UNIVERSITA' DEGLI STUDI DELLA BASILICATA
UNIVERSITÉ DE STRASBOURG

INTERNATIONAL PhD PROGRAM IN SCIENCES – CHEMICAL SCIENCES

ÉCOLE DOCTORALE DES SCIENCES CHIMIQUES UMR 7042

Co-tutorship thesis for the degree of:

Dottore di ricerca dell'Università degli Studi della Basilicata
Docteur de l'Université de Strasbourg
Date of defence**: 8 March 2024**

Scientific disciplinary sector: Supramolecular chemistry / CHIM06

A NEW TOTAL SYNTHESIS OF MYRICANOL:

THE INFLUENCE OF AN ENE-YNE SYSTEM

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Summary

Acknowledgments

I would like to thank Prof. Steve LANNERS, Prof. Irene IZZO, Prof. Stefano SUPERCHI, and Prof. Raphael ROBIETTE for accepting to be members of the jury for my PhD defense.

I want to express my gratitude to my Professor, Dr. Lucia CHIUMMIENTO, whom I met during my undergraduate studies. She has been with me throughout my doctoral journey, and I owe a significant part of who I am, both professionally/scientifically and personally, to her. Her profound knowledge and passion for organic chemistry inspired my interest in the subject, evolving my curiosity into a passion that I have always strived to honor in my own way. My gratitude towards her cannot be adequately conveyed in a few lines; any words would seem trivial compared to my true appreciation.

I extend my thanks to the rest of the research group at the University of Basilicata. I thank Prof. Paolo LUPATTELLI for his constant availability and kindness, supporting me throughout my doctoral studies. I also thank Prof. Maria FUNICELLO for her support and humanity.

Special thanks go to my thesis director, Prof. Gilles HANQUET, who has supported me from the beginning. It has been a great honor to be his student, and I am impressed by his deep knowledge of organic chemistry, as well as his humanity and availability.

I express my gratitude to Dr. Sabine CHOPPIN for the support provided during my doctoral period. Her consistent support was crucial to my doctoral journey, motivating and assisting me during the most challenging moments.

I extend my thanks to the rest of the group at the University of Strasbourg. I thank the research unit director, Frederic LEROUX, as well as Dr. Armen PANOSSIAN, Dr. Morgan DONNARD, Mathieu CHESSE, Didier BOETTGER, Emeric WASIELEWSKI and Alexandre DESTHEVES for their technical, scientific, and administrative support during my time in Strasbourg.

I thank the coordinator, Prof. Patrizia FALABELLA, and the department director, Prof. Roberto TEGHIL, for their support and availability.

I would like to sincerely thank Matteo, whom I met in Strasbourg, for all the advice, help, and shared moments. He has been an important friend and equally valuable support since the early days in Strasbourg.

I express my thanks to friends in Potenza, including Annamaria, Pierantonio, Nunzio, Carlotta, Marilena, Umberto, Marinunzia, Angelica, Francesco, Giuseppe, Incoronata and Francesca. Special thanks to Michele, with whom I shared a significant part of my experiences, happy moments, and concerns. I also thank Fausto, with whom I have shared my journey since the early years of university, thanks to Antonio, Marco, Francesco, Simona, Sara and Annapia; many thanks to Antonio, Letizia, and Francesco for all the moments spent together.

Thanks to friends in Strasbourg, including Youssef, Vera, Yousef, Liset, Aurora, Proveen, Zaur, Francesco, Jeanne, Ilde, Dina, Rauf, Pietro, Giulio, Anna, Emma, Khan, Mauricio, Anthony, Carl, Niels, Vera, and Sofia. I have shared many of my best moments in Strasbourg with them

I thank Valentina, who has always been by my side, in both good and bad times, sharing among the happiest moments of my life and, in some way, even the saddest and most painful ones.

I express my gratitude to my colleagues Canio, Federica, Anna, and Giusy for their support and for sharing anxieties and concerns with me.

I extend my thanks to the colleagues in Strasbourg: Nicolas, Florian, Anais, Lilian, Celia, Geoffrey, Guillaume, Armand, Augustin, Amelia, and Stephane, for their warm welcome, assistance, and all the beautiful moments shared.

I thank my family, my mother Maria, my father Giovanni, my brother Francesco, and his girlfriend Anastasia. I express my gratitude to my grandmother Lucia, my uncle Rocco, and my grandfather Salvatore, who left us during my doctoral journey. Your memory will always remain alive in me, and I dedicate this doctoral thesis to you.

Abstract – English

A new total synthesis of myricanol:

The influence of an ene-yne system

Introduction

Myricanol is a cyclic diarylheptanoid ([7,0]-meta,meta-cyclophane) belonging to the class of diarylheptanoids (**Figure 1**), extracted from various species within the *Myricaceae* family such as *Myrica conifera*[1], *Myrica nagi*[2], *Myrica gale*[3], and particularly from *Myrica rubra*[4]. Diarylheptanoids are widely known for their anti-inflammatory, antioxidant, antitumor, hepatoprotective, and neuroprotective properties[5].

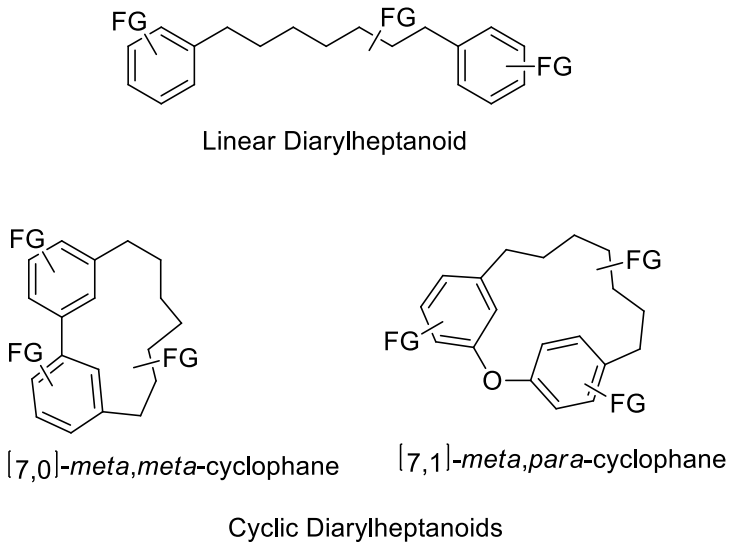


Figure 1. Diarylheptanoids

The main objective of this thesis is the total synthesis of myricanol (**Figure 1**), a natural compound with significant biological activities[6]. In particular, its remarkable anti-Alzheimer's properties make it a potential drug for the treatment of various tauopathies, as it has the ability to reduce levels of tau protein that tend to pathologically accumulate in phosphorylated forms in certain neurodegenerative diseases[6].

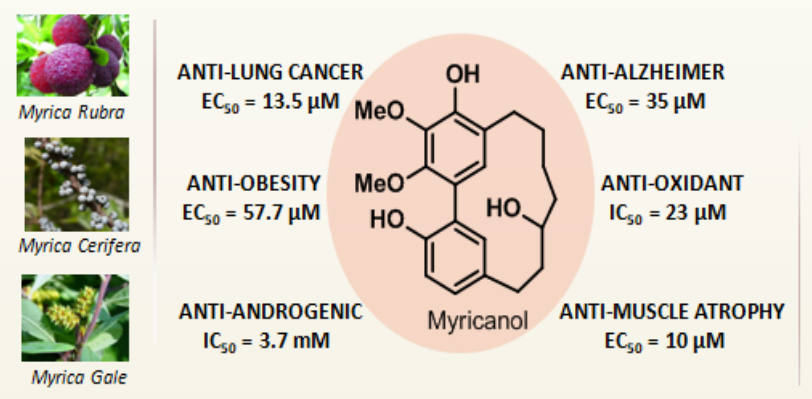
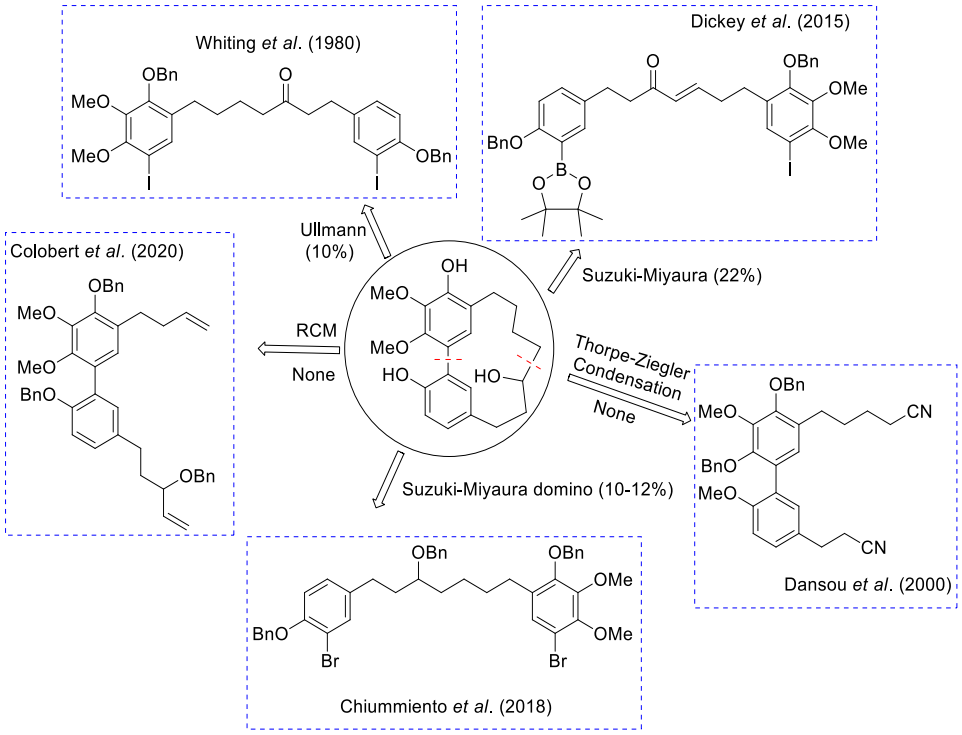


Figure 2. Biological activities

The following **Scheme 1** briefly illustrates the synthetic approaches reported in the literature[6]; 2 synthesis attempts and 3 total syntheses are outlined. The best result, in terms of yield, was achieved in 2018[7] by the research group where this thesis work was conducted, obtaining racemic myricanol in 9 steps with a 4.9% yield, a competitive yield if compared to the result obtained by Dickey *et al.* in 2015[8] (2.0% yield in 7 steps but starting from non-commercial compounds).

The first synthesis attempt of myricanol dates back to 1980 by Whiting and coworkers[9] with a 0.21% yield in 14 steps. A subsequent attempt to synthesize a methyl-myricanone analog took place in 2000 by Dansou and colleagues[10]; finally, the last synthesis attempt was carried out by Colobert *et al.* in 2020[11] using a ring-closing metathesis that, however, resulted in an undesired dimer. The same research group[12] later published the synthesis of isomiricanol (an *ortho,meta*-cyclophane) using the same cyclization reaction as the previous synthesis attempt, achieving high yields. According to these results, it is evident that the strong ring strain inherent in *meta,meta*-cyclophanic systems is responsible for the poor reactivity of those substrates towards macrocyclization, hence the need to explore alternative synthetic strategies.



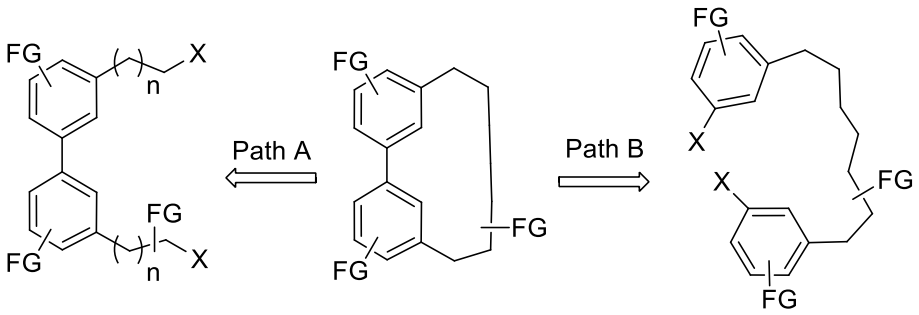
Scheme 1. Total synthesis

Retrosynthetic approaches

Generally, retrosynthetic approaches for the preparation of cyclic diarylheptanoids can be broadly divided into 2 main categories (**Scheme 2**):

Path A: The macrocyclization is performed on the diaryl system, building the heptanoic chain in the final stage; examples of this approach are the two synthesis attempts in **Scheme 1** (Dansou et al. and Colobert et al.)[10,11.]

Path B: The macrocyclization involves the properly functionalized biaryl system; examples of this category include the three total syntheses reported in the literature and outlined in the previous **Scheme 1**[7-9].



Scheme 2. Retrosynthetic approaches

Both synthetic approaches, path A and path B, have been explored in the course of this thesis and will be discussed below.

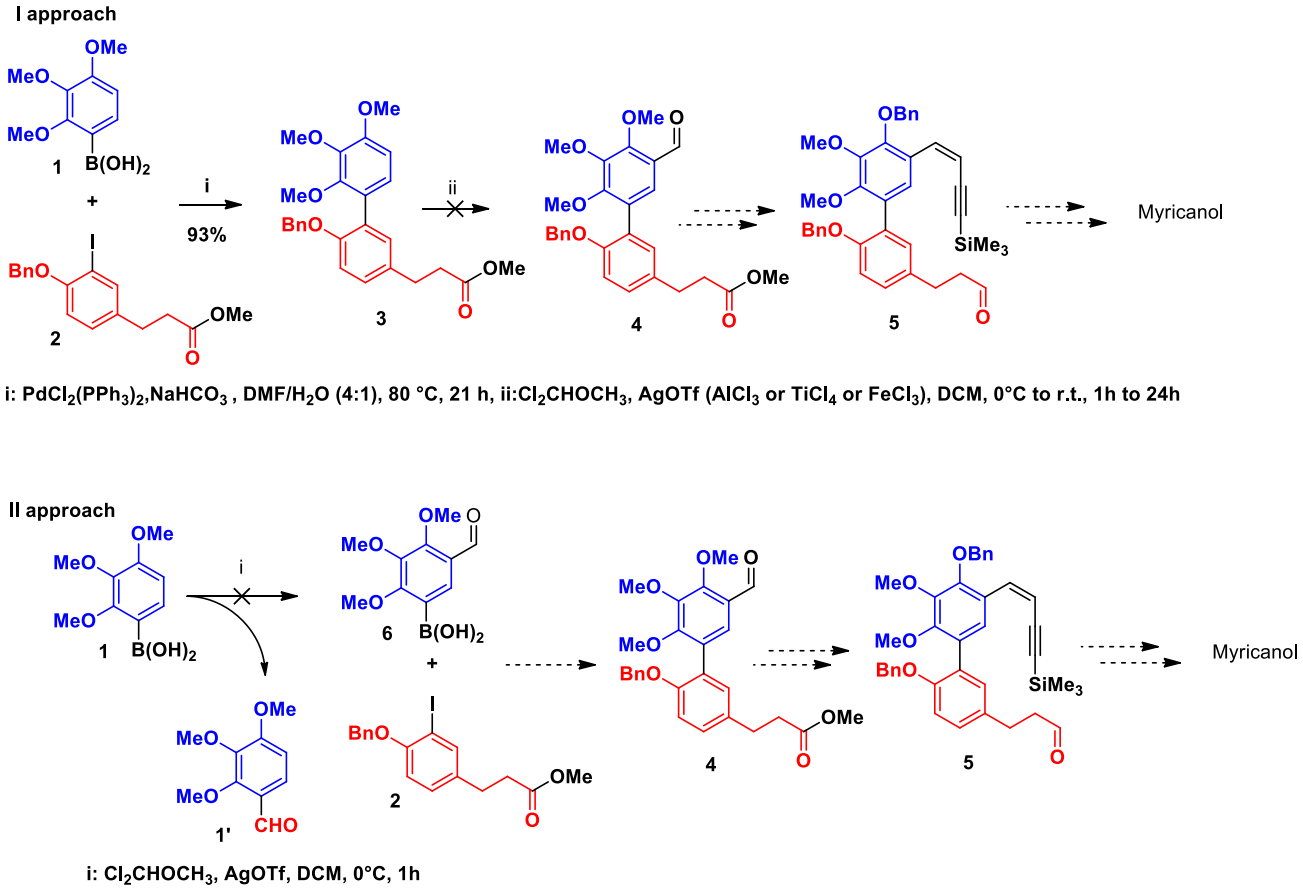
Firstly, this thesis aims primarily to investigate the optimal conditions to make cyclization less unfavorable using an unsaturated and thus "rigid" seco-precursor to limit conformational degrees of freedom during cyclization.

In other words, a higher degree of unsaturation would lead to a less significant entropy change, and at the same time, the presence of *cis* double bonds would ensure a higher probability of "encounter" between the ends involved in cyclization. For these reasons, the main objective of this thesis was the synthesis of polyunsaturated acyclic systems to study the influence of such systems on macrocyclization.

Path A

Path A. First synthetic approach

The first approach (I) involved a cross-coupling reaction between two commercial compounds (**1** and **2**), followed by a formylation of the resulting biaryl compound, and then a Julia olefination, cyclization, and reduction. However, this strategy was abandoned since the formylated biaryl system (**4**) was not obtained with a good yield.

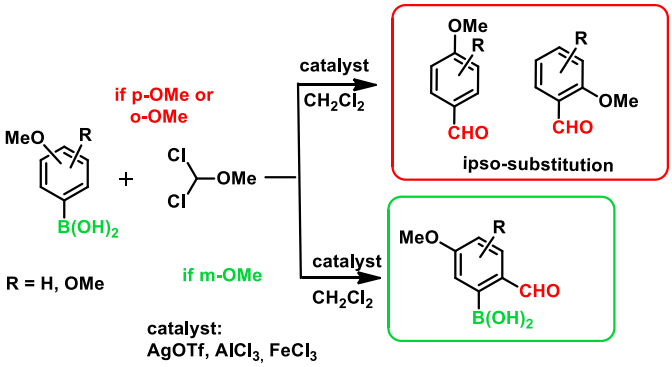


Scheme 3. First and second synthetic approaches

Path A. Second synthetic approach

In the second synthetic approach (II), an attempt was made to overcome the formylation of the biaryl system by formylating an arylboronic acid (**1**) prior to its use in the subsequent cross-coupling reaction. This was expected to lead to the formation of the desired biaryl aldehyde **4**.

Unexpectedly, formylation resulted in the formation of an *ipso*-formylated compound (compound **1'**). This undesired outcome provided the basis for an extensive formylation study on various electron-rich arylboronic acids using three different formylation conditions, those results were published[13] (**Scheme 4**)

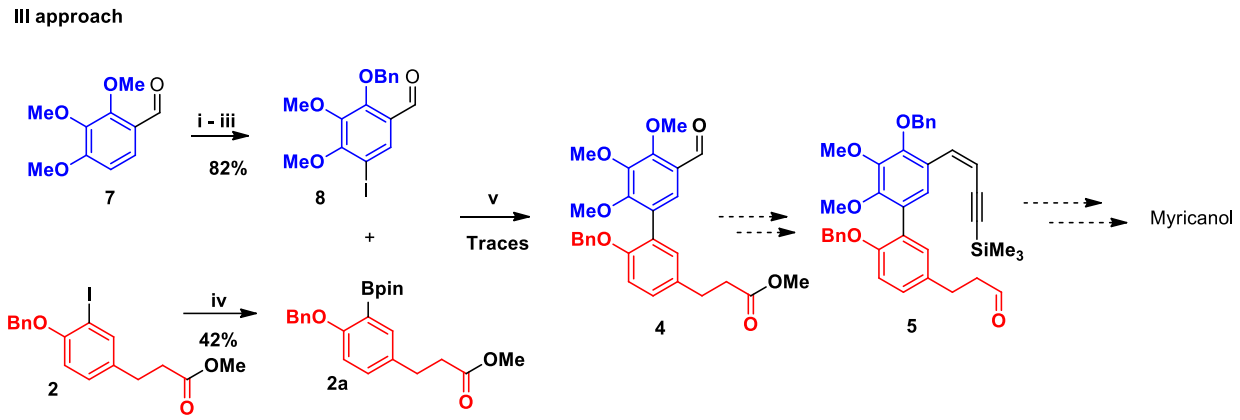


Scheme 4. Rieche formylation on boronic acids

Path A. Third synthetic approach

The third synthetic approach (**Scheme 5**), compared to the previous ones, involved the generation of arylboronic acids through the borylation of their respective aryl halides. The arylboronic ester was generated on the less electron-rich system and was coupled with the iodinated benzaldehyde (**8**) through an intermolecular Suzuki reaction. Unfortunately, the various coupling attempts did not yield the expected product in good yields, providing almost exclusively the deiodinated compound. It was considered to reverse the roles of the coupling partners and thus the arylboronic ester was generated on compound **7** and was coupled with the halogenated ester **2**.

Unfortunately, even in this case, the desired biaryl compound **4** was not obtained.



i. $AlCl_3$ (3.8 eq), NaI (2.7 eq), DCM/ACN 1/1, r.t., 4h; ii. I_2 (1.5 eq), Ag_2SO_4 (1.5 eq), DCM, r.t., 6h; iii. BnBr (1.2 eq), K_2CO_3 (2.0 eq), MeCN, 55°C, 12h; iv $B_2(pin)_2$, KOAc,$PdCl_2(dppf)_2$-CH_2Cl_2 80°C, v $PdCl_2(PPh_3)_2$ (or $Pd(dppf)Cl_2$), Base, Solvent, 80 to 100 °C, 20 to 26h.

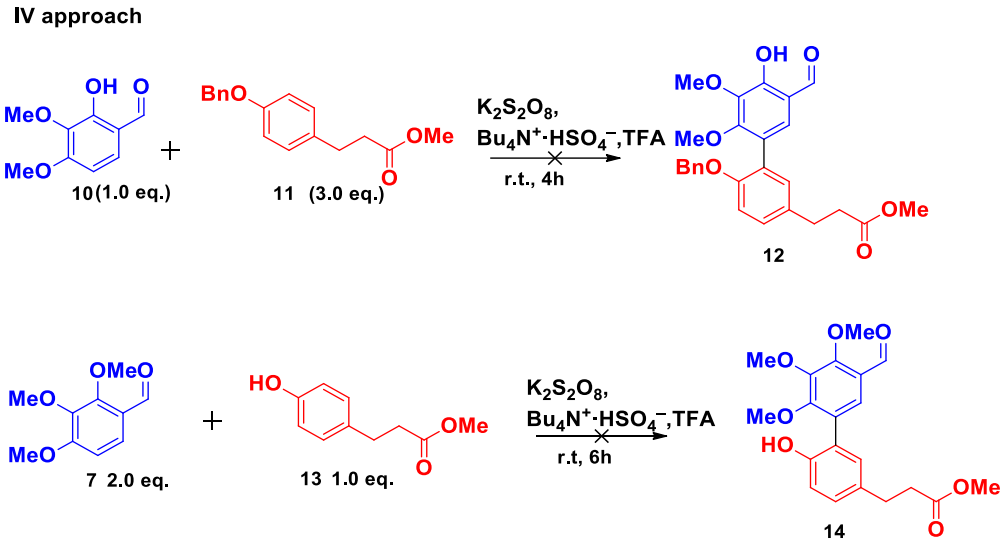
Scheme 5. Third synthetic approach

Path A. Fourth synthetic approach

The fourth approach involved a radical cross-coupling between the dehalogenated fragments **10** and **11** **(Scheme 6)**.

This fourth synthetic strategy appears to be the most direct, but dealing with multifunctionalized products could lead to various side reactions: the mechanism proceeds through the formation of the phenoxide radical, which could directly react or rearrange by delocalizing the radical to the *para* position. At this point, the *ortho*-directed coupling on the deactivated aromatic system would lead to the formation of the desired product.

Alternatively, the roles of coupling partners were reversed. Starting from trimethoxybenzaldehyde (**7**) and phenol **13** (**Scheme 6**), but unfortunately, this last attempt did not yield the expected product **14**.



Scheme 6. Radical cross-coupling reactions

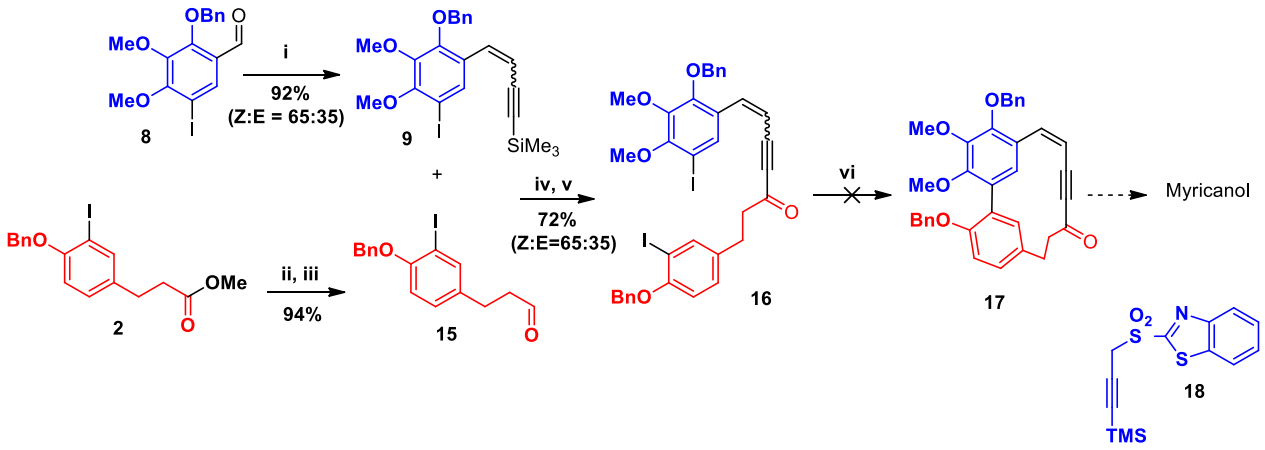
Path B

Path B. First synthetic approach

The path B was also considered, aiming an intramolecular cross-coupling on a linear diarylheptanoid (**Scheme 7**).

The ene-yne (**9**) was synthesized with an excellent overall yield, although the two *cis* and *trans* stereoisomers were not separable. The subsequent addition reaction presented several issues: the acetylide resulting from fluoride-mediated desilylation could act as a nucleophile, providing the coupled system, or act as a base, deprotonating the propionic aldehyde and leading to the self-condensation product. Various conditions were tested, and finally, the maximum yield obtained was 86%, with 65% of the cis system, subsequently oxidized to ketone (**16**).

The synthesized product underwent a Suzuki-Miyaura domino reaction, resulting in substrate degradation with no trace of the desired cyclization compound (**17**).

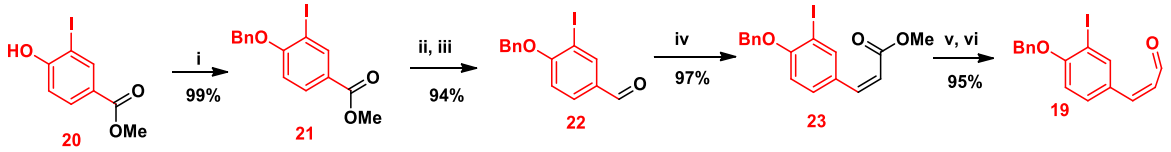


i: KHMDS (1.5 eq), **13** (1.6 eq), THF, -65°C, 12h; ii: DIBALH (2 eq), DCM, -60°C, 2h; iii: Dess-Martin periodinane (1.5eq), DCM, 0°C, 3h, vi: TBAF (0.15eq), THF, ref, 1h; v: Dess-Martin periodinane (1.5eq), DCM, -10°C, 3h; vi: $Pd(dppf)Cl_2$ (0.1 eq), KOAc(10 eq), $B_2(pin)_2$ (1.2 eq.) DMSO, 80°C, 1h.

Scheme 7. Path B. First synthetic approach

Path B. Second synthetic approach

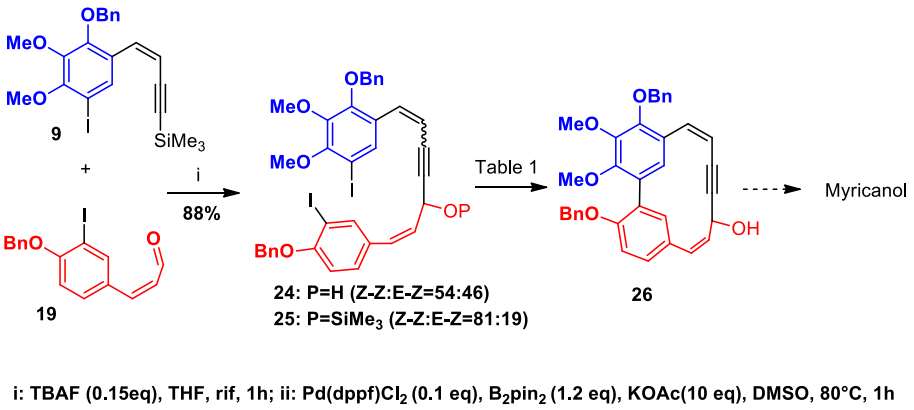
In order to test the macrocyclization on a more "rigid" and directed system, a second *cis* double bond was introduced, making the aldehyde **19** non-enolizable (**Scheme 8**).



i: BnBr (1.2 eq), K_2CO_3(2.0 eq), MeCN, 55°C, 14h; ii: Dibal-H (2.0 eq), DCM, -60°C, 3h; iii: Dess-Martin Periodinane, DCM, 0°C, 3h; iv: Bis(2,2,2-trifluoroethyl)(methoxy-carbonylmethyl)phosphinate (1.5 eq), 18-Crown-6 (5.5eq), KHMDS (2.0 eq), THF, -78°C, 14h; v: Dibal-H (2.0 eq), DCM, 2h; vi: Dess-Martin Periodinane (1.5 eq), DCM, 0°C, 3h.

Scheme 8. Synthesis of **19**

Under the tested reaction conditions, using TBAF or TBAT as fluoride donors, the cis-**19** aldehyde isomerized into the trans-aldehyde, which was unreactive under the tested reaction conditions (**Scheme 9**). The addition reaction, carried out with 0.15 equivalents of TBAF in THF at reflux for one hour, yielded a mixture of **24** (Z-Z: E-Z = 54: 46) and **25** (Z-Z: E-Z =81: 19) with a yield of 88% (**24**: **25** = 4: 1).



Scheme 9. Path B. Second synthetic approach

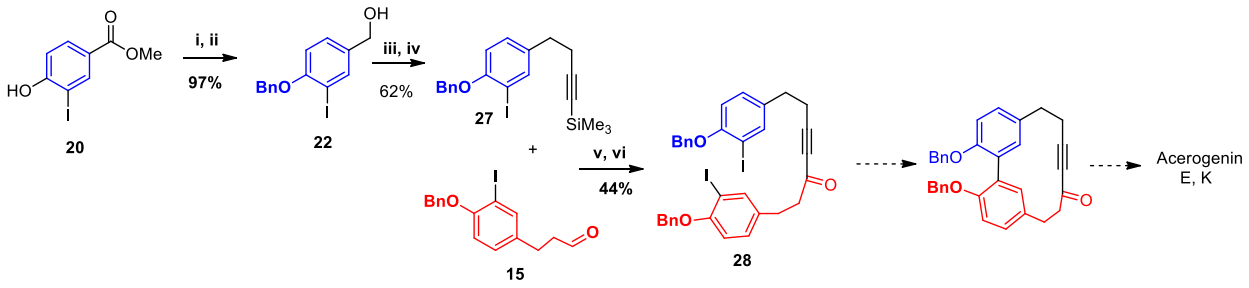
The *seco*-precursor was obtained with excellent yield and subjected to various Suzuki-Miyaura domino cyclization conditions. If the reaction was carried out at 80°C, degradation is observed within a few minutes on both the silyl ether (**25**) and the free alcohol (**24**). In a single case, traces of the desired cyclized product (**26**) were observed. Ullmann Pd-, Ni-, or Cu-catalyzed reactions were also tested, some of those attempts are reported in **Table 1**. The desired cyclized product was obtained only in traces in a Suzuki-Miyaura trial on substrate **24**.

Entry	Sub	Catalyst	T°C	Conv	Result
1	**24**	$PdCl_2(dppf)$, B_2pin_2	80	100	Cyclization (Traces)
2	**24**	Cu	120	10	Dehalogenation
3	**24**	$NiCl_2(PPh_3)_2$, Zn	60	100	Degradation
4	**24**	$PdCl_2(dppf)$	80	100	Degradation
5	**25**	$PdCl_2(dppf)$, B_2pin_2	80	100	Degradation
6	**25**	Cu	120	100	**24** + dehalogenation (traces)
7	**25**	$NiCl_2(PPh_3)_2$, Zn	60	100	**24**

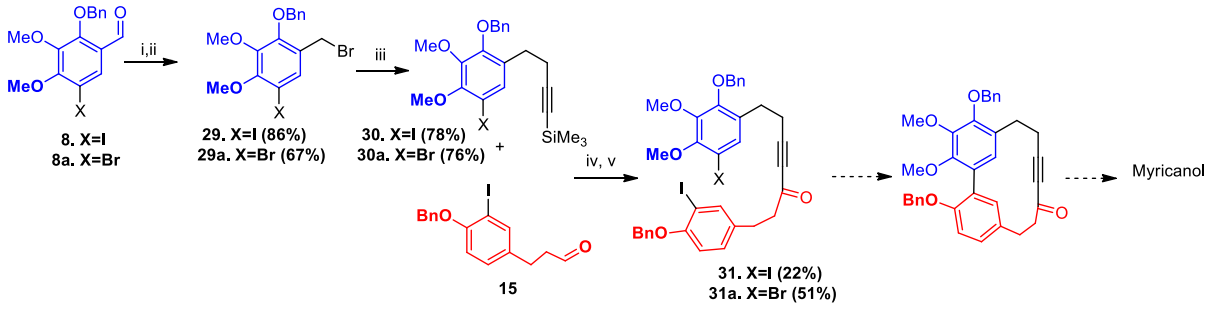
Table 1. Macrocyclization attempts on **24** and **25**

Path B. Third synthetic approach.

Less strained and simpler cyclic systems without *cis* double bonds were identified, and synthetic strategies were designed for them (**Scheme 10**). Therefore, a parallel study aimed to the total synthesis of acerogenin E and K, simpler cyclic diarylheptanoids, was conducted (**Scheme 10**).



i. BnBr (1.2 eq), K_2CO_3 (1.5 eq.), ACN, r.t., 14h;ii. DibaI-H (2.5 eq.),DCM, 0°C, 6h;55°C, 12h; iii. Br_2 (1.5eq), PPh_3 (2.0 eq), Imidazole (3.0 eq), DCM, 0°C, 1h; iv 1-TMS-Propyne (1.7eq), n-BuLi (1.5eq), THF, 0°C to -78°C, 1h; v TBAF (0.15 eq), THF, Ref, 1h; vi. Dess-Martin periodinane (1.5 eq), DCM, 0°C, 3h.



i: DibaI-H (2.0 eq), -60°C, DCM, 1h; ii: Br_2 (1.5eq), PPh_3 (2.0 eq), Imidazole (3.0 eq), DCM, 0°C, 1h; iii. 1-TMS-Propyne (1.7eq), n-BuLi (1.5eq), THF, 0°C to -78°C, 1h; iv TBAF (0.15 eq), THF, Ref, 1h; v. Dess-Martin periodinane (1.5 eq), DCM, 0°C, 3h.

Scheme 10. Path B. Third synthetic approach

The first Ni-catalyzed cyclization trials conducted on substrate **28** yielded encouraging results. Currently, the cyclization on compound **28** (for the synthesis of acerogenin E and K) and on compounds **31** and **31a** (for the synthesis of miricanol) is under optimization.

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Abstract- <u>Italiano</u>

Un nuovo approccio alla sintesi del miricanolo: l' influenza del sistema ene-ino.

Introduzione

Il miricanolo è un diarileptanoide ciclico ([7,0]-*meta,meta*-ciclofano) appartenente alla classe dei diarileptanoidi (**Figura 1**) estratto da diverse specie appartenenti alla famiglia delle *Myricaceae* come la *Myrica conifera*[1], *Myrica nag*i[2], *Myrica gale*[3] ed in particolare la *Myrica rubra*[4].

I diarileptanoidi sono ampiamente conosciuti per le loro proprietà antinfiammatorie, antiossidanti, antitumorali, epatoprotettive e neuroprotettive[5].

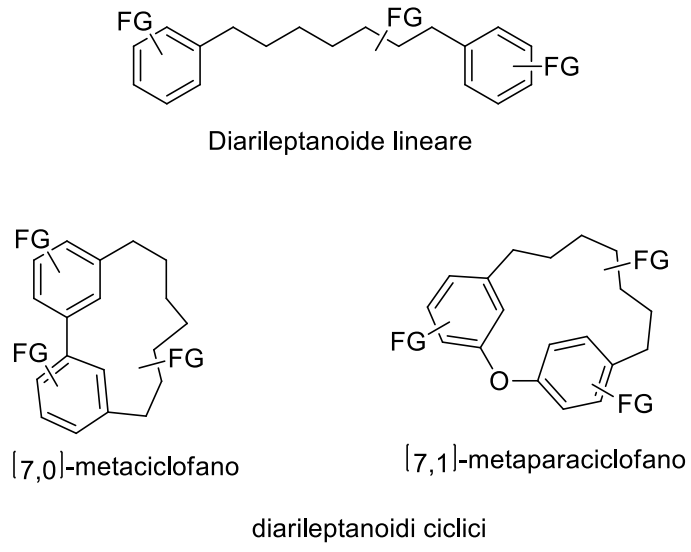


Figura 1.Diarileptanoidi

Il principale obiettivo di questa tesi di dottorato è una nuova sintesi totale del miricanolo (**Figura 1**), composto naturale con importanti attività biologiche[6]. In particolare, le sue notevoli proprietà anti-Alzheimer lo rendono un potenziale farmaco per il trattamento di varie taupatie, in quanto è in grado di ridurre i livelli di proteina tau che tendono ad accumularsi in forma fosforilata in modo patologico in certe malattie neurodegenerative[6].

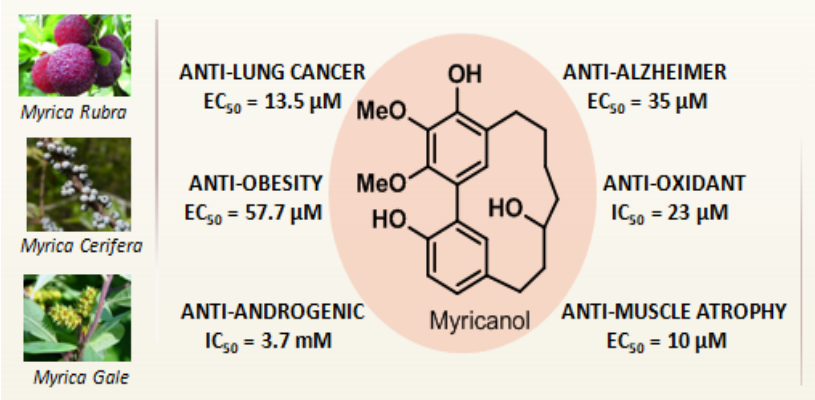
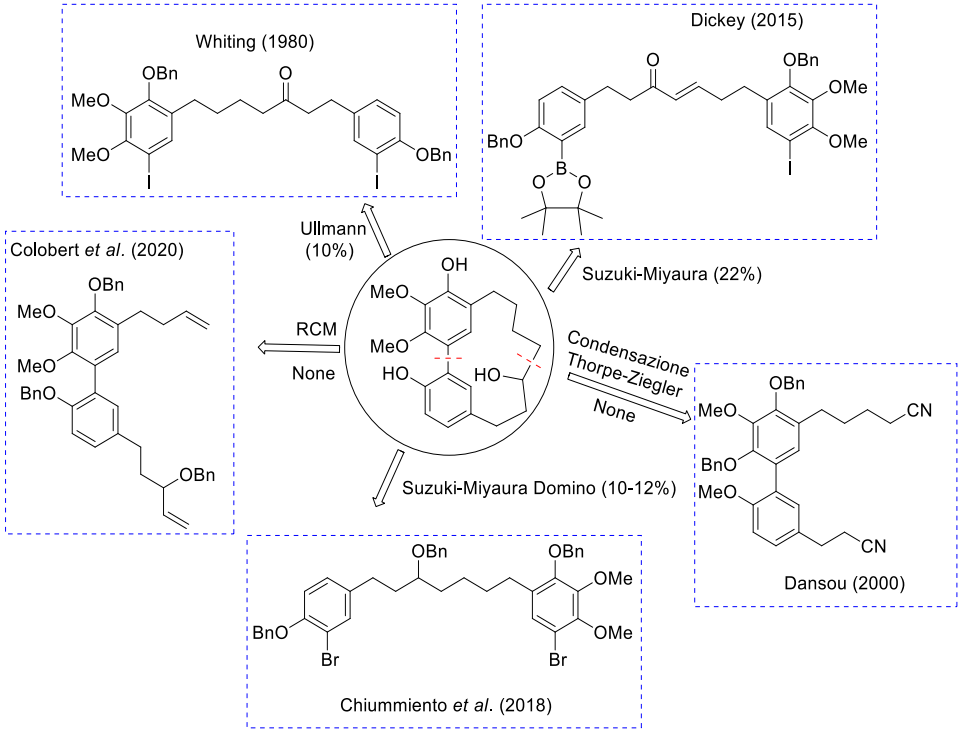


Figura 2. Attività biologiche del miricanolo

Lo **Schema 1** seguente mostra brevemente gli approcci sintetici riportati in letteratura[6]; Sono riportati 2 tentativi di sintesi e 3 sintesi totali. Il miglior risultato, in termini di resa, è stato ottenuto nel 2018[7] dal gruppo di ricerca presso cui è stato eseguito questo lavoro di tesi, ossia, è stato ottenuto il miricanolo in forma racemica in 9 passaggi con il 4.9% di resa, un risultato competitivo rispetto a quanto ottenuto dal gruppo di ricerca americano di Dickey e collaboratori nel 2015[8] con il 2.0% di resa in 7 passaggi ma partendo da frammenti non commerciali.

Il primo tentativo di sintesi del miricanolo risale al 1980 ad opera di Whiting e collaboratori[9] con appena lo 0.21% di resa in 14 passaggi. Un successivo tentativo di sintesi del metil-miricanone analogo risale al 2000 ad opera di Dansou e collaboratori[10]; infine, l' ultimo tentativo di sintesi è stato effettuato da Colobert *et al.* nel 2020[11] , stesso gruppo di ricerca presso il quale è stato svolto questo lavoro di tesi, mediante una ring-closing metatesi che ha però portato ad un dimero indesiderato. Lo stesso gruppo di ricerca,[12] ha successivamente pubblicato la sintesi dell' isomiricanolo (un *orto,meta*-ciclofano) utilizzando la medesima reazione di ciclizzazione utilizzata per il tentativo di sintesi precedente, ottenendo rese elevate . Da questi risultati si evince che la forte tensione d' anello propria

dei sistemi *meta,meta*-ciclofanici è responsabile della scarsa reattività dei substrati coinvolti nella macrociclizzazione e dunque ne deriva la necessità di ricercare strategie sintetiche alternative per la sintesi di questi composti.



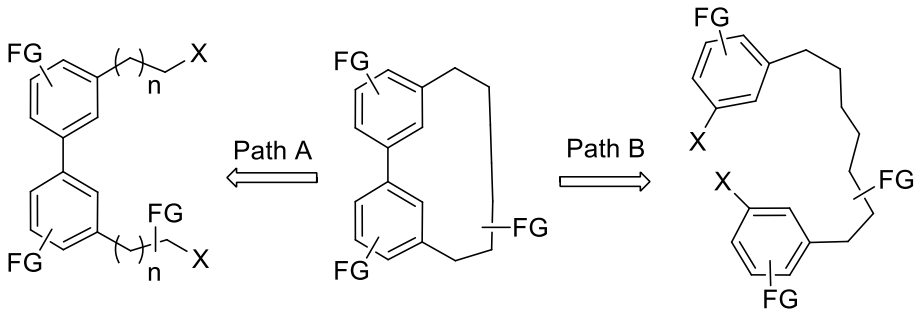
Schema 1. Sintesi totali

Approcci sintetici:

Generalmente, gli approcci retrosintetici per la preparazione di diarileptanoidi ciclici possono essere sommariamente suddivisi in 2 categorie (**Schema 2**):

- Path A la macrociclizzazione viene effettuata sul sistema biarilico cercando di costruire nello stadio finale la catena eptanoica; ne sono un esempio i due tentativi di sintesi dello **Schema 1** (Dansou *et al.* e Colobert *et al.*) [10,11]

- Path B : :la macrociclizzazione interessa il sistema biarilico opportunamente funzionalizzato; a questa categoria appartengono, ad esempio, le tre sintesi totali riportate in letteratura e riportate nello **Schema 1** precedente.



Schema 2. Approcci retrosintetici

Entrambi gli approcci sintetici, path A e path B, sono stati esplorati nel corso di questa tesi e verranno discussi di seguito.

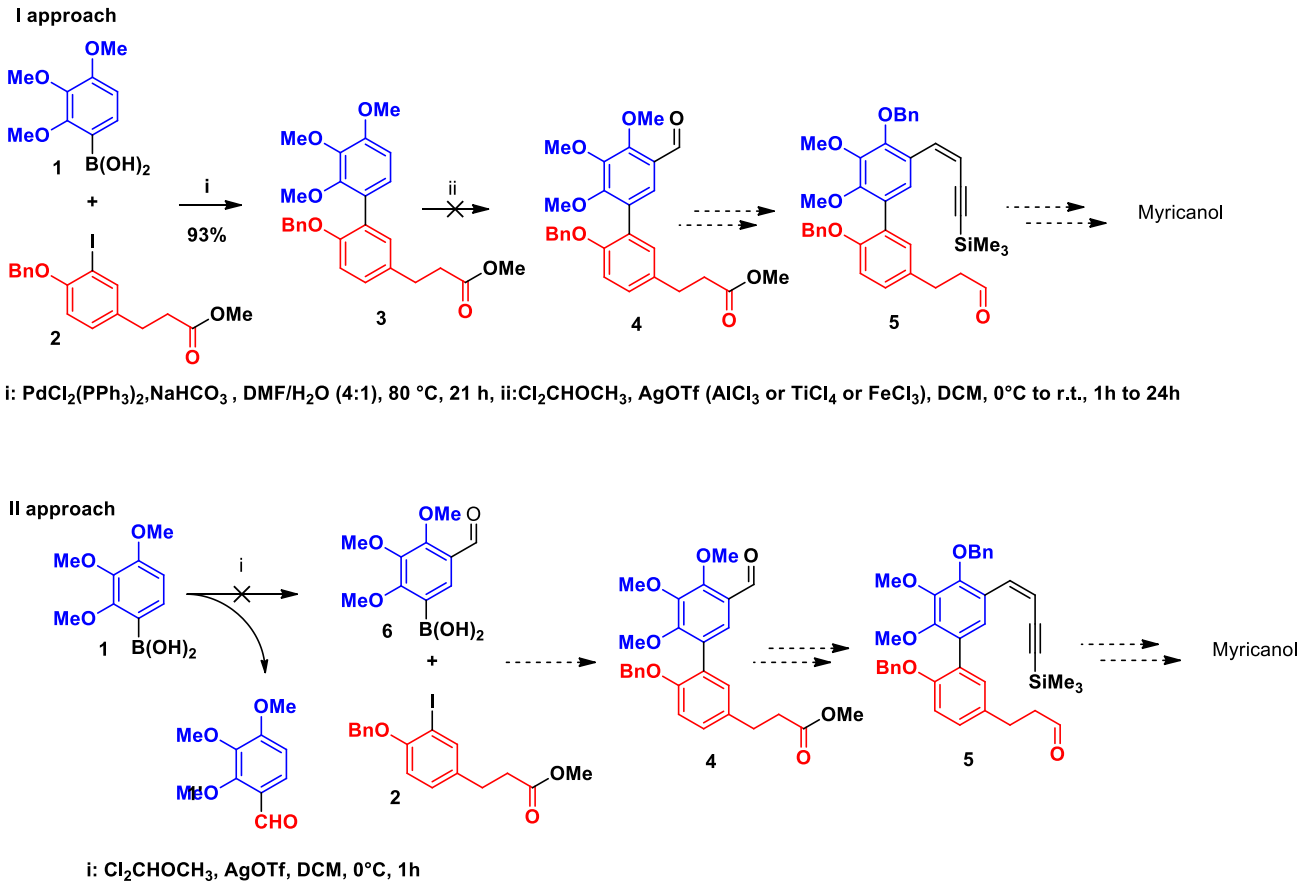
In primo luogo, questa tesi mira principalmente ad indagare le condizioni ottimali per rendere la ciclizzazione meno sfavorita utilizzando un *seco*-precursore insaturo e quindi "rigido" per limitare le variazioni dei gradi di libertà conformazionali durante la ciclizzazione. In altre parole, il maggiore grado di insaturazione porterebbe a una variazione dell'entropia meno significativa e, allo stesso tempo, la presenza di doppi legami *cis* garantirebbe una maggiore probabilità di "incontro" tra le estremità coinvolte nella ciclizzazione. Per questi motivi, l'obiettivo di questa tesi è stato la sintesi di sistemi aciclici poliinsaturi e lo studio dell' influenza di tali sistemi sulla macrociclizzazione.

Path A

Path A. Primo approccio sintetico

Nel tentativo di partire da un sistema biciclico e quindi seguire la via A, il primo approccio (I) ha previsto una reazione di cross-coupling tra due composti commerciali (**1** e **2**), seguito dalla formilazione del composto biarilico risultante e quindi da una olefinazione di Julia, ciclizzazione e riduzione.

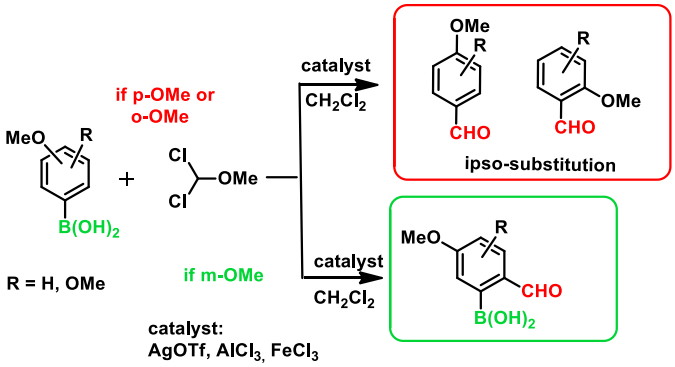
Tuttavia, questa strategia è stata abbandonata a causa della difficoltà di formare il sistema biarilico formilato (**4**).



Schema 3. Primo e secondo approccio sintetico

Path A. Secondo approccio sintetico

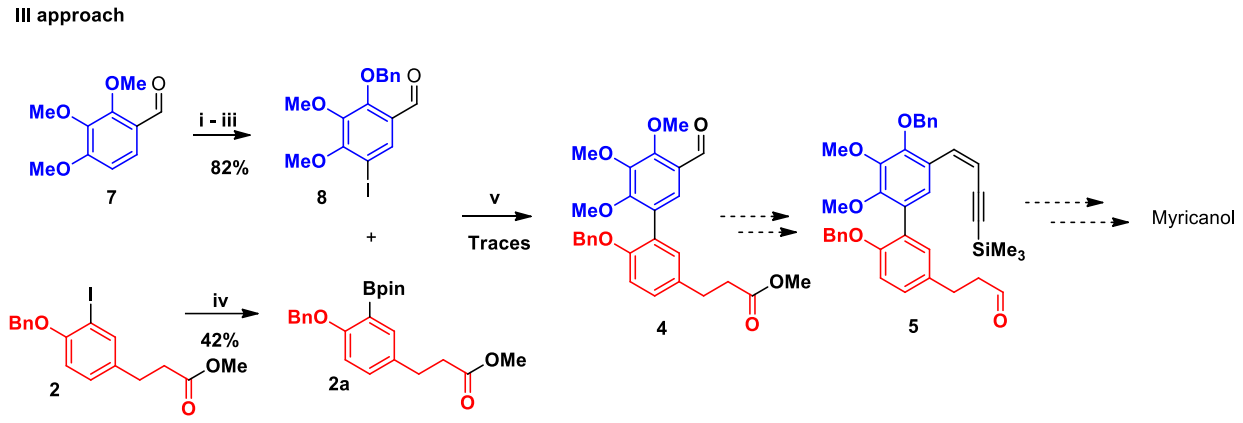
Nel secondo approccio sintetico (**II**) si è cercato di oltrepassare la formilazione del sistema biarilico effettuando la formilazione prima di un acido arilboronico (**1**), da utilizzare nella successiva reazione di cross-coupling, che avrebbe portato alla formazione dell' aldeide biarilica **4** desiderata ; inaspettatamente, la formilazione ha portato alla formazione di un composto *ipso*-formilato (composto **1'**). Questo risultato indesiderato ha fornito l'idea per uno studio estensivo di formilazione su diversi acidi arilboronici elettron-ricchi utilizzando tre differenti condizioni di formilazione ed i risultati ottenuti sono stati pubblicati[13] (**Schema 4**),



Schema 4. Formilazione di Rieche di acidi arilboronici

Path A. Terzo approccio sintetico

Il terzo approccio sintetico (**Schema 5**), rispetto ai precedenti, ha comportato la generazione degli acidi arilboronici dei partner di accoppiamento, Si è cercato di generare l'estere arilboronico sull'arile meno ossigenato e accoppiarlo con la benzaldeide iodurata (**8**) tramite una reazione di Suzuki intermolecolare. Purtroppo, i vari tentativi di accoppiamento effettuati non hanno portato al prodotto atteso con buone rese, fornendo quasi esclusivamente il composto deiodurato. Si è pensato di invertire i ruoli dei partner di accoppiamento e dunque di generare l'estere arilboronico sul composto **7** e di accoppiarlo con l' estere **2**, purtoppo, anche in questo caso, non è stato ottenuto il composto biarilico **4**.



i. $AlCl_3$ (3.8 eq), NaI (2.7 eq), DCM/ACN 1/1, r.t., 4h; ii. I_2 (1.5 eq), Ag_2SO_4 (1.5 eq), DCM, r.t., 6h; iii. BnBr (1.2 eq), K_2CO_3 (2.0 eq), MeCN, 55°C, 12h; iv $B_2(pin)_2$, KOAc,$PdCl_2(dppf)_2$-CH_2Cl_2 80°C, v $PdCl_2(PPh_3)_2$ (or $Pd(dppf)Cl_2$), Base, Solvent, 80 to 100 °C, 20 to 26h.

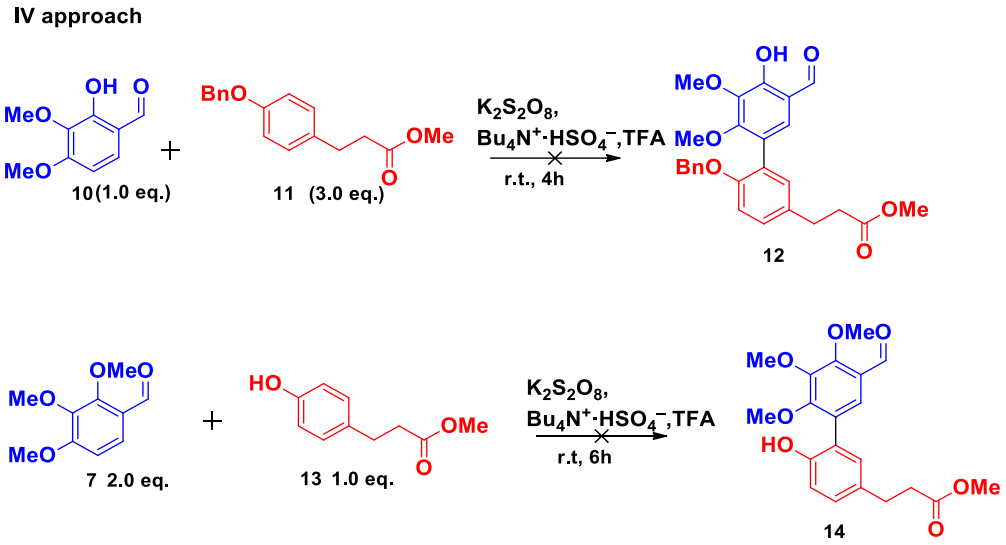
Schema 5. Terzo approccio sintetico

Path A. Quarto approccio sintetico

Il quarto possibile approccio ha consistito nell' utilizzo di frammenti dealogenati (**10** e **11**) accoppiati mediante formazione di radicali.

Questa quarta strategia sintetica appare la più immediata, ma dovendo operare con prodotti polifunzionalizzati diverse potrebbero essere le reazioni collaterali coinvolte: il meccanismo procede attraverso la formazione del radical-fenato, questi può reagire tal quale (prodotto collaterale) o riarrangiare delocalizzando il radicale in *para*; a questo punto l' accoppiamento *orto*-direzionato sull' aromatico disattivato porterebbe alla formazione del prodotto desiderato.

In alternativa, sono stati invertiti i ruoli dei partners di accoppiamento, ossia, partendo dalla trimetossibenzaldeide **(7)** e dal fenolo **13 (schema 6)**, è stato effettuato un tentativo di cross-coupling radicalica che non ha però fornito il prodotto atteso **14**.



Schema 6. Cross-coupling radicalico

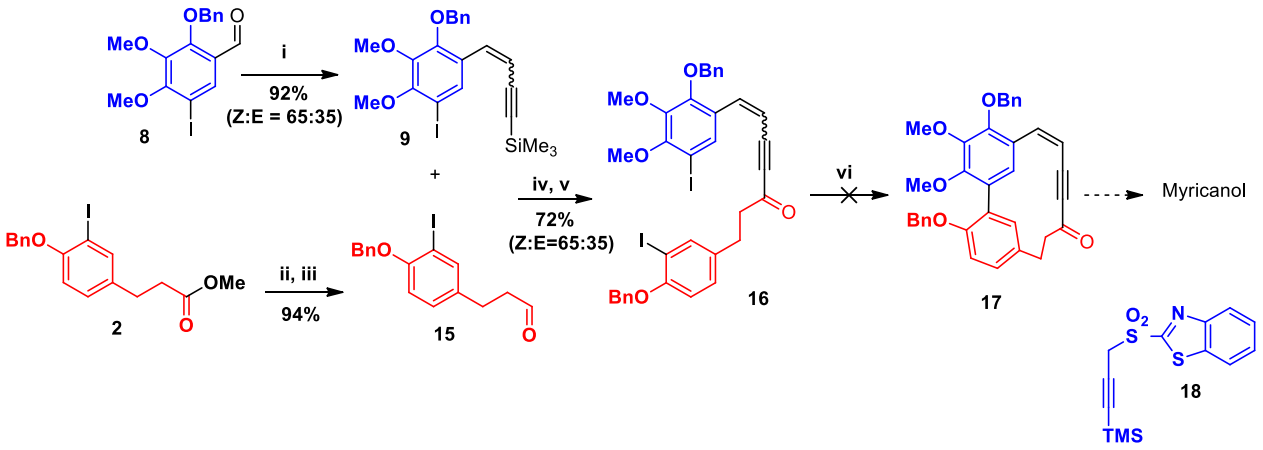
Path B

Path B. Primo approccio sintetico

Anche la strategia B è stata valutata, considerando di costruire (**Schema 7**), dapprima la catena laterale ed eseguire la macrociclizzazione mediante formazione del legame biarilico.

L' ene-ino (**9**) è stato sintetizzato con un'eccellente resa complessiva, sebbene i due stereoisomeri *cis* e *trans* non fossero separabili. La reazione di addizione successiva ha presentato diversi problemi: l'acetiluro risultante dalla desililazione mediata da fluoruro poteva agire da nucleofilo, fornendo il sistema accoppiato, oppure agire da base, deprotonando l'aldeide propionica e fornendo il prodotto di auto-condensazione. Sono state testate diverse condizioni e, infine, la resa massima ottenuta è stata del 86% con il 65% del sistema *cis*, successivamente ossidato a chetone (**16**).

Il prodotto sintetizzato è stato sottoposto alla reazione di Suzuki-Miyaura domino, che ha portato alla degradazione del substrato e nessuna traccia del composto di ciclizzazione desiderato (**17**).

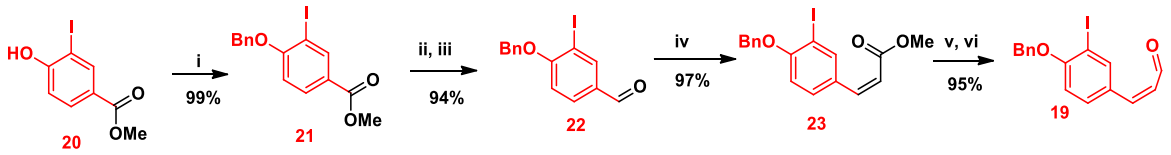


i: KHMDS (1.5 eq), **13** (1.6 eq), THF, -65°C, 12h; ii: DIBALH (2 eq), DCM, -60°C, 2h; iii: Dess-Martin periodinane (1.5eq), DCM, 0°C, 3h, vi: TBAF (0.15eq), THF, ref, 1h; v: Dess-Martin periodinane (1.5eq), DCM, -10°C, 3h; vi: $Pd(dppf)Cl_2$ (0.1 eq), KOAc(10 eq), DMSO, 80°C, 1h

Schema 7. Path B. I approccio sintetico

Path B. Secondo approccio sintetico

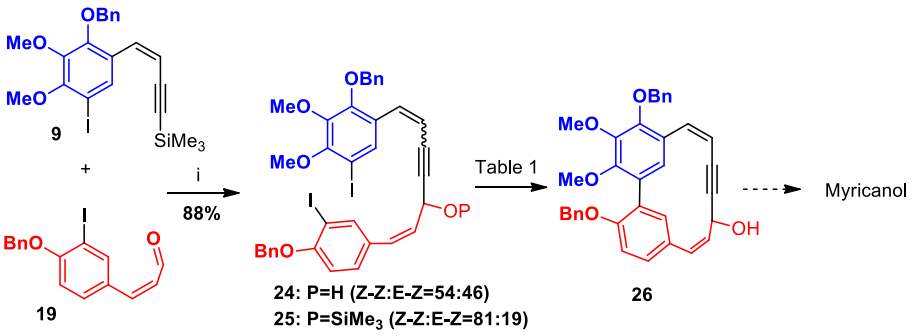
Per testare la ciclizzazione su un sistema più "rigido" e direzionato, è stato introdotto un secondo doppio legame *cis* rendendo l'aldeide **19** non enolizzabile (**Schema 8**).



i: BnBr (1.2 eq), K_2CO_3(2.0 eq), MeCN, 55°C, 14h; ii: Dibal-H (2.0 eq), DCM, -60°C, 3h; iii: Dess-Martin Periodinane, DCM, 0°C, 3h; iv: Bis(2,2,2-trifluoroethyl)(methoxy-carbonylmethyl)phosphinate (1.5 eq), 18-Crown-6 (5.5eq), KHMDS (2.0 eq), THF, -78°C, 14h; v: Dibal-H (2.0 eq), DCM, 2h; vi: Dess-Martin Periodinane (1.5 eq), DCM, 0°C, 3h.

Schema 8. Sintesi dell' aldeide **19**

Nelle condizioni di reazione testate, con TBAF o TBAT come composti donatori di fluoruro, l'aldeide *cis*-**19** si è isomerizzata in aldeide *trans*, che stranamente sembrava non reagire nelle condizioni di reazione utilizzate (**Schema 9**). La reazione di addizione, eseguita con 0,15 equivalenti di TBAF in THF a riflusso per un' ora, ha fornito una miscela di **24** (*Z-Z* : *E-Z* = 81: 19) e **25** (*Z-Z*: *E-Z* = 54: 46) con un rendimento dell'88% (**24: 25** = 4 : 1).



Schema 9. Path B. II approccio sintetico

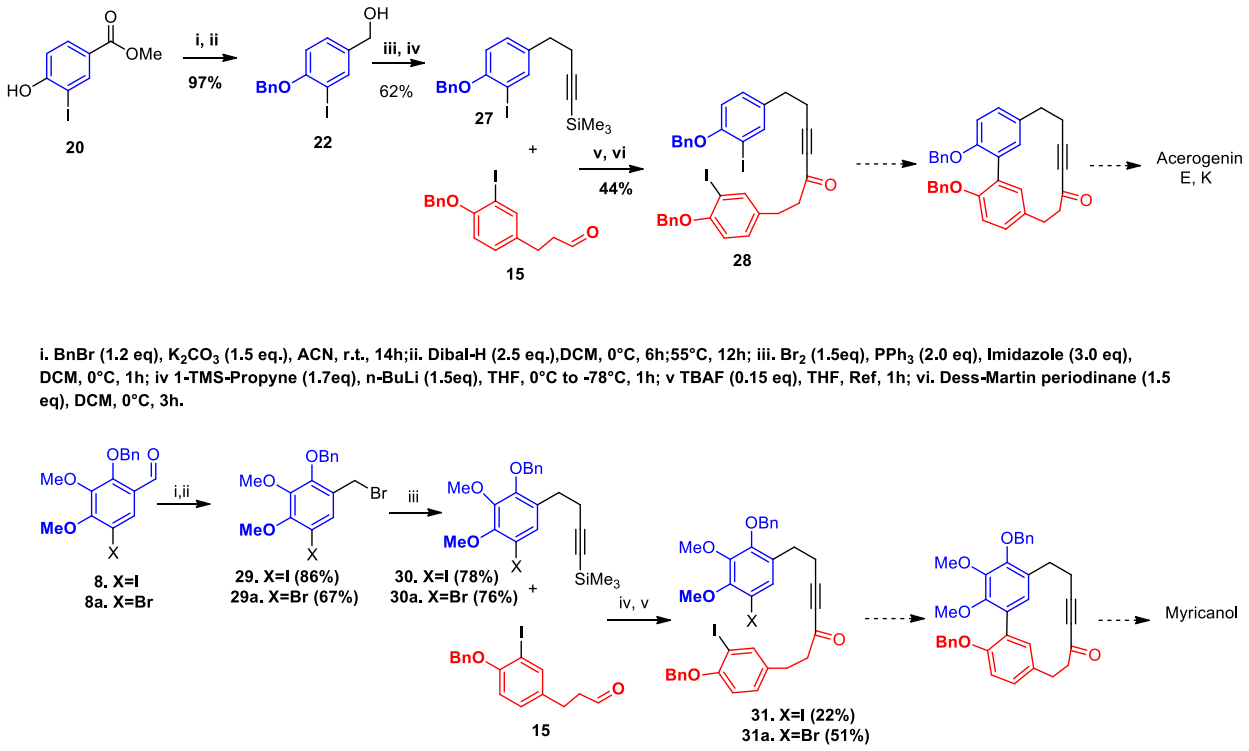
Il *seco*-precursore è stato ottenuto con una resa eccellente ed è stato sottoposto a diverse condizioni di ciclizzazione Suzuki-Miyaura domino: se la reazione viene eseguita ad 80°C, si osserva degradazione entro pochi minuti sia sul sililetere (**25**) che sull'alcol libero (**24**); in un solo caso sono state osservate tracce del prodotto ciclizzato desiderato (**26**). Sono state testate reazioni di Ullmann Pd-, Ni- o Cu-catalizzate, generando la specie di Ni(0) *in situ* mediante l'utilizzo di Zn come agente riducente[14-18] alcune delle quali sono riportate nella **Tabella 1**. Il prodotto ciclizzato desiderato è stato ottenuto solo in tracce in una prova di Suzuki-Miyaura sul substrato **24**.

Entry	Sub	Catalyst	T°C	Conv	Result
1	**24**	$PdCl_2(dppf)$, B_2pin_2	80	100	Cyclization (Traces)
2	**24**	Cu	120	10	Dehalogenation
3	**24**	$NiCl_2(PPh_3)_2$, Zn	60	100	Degradation
4	**24**	$PdCl_2(dppf)$	80	100	Degradation
5	**25**	$PdCl_2(dppf)$, B_2pin_2	80	100	Degradation
6	**25**	Cu	120	100	**24** + dehalogenation (traces)
7	**25**	$NiCl_2(PPh_3)_2$, Zn	60	100	**24**

Tabella 1. Prove di Macrociclizzazione su **24** e **25**

PathB. III approccio sintetico.

Sono stati identificati sistemi ciclici meno tensionati e più semplici senza doppi legami *cis*, e ne sono state progettate le strategie sintetiche (**Schema 10**). Pertanto, è stato effettuato uno studio parallelo finalizzato alla sintesi totale di acerogenina E e K, diarileptanoidi ciclici più semplici (**Schema 10**).



Schema 10. Path B. III approccio sintetico

Le prime prove di ciclizzazione Ni-catalizzate condotte sul substrato **28** hanno portato a risultati incoraggianti di ciclizzazione, attualmente è in fase di ottimizzazione la ciclizzazione sul composto **28,** (per la sintesi dell' acerogenina E e K) e sui composti **31 e 31a** per la sintesi del miricanolo.

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Abstract- <u>français</u>

Nouvelle approche pour la synthèse du myricanol : L'influence du système ène-yne.

Intoduction

Le myricanol est un diarylheptanoïde cyclique (7,0- *méta*,*méta*-diarylheptanoïde) appartenant à la classe des diarylheptanoïdes (**figure 1**), extrait de plusieurs espèces de la famille des *Myricaceae*, telles que *Myrica conifera*[1], *Myrica nagi*[2], *Myrica gale*[3], et plus particulièrement de *Myrica rubra*[4].

Les diarylheptanoïdes sont largement connus pour leurs propriétés anti-inflammatoires, antioxydantes, anticancéreuses, hépatoprotectrices et neuroprotectrices[5].

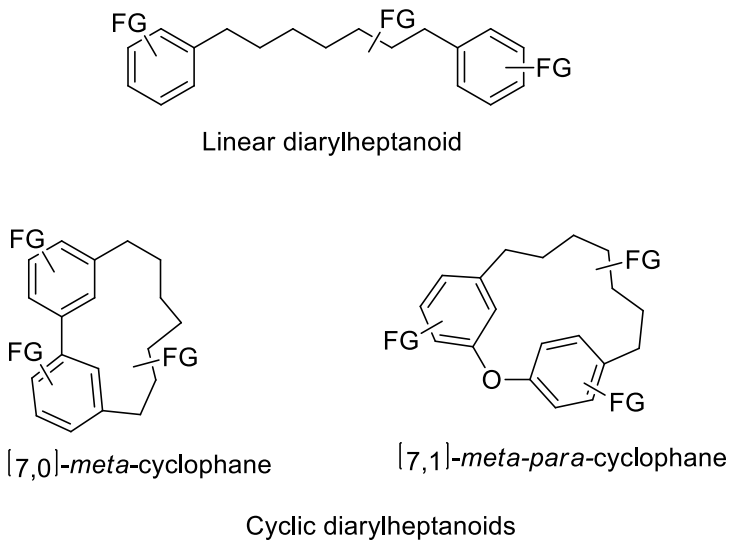


Figure 1.Différentes familles de diarylheptanoïdes

L'objectif principal de cette thèse de doctorat est la synthèse totale du myricanol (**Figure 2**), un composé naturel important aux activités biologiques intéressantes[6]. En particulier, ses remarquables propriétés anti-Alzheimer en font un candidat potentiel pour le traitement de diverses taupathies, car il est capable de réduire les niveaux de protéine Tau qui ont tendance à s'accumuler dans ces maladies neurodégénératives collectivement désignées sous le terme de taupathies[6].

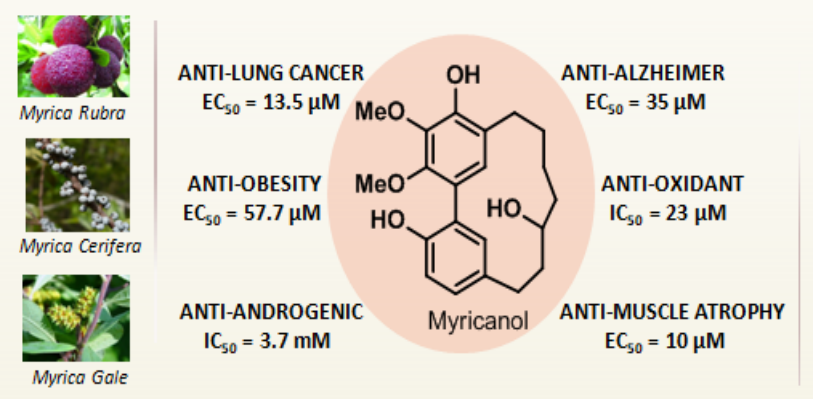


Figure 2. Activités biologiques du myricanol

Le **schéma 1** montre brièvement les approches synthétiques rapportées dans la littérature[6]. Il y a deux tentatives de synthèse et trois synthèses totales.La première synthèse du myricanol remonte à 1980 par Whiting *et al.*[7], avec un rendement de seulement 0,21 % en 14 étapes.

Le meilleur résultat en termes de rendement a été obtenu en 2018[8] par le groupe de recherche où ce travail de thèse a été effectué et qui a obtenu le myricanol racémique en 9 étapes avec un rendement de 4,9 %. De son côté, le groupe de recherche américain de Dickey le synthétisait en 2015[9] avec un rendement de 2,03 % pour 7 étapes, mais en partant de fragments non commerciaux.
Une tentative de synthèse d'un analogue de la méthyl-myricanone a été réalisée en 2000 par le groupe de Dansou[10].

Enfin, la dernière tentative de synthèse a été réalisée par notre groupe en 2020[11] en utilisant une macrocyclisation par RCM, mais qui a conduit à un dimère non désiré. Notre groupe de recherche[12] a ensuite publié la synthèse de l'isomyricanol (un *ortho*, *méta* -diarylheptanoïde) en utilisant la même stratégie synthétique que celle utilisée pour la tentative de synthèse précédente, obtenant des rendements élevés. Ces résultats démontrent que la contrainte cyclique d'un *ortho*, *méta*–diarylheptanoïde est moins importante que celle d'un *méta*, *méta*-diarylheptanoïde et donc soulignent la nécessité de rechercher des stratégies de synthèse alternatives pour ces derniers.

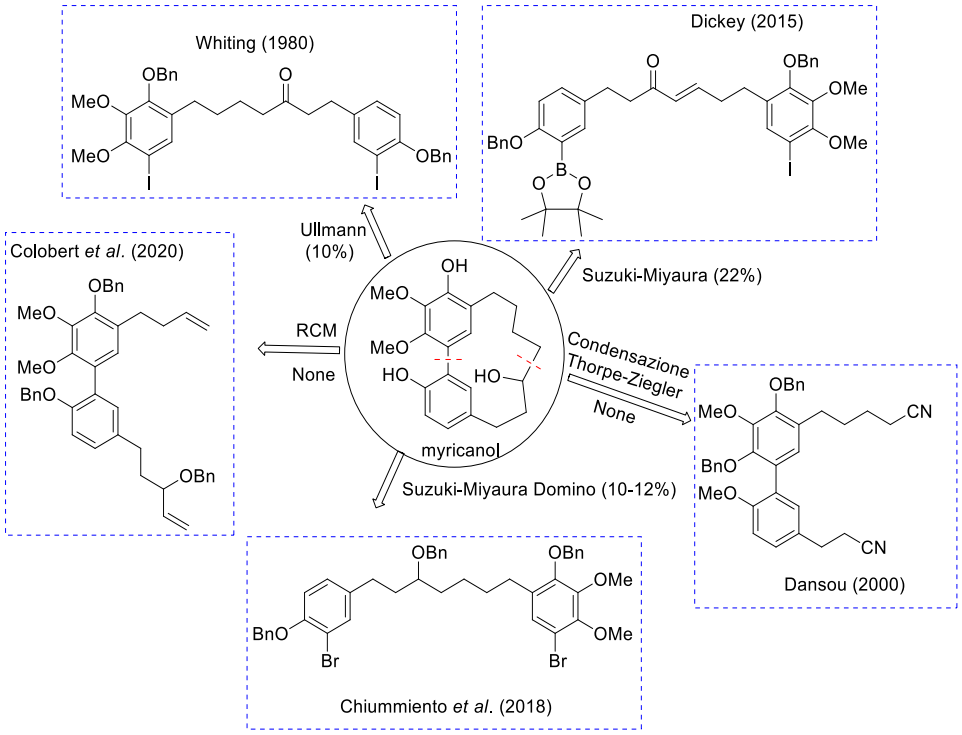


Schéma 1. Synthèses totales et tentatives rapportées dans la littérature[2]

Approches synthétiques:

Les approches rétrosynthétiques pour la synthèse des diarylheptanoïdes cycliques peuvent généralement être divisées en deux grandes catégories (**Schéma 2**) :

-Voie A : L'étape de macrocyclisation est réalisée à partir d'un système biarylique fonctionnalisé illustrée par les deux tentatives de synthèse du **schéma 1** (Dansou *et al.* et Colobert *et al.)*[10,11]

-Voie B : L'étape de macrocyclisation est effectuée sur un diarylheptanoïde linéaire illustrée par les trois synthèses totales rapportées dans la littérature et présentées dans le **schéma1**.

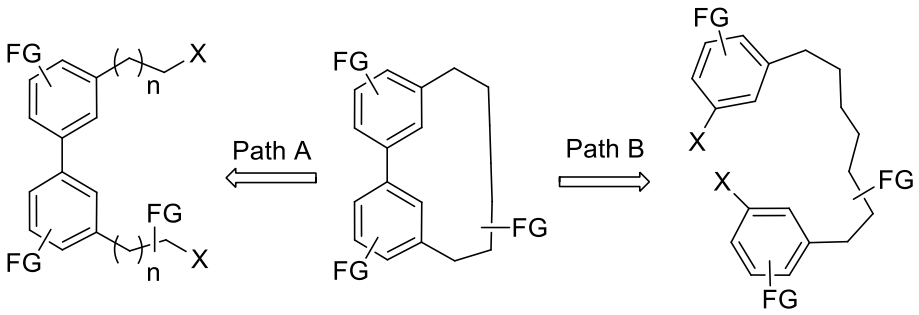


Schéma 2. Approches rétrosynthétiques

Les deux approches synthétiques, voie A et voie B, ont été explorées au cours de cette thèse et seront discutées ci-après.

