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TOWARDS THE ATROPO-STEREOSELECTIVE TOTAL SYNTHESIS OF MYRICANOL

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“Homo faber ipsius fortunae”

Appio Claudio Cieco

Ai miei genitori,

a mio fratello,

a mia sorella

e a Rocco

TOWARDS THE ATROPO-STEREOSELECTIVE TOTAL SYNTHESIS OF MYRICANOL

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ABSTRACT

ITALIANO

VERSO LA SINTESI ATROPO-STEREOSELETTIVA DEL MIRICANOLO

Introduzione e scopo della tesi

Lo scopo di questa tesi è la sintesi totale del miricanolo, un [7,0]-*meta*-ciclofano naturale che appartiene alla classe dei diarileptanoidi, composti con uno scheletro 1,7-diarileptanoico. I diarileptanoidi sono ampiamente riconosciuti per i loro effetti terapeutici e per le numerose attività biologiche, come antiinfiammatori, antiossidanti, antitumorali, epatoprotettivi e neuroprotettivi.[1]

I diarileptanoidi sono estratti da prodotti naturali in forma lineare e nelle forme cicliche di [7,0]-*meta,meta*-ciclofani e [7,1]-*meta,para*-ciclofani (**Figura A**)

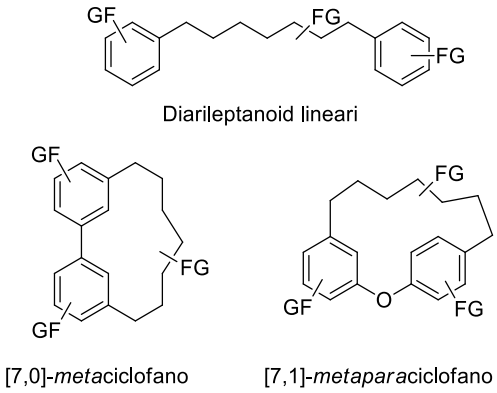


Figura A

Il miricanolo è un diarileptanoide ciclico estratto da diverse specie di *Myricaceae* come la *Myrica cerifera*[2], la *Myrica nagi*[3], la *Myrica gale*[4] e la *Myrica rubra*[5].

E' stato dimostrato che il miricanolo possiede un forte capacità di ridurre i livelli di proteina tau nelle cellule neuronali (effetto anti Alzheimer).[2,6] Per questo motivo abbiamo focalizzato la nostra attenzione su metodologie che ci potessero condurre alla sintesi stereoselettiva del (+)-a*R*,11*S*-miricanolo e del (-)-a*S*,11*R*-miricanolo (**Figura B**).

Dickey e il suo gruppo di ricerca hanno condotto dei test biologici per valutare i livelli di proteina tau nelle cellule HeLa-C3 trattate con il (+)-a*R*,11*S*-miricanolo isolato dalla *Myrica cerifera* (86%ee) e con il miricanolo racemo commercialmente disponibile (9% ee). Questo studio ha mostrato che soltanto la miscela scalemica del (+)-a*R*,11*S*-miricanolo riduceva i livelli di proteina tau.[2]

Lo stesso gruppo di ricerca ha poi pubblicatto, molto recentemente, un lavoro in cui contrariamente a ciò che era stato dimostrato precedentemente, emerge che il (-)-a*S*,11*R*-miricanolo (ottenuto per separazione all'HPLC chirale dal miricanolo racemo di sintesi) risulta il responsabile principale della riduzione del livello di proteina tau.[6]

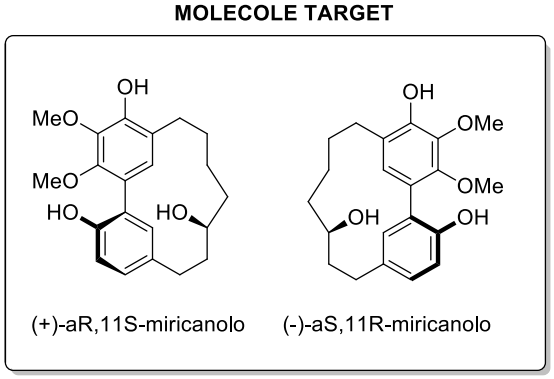


Figura B

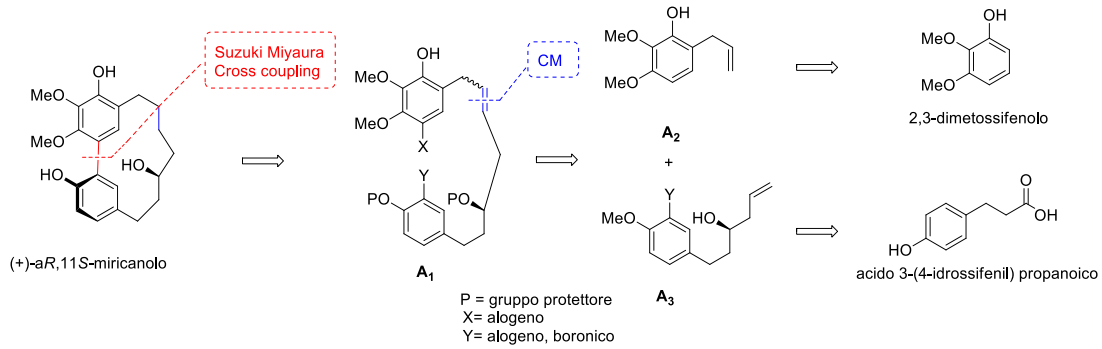
Il miricanolo racemo è inoltre in grado di abbassare i livelli di ossido nitrico (NO)[7] e possiede anche delle proprietà di anti-infiammatorie e anti-androgeniche[8]. Inoltre, degli studi molto recenti, hanno dimostrato che esso costituisce un buon candidato per la prevenzione e il trattamento del cancro al polmone.[9]

Alla luce di tutti questi dati bibliografici, appare chiaro come la chiralità assiale e centrale della molecola siano strettamente legate all'attività biologica della stessa. Per questo motivo il lavoro di questa tesi è focalizzato sulla preparazione del miricanolo sia in forma racemica sia enantiopura, mediante un approccio atropo-stereoselettivo. Fino ad ora, soltanto due sintesi del (+/-)-miricanolo sono state riportate e nessuna sintesi asimmetrica. Il miricanolo racemo è stato ottenuto con delle rese totali molto basse (0,21 % in 14 passaggi, come riportato da Whiting)[10], (2.03% in 7 passaggi partendo da frammenti non commerciali, come decritto da Dickey et *al*.)[6] , senza nessun controllo nè della chiralità centrale nè di quella assiale.

Approccio retrosintetico 1

Il nostro approccio retrosintetico è illustrato nello **Schema I.** Il miricanolo potrebbe essere ottenuto a partire dal precursore lineare $\mathbf{A_1}$ per mezzo di una reazione di Suzuki-Miyaura di tipo domino[11] che non è mai stata

provata prima su questo tipo di precursori. Il diarileptanoide dialogenato **A₁** potrebbe essere facilmente ottenuto utilizzando una reazione di cross-metatesi tra gli alcheni terminali **A₂** e **A₃**. Il fenolo C-allilico potrebbe essere preparato per riarrangiamento di Claisen dal corrispondente *O*-allilfenolo.[12] L'alcol homo-allilico **A₃** potrebbe invece derivare da un'allilazione classica racemica o enantioselettiva[13], e se la configurazione del centro stereogenico di **A₁** viene fissata come R, si potrebbe arrivare alla sintesi del (+)-a*R*,11*S*-miricanolo.



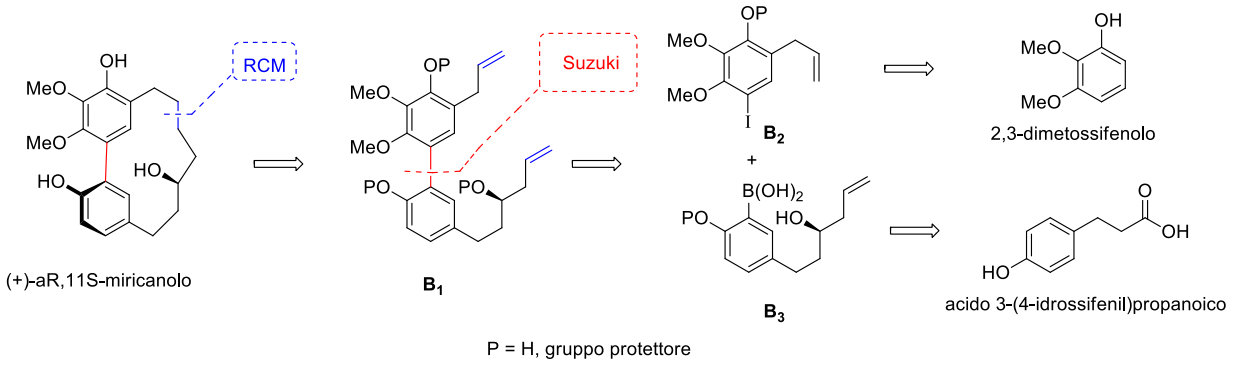
Schema I

I passaggi chiave di questa strategia sintetica sono rappresentati da: 1) il riarrangiamento di Claisen; 2) la cross-metatesi; 3) la macrociclizzazione mediante una Suzuki-Miyaura intramolecolare domino.

Come per la maggior parte dei prodotti ciclici, il passaggio chiave della sintesi del miricanolo, è sicuramente la formazione del macrociclo, che nel caso dei diarileptanoidi rappresenta un obiettivo molto importante. Le tensioni imposte dal sistema macrociclico impediscono generalmente la rotazione intorno al legame biarilico dei ciclofani, creando quindi le condizioni per l'atropoisomeria.[14]

Approccio retrosintetico 2

Un nuovo approccio retrosintetico è stato proposto per la sintesi del miricanolo (**Schema II**). In questo schema si propone di ottenere il macrociclo mediante una reazione di ring-closing-metatesi del composto **B₁**. Il biarile **B₁** potrebbe essere ottenuto da un accoppiamento di Suzuki-Miyaura intermolecolare tra il derivato alogenato **B₂** e l'acido boronico **B₃**.



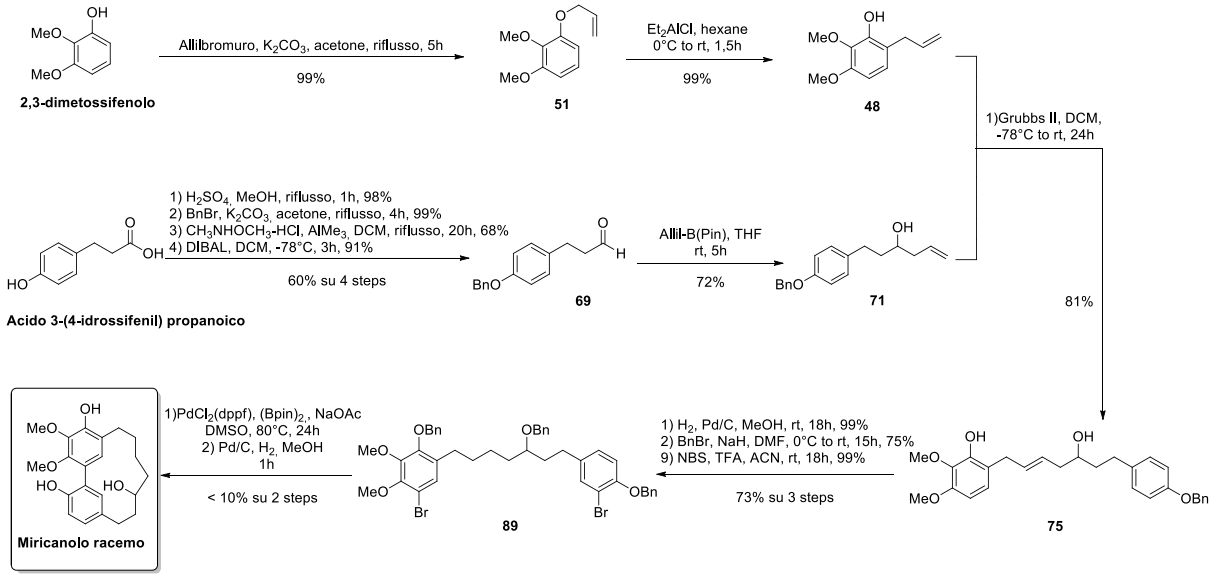
Schema II

I passaggi delicati di questo approccio sono costituiti da: 1) l'accoppiamento di Suzuki-Miyaura in presenza di doppi legami terminali; 2) l'alogenazione in presenza della funzione allilica per ottenere il substrato **B_2**.

I due approcci individuati sono stati studiati parallelamente.

Risultati riguardanti l'approccio 1

Per quanto riguarda lo schema retrosintetico proposto, i frammenti **48** e **71** sono stati sintetizzati con buone rese. (**Schema III**).



Schema III

Il composto **48** è stato ottenuto in 2 steps (allilazione e riarrangiamento di Claisen) con una resa totale del 98%. L'alcol homo-allilico **71** è stato ottenuto partendo dall'acido propanoico commerciale che è stato esterificato, protetto con un benzile e successivamente trasformato nella corrispettiva ammide di Weireb.[15] Quest'ultima è stata ridotta con DIBAL nell'aldeide **69,** che è stata ottenuta con un'ottima resa. L'aldeide **69** è stata anche utilizzata per la preparazione dell'alcol homo-allilico in forma enantiomericamente arricchita, utilizzando un allile complessato con il reattivo (*R*,*R*) Duthaler-Hafner[16]. L'alcol homo-allilico con il centro chirale di configurazione *R* è stato isolato con una resa del 70% e con un eccesso enantiomerico del 90%. In definitiva, l'alcol **71** è stato preparato in 5 passaggi con una resa complessiva del 60% e il suo analogo otticamente attivo è stato ottenuto nello stesso numero di passaggi con una resa totale del 59%. Per il momento, abbiamo scelto di usare solo il composto **71** racemo nella successiva reazione di cross-metatesi, lo scopo è stato quello di mettere a punto una metodologia efficace per la formazione diastereoselettiva del macrociclo che sia poi utilizzabile anche per l'approccio enantioselettivo. La reazione di cross-metatesi tra gli alcheni terminali **48** e **71** è stata ampiamente studiata fino a trovare le condizioni ottimizzate che ci hanno permesso di ottenere il diarileptanoide lineare **75** con una resa dell'80%.[17] Su questo prodotto sono state effettuate, in condizioni di idrogenazione catalitica, la rimozione del doppio legame e la debenzilazione del fenolo.

Successivamente il prodotto è stato completamente protetto sulle funzioni fenoliche e su quella alcolica con il gruppo benzilico. La dibromurazione, condotta sul prodotto protetto, ha portato ad isolare il substrato **89** con un'ottima resa. Il substrato **89** è stato sottoposto a diverse reazioni di Suzuki-Miyaura domino[11], come riportato nella seguente tabella.

Prove[a]	**Fonte di boro (1.2equiv.)**	**Base (10equiv.)**	**Solvente**	**T (°C)**	**T (h)**	**Miricanolo benzilato**[b]
1	$(BPin)_2$	NaOAc	DMSO	80	24	**(10%)**
2	$(BPin)_2$	KOAc	DMSO	80	24	-
3	$(BPin)_2$	NaOAc	Diossano	80	24	-
4	$(BPin)_2$	KOAc	Diossano	80	24	Tracce
5	Bpin-H	KOAc	DMSO	100	24	-
6	Bpin-H	NaOAc	DMSO	100	24	-

a. tutte le reazioni sono state condotte utilizzando $PdCl_2$(dppf) 10mol%; b. dopo debenzilazione quantitativa.

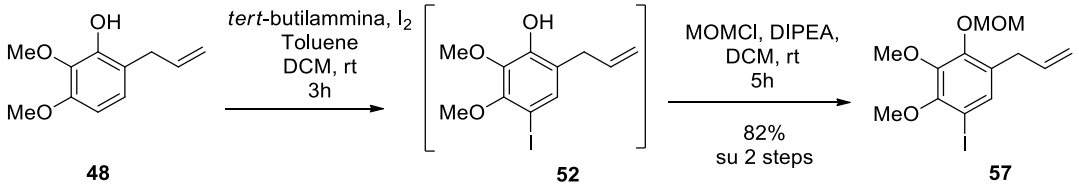
Tabella I

Come mostrato in tabella, la macrociclizzazione appare uno step molto complicato che soltanto nelle condizioni riportate per la prova 1, ci permette di osservare la formazione del prodotto ciclico, la cui resa è stata determinata soltanto dopo la debenzilazione quantitativa. Questo risultato non è del tutto sorprendente, dal momento che la formazione di cicli a 13 termini non è energeticamente favorita, soprattutto se si considara che le porzioni aromatiche coinvolte sono diversamente sostituite.

Ad ogni modo, possiamo affermare di aver ottenuto il miricanolo racemo con una sintesi convergente di 11 steps e una resa totale <2.55%, considerando che il prodotto finale non è stato isolato perfettamente puro.

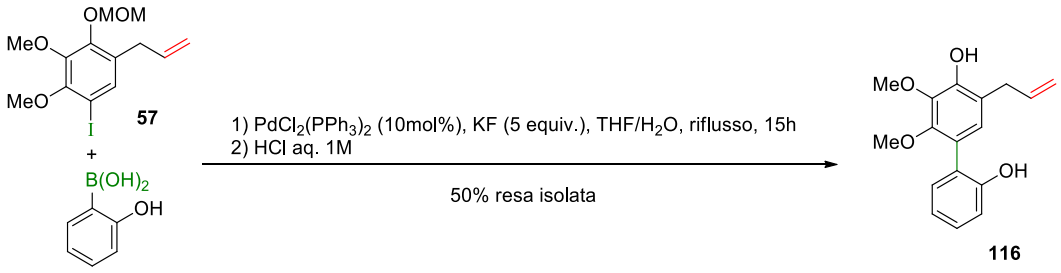
Risultati riguardanti l'approccio sintetico 2

Per il secondo approccio proposto (**Schema II**) si ha la necessità di preparare i frammenti $\mathbf{B_2}$ e $\mathbf{B_3}$**.** Il substrato **57** viene preparato in maniera quasi-quantitativa a partire dall'allil fenolo **48** che, messo in reazione con un complesso di iodio molecolare e tert-butilammina,[18] ci ha permesso di ottenere l'intermedio **52** successivamente protetto con MOMCl (**Schema IV**).



Schema IV

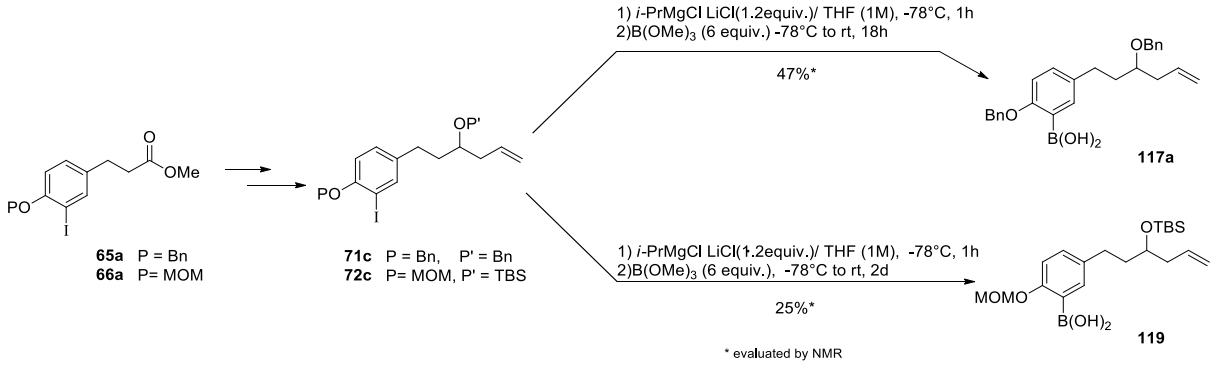
Studi sugli accoppiamenti di Suzuki-Miyaura intermolecolari tra lo ioduro **57** e l'acido *ortho*-fenil boronico commerciale ci hanno permesso, in consizioni ottimizzate, di poter ottenere il biarile **116** con una buona resa e soprattutto evitando di osservare l'isomerizzazione del doppio legame allilico (**Schema V**).



Schema V

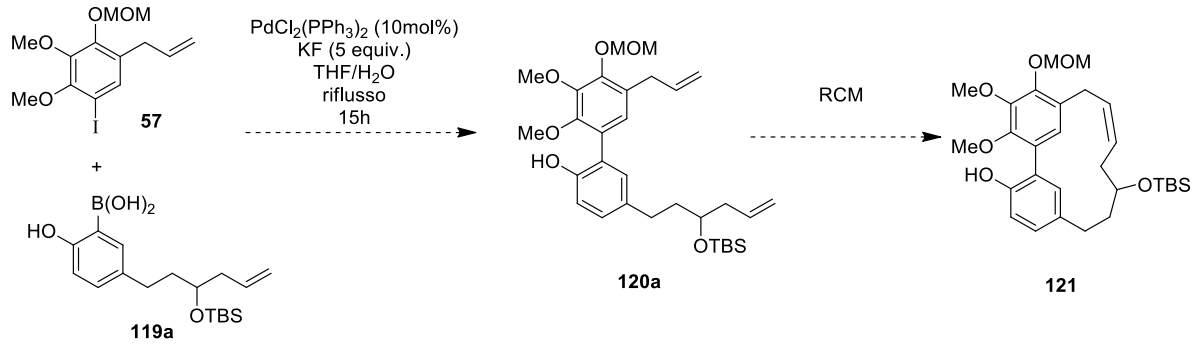
Incoraggiati da questi buoni risultati, ci siamo occupati della preparazione di acidi boronici aventi la struttura del frammento $\mathbf{B_3}$ (**Schema II**). La sintesi degli acidi **117a** e **119** è descritta nelo schema seguente

(**Schema VI**). I precursori alogenati e diversamente protetti **71c** e **72c** derivano dai corrispondenti metil esteri **65a** et **66a** seguendo la stessa sequenza di reazioni utilizzate per preparare l'alcol homoallilico **71** riportato nello schema III. Dopo numerose prove effettuate sui derivati iodurati, gli acidi **117a** e **119** sono stati finalmente ottenuti con rese accettabili utilizzando *i*-PrMgCl-LiCl e $B(OMe)_3$[19]. Prove ulteriori sono in corso per poter ottimizzare questo risultato.



Schema VI

Tra gli acidi boronici preparati, il substrato **119** appare particolarmente interessante, dal momento che potrebbe essere deprotetto selettivamente a dare il corrispondente *ortho*-fenolo, molto simile al boronico commerciale utilizzato nello **Schema V** e usarlo nella reazione di Suzuki-Miyaura nelle condizioni ottimizzate **(Schema VII)**.

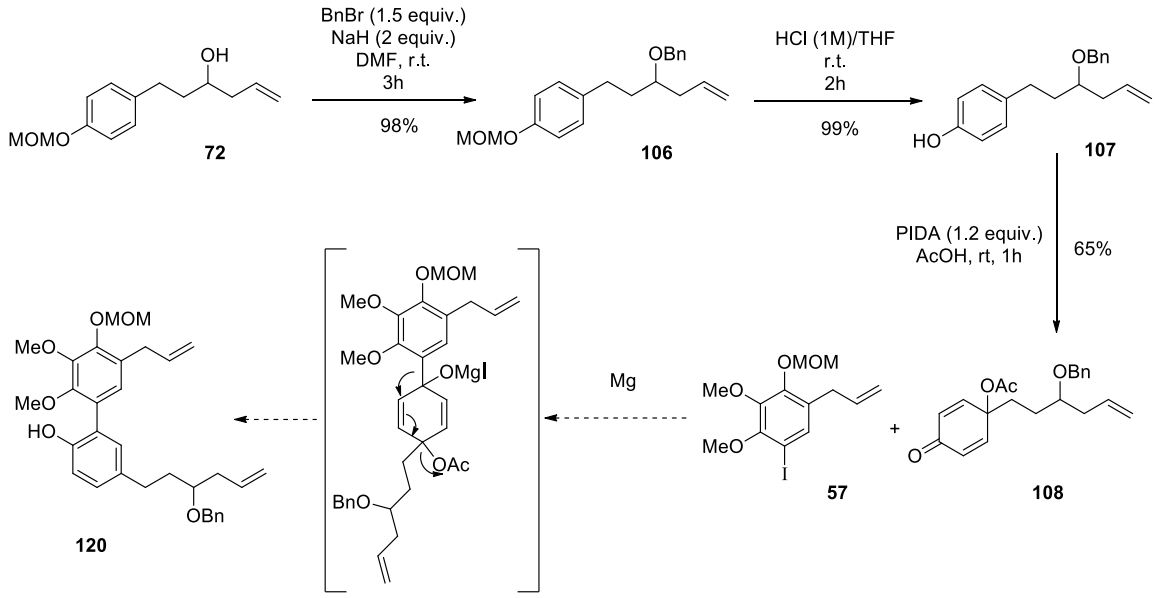


Schema VII

Una volta preparato il substarto **120a** esso sarà messo a reagire in condizioni di ring closing metatesi per dare il ciclo finale **121**.

Un'altra via è stata considerata per poter ottenere il biarile **120a**. Questa strategia è stata possibile in seguito agli studi condotti sulla trasformazione dei fenoli in condizioni ossidative. Come riportato nello schema

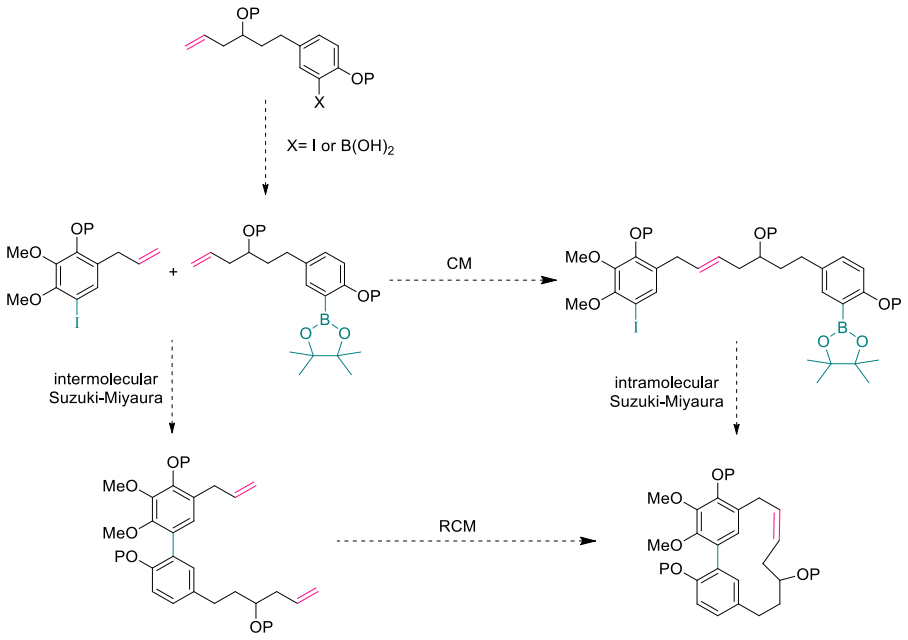
seguente, l'alcol homoallilico **72** è stato benzilato nel corrispondente **106**, e dopo la deprotezione selettiva dal gruppo MOM si è ottenuto il fenolo **107** in maniera quantitativa (**Schema VIII**).



Schema VIII

Il fenolo **107** è stato successivamente trattato con PIDA e acido acetico[20] a dare il dienone-acetato desiderato **108** con una buona resa. Attualmente sono in corso prove per la formazione del reattivo di Grignard dello ioduro **57**. L'idea è quella di ottenere il biarile **120** attraverso un attacco del Grignard sul dienone **108,** uno shift 1,2 e l'eliminazione del gruppo uscente acetato.

Altre startegie di sintesi per potere ottenere il miricaolo nella maniera più efficace possibile sono state proposte. Una via supplementare potrebbe essere, ad esempio, quella in cui l'acido boronico precedentemente preparato viene trasformato nel corrispettivo estere pinacolico. Quest'ultimo potrebbe altresì essere ottenuto mediante reazioni palladio catalizzate sul substrato iodurato precursore (**Schema IX**). L'estere boronico, più stabile dell'acido, potrebbe essere impiegato nella reazione di cross metatesi a dare un diarileptanoide lineare altamente funzionalizzato. Quest'ultimo, utilizzato nella reazione di Suzuki-Miyaura classica, potrebbe dare in maniera più efficiente il macrociclo del miricanolo rispetto a quanto osservato nella reazione di Suzuki-Miyaura di tipo domino. Inoltre, lo stesso estere boronico potrebbe essre impiegato come partner in una reazione di accoppiamento di tipo intermolecolare a dare il biarile corrispondete che potrebbe essere ciclizzato mediante ring closing metatesi (**Schema IX**).



Schema IX

Lo studio di tutte queste vie considerate ci porteranno a decretare la strategia migliore per poter portare a termine la sintesi diastereo ed enantioselettiva della stessa molecola.

Test biologici

Durante la preparazione dei precursori lineari del miricanolo mediante cross-metatesi, sono stati sintetizzati una serie di analoghi a struttuta diarilalchilica con catene carboniose più corte (4 o 6 atomi) o più lunghe (10 atomi).

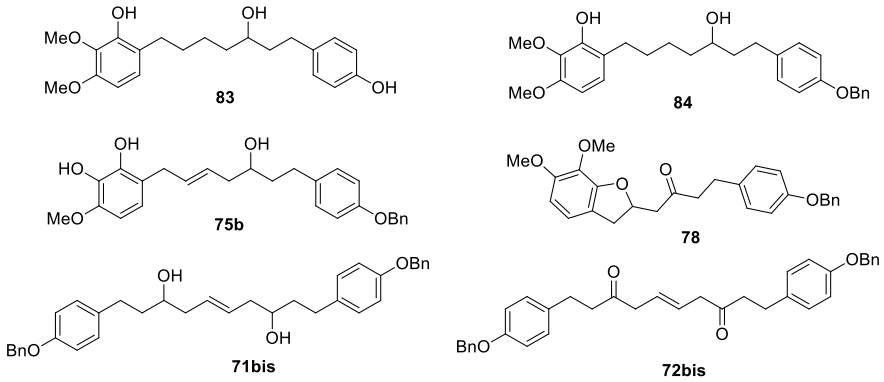


Figura C

I prodotti sintetizzati (**Figura C**) sono stati utilizzati per valutare l'effetto anti-infiammatorio su cellule umane U937 e su cellule murine BV-2. La vitalità cellulare è stata determinata mediante il saggio colorimetrico MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide].[21]

Lipopolisaccaride (LPS) è stato impiegato per innescare l'infiammazione nelle due linee cellulari considerate (U937 e BV-2). I livelli di ossido nitrico (NO) e di specie reattive all'ossigeno (ROS) sono stati misurati. I valori finali registrati sono stati confrontati all'attività espressa alla stessa concentrazione dalla curcumina, un diarileptanoide naturale, la cui attività anti-ossidante è ampiamente riconosciuta. Il confronto tra le molecole da noi preparate e la curcumina ha mostrato che la maggior parte dei prodotti sintetizzati hanno un'attività paragonabile o qualche volta migliore della curcumina. Le molecole particolarmente attive sono risultate essere la **71bis** e **72bis**. Questi composti, oltre che la lora attività antiossidante, appaiono strutture molto interessanti, visto che non sono mai state descritte prima in letteratura.

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VERS LA SYNTHESE ATROPO-STEREOSELECTIVE DU MYRICANOL

Introduction et but de la thèse

L'objectif de ce travail de thèse est la synthèse totale du myricanol d'une manière racémique puis stéréosélective. Ainsi le myricanol est un [7,0]-*meta*cyclophane naturel qui appartient à la famille des 1,7-diarylheptanoïdes, composé constitué de deux noyaux benzéniques reliés par une chaine à 7 carbones. Ces molécules sont reconnues comme étant de puissants agents thérapeutiques avec des activités biologiques intéressantes comme par exemple, des propriétés anti-inflammatoires, antioxydantes, anti-tumorales, hépatoprotectives et neuroprotectives.[1] Ces composés sont extraits de plantes/baies et se présentent soit sous une forme acyclique, soit cyclique comme pour les [7,0]-*meta,meta*-cyclophanes et les [7,1]-*meta,para*-cyclophanes (**Figure A**)

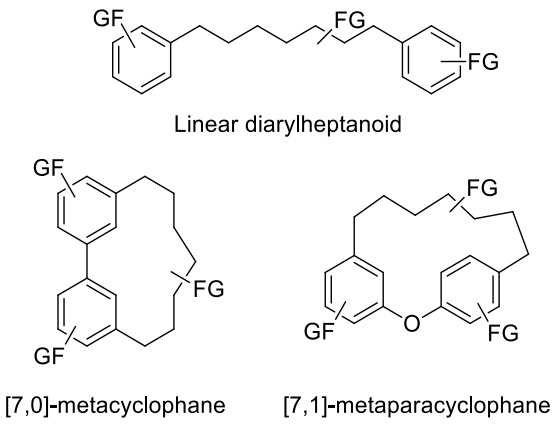

Figure A

Le myricanol est un diarylheptanoïde cyclique extrait de nombreuses species of *Myricaceae* as *Myrica cerifera*[2], *Myrica nagi*[3], *Myrica gale*[4], *Myrica rubra*[5].

Une activité biologique remarquable est le fort potentiel du myricanol, à réduire le niveau des protéines Tau, présentes dans le cerveau humain (effet anti Alzheimer).[1,2] En effet, en 2011, Dickey, a montré que le (+)-a*R*,11*S*-myricanol énantioenrichi du *Myrica cerifera*[3] (86% ee) permettait de réduire significativement le niveau des protéines Tau dans les cellules HeLa-C3, et ceci de manière plus efficace que le racémate commercialement disponible (9% ee). Très récemment, Dickey est parvenu à séparer les deux énantiomères du myricanol par chromatographie liquide, puis a montré que c'était l'atropoénantiomère, à savoir le (-)-

a*S*,11*R*-myricanol, qui était à l'origine de la diminution des cellules Tau.[2 1] Ceci montre bien l'importance de pouvoir préparer de facon énantiosélective les deux énantiomères pour poursuivre les investigations sur leur activité biologique.

Par ailleurs le myricanol sous sa forme racémique est également capable d'inhiber la production de NO·[7] et possède des propriétés anti-inflammatoires et des effets anti-androgèniques[8]. De plus, il a été montré récemment qu'il était un candidat clinique pour la prévention et le traitement du cancer du poumon.[9]

Actuellement seules deux synthèses racémiques du (+/-)-myricanol et aucune préparation asymétrique n'ont été rapportées dans la littérature. Ainsi le myricanol racémique a été obtenu avec un rendement très faible de 0,21% en 14 étapes par Whiting[10] et plus récemment par Dickey et *al*.[1] en 7 étapes avec un rendement de 2.03% à partir de matières premières avancées, mais dans les deux cas, sans aucune allusion à un contrôle de la chiralité centrale ou axiale de ce composé.

Compte tenu de la forte activité biologique du myricanol, ce travail de thèse a été consacré à une voie de préparation modulable et convergente du myricanol (synthèse racémique) mais aussi vers la préparation atropo-stéréosélective du (+)-a*R*,11*S*-myricanol ou du (-)-a*S*,11*R*-myricanol (**Figure B**). [2,6]

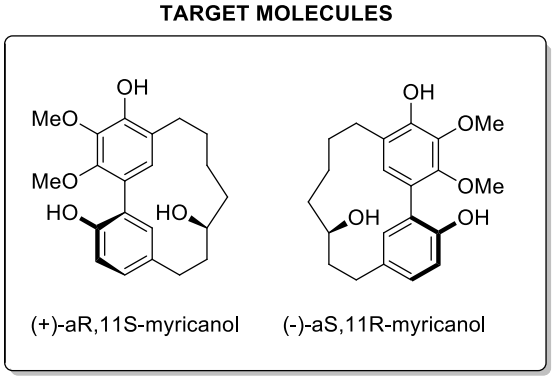

Figure B

Approche rétrosynthétique 1

Notre première approche rétrosynthétique du myricanol est illustrée par le **Schéma I.** Le myricanol, sous une forme racémique ou énantiopure, serait obtenu à partir du dérivé *seco* $\mathbf{A_1}$ par l'intermédiaire d'une réaction de Suzuki-Miyaura domino[11] qui n'a jamais été réalisé sur ce type de précurseur. Le diarylheptanoide dihalogéné $\mathbf{A_1}$ peut être facilement obtenu par métathèse croisée entre les oléfines terminales $\mathbf{A_2}$ et $\mathbf{A_3}$. Le phénol *C*-allylique $\mathbf{A_2}$ peut être obtenu par un réarrangement de Claisen à partir de l'O-allylphénol correspondant, préparé à partir du 2,3 diméthoxyphénol.[12] L'alcool homo-allylique $\mathbf{A_3}$. est

envisagé à partir d'un dérivé de l'acide propanoique. On peut aussi synthétiser le dérivé **A_3** avec un carbinol stéréogène, suivant la molécule finale souhaitée, à l'aide d'une allylation énantiosélective.[13]

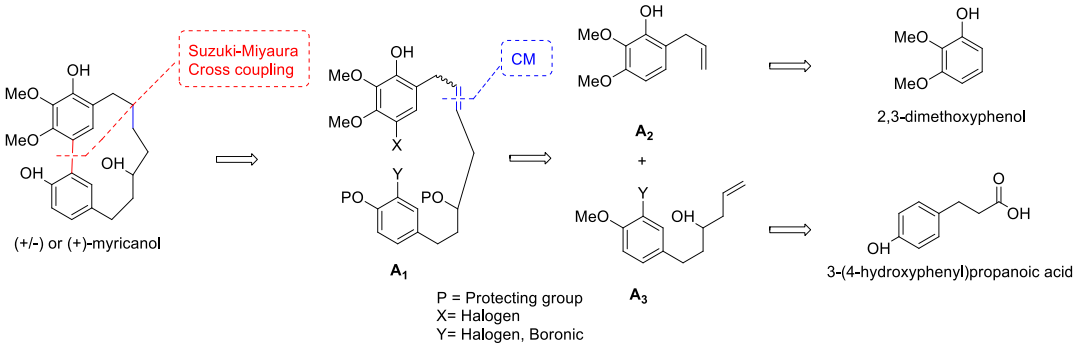

Schéma I

Les étapes clés de cette stratégie synthétique sont 1) la métathèse-croisée; et 2) la macrocyclisation[14] à l'aide d'un couplage domino intramoléculaire de Suzuki-Miyaura.

Approche rétrosynthétique 2

En parallèle, une seconde approche rétro synthétique a été étudiée avec deux autres étapes clés (Couplage de Suzuki-Miyaura intermoléculaire et métathèse cyclisante) est représentée sur le **Schéma II**. Ainsi l'étape de macrocyclisation pour préparer le myricanol serait une étape de métathèse cyclisante à partir du biaryle **B_1**.

Le biaryl **B_1** peut être construit par un couplage de Suzuki-Miyaura intermoléculaire entre le dérivé halogéné **B_2** et l'acide boronique **B_3**. Ces deux partenaires de couplage **B_2 et B_3** peuvent être efficacement préparés à partir du 2,3 diméthoxyphenol et de l'acide (4-hydroxyphenyl) propanoique suivant des protocoles similaires à ceux utilisés dans l'approche 1.

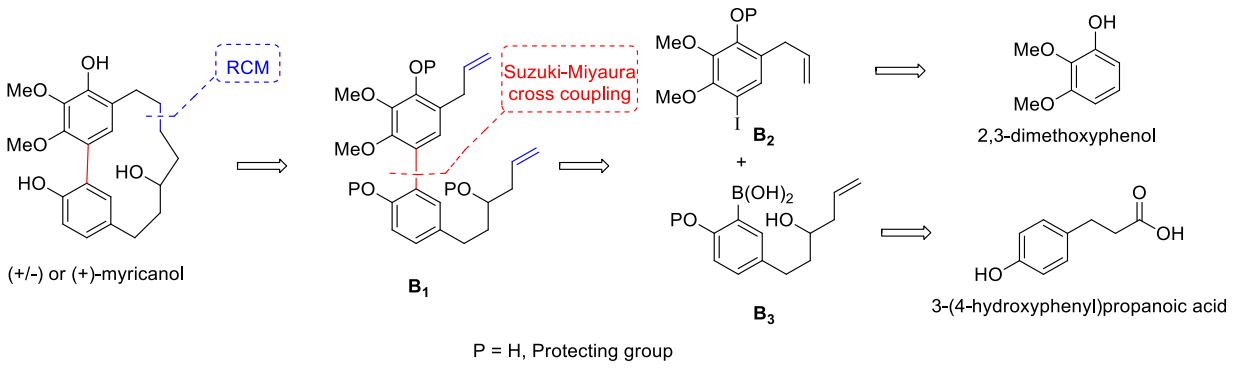

Schéma II

Resultats concernant l'approche synthétique 1

Pour ce qui concerne la première approche synthétique proposée, nous avons préparé les fragments clés **48** and **71** avec de très bons rendements (**Schéma III**).

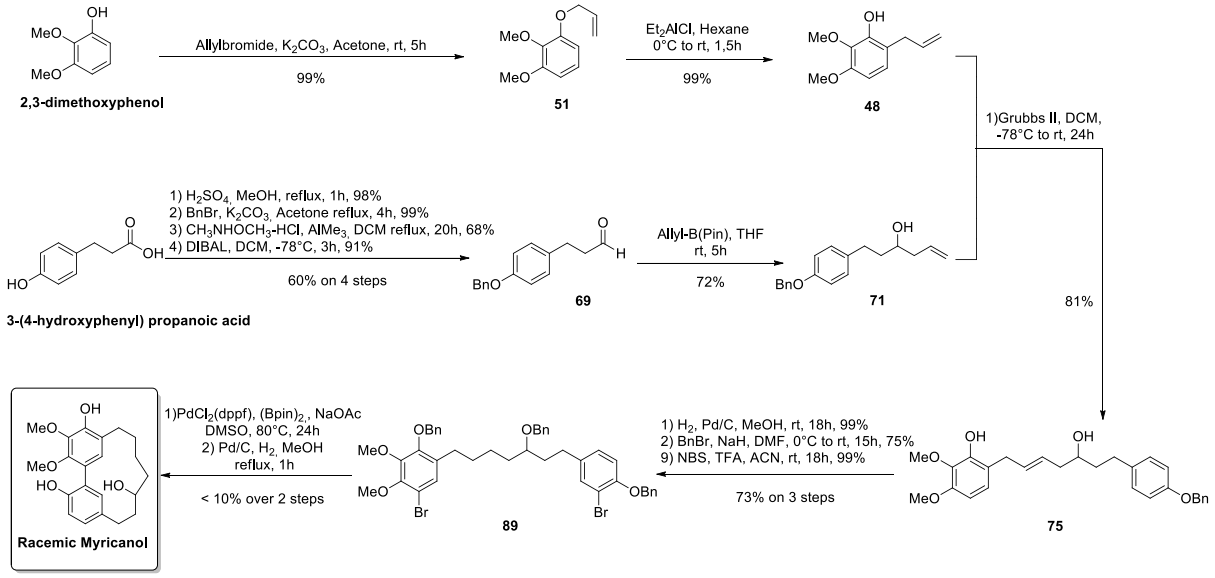

Schéma III

Le composé **48** a été obtenu en 2 étapes (allylation puis réarrangement de Claisen) avec un rendement total de 98%. L'alcool homo-allylique **71** a été synthétisé en partant de l'acide 3-(4-hydroxyphényl) propanoïque commercial qui a été estérifié puis protégé par un groupement benzyle. L'ester méthylique a été transformé en amide de Weinreb[15] laquelle a été réduite à l'aide de DIBAL en aldéhyde **69** avec un bon rendement. L'aldéhyde **69** peut être dérivé en alcool homo-allylique **71** sous une forme racémique (rdt 72%) ou énantioenrichi (rdt 70%, ee 90%) à l'aide d'une réaction d'allyle titanation asymétrique conduite en

présence du réactif énantiopur de Duthaler-Hafner[16]. Finalement l'alcool **71** a été préparé en 5 étapes avec un rendement total de 60% (forme racémique) et de 59% (forme énantioenrichie).

La métathèse croisée entre les alcènes terminaux **48** and **71**rac a été étudiée en faisant varier différents paramètres comme la température, la quantité de catalyseur, la nature du catalyseur. Après une période d'optimisation, l'utilisation du catalyseur de Grubbs II à basse T°C dans le CH_2Cl_2 a permis de préparer le diarylheptanoïde linéaire **75** avec un excellent rendement de 81%.[17]

Notons qu'à l'aide de la réaction de métathèse croisée, une dizaine de nouvelles molécules dérivés du myricanol, linéaires à longueur de chaine variée, a été synthétisée et leur activité biologique sera testée. Ces résultats seront présentés dans la partie activité biologique. (**Figure C**)

Après une hydrogénation quantitative de la double liaison, suivi de la benzylation des OH libres, le produit de bishalogénation **89** est obtenu avec un très bon rendement sur 3 étapes. (**Schéma III**) L'étape de macrocyclisation *via* un couplage de Suzuki-Miyaura en procédé domino[3] a été testée sur le dérivé dibromé **89.** Une étude d'optimisation des conditions expérimentales pour cette étape a été menée à bien et les résultats sont regroupés dans le **Tableau I**.

Entrée[a]	Boron source (1.2equiv.)	Base (10equiv.)	Solvent	T (°C)	T (h)	Myricanol benzylé[b]
1	$(BPin)_2$	NaOAc	DMSO	80	24	**(10%)**
2	$(BPin)_2$	KOAc	DMSO	80	24	-
3	$(BPin)_2$	NaOAc	Dioxane	80	24	-
4	$(BPin)_2$	KOAc	Dioxane	80	24	Trace
5	PinB-H	KOAc	DMSO	100	24	-
6	PinB-H	NaOAc	DMSO	100	24	-

a. toute les reactions ont étés conduits avec $PdCl_2$(dppf) 10mol%; b. après debenzylation quantitative.

Tableau I

Seules les conditions testées pour l'entrée 1 permettent de préparer le produit de cyclisation avec un faible mais encourageant rendement en présence de bispinacoborane, d'un excès de base forte à 80°C. La macrocyclisation apparait donc comme étant une étape très délicate de part l'accès à un cycle à 13 membres. Enfin le myricanol naturel, a été obtenu après une étape supplémentaire de débenzylation quantitative.

Pour conclure, cette voie de synthèse, la plus courte reportée et convergente conduit au myricanol racémique en 11 étapes et avec un rendement total <2.55%.

Resultats concernant l'approche synthétique 2

Pour la deuxième approche proposée (**Schéma II**) les deux partenaires de couplage $\mathbf{B_2}$ et $\mathbf{B_3}$ ont tout d'abord été préparés. Ainsi le composé iodé **57** a été préparé avec un excellent rendement à partir du phénol allylique **48,** préalablement préparé (**Schéma III**). Celui-ci, mis en réaction avec du diiode et de la *tert*-butylamine[18] a permis d'obtenir l'intermédiaire **52** qui est protégé *in situ* avec le chlorure de méthoxyéthoxyméthane en condition basique. (**Schéma IV**).

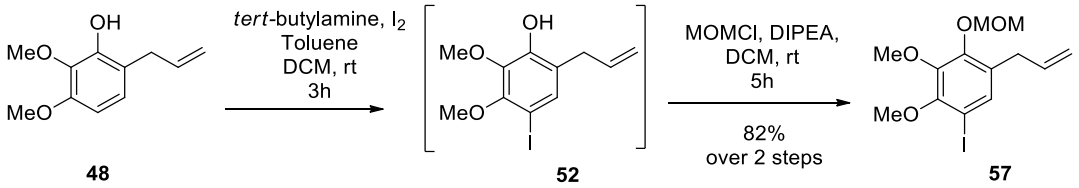

Schéma IV

Compte tenu des risques d'isomérisation de la double liaison terminale du composé **57**, lors du couplage de Suzuki-Miyaura, des études sur le couplage intermoléculaire ont été réalisées avec un acide boronique commercial. Ainsi en présence de palladium(II), le produit de couplage **116** est obtenu avec un rendement satisfaisant (**Schéma V**).

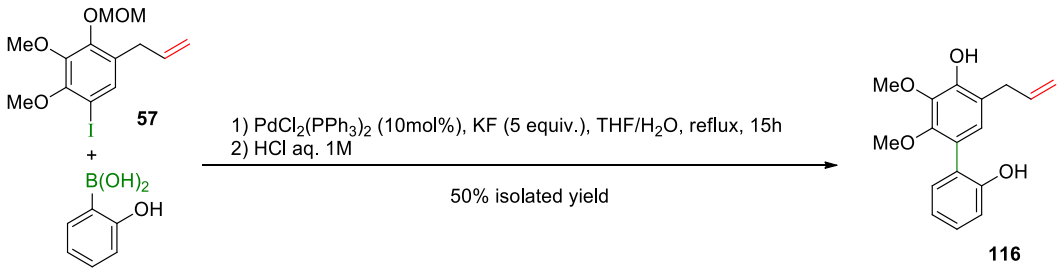

Schéma V

Encouragés par ces bons résultats, les acides **117a** et **119** ont été préparés comme décrit sur le schéma **VI**. A partir des précurseurs iodés diversement protégés **71c** et **72c** dérivés des esters méthyliques **65a** et **66a,** les acides boroniques **117a** et **119** ont été obtenus avec des rendements acceptables par un échange halogène métal avec *i*-PrMgCl-LiCl[19] suivi d'un piégeage avec du triméthylborate.

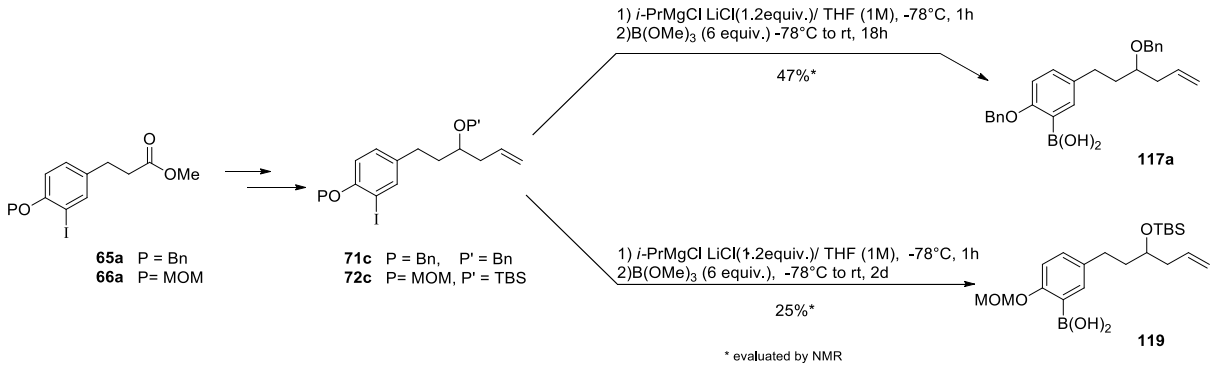

Schéma VI

Les conditions de couplage intermoléculaire de Suzuki-Miyaura préalablement optimisées (**schéma V**) seront testées en présence du partenaire iodé **57** et de l'acide boronique **119a** partiellement déprotégé pour accéder au biaryle **120a.** Ce dernier après métathèse cyclisante devrait nous conduire au cyclophane **121**, un précurseur avancé du myricacol **(Schéma VII)**.

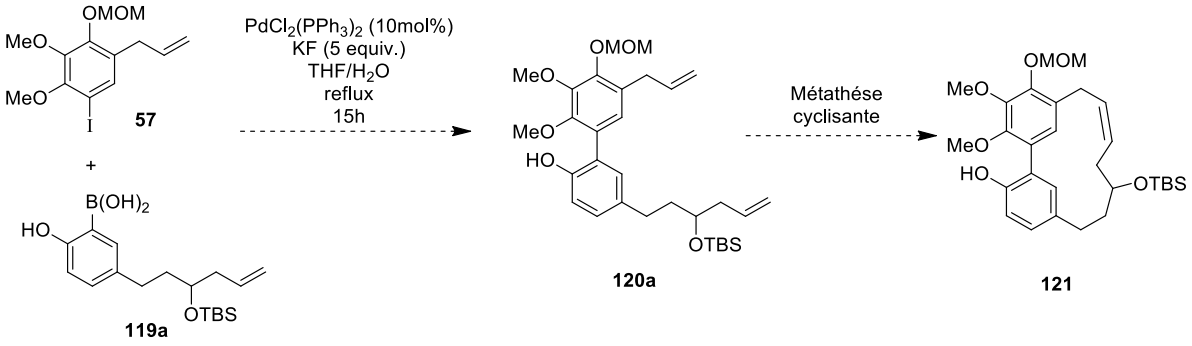

Schéma VII

Une autre voie a été envisagée pour la préparation d'un biaryl similaire à **120a** par le biais d'un couplage oxydant. Pour cela, le produit **108** est préparé à partir de l'alcool homoallylique **72.** Ce dernier a été benzylé en dérivé **106**, puis chimiosélectivement déprotégé en phénol **107** de façon quantitative (**Schéma VIII**).

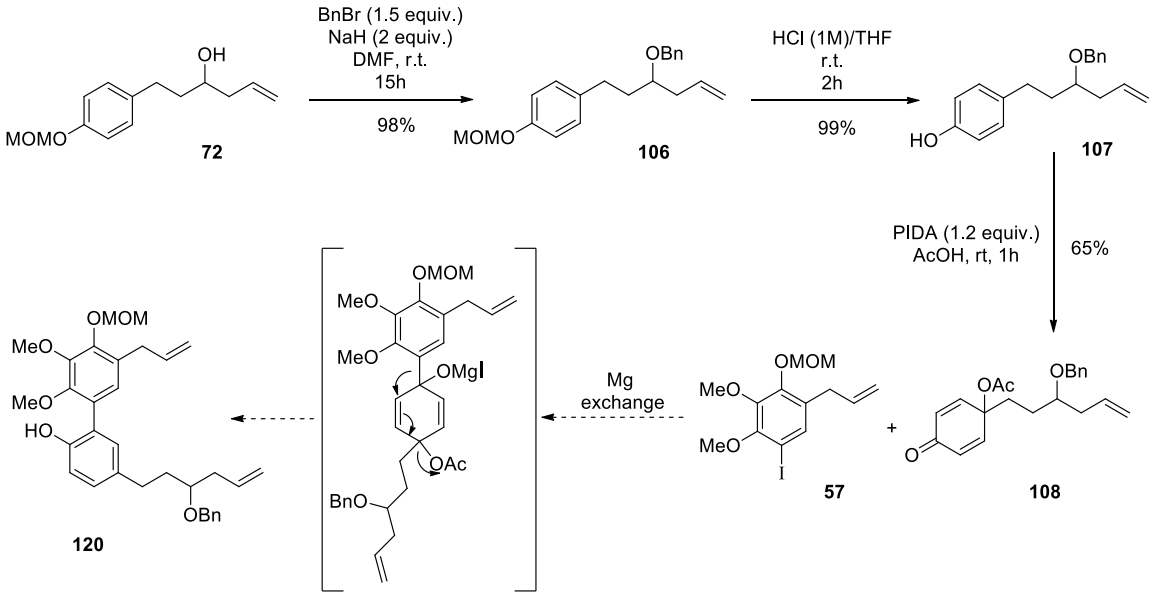

Schéma VIII

Le phénol **107** traité avec du PIDA et de l'acide acétique[20] forme le dièneone-acétate désiré **108** avec un bon rendement. Ainsi un réactif de Grignard préparé à partir de l'iodure **57** et de magnésium peut attaquer l'ènone en position 1,2 et conduire à un premier intermédiaire, qui après migration 1,2 du groupement alcool puis élimination du groupe partant acétate formera le biaryle **120** désiré.

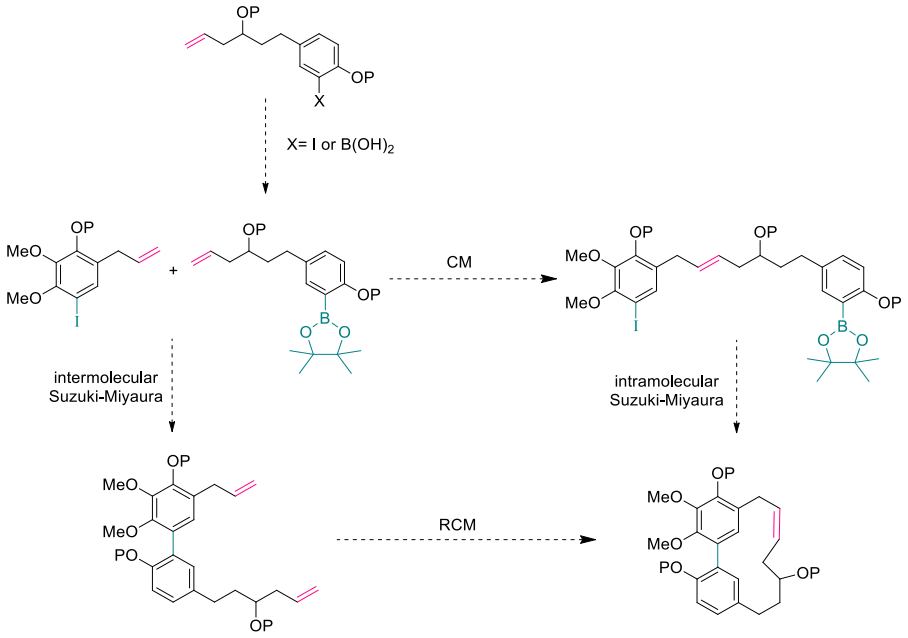

Schéma IX

Test biologiques

Pendant la préparation des précurseurs linéaires du myricanol par métathèse croisée, une série de 6 nouveaux analogues de structure diarylheptanoique à chaine carbonée courte (de 4 à 6 atomes) ou longue (10 atomes) a été préparée (**Figure C).**

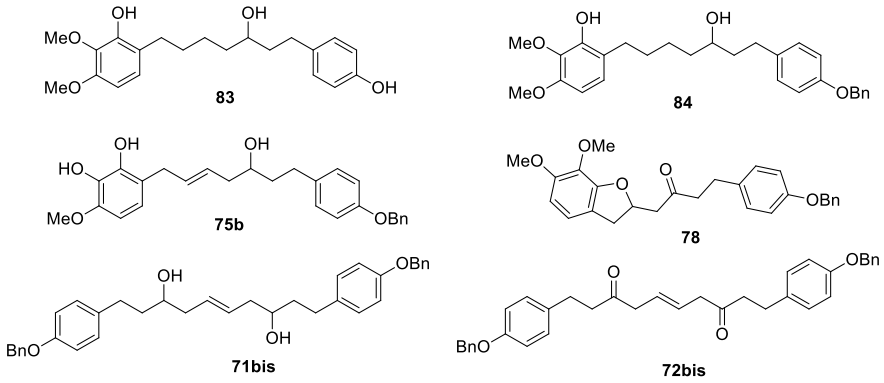

Figure C

Les produits synthétisés ont été été testés pour évaluer l'activité anti-inflammatoire sur les cellules humaines U937 et sur les cellules murine microglial BV-2. Pour se faire, la lipopolysaccharide (LPS) a été employée pour activer l'inflammation dans les deux lignées cellulaires U937 et BV-2. La vitalité cellulaire a été déterminée par un test colorimétrique MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide].[21]

De plus, d'autres tests pour évaluer l'activité antioxydante de ces molécules ont été effectués portant sur le taux d'oxyde nitrique (NO) et d'espèces réactives à l'oxygène (ROS) produits ou absorbés. Les valeurs mesurées ont été comparées à celle d'un autre diarylheptanoide, le curcumin, connu pour son anti-oxydante. La comparaison entre nos molécules et le curcumin a montré que dans la plupart des cas, les nouveaux produits de synthèse, surtout les composés **71bis** et **72bis** ont une activité comparable, voir meilleure au curcumin.

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LIST OF ABBREVIATIONS

1D	one-dimensional
2D	two-dimensional
A549	cells adenocarcinomic human alveolar basal epithelial cells
$[\alpha]_D$	specific rotation measured at 589nm (the sodium D line)
Aβ	amyloid beta
Å	Ångström
ACN	acetonitrile
AD	Alzheimer's disease
aq.	aqueous
$B_2(pin)_2$	pinacolato diboron
Bn	benzyl
°C	Celsius degree
CC	column chromatography
CD	circular dicroism
$CDCl_3$	deuterated chloroform
CIP	Cahn–Ingold–Prelog
CM	cross-metathesis
COSY	correlation spectroscopy
Cy	cyclohexane
DIBAL-H	diisobutyl aluminium hydride
DIPEA	diisopropyl ethyl amine
DMAP	4-(dimethylamino)pyridine

DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
EC_{50}	half maximal inhibitory concentration
EI	electron-impact ionization
EP	petroleum ether (boiling point: 40-60 °C)
equiv.	equivalent
EtOAc	ethyl acetate
EtOH	ethanol
GC	gas chromatography
HCl	hydrochloric acid
HPLC	high-performance liquid chromatography
HeLa	immortal cell line derived from cervical cancer
HR	high resolution
HSQC	heteronuclear single-quantum correlation
IC50	half maximal inhibitory concentration
iNOS	inducible nitric oxide synthase
KOAc	potassium acetate
(+)-L-DIPT	(+)-Diisopropyl L-tartrate
LPS	lipopolysaccharide
MeOD	deuterated methanol
MeOH	methanol
MOM	methoxymethyl
MS	mass spectrometry

MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
MW	microwave irradiation
n-BuLi	normal-butyl lithium
NBS	*N*-bromosuccinimede
NIS	*N*-iodosuccinimide
NMP	*N*-methylpirrolydone
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
PCC	piridinium chloro chromate
Pd/C	palladium on charcoal
$Pd_2(dba)_3$	Dipalladium-tris(dibenzylideneacetone)
Pd_2Cl_2 (dppf)	[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
PIDA (or DIB)	(Diacetoxyiodo)benzene
PIFA (or BTI)	Bis(trifluoroactoxy)iodobenzene
PPh_3	triphenylphosphine
ppm	parts per million
Py	pyridine
RCAM	ring closing alkyne metathesis
RCM	ring closing metathesis
R*f*	retention factor
ROS	reactive oxygen species
r.t.	room temperature
SAR	structure activity relationship
SET	single-electron transfer

S-Phos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
T	temperature
t	time
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TIR	tumor inhibition rate
TLC	thin layer chromatography
TON	turnover number
t_R	retention time
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)

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TOWARDS THE ATROPO-STEREOSELECTIVE TOTAL SYNTHESIS OF MYRICANOL

1 INTRODUCTION AND OBJECTIVES

Diarylalkanoids (C_6-C_n-C_6), natural phenolic compounds, have been isolated from wood, bark or leaves of many hardwoods including *Betulaceae*, *Leguminosae*, *Myricaceae, Zimberaceae* and *Proteaceae*[1]. An important subclass of these natural products is represented by the diarylheptanoids, polyoxygenated family bearing a 1,7-diphenylheptane skeleton. It may be divided into two subgroups, *i.e.* open chain and macrocyclic diarylheptanoids. In the latter the aromatic rings are connected to form a diarylether or a biaryl moiety. The first review of natural diarylheptanoids was published by Cleaton et *al*. where approximately 120 naturally occurring compounds were reported. In a second review including the literature of 1993-1999, 75 new diarylheptanoids were listed[2] and during the last decade more than 100 new other ones were reported both for their isolation and synthesis.[1,3] They are increasingly recognized as potential therapeutic agents for their numerous physiological activities such as anti-inflammatory, antioxidant, antitumor, estrogenic, leishmanicidal, melanogenesis inhibitory, hepatoprotective and neuroprotective.[3,4] Among them the first isolated and the most investigated natural diarylheptanoid is curcumin and is extracted from turmeric. (**Figure 1-1**) *Curcuma longa*, as orange-yellow crystalline powder is called the golden spice for its yellow colour and "miraculous" biological activities.[5] Some other *Curcuma* species, such as *Curcuma comosa* also produce curcumin and other diarylheptanoids with potent biological activities.[6,7]

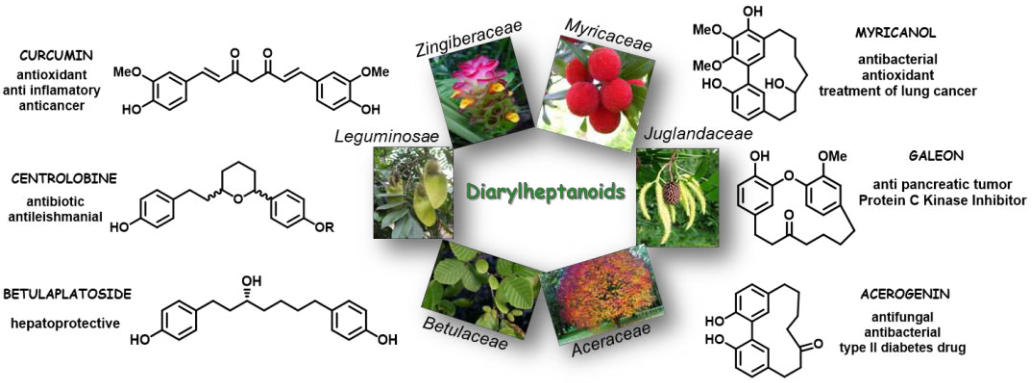

Figure 1-1 Diarylheptanoids from Nature

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Myricanol[8], a cyclic and not symmetric diarylheptanoid extracted from *Myricaceae* species with a [7,0]-*meta*cyclophane core, possess biological properties space from anti-oxidant[9], anti-inflammatory and anti-androgenic[10] to anti-tau[11] and anti-cancer[12].

The aim of this thesis is the total synthesis of racemic myricanol, using new and never explored synthetic methodologies for the formation of its biaryl motif. We will also investigate a synthetic strategy in order to perform the first stereoselective synthesis of myricanol, controlling the axial and the central chirality of this 13-membered macrocycle.

Moreover, because the total synthesis of myricanol involves the preparation of linear diarylheptanoids, a part of this thesis will be focused on the biological studies for the antioxidant activity of its linear precursors. (**Figure 1-2**)

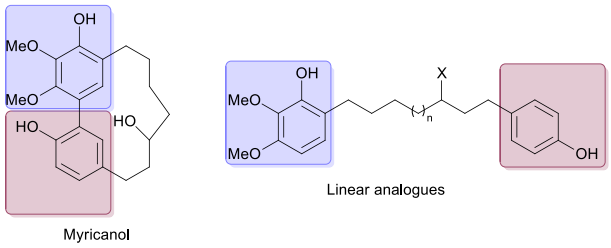

Figure 1-2 Target molecules

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[11] 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* (1), 38–44.
[12] Dai, G.; Tong, Y.; Chen, X.; Ren, Z.; Ying, X.; Yang, F.; Chai, K. *Int. J. Mol. Sci.* **2015**, *16* (2), 2717–2731.

2 MYRICANOL: A CYCLIC DIARYLHEPTANOID

2.1 THE NATURAL PRODUCT

Myrica is a genus of about 35–50 species of small trees and shrubs in the family *Myricaceae*, (order Fagales). These species are widely diffuse in Africa, Asia, Europe, North America and South America, and missing only in Australia. Botanists are usually split the genus into two genera on the basis of the catkin and fruit structure, restricting *Myrica* to a few species, and treating the others in *Morella*.[13]

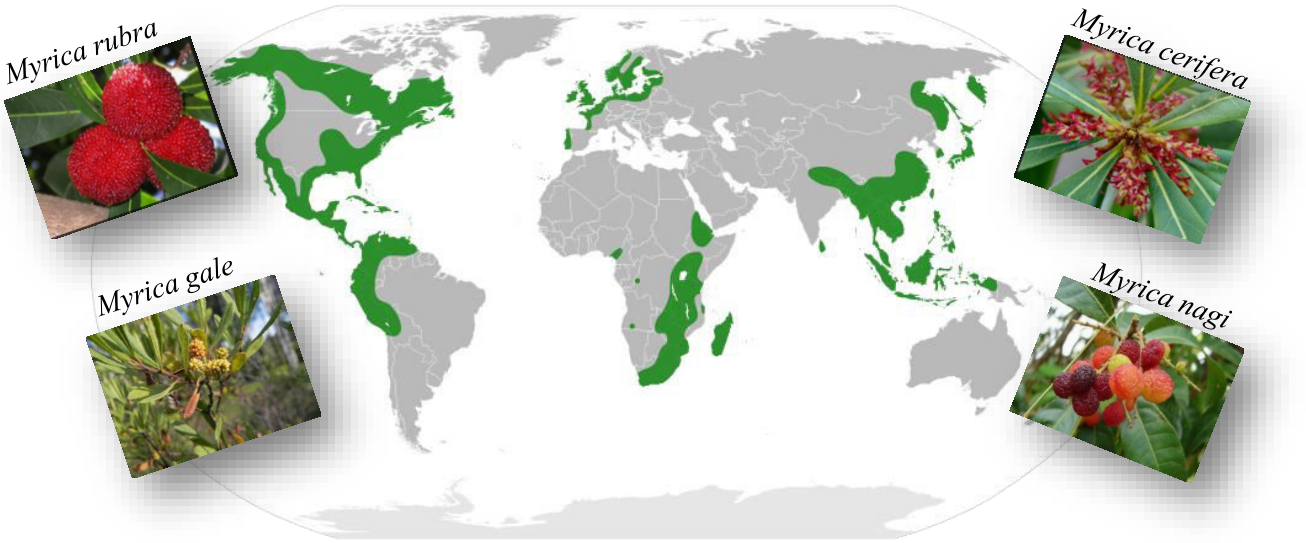


Figure 2-1 *Myricaceae* distribution in the world

Common names include **bayberry**, **bay-rum tree**, **candleberry**, **sweet gale**, and **wax-myrtle**. The generic name was derived from the Greek word μυρικη (*myrike*), meaning "fragrance". The wax coating on the fruit of several species, known as bayberry wax, has been used traditionally to make candles, as described in the novel of *The Swiss Family Robinson* (written by Johann David Wyss) and modeled on the original Robinson Crusoe history of Daniel Defoe.

The foliage of *Myrica gale* is a traditional insect repellent, used by campers to keep biting insects out of tents. The fruit of *Myrica rubra* is an economically important crop in China, sold fresh, dried, canned, for

[13] Huguet, V.; Gouy, M.; Normand, P.; Zimpfer, J. F.; Fernandez, M. P. *Mol. Phylogenet. Evol.* **2005**, *34* (3), 557–568.

juice, and for alcoholic beverages. Its bark is also used in traditional Japanese and Chinese medicine.[14][16] *Myrica* is used to spice beer and snaps in Denmark.

Various species of *Myrica* have been studied scientifically for horticultural characteristics or phytochemicals implications with health benefits. Dating to 1951, the horticultural literature includes studies on nitrogen-fixing ability of the root nodules system[15] and presence of *Frankia* bacteria having nitrogen-fixing properties in root nodules.[16]

A very rich literature describes the isolation from leaves, roots, bark and fruits of numerous secondary metabolites from *Myrica* species. The chemical characterizations and their biological properties are also reported. Cyclic diarylheptanoids can be isolated from the *M. rubra* [9,10,17], *M. cerifera*[11], *M. nagi (esculenta)*[18], *M. nana*[19], *M. gale*[20], *M. adenophora*[21] and *M. arborea*[22]. Most of extracted compounds from *Myrica* species are reported in **Figure 2-2**.

[14] Kawai, S.; Nakata, K.; Ohashi, M.; Nishida, T. *J. Wood Sci.* **2008**, *54* (3), 256–260.

[15] Vandenbosch, K. A.; Torrey, J. G. *Plant Physiol.* **1984**, *76* (3), 556–560.

[16] Huguet, V.; Mergeay, M.; Cervantes, E.; Fernandez, M. P. *Environ. Microbiol.* **2004**, *6* (10), 1032–1041.

[17] a) Akazawa, H.; Fujita, Y.; Banno, N.; Watanabe, K.; Kimura, Y.; Manosroi, A.; Manosroi, J.; Akihisa,T. *J. Oleo Sci.* **2010**, *59* (4), 213–221. b) Cheng, H. Y; Lin, T. C.; Ishimaru, K.; Yang, C. M.; Wang, K. C.; Lin, C. C. *Planta Med.* **2003**, *69* (10), 953–956. c) Bao, J.; Cai, Y.; Sun, M.; Wang, G.; Corke, H. *J. Agric. Food Chem.* **2005**, *53* (6), 2327–2332. d) Fang, Z.; Zhang, M.; Tao, G.; Sun, Y.; Sun, J. *J. Agric. Food Chem.* **2006**, *54* (20), 7710–7716. e) Yoshimura, M.; Yamakami, S.; Amakura, Y.; Yoshida, T. *J. Nat. Prod.* **2012**, *75* (10), 1798–1802. f) Z, L.; S, J.; Y, Z.; D, M.; X, L. *Nat. Prod. Commun.* **2009**, *4* (4), 513–516. g) Sakurai, N.; Yaguchi, Y.; Hirakawa, T.; Nagai, M.; Inoue, T. *Phytochemistry* **1991**, *30* (9), 3077–3079.

[18] a) Dawang, S.; Zuchun, Z.; Wong, H.; Lai, Y. F. *Phytochemistry* **1988**, *27* (2), 579–583. b) Panthari, P.; Kharkwal, H.; Kharkwal, H.; Joshi, D. D. *Int. J. Pharm. Pharm. Sci.* **2012**, *4*, 38–42. c) Kumar, A. *Int. Res. J. Pharm.* **2012**, *3* (12), 32–37.

[19] a) Yu, Y.-F.; Lu, Q.; Guo, L.; Mei, R.-Q.; Liang, H.-X.; Luo, D.-Q.; Cheng, Y.-X. *Helv. Chim. Acta* **2007**, *90* (9), 1691–1696. b) Wang, J.-F.; Zhang, C.-L.; Lu, Q.; Yu, Y.-F.; Zhong, H.-M.; Long, C.-L.; Cheng, Y.-X. *Helv. Chim. Acta* **2009**, *92* (8), 1594–1599.

[20] Sylvestre, M.; Legault, J.; Dufour, D.; Pichette, A. *Phytomedicine* **2005**, *12* (4), 299–304.

[21] Ting, Y.-C.; Ko, H.-H.; Wang, H.-C.; Peng, C.-F.; Chang, H.-S.; Hsieh, P.-C.; Chen, I.-S. *Phytochemistry* **2014**, *103*, 89–98.

[22] Tene, M.; Wabo, H. K.; Kamnaing, P.; Tsopmo, A.; Tane, P.; Ayafor, J. F.; Sterner, O. *Phytochemistry* **2000**, *54* (8), 975–978.

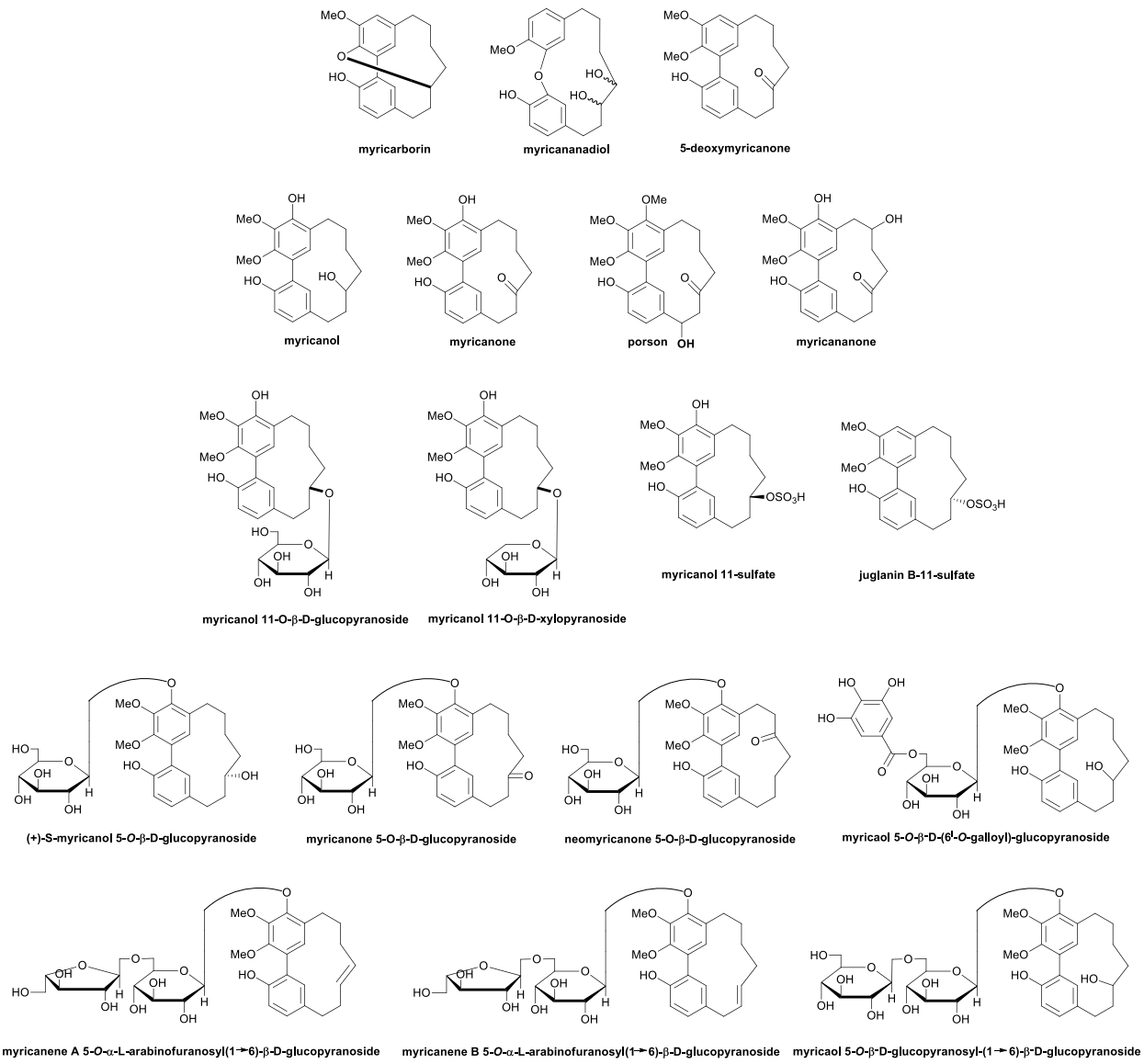


Figure 2-2 *Myrica* extracts

2.1.1 CHARACTERIZATION OF CHEMICAL STRUCTURE

Myricanol **1** and myricanone **3** (**Figure 2-2**) were extracted and structurally characterized for the first time in 1970 by M. J. Begley and D. A. Whiting. They isolated the compounds from stem-bark of Indian *Myrica nagi*.[811]. Facing uncommon chemical structures and difficulties to define the right position of the methoxy substituents, the authors performed an X-ray study (using the heavy atom method) to determine without any ambiguity the structure of these new compounds.

Consequently, extracted myricanol **1** was brominated and the resulting 16-bromomyricanol **2** was used to determine the absolute configuration at C-11 position. CD measurements revealed that myricanol had the same conformation in solution as in the crystalline state. The structure of 16-bromomyricanol obtained from X-ray analysis was compared to extracted myricanol and myricanone defining the correct structure of the two natural products as depicted in **Figure 2-3**

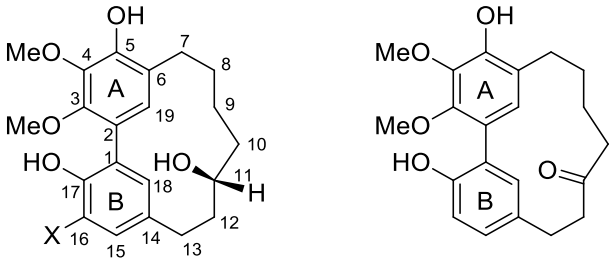


Figure 2-3 Bromomyricanol, myricanol, myricanone

X-ray crystallographic studies performed by Whiting in 1970 revealed two intramolecular hydrogen bonds in 16-bromomyricanol, 17-OH-3-O (2.7Å) and 5-OH-4-O (2.8Å), and an intermolecular hydrogen bond between 11-OH-5'-O (2.8 Å). In bromomyricanol one can observe a striking feature bending of the biphenyl nucleus as a consequence of the *meta*, *meta* bridge. The two angles at C1-C2-C3 and C2-C1-C17 were reported to be 130° and 126° respectively. The others two angles (C1-C2-C19 and C2-C1-C18) were described as 114° and 115°.

Angles around the inter-aryl bond (C-1-C-2) support the claim of such distortion. This bond is closely coplanar with ring A (**Figure 2-4**) and C-15 is 0,26Å above the mean plane of ring A. The dihedral angle between the mean planes of the two aromatic rings A and B is 33°.

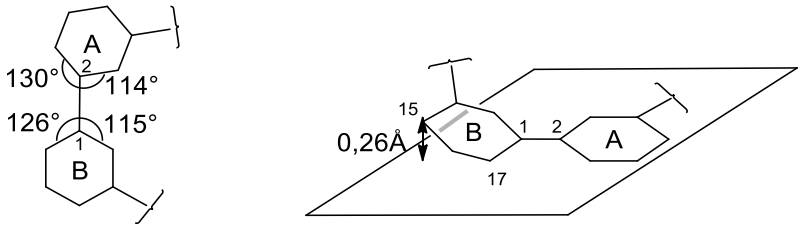


Figure 2-4 Bromo-myricanol configuration assignment by Whiting

Thus, from Whiting and co-workers studies[23] a 11-*R* configuration ($[\alpha]_D^{27.5}$ = -65.6°) and a negative Cotton effect was attributed to myricanol extracted from *Myrica nagi.*

When in 1996 Joshi et *al.* reported the X-ray analysis of racemic myricanol[24] they realized that their results were closely similar to those given by Whiting. They observed that the C1-C2-C3 and C2-C1-C17 angles were approximately 128° and that C1-C2-C19 and C2-C1-C18 measured to an average of 116°. They also found intermolecular hydrogen bonds between 11-OH-5'-O (2.771 Å), 17-OH-11'-O (2.783 Å) and 5-OH-11'-O (2.731 Å).

Surprisingly, myricanol extracted from diverse *Myrica* species gave different values of $[\alpha]_D$. (**Table 2-1**)

Myrica species	**$[\alpha]_D$**	**References**
Myrica nagi or esculenta	$[\alpha]_D^{27.5}$ = -65.6 $[\alpha]_D$ = -64	Begley, M. *al. J. Chem. Soc. C* **1971**, 3634–3642. Sun, D. W.et *al*. Phytochemistry **1988**, *27*, 579–583.
Myrica rubra	$[\alpha]_D$ = -62.9 $[\alpha]_D^{22}$ = -27.6 $[\alpha]_D^{24}$ = -48.3 $[\alpha]_D^{22}$ = +37.3	Inoue, T. et *al*. *Yakugaku Zasshi* **1984**, *104*, 37–41. Takeda, Y. et *al. Chem. Pharm. Bull.* **1987**, *35*, 2569–2573. Matsuda, H. et *al*. *Chem.Pharm. Bull.* **2002**, *50*, 208–215.
Myrica cerifera	$[\alpha]_D$ = 0.0 $[\alpha]_D^{20}$ = +48	Joshi, B. S. et *al*. *J. Nat. Prod.* **1996**, *59*, 759–764. Jones, J. R. et *al*. *J. Nat. Prod.* **2011**, *74*, 38–44.

Table 2-1 Specific rotation for extracted myricanols

[23] a) Begley, M. J.; Whiting, D. A. *J. Chem. Soc. Chem. Commun.* **1970**, 18, 1207–1208. b) Begley, M. J.; Campbell, R. V. M.; Crombie, L.; Tuck, B.; Whiting, D. A. *J. Chem. Soc. C Org.* **1971**, 3634–3642.

[24] 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.

As shown in **Table 2-1** the majority of extracted myricanols displayed negative rotations with the exception of one racemate and two positive values. The negative rotation is correlated to the 11*R*-configuration of the brominated derivative **2** of myricanol (**Figure 2-3**) determined *via* X-ray cristallography. In the work of Matsuda et *al.*[25] (-)-11*R*-myricanol ($[\alpha]_D^{24}$ = -48.3) was extracted from *Myrica rubra* species along with a (+)-*S*-myricanol 5-*O*-β-D-glucopyranoside (**Figure 2-2**) which was cleaved to the corresponding aglycone (+)-11-*S*-myricanol ($[\alpha]_D^{22}$ = +37.3) with 11*S* configuration confirmed by Mosher's analysis. Joshi et *al.*[24] extracted (±)-myricanol from *Myrica cerifera* in racemic form with a structure confirmed by accurate X-ray crystallographic studies and 1D/ 2D NMR experiments. The myricanol structure is axially dissymmetric due to the twisted biphenyl and contains one asymmetric centre. For this reason, the cyclic diarylheptanoid could exist as two diastereoisomers, each as a pairs of enantiomers: (a*S*,*S*), (a*R*,*R*) and (a*S*,*R*), (a*R*,*S*)[26](**Figure 2-5**).

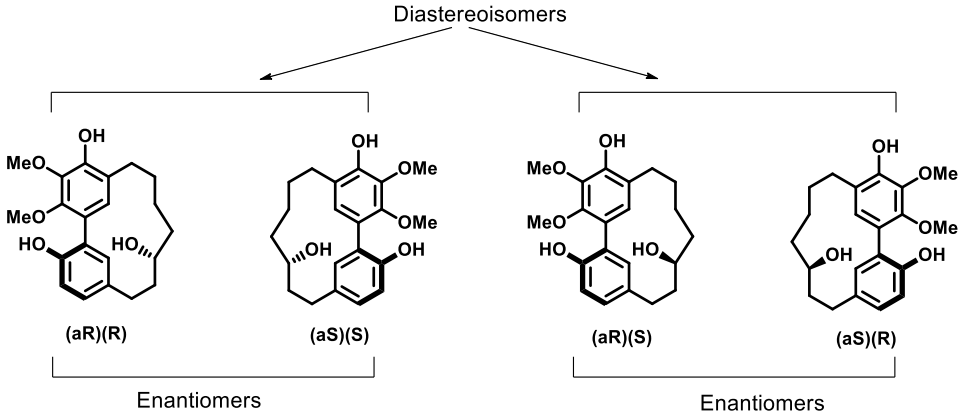


Figure 2-5 Possible stereoisomers of myricanol

The X-ray crystal structure of (±)-myricanol, isolated by Joshi and co-workers, contains only the enantiomeric pair (a*R*,*S*) and (a*S*,*R*). To explain this result, they performed some molecular mechanics calculations to minimize the energy of the diastereoisomeric pair (a*S*,*S*) and (a*S*,*R*). They demonstrated that the (a*S*,*R*) diastereoisomer was more stable than the (a*S*,*S*) diastereoisomer by 2.72kcal/mol.

Considering these previously reported informations on the structure of myricanol and matching the NMR and X-ray data with a positive Cotton effect, Jones et *al.*[11] reported for the first time the isolation from *Myrica cerifera* of (+)-a*R*,11*S*-myricanol as a natural product (Matsuda et *al*. described 9 years before the

[25] Matsuda, H.; Morikawa, T.; Tao, J.; Ueda, K.; Yoshikawa, M. *Chem. Pharm. Bull. (Tokyo)* **2002**, *50* (2), 208–215.
[26] The prefix "a" indicates the axial chirality in a dissymmetric biphenyl
Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of organic compounds*; Wiley: New York, **1994**.

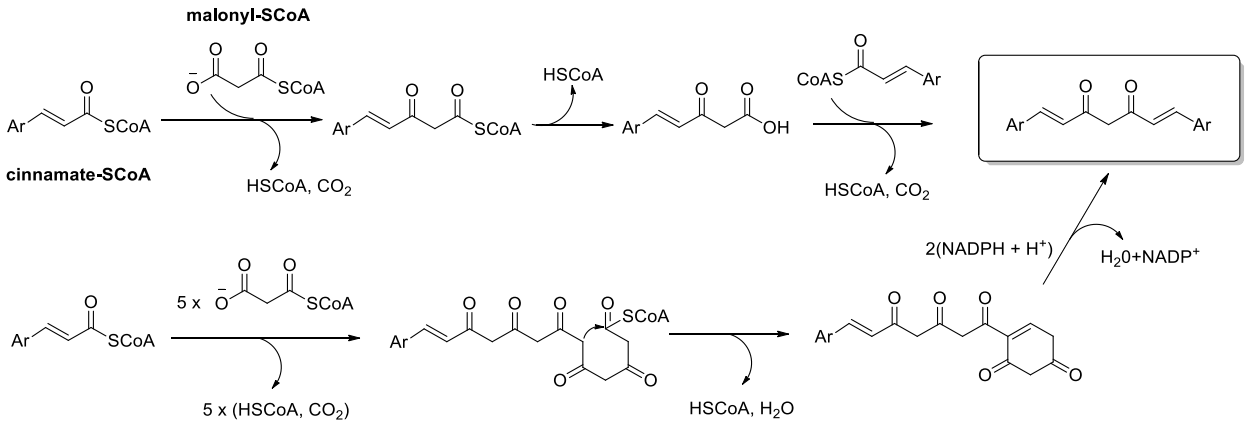
naturally occurring corresponding glycoside). It's important to underline that (+)-a*R*,11*S*-myricanol was extracted with 86% *ee* and not as an enantiopure isomer.

Finally, the isolation of the two possible stereoisomers of myricanol is highly dependant from the *Myrica* species source, the period of the collect and the methods used to extract the natural product. Therefore a stereoselective synthesis of enantiopure myricanol would be very helpful to study its biological properties.

2.2 BIOSYNTHESIS

Considering the importance of natural diarylheptanoids, their biosynthesis has been investigated from many researcher groups. In the case of phenylphenalenone derivatives [27] it has been reported that two phenylpropanoids and one malonyl-CoA are involved in the formation of the phenylphenalenone skeleton. However, there is no information about the biosynthetic pathways for cyclic diarylheptanoids.

Curcumin (**Figure 1-1**), the most prominent linear diarylheptanoid, is often recognized as a diferuloylmethane. This name indicates that its biosynthesis involves two cinnamate (ferulate) units (C_6-C_3) with a central methylene group provided by a malonate unit.[28] Roughley and Whiting carried out experiments using radioisotope labeled acetate and malonate that revealed a mechanism in which a cinnamate unit reacts with five acetate (or malonate) units followed by a cyclization.[29] In the **Scheme 2-1** are reported the two possible mechanisms suggested by Whiting and co-workers.



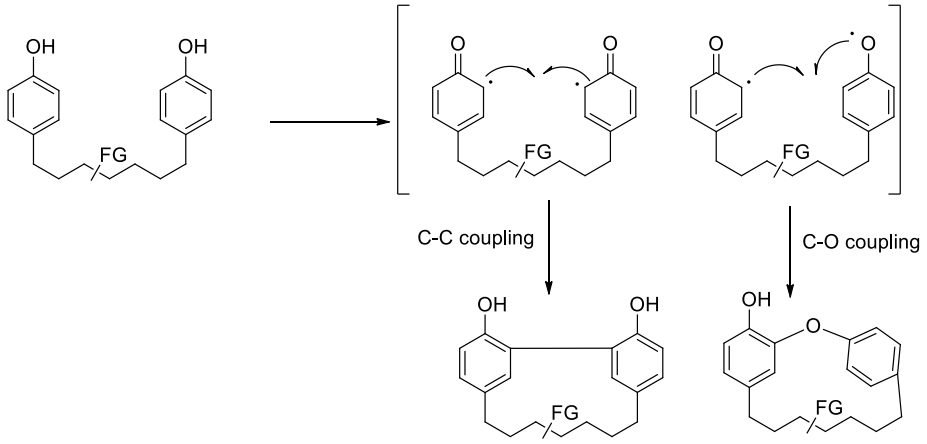
Scheme 2-1 Biosynthesis of curcumin

A more recent study of Ramirez-Ahumada et al.[30] detected the activity of curcuminoid synthase in turmeric, which required both 4-hydroxycinnamyl-CoA esters and malonyl-CoA for curcuminoid biosynthesis.

