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DIPLOMARBEIT

INVESTIGATIONS TOWARDS A BIOMIMETIC ACCESS TO NOTOINCISOL B

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Meinen Eltern gewidmet.

Im Zweifel für den Zweifel.

TOCOTRONIC

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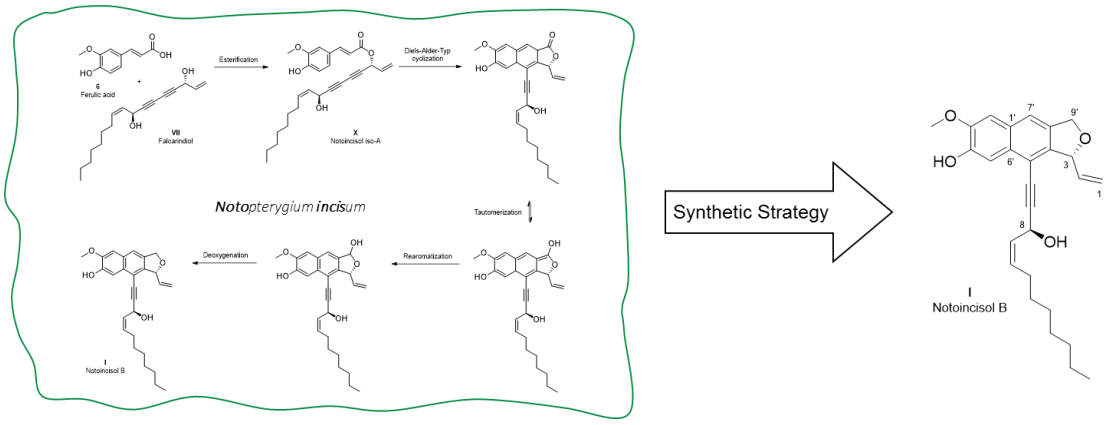
Abstract

Notoincisol B is a naturally occurring polyenyne-hybrid compound which was found to elicit promising partial-agonistic activity at the nuclear receptor PPARγ. The present thesis aimed at establishing a synthetic route towards Notoincisol B-type polyenyne-hybrids by mimicking their biogenic synthesis pathway.

The ligand-inducible cell nuclear receptor protein PPARγ (Peroxisome Proliferator-Activated Receptor gamma) is a key player in the transcriptional regulation of various important biological processes including lipid- and glucose metabolism, cell differentiation and inflammation. In recent years, clinically used full PPARγ agonists, such as thiazolidinediones (TZDs), had to be strictly regulated or even withdrawn from the market due to highly adverse side effects.

Urged by the need to identify novel PPARγ ligands, particularly partial agonists, new polyenyne-hybrid compounds, called Notoincisols, have recently been isolated from the traditional Chinese medical plant *Notopterygium incisum*. A few of these polyenyne-hybrids were found to act as promising partial PPARγ agonists. Among them, Notoincisol B represents a novel carbon skeleton which comprises a characteristic 1,3-dihydronaphtho[2,3-c]furan core structure. Given this structural novelty and the promising partial agonistic activity on PPARγ, Notoincisol B-type polyenynes are considered as highly suitable pharmaceutical lead candidates and hence require synthetic access.

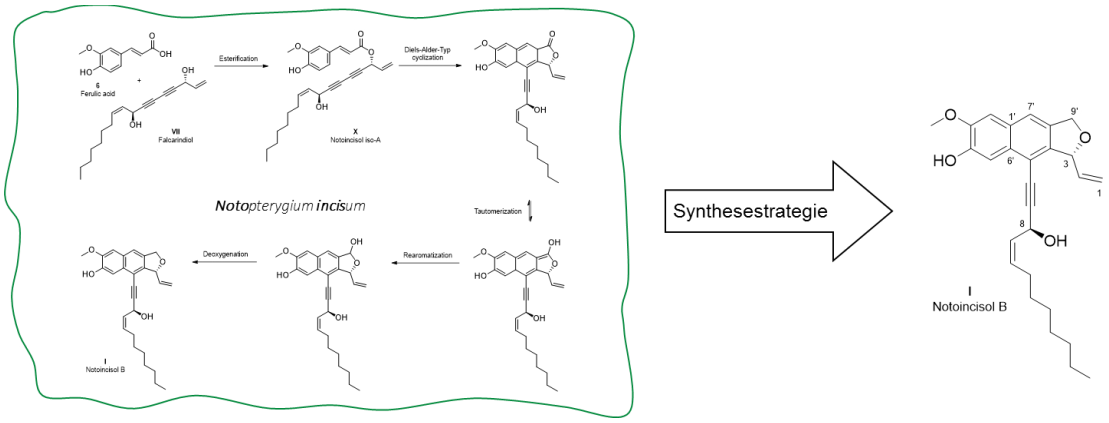


Kurzfassung

Notoincisol B ist eine natürlich vorkommende Polyenin-Hybrid Verbindung, welche sich in biologischen Tests als vielversprechender partieller Agonist des intrazellulären Rezeptor-Proteins PPARγ herausstellte. In der vorliegenden Arbeit wurde die Entwicklung einer Syntheseroute zu Polyenin-Hybrid Verbindungen vom Notoincisol B-Typ angestrebt. Im Besonderen wurde dabei die Möglichkeit der Nachahmung des biogenen Synthesewegs solcher Verbindungen untersucht.

PPARγ (Peroxisom-Proliferator-aktivierte Rezeptoren Gamma) gehören zur Klasse der intrazellulären Rezeptor-Proteine, die durch geeignete Liganden aktiviert werden können und danach an der transkriptorischen Regulierung von wichtigen biologischen Prozessen wie Fett- und Glukosemetabolismus, Zelldifferenzierung und Entzündungen beteiligt sind. Klinisch bedeutende, volle PPARγ Agonisten wie Thiazolidindione (TZDs) zeigen oft weitreichenden Nebenwirkungen und sind daher nur mehr sehr eingeschränkt in Verwendung.

Im Rahmen der Entwicklung neuer PPARγ Liganden, im Besonderen partieller Agonisten, konnten kürzlich neuartige Polyenin-Hybrid Verbindungen, sogenannte Notoincisole, aus der traditionellen chinesischen Heilpflanze *Notopterygium incisum* isoliert werden. Vorläufigen biologischen Untersuchungen zur Folge zeigen einige dieser neuen Verbindungen vielversprechende partiell-agonistische PPARγ Aktivitäten. Notoincisol B besitzt ein völlig neuartiges Kohlenstoff-Gerüst, welches eine charakteristische 1,3-Dihydronaphtho[2,3-c]furan Kernstruktur aufweist. Basierend auf diesen strukturellen sowie biologischen Eigenschaften stellt Notoincisol B eine geeignete Leitstruktur für pharmakologische Wirkstoffentwicklungen dar, die einen synthetischen Zugang erfordert.



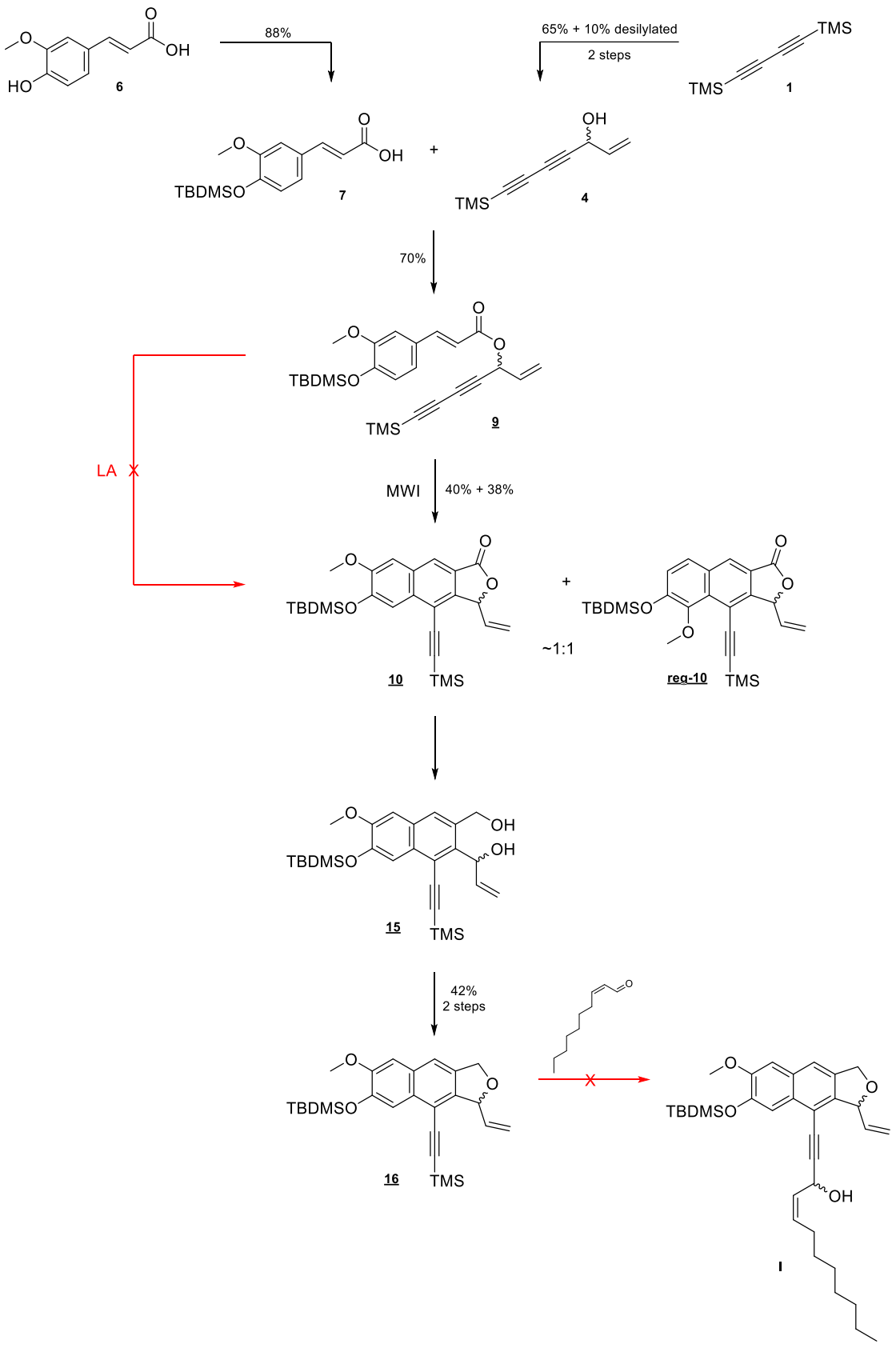
Durch eine schrittweise Untersuchung von synthetischen Schlüsselreaktionen, unter anderem einer dehydro-Diels-Alder Reaktion, einer enzymkatalysierten Racematspaltung sowie einer Lacton-Reduktion, konnte erfolgreich ein vielversprechender synthetischer Weg zu Verbindungen vom Notoincisol B-Typ etabliert werden. Darüber hinaus ermöglicht die entwickelte Synthesestrategie den Zugang zu völlig neuen, rein synthetischen Polyenin-Hybrid Verbindungen, welche möglicherweise ebenso interessant für biologische Tests auf PPARγ-Aktivität sind. Die vorliegende Arbeit diskutiert dabei aufgetretene Probleme, mögliche Optimierungsansätze sowie sich daraus ergebene zukünftige Strategien.

A General schemes

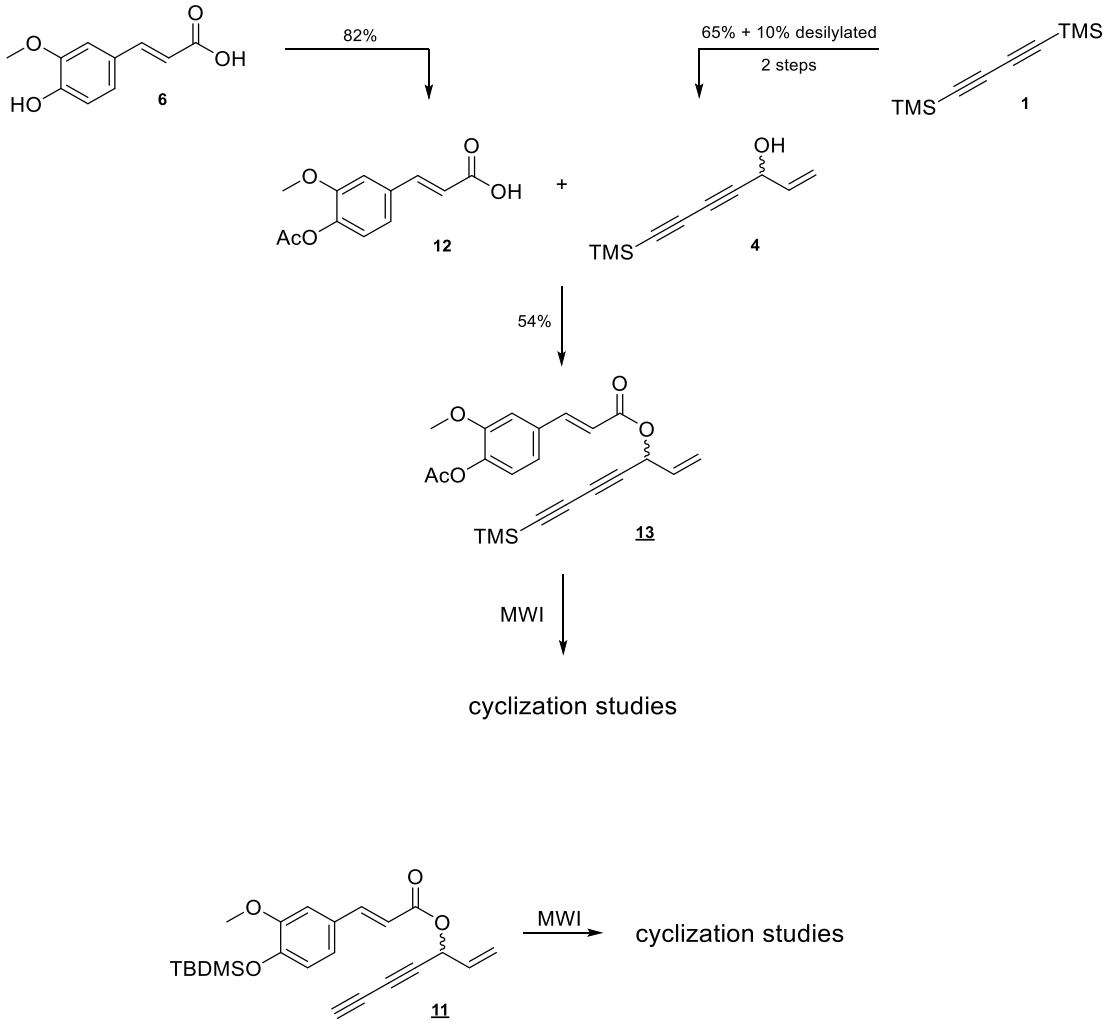
KEY All compounds prepared or used in this thesis are labelled with bold Arabic numbers. Compounds unknown to the literature are additionally underlined. General structures and compounds presented as literature examples are numbered in bold Roman numerals.

Literature citations are indicated by superscript Arabic numbers. Direct citations are additionally indicated by quotation marks.

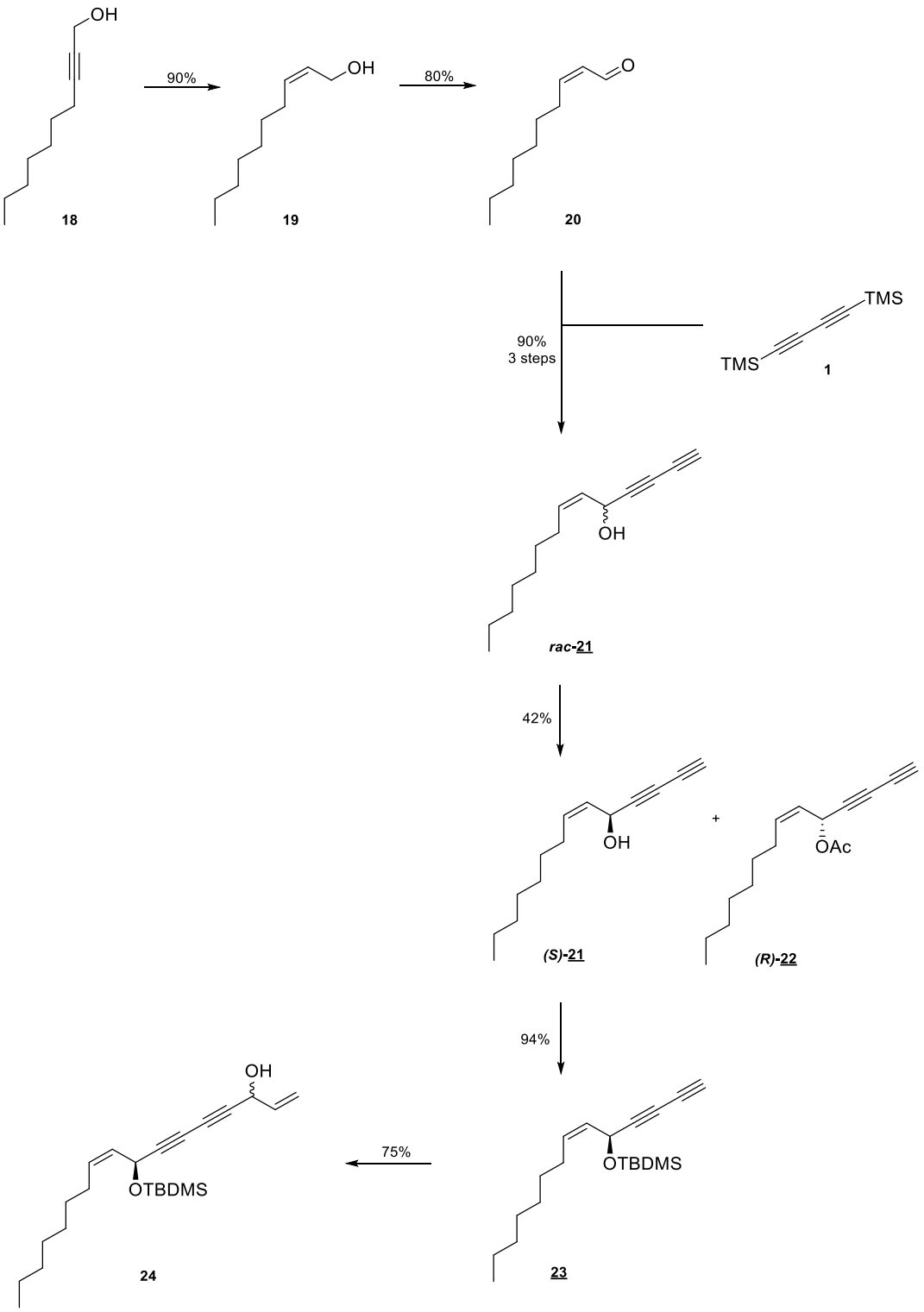
Studies on a Simplified Notoincisol B Model Scaffold I



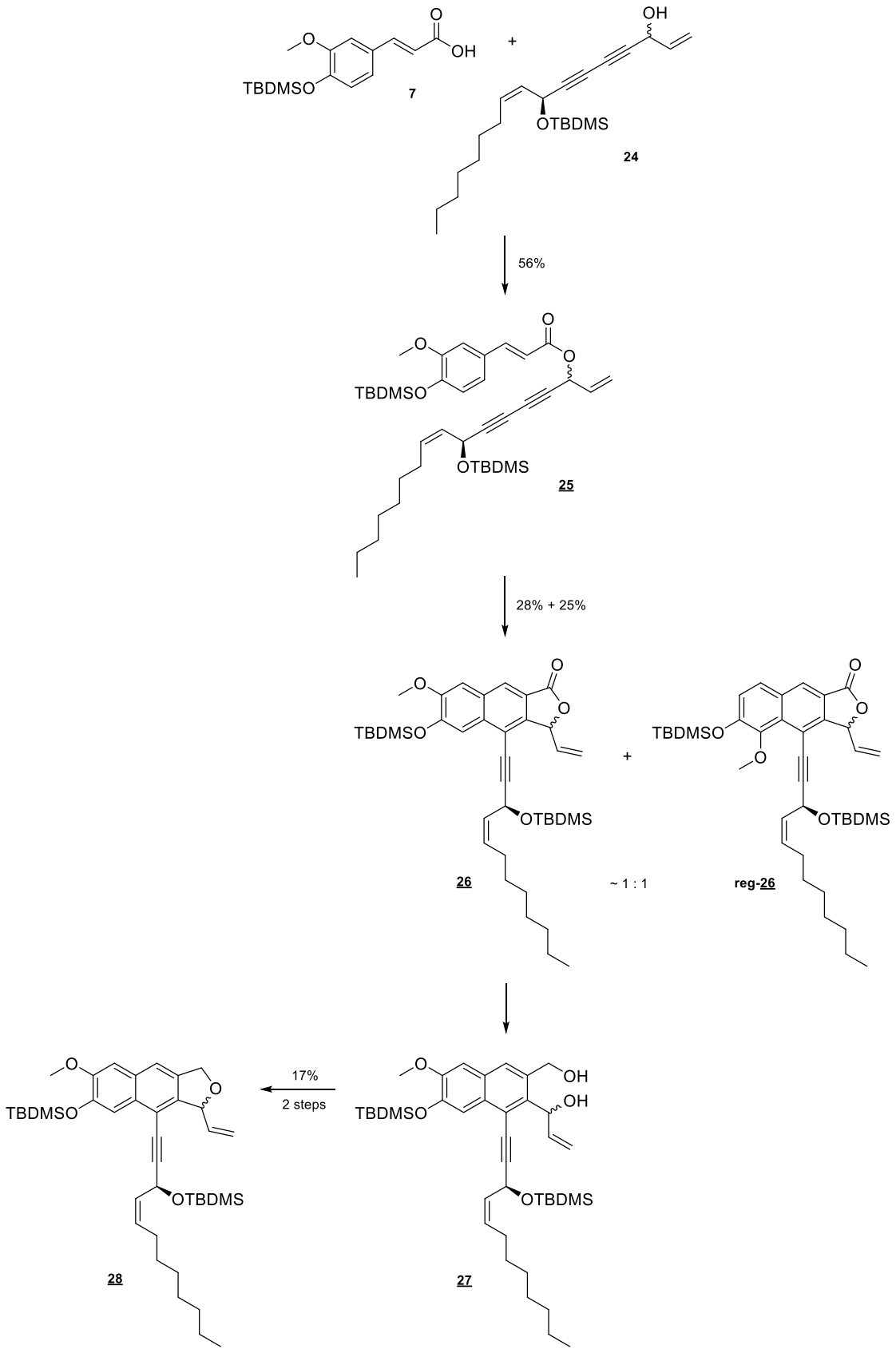
Studies on a Simplified Notoincisol B Model Scaffold II



Synthesis of the Polyenyne Building-Block 8-TBDMS-Falcarindiol



Synthesis of Complete Scaffolds



B Introduction

B I Peroxisome Proliferator-Activated Receptors Gamma (PPARγ)

B I.1 General Aspects and Biological Relevance

Peroxisome proliferator-activated receptors (PPARs) are ligand-inducible transcription factors which belong to the class of nuclear hormone receptor proteins.[1-3] By regulating the expression of specific gene networks, PPARs are acting as key-players in diverse biological processes. Most importantly, PPAR controlled target genes have emerged to be involved in glucose- and lipid- metabolism, cell differentiation and inflammation processes.[4]

To date, three different isoforms of human PPAR – PPARα, PPARβ/δ and PPARγ – have been identified. Besides their distinct tissue distribution, they differ from each other in terms of ligand specificities and physiological roles.[5-6] While PPARα is mainly expressed in heart, muscle, liver and kidney, PPARβ/δ can be ubiquitously found in various tissues. Both of these two subtypes are massively involved in the regulation of lipid metabolism.[7] Whereas the activation of the first PPAR isoform identified (PPARα), was described to "result in peroxisome proliferation in rodent hepatocytes", and therefore dedicated the name to these nuclear receptors, neither of the two other PPARs (PPARβ/δ and PPARγ) is known to elicit a similar response.[8]

Among the three PPAR isoforms, PPARγ appears to be the best studied one.[9] PPARγ can predominantly be found in cells of the fatty tissue (adipocytes) and in cells of the immune system (macrophages, B and T cells and dendritic cells) and is most decisively involved in the regulation of lipid metabolism, glucose homeostasis, adipocyte cell differentiation and inflammation processes. In addition, PPARγ appears in two distinct isoforms, PPARγ1 and PPARγ2, which slightly differ in terms of their structural properties and tissue distribution.[9-10]

Based on their diverse regulatory activities in metabolic and inflammatory processes, PPARγs have increasingly become attractive pharmacological targets to combat a variety of different diseases. It is well established that PPARγ controls the expression of various important factors which are capable of influencing whole-body insulin sensitivity. Resulting thereof, PPARγ activators like thiazolidinedione-type drugs (TZDs) are in clinical use for the treatment of type II diabetes and metabolic syndrome as so called "insulin sensitizing medications".[11]

Furthermore, the fact that PPARγ is also remarkably expressed in various cells of the immune system has particularly risen attention towards pharmacologically targeting these receptors in inflammation related pathological conditions.[12] In this regard, it has been shown that activation of PPARγ inhibits the function of important pro-inflammatory transcription factors (NF-κB, AP-1, NFAT and STAT), thereby reduces the formation of inflammatory signaling molecules and hence attenuates inflammation and tissue injury.[8, 13-14]

Closely related to the role of PPARγ in inflammation and adipocyte cell differentiation, recent investigations strongly emphasize the potential of PPARγ agonists in cancer treatment. Although the exact role of PPARγ in carcinogenesis, to date, remains still unclear and controversially discussed,[15] the fact that PPARγ is expressed in many human tumors is thought to present a new therapeutic handle in cancer treatment.[16]

B I.2 Mechanism of Action

The transcriptional regulation of target genes by PPARγ (Figure 1) is crucially influenced by interactions with co-repressor and co-activator protein complexes. In the so called non-liganded state, PPARγ interacts with co-repressor proteins, preventing PPARγ-DNA binding and consequently resulting in the inhibition of target gene expression.[12]

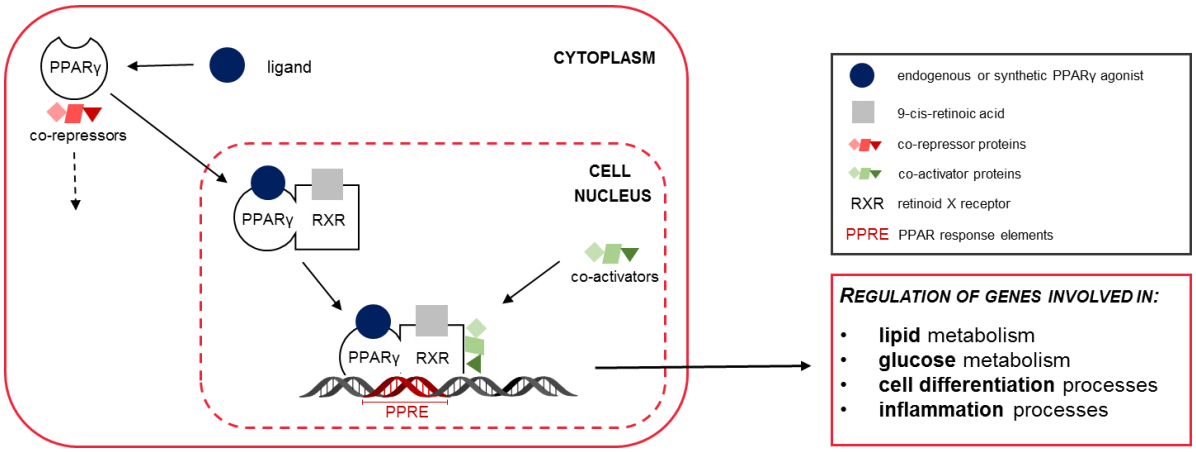


Figure 1: Basic mechanism of transcriptional regulation upon PPARγ activation.

Upon binding of a suitable agonistic ligand, PPARγ sheds the co-repressor complex and subsequently accumulates in the cell nucleus. Accordingly, active PPARγ proteins form heterodimers by binding with another ligand-activated nuclear receptor, called retinoid X receptor (RXR). The PPARγ-RXR dimer binds to a specific area (peroxisome-proliferator response element, PPRE) in the promoter region of the target DNA and finally triggers the transcription process upon recruitment of co-activator complexes.[7, 17-18]

B I.3 Overall Structure and Ligand Binding

The principal structural organization of PPARγ is similar to other types of nuclear hormone receptors, consisting of three main functional domains: (i) N-terminal: transcriptional activation domain, (ii) DNA-binding domain and (iii) C-terminal: ligand binding domain (LBD).[7] In regard to the modulation of PPARγ activity by specific ligands, the characteristics of the LBD are of particular interest. Hence, further considerations in this part are focusing on the structure and properties of the C-terminal LBD of PPARγ.

As a result of the great importance of PPARγ proteins in the regulation of several biological processes and their high potential as pharmaceutical targets to combat a variety of different diseases (part B I.1), their LBD has been intensively investigated and described in the literature over the past years. Several X-ray structures, in different binding states, have been reported and visualize that the PPARγ LBD is a remarkably large cavity (1300-1400 Å^3) compared to those of other nuclear hormone receptors.[19-21] In total, the LBD of PPARγ comprises of 13 α-helices and one small β-sheet, generating a characteristic Y-shaped binding pocket which can be divided into an entrance region and two separate arms (arm I and arm II, Figure 2).[22] While the outer entrance region is lined by several polar amino acids, arm I and arm II as well as the inner entrance region are substantially composed of hydrophobic residues. The only "polar" part of the inner region is located in arm I and comprises only of a few moderately polar amino acids (Ser289, His323, His449 and Tyr473), which proved to play decisive roles in ligand-PPARγ interactions.[21]

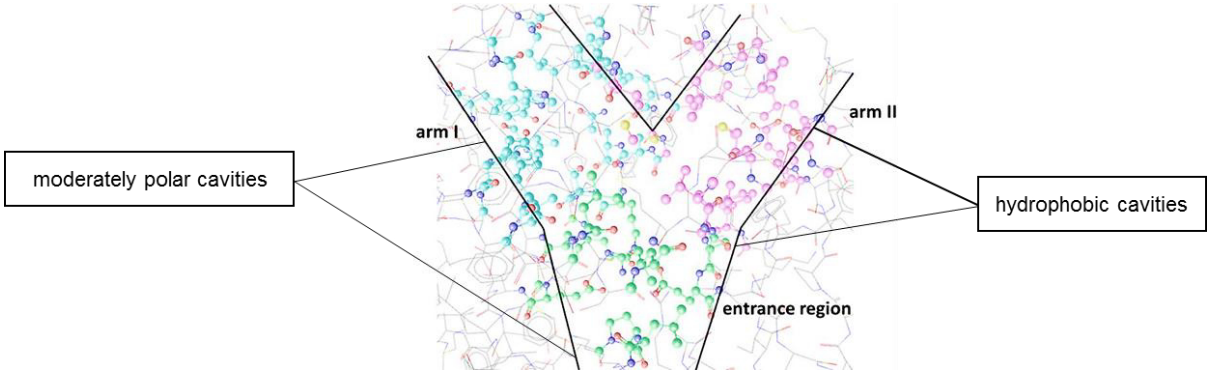


Figure 2: Schematic illustration of the Y-shaped PPARγ ligand binding domain, comprising an entrance region and two separate arms (arm I and arm II).[23]

Given the spacious and predominantly hydrophobic nature of the PPARγ LBD, typical receptor ligands are not limited to a little number of highly specific compounds as in case of most other nuclear receptors, but rather offer a wide structural diversity.[9] In general, PPARγ ligands are often grouped into two major classes: (i) endogenous ligands and (ii) synthetic ligands (Figure 3).[24]

Natural (endogenous) ligands of PPARγ mainly comprise lipid-like molecules, such as fatty acids (**II**) and eicosanoids (**III**), which have all shown to act as rather weak agonists and additionally only exist in low concentrations on a physiological level (Figure 3).[25] The fact that to date there is still no highly specific endogenous PPARγ ligand known remains controversially discussed in the literature and raised the hypothesis that PPARγs might act as universal physiological "lipid sensors" which are activated by the cellular presence of a variety of lipid-like molecules.[9, 26]

In contrast to the ongoing debate on the existence of specific endogenous ligands, it is well established that there is a series of highly specific synthetic full PPARγ agonists, most prominently the class of thiazolidinediones (Figure 3). While there is no doubt that pioglitazone (**IV**) and rosiglitazone (**V**), the two most important TZDs, are highly specific and potent PPARγ modulators able to activate these receptors already in nanomolar concentrations, such full agonistic activity has been reported to involve severe side effects.[27] As a consequence, most of the clinically relevant TZDs had to be strictly regulated or even withdrawn from the market.[22]

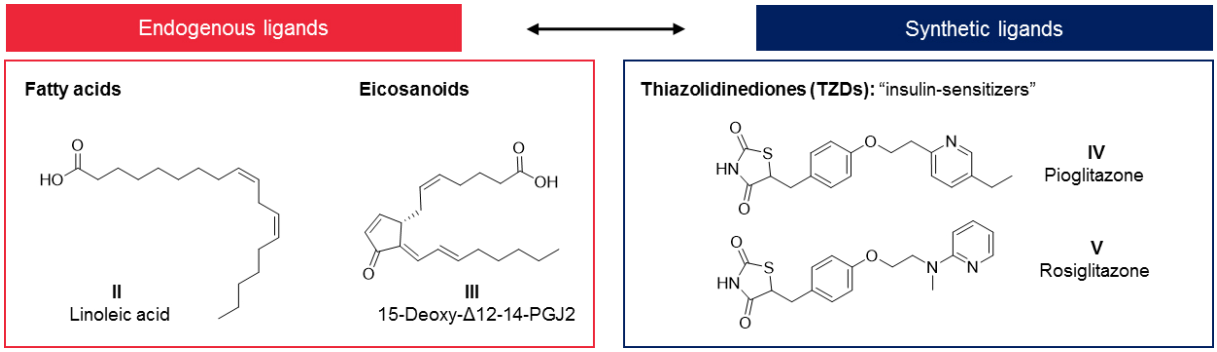


Figure 3: Major classification of PPARγ ligands and representative examples.

Although structural characteristics of PPARγs are fundamentally revealed and described in the literature, the high complexity of molecular regulation mechanisms (part B I.2) as well as the rather outstanding size and nature of their LBD, make structure-activity-relationship (SAR) studies particularly challenging in case of this nuclear hormone receptor.[22] In principle, endogenous and synthetic ligands of PPARγ share basic structural features: a polar "head group" (the thiazolidinedione-group in TZDs or the carboxylate group in fatty acids) is accompanied by a hydrophobic "tail". In many cases, agonistic activity of ligands is connected with the formation of a hydrogen-bond network between the polar "head-group" and the four polar residues in arm I of the LBD. Whereas the hydrophobic "tail" interacts with arm II and the hydrophobic part of the LBD entrance region (Figure 1).[21]

In recent years research has remarkably been directed towards the precise fine-tuning of molecular PPARγ-ligand interactions with the overall aim to identify new potent modulators which elicit reduced side effects compared to traditional synthetic full PPARγ agonists (e.g. TZDs). In this regard, the concept of partial agonism or selective PPAR modulation (SPPARM) has been regarded as a promising strategy. In general, such compounds would activate PPARγ more weakly and hence are believed to overcome unwanted side-effects while still triggering the desired regulatory mechanisms.[22]

B II Polyenynes

B II.1 Structural Aspects, Abundance and Biosynthesis

Polyenynes, often also referred as polyacetylenes, are a class of natural products which are typically characterized by their poly-unsaturated carbon skeleton, comprising two or more triple bonds and often closely adjacent double bonds. Most of these compounds feature primary or secondary alcohol moieties, frequently in allylic positions and are considered as rather unstable structures which are prone to isomerization and degradation processes.[28] The most prominent representatives of this compound class are the C_{17}-polyenyes of the falcarinol-type, including falcarinol (**VI**) and falcarindiol (**VII**) (Figure 4), which are widely distributed in *Apiaceae* and *Araliaceae* species and hence can be found in carrots and many common seasonings.[29]

Polyenynes are considered as secondary metabolites which are structurally derived from unsaturated fatty acids. The biosynthetic pathway towards C_{17}-falcarinol-type polyenynes is a multiple-step enzymatic cascade reaction starting from linoleic acid (**II**) which is directly obtained from primary fatty acid metabolism (Figure 4).[28] Several highly specific enzymes, including desaturases and acetylenases, perform a stepwise oxidation process in which the polyunsaturated carbon skeleton of the falcarinol-type is established. Once the complete unsaturated scaffold, comprising two adjacent triple bonds which are flanked by two double bonds, is generated, a subsequent decarboxylation step affords falcarinol (**VI**) and a final stereoselective hydroxylation leads to falcarindiol (**VII**).

