediction was then evaluated by isolation of corresponding neolignans from their natural sources or by chemical synthesis and subsequent administration in several assays to verify the predicted ability of the compounds. Four compounds were investigated, Dieugenol **90**, tetrahydrodieugenol **91**, Magnolol **1** and eugenol **92**.

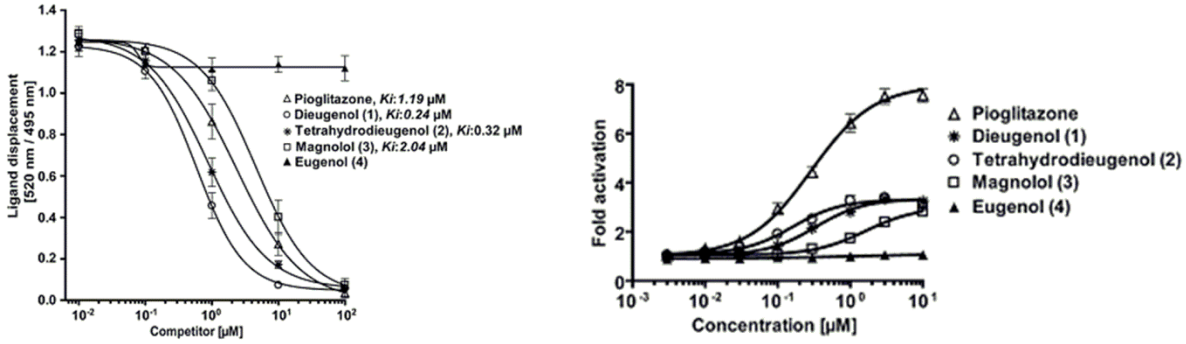


90 Dieugenol | **91** Tetrahydrodieugenol | **1** Magnolol | **92** Eugenol

Scheme 45

Competitive ligand binding assay has revealed that all of the compounds but eugenol bind to the receptor. Some of the neolignans actually bind with abinding affinity even higher than pioglitazone. Dieugenol and tetrahydrodieugenol bind to ligand binding domain with Ki = 0.24 and 0.32 μM, Magnolol with Ki = 2.04 μM (pioglitazone Ki = 1.19 μM).

Ability of the compounds to activate PPARγ and trigger the transcription was then evaluated by lucifarace reported gene assay. PPARγ was expressed in HEK-293 cells and cells were treated with neolignans. Concentration dependent response was observed in a concentration range similar to the pioglitazone.



Picture 6

As can be seen from the (right) graph in the picture 6, neolignans have shown partial agonistic behavior. It was later evaluated, that such behavior originates from the different cofactor recruitment pattern.

Such observation opens the possibility that various ligands can lead to different conformational changes and thus recruitment of different cofactors, leading to suppressed expression of the full range of genes, as observed in the case of pioglitazone. Such a property of the ligand-protein complex can eventually lead to the elimination of the side effects caused by the full agonist as a hypothesis for further compound development.

Moreover, Magnolol has also been shown to be a potent antagonist of COX-2 receptors.[16]

B V.5 Inflammation and polyenynes

Atanasov *et* al. have reported an effect of Falcarindiol and several related compounds on PPARγ receptors. In total, 6 polyenynes were evaluated. They were found to be partial agonists of the receptors with the maximal fold activation between 1.88 and 3.26 (for Falcarindiol) and EC_{50} in the range between 2.03 and 11.31 μM (with 3.29 μM for Falcarindiol).[74]

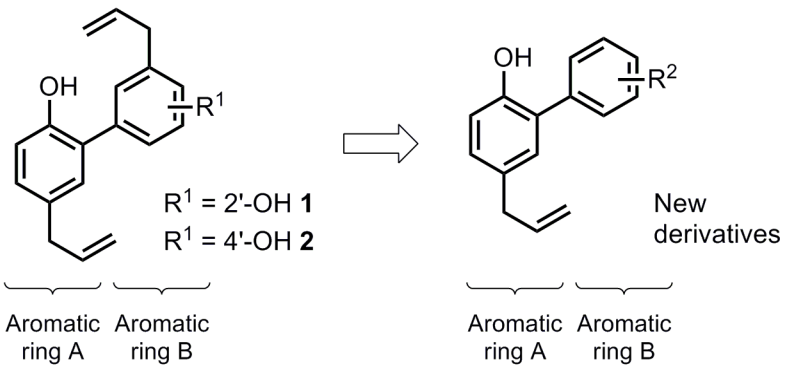
Recently, 11 new polyenynes were isolated from *Notopterygium incisum*, structurally evaluated and their effect on PPARγ was described by co-operation partners of this project. Amongst newly discovered natural products, which all were identified as partial agonists, Notoincisol A and Notoincisol B showed the best agonistic effect. 2.8and 2.3maximal fold activation was measured for Notoincisols A & B and EC_{50} of 2.3 μM and 1.7μM, respectively.[2]

These results make both Notoincisols suitable candidates for pharmaceutical leads. Therefore, development of a modular synthesis was desired.

C Synthesis of new Magnolol derivatives and their biological evaluation

This chapter describes a development of novel $GABA_A$ and PPARγ ligands. In the beginning, synthesis of the derivatives is described. Derivatives were synthesized in two ways, one, following the literature precedent[17] and *via* a novel synthetic strategy, eliminating the disadvantages of the literature pathway. Synthesized derivatives were evaluated for their biological effect.

Design of the new derivatives was envisioned as outlined in Scheme 46. Since Magnolol **1** and Honokiol **2** both contain the same aromatic ring (ring A), the strategy for design of novel derivatives consisted of maintaining the common part of the molecules unchanged; modifications were performed on the other ring, ring B. Allyl and hydroxyl groups from the ring B were removed and replaced by a simple chemical substituent. For the first generation of the library, various substituents were chosen with diverse chemical properties, in order to investigate the structure activity relationship. Second generation of the library was then designed based on the obtained results.

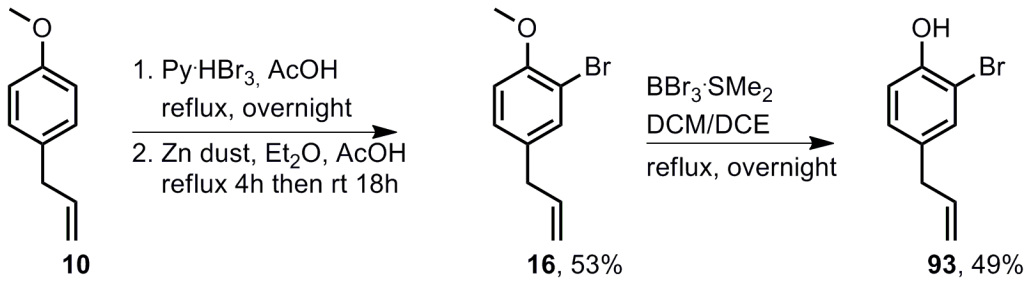


Scheme 46

C I Synthesis of novel derivatives

C I.1 Synthesis if novel derivatives *via* literature known pathway

Initially, synthesis of desired derivatives was envisioned *via* one of the methods discussed in introduction chapter. In the first step, either boronic acid introduction or bromination was planned, followed by Suzuki coupling with aryl bromide or boronic acid of interest, respectively. However, reproduction of the *o*-lithiation appeared to be rather challenging and the corresponding boronic acid was never obtained in good yields.[75] On the other hand, bromination into position two of 4-allyanisol**1** was found to be working sufficiently. Compound **10** was treated with pyridinium tribromide in refluxing acetic acid overnight.[17]After the work up, the crude mixture was redissolved in ether and treated with zinc dust in the presence of acetic acid, in order to restore the olefinic functionality, which undergoes undesired bromination under the given conditions. After a chromatographic purification, 4-allyl-2-bromoanisole **16** was obtained in 53% of yield. Next, intermediate **16** was submitted to demethylation. Treatment of **16** with tribromobarate-dimethylsulfide complex in boiling ether and acetic acid provided key phenol **93** in 49%.



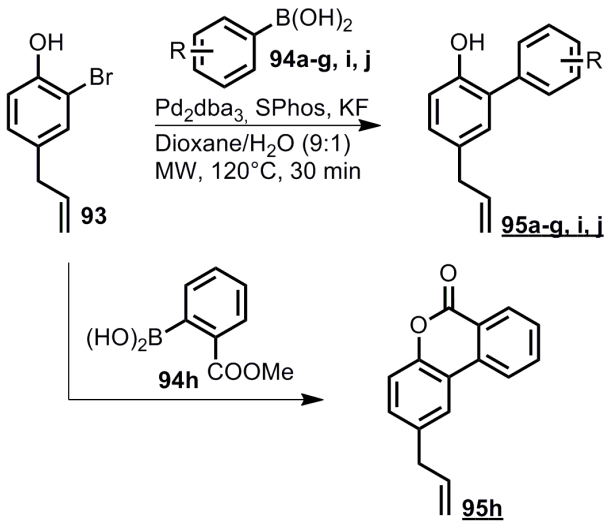
10 **16**, 53% **93**, 49%

Scheme 47

Bearing in mind advantages of microwave irradiation in organic synthesis[76], conditions reported by Chen[17] for Suzuki coupling (Pd_2dba_3, SPhos, KF in Dioxane/H_2O) were transferred from conventional heating mode to microwaves. All the other parameters were kept unchanged, as it was found to be crucial to use SPhos as a ligand and potassium fluoride as a base in order to avoid the isomerization of the allylic double bond towards thermodynamically more stable conjugated vinylic system. Phenyl boronic acid was chosen as first coupling partner representing a starting point for modification of the substitution pattern at the second aryl ring; this system served as “neutral” model compound from chemical as well as from medicinal chemistry point of view. After 30 minutes of microwave irradiation, GC/MS analysis revealed full consumption of the starting material and formation

of the desired product was confirmed. Reaction mixture was subjected to column chromatography and the final product was isolated in 56% yield.

Several derivatives were subsequently synthesized, utilizing the above described procedure (Scheme 48). First, focus was turned into the synthesis of derivatives bearing methoxy groups in positions 2, 3 and 4 of the aromatic ring B. Thus, **93** was coupled with 2-methoxy-, 3-methoxy- and 4-methoxyboronic acid (**94a**, **94b** and **94c**) and the corresponding derivatives **95a**, **95b** and **95c** were obtained in 31, 35 and 46% yield, respectively. Second series of derivatives contained nitro substituents, again in all possible positions of the aromatic ring B. Desired product were isolated in 15% in case of 2'-nitro derivative **95d**. In this case, the low yield was a consequence of two subsequent chromatographic purifications, since the product was not obtained pure after first column chromatography. 5-Allyl-3'-nitro-[1,1'-biphenyl]-2-ol **95e** was obtained in 55% yield, and derivative 5-allyl-4'-nitro-[1,1'-biphenyl]-2-ol **95f** was obtained in 20% yield. Again, two chromatographic purifications were required in order to obtain pure compound. As a final set of derivatives, an ester function was introduced. Desired compounds were obtained in 41 and 51% yield for meta and para substitution (**95i** and **95j**, respectively). Reaction with 2-methoxycarbonyl phenylboronic acid **95h**, however, did not lead to the desired product, but spontaneous lactonization was observed providing compound **95h**.



Compound	R	Yield [%]
95a	H	56
95b	*o*-OMe	31
95c	*m*-OMe	35
95d	*p*-OMe	46
95e	*o*-NO2	15
95f	*m*-NO2	55
95g	*p*-NO_2	20
95h	lactone	42
95i	*m*-COOMe	41
95j	*p*-COOMe	51

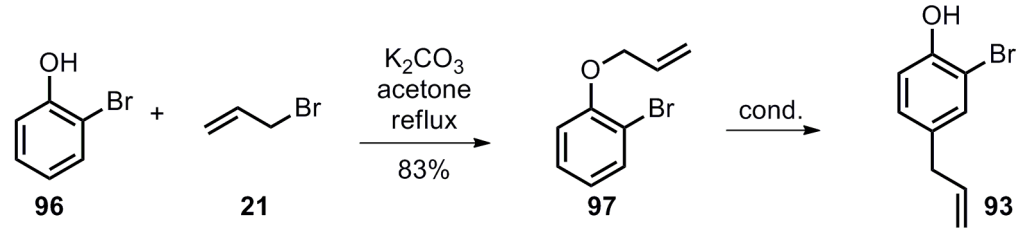
Scheme 48

C I.2 Development of novel synthetic strategy

C I.2.1 Unsuccessful attempts

Above described synthetic strategy consists of several steps, which were found to conflict with principles of modern synthetic organic chemistry. First of all, overbromination of the allylic double bond and subsequent necessity of debromination does not follow principles of atom economy. Moreover, overall efficiency for the preparation of key intermediate **93**, together with decreased structural complexity of new derivatives compared to the lead structures led to the decision to synthesize **93** in an alternative way or to find an entirely alternative approach to obtain desired derivatives. Several strategies were envisioned. Retrosynthetically, Suzuki coupling would remain the key step of the synthesis of the desired derivatives in order to achieve diversity.

Alternatively, intermediate **93** could be prepared utilizing *O*-allylation of 2-bromophenol and subsequent Cope-Claissen rearrangement.[77] Allyloxy-2-bromobenzene **97** was prepared in 83% yield by treatment of 2-bromophenol with allyl bromide in presence of potassium carbonate in acetone. Compound **97** was subsequently subjected to microwave irradiation either neat or in water as a solvent. However, no conversion was observed at the temperatures up to 200°C (Scheme 49).



96 **21** **97** **93**

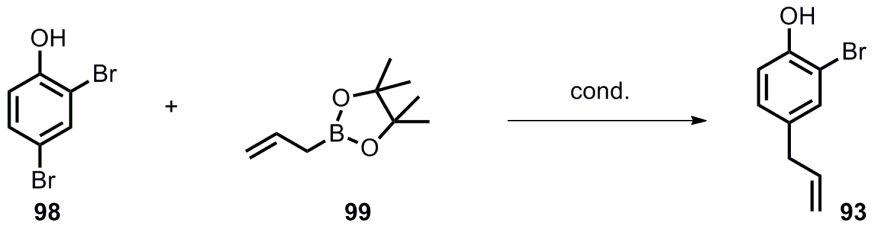
Entry	Temperature	Solvent	Conversion
1	100	-	no
2	180	-	no
3	200	-	no
4	160	H_2O	no

Scheme 49

Another synthetic strategy investigated to achieve intermediate **97** or its alternative, 4-allyl-2-chlorophenol, was based on a selective allylation of doubly substituted phenol.

Initially, 2,4-dibromophenol **98** was investigated as a starting substrate for the cross coupling with pinacolallyborate. Several conditions were tested. Using mixtures of toluene and water as a solvent, palladium tetrakis triphenyl phosphine as a catalys and cesium fluoride as a base were investigated for the transformation at 85 or 95°C, however, these

experiments did not lead to any conversion. Applying conditions of Chen[17] and Denton[18] did not improve the situation. Transferring the reaction to the microwave (under the Chen and Denton conditions), led to partial conversion of the starting material, however, there was not a distinct reactivity of bromine in position 2 and in position 4 and only doubly allylated product was detected in the according to GC/MS.



98 **99** **93**

Entry	"Pd"	Base	Ligand	Solvent	Heat. mode	temp.	Time	Conv.
1	$Pd(PPh_3)_4$	CsF	-	Tol/H_2O	conv.	85	overnight	no
2	$Pd(PPh_3)_4$	CsF	-	Tol/H_2O	conv.	95	overnight	no
3	Pd_2dba_3	KF	SPhos	diox/H_2O	conv.	90	24h	no
4	Pd_2dba_3	KF	SPhos	diox/H_2O	conv.	120	24h	no
5	Pd_2dba_3	KF	SPhos	diox/H_2O	MW	120	30 min	SM + biallylated

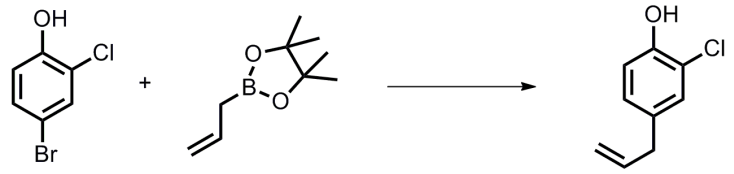
Scheme 50

Utilizing various halogen groups at the phenol was investigated as possible solution to this problem. Placing the more reactive halogen into the position 4 would lead to the selective allylation in this position. Subsequently, Suzuki coupling into position 2 would lead to the desired derivatives. Two possible compounds can be utilized: 4-iodo-2-bromophenol or 4-bromo-2-chlorophenol. As the prior precursor is not commercially available, the bromo analog was selected as starting material of choice.

4-Bromo-2-chlorophenol **100** was subjected to an extensive screening of reaction conditions for the coupling with pinacolallyborate **99**. Reactions were analyzed by means of TLC and GC/MS. Within the long term planning of the project, it was initially considered to develop conditions, suitable for transferring the process into the flow reactor. It was therefore important to ensure homogeneity of the reaction mixture or use a catalytic system, suitable for filling the cartridge of the available flow device. A more elaborate discussion of the attempts to carry out the reaction in the continuous flow fashion was part of a complementary PhD study.[78]

Initial attempts employing palladium tetrakistriphenyl phosphine as catalyst in the toluene/water mixture and with cesium fluoride or sodium carbonate as base did not lead to any success. With cesium fluoride at 85°C or 95°C no formation of the desired product was detected by GC/MS analysis. Instead, side product with the mass corresponding to the debrominated starting material was found to be present in the reaction mixture (Scheme 51, Table, entries 1-3). It was then tested to utilize the modified reaction conditions as reported

by Chen and Denton (Pd_2dba_3, SPhos, KF, 150°C, microwave irradiation). In spite of the fact, that partial conversion towards the desired product was observed, result was not very satisfactory, since reaction did not provide full conversion and in addition it was again accompanied with the side reaction, leading to 2-chlorophenol (Scheme 51, Table, entry 4). Exchange of the SPhos ligand by+/-BINAP did not lead to any improvement, but on the contrary, the overall conversion dropped in spite of the elevated temperature and still debromination took place as well (Scheme 51, Table, entry 5). Switching to dppf, on the other hand, turned out to be beneficial in regards of the conversion. Starting material was detected only in trace amounts, however also quantities of the side product increased relative to product (Scheme 51, Table, entry 6). At this stage, another problem was encountered: all of the above discussed conditions did not provide homogeneous mixtures, thus they were not suitable for the flow process. It was then tested, whereas simple filtration of the reaction mixture prior the reaction itself could solve the problem. Nevertheless, as turned out that reaction took place in heterogeneous fashion, since neither conversion nor debromination was observed after heating the filtrate to 150°C. Such a reaction outcome was independent on the amount of the catalyst loading and on the solvent used (Scheme 51, Table, entries 7-12).



100 **99** **101**

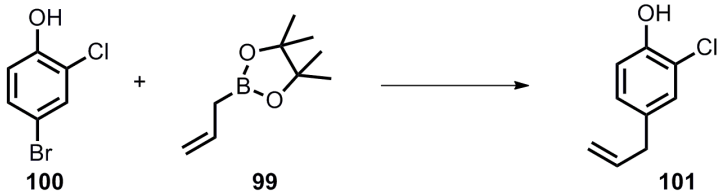
Entry	Pd source (mol%)	Additive	Solvent	Base (eq.)	Temp. °C	Reaction time (min)	Heating mode	Note	SM/SP/EP[1]
1	$Pd(PPh_3)_4$	-	Tol/H2O	CsF (2)	85	85	conv.	-	62/38/0
2	$Pd(PPh_3)_4$	-	Tol/H2O	CsF (2)	95	95	conv.	-	60/40/0
3	$Pd(PPh_3)_4$	-	Tol/H2O	Na_2CO_3 (2)	85	85	conv.	-	99/1/0
4	Pd_2dba_3 (5)	SPhos	diox/H2O	KF (2)	120	120	MW	not hom..	23/12/65
5	Pd_2dba_3 (5)	+/-BINAP	diox/H2O	KF (2)	150	150	MW	not hom.	58/15/27
6	Pd_2dba_3 (5)	dppf	diox/H2O	KF (2)	150	150	MW	not hom.	tr./39/61
7	Pd_2dba_3 (5)	dppf	diox/H2O	KF (2)	150	150	MW	inhomog. filtrated	100/0/0
8	Pd_2dba_3 (2)	dppf	diox/H2O	KF (2)	150	150	MW	inhomog. filtrated	100/0/0
9	Pd_2dba_3 (10)	dppf	diox/H2O	KF (2)	150	150	MW	inhomog. filtrated	100/0/0
10	Pd_2dba_3 (10)	dppf	diox/H2O	KF (4)	150	150	MW	inhomog. filtrated	100/0/0
11	Pd_2dba_3 (5)	dppf	dioxane	KF (2)	150	150	MW	inhomog. filtrated	100/0/0
12	Pd_2dba_3 (5)	dppf	THF/H_2O	KF (2)	150	150	MW	inhomog. filtrated	100/0/0

[1] Integration of peak area in GC/MS

Scheme 51

To overcome the problem, it was decided to switch to palladium catalysts encapsulated on resin (PdEn40®). Such a material can be purchased as either ligand free or ligand bound palladium source. Both options were tested: utilizing ligand free encapsulated $Pd(OAc)_2$ did not lead to any conversion (Scheme 52, Table, entry1). PdEn40® containing

bound ligands however failed no matter on the ligand type. Three ligands were tested, BINAP, tri-*o*-tolylphosphine, and triphenylphosphine, however only starting material was detected in the reaction mixture (Scheme 52, Table, entries 2-4). Utilizing ligand free encapsulated palladium acetate and addition of the dppf turned out to be beneficial. Several experiments were carried out, varying temperature and ligand loading. At 150°C, with 10 mol% of dppf, no side reaction was observed; however, conversion was far from complete (Scheme 52, Table, entry 5). Increasing the ligand loading to 15% led to full consumption of the starting material, however, side reaction was taking place (Scheme 52, Table, entry 6). Keeping the ligand loading at 10 mol% and increasing the reaction temperature to 170°C led to full consumption of precursors, however, formation of the sideproduct was increased (Scheme 52, Table, entry 7). Shortening the reaction time from 30 minutes to 10 minutes surprisingly turned out to be in favor of formation of the desired product over the side product (Scheme 52, Table, entry 8).



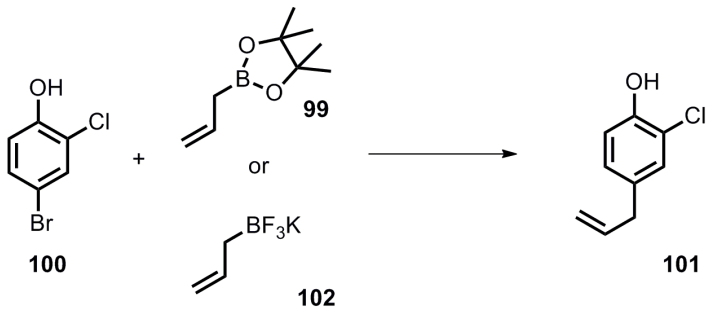
100 **99** **101**

Entry	Pd source (mol%)	Additive (mol%)	Solvent	Base (eq.)	Temp. °C	Reaction time (min)	SM/SP/EP[2]
1	PdEn40®	-	diox/H2O	KF	150	30	100/0/0
2	PdEn40® BINAP	-	diox/H2O	KF	150	30	100/0/0
3	PdEn40® TOTP	-	diox/H2O	KF	150	30	100/0/0
4	PdEn40® TPP	-	diox/H2O	KF	150	30	100/0/0
5	PdEn40®	dppf (10)	diox/H2O	KF	150	30	73/0/27
6	PdEn40®	dppf (15)	diox/H2O	KF	150	30	0/28/72
7	PdEn40®	dppf (10)	diox/H2O	KF	170	30	0/38/62
8	PdEn40®	dppf (10)	diox/H2O	KF	170	10	0/25/75

Scheme 52

This observation suggests that side product is rather formed *via* decomposition of the product than the debromination of the starting material. It was then rationalized that higher amounts of the ligand and higher temperatures cause the side reaction and therefore ligand loading was kept at 10 mol% and the temperature at 150°C, while the role of the base was investigated as the next step (Scheme 53). Several organic and inorganic bases were examined, including, triethylamine, sodium acetate sodium carbonate, sodium hydroxide and potassium carbonate. It was found that the base plays a crucial role in the course of the reaction. In all cases, all the starting material was fully consumed. The amount of the side product was then found to be dependent on the base used. Utilizing triethylamine as well as

sodium acetate and sodium carbonate did not lead to the suppression of the sidereaction (Scheme 53, Table, entries 2-3). However, only small quantities of 2-chlorophenol were detected when sodium hydroxide was used (Scheme 53, Table, entry 4). Shortening of the reaction time again proved to be beneficial and only trace amounts of side product were detected when reaction was performed at 150°C for 10 minutes, supporting the above mentioned hypothesis of the product decomposition (Scheme 53, Table, entry 5). The best result was obtained with potassium carbonate. Even after 30 minutes, only trace amounts of the side product were detected at 150°C. After Kugelrohr distillation 4-allyl-2-chorophenol can be isolated in 65% (Scheme 53, Table, entry 6). Side reaction can be successfully suppressed, when the reaction mixture is irradiated for 7 minutes. Product **101** was isolated in 77% (Scheme 53, Table, entry 7). Replacing pinacol allylboronate with potassium trifluoroborate was beneficial in regards of purification of the final compound, since pinacol fraction was found in some distilled fractions when using pinacol ester. Utilizing **102**, compound **101** was isolated in 80% yield (Scheme 53, Table, entry 8).



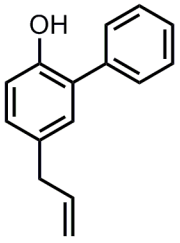
Entry	Pd source (mol%)	Borate	Additive (10 mol%)	Solvent	Base (eq.)	Temp. °C	Reaction time (min)	SM/SP/EP[2]	Yield (%)
1	PdEn40®	**99**	dppf	diox/H2O	TEA	150	30	0/43/57	n.d.
2	PdEn40®	**99**	dppf	diox/H2O	NaOAc	150	30	0/26/74	n.d.
3	PdEn40®	**99**	dppf	diox/H2O	Na_2CO_3	150	30	0/18/82	n.d.
4	PdEn40®	**99**	dppf	diox/H2O	NaOH	150	30	0/12/88	n.d.
5	PdEn40®	**99**	dppf	diox/H2O	NaOH	150	10	0/trace/100	n.d.
6	PdEn40®	**99**	dppf	diox/H2O	K_2CO_3	150	30	0/trace/100	65
7	PdEn40®	**99**	dppf	diox/H2O	K_2CO_3	150	7	0/0/100	77
8	PdEn40®	**102**	dppf	diox/H2O	K_2CO_3	150	7	0/0/100	80

Scheme 53

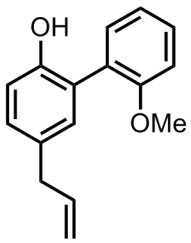
After this round of optimization of conditions, introduction of the ally group was under control. Next, the attention was focused on the Suzuki coupling in 2-position of 4-allyl-2-chloroanisol **101** with various arylboronic acids. Phenylboronic acid was chosen as a model substrate for the optimization of the reaction conditions, again. At first, the same reaction conditions as used in the allylation step were applied. Based on GC/MS analysis with dodecane as an internal standard, reaction proceeded with 35% conversion. Applying the modified condition of Denton (Pd_2dba_3, SPhos, KF, dioxane/water, MW, 150°C, 30 minutes) proved to be beneficial. GC/MS calculated conversion was 93%, however, the purification

turned out to be problematic. The compound was purified by means of column chromatography, using silica gel as a stationary phase. Still, after the chromatography, product was contaminated with aromatic impurity to a certain extent. Identification and the exact quantification was rather difficult due to overlap of peaks of the product with impurity in the aromatic region according to ^{1}H NMR spectra. It was however assumed that the aromatic signals belong to dibenzylidenacetone. Problem could be overcome by employing silver nitrate doped silicagel. It is known that olefins can coordinate to silver ions at the stationary phase, therefore an effect on the retention is observed.[79] Applying the silica gel and $AgNO_3$/doped silica in parallel fashion (practically, the column is filled in half with $AgNO_3$/doped silica and filled up with pure silica) led to elimination of the impurity content in the final product. Finally, the product could be isolated in 58%.

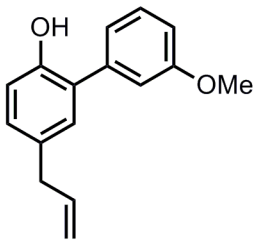
After the reaction was optimized, a first generation library of new derivatives was synthesized employing various boronic acids. As discussed in the introduction part, boronic acids were bearing various substituents with different chemical and electronic properties in order to investigate structure-activity relationship in all targeted proteins. Firstly, functional groups representing electron donating moieties was methoxy group. 4-Allyl-2-(2'-methoxylphenyl)phenol **95b** was obtained in 54% yield, 4-Allyl-2-(3'-methoxylphenyl)phenol **95c** in 48% and 4-Allyl-2-(4'-methoxylphenyl)phenol **95d** in 34%. From electron withdrawing groups, nitro and methoxycarbonyl groups were chosen. Ortho-, meta- and para nitro derivatives (**95e, 95f** and **95g,** resp.) were obtained in yields42, 86 and 60%, respectively. Problems were again encountered in the coupling with ortho-methoxycarbonylphenylboronic acid. In this case, spontaneous lactonization was observed as well as in the case of the coupling with 4-allyl-2-bromophenol **93**. Corresponding lactone **95h** was obtained in 31%. Coupling of **101** with metamethoxacarbonylphenylboronic acid **94i** provided 34% of desired product **95i** and para derivative **95j** was isolated in 36%.Finally, ortho-, meta- and paramethylboronic acids were coupled with intermediate **101**. The desired products **95k, 95l** and **95m** were obtained in 34, 39 and 46% yield, respectively.



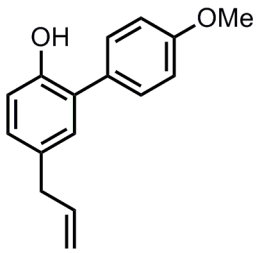
95a, 58%



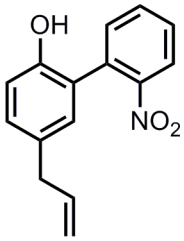
95b, 54%



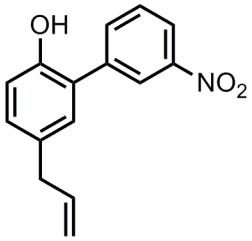
95c, 48%



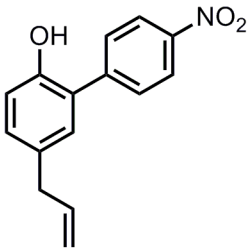
95d, 34%



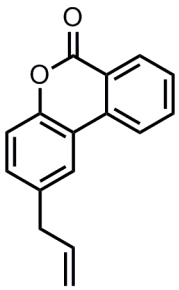
95e, 42%



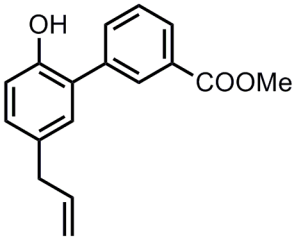
95f, 86%



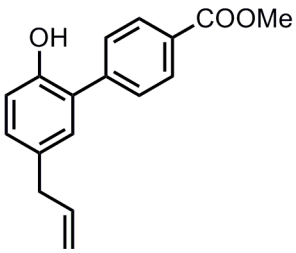
95g, 60%



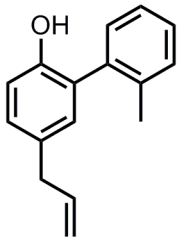
95h, 31%



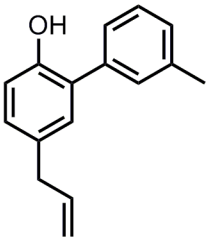
95i, 34%



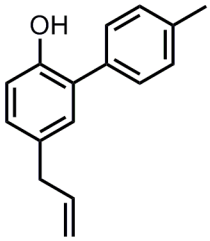
95j, 36%



95k, 34%



95l, 39%



95m, 48%

Scheme 54

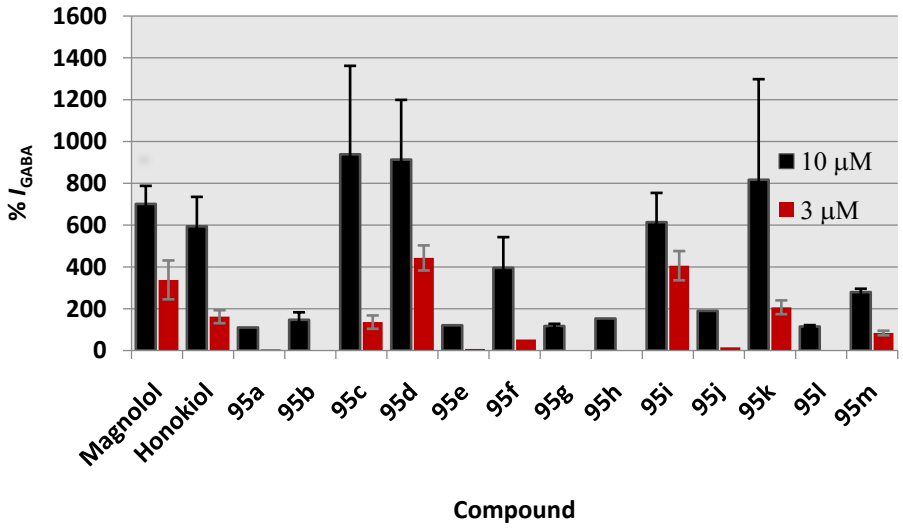
C IIEvaluation of the compound on $GABA_A$ receptors

C II.1 Two point pharmacology of new derivatives and SAR

Synthesized compounds were evaluated by means of two-electrode voltage clamp electrophysiology for their ability to modulate activity of $\alpha1\beta2\gamma2$ $GABA_A$ receptors from rat. Receptors of interest were recombinantely expressed in *Xenopus leavis* oocytes. Initial screens were carried out at GABA concentration triggering 3% of maximum GABA induced current. However later, measurements were carried out at the low GABA concentration capable of triggering 0.5% of the maximum GABA induced current (=GABA $EC_{0.5}$). Holding potential of the cell membrane was kept at -80 mV and investigated compounds were applied at two concentrations, 3 and 10 μM. All derivatives were found to be completely inactive in the absence of GABA, meaning they act as modulators only, not as agonists. Measurement of inactive compounds was carried out with two repetitions and data for active compounds was obtained from 5 oocytes from at least 4 different oocyte batches.

Several compounds were found to be inactive, however few were found to possess higher efficacy compared to the natural product leads, Magnolol and Honokiol. All the results are displayed in the Graph 1. Magnolol itself is capable of enhancing the GABA induced current (I_{GABA}) by factor of 338±93% at 3 μM and 702±86% at 10 μM. Efficacy of Honokiol is slightly lower, at 3 μM I_{GABA} equals 162 ± 31% and at 10 μM 594 ± 141%.The simplest derivative **95a**, having the ring B unsubstituted did not display any enhancement of the I_{GABA} at 3 μM and negligible 110 % at 10 μM. Methyl substitution in the ortho position of the ring B turned out to have a positive effect on efficacy. Compound **95k** (o-methyl substitution) enhanced I_{GABA} by 207 ± 33% at 3 μM and 817±481% at 10 μM. Other two methyl derivatives, bearing the substituents in the positions meta or para of the aromatic ring B, did not show any or only little activity. Compound **95l** did not enhance at all at 3 μM and by factor of 115 ± 7% at 10 μM. Compound **95m** showed enhancement of I_{GABA} by 280 ± 16% at 10 μM and 84 ± 11% at 3 μM. Methoxy group in the position ortho of the ring B did not have a significant effect on the modulation of I_{GABA}. At 10 μM current is enhanced by 147 ± 36% and at 3 μM compound **95b** is inactive. On the other hand, methoxy substitution in positions meta- and para- is beneficial: compound **95c** increases I_{GABA} by 939 ± 423%, however, activity drops when compound is applied at 3 μM to only 136 ± 32%, being lower than efficacy of Honokiol at the same concentration. The overall best efficacy of all the investigated compounds was measured for compound **95d** (p-methoxy): At 10 μM I_{GABA} is enhanced by 913 ± 286% and 3 μM by 443 ± 60%. Methoxycarbonyl substitution turned out

to be beneficial only if substituent is located in meta position of the aromatic ring B (compound **95i**). In such a case, enhancement of I_{GABA} is 614 ± 140% at 10 μM and 406 ± 70% at 3 μM. In two other cases, efficacies are rather negligible or compounds are completely inactive (for compound **95h** 153% at 10 μM and at 3 μM **95h** is completely inactive and for **95j** 190% at 10 μM and no activity at 3 μM). Derivatives bearing nitro substituents did not show any significant effect.**95e** enhanced I_{GABA} by 121% at 10 μM with no effect at 3 μM, **95f** enhanced I_{GABA} by 396 ± 147% at 10 μM but only 53% at 3 μM.**95g** at 10 μM increased I_{GABA} by 118 ± 10% and lost all the activity at 3 μM.

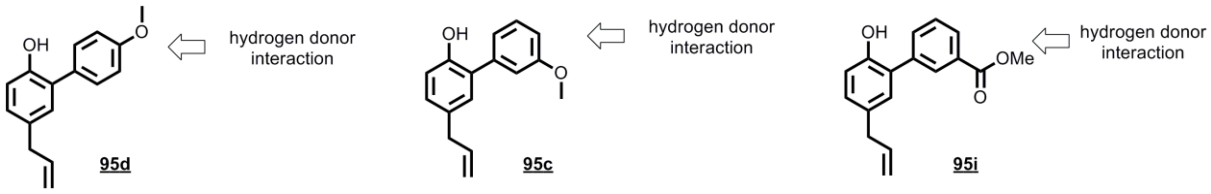


Graph 1

Derivatives **95c** and **95d**, both bearing electron donating methoxy substituents enhanced GABA induced current as well as compound **95i**, bearing electron withdrawing methoxycarbonyl group in position 2. Such observation indicates that electronic effect of the substituents did not reflected a significant influence on the modulatory properties of the molecules. Nevertheless, neither compound **95j**, bearing methoxycarbonyl group in strongly deactivating para position, nor derivatives decorated with strongly electron pulling nitro group (**95k** and **95m**) did show any significant effect. Moreover, methyl group in the ortho position weakly enhanced GABA induced current, suggesting that electron rich structure is slightly preferred. However, final conclusion about the electronic influence cannot be definitely drawn.

Since any conclusions regarding steric hindrance cannot be drawn either, possible explanation can be seen in the ability of methoxy and methoxycarbonyl group in positions meta or para to act as hydrogen donor acceptor. Bounding into the receptor pocket could be

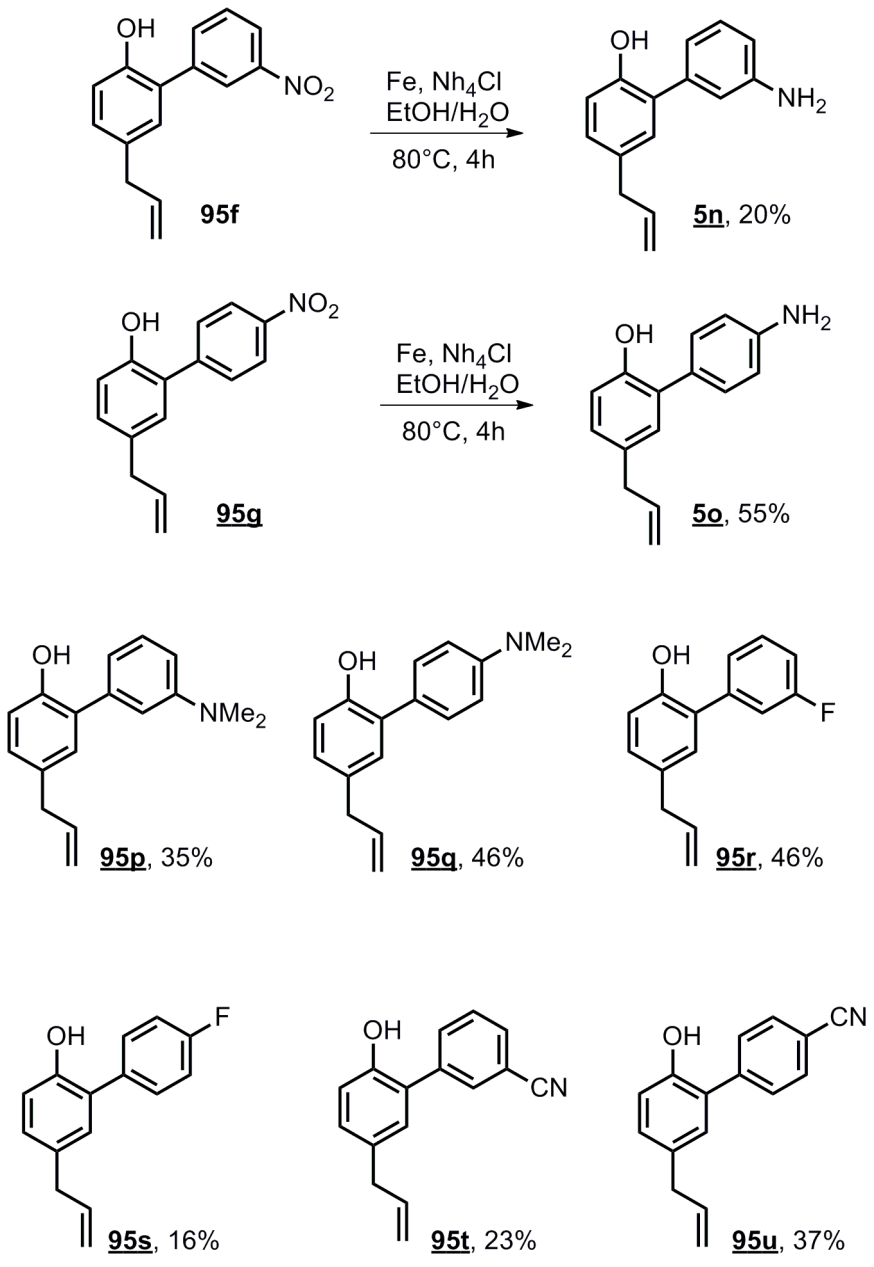
then mediated by the amino acid, bearing functionality with complementary property (Scheme 55).



Scheme 55

C II.2 Second generation of the library and subtype selectivity

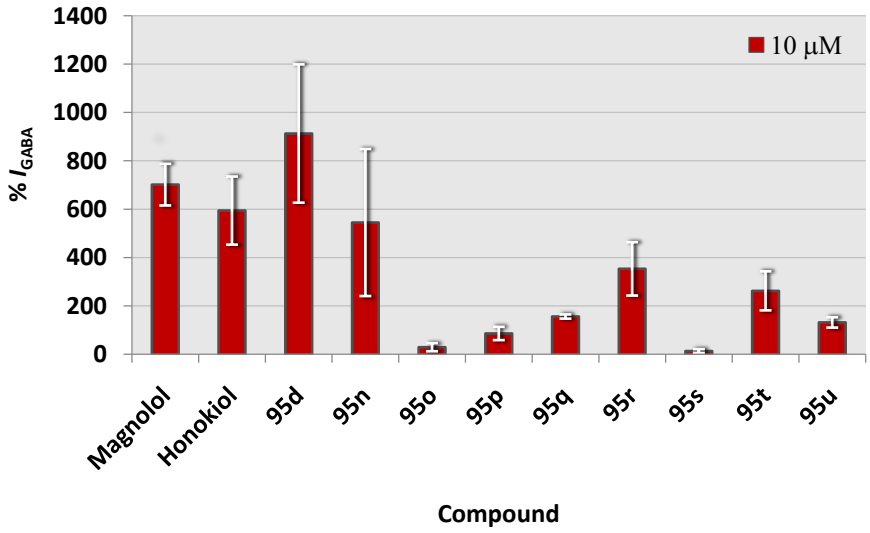
To evaluate the hypothesis and gain more insight into the structure and activity relationship, a second generation of the library was designed, comprising of derivatives having a functional group capable of accepting a hydrogen bond in positions meta and para. Moreover, substituents with both electron withdrawing and electron donating substituents were chosen in order to gain more information about the electronic effects and its influence upon the investigated biological action. From the electron withdrawing substituents fluoro and cyano derivatives were chosen; for electron donating moieties, amino and dimethylamino groups were synthesized and evaluated.



Scheme 56

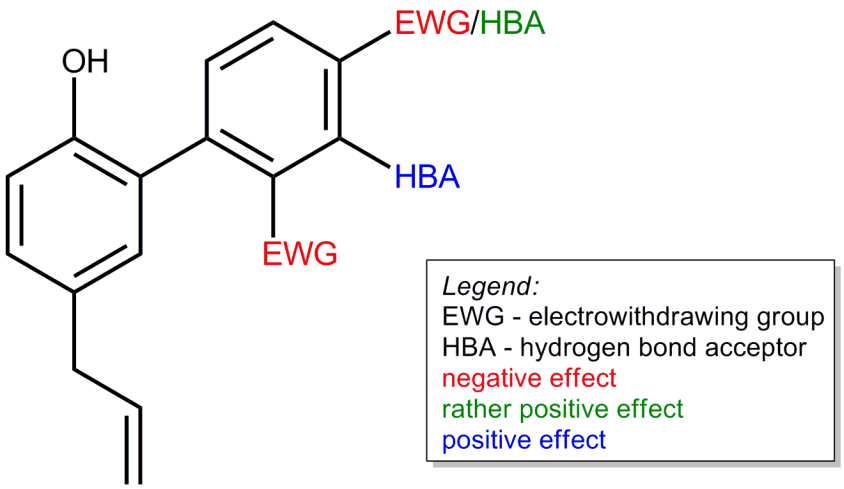
Amino derivatives were synthesized from corresponding nitro derivatives by reduction with iron (Scheme 56). Rest of the derivatives was synthesized *via* above described cross coupling.

Surprisingly, none of the compounds from the second generation of the library displayed an effect higher than the lead structures or the most effective hit from the first generation. However, the trend seemed to go along the outlined hypothesis. Compounds **95s** and **95u** bearing strongly withdrawing fluoro or cyano group in the deactivating para position did not show any or only negligible effect. Cyano substituent in meta position (**95t**) did not display any significant effect either, nevertheless, especially compound **95r** with meta fluoro substitution enhanced I_{GABA} by 353 ± 110%. Compounds bearing dimethyl amino in both positions (**95p**, **95q**) did not show any effect. Possible explanation can lie in the increased steric hindrance, however, such explanation is only speculative. Amino group in position para (**95o**) was also inactive. However, relatively strong effect was observer for compound **95n**, with amino group the position meta, which would again be in line with the above hypothesis.



Graph 2

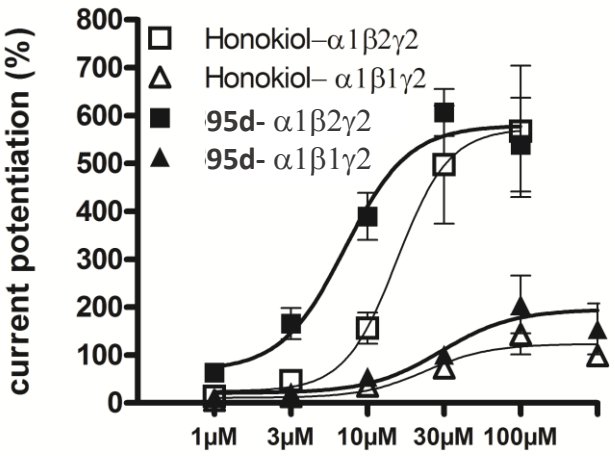
Results obtained from the second generation of the library confirmed a role of the electronic effect. Electron withdrawing substituents, particularly when located in deactivating positions, are not beneficial for the modulatory effect of the ligands. Compounds bearing a group capable to act as hydrogen bond acceptor are beneficial in the meta position.



Scheme 57

To investigate selectivity, the concentration dependent effect of **95d**, the best performing compound at 3μM (443±60% stimulation), was characterized in α1β2γ2 and α1β1γ2 receptors at a higher GABA concentration (at GABA EC_{10-20}) for a better comparison with published literature (EC_{10-20})[25], and compared with Honokiol. In α1β2γ2 the EC_{50} value was at approximately 7μM, (20μM for Honokiol) and the efficacy at 100μM was $539_{\pm 98}$%. The EC_{50} in the β1 containing subtype is 30μM (20μM for Honokiol), the efficacy only 206±60%. The effect of **95d** in a mutant α1β2N265Sγ2 receptor was investigated at $EC_{0.5}$ (Graph 3). This mutation in the β2 subunit is known to reduce the efficacy of several compounds including loreclezole and etomidate. With **95d** we observed a pronounced drop in response, confirming the key role of β2N265 for the beta subtype selectivity. The stimulation in the wild type receptor at the same compound concentration is 2462%for comparison.

Compounds not acting on β1 receptors are thought to be non-sedative - a desired property for compounds used as anxiolytic or anticonvulsive medication.