Concerning the formation of macrocyclic diarylheptanoids, it probably occurs through an intramolecular phenolic oxidative coupling[31]. Due to the respectively *para* position of the phenol groups and of the linear

[27] a) Hölscher, D.; Schneider, B. *J. Chem. Soc. Chem. Commun.* **1995**, 5, 525. b) Schneider, B.; Gershenzon, J.; Graser, G.; Hölscher, D.; Schmitt, B. *Phytochem. Rev.* **2003**, *2* (1-2), 31–43.
[28] Roughley, P. J.; Whiting, D. A. *Tetrahedron Lett.* **1971**, *12* (40), 3741–3746.
[29] Roughley, P. J.; Whiting, D. A. *J. Chem. Soc.Perkin 1* **1973**, 2379–2388.
[30] Ramirez-Ahumada, M. del C.; Timmermann, B. N.; Gang, D. R. *Phytochemistry* **2006**, *67* (18), 2017–2029.
[31] Barton, D. H. R.; Bracho, R. D.; Potter, C. J.; Widdowson, D. A. *J. Chem. Soc. Perkin 1* **1974**, 2278–2283.

chain, the cyclized natural products will be *meta*, *meta* when a biphenyl will be formed and *meta*, *para* in the diphenylether cyclophanes[3]. (**Scheme 2-2**)

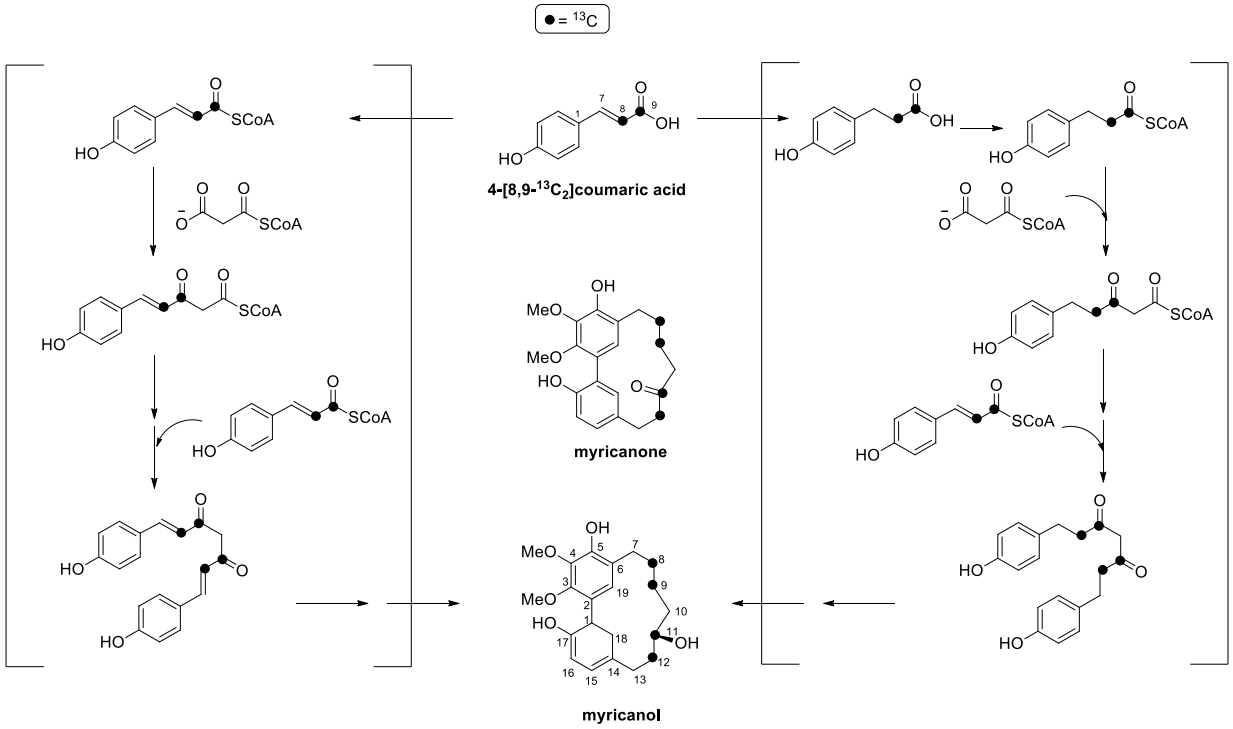


Scheme 2-2 Macrocyclization by oxidative coupling

Kawai and co-workers reported in two papers[14,32] a study on the biosynthesis of myricanol and myricanone. In the first work in 2008, they performed *in* vivo feeding experiments using ^{13}C-labeled 4-coumaric acid to grow *Myrica rubra* young shoots. Mass spectrometry (MS) and ^{13}C nuclear magnetic resonance (NMR) analysis indicated the involvement of two molecules of 4-coumaric acid for the formation of two cyclic diarylheptanoids, myricanol and myricanone. The NMR analysis of myricanol isolated after administration of 4-[8,9-$^{13}C_2$]coumaric acid demonstrated that the C-8 and C-9 atoms of 4-coumaric acid were incorporated into C-8, C-9, C-11 and C-12 of the corresponding myricanol. However, because there is no carbon–carbon double bond in the heptane side chain of myricanol and myricanone, it was unclear whether the saturated structure in myricanol was originated from dihydrocinnamic acid precursor(s) or from a cinnamic acid precursor followed by hydrogenation after condensation with a second cinnamate unit.

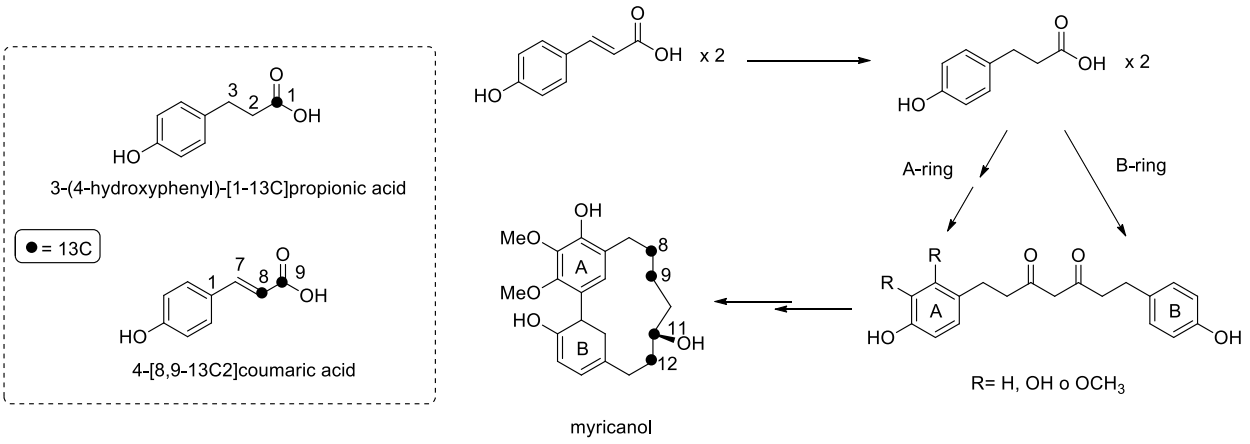
Moreover, the macrocyclization step and the origin of the methyl ether in myricanol and myricanone also remained to be resolved. In view of these results Kawai et *al*. proposed a biosynthetic mechanism as showed in **Scheme 2-3.**

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



Scheme 2-3 First biosynthesis proposed for myricanol and myricanone

In the second paper**,** they revealed that two molecules of 3-(4-hydroxyphenyl) propionic acid could also be a biosynthetic precursor of myricanol in *M. rubra,* **Scheme 2-4**. They observed that both 4-coumaric acid and its dihydro-derivative were incorporated into myricanol. Competitive feeding experiments with 4-[8,9-$^{13}C_2$]coumaric acid and 3-(4-hydroxyphenyl)-[1-^{13}C]propionic acid were performed in *M. rubra* to determine the preferential incorporation of these two precursors. ^{13}C-NMR studies indicated that 3-(4-hydroxyphenyl)-[1-^{13}C]-propionic acid was preferentially incorporated into myricanol. Analyzing these data, they provided evidence for a biosynthetic sequence originating from 4-coumaric acid and leading to myricanol, through 3-(4-hydroxyphenyl)-propionic acid, in *M. rubra*. (**Scheme 2-4**) The incorporation ratio of 4-[8,9-$^{13}C_2$]coumaric acid and 3-(4-hydroxyphenyl)-[1-^{13}C]propionic acid differ between C-9 (1:1.6) and C-11 (1:8.4) in the extracted myricanol. This result appeared very interesting to explain the non-symmetric structure of myricanol. Myricanol has two types of aromatic ring, one with two methoxyl and one hydroxyl group (ring A) and the other with just one hydroxyl function (ring B). If the chain of the diarylheptanoid would be built from the same two precursors, for example, 3-4-(hydroxyphenyl)-propionyl-CoA, the ratio of the incorporation at C-9 and C-11 may be indistinguishable as a consequence of the symmetry. Considering that this ratio is not the same, they asserted that hydroxylation (and/or methylation) of the A-ring may occur before the formation of diarylheptanoidic skeleton.



Scheme 2-4 Second biosynthesis proposed for myricanol and myricanone

Kawaii et *al*. in their second publication[32] affirmed that further study to confirm this hypothesis will be performed using ^{13}C-labeled caffeic, ferulic acid or their corresponding dihydro derivatives, but until now nothing has been published in this sense.

2.3 BIOLOGICAL ACTIVITIES

Myrica rubra is one of the most spread widely plant of *Myricaceae* in China and Japan and its bark was used since antiquity in folk medicine as astringent, antidiarrheic, antibacterial, antioxidant and anti-inflammatory. The inhibitory effects on the release of β -hexosaminidase from RBL-2H3 cells were examined, and several diarylheptanoids, myricanol, (+)-*S*-myricanol, myricanone, and myricanenes were found to show a good activity[25]. The anti-androgenic activity of extracts of *Myrica rubra* was shown by Matsuda et. *al*. which found in myricetin, myricanol and myricanone the main active compounds[10]. Glycosilated myricanol and myricanone were found to inhibit induction of inducible nitric oxide synthase[9].

Recent reviews on *Myrica nagi* plant reported in detail the "miraculous" and versatile properties of the extracts that show activities such as hepatoprotective, antioxidant, antibacterial, antifungal, anti-inflammatory and antiasthmatic.[18b),18c)]

Our interest in myricanol has been triggered by the anti-tau activity of this metabolite originaly disclosed by the group of Dickey.[11] Later on, a potent antitumoral activity against the lung cancer[12] was described. For this reason this two biological activities will be described with more details.

2.3.1 ANTI-TAU ACTIVITY

Tau proteins belong to the family of microtubule-associated proteins (MAPT). They are mainly expressed in neurons where they play an important role in the assembly of tubulin monomers into microtubules to constitute the neuronal microtubules network. Microtubules are responsible to mantain the cell shape and for axonal transport. Moreover, also tau proteins establish some links between microtubules and other cytoskeletal elements or proteins[33]. The proteins work together with a globular protein called tubulin to stabilize microtubules and aid the assembly of tubulin in the microtubules. Tau proteins achieve their control of microtubule stability through isoforms and phosphorylation. When tau proteins become defective and fail to adequately stabilize microtubules, pathologies of the nervous system can develop[34] (**Figure 2-6**). Intracellular aggregation of abnormal species of phosphorylated tau is a typical feature of a family of neurodegenerative diseases collectively referred to tauopathies. . More than 15 neurodegenerative diseases belong to this pathology, including Alzheimer and Parkinson. Hyperphosphorylation of tau proteins can

[33] Buée, L.; Bussière, T.; Buée-Scherrer, V.; Delacourte, A.; Hof, P. R. *Brain Res. Rev.* **2000**, *33* (1), 95–130.
[34] Spires-Jones, T. L.; Stoothoff, W. H.; de Calignon, A.; Jones, P. B.; Hyman, B. T. *Trends Neurosci.* **2009**, *32* (3), 150–159.

cause the formation of neurofibrillary tangles (NFTs) that are intracellular aggregates composed of paired helical filaments (PHFs).

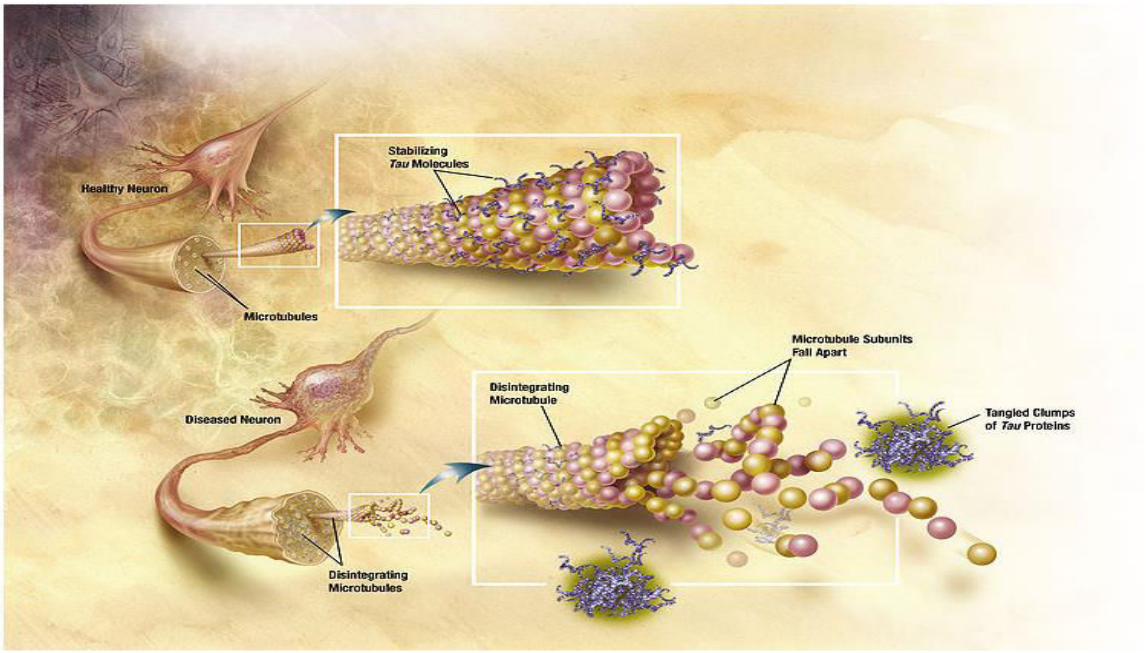


Figure 2-6 Neurofibrillary tangles

The result of the hyperphosphorylation consists in the disintegration of microtubule structure that allows the neuron to the death. It has been discover that while aggregation of hyperphosphorylated protein tau is visible evidence of tauophaties, these neurofibrillary tangles appear to be less toxic than soluble intermediates of protein tau. High levels of tau intermediates, particularly aberrant tau species fail to be cleared from cells, cause cognitive dysfunction leading to Alzheimer disease (AD) an more generally tauophaties. Indeed, agents that degrade or destabilize tau intermediates, clear aberrant tau species from cells, or are able to reduce intracellular tau levels, are promising therapeutics for AD and tauopathies.

Dickey and collaborators highly worked in this sense focusing their attention on the power of myricanol, extract from *Myrica cerifera*, to destabilize the microtubule associated protein tau.

They isolated the (+)-a*R*,11*S*-myricanol (86% *ee* from *Myrica cerifera*) (see 2.1.1) and they investigated protein tau levels in HeLa-C3 cells. After treating these murine brain cells with the same concentrations of the isolated scalemic compound and with commercially available "racemic" myricanol (actually 9% *ee*) they observed that tau levels in HeLa-C3 cells were significantly reduced by enantiomerically enriched (+)-a*R*,11*S*-myricanol (EC_{50} = 35μM).[11] In the **Figure 2-7** were reported the HPLC chiral separation of the

enantioenriched extract of myricanol (A), of the commercial racemate (B) and the profiles obtained to evaluate the tau levels in Hela-C3 (C e D).

In view of these very promising results, Dickey et *al.* reported two patents: in the first they reported the materials and methods for protein tau reduction in the treatment of neurodegenerative diseases using (+)-a*R*,11*S*-myricanol [35], in the second they described a series of myricanol derivatives investigated for the same biological activity[36].

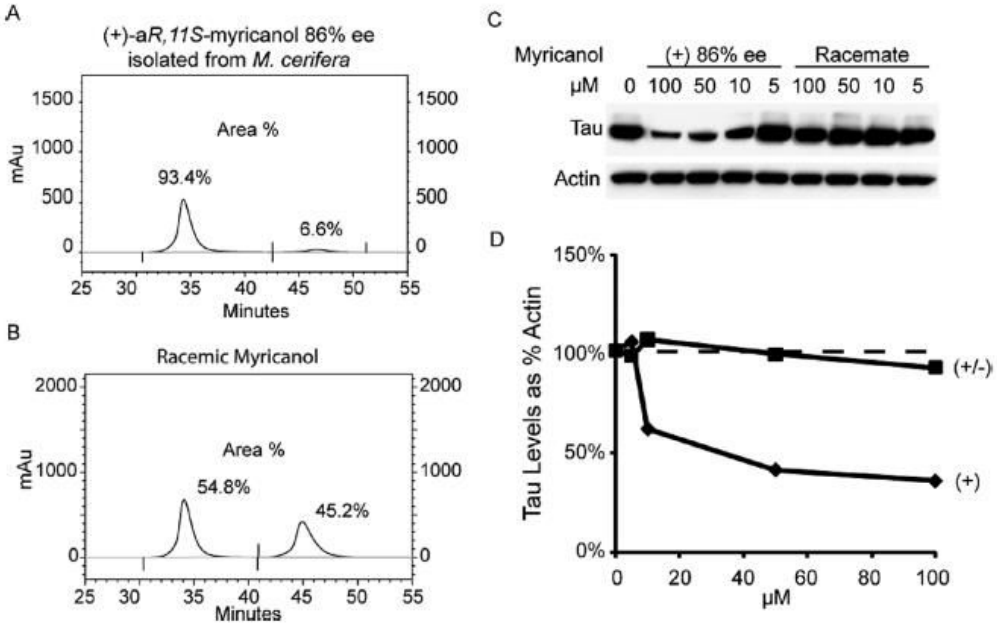


Figure 2-7 Anti-tau activity of (+)-a*R*,11*S*-myricanol

In contrast with their previous report, the same research group disclosed recently that the reduction of tau levels mainly originated from the (-)-a*S*,11*R*-myricanol.[37]

In this paper they reported the chemical synthesis of racemic myricanol (see 2.4.3). Chiral HPLC separation and X-ray analysis allowed to confirm that synthetic racemic myricanol is a mixture of two enantiomers (+)-a*R*,11*S*-myricanol (51%) and (-)-a*S*,11*R*-myricanol (49%) (see **Figure 2-5**). They surprisingly found

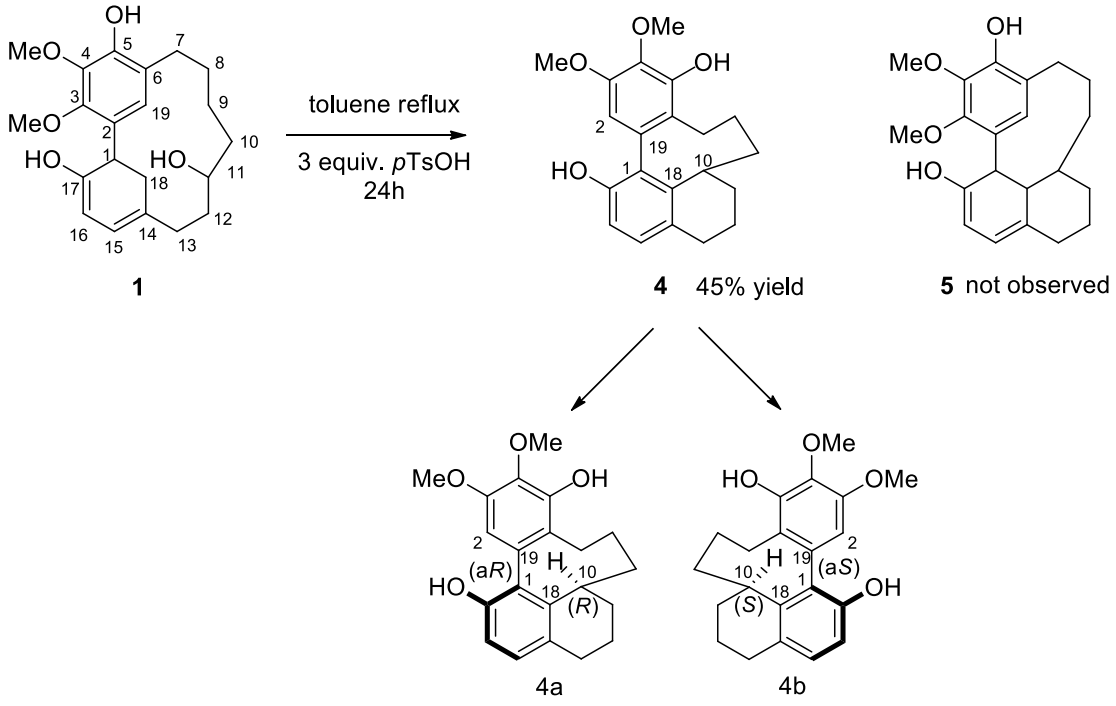
[35] Chad Dickey, Matthew Lebar, Bill J. Baker, Jeffrey Jones. MATERIALS AND METHODS FOR REDUCTION OF PROTEIN TAU AND TREATMENT OF NEURODEGENERATIVE DISEASES. US20130184353 A1, **2012**.

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

[37] 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.

that (-)-a*S*,11*R*-myricanol reduced tau levels in both cultured cells and *ex vivo* brain slices from a mouse model of tauophaty, but its enantiomer did not. They thought that the characteristic conformation of this enantiomer could be better metabolized in the cells, increasing the cell permeability.

Moreover, a structure-activity relationship (SAR) study revealed that the compound (**4**) resulting from an acid-catalyzed dehydration of myricanol (**1**) displayed a robust tau-lowering activity, comparable to (-)-a*S*,11*R*-myricanol. (**Scheme 2-5**) The rearranged unexpected molecule (**4**) was a mixture of two enantiomers **4a** and **4b** [(a*R*,10*R*) and (a*S*,10*S*) respectively] whose structures were elucidated by X-ray analysis. HPLC chiral separation afforded (+)-(**4**) ($[\alpha]_D^{20}$ = +93.6) and (-)-(**4**) ($[\alpha]_D^{20}$ = -100) which optical power wasn't attributed to the structure **4a** and **4b.** The two enantiomers were separately investigated for the tau lowering effect. Both molecules had similar activity against tau and this suggests that in this case the anti-tau activity is independent from chirality.



Scheme 2-5 Myricanol derivatives with anti-tau activity

2.3.2 ANTI-CANCER ACTIVITY

As described until now myricanol is a versatile bioactive agent that exhibits many biological activities. However, information regarding the anticancer mechanism of myricanol is limited. In the best of our knowledge anticancer activities of cyclic diarylheptanoids and particularly of myricanol appeared only in literature in 2000 and 2002 with two publications of Ishida J. et *al.* describing their inhibition of skin tumor[38] and their use as chemopreventives[39].

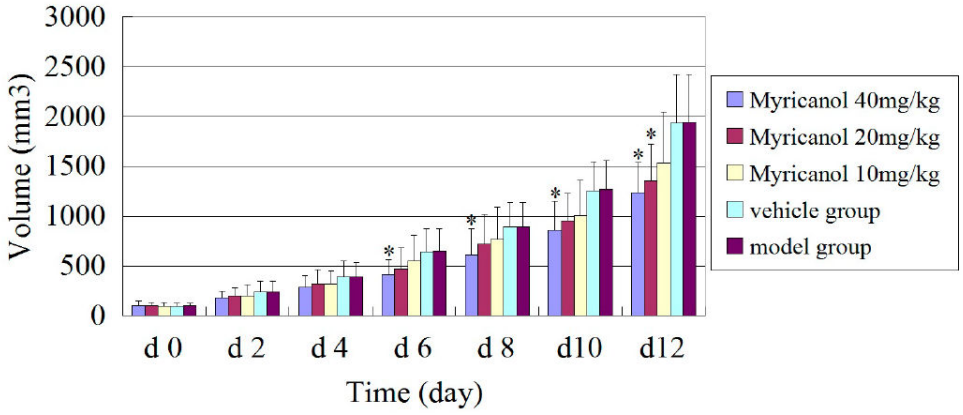
In 2012 appeared a patent submitted by Dai G.H. and collaborators from the Academy of traditional Chinese medicine in which was disclosed the application of myricanol and/or myricanone in preparing antitumor drugs.[40] The invention abstract speak about antitumor drugs for preventing and/or treating liver cancers, lung cancers, leukemia, stomach cancers and other tumors. They proved that myricanol and myricanone have good antitumor effects and cause low toxicity to normal cells.

Very recently (2014 and 2015) the same research group published two important works disclosing the potent activity of myricanol to reduce and treat human lung adenocarcinoma A549 cells.

Lung cancer is generally divided into small-cell lung cancer (SCLC) and non small-cell lung cancer (NSCLC). To this last one belong approximately 75-85% of all lung cancers. Even if new chemotherapeutic drugs have been tested on the affected people, no significant improvements in patient's prognosis have been achieved. For this reason the development of new therapeutic drugs for lung cancer is fundamentally important. Apoptosis is a physiological process that occurs during embryonic development and tissue homeostasis in adult animals. When a dysregulation of this normal process occurs, disease and death could be the imminent result. Cancer is a consequence of uncontrolled cell proliferation and apoptosis dysregulation. Thus, to develop preventive strategies for the cancer's control, a good point would be a programmed induction of apoptosis. In the study reported on Phytomedicine[41], Dai G. H. and collaborators shown that myricanol extracted from *M. rubra* bark significantly inhibited the growth of A549 cells in a dose-dependent manner, with EC_{50} of 4.85µg/mL. The cyclic diarylheptanoid decreased colony formation and induced A549 cell apoptosis. In the second study reported on the Internationl Journal of Molecular

[38] Ishida, J.; Kozuka, M.; Wang, H.-K.; Konoshima, T.; Tokuda, H.; Okuda, M.; Yang Mou, X.; Nishino, H.; Sakurai, N.; Lee, K.-H.; Nagai, M. *Cancer Lett.* **2000**, *159* (2), 135–140.
[39] Ishida, J. *Bioorg. Med. Chem.* **2002**, *10* (10), 3361–3365.
[40] Dai, G.; Yang, F.; Tong, Y.; Ren, Z.; Chen, Y. Application of myricanol and/or myricanone in preparing antitumor drugs. CN102552243 (A), July 11, 2012.
[41] Dai, G. H.; Meng, G. M.; Tong, Y. L.; Chen, X.; Ren, Z. M.; Wang, K.; Yang, F. *Phytomedicine* **2014**, *21* (11), 1490–1496.

Sciences[42] they explored the inhibiting effect and mechanism of myricanol on lung adenocarcinoma A549 xenografts in nude mice. For this research forty nude mices with subcutaneous A549 xenografts were randomly divided into five groups: high-dose myricanol (40 mg/kg body weight) group; middle-dose myricanol (20 mg/kg body weight) group; low-dose myricanol (10 mg/kg body weight) group; polyethylene glycol 400 vehicle group (1 mL/kg); and tumor model group. After 12 days of treatment they calculated the tumor inhibition rate (TIR, %). (**Figure 2-8**)



Antitumor effect of myricanol on an A549 cell xenograft model (n = 8, $\bar{x}$ ± SD).

Group and dose	Body Weight (g)		Tumor Weight (g)	TIR (%)
	Begin	End		
Myricanol (40 mg/kg)	20.9 ± 1.43	24.9 ± 2.21	1.894 ± 0.555 *	38.5
Myricanol (20 mg/kg)	21.4 ± 1.81	24.8 ± 2.13	2.239 ± 0.782 *	27.3
Myricanol (10 mg/kg)	22.1 ± 1.92	24.4 ± 2.12	2.628 ± 1.021	14.7
Vehicle group	21.7 ± 1.15	25.0 ± 2.05	3.079 ± 0.834	0.81
Model group	21.5 ± 1.28	25.3 ± 1.95	3.104 ± 0.901	-

* Compared with the vehicle group $p < 0.05$.

Figure 2-8 Antitumor effect of myricanol on an A549 cell xenograft model

As clearly showed in **Figure 2-8**, myricanol-induced inhibition of the A549 xenograft tumor volume in mice administered with myricanol at 40 and 20 mg/kg body weight concentrations were 39.4% and 25.5%, respectively. The TIRs of the three myricanol doses ranged from 14.9% to 38.5%.

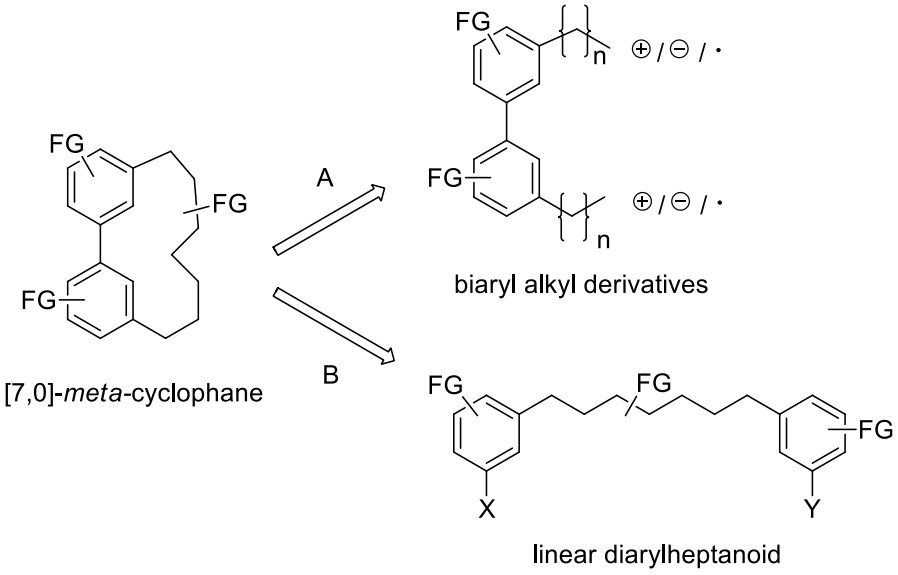
Therefore, according to this study, myricanol can significantly decelerate A549 xenograft growth *in vivo* by inducing apoptosis, for this reason it may be a clinical candidate to prevent and treat lung cancer.

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

2.4 STATE OF ART OF CHEMICAL SYNTHESIS

2.4.1 GENERAL APPROACH FOR SYNTHESIS OF [7,0]-*META*-CYCLOPHANES

The biaryl structural motif is a predominant feature in many pharmaceutically relevant and biologically active compounds. As a result, for over a century organic chemists have sought to develop new and more efficient aryl-aryl bond-forming methods.[43] Cyclophanic natural products comprise an intriguing class of structurally diverse compounds. As inherent for all cyclic compounds regardless of their origin, macrocyclization is naturally the most decisive step, which defines the overall efficiency of the synthetic pathway. Especially in small cyclophanic molecules, this key step constitutes an even greater challenge. Due to the strain imparted by the macrocyclic system, free rotation of the benzene ring(s) is often restricted depending on both the constitution of the tethered and the aromatic portions.[44] Among cyclophanic natural products, the diarylheptanoids are a structurally sub-class with their scaffold consisting of two benzene rings tethered by an oxygenated aliphatic heptyl chain. (**Scheme 2-6**)



Scheme 2-6 Cyclic diarylheptanoids synthetic approaches

[43] Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107* (1), 174–238.

[44] a)Gulder, T.; Baran, P. S. *Nat. Prod. Rep.* **2012**, *29* (8), 899. b) Kane, V. V.; De Wolf, W. H.; Bickelhaupt, F. *Tetrahedron* **1994**, *50* (16), 4575–4622.

The synthesis of [7,0]-*meta*-cyclophanes strictly depends from the adopted strategy. Generally they could be obtained from macrocyclization with the formation of the heptyl chain on a biaryl precursor (Path A) or from a macrocyclization by an aryl-aryl coupling (Path B). In both cases, these macrocyclizations are subjected to many constraints and the control of atropisomery in case of biaryl coupling[45] increasing the synthetic challenge that represents the preparation of such molecules. The main constraints featuring during cyclization are (1) torsional strain in the ring system; (2) steric interactions between hydrogens inside the 13-membered ring; (3) steric and electronic effects around the coupling sites in the case of an aryl-aryl coupling.

The most common reported macrocyclization reactions are: intramolecular ring closing metathesis (path A),[46] intramolecular Wittig type reactions (path A),[47] transition metal catalyzed reactions (path A or B),[43] intramolecular nucleophilic aromatic substitution (path B)[48] and intramolecular oxidative coupling (path B).[49] Considering the two different cyclization pathways A and B, the corresponding precursors could be obtained using different disconnections described below.

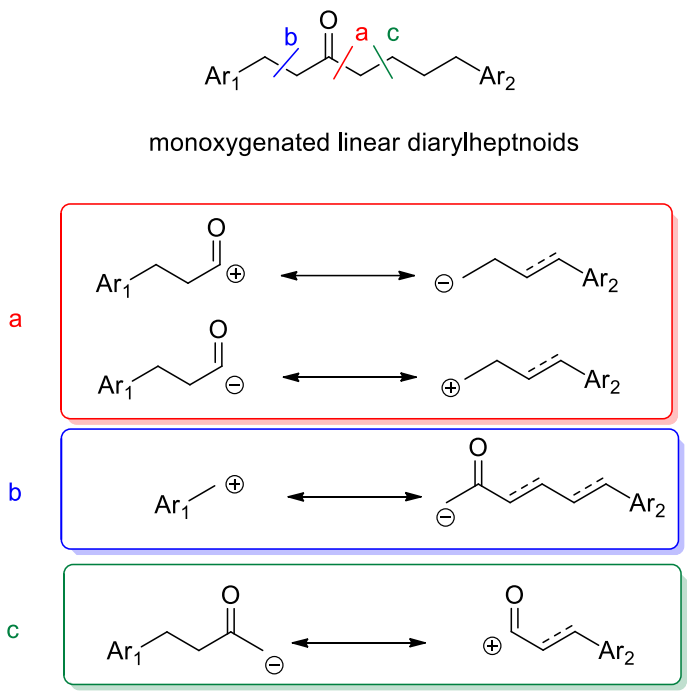
Macrocyclization *via* an intramolecular ring closure of the tethered heptyl chain (Path A)

Biaryl moiety of a [7,0]-*meta*-cyclophanic structure could be obtained through metal catalyzed cross-coupling reactions such as Ullmann coupling, Suzuki-Miyaura coupling, C-H activation or *via* intramolecular oxidative coupling.

Macrocyclization *via* an intramolecular aryl-aryl coupling (Path B)

[7,0]-*meta*cyclophanes can be prepared by intramolecular cyclization of linear diarylheptanoids. These cyclophanes precursors are easily accessible, using common organic reactions as depicted in **Scheme 2-7**.

[45] Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. *Chem. Rev.* **2011**, *111* (2), 563–639.
[46] Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44* (29), 4490–4527.
[47] Nicolaou, K. C.; Härter, M. W.; Gunzner, J. L.; Nadin, A. *Liebigs Ann.* **1997**, *1997* (7), 1283–1301.
[48] Zhu, J. *Synlett* **1997**, *1997* (2), 133–144.
[49] a) Aldemir, H.; Richarz, R.; Gulder, T. A. M. *Angew. Chem. Int. Ed.* **2014**, *53* (32), 8286–8293. b) Quideau, S.; Deffieux D., and Pouységu L. In *Comprehensive Organic Synthesis*; Oxford: Elsevier, 2014; Vol. 3, pp 656–740.



Scheme 2-7 Construction of linear diarylheptanoic chain

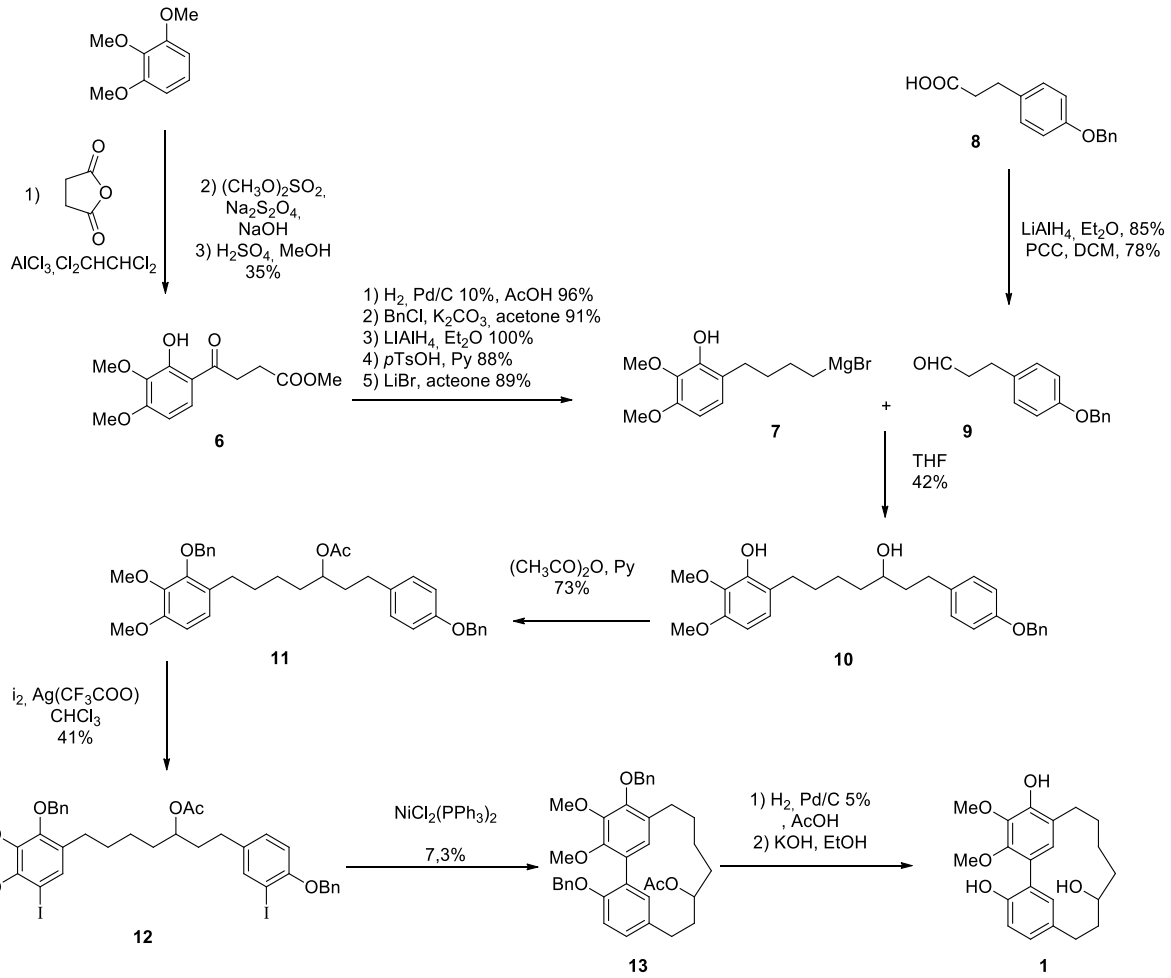
Linear diarylheptanoids can be disconnected according to path “a” featuring a nucleophilic addition to an aldehyde or a carbonyl *umpolung* on an electrophile; or according to path “b”or “c” which are respectively represented by an aldol condensation and a Wittig type reaction.

Considering these general accesses to [7,0]-*meta*-cyclophanes, we will see in the next paragraphs how myricanol and myricanone have been already synthesized. Only racemic synthesis have been reported so far.

2.4.2 TOTAL SYNTHESIS OF MYRICANOL AND MYRICANONE BY WHITING ET AL. (1980)

The first total synthesis of racemic myricanol was reported by Whiting et *al*., the same research group who first isolated and characterized this natural product.[50]

In three papers they described: 1) the construction of 1,7-diarylheptane skeleton of myricanol and myricanone. 2) the macrocyclization step and 3) they studied the factors affecting the cyclization step.

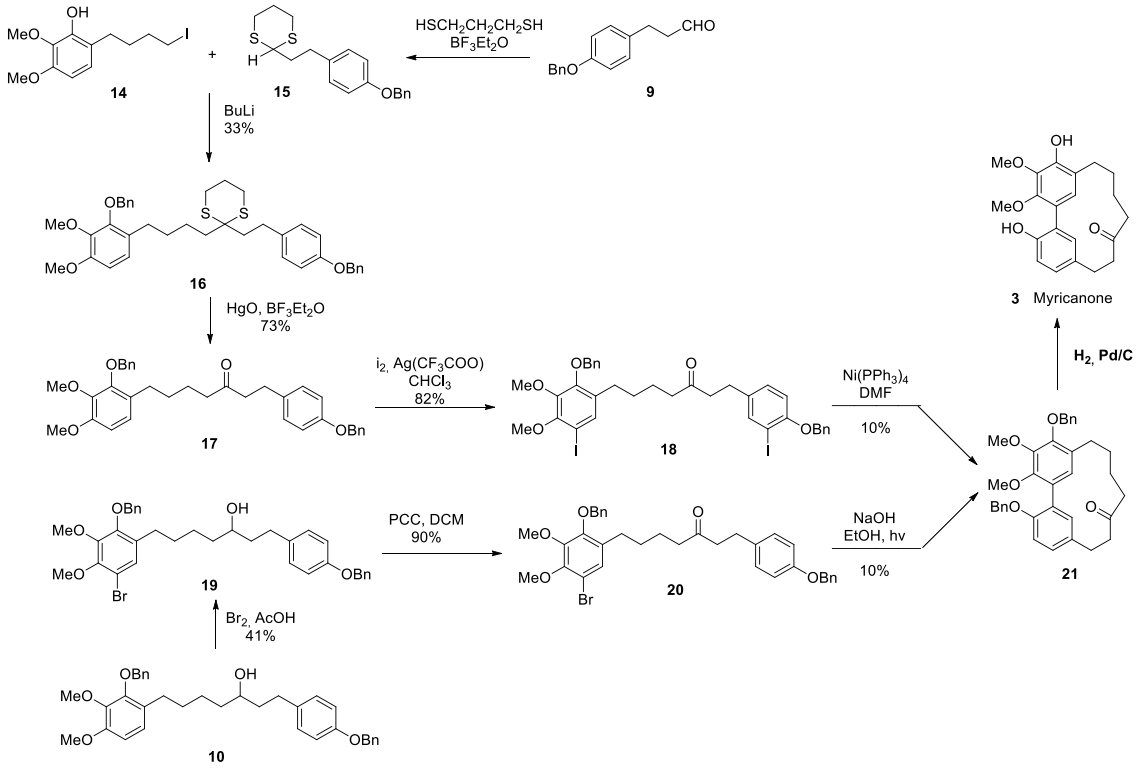


Scheme 2-8 Total synthesis of myricanol (Whiting et *al.)*

[50] 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.

According to **Scheme 2-8** myricanol was obtained in 14 steps in 0,21% overall yield. The main reactions used were a Friedel-Crafts acylation on the commercial 1,2,3-trimethoxybenzene, the transformation of the aryl-acyl compound **6** into the corresponding aryl-alkyl bromine that was converted into the Grignard reagent **7**. The substrate **7** reacted with a *p*-benzyloxypropionaldehyde **9** to afford the linear diarylheptanoid **10** in 42% yield which was subsequently protected and di-iodinated to compound **12** The macrocyclization reaction was performed using Ni(0) as catalyst delivering the desired product **13** in a surprinsingly low yield (7.3%) compared to the quite good 46% obtained for the cyclization giving rise to alnusone (a natural diarylheptanoid with one oxygenated substituent on each aromatic rings).[51] The last deprotection steps affording myricanol **1** were reported without any yield.

Myricanone **3** was prepared according to two different approaches depicted in **Scheme 2-9**. In one case the linear chain was build using *umpolung* strategy. Dithiane **15** was reacted with the iodide **14** in the presence of *n*-BuLi affording the linear diarylheptanoid **16** which was hydrolyzed into the corresponding ketone **17**.



Scheme 2-9 Total synthesis of myricanone (Whiting et *al.*)

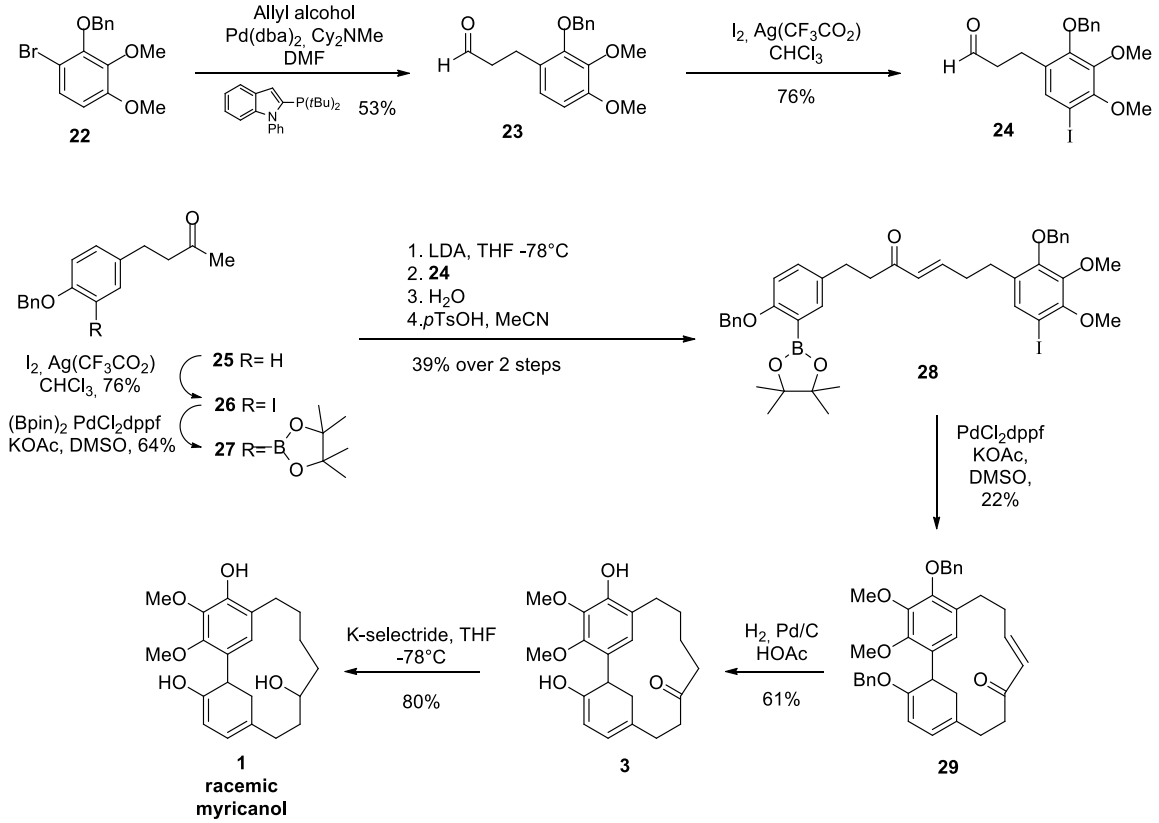
[51] Semmelhack, M. F.; Helquist, P.; Jones, L. D.; Keller, L.; Mendelson, L.; Ryono, L. S.; Gorzynski Smith, J.; Stauffer, R. D. *J. Am. Chem. Soc.* **1981**, *103* (21), 6460–6471.

Iodination of **17** followed by Ni(0) catalyzed cyclization gave rise to the myricanone precursor **21** in 10% yield. The second approach started with the diarylheptanoid **10** already prepared for the synthesis of myricanol **1** (**Scheme 2-9**). Mono-bromination of **10** followed by PCC oxidation of hydroxyl group gave bromo-ketone **20** which was subsequently submitted to a photocatalyzed cyclization delivering the cyclophane **21** in 10% yields. A catalytic hydrogenation of **21** selectively deprotected the benzyl ethers to afford myricanone **3**.

2.4.3 TOTAL SYNTHESIS OF MYRICANOL BY DICKEY ET AL.(2015)

Considering the biological importance of myricanol and the related studies on the anti-tau activity[11], Dickey's group reported a racemic myricanol synthesis last year.

They converted the bromide **22** into the corresponding phenylpropionaldehyde **23** by reductive coupling with an allylic alcohol. An *ortho*-methoxy-directed iodination of the aromatic ring afforded the aldehyde **24** which was coupled with the arylboronic ketone **27** resulting from consecutive iodination and borylation of methylketone **25**. The resulting linear diarylheptanoid **28** was involved in an intramolecular Suzuki-Miyaura reaction to give the macrocycle **29** in 22% yields. The cyclic compound was deprotected to myricanone **3** and subsequently reduced to racemic myricanol in 2.03% overall yield within 7 steps (**Scheme 2-10**).



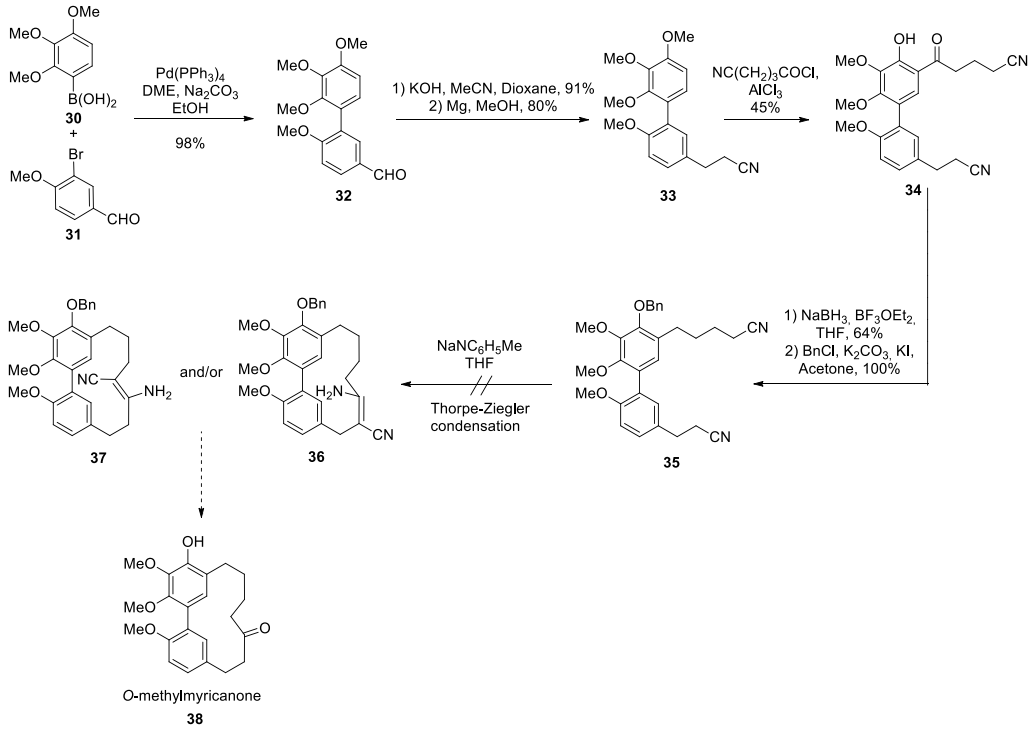
Scheme 2-10 Total synthesis of myricanol (Dickey et *al.*)

The key-step of this synthesis was the intramolecular Suzuki coupling giving the better yield obtain so far for installation of the biaryl core of myricanol.[37]

2.4.4 TOWARD THE SYNTHESIS OF *O*-METHYLMYRICANONE BY DANSOU ET AL.(2000)

Dansou *et al.* were interested on the synthesis *O*-methylmyricanone, a non-natural analogue of myricanone.[52] For this purpose they propose the first attempt of the synthesis of myricanol/myricanone derivatives *via* path A (see 2.4.1).

This synthesis started with the intermolecular construction of the biaryl core using a Suzuki-Miyaura coupling between readily accessible boronic acid **30** and bromo aldehyde **31**. The resulting coupling product **32** was homologated with two carbons on aldehyde and acylated under Friedel-Craft conditions which undergo simultaneously selective demethoxylation on the more electronrich ring of substrate **33** to afford the dicyano compound **34**. Clemmensen type reduction of the ketone **34** followed by protection of the phenol with BnCl gave rise to **35** which was submitted to different conditions of Thorpe Ziegler condensation without any success. The desired intramolecular condensed products **36** and/or **37** were not observed (**Scheme 2-11**).



Scheme 2-11 Towards the total synthesis of *O*-methylmyricanone

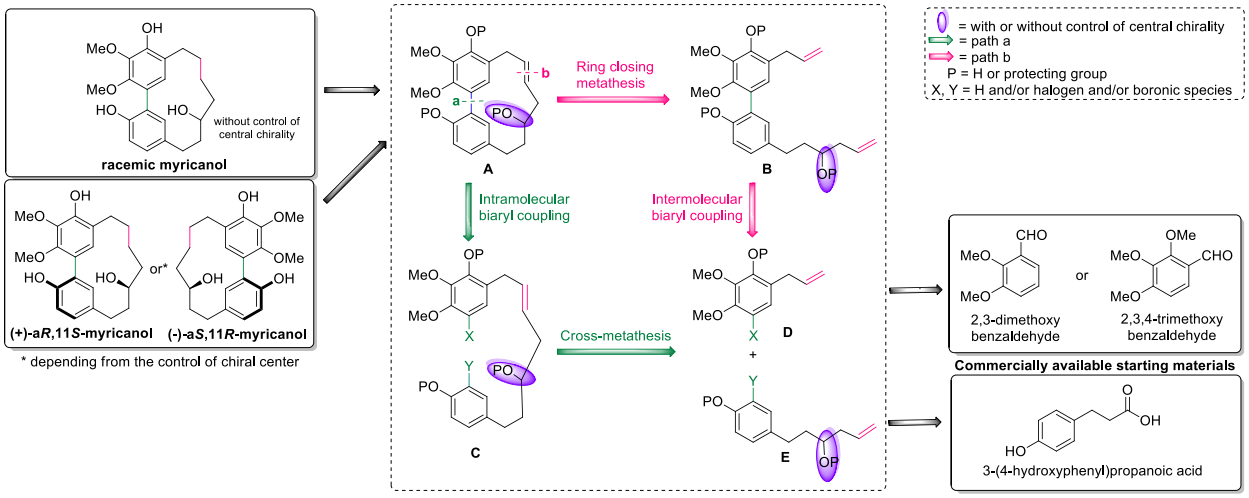
[52] Dansou, B.; Pichon, C.; Dhal, R.; Brown, E.; Mille, S. *Eur. J. Org. Chem.* **2000**, *2000* (8), 1527–1533.

3 DESIGN AND SELECTION OF THE SYNTHETIC ROUTE FOR MYRICANOL

3.1 RETROSYNTHETIC APPROACHES

Recent published works demonstrated that both scalemic (a*R*,*S*/a*S*,*R)* or pure (-)-a*S*,11*R*-myricanol are effective anti-tau components.[11,37] In this context, the aim of this thesis is to develop a high-yielding and stereoselective route for the production of synthetic (rac)-myricanol which will also be easily modified to an enantioselective version (see 2.3.1 and 2.3.2).

Considering the structure of myricanol, it was clear that macrocyclization and formation of the *m,m* heptylene linkage was the key synthetic challenge. Functional group interconversion of myricanol lead to the homoallylic benzyl ether **A** from which emerged two broad disconnections **Scheme 3-1**



Scheme 3-1 Retrosynthetic analysis for myricanol synthesis

Path a (disconnection on the biaryl bond) required the intramolecular biarylic C-C coupling (Suzuki-Miyaura coupling, Ullmann coupling, C-H activation, oxidative coupling) of the *seco*-precursor **C**. This diarylheptanoid might result from a cross metathesis reaction between the fragments **D** and **E** which in turn would be accessible from cheap commercially available starting materials. path b (disconnection on the chain) exploited the ring closing metathesis (RCM) in the construction of the macrocycle **A** and required the intermolecular biarylic C-C coupling of partners **D** and **E** to afford the cyclization precursor **B**.

Since we aspired to carry out subsequently an enantioselective version of the synthesis, we speculated, considering the work of Joshi *et al.*[24], that the macrocyclization of **B** or **C** bearing an enantiopure stereogenic carbinol could occur with any diastereoselectivity giving preferentially the natural enantiomer of myricanol.

In the next paragraph, we will present axial chirality and reactions developped in order to prepare atroposelective biaryles.

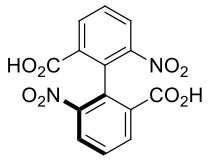
As a consequence of our retrosynthetic plan, the key reactions are on one hand the intra- (path a) or intermolecular (path b) biaryl coupling reaction and on the other hand the cross metathesis (path a) or the ring-closing metathesis (path b). This last one is proposed for the first time as a key reaction for the myricanol chain formation. Both classes of reactions will be detailed in next paragraph.

3.2 CONTROL OF AXIAL CHIRALITY

3.2.1 BIARYLS, AXIAL CHIRALITY AND CONFIGURATION OF ATROPISOMERS

Axially chiral biaryl skeletons are found in a wide variety of natural products, as alkaloids, coumarins, flavonoids, lignans, polyketides, tannins, terpenes and peptides.[45] They also served as priviledged framework for chiral reagents[53] in asymmetric catalysis, chiral phases for chromatography[54], chiral liquid crystals[55] and as chiral bioactive compounds in the pharmaceutical industry[56]. Because of their versatility, biaryl compounds represent important synthetic targets.

An axis of chirality is an axis about which a set of atoms/functional groups/ligands is held so that it results in a spatial arrangement that is not superimposable on its mirror image. Biaryls with an axial chirality can exist as atropisomers. Atropisomerism is a special isomerism which arise from a restricted rotation about the single bond that links the aryl moieties (two different planes). The conformers derived from atropisomerism are called atropisomers which can be isolated as separate chemical species. The term atropisomerism was made up in 1933 by Richard Kuhn [57], but the first time in which this phenomena was observed date back to the 1922 when Christie and Kenner successfully isolated *via* diastereoselective crystallization with a chiral resolving agent the (a*S*)- 6,6'-dinitro-[1,1'-biphenyl]-2,2'-dicarboxylic acid from the corresponding racemic mixture. [58] (**Figure 3-1**)



(a*S*)-6,6'-dinitro-[1,1'-biphenyl]-2,2'-dicarboxylic acid

Figure 3-1 First atropisomer isolated by Christie and Kenner in 1922

The biphenyl rings sit perpendicular in order to minimize steric hindrance between the four *ortho* substituents meaning that rotation about the biphenyl bond is greatly slowed.

[53] Mikami, K.; Yamanaka, M. *Chem. Rev.* **2003**, *103* (8), 3369–3400.
[54] Gübitz, G. *Chromatographia* **1990**, *30* (9-10), 555–564.
[55] Collings, P. J.; Hird, M. *Introduction to liquid crystals chemistry and physics*; Taylor & Francis: London; Bristol, PA, 1997.
[56] Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103* (3), 893–930.
[57] Kuhn, R. *Stereochemie*, K. Freudemberg.; 1933.
[58] Christie, G. H.; Kenner, J. *J. Chem. Soc. Trans.* **1922**, *121*, 614.

An arbitrary but useful definition of atropisomers was given in 1983 by M. Oki who took into account the interconversion of conformers in relation to the temperature. [59] He defined some important parameters to describe atropisomerism. The necessary conditions to have axial chirality are 1) a rotationally stable axis and 2) the presence of different substituents on both sides of the axis. The atropisomers are physically separable if, at a given temperature, they have a half-life of 1000 s (16.7 min). Moreover, M. Oki indicated the minimum free energy barriers, required to obtain configurationnaly stable biaryls, at different temperatures:

$\Delta G200K$ (-73°C) = 61.6 $kJmol^{-1}$ (15$Kcalmol^{-1}$)
$\Delta G300K$ (27°C) = 93.5 $kJmol^{-1}$ (22$Kcalmol^{-1}$)
$\Delta G350K$ (77°C) = 109 $kJmol^{-1}$ (26$Kcalmol^{-1}$)

The configurational stability of axially chiral biaryl compounds is determined by three major factors: 1) the (combined) steric demand of the substituents in proximity to the axis; 2) the existence, length, and rigidity of bridges; and 3) the involvement of atropisomerization mechanisms different from a merely physical rotation about the axis, for example, by photochemically or chemically induced processes[60].

As known, the configuration of a molecule having a chirality axis may be specified as *R* or *S* by application of the Cahn–Ingold–Prelog (CIP) priority rules. In 1958 K. Mislow described the absolute configuration of enantiopure biaryls using the CIP priority rules.[61] The descriptors *aR* and *aS* are sometimes used to distinguish axial chirality from other types (planar, central). Alternatively such molecules may be treated as helices and assigned *M* (minus) or *P* (plus) stereochemistry. For compounds with chirality axis, the descriptions *aR* correspond to *M* and *aS* correspond to *P*. The absolute axial configuration for a poly-*ortho'* substituted biaryl can be denoted by Newman projection along the biaryl axis. (**Figure 3-2**) After priority assignment to the substituents according to the CIP rules (for example A>B and A'>B'), the configuration is determined by following the shortest 90° path from the substituent of highest priority at the proximal ring (A) to the highest-ranking one at the distal ring (A'). If this 90° turn is counterclockwise the absolute configuration is *M*; if it is clockwise, then the descriptor is *P*.

[59] *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; Topics in Stereochemistry; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 1983; Vol. 14.
[60] 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.
[61] Mislow, K. *Angew. Chem.* **1958**, *70* (22-23), 683–689.

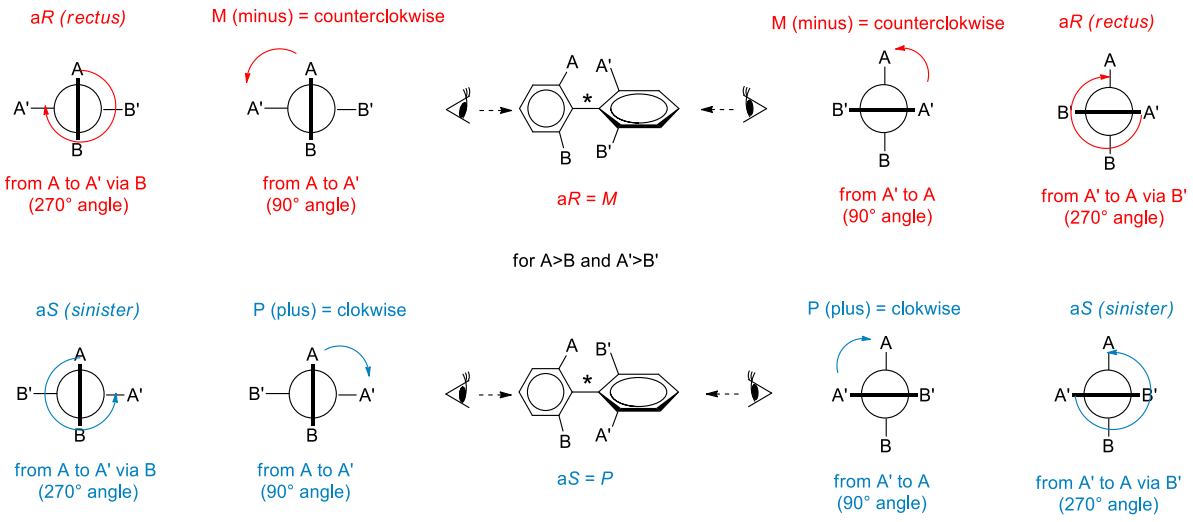


Figure 3-2 Biaryls configuration assignment

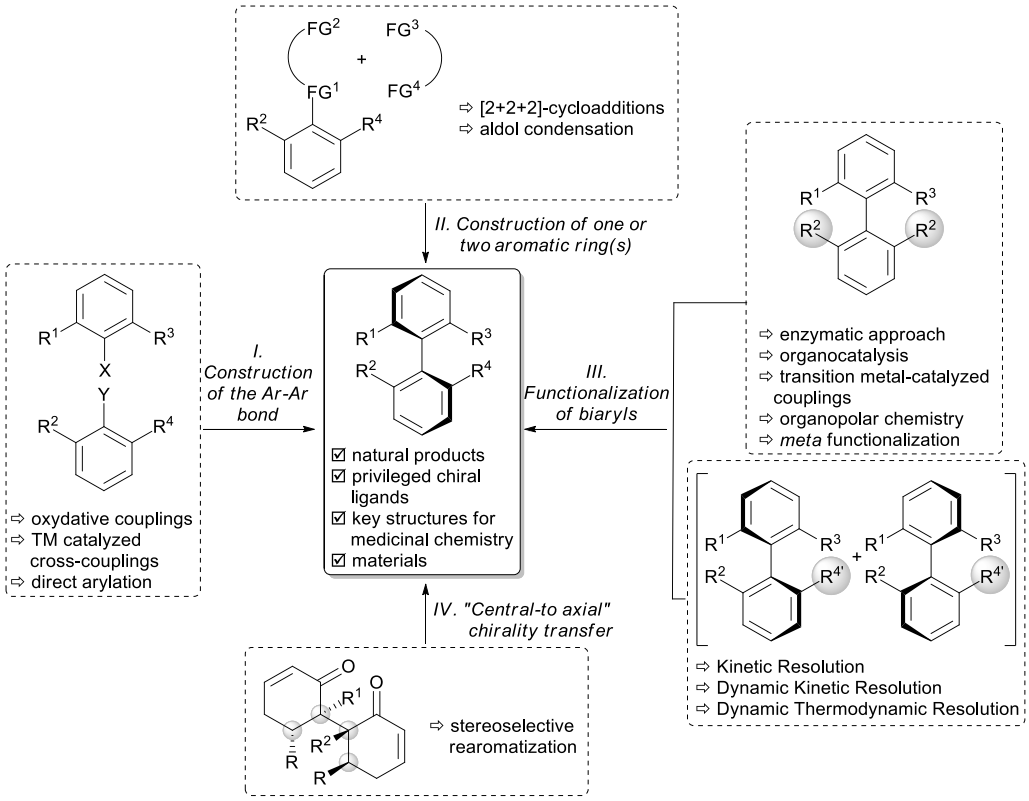
3.2.2 SYNTHETIC METHODS TO CONTROL AXIAL CHIRALITY

In this paragraph we will have a brief overview of the main methodologies, described until now, to prepare axially chiral biaryl compounds. Major advances to access such valuable building blocks have been reported in the last 20 years. These different synthetic strategies were discussed in details in an excellent review from Bringmann in 2005[60] and some more specialized articles focused on one type of synthetic route to afford axially chiral compounds.[55,62]

More recently in 2015 a general update combining recent advances and new concepts for the synthesis of axially stereoenriched biaryls have been reported by Colobert et *al.*[63] In this recent review modern approaches towards atropisomeric biaryls were presented and divided in four major categories (**Scheme 3-2**): I) stereoselective construction of biaryl; II) access to chiral biaryls *via* construction of (an) aromatic ring(s); III) stereoselective transformations of prochiral or racemic biaryls; IV) synthesis of optically enriched biaryls relying on a central-to-axial chirality transfer.

[62] 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.

[63] Wencel-Delord, J.; Panossian, A.; Leroux, F. R.; Colobert, F. *Chem. Soc. Rev.* **2015**, *44* (11), 3418–3430.



Scheme 3-2 Modern approaches toward atropisomeric biaryls

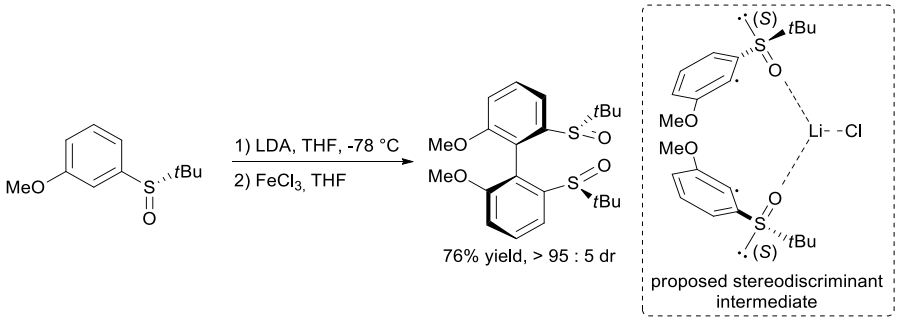
Considering that the retrosynthetic approach proposed for the total synthesis of myricanol is expected through an intermolecular or intramolecular C-C biaryl coupling (see 3.1), we will focused our attention to the category I involving the stereoselective construction of the Ar-Ar bond (**Scheme 3-2**). The three others categories will not be discussed in this thesis.

I. STEREOSELECTIVE CONSTRUCTION OF BIARYLS

Because biaryls were found in many important natural and synthetic chemical structures, the linkage of aryl moieties and the asymmetric induction during the coupling were widely studied and described from organic chemists. If steric hindrance around the Ar-Ar axis is generally essential to ensure the configurational stability of biaryls, it constitutes also an important obstacle to the biaryl coupling. For this reason powerful and innovative asymmetric catalytic systems have been developed. The most investigated methodology for the Ar-Ar coupling concerned the use of transition metals as catalysts allowing different types of coupling such as oxidative, Suzuki-Miyaura couplings and C-H arylation.

Intermolecular oxidative couplings

Many examples of asymmetric oxidative couplings catalyzed by Cu, V and Ru-based chiral catalytic systems were reported for the homocoupling of naphthols.[64] An highly effective and diastereoselective synthesis of axially chiral bis-sulfoxide ligands *via* oxidative aryl coupling was described by Zhou and co-workers.[65] They used a chiral sulfoxide moiety as an *ortho*-directing group and as chiral inductor too, in order to promote first the direct *ortho*-metallation of aryl sulfoxides and second the iron-catalyzed C-C coupling. During the radical coupling an excellent diatereoisomeric excess of axially chiral bis-sulfoxides was obtained. (**Scheme 3-3**)



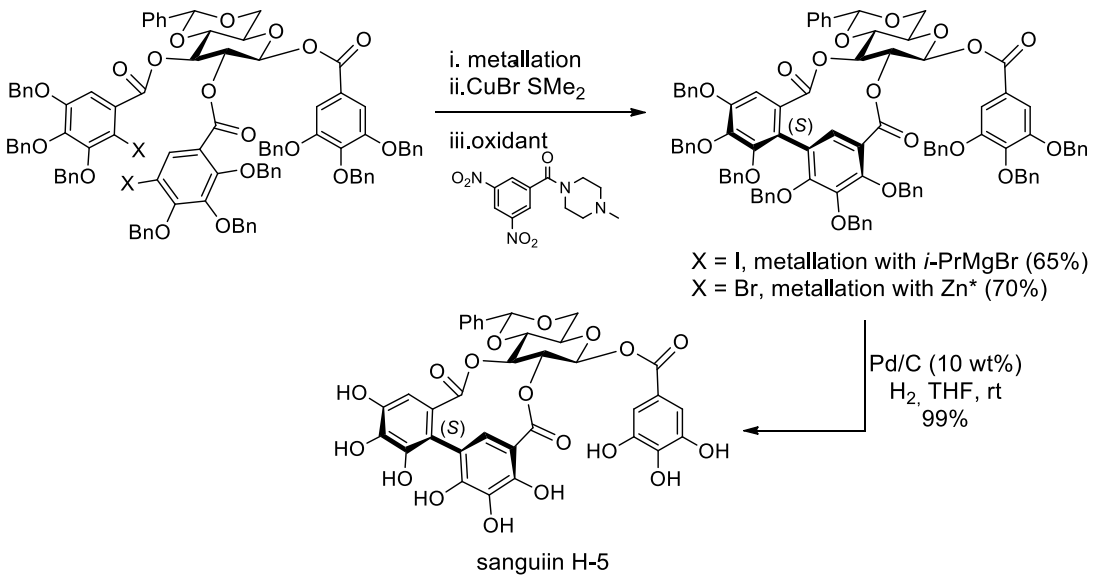
Scheme 3-3 Diastereoselective oxidative homocoupling of aryl sulfoxides

Examples of intramolecular oxidative and reductive coupling were also reported in literature. Generally, the chirality was transferred by stereogenic tethers[66] or by the substituents and the strain given by the cyclic system (as occured in natural products)[67].

Intramolecular oxidative couplings

An interesting illustration of an atropodiastereoselective intramolecular oxidative coupling was offered by Spring et *al.* for the total synthesis of ellagitannin natural product sanguiin H-5. Both organomagnesium and organozinc based metallation methodologies were used to efficiently construct the strained medium ring core of the natural product.[68]

[64] Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. *Chem. Soc. Rev.* **2009**, *38* (11), 3193–3207.
[65] Chen, Q.-A.; Dong, X.; Chen, M.-W.; Wang, D.-S.; Zhou, Y.-G.; Li, Y.-X. *Org. Lett.* **2010**, *12* (9), 1928–1931.
[66] Asakura, N.; Fujimoto, S.; Michihata, N.; Nishii, K.; Imagawa, H.; Yamada, H. *J. Org. Chem.* **2011**, *76* (23), 9711–9719.
[67] Shan, Z.-H.; Liu, J.; Xu, L.-M.; Tang, Y.-F.; Chen, J.-H.; Yang, Z. *Org. Lett.* **2012**, *14* (14), 3712–3715.
[68] Su, X.; Surry, D. S.; Spandl, R. J.; Spring, D. R. *Org. Lett.* **2008**, *10* (12), 2593–2596.



Scheme 3-4 Intramolecular oxidative coupling for total synthesis of sanguiin H-5

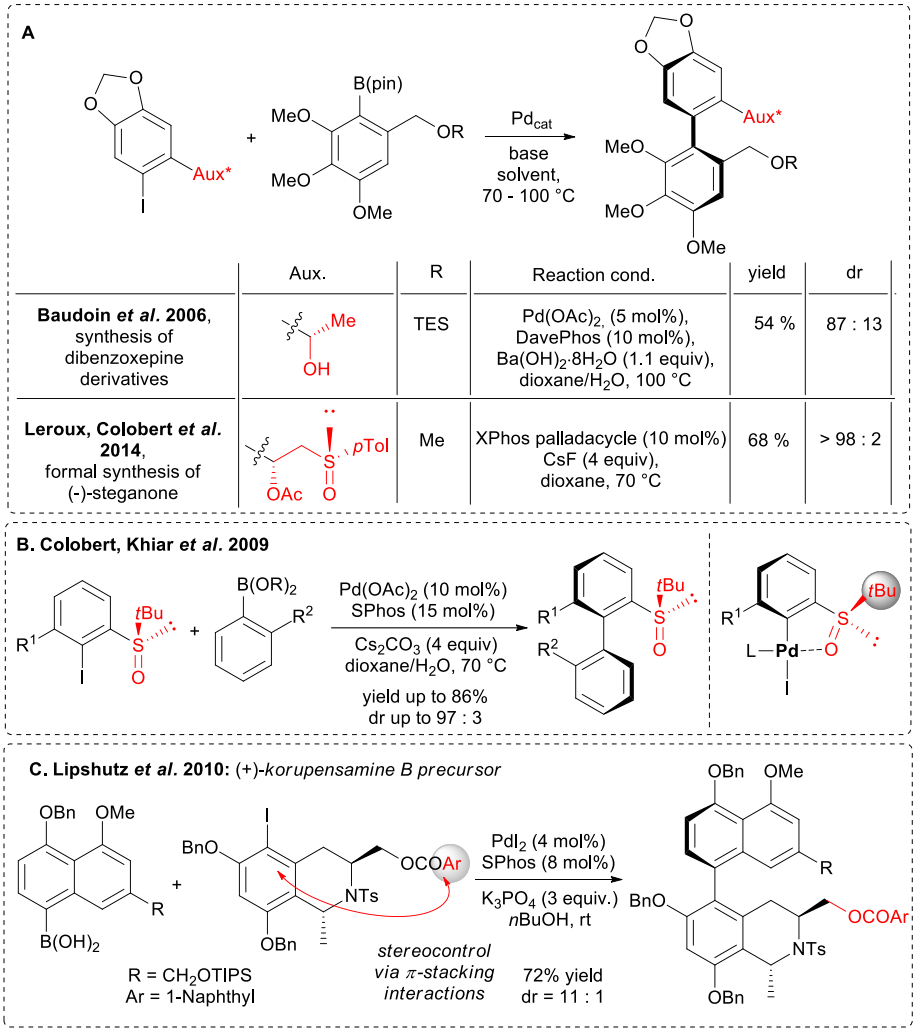
The synthesis of benzylated precursor of sanguiin H-5 was accomplished in one step after either the initial formation of an organomagnesium or organozinc intermediate. An intramolecular oxidative coupling of the resulting diarylcuprate allows diastereoselective and concomitant biaryl bond and medium ring formation (**Scheme 3-4**). The reaction proceeded with complete diastereoselectivity and in good isolated yield (65%-70%).

Diastereoselective and enantioselective intermolecular Suzuki-Miyaura couplings

Among the transition metal catalyzed Ar-Ar coupling, Suzuki-Miyaura was one of the most studied reaction to access chiral biaryls. The first asymmetric version of Suzuki-Miyaura coupling appeared in the late 1990s, when diastereoselective couplings were performed using one chiral partner bearing a motif such as a planar-chiral chromium complex or a stereogenic center.[69] In this context, as depicted in **Scheme 3-5-A**, benzylic alcohols or β-hydroxysulfoxides were employed as chiral auxiliaries and for example they are used in the total synthesis of dibenzoxepine derivatives[70], (-)-steganone[62a),62b),71] and for the synthesis of the biaryl part of vancomycin.[62c)] High diastereoselectivity was also assured employing *tert*-butyl sulfinyl group as chiral auxiliary[62d)], as described from Colobert et *al*., the chiral induction was probably due to the coordination between the chiral sulfoxide and the Pd-catalyst. (**Scheme 3-5-B**). A novel approach to transfer chiral

[69] a) Zhang, D.; Wang, Q. *Coord. Chem. Rev.* **2015**, *286*, 1–16.
b) Baudoin, O. *Eur. J. Org. Chem.* **2005**, *2005* (20), 4223–4229.
[70] Joncour, A.; Décor, A.; Thoret, S.; Chiaroni, A.; Baudoin, O. *Angew. Chem.* **2006**, *118* (25), 4255–4258.
[71] Yalcouye, B.; Choppin, S.; Panossian, A.; Leroux, F. R.; Colobert, F. *Eur. J. Org. Chem.* **2014**, *2014* (28), 6285–6294.

information during the biaryl coupling was presented by Lipshutz et *al.* for the total synthesis of (+)-korupensamine B.[62e] In this case, the high atroposelectivity was guaranteed by intramolecular π stacking interactions between the electron-rich tetrahydroisoquinoline motif and a temporarily installed aryl ester moiety that hinder one face of the aryliodide, giving a stereocontrolled Ar-Ar coupling (**Scheme 3-5-C**).

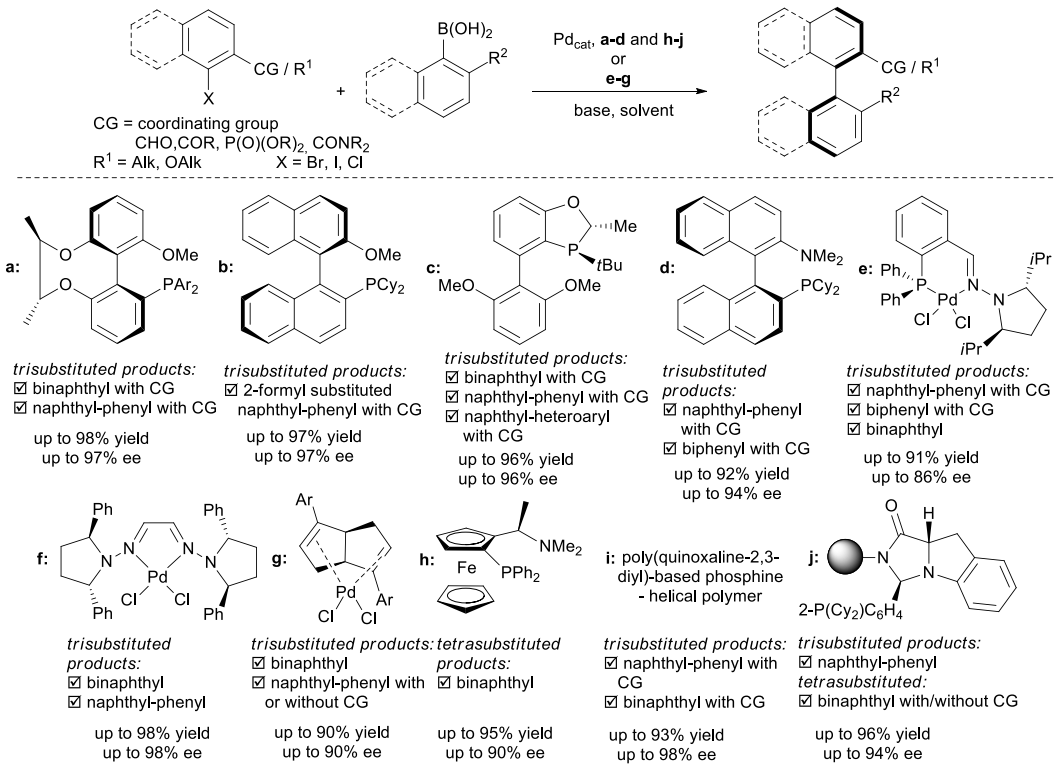


Scheme 3-5 Diastereoselective Suzuki-Miyaura coupling

The intermolecular enantioselective Suzuki-Miyaura biaryl coupling was firstly and independently reported by Buchwald[72] and Cammidge[73] that opened the route in this field. The main limitation of this approach was represented by the required high steric hindrance of both coupling partners and by the choice of the appropriate chiral ligand. For this scope have been designed different classes of mono and bidentate ligand

[72] Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122* (48), 12051–12052.
[73] Cammidge, A. N.; Crépy, K. V. L. *Chem. Commun.* **2000**, 18, 1723–1724.

and Pd-complexes (**a-j, Scheme 3-6**) in which stereoinduction is enhanced by an "anchoring effect" of a coordinating group (GC).[74] Despite of these advances the enantioselective Suzuki-Miyaura approach remains still restricted to tri-substituted binaphthyl or phenyl-naphthyl substrates and rarely is applicable to biphenyl compounds. Therefore the example of heterogeneous catalytic system (PEG-supported imidazoindole dicyclohexyl-phosphine copolymer **j**) reported by Uozumi was revealed as a powerful approach to finalize the Ar-Ar coupling with excellent enantiomeric excess.[74j] (**Scheme 3-6**)



Scheme 3-6 Enantioselective Suzuki-Miyaura coupling

[74] a) Wang, S.; Li, J.; Miao, T.; Wu, W.; Li, Q.; Zhuang, Y.; Zhou, Z.; Qiu, L. *Org. Lett.* **2012**, *14* (8), 1966–1969. b) Zhou, Y.; Wang, S.; Wu, W.; Li, Q.; He, Y.; Zhuang, Y.; Li, L.; Pang, J.; Zhou, Z.; Qiu, L. *Org. Lett.* **2013**, *15* (21), 5508–5511. c) Tang, W.; Patel, N. D.; Xu, G.; Xu, X.; Savoie, J.; Ma, S.; Hao, M.-H.; Keshipeddy, S.; Capacci, A. G.; Wei, X.; Zhang, Y.; Gao, J. J.; Li, W.; Rodriguez, S.; Lu, B. Z.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2012**, *14* (9), 2258–2261. d) Shen, X.; Jones, G. O.; Watson, D. A.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132* (32), 11278–11287. e) Bermejo, A.; Ros, A.; Fernández, R.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2008**, *130* (47), 15798–15799. f) Ros, A.; Estepa, B.; Bermejo, A.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. *J. Org. Chem.* **2012**, *77* (10), 4740–4750. g) Zhang, S.-S.; Wang, Z.-Q.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2010**, *12* (23), 5546–5549. h) Genov, M.; Almorín, A.; Espinet, P. *Chem. – Eur. J.* **2006**, *12* (36), 9346–9352. i) Yamamoto, T.; Akai, Y.; Nagata, Y.; Suginome, M. *Angew. Chem. Int. Ed.* **2011**, *50* (38), 8844–8847. j) Uozumi, Y.; Matsuura, Y.; Arakawa, T.; Yamada, Y. M. A. *Angew. Chem. Int. Ed.* **2009**, *48* (15), 2708–2710.

Diastereoselective intramolecular Suzuki-Miyaura coupling

Concerning the intramolecular Suzuki-Miyaura coupling (as key step for the preparation of axially chiral cyclic molecules), Zhu and co-workers reported two significant examples. Peptidic moieties are installed between two aromatic units and are used as chiral linkers to induce atroposelectivity during the macrocyclization. With this approach the DEFG ring of complestatin[75] and the cyclophanic system of arylomycins A_2 and B_2[76] were prepared (**Figure 3-3**).

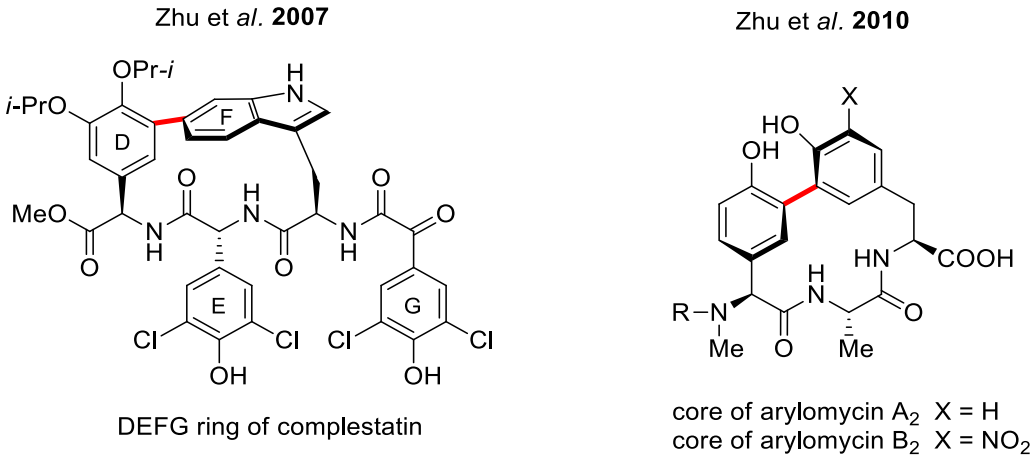
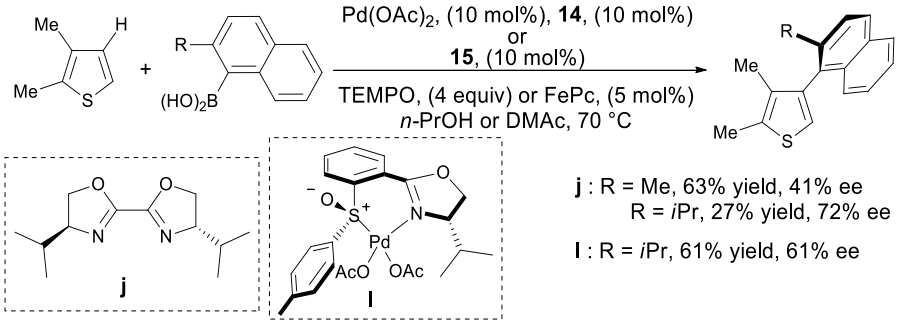


Figure 3-3 Natural products prepared by diastereoselective intramolecular Suzuki-Miyaura coupling

[75]Jia, Y.; Bois-Choussy, M.; Zhu, J. *Org. Lett.* **2007**, *9* (12), 2401–2404.
[76]Dufour, J.; Neuville, L.; Zhu, J. *Chem. - Eur. J.* **2010**, *16* (34), 10523–10534.

Atroposelective intermolecular C-H arylation

To the first category individued in the **Scheme 3-2** for Ar-Ar formation belongs also the C-H activation approach which is more and more employed to access biaryls. The first atropoenantioselective example of this kind of reaction was described by Yamaguchi and Itami in 2012.[77] They obtained moderate enantioselectivity with ligands **j** and **l** too, as depicted in the following scheme.



Scheme 3-7 Atroposelective direct arylation

These results have surely to be improved in terms of stereoselectivity and efficiency, but constitute an important starting point to underline the potential and challenge of atropostereoselective C-H arylations.

Intramolecular atropoenantioselective C-H direct arylation was also reported in literature for the synthesis of allocolchicinine, a seven-membered ring compound.[78] Major details concerning this approach will be found in paragraph 4.2.3.2.

[77]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.
[78]Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, No. 12, 1253.

3.3 METATHESIS REACTION

One of the key reactions of our total synthesis is olefin metathesis and according to the designed retrosynthetic paths, we plan to use a cross metathesis (CM) or a ring closing metathesis (RCM) for the synthesis of myricanol.

While no reference to metathetic pathways in obtaining myricanol can be found in literature a great variety of natural compounds with small, medium or macrocycles can now be routinely obtained, taking full advantage of the wide range of synthetic possibilities offered by alkene metathesis.[46,79] Indeed, working on parameters such as the influence of the catalyst, solvent, temperature and reactant concentrations can provide a good control of the metathesis process.[80]

The first example of "olefin metathesis reactions" was reported in the 1960s and was referred to petroleum industry.[81] However the catalytic mechanism, still accepted, was proposed only in 1971 by Chauvin and Hérisson.[82]

The reaction proceeds through four steps as depicted in Figure 3-4:

a) [2+2] cycloaddition of an alkene to a metal alkylidene that form a metallocyclobutane;
b) [2+2] cycloreversion to generate ethylene and a substrate-loaded metal carbine;
c) [2+2] cycloaddition of metal carbene with the second olefin;
d) [2+2] cycloreversion regenerate the metal alkylidene catalyst and the cross-coupled olefin.

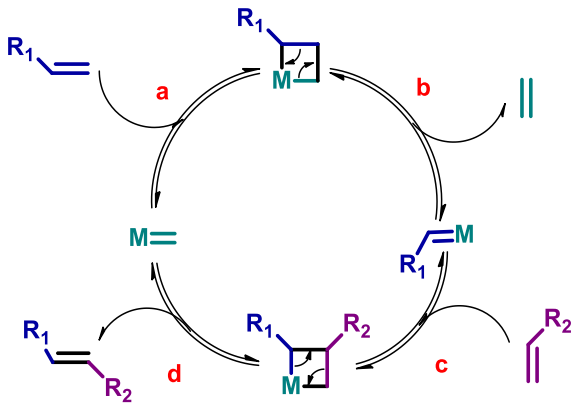


Figure 3-4 Metathesis reaction mechanism

[79] *Metathesis in natural product synthesis: strategies, substrates and catalysts*; Cossy, J., Arseniyadis, S., Meyer, C., Eds.; Wiley-VCH: Weinheim, **2010.**
[80] Kotha, S.; Dipak, M. K. *Tetrahedron* **2012**, *68* (2), 397–421.
[81] Edwin F, Peters, Lansing, and Bernard L. US PATENT 2,963,447, **1957.**
[82] Hérrison, J.-L.; Chauvin, Y. Makromol. Chem. **1971**, *141*, 161–167.

The metals employed for olefin metathesis were initially based on tantalum and tungsten. In the late1980s the quest for higher functional group tolerance allowed to the use of molybdenum complex (Shrock's catalyst) which was principally used in ring-closing metathesis (RCM) for the synthesis of many natural products.[79] Grubbs and co-workers hardly worked on these catalysts and in 1992 reported the first stable ruthenium complex used in both ring-opening and ring closing metathesis (ROM) and (RCM).[83] Further improvements of Grubbs catalyst allowed to prepare the benzylidene-bis(tricyclohexylphosphine)-dichlororuthenium, better known as Grubbs first generation catalyst that is air and moisture stable and highly functional groups-tolerant.[84] In 1999 was reported the second generation Grubbs catalyst in which one of two phosphines was replaced by a strongly donating N-heterocyclic carbene ligand that drastically improve the stability of the active species and accelerate the rate of initiation.[85] One year later Hoveyda and Blechert groups, independently reported the synthesis of the 2nd generation Hoveyda (or Hoveyda-Grubbs) Catalyst. It's widely used in cross metathesis (CM) and ring closing metathesis (RCM), in most circumstances is usually more reactive than the 2nd Generation Grubbs Catalyst at lower temperatures. It's useful for the efficient metathesis of electron-deficient substrates.[86]

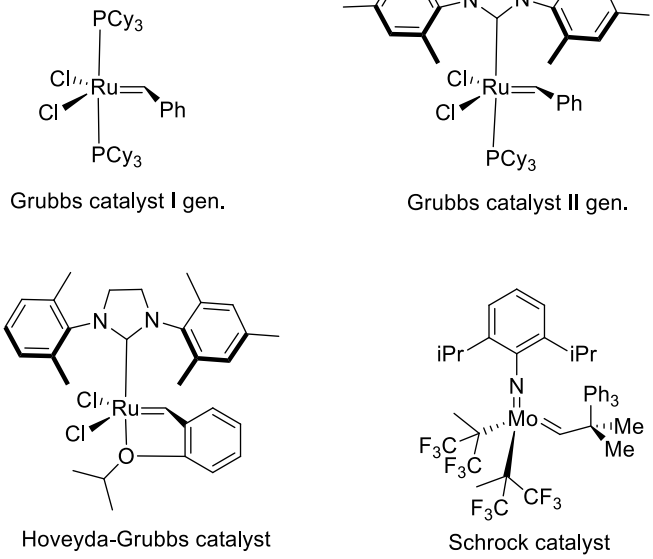


Figure 3-5 Metathesis catalysts

[83]Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114* (10), 3974–3975.

[84]a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem. Int. Ed. Engl.* **1995**, *34* (18), 2039–2041. b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118* (1), 100–110.

[85]Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1* (6), 953–956.

[86]a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122* (34), 8168–8179. B) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41* (51), 9973–9976.

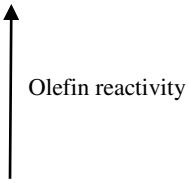
3.3.1 CROSS-METATHESIS (CM)

CM is a powerful tool in natural products chemistry particularly for functionalising terminal alkenes, appending a side chain to the core of a complex compound, or coupling two fragments in order to build the entire framework of the target molecule.