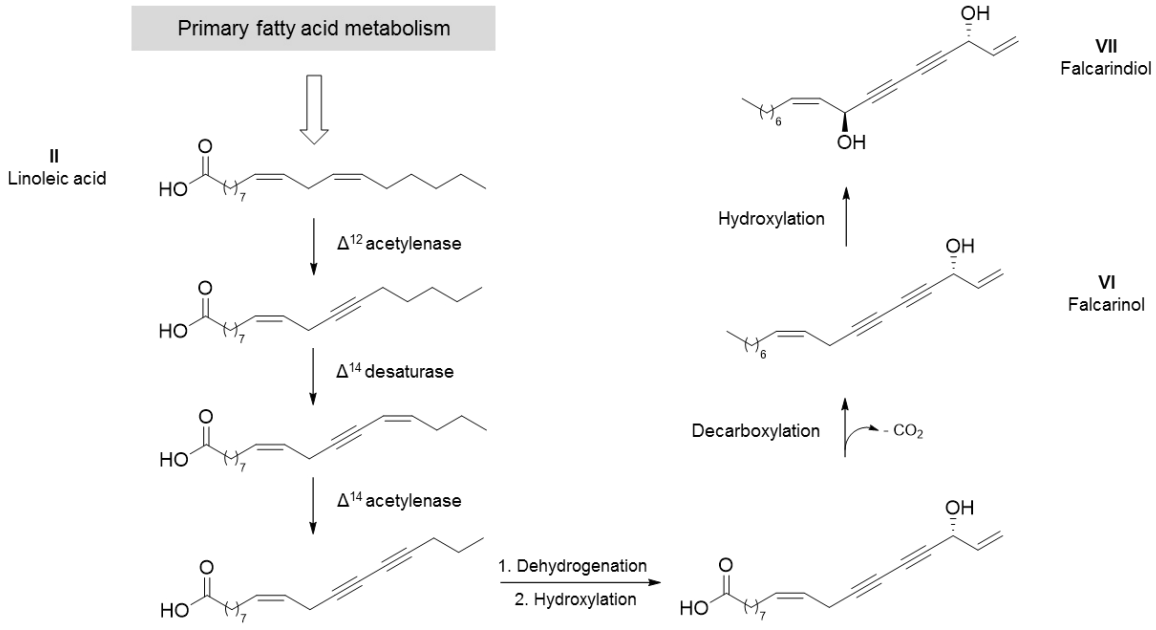


Figure 4: Biosynthetic pathway towards C_{17}-polyenyne compounds.[30]

B II.2 Polyenyne-Hybrid Compounds: The Notoincisol Subclass

In 2014 Liu, X. *et al.* reported the isolation of 11 new polyenyne derivatives from the rhizome and roots of the traditional Chinese medical plant *Notopterygium incisum* Ting ex H.T. Chang.[23] All new compounds were depicted as so called polyenyne-hybrid molecules, structurally composed of the C_{17}-polyenyne falcarindiol (**VII**) and different cyclic moieties. Among them, Notoincisol A-C (**VIII, I, IX**) represent a small subgroup of three closely related structures which are derived from the naturally abundantly occurring ferulic acid (**6**) and falcarindiol (**VII**) (illustrated in blue color, Figure 5). While Notoincisol A is a simple ester of falcarindiol (**VII**) and ferulic acid (**6**), Notoincisol B (**I**) and Notoincisol C (**IX**) represent two completely novel carbon scaffolds. Both molecules are comprising a characteristic cyclic core structure, consisting of a 1,3-dihydronaphtho[2,3-c]furan moiety (Figure 5).

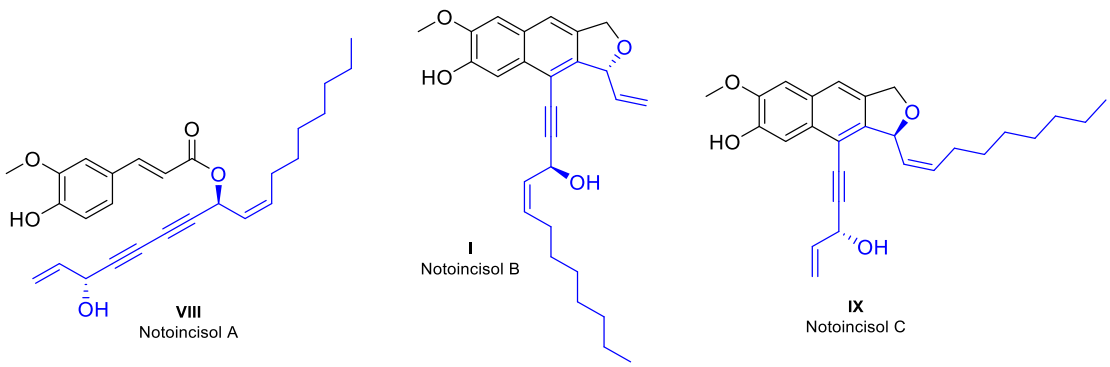


Figure 5: Structures of the polyenyne-hybrid compounds Notoincisol A-C. Falcarindiol-type polyenyne moieties are highlighted in blue.

Given the structural properties of the Notoincisol polyenyne-subclass, Liu, X. *et al.* suggested that these compounds originate from a common biosynthetic pathway, thereby indicating that Notoincisol B and C-type structures are cyclization products of falcarindiol and ferulic acid. Figure 6 illustrates the proposed biogenic route towards Notoincisol B and structural analogues. Starting from ferulic acid (**6**) and falcarindiol (**VII**), a regioselective esterification of the hydroxyl group in position 3 of the diol leads to a Notoincisol A-type intermediate which can be denoted as Notoincisol iso-A (**X**). A subsequent intramolecular Diels-Alder-type cyclization reaction generates the cyclic core structure which is characteristic for Notoincisol B and C-type polyenyne-hybrids. The proposed biogenic pathway towards these novel compounds is eventually concluded by a rearomatization process and a reduction step affording the final 1,3-dihydronaphtho[2,3-c]furan core-moiety of Notoincisol B (**I**).[23]

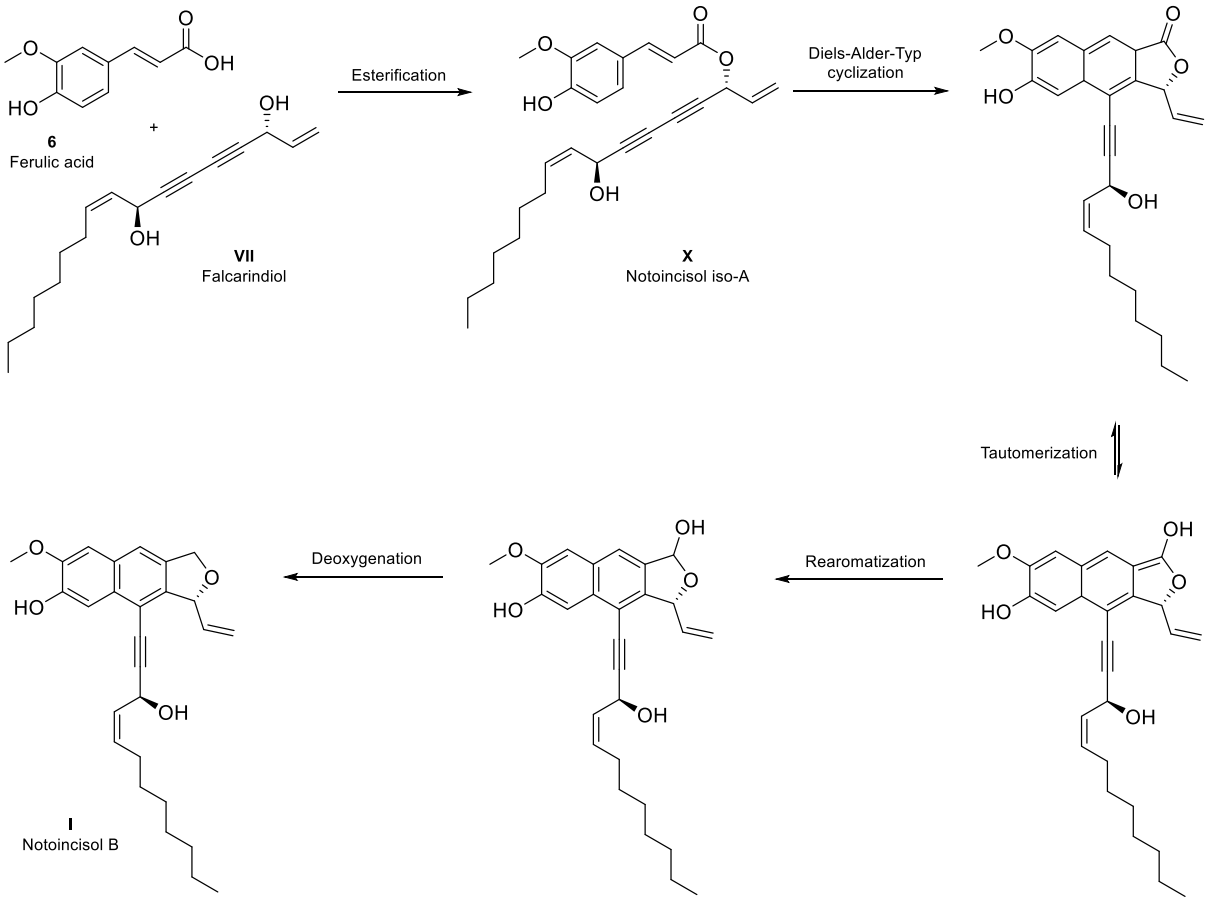


Figure 6: Proposed biosynthetic pathway towards Notoincisol B and structurally related polyenyne-hybrid compounds.[23]

B II.3 Bioactivity: PPARγ as a Molecular Target of Polyenynes

While natural products from diverse plant species have been in use for medical purposes since hundreds of years, polyenynes have been considered as undesired constituents of food plants as a consequence of their well-known neurotoxic and allergenic properties, for many decades.[29] However, in light of reported anti-cancerous, anti-inflammatory, anti-fungal and anti-bacterial effects, the pharmaceutical potential of polyenyne natural products has increasingly been studied over the last years.[31]

In 2013 Atanasov A.G. *et al.* reported for the first time that falcarindiol-type polyenynes from *Notopterygium incisum* Ting ex H.T. Chang are able to activate PPARγ.[32] In-depth investigations, including docking studies, suggested a promising partial agonistic activity pattern, specifically for PPARγ isoforms. Shortly thereafter Liu, X. *et al.* investigated newly identified polyenyne-hybrid compounds (part B II.2) on their potential to activate PPARγ.[23] Among all isolated substances, Notoincisol A (**VIII**) and Notoincisol B (**I**) exhibited the best agonistic effects. With EC_{50} values ranging from 1.7 to 2.3 µM and a maximal fold activation from 2.3 to 2.8, both compounds were identified as promising partial PPARγ agonists, compared to common synthetic full agonistic modulators like TZDs (Table 1).

Table 1: PPARγ agonistic effects of polyenyne-hybrids and pioglitazone.[23]

	EC_{50} (µM)	max. fold activation
Pioglitazone (IV**)†**	0.21	6.6
Notoincisol A (VIII**)°**	2.3	2.8
Notoincisol B (I**)°**	1.7	2.3

†tested at 5 µM
°tested at 10 µM

B III Objective

Given the structural novelty (B II.2) and the promising partial agonistic PPARγ activity exhibited in preliminary biological investigations (B II.3), Notoincisol B fulfills all criteria of a highly suitable pharmaceutical lead structure. Resulting thereof, the development of a synthetic strategy which enables access to this novel Notoincisol B-type carbon skeleton is strongly desired.

Within this thesis, the development of a synthetic strategy towards Notoincisol B-type polyenyne-hybrids was aimed for by mimicking their biogenic synthesis pathway. Therefore a successive investigation of the following synthetic key-steps was intended:

- Diels-Alder-type cyclization reaction: The synthetic feasibility of an intramolecular dehydro-inverse-electron demand Diels-Alder-type cyclization reaction between a styrene moiety originating from ferulic acid (**6**) and a falcarindiol (**VIII**)-originating alkyne moiety needed to be proven. Consequently a reliable synthetic protocol should be developed.
- Rearomatization: Following a successful cyclization step, a complete rearomatization of the cyclized system towards the final naphthalene moiety needed to be ensured.
- Reduction: A protocol for the final deoxygenation/reduction step, affording the complete 1,3-dihydronaphtho[2,3-c]furan moiety needed to be established.
- Stereochemistry: The natural stereochemical configuration (3R, 8S) of the target compound should be established within the synthetic route.

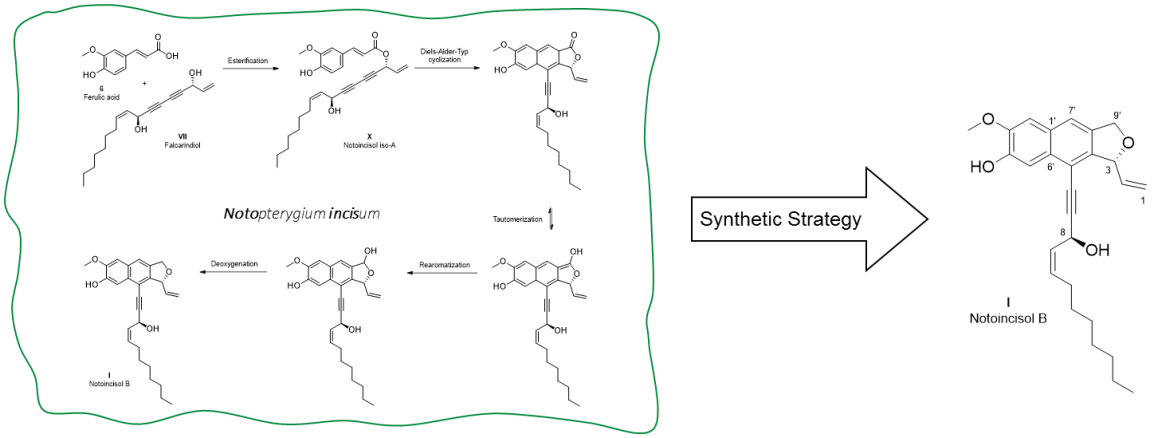


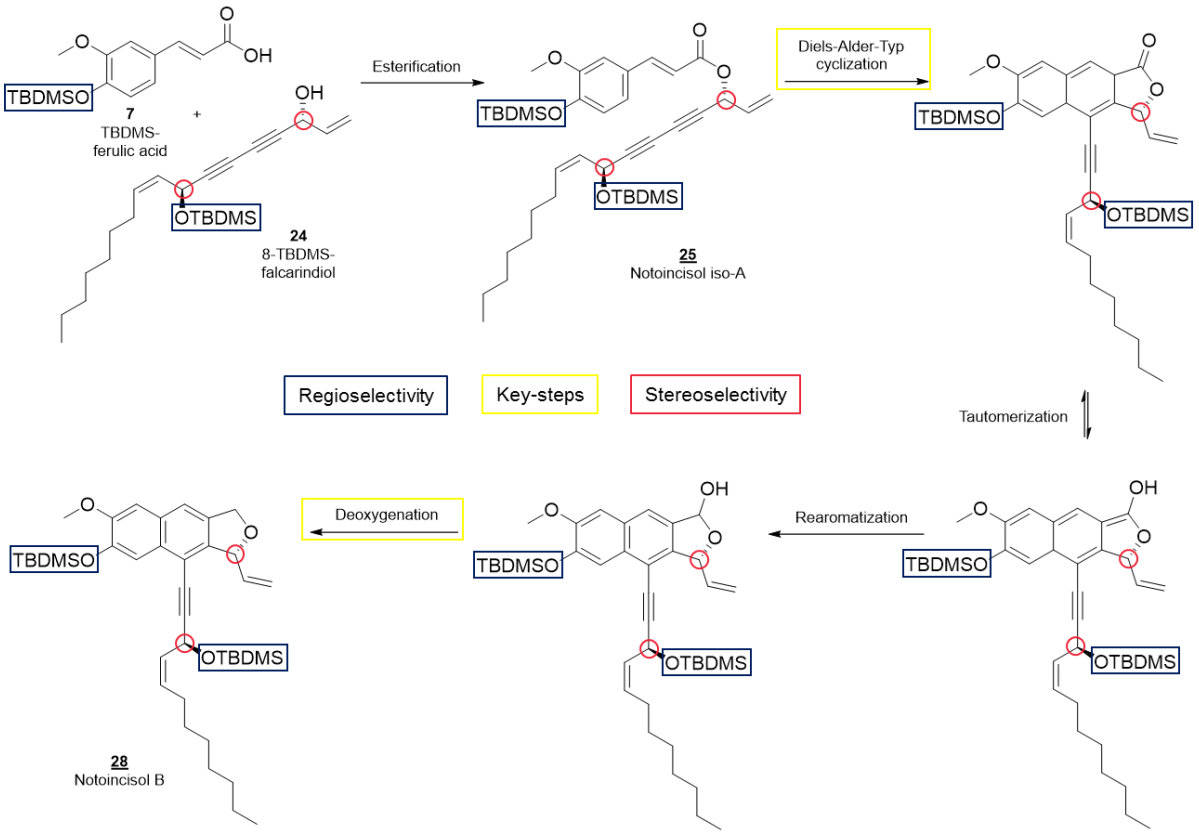
Figure 7: Schematic illustration of this thesis' objective: From the biogenic synthesis to a synthetic strategy towards Notoincisol B.

Following a step-wise investigation of the described synthetic key-challenges should eventually lead to a valuable synthetic route towards Notoincisol B-type polyenyne-hybrids and additionally allow a conclusion on the synthetic feasibility of the proposed biomimetic pathway.

C Results and Discussion

C I From the Biogenic Synthesis to a Synthetic Strategy

In recent studies within our laboratory several different pathways and synthetic strategies towards the synthesis of Notoincisol B-type polyenyne-hybrids have been thoroughly investigated, unfortunately all encountered major difficulties.[30, 33] In light of previously emerged challenges we set out to develop a completely new strategy by taking advance of nature's ideas for the synthesis of Notoincisol B-type polyenyne-hybrids. In this regard, the proposed biogenic synthesis pathway by Liu, X. *et al.* (part B II.2) appeared to serve as a fundamental starting point for strategic synthesis planning.[23]



Scheme 1: From the biogenic pathway of polyenyne-hybrids to a synthetic strategy towards Notoincisol B: key-challenges.

Attempting to transform the given biogenic pathway into a valuable synthetic route, several key-challenges needed to be considered (Scheme 1). While in the natural environment selectivity of chemical transformations is frequently accomplished via the support of enzyme catalysis[28], chemical laboratory synthesis often needs auxiliary strategies. Hence, given the structural properties of the target compound, regioselectivity as well as control over stereochemical configuration needed to be achieved. In order to ensure regioselective esterification of the hydroxyl group in position 3 of the

falcarindiol polyenyne moiety, a silyl-protecting group strategy was implemented, affording TBDMS-ferulic acid (**7**) and 8-TBDMS-falcarindiol (**24**) as major starting building blocks for the biomimetic synthesis route.

The falcarindiol (**24**) polyenyne moiety is a well-known structure and several chemical total synthesis strategies for this compound have already been established and entirely reported in the literature.[34-38] Within this thesis, a new strategy towards this building block was followed. Associated retrosynthetic analysis and synthetic considerations are comprehensively outlined and discussed in part C III.1. In principle, falcarindiol (**24**) includes two stereocenters which are reported to exist in a (3R,8S)-configuration in naturally occurring polyenyne-hybrids from *Notopterygium incisum*.[23] Accordingly, this natural stereochemical information was planned to be implemented by means of well literature reported enzymatic kinetic resolution procedures.[30, 39-40]

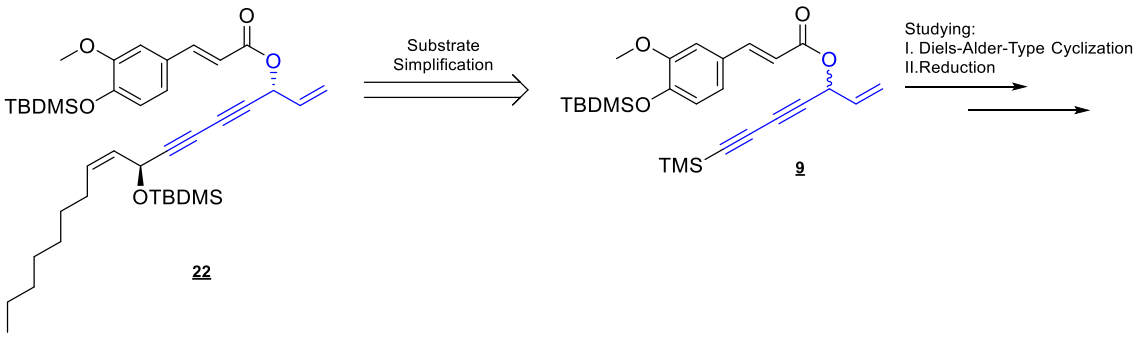
Once starting compounds **24** and **7** would be in hand, a simple esterification step under modified Steglich-conditions would lead to intermediate compound **25**, which is a regioisomer of naturally occurring Notoincisol A (**VIII**) and hence can be denoted as Notoincisol iso-A. This part of the proposed synthetic route corresponds well to the previously in our laboratory established synthesis of Notoincisol A-type polyenyne-hybrids and therefore was considered as a straight forward strategy.[30]

The Notoincisol iso-A-type structure **25** represents a key-intermediate in the outlined biomimetic synthesis pathway as it serves as the precursor molecule for the intramolecular Diels-Alder-type cyclization reaction aiming to establish the characteristic Notoincisol B core scaffold. Noteworthy, in contrast to the control over regioselectivity and stereochemical configuration in the natural environment, which is most likely achieved *via* the support of enzyme catalysis, it is hypothesized that this cyclization step proceeds in a non-enzymatic fashion within the biogenic pathway. Taking into account the reported sensitive nature of Notoincisol-A-type polyenynes[23] as well as major difficulties which were encountered in similar cyclization reactions within previous strategies,[30] this step appeared to be one of the key-challenges in the proposed biomimetic pathway. Resulting thereof, thorough studies on this type of dehydro-inverse electron-demand Diels-Alder cyclization reaction were considered to be crucial for the overall success of the presented synthetic approach (part C II.2).

Following a successful cyclization step, the complete rearomatization of the cyclized system towards the final naphthalene moiety had to be considered in the synthesis planning. Liu, X. *et al.* hypothesized within their proposed biogenic pathway that upon a classical [4+2]-cycloaddition, a successive tautomerization-rearomatization mechanism eventually affords the final naphthalene core, which possesses a benzannulated lactol moiety (Scheme 1). Although at that point it was not predictable whether the successfully cyclized substrate would indeed possess a lactole moiety or rather a corresponding lactone as claimed in comparable literature-known reactions,[41-44] we clearly aimed for a one-step cyclization-rearomatization reaction in the best case.

The biogenic pathway towards Notoincisol B-type polyenynes is concluded by means of a reductive deoxygenation of the formed lactol (or lactone) moiety to afford the final 1,3-dihydronaphtho[2,3-c]furan core structure. Even though the reduction of lactols or esters has increasingly been

recognized in the literature as a general method to access the corresponding cyclic or linear ether moieties,[45] many reported and recently developed transformations involve conditions, like transition metal catalysis[46-47] or the employment of radical species,[48-49] which would considerably raise concerns about their applicability on Notoincisol B-type substrates, given the structural characteristics of these compounds. Consequently, the final reduction step towards the 1,3-dihydronaphtho[2,3-c]furan moiety of the target compound appeared to be a second key-challenge within the proposed pathway, which needed to be considered in thorough investigations (part C II.3).



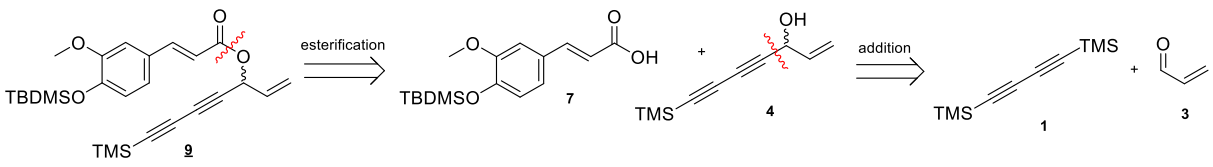
Scheme 2: Initial simplification of the target compound – introducing a model substrate.

In light of the outlined challenges within the proposed biomimetic synthesis pathway, a synthetic strategy needed to be developed allowing most efficiently the accurate evaluation of synthetic key-steps. Therefore, compound **9** was designed as a model substrate which initially exhibited a significantly simplified carbon skeleton compared to its "parent compound" **25** (Scheme 2). The implemented simplifications aimed to facilitate the access to a valuable cyclization precursor by initially omitting the elaborate synthesis of the well-known falcarindiol building block (**24**, part C III.1) while keeping several key-features present in the molecule. Most importantly, the core 1,3-diyne moiety was entirely conserved in the model compound. This enabled the adequate mimicking of the electronic properties of the complete scaffold, which is a characteristic of particular importance in regard to Diels-Alder type cyclization reactions. In addition, initial studies were performed on racemic compound **9**, regardless of any stereochemical considerations.

C II Studies on a Simplified Notoincisol B Model Scaffold

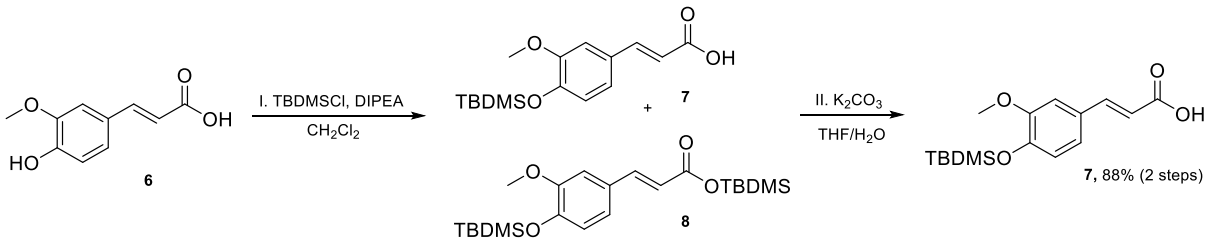
C II.1 Synthesis of the Precursor Substrate (9)

Simplified precursor substrate **9** is an ester of the naturally occurring ferulic acid **6** and the poly-unsaturated secondary alcohol **4**. With regard to regioselectivity, a protecting group at the phenolic hydroxyl group of the acid moiety needed to be established, affording compound **7** as a starting material for the esterification. Retrosynthetic analysis (Scheme 3) further revealed that alcohol **4** could be obtained by an addition reaction of commercially available 1,4-bis(trimethylsilyl)buta-1,3-diyne **1** to the simple aldehyde precursor acrolein **3**.



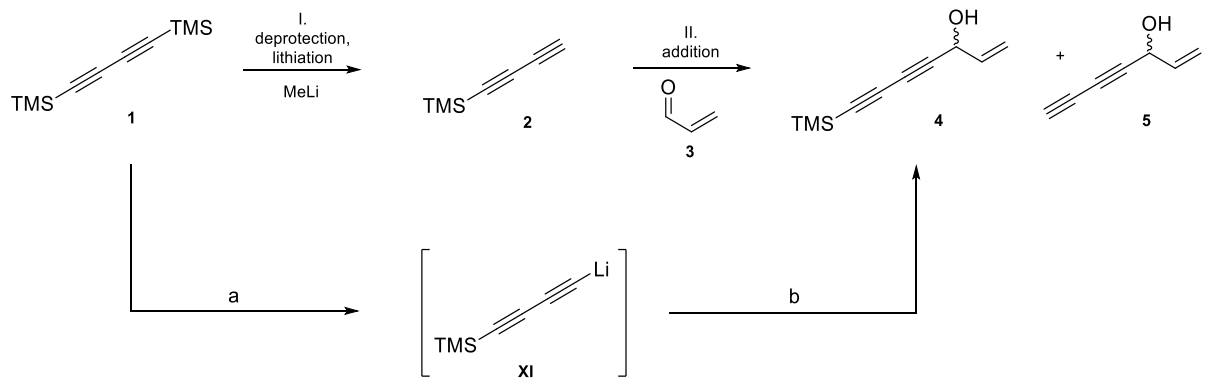
Scheme 3: Retrosynthetic analysis – model substrate 9.

In full awareness of the well-known fact that TBDMS-protection of ferulic acid **6** under standard conditions using TBDMS-chloride and DIPEA (or imidazole) in CH_2Cl_2 as a solvent results in the formation of a product mixture of desired compound **7** and unwanted silyl ester **8**,[30] a two-step procedure was followed in which **8** was immediately hydrolyzed in the second step, affording target compound TBDMS-ferulic acid **7** in 88% overall yield (Scheme 4).[50]



Scheme 4: Two-step protection of ferulic acid.

For the synthesis of the poly-unsaturated alcohol moiety **4**, two closely related strategies appeared to be conceivable (Scheme 5). First, selective mono-desilylation of starting material **1** upon treatment with MeLi would lead to intermediate **2**, which could be isolated and purified. Terminal alkyne-deprotonation and subsequent addition to acrolein **3** would give product **4**.[51] However, this approach turned out to be rather unconvincing as the isolation and purification of intermediate **2** was associated with major product losses as a consequence of its volatility (23% isolated yield of **4** over 2 steps). Alternatively, Holmes A. B. *et al.* already reported in 1979 that the treatment of bis-TMS-protected alkynes like **1** with MeLi or MeLi-LiBr complex solutions results in the quantitative formation of a mono-lithiated species **XI** which may directly be converted into product alcohol **4** upon addition of electrophile **3**.[52] Following such an *in situ* deprotection-addition reaction would circumvent work-up related issues described above and hence was investigated in greater detail.



Scheme 5: Two followed strategies towards unsaturated alcohol 4, with the *in situ* approach appearing to be more convenient.

While at first sight access to alcohol **4** via the outlined one-pot reaction appeared to be a straight forward approach based on literature reports,[39, 53-54] closer investigations of reaction conditions for both sub-steps (a and b, Scheme 5) were urgently needed in order to overcome several challenges and increase low yield (<<50%).

First, selective mono-desilylation and *in situ* lithiation of the terminal alkyne using MeLi as a reagent (1.05 eq., anhydrous THF as a solvent) to give intermediate **XI** (a, Scheme 5) could be achieved in accordance with a reported protocol by Baldwin J. E. *et al.*[53] It turned out that temperature was a major parameter within this reaction and keeping it low at -20 °C during the whole deprotection process resulted in quantitative formation of intermediate **XI** after 3 h, as followed by means of GC-MS (samples were quenched by adding a saturated aqueous NH_4Cl solution). In contrast, protocols claiming this step to proceed at 0 °C to rt could not be reproduced as prolonged reaction times (>10 h) and incomplete conversion of starting material **1** were observed.[52, 54]

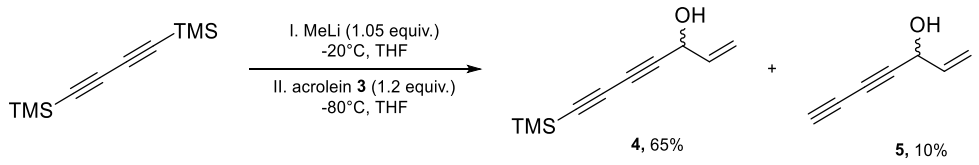
Table 2: Detailed results of empirical investigations of reaction conditions for the one-pot deprotection-addition reaction towards alcohol 4, step b (Scheme 5). Best conditions are highlighted.

Entry	Parameter		Screened Conditions				
1	Temperature [°C]		0	-20	-20 to rt	-80	-80 to rt
2	Reaction Time [h]		1		2		3
3	Equiv. acrolein		1.2	1.2+1	2	3	5
4	Addition of acrolein		pure, dropwise		One-shot		dilution, dropwise
5	Reactivity of organolithium species		without a ligand		addition of TMEDA		
6	Molarity [M]		0.27		0.51		
7	Work-up strategy	Temperature [°C]	rt		-30 °C		
		Quenching agent	buffer (pH~6)	H_2O	NH_4Cl (sat.)		NH_4Cl (sol.)

Once convenient conditions for the mono-lithiation of 1,3-diyne starting compound **1** were at hand, the second sub-step, comprising the addition of the terminal alkyne to acrolein **3** (b, Scheme 5), had to be considered in further detail. Table 2 sums up all investigated parameters and conditions for this sub-step, final conditions are highlighted. Two factors in this step appeared to essentially impact the overall yield of the reaction:

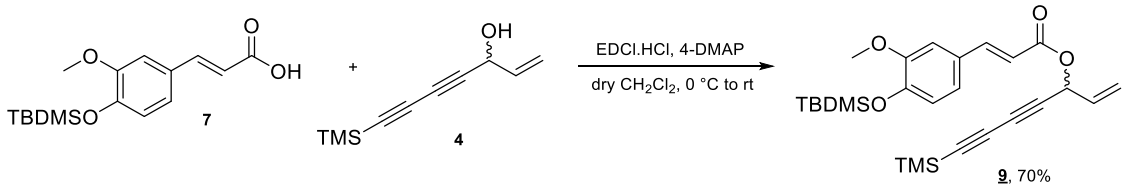
First, GC-MS analysis revealed that intermediate **XI** was not fully consumed upon addition of the electrophile acrolein. Thus, several parameters were investigated, attempting to further push the conversion of lithiated species **XI** (Table 2, entry 1-5). Among them, the nature of the electrophile acrolein itself turned out to be a particular issue. On the one hand, it proved to be beneficial to refine commercially available acrolein towards high-quality dryness by means of distillation over a drying agent. On the other hand it is well known that acrolein is an enormously reactive compound, especially in pure form, which readily undergoes 1,2- as well as 1,4-additions with various nucleophiles. In particular, its high tendency for polymerization *via* ionic or radical mechanisms led to massive side reactions, especially when used in large excess (Table 2, entry 3). Consequently, controlling the reactivity of the electrophile by means of temperature and dilution turned out to be extremely beneficial (Table 2, entry 1 and 4).

Second, undesired partial deprotection of product **4**, particularly upon work-up, resulted in formation of by-product **5** (Scheme 5). Although at that point it was not predictable whether the terminal alkyne protection of compound **4** indeed would be needed in upcoming reaction steps, with regard to potentially harsh reduction conditions towards the final 1,3-dihydronaphtho[2,3-c]furan core structure (part C II.3), the preservation of the terminal TMS-group appeared to be convincing. Thorough investigations of different work-up strategies (Table 2, entry 7) helped to minimize the formation of by-product **5**, although it could not be completely prevented. Fortunately, separation of **4** and **5** could easily be achieved by means of flash chromatography. Scheme 6 summarizes the final conditions and results of the one-pot synthesis of alcohol **4** which was eventually obtained in 65% overall yield. In addition, by-product **5** was also used for further investigations in connection with the Diels-Alder cyclization reaction (part C II.2).



Scheme 6: Final conditions and results of the one-pot deprotection-addition reaction towards alcohol 4.