Tout d'abord, cette thèse vise principalement à explorer les conditions optimales pour rendre la cyclisation moins défavorable en utilisant un *séco*-précurseur insaturé et donc "rigide" en limitant les variations des degrés de liberté conformationnelles pendant la cyclisation. En d'autres termes, un plus grand degré d'insaturation entraînerait une variation d'entropie moins significative et, en même temps, la présence de doubles liaisons *cis* garantirait une probabilité plus élevée de "rencontre" entre les extrémités impliquées durant la cyclisation. Pour ces raisons, l'objectif de cette thèse a été la synthèse de systèmes acycliques polyinsaturés et l'étude de l'influence des systèmes insaturés sur les macrocyclisations.

Approche synthétique selon la voie A

Voie A. Première Approche

La première approche implique une réaction de couplage croisé de deux composés commerciaux (**1** et **2**), suivie par la formation du composé biarylique résultant suivi d'une oléfination de Julia, d'une cyclisation et d'une réduction. Cependant, cette stratégie a été abandonnée en raison de la difficulté de former le système biarylique formylé (**4**) (**schéma 3**).

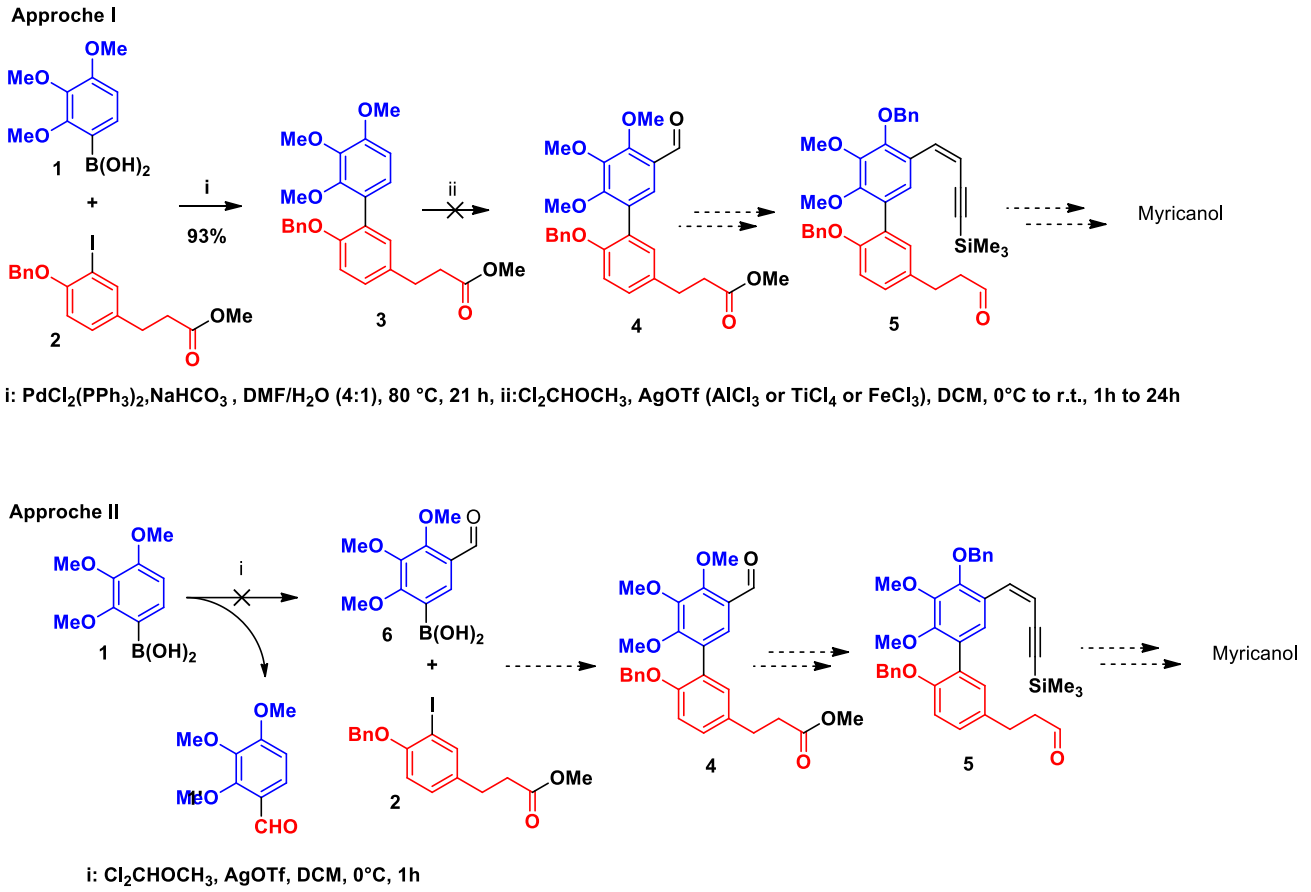


Schéma 3. Première et deuxième approches utilisant la voie A

Voie A : Deuxième approche

Une deuxième approche de synthèse a été explorée pour contourner l'étape de formylation du système biarylique. Dans cette approche, l'objectif était de formyler directement un acide boronique (**1**) pour obtenir un partenaire de couplage déjà formylé pour la réaction de couplage croisé conduisant à la formation de l'aldéhyde biarylique **4** souhaité (Schéma **3**). Cependant, de manière inattendue, la formylation a abouti à la formation d'un composé *ipso*-formylé (composé **1'**). Ce résultat indésirable nous a ensuite incité à étudier la formylation sur divers acides boroniques substitués, en utilisant trois méthodes de formylation différentes. Les résultats de cette étude ont été publiés[13] (**Schéma 4**).

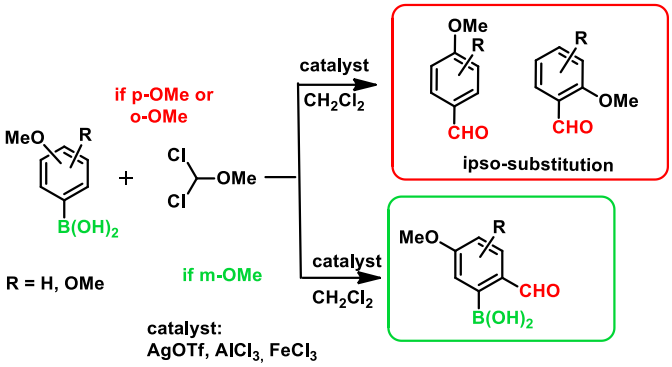


Schéma 4. Formylation sur divers acides boroniques substitués

Voie A. Troisième approche

Contrairement aux deux approches précédentes, cette troisième stratégie consiste à inverser les partenaires de couplage. L'objectif est de générer l'ester boronique sur le fragment sud et de le coupler avec le benzaldéhyde **8** par une réaction de Suzuki intermoléculaire (**Schéma 5**). Malheureusement, diverses tentatives de couplage n'ont pas donné le produit attendu avec un bon rendement, fournissant presque exclusivement le composé déiodé. On a alors envisagé d'inverser les rôles des partenaires de couplage, c'est-à-dire de générer l'ester boronique sur le composé **7** et de le coupler avec l'ester **2**. Malheureusement, même dans ce cas, le composé biaryle **4** n'a pas été obtenu.

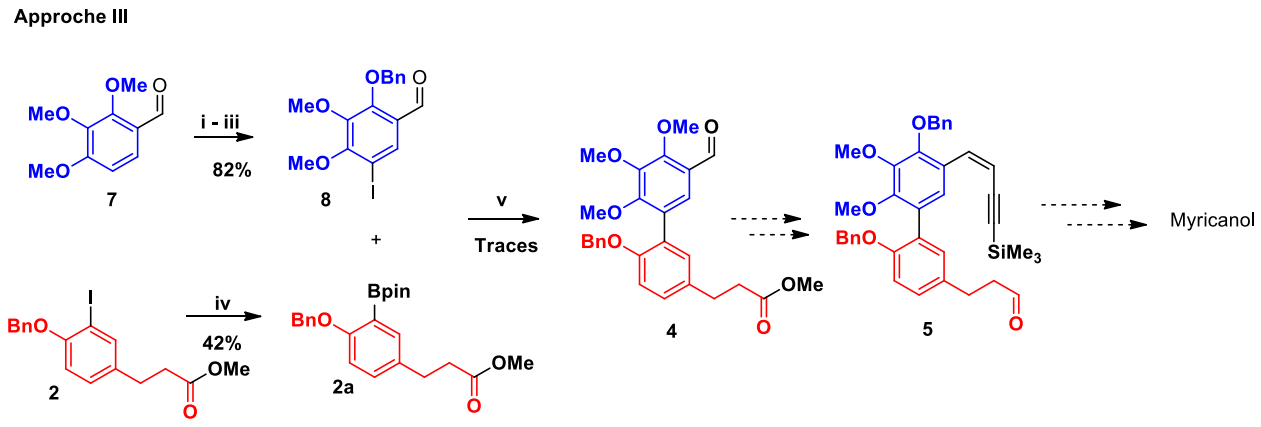


Schéma 5. Voie A. Troisième approche

Voie A. Quatrième approche

Une quatrième approche potentielle consiste à condenser les fragments halogénés (**10** et **11**) par une réaction de couplage radicalaire.

Cette quatrième stratégie synthétique semble être la plus directe, mais étant donné les multiples fonctionnalités des produits, diverses réactions secondaires peuvent être impliquées : le mécanisme passe par la formation du radical-phénol, qui peut réagir tel quel (produit secondaire) ou se réarranger en délocalisant le radical en position *para*. À ce stade, un couplage dirigé en *ortho* sur le composé **11** doit aboutir à la formation du produit souhaité **12**.

En outre, les rôles des partenaires de couplage ont été inversés. C'est-à-dire, en partant du triméthoxybenzaldéhyde (**7**) et du phénol **13** (**Schéma 6**), une tentative de couplage radicalaire a été effectuée, mais elle n'a malheureusement pas fourni le produit **14** attendu.

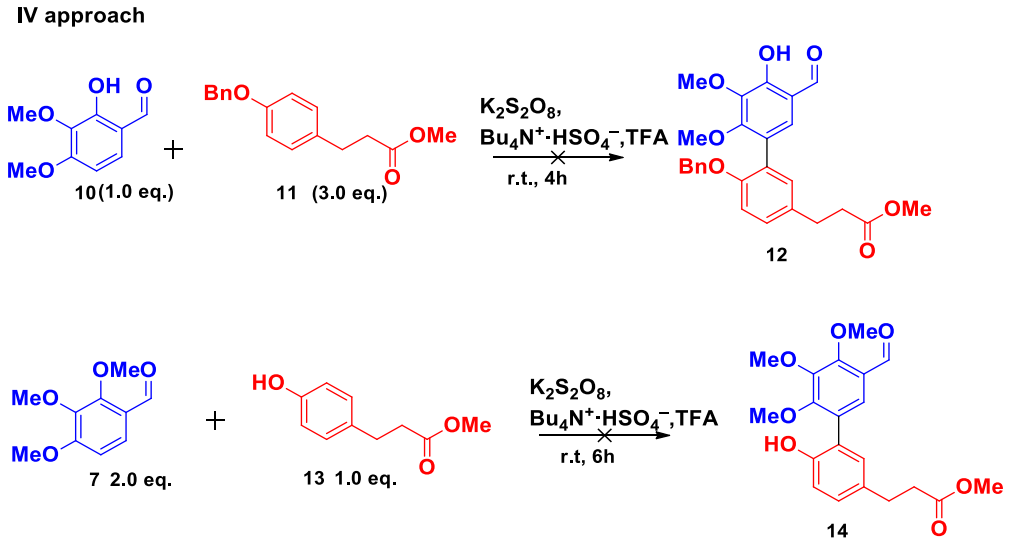


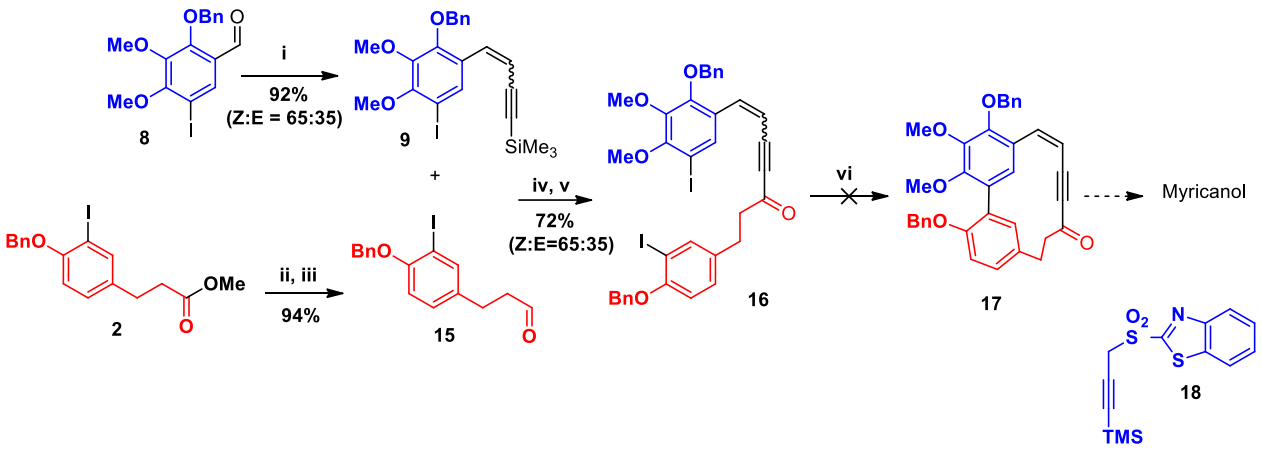
Schéma 6. Voie A.couplage radicalaire

Approche synthétique selon la voie B

Voie B. Première Approche

La première approche de la voie B (**Schéma 7**) a été investiguée et consiste à construire d'abord la chaîne latérale puis à former la liaison biarylique.

L'ényne (**9**) a été synthétisée avec un rendement global excellent, bien que les deux isomères *cis* et *trans* ne soient pas séparables. La réaction d'addition suivante a posé plusieurs problèmes : l'acétylure résultant de la désilylation catalysée par le fluorure pouvait agir comme un nucléophile, fournissant le système couplé, ou comme une base, déprotonant l'aldéhyde propionique et fournissant le produit d'auto-condensation. Diverses conditions ont été testées, et finalement, le rendement maximum de condensation obtenu a été de 86 % avec 65 % du système *cis*. L'alcool propargylique issu de l'addition avec l'aldéhyde **15** a ensuite été oxydé en cétone (**16**). Le produit résultant a été soumis à la réaction de Suzuki-Miyaura domino, qui a conduit à la dégradation du substrat, sans aucune trace du composé de macrocyclisation souhaité (**17**).

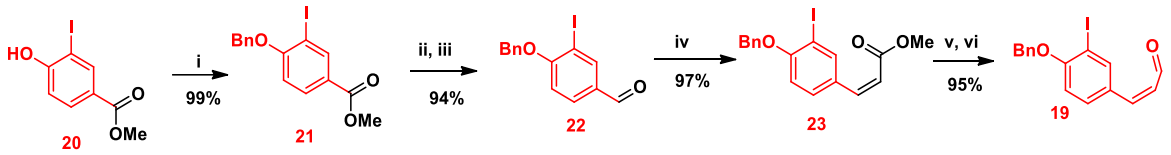


i: KHMDS (1.5 eq), **13** (1.6 eq), THF, -65°C, 12h; ii: DIBALH (2 eq), DCM, -60°C, 2h; iii: Dess-Martin periodinane (1.5eq), DCM, 0°C, 3h, iv: TBAF (0.15eq), THF, ref, 1h; v: Dess-Martin periodinane (1.5eq), DCM, -10°C, 3h; vi: $Pd(dppf)Cl_2$ (0.1 eq), KOAc(10 eq), DMSO, 80°C, 1h

Schéma 7.Voie B. Première Approche

Path B. Deuxième Approche Synthétique

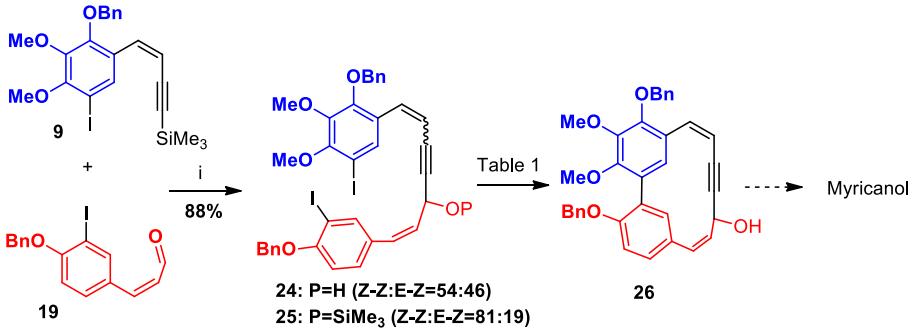
Pour tester la cyclisation sur un système plus "rigide" et orienté, une deuxième double liaison *cis* a été introduite, rendant l'aldéhyde **19** non énolisable (**Schéma 8**).



i: BnBr (1.2 eq), K_2CO_3(2.0 eq), MeCN, 55°C, 14h; ii: Dibal-H (2.0 eq), DCM, -60°C, 3h; iii: Dess-Martin Periodinane, DCM, 0°C, 3h; iv: Bis(2,2,2-trifluoroethyl)(methoxy-carbonylmethyl)phosphinate (1.5 eq), 18-Crown-6 (5.5eq), KHMDS (2.0 eq), THF, -78°C, 14h; v: Dibal-H (2.0 eq), DCM, 2h; vi: Dess-Martin Periodinane (1.5 eq), DCM, 0°C, 3h.

Schéma 8. Synthèse du composé **19**

Dans les conditions de réaction testées, avec TBAF ou TBAT comme donneurs de fluorure, l'aldéhyde *cis* **19** s'est isomérisé en aldéhyde *trans*, qui, de manière surprenante, semblait ne pas réagir dans les conditions de réaction (**Schéma 9**). La réaction d'addition, effectuée avec 0,15 équivalents de TBAF dans le THF sous reflux pendant 1 heure, a fourni un mélange de produits **24** (*Z-Z:E-Z* = 81:19) et de **25** (*Z-Z:E-Z* = 54:46) avec un rendement de 88%.



i: TBAF (0.15eq), THF, rif, 1h; ii: $Pd(dppf)Cl_2$ (0.1 eq), B_2pin_2 (1.2 eq), KOAc(10 eq), DMSO, 80°C, 1h

Schéma 9. Path B. Deuxième Approche Synthétique

Le *seco*-précurseur a été obtenu avec un excellent rendement et a été soumis à différentes conditions de cyclisation Suzuki-Miyaura domino : si la réaction est effectuée à 80°C, une dégradation est observée en quelques minutes à la fois sur le silyléther (**25**) et sur l'alcool libre (**24**) ; dans un seul cas, des traces du produit cyclisé souhaité (**26**) ont été observées. Des réactions catalysées par Pd, Ni ou Cu ont été testées, générant la forme Ni(0) *in situ* à l'aide de Zn comme agent réducteur, certaines d'entre elles sont répertoriées dans le **Tableau 1**. Le produit cyclisé souhaité n'a été obtenu qu'en

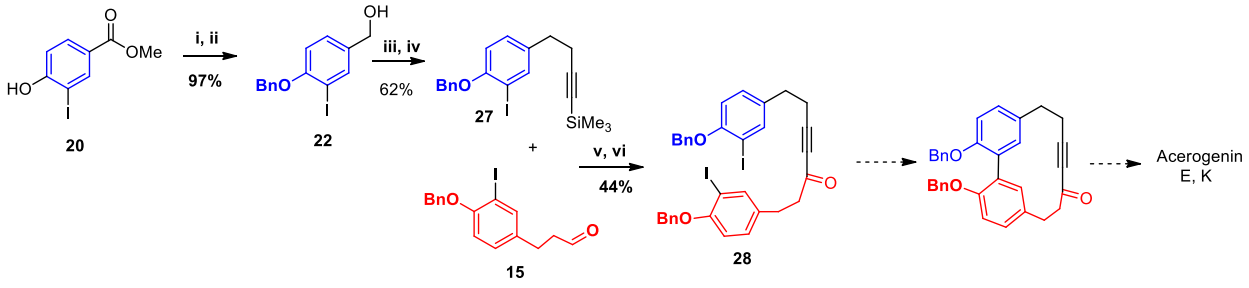
traces dans un test Suzuki-Miyaura sur le substrat **24**.

Entry	Sub	Catalyst	T°C	Conv	Result
1	**24**	$PdCl_2(dppf)$, B_2pin_2	80	100	Cyclization (Traces)
2	**24**	Cu	120	10	Dehalogenation
3	**24**	$NiCl_2(PPh_3)_2$, Zn	60	100	Degradation
4	**24**	$PdCl_2(dppf)$	80	100	Degradation
5	**25**	$PdCl_2(dppf)$, B_2pin_2	80	100	Degradation
6	**25**	Cu	120	100	**24** + dehalogenation (traces)
7	**25**	$NiCl_2(PPh_3)_2$, Zn	60	100	**24**

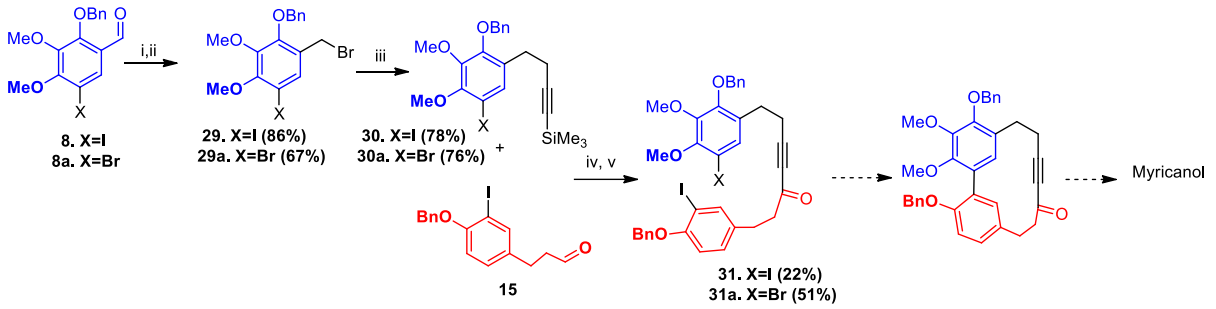
Tableau 1. Tentatives decyclisation des *seco*-precurseurs **24** et **25**

Voie B. Troisième approche synthétique

Des systèmes cycliques moins tendus et plus simples sans double liaison*cis*ont été identifiés, et des stratégies de synthèse ont été conçues pour ces derniers (**Schéma 10**). Par conséquent, une étude parallèle a été menée en vue de la synthèse totale des acérogénines E et K, diarylheptanoïdes cycliques plus simples, et qui pourra être extrapolé à la synthèse du myricanol (**Schéma 10**).



i. BnBr (1.2 eq), K_2CO_3 (1.5 eq.), ACN, r.t., 14h;ii. Dibal-H (2.5 eq.),DCM, 0°C, 6h;55°C, 12h; iii. Br_2 (1.5eq), PPh_3 (2.0 eq), Imidazole (3.0 eq), DCM, 0°C, 1h; iv 1-TMS-Propyne (1.7eq), n-BuLi (1.5eq), THF, 0°C to -78°C, 1h; v TBAF (0.15 eq), THF, Ref, 1h; vi. Dess-Martin periodinane (1.5 eq), DCM, 0°C, 3h.



i: Dibal-H (2.0 eq), -60°C, DCM, 1h; ii: Br_2 (1.5eq), PPh_3 (2.0 eq), Imidazole (3.0 eq), DCM, 0°C, 1h; iii. 1-TMS-Propyne (1.7eq), n-BuLi (1.5eq), THF, 0°C to -78°C, 1h; iv TBAF (0.15 eq), THF, Ref, 1h; v. Dess-Martin periodinane (1.5 eq), DCM, 0°C, 3h.

Schéma 10. Voie B. Troisième approche synthétique et accès aux acérogénines E et K

Les premiers essais de cyclisation catalysée par le Ni(0) réalisés sur le substrat **28** ont donné des résultats encourageants pour la cyclisation. Actuellement, la synthèse et la cyclisation du composé **28** sont en cours d'optimisation, ce qui devrait permettre la synthèse de l'acérogénine E et K. Simultanément, la synthèse du composé **31** en vue de la synthèse totale du myricanol est en cours d'optimisation.

Une synthèse totale énantiosélective du myricanol pourrait être développée en utilisant des additions énantiosélectives (par exemple, en utilisant $Zn(OTf)_2$ et la méthyléphédrine dans les conditions de Carreira)[19]. Si la stratégie synthétique s'avère efficace, cette méthodologie pourrait être étendue à d'autres diarylheptanoïdes cycliques d'intérêt biologique[20].

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List of Abbreviations

1D	one-dimensional
2D	two-dimensional
Aβ	amyloidbeta
Å	Ångström
ACN	acetonitrile
AD	Alzheimer’sdisease
aq.	aqueous
$B_2(pin)_2$	pinacolatodiboron
Bn	benzyl
°C	Celsiusdegree
CC	columnchromatography
CD	circulardicroism
CIP	Cahn–Ingold–Prelog
CM	cross-metathesis
COSY	correlationspectroscopy
Cy	cyclohexane
DIBAL-H	diisobutyl aluminiumhydride
DIPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine

DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
EC_{50}	halfmaximalinhibitoryconcentration
EI	electron-impactionization
EP	petroleumether(boilingpoint: 40-60 °C)
eq.	equivalent
EtOAc	ethylacetate
EtOH	ethanol
EWG	Electron withdrawing group
GC	gaschromatography
HCl	hydrochloricacid
HPLC	high-performanceliquidchromatography
HR	highresolution
HSQC	heteronuclearsingle-quantumcorrelation
IC50	halfmaximalinhibitoryconcentration
iNOS	induciblenitricoxidesynthase
KOAc	potassiumacetate
(+)-L-DIPT	(+)-DiisopropylL-tartrate
MeOH	methanol
MOM	methoxymethyl
MS	massspectrometry

MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide
MW	microwaveirradiation
n-BuLi	normal-butyllithium
NBS	*N*-bromosuccinimede
NIS	*N*-iodosuccinimide
NMP	*N*-methylpirrolydone
NMR	nuclear magneticresonance
NOESY	nuclearOverhausereffectspectroscopy
PCC	piridiniumchlorochromate
Pd/C	palladiumon charcoal
$Pd_2(dba)_3$	Dipalladium-tris(dibenzylideneacetone)
$Pd_2Cl_2(dppf)$	[1,1′Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
PIDA(orDIB)	(Diacetoxyiodo)benzene
PIFA(orBTI)	Bis(trifluoroactoxy)iodobenzene
PPh_3	triphenylphosphine
ppm	partspermillion
Py	pyridine
RCAM	ringclosingalkynemetathesis
RCM	ringclosingmetathesis
R*f*	retentionfactor
ROS	reactiveoxygenspecies
r.t.	roomtemperature
SAR	structureactivityrelationship
SET	single-electrontransfer

S-Phos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
T	temperature
t	time
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TFA	trifluoroaceticacid
TIR	tumorinhibitionrate
TLC	thinlayerchromatography
TON	turnovernumber
t_R	retentiontime
W	Watt
X-Phos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
X.Phos Pd G2	Chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II)

List of Tables

List of Schemes

List of Figures

Introduction

Introduction

The *Myricaceae* family (**Figure 1**), belonging to the Fagales order, includes shrubs widely distributed in Southeast Asia, Central America, North America, Europe, and Africa but absent in Australia. Thanks to their soothing properties, they have long been used in traditional Chinese medicine[1-3] . The resin from *Myrica gale* shrubs is traditionally employed as a natural insect repellent[4]. In Northern Europe, it is used to flavor alcoholic beverages. Some indigenous communities in Western Canada use *Myrica gale*-based infusions to treat fever, stomachaches and respiratory issues. In Scotland, the essential oil from *Myrica*, with its anti-androgenic properties, is used to treat acne.[5].

The resin from *Myrica cerifera* is used in the production of scented candles. *Myrica rubra*, widely found in Southeast Asia, is used for ornamental purposes in parks and streets. Its fruits can be consumed fresh, dried, or fermented into alcoholic beverages. It is also used in the preparation of preserves, juices, or as a natural colorant[6].

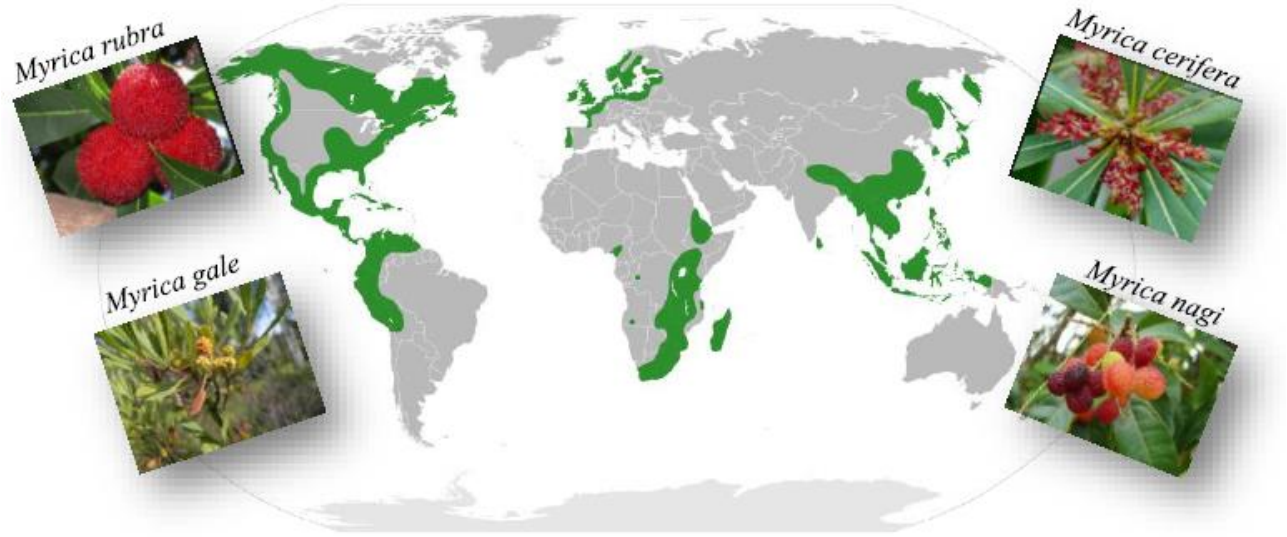

Figure 1. Distribution of *Myricaceae*

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[4] Skene, K. R.; Sprent, J. I.; Raven, J. A.; Herdman, L. *J. Ecol.***2000**, 88, 1079–1094.
[5] Asnaashari, S.; Kazemnezhad, M.; Masoud, F.; Javadzadeh, Y. *J. Herbal Med.* **2023**, 38, 100642.
[6] Fang-Yong, C.; Ji-Hong, L. *Scientia Horticulturae* **2014**, 170, 169-175.

Myricanol is a cyclic diarylheptanoid ([7,0]-*meta,meta*-cyclophane) belonging to the class of diarylheptanoids (**Figure 2**). It is extracted from various species within the *Myricace*ae family, such as *Myrica conifera*[7], *Myrica nagi*[8], *Myrica gale*[9], and particularly from *Myrica rubra*[10].

Diarylheptanoids are well-known for their anti-inflammatory, antioxidant, antitumor, hepatoprotective, and neuroprotective properties[11].

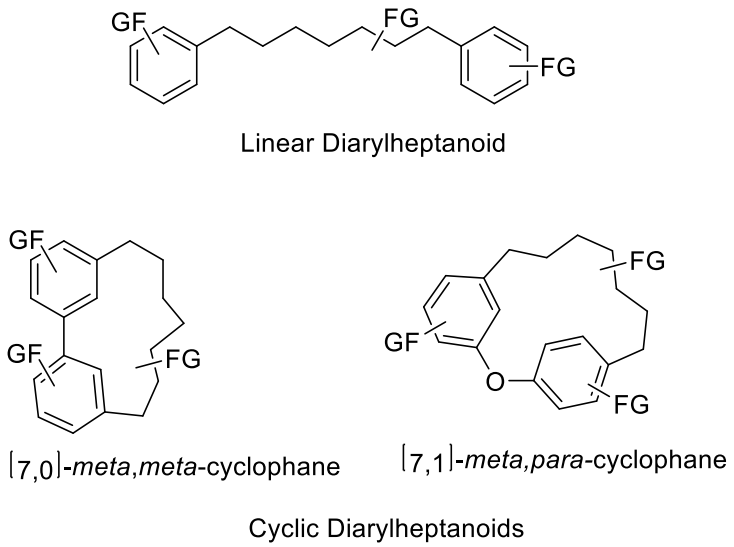

Figure 2. The diarylheptanoids familly

Myricanol (**Figure 3**) exhibits central chirality due to the stereogenic center at C-11 and axial chirality arising from the non-coplanarity of the two benzene rings (Atropoisomerism, that is a type of isomerism caused by a limited rotation around the single bond that connects the aryl moieties).

Consequently, there are four possible stereoisomers, namely, 2 pairs of diastereomeric enantiomers: (a*S*,*S*) and (a*R*,*R*); (a*S*,*R*) and (a*R*,*S*).

It's important to note that both pairs of enantiomers have never been isolated; from both natural extracts and laboratory synthesis, only one pair of enantiomers has been identified as a scalemic or racemic mixture of (a*S*,*R*) and (a*R*,*S*).

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[7] Per, C.; Claeson, U. P.; Tuchinda, P.; Reutrakul, V. In *Studies in Natural Products Chemistry;* Elsevier, **2002**; Vol. 26, pp 881-908.
[8] Zhu, J.; Islas-Gonzalez, G.; Bois-Choussy, M. Org. *Prep. Proced. Int.* **2000**, 32 (6), 505-546.
[9] Lv. H.; She, G. *Nat. Prod. Commun.* **2010**, 5 (10), 1687-1708.
[10] Gupta, S. C.; Patchva, S.; Koh, W.; Aggarwal, B. *Clin. Exp. Pharmacol. Physiol.* **2012**, 39(3), 283-299.
[11] Rowe, J. W. Natural products of Wood Plants: Chemical Extraneous to the Lignocellulosic Cell Wall; Springer Science & Business Media, **2012**.

In **Figure 3**, the four possible stereoisomers of myricanol are shown, but only structures 'a' and 'd' have been observed, with the enantiomeric excess depending on the *Myrica* species and the extraction conditions used.

Probably, the central chirality influences the axial chirality, meaning that the position of the hydroxyl group at C-11 could play a fundamental role in determining the dihedral angle of the biaryl bond and, consequently, the position of the hydroxyl group at C-17 relative to the plane of the aromatic ring "A."

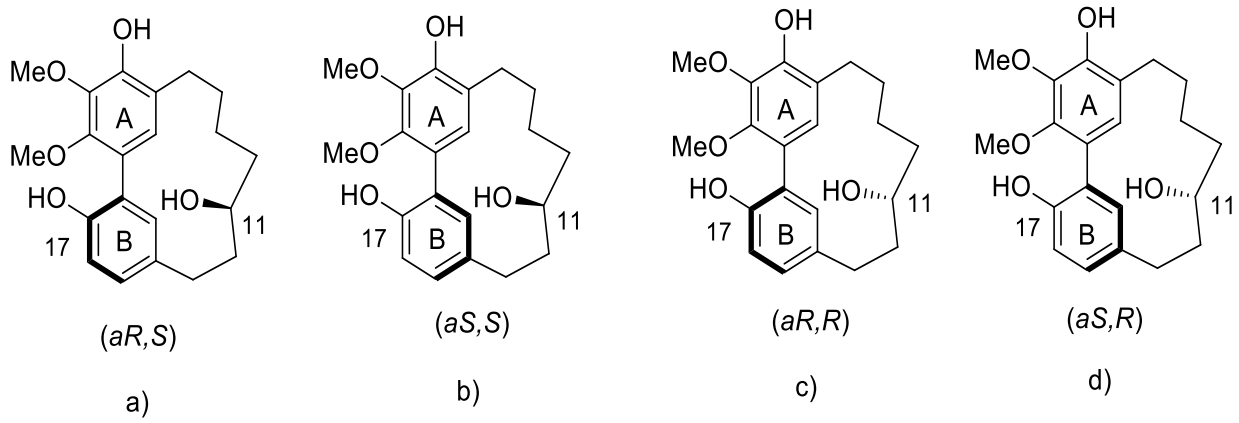


Figure 3. Possible stereoisomers of myricanol

Myricanol exhibits significant anti-inflammatory properties[11], anti-androgenic effects[12], and it exhibits the ability to inhibit nitric oxide synthesis in living organisms by macrophages during the immune response[13].

[11] Rowe, J. W. Natural products of Wood Plants: Chemical Extraneous to the Lignocellulosic Cell Wall; Springer Science & Business Media, **2012**.

[12] Begley, M.J.; Campbell, R. V. M.; Crombie, L.; Tuck, B; Whiting, D.A. *J. Chem Soc. C. Org.* **1971**, 3634-3642.

[13] Tao J.; Morikawa T.; Toguchida I.;, Ando S.; Yoshikawa M.; Yoshikawa M.; *Bioorganic & Medicinal Chemistry* 10, **2002,** 4005–4012.

CHAPTER 1-Biological activities and synthesis

1.1.- Anti cancer and anti-Tau activities

1.1.1-Anti cancer activity

A recent study has demonstrated the undeniable capacity of myricanol to suppress and/or slow down the growth of *in vivo* lung adenocarcinomas (**Figure 4)** by inducing apoptosis. It also upregulates the expression of pro-apoptotic Bax mRNA while downregulating the expression of anti-apoptotic Bcl-2 mRNA, vascular endothelial growth factor (VEGF), survivin, and hypoxia-inducible factor (HIF)-1α[14].

Figure 4 illustrates a noticeable decrease in the growth rate of the tumor volume in rodents treated with myricanol.

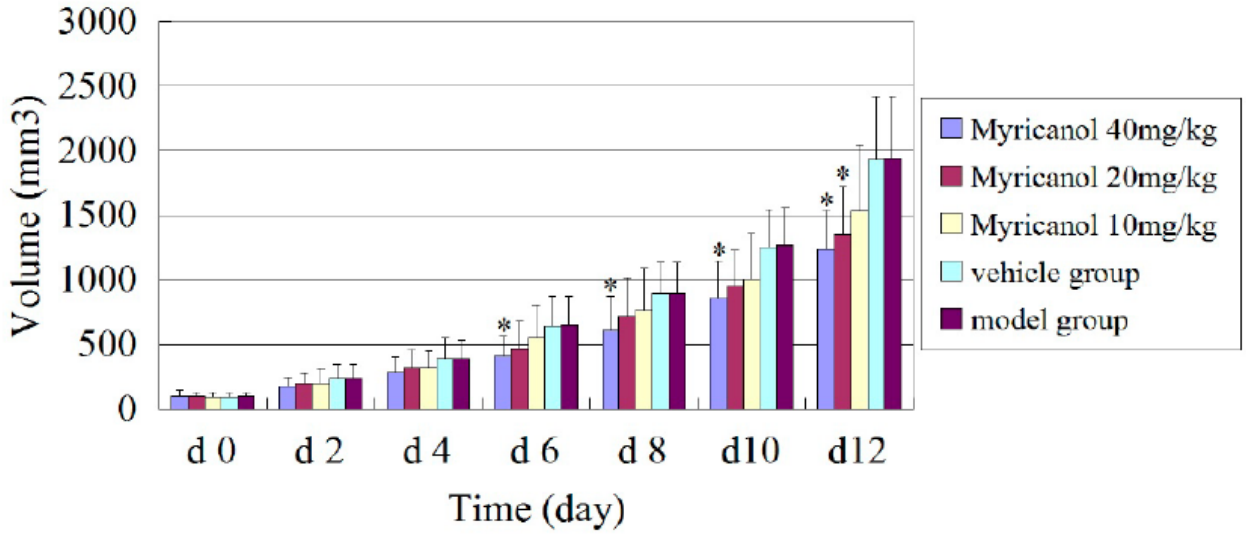


Figure 4. Decrease in the growth rate of the tumor volume

Furthermore, myricanol has been shown to reduce Tau protein levels in neuronal cells, thus exerting an anti-Alzheimer's effect[15]. However, which of the two main enantiomers is responsible for this effect is a matter of controversy, and it will be discussed in the following section.

[14] Dai G.; Tong Y.; Chen X.; Ren Z.; Ying X.; Yang F.; Chai K. Int. *J Mol. Sci.* **2015**, 16(2), 2717-2731.

[15] Jones J. R.; Lebar M. D.; Jinwal U. K.; Abisambra J. F.; Koren J.; Blair L.; O'Leary J. C.; Davey Z.; Trotter J.; Johnson A. G.; Weeber E.; Eckman C. B.; Baker B. J.; Dickey C. A. *J. Nat. Prod*. **2011**, 74, 38–44.

1.1.2-Anti-Tau activity of myricanol

Tau proteins, associated with neuronal microtubules, normally serve the function of stabilizing them. Microtubules play a crucial role in maintaining cell shape and axonal transport. Tau proteins control microtubule stability through various isoforms and phosphorylation states. When Tau proteins malfunction and are unable to effectively stabilize microtubules, they can lead to the development of nervous system pathologies[16]

The intracellular aggregation of abnormal phosphorylated Tau species is a common characteristic of a group of neurodegenerative diseases collectively known as taupathies. This category includes more than 15 neurodegenerative diseases, such as Alzheimer's and Parkinson's. The hyperphosphorylation of Tau proteins can result in the formation of neurofibrillary tangles (NFTs), which are intracellular aggregates composed of paired helical filaments (PHFs) (see **Figure 5**)[16].

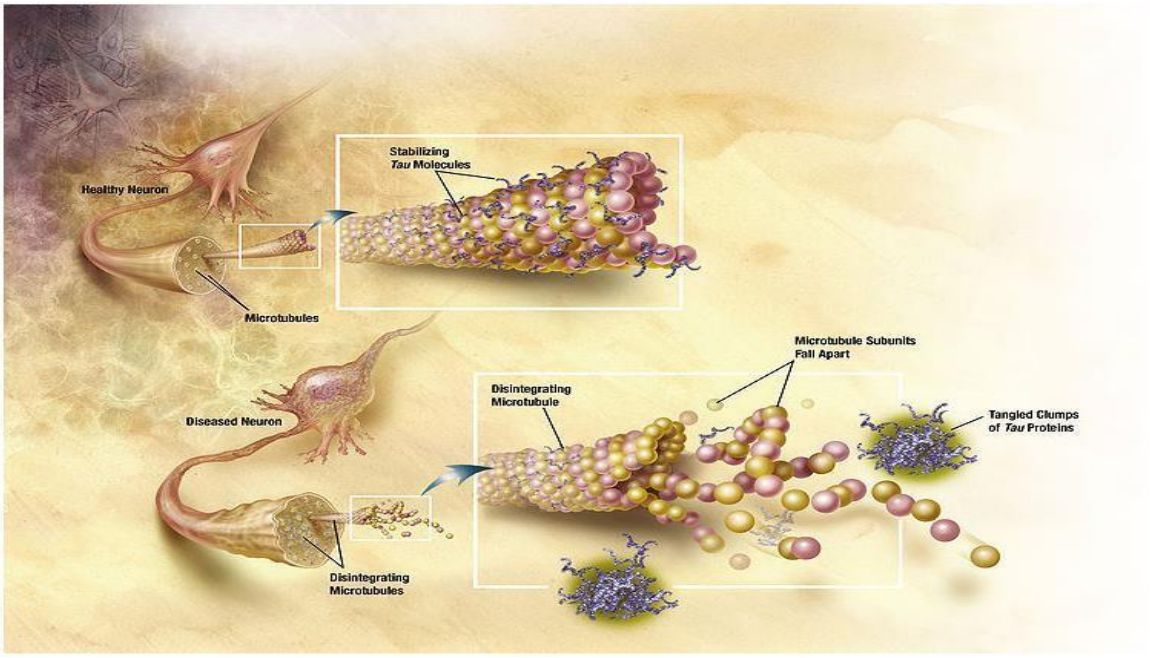


Figure 5. Neurofibrillary tangles.

In certain pathological conditions (taupathies), the Tau protein undergoes hyperphosphorylation, losing its stabilizing abilities, which leads to microtubule structure disintegration and neuronal death. Abnormal species of phosphorylated Tau proteins form intracellular neurofibrillary aggregates, long

[16] Spires-Jones, T.L.; Stoothoff, W. H.; De Calignon, A.; Jones, P. B.; Hyman, B.T. *Trends Neurosci.* **2009**, 32(3), 150-159.

believed to be the primary culprits in synaptic plasticity damage and cognitive dysfunction[17]. However, it is now known that the accumulation of soluble phosphorylated Tau intermediates, rather than visible neurofibrillary aggregates, are the primary contributors to cognitive dysfunction that leads to the development of Alzheimer's disease and other tauopathies[18-21].

In any case, the removal of excess Tau protein in Alzheimer's patients may represent a promising therapeutic approach.

[17] Polydoro, M.; Acker, C. M.; Duff, K.; Castillo, P. E.; Davies, P. J. Neurosci. **2009**, 29, 10741–10749**.**

[18] Oddo, S.; Vasilevko, V.; Caccamo, A.; Kitazawa, M.; Cribbs, D. H.; LaFerla, F. M. *J. Biol. Chem*. **2006**, 281, 39413–39423.

[19] Santacruz, K.; Lewis, J.; Spires, T.; Paulson, J.; Kotilinek, L.; Ingelsson, M.; Guimaraes, A.; DeTure, M.; Ramsden, M.; McGowan, E.; Forster, C.; Yue, M.; Orne, J.; Janus, C.; Mariash, A.; Kuskowski, M.; Hyman, B.; Hutton, M.; Ashe, K. H. *Science***2005**, 309, 476– 481.

[20] Spires-Jones, T. L.; de Calignon, A.; Matsui, T.; Zehr, C.; Pitstick, R.; Wu, H. Y.; Osetek, J. D.; Jones, P. B.; Bacskai, B. J.; Feany, M. B.; Carlson, G. A.; Ashe, K. H.; Lewis, J.; Hyman, B. T. J. *Neurosci*. **2008**, 28, 862–867.

[21] Roberson, E. D.; Scearce-Levie, K.; Palop, J. J.; Yan, F.; Cheng, I. H.; Wu, T.; Gerstein, H.; Yu, G. Q.; Mucke, L. *Science* **2007**, 316, 750– 754.

Anticipating the significant potential of myricanol, Dickey's research group has filed two patents related to the use of (+)-a*R*,11*S*-myricanol and its derivatives for reducing Tau protein levels in Alzheimer's treatment[22-23](**Figure 6**).

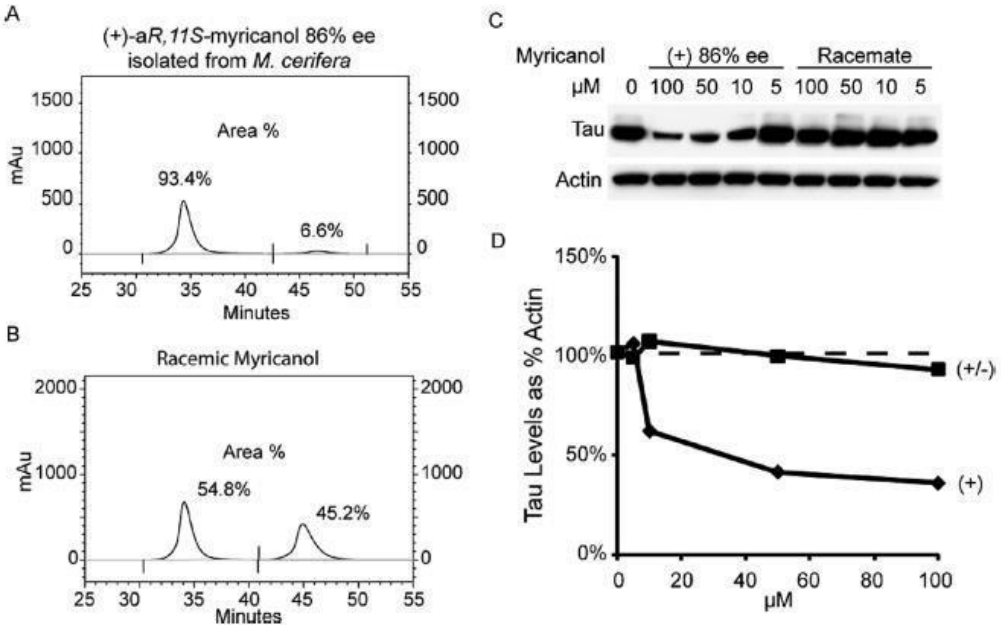


Figure 6. Anti-Tau activity of (+)-*aR,11S*-myricanol[24].

In the first, they detailed the materials and methods for reducing protein Tau levels in the treatment of neurodegenerative diseases using (+)-a*R*,11*S*-myricanol[22], while in the second one, they explored a series of myricanol derivatives investigated for the same biological activity[23].

However, in contrast to their earlier report, the same research group more recently revealed that the reduction of Tau levels primarily resulted from (-)-a*S*,11*R*-myricanol[24]. In their paper, they provided the chemical synthesis of racemic myricanol. Chiral HPLC separation and X-ray analysis confirmed that synthetic racemic myricanol is a mixture of two enantiomers, (+)-a*R*,11*S*-myricanol (51%) and (-)-a*S*,11*R*-myricanol (49%).

[22] Chad Dickey, Matthew Lebar, Bill J. Baker, Jeffrey Jones. MATERIALS AND METHODS FOR REDUCTION OF PROTEIN TAU AND TREATMENT OF NEURODEGENERATIVE DISEASES. US20130184353 A1, **2012.**

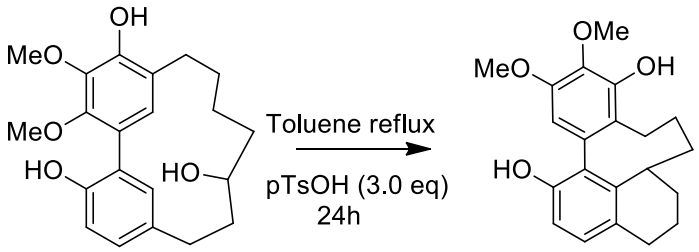
[23] Chad Dickey, Umesh JINWAL, Bill J. Baker, Laurent CALCUL. MYRICANOL DERIVATIVES AND USES THEREOF FOR TREATEMENT OF NEURODEGENERATIVE DISEASES. WO2013152350 A1, **2013**.

[24] Martin, M. D.; Calcul, L.; Smith, C.; Jinwal, U. K.; Fontaine, S. N.; Darling, A.; Seeley, K.; Wojtas,L.; Narayan, M.; Gestwicki, J. E.; Smith, G. R.; Reitz, A. B.; Baker, B. J.; Dickey, C. A. *ACS Chem.Biol.***2015**, *10* (4), 1099–1109.

Surprisingly, they discovered that (-)-a*S*,11*R*-myricanol reduced Tau levels in both cultured cells and *ex-vivo* brain slices from a mouse model of taupathy, while its enantiomer did not. They speculated that the specific conformation of this enantiomer might enhance its metabolism within the cells, thereby increasing cell permeability.

Furthermore, a structure-activity relationship (SAR) study[24] revealed that the compound resulting from the acid-catalyzed dehydration of myricanol, exhibited robust Tau-lowering activity comparable to (-)-a*S*,11*R*-myricanol (**Scheme 1**). The unexpectedly rearranged molecule turned out to be a mixture of two enantiomers whose structures were elucidated through X-ray analysis.

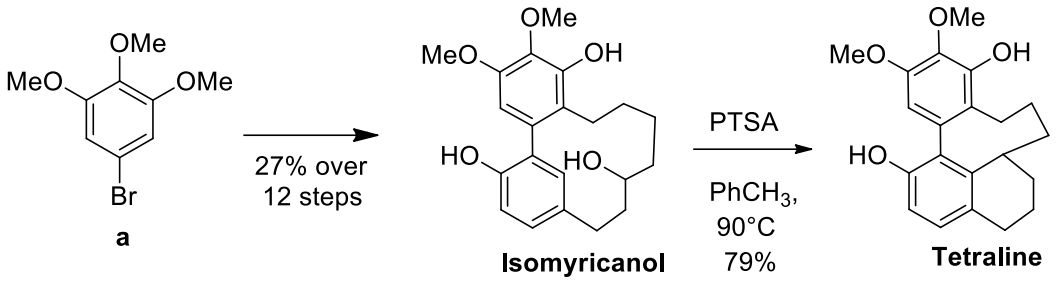
HPLC chiral separation yielded (+)-(4) ($[\alpha]_D^{20}$ = +93.6) and (-)-(4) ($[\alpha]_D^{20}$ = -100), but both enantiomers were separately evaluated for their Tau-lowering effect, and remarkably, both molecules displayed similar activity against tau. This suggests that in this case, the anti-Tau activity is independent from chirality.



Scheme 1. Acid-catalyzed dehydration of myricanol

A direct total synthesis of this biologically active compound would certainly represent an exciting achievement. Recently, our group reported the synthesis of the bioactive tetracyclic derivative in 14 steps with an overall yield of 21%, starting from the total synthesis of iso-myricanol (as illustrated in **Scheme 2**)[25]. The total synthesis of the natural compound actinidione was also achieved.

[25] Massé, P.; Choppin, S.; Chiummiento, L.; Colobert, F.; Hanquet, G. *J. Org. Chem.* **2021**, 86 (3), 3033–3040.



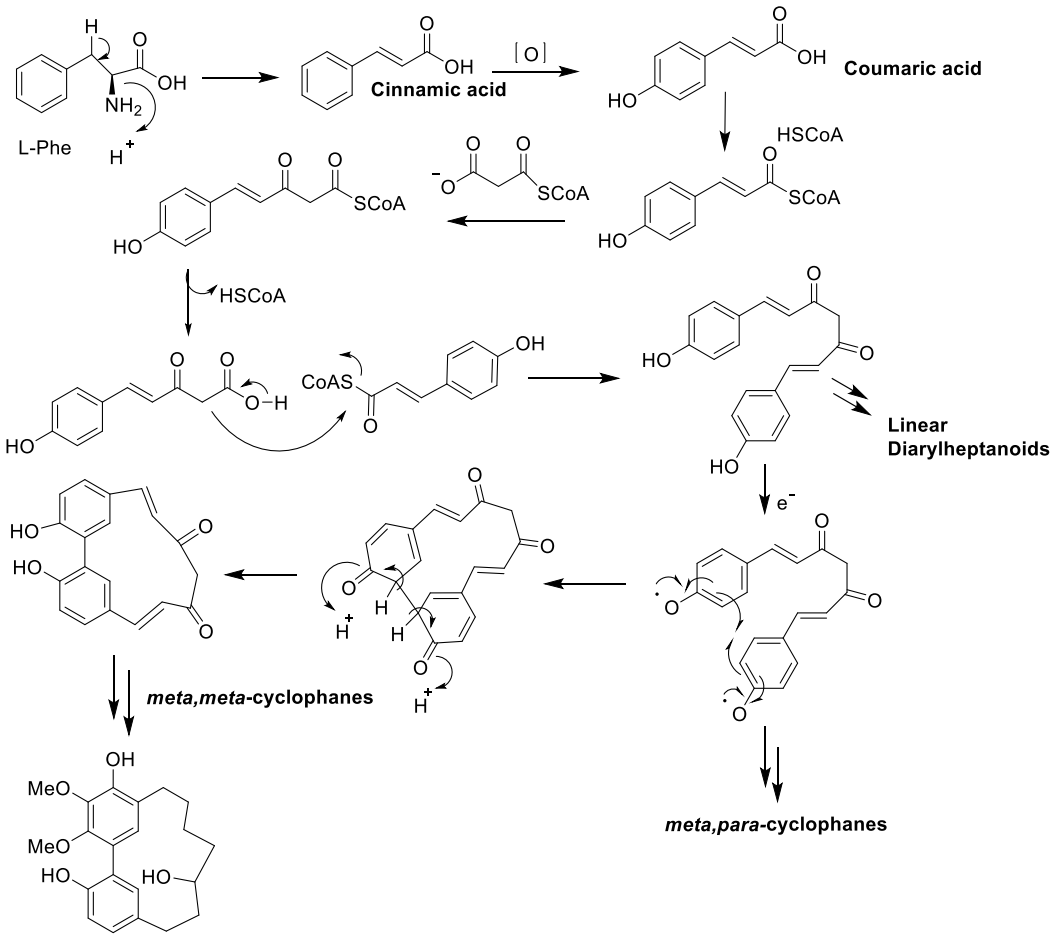
Scheme 2. Total synthesis of tetraline[25]

Due to its proven therapeutic effects and its specific physical properties that suggest the possibility of it meeting the Lipinski's rule (an empirically deduced algorithm for identifying molecules suitable for development and design as drugs), myricanol can be regarded as an ideal candidate for the study and design of a new anti-Alzheimer's drug [26].

[26] Jones J. R.; Lebar M. D.; Jinwal U. K.; Abisambra J. F.; Koren J.; Blair L.; O'Leary J. C.; Davey Z.; Trotter J.; Johnson A. G.; Weeber E.; Eckman C. B.; Baker B. J.; Dickey C. A. *J. Nat. Prod*. **2011**, 74, 38–44.

1.1.3–Biosynthesis

A possible biosynthetic pathway for diarylheptanoids, starting from phenylalanine and passing through coumaric acid, is outlined in **Scheme 3**. The diaryl radical can undergo C-C coupling (as shown in the scheme) leading to the formation of *meta*-cyclophanes. Alternatively, it can undergo C-O coupling, resulting in the formation of diaryl ether cyclophanes.



Scheme 3. Proposed biosynthesis of diarylheptanoids

Alternatively[27], coumaric acid could be first reduced to 3-(4-hydroxyphenyl)propionic acid, which could then enter a mechanism similar to the one outlined previously (**Figure 7**).

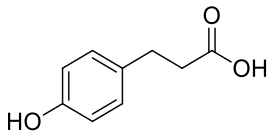


Figure 7. 3-(4-hydroxyphenyl)propionic acid

Kawai *et al.*[27], using labeled coumaric acid, have confirmed the involvement of both coumaric acid itself and 3-(4-hydroxyphenyl)propionic acid in myricanol biosynthesis. It has been hypothesized that hydroxylation and methylation (depicted as the final synthetic step in **Scheme 3**) may occur before the formation of the biaryl ring[27]. Furthermore, it is presumed that coumaric acid and 3-(4-hydroxyphenyl)propionic acid are incorporated into the biaryl system at different ratios. In other words, one of the two substrates likely undergoes functionalizations, methylations, and hydroxylations before reacting with the second substrate, resulting in the formation of an asymmetric coupled system. Through intramolecular oxidative C-C coupling, this system leads to the formation of the *meta,meta*-cyclophane.

[27] Kawai, S.; Nakata, K.; Ichizawa, H.; Nishida, T. J. *Wood Sci* .**2010**, 56 (2), 148-153.

1.2- The formation of Biaryl bonds

This section will present the most common methodologies used for constructing macrocyclic systems and discuss the main challenges associated with the choice of different approaches. Following that, three total syntheses of Myricanol reported in the literature will be discussed. The best result in terms of yield was achieved in 2018 by the research group where this thesis work was conducted[28]. Specifically, Myricanol racemate was obtained in 9 steps with a 4.9% yield, which was competitive with the result obtained by the American research group led by Dickey and coworkers in 2015, with a 2.03% yield in 7 steps but starting from non-commercially available fragments [24].

The first attempt to synthesize Myricanol dates back to 1980, carried out by Whiting and coworkers, with a yield of only 0.21% in 14 steps[29]. Subsequently, there will be a report of an attempt to synthesize Myricanone by Dansou *et al*. in 2000[30]. Given Myricanol's excellent potential as an ideal candidate for the design and development of a new anti-Alzheimer's drug, the aim of this thesis is to propose a new synthetic approach, with a particular focus on overcoming the problems associated with previous attempts. The goal is to achieve higher yields in key reactions, by using cheap commercially available substrates.

Macrocyclization is the most important step in determining the overall efficiency of the synthetic route. This crucial process is made significantly more difficult in small cyclophanic compounds. Because of the strain given by the macrocyclic system, free rotation of the benzene ring(s) is frequently limited, depending on the composition of both the tethered and aromatic parts.[31]

[28] Bochicchio, A.; Schiavo, L.; Chiummiento, L.; Lupattelli, P.; Funicello, M.; Hanquet, G.; Choppin, S.; Colobert, F. *Org. Biomol. Chem.*, **2018**, 16, 8859-8869.
[29] a)Henley-Smith, P.; Whiting, D.A.; Wood, A.F. *J. Chem. Soc. Perkin 1*, **1980**, 614-622. b) Whiting, D.A.; Wood, A.F. *J. Chem. Soc. Perkin 1*, **1980**, 623-628. c) Mohamed, S. E. N.; Whiting, D.A. *J. Chem. Soc. Perkin 1*, **1983**, 2577-2582.
[30] Dansou, B.; Pichon, C.; Dhal, R.; Brown, E.; Mille, S. *Eur. J. Org. Chem*. **2000**, 2000 (8), 1527-1533.
[31] Gulder,T.; Baran,P.S. *Nat.Prod.Rep.***2012**,*29*(8),899. b)Kane,V.V.; DeWolf,W.H.; Bickelhaupt,F. *Tetrahedron* **1994**, *50*(16), 4575–4622.

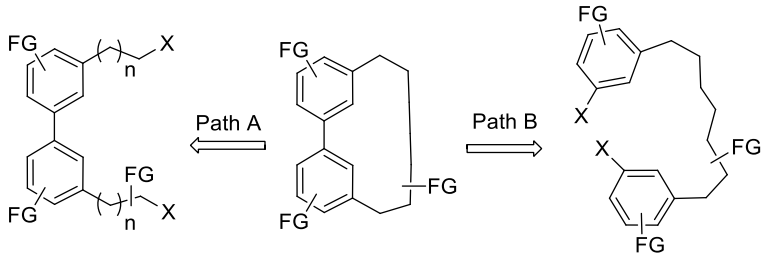
Natural cyclophanic products are an interesting family of structurally varied molecules. The diarylheptanoids are a structurally distinct subclass of cyclophanic natural compounds, with a scaffold composed of two benzene rings linked by an oxygenated aliphatic heptyl chain.

Organic chemists have been working for over a century to create new and more efficient methods to create aryl-aryl bonds.[32]

[7,0]-*meta,meta*-cyclophanes could be synthesized via macrocyclization with the formation of the heptyl chain on a biaryl precursor (Path A) or via aryl-aryl coupling on a linear diarylheptanoids (Path B) (**Scheme 4**). In both situations, by the way, these macrocyclizations are subject to several limitations, with the control of atropoisomery (see section 1.2.2) in the case of biaryl coupling enhancing the synthetic challenge that such compounds provide[33] due to the torsional strain in cycle and the steric interactions between hydrogens within the 13-membered ring on the one hand, and on the other, and steric and electronic effects around the coupling sites in the case of an aryl-aryl coupling.

In any case, these two main pathways will be investigated throughout this thesis. Below, some examples related to methodologies for building the macrocycles according to path A or path B are provided.

The Wittig-type reaction[34], the Thorpe-Ziegler reaction[35], and olefin metathesis[36] reactions were employed for the C–C bond formation in the heptane moiety (Path A) while the Suzuki-Miyaura (domino) reaction, the Ullmann coupling, or a photochemical cyclization were applied to the synthesis of cyclic diarylheptanoids at the final step (Path B). Those examples will be discussed in the next sections.



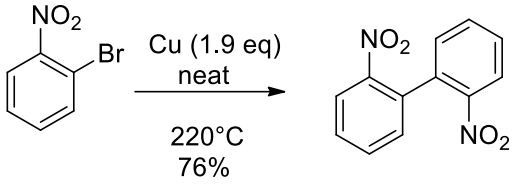
Scheme 4. General Path A and Path B

[32] Alberico,D.; Scott, M. E.; Lautens,M. *Chem.Rev.* **2007**, *107*(1),174–238.
[33] Bringmann,G.; Gulder,T.; Gulder,T.A. M.; Breuning, M.*Chem.Rev.* **2011**, *111*(2), 563–639.
[34] Wittig, G.; Geissler, G. *Ann. Chem.***1953**, 580, 44–57.
[35] Moore, C.W.; Thorpe, J.F. *J. Chem. Soc. Trans.***1908**, 93, 165–187.
[36] Grubbs, R.H.; Brunck, T.K. *J. Am. Chem. Soc.***1972**, 94, 2538–2540.

The following sections will cover the fundamental approaches to biaryl coupling and will feature the presentation and discussion of both intermolecular reactions (Path A) and intramolecular reactions (Path B) through illustrative examples of Ullman reactions, Suzuki-Miyaura and oxidative coupling reactions.

1.2.1-Copper Catalyzed Ullmann coupling

The first example of the Ullmann reaction dates back to 1901[37] (**Scheme 5**), an homocoupling reaction between bromonitrobenzene using stoichiometric excess of copper powder under neat reaction conditions at 220°C.



Scheme 5. Ullmann homocoupling

Since then, the Ullmann coupling has been extensively studied, and its applications have been thoroughly reviewed[38].

Generally, classic Ullmann reactions tend to proceed with better yields when groups with lone pairs are present in the *ortho* position, regardless of the electron donating or withdrawing nature of the groups[39] .

Normally the Ullmann coupling were performed at high temperatures in DMF[40] instead mild intramolecular Ullmann coupling of aryl halide were accomplished with Cu(I) thiophene-2-carboxylate in NMP with good yields (**Scheme 6**).

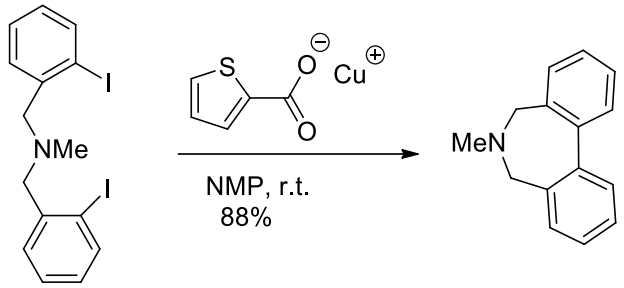
[37] Ullmann,F.; Bielecki,J.*BerichteDtsch.Chem.Ges.***1901**,*34*(2), 2174–2185.

[38] a) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102* (5), 1359–1470. b) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248* (21–24), 2337–2364. c)Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108* (8), 3054–3131. d) *Copper-Mediated Cross-Coupling Reactions*; Evano, G., Blanchard, N., Eds.; John Wiley & Sons, Inc.: Hoboken, NJ, USA, **2013.**

[39] Forrest J. *J.chem soc.* **1960**, 592.

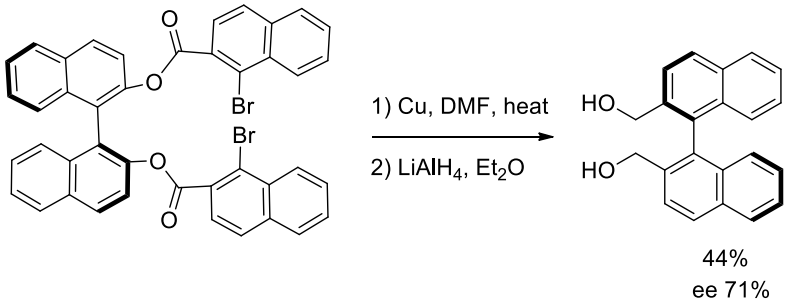
[40] Kornblum, N.; Kendall, D.L. *J.am.chem.soc.* **1952**, 74, 5782.

Homocoupling of iodo-benzoate were performed with high yields at r.t. by using CuI, while low reaction yields were obtained when CuBr or CuCl were used.[41]



Scheme 6. Intramolecular Ullmann coupling[41]

Another example of intramolecular, atroposelective Ullmann coupling was reported by Miyano et *al*. who used temporary chiral tether to obtain (*S*)-2,2'-di(hydroxymethyl)-1,1'-binaphthyl in a moderate optical purity[42] (**Scheme 7**).



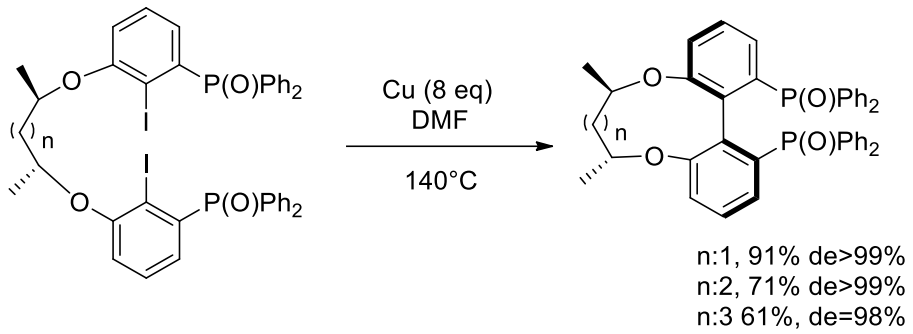
Scheme 7.Synthesis of (*S*)-2,2'-di(hydroxymethyl)-1,1'-binaphthyl using Ullmann coupling reaction

Others examples to perform diastereoselective intermolecular Ullmann couplings were also extensively studied in which tethers bearing central chirality were employed . For example, the biaryl bisphosphine oxides were obtained with excellent diastereoselectivity (over 98%) and the highest yield with shorter tether length[43] (**Scheme 8**).

[41] Zhang, S.; Zhang, D.; Liebeskind, L.S. *J. Org. Chem*. **1977**, 62, 2312.

[42] a) Miyano, S.; Tobita, M.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1981**, *54* (11), 3522–3526. b)Miyano, S.; Fukushima, H.; Handa, S.; Ito, H.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1988**, *61* (9),3249–3254.

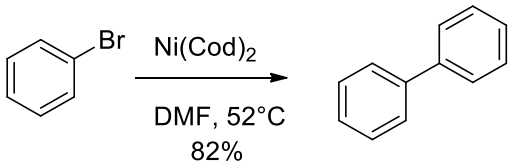
[43] Qiu, L.; Kwong, F. Y.; Wu, J.; Lam, W. H.; Chan, S.; Yu, W.-Y.; Li, Y.-M.; Guo, R.; Zhou, Z.;Chan, A. S. C. *J. Am. Chem. Soc*.**2006**,*128*(17),5955–5965.



Scheme 8. Diasteroselective intramolecular Ullmann coupling[43]

1.2.2-Nickel Catalyzed Ullmann coupling

Semmelhack and co-workers described a nickel catalyzed reductive homocoupling of aryl halide as an alternative to copper Ulmann coupling, in which the major advance was to perform the coupling at lower temperatures as well (**Scheme 9**).[44]



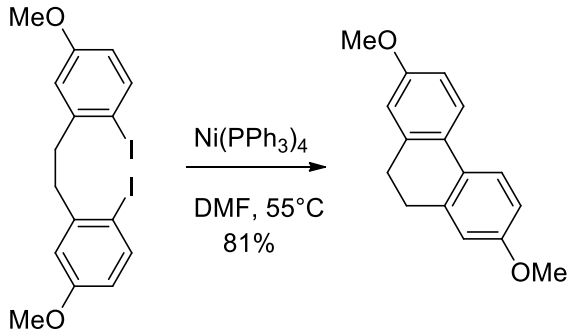
Scheme 9. Nickel-catalyzed homocoupling reaction

An issue with the use of nickel(0) species is their high air sensitivity. Therefore, effective methods for generating the active Ni(0) species have been proposed over the years. Rieke and co-workers described a method for preparation of Ni(0) via reduction of Ni(II) halides with Li metal/naphtalene in glyme[45-47].

[44] Semmelhack, M. F.; Helquist, P.; Jones, L.D. *J.Am.Chem.Soc*. **1971**, 93, 5908
[45] Rieke, R. D.; Burns, T.P.; Wehmeyer, R.M.; Kahn, B.E. In ACS Symposium Series; Suslick, K.S., Ed.; **1987**; Vol. 333, pp. 223-245.
[46] Matsumoto, H.; Inaba, S.-i.; Rieke, R.D. J.Org.Chem. **1983**, 48, 840.
[47] Inaba, S.-i.; Matsumoto, H.; Rieke, R. D. Tetrahedron Lett. **1982**, 23, 4215.

Ni(0) can also be prepared by electrolysis by using a platinum cathode and a nickel anode in a DMF solution of Bu_4NBF_4[48] or by *in situ* preparation of the active Ni(0) specie of $Ni(PPh_3)_4$ by using $Ni(PPh_3)_2Cl_2$, Zn dust as reducing agent, in the presence of an excess of PPh_3,[49] the Ni(0) source could also be used in catalytic amounts being regenerated by Zn dust.

Reactions which did not work in the Cu-catalyzed Ullmann coupling could be performed by using a Ni(0) source,[50-52] moreover, while intramolecular $Ni(cod)_2$ catalyzed reactions gave low yield, $Ni(PPh_3)_4$ in DMF furnished higher yield[52] as showed in the example below (**Scheme 10**).

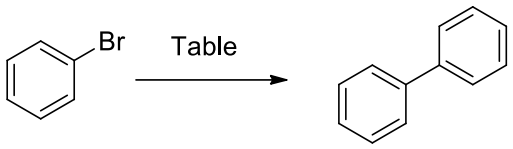


Scheme 10. Ni-Catalyzed intramolecular coupling

Generally, EWD-substituents tend to favor the intramolecular coupling while electron-donating groups disfavor it[46,53]. *Ortho* substituents usually inhibit the nickel-catalyzed coupling[46,49,50,51,54] but increasing catalytic amounts of the Ni(0) source, in the presence of stoichiometric amounts of Et_4NI, the reaction yield can be increased[55]. Nickel complex reducing agents (NiCRA), prepared by reduction of $Ni(OAc)_2$ with alkali metal hydrides and alcohol[56-57], can also allow the coupling of *ortho-ortho* substituted biphenyl compounds.[56]

The use of additives could also improve the reaction yields especially when it is up to aryl-Cl substrates since they are unreactive unless KI is added[54], the addition of KI also allows THF to be used as the solvent instead of DMF[55] without any excess of PPh_3 (**Table 1**).

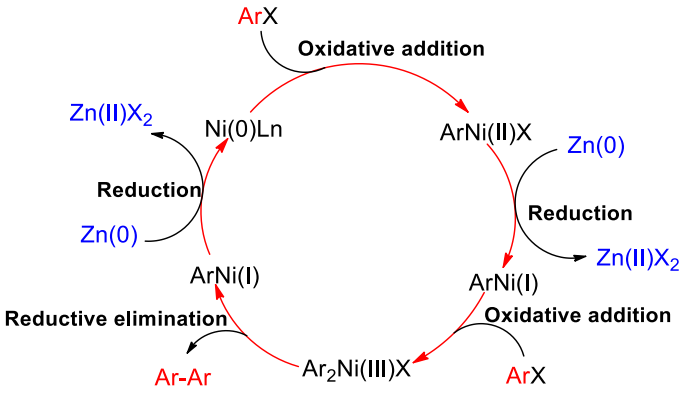
[48] Nakajima, R.; Shintani, Y.; Hara, T. *Bull Chem. Soc. Jpn*. **1980**, 53, 1767.
[49] Kende, A. S.; Liebeskind, L.S.; Braitsch, D.M. *Tetrahedron Lett*. **1975**. 3375.
[50] Zembayashi, M.; Tamao, K.; Yoshida, J.-i.; Kumada, M. *Tetrahedron Lett*. **1977**. 4089.
[51] Semmelhack, M.F.; Helquist, P.; Jones, L.D.; Keller, L.; Mendelson, L.; Ryono, L.S.; Smith, J.G.; Stauffer, R.D. *J. Am. Chem. Soc*.**1981**, 103, 6460.
[52] Semmelhack, M.F.; Ryono, L.S. *J. Am. Chem. Soc*. **1975**, 97, 3875.
[53] Colon, I.; Kelsey, D. R. *J. Org. Chem*.**1986**, 51, 2627.
[54] Chao, C. S.; Cheng, C. H.; Chang, C. T. *J. Org. Chem*. **1983**, 48, 4904.
[55] Iyoda, M.; Otsuka, H.; Sato, K.; Nisato, N.; Oda, M. *Bull. Chem. Soc. Jpn*. **1990**, 63, 80
[56] Lourak, M.; Vanderesse, R.; Fort, Y.; Caubère, P. *J. Org. Chem*.**1989**, 54, 4840.
[57] Massicot, F.; Schneider, R.; Fort, Y. *J. Chem. Res. (S)*. **1999**, 664.



Conditions	Yield
$Ni(PPh_3)_2Cl_2$ / Zn / PPh_3 (1 / 1 / 2), DMF, 50°C	73% (U.122)
$Ni(PPh_3)_2Cl_2$ / Zn / PPh_3 /KI (0.05 / 1 / 0.4 / 1) DMF, r.t.	81% (U.123)
$Ni(PPh_3)_2Cl_2$ / Zn / PPh_3 /KI (0.1 / 1.5 / 1) THF, 50°C	92% (U.139)

Table 1. Ni-catalyzed Ullmann like reaction with additives

The mechanism[58] of this reaction likely involves Ni(I) and Ni(III) intermediates. The presence of zinc (Zn) is crucial as it plays a role in the catalytic cycle (**Scheme 11**). The iodine (I-) source allows for the substitution of a chloride ion (Cl^-) in the ArNi(II)Cl species, resulting in ArNi(II)I. At this stage, iodine may facilitate electron transfer between nickel and zinc[50,53,55,59]. This mechanistic hypothesis could explain the improved yields observed when KI was added.

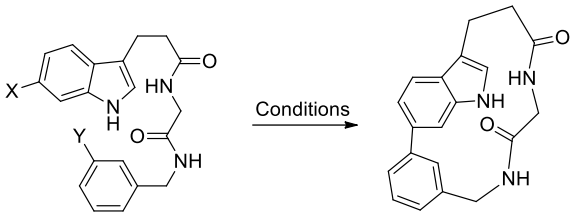


Scheme 11. Catalytic cycle of Ni-catalyzed Ullmann like reaction

A publication from 1998[60] describes the successful total synthesis of a 17-membered macrocycle (**Table 2**). The final macrocyclization did not yield positive results under Suzuki-Miyaura conditions

[58] Amatore, C.; Jutand, A. *Organometallics*. **1988**, 7, 2203.
[59] Takagi, K.; Hayama, N.; Inokawa, S. *Bull Chem. Soc. Jpn*. **1980**, 53, 3691.
[60] Carbonnelle, A.-C.; Zamora, E. G.; Beugelmans, R.; Roussi, G. *Tetrahedron Letters***1998**, 39, 4471-4472.