This process is extremely facile when the desired olefinic product is symmetrical such that a single is used in the metathesis reaction[87] but is limited by a lack of control when performed with two different olefinic partners. In this case the reaction can lead to three different products arising from both homocoupling and cross-coupling. One of the first example of a highly controllable intermolecular metathesis was reported by Crowe *et al.* who were able to take advantage of the differential reactivity of the two coupling partners to control the outcome of the reaction.[88] Later on, Grubbs et *al*. proposed a general ranking of olefin reactivity in cross-metathesis based on their relative abilities to undergo homodimerization *via* cross metathesis and the susceptibility of their homodimers toward secondary metathesis reaction.[89] As described in the paper, if a metathesis catalyst with the appropriate activity is employed, selective cross metathesis reactions can be achieved with a wide variety of electron-rich, electron-deficient, and sterically bulky olefins.

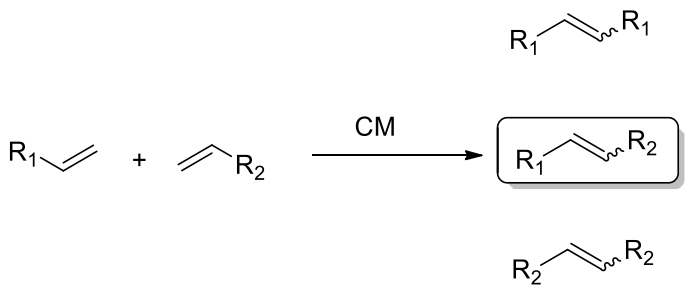
The olefins are divided in four categories:

- Type I : olefins that undergo rapid homodimerization;
- Type II : olefins that undergo low homodimerization;
- Type III : olefins that undergo no homodimerization;
- Type IV : olefines inert to CM.



According to Grubbs model, if metathesis occurs between two type I olefins, a nonselective cross metathesis will take place and the products will be formed following a statistical distribution since the rate of homodimerization of R_1 and R_2 is similar and the reactivity of homodimers and cross-coupled products toward secondary metathesis events are equally probable (**Scheme 3-8**).

[87]Diver, S. T.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119* (22), 5106–5109.
[88]a) Crowe, W. E.; Zhang, Z. J. *J. Am. Chem. Soc.* **1993**, *115* (23), 10998–10999.
b) Crowe, W. E.; Goldberg, D. R. *J. Am. Chem. Soc.* **1995**, *117* (18), 5162–5163.
[89]Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125* (37), 11360–11370.



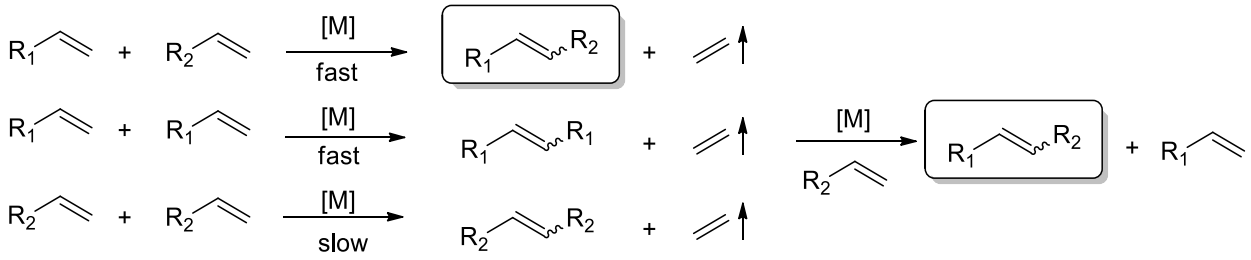
R_1/R_2	CM product selectivity
1/1	50%
2/1	66%
4/1	80%
10/1	91%
20/1	95%

Scheme 3-8 Statistical distribution of CM products

In this case, self-dimerization reaction of the more valuable olefin may be minimized by the use of an excess of the more readily available alkene to give the desired cross-coupled product in good yield.

When the CM occurs between two olefins of the same type (non type I) a non selective CM will take place.

Otherwise, if the reactive olefins are of different types (for example type I with type II or type III), a selective CM will occur and final products will not follow the statistical distribution. Indeed, olefins of different types present dimerization rates that are usually slower than CM product formation. Type I olefin may initially homodimerize, but this homodimer could be involved in a secondary metathesis process in which starting terminal olefin is regenerated. Type I olefin and its homodimer readily react with type II/III olefin to give the desired cross product. The final mixture will have not a statistical distribution of coupled products. This is due to the inability of the catalyst to efficiently convert the cross desired product to others *via* secondary metathesis. (**Scheme 3-9**)



Scheme 3-9 Selective cross-metathesis between different type olefins

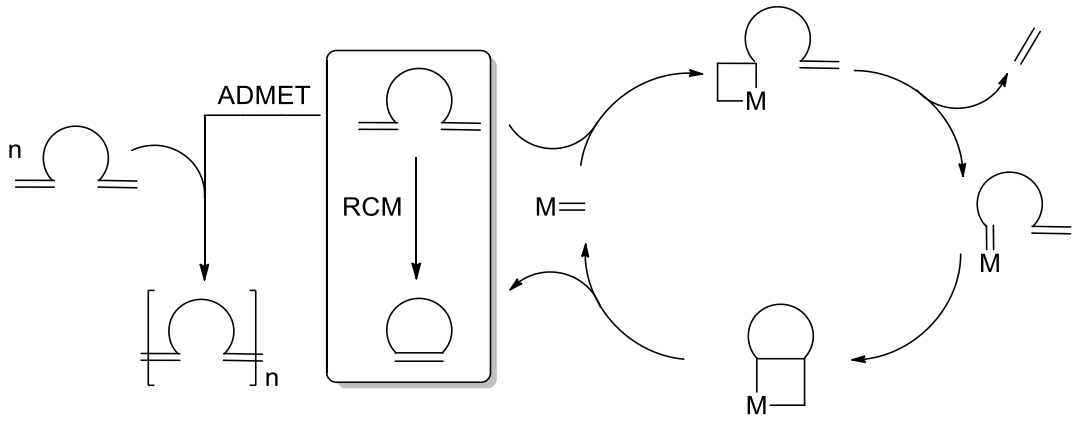
Considering the keys fragments identified for the total synthesis of myricanol (see 3.1) we can categorize the allylbenzene derivative **D** as a type I olefin and the homoallylic alcohols **E** as a type II olefin that generally exhibit a good CM reactivity. Indeed, homoallylic alcohols, especially when unprotected, are

often superior coupling partners in comparison to their oxidized keto variants, as reported in the *Handbook of metathesis.*[90]

3.3.2 RING CLOSING METATHESIS (RCM)

The power of olefin metathesis reactions in the field of natural products has mainly centered upon its application to the formation of unsaturated system by intramolecular metathesis. Since many synthetic targets are cyclic molecules (natural products, drugs, etc.)[91] cyclization by RCM is often one of the last synthetic step (the key step) in which a new C=C bond is formed. In this case cyclization occurs in presence of olefins that are inert towards various reaction conditions and that allow to build the metathesis precursor molecule without compatibility problems with other functional groups. Moreover the final endocyclic double bond could be retain or reduced, depending on the target molecule.

Usually the cycle formation is entropically favoured, above all for small cycle. Otherwise, for the synthesis of macrocycles it could be possible to induce an intramolecular metathesis working at high dilution. Usually for cycle with size ≤ 8 the double bond configuration is *Z*, whereas for higher number chains the *E*/*Z* configuration isn't always predictable.



Scheme 3-10 Ring closing metathesis mechanism

[90] a) *Handbook of metathesis. Vol. 2: Applications in organic synthesis*, 2. ed.; Grubbs, R. H., O'Leary, D. J., Eds.; Wiley-VCH: Weinheim, 2015. b) Maishal, T. K.; Sinha-Mahapatra, D. K.; Paranjape, K.; Sarkar, A. *Tetrahedron Lett.* **2002**, *43* (12), 2263–2267.

[91] Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *479* (7371), 88–93.

As showed in **Scheme 3-10** the diene could undergo a RCM with elimination of ethylene or could give a polymer by the acyclic diene metathesis polimerization (ADMET). Reaction pathway of diene depends on catalyst, dilution, ring size, and substrate (functional groups and steric factors). Intermolecular ADMET can generally be prevented by using the same techniques (slow addition or high dilution) proven to be effective in many macrolactonization strategies.[92]

Depending on the functional groups on the molecule, the synthesis of 5-7 membered rings appear easy, if catalyst is properly chosen (amine cases are not so easy and need carbamate protecting group)[93]. The choice of catalyst depends on olefin substitution, molybdenum and ruthenium are usually more effective for highly substituted olefins. Usually ruthenium catalysts are preferred to molybdenum ones because they are more easy to handle and more tolerant to various functional groups. [94]

For the medium size rings (7-13 carbon) cyclization appears less evident and sometime substrates are more prone to intermolecular acyclic diene metathesis reactions (ADMET). The cyclization could be favoured using some cyclic conformational constraints on the reacting molecule.[95]

In the case of macrocyclization (rings with more than 13 atoms) some experimental considerations have to be respected. The rate of oligomerization can be controlled by working at high level dilution or by adding slowly the diene to the catalyst solution. In these reactions higher temperature are generally required. The presence of polar groups and steric hindrance close to the double bonds significantly lowers yield.[93]

As part of the remarkable studies on RCM by the group of Fürstner since the early nineteen nineties, leading to the synthesis of naturally occurring macrolactones family[96], a chemical approach based on RCM as the key step was materialized in 1999, accomplishing on one hand the total synthesis of zeranol and on the other hand, a closer understanding of the essential parameters for successful macrocyclization.[97]

Before Fürstner works, it was believed that only conformationally predisposed dienes could be used for the formation of medium or large cyclic systems. [98] In contrast, the total synthesis of numerous natural

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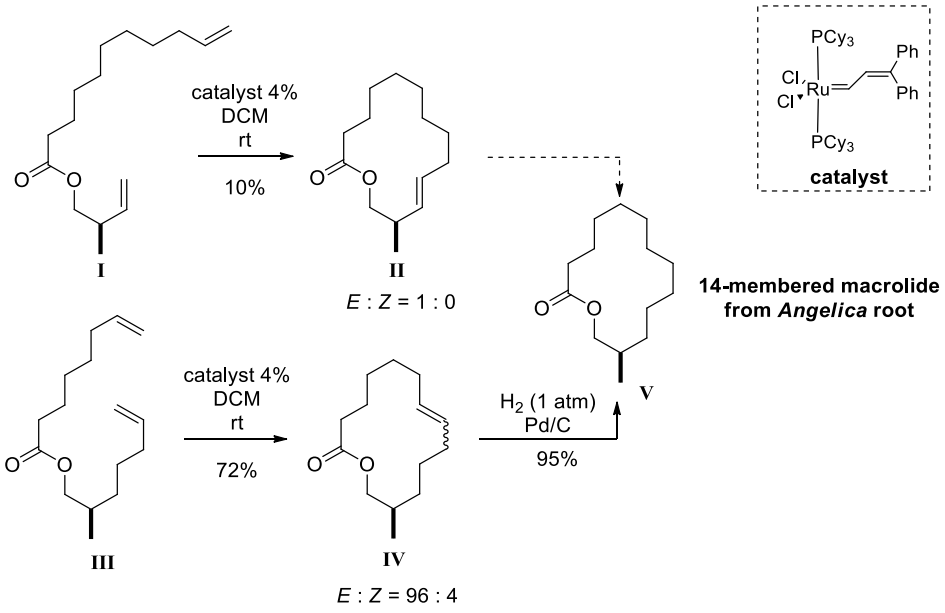
[92] Forbes, M. D. E.; Patton, J. T.; Myers, T. L.; Maynard, H. D.; Smith, D. W.; Schulz, G. R.; Wagener, K. B. *J. Am. Chem. Soc.* **1992**, *114* (27), 10978–10980.
[93] Fürstner, A. In *Alkene Metathesis in Organic Synthesis*; Fürstner, P. A., Ed.; Topics in Organometallic Chemistry; Springer Berlin Heidelberg, 1998; pp 37–72.
[94] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1* (6), 953–956.
[95] Delgado, M.; Martín, J. D. *J. Org. Chem.* **1999**, *64* (13), 4798–4816.
[96]a) Fürstner, A.; Kindler, N. *Tetrahedron Lett.* **1996**, *37* (39), 7005–7008. b) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61* (12), 3942–3943. c) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61* (25), 8746–8749. d) Fürstner, A.; Langemann, K. *Synthesis* **1997**, *1997* (07), 792–803. e) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119* (39), 9130–9136. f) Fürstner, A.; Müller, T. *Synlett* **1997**, *1997* (8), 1010–1012. g) Fürstner, A.; Koch, D.; Langemann, K.; Leitner, W.; Six, C. *Angew. Chem. Int. Ed. Engl.* **1997**, *36* (22), 2466–2469.
[97] Fürstner, A.; Seidel, G.; Kindler, N. *Tetrahedron* **1999**, *55* (27), 8215–8230.
[98]Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28* (11), 446–452.

macrolides reported latter witnessed that *seco*-precursors devoid of any conformational constraints can be efficiently cyclized by RCM. RCM was also one of the most efficient approach to cyclize large ring system compared to all current alternatives. [99] Very recently, the role of the structural or induced preorganization of the macrocyclization precursors have been reviewed. [100]

According to Fürstner and co-workers, since RCM generates two molecules (cyclized product and evaporative loss of ethylene) from one, the gain in entropy should provide sufficient driving force, independently of ΔH value, to the formation of highly flexible macrocycle from equally flexible acyclic diene precursor.[96b] They discovered that neither a conformational predisposition of starting material toward RCM nor the ring size formed are revelant factors for cyclization. Conversely the main influencing factors for RCM appeared to be the functional groups (ester, ketone, ether, urethane, etc.) that could interact with catalyst and furthermore the proper distance between the key substituent and the alkenes to be metathesized.

A significant example in which ring closure was revealed to be more dependant from the site of the closure than from the size of the forming ring was illustrated in **Scheme 3-11.**



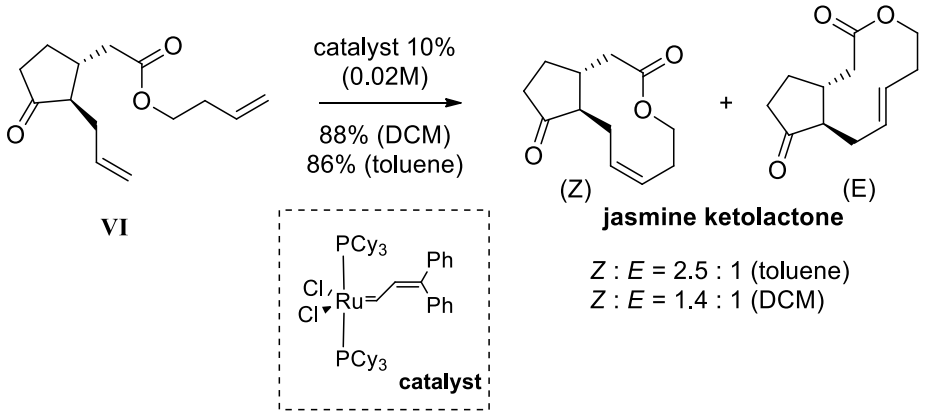
Scheme 3-11 Conformationally unbiased RCM of a natural macrolide

Fürstner and Langemann described the synthesis of a series of musk-odored natural macrolides as the 14-membered macrolide **V**, minor component of *Angelica* root.[96b] They individuated two different terminal

[99] Roxburgh, C. J. *Tetrahedron* **1995**, *51* (36), 9767–9822.
[100] Martí-Centelles, V.; Pandey, M. D.; Burguete, M. I.; Luis, S. V. *Chem. Rev.* **2015**, *115* (16), 8736–8834.

alkene precursors as starting materials (**I** and **III**) and they disclosed that macrolide **II** was obtained in a much lowered yield (10%) compared to cyclized compound **IV** (72%) under the same conditions. The poor reactivity of **III** was explained by the possible steric hindrance of the methyl substituent adjacent to the terminal alkene and/or from a possible coordination of catalyst with the proximal ester group giving rise to an unproductive chelate chelate complexe. This effect did not occur on substrate **I** where terminal olefins are properly distant, avoiding steric effects as well as possible coordination.[101]

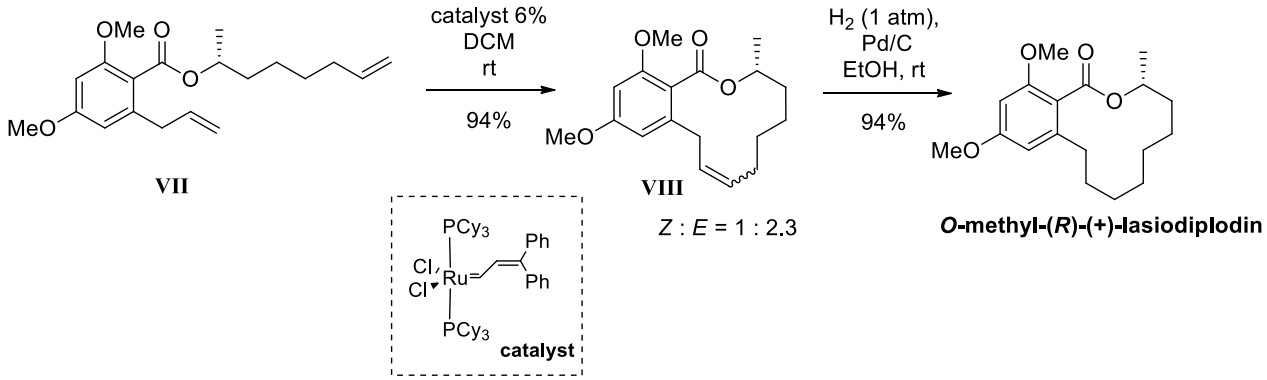
In 1997 Fürstner and Müller reported the first example of the synthesis of a 10-membered ring like jasmine ketolactone (*Z* and *E* isomers) by ring closing metathesis.[96f] This approach was much more efficient compared to all known reported synthesis involving other macrolactonization methods.[102] The synthesis depicted in **Scheme 3-12** highlights how RCM was used to prepare a 10-membered ring which, among the medium rings, are considered to be the most difficult to cyclize.[103]



Scheme 3-12 First synthesis of jasmine ketolactone by RCM

A RCM example that could be considered useful for our scope (as proposed in the retrosynthetic approach for myricanol, paragraph 3.1) is offered by the total synthesis of *O*-methyl-(*R*)-(+)-lasiodiplodin described by Fürstner and Kindler.[96a] The preparation of this 12-membered macrolide was accomplished by a quantitative RCM starting from the corresponding allylbenzene precursor **VII**, followed by a complete hydrogenation of the double bond in the cyclic system **VIII**. (**Scheme 3-13**)

[101] a) Feldman, J.; Murdzek, J. S.; Davis, W. M.; Schrock, R. R. *Organometallics* **1989**, *8* (9), 2260–2265.
b) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114* (18), 7324–7325.
[102] a) Gerlach, H.; Künzler, P. *Helv. Chim. Acta* **1978**, *61* (7), 2503–2509. b) Shimizu, I.; Nakagawa, H. *Tetrahedron Lett.* **1992**, *33* (34), 4957–4958. c) Nishi, T.; Kitahara, T. *Proc. Jpn. Acad. Ser. B* **1995**, *71* (1), 20–23.
[103] a) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48* (28), 5757–5821. b) Rousseau, G. *Tetrahedron* **1995**, *51* (10), 2777–2849. c) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14* (4), 95–102.



Scheme 3-13 Synthesis of *O*-methyl-(*R*)-(+)-lasiodiplodin by RCM

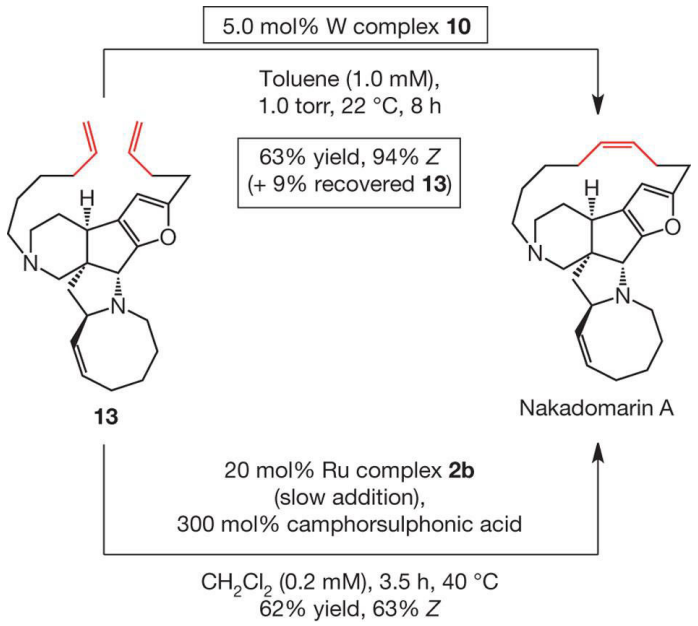
Although medium-size and macrocyclic rings could be forged efficiently by RCM, the resulting olefins are often obtained as mixtures of *E* and *Z* isomers with neither predictable nor controllable ratio. This inherent issue constitute a significant drawback in many total synthesis, as it was for example reported from the epothilone case by Nicolaou and co-workers.[104] Different approaches have been developed to overcome this drawback, for example, through the implementation of ring-closing alkyne metathesis (RCAM) followed by Lindlar or Birch-type reduction to generate stereoopure *Z* or *E* macrocycles respectively.[79,105]

Accordingly, a considerable effort has been expanded in the search for metathesis catalysts exhibiting kinetic selectivity. This has resulted in 2011 to the disclosing of the first example of catalyst system capable of performing a *Z*-selective macrocyclic RCM reaction using tungsten to generate the 15-membered core of nakadomarin A (**Scheme 3-14**).[106]

[104] Nicolaou, K. C.; King, N. P.; He, Y. In *Alkene Metathesis in Organic Synthesis*; Fürstner, P. A., Ed.; Topics in Organometallic Chemistry; Springer Berlin Heidelberg, **1998**; pp 73–104.

[105] a) Gebauer, K.; Fürstner, A. *Angew. Chem. Int. Ed.* **2014**, *53* (25), 6393–6396. b) Fürstner, A.; Davies, P. W. *Chem. Commun.* **2005**, No. 18, 2307–2320.

[106] Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *471* (7339), 461–466.



Scheme 3-14 Total synthesis of nakadomarin A

On the other hand, Grubbs and co-workers and also other research groups, have developed recently a new family of efficient ruthenium-based catalysts that yield *Z*-selective macrocyclization (up to 95%) providing simultaneously high TON values.[107] The same kind of catalysts has been also used to obtain the almost pure *E*-macrocycle by *Z*-selective ethenolysis of the *E/Z* mixture.[108]

[107] Marx, V. M.; Herbert, M. B.; Keitz, B. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2013**, *135* (1), 94–97.

[108] a) Zhang, H.; Yu, E. C.; Torker, S.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136* (47), 16493–16496. b) Mangold, S. L.; O'Leary, D. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **2014**, *136* (35), 12469–12478.

4 TOWARDS THE SYNTHESIS OF MYRICANOL

4.1 PREPARATION OF FRAGMENTS D AND E TYPE

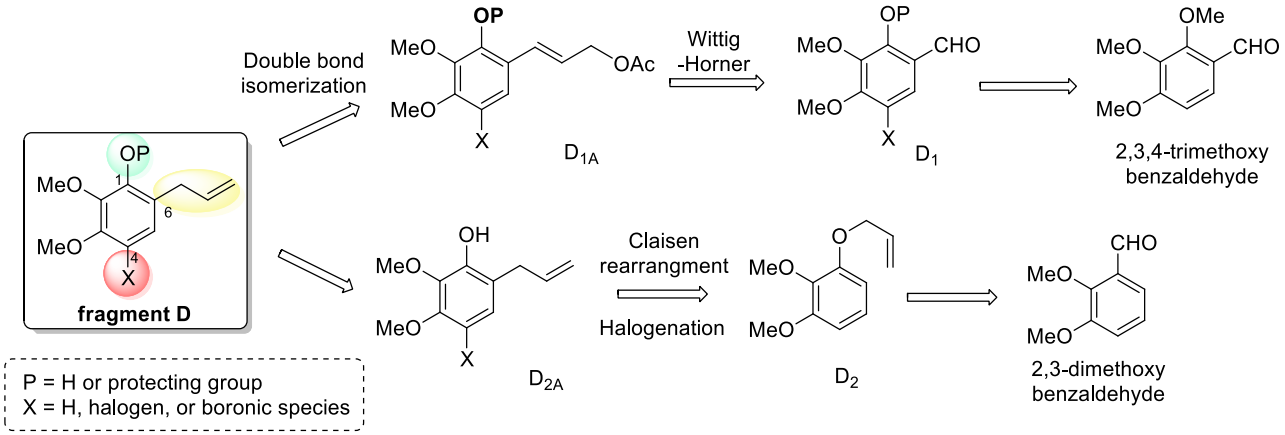
As previously mentioned, we envisioned to tackle the total synthesis of myricanol *via* two different convergent synthetic routes starting from the same precursors **D** and **E.** The preparation of these easily available compounds will allow us to study key-steps such as the intramolecular biarylic C-C coupling leading to **C** (path a) or the intramolecular metathesis leading to **B** (path b) (see 3.1).

4.1.1 Fragments D type retrosynthetic analysis

Building block **D** has to be functionalized with specific substituents such as:

- an allylic part on C6 in order to test the metathesis reaction;
- a halogen/boronic ester on C4 in order to perform the Suzuki-Miyaura cross coupling (first reaction) or hydrogen considering a cross metathesis as first reaction;
- a protecting group on the phenol.

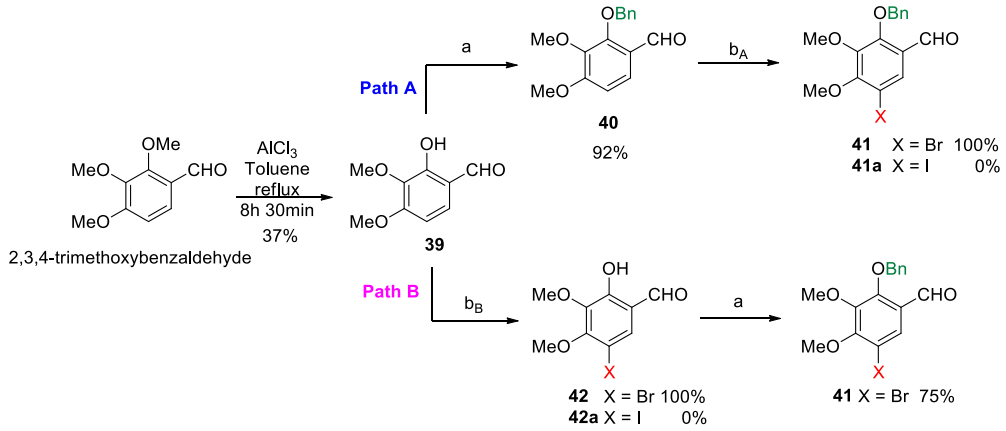
The building block **D** could be obtained through two pathways starting from commercially available 2,3,4-trimethoxybenzaldehyde using a Wittig-Horner/double bond isomerisation sequence or from 2,3-dimethoxybenzaldehyde using a Claisen rearrangement (see **Scheme 4-1**).



Scheme 4-1 Retrosynthetic approaches to building block D

4.1.1.1 First generation strategy: *2,3,4-trimethoxybenzaldehyde approach*

The synthesis of fragment **D** commenced with the selective demethylation of 2,3,4-trimethoxybenzaldehyde in *ortho* position to aldehyde using $AlCl_3$ in refluxed toluene (**Scheme 4-2**). The bromination of the resulting phenol **39** was first performed quantitatively to give the corresponding benzyl ether **40** (92% over two steps). Surprisingly, the corresponding iodination was totally uneffective after several trials and we decided to try a direct iodination of the phenol **39**, unfortunately without any success, which ended our efforts to prepare the iodinated aldehyde **41a**. Confident of the positive outcome of the previous bromination, we subjected phenol **39** to the same procedure and obtained after subsequent benzylation, aldehyde **41** in 75% yields over two steps (**Scheme 4-2**).

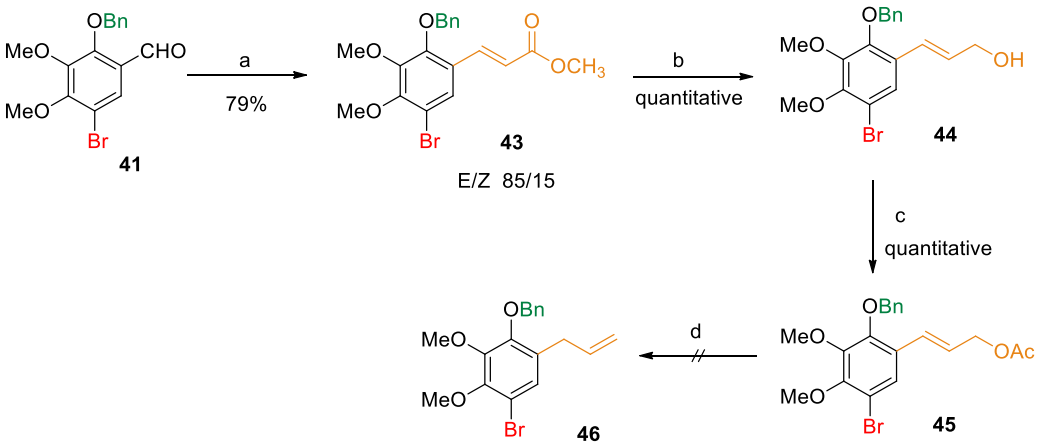


a) Benzylbromide, K_2CO_3, acetone, reflux, 5h; b_A) for **41** Br_2, CH_3COONa,CH_3COOH, r.t., 22h; for **41a** I_2, CH_3COONa,CH_3COOH, r.t., 2d; b_B) for **42** Br_2, CH_3COONa,CH_3COOH, r.t., 2h; for **42a** I_2, CH_3COONa,CH_3COOH, r.t., 6d; for **42a** NIS, CF_3COOH,CH_3CN, r.t., 3d;

Scheme 4-2 Functionalization of 2,3,4-trimethoxybenzaldehyde

According to the observed overall yields we selected the first sequence (path A) to prepare **41**, since it is a more efficient scale up procedure.

Methyl (triphenylphosphoranylidene)acetate was used as Wittig reagent for the two-carbon homologation of aldehyde **41** to the α,β-unsaturated ester **43** (**Scheme 4-3**). Unsaturated ester **43** was quantitatively reduced into allylic alcohol **44** and transformed into the corresponding acetate **45**.



a) $(Ph)_3P$=CHCOOMe, DCM, 5h, rt; b) DIBAL, DCM, 0°C. 10h; c) Acetic anhydride, Py, rt, 18h; d) $Pd(PPh_3)_4$, SmI_2, H_2O, THF, rt.

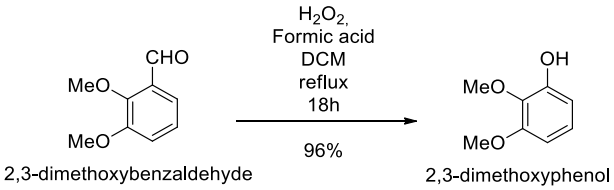
Scheme 4-3 Preparation of a brominated D fragment

With the compound **45** in hand, we applied the conditions described by Mikami et *al.*, [109] namely the addition of $Pd(PPh_3)_4$ (5mol%) in the presence of SmI_2 (2.5equiv.) and H_2O (10equiv.) as proton source. As no trace of isomerisation product **46** was observed, we embarked on the second synthetic sequence which involved a Claisen rearrangement as the decisive step. This second generation approach represented an important shortcut, since fragment **D** could be obtained in four steps instead of seven.

[109] Yoshida, A.; Hanamoto, T.; Inanaga, J.; Mikami, K. *Tetrahedron Lett.* **1998**, *39* (13), 1777–1780.

4.1.1.2 Second generation strategy: 2,3-dimethoxy phenol approach

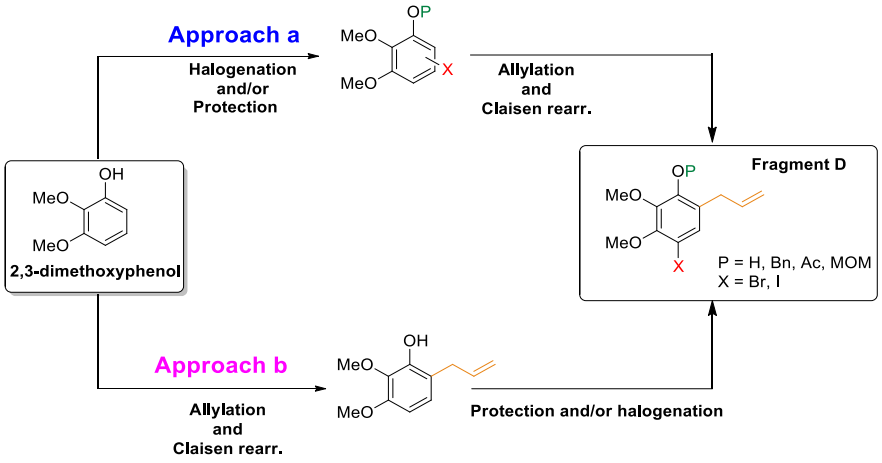
The synthesis commenced with the preparation of 2,3-dimethoxyphenol from the corresponding aldehyde *via* Dakin oxidation reaction [110]. (**Scheme 4-4**)



Scheme 4-4 2,3-dimethoxybenzaldehyde oxidation

We proposed two different pathways in which 2,3-dimethoxyphenol could be employed as starting material. As depicted in **Scheme 4-5**, the starting phenol could be provided by two synthetic pathways.

An approach a in which a direct halogenation on the phenol or on the protected phenol was considered followed by a Williamson etherification (allylation) and a Claisen rearrangement in order to obtain the target fragment **D.** A second approach b was proposed which consisted to start with an allylation of 2,3-dimethoxyphenol followed by a Claisen rearrangement, after protection of the phenol, halogenation would be studied and could give rise to the highly functionalized fragment **D.**



Scheme 4-5 Towards fragment D *via* 2,3-dimethoxyphenol

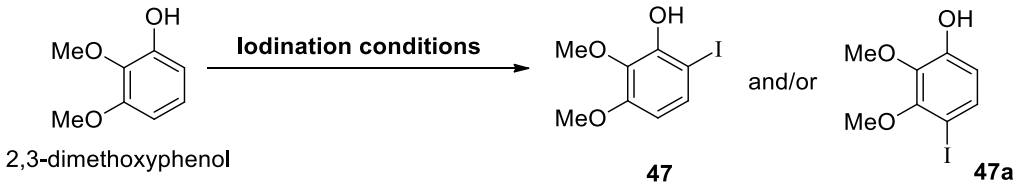
[110] Dakin, H. D. Am. *Chem. J.* **1909**, *42*, 477-498.

4.1.1.2.1 Approach a

One more time considering the next key reaction (the cross coupling Suzuki-Miyaura), we envisioned to prepare the iodinated compound.

First of all, we decided to try iodination on 2,3-dimethoxyphenol.

The first conditions used were described by Khalilzadeh, M. A. et *al.* [111] who reported the iodination of 2,3-dimethoxyphenol in presence of HIO_4/Al_2O_3 affording the *para*-iodinated phenol **47a** with 75% yield. Indeed, the possibility to introduce regioselectively the iodine in the *para* position to the phenol could be very useful for the synthesis of the fragment **D** type. We repeated the same experiment, as reported in **Table 4-1** entry 1, and we didn't obtain the desired product **47a**, only compound **47** was isolated in 10% yield. The structure of the compound **47** was confirmed by 1D and 2D NMR experiments, disclosing that the *ortho* orientation involved by the hydroxyl group is stronger than the methoxyl group. We tried different halogenation conditions and for every attempt **47** was the only isolated product with moderate to excellent yield depending on the conditions (**Table 4-1**, entries 2 and 4).

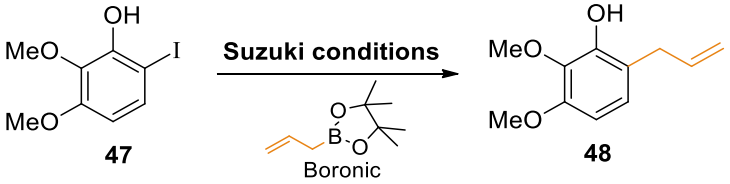


Entry	Iodination conditions	Yield (47 : 47a)
1	HIO_4/Al_2O_3, Dioxane/H_20, reflux[111]	10% : -
2	NIS (1.2 equiv.), TsOH, ACN, rt[112]	94% : -
3	NIS (1.2 equiv.), TFA, ACN, rt[113]	-
4	$NaHCO_3$, I_2(1.2 equiv.), THF/H_2O, 0°C[114]	50% : -

Table 4-1 Iodination study on 2,3-dimethoxyphenol

[111] Khalilzadeh, M. A.; Hosseini, A.; Shokrollahzadeh, M.; Halvagar, M. R.; Ahmadi, D.; Mohannazadeh, F.; Tajbakhsh, M. *Tetrahedron Lett.* **2006**, *47* (21), 3525–3528.
[112] Bovonsombat, P.; Leykajarakul, J.; Khan, C.; Pla-on, K.; Krause, M. M.; Khanthapura, P.; Ali, R.; Doowa, N. *Tetrahedron Lett.* **2009**, *50* (22), 2664–2667.
[113] Castanet, A.-S.; Colobert, F.; Broutin, P.-E. *Tetrahedron Lett.* **2002**, *43* (29), 5047–5048.
[114] Berliner, M. A.; Cordi, E. M.; Dunetz, J. R.; Price, K. E. *Org. Process Res. Dev.* **2010**, *14* (1), 180–187.

With the iodide **47** in hand, we tried to introduce the allylic moiety mediated by a palladium catalysed allylation in presence of allylpinacolborane. [115] Unfortunately, the three different conditions tested for Suzuki reactions failed and only starting material was quantitatively recovered. (**Table 4-2**)

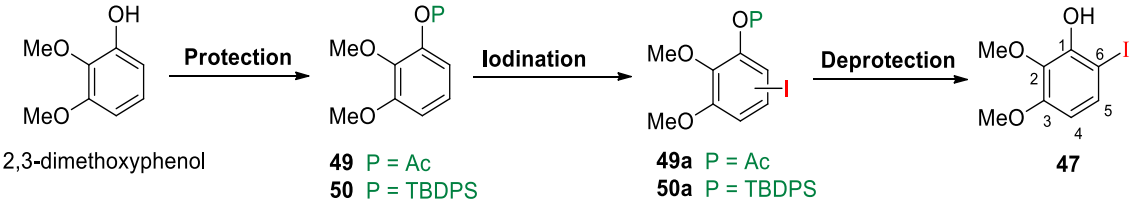


Entry	Boronic	Suzuki conditions	Yield48
1	1.5equiv.	$Pd(PPh_3)_4$(7mol%), KF(4equiv.), THF(0.1M), 85°C, 9h	--/s.m.
2	1.5equiv.	$Pd(PPh_3)_4$(7mol%), KF(4equiv.), THF(0.1M), 85°C, 13h	--/s.m.
3	1.5equiv.	$Pd(PPh_3)_4$(7mol%), Na_2CO_3(9equiv.), toluene(0.05M), 110°C,14h	--/s.m.

Table 4-2 Suzuki-Miyaura reaction on 4-iodo-2,3-dimethoxyphenol

Considering the literature, we suggested that in order to lead iodination in the *para* position of 2,3-dimethoxyphenol, we have to protect the free OH with different bulky protecting groups such as an acetyl group (**49**) or a more bulky *tert*-butyldiphenylsilyl group (**50**) (**Table 4-3**). On the protected products **49** and **50,** prepared in classical conditions, iodination was performed (**Table 4-3**, entries 1 and 2). Thus with NIS in slightly acid condition, the desired iodinated compound **49a** and **50a** were obtained with respectively 99% and 79% yield. At this stage it was difficult to determine the regioselectivity of the iodination, that's why the compounds have to be deprotected. Deprotection of **49a** and **50a** gave rise to **47**, showing that even with a very bulky protecting group such as TBDPS, the iodination occured preferentially at position 6 compared to 4.

[115] Gerbino, D. C.; Mandolesi, S. D.; Schmalz, H.-G.; Podestá, J. C. *Eur. J. Org. Chem.* **2009**, *2009* (23), 3964–3972.



2,3-dimethoxyphenol

49 P = Ac
50 P = TBDPS

49a P = Ac
50a P = TBDPS

47

Entry	Protection	Yield	Iodination	Yield	Deprotection	Yield
1	Ac_2O, Py, rt, 18h	66%(**49**)	NIS, CH_3CN, TFA, rt, 5h	99%(**49a**)	NH_4OAc, MeOH, rt, 2d	99%(**47**)
2	TBDPSCl, Imidazole, DCM, rt, 18h	62%(**50**)*	NIS, CH_3CN, TFA, rt, 16h	79%(**50a**)	TBAF, THF, 0°C, 2h	89%(**47**)

*conversion evaluated by GC-MS

Table 4-3 *Para*-iodination attempts on protected phenols 49 and 50

We continued our investigation taking into account the results reported by De Rossi and coworkers which described halogenation in presence of β-cyclodextrin in apolar solvent at room temperature. Indeed β-cyclodextrin could include in its hydrophobic cavity the phenol ring and could allow a possible regioselective halogenation depending from the disposition of phenol inside the truncated cone of β-cyclodextrin[116] (**Figure 4-1**).

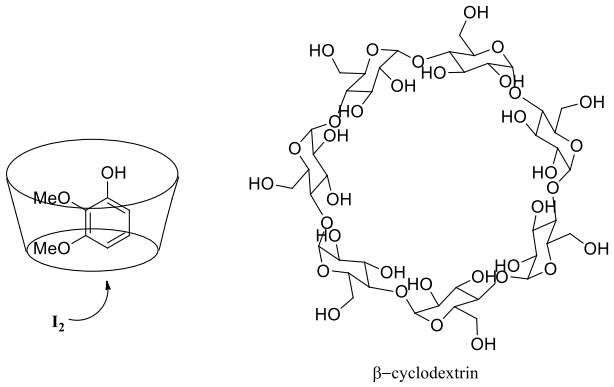
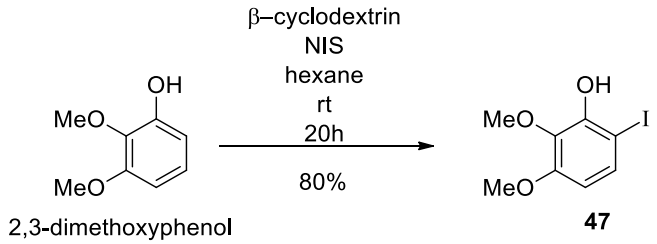


Figure 4-1 Iodination in presence of β-cyclodextrin

The employed new conditions are depicted in **Scheme 4-6**. Unfortunately, these conditions did not afford the expected *para*-regioisomer **47a**, the only recollected product was the isomer **47**.

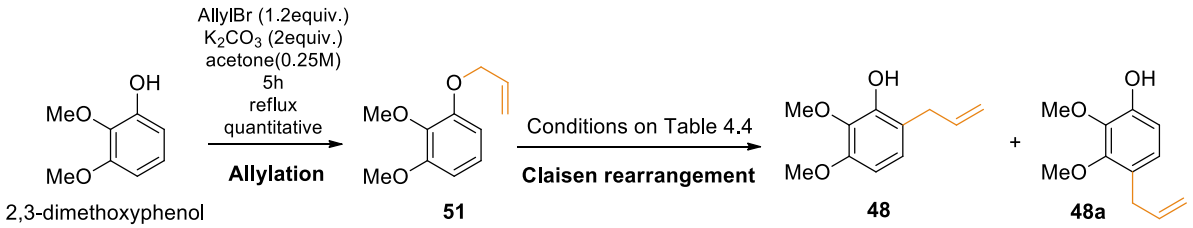
[116]a) Veglia, A. V.; De Rossi, R. H. *J. Org. Chem.* **1988**, *53* (22), 5281–5287. b) Suresh, P.; Annalakshmi, S.; Pitchumani, K. *Tetrahedron* **2007**, *63* (23), 4959–4967. c) Chelli, S.; Majdoub, M.; Jouini, M.; Aeiyach, S.; Maurel, F.; Chane-Ching, K. I.; Lacaze, P.-C. *J. Phys. Org. Chem.* **2007**, *20* (1), 30–43.



Scheme 4-6 Iodination in presence of β-cyclodextrin

4.1.1.2.2 Approach b (Claisen rearrangement)

In approach b the phenol was protected as an allyl ether, in order to use this protecting group in a subsequent regioselective Claisen rearrangement reaction, to install the allyl function in position 6 of 2,3-dimethoxyphenol. (**Scheme 4-7**)



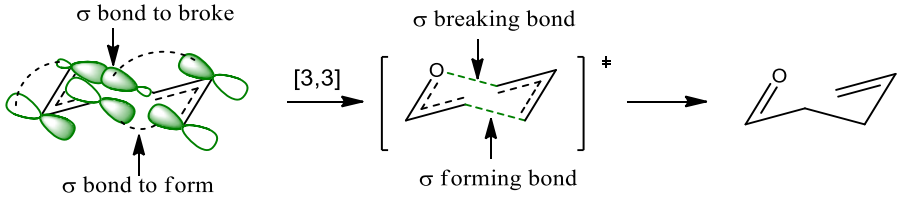
Scheme 4-7 Allylation and Claisen rearrangement approach

Allylation of phenol with allylbromide in presence of K_2CO_3 as the base and acetone as the solvent afforded after 5h the corresponding allyl ether **51** with a quantitative yield. On the substrate **51** Claisen rearrangement was tried. Several conditions were experimented and as emerge in the **Table 4-4** the obtention of **48** as only product hasn't been easy.

Before doing some comments about the results obtained in the Claisen rearrangement, in the next pages we will describe with more details this reaction due to the importance in our synthesis.

Claisen rearrangement

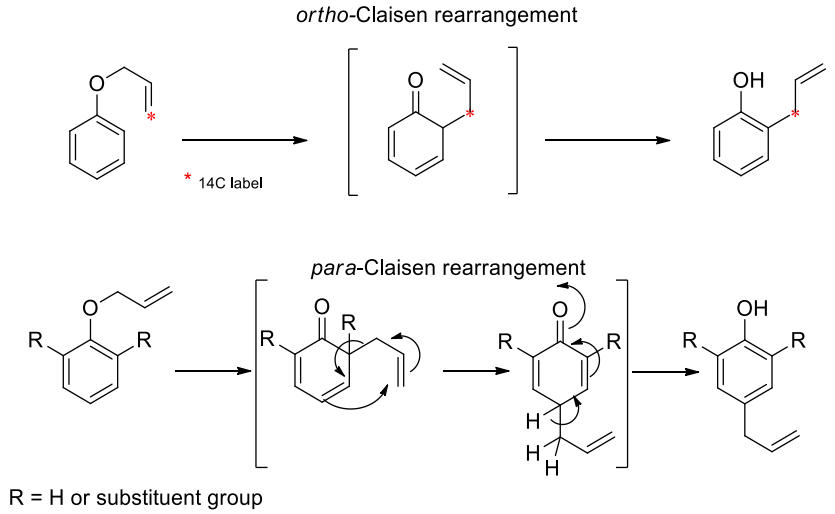
Ludwig Claisen decscribed for the first time in 1912 the thermal rearrangement of allylphenol ethers to the corresponding C-allylphenols[117], providing a first example of [3,3]-sigmatropic rearrangement. This reaction can be described as a suprafacial, concerted [3,3]-sigmatropic rearrangement that proceed *via* six membered chairlike transition state, formed by a combination of σ and π overlap of 2p atomic orbitals belonging to the carbon atoms of both allyl fragments involved.(**Scheme 4-8**)



Scheme 4-8 Claisen rearrangement transition state

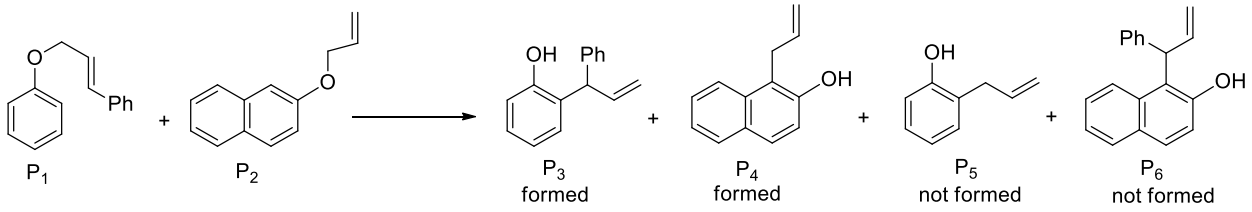
[117]Claisen, L. *Berichte Dtsch. Chem. Ges.* **1912**, *45* (3), 3157–3166.

The elucidation of mechanism for *O*-arylallylphenol arise from experiments led with ^{14}C-labeled allyl phenol ether[118] that demonstrated the presence of labelled carbon on the benzylic position after the formation of new σ-bond (**Scheme 4-9**). If on the allylarylether both *ortho*-positions are substituted, but not necessarily, the allyl group could undergo a secondary rearrangement (Cope rearrangement) to afford the corresponding *para*-allylphenol.[119]



Scheme 4-9 *Ortho* and *para* aromatic Claisen rearrangement

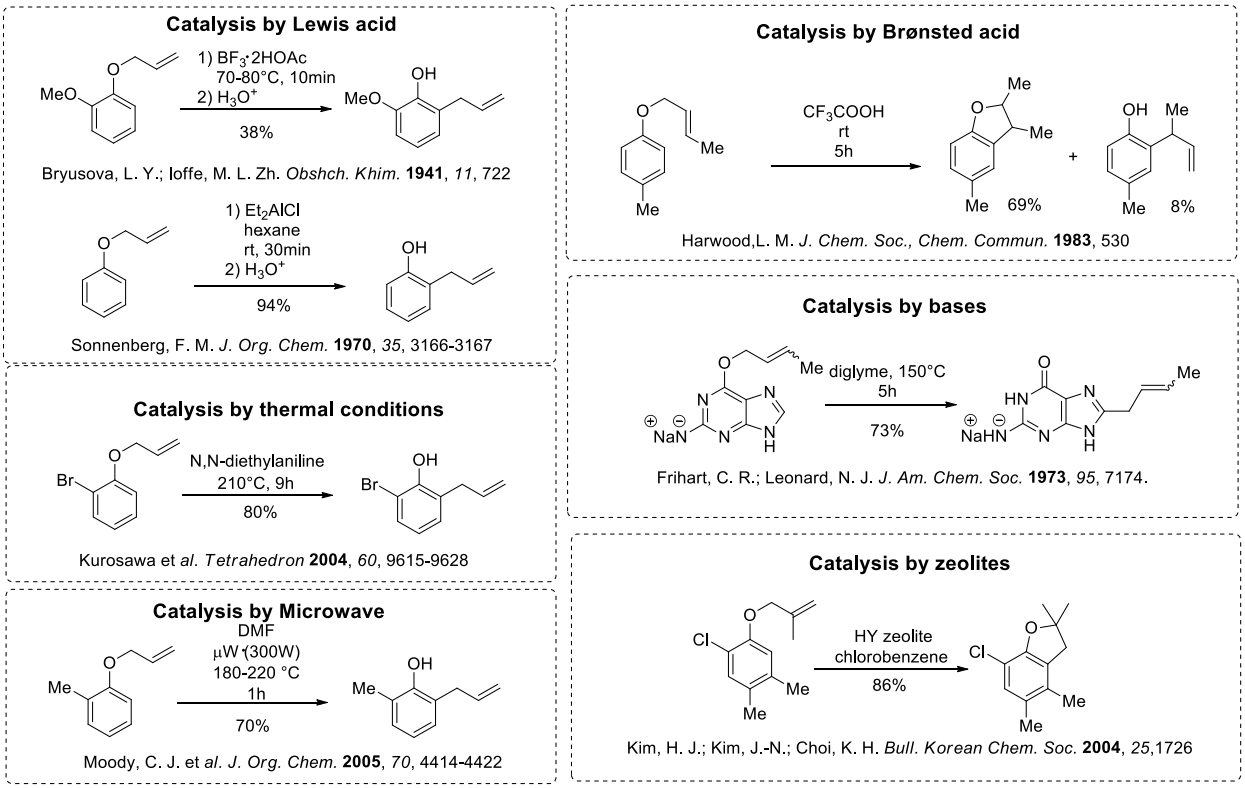
Further studies have also clarified that the Claisen rearrangement occurs in an intramolecular way. Indeed, heating separately and simultaneously the substrate $\mathbf{P_1}$ and $\mathbf{P_2}$ (**Scheme 4-10**) the final products were the same in both cases. There was no evidence of crossover products formation $\mathbf{P_5}$ and $\mathbf{P_6}$ and this indicates that rearrangement must be intramolecular.[120]



Scheme 4-10 Evidence of intramolecular mechanism Claisen rearrangement

[118]Ryan, J. P.; O'Connor, P. R. *J. Am. Chem. Soc.* **1952**, *74* (23), 5866–5869.
[119]Pearl, I. A. *J. Am. Chem. Soc.* **1948**, *70* (5), 1746–1748.
[120]Hurd, C. D.; Schmerling, L. *J. Am. Chem. Soc.* **1937**, *59* (1), 107–109.

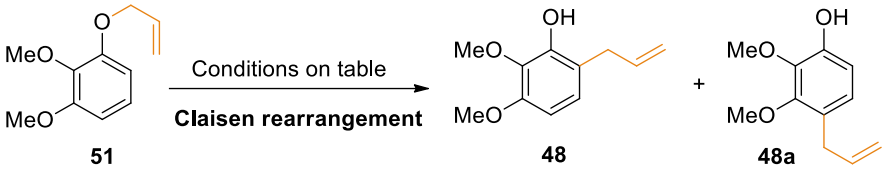
As reported in numerous rewiews[121] on Claisen rearrangement, the reaction could be catalyzed by Lewis[122] and Brønsted[123] acid, by bases,[124] by thermal conditions[125], by microwave[126], by zeolites[127], as reported in **Scheme 4-11**.



Scheme 4-11 Claisen rearrangement catalysis

Taking into account literature concerning Claisen rearrangement and considering that this reaction was never performed before on substrate **51**, we carried out a screening of possible conditions as reported in the following table.

[121] a) Lutz, R. P. *Chem. Rev.* **1984**, *84* (3), 205–247. b) Majumdar, K. C.; Alam, S.; Chattopadhyay, B. *Tetrahedron* **2008**, *64* (4), 597–643. c) Martín Castro, A. M. *Chem. Rev.* **2004**, *104* (6), 2939–3002.
[122] Sonnenberg, F. M. *J. Org. Chem.* **1970**, *35* (9), 3166–3167.
[123] Harwood,L. M. J. Chem. Soc., Chem. Commun. **1983**, 530
[124] Frihart, C. R.; Leonard, N. J. *J. Am. Chem. Soc.* **1973**, *95* (21), 7174–7175.
[125] Kurosawa, W.; Kobayashi, H.; Kan, T.; Fukuyama, T. *Tetrahedron* **2004**, *60* (43), 9615–9628.
[126] Davis, C. J.; Hurst, T. E.; Jacob, A. M.; Moody, C. J. *J. Org. Chem.* **2005**, *70* (11), 4414–4422.
[127] Kim, H. J.; Kim, J.-N.; Choi, K. H. Bull. Korean Chem. Soc. **2004**, *25*,1726.



Entry	Claisen conditions	Conversion[a]	(48 : 48a)[a]
1	DMF (0.13M), oil bath, 120°C, 1h	s.m.	- : -
2	DMF (0.8M), MW (330W), 200°C, 1h	5%	- : -
3	*N,N*-dimethylaniline, oil bath, 190°C, 25h	100%	65 : 35
4	*N,N*-diethylaniline, oil bath, 190°C, 18h	100%	65 : 35
5	NMP, oil bath, 180°C, 48h	s.m.	- : -
6	neat, MW (330W), 200°C, 1h	31%	71 : 29
7	neat, heat gun, 1h	95%	65 : 35
8	neat, oil bath, 180°C, 8h	95%	67 : 33
9	AcOH (0.06M), oil bath, 120°C, 7h	s.m.	- : -
10	DIBAL, DCM, rt, 1h, 3.5h	s.m.	- : -
11	Et_2AlCl, hexane, 0°C, 1,5h	100%	100 : -
12	Me_2AlCl, hexane, 0°C, 1,5h	100%	100 : -

a.Conversion and regioisomeric ratio were evaluated by ^{1}H-NMR analysis

Table 4-4 Claisen rearrangement conditions

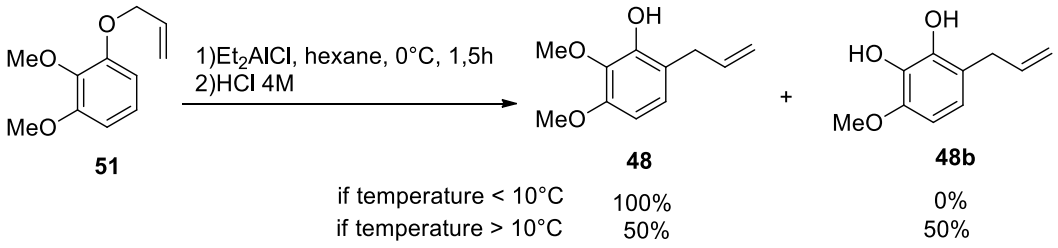
We started our test with classical thermal conditions using DMF[122] (entry 1) as solvent heating the reaction mixture in oil bath (entry 1) or with microwaves (entry 2)[126] but no rearrangement occurred in these conditions. Using tertiary aromatic amines as solvent (entry 3 and 4) as reported by Baker A. W. and Shulgin A. T., [128] we observed the complete conversion of starting material. Unfortunately the ^{1}H-NMR spectra showed a mixture of two inseparable regioisomers in which the major compound was the *ortho* rearranged **48**. The use of *N*-methylpyrrolidone[129] as the solvent allowed to recuperate only starting material (entry 5). As observed and as described in literature, solvent appeared as an important factor that could influence the rearrangement reaction.[130] We decided to use *O*-allylphenol in neat[131] form, changing just the heating source (entry 6, 7, 8). MW conditions gave a better regioisomeric ratio between **48** and **48a**, but the

[128] Shulgin, A. T.; Baker, A. W. *J. Org. Chem.* **1963**, *28* (9), 2468–2469.
[129] Koyama, E.; Yang, G.; Hiratani, K. *Tetrahedron Lett.* **2000**, *41* (42), 8111–8116.
[130]Ganem, B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35* (9), 936–945.
[131] Organic Syntheses, Coll. Vol. 3, p.418 (**1955**); Vol. 25, p.49 (**1945**)

conversion of starting material was lower. On the contrary the other two reactions performed using the heat gun and the oil bath respectively, gave a total starting material's conversion and with an average rapport of 66:34 between the two possible products. Conditions with a Brønsted acid[132] were tried (entry 9) but none rearranged product was observed. Diisobutylaluminium hydride (DIBAL)[121b] was also employed and again only **51** was recovered at the end of reaction (entry 10). Finally the attempts made with Et_2AlCl and Me_2AlCl gave the complete conversion of **51** to the only desired regioisomer **48**.[133]

The coordination of aluminum to the oxygen bearing the allyl group allowed to obtain a partially positive charge that favored the concerted mechanism of Claisen rearrangement increasing the rate of the reaction. We need to combine a decrease of the reaction temperature to 0°C and the hydrolysis of the reaction after 1.5h to avoid the second *para*-rearrangement which could led to the product **48a**. The reaction catalyzed by Et_2AlCl or Me_2AlCl proceed with the evolution of ethane or methane depending from the aluminum source employed.[122,134]

Moreover a crucial point of this rearrangement is to perform the acid hydrolysis at low temperature (maximum 10°C) (entries 11 and 12). Indeed if the temperature reach higher values, a by-product due to an *ortho*-demethoxylation **48b** was formed in a mixture 1:1 with the expected compound **48**. It is important to note that these two compounds are easily separated by column chromatography on silica gel (**Scheme 4-12**).

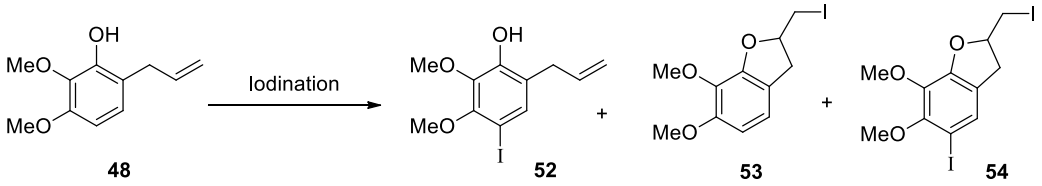


Scheme 4-12 Claisen rearrangement with Et_2AlCl

With the optimized conditions for Claisen rearrangement on our substrate we were able to prepare compound **48** in only 3 steps (from 2,3-dimethoxybenzaldehyde to 2,3-dimethoxyallylphenol) with an overall yield of 97%.

[132] Tisdale, E. J.; Vong, B. G.; Li, H.; Kim, S. H.; Chowdhury, C.; Theodorakis, E. A. *Tetrahedron* **2003**, *59* (35), 6873–6887.
[133] Tripathi, S.; Chan, M.-H.; Chen, C. *Bioorg. Med. Chem. Lett.* **2012**, *22* (1), 216–221.
[134] Snider, B. B.; Rodini, D. J.; Karras, M.; Kirk, T. C.; Deutsch, E. A.; Cordova, R.; Price, R. T. *Tetrahedron* **1981**, *37* (23), 3927–3934.

With the idea to prepare the iodinated or brominated phenol **48**, we investigated chemo and regioselective halogenation conditions. Classical reagents used as iodine source, NIS and I_2 were tested in different quantities for the iodination step on the phenol **48.** The results of iodination are reported in the following table. (**Table 4-5**)



Entry*	Iodination conditions	Temp (°C)	T (h)	52 (%)	53 (%)	54 (%)
1[a]	NIS (1equiv.),	0	3	0	45	0
2[a]	NIS (2equiv	0	3	0	59	0
3[a,c]	NIS (3.5equiv.)	0	3	0	86	0
4[b]	I_2 (2equiv.), *i*-$BuNH_2$ (4equiv.)	rt	5	60	0	27
5[b]	I_2 (2equiv), *i*-$BuNH_2$ (4equiv.)	rt	3	71	0	3
6[b]	I_2 (1.5equiv),*i*-$BuNH_2$ (3equiv.)	0	5	50	0	7
7[b]	I_2 (2equiv), *i*-Pr_2NH (4equiv.)	rt	5	0	0	0
8[b]	I_2 (2equiv), *t*-$BuNH_2$ (4equiv.)	rt	5	90	0	4

* regioisomeric ratio evaluated by GC-MS

a solvent CH_3CN

b solvent: toluene, DCM

c. NIS was also remplaced by NBS, but polybrominated products were observed by GC-MS

Table 4-5 Iodination on 2,3-dimethoxy-6-allylphenol

Surprisingly, iodination at low temperature performed with NIS afforded the undesirable dihydrobenzofuran **53** which could be easily separated from the unreacted starting material **48** (entries 1-3). The formation of this compound could be rationalyzed by the formation of the iodonium species attacked by the phenol (intramolecular cyclisation). No other products are observed.

In order to see the reactivity of NBS in the same conditions of entry 3, this reaction was tested but led to a complex mixture of mono or polybrominated compounds, detected by GC-MS analysis (**Table 4-5**). Surprisingly, the cyclised compound was not formed that showed a strong difference of reactivity for NBS compared to NIS.

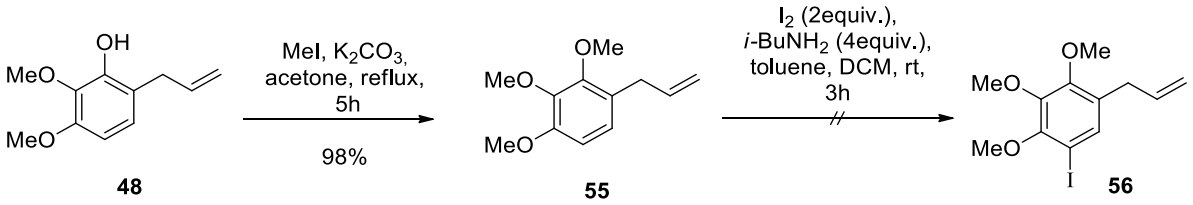
When the reaction was carried out with molecular iodine in presence of amine and toluene we observed a really different result from which obtained with NIS. The reaction was performed adding dropwise a solution of phenol **48** in DCM to a mixture of I_2, *iso*-butylamine (*i*-$BuNH_2$) and toluene giving preferentially **52** (entry 4). That's means that in these conditions, we were able to introduce in a chemo and regioselective way the iodine on the *para*-phenol position, leaving allylic function completely untouched. This was a very encouraging and also unexpected result, if we compare the trend of our reaction to that reported from Brookes P. A. et *al*. [135] The reaction stopped after 5h, revealing the formation of products **52** (60%) and **54** (27%) with 13% of unreacted starting material **48**. The ratio of products was evaluated by GC-MS, considering that the unreacted phenol **48** and the halogenated substrate **52** were unseparable by column chromatography. With the aim to obtain a better yielf for **52,** we repeated the reaction in the conditions reported in entries 5-8. In entry 5 we observed that, stopping the reaction after 3h the formation of diiodinated product **54** was reduced. This suggests that the formation of **54** starts only when the concentration of the kinetically favoured iodinated compound **52** is maximal**,** that's means that the iodocyclization occurred on the already iodinated substrate **52** and not on the cyclic iodo-derivative **53**. This could explain why product **53** was never observed. We realized that the use of di*iso*-propylamine (*i*-Pr_2NH) was completely unsuccessful (entry 7, only starting material was recollected). On the contrary *tert*-butylamine, *t*-$BuNH_2$ (entry 8) allowed to observe a quite completely selective iodination affording substrate **52** in an excellent conversion.

During the reaction there is an *in-situ* formation of a charge-transfer complex in which amine acts as donor and I_2 as acceptor. This complex, stabilized in toluene, constitutes the reacting iodinating species.[135,136] During the reaction the amine-I_2 complex was probably coordinated by the free OH of the phenol **48.** We have no evidence of the mechanism involved in this process, but experimentally we observed that if the iodination reaction was tried on the protected phenol **55** (**Scheme 4-13**), in the same conditions reported in entry 5 of **Table 4-5,** none iodinated product was observed, neither on the aromatic ring nor on the allylic chain.

---

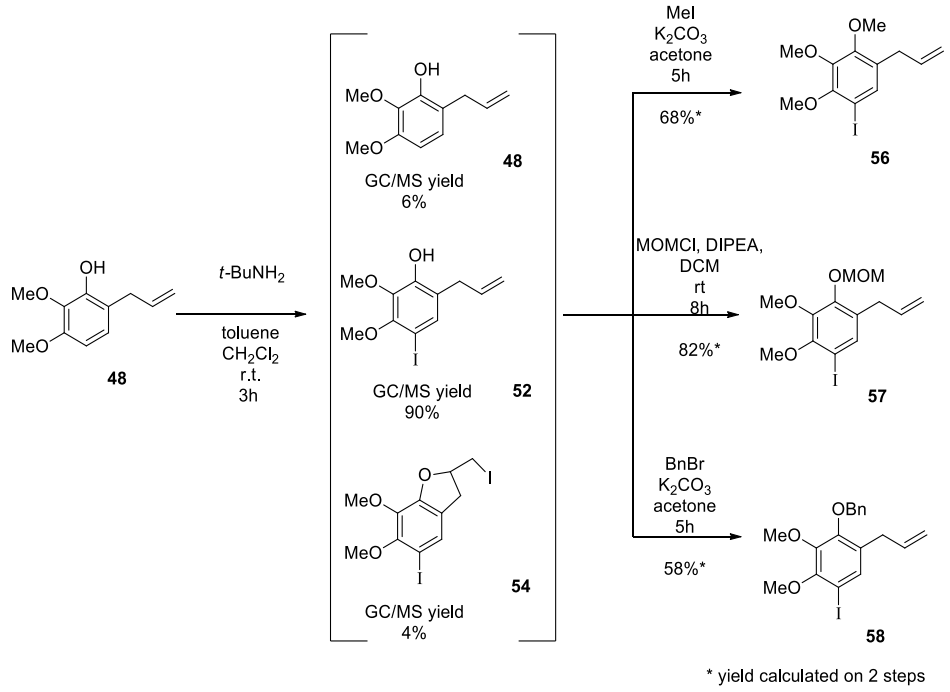
[135] Brookes, P. A.; Cordes, J.; White, A. J. P.; Barrett, A. G. M. *Eur. J. Org. Chem.* **2013**, *2013* (32), 7313–7319.

[136] a) Kobinata, S.; Nagakura, S. *J. Am. Chem. Soc.* **1966**, *88* (17), 3905–3909. b) Frota, L. C. R. M. da; Canavez, R. C. P.; Gomes, S. L. da S.; Costa, P. R. R.; Silva, A. J. M. da. *J. Braz. Chem. Soc.* **2009**, *20* (10), 1916–1920. c) Haas, J.; Bissmire, S.; Wirth, T. *Chem. - Eur. J.* **2005**, *11* (19), 5777–5785. d) Nelson, P. H.; Carr, S. F.; Devens, B. H.; Eugui, E. M.; Franco, F.; Gonzalez, C.; Hawley, R. C.; Loughhead, D. G.; Milan, D. J.; Papp, E.; Patterson, J. W.; Rouhafza, S.; Sjogren, E. B.; Smith, D. B.; Stephenson, R. A.; Talamas, F. X.; Waltos, A.-M.; Weikert, R. J.; Wu, J. C. *J. Med. Chem.* **1996**, *39* (21), 4181–4196. e) Yonezawa, S.; Komurasaki, T.; Kawada, K.; Tsuri, T.; Fuji, M.; Kugimiya, A.; Haga, N.; Mitsumori, S.; Inagaki, M.; Nakatani, T.; Tamura, Y.; Takechi, S.; Taishi, T.; Ohtani, M. *J. Org. Chem.* **1998**, *63* (17), 5831–5837.



Scheme 4-13 Iodination on a protected phenol with amine-I_2 complex

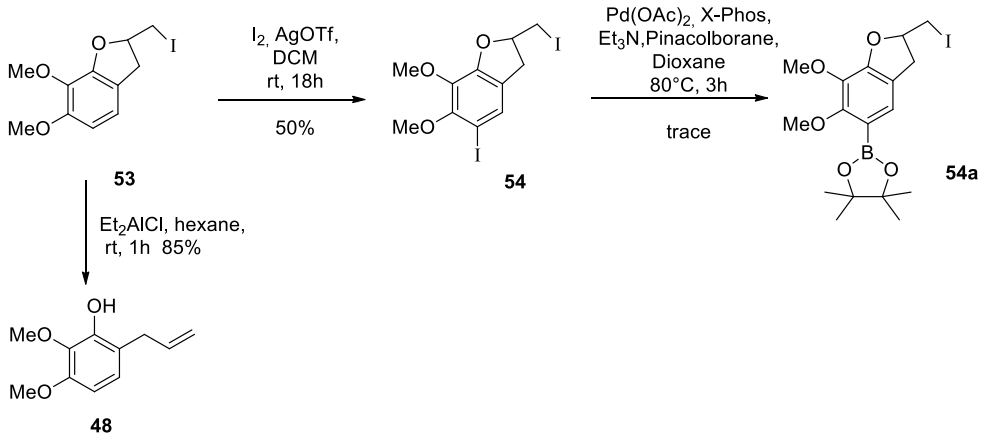
In order to separate the desired iodinated **52** from the mixture with **48** and **54 (Table 4-5),** we performed a protection of the phenolic part. We were pleased to observe that the different iodinated ethers with a OMe (**56**), OMOM (**57**) or OBn (**58**) were efficiently separated from the other products and were obtained with moderate to good yield over two steps. **Scheme 4-14.**



Scheme 4-14 Protection of iodinated phenol 52

Compounds **56**, **57** and **58** constitute three important fragments that will be used to carry out the total synthesis of myricanol.

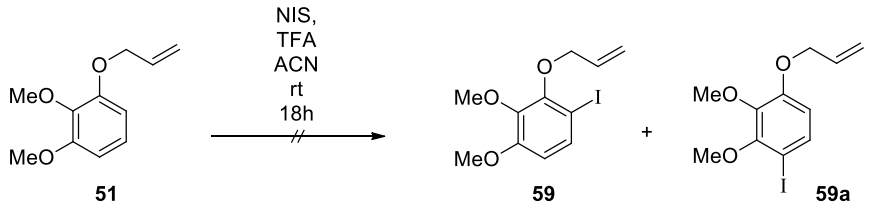
To follow up the dihydrobenzofuran **53**, we investigated a successfull derivation to diiodinated compound **54** *via* classical iodination conditions followed by the preparation of a pinacol boronic ester **54a** by a palladium catalysed reaction.



Scheme 4-15 Functionalization of iodocyclized product 53

Scheme 4-15 illustrates how product **53** was additionally functionalized. First of all we tried to introduce another iodine to be transformed in a boronic derivative for an intermolecular biaryl coupling. Using I_2 in presence of AgOTf, product **54** was obtained with only 50% yield. When the essay of Pd-catalyzed borylation was done only trace of product **54a** was formed. Therefore thinking that the formation of dihydrobenzofuran **53** could be considered as a "protecting group" of the allylic double bond, we tried to open the dihydrofuryl ring to restore the allylic moiety.[137] We tried different reaction conditions on compound **53:** the neat product stirred under a tungsten lamp of 100W; UV irradiation at 310nm; BBr_3 as Lewis acid. Only when Et_2AlCl was employed (as reported in the **Scheme 4-15)** the cycle was opened and **48** was obtained in a quite quantitative yield.

In this approach before starting the study of the key Claisen rearrangement of allylic ether **51 (Table 4-4** and **Scheme 4-12),** we tried also to perform the halogenation of **51**. An essay of iodination was done in presence of NIS with a catalytic amount of trifluoroacetic acid (TFA), but after 18h, only unreacted starting product **51** was recovered quantitatively. (**Scheme 4-16**)



Scheme 4-16 Iodination on 1-(allyloxy)-2,3-dimethoxybenzene 51

[137] Gauthier, J. Y.; Guindon, Y. *Tetrahedron Lett.* **1987**, *28* (48), 5985–5988.

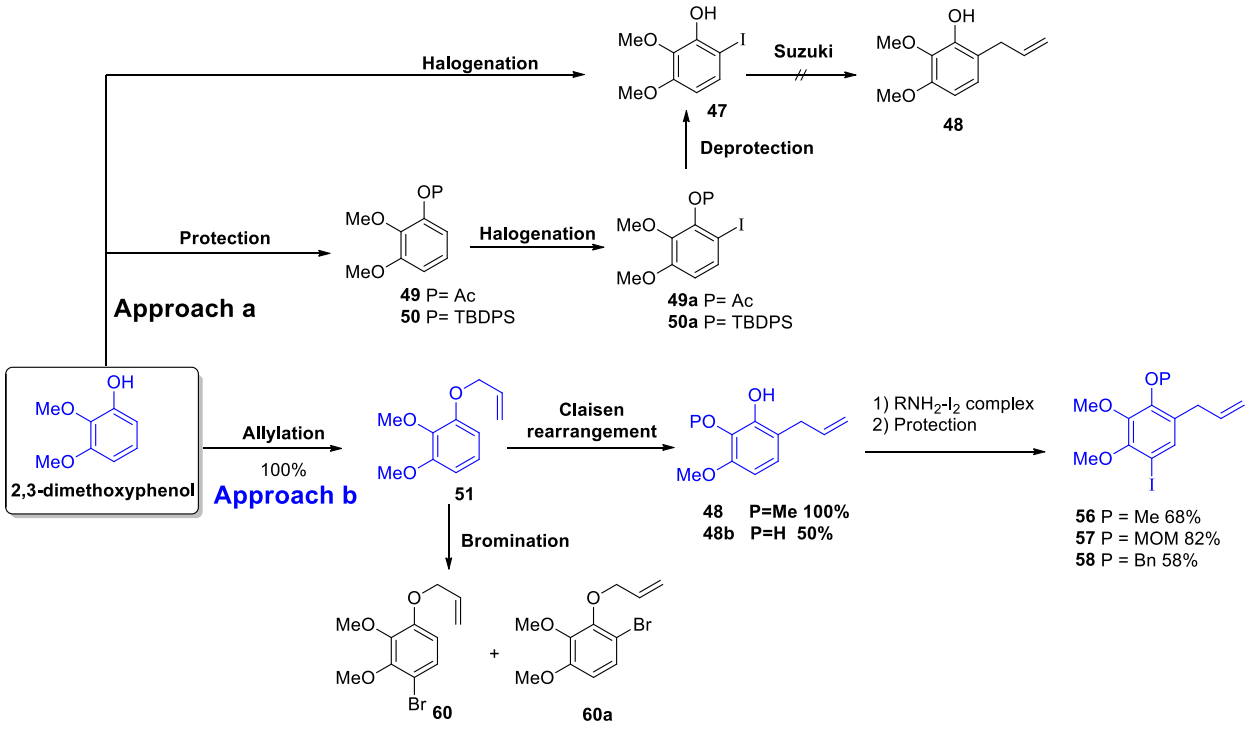
Similar conditions (NBS, TFA, CH_3CN) were used to try the introduction of bromine on the aromatic ring of 1-(allyloxy)-2,3-dimethoxybenzene. Surprisingly, these conditions afforded two unseparable monobrominated regioisomers **60** and **60a** in a ratio of 50:50.

Scheme 4-17 Bromination on the 1-(allyloxy)-2,3-dimethoxyphenol

Unfortunately, even if the reaction was tried at lower temperature (-78°C), in order to see if the regioisomer **60a** could be fomed at first during the halogenation, the ratio observed between the brominated compounds **60** an **60a** was rigourously similar (50:50) with a decrease of the yield.

4.1.2 Conclusion on the D type fragments

Through the different approaches tested for the preparation of **D** type's fragments, we can conclude that the 2,3-dimethoxyphenol was the best starting substrate. Effectively, when synthesis was performed with the 2,3-dimethoxyphenol (commercially available substrate) we are able to prepare in only 4 steps considering the approach b the key fragments **56**, **57** and **58.** (**Scheme 4-18).** These synthons will be very useful for total synthesis of myricanol, especially for an intermolecular biaryl coupling approach. Moreover, we could also consider the fragment-**48** as a good myricanol precursor, taking into account that it could be involved in a cross-metathesis reaction with a fragment **E** type. A halogenation step could be planned in a second time.



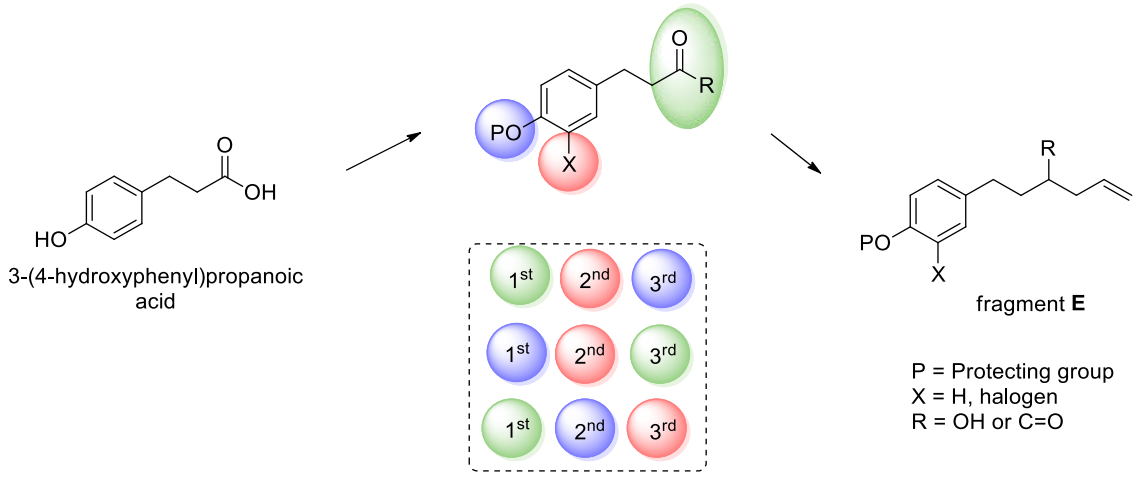
Scheme 4-18 Summary of fragment D synthesis

The derivatization of allyl iodinated compounds **56**, **57** and **58** to the corresponding boronic species for the study of biaryl coupling reaction will be presented in the section relative to Suzuki coupling.

4.1.3 Fragments E type retrosynthetic analysis

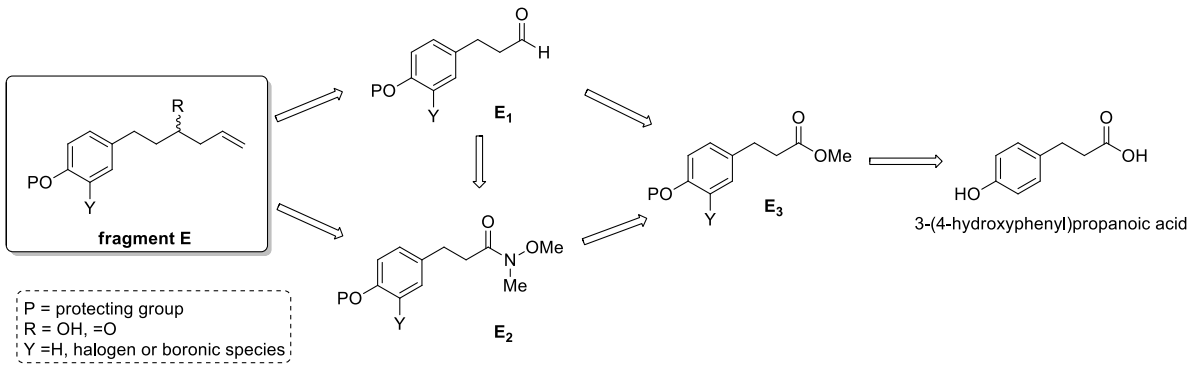
The synthesis of fragments **E** could be envisioned starting from commercially available 3-(4-hydroxyphenyl)propanoic acid. For further coupling reaction on this starting product, three different transformations should be realized. Indeed, as depicted in **Scheme 4-19**, considering the 3-(4-hydroxyphenyl)propanoic acid as starting point, we have to protect the phenol (blue color), in some instance to introduce an halogen in *ortho* position to the hydroxyl group (red color) and to transform the carboxylic acid in a more reactive function (green color) as aldehyde or Weinreb amide that could be used to obtain fragment **E**. The order in which we achieved these three reactions could be different as shown in **Scheme 4-19**. In addition the presence of a halogen or not will depend by which biaryl coupling reaction we will perform.

Moreover in order to perform a enantioselective synthesis of myricanol, we will have to obtain fragment **E** in optically pure form using stereoselective methodologies.



Scheme 4-19 Functionalization of 3-(4-hydroxyphenyl) propanoic acid

The **E** type's fragments selected as precursor of myricanol have as common skeleton, a disubstituted phenol bearing in *para* position a chain of six carbon's atom and in *ortho* an halogen or a boronic species. In the following scheme are reported the retrosynthetic approaches considered for the preparation of the desired fragments **E**. 3-(4-hydroxyphenyl)propanoic acid should be transformed either in an aldehyde $\mathbf{E_1}$ or a Weinreb amide $\mathbf{E_2}$ allowing the coupling with respectively an allylborane and an allylGrignard.



Scheme 4-20 Retrosynthetic approaches for E type's fragments

Due to the numerous possibilities to combine the order of functionalization of starting propanoic acid (**Scheme 4-19**), we divided the reactions performed in two groups. First group of reactions will concern the preparation of **E** type's fragments without introduction of the halogen in *ortho* position of the hydroxyl group (**Scheme 4-21**), second group will concern the halogenated **E** type's fragments (**Scheme 4-22**).

4.1.3.1 E type's fragments without halogen

The preparation of fragments E without halogen (**Scheme 4-21**) started from commercially available 3-(4-hydroxyphenyl)propanoic acid, which was transformed following two different strategies.

The first strategy consist in converting the starting carboxylic acid into the Weinreb amide **61,** that was obtained with a 47% yield.[138] The amide **61** was then protected at the phenol position and the benzylic ether **62** was achieved in good yield (80%)**.** In addition compound **62** can also be synthesized through the methyl ester **64** obtained in a quantitative way from the starting propionic acid. The hydroxyl group was protected as a benzyl (Bn) or methoxymethyl (MOM) ether to afford **65** and **66** in excellent yields. We observed also that during the MOM protection, if reaction time exceeded 6h, a transesterification occurred in which the methyl group was replaced by the methoxymethyl group to give **68** in 60% yield. Moreover the dibenzylated compound **67** was directly obtained performing a classical benzylation of the starting propionic acid with BnBr allowing to protect not only the phenol, but also the carboxylic acid in a quantitative way. The protected esters (**65**, **66, 68**) were transformed into the corresponding aldehydes **69** and **70** *via* ester reduction with DIBAL in dichloromethane. This reduction gave always mixtures of the aldehyde and the corresponding primary alcohol (50/50) that were completely oxidized to the aldehyde with Dess-Martin

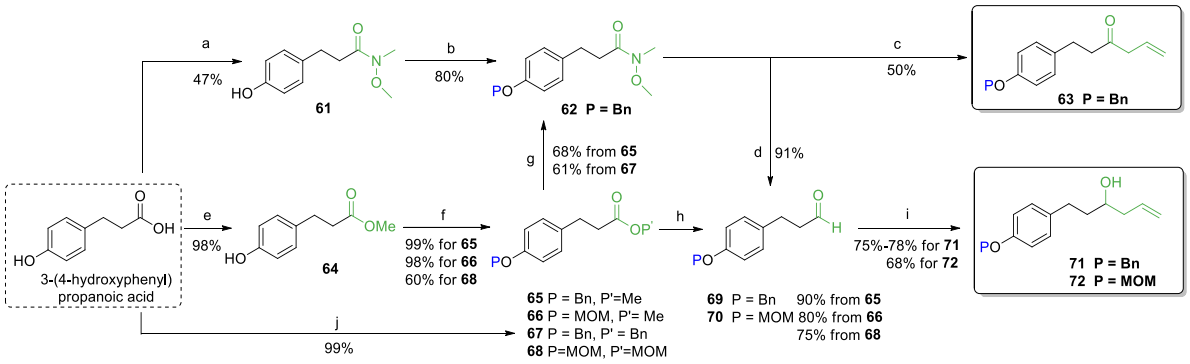
[138] De Luca, L.; Giacomelli, G.; Taddei, M. *J. Org. Chem.* **2001**, *66* (7), 2534–2537.

periodinane. Otherwise, protected esters **65** and **68** were converted to Weinreb amide **62** with an average yield of 63%.

Starting from the Weinreb amide **62**, addition of the allylmagnesium bromide in THF afforded the β,γ-unsaturated ketone **63** in 50% yield while addition of allyl magnesium bromide or allylpinacolborane to the aldehydes **69** or **70** gave the corresponding homoallylic alcohols **71** and **72** in respectively 75-78% and 68% yield. The yields obtained were quite comparable and even if allylpinacolborane gave better yield, on large scale allylmagnesium bromide was preferred due to its lower cost.

If we compared the overall yield for the synthesis of **63** and **71**, the strategies through the methylester **64** are undoubtedly more efficient giving on one hand the β,γ-unsaturated ketone **63** in 32% overall yield in 4 steps (against 19% in 3 steps through the Weinreb amide) and on the other hand the homoallylic alcohols **71** in 60,4% overall yield in 4 steps (against 23% in 4 steps through the Weinreb amide). In addition the homoallylic alcohol **72** was obtained in lower overall yield (26,5%) showing different reactivities with the MOM protected ether.

Importantly is the isomerization of **63** through flash column chromatography giving the corresponding α,β-unsaturated ketone even though 10% of thiethylamine (Et_3N) is added to the elution solvent. For this reason **63** would be used in a crude form in the subsequent reaction.

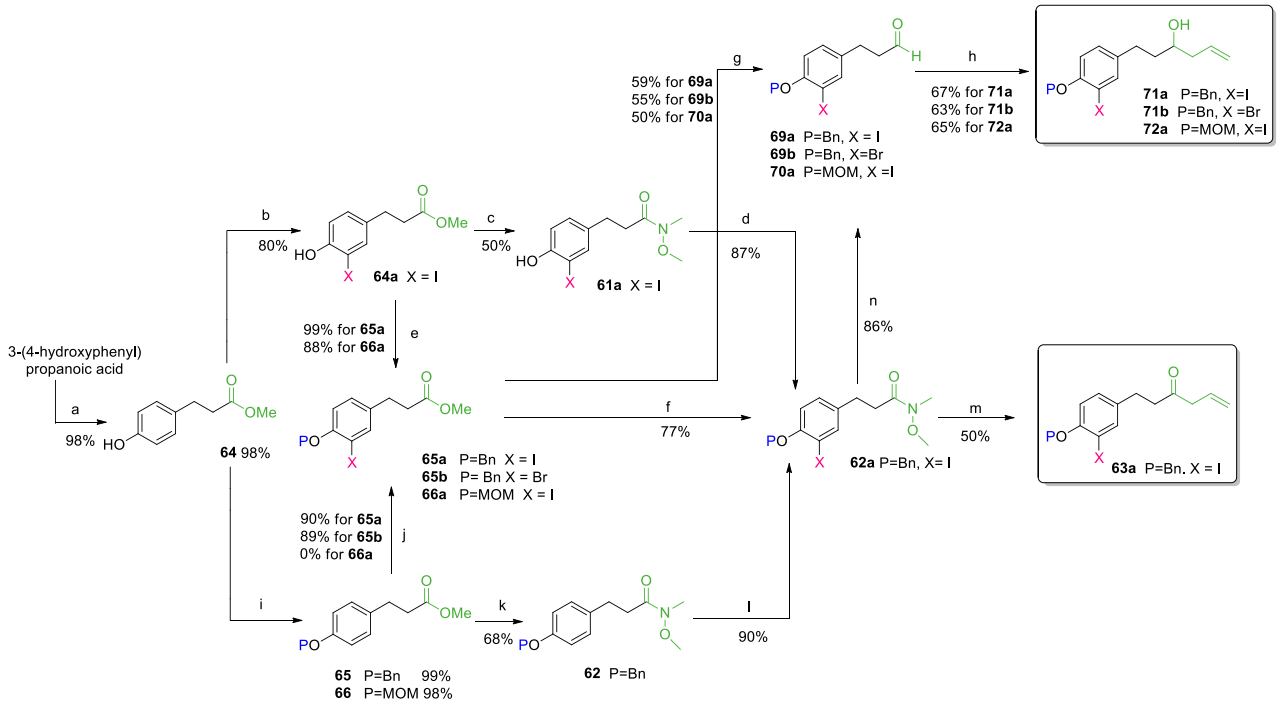


a) 2-Chloro-4,6-dimethoxy-1,3,5-triazine, N-methylmorpholine, CH_3NHOCH_3-HCl,THF,rt, 4h; b) BnBr, K_2CO_3, NaI, acetone, reflux, 4h; c) AllylMgBr, THF; d) DIBAL-H, DCM, -78°C, 2.5h; e)H_2SO_4, MeOH, reflux,1h; f) BnBr, K_2CO_3, NaI, acetone, reflux, 4h or MOMCl, DIPEA, DCM, rt, 6h; 9) CH_3NHOCH_3HCl, $AlMe_3$, DCM, reflux, 20h; ,3h; h) $LiAlH_4$, Et_2O, 0°C to rt, or DIBAL-H, DCM, -78°C; then DMP, DCM,r.t,2h; i) AllylMgBr or Allylpinacolborane, THF, rt,5h; j) BnBr, K_2CO_3, NaI, acetone, reflux, 4h;

Scheme 4-21 E type's fragments without halogen

4.1.3.2 E type's fragments with halogen

As depicted in **Scheme 4-22**, multiple ways to prepare the desired halogenated fragments **E** were tried, showing the versatility with which these intermediates can be managed. Moreover, because the principal aim of this thesis is the total synthesis of a natural product, we tried different pathways to prepare the same substrate as effectively as possible. As for the fragments **E** without halogen, we considered the protection of the phenol as a benzyl (Bn) and a methoxymethyl (MOM) ether and the essays of halogenation were done with the aim to introduce iodine and bromine.



a) H_2SO_4, MeOH, reflux,1h; **b)** I_2, Ag_2SO_4, DCM, rt, 2h; **c)** CH_3NHOCH_3HCl, $AlMe_3$, DCM, reflux, 20h; **d)** BnBr, K_2CO_3, NaI, acetone, reflux, 4h, **e)** BnBr, K_2CO_3, NaI, acetone, reflux, 4h, or MOMCl, DIPEA, DCM, 6h; **f)** CH_3NHOCH_3HCl, $AlMe_3$, DCM, reflux, 20h; **g)** DIBAL, DCM, -78°C,3h then DMP, DCM, r.t, 2h; **h)** allylMgBr or allylpinacolborane, THF, rt; **i)** BnBr, K_2CO_3, NaI, acetone, reflux, 4h or MOMCl, DIPEA, DCM, 6h; **j)** I_2,Ag_2SO_4, DCM, 3h or NBS, CF_3COOH, CH_3CN, 8h; **k)** CH_3NHOCH_3HCl, $AlMe_3$, DCM, reflux, 20h; **l)** I_2,Ag_2SO_4, DCM, 3h; **m)** allylMgBr, THF, rt, 5h; **n)** DIBAL, DCM, -78°C;3h.