The final step towards precursor substrate **9** was conducted in accordance with a modified Steglich-esterification protocol which was previously used in our laboratory within the total synthesis of the polyenyne-hybrid Notoincisol A (Scheme 7).[30] While small scale experiments (0.17 mmol of **4**) gave excellent yields of 85%, upscaling (1.12 mmol of **4**) led to a slightly diminished, but still solid yield of 70% of precursor substrate **9**.



Scheme 7: Synthesis of precursor substrate 9 via modified Steglich conditions.

C II.2 Key-Step I: Dehydro-Inverse-Electron Demand Diels-Alder Reaction

C II.2.1 Primary Strategy

Striving to explore the synthetic feasibility of the key-step cyclization reaction towards the characteristic tricyclic Notoincisol B core structure, a thorough analysis of structural and mechanistic aspects revealed the fundamental nature of the present reaction and set the direction for experimental investigations: Ester **9** (and similarly its "parent" compound **25**) incorporates a styrene moiety as a diene and an alkyne moiety as a dienophile (Figure 8, A). These functional groups are rightly arranged to enable an intramolecular [4+2]-cycloaddition following a concerted mechanism, typical for Diels-Alder-type reactions.

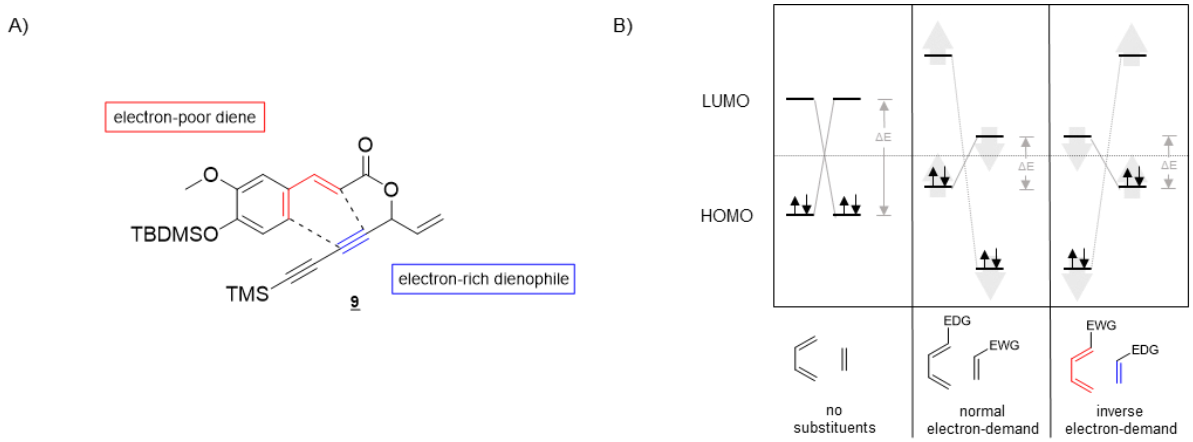


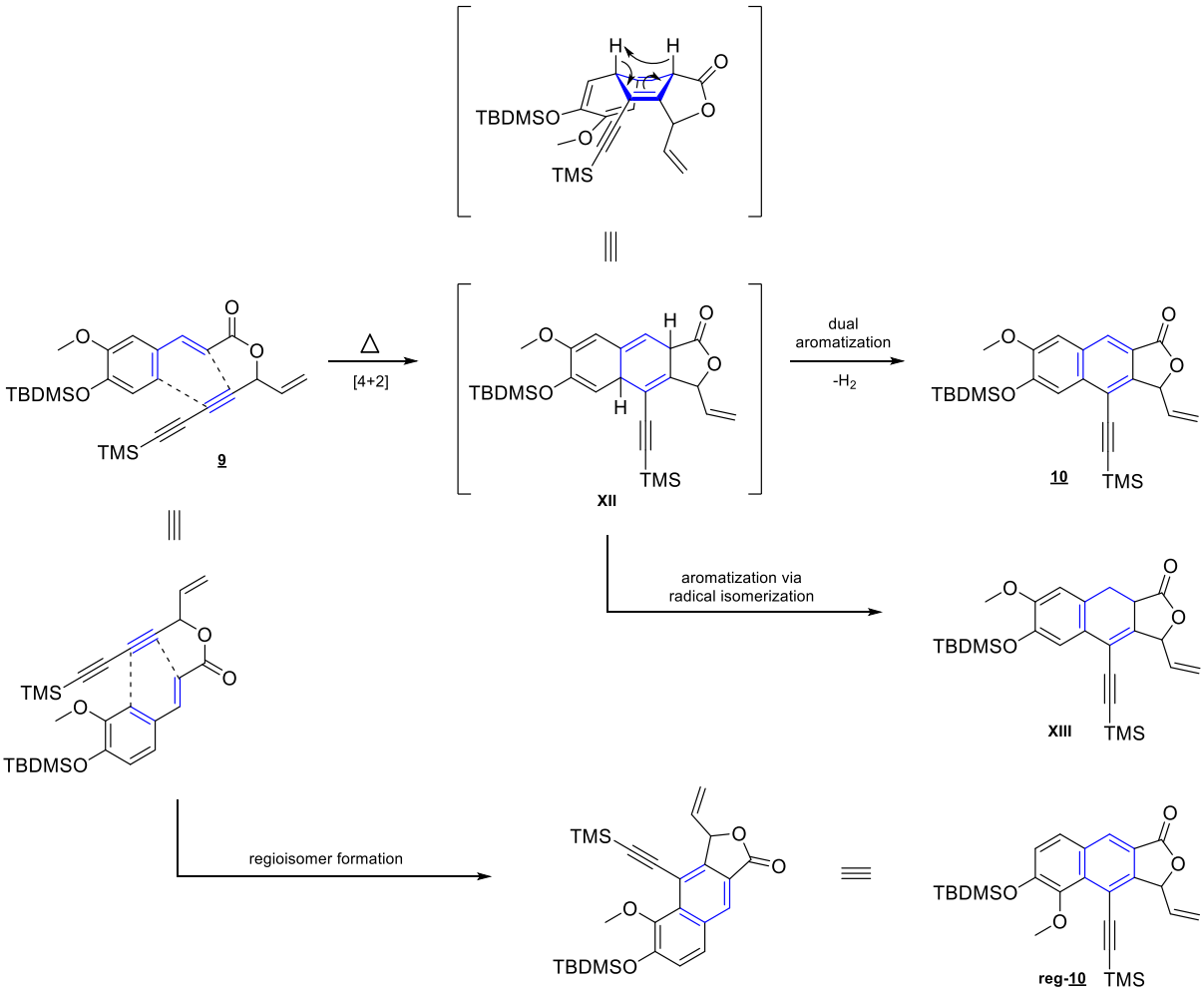
Figure 8: A) Envisaged intramolecular, dehydro-inverse-electron demand Diels-Alder cyclization reaction. B) Electronic characteristics of Diels-Alder reactions.[55]

In particular, two structural characteristics of the present substrate need to be pointed out as they distinguish this particular reaction from classical Diels-Alder cyclizations and decisively influence reaction mechanism and conditions. Firstly, given an electron-withdrawing ester group in direct proximity to the diene moiety as well as a rather electron-rich alkyne moiety acting as the dienophile, the electronic properties are inversed compared to classical Diels-Alder cyclizations (Figure 8, B). This is of particular relevance in regard to possible strategies which aim to promote the striven cyclization by means of catalysis (e.g. Lewis acids) or the influence of different protecting groups (part C II.2.2).

Secondly, a styrene moiety is a rather unusual diene component which is not frequently found in Diels-Alder reactions. As a consequence of the partly aromatic character of the styrene-diene, aromaticity needs to be abrogated transitionally in the course of the [4+2]-cycloaddition step, eventually necessitating an additional rearomatization sub-step. Hence, these types of so called dehydro-Diels-Alder reactions generally occur in two subsequent mechanistic steps, whereby a concerted electron shift in a classical [4+2]-cycloaddition is followed by a rearomatization process.[56]

In recent years remarkable progress has been reported in the literature on such dehydro-Diels-Alder-type cyclization reactions.[57] Most notably the work of Kocsis L.S. *et al.* who described the successful application of dehydro-Diels-Alder reactions on various different styrene-yne-systems[44, 58] and

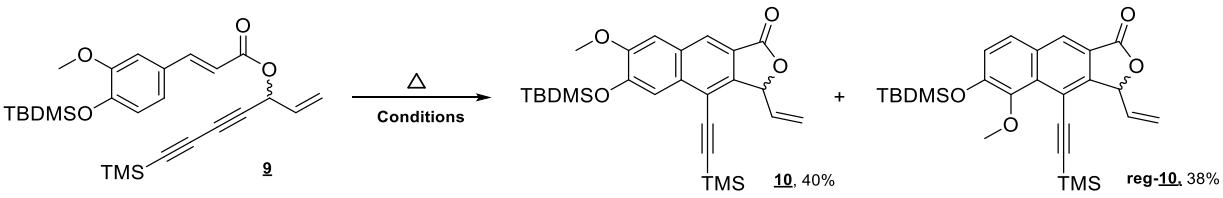
performed in-depth mechanistic studies on this reaction type.[56] Thereby it has been revealed that substrates similar to compound **9** undergo thermally induced intramolecular dehydro-Diels-Alder cyclizations via a two-step mechanism which is outlined with substrate **9** in Scheme 8. In an initial [4+2]-cycloaddition tetraene intermediate **XII** is formed as a primary cycloadduct. Subsequently, a dual aromatization process would establish the desired naphthalene moiety and afford lactone **10** as the cyclization product. Kocsis L.S. *et al.* found that this complete aromatization of the cyclized system proceeds *via* a unimolecular elimination of molecular hydrogen. Alternatively, a second pathway starting from the same intermediate **XII** would give dihydronaphthalene **XIII** as the final cyclization product following a radical isomerization process. [56]



Scheme 8: Mechanistic considerations and possible reaction outcomes of the Diels-Alder-type cyclization in accordance with detailed mechanistic investigations by Kocsis, L.S. *et al.*[44, 56]

Notably, Kocsis L.S. *et al.* postulated that naphthalene products like **10** are not directly produced from the dihydronaphthalene species. In fact, in an early report in 2012, the same group claimed that they failed to convert similar dihydronaphthalene products to the corresponding fully aromatized naphthalene structures by means of an additional oxidation step.[58] Fortunately, they later reported that a full control over selectivity towards either the naphthalene (**10**) or the dihydronaphthalene (**XIII**) species could be achieved by means of different reaction solvents.[44] This report in particular presented a suitable entrance point for the considerations within this work.

Aiming for a one-step cyclization-aromatization protocol which enables access to the desired completely aromatized naphthalene core structure **10**, exclusively, without any undesired dihydronaphthalene by-product, substrate **9** was subjected to different thermal conditions (Scheme 9).



Entry	Conditions			Result	
	Solvent	T [°C]	Δ	Full conversion in t [min]	10 : reg-10
1	$PhNO_2$	180	MWI	10	~1:1
2	m-xylene	180	MWI	20	~1:1
3	$PhNO_2$	180	heat	30	~1:1
4	m-xylene	180	heat	60	~1:1
5	$PhNO_2$	150	heat	60	~1:1
6	m-xylene	150	heat	90	~1:1
7	10% $PhNO_2$ in m-xylene	180	MWI	15	~1:1

Scheme 9: Investigated reaction conditions for the thermal cyclization of compound 9.

In general, cyclization of compound **9** towards the desired naphthalene core structure could be successfully achieved under all tested conditions (Scheme 9, entry 1-7). The formation of regioisomer **reg-10** in similar quantities as the desired compound **10** is not surprising given the unsymmetrical nature of substrate **9** and the presence of two very similar ortho-positions on the aromatic moiety. The low steric hindrance between the short alkyne-chain of compound **9** and the small methoxy-group in direct proximity to one ortho-position turned out to be insufficient in order to increase regioselectivity towards the desired compound **10**. The precise mechanism of the formation of **reg-10** is thoroughly outlined in Scheme 8. While Kocsis L.S. *et al.* reported similar obvious regioisomer formations within their studies,[44] oddly Park J.-E. *et al.* did not.[43]

Based on the reports by Kocsis L.S. *et al.,* nitrobenzene ($PhNO_2$) was initially used as a reaction solvent, aiming to avoid the formation of the dihydronaphthalene (**XIII**) species. Indeed, complete selectivity towards the fully aromatized naphthalene core structure (Scheme 9, entry 1) could be observed. It is known that nitrobenzene has an oxidative ability and hence pushes the cyclizing system towards a complete aromatization by exerting an additional dehydrogenative effect which is driven by the reduction of nitrobenzene to aniline.[44] However, the fact that in none of the performed experiments, neither in nitrobenzene nor by using m-xylene as a solvent, any signs of the undesired dihydronaphthalene (**XIII**) were observed, was quite remarkable.

In an attempt to optimize cyclization conditions and further explore the reliability of the present reaction, several critical parameters were successively varied (Scheme 9). While unfortunately no handle could be found to increase regioselectivity towards the desired compound **10**, solvent, temperature and the heating-method revealed a massive impact on reaction time.

In principle, microwave irradiation (MWI) turned out to be a superior heating method with the cyclization proceeding three times faster, compared to a conventional heating technique (comparing entries 1/3, entries 2/4, Scheme 9). The influence of temperature on the cyclization reaction was only briefly considered as it could be quickly revealed that a decrease in temperature by 30 °C led to a substantial increase in reaction time (comparing entry 3/5, entry 4/6, Scheme 9). Besides nitrobenzene, which proved to be a beneficial solvent for this reaction, m-xylene was also tested as it has been reported as a very common solvent in similar thermally induced reactions.[59] Although outcomes were quite similar in case of both solvents, reactions generally proved to proceed nearly two times faster in nitrobenzene (Scheme 9). One major drawback of nitrobenzene as a solvent turned out to be its high boiling point. The removal of larger quantities of nitrobenzene during the work-up procedure was a tedious process which required elevated temperatures and high vacuum. Unfortunately, removal by means of chromatographic methods was not possible as nitrobenzene and **reg-10** appeared to have overlapping R_f values. Based on the fact that the beneficial properties of nitrobenzene for the present reaction were mainly derived from its oxidative ability, it was then considered to reduce the used quantity from solvent- to reagent-level, in order to simplify work up procedures. Indeed, Kocsis L.S. *et al.* reported within their work that 8 equiv. of $PhNO_2$ were already enough to obtain the same results as in case of a larger excess. Consequently, the procedure for cyclization of compound **9** could be modified and best results were eventually obtained using a solvent mixture of $PhNO_2$ and m-xylene. The final conditions are stated in Scheme 9, entry 7 and afforded 40% of **10** and 38% of **reg-10** after 10-15 min at 180 °C under MWI. Noteworthy, this simple and efficient cyclization procedure did not require inert gas atmosphere, in contrast to similar literature reported dehydro-Diels-Alder cyclizations.[59]

The two formed regioisomers differed remarkably in terms of their physicochemical properties. While **10** was found to absorb UV-light well at common 256 nm, **reg-10** was scarcely visible at 256 nm but showed remarkable absorbance at 366 nm. In addition, **reg-10** appeared as a yellow oil which was hardly solidifying at ambient temperatures whereas product **10** gave a highly crystalline beige solid. This appearance is in accordance with the well-known fact that molecules comprising a higher symmetry are more easily regularly arranged and hence crystalize more readily. The novel structure of compound **10** could be also proven *via* X-ray crystal structure (Figure 9).

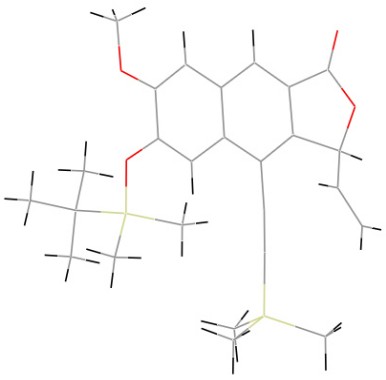


Figure 9: X-ray crystal structure of compound 10.[1]

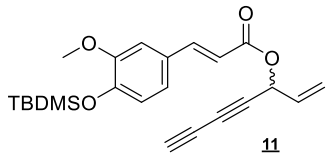
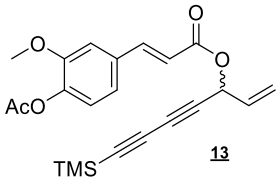
[1] M.Weil, Institute of Chemical Technologies and Analytics, TU Wien

C II.2.2 Additional Studies on the Cyclization Reaction

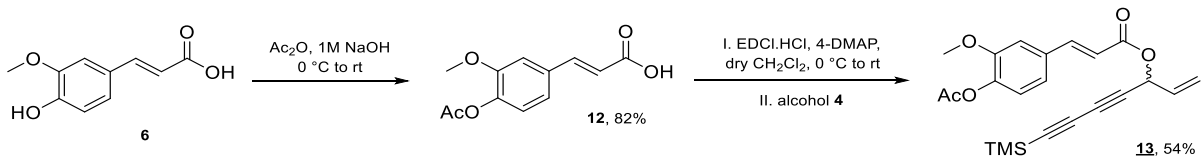
Once the accessibility of the tricyclic Notoincisol B-core structure was successfully proven *via* the outlined dehydro-Diels-Alder reaction, further investigations on this key-step cyclization were intended to deliver additional information about the applicability and feasibility of the reaction.

First, subjecting substrate **11** (Table 3, entry 1) to the established cyclization conditions (Scheme 9, entry 7) resulted in the identical reaction and formation of regioisomers as in case of compound **9**, as followed by means of TLC. Hence, the presence of a silyl-protecting group on the terminal alkyne was not found to have any influence on the cyclization process, which was of particular relevance in view of the striven reaction involving the complete Notoincisol iso-A scaffold (part C III.2).

Table 3: Investigations towards the cyclization reaction using alternative substrates.

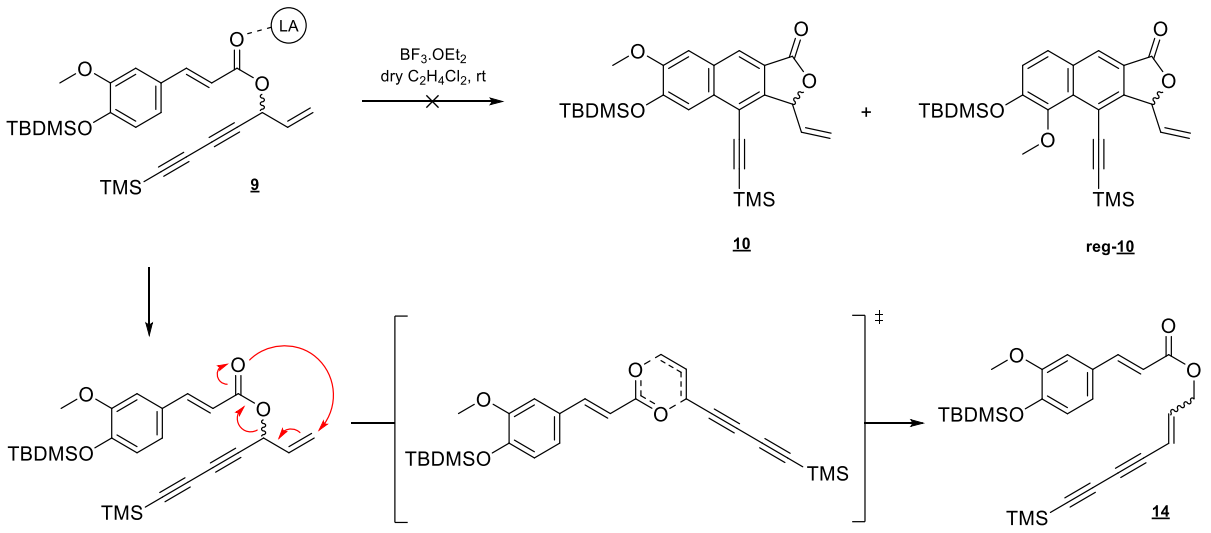
Entry	Substrate	Result
1	 **11**	Formation of regioisomers, similar reactivity as substrate **9**,
2	 **13**	Formation of regioisomers, similar reactivity as substrate **9**,

Diels-Alder-type cyclizations are known to be decisively influenced by the electronic properties of the participating diene and dienophile species. As stated above, based on the electron-poor character of the styrene-diene moiety and the rather electron-rich alkyne-dienophile, the electronic properties are inversed compared to classical Diels-Alder reactions in the present cyclization (Figure 8 A, part C II.2.1). Resulting thereof, it was hypothesized that the establishment of an electron-withdrawing group on the aromatic moiety of the substrate may exert a promotive effect on the cyclization by further lowering the LUMU energy of the electron-poor styrene-diene system (Figure 8 B, part C II.2.1). This could most easily be achieved by installing an electron-withdrawing protecting group, like an acetate, on the free phenol position of ferulic acid. In order to explore this hypothesis cyclization precursor **13** was synthesized following the same route as in case of compound **9** (Scheme 10).



Scheme 10: Synthesis of additional model substrate 13.

Cyclization of substrate **13** was then investigated under various reaction conditions similar to those stated in Scheme 9. However, no significant difference in reactivity compared to compound **9** could be observed and a similar formation of regioisomers was monitored (Table 3, entry 2).



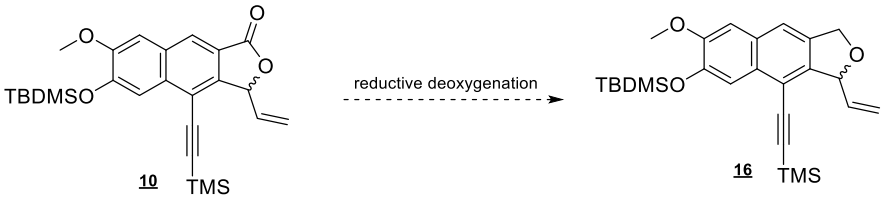
Scheme 11: Failed attempt to cyclize substrate 9 *via* the support of Lewis acid catalysis. A possible mechanism of the observed rearrangement is outlined.

There are several examples in the literature describing the support of Diels-Alder type cyclization reactions by means of Lewis acid catalysis.[60-61] Moreover, in particular the present intramolecular cyclization reaction of Notoincisol A-type substrates is hypothesized to proceed *via* a non-enzyme catalyzed pathway within the natural environment, thereby strongly indicating simple acid catalysis. Accordingly, it appeared to be evident to investigate whether the cyclization of model substrate **9** can be achieved under Lewis acid catalysis, thereby avoiding the need of thermal induction.

Unfortunately, subjecting substrate **9** to Lewis acidic conditions by using $BF_3.OEt_2$ as a frequently reported Lewis acid in Diels-Alder reactions[62-63] did not result in the formation of cyclized compounds **10** respectively **reg-10** (Scheme 11). Surprisingly, upon addition of the Lewis acid to a solution of substrate **9** in 1,2-dichloroethane ($C_2H_4Cl_2$) at rt, an immediate quantitative rearrangement reaction occurred which afforded compound **14**, as unambiguously identified by means of ^{1}H-NMR and correlation spectra (HSQC, COSY). It appeared that the Lewis acid initiated a rearrangement process which resulted in the isomerization of the branched to the corresponding linear ester moiety. This reaction may have decisively been driven by the formation of the most stable conjugated system. Similar acid catalyzed allylic rearrangements are known to proceed with smaller ester moieties like acetates and are often used by purpose to obtain access to linear allyl acetates from their branched isomers.[64] The fact that this transformation occurred with bulky ester **9** is quite remarkable and was not expected. Although no mechanistic details about this type of rearrangement are known so far, in Scheme 11 a possible mechanism is outlined. The occasion to form a 6-membered transition state might additionally act as a favorable driving force for this undesired reaction.

C II.3 Key-Step II: Lactone Reduction

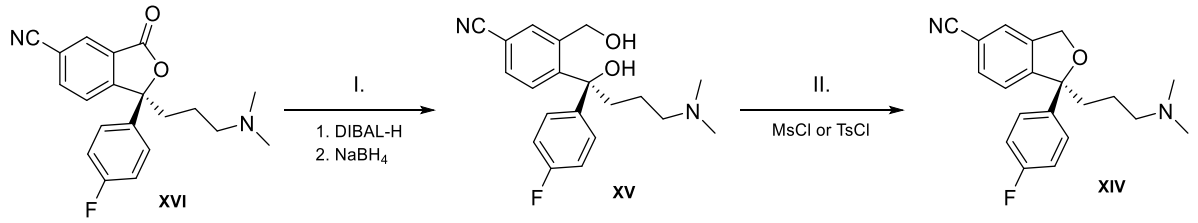
Following the successful verification of the key-step cyclization reaction to build up the tricyclic Notoincisol B core structure (part C II.2.1), two major divergences appeared at that point compared to the proposed biogenic synthesis pathway (part C I, Scheme 1). Firstly, the established cyclization protocol enabled the direct access to the fully aromatized naphthalene core structure in one reaction step, whereby in contrast to the proposed biogenic pathway the necessity of an additional aromatization step could be avoided. Secondly, Liu *et al.* proposed that within the natural environment the final cyclization-rearomatization products of Notoincisol iso-A-type substrates (**25**, part C I, Scheme 1) exhibit a naphthalene core with a benzannulated lactol moiety. Contrary, the synthetically derived product of the intramolecular dehydro-Diels-Alder reaction obviously appeared as a benzannulated lactone structure (**10**). This was of particular relevance in regard to the second synthetic key-step within the developed route, as the presence of a lactone moiety set the direction for the striven reductive deoxygenation step towards the final Notoincisol B-type 1,3-dihydronaphtho[2,3-c]furan core structure (**16**, Scheme 12).



Scheme 12: Envisaged conversion of lactone 10 into cyclic ether 16.

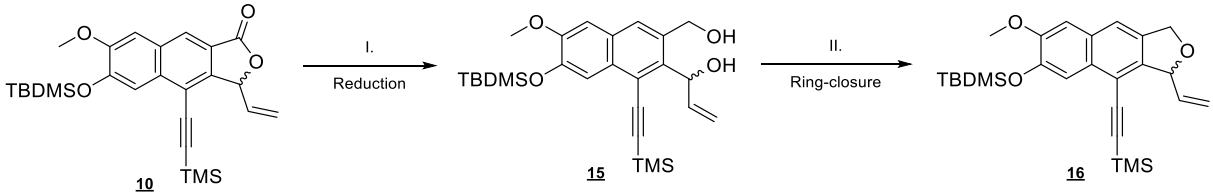
Based on the structural properties of substrate **10**, the availability of suitable reduction procedures to convert the lactone moiety into the corresponding cyclic ether appeared to be strictly limited. The presence of several unsaturated moieties including a seemingly troublesome allyl group in direct proximity to the ester moiety, made the utilization of common methods involving transition metal catalysis[46-47] or radical species[48] in Barton–McCombie-type deoxygenations[49] not promising. Moreover, a two-step procedure comprising an initial reduction of the lactone to the lactol followed by a treatment with $Et_3SiH/BF_3.OEt_2$ as described by Kraus G. A. *et al.*[65], might have also risen stability issues, given the observations made with the present substrate under Lewis acidic conditions (part C II.2.2).

Inspiration for a suitable reduction protocol eventually came from the industrially well-established synthesis of the antidepressant drug Escitalopram (**XIV**).[66] Bøgesø K. and co-workers accessed the Escitalopram core structure, which comprises a similar 1,3-dihydroisobenzofuran moiety like in Notoincisol B (and hence compound **16**), *via* a stereoselective intramolecular nucleophilic ring-closure reaction starting from the corresponding diol structure **XV** (Scheme 13, step II). Additionally, Huang L. *et al.* have reported very recently that this diol precursor can be easily obtained from the corresponding lactone **XVI** under reductive conditions (Scheme 13, step I).[67]



Scheme 13: Literature reported synthesis of Escitalopram as an inspiration to access compound 16.[66-67]

These reports decisively paved the way to develop a similar strategy for the reduction of lactone **10** and thereby access the desired 1,3-dihydronaphtho[2,3-c]furan core structure (Scheme 14).



Scheme 14: Strategy the access the Notoincisol B 1,3-dihydronaphtho[2,3-c]furan core structure *via* a reduction-cyclization sequence.

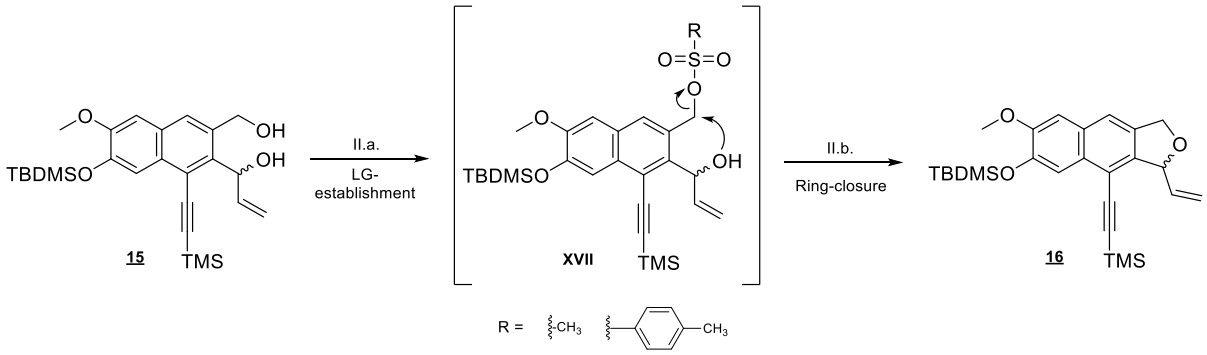
For the first step (I. Reduction, Scheme 14) Huang L. and co-workers reported a two-step protocol in which they successively used mild conditions with DiBAL-H and $NaBH_4$ to reduce lactone **XVI** via a lactole intermediate to the corresponding diol **XV**, most likely due to the presence of a sensitive nitrile group in Escitalopram. In regard to the reduction of compound **10** to diol **15**, it seemed more attractive to establish a one-step reduction protocol by using the more powerful reducing agent $LiAlH_4$. In initial experiments treatment of lactone **10** with 1.5 equiv. of $LiAlH_4$ at 0 °C quickly resulted in the formation of one major species as monitored by means of TLC, however, upon work-up the presence of several additional spots strongly indicated a decomposition of the substrate. In fact, NMR analysis revealed that the desired diol **15** was successfully formed but unfortunately accompanied by major amounts of decomposition products. While reducing the amount of reduction reagent to 1.0 equiv. led to a similarly fast reaction with the same decomposition problems, 0.8 equiv. $LiAlH_4$ gave incomplete conversion of starting material accompanied by decompositions. These results strongly suggested that $LiAlH_4$ as a reduction reagent might be too harsh for the present substrate.

Resulting thereof, alternative one-step lactone-reduction protocols were investigated. One possible method was used by Moni L. *et al.* for preparation of similar diol structures starting from the corresponding lactone precursors and involved $LiBH_4$ as a more benign reduction reagent compared to $LiAlH_4$ but still capable of reducing ester moieties.[68] $LiBH_4$ can either be used as obtained from commercial suppliers or can be prepared *in situ* from $NaBH_4$ and LiBr.[69] Both variants were tested on substrate **10**, however, despite the fact that initial product formation could be monitored, prolonged reaction times of more than 48 h generally led to an increasing formation of decomposition products, as followed by means of TLC.

As a consequence, it was then hypothesized that the observed decomposition of substrate **10** upon treatment with the tested reduction agents might rather be a matter of limited product-stability of the desired diol **15** than of harsh reaction conditions. Accordingly, experiments with $LiAlH_4$ as a reagent were reinvestigated following the approach to use the resulting diol **15** immediately for the

next reaction step without any further purification. Indeed, careful work-up and immediate use of **15** for the next reaction step enabled a spot to spot reaction, as monitored by TLC. In particular, it could be observed that diol **15** was quite stable in solution but remarkably decomposed upon concentrating in vacuum at ambient temperature.

With suitable reduction conditions for the first step of the envisaged reduction-cyclization sequence towards the desired Notoincisol B core structure in hand, the second sub-step was considered in greater detail. The principle plan for this reaction involved an intramolecular ring-closure reaction of diol **15**, thereby closely following the strategy of Bøgesø K. and co-workers. Such intramolecular nucleophilic substitutions can be achieved via an *in situ* establishment and replacement of a labile ester moiety (Scheme 15).

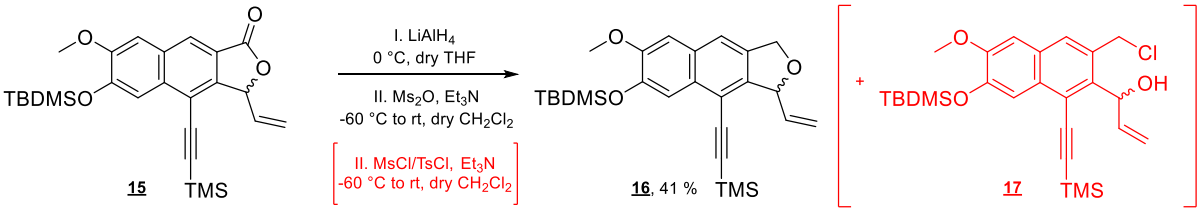


Scheme 15: Strategy for the cyclization of diol 15 towards the final core structure 16.

Usage of either mesylate or tosylate as suitable leaving groups (LG) in such reactions is well recognized in the literature and has also been reported by Bøgesø K. *et al.* in their route towards Escitalopram (**XIV**).[66, 70] With regard to future stereochemical aspects, when striving for an enantioselective synthesis of the whole target compound (part C III.2), the selective establishment of the mentioned LG on the primary alcohol moiety of compound **15** in order to obtain intermediate **XVII** exclusively needed to be particularly considered. Mesylation or tosylation of the secondary alcohol moiety of substrate **15** could consequently lead to an undesired nucleophilic attack of the primary alcohol at the chiral center and, hence, result in an inversion of the stereochemical configuration. As in this case it would have to be assumed that such undesired wrongly directed cyclization would not exclusively proceed but rather occur as a side reaction, this would finally result in an erosion or even loss of chirality and not in a neat inversion of the configuration. Fortunately, it is well accepted that primary alcohol moieties in general offer a remarkably increased reactivity compared to secondary ones and hence chemoselective sulfonation was assumed to be possible in this case. In addition, neither Bøgesø K. *et al.* nor Huang L. *et al.* reported any such issues within their synthetic pathways, although it has to be pointed out that Escitalopram comprises an even less reactive and sterically more hindered tertiary alcohol moiety compared to the secondary one in Notoincisol B-type substrates.

In view of the outlined circumstances, it was attempted to establish a protocol which particularly takes into account the need of a chemoselective sulfonation. Therefore, control over reaction kinetics by means of temperature should additionally favor a selective reaction of the primary alcohol moiety. Consequently, intermediate diol **15** was treated with sulfonyl chlorides (MsCl and

TsCl) in the presence of Et_3N in CH_2Cl_2 as a solvent at -60 °C and gradually warmed to rt. While formation of product **16** could be monitored after 3 h by means of TLC and GC-MS, a remarkable amount of side product was also observed via TLC but not detectable on GC-MS. In fact, NMR analysis of the separated reaction products strongly indicated the formation of chlorinated compound **17** as a major side product in case of both used sulfonating agents, MsCl and TsCl (Scheme 16).

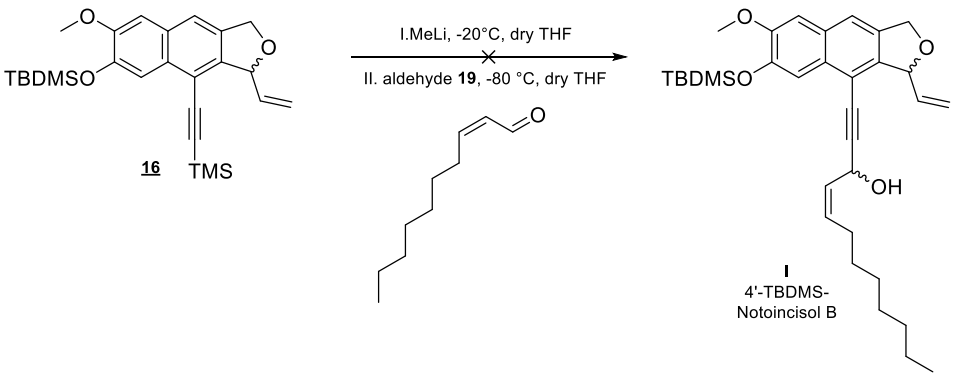


Scheme 16: Final conditions of the reduction-cyclization sequence towards the Notoincisol B core structure. Undesired side reaction observed with MsCl/TsCl depicted in red brackets.