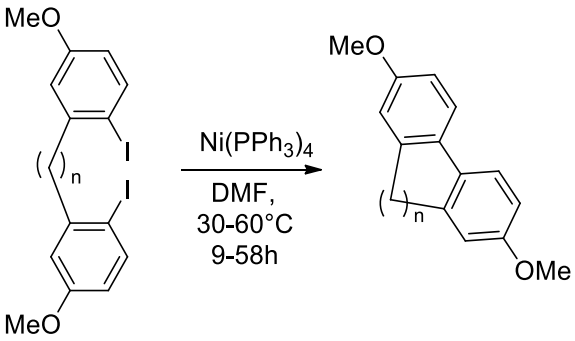
or via Cu-catalyzed Ullmann reaction. Instead, it resulted in the synthesis of the macrocycle through a Ni-catalyzed Ullmann-like cyclization with *in-situ* generation of the $Ni(PPh_3)_4$ species.



X	Y	Catalyst	Yield
Br	**$B(OH)_2$**	**$Pd(AcO)_2$,**	**0**
Br	Br	CuCN	**0**
Br	**Br**	$Ni(PPh_3)_2Cl_2$, Zn, PPh_3	**17**

Table 2. Total synthesis of a 17-membered ring macropolypeptide

An extensive study was published by Semmelhack in 1981[51] in which a series of biaryls was synthesized strating from diiodides chosen to test the ring size limitations in the cyclization process[51] (**Table 3**). Excellent cyclization yields were obtained in each case.



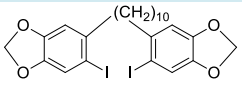
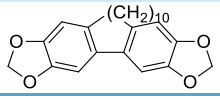
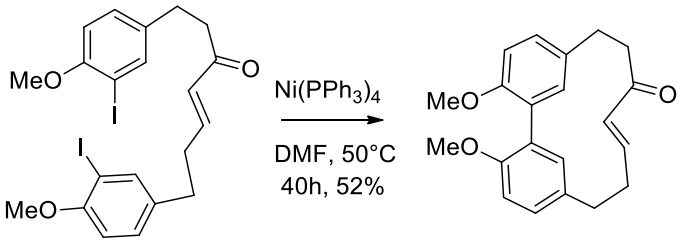
Substrate	Product	Yield
n=2	**n=2**	**81%**
n=3	**n=3**	**83%**
n=4	**n=4**	**76%**
n=5	**n=5**	**85%**
n=6	**n=6**	**38%**
		58%

Table 3. Ni-catalyzed cyclizations[51]

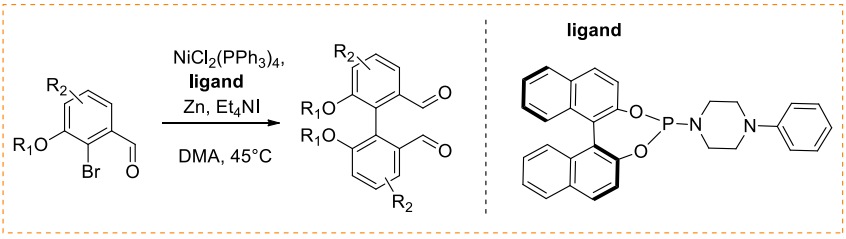
Finally, Semmelhack also reported the total synthesis of the cyclic diarylheptanoid alnusone (**Scheme 12**)[51].



Scheme 12. Total synthesis of alnusone

The crucial macrocyclization step (before demethylation to afford Alnusone) gave a 52% yield by using $Ni(PPh_3)_4$ as the Ni(0) source in DMF.

In the section 1.3.1 will be discussed another important Ni-catalyzed macrocyclization by Whiting *et al.* about the total synthesis of Myricanol[29]. The first example of a nickel-catalyzed asymmetric Ullmann coupling were reported in 2010, tetra-*ortho*-substituted biaryl compounds were atroposelectivily synthesized by using a chiral BINOL based monodentate phosphoramidite ligand. Moreover, the formal synthesis of (+)-isoschizandrin was also accomplished[61] (**Table 4**).



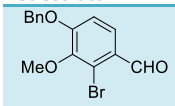
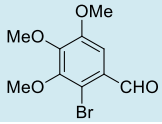
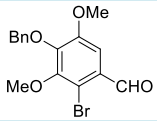
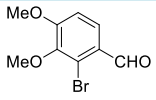
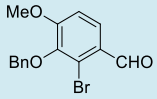
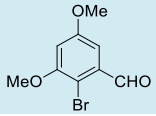
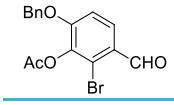
Substrate	Yield (%)	ee (%)	Substrate	Yield (%)	ee (%)
	62	61		67	68
	60	58		55	58
	62	58		65	44
	31	15			

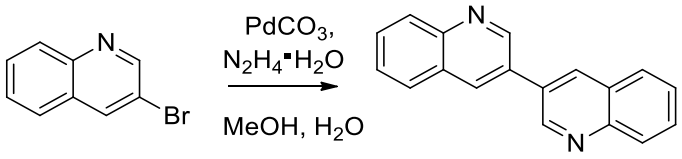
Table 4. Ni-catalyzed atroposelective Ullmann Coupling selected examples

1.2.3-Palladium catalyzed Ullmann-like coupling

[61] Chen, W.-W.; Zhao, Q.; Xu, M.-H.; Lin, G.-Q. *Organic Letters***2010**, 12(5), 1072-1075.

The use of palladium-catalyzed reductive coupling of aryl halides has been established as a valuable substitute for the conventional copper-mediated Ullmann reaction. This change is primarily attributed to the mild reaction conditions and the high tolerance of starting materials[62-64]. However, the palladium-catalyzed reductive coupling needs a reducing agents to start the catalytic cycle. The need for *in situ* regeneration of the active Pd(0) species also arises because of it tendency to agglomeration, leading to the formation of a black sediment and loss of catalytic activity.

The first reported Pd-catalyzed Ullmann-like coupling was reported in the early '30s in the presence of hydrazine[65-67], some examples are reported in the following **Scheme 13**.



Scheme 13. Pd-catalyzed homocoupling

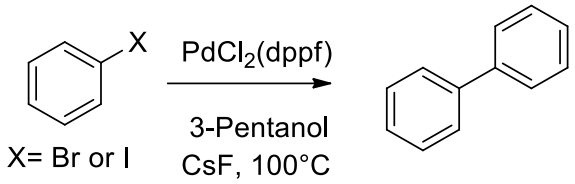
It has been shown that steric constraints are particularly affecting the Pd-catalyzed homocoupling compared to Ni- and Cu-catalyzed reactions[68]. When *ortho* substituents are present, the reaction yield dramatically decreases, while, the reaction doesn't work at all with 2,6-disubstituted aryl halides.

The nature of the halide also have an important influence on the reaction, biphenyl formation from iodobenzenes occurred in 75% yield while, under the same conditions, the bromobenzene afforded the biphenyl compound with a 25% yield.[69]

[62] Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.***2002**, 102, 1359.
[63] a) Hennings, D. D.; Iwama, T.; Rawal, V. H. *Org. Lett.***1999**, 1, 1205. b) Kuroboshi, M.; Waki, Y.; Tanaka, H. *J. Org. Chem.***2003**, 68, 3938.
[64] Tsuji, J. *Palladium Reagents and Catalysts*, 2nd ed., Wiley, New York, **2004**; Chapter 2.
[65] Busch, M.; Weber, W. *J. Prakt. Chem*. **1936**, 146, 1.
[66] Uyeda, K. *Yakugaku Zasshi*, **1931**, 51, 495; *Chem Abstr*. **1931**, 2, 5427.
[67] Nakajima, R.; Iida, H.; T. *Bull. Chem. Soc. Jpn*. **1990**, 63, 636.
[68] Clark, F. R.; Norman, R. O. C.; Thomas, C.B. *J. Chem. Soc. Perkin Trans. I*, **1975**, 121.
[69] Dyker, G. *J. Org. Chem*. **1993**. 58, 234.

In a more recent publication it has been found that the palladium-catalyzed reductive homocoupling could be carried out in dimethyl sulfoxide (DMSO) without any external reductants.[70] Although the solvent DMSO molecules were shown to be involved in the regeneration of Pd(0), the oxidation products, arising from DMSO were not identified, probably due to the complicated oxidation of DMSO[70].

The same group reported their initial results of the Pd(dppf)Cl_2-Ullmann-like homocoupling of aromatic halides in 3-pentanol (or 2-propanol)[71] with high yields (**Table 5**). Interestingly the reaction worked well with Pd(dppf)Cl_2but with Pd(PPh_3)$_4$ and $PdCl_2$ didn't work at all[71]

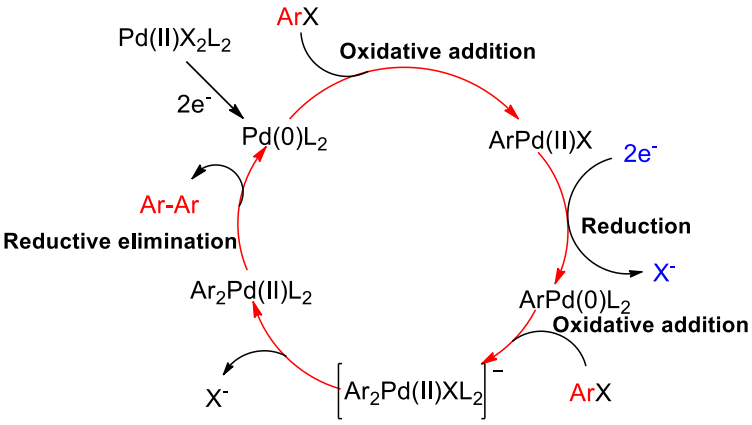


Substrate	Conversion	time	Biphenyl Yield (%)	Dehalogenated Yield (%)
C_6H_5Br	100	8	88	11
C_6H_5I	100	5	89	10
4-FC_6H_4I	100	29	60	40
4-$CF_3C_6H_4I$	100	30	75	25
2-$CH_3C_6H_4I$	100	12	0	100
4-$CH_3C_6H_4I$	100	12	3	97

Table 5. Reported Pd-catalyzed homocouplings

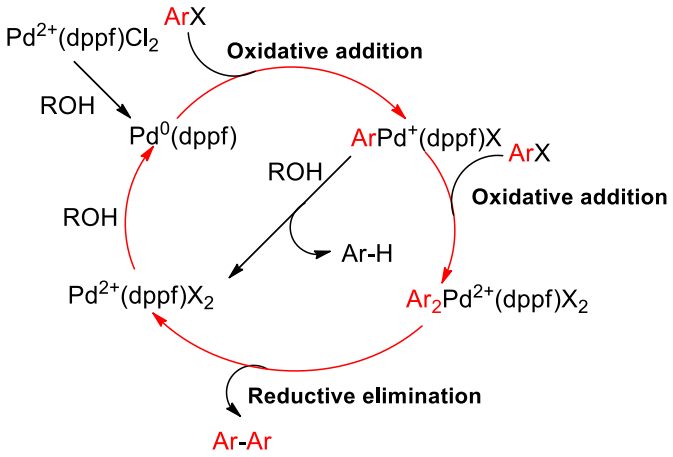
The mechanism of this reaction, similar to the Ni-catalyzed reaction discussed above, seems to involve only Pd(0) and Pd(II) species[72-78], (**Scheme 14).**

[70] Qi, C.; Sun, X.; Lu, C.; Yang, J.; Du, Y.; Wu, H.; Zhang, X.-M. *J. Organomet. Chem*. **2009**, 694, 2912.
[71] Zeng, M.; Du, Y.; Shao, L.; Qi, C.; Zhang, X.-M. *J. Org. Chem*. **2010**, 75, 2556–2563.
[72] Jutand, A.; Mosleh, A. *J. Org. Chem.***1997**, 62, 261.
[73] Amatore, C.; Carré, E.; Jutand, A.; Tanaka, H.; Ren, Q.; Torii, S. *Chem Eur. J.***1996**, 2, 957.



Scheme 14. Pd-catalyzed homocoupling proposed mechanism

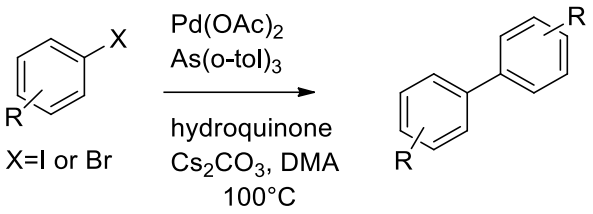
An alternative mechanism, involving Pd(I) species, was proposed when Pd(dppf)Cl_2 in DMSO (or alcohol) were used (**Scheme 15**)[71].



Scheme 15. Pd-catalyzed homocoupling alternative mechanism in DMSO or ROH[71]

There are also examples of inter and intramolecular Pd catalyzed Ullmann reactions (**Table 6**) on various substrates with good yields under mild reaction conditions[63].

[74] Amatore, C.; Jutand, A. *J. Organomet. Chem*. **1999**, 576, 254.
[75] Amatore, C.; Jutand, A. *Acc. Chem. Res*. **2000**, 314.
[76] Yamamoto, A.; Kayaki, Y.; Nagayama, K.; Shimizu, I. *Synlett***2000**, 925.
[77] Grushin, V. V.; Alper, H. *Chem. Rev.***1994**, 94, 1047.
[78] Jutand, A.; Mosleh, A. *Organometallics* **1995**, 14, 1810.



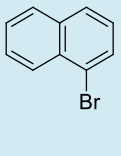
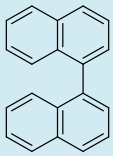
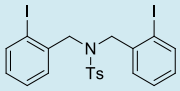
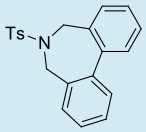
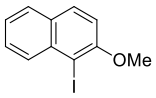
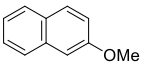
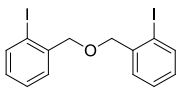
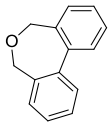
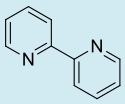
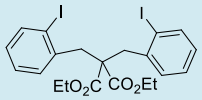
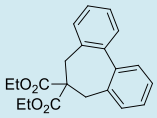
Substrate	Product	Yield(%)	Substrate	Product	Yield(%)
		90			82
		91			61
		72			65

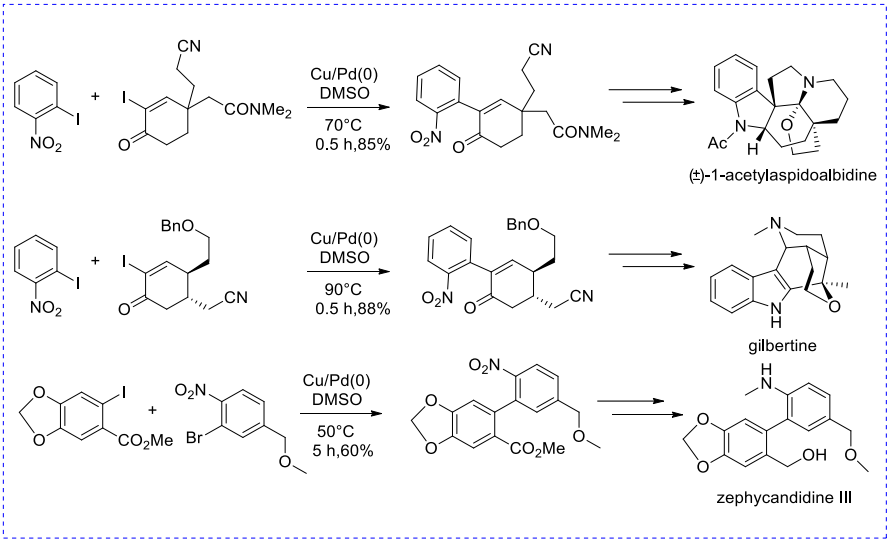
Table 6. Intermolecular and intramolecular Pd-Catalyzed Ullmann reaction

1.2.4- Pd/Cu catalyzed Ullmann coupling

Pd/Cu catalyzed Ullmann couplings were successfully used for several total syntheses examples of a range of structurally challenging natural products[79].

The next **Scheme 16** focuses on the Pd-catalyzed step for some selected examples.

[79] Khan, F.; Dlugosch, M.; Liu, X.; Banwell, M. G. *Acc. Chem. Res.***2018**, 51 (8), 1784–1795.



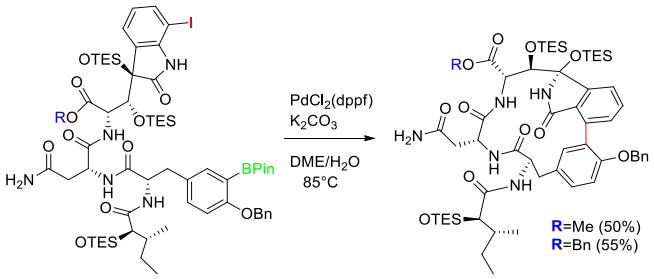
Scheme 16. Selected Pd/Cu-catalyzed Ullmann examples

1.2.5- Suzuki-Miyaura Reaction

The Pd-catalyzed Suzuki–Miyaura cross-coupling of boronic species and aryl halides, since its discovery in the late 1970s,[80] has emerged as a synthetic method that tolerates a wide range of functional groups providing reliable and efficient access to C-C bond formation more particularly to the biaryl motifs[81] and it is one of the most widely applied methods in inorganic chemistry.[82]

This chemistry has found numerous applications on academic and pharmaceutical industry.[83]

An example of intramolecular Suzuki-Miyaura cross-coupling reaction has been applied to install the biaryl motif of diverse macrocycles, such as for the core of TMS-95[84] (**Scheme 17**).



Scheme 17. Synthesis of macrocyclic core of TMC-95

[80] a) Miyaura, N.; Suzuki, A. *J. Chem. Soc. Chem. Commun.* **1979**, *19*, 866. B) Miyaura, N.; Yanagi,T.; Suzuki, A. *Synth. Commun.* **1981**, *11* (7), 513–519. c) Suzuki, A. *Acc. Chem. Res.* **1982**, *15* (6),178–184. d) Suzuki, T.; Hotta, H.; Hattori, T.; Miyano, S. *Chem. Lett.* **1990**, *19* (5), 807–810. e)Miyaura,N.;Suzuki, A.*Chem.Rev.* **1995**, *95*(7),2457–2483.

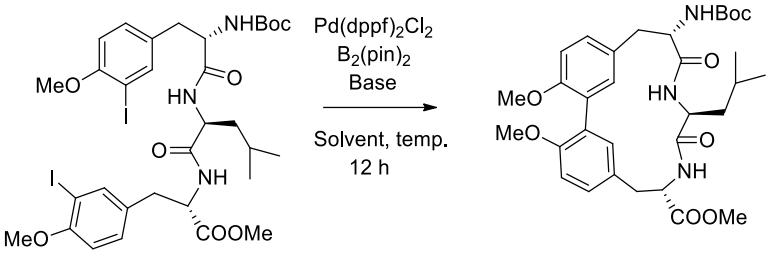
[81] Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. *Chem. Rev.* **2011**, *111* (2), 563–639.

[82] Kotha,S.; Lahiri,K.;Kashinath, D.*Tetrahedron* **2002**,*58*(48), 9633–9695.

[83] Magano,J.;Dunetz,J. R.*Chem. Rev.* **2011**, *111* (3),2177–2250.

[84] Coste,A.; Bayle,A.;Marrot,J.; Evano, G. *Org.Lett.***2014**, *16*(5),1306–1309.

Zhu and Carbonnelle[85] developed a one-pot macrocyclization procedure involving the *in situ* formation of a pinacol boronic ester followed by an intramolecular Suzuki-Miyaura cross-coupling; a 15-membered ring *m*,*m*-cyclophane was achieved in 45% yield (**Table 7**), it was shown that little variations of the reaction conditions were dramatically lowering the macrocyclization yield to 10% or traces; several side reactions could take place such as halogen reduction, intramolecular couplings and double Miyaura borylation.



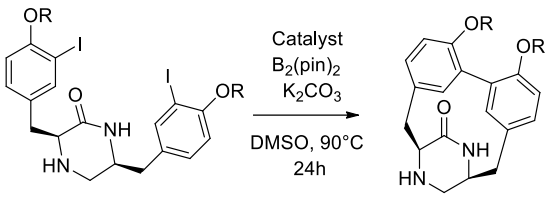
Base	Solvent	Conc M	Temp °C	Yield (%)
KOAC	DMSO	0.005	40-45	trace
KOAC	DMSO	0,02	40-45	trace
KOAC	DMSO	0.005	80-85	10%
KOAC	DMSO	0.02	80-85	45%
KOAC	DME	0.2	80-85	0%
KOAC	DME	0.02	80-85	0%
Na_2CO_3	DME	0.02	80-85	0%
K_2CO_3	DMSO	0.02	80-85	trace
KOAc-K_2CO_3	DMSO	0.02	80-85	trace

Table 7. One pot macrocyclization by Zhu and Carbonnelle[85]

Hutton *et al.*[86] reported the total synthesis of myclocyclosin, a natural diketopiperazine, by using the same one-pot process; the essays conducted with Ni-catalyzed Ullman-type macrocyclization (entries 1-2) were unsuccessful (**Table 8**).

[85] Carbonnelle,A.-C.;Zhu, J.*Org. Lett.* **2000**, *2*(22),3477–3480.

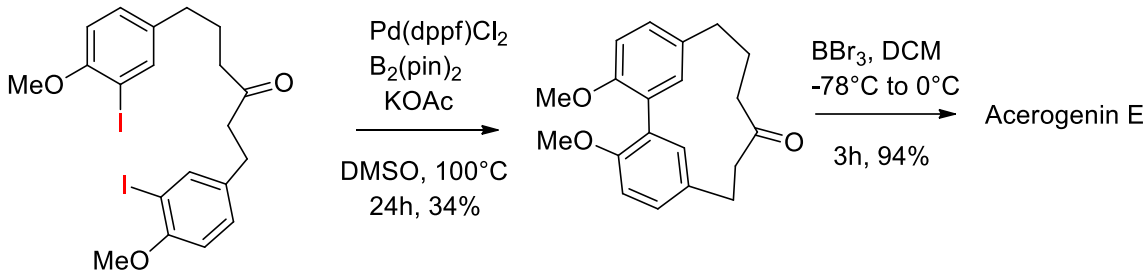
[86] Cochrane,J.R.;White,J.M.;Wille, U.;Hutton, C.A.*Org.Lett.***2012**, *14*(9), 2402–2405.



R	$B_2(pin)_2$ (equiv.)	Catalyst	Yield (%)
Bn	-	$NiCl_2(PCy_3)_2$, Zn, PPh_3	0
Bn	-	$Ni(PPh_3)_4$	0
H	1.2	$Pd(dppf)\cdot CH_2Cl_2$	0
Bn	1.2	$Pd(dppf)\cdot CH_2Cl_2$	33
Bn	**1.0**	**$Pd(dppf)\cdot CH_2Cl_2$**	**42**
Bn	0.6	$Pd(dppf)\cdot CH_2Cl_2$	27

Table 8. Macrocyclization for the total synthesis of myclocyclosin[86]

Usuki and Ogura[87] reported the total synthesis of acerogenin E and K (myricanol's analogues) by using the same conditions developed by Zhu[85], (**Scheme 18**). Macrocyclization attempt was achieved by using a one-pot Suzuki-Miyaura domino reaction with a 34% yield.

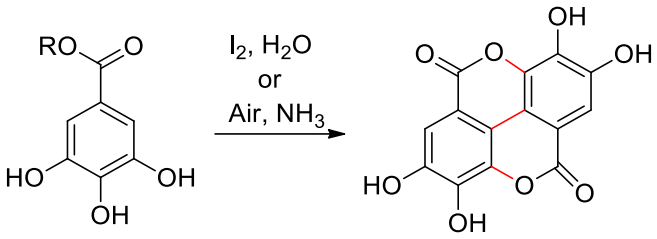


Scheme 18. Total synthesis of acerogenin E[87]

[87] Ogura,T.; Usuki,T.*Tetrahedron***2013**,*69*(13),2807–2815.

1.2.6- Oxidative Coupling

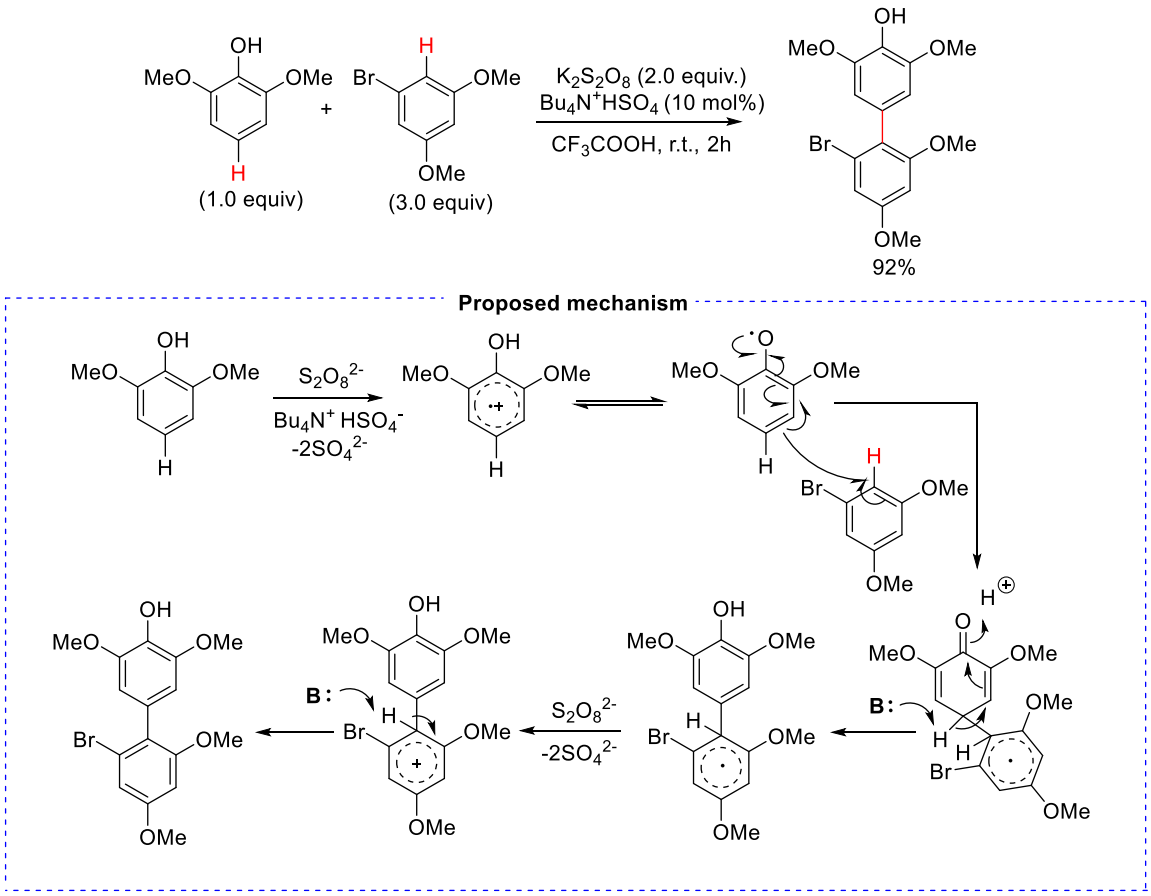
The first oxidative biaryl cross-coupling reaction was reported in 1871 by Griessmayer, it describes the reaction of gallic acid (3,4,5-trihydroxybenzoic acid) or its ester to produce the ellagic acid using molecular iodine or air/NH_3 as oxidants[88] (**Scheme 19**)



Scheme 19. Griessmayer oxidative coupling

Since then, the oxidative couplings were widely investigated by organic chemists mainly because of its ability to rapidly access C-C coupling of biaryl natural compounds through a biomimetic synthesis. Several oxidazing agents were investigated such as Mn(acac)3/TFA, CoF_3/TFA, $Fe(ClO_4)_6H_2O$/TFA;[89] or DDQ/TFA;[90] , Tl_2O_3/BF_3Et_2O/TFA.[91] VOF_3/TFA/DCM;[92] and PIFA/BF_3Et_2O/DCM;[93]or still rongalite[94] or $K_2S_2O_8$ /$Bu_4N^+ \cdot HSO_4^-$[95].

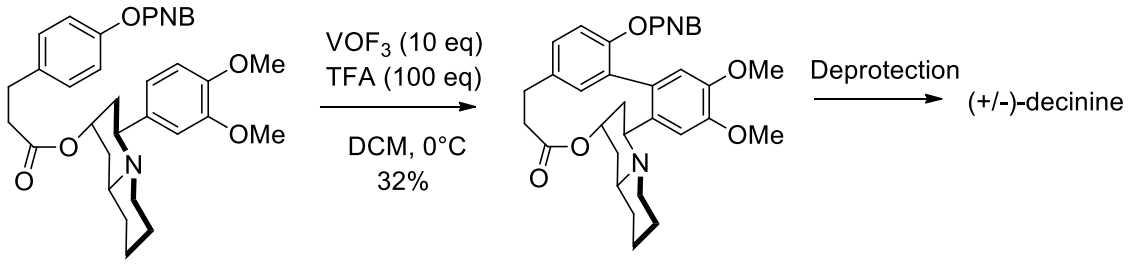
[88] Griefsmayer,V. *Ann.Chem.Pharm.***1871**,*160*(1),40–56.
[89] Tanaka,M.; Mukaiyama, C.;Mitsuhashi,H.;Maruno,M.;Wakamatsu,T.*J. Org.Chem.***1995**, *60*(14),4339–4352.
[90] Palter,A.;Ward, R. S.;Jones, D. M.;Maddocks, P.*J.Chem. Soc.[Perkin 1]***1993**, No. 21, 2631–2637.
[91] Enders,D.; Lausberg,V.; Signore,G.D.; Berner,O.M. *Synthesis* **2002**,*2002*(04),515–522.
[92] Shan,Z.-H.;Liu,J.;Xu,L.-M.;Tang,Y.-F.;Chen,J.-H.;Yang,Z.*Org.Lett.***2012**,*14*(14),3712–3715.
[93] Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, Y. *Tetrahedron* **2009**, *65* (52),10797–10815.
[94] Yu, F.; Mao, R.; Yu, M.; Gu, X.; Wang, Y. *J. Org. Chem.***2019**, 84 (16), 9946–9956.
[95] More, N. Y.; Jeganmohan, M. *EurJoc.***2017**, 29, 4305-4312.



Scheme 20. Oxidative Cross-Coupling – Proposed Mechanism

The **Scheme 20** shows the use of $K_2S_2O_8$ /$Bu_4N^+ \cdot HSO_4^-$ in a oxidative cross-coupling study, the $K_2S_2O_8$ reacts with substituted phenol forming a cationic phenol radical intermediate. Then, the aromatic substrate undergoes the nucleophilic addition with the radical phenol intermediate, forming the cross-coupling product[95].

Yang and co-workers reported the total synthesis of (+/-)-decinine, a 12- membered ring alkaloid[92] by using the VOF_3/TFA/DCM system to afford the intramolecular oxidative coupling obtaining the biarylic compound in 32% yield (**Scheme 21**).



Scheme 21. Intramolecular oxidative coupling during the synthesis of (+/-)-decinine

1.2.7- Control of axial chirality

Natural compounds containing axially chiral biaryl skeletons include alkaloids, coumarins, flavonoids, tannins, terpenes, and peptides[81]. They are also used as a privileged framework for chiral reagents[96] in asymmetric catalysis, chiral phases for chromatography[97], chiral liquid crystals[98], and chiral bioactive compounds[99] in the pharmaceutical sector.

The term atropisomerism (conied by Richard Kuhn in 1933)[100] refers to a type of isomerism caused by a limited rotation around the single bond that connects the aryl moieties (two distinct planes). Atropisomers are then conformers formed from atropisomerism that can be separated as independent chemical entities.

The biphenyl rings are perpendicular in order to decrease steric hindrance between the four *ortho* substituents, resulting in considerably slower rotation about the biphenyl bond.

M. Oki[101] defined some key parameters for describing atropisomerism; a rotationally stable axis and the existence of different substituents on both sides of the axis are required for axial chirality. If the atropisomers have a half-life of 1000 s (16.7 min) at a given temperature, they are physically separable. M. Oki also specified the minimum free energy barriers required to create configurationally stable biaryls at various temperatures, which are:

$\Delta G^{\ddagger}$200K (-73°C)= 61.6kJmol^{-1} (15Kcalmol^{-1});

$\Delta G^{\ddagger}$300K (27°C) = 93.5 kJmol^{-1} (22Kcalmol^{-1});

$\Delta G^{\ddagger}$350K (77°C) = 109kJmol^{-1} (26Kcalmol^{-1})

The well known Cahn-Ingold-Prelog (CIP) priority criteria can be used to specify the configuration of a molecule with a axial chirality as *R* or *S*. K. Mislow used the CIP priority rules to define the absolute configuration of enantiopure biaryls in 1958.[102]

---

[96] Mikami,K.;Yamanaka, M.*Chem. Rev.* **2003**, *103*(8),3369–3400.

[97] Kuhn,R.*Stereochemie*,K.Freudemberg.;1933.

[98] Collings,P.J.;Hird,M.*Introductiontoliquidcrystalschemistryandphysics*;Taylor&Francis:London;Bristol, PA, 1997.

[99] Horton,D.A.;Bourne,G.T.; Smythe, M.L.*Chem.Rev.* **2003**,*103*(3),893–930.

[100] Gübitz,G.*Chromatographia* **1990**,*30*(9-10),555–564.

[101] Allinger,N.L.,Eliel,E.L.,Wilen,S.H.,Eds.;TopicsinStereochemistry;JohnWiley&Sons, Inc.:Hoboken, NJ,USA, 1983;Vol. 14.

[102] a) Mislow, K. *Angew. Chem.* **1958**, *70* (22-23), 683–689. b) Bringmann, G.; Hinrichs, J.; Pabst, T.;Henschel,P.;Peters,K.; Peters, E.-M. *Synthesis* **2001**,*2001* (01), 0155–0167.

To distinguish axial chirality from others (planar or central), the descriptors a*R* and a*S* are commonly used. These molecules can also be considered as helices and can be assigned a *M* (*minus*) or a *P* (*plus*) stereochemistry. For molecules having chirality axis, the descriptors a*R* and a*S* correspond to M and P, respectively. The absolute axial configuration for a poly-*ortho* substituted biaryl can be denoted by Newman projection along the biaryl axis following priority assignment to the substituents according to CIP rules, the configuration is determined by taking the shortest 90° path from the highest-priority substituent at the proximal ring (A) to the highest-ranking one at the distal ring (A'). The absolute configuration is *M* if the 90° turn is counterclockwise; if it is clockwise, the descriptor is *P*.

In this paragraph, we will provide a concise overview of the main methodologies that have been described thus far for the preparation of axially chiral biaryl compounds. Significant progress in accessing these valuable building blocks has been documented over the past two decades. These various synthetic approaches were extensively reviewed by Bringmann in 2005,[103] and several specialized articles have delved into specific synthetic routes for generating axially chiral compounds.[98, 104]

More recently, in 2015, a comprehensive update that amalgamates recent advancements and novel concepts for synthesizing axially stereoenriched biaryls was presented by Colobert et al.[105]

In this recent review, modern strategies for atropisomeric biaryls were categorized into four major groups:

I) The stereoselective construction of biaryls.
II) The generation of chiral biaryls through the construction of (an) aromatic ring(s).
III) Stereoselective transformations of prochiral or racemic biaryls.
IV) The synthesis of optically enriched biaryls, relying on central-to-axial chirality transfer.

.I) The stereoselective construction of biaryls

Biaryls play a pivotal role in numerous significant natural and synthetic chemical compounds. The linkage of aryl moieties and the induction of asymmetry during coupling have been extensively

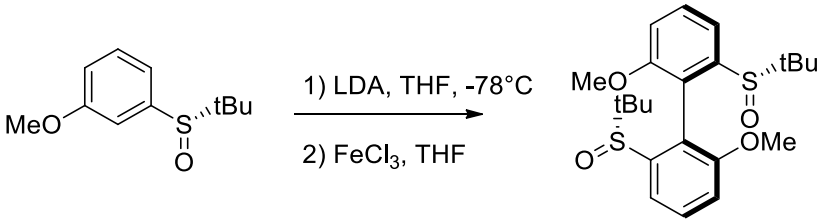
[103] Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew.Chem. Int. Ed.***2005**, *44*(34), 5384–5427.
[104] a)Broutin,P.-E.;Colobert,F.*Org.Lett.***2003**,*5*(18),3281–3284.b)Broutin,P.-E.;Colobert,F.*Org.Lett.* **2005**, *7* (17), 3737–3740. c) Leermann, T.; Broutin, P.-E.; Leroux, F. R.; Colobert, F. *Org.Biomol. Chem.* **2012**, *10* (20), 4095–4102. d) Colobert, F.; Valdivia, V.; Choppin, S.; Leroux, F. R.;Fernández, I.; Álvarez, E.; Khiar, N. *Org. Lett.* **2009**, *11* (22), 5130–5133. e) Huang, S.; Petersen, T.B.;Lipshutz, B. H. *J. Am.Chem. Soc.***2010**, *132*(40),14021–14023.
[105] Wencel-Delord, J.; Panossian, A.; Leroux, F. R.; Colobert, F. *Chem. Soc. Rev.* **2015**, *44* (11), 3418–3430.

researched and documented by organic chemists. While steric hindrance around the Ar-Ar axis is typically crucial for ensuring the configurational stability of biaryls, it also poses a significant challenge to biaryl coupling. Consequently, robust and innovative asymmetric catalytic systems have been devised.

The most extensively explored methodology for Ar-Ar coupling revolves around the use of transition metals as catalysts, enabling various coupling types, including oxidative couplings, Suzuki-Miyaura couplings, and C-H arylation.

1.2.7.1-Intermolecular oxidative couplings

Numerous instances of asymmetric oxidative couplings catalyzed by Cu, V, and Ru-based chiral catalytic systems have been documented for the homocoupling of naphthols.[106] An exceptionally effective and diastereoselective approach to synthesizing axially chiral bis-sulfoxide ligands via oxidative aryl coupling was detailed by Zhou and his colleagues.[107] They employed a chiral sulfoxide moiety, acting as both an *ortho*-directing group and a chiral inductor, to facilitate the initial *ortho*-metalation of aryl sulfoxides and subsequently, the iron-catalyzed C-C coupling. This process yielded an outstanding diastereoisomeric excess of axially chiral bis-sulfoxides during the radical coupling (**Scheme 22**).



Scheme 22. Diastereoselective oxidative homocoupling[107]

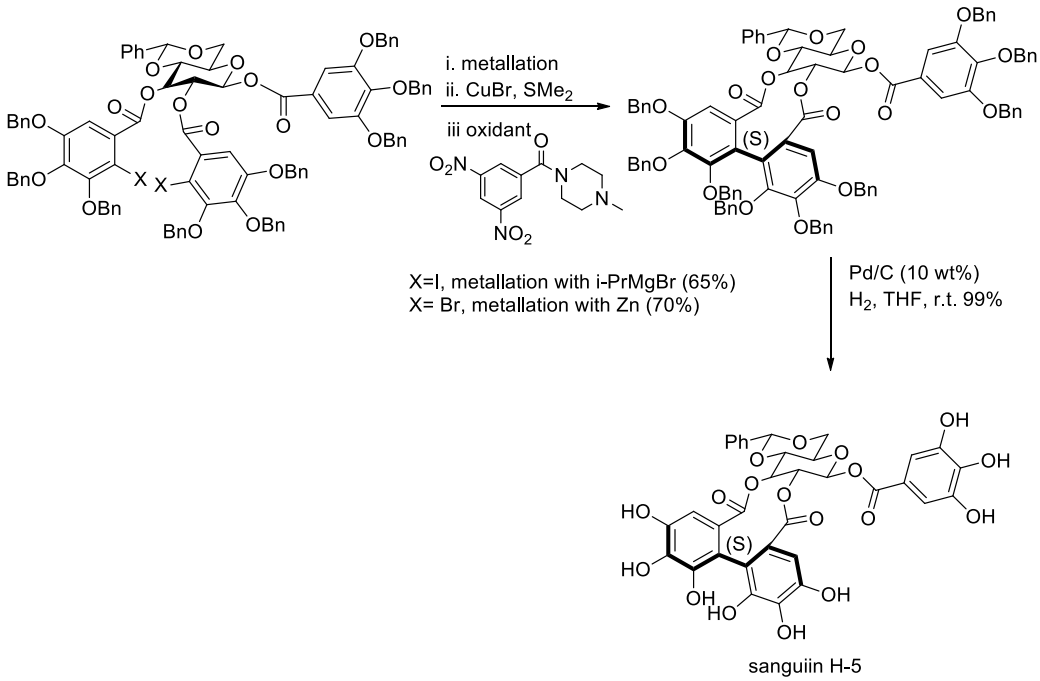
Examples of intramolecular oxidative and reductive couplings have also been documented in the literature. Typically, chirality transfer was accomplished either through stereogenic tethers[108] or through substituents and the strain inherent in the cyclic system, as observed in natural products.[109]

[106] Kozlowski,M. C.;Morgan,B. J.; Linton, E. C.*Chem.Soc.Rev.* **2009**,*38* (11), 3193–3207.
[107] Chen, Q.-A.; Dong, X.; Chen, M.-W.; Wang, D.-S.; Zhou, Y.-G.; Li, Y.-X. *Org. Lett.* **2010**, *12* (9),1928–1931.
[108] Asakura,N.;Fujimoto, S.;Michihata,N.;Nishii,K.; Imagawa, H.; Yamada, H.*J.Org. Chem.***2011**,*76* (23), 9711–9719.
[109] Shan,Z.-H.;Liu,J.;Xu,L.-M.;Tang,Y.-F.;Chen,J.-H.;Yang,Z.*Org.Lett.***2012**,*14*(14),3712–3715.

1.2.7.2-Intramolecular oxidative couplings

An intriguing demonstration of atropodiastereoselective intramolecular oxidative coupling was presented by Spring et al. during the total synthesis of the ellagitannin natural product sanguiin H-5 (**Scheme 23**).[110]

They effectively employed both organomagnesium and organozinc-based metalation methodologies to construct the strained medium-ring core of the natural product.[110]



Scheme 23. Total synthesis of sanguiinH-5

The synthesis of the benzylated precursor of sanguiin H-5 was achieved in a single step, following the initial formation of either an organomagnesium or organozinc intermediate.

Subsequently, an intramolecular oxidative coupling of the resulting diarylcuprate facilitated both diastereoselective biaryl bond formation and the concurrent creation of the medium-sized ring. This reaction exhibited complete diastereoselectivity and yielded a satisfactory isolated yield of 65% to 70%.

[110] Su,X.;Surry,D. S.;Spandl, R.J.;Spring,D. R.*Org.Lett.***2008**,*10* (12),2593–2596.

1.2.7.3-Diastereoselective and enantioselective intermolecular Suzuki-Miyaura couplings

Within the realm of transition metal-catalyzed Ar-Ar coupling, the Suzuki-Miyaura reaction has been extensively studied for accessing chiral biaryls.

The first asymmetric version of the Suzuki-Miyaura coupling emerged in the late 1990s, featuring diastereoselective couplings that involved one chiral partner bearing a motif such as a planar-chiral chromium complex or a stereogenic center.[111] In this context, benzylic alcohols or β-hydroxysulfoxides were employed as chiral auxiliaries. For example, they employed in the total synthesis of dibenzoxepine derivatives,[112] (-)-steganone,[113-115] and in the synthesis of the biarylic system of vancomycin.[116]

High diastereoselectivity was also achieved by employing the *tert*-butyl sulfinyl group as a chiral auxiliary.[117]

1.2.7.4-Diastereoselective intramolecular Suzuki-Miyaura coupling

Regarding intramolecular Suzuki-Miyaura coupling, a pivotal step in the preparation of axially chiral cyclic molecules, Zhu and colleagues have reported two noteworthy examples. They have introduced peptidyl moieties between two aromatic units, employing them as chiral linkers to induce atroposelectivity during macrocyclization. This approach was employed to prepare the DEFG ring of complestatin[118] and the cyclophanic system of arylomycins A2 and B,[119] as depicted in **Figure 8**.

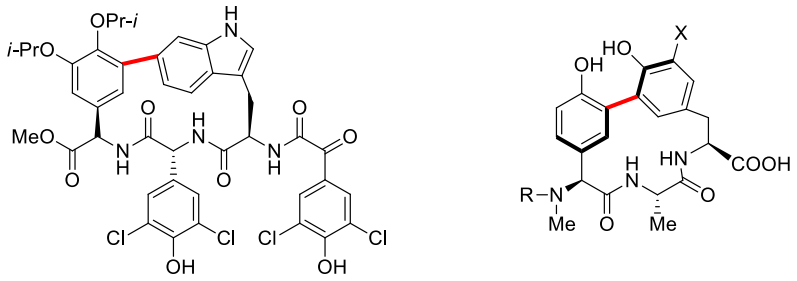


Figure 8. Diastereoselective intramolecular Suzuki-Miyaura coupling

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[111] a)Zhang,D.;Wang,Q.*Coord.Chem.Rev.***2015**,*286*,1–16.b)Baudoin,O.*Eur.J.Org.Chem.***2005**,*2005*(20),4223–4229.
[112] Joncour,A.;Décor,A.;Thoret,S.;Chiaroni,A.;Baudoin,O.*Angew.Chem.***2006**,*118*(25),4255–4258.
[113] Broutin,P.-E.;Colobert,F.*Org.Lett.***2003**,5(18),3281–3284.
[114] Broutin,P.-E.;Colobert,F.*Org.Lett.* **2005**, *7* (17), 3737–3740
[115] Yalcouye,B.;Choppin,S.;Panossian,A.;Leroux,F.R.;Colobert,F. *Eur.J.Org.Chem.***2014**,*2014*(28),6285–6294.
[116] Leermann, T.; Broutin, P.-E.; Leroux, F. R.; Colobert, F. *Org.Biomol. Chem.* **2012**, *10* (20), 4095–4102.
[117] Colobert, F.; Valdivia, V.; Choppin, S.; Leroux, F. R.;Fernández, I.; Álvarez, E.; Khiar, N. *Org. Lett.* **2009**, *11* (22), 5130–5133
[118] Jia,Y.; Bois-Choussy,M.;Zhu, J. *Org.Lett.***2007**,*9*(12),2401–2404.
[119] Dufour,J.;Neuville, L.;Zhu,J.*Chem.-Eur.J.* **2010**,*16* (34),10523–10534.

Intramolecular atropoenantioselective C-H direct arylation has also been documented in the literature,[120] particularly for the synthesis of allocolchicinine, a seven-membered ring compound.[121]

[120] a)Yamaguchi,K.;Yamaguchi,J.;Studer,A.;Itami,K.*Chem.Sci.***2012**,*3*(6),2165–2169.b)Yamaguchi,K.;Kondo,H.;Yamaguchi,J.; Itami, K.*Chem.Sci.* **2013**,*4*(9), 3753–3757.

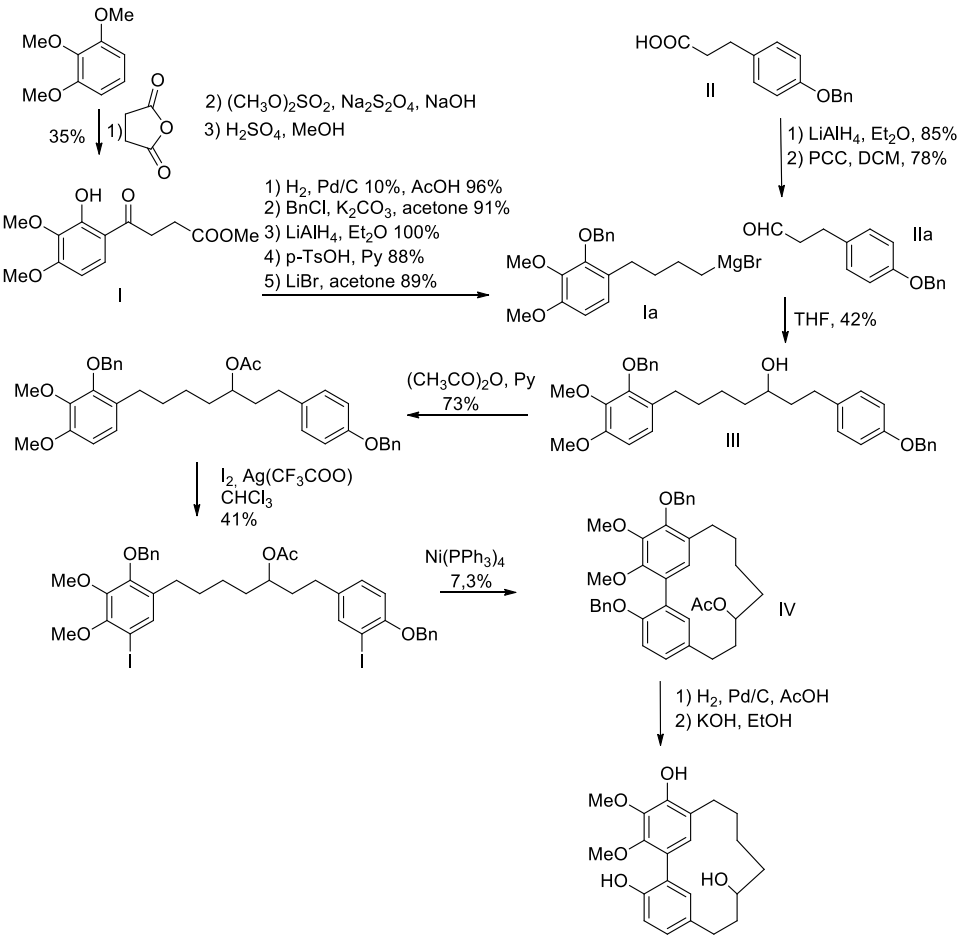
[121] Campeau,L.-C.; Fagnou,K.*Chem.Commun.***2006**,No. 12,1253.

1.3- State of the art of total synthesis

1.3.1- Total synthesis by Whiting

Thanks to advances in Alzheimer's disease research and treatment, significant attention was directed toward myricanol. The first attempt of its synthesis dates back to 1980 [29] and it is illustrated in **Scheme 24**. This pioneering work was carried out by the research team led by Whiting, who had previously isolated and characterized myricanol for the first time a few years earlier.

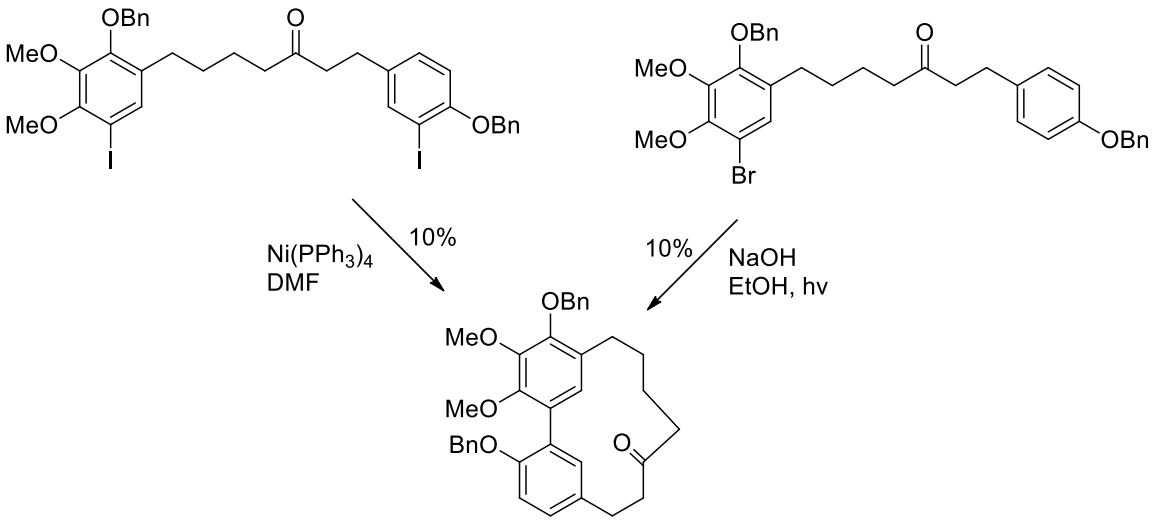
The synthesis starts with 1,2,3-trimethoxybenzene (a commercially available product), which undergoes acylation. The resulting product **I** was benzylated and transformed into the Grignard reagent **Ia**. This reagent, upon reacting with aldehyde **IIa** (obtained through the reduction-oxidation of **II**), leads to the formation of the linear diaryleptanoid **III**. Subsequent acetylations, iodinations, and a Ni-catalyzed intramolecular cross-coupling (with a yield of 7.3%) resulted in the formation of product **IV**. Deprotection of the latter yields myricanol.



Scheme 24. Total synthesis of myricanol (Whiting *et al*.)

The macrocyclization step is particularly challenging, with only a 7.3% yield. This outcome is quite surprising when compared to similar reactions on comparable substrates.[51]

The same research group has reported the synthesis of myricanone using two different approaches. In both cases, whether Ni-catalyzed or photocatalyzed, the yield of the intramolecular cyclization does not exceed 10% (see **Scheme 25**), and the overall yield of myricanone remains below 2%.



Scheme 25. Total synthesis of myricanone (Whiting *et al)*

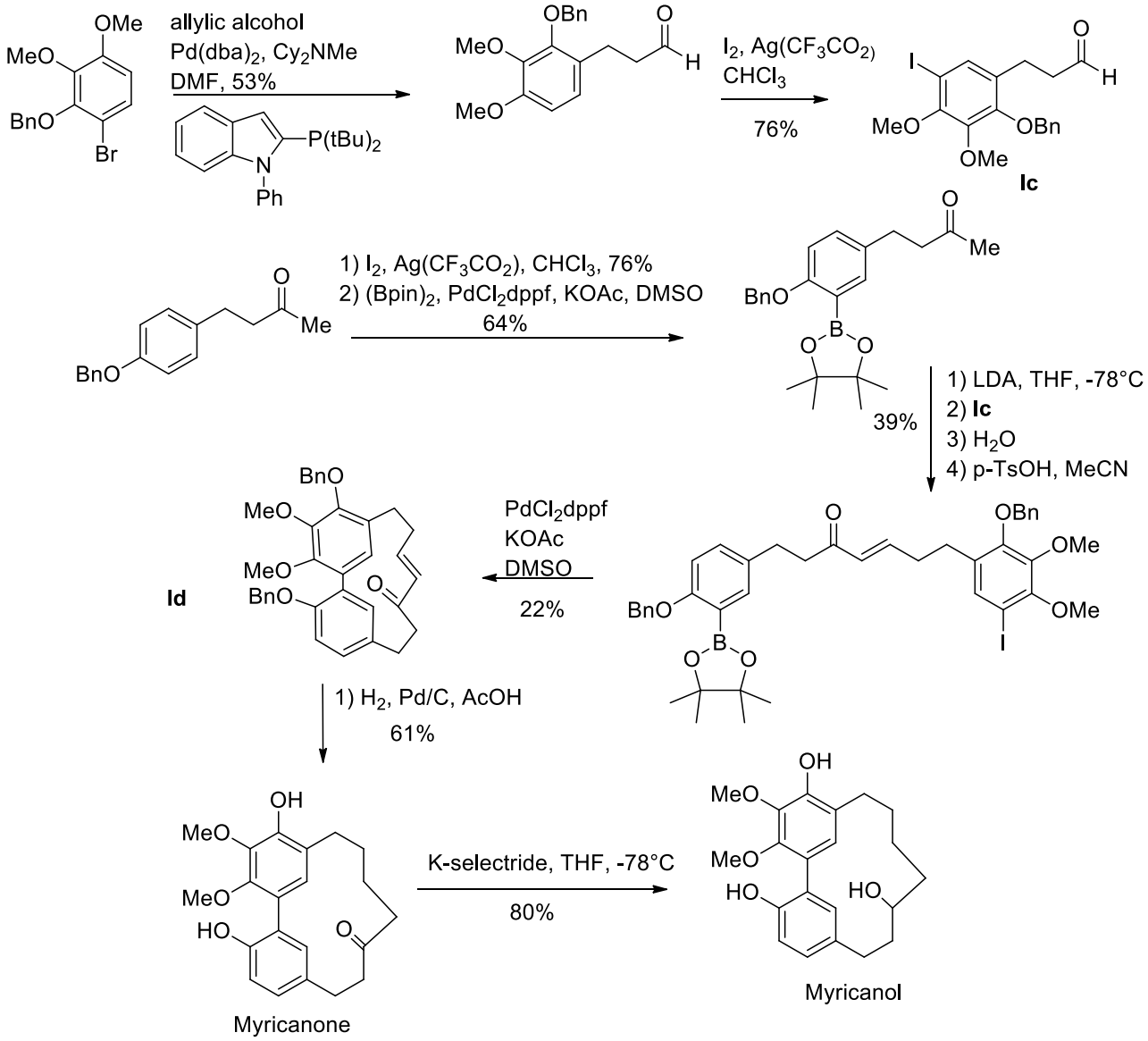
As suggested by Whiting, the lower yield in the Ni-catalyzed cyclization for the total synthesis of myricanol compared to a similar reaction conducted by Semmelhack for the total synthesis of alnusone[51] may primarily be attributed to the presence of a double bond at positions 4,3. In the Whiting total synthesis, the cyclizations of the *seco*-precursors are likely to experience greater steric hindrance. A study of molecular models indicates that the introduction of the 3,4-double bond, in fact, reduces both angle strain and van der Waals hydrogen interactions inside the macrocycle[29].

The influence of side chain functionalities on the ease of cyclization was the primary focus of this thesis.

1.3.2- Total synthesis by Dickey

The total synthesis by Dickey *et al.* is depicted in **Scheme 26**[23]

The first step involves a reductive coupling with allylic alcohol, forming phenylpropionaldehyde, which, through *ortho*-methoxy directed iodination, afforded the aldehyde **Ic**. By aldol condensation, compound **Ic** was coupled with the aryl pinacol boronate, resulting in the corresponding diaryleptanoid pinacol boronate, which then participates in an intramolecular Pd-catalyzed Suzuki-Miyaura reaction to form macrocycle **Id**. Subsequent deprotection and reduction of myricanone yielded myricanol with a total yield of 2.03%.



Scheme 26. Total synthesis of myricanol (Dickey et *al.*)

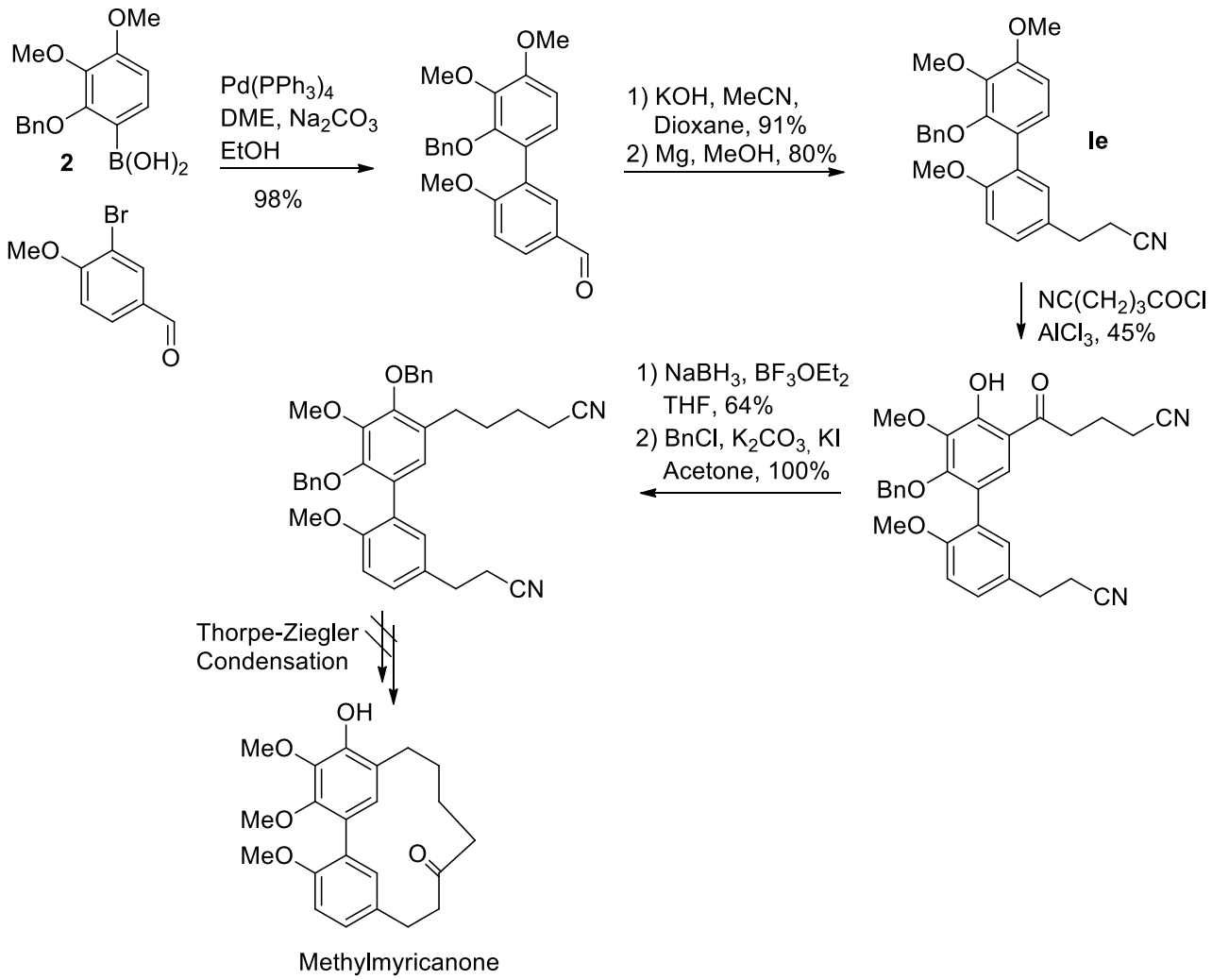
Although the intramolecular coupling through Suzuki-Miyaura is not exceptionally high in yield (22%), it still represents a significant improvement when compared to the results previously obtained by Whiting for intramolecular cross-coupling reactions.

The reason why biaryl bond formation poses a significant challenge in both Whiting's total synthesis (**Scheme 25**) and Dickey's synthesis (**Scheme 26**) is likely due to the presence of substantial ring strain. The open-chain product is likely more stable than the macrocycle.

The difference in cross-coupling yields between Dickey's synthesis (22%) and Whiting's (7-10%) may also arise from the reduced conformational freedom of the side chain, which appears more rigid and directed in compound **Id** due to the presence of the double bond.

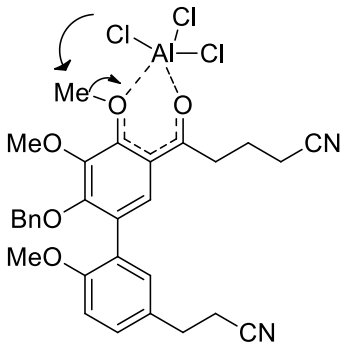
1.3.3 –Total synthesis of methyl-myricanone by Dansou (2000)

Dansou and coworkers proposed a different approach for the total synthesis of methylmyricanone[30]. Although the synthesis was not successful, it is also reported because it includes some interesting key steps, such as the construction of the biaryl system followed by the chain insertion via regioselective acylation. These concepts were further adapted and integrated into the design of the initial synthetic strategy developed in this thesis work. The attempted total synthesis of myricanone by Dansou is depicted in the following **scheme 27**:



Scheme 27 . Methylmyricanone Total synthesis attempt by Dansou et *al.*

The first step consists in an intermolecular Suzuki-Miyaura cross-coupling; the second one of aldehyde homologation was followed by a Friedel-Crafts acylation. Under these conditions, simultaneous regioselective demethylation of compound **Ie** occured. This demethylation likely proceeds through the formation of a chelate with aluminum trichloride (see **Scheme 28**).

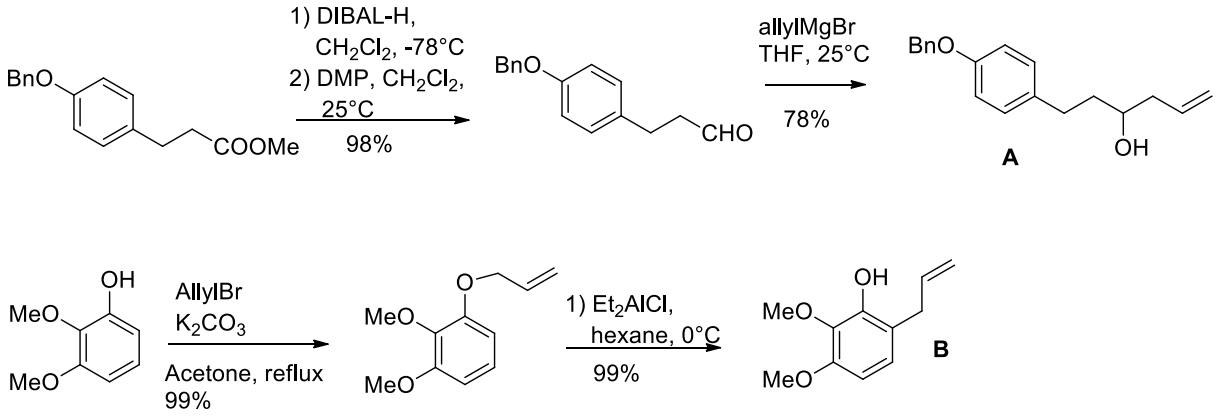


Scheme 28. Regioselective demethylation

The demethylation process yielded the diaryldiketone, followed by a reduction under Clemmensen conditions and protection through benzylation. At this point, the expectation was to obtain condensation products under Thorpe-Ziegler conditions ($NaNC_6H_5Me$), but these products were not obtained, leaving the synthesis of methylmyricanone incomplete.

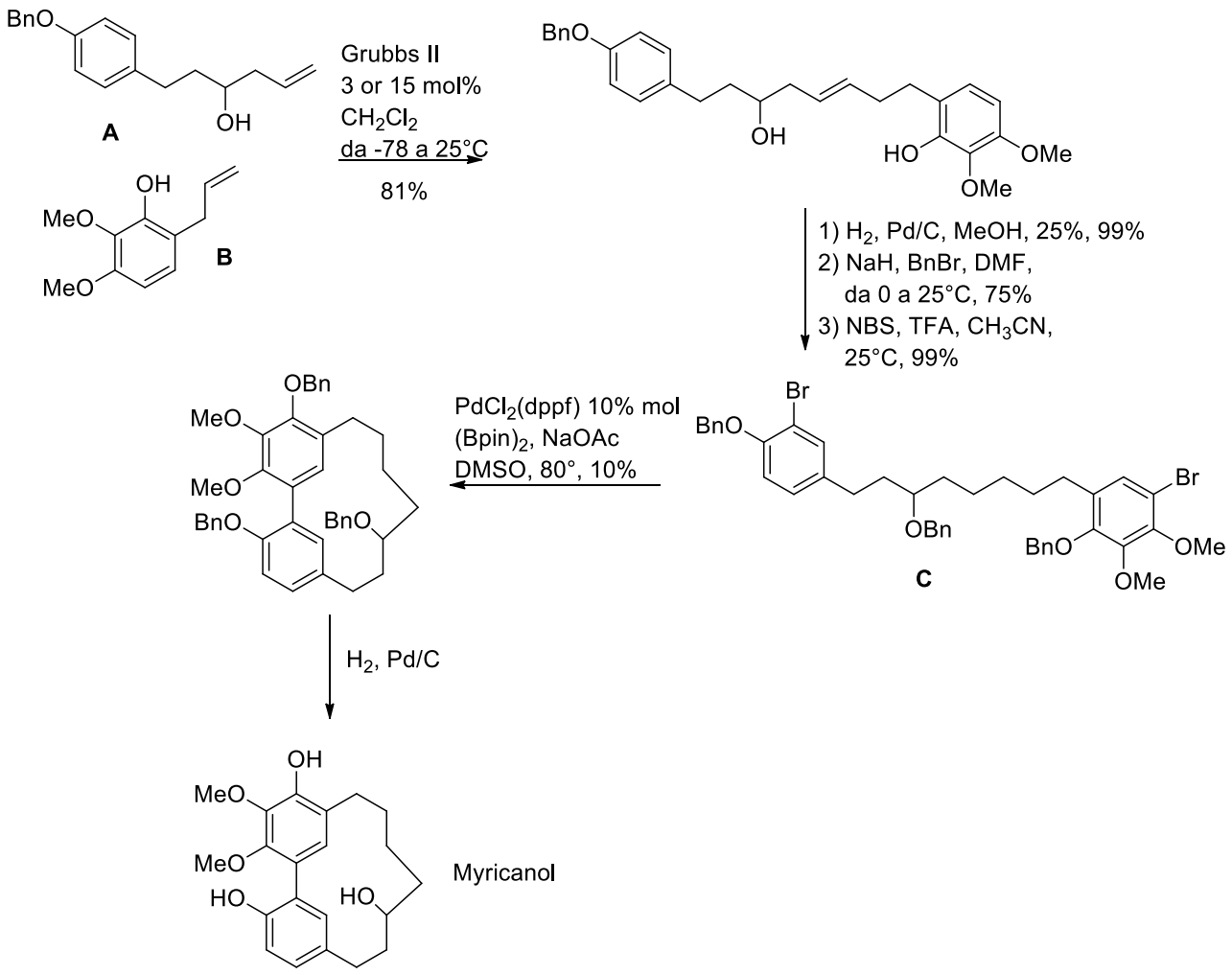
1.3.4- Total synthesis of myricanol by Chiummiento (2018)

The third total synthesis of myricanol (2018)[28] performed in the frame of the collaboration between Potenza and Strasbourg utilizes an intramolecular cross-coupling reaction of the diarylheptanoid (**Scheme 29**), which is obtained by a cross-metathesis of fragments **A** and **B** (**Scheme 30**).



Scheme 29. Synthesis of **A** and **B**

Fragment **A** was synthesized through allylation of the aldehyde arising from the commercial ester, while fragment **B** was synthesized from a commercial product through allylation and the following *ortho*-Claisen rearrangement. Both steps are characterized by excellent yields.

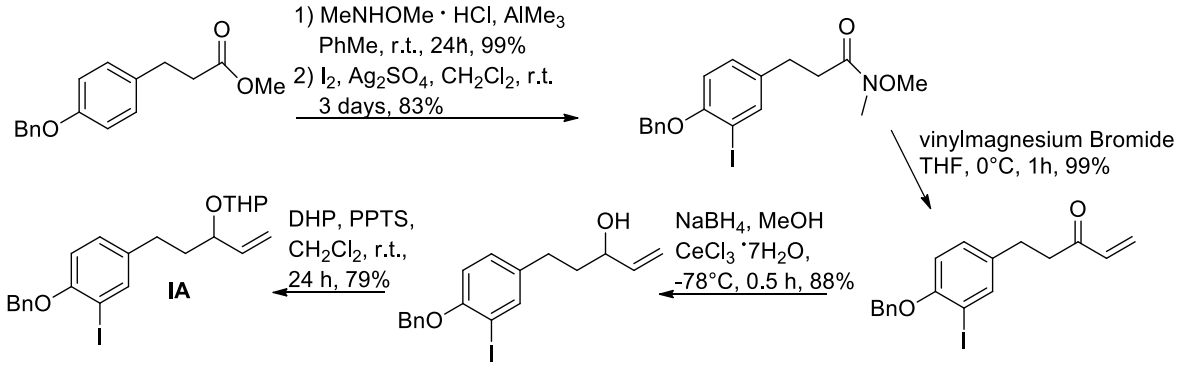


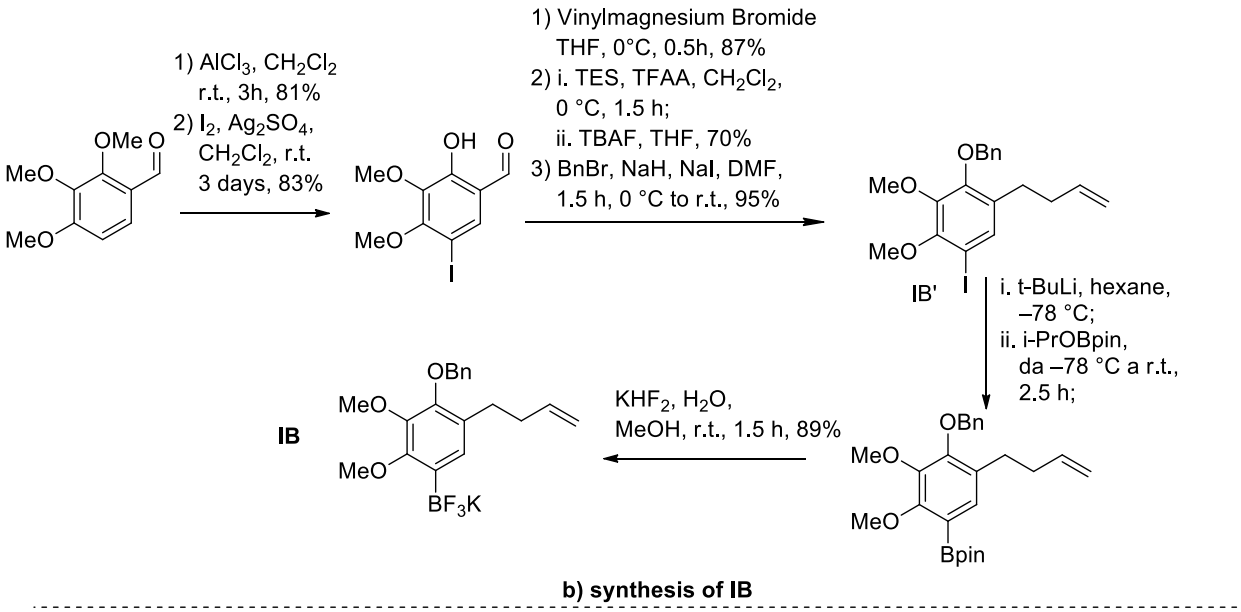
Scheme 30. Synthesis of myricanol (cross-metathesis and Suzuki-Miyaura domino)

The cross-metathesis of fragments **A** and **B** led to the linear diarylheptanoid (**Scheme 30**), which, after reduction, benzylation, and bromination, provides the protected brominated diarylheptanoid **C**. At this point, the intramolecular Suzuki-Miyaura reaction, with *in situ* generation of the aryl pinacol boronate followed by reduction with H_2 on Pd/C, resulted in the formation of myricanol. The critical step was the intramolecular cross-coupling, which gave a 10% yield. It was suggested that, for this type of Suzuki-Miyaura domino reaction, the substrate's symmetry plays a significant role in influencing the yield. Similar reactions with symmetric substrates, where both fragments have identical electronic properties on the aryl part, are characterized by better yields[28].

1.3.4- A Recent total synthesis Attempt and total Synthesis of isomyricanol (2020)

A recent synthetic attempt of myricanol from 2020[122] by the University of Strasbourg in collaboration with the University of Basilicata involves, in contrast to the 2018 total synthesis, an initial intermolecular Suzuki-Miyaura reaction to the biaryl system followed by the subsequent ring-closing metathesis. The synthetic methodologies used for the synthesis of fragments **IA** and **IB**, which are employed in the subsequent cross-coupling reaction, are presented in the **Scheme 31**.





Scheme 31. Synthesis of **IA** and **IB**

[122] Massé, P.; Choppin, S.; Chiummiento, L.;, Hanquet, G.; Colobert,F. *Synlett***2020**; 31(06), 559-564.

Fragment **IA** was synthesized from a derivatized commercial ester, initially modified to a Weinreb amide, iodinated, and subsequently, after vinylization on the amide, yielding the corresponding α-β-unsaturated compound. Reduction by Luche reaction and protection provided fragment **IA**.

Fragment **IB** was derived from the commercially available trimethoxybenzaldehyde, which was regioselectively demethylated and iodinated. The ensuing allylation step led to the formation of an alcohol, which, following reduction with TES/TFA and benzylation, gave rise to aryl iodide **IB'**. Through a halogen-lithium exchange reaction in anhydrous hexane using *tert*-BuLi and isopropylpinacolborane, the corresponding pinacol boronate was formed. Consequently, fragment **IB** was obtained by treating the pinacol boronate with an aqueous solution of KHF_2 in methanol (comprising a total of 7 steps and 25% yield).

These synthesized fragments were coupled through an intramolecular Suzuki-Miyaura reaction, thus forming biaryl compound **IC** in **Scheme 32**. However, the ring-closing metathesis reaction for this compound did not yield the desired product **ID**, which serves as a precursor to myricanol.