Graph 3

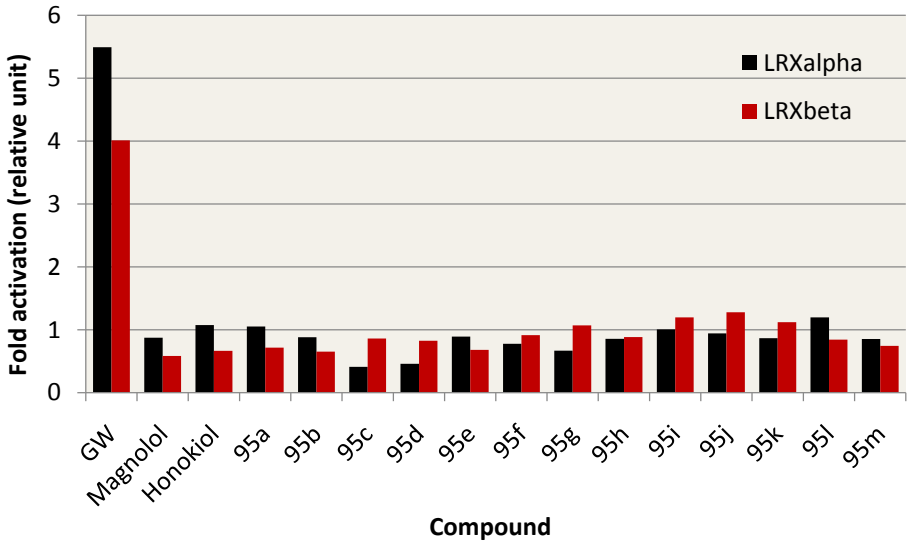
To conclude, several synthesized compounds were found to be positive modulators of $GABA_A\alpha1\beta2\gamma2$ receptor. A preliminary structure activity relationship was discussed based on the currently available limited data set. To a certain extent a hypothesis can be envisioned that groups with hydrogen bond acceptor properties particularly in the meta positions are beneficial. In addition, negative influence of electron withdrawing substitution was observed, in particular if located in deactivating position of the aromatic ring.

C III Evaluation of the derivatives as potential anti-inflammatory agents

C III.1 Activity at nuclear transcription factors

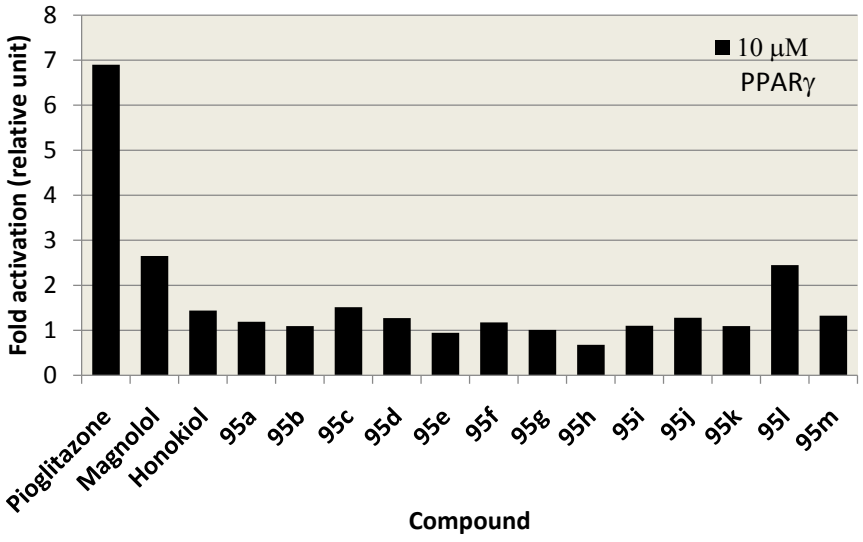
Derivatives of the first generation library were also evaluated for their ability to activate PPARγ receptor, RXRα, LXRα and LXRβ receptors in luciferase reporter gene assay.

It was determined that all of the synthesized compounds did not show any significant agonistic effect at PPARγ receptor and similarly, effect of the compounds at LXRα or LXRβ receptors was negligible. On the other hand, several compounds were found to be agonists of RXRα receptor. Results of measurement on LXR receptors are depicted in the graph 4.



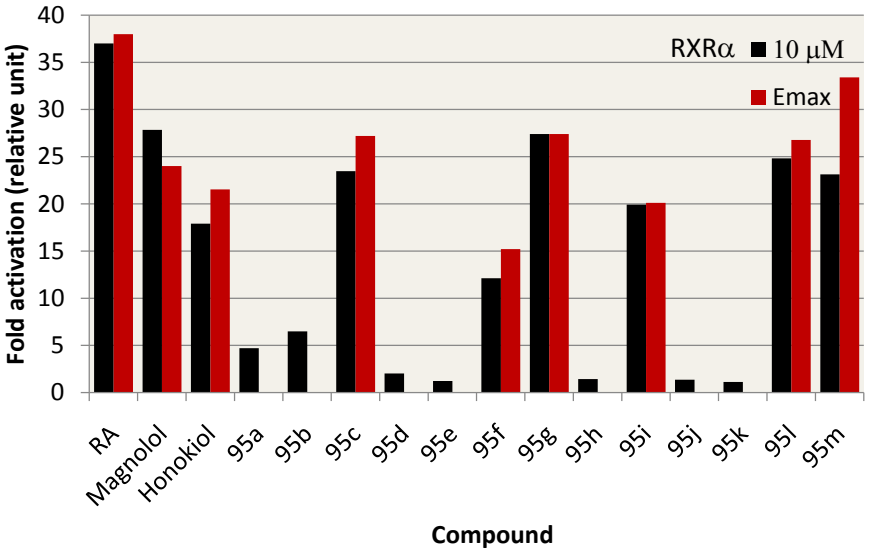
Graph 4

In the graph 5, results obtained for PPARγ receptors are summarized. Y axis represents the fold activation of the receptor with corresponding compound relative to the non-treated system, containing DMSO as vehicle. Magnolol itself is capable of enhancing the PPARγ activity 2.65times and Honokiol 1.44 times, which is below the detection limit of the assay. Efficacy of all the compounds was lower than efficacy of Magnolol. Only in one single case, compound **95l**, bearing methyl group in meta position of the aromatic ring B enhanced the performance of PPARγ by factor 2.45, which is close to the performance of Magnolol and higher then Honokiol. Therefore, compound **95l** is capable of activating PPARγ receptor, however, the efficacy is rather negligible.

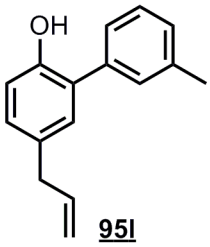


Graph 5

In contrast, several hits were identified for the RXRα receptor. Compounds were compared to positive control, retinoic acid (RA) and to both lead structures. Efficacy values at 10 μM and maximal efficacies are depicted in the graph below (Graph 6).Compared to lead structures, several compounds were found to have improved properties compared to Magnolol (28 fold activation at10 mM, E_{max} of 24[80], EC_{50} = 3.39) and Honokiol at 10 mM (18 fold activation an 10 mM, E_{max}21.5, EC_{50} = 1.07 μM). In particular, compounds having methyl or nitro substituents in meta and para position (**95l**, **95m**, **95f**, **95g**) or compounds **95i** and **95c** with meta methoxycarbonyl respectively methoxy groups in meta position also showed strong agonistic properties. Any compound with para substitution did not show any effect. At 10 μM compound **95l** with meta methyl group led to the 24.8 fold increase in receptor with maximal efficacy of 26.8 fold increase. Good efficacy values are supported with good potency of the compound with EC_{50} = 1.08 μM. At 10 μM, compound **95m** bearing para methyl substituent enhanced the activity of the receptor by factor of 23.1, little less than compound **95l**. However, maximal efficacy was 33.4 fold activation of the receptor, which was the highest obtained value. EC_{50} of the compound was 7.89 μM. Compound **95c**, bearing meta methoxy substitution activated RXRα receptor by factor 23.5 at 10 μM with maximal efficacy of 27.2 fold increased in activity and EC_{50} of 6.35 μM. Compound **95i** enhanced the activity of the receptor 19.9 times at 10 μM and maximal efficacy of 20.1. EC_{50} of **95i** is 2.19 μM. Structure **95g** with para nitro substitution also shown good agonistic property. At 10 μM activity of RXR receptor increased 27.4 times, which was at the same time the maximal activation. This compound has EC_{50} of 4.21 μM. Last but not least, compound **95f** with meta nitro substitution did not show efficacies as high as above discussed derivatives (12.1 at 10 μM and 15.2 Emax), however the EC_{50} lies in the high nanomolar range (EC_{50} = 410 nM). Compound **95f** can be therefore characterized as a potent partial agonist of RXRα receptor.

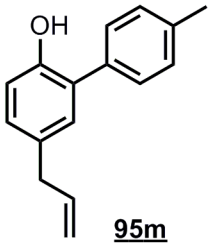


Graph 6



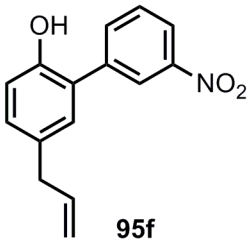
95l

E (10 μM) = 24.8
E (max) = 26.8
EC_{50} = 1.08 μM



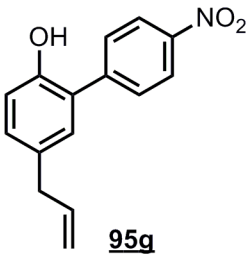
95m

E (10 μM) = 23.1
E (max) = 33.4
EC_{50} = 7.89 μM



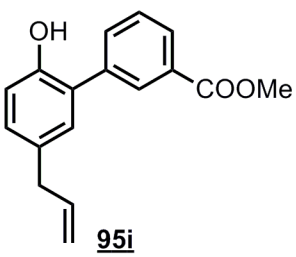
95f

E (10 μM) = 12.1
E (max) = 15.2
EC_{50} = 0.41 μM



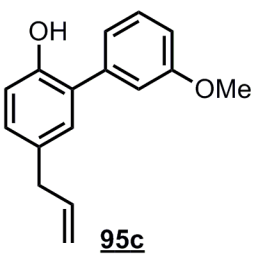
95g

E (10 μM) = 27.4
E (max) = 27.4
EC_{50} = 4.21 μM



95i

E (10 μM) = 19.9
E (max) = 20.1
EC_{50} = 2.19 μM



95c

E (10 μM) = 23.4
E (max) = 27.2
EC_{50} = 6.35 μM

Scheme 58

In conclusion to the activity of the compounds on the nuclear transcription factor, involved in the regulation of inflammation, several compounds were found to be selectively

able to modify the activity of RXRα receptors. Such action profile significantly differs from the profile of lead compounds Magnolol and Honokiol which were found to be dual PPARγ and RXRα agonists. All of the discovered compounds can be described as partial agonists of RXRα receptor.

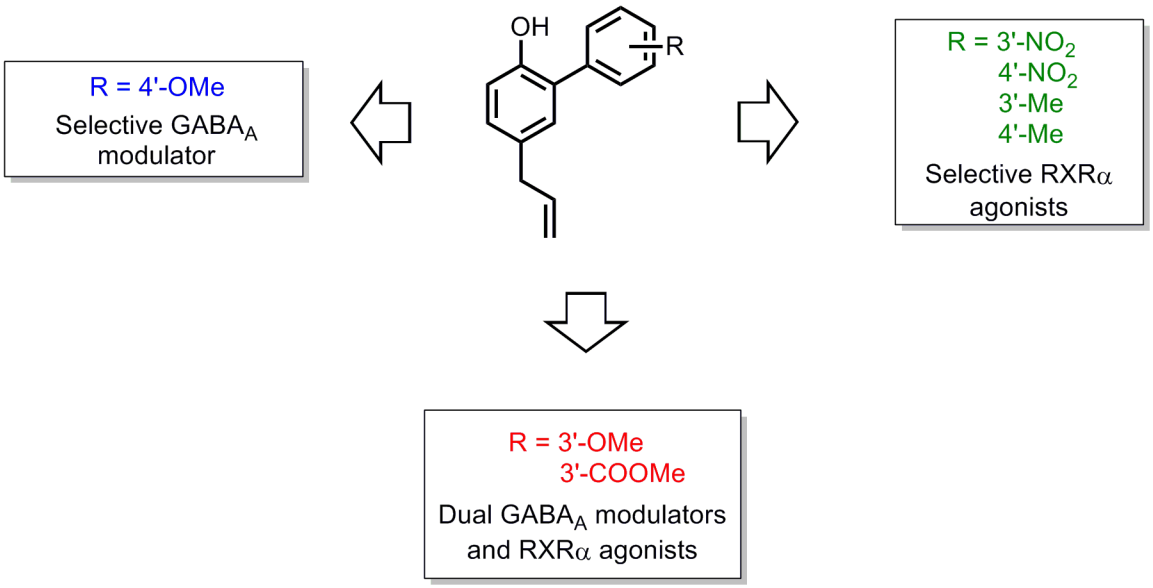
C IV Selectivity profiles of the new derivatives

None of the investigated compounds were active at PPARγ or LXR receptors. Therefore, only $GABA_A$ and RXRα receptors will be considered within the further classification of ligands.

Several compounds were active on both $GABA_A$ and RXRα receptors (**95c** and **95i**).

It was found, that substitution of the aromatic B ring plays a crucial role in the selectivity of the new derivatives towards different targets. Compound **95d**, having methoxy group in the para position of the aromatic ring B was found to be a selective $GABA_A$ modulator, while there was no effect observed at RXRα receptor. Moreover, compound **95d** showed a subtype selectivity towards the α1β2γ2 receptor subtype, over the α1β1γ2. Compounds not acting on β1 containing subtypes are thought to be non-sedative, which is a desired property for anxiolitic or antiepileptic drug candidate.

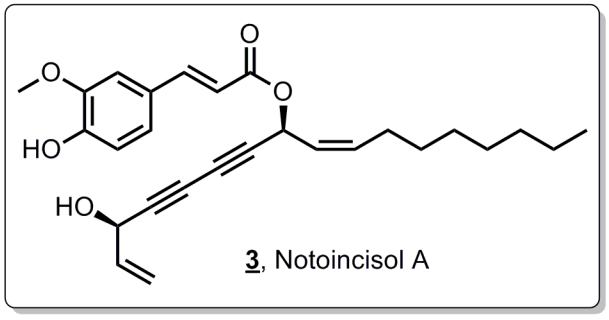
On the other hand, compounds **95f** and **95g**, bearing nitro groups in the meta respectively para position of the aromatic ring B, as well as compounds **95l** and **95m** with meta and para methyl decoration, turned out to be inactive at the $GABA_A$ receptor, while it was found to be selective RXRα agonist.



Scheme 59

D Synthesis of Notoincisol A and its stereoisomers for biological evaluation

This chapter describes the first total synthesis of the recently discovered natural product, Notoincisol A (Scheme 60). Notoincisol A contains two stereogenic centers, thus, four possible stereoisomers can be formed. Herein, chemically controlled synthesis of all possible stereoisomers is described and the isolated natural product is then compared by means of optical rotation. Stereochemistry of the natural product was confirmed. At the time of writing of this thesis, Notoincisol A and all the stereoisomers were investigated for their effect at $GABA_A$ receptors and PPARγ.

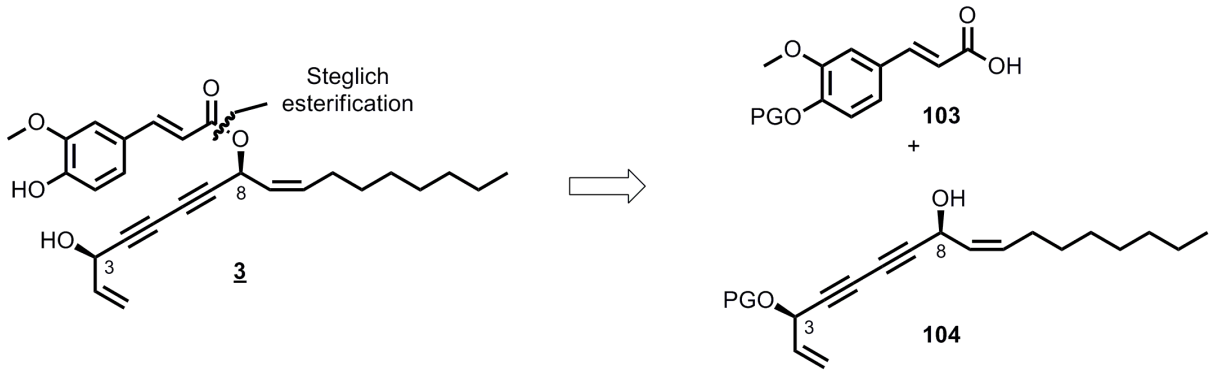


3, Notoincisol A

Scheme 60

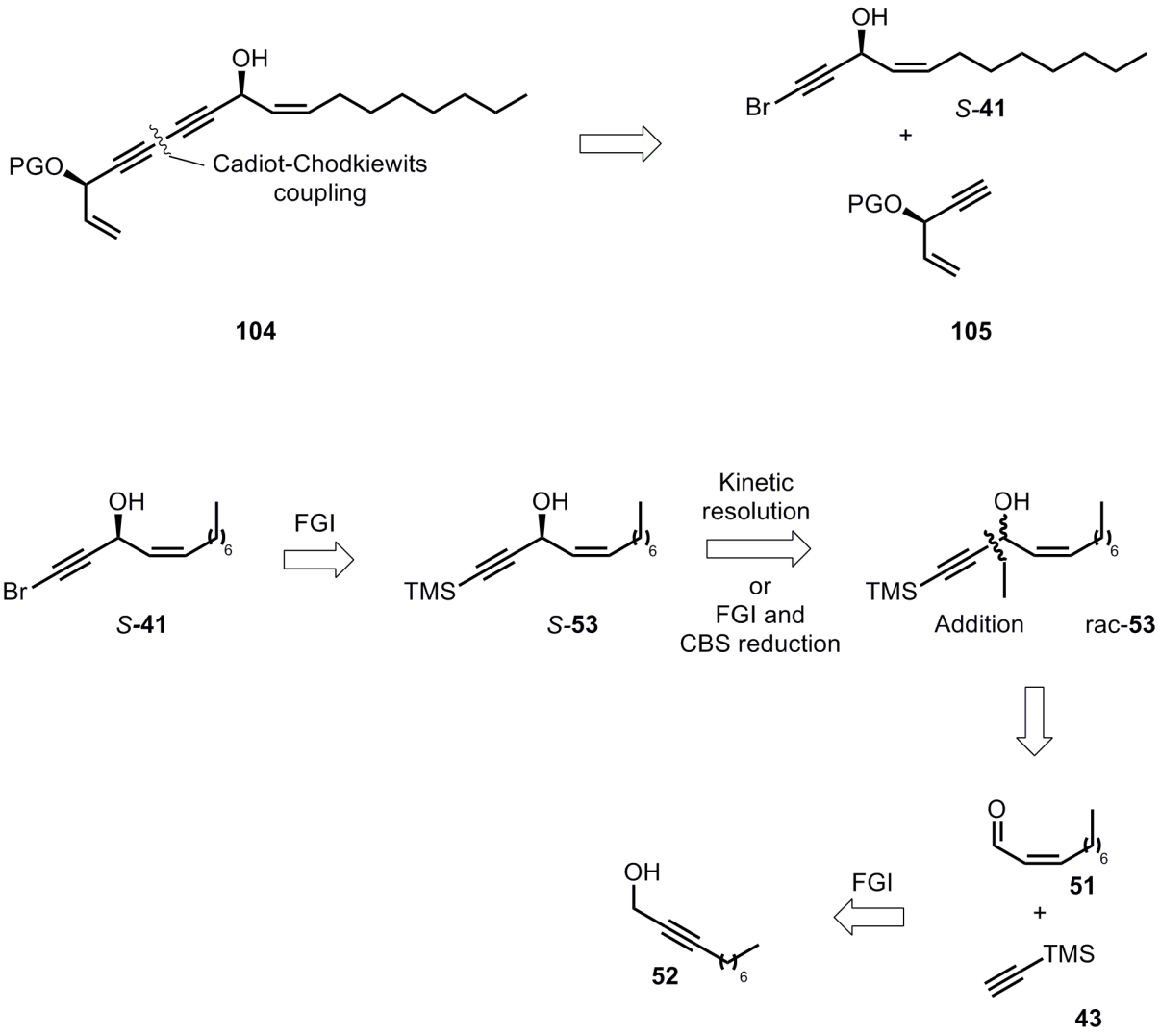
D I Retrosynthetic analysis of Notoincisol A

Notoincisol A is a structurally related compound to Falcarindiol. Difference between these two compounds lies at the hydroxyl group at the carbon number eight. While Falcarindiol possesses the hydroxyl group in the free form, Notoincisol A is esterified at this position with *trans*-ferulic acid. Consequently, first retrosynthetic cut would be the cleavage of the ester bond, leaving behind the Falcarindiol motif and commercially available *trans*-ferulic acid (Scheme 61). Naturally, protection of the phenolic OH group of ferulic acid **103** and the hydroxyl group in the position three of the aliphatic carbon backbone is required in order to avoid the esterification of these hydroxyl groups.



Scheme 61

Retrosynthetic analysis of the aliphatic backbone reveals that a next cut would be a disconnection of two triple bonds, leading to two distinct alkynes (Scheme 62). There is a method available for a cross coupling of acetylenes, taking advantage of a copper catalyst. Reaction between free alkyne and a bromoacetylene was described by Cadiot and Chodkiewits subsequently becoming a name-reaction recognizing the contributions by these two scientists. In the particular case, one can either brominate (*R*)-pent-1-en-4-yn-3-ol **105** or (*S,Z*)-dodec-4-en-1-yn-3-ol *S*-**41**. There is a literature precedent for both cases. It was chosen to proceed with the latter and use brominated alkyne *S*-**41**.



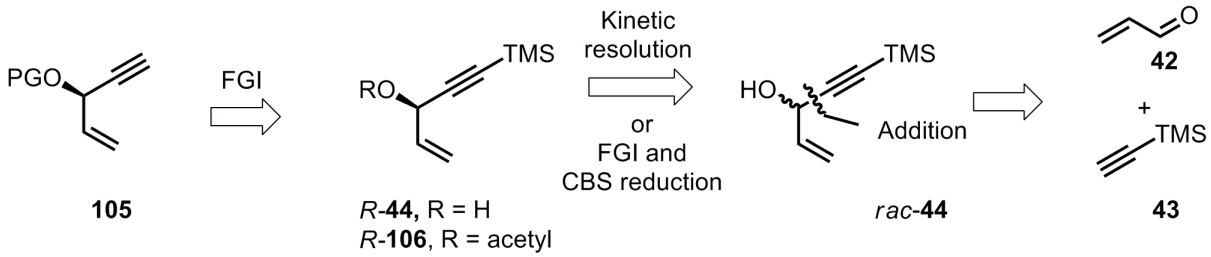
Scheme 62

Further retrosynthetic analysis of the long chained alkyne *S*-**41** reveals functional group interconversion. Bromine is introduced into the alkyne moiety in two retrospective steps, debromination and TMS introduction. Such approach leads to the enantiomerically pure intermediate *S*-**53**. The correct stereochemistry can be achieved *via* several methods[3-7]. Stereoselective CBS reduction of the corresponding ketone, utilizing the right catalyst is one option previously described in the literature within the synthesis of Falcarindiol. Additionally, lipase mediated kinetic resolution is another possibility. Both methods lead to the same key intermediate *rac*-**53**. Recently, enantioselective addition of acetylene to aldehydes was described as well. However, this metal catalysed method requires synthesis of a non-commercially available ligand.[7]

Racemic alcohol *rac*-**53** can be obtained *via* addition of trimethylsilylacetylene to the corresponding α,β-unsaturated aldehyde **51**, as deprotonated alkyne is a rather hard nucleophile, preferring 2-addition over Michael addition. (*Z*)-Dec-2-enal **51** can be derived

from commercially available dec-2-ynol **52** *via* oxidation of primary alcohol to aldehyde and stereoselective hydrogenation of the triple bond to *Z*-alkene.

Retrosynthesis of the short alkyne **105** is depicted in scheme 63. It is based on the same reaction steps as the previously described synthesis of intermediate *S*-**53**. Functional group interconversion, namely hydroxyl protection and hydrolysis, leads to synthon *R*-**41** or *R*-**106**. Stereochemistry is introduced as in the previous step either *via* enzymatic kinetic resolution or oxidation/CBS reduction of synthon *rac*-**44**. This synthon can be obtained *via* nucleophilic addition of TMS-acetylene to acrolein, following the same rules as discussed above: addition of the hard nucleophile to hard electrophilic carbonyl position of acrolein.

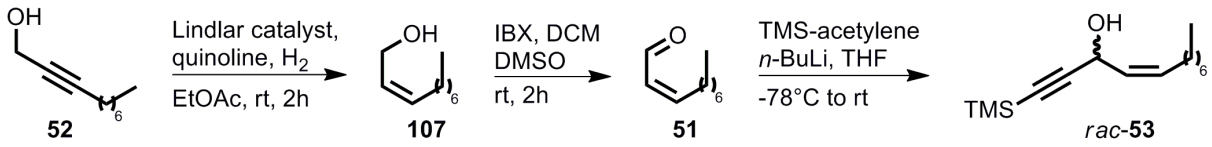


Scheme 63

Retrosynthetic analysis of all other stereoisomers would differ only in the step, where chirality is introduced. Here, utilization of the lipase mediated kinetic resolution seems to be beneficial, since in such an approach, both possible enantiomers of both building blocks **44** and **53** can be delivered in one single operation.

D II Synthesis of racemic alcohol *rac*-53

Synthesis of *rac*-**53** was reported in the work of Tamura[3] and Schmiech. It was based on Lindlar reduction of alkyne **52**, subsequent IBX oxidation of the resulting Z-alkyne to α,β-unsaturated aldehyde **51** and addition of TMS-acetylene to the carbonyl (Scheme 64). However, several problems were encountered. On one hand, Lindlar reduction turned out to be highly unreliable. In spite of the initial success, over-reduction to alkane was observed while attempts to reproduce the reaction were conducted. This could be judged from the absence of olefinic signals in crude ^{1}H-NMR spectra of the reaction mixture (Scheme 64, Table, entry 1-2). Several measures were undertaken in order to avoid undesired over-reduction. Initially, a GC/MS method was developed for a quick analysis of the reaction mixture prior to work-up. Peaks of starting material, desired product and side product were identified. With the given method, retention time of the side product was 4.17 minutes, desired product eluted at 4.77 minutes and starting material at 5.12 minutes. There was a complication related to the GC/MS analysis. Ionizability of the starting material and the desired product turned out to be much higher than the ionizability of the over-reduced side product. Thus, appearance of any minor peak of side product could indicate a major presence of the undesired alkane. In such case, ^{1}H-NMR analysis was carried out in order to confirm and quantify the components in the reaction mixture based on molar composition.

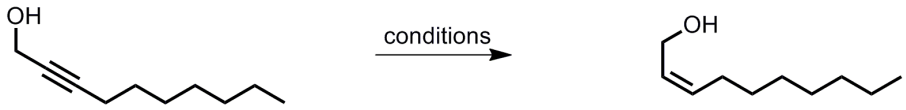


Scheme 64

First, the reaction was carried out with a fresh batch of catalyst, however without success. The distribution between the product and side product was approximately 1:1 entry 3). Even though, the solvent used for the reaction was distilled prior to the reaction, it was hypothesized that insufficient drying and presence of water can lead to the washing out of the inorganic components of the Lindlar catalyst and thus its poisoning, which could be the cause of the unwanted reaction. Control experiment with wet solvent led to the formation of the alkane, supporting the hypothesis (entry 4). However, extended drying of ethyl acetate (one hour of refluxing over phosphorus pentoxide) did not lead to any improvement (entry 5). Presence of the peak at 4.16 in the GC/MS spectra (even though with relatively smaller intensity compared to the desired product) revealed the formation of alkane. ^{1}H-NMR showed that the over-reduced product is the main component of the reaction mixture and desired product was present only in small amount (1:4 in favor of side product). Next,

quinoline was added to the reaction mixture, based on the know effect of this additive to suppress overreduction. After two hours, GC/MS analysis revealed conversion towards the desired product, but the consumption of the starting material was far from complete (entry 6). After another hour, a small peak of the side product appeared in the GC/MS spectrum in addition to peaks of starting material and desired product (entry 7). The reaction mixture was then stirred overnight. Analysis of the mixture the next day revealed a full consumption of the substrate (GC/MS), but the presence of the alkane was confirmed by both GC/MS and ^{1}H-NMR analysis (entry8).

As the data suggested, the formation of the side product starts not immediately, but after some of the substrate is converted to the desired alkene. It was then investigated, whether the desired reaction could be either a) speeded up by using increased amounts of the catalyst, b) formation of the side product slowed down with increased amount of quinoline or c) formation of the side product slowed down with decreased reaction temperature. In the first case, catalyst loading was doubled to 20 weight percent relative to the substrate (entry 9). In case b) the amount of quinoline was doubled (entry 10) and in case c) amount of reagents was kept the same and the reaction was carried out at 0°C (entry 11). Nevertheless, in all cases GC/MS analysis confirmed the formation of the undesired alkane, thus, further analysis was abandoned.



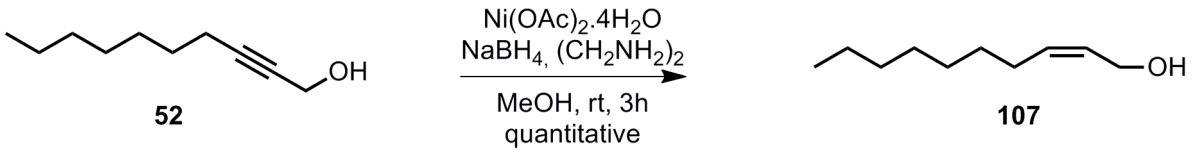
52 **107**

Entry	Catalyst (w%)	Additive (amount)[1]	Solvent	Temp.	Time (h)	Consumption	Overreduction	Ratio[4]
1	Lindlar (10)	-	EtOAc	rt	2	full	no	no
2	Lindlar (10)	-	EtOAc	rt	2	incomplete	yes	nd
3	Lindlar (10)[2]	-	EtOAc	rt	on	incomplete	yes	1:1.1
4	Lindlar (10)	-	EtOAc (wet)	rt	on	incomplete	yes	1:0.4
5	Lindlar (10)	-	EtOAc[3]	rt	on	incomplete	yes	4:1
6	Lindlar (10)	quinoline (1)	EtOAc	rt	2	incomplete	no	1:0[5]
7	Lindlar (10)	quinoline (1)	EtOAc	rt	3	incomplete	no	1:0[5]
9	Lindlar (10)	quinoline (1)	EtOAc	rt	12	full	yes	0.9:1
10	Lindlar (20)	quinoline (1)	EtOAc	rt	2	incomplete	yes[5]	nd
11	Lindlar (10)	quinoline (2)	EtOAc	rt	2	incomplete	yes[5]	nd
12	Lindlar (10)	quinoline (1)	EtOAc	0°C	2	incomplete	yes[5]	nd

[1] % of the volume of the solvent
[2] new catalyst batch
[3] extensively dried for 1 hour under reflux over P_2O_5
[4] product/sideproduct. Determined from ^{1}H NMR
[5] determined from GC/MS analysis of the reaction mixture

Scheme 65

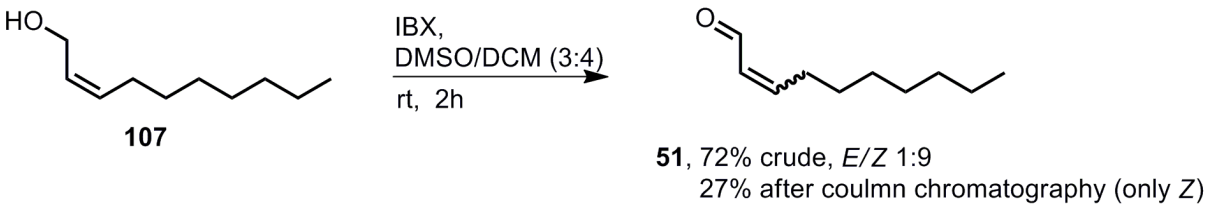
After the failed attempts with Lindlar catalyst, it was decided to switch to nickel P-2 reduction.[81, 82] It is known that nickel(II) salts can be reduced by borohydrides in alcoholic solvents; thee formed species is capable of *cis* hydrogenation of acetylenes in the same manner as the Lindlar catalyst. Treatment of dec-2-ynol with such a catalytic system in methanol in presence of 1,2-ethylendiamine indeed provided exclusively the desired product in quantitative fashion. GC/MS analysis revealed full consumption of the starting material and no signs of overeduction were found in the spectra. ^{1}H-NMR analysis of the crude mixture confirmed the formation of the desired dec-2-enol. Product was obtained after simple filtration through a pad of celite under reduced pressure and evaporation of the solvent. No further purification was necessary.



Scheme 66

Another problem was encountered with the oxidation of the *Z*-allylic alcohol to the α,β-unsaturated aldehyde. It was observed that partial isomerization of the double bond takes place and a certain amount of *E*-dec-2-enal was detected in the reaction mixture. Isomerization can be followed *via* TLC (after staining with PMA), as both isomers differ slightly in the R_f value (0.43 for *E* isomer versus 0.48 for the *Z*-isomer, using a mixture of petroleum ether/ethyl acetate 4:1). In ^{1}H-NMR spectra, the shift of the olefinic protons differs as well. Signals of *Z*-olefin appear at 5.93 ppm as a not very well resolved doublet of doublets (measurement carried out at 200 MHz) and at 6.61 ppm as doublet of triplets with coupling constant *J* = 11.2 Hz. Signals of the *E* isomer appear at 6.09 ppm as doublet of doublets and 6.83 ppm as doublet of triplets with the coupling constant *J* = 15.6 Hz. Besides TLC and NMR control, the mixture can be analyzed by GC/MS.

In spite of the fact that both compounds have very similar retention factors, it was possible to separate them *via* column chromatography, using hundred times excess of the silica and petroleum ether/ethyl acetate (97:3) mixture. However, pure compounds were obtained at the cost of yield. Rather limited stability of the aldehydes and huge excess of the silica gel caused major losses of the product and desired *Z*-isomer was isolated in 27%, while crude reaction mixture was obtained in 72% (mixture of the isomers.).

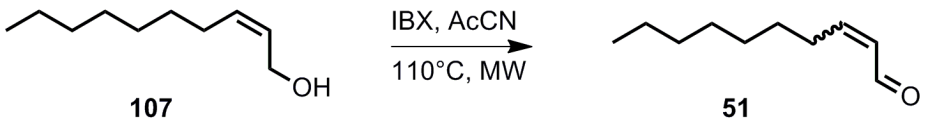


107

51, 72% crude, *E/Z* 1:9
27% after coulmn chromatography (only *Z*)

Scheme 67

It was therefore desirable to develop a method to avoid column chromatography. The DMSO/DCM solvent system was changed to acetonitrile, and the reaction was carried out in a microwave reactor (110 °C) as reported for similar oxidation by More.[83] Reaction progress was monitored by TLC. Using 3 equivalents of IBX, the reaction was not completed after 30 minutes (Scheme 68, Table entry 1) and the same outcome was observed after 60 and 90 minutes (entries 2 and 3). Then, another equivalent of IBX was added and the mixture was heated for another 30 minutes. It was found that the starting material was fully consumed (entry 4). The reaction was then repeated directly with four equivalents of IBX for 120 minutes (entry 5). NMR analysis of the crude mixture revealed, that both isomers were present in the reaction mixture in the ratio 1:3.9 in favor of undesired *E*-isomer. Moreover, signs of decomposition were observed in the crude spectra. Several additional unidentified olefinic signals appeared and intensity of the aliphatic signals was disproportionally higher compared to the olephinic signals of both *E* and *Z*-isomers (signals of isomers integrated together and compared to the unresolved aliphatic signal).



107 **51**

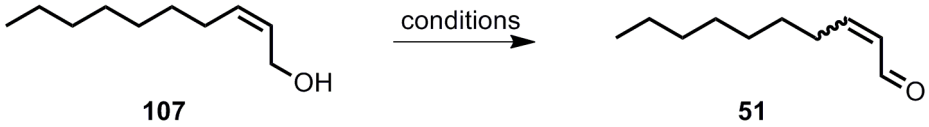
Entry	Time	IBX (eq.)	Consumption	*Z/E* ratio	Comment
1	30	3	incomplete	nd	-
2	60	3	incomplete	nd	-
3	90	3	incomplete	nd	-
4	120	4[1]	full	nd	-
5	120	4	full	1:3.9	decomposition

[1] one equivalent of IBX added after 90 minutes to the mixtrure containing 3 equivalents

Scheme 68

After above described failures, several different oxidation methods were investigated. Applying Swern oxidation conditions did not lead to any conversion as confirmed by GC/MS (Scheme 69, Table entry 1). Several attempts were made to use TEMPO and various co-oxidants. Initially, the reaction with TEMPO in the presence of iron(III) nitrate nonahydrate, sodium chloride and molecular oxygen in DCE was investigated (entry 2). However, such

conditions did not lead to any conversion even if reacted overnight, as confirmed by GC/MS. Changing reaction conditions to TEMPO/diacetoxyiodobenzoic acid (0.25/2.5 equivalents, respectively) in DCM led to partial conversion, unfortunately to the wrong isomer (entry3). Herein, two problems were to be overcome: completion of the conversion and changing the selectivity towards the desired isomer. The first issue could be solved with increasing the amount of oxidants to 0.3 and 3 equivalents. Nevertheless, exclusively *E* isomer was obtained (entry 4). Lowering the polarity of the solvent by using a mixture of DCM/pentane (1:9) led to the formation of a mixture of isomers (1:1), but conversion was incomplete (entry 5).



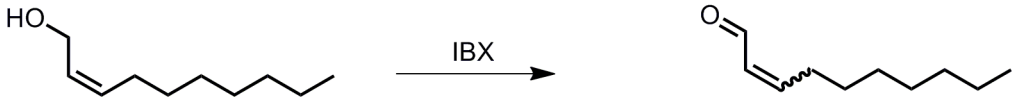
107 **51**

Entry	Oxidation system (eq.)	Solvent	Conversion	*Z/E* ratio
1	DMSO, $(COCl)_2$ Et_3N	DCM	no	-
2	TEMPO, NaCl, $Fe(NO_3)_3.9H_2O$, O_2	DCE	no	-
3	TEMPO (0.25) DIB (2.5)	DCM	partial	only *E*
4	TEMPO (3) DIB (0.3)	DCM	full	only *E*
5	TEMPO (3) DIB (0.3)	DCM/pentane 1:9	partial	1:1

Scheme 69

Analyzing the obtained results, it was realized that the most promising results were so far obtained with IBX as the oxidant. Therefore, it was decided to revisit the IBX protocol and investigate closely the role of the solvent and its polarity as it was noticed that reaction in pure DCM and DCM/pentane mixture run with significant difference (Scheme 70, Table entries 4 and 5). Such observation provided a hint that *Z*-selectivity might be dependent of the polarity of the solvent. However, decreasing the solvent polarity also limits the solubility of IBX. Looking into literature, it can be noticed that such an IBX oxidation is often carried out in polar solvents such as DMSO or acetonitrile. Performing the reaction in pure acetonitrile led to incomplete conversion and formation of both isomers in the ratio 1:1 (Scheme 70, Table entry 1). The reaction outcome did not change significantly when acetonitrile was used together with DCM either in ratio 1:1 or 1:3. In both cases remaining

starting material was detected in the reaction mixture together with both isomers in 1:1 ratio approximately (entries 2 and 3).



107 **51**

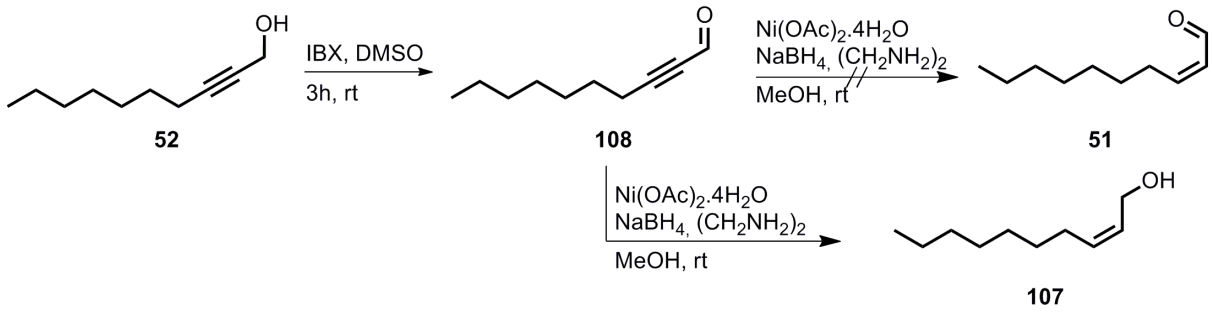
Entry	Ratio of solvents	Temp.(°C)	Time (h)	Conversion	*E/Z* ratio
1	AcCN/DCM 1:0	rt	15	incomplete	1:1
2	AcCN/DCM 1:1	rt	15	incomplete	1:1
3	AcCN/DCM 1:3	rt	15	incomplete	1:1
4	DMSO/DCM 3:4	rt	2	full	1:9
5	DMSO/DCM 3:4	0°C	12	traces	-
6	DMSO/DCM 3:4	-15°C	12	no	-
7	DMSO/DCM 1:3	rt	2	full	3:97
8	DMSO/DCM1:5	rt	2	traces	-
9	DMSO/DCM 1:4.7 to 1:3.5	rt	2	full	only *Z*

Scheme 70

The situation changed when a DMSO/DCM mixture was reinvestigated. Initial attempts were discussed before (page 95/96). It was then decided to try to carry out the reaction at lower temperature with a DMSO/DCM mixture in the ration 3:4. At 0°C conversion was very sluggish and only minor conversion was observed after overnight stirring. At-15°C, no conversion at all was detected *via* GC/MS. Such a loss of reactivity can be explained by rather poor solubility of IBX in organic solvents, herein pronounced with the low temperature. Subsequently, the role and ratio of the solvents was investigated in more details. The reaction was initially carried out in pure DCM (entry 3) and in pure DMSO (entry 4). In the first case, there was no conversion observed. Nevertheless, the reaction was completed in 2 hours in DMSO, however ratio of the isomers was4.4:1 in favor of desired Z-isomer (entry 5). This result was so far the second best obtained, after the initial attempt with the same reaction mixture in DMSO/DCM 3:4 giving a *Z/E* ratio of 9:1. It also clearly confirmed the importance of the polarity of the solvent. It was thus necessary to fine tune the ratio to ensure proper solubility/Z-selectivity. Using a 1:3 DMSO/DCM mixture led to the significant improvement. Complete conversion of starting material was observed in favor of the Z-olefin over the *E*-olefin in a ratio of 93:7 (entry 6). Further increasing the amount of DCM led to insignificant conversion, due to the solubility issues of IBX (entry 7). The reaction was then carried out in a DMSO/DCM mixture with a ratio of solvents of 1:4.7 (2.95 mL of DMSO and 13.78 mL of DCM) and was monitored by means of TLC. After two hours, there was a conversion but the reaction was not completed. The same was observed after 2.5 hours. It was decided to add additional 0.2 mL of DMSO (6.8% of initial DMSO amount). After

another thirty minutes, TLC analysis again showed incomplete conversion, however, no trace of unwanted *E*-alkene was visible. Another small amount of DMSO (0.1 mL) was added and the reaction mixture was stirred for half an hour and analyzed by TLC. Disappearance of the starting material was obvious but the reaction was still not finished. Again, exclusively Z-isomer was detected. Another addition of DMSO (0.05 mL) and stirring for next half an hour resulted in full consumption of the starting material and only desired product was detected after the staining of the TLC plate (entry 8). The reaction was then worked up. Unfortunately, after the work up, traces of the side product were again found suggesting that isomerisation takes place partially during the work up). The reaction was repeated in the same fashion with the difference that each time 6.8% of initial amount of DMSO was added. According to TLC, no side product was formed during the reaction. After the completion, the reaction mixture was cooled to 0°C and quenched with precooled sodium bicarbonate and all following operations (filtration, extraction) were carried out with precooled chemicals and glassware. Evaporation of the solvents was carried out at room temperature. This procedure ensured an exclusive formation of the desired product, which could be immediately used for the next step without any chromatographic purification. Crude mixture was obtained in quantitative amount and ^{1}H NMR revealed sufficient purity and solely product was detected in the crude material.

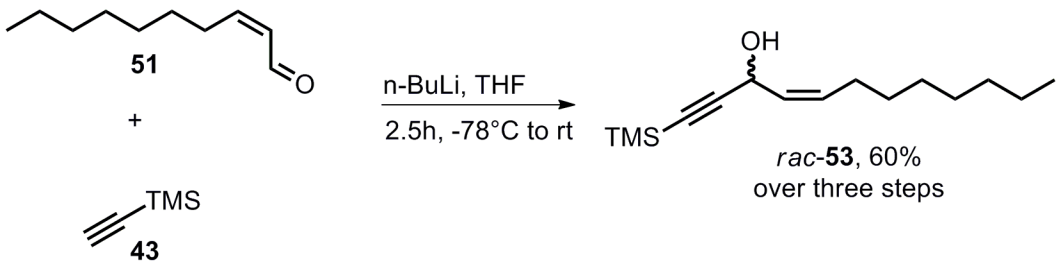
There was another strategy outlined in order to avoid the above discussed problem of isomerization of the double bond during the oxidation step. It was investigated, whether changing of events would be beneficial. In this case, dec-2-ynol would be oxidized first to the corresponding dec-2-ynal, where isomerization of the double bond is not possible due to its absence. In the consecutive step alkyne would be subjected to the reduction. Oxidation of dec-2-ynol was carried out with IBX in pure DMSO, yielding quantitatively the aldehyde. However, subjecting dec-2-ynal to the P2- nickel reduction led to overeducing the aldehyde back to the alcohol and decenol was obtained instead of the desired dec-2-enal (Scheme 71).



Scheme 71

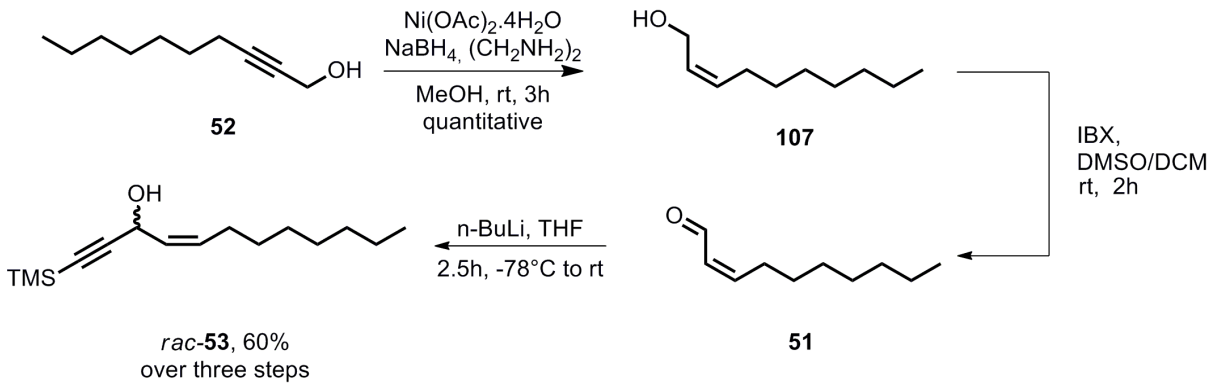
After the optimization of the oxidation was completed, the attention was focused on the addition of trimethylsilyl acetylene to the aldehyde. Rather hard nucleophilicity of the

acetilide anion formed after deprotonation with *n*-BuLi leads preferably to the attack of carbonyl carbon in contrast to the Michael addition at the remote beta position of the α,β-unsaturated system. Deprotonation was carried out at -78°C and after the addition of aldehyde **51**, which was added as a crude material from the previous step, the reaction mixture was allowed to heat to room temperature. The reaction was finished in two hours. After work up, the crude reaction mixture could be used for further transformation.



Scheme 72

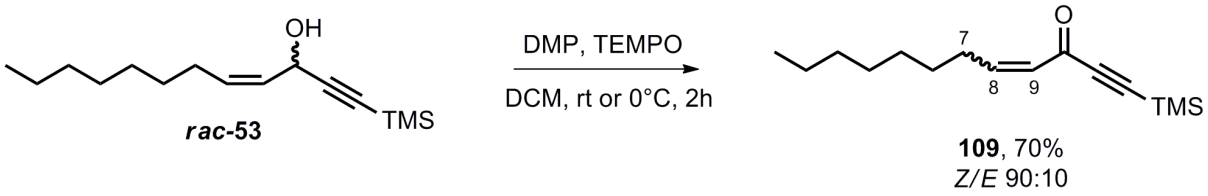
In summary, racemic key intermediate *rac*-**53** was prepared in overall 60% yield, after three steps. The entire synthesis is depicted in Scheme 73.



Scheme 73

D III Introduction of chirality at carbon 8

Within the synthesis of Falcarindiol reported by Schmiech[4] and Tamura[3], chirality at carbon 8 was introduced *via* reoxidation of the secondary alcohol *rac*-**53** and subsequent stereoselective reduction of the ketone to the chiral secondary alcohol; the desired stereochemistry was established using corresponding CBS catalyst. Such an approach has several disadvantages: (I) reoxidation of the racemic secondary alcohol leads to partial isomerization of the double bond. Oxidation utilizing DMP/TEMPO in DCM led to isomerization, as observed by TLC, where two spots were detected after running the TLC in petroleum ether/ethyl acetate mixture (95:5) and staining the plate with PMA stain (major spot with Rf value of 0.59 and minor spot with Rf value of 0.45). In addition, protons attached at carbon number 7 (Scheme 74) give two signals in ^{1}H NMR spectra (2.52 and 2.72 ppm). Integration of the area of both peaks reveals the ratio of *E/Z* to be 90:10. Due to overlap of the olefinic peaks, additional analysis is not possible. Isomerization of the *Z* olefin is also reported by Schmiech.[4] (II) to achieve the synthesis of both enantiomeric building blocks (and further, synthesis of all four stereoisomers of Notoincisol A) requires reoxidation to the ketone and separate reductions towards each enantiomer with both antipodes of the CBS catalyst. (III) the price of the oxazoborate is rather high and necessity of both optical isomers of the catalyst makes such an approach unattractive.