The most convenient way to avoid the encountered formation of side product **17** appeared to be a change of the sulfonating agent from sulfonyl chlorides to the corresponding anhydrides. Indeed, employing Ms_2O as a reagent for the establishment of the LG prevented the formation of **17** and afforded product **16** exclusively. Repeated small scale (0.06 mmol) experiments yielded compound **16** in 35-45% over two steps which may likely be improved in larger scale experiments.

C II.4 Attempt to complete *rac*-Notoincisol B Synthesis *via* Model Scaffold Approach

The established synthetic access to the Notoincisol B core structure **16** raised the possibility to complete the whole synthesis of the target compound in a racemic version by using this model-scaffold structure as a central key-building block. Therefore a simple lithiation-addition reaction of compound **16** to aldehyde **20** (part C III.1) was intended to afford target molecule **I** as a mixture of two diastereoisomers, each of which would be racemic. In order to achieve the lithiation of the TMS-protected terminal alkyne in substrate **16**, the same *in situ* desililytion-lithiation methodology, which has previously been used and optimized for the synthesis of compound **4** (part C II.1), was planned to be employed in this reaction.



Scheme 17: Failed attempt to complete *rac*-Notoincisol B synthesis by using core structure 16 as central key-building block.

Surprisingly, treatment of compound **16** with MeLi under exactly the same conditions as reported within the synthesis of compound **4** did not result in the striven deprotective-lithiation, as followed by means of TLC (samples were quenched by adding a saturated aqueous NH_4Cl solution). Hence, the aimed addition to aldehyde **20** could not be achieved within this reaction (Scheme 17). Suggested future alternative strategies which are closely related to this approach, using compound **16** as a valuable precursor, are comprehensively outlined and discussed in part D II.

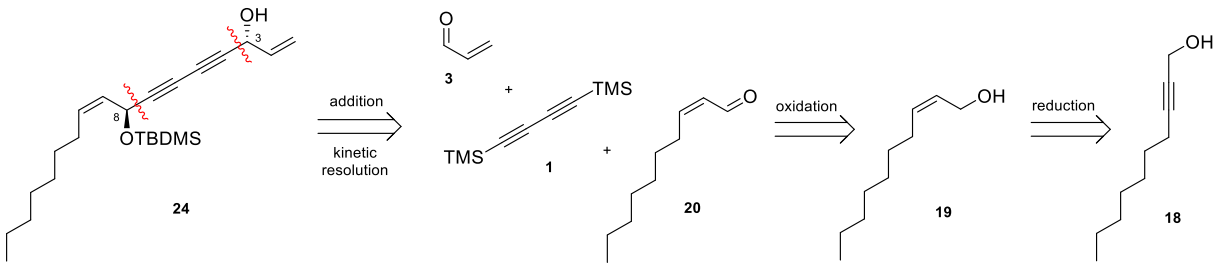
C III Synthesis of Complete Scaffolds

Following the ideas of the proposed biogenic synthesis pathway, detailed investigations of synthetic key-steps by employing a simplified Notoincisol B model scaffold successfully proved the access to the characteristic cyclic core structure of the target compound. Accordingly, the synthetic route towards Notoincisol B was paved and hence we set out to apply the developed methodology on the synthesis of the complete target scaffold.

C III.1 Synthesis of the Polyenyne Building Block 8-TBDMS-Falcarindiol

Preparation of the complete target compound in accordance with the established biomimetic pathway required the availability of two major starting building blocks. Besides the readily accessible TBDMS-ferulic acid (**7,** Scheme 4, part C II.1), the synthesis of the complete polyenyne moiety 8-TBDMS-falcarindiol (**24**) needed to be considered.

As already briefly discussed in part C I, falcarindiol (**24**) represents a well-known structure and several chemical total synthesis strategies for this natural compound have already been established and entirely reported in the literature.[34-38] Inspired by the methodology employed in the synthesis of the simplified precursor alcohol **4** (part C II.1), a new strategy towards the falcarindiol building block was followed within this work. Scheme 18 depicts the associated retrosynthetic analysis.

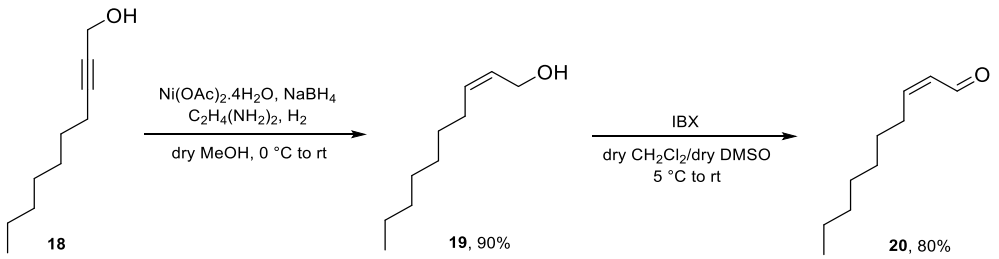


Scheme 18: Retrosynthetic analysis of the falcarindiol building block 24.

In principle, the developed strategy was based on two similar retrosynthetic cuts between the central 1,3-diyne block and the two secondary alcohol moieties. Both alcohol functionalities were aimed to be derived from the addition of commercially available 1,4-bis(trimethylsilyl)buta-1,3-diyne **1** to the corresponding aldehyde species. Obviously on the one hand the simple aldehyde precursor acrolein (**3**) was planned to act as an electrophile, which is in complete accordance to the previously discussed synthesis of compound **4**. On the other hand, the second alcohol moiety would originate

from the addition of the central alkyne block to the long-chained unsaturated aldehyde (Z)-dec-2-enal (**20**). The synthesis of this compound is well reported in the literature and in particular our laboratory has previously established a convincing synthetic access to this structure, overcoming several known challenges.[30, 33] In view of the stereochemical information of the falcarindiol building block, an enzymatic kinetic resolution was planned to be employed in order to establish the desired configuration of (3R,8S).[30, 39-40]

With regard to regioselectivity, the particular pathway towards Notoincisol B required an adequate protection of the hydroxyl group in position 8 of falcarindiol (**24**) which was planned to be readily achieved by means of a silyl protecting group strategy. Consequently the chiral center at carbon 8 needed to be established prior to the one at carbon 3 and, hence, the synthetic sequence towards building block **24** was defined to start with the synthesis of the unsaturated aldehyde **20** (Scheme 19).



Scheme 19: Synthesis of (Z)-dec-2-enal (20).

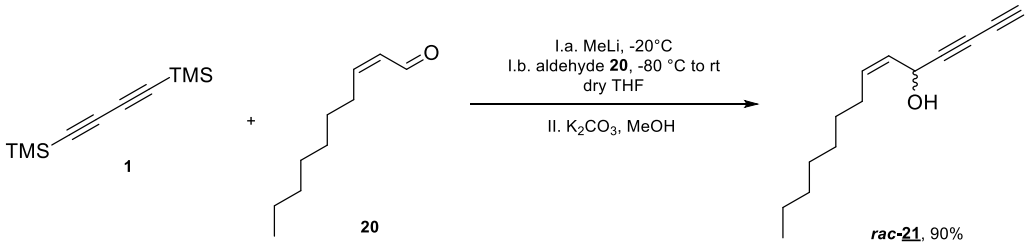
A convenient synthetic access to compound **20** was earlier described by Tamura *et al.* and Schmiech *et al.*[35-36] Both started from commercially available alkyne **18** and utilized a common Lindlar catalyst for the selective reduction of the triple bond to the (Z)-alkene. Subsequent selective oxidation with MnO_2 respectively a TEMPO/BAIB system was claimed to afford aldehyde **20**. In contrast to these reports, co-workers from our laboratory previously reported several problems in the reproduction of the mentioned protocols and established major improvements of the methodology towards this compound, which the present work could fundamentally riley from.[30, 33]

Firstly, selective catalytic hydrogenation of alkyne **18** under Lindlar-conditions has been reported to cause undesired over-reduction to the corresponding alkane species. To avoid this issue, a catalytic system based on nickel boride was utilized for the reduction of compound **18**. In this process nickel(II)acetate forms the catalytic species upon treatment with $NaBH_4$ in methanol.[71] Subjecting alkyne **18** to this so called nickel P-2 system afforded compound **19** exclusively in 90% yield (Scheme 19).

Secondly, it is well-known that target aldehyde **20** is readily prone to isomerization, most decisively based on the conjugation of the double bond and the carbonyl moiety. Hence, the formation of the (E)-isomer as an undesired side product, which is hardly separable from the (Z)-product, needed to be prevented. Fortunately, an efficient oxidation procedure involving the hypervalent iodo-reagent IBX as an oxidant in a solvent system of anhydrous CH_2Cl_2 and DMSO has previously been established in our laboratory for this transformation. [30, 33] Two major parameters have been reported to massively influence the product stability of **20** towards isomerization, which could also be observed

within the present investigations. Besides the fact that elevated temperatures during work-up procedures led to partial formation of the (E)-isomer, aldehyde **20** was also found to isomerize during the reaction, especially upon prolonged reaction times. This particular effect can be explained by the acidity of the reagent IBX. 2-Iodoxybenzoic acid (IBX) is reported to have a pK_a value of 6.65 in DMSO which may consequently trigger an acid-catalyzed isomerization process.[72] While IBX is nearly insoluble in CH_2Cl_2, it is well soluble in DMSO. Resulting thereof, the most efficient way to avoid isomerization of compound **20** during the reaction appeared to be utilization of as little DMSO as inevitably necessary to reach full conversion. This could be achieved by initially using a remarkable access of CH_2Cl_2 and successively adding small portions of DMSO in an interval of 30 min until full conversion of the starting material was reached, as monitored by TLC. Following this protocol, isomerization could be minimized (≤2% (E)-isomer according to NMR) and compound **20** was exclusively obtained in 80% yield. It has to be pointed out that work-up procedures were performed as fast as possible at T ≤ rt and aldehyde **20** was used without any further purification for the next step in order to prevent post-reaction isomerization.

Subsequently, the addition of diyne **1** to aldehyde **20** was intended to establish the first alcohol moiety of the targeted diol building block. Therefore, the same *in situ* desililytion-lithiation methodology, which has previously been used and optimized for the synthesis of compound **4** (part C II.1), was employed (Scheme 20).



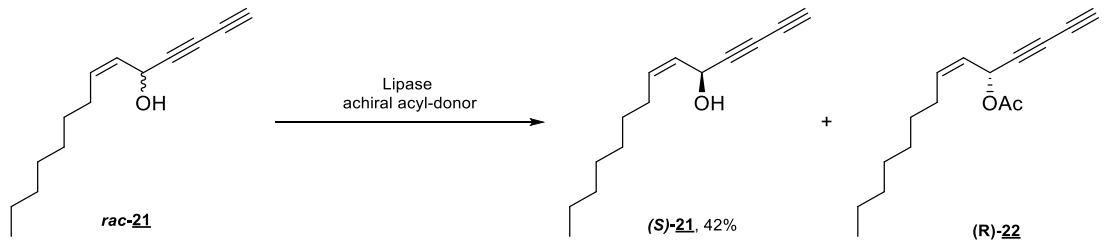
Scheme 20: Synthesis of falcarindiol precursor *rac*-20.

Accordingly, mono-lithiation of compound **1** was again carried out at -20 °C using MeLi as a reagent. Subsequent addition of a solution of crude aldehyde **20** in dry THF at -80 °C and gradual warming to rt resulted in complete conversion of starting materials after 2.5 h as monitored by TLC and GC-MS. In contrast to the synthesis of compound **4**, no signs of undesired side reactions were observed in this identical transformation. Despite the fact that aldehyde **20** includes a similar α,β-unsaturated moiety, compared to acrolein it is remarkably less prone to 1,4-addition and polymerization side reactions as a consequence of its sterically hindered β-position. Similarly as in case of compound **4**, partial desilylation of the second terminal alkyne moiety resulted in an initial product mixture of ***rac*-21** and its TMS-protected analogue. In light of the further planned synthetic sequence, which did not require the presence of such terminal alkyne protection, the crude mixture was immediately treated with K_2CO_3 in methanol, affording ***rac*-21** exclusively in 90% yield upon purification via flash chromatography.

Striving to synthesize the target compound in an optically pure form, the stereochemical configuration of building block **21** needed to be considered in greater detail. In principle, the polyenyne structure falcarindiol (**24**) includes two stereocenters which have been reported to exist in

a (3R,8S)-configuration in naturally occurring polyenyne-hybrids from *Notopterygium incisum*.[23] Several different approaches have been described in the literature in order to implement this stereochemical information within the chemical synthesis of the natural product. Tamura *et al.* and Schmiech *et al.* both utilized a two-step protocol to introduce chirality at C-8 of falcarindiol by oxidizing the alcohol moiety to the corresponding ketone followed by an enantioselective reduction under CBS-conditions.[35-36] While the oxidation step within this strategy has been reported to be accompanied by an undesired partial isomerization of the (Z)-double bond, a more convenient alternative approach to introduce chirality at C-8 involves enzyme catalysis. In this regard, the concept of enzyme catalyzed kinetic resolutions, to resolve racemic mixtures of secondary alcohols, encompasses an enzyme which catalyzes the transesterification reaction from an achiral acyl-donor to one of the two enantiomers of the substrate in a higher reaction rate than to the other (Scheme 22). In the best case, such enzyme-catalysts show very high degrees of enantioselectivity, meaning that only one enantiomer is accepted as a substrate. Consequently these transformations result in a mixture of one untouched enantiomer as an alcohol and the other enantiomer as an acetate, which can be readily separated by means of flash chromatography.

Inspiration for the utilization of an enzyme catalyzed kinetic resolution to establish the right stereochemistry on substrate **21** came from a laboratory internal protocol which has previously been used by former co-workers to resolve similar falcarindiol precursors.[30] Moreover, several additional references reported the successful application of enzymatic kinetic resolutions on substrates closely related to compound **21**.[39-40] Based on these literature reports, two different lipases, Amano Lipase PS and Lipase B *Candida antarctica*, were closer considered as suitable catalysts for the present resolution of compound **21**. In all reported cases, both enzymes showed a high degree of selectivity for the (R)-enantiomer of these substrates, meaning that the desired (S)-alcohol stays untouched. This has also been found to be in close accordance with Kazlauskas' empirical rule for the enantiopreference of lipases.[73]

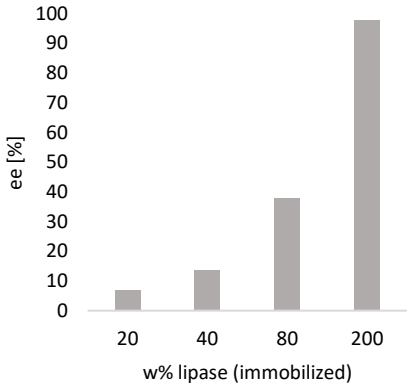


Scheme 21: Enzymatic kinetic resolution of compound *rac*-21.

In order to test for suitable reaction conditions, an analytical strategy was set up based on a chiral HPLC analysis which enabled monitoring of all possible enantiomers, alcohol and acetate, within one single run (also see Appendix F I). Preliminary screening reactions involving both mentioned lipases quickly revealed that Amano Lipase PS, which is commercially available immobilized on diatomite, was a superior catalyst for the present reaction. Lipase B *Candida Antarctica* generally showed low conversion and the formation of an unidentified side product (comparing entry 1-3, Figure 10).

Accordingly, different conditions with Amano Lipase PS as a catalyst were tested, aiming to push the reaction towards full conversion of the undesired (R)-enantiomer. While temperature (rt or 40 °C, comparing entry 6-7 and 8-9, Figure 10), amount of acyl-donor (vinyl acetate, comparing entry 1, 4 and 5, Figure 10) and substrate concentration (entry 8 and 10, Figure 10) only revealed negligible impact on the degree of conversion, catalyst loading (w% lipase) essentially did. Apart from all other parameters, the graph in **Error! Reference source not found.** impressively depicts the observed nfluence of the amount of lipase on the degree of conversion and hence the optical purity of the target compound **(S)-21**.

Final conditions are stated in **Error! Reference source not found.**, entry 12 and afforded compound **S)-21** in 42% with an ee-value of greater than 98% (as determined by means of chiral HPLC) after flash chromatography. Although the finally achieved enantiomeric excess (ee) of **(S)-21** was nearly perfect, the necessity to use a high amount of enzyme (200 w% immobilized Amano Lipase PS, not pure enzyme) renders this process rather inappropriate for future applications. Based on the fact that there are already literature reported procedures which claim to access enantiomerically pure falcarindiol building blocks in a more economical way, no further investigations or optimizations on this process were done within the present work.

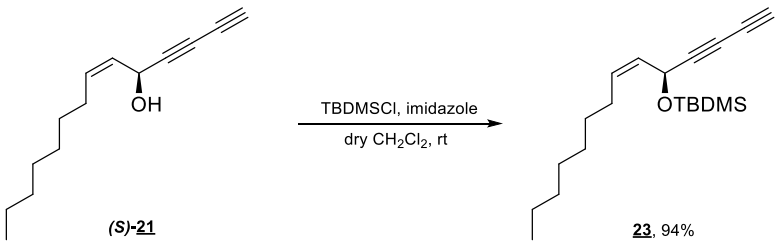


Entry	Lipase	Solvent	T [°C]	c [M]	w% lipase	eq. vinyl acetate	conversion to (R)-22 after 48h [%]
1[30]	Amano Lipase PS	MTBE	rt	0.3	20	1.2	11
2[40]	Lipase B *C. Antarctica**	Hexane	rt	0.3	17	2.8	<5
3[39]	Lipase B *C. Antarctica**	DIPEA	rt	0.04	100	5.0	<10
4	Amano Lipase PS	MTBE	rt	0.3	20	5.0	<10
5	Amano Lipase PS	MTBE	rt	0.3	20	2.0	12
6	Amano Lipase PS	MTBE	rt	0.3	40	2.0	21
7	Amano Lipase PS	MTBE	40	0.3	40	2.0	18
8	Amano Lipase PS	MTBE	rt	0.3	80	2.0	35
9	Amano Lipase PS	MTBE	40	0.3	80	2.0	28
10	Amano Lipase PS	MTBE	rt	0.03	80	2.0	39
11	Amano Lipase PS	MTBE	rt	0.3	200	2.0	47
12	Amano Lipase PS	MTBE	rt	0.1	200	2.0	≥47

*side product formation

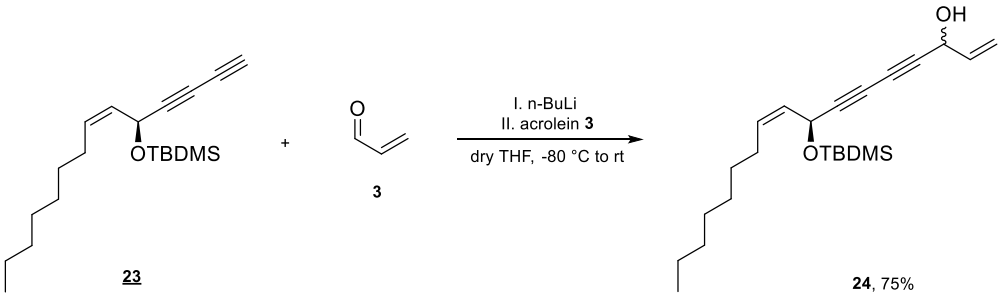
Figure 10: Enzymatic kinetic resolution to resolve *rac*-21. Screened parameters and conditions, final conditions are highlighted.

Subsequently, TBDMS-protection of optically pure **(S)-21** under standard conditions[74] using TBDMS-chloride and imidazole in CH_2Cl_2 as a solvent afforded building block **23** in 94% upon purification *via* flash chromatography (Scheme 22).



Scheme 22: TBDMS-protection of (S)-21.

With compound **23** in hand, the synthesis of key-building block 8-TBDMS-falcarindiol **24** was aspired to be completed by means of an addition reaction of **23** to the simple aldehyde precursor acrolein **3** (Scheme 23). Based on the fact that the configuration of substrate **23** has been established as (S), deprotonation of the terminal alkyne with n-BuLi and subsequent non-asymmetrical addition to the electrophile **3** affords two diastereoisomers (3R,8S and 3S,8S) which were planned to be separated chromatographically. Eventually, the desired (3R,8S)-isomer should be readily identified by comparing the specific rotation with literature values.[34]



Scheme 23: Synthesis of 8-TBDMS-falcarindiol 24 via lithiation-addition reaction.

Treating compound **23** with n-BuLi at -80 °C followed by the addition of a solution of acrolein in anhydrous THF immediately resulted in the formation of the product species, as monitored by means of TLC. In full awareness of the problems which were previously encountered in reactions involving acrolein as an electrophile, it was not surprising that a full conversion of starting material **23** was hardly reached in the course of this transformation. Upon work-up and purification *via* common flash chromatography, 8-TBDMS falcarindiol **24** was isolated in 75% yield along with 10% of starting material **23**.

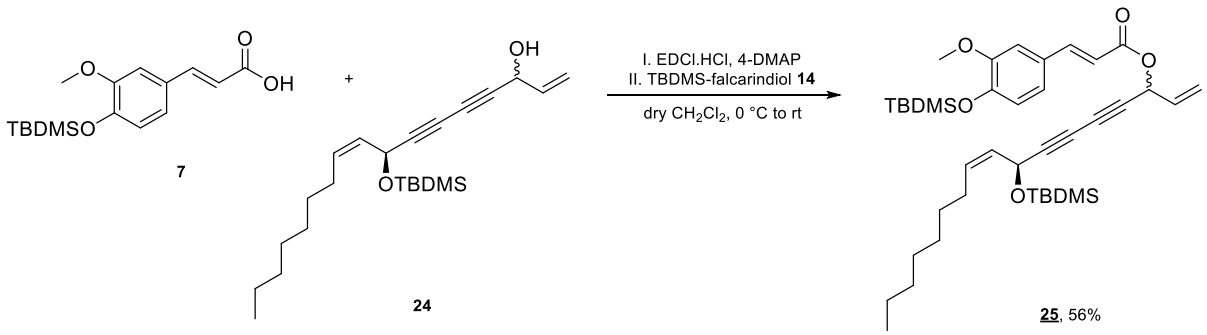
It turned out more astonishing, that neither on TLC nor on standard column chromatography any indications of two product species, meaning the two diastereoisomers, could be observed. In fact, while ^{1}H-NMR, ^{13}C-NMR and correlation spectra unambiguously confirmed the structure of the desired 8-TBDMS-falcarindiol building block, no signs of two physicochemically different isomer species could be revealed. It is noteworthy, that there are some reports in the literature claiming that falcarindiol-type polyenynes were found to exhibit rather unusual stereochemical properties. In particular, Bernart M. W. *et al.* reported that the configuration at C-3 of falcarindiol has no influence

on the optical rotation of the whole structure at all.[75] Consequently, they claimed that the optical rotations of the (3R,8S)- and (3S,8S)-diastereoisomers are nearly identical. Moreover, Seger C. *et al.* supported this assumption within their studies by stating that a positive optical rotation value is indication enough to assume a (8S)-configuration of falcarindiol, regardless of the configuration at C-3.[76] Indeed, the differences in specific rotations of (3R,8S)- and (3S,8S)-falcarindiol reported by Tamura *et al.* might be within experimental errors.[35] However, despite these literature documented unconventional properties in terms of specific optical rotations, the fact that **24** appeared as one single species on a chromatographic- as well as on NMR-level was quite remarkable.

In spite of this unexpected analytical data, the possibility that the lithiation-addition reaction affording compound **24** (Scheme 23) proceeded via a surprising diastereoselective mechanism was considered as highly unlikely. Further attempts to resolve the diastereoisomeric mixture of compound **24** by means of HPLC were not successful. Accordingly, at that point it was hypothesized that the esterification of the hydroxyl group at C-3 of compound **24** within the next reaction step might increase the physicochemical difference between the two diastereoisomers and hence enable the distinction and consequently the separation of the two species.

C III.2 Synthesis of Notoincisol iso-A, Notoincisol B-lactone and Notoincisol B Scaffolds

Subjecting 8-TBDMS-falcarindiol **24** to the same esterification conditions as previously used for the synthesis of model substrate **9** (Scheme 7, part C II.1) afforded compound **25** in 56% after purification *via* column chromatography (Scheme 24). Structure **25** is a purely synthetic, so far not reported, regioisomer of the naturally occurring polyenyne-hybrid Notoincisol A (8, part B II.2) and hence can be denoted as Notoincisol iso-A (in protected form).



Scheme 24: Synthesis of Notoincisol iso-A 25.

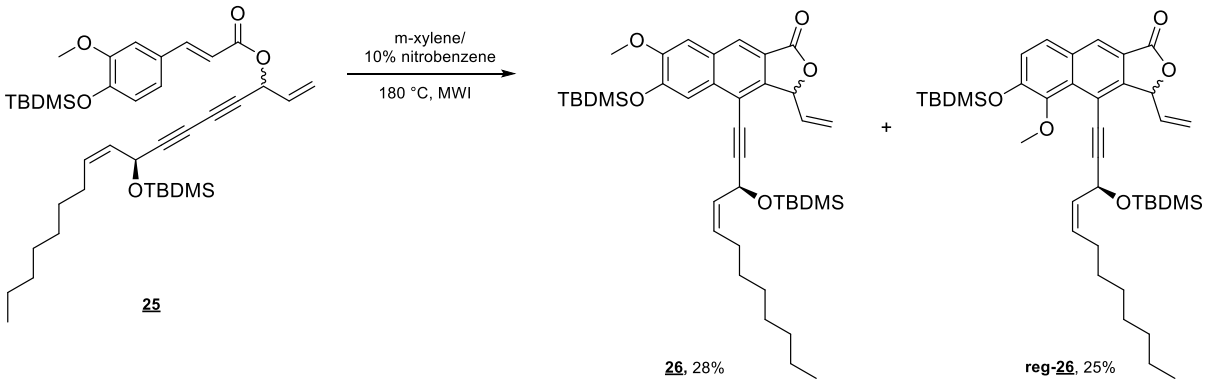
Highly controversial to common expectations and to the raised hypothesis that the esterification of the hydroxyl moiety on C-3 of building block **24** would lead to an increased difference in the physicochemical properties of the diastereoisomers, compound **25** appeared as one single species in all analytical data. In particular the observation that ^{13}C-NMR shifts were found to perfectly correspond to one single ester species, without any indications of the presence of two different isomers, was remarkable. Consequently, all efforts to identify or even separate isomers at this stage of the synthetic pathway remained unsuccessful. Such exceptional physicochemical behavior has previously not been reported with polyenyne-hybrids to the best of our knowledge and might be

dedicated to the unique structural nature of these compounds. The rigidity of the present alkyne system, which separates the two stereocenters, is likely the decisive origin of these unusual properties.

Despite the outlined issues regarding the stereochemistry of compound **25**, the synthetic pathway towards Notoincisol B was continued in order to verify the principle accessibility of the target compound within the developed route, thereby striving for an identification and separation of the isomeric species at a later point in the synthesis.

Subjecting ester **25** to the established thermal cyclization conditions (part C II.2) resulted in a similar formation of regioisomers **26** and **reg-26** as observed within the cyclization-studies on model substrate **9** (Scheme 25). The presence of the sterically more demanding complete falcarindiol moiety did not result in a significant gain of regioselectivity towards the desired compound **26**. Similar observations have also been reported by Kocsis L.S. *et al.* who claimed that regioselectivity could not be influenced within their studies on dehydro-Diels-Alder reactions by adding bulkier substituents to the alkyne-dienophile moiety.[44]

It seems noteworthy, that compared to the cyclization of model compound **9**, a slight increase in reaction times (10-15 min) could be observed with compound **25** under the same conditions. This circumstance was attributed to the presence of the sterically more demanding alkane chain. While the interaction of this alkane residue with the small methoxy-group in direct proximity to one ortho-position turned out to be negligibly and insufficient in order to influence regioselectivity, the flexibility of this chain is likely to cause an increase in steric hindrance between the whole dienophile and diene moiety in general, resulting in an extended reaction time.

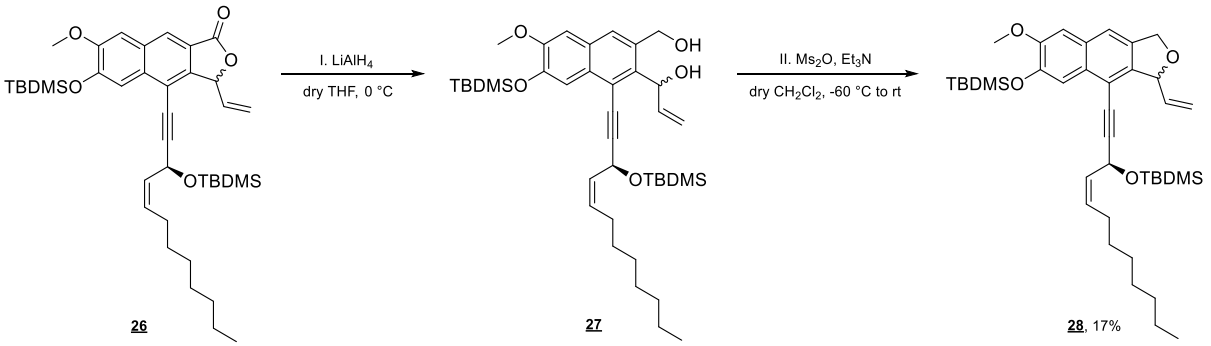


Scheme 25: Synthesis of Notoincisol B-lactone.

Although TLC analysis only indicated the formation of two species, which were readily separable *via* common column chromatography, at that point NMR analysis clearly revealed that each cyclization product (**26**, **reg-26**) consisted of two distinct diastereoisomers (3R,8S and 3S,8S, respectively). While it appeared that the cyclization eventually led to a detectable physicochemical difference between these isomers, and hence confirmed the assumption that the lithiation-addition reaction affording compound **24** (Scheme 23) indeed did not undergo an exceptional diastereoselective mechanism, the observed marginal difference between these diastereoisomers was quite remarkable. In fact, only individual atoms revealed clearly pronounced differences in ^{1}H– and particularly ^{13}C-NMR-shifts.

Given the similar behavior of the present diastereoisomers on common TLC and column chromatography along with the spectroscopic data described, it was not surprising that all attempts to separate these species by means of HPLC were not successful at this stage of the synthetic pathway.

Compound **26** represents a completely novel polyenyne-hybrid structure which is the (protected) lactone-analogue of the naturally occurring target compound Notoincisol B and hence can be denoted as Notoincisol B-lactone. In order to convert the lactone moiety of compound **26** towards the final 1,3-dihydronaphtho[2,3-c]furan core structure of Notoincisol B, the previously established reduction-cyclization sequence (part C II.3) was eventually applied on the whole target compound (Scheme 26).



Scheme 26: Synthesis of the complete Notoincisol B scaffold 28.

Fortunately, both sub-steps, the reductive lactone-opening followed by the intramolecular nucleophilic substitution affording the final ring structure, proceeded in complete accordance with the reactions on the simplified model scaffold (part C II.3). Accordingly, the isolation of compound **28** successfully proved the synthetic access to the desired Notoincisol B scaffold *via* the established biomimetic pathway. The yield of this two-step sequence reaction may not be considered as representative as the reactions on the complete scaffold were performed in a raw discovery-modus and may likely be improved in larger scale experiments.

As a consequence of the revealed and extensively outlined exceptional stereochemical properties of Notoincisol-type polyenyne hybrid structures, compound **28** was isolated as a mixture of two diastereoisomers. While the ratio of the present (3R,8S)- and (3S,8S)-isomers appeared to be equal, as expected and indicated by ^{13}C-NMR analysis, attempts to separate them *via* HPLC unfortunately remained unsuccessful.

C IV Spectroscopic Characterization of Core Scaffolds

Within this thesis prepared Notoincisol B-type polyenyne hybrid structures represent novel scaffolds which have not been reported or studied in the literature so far. While “parent compound” Notoincisol B itself has been isolated as a natural product from *Notopterygium incisum* and accordingly comprehensive spectroscopic data is available in the literature,[23] it appears to be fundamental to outline the spectroscopic characteristics of the synthetically derived analogues and compare them to the natural equivalent. Hence, this part is aimed to point out the spectroscopic characteristics of the particular Notoincisol B-type 1,3-dihydronaphtho[2,3-c]furan core structure and its lactone analogue and thereby deliver a prove for the synthetic access which has been developed within this work.

The presented ppm range in the following spectra was chosen to focus on the cyclic core structure of the target molecules as the central area of interest.

C IV.1 Lactone-Analogue: Naphtho[2,3-c]furan-1(3H)-one Scaffold

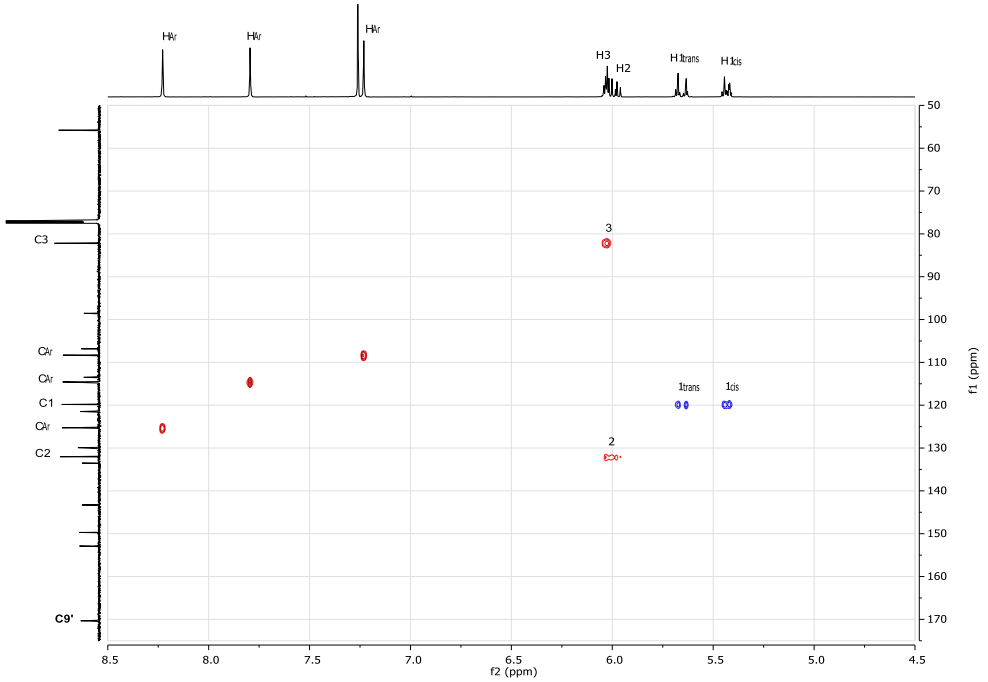
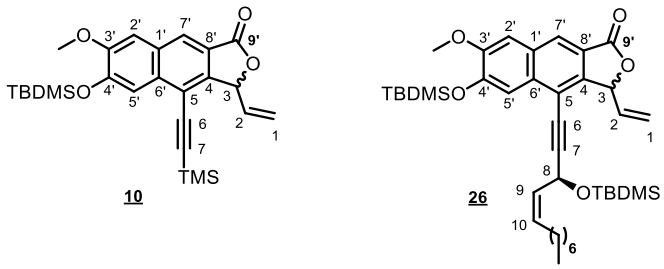


Figure 11: HSQC spectra of model lactone 10.