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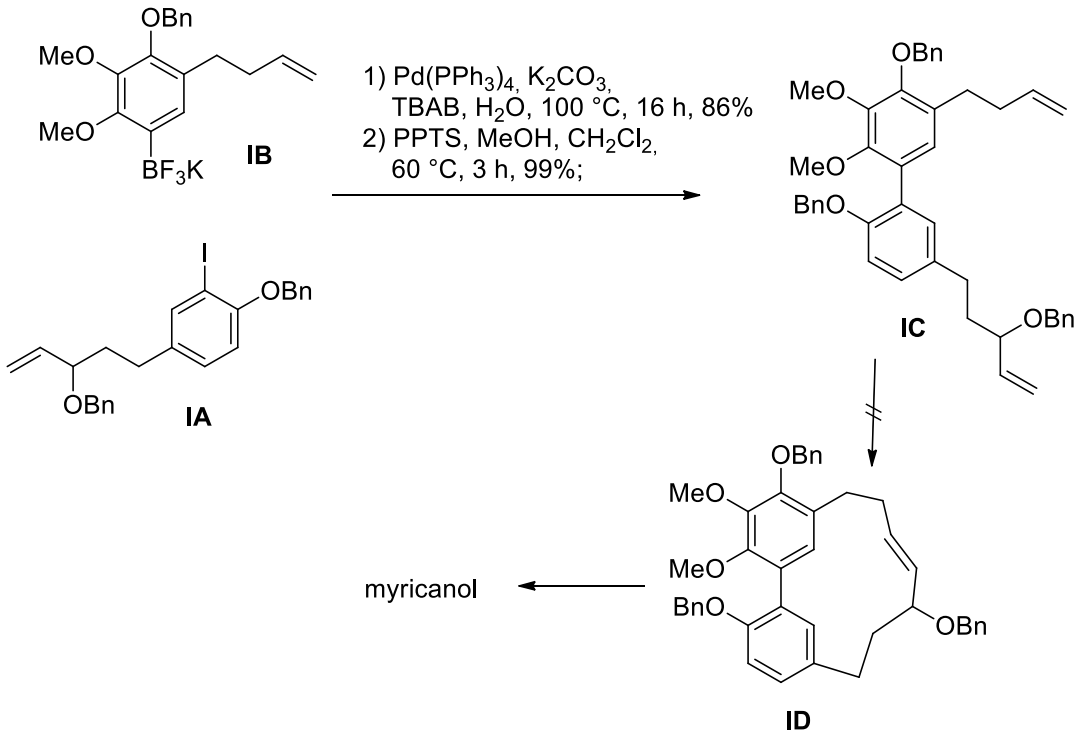


Scheme 32. Myricanol total synthesis attempt

The ring-closing metathesis of the α-β-unsaturated ketone resulting from the deprotection/oxidation of the biaryl **IC** has instead led to the formation of the undesired dimer shown in **Figure 9**, despite the reaction being conducted under conditions of extreme dilution. Ring strain favored the formation of the dimer rather than the desired product.

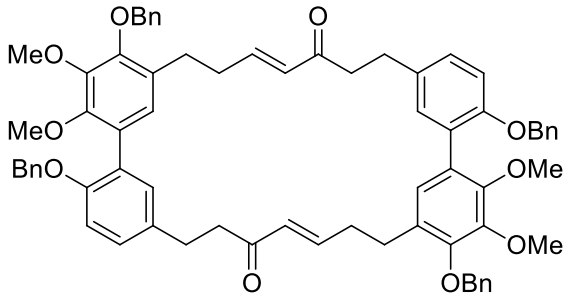
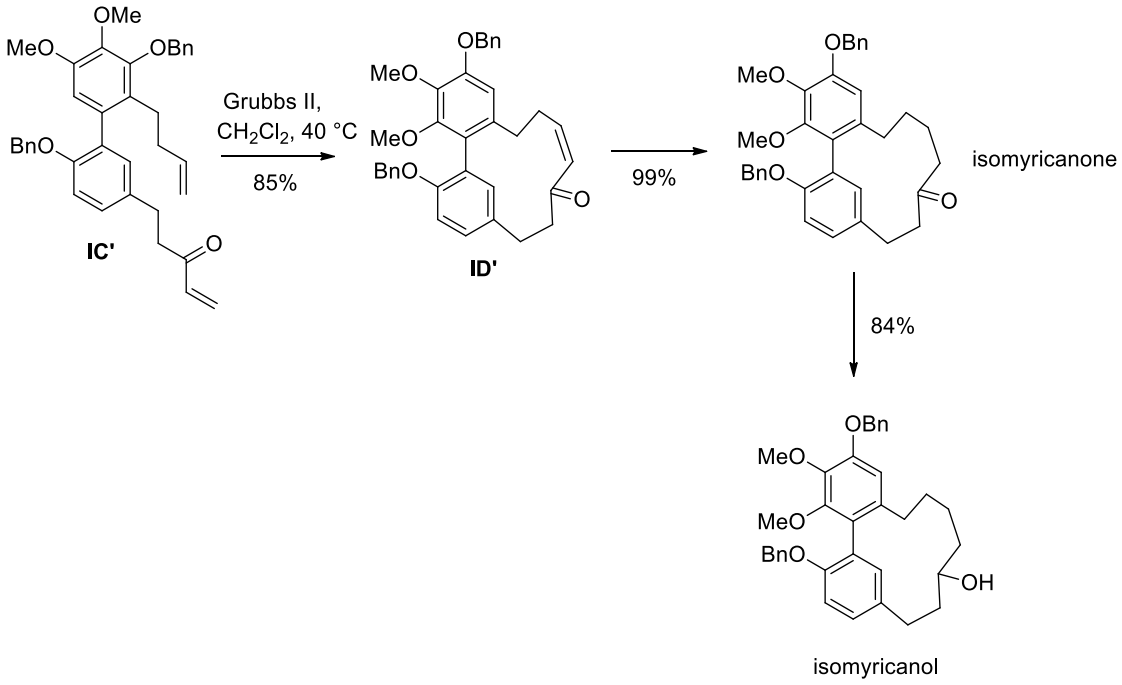


Figure 9. Unintended formation of the dimer

The same group reported the total synthesis of isomyricanol and isomyricanone (**Scheme 33**) by using the same synthetic strategy previously described achieving the desired macrocycle with 85% yield. This implies that the ring strain is fully released in an *ortho,meta*-diarylheptanoid compared to a *meta,meta*-diarylheptanoid.[25]

Finally, isomyricanone, was furnished in 12 steps with an overall yield of 33%.



Scheme 33. Total synthesis of isomyricanone and isomyricanol

CHAPTER 2- Retrosynthesis

2.1-Introduction

In light of the various total syntheses and attempted total syntheses of myricanol and myricanone, and considering the significant pharmacological potential of these compounds, this thesis aimed to design a synthetic methodology that could lead to the total synthesis of myricanol in a few key steps with good yields. Recent publications regarding the synthesis of macrocycles analogous to myricanol were considered, and the challenges from previous work were analyzed. The possibility of an asymmetric synthesis was explored, with the aim of achieving stereoselectivity for both axial chirality (atropisomerism) and central chirality (C-11).

The dihedral angle between two aryl groups is typically determined by two factors: steric hindrance and the overlap of molecular orbitals:

1. Minimal steric hindrance between the two substituents occurs when the dihedral angle is 90°.
2. Maximum orbital overlap between the molecular orbitals of the two rings occurs at dihedral angles of 0°. The dihedral angle results from a compromise between these two factors and is generally around 40°.

Axial chirality could potentially be controlled in several ways as discussed in the **section 1.2.7**:

1-Intermolecular oxidative couplings

2-Intramolecular oxidative couplings

3-Diastereoselective and enantioselective intermolecular Suzuki-Miyaura couplings

4-Diastereoselective intramolecular Suzuki-Miyaura coupling

As previously mentioned, the only isolated stereoisomers, as a scalemic mixture, among the four possible ones were a*R*,*S* and a*S*,*R* (**Figure 10**). It is worth noting that the data reported in the literature are based on X-ray crystallography, and it cannot be ruled out that the behavior of myricanol in the solid state may differ significantly from that in solution.

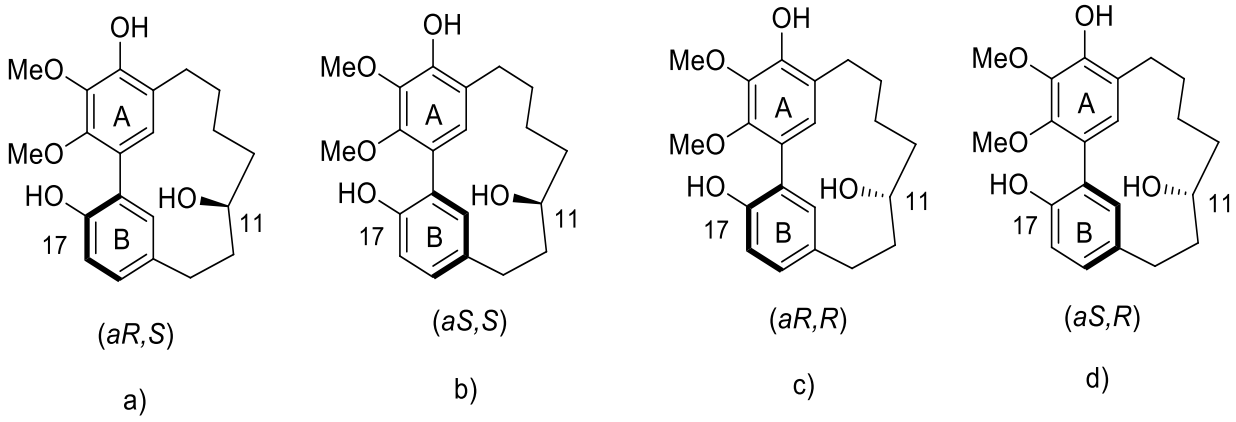


Figure 10. Stereoisomers of myricanol

Joshi *et al.*[123] confirmed the presence of intermolecular hydrogen bonds between 17-OH and 11'-O (2.783 Å) and, based on molecular mechanics calculations, demonstrated that the energy difference between the diastereoisomer (*aS,R*) and the diastereoisomer (*aS,S*) is 2.72 kcal/mol.

In light of these considerations, it would be interesting to achieve an enantioselective reduction of myricanone, which should generate only one of the four possible stereoisomers. For example, by conducting an enantioselective reduction to obtain enantiomer 11-*R*, a form of dynamic kinetic resolution could be observed. The rotational barrier in myricanone may not be high enough to generate atropisomerism. Therefore, both conformers of myricanone would react to form only the diastereoisomer (*aS,R*), where the axial chirality is induced by the spatial arrangement of OH at C-11.

According to another hypothesis, atropisomerism is not induced by central chirality, but the energy barrier is high enough to prevent rotation in myricanone. In this case, the hypothetical experiment mentioned earlier would still lead to only one diastereoisomer, but no dynamic kinetic resolution would occur, meaning one of the two atropisomers would remain unreacted.

Central chirality at C-11 can be introduced through a stereoselective reduction of myricanone. numerous examples of enantioselective reductions of ketones to optically active alcohols[124-126] are reported. Below, a few examples are briefly presented.

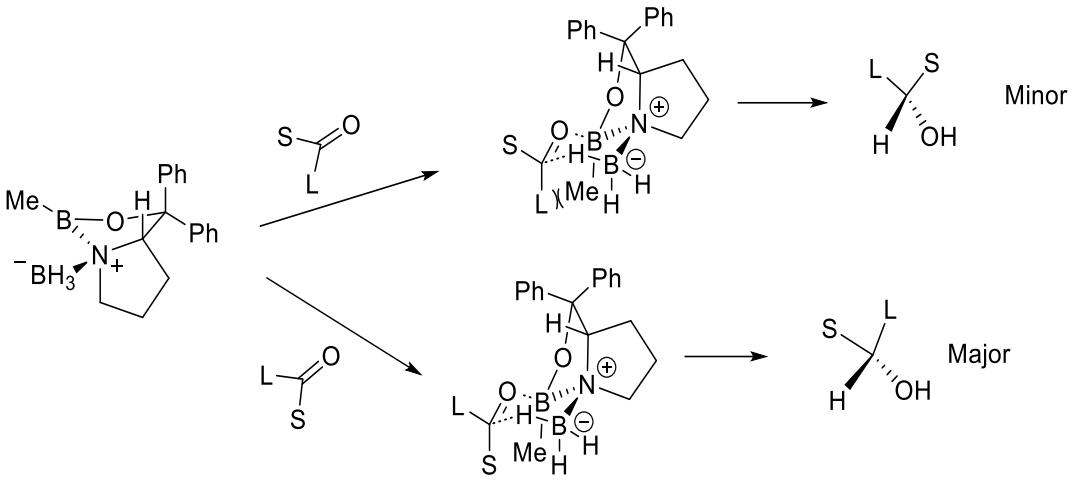
[123] Joshi, B.S.; Pelletier, S.W.; Newton, M.G.; Lee, D.; McGaughey, G.B.; Puar, M.S. *J. Nat. Prod.* **1996**, 59 (8), 759-764.

[124] Itsuno, S. Enantioselective Reduction of Ketones. In *Organic Reactions*; Denmark, S. E., Ed.; Wiley, **1998**; pp 395–576.

[125] Echeverria, P.-G.; Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V. *Synthesis***2016**, 48.

[126] Zhou, J.; Xu, G.; Ni, Y. *ACS Catal.* **2020**, 10, 19, 10954–10966.

The use of oxazaborolidines, in the presence of BH_3, leads to a diastereotopic chair-like transition state in which boron coordinates the carbonyl oxygen of the substrate. The most stable transition state is the one where the bulkier substituent (L) of the carbonyl is placed in a pseudoequatorial position (**Scheme 34**).



Scheme 34. Enantioselective reductions of ketones with oxazaborolidines

Another method used for the asymmetric reduction of ketones involves a transition metal complexed with chiral ligands. One of the most commonly used chiral ligands is BINAP, which forms a chelate with a transition metal (Rhodium and Ruthenium are the most commonly used). The substrate will be coordinated by the transition metal, arranging its substituents to minimize steric hindrance with the BINAP substituents (**Figure 11**).

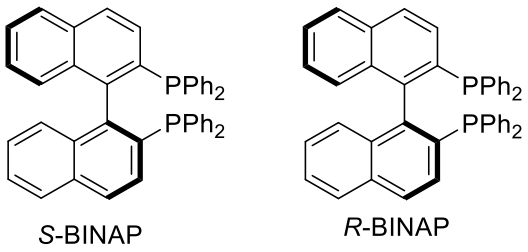
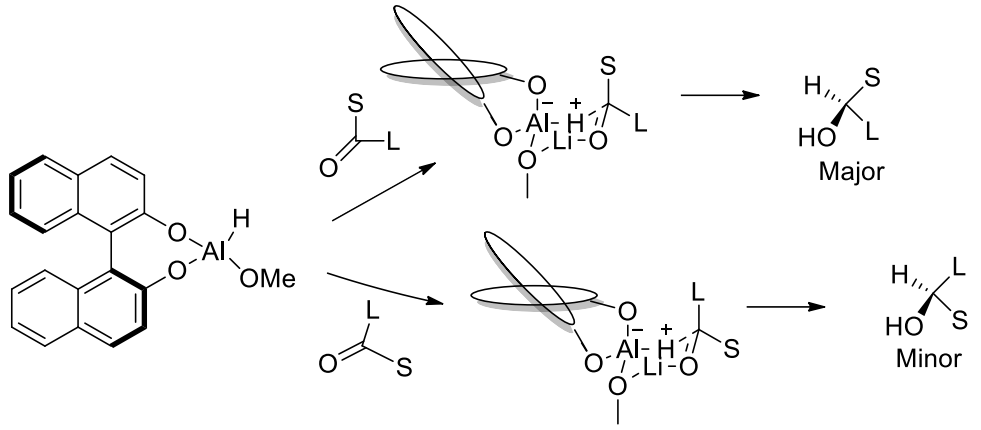


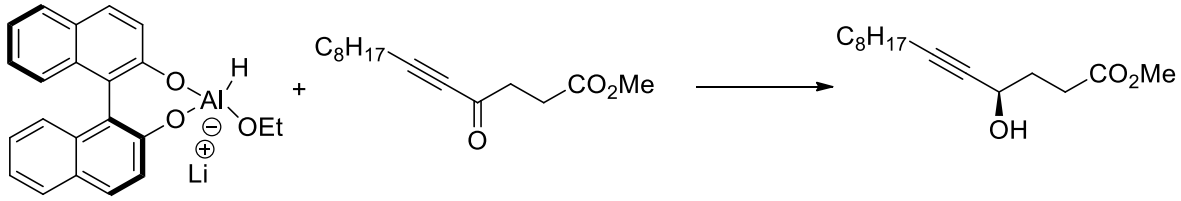
Figure 11. *R/S*-BINAP

Another method for asymmetric synthesis involves the use of a chiral reagent (**Scheme 35, Scheme 36**). For example, BINAL-H is an asymmetric derivative of the corresponding DIBAL-H, which is used for ketone reductions.



Scheme 35. Reduction with BINAL-H

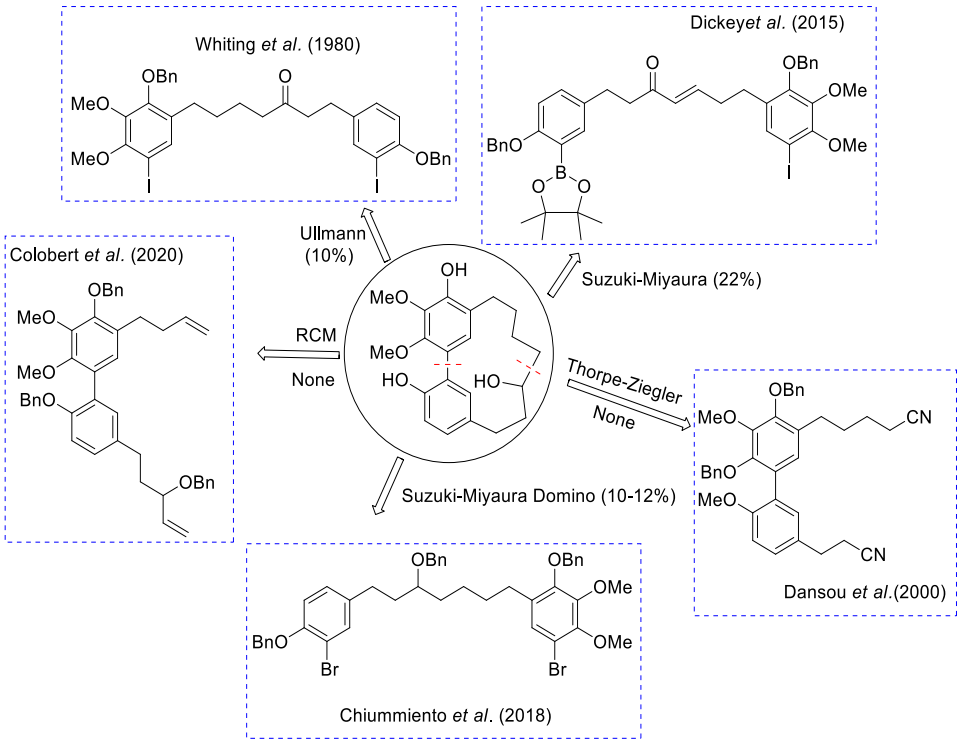
Again, the transition state is a 6-membered chair-like cycle. The substrate can place its bulkiest group either pseudoequatorially (more stable) or pseudaxially (bulkier and thus less stable) and enantioselectivity seems to improve when the ketone has an unsaturated substituent (**Scheme 36**).



Scheme 36. Reduction of a ketone with an unsaturated substituent

2.2- Proposed retrosynthetic approaches

The synthesis attempts and the three total syntheses of myricanol previously described (briefly outlined in **scheme 37**) are characterized by a particularly critical step: the formation of the macrocycle.



Scheme 37. Reported total syntheses of myricanol

The difficulty of this cyclization likely stems from a thermodynamic control: the spontaneity of a reaction depends on the change in Gibbs free energy (ΔG) for the reaction:

$$\Delta G = \Delta H - T\Delta S$$

While ΔH depends on the type of reaction and compounds under consideration, ΔS is closely related to the reduction in degrees of conformational freedom during the cyclization process. Entropy associated with a specific conformation is, in accordance with statistical thermodynamics, defined by Boltzmann's equation:

$$S = K\ln W$$

Here, W is the statistical weight of a particular conformation, defined as the ratio of the number of possible spatial arrangements of that conformation to the total number of possible spatial arrangements of all possible conformations. Evidently, a cyclized system is characterized by a much smaller number

of possible conformations compared to the same acyclic system. The cyclization process is, therefore, accompanied by a reduction in entropy that makes the process unfavorable.

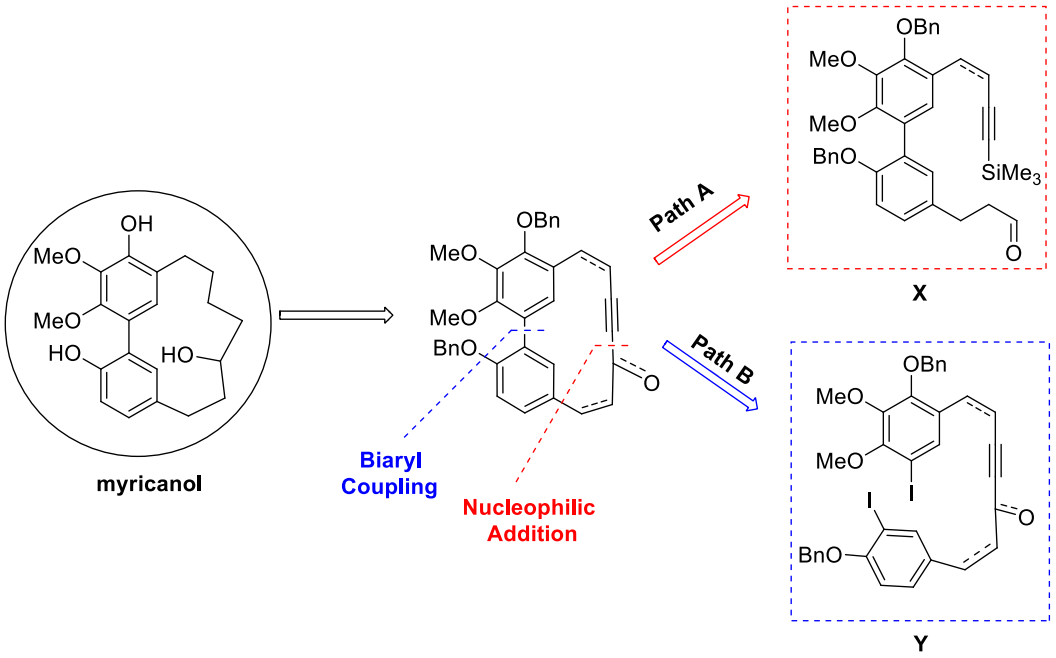
In these terms, if the reaction involves a substrate with an already rigid side chain, characterized by a low number of conformational degrees of freedom, the entropy change during the cyclization reaction would be less unfavorable regarding ΔG. In other words, the formation of a 13-membered ring from a polysaturated acyclic system is less disfavored compared to the formation of the same ring starting from an aliphatic system.

Consequently, a first retrosynthetic step, shown in **scheme 38**, involves a selected polyunsaturated system (X or Y) characterized by a rigid structure (with few conformational degrees of freedom and already directed by the *cis* configuration of the double(s) bond(s)) as the starting substrate for the macrocyclization.

The weight of ΔH to the ΔG could also be crucial, and this factor essentially depends on the thermodynamic stability of the macrocycle formed, and therefore, to some extent, on the ring strain of the cyclized compound. The choice of the seco-precursor should also take this factor into account; so, different polyunsaturated systems, with increasing degrees of rigidity, can be used as *seco*-precursors in order to experimentally assess the influence of the degree of unsaturation on the macrocyclization reaction.

The final step is thus an intermolecular nucleophilic attack on the aldehyde (Path A, red) or an intramolecular cross-coupling (Path B, blue). In this synthetic approach (and in the subsequent designed ones), the only ways to control central chirality is to oxidize myricanol to myricanone and then reduce it again to alcohol using one of the enantioselective reduction methods described in the previous section, alternatively, an enantioselective addition reaction could be used.

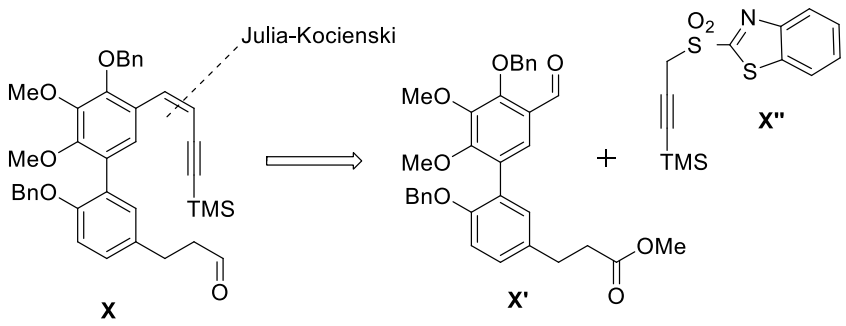
Both retrosynthetic **path A** and **path B** will be explored.



Scheme 38. Retrosynthetic paths for myricanol's synthesis

2.3- Path A

The ene-yne system (**X**), precursor to be used in the last step of cyclization by nucleophilic addition, could be obtained, for example, with the required *cis* configuration of the alkene, by a modified Julia olefination (**Scheme 39**), a widely used reaction for synthesizing *cis* ene-yne systems[127-128] starting from the aldehyde **X'** and the alkynylsulfone **X''**.

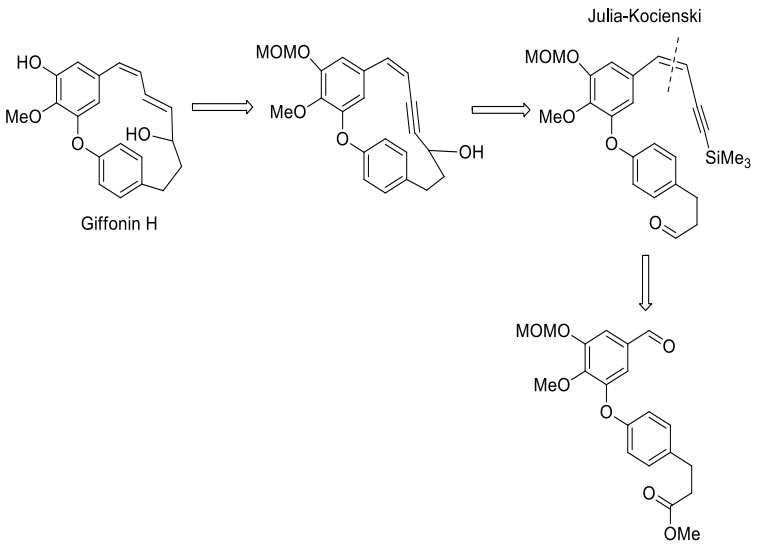


Scheme 39. Retrosynthesis of **X** via path A

[127] Bonini, C.; Chiummiento, L.; Videtta, V. *Synlett*, **2006**(13), 2079-2082.

[128] Bonini, C.; Chiummiento, L.; Videtta, V. *Synlett*, **2005**(20), 3067-3070.

A similar retrosynthetic approach (Julia followed by cyclization) was adopted in 2019 by a South Korean research group for the synthesis of Giffoin H[129] (**Scheme 40**), a cyclic diarylether analogue of myricanol.



Scheme 40. Total synthesis of Giffonin H

So, a first total synthesis strategy of myricanol could involve a modified Julia olefination reaction on the advanced biaryl system, followed by a reduction of the ester to the aldehyde, and finally a fluoride-mediated cyclization (similar to the Giffonin synthesis).

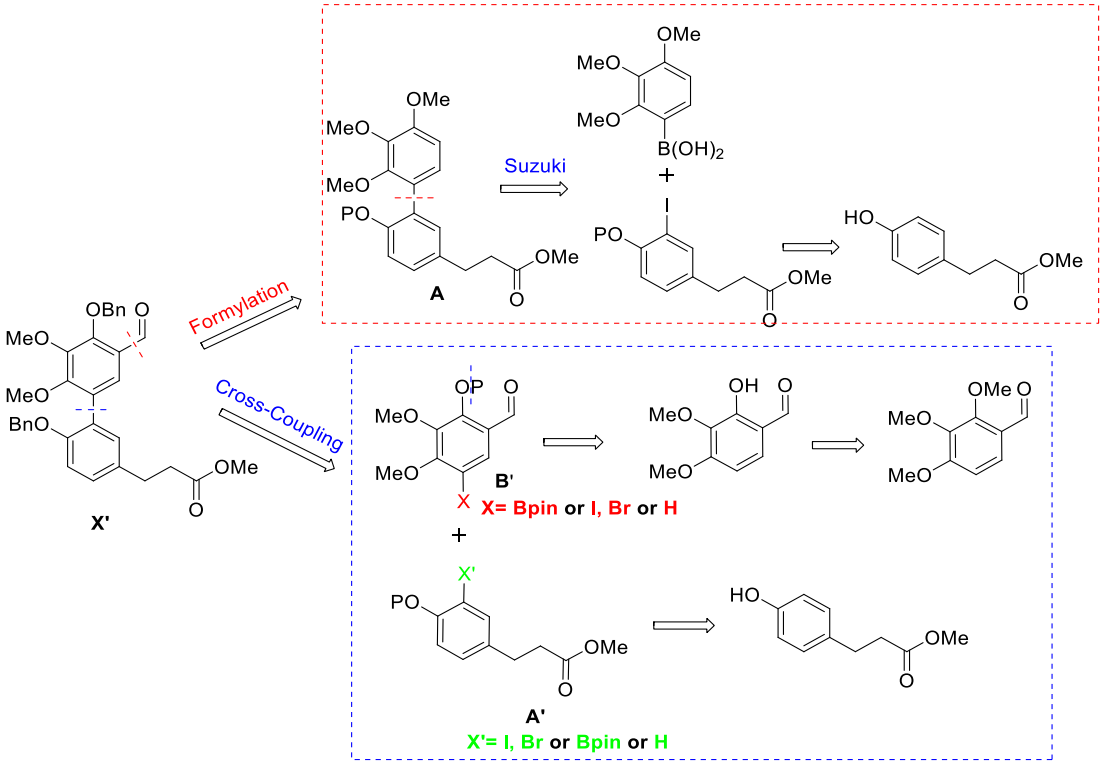
However, it's essential to emphasize that Giffonin H, a diarylether, is structurally different from myricanol, the target molecule of this thesis. The oxygen bridge between the two aryl groups offers significantly different flexibility, resulting in a macrocycle that is much less strained. Therefore, the thermodynamic difference between the two diaryleptanoids could be significant.

As already discussed in Chapter **1.3**, an illustrative example of the importance of ring strain on the ease of macrocyclization was reported; our research group, in fact, reported an efficient synthesis of an *ortho-meta* diaryleptanoid with a 12-membered ring by using a ring-closing metathesis (74), a methodology that did not yield encouraging results in the previous synthesis of myricanol, a *meta-meta* diaryleptanoid with a 13-membered ring.[25]

[129] Park, S., Kim, S. H., Jeong, J. H., & Shin, D. *Organic Chemistry Frontiers*, **2019**, 6(5), 704-708.

2.3.1-Retrosynthesis of the biarylic aldehyde X'

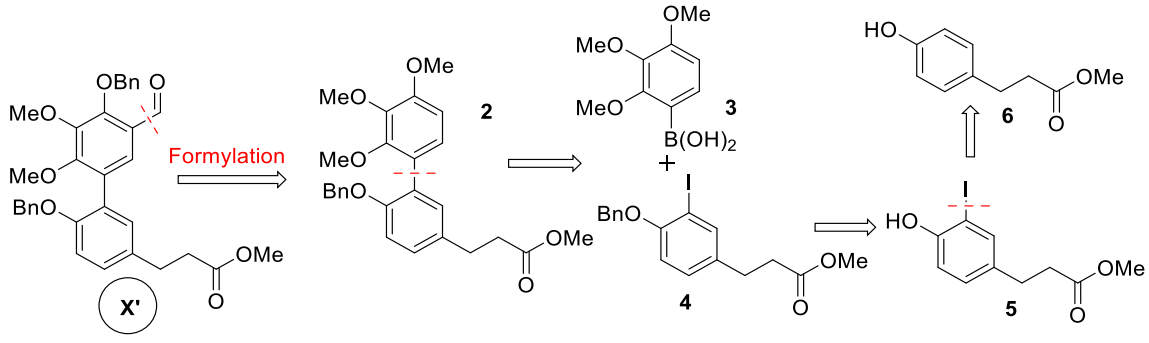
In **Scheme 41**, three of the possible retrosynthetic sequences for compound **X'** (Path A) are outlined:



Scheme 41. Retrosynthesis of **X'**

2.3.1.1-retrosynthetic approach via formylation:

As reported in **Scheme 42**, the initial disconnection on compound **X'** involves the formylation of compound **2**. The biaryl **2**, in turn, can be obtained through a cross-coupling reaction between the commercially available boronic acid (**3**) and the iodinated compound **4**, which can be prepared through iodination and protection of the corresponding phenolic propionyl ester (commercially available).

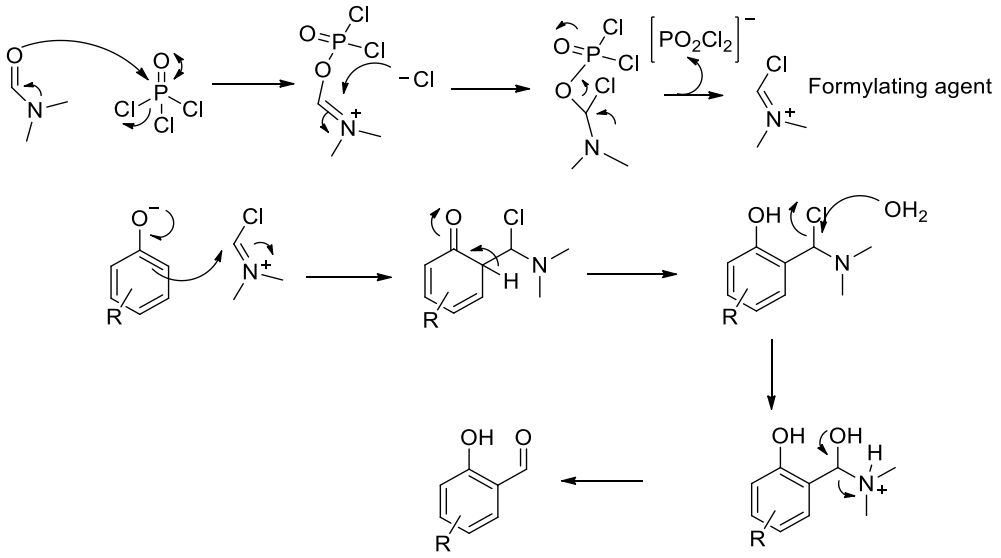


Scheme 42. First retrosynthetic approach

Regarding the formylation, the Gattermann-Koch formylation is widely used in industrial settings. In this process carbon monoxide reacts with HCl to form an acyl chloride, which is activated by forming a Lewis acid-base adduct with $AlCl_3$. However, such a reaction is not suitable for laboratory synthesis due to the toxicity of carbon monoxide, high temperatures, and high operating pressures required. Moreover, it is not suitable for phenolic substrates.[130]

The Reimer-Tiemann formylation involves chloroform and a strong base. Under these conditions, both chloroform (which, once deprotonated, undergoes α-elimination to form dichlorocarbene) and phenol are deprotonated. The reaction between deprotonated phenol and dichlorocarbene leads to the formation of dichloromethylphenol, which, upon basic hydrolysis, provides the formylated phenol.[131]

One of the most well-known formylation reactions is the Vilsmeier-Haack reaction (**Scheme 43**). This reaction proceeds through the formation of a formylating agent (by reaction between dimethylformamide with phosphoryl oxychloride), which, when reacting with the substrate, leads to an aryl-dimethylchloromethylamine, and subsequent hydrolysis provides the formylated product.

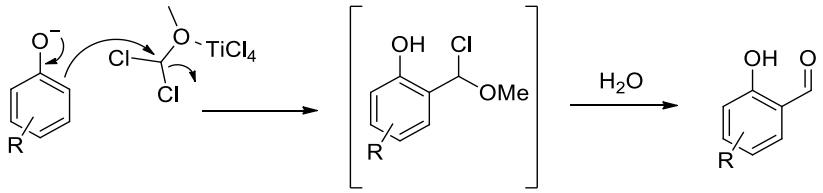


Scheme 43. Vilsmeier-Haack formylation reaction

Another example is the Rieche formylation, as shown in **Scheme 44**. The reaction involves dichloromethyl methyl ether as the formylating agent and a Lewis acid as a mediator. Firstly, an acid-base adduct is formed between dichloromethyl methyl ether (the formylating agent) and titanium

[130] Truce, W. E. *Organic Reactions*, **2011**, 37–72.
[131] Hine, J.; Van Der Veen, J. M. *J. Am. Chem. Soc.* **1959**, 81(24), 6446–6449.

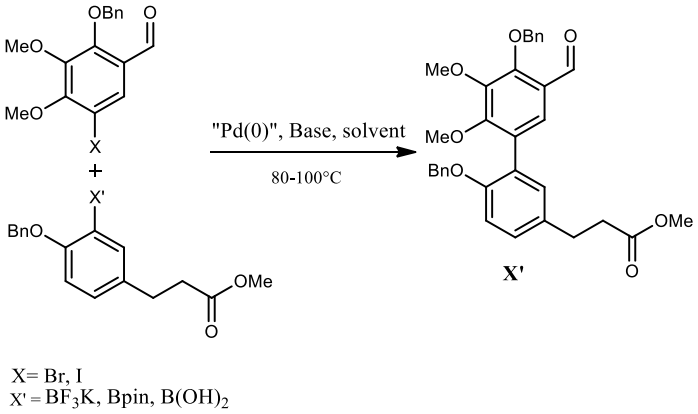
tetrachloride (or another Lewis acid such as $FeCl_3$ or $AlCl_3$ or AgOTf). Due to the adduct formation, the charge on oxygen is delocalized, making the methyl group activated for nucleophilic attack by the aromatic substrate. This leads to the formation of chloromethoxybenzyl derivative, which, upon hydrolysis, provides the aldehyde.



Scheme 44. Rieche formylation reaction

2.3.1.2-Retrosynthetic approach via a cross-coupling:

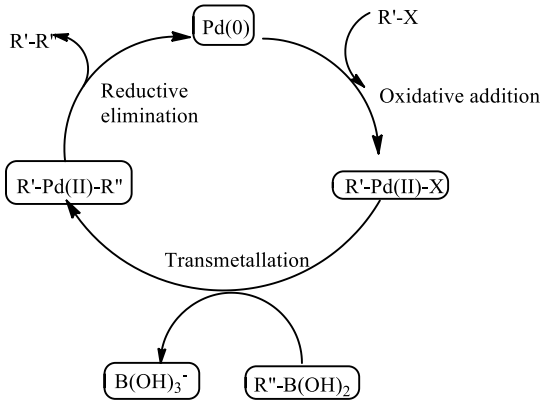
One possible disconnection of compound **X'** concerns the biaryl bond, which could be formed through an intermolecular cross-coupling reaction of the two fragments **A'** and **B'**. A large number of such cross-coupling reactions have been studied (reported in the Chapter 1.2), with one of the most common being the Suzuki-Miyaura reaction. In this reaction, the substrates are aryl halides and aryl boronic acid derivatives, generally using a Pd(0) species as the catalyst. The presence of a base is necessary to activate the organoboron species during transmetalation. The catalytic cycle of the Suzuki-Miyaura reaction involves oxidative addition to Pd(0) by the aryl halide, leading to the formation of a Pd(II) species. Subsequent transmetalation with the activated organoboron species and the reductive elimination step generates the desired biaryl coupling product (**Scheme 45**).



Scheme 45. Suzuki-Miyaura cross-coupling reaction

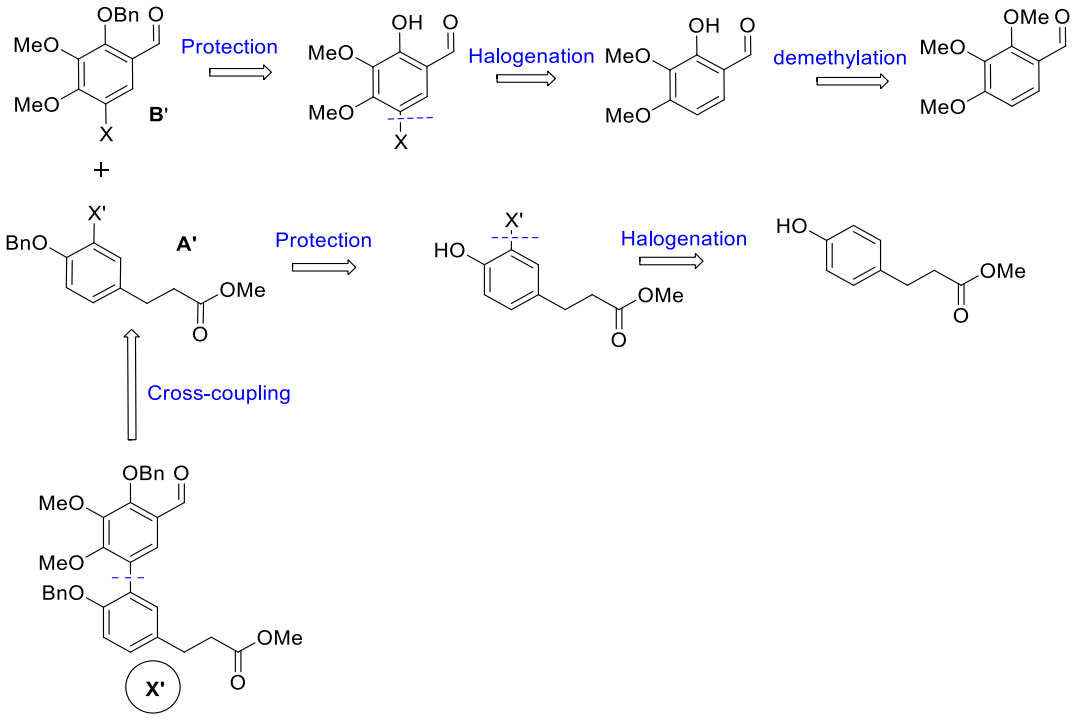
Among various cross-coupling reactions, the Suzuki-Miyaura reaction, which is undoubtedly one of the most well-studied and widely used cross-coupling methods was initially investigated in this thesis

work. It is an highly versatile reaction, offering good yields and relatively straightforward boronate generation (**Scheme 46**).



Scheme 46. Catalytic Cycle of the Suzuki-Miyaura reaction

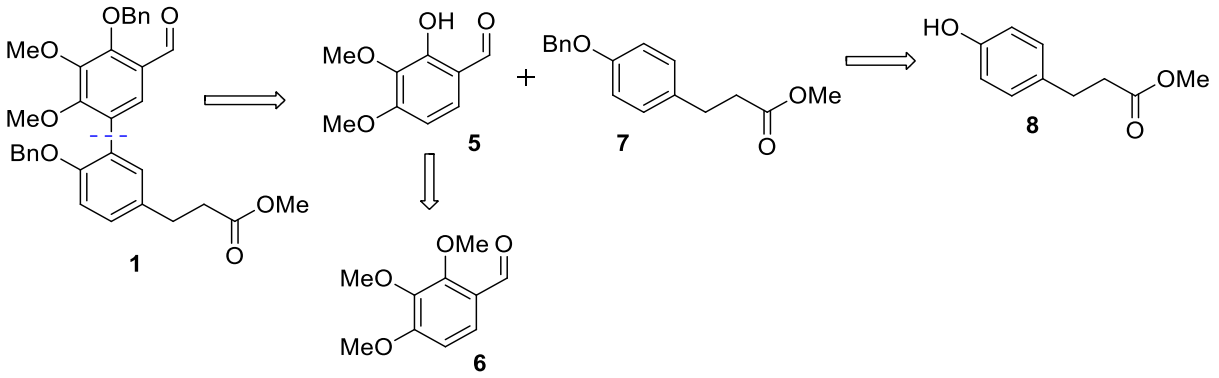
The first coupling partner **A'** can be synthesized from a commercially available ester through iodination (or bromination) and protection of the hydroxyl group through benzylation. The second partner **B'** can be synthesized from trimethoxybenzaldehyde by demethylation and iodination (or bromination). At this stage, the boronate can be generated on one of the two fragments **A'** or **B'**. (**Scheme 47**)



Scheme 47. Retrosynthetic approach via a Suzuki—Miyaura cross-coupling

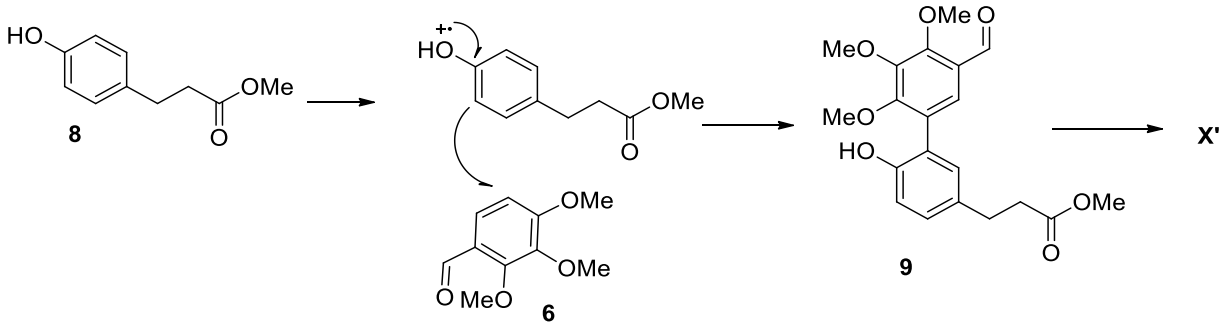
2.3.1.3-Retrosynthetic approach via a radical cross-coupling reaction:

This approach (**Scheme 48**) involves the disconnection of the biaryl bond. However, in this case, unlike the previous one, the biaryl system is prepared from halogenated fragments (**5** and **6**) through a radical cross coupling reaction (discussed in chapter 1.2).



Scheme 48. Third retrosynthetic approach to myricanol

The fragment **5** can be easily obtained through the regioselective demethylation of **6**. Fragment **7** arises from benzylation of **8**, or also, the products **6** and **8** could potentially be used in the same reaction type. This strategy appears to be the most straightforward, but due to the use of highly functionalized compounds (**Scheme 49**), various collateral reactions might be involved. The mechanism should proceed through the formation of the phenol radical, rearrangment delocalizing the radical to the *para* position. The *ortho*-directed coupling on the deactivated aromatic system would yield the desired product. Alternatively, the roles of the coupling partners could be reversed. Starting from trimethoxybenzaldehyde (**6**) and phenol **8** (**Scheme 49**), it might be possible to form the biaryl **9**, which, through demethylation and benzylation, could yield product **X'**.



Scheme 49. Radical Cross-coupling towards myricanol precursor **9**

2.4- Path B

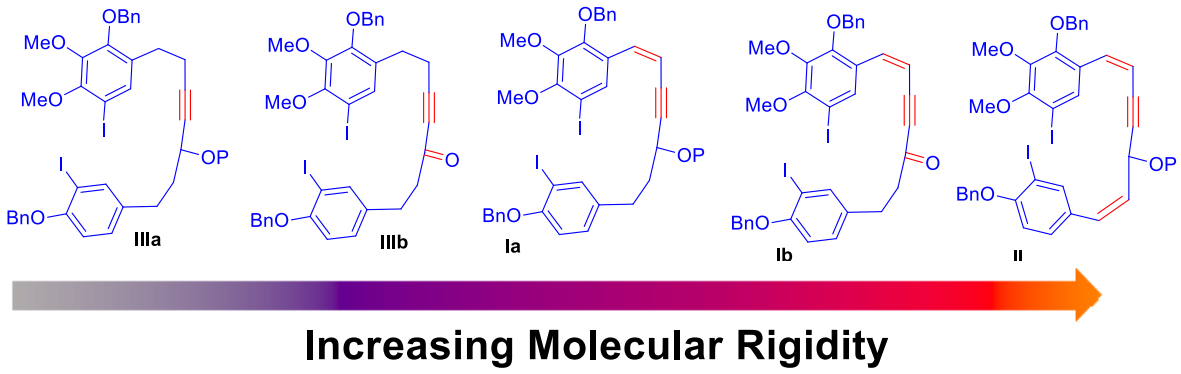
The retrosynthetic approaches discussed in the previous section for path A (section 2.3) can clearly be extended to path B by simply reversing the order of the addition and cross-coupling reactions.

-In Path A, an intermolecular cross-coupling is used between two partners to form the biaryl system that should be functionalized and ultimately cyclized through the addition reaction.

-In Path B, on the other hand, an intramolecular coupling is employed on a linear diaryleptanoid system, which is itself obtained through an addition reaction between two advanced fragments.

In either case, functionalizing a complex biaryl system (path A) can be more challenging than constructing advanced reaction fragments to be coupled in the final step of the synthetic strategy. In other words, a convergent total synthesis strategy is certainly more promising than a linear synthesis strategy.

However, as previously discussed, the degree of unsaturation in the starting substrate can play a decisive role in the cyclization reaction. While a more rigid system offers limited entropic changes during cyclization, it may also lead to a highly unstable and thermodynamically inaccessible cyclized system. Therefore, it was considered to investigate a series of *seco*-precursors with increasing degrees of rigidity to evaluate the influence of unsaturated systems on the macrocyclization reaction. In the following Scheme, six different *seco*-precursors are shown, and their synthesis will be covered in the subsequent chapter (**Scheme 50**).

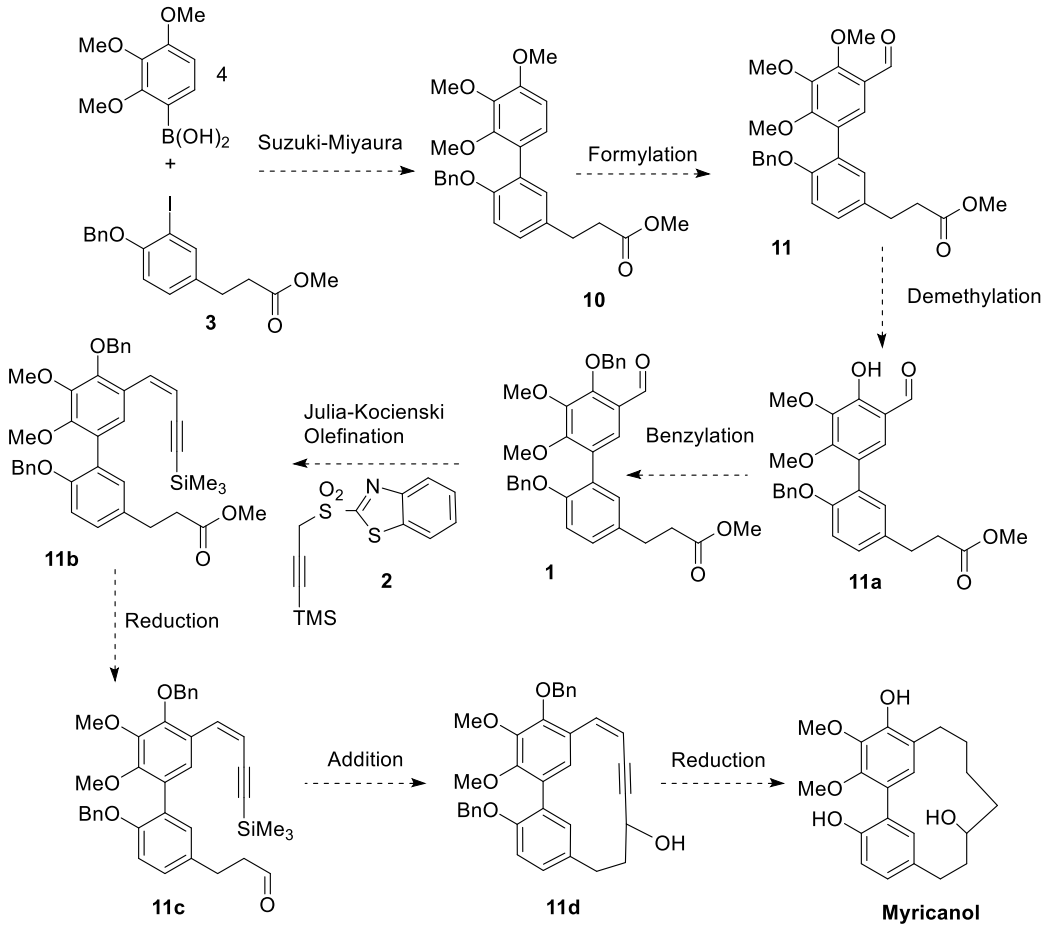


Scheme 50. Polyunsaturated *seco*-precursors of myricanol

CHAPTER 3- Results

3.1- Path A. First approach

The initial planned synthetic strategy (**Scheme 51**) involved a Suzuki-Miyaura cross-coupling reaction starting from commercial boronic acid (**4**) and aryl iodide (**3**) (derived from commercially available methyl 4-hydroxyphenylpropionate, iodinated, and subsequently protected, resulting in the formation of compound **3)**.

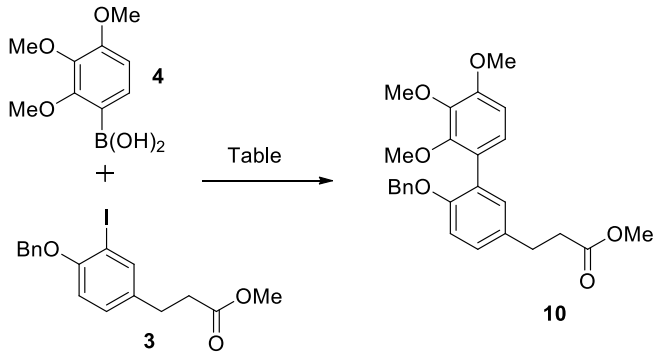


Scheme 51. Path A: 1st pathway

The subsequent formylation of compound **10** would lead to the biaryl aldehyde **11**. Subsequently, regioselective demethylation at the methoxy in *ortho* position to the aldehyde moiety would yield the corresponding phenol. This phenol, when suitably protected as a benzyl ether, would provide compound **1**. The modified Julia olefination reaction conducted with sulfone **2** would form the ene-yne system ready to react with the aldehyde obtained from the ester reduction. The cyclization mediated by fluoride would yield the *meta-meta*-cyclophane system, a precursor to myricanol.

3.1.1- Cross-Coupling attempts

The Suzuki-Miyaura reaction (**Scheme 52**) was carried out between boronic acid **4** and the halogenated ester **3**, the boronic acid was first dissolved in ethanol and activated with sodium carbonate, and then gradually added to the solution containing the aryl iodide and the catalyst in DME at 80°C. The desired compound was obtained with 44% yield and 48% of conversion (entry 1), while, by using $PdCl_2(PPh_3)_2$ with $NaHCO_3$ in DMF/H_2O (4:1) for 22 hours, the desired compound was obtained with 93% yield and 99% of conversion (entry 3).



Entry	4 (eq)	Conditions	T	t	Conversion	Yield
1	1.4	$Pd(PPh)_3$ (0.05eq), Na_2CO_3 (1.4eq), DME, EtOH	80°C	27h	48%	44%
2	1.5	**$PdCl_2(PPh_3)_2$ (0.05 eq), $NaHCO_3$ (1.4 eq), DMF/H_2O (4:1)**	80 °C,	5 h,	77%	67%
3	1.5	$PdCl_2(PPh_3)_2$ (0.05eq), $NaHCO_3$ (1.4 eq), DMF/H_2O (4:1),	80 °C,	**22 h,**	99%	93%

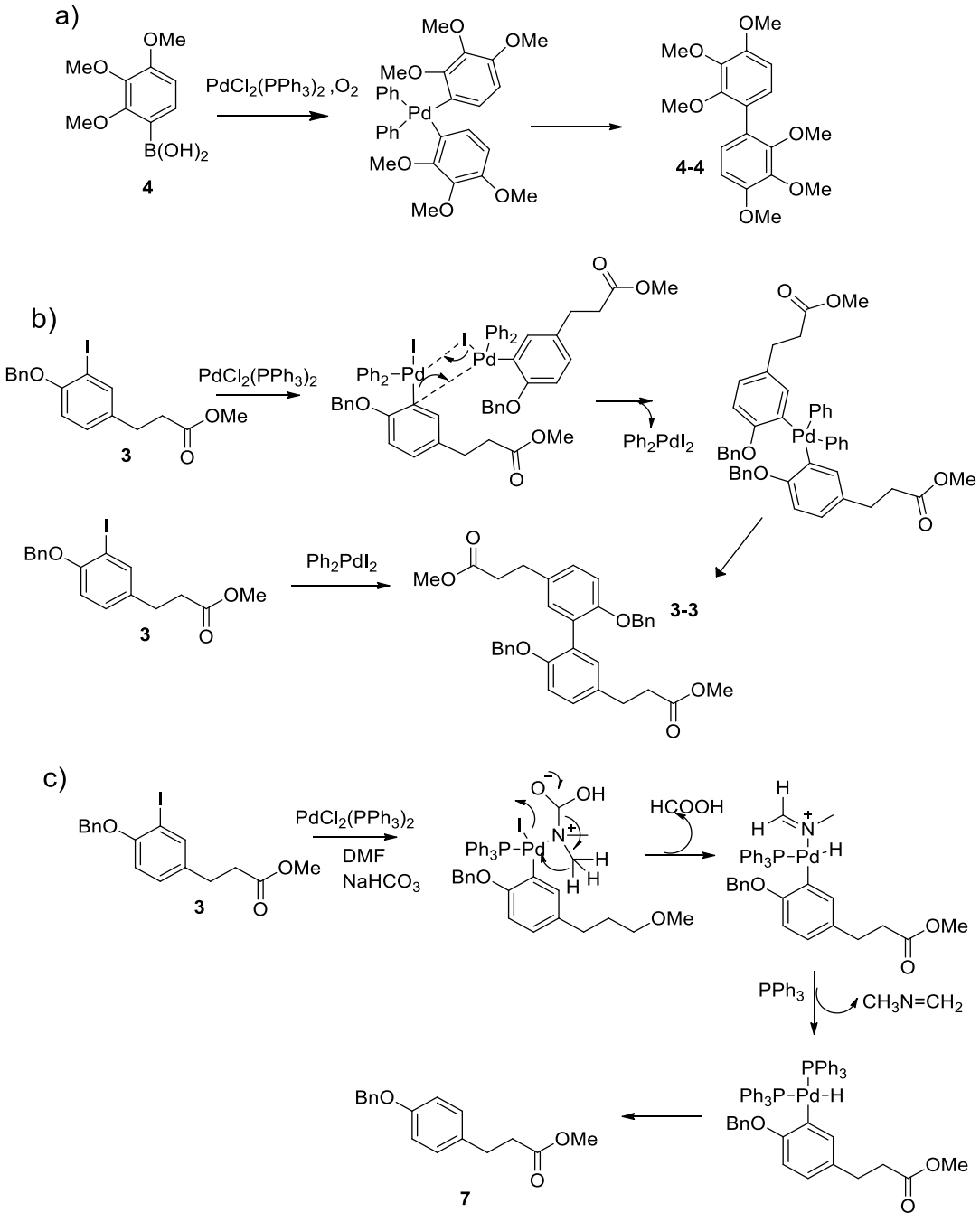
Scheme 52. Suzuki Cross-coupling between **3** and **4**

In addition to product **10**, undesired homo-coupling products were obtained, specifically the dimer of boronic acid **4** and compound **3** and traces of the dehalogenated ester.

The dimer of boronic acid results from the oxygen mediated oxidation of Pd(0) to Pd(II).

The Pd(II) complex can then react with two molecules of arylboronic acid to form, through reductive elimination, the homo-coupling product of **4** (**Scheme 53a**).

The Ar-Pd-X species formed in the first step of oxidative addition can undergo metathesis with another molecule of Ar-Pd-X, forming the Ar-Pd-Ar species, which, after reductive elimination, yields the homo-coupling product of **3** (**Scheme 53b**). Another possible side reaction involves the dehalogenation of the iodinated reagent, where the Ar-Pd-X species can abstract a proton from DMF, producing the dehalogenated product **7** (**Scheme 53c**).

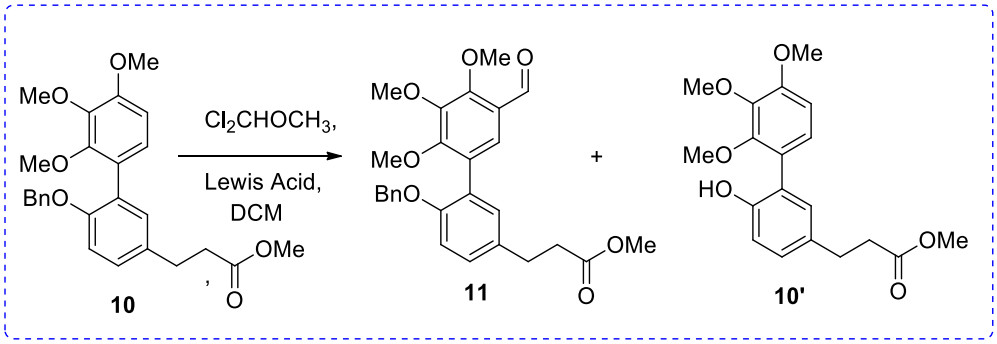


Scheme 53. Possible formation of side products during the coupling reaction of **3** and **4**

3.1.2- Formylation attempts

The formylation of compound **10** was carried out using dichloromethyl methyl ether in dichloromethane in the presence of a Lewis acid as a catalyst (Rieche formylation). Under these conditions, demethylation of the product should also occur.

Rieche Formylation can be conducted with $FeCl_3$, $AlCl_3$, $TiCl_4$[132], or AgOTf[133]. The reaction mechanism is believed to involve the formation of a Lewis acid-base adduct between the catalyst and the oxygen of dichloromethyl methyl ether, leading to the activation of the latter.



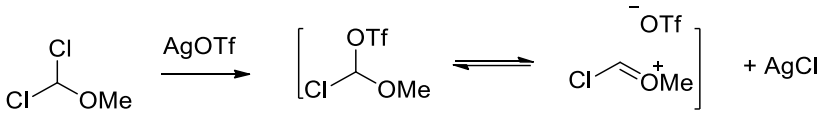
Entry N.	Cl_2CHOCH_3 (eq)	Lewis Acid (eq)	T (°C)	time	Product	Yield (%)
1	(1.2 eq)	$TiCl_4$ (2.2 eq)	0°-t.a	6 h	**10'**	N/A
2	(1.2 eq)	$TiCl_4$ (2.4 eq)	0°	18h	**10'**	N/A
3	(1.2 eq)	$AlCl_3$ (1.2 eq)	0°-t.a.	3h	No reaction	N/A
4	(5 eq)	$AlCl_3$ (2.0 eq)	t.a.	22h	No reaction	N/A
5	(3 eq)	AgOTf (3.0 eq)	-78° – 0°	45 min.	**11** + mixture of compounds	trace
6	(3 eq)	AgOTf (3.0 eq)	0°	3 h	**11** + mixture of compounds	8%

Scheme 54. Rieche formylation of compound **10**

[132] Warashina, T.; Matsuura, D.; Kimura, Y. *tetrahedron* 75, **2019**, 608-616.
[133] Ohsawa, K.; Yoshida, M.; Takayuki, M. *J. Org. Chem.* **2013**, 78, 7, 3438–3444.

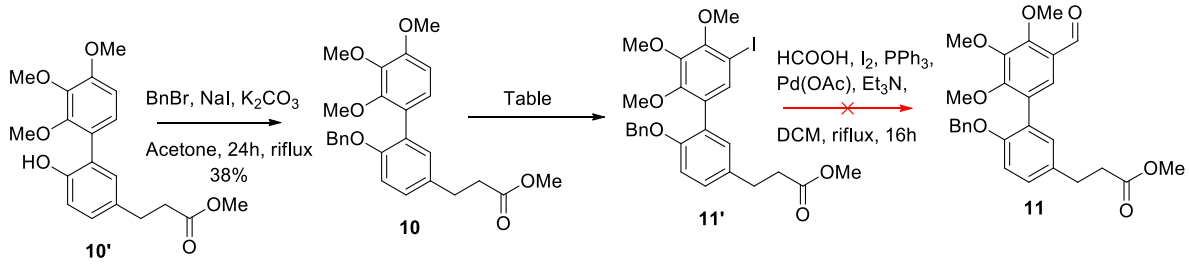
The first formylation attempt was conducted in the presence of $TiCl_4$ and resulted exclusively in the debenzylated product (**Scheme 54**). However, despite of the use of different reaction conditions such as temperature, reaction time and catalyst, similar results were obtained.

It is conceivable that the reaction mechanism involves the formation of a Lewis acid-base adduct between the catalyst and the oxygen of the dichloromethyl methyl ether, leading to its activation. However, the involvement of transition metals in electrophilic aromatic substitution reactions is plausible. Retro π-donation (by the π* orbitals of the aromatic ring) renders the substrate more electron-rich and thus more reactive. Therefore, it is reasonable to hypothesize that the formylation mechanism includes not only the activation of the formylating agent but also the formation of Lewis acid-base adducts with the aromatic systems (and methoxy substituents) of the substrate, leading to debenzylation under acidic conditions. Attempts of formylation using $AlCl_3$ as the catalyst, with varying stoichiometric ratios and temperatures, did not yield any reaction. Further formylation attempts with AgOTf, whose mechanism (**Scheme 55**) involves the activation of the ether through the substitution of a chloride with a triflate group, resulted in the formation of traces of the desired product and a complex mixtures of unidentified products.



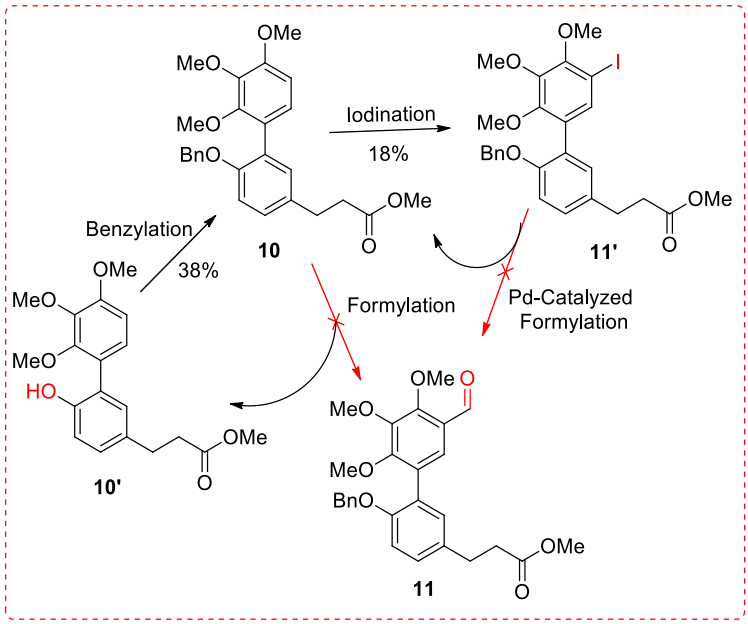
Scheme 55. Rieche formylation with AgOTf

The debenzylated compound **10'** was subjected to benzylation (**Scheme 56**) and iodination in order to obtain compound **11'**, which was then subjected to a Pd-catalyzed formylation for regenerating the desired compound **11**. Unfortunately, this attempt was unsuccessful and only the dehalogenated compound **10** was obtained, the results for the first approach are summarized in the scheme **57** and a second synthetic approach was considered (next section).



Entry	Conditions	Solvent	T (°C)	time	Product (yield%)
1	NIS (1.1 eq), TFA (0.3 eq)	ACN	r.t.	8h	**11' (6%)**
2	Ag_2SO_4 (1.5 eq), I_2 (1.5 eq)	DCM	r.t.	22h	**11' (18%)**

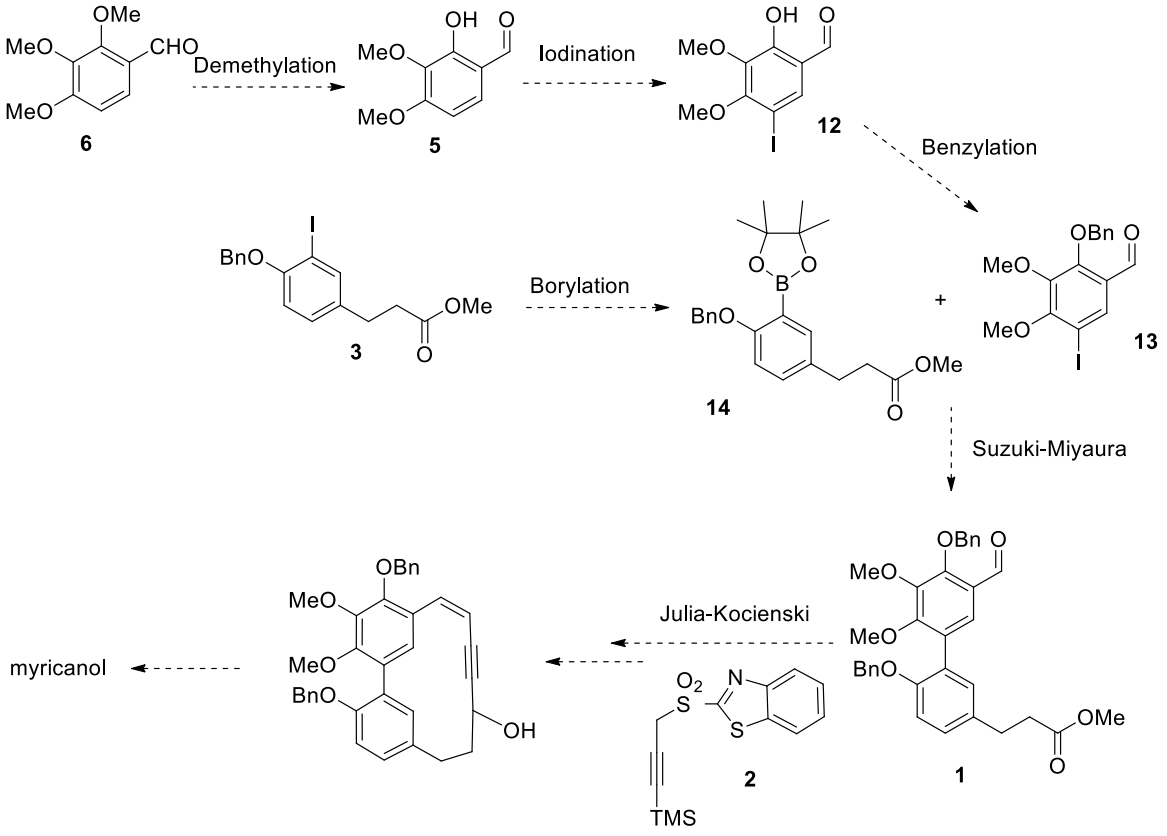
Scheme 56. Alternative approach to **11**



Scheme 57. Summary of the first approach (Path A)

3.2-Path A. Second approach

In light of the unsuccessful formylation results on the biaryl system, an alternative approach was undertaken. Initially, the advanced fragments **13** and **14** (as illustrated in **Scheme 58**) were prepared, They should be involved in a cross-coupling reaction to access the formylated product **1**. This latter should be the same precursor of the previous synthetic approach.



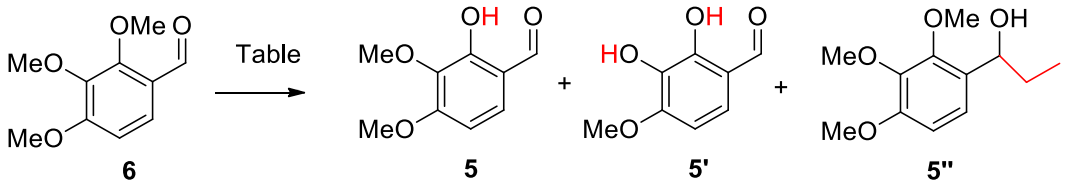
Scheme 58. Path A. 2nd pathway

The aldehyde **13**, the first cross-coupling partner, can be synthesized through a sequence of demethylation, iodination, and benzylation of the commercially available trimethoxybenzaldehyde. The second cross-coupling partner, the pinacol boronate **14**, on the other hand, can be obtained by borylation of compound **3**.

3.2.1- Synthesis of the first cross-coupling partner

3.2.1.1-First step: Regioselective demethylation

The regioselective demethylation of the methoxy group at C-2 of 2,3,4-trimethoxybenzaldehyde can be performed using a Lewis acid such as $AlCl_3$, as illustrated in **Scheme 59**.



Scheme 59. Demethylationof 6

Entry	Lewis acid (eq.)	Solvent	T (°C)	time	Product	Conv.	Yield of 5
1	$AlCl_3$ (1.5 eq)	DCM	-5°-r.t.	5h	/	/	/
2	$AlCl_3$ (6 eq)	DCM	0- r.t.	5h	5 +5’	70%	<10%
3	$AlCl_3$ (6 eq) Et_2AlCl (2 eq)	DCM	0- r.t.	1h	5 + 5’+ byproducts	N/A	14%
4	Et_2AlCl(2 eq)	DCM	.0- r.t.	2h	5’’	N/A	/
5	$AlCl_3$ (3.7 eq) NaI (2.8 eq)	DCM/ACN	0- r.t.	4h	5 + 5’	100%	80%
6	$AlCl_3$ (1.5 eq) NaI (1.5 eq)	DCM/ACN	0	4h	5	100%	99%

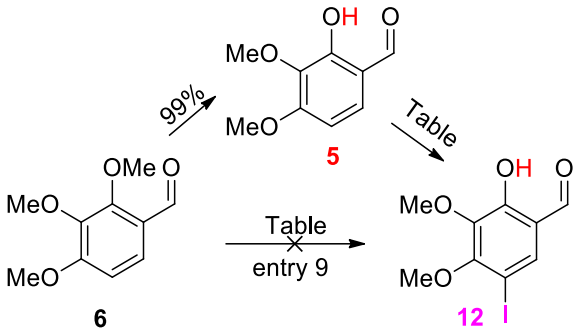
Table 9. Demethylationof aldehyde **6**

Based on the experiments conducted (**Table 9**), it became evident that the mere presence of $AlCl_3$ was insufficient unless a strong excess was used (**entry 2**) giving a double demethylated sideproduct **5’** as the major product. The active participation of a nucleophile (I^-) is essential. Notably, when diethylaluminum chloride was employed, alkylation of the aldehyde occurred (**entry 4**). It is important to highlight the sensitivity of this reaction during the quenching, as it potentially yield **5’** once quenched in water (entry 2, 3 and 5). Through several trials, reaction conditions were optimized. The best conditions involved the use of 1.5 equivalents of $AlCl_3$ and 1.5 equivalents of NaI (added in a *one-pot* at 0°C) in DCM/ACN (1:1). After 4-hours, the demethylated product was achieved with an

impressive 99% yield by quenching with the Rochelle salt (potassium sodium tartate) at 0°C, under those conditions, the formation of challenging-to-handle emulsions is effectively prevented.

3.2.1.2-Second step: Iodination

Iodination attempts on the compound **5** are reported in the following **table 10**,



N	sub	Cat.	I_2 (eq)	Solv.	Time	Prod (yield)	conv	Work-up
1	5	Ag_2SO_4 (1.5)	1.5	DCM	20	12 (24%)	100	Filtration on silica,
2	5	Ag_2SO_4 (1.5)	1.5	DCM	24	12 (55%)	100	Filtration on Celite
3	5	Ag_2SO_4 (1.5)	1.5	DCM	6	12 (47%)	94	Filtration on Celite
4	5	Ag_2SO_4 (0.3)	1.5	DCM	20	12(14%)	19	Filtration on Celite
5	5	Ag_2SO_4 (1.5)	2.0	DCM	4	12 (52%)	99	Filtration on celite
6	5	AgOTf (2.0)	2.0	DCM	20	Mix	40	Filtration on Celite
7	5	Ag_2O (2.0)	2.0	DCM	16	0	0	Filtration on Celite
8	5	Ag_2SO_4 (1.5)	2.0	ACN	16	12(12%)	100	Filtration on Celite
9	6	$AlCl_3$ (2.0)	1.5	DCM	16	5 (88%)	100	Rochelle Salt
10	5	NIS, TFA	/	ACN/DCM	18	/	/	

11	5	NIS, TFA	/	ACN	18	12 (28%)	/
12	5	NIS, p-TsOH	/	ACN	18	12 (92%)	99

Table 10. Iodination of compound **5**

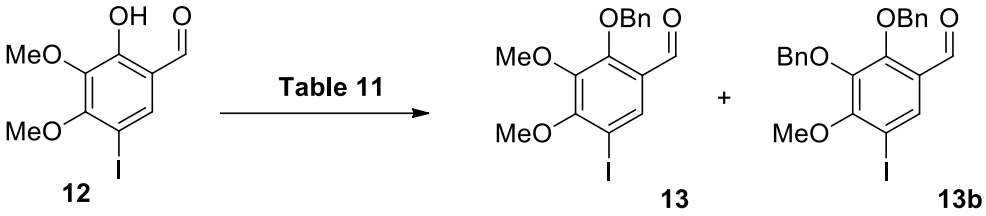
The work-up of this reaction seems to have a crucial role on the isolated yield, in fact, most of the performed attempts gave a full conversion, without side products and the lower isolated yield does not have an immediate explanation. Probably, the formation of *in situ* silver salt is able to "trap" part of the product, different solvents and work-ups were tried in order to obtain a better yield.

When the reaction mixture was filtrated on celite a better isolated yield was obtained (55%, entry 2). By decreasing the reaction time (entry 3) no improvement was observed, while using catalytic amounts of silver sulfate (Ag_2SO_4 , entry 4), partial conversion of the substrate was observed. Increasing the equivalents of iodine (entry 5) did not lead to any improvement, even though the conversion was complete after 4 hours of reaction. However, using silver trifluoroacetate (AgOTf, entry 6) resulted in the formation of byproducts, while no reaction was observed with silver oxide (Ag_2O,entry 7).

By changing the solvent to ACN, only 12% isolated yield was obtained (entry 8). To address this, $AlCl_3$ was used as the catalyst instead of Ag_2SO_4 directly on the methylated substrate (**6**), aiming for both demethylation and iodination, simultaneosly. This approach provided the mono-demethylated product with an 88% yield (entry 9).