Scheme 4-22 E type's fragments with halogen

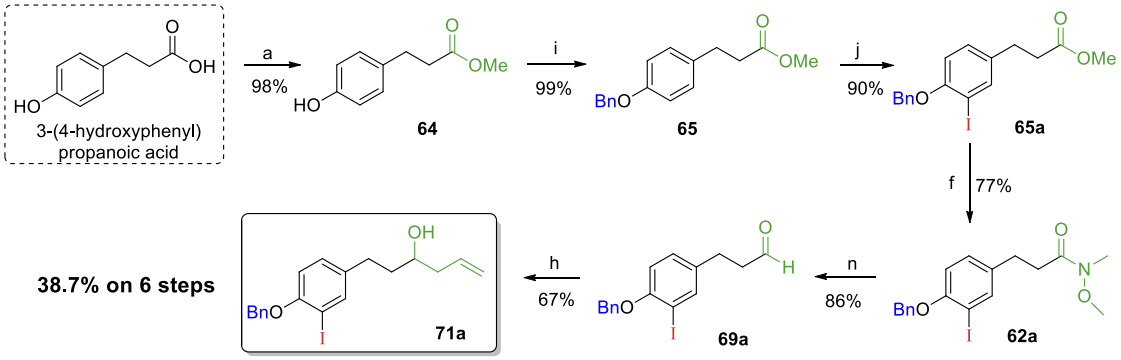
Considering the high number of intersection of different paths (**Scheme 4-22**), all reactions done will be not described in detail, but for each final product we will described the easiest and efficient route. For the synthesis of **71a** bearing an iodide in *ortho* position of the benzylic ether, six possible pathways can be followed. Analyzing the overall yield obtained for each sequence of reactions, we realized that path 5 (**Table 4-6**) is the most efficient.

Path	Sequence	Overall yield (71a)	N° steps
1	a,b,c,d,n,h	19.6%	6
2	a,b,e,g*,h	30.6%	6
3	a,b,e,f,n,h	34.4%	6
4	a,i,j,g*,h	33.9%	6
5	a,i,j,f,n,h	38.7%	6
6	a,i,k,l,n,h	33.9%	6

*2 steps reduction and oxidation

Table 4-6 Possible paths for the synthesis of 1-(4-(benzyloxy)-3-iodophenyl)hex-5-en-3-ol (71a)

The details of this sequence are illustrated in the following **Scheme 4-23**. Path 5 involved a starting Fischer esterification giving **64**, the synthesis of the benzylic ether **65** using BnBr and K_2CO_3 as base, the halogenation with I_2, Ag_2SO_4 in *ortho*-position to obtained the aryliodide **65a**, the transformation of the methylester into the corresponding Weinreb amide **62a** in presence of *N,O*-Me(OMe)NH HCl. This amide was then reduced into the aldehyde **69a** which was treated whit allylpinacolborane affording the desired homoallylic alcohol **71a** in an overall yield of 38.7% in 6 steps.

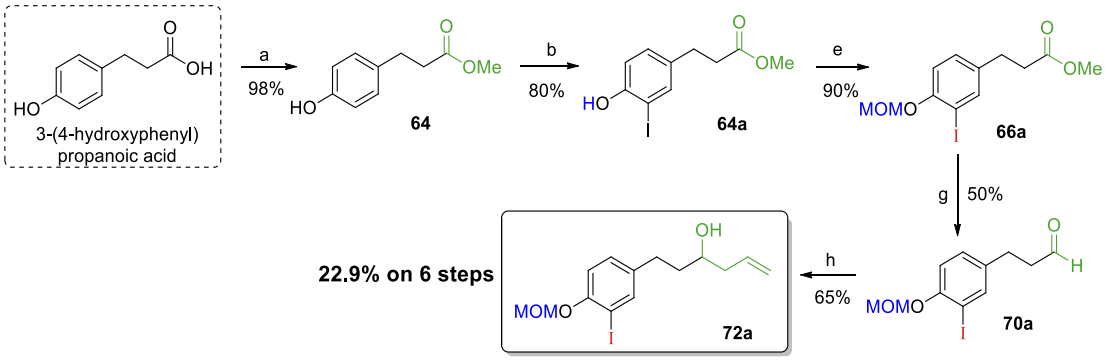


a) H_2SO_4, MeOH, reflux,1h; **i)** BnBr, K_2CO_3, NaI, acetone, reflux, 4h; **j)** I_2, Ag_2SO_4, DCM, rt, 2h; **f)** CH_3NHOCH_3HCl, $AlMe_3$, DCM, reflux; **n)** DIBAL, DCM, -78°C,3h; **h)** allylpinacolborane, THF, rt, 4h.

Scheme 4-23 Best path for the synthesis of 1-(4-(benzyloxy)-3-iodophenyl)hex-5-en-3-ol (71a)

Considering the preparation of the iodinated phenol protected with MOM **72a**, the best overall yield was obtained using a different strategy as for the synthesis of **71a**. Indeed, as shown in **Scheme 4-24** it was necessary to introduce first iodine to give **64a** and then the protecting methoxymethyl group, in order to

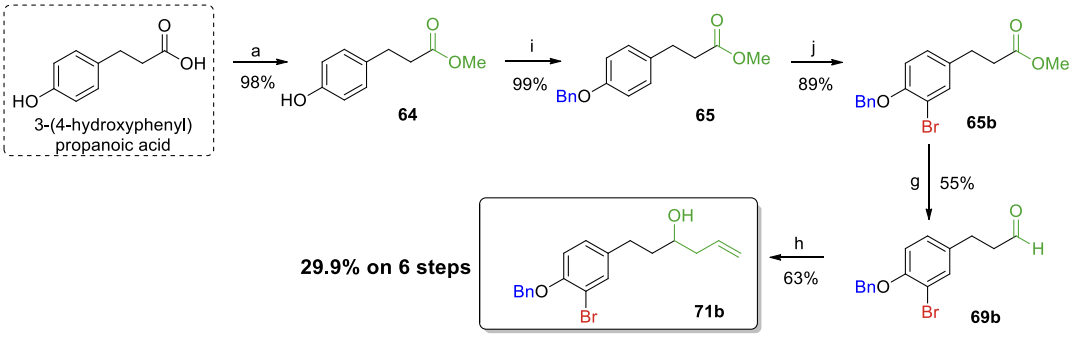
avoid the deprotection of the MOM ether during the iodination. [139] The protected iodinated ester **66a** was then reduced with DIBAL[140] giving as above a 50:50 mixture of alcohol and aldehyde detected by GC-MS and ^{1}H NMR. The mixture was oxidized with Dess-Martin periodinane to afford in a quantitative yield the aldehyde **70a** which in a crude form was used with allylmagnesium bromide. The final desired fragment **72a** was achieved with an overall yield of 22.9% in 6 steps.



a) H_2SO_4, MeOH, reflux,1h; **b)** I_2, Ag_2SO_4, DCM, rt, 2h; **e)** MOMCl, DIPEA, DCM, rt, 6h; **g)** DIBAL, DCM, -78°C,3h; **then** DMP, DCM, rt, 2h; **h)** allylmagnesium bromide, THF, rt, 4h.

Scheme 4-24 Best path for the synthesis of 1-(3-iodo-4-(methoxymethoxy)phenyl)hex-5-en-3-ol (72a)

Besides the iodinated fragments we worked also on the preparation of a brominated one, which will be useful for further and subsequent reactions to complete the total synthesis. In the **Scheme 4-25** is reported the sequence of reactions to prepare the brominated homoallylic alcohol **71b**.



a) H_2SO_4, MeOH, reflux,1h; **i)** BnBr, NaI, K_2CO_3, acetone, reflux, 4h; **j)** NBS, TFA, ACN, rt, 8h; **g)** DIBAL, DCM, -78°C,3h; then DMP, DCM, rt, 2h; h) allylmagnesium bromide, THF, rt, 4h.

Scheme 4-25 Preparation of 1-(4-(benzyloxy)-3-bromophenyl)hex-5-en-3-ol (71b)

[139] a) Jin, Y. L.; Kim, S.; Kim, Y. S.; Kim, S.-A.; Kim, H. S. *Tetrahedron Lett.* **2008**, *49* (48), 6835–6837.
b) Keith, J. M. *Tetrahedron Lett.* **2004**, *45* (13), 2739–2742.
[140] Cornil, J.; Gonnard, L.; Guérinot, A.; Reymond, S.; Cossy, J. *Eur. J. Org. Chem.* **2014**, *2014* (23), 4958–4962.

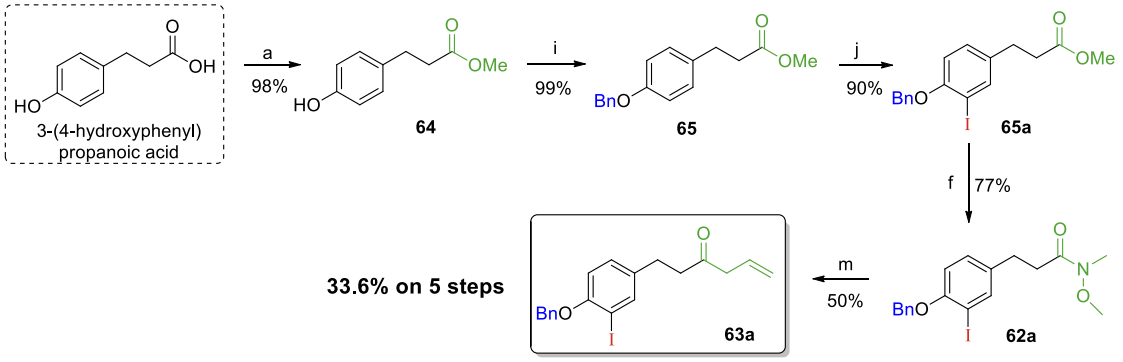
The brominated compound **71b** was obtained using exactly the same strategy as for the synthesis of the iodinated compound **72a** except the protection as a benzyl ether and the brominated step instead of the iodination giving **71b** in an overall yield of 29.9% in 6 steps. The special characteristic of **71b** is that it has a flower's smell compared to the odorless iodinated **71a**.

Considering now the preparation of the β,γ-unsaturated ketone **63a** different routes were used, as illustrated in **Table 4-7**. Path 3 represents the most efficient one, affording the desired product in 5 steps and 33.6% of yield.

Path	Sequence	Overall yield (63a)	N° steps
1	a,b,c,d,m	17.0%	5
2	a,b,e,f,m	29.9%	5
3	a,i,j,f,m	33.6%	5
4	a,i,k,l,m	29.68%	5

Table 4-7 Possible paths for the synthesis of 1-(4-(benzyloxy)-3-iodophenyl)hex-5-en-3-one (63a)

The strategy employed is depicted in the following **Scheme 4-26** showing the same sequence of reactions as in **Scheme 4-23**, except the last step which is the addition of allylmagnesium bromide directly to the Weinreb amide **62a** with a complete conversion of the starting material but the column chromatography purification allow to isolate the desired fragment **63a** with only 50% yield.



a) H_2SO_4, MeOH, reflux,1h; **i)** BnBr, K_2CO_3, NaI, acetone, reflux, 4h; **j)** I_2, Ag_2SO_4, DCM, rt, 2h; **f)** CH_3NHOCH_3HCl, $AlMe_3$, DCM, reflux; **m)** allylmagnesium bromide, THF, rt, 4h.

Scheme 4-26 Best path for the synthesis of 1-(4-(benzyloxy)-3-iodophenyl)hex-5-en-3-one (63a)

4.1.3.3 Enantioselective allylations

The total synthesis of myricanol should be envisioned also in a enantioselective way controlling the stereogenic carbinol as well as the axial chirality of the biaryl. In this context we developed a stereoselective synthesis of fragment **E** through the enantioselective allylation of the aldehyde **69** bearing a benzyl ether**.**

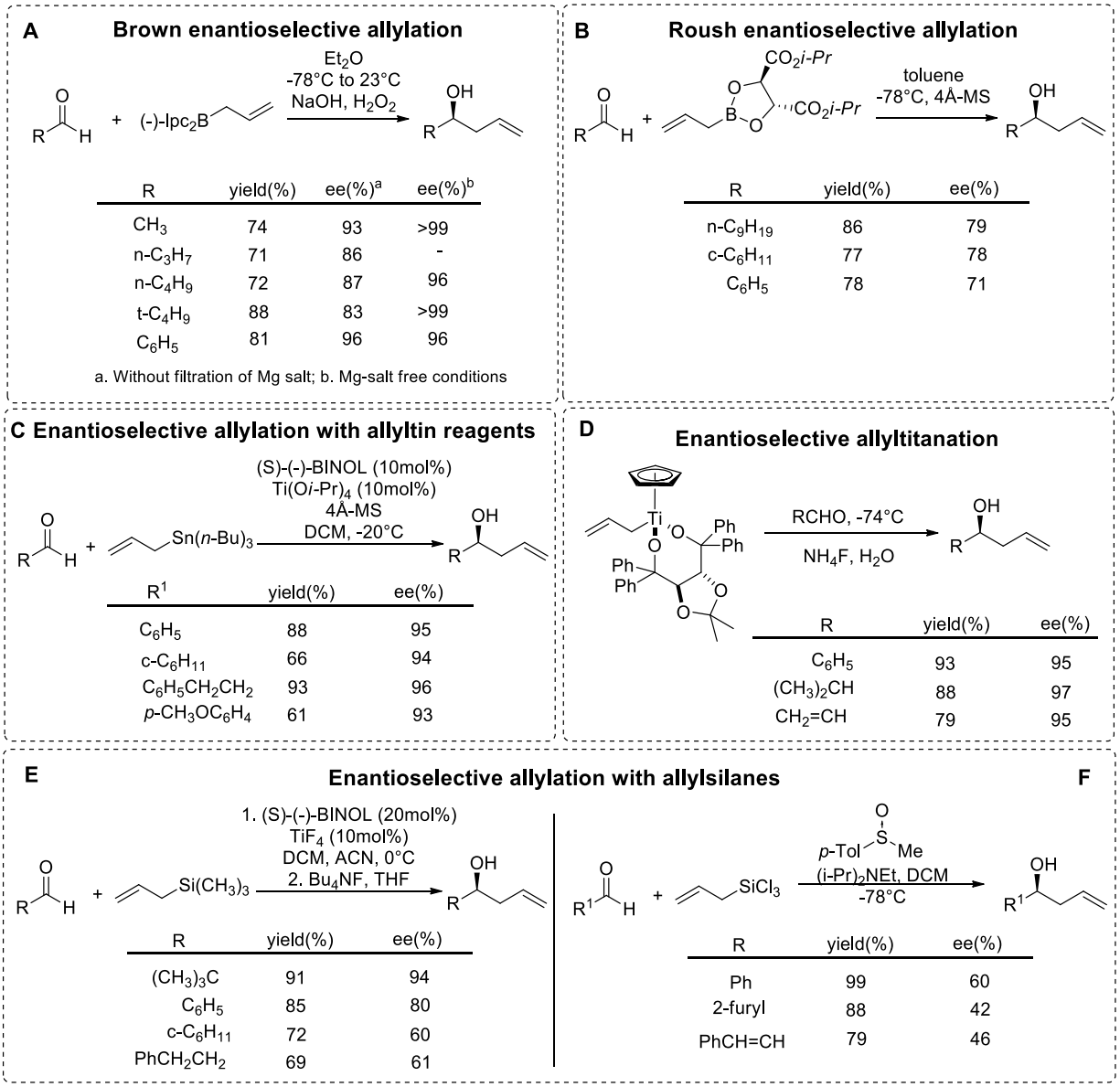
The enantioselective allylation of aldehydes represents one of the most investigated reaction to obtain chiral homoallylic alcohols[141], useful building blocks for the synthesis of more complex molecules as well as natural products.[142]

The first example of the enantioselective synthesis of homoallylic alcohols was reported by R. W. Hoffman in 1978, he studied the reaction between aliphatic aldehydes and (+)-camphor allylboronic ester derivatives.[143] After this report, other research groups worked on this very useful reaction.[141] Importantly, H.C. Brown, for example, reported the application of *β*-allyldiisopinocamphenylborane [144] to the enantioselective allylation with excellent enantioselectivities. Besides W.R. Roush examined the reaction of diisopropyltartrate allylboronate derivatives with aldehydes.[145] Compared to allylborane derivatives, also allylstannanes [146] and allylsilanes [147] have proven to be very efficient reagents in the enantioselective allylation of aldehydes. Lewis acid (Sakurai and Hosomi) [148] and Lewis base (Denmark [149] and Kobayashi[150]) catalyzed enantioselective allylations with organosilicate intermediates. Moreover, with the

[141] Fleming, I.; Trost, B. M. *Comprehensive organic synthesis: selectivity, strategy, and efficiency in modern organic chemistry*; Elsevier: Amsterdam, **1991**.
[142] Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2008**, *47* (9), 1560–1638.
[143] Herold, T.; Hoffmann, R. W. *Angew. Chem. Int. Ed. Engl.* **1978**, *17* (10), 768–769.
[144] a) Kramer, G. W.; Brown, H. C. *J. Org. Chem.* **1977**, *42* (13), 2292–2299. b) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51* (4), 432–439. c) Brown, H. C.; Singaram, B. *J. Org. Chem.* **1984**, *49* (5), 945–947. d) Brown, H. C.; Desai, M. C.; Jadhav, P. K. *J. Org. Chem.* **1982**, *47* (26), 5065–5069. e) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56* (1), 401–404.
[145] a) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107* (26), 8186–8190. b) Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108* (2), 294–296. c) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112* (17), 6348–6359.
[146] a) Boldrini, G. P.; Lodi, L.; Tagliavini, E.; Tarasco, C.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1987**, *52* (24), 5447–5452. b) Keck, G. E.; Krishnamurthy, D. *Org. Synth.* **1998**, *75*, 12.
[147] a) Chan, T. H.; Wang, D. *Tetrahedron Lett.* **1989**, *30* (23), 3041–3044. b) Gauthier, D. R.; Carreira, E. M. *Angew. Chem. Int. Ed. Engl.* **1996**, *35* (20), 2363–2365.
[148] Fleming, I.; Dunoguès, J.; Smithers, R. In *Organic Reactions*; John Wiley & Sons, Inc., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, USA, **1989**; pp 57–575.
[149] Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59* (21), 6161–6163.
[150] Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59* (22), 6620–6628.

development of organotitanium chemistry, a series of enantioselective allyltitanation were also described (Hafner and Cossy).[151]

In the following schemes are briefly reported enantioselective methodologies for allylation that will be also used for our synthetic purpose.



R	yield(%)	ee(%)[a]	ee(%)[b]
CH_3	74	93	>99
n-C_3H_7	71	86	-
n-C_4H_9	72	87	96
t-C_4H_9	88	83	>99
C_6H_5	81	96	96

a. Without filtration of Mg salt; b. Mg-salt free conditions

R	yield(%)	ee(%)
n-C_9H_{19}	86	79
c-C_6H_{11}	77	78
C_6H_5	78	71

R^1	yield(%)	ee(%)
C_6H_5	88	95
c-C_6H_{11}	66	94
$C_6H_5CH_2CH_2$	93	96
p-$CH_3OC_6H_4$	61	93

R	yield(%)	ee(%)
C_6H_5	93	95
$(CH_3)_2CH$	88	97
CH_2=CH	79	95

R	yield(%)	ee(%)
$(CH_3)_3C$	91	94
C_6H_5	85	80
c-C_6H_{11}	72	60
$PhCH_2CH_2$	69	61

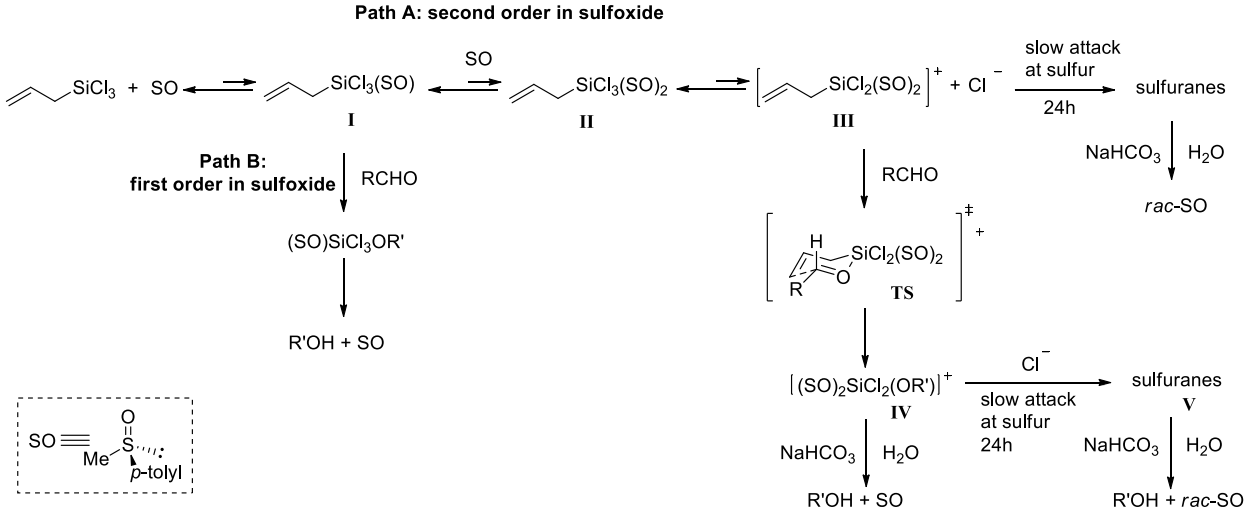
R	yield(%)	ee(%)
Ph	99	60
2-furyl	88	42
PhCH=CH	79	46

Scheme 4-27 Methodologies for enantioselective allylations

[151] a) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114* (7), 2321–2336. b) BouzBouz, S.; Cossy, J. *Org. Lett.* **2000**, *2* (4), 501–504. c) BouzBouz, S.; Cossy, J. *Org. Lett.* **2000**, *2* (25), 3975–3977.

4.1.3.3.1 Allylation with sulfoxide as chiral auxiliary

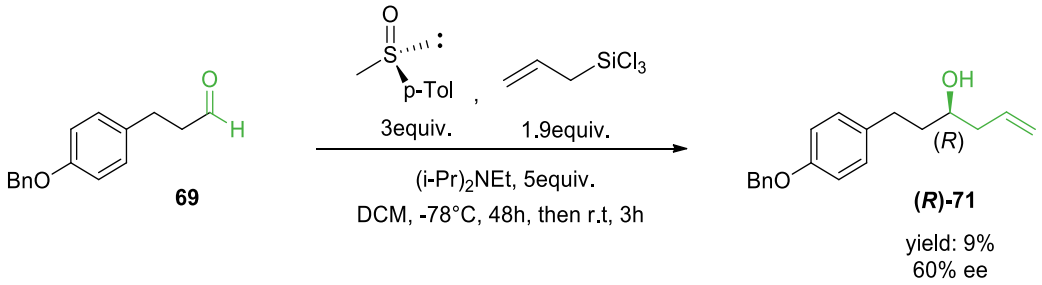
To perform the enantioselective allylation on 3-(4-(benzyloxy)phenyl)propanal **69**, we choose at first the methodology reported by Massa A. et *al*[152] in which the allylation of an aldehyde was undergone in presence of a chiral sulfoxide as a Lewis base and allyltrichlorosilane. As reported in **Scheme 4-27**, confition **F**, the enantiomeric excess of the homoallylic alcohols prepared with this methodology remains moderate (not exceed 60%*ee*).The detailed study of the reaction conditions from the authors showed that the use of *p*-tolylmethylsulfoxide in presence of diisopropylethylamine allowed to avoid the rapid decomposition of the sulfoxide and so the inhibition of the allylation. Moreover, mechanism of this reaction was investigated[153] combining kinetic measurements, conductivity analysis and quantum chemical calculations. These studies indicated that the reaction proceeds through a dissociative pathway in which an octahedral cationic complex with two sulfoxides is involved (**TS**) and that the lack of turnover is due to the formation of neutral sulfurane derivatives (**Scheme 4-28**).



Scheme 4-28 Mechanism proposed by Massa et al. for the enantioselective allylation with a chiral sulfoxide

Despite the moderate *ee* reported for this reaction we decided to try the conditions reported by Massa et *al.* considering that they were never applied to aldehyde such as **69**. As depicted in **Scheme 4-29**, the reaction was stopped after 51h to obtain only 9% of desired product with a moderate enantiomeric excess (60%*ee*).

[152] Massa, A.; Malkov, A. V.; Kočovský, P.; Scettri, A. *Tetrahedron Lett.* **2003**, *44* (38), 7179–7181.
[153] Monaco, G.; Vignes, C.; De Piano, F.; Bosco, A.; Massa, A. *Org. Biomol. Chem.* **2012**, *10* (48), 9650.

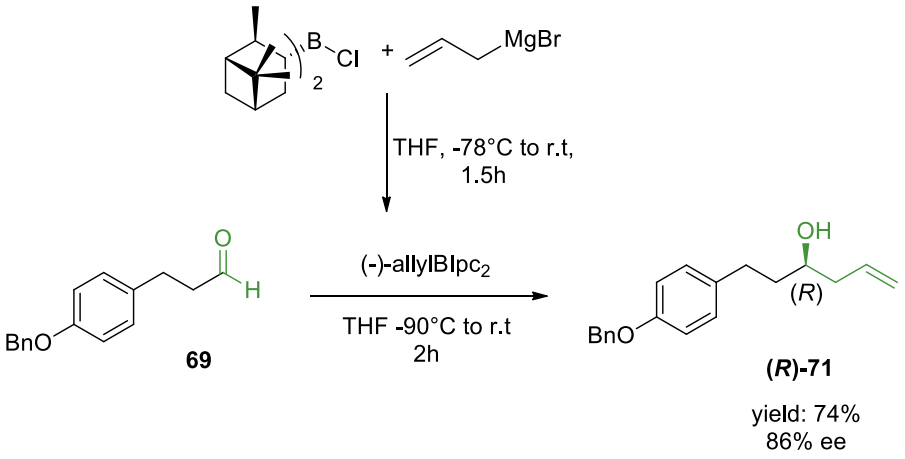


Scheme 4-29 Enantioselective allylation with chiral sulfoxide

Unfortunately, these conditions didn't afford good results in term of yield and enantiomeric excess. For this reason we didn't investigate further this methodology and we tried the wellknown enantioselective Brown's allylation.

4.1.3.3.2 Brown's allylation

Brown asymmetric allylation is one of the most frequently used enantioselective allylation in literature. B-allyldiisopinocamphenylborane ($Ipc_2B\text{-}CH_2CH{=}CH_2$) has been already used on the aldehyde **69** to obtain the corresponding pure homoallylic alcohol in high yield and enantiomeric excess.[154]



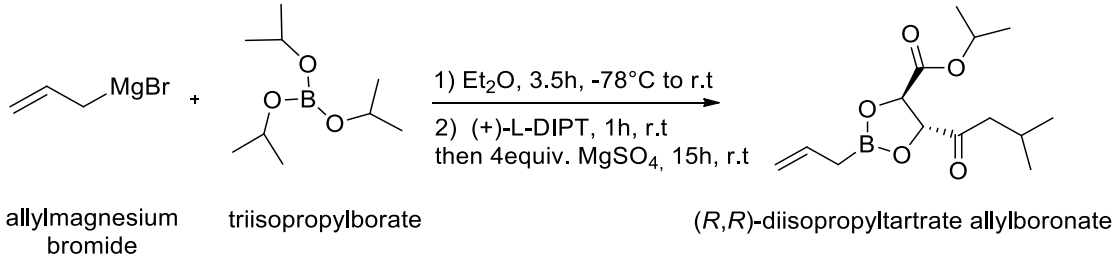
Scheme 4-30 Brown enantioselective allylation

As reported in **Scheme 4-30**, the (-)-B-allyldiisopinocamphenylborane was initially prepared at -78°C from allylmagnesium bromide and (-)-chlorobis({2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl})borane. To this solution cooled at -90°C was added dropwise the aldehyde **69** and after 2h of reaction, the desired (*R*)-homoallylic alcohol (*R*)-**71** was obtained with in 74% yield and 86% *ee*.

[154] a) Álvarez-Bercedo, P.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2006**, *62* (41), 9641–9649.
b) Voigt, T.; Gerding-Reimers, C.; Ngoc Tran, T. T.; Bergmann, S.; Lachance, H.; Schölermann, B.; Brockmeyer, A.; Janning, P.; Ziegler, S.; Waldmann, H. *Angew. Chem. Int. Ed.* **2013**, *52* (1), 410–414. c) Jennings, M. P.; Clemens, R. T. *Tetrahedron Lett.* **2005**, *46* (12), 2021–2024.

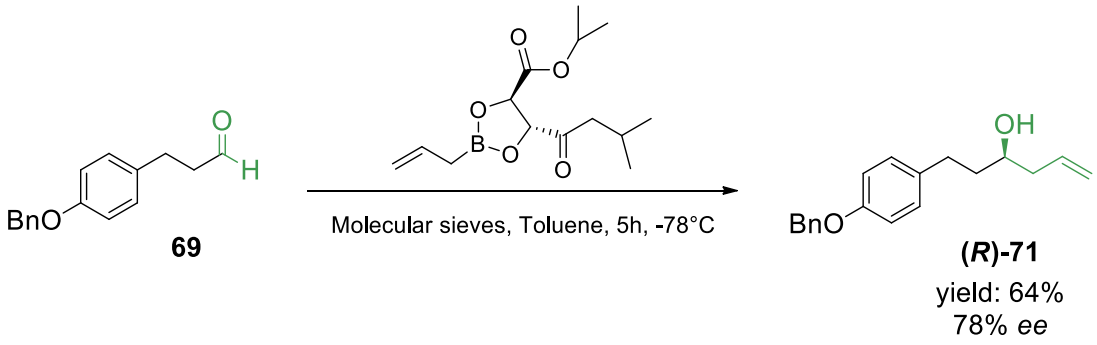
4.1.3.3.3 Roush allylation

Roush allylation was also tried on aldehyde **69**. In a first step (*R*,*R*)-diisopropyltartrate allylboronate was formed in presence of commercial allylmagnesium bromide, triisopropylborate and and (+)-diisopropyl L-tartrate [(+)-L-DIPT][155] (**Scheme 4-31**).



Scheme 4-31 (*R*,*R*)-diisopropyltartrate allylboronate preparation

To the crude (*R*,*R*)-diisopropyltartrate allylboronate treated with 4-Å molecular sieves in toluene, was added dropwise a solution of 3-(4-(benzyloxy)phenyl)propanal **69** in toluene. The reaction stirred for 5h gave after purification the desired (*R*)-**71** with 64% yield and 78%*ee* (**Scheme 4-32**).



Scheme 4-32 Roush enantioselective allylation

As the results with Roush's methodology were not satisfying, we decided to use the efficient allyltitanation reported by J. Cossy.

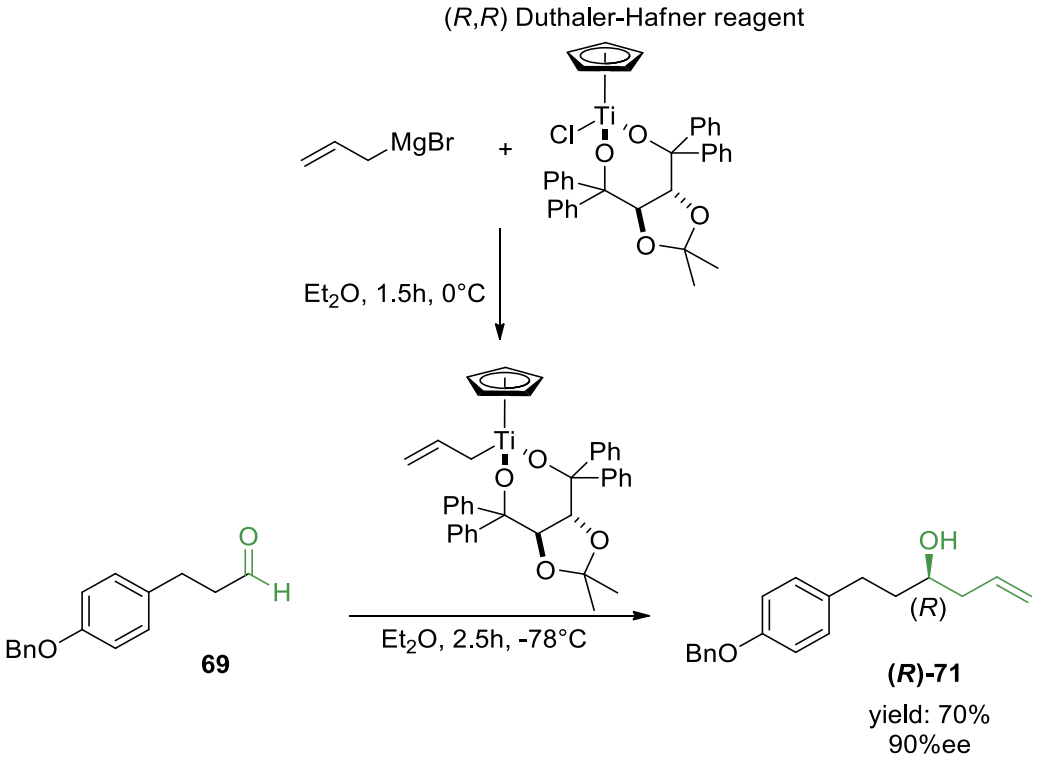
[155] Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Park, J. C. *J. Org. Chem.* **1990**, *55* (13), 4109–4117.

4.1.3.3.4 Enantioselective allyltitanation

Enantioselective allyltitanation of aldehyde **69** was already described with allyltributylstannane in presence of BINOL /(*i*-PrO)$_4$Ti[156] or [1,1'-Binaphthalene]-2,2'-diol/(*i*-PrO)$_4$Ti[157].

Cossy et *al*. reported the efficient enantioselective allyltitanation with the (*S*,*S*) Duthaler-Hafner reagent on a differently protected aldehyde **69** (TBS instead of Bn).[158]

In our case allylmagnesium bromide with (*R*,*R*) Duthaler-Hafner reagent in Et_2O and after the formation of the allyltitanium species, aldehyde **69** was added. Purification of crude afforded the desired (*R*)-**71** with a very good yield (70%) and an excellent enantiomeric excess (90%*ee*).



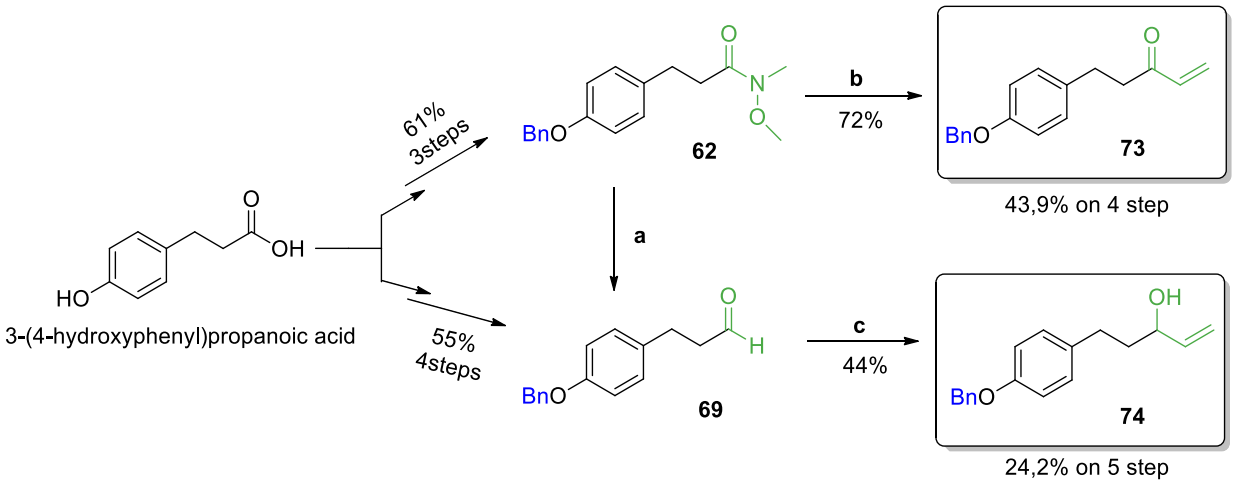
Scheme 4-33 Enantioselective allyltitanation

[156] Chinnababu, B.; Reddy, S. P.; Rao, C. B.; Rajesh, K.; Venkateswarlu, Y. *Helv. Chim. Acta* **2010**, *93* (10), 1960–1966.
[157] Rogano, F.; Rüedi, P. *Helv. Chim. Acta* **2010**, *93* (7), 1281–1298.
[158] Cornil, J.; Gonnard, L.; Guérinot, A.; Reymond, S.; Cossy, J. *Eur. J. Org. Chem.* **2014**, *2014* (23), 4958–4962.

4.1.4 Synthesis of fragments 73 and 74 bearing an α,β-unsaturated ketone or alcohol

After the preparation of E type's fragments, useful as precursors of myricanol, we tried to prepare using the same methodology the fragments bearing an α,β-unsaturated ketone **73** or alcohol **74** that could give access to analogues of myricanol.

We employed Weinreb amide **62** and aldehyde **69** (whose preparation has been already described) in reaction with vinylmagnesium bromide to afford the corresponding α,β-unsaturated ketone **73** and the allylic alcohol **74** (**Scheme 4-34**).



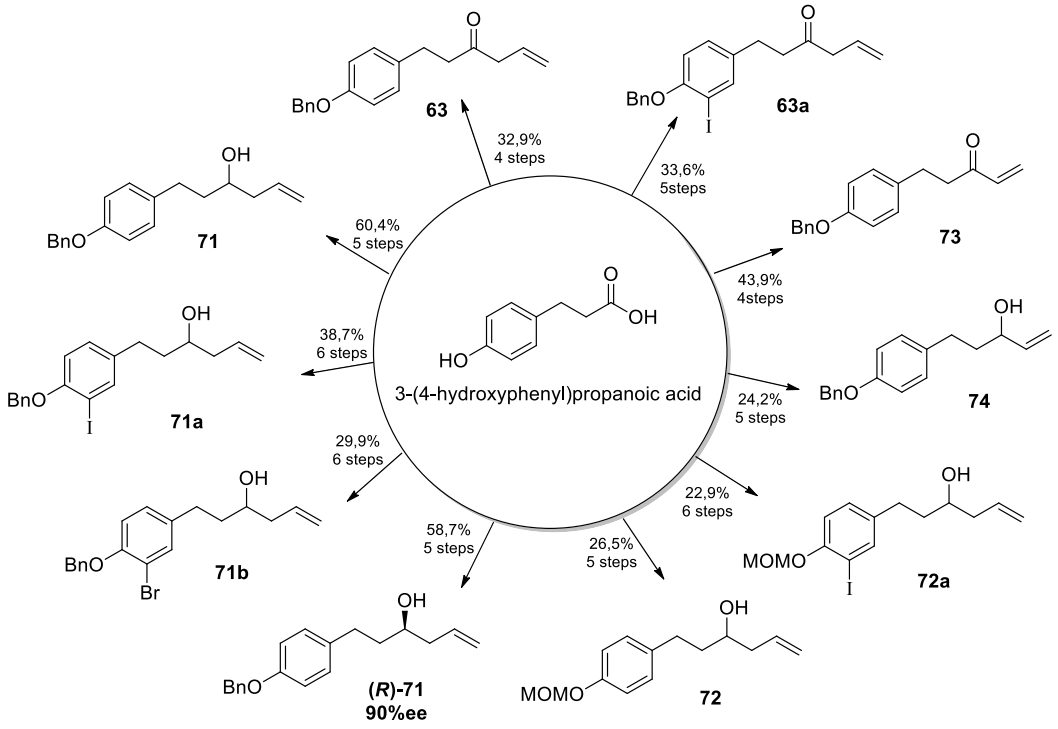
Scheme 4-34 Synthesis of fragments 73 and 74

The product **73** and **74** were obtained with acceptable yields (72% and 44% respectively and considering the last synthesis step) and due to their 5 atom carbon's chain, they constitute synthetic precursors of linear diarylhexanoid compounds which could be obtained by a cross metathesis reaction with allyl benzene derivatives (see 4.2.1).

4.1.5 Conclusion on the synthesis of E type fragments

In the following figure are reported all the advanced **E** type fragments that we prepared starting from the starting common substrate 3-(4-hydroxyphenyl)propanoic acid.

All these fragments constitute important synthetic precursors of myricanol or their analogues.



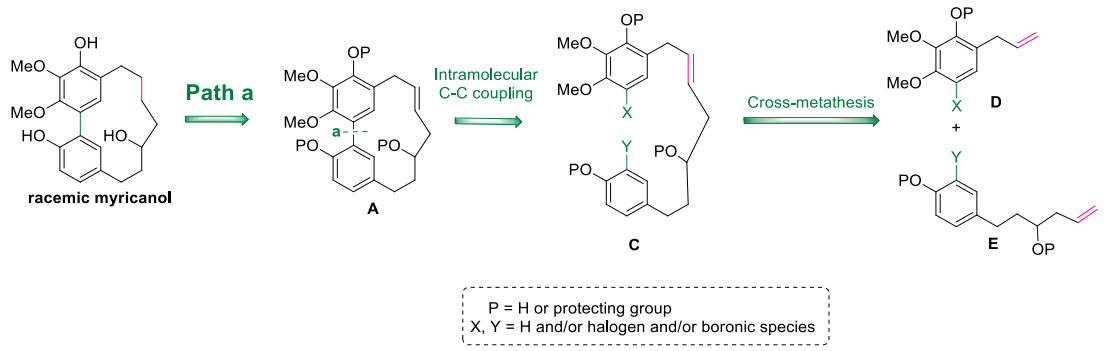
Scheme 4-35 Fragments E type summary

4.2 PATH A : MACROCYCLIZATION BY BIARYL FORMATION

As illustrated above, the **D** and **E** fragments, useful for the total synthesis of myricanol, were prepared and we are now able to couple them.

Considering the retrosynthetic approach discussed on paragraph 3.1, the **D** type and **E** type fragments could be involved in two different paths: the first one in which they are used to form first the linear chain (path a) and the second one in which the prepared fragments are used to install first the biaryl core of myricanol (path b).

Now, we will focus our attention on the "path a" that is depicted in the **Scheme 4-36**. From this path we expected to obtain myricanol from the macrocylization to [7,0]-*meta*cyclophane **A**, involving a biaryl coupling of linear diarylheptanoid **C**, which would be obtained from cross-metathesis reaction of fragments **D** and **E**.



Scheme 4-36 Path a= intramolecular macrocyclization and cross-metathesis

The formation of carbon-carbon double bonds by olefin metathesis is among the most powerful and applicable synthetic tool of modern organic chemistry.[159] In particular, cross-metathesis (CM) reactions which can be formally described as the intermolecular mutual exchange of alkylidene (or carbene) fragments between two olefins promoted by ruthenium-based catalysts, have been widely utilized in the synthesis of natural products.[160] As in the case of most transformations, the two most important questions concerning any CM reaction are those of efficiency and selectivity. The goal is to achieve high yields of the cross-product with minimal amount of competiting dimerization products. In the majority of CM reactions (particularly when the produced olefin is an intermediate of a total synthesis) *E/Z* selectivity is

[159] Chauvin, Y. *Angew. Chem. Int. Ed.* **2006**, *45* (23), 3740–3747.

[160] *Metathesis in natural product synthesis: strategies, substrates and catalysts*; Cossy, J., Arseniyadis, S., Meyer, C., Eds.; Wiley-VCH: Weinheim, **2010**.

also a crucial issue.[106] Alongside their efforts, many research groups contributed, since decades, to the discovery of new and more efficient catalysts, in term of activity, selectivity and tolerance to different functional groups.

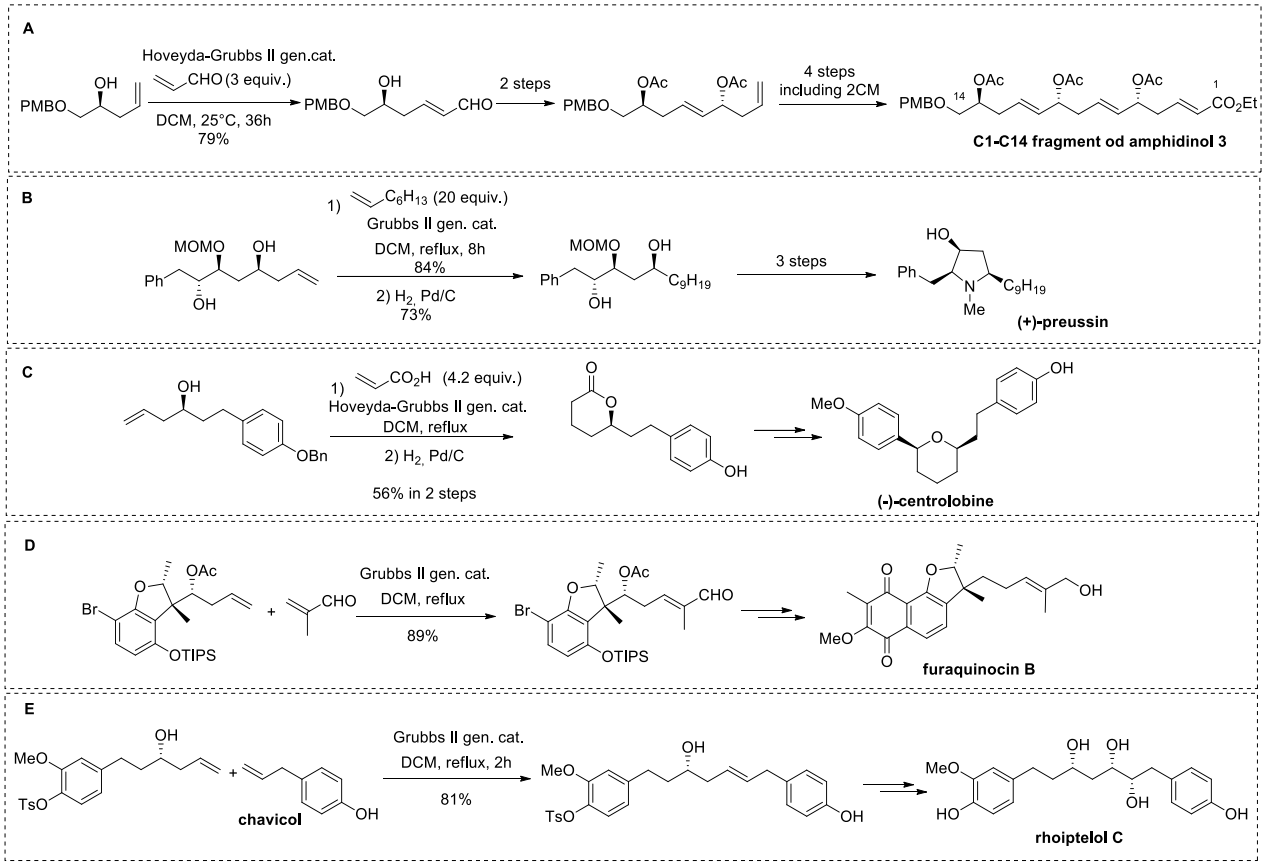
The coming paragraph will give a detailed description of our efforts and extensive experimentation to this reaction as an efficient tool for the preparation of our coupling precursor **C.**

4.2.1 PREPARATION OF LINEAR DIARYLHEPTANOIDS BY CROSS-METATHESIS REACTION

Considering the Grubbs classification of terminal olefins (paragraph 3.3.1) and the keys fragments identified for the total synthesis of myricanol, we can classify the allylbenzene derivatives **D** as a type I olefin and the homoallylic alcohols **E** as a type II olefin, both of them generally exhibiting a good CM reactivity. Since the cross-metathesis partners chosen for the formation of the linear chain belong to different classes, the use of an excess of the easily homodimerizable type I (olefin **D** fragment) compared to the less homodimerizable type II (olefin **E** fragment) is mandatory.

The well-known good reactivity of homoallylic alcohols in cross-metathesis justified their wide use as intermediates in total synthesis. For example Cossy and BouzBouz reported the employment of free homoallylic alcohols in the frame of preparation of C1-C14 fragment of amphidinol 3, [161] for the total synthesis of (+)-preussin[162] or for the total synthesis of (-)-centrolobine[163] (**Scheme 4-37**, **A**, **B** and **C**). In these reports, cross-metathesis reactions were usually performed with Grubbs II catalyst at room temperature or reflux in DCM, affording the desired coupling products in good yield. Trost et *al*. reported the total synthesis of furaquinocin B *via* cross-metathesis of an acetylated homoallylic alcohol and metacrolein using such conditions[164] (**Scheme 4-37**, **D**). Venkateswarlu et *al.* efficiently cross-coupled in the presence of Grubbs II catalyst, an aromatic homoallylic alcohol and cavichol (*para*-hydroxyallylbenzene) within 2h in refluxing DCM for the synthesis of rhoiptelol C[165] (**Scheme 4-37**, **E**).

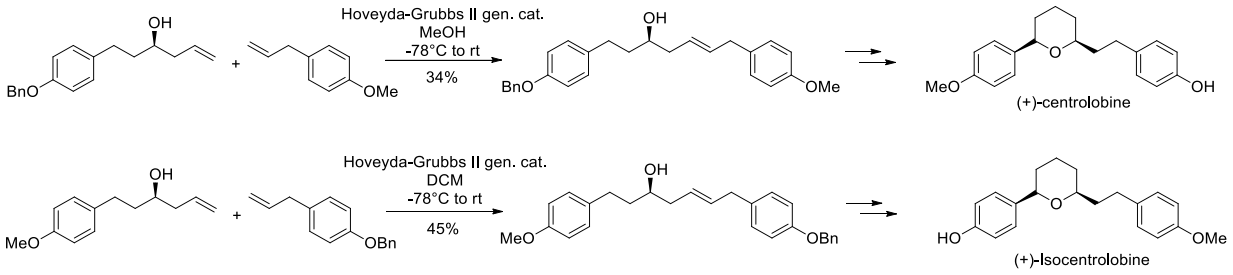
[161] BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3* (10), 1451–1454.
[162] Canova, S.; Bellosta, V.; Cossy, J. *Synlett* **2004**, *10*, 1811–1813.
[163] Boulard, L.; BouzBouz, S.; Cossy, J.; Franck, X.; Figadère, B. *Tetrahedron Lett.* **2004**, *45* (35), 6603–6605.
[164] Trost, B. M.; Thiel, O. R.; Tsui, H.-C. *J. Am. Chem. Soc.* **2003**, *125* (43), 13155–13164.
[165] Purushotham Reddy, S.; Chinnababu, B.; Venkateswarlu, Y. *Helv. Chim. Acta* **2014**, *97* (7), 999–1003.



Scheme 4-37 Examples of homoallylic alcohols employed in CM

To the best of our knowledge, only two examples of CM reactions involving homoallylic alcohols carried out at -78°C have been described in litterature. Indeed, Ruëidi et Rogano reported in their synthesis of (+) and (-)-centrolobine[166] and (+) and (-)-isocentrolobine.[167] a CM between a *para*-disubstituted aromatic homoallylic alcohol and a *para*-methoxy allylbenzene promoted by the Hoveyda-Grubbs II catalyst. They surprisingly disclosed that the CM was ineffective at room temperature or in refluxing DCM and alternatively observed acceptable yields when the catalyst was added at -78°C (**Scheme 4-38).**

[166] Rogano, F.; Rüedi, P. *Helv. Chim. Acta* **2010**, *93* (7), 1281–1298.
[167] Rogano, F.; Froidevaux, G.; Rüedi, P. *Helv. Chim. Acta* **2010**, *93* (7), 1299–1312.



Scheme 4-38 Examples of CM at -78°C

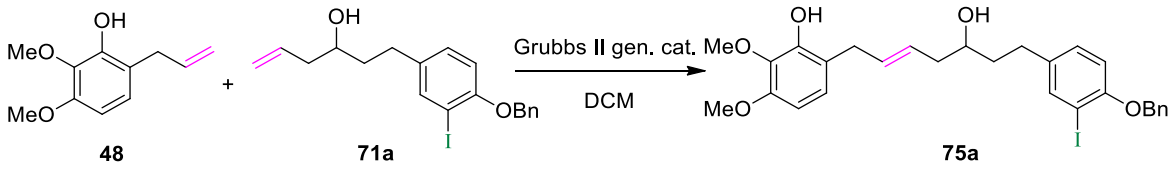
Taking into account this literature background, the homoallylic alcohols**71** (**Table 4-8**) or **71a** (**Table 4-9**) and allylphenol **48** were subjected to similar conditions (Grubbs-II catalyst in DCM, they use Hoveyda Grubbs). Some other experiments have been carried out with small modifications, such as stoichiometry (based on one equivalent of the most elaborated partners **71** or **71a**), catalyst loading or reaction time and temperature. As previously mentioned, since **48** was promoted to homodimerization (type I olefin), it had to be use in excess in order to improve the yield of cross-coupling product.

It has to be noted that regarding the second principle of green chemistry, atom economy introduced in the early 1990 by Trost and Sheldon to emphasize the importance of minimizing the waste, the olefin **48** used in excess is easily prepared in just two quantitative steps and it could be also recovered at the end of reaction to be employed in a new process.

The outcomes of CM reactions between homoallylic alcohol **71a** and allylphenol **48** are consigned in **Table 4-8**.

The CM reactions were performed using Grubbs II generation catalyst, DCM as solvent and fixing the equivalent of homoallylic alcohol **71a** employed to 1. The equivalents of **48** and catalyst, the temperature and the reaction time constitute the parameters on which we worked to optimize reaction conditions.

3 or 15% of catalyst were first added to a DCM solution of **71a** and 4 equivalents of allyl phenol **48** at room temperature (**Table 4-8**, entries 1 and 2). The mixtures were warmed until DCM reflux and after 3.5h, work up and purification lead to only 35 and 40% yields respectively along with 10% of the isomerized CM coupling product bearing an α,β unsaturated alcohol. When the reaction was performed at room temperature (**Table 4-8,** entry 3), we observed a slight improvement of the yield compared to the precedent trials.



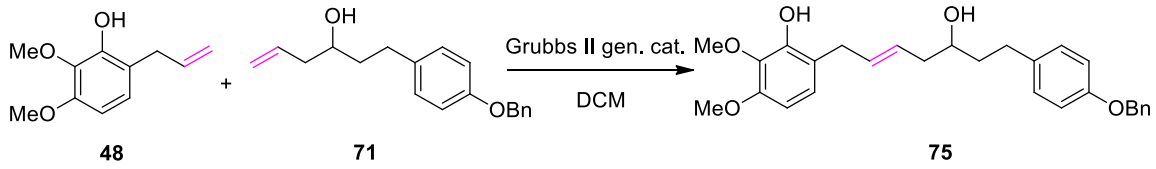
Entry	48	71a	Grubbs II (mol%)	Temperature	Time	75a (yield)[c]
1	4 equiv.	1 equiv.	3	r.t. to reflux	3,5h	35%[a]
2	4 equiv.	1 equiv.	15	r.t. to reflux	3.5h	40%[a]
3	4 equiv.	1 equiv.	15	r.t.	24h	45%
4	4equiv.	1 equiv.	5+5[b]+5[b]	-78°C to r.t.	36h	70%
5	4equiv.	1 equiv.	30	-78°C to r.t.	24h	62%
6	4equiv.	1 equiv.	30+10[c]	-78°C to r.t.	24h	71%
7	3 equiv.	1 equiv**.**	15	-78°C to r.t.	24h	59%
8	5 equiv.	1 equiv.	15	-78°C to r.t.	24h	82%
9	5 equiv.	1 equiv.	20+5[b]	-78°C to r.t.	24h	62%
10	5+1 equiv.[b]	1 equiv.	30	-78°C to r.t.	24h	52%

a. 10% of isomerized CM product with α,β unsaturated alcohol; b. added at rt after 12 h; c. *E/Z* ratio : 93/7 determined by ^{1}H NMR.

Table 4-8 Attempts of CM reaction between 48 and 71a

Considering the work described by Ruëidi and Rogano, we started to investigate a series of reaction in which Grubbs II catalyst was added at -78°C. Pleasingly, when the reaction mixture was warmed to room temperature following the catalyst addition at -78°C, the coupling displayed an obvious surge in yields whatever any modulation of the other reaction parameters (**Table 4-8**, entries 4-10). Eventually the optimized yields were obtained for 24h of stirring of 5 equivalents of **48** in the presence of 15mol% of Grubbs II catalyst (**Table 4-8**, entry 8). We isolated in this case the coupling product in a yield up to 82% which was not improved by using larger amounts of catalyst and/or **48** (**Table 4-8**, entry 9,10).

On the other hand, analogous metathesis reactions have been simultaneously performed, involving homoallylic alcohol **71** (**Table 4-9**). A first set of experiments has been performed by adding Grubs-II or Grubs-Hoveyda catalysts (15%) at room temperature on a 4/1 mixture of **71** and **48** in DCM and warmed to reflux, affording modest yields of olefin **75** spanning from 31% to 53% (**Table 4-9**, entry 1 and 2). In the line of the CM of **71a** previously disclosed (**Table 4-8**), a considerable improvement was observed when the same reaction was repeated at -78°C giving the coupling product in 70% yield (**Table 4-9**, entry 3).



48 **71** **75**

Entry	48	71	Grubbs II (mol%)	Temperature	Time	75 (yield)[c]
1	4 equiv.	1 equiv.	15	r.t. to reflux	5h	53%[a]
2	4 equiv.	1 equiv.	15[b]	r.t. to reflux	3.5h	31%[c]
3	4 equiv.	1 equiv.	15	-78°C to r.t	24h	70%
4	4 equiv.	1 equiv.	10	-78°C to r.t	24h	72%
5	4 equiv.	1 equiv.	5	-78°C to r.t	24h	78%
6	3 equiv.	1 equiv.	5	-78°C to r.t	24h	61%
7	4 equiv.	1 equiv.	3	-78°C to r.t	24h	81%
8	4 equiv.	1 equiv.	3	r.t	24h	35%

a.10% of isomerized CM product with α,β unsaturated alcohol; b. Hoveyda-Grubbs was employed; c. *E/Z* ratio : 93/7 determined by ^{1}H NMR.

Table 4-9 Attempts of CM between 48 and 71

With the aim to reduce the amount of the expensive Grubbs II catalyst, further reactions were performed by addition of 5 or 3 mol% of catalyst (**Table 4-9**, entry 5 and 7) at -78°C and subsequent stirring at room temperature to afford the coupling product **75** in excellent yields (78% and 82% respectively). One more time, we observed that the same reaction performed directly at room temperature lead to a drastic drop of the yield (**Table 4-9**, entry 8).

^{1}H NMR analysis of the coupling products **75a** and **75** revealed a stereoisomeric ratio *E/Z*: 93/7 whatever the reaction conditions used. According to Grubbs[89] observations, about 30-40% of **48** homodimer (**48bis**) and 10-15% of **71** homodimer (**71bis**) were isolated along with the corresponding expected coupling products (**Figure 4-2**).

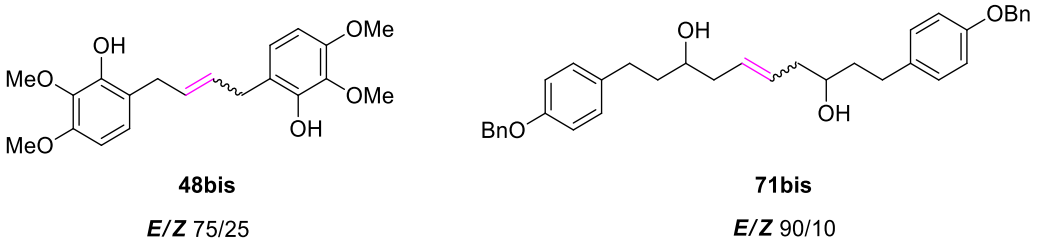


Figure 4-2 Homodimers from CM

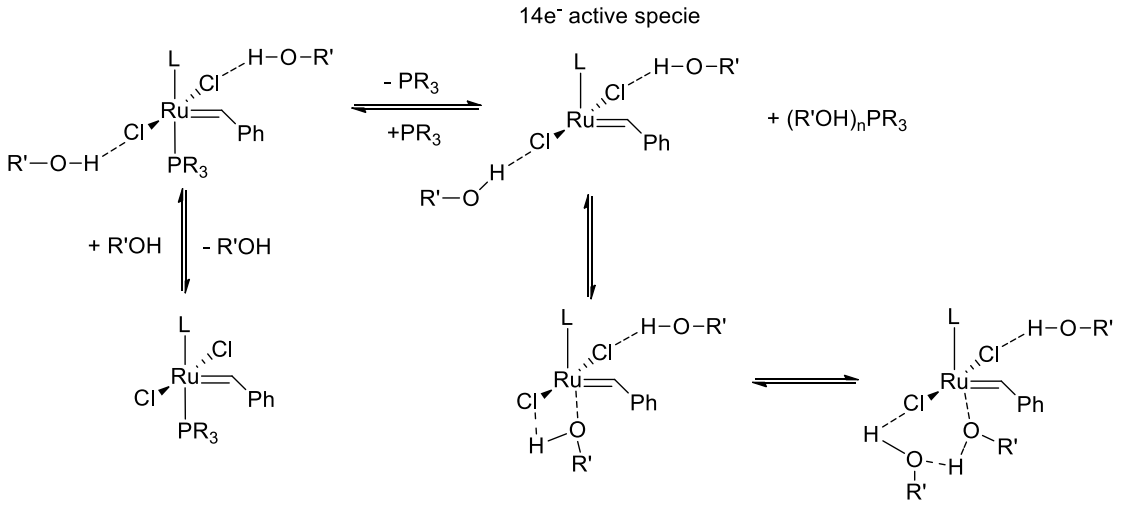
Since CM is a reversible process, we tried to use the homodimer **48bis** as a substrate equivalent to **48** in a CM reaction with **71.** Under the conditions depicted in **Table 4-9** entry 5, product **76** was obtained in 52% yield, showing how the side homodimeric product of the parent reaction (**48bis**) can be recycled and employed in a new CM affording the desired cross-coupling product in good yield.

The cross metathesis described so far have been performed with a low quantity of catalyst in excellent yields on a free homoallylic alcohol (**71** or **71a**) and a C-allyl phenol **48**. Importantly when we tried the CM reaction using acetylated **48** and **71** and following the conditions depicted in entry 5 (**Table 4-9**), the diacetylated cross-coupled product was obtained in only 21% yield. This result suggested that the free OH contributes to the efficiency of the reaction.

The effect of free OH (phenol or alcohol) has been already reported in literature.[90b,168] Formann et *al.* widely described the influence of phenol and free OH in a CM reaction with experiments and mechanistic studies to confirm this hypothesis. [169] Indeed, phenol used as additive in CM reactions allow to improve the yield and this behaviour could be explained by the presence of the free OH giving a hydrogen bond with the chlorine atom of the catalyst. This interaction could be able to favour the decoordination of one phosphine ligand, on the catalyst allowing more efficiently the formation of the active 14-electron species. The hydrogen bond is also involved in the stabilization of the hemilabile 14-electron key intermediate species, avoiding its decomposition and allowing the life extension of the active intermediate catalyst. Free OH are

[168] Lin, Y. A.; Davis, B. G. *Beilstein J. Org. Chem.* **2010**, *6*, 1219–1228.
[169] Forman, G. S.; McConnell, A. E.; Tooze, R. P.; Janse van Rensburg, W.; Meyer, W. H.; Kirk, M. M.; Dwyer, C. L.; Serfontein, D. W. *Organometallics* **2005**, *24* (19), 4528–4542.

substantially responsible to accelerate the initial rate of the process and extend the TON of the catalytic cycle (**Scheme 4-39**).

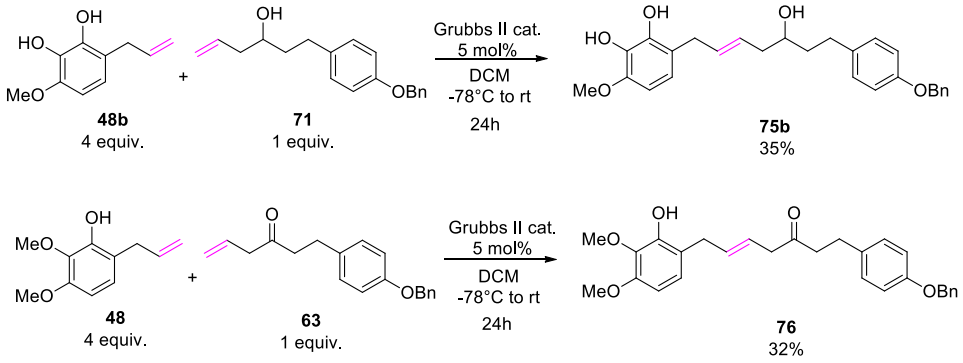


Scheme 4-39 CM enhanced by free OH

After CM investigations[170], **D** and **E** type's fragments already synthesized were employed in CM in order to study their reactivity and to prepare a series of linear analogues of myricanol whose biological activities will be tested in Chapter 5. An essay was realized employing allyl catechol **48b** and homoallylic alcohol **71** (**Scheme 4-40**). The yield of **75b** was really lowered (35%) compared to that obtained using the same conditions with the allyl phenol **48** (78%) (**Table 4-9**, entry 5). This was probably due to the lower solubility of catechol **48b** in DCM at -78°C. Indeed, when a solution of compound **48b** in DCM was cooled at -78°C we started to observe the formation of a quite slurry mixture that became more solid after the addition of catalyst (this situation was never observed with phenol **48**). This situation probably slowed down the reaction rate, which could have been restored when room temperature was reached (slurry solution become limpid and homogenous). The resulting yield of **75b** (35%) is in linear relation with the yield obtained for **75** (35%) when CM was performed at room temperature (**Table 4-9**, entry 8). None homodimerization of **48b** was observed, or maybe, even if it occurred, the product was not isolated after column chromatography, probably due to its high polarity.

[170] The conditions reported in entry 5 (**Table 4-9**) were used for the preparation of linear analogues of **75**, because their synthesis has been performed before we found the best conditions of entry 7 (**Table 4-9**) (3mol% of catalyst).

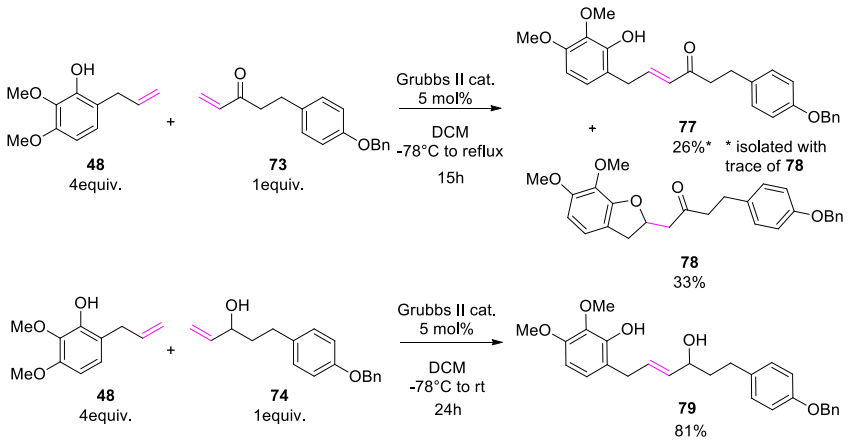
Moreover we studied the reactivity of the β,γ-unsaturated ketone **63** and as already reported in the *Handbook of metathesis*[90a], the oxidized form of homoallylic alcohols are in general less reactive in CM. The diarylheptanoid **76** was recovered with only 32% of yield and none formation of homodimerized **63** was observed, conversely to what observed for the substrate **71** (**Scheme 4-40).**



Scheme 4-40 Preparation by CM of linear diarylheptanoids analogues 75b and 76

The best CM conditions (**Table 4-9,** entry 5) were also applied on substrates **73** and **74** belonging to type II olefins as **71 (Scheme 4-40)**. The essay performed with the vinyl ketone **74** allowed us to isolate two products **77** and **78** after a tricky purification by flash chromatography (almost same retention time on TLC). Analysing and comparing the crude ^{1}H-NMR and the pure obtained fractions after purification, we realized that product **78** wasn't present in crude, but it was probably formed by an intramolecular oxa-Michael cyclization that occurred during the silica gel purification. Therefore we excluded that this cyclization would occur from an olefin cross-metathesis-intramolecular oxa-Michael cascade reaction as reported by You and collaborators who observed this cascade reaction during cross-metathesis with Hoveyda-Grubbs II catalyst of similar substrates.[171] In addition the CM reaction between **48** and the allylic alcohol **74** gave the coupling product in an excellent 81% yield. For both reactions reported in **Scheme 4-41**, none homo-coupling product of vinyl ketone **73** and allylic alcohol **74** was observed, as predicted for type II alkene.[172]

[171] Zhang, J.-W.; Cai, Q.; Gu, Q.; Shi, X.-X.; You, S.-L. *Chem. Commun.* **2013**, *49* (70), 7750.
[172] Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122* (15), 3783–3784.

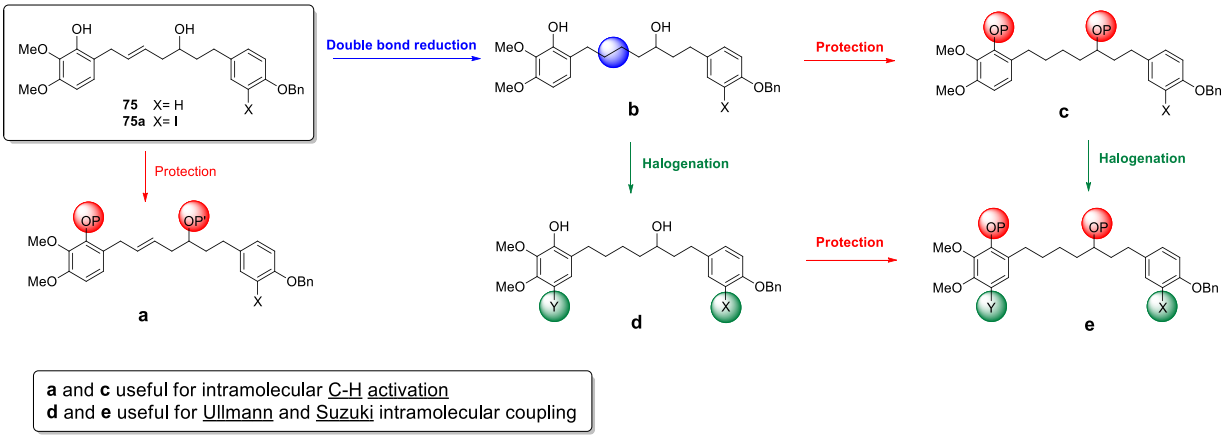


Scheme 4-41 Preparation by CM of linear diarylhexanoids shorter analogues 77, 78 and 79

4.2.2 FUNCTIONALIZATION OF LINEAR DIARYLHEPTANOIDS

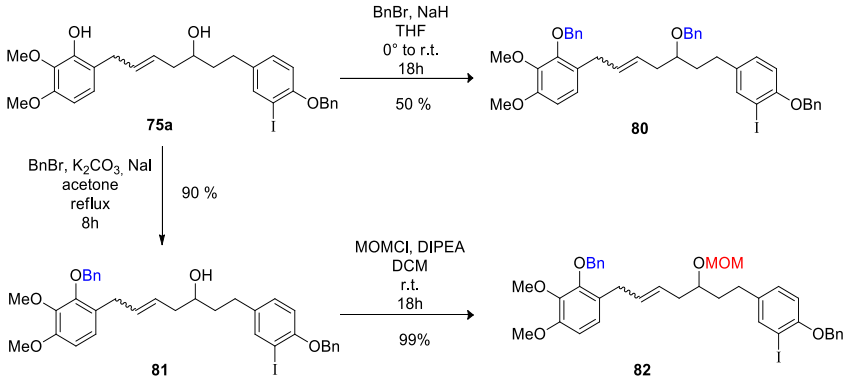
After the preparation of linear diarylheptanoids **75** and **75a,** our attention was focused on the halogenation of their aromatic part which will be involved into an intramolecular biaryl cross-coupling to obtain the desired macrocycle. Indeed, Ullmann, Suzuki macrocyclizations or intramolecular biaryl coupling involving a C-H activation step in presence of aryl halides could be the possible approaches we thought about for the installation of the biaryl moiety.

Scheme 4-42 shows the possible routes to prepare highly functionalized diarylheptanoids. Fragments **75** and **75a** could be protected, monohalogenated, di-halogenated, in presence or absence of the double bond on the chain. For example, monohalogenated derivatives could be used in C-H macrocyclization, while di-halogenated compounds could be involved in Ullmann or Suzuki intramolecular coupling.



Scheme 4-42 Functionalization of linear diarylheptanoids

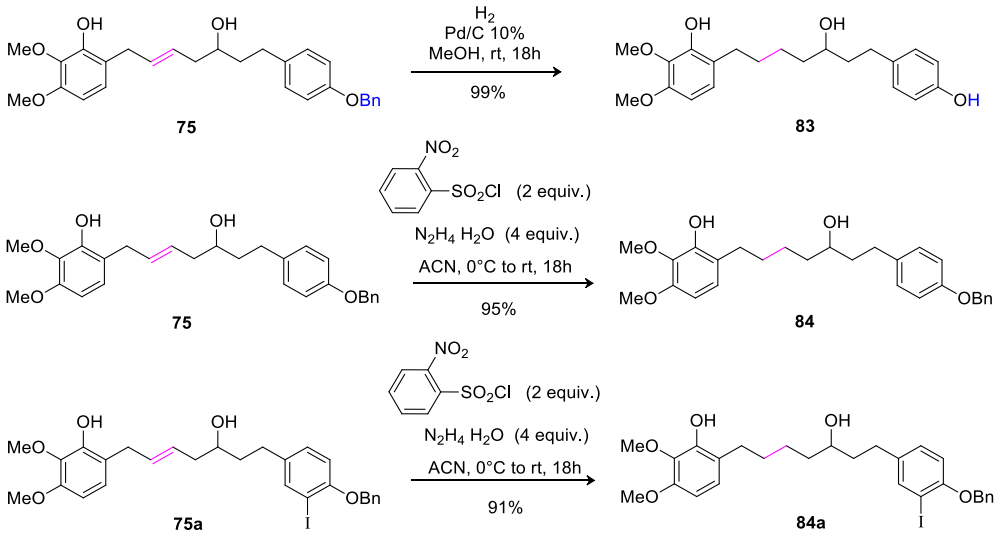
First the protection of the two free OH on **75a** was performed. Benzylation with BnBr and NaH in THF afforded the tribenzylated compound **80** in 50% yield while using BnBr, K_2CO_3 and NaI in acetone allowed a regioselective protection of the phenol giving the dibenzylated compound **81** in 90% yield; the following protection of the secondary alcohol as a methoxymethyl ether gave **82** in high yield (**Scheme 4-43**). These mono-halogenated compounds constitute good candidates to perform the C-H macrocyclization involving a C-H activation step.



Scheme 4-43 OH protection on linear diarylheptanoids

The presence of the unsaturation on the chain of starting fragments **75** and **75a** could interfere with the subsequent halogenation of the aromatic rings. For this reason the hydrogenation of the internal olefins of **75** and **75a** was performed. **Scheme 4-44** clearly shows that the hydrogenated products **83**, **84** and **84a** are easily obtained after 18h of reaction in quantitative yields. However, we have to note that the hydrogenation occured using different methodologies depending on the starting product. For the reduction of the double bond of **75**, classical hydrogenation conditions *i.e.* H_2, Pd/C 10% in MeOH at room temperature was used, affording the reduced and debenzylated linear diarylheptanoid **83**, which could be considered as the first linear analogue of myricanol.[173]

[173] a) Bieg, T.; Szeja, W. *Synthesis* **1985**, *1985* (01), 76–77. b) Rylander, P. N. *Catalytic hydrogenation in organic syntheses*; Academic Press: New York, **1979**.



Scheme 4-44 Double bond reduction of 75 and 75a

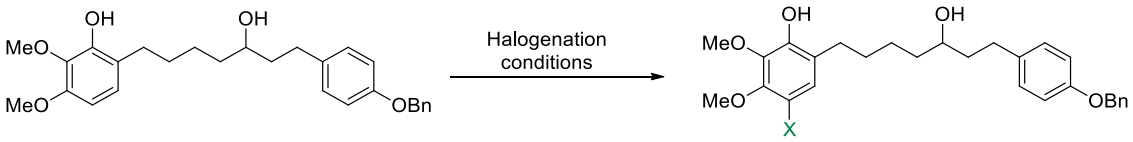
In these conditions the hydrogenolysis favoured also the debenzylation which could be useful if we want to change the protecting group of the benzylated phenol.

For this reason a chemioselective hydrogenation that will not be accompanied with the deprotection of the benzyl group was employed for example the diimide reduction that is widely used in natural product synthesis and that allow to selectively reduce C=C double bond. [174] In our particular case the *cis*-diimide arise from the one-pot formation of 2-nitrobenzenesulfonylhydrazide obtained by mixing hydrated hydrazine and *ortho*-nitrobenzensulfonylchloride, as reported by Carbery and Marsh. [175] Using this methodology, we were able to prepare in excellent yield substrates **84** and **84a.** It's important to observe that with diimide approach we can reduce the double bond in presence of halogen as iodine. The presence on the same molecule of a double bond and iodine prevent the hydrogenation with Pd which prefers to reduce the C-I bond instead of the double bond.

On phenol **84** with the reduced chain, a series of regioselective halogenations were tried in order to prepare compounds **86** and **87**. **Table 4-10** shows the essays of halogenation with Br_2, NBS, I_2 and NIS. We surprisingly discovered that while the brominated **86** was easily obtained (entry 1 and 2), the corresponding iodinated product **87** wasn't isolated using the conditions depicted in entry 3 and 4. Indeed, in presence of NIS only starting material was recollected after 18h of reaction (entry 3). With stronger conditions as I_2 and

[174] Hünig, S.; Müller, H. R.; Thier, W. *Angew. Chem. Int. Ed. Engl.* **1965**, *4* (4), 271–280.
[175] Marsh, B. J.; Carbery, D. R. *J. Org. Chem.* **2009**, *74* (8), 3186–3188.

CF_3CO_2Ag frequently used for the iodination of very electronrich benzene[71], we observed the oxidation of phenol to ~~a~~ dienone, as observed with hypervalent iodine.[176]



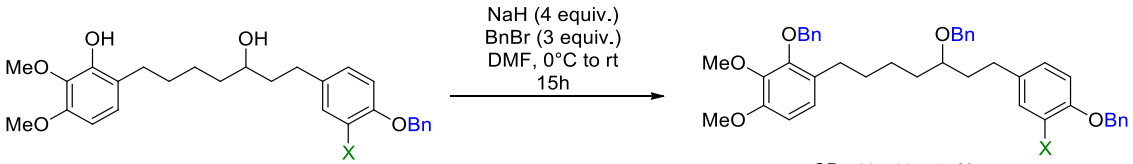
84 **86** X = Br **87** X = I

Entry	Halogenantion Conditions	T	t	Yield	Prod.
1	NBS(1.2equiv.), TFA (0.3 equiv.), ACN	r.t.	18h	90%	**86**
2	Br_2(1.2equiv.), AcOH	r.t.	18h	40%	**86**
3	NIS(1.2equiv.), TFA(0.3equiv.), ACN	r.t.	18h	s.m.	**87**
4	I_2(1.2equiv.), CF_3CO_2Ag(1.2equiv.), $CHCl_3$	-15°C	15min	-[a]	**87**

a. the oxidation of free aromatic phenol was observed

Table 4-10 Halogenation of diarylheptanoid 84

Tests of halogenation were also performed on protected diarylheptanoids **85** and **85a,** obtained in good yield after treatment of **84** and **84a** with benzylbromide and NaH in DMF (**Scheme 4-45**).

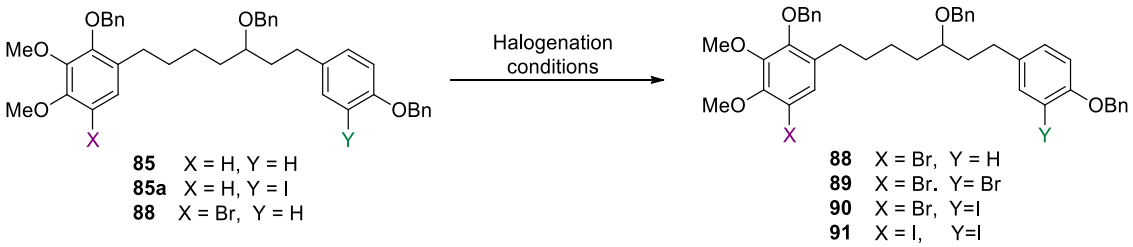


84 X = H **84a** X = I **85** X = H 75% **85a** X = I 71%

Scheme 4-45 Benzylation of linear diarylheptanoids 84 and 84a

The halogenation of **85** and **85a** were performed using NIS and NBS as halogen sources and depending on the starting substrates, we obtained mono or dihalogenated products, with similar or different halogen on the two aromatic rings (**Table 4-11**).

[176] a) Mehta, G.; Maity, P. *Tetrahedron Lett.* **2007**, *48* (50), 8865–8868. b) Quideau, S.; Looney, M. A.; Pouységu, L. *Org. Lett.* **1999**, *1* (10), 1651–1654.



85 X = H, Y = H
85a X = H, Y = I
88 X = Br, Y = H

88 X = Br, Y = H
89 X = Br. Y= Br
90 X = Br, Y=I
91 X = I, Y=I

Entry	S.M.	X	Y	Hal. conditions	T	t	Yield	Product	X	Y
1	**85**	H	H	NBS (1.2 equiv.)[a]	r.t.	18h	99%	**88**	Br	H
2	**88**	Br	H	NBS (1.2 equiv.)[a]	r.t.	18h	99%	**89**	Br	Br
3	**85**	H	H	NBS (2.2 equiv.)[b]	r.t.	18h	99%	**89**	Br	Br
4	**88**	Br	H	NIS(1.2 equiv.)[a]	r.t.	18h	77%	**90**	Br	I
5	**85a**	H	I	NBS(1.2 equiv.)[a]	r.t.	18h	91%	**90**	Br	I
6	**85a**	H	I	NIS(1.2 equiv.)[a]	r.t.	18h	99%	**91**	I	I
7	**85**	H	H	NIS (5equiv.)[c]	r.t.	36h	70%	**91**	I	I

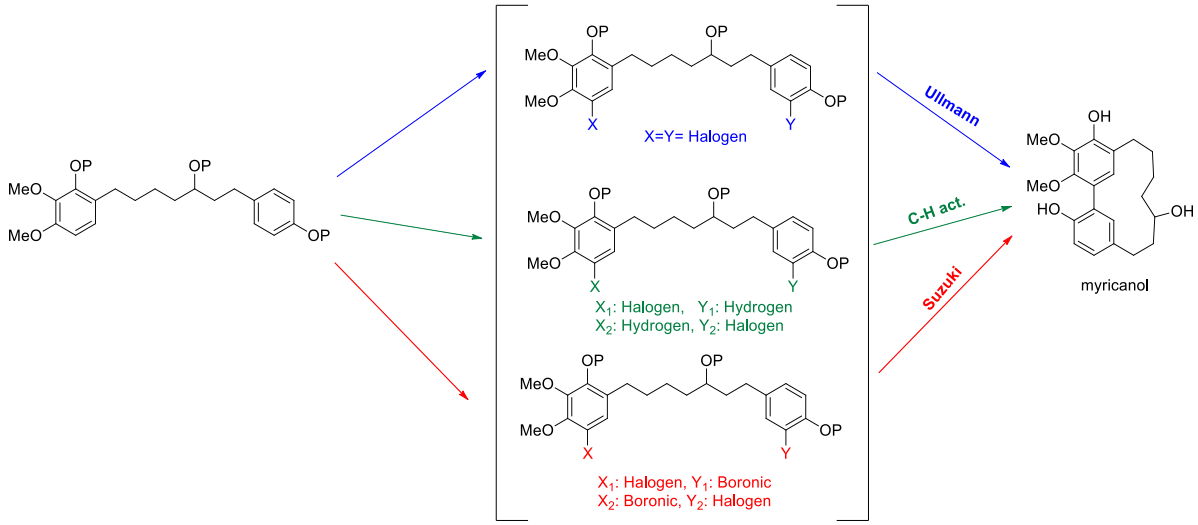
a. the reaction was performed in ACN(0.25M) and using 0.3equiv. of TFA; b. the reaction was performed in ACN(0.25M) and using 0.6equiv of TFA; c. the reaction was started with 2.2 equiv. of NIS, but subsequent addition until 5equiv were done, ACN and TFA employed as usual..

Table 4-11 Halogenation of completely benzylated diarylheptanoids

As illustrated in **Table 4-11** all the reactions performed gave excellent results, showing that halogenations worked in a perfect regioselective way. In entry 1 the mono bromination of the more electronrich ring of **85**, gave **88** in quantitative way. This product could be used in an intramolecular C-H macrocyclization to obtain myricanol macrocycle, or could be used for a second halogenation as reported in entry 2 giving the dibrominated compound **89** in high yield. Due to the good results obtained for the monobromination, we tried to obtain **89** in one step. The reaction reported in entry 3 afforded the desired compound in excellent yield, showing that depending on the number of equivalents of NBS, we are able to obtain the mono or di-brominated product. In entry 4 was reported the iodination of compound **88** which was efficiently transformed giving the bromo-iodinated compound **90** (77%yield). **90** was also obtained by bromination of **85a** (entry 5). We finally tried to synthesize the di-iodinated substrate **91** (entry 6 and 7) which was easily prepared starting from the mono-iodinated **85a**, while starting from **85,** subsequent additions of aliquots of NIS was necessary.

4.2.3 METHODS FOR FOR MACROCYCLIZATION BY BIARYL COUPLING

As already discussed, halogenations of the biaryl moieties is due to the idea to install the biaryl motif of myricanol *via* an intramolecular cross-coupling. The following scheme illustrates the approaches considered to reach the goal.

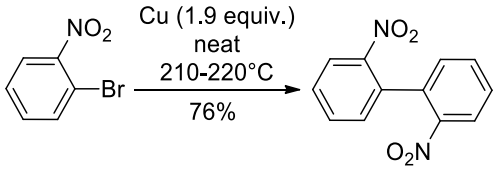


Scheme 4-46 Possible approaches for intramolecular macrocyclization

In the next pages of this thesis will be presented the different approaches tried to conclude the total synthesis of myricanol.

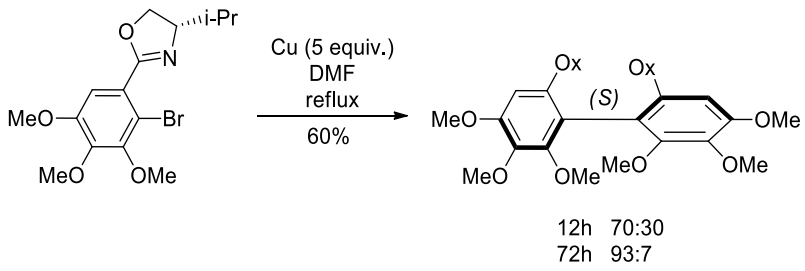
4.2.3.1 Ullmann coupling

The history of copper-promoted aryl–aryl bond formations started when Fritz Ullmann and Jean Bielecki reported in 1901 a copper catalyzed biaryl coupling. They experimented that mixing under neat conditions the *o* -bromonitrobenzene with 1.9 equiv of copper powder at 210–220°C, the homocoupling product was formed (*i.e*. 2,2'-dinitrobiphenyl) in 76% yield with concomitant production of CuBr.[177]



Scheme 4-47 Copper(0)-mediated homocoupling of *o*-bromonitrobenzene

Since then, the Ullmann coupling has been extensively studied, and its applications have been thoroughly reviewed.[178] Due to their cost-effectiveness and environmentally benign characteristics, the interest towards the first-row transition metals was renewed allowing a resurgence of Ullmann chemistry. As already described in the paragraph concerning the control of axial chirality in biaryl moieties (see 3.2.2), Ullman reaction was widely investigated for the atroposelective coupling. Meyers and Nelson, for example, introduced a chiral oxazoline as auxiliary to synthesize efficiently a C_2-chiral biaryl.[179]



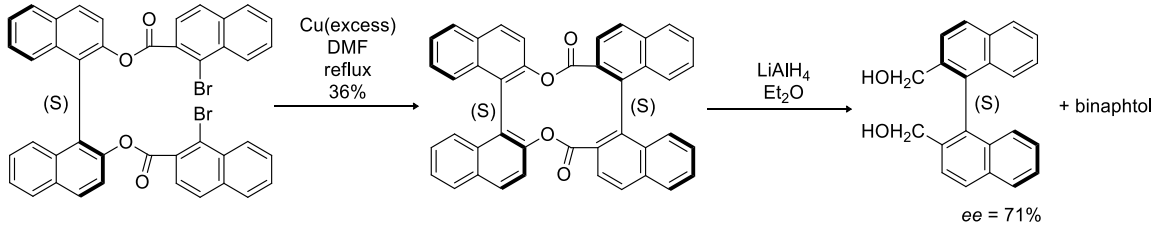
Scheme 4-48 Diastereoselective homocoupling of *o*–bromooxazolinylbenzene by Meyers at *al*.

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

[178] 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**.

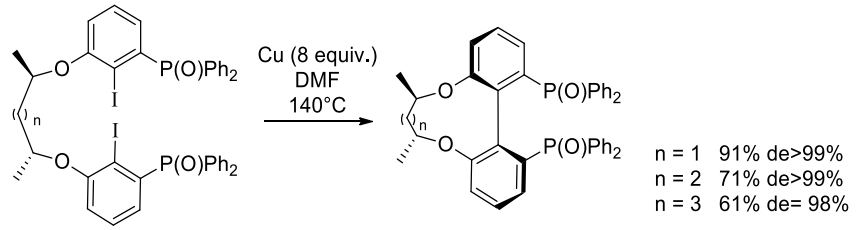
[179] a) Nelson, T. D.; Meyers, A. I. *Tetrahedron Lett.* **1993**, *34* (19), 3061–3062. b) Nelson, T. D.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35* (20), 3259–3262. c) Meyers, A. I.; Nelson, T. D.; Moorlag, H.; Rawson, D. J.; Meier, A. *Tetrahedron* **2004**, *60* (20), 4459–4473.

Concerning the intramolecular Ullmann coupling, a nice example 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[180] (**Scheme 4-49**).



Scheme 4-49 Diastereoselective intramolecular Ullmann coupling by Myano et *al*.

Others examples in which were employed tethers bearing central chirality were also extensively studied. For example, (*o*-iodophenyl)diphenylphosphine oxides linked by chiral diol tether underwent intramolecular Ullmann coupling in presence of excess Cu powder. The biaryl bisphosphine oxides were obtained with excellent diastereoselectivity (over 98%) independently from the length of the tethers and the best yield was obtained when the tether was smaller.[181] (**Scheme 4-50**)

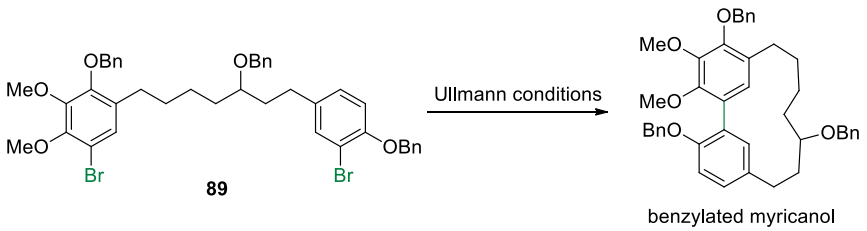


Scheme 4-50 Diastereoselective intramolecular Ullman coupling by Chan et *al*.

In view of this literature, we thought to use Cu powder for the intramolecular macrocyclization of myricanol starting from the di-brominated substrate **89.** In the following table are reported the reactions tried. Both neat and in solution conditions were experimented.

[180] 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.

[181] 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.



Entry	Ullmann conditions	T	t	Yield
1	Cu (1.9 equiv.), DMF	110°C then 160°C	3h then 23h	-[a]
2	Cu (10 equiv.), DMF	160°C	40h	-[a]
3	Cu (10 equiv.), neat	220°C	40h	-[b]

a. only starting material recovered; b. starting material with 10% of dehalogenated compound.