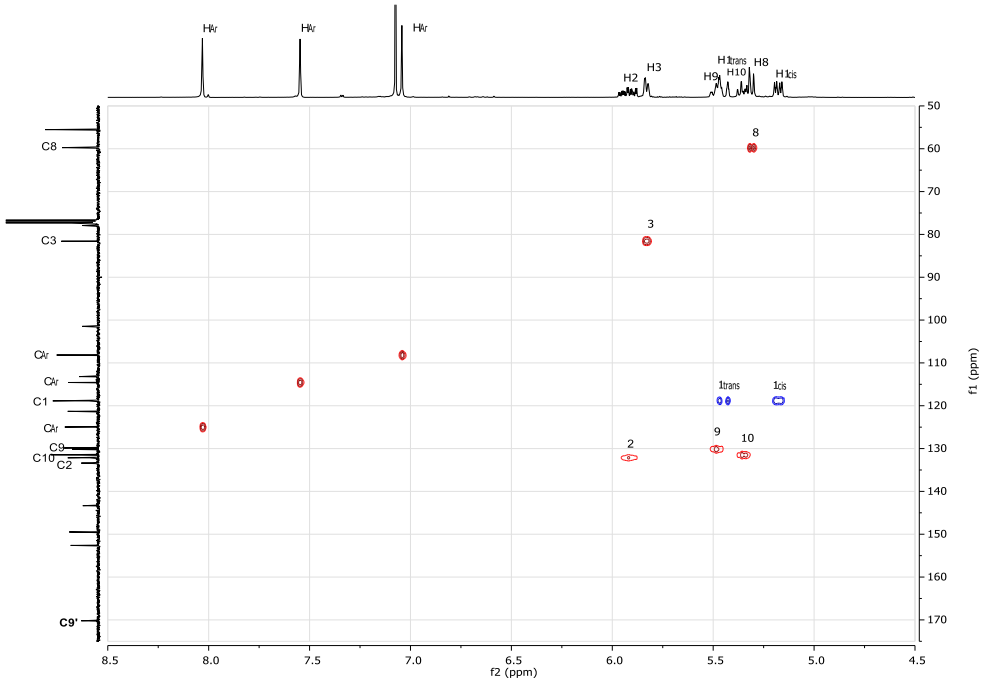


Figure 12: HSQC spectra of Notoincisol B-lactone 26.

Figure 11 depicts the HSQC spectrum of the simplified Notoincisol B-lactone model scaffold **10**, as obtained upon intramolecular dehydro-Diels-Alder reaction of precursor substrate **9**. Comparatively, the analogous spectrum of the complete Notoincisol B-lactone structure (**26**), derived *via* cyclization of Notoincisol iso-A (**25**), is presented in Figure 12.

Both spectra clearly reveal the central tricyclic structural motif which is characteristic for the lactone analogues of the target compound Notoincisol B. In particular, three singlet signals in the aromatic area (Ar) confirm the presence of the completely aromatized naphthalene moiety. Besides that, both compounds share the identical benzannulated lactone scaffold which includes a characteristic allylic moiety. This functional group is readily identified by four particular signals in the ^{1}H and HSQC spectra which are characteristic for all Notoincisol B-type structures: C-1 is a terminal methylene moiety, comprising two distinct protons (H1^{cis} and H1^{trans}) which typically show geminal coupling. In HSQC spectra such CH_2 groups are phased down which is indicated by blue colored signals. H1^{cis} and H1^{trans} both show a vicinal coupling to H2 and sometimes a long range coupling to H3. H2 typically shows a vicinal coupling to H1^{cis}, H1^{trans} and H3 and consequently appears as a characteristic doublet of doublet of doublets (ddd) in ^{1}H-NMR spectra which is often not resolved and hence depicts a multiplet. H3 is the proton on the stereocenter at C-3 which readily couples to H2, long-range coupling to H1^{cis} and H1^{trans} is not always resolved in ^{1}H-NMR spectra. In general, hardly tangible multiplicities of signals in the ^{1}H-NMR spectrum of compound **10** are attributed to the fact that the spectrum is not unambiguously of first order.

While signals 1-3 are characteristic for all Notoincisol B-type cyclic core structures, the complete target scaffolds such as Notoincisol B-lactone **26** additionally comprise signals of protons H8, H9 and H10 within the depicted ppm range. These are typical for the secondary alcohol moiety on C-8 and the adjacent (Z)-double bond of the long alkene residue.

Moreover, most noteworthy, the ^{13}C-spectra of the lactone analogues of Notoincisol B which are depicted in Figure 11 and Figure 12 both show a characteristic quaternary carbon signal at 170.3 ppm (no signal in HSQC spectra) which indicates the presence of the carbonyl moiety at C9'.

Given the fact that compound **26** was obtained as a not separable mixture of diastereoisomers (3R,8S and 3S,8S), individual signals in the ^{1}H-NMR spectrum (e.g. H2 and H1^{cis}) clearly indicate the presence of two distinct species. While ^{13}C-NMR is even more unambiguous, the resolution in HSQC spectra is obviously too low to illustrate the marginal shift difference between the two similar isomers.

C IV.2 Notoincisol B: 1,3-dihydronaphtho[2,3-c]furan Scaffold

Analyzing the HSQC spectra of the final Notoincisol B core structure (**16** in Figure 13, **28** in Figure 14), identical aromatic (Ar) and allylic signals (1-3) as in case of the lactone analogues **10** and **26** are revealed. The final cyclic 1,3-dihydronaphtho[2,3-c]furan scaffold was derived *via* a reductive deoxygenation step, transforming the lactone moiety into the corresponding cyclic ether. Resulting thereof, the former lactone-carbonyl moiety on C9' was converted into a new methylene group, which is clearly indicated by a ppm-shift of C9' from 170.3 ppm to 72.3 ppm. In addition, the two new H9' are distinct diastereotopic protons which can be readily identified in the HSQC spectrum (two new signals in blue at 72.3 ppm). Identical to lactone analogue **26**, the complete Notoincisol B scaffold of compound **28** also includes a second asymmetric center (C-8) and the long unsaturated alkene moiety (C-9, C-10).

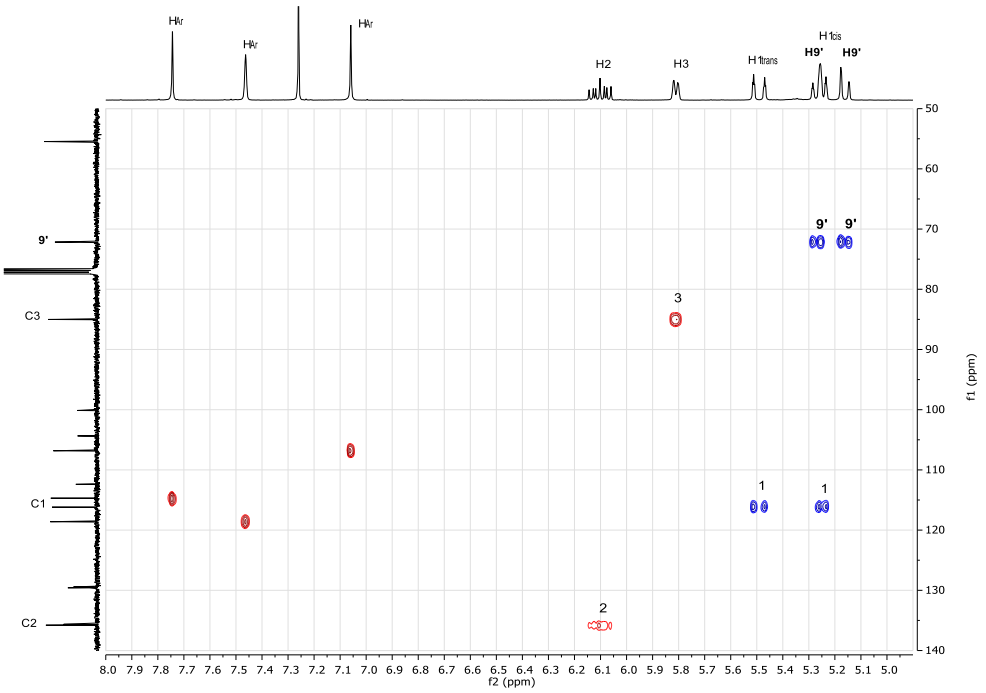
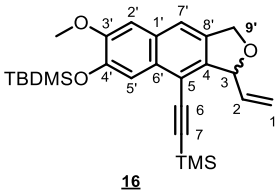


Figure 13: HSQC spectra of final model scaffold 16.



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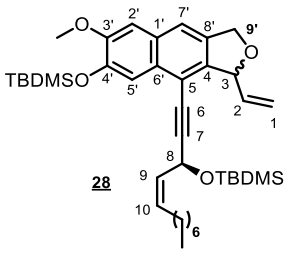

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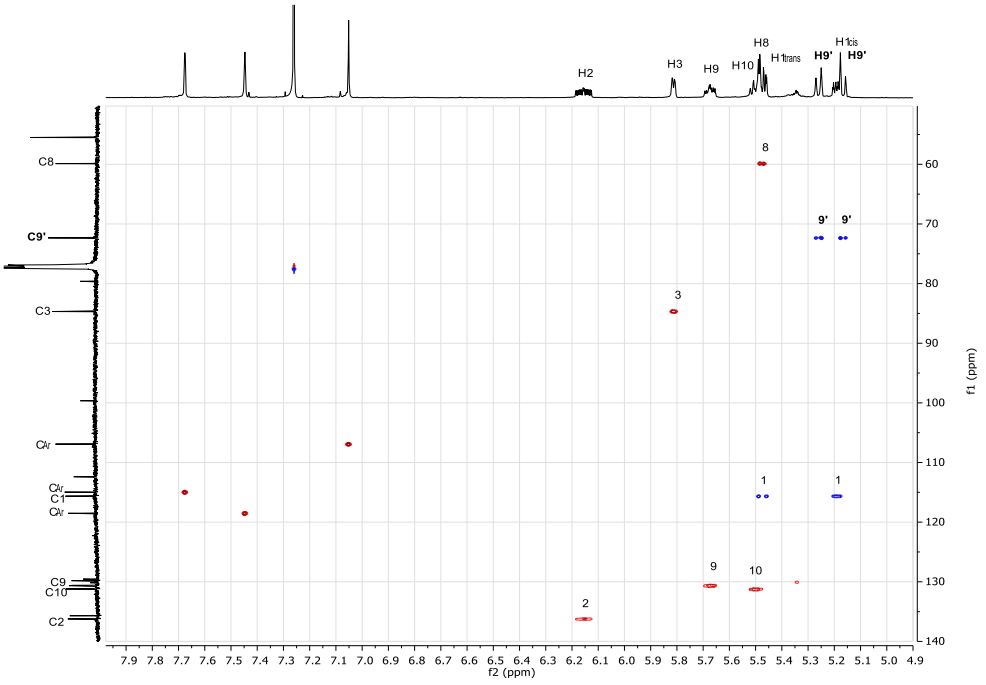


Figure 14: HSQC spectra Notoincisol B scaffold 28.

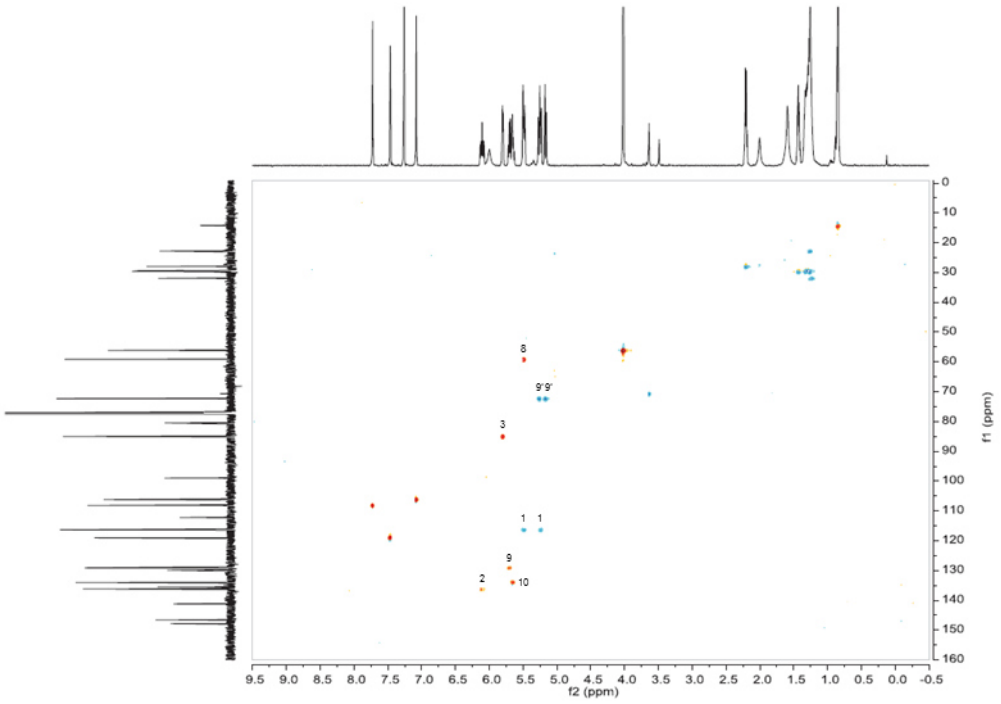


Figure 15: HSQC of natural Notoincisol B.[23]

Comparing these core structure signals of compound **16** (Figure 13) and **28** (Figure 14) to the spectrum of naturally derived Notoincisol B (Figure 15) clearly demonstrates the structural identity of the synthetic compounds. Shift deviations of signals 9 and 10 are attributed to the presence of silyl-protecting groups in the synthesized substrates (Table 4).

Table 4: Comparison of Key-signal shifts.

C	Shift [ppm]		
	Natural Product	Synthetic Compound **28**	Model Compound **16**
1	116.3	115.6	116.3
2	136.2	136.2	135.9
3	85.0	84.7	85.2
8	59.1	59.9	-
9	129.1	130.6	-
10	134.0	131.2	-
9’	72.3	72.3	72.3

D Conclusion and Perspective

D I Concluding the Present Work

Following nature's ideas for the synthesis of Notoincisol B-type polyenyne-hybrid compounds, the biogenic synthesis pathway was used as a template to develop a synthetic strategy towards these novel structures. Initial investigations of synthetic key-steps by employing a model substrate successfully proved synthetic access to the characteristic 1,3-dihydronaphtho[2,3-c]furan core structure of Notoincisol B. Thereby several challenges needed to be overcome before the applicability of the developed methodology could be demonstrated on the whole target scaffold. In particular, on the way towards the synthesis of the complete Notoincisol B structure, exceptional and unexpected stereochemical properties of these types of polyenyne-hybrid compounds have been revealed and will impact future synthetic strategies (part D II).

First, simplified model precursor **9** was obtained in few synthetic steps based on an optimized *in situ* desilylation-lithiation methodology starting from commercially available 1,3-diyne **1**. Subsequently, compound **9** was employed to successfully prove the feasibility of the key-cyclization step setting up the tricyclic Notoincisol B core structure. The established protocol for this thermally induced dehydro-Diels-Alder reaction not only enabled simple synthetic access to the lactone analogue of the desired core structure, but also complete rearomatization towards the final naphthalene moiety within the same step. Unfortunately, no control over regioselectivity could be obtained in this cyclization, hence desired product **10** was accompanied by equal amounts of **reg-10**. However, this may not necessarily be considered as a major flaw since it additionally enables access to a new structural pattern which might be valuable in future SAR-studies of these compounds. The attempt to cyclize the present styrene-yne system in a biomimetic fashion *via* Lewis acid catalysis resulted in an unexpected allylic-rearrangement which will render future investigations in this direction not very promising.

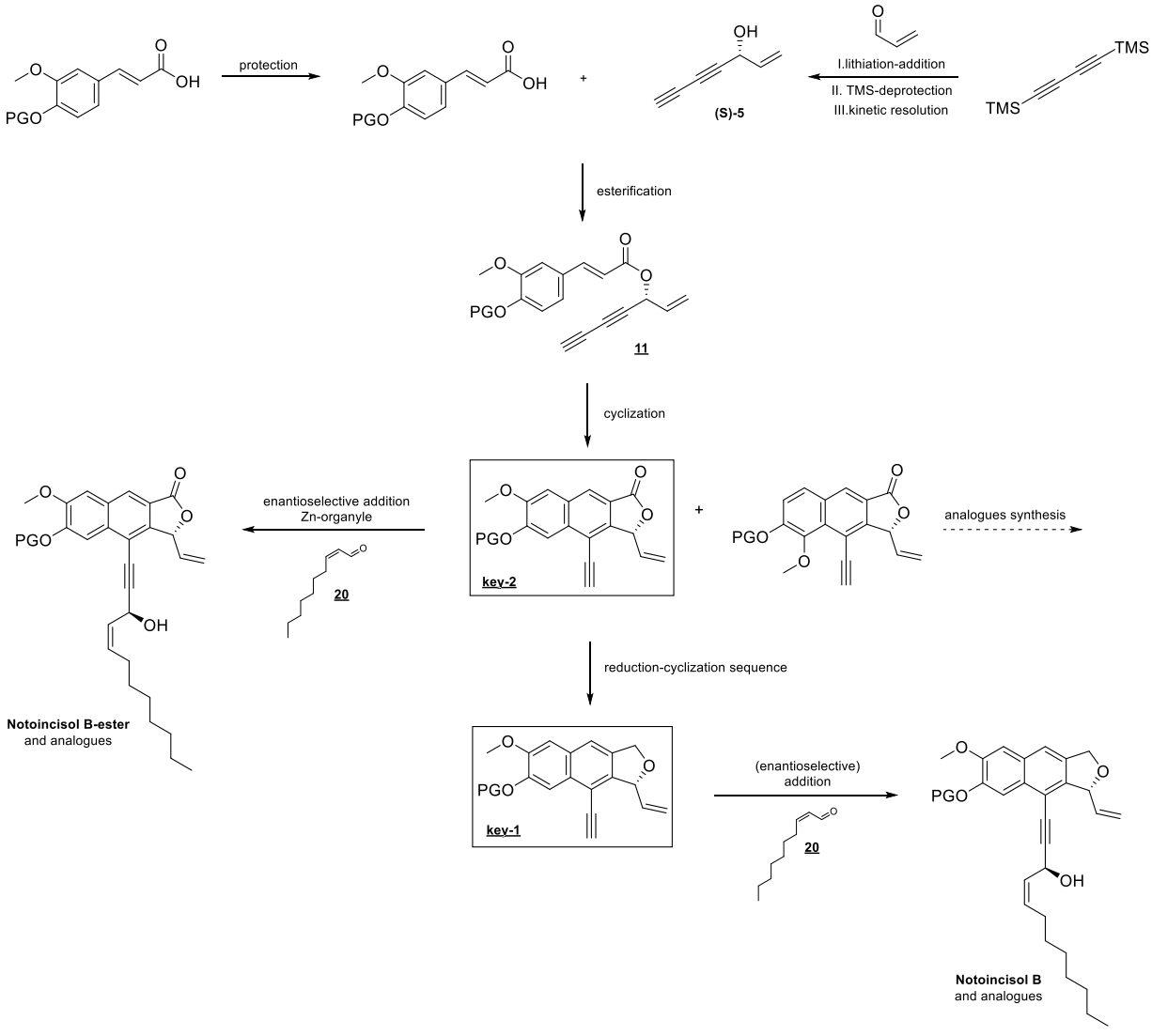
Second, cyclization product **10** was used to investigate the final reductive deoxygenation step towards the characteristic 1,3-dihydronaphtho[2,3-c]furan core moiety of Notoincisol B. In this regard, a reduction-cyclization sequence reaction could be established and successfully applied on the conversion of the lactone moiety **10** to the final core structure **16**.

With suitable protocols for synthetic key-steps in hand, we set out to apply the developed methodology to the synthesis of the complete target scaffold. Thereby a new approach for the synthesis of key-building block 8-TBDMS-falcarindiol (**24**) was followed. This strategy relied on the same *in situ* desilylation-lithiation methodology of commercially available 1,3-diyne **1**, which was previously used and optimized for the synthesis of the model substrate. Although this route appeared to be straight forward and easily feasible, unexpected issues occurred in terms of the implementation of the right stereochemical configuration. Obtained diastereoisomers showed nearly identical physicochemical properties and hence could neither be distinguished analytically nor be separated preparatively.

Further steps within the synthesis of the complete target compound proceeded as expected and proposed within the developed biomimetic strategy. Hence, access to the novel polyenyne-hybrid compound Notoincisol B-lactone as well as to the final target scaffold of Notoincisol B could be successfully proven. Although upon the cyclization-step analytical distinction between the two obtained diastereoisomers was finally possible on a spectroscopic level (^{1}H-, ^{13}C-NMR), unfortunately all attempts to separate these species by means of HPLC remained unsuccessful.

D II Future Prospects Based on this Work

The synthetic methodology developed in this work as well as the challenges encountered within the synthesis of the complete target scaffold may pave the way for future synthetic strategies to access a series of Notoincisol B-type polyenyne hybrid compounds. Accordingly, this part aims to outline two major approaches which might be used as an entrance in future studies striving for the synthesis of biologically active Notoincisol B analogues.



Scheme 27: Potential future strategy utilizing core structures as key-building blocks.

The first approach is closely related to the performed studies on the simplified Notoincisol B scaffold which provided a valuable synthetic access to the cyclic core structure of the target compound (part C II). In fact, these core structures might be utilized as central key-building blocks for the synthesis of Notoincisol B and a variety of structural analogues (Scheme 27).

Part C II.4 outlined an unsuccessful attempt to complete the synthesis of the target compound by means of a simple addition reaction of core structure **16** to the aldehyde **20**. The problem encountered within this approach was based on a failed *in situ* desililytion-lithiation methodology which prevented lithiation of the terminal alkyne moiety. However, this issue might be overcome easily and consequently render this approach a valuable strategy.

It has been shown that the terminal alkyne TMS-protection is not essentially needed in the developed pathway, hence prior deprotection of alcohol **4** in $MeOH/K_2CO_3$ would be a convincing strategy. Once building block **key-1** would be in hand, deprotonation of the free terminal alkyne by means of a strong base and subsequent addition to aldehyde **20** would enable access to the target compound (Scheme 27). In light of the outlined exceptional stereochemical properties of these polyenyne-hybrid structures it would be highly advisable to implement the desired stereochemistry on both chiral centers independently. Regarding the stereocenter on C-3, this could be readily achieved *via* a literature reported enzymatic kinetic resolution of compound **5** to afford **(S)-5**.[40] A convincing method to introduce chirality on C-8 would be *via* enantioselective addition of the terminal alkyne in substrate **key-1** to aldehyde **20**. In this regard, the asymmetric addition of alkynes to aldehydes using mild organozinc species and BINOL–based or amino-alcohol-based chiral catalysts, is highly recognized in the literature.[37, 77-78]

Based on this outlined idea to utilize building block **key-1** for the synthesis of Notoincisol B and analogues, Notoincisol B-lactone type polyenyne-hybrids could be derived in a similar way. The proposed asymmetric addition using an organozinc species and a chiral catalyst has been shown to tolerate a variety of different functional groups, including esters. Accordingly, the same methodology could be employed in the reaction of **key-2** and aldehyde **20**, affording the Notoincisol B-lactone scaffold in an enantioselective way. In particular, it has to be pointed out that this synthetic pathway would readily enable access to a variety of different structural analogues of Notoincisol B (-lactone) by a simple variation of the aldehyde electrophile.

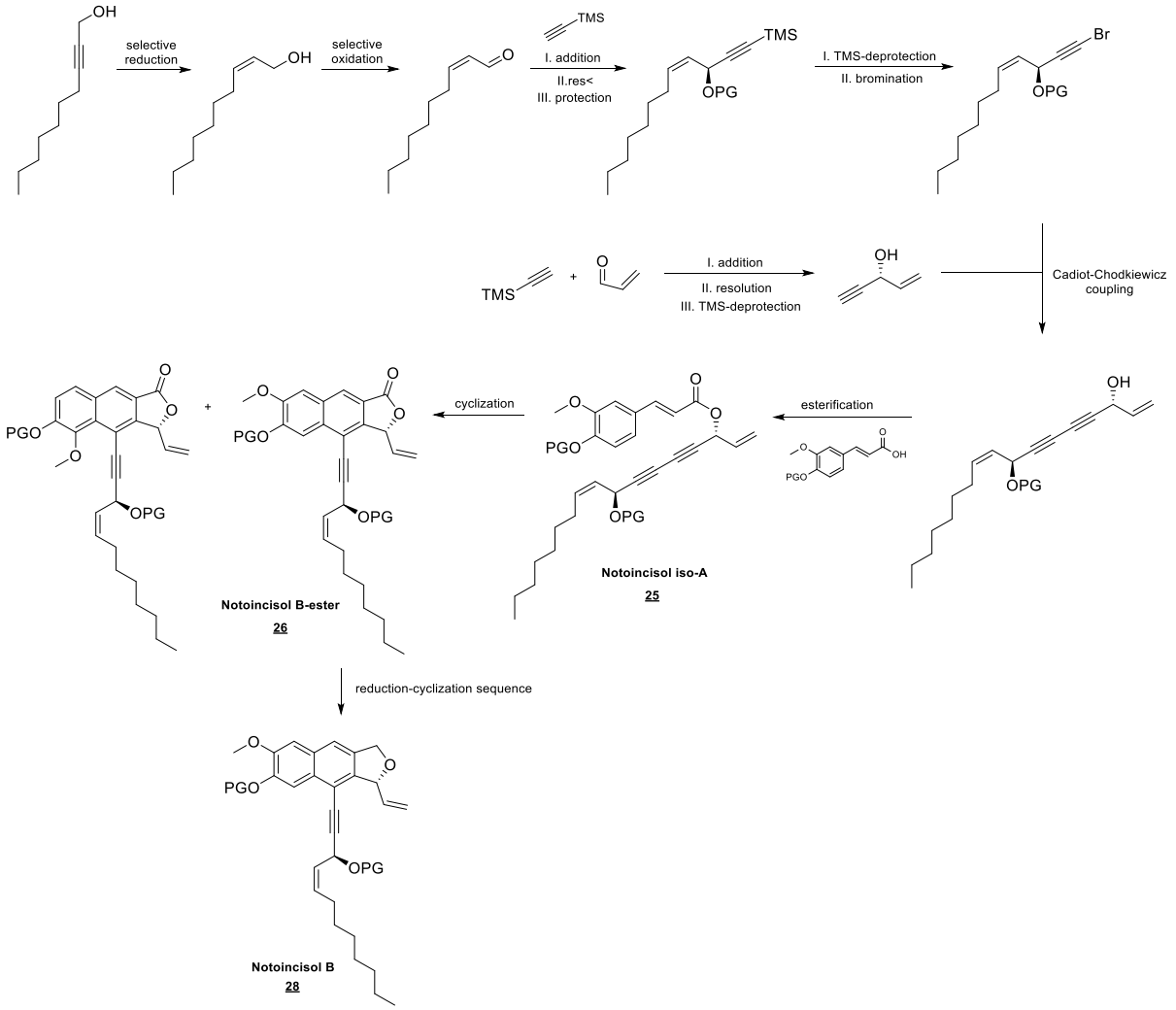
In case of a non-enantioselective addition of **key-1** or **key-2** to aldehyde **20**, obtained diastereoisomers could possibly be separated by means of another enzymatic kinetic resolution. Alternatively, after global deprotection, separation *via* preparative HPLC, could be more readily possible as it has been observed with the silyl-protected substrates prepared in this thesis.

The second approach (Scheme 28) entirely relies on already established methodologies and is in complete accordance with the biomimetic pathway. Although this strategy would not enable the modularity of the first outlined approach, it would be a straight forward plan towards the target compound based on this work and previous works of our group.

The central part of this pathway is based on an alternative synthetic route towards the key building block 8-TBDMS-falcarindiol **24**, thereby taking into account the problems encountered within this thesis in regard to the stereochemistry of this structural moiety. In fact, as previously mentioned, the

configuration of both stereocenters needs to be established separately in order to avoid formation of diastereoisomers. Former co-workers established a synthetic pathway towards building block **24** which relies on a final Cadiot-Chodkiewicz alkyne-hetero-coupling reaction of two secondary alcohol moieties. The right stereochemical configuration in both alcohol substrates can be introduced by means of an enzymatic kinetic resolution, prior to the coupling step, thus formation of diastereoisomers can be prevented.

Once optically pure compound **24** is in hand, the synthetic methodology developed in this thesis enables the access to the target scaffolds (Scheme 28).



Scheme 28: Potential future strategy – alternative route towards 8-TBDMS-falcarindiol based on previous works from our group.

Both outlined approaches towards Notoincisol B-type polyenyne hybrids entirely riley on the styrene-yne cyclization reaction, which has been established within this work. Unfortunately, no control over regioselectivity could be obtained in this reaction so far, resulting in the formation of similar quantities of **26** and **reg-26** respectively **10** and **reg-10**. One possible future handle to increase regioselectivity towards the desired isomers (**26** and **10**) could be to exchange the small methoxy moiety on the natural ferulic acid precursor by a larger isopropoxy group, thereby aiming to direct the cyclization.

E Experimental part

E I General Notes – Materials and Methods

Unless otherwise noted, **chemicals** were purchased from commercial suppliers and used without further purification.

Anhydrous CH_2Cl_2, Et_2O, THF and MeOH were obtained from a dispensing system in which commercial material is passed through a cartridge, containing activated alumina (PURESOLV, Innovative Technology) and stored under nitrogen.

Anhydrous DMSO was obtained by treating pre-dried solvent with activated molecular sieve under vacuum. Water content was determined by means of Karl Fischer titration.

Solvents for preparative chromatography were used as obtained from commercial sources, except LP, which was distilled under reduced pressure prior to use.

Acrolein (purity ≥ 89.5 %, 0.25 - 0.35 % stabilizer hydroquinone, ≤ 10.0 % H_2O) from commercial source was distilled over anhydrous $CuSO_4$ under argon atmosphere prior to use.

Melting ranges were determined using a Büchi Melting Point B-545 and are uncorrected.

Specific rotation was measured on an Anton Paar MCP500 polarimeter at individually specified conditions. $[\alpha]_D^{20}$ values are reported in units of deg·mL·g^{-1}·dm^{-1}.

Microwave reactions were performed on a Biotage Initiator EXP EU Microwave Synthesizer unit. General conditions used: 0.2-2 mL, 2-5 mL or 10-20 mL Biotage MW-vials, pre-stirring: 10 sec, absorption level: low

Thin Layer Chromatography (TLC) was performed on aluminum-backed Merck silica gel 60 with fluorescence indicator F_{254}. Spots were either visualized under UV light (254 nm or 366 nm) or by staining with $KMnO_4$ or p-anisaldehyde dip-reagents (both staining reagents were used generally, Table 5).

Table 5: Recipes for TLC staining solutions used in this thesis.

TLC staining solution 1 ($KMnO_4$)		**TLC staining solution 2 (p-anisaldehyde)**	
6 g	$KMnO_4$	3.5 mL	p-Anisaldehyde
0.5 g	KOH	15 mL	Acetic acid
40 g	K_2CO_3	50 mL	H_2SO_4 conc.
600 mL	deion. H_2O	350 mL	EtOH

Preparative chromatography was either performed on a Büchi Sepacore Flash System (2 x Büchi Pump Module C-605, Büchi Pump Manager C-615, Büchi UV Photometer C-635, Büchi Fraction Collector C-660) or standard manual glass columns using silica gel from Merck (40-63 µm) and LP / EtOAc respectively hexane / EtOAc mixtures as mobile phase. In case of small scale experiments preparative Thin Layer Chromatography (preparative TLC) was performed as individually indicated, using UNIPLATE Preparative Silica Gel Plates (20 x 20 cm, 1000 microns).

Analytical Chromatography-Spectroscopy

Gas Chromatography-Mass Spectroscopy (GC-MS)

Instrument	Thermo Scientific Trace 1300 GC / ISQ LT Single Quadrupole Mass Spectrometer unit; standard capillary column BGB 5 (0.25 µm film; 30 m x 0.25 mm ID); standard parameters: Electron Impact ionization (EI, 70 eV); 1 µL injection volume (hot needle-technique); 250 °C injector block temperature; 2 mL / min carrier gas flow (helium); 300 °C MS-transferline temperature.
Method 1	60 °C (2 min), to 120 °C (10 °C / min), 120 °C (1 min), to 300 °C (35 °C / min), 300 °C (2 min)
Method 2	100 °C (2 min), to 300 °C (35 °C / min), 300 °C (2 min)
Method 3	100 °C (2 min), to 300 °C (35 °C / min), 300 °C (6 min)

Data is reported in the form: *retention time* (min); *m/z* (of M^+ or $M\text{-}H^+$ and main fragments) (relative intensity)

High Pressure Liquid Chromatography (HPLC) was used for reaction control in enzymatic kinetic resolutions and to determine enantiomeric excess of the resulting product.

Instrument: Dionex UltiMate 3000; RS Diode Arrey Detector; Diacel CHIRALPAK AS-H column

Method: 1 mL/min flow rate; heptane / i-PrOH, using gradient from 99.9% heptane to 97.5% in 35 min; detection at 220 nm

Liquid Chromatography-Mass Spectroscopy (LC-MS) was used to confirm molecular mass of reaction products not sufficiently volatile.

Instrument: HPLC system of Agilent Technologies (Agilent 1200 Series G1367B HiP ALS Autosampler; Agilent 1100 Series G1311A Quat Pump; Agilent 1100 Series G1379A Degasser; Agilent 1200 Series G1316B TCCSL; An Agilent 1260 Infinity G1315D DAD; Esquire HCT Ion Trap MS of Bruker)

Method: 1.5 mL/min flow rate; MeCN / H_2O, using gradient form 0% to 100% MeCN in 5 min

Liquid Chromatography-High Resolution Mass Spectroscopy (LC-HRMS) was carried out from methanol solutions (concentration: 10 µM).

Instrument: HTC PAL system autosampler (CTC Analytics AG, Zwingen, Switzerland); Agilent 1100/1200 HPLC with binary pumps, degasser and column thermostat (Agilent Technologies, Waldbronn, Germany); Agilent 6230 AJS ESI–TOF mass spectrometer (Agilent Technologies, Palo Alto, United States).

Nuclear Magnetic Resonance (NMR) spectroscopy

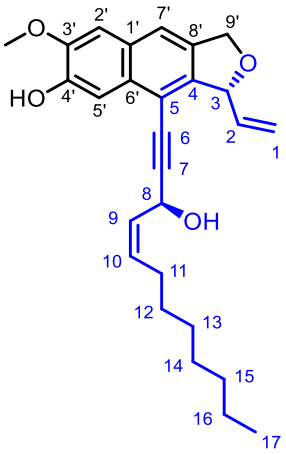
NMR spectra were recorded from $CDCl_3$ or d_6-DMSO solutions on an Avance UltraShield 400 (400 MHz) or Avance III HD 600 (600 MHz) spectrometer as indicated individually. Chemical shifts are reported in ascending order in ppm, using tetramethylsilane (TMS, δ = 0 ppm) as an internal standard. Whenever possible, calibration relative to residual solvent signals (^{1}H: δ = 7.26 ppm ($CDCl_3$), δ = 2.50 ppm (d_6-DMSO); ^{13}C: δ = 77.16 ppm ($CDCl_3$), δ = 39.52 ppm (d_6-DMSO)) was performed.[79]

Multiplicities of signals are indicated as follows:

^{1}H: singlet (s), broad signal (bs), doublet (d), triplet (t), quadruplett (q), multiplet (m) and combinations of these

^{13}C: quarternary C (s), CH (d), CH_2 (t), CH_3 (q)

In general, signal assignment to individual atoms is illustrated via a coherent numbering system based on a literature reported labeling system for the target compound Notoincisol B.[23] To offer a clear scheme, structural precursors and intermediates are not numbered individually according to nomenclature rules, but consistently numbered using the general system based on the target compound as indicated below.