Finally, the iodination of **6** using NIS, both in ACN/DCM or ACN with TFA (0.3 equiv.), did not yield good results (entry 10-11). Unexpectedly, the iodination using NIS in ACN with p-TsOH (1.0 equiv.) led to an almost complete conversion and an isolated yield of 92%. (entry 12)

3.2.1.3-Third step. Benzylation



Entry	Conditions	Solvent	T (°C)	time	Product	Isolated Yield (%)
1	BnBr (1.2 eq) K_2CO_3 (2.0 eq) NaI (0.07 eq)	Acetone	reflux	24h	**13**	15%
2	BnBr (1.2 eq) NaH (2.5 eq)	DMF	100° C	18h	**13**	42%
3	BnBr (1.2 eq) K_2CO_3 (2.0 eq)	DMF	100° C	18h	**13**	75%
4	BnBr (1.2 eq) K_2CO_3 (2.0 eq) NaI (0.07)	DMF	100° C	18h	**13** + **13b** (66:33)	/
5	BnBr (1.2 eq) K_2CO_3 (2.0 eq) NaI (0.07 eq)	DMF	75°C	18h	**13** + **13b** (89:11)	/
6	BnBr (1.2 eq) K_2CO_3 (2.0 eq)	ACN	55°C	4h	**13**	quantitative
7	BnBr (1.2 eq) K_2CO_3 (2.0 eq)	ACN	r.t.	8h	**13**	quantitative

Table 11. Benzylation of compound **12**

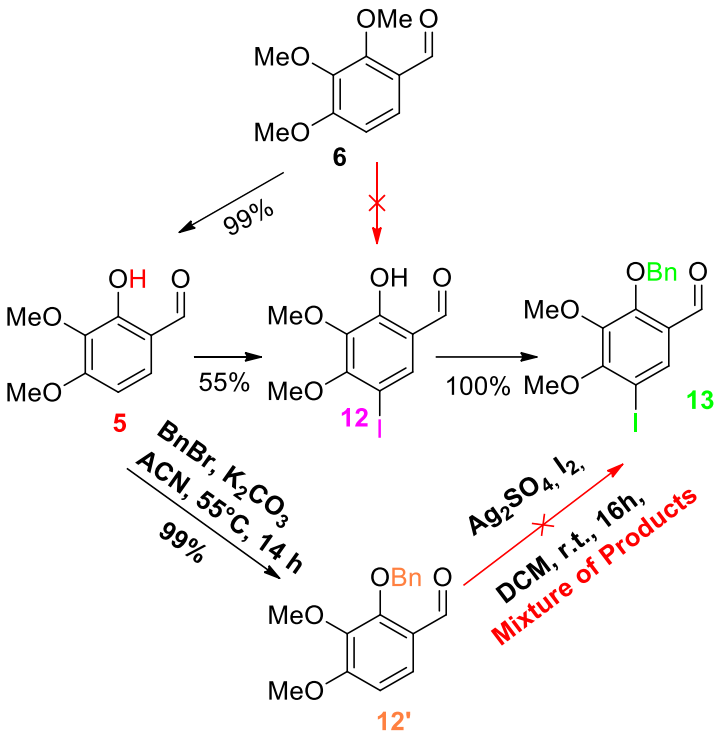
The benzylating reaction conducted in acetone with benzyl bromide and potassium carbonate (entry 1) provided only a 15% yield. by conducting the reaction in DMF andbyincreasing the temperature, the yield significantly improved. A different base led to a decrease of the reaction yield to 42%.

A surprising outcome was observed when the reaction was carried out in DMF at 100°C in the presence of catalytic amounts of NaI. Under these conditions, demethylation occurred, resulting in double benzylations. The product of double benzylations was chromatographically unseparable from

the desired product due to their identical *Rf* values.

When the reaction was conducted in ACN, it was completed within 4 hours at 55°C with quantitative yield, while at room temperature, more time was required to achieve complete conversion and quantitative yield .

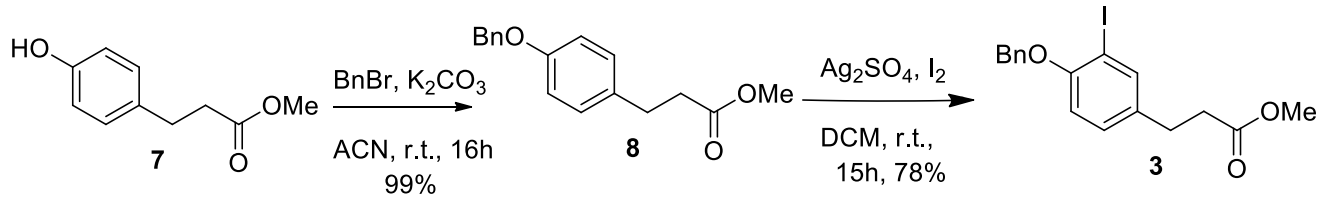
Alternatively, compound **5** was first benzylated and then iodinated. The benzylating step provided the desired compound with a 99% yield. However, the subsequent iodination step resulted in a mixture of products. This approach is presented along with a summary of the synthesis of the first cross-coupling partner in **Scheme 60**.



Scheme 60. Summary of the synthesis for compound **13**

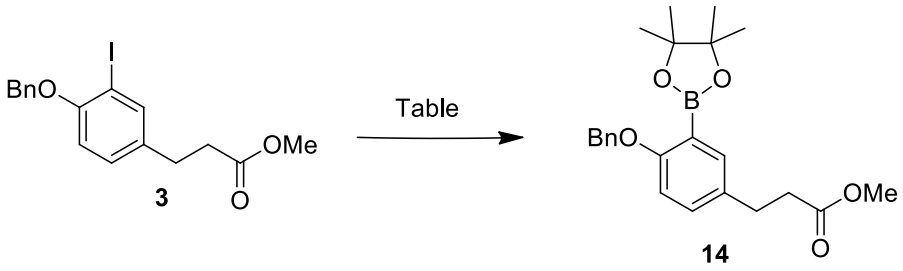
3.2.2- Synthesis of the second cross-coupling partner

The compound **3** was synthesized starting from **7** through a benzylation and iodination (**Scheme 61**).



Scheme 61. Synthesis of compound **3**

The pinacol boronate **14** was generated on compound **3** at 80°C using 3 equivalents of potassium acetate and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride as the catalyst, following the times and conditions listed in **Table 12**.

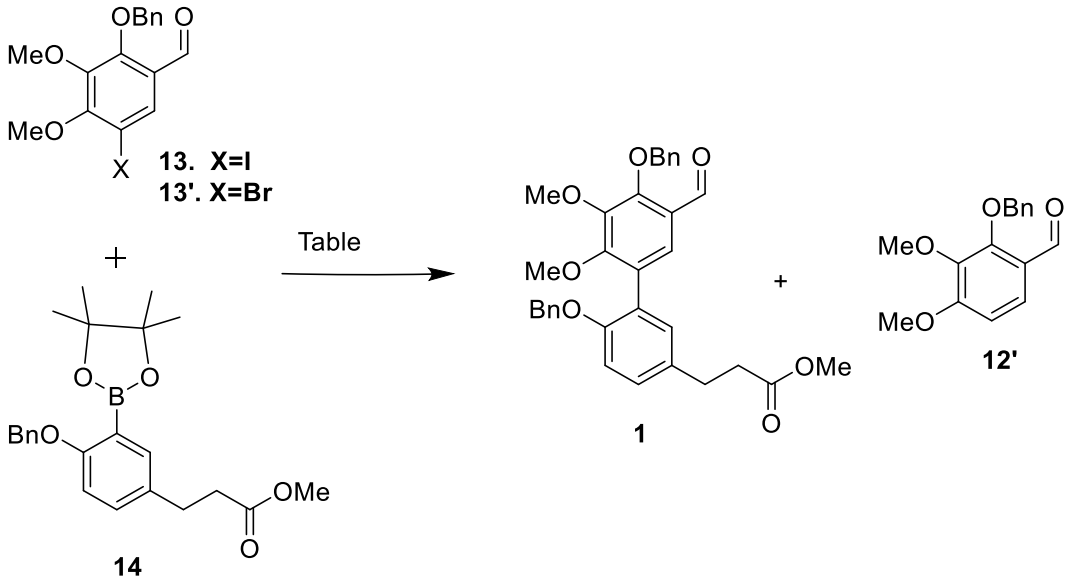


Entry	$B_2(pin)_2$ (eq.)	Solvent	time	14 Yield (%)
1	1.2	dioxane	2h	traces
2	1.3	DMSO	4h	9%
3	2	DMSO	6h	42%
4	5	DMSO	20h	42%

Table 12. Synthesis of compound **14**

The best reaction conditions for generating the pinacol boronate (the second cross-coupling partner) were achieved using 2 equivalents of diboropinacolate in anhydrous dimethyl sulfoxide (**Table 12, entry 3**). Increasing equivalents of diboropinacolate and reaction times did not yield any improvement in the isolated yield.

3.2.3- Cross-coupling attempts between 13 and 14



Entry	Pinacol boronate (eq.)	X	Catalyst (0.05 eq)	Base (1.2 eq)	Solvent	T (°C)	Time	Product
1	1.2	I	$PdCl_2(PPh_3)_2$	$NaHCO_3$	DMF/H_2O	80	26h	Traces + 12’
2	1.4	I	$PdCl_2(dppf)_2$	$NaHCO_3$	DMF/H_2O	80	22h	Traces+ 12’
3	1.2	I	$PdCl_2(dppf)_2$	Cs_2CO_3	Dioxane	100	20h	12’
4	1.2	I	$PdCl_2(PPh_3)_2$	KF	DMF/H_2O	80	20h	12’
5	1.2	Br	$PdCl_2(PPh_3)_2$	$NaHCO_3$	DMF/H_2O	80	8h	/

Table 13. Cross-coupling attempts

The first cross-coupling attempt (**Table 13**) was carried out under the same reaction conditions as used in the first synthetic approach (section 3.1.1). However, in this case, only traces of the coupled product were obtained, and after 26 hours, only the dehalogenated product **12’**was observed. The same reaction was repeated with increased stoichiometric ratios of the boronic acid, but after over 20 hours of reaction, no progress was observed compared to the previous attempt.

Another attempt was conducted in dioxane, using cesium carbonate as the base and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride as the catalyst. After 20 hours of reaction, only **12’** was obtained.

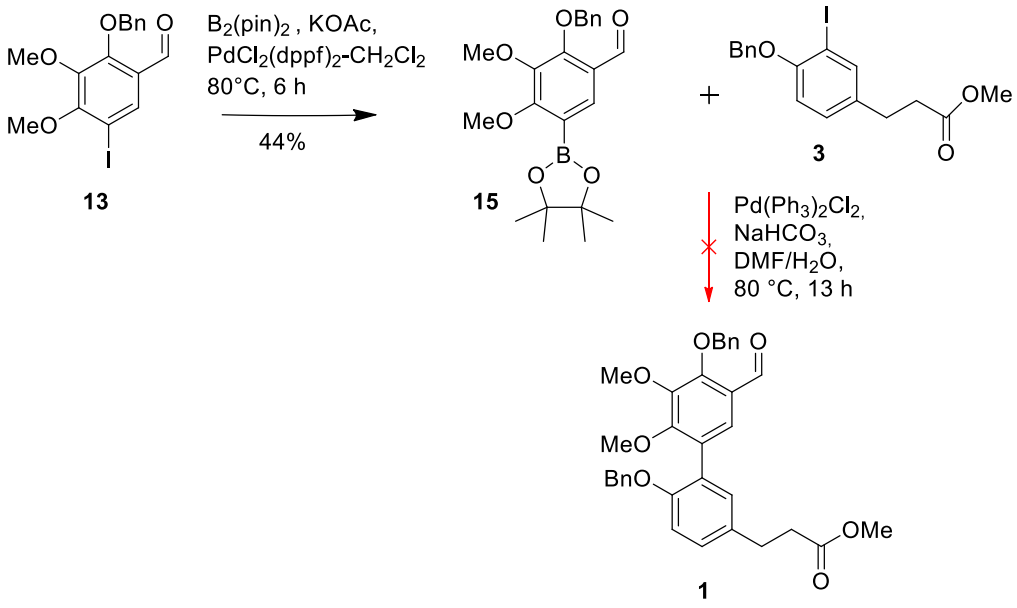
Also using potassium fluoride , after 20 hours of reaction, , only the **12'** was obtained.

A final attempt was conducted on **13'** (X=Br), but after 8 hours, no coupling product was observed.

The reason for this unsuccess might be due to the highly electron-rich aryl halide used, which, due to its electron-rich nature (two methoxy and one hydroxy groups), readily underwent protonation rather than participating in the transmetalation reaction with the boronic partner.

Moreover the reactivity of the pinacol boronate was quite different respect to the experimented one in the first synthetic strategy, where a side product of the Suzuki-Miyaura reaction is the boronate dimer. Now , however, the boronate not only did not participate in the cross-coupling reaction but also did not provide any homo-coupling products.

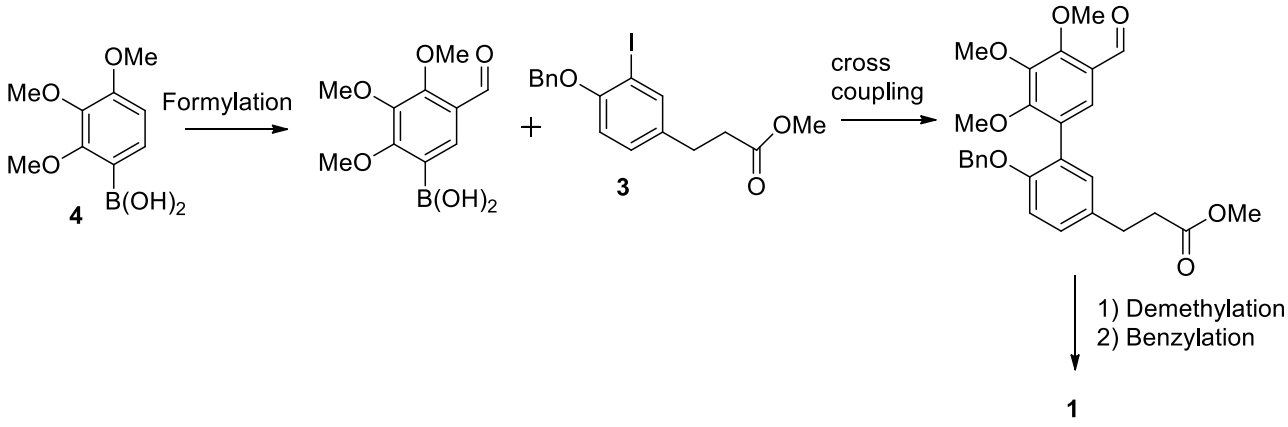
To address these issues, it was decided to reverse the coupling partners. Therefore, the idea was to generate the pinacol boronate on fragment **13** and perform the cross-coupling with aryl iodide **3** (**Scheme 62**). In this case, the aryl halide **3** would be less reactive towards dehalogenation. Unfortunately, this cross-coupling attempt did not yield the desired compound under the investigated reaction conditions.



Scheme 62. Cross-coupling between compounds **3** and **15.**

3.2.4- Formylation of aryl boronic acids

Simultaneously with the synthetic approach just described, an attempt was made to generate the *meta* functionalized aldehyde starting from a commercially available aryl boric acid **4** (**Scheme 63**). There are no examples in the literature of such formylation attempts on aryl boronic acids.



Scheme 63. Formylation on **4** and cross-coupling

For this reaction, the Rieche formylation conditions (**Scheme 63**) were used, involving the use of dichloromethyl methyl ether as the formylating agent in the presence of a Lewis acid as a mediator.
The formylation of substrate **4** (**Scheme 63**) in the presence of AgOTf unexpectedly resulted in quantitative ipso-formylation. The same substrate was tested with other Lewis acids such as $AlCl_3$ and $FeCl_3$, yielding the same product. Therefore, the general reactivity of boronic acids towards Rieche formylation was further investigated[134]since there are limited examples of formylation reactions specifically involving arylboronic acids[135].

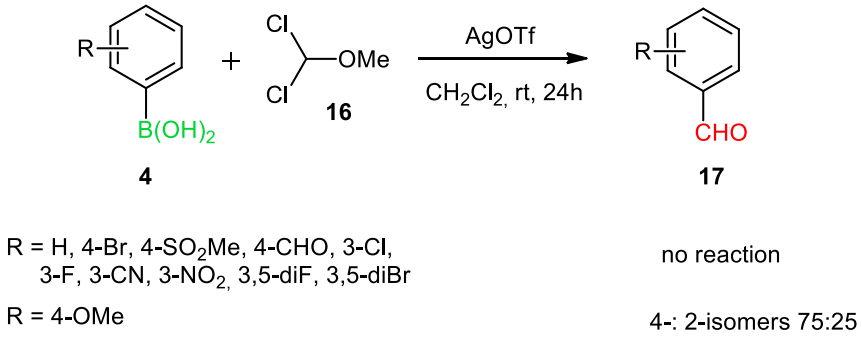
No reaction was observed in the presence of electron-withdrawing group (EWG) (CN, CHO, CF_3,NO_2, SO_2Me), or halogens (F, Cl, Br), even at higher temperatures or longer reaction times, only the starting substrate was recovered.
Surprisingly, 4-methoxyphenyl boronic acid **4a** resulted in a 75:25 mixture of 4- and 2-methoxybenzaldehyde.

[134] Santarsiere, A.; Funicello, M.; Lupattelli, P.; Choppin, S.; Colobert, F.; Hanquet, G.; Chiummiento, L.. *ChemistrySelect* , **2023**, 8 (34), e20230210.
[135] a) H. Huang, C. Yu, X. Li, Y. Zhang, Y. Zhang, X. Chen, P. S. Mariano, H. Xie, W. Wang, *Angew. Chem. Int. Ed.* **2017**, *56*, 8201-8205 and references cited therein; b) D. Petruzziello, A. Gualandi, H. Giaffar, V. Lopez-Carrillo, P. G. Cozzi, *Eur. J. Org. Chem.* **2013**, 4909-4917.

Motivated by this intriguing outcome, we proceeded to investigate this reaction using different Lewis acids. The results are summarized in **Table 14**. Formylation of **4a** using AgOTf (**method A**) led to a 3:1 ratio of the 4-/2-regioisomers **17a:17a'**, whereas $AlCl_3$ (**method B**) or $FeCl_3$ (**method C**) exclusively yielded the *ipso*-formylated product **17a**. It is noteworthy that when 4-methoxybenzene was subjected to formylation with AgOTf[133] or $AlCl_3$[132], a mixture of regioisomers **17a**:**17a'** was obtained in a 1:1.5 or 1:1.2 ratio, respectively.

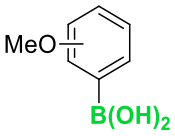
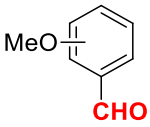
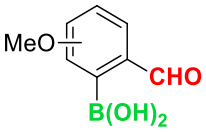
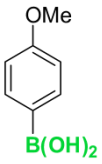
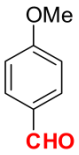
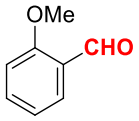
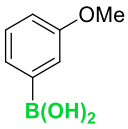
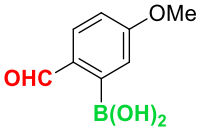
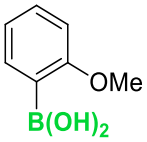
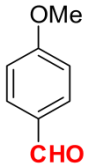
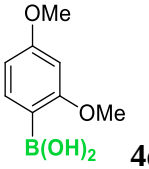
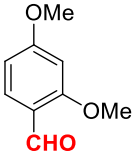
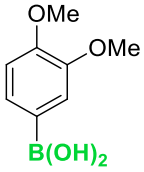
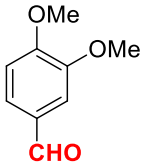
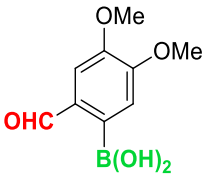
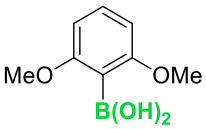
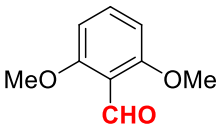
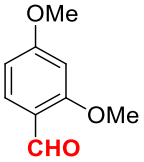
The improved regioselectivity observed for 4-methoxyphenyl boronic acid prompted us to extend this reaction to various mono- and poly-methoxyphenylboronic acids. Hence, 3-methoxy- and 2-methoxyphenylboronic acids **4b** and **4c** were subjected to the same reaction conditions (Table 14, entries 2 and 3). Surprisingly, formylation of 3-methoxyphenylboronic acid **4b** (entry 2) yielded **18b**, a formylated boronic acid, as the exclusive product with a modest yield. On the other hand, formylation of 2-methoxyphenylboronic acid **4c** (entry 3) resulted in the formation of 4-methoxybenzaldehyde **17a**, deviating from the expected mixture of regioisomers **17a:17a'**.

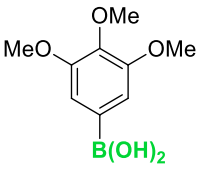
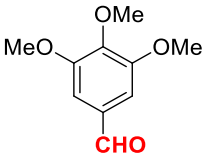
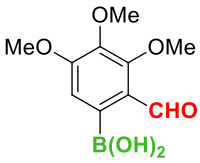
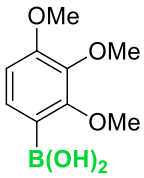
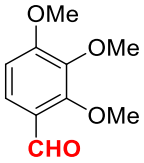
Furthermore, the formylation of 2,4-dimethoxyphenylboronic acid **4d** (entry 4) led to the *ipso*-formylation product **17d** with moderate to excellent yield, where both substituents occupied the *ortho*- and *para*-positions relative to the formyl groups. In the case of compound **4e** (entry 5) containing both *para* and *meta* substituents, the reaction produced aldehydes **17e** as the primary product, along with **18e**[136]. Notably, 2,6-dimethoxyphenylboronic acid **4f** (entry 6) predominantly yielded the regioisomer **17d**, which, in this case, could be attributed to steric hindrance at the *ipso*-position.



Scheme 64. Formylation of aryl boronic acids with AgOTf.

[136] A. Mondal, R. Hazra, J. Grover, M. Raghu, S. S. V. Ramasastry, *ACS Catal.***2018**, *8*, 2748-2753.

entry	Substrate **4**	method	Product **17** (%)[b] and/or **17'**(%)[b] and/or **18** (%)[b]			
	 **4**		 **17**		 **18**	
1	 **4a**	**A** **B** **C**	 **17a**	75 100 92	 **17a'**	25 0 0
2	 **4b**	**A** **B** **C**			 **18b**	18 58 56
3	 **4c**	**A** **B** **C**	 **17a**	21 13 48		
4	 **4d**	**A** **B** **C**	 **17d**	99 25 98		
5	 **4e**	**A** **B** **C**	 **17e**	87 88 85	 **18e**	0 12 15
6	 **4f**	**A** **B** **C**	 **17f**	0 16 0	 **17d**	85 59 60

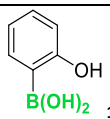
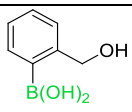
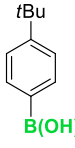
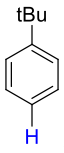
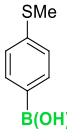
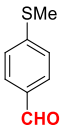
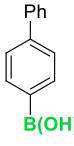
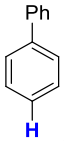
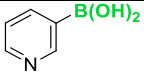
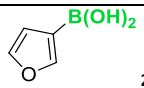
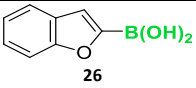
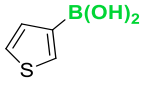
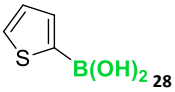
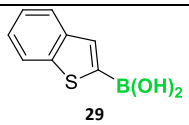
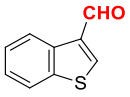
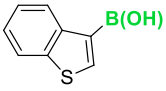
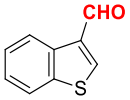
7	 **4g**	**A**	 **17g**	ND	 **18g**	ND
		B		8		7
		C		0		82
8	 **4h**	**A**	 **17h**	100		
		B[c]		0		
		C		100		

[a] Reaction conditions: **method A** (AgOTf, 1.0 eq., 1-3 h) or **method B** ($AlCl_3$, 1.2 eq., 24 h) or **method C** ($FeCl_3$, 1.0 eq., 24 h), from 0°C to rt.
[b] Yields of isolated compounds.
[c] 1,2,3-trimethoxybenzene was obtained in quantitative yield.

Table 14. Formylation of aryl boronic acids

The Rieche reaction performed on the 3,4,5-trimethoxy derivative **4g** (entry **7**) yielded both compounds **17g** and **18g** in varying ratios depending on the reaction conditions. In contrast the isomeric 2,3,4-trimethoxyphenylboronic acid **4h** quantitatively formed the *ipso*-formylated compound **17h** using methods **A** and **C**, while the corresponding protodeboronated 1,2,3-trimethoxybenzene was obtained when $AlCl_3$ was used as the Lewis acid (method **B**, entry 8).

In order to extend the scope of these methodologies, other electron-rich phenyl boronic acids and some heteroarylboronic acids were subjected to the Reiche formylation reaction (see **table 15**).

Entry	Substrate Ar–B(OH)$_2$ / Het-B(OH)$_2$	Method	Product (%)[b]
1	 **19**	**A** **C**	degradation
2	 **20**	**A** **C**	degradation
3	 **21**	**C**	 **31**(90)
4	 **22**	**C**	 **32**(75)
5	 **23**	**C**	 **33**(87)
6	 **24**	**A** **C**	/
7	 **25**	**A** **C**	degradation
8	 **26**	**A** **C**	degradation
9	 **27**	**C**	/
10	 **28**	**C**	/
11	 **29**	**C**	 **34**(56)
12	 **30**	**C**	 **34**(95)

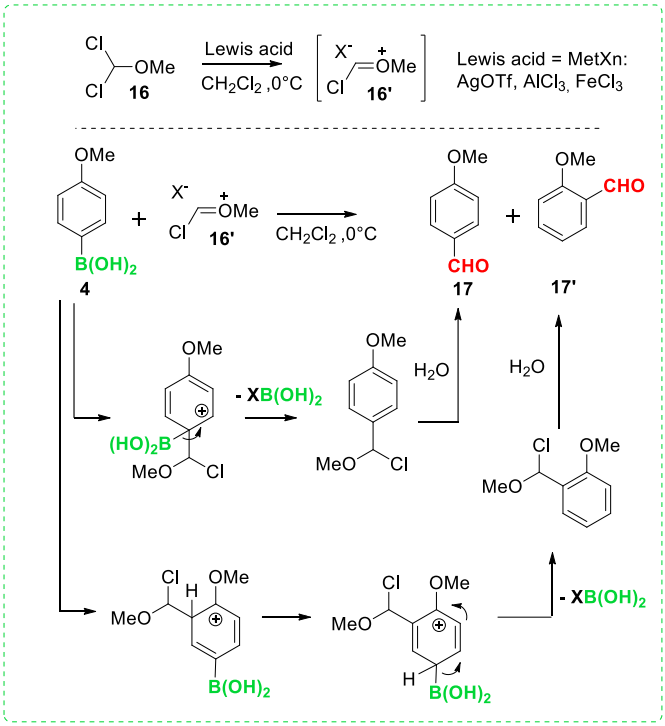
[a] Reaction conditions: **method A**(AgOTf, 1.0 eq., 1-3 h) or **method C** ($FeCl_3$, 1.0 eq., 24 h),from 0°C to rt.[b] Yields of isolated compounds.

Table 15. Formylation of arylboronic acids

The formylation of boronic acids bearing the 2-OH and 2-CH_2OH groups, compounds **19** and **20**, respectively, resulted in substrate degradation (entries 1 and 2).The formylation carried out on compounds **21** and **23**, bearing a 4-*t*Bu or 4-Ph groups (entries 3 and 5) resulting, in both cases, in the exclusive formation of the protodeboronation products **31** and **33**, while 4-MeS-phenyl boronic acid **22** furnished the desired formylated product **32** with 75% yield (entry 4).

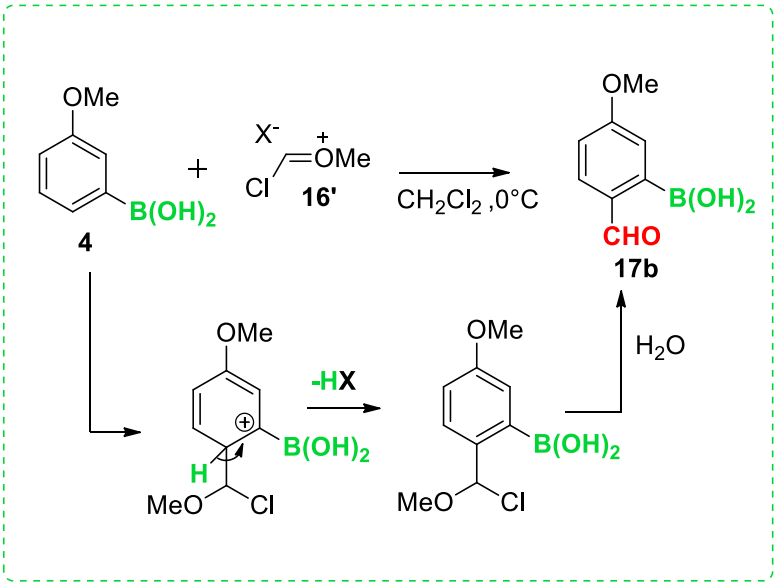
Heteroarylboronic acids as the 3-pyridine derivative, compound **24**, was found to be completely unreactive under the investigated reaction conditions (entry 6) while whose containing oxygen, 3-furyl and 2-benzofuryl boronic acids, **25** and **26**, did not result in the expected formylated but rather in the degradated substrates (entries 7 and 8). On the other hand, sulfur-containing heteroarenes such as 2-thiophenyl and 3-thiophenyl boronic acids resulted as unreactive compounds while the 2-benzothiophenyland 3-benzothiophenyl derivatives, compounds **29** and **30**, provided both the formylated compound **34** with 56% and 95% yield (entries 11 and 12, respectively).

Considering that the position and nature of the substituents influenced both the yield and regioselectivity of the phenylboronic acid formylation, an electrophilic aromatic substitution mechanism can explain the observed results. A plausible mechanism is proposed in **Scheme 65**.



Scheme 65. Proposed mechanism for the formylation of 4-OMe-Phenylboronic acids[134]

Electron-rich aryl boronic acids exhibited regioselective formation of *ipso*-substituted aryl aldehydes when the boronic moiety was located at an activated position. Regioisomers could arise from the addition of the electrophile **16'** at other mesomeric-activated positions. Subsequently, the hydrogen shift on the carbon bearing the boron allows protodeboronation. Infact no traces of precursors with simultaneous co-presence of the boronic and formyl moieties on the ring were detected, as well as simply protodeboronated compounds. When the boronic moiety was located in a deactivated position, formylated phenylboronic acids were observed (**Scheme 66**)

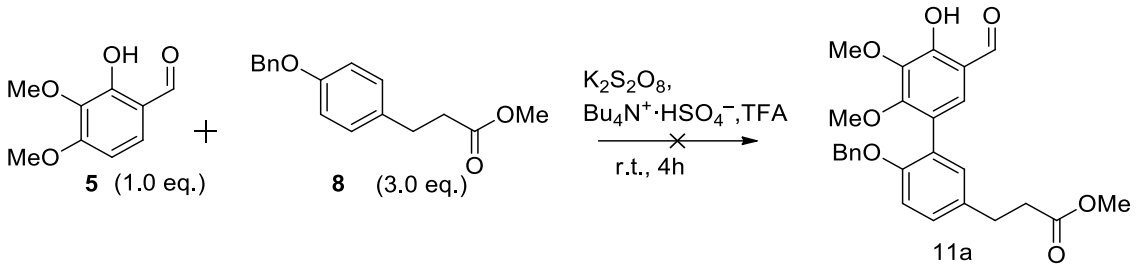


Scheme 66. Proposed mechanism for the formylation 3-OMe-phenyl boronic acids.[134]

It appears that AgOTf is the most reactive system, as it generally provides higher yields and shorter reaction time, although with lower regioselectivity when compared to other systems. On the other hand, $AlCl_3$ generally resulted in poor reaction yields and required longer reaction times; however, it exhibited better regioselectivity. Finally, $FeCl_3$ emerged as the most efficient Lewis acid, displaying both high regioselectivity and good to excellent yields.

3.3- Radical cross-coupling attempts

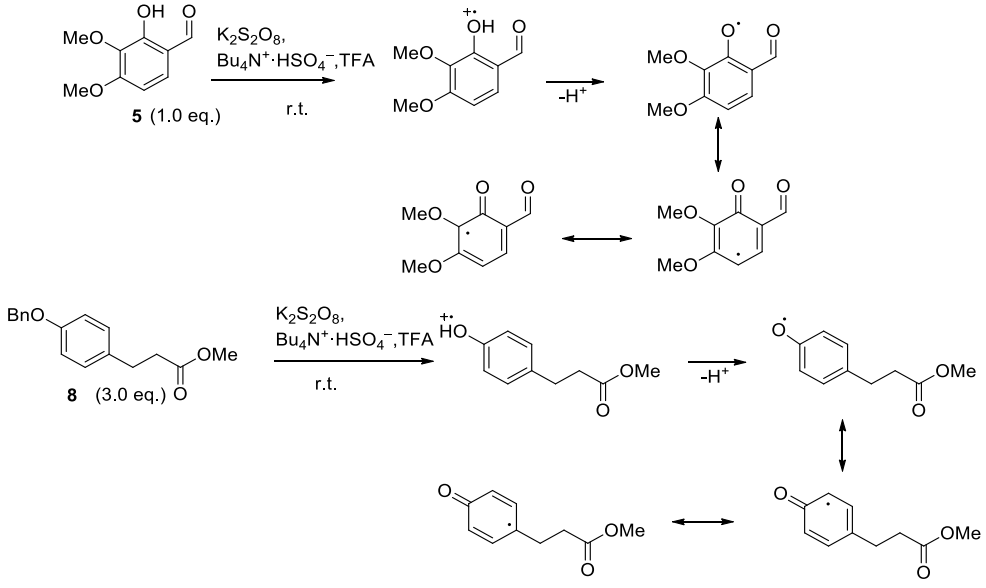
One final synthetic approach of Path A involves an oxidative radical coupling of fragments **5** and **8**



Scheme 67. Radical coupling

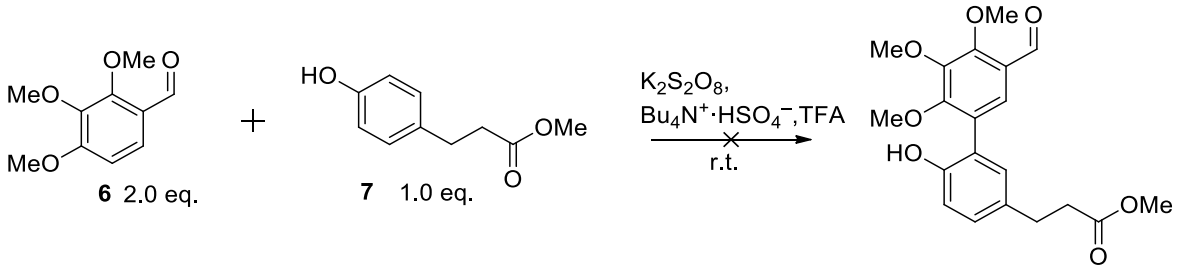
The reaction was conducted using potassium persulfate as a radical initiator in trifluoroacetic acid (TFA), with tetrabutylammonium hydrogen sulfate as a catalyst, and 3 equivalents of benzyl ester **8**[36]. After 4 hours at room temperature under inert atmosphere, the starting material **5** had completely disappeared, and excess starting material **8** was nearly exhausted. Complex mixtures of products were obtained, with no signals corresponding to aldehydes or benzyl groups.

It is likely that under these reaction conditions, debenzylization of reagent **8** occurred, leading to the formation of phenolic radical cations on both products. The aldehyde might have undergone radical attack, or the phenolic radical cation derived from aldehyde **5** could have rearranged, delocalizing the radical onto the aldehyde group, which then participated in the reaction (**Scheme 68**).



Scheme 68. Hypothetical radical species present during the radical coupling of **5** and **8**

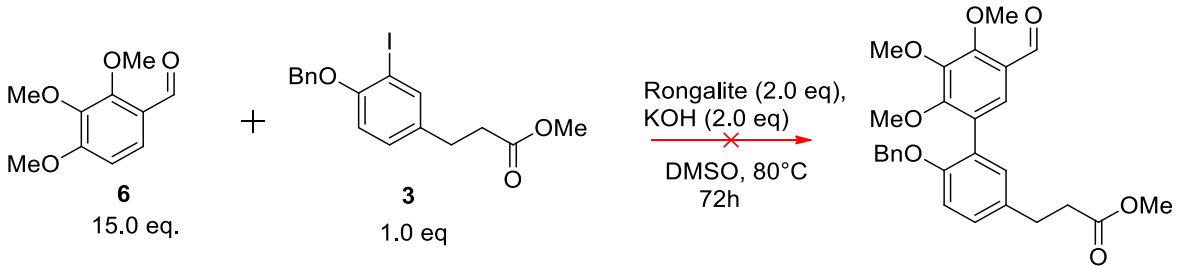
The same reaction was repeated at 0°C, reducing the stoichiometric excess from 3 to 1.5 equivalents. After 6 hours of reaction, the same undesired products were obtained, although in reduced amounts. In any case, to overcome these issues, it was decided to proceed with a radical coupling by reversing the cross-coupling partners (**Scheme 69**).



Scheme 69. Radical coupling between **6** and **7**

Starting with trimethoxybenzaldehyde **6** and phenolic ester **7**, the radical cation will be generated on the latter. This approach avoids issues related to the excessive reactivity of the phenolic radical cations generated on compound **5** in the previous reaction. The reaction was conducted in TFA, with potassium persulfate and tetrabutylammonium hydrogen sulfate as the catalyst. Using 2 equivalents of trimethoxybenzaldehyde **6**. After 6 hours, no reaction progress was observed.

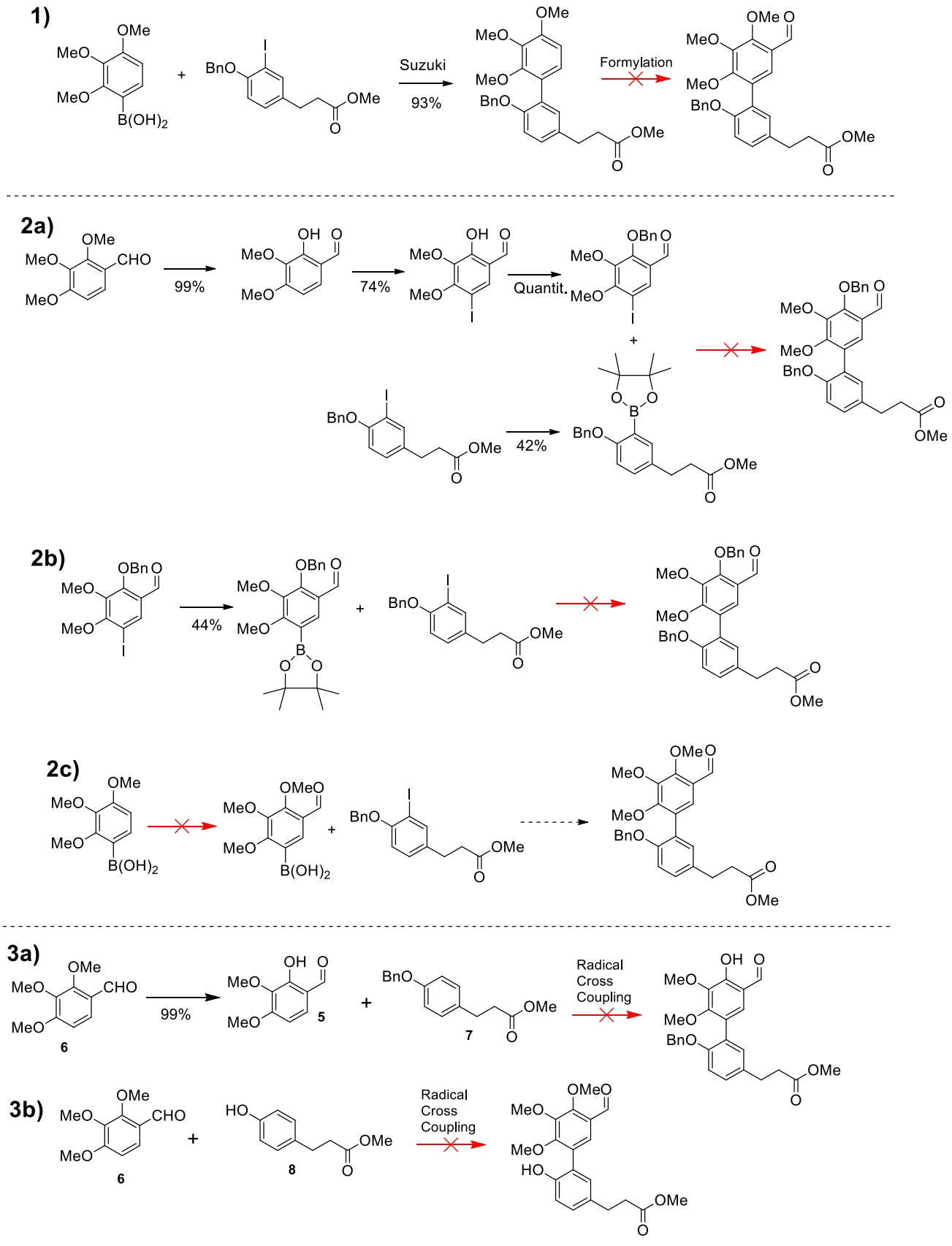
Another attempt was made to achieve the desired biaryl compound by using a rongalite ($Na^+HOCH_2SO_2^-$)-promoted cross-coupling involving aryl radicals generated from the corresponding aryl halide (**Scheme 70**)[95], but after 72h at 80 °C no reaction occurred.



Scheme 70. Rongalite-promoted radical coupling

3.3.2- General conclusion for the Path A

In Scheme **71**, the synthetic approaches used are summarized, none of which yielded the desired results. Despite optimizing conditions and yields for some reactions, it was not possible to synthesize myricanol following this initial synthetic approach. However, the side reaction of boronic acid **4** provided an opportunity to investigate the general reactivity of boronic acids toward Rieche formylation [134].



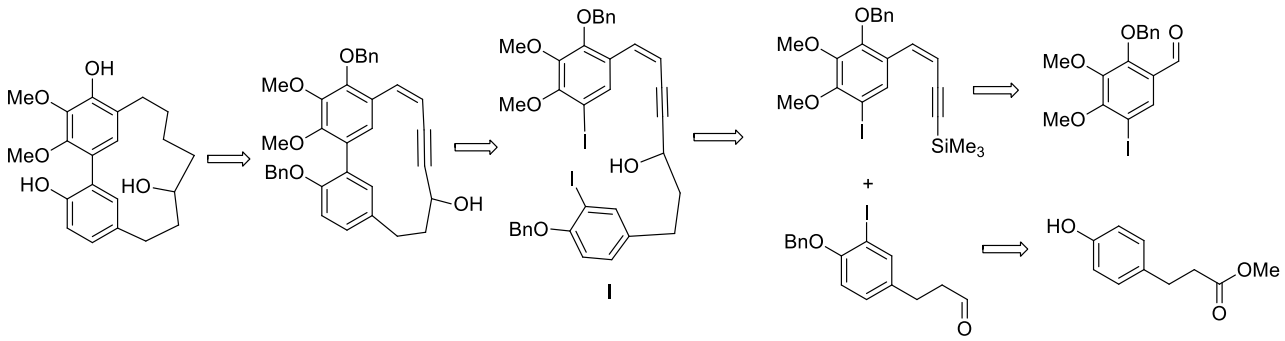
Scheme 71. Summary of "Path A" results

3.4- PATH B – Synthesis of the first *seco*-precursor

So far, we have discussed the first retrosynthetic approach (Path A), which, despite employing three different synthetic strategies, did not lead to the synthesis of the desired biaryl aldehyde.
Therefore, the alternative synthetic approach (Path B) was considered, which involves the initial construction of the side chain to form the *seco*-precursor, followed by cyclization via metal-catalyzed cross-coupling.

The following pages will focus on the various synthetic strategies used along Path B.

Starting from advanced fragments, we would first have a nucleophilic attack mediated by fluoride on the enyne system, followed by the last step of intramolecular cross-coupling (**Scheme 72**).

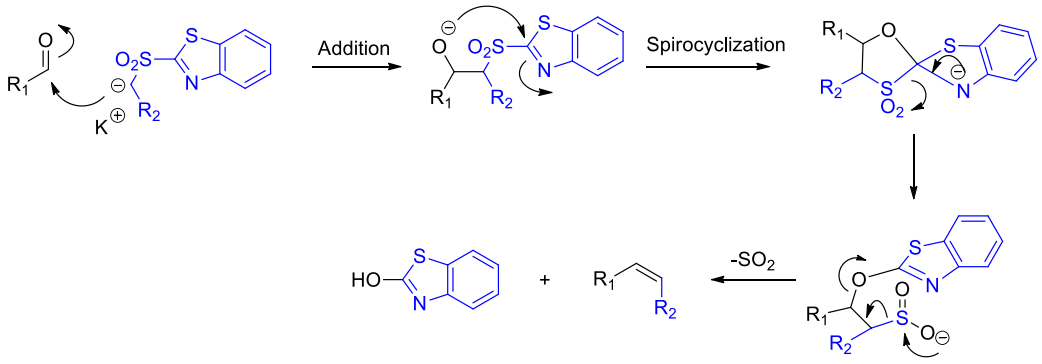


Schema 72. Retrosynthesis of the *seco*-precursor **I**

3.4.1- Modified Julia Olefination

The Julia olefination was discovered by S. A. Julia, and it is distinct from the older Julia–Lythgoe olefination, which was discovered by M. Julia[137]. The Julia–Lythgoe olefination represents an indirect method for alkene synthesis, involving the addition of phenyl sulfone anions to carbonyl compounds followed by an additional step of reductive desulfonylation[138-142].

The modified Julia olefination is a one pot version of the Julia–Lythgoe olefination, it is a synthetic method for creating alkenes through the reaction of a sulfone with a carbonyl compound[143]. The presence of an aryl group is crucial allowing a spontaneous Smiles rearrangement[144] which leads to the elimination of sulfur dioxide and an aryloxide anion yielding an alkene and benzothiazole in one pot (**Scheme 73**). While the initial description of this reaction utilized benzothiazole-sulfones (BT-sulfones), various alternative aryl groups are available.[145-148]



Scheme 73. Modified Julia olefination Mechanism

[137] Julia, M.; Paris, J.-M. *Tetrahedron Lett***. 1973**, 4833.

[138] Kocienski, P. In Comprehensive Organic Synthesis, 1st ed.; Trost, B. M., Fleming, I., Eds.; Elsevier: Oxford, **1991**; Vol. 6, pp 975–1010.

[139] Dumeunier, R.; Marko, I. E. The Julia Reaction. In Modern Carbonyl Olefination; Takeda, T., Ed. Wiley: Weinheim, Germany, **2004**; pp 104–150.

[140] Alonso, D. A.; Najera, C. *Org. React*. **2008**, 72, 367.

[141] Marko, I. E.; Pospisil, *J. Sci. Synth.* **2010**, 47a, 105.

[142] Blakemore, P. R. In Comprehensive Organic Synthesis, 2nd Ed.; Knochel, P., Molander, G. A., Eds.; Elsevier: Oxford, **2014**; Vol. 1, pp 516–608.

[143.] Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett*. **1991**, 32, 1175.

[144] Plesniak, K.; Zarecki, A.; Wicha, *J. Top. Curr. Chem*. **2007**, 275, 163.

[145] Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chim. Fr*. **1993**, 130, 856.

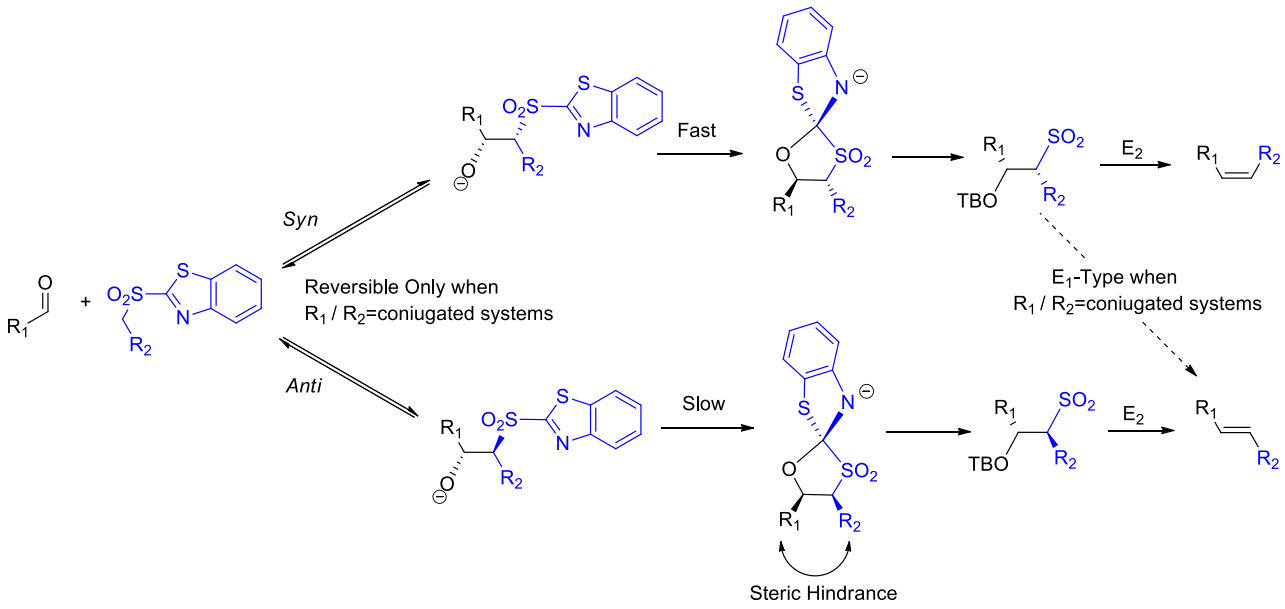
[146] Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.

[147] Kocienski, P. J.; Bell, A.; Blakemore, P. R. *Synlett***2000**, 365.

[148] Alonso, D. A.; Najera, C.; Varea, M. *Tetrahedron Lett*. **2004**, 45, 573.

3.4.1.1-Stereochemistry

The first addition step on the aldehyde can be *syn* or *anti*, forming the corresponding *syn* and *anti* β-alkoxy sulfones. This step is not reversible if the sulfone anion is not stabilized, while it is reversible if the sulfone has an anion-stabilizing group allowing these intermediates to undergo equilibration through a retroaddition and re-addition mechanism. However, because the spirocyclization is faster on the *syn*-β-alkoxy sulfones, since the *trans* spirocycle derived from it exhibits a lower strain compared to the *cis* spirocycle derived from the *anti*-β-alkoxy sulfones[149], so, when the initial addition reaction is reversible a (*Z*)-selective modified Julia olefination can be observed. But, it should be considered that the last step (elimination of SO_2 and HOBT) is stereospecific only when R_1 and R_2 are non-conjugating substituents and in such cases, elimination occurs with a concerted E2-like mechanism wherein the OBT and SO_2 groups have an antiperiplanar alignment, and the *anti*-spirocycle leads to the (*E*) alkene whereas *syn*-spirocycle affords the (*Z*) alkene. Unsaturated R_1 or R_2 could lead to a non-stereospecific E1-type elimination via zwitterion leading preferentially to the (*E*) alkene in both cases, especially at high temperatures[150]. All those possible pathways are summarized in the following **Scheme 74**.



Scheme 74. Modified Julia olefination pathways

The presence or absence of conjugating substituents in each coupling partner has the most profound

[149] Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Bull. Soc. Chim. Fr*. **1993**, 130, 336.
[150] Aissa, C. Eur. J. Org. Chem. **2009**, 1831.

effect on stereoselectivity, and reactions are usefully divided into four substrate pair classes according to this principle.[145]:

1)-Type I Reactions: neither component conjugated.

The stereochemistry, in this case, is determined by the kinetic diastereoselectivity in the initial addition step

Conditions promoting the dissociation of the metal cation, for example, KHMDS in tetrahydrofuran with 18-crown-6-ether[151] favor the (*E*) products.

2)- Type II Reactions: conjugated sulfone anions.

The ultimate stereochemical outcome of olefination is not a simple consequence of diastereoselectivity in the initial step since retroaddition and re-addition mechanism can occur,

Furthermore, because *syn* alkoxy sulfone cyclize faster than the *anti* alkoxy sulfone, the preferred formation of *cis* alkenes is predicted in cases where retroaddition is more facile than spirocyclization, and the elimination follows a stereospecific pathway.

3)- **Type III Reactions: conjugated carbonyl compounds**

Julia olefinations involving non-conjugated sulfone anions and α aryl aldehydes result in the formation of (*E*)[145] alkenes, the kinetic diastereoselectivity in the initial addition step do not determine the final alkene configuration, It is probably involved a zwitterionic pathway[145] because R_2 is able to stabilize the adjacent carbocation. A (*E*) alkene will be formed regardless of the original *syn* or *anti* configuration of the aryloxy sulfinate, a *syn* periplanar elimination could also be involved.

4)- Type IV Reactions: both components conjugated.

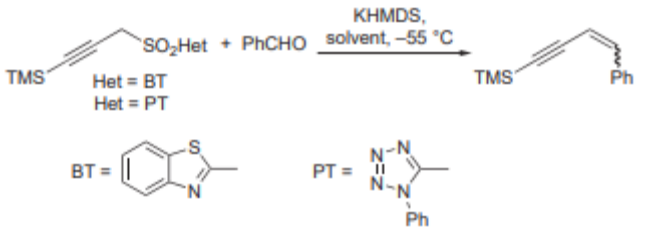
When both R_1 and R_2 are conjugating groups, all of the mechanisms reported in **the Scheme 74** could come into play. Prediction of the stereochemical in such cases is difficult unless similar examples are reported.

3.4.1.2-Modified Julia olefination attempts

Going back to the proposed synthetic approach, we encounter Type 4 reactions where both components

[151] Pospisil, J. *Tetrahedron Lett*. **2011**, 52, 2348.

are conjugated. Fortunately, there are documented few examples of Julia olefination reactions that result in the formation of 1,3-ene-ynes from aromatic aldehydes.[127,128]An example is reported in the following **Table 16.**



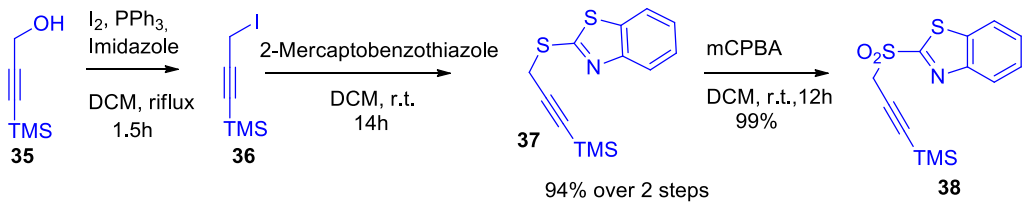
Entry	Sulfone	Solvent	Method A[a] or B[b]	Ratio *Z*/*E*[c]	Yields (%)
1	Het = BT	THF	**A**	87:13	50
2	Het = BT	THF	**B**	**96:4**	**80**
3	Het = BT	DME	**A**	98:2	31
4	Het = BT	THF	**B**	98:2	38

[a] Method **A**: premetallated conditions: base added to sulfone, aldehyde added thereafter.
[b] Method **B**: Barbier conditions: base added to sulfone and aldehyde.
[c] The ratios were determined by GC-MS analysis.
[d] Yields (%) after chromatographic purification on silica gel.

Table 16. synthesis of 1,3 ene-ynes(Bonini et *al.*)[127]

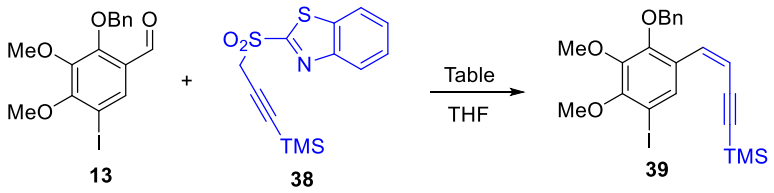
Those conditions, both A= Premetallation conditions or B=Barbier conditions were investigated for the synthetic strategy discussed below.

The sulfone for the subsequent Julia reaction was synthesized from the corresponding propargylalcohol, as shown in the following **Scheme 75**, Compound **13** was synthesized using the optimized conditions described in the previous sections.



Scheme 75. Synthesis of **38**

The modified Julia reaction was conducted under various conditions, as shown in **Table 17**.



Entry	13 (eq)	KHMDS (eq)	T (h)/ t (°C)	Yield (Z/E)	Method (a=premetallation b= Barbier's conditions)
1	1.6	1.2	4h (-40°C) 12h (r.t.)	17% (65/35)	b
2	1.6	1.4	4h (-60°C) 12h (r.t.)	35% (62/38)	b
3	1.6	1.6	4h (-55°C) 14 h (r.t.)	14% (55/45)	b
4	1.6	1.2	22h (-60°C) 1h (r.t.)	65% (70/30)	b
5	1.6	1.4	3h (-60°C) 0.5h (r.t.)	81% (65/35)	b
6	0.80	1.4	2h (-60°C) 0.5h (r.t.)	42% (65/35)	b
7	1.25	1.4	2h (-55°C) 0.5 h (r.t.)	57% (65/35)	b
8	0.6	2.0	14h (-60°C) 0.5h (r.t.)	10% + Mixture of products	b
9	0.7	1	4h (-60°C) 0.5h (r.t.)	33% (59/41)	**a**
10	1.5	1.4	4h (-60°C) 0.5h (r.t.)	70% (63/37)	**a**
11	1.4	1.2	3.5h (-60°C) 0.5h (r.t.)	73% (65/35)	**a**
12	1.6	1.55	17h (-55°C) 0.5h (r.t.)	92%(65/35)	**a**

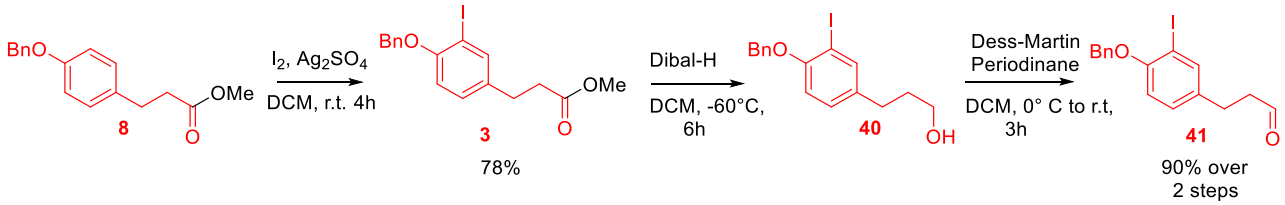
Table 17. Reaction between **13** and **38**

The best reaction yield achieved was 92% with a 65% *cis* isomer yield (**Entry 12**) using an excess of sulfone and the method A (premetallation). Surprisingly, when a large excess of base was used (Entry 8), a mixture of unseparable byproducts and a 10% yield, based on the crude reaction mixture, were obtained.

The *Z/E* mixture obtained cannot be separated since the products have the same retention factor (R_f).

3.4.2. – Addition attempts

The aldehyde was synthesized through iodination and subsequent reduction/oxidation of the ester **8** (**Scheme 76**).

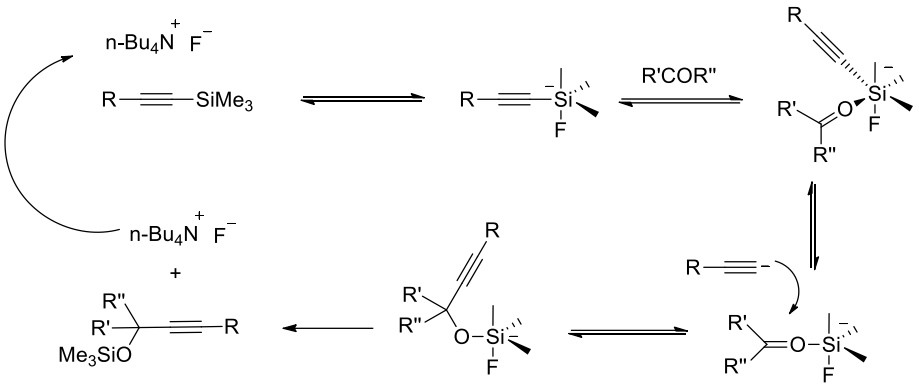


Scheme 76. Syntheis of **41**

The next addition step posed a significant challenge, requiring multiple adjustments to the reaction conditions in pursuit of optimal yield. However, the prevailing outcome in each case was the formation of the protodesilylation product and the self-condensationof the aldehyde.

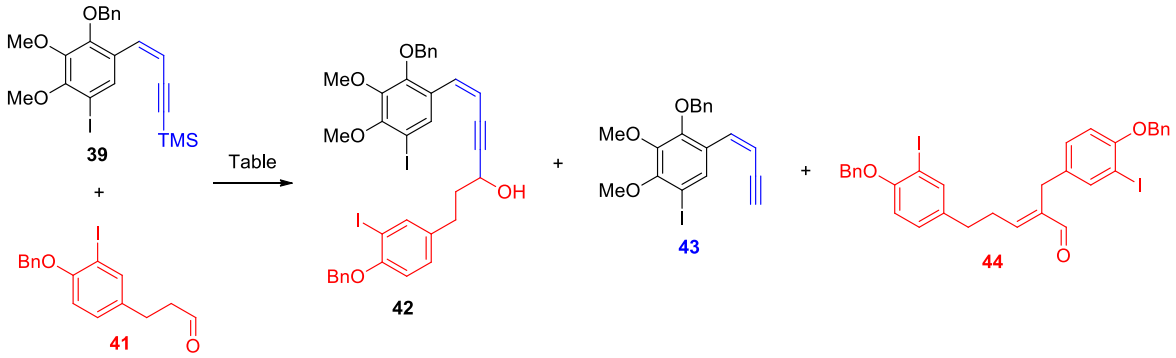
Numerous examples of trialkylsilylalkynes additions to aldehydes or ketones are reported, employing TBAF as the source of fluoride. Various trialkylsilylalkynes, both aliphatic and aromatic, were tested for their addition to both aromatic and aliphatic aldehydes.[152] This reaction involves the use of catalytic amounts of TBAF, with the latter being regenerated following the **scheme 77** outlined by Chintareddy and coworkers in 2011.[152]

[152] Chintareddy, V. R.; Wadhwa, K.; Verkade, J. G. *J. Org. Chem.***2011**, 76 (11), 4482–4488.



Scheme 77. Proposed mechanism of TBAF Catalyzed addition[152]

The total synthesis of Giffonin H by Park and coworkers[129] relays on the catalytic addition of fluorine for the formation of a cycle diarylether. In the following Table are reported the tested conditions.



Entry[a]	39 (eq) Z/E: 65/35	41 (eq)	Catalyst (eq)	t (h)	Product	Conversion
1	1.0	1.2	TBAF (0.3)	2h	**43** + **44**	100
2	1.0	1.2	TBAF (0.1)	1h	**43** +**44**	68
3	1.0	1.2	TBAF (0.1)	2h	**43** + **44**	65
4	1.0	1.8	TBAF (0.05)	2h	No reaction	
5	1.0	1.8	TBAF (0.2)	1h	**42** (8% only Z) + **43** + **44**	100
6	1.0	1.8	TBAF (1.0)	1h	**42** (traces) + **43** + **44**	100

7	2.0	1.0	TBAF (0.2)	1h	**42** (23% only Z) + **43** + **44**	100
8[b]	1.8	1.0	TBAF (0.2)	1h	**43** + **44**	100
9	1.8	1.0	TBAT (0.2)	3h	**43**+ **44**	10
10	1.8	1.0	TBAT (1.0)	3h	**42** (15% only Z) + **43**+ **44**	80
11	2.0	1.0	CsF (7.0)	4h	**43** (traces)	
12	2.0	1.0	CsF (7.0) 18-Crown-6(3.0)	1h	**43**	100

[a] Reactions were conduced in THF (0.25M) at r.t. [b] Aldehyde added after TBAF

Table 18. Fluoride mediated additions of **39** and **41**

The starting substrate for all experiments is a mixture of *Z/E* isomers in a ratio of 65/35, as these two products were not separable.

When the reaction was carried out using TBAF, even in catalytic amounts, the formation of the protodesilylation product **43** was consistently the major outcome.

Under the same conditions, aldehyde **41** underwent self-condensation (entries 1-8).
When TBAT was employed as the fluoride source, stoichiometric amounts were required to afford complete desilylation of the substrate and the formation of auto-condensated product persisted.

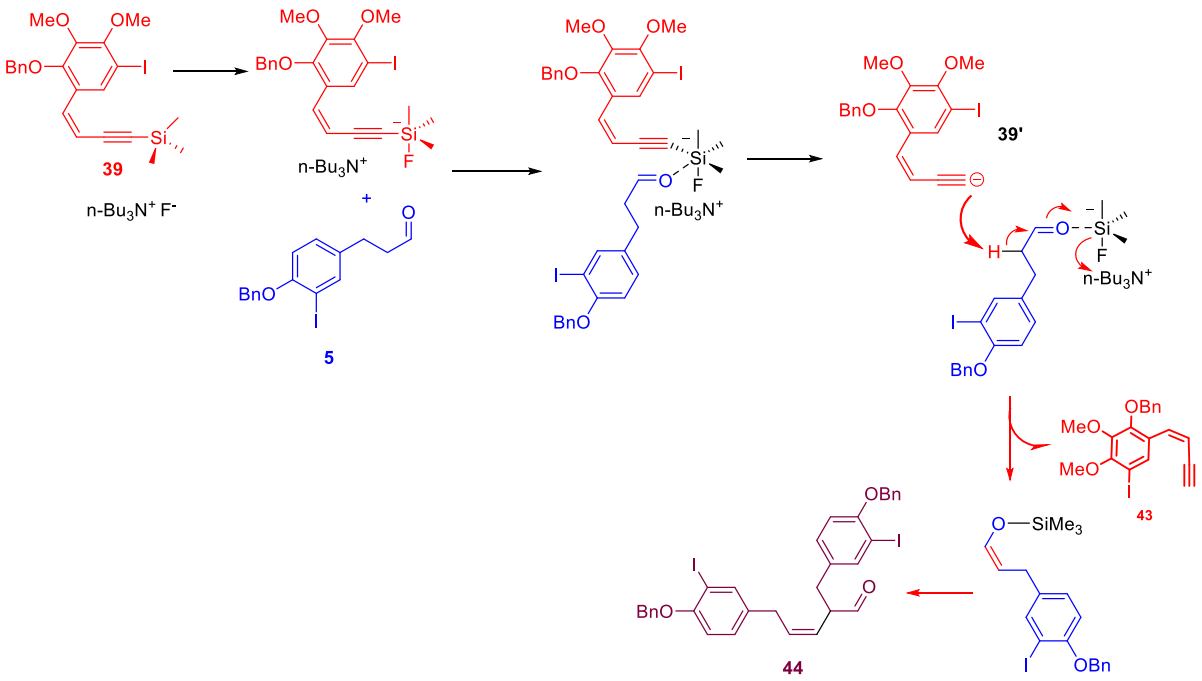
Using CsF, only traces of desilylation were observed, and the presence of 18-crown-6-ether was necessary to increase the availability of fluoride for desilylation.

Initially, it was thought that the nearly exclusive formation of protodesilylation product **43** might be due to the non-anhydrous nature of commercial TBAF and that fluoride, in turn, was causing aldehyde self-condensation.
Therefore, a test was conducted in the absence of substrate **39**, where only aldehyde **41** and TBAF (1 equiv) were used, but under these conditions no traces of self-condensation product was observed. Consequently, a mechanism was proposed to explain the formation of the self-condensation product

and, at the same time, for the complete desilylation even in catalytic amounts of TBAF (**Scheme 78**).

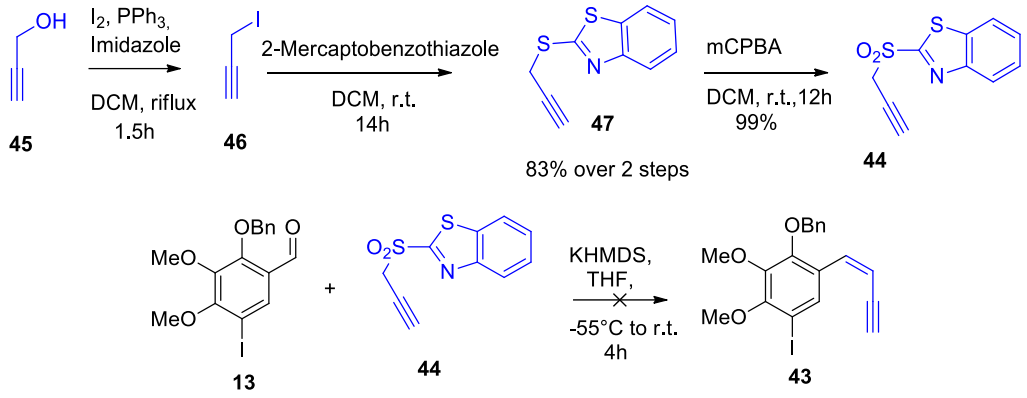
Alternatively, it could be hypothesized that catalytic amounts of TBAF are justified because the alkoxide formed following addition is already capable of desilylating substrate **39**, leading to the formation of the corresponding acetylide. However, in this case, this latter hypothesis can be rejected since during the experiments conducted, no traces of the desired coupling product or silylether were observed.

According to the proposed mechanism, acetylide **39'**, once formed, could act as a nucleophile to provide the desired addition product or act as a base (red arrow) to yield desilylated product **43**, regenerate the catalyst, and form a silyl enol ether, ultimately leading to the formation of self-condensation product **44**.



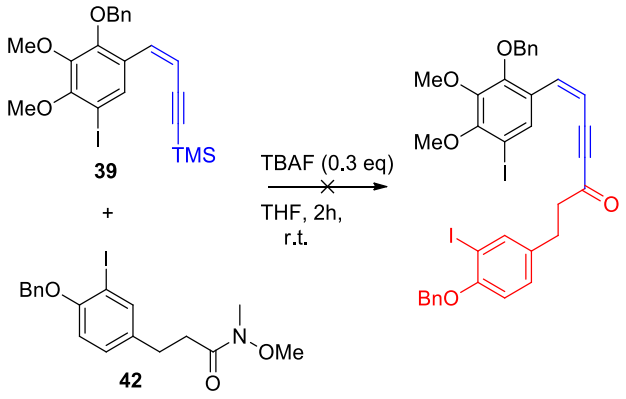
Scheme 78. Postulated mechanism

However, the desilylated compound **43** can still be utilized to afford the *seco*-precursor **42** as discussed below. Additionally, an attempt was made to synthesize the desilylated ene-yne **43** directly via a modified Julia olefination (**Scheme 79**), starting from a sulfone **44** synthesized according to **Scheme 79**. Under these conditions, a mixture of products were obtained, likely due to the possible involvement of the terminal triple bond of the sulfone in the reaction.



Scheme 79. Synthesis attempt of **43**

Another addition attempt was carried out on a Weinreb amide according to the following **Scheme 80**, but no results were obtained.



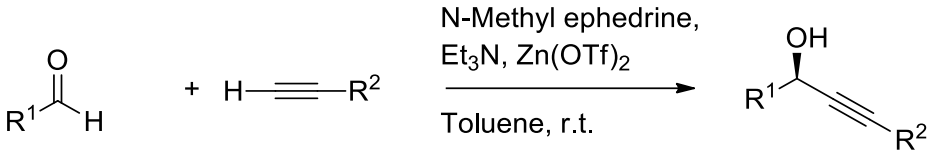
Scheme 80. Addition on Weinreb ammide

In any case, compound **43** resulting from the protodesilylation as described in **Scheme 78** above can also be used to access the corresponding chiral propargylic alcohol, which presumably would allow for the control of chirality at C-11 of myricanol.

Various examples of asymmetric additions of this kind are reported in the literature, both on aromatic and aliphatic aldehydes. In particular, Carreira developed an efficient system in 2001 under mild reaction conditions for generating organozinc and subsequently performing an asymmetric addition, even in the presence of traces of water[153-154].

[153] Boyall, D.; Frantz, D. E.; Carreira, E. M. *Organic Letters***2002**, 4 (15), 2605-2606.
[154] Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.***2001**, 123, 9687-9688.

In the following **Table 19**, some of the experiments conducted by Carreira on aliphatic aldehydes are illustrated.



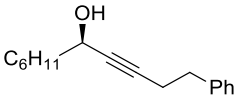
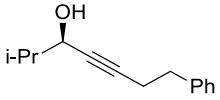
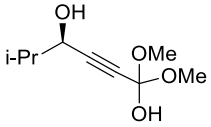
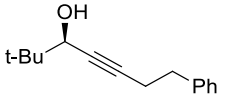
Entry	Product	Yield	% ee
1		94%	97%
2		88%	99%
3		92%	95%
4		85%	99%

Table 19. Reported Carreira's additions[153]

Furthermore, various other examples of asymmetric addition have been reported, including the use of the $ZnEt_2$ BINOL/$Ti(O^iPr)_4$ system.[155-160]

However, the first step of organozinc formation requires high temperature, but since a method to form organozinc reactants at room temperature by using DMSO, DMF, or HMPA has been reported.[161] In 2004, a group of researchers from the University of Virginia, Gao *et al.*[162], developed a method which combine those methodologies witha Zn-Catalyzed addition, generating organozinc with HMPA at room temperature in the presence of the BINOL/$Ti(OiPr)_4$ system to obtain chiral propargylic alcohols.

[155] Moore, D.; Pu, L. *Org. Lett.***2002**, 4, 1855–1857.
[156] Gao, G.; Moore, D.; Xie, R.-G.; Pu, L. *Org. Lett.***2002**, 4, 4143–4146.
[157] Marshall, J. A.; Bourbeau, M. P. *Org. Lett.***2003**, 5, 3197–3199.
[158] Pu, L. *Tetrahedron***2003**, 59, 9873–9886.
[159] Lu, G.; Li, X.; Chan, W. L.; Chan, A. S. C. *J. Chem. Soc. Chem. Commun.***2002**, 2, 172–173.
[160] Li, X.; Lu, G.; Kwok, W. H.; Chan, A. S. C. *J. Am. Chem. Soc.***2002**, 124, 12636–12637.
[161] Okhlobystin, O. Y.; Zakharkin, L. I. *J. Organomet. Chem.***1965**, 3, 257–258.
[162] Gao, G.; Xie R.-G.; Pu, L. *PNAS*, **2004**, 101 (15), 5417-5420.

Given the encouraging results reported in the literature described above, which are particularly efficient for both aliphatic and aromatic alkynes on either aromatic and aliphatic aldehydes, various addition experiments were conducted for the synthesis of compound **42** (**Table 20**).

In addition, base-mediated reactions were tested (**entries 1-5, Table 20**), which unfortunately did not yield the expected results. While it is likely that KHMDS and TBD bases are not strong enough, as their pKa values are comparable to those of the alkyne (pKa approximately 25-26), sodium amide and LDA should have effectively allowed deprotonation and addition. However, the aldehyde may not be a strong enough electrophile to participate in this reaction.

Therefore, an attempt was made using a zinc-catalyzed system (entries 6-9) that would simultaneously activate the aldehyde. The reaction with $ZnEt_2$/imidazole (Entry 9) did not proceed, and literature reports the use of N-methyl imidazole in catalytic amounts. Its function is to activate $ZnEt_2$ for organozinc formation[163]. Although reactions catalyzed by imidazole[164]with comparable yields are reported as well.

It is not clear whether the failure to obtain the desired product can be attributed to the lack of organozinc formation or if, after its formation, it is not reactive enough. It is known that in the absence of binol or titanium isopropoxide, the reaction of an organozinc with the aldehyde is quite slow.[165]

It has been observed that several ligands can accelerate the addition (as well as exert enantiomeric control), such as various amino-alcohols, like the previously mentioned methyl ephedrine for the synthesis of asymmetric propargylic alcohols[154]

Therefore, a test was conducted in the absence of substrate **39**, where only aldehyde **41** and TBAF (1 equiv) were used, but under these conditions no traces of self-condensation product was observed. Consequently, a mechanism was proposed to explain the formation of the self-condensation product and, at the same time, for the complete desilylation even in catalytic amounts of TBAF (**Scheme 78**).

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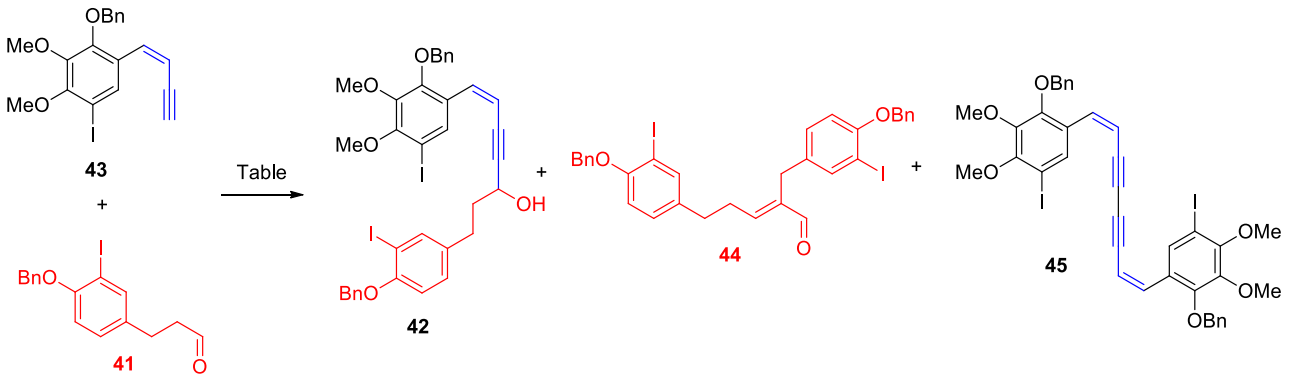
[163] Yang, Y.; Yu, X.-Q.; Pu, L. *Chem. Eur. J.*, **2009**, 15, 5104–5107.
[164] Yang, F.; Xi, P.; Yang, L.; Lan, J.; Xie, R.; You, J. *J. Org. Chem.*, **2007**, 72, 5457-5460.
[165] Ding, K.; Ishii, A.; Mikami, K. Angew. Chem., Int. Ed. **1999**, 38, 497-501.