Table 4-12 Ullmann reaction on substrate 89

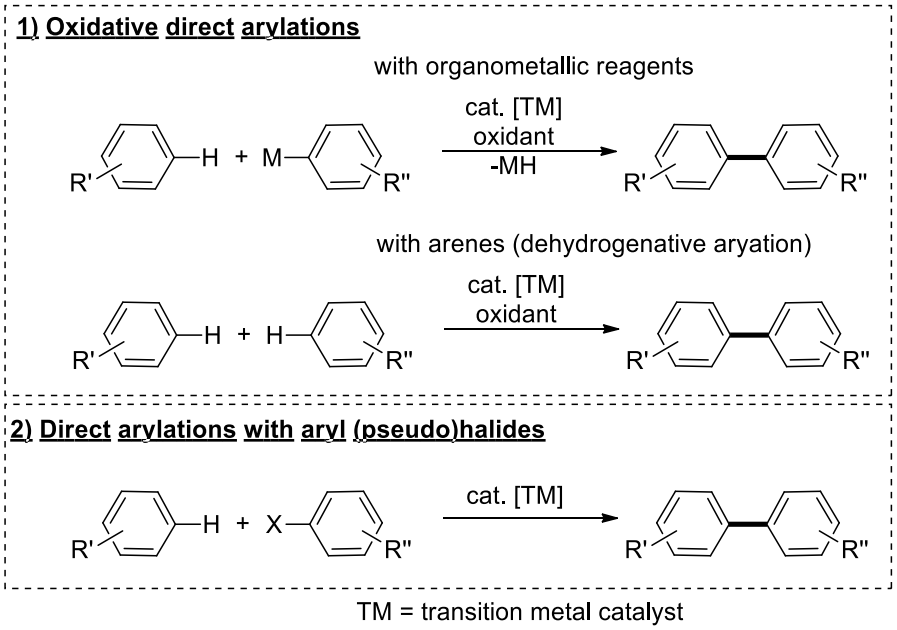
As shown in **Table 4-12**, the cyclized product was never observed. The first tentative with 1.9 equivalent of Cu gave only the starting product (entry 1). The same result was observed using an excess of copper at reflux of DMF during 40h (entry 2). Even if the reaction was performed in absence of solvent at 220°C, the desired product wasn't formed and we could just observed a weak dehalogenation of starting material.

This result could be expected given the size of the macrocycle that has to be formed (13-membered ring).

4.2.3.2 C-H macrocyclization

Although numerous metal catalyzed methodologies for the formation of biaryl have been reported in literature, direct arylation constitutes an important alternative to the traditional aryl-aryl cross-coupling reactions. In the classical sp^2-sp^2 cross-coupling reactions, the required organometallic nucleophilic species are obtained from expensive arylhalides often not commercially available. Thus, direct arylation reactions through cleavage of C-H bonds represent an environmentally and economically more attractive strategy.[182]

Two different categories of catalytic direct arylations by activation of C-H bonds could be considered on the basis of the nature of the coupling partners: 1) oxidative arylations in which an oxidant and stoichiometric amount of organometallic reagents or (hetero)arenes were required as arylating agents; 2) direct arylations with aryl (pseudo)halides that are employed as electrophilic coupling partners (**Scheme 4-51**).

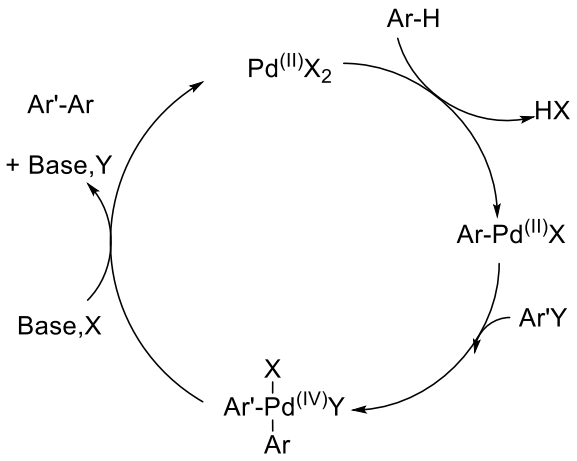


Scheme 4-51 Strategies for catalytic direct arylation for the synthesis of biaryls.

[182] a) *Modern tools for the synthesis of complex bioactive molecules*; Cossy, J., Arseniyadis, S., Eds.; John Wiley & Sons: Hoboken, N.J, **2012**. b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110* (2), 624–655. c) Ackermann, L.; Vicente, R.; Kapdi, A. *Angew. Chem. Int. Ed.* **2009**, *48* (52), 9792–9826.

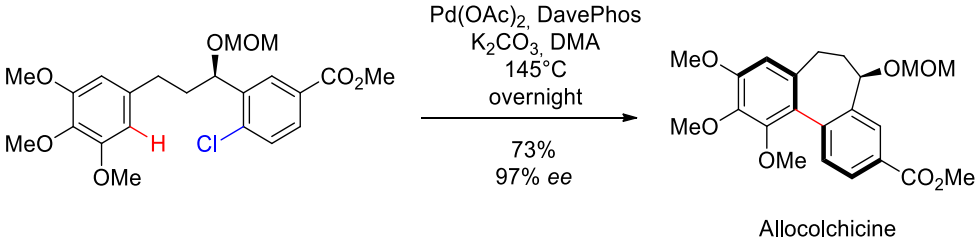
Several transition metals have been used to perform C-H activation, as ruthenium, rhodium, palladium, and copper.[183]

In the biaryl macrocyclization towards myricanol, we envisaged an intramolecular direct arylation with arylhalide. As mechanism for the direct arylation with arylhalide, a palladium(II)/palladium(IV) catalytic cycle was proposed (**Scheme 4-52**).



Scheme 4-52 Mechanism of Pd(II)/Pd(IV) direct arylation

Concerning intramolecular biaryl macrocyclization involving a C-H arylation step of arylhalides, we found an interesting example reported by Fagnou at *al*. for the synthesis of allocolchicine, a promising antitumor agent that is a seven-membered ring biaryl analogue of naturally occurring colchicine.[78]

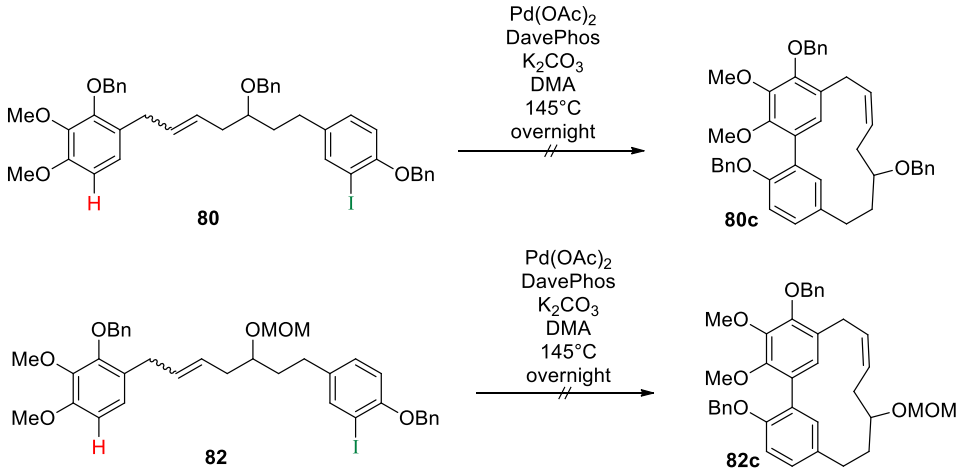


Scheme 4-53 Allocolchicine synthesis via oxidative arylation

As shown in **Scheme 4-53** the desired product was obtained with a good yield and an excellent enantiomeric excess.

[183] a) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111* (3), 1215–1292. b) Chen, Z.; Wang, B.; Zhang, J., Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2015**, *2*, 107.

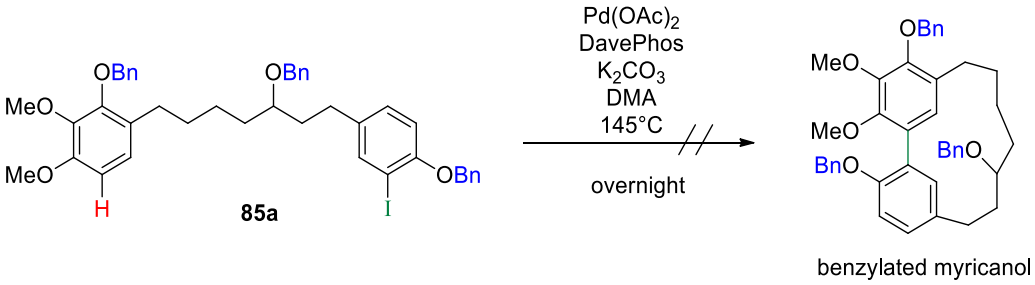
Although the ring formed in allocolchicine was an 8 membered ring, we decided to apply the same reaction conditions used by Fagnou on our mono-iodinated compounds **80** and **82**.



Scheme 4-54 Oxidative arylation on 80 and 82

Whatever the protection of the starting product, we didn't obtain the cyclized products; the analysis of the fractions derived from column chromatography purifications allowed to identify about 30% of de-iodinated compound in both reactions. The NMR spectra of other chromatography's fractions were complex and apparently corresponded to more than one product.

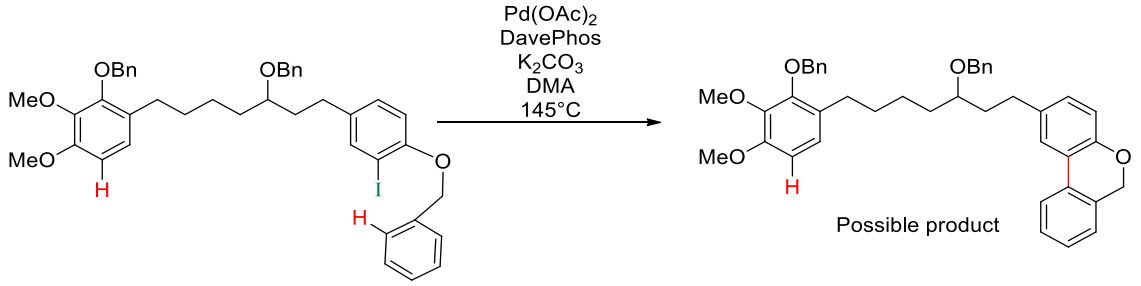
At that time we supposed that the stereochemistry of the double bond (*E/Z*: 93/7) could hindered the macrocyclization and we repeated the same reaction on the diarylheptanoid **85a** whose double bond was reduced.



Scheme 4-55 Direct arylation on 85

Unfortunately, this essay also failed and again de-iodinated product was obtained with some others non identified products. Importantly we observed by ^{1}H-NMR analysis of the de-iodinated product that the chemical shift of the benzylic protons of the benzyl group *ortho* to the iodine in the starting material was

different compared to synthesized de-iodinated compound **85**. We hypothesized without proof the formation of a benzo[c]chromene core, arising from C-H activation of the benzylic methylene, reported by Fagnou on a similar substrate.[184]



Scheme 4-56 C-H activation on the protecting group

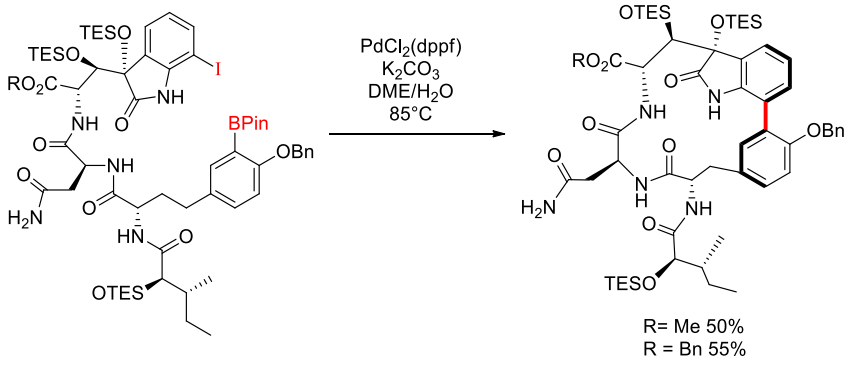
[184] Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126* (30), 9186–9187.

4.2.3.3 Suzuki cross-coupling reaction

Another classical cross-coupling approach was experimented for the macrocyclization of myricanol. The reaction studied to obtain the 13-membered ring was the Suzuki-Miyaura coupling.

The Pd(0)-catalyzed Suzuki–Miyaura cross-coupling of boronic species and organic halides is one of the most widely applied methods in modern synthetic organic chemistry.[185] Since its discovery in the late 1970s, the Suzuki−Miyaura coupling[186] 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[187]. This chemistry has found numerous applications on academic as well as in pharmaceutical industry.[188] The recent studies for the improvement of this reaction are focused on the development of more active catalyst/ligand combinations allowing low catalyst loadings and large scale applications and on the use of cheaper but less reactive aryl chloride.[189]

Intramolecular Suzuki-Miyaura cross-coupling reaction have been applied to install the biaryl motif of diverse macrocycles, as for example for the macrocyclic core of TMC-95[190] (**Scheme 4-57**), or in the total synthesis of signal peptidase inhibitors arylomycins A2 and B2[76] and for the synthesis of DEFG ring of complestatin[75] (see **Figure 3-3**), just to mentioned a few.



Scheme 4-57 Preparation of macrocyclic core of TMC-95 by intramolecular Suzuki-coupling reaction

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

[186] 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.

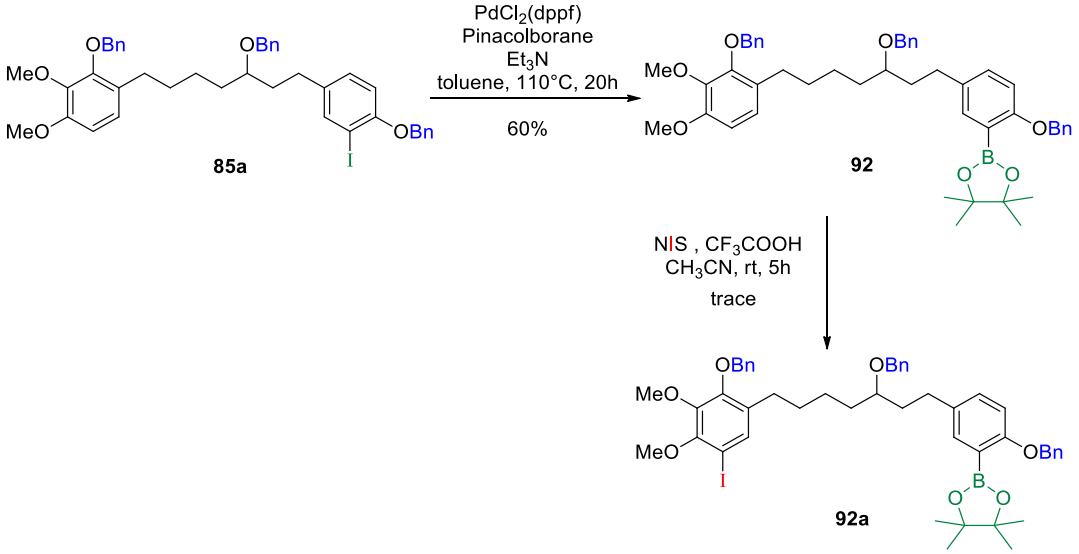
[187] Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. *Chem. Rev.* **2011**, *111* (2), 563–639.

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

[189] Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41* (22), 4176–4211.

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

Concerning the synthesis of the macrocycle of myricanol by a biaryl Suzuki-Miyaura cross-coupling macrocyclization, our initial idea was to generate from the monohalogenated compound **85a** the corresponding boronic derivative **92** which would be halogenated to obtain the Suzuki-Miyaura precursor **92a** (**Scheme 4-58**).

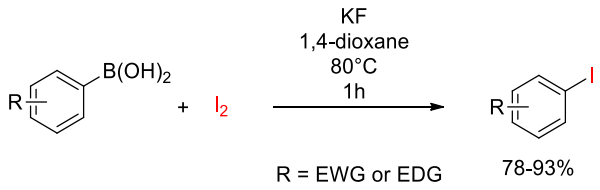


Scheme 4-58 Preparation of the intramolecular Suzuki-Miyaura cross-coupling precursor 92a

The Pd-catalyzed borylation of compound **85a** with pinacolborane gave the pinacolboronic ester **92** in good yield. Then we performed the iodination of **92** using NIS with TFA in ACN and we obtained a quite incomprehensible mixture of products. On the NMR spectra only traces of the desired product **92a** were detected as well as the dehalogenated product **85** with the monohalogenated **85a**. One explanation should be that the boronic species easily underwent an ipso-substitution with iodine and/or a protodeboronation[191] as also reported by Chiummiento et *al.*[192] (**Scheme 4-59**).

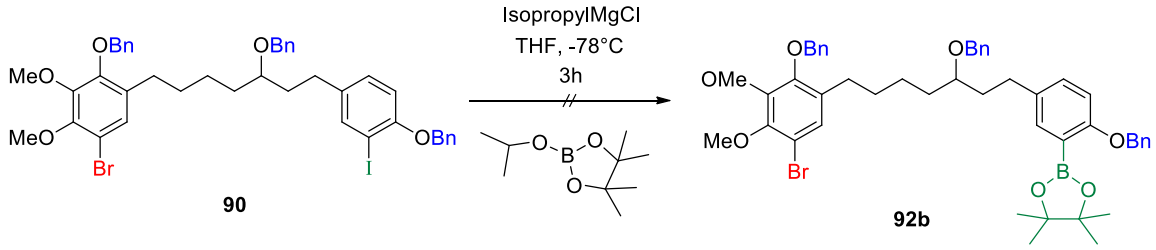
[191] a) Thiebes, C.; Thiebes, C.; Prakash, G. K. S.; Petasis, N. A.; Olah, G. A. *Synlett* **1998**, *1998* (2), 141–142. b) Ahn, S.-J.; Lee, C.-Y.; Kim, N.-K.; Cheon, C.-H. *J. Org. Chem.* **2014**, *79* (16), 7277–7285. c) Szumigala, R. H.; Devine, P. N.; Gauthier, D. R.; Volante, R. P. *J. Org. Chem.* **2004**, *69* (2), 566–569.

[192] Tramutola, F.; Chiummiento, L.; Funicello, M.; Lupattelli, P. *Tetrahedron Lett.* **2015**, *56* (9), 1122–1123.



Scheme 4-59 *Ipso*-substitution of aryl boronic acids with iodine

Therefore we tried to obtain the boronic derivative by a magnesium-halogen exchange starting from the bromo-iodo compound **90**; our idea was a chemoselective magnesium-iodine exchange as already reported for aromatic dihalogenated system[193] (**Scheme 4-60**).



Scheme 4-60 Borylation through Mg-I exchange

Unfortunately, we didn't obtained the desired product, but a mixture of inseparable and unidentifiable compounds, showing that this borylation wasn't selective on the iodinated position, but afforded a mixture of borylated, halogenated and dehalogenated products.

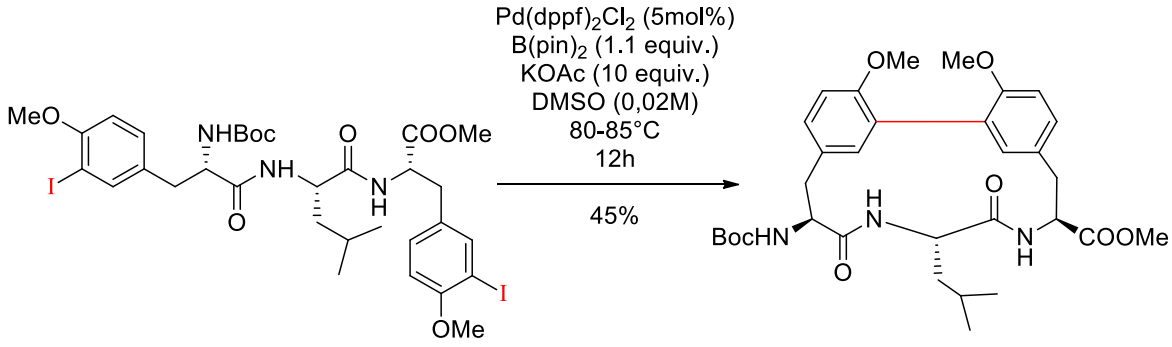
At that point, we thought to change our strategy and to use the di-halogenated diarylheptanoids in a palladium catalyzed process that could allow a one step borylation/Suzuki-Miyaura cross-coupling macrocyclization.

Despite the efficiency and the importance of Suzuki-Miyaura cross-coupling reactions, numerous limitations[194] linked to availability, preparation, isolation of boronic species have spurred diverse research groups towards a one-pot approach. The first system of one-pot borylation/Suzuki-Miyaura cross-coupling reaction was reported by Miyaura in 1997.[195] The procedure involved the *in situ* conversion of an aryl triflate into a boronate ester followed by the addition of a second aryl triflate along with the palladium catalyst and base. This example opened the route to the development of a one-pot cross-coupling reaction

[193] Diemer, V.; Leroux, F. R.; Colobert, F. *Eur. J. Org. Chem.* **2011**, *2011* (2), 327–340.
[194] Molander, G. A.; Canturk, B. *Angew. Chem. Int. Ed.* **2009**, *48* (49), 9240–9261.
[195] Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38* (19), 3447–3450.

that justify the increasing literature concerning C-H or C-X borylation/Suzuki-Miyaura coupling for the preparation of unsymmetrical biaryl compounds.[196]

Among these reports we found particularly interesting the work reported by Zhu and Carbonnelle[197] in which a novel macrocyclization procedure was developed on the basis of a domino process involving the *in situ* formation of a pinacol boronic ester. In this paper a linear aryl diiodide was converted into the corresponding 15-membered *m*,*m*-cyclophane *via* a Miyaura's arylboronic ester synthesis and an intramolecular Suzuki macrocyclization (**Scheme 4-61**).



Scheme 4-61 Domino Suzuki-Miyaura process by Zhu et *al.*

As depicted in the previous scheme the desired product was obtained in 45% yield that could be considered as an excellent result for a *one-pot* macrocycle formation. Moreover, this yield arise from numerous essays done in which was clearly demonstrated that little variations of the reaction conditions could drastically lowered the cyclization to 10% or traces of product. This publication clearly underline how delicate is this reaction, during which different reactions could occur as double borylation, halogen reduction, intermolecular couplings. The molarity of the starting product was revealed to be an important factor for the success of the process.

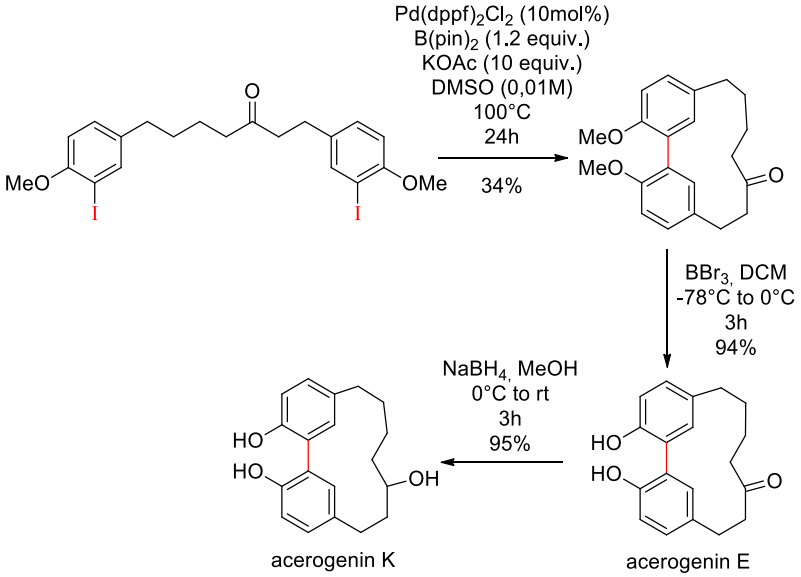
Some years later, Usuki and Ogura used the same conditions reported by Zhu for the total synthesis of acerogenin E and K, a 13-membered ring natural product belonging to diarylheptanoid family (as myricanol)[198] (**Scheme 4-62**). In their work was shown that the total synthesis of acerogenin E and K failed using Ullmann conditions and was accomplished using Miyaura arylborylation-intramolecular Suzuki

[196] a) Hurst, T. E.; Macklin, T. K.; Becker, M.; Hartmann, E.; Kügel, W.; Parisienne-La Salle, J.-C.; Batsanov, A. S.; Marder, T. B.; Snieckus, V. *Chem. - Eur. J.* **2010**, *16* (27), 8155–8161. b) Klečka, M.; Pohl, R.; Klepetářová, B.; Hocek, M. *Org. Biomol. Chem.* **2009**, *7* (5), 866–868. c) Baudoin, O.; Cesario, M.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **2002**, *67* (4), 1199–1207. d) DiMauro, E. F.; Vitullo, J. R. *J. Org. Chem.* **2006**, *71* (10), 3959–3962. e) Broutin, P.-E.; Čerňa, I.; Campaniello, M.; Leroux, F.; Colobert, F. *Org. Lett.* **2004**, *6* (24), 4419–4422.

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

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

cross-coupling reaction developed by Zhu. Again the concentration of the starting product appeared as a crucial point. Indeed acerogenin's macrocycle was obtained in 34% yield using a lower concentration (0,01M) compared to that employed by Zhu (0,02M). When the reaction was tried at 0,02M, the macrocycle was obtained with only 5% yield.

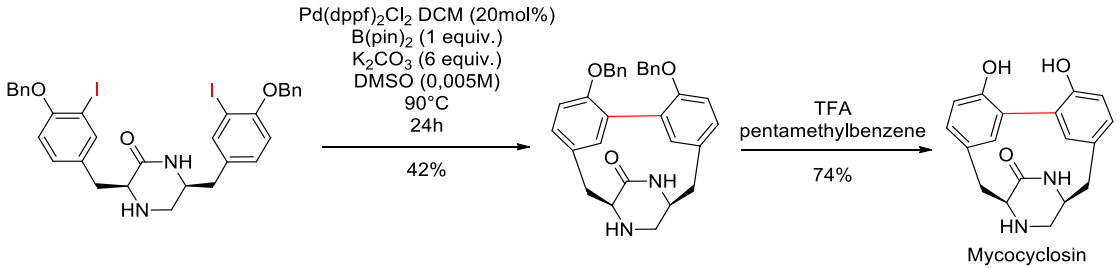


Scheme 4-62 Total synthesis of acerogenin E, K by Usuki et *al*.

Myclocyclosin, a natural diketopiperazine, was also obtained with a Suzuki-Miyaura domino process by Hutton and *al*.[199] After unsuccessful numerous essays with Ni-catalyzed Ullman-type process they switched to *one-pot* Pd-catalyzed Miyaura borylation/Suzuki coupling to obtain the desired product with 42% yield (**Scheme 4-63**).

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

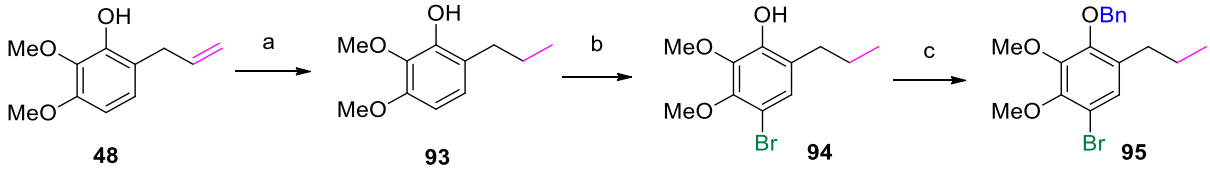
The synthesized mycocyclosin was analyzed by X-ray and low temperature NMR studies were performed and it was surprisingly discovered that despite the strained cycle, the rotation barrier of the two atropoisomers is sufficiently low that a rapid interconversion occur at room temperature.



Scheme 4-63 Total synthesis of mycocyclosin by Hutton et *al.*

Taking account these excellent results we decided to try the Suzuki-Miyaura domino process on our substrate, in order to form the 13-membered ring of myricanol.

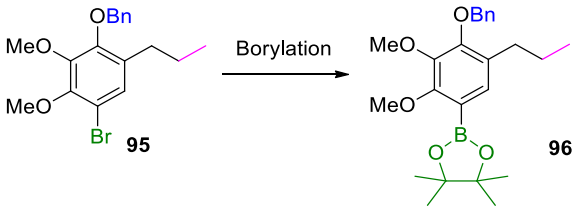
The first essays for domino process were done using $Pd(OAc)_2$ and S-Phos, in presence of Et_3N as base. The choice of these conditions arise from borylation tests performed on a prepared model fragment with the aim to find the best conditions to introduce the boronic ester on our electron rich substrate. **Scheme 4-64** and **Table 4-13** shows the preparation of fragment **95** and its borylation.



a.Pd/C 10%, NH_4COOH (4 equiv), MeOH, reflux, 40min, 100%; b. NBS (1 equiv), TFA (0,3 equiv.), ACN, 3h, rt, 99%; c. BnBr (1.2 equiv), K_2CO_3 (2 equiv.), acetone, reflux, 5h, 98%

Scheme 4-64 Preparation of model fragment

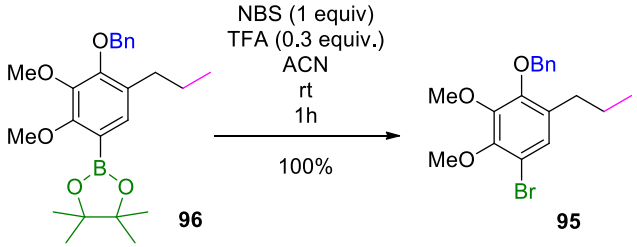
As depicted in **Table 4-13,** boronic ester **96** was obtained in good yield using either $Pd(OAc)_2$ with S-Phos, pinacolborane and Et_3N in dioxane at 80 °C or $PdCl_2(dppf)$, pinacolborane and Et_3N in toluene at 110 °C (entries 1 and 2). Surprisingly none formation of the boronic ester was observed if the reaction was performed with bispinacolato diboron; only dehalogenated compound was found (entry3).



Entry	Pd/mol%	Ligand/equiv.	Boron/equiv.	Base/equiv.	Solvent	T °C	t (h)	96 (%)
1	$Pd(OAc)_2$/5	S-Phos/0.2	Bpin-H/3	Et_3N/4	Dioxane	80	3	52
2	$PdCl_2(dppf)$/5	-	Bpin-H/1.2	Et_3N/8	Toluene	110	3	50
3	$Pd(OAc)_2$/5	S-Phos/0.2	$B(pin)_2$/1.2	Et_3N/4	Dioxane	80	3	-

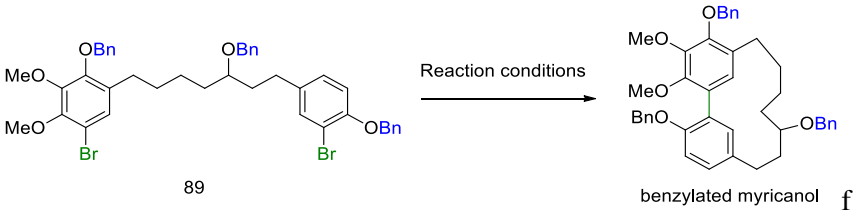
Table 4-13 Borylation on model fragment

Moreover to confirm the result of *ipso* substitution obtained for the halogenation of product **92** (**Scheme 4-65**), the boronic ester **96** was submitted to NBS in ACN and after 1 hour of reaction we observed a complete transformation of the boronic species into the corresponding brominated compound **95**.



Scheme 4-65 *Ipso*-substitution of boronic ester 96

We then applied the selected conditions *i.e.* $Pd(OAc)_2$, Et_3N and pinacolborane for the *one-pot* Pd-catalyzed Miyaura borylation/Suzuki coupling on our linear dibrominated diarylheptanoid **89**.

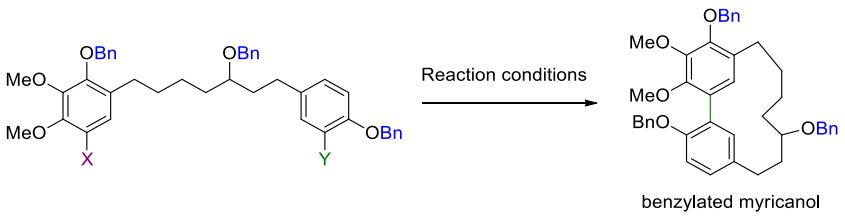


Entry	SM	$Pd(OAc)_2$ mol%	S-Phos equiv.	PinB-H equiv.	Et_3N equiv.	Solvent (0,002M)	T °C	t h	Product %
1	**89**	5	0,2	3	4	Dioxane	80	3h	-
2	**89**	5	0,2	1	4	Dioxane	80	3h	-
3	**89**	5	0,2	1	4	Dioxane	80	20h	-

Table 4-14 Intramolecular Suzuki-Miyaura domino reaction on 89

Using 1 or 3 equivalent of pinacolborane, we did not observe the cyclized product (**Table 4-14**). We only identified the bi-dehalogenated compound, the mono-dehalogenated compound on the less electron rich aromatic ring and a mixture of undistinguishable borylated compounds.

At that point we decided to use the same conditions reported by Zhu[197] to accomplish this macrocyclization. The essays, reported in **Table 4-15** were performed on different halogenated starting materials.



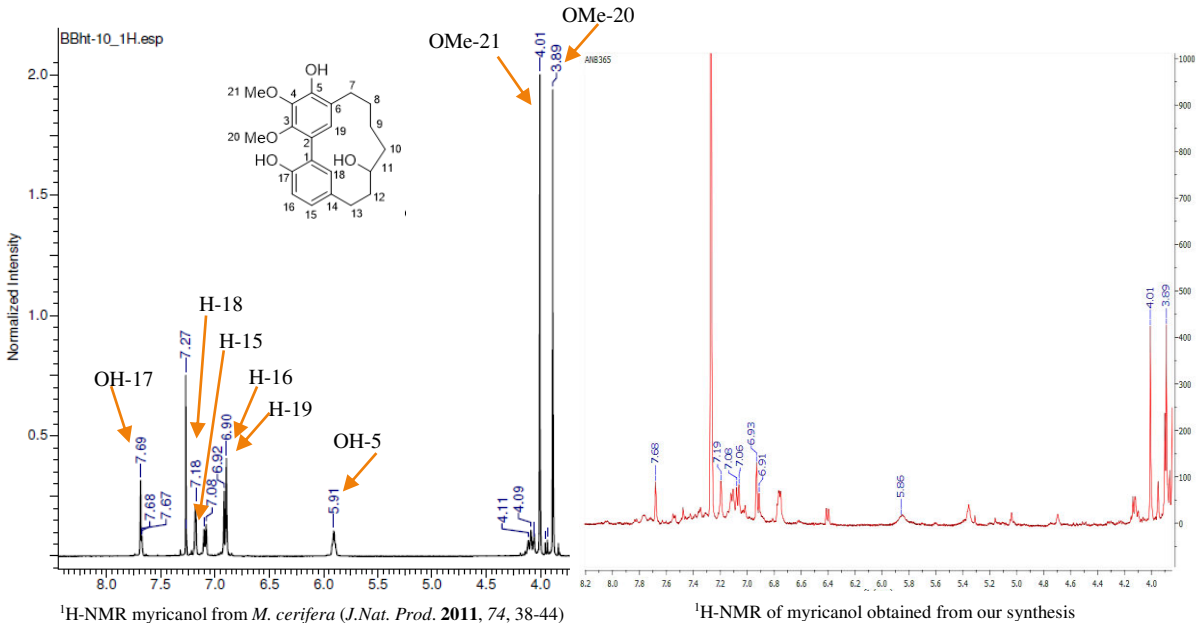
Entry	X	Y	s.m.	$PdCl_2$(dppf) mol%	Boron (1,2equiv.)	Base (10equiv.)	Solvent (0,002M)	T °C	t h	Prod. %
1	Br	Br	**89**	10	$(BPin)_2$	NaOAc	DMSO	80	24h	≈10[a]
2	Br	Br	**89**	10	$(BPin)_2$	KOAc	DMSO	80	24h	-
3	Br	Br	**89**	10	$(BPin)_2$	NaOAc	Dioxane	80	24h	-
4	Br	Br	**89**	10	$(BPin)_2$	KOAc	Dioxane	80	24h	trace
5	Br	Br	**89**	10	PinB-H	KOAc	DMSO	100	24h	-
6	Br	Br	**89**	10	PinB-H	NaOAc	DMSO	100	24h	-
7	Br	I	**90**	10	$(BPin)_2$	NaOAc	DMSO	100	24h	-
8	Br	I	**90**	10	$(BPin)_2$	NaOAc	DMSO	180	10h	-
9	I	I	**91**	10	$(BPin)_2$	NaOAc	DMSO	180	10h	trace

a. Yield evaluated after quantitative debenzylation, product was not isolate completely pure.

Table 4-15 Intramolecular Suzuki-Miyaura domino reaction on 89, 90 *and 91*

Using the conditions reported in entry 1 of **Table 4-15**, we obtained the desired 13-membered ring of benzylated myricanol. It's important to note that the starting material was a dibrominated compound and not a diiodinated one as reported in all the macrocyclization domino processes accomplished by Zhu. Importantly the product was recognized only after a quantitative debenzylation that afforded myricanol

with a yield of ≈10% evaluated in two steps. The ^{1}H-NMR spectra of synthesized myricanol is identical to the one reported for the myricanol natural product.[11] It was possible to individuate the diagnostic peak of biaryl system, but unfortunately the product was not perfectly pure and due to the small amount obtained, it was impossible to purify it to perform a complete characterization (**Figure 4-3**).



^{1}H-NMR myricanol from *M. cerifera* (*J.Nat. Prod.* **2011**, *74*, 38-44)

^{1}H-NMR of myricanol obtained from our synthesis

Figure 4-3 ^{1}H-NMR spectra of natural and synthesized myricanol

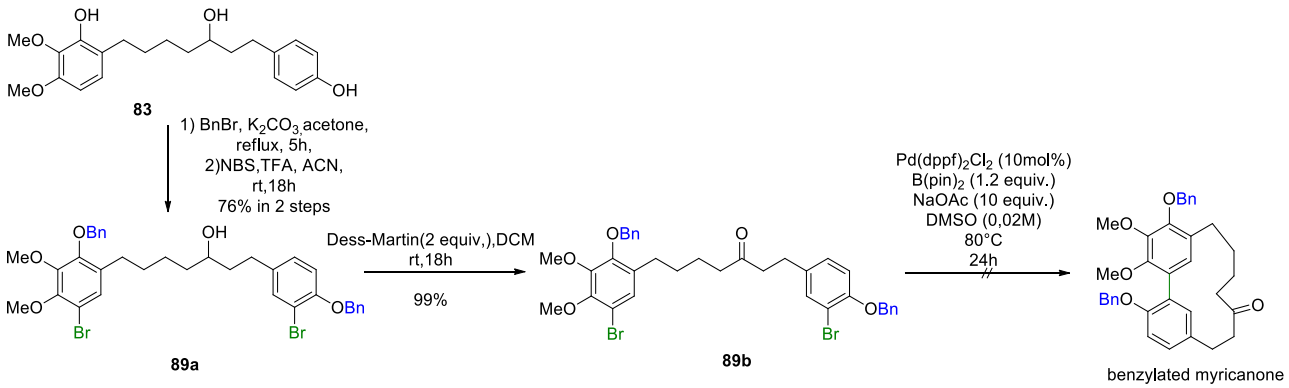
Others attempts of Suzuki-Miyaura domino reaction were experimented changing the source of boron, the base or solvent. None of essays (entries 2-9, **Table 4-15**,) allowed to obtain again the macrocycle except for entry 4 and 9 in which cyclized product was observed in traces.

We were aware that the obtained macrocyclization yield is not really satisfying but this reaction merits some comments. Our macrocyclization yield is in concordance with that reported by Whiting and co-workers[50b] that obtained the myricanol macrocycle by a Ni(0) catalytic process and this is probably due to the two not symmetric aromatic portion involved in this intramolecular cyclization. We have also to consider that Dickey and co-workers[37] have obtained the myricanol macrocycle with 22% yield starting from an already bi-functionalized substrate with halide and boron that underwent a classical Suzuki cross-coupling (see 2.4).

Finally we used the best *one-pot* Pd-catalyzed Miyaura borylation/Suzuki coupling conditions giving the benzylated myricanol on dibrominated substrate **89**, on a ketoderivative diarylheptanoids **89b,** obtained

with high yields through benzylation and halogenation of **83** followed by an oxidation with Dess-Martin periodiane of **89a** (**Scheme 4-66**).

The presence of a carbonyl moiety on the chain should change the conformation of the molecule and facilitate the macrocyclization.[44a]



Scheme 4-66 Domino Suzuki-Miyaura process on keto derivative 89b

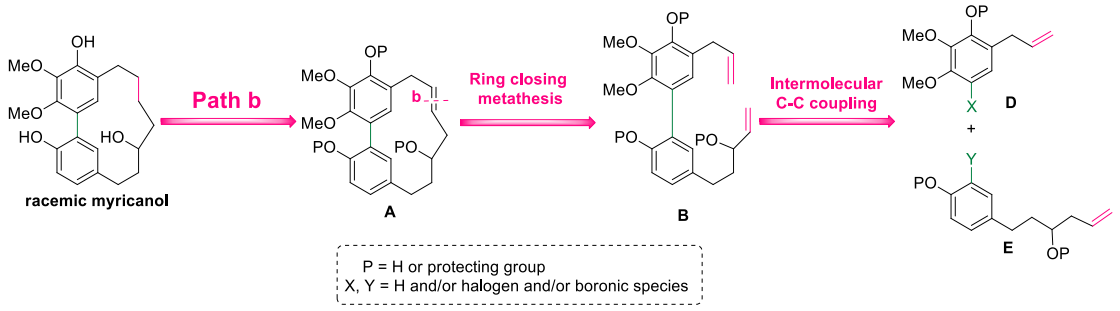
Unfortunately, this essay of macrocyclization failed and as usual we could only recover 20% of dehalogenated product and 30% of starting material. The remaining crude column chromatography fractions resulted in a mixture of products in which we didn't distinguish the cyclized product.

In conclusion we finally succeeded to perform the total synthesis of myricanol using a *one-pot* Pd-catalyzed Miyaura borylation/Suzuki coupling and for the best of our knowledge this result constitutes the first example in which this approach is applied to the synthesis of myricanol. Further studies to improve the yield are actually in progress in our laboratory.

4.3 PATH B: INTERMOLECULAR BIARYL FORMATION TOWARDS RING CLOSING METATHESIS

Myricanol has never been synthetized by first an intermolecular formation of the biaryl moiety and a subsequent macrocyclization by coupling of the alkylmoities. Just one example was reported in the literature by Dansou et *al.*[52] for the preparation of *O*-methylmyricanone, a methylated analogue of myricanone. In their case, the biaryl was installed with success, but unfortunately the cyclization using a Thorpe-Ziegler condensation of two nitrile moieties failed.

Referring to the general retrosynthetic approach proposed at the beginning of the third chapter of this thesis (see 3.1), we individuated two possible paths for the total synthesis of myricanol. In path a, firstly formation of the linear chain and then macrocyclization through an intramolecular biaryl coupling, was already discussed on the previous paragraph of this chapter (see 4.2). Herein, we presented the second retrosynthetic approach (path b) for the synthesis of myricanol.



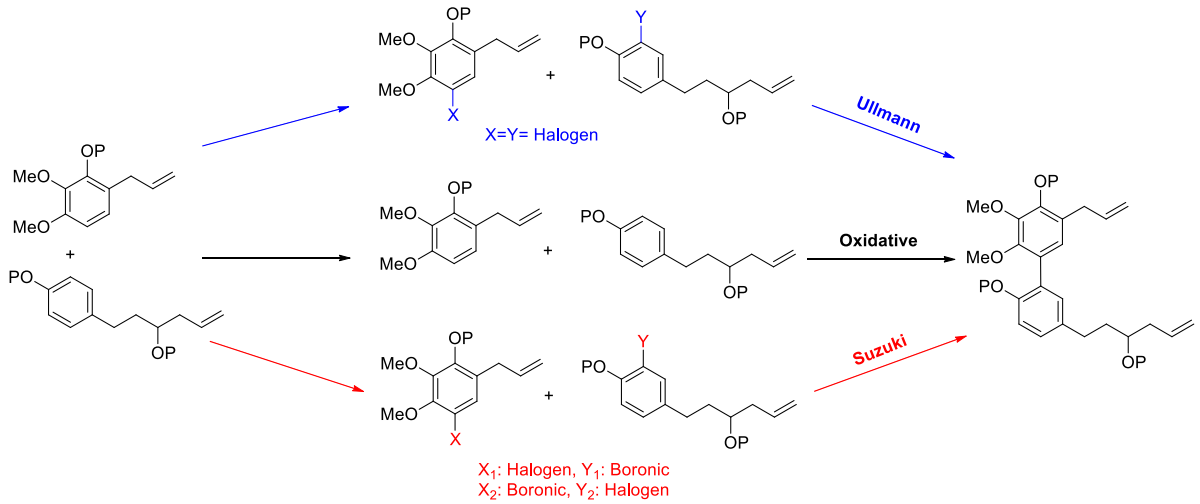
Scheme 4-67 Path b= intermolecular biaryl cross-coupling and ring closing metathesis

As illustrated in the retrosynthetic **Scheme 4-67**, we proposed to prepare the intermediate **A** from the corresponding biaryl **B** through a ring closing metathesis (RCM) process. Fragment **B** could arise from a direct intermolecular biaryl cross-coupling between the two advanced fragments **D** and **E**.

Next pages will be essentially focused on the methodologies used to perform the biaryl coupling of fragments **D** and **E** (and their precursors).

4.3.1 METHODS FOR BIARYL COUPLING

In the following scheme are reported the three different classes of reactions examined to accomplish the installation of the biaryl moiety: 1) Ullmann coupling, 2) oxidative coupling and finally 3) Suzuki-Miyaura cross-coupling reactions.

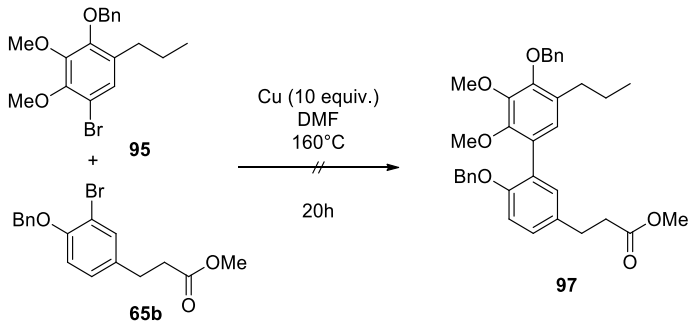


Scheme 4-68 Possible approaches for the intermolecular biaryl synthesis

4.3.1.1 Ullmann cross-coupling reaction

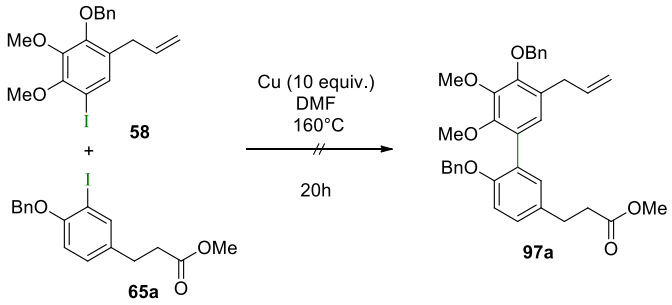
The first attempts of an intermolecular biaryl cross-coupling reaction were done using the copper catalyzed Ullmann coupling whose conditions has been already discussed in paragraph 4.2.3.1 when the same approach was tested in an intramolecular way.

An equal ratio of the model fragment **95** and the methylester **65b**, both brominated, were mixed with 10 equivalents of copper powder in DMF as solvent. The mixture was stirred and heated at 160°C for 20h in a sealed tube. Copper was filtrated away and NMR and GC-MS analysis as well, showed a mixture of unreacted starting materials. None formation of coupled product **97** was revealed (**Scheme 4-69**).



Scheme 4-69 Intermolecular Ullmann coupling on brominated fragments

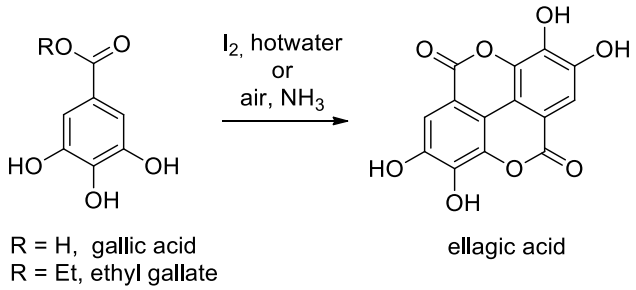
The reaction was repeated using the same conditions on different substrates. The iodinated compound **58** and **63a** were stirred in presence of copper and DMF at 160°C for 20h. Again the coupling product wasn't observed by NMR and GC-MS analysis, but in this case dehalogenation and partial isomerization of the double bond from the allylic to the styrenic position of **58** was observed. Compound **65a** was recovered completely unreacted (**Scheme 4-70**). The same behavior was observed when the reaction was repeated in absence of DMF, using starting compounds **58** and **65a** in the neat form.



Scheme 4-70 Intermolecular Ullmann coupling on iodinated fragments

4.3.1.2 Oxidative coupling

V. Griessmayer reported the first example of an oxidative biaryl cross-coupling reaction in 1871 describing the conversion of gallic acid (3,4,5-trihydroxybenzoic acid) or its ethyl ester into the naturally occurring biaryl bislactone ellagic acid using molecular iodine or air as oxidants.[200] (**Scheme 4-71**)

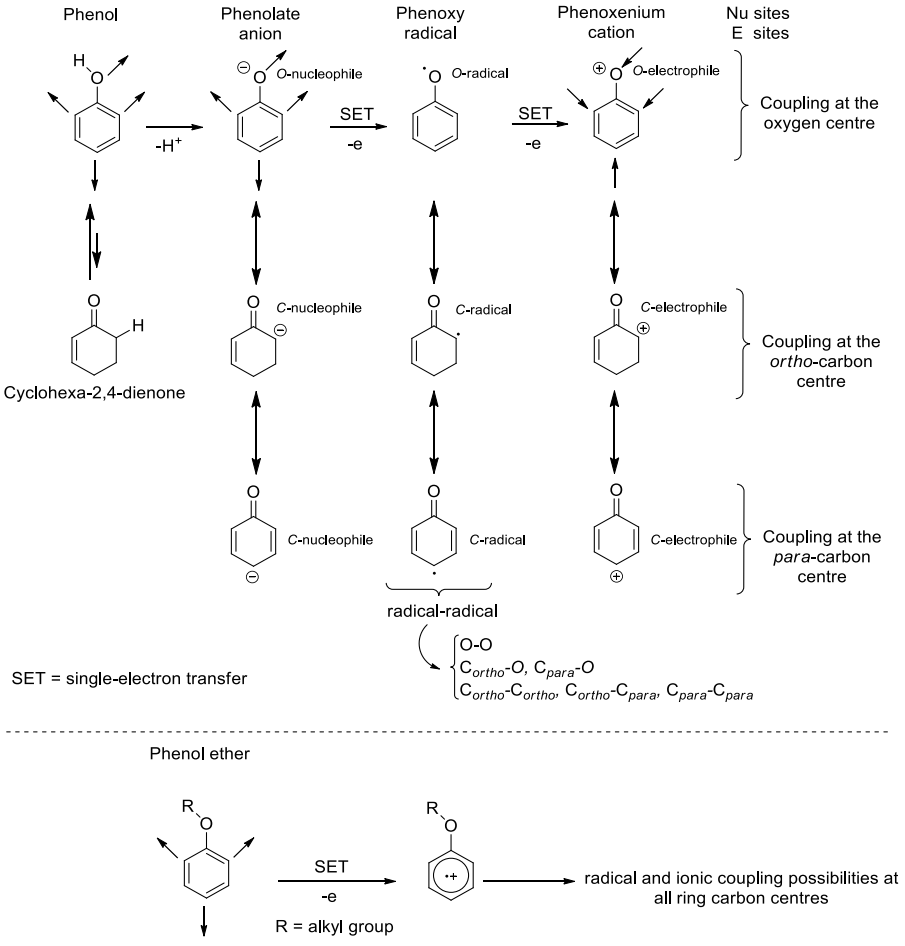


Scheme 4-71 First C-C oxidative coupling reported by Griessmayer

Since then numerous halogen-based, oxygen-based, metal-based inorganic, organic, and enzymatic oxidants, as well as anodic oxidation, have been utilized through the years to promote the formation of C–C and also C–O coupling products from various phenols or their simple ethers. The oxidative couplings are widely investigated by organic chemists because it offers the possibilities to access rapidly to C-C coupling biaryl unit and because it is highly related to the biosynthesis of natural products as polyphenols, alkaloids, terpenoids, polyketides and glycopeptides. These natural compounds, which constitute important synthetic targets, are sometimes obtained from biomimetic routes through an oxidative coupling of phenolic precursors. In the numerous review concerning oxidative couplings, reported by Musso,[201] Scott,[202] McDonald and Hamilton,[203] Waters,[204] Whiting,[205] Rieker,[206] Lessene and Feldman,[207] Yamamura and Nishiyama,[208] Quideau, Deffieux and Pouységu[209] the mechanistic studies came out, showing that the trend of these reactions are not always predictable.

[200] Griefsmayer, V. *Ann. Chem. Pharm.* **1871**, *160* (1), 40–56.
[201] Musso, H. *Angew. Chem. Int. Ed. Engl.* **1963**, *2* (12), 723–735.
[202] Scott, A. I. *Q. Rev. Chem. Soc.* **1965**, *19* (1), 1.
[203] McDonald, P. D.; Hamilton, G. A. Mechanisms of Phenolic Oxidative Coupling Reactions. In Oxidation in Organic Chemistry; Trahanovsky, W. S., Ed.; Academic Press: New York, London, **1973**, Part B, Chapter II; pp 97–134.
[204] Waters, W. A. *J. Chem. Soc. B Phys. Org.* **1971**, 2026.
[205] Whiting D. A. Oxidative Coupling of Phenols and Phenol Ethers. In Comprehensive Organic Synthesis; Trost, B., Fleming, I., Pattenden, G., Eds.; PergamonPress: Oxford, **1991**, Vol. 3, Chapter 2.9; pp 659–703.
[206] Eickhoff, H.; Jung, G.; Rieker, A. *Tetrahedron* **2001**, *57* (2), 353–364.
[207] Lessene, G.; Feldman, K. S. Modern Arene Chemistry; Astruc, D., Ed.; Wiley-VCH: Weinheim, **2002**, Chapter 14; pp 479–538.
[208] Yamamura, S.; Nishiyama, S. *Synlett* **2002**, 533–543.
[209] Quideau, S.; Pouységu, L.; Deffieux, D. *Curr. Org. Chem*. **2004**, 8, 113–148.

As showed in **Scheme 4-72**, a phenol could be considered as an aromatic (stable) enol tautomer of a cyclohexadienone allowing an oxidative process. If phenol is deprotonated, the phenolate anion is formed affording an *O*-nucleophilic species. This anion could be delocalized in the *ortho* and *para* position of the aromatic ring that became *C*-nucleophilic sites. In an oxidative process, consecutive single-electron transfer (SET) could occur in which phenolate anion could be oxidized first to the corresponding phenoxy radical and then to the phenoxenium cation. All these species generate radical and electrophilic species on the oxygen and on the *ortho* and *para* C. This elucidate that an oxidative coupling could occur from a reaction between nucleophile-electrophile or between the coupling of two radicals. Starting from the phenol ether, a SET process delocalize radical and cation on all the ring allowing the coupling reaction to all ring carbon centers.[210]

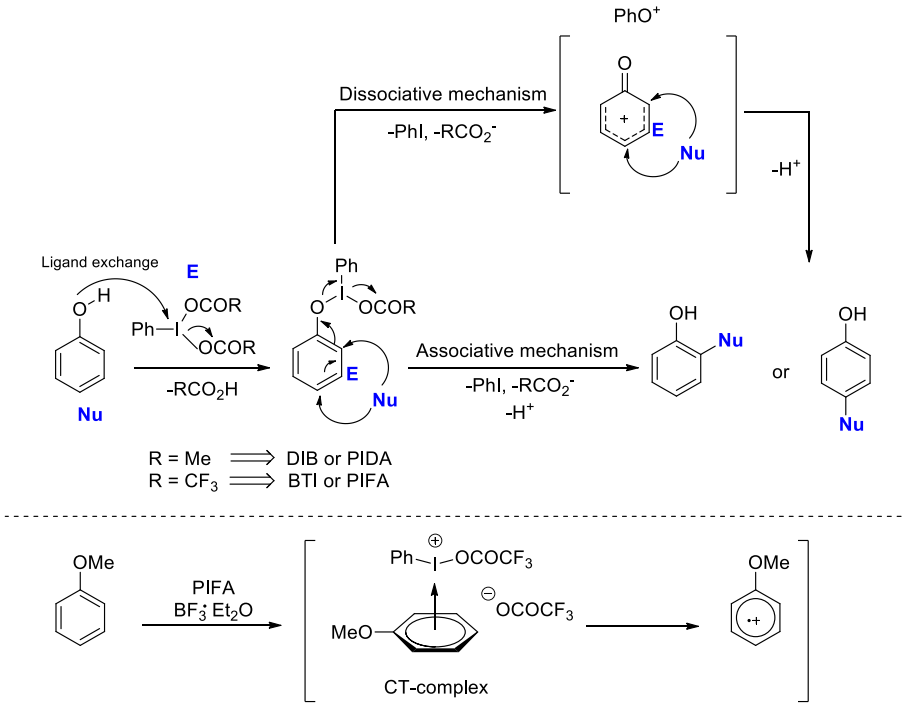


Scheme 4-72 Reactive sites of phenols during an oxidative process

[210] Quideau, S.; Deffieux, D.; Pouységu, L. In *Comprehensive Organic Synthesis II*; Elsevier, **2014**; pp 656–740.

The choice of the oxidizing agent, the protonation state of starting phenol, the type of solvent and the structure of the starting phenol or phenol ether constitute some of the numerous factors which can influence the behavior of an oxidative coupling. The oxidant/solvent systems commonly used are: 1) VOF_3/TFA/DCM;[67] 2) PIFA/BF_3 Et_2O/DCM;[211] 3) $Ru(OCOCF_3)_4$/TFA/DCM/BF_3 OEt_2 or $FeCl_3$/TFA or $Mn(acac)_3$/TFA or CoF_3/TFA or $Fe(ClO_4)$ $6H_2O$/TFA;[212] 4) DDQ/TFA;[213] 5) Tl_2O_3/BF_3 Et_2O/TFA.[214]

Among these reagents the most frequently used to generate phenoxenium ions or equivalents derived from phenols are hypervalent iodine(III) compounds, such as (diacetoxyiodo)benzene (DIB or PIDA) and [bis(trifluoroacetoxy)iodo]benzene (BTI or PIFA). Iodine(III) acts as an electrophilic centre (as metal-based two-electron oxidant) while phenol acts as a nucleophile. After a ligand exchange step the resulting transient phenoxyiodo species can afford the substituted products in *ortho* or *para* position to the phenol by a dissociative or associative mechanism.

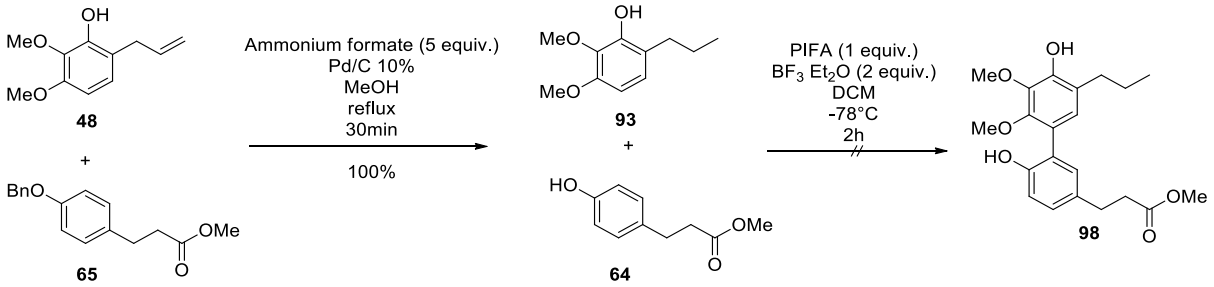


Scheme 4-73 Oxidative coupling promoted by PIFA or PIDA

[211] Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, Y. *Tetrahedron* **2009**, *65* (52), 10797–10815.
[212] Tanaka, M.; Mukaiyama, C.; Mitsuhashi, H.; Maruno, M.; Wakamatsu, T. *J. Org. Chem.* **1995**, *60* (14), 4339–4352.
[213] Palter, A.; Ward, R. S.; Jones, D. M.; Maddocks, P. *J. Chem. Soc. [Perkin 1]* **1993**, No. 21, 2631–2637.
[214] Enders, D.; Lausberg, V.; Signore, G. D.; Berner, O. M. *Synthesis* **2002**, *2002* (04), 515–522.

Hypervalent iodine(III) reagents, particularly PIFA, was also found efficient in oxidative coupling performed on phenol ethers. Indeed, after activation of PIFA by a Lewis acid as BF_3 etherate, the reaction with a phenol ether forms a charge-transfer (CT) complex and SET occurs from the electron-rich phenolether moiety to the PIFA-derived iodonium centre, generating a reactive radical cation species (**Scheme 4-73**). Such type of conditions were used by Kita and co-workers to perform intramolecular phenol ether coupling.[215]

To perform the oxidative coupling towards the myricanol's biaryl, we used the PIFA conditions. We chose fragments **48** and **65** as starting materials and after quantitative double bond hydrogenation and debenzylation the mixture of **93** and **64** was stirred at -78°C with PIFA/BF_3Et_2O for 2h. We expected that the more electron-rich phenol **93** would probably give a radical cation and the nucleophilic attack from the less electron-rich **64** could occur.



Scheme 4-74 Oxidative coupling of fragment 48 and 65 in presence of PIFA

The reaction gave a very complicated mixture of products in which we could observe the presence of unreacted starting materials and unidentified compounds as major products. We were able to isolate the homocoupled compound **64bis** with 4% yield. (**Figure 4-4**)

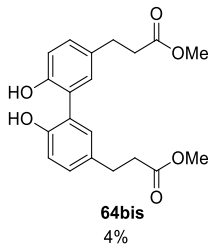
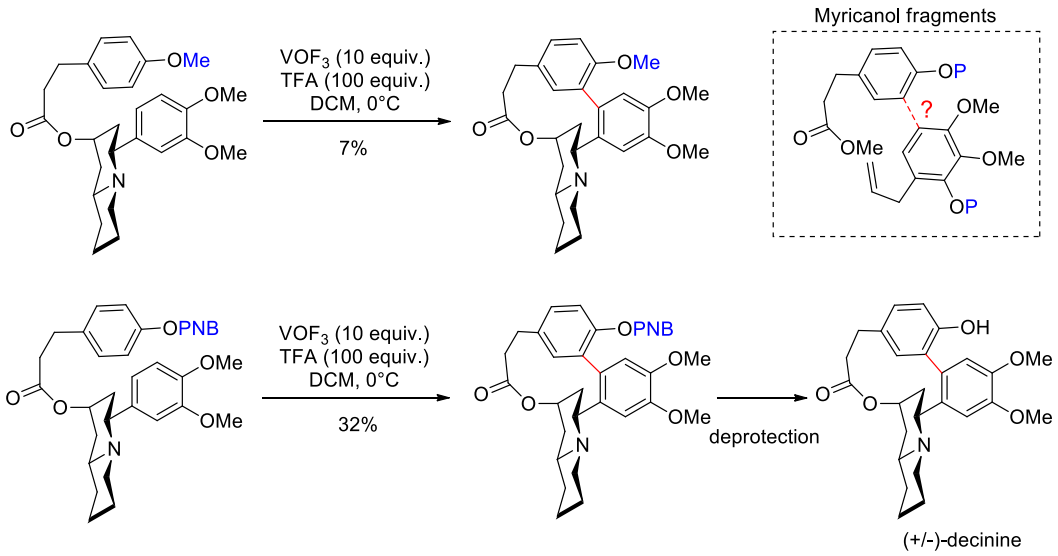


Figure 4-4 Isolated product after oxidative coupling with PIFA

[215] a) Kita, Y.; Gyoten, M.; Ohtsubo, M.; Tohma, H.; Takada, T. *Chem. Commun.* **1996**, *12*, 1481. b) Hamamoto, H.; Anilkumar, G.; Tohma, H.; Kita, Y. *Chem. Commun.* **2002**, *5*, 450–451.

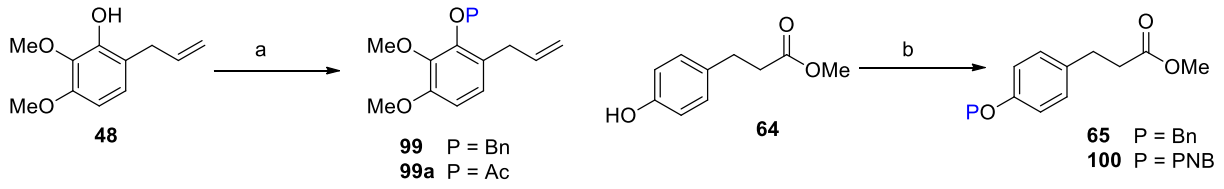
Performing the reaction at -30°C instead of -78°C led to the complete disappearance of starting materials with a concomitant formation of a really complex mixture of oxidized products, neither separable nor identifiables.

In the frame of the synthesis of natural products involving oxidative coupling, we found an interesting reference of Yang and co-workers on the total synthesis of (+/-)-decinine, a 12- membered ring compound belonging to the alkaloid family.[67] They used a VOF_3-mediated nonphenolic oxidative biaryl coupling for the formation of the macrocyclic ring. The yield of the macrocyclization is really dependent on the phenol protecting group, 7% with a methoxy or 32% with a *para*-nitrobenzyl group (**Scheme 4-75**).



Scheme 4-75 Total synthesis of (+/-)-decinine by oxidative coupling

These VOF_3-mediated nonphenolic oxidative conditions were tried on our fragments with different protections of the hydroxyl group as depicted in the following scheme.

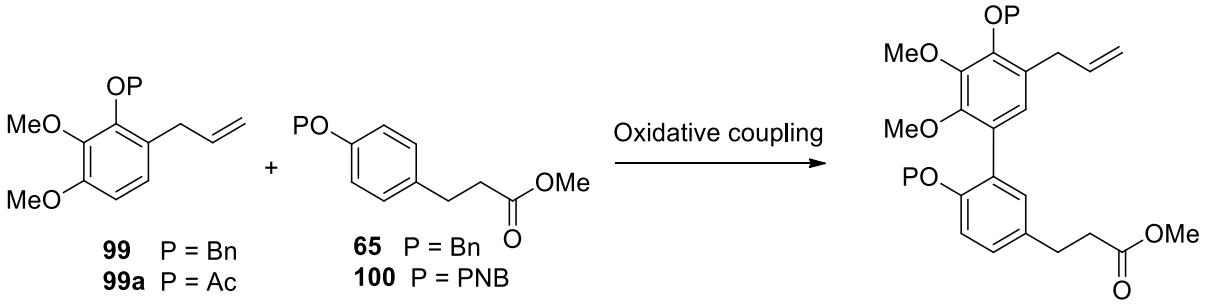


a. for **99** = BnBr, K_2CO_3, NaI, acetone, reflux, 3h, 99%;
for **99a** = Ac_2O, Py, rt, 2h, 82%

b. for **65** = BnBr, K_2CO_3, NaI, acetone, reflux, 4h, 99%;
for **100** = PNB-Br, K_2CO_3, acetone, reflux, 3h, 99%

Scheme 4-76 Preparation of fragments for oxidative coupling

Phenol **48** was protected to the corresponding benzylated (**99**) and acetoxylated substrates (**99a**). On the contrary **64** was protected with benzyl bromide (**65**) or with *para*-nitrobenzyl bromide (PNB) (**100**). **Table 4-16** summarizes the oxidative couplings starting from these protected substrates.



Entry	Partners of coupling	Oxidative conditions	Product %
1	**99+100**	VOF_3 (10 equiv.), TFA (100 equiv.), DCM, 0°C	Degraded products
2	**99+100**	VOF_3 (2 equiv.), TFA (20 equiv.), DCM, 0°C	Complex mixture
3	**99+63**	VOF_3 (2 equiv.), TFA (20 equiv.), DCM, 0°C	Complex mixture
4	**99a+63**	VOF_3 (2 equiv.), TFA (20 equiv.), DCM, 0°C	Trace of product

Table 4-16 Oxidative couplings with VOF_3

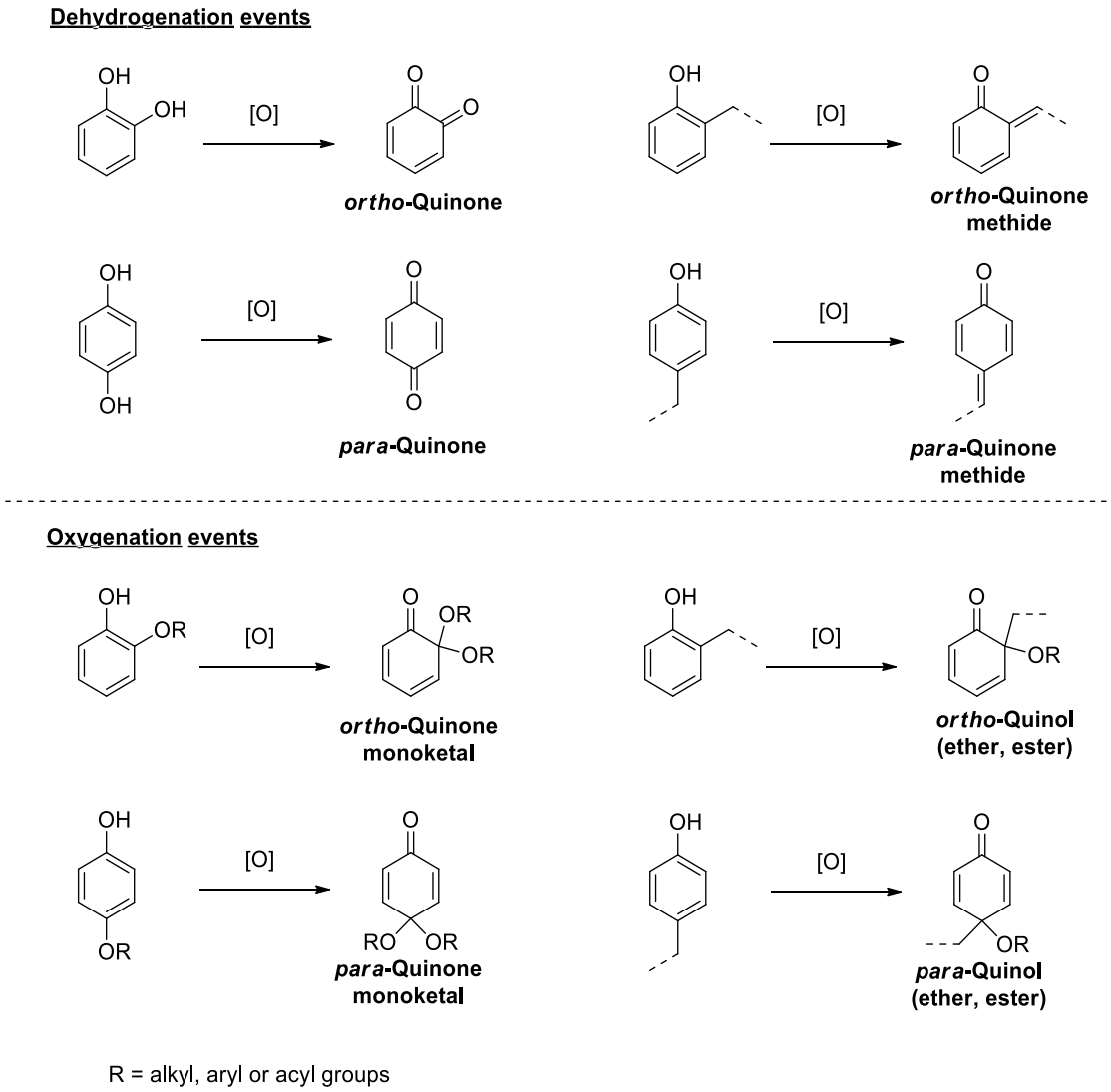
Starting from **99** and **100** and using the same conditions as reported for the total synthesis of decinine (**Scheme 4-75**) only degraded products were recovered (entry 1, **Table 4-16**). Therefore we decreased the amount of VOF_3 (2 equivalents) and we obtained a complex mixture of products (entry 2, **Table 4-16**); GC-MS analysis showed the mass corresponding to homocoupled products of **99** and **100**. The same result was observed starting from the two benzylated substrates **99** and **65** (entry 3). However we observed traces of the coupled product when the reaction was repeated between the acetoxylated **99a** and benzylated substrates **65** (entry 4).

These preliminary essays of oxidative coupling on our fragments showed us the complexity of this reaction that was probably increased by the really hindered trioxygenated ring of one of the two partners.

Due to the difficulty to understand what really happened during this oxidative coupling, we turned our attention to an intermolecular biaryl coupling involving a dienone acetate intermediate.

4.3.1.2.1 Intermolecular biaryl coupling via a dienone acetate intermediate

Another facet of the oxidative coupling of phenols and phenol ethers involves their oxidative dearomatization into electrophilic quinonoid species as reported in **Scheme 4-77** (*i.e.*, *ortho*- or *para*-quinones, -quinone methides, -quinone monoketals, -quinols).[49b]



Scheme 4-77 Quinonoid species from pheol and phenol ether

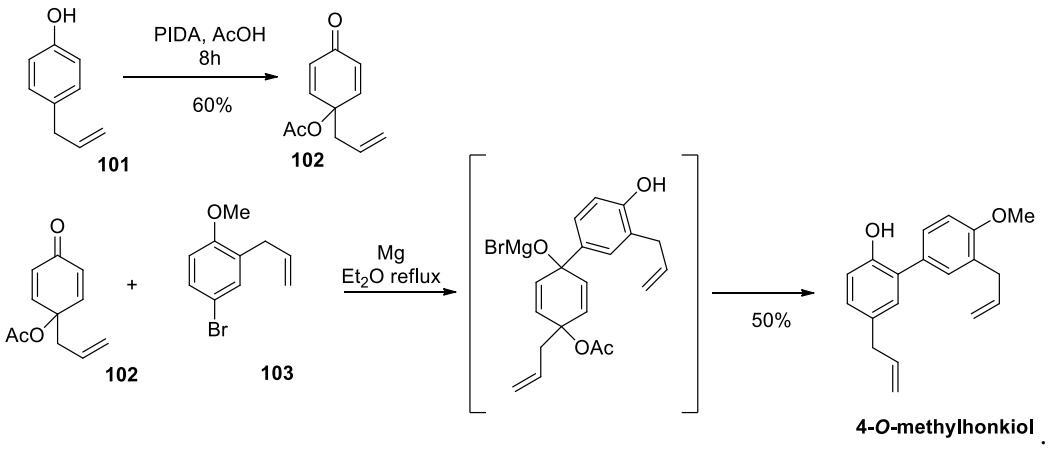
These species can react together in cycloaddition (*e.g.,* (hetero)-Diels–Alder reactions) as reported by Quideau for the synthesis of (+)-Aquaticol[216]. Moreover, this type of oxidative phenolic coupling has been

[216] Gagnepain, J.; Castet, F.; Quideau, S. *Angew. Chem. Int. Ed.* **2007**, *46* (9), 1533–1535.

exploited to obtain biaryl systems and to elaborate structurally more complex and nonaromatic architectures via C–C bond formation(s) as described by Kita[217].

Considering this feature of phenols to form quinonoids and looking for examples in literature reporting the para-quinol formation, we found a very interesting publication on the total synthesis of 4-*O*-methylhonkiol.[218]

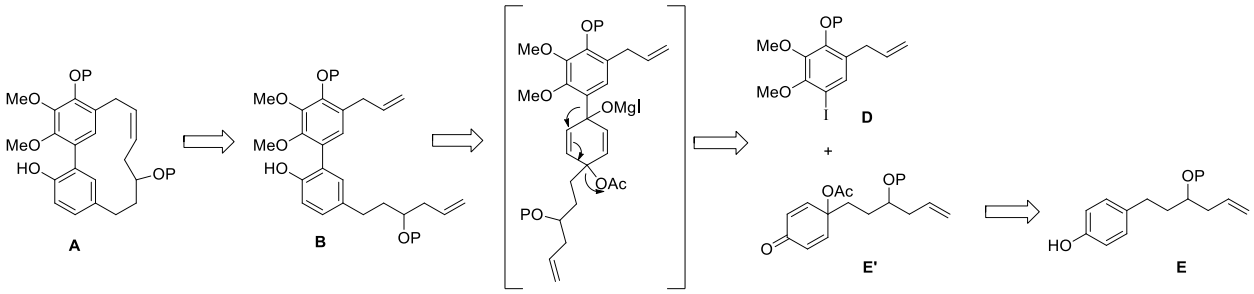
In this publication a *para*-allylphenol **101** was oxidized to the corresponding acetate dienone **102** with PIDA in presence of acetic acid. The synthesis was completed by coupling the corresponding Grignard reagent of bromide **103** with dienone **102**. This step occurs presumably, via acetate elimination and a 1,2-shift of the aryl group to afford the 4-*O*-methylhonkiol with 50% yield (**Scheme 4-78**).



Scheme 4-78 Total synthesis of 4-*O*-methylhonkiol via dienone acetate intermediate

Therefore we proposed the following retrosynthetic strategy (**Scheme 4-79**) for the synthesis of the biaryl core of myricanol which would be obtained by attack of a dienone acetate **E'** by the Grignard reagent of **D**.

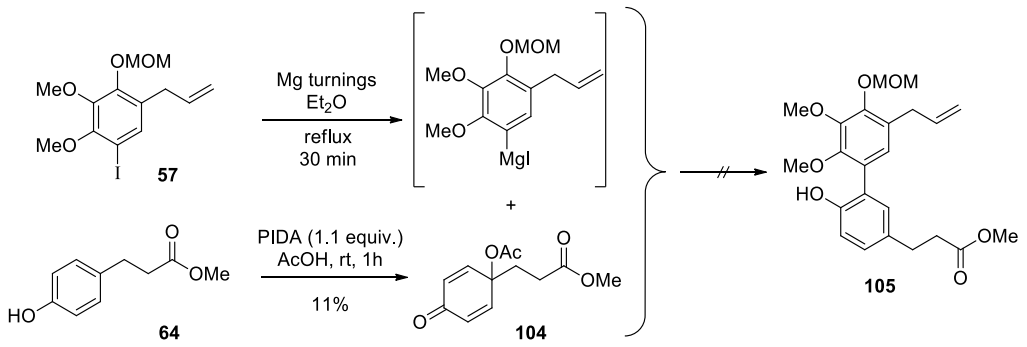
[217] Dohi, T.; Washimi, N.; Kamitanaka, T.; Fukushima, K.; Kita, Y. *Angew. Chem. Int. Ed.* **2011**, *50* (27), 6142–6146.
[218] a) Takeya, T.; Okubo, T.; Tobinaga, S. *Chem. Pharm. Bull. (Tokyo)* **1986**, *34* (5), 2066–2070. b) Denton, R. M.; Scragg, J. T.; Saska, J. *Tetrahedron Lett.* **2011**, *52* (20), 2554–2556.



Scheme 4-79 Retrosynthetic approach involving for dienone acetate coupling

At first we tried to transform the methylester **64** into the corresponding dienone acetate **104** (**Scheme 4-80).** The reaction was performed with PIDA (diacethoxyiodobenzene) in presence of acetic acid, through an oxidative process, the dienone **104** was formed but the resulting yield was only 11%. The reaction was repeated also at lower temperature, but no formation of the oxa-spirocyclic compound was observed as reported for similar substrates in literature.[219]

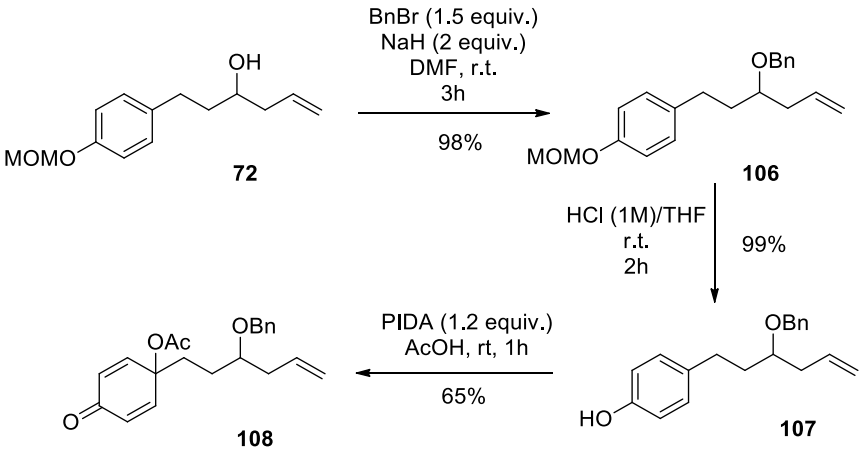
Despite the low yield of **104**, its coupling with **57** previously stirred at reflux temperature of Et_2O with Mg turnings was performed. We obtained only dehalogenated **57** and unreacted **104**. We performed the addition of dienone **104** with commercial phenylmagnesium bromide. In this case the coupling product was formed, clarifying that our dienone could undergo Grignard attack. Another test was done by treating iodine **57** with 1.1 equivalent of *n*-BuLi and addition of the formed organolithium species to **104** but none reaction occurred.



Scheme 4-80 Dienone acetate coupling with 57

[219] a) Vo, N. T.; Pace, R. D. M.; O'Har, F.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130* (2), 404–405. b) Novak, M.; Glover, S. A. *J. Am. Chem. Soc.* **2004**, *126* (25), 7748–7749. c) Jones, K. M.; Hillringhaus, T.; Klussmann, M. *Tetrahedron Lett.* **2013**, *54* (25), 3294–3297.

Considering the formation of dienone **104** with a very low yield, we next prepared the fragments **E'** bearing a homoallylic alcohol as expected in the retrosynthetic **Scheme 4-79**, we prepared the fragments **E'** bearing a homoallylic alcohol. Indeed, as reported in the following scheme, the homoallylic alcohol **72** was quantitatively protected with benzyl bromide to give **106**. The use of HCl (1M) in THF removes the MOM protecting group. Phenol **107** was obtained in quantitative yield. **107** was then treated with 1.2 equivalent of PIDA in AcOH and the desired product **108** was isolated in 65% yield.



Scheme 4-81 Preparation of dienone acetate 108

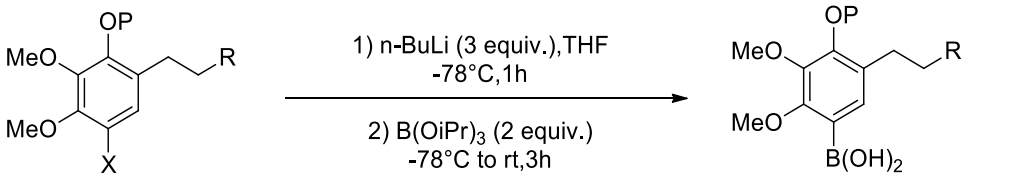
Having **108** in hand, coupling with the Grignard reagent of **57** would be performed in a near future.

4.3.1.3 Suzuki coupling

In this part of manuscript, we will present the work done to perform the intermolecular Suzuki-Miyaura cross-coupling between the **D** and **E** type's fragments borylated or halogenated.

4.3.1.3.1 Borylation of D type's fragments and Suzuki coupling with E type fragment

The synthesis of the boronic acids of the halogenated **D** type's fragments were performed by BuLi exchange followed by addition of triisopropylborate.[220] (**Scheme 4-82**)



56 P: Me, X: I, R: $=CH_2$
57 P: MOM, X: I, R: $=CH_2$
58 P: Bn, X: I, R: $=CH_2$
95 P: Bn, X: Br, R: $-CH_3$

56a P: Me, R: $=CH_2$ 84%
57a P: MOM, R: $=CH_2$ 50%**
58a P: Bn, R: $=CH_2$ 50%**
95a P: Bn, R: $-CH_3$ 0%

** product contains some impurity

Scheme 4-82 Borylation by nBuLi exchange with halogen on D type's fragments

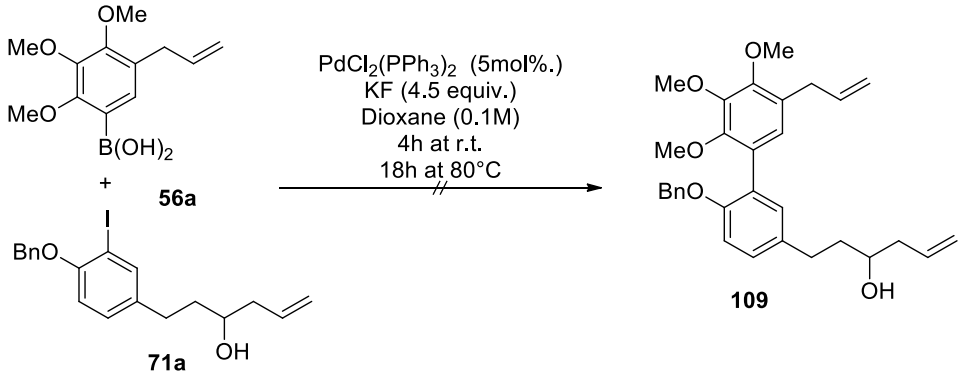
Initially the reaction was tried on substrate **56** with 1.2 equivalent of freshly titrated *n*BuLi, but none formation of the desired product **56a** was observed. As the iodinated product was recovered almost quantitatively, we thought that a stoichiometric quantity of BuLi wasn't enough to promote the iodine-lithium exchange. For this reason we employed directly 3 equivalent of BuLi. After 1h at -78°C, triisopropylborate [$B(OiPr)_3$] was added and the reaction was allowed to warm to room temperature for about 3h. After acidic quenching and purification of crude, we isolated the desired boronic acid **56a** with 84% yield. (**Scheme 4-82**). Using the same procedure, MOM protected compound **57** was transformed into the boronic acid **57a**, but it was impossible to obtain an isolated pure product.

The iodine-lithium exchange performed on **58** followed by addition of [$B(OiPr)_3$] gave the desired product with about 50% yield but the ^{1}H-NMR spectrum revealed some impurity that we were unable to eliminate. The same conditions used on the bromide **95** did not give the corresponding boronic acid.

With the boronic acids in our hands, we decided to perform first the Suzuki-Miyaura coupling between **56a** and **71a**. Efficient Suzuki cross-coupling reactions at room temperature were reported by Fu.[221] In order to

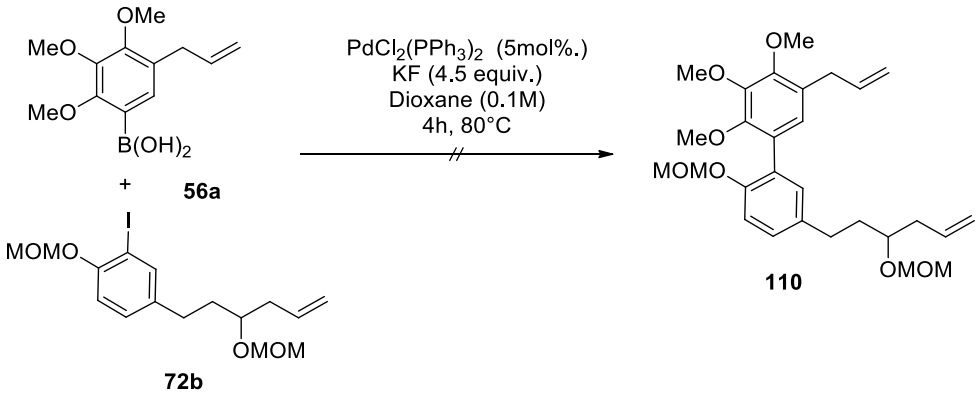
[220] Leão Lana, E. J.; Carazza, F.; Aparacida de Oliveira, R. *Helv. Chim. Acta* **2004**, *87* (7), 1825–1831.
[221] Fu, G. C. *Acc. Chem. Res.* **2008**, *41* (11), 1555–1564.

avoid the Pd-catalyzed isomerization of the allylic double bond, we tried this coupling reaction 4h at room temperature (**Scheme 4-83**) but no reaction occurred. Increasing the temperature from 25 °C to 80 °C during 18h did not afford compound **109**; only partially dehalogenated and deborylated products were isolated.



Scheme 4-83 Suzuki-Miyaura reaction at room temperature between 56a and 71a

Then we tried the Suzuki cross-coupling reaction (**Scheme 4-84**) between boronic acid **56a** and **72b** whose both hydroxyl groups are protected as MOM ethers (See 4.1.3 for its preparation).



Scheme 4-84 Suzuki-Miyaura reaction on 56a and 72b

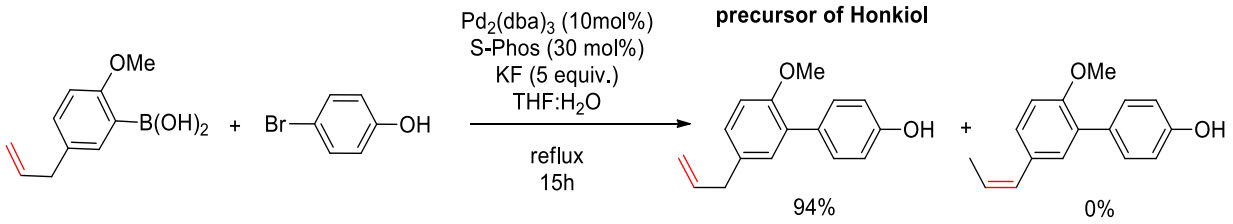
Also in this case the usual dehalogenated and deborylated compounds were found after purification together with unclear products on which partial isomerization of the allylic double bond was observed.

Taking account this unsatisfactory results we turned our attention to the borylation of **E** type's fragments and Suzuki cross-coupling reaction with **D** type's fragments.

4.3.1.3.2 Borylation of E type's fragments and Suzuki coupling with D type's fragments

First of all in order to avoid the loss of **E** type's fragments that required a multistep preparation, we chose commercially available (2-hydroxyphenyl)boronic acid as model.

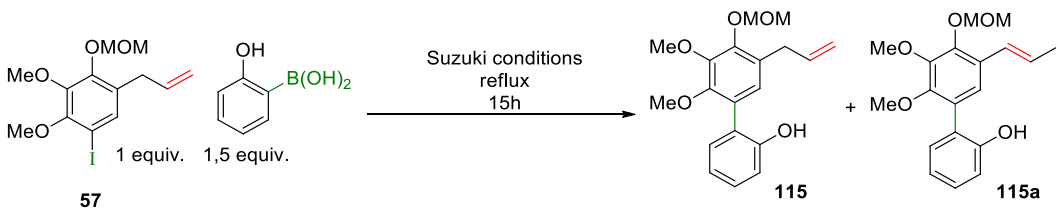
Denton et *al*. reported for the synthesis of a natural product honkiol,[222] a Suzuki-Miyaura cross-coupling reaction using an aryl boronic acid bearing an allylic double bond. After optimization of the coupling conditions, they found that tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] and S-Phos in presence of KF as base and THF:H_20 as solvent gave with 94% yield the desired coupling product without any trace of isomerized product (**Scheme 4-85**).



Scheme 4-85 Suzuki-Miyaura coupling reaction for synthesis of honkiol

We applied these conditions on our substrates, using X-Phos as ligand, as reported in **Table 4-17** (entry 1). We used 1 equivalent of substrate **57** and 1.5 equivalent of (2-hydroxyphenyl)boronic acid and we obtained a mixture 1:1 of two regioisomers **115** and **115a**.

[222] Denton, R. M.; Scragg, J. T.; Galofré, A. M.; Gui, X.; Lewis, W. *Tetrahedron* **2010**, *66* (40), 8029–8035.



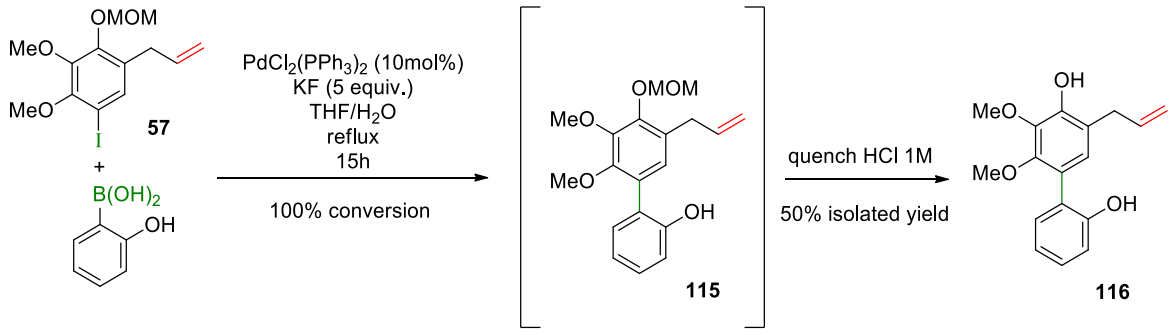
57 115 115a

Entry[a]	Pd source (10 mol%)	Ligand (30mol%)	115:115a [b]
1	$Pd_2(dba)_3$	X-Phos	50%:50%
2	$Pd_2(dba)_3$	PPh_3	90%:10%
3	$Pd(PPh_3)_4$		95%:5%
4	Pd-GL-X-Phos		5%:95%
5	$PdCl_2(PPh_3)_2$		100%[c]:0%
6	$PdCl_2(dppf)_2$		90%:10%

a.condition: KF (5equiv), THF/H_2O (10:1), b. conversion evaluated GC-MS, c. total conversion of s.m(100%), the MOM hydrolized product was isolated with 50% yield after acid quench of reaction.