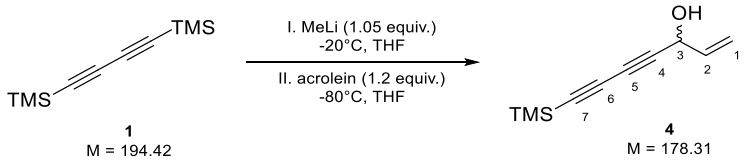


Peak assignment is based on correlation experiments (COSY, HSQC), by comparison of newly synthesized compounds with one another and by comparing with literature values. In case of diastereoisomeric mixtures, signals related to one diastereoisomer are continuously marked with an asterisk (*) when distinctly differing from the other one. If individual assignment of aromatic or alkyne signals was not doubtlessly possible, they are referred to as “Ar” respectively “alkyne”.

E II Studies on a Simplified Notoincisol B Model Scaffold

E II.1 Synthesis of a Simplified Core Structure

E II.1.1 7-(Trimethylsilyl)hepta-1-en-4,6-diyn-3-ol (**4**)



1 M = 194.42 **4** M = 178.31

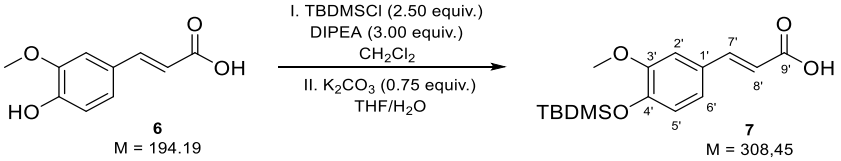
Procedure[53]: A 100 ml three-necked flask, equipped with magnetic stirrer, septum, balloon and low temperature thermometer was charged with 1,4-bis(trimethylsilyl)buta-1,3-diyne **1** (2.00 g, 10.29 mmol, 1.00 equiv.). The atmosphere was changed to argon using standard Schlenk line technique, anhydrous THF (20 mL, c = 0.51 M) was added via syringe and the solution was cooled to -20 °C in a MeOH / liquid N_2 bath. Then, MeLi (1.6 M in Et_2O, 6.75 mL, 10.80 mmol, 1.05 equiv.) was added dropwise and the resulting light-yellowish reaction mixture was stirred at that temperature for 3 h (reaction progress was checked with GC-MS, method 1). Upon complete mono-desilylation, the mixture was cooled to -80 °C and a solution of freshly distilled acrolein (0.83 mL, 12.34 mmol, 1.20 equiv.) in anhydrous THF (20 ml, c = 0.6 M) was added dropwise via syringe over 20 min. The reaction was gradually warmed to rt over a period of 3 h, resulting in a color change to a dark orange solution.

Work-up: The mixture was cooled to -30 °C, solid NH_4Cl (10 g) was added in one batch and vigorously stirred for 10 min. Subsequently, the cooling bath was removed and a saturated aqueous NH_4Cl solution (40 mL) was added slowly over 5 min while preventing the temperature from rising above +10 °C. The mixture was extracted with Et_2O (4 x 40 mL) whereby the pH of the aqueous phase was kept at 6-7. The combined organic layers were washed with a saturated aqueous NH_4Cl solution (1 x 50 mL) and brine (1 x 50 mL), followed by drying over Na_2SO_4. The solution was filtered through a pad of Celite (pre-conditioned with Et_2O) and solvents were evaporated under reduced pressure. Purification *via* flash chromatography (130 g SiO_2, flow rate 50 mL / min, using gradient LP to LP : EtOAc = 10 : 1 in 15 min, then 10 : 1 isocratically 20 min) afforded title compound **4** as a yellowish oil.

Reaction time	6 h
Yield	1.2 g (65%) + 0.1 g (10%) desilylated product
Appearance	yellowish oil
TLC	R_f (LP:EtOAc = 10:1) = 0.26
Molecular formula, m.w.	$C_{10}H_{14}OSi$, 178.31
^{1}H-NMR (400 MHz, $CDCl_3$)	**4:** δ = 0.20 (s, 9H, -Si(C$\underline{H}_3$)$_3$), 1.87 (bs, 1H, -O$\underline{H}$), 4.93 (dt, J = 5.4, 1.5 Hz, 1H, H3), 5.26 (ddd, J = 10.1, 1.4, 0.9 Hz, 1H, H1^{cis}), 5.48 (ddd, J = 17.1, 1.5, 0.9 Hz, 1H, H1^{trans}), 5.94 (ddd, J = 17.0, 10.2, 5.3 Hz, 1H, H2) ppm.

^{1}H-NMR (400 MHz, $CDCl_3$)	**5:** δ = 2.08 (bs, 1H, -OH), 2.23 (d, J = 1.0 Hz, 1H, H7), 4.93 (d, J = 5.3 Hz, 1H, H3), 5.28 (ddd, J = 10.2, 1.4, 0.9 Hz, 1H, $H1^{cis}$), 5.49 (ddd, J = 17.1, 1.6, 0.9 Hz, 1H, $H11^{trans}$), 5.95 (ddd, J = 17.1, 10.2, 5.3 Hz, 1H, H2) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	**4:** δ = -0.4 (q, -Si($\underline{C}H_3)_3$), 63.6 (d, C3), 71.3 (s,C7), 76.1 (s, C6), 87.1 (s, C5), 88.6 (s, C4), 117.5 (t, C1), 135.9 (d, C2) ppm.
GC-MS (Method 1)	mono-desilylated **4**: 2.69 min; 122.0 (M^+, 25), 107 (100), 91 (5), 77 (10), 53 (7) **4**: 10.34 min; 177.1 (M-H^+, 6), 163.0 (100), 135.0 (45), 123.0 (36), 107 (40), 75 (46)
Comment	Compound **4** is reported in the literature[53], but no spectral data is given. Reported spectral data[39-40] for the desilylated compound correspond well to **4** without TMS.

E II.1.2 (E)-3-(4-((*tert*-Butyldimethylsilyl)oxy)-3-methoxyphenyl)acrylic acid (**7**)



Procedure[50] step I: A 100 mL round-bottom flask, equipped with magnetic stirrer, septum and balloon was charged with *trans*-ferulic acid **6** (1.50 g, 7.73 mmol, 1.00 equiv.). The atmosphere was changed to argon using standard Schlenk line technique and anhydrous CH_2Cl_2 (10 mL, final molarity c = 0.51 M) was added via syringe. The suspension was cooled to <5 °C using an ice bath and subsequently N,N-diisopropylethylamine (4.00 mL, 23.17 mmol, 3.00 equiv.) was added dropwise. Meanwhile, in a second reaction vessel *tert*-butyldimethylsilyl chloride (2.91 g, 19.31 mmol, 2.50 equiv.) was dissolved in anhydrous CH_2Cl_2 (5 mL) under argon atmosphere and the solution was added dropwise to the pre-cooled reaction mixture, resulting in a clear yellow solution. The cooling bath was removed and the mixture was stirred at rt for 30 hours (reaction progress was checked by TLC, LP : EtOAc = 3 : 2), observing a color change to dark orange.

Work-up step I: Upon completion, the mixture was diluted with EtOAc (40 mL) and H_2O (40 mL) was added. Subsequently, layers were separated and the aqueous phase was extracted with EtOAc (1 x 30 mL). The combined organic phases were successively washed with 1 N HCl (3 x 30 mL) and brine (1 x 30 mL), dried over Na_2SO_4 and solvents were evaporated under reduced pressure to afford a yellow oil as an intermediate.

Procedure step II: The crude intermediate was dissolved in THF (10 mL, c = 0.8 M) and H_2O (1 mL), solid K_2CO_3 (0.800 g, 5.79 mmol, 0.75 equiv.) was added and the resulting suspension was stirred at rt for 3 h (reaction progress was checked with TLC, LP : EtOAc = 3 : 2).

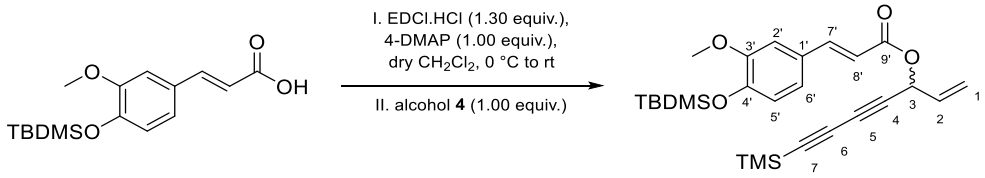
Work-up step II: Upon completion, EtOAc (20 mL) and H_2O (20 mL) were added and layers were separated. The organic phase was successively washed with 1 N HCl (3 x 30 mL) and brine (1 x 30 mL), dried over Na_2SO_4 and solvents were evaporated under reduced pressure yielding the title compound **7** as a beige solid which was used for the next step without any further purification.

Reaction time	33 h
Yield	2.1 g (88%)
Appearance	beige solid
TLC	R_f (LP:EtOAc = 3:2) = 0.28
m_P	**7:** 150.9 - 151.2 °C (lit.:[80] 150-152 °C)
Molecular formula, m.w.	$C_{16}H_{24}O_4Si$, 308.45
^{1}H-NMR (400 MHz, d^6-DMSO)	δ = 0.13 (s, 6H,-Si(C<u>H</u>$_3$)$_2$), 0.95 (s, 9H, -SiC(C<u>H</u>$_3$)$_3$), 3.81 (s, 3H, -OC<u>H</u>$_3$), 6.44 (d, J = 16.0 Hz, 1H,H8'), 6.84 (d, J = 8.1 Hz, 1H, H5'), 7.13 (dd, J = 8.2, 2.0 Hz, 1H, H6'), 7.34 (d, J = 2.0 Hz, 1H, H2'), 7.51 (d, J = 16.0 Hz, 1H, H7'), 12.23 (s, 1H, -COO<u>H</u>) ppm.

^{13}C NMR (100 MHz, d^6-DMSO) δ = -4.7 (q, ,-Si(<u>C</u>H$_3$)$_2$), 18.2 (s, -Si<u>C</u>(CH$_3$)$_3$), 25.5 (q, -SiC(<u>C</u>H$_3$)$_3$), 55.5 (q, -O<u>C</u>H$_3$), 111.4 (d, C2'), 117.2 (d, C8'), 120.5 (d, C5'), 122.3 (d, C6'), 128.4 (s, C^{Ar}), 144.0 (d, C7'), 146.4 (s, C^{Ar}), 150.8 (s, C^{Ar}), 167.8 (s, -<u>C</u>OOH) ppm.

Comment This compound is literature known, spectral data are in accordance with the literature.[30, 50]

E II.1.3 7-(Trimethylsilyl)hepta-1-en-4,6-diyn-3-yl (E)-3-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl)acrylate (**9**)



7
M = 308,45

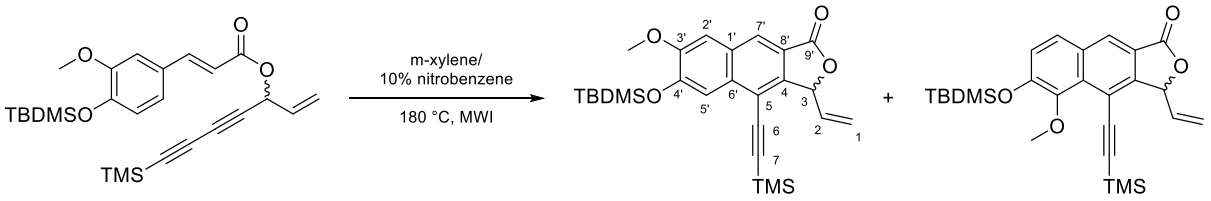
9
M = 468.74

Procedure[30]: A 50 mL round-bottom flask was charged with a stirring bar, TBDMS-ferulic acid **7** (0.450 g, 1.46 mmol, 1.30 equiv.), 4-DMAP (0.137 g, 1.12 mmol, 1.00 equiv.) and EDCI.HCl (0.280 g, 1.46 mmol, 1.30 equiv.). The atmosphere was changed to argon using standard Schlenk line technique, the vessel was sealed with a septum (equipped with a balloon) and cooled to 0 °C in an ice bath. Anhydrous CH_2Cl_2 (7 mL, final molarity c = 0.11 M) was added *via* syringe and the resulting yellow solution was kept at 0 °C for 30 min. Meanwhile, in a second reaction vessel alcohol **4** (0.200 g, 1.12 mmol, 1.00 equiv.) was dissolved in anhydrous CH_2Cl_2 (3 mL) under argon atmosphere and the solution was added dropwise to the activated carboxylic acid at 0 °C. The whole reaction mixture was warmed to rt and stirred for 2 h (reaction progress was checked with TLC, LP : EtOAc = 10 : 1).

Work-up: Upon completion, the mixture was cooled to 0 °C and HCl (0.5 N, 2 mL) was added dropwise. The aqueous phase was extracted with CH_2Cl_2 / Chloroform (1 x 10 mL + 10 mL) and the combined organic phases were washed with 0.5 N HCl (3 x 15 mL), dried over Na_2SO_4 and solvents were evaporated under reduced pressure. Purification *via* flash chromatography (90 g SiO_2, flow rate 30 mL / min, using gradient LP to LP : EtOAc = 10 : 1 in 30 min) afforded the title compound **9** as a light green oil.

Reaction time	2.5 h
Yield	0.370 g (70%)
Appearance	highly viscose light green oil
TLC	R_f (LP:EtOAc = 10:1) = 0.58
Molecular formula, m.w.	$C_{26}H_{36}O_4Si_2$, 468.74
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 0.17 (s, 6H, TBDMS (-Si(C$\underline{H}_3$)$_2$)), 0.19 (s, 9H, TMS (-Si(C$\underline{H}_3$)$_3$)), 0.99 (s, 9H, TBDMS (-SiC(C$\underline{H}_3$)$_3$)), 3.83 (s, 3H, -OC$\underline{H}_3$), 5.37 (dt, J = 10.1, 1.0 Hz, 1H, H1^{cis}), 5.59 (ddd, J = 17.0, 1.3, 1 Hz, 1H, H1^{trans}), 5.93 (ddd, J = 17.0, 10.1, 5.7 Hz, 1H, H2), 6.06 (dt, J = 5.7, 1.3 Hz, 1H, H3), 6.30 (d, J = 15.9 Hz, 1H, H8'), 6.84 (d, J = 8.7 Hz, 1H, H^{Ar}), 7.02 (m, 2H, H^{Ar}), 7.66 (d, J = 15.9 Hz, 1H, H7') ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ = -4.4 (q, TBDMS (-Si($\underline{C}$H$_3$)$_2$)), -0.4 (q, TMS (-Si($\underline{C}$H$_3$)$_3$)), 18.6 (s, TBDMS (-Si$\underline{C}$(CH$_3$)$_3$)), 25.8 (q, TBDMS (-SiC($\underline{C}$H$_3$)$_3$)), 55.6 (q, -O$\underline{C}$H$_3$), 64.4 (d, C3), 71.8 (s, C^{alkyne}), 72.9 (s, C^{alkyne}), 87.1 (s, C^{alkyne}), 88.7 (s, C^{alkyne}), 111.0 (d, C^{Ar}), 114.8 (d, C8'), 119.8 (t, C1), 121.2 (d, C^{Ar}), 122.6 (d, C^{Ar}), 128.2 (s, C^{Ar}), 132.3 (d, C2), 146.4 (d, C7'), 148.0 (s, C^{Ar}), 151.3 (s, C^{Ar}), 165.7 (s, C9') ppm.
LC-HRMS (ESI)	calculated for M+Na$^+$: 491.2044, found 491.2055, Δ: 2.25 ppm

E II.1.4 4'-((*tert*-Butyldimethylsilyl)oxy)-3'-methoxy-5-((trimethylsilyl)ethynyl)-3-vinylnaphtho[2,3-c]furan-1(3H)-one (**10**)
and
4'-((*tert*-Butyldimethylsilyl)oxy)-5'-methoxy-5-((trimethylsilyl)ethynyl)-3-vinylnaphtho[2,3-c]furan-1(3H)-one (**reg-10**)



9 M = 468.74 | **10** M = 466.72 | **reg-10** M = 466.72

Procedure[44]: A 20 mL MW-vial, equipped with a stirring bar, was charged with ester **9** (0.400 g, 0.85 mmol, 1.00 equiv.), m-xylene (12.6 mL) and $PhNO_2$ (1.4 mL ≙ 10% (v/v%) $PhNO_2$ in m-xylene, final molarity c = 0.06 M). The vial was sealed and heated via MWI to 180 °C for 15 min, resulting in a color change from a light green to a dark brown solution (reaction progress was checked with TLC, LP : EtOAc = 10 : 1).

Work-up: Upon completion, the crude mixture was transferred into a flask and solvents were evaporated in high vacuum at 60-70 °C. The two resulting regioisomers **10** and **reg-10** were separated and purified via flash chromatography (180 g SiO_2, flow rate 50 mL / min, using gradient LP to LP : EtOAc = 10 : 1 in 30 min, then 10 : 1 isocratically 10 min).

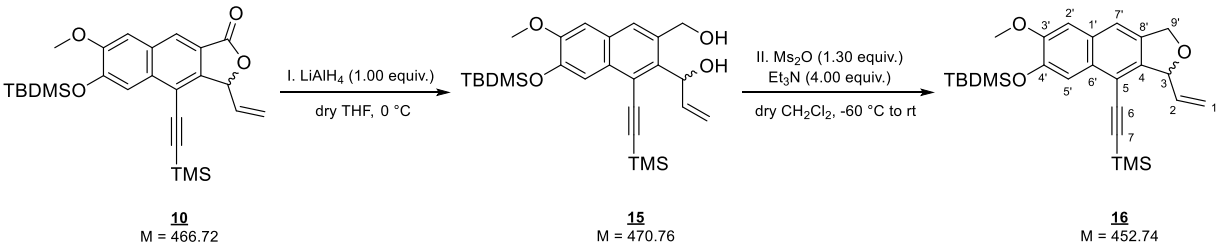
Reaction time	15 min
Yield	0.160 g (40%) of **10** and 0.151 g (38%) of **reg-10**
Appearance	**10:** highly beige crystals **reg-10:** yellow oil
TLC	**10:** R_f (LP:EtOAc = 10:1) = 0.20 (UV: 254 nm) **reg-10:** R_f (LP:EtOAc = 10:1) =0.38 (UV: 366 nm)
m_P	**10:** 167.4 - 168.0 °C
Molecular formula, m.w.	$C_{26}H_{34}O_4Si_2$, 466.72
^{1}H-NMR (400 MHz, $CDCl_3$)	**10:** δ = 0.27 (s, 6H, TBDMS (-Si(CH_3)$_2$)), 0.32 (s, 9H, TMS (-Si(CH_3)$_3$)), 1.05 (s, 9H, TBDMS (-SiC(CH_3)$_3$)), 3.97 (s, 3H, -OCH_3), 5.37 – 5.51 (m, 1H, H1^{cis}), 5.59 – 5.77 (m, 1H, H1^{trans}), 5.92 – 6.12 (m, 2H, H2, H3), 7.23 (s, 1H, H^{Ar}), 7.80 (s, 1H, H^{Ar}), 8.23 (s, 1H, H^{Ar}) ppm.
^{13}C NMR (150 MHz, $CDCl_3$)	**10:** δ = -4.44 (q, TBDMS (-SiCH_3)), -4.43 (q, TBDMS (-SiCH_3)), 0.0 (q, TMS (-Si(CH_3)$_3$)), 18.8 (s, TBDMS (-SiC(CH_3)$_3$)), 25.8 (q, TBDMS (-SiC(CH_3)$_3$)), 55.8 (q, -OCH_3), 82.2 (d, C3), 98.5 (s, C^{Ar} or C^{alkyne}), 106.8 (s, C^{Ar} or C^{alkyne}), 108.3 (d, C^{Ar}), 113.5 (s, C^{Ar} or C^{alkyne}), 114.6 (d, C^{Ar}), 119.8 (t, C1), 121.5 (s, C^{Ar}), 125.3 (d, C^{Ar}), 129.9 (s, C^{Ar}), 132.0 (d, C2), 133.5 (s, C^{Ar}), 143.3 (s, C^{Ar}), 149.7 (s, C^{Ar}), 152.9 (s, C^{Ar}), 170.3 (s, C9') ppm.

^{1}H-NMR (400 MHz, $CDCl_3$) **reg-<u>10</u>:** δ = 0.26 (s, 3H, TBDMS (-SiC<u>H</u>$_3$)), 0.26 (s, 3H, TBDMS (-SiC<u>H</u>$_3$)), 0.32 (s, 9H, TMS (Si(C<u>H</u>$_3$)$_3$)), 1.06 (s, 9H, TBDMS (-SiC(C<u>H</u>$_3$)$_3$)), 3.92 (s, 3H, -OC<u>H</u>$_3$), 5.40 (dt, J = 10.3, 1.2 Hz, 1H, H1^{cis}), 5.62 (dt, J = 16.9, 1.2 Hz, 1H, H1^{trans}), 6.07 (d, J = 6.0 Hz, 1H, H3), 6.16 (ddd, J = 16.9, 10.3, 6.0 Hz, 1H, H2), 7.22 (d, J = 8.9 Hz, 1H, H^{Ar}), 7.69 (d, J = 8.9 Hz, 1H, H^{Ar}), 8.30 (s, 1H, H^{Ar}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) **reg-<u>10</u>:** δ = -4.19 (q, TBDMS (-Si<u>C</u>H$_3$)), -4.18 (q, TBDMS (-Si<u>C</u>H$_3$)), 0.1 (q, TMS (-Si(<u>C</u>H$_3$)$_3$)), 18.5 (s, TBDMS (-Si<u>C</u>(CH$_3$)$_3$)), 25.8 (q, TBDMS (-SiC(<u>C</u>H$_3$)$_3$)), 61.4 (q, -O<u>C</u>H$_3$), 82.3 (d, C3), 101.4 (s, C^{Ar} or C^{alkyne}), 105.3 (s, C^{Ar} or C^{alkyne}), 111.8 (s, C^{Ar} or C^{alkyne}), 119.5 (t, C1), 121.4 (s, C^{Ar} or C^{alkyne}), 123.9 (d, C^{Ar}), 127.2 (d, C^{Ar}), 127.5 (d, C^{Ar}), 130.7 (s, C^{Ar}), 131.5 (d, C2), 132.8 (s, C^{Ar}), 146.4 (s, C^{Ar}), 148.0 (s, C^{Ar}), 149.6 (s, C^{Ar}), 170.0 (s, C9') ppm.

LC-HRMS (ESI) **<u>10</u>:** calculated for M+H$^+$: 467.2068, found 467.2043, Δ: 5.37 ppm
reg-<u>10</u>: calculated for M+H$^+$: 467.2068, found 467.2079, Δ: 2.21 ppm

E II.1.5 *tert*-Butyl((7-methoxy-4-((trimethylsilyl)ethynyl)-3-vinyl-1,3-dihydronaphtho[2,3-c]furan-6-yl)oxy)dimethylsilane (**16**)



10
M = 466.72

15
M = 470.76

16
M = 452.74

Procedure[68] step I: A reaction vessel was charged with a stirring bar and $LiAlH_4$ (2.4 mg, 0.06 mmol, 1.0 equiv.) and sealed with a septum. The atmosphere was changed to argon using standard Schlenk line technique, anhydrous THF (0.3 mL) was added *via* syringe and the resulting suspension was cooled to 0 °C in an ice bath. Meanwhile, in a second reaction vessel, lactone **10** (30.0 mg, 0.06 mmol, 1.00 equiv.) was dissolved in anhydrous THF (0.3 mL, final molarity c = 0.11 M) under argon atmosphere. The solution was added dropwise to the suspension of $LiAlH_4$ at 0 °C resulting in a clear yellow reaction mixture which was stirred at that temperature for 30 min (reaction progress was checked with TLC, LP : EtOAc = 2 : 1).

Work-up step I: Upon completion, the reaction was carefully quenched by slowly adding a saturated aqueous NH_4Cl solution (3 mL). The resulting mixture was thoroughly extracted with EtOAc (5 x 2 mL) and the combined organic phases were washed with brine (1 x 5 mL), dried over Na_2SO_4 and solvents were evaporated under reduced pressure at 30 °C. Time at p_{min} was kept a minimum (instability of diol upon concentrating) and the resulting orange oil was "washed" once with the solvent for the next step (CH_2Cl_2) by dissolving and evaporating again, affording the intermediate diol **15** quantitatively which was immediately used for the next step without any further purification.

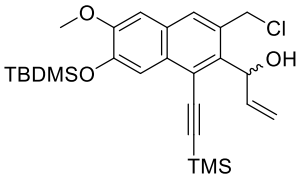
Procedure[67] step II: Diol **15** (30.0 mg, 0.06 mmol, 1.00 equiv.) was dissolved in anhydrous CH_2Cl_2 (0.6 mL) under argon atmosphere in a sealed (septum) reaction vessel, equipped with a stirring bar. Et_3N (36 µL, 0.26 mmol, 4.00 equiv.) was added in one portion and the reaction mixture was cooled to -60 °C in a MeOH / liquid N_2 bath. Meanwhile, in a second reaction vessel Ms_2O (17.0 mg, 0.10 mmol, 1.50 equiv.) was dissolved in anhydrous CH_2Cl_2 (0.2 mL, final molarity c = 0.08 M) under argon atmosphere. The resulting solution was added dropwise to the reaction mixture and the whole mixture was gradually warmed to -20 °C within one hour. Subsequently, the cooling bath was removed and the reaction mixture was allowed to reach rt and stirred o.n. (reaction progress was checked with TLC, LP : EtOAc = 2 : 1).

Work-up step II: Upon completion, the reaction was cooled to 0 °C and quenched by slowly adding a saturated aqueous NH_4Cl solution (3 mL). The organic phase was diluted with EtOAc (3 mL), layers were separated and the aqueous phase was extracted with EtOAc (3 x 2 mL). The combined organic phases were washed with a saturated aqueous NH_4Cl solution (1 x 2mL) followed by a saturated aqueous $NaHCO_3$ solution (1 x 2 mL) and brine (1 x 2 mL), dried over Na_2SO_4 and solvents were evaporated under reduced pressure. Purification *via* preparative TLC (Hexane : EtOAc = 5 : 1) afforded the title compound **16** as a yellow oil.

Reaction time	20 h
Yield	12 mg (41%) of ether **16**
Appearance	**15:** orange oil
	16: yellow oil
TLC	**15:** R_f (LP:EtOAc = 2:1) = 0.27
	16: R_f (LP:EtOAc = 2:1) = 0.78
Molecular formula, m.w.	**15:** $C_{26}H_{38}O_4Si_2$, 470.76
	16: $C_{26}H_{36}O_3Si_2$, 452.74
^{1}H-NMR (600 MHz, $CDCl_3$)	**15:** δ = 0.23 (s, 6H, TBDMS (-Si(CH_3)$_2$)), 0.32 (s, 9H, TMS (-Si(CH_3)$_3$)), 1.04 (s, 9H, TBDMS (-SiC(CH_3)$_3$)), 3.92 (s, 3H, -OCH_3), 4.57 (d, J = 12.3 Hz, 1H, H9'), 5.11 (d, J = 12.3 Hz, 1H, H9'), 5.22 (ddd, J = 10.5, 2.0, 1.5 Hz, 1H, H1^{cis}), 5.43 (ddd, J = 17.2, 2.0, 1.5 Hz, 1H, H1^{trans}), 6.22 (ddd, J = 17.2, 10.5, 4.4 Hz, 1H, H2), 6.32 (dt, J = 4.4, 2.0 Hz, 1H, H3), 7.04 (s, 1H, H^{Ar}), 7.63 (s, 1H, H^{Ar}), 7.75 (s, 1H, H^{Ar}) ppm.
^{13}C NMR (150 MHz, $CDCl_3$)	**15:** δ = -4.5 (q, TBDMS (-Si(CH_3)$_2$)), 0.2 (q, TMS, (-Si(CH_3)$_3$)), 18.7 (s, TBDMS (-SiC(CH$_3$)$_3$)), 25.9 (q, TBDMS (-SiC(CH_3)$_3$)), 55.6 (q, -OCH_3), 64.7 (t, C9'), 74.5 (d, C3), 101.5 (s, C^{Ar} or C^{alkyne}), 105.3 (s, C^{Ar} or C^{alkyne}), 106.8 (d, C^{Ar}), 114.7 (t, C1), 115.6 (d, C^{Ar}), 118.4 (s, C^{Ar} or C^{alkyne}), 129.0 (s, C^{Ar}), 129.5 (s, C^{Ar}), 129.9 (d, C^{Ar}), 134.9 (s, C^{Ar}), 139.3 (d, C2), 139.3 (s, C^{Ar}), 147.1 (s, C^{Ar}), 152.4 (s, C^{Ar}) ppm.
^{1}H-NMR (400 MHz, $CDCl_3$)	**16:** δ = 0.23 (s, 6H, TBDMS (-Si(CH_3)$_2$)), 0.30 (s, 9H, TMS (-Si(CH_3)$_3$)), 1.04 (s, 9H, TBDMS (-SiC(CH_3)$_3$)), 3.92 (s, 3H, -OCH_3), 5.16 (d, J = 12.2 Hz, 1H, H9'), 5.21 – 5.30 (m, 2H, H1^{cis}, H9'), 5.49 (dt, J = 17.0, 1.5 Hz, 1H, H1^{trans}), 5.81 (dd, J = 6.4, 1.5 Hz, 1H, H3), 6.10 (ddd, J = 17.0, 10.2, 6.4 Hz, 1H, H2), 7.06 (s, 1H, H^{Ar}), 7.46 (s, 1H, H^{Ar}), 7.74 (s, 1H, H^{Ar}) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	**16:** δ = -4.5 (q, TBDMS (-Si(CH_3)$_2$)), 0.1 (q, TMS (-Si(CH_3)$_3$)), 18.7 (s, TBDMS (-SiC(CH$_3$)$_3$)), 25.9 (q, TBDMS (-SiC(CH_3)$_3$)), 55.6 (q, -OCH_3), 72.3 (t, C9'), 85.2 (d, C3), 100.3 (s, C^{Ar} or C^{alkyne}), 104.5 (s, C^{Ar} or C^{alkyne}), 107.0 (d, C^{Ar}), 112.5 (s, C^{Ar} or C^{alkyne}), 114.8 (d, C^{Ar}), 116.3 (t, C1), 118.8 (d, C^{Ar}), 129.6 (s, C^{Ar}), 129.7 (s, C^{Ar}), 135.8 (s, C^{Ar}), 135.9 (d, C2), 140.6 (s, C^{Ar}), 146.5 (s, C^{Ar}), 152.1 (s, C^{Ar}) ppm.
LC-HRMS (ESI)	**15:** calculated for M+H$^+$: 471.2381, found 471.2393, Δ: 2.47 ppm
GC-MS (Method 3)	**16:** 10.19 min; 452.2 (M$^+$, 5), 395.2 (80), 380.1 (17), 365.1 (19) 325. 1 (28), 73.0 (100)

Side Product (with MsCl and TsCl as reagents):

1-(7-((tert-Butyldimethylsilyl)oxy)-3-(chloromethyl)-6-methoxy-1-((trimethylsilyl)ethynyl)naphthalen-2-yl)prop-2-en-1-ol (**17**)

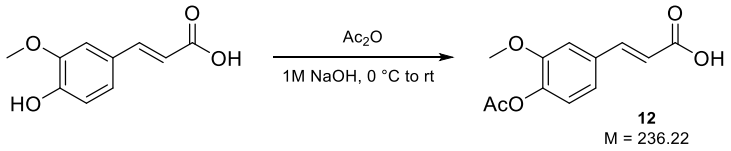


17
M = 489.20

Appearance	light yellow oil
TLC	R_f (LP:EtOAc = 2:1) = 0.89
Molecular formula, m.w.	$C_{26}H_{37}ClO_3Si_2$, 489.20
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 0.23 (s, 6H, TBDMS (-Si(CH_3)$_2$)), 0.33 (s, 9H, TMS (-Si(CH_3)$_3$)), 1.04 (s, 9H, TBDMS (-SiC(CH_3)$_3$)), 3.18 (d, J = 6.8 Hz, 1H, -OH), 3.93 (s, 3H, -OCH_3), 4.87 (d, J = 11.8 Hz, 1H, H9'), 4.99 (d, J = 11.8 Hz, 1H, H9'), 5.23 (dt, J = 10.5, 1.7 Hz, 1H, H1^{cis}), 5.36 (dt, J = 17.2, 1.7 Hz, 1H, H1^{trans}), 6.11 (ddt, J = 6.7, 4.5, 2.0 Hz, 1H, H3), 6.28 (ddd, J = 17.2, 10.5, 4.5 Hz, 1H, H2), 7.06 (s, 1H, H^{Ar}), 7.74 (s, 1H, H^{Ar}), 7.75 (s, 1H, H^{Ar}) ppm.

E II.2 Synthesis of Other Model Compounds

E II.2.1 (E)-3-(4-Acetoxy-3-methoxyphenyl)acrylic acid (**12**)



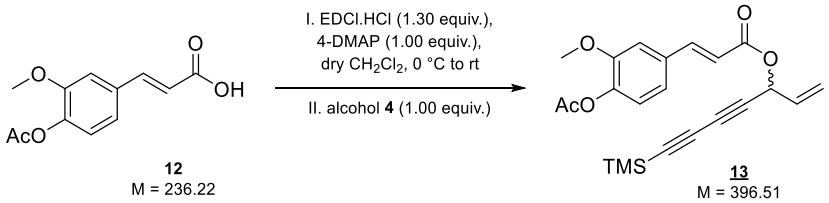
12
M = 236.22

Procedure[81]: In a 250 mL round-bottom flask, equipped with a magnetic stirrer, *trans*-ferulic acid **6** (3.0 g, 15.45 mmol, 1.0 equiv.) was dissolved in 1 N NaOH (40 mL) and the solution was cooled to 0 °C in an ice bath. Then, acetic anhydride (5.85 mL, 61.80 mmol, 4 equiv.) was added dropwise, immediately resulting in the formation of a white precipitate. The whole mixture was warmed to rt and stirred for 2.5 h (reaction progress was checked with TLC, CH_2Cl_2 : MeOH = 9 : 1).

Work-up: Upon completion, the formed precipitate was filtered off under reduced pressure, washed with H_2O (5 x 15 mL) and dried under vacuum. Purification via recrystallization from 70% EtOH afforded title compound **12** as a colorless crystalline solid.

Reaction time	2.5 h
Yield	3.0 g (82%)
Appearance	colorless crystals
TLC	R_f (CH_2Cl_2:MeOH = 9:1) = 0.44
m_P	**12:** 203.3 – 203.5 °C (lit.:[82] 202-203 °C)
Molecular formula, m.w.	$C_{12}H_{12}O_5$, 236.22
^{1}H-NMR (400 MHz, d^6-DMSO)	δ = 2.26 (s, 3H, -OCC<u>H</u>$_3$), 3.82 (s, 3H, -OC<u>H</u>$_3$), 6.59 (d, J = 16.0 Hz, 1H, H8'), 7.12 (d, J = 8.2 Hz, 1H, H5'), 7.26 (dd, J = 8.2, 1.9 Hz, 1H, H6'), 7.48 (d, J = 1.9 Hz, 1H, H2'), 7.58 (d, J = 16.0 Hz, 1H, H7'), 12.42 (s, 1H, -COO<u>H</u>) ppm.
^{13}C NMR (100 MHz, d^6-DMSO)	δ = 20.4 (q, -OC<u>C</u>H$_3$), 56.0 (q, -OC<u>H</u>$_3$), 111.8 (d, C2'), 119.5 (d, C8'), 121.4 (d, C6'), 123.2 (d, C5'), 133.3 (s, CAr), 140.8 (s, CAr), 143.4 (d, C7'), 151.2 (s, C^{Ar}), 167.6 (-O<u>C</u>CH$_3$ or -<u>C</u>OOH), 168.4 (-O<u>C</u>CH$_3$ or -<u>C</u>OOH) ppm.
Comment	This compound is literature known, spectral data are in accordance with the literature.[81-82]

E II.2.2 7-(Trimethylsilyl)hepta-1-en-4,6-diyn-3-yl (E)-3-(4-acetoxy-3-methoxyphenyl)acrylate (**13**)



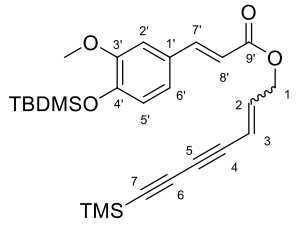
Procedure[30]: A reaction vessel was charged with a stirring bar, Ac-ferulic acid **12** (0.138 g, 0.58 mmol, 1.30 equiv.), 4-DMAP (55 mg, 0.45 mmol, 1.00 equiv.) and EDCI.HCl (0.112 g, 0.583 mmol, 1.30 equiv.). The atmosphere was changed to argon using standard Schlenk line technique and the vessel was sealed with a septum (equipped with a balloon). Anhydrous CH_2Cl_2 (3 mL, final molarity c = 0.11 M) was added *via* syringe, the resulting yellow solution was cooled to 0 °C in an ice bath and stirred at that temperature for 30 min. Meanwhile, in a second reaction vessel alcohol **4** (80 mg, 0.45 mmol, 1.00 equiv.) was dissolved in anhydrous CH_2Cl_2 (1 mL) under argon atmosphere and the solution was added dropwise to the activated carboxylic acid at 0 °C. The whole reaction mixture was warmed to rt and stirred for 2 h (reaction progress was checked with TLC, LP : EtOAc = 10 : 1).