Entry	43 (eq)	41 (eq)	Conditions	Solvent	T (°C)	t (h)	Product	Conversion
1	2.0	1.0	KHMDS (1.4)	THF	r.t.	8h	/	/
2	2.0	1.0	$NaNH_2$ (1.0)	THF	r.t.	2h	/	/
3	2.0	1.0	LDA (1.0)	THF	r.t.	2h	/	/
4	2.0	1.0	TBD (1.0)	ACN	r.t.	2h	/	/
5	2.0	1.0	n-BuLi (0.4)	THF	-78°C	1h	**Dehalogenation** (27%)	/
6	1.2	1.0	ZnOTf (1.2) Et_3N (1.2)	Toluene	r.t.	2h	/	/
7	1.2	1.0	ZnOTf (1.2) Et_3N (1.2)	Toluene	80°C	2h	/	/
8	1.2	1.0	ZnOTf (2.2) Et_3N (2.2)	Toluene	80°C	4h	**44**	88%
9	1.2	1.0	$ZnEt_2$(1.2) Imidazole (0.1)	DCM	r.t.	6h	/	/
10	1.2	1.0	ZnOTf (1.2) (+)-N-Methyl-ephedrine (1.2) Et_3N (1.2)	Toluene	r.t.	3h	/	/
11	1.5	1.0	$ZnEt_2$(1.0) HMPA(2.0) (S)-BINOL	DCM	r.t.	7h	/	/

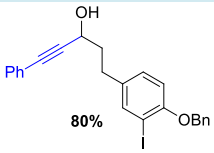
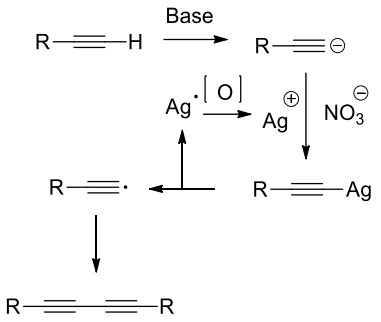
			(0.1) $Ti(OiPr)_4$ (0.25)					
12	1.5	1.0	$ZnEt_2$ (1.0) (S)-BINOL (0.1) $Ti(OiPr)_4$ (0.25)	Toluene DCM	Riflux r.t.	2h 2h	/	/
13	3.0	1.0	$ZnEt_2$ (1.0) (S)-BINOL (0.1) $Ti(OiPr)_4$ (0.25)	Toluene DCM	Riflux Riflux	2h 2h	/	/
14	 (2.0)	1.0	$ZnEt_2$ (1.0) (S)-BINOL (0.1) $Ti(OiPr)_4$ (0.25)	Toluene DCM	Riflux r.t.	2h 2h	 + 	82
15	1.5	1.0	AgOTf BINAP	PhCl	r.t.	18h	**45** (37%)	65

Table 20. Addition conditions study for the coupling reaction between **43** and **41**

Entry 15 provided the homocoupling product of the starting substrate. Surprisingly, only the *cis* ene-yne system appears to have participated in the reaction forming the corresponding dimer, there is no evidence of the *trans* ene-yne dimer in the reaction mixture. Traditional Glaser reactions are typically catalyzed by copper,[166-168] or palladium,[169] There are also examples of Glaser reactions catalyzed by iron/copper[170] or nickel.[171] More recently, an example of gold-catalyzed homocoupling was reported.[172]

However, there are no known examples of Glaser reactions under the conditions used in this work, although an example of Ag-catalyzed Glaser reaction was reported in 2014, proceeding through a radical mechanism.[173]

[166] R. Rossi, A. Carpita, C. Bigelli, *Tetrahedron Lett.***1985**, 26, 523.
[167] Y.-N. Li, J.-L. Wang, L.-N. He, *Tetrahedron Lett.***2011**, 52, 3485.
[168] T.-M. Wu, S.-H. Huang, F.-Y. Tsai, *Appl. Organomet. Chem.***2011**, 25, 395.
[169] Merkul, E.; Urselmann, D.; Müller, T. J. J. Eur. *J. Org. Chem.* **2011**, 238.
[170] Meng, X.; Li, C.; Han, B.; Wang, T.; Chen, B. *Tetrahedron***2010**, 66, 3468.
[171] Cheng, T.-P.; Liao, B.-S.; Liu, Y.-H.; Peng, S.-M.; Liu, S.-T. *Dalton Trans.***2012**, 41, 3468.
[172] Peng, Y. *J. Chem. Res.***2013**, 37, 174.
[173] Moa, G.; Tian, Z.; Lia, J.; Wen, G.*; Yang, X. *Appl. Organomet. Chem.***2015**, 29, 231–233.



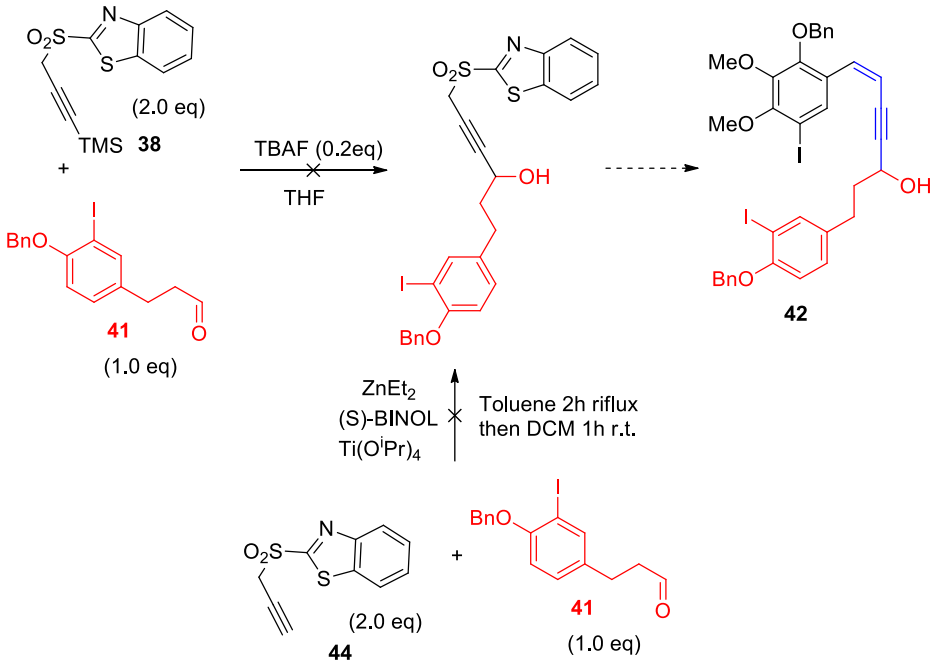
Scheme 81. Proposed mechanism for Ag-catalyzed Glaser coupling

Most likely, the reaction conducted on substrate **43** proceeds through a similar mechanism, although it occurs under different reaction conditions. What might be more interesting is the reason behind the exclusive reactivity of the *cis* isomer among the two isomers.

3.4.3- Alternative synthetic approaches to 42

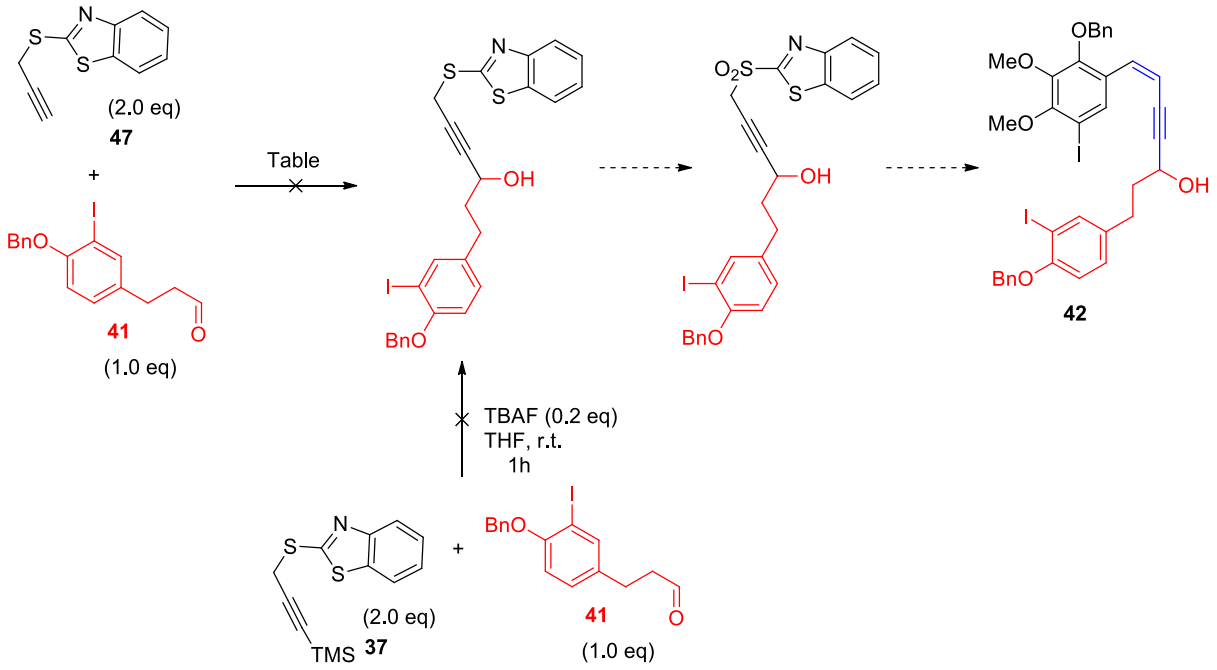
In any case, for the substrate of interest, both the modified Julia olefination and the subsequent addition posed a challenge. In the first case, it led to obtaining a *cis/trans* ratio of 65/35 at best, and in the second case, a fluoride-mediated addition yielded only a 23% yield. It's interesting to note that the product obtained surprisingly was solely the *cis* propargylic alcohol, as the *trans* ene-yne, once again, was unreactive under the tested reaction conditions.

Therefore, in an attempt to bypass the issues encountered with the *seco*-precursor synthesis, further synthetic strategies were explored. Initially, the idea was to synthesize a propargylic alcohol sulfone to undergo a Julia olefination directly, yielding compound **42** according to **Scheme 82**.



Scheme 82. Alternative synthetic approaches to **42**

Since it was not possible to obtain the desired compound either through a fluoride-mediated reaction (starting from sulfone **37**) or through a zinc-catalyzed reaction (starting from sulfone **44**), sulfides **47** and **37** were tested aiming compound **42** through addition, oxidation, and Julia olefination (**Scheme 83**).

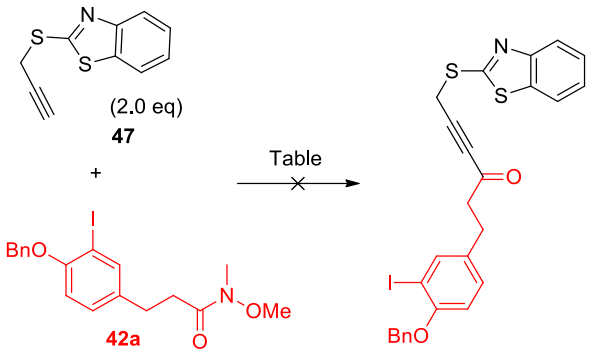


Scheme 83. Alternative synthetic approaches to **42**

Entry	47 (eq)	41 (eq)	Conditions	Solvent	T (°C)	t (h)	Product	Conversion
1	1.8	1.0	$ZnEt_2$ (1.0) (S)-BINOL (0.1) $Ti(OiPr)_4$ (0.25)	Toluene DCM	Riflux r.t.	2h 4h	/	/
2	1.8	1.0	ZnOTf (1.2) (+)-N-Methyl-ephedrine (1.2) Et_3N (1.2)	Toluene	r.t.	4h	/	/
3	2.0	1.0	n-BuLi (1.0)	THF	-78°C	2h	**48** + **Mixture of products**	98

Table 21. Addition attempts between **47** and **41**

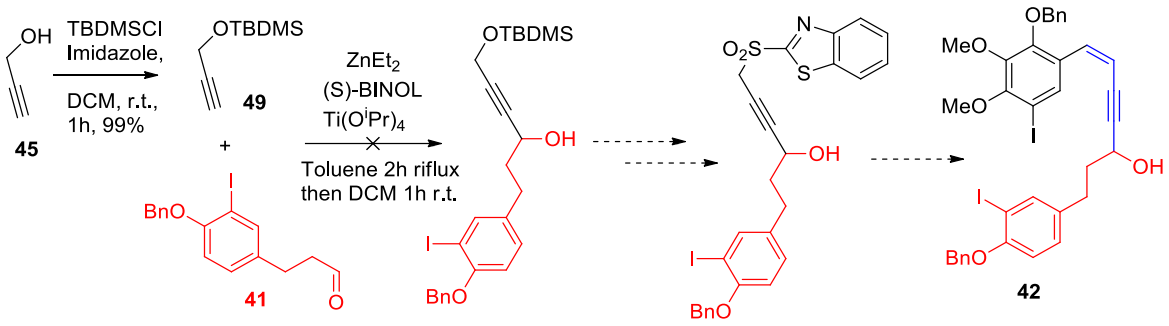
Another attempt was conducted on the Weinreb amide following the scheme below, but no positive results were obtained.



Scheme 84. Addition attempt on Weinreb ammide

Attempts to catalyze the addition of sulfide **47** to aldehyde **41** using zinc did not result in any reaction, while base-mediated addition led to the formation of allene **48 (Table 10)**, which in turn underwent side reactions with aldehyde **41**, resulting in a mixture of unidentified products.

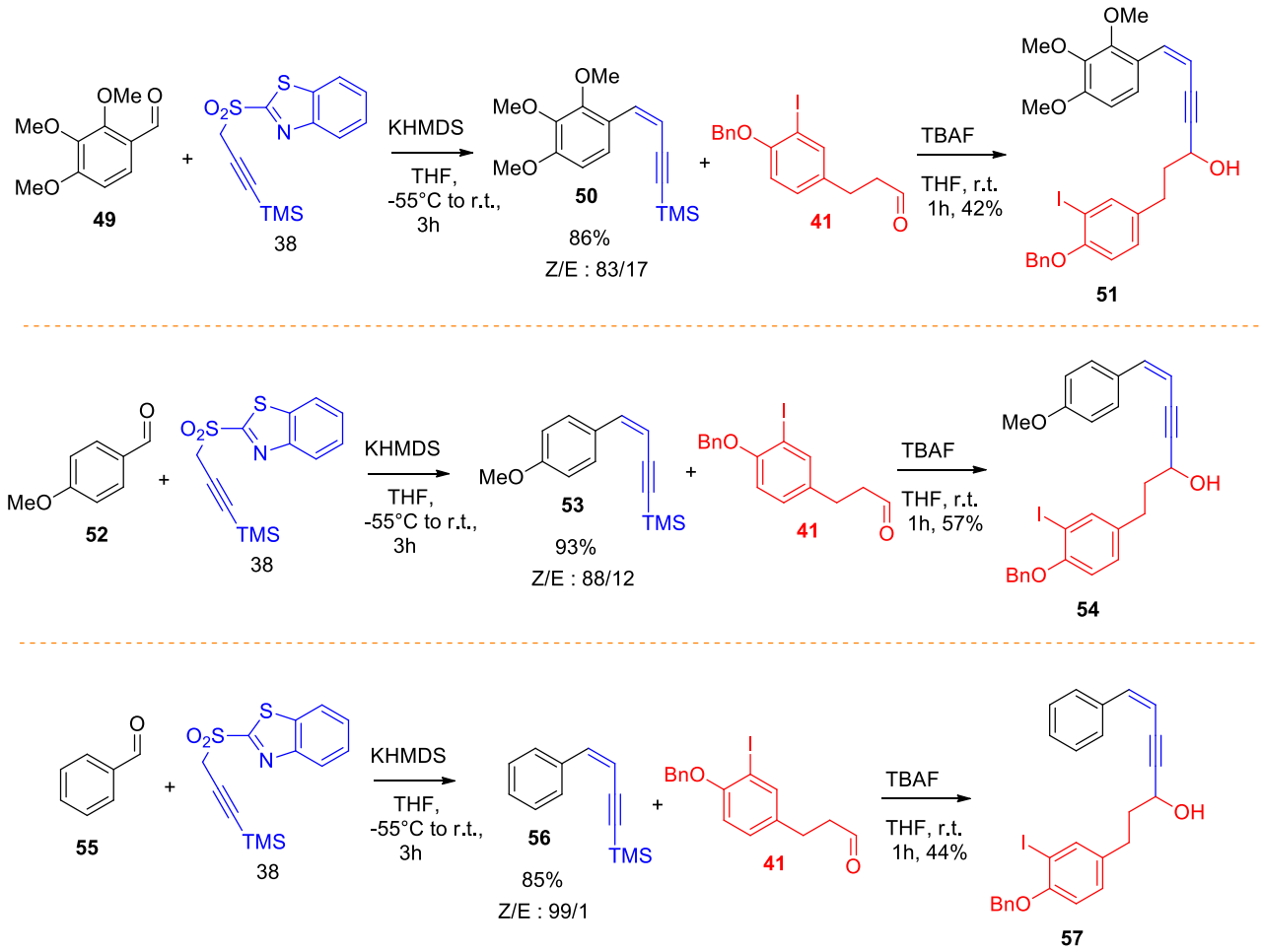
At this point, another synthetic strategy was investigated (**Scheme 85**) starting from the protected propargylic alcohol, with the aim of reaching the corresponding sulfone to be then subjected to a modified Julia olefination to obtain compound **42**. Again, the asymmetric addition reaction did not yield the expected product.



Scheme 85. Alternative synthetic approaches to **42**

3.4.4- Synthesis of other linear unsaturated Diarylheptanoids

As previously described, the modified Julia olefination on the target system **13** to obtain compound ene-yne **43** resulted in, at the best of the conducted trials, a 92% yield with a *Z/E* ratio of 65/35 (**see 3.4.1**). However, the subsequent addition provided unsatisfactory results despite the various conditions attempted. The highest yield obtained was 23% using a TBAF-catalyzed fluoride addition (**see 3.4.2**). To further test the proposed synthetic approach, the synthesis of three additional different diarylheptanoids was conducted using the same methodology. In the following **Scheme 86**, the synthesis of these linear diarylheptanoids **51**, **54**, and **57**, are presented, with overall yields of 36%, 53%, and 37.4%, respectively. It is evident that both the Julia olefination and the subsequent addition are significantly influenced by the substrate's nature.



Scheme 86. Synthesis of linear unsaturated diarylheptanoids

Therefore, myricanol cannot be efficiently synthesized using the previously discussed synthetic strategy. To address the issue encountered with the addition step, a different synthetic approach was proposed and followed. This new strategy involves the introduction of a second *cis* double bond onto aldehyde **41**, making it non-enolizable.

This modification aims to circumvent the main problems associated with fluoride-catalyzed addition reactions discussed in the previous sections, as the failure to obtain the desired propargylic alcohol is primarily attributed to the self-condensation of aldehyde **41** to **44**.

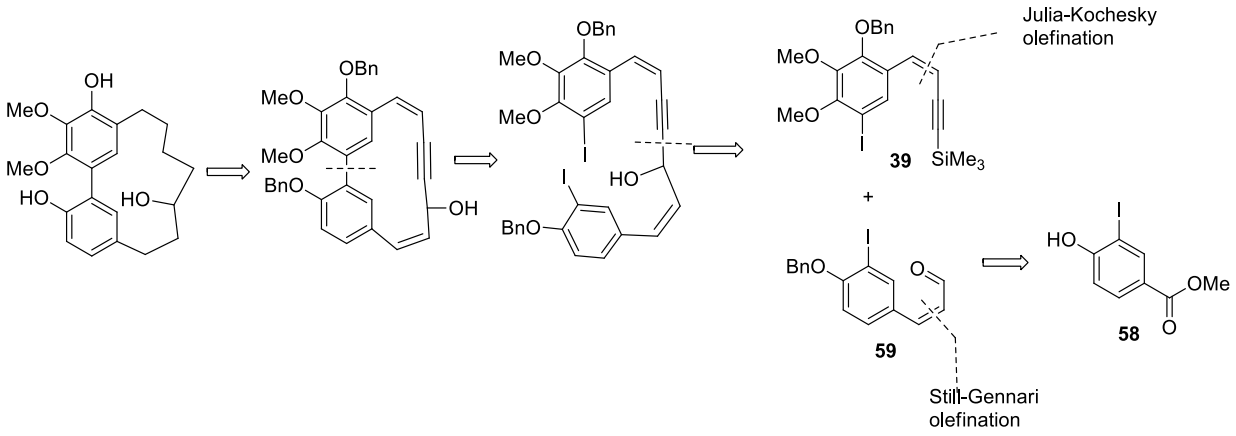
3.5- Synthesis of the second *seco*-precursor

Scheme 87 represents a possible retrosynthetic approach to the synthesis of the second *seco*-precursor. In contrast to the first previously discussed one (section 3.4), the second *seco*-precursor features a new *cis* double bond.

Introducing an additional unsaturation on one side may offer the advantage of investigating the reactivity of an even more rigid precursor to test how structural rigidity influences the subsequent cyclization reaction.

The main goal of this thesis is to find a way to promote the final intramolecular cyclization step in the synthesis of highly strained macrocycles.

It is worth noting that the retrosynthetic scheme outlined in the subsequent illustration diverges from the synthesis of the initial *seco*-precursor solely in its incorporation of a *cis* double bond, an aspect that could be introduced by the Still-Gennari olefination.



Schema 87. Retrosynthesis of the second *seco*-precursor

The synthesis of the α,β-unsaturated aldehyde (compound **59**) from the commercially available compound **58** and the subsequent addition and cyclization reactions will be discussed in this section.

3.5.1 - Synthesis of the α,β-Unsaturated Aldehyde

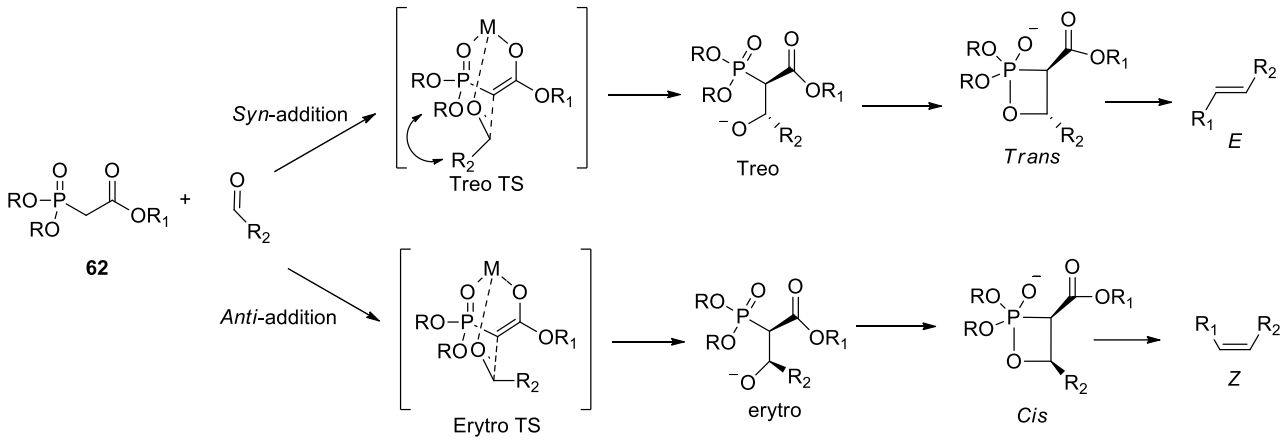
The synthesis of the α,β-unsaturated aldehyde involved the Still-Gennari olefination, a well known variant of the HWE reaction that enables the synthesis of *Z*-α,β-unsaturated esters with high stereoselectivity. The Still-Gennari olefination is typically conducted in the presence of strong bases, such as potassium hexamethyldisilazide (KHMDS), with the addition of 18-crown-6-ether.[174-175]

The mechanism of the classical HWE reaction[176-181] involves two reversible steps. The initial step, is a phosphonate-stabilized carbanion addition (either *syn* or *anti*) to the carbonyl group of the aldehyde or ketone, leading to the formation of an oxaphosphetane. The subsequent second step involves an irreversible phosphate elimination, resulting in the formation of the olefin.

The high *E*-selectivity observed in the standard HWE reaction is attributed to the preferential formation of the thermodynamically favored *trans* oxaphosphetane due to equilibration between intermediates. It has been reported that the stereoselectivity of the reaction is highly reliant upon the nature of the employed phosphonate.

The presence of electron-withdrawing groups (EWG) on the phosphonate such as trifluoroethyl derivative plays a crucial role in stabilizing the *cis* oxaphosphetane intermediate, ultimately leading to the formation of the *Z*-alkene.[182,183]

[174] Janicki, I.; Kiełbasiński, P. *Advanced Synthesis & Catalysis***2020**, *362*(13), 2552-2596.
[175] Still, C. W.; Gennari, C. *Tetrahedron Letters***1983**, *24*(41), 4405-4408.
[176] Lefèbvre, G.; Seyden-Penne, J. *J. Chem. Soc. D***1970**, 1308-1309.
[177] Deschamps, B.; Lefebvre, G.; Seyden-Penne, J. *Tetrahedron***1972**, 28, 4209-4222.
[178] Deschamps, B.; Lefebvre, G.; Redjal, A.; Seyden-Penne, J. *Tetrahedron***1973**, 29, 2437-2444.
[179] Redjal, A.; Seyden-Penne, J. *Tetrahedron Lett.***1974**, 19, 1733-1736.
[180] Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.***1989**, 89, 863-927.
[181] Blakemore, P. R. in *Comprehensive Organic Synthesis II* (Second Edition), (Eds: P. Knochel, G. A. Molander), Elsevier, **2014**, pp. 516-608.
[182] Motoyoshiya, J.; Kusaura, T.; Kokin, K.; Yokoya, S.; Takaguchi, Y.; Narita, S.; Aoyama, H. *Tetrahedron***2001**, *57*, 1715-1721.
[183] *Stereoselective Alkene Synthesis* in *Topics in Current Chemistry* (Ed.: J. Wang), Springer, Berlin, **2012**.



Scheme 88. Still-Gennari reaction mechanism

The addition of 18-crown-6-ether also plays a crucial and fundamental role in obtaining the *Z*-olefin. Its ability to chelate the counterion of the used base hinders the equilibration of intermediates, favoring the kinetic *Z*-product over the thermodynamic one.
When the reaction was conducted with KHMDS without 18-crown-6-ether, lower stereoselectivity was observed[175]. Of course, temperature is another important parameter, so that to remain under kinetic control this reaction was carried out at low temperatures.

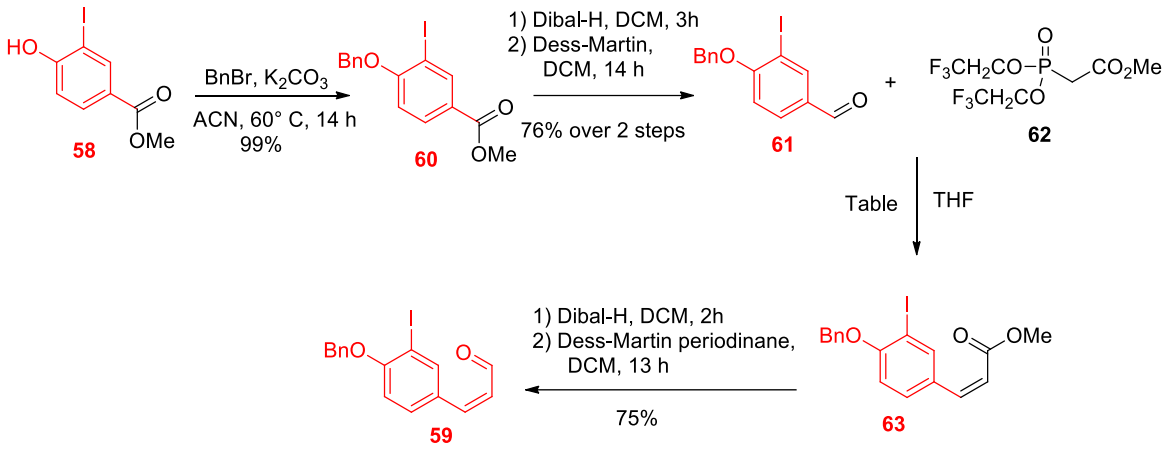
The α,β-unsaturated aldehyde **59** was synthesized following the **Scheme 89**. Starting from the commercially available product **58**, the first step was the benzylation, followed by the reduction/oxidation process, yielding the aldehyde **61**. Subsequently, the Still-Gennari reaction was carried out under the conditions outlined in **Table 22**, reported in a publication on a similar substrate[184],

The Still-Gennari reaction resulted in the ester **63** with a 99% yield and 98% of *Z*. In this case, the *Z/E* mixture is readily separable.

The subsequent reduction/oxidation provided the α,β-unsaturated aldehyde in two steps with a 75% overall yield. Aldehyde **59** exhibited notable instability, spontaneously isomerizing to the corresponding *trans* isomer. It was observed that in $CDCl_3$, rapid isomerization occurred during the evaporation of the solvent under reduced pressure as well as a partial isomerization was observed

[184] Chausset-Boissarie, L.; Àrvai, R.; Cumming, G. R.; Guénée, L.; Kündig, E. P. *Org. Biomol. Chem.***2012**, *10*, 6473-6479.

during purification on silica gel. This acid-catalyzed isomerization is attributable to the oxygen activation in the *para* position to the double bond. As discussed in the following section, isomerization posed an issue during the addition reaction (Section 3.5.2).



Scheme 89. Synthesis of aldehyde **59**

Entry	62 (eq)	18-crown-6-ether (eq)	KHMDS 15% (eq)	T (°C)	t (h)	Product 59 (yield)	*Z/E*	Conv.
1	1	5	1	-78	1	(27%)	98/2	35%
2	1.1	5.5	**1**	-78	4	(26%)	98/2	30%
3	1.1	5.5	**2**	-78	4	(29%)	98/2	34%
4	**1.5**	5	1.9	-78	5	(57%)	97/3	59%
5	**1.5**	5	1.9	-78 to **-55**	14	(74%)	97/3	86%
6	**1.5**	5	2.0	**-78 to r.t.**	20	(93%)	98/2	100%
7	1.5	5	2.0	**-55**	8	(99%)	98/2	100%

Table 22. Still-Gennari Olefination of aldehyde **61**

All experiments were performed at low temperatures to favor kinetic control, and the reaction involves an initial pre-activation of the phosphonate followed by the addition of the aldehyde dissolved in THF or added directly as a solid.

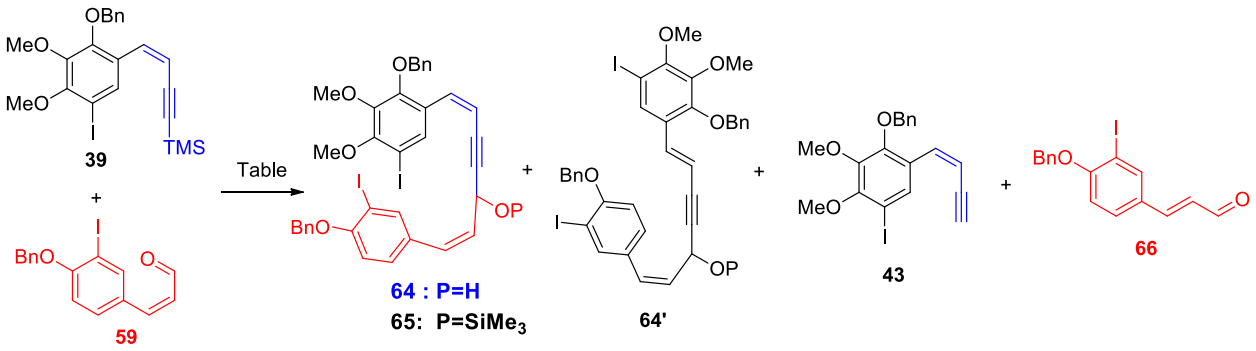
A slight increase in temperature did not result in a decrease of stereoselectivity, although it led to higher yields. Interestingly, it was observed that adding the aldehyde as a solid, rather than as a solution in THF, the yield improved without affecting the stereoselectivity (**entry 7**).

A slight excess of phosphonate also contributed to an increase in the reaction yield, going from 29% to 57% (**entry 3, 4**) of isolated yield under the same reaction conditions. The increasing of the equivalents of the base, on the other hand, only led to a slight improvement in yield (**entry 3**).

Ultimately, the optimal reaction conditions were those reported in **entry 7**, where the reaction was carried out at -55°C with 1.5 equivalents of phosphonate **62**.

3.5.2- Addition attempts on the α,β-unsaturated aldehyde

As previously discussed, the introduction of a *cis* double bond served for the main purposes: to build a *seco*-precursor characterized by increased rigidity, to assess the influence of the polyunsaturated system on the macrocyclizations of highly strained systems.
The addition reactions conducted by the aryl iodide **39** (*E*) and **39** (*Z*) on aldehyde **59** are presented below (**Scheme 90**, **Table 23**).



Scheme 90. Addition attempts on the α,β-unsaturated aldehyde **59**

Entry	39 ene-yne (eq)	Cat. (eq)	T(°C)	Solv	t(h)	Product	Yield (64:64')	Conv.
1	(1.8)	TBAF (0.2)	**r.t.**	THF	1	**64**	**43** (77:23)	91
2	(1.8)	**$AgNO_3$ (0.1)**	r.t.	Acetone	24		/	100
3	(1.8)	**TBAT (1.0)**	55	THF	1	**64**	10%	85
4	**43** (1.8)	**ZnOTf (1.5) Methyleph . (1.5eq)**	r.t.	**Toluene**	15		/	/
5	1.8	TBAF (0.2eq)	85	**Dyglime**	2	**64**	5%	83
6	1.8	TBAF (0.2eq)	90	**Dioxane**	2	**64**	Traces	100
7	1.8	TBAF (0.2 eq)	**0**	THF	1	**64**	15% (77:23)	52
8	1.8	TBAF (0.2eq)	**55**	THF	1	**64**	70% (72:28)	100
9	**2.5**	TBAF (0.2eq)	55	THF	1	**64**	66% (76:24)	100
10	1.8	TBAF **(1.0 eq)**	55	THF	1	**64**	Traces	100
11	1.8	TBAF **(0.1 eq)**	55	THF	2	**64**	31% (68:32)	65
12	1.8	TBAF **(0.15 eq)**	55	THF	2	**64 + 65**	*87% (70:30)	94
13	1.8	TBAF (0.15 eq)	**Reflux.**	THF	1	**64 + 65**	*88% (72:28)	100

***Crude Yield**

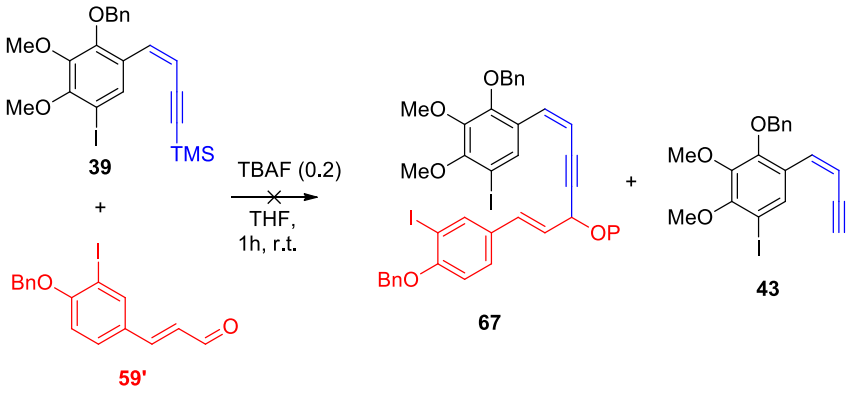
Table 23. Addition attemptson the α,β-unsaturated aldehyde **59**

The reaction (entry 1), conducted under the same reaction conditions tested for the synthesis of the first

seco-precursor (Section 3.4.2) with TBAF (0.2 eq), yielded to 43% yield. This already represents a significant improvement in yield compared to the analogous reaction conducted on the saturated aldehyde (**41**). During the reaction, it was observed that, under the conditions used, aldehyde **59** isomerized to its *trans* form, which proved to be completely unreactive. Four possible products would be expected from this reaction (given the coexistence of *cis* compound **39**, *trans* compound **39**, and aldehydes **59** *cis* and *trans*). However, among the identified products, only the stereoisomers **64** (Z-Z) and **64'** (*E-Z*) were found. Further attempts were made using aldehyde *trans* **59** directly as the substrate (**Scheme 91**), but no reaction products were obtained, except for the protodesilylation product **43**.

Various reaction parameters were studied to optimize the yield. Firstly, other catalysts were tested such as silver nitrate without success (**entry 2**), or TBAT with only a 10% yield (**entry 3**). It is worth to note that TBAT was used in stoichiometric amount rather than catalytic, likely because of its poor solubility, which prevented the complete desilylation of the starting substrate. Conditions reported by Carreira for asymmetric addition starting from the desilylated substrate **43** were also attempted (**entry 4**), but no promising results were obtained in all three cases. In the subsequent attempts (**entry 5** and **6**), the solvent and reaction temperature were modified, resulting in only traces of the product.

At lower temperatures (**entry 7**), incomplete desilylation was observed. Nevertheless, there was a slight improvement in terms of stereoselectivity, resulting in a product ratio *(Z-Z)/(E-Z)* of 77/23 albeit with a lower yield of only 15% with 52% conversion.
When the reaction was conducted at 55°C (**entry 8**) a slight deterioration in terms of stereoselectivity was observed but a significant enhancement in overall yield, increased from 43% to 70%. Attempting to boost the reaction towards the desired products, the amount of **39** was increased to 2.5 equivalents (**entry 9**). Surprisingly, this led to a decrease of reaction yield. Subsequent experiments were carried out at 55°C by modifying the equivalents of the catalyst; using 1.0 eq of TBAF (**entry 10**) only traces of the product were detected. This experimental data might indicate that in the presence of larger quantities of TBAF protodesilylation becomes the favored reaction. Conversely, using a lower quantity of TBAF (0.1 eq, **entry 11**), the reaction yield tended to decrease providing only a 65% of conversion of ene-yne compound). The optimal compromise appeared to be the use of 0.15 eq of TBAF (**entries 12** and **13**), which resulted in the highest yields (87% and 88%). In these reaction conditions, it was also possible to observe the formation of silyl ether **65**, which was not detectable when 0.2 eq of the catalyst were used.



Scheme 91. Addition attempt on *trans* aldehyde

The silyl ether **65** can be hydrolyzed to the corresponding alcohol under acidic conditions. However, when isolating compound **65**, a discrepancy in terms of stereoselectivity compared to alcohol **64** was observed. In fact, as reported in **Table 12** (**entry 13**), the overall reaction yield, considering both the alcohol and the silyl ether, is 88%, with 72% of the *Z-Z* stereoisomer.

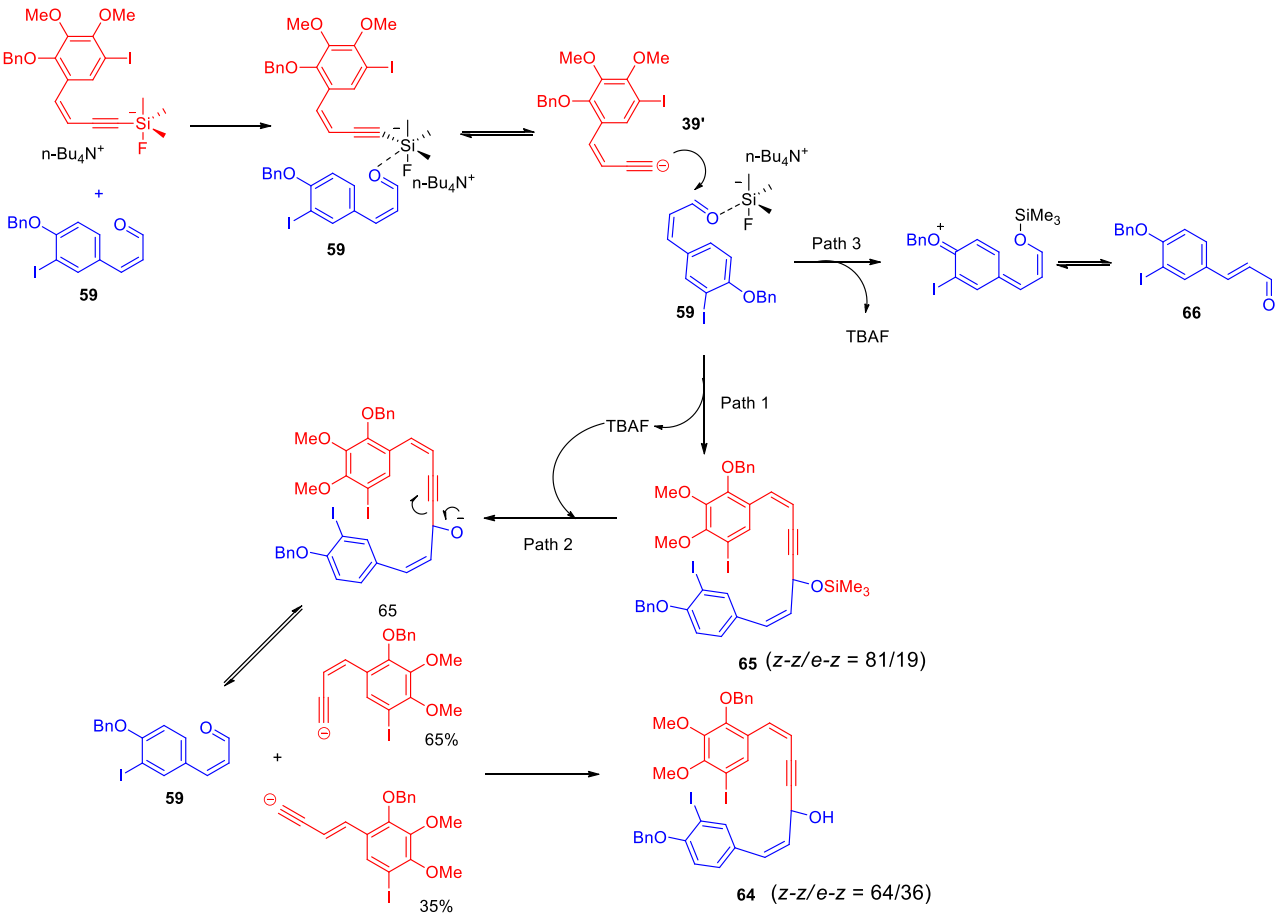
On the other hand, if we consider the isolated silyl ether, we observe a *Z-Z/E-Z* ratio of 81%, compared to the 64% *Z-Z* ratio of the isolated alcohol.

The isomerization can be rationalized through path 3 as depicted in **Scheme 92**. This pathway may be disfavored if electronically withdrawing protecting groups were used instead of electron-donating ones. One possible example could be the use of the 4-nitrobenzyl group[185]or photolabile *o*-nitrobenzyl derivatives.[186]

Experimentally, it has been observed that once the silyl ether is isolated, subjecting it to desilylation with TBAF does not result in isomerization, and the *Z-Z/E-Z* ratio remains unaltered in the obtained alcohol. Therefore, the lower *Z-Z/E-Z* ratio observed for product **64** cannot simply be attributed to the isomerization of silyl ether **65** in the presence of TBAF, which would then lead to the formation of alcohol **64**.

[185] Kukase, K.; Tanaka, H.; Torii, S.; Kusumoto, S. *Tetrahedron Letters***1990**, *31*(3), 389-392.
[186] Klán, P.; Šolomek, T.; Bochet, C. G.; Blanc, A.; Givens, R.; Rubina, M.; Popik, V.; Kostikov, A.; Wirz, J. *Chem. Rev.***2013**, *113*(1), 119–191.

One possible speculation that could explain the experimental results lies in the fact that the more reactive *cis*-ene-yne reacts more rapidly, leading to the rapid formation of silyl ether **65** according to the mechanism depicted in **Scheme 92** (path 1), resulting in the formation of product **65** (81% *Z*-*Z*). In the presence of TBAF, product **65** may undergo further desilylation (path 2), leading to the formation of the corresponding alkoxide, which could then undergo retroaddition, reforming aldehyde **59** and acetylide **39'**. At this point, the aldehyde can be attacked by both Z and E acetylides **39'** and **39'**, resulting in a mixture of isomers that faithfully reflects the *Z/E* ratio of the starting substrate. Consequently, this leads to the formation of alcohol **64** with a *Z*-*Z*/*E*-*Z* ratio of 64/36.

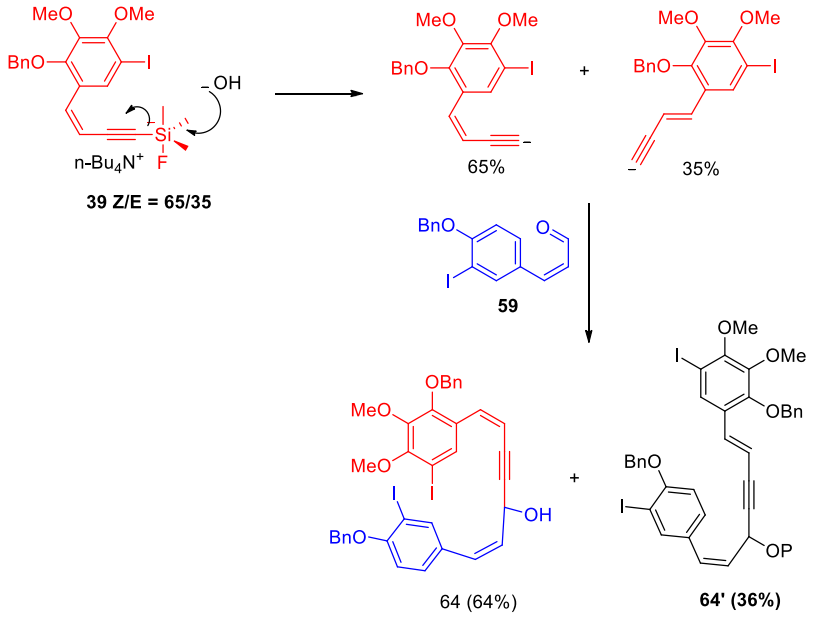


Scheme 92. Proposed mechanism for the formation of enyne **64**

Another possible explanation could involve two slightly different reaction mechanisms: In the first case, the reaction proceeds as described in path 1 of the previously discussed **scheme 92**. In the second case, an alternative reaction mechanism, illustrated in the following **scheme 93,** could be involved,

where the initial desilylation of the starting substrate occurs, resulting in the formation of *Z* and *E* acetylides **39'** due to the presence of small amounts of OH^- in the commercially available TBAF (arising from the reaction with water producing TBA bifluoride and TBA hydroxide) , followed by their direct addition to aldehyde **59**, leading to the direct formation of the corresponding alcohol.

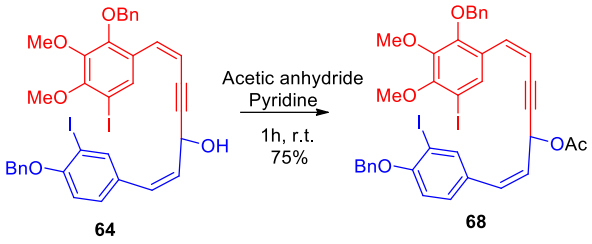
Clearly, neither of the two proposed hypotheses has been confirmed, and they are only speculations aimed to finding a reasonable explanation for the obtained experimental results. If freshly prepared anhydrous TBAF were used, it could help determine whether the proposed mechanisms is involved. Anhydrous TBAF can be prepared by aromatic nucleophilic substitution at low temperatures, starting from hexafluorobenzene and tetrabutylammonium cyanide[187].



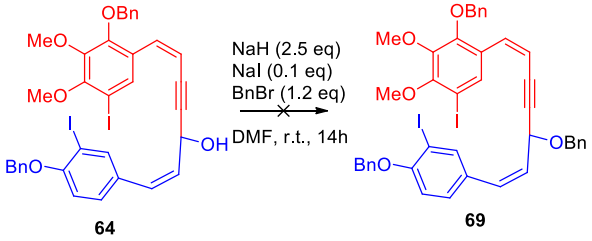
Scheme 93. Alternative proposed mechanism for the formation of enyne **64**

In any case, alcohol **64** obtained was subjected to acetylation (**Scheme 94**), yielding compound **68** for subsequent cyclization (**Section 3.5.3**). A benzylation attempt was also conducted, which unfortunately resulted in the degradation of the starting substrate, an acid catalyzed trichloroacetamidate benzylation could be an alternative solution to afford benzylation since the alcohol **64** can undergo retroaddition (**Scheme 95**).

[187] Sun, H.; DiMagno, S. G. *J. Am. Chem. Soc*. **2005**, 127(7), 2050–2051.

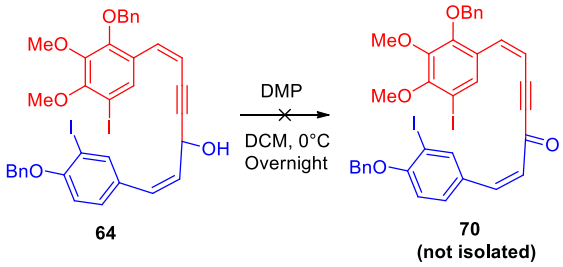


Scheme 94. Acetylation of **64**



Scheme 95. Benzylation of **64**

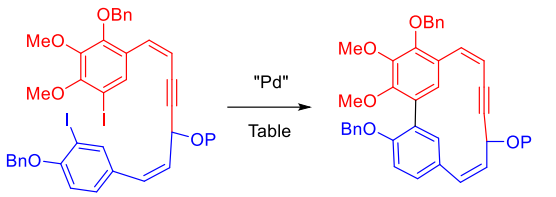
In an effort to achieve a seco-precursor with enhanced rigidity, compound **64** was subjected to oxidation (**Scheme 96**). This led to a mixture of unwanted products, including the desired product **70**, which, regrettably, couldn't be isolated from the rest of the mixture.



Scheme 96. Oxidation to **70**

3.5.3- Macrocyclization attempts on the second *seco*-precursor

The *seco*-precursor **64** (and **65**) obtained was subjected to a cyclization reaction under various conditions, as described in **Scheme 97**



64. P=H
65. P=SiMe$_3$
68. P=OAc

71. P=H
72. P=SiMe$_3$
73. P=OAc

Scheme 97. Pd-catalyzed Macrocyclization

N.	Sub. (Z-Z%)	$B_2(pin)_2$	$PdCl_2dppf$	Solv	t(h)	T°C	Conditions	Result	Conv.
1	**68**	1.2	0.1	DMSO	16	80	Method A	Degradation	100
2	**64**	1.2	0.1	DMSO	18	80	Method B	**71**(2.2 mg)	100
3	**64** (77%)	1.2	0.1	DMSO	16	80	Method A	Degradation	100
4	**64**(76%)	1.2	0.1	DMSO	15	80	Method B	Degradation	100
5	**64**(72%)	1.2	0.1	DMSO	1h	80	Method C	Degradation	100
6	**64** (53%)	1.2	0.1	DMSO	1.5h	r.t.	Method B	Unknown byprod	100
7	**64** (95%)	1.2	0.1	DMSO + H_2O (5%)	1.5h	r.t.	Method B	Unknown byprod	80
8	**65**(81%)	1.2	0.1	DMSO	1 h	r.t.	Method B	**64**	100
9	**64** (95%)	0	0.1	DMSO	14 h	65° - r.t	Method B	Unknown byprod	100

***Method A = Solvent added after catalyst; Method B= Cat. Added after solvent at r.t.; Method C = Cat. Added after solvent at 80°C;**

Table 24. Macrocyclization attempts of *seco*-precursors **64**, **65** and **66**

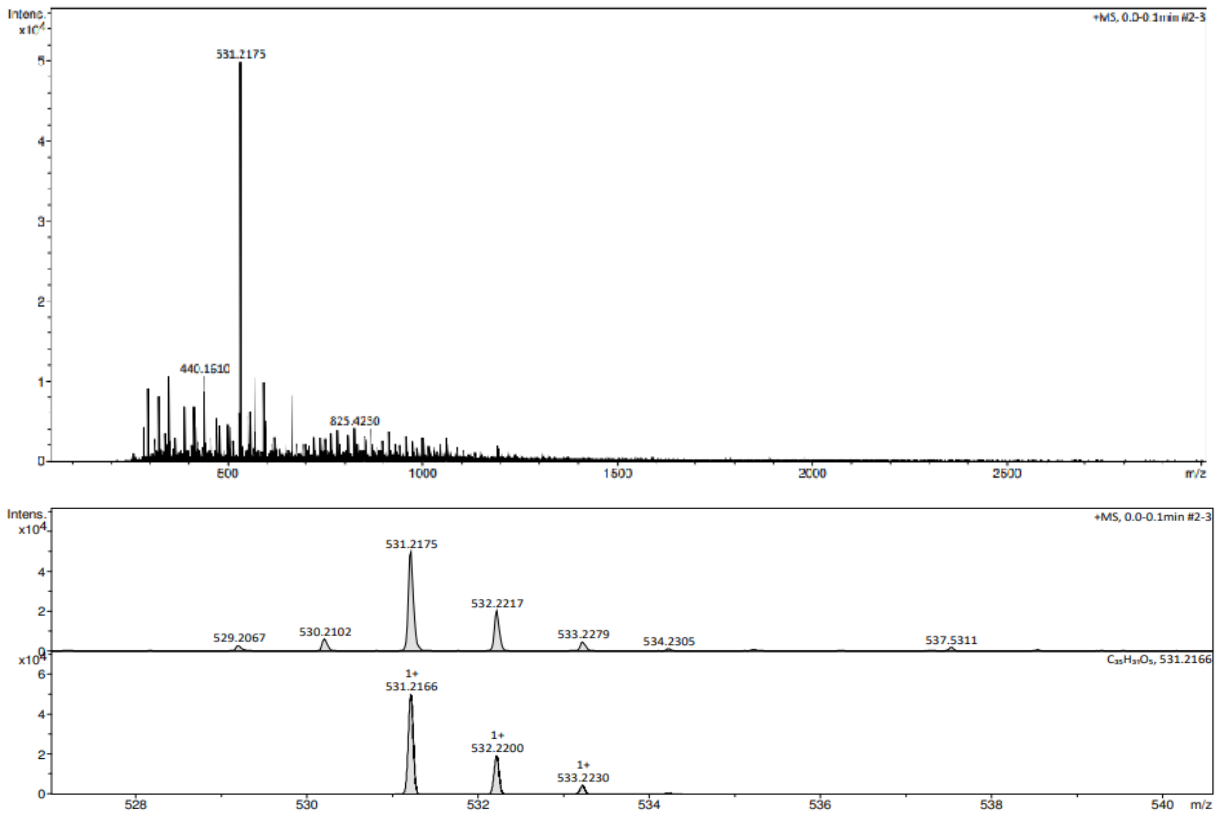
The first cyclization attempt (**entry 1**) was conducted on acetylated alcohol **68** under the Suzuki-Miyaura domino cyclization conditions previously used in the latest publication of the myricanol's total synthesis[20], resulted in complete conversion of the starting substrate but yielded non-interpretable results. From the crude reaction mixture, it was not possible to identify any signal from the starting compound or any potential cyclization product.

The second cyclization attempt (**entry 2**), carried out on the free alcohol **64** using small amounts of the substrate, produced a crude reaction mixture that, when analyzed by ^{1}H NMR and HRMS (**Figure 12**), predominantly exhibited the cyclization product. However, due to the small amounts involved, complete characterization of the cyclized compound was not feasible.

Subsequent trials (**entry 3-5**) were conducted under the same conditions, using larger amounts of starting substrate with the aim of obtaining the cyclized product that would lead to myricanol upon reduction.
Unfortunately, the result obtained in the previous attempt (**entry 2**) could not be reproducible. It was thought that the order of catalyst addition relative to the solvent might play a role in determining the cyclization or degradation of the starting substrate. Therefore, in **entry 3**, the solvent was added after the catalyst, in **entry 4**, the solvent was added before the catalyst, and in **entry 5**, the catalyst was added to the reaction mixture previously brought to 80°C.
In any case, the reaction result led to the degradation of the starting material even after just 1 hour of reaction at 80°C (**entry 5**).

It was then hypothesized that temperature played a crucial role in determining the degradation of the starting substrate. Subsequent trials were conducted at room temperature in DMSO or DMSO + H_2O, resulting in a collateral product of boronation on the triple bond, which was not clearly identified but did not correspond to the expected cyclization product.

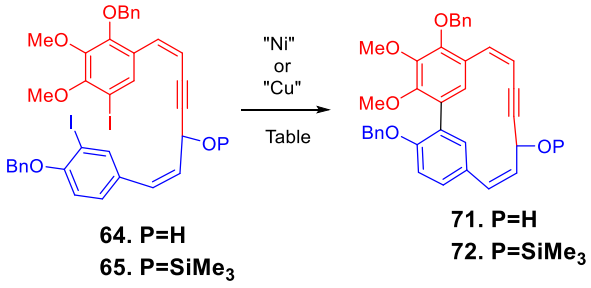
Silyl ether **65** was also tested under the same conditions, producing compound **64**, which subsequently underwent the same reactions as in the previous attempts. A final experiment involved an Ullmann-like coupling (in the absence of $B_2(pin)_2$), but it did not yield the desired cyclization product.



HRMS (ESI+): m/z calcd $[M + H]^+$: 531.2166 ; found : 531.2175

Figure 12. HRMS of the addition's reaction crude

It was then decided to investigate the use of nickel and copper to achieve cyclization (**Scheme 98**).



64. P=H
65. P=SiMe$_3$

71. P=H
72. P=SiMe$_3$

Scheme 98. Ni- or Cu-catalyzed Macrocyclization

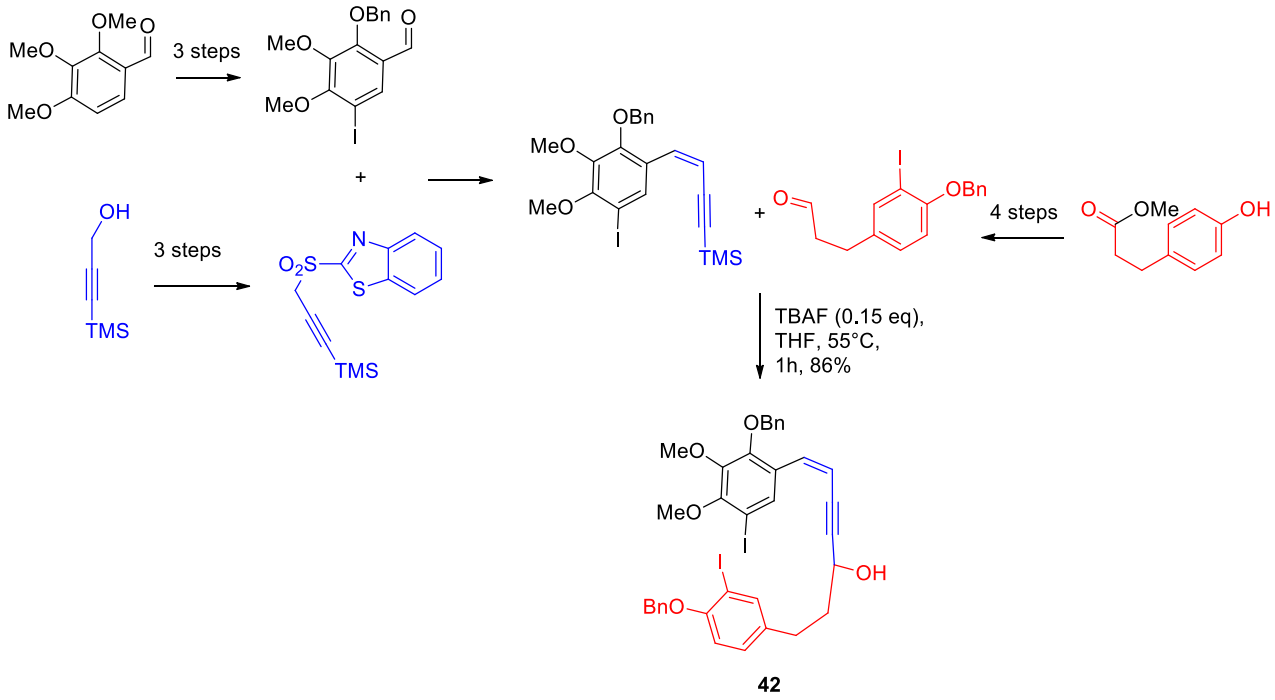
N.	Sub. (Z-Z%)	Catalyst	Solv	t(h)	T°C	Result	Conv.
1	**65 (72%)**	Cu	DMF (2mM)	16	120	**64**	100
2	**64** (77%)	Cu	DMF (2mM)	16	120	Traces of Dehalogenation	10
3	**64** (95%)	$NiCl_2(PPh_3)_2$, Zn	DMF (2mM)	16	60	Traces of phenylbenzene	100

Table 25. Ni- or Cu-Catalyzed Macrocyclization attempts

Substrates **64** (alcohol) and **65** (silyl ether) were subjected to cyclization attempts catalyzed by elemental copper in DMF at elevated temperatures. However, these efforts yielded only the desilylation of the starting substrate (**entry 1**) and the formation of minor amounts of dehalogenation products (**entry 2**). Subsequently, a nickel-catalyzed experiment was conducted, involving the *in situ* generation of the $Ni(PPh_3)_4$ species through zinc powder reduction. Remarkably, this reaction resulted in the complete conversion of the starting material, although accompanied by a probable degradation process, and unanticipated traces of phenylbenzene formation were observed (**entry 3**).

3.5.4- Macrocyclization attempts on the first *seco*-precursor

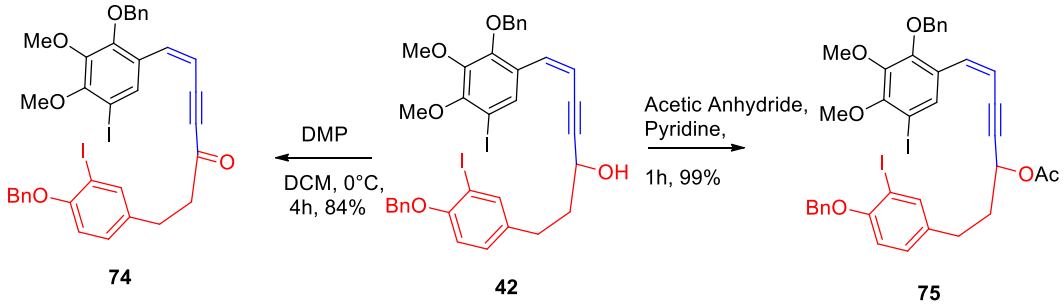
Since it was not possible to obtain the desired compound, the first *seco*-precursor, whether oxidized or acetylated, was tested for cyclization. This was accomplished according to the synthetic scheme outlined below (**Scheme 99**), which is briefly summarized here and discussed in detail in Section 3.4. Interestingly, by using the optimized addition conditions for the synthesis of the second *seco*-precursor, it was possible to achieve an 86% yield of addition. Strangely, in this case, no traces of the protected silyl ether product were detected.



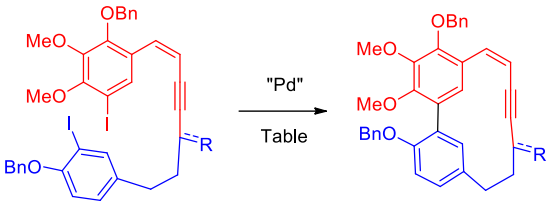
Scheme 99. Synthesis of the first *seco*-precursors **42**

The *seco*-precursor **42** was subjected to acetylation or oxidation according to the following **Scheme 100**, resulting in the compounds **74** and **75**. These compounds were then subjected to cyclization as reported in **Table 26.**

Therefore, three cyclization attempts were conducted via Suzuki-Miyaura domino reaction on the ketone (**74**) or the acetylated compound (**75**). Interestingly, when the reaction was carried out at room temperature, no reaction was observed. However, if conducted at 60°C, rapid degradation of the starting substrate was observed (entry 2, 3, **Table 26**).



Scheme 100. Synthesis of **74** and **75**



74. R=O
75. R=OAc

76. R=O
77. R=OAc

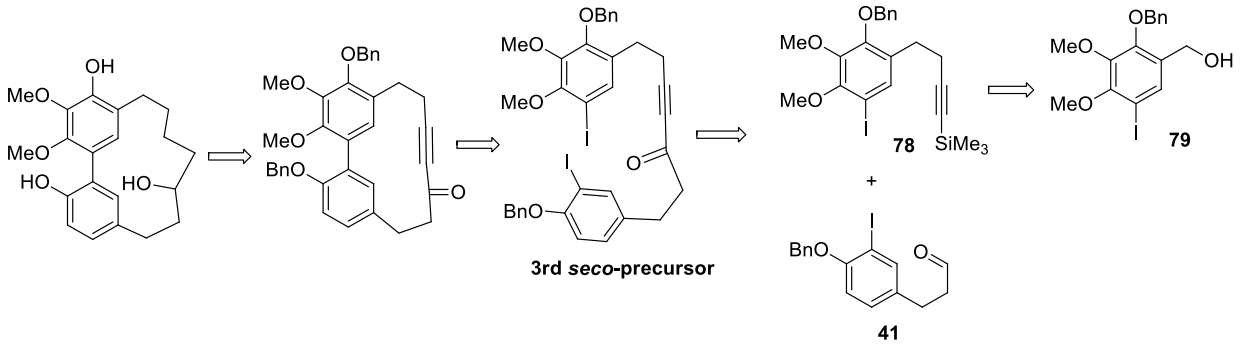
N.	Sub. (Z-Z%)	$B_2(pin)_2$	$PdCl_2dppf$	Solv	t(h)	T°C	Result	Conv.
1	**74**	1.2	0.1	DMSO	14	r.t.	No reaction	
2	**74**	1.2	0.1	DMSO	1h	60°C	**Degradation**	100
3	**75**	1.2	0.1	DMSO	15	80°C	**Degradation**	100

Table 26. Macrocyclization attempts of **74** and **75**

In light of the disappointing results obtained regarding the final macrocyclization step, it was postulated that the rapid degradation of the starting substrate observed in various experiments conducted at temperatures ranging from 60 to 80 degrees may be attributed to the presence of conjugated unsaturated systems in conjunction with the propargyl alcohol functionality. Furthermore, the macrocyclization might be hindered due to the high ring strain inherent in the treated polyunsaturated macrocycles. Therefore, the investigation shifted towards other *seco*-precursors characterized by the absence of the enyne system, which, upon cyclization, could form macrocycles with lower ring strain. The following paragraphs will focus on the synthesis and cyclization of two additional *seco*-precursors. Initially, experiments were conducted on a more readily synthesized model system, a precursor of diaryleptanoids analogous to myricanol (such as alnusone, acerogenin K, and acerogenin E).

3.6- Retroynthesis of the the third *seco*-precursor and its analogue

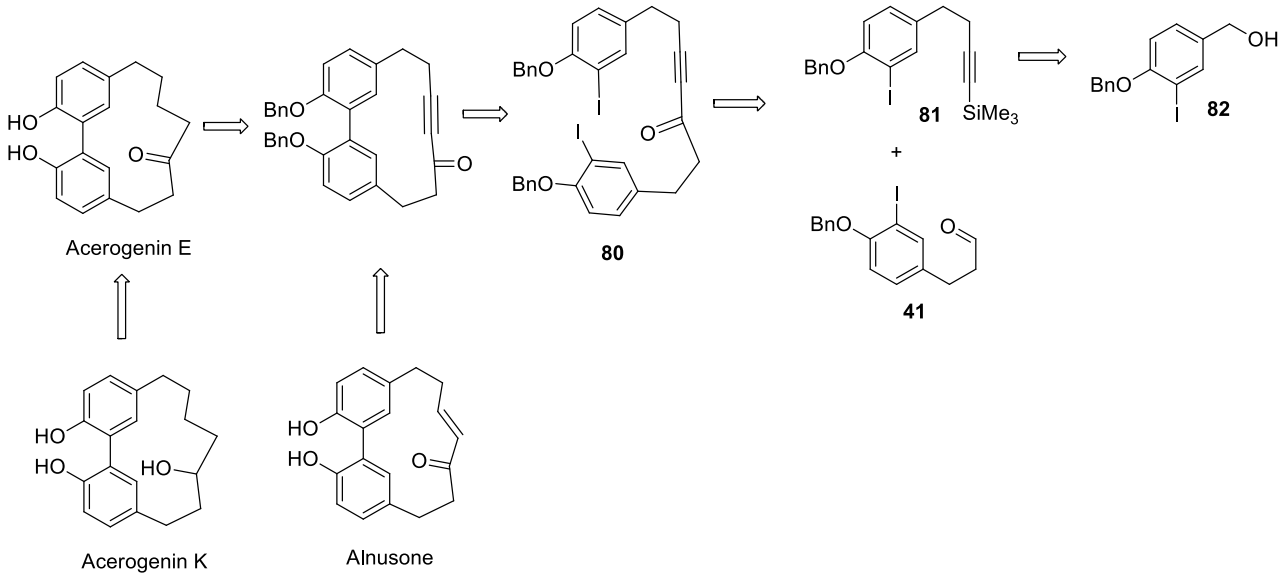
The following **Scheme 101** describes a possible retrosynthetic approach for the third seco-precursor.



Scheme 101. Retrosynthesis of the third *seco*-precursor

In this case, unlike the previously discussed seco-precursors, there are no *cis* double bonds, and the *seco*-precursor is a simple propargylic alcohol (or ketone). It can arise from the coupling of the TMS alkyne **78** with propionic aldehyde **41**. Compound **78**, in turn, can be obtained from alcohol **79** through bromination and nucleophilic substitution by the organolithium.

As previously mentioned, experiments were conducted simultaneously on the standard myricanol precursor and on a more readily synthesized analogue (**Scheme 102**) that can be prepared using a similar approach. The cyclized product alnusone or acerogenin E (reduced to acerogenin K) could be achieved.



Scheme 102. Retrosynthesis of the *seco*-precursor **80**

3.6.1- Synthesis of the TMS-Propyne 81

The following **Scheme 103** illustrates the synthesis of compound **81**. The first step involves a benzylation, purified by recrystallization. The second step consists of a reduction, yielding the alcohol **82**, that, when subjected to Appel bromination, provided compound **83** with a 74% isolated yield (and complete conversion).

Compound **83** was then subjected to an SN_2 reaction . The firstly step involves the *in-situ* generation of the organolithium, subsequently it was added to the benzyl bromide 83.given the SN_2 product **81.**

Table 27 shows various experimental conditions tested for the synthesis of product **81**. The first trial (entry 1) was conducted using 1.7 eq of **84** and 1.5 eq of n-BuLi. The generation of organolithium **85** was carried out at -65°C for 10 minutes and then transferred to the substrate **83** dissolved in THF at -78°C. However, only a 6% yield was obtained.

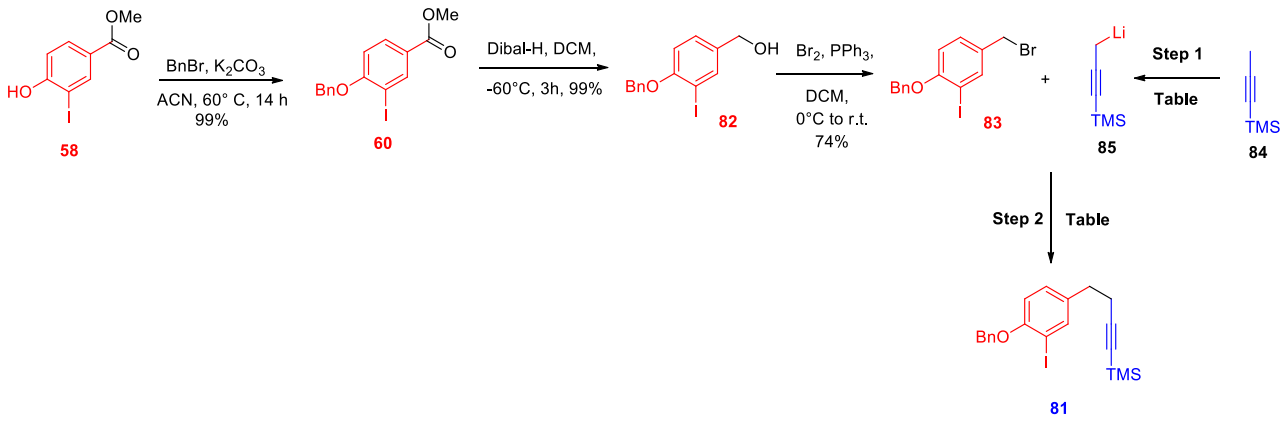
The second trial (entry 2) was conducted under the same reaction conditions, but the time for the first step was increased to 40 minutes thus allowing the formation of the organolithium. Unfortunately, no traces of the desired product were detected in the crude reaction mixture.

In the third trial (entry 3), the time for the second step of the reaction was also increased, but no improvement was observed. Higher temperatures may be required for organolithium formation. In the fourth trial (entry 4), the temperature for the first step was increased to -40 degrees for 15 minutes, resulting in a slight improvement.

The fifth trial (entry 5) involved a variation of the temperature during the first step. n-BuLi was added at -60°C and the reaction was maintained at this temperature for 15 minutes before being raised to 0°C for 45 minutes. The organolithium was then transferred to substrate **83**, yielding a 34% yield after 1 hour at -78°C.

In the sixth trial, n-BuLi was added directly at 0°C and left for 40 minutes before the second step. Strangely, no nucleophilic substitution product was obtained. One speculation for the failed reaction attempt of entry 6 could involve the possible degradation of TMS-propyne **84** by *n*-BuLi due to the temperatures and reaction times involved. In the last trial (entry 7), by reducing the time of the first

step at 0°C to 30 minutes, an isolated yield of 84% with a 90% conversion was achieved, no side reaction products were identified.



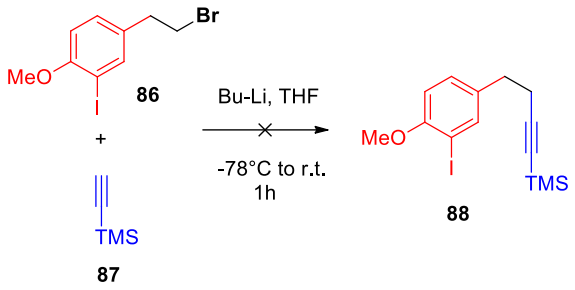
Scheme 103. Synthesis of TMS-propyne **81**

Entry	84(eq)	n-BuLi (eq)	THF (mM)	1 step T	1 step t	2 step T	2 step t	Results	Conv
1	1.7	1.5	0.2	-65°C	10 min	-78°C	1h	**81** (6%)*	
2	1.9	1.7	0.22	-65°C	**40 min**	-78°C	1h	/	/
3	1.9	1.7	0.22	-65°C	40 min	-78°C	**16h**	/	/
4	1.9	1.7	0.2	**-40°C**	**15 min**	-78°C	1h	**81**(20%)	
5	1.9	1.7	0.2	**-60°C Then 0°C**	**15min 45 min**	-78°C	1h	**81**(34%)	40%
6	1.9	1.7	0.2	**0°C**	**40 min**	-78°C	1h	/	/
7	1.9	1.7	0.18	**0°C**	**15 min**	-78°C	30 min	**81** (84%)	90%

***Crude Yield**

Table 27. Synthesis of TMS-Propyne **81**

An alternative attempt was made for the synthesis of **81** , which is reported in the **scheme 104** starting from the TMS-acetylene precursor, albeit without success.



Scheme 104. Attempt to the synthesis of **81**

3.6.2- Cyclization attempts on the third *seco*-precursor

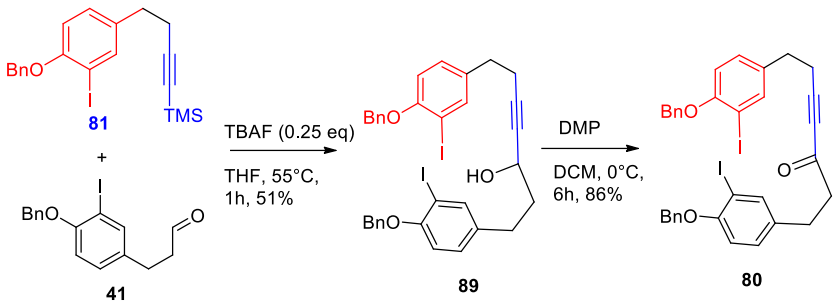
The addition of TMS-propyne **81** to propionic aldehyde **41**, using the same optimized reaction conditions as in the synthesis of the previous *seco*-precursors, provided the propargylic alcohol **89** with a 24% isolated yield, While a slight increase in the amounts of TBAF involved (from 0.15 to 0.25 equiv.) resulted in an improvement in yield, achieving an isolated yield of the propargyl alcohol **89** of 51%

The subsequent oxidation with DMP yielded the secoprecursor **80** (**Scheme 105**), which, when subjected to Ni-catalyzed cyclization (**Scheme 106**), produced a compound that, at the present time, is not yet clearly identified.

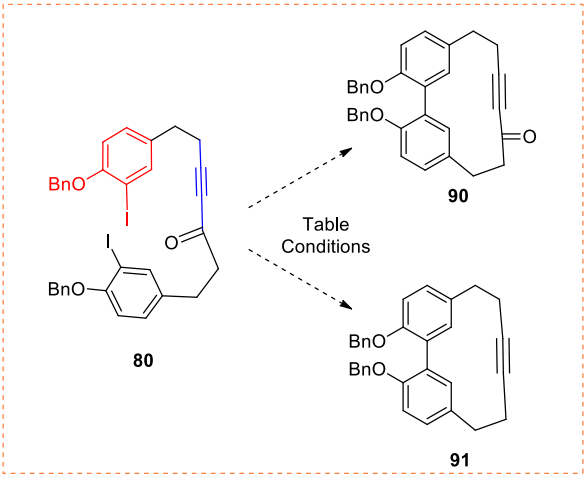
Preliminary analyses suggest that it might be the desired cyclized product (in this case, there would be a 81% yield). Another proposed hypothesis is that it might be a cyclic diarylhexanoid (**91**), as Ni-catalyzed decarbonylative coupling are reported in the literature[188]. However, the *m/z* ratio of the obtained compound seems to coincide with the desired diarylheptanoid system **90**. Further experiments with larger amounts are necessary to confirm the obtained result.

The same reaction needs to be repeated using different metals to compare the outcome with the previously discussed Pd and/or Cu-catalyzed macrocyclizations on the *seco*-precursors with higher rigidity discussed in the previous sections. Current affords are focused on this cyclization attempt and, simultaneously, its extension to the synthesis of myricanol.

[188] Morioka, T.; Nishizawa, A.; Furukawa, T.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2017**, *139*(4), 1416–1419.