Table 4-17 Suzuki-Miyaura coupling reaction between 57 and (2-hydroxyphenyl)boronic acid

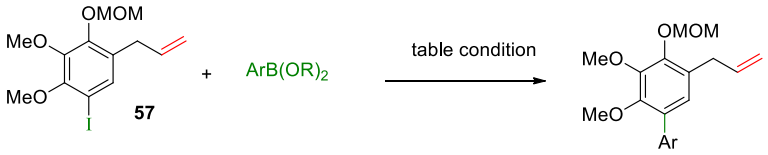
Different Suzuki cross-coupling reactions were tested changing only the catalytic system. Changing the ligand (PPh_3 instead of X-Phos) allowed to obtain **115** and **115a** in an interesting 90:10 ratio. Surprisingly we observed that with a second generation X-Phos precatalyst (entry 4) the major isomer formed is **115a.** Finally using $PdCl_2(PPh_3)_2$ (entry 5) gave only **115**. The acidic quench of the reaction with HCl (1M) allowed to isolate with 50% yield the deprotected coupled compound **116** without isomerization of the allylic double bond (**Scheme 4-86**).

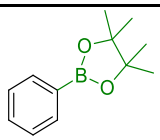
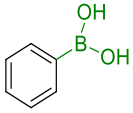
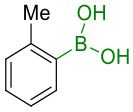
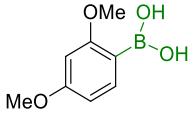


Scheme 4-86 Suzuki-Miyaura conditions that avoid double bond isomerization

Accordingly trials with other commercial boronic species (acid or ester) were performed with substrate **57** (**Table 4-18**).

Except for the entry 1 in which similar Denton conditions were tried, the other tests were carried out with $PdCl_2(PPh_3)_2$. But the results were different, except for the entry 4 in which coupling reaction occurred. Otherwise only starting materials, dehalogenated **57** and side-products were formed. The analysis of this results brought us to conclude that the free OH in *ortho* position to the boronic acid is important and probably involved in some coordination with palladium that favoured the reaction. Indeed, when boronic acid are involved in Suzuki-Miyaura coupling reactions, multiple factors could influence the rate of transmetallation, as reported by Jutand and co-workers.[223]



Entry[a]	ArB(OR)$_2$	Pd Source 10mol%	Ligand 30mol%	Products
1		$Pd_2(dba)_3$	X-Phos	Trace + s.m.
2		$PdCl_2(PPh_3)_2$		byproducts + dehalogenated sm
3		$PdCl_2(PPh_3)_2$		byproducts + dehalogenated sm
4		$PdCl_2(PPh_3)_2$		50%:30%[b] + 20% dehalogenated s.m.

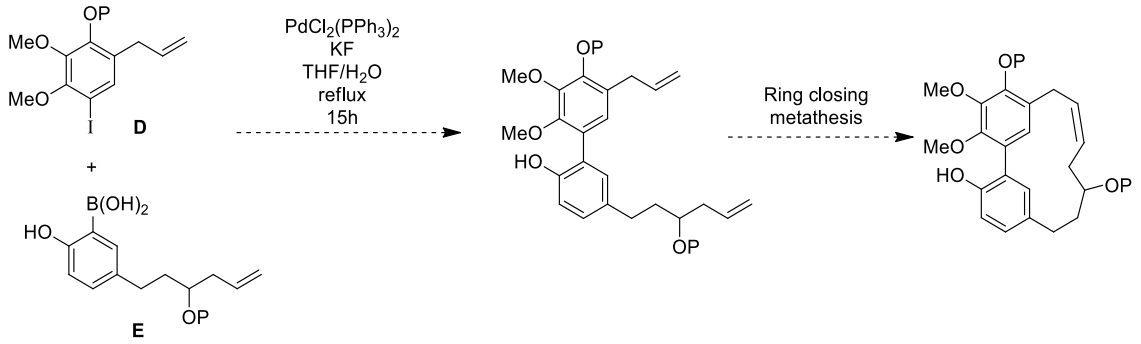
a. condition: KF (5equiv), THF/H_2O (10:1), b. ratio between the two regioisomers

Table 4-18 Suzuki-Miyaura coupling between 57 and boronic species

[223] Amatore, C.; Le Duc, G.; Jutand, A. *Chem. - Eur. J.* **2013**, *19* (31), 10082–10093.

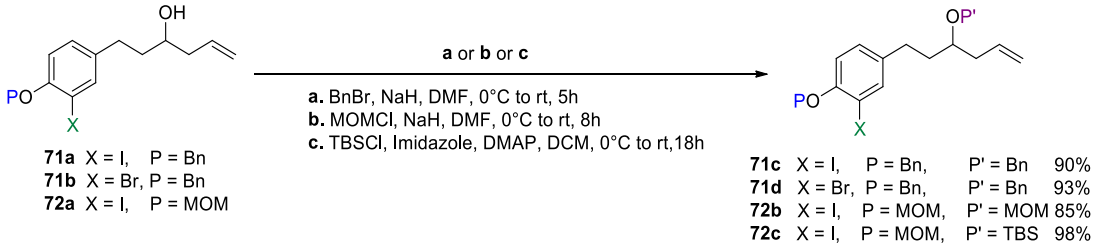
Considering this factor, we decided to install a boronic acid on the **E** types's fragments with a free hydroxyl group, in *ortho* position to the boron.

The intermolecular biaryl coupling expected will be performed between an iodinated **D** type's fragment and an *O*-hydroxyphenyl boronic acid **E** type (**Scheme 4-87**).



Scheme 4-87 Suzuki-Miyaura intermolecular cross-coupling reaction

Before to start with the tests of borylation, we protected the secondary alcohol of **E** type's fragments as reported in **Table 4-19.** The substrates **71a**, **71b** and **72a** were respectively transformed into **71c**, **71d**, **72b** and **72c** in quantitative or quasi-quantitative yield. As showed in **Table 4-19** we prepared iodinated and brominated compounds with identical protecting groups on phenol and alcoholic position or with different protecting groups as in the case of **72c**. This library of compounds was prepared to test borylation reactions.

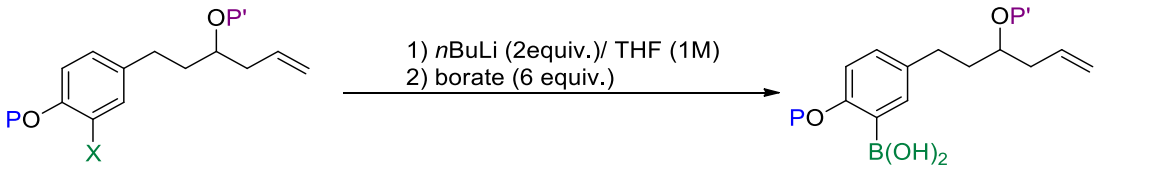


Entry	SM	X	P	Protection conditions	P'	Prod.	Yield
1	**71a**	I	Bn	BnBr, NaH, DMF, 0°C to rt, 5h	Bn	**71c**	90%
2	**71b**	Br	Bn	BnBr, NaH, DMF, 0°C to rt, 5h	Bn	**71d**	93%
3	**72a**	I	MOM	MOMCl, NaH, DMF, 0°C to rt, 8h	MOM	**72b**	85%
4	**72a**	I	MOM	TBSCl, Imidazole, DMAP, DCM, 0°C to rt,18h	TBS	**72c**	98%

Table 4-19 Secondary alcohol's protection of E type's fragments

The first borylations were tried using *n*-BuLi and different borates to find the suitable conditions.[224]

In the following table are reported a series of reactions performed on the substrates **71a**, **72a**, **71c** and **72b**. In all the performed reactions, 2 equivalents of *n*-BuLi and 6 equivalents of borate (independently from their nature) were used. The first essay was done on the monobenzylated compound **71a**; addition of *n*-BuLi at -78°C followed by addition of triisopropylborate and the mixture is allowed to warm at room temperature all night long. The NMR analysis of the crude showed the formation of the dehalogenated compound in mixture with starting product. The same result was obtained when the reaction was done on dibenzylated **71c** (entry 2). In entries 3 and 4 of the **Table 4-20**, the mixture was stirred for 30min in presence of *n*-BuLi, but again starting materials and dehalogenated products were found in the crude.



71a X = I, P = Bn, P' = H
72a X = I, P = MOM, P' = H
71c X = I, P = Bn, P' = Bn
72b X = I, P = MOM, P' = MOM

117 P = Bn, P' = H
118 P = MOM, P' = H
117a P = Bn, P' = Bn
118a P = MOM, P' = MOM

Entry	Sub.	*n*BuLi (T/t)	Borate	Borate addition (T/t)	Product*
1	**71a**	-78°C, 10min	B(*i*-OPr)$_3$	-78°C to rt, 18h	-
2	**71c**	-78°C, 10min	B(*i*-OPr)$_3$	-78°C to rt, 18h	-
3	**72a**	-78°C, 30min	B(*i*-OPr)$_3$	-78°C to rt, 18h	-
4	**72b**	-78°C, 30min	B(*i*-OPr)$_3$	-78°C to rt, 1h	-
5	**72a**	-78°C, 1h	B(OMe)$_3$	-78°C to rt, 18h	-
6	**72a**	-78°C, 1h	B(OEt)$_3$	-78°C to rt, 18h	-
7	**71c**	-78°C, 3h	B(*i*-OPr)$_3$	-15°C to rt, 4d	-

*Only starting material and dehalogenated products were recollected.

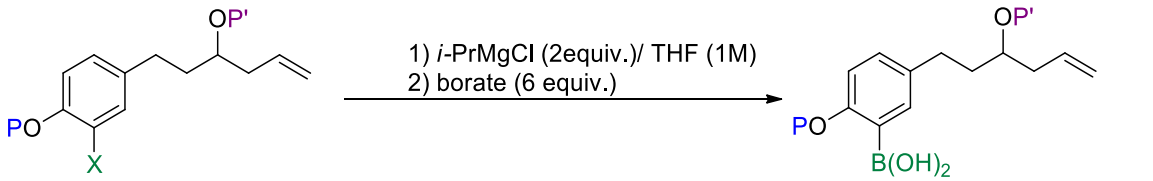
Table 4-20 Borylation promoted by nBuLi exchange

[224] a) Lin, J. M.; Prakasha Gowda, A. S.; Sharma, A. K.; Amin, S. *Bioorg. Med. Chem.* **2012**, *20* (10), 3202–3211. b) Palmer, F. N.; Lach, F.; Poriel, C.; Pepper, A. G.; Bagley, M. C.; Slawin, A. M. Z.; Moody, C. J. *Org. Biomol. Chem.* **2005**, *3* (20), 3805–3811.

Others tests were done stirring **72a** one hour with nBuLi with differents boronic esters but no traces of the desired boronic acid were observed (entry 5 and 6). The last attempt was performed on **71c**; *n*-BuLi was added at -78°C, the solution was stirred for 3h during which the temperature reached -15°C. At this temperature the borate was added and the solution was allowed to stir for 4days. Despite all these efforts, boronic acid wasn't obtained.

Disappointed by this results, we decided to try halogen exchange with magnesium in place of lithium as already used by Colobert et *al*. for iodinated substrates.[225]

In this case we focused our tests on **71c** and **71a** and we finally observed (entry 1, **Table 4-21**) the formation of the desired boronic acid **117a** that was isolated after a column chromatography with a 24% yield. Because this result was obtain after stirring for 3 days the mixture with triisopropylborate, we tried to reduce the reaction time repeating the same conditions (entry 2) and stopping the reaction after 18h of reaction. Unfortunately only dehalogenated product was obtained. Other attempts were realized adding *i*-PrMgCl at 0°C instead of -78°C (entry 3 and 4), but also these tests were unsuccessful, as well as the one performed on **72b** (entry5).



71c X = I, P = Bn, P' = Bn
72b X = I, P = MOM, P' = MOM

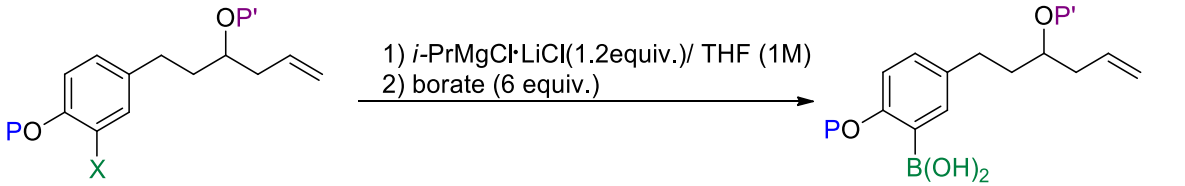
117a P = Bn, P' = Bn
118a P = MOM, P' = MOM

Entry	Sub.	*i*-PrMgCl (T/t)	Borate	Borate addition (T/t)	Product
1	**71c**	-78°C, 1h	B(*i*-OPr)$_3$	-78°C to rt, 3d	24% (**117a**)
2	**71c**	-78°C, 1h	B(*i*-OPr)$_3$	-78°C to rt, 18h	-
3	**71c**	0°C, 1h	B(*i*-OPr)$_3$	0°C to rt, 1.5h	
4	**71c**	0°C, 3.5h	B(*i*-OPr)$_3$	0°C to rt, 4d	
5	**72b**	-78°C, 1h	B(*i*-OPr)$_3$	-78°C to rt, 18h	

Table 4-21 Borylation promoted by i-PrMgCl exchange

[225] Leermann, T.; Leroux, F. R.; Colobert, F. *Org. Lett.* **2011**, *13* (17), 4479–4481.

Another possibility was to use the turbo Grignard *i*-PrMgCl-LiCl widely investigated by Knochel and coworkers.[226] In the **Table 4-22** are reported the results obtained performing the reactions with 1.2 equivalents of *i*-PrMgCl-LiCl. The first attempt (entry 1) on **71c** with triisopropylborate gave a ratio 71%: 29% of the dehalogenated starting material and the desired product. With trimethylborate (entry 2) the desired product **117a** was obtained with a ratio almost 50:50 compared to the dehalogenated product. Trimethoxyborate was also employed with **72c** (entry 3) giving **119** and the dehalogenated product in a 75:25 ratio. Same conditions were tried on the brominated product **71d** affording only starting material.



71c X = I, P = Bn, P' = Bn
71d X = Br, P = Bn, P' = Bn
72c X = I, P= MOM, P' = TBS

117a P = Bn, P' = Bn
119 P = MOM, P' = TBS

Entry	Sub.	*i*-PrMgCl Li (T/t)	Borate	Borate addition (T/t)	Product*
1	**71c**	-78°C, 1h	B(*i*-OPr)$_3$	-78°C to rt, 18h	71%/29% dehalog./**117a**
2	**71c**	-78°C, 1h	B(OMe)$_3$	-78°C to rt, 18h	53%/47% dehalogen./**117a**
3	**72c**	-78°C, 1h	B(OMe)$_3$	-78°C to rt, 2d	75%/25% dehalogen./**119**
4	**71d**	-78°C, 1h	B(OMe)$_3$	-78°C to rt, 18h	s.m.

*Ratio determined by NMR analysis

Table 4-22 Borylation promoted by *i*-PrMgCl LiCl exchange

Currently we are working on this step trying to improve the yield of this reaction. In particular we would optimize the results on substrates with different protecting groups (like in entry 3) in order to perform a

[226] a) Knochel, P.; M. Barl, N.; Werner, V.; Sämann, C. *HETEROCYCLES* **2014**, *88* (2), 827. b) Klatt, T.; Markiewicz, J. T.; Sämann, C.; Knochel, P. *J. Org. Chem.* **2014**, *79* (10), 4253–4269. c) Krasovskiy, A.; Straub, B. F.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45* (1), 159–162.

selective deprotection on phenol in order to have a free hydroxyl group in *ortho* position of the formed boronic acid.

This boronic acid will be used in Suzuki-Miyaura cross-coupling reactions, following the best conditions found to avoid isomerization of allylic double bond (see **Scheme 4-86**). Therefore the following synthesis towards myricanol would be the RCM.

5 BIOLOGICAL EVALUATION OF LINEAR DIARYLALKYL COMPOUNDS

5.1 OBJECTIVES

In the previous chapter we have disclosed the preparation of linear diarylalkanoids with different chain lengths (see paragraph 4.2.1). Natural diarylheptanoids extracted from *Aceraceae*, *Betulacea*e, *Zingiberaceae*, *Leguminosae*, *Juglandaceae*, *Myricaceae* etc. are increasingly recognized as potential therapeutic agents for their numerous physiological activities such as anti-inflammatory, antioxidant, antitumor, estrogenic, leishmanicidal, anti-melanogenesis, hepatoprotective and neuroprotective.[3,4]

For these reasons, we decided to evaluate the biological activities of the prepared diarylalkanoids. Since myricanol shows antioxidant[9] and anti-tau activity[37], it was appropriate to opt, in the first place, for an anti-inflammatory evaluation of our linear analogues. The oxidative stress is, indeed, one of the most important factors involved in inflammatory and in the neurodegenerative disease (as Alzheimer disease).

The molecules tested are depicted in the following figure. Aside from diarylheptanoids **75a**, **83** and **84**, we decided to screen also the diarylhexanoid **78** and the homocoupled products derived from cross-metathesis reaction **48bis** and **71bis.** Moreover, a Dess-Martin oxidation of **71bis** afforded quantitatively the diketone **72bis** which was also evaluated. Interestingly **71bis** and **72bis** are new diaryldecanoids.

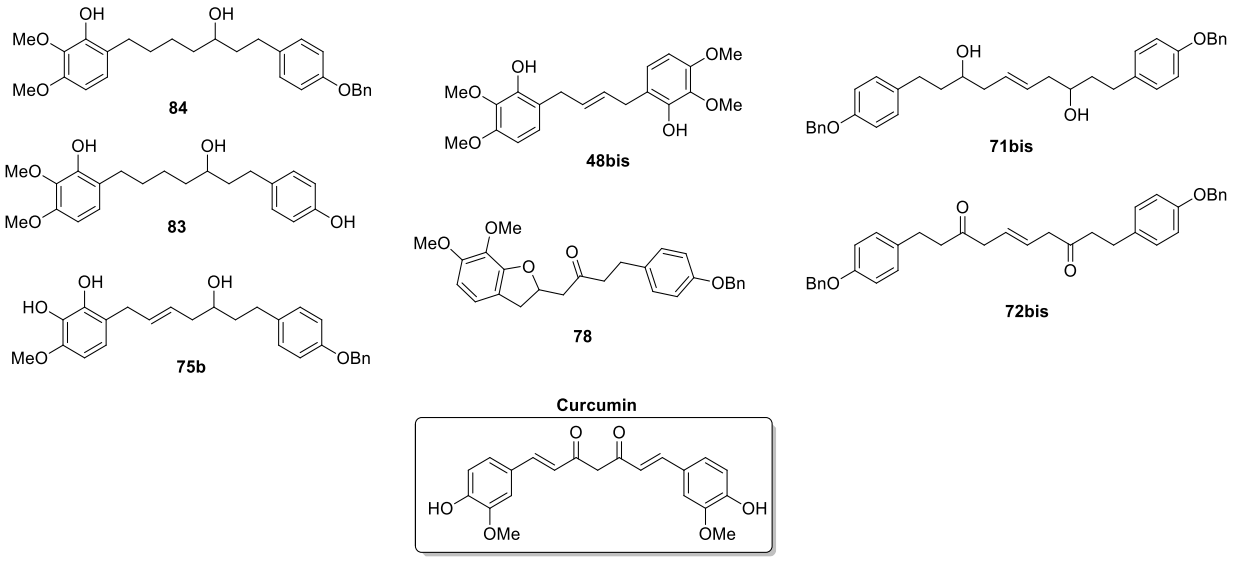


Figure 5-1 Molecule evaluated for their antioxidant properties

Curcumin was choosen as reference in our experiements. It is an orange-yellow crystalline powder that was first described in 1910 by Lampe and Milobedeska. Due to its yellow colour and the "miraculous" biological activities, Curcumin is defined as the golden spice.[5] Curcumin possess pleiotropic activities due to polyphenol structure that modulate multiple signalling molecules. First demonstrated to have antibacterial

activity in 1949, curcumin has since been shown to have anti-inflammatory, anti-oxidant, pro-apoptotic, chemopreventive, chemotherapeutic, antiproliferative, antiparasitic and antimalarial properties as well.[227]

In the following pages will be reported the biological tests done on the prepared molecules from the laboratory of biology of Dr. Infatino of University of Basilicata. The aim of these tests was to understand the ability of prepared molecules to suppress cellular inflammation. Two typical cellular lines of inflammatory system were used: human U937 and murine BV-2 cells.

[227] Maheshwari, R. K.; Singh, A. K.; Gaddipati, J.; Srimal, R. C. *Life Sci.* **2006**, *78* (18), 2081–2087.

5.2 CYTOTOXICITY TEST

Since these curcumin analogues were newly synthetized, first their cytotoxic effects were determined by the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) uptake method in U937 and BV-2 cell lines. **Figure 5-2** summarizes the relative cell viability of U937 and BV-2 cells, respectively, treated with our compounds, compared to the leading curcumin. Curcumin showed no cytotoxicity up to 100 nM in both cell lines **Figure 5-2** but was toxic at 1 µM in U937 cells (**Figure 5-2, A**). Compounds **75b**, **78**, **83** and **84** were not toxic up to 1 µM in both cell lines. All the compounds affected the viability of U937 and BV-2 cells starting at 5 µM. Indeed no effect was detected from any compounds at 10 nM in both tested cells. For this reason we chose 10 nM as optimal concentration to evaluate the anti-inflammatory effect of synthesized compounds.

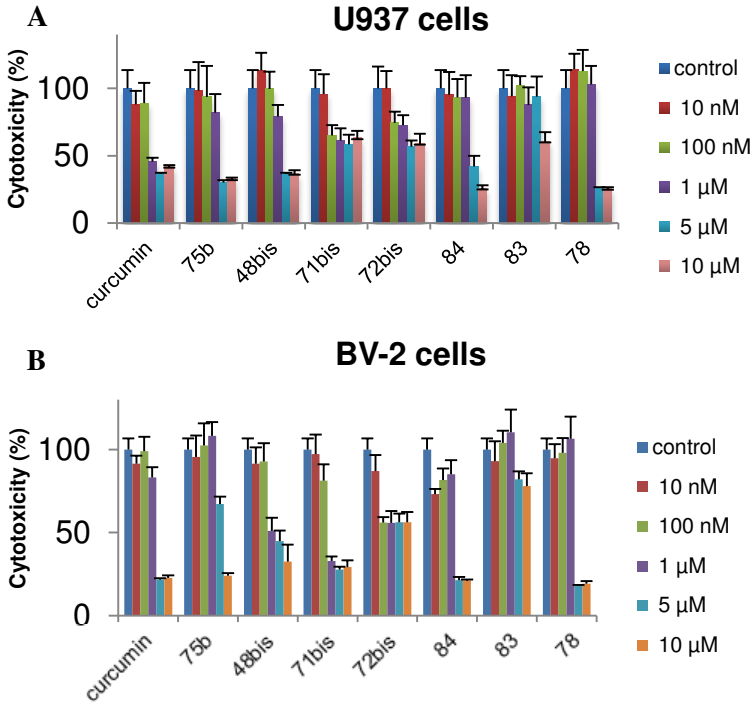


Figure 5-2 Cytotoxic effect of polyoxygenated diaryl-alkyl compounds

U937 cells (A) and BV-2 cells (B) were treated with DMSO (control, blue), 0.01 (red), 0.1 (green), 1 (violet), 5 (light blue) or 10 µM (orange) curcumin, **48bis**, **71bis**, **72bis**, **75b, 78, 83, 84** compounds. After 72 h cytotoxicity was measured by MTT assay. Means ± S.D. of eight replicate independent experiments are shown; differences between samples were significant ($p < 0.05$, one-way ANOVA). Where indicated differences between samples and relative controls (set at 100%) (*$p < 0.05$, **$p < 0.01$, Student's t-test) were significant.

5.3 ROS AND NO EVALUATION ON U937 AND BV-2 CELLS

ROS (Reactive oxygen species) and NO (Nitric Oxide) are two of well-characterized chemokines that play an important role in inflammation.[228] Intense production of ROS and NO contributes significantly to the pathological complications observed in various diseases[229]. Curcumin and its seven synthetic analogues were evaluated for their ability to inhibit the ROS and NO synthesis in U937 and BV-2 cells stimulated by LPS (Lipopolysaccharides). Macrophages were stimulated with LPS in the presence or absence of each compound at a concentration of 10 nM, where the leading compound curcumin showed a significant inhibition against ROS and NO production without affecting cell vitality. The cells were pre-incubated for 30 minutes with curcumin analogues or DMSO as a negative control. Thereafter, cells were treated with LPS (400 ng/ml) for 24 hours at 37°C. ROS and NO levels were detected through a fluorescence microplate reader. **Figure 5-3** (**A** and **B**) display the anti-inflammatory evaluation of each compound in U937 cells. Curcumin reduced LPS- mediated ROS and NO production at 71% and 79% in U937 cells, (**A** and **B**), respectively. The majority of the tested compounds inhibited LPS-induced ROS and NO synthesis at different degrees.

[228] Infantino, V.; Convertini, P.; Cucci, L.; Panaro, M. A.; Di Noia, M. A.; Calvello, R.; Palmieri, F.; Iacobazzi, V. *Biochem. J.* **2011**, *438* (3), 433–436.

[229] Valko, M.; Leibfritz, D.; Moncol, J.; Cronin, M. T. D.; Mazur, M.; Telser, J. *Int. J. Biochem. Cell Biol.* **2007**, *39* (1), 44–84.

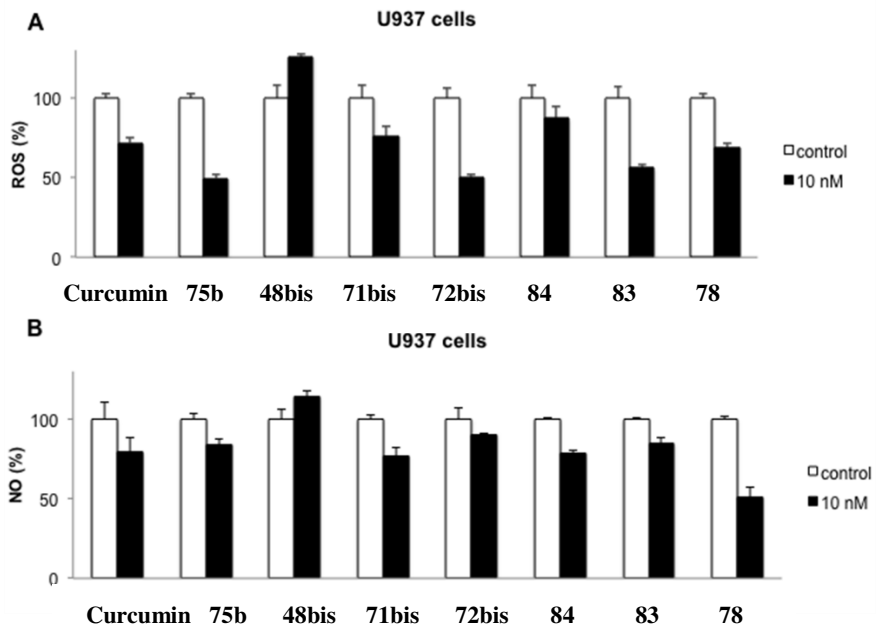


Figure 5-3 Evaluation of ROS and NO on U937 cells

U937 cells were treated with LPS in presence or absence of **48bis**, **71bis**, **72bis**, **75b, 78, 83,** and **84** and then used to quantify ROS and NO. Means ± S.D. of six duplicate independent experiments are shown; differences between samples and relative controls were significant ($P < 0.05$, one-way ANOVA).

Compounds **75b**, **72bis** and **83**, exhibited higher inhibitory ability in terms of ROS than the leading curcumin in U937 cells (**Figure 5-3-A**). With regards to NO, only **78** showed inhibition of NO over 30% compared to the leading curcumin in U937 cells. Compounds **71bis** and **84** were as potent as curcumin in inhibiting LPS-induced NO synthesis (**Figure 5-3-B**).

Microglial cells (BV-2 cells) are resident macrophages of the nervous system with pivotal roles in innate immune regulation and neuronal homeostasis.[230] Since curcumin inhibits the activation of microglial cells by diminishing the synthesis of nitric oxide[231] in another set of experiments we tested BV-2 microglial cells for ROS and NO production with our compounds (**Figure 5-4 A** and **B**). No significant difference was observed between curcumin and its analogues in BV-2 ROS production. However, all compounds displayed a significant reduction of ROS levels when compared to control (**Figure 5-4 A**). In **Figure 5-4 B** is showed the NO production in BV-2 cells. In these microglial cells, the tested compounds except compound **48bis** showed a reduction of NO

[230] Giulian, D.; Li, J.; Bartel, S.; Broker, J.; Li, X.; Kirkpatrick, J. B. *The Journal of neuroscience* **1995**, *15*(11), 7712-7726.

[231] Jung, K. K.; Lee, H. S.; Cho, J. Y.; Shin, W. C.; Rhee, M. H.; Kim, T. G.; Kang, J. H.; Kim, S. H.; Hong, S.; Kang, S. Y. *Life Sci.* **2006**, *79* (21), 2022–2031.

levels with respect to the leading curcumin. Among them, **71bis** and **72bis** had the strongest inhibitor effect on LPS-induced NO production in BV-2 cells (**Figure 5-4 B**).

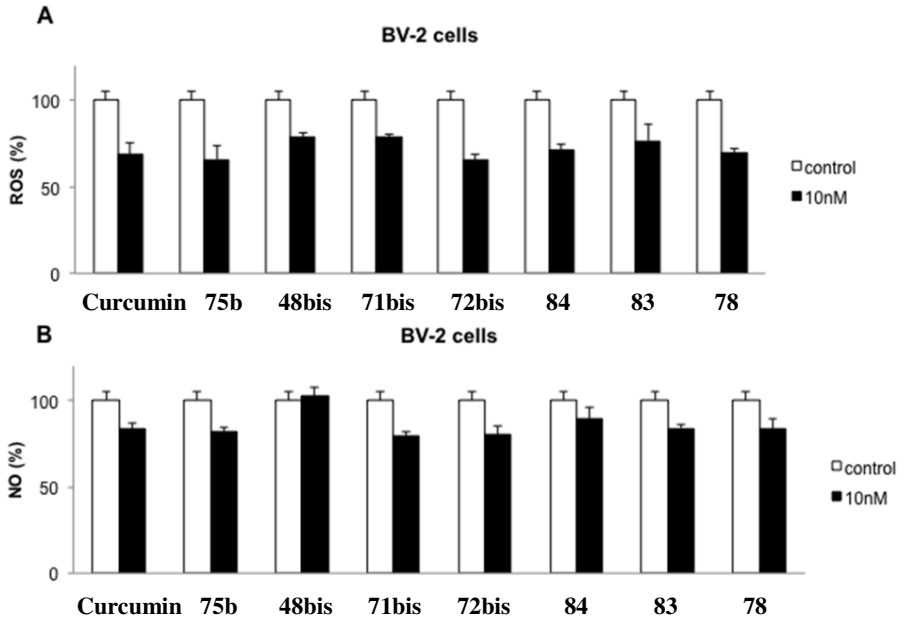


Figure 5-4 Evaluation of ROS and NO on BV-2 cells

BV-2 cells were treated with LPS in presence or absence of **48bis**, **71bis**, **72bis**, **75b, 78, 83, 84** and then used to quantify ROS and NO. Means ± S.D. of six duplicate independent experiments are shown; differences between samples and relative controls were significant ($P < 0.05$, one-way ANOVA).

Interestingly compounds **75b**, **71bis**, **72bis** most inhibit ROS and NO synthesis in both cell lines.

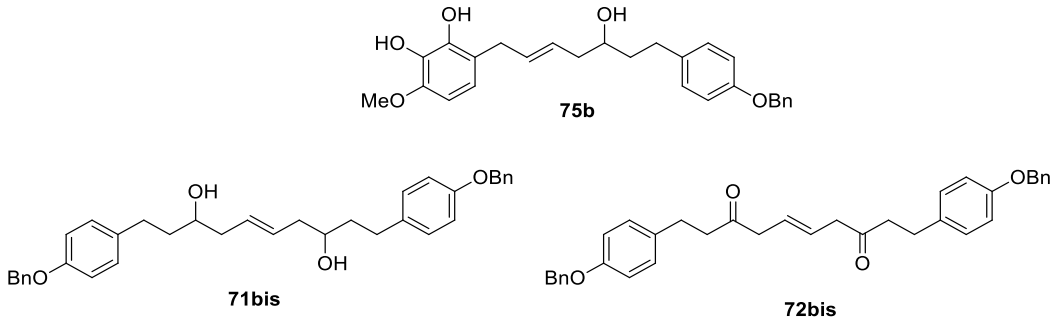


Figure 5-5 More active molecules 75b, 71bis and 72bis

A possible explanation could be the presence of allylic moiety in the chain of each molecule. Methylene bridge of the homoallylic alcohol or β,γ-unsaturated ketone could be involved in the delocalization of probably formed radical. The significant inhibitory activity of the compound **72bis** is most likely due to its carbonyl groups inside the long linear chain, which can delocalize electrons from free radicals during

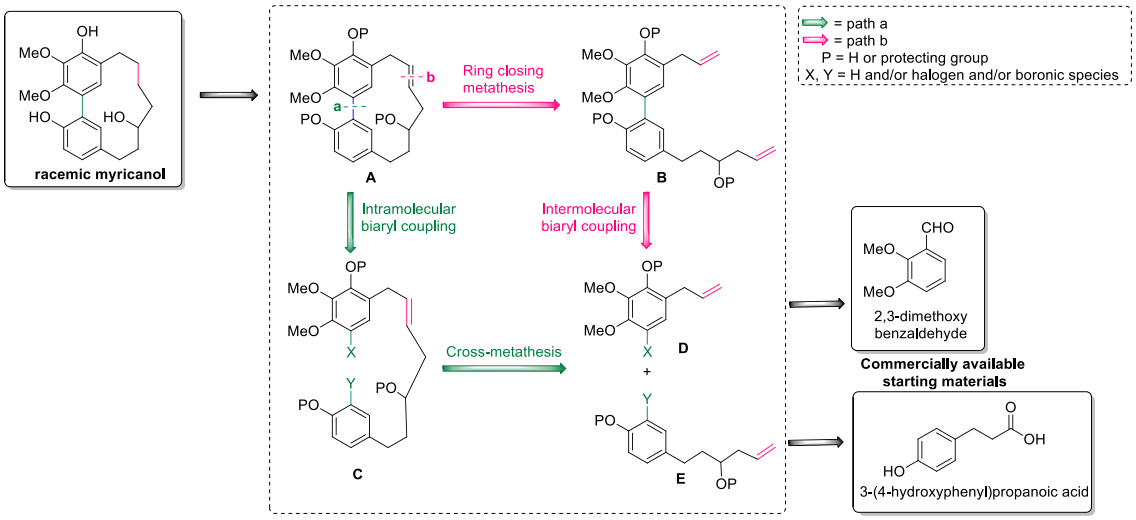
inflammation. Also noteworthy is the fact that compound **48bis** shows no anti-inflammatory properties. Our hypothesis is that the long linear chain is important for the anti-inflammatory activity since compound **48bis** is the shortest with only 4 carbons, without a homoallylic alcohol or ketone inside. This is also supported by the strong inhibitory activity of compounds **71bis** and **72bis**, which have a linear chain of 10 carbons with oxygenated and unsaturated positions that delocalize electrons better than curcumin.

All these results indicate that the long chain with carbonyl groups and the double bond inside is important for the antioxidant activity. Future investigation could demonstrate whether these compounds have a molecular target(s) in inflammation or act as free radical scavengers.

6 GENERAL CONCLUSIONS AND PERSPECTIVES

The main topic of this thesis is the search for a succinct and reliable route towards an atropo-stereoselective synthesis of myricanol, a pathway studded with numerous stumbling blocks and detours.

For this purpose, we envisioned to construct the [7,0]-*meta*cyclophane core of myricanol *via* two possible ways. The first one (path a, **Scheme 6-1**) required the intramolecular biarylic C-C coupling (Suzuki-Miyaura, Ullman, C-H activation, oxidative coupling) of the *seco*-precursor **C**. This diarylheptenoid might result from a cross metathesis reaction between the fragments **D** and **E** which in turn would be accessible from cheap commercially available starting materials. The second one (path b, **Scheme 6-1**) exploited the ring closing metathesis (RCM) in the construction of the macrocycle **A** and required the intermolecular biarylic C-C coupling of partners **D** and **E** to afford the cyclization precursor **B**.



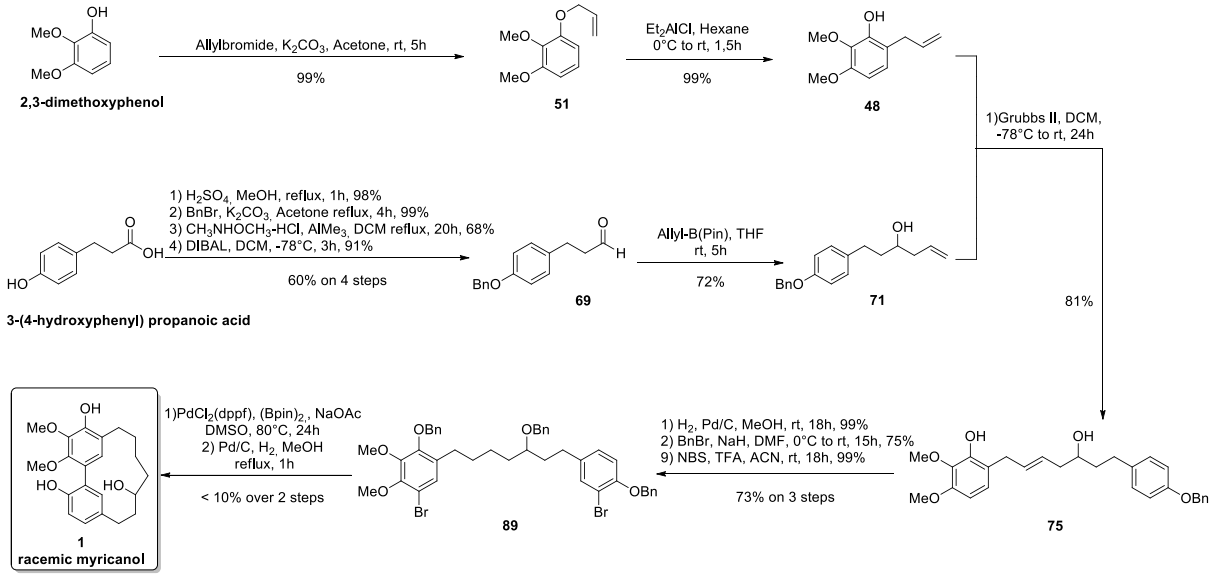
Scheme 6-1 Approaches considered for preparation of myricanol

The two pathways (path a and b) shared the common starting fragments **D** and **E**. The initial part of this thesis concerned their synthesis. The fragments were prepared with and without halogens on the aromatic rings.

The path a was investigated first and after numerous optimization of firstly cross metathesis reaction and secondly macrocyclization gave the desired myricanol.

The crucial macrocyclization of **89** (**Scheme 6-2**) has turned out to be highly difficult whatever coupling methods tested, yielding the final myricanol in less than 10% yield (yield was not exactly determined because the final product was obtained with some unknown and not quantifiable impurities) after benzyl ethers cleavage using a domino process developed by Zhu and *coll*. Nevertheless, as illustrated in **Scheme 6-2**, myricanol was synthetized in 2.55% yield over 11 steps which competes favourably the sequence

reported by Whiting (0.21% in 14 steps, see 2.4.2) and even the sequence reported by Dickey (2.03% over 7 steps, starting from already functionalized and not commercially available compounds, see 2.4.3).



Scheme 6-2 Total synthesis of myricanol

The more difficult steps of this synthesis have been:

1. Claisen rearrangement of *O*-allylphenol **51**: despite numerous conditions tried, only using Et_2AlCl we were able to obtain regioselectively and quantitatively the *C*-allyphenol **48** (see 4.1.1.2.2).

2. Cross-metathesis between **48** and **71**: a series of tests were done to improve the yield of this reaction. The best result was obtained using a ratio 4:1 of **48** and **71**, respectively and 3mol% of catalyst Grubbs II rigorously added at -78°C. This allowed to obtain **75** in 80% yield (see 4.2.1).

3. Macrocyclization: different C-C coupling methods were investigated (Ullmann coupling, CH-arylation, Suzuki-Miyaura coupling). Only the methodology tuning by Jieping Zhu and collaborators gave the macrocycle in a domino process including the synthesis of an arylboronic ester which is involved in the intramolecular Suzuki coupling (see 4.2.3.3).

The total synthesis of myricanol have been accomplished by using two methodologies (cross-methatesis and Suzuki-Miyaura domino process) never reported before for the obtention of this natural [7,0]-*meta*-cyclophane.

Moreover, during the preparation of linear diarylalkyl derivatives using CM reaction, we were able to prepare compounds**75b**, **71bis** and **72bis** that were revealed good ROS and NO inhibitor in U937 and BV-2 cell lines (in the performed biological tests, curcumin was used as reference).

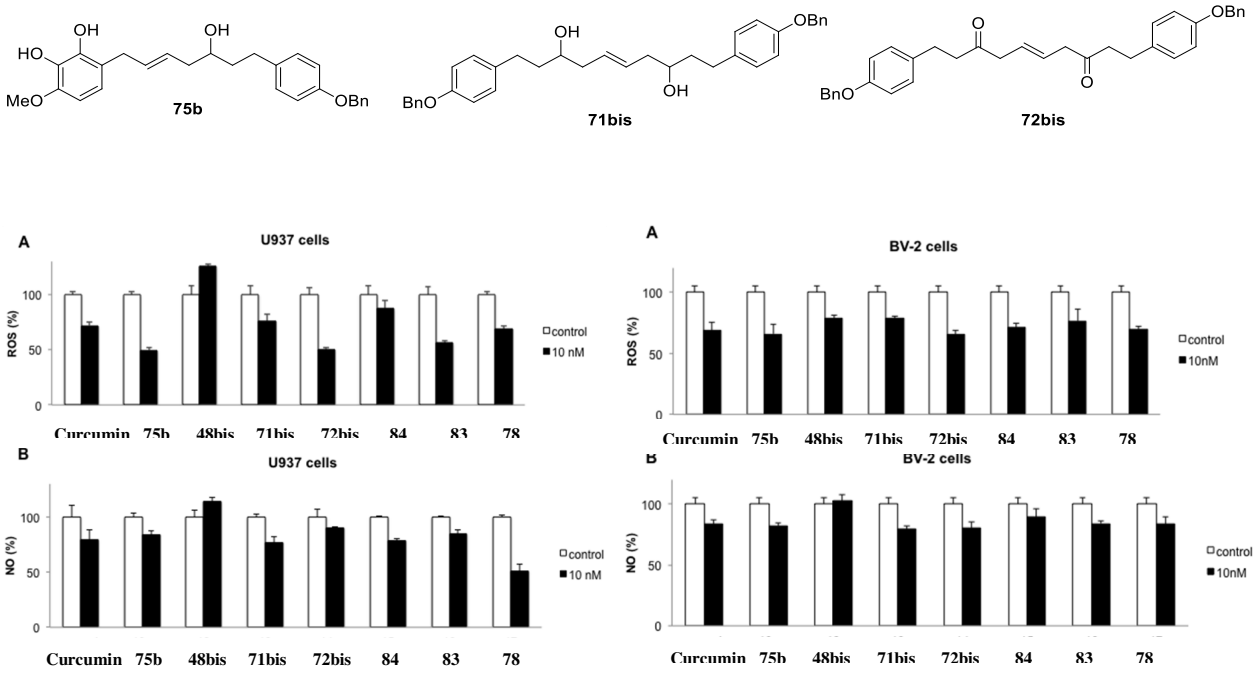
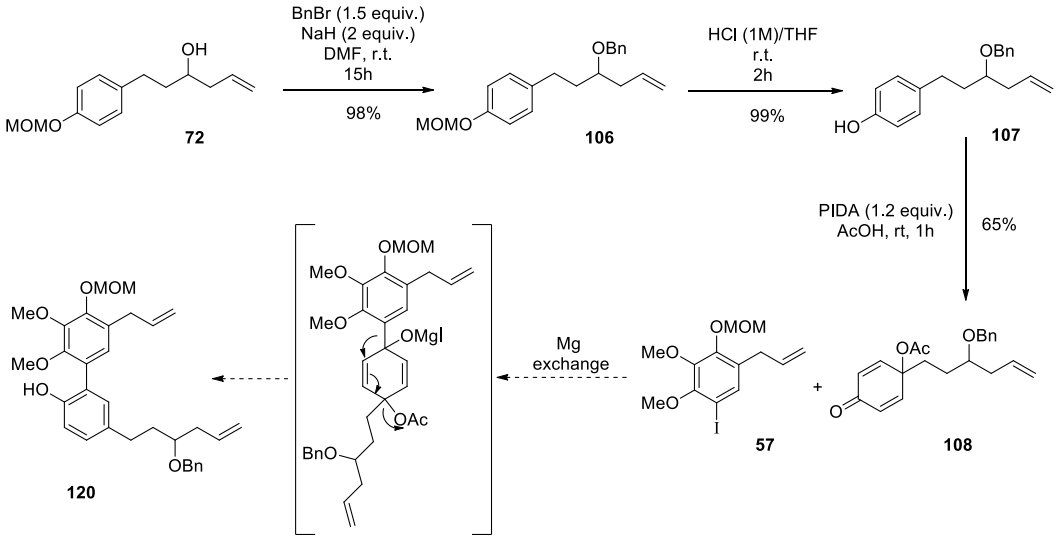


Figure 6-1 Prepared molecules75b, 71bis and 72bis inhibit NOS and NO in U937 and BV-2 cell lines

Path b (pink color in **Scheme 6-1)** was also investigated to prepare myricanol by an initial biaryl formation and a subsequent cyclization using RCM. This type of approach have never been finalized before. The only attempt reported by Dansou (see 2.4.4) for the synthesis of a myricanol analogue, failed in the last step of cyclization.

Again many methodologies were considered for the intramolecular biaryl installation as Ullman, oxidative and Suzuki-Miyaura coupling. If Ullman and oxidative biaryl couplings were completely abandoned, Suzuki-Miyaura coupling and the biaryl core installed by an addition on a dienone acetate intermediate seemed promising routes to reach our goal.

After an appropriate functionalization of homoallylic alcohol **72** to give the free phenol **107**, oxidative condition as PIDA in presence of acetic acid as nucleophile, gave the dienone acetate **108** in good yield (**Scheme 6-3**). The intermediate **108** is a good intermediate for the nucleophilic attack of a Grignard derivative of **57**. We worked hard on the formation of the Grignard species of iodide **57**, which probably due to its hindrance appears difficult to prepare.

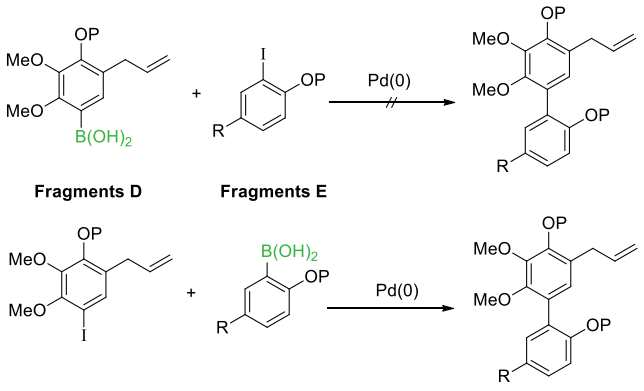


Scheme 6-3 Dienone acetate approach and perspectives

This methodology, if feasible, could be an elegant way to prepare myricanol's biaryl without using transition metals. Of course the subsequential RCM on **120** remains to be investigated to reach myricanol.

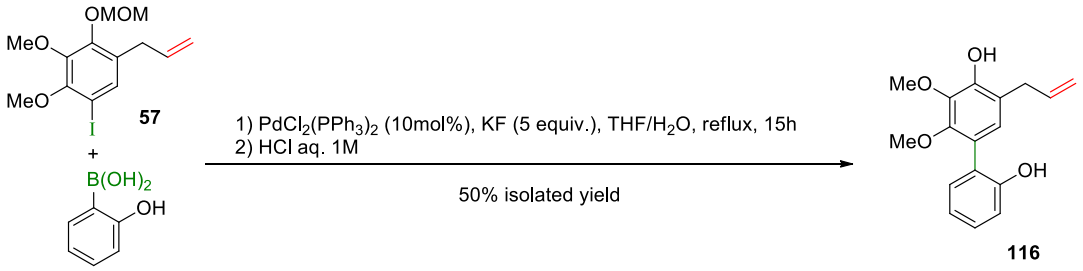
Concerning the intermolecular Suzuki-Miyaura coupling, considerable efforts have been done to generate the boronic derivatives and to couple the two aryl moieties.

Among all performed tests, one can affirm that despite boronic acids were easily obtained on the **D** type's fragments, it seemed better to generate the boronic species on the **E** type's fragments in view of the cross-coupling reaction. During the Suzuki-Miyaura cross-couplings, the boronic acids of the more electron rich fragments (**D**) never allowed to obtain the cross-coupling products, while biaryl moiety was generated if boronic acids is on the less electron rich moiety (**fragment E**) of myricanol (**Scheme 6-4**).



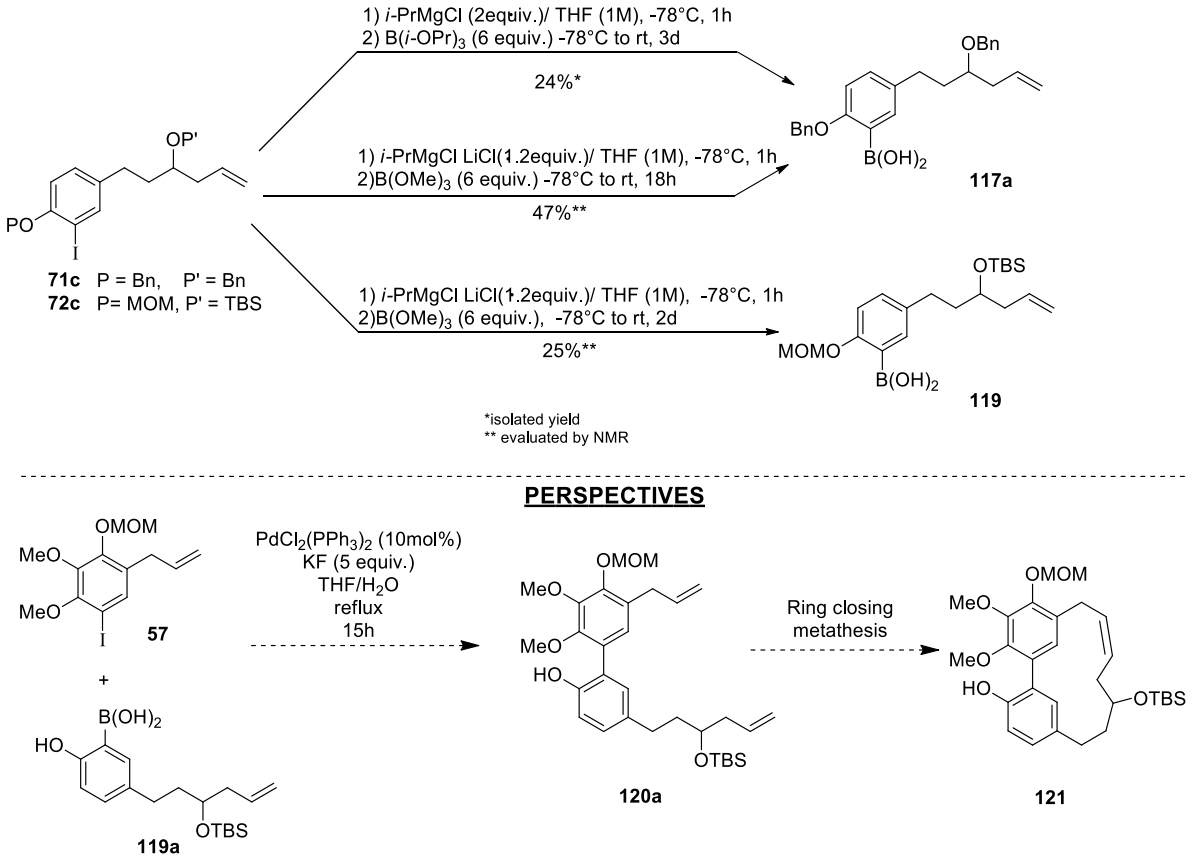
Scheme 6-4 General behaviour observed for intermolecular Suzuki-Miyaura coupling

These results induced us to explore the Suzuki-Miyaura reaction in which boronic species were on fragment **E.** Optimized conditions with commercially available boronic acids were found (**Scheme 6-5**) in order to install the biaryl scaffold, avoiding the palladium catalyzed isomerization of allylic group on **57**. We furthermore experimented that a free phenol in *ortho* position to the boronic acid unrolled a crucial role for the efficiency of the coupling avoiding any isomerization.



Scheme 6-5 Optimized Suzuki-Miyaura conditions to avoid double bond isomerization

This reaction model opened the route to the boronic acid preparation on **E** type's fragments. After early unsuccessful tests on the halogenated **E** fragments with *n*BuLi and differents borate, we finally obtained the boronic acid **117** in 24% yield by using *i*-PrMgCl and $B(i\text{-}OPr)_3$. The best results were observed performing borylation with *i*-PrMgCl LiCl and $B(OMe)_3$. In these conditions boronic acids **117a** and **119** were obtained with about 50% and 25% of yields, respectively. Compound **119** appears particularly interesting for our synthetic aim. MOM protection could be easily deprotected to afford a boronic acid with a free *ortho* hydroxyl group that, could be a good candidate to accomplish the C-C couplings en route to the myricanol (**Scheme 6-6**).

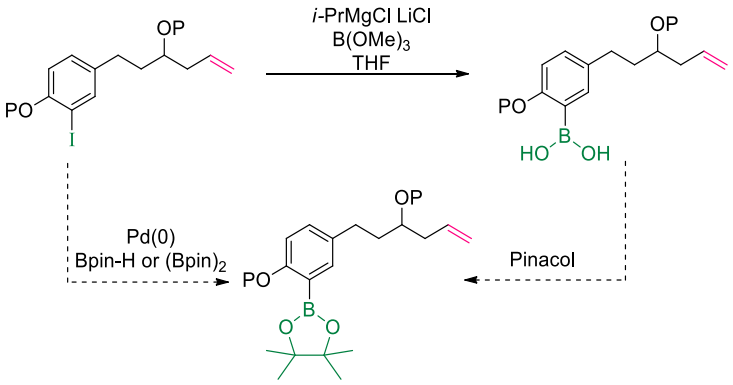


Scheme 6-6 Boronic acid preparation and perspectives on Suzuki-Miyaura coupling

Our perspectives concerning this path are the optimization of the boronic acid preparation of **119** or derivatives. A selective phenol deprotection will be used to obtain **119a** or analogues, which will be involved in Suzuki-Miyaura cross-coupling reactions, using the optimized conditions. If the coupling occurs giving **120a** without isomerization of the double bond, RCM will be investigated to perform the macrocylization (**Scheme 6-6**).

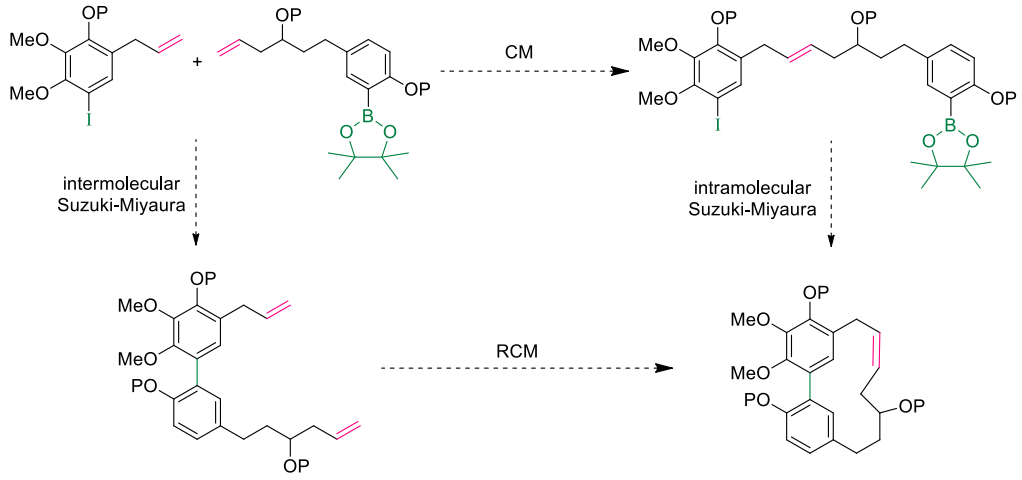
We also envisage to generate more stable pinacol boronic ester[232] by esterification of **117a** (or analogues) or to perform a palladium-catalyzed borylation with pinacolborane on the halogenated **E** fragments (**Scheme 6-7**).

[232] a) Takagi, A.; Ikawa, T.; Kurita, Y.; Saito, K.; Azechi, K.; Egi, M.; Itoh, Y.; Tokiwa, H.; Kita, Y.; Akai, S. *Tetrahedron* **2013**, *69* (21), 4338–4352. b) Lennox, A. J. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.* **2014**, *43* (1), 412.



Scheme 6-7 Perspectives on the preparation of boronic ester of E fragments

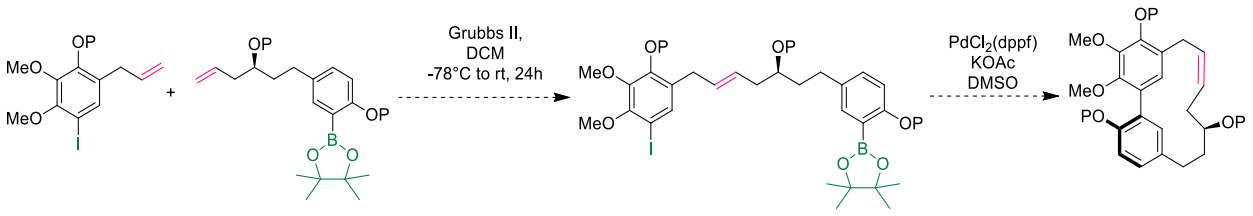
With the boronic ester in hands, we will study the reactivity of either the intermolecular Suzuki-Miyaura reactions with halogenated **D** fragments or of the cross-metathesis reactions for the construction of an already functionalized linear diarylheptanoid. The final intramolecular Suzuki-Miyaura cross-coupling could be more succesfull (**Scheme 6-8**).



Scheme 6-8 Perspectives on Suzuki-Miyaura coupling with boronic ester

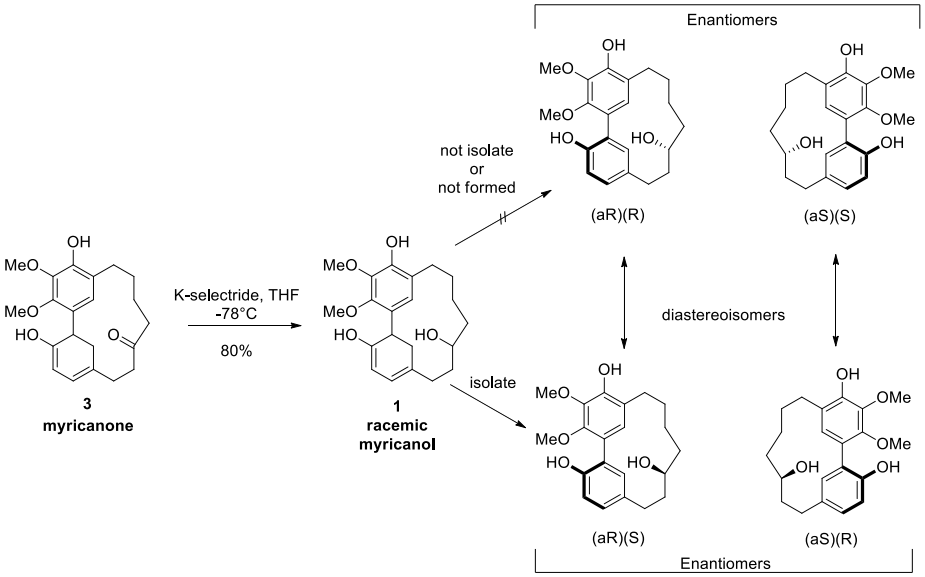
Obviously our aim would be to synthesize myricanol also with the enantiomerically pure **E** type fragment.

Considering the reported literature for the isolation and characterization of myricanol, we can not affirm that the axial chirality of the biaryl would be controlled during the macrocyclization. One could imagine that the stereogenic carbinol could induce atropodiastereoselectivity during the macrocyclization giving preferentially one couple of enantiomer, but some doubt remains about this stereoselective effect.



Scheme 6-9 Perspectives for the atropo-stereoselective synthesis of myricanol

When Dickey at *al.* reported the synthesis of racemic myricanol[37] the last step is the reduction of the corresponding precursor myricanone with K-selectride and the product submitted to chiral HPLC separation gave a racemic mixture 1:1 of two enantiomers that were identified to be a*S*,*R* and a*R*,*S* by X-ray analysis. This result could be interpreted in two ways. 1) The reduction with the hindered K-selectride is totally diastereoselective and consequently only two enantiomers a*S*,*R* and a*R*,*S* are obtained; 2) or chiral HPLC did not allow the separation of the four possible isomers and only the two enantiomers a*S*,*R* and a*R*,*S* crystallized (**Scheme 6-10**).



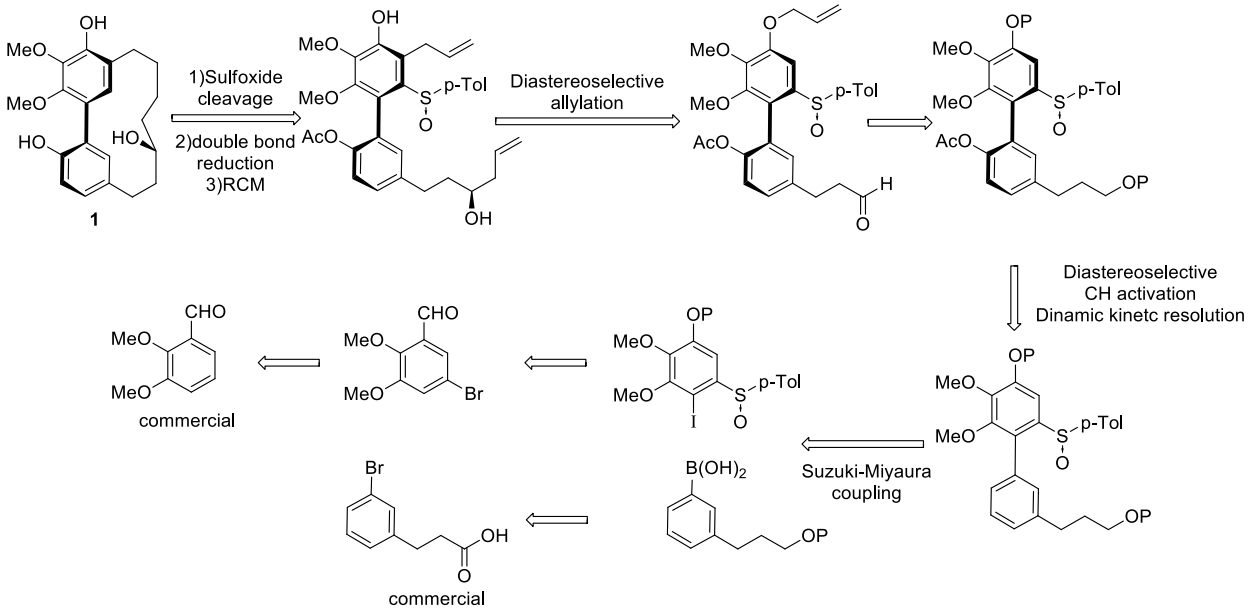
Scheme 6-10 Dickey isolation of myricanol enantiomers a*S*,*R* and a*R*,*S*

Indeed the chiral HPLC separation, reported in the work of Dickey shows a chromatogram constituted by only two peaks. So a question remains opened, after the ketone reduction of myricanone only two products are formed, or the atropisomers are undistinguishable on HPLC chromatography? We can not exclude that an axial rotation occurs in solution. Obviously these hypothesis could be confirmed or disproved if the

substrate involved in the macrocyclization by biaryl coupling would bear an enantiomerically pure stereogenic carbinol.

The evaluation of energy barriers to axial rotation using quantum mechanics calculation could also be another aspect to investigate. Density functional theory calculation (DFT), combined with temperature dependent high performance liquid chromatography (HPLC) and circular dichroism (CD) mesurements could elucidate our doubt on myricanol atropoismers, as recently reported to define the axial chirality of new drugs.[233]

Another perspective could be to control of the axial chirality through sulfoxide-directed asymmetric C-H bond activation and dynamic kinetic resolution[234] and to perform the macrocyclization of the enantiopure substrate with controlled axial and central chiralities (**Scheme 6-11**).



Scheme 6-11 New retrosynthetic idea for atropo-stereoselective synthesis of myricanol

[233] a) LaPlante, S. R.; Edwards, P. J.; Fader, L. D.; Jakalian, A.; Hucke, O. *ChemMedChem* **2011**, *6* (3), 505–513. b) Bihlmeier, A.; Rotzler, J.; Rickhaus, M.; Mayor, M.; Klopper, W. *Phys Chem Chem Phys* **2015**, *17* (17), 11165–11173.

[234] Hazra, C. K.; Dherbassy, Q.; Wencel-Delord, J.; Colobert, F. *Angew. Chem. Int. Ed.* **2014**, *53* (50), 13871–13875.

7 EXPERIMENTAL SECTION

7.1 MATERIAL AND METHODS: CHEMICAL PART

Commercially obtained reagents and solvent were used as received after adequate checks of purity (titration, NMR) from Sigma Aldrich, TCI and Alfa aesar. 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.[235] DCM was dried over CaH_2 under argon. Diisopropylamine and triethylamine were 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.

^{1}H, ^{13}C, ^{11}B, NOESY, COSY and HETCOR NMR spectra were recorded on Brucker Avance 400MHz and 300MHz from ECPM-NMR service of University of Strasbourg and on Varian 400 MHz and 500MHz from CIGAS of University of Basilicata. Samples were prepared using $CDCl_3$ and $(CD_3)_2CO$ and $(CD_3)_2SO$. Chemical shifts were referred to 7.27ppm (^{1}H) and 77.00ppm (^{13}C) for $CDCl_3$, to 2.05ppm (^{1}H) and 29.84ppm (^{13}C) for $(CD_3)_2CO$ and 2.50ppm (^{1}H) and 39.52ppm (^{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 ^{1}H-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 250nm and revealed with a solution of anisaldehyde (5.1mL of *p*-anysaldehyde, 2.1mL of acetic acid, 6.9mL of concentered sulfuric acid, 186mLof 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.[236] Grignard reagents (allylMgBr, vinylMgBr, *i*-PrMgCl and *i*-PrMgCl LiCl) were titrated using salicylaldehyde phenylhydrazone as an indicator.[237]

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. The angles of rotation were measured on a Perkin Elmer Polarimeter 341 and denoted as specific rotations: $[\alpha]_D^{20}$.

[235] Schlenk, W.; Bergmann, E. *Justus Liebigs Ann. Chem.* **1928**, *464* (1), 1–21.
[236] Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc. Chem. Commun.* **1980**, 3, 87–88.
[237] Love, B. E.; Jones, E. G. *J. Org. Chem.* **1999**, *64* (10), 3755–3756.

7.2 MATERIAL AND METHODS BIOLOGICAL PART

7.2.1 Cell culture and treatment

Human monocytic/macrophage cells from hystiocytoma, U937 cells (ICLC HTL 94002-Interlab Cell Line Collection), were grown in Roswell Park Memorial Institute (RPMI) 1640 medium with 10% fetal bovine serum supplemented with 2 mM L-glutamine, 100 U penicillin, and 100 μg/ml streptomycin at 37°C in 5% CO_2. The BV-2 murine microglial cell line was maintained in Dulbecco's modified Eagle medium (DMEM) supplemented with 10% heat inactivated fetal bovine serum, 100 U penicillin and 100 μg/ml streptomycin at 37°C in a humidified atmosphere containing 5% CO. Where indicated U937 and BV2 cells were treated for 24 hours with 400 ng/ml bacterial LPS (Sigma) after adding curcumin and its analogues for 30 minutes.

7.2.1 Cell viability

Cell viability was evaluated by a modified MTT assay (CellTiter 96® Non-Radioactive Cell Proliferation Assay, Promega, Madison, WI, USA). In brief, U937 and BV-2 cells were treated for 72 hours with curcumin and its analogues at 10 nM, 100 nM, 1, 5 and 10 μM. The level of formazan product was determined by measuring its absorbance at 570 nm using a 96-well plate reader (GloMax, Promega).

7.2.1 ROS and NO detection

For ROS analysis, U937 and BV-2 treated cells were incubated with 10 μM 6-Carboxy-2',7'-Dichlorodihydrofluorescein Diacetate (DCFH2-DA, Life Technologies) for 30 minutes (BBRC 2013 ATP-citrate lyase paper). Nitrite formation was measured by using 4-Amino-5-Methylamino-2',7'-Difluorofluorescein Diacetate (DAF-FM Diacetate, Life Technologies) according to manufacture's protocol. The fluorescence was revealed by GloMax plate reader (Promega).

7.2.1 Statistical analysis

Statistical significance of difference was determined using one-way ANOVA. Results are presented as means ± S.D of, at least, four independent experiments. Differences were considered as significant ($P < 0.05$; *) and very significant ($P < 0.01$; **).

7.3 GENERAL PROCEDURES AND PRODUCTS' CHARACTERIZATION

7.3.1 General procedure for Benzylation

Method A (Phenol)[238]

In a solution of phenol (1equiv.) in acetone (0.25M) was added K_2CO_3 (2equiv.) after stirring 10 min., benzyl bromide (1.2equiv.) and NaI or TBAI (0.07equiv.) 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 (3x50mL/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 B (Phenol/Alcohol)

In a solution of phenol (1equiv.) in anhydrous DMF (0.25M) was added NaH 60% dispersion in mineral oil (2.5equiv.) at 0°C. The mixture was stirred for almost 10min after which benzyl bromide (1.2equiv.) and NaI (0.07equiv.) 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 (3x30mL/mmol). The combined organic extracts were washed with brine (3x30mL/mmol) and with water (3x40mL/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.

7.3.2 General procedure for Weinreb amide

N,O-dimethylhydroxylamine hydrochloride (3equiv) was dissolved in dry DCM (0.3M) under inert atmosphere. Then, a solution of $AlMe_3$ (3equiv., 2M in toluene) was added dropwise at room temperature. The mixture was stirred for 30min and a solution of starting ester (1equiv.) in dry DCM (0.3M) was prepared and added to the mixture. The mixture was heated to reflux overnight. The solution became yellow. The reaction was slowly hydrolyzed with an aqueous solution of HCl (0.5M, 10mL/mmol). The aqueous layer was extracted with DCM (3X10mL/mmol). The organic layers were washed with saturated aqueous solution of $NaHCO_3$, dried on Na_2SO_4 and evaporated under reduced pressure. Crude product was purified by silica gel chromatography to obtain the pure product.

[238] Christiansen, E.; Due-Hansen, M. E.; Urban, C.; Merten, N.; Pfleiderer, M.; Karlsen, K. K.; Rasmussen, S. S.; Steensgaard, M.; Hamacher, A.; Schmidt, J.; Drewke, C.; Petersen, R. K.; Kristiansen, K.; Ullrich, S.; Kostenis, E.; Kassack, M. U.; Ulven, T. *ACS Med. Chem. Lett.* **2010**, *1* (7), 345–349.

7.3.3 General procedure for Bromination

Method A[239]

To a solution of aryl substrate (1equiv.) in AcOH (0.40M) was added AcONa (2 equiv.) and liquid Br_2 (1.1equiv.). The solution was stirred at room temperature until disappearing of starting material. Reaction was followed by TLC or by GC-MS. The mixture was quenched with water, extracted with DCM (3x30mL/mmol). The organic layers were washed with water (2x25mL/mmol) and with a saturated aqueous solution of $NaHCO_3$ (2x25mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude reaction was purified by silica gel chromatography.

Method B[113]

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 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 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.

7.3.4 General procedure for iodination

Method A[238]

Starting aromatic compound (1equiv.), I_2 (1equiv.) and Ag_2SO_4 (1equiv.) were dissolved in DCM (0.25M) 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 (2x10mL/mmol) and brine (2x10mL/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 B[113]

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

[239] Sörgel, S.; Azap, C.; Reißig, H.-U. *Eur. J. Org. Chem.* **2006**, *2006* (19), 4405–4418.

under reduced pressure gave the crude product that was purified by silica gel chromatography or if pure used with any further purification.

7.3.5 General procedure for acetylation

To a solution of phenol/ alcohol (1equiv.) in Py (1mL/mmol) was added acetic anhydride (1mL/mmol). The solution was stirred at room temperature until complete transformation of starting material. The reaction was quenched with water and aqueous layer was extracted with EtOAc (3x10mL/mmol). The resulted organic extracts were washed with saturated aqueous solution of NaCl. Organic layers were unified, dried on Na_2SO_4 and concentered under reduced pressure to afford the crude product, sometimes obtained pure with no need to further purification.

7.3.6 General procedure for MOM protection[240]

To a cooled (0 °C) solution of secondary alcohol or phenol (1 equiv.) in anhydrous DCM (0.3 M) were added *N*,*N*-diisopropylethylamine (6equiv.) or NaH (6 equiv., 60% dispersion in mineral oil) and MOMCl (6equiv.) under Ar. After being stirred at room temperature until complete transformation of starting material, the reaction mixture was quenched with saturated aqueous NH_4Cl (2x10mL/mmol) and diluted with EtOAc (30mL/mmol). The layers were separated and the aqueous layer was extracted with EtOAc (2x30mL/mmol). The combined organic layers were washed successively with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography to give the corresponding MOMO ether.

7.3.7 General procedure for aldehyde allylation

Method A:

At -78°C, to a solution of crude aldehyde (1equiv) in THF (0,3M) was added, dropwise and under argon, a solution of allylmagnesium bromide (1equiv., 1M in diethyl ether). The solution was stirred for 2h and allowed to warm to r.t.. The mixture was then quenched with water (10mLXmmol) and stirred 10 minutes. The mixture was extracted with DCM (3x10mLXmmol) and the organic layers were dried on Na_2SO_4 and concentrated under vacuum. The crude product was purified by silica gel chromatography.

[240] Kim, M. J.; Sohn, T.; Kim, D.; Paton, R. S. *J. Am. Chem. Soc.* **2012**, *134* (49), 20178–20188.

Method B:

A solution of crude aldehyde (1equiv.) in THF (0,3M) was added under argon to a solution of allyl boronic acid pinacol ester (1equiv.) in THF (1M). The solution was stirred at room temperature for 5h. The solution was then quenched with water (10mLXmmol) and stirred 10 minutes. The mixture was extracted with DCM (3x10mLXmmol) and the organic layers were dried on Na_2SO_4 and concentrated under vacuum. The crude product was purified by silica gel chromatography.

7.3.8 General procedure for cross-metathesis:

To a solution of homoallyilic alcohol or γ,β-unsaturated ketone (100mg, 1eq) and the allylphenols (4eq) in dry DCM (0,08M), was added dropwise a solution of second generation Grubbs catalyst (3 or 5mol%) in dry DCM (0,02M), under Ar atmosphere at -78°C. The reaction mixture was stirred at -78°C and allowed to warm to r.t. for 1 day under stirring. The mixture was evaporated and the crude was purified by silica gel chromatography (preparation: cyclohexane, elution: from pure cyclohexane to cyclohexane/EtOAc, 4/1 to 3/2).

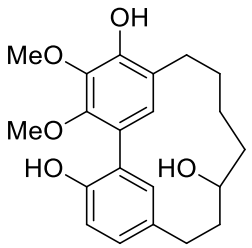
7.3.9 General procedure for debenzylation and double C=C bond hydrogenation:

Hydrogenation of cross-metathesis products (1mmol), was performed under H_2 atmosphere in presence of Pd/C (10mol%), using MeOH (0,5M) as a solvent. The reaction was monitored by TLC and the mixture was passed through a pack of celite and washed with MeOH once full conversion of the starting material was observed. The solvent was removed under vacuum to afford the pure desired product.

7.3.10 General procedure for diimide hydrogenation of C=C double bond[175]

To a cooled (0°C) and vigorously stirred solution of 2-nitrobenzenesulfonylchloride (2 equiv.) and alkene (1 equiv.) in dry MeCN (0.2M) was slowely added (dropwise) hydrazine hydrate (4 equiv.). The resulting suspension was allowed to slowely warm to room temperature, stirring vigorously for all night long. After 18 h of reaction, the crude was filtered and washed with EtOAc. The residue was dried on Na_2SO_4, filtered and dried at vacuum. The crude was subsequentely purified by a silica gel pad.

7.3.11 Myricanol (1)



Chemical Formula: $C_{21}H_{26}O_5$
Exact Mass: 368.18 g/mol
Molecular Weight: 358.43 g/mol

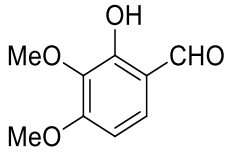
To a flask containing NaOAc (10 equiv., 12.7mmol, 1.04g), $Pd(dppf)_2Cl_2$ (0.10 equiv., 0.127mmol, 0.104g), bis(pinacolato)diboron (1.1 equiv., 1.52mmol, 1.04g) and dibromide **89** (1.0 equiv., 1.27mmol, 1.0g) was added degassed DMSO (64mL, 0.02 M). After being heated under argon at 80 °C for 24 h, the reaction mixture was allowed to cool at room temperature and then quenched with a saturated aqueous solution of NH_4Cl (40mL). The mixture was extracted with EtOAc (3x40mL). The organic layers was separated, dried over Na_2SO_4, filtered and concentred under vacuum. The crude was purified on silica gel chromatography (pure EP to EP/EtOAc 9.5/0.5 V/V). The recollected fractions (except for the individuated unreacted starting material and its dehalogenated derivatives) resulted complicated to interpret and for this reason were subjected to catalytic debenzylation by use of Pd/C 10%, H_2 and MeOH as solvent.

In one of debenzylated fractions diagnostic myricanol peak were individuated, unfortunately the product was not completely pure and the characterization of prepared myricanol was not possible (see **Figure 4-3** for ^{1}H-NMR). We estimated to have obtained a yield ≈10% considering the two steps (Suzuki-domino coupling and debenzylation).

7.3.12 Experimental part for fragments D and E and derivatives

All the characterized compound were reported in ascending order of number.

2-hydroxy-3,4-dimethoxybenzaldehyde[241] (39)



Chemical Formula: $C_9H_{10}O_4$
Exact Mass: 182.06 g/mol
Molecular Weight: 182.17 g/mol

Anhydrous $AlCl_3$ (0.71 g, 5.3mmol) and commercial 2,3,4-trimethoxybenzaldehyde (1.00 g, 5.09 mmol) were dissolved in dry toluene (10.2 mL) and vigorously stirred under argon. The mixture was refluxed for 8.5 h and after cooling to room temperature, HCl was added. The mixture was extracted with Et_2O (2×50 mL). The combined organic layers were washed twice with water. To remove the residual starting compound, the solution was washed with 1M NaOH (25 mL). The basic solution was immediately cooled and acidified with 17% HCl to pH 1 and washed with Et_2O (3×50 mL). The organic extract was dried over Na_2SO_4, filtered and evaporated under reduced pressure. This provided a viscous brown oil compound.

Time = 8.5h

Yield = 345mg (37%).

***R*f** = 0.35 (EP/EtOAc = 7:3)

^{1}H NMR (400 MHz, DMSO-d6), δ: 3.71 (s, 3H-OC*H*$_3$); 3.89 (s, 3H-OC*H*$_3$); 6.75 (d, 1H, *J*=8.80Hz, Ar-*H*); 7.48 (d, 1H, *J*=8.80Hz, Ar-*H*); 10.03 (s, 1H, C*H*O).

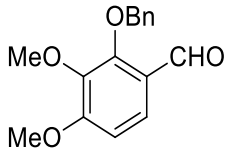
^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.89 (s, 3H-OC*H*$_3$); 3.94 (s, 3H-OC*H*$_3$); 6.59 (d, 1H, *J*=8.80Hz, Ar-*H*); 7.28 (d, 1H, *J*=8.80Hz, Ar-*H*); 9.73 (s, 1H, C*H*O).

^{13}C NMR (100 MHz, $CDCl_3$), δ: 56.09 (O*C*H$_3$); 60.10 (O*C*H$_3$); 103.95 (*C*H-Ar); 116.45 (q, *C*-CHO); 130.24 (*C*H-Ar); 136.04 (q, *C*-OCH$_3$); 154.34 (q, *C*-OH); 159.33 (q, *C*-OCH$_3$); 194.91 (*C*HO).

EIMS *m/z* 182 $[M]^+$(100), 167 (20), 139(50)

[241] Nakanishi, T.; Suzuki, M. *Org. Lett.* **1999**, *1* (7), 985–988.

2-(benzyloxy)-3,4-dimethoxybenzaldehyde (40)



Chemical Formula: $C_{16}H_{16}O_4$
Exact Mass: 272.10 g/mol
Molecular Weight: 272.30 g/mol

The product was obtained from aldehyde **39** (0.50g, 2.74mmol) following the general procedure for benzylation of phenol-Method A (see 7.3). Purification by silica gel chromatography afforded the pure product as a transparent oil.

Time = 5h

Yield = (0.68g, 2.52mmol) 92%.

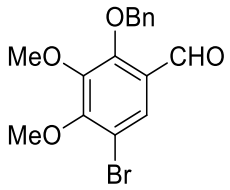
***R*f** = 0.5 (EP/EtOAc = 7:3)

^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.91 (s, 3H-OC*H*$_3$); 3.94 (s, 3H-OC*H*$_3$); 5.21 (s, 2H, CH_2-Bn); 6.76 (d, 1H, *J*=8.80Hz, Ar-*H*); 7.37 (m, *5*H, Bn); 7.58 (d, 1Hz, *J*=8.80, Ar-*H*); 10.10 (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).

EIMS *m/z* 272 $[M]^+$(10), 243 (30), 91(100)

2-(benzyloxy)-5-bromo-3,4-dimethoxybenzaldehyde (41)



Chemical Formula: $C_{16}H_{15}BrO_4$
Exact Mass: 350.02 g/mol
Molecular Weight: 351.19 g/mol

The product was obtained from benzylated aldehyde **40** (0.10g, 0.36mmol) following the general procedure for bromination-Method A (see 7.3) stirring the mixture for 22h, and from benzylation of phenol **42** (0.10g, 0.38mmol) with general procedure (Method A) after 18h of reaction. Purification by silica gel chromatography afforded the pure product as a transparent oil.

Time = 22h from **40**,
5h from **42**

Yield = (0.12g, 0.36mmol) 100% from **40**,
(0.10g, 0.28mmol) 75% from **42**

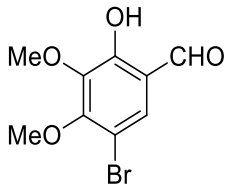
***R*f** = 0.6 (EP/EtOAc = 7:3)

^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.96 (s, 3H-OC*H*$_3$); 4.03 (s, 3H-OC*H*$_3$); 5.22 (s, 2H, CH_2-Bn); 7.38 (m, *5*H, Bn); 7.76 (s, 1H, Ar-*H*); 10.06 (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 (42)



Chemical Formula: $C_9H_9BrO_4$
Exact Mass: 259.97 g/mol
Molecular Weight: 261.07 g/mol

The product was obtained from phenol **39** (0.10g, 0.55mmol) following the general procedure for bromination-Method A (see 7.3) stirring the mixture for 2h. Purification by silica gel chromatography afforded the pure product as a yellow solid.

Time = 2h

Yield = (0.14g, 0.36mmol) 100%

Mp = 54-55°C

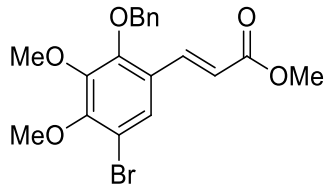
***R*f** = 0.6 (EP/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.93 (s, 3H-OC*H*$_3$); 4.06 (s, 3H-OC*H*$_3$); 5.22 (s, 2H, C*H*$_2$-Bn); 7.50 (s, 1H, Ar-*H*); 9.74 (s, 1H, C*H*O); 11.20 (s, 1H, O*H*).

^{13}C NMR (100 MHz, $CDCl_3$), δ: 61.13 (O*C*H$_3$); 61.38 (O*C*H$_3$); 106.83 (q, *C*-Br); 118.13 (q, *C*-CHO); 131.49 (*C*H-Ar); 141.30 (q, *C*-OCH$_3$); 156.22 (q, *C*-OH); 156.66 (q, *C*-OCH$_3$); 194.49 (*C*HO).

EIMS *m/z* 260 $[M]^+$(100), 217 (50), 123(20), 95(45).

(E)-methyl 3-(2-(benzyloxy)-5-bromo-3,4-dimethoxyphenyl)acrylate (43)



Chemical Formula: $C_{19}H_{19}BrO_5$
Exact Mass: 406.04 g/mol
Molecular Weight: 407.26 g/mol

To a solution of benzyl aldehyde **41** (0.05 g, 0.142mmol) in anhydrous DCM (0.1M) methyl (triphenylphosphoranylidene)acetate (1.1 equiv.) was added at room temperature. The mixture was stirred for 5h and quenched with water. The aqueous layers were extracted with EtOAc (3x5mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude of reaction was purified by silica gel chromatography to afford the desired product as a pale yellow oil. The product **43** was obtained as a mixture *cis*/*trans* 15:85.

Time = 5h

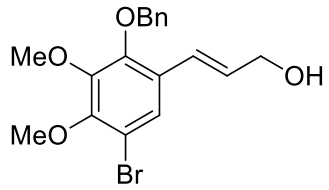
Yield = (0.046g, 0.112mmol) 79%

***R*f** = 0.5 (EP/EtOAc = 9:1)

^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.78 (s, 3H-COOC*H*$_3$); 3.91 (s, 3H-OC*H*$_3$); 3.94 (s, 3H-OC*H*$_3$); 5.03_{cis} (s, 2H, C*H*$_2$-Bn); 5.05_{trans} (s, 2H, C*H*$_2$-Bn); 5.92_{cis} (d, 1H, J_{cis}=12.4Hz, C*H*-styrenic); 6.32_{trans} (d, 1H, J_{trans}=16.4Hz, C*H*-styrenic); 6.94_{cis} (d, 1H, J_{cis}=12.4Hz, C*H*-styrenic); 7.38 (m, 6H, Ar-*H*+ Bn); 7.81_{trans} (d, 1H, J_{trans}=16.4Hz, C*H*-styrenic).

EIMS *m/z* 406 $[M]^+$(60), 374 (80), 345(90), 207(100), 91(80).

(E)-3-(2-(benzyloxy)-5-bromo-3,4-dimethoxyphenyl)prop-2-en-1-ol (44)



Chemical Formula: $C_{18}H_{19}BrO_4$
Exact Mass: 378.05 g/mol
Molecular Weight: 379.25 g/mol

To a solution of **43** (0.046g, 0.112 mmol) in DCM (1 mL) was added a solution of DIBAL (1 M in hexane, 224 μL, 0.224 mmol) at 0 °C. The solution was stirred for 10 h and allowing to warm at room temperature. The reaction was quenched with MeOH, the mixture was stirred for 30min and filtered over Celite to remove the aluminium salts. The filtrate was concentrated under reduced pressure to afford crude product **44** as a viscous transparent oil (mixture *cis*/*trans* 15:85).

Time = 10h

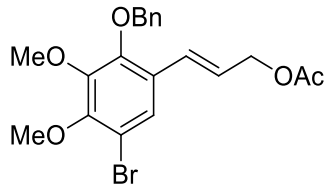
Yield = (0.042g, 0.112mmol) 100%

***R*f** = 0.35 (EP/EtOAc = 9:1)

^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.86 (s, 3H-OCH_3); 3.87 (s, 3H-OCH_3); 4.19 (d, 2H, J_{trans}=15.6Hz, CH_2OH); 5.02$_{cis}$ (s, 2H, CH_2-Bn); 5.04$_{trans}$ (s, 2H, CH_2-Bn); 5.83$_{cis}$ (m, 1H, C*H*-styrenic); 6.23$_{trans}$ (m, 1H, C*H*-styrenic); 6.45$_{cis}$ (d, 1H, J_{cis}=12.4Hz, C*H*-styrenic); 6.73$_{trans}$ (d, 1H, J_{trans}=16.4Hz, C*H*-styrenic); 6.92 (s, 1H, Ar-*H*); 7.41 (m, 5H, Ar-*H*).

EIMS *m/z* 378 $[M]^+$(20), 348 (15), 242(10), 91(100).

(E)-3-(2-(benzyloxy)-5-bromo-3,4-dimethoxyphenyl)allyl acetate (45)



Chemical Formula: $C_{20}H_{21}BrO_5$
Exact Mass: 420.06 g/mol
Molecular Weight: 421.28 g/mol

Substrate **44** (0.042g, 0.112 mmol) was obtained following the general procedure for acetylation (see 7.3) of phenol/alcohol. The crude of reaction was filtered through silica pad to afford the pure product as a yellow oil as a mixture *cis*/*trans* 15:85.

Time = 18h

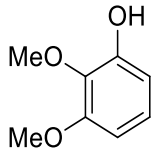
Yield = (0.047g, 0.112mmol) 100%

***R*f** = 0.45 (EP/EtOAc = 9:1)

^{1}H NMR (400 MHz, $CDCl_3$), δ: 2.12 (s, 3H-COCH_3); 3.91 (s, 3H-OCH_3); 3.94 (s, 3H-OCH_3); 4.65 (d, 2H, J_{trans}=15.6Hz, CH_2OH); 5.01_{cis} (s, 2H, CH_2-Bn); 5.05_{trans} (s, 2H, CH_2-Bn); 5.85_{cis} (m, 1H, C*H*-styrenic); 6.23_{trans} (m, 1H, C*H*-styrenic); 6.62_{cis} (d, 1H, J_{cis}=12.4Hz, C*H*-styrenic); 6.78_{trans} (d, 1H, J_{trans}=16.4Hz, C*H*-styrenic); 7.15 (s, 1H, Ar-*H*); 7.41 (m, 5H, Ar-*H*).

EIMS *m/z* 420 $[M]^+$(20), 390 (15), 284(10), 91(100), 43(50).

2,3-dimethoxyphenol



Chemical Formula: $C_8H_{10}O_3$
Exact Mass: 154.06 g/mol
Molecular Weight: 154.16 g/mol

The 2,3-dimethoxybenzaldehyde (1equiv., 54.3mmol, 9.0g) was dissolved in DCM (271mL). This mixture was vigorously stirred, the hydrogen peroxide (2.5equiv., 135.75mmol, 13.98mL aqueous solution 30%) and formic acid (4equiv., 217.2mmol, 9.95mL) were added. The flask was fitted with a reflux condenser and heated to reflux for 18h. After cooling, 140mL of 1.5N sodium hydroxide was added to the flask. The mixture was stirred for 15 minutes. The organic layer was separated and concentrated to residue using a rotary evaporator. The residue was combined with the aqueous solution and 94mL of methanol was added. The solution was stirred for 30 minutes and the methanol removed under vacuum. The neutral materials were removed from the aqueous residue by extracting with DCM (2x144mL). The solution pH was adjusted to 1 with HCl concentrated. The product of reaction was extracted with DCM (3x144mL). The organic solution containing the neutrals as well as the one containing the product were separately dried over Na_2SO_4, filtrated and concentrated under vacuum pressure. The product was obtained pure as a yellow oil.