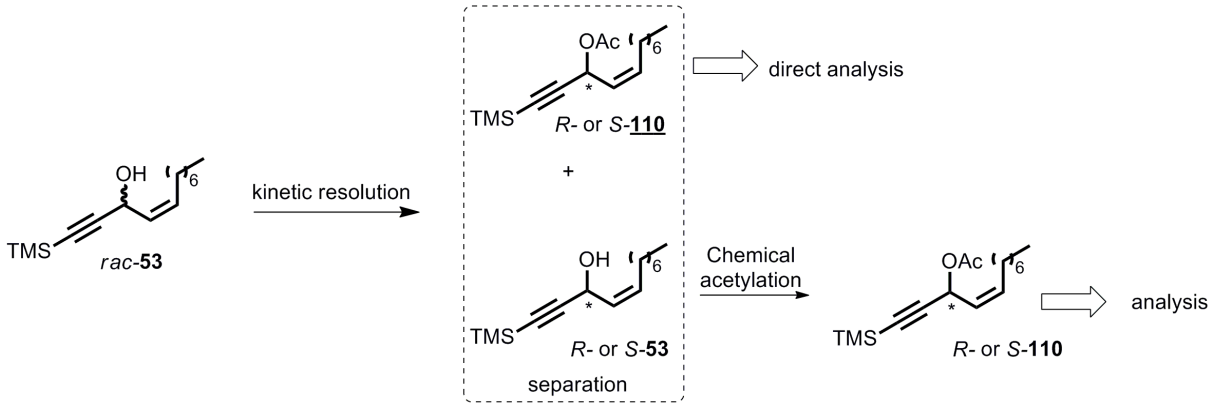
Scheme 74

The mixture of isomers can be subjected to column chromatography. However, even 100 times mass excess of silica and low polarity of the eluent (1% of ethyl acetate in petroleum ether) does not ensure complete separation of isomers. Most fractions contain a mixture of both isomers and only few contain pure desired *Z* isomer.

Alternatively, in theory, chiral centers could be generated by kinetic resolution, using lipase. In such a case, at least some of the above outlined disadvantages could be circumvented. Kinetic resolution would deliver both enantiomers in one single operation using a catalyst, which is cheaper compared to the CBS catalyst. However, there is no literature precedent for acetylation of alcohol *rac*-**53** using lipase, thus it was not clear whereas *rac*-**53** was a substrate acceptable by any lipase. Two lipases were tested, Lipase AY 30 and amano lipase PS. The reaction was controlled by means of TLC. A new, spot, with

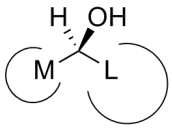
higher R_f value was detected for the reaction using amano lipase PS, suggesting acetylation of the alcohol *rac*-**53**. No conversion was observed using lipase AY 30.

Amano lipase PS was subjected to further investigations. Firstly, a method for determining the optical purity was developed. Attempts to resolve racemic alcohol *rac*-**53**by chiral HPLC failed. No peak separation was achieved despite the fact that several methods were tested on different chiral columns. Success was, nevertheless, achieved with acetylated racemic mixture. Two peaks were present in the chromatogram with the retention times of 10.00 and 11.02 minutes (see experimental part). The assay for determining the optical purity was therefor set as follows: the reaction was carried out at different conditions and then ester and alcohol were separated by column chromatography. A fraction of the remaining alcohol was acetylated and used as such for analysis (Scheme 75**)**.



Scheme 75

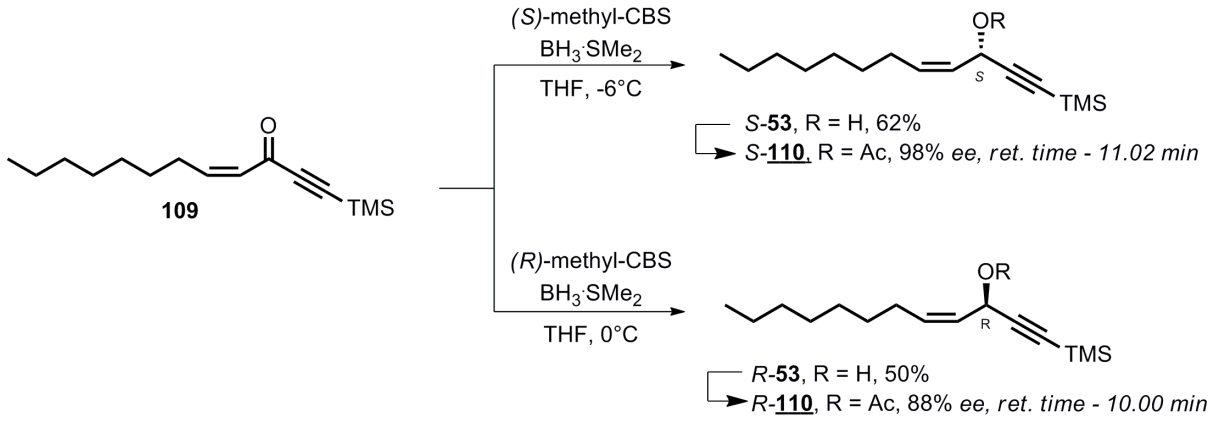
For determining the absolute stereochemistry, one could employ Kazlauskas rules. The empirical rule developed in the early 1990s postulates that one of the enantiomers would react faster based on the size of two residues adjacent to the chiral center of the secondary alcohol (Scheme 76). The size of the substituents affects the effectivity of binding of the substrate in the catalytically active center of the enzyme.



Scheme 76

However, it does not seem trivial to predict, whether the rigid TMS acetylene residue or the long, but flexible olefin chain should be considered as large residue and which of them should play the role of the medium sized substituent. Therefore, ketone **109** was reduced, using *S*-CBS catalyst to the corresponding *S* alcohol, subsequently acetylated chemically and used as a standard for chiral HPLC analysis. It was demonstrated that the *S* enantiomer

elutes at 11.02 minutes. Control experiment, when *R*-CBS catalyst was used to reduce ketone **109** to the *R*-alcohol (and subsequent chemical acetylation), proved that the peak at 10.00min. represents the *R*-enantiomer.

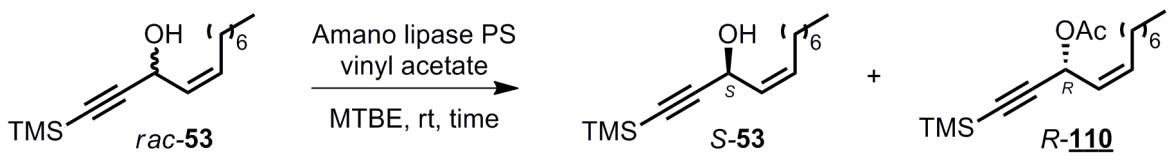


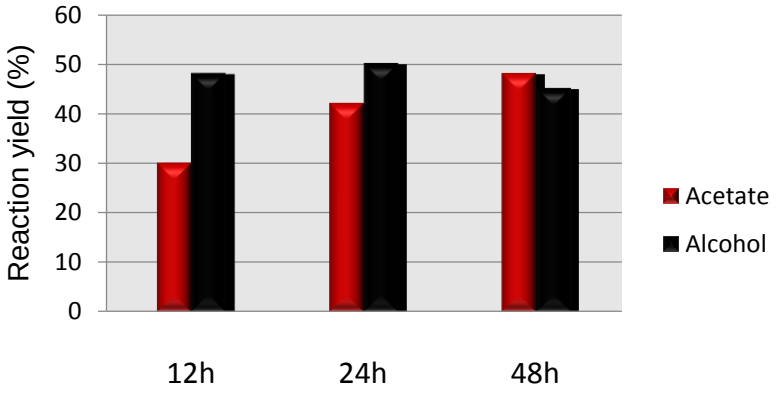
Scheme 77

Racemic alcohol *rac*-**53** was then subjected to the lipase acetylation for 4 hours. After separation of the spots, 30% (out of theoretical 50%) of the acetate and 48% of remaining alcohol were isolated. Chiral HPLC analysis revealed that acetate was obtained with excellent optical purity, with an enantiomeric excess higher than 99%. However, optical purity of the alcohol was low. Chemical acetylation and consecutive analysis showed that the enantiomeric excess was only moderate50%.

It was, however possible to determine the absolute stereochemistry of the formed product. Since the isolated ester eluted at 10.00 min, it was deduced that the *R* enantiomer of the alcohol undergoes preferably the acetylation by the lipase. The *S* enantiomer remains untouched.

Poor optical purity of the remaining alcohol and excellent optical purity of the ester led to the conclusion, that the reaction was not finished in 4 hours. Therefore, another experiment was set up, extending the reaction time to 24 hours. After column chromatography, acetylated *S* enantiomer was obtained in 42% yield, again with an *ee* higher than 99%. The alcohol was obtained quantitatively, with promising, but still not ideal *ee* of 86%. Another prolongation of the reaction time led to success. After 36 hours, 48% of acetate and 45% of alcohol were isolated, both with enantiomeric excess greater than 99%.





Scheme 78

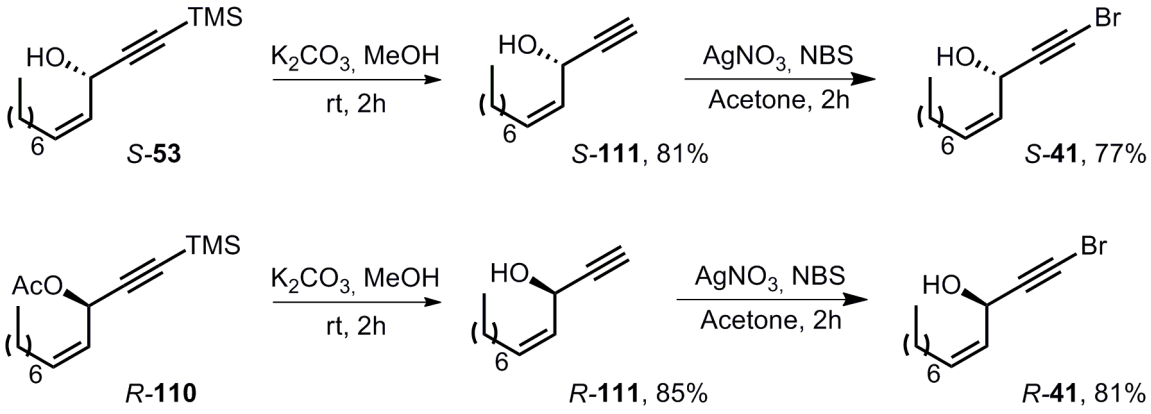
The obtained results were satisfactory for further synthesis and all problems discussed earlier in this chapter were successfully circumvented. (I) there was no isomerization of the double bond system observed, (II) both enantiomers were obtained in a single step with excellent *ee*, (III) Amano lipase PS is significantly cheaper than the CBS catalyst. Therefore, the developed method can be considered as an improvement compared to the approach reported for the synthesis of Falcarindiol, in particular, when all possible stereoisomers are aimed to be synthesized. In addition, overall yield starting from the racemic alcohol *rac*-**53** to *S*-**53** improves. While the oxidation/CBS reduction sequence (taking into account that half of the ketone **109** would be used for reduction towards *S* and the other half for reduction towards *R* alcohol) yield the *S* enantiomer in 21% in two steps, lipase mediated synthesis yields the same compound in 45% yield in a single step.

D IV Synthesis of alkynylbromides

Next, it was necessary to introduce bromine to the terminal alkyne carbon. In case of *S*-enantiomer *S*-**53** hydrolysis of the trimethylsilyl group had to be carried out initially; in case of acetylated *R*-enantiomer *R*-**110**, the ester group had to be hydrolyzed as well. Both alcohol *S*-**53** and ester*R*-**110** were treated with potassium carbonate in methanol. It turned out that in case of ester *R*-**110**, acetyl hydrolysis and cleavage of TMS group can be carried out in one step. Desired products *S*-**111** and *R*-**111** were obtained in 81% and 85% yield, respectively.

Free terminal alkynes were afterwards subjected to bromination conditions. Treatment of *S*-**111** and *R*-**111** with NBS in acetone in presence of a catalytic amount of silver nitrate led to the formation of the terminal alkynyl bromides. It was not necessary to purify the compounds after the extraction step by any means, as was revealed from ^{1}H and ^{13}C

NMR spectra. The *S*-enantiomer *S*-**113** was isolated in 81% yield and *R*-enantiomer *R*-**113** in 77% (Scheme 79)

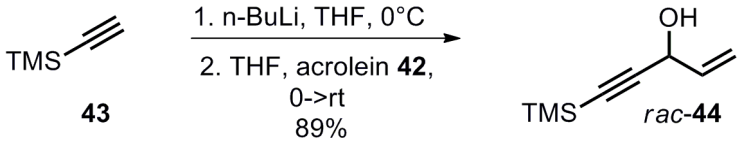


Scheme 79

D V Synthesis of alkynes *R*-113 and *S*-113

Synthesis of the enantiomerically pure alkynes *R*-**113** and *S*-**113**can take advantage either of kinectic resolution with lipase or again, reoxidation of the racemic secondary alcohol *rac*-**44** to the corresponding ketone and subsequent CBS reduction. Herein, the problem of the double bond isomerisation is eliminated, however, due to the same reasons as discussed in chapter D III, lipase kinetic resolution was chosen as a tool for obtaining both enantiomers.

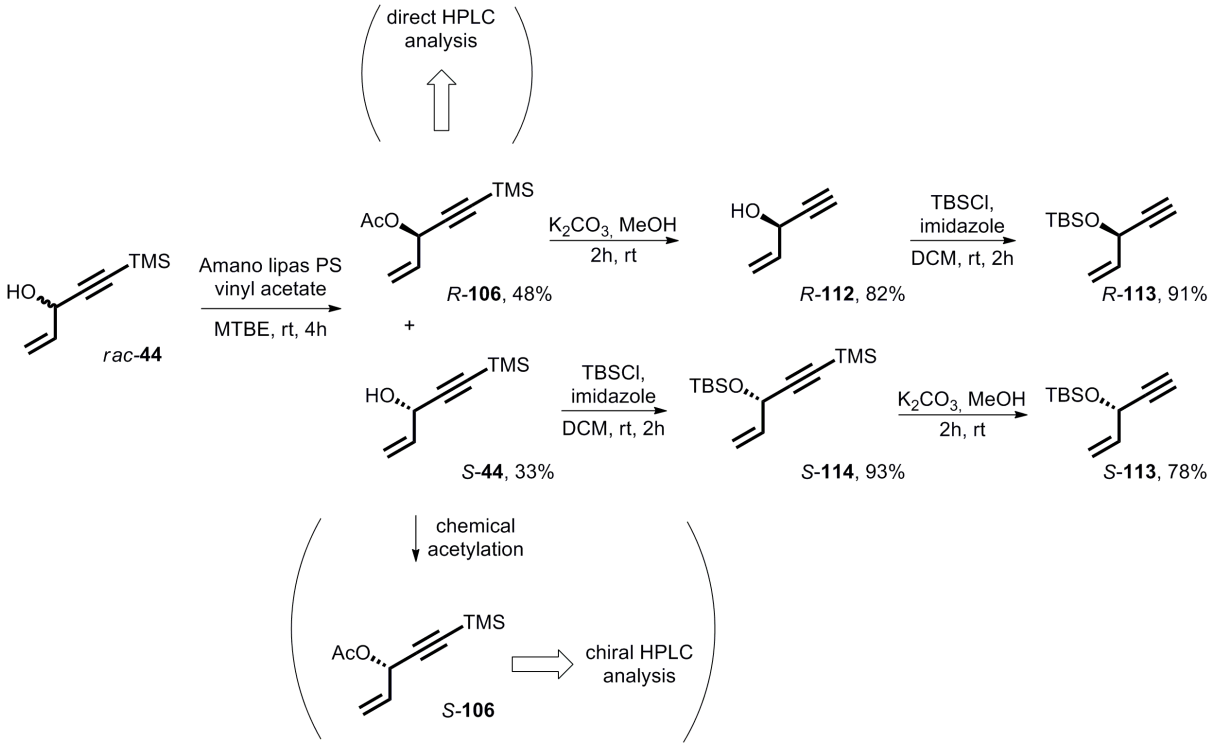
Racemic alcohol *rac*-**44** was synthesized according to the literature precedent.[3, 6] Deprotonation of TMS acetylene with *n*-BuLi in dry THF at -78°C and subsequent treatment of formed anion with acrolein and stirring for 2 hours at room temperature provided desired alcohol *rac*-**44** in 89%.



Scheme 80

In the next step, kinetic resolution of the alcohol with lipase was investigated. Control of the optical purity was performed again by means of chiral HPLC. Similarly as in the case of the long chained alcohol *rac*-**53**, it was not possible to resolve free alcohol *rac*-**44** on any of the available chiral columns. Therefore, acetylation had to be carried out again. Racemic ester *rac*-**106** was then injected into the chiral column and enantiomers were resolved. One of the enantiomers eluted at 7.83 minutes, whereas the other at 10.71 minutes.

In the work of Mann *et* al., kinetic resolution was performed in dry hexanes in presence of molecular sieves and the reaction was catalyzed with Amano lipase PS.[6] However, treatment of the alcohol *rac*-**44** with amanolipase PS at the same conditions as used for kinetic resolution of alcohol *rac*-**53** (MTBE, vinyl acetate) led to good results as well. In 4 hours 48% of alcohol and 33% of acetate were isolated with optical purities higher than 99% *ee*. Absolute configuration was assigned based on literature precedent[6] and Kazlauskas rules which was also confirmed by means of optical rotation of both acetylated alcohol and free alcohol. As expected, *R*-enantiomer undergoes acetylation leading to (*R*)-5-(trimethylsilyl)pent-1-en-4-yn-3-yl acetate *R*-**106** and *S*-alcohol *S*-**44** remains untouched (Scheme 81).



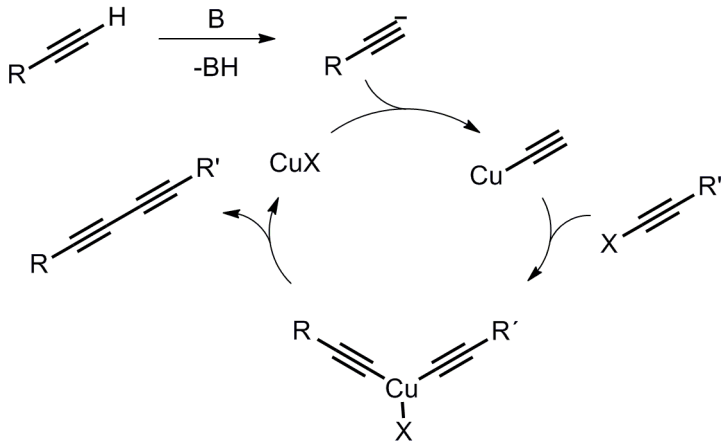
Scheme 81

Further modifications of *R*-**106** consisted of hydrolysis of both acetyl and TMS groups. This can be carried out again in one step upon treatment of *R*-**106** with potassium carbonate in methanol. (*R*)-Pent-1-en-4-yn-3-ol *R*-**112** was obtained in 82% yield. Because of high solubility of the alcohol in water, repeated extraction was necessary, and the presence of the product in aqueous layer was controlled after each extraction step. Moreover, drying of the compound was not carried out at the lowest possible pressure, in order to avoid evaporation of the product. Compound *R*-**112** was subsequently protected with a TBS group. Treatment of *R*-**112** with TBS-chloride in dry DCM in the presence of imidazole yielded enantiomerically pure alkyne *R*-**113** in 91%.

For further modifications of *S*-**44** the order of events was changed, in order to avoid water solubility and volatility problems of pent-1-en-4-yn-3-ol*R*-**112** and possible losses. Protection of the free hydroxyl group with the heavy TBS group ensured a high boiling point of the product and its hydrophobicity. Product *S*-**114** was obtained in 93%. Treatment of *S*-**114** with potassium carbonate led to formation of the desired alkyne *S*-**113** in 78% yield.

D VI Finalization of the total synthesis

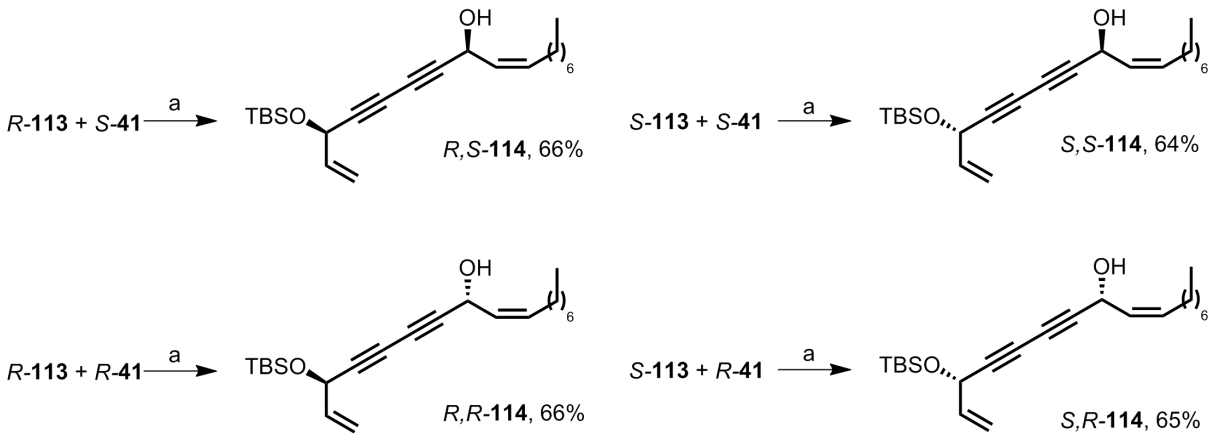
After successful preparation of the enantiomerically pure alkynes and bromoalkynes, attention was focused on the crucial step of the synthesis, formation of the alkyne-alkyne bond. The Cadiot-Chodkiwitz coupling reaction was utilized representing a copper catalyst mediated transformation in the presence of a base. In the initial step, free terminal alkyne is deprotonated and coordinates to the copper center. In the second step, bromoalkyne oxidatively adds to the metal center, which is followed by reductive elimination to liberate unsymmetrical bisalkyne and copper(I) catalyst is regenerated (Scheme 82).



Scheme 82

Cadiot-Chodkiewitz coupling between alkynyl bromides *S*-**41** respectively *R*-**41** and alkynes *S*-**113** respectively *R*-**113** leads to the Falcarindiol backbone with a protected hydroxyl group in position 3 of the aliphatic chain, a structure suitable for regioselective esterification of the hydroxyl group in position 8.

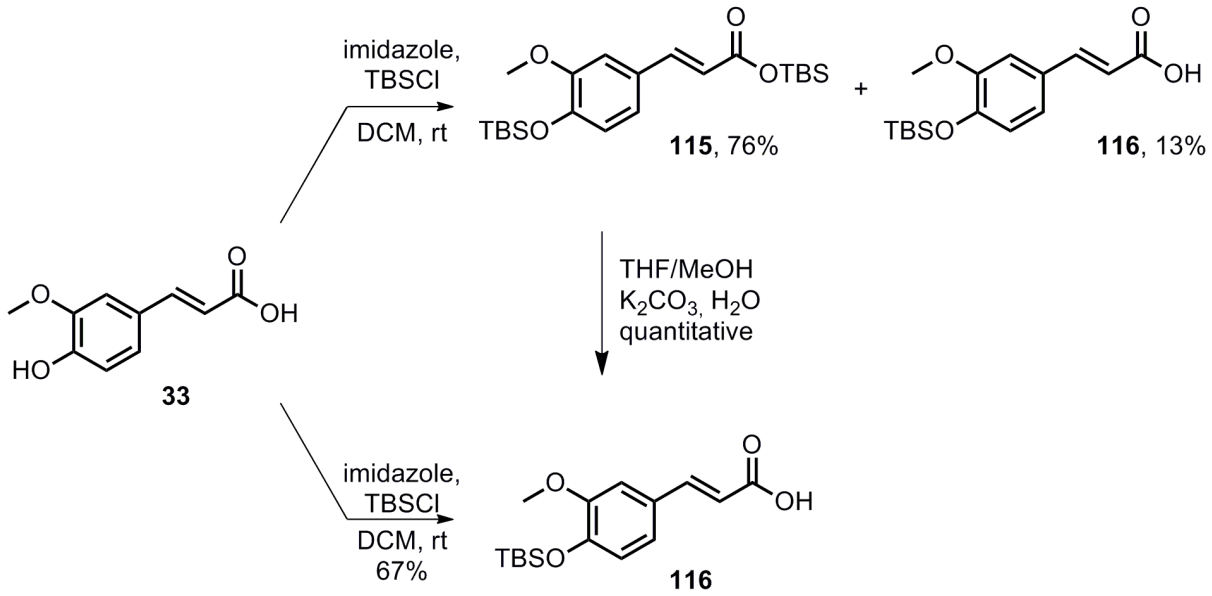
Coupling was carried out in a methanol/water mixture in the presence of copper(I)chloride and ethylenamine. Reaction between (*S*,*Z*)-1-bromododec-4-en-1-yn-3-ol *S*-**41** and (*R*)-tert-butyldimethyl(pent-1-en-4-yn-3-yloxy)silane*R*-**113** yielded 66% of the desired bialkynyl *RS*-**114**. Reaction between *S*-**41** and*S*-**113** yielded 64% of compound *SS*-**114**. Alkynyl bromide *R*-**41** coupled with the *R*-enantiomer *R*-**114** in 66% yield of *RR*-**114** and the reaction with *S*-enantiomer delivered 65% of product *SR*-**114** (Scheme 83).



Scheme 83(**a**) $NH_2OH.HCl$, $EtNH_2$, CuCl, H_2O/MeOH,0°C - rt, 2h;

In the next step, free hydroxyl group in the position 8 of the aliphatic backbone was esterified with ferulic acid, which was beforehand protected with TBS group at the phenolic position.

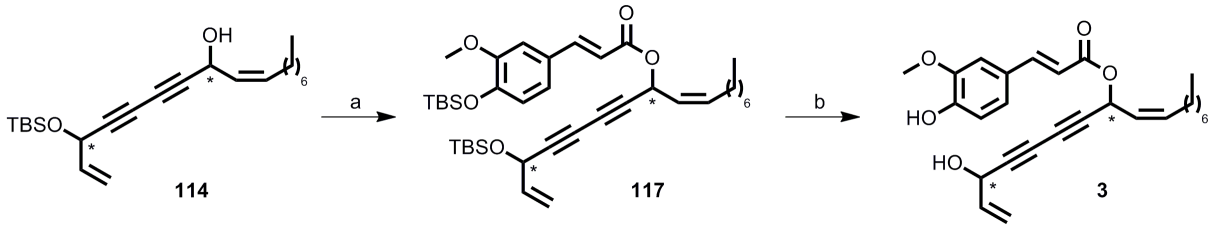
Protection of ferulic acid was carried out with TBS-chloride and imidazole. Interestingly, using DMF as a solvent resulted in the introduction of the TBS group only into the desired phenolic position, however, TBS-ferulic acid **116** was isolated in only 67% yield. When DMF was replaced with DCM, desired ferulic acid with TBS protected phenolic OH was isolated only in 13% yield and formation of the TBS ester was observed in addition to the protection of the phenolic OH (Scheme 84). Silyl ester **115** was isolated in 76%. Basic hydrolysis with potassium carbonate proceeded quantitatively, providing desired product **116** in overall 89% from ferulic acid, but at the cost of atom efficiency.



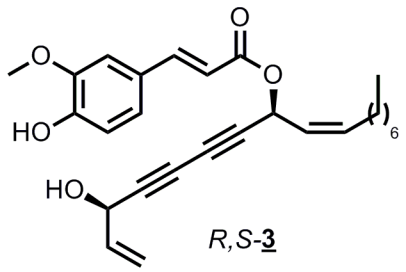
Scheme 84

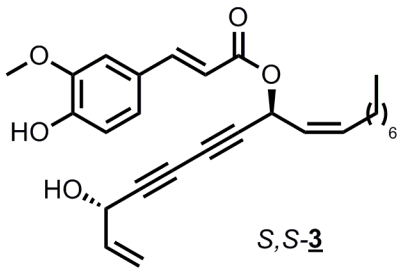
Firstly, *RS*-**<u>114</u>** was subjected to Steglich esterification with excess of **116**, using DCC. However, after coupling, the desired product was contaminated with dicyclohexyl urea

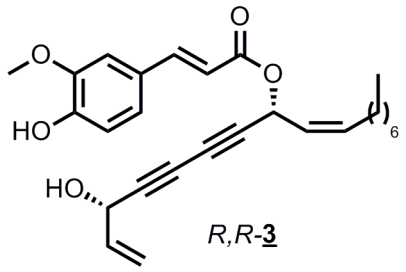
(DCU), formed during the reaction as a by-product. Replacing DCC with EDCI, turned out to be beneficial. The corresponding urea derivate could be removed from the reaction mixture by acidic washing. Additionally, using EDCI instead of DCC positively influenced the reaction yield. While the reaction utilizing DCC furnished 34% of desired product (calculated yield, mass corresponding to 46% of the reaction yield recovered, with the molar ratio of product and DCU 1:1, as revealed from ^{1}H NMR), EDCI esterification afforded 81% of desired ester. Coupling of *SS*-**114**, *RR*-**114** and *SR*-**114** proceeded with 79%, 78% and 78%, respectively (Scheme 85).

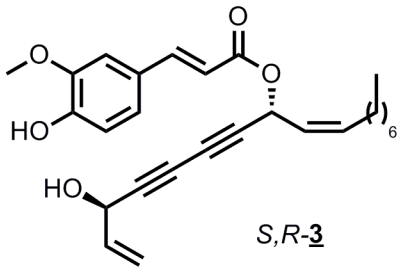


Entry	Starting material	Esterification (product, yield)	Deprotection (product, yield)
1	*R,S*-**114**	*R,S*-**117**, 81%	*R,S*-**3**, 83%
2	*S,S*-**114**	*S,S*-**117**, 79%	*S,S*-**3**, 76%
3	*R,R*-**114**	*R,R*-**117**, 78%	*R,R*-**3**, 78%
4	*S,R*-**114**	*S,R*-**117**, 78%	*S,R*-**3**, 75%









Scheme 85(a)**33**, EDCI, DMAP, rt, 2h; (b) HF/pyridine, THF, 0°C - rt, 2h

In the final step, global deprotection of TBS was carried out. All stereoisomers **114** were treated with HF/pyridine in THF, affording final products *RS*-**3**, *SS*-**3**, *RR*-**3** and *SR*-**3** in yields from 83%, 76%, 78% and 75% respectively (Scheme 85).

D VII Confirmation of absolute stereochemistry

The absolute stereochemistry was confirmed by means of optical rotation. As reported by Liu et al. optical rotation of the isolated natural product was $[\alpha]_D^{20}$= +85.5(*c* 0.09, MeOH).[2] Values measured for the synthetic compounds are depicted in table 1. For compound *RS*-**3**, with configuration of the chiral centers 3*R*,8*S*, value of +87.7° was measured. For compound *RS*-**3**, the enantiomer of *RS*-**3**, with configuration 3*S*,8*R,*-85.9° was measured. For *SS*-**3**+143.1° was measured and for *RR*-**3**$[\alpha]_D^{20}$ of-139.8° was measured. Such results confirm the absolute stereochemistry of Notoincisol A being 3*R*,8*S*.

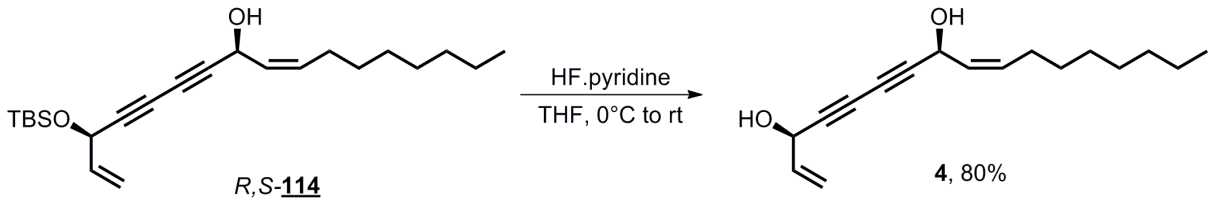
Compound	$[\alpha]_D^{20}$ (*c* 0.09, MeOH)
R,S-**3**	+ 87.7°
S,S-**3**	+ 143.1°
R,R-**3**	- 139.8°
S,R-**3**	- 85.9°
Natural product	+85.5°

Table 1

E Synthesis of Falcarindiol

E I Synthesis of Falcarindiol

Falcarindiol was prepared from the intermediate *RS*-**114**. Treatment of *RS*-**114** with HF.pyridine in THF provided the natural product in 80%



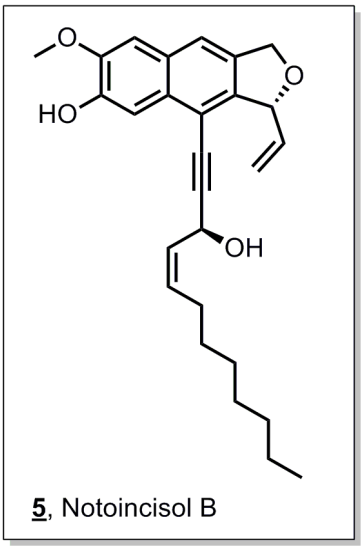
R,S-**114** **4**, 80%

Scheme 86

F Towards Notoincisol B

This chapter discusses progress in the total synthesis of the recently isolated and described natural product Notoincisol B (**5**, Scheme 87). At the time of finalizing this thesis, synthesis of the natural product was not finalized. However, progress on the topic is described. Two retrosynthetic pathways were designed and investigated, but one was discontinued as it was not working. Within the second investigated pathway and severe problems with the key step occurred and so far there has not been a solution to it. However, several possibilities are outlined and suggested to solve the problems.

Development of synthetic methodology is from significant part described on the model substrate and deals with racemic material. However, stereoselective synthesis of desired building block is the same as described for Notoincisol A in the section D.

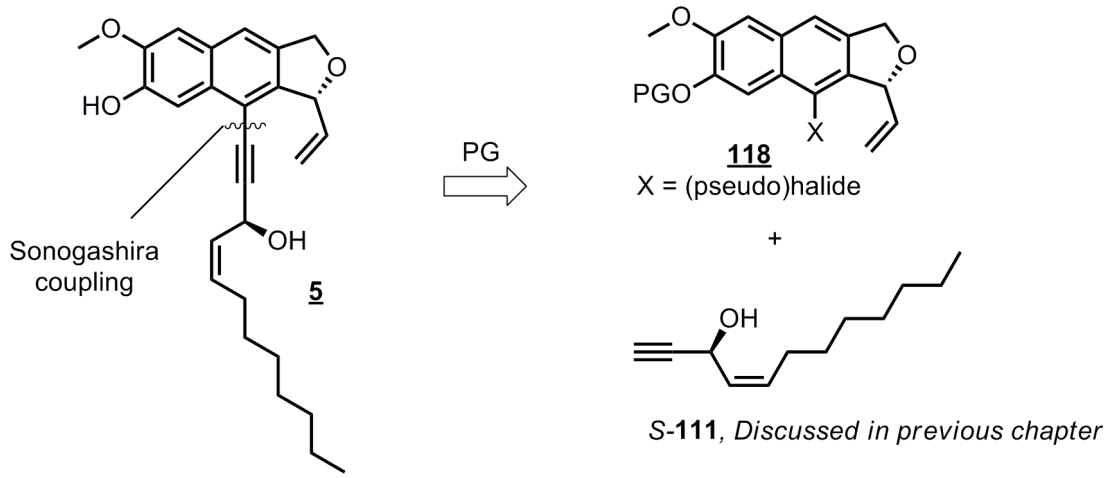


5, Notoincisol B

Scheme 87

F I Retrosynthetic analysis – early disconnection

Looking at the structure of Notoincisol B, first obvious retrosynthetic cut (not considering protection/deprotection chemistry) would be a disconnection of the aromatic core and the acetylene. Of course, in forward synthesis, Sonogashira coupling would be a suitable tool for a construction of such a bond. This retrosynthetic disconnection would lead to two major building blocks, aliphatic part *S*-**111** and aromatic part **118** (Scheme 88). Synthesis of the aliphatic part *S*-**111** is described in the previous chapter, thus it will not be discussed here again. Retrosynthetic analysis of the aromatic part **118** revealed two possible ways towards **118**. Both pathways are based on intramolecular Diels-Alder reaction and are discussed in following subchapters.



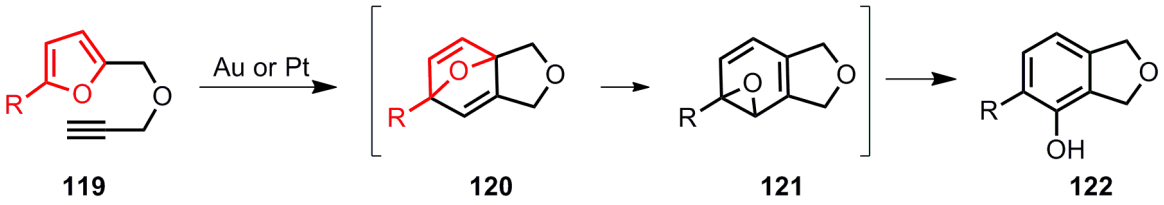
Scheme 88

F II Pathway I – metal assisted intramolecular Diels-Alder reaction as a key step

F II.1 Pathway I – retrosynthetic analysis

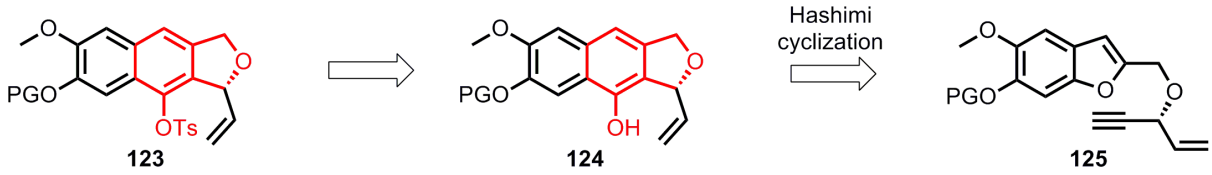
Pathway I relies on the chemistry developed in the laboratories of Hashimi (Scheme 89).[84-87] He reported gold or platinum catalyzed intramolecular Diels-Alder reactions of propargyloxymethyl substituted furans, followed by sigmatropic rearrangement and rearomatization/epoxide opening, leading to the 1,3-dihydroisobenzofuran, structural motif contained in Notoincisol B, moreover decorated in the position 4 with hydroxyl group. Such a

hydroxyl group can play an important role of a handle installed in the right position for further modifications, e.g. conversion to tosylate, capable of Sonogashira coupling.



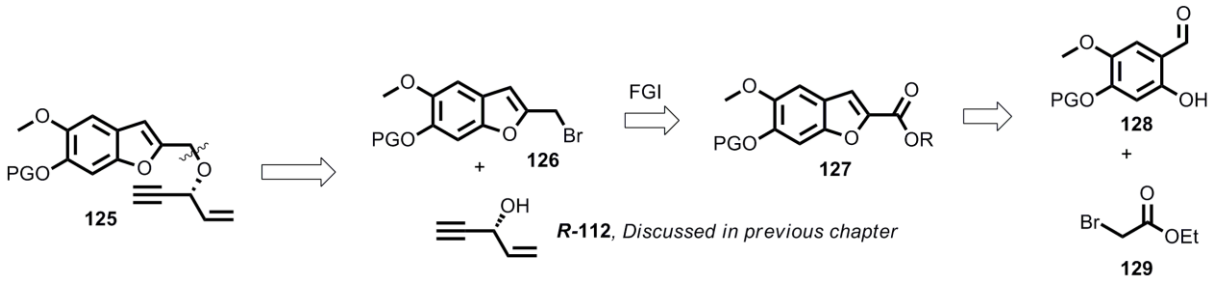
Scheme 89

In the case of Notoincisol B, retrosynthetic disconnection, following the Hashimi chemistry, would lead to the highly substituted benzofuran **125** (Scheme 90).



Scheme 90

Next retrosynthetic cut would lead to the disconnection between secondary alcohol *R*-**112** and substituted 2-bromomethylbenzofuran **126**. Synthesis of the alcohol *R*-**112** is discussed in the previous chapter, thus it will not be discussed here again. **126** can be synthesized from ester **127** *via* reduction to alcohol and subsequent conversion of alcohol to bromide. Finally, ester **127** can be synthesized *via* nucleophilic substitution of **129** with 2-bromoethylacetate and subsequent condensation.

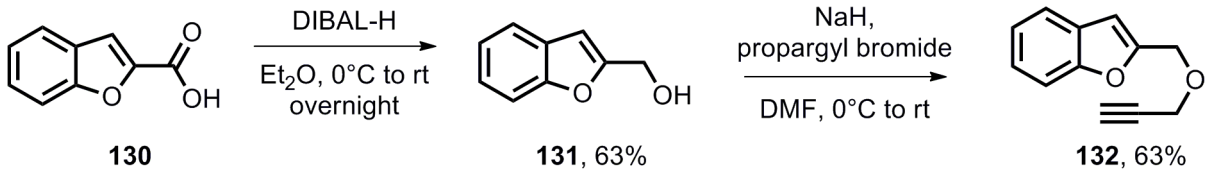


Scheme 91

F II.2 Reaction on the model system

Before starting with the synthesis of the highly substituted benzofuran **125**, it was decided to test the key cyclization on a simplified model substrate. Simple benzofuran-2-carboxylic acid **130** was chosen, which was initially reduced with DIBAL-H to corresponding benzofuryl-2-methanol **131** in 63% of yield. Deprotonation of **131** with sodium hydride and

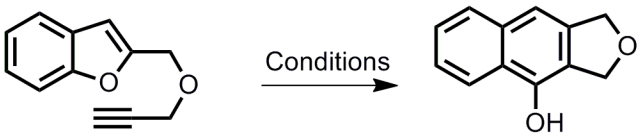
subsequent treatment with propargyl bromide furnished 2-(propargyloxymethyl)benzofuran **132** in 63%, which then served as model substrate for the Hashimi cyclization.



130 **131**, 63% **132**, 63%

Scheme 92

Ether **132** was subjected to several conditions for Hashimi cyclization. Reaction was monitored by means of TLC. Staring material has a retention factor R_f = 0.55, when petroleum ether/ethyl acetate mixture (9:1) is used as eluent. First, **38** was treated with $AuCl_3$ in acetonitril at room temperature.[84-87] There was no conversion observed, according to TLC after 3, 24 and 48 hours. Same results were obtained, when temperature was increased to 50, 100 or 120°C. Changing solvent to DCM did not lead to any improvement. Increasing the temperature to 180°C together with use of high boiling DMA did not lead to success either. Unfortunately, changing the catalyst to $PtCl_2$ did not improve the situation. Results are depicted in the Scheme 93.



132 **133**

Entry	Solvent	Catalyst	T (°C)	Yield (%)
1	CH_3CN	$AuCl_3$	r.t.	0
2	CH_3CN	$AuCl_3$	50	0
3	CH_3CN	$AuCl_3$	100	0
4	CH_3CN	$AuCl_3$	120	0
5	DCM	$AuCl_3$	50	0
6	DMA	$AuCl_3$	180	0
7	Acetone	$PdCl_2$	50	0
8	DMA	$PdCl_2$	180	0

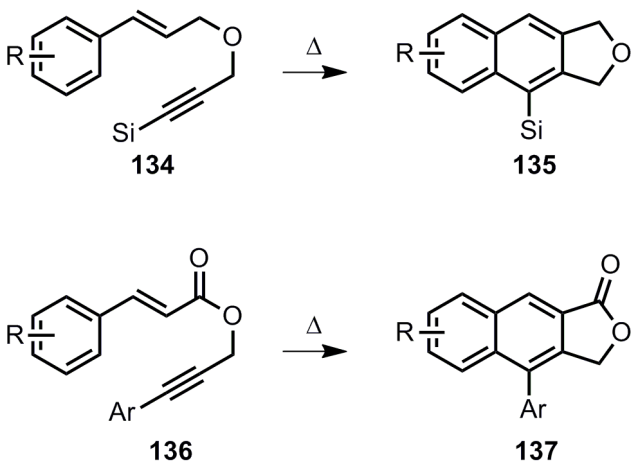
Scheme 93

After above discussed experiments had failed, it was decided to stop focusing the attention on the synthesis of Notoincisol B *via* Hashimi metal assisted cyclization, as 2-(propargyloxymethyl)benzofuran **132** was not suitable substrate. There were no further attempts regarding this strategy and an alternative pathway came under consideration.

F III Pathway II – thermal intramolecular dehydrogenative Diels-Alder

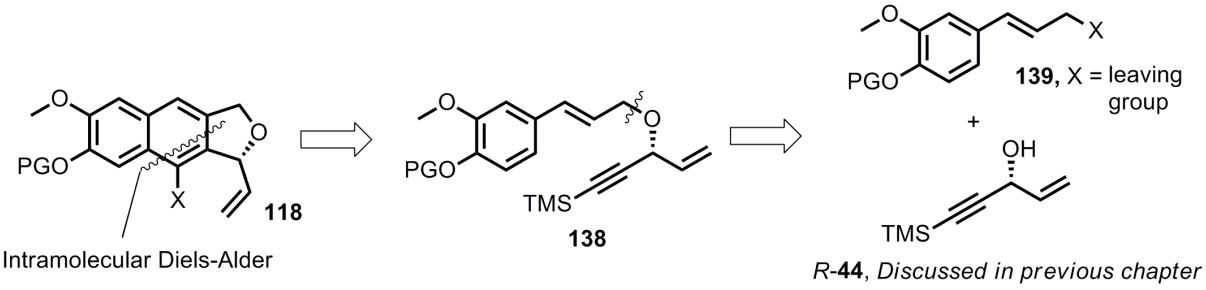
F III.1 Pathway II – retrosynthetic analysis

Pathway II was based on intramolecular dehydrogenative Diels-Alder reaction of propargyl ethers. Such methodology was reported by Ozawa *et* al.[88] Later, similar transformation was reported by Park *et* al., but employing esters instead of ethers.[89]



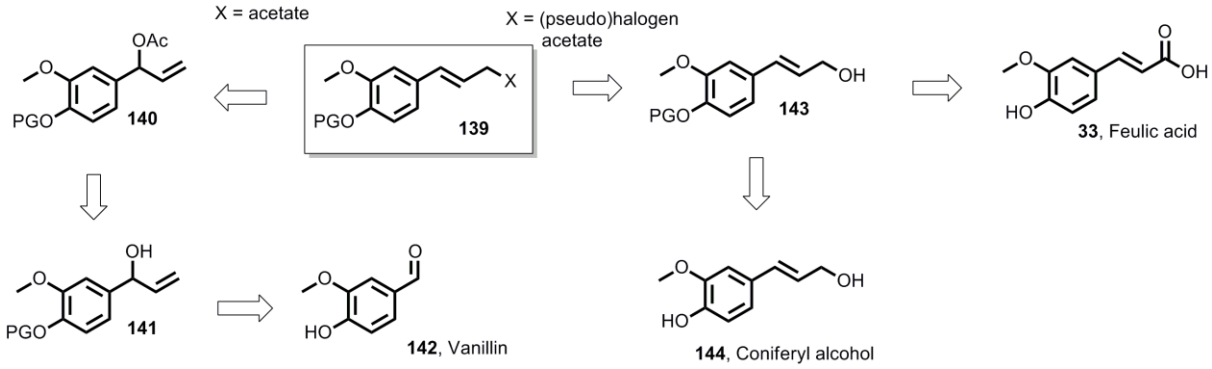
Scheme 94

Taking advantage of such method, retrosynthetic cut of aromatic intermediate **118** would lead to the ether **138**. Further analysis reveals that ether **138** can be prepared from alcohol *R*-**44** and allylic structure **139**, bearing a leaving group. Formation of the ether bond can be mediated by either nucleophilic substitution or some other ether bond formation method, e.g. metal assisted C-O coupling. Formation of alcohol *R*-**44** is discussed in the previous chapter.



Scheme 95

There are several options how to achieve compound **139**, leading to various commercially available building blocks. One can start with vinyl magnesium bromide addition to protected vanillin **142**, further acetylation and rearrangement of branched acetate **141** to linear acetate **139**. Another possibility is to start from ferulic acid **33**, protection of the phenolic alcohol, further reduction of carboxylic acid and desired modification of allylic alcohol. Alternatively, selective protection and modifications of allylic alcohol of coniferyl alcohol **144** is another possibility.