Work-up: Upon completion, the mixture was cooled to 0 °C and 0.5 N HCl (2 mL) was added dropwise. The aqueous phase was extracted with CH_2Cl_2 / Chloroform (1 x 10 mL + 10 mL) and the combined organic phases were washed with 0.5 N HCl (3 x 15 mL), dried over Na_2SO_4 and solvents were evaporated under reduced pressure. Purification *via* flash chromatography (30 g SiO_2, flow rate 30 mL / min, using gradient LP to LP : EtOAc = 5 : 1 in 15 min, then isocratically LP for 15 min) afforded title compound **13** as a light yellow/green oil.

Reaction time	1.5 h
Yield	95 mg (54%)
Appearance	light green/yellow oil
TLC	R_f (LP:EtOAc = 5:1) = 0.45
Molecular formula, m.w.	$C_{22}H_{24}O_5Si$, 396.51
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 0.19 (s, 9H, TMS (-Si(CH_3)$_3$)), 2.32 (s, 3H, -OC$\underline{C}H_3$), 3.85 (s, 3H, -OCH_3), 5.38 (d, J = 10.1 Hz, 1H, H^{cis}), 5.60 (d, J = 17.0 Hz, 1H, H^{trans}), 5.94 (ddd, J = 17.0, 10.1, 5.7 Hz, 1H, H2), 6.05 (dt, J = 5.7, 1.2 Hz, 1H, H3), 6.38 (d, J = 16.0 Hz, 1H, H8'), 7.01 – 7.20 (m, 3H, HAr), 7.69 (d, J = 16.0 Hz, 1H, H7') ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ = -0.4 (q, TMS (-Si(CH_3)$_3$))), 20.8 (q, -O$\underline{C}CH_3$), 56.0 (q, -OCH_3), 64.7 (d, C3), 71.9 (s, C^{alkyne}), 72.7 (s, C^{alkyne}), 87.0 (s, C^{alkyne}), 88.9 (s, C^{alkyne}), 111.4 (d, C^{Ar}), 117.4 (d, C8'), 119.9 (t, C1), 121.5 (d, C^{Ar}), 123.4 (d, C^{Ar}), 132.1 (d, C2), 133.2 (s, C^{Ar}), 141.8 (s, C^{Ar}), 145.5 (d, C7'), 151.5 (s, C^{Ar}), 165.3 (s, C9'), 168.8 (s, -O$\underline{C}CH_3$) ppm.

Failed cyclization of **9** *via* Lewis acid catalysis: undesired rearrangement product **14:**

E II.2.3 7-(Trimethylsilyl)hepta-2-en-4,6-diyn-1-yl (2E)-3-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl)acrylate(**14**)



14
M = 468.74

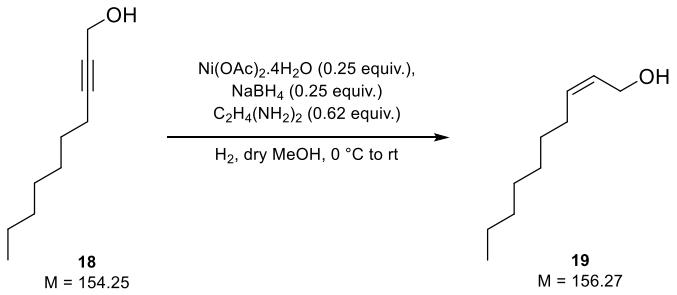
Treatment of compound **9** with $BF_3.OEt_2$ (1.00 equiv.) in dichloroethane ($C_2H_4Cl_2$) at rt resulted in an immediate quantitative rearrangement reaction affording compound **14**.

Crude Appearance	brown oil
TLC	R_f (LP:EtOAc = 10:1) = 0.47
Molecular formula, m.w.	$C_{26}H_{36}ClO_4Si_2$, 468.74
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 0.17 (s, 6H, TBDMS (-Si(CH_3)$_2$)), 0.21 (s, 10H, TMS (-Si(CH_3)$_3$)), 0.99 (s, 9H, TBDMS (-SiC(CH_3)$_3$)), 3.84 (s, 3H, -OCH_3), 4.75 (dd, J = 5.6, 1.8 Hz, 1H, B), 5.82 (dt, J = 15.9, 1.8 Hz, 1H, H3), 6.30 (d, J = 15.9 Hz, 1H, H8'), 6.39 (dt, J = 15.9, 5.6 Hz, 1H, H2), 6.82 – 6.88 (m, 1H, H^{Ar}), 7.00 – 7.05 (m, 2H, H^{Ar}), 7.64 (d, J = 15.9 Hz, 1H, H7') ppm.

E III Synthesis of Complete Scaffolds

E III.1 Synthesis of the Polyenyne Building-Block 8-TBDMS-Falcarindiol

E III.1.1 (Z)-Dec-2-en-1-ol (**19**)



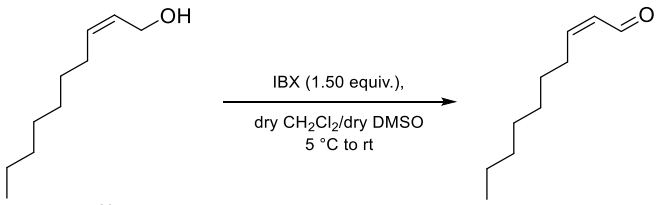
Procedure[33]: A 100 ml three-necked flask, equipped with magnetic stirrer, septum and gas inlet was charged with Ni(II)$(OAc)_2.4H_2O$ (1.61 g, 6.48 mmol, 0.25 equiv.). The atmosphere was changed to argon using standard Schlenk line technique, anhydrous MeOH (42 ml, c = 0.15 M) was added *via* syringe and the resulting green solution was cooled to 0 °C in an ice bath. $NaBH_4$ (0.245 g, 6.48 mmol, 0.25 equiv.) was added in five portions, immediately resulting in the formation of a black suspension. After stirring the mixture for 20 min at 0 °C, ethylenediamine (0.966 g, 16.08 mmol, 0.62 equiv.) was added in one portion. In a second reaction vessel dec-2-yn-1-ol **18** (4.00 g, 25.93 mmol, 1.00 equiv.) was dissolved in anhydrous MeOH (14 mL, c = 1.85 M, final molarity c = 0.46 M) under argon atmosphere. The solution was added dropwise to the catalytic system at 0 °C and the whole mixture was subsequently warmed to rt. The atmosphere was changed to H_2 using standard Schlenk line technique and a H_2-balloon and the reaction was stirred at rt for 3 h (reaction progress was checked with TLC, LP : EtOAc = 5 : 1).

Work-up: Upon completion, the reaction mixture was flashed through a pad of silica (20 g SiO_2) using Et_2O as an eluent. Solvents were removed under reduced pressure at 30 °C and the resulting residue was taken up in Et_2O (30 mL), washed with H_2O (1 x 20 mL) and brine (1 x 20 mL), dried over Na_2SO_4 and solvents were evaporated again under reduced pressure at 30 °C. Purification via flash chromatography (180 g SiO_2 per 2g crude product, flow rate 50 mL / min, using gradient LP to LP : EtOAc = 5 : 1 in 35 min, then 10 : 1 isocratically 5 min) afforded the title compound **19** as a colorless oil.

Reaction time	3 h
Yield	3.7 g (90%)
Appearance	colorless oil
TLC	R_f (LP:EtOAc = 5:1) = 0.39
Molecular formula, m.w.	$C_{10}H_{20}O$, 156.27
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 0.88 (t, J = 6.6 Hz, 3H, H17), 1.22 – 1.40 (m, 10H, H12-16), 2.06 (q, J = 7.0 Hz, 2H, H11), 4.19 (d, J = 6.2 Hz, 2H, H8), 5.48 – 5.66 (m, 2H, H9, H10) ppm.

^{13}C NMR (100 MHz, $CDCl_3$)	δ = 14.2 (q, C17), 22.8 (t, CH_2 (C12-C16)), 27.6 (t, C11), 29.3 (t, CH_2 (C12-C16)), 29.3 (t, CH_2 (C12-C16)), 29.7 (t, CH_2 (C12-C16)), 32.0 (t, CH_2 (C12-C16)), 58.7 (t, C8), 128.4 (d, C9 or C10), 133.4 (d, C10 or C9) ppm.
GC-MS (Method 2)	**19:** 4.26 min; 138.1 (12), 110.1 (14), 95.0 (28), 81.1 (47), 67.0 (50), 57 (100)
Comment	This compound is literature known, spectral data are in accordance with literature.[30, 33, 83]

E III.1.2 (Z)-Dec-2-enal (**20**)



19
M = 156.27

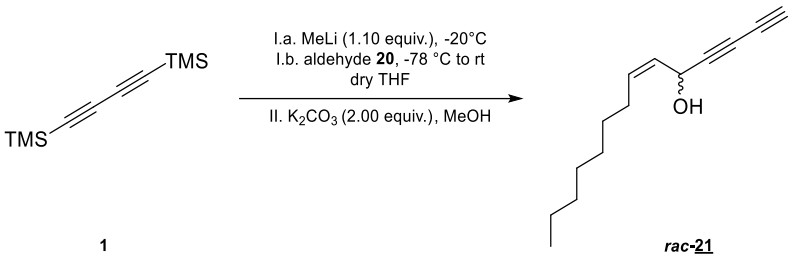
20
M = 154.25

Procedure[33]: A 100 ml three-necked flask, equipped with magnetic stirrer, septum and balloon was charged with IBX (2.69 g, 9.60 mmol, 1.50 equiv.). The atmosphere was changed to argon using standard Schlenk line technique, anhydrous CH_2Cl_2 (7 mL) and anhydrous DMSO (1.5 mL, initial ratio CH_2Cl_2 : DMSO ~ 4.5 : 1) were added *via* syringe and the resulting suspension was cooled in an ice bath. Meanwhile, in a second reaction vessel (Z)-dec-2-en-1-ol **19** (1.00 g, 6.40 mmol, 1.00 equiv.) was dissolved in anhydrous CH_2Cl_2 (6.5 mL) and anhydrous DMSO (1.5 mL, final molarity c = 0.39 M) under argon atmosphere. The solution was added to the suspension of IBX and the whole reaction mixture was warmed to rt. After 1 h (no reaction progress was visible anymore according to TLC, LP : EtOAc = 10 : 1 and GC-MS, method 2) anhydrous DMSO (0.3 mL) was added every 30 min (final ratio CH_2Cl_2 : DMSO ~ 3 : 1) until full conversion of the starting material was reached (TLC).

Work-up: All working steps where performed as fast as possible at T ≤ rt to prevent isomerization. Upon completion, the reaction mixture was cooled to 0 °C in an ice bath and a precooled saturated aqueous $NaHCO_3$ solution (10 mL) was added. The whole mixture was filtered through a pad of Celite under reduced pressure, using Et_2O as an eluent. Layers were separated and the organic phase was washed thoroughly with a saturated aqueous $NaHCO_3$ solution (3 x 20 mL) and brine (4 x 20 mL), dried over Na_2SO_4 and solvents were removed under reduced pressure at T ≤ rt, affording the title compound **20** as a yellow oil. The crude material was immediately used for the next step without any further purification.

Reaction time	3 h
Yield	0.795 g (80%)
Appearance	yellow oil
TLC	R_f (LP:EtOAc = 10:1) = 0.54
Molecular formula, m.w.	$C_{10}H_{18}O$, 154.25
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 0.84 – 0.91 (m, 3H, H17), 1.21 – 1.39 (m, 8H, H13-H16), 1.51 (tt, J = 7.9, 6.5 Hz, 2H, H12), 2.60 (qd, J = 7.5, 1.5 Hz, 2H, H11), 5.95 (ddt, J = 11.2, 8.2, 1.5 Hz, 1H, H9), 6.63 (dt, J = 11.2, 8.2 Hz, 1H, H10), 10.08 (d, J = 8.2 Hz, 1H, H8) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ = 14.2 (q, C17), 22.7 (t, CH_2 (C12-16)), 28.1 (t, C11), 29.1 (t, CH_2 (C12-16)), 29.2 (t, CH_2 (C12-16)), 29.3 (t, CH_2 (C12-16)), 31.8 (t, CH_2 (C12-16)), 130.3 (d, C9), 153.7 (d, C10), 191.1 (d, C8) ppm.
GC-MS (Method 2)	**20:** 4.14 min; 136.1 (0.5), 123.1 (1), 110.1 (21), 83.0 (85), 70.0 (100), 55.0 (48)
Comment	This compound is literature known, spectral data are in accordance with literature.[30, 33, 84]

E III.1.3 (Z)-Tetradec-6-en-1,3-diyn-5-ol (**rac-21**)



1
M = 194.42

***rac*-21**
M = 204.31

Procedure[53] step I: A 100 ml three-necked flask, equipped with magnetic stirrer, septum, balloon and low temperature thermometer was charged with 1,4-bis(trimethylsilyl)buta-1,3-diyne **1** (0.750 g, 3.86 mmol, 1.00 equiv.). The atmosphere was changed to argon using standard Schlenk line technique, anhydrous THF (20 ml, c = 0.51 M) was added *via* syringe and the solution was cooled to -20 °C in a MeOH / liquid N_2 bath. Then, MeLi (1.6 M in Et_2O, 2.65 mL, 4.24 mmol, 1.1 equiv.) was added dropwise and the resulting light-yellowish reaction mixture was stirred at that temperature for 3 h (reaction progress was checked with GC-MS, method 1). Upon complete mono-desilylation, the mixture was cooled to -80 °C and a solution of aldehyde **20** (0.655 g, 4.24 mmol, 1.10 equiv.) in anhydrous THF (7 ml, c = 0.6 M) was added dropwise *via* syringe over 10 min. The cooling bath was removed and the reaction mixture was warmed to rt over a period of 1 h, resulting in a color change to a dark orange solution (reaction progress was checked with TLC, LP : EtOAc = 10 : 1).

Work-up step I: Upon completion after 2.5 h, the mixture was cooled to -30 °C and a saturated aqueous NH_4Cl solution (20 mL) was added slowly over 5 min whereby the temperature was kept below +10 °C. Stirring was continued for 15 min while warming the mixture to rt. The organic phase was diluted with Et_2O (20 mL) and layers were separated. The aqueous phase was extracted with Et_2O (3 x 20 ml), the combined organic layers were washed with brine (1 x 20 mL), dried over Na_2SO_4 and solvents were removed under reduced pressure, affording a mixture of alcohol ***rac*-21** and its TMS-protected analogue.

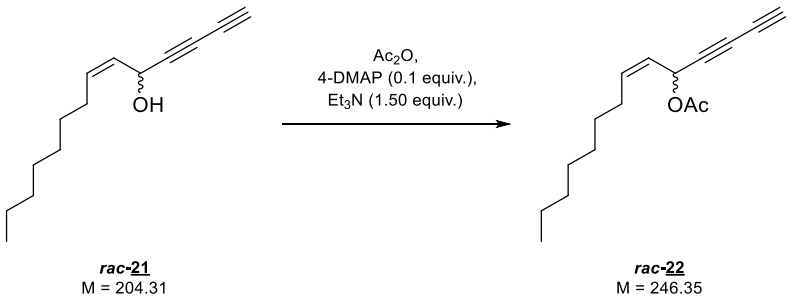
Procedure step II: The crude product was dissolved in MeOH (20 mL, c = 0.2 M), solid K_2CO_3 (1.10 g, 7.72 mmol, 2.00 equiv.) was added in one batch and the resulting suspension was stirred for 30 min (reaction progress was checked with TLC, LP : EtOAc = 10 : 1).

Work-up step II: Upon completion, H_2O (20 mL) was added and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine (1 x 20 mL), dried over Na_2SO_4 and solvents were removed under reduced pressure. Purification *via* flash chromatography (90 g SiO_2, flow rate 50 mL / min, starting isocratically with LP for 5 min., then using gradient LP to LP : EtOAc = 8 : 1 in 5 min., then 8 : 1 isocratically 15 min) afforded title compound **rac-21** as an orange oil.

Reaction time	3 h
Yield	0.721 g (90%)
Appearance	orange oil
TLC	R_f (LP:EtOAc = 10:1) = 0.31 (respectively 0.41 with TMS)
Molecular formula, m.w.	$C_{14}H_{20}O$, 204.31

^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 0.85 – 0.92 (m, 3H, H17), 1.22 – 1.46 (m, 10H, H12-H16), 1.98 (bs, 1H, -OH), 2.11 (qd, J = 7.4, 1.5 Hz, 2H, H11), 2.21 (d, J = 1.0 Hz, 1H, H4), 5.18 (dt, J = 8.3, 1.0 Hz, 1H, H8), 5.51 (ddt, J = 10.7, 8.3, 1.5 Hz, 1H, H9), 5.62 (dtd, J = 10.7, 7.4, 1.0 Hz, 1H, H10) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ = 14.2 (q, C17), 22.8 (t, CH_2 (C12-C16)), 27.8 (t, C11), 29.2 (t, CH_2 (C12-C16)), 29.3 (t, CH_2 (C12-C16)), 29.4 (t, CH_2 (C12-C16)), 31.9 (t, CH_2 (C12-C16)), 58.6 (d, C8), 67.6 (s, C^{alkyne}), 68.9 (d, C4), 69.2 (s, C^{alkyne}), 76.2 (s, C^{alkyne}), 127.6 (d, C9), 135.0 (d, C10) ppm.
GC-MS	**Method 1** mono-desilylated **1**: 2.69 min, 122.0 (M^+, 27) **Method 2** TMS-protected **rac-21:** 6.98 min; 261.1 (3), 205.1 (7), 191.0 (19), 107.0 (25), 75.0 (48), 73.0 (100) **Method 2** ***rac*-21:** 5.93 min; 161.1 (1), 147.1 (5), 133.1 (27), 119.0 (34), 105.0 (61), 91.0 (100), 77.0 (38), 55.0 (28)
LC-HRMS (ESI)	calculated for $M+H^+$: 205.1587, found 205.1574, Δ: 6.08 ppm

E III.1.4 (Z)-Tetradec-6-en-1,3-diyn-5-yl acetate (**22**)



***rac*-21**
M = 204.31

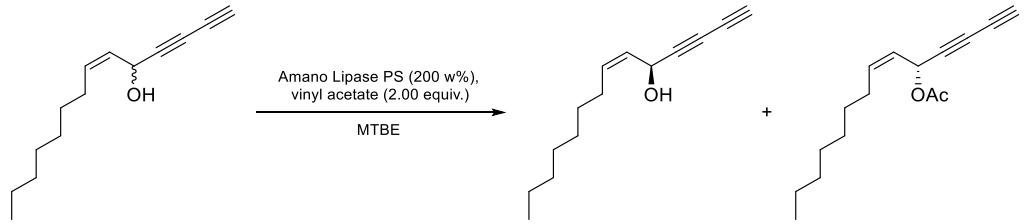
***rac*-22**
M = 246.35

Procedure[40]: A GC-vial was charged with a stirring bar, alcohol ***rac*-21** (20 mg, 0.09 mmol, 1.00 equiv.) and 4-DMAP (1 mg, 0.01 mmol, 0.10 equiv.). The atmosphere was changed to argon using standard Schlenk line technique, Et_3N (15 mg, 21 µL, 1.50 equiv.) and acetic anhydride (0.2 mL, c = 0.5 M) were added *via* syringe and the mixture was stirred for 1.5 h (reaction progress was checked with TLC, LP : EtOAc = 10 : 1).

Work-up: Upon completion, H_2O (0.2 mL) was added and the reaction mixture was extracted with Et_2O (3 x 0.2 mL). The combined organic phases were dried over Na_2SO_4 and solvents were removed under reduced pressure, affording title compound ***rac*-22** as an orange oil which was not further purified.

Comment	Analytical scale for chiral HPLC analysis.
Reaction time	1.5 h
Yield	20 mg (83%)
Appearance	orange oil
TLC	R_f (LP:EtOAc = 10:1) = 0.65
Molecular formula, m.w.	$C_{16}H_{22}O_2$, 246.35
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 0.76 – 0.93 (m, 3H, H17), 1.21 – 1.44 (m, 10H, H12-16), 2.08 (s, 3H, -OCC$\underline{H}_3$), 2.14 (qd, J = 7.5, 1.6 Hz, 2H, H11), 2.21 (d, J = 1.0 Hz, 1H, H4), 5.48 (ddt, J = 10.5, 8.8, 1.6 Hz, 1H, H9), 5.68 (dtd, J = 10.5, 7.5, 1.1 Hz, 1H, H10), 6.12 (dt, J = 8.8, 1.1 Hz, 1H, H8) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ = 14.3 (q, C17), 21.1 (q, -OC$\underline{C}H_3$), 22.8 (t, CH_2 (C12-16)), 28.0 (t, C11), 29.2 (t, 2 x CH_2 (C12-16)), 29.3 (t, CH_2 (C12-16)), 31.9 (t, CH_2 (C12-16)), 60.0 (d, C8), 67.4 (s, C^{alkyne}), 69.2 (d, C4), 69.7 (s, C^{alkyne}), 72.9 (s, C^{alkyne}), 123.7 (d, C9), 136.7 (d, C10), 169.6 (s, -O$\underline{C}CH_3$) ppm.
LC-HRMS (ESI)	calculated for $M+H^+$: 247.1693, found 247.1699, Δ: 2.55 ppm

E III.1.5 (S,Z)-Tetradec-6-en-1,3-diyn-5-ol (**(S)-21**)



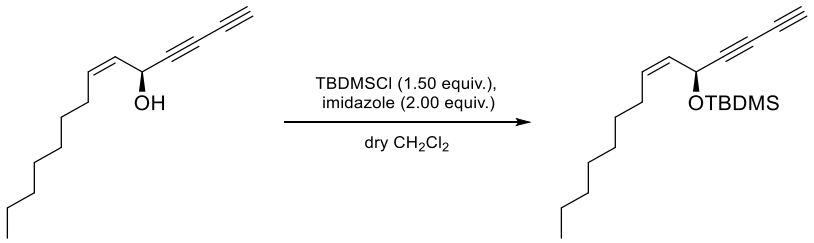
***rac*-21** M = 204.31 | ***(S)*-21** M = 204.31 | **(R)-22** M = 246.35

Procedure[30]: A reaction vessel was charged with a stirring bar, alcohol ***rac*-21** (100 mg, 0.49 mmol, 1.00 equiv.), vinyl acetate (90 µL, 0.98 mmol, 2.00 equiv.), MTBE (7.5 mL, c = 0.07 M) and Amano Lipase PS (immobilized on diatomite, 200 mg, 200 w%). The vessel was sealed with a septum and the resulting suspension was stirred for 40 h at rt (reaction progress was checked *via* chiral HPLC).

Work-up: Upon complete conversion of the undesired (R)-enantiomer to the corresponding acetate, the catalyst was filtered through a pad of Celite, rinsed with Et_2O and solvents were removed under reduced pressure. Flash chromatography (10 g SiO_2, isocratically LP : EtOAc = 10 : 1) afforded title compound **(S)-21**.

Reaction time	40 h
Yield	**(S)-21:** 42 mg (42%, theoretical maximum yield is 50%)
Appearance	**(S)-21:** orange oil, **(R)-22:** orange oil
TLC	**(S)-21:** R_f (LP:EtOAc = 10:1) = 0.31, **(R)-22:** R_f (LP:EtOAc = 10:1) = 0.65
Molecular formula, m.w.	**(S)-21:** $C_{14}H_{20}O$, 204.31, **(R)-22:** $C_{16}H_{22}O_2$, 246.35
^{1}H-NMR (400 MHz, $CDCl_3$)	**(S)-21:** δ = 0.85 – 0.92 (m, 3H, H17), 1.22 – 1.46 (m, 10H, H12-H16), 1.98 (bs, 1H, -OH), 2.11 (qd, J = 7.4, 1.5 Hz, 2H, H11), 2.21 (d, J = 1.0 Hz, 1H, H4), 5.18 (dt, J = 8.3, 1.0 Hz, 1H, H8), 5.51 (ddt, J = 10.7, 8.3, 1.5 Hz, 1H, H9), 5.62 (dtd, J = 10.7, 7.4, 1.0 Hz, 1H, H10) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	**(S)-21:** δ = 14.2 (q, C17), 22.8 (t, CH_2 (C12-C16)), 27.8 (t, C11), 29.2 (t, CH_2 (C12-C16)), 29.3 (t, CH_2 (C12-C16)), 29.4 (t, CH_2 (C12-C16)), 31.9 (t, CH_2 (C12-C16)), 58.6 (d, C8), 67.6 (s, C^{alkyne}), 68.9 (d, C4), 69.2 (s, C^{alkyne}), 76.2 (s, C^{alkyne}), 127.6 (d, C9), 135.0 (d, C10) ppm.
^{1}H-NMR (400 MHz, $CDCl_3$)	**(R)-22:** δ = 0.76 – 0.93 (m, 3H, H17), 1.21 – 1.44 (m, 10H, H12-16), 2.08 (s, 3H, -OAc), 2.14 (qd, J = 7.5, 1.6 Hz, 2H, H11), 2.21 (d, J = 1.0 Hz, 1H, H4), 5.48 (ddt, J = 10.5, 8.8, 1.6 Hz, 1H, H9), 5.68 (dtd, J = 10.5, 7.5, 1.1 Hz, 1H, H10), 6.12 (dt, J = 8.8, 1.1 Hz, 1H, H8) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	**(R)-22:** δ = 14.3 (q, C17), 21.1 (q, -OAc), 22.8 (t, CH_2 (C12-16)), 28.0 (t, C11), 29.2 (t, 2 x CH_2 (C12-16)), 29.3 (t, CH_2 (C12-16)), 31.9 (t, CH_2 (C12-16)), 60.0 (d, C8), 67.4 (s, C^{alkyne}), 69.2 (d, C4), 69.7 (s, C^{alkyne}), 72.9 (s, C^{alkyne}), 123.7 (d, C9), 136.7 (d, C10), 169.6 (s, -OAc) ppm.
Chiral HPLC	**(S)- 21:** 26.8 min; **(R)-22:** 6.2 min
$[\alpha]_D^{20}$	**(S)- 21:** +268.579° (c = 1 / $CHCl_3$)
e.e.:	**(S)- 21:** >98% (HPLC)
LC-HRMS (ESI)	**(S)-21:** calculated for M+H$^+$: 205.1587, found 205.1574, Δ: 6.08 ppm
LC-HRMS (ESI)	**(R)-22:** calculated for M+H$^+$: 247.1693, found 247.1699, Δ: 2.55 ppm

E III.1.6 (S,Z)-*tert*-Butyldimethyl(tetradec-6-en-1,3-diyn-5-yloxy)silane (**23**)



***(S)*-11**
M = 204.31

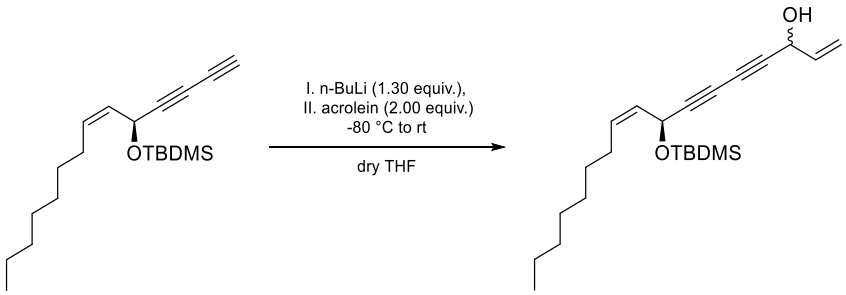
13
M = 318.58

Procedure[74]: A reaction vessel was charged with a stirring bar, (S,Z)-tetradec-6-en-1,3-diyn-5-ol **(S)-21** (45 mg, 0.22 mmol, 1.00 equiv.) and imidazole (30 mg, 0.44 mmol, 2.0 equiv.) and sealed with a septum. The atmosphere was changed to argon using standard Schlenk line technique and anhydrous CH_2Cl_2 (1.5 mL) was added *via* syringe. In a second reaction vessel tert-butyldimethylsilyl chloride (50 mg, 0.33 mmol, 1.50 equiv.) was dissolved in anhydrous CH_2Cl_2 (0.2 mL, final molarity c = 0.15 M) under argon atmosphere and the solution was added dropwise to the reaction mixture, immediately resulting in the precipitation of a colorless solid. The mixture was stirred at rt for 1 h (reaction progress was checked with TLC, LP : EtOAc = 10 : 1).

Work-up: Upon completion, a saturated aqueous NH_4Cl solution (3 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 2 mL). The combined organic layers were washed with a saturated aqueous NH_4Cl solution (1 x 3 mL), dried over Na_2SO_4 and solvents were removed under reduced pressure. Purification *via* flash chromatography (7 g SiO_2, isocratically LP then LP : EtOAc = 25 : 1) afforded title compound **23** as a light orange oil.

Reaction time	1 h
Yield	66 mg (94%)
Appearance	light orange oil
TLC	R_f (LP:EtOAc = 25:1) = 0.80
Molecular formula, m.w.	$C_{20}H_{34}OSi$, 318.58
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 0.12 (s, 3H, -Si(C$\underline{H}_3$)), 0.14 (s, 3H, -Si(C$\underline{H}_3$)), 0.86-0.88 (m, 3H, H17), 0.90 (s, 9H, -Si(C$\underline{H}_3$)$_3$), 1.15 – 1.47 (m, 10H, H12- H16), 2.07 (m, 2H, H11), 2.17 (d, J = 1.0 Hz, 1H, H4), 5.06 – 5.31 (m, 1H, H8), 5.36 – 5.59 (m, 2H, H9, H10) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ = -4.6 (q, TBDMS (-Si($\underline{C}$H$_3$)$_2$)), -4.4 (q, TBDMS (-Si($\underline{C}$H$_3$)$_2$)), 14.3 (q, C17), 18.4 (s, TBDMS (-Si$\underline{C}$(CH$_3$)$_3$)), 22.8 (t, CH_2 (C12-16)), 25.9 (q, TBDMS (-SiC($\underline{C}$H$_3$)$_3$)), 27.9 (t, C11), 29.3 (t, CH_2 (C12-16)), 29.4 (t, CH_2 (C12-16)), 29.4 (t, CH_2 (C12-16)), 31.9 (t, CH_2 (C12-16)), 59.4 (d, C8), 67.9 (s, C^{alkyne} (C5, C6 or C7)), 68.4 (d, C4), 68.4 (s, C^{alkyne} (C5, C6 or C7)), 77.1 (s, C^{alkyne} (C5, C6 or C7)), 129.2 (d, C10 or C9), 132.4 (d, C9 or C10) ppm.
$[\alpha]_D^{20}$	+123.34° (c = 1 / $CHCl_3$)

E III.1.7 (8S,Z)-8-((*tert*-Butyldimethylsilyl)oxy)heptadec-1,9-dien-4,6-diyn-3-ol (8-TBDMS-falcarindiol **24**)



23
M = 318.58

24
M = 374.64

Procedure: A 25 ml three-necked flask, equipped with magnetic stirrer, septum, balloon and low temperature thermometer was charged with (S,Z)-*tert*-butyldimethyl(tetradec-6-en-1,3-diyn-5-yloxy)silane **23** (0.130 g, 0.41 mmol, 1.00 equiv.). The atmosphere was changed to argon using standard Schlenk line technique, anhydrous THF (3 mL, c = 0.14 M) was added *via* syringe and the solution was cooled to -80 °C in a MeOH / liquid N_2 bath. Then, n-BuLi (1.6 M in hexanes, 0.33 mL, 0.53 mmol, 1.30 equiv.) was added dropwise whereby a color change from light orange to dark brown was visible. The resulting mixture was stirred at -80 °C for 45 min. Subsequently, a solution of freshly distilled acrolein (55 µl, 0.82 mmol, 2.00 equiv.) in anhydrous THF (1 ml, c = 0.82 M) was added dropwise *via* syringe over 5 min. Upon addition, the reaction mixture turned light yellow and darkened remarkably again when gradually warmed to rt over 3 h (reaction progress was checked with TLC, LP : EtOAc = 10 : 1).

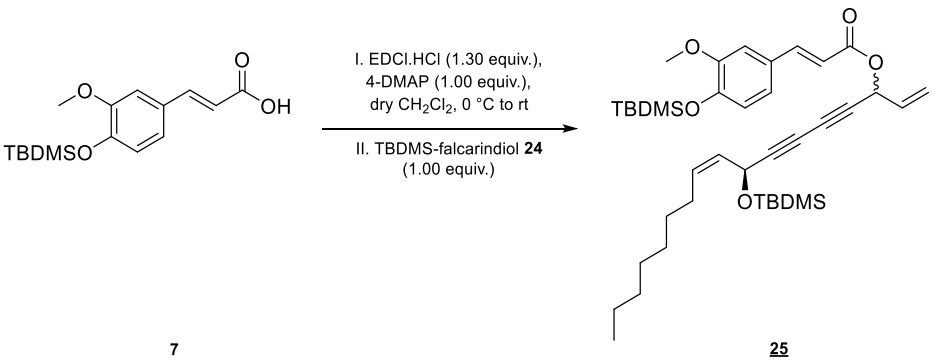
Work-up: After no reaction progress was observable anymore according to TLC (starting material never completely disappears), the mixture was cooled to -30 °C and a saturated aqueous NH_4Cl solution (3 mL) was added slowly over 5 min whereby the temperature was prevented from rising above +10 °C. Stirring was continued for 15 min while warming the mixture to rt. The organic phase was diluted with EtOAc (3 mL) and layers were separated. The aqueous phase was extracted with EtOAc (3x 10 mL), the combined organic layers were washed with a saturated aqueous NH_4Cl solution (2 x 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4 and solvents were removed under reduced pressure. Purification *via* flash chromatography (9 g SiO_2, flow rate 15 mL / min, 5 min LP then gradient LP to LP : EtOAc = 10 : 1 in 15 min, then 10 : 1 isocratically 15 min) afforded title compound **24** as a yellowish oil.