Time = 18h

Yield = (8.0g; 52.13mmol) 96%

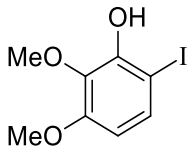
R_f = 0.5 (EP/EtOAc = 5:5)

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 3H, OC*H*$_3$); 3.83 (s, 3H, OC*H*$_3$); 5.70 (s, 1H, O*H*); 6.40 (d, *J* = 9Hz, 1H, Ar-*H*); 6.53 (d, *J* = 9Hz, 1H, Ar-*H*); 6.85 (t, *J* = 9Hz, 1H, Ar-*H*)

^{1}C NMR (75 MHz, $CDCl_3$) δ 55.74 (O*C*H$_3$); 60.91 (O*C*H$_3$); 104.16 (*C*H-Ar); 108.24 (*C*H-Ar); 124.06 (*C*H-Ar); 135.63 (q, *C*OCH$_3$); 149.60 (q, *C*OH); 152.61 (q, *C*OCH$_3$)

EIMS *m/z* 154 $[M]^+$ (100), 139 (70), 111 (20)

6-iodo-2,3-dimethoxyphenol (47)[112]



Chemical Formula: $C_8H_9IO_3$
Exact Mass: 279.96 g/mol
Molecular Weight: 280.06 g/mol

To a solution of 2,3-dimethoxyphenol (1 equiv., 3.24mmol, 0.50g) in ACN (65mL) and *para*-toluensolfonic acid *p*-TsOH (1 equiv., 3.24mmol, 0.62g) was added NIS (1 equiv., 3.24mmol, 0.73g). The mixture was stirred for 3h and quenched with water. The aqueous layers was extracted with EtOAc (3x30mL). The organic extracts were washed with a saturated aqueous solution of $NaHSO_3$ (2x15mL) and with a saturated aqueous solution of $Na_2S_2O_3$ (2x15mL), dried on Na_2SO_4, filtered and concentred under vacuum pressure. The obtained crude product was filtered through a silica pad to afford a transparent oil.

Time = 3h

Yield = (0.85g; 3.04mmol) 94%

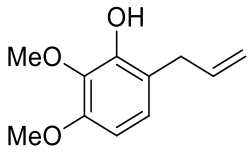
R_f = 0.3 (EP/Et_2O = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H, OC*H*$_3$); 3.90 (s, 3H, OC*H*$_3$); 6.25 (s, 1H, O*H*); 6.34 (d, *J* = 8.8Hz, 1H, Ar-*H*); 7.35 (d, *J* = 8.8Hz, 1H, Ar-*H*).

^{1}C NMR (400 MHz, $CDCl_3$) δ 56.00 (O*C*H$_3$); 61.15 (O*C*H$_3$); 71.52 (*C*-I); 106.43 (*C*H-Ar); 132.71 (*C*H-Ar); 135.42 (q, *C*OCH$_3$); 149.30 (q, *C*OH); 152.81 (q, *C*OCH$_3$);

EIMS *m/z* 280 $[M]^+$ (100), 263 (40), 222 (10), 123(20), 95(20).

6-allyl-2,3-dimethoxyphenol (48)



Chemical Formula: $C_{11}H_{14}O_3$
Exact Mass: 194.09 g/mol
Molecular Weight: 194.23 g/mol

To a solution of **51** (1 equiv., 5.50mmol, 1.1g) in dry hexane (10mL), was added dropwise a 1M solution of Et_2AlCl in hexane (1.41 equiv, 7.7mmol, 7.7mL), at 0°C and under inert atmosphere. The mixture was strongly stirred at 0°C for 1h15. Formation of an orange solid (gum) was observed. The reaction was quenched by diluting the mixture with hexane (200mL) and pouring it into an aqueous solution of HCl solution (4M, 350mL). Dissolution of the orange gum was observed. The mixture was extracted with EtOAc (3x200mL), dried over Na_2SO_4 and evaporated under reduced pressure to dryness to obtain the product as a brown oil.

Time = 1.25h

Yield = (1.1g; 5.50mmol) 99%

$\mathbf{R}_f$ = 0.5 (EP/Et_2O = 8:2)

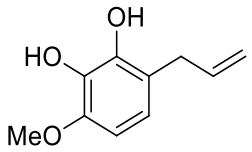
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.34 (d, 2H, J = 6.0Hz, *C*H_2-allyl); 3.84 (s, 3H, OC*H*$_3$); 3.89 (s, 3H, OC*H*$_3$); 5.02 (d, 1H, J_{cis} = 10.4 Hz, C*H*-allyl), 5.04 (d, 1H, J_{trans} = 17,0 Hz, C*H*-allyl), 5.88 (bs, 1H, O*H*), 5.96 (m, 1H, C*H*-allyl), 6.42 (d, 1H, *J* = 8.4 Hz, Ar-*H*), 6.78 (d, 1H, *J* = 8.4 Hz, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 33.71 (Ar-*C*H_2), 56.05 (O*C*H_3), 61.13 (O*C*H_3), 103.63 (*C*H-Ar), 115.46 (*C*H_2-allyl), 119.37 (q, *C*-allyl), 124.33 (*C*H-Ar), 135.61 (*C*H-allyl), 137.10 (q, *C*OCH_3), 147.42 (q, *C*OH), 150.91 (q, *C*OCH_3).

EIMS *m/z* 194 $[M]^+$(100), 179 (20), 163 (14), 147 (40);

anal. C 68.05 , H 7.24 %, calcd for $C_{11}H_{14}O_3$, C 68.02, H 7.27 %.

3-allyl-6-methoxybenzene-1,2-diol (48b)



Chemical Formula: $C_{10}H_{12}O_3$
Exact Mass: 180.08 g/mol
Molecular Weight: 180.20 g/mol

The product is obtained in 50% yield as a white-transparent crystal using the same protocol of product **48**. The product is obtained if during the acid quench of Claisen rearrangement the mixture temperature exceed 10°C.

Time = 1.25h

Yield = (1.1g; 5.50mmol) 99%

M.p. = 55°C

R_f = 0.3 (EP/EtOAc = 8:2)

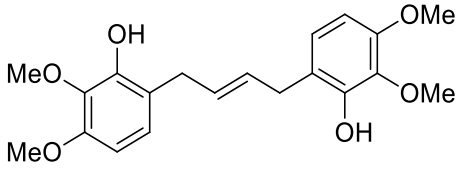
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.36 (d, 2H, J = 6.5Hz, *C*H_2-allyl); 3.86 (s, 3H, OC*H*$_3$); 5.15-4.99 (m, 2H, CH-allyl); 5.37 (s, 1H, O*H*), 5.39 (s, 1H, O*H*), 6.00 (m, 1H, C*H*-allyl), 6.43 (d, 1H, *J* = 8.4 Hz, Ar-*H*); 6.62 (d, 1H, *J* = 8.4 Hz, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 33.71 (Ar-*C*H_2), 56.12 (O*C*H_3), 102.63 (*C*H-Ar), 115.44 (*C*H_2-allyl), 119.78 (q, *C*-allyl), 122.02 (*C*H-Ar), 132.33 (*C*H-allyl), 137.02 (q, *C*OH), 141.95 (q, *C*OH), 145.42 (q, *C*OCH_3).

EIMS *m/z* 194 $[M]^+$(100), 179 (20), 163 (14), 147 (40);

anal. C 66.63 , H 6.69 %, calcd for $C_{10}H_{12}O_3$, C 66.65, H 6.71 %.

(*E*)-6,6'-(but-2-ene-1,4-diyl)bis(2,3-dimethoxyphenol) (48bis)



Chemical Formula: $C_{20}H_{24}O_6$
Exact Mass: 360.16 g mol
Molecular Weight: 360.40 g/mol

The substrate was obtained in 30-40% yield as secondary product from cross-metathesis reaction between phenol **48** and homoallilic alcohol **71** following the general procedure reported in 7.3.8. The product was isolated in mixture with 25% of *Z* isomer.

$\mathbf{R}_f$ = 0.6 (EP/EtOAc = 8:2)

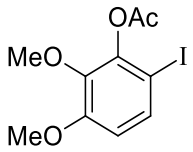
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.31 (d, 2H, *J* = 4.8Hz, C*H*$_2$); 3.85 (s, 6H, OC*H*$_3$); 3.90 (s, 6H, OC*H*$_3$); 5.67 (m, 2H, C*H*-allyl); 5.85 (s, 1H, O*H*); 6.42 (d, 2H, *J* = 8.4 Hz, Ar-*H*); 6.80 (d, 2H, *J* = 8.4 Hz, Ar-*H*).

^{13}C NMR (75 MHz, $CDCl_3$) δ 32.24 (*C*H$_2$); 55.79 (O*C*H$_3$); 60.86 (O*C*H$_3$); 103.47 (*C*H-Ar); 120.00 (q, *C*-Ar); 123.95 (*C*H-Ar); 129.37 (*C*H=*C*H); 135.39 (q, *C*-OCH$_3$); 147.16 (q, *C*-OH); 150.62 (q, *C*-OCH$_3$).

EIMS *m/z* 360 $[M]^+$(20), 194(50), 179 (20), 163 (14), 147 (40).

anal. C 66.68 , H 6.74 %, calcd for $C_{20}H_{24}O_6$, C 66.65, H 6.71 %.

6-iodo-2,3-dimethoxyphenyl acetate (49a)



Chemical Formula: $C_{10}H_{11}IO_4$
Exact Mass: 321.97 g/mol
Molecular Weight: 322.10 g/mol

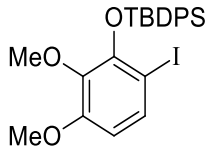
The substrate **49a** was obtained following the general procedure of acetylation (see 7.3) on 2,3-dimethoxyphenol (1equiv., 2.55mmol, 0.50g), after 18h of reaction the desired product was obtained with 66% yield (1.68mmol, 0.33g). Subsequently the protected phenol **49** was halogenated following the general procedure for iodination with NIS (method B). The reaction was stirred for 5h. Purification by column chromatography (EP/Et_2O 8/2) gave the product as yellow oil in quantitative yield (1.68mmol, 0.54g).

$\mathbf{R}_f$ = 0.4 (EP/Et_2O = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H, COCH_3); 3.82 (s, 3H, OCH_3); 3.86 (s, 3H, OCH_3); 6.27 (d, J = 8.8Hz, 1H, Ar-*H*); 7.48 (d, J = 8.8Hz, 1H, Ar-*H*).

EIMS *m/z* 322 $[M]^+$ (30), 280 (100), 264 (40), 43(15).

tert-butyl(6-iodo-2,3-dimethoxyphenoxy)diphenylsilane (50a)



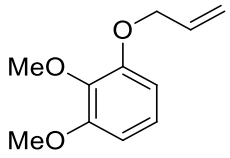
Chemical Formula: $C_{24}H_{27}IO_3Si$
Exact Mass: 518.08 g/mol
Molecular Weight: 518.46 g/mol

In a 2 necks flask under argon atmosphere 2,3-dimethoxyphenol (1 equiv., 0.32mmol, 0.050g) was dissolved in DCM (2mL). To this solution were added imidazole (2 equiv., 0.64mmol, 0.043g) and a solution of *tert*-butyl(chloro) diphenylsilane (TBDPSCl) (1.2 equiv., 0.38mmol, 99µL) in DCM (1mL) at room temperature. The solution was stirred for 18h. The mixture was quenched with water (5mL) and extracted with DCM (3x15mL). The organic layers were washed with BRINE (2x15mL), dried on Na_2SO_4 and concentered under reduced pressure. The crude of reaction purified by column chromatography afford the desire product with 62% (0.077g, 0.19mmol). This oil was directly iodinated, using the general procedure of iodination (Method B) with NIS (1.1 equiv., 0.21mmol, 0.053g). Final product **50a** was obtained after 16h of reaction with 79% yield (0.15mmol, 0.077g) as a viscous pale yellow oil.

$\mathbf{R}_f$ = 0.6 (EP/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 9H, SiC(CH_3)$_3$); 3.82 (s, 3H, OCH_3); 3.86 (s, 3H, OCH_3); 6.27 (d, *J* = 8.8Hz, 1H, Ar-*H*); 7.48 (d, *J* = 8.8Hz, 1H, Ar-*H*).

1-(allyloxy)-2,3-dimethoxybenzene (51)



Chemical Formula: $C_{11}H_{14}O_3$
Exact Mass: 194.09 g/mol
Molecular Weight: 194.23 g/mol

In a solution of 2,3-dimethoxyphenol (1equiv., 46.3mmol, 9.0g) in acetone (185mL) was added K_2CO_3 (2equiv., 92.6nnol, 12.78g) after stirring 10 min., benzyl bromide (1.2equiv., 55.5mmol, 4.72mL were added. The reaction was stirred at reflux for 5h until complete transformation of starting phenol. The reaction was quenched with H_2O and extracted with EtOAc (3x50mL/mmol). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude reaction was purified through a silica pad to afford the desired **51** as a brown oil.

Time = 5h

Yield = (9.0g; 46.3mmol) 99%

$\mathbf{R}_f$ = 0.5 (EP/Et_2O = 8:2)

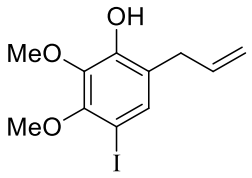
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3); 4.59 (d, J = 5.2Hz, 2H, Ar-OCH_2); 5.26 (dd, 1H, J_{cis} = 10.4Hz, 0.8 Hz, C*H*-allyl), 5.39 (dd, J_{trans} = 17.2 Hz; 0.8 Hz, 1H, C*H*-allyl), 6.04 (m, 1H, C*H*-allyl), 6.57 (d, J = 8.4 Hz, 2H, 2Ar-*H*), 6.94 (t, J = 8.0 Hz, 1H, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.1 (O*C*H_3), 60.8 (O*C*H_3), 69.9 (O*C*H_2-allyl), 105.5 (*C*H-Ar), 107.2 (*C*H-Ar), 117.4 (*C*H_2-allyl), 123.4 (*C*H-Ar), 133.5 (*C*H-allyl), 138.7 (q, *C*OCH3), 152. 5 (q, *C*O-allyl), 153.7 (q, *COCH*$_3$).

EIMS *m/z* 194 $[M]^+$ (100), 179 (10), 153 (80), 138 (10), 125 (100), 110 (70), 95 (50);

anal. C 68.05 , H 7.24 %, calcd for $C_{11}H_{14}O_3$, C 68.02, H 7.27 %.

6-allyl-4-iodo-2,3-dimethoxyphenol (52)



Chemical Formula: $C_{11}H_{13}IO_3$
Exact Mass: 319.99 g/mol
Molecular Weight: 320.12 g/mol

A solution of I_2 (2 equiv., 5.15mmol, 1.30g) and *t*-$BuNH_2$ (4 equiv., 10.30mmol, 1.08mL) in toluene (0.1M, 45mL) was stirred for 1h at room temperature. To this mixture at 0°C was slowly added a solution of allylphenol **48** (1 equiv., 2.57mmol, 0.50g) in DCM (0.2M, 12.4mL). The mixture was stirred at room temperature and followed by GC-MS and TLC (EP/EtOAc 9:1). After 5h the solution was diluted with EtOAc (40mL). The organic layer was washed with water (2x30mL), with a saturated aqueous solution of $Na_2S_2O_3$ (2x30mL) and with BRINE (2x30mL). Organic layers were dried on Na_2SO_4, filtered and reduced to rotavapor to dryness. The crude product (yellow oil) was constituted by 90% of desired product **52**, it contained also 6% of starting phenol **48** and 4% of diiodinated substarte **54.** To correctly characterize product **52,** we first protected its phenol function with methoxymethyl group. We isolated the pure product **57** and we hydrolysed MOM group with HCl 1M to obtain the pure iodinated phenol **52.**

Time = 5h

Yield = 90% (conversion)

$\mathbf{R}_f$ = 0.5 (EP/EtOAc = 8:2)

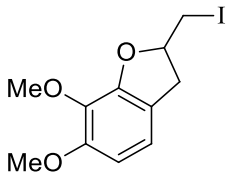
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.31 (d, 2H, J = 6.4Hz, CH_2-allyl); 3.83 (s, 3H, OCH_3); 3.93 (s, 3H, OCH_3); 5.07 (d, 1H, J_{cis} = 10.4 Hz, C*H*-allyl), 5.10 (d, 1H, J_{trans} = 17,0 Hz, C*H*-allyl), 5.85 (s, 1H, O*H*), 5.94 (m, 1H, C*H*-allyl), 7.24 (s, 1H, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 33.36 (*C*H_2-allyl), 60.44 (O*C*H_3), 60.94 (O*C*H_3), 79.42 (q, *C*-I), 116.12 (*C*H_2-allyl), 124.44 (q, *C*-allyl), 133.21 (*C*H-allyl), 135.81 (*C*H-Ar), 139.64 (q, *C*OCH_3), 147.87 (q, *C*OH), 150.29 (q, *C*OCH_3).

EIMS *m/z* 320 $[M]^+$(100), 277 (50), 43 (20);

anal. C 41.31 , H 4.15 %, calcd for $C_{11}H_{13}IO_3$, C 41.27, H 4.09 %.

2-(iodomethyl)-6,7-dimethoxy-2,3-dihydrobenzofuran (53)



Chemical Formula: $C_{11}H_{13}IO_3$
Exact Mass: 319.99 g/mol
Molecular Weight: 320.12 g/mol

To a solution of starting phenol **48** (1 equiv., 2.57mmol, 0.50g) in ACN (0.25M, 10.28mL) was added at 0°C NIS (3.5 equiv., 8.99mmol, 2.02g). The mixture was stirred at 0°C for 3h after which starting phenol **48** appeared completely reacted. The mixture was quenched with water (10mL). Extraction of aqueous layers was done with EtOAc (3x30mL). The combined organic extracts were washed with a saturated aqueous solution of $Na_2S_2O_3$ (3x25mL), 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 (EP/EtOAc 9/1) affording the right product **53** as a brown oil.

Time = 3h

Yield = (2.21mmol, 0.71g) 86%

$\mathbf{R}_f$ = 0.6 (EP/EtOAc = 9:1)

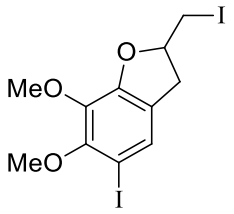
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.00 (dd, 1H, J = 16Hz, 6.5Hz, C*H*-furan); 3.35 (dd, 1H, *J* = 11.6Hz, 6.5Hz, C*H*-furan), 3.38 (m, 1H, CH_2-I), 3.47 (dd, 1H, *J* = 10.4Hz, 4.8 Hz, CH_2-I); 3.84 (s, 3H, OCH_3); 3.94 (s, 3H, OCH_3); 4.91 (m, 1H, OC*H*-furan); 6.43 (d, 1H, *J* = 8.5Hz, Ar-*H*); 6.78 (d, 1H, *J* = 8.5Hz, Ar-*H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 9.36 (*C*H_2-I); 36.21 (*C*H_2-furan); 56.54 (O*C*H_3), 60.08 (O*C*H_3), 83.42 (O*C*H-furan); 105.05 (Ar-*H*); 118.51 (q, *C*-furan); 120.53 (Ar-*H*); 132.84 (q, *C*O-furan); 152.03 (q, *C*OCH_3); 153.11 (q, *C*OCH_3).

EIMS *m/z* 320 $[M]^+$(100), 193 (80), 133 (70), 77(55);

anal. C 41.21 , H 4.10 %, calcd for $C_{11}H_{13}IO_3$, C 41.27, H 4.09 %.

5-iodo-2-(iodomethyl)-6,7-dimethoxy-2,3-dihydrobenzofuran (54)



Chemical Formula: $C_{11}H_{12}I_2O_3$
Exact Mass: 445.89 g/mol
Molecular Weight: 446.02 g/mol

To a solution of 2-(iodomethyl)-6,7-dimethoxy-2,3-dihydrobenzofuran (**53**) (1 equiv., 0.90 mmol, 0.30g) in DCM (0,2M, 4.5mL) were added (1.5equiv., 1.4 mmol, 0.26g) of I_2 and (1.5equiv., 1.4 mmol, 0.24g) of AgOTf. The mixture was stirred for 18h at room temperature. The reaction was quenched with water (20mL) and the aqueous layer was extracted with EtOAc (3x30mL) and washed with a saturated aqueous solution of $Na_2S_2O_3$ (2x20mL). The organic layers were dried on Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (EP/Et_2O 8/2) to give the pure product **54** as a pale yellow oil.

Time = 18h

Yield = (0.45mmol, 0.20g) 50%

$\mathbf{R}_f$ = 0.4 (EP/EtOAc = 9:1)

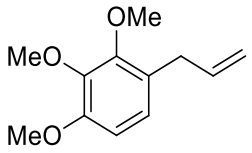
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (dd, 1H, J = 16Hz, 6.4Hz, C*H*-furan); 3.34 (dd, 1H, *J* = 11.6Hz, 6.4Hz, C*H*-furan), 3.37 (m, 1H, CH_2-I), 3.44 (dd, 1H, *J* = 10.4Hz, 4.8 Hz, CH_2-I); 3.87 (s, 3H, OCH_3); 3.94 (s, 3H, OCH_3); 4.92 (m, 1H, OC*H*-furan); 7.21 (s,1H, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.53 (*C*H_2-I); 35.62 (*C*H_2-furan); 60.61 (O*C*H_3), 60.93 (O*C*H_3), 80.62 (O*C*H-furan); 83.05 (q, *C*-I); 125.13 (q, *C*-furan); 127.53 (Ar-*H*); 137.81 (q, *C*O-furan); 147.83 (q, *C*OCH_3); 154.02 (q, *C*OCH_3).

EIMS *m/z* 446 $[M]^+$(100), 403 (5), 375 (5), 177(30);

anal. C 29.59 , H 2.75 %, calcd for $C_{11}H_{12}I_2O_3$, C 29.62, H 2.71 %.

1-allyl-2,3,4-trimethoxybenzene (55)



Chemical Formula: $C_{12}H_{16}O_3$
Exact Mass: 208.11 g/mol
Molecular Weight: 208.25 g/mol

To a solution of phenol **48** (1equiv., 0.51mmol, 0.1g) in acetone (0.1M, 4mL) was added K_2CO_3 (2equiv., 1.10mnol, 0.15g). After stirring 10 min., methyl iodide (1.2equiv., 0.61mmol, 0.04mL) were added. The reaction was stirred at reflux temperature for 5h until complete transformation of starting phenol. The reaction was quenched with H_2O (5mL) and extracted with EtOAc (3x10mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude reaction was purified through a silica pad to afford the desired **55** as a brown oil.

Time = 5h

Yield = (0.50mmol, 0.10g) 98%

$\mathbf{R}_f$ = 0.4 (EP/EtOAc = 8:2)

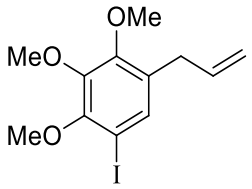
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.46 (d, 2H, *J* = 6.0Hz, C*H*$_2$-allyl); 3.86 (s, 3H, OC*H*$_3$); 3.89 (s, 6H, OC*H*$_3$); 5.04 (m, 2H, C*H*$_2$-allyl); 6.00 (m, 1H, C*H*-allyl); 6.64 (d, 1H, *J* = 8.0Hz, Ar-*H*); 6.84 (d, 1H, *J* = 8.0Hz, Ar-*H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 33.81 (*C*H$_2$-allyl); 56.03 (OCH$_3$); 60.71 (OCH$_3$); 60.92 (OCH$_3$); 107.34 (*C*H-Ar); 115.52 (*C*H$_2$-allyl); 123.92 (q, *C*-allyl); 126.12 (*C*H-Ar); 137.62 (q, *C*OCH$_3$); 142.32 (q, *C*OCH$_3$); 151.70 (q, *C*OCH$_3$).

EIMS *m/z* 208 $[M]^+$(100), 177 (30), 151 (10), 133(30);

anal. C 69.24, H 7.73 %, calcd for $C_{12}H_{16}O_3$, C 69.21, H 7.74 %

1-allyl-5-iodo-2,3,4-trimethoxybenzene (56)



Chemical Formula: $C_{12}H_{15}IO_3$
Exact Mass: 334.01 g/mol
Molecular Weight: 334.15 g/mol

To a solution of phenol **52** (1equiv., 0.31mmol, 0.1g) in acetone (0.1M, 3mL) was added K_2CO_3 (2equiv., 0.62mnol, 0.08g). After stirring 10min., iodomethane (1.2equiv., 0.37mmol, 0.02mL) were added. The reaction was stirred at reflux temperature for 5h until complete transformation of starting phenol. The reaction was quenched with H_2O (5mL) and extracted with EtOAc (3x10mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude reaction was purified through a silica pad to afford the desired **56** as a pale yellow oil.

Time = 5h

Yield = (0.21mmol, 0.07g) 68%

R_f = 0.4 (EP/EtOAc = 8:2)

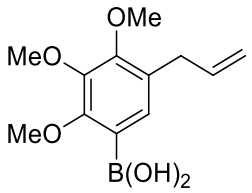
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.30 (d, 2H, *J* = 7.0Hz, C*H*$_2$-allyl); 3.85 (s, 3H, OC*H*$_3$); 3.86 (s, 3H, OC*H*$_3$); 3.90 (s, 3H, OC*H*$_3$); 5.07 (m, 2H, C*H*$_2$-allyl); 6.00 (m, 1H, C*H*-allyl); 7.29 (s, 1H, Ar-*H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 33.62 (*C*H$_2$-allyl); 60.83 (O*C*H$_3$); 60.91 (O*C*H$_3$); 61.00 (O*C*H$_3$); 85.04 (*C*-I); 116.23 (*C*H$_2$-allyl); 131.62 (q, *C*-allyl); 133.25 (*C*H-Ar); 136.63 (*C*H-allyl); 146.64 (q, *C*OCH$_3$); 152.23 (q, *C*OCH$_3$); 152.54 (q, *C*OCH$_3$).

EIMS *m/z* 334 $[M]^+$(100), 319 (10), 292 (10), 192 (15), 177(20);

anal. C 43.17, H 4.55 %, calcd for $C_{12}H_{15}IO_3$, C 43.13, H 4.52 %

(5-allyl-2,3,4-trimethoxyphenyl)boronic acid (56a)



Chemical Formula: $C_{12}H_{17}BO_5$
Exact Mass: 252.12 g/mol
Molecular Weight: 252.07 g/mol

Substrate **56** (1equiv., 0.15mmol, 0,05g) was dissolved in 5mL (0.3M) of anhydrous THF under inert atmosphere. The mixture was stirred and allowed to -78°C. To this solution n-BuLi (3equiv., 0.45mmol, 0.45mL, solution 1M in hexane) was added dropwise. The mixture was stirred for 1h at -78°C during which a change of colour solution from transparent to yellow was observed. After 1h, $B(O\textit{i}Pr)_3$ (2equiv., 0.30mmol, 0.07mL) was slowly added at -78°C. The mixture was stirred for 3h at same temperature after that the solution was allowed to warm to room temperature for additionally 4h. The reaction was quenched with 5mL of water and the resultant solution was extracted three times with 10 mL of ethyl ether. The collected organic layers were dried using Na_2SO_4, filtered and concentred under reduced pressure. The crude was purified by silica gel column chromatography (DCM/MeOH 100/1 V/V) to obtain the desired product as white butter.

Time = 4h (-78°C) + 4h (-78°C to rt)

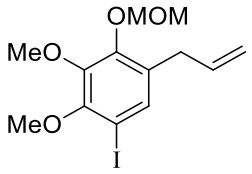
Yield = (0.13mmol, 0.033g) 84%

R_f = 0.6 (DCM/MeOH) = 100:1

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.04(bs, BO*H*); 3.56 (d, 2H, J = 13.5Hz, CH_2-Ar); 3.84 (s, 3H, OCH_3); 3.88 (s, 3H, OCH_3); 4.02 (s, 3H, OCH_3); 5.05 (m, 2H, CH_2-allyl); 5.93 (m, 1H, C*H*-allyl); 6.84 (s, 1H, Ar-*H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 33.65 (*C*H_2-allyl); 56.83 (O*C*H_3); 60.94 (O*C*H_3); 61.05 (O*C*H_3); 115.23 (*C*H_2-allyl); 117.35 (q, C-B); 123.62 (q, *C*-allyl); 129.86 (*C*H-Ar); 136.63 (*C*H-allyl); 140.64 (q, *C*OCH_3); 146.34 (q, *C*OCH_3); 152.21 (q, *C*OCH_3).

1-allyl-5-iodo-3,4-dimethoxy-2-(methoxymethoxy)benzene (57)



Chemical Formula: $C_{13}H_{17}IO_4$
Exact Mass: 364.02 g/mol
Molecular Weight: 364.18 g/mol

The product was obtained following the general procedure for MOM protection (see 7.3). The reaction was performed starting from crude mixture containing phenol **52** in 90% (1equiv., 3.10mmol, 1.0g). The mixture was stirred for 8h at room temperature. The crude was purified by silica gel chromatography to afford as a transparent oil.

Time: 8h

Yield: (2.54mmol, 0.93g) 82%

$\mathbf{R}_f$ = 0.6 (EP/EtOAc = 9:1)

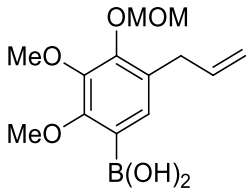
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.37 (d, 2H, J = 6.6Hz, CH_2-allyl); 3.58 (s, 3H, OCH_3-MOM); 3.84 (s, 3H, OCH_3); 3.86 (s, 3H, OCH_3); 5.06 (m, 2H, CH_2-allyl); 5.12 (s, 2H, CH_2-MOM); 5.93 (m, 1H, CH-allyl); 7.31 (s, 1H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 33.44 (CH$_2$-allyl); 57.29 (OCH$_3$-MOM); 60.52 (OCH$_3$); 60.58 (OCH$_3$); 85.32 (q, C-I); 99.06 (CH$_2$-MOM); 116.18 (CH$_2$-allyl); 131.51 (q, C-allyl); 133.08 (CH-Ar); 136.09 (CH-allyl); 145.91 (q, COCH$_3$); 149.35 (q, CO-MOM); 151.97 (q, COCH$_3$).

EIMS *m/z* 364 $[M]^+$(100), 319 (45), 292 (10), 237 (15), 177(30);

anal. C 42.90, H 4.75 %, calcd for $C_{13}H_{17}IO_4$, C 42.87, H 4.71 %

(5-allyl-2,3-dimethoxy-4-(methoxymethoxy)phenyl)boronic acid (57a)



Chemical Formula: $C_{13}H_{19}BO_6$
Exact Mass: 282.13 g/mol
Molecular Weight: 282.10 g/mol

Substrate **56** (1equiv., 1.9mmol, 0,7g) was dissolved in 6mL (0.3M) of anhydrous THF under inert atmosphere. The mixture was stirred and allowed to -78°C. To this solution n-BuLi (3equiv., 5.7mmol, 5.7mL, solution 1M in hexane) was added dropwise. The mixture was stirred for 1h at -78°C during which a change of colour solution from transparent to yellow was observed. After 1h, $B(OiPr)_3$ (2equiv., 3.8mmol, 0.9mL) was slowly added at -78°C. The mixture was stirred for 3h at same temperature after that the solution was allowed to warm to room temperature for additionally 4h. The reaction was quenched with 5mL of water and the resultant solution was extracted three times with 10 mL of ethyl ether. The collected organic layers were dried using Na_2SO_4, filtered and concentred under reduced pressure. The crude was purified by silica gel column chromatography (DCM/MeOH 100/1 V/V) to obtain the desired product as white butter. The product was not obtained pure, so the calculated yield include also some impurity.

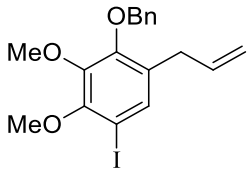
Time = 4h (-78°C) + 4h (-78°C to rt)

Yield = (0.268g) 50%

$\mathbf{R}_f$ = 0.35 (DCM/MeOH) = 100:1

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.36 (d, 2H, J = 6.8Hz, CH_2-Ar); 3.58 (s, 3H, OCH_3-MOM); 3.88 (s, 3H, OCH_3); 3.91 (s, 3H, OCH_3); 5.02 (m, 2H, CH_2-MOM); 5.05 (m, 2H, CH_2-allyl); 5.93 (m, 1H, CH-allyl); 6.53 (s, 1H, Ar-H).

1-allyl-2-(benzyloxy)-5-iodo-3,4-dimethoxybenzene (58)



Chemical Formula: $C_{18}H_{19}IO_3$
Exact Mass: 410.04 g/mol
Molecular Weight: 410.25 g/mol

Benzylated product **58** was obtained using general procedure for benzylation-Method A (see 7.3). The reaction was performed starting from crude mixture containing phenol **52** in 90% (1equiv., 3.10mmol, 1.0g). The mixture was stirred for 5h at room temperature. The crude was purified by silica gel chromatography to afford as a transparent oil.

Time: 5h

Yield: (1.79mmol, 0.74g) 58%

$\mathbf{R}_f$ = 0.6 (EP/EtOAc = 9.5:0.5)

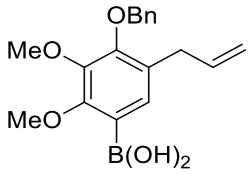
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.23 (d, 2H, J = 6.7Hz, CH_2-allyl); 3.86 (s, 3H, OCH_3); 3.89 (s, 3H, OCH_3); 5.01 (m, 2H, CH_2-allyl); 5.12 (s, 2H, CH_2-Bn); 5.81 (m, 1H, CH-allyl); 7.23 (s, 1H, Ar-H); 7.34 (m, 5H, Bn)

^{13}C NMR (100 MHz, $CDCl_3$) δ: 33.35 (CH_2-allyl); 60.07 (OCH_3); 60.68 (OCH_3); 75.23 (CH_2-Bn); 86.12 (q, C-I); 116.78 (CH_2-allyl); 126.45 (CH-Bn); 126.95 (CH-Bn); 128.67 (CH-Bn); 130.23 (q, C-allyl); 134.28 (CH-Ar); 136.09 (CH-allyl); 136.34 (q, C-Bn); 146.21 (q, COCH$_3$); 151.31 (q, COCH$_2$Bn); 155.97 (q, COCH$_3$).

EIMS *m/z* 410 $[M]^+$(5), 319 (10), 283 (15), 177 (10), 91(100);

anal. C 52.75, H 4.70 %, calcd for $C_{18}H_{19}IO_3$, C 52.70, H 4.67 %

(5-allyl-4-(benzyloxy)-2,3-dimethoxyphenyl)boronic acid (58a)



Chemical Formula: $C_{18}H_{21}IO_5$
Exact Mass: 328.15 g/mol
Molecular Weight: 328.17 g/mol

Substrate **58** (1equiv., 0.12mmol, 0,057g) was dissolved in 5mL (0.3M) of anhydrous THF under inert atmosphere. The mixture was stirred and allowed to -78°C. To this solution n-BuLi (3equiv., 0.36mmol, 0.36mL, solution 1M in hexane) was added dropwise. The mixture was stirred for 1h at -78°C during which a change of colour solution from transparent to yellow was observed. After 1h, $B(O\textit{i}Pr)_3$ (2equiv., 0.24mmol, 0.06mL) was slowly added at -78°C. The mixture was stirred for 3h at same temperature after that the solution was allowed to warm to room temperature for additionally 4h. The reaction was quenched with 5mL of water and the resultant solution was extracted three times with 10 mL of ethyl ether. The collected organic layers were dried using Na_2SO_4, filtered and concentred under reduced pressure. The crude was purified by silica gel column chromatography (DCM/MeOH 100/1 V/V). The product was not obtained pure, so the calculated yield include also some impurity.

Time = 4h (-78°C) + 4h (-78°C to rt)

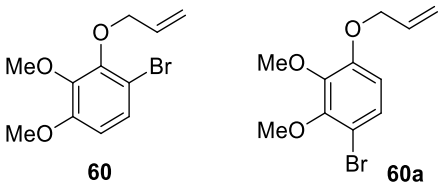
Yield = (0.020g) 50%

$\mathbf{R}_f$ = 0.4 (DCM/MeOH) = 100:1

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.32 (d, 2H, J = 6.5Hz, CH_2-Ar); 3.90 (s, 3H, OCH_3); 4.00 (s, 3H, OCH_3); 5.01 (m, 2H, CH_2-allyl); 5.08 (s, 2H, CH_2-Bn); 5.85 (s, 1H, Ar-*H*); 5.93 (m, 1H, C*H*-allyl); 7.38 (m, 6H, Bn-*H*, Ar-*H*).

2-(allyloxy)-1-bromo-3,4-dimethoxybenzene (60)

1-(allyloxy)-4-bromo-2,3-dimethoxybenzene (60a)



Chemical Formula: $C_{11}H_{13}BrO_3$
Exact Mass: 272.00 g/mol
Molecular Weight: 273.12 g/mol

Brominated product **60** and **60a** were obtained as a mixture 1:1 after performing bromination of substarte **51.** Starting *O*-allylbenzene **51** (1 equiv., 0.51mmol, 0.10g) was stirred with NBS in ACN for 5h according to the general procedure-Method B (see 7.3). Otherwise **51** was used in the same general condition, changing the solvent in THF and the adding NBS at -78°C. In this last case the mixture was allowed to warm until room temperature and stirred for 22h.

In both reactions was isolate a transparent oil in which **60** and **60a** were found in the same regioisomeric ratio (1:1). The two regioisomers weren't separable with column chromatography, but they were identified by ^{1}H-NMR.

Time: 5h or 22h

Yield: (0.51mmol, 0.14g) 50% (**60**):50% (**60a**)

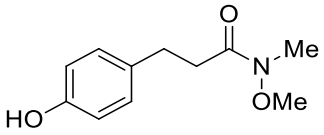
$\mathbf{R}_f$ = 0.5 (EP/Et_2O = 9:1)

^{1}H NMR 60 or 60a (400 MHz, $CDCl_3$) δ 3.82 (s, 3H, OCH_3); 3.85 (s, 3H, OCH_3); 4.56 (d, 2H, *J* = 5.2Hz , Ar-OCH_2); 5,22 (d, 1H, J_{cis} = 13 Hz, C*H*-allyl); 5.38 (d, 1H, J_{trans} = 17.2 Hz, C*H*-allyl); 6,11 (m, 1H, C*H*-allyl); 6,56 (d, 1H, *J* = 8.8Hz, Ar-*H*); 7,19 (d, 1H, *J* = 8.8Hz, Ar-*H*).

^{1}H NMR 60 or 60a (400 MHz, $CDCl_3$) δ 3.87 (s, 3H, OCH_3); 3.89 (s, 3H, OCH_3); 4.54 (d, 2H, *J* = 5.2Hz , Ar-OCH_2); 5,27 (d, 1H, J_{cis} = 13 Hz, C*H*-allyl); 5.40 (d, 1H, J_{trans} = 17.2 Hz, C*H*-allyl); 6,02 (m, 1H, C*H*-allyl); 6,56 (d, 1H, *J* = 8.8Hz, Ar-*H*); 7,15 (d, 1H, *J* = 8.8Hz, Ar-*H*).

EIMS *m/z* 272 $[M]^+$(60), 231 (100), 216 (15), 188 (50), 124(65).

3-(4-hydroxyphenyl)-N-methoxy-N-methylpropanamide[242] (61)



Chemical Formula: $C_{11}H_{15}NO_3$
Exact Mass: 209.11 g/mol
Molecular Weight: 209.24 g/mol

To a solution of commercial 4-hydroxyphenylpropionic acid (1 equiv., 3.00mmol, 0.50g) in THF (9mL) were added CDMT (2-chloro-4,6-dimethoxy-1,3,5-triazine) (1.2equiv., 3.6mmol, 0.63g) and NMM (n-methylmorpholine) (3equiv., 9.02mmol, 0.99mL) at room temperature. A white precipitate was formed. The solution was stirred for 1,5h during which a white precipitate was formed. Subsequently N,O-dimethylhydroxylamine hydrochloride (1equiv., 3.00mmol, 0.29g) was added. The mixture was stirred for 6h and then quenched with 10mL of water. The aqueous layers was extracted three times with diethyl ether (20mL). The organic layer was dried on Na_2SO_4. The crude reaction was purified twice by silica gel chromatography to afford the Weinreb amide **61** as a transparent oil.

Time: 7.5h

Yield: (1.41mmol, 0.29g) 47%

R_f = 0.5 (Cy/EtOAc = 8:2)

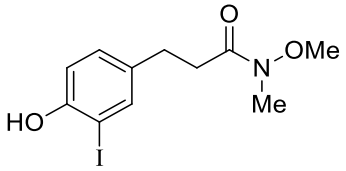
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73 (t, 2H, J = 7.1Hz, CH_2); 2.88 (t, 2H, J = 7.7Hz, CH_2); 3.18 (s, 3H, NCH_3); 3.58 (s, 3H, NOCH_3); 6.80 (d, 2H, J = 8.4Hz, Ar-*H*); 7.04 (d, 2H, J = 8.4Hz, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.85 (N*C*H$_3$); 32.13 (*C*H$_2$); 33.93 (*C*H$_2$); 61.16 (NO*C*H$_3$); 115.37 (*C*H-Ar); 129.30 (*C*H-Ar); 132.20 (q, *C*-alkyl); 154.74 (q, *C*-OH); 174.12 (q, *C*O-amide).

anal. C 63.18, H 7.29, N 7.73 %, calcd for $C_{11}H_{15}NO_3$, C 63.14, H 7.23, N 6.69 %

[242] De Luca, L.; Giacomelli, G.; Taddei, M. *J. Org. Chem.* **2001**, *66* (7), 2534–2537.

3-(4-hydroxy-3-iodophenyl)-N-methoxy-N-methylpropanamide (61a)



Chemical Formula: $C_{11}H_{14}INO_3$
Exact Mass: 335.00 g mol
Molecular Weight: 335.14 g/mol

Amide **61a** was obtained from the methyl ester **64a** following the general procedure for Weinreb amide preparation (see 7.3.2)

N,O-dimethylhydroxylamine hydrochloride (3equiv., 9.80mmol, 0.95g), $AlMe_3$ (3equiv., 4.9mL, 2M in toluene) and methylester **64a** (1equiv., 3.27mmol, 1.00g) were used. Crude product was purified by silica gel chromatography (Cyclohexane/EtOAc, 4:6) to obtain the product as a tranparent oil.

Time = 20h

Yield = (1.63mmol, 0.55g) **50%**

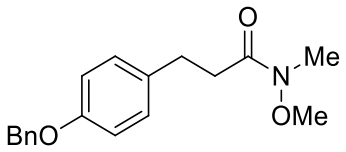
$\mathbf{R}_f$ = 0.52 (Cy/EtOAc = 4:6)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (t, 2H, J = 7.5 Hz, CH_2); 2.86 (t, 2H, J = 7.5 Hz, CH_2); 3.18 (s, 3H, N-CH_3); 3.62 (s, 3H, N-OCH_3); 5.19 (bs, 1H, O*H*); 6.91 (d, 2H, J = 8.3Hz, Ar-*H*); 7.11 (dd, 2H, J_{ortho} = 8.4Hz, J_{meta} = 2.0Hz, Ar-*H*), 7.53 (d, 1H, J_{meta} = 1.9 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)

anal. C 39.48, H 4.25, N 4.22 %, calcd for $C_{11}H_{14}INO_3$, C 39.42, H 4.21, N 4.18 %

3-(4-(benzyloxy)phenyl)-N-methoxy-N-methylpropanamide (62)



Chemical Formula: $C_{18}H_{21}NO_3$
Exact Mass: 299.15 g/mol
Molecular Weight: 299.36 g/mol

Product **62** was obtained after benzylation of phenol **61** (1 equiv., 0.48mmol, 0.10g), using general procedure for benzylation method A (see 7.3). It was obtained after 4h of reaction with a yield of 80%.

Otherwise, amide **62** was obtained from the methyl ester **65** or benzyl ester **67** following the general procedure for Weinreb amide preparation (see 7.3.2)

N,O-dimethylhydroxylamine (3equiv., 33.7mmol, 3.29g), $AlMe_3$ (3equiv., 16.7mL, 2M in toluene) and methylester **65** (1equiv., 11.1mmol, 3.02g) were used. Crude product was purified by silica gel chromatography (Cyclohexane/EtOAc, 3:2) to obtain the product as a pale yellow oil.

The same procedure was used if reaction was done with **67** (1 equiv., 5.55mmol, 1.9g) as starting material.

Time: 4h from **61**
20h from **65** and **67**

Yield: (0.38mmol, 0.11g) 80% from benzylation of **61**
(7.62mmol, 2.28g) 68% from **65**
(3.38mmol, 1.01g) 61% from **67**

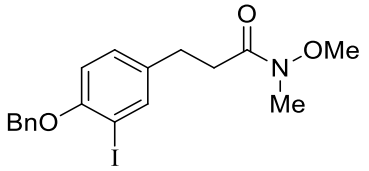
$\mathbf{R}_f$ = 0.5 (Cy/EtOAc = 6:4)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71 (t, 2H, *J* = 7.6Hz, CH_2); 2.91 (t, 2H, *J* = 7.6Hz, CH_2); 3.18 (s, 3H, NCH_3); 3.60 (s, 3H, NOCH_3); 5.05 (s, 2H, CH_2-Bn); 6.93 (d, 2H, *J* = 8.5Hz, Ar-*H*); 7.15 (d, 2H, *J* = 8.5Hz, Ar-*H*); 7.47-7.27 (m, 5H, C*H*-Bn).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.85 (N*C*H_3); 32.21 (*C*H_2); 33.93 (*C*H_2); 61.16 (NO*C*H_3); 70.04 (*C*H_2-Bn); 114.81 (*C*H-Ar); 127.40 (*C*H-Bn); 127.82 (*C*H-Bn); 128.50 (*C*H-Bn); 129.30 (*C*H-Ar); 133.72 (q, *C*-alkyl); 137.13 (q, C-Bn); 157.24 (q, *C*-OH); 173.72 (q, *C*O-amide).

anal. C 71.99, H 7.33, N 4.54 %, calcd for $C_{18}H_{21}NO_3$, C 77.22, H 7.07, N 4.68 %

3-(4-(benzyloxy)-3-iodophenyl)-N-methoxy-N-methylpropanamide (62a)



Chemical Formula: $C_{18}H_{20}INO_3$
Exact Mass: 425.05 g/mol
Molecular Weight: 425.26 g/mol

Amide **62a** was obtained from three different procedure:

Procedure A: Starting from iodinated amide **61a** (1 equiv., 1.49mmol, 0.50g) and following the general procedure of benzylation (see 7.3.1). The product was obtained as a transparent oil in **87% yield**. (1.29mmol, 0.55g)

Procedure B: Starting from iodinated methyl ester **65a** (1 equiv., 1.26mmol, 0.50g) and following the general procedure for Weinreb amide formation (see7.3.2). The product was obtained as a transparent oil in **77% yield**. (0.97mmol, 0.41g)

Procedure C: Starting from Weinreb amide **62** (1 equiv., 1.67mmol, 0.50g) and following the general procedure of iodination (Method A see 7.3.4). The product was obtained as a transparent oil in **90% yield**. (1.50mmol, 0.64g)

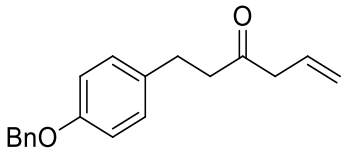
R_f = 0.57 (Cy/EtOAc = 4:6)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (t, 2H, J = 7.5 Hz, CH_2); 2.86 (t, 2H, J = 7.5 Hz, CH_2); 3.17 (s, 3H, N-CH_3); 3.61 (s, 3H, N-OCH_3); 5.12 (s, 2H, CH_2-Bn); 6.77 (d, 2H, J = 8.5Hz, Ar-H); 7.13 (dd, 2H, J_{ortho} = 8.5Hz, J_{meta} = 2.0Hz, Ar-H), 7.38 (m, 5H, Bn-H); 7.66 (d, 1H, J_{meta} = 1.9 Hz. Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.27 (N-CH$_3$); 32.23 (ArCH$_2$CH$_2$); 33.74 (ArCH$_2$$CH_2$); 61.25 (N-O$CH_3$); 70.99 ($CH_2$-Bn); 86.83 (q, C-I); 112.74 (CH-Ar); 127.01 (CH-Bn); 127.85 (CH-Bn); 128.54 (CH-Bn); 129.47 (CH-Ar); 136.00 (q, C-Ar); 136.65 (q, C-Bn); 139.29 (CH-Ar); 155.67 (q,CO-Ar); 173.56 (q, C=O).

anal. C 50.79, H 4.74, N 3.27 %, calcd for $C_{18}H_{20}INO_3$, C 50.84, H 4.74, N 3.29 %

1-(4-(benzyloxy)phenyl)hex-5-en-3-one (63)



Chemical Formula: $C_{19}H_{20}O_2$
Exact Mass: 280.15 g/mol
Molecular Weight: 280.36 g/mol

To an ice-cold solution of the Weinreb amide **62** (1equiv., 1.53mmol, 0.44g,) in 4.7mL of anhydrous THF was added dropwise a solution of allylmagnesium bromide 1M in diethyl ether (2.75equiv., 4.2 mmol, 4.2mL,) and stirred at the same temperature for 2.5h. The reaction was quenched by careful addition of an aqueous 10% HCl solution (16 mL) and stirred for 5 min. The resulting solution was extracted with ethyl acetate (3x10mL), the combined extracts were washed sequentially with water (30mL) and brine (30mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the almost pure product in 98% yield (1.50mmol, 0.42g). If crude was purified by silica gel chromatography, the isomerization of terminal double bond occurs and only 50% of product **63** was obtained as a brown oil.

Time: 2.5h

Yield: (0.75mmol, 0.21g) 50%

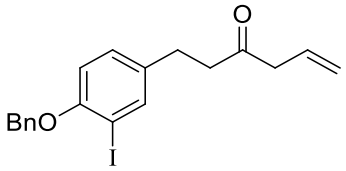
$\mathbf{R}_f$ = 0.4 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74 (t, 2H, J = 8.0Hz, CH_2); 2.85 (t, 2H, J = 8.0Hz, CH_2); 3.15 (d, 2H, J = 8.0Hz, CH_2-CH=CH_2); 5.05 (s, 2H, CH_2-Bn); 5.13 (d, 1H, J_{trans} = 17.0Hz, CH=CH_2); 5.18 (d, 1H, J_{cis} = 12.0Hz, CH=CH_2); 5.96-5.83 (m, 1H, CH_2-CH=CH_2); 6.90 (d, 2H, J = 8.4Hz, Ar-H); 7.10 (d, 2H, J = 8.4Hz, Ar-H); 7.45-7.31 (m, 5H, Bn).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.85 (Ar-$C$$H_2$); 44.1 ($CH_2$$C$$H_2$CO); 48.0 (CO$C$$H_2$CH=$CH_2$); 70.02 ($C$$H_2$-Bn); 114.92 ($C$H-Ar); 118.93 (CH=$C$$H_2$); 127.43 ($C$H-Bn); 127.94 ($C$H-Bn); 128.65 ($C$H-Bn); 129.32 ($C$H-Ar); 130.52 ($C$H=$CH_2$); 133.31(q, C-Ar); 137.13 (q, C-Bn); 157.14 (q, C-OBn); 207.92 (q, CO).

anal. C 81.45, H 7.23 %, calcd for $C_{19}H_{20}O_2$, C 81.40, H 7.19 %

1-(4-(benzyloxy)-3-iodophenyl)hex-5-en-3-one (63a)



Chemical Formula: $C_{19}H_{19}IO_2$
Exact Mass: 406.04 g/mol
Molecular Weight: 406.26 g/mol

To an ice-cold solution of the Weinreb amide **62a** (1equiv., 1.17mmol, 0.50g,) in 4.7mL of anhydrous THF was added dropwise a solution of allylmagnesium bromide 1M in diethyl ether (2.75equiv., 3.23mmol, 3.23mL) and stirred at the same temperature for 2.5h. The reaction was quenched by careful addition of an aqueous 10% HCl solution (16 mL) and stirred for 5 min. The resulting solution was extracted with ethyl acetate (3x10mL), the combined extracts were washed sequentially with water (30mL) and brine (30mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the almost pure product in 98% yield (1.14mmol, 0.47g). If crude was purified by silica gel chromatography, the isomerization of terminal double bond occur and only 50% of pure product **63a** was obtained as a brown oil.

Time = 2.5h

Yield = (0.75mmol, 0.23g) 50%

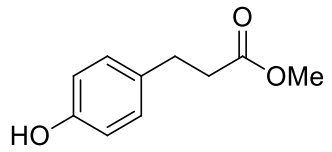
$\mathbf{R}_f$ = 0.5 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.72 (t, 2H, J = 8.0Hz, CH_2); 2.80 (t, 2H, J = 8.0Hz, CH_2); 3.15 (d, 2H, J = 8.0Hz, CH_2-CH=CH_2); 5.12 (s, 2H, CH_2-Bn); 5.13 (d, 1H, J_{trans} = 17.0Hz, CH=CH_2); 5.19 (d, 1H, J_{cis} = 12.0Hz, CH=CH_2); 5.89 (m, 1H, CH_2-CH=CH_2); 6.76 (d, 2H, J = 8.4Hz, Ar-H); 7.08 (dd, 2H, J_{ortho} = 8.4Hz, J_{meta} = 2.0Hz, Ar-H); 7.38 (m, 5H, Bn); 7.62 (dd, 1H, J_{meta} = 2.0Hz, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.13 (Ar-CH$_2$); 43.67 (CH_2CH_2 CO); 47.88 (COCH$_2$CH=CH$_2$); 70.92 (CH$_2$-Bn); 86.82 (q, C-I); 112.67 (CH-Ar); 119.00 (CH=CH$_2$); 126.94 (CH-Bn); 127.39 (CH-Bn); 128.48 (CH-Bn); 129.31 (CH-Ar); 130.29(CH=CH$_2$); 135.54 (q, C-Ar); 136.55 (q, C-Bn); 139.12 (CH-Ar); 155.62 (q, C-OBn); 207.37 (q, C=O).

anal. C 56.21, H 4.75 %, calcd for $C_{19}H_{19}IO_2$, C 56.17, H 4.71 %

Methyl 3-(4-hydroxyphenyl)propanoate (64)[238]



Chemical Formula: $C_{10}H_{12}O_3$
Exact Mass: 180.08 g/mol
Molecular Weight: 180.20 g/mol

Concentrated H_2SO_4 (12,5mL) was added to a suspension of commercially available 3-(4-hydroxyphenyl)propanoic acid (1equiv., 90.78mmol, 15.07g) in methanol (65mL) 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 (3x250mL) and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give a white solid. in 98% yield (87.15mmol, 15.74g).

Time = 1h

Yield = (87.15mmol, 15.74g) 98%

M.p.= 40-41°C

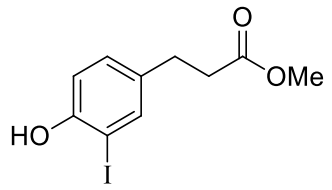
R_f = 0.5 (EP/Et_2O = 5:5)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (t, 2H, *J* = 7.8Hz, C*H*$_2$); 2.89 (t, 2H, *J* = 7.8Hz, C*H*$_2$); 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 (100 MHz, $CDCl_3$) δ: 30.10 (Ar-*C*H_2); 36.03 (*C*H_2); 51.66 (O*C*H_3); 115.34 (*C*H-Ar); 129.39 (*C*H-Ar); 132.56 (q, *C*-alkyl); 157.09 (q, *C*-OH); 173.67 (q, *C*O).

EIMS *m/z* 180 $[M]^+$(40), 107 (100).

Methyl 3-(4-hydroxy-3-iodophenyl)propanoate[238] (64a)



Chemical Formula: $C_{10}H_{11}IO_3$
Exact Mass: 305.98 g mol
Molecular Weight: 306.10 g/mol

Methyl 3-(4-hydroxyphenyl)propanoate **64** (1equiv., 69.44mmol, 12,50g) , I_2 (1equiv., 69.44mmol, 17.65g) and Ag_2SO_4 (1equiv., 69.44mmol, 21.65g) were used following the genral procedure for iodination (Method A, see 7.3.1) to prepare iodinated derivative **64a**. The product was obtained as a white solid.

Time = 2h

Yield= (54.8mmol, 16.78g) 80%

M.p. = 88-90°C

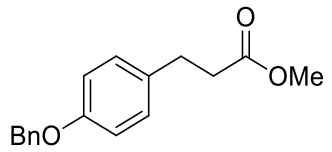
$\mathbf{R}_f$ = 0.6 (Cy/EtOAc = 5:5)

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.60 (t, 2H, J = 9Hz, CH_2); 2.87 (t, 2H, J = 7.8Hz, CH_2); 3.69 (s, 3H, OCH_3); 5.25 (s, 1H, O*H*); 6.91 (d, 2H, J = 8.5Hz, Ar-*H*); 7.09 (dd, 2H, J_{ortho} = 8.5Hz, J_{meta} = 2.5Hz, Ar-*H*); 7.51 (d, 1H, J_{meta} = 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).

EIMS *m/z* 305 $[M]^+$(40), 179 (100).

Methyl 3-(4-(benzyloxy)phenyl)propanoate (65)



Chemical Formula: C17H18O3
Exact Mass: 270.13 g/mol
Molecular Weight: 270.32 g/mol

Ester **65** was obtained following the general procedure for phenol benzylation-method A (see 7.3). (1equiv., 27.7mmol, 5g) of methyl 3-(4-hydroxyphenyl)propanoate **64** were involved in the reaction. The crude was purified by trituration in pentane that allowed to obtain the pure product as a withe solid.

Time = 4h

Yield = (27.6mmol, 7.45g) 99%

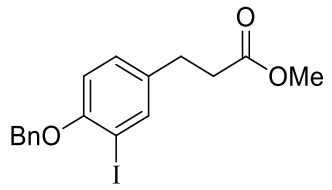
$\mathbf{R}_f$ = 0.5 (EP/Et_2O = 6:5)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (t, 2H, *J* = 7.8Hz, CH_2); 2.91 (t, 2H, *J* = 7.8Hz, CH_2); 3.68 (s, 3H, OCH_3); 5.05 (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: 30.06 (Ar-*C*H_2); 35.90 (*C*H_2); 51.50 (O*C*H_3); 69.99(CH_2-Bn); 114.85 (*C*H-Ar); 127.39 (C*H*-Bn); 127.85 (C*H*-Bn); 128.51 (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).

EIMS *m/z* 180 $[M]^+$(40), 107 (60), 91(100).

Methyl 3-(4-(benzyloxy)-3-iodophenyl)propanoate (65a)



Chemical Formula: $C_{17}H_{17}IO_3$
Exact Mass: 396.02 g/mol
Molecular Weight: 396.22 g/mol

Product **65a** was obtained from two different synthetic route:

Prodedure A: From the iodination of methyl ester **65** (1equiv, 8.17mmol, 2.5g) following the general procedure (Method A) described in 7.3.4. The product was obtained as a withe solid in **90% yield** (7.35mmol, 2.91g);

Procedure B: From the benzylation of phenol **64a** (1equiv., 16.34mmol, 5g) following the general procedure for benzylation described in 7.3.1. The product was obtained as a withe solid in **99% yield** (16.34mmol, 6.47g);

M.p. = 67-70°C

$\mathbf{R}_f$ = 0.5 (Cy/EtOAc = 6:5)

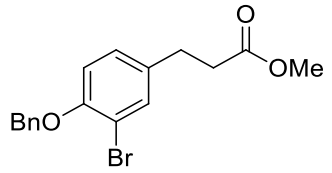
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.59 (t, 2H, J = 7.8Hz, CH_2); 2.86 (t, 2H, J = 7.8Hz, CH_2); 3.68 (s, 3H, OCH_3); 5.13 (s, 2H, CH_2-Bn); 6.78 (d, 2H, J = 8.5Hz, Ar-*H*); 7.11 (dd, 2H, J_{ortho} = 8.5Hz, J_{meta} = 2.2Hz, Ar-*H*); 7.38 (m, 5H, C*H*-Bn); 7.65 (dd, 1H, J_{ortho} = 2.2 Hz).

^{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 (CH_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).

EIMS *m/z* 396 $[M]^+$(40), 305 (60), 270(30), 91(100).

anal. C 51.57, H 4.39 %, calcd for $C_{17}H_{17}IO_3$, C 51.53, H 4.32 %

Methyl 3-(4-(benzyloxy)-3-bromophenyl)propanoate (65b)



Chemical Formula: $C_{17}H_{17}BrO_3$
Exact Mass: 348.04 g/mol
Molecular Weight: 349.22 g/mol

Product **65b** was obtained following the general procedure of bromination with NBS, Method B (see 7.3.3) starting from methyl ester **65** (1equiv, 8.17mmol, 2.5g). The pure product was obtained as a yellow oil.

Time = 8h

Yield = (7.27mmol, 2.54g) **89%**

$\mathbf{R}_f$ = 0.45 (Cy/EtOAc = 6:5)

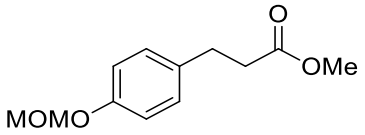
^{1}H NMR (500 MHz, $CDCl_3$) δ 2.58 (t, 2H, J = 7.8Hz, CH_2); 2.86 (t, 2H, J = 7.8Hz, CH_2); 3.66 (s, 3H, OCH_3); 5.13 (s, 2H, CH_2-Bn); 6.85 (d, 2H, J = 8.5Hz, Ar-*H*); 7.05 (dd, 2H, J_{ortho} = 8.5Hz, J_{meta} = 2.2Hz, Ar-*H*); 7.31 (m, 1H, C*H*-Bn); 7.37 (m, 3H, 2C*H*-Bn, 1Ar-*H*); 7.46 (d, 2H, J = 9Hz, C*H*-Bn);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 29.53 (Ar-*C*H_2); 35.47 (Ar-*C*H_2); 51.49 (O*C*H_3); 70.74 (CH_2-Bn); 113.76 (*C*H-Ar); 113.84 (q, *C*-Br); 126.81 (C*H*-Ar); 127.72 (C*H*-Bn); 127.99 (C*H*-Bn); 128.37 (*C*H-Bn); 132.98 (*C*H-Ar); 134.35 (q, C-Ar); 136.75 (q, *C*-Bn); 154.24 (q, *C*-OBn); 173.15 (q, *C*=O).

EIMS *m/z* 348 $[M]^+$(20), 275 (5), 91(100), 65(10).

anal. C 51.50, H 5.01 %, calcd for $C_{17}H_{17}BrO_3$, C 58.47, H 4.91 %

Methyl 3-(4-(methoxymethoxy)phenyl)propanoate (66)



Chemical Formula: $C_{12}H_{16}O_4$
Exact Mass: 224.10 g/mol
Molecular Weight: 224.25 g/mol

Methyl ester **66** was prepared following the general procedure for MOM protection (see 7.3). The product was prepared starting from methyl ester **64** (1equiv., 8.3mmol, 1.5g).

Time = 6h

Yield= (8.13mmol, 1.82g) 98%

R_f = 0.4 (EP/EtOAc = 8:2)

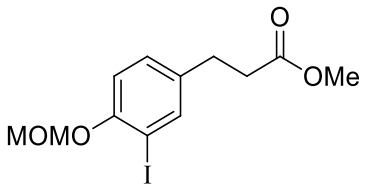
^{1}H NMR (500 MHz, $CDCl_3$) δ 2.60 (t, 2H, *J* = 7.8Hz, CH_2); 2.89 (t, 2H, *J* = 7.8Hz, CH_2); 3.47 (s, 3H, OCH_3-MOM); 3.67 (s, 3H, OCH_3); 5.14 (s, 2H, CH_2-MOM); 6.96 (d, 2H, *J* = 8.5Hz, Ar-*H*); 7.11 (d, 2H, *J* = 8.5Hz, Ar-*H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 30.15 (Ar-*C*H_2); 35.92 (*C*H_2); 51.52 (O*C*H_3); 56.00 (O*C*H_3-MOM); 94.55(CH_2-MOM); 116.45 (*C*H-Ar); 129.16 (C*H*-Ar); 133.94 (q, *C*-alkyl); 155.72 (q, *C*-OMOM); 173.38 (q, *C*O).

EIMS *m/z* 224 $[M]^+$(60), 194(20), 151(25), 121(50), 45(100).

anal. C 64.31, H 7.22 %, calcd for $C_{12}H_{16}O_4$, C 64.27, H 7.19 %

Methyl 3-(3-iodo-4-(methoxymethoxy)phenyl)propanoate (66a)



Chemical Formula: $C_{12}H_{15}IO_4$
Exact Mass: 350.00 g/mol
Molecular Weight: 350.15 g/mol

Methyl ester **66a** was obtained from the protection with MOM group of phenol **64a** (1equiv., 8.17mmol, 2.5g) following the general procedure for MOM protection described in 7.3.6. The product was obtained as a transparent oil.

Time = 8h

Yield = (7.18mmol, 2.51g) **88%**

$\mathbf{R}_f$ = 0.4 (Cy/EtOAc = 6:5)

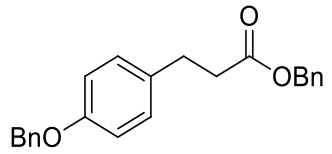
^{1}H NMR (500 MHz, $CDCl_3$) δ 2.60 (t, 2H, J = 7.8Hz, CH_2); 2.87 (t, 2H, J = 7.8Hz, CH_2); 3.52 (s, 3H, OCH_3-MOM); 3.68 (s, 3H, OCH_3); 5.22 (s, 2H, CH_2-MOM); 6.98 (d, 2H, J = 8.5Hz, Ar-*H*); 7.11 (dd, 2H, J_{ortho} = 8.5Hz, J_{meta} = 2.2Hz, Ar-*H*); 7.58 (d, 2H, J_{meta}= 2.2Hz, C*H*-MOM);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 30.01 (Ar-*C*H_2); 35.90 (*C*H_2); 51.81 (O*C*H_3); 55.80 (O*C*H_3-MOM); 85.79 (q, *C*-I), 94.53(CH_2-MOM); 112.45 (*C*H-Ar); 128.96 (C*H*-Ar); 133.93 (q, *C*-Ar); 141.56 (C*H*-Ar); 156.72 (q, *C*-OMOM); 173.15 (q, *C*=O).

EIMS *m/z* 350 $[M]^+$(60), 320(20), 277(25), 247(15), 45(100).

anal. C 41.20, H 4.39 %, calcd for $C_{12}H_{15}IO_4$, C 41.16, H 4.32 %

Benzyl 3-(4-(benzyloxy)phenyl)propanoate (67)



Chemical Formula: $C_{23}H_{22}O_3$
Exact Mass: 346.16 g/mol
Molecular Weight: 346.42 g/mol

Ester **67** was obtained following the general procedure for phenol benzylation-method A (see 7.3). (1equiv., 6.02mmol, 1g) of commercial 3-(4-hydroxyphenyl)propionic acid were involved in the reaction with 2.2 equivalents of benzylbromide. The crude was purified by trituration in pentane that allowed to obtain the pure product as a transparent oil.

Time= 4h

Yield = (6.00mmol, 1.0g) 99%

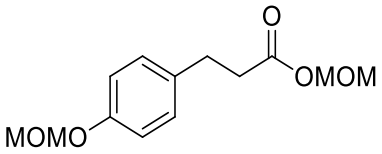
R_f = 0.55 (EP/Et_2O = 6:5)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (t, 2H, *J* = 8.0Hz, C*H*$_2$); 2.92 (t, 2H, *J* = 8.0Hz, C*H*$_2$); 5.04 (s, 2H, C*H*$_2$-Bn); 5.12 (s, 2H, C*H*$_2$-Bn); 6.90 (d, 2H, *J* = 8.5Hz, Ar-*H*); 7.11 (d, 2H, *J* = 8.5Hz, Ar-*H*); 7.49 – 7.32 (m, 5H, C*H*-Bn).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.11 (Ar-*C*H_2); 36.15 (*C*H_2); 66.22 (COC*H*$_2$-Bn); 70.04 (C*H*$_2$-Bn); 114.87 (*C*H-Ar); 127.44 (C*H*-Bn); 127.90 (C*H*-Bn); 128.18 (C*H*-Bn); 128.19 (*C*H-Bn); 128.52 (*C*H-Bn); 128.56 (*C*H-Bn); 129.27 (*C*H-Ar); 132.77 (q, *C*-alkyl); 135.95 (q, *C*-Bn); 137.14 (q, *C*-Bn); 157.33 (q, *C*-OBn); 172.76 (q, *C*O).

anal. C 79.78, H 6.43 %, calcd for $C_{23}H_{22}O_3$, C 79.74, H 6.40 %

Methoxymethyl 3-(4-(methoxymethoxy)phenyl)propanoate (68)



Chemical Formula: $C_{13}H_{18}O_5$
Exact Mass: 254.12 g/mol
Molecular Weight: 254.28 g/mol

Methyl ester **68** was prepared following the general procedure for MOM protection (see 7.3). The product was prepared starting from methyl ester **64** (1equiv., 8.3mmol, 1.5g). It was obtained as a yellow oil.

Time = 20h

Yield = (4.98mmol, 1.27g) 60%

$\mathbf{R}_f$ = 0.3 (EP/EtOAc = 8:2)

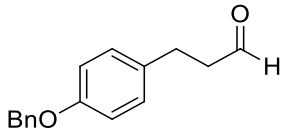
^{1}H NMR (500 MHz, $CDCl_3$) δ 2.67 (t, 2H, J = 7.5Hz, CH_2); 2.94 (t, 2H, J = 7.5Hz, CH_2); 3.43 (s, 3H, OCH_3-MOM); 3.49 (s, 3H, OCH_3-MOM); 5.17 (s, 2H, CH_2-MOM); 5.24 (s, 2H, CH_2-MOM); 6.98 (d, 2H, J = 8.5Hz, Ar-H); 7.14 (d, 2H, J = 8.5Hz, Ar-H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 29.95 (Ar-CH$_2$); 36.07 (CH$_2$); 55.92 (OCH$_3$-MOM); 57.58 (OCH$_3$-MOM); 90.36 (CH$_2$-MOM); 94.49 (CH$_2$-MOM); 116.34 (CH-Ar); 129.26 (CH-Ar); 133.68 (q, C-alkyl); 155.71 (q, C-OMOM); 172.50 (q, CO).

EIMS *m/z* 254 $[M]^+$(30), 222(20), 200(80), 45(100).

anal. C 61.38, H 7.13 %, calcd for $C_{13}H_{18}O_5$, C 61.40, H 7.14 %

3-(4-(benzyloxy)phenyl)propanal (69)



Chemical Formula: $C_{16}H_{16}O_2$
Exact Mass: 240.12 g/mol
Molecular Weight: 240.30 g/mol

Procedure A: To a solution of the previously synthesized ester **65** (1 equiv, 3.70 mmol, 1.0 g,) in DCM (30mL) was added DIBAL-H (2 equiv., 7.4 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 (40mL) 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, the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to get aldehyde **69** in mixture with the corresponding alcohol (50%-50% evaluated by 1H-NMR). The crude product (0.98g) was dissolved in DCM (15mL) and Dess-Martin Periodinane (1 equiv., 3,70mmol, 1.57g) was added at room temperature. The mixture was stirred for 2h, quenched with water and extracted with DCM. The organic layers were dried on Na_2SO_4 filtered and concentrated under reduced pressure to give the aldehyde **69** in a quantitative way (observed on GC-MS).

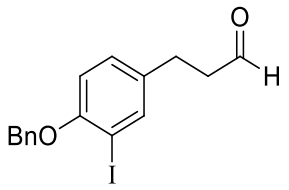
Procedure B: To a solution of the previously synthesized Weinreb amide **62** (1 equiv, 3.33 mmol, 1.0 g,) in DCM (28 mL) was added DIBAL-H (2 equiv., 6.6 mL, 1M in toluene,) dropwise at -78 °C. The mixture was stirred at - 78 °C for 3 h before quenching with a saturated aqueous solution of diethyl tartrate sodium potassium (40mL) 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, the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude aldehyde **69** (91% yield evaluated from ^{1}H-NMR).

The aldehyde was recovered as a dense viscous white liquid easily degradable at room temperature and not purificable by column chromatography. For this reason the crude product was rapidly characterized with only ^{1}H-NMR and immediatedly put in reaction or stock in the freezer at -20°C.

$\mathbf{R}_f$ = 0.4 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74 (t, 2H, *J* = 7.6Hz, CH_2); 2.88 (t, 2H, *J* = 7.6Hz, CH_2); 5.04 (s, 2H, CH_2-Bn); 6.89 (d, 2H, *J* = 8.4Hz, Ar-*H*); 7.09 (d, 2H, *J* = 8.5Hz, Ar-*H*); 7.42 (m, 5H, Bn-*H*); 9.81 (s, 1H, C*H*O).

3-(4-(benzyloxy)-3-iodophenyl)propanal (69a)



Chemical Formula: $C_{16}H_{15}IO_2$
Exact Mass: 366.01 g mol
Molecular Weight: 366.19 g/mol

Procedure A: To a solution of the previously synthesized ester **65a** (1 equiv, 3.96 mmol, 1.0 g,) in DCM (40mL) was added DIBAL-H (2 equiv., 7.92 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 (50mL) 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 **69a** in mixture with the corresponding alcohol (50%-50% evaluated by 1H-NMR). The crude product (0.95g) was dissolved in DCM (15mL) and Dess-Martin Periodinane (1 equiv., 3,96mmol, 1.68g) was added at room temperature. The mixture was stirred for 2h, quenched with water and extracted with DCM. The organic layers were dried on Na_2SO_4 filtered and concentrated under reduced pressure to give the aldehyde **69a** in a quantitative way (observed on GC-MS).

Procedure B: To a solution of the previously synthesized Weinreb amide **62a** (1 equiv, 2.35 mmol, 1.0 g,) in DCM (20 mL) was added DIBAL-H (2 equiv., 4.70 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 (30mL) 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, the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude aldehyde **69a** (86% yield evaluated from ^{1}H-NMR).

The aldehyde was recovered as a dense viscous white liquid easily degradable at room temperature and not purificable by column chromatography. For this reason the crude product was rapidly characterized with ^{1}H-NMR and immediatedly put in reaction or stock in the freezer at -20°C. A not clean ^{13}C-NMR was also obtained, the characteristic peaks of aldehyde were individuated.

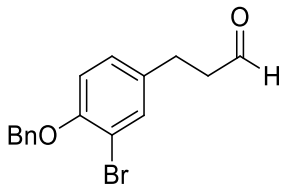
$\mathbf{R}_f$ = 0.35 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 (t, 2H, J = 7.6Hz, CH_2); 2.87 (t, 2H, J = 7.6Hz, CH_2); 5.13 (s, 2H, CH_2-Bn); 6.78 (d, 2H, J = 8.4Hz, Ar-*H*); 7.10 (dd, 2H, J_{ortho} = 8.5Hz, J_{meta} = 2.2Hz, Ar-*H*); 7.39 (m, 3H, Bn-*H*); 7.49 (d, 2H, J = 7.0 Hz, Bn-*H*); 7.65 (d, 1H, J_{meta} = 2.2 Hz, Ar-*H*), 9.81 (s, 1H, C*H*O).

^{13}C NMR (101 MHz, $CDCl_3$) δ 26.67 (*C*H_2); 45.25 (*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), 201.12 (q, *C*HO).

EIMS *m/z* 366 $[M]^+$(10), 276(25), 91 (100).

3-(4-(benzyloxy)-3-bromophenyl)propanal (69b)



Chemical Formula: $C_{16}H_{15}BrO_2$
Exact Mass: 318.03 g mol
Molecular Weight: 319.19 g/mol

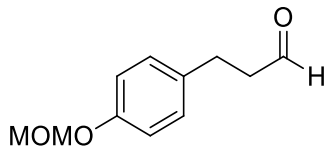
To a solution of the previously synthesized ester **65b** (1 equiv, 2.86 mmol, 1.0 g,) in DCM (35mL) was added DIBAL-H (2 equiv., 5.73 mL, 1M in toluene,) dropwise at -78 °C. The mixture was stirred at -78 °C for 3 h before quenching with a saturated aqueous solution of diethyl tartrate sodium potassium (40mL) 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 **69a** in mixture with the corresponding alcohol (50%-50% evaluated by 1H-NMR). The crude product (0.93g) was dissolved in DCM (15mL) and Dess-Martin Periodinane (1 equiv., 2.86mmol, 1.21g) was added at room temperature. The mixture was stirred for 2h, quenched with water and extracted with DCM. The organic layers were dried on Na_2SO_4 filtered and concentrated under reduced pressure to give the aldehyde **69b** in a quantitative way (observed on GC-MS).

The aldehyde was recovered as a viscous liquid easily degradable at room temperature and not purificable by column chromatography. For this reason the crude product was rapidly characterized with ^{1}H-NMR and immediatedly put in reaction or stock in the freezer at -20°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 (t, 2H, J = 7.6Hz, CH_2); 2.86 (t, 2H, J = 7.6Hz, CH_2); 5.13 (s, 2H, CH_2-Bn); 6.84 (d, 2H, J = 8.4Hz, Ar-*H*); 7.05 (dd, 2H, J_{ortho} = 8.5Hz, J_{meta} = 2.2Hz, Ar-*H*); 7.40 (m, 6H, 5Bn-*H*, 1Ar-*H*); 9.80 (s, 1H, C*H*O).

EIMS *m/z* 318 $[M]^+$(10), 91 (100), 65(25).

3-(4-(methoxymethoxy)phenyl)propanal (70)



Chemical Formula: $C_{11}H_{14}O_3$
Exact Mass: 194.09 g/mol
Molecular Weight: 194.93 g/mol

To a solution of the previously synthesized ester **66** (1 equiv, 4.45mmol, 1.0g,) in DCM (40mL) was added DIBAL-H (2 equiv., 8.9 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 (50mL) 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, the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to get aldehyde **70** in mixture with the corresponding alcohol (50%-50% evaluated by ^{1}H-NMR). The crude product (0.95g) was dissolved in DCM (15mL) and Dess-Martin Periodinane (1 equiv., 4.45mmol, 1.89g) was added at room temperature. The mixture was stirred for 2h, quenched with water and extracted with DCM. The organic layers were dried on Na_2SO_4 filtered and concentrated under reduced pressure to give the aldehyde **70** as a yellow pale oil in **80% yield** (determined by ^{1}H-NMR).

Same procedure was used starting from ester **68** (1 equiv, 3.93mmol, 1.0g,). The product was obtained with **75%yield** (determined by ^{1}H-NMR).

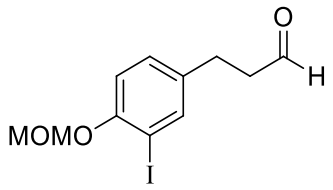
The aldehyde resulted easily degradable at room temperature and not purificable by column chromatography. For this reason the product was rapidly characterized with only ^{1}H-NMR and immediatedly put in reaction or stock in the freezer at -20°C.

$\mathbf{R}_f$ = 0.45 (Cy/EtOAc = 8:2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.75 (t, 2H, J = 7.5Hz, CH_2); 2.89 (t, 2H, J = 7.5Hz, CH_2); 3.46 (s, 3H, CH_3-MOM); 5.15 (s, 2H, CH_2-MOM); 6.96 (d, 2H, J = 8.5Hz, Ar-*H*); 7.11 (d, 2H, J = 8.5Hz, Ar-*H*); 9.80 (s, 1H, C*H*O).

EIMS *m/z* 194 $[M]^+$(50), 149(20), 45 (100).

3-(3-iodo-4-(methoxymethoxy)phenyl)propanal (70a)



Chemical Formula: $C_{11}H_{13}IO_3$
Exact Mass: 319.99 g/mol
Molecular Weight: 320.12 g/mol

To a solution of the previously synthesized ester **66a** (1 equiv, 2.85 mmol, 1.0 g,) in DCM (35mL) was added DIBAL-H (2 equiv., 5.73 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 (40mL) 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 **69a** in mixture with the corresponding alcohol (50%-50% evaluated by 1H-NMR). The crude product (0.97g) was dissolved in DCM (15mL) and Dess-Martin Periodinane (1 equiv., 2.85mmol, 1.21g) was added at room temperature. The mixture was stirred for 2h, quenched with water and extracted with DCM. The organic layers were dried on Na_2SO_4 filtered and concentrated under reduced pressure to give the aldehyde **70a** in a quantitative way (observed on GC-MS).

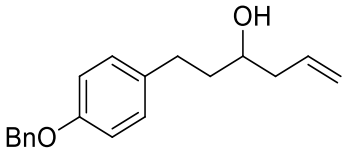
The aldehyde was recovered as a viscous liquid easily degradable at room temperature and not purificable by column chromatography. For this reason the crude product was rapidly characterized with ^{1}H-NMR and immediatedly put in reaction or stock in the freezer at -20°C.

$\mathbf{R}_f$ = 0.5 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76 (t, 2H, J = 7.6Hz, CH_2); 2.86 (t, 2H, J = 7.6Hz, CH_2); 3.50 (s, 3H. OCH_3-MOM); 5.21 (s, 2H, CH_2-MOM); 6.98 (d, 2H, J = 8.4Hz, Ar-*H*); 7.10 (dd, 2H, J_{ortho} = 8.5Hz, J_{meta} = 2.2Hz, Ar-*H*); 7.62 (d, 1H, J_{meta} = 2.2Hz, Ar-*H*); 9.80 (s, 1H, C*H*O).

EIMS *m/z* 320 $[M]^+$(50), 289(20), 247(15), 45 (100).

1-(4-(benzyloxy)phenyl)hex-5-en-3-ol (71)



Chemical Formula: $C_{19}H_{22}O_2$
Exact Mass: 282.16 g mol
Molecular Weight: 282.38 g/mol

Precedure A: Homo allylic alcohol **71** was prepared following the general procedure for the allylation of an aldehyde (Method A: see 7.3.7). The reaction was carried out At -78°C, using the previously prepared crude aldehyde **69** (1 equiv., 4.08mmol, 978.60mg) and allylmagnesium bromide (1 equiv., 4.04mmol, 4.04mL, 1M in diethyl ether). The crude product was purified by silica gel chromatography (cyclohexane/EtOAc, 4/1) to obtain the product as a white solid (3.06mmol, 862.92mg, **75% yield**).

Procedure B: Homoallylic alcohol **71** was prepared following the general procedure for the allylation of an aldehyde (Method B: see 7.3.7). Crude aldehyde **69** (1equiv., 4.08mmol, 978.6mg) and a solution of allyl boronic acid pinacol ester (1 equiv., 4.08mmol, 0.76mL) in THF (4mL, 1M) were used. The crude product was purified by silica gel chromatography (cyclohexane/EtOAc, 4/1) to obtain product **71** as a white solid (3.18mmol, 897.4mg, 78% yield).

M.p.= 62-63°C

R_f = 0.5 (Cy/EtOAc = 6:4)

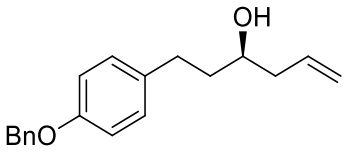
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76 (m, 2H, $ArCH_2CH_2CHOH$); 2.18 (m, 1H, $OHCHCH_2CH{=}CH_2$); 2.34 (m, 1H, $OHCHCH_2CH{=}CH_2$); 2.63 (m, 1H, $ArCH_2$); 2.75 (m, 1H, $ArCH_2$); 3.67 (m, 1H, CHOH); 5.05 (s, 2H, CH_2-Bn); 5.15 (dd, 2H, J = 12Hz, J = 2Hz, $CH{=}CH_2$), 5.82 (m, 1H, $CH{=}CH_2$); 6.91 (d, 2H, J = 8.5Hz, Ar-*H*); 7.12 (d, 2H, J = 8.5Hz, Ar-*H*); 7.37 (m, 5H, Bn-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.12 (Ar-CH_2); 38.60 ($ArCH_2CH_2CHOH$); 42.03 ($OHCHCH_2CH{=}CH_2$); 69.94 (CHOH); 70.12 (CH_2-Bn); 118.21 ($CH{=}CH_2$); 114.84 (CH-Ar); 127.42 (CH-Bn); 127.83 (CH-Bn); 128.52 (CH-Bn); 129.31 (CH-Ar); 134.41 (q, *C*-Ar); 134.63 ($CH{=}CH_2$); 137.25 (q, *C*-Bn); 157.13 (q, *C*-Ar).

EIMS *m/z* 282 $[M]^+$(30), 191(40), 91(100).

anal. C 80.85, H 7.87 %, calcd for $C_{19}H_{22}O_2$, C 80.82, H 7.85 %

(*R*)-1-(4-(benzyloxy)phenyl)hex-5-en-3-ol [(*R*)-71]



Chemical Formula: $C_{19}H_{22}O_2$
Exact Mass: 282.16 g mol
Molecular Weight: 282.38 g/mol

Procedure for enantioselective allylation with sulfoxide as chiral auxiliary:[153]

Distilled diisopropylethylamine (5.0equiv., 5.45mmol, 0.95mL) and allytrichlorosilane (1.9equiv., 2.10mmol, 0.3mL), were successively added to a solution of the (+)-(*R*)-methyl-p-tolyl sulfoxide (2.9equiv., 154.2mmol, 0.482g) in dry DCM (10mL) at -78°C under inert atmosphere. The mixture was stirred for 5min. Aldehyde **69** (1equiv., 1.09mmol, 0.262g) was then added and the reaction mixture was stirred at -78°C for 48h and was allowed to warm to room temperature for 3h. The mixture was then poured into an ice-cooled mixture of DCM (40mL) and saturated aqueous $NaHCO_3$ (40mL). The organic layer was separated and the aqueous phase was extracted with DCM (3x70mL). The combined organic extracts were washed with brine (50mL), dried over Na_2SO_4 and evaporated at reduced pressure. The crude product was purified by silica gel chromatography (preparation: pure cyclohexane, elution: pure cyclohexane and cyclohexane/EtOAc, 4/1, V/V). The product was obtained as a white solid in only **8%yield** (0.09mmol, 0.025g) and **60%ee**. The optical purity was determined by HPLC chiral chromatography using a CHIRACEL OD-H column (250mm, 4.6mm, 3.5µm), eluent: 80:20 hexane/isopropanol, flow: 0.5mL/min, sample concentration: 1mg/mL, injection volume: 20µL, retention time: (*S:*12.3min*, R:*14,5min*).*

Procedure for Brown's enantioselctive allylation:[154]

Allylmagnesium bromide (1.3equiv., 0.55mmol, 0.55mL, 1M in Et_2O) was added dropwise to a solution of (-)-B-chlorodiisopinocampheylborane (1.3equiv., 0.55mmol, 0.173g,) in of dry THF (2.5mL) with mechanical stirring at -78°C. The mixture was stirred at -78°C for 1h and then warmed to r.t (removing of the bath) within 1h20min. The mixture was cooled down to -90°C and a solution of aldehyde **69** (1equiv., 0.42mmol, 0.10g) in THF (0.20mL, 2M) was added dropwise. The temperature was maintained at -90°C during the addition and the mixture was stirred 1h at -90°C and let warmed to r.t (removing of the bath) within 1h. The mixture was quenched with H_2O_2 30% (2mL) and an aqueous solution of NaOH (2M, 2mL) at 0°C. It was stirred 1.5h at r.t. and then extracted with EtOAc (3X10mL), washed with water (20mL) and brine (20mL). Organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to dryness.

Crude product was purified by silica gel chromatography (preparation: cyclohexane, elution: cyclohexane and cyclohexane/EtOAc, 4/1, V/V) to obtain the product as a white solid (0.065g, **74%yield**, **86%ee**).
The optical purity was determined by HPLC chiral chromatography using a CHIRACEL OD-H column (250mm, 4.6mm, 3.5µm), eluent: 80/20 hexane/isopropanol, flow: 0.5mL/min, sample concentration: 1mg/mL, injection volume: 20µL, retention time: (*S:*12.3min*, R:*14,5min*).*

Procedure for Roush's enantioselective allylation:[155]

A solution of triisopropyl borate (1equiv., 4.33mmol, 1mL) in dry Et_2O (1.1mL) and allylmagnesium bromide in Et_2O (1equiv., 4.4mL, 1M) were added dropwise simultaneously, but separately, to 1.1mL of dry Et_2O at -78°C. This mixture was stirred for 0.5 h at -78 °C, allowed to warm to room temperature (bath of dry ice/acetone removed), and stirred for 3h at r.t. The slurry was recooled to 0°C, and then an aqueous solution of HCl (4mL, 1N solution saturated with NaCl) was added dropwise. The mixture was stirred 15min at 0°C and warmed to room temperature, and stirring was continued for 15min. The organic layer was separated and directly treated with (+)-(*R*,*R*)-Diisopropyl L-tartrate (DIPT)(1equiv., 4.74mmol, 1mL). The aqueous phase was extracted with dry DCM/Et_2O solution (1/5, V/V, 3X6mL) and transferred to the schlenck containing first organic layer and (*R*,*R*)-DIPT. The combined organic layers were stirred 1h and anhydrous Na_2SO_4 (4equiv., 2.58g) were added. The mixture was stirred for 1night at r.t. It was then evaporated under reduced pressure to give a clear, slightly yellow, semiviscous liquid (1.23g) of 4,5-bis(propan-2-yl)(4*R*,5*R*)-2-(prop-2-en-1-yl)-1,2,3-dioxaborolane-4,5-dicarboxylate.

A solution of crude just prepared product in dry toluene (0.8mL, 0.22g/mL) was treated with 4Å molecular sieves (powder, 90mg) and was stirred for 15min. Then, it was cooled to -78°C, and a solution of starting aldehyde **69** (1.5equiv., 0.62mmol, 0.150g) in dry toluene (1mL, 0.62M) was added dropwise. The mixture was stirred 5h at the same temperature.The reaction mixture was quenched with NaOH (5mL, 1M) and 5mL of Et_2O. The two phases mixture were stirred for 30min at room temperature to hydrolyze DIPT and then were separated extracting with Et_2O (3X7mL). Organic layer was dried over Na_2SO_4, filtered and evaporated under reduce pressure to dryness to give a crude product. The crude was purified twice by chromatography (preparation: cyclohexane, elution: cyclohexane and cyclohexane/EtOAc, 4/1) affording the desired product in **64%yield**(3.93mmol, 0.11g), **78%ee**. The optical purity was determined by HPLC chiral chromatography using a CHIRACEL OD-H column (250mm, 4.6mm, 3.5µm), eluent: 80/20 hexane/isopropanol, flow: 0.5mL/min, sample concentration: 1mg/mL, injection volume: 20µL, retention time: (*S:*12.3min*, R:*14,5min*).*

Procedure for enantioselective allyltitanation:[158]

Allylmagnesium bromide in Et_2O (1.2equiv., 0.28mmol, 0.28mL, 1M solution), was added dropwise at 0°C under argon to a solution of (*R*,*R*) Duthaler-Hafner reagent (1,4equiv., 0,33mmol, 0.20g), in dry Et_2O (4mL, 0.083M). After stirring for 1.5h at 0°C, the slightly orange suspension was coolded to -78°C and starting aldehyde **69** (1equiv., 0,24mmol, 0.057g) dissolved in dry ether (0,75mL, 0.32M) was added. The mixture was stirred at -78°C for 5.5h after which was treated with 4mL of saturated aqueous solution of NH_4Cl and warmed to room temperature for 15h. It was filtered over Celite and extracted with ether (3x7mL). The combined organic phases were washed with brine (10mL), dried over Na_2SO_4, and evaporated under reduced pressure to give a solid. This crude solid was stirred with pentane (5mL) and filtered. The filtrate was evaporated under reduced pressure to give a white solid which was purified by silica gel column chromatography (preparation: cyclohexane, elution: cyclohexane/EtOAc, 4/1,V/V). Pure desired product was obtained in **70% yield** (0.16mmol, 0.047g). A pure fraction was analyzed by chiral HPLC to determine the ee, using CHIRACEL OD-H (250mm, 4.6mm, 3.5µm), 80/20 hexane/isopropanol, 0.5mL/min, 1mg/mL, 20µL injection in order to determine the enantiomeric excess (**90%ee**). Retention time: (*S:*12.3min, *R:*14,5min).

M.p.= 61-63°C

R_f = 0.5 (Cy/EtOAc = 6:4)

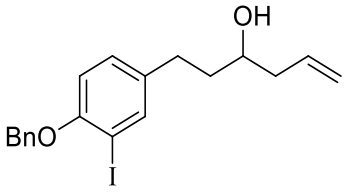
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76 (m, 2H, $ArCH_2CH_2CHOH$); 2.18 (m, 1H, $OHCHCH_2CH=CH_2$); 2.34 (m, 1H, $OHCHCH_2CH=CH_2$); 2.63 (m, 1H, $ArCH_2$); 2.75 (m, 1H, $ArCH_2$); 3.67 (m, 1H, CHOH); 5.05 (s, 2H, CH_2-Bn); 5.15 (dd, 2H, *J* = 12Hz, *J* = 2Hz, $CH=CH_2$), 5.82 (m, 1H, $CH=CH_2$); 6.91 (d, 2H, *J* = 8.5Hz, Ar-*H*); 7.12 (d, 2H, *J* = 8.5Hz, Ar-*H*); 7.37 (m, 5H, Bn-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.12 (Ar-CH_2); 38.60 ($ArCH_2CH_2CHOH$); 42.03 ($OHCHCH_2CH=CH_2$); 69.94 (CHOH); 70.12 (CH_2-Bn); 118.21 ($CH=CH_2$); 114.84 (CH-Ar); 127.42 (CH-Bn); 127.83 (CH-Bn); 128.52 (CH-Bn); 129.31 (CH-Ar); 134.41 (q, *C*-Ar); 134.63 ($CH=CH_2$); 137.25 (q, *C*-Bn); 157.13 (q, *C*-Ar).