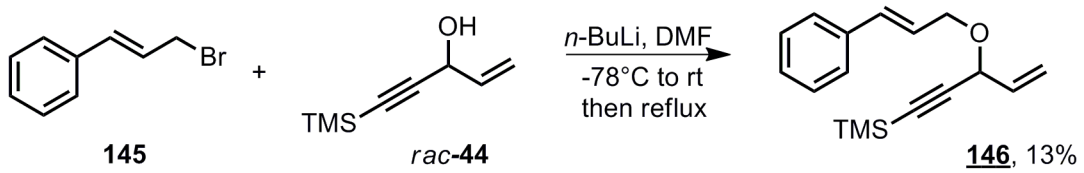


Scheme 96

F III.2 Formation of the ether bond

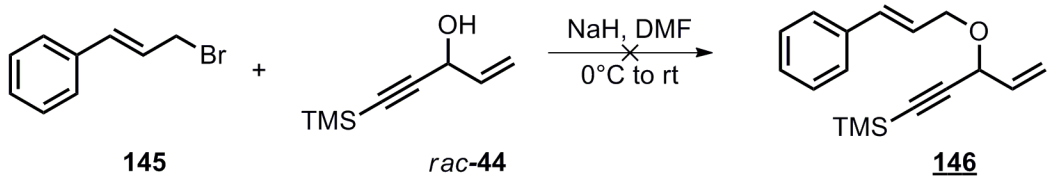
F III.2.1 Nucleophilic substitution

Similarly as in the previous case, development of the synthetic strategy was initially carried out on cheap and readily available model material. In the beginning, several attempts to form the ether bond *via* nucleophilic substitution were undertaken. Alcohol *rac*-**44** was synthesized as described in the previous chapter and was reacted with cinnamyl bromide **145**. Initially, alcohol *rac*-**44** was deprotonated with *n*-BuLi and then treated with **145** in refluxing DMF. Under such conditions only 13% of the desired ether was isolated. Additionally, huge amount of the cinnamyl bromide was recovered (in spite of the fact that, cinnamyl bromide was used in excess, higher than theoretical amount was recovered), but there was not any alcohol left in the reaction mixture.



Scheme 97

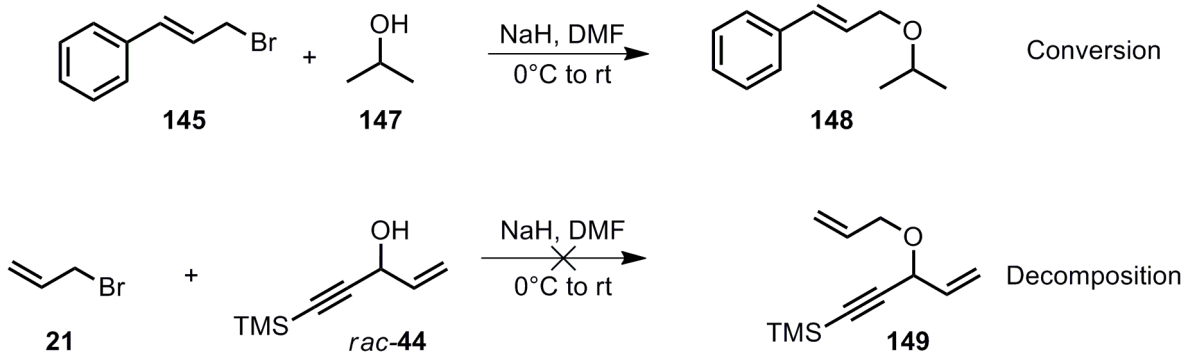
Another attempt was to use sodium hydride. After the deprotection of *rac*-**44** at 0°C, cinnamyl bromide was added and mixture was stirred at room temperature. Crude NMR did not reveal any formation of the desired product. Moreover, alcohol *rac*-**44** was not detected in the reaction mixture.



145 *rac*-**44** **146**

Scheme 98

In order to point out the problem, cinnamyl bromide **145** was reacted with isopropyl alcohol **147** and alcohol *rac*-**44** was subjected to allylation with ally bromide **21**. While reaction between cinnamyl bromide **145** and isopropanol **147** proceeded well, allylation of the alcohol *rac*-**44** failed and only decomposition of the material was observed.

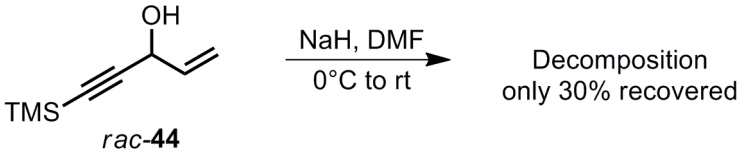


145 **147** **148**

21 *rac*-**44** **149**

Scheme 99

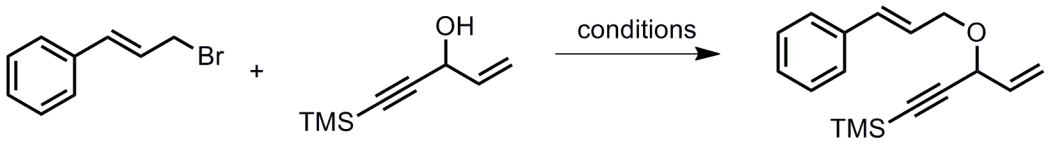
It was rationalized that alcohol *rac*-**44** is not stable in the presence of strong base or harsh conditions. It was then demonstrated by treatment of the alcohol by just NaH in DMF without addition of cinnamylbromide at room temperature. After the workup, only 30% of the material was recovered.



rac-**44**

Scheme 100

Using weaker base as potassium carbonate or triethylamine did not lead to any conversion. Utilizing silver carbonate to facilitate the cleavage of bromine mediated by silver cations led to negligible conversion and moreover decomposition is observed.



145 *rac*-**44** **146**

Entry	Base	Solvent	Temperature	Result
1	K_2CO_3	Acetone	reflux	no conversion
2	TEA	Acetone	reflux	no conversion
3	Ag_2CO_3	Acetone	reflux	decomposition

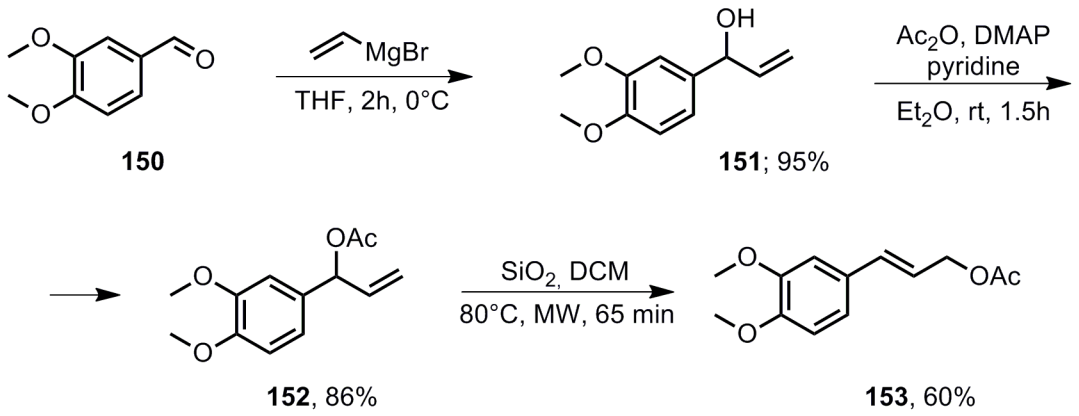
Scheme 101

After above discussed failures, it was decided to leave attempts to carry out the nucleophilic substitution.

F III.2.2 Ether bond formation *via* metal assisted C-O coupling

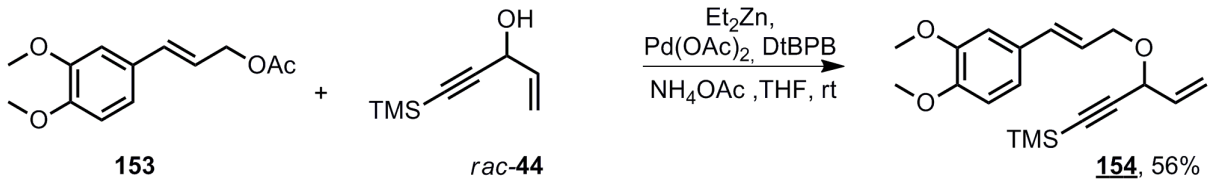
There has been a method for formation of the allylic ethers described, relying on the palladium assisted cross coupling.[90] Method applies on structurally related molecules, as it would be necessary in the case of Notoincisol B. General problem with metal assisted C-O coupling of aliphatic alcohols is associated to their nucleophilicity. As such, alcohols are not very nucleophilic. Deprotonation requires strong bases, which might have a negative impact on the stability of the entire molecule (as demonstrated in the case of alcohol *rac*-**44**) or can reflect in depreciation of the stereochemical information. Moreover, when formation of the allylic ether is required, there is an apparent difference in the hardness of the η^3-allylic electrophile and alkoxide nucleophile. Therefore, addition of a Zn salt turned out to be beneficial. Effect of increasing of the acidity of alcohols by zinc was observed in the metaloenzymes, containing zinc in the reaction center.

Cross-couplings is carried out between aliphatic alcohol (possibly also allylic and propargylic) and allyl acetate. In our laboratory, there was a compound available, which again served as model substrate. However, compound **153** was later resynthesized starting from 3,4-dimethoxybeznaldehyde by addition of vinylmagnesiumbromide affording the compound **151** in 95%. Acetylation of **151** furnished the branched acetate **152** in 82% of the yield. Compound **152** was subsequently rearranged in the presence of silica gel to the desired linear acetate **153** in 60%.



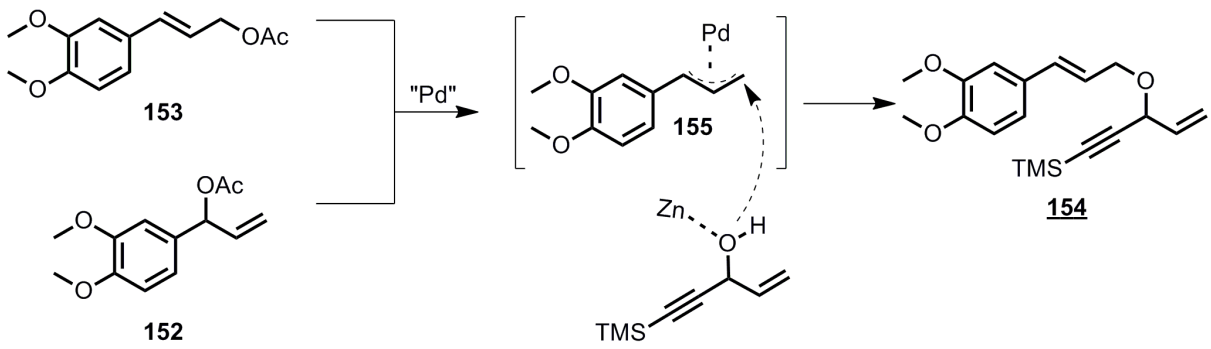
Scheme 102

Cross coupling was initially conducted with excess allyl acetate, as reported for the coupling with allylic alcohol. Reaction afforded 42% of desired racemic product. There was not any alcohol*rac*-**44** left in the reaction mixture, however high amount of allyl acetate was recovered. Such an observation led to the assumption of a reduced stability of the alcohol **25** under the reaction conditions, as already seen before. Therefore, the ratio of the reactants was swapped and alcohol *rac*-**44** was used in excess. After two hours, reaction was completed and desired ether was isolated in 56%.



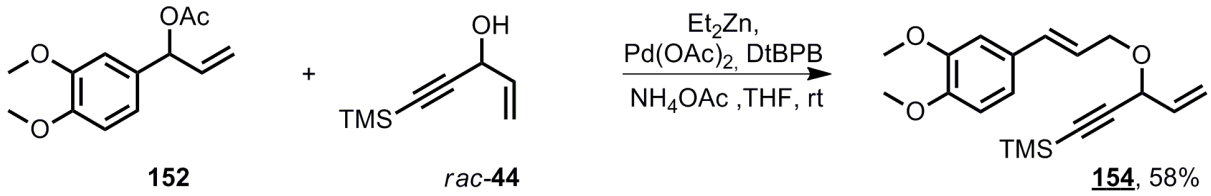
Scheme 103

Considering the reaction mechanism of the coupling it could be expected, that branched and linear acetate (**152** and **153**, respectively) should eventually provide the same coupling product, when reacted with alcohol *rac*-**44** under the coupling conditions. Explanation can be found in the formation of the common intermediate **155**. After treatment of **152** and **153** with palladium, oxidative addition leads to the formation of η^3-allyl-Pd species. Nucleophile then approaches from the less satirically shielded site and thus forms the terminal ether.



Scheme 104

Branched acetate **152** was then subjected to the reaction instead of linear acetate **153** and indeed, linear ether **154** was isolated in 58% of yield. In such a way, rearrangement of the branched acetate **152** to linear acetate **153** can be circumvented and one step can be saved.



Scheme 105

However, C-O coupling between alcohol *rac*-**44** and allylacetes**152** or**153**turned out to be problematic, as transformations were highly irreproducible in particular when modifying the scale. Even when reactions were repeated several times under exactly same conditions with the identical procedure, the results differed significantly. Firstly, isolated yields varied. Yields mentioned above were the best result obtained. Nevertheless, isolated yields lied in the range of 33-58%. Secondly, consumption of the starting material appeared to be irreproducible as well. In few cases, staring acetate was consumed within one hour, but in several cases complete consumption was not achieved at all and addition of a new batch of catalytic system was required in order to achieve full consumption of the material. Moreover, undefined side products were formed, as judged from TLC, where several additional spots were visible. Additionally, attempts to scale up the reaction failed, since above mentioned issues became pronounced.

Several attempts to suppress the side reactions were carried out. For instance ratio between palladium acetate and ligand, role of NH_4OAc were investigated or extra dry THF was used. However, any particular success was not achieved. Results are summarized in Table 2. Irreproducibility of the applied protocol is obvious from last three entries, where the role of the extra dry THF was tested. After initial success, reproduction of the reaction twice generated two different outcomes.

Entry	Variation to standard conditions	Acetate consumption (TLC)	Significant side reactions (TLC)
1	Pd:ligand 1:2	incompete	Yes
2	Pd:ligand 1:1	incompete	Yes
3	No NH_4OAc	incompete	Yes
4	Double amount NH_4OAc	incompete	Yes
5	Extra dry THF	full	No
6	Extra dry THF	incompete	No
7	Extra dry THF	incompete	Yes

Table 2

There is still room for improvement regarding the coupling between either branched or linear acetate **152**, resp. **153** with alcohol *rac*-**44**. However, for the further investigation, it was decided to continue with the achieved results.

F III.3 Thermal cyclization of ether 154 and halodesilylation

F III.3.1 Cyclization

There were two reports describing an intramolecular Diels-Alder reaction employing alkyne as dienophile and styrene moiety as diene. In the early report by Ozawa et al. [78] influence of the alkyne substituent is investigated, covering various silyl groups and esters. It was revealed that TMS group is advantageous over other silanes and also over ester groups. In case of ester groups, cyclization proceeded as well, however, further aromatization did not occur. TMS group is also suitable or the synthesis of Notoincisol B, since it can be easily converted into halide by halodesilylation reaction. In the later report, acetylene was functionalized by aromatic moiety, which is less suitable for the purposes of the synthesis of Notoincisol B.[88, 89]

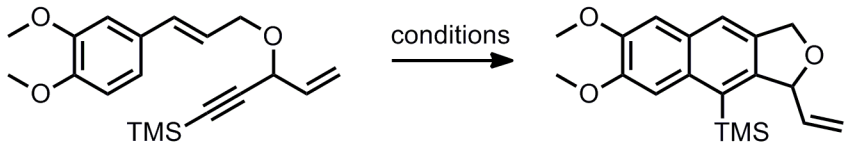
Ether **154** was therefore subjected to the conditions described by Ozawa. Starting material was dissolved in xylene, degassed by bubbling argon through the mixture in an ultrasound bath and subsequently the mixture was heated to 160°C for 48 hours. Reaction was monitored by means of GC/MS. There was a peak detected in the GC/MS spectrum, displaying the mass corresponding to the mass of the expected product. Nevertheless, there was a number of different peaks present in the spectrum as well, indicating a decomposition of the material. Transferring the reaction from conventional batch to microwave did not prove to be beneficial and major decomposition was observed, when reaction carried out in xylene. Slightly better results were obtained when the reaction was performed neat, however, indications of decomposition were still noticeable (Scheme 106, Table, entries 1-3).

It was then hypothesized that starting material is not compatible with the harsh reaction conditions and therefore, either temperature needs be lowered or system has to be somehow activated. Activation of the alkynes is known to be carried out with Lewis acids such as gold or platinum. Besides that, iodine was reported to facilitate the activation of the triple bond as well. Coordination to the acetylene leads to the lowering of the LUMO orbital energy of the dienophile, thus such activation is only useful under the assumption that Diels-Alder reaction takes place under the standard and not reverse electron demand.

Using platinum(II)chloride in either ethylene chloride or toluene at different temperatures (rt to 100°C) did not lead to either any conversion; at higher temperature complete loss of material was observed due to degradation. Results are summarized in the table in Scheme 106, entries 4-8). Exploiting gold (III)chloride or iodine resulted in decomposition of the material as well (entries 9-10).

Another attempt to avoid the decomposition of the material was decreasing of reaction temperature. Surprisingly, at 100 or 120°C formation of the desired product was suppressed and decomposition was more distinct (entries 11-12). Such an observation

eventually led to the assumption that the harsh conditions affect rather staring material than the product, and therefore, cyclization has to be carried out fast enough to avoid degradation of the educt. Thus, reaction was carried out at 180°C and indeed, marks of decompositions were minimalized and dominant peak in the GC/MS belonged to the desired product, which was isolated in acceptable 67% (entry 13).



154 **156**

Entry	Temperature (°C)	Mode of heating	Solvent	Catalyst	Time (h)	Conversion yield
1	160	conv.	xylene*	-	14	yes/decomp.
2	160	MW	xylene*	-	0.5	decomp.
3	160	MW	neat	-	0.5	yes/decomp.
4	rt	-	toluene	$PtCl_2$	14	no
5	50	conv.	toluene	$PtCl_2$	14	no
6	100	conv.	toluene	$PtCl_2$	14	decomp.
7	rt	-	CH_2Cl_2	$PtCl_2$	14	no
8	50	conv.	CH_2Cl_2	$PtCl_2$	14	no
9	rt	conv.	CH_2Cl_2	$AuCl_3$	14	decomp.
10	rt	-	CH_2Cl_2	I_2	14	decomp.
11	100	conv.	xylene*	-	14	decomp.
12	120	conv.	xylene*	-	14	decomp.
13	180	conv.	xylene*	-	14	yes (67%)

* degassed

Scheme 106

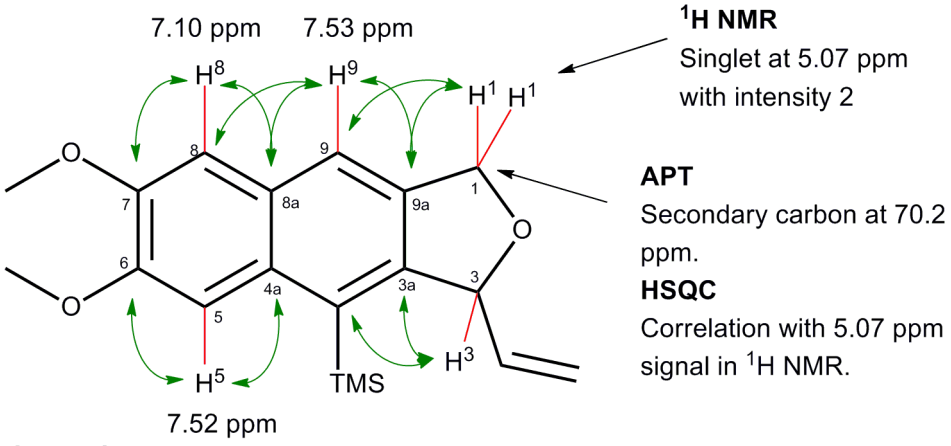
It was necessary to ensure the proper heating of the reaction mixture. Wheaton vial needed to be heated above the level of the solvents, in order to avoid the cooling of the reaction mixture be ambient air. Cooling by the air was sufficient to negatively influence the reaction outcome.

Structure of the product of cyclization was determined using various NMR techniques. Besides the ^{1}H NMR, APT, HSQC and HMBC spectra were recorded. Assignments were based on the assumption that singlet at 5.07 ppm in ^{1}H NMR spectra with intensity 2 belong to the protons H1 and carbon signal at 70.2 ppm in APT spectra with negative amplitude belong to the carbon C1 (Scheme 107). Such assumption was based on a chemical shift and multiplicity of the signals and was strengthened from evaluation of HSQC spectrum, where correlation between these two signals was found. Further, in HMBC spectra,

correlation between signal ofH1 and tertiary carbon signal at 120.2 ppm proved that signal belong to carbon C9. HSQC spectrum revealed that signal at 7.53 ppm in ^{1}H NMR spectrum belong to proton H9, as correlation between signals as 120.2 and 7.53 ppm was found. Lack of correlation between signal at 7.53 with carbons C6 and C7 (whereas two other aromatic carbons show such correlations) confirms this assignment. Carbon C8 could be assigned from HMBC spectra, where correlation with proton H9 is found. Signal occurs with chemical shift of 107.4 pm and in HSQC spectrum correlates with signal at 7.10 ppm confirming it to belong to proton H8. In ^{1}H NMR spectra, last signal in aromatic region with the shift of 7.52 ppm can be assigned to H5.

Assignment of quaternary carbons (determined from APT) was based on correlations in HMBC spectra. Carbon C9a was confirmed to have a signal at 144.5 ppm as correlations with both H9 and H1 was found. Both protons H8 and H9 correlate with signal at 132.7 ppm, indicating that the signal belong to the carbon C8a. Correlation between proton H5 and signal at 128.6 determined this signal to belong to carbon C4a. Correlation between proton H3 and signal of quartenary carbon at 136.0 identifies the signal to belong to carbon C3a, there is also correlation found with proton H1. Weak correlation between H3 and signal at 128.6 indicates this signal to belong to carbon C4.

Eventhough the resolution of the signals of carbons C6 and C7 is not optimal in 2D HMBC spectrum, one can still judge that signal of proton H5 correlates with the signal at 148.5 ppm (C6) and signal of proton H8 correlates with signal at 148.8 ppm, indicating that signal belongs to carbon C7. No clear judgment can be made about signals of methoxy groups, since in APT spectrum only one signal for both groups appears and resolution of the proton signals in HMBC is not good enough to make any conclusions.



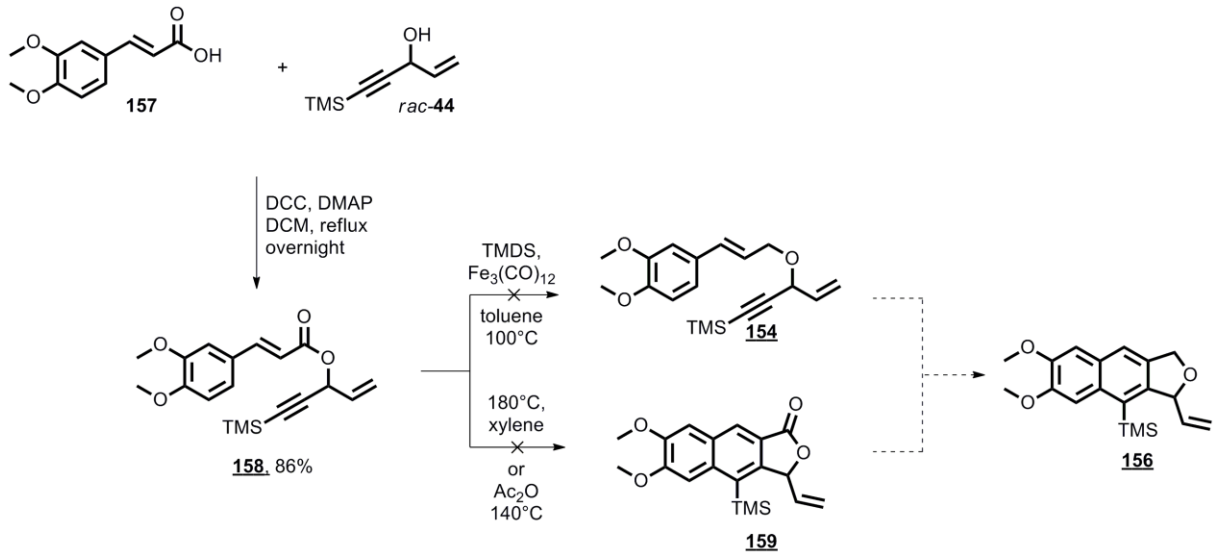
Legend:
Red bondings depicts correlation in HSQC between linked nuclei
Green arrow depicts correlation in HMBC spectra

Scheme 107

F III.3.2 Attempts to circumvent the direct ether bond formation

After successfully establishing the critical cyclization step, ether formation within the previous step was revisited and new strategies were developed to avoid problems as encountered for the synthesis of compound **154**. The novel approach relied on the less problematic formation of the ester instead of ether and consecutive reduction to ether, which would be followed up by the cyclization. Alternatively, ether can be cyclized first to the lactone and then reduced to the cyclic ether.

Formation of the ester proceeded without problems, yielding ester **158** in 86% (7% of protodesilylated ester was isolated as well). Compound **158** was then subjected to reduction conditions reported by Das *et* al.[91] Under such conditions, various esters can undergo reduction to the corresponding ether. However, reduction of α,β-unsaturated esters was not reported. **158** remained untouched in the reaction mixture. Second strategy proved to fail as well: Exposing ester **158** to 180°C in degassed xylene led to negligible conversion in 14 hours. Extending the reaction time led only to the decomposition of the material. Applying the conditions of Park, 140°C in acetic anhydride did not afford the lactone either. Consequently, further exploitation of alternative routes was abandoned.

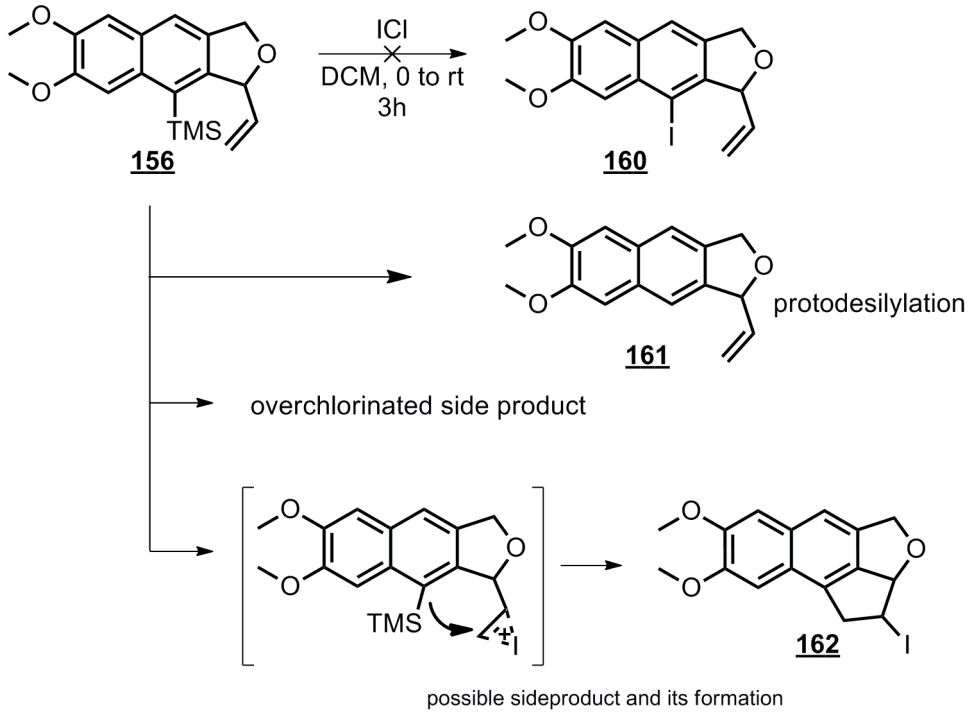


Scheme 108

F III.3.3 Halodesilylation

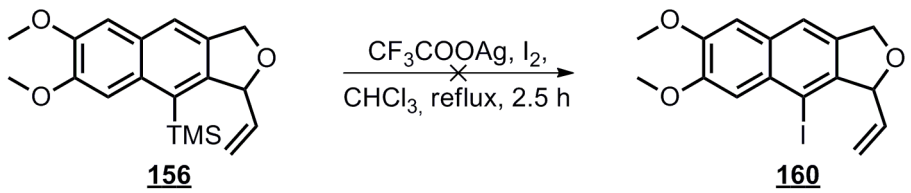
Next step was a conversion of TMS group into bromine or iodine as halide capable of cross-coupling. Standard iododesilylation reaction is carried out with iodine monochloride. However, treatment of compound **156** with ICl did not lead to the desired transformation, probably due to the presence of the double bond. Besides the compound with the mass corresponding to the overchlorinated product (possibly chlorination of the double bond occurs during the reaction) and protodesilylated compound, product with the corresponding

mass was detected as well. After column chromatography several fractions were isolated from which the one containing the molecule of the right mass was isolated in 20% yield and analyzed by ^{1}H NMR spectroscopy. Surprisingly, ^{1}H NMR revealed the absence of the olefinic signals and additional signals with the intensity of two and chemical shift of 4.17 ppm to 4.41 ppm. Such spectrum could correspond to the side product **162** (Scheme 109) which could be possibly formed by activation of the double bond with iodine and subsequent nucleophilic attack of the activated double bond by the carbon bearing the TMS group. However, such reaction is unprecedented, structure was not further elucidated and side reaction was not further investigated.



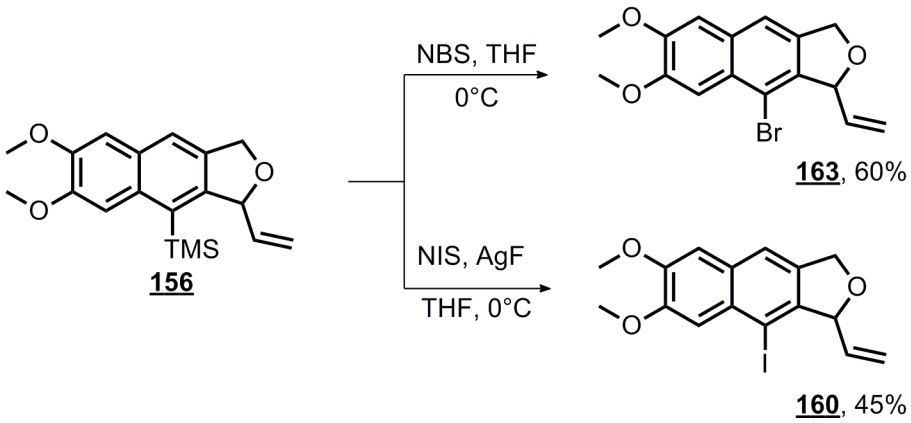
Scheme 109

Within another attempt iodine and silver acetate were employed in the iodination step to facilitate the leaving of the TMS group. Judging from the crude ^{1}H NMR, TMS was cleaved but absence of the olefinic signals (and absence of the signals discussed above) suggests iodination of the double bond.



Scheme 110

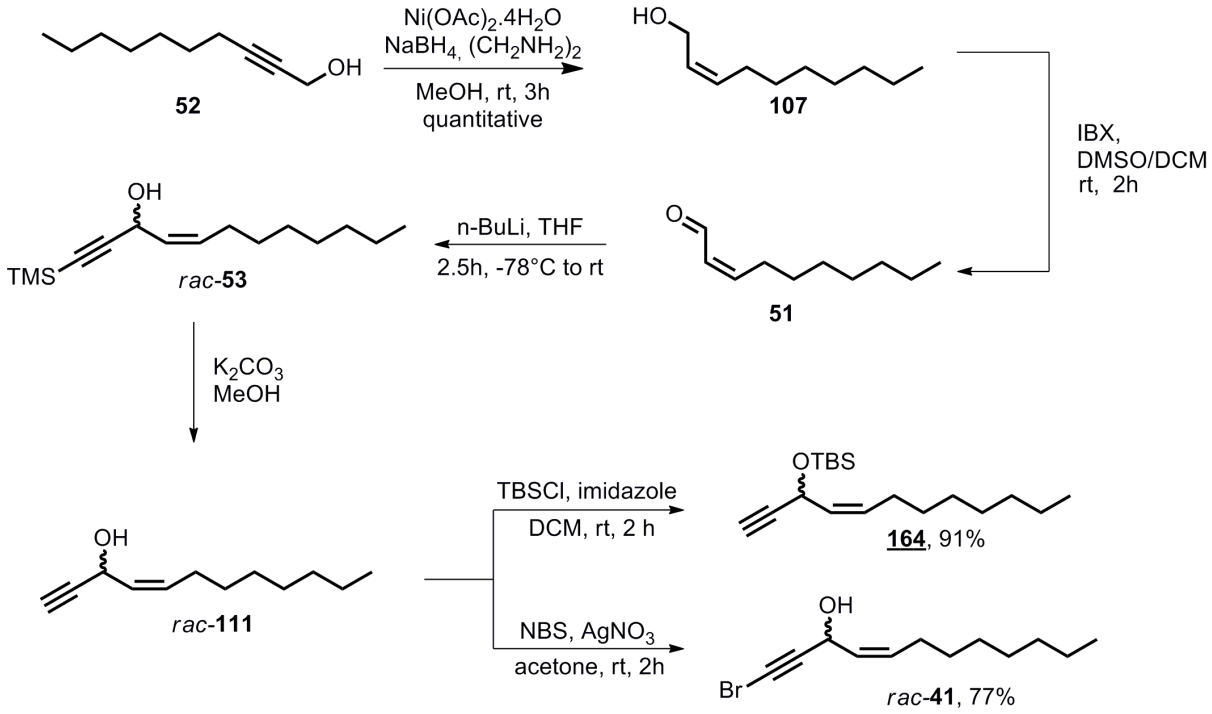
Successful attempt to introduce halides were performed with NBS or NIS for introduction bromine or iodine, respectively. Utilization of NBS furnished compound **163** as desired aryl bromide in 60% yield. Treatment of **156** with NIS in the presence of AgF salt afforded corresponding aryl iodide **160** in 45%. However, iodination with the NIS turned out to be rather irreproducible, most likely as a consequence of the decomposition of silver fluoride. Due to the time limitation, reaction was not further investigated.



Scheme 111

F III.4 Synthesis of the aliphatic alcohol

Synthesis of the aliphatic alcohol was carried out as described in the previous chapters. Only difference is that alcohol was used as racemic mixture, for the optimization of the final coupling. If required, alcohol was also protected with TBS protecting group, subjecting to the illation conditions (TBSCl, DCM, imidazole), yielding 91% of product **164** or subjected to further modifications as for instance bromination of the acetylene with NBS in the presence of silver nitrate, yielding 77% of brominated alkyne *rac*-**41**.

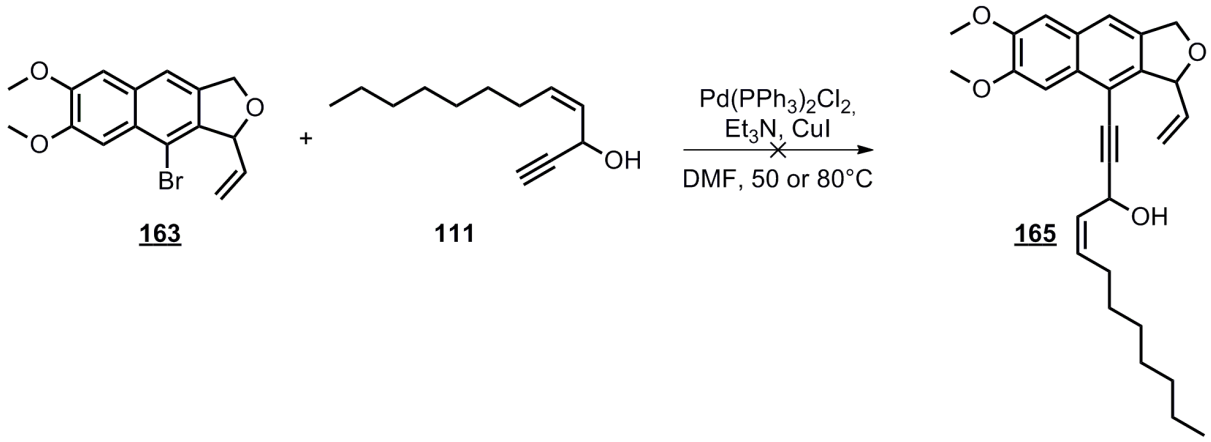


Scheme 112

F III.5 Final coupling

F III.5.1 Sonogashira coupling

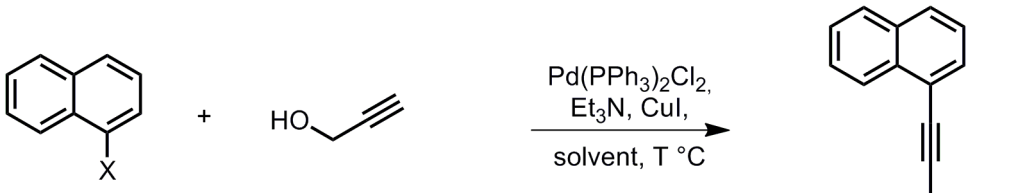
Aryl bromide **163** and aliphatic alcohol **111**, containing terminal acetylene were subjected to the Sonogashira conditions. Reaction was carried out at two different temperatures. At 50 °C, GC/MS analysis revealed the presence of the aryl bromide, indicating no conversion. Similar conclusion can be withdrawn from ^{1}H NMR, where starting aryl bromide was found to be present. At 80°C, crude ^{1}H NMR revealed decomposition of the material. In both cases there was not any alkyne detected in the reaction mixture.



163 **111** **165**

Scheme 113

After initial unsuccessful attempts, it was decided to reinvestigate reaction conditions. Due to limited amount of the material in hands, model substrate was chosen, consisting of 1-bromonaphthalene **166** and propargyl alcohol **167**, compounds having similar structural features in the close proximity to the reaction center . Reactions were monitored by means of TLC and GC/MS analysis with dodecane as internal standard for comparison of relative conversion/consumption of the product, respectively starting material, however, analysis of results was complicated due to the broad indistinct signal of the product in the GC/MS spectra. Under the tested conditions full consumption was never achieved. Firstly, attention was focused on the reaction temperature. In DMF reaction proceeded only at 80°C. Two reactions were tested, one with ratio of copper and palladium catalyst 1:1 and second with the double amount of palladium (Scheme 114, Table, entries 1-2). As expected, higher catalytic load led to the higher formation of the product. At 50°C and room temperature there was not conversion observed at all (entries 3-4). Similarly, no conversion was observed at room temperature or 50°C, when THF was used as a solvent (entries 5-6). Performing reaction in triethylamine as a solvent led to the best results (entries 7-9). Even though, at ambient temperature, any conversion was observed as well, at 50°C formation of the product was detected as well as at 80°C.



166a, X = Br
166b, X = I

167

168

Entry	Ar-X	Solvent	Pd load	Cu load	Temperature	Conversion
1	**166a**	DMF	5 mol%	5 mol%	80°C	yes
2	**166a**	DMF	10 mol%	5 mol%	80°C	yes
3	**166a**	DMF	5 mol%	5 mol%	50°C	no
4	**166a**	DMF	5 mol%	5 mol%	ambient	no
5	**166a**	THF	5 mol%	5 mol%	ambient	no
6	**166a**	THF	5 mol%	5 mol%	50°C	no
7	**166a**	Et_3N	5 mol%	5 mol%	ambient	no
8	**166a**	Et_3N	5 mol%	5 mol%	50°C	yes
9	**166a**	Et_3N	5 mol%	5 mol%	80°C	yes
10	**166b**	Et_3N	5 mol%	5 mol%	80°C	yes

Scheme 114

Considering that best results were obtained when the reaction was conducted in the organic base, several bases were further tested. Nevertheless, reaction in Hunig's base, pyridine, piperidine or pyrrolidine did not proceed. For comparison, reactions were also carried out in THF using the same bases. There were traces of the product detected when using piperidine and pyrrolidine as a base.

166

167

168

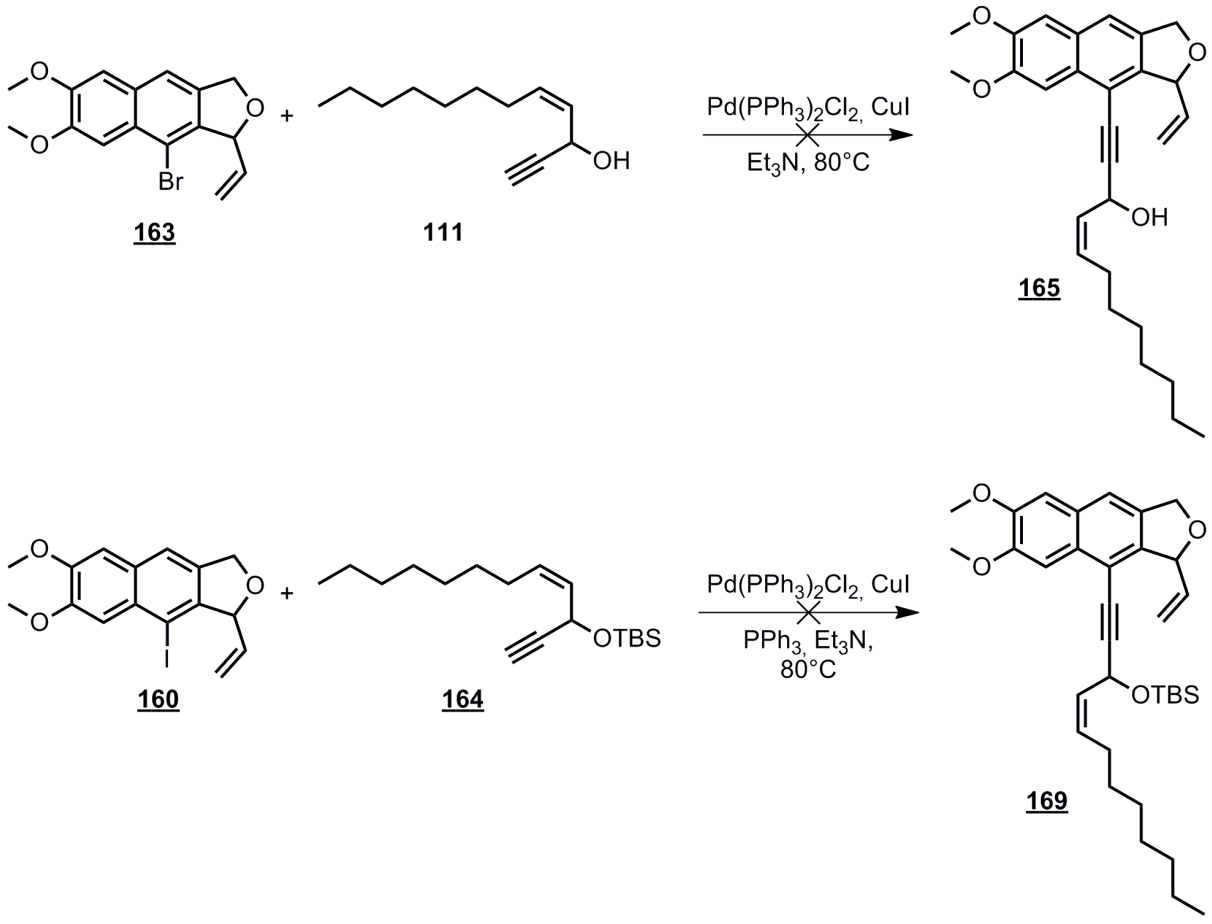
Entry	Solvent	Base	Cnversion
1	-	Hunig base	no
2	-	Pyridine	no
3	-	Piperidine	no
4	-	Pyrolidine	no
5	THF	Hunig base	no
6	THF	Pyridine	no
7	THF	Piperidine	traces
8	THF	Pyrolidine	traces

Scheme 115

Naphthalene bromide was then replaced with naphthalene iodide. In the reaction with propargyl alcohol, performed in the triehylamine as solvent at 50°C, so far best result

was achieved, as judged from GC/MS spectra with dodecane as internal standard, even though, still, full conversion was not achieved.

Conditions providing best results of the screening were then applied on the reaction between aromatic bromide **163** and alkyne **111**. Additionally, aromatic iodide **160** was employed in the reaction with **164**. Both reactions provided comparable outcome. TLC analysis revealed full consumption of the both educts and new spot was present at the TLC plate. Reaction mixture was analyzed by several available analytical tools as for instance GC/MS or LC/MS. However, any of the analysis did not turn out to be conclusive. There was not a peak in GC/MS spectra, which would correspond to the final product. LC/MS analysis provided similar results. Nevertheless, problem with ionizability might be an issue complicating the analysis. Therefore it was decided to isolate the newly formed spot and analyze it.



163 **111** **165**

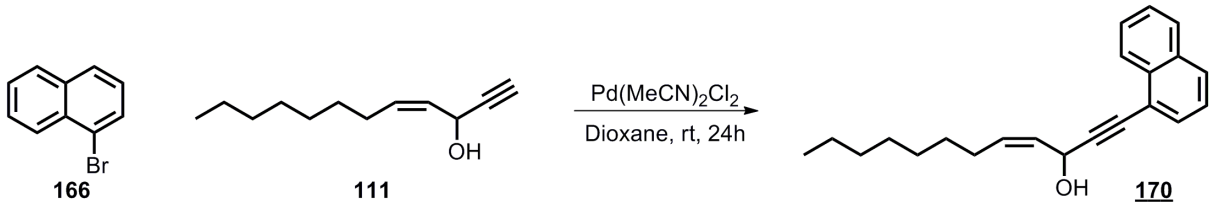
160 **164** **169**

Scheme 116

However, after isolation, only small quantity of the material were recovered in both cases, corresponding to poor 19% and 17% (aryl bromide and aryl iodide precursors, respectively) of the theoretical yield. Moreover, ^{1}H NMR spectrum did not seem to belong to single compound. Number of aromatic protons, number of olephinic protons and the

protons with higher chemical shift (in the region between 5 and 6 ppm) corresponded with number of protons in the final product (also theoretical chemical shift would agree), nevertheless, intensity of the signals in the aliphatic region was disproportionately higher than it would be expected, indicating the contamination of the product with aliphatic impurity. Thus, presence of the desired product could not be excluded, but it could not be confirmed either.

It was then hypothesized that high temperature can actually lead to the degradation of the starting alkyne, since it was never detected back in the reaction mixture. Therefore, several attempts were taken to carry out the Sonogashira coupling at room temperature. Some protocols were described, utilizing various bulky ligands (see the table) and $Pd(MeCN)_2Cl_2$ as a palladium source. Application of such reaction conditions on the model reaction between naphthalene bromide and alkyne **166** however did not lead to any conversion as confirmed by TLC.



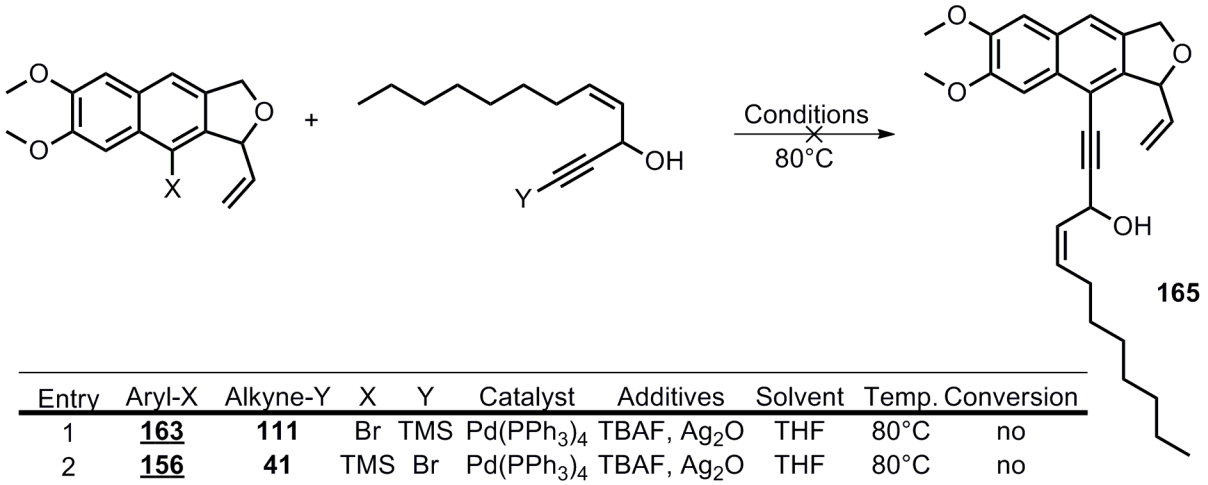
166 **111** **170**

Entry	Ligand	Base	Additive	Conversion (TLC)
1	XPhos	Cs_2CO_3	-	no
2	*t*-BuPhos	Cs_2CO_3	-	no
3	*t*-$Bu_3PH.BF_4$	Cs_2CO_3	-	no
4	Cy_3P	Cs_2CO_3	-	no
5	XPhos	DIPA	CuI	no
6	*t*-BuPhos	DIPA	CuI	no
7	*t*-$Bu_3PH.BF_4$	DIPA	CuI	no
8	Cy_3P	DIPA	CuI	no

Scheme 117

F III.5.2 Alternative cross-coupling

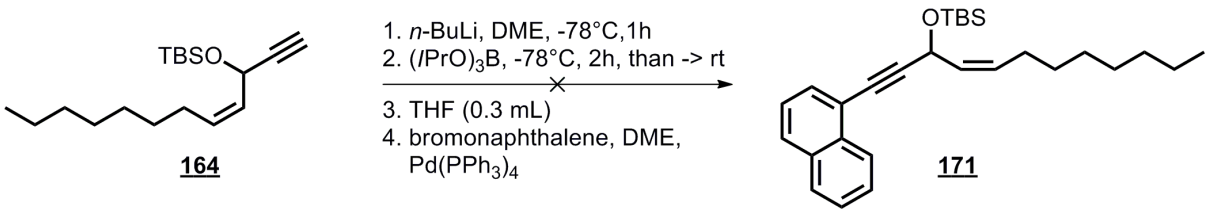
After failed attempts of Sonogashira coupling, several different, known cross-coupling reactions were performed as well. First, Hiyama coupling was investigated.[92] Here, both possible variations were tested, where bromine was either at the aromatic moiety and TMS group was introduced into the alkyne (Scheme 118, entry 1) or vice versa (entry 2). In both cases conversion was not observed, according to TLC and GC/MS analysis.