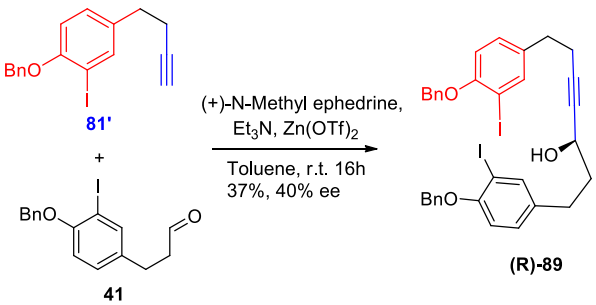
Scheme 105. Synthesis of **80**



N.	Sub.	Catalyst	Solv	t(h)	T°C	Result	Conv.
1	**80**	$NiCl_2(PPh_3)_2$, Zn	DMF (2mM)	3h	60	**90 or 91 (to be confirmed)**	100

Table 28. Ni-Catalyzed macrocyclization of **80**

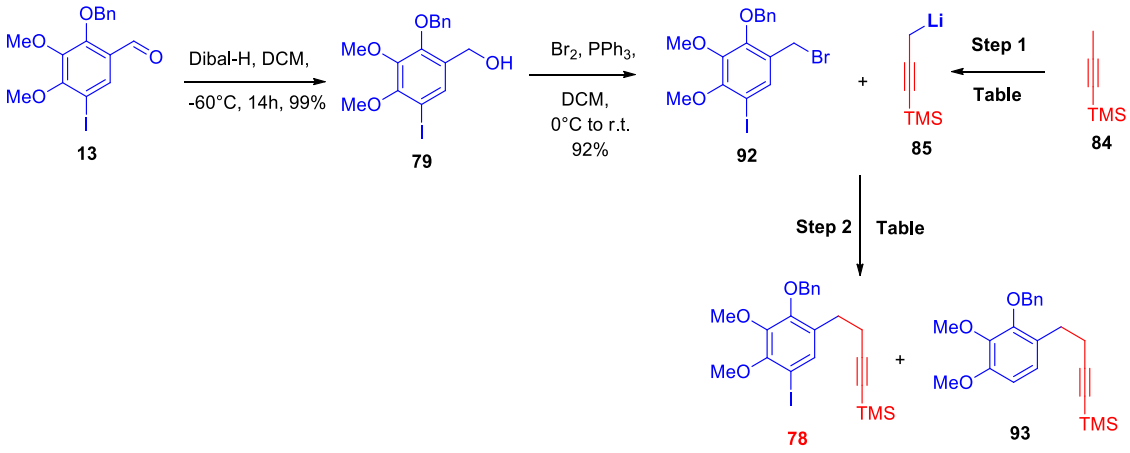
Furthermore, an attempt at asymmetric addition was made to obtain compound **(R)-89**. A Carreira addition[153,154] was carried out, yielding only 37%, with an enantiomeric excess (ee) of 40% (**Scheme 106**). However, this trial opened the possibility of reusing the desilylated compound **81'** (arising from TBAF-catalyzed addition reactions) and planning an asymmetric synthesis of myricanol (see Chapter 4).



Scheme 106. Carreira Asymmetric addition on aldehyde **41**

Currently, we are simultaneously working on the extension of this cyclization attempt to the synthesis of myricanol whose synthesized precursors are summarized in the following **Scheme 107**.

The reduction of aldehyde **13**, followed by bromination, led to compound **92**, which, through nucleophilic substitution with organolithium **85**, provided the desired compound **78**. Collateral products of deiodination of **88** and nucleophilic substitution/deiodination, resulting in compound **93**, were also obtained when the equivalents of *n*-BuLi and TMS-propyne **84** used were increased (entry 2).



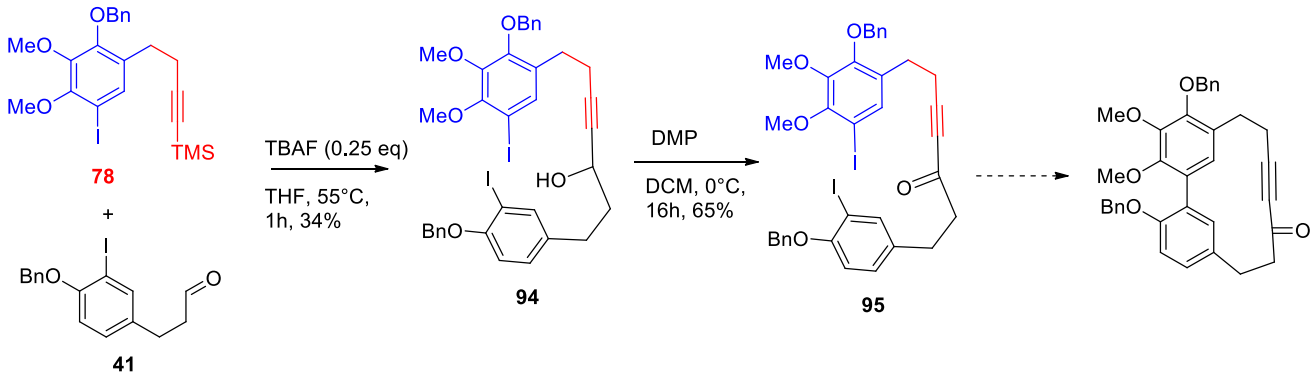
Scheme 107. Synthesis of **78**

Entry	84(eq)	n-BuLi (eq)	THF (mM)	1 step T	1 step T	2 step T	2 step t	Result	Conv
1	1.9	1.7	0.2	0°C	15 min	-78°C	1h	**78** (78%)	91%
2	**3.0**	**2.7**	0.2	0°C	15 min	-78°C	1h	**78** (32%) + **93** (18%) + **Dehalogenation** (12%)	70%

Table 29. synthesis of **78**

The subsequent addition reaction on aldehyde **41**, conducted using 0.25 equiv. of TBAF, resulted in compound **94** with a 34% yield. The subsequent oxidation provided the seco-precursor **95** with a 65% yield. Since the conversion of this reaction was complete, it is likely that the product may undergo partial degradation if left overnight.

Compound **95** will then need to undergo cyclization to furnish the cyclized precursor of myricanol. (**Scheme 108**)

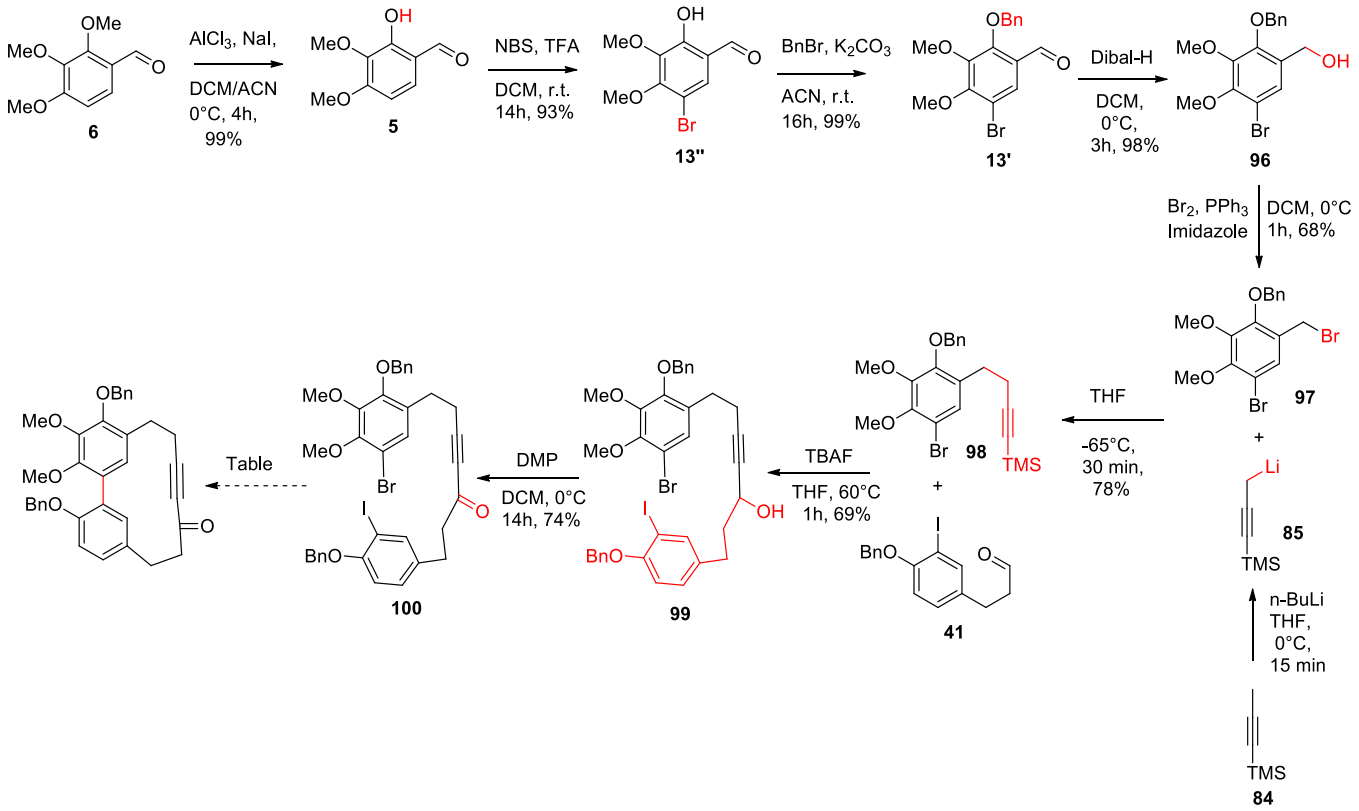


Scheme 108. Addition and oxidation reactions for the synthesis of the *seco*-precursor **95**

Alternatively, one could also plan a synthetic strategy for the synthesis of a *seco*-precursor bearing different halides to attempt a direct regioselective borylation at one of the two fragments (**Scheme 109**); the final cyclization could be carried out using a Suzuki or a Kumada cross-coupling involving the *in situ* generation of a Grignard reagent or an organolithium reagent[189,190].

Starting from the commercial compound **6**, demethylation, bromination, and benzylation were carried out to afford compound **13'**. Subsequent reduction with Dibal-H and Appel bromination provided the brominated compound **97**. The following nucleophilic substitution yielded compound **98** with a 78% yield. This compound, upon TBAF-catalyzed addition on aldehyde **41**, produced propargyl alcohol **99**, which was further oxidized to the *seco*-precursor **100**. The cyclization attempts on the latter compound are reported in **Table 30**; the initial cyclization attempt under Suzuki-Miyaura conditions resulted in the degradation of the starting substrate, similar to previous cases. The second Ni-catalyzed trial led to a mixture of products, and finally, a Kumada cross-coupling test (entry 3) did not yield a better outcome.

[189] Bhattacharjya, A.; Klumphu, P.; Lipshutz, B. *Nat Commun*, **2015**, 6, 7401.
[190] Pinxterhuis, E. B.; Visser, P.; Esser, I.; Gualtierotti, J.-B.; Feringa, B. L. *Angew. Chem. Int. Ed*, **2018**, 130 (30), 9596-9599.



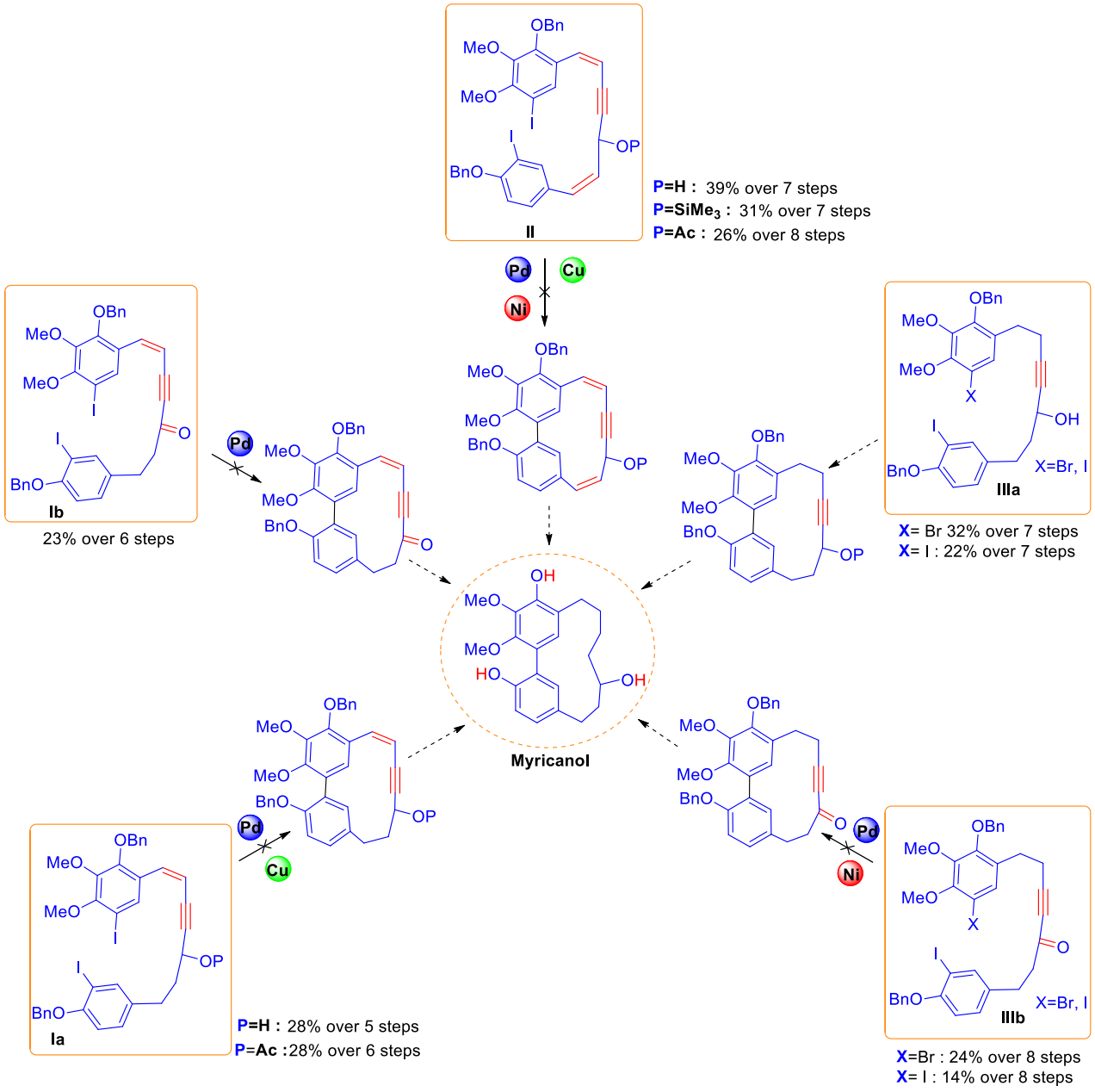
Scheme 109- Alternative total synthesis of myricanol via Suzuki or Kumada cross-coupling

N.	Catalyst	Solv	t(h)	T°C	Result	Conv.
1	$NiCl_2(PPh_3)_2$, Zn	DMF (2mM)	3h	60	**Mixture of compounds**	40
2	$Pd(dppf)Cl_2$, B_2pin_2	DMSO	14h	80	**Degradation**	100
3	$Pd(OAc)_2$, Mg	Formalin	14h	70	**Deiodination, Reduction**	55

Table 30. macrocyclization attempts of compound **100**

3.7- Path B. Conclusions

The following **Scheme 110** illustrates the conclusions for Path B. Three *seco*-precursors were synthesized, and the synthesis of the other two *seco*-precursors (with lower rigidity) is currently in progress. Moreover, two simplified *seco*-precursors have been prepared and tested for the synthesis of acerogenin K, E, and alnusolone. However, the synthesis of the last *seco*-precursor, with a higher degree of rigidity, was not successful (not shown in the scheme).



Scheme 110. Summary of Path B

The Scheme also includes the respective yields for each *seco*-precursor starting from the corresponding commercial products. *Seco*-precursor **Ia** was synthesized with a 28% yield in 5 steps in the alcohol form and with a 28% yield in 6 synthetic steps in the acetylated form. *Seco*-precursor **Ib** was obtained with a 23% yield in 6 steps, while **II** was synthesized in the form of free alcohol (7 steps, 39%), silyl ether (7 steps, 31%), or acetylated (26% in 8 steps). The seco-precursors **IIIa** and **IIIb** were synthesized with a 32% and 24% yield (when X= Br) or 22% and 14% (if X=I). The Ni, Cu, or Pd-catalyzed cyclization tests conducted on the various *seco*-precursors are reported in the scheme. Only the Suzuki-Miyaura test, conducted on the free alcohol form of **II**, resulted in traces of the cyclized product. Further Ni or Cu-catalyzed tests will need to be conducted on the remaining *seco*-precursors.

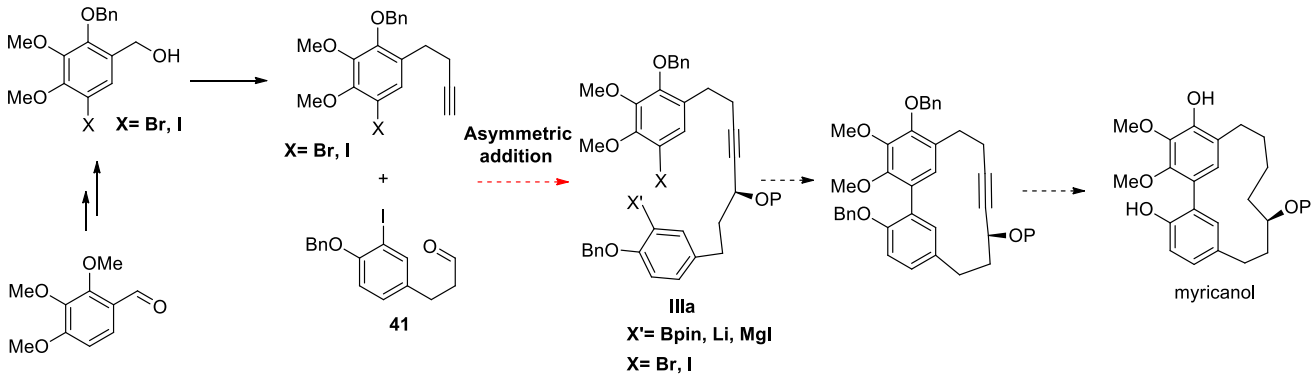
The biological properties of the synthesized seco-precursors can be investigated to understand whether the cyclic system is essential for the biological activity of myricanol.

CHAPTER 4 - Conclusions and Perspectives

4.1- General Conclusions and Perspectives

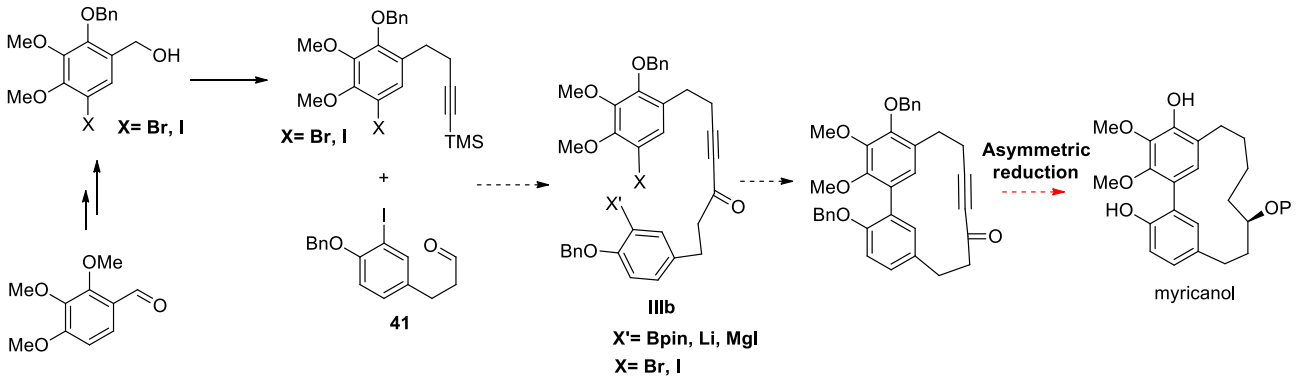
As highlighted in **Section 3.3.2** - Path A - Conclusions and **Section 3.7** - Path B - Conclusions, it was not possible to achieve an efficient total synthesis of myricanol. Although traces of the cyclized product that can be reduced to myricanol were obtained, the latest synthetic approach used in Path B, involving the synthesis of the third seco-precursor, which is less rigid than the previous ones, has yielded encouraging results in the macrocyclization of an analogue *seco*-precursor of myricanol (**section 3.6.2**). These results, once confirmed and extended to the synthesis of myricanol using the same synthetic strategy, would lead to an efficient total synthesis.

In any case, a slightly modified synthetic methodology could be planned for an asymmetric total synthesis of myricanol (**Scheme 111**) involving a Zn-catalyzed asymmetric addition[153,154]. The resulting asymmetric propargylic alcohol can be protected and cyclized to form the desired product. Presumably, by controlling the central chirality should already induce control over axial chirality. In other words, the asymmetric synthesis illustrated in the Scheme would be enantioselective and diastereoselective.



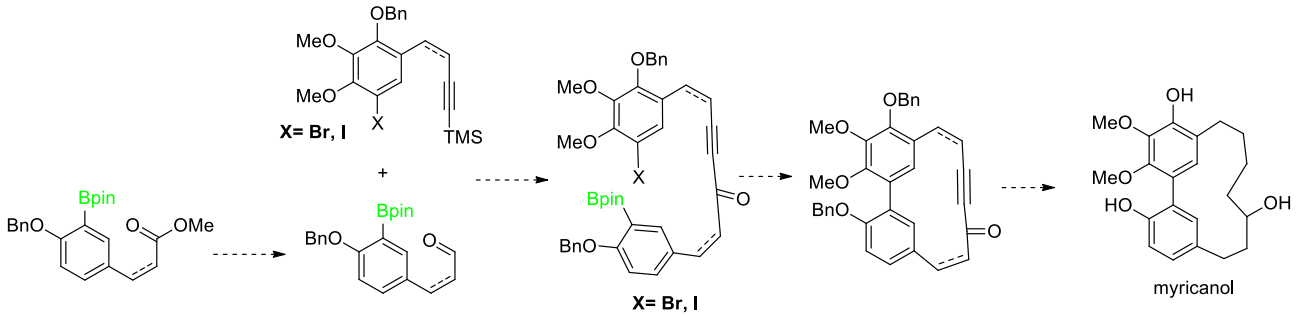
Scheme 111- Asymmetric total synthesis of myricanol via asymmetric addition

Alternatively, one could consider synthesizing the propargyl ketone derivative (**Scheme 112**) to be then asymmetrically reduced by one of the methods illustrated in **Section 2.1**, considering that enantioselectivity seems to improve when the ketone has an unsaturated substituent, as reported previously.



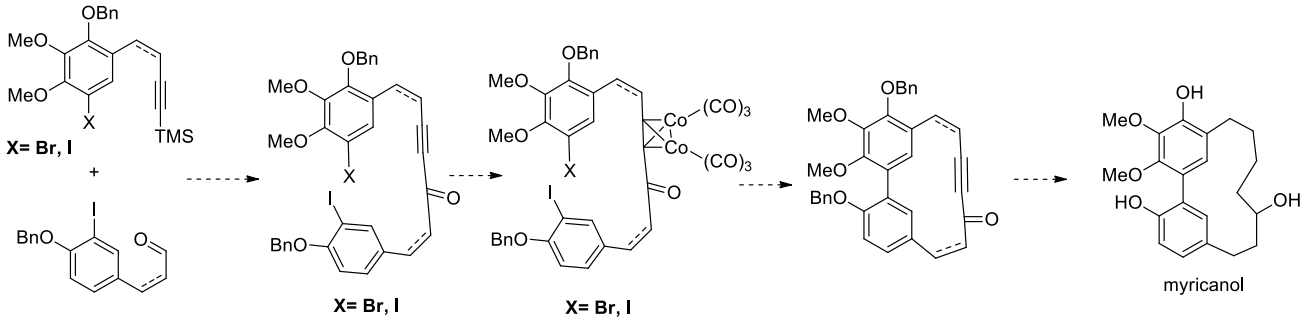
Scheme 112- Asymmetric total synthesis of myricanol via asymmetric reduction

Since the Suzuki-Miyaura domino conditions resulted in the degradation of the starting substrate, this likely occurs due to an immediate initial borylation step on the triple bond with subsequent intra- and intermolecular reactions. A viable alternative to circumvent the triple bond borylation issue could involve the use of two separate steps of borylation and cross-coupling (**Scheme 113**).



Scheme 113. Total synthesis of myricanol from previously borylated compounds

A second approach may involve an additional step of triple bond protection with octacarbonyl dicobalt (**Scheme 114**)[191,192]



Scheme 114. Synthesis of myricanol by alkyne protection with $Co_2(CO)_8$

[191] Seyferth, D.; Nestle, M. O.; Wehman, A. T. J. Am. Chem. Soc. **1975**, 97, 7417, and references given.
[192] Nicholas, K. M.; Pettit, R. Tetrahedron Lett. **1971**, 3475.

CHAPTER 5 - Experimental Section

5.1-Material and methods

Commercially reagents and solvent were used as received after adequate checks of purity (titration, NMR) from Sigma Aldrich, TCI and AlfaAesar. Et_2O, 1,4-dioxane and THF were dried by distillation over sodium/benzophenone after the characteristic blue color of sodium diphenyl ketyl (benzophenone sodium radical –anion) had been found to persist.[193] DCM was dried over CaH_2 under argon. Triethylamine was dried over KOH under argon. Melting ranges (M.p.) given were found to be reproducible after recrystallization. Commercially dry hexane was used as received from Sigma Aldrich.

^1H, ^{13}C, ^{11}B, NOESY, COSY and HETCOR NMR spectra were recorded on Brucker Avance 400 MHz and 500 MHz from ECPM-NMR service of University of Strasbourg and on Varian 400 MHz and 500 MHz from Department of Science of University of Basilicata. Samples were prepared using $CDCl_3$ and $(CD_3)_2CO$ and $(CD_3)_2SO$ as solvents. Chemical shifts were referred to 7.27 ppm (^1H) and 77.00 ppm (^{13}C) for $CDCl_3$, to 2.05ppm (^1H) and 29.84 ppm (^{13}C) for $(CD_3)_2CO$ and 2.50 ppm (^1H) and 39.52 ppm (^{13}C) for $(CD_3)_2SO$. Chemical shifts are expressed in part per million (ppm) and coupling constants *J* in Hertz. Multiplicities were abbreviated as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet) and m (multiplet) for ^1H-NMR. For ^{13}C-NMR *q* is referred to a quaternary carbon.

Unless stated otherwise, purifications were performed by column chromatography on silica gel by using MERCK silica (40-63μm). Reactions were monitored by analysis over thin layer chromatography (TLC) with Alugram® Xtra SIL G/UV (Macherey-Nagel) plates and 0.25 mm Merck silica-gel (60-F254) plates. TLC were visualized by UV fluorescence at 250 nm and revealed with a solution of anisaldehyde (5.1 mL of *p*-anysaldehyde, 2.1 mL of acetic acid, 6.9 mL of concentred sulfuric acid, 186 mL of EtOH 95%). *n*-Butyllithium (1.6 M in hexanes, Aldrich) was used as solutions and its concentration was determined following the Mark R. Winkle, Janet M. Lansinger and Robert C. Ronald titration method for organolithium reagents using 2,3-dimethoxybenzyl alcohol.[194]

Mass spectra and elementary analysis were carried out by the Analytical Service of the University of Strasbourg or by a Hewlett Packard GC/MS 6890-5973 with an EI source from "Giacomo Mauriello" laboratory of University of Basilicata.

5.2-General Procedures

5.2.1-Suzuki-Miyaura cross-coipling reaction

Method 1

To a solution of the starting iodinated product (1 equiv.) in DMF/H_2O (4:1, 5 mL/mmol) under an inert atmosphere, boronic acid (1.4 equiv.), $NaHCO_3$ (1.4 equiv.), and $PdCl_2(PPh_3)_2$ (0.05 equiv.) were added. The solution was stirred for 10 minutes at room temperature and then heated to 80°C for 7 hours. After cooling, the solution was diluted with AcOEt and washed with a saturated solution of NH_4Cl, brine, and water. The organic phases were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography on silica gel using a mobile phase consisting of a mixture of petroleum ether and ethyl acetate (PE/EtOAc 7:3).

Method 2

To a suspension of $Pd(PPh_3)_4$ in dry and degassed DME, the starting iodinated product (1 equiv.) was added, and the solution was left stirring for 10 minutes at room temperature. Then, boronic acid (1.2 equiv.) in ethanol and Na_2CO_3 were added, and the solution was heated to reflux for 18 hours, then cooled and filtered. After cooling, the solution was diluted with DCM and washed with a saturated solution of NH_4Cl, brine, and water. The organic phases were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography on silica gel using a mixture of petroleum ether and ethyl acetate (PE/EtOAc 7:3) as the eluent.

Method 3

To a solution of the starting iodinated product (1 equiv.) in dry dioxane (4 mL/mmol) under inert atmosphere, 1.2 equiv. of boronic acid, 2 equiv. of Cs_2CO_3 (in a 1 mmol/1 mL aqueous solution), and 0.1 equiv. of 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride (Pd $(ddpf)_2Cl_2$) catalyst were added. The solution, under agitation and inert atmosphere, was heated to 100°C. After cooling, the solution was diluted with DCM and washed with a saturated solution of NH_4Cl, brine, and water. The organic phases were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography on silica gel using a petroleum ether and ethyl acetate (PE/EtOAc 7:3) as the eluent.

Method 4

To a solution of the starting iodinated product (1 equiv.) in DMF/H_2O (4:1, 5 mL/mmol), boronic acid (1.4 equiv.), KF (4.5 equiv.), and Pd $(PPh_3)_2Cl2$ (0.05 equiv.) were added. The solution was stirred for 10 minutes at room temperature, under an inert atmosphere, and then heated to 80°C for 7 hours. After cooling, the solution was diluted with AcOEt and washed with a saturated solution of NH_4Cl, brine, and water. The organic phases were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography on silica gel using petroleum ether and ethyl acetate (PE/EtOAc 7:3) as the eluent.

5.2.2-General procedure for benzylation

Method 1

In a solution of phenol (1 equiv.) in acetone (0.25 M) was added K_2CO_3 (2 equiv.) after stirring 10 min., benzyl bromide (1.2 equiv.) and NaI or TBAI (0.07 equiv.) were added. The reaction was stirred at reflux until complete transformation of starting phenol. The reaction was quenched with H_2O and extracted with EtOAc (3x50 mL/mmol). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude reaction was purified by chromatography on silica gel.

Method 2

In a solution of phenol (1equiv.) in anhydrous DMF (0.25M) was added NaH 60% dispersion in mineral oil (2.5 equiv.) at 0°C. The mixture was stirred for almost 10min after which benzyl bromide (1.2equiv.) and NaI (0.07 equiv.) were added. The reaction was stirred at room temperature until complete benzylation of starting phenol and/or alcohol. The reaction was quenched at 0°C adding slowly a saturated solution of NH_4Cl (25mL/mmol). The aqueous phase was extracted with EtOAc (3x30 mL/mmol). The combined organic extracts were washed with brine (3x30 mL/mmol) and with water (3x40 mL/mmol). The resulting organic layers were dried over Na_2SO_4, filtered and concentrated under *vacuum*. The crude reaction was purified by silica gel chromatography to remove excess of DMF and benzylbromide.

Method 3

In a solution of phenol (1equiv.) in ACN (0.25 M) was added K_2CO_3 (2equiv.) after stirring 10 min., benzyl bromide (1.2 equiv.) was added. The reaction was stirred at 55°C until complete transformation of starting phenol. The reaction was quenched with H_2O and extracted with EtOAc (3x50 mL/mmol). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude reaction was purified by chromatography on silica gel.

5.2.3-General demethylation procedure

Method 1

To a solution of the substrate (1.0 equiv.) in DCM (5 mL), $AlCl_3$ (1.5 equiv.) was added in a single portion at -5°C. After stirring the solution for 5 minutes at the same temperature, the reaction mixture was allowed to stir at 25°C for the necessary time. The reaction mixture was then treated with cold water and extracted with DCM. The combined organic phases were washed with a saturated solution of $NaHCO_3$ and brine, and finally dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the product was purified by column chromatography on silica gel using petroleum ether and ethyl acetate (PE/EtOAc 7:3) as the eluent.

Method 2

To a solution of the substrate (1.0 equiv.) in dry DCM (5 mL), $AlCl_3$ (6 equiv.) was added gradually at 0°C. The solution was left stirring at 15°C. The reaction mixture was then treated with cold water and extracted with DCM. The combined organic phases were washed with a saturated solution of $NaHCO_3$ and brine, and finally dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the product was purified by column chromatography on silica gel using petroleum ether and ethyl acetate (PE/EtOAc 7:3) as the eluent.

Method 3

To a solution of the substrate (1.0 equiv.) in dry DCM and ACN (1:1, 1 mL/mmol), one-pot $AlCl_3$ (1.5 equiv.) and NaI (1.5 equiv.) were added at 0°C. The solution was left stirring at room temperature. The

reaction mixture was then treated with cold water and extracted with DCM. The combined organic phases were washed with a saturated solution of $NaHCO_3$ and brine, and finally dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the product was purified by column chromatography on silica gel using a mixture of petroleum ether and ethyl acetate (PE/EtOAc 7:3) as the eluent.

5.2.4-General procedure for iodination

Method 1

Starting aromatic compound (1equiv.uiv.), I_2 (1equiv.) and Ag_2SO_4 (1equiv.) were dissolved in DCM (0.25 M) and stirred at room temperature until completed halogenation. The solution is filtered, washed with saturated aqueous solution of $Na_2S_2O_3$ (2x10mL/mmol), H_2O (2x10 mL/mmol) and brine (2x10 mL/mmol), dried over Na_2SO_4 and concentrated under reduced pressure to give the final product that could be used without any further purification if the reaction was quantitative.

Method 2

To a solution of starting aryl substrate (1equiv.) in ACN (0.25M) and TFA (0.3equiv.) was added NIS (1.1 equiv.). The mixture was stirred at room temperature and followed by TLC, GC-MS or NMR. When the starting material appeared completely reacted the mixture was quenched with water. Extraction of aqueous layers was done with EtOAc (3x30mL/mmol) and the combined organic extracts were washed with a saturated aqueous solution of $Na_2S_2O_3$, dried over Na_2SO_4 and filtered. Concentration of organic phase under reduced pressure gave the crude product that was purified by silica gel chromatography or, if pure, used withoutpurification.

5.2.5-General procedure for the synthesis of aryl pinacol boronate

To a solution of the starting substrate (1 equiv.) in anhydrous DMSO (1 mL/mmol), 2 equiv. of bis(pinacolate)diboron and 3 equiv. of KOAc were added. The solution was degassed with argon for 10 minutes, and 0.1 equiv. of the complex $Pd(dppf)Cl_2$ in DCM was added. The resulting suspension was heated to 80°C under agitation and in an inert atmosphere. The solution was then brought to room temperature and quenched with water. The solution was extracted with ethyl acetate (3 x 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and after filtration, the solvent was

evaporated under reduced pressure. The product was purified by column chromatography on silica gel using petroleum ether and ethyl acetate (PE/EtOAc 7:3) as the eluent.

5.2.7-General procedure for bromination

To a solution of starting aryl substrate (1equiv.) in ACN (0.25M) and TFA (0.3equiv.) was added NBS (1.1 equiv.). The mixture was stirred at room temperature and followed by TLC, GC-MS or NMR. When the starting material was completely reacted the mixture was quenched with water. Extraction of aqueous layers was done with EtOAc (3x30 mL/mmol) and the combined organic extracts were dried over Na_2SO_4 and filtered. Concentration of organic phase under reduced pressure gave the crude product that was purified by silica gel chromatography.

5.2.8-General procedure for Rieche formylation

Method 1:

A suspension of substrate (1.00 mmol, 1 equiv..) and AgOTf (1.00 mmol, 1 equiv..,) in dry DCM (4mL/mmol) was stirred at 0 °C under argon atmosphere, after 10 min Cl_2CHOCH_3 (1.00 mmol, 1 equiv..) was added dropwise, after being stirred at room temperature for 24h the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The reaction mixture was filtered through a pad of Celite. The organic layer was separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine and dried with Na_2SO_4. The crude was concentrated *in vacuo* and purified by flash column chromatography on silica gel (hexane:EtOAc 8:2 or DCM: MeOH 9:1) to afford the benzaldehyde

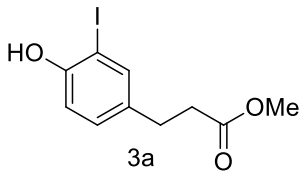
Method 2

A suspension of substrate (1.00 mmol, 1 equiv..) and $AlCl_3$ (1.2 mmol, 1.2 equiv..) in dry DCM (4mL/mmol) was stirred at 0 °C under argon atmosphere, after 10 min Cl_2CHOCH_3 (1.00 mmol, 1 equiv..) was added dropwise, after being stirred at room temperature for 24h the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The reaction mixture was filtered through a pad of Celite. The organic layer was separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine and dried with Na_2SO_4. The crude was concentrated *in vacuo* and purified by flash column chromatography on silica gel (hexane:EtOAc 8:2 or DCM: MeOH 9:1) to afford the benzaldehyde

Method 3.

To a solution of substrate (1.0 mmol, 1 equiv..) in DCM (4mL/mmol), $FeCl_3$ (1.0 mmol, 1.2 equiv..) was added, after stirring for 10 min at 0°C and under argon atmosphere, Cl_2CHOCH_3 (1.0 mmol, 1 equiv.) was dropwise added, after 24h stirred at room temperature the reaction mixture was quenched with HCl 10%. The organic layer was separated, and the aqueous layer was extracted twice with DCM. The combined organic layers were washed with $NaHCO_3$ and brine, dried with Na_2SO_4, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (hexane:EtOAc 8:2 or DCM: MeOH 9:1) to afford the desired benzaldehyde.

Methyl 3-(4-hydroxy-3-iodophenyl)propanoate (3a)



3a

Chemical Formula: $C_{17}H_{17}IO_3$
Molecular Weight: 396,22

Methyl 3-(4-hydroxyphenyl)propanoate **7** (1equiv., 13.89mmol, 2,50g), I_2 (1equiv., 13.89 mmol, 3.53g) and Ag_2SO_4 (1equiv., 13.89 mmol, 4.33g) were used following the general procedure for iodination to prepare iodinated derivative **3a**. The product was obtained as a white solid.

Time = 6h

Yield= (8.78 mmol, 2.72 g) 65%

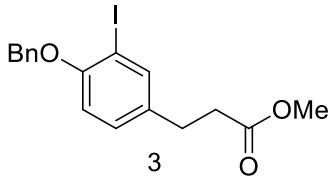
M.p. = 88-90°C

R*f* = 0.6 (PE/EtOAc = 5:5)

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.60 (t, 2H, *J* = 9Hz, C*H*$_2$); 2.87 (t, 2H, *J* = 7.8Hz, C*H*$_2$); 3.69 (s, 3H, OC*H*$_3$); 5.25 (s, 1H, O*H*); 6.91 (d, 2H, *J* = 8.5Hz, Ar-*H*); 7.09 (dd, 2H, *J'* = 8.5Hz, *J''* = 2.5Hz, Ar-*H*); 7.51 (d, 1H, *J* = 2.5Hz, Ar-*H*).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.10 (Ar-*C*H_2); 36.00 (*C*H_2); 51.66 (O*C*H_3); 89.59 (q, *C*-I); 115.31 (*C*H-Ar); 130.16 (*C*H-Ar); 134.70 (q, *C*-alkyl); 133.77 (q, C-Ar); 153.35 (q, *C*-OH); 173.10 (q, *C*=O).

Methyl 3-(4-(benzyloxy)-3-iodophenyl)propanoate (3)



Chemical Formula: $C_{17}H_{17}IO_3$
Molecular Weight: 396,22

Product **3** was obtained from two different synthetic route:

Procedure 1:

From the iodination of methyl ester **7** (1equiv, 3.27 mmol, 1g) following the general procedure (Method 1). The product was obtained as a white solid in **78% yield** (1.0 g);

Procedure 2:

From the benzylation of phenol **3a** (1equiv., 3.27 mmol, 1g) following the general procedure for benzylation Method 3. **99% yield** (1.29 g);

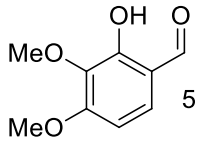
M.p. = 67-70°C

R*f* = 0.5 (PE/EtOAc = 6:5)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.59 (t, 2H, *J* = 7.8Hz, C*H2*); 2.86 (t, 2H, *J* = 7.8Hz, C*H2*); 3.68 (s, 3H, OC*H*3); 5.13 (s, 2H, C*H*2-Bn); 6.78 (d, 2H, *J* = 8.5Hz, Ar-*H*); 7.11 (dd, 2H, *J'* = 8.5Hz, *J''* = 2.0 Hz, Ar-*H*); 7.38 (m, 5H, C*H*-Bn); 7.65 (dd, 1H, *J* = 2.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.55 (Ar-*C*H_2); 35.62 (Ar-*C*H_2); 51.64 (O*C*H_3); 76.59 (C*H*$_2$-Bn); 86.81 (q, *C*-I); 112.71 (*C*H-Ar); 127.00 (C*H*-Bn); 127.85 (C*H*-Bn); 128.54 (C*H*-Bn); 129.24 (*C*H-Ar); 135.11 (q, *C*-Ar); 136.60 (q, C-Ar); 139.24 (q, *C*-Bn); 155.82 (q, *C*-OBn); 173.08 (q, *C*=O).

2-Hydroxy-3,4-dimethoxybenzaldehyde (5)



Chemical Formula: $C_9H_{10}O_4$
Exact Mass: 182,06

The compound **5** was obtained from 1,2,3-trimethoxybenzaldehyde (120mg) by using the general procedure for demethylation **method 1**

The compound **5** was obtained from 1,2,3-trimethoxybenzaldehyde (240mg) by using the general procedure for demethylation **method 2**

The compound **5** was obtained from 1,2,3-trimethoxybenzaldehyde (10 g) by using the general procedure for demethylation **method 3**

Time = 6h **method 1**

4h **method 2**

6h **method 3**

Conversion= 63% **method 1**

100% **method 2 e method 3**

Yield = (15.2 mg) 13.8% **method 1**

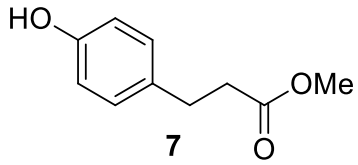
(0.176 mg) 80 % **method 2**

(9.04 g) 99% **method 3**

***R*f** = 0.6 (EP/EtOAc = 8:2)
^{1}H NMR (400 MHz, CDCl3) δ_H = 3.91 (s, 3H, CH_3-O), 3.96 (s, 3H, CH_3-O), 6.61 (d, 1H, *J*=8.4Hz, H-Ar), 7.29 (m, 1H, Ar-H), 9.75 (s, 1H, HCO), 11.20 (s, 1H, OH).

^{13}C NMR (100 MHz, CDCl3), δ: 56.09 (O*C*H3); 60.10 (O*C*H3); 103.95 (*C*H-Ar); 116.45 (q, *C*-CHO); 130.24 (*C*H-Ar); 136.04 (q, *C*-OCH3); 154.34 (q, *C*-OH); 159.33 (q, *C*-OCH3); 194.91 (*C*HO).

Methyl 3-(4-hydroxyphenyl)propanoate (7)



7

Chemical Formula: $C_{10}H_{12}O_3$
Exact Mass: 180,08

Concentrated H_2SO_4 (8,3mL) was added to a suspension of commercially available 3-(4-hydroxyphenyl)propanoic acid (1equiv., 60,24mmol, 10g) in methanol (43mL) and the solution was refluxed for 1h. After cooling to room temperature, an aqueous solution of NaOH 10% (50mL) was added to neutralize the solution. The resulting mixture was allowed to stand for 15 min, before being poured into a cool beaker, and made up to 1.5L with water. The aqueous phase was extracted with AcOEt (3x150mL) and the organic layer was washed with brine, dried over Na2SO4 and concentrated under reduced pressure to give a white solid. in 95% yield (57,5 mmol, 10,39g).

Time = 1h

Yield = (57,5 mmol, 10,39g) 95%

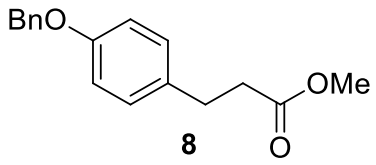
M.p.= 42-45°C

Rf = 0.5 (EP/Et2O = 5:5)

^{1}H NMR (400 MHz, CDCl3) δ 2.61 (t, 2H, *J* = 7.8Hz, C*H2*); 2.90 (t, 2H, *J* = 7.8Hz, C*H2*); 3.67 (s, 3H, OC*H*3); 4.74 (s, 1H, O*H*); 6.76 (d, 2H, *J* = 8.5Hz, Ar-*H*); 7.07 (d, 2H, *J* = 8.5Hz, Ar-*H*).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 30.10 (Ar-*C*H_2); 36.00 (*C*H_2); 51.66 (O*C*H_3); 89.59 (q, *C*-I); 115.31 (*C*H-Ar); 130.16 (*C*H-Ar); 134.70 (q, *C*-alkyl); 133.77 (q, C-Ar); 153.35 (q, *C*-OH); 173.10 (q, *C*=O).

Methyl 3-(4-(benzyloxy)phenyl)propanoate (8)



8

Chemical Formula: $C_{17}H_{18}O_3$
Exact Mass: 270,13

Ester **8** was obtained following the general procedure for benzylation-**method 3**. (1equiv., 55,4mmol, 10g) of methyl 3-(4-hydroxyphenyl)propanoate **7** were used. The crude was purified by trituration in pentane that allowed to obtain the pure product as a withe solid.

Time = 4h

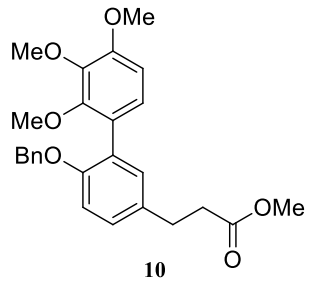
Yield = (55,2mmol, 14,9g) 99%

Rf = 0.5 (EP/Et2O = 6:5)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (t, 2H, *J* = 7.8Hz, CH_2); 2.90 (t, 2H, *J* = 7.8Hz, CH_2); 3.68 (s, 3H,OCH_3); 5.04 (s, 2H, CH_2-Bn); 6.92 (d, 2H, *J* = 8.5Hz, Ar-*H*); 7.13 (d, 2H, *J* = 8.5Hz, Ar-*H*); 7.48 – 7.29 (m, 5H, C*H*-Bn).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.07 (Ar-*C*H_2); 35.91 (*C*H_2); 51.51(O*C*H_3); 70.00 (CH_2-Bn); 114.85 (*C*H-Ar); 127.38 (C*H*-Bn); 127.84 (C*H*-Bn); 128.50 (C*H*-Bn); 129.19 (*C*H-Ar); 132.84 (q, *C*-alkyl); 137.10 (q,*C*-Bn); 157.29 (q, *C*-OBn); 173.32 (q, *C*O).

Methyl 3-(6-(benzyloxy)-2',3',4'-trimethoxy-[1,1'-biphenyl]-3-yl)propanoate (10)



10

Chemical Formula: $C_{26}H_{28}O_6$

Exact Mass: 436,19

Compound **10** was obtained by using the general procedure for Suzuki-Miyaura cross-coupling method 1:

100 mg of **3** and 74.2 mg of 2,3,4-Trimethoxyphenylboronic acid were used.

Compound **10** was obtained by using the general procedure for Suzuki-Miyaura cross-coupling method 2:

251 mg of **3** and 161.33 mg of 2,3,4-Trimethoxyphenylboronic acid were used.

Time : 22h **method 1**

27h **method 2**

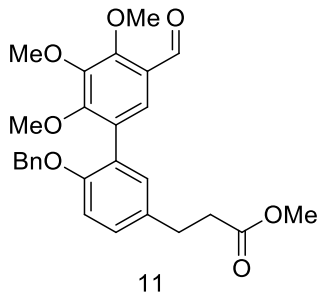
Yield: (101.8 mg), 93% **method 1**

(122.1 mg), 44% **method 2**

^{1}H NMR (400 MHz, CDCl3) δ_H= 2.63 (t, 2H, *J*=8.0, C*H*$_2$), 2.91 (t, 2H, *J*=8.0, C*H*$_2$), 3.66 (s, 3H, C*H*$_3$-O) 3.89 (s, 9H, C*H*$_3$-O-Ar), 5.03 (s, 2H, C*H*$_2$-Ar), 6.71 (d, 1H, *J*=8.4Hz, Ar-*H*), 6.93 (d, 1H, *J*=8.4Hz, Ar-*H*), 6.97 (d, 1H, *J*=8.8 Hz, Ar-*H*), 7.1 (m, 2H, Ar-*H*), 7.27 (m, 5H, Ar-*H*).

^{13}C NMR (100 MHz, CDCl3) δ_C= 30.14 (*C*H_2), 35.95 (*C*H_2), 51.54 (O-*C*H_3), 56.01 (*C*H_2-Ar), 60.41 (Ar-O-*C*H_3), 60.87 (Ar-O-*C*H_3), 60.90 (Ar-O-*C*H_3), 106.74 (*C*-Ar), 113.11 (*C*-Ar), 125.50 (*C*-Ar), 125.57 (*C*-Ar), 126.83 (*C*-Ar), 127.45 (*C*-Ar), 128.11 (*C*-Ar), 128.29 (*C*-Ar), 131.44 (*C*-Ar), 132.66 (*C*-Ar), 137.53 (*C*-Ar), 142.01 (*C*-Ar), 151.87 (*C*-Ar), 153.04 (q, *C*-Ar), 154.72 (q, *C*-Ar), 173.46 (q, *C*=O).

Methyl 3-(6-(benzyloxy)-5'-formyl-2',3',4'-trimethoxy-[1,1'-biphenyl]-3-yl)propanoate (11)



11

Chemical Formula: $C_{27}H_{28}O_7$
Exact Mass: 464,18

Method 1:

To a suspension of the starting material **10** (33.1 mg, 1 equiv) and AgOTf (58.45 mg, 3 equiv) in dry DCM (2 mL) at -78°C, a solution of dichloromethyl methyl ether (20.5 µL, 26.08 mg, 3 equiv) in dry DCM (1 mL) was added dropwise under inert atmosphere and left stirring for 30 minutes at -78°C. The solution was then brought to 0°C and stirred for an additional 15 minutes. The reaction was quenched with a saturated solution of sodium bicarbonate and extracted with EtOAc (3 x 10 mL). The organic phases were washed with brine, dried, and concentrated under reduced pressure. The product was purified by column chromatography on silica gel using as eluent a mixture of petroleum ether and ethyl acetate (7:3).

Method 2:

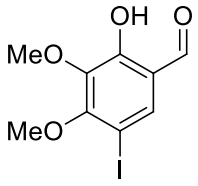
The starting material **10** (1 equiv) in dry DCM (5 mL/mmol) under inert atmosphere at 0°C was treated with AgOTf (3 equiv). A solution of dichloromethyl methyl ether (3 equiv) in dry DCM (1 mL) was added dropwise, and the mixture was left stirring for 2 hours at 0°C. The solution was then raised to 10°C and stirred for 1 hour. The reaction was quenched with a saturated solution of sodium bicarbonate and extracted with EtOAc (3 x 10 mL). The organic phases were washed with brine, dried, and concentrated under reduced pressure. The product was purified by column chromatography using as eluent a mixture of petroleum ether and ethyl acetate (7:3).

Time = 45 minutes (Method 1) 3 hours (Method 2)

Yield = 4.8% (Method 1); 8% (Method 2)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H= 2.58 (t, 2H, *J*=8.0, C*H*$_2$), 2.89 (t, 2H, *J*=8.0, C*H*$_2$), 3.58 (s, 3H, C*H*$_3$-O) 3.85 (s, 9H, C*H*$_3$-O-Ar), 5.03 (s, 2H, C*H*$_2$-Ar), 7.42 (s, 1H, Ar-*H*), 7.44 (s, 1H, Ar-*H*), 7.0 (m, 2H, Ar-*H*), 7.26 (m, 5H, Ar-*H*), 10.25 (s, 1H, *H*CO).

2-Hydroxy-5-iodo-3,4-dimethoxybenzaldehyde (12)



12

Chemical Formula: $C_9H_9IO_4$
Exact Mass: 307,95

Compound **12** was obtained from compound **5** (70 mg) by using the general procedure for Iodination method 1:

Compound **12** was obtained from compound **5** (1 g) by using the general procedure for Iodination method 2:

method 1:

Time= 18 h

Conversion= 77%

Yield= (32.6mg) 28%

method 2:

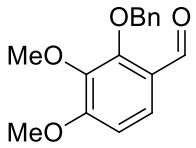
Time= 24 h

Yield= (0.92 g) 55%

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 3.94 (s, 3H,C*H*$_3$-O), 4.05 (s, 3H, C*H*$_3$-O), 7.72 (s, 1H, Ar-H), 9.75 (bs, 1H, O-*H*),11.24 (s, 1H, C*H*O).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C= 61.19 (O*C*H$_3$), 61.42 (O*C*H$_3$), 79.35 (*C*-Ar), 119.74 (*C*-Ar), 137.85 (q, *C*-I), 140.50 (q,*C*-Ar), 157.36 (q,*C*-Ar), 158.85 (q,*C*-Ar), 194.46 (q, C=O).

2-(benzyloxy)-3,4-dimethoxybenzaldehyde (12')



12'

Chemical Formula: $C_{16}H_{16}O_4$
Exact Mass: 272,10

The product was obtained from aldehyde **5** (0.50g, 2.74mmol) following the general procedure for benzylation Method 3. Purification by silica gel chromatography afforded the pure product as a transparent oil.

Time = 5h

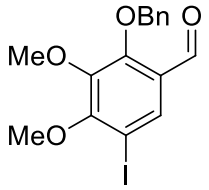
Yield = (0.73g, 2.71mmol) 99%.

***R*f** = 0.5 (EP/EtOAc = 7:3)

^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.91 (s, 3H-OC*H*$_3$); 3.95 (s, 3H-OC*H*$_3$); 5.22 (s, 2H, CH_2-Bn); 6.76 (d, 1H, *J*=8.80Hz, Ar-*H*); 7.37 (m, *5*H, Bn); 7.59 (d, 1H, *J*=8.80, Ar-*H*); 10.09 (s, 1H, C*H*O).

^{13}C NMR (100 MHz, $CDCl_3$), δ: 58.15 (O*C*H$_3$); 60.97 (O*C*H$_3$); 75.91 (*C*H$_2$-Bn); 103.95 (*C*H-Ar); 123.26 (*C*H-Ar); 127.80 (*C*H-Bn); 127.93 (*C*H-Bn); 128.12 (*C*H-Bn); 149.01 (q, *C*-CHO); 140.89 (q, *C*-OCH$_3$);155.43 (q, *C*-OH); 157.35 (q, *C*-OCH$_3$); 190.21 (q, *C*HO).

2-(Benzyloxy)-5-iodo-3,4-dimethoxybenzaldehyde (13)



13

Chemical Formula: $C_{16}H_{15}IO_4$
Exact Mass: 398,00

Compound **13** was obtained from compound **12** (1.0 g) by using the general procedure for benzylation method 3

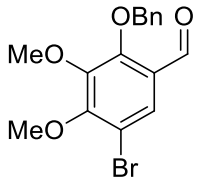
Time : 6h

Yield = (1.29g) quantitative

^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.94 (s, 3H-OC*H*$_3$); 4.01 (s, 3H-OC*H*$_3$); 5.22 (s, 2H, C*H*$_2$-Bn);; 7.37 (m, *5*H, Bn); 7.98 (s, 1H, *J*=8.80, Ar-*H*); 10.03 (s, 1H, C*H*O).

^{13}C NMR (100 MHz, $CDCl_3$), δ: 61.27 (O*C*H$_3$); 61.42 (O*C*H$_3$); 76.97 (*C*H$_2$-Bn); 86.36 (*C*-I); 127.67 (*C*H-Bn); 128.77 (*C*H-Bn); 128.92 (*C*H-Bn); 128.95 (*C*H-Bn), 132.65 (*C*H-Bn); 136.05 (q, *C*H-Bn); 146.35 (q, *C*-OCH$_3$); 156.53 (q, *C*-OBn); 159.03 (q, *C*-OCH$_3$); 187.85 (q, *C*HO).

2-(Benzyloxy)-5-bromo-3,4-dimethoxybenzaldehyde (13')



13'

Chemical Formula: $C_{16}H_{15}BrO_4$
Exact Mass: 350,02

The product **13'** was obtained from benzylated aldehyde **12'** (0.20g, 0.73mmol) following the general procedure for bromination or from benzylation of phenol **13''** (2g, 7.6 mmol) following the general procedure for benzylation 3. Purification by silica gel chromatography afforded the pure product as a transparent oil.

Time = 18h from **12'**,

6h from **13'**

Yield = (0.22g, 0.65 mmol) 90% from **12'**,

(2.6 g, 7.52mmol) 99% from **13''**

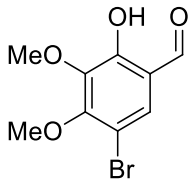
Rf = 0.5 (EP/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.98 (s, 3H-OC*H*$_3$); 4.04 (s, 3H-OC*H*$_3$); 5.25 (s, 2H, CH_2-Bn); 7.40 (m, *5*H, Bn); 7.76 (s, 1H, Ar-*H*); 10.05 (s, 1H, C*H*O).

^{13}C NMR (100 MHz, $CDCl_3$), δ: 61.30 (O*C*H$_3$); 61.39 (O*C*H$_3$); 76.71 (*C*H$_2$-Bn); 112.82 (q, *C*-Br); 126.45 (*C*H-Ar); 126.65 (*C*H-Bn); 128.67 (*C*H-Bn); 128.78 (*C*H-Bn); 135.84 (*C*H-Ar); 147.24 (q, *C*-OCH$_3$); 155.36 (q, *C*-OH); 156.63 (q, *C*-OCH$_3$); 187.85 (*C*HO).

EIMS *m/z* 350 $[M]^+$(2), 260 (30), 91(100)

5-Bromo-2-hydroxy-3,4-dimethoxybenzaldehyde (13'')



13"

Chemical Formula: $C_9H_9BrO_4$
Exact Mass: 259,97

The product **13''** was obtained from phenol **5** (2g, 1.09mmol) following the general procedure for bromination stirring the mixture for 20h. Purification by silica gel chromatography afforded the pure product as a yellow solid.

Time = 20h

Yield = (2.6g, 1.01 mmol) 93%

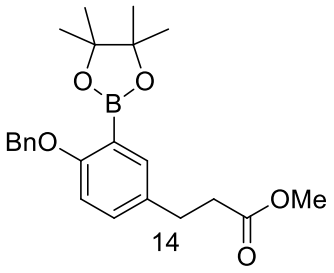
Mp = 59-60°C

***R*f** = 0.6 (EP/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.93 (s, 3H-OC*H*$_3$); 4.05 (s, 3H-OC*H*$_3$); 5.20 (s, 2H, C*H*$_2$-Bn); 7.50 (s, 1H, Ar-*H*); 9.75 (s, 1H, C*H*O); 11.24 (s, 1H, O*H*).

^{13}C NMR (100 MHz, $CDCl_3$), δ: 61.12 (O*C*H$_3$); 61.37 (O*C*H$_3$); 106.83 (q, *C*-Br); 118.12 (q, *C*-CHO); 131.47 (*C*H-Ar); 141.30 (q, *C*-OCH$_3$); 156.22 (q, *C*-OH); 156.67 (q, *C*-OCH$_3$); 194.50 (*C*HO).

Methyl 3-(4-(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (14)



Chemical Formula: $C_{23}H_{29}BO_5$
Exact Mass: 396,21

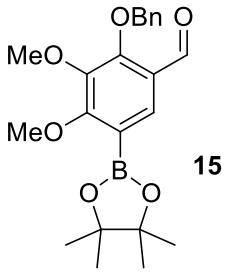
Compound **14** was obtained from compound **3** (0.34 mmol, 137 mg) by using the General procedure for the synthesis of aryl pinacol boronate.

Time= 6 h

Yield = (0.15mmol, 58.1 mg) 42%

^{1}H NMR (400 MHz, $CDCl_3$) δ_H= 1.36 (s, 12H, C*H*$_3$), 2.60 (m, 2H, C*H*$_2$), 2.89 (m, 2H, C*H*$_2$), 3.66 (s, 3H, O-C*H*$_3$), 5.09 (s, 2H, Ar-C*H*$_2$), 6.85 (d, 1H, *J*=8.4 Hz, Ar-*H*), 7.22 (dd, 1H, *J'*=8.4 Hz, *J''*=2.5 Hz, Ar-*H*), 7.28-7.38 (m, 4H, Ar-*H*), 7.51 (d, 1H, *J*=2.0 Hz), 7.58 (m, 1H, Ar-*H*) 7.60 (d, 1H, *J*=7.3 Hz, Ar-*H*).

2-(Benzyloxy)-3,4-dimethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (15)



15

Chemical Formula: $C_{22}H_{27}BO_6$
Exact Mass: 398,19

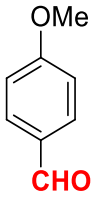
Compound **15** was obtained from compound **13** (0.057 mmol, 20 mg) by using the General procedure for the synthesis of aryl pinacol boronate.

Time= 6 h

Yield = (9.6mg) 44%

^{1}H NMR (400 MHz, $CDCl_3$) δ_H =0.06 (s, 12H, C*H*$_3$), 3.84 (s, 3H,C*H*$_3$-O), 3.96 (s, 3H, C*H*$_3$-O), 7.25 (s, 1H, Ar-*H*), 7.36-7.46 (m, 5H, Ar-*H*).

4-Methoxybenzaldehyde (17a)



17a

Chemical Formula: $C_8H_8O_2$
Exact Mass: 136,05

The compound was obtained from 50mg of the commercially available 4-methoxyphenyllboronic acid **4a** by using **General procedure for Rieche formylation <u>method 1</u>, <u>2</u> or <u>3</u>.**

Yield= 75% method 1

100% method 2

92% method 3

The compound was also obtained from 50mg of the commercially available 2-methoxyphenyllboronic acid **4c** by using **General procedure for Rieche formylation <u>method 1</u>, <u>2</u> or <u>3</u>.**

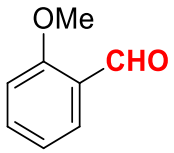
Yield= 21% method 1

13% method 2

48% method 3

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 3H, OC*H*$_3$), 7.01 (d,1H, *J*=8.0 Hz, Ar–*H*), 7.84 (d, 1H, *J*=8.0 Hz, Ar-*H*), 9.89 (s, C*H*O).

2-Methoxybenzaldehyde (17a')



17a'

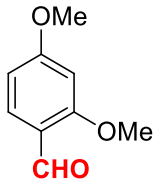
Chemical Formula: $C_8H_8O_2$
Exact Mass: 136,05

The compound was obtained from 50mg of the commercially available 4-methoxyphenyllboronic acid **4a** by using **General procedure for Rieche formylation <u>method 1</u>.**

Yield= 25%

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.93 (s, 3H, OC*H*$_3$), 6.98-7.05 (m,2H, Ar–*H*), 7.55 (t, 1H, *J*=8.0 Hz, Ar-*H*),), 7.83 (d, 1H, *J*=8.0 Hz, Ar-*H*) 10.48 (s, C*H*O).

2,4-dimethoxybenzaldehyde (17d)



17d

Chemical Formula: $C_9H_{10}O_3$
Exact Mass: 166,06

The compound was obtained from 50mg of the commercially available 2,4-di-methoxyphenyllboronic acid **4d** by using **General procedure for Rieche formylation <u>method 1</u>, <u>2</u> or <u>3</u>.**

Yield= 99% method 1

25% method 2

98% method 3

The compound was also obtained from 50mg of the commercially available 2,6-di-methoxyphenyllboronic acid **4f** by using **General procedure for Rieche formylation <u>method 1</u>, <u>2</u> or <u>3</u>.**

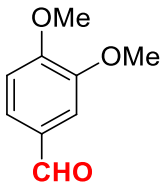
Yield= 85% method 1

59% method 2

60% method 3

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.93 (s, 3H, OC*H*$_3$), 6.45 (s,1H, Ar–*H*), 6.56 (d, 1H, *J*=8.0 Hz, Ar-*H*), 7.82 (d, 1H, *J*=8.0 Hz, Ar-*H*) 10.29 (s, C*H*O).

3,4-dimethoxybenzaldehyde (17e)



17e

Chemical Formula: $C_9H_{10}O_3$
Exact Mass: 166,06

The compound was obtained from 50mg of the commercially available 3,4-di-methoxyphenyllboronic acid **4e** by using **General procedure for Rieche formylation <u>method 1</u>, <u>2</u> or <u>3</u>.**

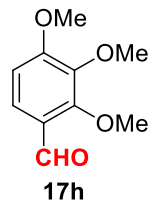
Yield= 87% method 1

88% method 2

85% method 3

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.95 (s, 3H, OC*H*$_3$), 3.98 (s, 3H, OC*H*$_3$), 6.99 (d,1H, *J*= 8.0 Hz, Ar–*H*), 7.41 (s, 1H, Ar-*H*), 7.47 (d, 1H, *J*=8.0 Hz, Ar-*H*) 9.85 (s, C*H*O).

2,3,4-trimethoxybenzaldehyde (17h)



17h

Chemical Formula: $C_{10}H_{12}O_4$
Exact Mass: 196,07

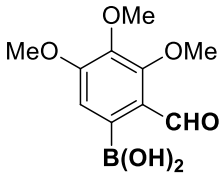
The compound was obtained from 50mg of the commercially available 2,3,4-trimethoxyphenyllboronic acid **4h** by using **General procedure for Rieche formylation <u>method 1</u> or <u>3</u>.**

Yield= 100% method 1

100% method 3

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 3H, OC*H*$_3$), 3.93 (s, 3H, OC*H*$_3$), 4.05 (s, 3H, OC*H*$_3$), 6.99 (d,1H, *J*= 8.0 Hz, Ar–*H*), 7.76 (d, 1H, *J*=8.0 Hz, Ar-*H*), 7.62 (d, 1H, *J*=8.0 Hz, Ar-*H*) 10.25 (s, C*H*O).

(2-formyl-3,4,5-trimethoxyphenyl)boronic acid (18g)



18g

Chemical Formula: $C_{10}H_{13}BO_6$
Exact Mass: 240,08

The compound was obtained from 50mg of the commercially available 3,4,5-trimethoxyphenyllboronic acid **4g** by using **General procedure for Rieche formylation <u>method 2</u> or <u>3</u>.**

Yield= 7% method 2

82% method 3

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.93 (s, 3H, OC*H*$_3$), 4.02 (s, 6H, OCH_3), 7.60 (s,1H, Ar–H), 10.30 (s, CHO),

^{13}C NMR (100 MHz, $CDCl_3$): δ 56.17, 60.90,61.63,116.71,126.61, 136.00, 143.25, 158.72, 160.18,

194.75.

benzo[b]thiophene-3-carbaldehyde (34)

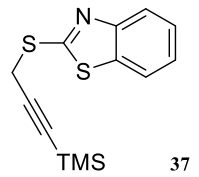
34

Chemical Formula: C_9H_6OS
Exact Mass: 162,01

The compound was obtained from 50mg of the commercially available benzo[b]thiophen-3-ylboronic acid by using **General procedure for Rieche formylation <u>method 3</u>.** 95% **yield.**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (t,1H, *J*= 8.0 Hz, Ar–*H*), 7.52 (t,1H, *J*= 8.0 Hz, Ar–*H*), 7.90 (d, 1H, *J*=8.0 Hz, Ar-*H*), 8.34 (s, 1H, Ar-*H*) 8.69 (d, 1H, *J*=8.0 Hz, Ar-*H*) 10.16 (s, C*H*O).

2-((3-(trimethylsilyl)prop-2-yn-1-yl)thio)benzo[d]thiazole (37)



37

Chemical Formula: $C_{13}H_{15}NS_2Si$
Exact Mass: 277,04

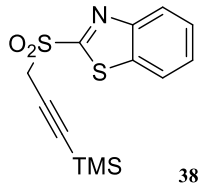
To a solution of 3-(trimethylsilyl)propargylic alcohol (1 equiv, 0.74 mmol, 95.15 mg) in DCM (13 mL), triphenylphosphine (1.3 equiv, 0.96 mmol, 252 mg), imidazole (3.0 equiv, 2.27 mmol, 155 mg), and I_2 (1.25 equiv, 235 mg, 0.93 mmol) were added. The temperature was raised to reflux. After 1 hour, complete conversion of the alcohol to the corresponding iodide was observed by TLC analysis. The solution was cooled to room temperature, and mercaptobenzothiazole (1.2 equiv, 0.94 mmol, 158.4 mg) was added. After 4 hours, complete conversion to the corresponding sulfide was observed. The solution was hydrolyzed with a saturated solution ofNH_4Cl, and the organic phase was washed with brine, dried, and concentrated under reduced pressure. The product was purified by column chromatography on silica gel.

Reaction time = 5 h

Yield = (193 mg) 94%

^{1}H NMR (400 MHz, $CDCl_3$) δ_H= 0.17 (s, 9H, C*H*$_3$), 4.17 (s, 2H, C*H*$_2$-S), 7.32 (dd, 1H, *J*= 7.6 Hz, *J*=8.0 Hz, Ar-*H*), 7.44 (dd, 1H, *J*=7.6 Hz, *J*=8.0 Hz, Ar-*H*), 7.79 (d, 1H, *J*=7.6 Hz, Ar-*H*), 7.91 (d, 1H, *J*=8.0 Hz, Ar-*H*).

2-((3-(trimethylsilyl)prop-2-yn-1-yl)sulfonyl)benzo[d]thiazole (38)



38

Chemical Formula: $C_{13}H_{15}NO_2S_2Si$
Exact Mass: 309,03

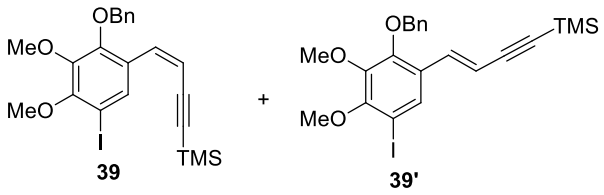
The compound **38** was prepared by dissolving sulfide **37** (1 equiv, 0.36 mmol, 99.5 mg) in DCM (9 mL). To the stirring solution, m-CPBA (1 equiv, 1.63 mmol, 281.11 mg), previously dissolved in 6 mL of DCM, was added. The solution was stirred for 6 hours. The solution was then washed with 2 M KI, a saturated solution of sodium thiosulfate, a saturated solution of $NaHCO_3$, and finally with H_2O. The solution was dehydrated using anhydrous Na_2SO_4, and the solvent was removed under reduced pressure.

Reaction time = 24 hours

Yield = (110.2 g) 98.4%

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 0.01 (s, 9H, C*H*$_3$), 4.39 (s, 2H, C*H*$_2$-S), 7.63 (m, 2H, Ar-*H*), 8.03 (d, 1H, *J*=7.2 Hz, Ar-*H*), 8.25 (d, 1H, *J*=8.0 Hz, Ar-*H*).

(Z)-(4-(2-(benzyloxy)-5-iodo-3,4-dimethoxyphenyl)but-3-en-1-yn-1-yl)trimethylsilane (39) and **(E)-(4-(2-(benzyloxy)-5-iodo-3,4-dimethoxyphenyl)but-3-en-1-yn-1-yl)trimethylsilane**



Chemical Formula: $C_{22}H_{25}IO_3Si$
Exact Mass: 492,06

<u>Method 1</u> (Barbier conditions):

To a stirred solution of sulfone **38** (1 equiv, 0.07 mmol) and aldehyde **13** (1.6 equiv, 0.08 mmol) in THF (2 mL) at –60 °C KHMDS 0.5 M in toluene (1.2 equiv, 0.12 ml) was dropwise added. The resultant yellow solution was stirred at –65 °C for 4 h and allowed to warm to r.t. for 1 h. The mixture was then diluted with Et_2O and washed with H_2O. The aqueous solution was extracted with Et_2O and the combined organic layers were washed with brine and dried over Na_2SO_4. filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel to afford the desired compound **39** and **39'**. The two stereoisomers were not separable by column chromatography **39**:**39'** = 65;35)

<u>Method 2:</u> (pre-metalation)

To a stirred solution of sulfone **38** (1 equiv, 0.07 mmol) in THF (2 mL) at –60 °C, KHMDS 0.5 M in toluene (1.2 equiv, 0.12 ml) was dropwise added. The resultant yellow solution was stirred at –55 °C for 10 minutes, aldehyde **13** (1.6 equiv, 0.08 mmol) was added as a solid. The resultant solution was stirred at –55 °C for 4 h and allowed to warm to r.t. for 1 h. The mixture was then diluted with Et_2O and washed with H_2O. The aqueous solution was extracted with Et_2O and the combined organic layers were washed with brine and dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel to afford the desired compound **39**. The two stereoisomers were not separable by column chromatography **39**:**39'** = 65:35)

Yield : 92% Method 2 (Pre-metalation)

Yield : 81% Method 1 (Barbier conditions)

***R*f** = 0.8 (EP/EtOAc = 9:1)

39

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.3 (s, 9H, Si-C*H*$_3$), 3.90 (s, 3H, O-*CH*$_3$), 3.93 (s, 3H, O-*CH*$_3$), 5.00 (s, 2H, Ar-*CH*$_2$), 5.69 (d, 1H, J_{cis}=12.0 Hz, *CH*-Styrenic), 6.82 (d, 1H, J_{cis}=12.0 Hz, *CH*-Styrenic), 6.34-7,47 (m, 5H, Ar-*H),* 8.77 (s,1H, Ar–*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 0.41 (Si-*C*H_3), 61.45 (O-*C*H_3), 76.30 (Ar-*C*H_2), 85.56 (*C*-I), 97.00 (q, *C alkyne*) , 103.48 (q, *C alkyne*), 108.10 (*C*H-Styrenic), 128.52 (*C*-Bn), 128.57 (*C*-Bn), 128.65 (q, *C*-Ar), 129.92 (*C*-Bn), 131.73 (*C*-Bn), 132.46 (*C*-Bn), 135.73 (CH-Styrenic), 137.16 (q, *C*-OCH_3), 146.62 (q, *C*-OCH_2Bn), 154.23 (q, *C*-OCH_3).

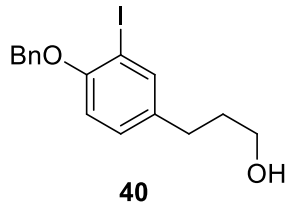
39'

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.21(s, 9H, Si-C*H*$_3$), 3.89 (s, 3H, O-*CH*$_3$), 3.90 (s, 3H, O-*CH*$_3$), 5.01 (s, 2H, Ar-*CH*$_2$), 6.08 (d, 1H, J_{trans}=16.0 Hz, *CH*-Styrenic), 7.07 (d, 1H, J_{trans}=16.0 Hz, *CH*-Styrenic), 6.34-7,47 (m, 5H, Ar-*H),* 7.57 (s,1H, Ar–*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 0.25 (Si-*C*H_3), 61.28 (O-*CH*$_3$), 76.15(Ar-*C*H_2), 86.30 (*C*-I), 103.60 (q, *C alkyne*) , 107.82 (q, *C alkyne*) 109.64 (*C*H-Styrenic), 128.52 (*C*-Bn), 128.57 (*C*-Bn), 128.94 (q, Ar-*C*), 129.92 (*C*-Bn), 131.73 (*C*-Bn), 132.46 (*C*-Bn), 135.73 (CH-Styrenic), 137.26 (q, *C*-OCH_3), 146.67 (q, *C*-OCH_2Bn), 154.23 (q, *C*-OCH_3).

HRMS (ESI+): *m/z* calcd for $C_{22}H_{26}IO_3Si$ $[M + H]^+$: 493.0690; found 493.0658

3-(4-(benzyloxy)-3-iodophenyl)propan-1-ol (40)



40

Chemical Formula: $C_{16}H_{17}IO_2$
Exact Mass: 368,03

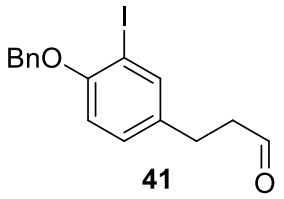
To a solution of the previously synthesized ester **3** (1 equiv, 2,52 mmol, 1.0 g,) in DCM (30mL) was added DIBAL-H (2 equiv., 5.03 mL, 1M in toluene,) dropwise at 0 °C. The mixture was stirred at 0 °C for 3 h before quenching with a saturated aqueous solution of diethyl tartrate sodium potassium (50 mL) at 0 °C. The temperature was allowed to warm to r.t and the mixture was stirred all night long. The phases were separated, the aqueous layer was extracted with DCM, combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to get alcohol **40**. The resulting residue was purified by column chromatography on silica gel to afford the desired compound **40.**

Yield= (2,5 mmol, 918mg) 99%

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81-1.88 (m, 2H, C*H*$_2$-CH_2OH), 2.62 (t, 2H, *J*=8.0 Hz, *CH*$_2$), 3.65 (t, 2H, *J*=8.0 Hz, *CH*$_2$OH), 5.13 (s, 2H, *CH*$_2$Bn), 6.78 (d, 1H, *J*=8.0 Hz, Ar–*H*), 7.10 (dd, 1H, , J^1=8.0 Hz, J^2=2.0 Hz, Ar–*H*), 7.28-7,52 (m, 5H, Ar-*H),* 7.57 (d,1H, J^2=2.0 Hz, Ar–*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 30.65 (*C*H_2), 34.20 (*C*H_2-CH_2OH), 62.04 (*C*H_2OH), 71.02 (*CH*$_2$Bn), 86.86 (*C*-I), 112.72 (Ar-*C)*, 127.02 (*C*-Bn), 128.55 (*C*-Bn), 129.32 (*C*-Bn), 136.46 (*C*-Bn), 136.69 (*C*-Bn), 155.53 (*C*-OBn).