Reaction time	4h
Yield	0.115 g (75%)
Appearance	yellowish oil
TLC	R_f (LP:EtOAc = 10:1) = 0.30
Molecular formula, m.w.	$C_{23}H_{38}O_2Si$, 374.64

^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 0.11 (s, 3H, TBDMS (-Si(C<u>H</u>$_3$))), 0.13 (s, 3H, TBDMS (-Si(C<u>H</u>$_3$))), 0.86 – 0.89 (m, 2H, H17), 0.89 (s, 9H, TBDMS (-SiC(C<u>H</u>$_3$)$_3$), 1.18 – 1.45 (m, 10H, H12-16), 1.90 (d, J = 6.2 Hz, 1H, -O<u>H</u>), 2.00 – 2.14 (m, 2H, H11), 4.87 – 5.00 (m, 1H, H3), 5.15 – 5.22 (m, 1H, H8), 5.26 (dt, J = 10.1, 1.1 Hz, 1H, H1^{cis}), 5.39 – 5.59 (m, 3H, H1^{trans}, H9, H10), 5.94 (ddd, J = 17.1, 10.2, 5.3 Hz, 1H, H2) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	δ = -4.60 (q, TBDMS (-Si(<u>C</u>H$_3$))), -4.37 (q, TBDMS (-Si(<u>C</u>H$_3$))), 14.3 (q, C17), 18.4 (s, TBDMS (-Si<u>C</u>(CH$_3$)$_3$)), 22.8 (t, CH_2 (C12-16)), 25.9 (q, TBDMS (SiC(CH$_3$)$_3$)), 27.9 (t, C11), 29.3 (t, CH_2 (C12-16)), 29.4 (t, CH_2 (C12-16)), 29.4 (t, CH_2 (C12-16)), 32.0 (t, CH_2 (C12-16)), 59.6 (d, C8), 63.7 (d, C3), 68.0 (s, C^{alkyne} (C4, C5, C6 or C7)), 70.8 (s, C^{alkyne} (C4, C5, C6 or C7)), 77.7 (s, C^{alkyne} (C4, C5, C6 or C7)), 80.9 (s, C^{alkyne} (C4, C5, C6 or C7)), 117.4 (t, C1), 129.3 (d, C9 or C10), 132.3 (d, C9 or C10), 136.0 (d, C2) ppm.
Comment	This compound is literature known, spectral data are in accordance with literature.[34]

E III.2 Notoincisol iso-A, Notoincisol B-lactone and Notoincisol B

E III.2.1 (8S,Z)-8-((*tert*-Butyldimethylsilyl)oxy)heptadec-1,9-dien-4,6-diyn-3-yl (E)-3-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl)acrylate (Notoincisol iso-A **25**)



7
M = 308.45

25
M = 665.07

Procedure[30]: A reaction vessel was charged with a stirring bar, TBDMS-ferulic acid **7** (0.128 g, 0.42 mmol, 1.30 equiv.), 4-DMAP (0.039 g, 0.32 mmol, 1.00 equiv.) and EDCI.HCl (0.080 g, 0.42 mmol, 1.30 equiv.). The atmosphere was changed to argon using standard Schlenk line technique and the vessel was sealed with a septum (equipped with a balloon). Anhydrous CH_2Cl_2 (2 mL, final molarity c = 0.11 M) was added *via* syringe, the resulting yellow solution was cooled to 0 °C in an ice bath and stirred at that temperature for 30 min. Meanwhile, in a second reaction vessel 8-TBDMS-falcarindiol **24** (0.120 g, 0.32 mmol, 1.00 equiv.) was dissolved in anhydrous CH_2Cl_2 (1 mL) under argon atmosphere. The solution was added dropwise to the activated carboxylic acid at 0 °C. The whole reaction mixture was warmed to rt and stirred for 2.5 h (reaction progress was checked with TLC, LP : EtOAc = 10 : 1).

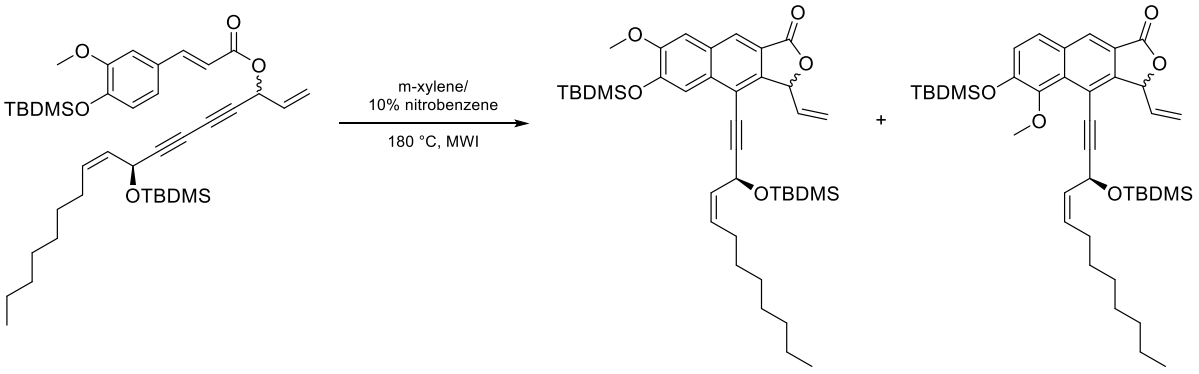
Work-up: Upon completion, the mixture was cooled to 0 °C and 0.5 N HCl (1.5 mL) was added dropwise. The aqueous phase was extracted with CH_2Cl_2 / chloroform (1 x 10 mL + 10 mL) and the combined organic phases were washed with 0.5 N HCl (3 x 15 mL), dried over Na_2SO_4 and solvents were evaporated under reduced pressure. Purification *via* flash chromatography (30 g SiO_2, flow rate 30 mL / min, using gradient hexane to hexane : EtOAc = 30 : 1 in 40 min) afforded title compound **25** as a yellow oil.

Reaction time	2.5 h
Yield	0.120 g (56%)
Appearance	yellow oil
TLC	R_f (LP:EtOAc = 10:1) = 0.62
Molecular formula, m.w.	$C_{39}H_{60}O_5Si_2$, 665.07

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.11 (s, 3H, TBDMS (-Si(C<u>H</u>$_3$))), 0.13 (s, 3H, TBDMS (-Si(C<u>H</u>$_3$))), 0.17 (s, 6H, TBDMS (-Si(C<u>H</u>$_3$)$_2$)), 0.82 – 0.88 (m, 3H, H17), 0.89 (s, 9H, TBDMS (-SiC(C<u>H</u>$_3$)$_3$)), 0.99 (s, 9H, TBDMS (-SiC(C<u>H</u>$_3$)$_3$)), 1.18 – 1.42 (m, 10H, H12-H16), 2.01 – 2.11 (m, 2H, H11), 3.83 (s, 3H, -OC<u>H</u>$_3$), 5.13 – 5.23 (m, 1H, H8), 5.36 (dt, J = 10.1, 1.0 Hz, 1H, H1^{cis}), 5.41 – 5.53 (m, 2H, H9, H10), 5.59 (ddd, J = 17.0, 1.3, 0.8 Hz, 1H, H1^{trans}), 5.94 (ddd, J = 17.0, 10.1, 5.6 Hz, 1H, H2), 6.08 (dq, J = 5.6, 0.8 Hz, 1H, H3), 6.30 (d, J = 15.9 Hz, 1H, H7'), 6.84 (d, J = 8.6 Hz, 1H, H^{Ar}), 6.98 – 7.06 (m, 2H, H^{Ar}), 7.66 (d, J = 15.9 Hz, 1H, H8') ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.6 (q, TBDMS (-Si(<u>C</u>H$_3$))), -4.4 (q, TBDMS (-Si(<u>C</u>H$_3$)$_2$)), -4.4 (q, TBDMS (-Si(<u>C</u>H$_3$))), 14.3 (q, C17), 18.3 (s, TBDMS (-Si<u>C</u>(CH$_3$)$_3$)), 18.6 (s, TBDMS (-Si<u>C</u>(CH$_3$)$_3$)), 22.8 (t, CH_2 (C12-16)), 25.8 (q, TBDMS (-SiC(<u>C</u>H$_3$)$_3$)), 25.9 (q, TBDMS (-SiC(<u>C</u>H$_3$)$_3$)), 27.9 (t, C11), 29.3 (t, CH_2 (C12-16)), 29.4 (t, CH_2 (C12-16)), 29.4 (t, CH_2 (C12-16)), 31.9 (t, CH_2 (C12-16)), 55.6 (q, -OC<u>H</u>$_3$), 59.6 (d, C8), 64.5 (d, C3), 68.0 (s, C^{alkyne}), 71.4 (s, C^{alkyne}), 74.5 (s, C^{alkyne}), 81.0 (s, C^{alkyne}), 111.0 (d, C^{Ar}), 114.9 (d, C7'), 119.6 (t, C1), 121.2 (d, C^{Ar}), 122.7 (d, C^{Ar}), 128.2 (s, C^{Ar}), 129.2 (d, C9 or C10), 132.3 (d, C9 or C10), 132.4 (d, C2), 146.3 (d, H8'), 148.0 (s, C^{Ar}), 151.3 (s, C^{Ar}), 165.7 (s, C9') ppm.

E III.2.2 6-((*tert*-Butyldimethylsilyl)oxy)-4-((S,Z)-3-((*tert*-butyldimethylsilyl)oxy)dodec-4-en-1-yn-1-yl)-7-methoxy-3-vinylnaphtho[2,3-c]furan-1(3H)-one (Notoincisol B-lactone **26**) and 6-((*tert*-Butyldimethylsilyl)oxy)-4-((S,Z)-3-((*tert*-butyldimethylsilyl)oxy)dodec-4-en-1-yn-1-yl)-5-methoxy-3-vinylnaphtho[2,3-c]furan-1(3H)-one (**reg-26**)



25
M = 374.64

26
M = 663.06

reg-26
M = 663.06

Procedure[44]: A 5 mL MW-vial, equipped with a stirring bar, was charged with ester **25** (0.110 g, 0.165 mmol, 1.00 equiv.), m-xylene (2.7 mL) and $PhNO_2$ (0.3 mL ≙ 10% (v/v%) $PhNO_2$ in m-xylene, final molarity c = 0.06 M). The vial was sealed and the solution was heated *via* MWI to 180 °C for 1 h, resulting in a color change from a light yellow to a dark brown solution (reaction progress was checked with TLC, LP : EtOAc = 10 : 1).

Work-up: Upon completion, the crude mixture was transferred into a flask and solvents were evaporated in HV at 60-70 °C. The two resulting regioisomers **26** and **reg-26** were separated and purified *via* flash chromatography (30 g SiO_2, flow rate 20 mL / min, using gradient hexane : EtOAc = 40 : 1 to hexane : EtOAc = 10 : 1 in 10 min, then 10 : 1 isocratically 20 min).

Reaction time	1 h
Yield	31 mg (28%) of **26** and 27 mg (25%) of **reg-26**
Appearance	**26:** yellow oil
	reg-26: yellow oil
TLC	**26:** R_f (LP:EtOAc = 10:1) = 0.24 (UV: 254 nm)
	reg-26: R_f (LP:EtOAc = 10:1) = 0.40 (UV: 366 nm)
Molecular formula, m.w.	$C_{39}H_{58}O_5Si_2$, 663.06
^{1}H-NMR (400 MHz, $CDCl_3$)	**26:** δ = 0.17 – 0.19 (m, 6H, TBDMS (-Si(CH_3)$_2$) / TBDMS* (-Si(CH_3)$_2$)), 0.25 (t, J = 2.4 Hz, 6H, TBDMS (-Si(CH_3)$_2$) / TBDMS* (-Si(CH_3)$_2$)), 0.79 – 0.85 (m, 3H, H17), 0.94 (s, 9H, TBDMS (-SiC(CH_3)$_3$)), 1.05 (s, 9H, TBDMS (-SiC(CH_3)$_3$)), 1.16 – 1.47 (m, 10H, CH2 (C12-C16) / (C12*-C16*)), 2.12 – 2.23 (m, 2H, H11), 3.96 (s, 3H, -OCH_3), 5.33 – 5.40 (m, 1H, $H1^{cis}$ / $H1^{cis}$*), 5.50 (dd, J = 8.3, 1.1 Hz, 1H, H8 / H8*), 5.51 – 5.58 (m, 1H, H10 / H10*), 5.60 – 5.65 (m, 1H, $H1^{trans}$ / $H1^{trans}$*), 5.65 – 5.70 (m, 1H, H9 / H9*), 5.99 – 6.04 (m, 1H, H3 / H3*), 6.05 – 6.18 (m, 1H, H2 / H2*), 7.23 (s, 1H, H^{Ar}), 7.73 (s, 1H, H^{Ar}), 8.22 (s, 1H, H^{Ar}) ppm.

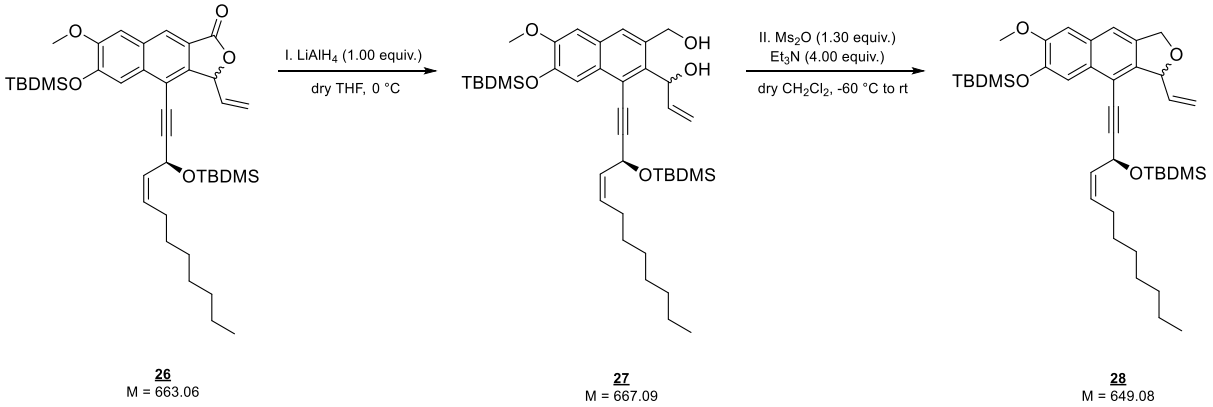
^{13}C NMR (100 MHz, $CDCl_3$) **26:** δ = -4.4 (q, TBDMS (-Si(CH$_3$)$_2$) and/or *), -4.4 (q, TBDMS (-Si(CH$_3$)$_2$) and/or *), -4.4 (q, TBDMS (-Si(CH$_3$)$_2$) and/or *), -4.3 (q, TBDMS (-Si(CH$_3$)$_2$) and/or *), -4.2 (q, TBDMS (-Si(CH$_3$)$_2$)*), -4.2 (q, TBDMS (-Si(CH$_3$)$_2$)), 14.2 (q, C17), 18.4 (s, TBDMS (-SiC(CH$_3$)$_3$)*), 18.4 (s, TBDMS (-SiC(CH$_3$)$_3$)), 18.7 (s, TBDMS (-SiC(CH$_3$)$_3$)), 22.8 (t, CH_2 (C12-C16)), 25.8 (q, TBDMS (-SiC(CH$_3$)$_3$)), 25.9 (q, TBDMS (-SiC(CH$_3$)$_3$)*), 26.0 (q, TBDMS (-SiC(CH$_3$)$_3$)), 28.0 (t, C11), 29.3 (t, CH_2 (C12-C16)), 29.5 (t, CH_2 (C12-C16)), 29.6 (t, CH_2 (C12-C16)), 31.9 (t, CH_2 (C12-C16)), 55.7 (q, -OCH$_3$), 59.9 (d, C8*), 59.9 (d, C8), 78.0 (s, C^{alkyne}*), 78.1 (s, C^{alkyne}), 81.7 (d, C3), 101.6 (s, C^{Ar}* or C^{alkyne}*), 101.6 (s, C^{Ar} or C^{alkyne}), 108.3 (d, C^{Ar}), 113.3 (s, C^{Ar} or C^{alkyne}), 114.7 (d, C^{Ar}*), 114.7 (d, C^{Ar}), 119.0 (t, C1), 121.4 (s, C^{Ar}), 125.1 (d, C^{Ar}), 130.0 (s, C^{Ar}), 130.3 (d, C9*), 130.3 (d, C9), 131.6 (d, C10), 132.2 (d, C2*), 132.3 (d, C2), 133.5 (s, C^{Ar}*), 133.5 (s, C^{Ar}), 143.4 (s, C^{Ar}*), 143.5 (s, C^{Ar}), 149.6 (s, C^{Ar}), 152.7 (s, C^{Ar}), 170.3 (s, C9') ppm.

^{1}H-NMR (400 MHz, $CDCl_3$) **reg-26:** δ = 0.14 – 0.19 (m, 6H, TBDMS (-Si(CH$_3$)$_2$) / TBDMS* (-Si(CH$_3$)$_2$)), 0.24 (s, 6H, TBDMS (-Si(CH$_3$)$_2$), 0.82 – 0.88 (m, 3H, H17 / H17*), 0.94 (s, 9H, TBDMS (-SiC(CH$_3$)$_3$)), 1.06 (s, 9H, TBDMS (-SiC(CH$_3$)$_3$)), 1.18 – 1.49 (m, 10H, CH_2 (H12-16) / (H12*-H16*)), 2.13 – 2.22 (m, 2H, H11), 3.90 (s, 3H, -OCH_3 / -OCH_3*), 5.29 – 5.39 (m, 1H, $H1^{cis}$ / $H1^{cis}$*), 5.48 – 5.52 (m, 1H, H8 / H8*), 5.52 – 5.56 (m, 1H, H10 / H10*), 5.58 – 5.65 (m, 1H, $H1^{trans}$ / $H1^{trans}$*), 5.65 – 5.69 (m, 1H, H9 / H9*), 6.02 – 6.09 (m, 1H, H3 / H3*), 6.17 – 6.32 (m, 1H, H2 / H2*), 7.22 (d, J = 8.9 Hz, 1H, H^{Ar}), 7.68 (d, J = 8.9 Hz, 1H, H^{Ar}), 8.28 (s, 1H, H^{Ar}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) **reg-<u>26</u>:** δ = -4.5 (q, TBDMS (-Si(<u>C</u>H_3)$_2$) and/or *), -4.4 (q, TBDMS (-Si(<u>C</u>H_3)$_2$) and/or *), -4.3 (q, TBDMS (-Si(<u>C</u>H_3)$_2$) and/or *), -4.3 (q, TBDMS (-Si(<u>C</u>H_3)$_2$) and/or *), -4.3 (q, TBDMS (-Si(<u>C</u>H_3)$_2$) and/or *), 14.2 (q, C17), 18.4 (s, TBDMS* (-Si<u>C</u>$(CH_3)_3$)), 18.4 (s, TBDMS (-Si<u>C</u>$(CH_3)_3$)), 18.5 (s, TBDMS (-Si<u>C</u>$(CH_3)_3$)), 22.8 (t, CH_2 (C12-16)), 25.8 (q, TBDMS (-SiC(<u>C</u>H_3)$_3$)), 26.0 (q, TBDMS (-SiC(<u>C</u>H_3)$_3$)), 28.0 (t, C11*), 28.0 (t, C11), 29.3 (t, CH_2 (C12-16)), 29.5 (t, CH_2* (C12-16)), 29.6 (t, CH_2 (C12-16)), 29.6 (t, CH_2* (C12-16)), 29.6 (t, CH_2 (C12-16)), 31.9 (t, CH_2 (C12-16)), 60.1 (d, C8*), 60.2 (d, C8), 61.4 (q, -OCH_3*), 61.5 (q, -OCH_3), 80.9 (s, C^{alkyne}*), 80.9 (s, C^{alkyne}), 81.9 (d, C3*), 82.0 (d, C3), 100.0 (s, C^{Ar}* or C^{alkyne}*), 100.1 (s, C^{Ar} or C^{alkyne}), 111.7 (s, C^{Ar}* or C^{alkyne}*), 111.7 (s, C^{Ar} or C^{alkyne}), 118.4 (t, C1*), 118.7 (t, C1), 121.3 (s, C^{Ar}* or C^{alkyne}*), 121.3 (s, C^{Ar} or C^{alkyne}), 124.1 (d, C^{Ar}), 127.1 (d, C^{Ar}), 127.2 (d, C^{Ar}*), 127.3 (d, C^{Ar}), 130.4 (d, C9*), 130.4 (d, C9), 130.9 (s, C^{Ar}), 131.2 (d, C10*), 131.2 (d, C10), 131.9 (d, C2*), 131.9 (d, C2), 132.7 (s, C^{Ar}*), 132.7 (s, C^{Ar}), 146.6 (s, C^{Ar}*), 146.7 (s, C^{Ar}), 147.5 (s, C^{Ar}*), 147.6 (s, C^{Ar}), 149.5 (s, C^{Ar}*), 149.5 (s, C^{Ar}), 170.1 (s, C9') ppm.

LC-MS (ESI) **<u>26</u>:** calculated for M+H^+: 663.4, found 663.6
reg-<u>26</u>: calculated for M+H^+: 663.4, found 663.5

E III.2.3 *tert*-Butyl(((3S,Z)-1-(6-((tert-butyldimethylsilyl)oxy)-7-methoxy-3-vinyl-1,3-dihydronaphtho[2,3-c]furan-4-yl)dodec-4-en-1-yn-3-yl)oxy)dimethylsilane (TBDMS-Notoincisol B **28**)



26 M = 663.06 **27** M = 667.09 **28** M = 649.08

Procedure[68] step I: A reaction vessel was charged with a stirring bar and $LiAlH_4$ (1.7 mg, 0.05 mmol, 1.0 equiv.) and sealed with a septum. The atmosphere was changed to argon using standard Schlenk line technique, anhydrous THF (0.3 mL) was added *via* syringe and the resulting suspension was cooled to 0 °C in an ice bath. Meanwhile, in a second reaction vessel, lactone **26** (30.0 mg, 0.05 mmol, 1.00 equiv.) was dissolved in anhydrous THF (0.3 mL, final molarity c = 0.11 M) under argon atmosphere. The solution was added dropwise to the suspension of $LiAlH_4$ at 0 °C resulting in a clear yellow reaction mixture which was stirred at that temperature for 20 min (reaction progress was checked with TLC, LP : EtOAc = 2 : 1).

Work-up step I: Upon completion, the reaction was carefully quenched by slowly adding a saturated aqueous NH_4Cl solution (3 mL). The resulting mixture was thoroughly extracted with EtOAc (5 x 2 mL) and the combined organic phases were washed with brine (1 x 5 mL), dried over Na_2SO_4 and solvents were evaporated under reduced pressure at 30 °C. Time at p_{min} was kept a minimum (instability of diol upon concentrating) and the resulting orange oil was "washed" once with the solvent for the next step (CH_2Cl_2) by dissolving and evaporating again, yielding the intermediate diol **27** quantitatively which was immediately used for the next step without any further purifications.

Procedure[67] step II: Diol **27** (30.0 mg, 0.05 mmol, 1.00 equiv.) was dissolved in anhydrous CH_2Cl_2 (0.6 mL) under argon atmosphere in a sealed (septum) reaction vessel, equipped with a stirring bar. Et_3N (25.0 µL, 0.18 mmol, 4.00 equiv.) was added in one portion and the reaction mixture was cooled to -60 °C in a MeOH / liquid N_2 bath. Meanwhile, in a second reaction vessel Ms_2O (12.0 mg, 0.07 mmol, 1.50 equiv.) was dissolved in anhydrous CH_2Cl_2 (0.2 mL, final molarity c = 0.06 M) under argon atmosphere. The resulting solution was added dropwise to the reaction mixture and the whole mixture was gradually warmed to -20 °C in one hour. Subsequently, the cooling bath was removed and the reaction mixture was allowed to reach rt and stirred for 3 h (reaction progress was checked with TLC, LP : EtOAc = 2 : 1).

Work-up step II: Upon completion, the reaction was cooled to 0 °C and quenched by slowly adding a saturated aqueous NH_4Cl solution (3 mL). The organic phase was diluted with EtOAc (3 mL), layers were separated and the aqueous phase was extracted with EtOAc (3 x 2 mL). The combined organic phases were washed with a saturated aqueous NH_4Cl solution (1 x 2mL) followed by a saturated aqueous $NaHCO_3$ solution (1 x 2 mL) and brine (1 x 2 mL), dried over Na_2SO_4 and solvents were evaporated under reduced pressure. Purification *via* preparative TLC (hexane : EtOAc = 5 : 1) afforded the title compound **28** as a yellow oil.

Reaction scale	30.0 mg (0.05 mmol) of lactone **26**
Reaction time	20 min + 4 h
Yield	5 mg (17%)
Appearance	**27:** orange oil
	28: yellow oil
TLC	**27:** R_f (LP:EtOAc = 2:1) = 0.35
	28: R_f (LP:EtOAc = 5:1) = 0.69
Molecular formula, m.w.	**27:** $C_{39}H_{62}O_5Si_2$, 667.09
	28: $C_{39}H_{60}O_4Si_2$, 649.08
^{1}H-NMR (600 MHz, $CDCl_3$)	**28:** δ = 0.15 – 0.20 (m, 6H, TBDMS (-Si(CH_3)$_2$) / TBDMS* (-Si(CH_3)$_2$), 0.20 – 0.25 (m, 6H, TBDMS (-Si($\underline{C}H_3$)$_2$) / TBDMS* (-Si($\underline{C}H_3$)$_2$), 0.77 – 0.91 (m, 3H, H17 / H17*), 0.93 (s, 9H, TBDMS (-SiC($\underline{C}H_3$)$_3$)), 1.04 (s, 9H, TBDMS (-SiC($\underline{C}H_3$)$_3$)), 1.18 – 1.43 (m, 10H, CH2 (C12-16) / (C12*-16*)), 2.13 – 2.18 (m, 2H, C11), 3.91 (s, 3H, -$\underline{C}H_3$), 5.15 – 5.19 (m, 1H, H9'), 5.18 – 5.21 (m, 1H, H1^{cis} / H1^{cis*}), 5.24 – 5.29 (m, 1H, H9'), 5.45 – 5.49 (m, 2H, H1^{trans} / H1^{trans}*, H8 / H8*), 5.50 – 5.53 (m, 1H, H10 / H10*), 5.64 – 5.71 (m, 1H, H9 / H9*), 5.81 (dd, J = 5.5, 1.5 Hz, 1H, H3), 6.10 – 6.20 (m, 1H, H2), 7.05 (s, 1H, C^{Ar}), 7.45 (s, 1H, C^{Ar}), 7.68 (s, 1H, C^{Ar}) ppm.
^{13}C NMR (150 MHz, $CDCl_3$)	**28:** δ = -4.5 (q, TBDMS (-Si($\underline{C}H_3$)$_2$) and/or *), -4.4 (q, TBDMS (-Si($\underline{C}H_3$)$_2$) and/or *), -4.4 (q, TBDMS (-Si($\underline{C}H_3$)$_2$) and/or *), -4.4 (s, TBDMS* (-Si($\underline{C}H_3$)$_2$)), -4.4 (q, TBDMS (-Si($\underline{C}H_3$)$_2$)), -4.2 (q, TBDMS* (-Si($\underline{C}H_3$)$_2$)), -4.1 (q, TBDMS (-Si($\underline{C}H_3$)$_2$)), 14.2 (q, C17), 18.4 (s, TBDMS* (-Si$\underline{C}$(CH_3)$_3$)), 18.4 (s, TBDMS (-Si$\underline{C}$(CH_3)$_3$)), 18.7 (s, TBDMS (-Si$\underline{C}$(CH_3)$_3$)), 22.8 (t, CH_2 (C12-C16)), 25.9 (q, TBDMS (-SiC($\underline{C}H_3$)$_3$), 26.0 (q, TBDMS* (-SiC($\underline{C}H_3$)$_3$)), 26.0 (q, TBDMS (-SiC($\underline{C}H_3$)$_3$)), 28.0 (t, C11), 29.3 (t, CH_2 (C12-C16)), 29.5 (t, CH_2 (C12-C16)), 29.6 (t, CH_2 (C12-C16)), 31.9 (t, CH_2 (C12-C16)), 55.5 (q, -O$\underline{C}H_3$), 59.9 (d, C8*), 59.9 (d, C8), 72.3 (t, C9'), 79.6 (s, C^{alkyne}*), 79.6 (s, C^{alkyne}), 84.7 (d, C3), 99.6 (s, CAr* or C^{alkyne}*), 99.6 (s, C^{Ar} or C^{alkyne}), 106.9 (d, CAr), 112.4 (s, C^{Ar} or C^{alkyne}), 115.0 (d, C^{Ar}*), 115.0 (d, C^{Ar}), 115.6 (t, C1*), 115.6 (t, C1), 118.5 (d, C^{Ar}*), 118.5 (d, C^{Ar}), 129.5 (s, C^{Ar}*), 129.5 (s, C^{Ar}), 129.8 (s, C^{Ar}), 130.6 (d, C9*), 130.7 (d, C9), 131.2 (d, C10*), 131.2 (d, C10), 135.7 (s, CAr), 136.2 (d, C2*), 136.2 (d, C2), 140.7 (s, C^{Ar}*), 140.7 (s, C^{Ar}), 146.4 (s, C^{Ar}), 151.9 (s, C^{Ar}*), 151.9 (s, C^{Ar}) ppm.

F Appendix

F I Chiral HPLC Analysis of Compound 21

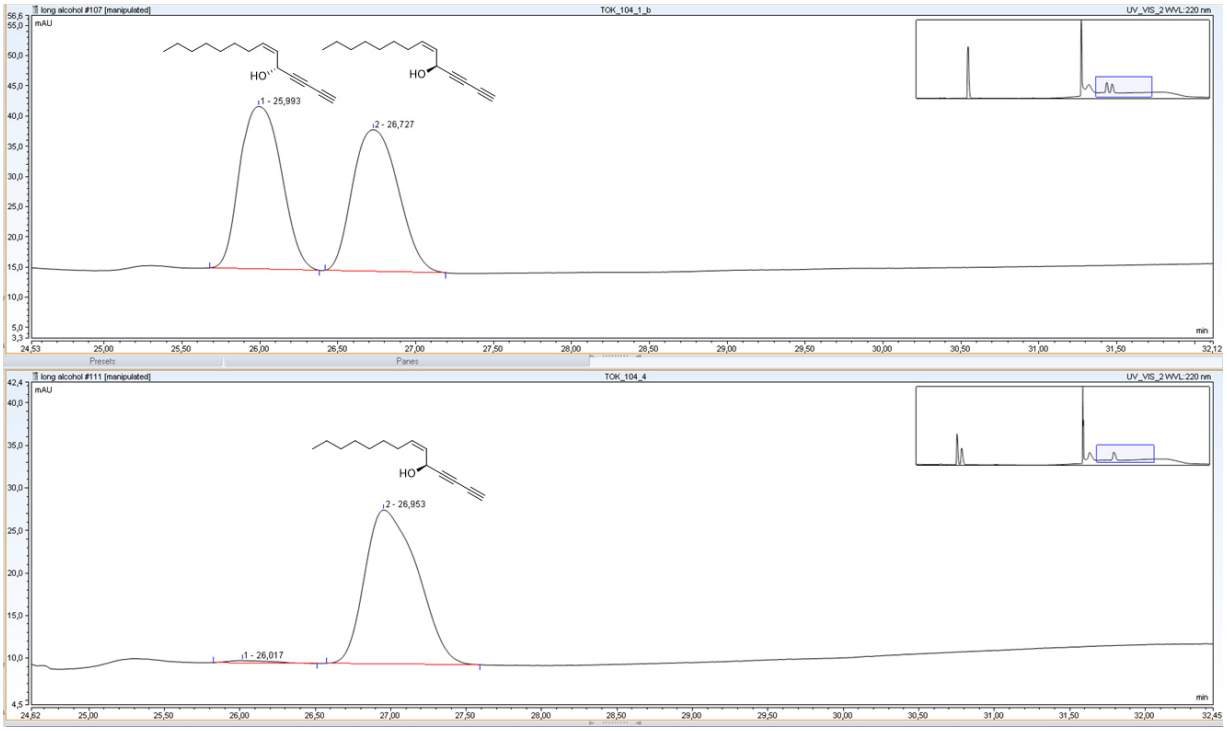


Figure 16: HPLC chromatograms before and after kinetic resolution of compound 21.

F II Curriculum vitae

Personal Profile

Name:	Thomas Kremsmayr
Date of birth:	23.05.1991
Place of birth:	Steyr, Upper Austria
Address:	Döblergasse 1/11, 1070 Vienna, Austria
Mai:	thomas.kremsmayr@gmail.com

Education

2014-2017:	**MSc Technical Chemistry**, TU Wien Studies focused on applied synthetic chemistry with a particular emphasis on bioorganic chemistry and medicinal chemistry.
2015:	**MSc Term Abroad, Technical University of Denmark** Courses in Pharmaceutical Drug Development, Biomolecular Chemistry, Bioinorganic Chemistry and Microbiology.
2010-2014:	**BSc Technical Chemistry**, TU Wien Graduated with distinction.
2001-2009:	**Secondary School – BRG Steyr** Academic secondary school with a focus on natural science – graduated (Matura – equivalent to A-levels).

Research Experience

03/2016-02/2017:	**Master Thesis**, TU Wien Title: "Investigations Towards the Biomimetic Access to Notoincisol B" Supervision: Prof. Marko D. Mihovilovic
06/2014-08/2014:	**Internship Group Prof. Gärtner**, TU Wien Supervision: Assistant Prof. Katharina Schröder, Dr. Anna Ressmann Content: "Toward a benign strategy for the manufacturing of betulinic acid"
02/2013-06/2013:	**Bachelor Thesis**, TU Wien Title: "Synthesis of pyrazoloquinolinones as ligands for $GABA_A$-receptors" Supervision: Prof. Marko D. Mihovilovic, Dr. Laurin Wimmer

06/2014-08/2014:	**Internship Group Prof. Mihovilovic**, TU Wien Supervision: Dr. Laurin Wimmer Content: Studies towards the synthesis of pyrazoloquinolinones and imidazoquinolines as potential $GABA_A$ receptor ligands.

Work Experience

09/2016:	**Student assistant in a laboratory course**, TU Wien Course name: "Fundamentals of Organic Chemistry" at the Institute of Applied Synthetic Chemistry
2015 and 2016:	**Student assistant in a laboratory course**, TU Wien "Synthesis Laboratory Course" at the Institute of Applied Synthetic Chemistry Duration: summer term
2014:	**Student assistant in a laboratory course**, TU Wien "Fundamentals of Chemistry" at the Institute of Applied Synthetic Chemistry Duration: summer term
08/2010:	**Voluntary service and cross-cultural experience** Work in an orphanage in Nairobi, Kenya (Limuru Children's Centre)
10/2009-06/2010:	**Civilian service** Police Department Steyr, Upper Austria

Publications

2017:	Ressmann, A. K.; Kremsmayr, T.; Gaertner, P.; Zirbs, R.; Bica, K., Toward a benign strategy for the manufacturing of betulinic acid. Green Chem. 2017

Language Skills

German:	native
English:	fluent (proficient user, C2, TOEFL IBT (22.02.2014): 110)
French:	solid working knowledge
Danish:	basic communication skills (unit 1 at Danish education 3)

F III List of Abbreviations

aqu.	Aqueous
BAIB	(Diacetoxyiodo)benzene
$BF_3{\cdot}OEt_2$	Boron trifluoride diethyl etherate
DIPEA	N,N-Diisopropylethylamin
DMSO	Dimethyl sulfoxide
EDG	Electron donating group
ee	Enantiomeric access
ESI	Electrospray ionization
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
equiv.	Equivalent
EWG	Electron withdrawing group
HPLC	High-performance liquid chromatography
HR-MS	High-resolution mass spectroscopy
HOMO	Highest occupied molecular orbital
IBX	2-Iodoxybenzoic acid
LA	Lewis acid
LBD	Ligand binding domain
LG	Leaving group
LP	Light petroleum (boiling point approx. 40 – 60 °C)
LUMO	Lowest unoccupied molecular orbital
MeOH	Methanol
MsCl	Methanesulfonyl chloride
Ms_2O	methylsulfonyl methanesulfonate
MTBE	2-Methoxy-2-methylpropan
m.w.	Molecular weight
MWI	Microwave irradiation
NMR	Nuclear magnetic resonance
NEt_3	Triethylamine
$PhNO_2$	Nitrobenzene
ppm	Parts per million (NMR)
R_f	Retention factor (TLC)
rt	Room temperature
SAR	Structure–activity relationship
sat.	Saturated
TEMPO	(2,2,6,6-tetramethyl-piperidin-1-yl)oxyl
TLC	Thin layer chromatography
TMEDA	N,N,N',N'-Tetramethylethylendiamin
TSCl	p-Toluolsulfochlorid
TZDs	Thiazolidinediones

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