Entry	Aryl-X	Alkyne-Y	X	Y	Catalyst	Additives	Solvent	Temp.	Conversion
1	**163**	**111**	Br	TMS	$Pd(PPh_3)_4$	TBAF, Ag_2O	THF	80°C	no
2	**156**	**41**	TMS	Br	$Pd(PPh_3)_4$	TBAF, Ag_2O	THF	80°C	no

Scheme 118

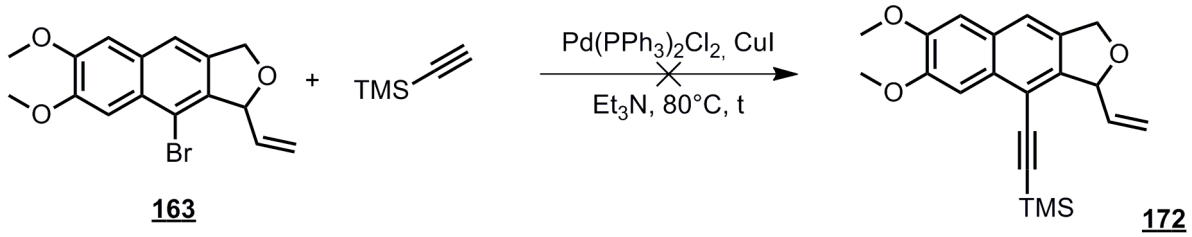
Next, Suzuki coupling of *in situ* formed alkynyl borate[93] with bromonaphthalene **166** was tested, however, without success as well. LC/MS analysis did not reveal any conversion towards the desired product.



Scheme 119

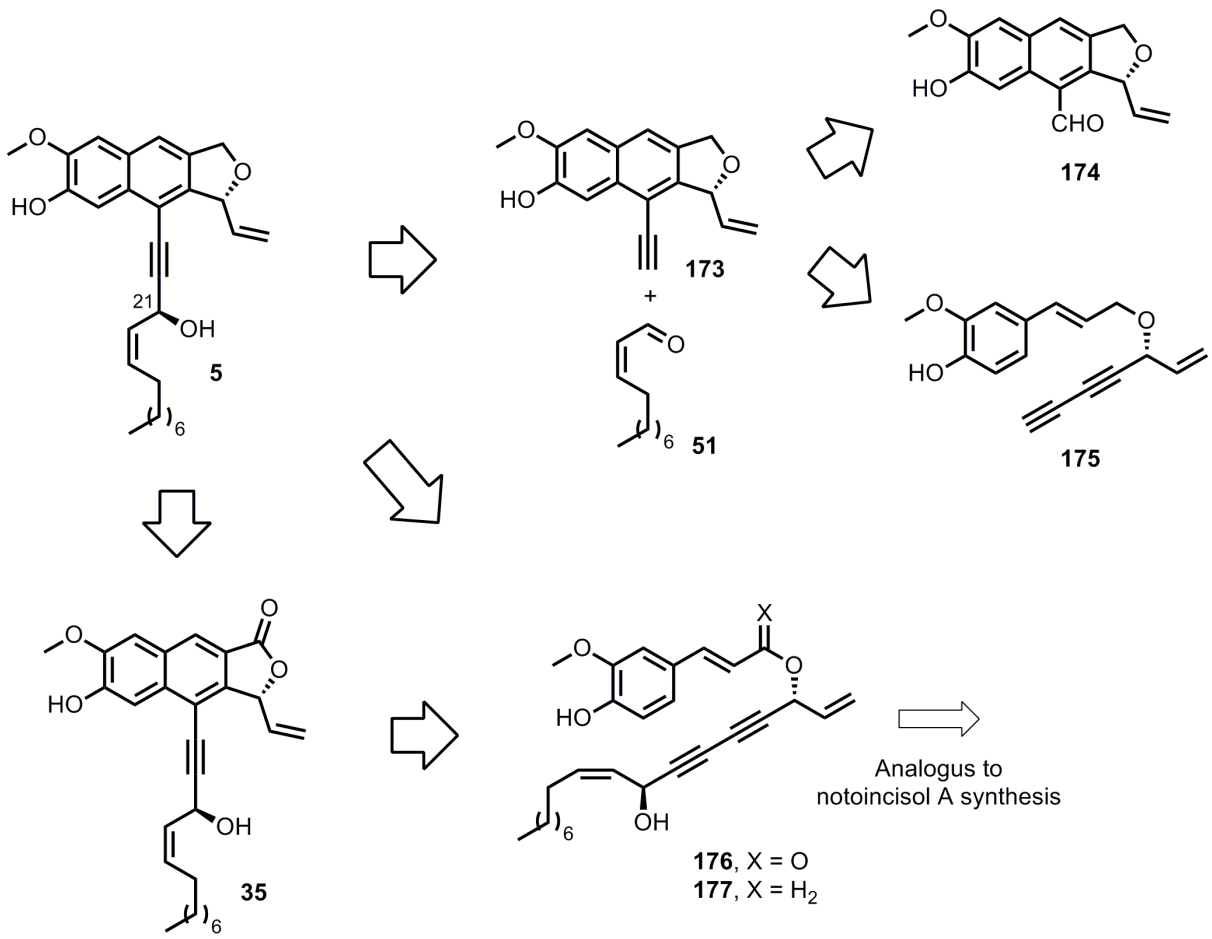
F III.6 Outline of possible alternative approaches

Since cross-coupling strategy for the last step of the sequence towards Notoincisol B failed, alternative approaches are outlined below. Two main strategies are depicted. Retrosynthetic disconnection between alkyne and aromatic ring is avoided in both alternatives. In the first alternative pathway, retrosynthetic disconnection would take place between the alkyne and tertiary carbon-21. Such disconnection would lead to α,β-unsaturated aldehyde **51** and aromatic part with the alkyne already incorporated. Introduction of the alkyne can be mediated either by coupling of **163** with TMS-acetylene and subsequent protodesylilation or by Corey-Fuchs reaction, starting from corresponding aldehyde. Along this line, coupling of aryl bromide **163** with TMS acetylene at above discussed conditions (F II 5.1.) was performed, however without any conversion of the starting material, as confirmed by TLC and GC/MS analysis. Another option would be cyclization of the bisalkyne species, as depicted in the Scheme 121. Aldehyde **174** could be synthesized either from aryl halide by lithiation and treatment with carbonyl source, as for instance DMF, or *via* metal assisted carbonylation. Second option would be a thermal cyclization, similar to discussed in the section F III 3.1, having ester functionality instead of TMS group, and subsequent reduction. Synthesis if bisalkyne **175** could again take an advantage of Cadiot-Chodkiewitz reaction.



163 **172**

Scheme 120



Scheme 121

Second outlined strategy is inspired by proposed biosynthesis of Notoincisol B[2] and relies on cyclization of the ester **176** or ether **177**. Compound **176** is an isomer of Notoincisol A, bearing ferulic acid in the position 3 instead of 8. Therefore, same chemistry as in case of Notoincisol A can be applied, but with the reverse protection group strategy. Hydroxyl group in position 8 would have to be protected, in order to ensure correct regioselectivity.

G Conclusion and perspective

In the first part of the thesis, synthesis, biological evaluation and selectivity profile of new derivatives of natural products Magnolol and Honokiol are discussed. Simple synthetic methodology was developed to achieve novel derivatives, which consists of two consecutive metal assisted cross coupling reaction steps. In the first step, allyl moiety is regioselectively introduced into position 4 of 4-bromo-2-chlorophenol. In the second step, arylboronic acid decorated with the substitution of interest is introduced.

Synthesized derivatives were evaluated for their biological performance at $GABA_A$ receptors as well as for their potential anti-inflammatory activity, mediated by an interaction with various nuclear transcription factors, involved in the physiology of inflammation.

Several derivatives were found to have an influence on some of the investigated targets. Moreover, it was demonstrated that substitution pattern of aromatic ring B of the novel derivatives plays a crucial role for selectivity of the new compounds. Compound bearing methoxy substituent in position para of the aromatic ring B was found to be selective for modulation of $GAGA_A$ receptors. Additionally, subtype selectivity of the compound for most abundant $\alpha1\beta2\gamma2$ subtype over $\alpha1\beta1\gamma2$ subtype was observed. Such a property is thought to avoid the undesired ataxic effect and compounds non acting at $\beta1$ are considered as non-sedative, which is a desirable property for anxiolitic or antiepileptic drug.

Compounds bearing nitro and methyl substituents in meta and para position were found to be selective RXRα agonists, with no or little effect on $GABA_A$ receptors.

Compounds with methoxy and methoxycarbonyl substituents in position meta were found to have an effect on both investigated targets.

None of the synthetic derivatives did show any effect on PPARγ, LXRα and LXRβ receptors.

The value of the results consists of the simplification of the targeted compounds compared to the lead structures or synthetic derivatives published before, and yet improving the pharmacological properties.

In the second part of this thesis, synthesis of new natural products Notoincisol A and Notoincisol B, or the progress within, is described. Synthesis of Notoincisol A was achieved, together with all possible three stereoisomers of the natural product. Stereochemistry of the natural product was then confirmed by means of comparison of optical rotation of synthetic compounds and isolated natural product, confirming absolute configuration to be *3R*,*8S*. At the time of the writing of the thesis, compounds are being investigated for their biological effect at $GABA_A$ receptors, as well as at nuclear transcription factors.

Synthesis of Notoincisol B was not finalized at the time of the writing of this thesis. Synthetic strategy was, however, developed to an advanced stage on the model substrate.

There are many options for further investigation of the Magnolol derivatives, in particular at $GABA_A$ receptors, where certain trends supporting the effect of the compounds were observed. It would be definitely of the interest to investigate the influence of the substitution of the aromatic ring A.

With the standing synthesis of Notoincisol A, new possibility arises for preparing derivatives for structural activity relationship investigation, if the compound or any of the synthesized stereoisomers show a promising effect on either $GABA_A$ receptor or any of the nuclear transcription factors.

The synthesis of Notoincisol B needs to be finalized. Several suggestions were outlined in the result and discussion part, avoiding the problematic step in the currently investigated strategy.

H Experimental part

H I Materials and methods – chemical synthesis

Unless noted otherwise, all reagents were purchased from commercial suppliers and used without further purification.

Microwave reactions were carried out in a BIOTAGE® Initiator sixty.

GC/MS spectra were measured on a Thermo Finnigan system: GC: Focus GC with a BGB5 column (l = 30 m, d_i = 0.25 mm, 0.25 μm film), MS: DSQ II with quadrupol (EI) – Instrument I or Thermo Ion Trap ITQ 100: Trace ultra with PTV with a BGB-5 column, MS: Ion trap detector (EI and CI).- Instrument II.

For thin layer chromatography, aluminium backed silica gel 60 F254 (Merck) was used.

Medium pressure liquid chromatography was performed on a Büchi Sepacore™ Flash System. Pump-System: 2x Büchi Pump Module C-605, Büchi Pump Manager C-615; detector: Büchi UV Photometer C-635; fraction collector: Büchi Fraction Collector C-660 or standard manual glass columns using silica gel from Merck (40-63 μm)

^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker AC 200 (200 MHz) or a Bruker Avance 400 (400MHz) spectrometer using $CDCl_3$ as solvent. An assignment of the signals was based on correlation experiments or software prediction. Ambiguous assignment is marked with an asterisk.

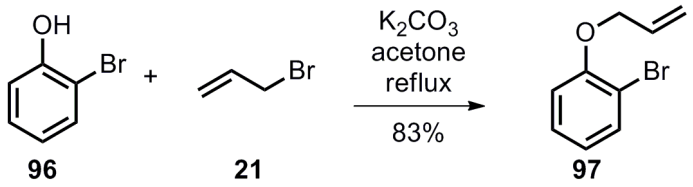
Melting points were recorded on a Büchi B-545 melting point apparatus. HRMS were measured at Shimadzu HPLC-IT-TOF mass spectrometer with either APCI or ESI ionization method.

Optical purity was determined by Thermo Scientific/HPLC Ultimate 3000 HPLC with DAD and IR detectors, using chiralpack® I.A column with 99.9:0.1 heptane/isopropanol solvent mixture and 0.8 mL/min flowrate.

Specific rotation was measured on an Anton Paar MCP500 polarimeter at the specified conditions.

H II Synthesis of Magnolol derivatives

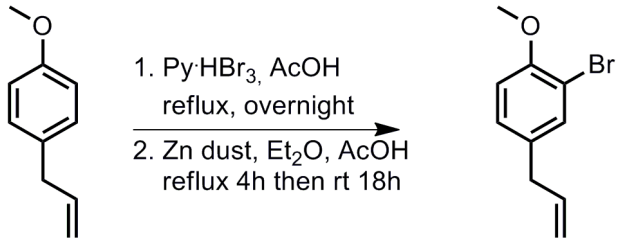
H II.1 1-allyloxy-2-bromobenzene **97**



96 **21** **97**

Procedure	Potassium carbonate (877 mg, 6.36 mmol) was added to a solution of **96** (1 g, 5.78 mmol) in acetone (15 mL) and **21** (832 mg, 6.94 mmol);the solution was heated to reflux for 18 h. The reaction was cooled to room temperature and H_2O (5 mL) was added. The reaction was stirred for a further 15 min before being diluted with CH_2Cl_2(20 mL), washed with brine (3x20 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography(petrol/EtOAc, 3:1) gave **7**as yellow oil.
Reaction scale	1 g (5.78 mmol)
Reaction time	overnight
Purification	Column chromatography
Yield	1.02g (83%)
Appearance	yellowish oil
Sum formula, m.w.	C_9H_9BrO, 213.07.g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 4.52 (d, *J* = 5.0, 2H, -C<u>H$_2$</u>-), 5.30 (d, *J* = 10.6 Hz, 1H, -CH=C<u>H$_2$</u>*cis*), 5.48 (d, *J* = 17.2 Hz, 1H, -CH=C<u>H$_2$</u>*trans*), 6.03-6.11 (m, 1H, -C<u>H</u>=CH$_2$), 6.82-6.90 (m, 2H, Ar-<u>H4</u> and Ar-<u>H6</u>), 7.27 (m, 2H, Ar-H5), 7.54 (d, *J* = 7.9 Hz, 1H, Ar-H3)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ = ^{13}C NMR ($CDCl_3$)δ =69.9 (t, -CH_2-), 112.5 (s, C2), 113.8 (d, C6), 118.1 (t, -CH=C<u>H$_2$</u>), 122.3 (d, C4), 128.7 (d, C5), 132.7* (d), 133.7* (d), 155.2 (s, C1)

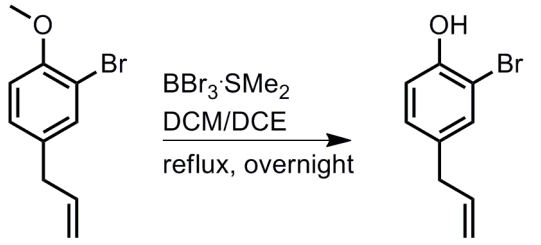
H II.2 4-Allyl-2-bromoanisol **16**



10 **16**, 53%

Procedure	4-Allylanisole **10** (5.0 g, 33.7 mmol) was dissolved in acetic acid (100mL) and to this solution pyridinium hydrobromide perbromide (30.2 g, 94.4 mmol) was added and the mixture was stirred overnight. Most of the acetic acid was removed in vacuo leaving a red oil that was taken up in toluene (100 ml), washed once with 50 ml water and three times with 50 ml saturated aqueous sodium bicarbonate solution, and finally dried over anhydrous sodium sulfate. Removal of the toluene in vacuo left pale yellow oil. Treatment of this oil in 80 ml diethylether with 5 g zinc dust and 3.4 ml of acetic acid under reflux for 4 h was followed by stirring at room temperature for 18 h. Mixture was washed once with 50 mL of water and two times with 50 mL of sodium bicarbonate and organic phase was dried over sodium sulfate and evaporated. Chromatography of the residue wit PE/EtOAc mixture provided the compound as colorless oil.
Reaction scale	5 g (33.7 mmol)
Reaction time	overnight then 22 hours
Purification	Column chromatography
Yield	4.06g (53%) yellowish oil
Formula, m.w.	C_9H_9BrO, 213.07 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = ^{1}H NMR ($CDCl_3$,): 3.32(d, 2H, *J*= 6.5 Hz, -C$\underline{H_2}$), 3.88 (s, 3H, -OC$\underline{H_3}$), 5.03-5.11 (m, -CH=C$\underline{H_2}$), 5.93-6.03 (m, 1H), 6.83 (d, 1H, *J* = 8.4 Hz, H5 or H6), 7.03 (m, 1H, H5 or H6), 7.39(s, 1H, H3)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ = ^{13}C NMR($CDCl_3$), 38.7 (t, -CH_2-), 56.3(q, -OCH_3), 111.7 (d, C6), 112.1 (t), 116.0 (t, -CH=CH_2), 128.5 (s, C2), 133.4 (d, C3), 133.8 (s, C4), 137.0 (d, -CH=CH_2), 154.4 (s, C1)

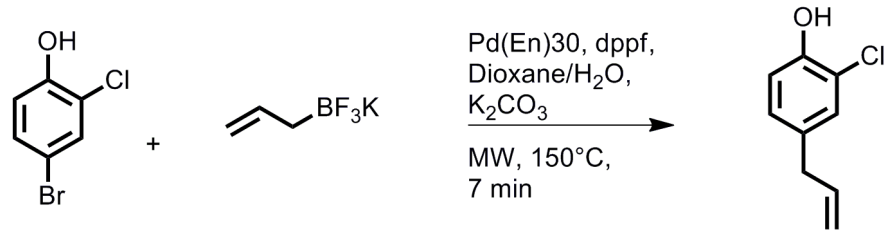
H II.3 4-Allyl-2-bromophenol **93**



16 **93**, 49%

Procedure	$BCl_3.SMe_2$ (8.6 g, 27.5 mmol in a 14 mL of CH_2Cl_2) was added to a solution of **16** (2.5 g, 11 mmol) in DCE (5 mL) and the mixture was heated to reflux for 18 h. The reaction was cooled to room temperature and H_2O (5 mL) was added. The reaction was stirred for a further 15 minutes before being diluted with CH_2Cl_2(20 mL), washed with brine (3x20 mL), dried over $MgSO_4$and concentrated in vacuo. Purification by flash chromatography(PE/EtOAc, 3:1) gave **3**.
Reaction scale	2.5 g (11 mmol)
Reaction time	overnight
Purification	Column chromatography
Yield	3.8 g (49%)
Appearance	yellowish oil
Sum formula, m.w.	C_9H_9BrO, 213.07.g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = ^{1}H NMR ($CDCl_3$) δ = 3.33 (2H, d, *J*= 7.0 Hz. –C<u>H</u>$_2$-), 5.13–5.08 (2H, m, -CH=C<u>H</u>$_2$), 5.45 (1H, s, -OH), 5.98–5.91 (1H, m, -C<u>H</u>=CH$_2$), 6.98 (1H, d,*J*= 8.5 Hz), 7.07 (1H, dd, *J*= 8.5 Hz ,*J*= 2.0 Hz), 7.31 (2H, d, *J* = 2 Hz),
^{13}C-NMR (400 MHz, $CDCl_3$)	δ = ^{13}C NMR ($CDCl_3$)δ =38.9 (t, -CH_2)-, 110.1 (s, C2), 115.9, (t, -CH=<u>C</u>H$_2$), 116.2, (d, C6), 129.39*(d), 131.8* (d), 133.7 (s, C4), 137.0 (-<u>C</u>H=CH$_2$), 150.6 (s, C1).

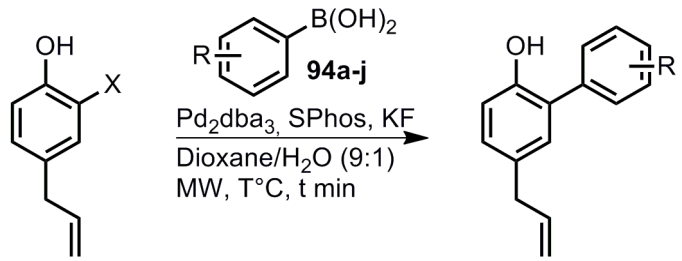
H II.4 4-Allyl-2-chlorophenol **101**



100 **102** **101**, 80%

Procedure	4-Bromo-2-chlorophenol **100** (1.5 g, 7.25 mmol) was charged into the microwavevial, together with potassium allyltriflouroborate (534.2 mg, 3.61 mmol), Pd(En)30^{TM} (300 mg, 0.05 equiv.), dppf (134 mg, 0.1 equiv.) and K_2CO_3 (667 mg, 14.5 mmol). A mixture of dioxane/water (9:1) was added (20 mL), the vial was flushed with argon and sealed. The reaction solution was heated to 150 °C for 7 minutes in a microwave oven (Biotage Initiator 60). After complete reaction the mixture was filtered through a pad of Celite, the solvent was evaporated under reduced pressure and compound **6** was purified *via* Kugelrohr distillation.
Reaction scale	1.5 g (7.25 mmol)
Reaction time	7 min
Purification	Kugelrohr distillation (0.1 bar, 100°C)
Yield	0.977 mg (80%) yellowish oil
Sum formula, m.w.	C_9H_9ClO, 168.62 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = δ 3.30 (d, *J* = 3.3 Hz, 2H, -C$\underline{H}_2$-), 5.02-5.10 (m, 2H, -CH=C$\underline{H}_2$), 5.42 (s, 1H, -O$\underline{H}$), 5.82-6.02 (m, 1H, -C$\underline{H}$=CH$_2$), 6.92-7.03 (m,2H, Ar-H*),7.15 (d, *J* = 7.1 Hz, 1H, Ar-H*)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ = δ 39.2 (t, -CH_2-), 116.2 (t, -CH=$\underline{C}H_2$), 116.3 (d, C6), 119.8 (s, C2), 128.7* (d), 129.0* (d), 133.4 (s, C4), 137.2 (d, -$\underline{C}$H=CH$_2$) and 149.7 (s, C1)

H II.5 Suzuki coupling general procedures



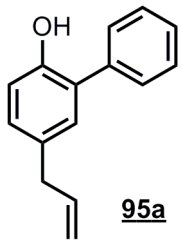
93, X= Br
101, X = Cl

95a-j

General procedure A 4-Allyl-2-bromophenol **3** (100 mg, 0.47 mmol) was charged into a microwave vial, together with potassium fluoride (67.2 mg, 1.17 mmol), Pd_2dba_3 (21.5 mg, 0.05 equiv.), SPhos (19.3 mg, 0.1 equiv.) and corresponding arylboronic acid (0.71 mmol, 1.5 equiv.). A dioxane/water mixture (9:1) was added (5 mL) and the *via*l was flushed with argon and sealed. The reaction mixture was irradiated with microwaves at 120 °C for 30 minutes. After completion of the reaction, the reaction solution was filtered through a pad of Celite, the solvent was evaporated under reduced pressure and the crude material was absorbed onto silica gel. Purification was carried out by column chromatography with silicagel/$AgNO_3$ doped silicagel (in serial connection of columns).

General procedure B Compound **6** (80 mg, 0.47 mmol) was charged into a microwave*via*l, together with potassium fluoride (67.2 mg, 1.17 mmol), Pd_2dba_3 (21.5 mg, 0.05 equiv.), SPhos (19.3 mg, 0.1 equiv.) and the corresponding boronic acid (0.71 mmol, 1.5 equiv.). A dioxane/water mixture (9:1) was added (5 mL) and the *via*l was flushed with argon and sealed. The reaction mixture was irradiated with microwaves at 150 °C for 10 minutes. After completion of the reaction, the reaction solution was filtered through a pad of Celite, the solvent was evaporated under reduced pressure and the crude material was absorbed onto silica gel. Purification was carried out by column chromatography using PE/EtOAc mixture (0-5% gradient if not stated differently).

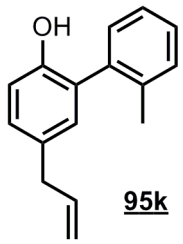
H II.6 4-Allyl-2-phenylphenol **95a**



95a

Procedure	Prepared according to the general procedure A or B with phenylboronic acid as coupling partner
Reaction scale	0.47 mmol (100 mg of **93** or 80 mg of **101**)
Reaction time	Method A: 30 min, Method B: 10 min
Purification	MPLC, PE/EtOAc 0-5% gradient, 9 g silica 60
Yield	Method A: Method B:55.3 mg (56%)
Appearance	colorless oil
Sum formula, m.w.	$C_{15}H_{14}O$, 210.27 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 3.37 (d, *J* = 6.7 Hz, 2H, -C$\underline{H}_2$-), 5.04-5.14 (m, 3H, -CH=C$\underline{H}_2$and -O$\underline{H}$), 5.88-6.05 (m, 1H, -C$\underline{H}$=CH$_2$), 6.90-6.95 (dd, *J* = 7.4 Hz and 1.3 Hz, 1H, Ar-H*), 7.07-7.11 (m,2H, Ar-H*), 7.38-7.50 (m, 5H, Ar-H*).
^{13}C-NMR (400 MHz, $CDCl_3$)	δ = 39.5 (t, -$\underline{C}$H$_2$-), 115.8 (t, -CH=$\underline{C}$H$_2$), 115.9 (d, C6), 128.0 (d, C4'), 128.1 (s, C2), 129.2 (2C, d, C2' and C6' or C3' and C5'), 129.3* (d), 129.4 (2C, d, C2' and C6' or C3' and C5'), 130.4* (d), 132.5 (s, C4), 137.3 (s, C1'), 137.9* (d) and 150.9 (s, C1)
GC/MS	Instrument I, method I Retention time: 8.41 min Main fragments: 210.10, 165.11, 153.07, 152.07, 133.06, 115.08, 89.09, 78.12, 77.08, 63.09, 51.04
HRMS	$[M+H]^+$*m*/*z*calcd 211.1117, found 211.1114

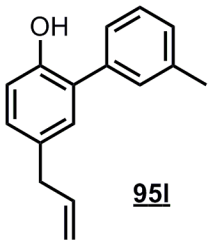
H II.7 4-Allyl-2-(2'-methylphenyl)phenol **95k**



95k

Procedure	Prepared according to the general procedure B with 2-methylphenylboronic acid as coupling partner
Reaction scale	0.47 mmol (100 mg of **93** or 80 mg of **101**)
Reaction time	10 min
Purification	MPLC, PE/EtOAc 0-5% gradient with addition of 2% Et_2N to the eluent, 9 g silica 60
Yield	36 mg (34%)
Appearance	yellowish oil
Sum formula, m.w.	$C_{16}H_{16}O$, 224.30 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 2.15 (s, 3H, C<u>H</u>$_3$), 3.33 (d, *J* = 6.7 Hz, 2H, -C<u>H</u>$_2$-), 5.00-5.10 (m, 2H, -CH=C<u>H</u>$_2$), 4.63 (s, 1H, -O<u>H</u>), 5.86-6.06 (m, 1H, -C<u>H</u>=CH$_2$), 6.88-6.91 (m, 2H, Ar-H*), 7.05-7.10 (dd, *J* =7.9 Hz and 2.1 Hz, 1H, Ar-H*), 7.20-7.31 (m, 4H, Ar-H*)
^{13}C-NMR (200 MHz, $CDCl_3$)	δ 19.9 (q, Ar-<u>C</u>H$_3$), 39.5 (t, -CH$_2$-), 115.3 (d, C6), 115.7 (t, -CH=<u>C</u>H$_2$), 126.6* (d), 127.7* (s, C2), 128.6* (d), 129.3* (d), 130.3* (d), 130.6* (d), 130.8* (d), 132.0* (s), 136.0* (s), 137.5* (s), 138.0 (d, -<u>C</u>H=CH$_2$), 150.9 (s, C1)
GC/MS	Instrument I, method I Retention time: 8.71 min Main fragments: 224.18, 223.18, 209.16, 195.15, 181.14, 165.13, 133.12
HRMS	$[M+H]^+$ *m/z* calcd 225.1274, found 225.1263

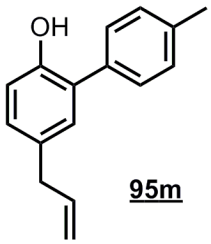
H II.8 4-Allyl-2-(3'-methylphenyl)phenol **95l**



95l

Procedure	Prepared according to the general procedure B with 3-methylphenylboronic acid as coupling partner
Reaction scale	0.47 mmol (100 mg of **93** or 80 mg of **101**)
Reaction time	10 min
Purification	MPLC, PE/EtOAc 0-5% gradient with addition of 2% Et_2N to the eluent, 9 g silica 60
Yield	41 mg (39%)
Appearance	yellowish oil
Sum formula, m.w.	$C_{16}H_{16}O$, 224.30 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 2.43 (s, 3H, -C<u>H</u>$_3$), 3.37 (d, *J* = 6.7 Hz, 2H, -C<u>H</u>$_2$-), 5.04-5.14 (m, 3H, -CH=C<u>H</u>$_2$ and -OH), 5.89-6.09 (m, 1H, -C<u>H</u>=CH$_2$), 6.90-6.94 (dd, *J* = 7.7 Hz and 0.7 Hz, 1H, Ar-H*), 7.06-7.11 (m, 2H, Ar-H*), 7.20-7.26 (m, 3H, Ar-H), 7.35-7.42 (m, 1H, Ar-H*)
^{13}C-NMR (200 MHz, $CDCl_3$)	δ 21.6 (q, Ar-CH_3), 39.6 (t, -CH_2-), 115.7 (t, -CH=<u>C</u>H$_2$), 115.8 (d, C6), 126.2* (d), 128.2 (s, C2), 128.8* (d), 129.3* (d), 129.3* (d), 129.9* (d), 130.3* (d), 132.4 (s, C4), 137.2 (s, C1'), 137.9 (d, -<u>C</u>H=CH$_2$), 139.2 (s, C3'), 150.9 (s, C6).
GC/MS	Instrument I, method I Retention time: 9.26 min Main fragments: 224.12, 223.08, 209.09, 181.08, 165.08, 152.08, 133.08, 115.06, 89.08, 77.05
HRMS	$[M+H]^+$ *m/z* calcd 225.1274, found 225.1264

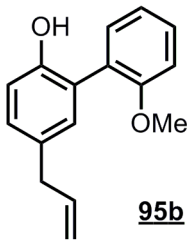
H II.9 4-Allyl-2-(4'-methylphenyl)phenol **95m**



95m

Procedure	Prepared according to the general procedure B with 4-methylphenylboronic acid as coupling partner
Reaction scale	0.47 mmol (100 mg of **93** or 80 mg of **101**)
Reaction time	10 min
Purification	MPLC, PE/EtOAc 0-5% gradient with addition of 2% Et_2N to the eluent, 9 g silica 60
Yield	48 mg (46%)
Appearance	yellowis oil
Sum formula, m.w.	$C_{16}H_{16}O$, 224.30 $g.mol^{-1}$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 2.43 (s, 3H, C<u>H</u>$_3$), 3.37 (d, *J* = 6.7 Hz, 2H, -C<u>H</u>$_2$-), 5.04-5.15 (m, 3H, -CH=C<u>H</u>$_2$ and -OH), 5.89-6.10 (m, 1H, -C<u>H</u>=CH_2), 6.90-6.95 (dd, *J* = 7.2 Hz and 1.5 Hz, 1H, Ar-H*), 7.07-7.11 (m, 2H, Ar-H*), 7.26-7.40 (m, 4H, Ar-H')
^{13}C-NMR (200 MHz, $CDCl_3$)	^{13}C-NMR (200 MHz, $CDCl_3$): δ 21.3 (q, Ar-CH_3), 39.5 (t, -CH_2-), 115.7 (t, -CH=CH_2), 115.8 (d, C6), 128.1 (s, C2), 129.0 (2C, d, C2' and C6' or C3' and C5'), 129.1* (d), 130.1 (2C, d, C2' and C6' or C3' and C5'), 130.4* (d), 132.4* (s), 134.3* (s), 137.8 (s, C1'), 137.9 (d, -<u>C</u>H=CH_2), 150.9 (s, C1).
GC/MS	Instrument I, method I Retention time: 9.26 min Main fragments: 224.11, 223.09, 209.10, 181.08, 165.08, 152.07, 133.07, 115.06, 89.08, 77.05
HRMS	$[M+H]^+$ *m/z* calcd 225.1274, found 225.1275

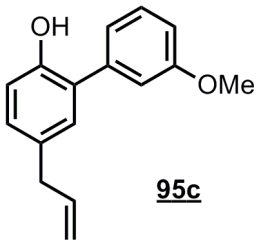
H II.10 4-Allyl-2-(2'-methoxylphenyl)phenol **95b**



95b

Procedure	Prepared according to the general procedure A or Bwith 2-methoxyphenylboronic acid as coupling partner
Reaction scale	0.47 mmol (100 mg of **93** or 80 mg of **101**)
Reaction time	Method A: 30 min, Method B: 10 min
Purification	Method A: MPLC, PE/EtOAc 0-5%, 9 g silica 60 Method B: MPLC, PE/EtOAc 0-5% gradient with addition of 2% Et_2N to the eluent, 9 g silica 60
Yield	Method A:35 mg (31%) Method B**:** 61 mg (54%)
Appearance	yellowish oil
Sum formula, m.w.	$C_{16}H_{16}O_2$, 240.30 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 3.39 (d, *J* = 6.7 Hz, 2H, -C$\underline{H_2}$-), 3.91 (s, 3H, OC$\underline{H_3}$), 5.04-5.15 (m, 2H, -CH=C$\underline{H_2}$), 5.90-6.10 (m, 1H, -C$\underline{H}$=CH_2), 6.17 (s, 1H, -O$\underline{H}$), 6.97 (d, *J* = 8.2 Hz, 1H, Ar-H6), 7.03-7.16 (m, 4H, Ar-H*), 7.33-7.44 (m, 2H, Ar-H*);
^{13}C-NMR (50 MHz, $CDCl_3$)	δ 39.6 (t, -CH_2-), 56.3 (q, -OCH_3), 111.6 (d, C6), 115.7 (t, -CH=$\underline{C}H_2$), 117.6 (d, C3'), 122.4 (d, C5'), 126.3* (s), 127.4* (s), 129.4* (d), 129.5* (d), 131.4* (d), 132.6* (s), 132.6 (d), 137.9 (d), 152.2 (s, C1), 155.6 (s, C2')
GC/MS	Instrument I, method I Retention time: 10.27 min Main fragments: 240.06, 207.02, 197.03, 181.05
HRMS	HRMS $[M+H]^+$*m/z* calcd 241.1223, found 241.1213

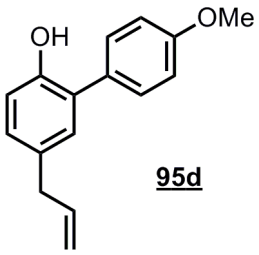
H II.11 4-Allyl-2-(3'-methoxylphenyl)phenol **95c**



95c

Procedure	Prepared according to the general procedure A or Bwith 3-methoxyphenylboronic acid as coupling partner
Reaction scale	0.47 mmol (100 mg of **93** or 80 mg of **101**)
Reaction time	Method A: 30 min, Method B: 10 min
Purification	Method A: MPLC, PE/EtOAc 0-5%, 9 g silica 60 Method B: MPLC, PE/EtOAc 0-5% gradient with addition of 2% Et_2N to the eluent, 9 g silica 60
Yield	Method A: 40 mg (35%) Method B: 54 mg (48%)
Appearance	yellowish oil
Sum formula, m.w.	$C_{16}H_{16}O_2$, 240.30 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 3.36 (d, *J* = 6.7 Hz, 2H, -C$\underline{H_2}$-), 3.84 (s, 3H, OC$\underline{H_3}$), 5.03-5.13 (m, 2H, -CH=C$\underline{H_2}$),5.20 (s, 1H, -O$\underline{H}$), 5.87-6.07 (m, 1H, -C$\underline{H}$=CH_2), 6.89-7.10 (m, 6H, Ar-H*), 7.35-7.43 (at, 1H, Ar-H*);
^{13}C-NMR (200 MHz, $CDCl_3$)	δ 39.5 (t. -CH_2-), 55.5 (q, -OCH_3), 113.7* (d,), 114.7* (d), 115.8* (t), 115.9* (d), 121.3* (d), 127.9 (s, C2), 129.4* (d), 130.2* (d), 130.5* (d), 132.4 (s, C4), 137.8 (d, -$\underline{C}$H=CH_2), 138.7 (s, C1'), 150.9 (s, C1), 160.4 (s, C3')
GC/MS	Instrument I, method I Retention time: 9.74 min Main fragments: 240.06, 225.04, 197.05, 181.04, 165.06, 152.05, 133.05 115.08, 76.98
HRMS	HRMS $[M+H]^+$*m/z* calcd 241.1223, found 241.1216

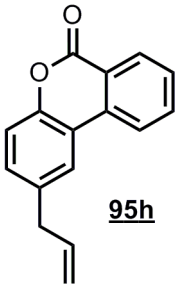
H II.12 4-Allyl-2-(4'-methoxylphenyl)phenol **95d**



95d

Procedure	Prepared according to the general procedure A or Bwith 4-methoxyphenylboronic acid as coupling partner
Reaction scale	0.47 mmol (100 mg of **93** or 80 mg of **101**)
Reaction time	Method A: 30 min, Method B: 10 min
Purification	Method A: MPLC, PE/EtOAc 0-5%, 9 g silica 60 Method B: MPLC, PE/EtOAc 0-5% gradient with addition of 2% Et_2N to the eluent, 9 g silica 60
Yield	Method A: 52 mg (46%) Method B: 38 mg (34%)
Appearance	yellowish oil
Sum formula, m.w.	$C_{16}H_{16}O_2$, 240.30 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 3.36 (d, *J* = 6.7 Hz, 2H, -C<u>H</u>$_2$-), 3.86 (s, 3H, -C<u>H</u>$_3$), 5.04-5.14 (m, 3H, -CH=C<u>H</u>$_2$ and - O<u>H</u>), 5.89-6.09 (m, 1H, -C<u>H</u>=CH$_2$), 6.89-7.09 (m, 5H, Ar-H*), 7.36-7.44 (m, 2H, Ar-H*);
^{13}C-NMR (200 MHz, $CDCl_3$)	δ 39.5 (t, -CH_2-), 55.5 (q, -OCH_3), 114.8 (2C, d, C3' and C5'), 115.7 (t, -CH=CH_2), 115.8 (d, C6), 127.8 (s, C2), 128.9* (d), 129.5 (s, C1*), 130.4 (3C, d, C2' and C6' and *), 132.4 (s, C4), 137.9 (d, -<u>C</u>H=CH_2), 150.9 (s, C1), 159.4 (s, C4').
GC/MS	Instrument I, method I Retention time: 10.27 min Main fragments: 240.14, 239.17, 225.13, 152.12, 141.09, 128.11, 115.07
HRMS	HRMS $[M+H]^+$*m/z* calcd 241.1223, found 241.1214

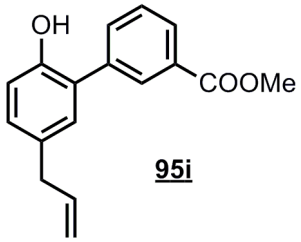
H II.13 2-Allyl-*6H*-benzo[*c*]chromen-6-one **95h**



95h

Procedure	Prepared according to the general procedure A or Bwith 2-methoxycarbonylphenylboronic acid as coupling partner
Reaction scale	0.47 mmol (100 mg of **93** or 80 mg of **101**)
Reaction time	Method A: 30 min, Method B: 10 min
Purification	Method A: MPLC, PE/EtOAc 0-5%, 9 g silica 60 Method B: MPLC, PE/EtOAc 0-5% gradient, 4.5 g silica 60, 4.5 g of 20% $AgNO_3$ doped silica (in serial connections of columns)
Yield	Method A: 47 mg (42%) Method B:34 mg (31%)
Appearance	yellow solid
Melting point	103.6-104.8°C
Sum formula, m.w.	$C_{16}H_{12}O_2$, 236.27 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 3.51 (d, *J* = 6.6 Hz, 2H, -C$\underline{H_2}$-), 5.12-5.16 (m, 2H, -CH=C$\underline{H_2}$), 5.97-6.05 (m, 1H, -C$\underline{H}$=CH_2), 7.32 (d,*J* = 1.2 Hz, 2H, Ar-H*), 7.57-7.61 (at, 1H, Ar-H*), 7.81-7.85 (at, 1H, Ar-H*),7.87 (s, 1H, Ar-H2), 8.14 (d, *J* = 8.1 Hz, 1H, Ar-H*), 8.41 (d, *J* = 7.9 Hz, 1H, Ar-H10)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ39.9 (t, -CH_2-), 116.7 (t, -CH=$\underline{C}H_2$), 117.9 (d, C4), 118.0* (s), 121.4* (s), 121.8* (d), 122.6* (d), 129.0* (d), 130.8* (d), 131.1* (d), 134.9 (d, -$\underline{C}$H=CH_2), 135.0 (s, C10), 136.5 (s, C2), 137.0 (d), 150.0 (s, C5), 161.5 (s, -C(O)O-)
GC/MS	Instrument I, method I Retention time: 11.29 min Main fragments: 236.10, 235.09, 191.10, 152.09, 89.09
HRMS	$[M+H]^+$ *m/z* calcd 237.0910, found 237.0902

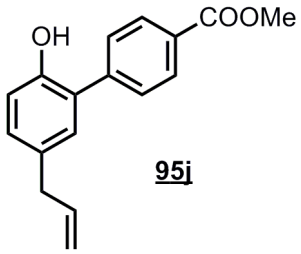
H II.14 4-Allyl-2-(3'-methoxycarbonylphenyl)phenol **95i**



95i

Procedure	Prepared according to the general procedure A or Bwith 3-methoxycarbonylphenylboronic acid as coupling partner
Reaction scale	0.47 mmol (100 mg of **93** or 80 mg of **101**)
Reaction time	Method A: 30 min, Method B: 10 min
Purification	Method A: MPLC, PE/EtOAc 0-5%, 9 g silica 60 Method B: MPLC, PE/EtOAc 0-5% gradient, 4.5 g silica 60, 4.5 g of 20% $AgNO_3$ doped silica (in serial connections of columns)
Yield	Method A: 52 mg (41%) Method B: 43 mg (34%),
Appearance	yellowish oil
Sum formula, m.w.	$C_{17}H_{16}O_3$, 268.31 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 3.35-3.38 (d, *J* = 6.7 Hz, 2H, -C$\underline{H_2}$-),3.94, (s, 3H, -C(O)OC$\underline{H_3}$) 4.94 (s, 1H, -O$\underline{H}$), 5.04-5.14 (m, 2H, -CH=C$\underline{H_2}$), 5.88-6.08 (m, 1H, -C$\underline{H}$=CH_2), 6.88-6.93 (dd, *J* = 6.9 Hz and 1.9 Hz, 1H, Ar-H6), 7.08-7.13 (m, 2H, Ar-H*),7.50-7.60 (m, 1H, Ar-H*), 7.67-7.73 (m, 1HAr-H*), 8.03-8.11 (m, 1H, Ar-H*), 8.16-8.18 (m, 1H, Ar-H*)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ 39.5 (t, -CH_2-), 55.5 (q, -OCH_3), 114.8* (2C, d), 115.7 (t, -CH=$\underline{C}H_2$), 115.8* (d), 127.8 (s, C2), 128.9* (d), 129.5* (s), 130.4* (3C, d), 132.4* (s), 137.9 (d, -$\underline{C}$H=CH_2), 150.9 (s, C1), 159.4 (s, -$\underline{C}$OOMe).
GC/MS	Instrument I, method I Retention time: 11.29 min Main fragments: 268.11, 237.11, 236.10, 235.09, 209.09, 208.11, 207.10, 181.09, 178.10, 168.08, 165.09, 152.09, 118.11, 76.07
HRMS	$[M+H]^+$ *m/z* calcd 269.1172, found 269.1181

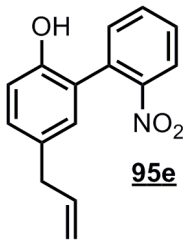
H II.15 4-Allyl-2-(4'-methoxycarbonylphenyl)phenol **95j**



95j

Procedure	Prepared according to the general procedure A or B with 4-methoxycarbonylphenylboronic acid as coupling partner
Reaction scale	0.47 mmol (100 mg of **93** or 80 mg of **101**)
Reaction time	Method A: 30 min, Method B: 10 min
Purification	Method A: MPLC, PE/EtOAc 0-5%, 9 g silica 60 Method B: MPLC, PE/EtOAc 0-5% gradient, 4.5 g silica 60, 4.5 g of 20% $AgNO_3$ doped silica (in serial connections of columns)
Yield	Method A: 64 mg (51%) Method B: 45 mg (36%)
Appearance	yellowish solid
Melting point	66.7-68.4°C
Sum formula, m.w.	$C_{17}H_{16}O_3$, 268.31 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 3.35-3.38 (d, *J* = 6.7 Hz, 2H-C$\underline{H}_2$-), 3.95 (s, 3H-C(O)OC$\underline{H}_3$), 4.95 (s, 1H, -O$\underline{H}$), 5.04-5.14 (m, 2H, -CH=C$\underline{H}_2$), 5.88-6.07 (m, 1H, -C$\underline{H}$=CH_2), 6.89-6.93 (dd, *J* = 7.4 Hz and 1.3 Hz, 1H, Ar-H6), 7.09-7.14 (m, 2H, Ar-H3 and Ar-H4), 7.56-7.60 (m, 2H, Ar-H2' and Ar-H6'), 8.12-8.16 (m, 2H, Ar-H3' and Ar-H5')
^{13}C-NMR (400 MHz, $CDCl_3$)	δ39.3 (t, -CH_2-), 52.2 (q, OCH_3), 115.8 (t, -CH=$\underline{C}H_2$), 116.2 (d, C6), 127.1 (s, C1'), 129.1 (3C, d, C3' and C5' and *), 129.8* (d), 130.2 (2C, d, C2' and C6'), 130.3 (d), 132.6 (s, C4'), 137.5 (s, C4), 142.3 (s, C1'), 150.8 (s, C1), 166.9 (s, -$\underline{C}$OOMe)
GC/MS	Instrument I, method I Retention time: 11.37 min Main fragments: 268.12, 237.10, 181.09, 178.10, 168.07
HRMS	$[M+H]^+$ *m/z* calcd 269.1172, found 269.1159

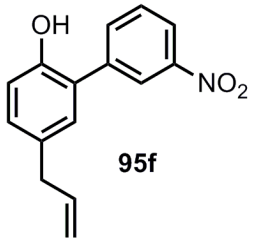
H II.16 4-Allyl-2-(2'-nitrophenyl)phenol **95e**



95e

Procedure	Prepared according to the general procedure A or B with 2-nitrophenylboronic acid as coupling partner
Reaction scale	0.47 mmol (100 mg of **93** or 80 mg of **101**)
Reaction time	Method A: 30 min, Method B: 10 min
Purification	Method A: MPLC, PE/EtOAc 0-5%, 9 g silica 60 Method B: MPLC, PE/EtOAc 0-5% gradient, 4.5 g silica 60, 4.5 g of 20% $AgNO_3$ doped silica (in serial connections of columns)
Yield	Method A: 18 mg (15%) Method B: 50 mg (42%)
Appearance	yellow oil
Sum formula, m.w.	$C_{15}H_{13}NO_3$, 255.27 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 3.35-3.39 (d, *J* = 6.7 Hz, 2H, -C$\underline{H_2}$-)4.88 (s, 1H, -O$\underline{H}$), 5.04-5.13 (m, 2H, -CH=C$\underline{H_2}$), 5.88-6.08 (m, 1H, -C$\underline{H}$=CH_2), 6.75-6.79 (d, *J* = 8.1 Hz, 1H, Ar-H6), 7.04-7.12 (m, 2H, Ar-H*), 7.41-7.55 (m, 2H, Ar-H*), 7.61-7.70 (m, 1H, Ar-H*), 7.94-7.99 (m, 1H, Ar-H*)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ39.4 (t, -CH_2-), 115.8 (t, -CH=$\underline{C}H_2$),116.0 (d, C6), 124.3 (d), 125.0 (s, C2), 128.5 (d), 130.0* (2C d, s), 132.8* (2C, d), 132.9 (s C4 or C1'), 133.0 (d, C3), 137.6 (d, -$\underline{C}$H=CH_2), 149.7 (s, C2'), 150.8 (s, C6)
GC/MS	Instrument I, method I Retention time: 11.37 min Main fragments: 255.11, 208.09, 207.07, 181.11, 178.12, 168.11, 152.11, 139.09, 115.09, 96.09, 91.05, 89.10, 79.09, 77.08, 76.11, 70.08, 61.08
HRMS	HRMS $[M-H]^-$ *m/z* calcd 254.0823, found 254.0813

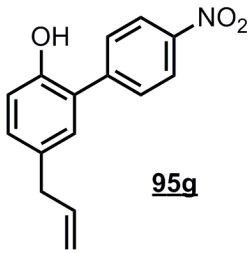
H II.17 4-Allyl-2-(3'-nitrophenyl)phenol **95f**[19]