3-(4-(benzyloxy)-3-iodophenyl)propanal (41)



41

Chemical Formula: $C_{16}H_{15}IO_2$
Exact Mass: 366,01

Method 1: To a solution of the previously synthesized ester **3** (1 equiv, 2,52 mmol, 1.0 g,) in DCM (30mL) was added DIBAL-H (2 equiv., 5.03 mL, 1M in toluene,) dropwise at -78 °C. The mixture was stirred at -78 °C for 3 h before quenching with a saturated aqueous solution of diethyl tartrate sodium potassium (50 mL) at - 78 °C. The temperature was allowed to warm to r.t and the mixture was stirred all night long. The phases were separated, the aqueous layer was extracted with DCM, combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to get aldehyde **41** in mixture with the corresponding alcohol **40**. The resulting residue was purified by column chromatography on silica gel to afford the desired compound **41.**

Method 2: To a solution of the previously synthesized Weinreb amide **42a** (1 equiv, 0.47 mmol, 0.2 g,) in DCM (5 mL) was added DIBAL-H (2 equiv., 0.95 mL, 1M in toluene,) dropwise at -78 °C. The mixture was stirred at - 78 °C for 3 h before quenching with a saturated aqueous solution of diethyl tartrate sodium potassium (10mL) at - 78 °C. The temperature was allowed to warm to r.t and the mixture was stirred all night long. The phases were separated, the aqueous layer was extracted with Et_2O, the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel to afford the desired compound **41**.

Method 3: To a solution of alcohol **40** (1.8 g, 4.89 mmol) in DCM (15mL), Dess-Martin periodinane (1.5 equiv., 7.33 mmol, 1.04g) was added at 0°C. The mixture was stirred for 3h, quenched with water and extracted with DCM. The organic layers were dried on Na_2SO_4 filtered and concentrated under reduced pressure. The resulting residue was purified by column

chromatography on silica gel to afford the desired compound **41.**

The aldehyde was recovered as a viscous white liquid.

R*f* = 0.3 (EP/EtOAc = 8:2)

Yield : 55% Method 1

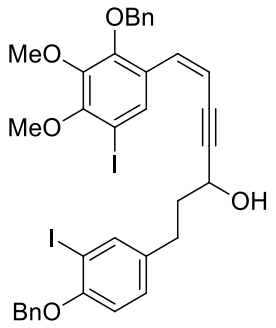
Yield : 72% Method 2

Yield : 84% Method 3

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74 (m, 2H, C*H*$_2$); 2.86 (t, 2H, *J* = 7.6Hz, C*H*$_2$); 5.12 (s, 2H, C*H*$_2$-Bn); 6.77 (d, 2H, *J* = 8.0Hz, Ar-*H*); 7.10 (dd, 2H, *J* = 8.0Hz, *J* = 2.0 Hz, Ar-*H*); 7.29-7.38 (m, 3H, Bn-*H*); 7.48 (d, 2H, *J* = 7.0 Hz, Bn-*H*); 7.64 (d, 1H, *J* = 2.0 Hz, Ar-*H*), 9.80 (t, 1H,*J*=1.6Hz, C*H*O).

^{13}C NMR (101 MHz, $CDCl_3$) δ 26.68 (*C*H$_2$); 45.28 (*C*H$_2$); 70.99 (*C*H$_2$-Bn); 86.95 (q, *C*-I); 112.75 (*C*H-Ar); 126.98 (*C*H-Bn); 127.86 (*C*H-Bn); 128.54 (*C*H-Bn); 129.27 (*C*H-Ar); 134.91(q, *C*-Ar); 136.54 (q, *C*-Bn); 139.18 (*C*H-Ar), 155.82 (q, *C*-OAr), 201.10 (q, *C*HO).

(Z)-1-(4-(benzyloxy)-3-iodophenyl)-7-(2-(benzyloxy)-5-iodo-3,4-dimethoxyphenyl)hept-6-en-4-yn-3-ol (42)



42

Chemical Formula: $C_{35}H_{32}I_2O_5$
Exact Mass: 786,03

To a solution of trimethylsilyl alkyne (2.0 equiv.) and aldehyde **41** (1.0 equiv.) at 55°C, TBAF (15 mol % in dry THF) was added and then the reaction mixture was stirred at room temperature for 1 h. This was followed by the addition of 1 M aqueous HCl (1.0 mL) and further stirring for 15 minutes at room temperature, The reaction mixture was neutralized with aqueous $NaHCO_3$ and then it was extracted with ethyl acetate. The organic layers were collected and dried with anhydrous Na_2SO_4 followed by solvent removal under reduced pressure, The resulting residue was purified by column chromatography on silica gel to afford the desired compound **42** as an oil.

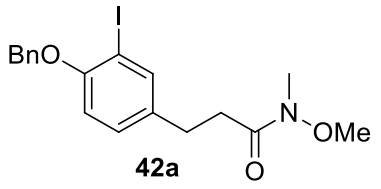
Yield= 86%

Rf= 0.25 (EP/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (m, 2H, C*H*$_2$-CHOH); 2.75 (m, 2H, C*H*$_2$); 3.90 (s, 3H, O-C*H*$_3$); 3.91 (s, 3H, O-C*H*$_3$); 4.58 (m, 1H, C*H*-OH); 5.01 (s, 2H, C*H*$_2$- Bn); 5.12 (s, 2H, C*H*$_2$- Bn); 5.69 (dd, 1H, *J'*=12.0Hz, *J''*=1.9Hz, C*H* styrenic) 6.76 (d, 2H, *J* = 8.0Hz, Ar-*H*); 6.82 (d, 1H, *J*=12.0Hz, C*H* styrenic); 7.11 (dd, 2H, *J* = 8.0Hz, *J* = 2.0 Hz, Ar-*H*); 7.30-7.49 (m, 10H, Bn-*H*); 7.69 (d, 1H, *J* = 2.0 Hz, Ar-*H*), 8.77 (s,1H, Ar–*H*).

HRMS (ESI+): *m/z* calcd for $C_{32}H_{32}{}^{127}I_2O_5{}^{23}Na$ $[M + Na]^+$: 809.02313; found 809.0223

3-(4-(Benzyloxy)-3-iodophenyl)-*N*-methoxy-*N*-methylpropanamide (42a)



42a

Chemical Formula: $C_{18}H_{20}INO_3$
Exact Mass: 425,05

Amide **42a** was obtained from iodinated amide **42b** (1 equiv., 1.49mmol, 0.50g) following the general procedure of benzylation Method 3. The product was obtained as a transparent oil.

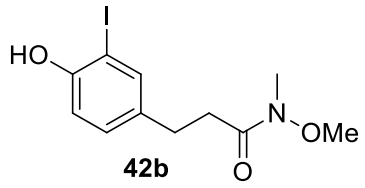
Yield= 85% (1.29 mmol, 0.55g)

R*f* = 0.6 (PE/EtOAc = 4:6)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (t, 2H, *J* = 7.5 Hz, C*H*$_2$); 2.88 (t, 2H, *J* = 7.5 Hz, C*H*$_2$); 3.17 (s, 3H, N-C*H3*); 3.61 (s, 3H, N-OC*H*$_3$); 5.12 (s, 2H, C*H*$_2$-Bn); 6.77 (d, 2H, *J* = 8.5Hz, Ar-*H*); 7.12 (dd, 2H, *J'* =8.5Hz, *J''* = 2.0Hz, Ar-*H*), 7.29-7.38 (m, 5H, Bn-*H*); 7.66 (d, 1H, *J* = 1.9 Hz. Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.27 (N-*C*H_3); 32.23 (Ar*C*H_2CH_2); 33.74 (ArCH_2*C*H_2); 61.25 (N-O*C*H_3);70.99 (*C*H_2-Bn); 86.83 (q, *C*-I); 112.74 (*C*H-Ar); 127.01 (*C*H-Bn); 127.85 (*C*H-Bn); 128.54 (*C*H-Bn); 129.47 (*C*H-Ar); 136.00 (q, *C*-Ar); 136.65 (q, *C*-Bn); 139.29 (*C*H-Ar); 155.67 (q, C*O*-Ar); 173.56 (q, CO).

3-(4-Hydroxy-3-iodophenyl)-*N*-methoxy-*N*-methylpropanamide (42b)



42b

Chemical Formula: $C_{11}H_{14}INO_3$
Exact Mass: 335,00

N,O-dimethylhydroxylamine hydrochloride (3equiv., 9.80 mmol, 0.95g) was dissolved in dry DCM (0.3M) under inert atmosphere. Then, a solution of $AlMe_3$ (3equiv., 4.9.mL, 2M in toluene) was added dropwise at room temperature. The mixture was stirred for 30 min and a solution of starting ester **3a** (1equiv., 3.27 mmol, 1.0g) in dry DCM (0.3M) was prepared and added to the mixture. The mixture was heated to reflux overnight. The reaction was slowly hydrolyzed with an aqueous solution of HCl (0.5M, 100mL). The aqueous layer was extracted with DCM (3X100 mL). The organic layers were washed with saturated aqueous solution of $NaHCO_3$, dried on Na_2SO_4 and evaporated under reduced pressure. The Crude product was purified by silica gel chromatography to obtain the compound **42b**

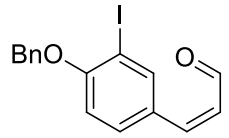
Yield = 45% (1.47mmol,0.49g)

R*f* = 0.5 (PE/EtOAc = 4:6)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (t, 2H, *J* = 7.5 Hz, C*H*$_2$); 2.87 (t, 2H, *J* = 7.5 Hz, C*H*$_2$); 3.18 (s, 3H, N-C*H*$_3$); 3.62 (s, 3H, N-OC*H*$_3$); 5.19 (bs, 1H, O*H*); 6.91 (d, 2H, *J* = 8.0 Hz, Ar-*H*); 7.11 (dd, 2H, *J'* = 8.5 Hz, *J''* = 2.0Hz, Ar-*H*), 7.53 (d, 1H, *J* = 2.0 Hz. Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$)δ: 29.23 (N-*C*H$_3$); 33.77 (Ar*C*H$_2$*C*H$_2$); 61.25 (N-O*C*H$_3$); 85.57 (q, *C*-I); 114.96 (*C*H-Ar); 130.36 (*C*H-Ar); 135.58 (q, *C*-Ar); 137.84 (*C*H-Ar); 153.21 (q, C*O*-Ar); 173.56 (q, C=O).

(*Z*)-3-(4-(benzyloxy)-3-iodophenyl)acrylaldehyde (59)



59

Chemical Formula: $C_{16}H_{13}IO_2$
Exact Mass: 364,00

To a solution of alcohol **59a** (622 mg, 1.70 mmol) in DCM (15mL), Dess-Martin periodinane (1.5 equiv., 2.55 mmol, 362 mg) was added at 0°C. The mixture was stirred for 3 h, quenched with water and extracted with DCM. The organic layers were dried on Na_2SO_4 filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel to afford the desired compound **59.**

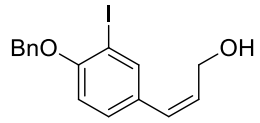
Yield= 79% (1.34 mmol, 488.3 mg)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (s, 2H, CH_2Bn); 6.12 (d, 1H, J_{cis} = 12.0 Hz, C*H* styrenic); 6.13 (d, 1H, J_{cis} = 12.0 Hz, C*H* styrenic); 6.87 (d, 2H, *J* = 8.0, Ar-*H*); 7.30- 7.52 (m, 6H, *J* = 2.0 Hz. Ar-*H*); 7.88 (d, 1H, *J*=1.96Hz, Ar-*H*); 9.97 (d,1H, J=8.0 Hz, C*H*O).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 70.68, 86.57, 111.71, 126.62, 127.81, 128.35, 128.58, 129.45, 131.09, 135.51, 140.52, 146.07, 158.16, 191.60.

HRMS (ESI+): *m/z* calcd for $C_{16}H_{14}IO_2$ $[M + H]^+$: 365.0033; found 365.0030

(*Z*)-3-(4-(benzyloxy)-3-iodophenyl)prop-2-en-1-ol (59a)



59a

Chemical Formula: $C_{16}H_{15}IO_2$
Exact Mass: 366,01

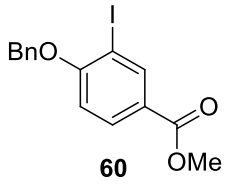
To a solution of the previously synthesized ester **63** (1 equiv, 1.77mmol, 0.7g) in DCM (18mL) was added DIBAL-H (2 equiv., 3.54 mL, 1 M in toluene,) dropwise at -40 °C. The mixture was stirred at -40 °C for 3 h before quenching with a saturated aqueous solution of diethyl tartrate sodium potassium (25 mL) at - 40 °C. The temperature was allowed to warm to r.t and the mixture was stirred all night long. The phases were separated, the aqueous layer was extracted with DCM, combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel to afford the desired compound **59a.**

Yield= 95% (1,68 mmol, 617,74 g)

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.43 (m, 2H, C*H*$_2$OH); 5.19 (s, 2H, C*H*$_2$Bn); 5.84 (m, 1H, C*H*-CH_2OH); 6.45 (d, 1H, J_{cis} = 12.0 Hz, C*H* styrenic); 7.16 (dd, 1H, *J'* = 8.0, *J''* = 4.0, Ar-*H*); 7.20 (d, 1H, *J*=8.0, Ar-*H*); 7.25- 7.52 (m, 6H, *J* = 2.0 Hz. Ar-*H*); 7.70 (d, 1H, *J*=4.0Hz, Ar-*H*);

^{13}C NMR (100 MHz, $CDCl_3$) δ: 59.55, 70.93, 86.61, 112.17, 126.98, 127.95, 128.60, 129.21, 129.89, 131.42, 136.36, 140.52, 146.07, 156.40.

Methyl 4-benzyloxy-3-iodobenzoate (60)



60

Chemical Formula: $C_{15}H_{13}IO_3$
Exact Mass: 367,99

Ester **60** was obtained from iodinated amide phenol (1 equiv., 5.39mmol, 1.5g) following the general procedure of benzylation Method 3 using 0,77mL of BnBr and 1,49 g of K_2CO_3 in 21.5 mL of ACN. The product was obtained as a white solid.

Yield= quantitative (5.38mmol, 1.98 g)

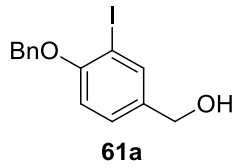
R_f= 0.75 (PE/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H, O-C*H*$_3$), 5.15 (s, 2H, C*H*$_2$-Bn), 6.82 (d, 1H, *J*=8.0 Hz, Ar-*H*), 7.32-7.49 (m, 5H, Ar-*H*), 7.95 (dd, 1H, *J*'=8.2 Hz, *J*''=4Hz, Ar-*H*); 8.49 (d, 1H, J=2.0 Hz, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 52.17, 70.94, 86.12, 111.48, 124.52, 125.98, 127.57, 128.64, 131.53, 135.78, 141.04, 160.67, 166.41.

HRMS (ESI+): *m/z* calcd for $C_{15}H_{13}IO_3$ $[M + Na]^+$: 390.9807; found 390.9795

4-Benzyloxy-3-iodophenyl-methanol (61a)



61a

Exact Mass: 340,00
Chemical Formula: $C_{14}H_{13}IO_2$

To a solution of the previously synthesized ester **60** (1 equiv, 5,38mmol, 1.98g) in DCM (80mL) was added DIBAL-H (2.5 equiv., 13.4 mL, 1M in toluene,) dropwise at -40 °C. The mixture was stirred at -40 °C for 3 h before quenching with a saturated aqueous solution of diethyl tartrate sodium potassium (100mL) at - 40 °C. The temperature was allowed to warm to r.t and the mixture was stirred all night long. The phases were separated, the aqueous layer was extracted with DCM, combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel to afford the desired compound **61a.**

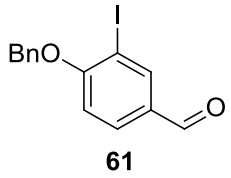
Yield= 99% (5.33 mmol, 1.8g)

$\boldsymbol{R_f}$= 0.1 (PE/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) 4.57 (s, 2H, C*H*$_2$OH); 5.16 (s, 2H, C*H*$_2$-Bn); 6.83 (d, 1H, *J*=8.0Hz, Ar-*H*), 7.26 (dd, 1H, *J*'=8.0Hz, *J*''=2.0Hz, Ar-*H*); 7.29-7.52 (m, 5H, Ar-*H*); 7.82 (d, 1H, J=2.2 Hz, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 64.13, 70.97, 86.85, 112.63, 126.99, 127.93, 129.59, 136.44, 136.45, 138.43.

4-Benzyloxy-3-iodobenzaldehyde (61)



61

Chemical Formula: $C_{14}H_{11}IO_2$
Exact Mass: 337,98

To a solution of alcohol **61a** (5.33 mmol, 1.8g) in DCM (45mL), Dess-Martin periodinane (1.5 equiv., 8.0 mmol, 3.4g) was added at 0°C. The mixture was stirred for 3h, quenched with water and extracted with DCM. The organic layers were dried on Na_2SO_4 filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel to afford the desired compound **61.**

Yield= 97% (5.17mmol, 1.77g)

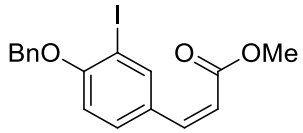
Rf= 0.3 (PE/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 5.25 (s, 1H, C*H*$_2$-Bn); 6.94 (d, 1H, *J*= 8.5 Hz, Ar-*H*); 7.31-7.51 (m, 5H, Ar-*H*); 7.81 (dd, 1H, *J*= 8.5Hz, *J*''=4.0 Hz, Ar-*H*); 8.33 (d, 1H, *J*=2.0 Hz, Ar-*H*); 9.81 (s, 1H, C*H*O).

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 71.17, 111.99, 126.96, 128.28, 128.75, 131.92, 141.18, 189.40.

HRMS (ESI+): *m/z* calcd for $C_{14}H_{11}IO_2$ $[M + H]^+$: 338.9877; found 338.9889.

(*Z*)-methyl 3-(4-benzyloxy-3-iodophenyl)acrylate (63)



63

Chemical Formula: $C_{17}H_{15}IO_3$
Exact Mass: 394,01

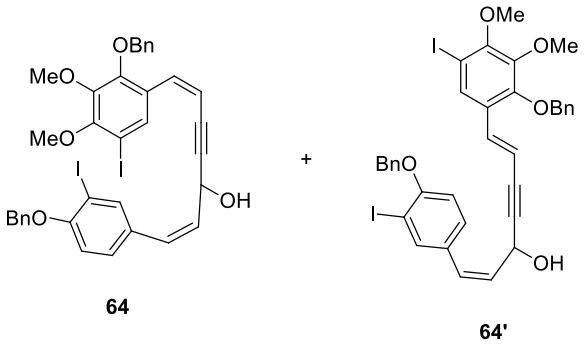
18-Crown-6 (5.0 equiv. 6.6 g, 25 mmol) was dissolved under argon in THF (100 mL) and the solution was cooled to -78 ◦C. KHMDS (2.0 equiv, 0.5 M in toluene, 20 mL, 10 mmol) was added via septum and the mixture was stirred for 10 min. Bis(2,2,2-trifluoroethyl)(methoxy-carbonylmethyl)phosphinate (1.5 equiv., 1.57 mL, 2.4 g, 7.5 mmol) was added and the reaction mixture was stirred for 10 min. Aldehyde **61** (1.0 equiv., 1.7 g, 5.03 mmol) was added as a solid and stirring was continued for an additional 45 min. The reaction was quenched with brine and extracted with DCM (3 × 30 mL); the combined organic layers were washed with brine (3 × 100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was then purified by flash column chromatography on silica gel to yield a yellow foam.

Yield= (4.88 mmol, 1.92 g) 97%

^{1}H NMR (400 MHz, $CDCl_3$) δ : 3.74 (s, 3H, O-C*H*$_3$); 5.17 (s, 2H, C*H*$_2$-Bn); 5.87 (d, 1H, J_{cis}= 12.0 Hz, C*H* Styrenic), 5.75 (d, 1H, J_{cis}= 12.0 Hz, C*H* Styrenic); 6.82 (d, 1H, J=8.0 Hz, Ar-*H*), 7.30-7.51 (m, 5H, Ar-*H*); 7.72 (dd, 1H, *J'*=8.0Hz, *J''*=2.0Hz, Ar-*H*); 8.17 (d, 1H, *J*=2.1 Hz, Ar-*H*).

HRMS (ESI+): *m/z* calcd for $C_{17}H_{15}IO_3$ $[M + K]^+$: 432.9698; found 432.9667.

(*1Z,6Z*)-1-(4-(benzyloxy)-3-iodophenyl)-7-(2-(benzyloxy)-5-iodo-3,4-dimethoxyphenyl)hepta-1,6-dien-4-yn-3-ol (64) and (**1*Z,6E*)-1-(4-(benzyloxy)-3-iodophenyl)-7-(2-(benzyloxy)-5-iodo-3,4-dimethoxyphenyl)hepta-1,6-dien-4-yn-3-ol (64')**



Chemical Formula: $C_{35}H_{30}I_2O_5$
Exact Mass: 784,02

To a solution of trimethylsilyl alkyne (2.0 equiv.) and aldehyde (1.0 equiv.) at 55°C, TBAF (15 mol % in dry THF) was added and then the reaction mixture was stirred for 1 h. This was followed by the addition of 1 M aqueous HCl (1.0 mL) and further stirring for 15 min at room temperature, The reaction mixture was neutralized with aqueous $NaHCO_3$ and then it was extracted with ethyl acetate. The organic layers were collected and dried with anhydrous Na_2SO_4 followed by solvent removal under reduced pressure, The product was then purified by flash column chromatography on silica gel to yield a yellow oil. The two stereosimers **64** and **64'** were not separable by column chromatography; (**64**:**64'** = 64/36).

Yield= 18%

Rf= 0.65 (EP/EtOAc = 8:2)

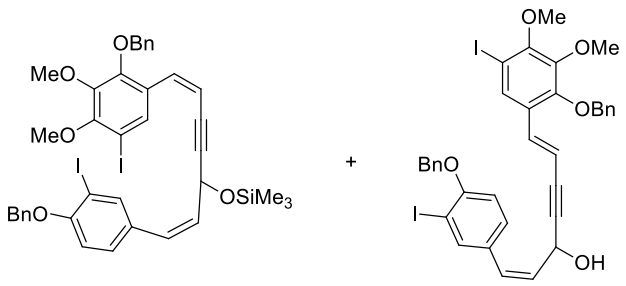
64

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3H, O-C*H*$_3$); 3.91 (s, 3H, O-C*H*$_3$); 5.01 (s, 2H, C*H*$_2$- Bn); 5.17 (s, 2H, C*H*$_2$- Bn); 5.38 (m, 1H, C*H*-OH); 5.71 (dd, 1H, *J'*=12.0 Hz, J''=2.0Hz, C*H* Styrenic); 5.90 (dd, 1H, *J'*=12.0 Hz, *J''*=10.5 Hz, C*H* Styrenic); 6.56 (d, 1H, *J*=12.0 Hz, C*H* Styrenic); 6.83 (d, 1H, *J* = 12.0 Hz, C*H* Styrenic); 6.85 (d, 1H, *J* = 8.0 Hz, Ar-*H*); 7.30-7.53 (m, 10H, Bn-*H*); 7.79 (d, 1H, *J* = 2.0 Hz, Ar-*H*); 8.57 (s, 1H, Ar-*H*).

64'

^{1}H NMR (400 MHz, $CDCl_3$) 3.90 (s, 3H, O-C*H*$_3$); 3.91 (s, 3H, O-C*H*$_3$); 5.02 (s, 2H, C*H*$_2$- Bn); 5.17 (s, 2H, C*H*$_2$- Bn); 5.33 (m, 1H, C*H*-OH); 5.80 (dd, 1H, *J'*=16.0 Hz, *J''*=11.0 Hz, C*H* Styrenic); 6.12 (dd, 1H, *J'*=16.0 Hz, J''=2.0Hz, C*H* Styrenic) 6.50 (d, 1H, *J*=12.0 Hz, C*H* Styrenic); 6.85 (d, 1H, *J* = 8.0 Hz, Ar-*H*); 7.06 (d, 1H, *J* = 16.0 Hz, C*H* Styrenic); 7.30-7.53 (m, 10H, Bn-*H*); 7.58 (s, 1H, Ar-*H*); 7.81 (d, 1H, *J* = 2.0 Hz, Ar-*H*).

(*1Z,6Z*)-1-(4-(benzyloxy)-3-iodophenyl)-7-(2-(benzyloxy)-5-iodo-3,4-dimethoxyphenyl)hepta-1,6-dien-4-yn-3-yl)oxy)trimethylsilane (65) and **(*1Z,6E*)-1-(4-(benzyloxy)-3-iodophenyl)-7-(2-(benzyloxy)-5-iodo-3,4-dimethoxyphenyl)hepta-1,6-dien-4-yn-3-yl)oxy)trimethylsilane (65')**



65 **65'**

Chemical Formula: $C_{38}H_{38}I_2O_5Si$

Exact Mass: 856,06

To a solution of trimethylsilyl alkyne (2.0 equiv.) and aldehyde (1.0 equiv.) at 55°C, TBAF (15 mol % in dry THF) was added and then the reaction mixture was stirred for 1 h. This was followed by the addition of 1 M aqueous HCl (1.0 mL) and further stirring for 15 min at room temperature, The reaction mixture was neutralized with aqueous $NaHCO_3$ and then it was extracted with ethyl acetate. The organic layers were collected and dried with anhydrous Na_2SO_4 followed by solvent removal under reduced pressure, The product was then purified by flash column chromatography on silica gel to yield a yellow oil. The two stereosimers **65** and **65'** were not separable by column chromatography; (**65**:**65'** = 81/19)

Yield= 71%

Rf= 0.65 (EP/EtOAc = 8:2)

65

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.16 (s, 9H, C*H*$_3$-Si); 3.91 (s, 3H, O-C*H*$_3$); 3.92 (s, 3H, O-C*H*$_3$); 5.02 (s, 2H, C*H*$_2$- Bn); 5.18 (s, 2H, C*H*$_2$- Bn); 5.41 (m, 1H, C*H*-OSiMe$_3$); 5.74 (dd, 1H, *J'*=12.0 Hz, J''=2.0Hz, C*H* Styrenic); 5.94 (dd, 1H, *J'*=12.0 Hz, *J''*=10.5 Hz, C*H* Styrenic); 6.51 (d, 1H, *J*=12.0 Hz, C*H* Styrenic); 6.84 (d, 1H, *J* = 12.0 Hz, C*H* Styrenic); 6.85 (d, 1H, *J* = 8.0 Hz, Ar-*H*); 7.30-7.53 (m, 10H, Bn-*H*); 7.80 (d, 1H, *J* = 2.0 Hz, Ar-*H*); 8.58 (s, 1H, Ar-*H*).

^{13}C NMR (101 MHz, $CDCl_3$) δ 0.00, 59.40, 60.46, 60.65, 70.40, 75.31, 82.62, 84.67, 84.67, 85.64, 95.55, 107.20, 111.75, 126.46, 127.42, 127.53, 127.74, 127.82, 127.99, 128.04, 128.08, 129.21, 129.56, 130.52, 130.98, 131.16, 131.37, 131.65, 134.36, 139.37, 139.42, 145.82, 150.88, 153.26, 155.94

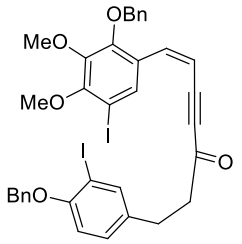
65'

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 0.19 (s, 9H, C*H*$_3$-Si); 3.91 (s, 3H, O-C*H*$_3$); 3.92 (s, 3H, O-C*H*$_3$); 5.03 (s, 2H, C*H*$_2$- Bn); 5.18 (s, 2H, C*H*$_2$- Bn); 5.34 (m, 1H, C*H*-$OSiMe_3$); 5.82 (dd, 1H, *J'*=16.0 Hz, *J''*=11.0 Hz, C*H* Styrenic); 6.15 (dd, 1H, *J'*=16.0 Hz, J''=2.0Hz, C*H* Styrenic) 6.44 (d, 1H, *J*=12.0 Hz, C*H* Styrenic); 6.85 (d, 1H, *J* = 8.0 Hz, Ar-*H*); 7.08 (d, 1H, *J* = 16.0 Hz, C*H* Styrenic); 7.30-7.53 (m, 10H, Bn-*H*); 7.59 (s, 1H, Ar-*H*); 7.80 (d, 1H, *J* = 2.0 Hz, Ar-*H*).

HRMS (ESI+): *m/z* calcd for $C_{38}H_{38}I_2O_5Si$ $[M + Na]^+$: 879.0470; found 879.0488

,

(*Z*)-1-(4-(benzyloxy)-3-iodophenyl)-7-(2-(benzyloxy)-5-iodo-3,4-dimethoxyphenyl)hept-6-en-4-yn-3-one (74).



74

Chemical Formula: $C_{35}H_{30}I_2O_5$
Exact Mass: 784,02

To a solution of alcool **42** (1 equiv., 0.051mmol, 40mg) in DCM (2mL), Dess-Martin periodinane (1.5 equiv., 0.076 mmol, 32.5mg) was added at 0°C. The mixture was stirred for 3h, quenched with water and extracted with DCM. The organic layers were dried on Na_2SO_4 filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel to afford the desired compound **74.**

Yield = (0.043 mmol, 33.6 mg) **84%**

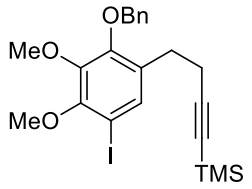
Rf= 0.3 (PE/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80 (m, 2H, C*H*$_2$-CHOH); 2.96 (m, 2H, C*H*$_2$); 3.83 (s, 3H, O-C*H*$_3$); 3.86 (s, 3H, O-C*H*$_3$); 4.96 (s, 2H, C*H*$_2$- Bn); 5.04 (s, 2H, C*H*$_2$- Bn); 5.65 (dd, 1H, *J'*=12.0Hz, *J''*=1.9Hz, C*H* styrenic) 6.68 (d, 2H, *J* = 8.0Hz, Ar-*H*); 6.99 (d, 1H, *J*=12.0Hz, C*H* styrenic); 7.04 (dd, 2H, *J* = 8.0Hz, *J* = 2.0 Hz, Ar-*H*); 7.22-7.42 (m, 10H, Bn-*H*); 7.61 (d, 1H, *J* = 2.0 Hz, Ar-*H*), 8.40 (s,1H, Ar–*H*).

^{13}C NMR (101 MHz, $CDCl_3$) δ 28.37, 47.14, 60.40, 61.18, 70.99, 76.04, 88.79, 89.74, 91.30, 93.45, 105.01, 112.68, 127.01, 127.86, 128.62, 129.37, 129.95, 130.40, 132.28, 134.84, 137.87, 139.37, 141.13, 151.69, 155.76, 186.05.

HRMS (ESI+): *m/z* calcd for $C_{32}H_{30}{}^{127}I_2O_5$ $[M + Na]^+$: 807.00748; found 807.0060

(4-(2-(benzyloxy)-5-iodo-3,4-dimethoxyphenyl)but-1-yn-1-yl)trimethylsilane (78)



78

Chemical Formula: $C_{22}H_{27}IO_3Si$
Exact Mass: 494,08

A solution of 1-TMS-propyne (2.0 equiv., 0.245 mL, 1.6 mmol) in dry THF (7.5 mL) was treated dropwise with n-BuLi (1.75 equiv. 1.4 mmol, 0.652 mL, 2.2 M solution in hexanes) at 0 ºC. The solution was stirred for 15 min, and transferred via cannula to another solution of **92** (1.0 equiv., 0.82 mmol, 380 mg,) in THF (2.5 mL) while maintaining at –65 ºC. After stirring at –65 ºC for 10 min, the reaction was allowed to reach rt and stirred for 30 min. The reaction was quenched with 5% HCl and the volatiles 3) and the combined ×were removed under vacuo. The reaction was extracted with ether (10 mL organic layers were washed with water, brine and dried over $MgSO_4$. The mixture was filtered and evaporated to give crude. The resulting residue was purified by column chromatography on silica gel to afford the desired compound **78**

Rf = 0.6 (EP/EtOAc = 9:1)

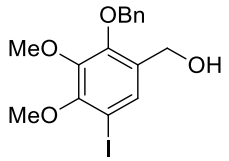
Yield = (0.64 mmol, 316 mg) 78%

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.14 (s, 9H, C*H*$_3$-Si); 2.40 (t, 2H, *J*=8.0 Hz, *CH*$_2$); 2.70 (t, 2H, *J*=8.0 Hz, *CH*$_2$-Bn); 3.88 (s, 3H, O-C*H*$_3$); 3.91 (s, 3H, O-C*H*$_3$); 5.06 (s, 2H, C*H*$_2$-Bn); 7.34-7.45 (m, 6H, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 0.00, 20.75, 28.58, 60.71, 60.84, 75.05, 84.73, 85.44, 106.25, 127.82, 127.95, 128.32, 128.36, 132.01, 133.51, 137.26, 146.45, 151.16, 152.26.

HRMS (ESI+): *m/z* calcd for $C_{22}H_{27}IO_3Si$ $[M + Na]^+$: 517.0671; found 517.0666.

(2-Benzyloxy-5-iodo-3,4-dimethoxyphenyl)methanol (79).



79

Chemical Formula: $C_{16}H_{17}IO_4$
Exact Mass: 400,02

To a solution of the previously synthesized aldehyde **13** (1 equiv, 0.36 mmol, 140 mg) in DCM (5mL) was added DIBAL-H (2.5 equiv., 0.9 mL, 1M in toluene,) dropwise at -40 °C. The mixture was stirred at -40 °C for 3 h before quenching with a saturated aqueous solution of diethyl tartrate sodium potassium (10mL) at - 40 °C. The temperature was allowed to warm to r.t and the mixture was stirred all night long. The phases were separated, the aqueous layer was extracted with DCM, combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel to afford the desired compound **79.**

Yield= (0.35 mmol, 140mg) 99%

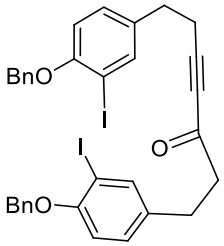
R_f= 0.2 (PE/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H, O-CH_3); 3.93 (s, 3H, O-CH_3); 4.46 (m, 2H, CH_2-OH); 5.12 (s, 2H, CH_2-Bn); 7.33-7.43 (m, 5H, Ar-*H*); 7.46 (s, 1H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 60.76, 60.92, 75.58, 85.28, 128.44, 128.46, 128.69, 132.41, 132.44, 136.96, 146.48, 151.05, 153.59.

HRMS (ESI+): *m/z* calcd for $C_{16}H_{17}IO_4$ $[M]^+$: 399.00988; found 399.0107

1,7-bis(4-(benzyloxy)-3-iodophenyl)hept-4-yn-3-one (80)



80

Chemical Formula: $C_{33}H_{28}I_2O_3$
Exact Mass: 726,01

To a solution of alcohol **89** (1.0 equiv., 0.034mmol, 25mg) in DCM (1mL), Dess-Martin Periodinane (1.5 equiv., 0.051 mmol, 21mg) was added at 0°C. The mixture was stirred for 3h, quenched with water and extracted with DCM. The organic layers were dried on Na_2SO_4 filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel to afford the desired compound **80.**

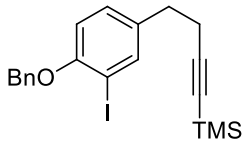
Yield= 86% (0.029 mmol, 21.5mg)

Rf= 0.5 (PE/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (t, 2H, *J*=8.0 Hz, C-*H*$_2$); 2.80 (m, 6H, *CH*$_2$); 5.11 (s, 2H, C*H*$_2$-Bn); 5.12 (s, 2H, C*H*$_2$-Bn); 6.75 (d, 1H, *J*= 8.0Hz, Ar-*H*), 6.79 (d, 1H, *J*= 8.0Hz, Ar-*H*) 7.06 (dd, 1H, *J'*=8.0Hz, *J''*=2.0 Hz, Ar-*H*); 7.13 (dd, 1H, *J'*=8.0Hz, *J''*=2.0 Hz, Ar-*H*);7.30-7.51 (m, 10H, Ar-*H*); 7.63 (d, 1H, *J*=2.0 Hz, Ar-*H*). 7.69 (d, 1H, *J*=2.0 Hz, Ar-*H*).

^{13}C NMR (101 MHz, $CDCl_3$) δ 21.55, 28.78, 32.70, 47.21, 71.19, 81.88, 87.11, 87.13, 93.69, 112.87, 112.92, 127.26, 128.14, 128.17, 128.83, 128.85, 129.67, 129.71, 134.36, 135.10, 136.76, 136.85, 139.52, 139.70, 156.01, 156.35, 186.97.

(4-(4-Benzyloxy-3-iodophenyl)but-1-yn-1-yl)trimethylsilane (81)



81

Chemical Formula: $C_{20}H_{23}IOSi$

Exact Mass: 434,06

A solution of 1-TMS-propyne (1.9 equiv., 0.094 mL, 0.63 mmol) in dry THF (2.5 mL) was treated dropwise with n-BuLi (1.7 equiv. 0.57 mmol, 0.35 mL, 1.6 M solution in hexanes) at 0 ºC. The solution was stirred for 15 min, and transferred via cannula to another solution of **83** (1.0 equiv., 0.33 mmol, 135 mg,) in THF (1 mL) while maintaining at –78 ºC. After stirring at –78 ºC for 1 h, the reaction was allowed to reach rt and stirred for 1 h. The reaction was quenched with 5% HCl and the volatiles 3) and the combined ×were removed under vacuo. The reaction was extracted with ether (10 mL organic layers were washed with water, brine and dried over $MgSO_4$. The mixture was filtered and evaporated to give crude. The resulting residue was purified by column chromatography on silica gel to afford the desired compound **81**

Rf = 0.6 (EP/EtOAc = 9:1)

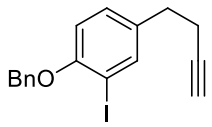
Yield = (0.28 mmol, 120 mg) 84%

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 9H, C*H*$_3$-Si); 2.45 (t, 2H, *J*=8.0 Hz, *CH*$_2$); 2.71 (t, 2H, *J*=8.0 Hz, *CH*$_2$-Bn) 5.13 (s, 2H, C*H*$_2$-Bn); 6.77 (d, 1H, *J*= 8.0Hz, Ar-*H*), 7.11 (dd, 1H, *J'*=8.0Hz, *J''*=2.0 Hz, Ar-*H*), 7.29-7.51 (m, 5H, Ar-*H*); 7.69 (d, 1H, *J*=2.0 Hz, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 0.10, 20.66, 33.27, 68.79, 69.77, 85.61, 86.43, 114.54, 127.24, 127.62, 128.31, 129.29, 134.96, 136.12, 139.32, 155.17.

HRMS (ESI+): *m/z* calcd for $C_{20}H_{23}IOSi$ $[M + Na]^+$: 457.04551; found 457.0451

1-(benzyloxy)-4-(but-3-yn-1-yl)-2-iodobenzene (81')



81'

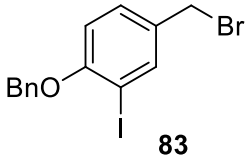
Chemical Formula: $C_{20}H_{23}IOSi$
Exact Mass: 362,02

Compound **81'** was obtained as a side product arising from desilylation of compound **80** during the fluoride mediated addition for the synthesis of the propargyl alcool **89.**

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (t, 1H, *J*=2,5 Hz, C-*H*); 2.47 (dt, 2H, *J'*=8.0 Hz, *J''*= 2.4Hz, CH_2-C); 2.77 (t, 2H, *J*=8.0 Hz, CH_2-Bn) 5.14 (s, 2H, CH_2-Bn); 6.81 (d, 1H, *J*= 8.0Hz, Ar-*H*), 7.16 (dd, 1H, *J'*=8.0Hz, *J''*=2.0 Hz, Ar-*H*), 7.32-7.56 (m, 5H, Ar-*H*); 7.72 (d, 1H, *J*=2.0 Hz, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 20.43, 33.12, 69.14, 70.66, 83.25, 86.59, 112.31, 126.73, 127.62, 128.31, 129.18, 134.73, 136.37, 139.12, 155.60.

1-Benzyloxy-4-bromomethyl-2-iodobenzene (83)



83

Chemical Formula: $C_{14}H_{12}BrIO$

Exact Mass: 401,91

To a solution of triphenylphosphine (PPh_3) (139 mg, 0.52 mmol) and imidazole (62 mg, 0.92 mmol) in DCM (3 mL), bromine (Br_2) (0.027 mL, 0.52 mmol) was added in dropwise at 0 °C. The solution of **61a** (1 equiv., 0.46mmol, 156mg) in DCM (1 mL) was added to the above solution dropwise at 0 °C. Then, the reaction mixture was stirred for 1 h at rt and quenched with satd. NH_4Cl (10 mL). The aqueous layer was extracted with DCM and the combined organic layers were washed with satd. NH_4Cl (5 mL), brine, dried over Na_2SO_4,and filtered. The filtrate was concentrated under vacuo. The crude solid was triturated with 15% EtOAc in hexanes (20 mL). Filtered off unwanted solid and the resulting filtrate was concentrated to furnish **83** as a white glassy solid

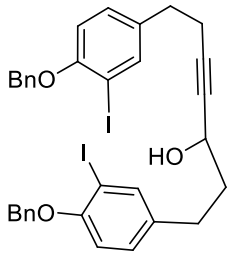
Yield = (0.34 mmol, 137 mg) 74%

Rf= 0.8 (PE/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (s, 2H, CH_2-Br); 5.16 (s, 2H, CH_2-Bn); 6.80 (d, 1H, *J*= 8.0Hz, Ar-*H*), 7.30 (d, 1H, *J'*=8.0Hz, *J''*=2.0 Hz, Ar-*H*), 7.32-7.56 (m, 5H, Ar-*H*); 7.83 (d, 1H, *J*=2.0 Hz, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 32.23, 70.96, 76.71, 77.02, 77.23, 77.34, 86.74, 112.45, 126.96, 128.01, 128.63, 130.30, 132.20, 136.20, 140.15, 157.29

,. **1,7-Bis(4-(benzyloxy)-3-iodophenyl)hept-4-yn-3-ol (89)**



89

Chemical Formula: $C_{33}H_{30}I_2O_3$

Exact Mass: 728,03

To a solution of trimethylsilyl alkyne (2.0 equiv.) and aldehyde (1.0 equiv.) at 55°C, TBAF (15 mol % in dry THF) was added and then the reaction mixture was stirred at room temperature for 1 h. This was followed by the addition of 1 M aqueous HCl (1.0 mL) and further stirring for 15 min at room temperature, The reaction mixture was neutralized with aqueous $NaHCO_3$ and then it was extracted with ethyl acetate. The organic layers were collected and dried with anhydrous Na_2SO_4 followed by solvent removal under reduced pressure, The resulting compound **89** was not purified but it was identified by ^{1}HNMR and directly oxidated to ketone **80.**

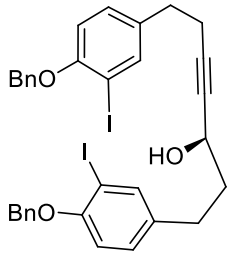
Yield= 51%

Rf= 0.25 (EP/EtOAc = 8:2)

^{1}H NMR (400 MHz, CDCl3) δ 2.46 (m, 2H, C*H*$_2$-CHOH); 2.60 (t, 2H, *J*=8.0 Hz, C*H*$_2$); 2.70 (t, 2H, *J*=8.0 Hz, C*H*$_2$); 4.30 (m, 1H, C*H*-OH); 5.06 (s, 4H, C*H*$_2$- Bn); 5.12 (s, 2H, C*H*$_2$- Bn); 6.74 (m, 4H, Ar-*H*); 7.03 (dd, 2H, *J* = 8.0Hz, *J* = 2.0 Hz, Ar-*H*); 7.11 (dd, 2H, *J* = 8.0Hz, *J* = 2.0 Hz, Ar-*H*); 7.27-7.49 (m, 10H, Bn-*H*); 7.62 (d, 1H, *J* = 2.0 Hz, Ar-*H*), 7.67 (d, 1H, *J* = 2.0 Hz, Ar-*H*).

HRMS (ESI+): *m/z* calcd for $C_{33}H_{30}I_2O_3$ $[M + Na]^+$: 751.01765; found 751.0148

(R)-1,7-bis(4-(benzyloxy)-3-iodophenyl)hept-4-yn-3-ol ((R)-89)



89

Chemical Formula: $C_{33}H_{30}I_2O_3$
Exact Mass: 728,03

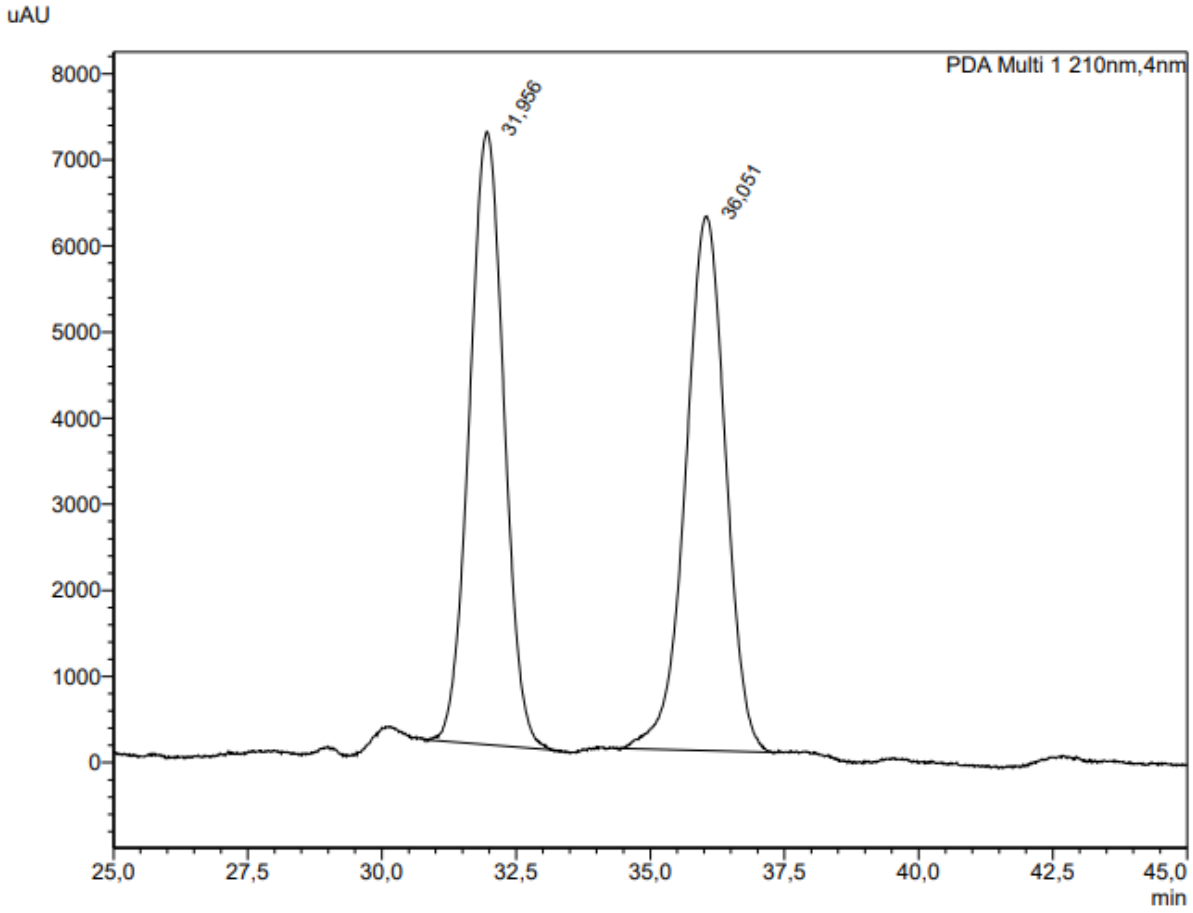
A 10 mL flask was charged with $Zn(Otf)_2$ (1.1 equiv., 0.18 mmol, 67 mg) and (+)-N-Methylephedrine (1.2 equiv., 0.20 mmol, 35.64 mg) and purged with argon for 15 min. To the flask was added toluene (0.5 mL) and Et_3N (1.2 equiv., 0.20mmol, 20.13 mg). The resulting mixture was stirred at r.t. for 2 hours before alkyne **81'** was added (1.2 equiv., 0.20 mmol, 72 mg). After 15 min of stirring the aldehyde **41** (1.0 equiv., 0.17mmol, 61 mg) was added. After 16 hours the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (1.0 mL). The reaction mixture was poured into a separatory funnel containing diethyl ether (3 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 3 mL). The combined organic layers were washed with brine (3 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to afford the desired compound **(R)-89** with 37% yield and 43% ee.

Rf= 0.25 (EP/EtOAc = 8:2)

^{1}H NMR (400 MHz, CDCl3) δ 2.46 (m, 2H, C*H*$_2$-CHOH); 2.60 (t, 2H, *J*=8.0 Hz, C*H*$_2$); 2.70 (t, 2H, *J*=8.0 Hz, C*H*$_2$); 4.30 (m, 1H, C*H*-OH); 5.06 (s, 4H, C*H*$_2$- Bn); 5.12 (s, 2H, C*H*$_2$- Bn); 6.74 (m, 4H, Ar-*H*); 7.03 (dd, 2H, *J* = 8.0Hz, *J* = 2.0 Hz, Ar-*H*); 7.11 (dd, 2H, *J* = 8.0Hz, *J* = 2.0 Hz, Ar-*H*); 7.27-7.49 (m, 10H, Bn-*H*); 7.62 (d, 1H, *J* = 2.0 Hz, Ar-*H*), 7.67 (d, 1H, *J* = 2.0 Hz, Ar-*H*).

HRMS (ESI+): *m/z* calcd for $C_{33}H_{30}I_2O_3$ $[M + Na]^+$: 751.01765; found 751.0148

The optical purity was determined by HPLC chiral chromatography using a CHIRACEL OD-H column (250mm, 4.6mm, 3.5µm), eluent: 90:10 hexane/isopropanol, flow: 0.5mL/min, sample concentration: 0.2 mg/mL, injection volume: 20µL, retention time: (*S:*32,244 min, *R:*36,426 min*)*.

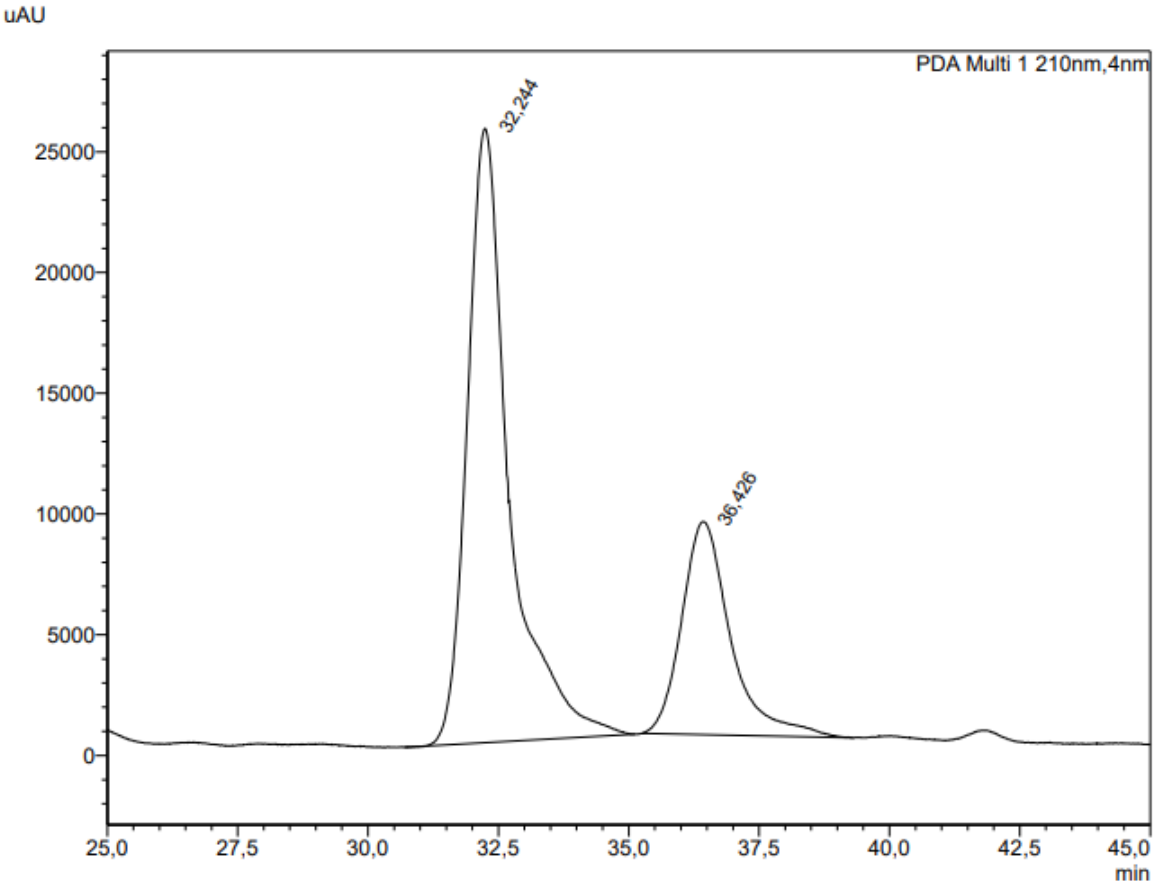


<PDA Chromatogram>

Peak Table

PDA Ch1 210nm

Peak#	Ret. Time	Area	Height	Area%	Capacity Factor(k')	Resolution(USP)	Lambda max
1	31,956	318277	7118	49,705	--	--	207/284/291
2	36,051	322054	6204	50,295	0,128	3,239	206/283/488/583
Total		640331	13322	100,000			

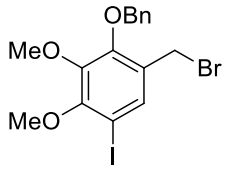


Peak Table

PDA Ch1 210nm

Peak#	Ret. Time	Area	Height	Area%	Capacity Factor(k')	Resolution(USP)	Lambda max
1	32,244	1425222	25431	71,286	--	--	207/284/658/486/404
2	36,426	574072	8818	28,714	0,130	2,918	207/285/658/375/399
Total		1999294	34249	100,000			

2-Bbenzyloxy-1-(bromomethyl)-5-iodo-3,4-dimethoxybenzene (92)



92

Chemical Formula: $C_{16}H_{16}BrIO_3$
Exact Mass: 461,93

To a solution of triphenylphosphine (PPh_3) (278 mg, 1.04 mmol) and imidazole (124 mg, 1.84 mmol) in DCM (6 mL), bromine (Br_2) (0.054 mL, 1.04 mmol) was added dropwise at 0 °C. The solution of **79** (1 equiv., 0.92mmol, 313mg) in DCM (2 mL) was added to the above solution dropwise at 0 °C. Then, the reaction mixture was stirred for 1 h at rt and quenched with satd. NH_4Cl (10 mL). The aqueous layer was extracted with DCM and the combined organic layers were washed with satd. NH_4Cl (5 mL), brine, dried over Na_2SO_4,and filtered. The filtrate was concentrated under vacuo. The resulting residue was purified by column chromatography on silica gel to afford the desired compound **92** as a white glassy solid.

Yield = (0.85 mmol, 391mg) 92%

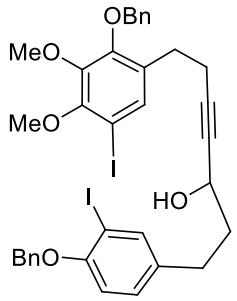
Rf= 0.8 (PE/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H, O-C*H*$_3$); 3.92 (s, 3H, O-C*H*$_3$); 4.47 (s, 2H, C*H*$_2$-Br); 5.15 (s, 2H, C*H*$_2$-Bn); 7.30-7.50 (m, 5H, Ar-*H*); 7.53 (s, 1H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 40.49, 60.40, 61.07, 75.69, 85.28, 128.40, 128.60, 129.29, 133.98, 134.25, 136.97, 146.75, 151.64.

HRMS (ESI+): *m/z* calcd for $C_{16}H_{16}BrIO_3$ $[M + Na]^+$: 484.92197; found 484.9220

1-(4-(benzyloxy)-3-iodophenyl)-7-(2-(benzyloxy)-5-iodo-3,4-dimethoxyphenyl)hept-4-yn-3-ol (94)



94

Chemical Formula: $C_{35}H_{34}I_2O_5$
Exact Mass: 788,05

To a solution of trimethylsilyl alkyne (2.4 equiv., 0.56 mmol, 275 mg) and aldehyde (1.0 equiv., 0,23 mmol, 85 mg) in THF (1.8 mL) at 55°C, TBAF (25 mol %, 1M in dry THF, 0.058 mmol, 0.058 mL) was added and then the reaction mixture was stirred at room temperature for 1 h. This was followed by the addition of 1 M aqueous HCl (1.0 mL) and further stirring for 15 min at room temperature, The reaction mixture was neutralized with aqueous $NaHCO_3$ and then it was extracted with ethyl acetate. The organic layers were collected and dried with anhydrous Na_2SO_4 followed by solvent removal under reduced pressure, The resulting residue was purified by column chromatography on silica gel to afford the desired compound **94.**

Yield= (0.078 mmol, 61.6 mg) 34%

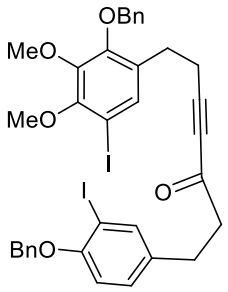
Rf= 0.2 (EP/EtOAc = 8:2)

^{1}H NMR (400 MHz, CDCl3) δ 1.90 (m, 2H, CH_2-CHOH), 2.40 (m, 2H, CH_2); 2.63 (t, 2H, *J*=8.0 Hz, CH_2); 2.69 (t, 2H, *J*=8.0 Hz, CH_2); 3.87 (s, 3H, O-CH_3); 3.90 (s, 3H, O-CH_3); 4.28 (m, 1H, C*H*-OH); 5.06 (s, 2H, CH_2- Bn); 5.12 (s, 2H, CH_2- Bn); 6.76 (d, 2H, *J*=8.0 Hz, Ar-*H*); 7.06 (dd, 2H, *J* = 8.0Hz, *J* = 2.0 Hz, Ar-*H*); 7.32-7.50 (m, 11H, Bn-*H*); 7.64 (d, 1H, *J* = 2.0 Hz, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 19.76, 28.88, 30.03, 39.52, 60.89, 61.02, 61.77, 71.01, 75.26, 81.99, 85.04, 85.12, 86.85, 112.72, 127.00, 127.02, 127.85, 128.03, 128.21, 128.55, 128.57, 129.44, 132.08, 133.54, 136.08, 136.69, 137.34, 139.38, 146.69, 151.38, 152.51, 155.54

HRMS (ESI+): *m/z* calcd for $C_{35}H_{34}I_2O_5$ $[M + Na]^+$: 811.03878; found 811.0362

1-(4-(benzyloxy)-3-iodophenyl)-7-(2-(benzyloxy)-5-iodo-3,4-dimethoxyphenyl)hept-4-yn-3-one (95)



95
Chemical Formula: $C_{35}H_{32}I_2O_5$
Exact Mass: 786,03

To a solution of alcohol **94** (1.0 equiv., 0.078mmol, 61.6mg) in DCM (1mL), Dess-Martin Periodinane (1.5 equiv., 0.12 mmol, 50mg) was added at 0°C. The mixture was stirred for 16h, quenched with water and extracted with DCM. The organic layers were dried on Na_2SO_4 filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel to afford the desired compound **95** as a yellowish oil.

Yield= (0.051 mmol, 39.8mg) **65%**

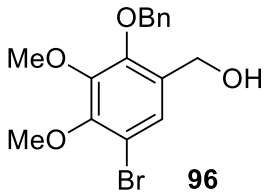
Rf= 0.5 (PE/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51 (t, 2H, *J*=8.0 Hz, C-*H*$_2$); 2.71 (t, 2H, *J*=8.0 Hz, C-*H*$_2$); 2.77-2.85 (m, 4H, *CH*$_2$); 3.88 (s, 3H, O-*CH*$_3$); 3.90 (s, 3H, O-*CH*$_3$); 5.08 (s, 2H, C*H*$_2$-Bn); 5.12 (s, 2H, C*H*$_2$-Bn); 6.76 (d, 1H, *J*= 8.0Hz, Ar-*H*), 7.06 (dd, 1H, *J'*=8.0Hz, *J''*=2.0 Hz, Ar-*H*); 7.26-7.51 (m, 11H, Ar-*H*); 7.63 (d, 1H, *J*=2.0 Hz, Ar-*H*).

^{13}C NMR (101 MHz, $CDCl_3$) δ 19.94, 28.14, 28.45, 47.01, 60.90, 61.02, 70.98, 75.26, 81.42, 85.05, 86.88, 93.69,112.71, 127.00, 127.87, 128.06, 128.29, 128.56, 128.61, 129.40, 131.15, 133.43, 134.92, 136.61, 137.22, 139.28, 146.69, 151.34, 152.85, 155.76, 186.62.

HRMS (ESI+): *m/z* calcd for $C_{35}H_{32}I_2O_5$ $[M + Na]^+$: 809.02313; found 809.0204

(2-(benzyloxy)-5-bromo-3,4-dimethoxyphenyl)methanol (96)



96

Chemical Formula: $C_{16}H_{17}BrO_4$
Exact Mass: 352,03

To a solution of the previously synthesized aldehyde **13'** (1 equiv, 4.07 mmol, 1.43 g) in DCM (49mL) was added DIBAL-H (2.5 equiv., 10.18 mL, 1M in toluene,) dropwise at -40 °C. The mixture was stirred at -40 °C for 3 h before quenching with a saturated aqueous solution of diethyl tartrate sodium potassium (100mL) at - 40 °C. The temperature was allowed to warm to r.t and the mixture was stirred all night long. The phases were separated, the aqueous layer was extracted with DCM, combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel to afford the desired compound **96** as a colorless oil**.**

Yield = (3.98 mmol, 1,4 g) 98%

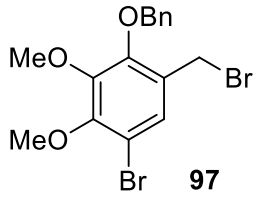
Rf= 0.2 (PE/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H, OC*H*$_3$); 3.95 (s, 3H, OC*H*$_3$); 4.47 (s, 2H, C*H*$_2$-OH) 5.11 (s, 2H, C*H*$_2$-Bn); 7.25 (s, 1H, Ar-*H*), 7.35-7.42 (m, 5H, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 60.84, 61.09, 61.17, 75.57, 111.66, 126.66, 128.46, 128.52, 128.68, 131.58, 136.94, 147.39, 149.85, 151.01.

HRMS (ESI+): *m/z* calcd for $C_{16}H_{17}BrO_4$ $[M + K]^+$: 390.9945; found 390.9942

2-(benzyloxy)-5-bromo-1-(bromomethyl)-3,4-dimethoxybenzene (97)



97

Chemical Formula: $C_{16}H_{16}Br_2O_3$
Exact Mass: 413,95

To a solution of triphenylphosphine (PPh_3) (888 mg, 3.32 mmol) and imidazole (396 mg, 5.88 mmol) in DCM (19 mL), bromine (Br_2) (0.17 mL, 3.32 mmol) was added dropwise at 0 °C. The solution of **96** (1 equiv., 2.94mmol, 1g) in DCM (6 mL) was added to the above solution dropwise at 0 °C. Then, the reaction mixture was stirred for 1 h at rt and quenched with satd. NH_4Cl (30 mL). The aqueous layer was extracted with DCM and the combined organic layers were washed with satd. NH_4Cl (15 mL), brine, dried over Na_2SO_4,and filtered. The filtrate was concentrated under vacuo. The resulting residue was purified by column chromatography on silica gel to afford the desired compound **97** as a colorless oil.

Yield = (2.0 mmol, 828 mg) 68%

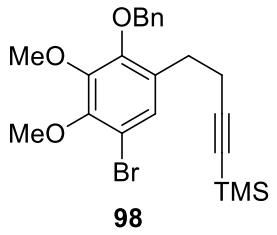
Rf= 0.8 (PE/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H, O-C*H*$_3$); 3.94 (s, 3H, O-C*H*$_3$); 4.40 (s, 2H, C*H*$_2$-Br); 5.18 (s, 2H, C*H*$_2$-Bn); 7.31 (s, 1H, Ar-H); 7.36-7.44 (m, 5H, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 27.48, 61.13, 61.18, 75.31, 111.71, 128.26, 128.38, 128.40, 128.42, 128.56, 128.61, 128.73, 136.99, 147.75, 150.56, 151.91.

HRMS (ESI+): *m/z* calcd for $C_{16}H_{16}Br_2O_3$ $[M + K]^+$: 452.9098; found 452.9096.

(4-(2-(benzyloxy)-5-bromo-3,4-dimethoxyphenyl)but-1-yn-1-yl)trimethylsilane (98)



98

Chemical Formula: $C_{22}H_{27}BrO_3Si$
Exact Mass: 446,09

A solution of 1-TMS-propyne (1.9 equiv. 1.83 mmol, 0.273 mL,) in dry THF (8.5 mL) was treated dropwise with n-BuLi (1.7 equiv. 1.63 mmol, 0.74 mL, 2.2 M solution in hexanes) at 0 ºC. The solution was stirred for 15 min, and transferred via cannula to another solution of **97** (1.0 equiv., 0.97 mmol, 400 mg,) in THF (2.8 mL) while maintaining at –65 ºC. After stirring at –65 ºC for 10 min, the reaction was allowed to reach rt and stirred for 30 min. The reaction was quenched with 5% HCl and the volatiles 3) and the combined ×were removed under vacuo. The reaction was extracted with ether (10 mL organic layers were washed with water, brine and dried over $MgSO_4$. The mixture was filtered and evaporated. The resulting residue was purified by column chromatography on silica gel to afford the desired compound **98** as a yellowish oil.

Rf = 0.6 (EP/EtOAc = 9:1)

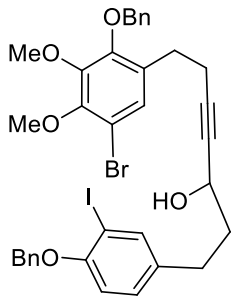
Yield = (0.76 mmol, 338 mg) 78%

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.14 (s, 9H, C*H*$_3$-Si); 2.40 (t, 2H, *J*=8.0 Hz, *CH*$_2$); 2.72 (t, 2H, *J*=8.0 Hz, *CH*$_2$-Bn), 3.91 (s, 3H, O-C*H*$_3$), 3.92 (s, 3H, O-C*H*$_3$), 5.06 (s, 2H, C*H*$_2$-Bn); 7.18 (s, 1H, Ar-*H*), 7.34-7.46 (m, 5H, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 0.00, 20.79, 28.75, 60.93, 61.01, 75.12, 85.55, 106.29, 111.08, 127.87, 127.90, 128.02, 128.42, 131.16, 137.30, 147.39, 149.74, 150.07.

HRMS (ESI+): *m/z* calcd for $C_{22}H_{27}BrO_3Si$ $[M + H]^+$: 447.0986; found 447.0996

1-(4-(benzyloxy)-3-iodophenyl)-7-(2-(benzyloxy)-5-bromo-3,4-dimethoxyphenyl)hept-4-yn-3-ol (99)



99

Chemical Formula: $C_{35}H_{34}BrIO_5$
Exact Mass: 740,06

To a solution of trimethylsilyl alkyne (2.2 equiv., 0.75 mmol, 336 mg) and aldehyde (1.0 equiv., 0,34 mmol, 125 mg) in THF (2.7 mL) at 55°C, TBAF (25 mol %, 1M in dry THF, 0.085 mmol, 0.085 mL) was added and then the reaction mixture was stirred at room temperature for 1 h. This was followed by the addition of 1 M aqueous HCl (1.0 mL) and further stirring for 15 min at room temperature, The reaction mixture was neutralized with aqueous $NaHCO_3$ and then it was extracted with ethyl acetate. The organic layers were collected and dried with anhydrous Na_2SO_4 followed by solvent removal under reduced pressure, The resulting residue was purified by column chromatography on silica gel to afford the desired compound **99** as a yellowish oil**.**

Yield= (0,23 mmol, 174mg) 69%

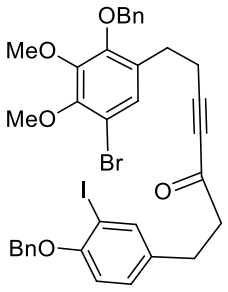
Rf= 0.2 (EP/EtOAc = 8:2)

^{1}H NMR (400 MHz, CDCl3) δ 1.93 (m, 2H, CH_2-CHOH), 2.41 (m, 2H, CH_2); 2.62 (t, 2H, *J*=8.0 Hz, CH_2); 2.71 (t, 2H, *J*=8.0 Hz, CH_2); 3.89 (s, 3H, O-CH_3); 3.92 (s, 3H, O-CH_3); 4.28 (m, 1H, C*H*-OH); 5.06 (s, 2H, CH_2- Bn); 5.12 (s, 2H, CH_2- Bn); 6.76 (d, 2H, *J*=8.0 Hz, Ar-*H*); 7.06 (dd, 2H, *J* = 8.0Hz, *J* = 2.0 Hz, Ar-*H*); 7.15 (d, 1H, *J* = 2.0 Hz, Ar-*H*); 7.32-7.50 (m, 11H, Bn-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 19.74, 29.04, 30.01, 39.49, 60.42, 61.05, 61.73, 71.00, 75.28, 82.00, 85.04, 86.85, 111.31, 112.72, 127.02, 127.78, 128.06, 128.22, 128.55, 128.57, 129.42, 131.22, 136.09, 136.08, 136.70, 137.32, 139.36, 147.59, 149.93 150.24, 155.54

HRMS (ESI+): *m/z* calcd for $C_{35}H_{34}BrIO_5$ $[M + Na]^+$: 763.05265; found 763.0498

1,7-bis(4-(benzyloxy)-3-iodophenyl)hept-4-yn-3-one (100)



100

Chemical Formula: $C_{35}H_{32}BrIO_5$
Exact Mass: 738,05

To a solution of alcohol **99** (1.0 equiv., 0.23mmol, 174mg) in DCM (2mL), Dess-Martin Periodinane (1.5 equiv., 0.34 mmol, 142mg) was added at 0°C. The mixture was stirred for 3h, quenched with water and extracted with DCM. The organic layers were dried on Na_2SO_4 filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel to afford the desired compound **100.**

Yield= (0.17 mmol, 125.5 mg) **74%**

Rf= 0.5 (PE/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (t, 2H, *J*=8.0 Hz, C-*H*$_2$); 2.73 (t, 2H, *J*=8.0 Hz, C-*H*$_2$); 2.76-2.85 (m, 4H, *CH*$_2$); 3.90 (s, 3H, O-*CH*$_3$); 3.92 (s, 3H, O-*CH*$_3$); 5.08 (s, 2H, C*H*$_2$-Bn); 5.12 (s, 2H, C*H*$_2$-Bn); 6.76 (d, 1H, *J*= 8.0Hz, Ar-*H*), 7.06 (dd, 1H, *J'*=8.0Hz, *J''*=2.0 Hz, Ar-*H*); 7.12 (s, 1H, Ar-*H*); 7.32-7.51 (m, 10H, Ar-*H*); 7.63 (d, 1H, *J*=2.0 Hz, Ar-*H*).

^{13}C NMR (101 MHz, $CDCl_3$) δ 19.92, 28.29, 28.46, 46.95, 61.07, 61.14, 70.98, 75.27, 81.40, 86.87, 93.67, 111.36, 112.71, 127.01, 127.68, 127.87, 128.09, 128.30, 128.56, 128.61, 129.37, 130.27, 134.90, 136.61, 137.21, 139.25, 147.61, 150.21, 150.28, 155.77, 186.61.

HRMS (ESI+): *m/z* calcd for $C_{35}H_{32}BrIO_5$ $[M + Na]^+$: 761.03700; found 761.0345

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Scientific Productions

Oral communications

1. A. Santarsiere, S. Choppin , F. Colobert , G. Hanquet , P. Lupattelli , M. Funicello and L. Chiummiento.
"The influence of unsaturated systems in the synthesis of cyclic diarylheptanoids: the total synthesis of Myricanol as a case study"
10-14 September 2023 Roma, Italy
XLI Convegno Nazionale della Divisione di Chimica Organica (CDCO 2023) (Atti Del Convegno, OC-03, pag.68).

2. A. Santarsiere, M. Funicello, P. Lupattelli and L. Chiummiento.
"L' influenza del grado di insaturazione sulle macrociclizzazioni: sintesi di diarileptanoidi ciclici"
29-30 June 2023 Reggio Calabria, Italy
XIX Convegno Nazionale sulle Reazioni Pericicliche e Sintesi di Etero e Carbocicli (CIRP 2023)
(Atti di Congresso, OC-07, pag. 22).

2. A. Santarsiere, M. Funicello, P. Lupattelli, L. Chiummiento, S. Choppin, F. Colobert and G. Hanquet.
"The ene-yne structural motif as a way to reach the myricanol**"**
19-21 September 2022, Matera, Italy
ChirItaly 2022 (Atti di convegno, O5, pag 21)

3. P. Lupattelli, T. Laurita, L. Chiummiento, M. Funicello, A. Santarsiere.
"From trans 2,3-diaryloxiranes to trans 2,3-diaryl-2,3-dihydrobenzofurans: toward the synthesis of ε-Viniferin and Gnetin C"
19-21 September 2022 Matera, Italy
ChirItaly 2022 (Atti di convegno, O3, pag 19)

4. A. Santarsiere, M. Funicello, P. Lupattelli, L. Chiummiento, S. Choppin, F. Colobert and G. Hanquet.
"A new total synthesis of Myricanol: the influence of an ene-yne system"
23-26 May 2022 Kolymbari, Crete, Greece
A PSE Young Scientists' Meeting (PSE-YSM2022) (Abstract book, OP20, pag 87)

5. A. Santarsiere, M. Funicello, P. Lupattelli, L. Chiummiento
"Rieche Formylation of Phenyl Boronic Acids"
29-30 November 2021 Milano, Italy

XXXV SYMPOSIUM NEW TRENDS IN ORGANIC SYNTHESIS (NTOS2021)

(Flash presentetion, First Session, n.6, http://sintesi.unimi.it/abstracts.html)

Poster communications

1. A. Santarsiere , S. Choppin, F. Colobert, G. Hanquet, M. Funicello, P. Lupattelli and L. Chiummiento.
   "A new approach to the total synthesis of Myricanol"
   18 October 2023 Strasbourg, France
   LIMA day

2. A. Santarsiere , S. Choppin, F. Colobert, G. Hanquet, M. Funicello, P. Lupattelli and L. Chiummiento
   "A new approach to the total synthesis of Myricanol"
   2-4 November 2022 École Polytechnique, **Palaiseau, France**
   JCO - Journées De Chimie Organique (Book of Abstract, P. A142, pag. 257).

3. A. Santarsiere, M. Funicello, P. Lupattelli, L. Chiummiento,
   "Synthesis of chiral oxazolidinones with promising anti-HIV activity "
   19-21 September 2022 Matera, Italy
   ChirItaly 2022 (Atti di convegno, P9, pag 62)

4. A. Santarsiere, M, Funicello, P. Lupattelli, L. Chiummiento
   "Synthesis of aryl aldehydes by Rieche formylation reactions of electron-rich phenyl boronic acids "
   14-23 September 2021
   XXVII Congresso Nazionale della Società Chimica Italiana (Book Of Abstract P3, ORG PO095)

Publications:

1. Santarsiere, A.; Funicello, M.; Lupattelli, P.; Choppin, S.; Colobert, F.; Hanquet, G.; Chiummiento, L.
   "Reactivity Insights of Methoxyphenyl Boronic Acids in Rieche Formylation Reaction"
   ChemistrySelect, **2023**, *8* (34), e20230210.

Alessandro SANTARSIERE

A NEW TOTAL SYNTHESIS OF MYRICANOL: THE INFLUENCE OF AN ENE-YNE SYSTEM

Résumé

L'objectif principal de cette thèse de doctorat est la synthèse totale du myricanol, un composé naturel important aux activités biologiques intéressantes. En particulier, ses remarquables propriétés anti-Alzheimer en font un candidat potentiel pour le traitement de diverses taupathies, car il est capable de réduire les niveaux de protéine Tau qui ont tendance à s'accumuler sous forme phosphorylée dans certaines maladies neurodégénératives.

Actuellement, seules trois synthèses racémiques du (+/-)-myricanol sont rapportées dans la littérature.

Tout d'abord, cette thèse vise principalement à explorer les conditions optimales pour rendre la cyclisation moins défavorable en utilisant un *séco*-précurseur insaturé et donc "rigide" en limitant les variations des degrés de liberté conformationnelles pendant la cyclisation.

Deux approches synthétiques ont été explorées au cours de cette thèse, d'une part l'étape de macrocyclisation est réalisée à partir d'un système biarylique fonctionnalisé, d'autre part, l'étape de macrocyclisation est effectuée sur un diarylheptanoïde linéaire.

Mots clés: myricanol, diarylheptanoïdes, couplage de Suzuki-Miyaura domino, anti-Alzheimer.

Abstract

The main objective of this thesis is the total synthesis of myricanol, a natural compound with significant biological activities. In particular, its remarkable anti-Alzheimer's properties make it a potential drug for the treatment of various tauopathies, as it has the ability to reduce levels of tau protein that tend to pathologically accumulate in phosphorylated forms in certain neurodegenerative diseases.

Actually only three synthesis of racemic (+/-) - myricanol have been reported in the literature. Firstly, this thesis aims primarily to investigate the optimal conditions to make cyclization less unfavorable using an unsaturated and thus "rigid" seco-precursor to limit conformational degrees of freedom during cyclization.

Two main synthetic approacheshave been explored in the course of this thesis, on one side, the macrocyclization involves the properly functionalized biaryl system, on the other side the macrocyclization is performed on a linear diarylheptanoid.

Keywords: myricanol, diarylheptanoides, Suzuki-Miyaura domino coupling, anti-Alzheimer.