95f

Procedure	Prepared according to the general procedure A or B with 3-nitrophenylboronic acid as coupling partner
Reaction scale	0.47 mmol (100 mg of **93** or 80 mg of **101**)
Reaction time	Method A: 30 min, Method B: 10 min
Purification	Method A: MPLC, PE/EtOAc 0-5%, 9 g silica 60 Method B: MPLC, PE/EtOAc 0-5% gradient, 4.5 g silica 60, 4.5 g of 20% $AgNO_3$ doped silica (in serial connections of columns)
Yield	Method A: 66 mg (55%) Method B: 103 mg (86%)
Appearance	yellowishsolid
Melting point	52.3-53.2°C
Sum formula, m.w.	$C_{15}H_{13}NO_3$, 255.27 $g.mol^{-1}$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 3.36-3.40 (d, *J* = 6.7 Hz, 2H, -C<u>H</u>$_2$-), 5.02-5.15 (m, 3H, -CH=C<u>H</u>$_2$and -O<u>H</u>), 5.88-6.08 (m, 1H, -C<u>H</u>=CH_2), 6.85-6.90 (dd,*J* = 6.4 Hz and 2.5 Hz, 1H, Ar-H6), 7.09-7.13 (m, 2H, Ar-H*), 7.56-7.64 (t, *J* = 7.9 Hz, 1H, Ar-H*), 7.86-7.90 (dt, *J* = 7.8 Hz and 1.3 Hz, 1H, Ar-H*), 8.17-8.23 (m, 1H, Ar-H*), 8.41-8.43 (at, 1H, Ar-H1')
^{13}C-NMR (400 MHz, $CDCl_3$)	δ39.4 (t, -CH_2-), 116.1 (t, -CH=<u>C</u>H_2),116.5 (d, C6), 122.2* (d),124.4* (d), 126.0 (s, C2), 129.5* (d), 130.2* (d), 130.7* (d), 133.2 (s, C4), 135.5 (d, -<u>C</u>H=CH_2 or C6'), 137.5 (d, -<u>C</u>H=CH_2 or C6'), 139.7 (s, C1'), 148.5 (s, C3'), 150.8 (s, C1)
GC/MS	Instrument I, method I Retention time: 11.66 min Main fragments: 255.09, 238.10, 208.10, 207.08, 181.09, 168.08, 165.09, 152.09, 139.07

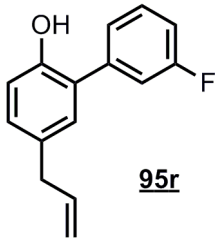
H II.18 4-Allyl-2-(4'-nitrophenyl)phenol **95g**



95g

Procedure	Prepared according to the general procedure A or B with 4-nitrophenylboronic acid as coupling partner
Reaction scale	0.47 mmol (100 mg of **93** or 80 mg of **101**)
Reaction time	Method A: 30 min, Method B: 10 min
Purification	Method A: MPLC, PE/EtOAc 0-5%, 9 g silica 60 Method B: MPLC, PE/EtOAc 0-5% gradient, 4.5 g silica 60, 4.5 g of 20% $AgNO_3$ doped silica (in serial connections of columns)
Yield	Method A: 24 mg (20%) Method B: 72 mg (60%)
Appearance	yellow oil
Sum formula, m.w.	$C_{15}H_{13}NO_3$, 255.27 $g.mol^{-1}$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 3.36-3.40 (d, *J* = 6.7 Hz, 2H, -C$\underline{H}_2$-), 4.90 (s, 1H, -O$\underline{H}$), 5.05-5.15 (m, 2H, -CH=C$\underline{H}_2$), 5.87-6.07 (m, 1H, -C$\underline{H}$-CH_2), 6.86-6.90 (dd, *J* = 6.5 Hz and 2.5, 1H, Ar-H6), 7.12-7.15 (m, 2H, Ar-H3 and Ar-H5), 7.69-7.74 (d, *J* = 8.8, Hz 2H, Ar-H2' and Ar-H6'), 8.28-8.32 (d, *J* = 8.8 Hz, 2H, Ar-H3' and Ar-H5')
^{13}C-NMR (400 MHz, $CDCl_3$)	δ39.4 (t, -CH_2-), 116.2 (t, -CH=$\underline{C}H_2$), 116.6 (d, C6), 124.0 (2C, d, C3' and C5'), 126.2 (s, C2), 130.2 (2C, d, C2' and C6'), 130.5* (d), 130.7* (d), 133.3 (s, C4), 137.4 (d, -$\underline{C}$H=CH_2), 144.8 (s, C1'), 147.1 (s, C4'), 150.8 (s, C1)
GC/MS	Instrument I, method I Retention time: 11.72 min Main fragments: 255.12, 254.10, 208.12, 181.10, 165.11, 152.10, 133.10
HRMS	HRMS $[M-H]^-$ *m/z* calcd 254.0823, found 254.0828

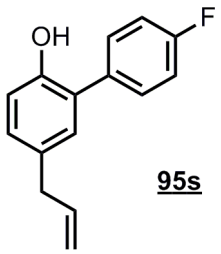
H II.19 4-Allyl-2-(3'-fluorophenyl)phenol **95r**



95r

Procedure	Prepared according to the general procedure B with 2-fluorophenylboronic acid as coupling partner
Reaction scale	74 mg (0.44mmol)
Reaction time	10 min
Purification	MPLC, PE/EtOAc 0-5% gradient, 9 g SiO_2, yielding 52 % which then had to be further purified by reverse phase preparative HPLC (6:4 MeOH/H_2O(1 % TFA)) yielding 16 % after extraction from the fractions and evaporation of the solvents.
Yield	46 mg (46%)
Appearance	yellow oil
Sum formula, m.w.	$C_{15}H_{13}FO$, 228.26 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 3.37 (d, *J* = 6.7 Hz, 2H, -CH_2-), 5.04-5.14 (m, 3H, -CH=CH_2 and O<u>H</u>), 5.87-6.08 (m, 1H, -C<u>H</u>=CH_2), 6.91 (d, *J* = 8.2 Hz, Ar-H6), 7.03-7.13 (m, 3H, Ar-H*), 7.17-7.29 (m, 2H, Ar-H*), 7.39-7.50 (m, 1H, Ar-H*)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ = 38.5 (t, -CH_2-), 14.8 (d, *J* = 21.2 Hz, C4'), 15.9 (t, -CH=<u>C</u>H_2), 16.2 (d, C6), 116.4 (d, *J* = 21.2 Hz, C2'), 124.8 (d, *J* = 2.8 Hz, C5'), 129.7*(d), 130.4* (d), 130.7* (d, *J* = 8.7 Hz), 131.6 (s, C1), 132.7 (s, C4), 136.7 (s, C1'), 137.7 (d, -<u>C</u>H=CH_2), 150.8 (s, C1) 167.5 (s, *J* = 177.4 Hz, C3')
GC/MS	Instrument I, method I Retention time: 8.87 min Main fragments: 228.10, 227.07, 201.06, 133.06
HRMS	**pending**

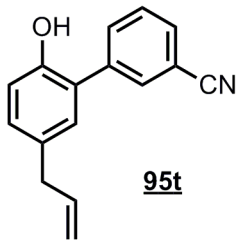
H II.20 4-Allyl-2-(4'-fluorophenyl)phenol **95s**



95s

Procedure	Prepared according to the general procedure B with 4-fluorophenylboronic acid as coupling partner
Reaction scale	37 mg (0.22mmol
Reaction time	10 min
Purification	MPLC, PE/EtOAc 0-5% gradient, 9 g SiO_2, yielding 52 % which then had to be further purified by reverse phase preparative HPLC (6:4 MeOH/H_2O(1 % TFA)) yielding 16 % after extraction from the fractions and evaporation of the solvents.
Yield	8 mg (16%)
Appearance	yellow oil
Sum formula, m.w.	$C_{15}H_{13}FO$, 228.26 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 3.36 (d, *J* = 6.6 Hz, 2H, -CH_2-), 4.97-5.13 (m, 3H, -CH=C$\underline{H}_2$), 5.87-6.07 (m, 1H, -CH=CH_2), 6.88-6.92 (d, 4H, Ar), 7.03-7.21 (m, 4H, Ar), 7.41-7.48 (m, 2H, Ar), 7.13 (s, 1H, Ar)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ = 38.5 (t), 114.9 (t, -CH=$\underline{C}H_2$), 115.0* (d), 115.2*(d), 126.2 (s, C2), 128.4* (d), 129.5* (d), 129.9* (d), 130.1* (d), 131.6 (s, C4), 132.4(s. *J* = 3.5 Hz, C1'), 136.8 (d. –CH=CH_2), 136.9* (d) 149.9 (s, C1), 161.6 (s, *J* = 155.4 Hz, C4')
GC/MS	Instrument I, method I Retention time: 8.87 min Main fragments: 228.17, 227.08, 183.05, 133.03, 70.04, 61.04

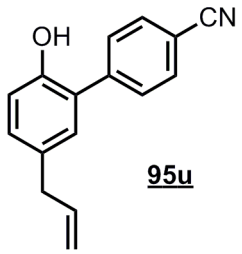
H II.21 4-Allyl-2-(3'-cyanophenyl)phenol **95t**



95t

Procedure	Prepared according to the general procedure B with 4-cyanophenylboronic acid as coupling partner
Reaction scale	100 mg (0.59mmol)
Reaction time	10 min
Purification	MPLC, PE/EtOAc 0-5% gradient, 18 g silica 60
Yield	32 mg (23%)
Appearance	yellow oil
Sum formula, m.w.	$C_{16}H_{13}NO$, 235.29 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 3.36-3.39 (d, *J* = 6.7 Hz, 2H, -CH=C<u>H</u>$_2$), 4.9 (s, 1H, -O<u>H</u>), 5.06-5.15 (m, 2H, -CH=C<u>H</u>$_2$), 5.87-6.08 (m, 1H, -C<u>H</u>=CH$_2$), 6.86-6.90 (d, *J* = 7.9 Hz, 1H, Ar-H6), 7.09-7.13 (m, 2H, Ar-H*), 7.52-7.85 (m, 4H, Ar-H*)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ = 39.4 (t, -CH_2-), 112.8 (s, C3'), 116.1 (t, -CH=<u>C</u>H$_2$), 116.5 (d, C6), 118.9 (s, -CN), 121.5* (s), 126.1* (s), 129.5* (d), 130.1* (d), 130.6* (d), 130.9* (d), 133.1* (d), 133.8* (d), 137.5 (d, -<u>C</u>H=CH$_2$), 139.3 (s, C1'), 150.9 (s, C1)
GC/MS	Instrument I, method I Retention time: 11.01 min Main fragments: 235.07, 234.03, 190.06, 132.98
HRMS	$[M-H]^-$ *m/z* calcd 234.0624, found 234.0925

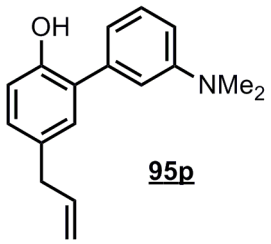
H II.22 4-Allyl-2-(4'-cyanoophenyl)phenol **95u**



95u

Procedure	Prepared according to the general procedure B with 4-cyanophenylboronic acid as coupling partner
Reaction scale	72 mg (0.42mmol)
Reaction time	10 min
Purification	MPLC, PE/EtOAc 0-5% gradient, 18 g silica 60
Yield	37 mg (37%)
Appearance	yellow oil
Sum formula, m.w.	$C_{16}H_{13}NO$, 235.29 $g.mol^{-1}$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 3.35-3.39 (d, *J* = 6.7 Hz, 2H, -C$\underline{H}_2$-), 5.04-5.4 (m, 2H, -CH=C$\underline{H}_2$),5.14 (s, 1H, -O$\underline{H}$), 5.87-6.07 (m, 1H, -C$\underline{H}$=CH_2), 6.86-6.91 (dd, *J* = 6.6 Hz, *J* = 1.2 Hz 2H, Ar-H6), 7.09-7.14 (m, 2H, Ar-H3 and Ar-H5), 7.64-7.74 (m, 4H, Ar-H')
^{13}C-NMR (400 MHz, $CDCl_3$)	δ = 39.4 (t), 110.7 (s, C4'), 116.0 (t. –CH=$\underline{C}H_2$), 116.6 (d, C6),119.0 (s, –CN), 126.5 (s, C2), 130.1 (d, 2C, C2' and C6'), 130.2* (d), 130.6* (d), 132.4 (d, 2C, C3' and C5'), 132,9 (s, C4), 137.5 (d, -$\underline{C}$H=CH_2), 143.0 (s, C1'), 151.0 (s, C1)
GC/MS	Instrument I, method I Retention time: 11.09 min Main fragments: 235.09, 234.08, 133.05

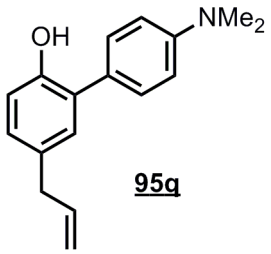
H II.23 4-Allyl-2-[3'-(N,N-dimethylamino)phenyl]phenol **95p**



95p

Procedure	Prepared according to the general procedure B with 3-*(N,N*-dimethylamino)phenylboronic acid as coupling partner
Reaction scale	30 mg (0.18mmol)
Reaction time	10 min
Purification	MPLC, PE/EtOAc 0-5% gradient, 9 g silica 60 leaving behind 56% of product with approximatly 10% of impurities. Impurities were removed by second column chromatography.
Yield	7 mg (16%)
Appearance	yellow oil
Sum formula, m.w.	$C_{17}H_{19}NO$, 253.34 $g.mol^{-1}$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 2.99 (s, 6H, $N(C\underline{H}_3)_2$), 3.01 (s, 1H, -O<u>H</u>), 3.46 (d, *J* = 6.7 Hz, 2H, -$C\underline{H}_2$-), 5.01-5.15 (m, 2H,-CH=$C\underline{H}_2$), 5.88-6.08 (m, 1H, -$C\underline{H}$=CH_2), 6.75-6.79 (m, 3H, Ar-H*), 6.93 (d,*J* = 8.8 Hz,1H, Ar-H*), 7.05-7.09 (m, 2H, Ar-H*) 7.31-7.39 (m, 1H, Ar-H*)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ = 39.6 (t, -CH_2), 40.7 (q, 2C-$N(CH_3)_2$), 112.1 (d, C1' or C3'), 112.7 (d, C1' or C3'), 115.6 (d, C6 or C6'), 115.7 (t, -CH=$\underline{C}H_2$), 116.8 (d, C6 or C6'), 128.9 (s, C2), 129.1(d), 130.1 (d), 130.3 * (d), 132.1 (s, C4), 137.9 (d and s, -$\underline{C}$H=$CH_2$and C1'), 150.1 (s, C2'), 151.4 (s, C1)
GC/MS	Instrument I, method I Retention time: 11.13 min Main fragments: 253.15, 262.13, 207.05

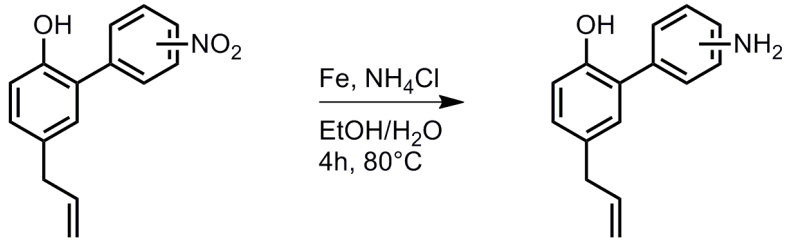
H II.24 4-Allyl-2-[4'-(N,N-dimethylamino)phenyl]phenol **95q**



95q

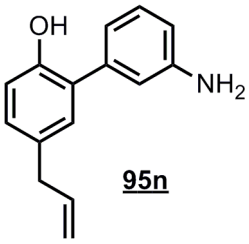
Procedure	Prepared according to the general procedure B with 4-*(N,N*-dimethylamino)phenylboronic acid as coupling partner
Reaction scale	68 mg (0.4mmol)
Reaction time	10 min
Purification	MPLC, PE/EtOAc 0-5% gradient, 9 g silica 60 leaving behind 56% of product with approximatly 10% of impurities. Impurities were removed by second column chromatography.
Yield	18 mg (18%)
Appearance	yellow oil
Sum formula, m.w.	$C_{17}H_{19}NO$, 253.34 $g.mol^{-1}$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 3.01 (s, 6H, $N(C\underline{H}_3)_2$), 3.35 (d, *J* = 6.7 Hz, 2H, -$C\underline{H}_2$-), 5.03-5.14 (m, 2H, -CH=$C\underline{H}_2$), 5.25 (bs, 1H, -O$\underline{H}$), 5.88-6.08 (m, 1H, -$C\underline{H}$=CH_2), 6.89-6.93 (m, 3H, Ar-H*), 7.02-7.04 (m, 2H, Ar-H*), 7.36 (d, *J* = 8.64 Hz, 2H, Ar-H*)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ = 39.6 (t, -CH=CH_2), 40.6 (q, 2C, $-N(CH_3)_2$), 113.0 (d, 2C, C3' and C5'), 115.5 (d, C6), 115.6 (t, -CH=$\underline{C}H_2$), 124.6* (s), 128.3* (s), 128.4* (d), 129.9 (d, 2C, C2' and C6'), 130.3* (d) 132.2 (s, C2), 138.0 (d, -$\underline{C}$H=CH_2), 150.3 (s, C1 or C4'), 151.1 (s, C1 or C4')
GC/MS	Instrument I, method I Retention time: 11.49 min Main fragments: 253.19, 252.19
HRMS	$[M+H]^+$ *m/z* calcd 254.1539, found 254.1534

H II.25 Reduction of nitroderivatives to amino derivatives – general procedure



General procedure Substrate was dissolved in EtOH/water (c = 1 mM) and amonium chloride (4.4 equiv.) with iron (50equiv.) were added. Mixture was heated to 80°C and stirred for 4 hours. Conversion was monitored via TLC. After complition, mixture was filtered through celite with EtOAc, solvents were evaporated. Remaining material was redissolved in EtOAc and washed three times with water. Combined organic layer were dried over Na2SO4 and solvent was evaporated under rediced pressure.

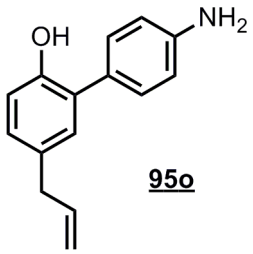
H II.26 4-Allyl-2-(3'-aminophenyl)phenol **95n**



95n

Procedure	Prepared according to the general procedure depicted above
Reaction scale	53 mg (0.21mmol)
Reaction time	4 h
Purification	MPLC, PE/EtOAc 10%,4.5 g silica 60
Yield	15 mg (32%)
Appearance	yellow oil
Sum formula, m.w.	$C_{15}H_{15}NO$, 225.29 $g.mol^{-1}$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 3.33-3.37 (d, *J* = 6.7 Hz, 2H, -C<u>H</u>$_2$-), 3.77 (bs, 2H, -N<u>H</u>$_2$), 5.03-5.13 (m, 2H, -CH=C<u>H</u>$_2$), 5.37 (bs, 1H, -O<u>H</u>), 5.88-6.04 (m, 1H, -C<u>H</u>=CH$_2$), 6.68-6.93 (m, 5H, Ar-H*), 7.20-7.30 (m, 2H, Ar-H*)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ = 39.5 (t, -CH_2-), 114.7* (d), 115.5* (d), 115.7 (t, -CH=<u>C</u>H$_2$), 115* (d), 119.0* (d), 129.2 (d), 128.2 (s, C2), 129.2* (d), 130.0* (d) 130.5* (d), 132.2 (s, C4), 137.9 (d, -<u>C</u>H=CH$_2$), 138.4 (s, C1'), 147.4 (s, C3'), 150.9 (s, C1)

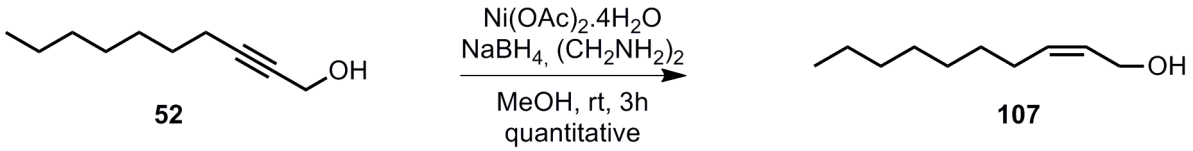
H II.27 4-Allyl-2-(4'-aminophenyl)phenol **95o**



95o

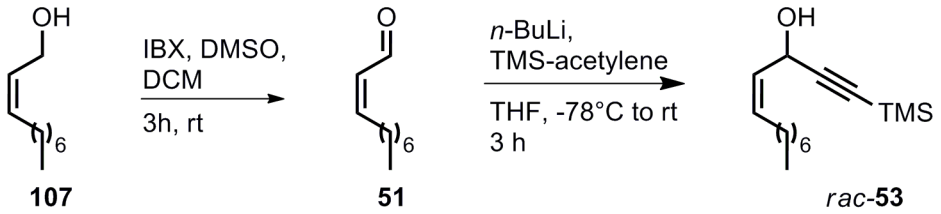
Procedure	Prepared according to the general procedure depicted above
Reaction scale	195 mg (0.76mmol)
Reaction time	4 h
Purification	MPLC, PE/EtOAc 10% 9 g silica 60
Yield	83 mg (49%)
Appearance	yellow solid
Melting point	97.3-94.5 °C
Sum formula, m.w.	$C_{15}H_{15}NO$, 225.29 $g.mol^{-1}$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 3.34 (d, *J* = 6.7 Hz, 2H, -C<u>H</u>$_2$-), 3.78 (bs, 2H, -N<u>H</u>$_2$), 5.02-5.13 (m, 3H, -CH=C<u>H</u>$_2$ and -O<u>H</u>), 5.87-6.07 (m, 1H, -C<u>H</u>=CH$_2$), 6.76-6.81 (m, 2H, Ar-H*), 6.87-6.92 (m, 1H, Ar-H*), 7.01-7.06 (m, 2H, Ar-H*), 7.21-7.26 (m, 2H, Ar-H*)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ = 39.5 (t, -CH$_2$-), 115.6 (t+d, 2C, -CH=<u>C</u>H$_2$and C6), 115.8 (d, 2C, C3' and C5'), 127.1 (s, C2 or C1'), 128.2 (s, C2 or C1'), 128.6* (d), 130.2 (d, 2C, C2' and C6'), 130.3* (d), 132.2 (s, C4), 138.0 (d, -<u>C</u>H=CH$_2$), 146.2 (s, C4'), 151.0 (s, C1)
HRMS	$[M+H]^+$ *m/z* calcd 226.1226, found 226.1221

H II.28 (*Z*)-Dec-2-en-1-ol **107**[5]



Procedure	In a 250 mL three neck round bottom flask equipped with septum and gas inlet, $Ni(OAc)_2.4H_2O$ (0.38 equiv., 14.4 mmol, 2.98 g) was dissolved in 47 mL of methanol, the atmosphere was changed to argon and the reaction mixture was cooled with an ice bath. $NaBH_4$ was added portion wise. The reaction mixture was allowed to warm to room temperature and was stirred for 15 minutes. Then, the atmosphere was exchanged for H_2. In a separate flask, dec-2-ynol (39 mmol, 6 g) was dissolved in 20 mL of methanol together with ethane-1,2-diamine (0.94 equiv., 35.7 mmol, 2.38 mL) and the reaction mixture was transferred *via* syringe into the mixture of the catalyst. The reaction was stirred at room temperature for 3 hours until full consumption of starting material was observed on TLC. The reaction mixture was filteredfilteredthrough a pad of celite under reduced pressure and solvents were evaporated under reduced pressure. The product was used as such for the next step.
Reaction scale	6 g, 39 mmol
Reaction time	3 h
Yield	6.08 g (quantitative)
Appearance	yellowish oil
Sum formula, m.w.	$C_{10}H_{20}O$, 156.27 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 0.88 (t, *J* = 6.70 Hz, 3H, H10), 1.27 (m, 10H, H5-H9), 2.05 (q, *J*= 6.3 Hz, 2H, H4), 4.17-4.21 (at, 2H, H1), 5.47-5.67 (m, 2H, H2 and H3)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ = 14.2 (q, C10), 22.8 (t, C9), 27.6 (t, C4) 29.3 (t, -CH_2-*), 29.3 (t, -CH_2-*), 29.7 (t, -CH_2-*), 32.0 (t, C8), 58.8 (t, C1), 128.4 (d, C2), 133.4 (d, C3)
GC/MS	Instrument I, Method I Retention time: 4.73 min Main fractions: 111.13, 97.06, 84.07, 83.07, 82.05, 70.04, 69.04, 68.08, 57.01, 56.03, 54.96

H II.29 (*Z*)-1-(Trimethylsilyl)dodec-4-en-1-yn-3-ol *rac*-**53**[5]



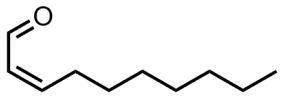
107 **51** *rac*-**53**

Procedure

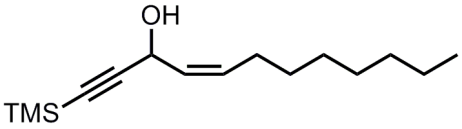
A 500 mL three neck round bottom flask equipped with septum and inert gas inlet was charged with (*Z*)-dec-2-ynol **107** (5.7 g, 36.4 mmol), dry DMSO (16.6 mL), dry DCM (78 mL) and IBX (1.5 equiv., 15.3 g, 54.7 mmol). The reaction mixture was stirred for 2 hours at room temperature and then 0.3 mL of DMSO was added every 10 minutes for one hour. After the reaction is complete, the mixture was cooled to 0°C; ice precooled $NaHCO_3$ was added (80 mL) and the resulting mixture was stirred for 15 minutes. All the work-up operations were carried out with precooled glassware and ice bath precooled chemicals. Solids were removed by filtration *via* a sinter-glass funnel under reduced pressure. The mixture was extracted with diethyl ether (100 mL) and washed successively with $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4, filtered and volatiles were evaporated under reduced pressure at room temperature. The crudematerial was used immediately for the next step.

TMS-acetylene (7.8 mL, 55.4 mmol) was charged into a preheated 250 mL three necked round bottom flask, equipped with low temperature thermometer, inert gas inlet and septum. The atmosphere was exchanged for argon and dry THF (34 mL) was added. The reaction mixture was cooled to -78°C, *n*-BuLi was added (1.6 M, 34.6 mL, 55.4 mmol) and the reaction mixture was stirred for 30 minutes at -78°C. In a separate flaskcrude (*Z*)-dec-2-ynal obtained in the previous step was dissolved in dry THF (48 mL) under inert atmosphere and subsequently transferred into the reaction mixture *via* syringe. The mixture was allowed to warm to room temperature and was stirred for 3 hours. After the reaction was finished, water (100 mL) was added,the mixture was extracted with ethyl

acetate (3 x 100 mL) and washed with brine (100 mL) and filtred through the pad of silica.

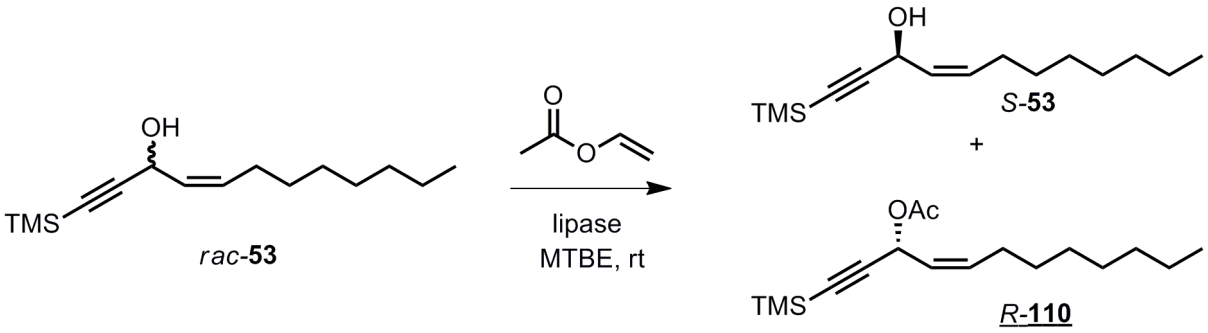


Appearance	yellowish oil
Sum formula, m.w.	$C_{10}H_{18}O$, 154.25 g.mol^{-1}
TLC	R_f = 0.32 (PE/Et_2O 9:1, 0.27 for *E* isomer)
^{1}H-NMR (200 MHz, $CDCl_3$)	δ0.82-0.90 (m, 3H, H10), 1.28-1.30 (m, 8H, H6-H9), 1.44-1.57 (m, 2H, H5), 2.54-2.67, (m, 2H, H4), 5.90-6.01 (m, 1H, H2), 6.57-6.70 (dt, *J* = 11.3 Hz, *J* = 8.2 Hz, H3), 10.08 (d, *J* = 8.02 Hz, H1))
Comment	Spectral data agree with the literature



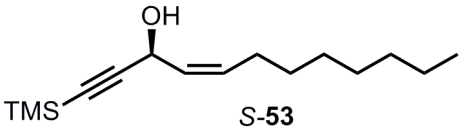
Reaction scale	5.7 g, 36.4 mmol
Reaction time	3 h + 3.5 h
Purification	Filtration through the pad of silica
Yield	5.51 g (60% over two steps)
Appearance	yellowish oil
Sum formula, m.w.	$C_{15}H_{28}OSi$, 252.47 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 0.16 (s, 9H, -Si($C\underline{H}_3$)$_3$), 0.84-0.87 (bs, 3H, H12), 1.27 (br, 10 H, H7-H11), 1.95 (bs, 1H, -O$\underline{H}$), 2.06-2.16 (m, 2H, H6), 5.10-5.14 (d, *J* = 6.90, 1H, H3), 5.47-5.63 (m, 2H, H4 and H5)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ = δ = -0.06 (q, $Si(CH_3)_3$), 14.2 (q, C12), 22.8 (t, C11), 27.7 (t, C6), 29.3 (t, -CH_2-*), 29.3 (t, -CH_2-*), 29.7 (t, -CH_2-*), 32.0 (t, C10), 58.8 (d, C3), 89.6 (s, C2), 105.8 (s, C1), 128.4 (d, C4), 133.4 (d, C5)
Comment	Spectral data agree with the literature

H II.30 Lipase kinetic resolution of racemic alcohol **53**



Procedure	A 250 mL round bottom flask was charged with racemic (*Z*)-1-(trimethylsilyl)dodec-4-en-1-yn-3-ol **53** (5.5 g, 21.78 mmol), lipase PS (1.1 g, 20 w%), vinyl acetate (2.3 mL, 25.05 mmol) and MTBE (77 mL). The flask was sealed with a septum and the reaction mixture was stirred for 36 hours. After the reaction was finished, the mixture was filtered through a pad of celite and solvents were evaporated in vacuum. Column chromatography (silicagel, PE/EtOAc 99:1) provided the desired products.
Reaction scale	5.5 g, 21.78 mmol
Reaction time	36 h

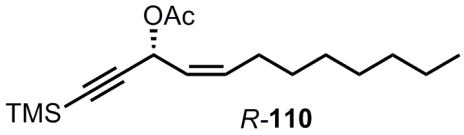
H II.31 (*S,Z*)-1-(Trimethylsilyl)dodec-4-en-1-yn-3-ol *S*-**53**[7]



Yield	2.47 g (45%,>99% *ee*)
Appearance	yellowish oil
Sum formula, m.w.	$C_{15}H_{28}OSi$, 252.47 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 0.16 (s, 9H, -Si($C\underline{H}_3$)$_3$), 0.84-0.87 (bs, 3H, H12), 1.27 (br, 10 H, H7-H11), 1.95 (bs, 1H, -O$\underline{H}$), 2.06-2.16 (m, 2H, H6), 5.10-5.14 (d, *J* = 6.90, 1H, H3), 5.47-5.63 (m, 2H, H4 and H5)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ = -0.06 (q, Si(CH_3)$_3$), 14.2 (q, C12), 22.8 (t, C11), 27.7 (t, C6), 29.3 (t, -CH_2-*), 29.3 (t, -CH_2-*), 29.7 (t, -CH_2-*), 32.0 (t, C10), 58.8 (d, C3), 89.6 (s, C2), 105.8 (s, C1), 128.4 (d, C4), 133.4 (d, C5)

TLC analysis	R_f= 0.48 (PE/EtOAc 4:1), stained with PMA
Comment	Spectrum identical as for racemic compound
Optical rotation:	$[\alpha]_D^{20}$= +117.1(*c* 1.47, $CHCl_3$)
	Lit.$[\alpha]_D^{20}$= +115(*c* 1.47, $CHCl_3$)[7]

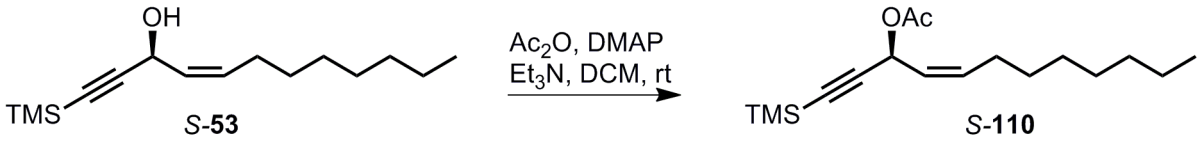
H II.32 (*R,Z*)-1-(Trimethylsilyl)dodec-4-en-1-yn-3-yl acetate *R*-**110**



R-**110**

Yield	2.94 g(48%,>99% *ee*)
Appearance	yellowish oil
Sum formula, m.w.	$C_{17}H_{30}O_2Si$, 294.50 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 0.15 (s, 9H, -Si(C$\underline{H}_3$)$_3$), 0.83-0.89 (t, *J* = 6.7 MHz, 3H, H12), 1.25 (bs, 10H, H7-H11), 2.06 (s, 3H, -C(O)C$\underline{H}_3$), 2.10-2.20 (q, *J* = 6.8 MHz, 2H, H6), 5.41 (m, 2H, H4 and H5), 6.08-6.12 (d, *J* = 8.3 MHz, 1H, H3)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ = -0.14 (q, 3C, -Si(C$\underline{H}_3$)$_3$), 14.2 (q, C12), 21.2 (q, -C(O)$\underline{C}H_3$, 22.8, (t, C11), 27.9 (t, C6), 29.3 (t, -CH_2-*), 31.9 (t, -CH_2-*), 60.4 (d, C3), 90.5 (s, C2), 102.0 (s, C1), 125.3 (d, C4), 135.6 (d, C5), 169.6 (s, -$\underline{C}$(O)CH_3)
TLC analysis	R_f = 0.75 (PE/EtOAc 4:1), stained with PMA
Optical rotation:	$[\alpha]_D^{20}$= -56.5 (*c* 1.0, $CHCl_3$)

H II.33 (*S,Z*)-1-(Trimethylsilyl)dodec-4-en-1-yn-3-yl acetate *S*-**110**

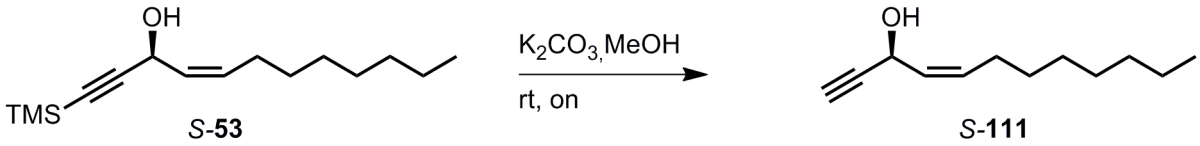


Comment Analytical scale for chiral HPLC analysis

Procedure A GC *via*lwas filled with a small amount of (*S,Z*)-1-(trimethylsilyl)dodec-4-en-1-yn-3-ol and approximately 1 mL of dichloromethane was added. DMAP (on the tip of a spatula) was added together with a few drops of triethylamine and aceticanhydride. The *via*l was sealed with a stopper and the reaction mixture was shaken for a couple of minutes. Conversion was controlled with TLC (compound *R*-**110** used as a reference). After completion, the reaction mixture quenched with water, organic phase was separated, dried over sodium sulfate and mixture was filtered through a pad of silica, using DCM as liquid phase. Subsequently, the solvent was evaporated under reduced pressure and the mixture was used as such for chiral HPLC analysis.

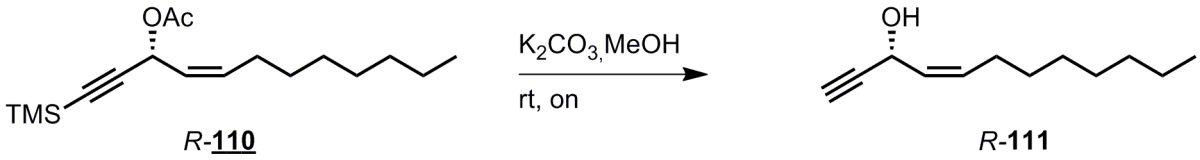
Appearance yellowish oil

H II.34 (*S*,*Z*)-Dodec-4-en-1-yn-3-ol *S*-**111**[3]



Procedure	A 100 mL round bottom flask was charged with (*S,Z*)-1-(trimethylsilyl)dodec-4-en-1-yn-3-ol **19a** (2.84 g, 11.2 mmol) and methanol (50 mL). Potassium carbonate (3.11 g, 22.4 mmol) was added and the reaction mixture was stirred at room temperature overnight. After the reaction was finished, water (50 mL) was added. The solution was transferred into a separation funnel and was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine, dried over sodium sulfate and volatiles were evaporated under reduced pressure. The mixture was re-dissolved in ethyl acetate/petroleum ether (1:9) and filtered through a pad of silica, using ethyl acetate/petroleum ether (1:9) as eluent, solvents were evaporated under reduced pressure and the resulting crude material used as such for the next step.
Reaction scale	2.84 g, 11.2 mmol
Reaction time	overnight
Yield	1.64 g (81%)
Appearance	yellowish oil
Sum formula, m.w.	$C_{12}H_{20}O$, 180.29 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 0.87 (t, *J* = 6.5 Hz, 3H, C12), 1.26 (bs, 10H, H7-H11), 2.08 (q, *J*= 6.5 Hz, 2H, H6), 2.26 (bs, 1H, -OH), 2.49 (d, *J* = 2.2 Hz, 1H, H1), 5.12-5.16 (m, 1H, H3), 5.54-5.66 (m, 2H, H4 and H5)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ = 14.2 (q, C12), 22.7, (t, C11), 27.7 (t, -C6), 29.3 (t, -CH_2-*), 29.4 (t, -CH_2-*), 29.5 (t, -CH_2-*), 31.9 (t, -CH_2-*), 58.1 (d, C3), 72.9 (d, C1), 84.2 (s, C2), 128.8 (d, C4), 134.1 (d, C5)
TLC analysis	R_f = 0.43 (PE/EtOAc 4:1), stained with PMA
Optical rotation:	$[\alpha]_D^{25}$= -118.6(*c* 1.0, $CHCl_3$) Lit.$[\alpha]_D^{20}$= +64.97(*c* 1.00, $CHCl_3$) [6,94]

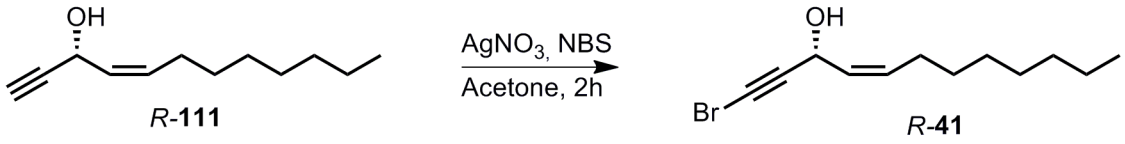
H II.35 (*R,Z*)-Dodec-4-en-1-yn-3-ol *R*-**111**[6]



R-**110** *R*-**111**

Procedure	A 100 mL round bottom flask was charged with (*S,Z*)-1-(trimethylsilyl)dodec-4-en-1-yn-3-ol *R*-**110** (2.84 g, 11.2 mmol) and methanol (50 mL). Potassium carbonate (3.11 g, 22.4 mmol) was added and the reaction mixture was stirred at room temperature overnight. After the reaction was completed, water (50 mL) was added. The reaction solution was transferred into a separation funnel and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine, dried over sodium sulfate and volatiles were evaporated under reduced pressure. The mixture was re-dissolved in ethyl acetate/petroleum ether (1:9) and filtered through a pad of silica, using ethyl acetate/petroleum ether (1:9) as eluent, solvents were evaporated under reduced pressure and the resulting crude material wasused as such for the next step.
Reaction scale	3.3 g, 11.2 mmol
Reaction time	overnight
Yield	1.72 g (85%)
Appearance	yellowish oil
Sum formula, m.w.	$C_{12}H_{20}O$, 180.29 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 0.87 (t, *J* = 6.5 Hz, 3H, C12), 1.26 (bs, 10H, H7-H11), 2.08 (q, *J*= 6.5 Hz, 2H, H6), 2.26 (bs, 1H, -OH), 2.49 (d, *J* = 2.2 Hz, 1H, H1), 5.12-5.16 (m, 1H, H3), 5.54-5.66 (m, 2H, H4 and H5)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ = 14.3 (q, C12), 22.8, (t, C11), 27.8 (t, -C6), 29.3 (t, -CH_2-*), 29.4 (t, -CH_2-*), 29.5 (t, -CH_2-*), 32.0 (t, -CH_2-*), 58.2 (d, C3), 73.1 (d, C1), 84.3 (s, C2), 128.9 (d, C4), 134.3 (d, C5)
TLC analysis	R_f = 0.43 (PE/EtOAc 4:1), stained with PMA
Optical rotation:	$[\alpha]_D^{25}$= +118.1 (*c* 1.0, $CHCl_3$)

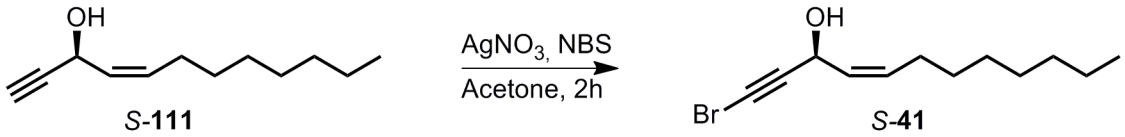
H II.36 (*R,Z*)-1-Bromododec-4-en-1-yn-3-ol *R*-**41**[3]



R-**111** *R*-**41**

Procedure	(*R,Z*)-Dodec-4-en-1-yn-3-ol *R*-**111**(700 mg, 3.88 mmol) was dissolved in acetone (15 mL), then silver nitrate (49 mg, 0.29 mmol) and *N*-bromosuccinimide (759.6 mg, 4.27 mmol) were added and the reaction mixture was stirred for 2 hours at room temperature. After the reaction was finished, the solution was cooled to 0°C, and 8 mL of water was added. The resulting mixture was stirred for 10 minutes and then extracted with diethyl ether (3 x 40 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate and volatiles were evaporated under reduced pressure, yielding colorless oil. The resulting crude material was confirmed to be pure enough and it was used as such for the next step.
Reaction scale	700 mg, 3.88 mmol
Reaction time	2 h
Yield	814.6 mg (81%)
Appearance	colorless oil
Sum formula, m.w.	$C_{12}H_{19}BrO$, 259.18 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 0.87 (t, *J* = 6.5 Hz, 3H, H12), 1.26 (bs, 10H,H7-H11), 2.11 (q, *J*= 6.8 Hz, 2H, H6), 2.47 (bs, 1H, -OH), 5.15 (d, *J* = 7.2 Hz, 1H, -OH), 5.46-5.62 (m, 2H, H4 and H5)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ = 14.2 (q, C12), 22.7 (t, C11), 27.7 (t, C6), 29.2 (t, -CH_2-*),29.3 (t, -CH_2-*), 29.4 (t, -CH_2-*), 31.9 (t, -CH_2-*), 45.4 (s, C1), 59.2 (d, C3), 80.3 (s, C2), 128.4, (d, C4), 134.2 (d, C5)
TLC analysis	R_f = 0.33 (PE/EtOAc 9:1), 0.43 (PE/EA 9:1), stained with PMA
Optical rotation:	$[\alpha]_D^{25}$= -78.9(*c*1.0, $CHCl_3$)

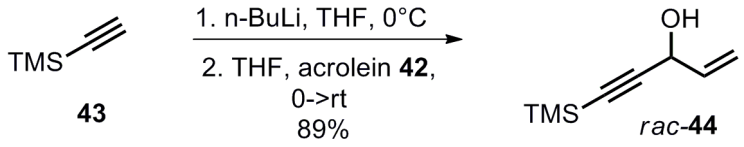
H II.37 (*S,Z*)-1-Bromododec-4-en-1-yn-3-ol *S*-**41**[3]



S-**111** *S*-**41**

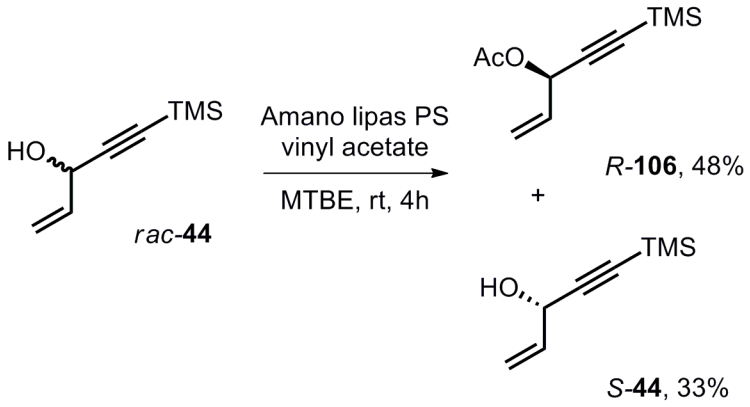
Procedure	(*S,Z*)-Dodec-4-en-1-yn-3-ol *S*-**111** (700 mg, 3.88 mmol) was dissolved in acetone (15 mL), then silver nitrate (49 mg, 0.29 mmol) and *N*-bromosuccinimide (759.6 mg, 4.27 mmol) were added and the reaction mixture was stirred for 2 hours at room temperature. After the reaction was finished, the solution was cooled to 0°C, and 8 mL of water was added. The resulting mixture was stirred for 10 minutes and then extracted with diethyl ether (3 x 40 mL). TheThe combined organic layers were washed with brine (20 mL), dried over sodium sulfate and volatiles were evaporated under reduced pressure, yielding colorless oil.
Reaction scale	700 mg, 3.88 mmol
Reaction time	2 h
Yield	774.3 mg (77%)
Appearance	colorless oil
Sum formula, m.w.	$C_{12}H_{19}BrO$, 259.18 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 0.87 (t, *J* = 6.5 Hz, 3H, H12), 1.26 (bs, 10H,H7-H11), 2.11 (q, *J*= 6.8 Hz, 2H, H6), 2.47 (bs, 1H, -OH), 5.15 (d, *J* = 7.2 Hz, 1H, -OH), 5.45-5.62 (m, 2H, H4 and H5)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ = 14.2 (q, C12), 22.7 (t, C11), 27.7 (t, C6), 29.2 (t, -CH_2-*), 29.3 (t, -CH_2-*), 29.4 (t, -CH_2-*), 31.9 (t, -CH_2-*), 45.4 (s, C1), 59.1 (d, C3), 80.3 (s, C2), 128.4, (d, C4), 134.2 (d, C5)
TLC analysis	R_f = 0.33 (PE/EtOAc 9:1), 0.43 (PE/EA 9:1), stained with PMA
Optical rotation:	$[\alpha]_D^{25}$= +79.8(*c*1.0, $CHCl_3$) Lit.$[\alpha]_D^{25}$= +79.8(*c*1.0, $CHCl_3$)

H II.38 5-(Trimethylsilyl)pent-1-en-4-yn-3-ol *rac*-**44**[3]



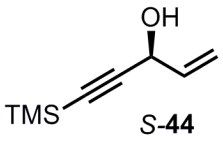
Procedure	An oven dried 500 mL three necked round bottom flask equipped with septum, gas inlet and low temperature thermometer was evacuated and the atmosphere was exchanged for argon. Trimethylsilylacetylene (5 mL, 3.45 g,35 mmol) and dry THF (140 mL) were added *via* septum. The reaction mixture was cooled to -78°C and *n*-BuLi (21.9 mL, 1.6 M, 35 mmol) was added slowly. The reaction solution was stirred for 30 minutes at -78°C and then acrolein was added in one portion. The mixture turned blanket blue. The cooling bath was removed and the reaction solution was allowed to reach room temperature and was stirred for two hours. When the reaction was finished (TLC), water was added (150 mL) and the mixture was extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Solvents were evaporated and the residue was submitted to column chromatography using silica and petroleum PE/EtOAc(90:10) yielding *rac*-**44** as colorless liquid.
Reaction scale	5 mL, 35 mmol
Reaction time	2.5 h
Purification	MPLC, PE/EtOAc 10%, silica 60
Yield	4.81 g (89%)
Appearance	colorless liquid
Sum formula, m.w.	$C_8H_{14}OSi$, 154.28 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ= 0.17 (s, 9H, -Si(C$\underline{H}_3$)$_3$), 2.35 (br, -OH), 4.86 (d, *J* = 5.1, 1H, H3), 5.17-5.23 (dt, *J* = 10.0 Hz, *J* = 1.2 Hz, 1H, H1 *cis*), 5.39-5.51 (dt, *J* = 17.0 Hz, *J* = 1.4 Hz, 1H, H1 *trans*), 5.42-5.52 (ddd, *J* = 17.0 Hz, *J* = 10.0 Hz, *J* = 5.1 Hz 1H, H2)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ = -0.09 (q, -Si(CH_3)$_3$), 63.6 (d, C3), 91.2 (s, C4), 104.2 (s, C5), 116.7 (t, C1), 136.8 (d, C2)
TLC analysis	R_f = 0.19 (PE/EtOAc 9:1), stained with PMA

H II.39 Kinetic resolution of racemic 5-(trimethylsilyl)pent-1-en-4-yn-3-ol **44**- procedure



Procedure	A 250 mL round bottom flask was charged with racemic 5-(trimethylsilyl)pent-1-en-4-yn-3-ol **44** (4.6 g, 29.8 mmol), lipase PS (915 g, 20 w%), vinyl acetate (3.16 mL, 2.95 g,34.3 mmol) and MTBE (107 mL). The flask was sealed with a septum and the reaction mixture was stirred for 3 hours. After the reaction was finished, the reaction mixture was filtered through a pad of celite and solvents were evaporated in vacuum. Column chromatography with silicageland PE/EtOAc (99:1) provided desired products.
Reaction scale	4.6 g, 29.8 mmol
Reaction time	4 h

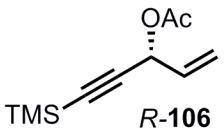
H II.40 (*S*)-5-(Trimethylsilyl)pent-1-en-4-yn-3-ol *S*-**44**[6]



Yield	2.21 g (48%,>99% *ee*)
Appearance	colorless liquid
Sum formula, m.w.	$C_8H_{14}OSi$, 154.28 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ= 0.17 (s, 9H, -Si($C\underline{H_3}$)$_3$), 2.21 (d, *J* = 6.3, 1H, -OH), 4.83-4.89 (d, *J* = 5.1, 1H, H3), 5.17-5.23 (dt, *J* = 10.0 Hz, *J* = 1.2 Hz, 1H, H1*cis*), 5.39-5.50 (dt, *J* = 17.0 Hz, *J* = 1.4 Hz, 1H, H1*trans*), 5.42-5.52 (ddd, *J* = 17.0 Hz, *J* = 10.0 Hz, *J* = 5.1 Hz 1H, H2)

^{13}C-NMR (50 MHz, $CDCl_3$)	δ = -0.08 (q, -Si(CH_3)$_3$), 63.6 (d, C3), 91.2 (s, C4), 104.2 (s, C5), 116.7 (t, C1), 136.8 (d, C2)
TLC analysis	R_f = 0.19 (PE/EtOAc 9:1), stained with PMA
Comment	Spectrum identical as for racemic compound
Specific rotation:	$[\alpha]_D^{25}$= +33.1 (*c* 1.2, $CHCl_3$)
	Lit.$[\alpha]_D^{25}$= +30.4 (*c* 1.2, $CHCl_3$)
Comment	Physical data agree with literature[6]

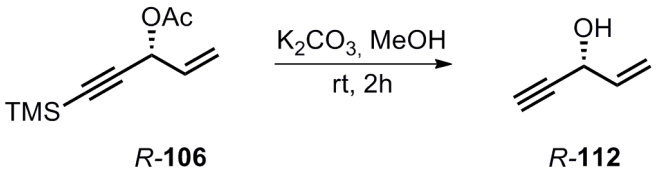
H II.41 (*R*)-5-(Trimethylsilyl)pent-1-en-4-yn-3-yl acetate *R*-**106**[95]



R-**106**

Yield	2.89 g (33%,>99% *ee*)
Appearance	yellowish oil
Sum formula, m.w.	$C_{17}H_{30}O_2Si$, 294.50 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 0.16 (s, 9H, -Si(C$\underline{H_3}$)$_3$), 2.07 (s, 3H, -C(O)C$\underline{H_3}$), 5.26-5.30 (m, 1H, H1), 5.47-5.58 (m, 1H, H1), 5.61-5.78 (m, 2H, H2 and H3)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ = -0.19 (q, -Si(CH_3)$_3$), 21.2 (q, -C(O)$\underline{C}H_3$), 64.7 (d, C3), 92.4 (s, C4), 100.2 (s, C5), 119.1 (t, C1), 132.9 (d, C2), 169.6 (s, -$\underline{C}$(O)CH_3)
TLC analysis	R_f = 0.40 (PE/EtOAc 9:1), stained with PMA
Specific rotation:	$[\alpha]_D^{25}$= -8.3 (*c* 1,4, $CHCl_3$)
	Lit.$[\alpha]_D^{25}$= -10.3 (*c* 1,4, $CHCl_3$)

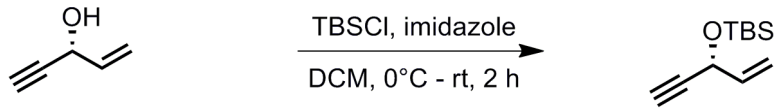
H II.42 (*R*)-Pent-1-en-4-yn-3-ol *R*-**112**[96]



R-**106** *R*-**112**

Procedure	(*R*)-5-(Trimethylsilyl)pent-1-en-4-yn-3-yl acetate **106** (1.62 g, 8.2 mmol) was charged into a100 mL round bottom flask. Then, 30 mL of methanol was added, followed by the addition of potassium carbonate (2.8 g, 20.5 mmol). The reaction mixture was stirred for 2 hours at room temperature. After the reaction was completed, water was added (30 mL) and the mixture was repeatedly extracted with diethylether, until no more product remained in the water phase, as controlled by TLC. The combined organic layers were washed with brine, dried over sodium sulfate and filtered. Solvents were evaporated and dried at 30°C at a minimum of 100 mbar. The mixture was re-dissolved in DCM and filtered through a pad of silica and the solvent was evaporated as described before, yielding 82% of alcohol *R*-**112** as colorless liquid.
Reaction scale	1.62 g, 8.2 mmol
Reaction time	2 h
Purification	filtration through a pad of silica 60 with DCM
Yield	552.04 mg (82%)
Appearance	colorless liquid
Sum formula, m.w.	C_5H_6O, 82.1 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 2.55-2.56 (d, *J* = 2.2 Hz, 1H, H5), 3.17-3.19 (d, *J* = 5.1, 1H, -OH), 4.85 (br, 1H, H3), 5.17-5.22 (d, *J* = 10.2 Hz, *J* = 1.3 Hz, 1H, H1, *cis*), 5.40-5.48 (d, *J* = 17.0 Hz, 1H, H1, *trans*), 5.85-6.01 (ddd, *J* = 17.0 Hz, *J* = 10.2 Hz, *J* = 5.3 Hz 1H, H2)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ = 62.8 (d, C3), 74.5 (d, C5), 82.7 (s, C4), 116.8 (t, C1), 136.5 (d, C2)
TLC analysis	R_f = 0.11 (PE/EA 9:1), stained with PMA
Specific rotation:	$[\alpha]_D^{25}$= -10.3 (*c* 0.17, MeOH)

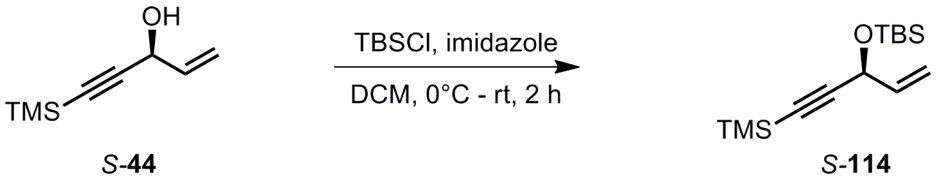
H II.43 (*R*)-tert-Butyldimethyl(pent-1-en-4-yn-3-yloxy)silane *R*-**113**[97]



R-**112** *R*-**113**

Procedure	(*R*)-Pent-1-en-4-yn-3-ol *R*-**112** (411 mg, 5 mmol) and imidazole (749 mg, 11 mmol) were dissolved in 35 mL of dry DCM. The mixture was cooled to 0 °C and TBSCl (829 mg, 5.5 mmol) was added. The ice bath was removed and the resulting mixture was stirred at room temperature for 2 hours. After 2 hours the reaction was quenched with water (30 mL), the layers were separated and the aqueous phase was extracted with DCM (2 x 30 mL). The combined organic layers were washed with brine, dried over sodium sulfate and filtered. The mixture was concentrated at reduced pressure. The resulting residue was passed through a pad of silica, using DCM as an eluent. The solvent was removed under reduced pressure, affording *R*-**113** in 91% as a colorless liquid.
Reaction scale	411 mg, 5 mmol
Reaction time	2 h
Purification	filtration through a pad of silica 60 with DCM
Yield	893.4 mg (91%)
Appearance	colorless liquid
Sum formula, m.w.	$C_{11}H_{20}OSi$, 196.36 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 0.14 (s, 3H, -$SiCH_3$), 0.15 (s, 3H, $SiCH_3$), 2.50 (d, *J* = 2.3 Hz, 1H, H5), 4.87-4.92 (m, 1H, H3), 5.13-5.20 (dt, *J* = 10.2 Hz, *J* = 1.4 Hz, 1H, H1 *cis*), 5.37-5.47 (dt, *J* = 16.8 Hz, *J* = 1.4 Hz, 1H, H1 *trans*), 5.85-6.01 (ddd, ^{3}J = 16.8 Hz, *J* = 10.2 Hz, *J* = 5.1 Hz, 1H, H2)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ = -4.8 (q, -$SiCH_3$), -4.5 (q, -$SiCH_3$), 18.5 (s, -Si$\underline{C}(CH_3)_3(CH_3)_2$), 25.9 (q, -$SiC(CH_3)_3(\underline{C}H_3)_2$), 63.6 (d, C3), 73.4 (d, C5), 83.6 (s, C4), 115.3 (s, C1), 137.7 (t, C2)
TLC analysis	R_f = 0.63 (PE/EtOAc 9:1), stained with PMA
Specific rotation:	$[\alpha]_D^{25}$= +26.7 (*c* 1.00, $CHCl_3$)

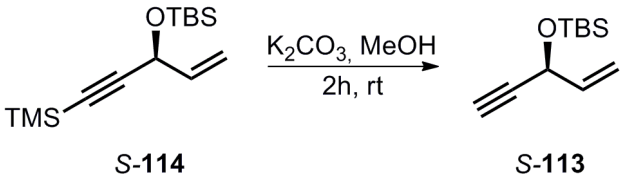
H II.44 (*S*)-tert-Butyldimethyl((5-(trimethylsilyl)pent-1-en-4-yn-3-yl)oxy)silane *S*-**114**[6, 97]



S-**44** *S*-**114**

Procedure	(*S*)-5-(Trimethylsilyl)pent-1-en-4-yn-3-ol *S*-**44** (1.7 g, 11 mmol) and imidazole (1.65 g, 11 mmol) were dissolved in 90 mL of dry DCM. The mixture was cooled to 0 °C and TBSCl (1.83 g, 12.4 mmol) was added. The ice bath was removed and the resulting mixture was stirred at room temperature for 2 hours. After 2 hours the reaction was quenched with water (90 mL), the layers were separated and the aqueous phase was extracted with DCM (2 x 90 mL). The combined organic layers were washed with brine, dried over sodium sulfate and filtered. The mixture was concentrated at reduced pressure. The resulting residue was passed through a pad of silica, using DCM as an eluent. The solvent was distilled off under reduced pressure, affording *S*-**114** in 93% as a colorless liquid.
Reaction scale	1.62 g, 8.2 mmol
Reaction time	2 h
Purification	filtration through a pad of silica 60 with DCM
Yield	2.05 g (93%)
Appearance	colorless liquid
Sum formula, m.w.	$C_{14}H_{28}OSi_2$, 268.54 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 0.14 (br, 6H, -SiC(CH_3)$_3$($C\underline{H}_3$)$_2$), 0.17 (s, 9H, -Si(CH_3)$_3$), 0.92 (s, 9H, -SiC($C\underline{H}_3$)$_3$(CH_3)$_2$), 4.87-4.91 (dt, *J* = 4.7 Hz, *J* = 1.6 Hz, 1H, H3), 5.11-5.18 (dt, *J* = 10.0 Hz, *J* = 1.6 Hz, 1H, H1 *cis*), 5.40-5.48 (d,*J* = 17.0 Hz, *J* = 1.6 Hz, 1H, H1 *trans*), 5.85-6.01 (ddd, *J* = 17.0 Hz, *J* = 10.0 Hz, *J* = 4.7 Hz, 1H, H2)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ = -4.6 (q, -SiC(CH_3)$_3$($\underline{C}H_3$)$_2$), -4.4 (q, -SiC(CH_3)$_3$($\underline{C}H_3$)$_2$), -0.1 (q, -Si(CH_3)$_3$), 18.5 (s, -Si$\underline{C}$(CH_3)$_3$(CH_3)$_2$), 26.0 (q, -SiC($\underline{C}H_3$)$_3$(CH_3)$_2$), 64.2 (d, C3), 90.2 (s, C4), 105.3 (s, C5), 115.0 (d, C1), 137.7 (d, C2)
TLC analysis	R_f = 0.88(PE/EtOAc 9:1), stained with PMA
Specific rotation:	$[\alpha]_D^{24.5}$= -31.7 (*c* 1.00, $CHCl_3$) (Lit. -39.9(*c* 1.00, $CHCl_3$)

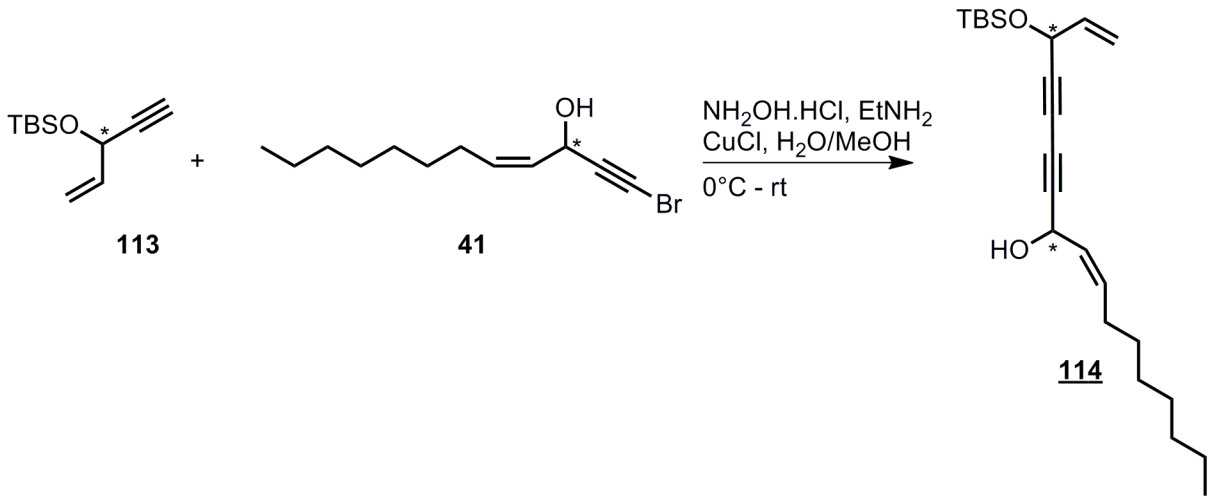
H II.45 (*S*)-tert-Butyldimethyl(pent-1-en-4-yn-3-yloxy)silane *S*-**113**[97]



S-**114** *S*-**113**

Procedure	(*S*)-tert-Butyldimethyl((5-(trimethylsilyl)pent-1-en-4-yn-3-yl)oxy)silane *S*-**114**(1.88 g, 7 mmol) was chargedinto a 100 mL round bottom flask. 50 mL of methanol was added, followed by the addition of potassium carbonate (1.93 g, 14 mmol). The reaction mixture was stirred for 2 hours at room temperature. After the reaction was completed, water was added (30 mL) and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate and filtered. Solvents were evaporated under reduced pressure. The mixture was re-dissolved in DCM and filtered through a pad of silica and concentrated under reduced pressure, yielding 78% of alkyne *S*-**113** as colorless liquid.
Reaction scale	1.88 g, 7 mmol
Reaction time	2 h
Purification	filtration through a pad of silica 60 with DCM
Yield	1.07 g (78%)
Appearance	colorless liquid
Sum formula, m.w.	$C_{11}H_{20}OSi$, 196.36 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 0.14 (s, 3H, -$SiCH_3$), 0.15 (s, 3H, $SiCH_3$), 2.50 (d, *J* = 2.3 Hz, 1H, H5), 4.87-4.92 (m, 1H, H3), 5.13-5.20 (dt, *J* = 10.2 Hz, *J* = 1.4 Hz, 1H, H1 *cis*), 5.37-5.47 (dt, *J* = 16.8 Hz, *J* = 1.4 Hz, 1H, H1 *trans*), 5.85-6.01 (ddd, ^3J = 16.8 Hz, *J* = 10.2 Hz, *J* = 5.1 Hz, 1H, H2)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ = -4.8 (q, -$SiCH_3$), -4.5 (q, -$SiCH_3$), 18.5 (s, -Si$\underline{C}(CH_3)_3(CH_3)_2$), 25.9 (q, -$SiC(CH_3)_3(\underline{C}H_3)_2$), 63.6 (d, C3), 73.5 (d, C5), 83.6 (s, C4), 115.3 (s, C1), 137.6 (t, C2)
TLC analysis	R_f = 0.63(PE/EtOAc 9:1), stained with PMA
Specific rotation:	$[\alpha]_D^{25}$= -27.4 (*c* 1.00, $CHCl_3$)

H II.46 Cadiot-Chodkiewidz coupling – general procedure

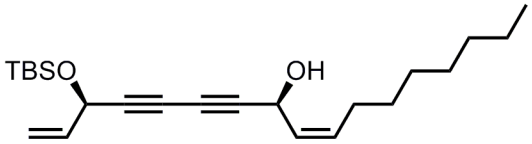


113 **41** **114**

General procedure

A Wheaton vial was charged with hydroxyl amine hydrochloride (27.8 mg, 0.4 mmol), copper chloride (5 mg, 0.05 mmol), 70% aqueous solution of ethylamine (1 mL), H_2O (0.33 mL) and MeOH (3.65 mL). The atmosphere was exchanged for argon and the mixture cooled to 0 °C. (*R*) or (*S*)-*tert*-butyldimethyl(pent-1-en-4-yn-3-yloxy)silane **113** (491 mg, 2.5 mmol) was dissolved in methanol (1.1 mL) and added to the catalytic system. Then (*S,Z*) or (*R,Z*)-1-bromododec-4-en-1-yn-3-ol **41** (295 mg, 1 mmol) was dissolved in 1.1 mL of methanol and was added into the reaction mixture. The reaction mixture was stirred for 1 hour at 0 °C and after the reaction was finished it was quenched with saturated ammonium chloride (4 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine (20 mL) and dried over sodium sulfate and solvents were evaporated under reduced pressure at room temperature. The product was purified by column chromatography using silica as a stationary phase and PE/EtOAc (95:5) as an eluent.

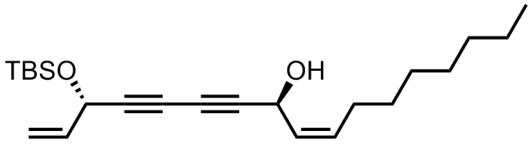
H II.47 (*3R,8S,Z*)-3-((tert-Butyldimethylsilyl)oxy)heptadeca-1,9-dien-4,6-diyn-8-ol *R,S*-**114**



R,S-**114**

Procedure	Prepared according to the general procedure
Reaction scale	259 mg, 1 mmol
Reaction time	2 h
Yield	247.3 mg (66%)
Appearance	colorless oil
Sum formula, m.w.	$C_{23}H_{38}O_2Si$, 374.63 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 0.12 (s, 3H, -SiC$\underline{H_3}$), 0.14 (s, 3H, -SiC$\underline{H_3}$), 0.91 (s, 12H, -SiC(C$\underline{H_3}$)$_3$and H17), 1.27-1.42 (m, 10H, H12-H16), 1.84 (d,*J* = 5.3 Hz, 1H, -OH), 2.06-2.16 (q, *J* = 6.8 Hz, 2H, H11), 4.93 (d, *J* = 4.9 Hz, 1H, H3), 5.14-5.22 (m, 2H, H1 *cis* and H8), 5.33-5.43 (dt, *J* = 17.0 Hz, *J* = 1.4 Hz, 1H, H1 *trans*), 5.47-5.68 (m, 2H, H9 and H10), 5.78-5.94 (m, 1H, H2)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ = -4.8 (q, -Si$\underline{C}H_3$), -4.5 (q, -Si$\underline{C}H_3$), 14.2 (q, C17), 18.4 (s, -Si$\underline{C}(CH_3)_3$), 22.8 (t, C16), 25.9 (q, -SiC($\underline{C}H_3)_3$), 27.8 (t, -CH_2-*), 29.3 (t, -CH_2-*), 29.3 (t, -CH_2-*), 29.4 (t, -CH_2-*), 31.9 (t, C15), 58.8 (d, C8), 64.2 (d, C3), 69.2 (s, C5 or C6), 69.4 (s, C5 or C6), 79.3 (s, C4 or C7), 79.5 (s, C4 or C7), 115.8 (t, C1), 127.9 (d, C9), 134.7 (d, C10), 136.8 (d, C2)
TLC analysis	R_f = 0.31 (PE/EtOAc 9:1), stained with PMA
Specific rotation:	$[\alpha]_D^{25}$= +208.2 (*c*1.0, $CHCl_3$)

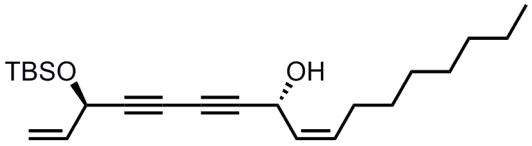
H II.48 (*3S,8S,Z*)-3-((tert-Butyldimethylsilyl)oxy)heptadeca-1,9-dien-4,6-diyn-8-ol *S,S*-**114**



S,S-**114**

Procedure	Prepared according to the general procedure
Reaction scale	259 mg, 1 mmol
Reaction time	2 h
Yield	239.8 mg (64%)
Appearance	colorless oil
Sum formula, m.w.	$C_{23}H_{38}O_2Si$, 374.63 g.mol^{-1}
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 0.12 (s, 3H, -SiC$\underline{H}_3$), 0.14 (s, 3H, -SiC$\underline{H}_3$), 0.86-0.91 (m, 12H, -SiC(C$\underline{H}_3$)$_3$and H17), 1.27 (b, 8H, H13-H16), 1.37-1.40 (m, 2H, H12 1.80 (d,*J*= 5.4 Hz 1H, -OH), 2.11 (q, *J* = 6.8 Hz, 2H, H11), 4.94 (d, *J* = 4.9 Hz, 1H, H3), 5.15-5.22 (m, 2H, H1 *cis* and H8), 5.36-5.41 (dt, *J* = 17.0 Hz, *J* = 1.4 Hz, 1H, H1 *trans*), 5.49-5.64 (m, 2H, H9 and H10), 5.82-5.91 (m, 1H, H2)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ = -4.8 (q, -Si$\underline{C}H_3$), -4.6 (q, -Si$\underline{C}H_3$), 14.2 (q, C17), 18.4 (s, -Si$\underline{C}(CH_3)_3$), 22.8 (t, C16), 25.9 (q, -SiC($\underline{C}H_3$)$_3$), 27.8 (t, -CH_2-*), 29.2 (t, -CH_2-*), 29.3 (t, -CH_2-*), 29.4 (t, -CH_2-*), 31.9 (t, C15), 58.8 (d, C8), 64.2 (d, C3), 69.2 (s, C5 or C6), 69.4 (s, C5 or C6), 79.4 (s, C4 or C7), 79.5 (s, C4 or C7), 115.8 (t, C1), 128.0 (d, C9), 134.7 (d, C10), 136.9 (d, C2)
TLC analysis	R_f = 0.31 (PE/EtOAc 9:1), stained with PMA
Specific rotation:	$[\alpha]_D^{25}$= +145.2 (*c*1.0, $CHCl_3$)

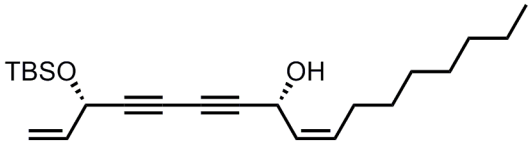
H II.49 (*3R,8R,Z*)-3-((tert-Butyldimethylsilyl)oxy)heptadeca-1,9-dien-4,6-diyn-8-ol *R,R*-**114**



R,R-**114**

Procedure	Prepared according to the general procedure
Reaction scale	259 mg, 1 mmol
Reaction time	2 h
Yield	247.3 mg (66%)
Appearance	colorless oil
Sum formula, m.w.	$C_{23}H_{38}O_2Si$, 374.63 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 0.12 (s, 3H), 0.14 (s, 3H), 0.91 (s, 9H), 1.27 (br, 10H), 1.83 (d,*J* = 5.3 Hz, 1H), 2.06-2.16 (q, *J* = 6.8 Hz, 2H), 4.94 (d, *J* = 4.9 Hz, 1H, H3), 5.14-5.22 (m, 2H), 5.33-5.43 (dt, *J* = 17.0 Hz, *J* = 1.4 Hz, 1H), 5.47-5.68 (m, 2H), 5.78-5.94 (m, 1H)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ = -4.8 (q, -Si<u>C</u>H_3), -4.6 (q, -Si<u>C</u>H_3), 14.2 (q, C17), 18.4 (s, -Si<u>C</u>$(CH_3)_3$), 22.8 (t, C16), 25.9 (q, -SiC($\underline{C}H_3)_3$), 27.8 (t, -CH_2-*), 29.2 (t, -CH_2-*), 29.3 (t, -CH_2-*), 29.4 (t, -CH_2-*), 31.9 (t, C15), 58.8 (d, C8), 64.2 (d, C3), 69.2 (s, C5 or C6), 69.4 (s, C5 or C6), 79.4 (s, C4 or C7), 79.5 (s, C4 or C7), 115.8 (t, C1), 128.0 (d, C9), 134.7 (d, C10), 136.9 (d, C2)
TLC analysis	R_f = 0.31 (PE/EtOAc 9:1), stained with PMA
Specific rotation:	$[\alpha]_D^{25}$= -148.1 (*c*1.0, $CHCl_3$)

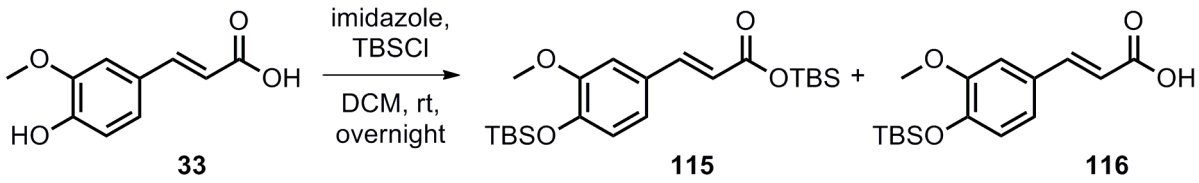
H II.50 (*3S,8R,Z*)-3-((tert-Butyldimethylsilyl)oxy)heptadeca-1,9-dien-4,6-diyn-8-ol *S,R*-**114**



S,R-**114**

Procedure	Prepared according to the general procedure
Reaction scale	259 mg, 1 mmol
Reaction time	2 h
Yield	243.5 (65%)
Appearance	colorless oil
Sum formula, m.w.	$C_{23}H_{38}O_2Si$, 374.63 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 0.12 (s, 3H), 0.14 (s, 3H), 0.91 (s, 9H), 1.27-1.42 (m, 10H), 1.80 (d, *J* = 5.3 Hz, 1H), 2.06-2.16 (q, *J* = 6.8 Hz, 2H), 4.94 (d, *J* = 4.9 Hz, 1H, H3) 5.13-5.23 (m, 2H), 5.33-5.43 (dt, *J* = 17.0 Hz, *J* = 1.4 Hz, 1H), 5.46-5.68 (m, 2H), 5.78-5.94 (m, 1H)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ = -4.8 (q, -Si<u>C</u>H_3), -4.6 (q, -Si<u>C</u>H_3), 14.2 (q, C17), 18.4 (s, -Si<u>C</u>$(CH_3)_3$), 22.8 (t, C16), 25.9 (q, -SiC($\underline{C}H_3)_3$), 27.8 (t, -CH_2-*), 29.2 (t, -CH_2-*), 29.3 (t, -CH_2-*), 29.4 (t, -CH_2-*), 31.9 (t, C15), 58.8 (d, C8), 64.2 (d, C3), 69.2 (s, C5 or C6), 69.4 (s, C5 or C6), 79.4 (s, C4 or C7), 79.5 (s, C4 or C7), 115.8 (t, C1), 128.0 (d, C9), 134.7 (d, C10), 136.9 (d, C2)
TLC analysis	R_f = 0.31 (PE/EtOAc 9:1), stained with PMA
Specific rotation:	$[\alpha]_D^{25}$= -215.6 (*c*1.0, $CHCl_3$)

H II.51 Protection of ferulic acid – general procedures



33 **115** **116**

Procedure A, part I *trans*-Ferulic acid **31** (4 g, 20.6 mmol) and imidazole (6.8 g, 20.6 mmol) were dissolved in 140 mL of dry DCM. The mixture was cooled to 0 °C and TBSCl (1.83 g, 12.4 mmol) was added. The ice bath was removed and the resulting mixture was stirred at room temperature overnight. Then, the reaction was quenched with water (140 mL), the layers were separated and the aqueous phase was extracted with DCM (2 x 140 mL). The combined organic layers were washed with brine (200 mL), dried over sodium sulfate and filtered. The mixture was concentrated at reduced pressure. The resulting residue was passed through a pad of silica, using DCM as an eluent. Thesolvent was distilled off under reduced pressure, and the product was subjected to column chromatography with silica and MeOH/DCM 0-10% of MeOH, affording76% of ester **32** and 13% of TBS-ferulic acid **33**.

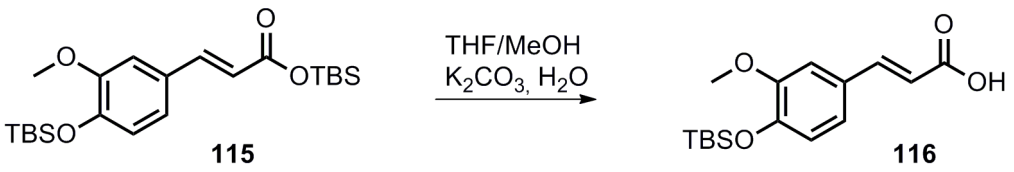
Reaction scale 4 g, 20.6 mmol

Reaction time overnight

Purification Column chromatography with silica and MeOH/DCM 0-10% of MeOH

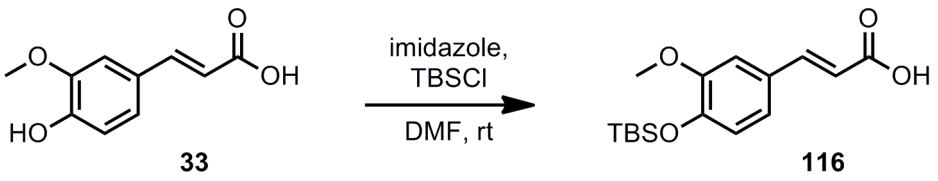
Yield **32** 6.92 g (76%)

33825.2 mg(13%)



115 **116**

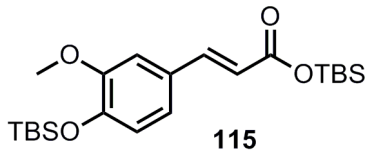
ProcedureA, part II	*trans*-Ferulic-TBS ester (6.6 g, 15.6 mmol) was dissolved in 270 mL of THF/MeOH mixture (70:200 mL). An aqueous solution of K_2CO_3 (5.5 mg in 67 mL of H_2O) was added dropwise at room temperature and the reaction mixture was stirred for 30 minutes. Organic solvents were then evaporated. Et_2O and brine were added. Mixture was cooledto 0 °C, and aqueous layer was acidified with 10% HCl to pH 6. The mixture was extracted with ether, dried over sodium sulfate, filtered and after evaporation of the solvent,the desired product was recovered quantitatively.
Reaction scale	6.6 g, 15.6 mmol
Reaction time	30 min
Purification	used without further purification
Yield	4.8 g (quantitative)



33 **116**

Procedure B	*Trans*-ferulic acid **31** (291 mg, 1.5 mmol) and imidazole (1 g, 15 mmol) were dissolved in 9 mL of dry DMF. The mixture was cooled to 0 °C and TBSCl (1.83 g, 12.4 mmol) was added. The ice bath was removed and the resulting mixture was stirred at room temperature overnight. Then, the reaction was quenched with water (10 mL), the layers were separated and the aqueous phase was extracted with DCM (2 x 10 mL). The combined organic layers were washed with brine (15 mL), dried over sodium sulfate and filtered. The mixture was concentrated at reduced pressure. The resulting residue was passed through a pad of silica, using DCM as an eluent. The solvent was distilled off under reduced pressure, affording **33** in 63% as a white solid.
Reaction scale	291 mg, 1.5 mmol
Reaction time	overnight
Purification	filtration through a pad of silica 60 with DCM
Yield	291.2 mg (63%)

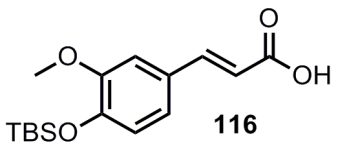
H II.52 (*E*)-tert-Butyldimethylsilyl3-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl)acrylate **115**[98]



115

Procedure	Procedure A, part I
Appearance	white solid
Sum formula, m.w.	$C_{22}H_{38}O_4Si_2$, 422.7 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 0.17 (s, 6H, -Si($C\underline{H}_3$)$_2$*), 0.33 (s, 6H-Si($C\underline{H}_3$)$_2$*), 0.99 (s, 18H, -SiC($C\underline{H}_3$)$_3$), 3.84 (s,3H, OCH_3), 6.23-6.30 (d, *J* = 15.8 Hz, 1H, H8), 6.81-6.86 (d, *J* = 8.8 Hz, 1H, H5), 7.00-7.02 (m, 1H, H2 and H6), 7.50-7.58 (d, *J* = 15.8 Hz, 1H, H7)
TLC analysis	R_f = 0.82 (PE/EtOAc 9:1)

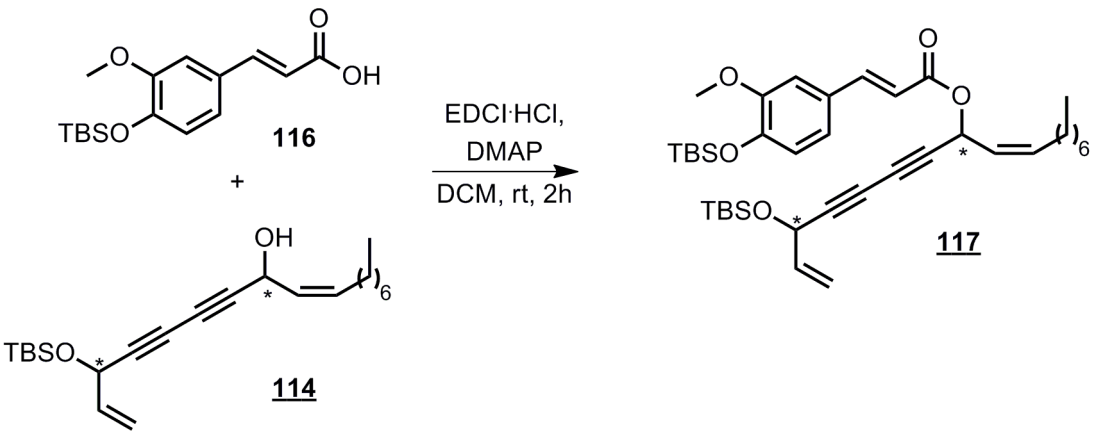
H II.53 (*E*)-3-(4-((tert-Butyldimethylsilyl)oxy)-3-methoxyphenyl)acrylic acid **116**[99]



116

Procedure	ProcedureA or B
Yield	5.65 g (89% - procedure A, over two steps), 291.2 mg (63% - procedure B),
Appearance	colorlesssolid
Melting point:	188.2-190.0 °C
Sum formula, m.w.	$C_{16}H_{24}O_4Si$, 308.14 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 0.18 (s, 6H, -Si(C$\underline{H}_3$)$_2$), 1.00 (s, 9H, -SiC(C$\underline{H}_3$)$_3$), 3.85 (s,3H, -OMe), 6.28-6.36 (d, *J* = 15.8 Hz, 1H, H8), 6.84-6.88 (d, *J* = 8.6 Hz, 1H, H5), 7.04-7.08 (m, 1H, H2 and H6), 7.68-7.76 (d, *J* = 15.8 Hz, 1H, H7)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ = -4.3 (q, 2C, -Si($\underline{C}$H$_3$)$_2$), 18.7 (s, -Si$\underline{C}$(CH$_3$)$_3$), 25.9 (q, -SiC($\underline{C}$H$_3$)$_3$), 111.3 (d, C2), 115.2 (d, C8), 121.4 (d, C5 or C6), 123.0 (d, C5 or C6), 128.1 (s, C1), 147.4, 148.3 (s, C4), 151.5 (s, C3), 172.8 (s, C9)
TLC analysis	R_f = 0.53 (DCM/MeOH 9:1)

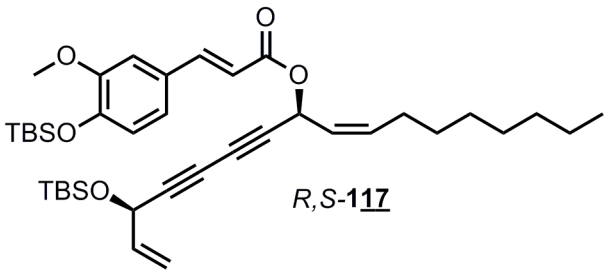
H II.54 General procedure for Steglich esterification using EDCI



General procedure

To a mixture of 3-methoxy-4-(*t*-butyldimethylsilyl)oxy cinnamic acid **33** (52 mg, 0.17 mmol,), DMAP (16 mg, 0.13 mmol) and 3-((tert-butyldimethylsilyl)oxy)heptadeca-1,9-dien-4,6-diyn-8-ol (50 mg, 0.13 mmol) **34** in dry DCM (1.2 mL), EDCI·HCl (33 mg, 0.17 mmol) was added under positive argon pressure at 0 °C. The reaction vessel was sealed and the mixture was allowed to warmto room temperature. After the reaction was completed (TLC), the mixture was cooled with anice bath and 2N HCl (1.2 mL) was added dropwise. The mixture was extracted with DCM (3 x 2 mL) and the combined organic mixtures were washed with brine (5 mL), dried over sodium sulfate and the solution was passed through a pad of celite. Volatiles were evaporated at reduced pressure at room temperature. Products were purified by column chromatography using silicagel and petroleum ether/ethyl acetate (95:5).

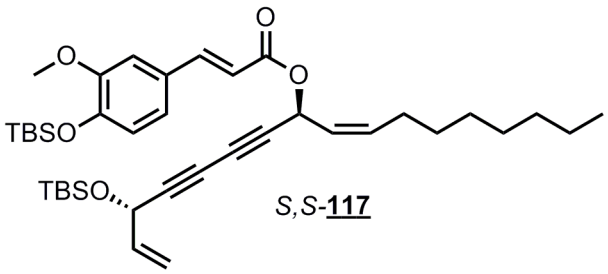
H II.55 (*E*)-(*3R,8S,Z*)-3-((tert-Butyldimethylsilyl)oxy)hexadeca-1,9-dien-4,6-diyn-8-yl-3-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl)acrylate *R,S*-**117**



R,S-**117**

Procedure	Prepared according to the general procedure
Reaction scale	50 mg, 0.13 mmol
Reaction time	2 h
Yield	70.0 mg (81%)
Appearance	colorless oil
Sum formula, m.w.	$C_{39}H_{60}O_5Si_2$, 665.06 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 0.12 (s, 3H, -$SiCH_3$*), 0.14 (s, 3H, -$SiCH_3$*), 0.17 (6H, -$Si(CH_3)_2$*), 0.83-0.91 (m, 12H, H17 and -$SiC(CH_3)_3$), 0.99 (s, 9H, -$SiC(C\underline{H}_3)_3$) 1.26-1.39 (m, 10H, H12-H16), 2.20 (q, *J* = 6.8 Hz, 2H, H11), 3.83 (s, 3H, -OCH_3), 4.93 (d, *J* = 4.9 Hz, 1H, H3), 5.13-5.19 (dt, *J* = 10.0 Hz, *J* = 1.2 Hz, 1H, H1 *cis*), 5.33-5.43 (dt, *J* = 16.8 Hz, *J* = 1.2 Hz, 1H, H1 *trans*), 5.50-5.72 (m, 2H, H9 and H10), 5.76-5.94 (m, 1H, H2), 6.25-6.33 (m, 2H, H8 and H8'), 6.84 (d, *J* = 8.8 Hz, 1H, H5'), 7.00-7.03 (m, 2H, H2' and H6'), 7.65 (d, *J* = 16.0 Hz, 1H, H7')
^{13}C-NMR (100 MHz, $CDCl_3$)	δ = -4.8 (q, -$SiCH_3$*), -4.5 (3C, q, -$SiCH_3$*), 14.2 (q, C17), 18.4 (s, -$Si\underline{C}(CH_3)_3$*), 18.6 (s, -$Si\underline{C}(CH_3)_3$*) 22.8 (t, C16), 25.8 (3C, q, -$SiC(\underline{C}H_3)_3$*), 25.9 (3C, q, -$SiC(\underline{C}H_3)_3$*), 28.1 (t, C11), 29.3 (t, -CH_2-*), 29.3 (2C, t, -CH_2-*), 32.0 (t, -CH_2-*), 55.6 (q, C8 or -OCH_3), 60.2 (d, C8 or -OCH_3), 64.1 (d, C3), 69.4 (s, C5 or C6), 69.7 (s, C5 or C6), 76.3 (s, C4 or C7), 79.6 (s, C4 or C7), 111.0* (d), 115,1* (d), 115.8* (t, C1), 121.2* (d), 122.6* (d), 124.3* (d), 128.3 (s, C1'), 136.5* (d), 136.8* (d), 146.1* (d), 147.9 (s, C4'), 151.3 (s, C3'), 165.8 (s, C9')
TLC analysis	R_f = 0.57 (PE/EtOAc 9:1), stained with PMA
Specific rotation:	$[\alpha]_D^{25}$=+91.8 (*c* 0.25, $CHCl_3$)

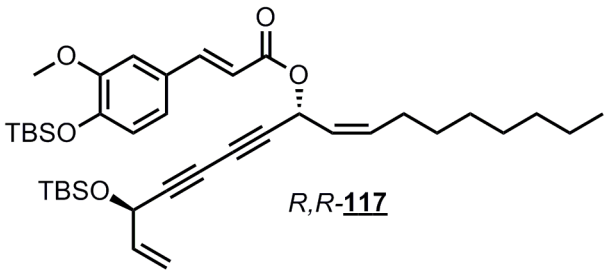
H II.56 (*E*)-(*3S,8S,Z*)-3-((tert-Butyldimethylsilyl)oxy)hexadeca-1,9-dien-4,6-diyn-8-yl-3-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl)acrylate *S,S*-**117**



S,S-**117**

Procedure	Prepared according to the general procedure
Reaction scale	50 mg, 0.13 mmol
Reaction time	2 h
Yield	68.3 mg (79%)
Appearance	colorless oil
Sum formula, m.w.	$C_{39}H_{60}O_5Si_2$, 665.06 g.mol^{-1}
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 0.12 (s, 3H, -$SiCH_3$*), 0.14 (s, 3H, -$SiCH_3$*), 0.17 (6H, -$Si(CH_3)_2$*), 0.85-0.91 (m, 12H, H17 and -$SiC(CH_3)_3$), 0.99 (s, 9H, -$SiC(C\underline{H}_3)_3$) 1.26-1.39 (m, 10H, H12-H16), 2.20 (q, *J* = 6.8 Hz, 2H, H11), 3.83 (s, 3H, -OCH_3), 4.93 (d, *J* = 4.9 Hz, 1H, H3), 5.13-5.19 (dt, *J* = 10.0 Hz, *J* = 1.2 Hz, 1H, H1 *cis*), 5.33-5.43 (dt, *J* = 16.8 Hz, *J* = 1.2 Hz, 1H, H1 *trans*), 5.50-5.72 (m, 2H, H9 and H10), 5.81-5.90 (m, 1H, H2), 6.25-6.33 (m, 2H, H8 and H8'), 6.84(d, *J* = 8.8 Hz, 1H, H5'), 7.00-7.03 (m, 2H, H2' and H6'), 7.65 (d, *J* = 16.0 Hz, 1H, H7')
^{13}C-NMR (100 MHz, $CDCl_3$)	δ = -4.8 (q, -$SiCH_3$*), -4.5 (3C, q, -$SiCH_3$*), 14.2 (q, C17), 18.4 (s, -$Si\underline{C}(CH_3)_3$*), 18.6 (s, -$Si\underline{C}(CH_3)_3$*) 22.8 (t, C16), 25.8 (3C, q, -$SiC(\underline{C}H_3)_3$*), 25.9 (3C, q, -$SiC(\underline{C}H_3)_3$*), 28.1 (t, C11), 29.3 (t, -CH_2-*), 29.3 (2C, t, -CH_2-*), 32.0 (t, -CH_2-*), 55.6 (q, C8 or -OCH_3), 60.2 (d, C8 or -OCH_3), 64.1 (d, C3), 69.4 (s, C5 or C6), 69.7 (s, C5 or C6), 76.3 (s, C4 or C7), 79.6 (s, C4 or C7), 111.0* (d), 115,1* (d), 115.8* (t, C1), 121.2* (d), 122.6* (d), 124.3* (d), 128.3 (s, C1'), 136.5* (d), 136.8* (d), 146.1* (d), 147.9 (s, C4'), 151.3 (s, C3'), 165.8 (s, C9')
TLC analysis	R_f = 0.57 (PE/EtOAc 9:1), stained with PMA
Specific rotation:	$[\alpha]_D^{25}$= +67.8 (*c* 0.25, $CHCl_3$)

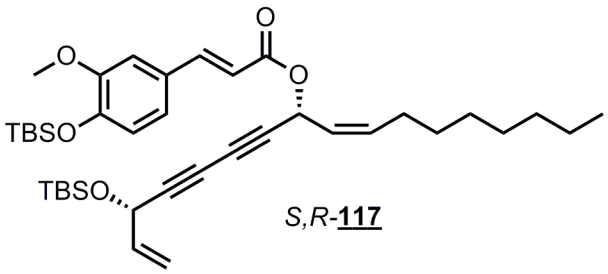
H II.57 (*E*)-(*3R,8R,Z*)-3-((tert-Butyldimethylsilyl)oxy)hexadeca-1,9-dien-4,6-diyn-8-yl-3-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl)acrylate *R,R*-**117**



R,R-**117**

Procedure	Prepared according to the general procedure
Reaction scale	50 mg, 0.13 mmol
Reaction time	2 h
Yield	67.4 mg (78%)
Appearance	colorless oil
Sum formula, m.w.	$C_{39}H_{60}O_5Si_2$, 665.06 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 0.12 (s, 3H, -$SiCH_3$*), 0.14 (s, 3H, -$SiCH_3$*), 0.17 (6H, -$Si(CH_3)_2$*), 0.83-0.91 (m, 12H, H17 and -$SiC(CH_3)_3$), 0.99 (s, 9H, -$SiC(C\underline{H}_3)_3$) 1.26-1.39 (br, 10H, H12-H16), 2.19 (q, *J* = 6.8 Hz, 2H, H11), 3.83 (s, 3H, -OCH_3), 4.93 (d, *J* = 4.9 Hz, 1H, H3), 5.14-5.19 (dt, *J* = 10.0 Hz, *J* = 1.2 Hz, 1H, H1 *cis*), 5.34-5.42 (dt, *J* = 16.8 Hz, *J* = 1.2 Hz, 1H, H1 *trans*), 5.50-5.72 (m, 2H, H9 and H10), 5.76-5.94 (m, 1H, H2), 6.25-6.33 (m, 2H, H8 and H8'), 6.84 (d, *J* = 8.8 Hz, 1H, H5'), 7.00-7.03 (m, 2H, H2' and H6'), 7.65 (d, *J* = 16.0 Hz, 1H, H7')
^{13}C-NMR (50 MHz, $CDCl_3$)	δ = -4.8 (q, -$SiCH_3$*), -4.5 (3C, q, -$SiCH_3$*), 14.2 (q, C17), 18.4 (s, -$Si\underline{C}(CH_3)_3$*), 18.6 (s, -$Si\underline{C}(CH_3)_3$*) 22.8 (t, C16), 25.8 (3C, q, -$SiC(\underline{C}H_3)_3$*), 25.9 (3C, q, -$SiC(\underline{C}H_3)_3$*), 28.1 (t, C11), 29.3 (t, -CH_2-*), 29.3 (2C, t, -CH_2-*), 32.0 (t, -CH_2-*), 55.6 (q, C8 or -OCH_3), 60.2 (d, C8 or -OCH_3), 64.1 (d, C3), 69.4 (s, C5 or C6), 69.7 (s, C5 or C6), 76.3 (s, C4 or C7), 79.6 (s, C4 or C7), 111.0* (d), 115,1* (d), 115.8* (t, C1), 121.2* (d), 122.6* (d), 124.3* (d), 128.3 (s, C1'), 136.5* (d), 136.8* (d), 146.1* (d), 147.9 (s, C4'), 151.3 (s, C3'), 165.8 (s, C9')
TLC analysis	R_f = 0.57 (PE/EtOAc 9:1), stained with PMA
Specific rotation:	$[\alpha]_D^{25}$= -67.6 (*c* 0.25, $CHCl_3$)

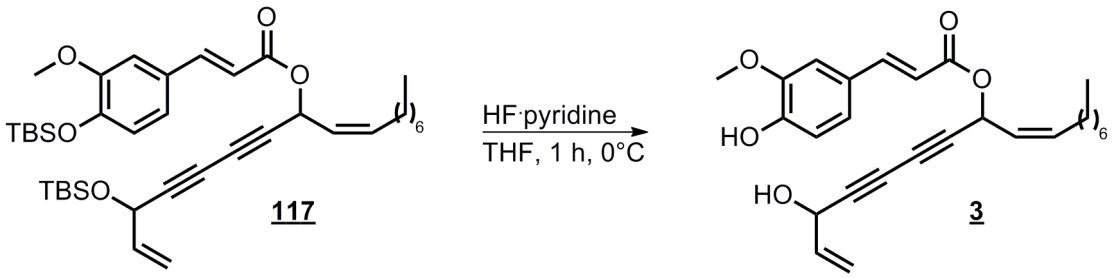
H II.58 (*E*)-(*3S,8R,Z*)-3-((tert-Butyldimethylsilyl)oxy)hexadeca-1,9-dien-4,6-diyn-8-yl-3-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl)acrylate *S,R*-**117**



S,R-**117**

Procedure	Prepared according to the general procedure
Reaction scale	50 mg, 0.13 mmol
Reaction time	2 h
Yield	67.4 mg (78%)
Appearance	colorless oil
Sum formula, m.w.	$C_{39}H_{60}O_5Si_2$, 665.06 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 0.12 (s, 3H, -$SiCH_3$*), 0.14 (s, 3H, -$SiCH_3$*), 0.17 (6H, -$Si(CH_3)_2$*), 0.83-0.91 (m, 12H, H17 and -$SiC(CH_3)_3$), 0.99 (s, 9H, -$SiC(C\underline{H}_3)_3$) 1.26-1.39 (m, 10H, H12-H16), 2.20 (q, *J* = 6.8 Hz, 2H, H11), 3.83 (s, 3H, -OCH_3), 4.93 (d, *J* = 4.9 Hz, 1H, H3), 5.13-5.19 (dt, *J* = 10.0 Hz, *J* = 1.2 Hz, 1H, H1 *cis*), 5.33-5.43 (dt, *J* = 16.8 Hz, *J* = 1.2 Hz, 1H, H1 *trans*), 5.50-5.72 (m, 2H, H9 and H10), 5.76-5.94 (m, 1H, H2), 6.25-6.33 (m, 2H, H8 and H8'), 6.84 (d, *J* = 8.8 Hz, 1H, H5'), 7.00-7.03 (m, 2H, H2' and H6'), 7.65(d, *J* = 16.0 Hz, 1H, H7')
^{13}C-NMR (50 MHz, $CDCl_3$)	δ = -4.8 (q, -$SiCH_3$*), -4.5 (3C, q, -$SiCH_3$*), 14.2 (q, C17), 18.4 (s, -$Si\underline{C}(CH_3)_3$*), 18.6 (s, -$Si\underline{C}(CH_3)_3$*) 22.8 (t, C16), 25.8 (3C, q, -$SiC(\underline{C}H_3)_3$*), 25.9 (3C, q, -$SiC(\underline{C}H_3)_3$*), 28.1 (t, C11), 29.3 (t, -CH_2-*), 29.3 (2C, t, -CH_2-*), 32.1 (t, -CH_2-*), 55.5 (q, C8 or -OCH_3), 60.2 (d, C8 or -OCH_3), 64.1 (d, C3), 69.4 (s, C5 or C6), 69.7 (s, C5 or C6), 76.3 (s, C4 or C7), 79.6 (s, C4 or C7), 111.0* (d), 115,1* (d), 115.8* (t, C1), 121.2* (d), 122.6* (d), 124.3* (d), 128.3 (s, C1'), 136.5* (d), 136.8* (d), 146.1* (d), 147.9 (s, C4'), 151.3 (s, C3'), 165.7 (s, C9')
TLC analysis	R_f = 0.57 (PE/EtOAc 9:1), stained with PMA
Specific rotation:	$[\alpha]_D^{25}$= -87.3 (*c* 0.25, $CHCl_3$)

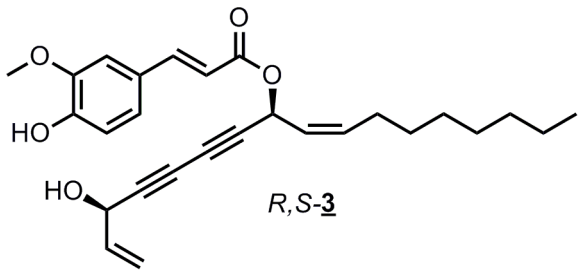
H II.59 General procedure for global deprotection



Procedure

To asolution of **117** (50 mg, 0.075 mmol) in THF (0.4 mL), HF.pyridine (70:30 mixture, 97.5 μL, 50 equiv. of HF) was added dropwise at 0 °C. The mixture was stirred at room temperature. After the reaction was completed (TLC), the mixture was cooled with an ice bath and saturated aq. $NaHCO_3$solution (~1 mL) was added. The mixture was extracted with ether (3 x 2 mL), the combined organic layers were washed with brine, dried over sodium sulfate and filtered. Volatiles were evaporated under reduced pressure at room temperature. The product was purified with column chromatography with silicagel and PE/EtOAc (4:1).

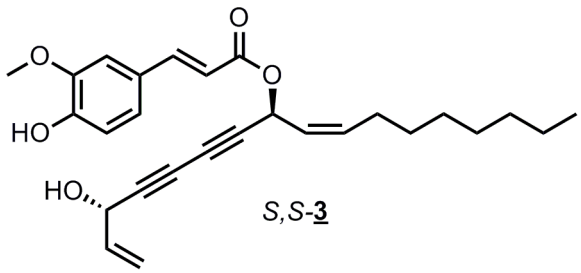
H II.60 (*3R,8S*)-Notoincisol A *R,S*-**3**



R,S-**3**

Procedure	Prepared according to the general procedure
Reaction scale	50 mg, 0.08 mmol
Reaction time	1 h
Yield	29.0 (83%)
Appearance	colorless oil
Sum formula, m.w.	$C_{27}H_{32}O_5$, 436.54 g.mol^{-1}
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 0.85-0.87 (t, *J* = 7.1 Hz, 3H, H17), 1.25-1.29 (s, 8H, H13-16), 1.35-1.43 (m, 2H H12), 1.96-1.97 (d, *J* = 6.4 Hz, 1H, -OH), 2.17-2.21 (q, *J* = 7.5 Hz, 2H, H11), 3.92 (s, 3H, -OCH_3), 4.93-4.94 (t, *J* = 5.1 Hz, 1H, H3), 5.25-5.27 (dt, *J* = 10.2 Hz, *J* = 1.1 Hz, 1H, H1 *cis*), 5.46-5.49 (d, *J* = 17.1 Hz, 1H, H1 *trans*), 5.54 (t, *J* = 9.7 Hz, 1H, H9), 5.68-5.72 (dt, *J* = 10.7, Hz, *J* = 7.5 Hz, 1H, H10), 5.89 (s, 1H, Ar-OH), 5.90-5.96 (ddd, *J* = 17.1, Hz, *J* = 10.2 Hz, *J* = 5.1 Hz, 1H, H2), 6.27-6.29 (m, 2H, H8 and H8'), 6.91-6.92 (d, *J* = 8.2 Hz, 1H, H5'), 7.02-7.03 (d, *J* = 1.8 Hz, 1H, H2'), 7.06-7.08 (dd, *J* = 8.2 Hz, ^4J = 1.8 Hz, 1H, H6'), 7.63-7.66 (d, *J* = 15.9 Hz, 1H, H7')
^{13}C-NMR (50 MHz, $CDCl_3$)	δ = 14.3 (q, C17), 22.8 (t, C16), 28.1 (t, C11), 29.3 (t, 3C, C12-C14), 32.0 (t, C15), 56.1 (q, 3'-O<u>C</u>H_3), 60.1 (s, C8'), 63.6 (s, C3), 69.3 (s, C6), 70.4 (s, C5), 77.0 (s, C7), 78.5 (s, C4), 109.4 (d, C2'), 114.6 (d, C8'), 114.8 (d, C5'), 117.6 (t, C1), 123.5 (d, C6'), 124.0 (d, C9), 126.9 (s, C1'), 135.8 (d, C2), 136.7 (d, C10), 146.2 (d, C7'), 146.9 (s, C3'), 148.3 (s, C4'), 165.8 (s, C9')
TLC analysis	R_f = 0.57 (PE/EtOAc 9:1), stained with PMA
Specific rotation	$[\alpha]_D^{20}$= +87.7(*c* 0.09, MeOH)

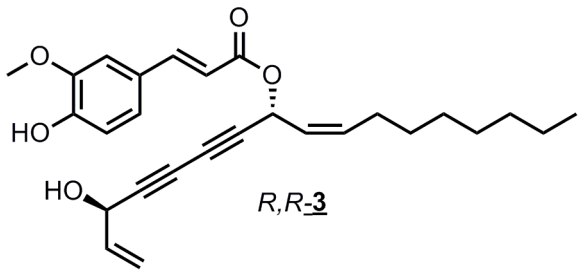
H II.61 (*3S,8R*)-Notoincisol A *S,S*-**3**



S,S-**3**

Procedure	Prepared according to the general procedure
Reaction scale	50 mg, 0.08 mmol
Reaction time	1 h
Yield	27 mg (76%)
Appearance	colorless oil
Sum formula, m.w.	$C_{27}H_{32}O_5$, 436.54 g.mol^{-1}
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 0.87 (t, *J* = 7.1 Hz, 3H, H17), 1.26-1.29 (m, 8H, H13-16), 1.36-1.43(m, 1H, H12) 1.92 (d, *J* = 6.4 Hz, 1H, C3-O<u>H</u>), 2.19 (q, *J* = 7.5 Hz, 2H, H11), 3.92 (s, 3H, OC<u>H</u>$_3$), 4.94 (t, *J* = 5.1 Hz, 1H, H3), 5.24-5.27 (dt, *J* = 10.2 Hz, *J* = 1.1 Hz, 1H, H1 *cis*), 5.47 (d, *J* = 17.1 Hz, 1H, H1 *trans*), 5.55 (t, *J* = 9.7 Hz, 1H, H9), 5.67-5.73 (dt, *J* = 10.8, Hz, *J* = 7.5 Hz, 1H, H10), 5.87 (s, 1H, Ar-O<u>H</u>), 5.89-5.97 (ddd, *J* = 17.1, Hz, *J* = 10.2 Hz, *J* = 5.1 Hz, 1H, H2), 6.26-6.30 (m, 2H, H8 and H8'), 6.92 (d, *J* = 8.2 Hz, 1H, H5'), 7.03 (d, *J* = 1.8 Hz, 1H, H2'), 7.06-7.09 (dd, *J* = 8.2 Hz, *J* = 1.8 Hz, 1H, H6'), 7.65 (d, *J* = 15.9 Hz, 1H, H7')
^{13}C-NMR (50 MHz, $CDCl_3$)	δ = 14.2 (q, C17), 22.8 (t, C16), 28.1(t, C11), 29.3 (t, 3C, C12-C14), 32.0(t, C15), 56.1 (q, 3'-O<u>C</u>H$_3$), 60.2 (s, C8'), 63.6 (s, C3), 69.4 (s, C6), 70.5 (s, C5), 77.0 (s, C7), 78.5 (s, C4), 109.5 (d, C2'), 114.7 (d, C8'), 114.9 (d, C5'), 117.5 (t, C1), 123.5 (d, C6'), 124.1 (d, C9), 127.0 (s, C1'), 135.9 (d, C2), 136.7 (d, C10), 146.1 (d, C7'), 146.9 (s, C3'), 148.3 (s, C4'), 165.8 (s, C9')
TLC analysis	R_f = 0.57 (PE/EtOAc 9:1), stained with PMA
Specific rotation:	$[\alpha]_D^{20}$= +143.1 (*c* 0.09, MeOH)

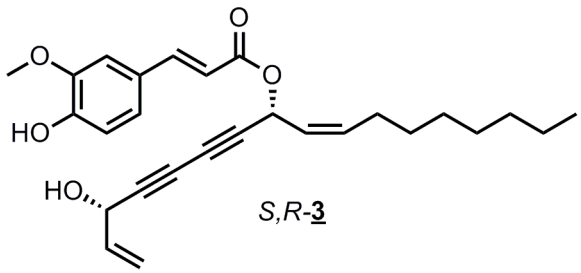
H II.62 (*3S,8R*)-Notoincisol A *R,R*-**3**



R,R-**3**

Procedure	Prepared according to the general procedure
Reaction scale	50 mg, 0.08 mmol
Reaction time	1 h
Yield	27.2 mg (78%)
Appearance	colorless oil
Sum formula, m.w.	$C_{27}H_{32}O_5$, 436.54 g.mol^{-1}
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 0.87 (t, *J* = 7.1 Hz, 3H, H17), 1.26-1.29 (m, 8H, H13-16), 1.36 (m, 1H, H12) 1.92 (d, *J* = 6.4 Hz, 1H, C3-O<u>H</u>), 2.19 (q, *J* = 7.5 Hz, 2H, H11), 3.92 (s, 3H, OC<u>H</u>$_3$), 4.94 (t, *J* = 5.1 Hz, 1H, H3), 5.25-5.27 (dt, *J* = 10.2 Hz, *J* = 1.1 Hz, 1H, H1 *cis*), 5.47 (d, *J* = 17.1 Hz, 1H, H1 *trans*), 5.56 (t, *J* = 9.7 Hz, 1H, H9), 5.67-5.73 (dt, *J* = 10.8, Hz, *J* = 7.5 Hz, 1H, H10), 5.87 (s, 1H, Ar-O<u>H</u>), 5.89-5.97 (ddd, *J* = 17.1, Hz, *J* = 10.2 Hz, *J* = 5.1 Hz, 1H, H2), 6.26-6.30 (m, 2H, H8 and H8'), 6.92 (d, *J* = 8.2 Hz, 1H, H5'), 7.03 (d, *J* = 1.8 Hz, 1H, H2'), 7.06-7.09 (dd, *J* = 8.2 Hz, *J* = 1.8 Hz, 1H, H6'), 7.65 (d, *J* = 15.9 Hz, 1H, H7')
^{13}C-NMR (100 MHz, $CDCl_3$)	δ = 14.2 (q, C17), 22.8 (t, C16), 28.1(t, C11), 29.3 (t, 3C, C12-C14), 32.0(t, C15), 56.1 (q, 3'-O<u>C</u>H$_3$), 60.2 (s, C8'), 63.6 (s, C3), 69.4 (s, C6), 70.5 (s, C5), 77.0 (s, C7), 78.5 (s, C4), 109.5 (d, C2'), 114.7 (d, C8'), 114.9 (d, C5'), 117.5 (t, C1), 123.5 (d, C6'), 124.1 (d, C9), 127.0 (s, C1'), 135.9 (d, C2), 136.7 (d, C10), 146.1 (d, C7'), 146.9 (s, C3'), 148.3 (s, C4'), 165.8 (s, C9')
TLC analysis	R_f = 0.57 (PE/EtOAc 9:1), stained with PMA
Specific rotation:	$[\alpha]_D^{20}$= -139.8 (*c* 0.09, MeOH)

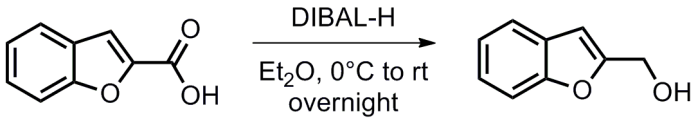
H II.63 (*3S,8R*)-Notoincisol A *S,R*-**3**



Procedure	Prepared according to the general procedure
Reaction scale	50 mg, 0.08 mmol
Reaction time	1 h
Yield	26.2mg (75%)
Appearance	colorless oil
Sum formula, m.w.	$C_{27}H_{32}O_5$, 436.54 g.mol^{-1}
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 0.86 (t, *J* = 7.1 Hz, 3H, H17), 1.25-1.29 (m, 8H, H13-16),1.38 (br, 1H, H12) 1.95 (d, *J* = 6.4 Hz, 1H, C3-OH), 2.19 (q, *J* = 7.5 Hz, 2H, H11), 3.92 (s, 3H, OCH_3), 4.94 (t, *J* = 5.1 Hz, 1H, H3), 5.24-5.27 (dt, *J* = 10.2 Hz, *J* = 1.1 Hz, 1H, H1 *cis*), 5.47 (d, *J* = 17.1 Hz, 1H, H1 *trans*), 5.56 (t, *J* = 9.7 Hz, 1H, H9), 5.67-5.73 (dt, *J* = 10.8, Hz, *J* = 7.5 Hz, 1H, H10), 5.88 (s, 1H, Ar-OH), 5.89-5.97 (ddd, *J* = 17.1, Hz, *J* = 10.2 Hz, *J* = 5.1 Hz, 1H, H2), 6.26-6.30 (m, 2H, H8 and H8'), 6.92 (d, *J* = 8.2 Hz, 1H, H5'), 7.03 (d, *J* = 1.8 Hz, 1H, H2'), 7.06-7.09 (dd, *J* = 8.2 Hz, *J* = 1.8 Hz, 1H, H6'), 7.65 (d, *J* = 15.9 Hz, 1H, H7')
^{13}C-NMR (50 MHz, $CDCl_3$)	δ = 14.2 (q, C17), 22.8 (t, C16), 28.1(t, C11), 29.3 (t, 3C, C12-C14), 31.9(t, C15), 56.1 (q, 3'-OCH_3), 60.2 (s, C8'), 63.6 (s, C3), 69.4 (s, C6), 70.4 (s, C5), 77.0 (s, C7), 78.5 (s, C4), 109.5 (d, C2'), 114.7 (d, C8'), 114.9 (d, C5'), 117.5 (t, C1), 123.5 (d, C6'), 124.0 (d, C9), 127.0 (s, C1'), 135.9 (d, C2), 136.7 (d, C10), 146.2 (d, C7'), 146.9 (s, C3'), 148.3 (s, C4'), 165.8 (s, C9')
TLC analysis	R_f = 0.57 (PE/EtOAc 9:1), stained with PMA
Specific rotation:	$[\alpha]_D^{20}$= -85.5 (*c* 0.09, MeOH)

H III Notoincisol B

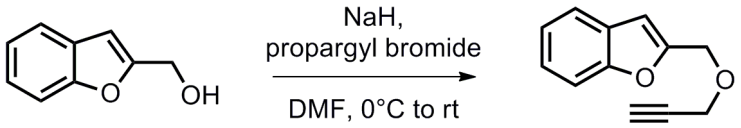
H III.1 Benzofuran-2-ylmethanol **131**[100]



130 **131**

Procedure	A solution of DIBAL-H (29.6 mL, 29.6 mmol) in toluene was added dropwiseto the solution of 2-benzofurancarboxylic acid **130** (1.2g, 7.4 mmol) in dry THF (60 mL) at 0°C. Mixture was stirred for 1 hour and then, MeOH (30 mL) was added, followed by saturated solution of potassium tartrate (30 mL). Resulting mixture was stirred for 10 minutes and was then extracted with EtOAc (2x100 mL). Combined oranic layers were washed with brine, dried over sodium sulfate, filtered and evaporated. Resulting mixture was purified by column chromatography with silicagel and PE/EtOAc (4:1)
Reaction scale	1.2 g, 7.4 mol
Reaction time	1 h
Yield	690.7 mg (63%)
Appearance	yellowish oil
Sum formula, m.w.	$C_9H_8O_2$, 148.16 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 2.65 (bs, 1H, OH), 4.74, (s, 2H, -C$\underline{H_2}$-OH), 6.63 (s, 1H, H3), 7.22-7.29 (m, 2H, H5 and H6), 7.44-7.56 (m, 2H, H4 and H7)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ =58.1(t), 104.2 (d, C3), 111.3* (d), 121.2* (d), 122.9* (d), 124.4* (d), 128.2 (s, C9), 155.1 (s, C2), 156.5 (s, C8)

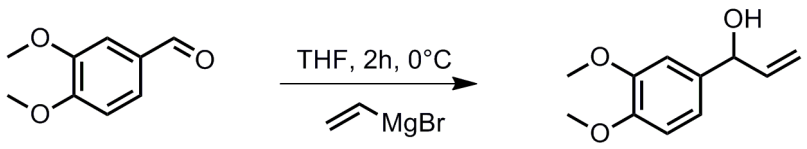
H III.2 2-((Prop-2-yn-1-yloxy)methyl)benzofuran **132**[101]



131 **132**

Procedure	To a stirred suspension of NaH (100mg of 60% in mineral oil, 2.50 mmol) in DMF (2 mL) a solution of 2-hydroxymethylbenzofuran **131**(375 mg, 2.50 mmol) in DMF (2 mL) was added at 0°C. After 30 min propargyl bromide (0.208 mL, 2.75 mmol) was added, and the mixture was stirred for 10 h at room temperature. After the reaction was completed water was added and the product was extracted with Et_2O (3 x 50 mL), dried over sodium sulfate, and purified by column chromatography with silicagel and PE/EtOAc(9:1) to yield a colorlessoil.
Reaction scale	375 mg, 2.50mmol
Reaction time	1 h
Yield	306 mg (63%)
Appearance	colorless oil
Sum formula, m.w.	$C_{12}H_{10}O_2$, 194.2 $g.mol^{-1}$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 2.51 (t,*J* = 2.3 Hz, 1H, -C≡C<u>H</u>), 4.25-4.26, (d,*J* = 2.3 Hz, 2H, ≡C-C<u>H$_2$</u>-O-), 4.74 (s, 1H, Ar-C<u>H$_2$</u>-O-), 6.75 (s, 1H, H3), 7.23-7.31 (m, 2H, H5 and H6), 7.47-7.59 (m, 2H, H4 and H7)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ =57.3 (t, ≡C-<u>C</u>H$_2$-O-), 63.8 (t, Ar-<u>C</u>H$_2$-O-), 75.3 (s, -<u>C</u>≡CH), 79.2 (d, -C≡<u>C</u>H), 106.6 (d, C3), 111.5 (d, C7), 121.3* (d), 122.9* (d), 124.7* (d), 128.1 (s, C9), 153.4 (s, C2), 155.4 (s, C8)

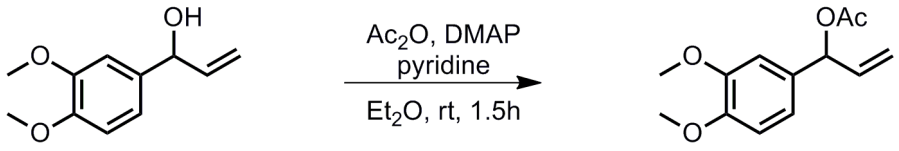
H III.3 1-(3,4-Dimethoxyphenyl)prop-2-en-1-ol **151**[102]



150 **151**

Procedure	Vinylmagnesium bromide (50 mL, 1M in THF) was added at 0°C to the solution of 3,4-dimethoxybenzaldehyde **150** (8.31 g, 0.05 mol) in dry THF (71 mL). Reactiom mixture was stirred at 0°C for 2 hours. After reaction was finished (TLC), mixture was diluted with ether (50 mL) and quenched with saturated solution of ammonium chloride (70 mL). Phases were separated and aqueous layer was washed twice with brine 70 mL, dried over sodium sulfate, filtered and concentrated. Compound was isolated as oil and used without any further purification.
Reaction scale	8.31 g, 43 mol
Reaction time	2 h
Yield	7.89 g (95%)
Appearance	yellowish oil
Sum formula, m.w.	$C_{11}H_{14}O_3$, 194.23 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 2.07 (s, 1H, -OH), 3.86, (s, 3H, -OCH_3), 3.88 (s, 3H, -OCH_3), 5.13-5.38 (m, 3H, -CH=C$\underline{H}_2$ and –C$\underline{H}$-OH), 5.96-6.12 (m, 1H, -C$\underline{H}$=CH_2), 6.78-6.91 (m, 4H, Ar-H)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ =55.9 (q, -OCH_3), 56.0 (q, -OCH_3), 75.1 (-$\underline{C}$HOH), 109.6 (d,C2), 111.1 (d,C5), 115.0 (t, -CH=$\underline{C}H_2$), 118.7 (d, C6), 135.4 (s, C1), 140.4 (d, -$\underline{C}$H=CH_2), 148.7 (s, C3 or C4), 149.2, (s, C3 or C4)
TLC analysis	R_f = 0.07 (PE/EtOAc4:1)

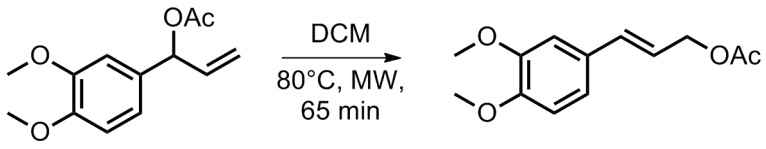
H III.4 1-(3,4-Dimethoxyphenyl)allyl acetate **152**[103]



151 **152**

Procedure	In preheated three-neck flask, equipped with argon inlet and thermometer, alcohol **151** (6.6 g, 33.8 mmol), DMAP (206 mg, 1.7 mmol) and pyridine (5.1 mL, 62.9 mmol) was dissolved in dry diethyl ether (5 mL). Mixture was cooled to 0°C and acetic anhydride (3.83 mL, 40.6 mmol) in dry diethyl ether (3mL) was added dropwise. Mixture was then warmed to room temperature and stirred for 24 hours. After completion, reaction mixture was diluted with ether (15 mL) and 2N HCl (15 mL) was added. Organic layer was separated, washed with water (20 mL), brine (20 mL) dried over sodium sulfate, filtered and concentrated. Product waspurified by column chromatography, using silicagel and PE/EtOAc(5-10% gradient) affording 86% of the desired product
Reaction scale	6.6 g, 33.8 mol
Reaction time	24 h
Yield	6.87 g (86%)
Appearance	colorless oil
Sum formula, m.w.	$C_{13}H_{16}O_4$, 236.3 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 2.10 (s, 3H, -C(O)C<u>H</u>$_3$), 3.87, (s, 3H, -OC<u>H</u>$_3$), 3.89 (s, 3H, -OC<u>H</u>$_3$), 5.21-5.33 (m, 2H. –CH=C<u>H</u>$_2$), 5.93-6.09 (m, 1H, –C<u>H</u>=CH$_2$), 6.21 (d, *J* = 5.7 Hz, 1H, -C<u>H</u>OH), 6.82-6.96 (m, 3H, Ar-H)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ = 20.7 (q, -C(O)<u>C</u>H$_3$), 55.3 (q, -OCH$_3$), 56.1 (q, -OCH$_3$), 75.4 (d, -<u>C</u>HOH), 110.1* (d), 110.6* (d), 115.8 (t, -CH=<u>C</u>H$_2$), 119.4* (d), 130.9 (s, C1), 135.9 (d, -<u>C</u>H=CH$_2$), 148.5 (s, 2C, C3 and C4), 169.2 (s, -<u>C</u>(O)CH$_3$)
TLC analysis	R_f = 0.17 (PE/EtOAc 4:1)

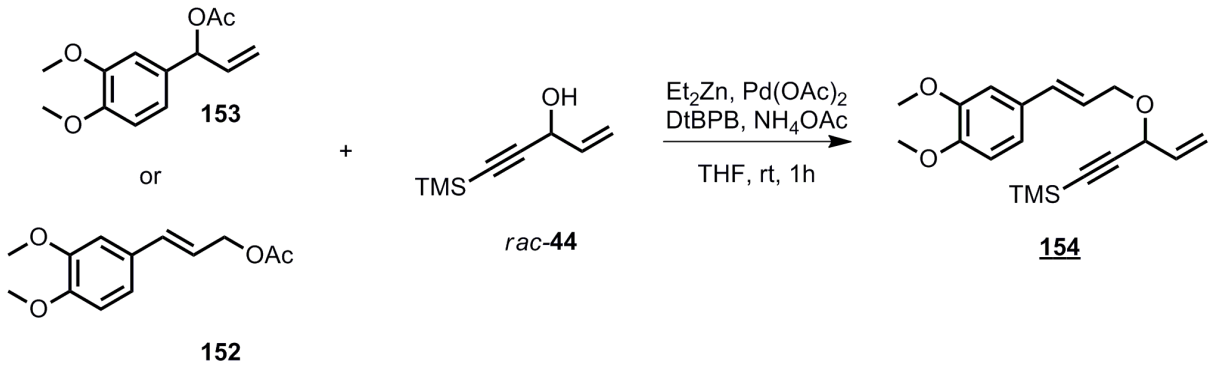
H III.5 (*E*)-3-(3,4-Dimethoxyphenyl)allyl acetate **153**[104]



152 **153**

Procedure	Branched acetate **152** (1 g, 4.23 mmol) was chargedinto the microwave vial.Silicagel (4g, 4 times weight excess) and DCM wereadded (15 mL). Mixture was irradiated by microwaves for 65 minutes at 80°C. After reaction was completed, solvent was evaporated and solid residue was applied on the top of solicagel column and purifiued using PE/EtOAc mixture (3:1). Product was obtained as colorless oil in 60% of yield
Reaction scale	1 g, 4.23mmol
Reaction time	65min
Yield	599.7 mg (60%)
Appearance	yellowish oil
Sum formula, m.w.	$C_{13}H_{16}O_4$, 236.3 g.mol^{-1}
^{1}H-NMR (200 MHz, CDCl3)	δ = 2.08 (s, 3H, -C(O)C<u>H</u>$_3$), 3.86, (s, 3H, -OCH$_3$), 3.89 (s, 3H, -OCH$_3$), 4.67-4.71 (dd, *J* = 6.6 Hz, *J* = 1.1 Hz, 2H, -CH$_2$-), 6.07-6.21 (dt, *J* = 15.8 Hz, *J* = 6.6 Hz, 1H, Ar-CH=C<u>H</u>-), 6.55-6.61, (d, *J* = 15.8 Hz, 1H, Ar-C<u>H</u>=CH-), 6.77-6.81 (d, *J* = 8.8 Hz, 1H, Ar-H2), 6.88-6.93 (m, 2H. Ar-H5 and Ar-H6)
^{13}C-NMR (400 MHz, CDCl3)	δ = 21.3(q, -C(O)<u>C</u>H$_3$), 55.8 (p, -OCH$_3$), 55.9 (q, -OCH$_3$), 65.5 (t, -CH$_2$-), 108.8* (d), 111.0* (d), 120.1* (d), 121.1* (d), 129.2 (s, -<u>C</u>H=CH$_2$), 134.3 (t), 149.0 (s), 149.2 (s,), 170.9 (s, -<u>C</u>(O)CH$_3$)
TLC analysis	Rf = 0.09 (PE/EtOAc 4:1)

H III.6 (*E*)-(3-((3-(3,4-Dimethoxyphenyl)allyl)oxy)pent-4-en-1-yn-1-yl)trimethylsilane **154**



Procedure In an oven dried and Schlencktechnique pretreated Wheaton vial, alcohol *rac*-**44** (65 mg, 0.42 mmol) in dry THF (0.3 mL) was treated with diethyl zinc (0.3 mL, 1M solution in THF) at rt and stirred for 30 minutes. In the other Wheaton vial (also preheated), $Pd(OAc)_2$ (7.0 mg, 0.03 mmol) and DtBPB (9.1 mg, 0.03 mmol) were weighted. Atmosphere was changed to agron and dry THF (0.3 mL) was added *via* syrringe. After complete dissolution, solution of acetate (100 mg, 0.42 mmol) in dry THF (0.2 mL - prepared in third Wheaton vial, also treated with argon) was added into the flask to the catalitic system and stirred for ca 5 min. Resulting mixture and the mixture of the activated alcohol were transferred *via* syringe to the ammonium acetate charged reaction vessel (preheated and with argon atmosphere). Mixture was stirred for 2h. After completion, mixture was passed through apad of celite, solvents were evaporated and mixture was directly applied on the column and subjected to column chromatography, using silicagel and PE/EtOAc mixture (95:5).

Reaction scale 100mg, 0.42 mmol

Reaction time 2 h

Yield 80.5 mg (58%from **153**)
77.7 mg (56% from **152**)

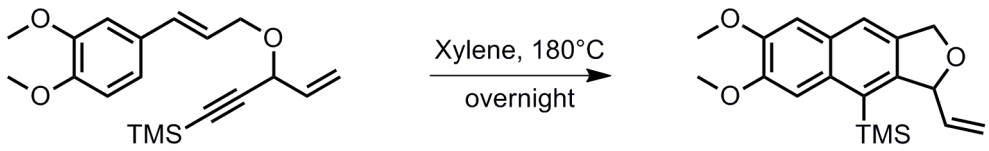
Appearance yellowish oil

Sum formula, m.w. $C_{19}H_{26}O_3Si$, 330.49 $g.mol^{-1}$

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 0.20 (s, 9H, -$Si(CH_3)_3$), 3.88, (s, 3H. –OCH_3), 3.89 (s, 3H, -OCH_3), 4.13-4.38 (m, 2H, -CH_2-), 4.68-4.71 (d, *J* = 5.7 Hz, 1H,

	H3), 5.26-5.33 (dt, *J* = 10.0 Hz, *J* = 1.4 Hz, 1H, H1 *cis*), 5.46-5.55 (dt, *J* = 17.0 Hz, *J* = 1.4 Hz, 1H, H1 *trans*), 5.85-6.01 (m, 1H, H2), 6.11-6.25 (m, 1H, Ar-CH=C<u>H</u>-), 6.53-6.61 (d, *J* = 15.8 Hz, 1H, Ar-C<u>H</u>=CH-), 6.79-6.83 (d, *J* = 8.2 Hz, 1H, Ar-H*), 6.90-6.96 (m, 2H, Ar-H*)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ = 0.01 (q, -Si(CH_3)$_3$), 56.0 (q, -OCH_3), 56.1 (q, -OCH_3), 68.9 (t, -CH_2-), 69.9 (d, C3), 92.6 (s, C5), 102.3 (s, C4), 109.0* (d), 111.2* (d), 118.3 (t, C1), 120.0* (d), 123.7* (d), 130.0 (s, C1´), 133.2 (d, C2 or Ar-<u>C</u>H=CH-), 135.1 (d, C2 or Ar-<u>C</u>H=CH-), 149.1 (s, C3' or C4'), 149.2 (s, C3' or C4')
TLC analysis	R_f = 0.21 (PE/EtOAc6:1)
HRMS	$[M+H]^+$ *m*/*z* calcd 331.1724, found 331.1732

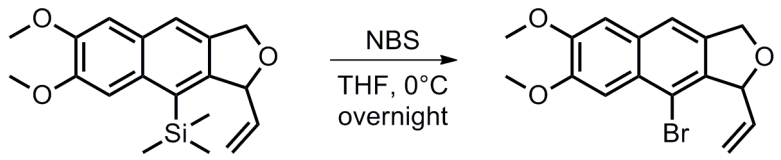
H III.7 (6,7-Dimethoxy-3-vinyl-1,3-dihydronaphtho[2,3-c]furan-4-yl)trimethylsilane **156**



154 **156**

Procedure	Ether **154** (100 mL, 0.3 mmol) was charged into the Wheaton vial and xylene was added (2.5 mL). Vessel was sealed with septum and mixture was degassed for 10 minutes by passing argon stream through the solvent (*via* needle) in ultrasound bath. After degassing, vial was sealed with high pressure resistant cap and mixture was heated to 180°C overnight. After reaction was finished, solvent was evaporated under the reduced pressure and mixture was directly subjected to the column chromatography, using silicagel and PE/EtOAc mixture (95:5). Compound was obtained as yellowis oil in 67%.
Reaction scale	100 mg, 0.42 mmol
Reaction time	overnight
Yield	92.4 (67%)
Appearance	yellowish oil
Sum formula, m.w.	$C_{19}H_{24}O_3Si$, 328.48 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 0.53 (s, 9H, -Si(CH_3)$_3$), 4.00, (s, 3H, -OCH_3), 4.01 (s, 3H, -OCH_3), 4.98-5.18 (m, 4H, H1 and –CH=CH_2), 5.97-6.15 (m,2H, -CH-CH_2 and H3), 7.10 (s, 1H, H8), 7.53 (s, 1H, H5), 7.54 (s, 1H, H9)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ = 2.2 (q, -Si(CH_3)$_3$), 55.9 (q, -OCH3), 70.2 (t, C1), 82.7 (d, C3), 107.4 (d, C8), 108.2 (d, C5), 116.1 (t, -CH=CH_2), 120.2 (t, C9), 128.6 (s, C4a), 129.0 (s, C4), 132.7 (s, C8a), 136.0 (s, C3a), 138.3 (d, -CH=CH_2), 144.5 (s, C9a), 148.5 (s, C6), 148.8 (s, C7)
TLC analysis	R_f= 0.15 (PE/EtOAc6:1)
GC/MS	Instrument I, Method I Retention time: 12.18 min Main fractions: 328.07, 313.05, 302.08, 301.05, 285.07, 273.06, 257.06, 255.06, 165.07, 153.07, 152.07, 143.07, 128.07, 73.07
HRMS	HRMS [M-H]$^-$ *m/z* calcd 329.1567, found 329.1560

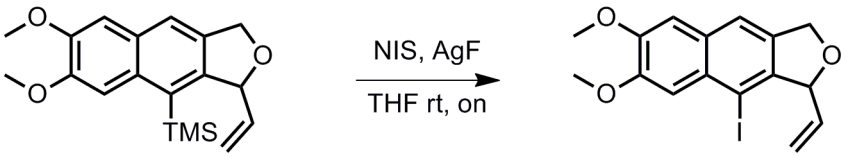
H III.8 9-Bromo-6,7-dimethoxy-1-vinyl-1,3-dihydronaphtho[2,3-c]furan **163**



156 **163**

Procedure	Silane **156** (137 mg, 0.42 mmol) and NBS (89.2 mg, 0.5 mmol) were charged into the Wheaton vial and atmosphere was changed to argon. Dry THF (0.5 mL) was added and mixture was stirred for 24 hours at 0°C. After stirring overnight, solvents were evaporated and mixture was subjected directly to the column chromatography, using silicagel and petrpleum ether/dichloromethan (1:1)
Reaction scale	137 mg, 0.42 mmol
Reaction time	24 h
Yield	84.5mg (60%)
Appearance	yellowish oil
Sum formula, m.w.	$C_{16}H_{15}O_3Br$, 335.19 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 4.01, (s, 3H, -OCH_3), 4.05 (s, 3H, -OCH_3), 5.18-5.54 (m, 4H, C1 and –CH=C$\underline{H}_2$), 5.75-5.79 (m,1H, H3), 6.04-6.20 (m, 1H, -C$\underline{H}$=CH_2), 7.09 (s, 1H, H8), 7.46 (s, 1H, H5), 7.52 (s, 1H, H9)
^{13}C-NMR (400 MHz, $CDCl_3$)	δ= 56.2 (q, 2C, -OCH_3), 72.7 (t, C1), 85.8 (d, C3), 105.7 (d, C8), 106.8 (d, C5), 115.0* (s), 117.1 (t, -CH=$\underline{C}H_2$), 117.9* (d), 127.7* (s), 130.5* (s), 135.3 (d, -$\underline{C}$H=CH_2), 137.0* (s), 138.4* (s), 150.3 (s, C6 or C7), 150.7 (s, C6 or C7)
TLC analysis	R_f= 0.08(PE/EtOAc6:1)
GC/MS	Instrument I, Method I Retention time: 12.76 min Main fractions: 335.03, 333.93, 320.96, 318.95, 308.97, 306.87, 280.98, 278.94, 207.02, 139.06
HRMS	HRMS $[M-H]^-$ *m/z* calcd 335.0277, found 335.0253

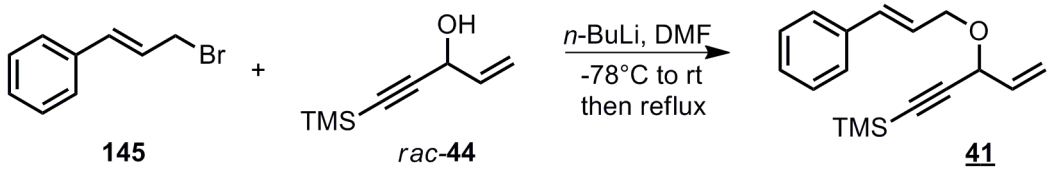
H III.9 9-iodo-6,7-dimethoxy-1-vinyl-1,3-dihydronaphtho[2,3-c]furan **160**



156 **160**

Procedure	An oven dried Wheaton vial was charged with AgF (154 mg, 1-22 mmol), NIS (274 mg, 1.22 mmol) and a solution of **156** in anhydrous THF (2.14 ml, 0.14 M, 0.3 mmol) under argon atmosphere. The mixture was stirred overnight in the dark at 0°C. After completion, the mixture was filtered through a short silica plug and concentrated. The residue was purified by silicagel chromatography using PE/EtOAc mixture (0-5% gradien over 20 minutes) to afford the product in 45%
Reaction scale	100 mg, 0.30 mmol
Reaction time	overnight
Yield	51.6 mg (45%)
Appearance	yellowish oil
Sum formula, m.w.	$C_{16}H_{15}O_3I$, 382.19 $g.mol^{-1}$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 4.01, (s, 3H, -OCH_3), 4.06 (s, 3H, -OCH_3), 5.19-5.56 (m, 4H, C1 and - -CH=C$\underline{H}_2$), 5.65-5.69 (dd, *J* = 5.9 Hz, *J* = 1.2 Hz, 1H, H3), 6.02-6.19 (m, 1H, -C$\underline{H}$=CH_2), 7.07 (s, 1H, Ar-H*), 7.47 (br, 2H, Ar-H*)
TLC analysis	R_f = 0.09 (PE/EtOAc 9:1)
GC/MS	Instrument II, Method II Retention time: 12.76 min Main fractions: 382.05, 355.02, 327.02, 200.13, 139.09

H III.10 **(*E*)-(3-(cinnamyloxy)pent-1-en-4-yn-5-yl)trimethylsilane 41**



145 *rac*-**44** **41**

Procedure	In the three-neck flask, equipped with thermometer, inert gas inlet and septum,*n*-BuLi (1.8 mL, 1.6M, 2.88 mmol) was added to the solution of alcohol *rac*-**44** (385.7 mg, 2.5 mmol) in dry THF (5 mL) at -78°C and mixture was stirred for 20 minutes. Allyl bromide (0.98 g, 5 mmol) was added in DMF (15 mL). Mixture was warmed to room temperature and then refluxed for 1 hour. After cooling to the room temperature, reaction was quenched with addition of saturated ammonium chloride (10 mL). Mixture was extracted with diethyl ether (3 x 15 mL). Combined organic layers were washed with brine, dried over sodium sulfate, filtered and solvents were evaporated under the reduced pressure. Mixture was subjected to the column chromatography using silicagel and PE/EtOAc mixture (0-40% gradient). Desired product was obtained in 13% as yellowish oil.
Reaction scale	385.7mg, 2.5 mmol
Reaction time	80 minutes
Yield	87 mg (13%)
Appearance	yellowish oil
Sum formula, m.w.	$C_{17}H_{22}OSi$, 270.44 g.mol^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ = 0.15 (s, 9H. –Si(CH_3)$_3$), 4.06-4.34 (m, 2H, -CH_2-), 4.62-4.66 (dt, *J* = 5.7 Hz, *J* = 1.4 Hz, 1H, H3), 5.41-5.50 (dt, *J* = 10.0 Hz, *J* = 1.4 Hz, 1H, H1 *cis*), 5.21-5.27 (dt, *J* = 17.0 Hz, *J* = 1.4 Hz, 1H, H1 *trans*), 5.80-5.97 (m, 1H, H2), 6.18-6.32 (m, 1H, Ar-CH=C<u>H</u>-), 6.55-6.63 (d, *J* = 16.0 Hz, 1H, Ar-C<u>H</u>=CH-), 7.18-7.37 (m, 5H, Ar-H)

I Appendix

I I Publications and conference activities

I I.1 Related to the thesis

- Lukas Rycek, Roshan Puthenkalam, Michael Schnürch, Margot Ernst, and Marko D. Mihovilovic "Metal-Assisted Synthesis of Unsymmetrical Magnolol Analogs and their Biological Assessment as $GABA_A$ Receptor Ligands." *Bioorg. Med. Chem. Lett.***, 2015**, *25* ,400-3.

2014 Natural Products and Drug Discovery - Future Perspectives, Vienna Austria (poster contribution)

International Symposium on Medicinal Chemistry. Lisbon. Portugal (poster contribution)

EFMC Young Medicinal Chemist Symposium. Lisbon, Portugal (poster contribution)

Meeting of the Paul Ehrlich MedChem Euro-PhD Network, Hradec Kralove, Czech Republic (poster contribution)

2013 European Symposium on Organic Chemistry, Marseille, France (poster contribution)

Blue Danube Symposium on Heterocyclic Chemistry, Olomouc, Czech Republic (oral contribution)

2012 Meeting of the Paul Ehrlich MedChem Euro-PhD Network (oral contribution)

I I.2 Publications unrelated to the thesis

- Laurin Wimmer, Lukas Rycek, Moumita Koley, and Michael Schnürch "Metal catalyzed cross-coupling reactions in the decoration of pyrimidine, pyridazine, and pyrazine" In Patonay Tomás (ed.), *Topics in Heterocyclic chemistry: Synthesis and Modification of Heterocycles by Metal Catalyzed Cross-coupling Reactions,* Springer – In print

- Gitte Van Baelen, Sander Kuijer, Lukáš Rýček, Sergey Sergeyev, Elwin Janssen, Frans J. J. de Kanter, Bert U. W. Maes, Eelco Ruijter and Romano V. A. Orru "Synthesis of 4-Aminoquinazolines by Palladium-Catalyzed Intramolecular Imidoylation of N-(2-Bromoaryl)amidines" *Eur. J. Chem*., **2011**, *17 (52),* 15039-15044

I II Curriculum vitae

Lukas Rycek, MSc.

Born	*11. 9. 1985*
Nationality	*Czech*

Higher Education

Sep 2011 – present	Ph. D. Program Technical Natural Sciences Vienna University of Technology (VUT), Austria Dissertation: *Synthesis of Natural Product Derivatives and Their Biological Evaluation as Potential Anti-inflammatory Agents and $GABA_A$ Receptor Modulators.* Supervised by Prof. Marko D. Mihovilovic
Sep 2009 – Aug 2011	Masters program Molecular design, Synthesis and Catalysis Vrije Universiteit Amsterdam, Holland Master Thesis: *Palladium catalyzed cross-coupling including isocyanide insertion. A new way to 4-aminoquinazolines and 5-aminopyrimido-pyrimidinones.* Supervised by Prof. Romano Orru
June 2011 – July 2011	Visit research stay at University of Antwerp in the group of Prof. Bert Maes
Sep 2005 – Feb 2009	Bachelor program Chemistry Masaryk University Brno, Czech Republic Bachelor Thesis: *Aromatic skeleton structure and stereochemistry Influence upon microwave initiated intramolecular cyclization of ortho-allyloxy carbaldehydes* Supervised by Prof. Milan Potacek
Nov 2008 – Dec 2008	Short Term Scientific Mission at Vrije Universiteit Amsterdam (STMS, COST, Action D32)

June 2008	Short Term Scientific Mission at Vrije Universiteit Amsterdam (STMS, COST Action D32)
Feb 2008 – May 2008	Erasmus exchange program at Vrije Universiteit Amsterdam

Work Experience

Since Sep 2011	Project Assistant at the Institute for Applied Synthetic Chemistry, VUT Research Group of Prof. Marko D. Mihovilovic

Language Skills

Czech	*Native*
English	*Fluent in written and spoken form*
German	*A2.2 level*

Further Education & Skills

- *Advanced user of PC*
- *Czech driving license B (< 3.5 t)*

Hobbies & Fields of Interest

- *Social activities*
- *Sport (football, table tennis, skiing, cross country skiing, ice hockey)*
- *Travelling*
- *Photography*
- *Reading*

I III List of abbreviations

5-LOX – 5-lipoxygenase
AcCN - Acetonitrile
BINAP - (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
CBS reduction – Corey-Bakshi-Shibata Reduction
^{13}C-NMR 13-Carbon nuclear magnetic resonance
^{1}H-NMR – 1-Hydrogen nuclear magnetic resonance
CNS – Central nervous system
COX – Cycloxygenase
Cy_3P – Tricyclohexylphosphine
dba - Dibenzylideneacetone
DCC – *N,N'*-Dicyclohexylcarbodiimide
DCE – 1,2-Dichloroethene
DCM - Dichloromethane
DIB – (Diacetoxyiodo)benzene
DIBAL – Diisobutylaluminium hydride
DIPA - Diisoprpylamine
DMA – Dimethylacetamide
DMAP – 4-Dimethylaminopyridine
DME – Dimethoxyethane
DMF – Dimethylformamide
DMP – Dess-Martin Periodinane
DMSO – Dimethylsulfoxide
dppf – 1,1'-Bis(diphenylphosphino)ferrocene
D*t*BPB – 2-(Di-*tert*-butylphosphino)biphenyl
EDCI – 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
GABA – Gama aminobutytic acid
GC – Gass chromatography
HRMS – High resolution mass spectroscopy
HUVEC – Human umbilical vein endothelial cells
IBX – 2-Iodoxybenzoic acid
IL – Interleukin
LC – Liquid chromatography
MS – Mass spectroscopy
MTBE – Methyltertbutyl ether
MW – Microwave
NBS – *N*-bromosuccinimede
NF-kB – Nuclear factor kappa B
NMPA – *N*-methyl-D-aspartate receptor
PMA – Phosphomolybdenic acid
PPAR – Peroxisom proliferator-activated receptor
RXR – Retinoid X receptor
S-Phos – 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TBAF – Tetra-*n*-butylammonium fluoride
TBS – tert-Butylchlorodimethyl-
t-BuXPhos – 2-Di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl
TEMPO – (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
THF – Tetrahydrofuran
TLC – Thin layer chromatography
TMDS – 1,1,3,3-Tetramethyldisilazane
TMS – Trimethylsilyl-
TNF – Tumor necrosis factor
VDR – Vitamine D receptor
X-Phos – 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Abbre*via*tions for NMR codes:
s – Singlet
d – Dublet
t – Triplet
m – Multiplet
q – Quartet
at – Apperent triplet
dd – Dublet of dublets
dt – Dublet of triplets
br – Broad signal

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