EIMS *m/z* 282 $[M]^+$(30), 191(40), 91(100).

anal. C 80.86, H 7.88 %, calcd for $C_{19}H_{22}O_2$, C 80.82, H 7.85 %

1-(4-(benzyloxy)-3-iodophenyl)hex-5-en-3-ol (71a)



Chemical Formula: $C_{19}H_{21}IO_2$
Exact Mass: 408.06 g/mol
Molecular Weight: 408.27 g/mol

Precedure A: Homo allylic alcohol **71a** was prepared following the general procedure for the allylation of an aldehyde (Method A: see 7.3.7). The reaction was carried out At -78°C, using the previously prepared crude aldehyde **69a** (1 equiv., 2.73mmol, 1.0g) and allylmagnesium bromide (1 equiv., 2.73mmol, 2.73mL, 1M in diethyl ether). The crude product was purified by silica gel chromatography (cyclohexane/EtOAc, 4/1) to obtain the product as a white solid (3.06mmol, 1.83mg, **67% yield**).

Procedure B: Homo allylic alcohol **71a** was prepared following the general procedure for the allylation of an aldehyde (Method B: see 7.3.7). Crude aldehyde **69a** (1 equiv., 2.73mmol, 1.0g) and a solution of allyl boronic acid pinacol ester (1 equiv., 2.73mmol, 0.53mL) in THF (2.73mL, 1M) were used. The crude product was purified by silica gel chromatography (cyclohexane/EtOAc, 4/1) to obtain product **71a** as a white solid (1.96mmol, 0.80g, **72% yield**).

M.p.= 66-68°C

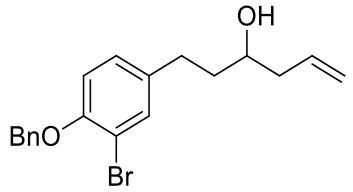
R_f = 0.5 (Cy/EtOAc = 6:4)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74 (m, 2H, $ArCH_2CH_2CHOH$); 2.16 (m, 1H, $OHCHCH_2CH{=}CH_2$); 2.29 (m, 1H, $OHCHCH_2CH{=}CH_2$); 2.61 (m, 1H, $ArCH_2$); 2.70 (m, 1H, $ArCH_2$); 3.65 (m, 1H, CHOH); 5.12 (s, 2H, CH_2-Bn); 5.12 (dd, 2H, J = 12Hz, J = 2Hz, $CH{=}CH_2$), 5.80 (m, 1H, $CH{=}CH_2$); 6.77 (d, 2H, J = 8.5Hz, Ar-*H*); 7.10 (dd, 2H, J_{ortho} = 8.5Hz, J_{meta} = 2.1Hz, Ar-*H*); 7.40 (m, 5H, Bn-*H*); 7.65 (J_{meta} = 2.1Hz, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.95 (Ar-CH_2); 38.45 ($ArCH_2CH_2CHOH$); 42.11 ($OHCHCH_2CH{=}CH_2$); 69.68 (CHOH); 71.01 (CH_2-Bn); 86.85 (q, *C*-I); 112.71 ($CH{=}CH_2$); 118.49 (CH-Ar); 127.01 (CH-Bn); 127.84 (CH-Bn); 128.54 (CH-Bn); 129.33 (CH-Ar); 134.50 (q, *C*-Ar); 136.69 ($CH{=}CH_2$); 136.72 (q, *C*-Bn); 139.31 (CH-Ar); 155.48 (q, *C*-Ar).

anal. C 55.92, H 5.13 %, calcd for $C_{19}H_{22}IO_2$, C 55.89, H 5.18 %

1-(4-(benzyloxy)-3-bromophenyl)hex-5-en-3-ol (71b)



Chemical Formula: $C_{19}H_{21}BrO_2$
Exact Mass: 360.07 g/mol
Molecular Weight: 361.27 g/mol

Homo allylic alcohol **71b** was prepared following the general procedure for the allylation of an aldehyde (Method A: see 7.3.7). The reaction was carried out At -78°C, using the previously prepared crude aldehyde **69b** (1 equiv., 3.14mmol, 1.0g) and allylmagnesium bromide (1 equiv., 3.14mmol, 3.14mL, 1M in diethyl ether). The crude product was purified by silica gel chromatography (cyclohexane/EtOAc, 4/1) to obtain the product as a transparent and flower parfumed oil.

Time = 3h

Yield= (1.98mmol, 0.71mg) 63%

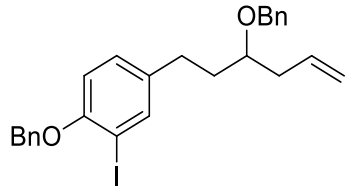
$\mathbf{R}_f$ = 0.4 (Cy/EtOAc = 6:4)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75 (m, 2H, $ArCH_2CH_2CHOH$); 2.15 (m, 1H, $OHCHCH_2CH{=}CH_2$); 2.28 (m, 1H, $OHCHCH_2CH{=}CH_2$); 2.62 (m, 1H, $ArCH_2$); 2.72 (m, 1H, $ArCH_2$); 3.62 (m, 1H, CHOH); 5.13 (s, 2H, CH_2-Bn); 5.14 (d, 2H, J = 12Hz, $CH{=}CH_2$), 5.81 (m, 1H, $CH{=}CH_2$); 6.83 (d, 2H, J = 8.5Hz, Ar-*H*); 7.05 (dd, 2H, J_{ortho} = 8.5Hz, J_{meta} = 2.1Hz, Ar-*H*); 7.37 (m, 6H, 5Bn-*H*,1Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.79 (Ar-CH_2); 38.33 ($ArCH_2CH_2CHOH$); 42.07 ($OHCHCH_2CH{=}CH_2$); 65.25 (CHOH); 70.96 (CH_2-Bn); 112.38 (q, *C*-Br); 114.00 ($CH{=}CH_2$); 118.39 (CH-Ar); 127.02 (C*H*-Bn); 127.86 (CH-Bn); 128.25 (C*H*-Bn); 128.53 (C*H*-Ar); 133.22 ($CH{=}CH_2$); 134.51 (q, *C*-Ar); 136.19 (q, *C*-Bn); 136.71 (CH-Ar); 153.19 (q, *C*-Ar).

anal. C 63.20, H 5.90 %, calcd for $C_{19}H_{21}BrO_2$, C 63.17, H 5.86 %

1-(benzyloxy)-4-(3-(benzyloxy)hex-5-en-1-yl)-2-iodobenzene (71c)



Chemical Formula: $C_{26}H_{27}IO_2$
Exact Mass: 498.11 g/mol
Molecular Weight: 498.40 g/mol

Product **71c** was obtained after the benzylation of alcohol **71a** (1equiv., 2.45mmol, 1.0g) following the general procedure for benzylation, Method B (see7.3.1). The crude product was purified by silica gel chromatography (Cy/EtOAc 8/2) to afford the pure product as a yellow oil.

Time = 5h

Yield= (2.20mmol, 1.1g) 90%

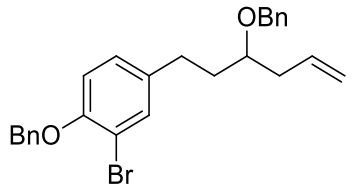
$\mathbf{R}_f$ = 0.5 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75 (m, 2H, $ArCH_2CH_2CH$); 2.38 (m, 2H, $CHCH_2CH{=}CH_2$); 2.54 (m, 1H, $CHCH_2CH{=}CH_2$); 2.68 (m, 1H, $ArCH_2$); 3.46 (m, 1H, CHOBn); 4.46 (AB_{system}, 2H, J=12Hz, $\Delta\nu$=21Hz, CH_2-Bn); 5.07 (m, 2H, $CH_2{=}CH_2$); 5.12 (s, 2H, CH_2-Bn); 5.86 (m, 1H, $CH{=}CH_2$); 6.76 (d, 2H, J = 8.5Hz, Ar-*H*); 7.05 (dd, 2H, J_{ortho} = 8.5Hz, J_{meta} = 2.1Hz, Ar-*H*); 7.39 (m, 5H, Bn-*H*); 7.61 (J_{meta} = 2.1Hz, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.45 (Ar-CH_2); 35.65 ($ArCH_2CH_2CH$); 38.16 ($CHCH_2CH{=}CH_2$); 70.85 (CH_2-Bn); 70.96 (CH_2-Bn); 78.56 (CHOBn); 86.98 (q, *C*-I); 113.24 ($CH{=}CH_2$); 118.45 (CH-Ar); 127.01 (CH-Bn); 127.59 (CH-Bn); 127.16 (CH-Bn); 128.13 (CH-Bn); 128.20 (CH-Bn); 128.46 (CH-Bn); 128.59 (CH-Ar); 133.58 (CH-Ar); 134.52 ($CH{=}CH_2$); 136.50 (q, *C*-Ar); 136.72 (q, *C*-Bn); 138.72 (CH-Ar); 154.48 (q, *C*-Ar).

anal. C 62.68, H 5.50 %, calcd for $C_{26}H_{27}IO_2$, C 62.66, H 5.46 %

1-(benzyloxy)-4-(3-(benzyloxy)hex-5-en-1-yl)-2-bromobenzene (71d)



Chemical Formula: $C_{26}H_{27}BrO_2$
Exact Mass: 450.12 g/mol
Molecular Weight: 451.40 g/mol

Product **71d** was obtained after the benzylation of alcohol **71b** (1equiv., 2.77mmol, 1.0g) following the general procedure for benzylation, Method B (see7.3.1). The crude product was purified by silica gel chromatography (Cy/EtOAc 8/2) to afford the pure product as a yellow oil.

Time = 5h

Yield= (2.58mmol, 1.16g) 93%

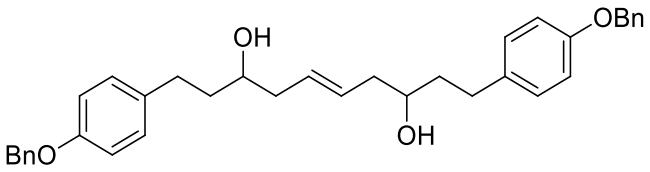
$\mathbf{R}_f$ = 0.45 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82 (m, 2H, $ArCH_2CH_2CH$); 2.37 (m, 2H, $CHCH_2CH{=}CH_2$); 2.57 (m, 1H, $CHCH_2CH{=}CH_2$); 2.70 (m, 1H, $ArCH_2$); 3.46 (m, 1H, CHOBn); 4.46 (AB_{system}, 2H, J=12Hz, $\Delta\nu$=21Hz, CH_2-Bn); 5.09 (m, 2H, $CH_2{=}CH_2$); 5.13 (s, 2H, CH_2-Bn); 5.84 (m, 1H, $CH{=}CH_2$); 6.83 (d, 2H, J = 8.5Hz, Ar-*H*); 7.00 (dd, 2H, J_{ortho} = 8.5Hz, J_{meta} = 2.1Hz, Ar-*H*); 7.40 (m, 6H, 5Bn-*H*, 1Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.44 (Ar-CH_2); 35.61 ($ArCH_2CH_2CH$); 38.12 ($CHCH_2CH{=}CH_2$); 70.91 (CH_2-Bn); 70.96 (CH_2-Bn); 77.49 (CHOBn); 112.32 (q, *C*-Br); 113.95 ($CH{=}CH_2$); 117.22 (CH-Ar); 127.00 (CH-Bn); 127.56 (CH-Bn); 127.79 (CH-Bn); 127.85 (CH-Bn); 128.17 (CH-Bn); 128.36 (CH-Bn); 128.54 (CH-Ar); 133.19 (CH-Ar); 134.55 ($CH{=}CH_2$); 136.43 (q, *C*-Ar); 136.71 (q, *C*-Bn); 138.68 (CH-Ar); 153.11 (q, *C*-Ar).

anal. C 69.21, H 6.04 %, calcd for $C_{26}H_{27}BrO_2$, C 69.18, H 6.03 %

(E)-1,10-bis(4-(benzyloxy)phenyl)dec-5-ene-3,8-diol (71bis)



Chemical Formula: $C_{36}H_{40}O_4$
Exact Mass: 536.29 g mol
Molecular Weight: 536.70 g/mol

The substrate was obtained in 10-15% yield as secondary product from cross-metathesis reaction between phenol **48** and homoallilic alcohol **71** following the general procedure reported in 7.3.8. The product was isolated in mixture with 10% of *Z* isomer as a white solid.

Mp = 102-103°C

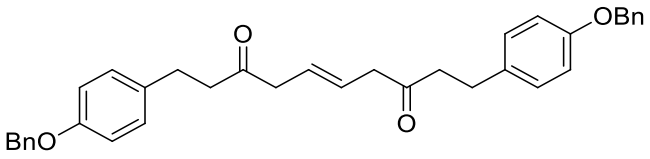
R_f = 0.2 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79 (m, 4H, $ArCH_2CH_2$); 2.17 (m, 4H, $CH_2CH{=}CHCH_2$); 2.70 (m, 4H, $ArCH_2$); 3.65 (bs, 2H, CHOH); 5.06 (s, 4H, CH_2Bn); 5.55 (m, 2H, CH=CH); 6.92 (d, 4H, *J* = 8.6 Hz, Ar-*H*); 7.13 (d, 4H, *J* = 8.6 Hz, Ar-*H*), 7.37 (m, 10H, Bn-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 31.14(Ar-CH_2); 38.72 ($ArCH_2CH_2CHOH$); 40.82, ($OHCHCH_2CH{=}CH_2$); 70.05 (CH_2-Bn); 70.09 (CH-OH); 114.81 (CH-Ar); 127.45(CH-Bn); 127.88 (CH-Bn); 128.54 (CH=CH); 129.31 (CH-Bn); 129.94 (CH-Ar); 134.32 (q, *C*-Ar); 137.19 (q, *C*-Bn); 157.04 (q, *C*-Ar).

anal. C 80.58, H 7.53 %, calcd for $C_{36}H_{40}O_4$, C 80.56, H 7.51 %

(E)-1,10-bis(4-(benzyloxy)phenyl)dec-5-ene-3,8-dione (72bis)



Chemical Formula: $C_{36}H_{36}O_4$
Exact Mass: 532.26 g mol
Molecular Weight: 532.67 g/mol

The product was prepared adding at room temperature Dess-Martin periodinane (2 equiv.; 0.18mmol, 76.3mg) to a solution of substrate **71bis** (1 equiv., 0.09mmol, 48mg) in DCM (2mL). The mixture was stirred for 2h, filtered and concentrated under vacuum pressure to afford the pure product in a quantitative way as a white solid.

Time = 2h

Yield = (0.09mmol, 47.9mg) 99%

Mp = 148-150°C

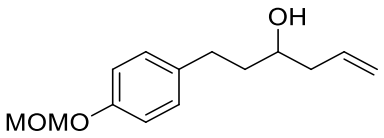
$\mathbf{R}_f$ = 0.4 (Cy/EtOAc = 6:4)

^{1}H NMR (400 MHz, Acetone) δ 2.65 (m, 8H, C*H*$_2$, Ar*C*H$_2$C*H*$_2$); 3.02 (m, 2H, C*H*$_2$CH=CHC*H*$_2$); 5.02 (s, 4H C*H*$_2$Bn); 5.55 (m, 2H, C*H*=C*H*); 6.84 (d, 4H, *J* = 8.5 Hz, Ar-*H*); 7.06 (d, 4H; *J* = 8.0 Hz, Ar-*H*); 7.30 (m, 10H, Bn-H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 29.86(Ar-*C*H$_2$); 44.10 (ArCH$_2$*C*H$_2$CH); 46.64 (CH*C*H$_2$CH=CH$_2$); 70.07 (*C*H$_2$-Bn); 114.84 (*C*H-Ar); 127.46(C*H*-Bn); 127.89 (C*H*-Bn); 128.56 (*C*H=*C*H); 129.30 (C*H*-Bn); 129.96 (C*H*-Ar); 134.39 (q, *C*-Ar); 137.24 (q, *C*-Bn); 157.25(q, *C*-Ar); 207.91 (q, C=O).

anal. C 81.20, H 6.83 %, calcd for $C_{36}H_{40}O_4$, C 81.17, H 6.81 %

1-(4-(methoxymethoxy)phenyl)hex-5-en-3-ol (72)



Chemical Formula: $C_{14}H_{20}O_3$
Exact Mass: 236.14 g/mol
Molecular Weight: 236.31 g/mol

Homo allylic alcohol **72** was prepared following the general procedure for the allylation of an aldehyde (Method A: see 7.3.7). The reaction was carried out at -78°C, using the previously prepared crude aldehyde **70** (1 equiv., 2.00mmol, 0.39g) and allylmagnesium bromide (1 equiv., 2.00mmol, 2.00mL, 1M in diethyl ether). The crude product was purified by silica gel chromatography (cyclohexane/EtOAc, 6/4) to obtain the product as a transparent oil.

Time = 2h

Yield = (1.36mmol, 0.32g) **68%**

$\mathbf{R}_f$ = 0.5 (Cy/EtOAc = 5:5)

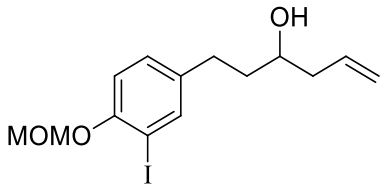
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.76 (m, 2H, $ArCH_2CH_2CHOH$); 2.18 (m, 1H, $OHCHCH_2CH{=}CH_2$); 2.33 (m, 1H, $OHCHCH_2CH{=}CH_2$); 2.64 (m, 1H, $ArCH_2$); 2.76 (m, 1H, $ArCH_2$); 3.48 (s, 3H, OCH_3-MOM); 3.67 (m, 1H, CHOH); 5.15 (dd, 2H, J = 12Hz, J = 2Hz, $CH{=}CH_2$); 5.16 (s, 2H, OCH_2-MOM); 5.82 (m, 1H, $CH{=}CH_2$); 6.97 (d, 2H, J = 8.5Hz, Ar-H); 7.13 (d, 2H, J = 8.5Hz, Ar-H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 31.18 (Ar-CH_2); 38.59 ($ArCH_2CH_2CHOH$); 42.06 ($OHCHCH_2CH{=}CH_2$); 55.93 (CH_3-MOM); 69.93 (CHOH); 94.63 (CH_2-MOM); 116.32 (CH-Ar); 118.32 ($CH{=}CH_2$); 129.36 (CH-Ar); 134.63 (q, C-Ar); 135.47 ($CH{=}CH_2$); 155.42 (q, C-ArOMOM).

EIMS *m/z* 236 $[M]^+$(20), 163(25), 151(30), 121(128), 45(100).

anal. C 71.20, H 8.55 %, calcd for $C_{14}H_{20}O_3$, C 71.16, H 8.53 %

1-(3-iodo-4-(methoxymethoxy)phenyl)hex-5-en-3-ol (72a)



Chemical Formula: $C_{14}H_{19}IO_3$
Exact Mass: 362.04 g/mol
Molecular Weight: 362.20 g/mol

Homo allylic alcohol **72a** was prepared following the general procedure for the allylation of an aldehyde (Method A: see 7.3.7). The reaction was carried out At -78°C, using the previously prepared crude aldehyde **70a** (1 equiv., 3.12mmol, 1.0g) and allylmagnesium bromide (1 equiv., 3.12mmol, 3.12mL, 1M in diethyl ether). The crude product was purified by silica gel chromatography (cyclohexane/EtOAc, 4/1) to obtain the product as a brown oil.

Time = 3h

Yield= (2.03mmol, 0.73g) 65%

$\mathbf{R}_f$ = 0.4 (Cy/EtOAc = 7:3)

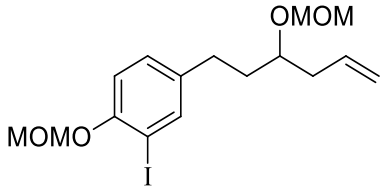
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74 (m, 2H, $ArCH_2CH_2CHOH$); 2.15 (m, 1H, $OHCHCH_2CH{=}CH_2$); 2.28 (m, 1H, $OHCHCH_2CH{=}CH_2$); 2.60 (m, 1H, $ArCH_2$); 2.68 (m, 1H, $ArCH_2$); 3.52 (s, 3H, OCH_3-MOM); 3.61 (m, 1H, CHOH); 5.15 (dd, 2H, J = 12Hz, J = 2Hz, $CH{=}CH_2$); 5.21 (s, 2H, CH_2-MOM); 5.81 (m, 1H, $CH{=}CH_2$); 6.98 (d, 2H, J = 8.5Hz, Ar-*H*); 7.12 (dd, 2H, J_{ortho} = 8.4Hz, J_{ortho} = 2.0Hz, Ar-*H*); 7.64 (J_{meta} = 2.1Hz, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.57 (Ar-CH_2); 38.31 ($ArCH_2CH_2CHOH$); 42.01 ($OHCHCH_2CH{=}CH_2$); 56.31(CH_3-MOM); 69.61 (CHOH); 87.21 (q, *C*-I); 95.04 (OCH_2-MOM); 114.89 ($CH{=}CH_2$); 118.31 (CH-Ar); 129.35 (C*H*-Ar); 134.44 (CH-Ar); 137.63 (q, *C*-Ar); 139.10 ($CH{=}CH_2$); 154.14 (q, *C*-Ar).

EIMS *m/z* 362 $[M]^+$(20), 288(15), 247(15), 207(10), 45(100).

anal. C 46.46, H 5.33 %, calcd for $C_{14}H_{19}IO_3$, C 46.42, H 5.29 %

2-iodo-1-(methoxymethoxy)-4-(3-(methoxymethoxy)hex-5-en-1-yl)benzene (72b)



Chemical Formula: $C_{16}H_{23}IO_4$
Exact Mass: 406.06 g/mol
Molecular Weight: 406.26 g/mol

Substarte **72b** was obtained from protection of alcohol **72a** (1 equiv., 4.14mmol, 1.5g) following the general procedure for MOM protection using NaH as base (see 7.3.6). The crude product was purified by column chromatography and pure procuvt was obtained as a transparent oil.

Time = 8h

Yield= (3.51mmol, 1.43g) 85%

$\mathbf{R}_f$ = 0.5 (Cy/EtOAc = 7:3)

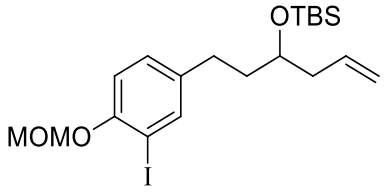
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76 (m, 2H, $ArCH_2CH_2CH$); 2.34 (m, 2H, $CHCH_2CH{=}CH_2$); 2.55 (m, 1H, $ArCH_2$); 2.65 (m, 1H, $ArCH_2$); 3.38 (s, 3H, OCH_3-MOM); 3.50 (s, 3H, OCH_3-MOM); 3.63 (m, 1H, CHOMOM); 4.74 (AB_{system}, 2H, J=12Hz, $\Delta\nu$=21Hz, CH_2-MOM); 5.08 (dd, 2H, J = 12Hz, J = 2Hz, $CH{=}CH_2$); 5.20 (s, 2H, CH_2-MOM); 5.80 (m, 1H, $CH{=}CH_2$); 6.96 (d, 2H, J = 8.5Hz, Ar-*H*); 7.09 (dd, 2H, J_{ortho} = 8.4Hz, J_{ortho} = 2.0Hz, Ar-*H*); 7.60 (J_{meta} = 2.1Hz, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.17 (Ar-CH_2); 35.88 ($ArCH_2CH_2CH$); 38.76 ($CHCH_2CH{=}CH_2$); 55.70 (CH_3-MOM); 56.31 (CH_3-MOM); 87.16 (q, *C*-I); 90.49 (CHOMOM); 93.08 (OCH_2-MOM); 95.05 (OCH_2-MOM); 114.88 ($CH{=}CH_2$); 117.39 (CH-Ar); 129.24 (CH-Ar); 134.21 (CH-Ar); 137.68 (q, *C*-Ar); 139.06 ($CH{=}CH_2$); 154.16 (q, *C*-Ar).

EIMS *m/z* 406 $[M]^+$(5), 333(30), 238(15), 45(100).

anal. C 47.31, H 5.73 %, calcd for $C_{16}H_{23}IO_4$, C 47.30, H 5.71 %

tert-butyl((1-(3-iodo-4-(methoxymethoxy)phenyl)hex-5-en-3-yl)oxy)dimethylsilane (72c)



Chemical Formula: $C_{20}H_{33}IO_3Si$
Exact Mass: 476.12 g/mol
Molecular Weight: 476.46 g/mol

In a 2 necks flask under argon atmosphere alcohol **72a** (1 equiv., 0.28mmol, 0.100g) was dissolved in DCM (2mL). To this solution at 0°C were added imidazole (2.5 equiv., 0.70mmol, 0.048g), DMAP (0.2equiv., 0.056mmol, 0.007g) and a solution of *tert*-butyl(chloro) dimethylsilane (TBSCl) (1.5 equiv., 0.41mmol, 0.062g) in DCM (1.5mL) at room temperature. The solution was stirred for 18h. The mixture was quenched with water (5mL) and extracted with DCM (3x15mL). The organic layers were washed with BRINE (2x15mL), dried on Na_2SO_4 and concentered under reduced pressure. The crude of reaction purified by column chromatography afford the desire product as a transparent oil.

Time = 18h

Yield= (0.28mmol, 0.133g) 99%

R_f = 0.7 (Cy/EtOAc = 9:1)

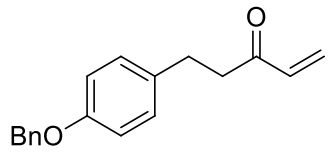
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 3H, Si-CH_3); 0.09 (s, 3H, Si-CH_3); 0.85 (s, 3H, Si-C(CH_3)$_3$); 0.90 (s, 6H, Si-C(CH_3)$_3$); 1.76 (m, 2H, ArCH$_2$CH_2CH); 2.24 (m, 2H, CHCH_2CH=CH$_2$); 2.53 (m, 1H, ArCH_2); 2.62 (m, 1H, ArCH_2); 3.40 (m, 1H, C*H*OTBS); 3.49 (s, 3H, OCH_3-MOM); 5.04 (dd, 2H, *J* = 12Hz, *J* = 2Hz, CH=CH_2); 5.19 (s, 2H, CH_2-MOM); 5.80 (m, 1H, C*H*=CH$_2$); 6.95 (d, 2H, *J* = 8.5Hz, Ar-*H*); 7.05 (dd, 2H, J_{ortho} = 8.4Hz, J_{ortho} = 2.0Hz, Ar-*H*); 7.57 (J_{meta} = 2.1Hz, Ar-*H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ: -4.07 (Si-*C*H$_3$); -3.05 (Si-*C*H$_3$); 18.15 (Si-C(*C*H$_3$)$_3$); 25.71 (Si-C(*C*H$_3$)$_3$); 25.92 (Si-C(*C*H$_3$)$_3$); 30.45 (Ar-*C*H$_2$); 38.58 (ArCH$_2$*C*H$_2$CH); 41.90 (CH*C*H$_2$CH=CH$_2$); 56.36 (*C*H$_3$-MOM); 71.41 (*C*HOTBS); 87.23 (q, *C*-I); 95.15 (O*C*H$_2$-MOM); 114.97 (CH=*C*H$_2$); 117.00 (*C*H-Ar); 129.29 (C*H*-Ar); 134.93 (*C*H-Ar); 138.29 (q, *C*-Ar); 139.10 (*C*H=CH$_2$); 154.14 (q, *C*-Ar).

EIMS *m/z* 476 $[M]^+$(2), 419 (30), 277(100), 247 (80), 187(25), 45(80)

anal. C 50.45, H 7.00 %, calcd for $C_{20}H_{33}IO_3Si$, C 50.42, H 6.98 %

5-(4-(benzyloxy)phenyl)pent-1-en-3-one (73)



Chemical Formula: $C_{18}H_{18}O_2$
Exact Mass: 266.13 g mol
Molecular Weight: 266.33 g/mol

To an ice-cold solution of Weinreb amide **62** (1.0 equiv.; 1.53mmol, 0.46g) in dry THF (4.7mL) was added dropwise a solution of vinylmagnesium bromide (2.75equiv., 4.20mmol, 6mL, solution 0.7M in THF) and stirred at the same temperature for 2h. The reaction was quenched by careful addition of an aqueous 10% HCl solution (16 mL) and stirred for 5 min. The resulting solution was extracted with EtOAc (3x10mL), the combined extract washed sequentially with water (30mL) and brine (30mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (preparation: cyclohexane, elution: pure cyclohexane and cyclohexane/EtOAc, 4/1) to obtain the product as a yellow oil.

Time = 2h

Yield = (1.10mmol, 0.29g) 72%

R_f = 0.55 (Cy/EtOAc = 8:2)

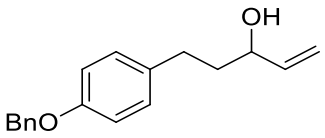
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.81 (m, 4H, ArCH_2CH_2); 5.05 (s, 2H, OCH_2-Bn); 5.83 (d, 1H, J_{cis}= 10.8Hz, CH=CH_2); 6.21 (d, 1H, J_{trans}= 17.6Hz, CH=CH_2), 6.36 (dd, 1H, *J* = 10.8Hz, *J* =17.6Hz, C*H*=CH_2), 6.91 (d, 2H, *J* = 8.4Hz, Ar-*H*); 7.12 (d, 2H, *J* = 8.4Hz, Ar-*H*), 7.37 (m, 5H, Bn-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.99 (ArCH$_2$*C*H$_2$); 41.47 (Ar*C*H$_2$*C*H$_2$); 70.07 (O*C*H$_2$-Bn); 114.90 (*C*H-Ar); 127.12 (*C*H-Bn); 127.45 (CH-Bn); 128.18 (CH=*C*H$_2$); 128.56 (*C*H-Bn); 129.31 (C*H*-Ar); 136.54 (*C*H=CH$_2$ + q, C-Bn); 137.12 (q, *C*-Ar); 157.23 (q, *C*-ArOBn); 199.92 (q, *C*O).

IR ν_{max} 3031, 2921,1678 (C=O), 1509 (C=C), 1236, 735, 695 cm^{-1}

anal. C 81.15, H 6.79 %, calcd for $C_{18}H_{18}O_2$, C 81.17, H 6.81 %

5-(4-(benzyloxy)phenyl)pent-1-en-3-ol[243] (74)



Chemical Formula: $C_{18}H_{20}O_2$
Exact Mass: 268.15 g/mol
Molecular Weight: 268.35 g/mol

A solution of vinylmagnesium bromide 0.7M in THF (1.5equiv., 3.15mmol, 4.5mL) was added dropwise to a solution of the aldehyde **69** (1.0equiv., 2.10mmol, 0.505g) in dry THF (4.3mL) at -78 ºC. The reaction was stirred for 30 minutes, warmed to 0 ºC and stirred for an additional 1.5hours. Reaction was then quench with 15mL of saturated aqueous NH_4Cl (15 mL), and extracted withAcOEt (3x10mL). The combined organic layers were combined, washed with sat aq solution of NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (silica gel: pure cyclohexane, elution: 4/1, V/V, cyclohexane/ AcOEt). The pure product was a beige butter.

Time = 2h

Yield = (1.38mmol, 0.37g) 44%

R_f = 0.35 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83 (m, 2H, $ArCH_2CH_2$); 2.69 (m, 2H, $ArCH_2CH_2$); 4.13 (m, 1H, CHOH); 5.05 (s, 2H, OCH_2-Bn); 5.14 (d, 1H, J_{trans}= 17.3Hz, $CH=CH_2$); 5.25 (d, 1H, J_{cis}= 10.4Hz, $CH=CH_2$), 5.91 (m, 1H, $CH=CH_2$), 6.91 (d, 2H, J = 8.4Hz, Ar-H); 7.13 (d, 2H, J = 8.4Hz, Ar-H), 7.38 (m, 5H, Bn-H).

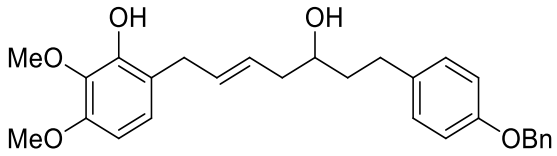
^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.23 ($ArCH_2CH_2$); 39.94 ($ArCH_2CH_2$); 70.07 (OCH_2-Bn); 73.12 (CHOH); 114.96 (CH-Ar); 119.18 ($CH=CH_2$); 127.18 (CH-Bn); 127.54 (CH-Bn); 128.64 (CH-Bn); 129.35 (CH-Ar); 135.23 (q, C-Ar); 136.12 (q, C-Bn); 137.54 ($CH=CH_2$); 156.23 (q, C-ArOBn).

anal. C 80.58, H 7.53 %, calcd for $C_{18}H_{20}O_2$, C 80.56, H 7.51 %

[243] Molander, G. A.; Jean-Gérard, L. *J. Org. Chem.* **2009**, *74* (3), 1297–1303.

7.3.13 Experimental part linear fragments

6-(7-(4-(benzyloxy)phenyl)-5-hydroxyhept-2-en-1-yl)-2,3-dimethoxyphenol (75)



Chemical Formula: $C_{28}H_{32}O_5$
Exact Mass: 448.22 g mol
Molecular Weight: 448.55 g/mol

The product was obtained following the general procedure of cross metathesis reaction (see 7.3.8). The better result was obtained when 4equiv. of allylphenol **48** (13.0mmol, 2.5g)**,** 1 equiv. of homoallylic alcohol **71** (3.22mmol, 0.90g) and 3mol% of Grubbs catalyst (0.097mmol, 0.082g) were used. The addition of catalyst was done rigorously at -78°C.

Time = 24h

Yield = (2.60mmol, 1.12g) 81%

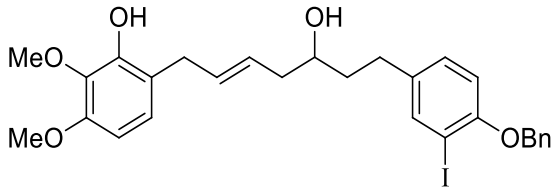
$\mathbf{R}_f$ = 0.35 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73 (m, 2H, ArCH$_2$C*H$_2$*); 2.21 (m, 1H, OHCHC*H$_2$*CH=CH); 2.27 (m, 1H, OHCHC*H$_2$*CH=CH); 2.63 (m, 1H, ArC*H$_2$*CH$_2$); 2.75 (m, 1H, ArC*H$_2$*CH$_2$); 3.32 (d, 2H, *J*=6.4Hz, ArC*H$_2$*CH=CH); 3.62 (m, 1H, OHC*H*); 3.84 (s, 3H, OC*H$_3$*); 3.89 (s, 3H, OC*H$_3$*); 5.05 (s, 2H, OC*H$_2$*Bn); 5.46 (m,1H, C*H*=CH); 5.72 (m,1H, CH=C*H*); 5.88 (s, 1H, OH); 6.42 (d, 1H, *J*=8.4Hz, Ar-*H*); 6.77 (d, 1H, *J*=8.4Hz, Ar-*H*); 6.90 (d, 2H, *J*=8.4Hz, Ar-*H*); 7.11 (d, 2H, *J*=8.4Hz, Ar-*H*); 7.38 (m,5H, Bn-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.12 (Ar*C*H$_2$); 32.9 (Ar*C*H$_2$); 38.6 (OHCH*C*H$_2$CH$_2$Ar); 40.71 (OHCH*C*H$_2$CH=CH); 55.84 (O*C*H$_3$); 60.92 (O*C*H$_3$); 70.07 (O*C*H$_2$-Bn); 73.12 (*C*HOH); 103.64 (*C*H-Ar); 114.82 (Ar-H); 119.52(q, C-Ar); 124.12 (*C*H-Ar); 126.74 (*C*H=CH); 127.55 (*C*H-Bn); 127.96 (CH-Bn); 128.56 (*C*H-Bn); 129.31 (C*H*-Ar); 132.84 (CH=*C*H); 134.62 (q, *C*-Ar); 137.35 (q, *C*-Bn); 137.39 (q, *C*-OCH$_3$); 147.23 (q, C-OH); 150.82 (q, *C*-OCH3); 157.15 (q, *C*-ArOBn).

anal. C 80.00, H 7.21 %, calcd for $C_{28}H_{32}O_5$, C 74.97, H 7.19 %

(*E*)-6-(7-(4-(benzyloxy)-3-iodophenyl)-5-hydroxyhept-2-en-1-yl)-2,3-dimethoxyphenol (75a)



Chemical Formula: $C_{28}H_{31}IO_5$
Exact Mass: 574.12 g mol
Molecular Weight: 574.45 g/mol

The product was obtained following the general procedure of cross metathesis reaction (see 7.3.8). The better result was obtained when 5equiv. of allylphenol **48** (5.15mmol, 1.0g)**,** 1 equiv. of homoallylic alcohol **71a** (1.28mmol, 0.52g) and 15mol% of Grubbs catalyst (0.19mmol, 0.163g) were used. The addition of catalyst was done rigorously at -78°C.

Time = 24h

Yield = (1.04mmol, 0.60g) 82%

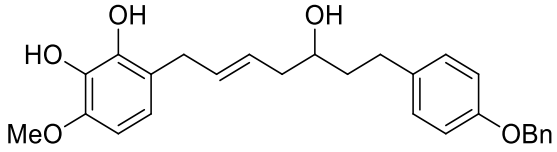
R_f = 0.3 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82 – 1.65 (m, 2H, $ArCH_2CH_2$); 2.09 (m, 1H, $OHCHCH_2CH{=}CH$); 2.37 – 2.20 (m, 1H, $OHCHCH_2CH{=}CH$); 2.81 – 2.53 (m, 2H, $ArCH_2CH_2$); 3.34 (d, 2H, *J*=6.4Hz, $ArCH_2CH{=}CH$); 3.61 (m, 1H, OHCH); 3.85 (s, 3H, OCH_3); 3.90 (s, 3H, OCH_3); 5.13 (s, 2H, OCH_2Bn); 5.57 – 5.40 (m,1H, CH=CH); 5.83 – 5.66 (m,1H, CH=CH); 5.97 (s, 1H, OH); 6.43 (d, 1H, *J*=8.4Hz, Ar-*H*); 6.78 (d, 2H, *J*=8.4Hz, Ar-*H*); 7.09 (dd, 1H, J_{otho}=8.4Hz, J_{meta}=2.1Hz, Ar-*H*); 7.45 – 7.29 (m,3H, Bn-*H*); 7.51 (d, 2H, *J* = 7.4 Hz, Bn-*H*); 7.66 (d, 1H, J_{meta}=2.1Hz, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.60 ($ArCH_2$); 32.87 ($ArCH_2$); 38.31 ($OHCHCH_2CH_2Ar$); 40.70 ($OHCHCH_2CH{=}CH$); 55.80 (OCH_3); 60.87 (OCH_3); 69.78(CHOH); 70.96 (OCH_2-Bn); 86.77 (q, *C*-I); 103.51 (CH-Ar); 112.66 (Ar-H); 119.47 (q, C-Bn); 124.04 (q, C-alkyl); 126.51 (CH=CH); 126.96 (CH-Bn); 127.77 (CH-Bn); 128.47 (CH-Bn); 129.28 (CH-Ar); 132.86 (CH=CH); 135.46 (q, *C*-Ar); 136.67 (q, *C*-Bn); 136.85 (q, *C*-OCH_3); 139.24 (CH-Ar); 147.21 (q, C-OH); 150.76 (q, *C*-OCH3); 155.39 (q, *C*-ArOBn).

anal. C 58.55, H 5.45 %, calcd for $C_{28}H_{31}IO_5$, C 58.54, H 5.44 %

(*E*)-3-(7-(4-(benzyloxy)phenyl)-5-hydroxyhept-2-en-1-yl)-6-methoxybenzene-1,2-diol (75b)



Chemical Formula: $C_{27}H_{30}O_5$
Exact Mass: 434.21 g mol
Molecular Weight: 434.52 g/mol

The product was obtained as a viscous oil using the general procedure of cross metathesis (see 7.3.8). 1 equiv. of homoallylic alcohol **71** (0.35mmol, 0.10g), 4 equiv. of allylphenol **48b** (1.43mmol, 0.256g) and 5mol% (0.017mmol, 0.015g) of Grubbs catalyst were employed.

Time = 24h

Yield = (0.12mmol, 0.05g) 35%

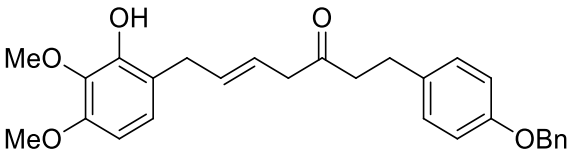
$\mathbf{R}_f$ = 0.3 (Cy/EtOAc = 6:4)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77 – 1.72 (m, 2H, ArCH$_2$C*H*$_2$); 2.31-2.11 (m, 2H, OHCHC*H*$_2$CH=CH); 2.78 – 2.59 (m, 2H, ArC*H*$_2$CH$_2$); 3.35 (d, 2H, *J*=6.2Hz, ArC*H*$_2$CH=CH); 3.69 – 3.31 (m, 1H, OHC*H*); 3.85 (s, 3H, OC*H*$_3$); 5.05 (s, 2H, OC*H*$_2$Bn); 5.57 – 5.45 (m,1H, C*H*=CH); 5.61 (bs, 1H, OH); 5.75-5.70 (m,1H, CH=C*H*); 6.42 (d, 1H, *J*=8.4Hz, Ar-*H*); 6.61 (d, 1H, *J*=8.4Hz, Ar-*H*); 6.91 (d, 2H, *J*=8.4Hz, Ar-*H*); 7.11 (d, 2H, *J*=8.4Hz, Ar-*H*); 7.50 – 7.24 (m,5H, Bn-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.89 (Ar*C*H$_2$); 33.04 (Ar*C*H$_2$); 38.50 (OHCH*C*H$_2$CH$_2$Ar); 40.61 (OHCH*C*H$_2$CH=CH); 56.10 (O*C*H$_3$); 70.02 (O*C*H$_2$-Bn); 70.82 (*C*HOH); 102.87 (*C*H-Ar); 114.73 (*C*H-Ar); 114.78 (q, C-Bn); 119.65 (*C*H-Ar); 120.14(q, C-Bn); 126.67 (*C*H=CH); 127.43 (*C*H-Bn); 127.84 (*C*H-Bn); 128.51 (*C*H-Bn); 129.30 (C*H*-Ar); 132.84 (CH=*C*H); 134.50 (q, *C*-Ar); 137.20 (q, *C*-OH); 142.08 (q, *C*-OCH$_3$); 145.52 (q, C-OH); 156.99 (q, *C*-ArOBn).

anal. C 74.62, H 6.63 %, calcd for $C_{27}H_{30}O_5$, C 74.63, H 6.96 %

(*E*)-1-(4-(benzyloxy)phenyl)-7-(2-hydroxy-3,4-dimethoxyphenyl)hept-5-en-3-one (76)



Chemical Formula: $C_{28}H_{30}O_5$
Exact Mass: 446.21 g mol
Molecular Weight: 446.53 g/mol

The product was obtained as a viscous oil using the general procedure of cross metathesis (see 7.3.8). 1 equiv. of γ,β-unsaturated ketone **63** (0.54mmol, 0.150g), 4 equiv. of allylphenol **48** (2.14mmol, 0.416g) and 5mol% (0.027mmol, 0.023g) of Grubbs catalyst were employed.

Time = 24h

Yield = (0.17mmol, 0.077g) 32%

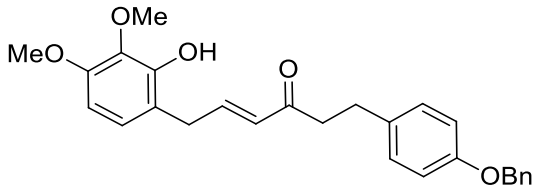
R_f = 0.4 (Cy/EtOAc = 6:4)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (t, 2H, *J*=8.2Hz, C*H*$_2$CH$_2$Ar); 2.82 (t, 2H, *J*=8.24Hz, CH$_2$C*H*$_2$Ar); 3.10 (d, 2H, *J*=6.8Hz, ArC*H*$_2$CH=CH); 3.31 (d, 2H, *J*=6.8Hz, ArCH$_2$CH=CHC*H*$_2$); 3.84 (s, 3H, OC*H*$_3$); 3.89 (s, 3H, OC*H*$_3$); 5.04 (s, 2H, OC*H*$_2$Bn); 5.53 – 5.60 (m,1H, C*H*=CH); 5.66-5.76 (m,1H, CH=C*H*); 5.84 (s, 1H, OH); 6.41 (d, 1H, *J*=8.4Hz, Ar-*H*); 6.77 (d, 1H, *J*=8.4Hz, Ar-*H*); 6.89 (d, 2H, *J*=8.4Hz, Ar-*H*); 7.08 (d, 2H, *J*=8.4Hz, Ar-*H*); 7.46 – 7.30 (m,5H, Bn-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.01 (Ar*C*H$_2$); 32.50 (Ar*C*H$_2$); 43.24 (O=CCH*C*H$_2$CH$_2$Ar); 47.22 (O=CCH*C*H$_2$CH=CH); 55.75 (O*C*H$_3$); 60.92 (O*C*H$_3$); 70.05 (O*C*H$_2$-Bn); 103.51 (*C*H-Ar); 114.49 (*C*H-Ar); 123.94 (q, C-Bn); 124.15 (*C*H-Ar); 126.38 (*C*H=CH); 127.44 (*C*H-Bn); 127.89 (*C*H-Bn); 128.55 (*C*H-Bn); 128.90 (CH=*C*H); 129.26 (C*H*-Ar); 133.18 (q, *C*-Ar); 137.16 (q, *C*-Bn); 137.85 (q, *C*-OCH$_3$); 150.77 (q, C-OH); 152.87 (q, *C*-OCH$_3$); 157.20 (q, *C*-ArOBn); 203.71 (q, C=O).

anal. C 74.30, H 6.75 %, calcd for $C_{28}H_{30}O_5$, C 75.31, H 6.77 %

(*E*)-1-(4-(benzyloxy)phenyl)-6-(2-hydroxy-3,4-dimethoxyphenyl)hex-4-en-3-one (77)



Chemical Formula: $C_{27}H_{28}O_5$
Exact Mass: 432.19 g mol
Molecular Weight: 432.51 g/mol

The product was obtained as a viscous oil using the general procedure of cross metathesis (see 7.3.8). 1 equiv. of α,β-unsaturated ketone **73** (0.37mmol, 0.100g), 4 equiv. of allylphenol **48** (1.50mmol, 0.291g) and 5mol% (0.018mmol, 0.016g) of Grubbs catalyst were employed. The product wasn't isolated perfectely pure, but with traces of 78, the Oxo-Michael cyclized product which was formed during column chromatography.

Time = 24h

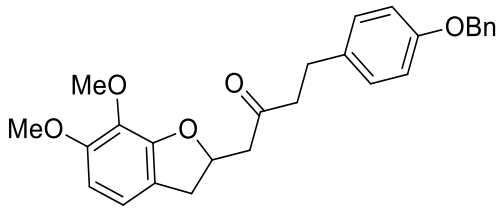
Yield = (0.10mmol, 0.042g) 26%

R_f = 0.45 (Cy/EtOAc = 6:4)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76 (m, 4H, CH_2CH_2Ar); 3.47 (d, 2H, *J*=8Hz, ArCH_2CH=CH); 3.84 (s, 3H, OCH_3); 3.91 (s, 3H, OCH_3); 5.04 (s, 2H, OCH_2Bn); 5.88 (s, 1H, OH); 6.06 (d, 1H, *J*=14.4Hz, O=CC*H*=CH); 6.42 (d, 1H, *J*=8.4Hz, Ar-*H*); 6.72 (d, 1H, *J*=8.4Hz, Ar-*H*); 6.90 (d, 2H, *J*=8.4Hz, Ar-*H*); 7.11 (d, 2H, *J*=8.4Hz, Ar-*H*); 7.46 – 7.30 (m,6H, 5Bn-*H,* 1CH_2C*H*=CHC=O).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.19 (Ar*C*H_2); 32.55 (Ar*C*H_2); 41.72 (O=C*C*H_2CH_2Ar); 55.85 (O*C*H_3); 60.97 (O*C*H_3); 70.06 (O*C*H_2-Bn); 103.75 (*C*H-Ar); 114.84 (*C*H-Ar); 120.78 (q, C-Bn); 124.46 (*C*H-Ar); 127.59 (*C*H-Bn); 127.89 (*C*H-Bn); 128.56 (*C*H-Bn); 129.26 (*C*H-Ar); 130.76 (*C*H=CH); 133.67 (q, *C*-Ar); 137.16 (q, *C*-OCH_3); 137.92 (q, *C*-Ar); 145.49 (CH=*C*H); 147.16 (q, C-OH); 151.33 (q, *C*-OCH_3); 157.15 (q, *C*-ArOBn); 199.86 (q, C=O).

1-(4-(benzyloxy)phenyl)-5-(6,7-dimethoxy-2,3-dihydrobenzofuran-2-yl)pentan-3-one (78)



Chemical Formula: $C_{27}H_{28}O_5$
Exact Mass: 432.19 g mol
Molecular Weight: 432.51 g/mol

The product was obtained as a viscous oil using the general procedure of cross metathesis (see 7.3.8). 1 equiv. of α,β-unsaturated ketone **73** (0.37mmol, 0.100g), 4 equiv. of allylphenol **48** (1.50mmol, 0.291g) and 5mol% (0.018mmol, 0.016g) of Grubbs catalyst were employed. The product was formed during the column chromatography purification from an Oxo-Michael cyclization of cross-metathesis product **77.**

Time = 24h

Yield = (0.17mmol, 0.077g) 33%

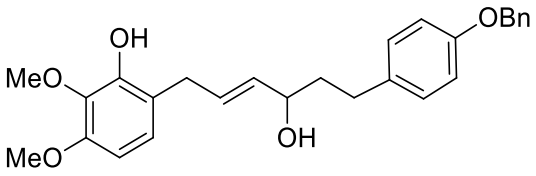
$\mathbf{R}_f$ = 0.43 (Cy/EtOAc = 6:4)

^{1}H NMR (400 MHz, $CDCl_3$) δ2.82 – 2.67 (m, 4H, CH_2CH_2Ar); 2.94 – 2.82 (m, 2H, ArCH_2); 3.06 (dd, 1H, *J*=16.6Hz, *J*=6.2Hz, ArCH_2-cycle); 3.36 (ddd, 1H, *J* = 15.2, 8.8, 0.8 Hz, ArCH_2-cycle), 3.83 (s, 3H, OCH_3); 3.91 (s, 3H, OCH_3); 5.04 (s, 2H, OCH_2Bn); 5.26 – 5.11 (m, 1H, C*H*-cycle), 6.41 (d, 1H, *J*=8.1Hz, Ar-*H*); 6.77 (d, 1H, *J*=8.4Hz, Ar-*H*); 6.90 (d, 2H, *J*=8.1Hz, Ar-*H*); 7.10 (d, 2H, *J*=8.1Hz, Ar-*H*); 7.46 – 7.29 (m,5H, Bn-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.71 (Ar*C*H_2); 35.38 (Ar*C*H_2); 45.35 (O=C*C*H_2CH_2Ar); 48.85 (O=C*C*H_2CH-cycle); 56.43 (O*C*H_3); 60.54 (O*C*H_3); 70.06 (O*C*H_2-Bn); 80.27 (*C*H-cycle); 104.61 (*C*H-Ar); 114.93 (*C*H-Ar); 118.35 (q, C-cycle); 120.78 (*C*H-Ar); 127.45 (*C*H-Bn); 127.92 (*C*H-Bn); 128.56 (*C*H-Bn); 129.27 (*C*H-Ar); 133.07 (q, *C*-Ar); 137.12 (q, *C*-Bn); 151.01 (q, C-Ocycle); 152.28 (q, *C*-OCH_3); 152.26 (q, *C*-OCH_3); 157.26 (q, *C*-ArOBn); 207.49 (q, C=O).

anal. C 74.96, H 6.50 %, calcd for $C_{27}H_{28}O_5$, C 74.98, H 6.53 %

(*E*)-6-(6-(4-(benzyloxy)phenyl)-4-hydroxyhex-2-en-1-yl)-2,3-dimethoxyphenol (79)



Chemical Formula: $C_{27}H_{30}O_5$
Exact Mass: 434.21 g mol
Molecular Weight: 434.52 g/mol

The product was obtained as a viscous oil using the general procedure of cross metathesis (see 7.3.8). 1 equiv. of α,β-unsaturated alchol **74** (0.37mmol, 0.100g), 4 equiv. of allylphenol **48** (1.50mmol, 0.291g) and 5mol% (0.018mmol, 0.016g) of Grubbs catalyst were employed.

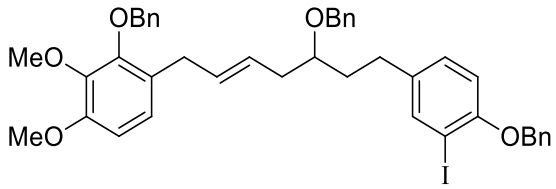
Time = 24h

Yield = (0.30mmol, 0.130g) 81%

$\mathbf{R}_f$ = 0.4 (Cy/EtOAc = 6:4)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87-1.75 (m, 2H, C*H*$_2$Ar); 2.68-2.57 (m, 2H, C*H*$_2$CH$_2$Ar); 3.43 (d, 2H, *J*=8Hz, ArC*H*$_2$CH=CH); 3.85 (s, 3H, OC*H*$_3$); 3.90 (s, 3H, OC*H*$_3$); 4.12 (m. 1H, C*H*OH); 5.04 (s, 2H, OC*H*$_2$Bn); 5.58-5.53 (m, 1H, C*H*=CH); 5.85-5.79 (m, 1H, CH=C*H*); 5.86 (s, 1H, OH); 6.42 (d, 1H, *J*=8.4Hz, Ar-*H*); 6.77 (d, 1H, *J*=8.4Hz, Ar-*H*); 6.89 (d, 2H, *J*=8.4Hz, Ar-*H*); 7.10 (d, 2H, *J*=8.4Hz, Ar-*H*); 7.46 – 7.30 (m, 5H, Bn-*H*).

(*E*)-2-(benzyloxy)-1-(5-(benzyloxy)-7-(4-(benzyloxy)-3-iodophenyl)hept-2-en-1-yl)-3,4-dimethoxybenzene (80)



Chemical Formula: $C_{42}H_{43}IO_5$
Exact Mass: 754.22 g mol
Molecular Weight: 754.69 g/mol

The desired product was prepared starting from the precursor **75a** (1 equiv., 0.348mmol, 0.20g). Benzylation was performed using the general procedure for phenol benzylation (Method B) using NaH as base (see 7.3.1). After column chromatography purification (Cy/EtOAc 8/2) pure product was obtained as a yellow brown oil.

Time = 18h

Yield = (0.174mmol, 0.131g) 50%

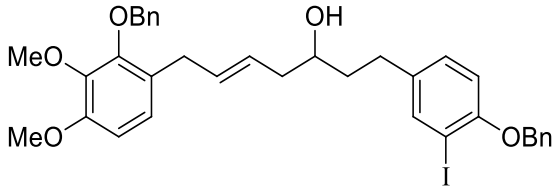
R_f = 0.5 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82 –1.72 (m, 2H, $ArCH_2CH_2$); 2.10 – 2.31 (m, 2H, $CHCH_2CH$=CH); 2.57-2.44 (m, 1H, $ArCH_2CH_2$); 2.73 – 2.59 (m, 1H, $ArCH_2CH_2$); 3.29 (d, 1H, *J*=7.7Hz, $ArCH_2CH$=CH); 3.44-3.37 (m, 1H, CHOBn); 3.86 (s, 3H, OCH_3); 3.88 (s, 3H, OCH_3); 4.88 (AB_{system}, 2H, *J*=12Hz, Δν=21Hz, CH_2-Bn, aliphatic chain); 5.04 (s, 2H, OCH_2Bn); 5.12 (s, 2H, OCH_2Bn); 5.50 – 5.40 (m,1H, CH=CH); 5.60 – 5.51 (m,1H, CH=CH); 6.62 (d, 1H, *J*=8.4Hz, Ar-*H*); 6.74 (d, 1H, *J*=8.4Hz, Ar-*H*); 6.82 (d, 1H, *J*=8.4Hz, Ar-*H*); 7.00 (dd, 1H, J_{ortho}=8.4Hz, J_{meta}=2.1Hz, Ar-*H*); 7.53 – 7.29 (m, 15H, Bn-*H*); 7.59 (d, 1H, J_{meta}=2.1Hz, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.56 ($ArCH_2$); 31.23 ($ArCH_2$); 36.05 ($CHCH_2CH_2Ar$); 37.32 ($OHCHCH_2CH$=CH); 56.80 (OCH_3); 60.90 (OCH_3); 69.96(OCH_2-Bn);71.23 (OCH_2-Bn); 74.32 (OCH_2-Bn); 79.03 (CHOBn); 85.77 (q, *C*-I); 105.51 (*C*H-Ar); 112.23 (*C*H-Ar); 120.47 (q, C-Ar); 123.75 (*C*H-Ar); 126.57 (*C*H=CH); 127.15 (*C*H-Bn); 127.43 (CH-Bn); 127.63 (CH-Bn); 127.67 (CH-Bn); 127.85 (CH-Bn); 128.95 (*C*H-Bn); 129.28 (C*H*-Ar); 132.91 (CH=*C*H); 136.66 (q, *C*-Ar); 136.76 (q, *C*-Bn); 141.24 (*C*H-Ar); 142.85 (q, C-OH); 150.81 (q, *C*-OCH_3); 151.06 (q, *C*-OCH3); 156.91 (q, *C*-ArOBn).

anal. C 66.85, H 5.76 %, calcd for $C_{42}H_{43}IO_5$, C 66.84, H 5.74 %

(*E*)-7-(2-(benzyloxy)-3,4-dimethoxyphenyl)-1-(4-(benzyloxy)-3-iodophenyl)hept-5-en-3-ol (81)



Chemical Formula: $C_{35}H_{37}IO_5$
Exact Mass: 664.17 g mol
Molecular Weight: 664.57 g/mol

The desired product was prepared starting from the precursor **75a** (1 equiv., 0.70mmol, 0.40g). Benzylation was performed using the general procedure for phenol benzylation (Method A) using K_2CO_3 as base (see 7.3.1). After column chromatography purification (Cy/EtOAc 8/2) pure product was obtained as a yellow brown oil.

Time = 18h

Yield = (0.626mmol, 0.416g) 90%

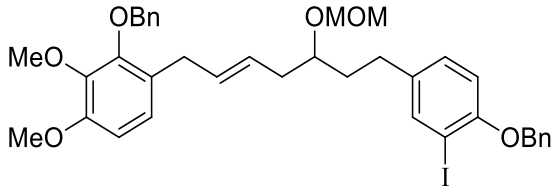
R_f = 0.4 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77 – 1.66 (m, 2H, $ArCH_2CH_2$); 2.11-2.01 (m, 1H, $CHCH_2CH=CH$); 2.28 – 2.18 (m, 1H, $OHCHCH_2CH=CH$); 2.60-2.52 (m, 1H, $ArCH_2CH_2$), 2.73 – 2.63 (m, 1H, $ArCH_2CH_2$); 3.27 (d, 2H, *J*=6.4Hz, $ArCH_2CH=CH$); 3.53 (m, 1H, OHCH); 3.87 (s, 3H, OCH_3); 3.89 (s, 3H, OCH_3); 5.05 (q, 2H, OCH_2Bn); 5.13 (s, 2H, OCH_2Bn); 5.57 – 5.40 (m,1H, CH=CH); 5.77 – 5.64 (m,1H, CH=CH); 6.65 (d, 1H, *J*=8.4Hz, Ar-*H*); 6.76 (d, 1H, *J*=8.4Hz, Ar-*H*); 6.81 (d, 1H, *J*=8.4Hz, Ar-*H*); 7.08 (dd, 1H, J_{ortho}=8.4Hz, J_{meta}=2.1Hz, Ar-*H*); 7.53 – 7.29 (m, 10H, Bn-*H*); 7.63 (d, 1H, J_{meta}=2.1Hz, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.62 ($ArCH_2$); 33.01 ($ArCH_2$); 38.32 ($CHCH_2CH_2Ar$); 40.72 ($OHCHCH_2CH=CH$); 56.07 (OCH_3); 60.90 (OCH_3); 69.85 (OCH_2-Bn); 71.01 (OCH_2-Bn); 75.14 (CHOBn); 86.81 (q, *C*-I); 107.56 (CH-Ar); 112.69 (CH-Ar); 123.84 (q, *C*-Ar); 126.66 (CH-Ar); 126.99 (CH=CH); 127.81 (CH-Bn); 127.97 (CH-Bn); 128.22 (CH-Bn); 128.36 (CH-Bn); 128.42 (CH-Bn); 128.51 (CH-Bn); 129.29 (CH-Ar); 133.26 (CH=CH); 136.69 (q, *C*-Bn); 136.83 (q, *C*-Bn); 137.78 (q, C-Ar); 139.27 (CH-Ar); 142.52 (q, C-OH); 150.57 (q, C-OCH_3); 152.26 (q, *C*-OCH3); 155.44 (q, *C*-ArOBn).

anal. C 66.27, H 5.60 %, calcd for $C_{35}H_{37}IO_5$, C 63.26, H 5.61 %

(*E*)-2-(benzyloxy)-1-(7-(4-(benzyloxy)-3-iodophenyl)-5-(methoxymethoxy)hept-2-en-1-yl)-3,4-dimethoxybenzene (82)



Chemical Formula: $C_{37}H_{41}IO_6$
Exact Mass: 708.19 g mol
Molecular Weight: 708.62 g/mol

The desired product was prepared starting from the precursor **81**(1 equiv., 0.15mmol, 0.10g). Protection with MOM was performed using the general procedure (see 7.3.6). The desired product **82** was obtained as a yellow oil, after column chromatography purification (Cy/EtOAc 8/2).

Time = 18h

Yield = (0.148mmol, 0.105g) 99%

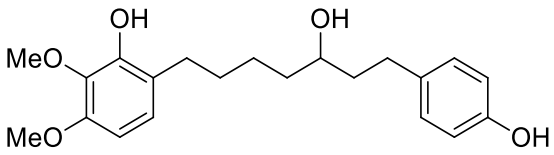
R_f = 0.55 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78 – 1.72 (m, 2H, ArCH$_2$C*H*$_2$); 2.28-2.25 (m, 2H, CHC*H*$_2$CH=CH); 2.55 – 2.45 (m, 1H, ArC*H*$_2$CH$_2$), 2.69 – 2.58 (m, 1H, ArC*H*$_2$CH$_2$); 3.27 (d, 2H, *J*=6.4Hz, ArC*H*$_2$CH=CH); 3.38 (s, 3H, OC*H*$_3$-MOM); 3.58 (m, 1H, MOMOC*H*); 3.86 (s, 3H, OC*H*$_3$); 3.88 (s, 3H, OC*H*$_3$); 4.66 (AB$_{system}$, 2H, *J*=20Hz, Δν=19.59Hz, C*H*$_2$MOM); 5.05 (s, 2H, OC*H*$_2$Bn); 5.13 (s, 2H, OC*H*$_2$Bn); 5.57 – 5.40 (m,1H, C*H*=CH); 5.77 – 5.64 (m,1H, CH=C*H*); 6.65 (d, 1H, *J*=8.4Hz, Ar-*H*); 6.75 (d, 1H, *J*=8.4Hz, Ar-*H*); 6.82 (d, 1H, *J*=8.4Hz, Ar-*H*); 7.04 (dd, 1H, J_{ortho}=8.4Hz, J_{meta}=2.1Hz, Ar-*H*); 7.53 – 7.29 (m, 10H, Bn-*H*); 7.63 (d, 1H, J_{meta}=2.1Hz, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.23 (Ar*C*H$_2$); 32.61 (Ar*C*H$_2$); 35.98 (CH*C*H$_2$CH$_2$Ar); 37.51 (CH*C*H$_2$CH=CH); 55.56 (O*C*H$_3$-MOM); 56.07 (O*C*H$_3$); 60.87 (O*C*H$_3$); 70.99 (O*C*H$_2$-Bn); 75.08 (O*C*H$_2$-Bn); 76.62 (*C*HOMOM); 86.78 (q, *C*-I); 95.52 (O*C*H$_2$OMOM); 107.56 (*C*H-Ar); 112.69 (*C*H-Ar); 123.82 (q, *C*-Ar); 126.72 (*C*H-Ar); 126.98 (*C*H=CH); 127.05 (*C*H-Bn); 127.80 (*C*H-Bn); 127.89 (*C*H-Bn); 128.14 (*C*H-Bn); 128.39 (*C*H-Bn); 128.50 (*C*H-Bn); 129.18 (*C*H-Ar); 131.91 (CH=*C*H); 136.68 (q, *C*-Bn); 136.96 (q, *C*-Bn); 137.86 (q, C-Ar); 139.20 (*C*H-Ar); 142.45 (q, C-OH); 150.47 (q, *C*-OCH$_3$); 152.11 (q, *C*-OCH3); 155.41 (q, *C*-ArOBn).

anal. C 66.69, H 5.81 %, calcd for $C_{37}H_{41}IO_6$, C 62.71, H 5.83 %

6-(5-hydroxy-7-(4-hydroxyphenyl)heptyl)-2,3-dimethoxyphenol (83)



Chemical Formula: $C_{21}H_{28}O_5$
Exact Mass: 360.19 g mol
Molecular Weight: 360.44 g/mol

Diarylheptanoid **83** was obtained treating substarte **75** (1equiv., 0.37mmol, 0.2g) with H_2 and Pd/C 10% following the general procedure of hydrogenolysis reported in 7.3.9.

Time = 18h

Yield = (0.37mmol, 0.134g) 99%

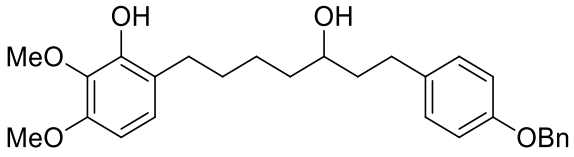
R_f = 0.35 (Cy/EtOAc = 6:4)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67-1.35 (m, 8H, CH_2); 2.66-2.52 (m, 3H, ArCH_2CH$_2$); 2.78-2.64 (m, 1H, ArCH_2CH$_2$); 3.67-3.57 (m, 1H, OHCH); 3.83 (s, 3H, OCH_3); 3.89 (s, 3H, OCH_3); 6.39 (d, 1H, *J*=8.4Hz, Ar-*H*); 6.75 (2d, 3H, *J*=8.4Hz, *J*=8.5Hz, Ar-*H*); 7.05 (d, 2H, *J*=8.4Hz, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.31 ($CH_2CH_2CH_2CHOH$); 29.38 (ArCH_2); 29.89 ($ArCH_2CH_2$); 31.11 (CH_2Ar); 37.34 ($CH_2CH_2CH_2CHOH$); 39.23(CH_2CH_2Ar); 55.81 (OCH_3); 60.91 (OCH_3); 71.37 (*C*HOH); 103.32 (*C*H-Ar); 115.23 (*C*H-Ar); 121.66 (q, C-Ar); 124.07 (*C*H-Ar); 129.47 (C*H*-Ar); 134.24 (q, *C*-Ar); 135.35 (q, *C*-OCH_3); 147.26 (q, C-OH); 150.41 (q, *C*-OCH3); 153.71 (q, *C*-OH).

anal. C 70.01, H 7.85 %, calcd for $C_{21}H_{28}O_5$, C 69.98, H 7.83 %

6-(7-(4-(benzyloxy)phenyl)-5-hydroxyheptyl)-2,3-dimethoxyphenol (84)



Chemical Formula: $C_{28}H_{34}O_5$
Exact Mass: 450.24 g mol
Molecular Weight: 450.57 g/mol

The product was prepared following the general procedure for diimide hydrogenation (see 7.3.10). For the reaction were employed 2-nitrobenzenesulfonylchloride (2 equiv., 0.76mmol, 0.170g), alkene **75** (1 equiv., 0.38mmol, 0.172g), hydrazine hydrate (4 equiv., 1.53mmol, 0.05mL). The crude of reaction was purified by a shorth silica gel pad. The pure product was obtained as a viscous oil.

Time = 18h

Yield = (0.36mmol, 0.162g) 95%

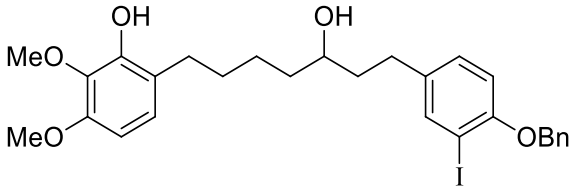
$\mathbf{R}_f$ = 0.4 (Cy/EtOAc = 6:4)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65-1.33 (m, 8H, CH_2); 2.60-2.44 (m, 3H, ArCH_2CH$_2$); 2.80-2.62 (m, 1H, ArCH_2CH$_2$); 3.67-3.57 (m, 1H, OHCH); 3.84 (s, 3H, OCH_3); 3.89 (s, 3H, OCH_3); 5.05 (s, 2H, CH_2-Bn); 6.41 (d, 1H, *J*=8.4Hz, Ar-*H*); 6.78 (d, 2H, *J*=8.4Hz, Ar-*H*); 6.91 (d, 2H, *J*=8.4Hz, Ar-*H*); 7.12 (d, 2H, *J*=8.4Hz, Ar-*H*); 7.45-7.33 (m, 5H, Bn-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.31 (CH$_2$*C*H$_2$CH$_2$CHOH); 29.32 (Ar*C*H$_2$); 29.87 (ArCH$_2$*C*H$_2$); 31.10 (*C*H$_2$Ar); 37.35 (CH$_2$CH$_2$*C*H$_2$CHOH); 39.21 (*C*H$_2$CH$_2$Ar); 54.76 (O*C*H$_3$); 60.84 (O*C*H$_3$); 70.04 (*C*H$_2$-Bn); 71.27 (*C*HOH); 103.34 (*C*H-Ar); 114.77 (*C*H-Ar); 121.64 (q, C-Ar); 124.02 (*C*H-Ar); 127.49 (C*H*-Bn); 127.90 (C*H*-Bn); 128.57 (C*H*-Bn); 129.34 (C*H*-Ar); 134.55 (q, *C*-Ar); 135.35 (q, *C*-Bn); 137.21 (q, *C*-OCH$_3$); 147.25 (q, *C*-OH); 150.39 (q, *C*-OCH3); 155.97 (q, *C*-ArOBn).

anal. C 74.66, H 7.64 %, calcd for $C_{28}H_{34}O_5$, C 74.64, H 7.61 %

6-(7-(4-(benzyloxy)-3-iodophenyl)-5-hydroxyheptyl)-2,3-dimethoxyphenol (84a)



Chemical Formula: $C_{28}H_{33}IO_5$
Exact Mass: 576.14 g mol
Molecular Weight: 576.46 g/mol

The product was prepared following the general procedure for diimide hydrogenation (see 7.3.10). For the reaction were employed 2-nitrobenzenesulfonylchloride (2 equiv., 1.04mmol, 0.231g), alkene **75** a (1 equiv., 0.52mmol, 0.30g), hydrazine hydrate (4 equiv., 2.08mmol, 0.07mL). The crude of reaction was purified by a shorth silica gel pad. The pure product was obtained as a viscous oil.

Time = 18h

Yield = (0.47mmol, 0.272g) 91%

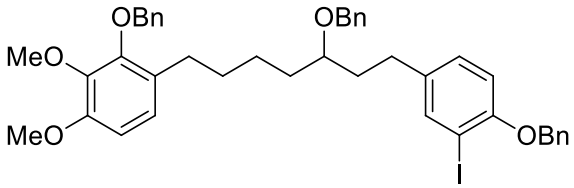
$\mathbf{R}_f$ = 0.45 (Cy/EtOAc = 6:4)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82-1.30 (m, 8H, CH_2); 2.65-2.51 (m, 3H, ArCH_2CH$_2$); 2.78-2.65 (m, 1H, ArCH_2CH$_2$); 3.68-3.54 (m, 1H, OHCH); 3.84 (s, 3H, OCH_3); 3.90 (s, 3H, OCH_3); 5.13 (s, 2H, CH_2-Bn); 5.87 (bs, 1H, OH phenolic); 6.41 (d, 1H, J=8.5Hz, Ar-H); 6.77 (d, 2H, J_{ortho}=8.5Hz, Ar-H); 7.10 (dd, 1H, J_{ortho}=8.3Hz, J_{meta}=2.0Hz, Ar-H); 7.32 (t, 1H, J=7.3Hz, Bn-H); 7.40 (t, 2H, J=7.4Hz, Bn-H); 7.50 (d, 2H, J=7.4Hz, Bn-H); 7.65 (d, 1H, J=2.0Hz, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.28 (CH$_2$$CH_2CH_2$CHOH); 29.36 (Ar$CH_2$); 29.85 (ArCH$_2$$CH_2$); 30.61 ($CH_2$Ar); 37.40 (CH$_2CH_2$$CH_2$CHOH); 39.03 ($CH_2CH_2$Ar); 55.79 (O$CH_3$); 60.87 (O$CH_3$); 71.00 ($CH_2$-Bn); 71.10 ($C$HOH); 86.82 (q, C-I); 103.32 (CH-Ar); 112.71 (CH-Ar); 121.58 (q, C-Ar); 124.03 (CH-Ar); 126.99 (CH-Bn); 127.80 (CH-Bn); 128.50 (CH-Bn); 129.27 (CH-Ar); 135.35 (q, C-Ar); 136.69 (q, C-Bn); 136.90 (q, C-OCH$_3$); 139.25 (CH-Ar); 147.25 (q, C-OH); 150.40 (q, C-OCH3); 155.43 (q, C-ArOBn).

anal. C 58.36, H 5.78 %, calcd for $C_{28}H_{33}IO_5$, C 58.34, H 5.77 %

2-(benzyloxy)-1-(5-(benzyloxy)-7-(4-(benzyloxy)phenyl)heptyl)-3,4-dimethoxybenzene (85)



Chemical Formula: $C_{42}H_{46}O_5$
Exact Mass: 630.33 g mol
Molecular Weight: 630.81 g/mol

The desired product was obtained after benzylation of **84** (1 equiv., 2.22mmol, 1.0g) following the general procedure Method B (see 7.3.1). After column chromatography purification, the pure substrate was obtained as a transparent oil.

Time = 15h

Yield = (1.66mmol, 1.05g) 75%

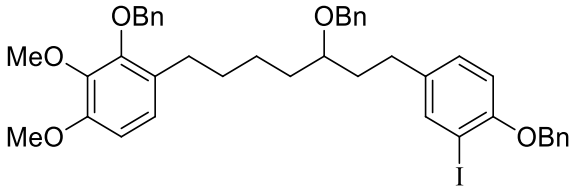
$\mathbf{R}_f$ = 0.5 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68-1.35 (m, 8H, CH_2); 2.55-2.49 (m, 3H, ArCH_2CH$_2$); 2.70-2.62 (m, 1H, ArCH_2CH$_2$); 3.50-3.30 (m, 1H, OHCH); 3.86 (s, 3H, OCH_3); 3.88 (s, 3H, OCH_3); 4.47 (AB_{system}, 2H, J=5.96Hz, $\Delta\nu$=12Hz, CH_2-Bn, aliphatic chain); 5.05 (s, 4H, CH_2-Bn); 6.63 (d, 1H, J=8.4Hz, Ar-H); 6.82 (d, 1H, J=8.4Hz, Ar-H); 6.89 (d, 2H, J=8.4Hz, Ar-H); 7.07 (d, 2H, J=8.4Hz, Ar-H); 7.45-7.33 (m, 15H, Bn-H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.17 (CH$_2$$CH_2CH_2$CHOH); 29.69 (Ar$CH_2$); 30.74 (ArCH$_2$$CH_2$); 30.99 ($CH_2$Ar); 33.54 (CH$_2CH_2$$CH_2$CHOH); 35.90 ($CH_2CH_2$Ar); 56.03 (O$CH_3$); 60.85 (O$CH_3$); 70.06 ($CH_2$-Bn); 70.74 ($CH_2$-Bn); 75.11 ($CH_2$-Bn); 78.25 ($C$HOH); 107.37 ($C$H-Ar); 114.74 ($C$H-Ar); 123.77 ($C$H-Ar); 127.43 (C$H$-Bn); 127.45 (C$H$-Bn); 127.78 (C$H$-Bn); 127.85 (C$H$-Bn); 127.87 (C$H$-Bn); 128.05 (C$H$-Bn); 128.31 (C$H$-Bn); 128.40 (C$H$-Bn); 128.54 (C$H$-Bn); 129.02 (q, C-Ar); 129.26 (CH-Ar); 134.87 (q, C-Ar); 137.24 (q, C-Bn); 138.02 (q, C-Bn); 139.02(q, C-Bn); 142.43 (q, C-OCH$_3$); 150.74 (q, C-ArOBn); 151.85(q, C-OCH$_3$); 156.94 (q, C-ArOBn).

anal. C 79.99, H 7.36 %, calcd for $C_{42}H_{46}O_5$, C 79.97, H 7.35 %

2-(benzyloxy)-1-(5-(benzyloxy)-7-(4-(benzyloxy)-3-iodophenyl)heptyl)-3,4-dimethoxybenzene (85a)



Chemical Formula: $C_{42}H_{45}IO_5$
Exact Mass: 756.23 g mol
Molecular Weight: 756.71 g/mol

The desired product was obtained after benzylation of **84a** (1 equiv., 1.21mmol, 0.70g) following the general procedure Method B (see 7.3.1). After column chromatography purification, the pure substrate was obtained as a transparent oil.

Time = 15h

Yield = (0.86mmol, 0.65g) 71%

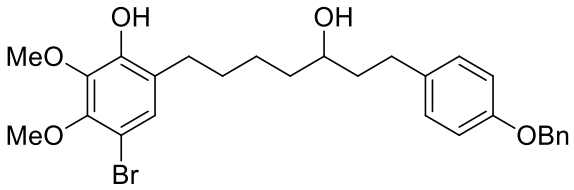
R_f = 0.55 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55-1.39 (m, 6H, CH_2); 1.81-1.74 (m, 2H, CH_2); 2.55-2.48 (m, 3H, ArCH_2CH$_2$); 2.65-2.60 (m, 1H, ArCH_2CH$_2$); 3.40-3.34 (m, 1H, OHCH); 3.86 (s, 3H, OCH_3); 3.89 (s, 3H, OCH_3); 4.46 (AB_{system}, 2H, J=12Hz, $\Delta\nu$=21Hz, CH_2-Bn, aliphatic chain); 5.05 (s, 2H, CH_2-Bn); 5.13 (s, 2H, CH_2-Bn); 6.64 (d, 1H, J=8.4Hz, Ar-H); 6.76 (d, 1H, J=8.4Hz, Ar-H); 6.83 (d, 2H, J=8.4Hz, Ar-H); 7.02 (dd, 1H, J_{ortho}=8.4Hz, J_{meta}=2.0Hz, Ar-H); 7.53-7.33 (m, 15H, Bn-H); 7.60 (d, 1H, J_{meta}=2.0Hz, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.13 (CH$_2$CH$_2$CH$_2$CHOH); 29.70 (ArCH$_2$); 30.28 (ArCH$_2$CH$_2$); 30.99 (CH$_2$Ar); 33.49 (CH$_2$CH$_2$CH$_2$CHOH); 35.73 (CH$_2$CH$_2$Ar); 56.06 (OCH$_3$); 60.87 (OCH$_3$); 70.78 (CH$_2$-Bn); 71.04 (CH$_2$-Bn); 75.13 (CH$_2$-Bn); 78.11 (CHOH); 86.81 (q, C-I); 107.42 (CH-Ar); 112.72 (CH-Ar); 123.79 (CH-Ar); 127.02 (CH-Bn); 127.50 (CH-Bn); 127.80 (CH-Bn); 127.83 (CH-Bn); 127.88 (CH-Bn); 128.06 (CH-Bn); 128.36 (CH-Bn); 128.41 (CH-Bn); 128.53 (CH-Bn); 129.00 (q, C-Ar); 129.24 (CH-Ar); 136.73 (q, C-Ar); 137.20 (q, C-Bn); 138.05 (q, C-Bn); 138.94 (q, C-Bn); 139.25 (CH-Ar); 142.46 (q, C-OCH$_3$); 150.76 (q, C-ArOBn); 151.89(q, C-OCH$_3$); 155.41 (q, C-ArOBn).

anal. C 66.65, H 5.99 %, calcd for $C_{42}H_{45}IO_5$, C 66.66, H 5.99 %

7-(2-(benzyloxy)-5-bromo-3,4-dimethoxyphenyl)-1-(4-(benzyloxy)phenyl)heptan-3-ol (86)



Chemical Formula: $C_{28}H_{33}BrO_5$
Exact Mass: 528.15 g mol
Molecular Weight: 529.46 g/mol

The product was obtained from the bromination of **84** (1equiv., 0.44mmol, 0.20g) following the general procedure with NBS, Method B (**90% yield** after 18h of reaction) or the general procedure reported in the Method A with Br_2.(40% yield after 18h of reaction) (see 7.3.3) Pure product was recollected after column chromatography as a yellow oil.

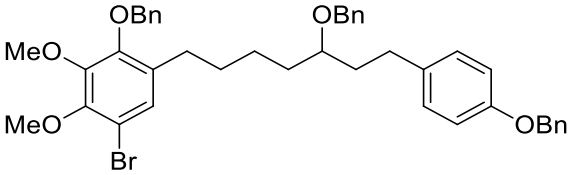
$\mathbf{R}_f$ = 0.45 (Cy/EtOAc = 6:4)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89-1.32 (m, 8H, CH_2); 2.57 (t, 2H, J=7.04Hz, ArCH_2); 2.66-2.58 (m, 1H, ArCH_2CH$_2$); 2.77-2.68 (m, 1H, ArCH_2CH$_2$); 3.70-3.59 (m, 1H, OHC*H*); 3.86 (s, 3H, OCH_3); 3.94 (s, 3H, OCH_3); 5.05 (s, 2H, CH_2-Bn); 5.83 (bs, 1H, OH); 6.91 (d, 2H, *J*=8.5Hz, Ar-*H*); 7.02 (d, 1H, Ar-*H*); 7.12 (d, 2H, *J*=8.5Hz, Ar-*H*); 7.51-7.30 (m, 5H, Bn-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.30 (CH$_2$*C*H$_2$CH$_2$CHOH); 29.32 (Ar*C*H$_2$); 29.57 (ArCH$_2$*C*H$_2$); 31.11 (*C*H$_2$Ar); 37.29 (CH$_2$CH$_2$*C*H$_2$CHOH); 39.26 (*C*H$_2$CH$_2$Ar); 60.64 (O*C*H$_3$); 61.07 (O*C*H$_3$); 70.05 (*C*H$_2$-Bn); 71.25 (*C*HOH); 106.36 (q, C-Br); 114.80 (*C*H-Ar); 125.86 (q, C-Ar); 127.00 (*C*H-Ar); 127.45 (*C*H-Bn); 127.47 (C*H*-Bn); 127.86 (C*H*-Bn); 128.53 (C*H*-Ar); 134.46(q, *C*-Ar); 137.19 (q, *C*-Bn); 140.38 (q, *C*-OCH$_3$); 146.78 (q, *C*-OH); 147.49 (q, *C*-OCH3); 157.00 (q, *C*-ArOBn).

anal. C 63.55, H 6.30 %, calcd for $C_{28}H_{33}BrO_5$, C 63.52, H 6.28 %

2-(benzyloxy)-1-(5-(benzyloxy)-7-(4-(benzyloxy)phenyl)heptyl)-5-bromo-3,4-dimethoxybenzene (88)



Chemical Formula: $C_{42}H_{45}BrO_5$
Exact Mass: 708.25 g mol
Molecular Weight: 709.71 g/mol85

Desired product was obtained from regioselective bromination of linear diarylheptanoid **85** (1 equiv., 1.59mmol, 1.00g) following the general procedure of bromination with NBS (see 7.3.3). Pure product was obtained after a silica gel chromatography as a yellow oil.

Time = 18h

Yield = (1.59mmol, 1.0g) 99%

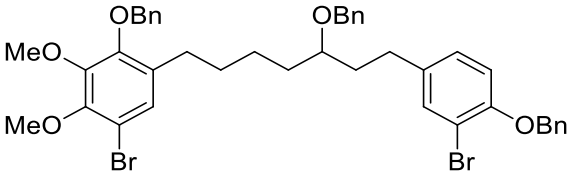
$\mathbf{R}_f$ = 0.5 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85-1.28 (m, 8H, CH_2); 2.55 (t, 2H, *J*=7.04Hz, ArCH_2); 2.67-2.58 (m, 1H, ArCH_2CH$_2$); 2.75-2.68 (m, 1H, ArCH_2CH$_2$); 3.45-3.38 (m, 1H, OC*H*); 3.92 (s, 3H, OCH_3); 3.93 (s, 3H, OCH_3); 4.49 (s, 2H, CH_2-Bn, aliphatic chain); 5.03 (s, 2H, CH_2-Bn); 5.06 (s, 2H, CH_2-Bn); 6.91 (d, 2H, *J*=8.5Hz, Ar-*H*); 7.08 (d, 2H, *J*=8.5Hz, Ar-*H*); 7.09 (s, 1H, Ar-*H*); 7.46-7.30 (m, 15H, Bn-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.36 (CH$_2$*C*H$_2$CH$_2$CH); 29.71 (Ar*C*H$_2$); 30.52 (ArCH$_2$*C*H$_2$); 31.14 (*C*H$_2$Ar); 37.26 (CH$_2$CH$_2$*C*H$_2$CH); 39.28 (*C*H$_2$CH$_2$Ar); 61.06 (O*C*H$_3$); 61.13 (O*C*H$_3$); 70.08 (*C*H$_2$-Bn); 71.19 (*C*HOH); 72.03 (*C*H$_2$-Bn); 75.24 (*C*H$_2$-Bn); 111.38 (q, C-Br); 114.83 (*C*H-Ar); 125.83 (q, C-Ar); 127.33 (*C*H-Ar); 127.43 (*C*H-Bn); 127.48 (C*H*-Bn); 127.80 (C*H*-Bn); 127.84 (C*H*-Bn); 127.90 (C*H*-Bn); 128.08 (C*H*-Bn); 128.39 (C*H*-Bn); 128.41 (C*H*-Bn); 128.53 (C*H*-Bn); 129.31 (C*H*-Ar); 133.42 (q, *C*-Ar); 134.45 (q, *C*-Bn); 137.19 (q, *C*-Bn); 137.47 (q, *C*-Bn); 147.57 (q, *C*-OCH$_3$); 149.26 (q, *C*-OCH3); 150.16 (q, *C*-OBn); 157.00 (q, *C*-ArOBn).

anal. C 71.10, H 6.40 %, calcd for $C_{42}H_{45}BrO_5$, C 71.08, H 6.39 %

2-(benzyloxy)-1-(5-(benzyloxy)-7-(4-(benzyloxy)-3-bromophenyl)heptyl)-5-bromo-3,4-dimethoxybenzene (89)



Chemical Formula: $C_{42}H_{44}Br_2O_5$
Exact Mass: 786.16 g mol
Molecular Weight: 788.60 g/mol

Desired product was obtained from bis-bromination of linear diarylheptanoid **85** (1 equiv., 0.8mmol, 0.5g) with 2.2 equiv of NBS, or from bromination of **88** (1 equiv., 0.8mmol, 0.5g) with 1.2 equiv. of NBS, following for both procedure the general protocol of bromination with NBS (see 7.3.3). Pure product was obtained after a silica gel column chromatography as a yellow-brown oil.

Time = 18h

Yield = (0.8mmol, 0.5g) 99%

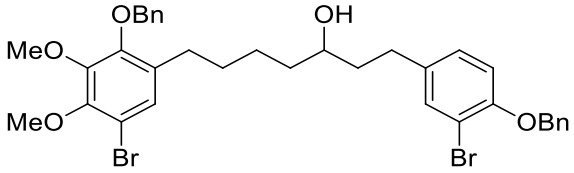
$\mathbf{R}_f$ = 0.5 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88-1.28 (m, 8H, CH_2); 2.51 (t, 2H, *J*=7.04Hz, ArCH_2); 2.69-2.56 (m, 1H, ArCH_2CH$_2$); 2.75-2.69 (m, 1H, ArCH_2CH$_2$); 3.37-3.34 (m, 1H, OC*H*); 3.90 (s, 3H, OCH_3); 3.91 (s, 3H, OCH_3); 4.45 (AB_{system}, 2H, *J*=12Hz, Δν=21Hz, CH_2-Bn, aliphatic chain); 5.01 (s, 2H, CH_2-Bn); 5.13 (s, 2H, CH_2-Bn); 6.83 (d, 2H, *J*=8.5Hz, Ar-*H*); 6.96 (dd, 2H, *J*=8.5Hz, *J*=2.1Hz, Ar-*H*); 7.07 (s, 1H, Ar-*H*); 7.48-7.34 (m, 16H, 15Bn-*H,* 1Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.38 ($CH_2CH_2CH_2CH$); 30.01 (ArCH_2); 31.52 (ArCH_2CH_2); 31.82 (CH_2Ar); 36.26 ($CH_2CH_2CH_2CH$); 38.28 (CH_2CH_2Ar); 61.03 (OCH_3); 61.10 (OCH_3); 70.08 (CH_2-Bn); 71.20 (*C*HOH); 73.14 (CH_2-Bn); 75.29 (CH_2-Bn); 111.40 (q, C-Br); 112.01 (q, C-Br); 114.56 (*C*H-Ar); 124.83 (q, C-Ar); 127.29 (*C*H-Ar); 127.32 (*C*H-Bn); 127.40 (C*H*-Bn); 127.76 (C*H*-Bn); 127.80 (C*H*-Bn); 127.85 (C*H*-Bn); 128.10 (C*H*-Bn); 128.25 (C*H*-Bn); 128.36 (C*H*-Bn); 128.51 (C*H*-Bn); 129.35 (C*H*-Ar); 133.65 (q, *C*-Ar); 135.21 (q, *C*-Bn); 137.25 (q, *C*-Bn); 137.50 (q, *C*-Bn); 147.55 (q, *C*-OCH_3); 149.30 (q, *C*-OCH3); 150.14 (q, *C*-OBn); 156.01 (q, *C*-ArOBn).

anal. C 64.02, H 5.66 %, calcd for $C_{42}H_{44}Br_2O_5$, C 63.97, H 5.62 %

1-(4-(benzyloxy)-3-bromophenyl)-7-(2-(benzyloxy)-5-bromo-3,4-dimethoxyphenyl)heptan-3-ol (89a)



Chemical Formula: $C_{35}H_{38}Br_2O_5$
Exact Mass: 696.11 g mol
Molecular Weight: 698.48 g/mol

Desired product was obtained from linear diarylheptanoid **83** (1 equiv., 1.65mmol, 0.60g) which was first benzylated at the phenolic position, following the general procedure for benzylation (see 7.3.1) The resulting product was directely halogenated with 2.2 equiv of NBS as described in the general protocol of bromination Method B (see 7.3.3). Product was obtained as a yellow oil.

Time = 23h

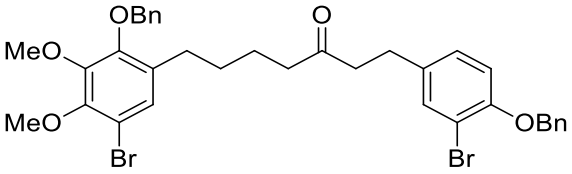
Yield = (1.25mmol, 0.87g) 76%

$\mathbf{R}_f$ = 0.4 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75-1.18 (m, 8H, CH_2); 2.51 (t, 2H, *J*=8.0Hz, ArCH_2); 2.63-2.41 (m, 1H, ArCH_2CH$_2$); 2.75-2.69 (m, 1H, ArCH_2CH$_2$); 3.58-3.47 (m, 1H, OC*H*); 3.90 (s, 3H, OCH_3); 3.92 (s, 3H, OCH_3); 4.70 (s, 1H, OH); 5.03 (s, 2H, CH_2-Bn); 5.13 (s, 2H, CH_2-Bn); 6.86 (d, 2H, *J*=8.3Hz, Ar-*H*); 7.04 (dd, 2H, *J*=8.3Hz, *J*=2.1Hz, Ar-*H*); 7.07 (s, 1H, Ar-*H*); 7.67-7.30 (m, 10H, Bn-*H*).

anal. C 60.20, H 5.46 %, calcd for $C_{35}H_{38}Br_2O_5$, C 60.18, H 5.48 %

1-(4-(benzyloxy)-3-bromophenyl)-7-(2-(benzyloxy)-5-bromo-3,4-dimethoxyphenyl)heptan-3-one (89b)



Chemical Formula: $C_{35}H_{36}Br_2O_5$
Exact Mass: 694.09 g mol
Molecular Weight: 696.47 g/mol

Alcohol **89a** (1 equiv., 0.14mmol, 0.10g) was dissolved in DCM (10mL). To this solution was added Dess-Martin Periodinane (2 equiv., 0.28mmol, 0.12g) at room temperature. The solution was stirred for all night long (18h). The mixture was quenched with water (10mL). The organic layer was separated, dried on Na_2SO_4, filtered and concentred under reduced pressure. The crude was rapidly purified on a silica gel pad to afford the pure product as a quite transparent oil.

Time = 18h

Yield = (0.14mmol, 0.87g) 99%

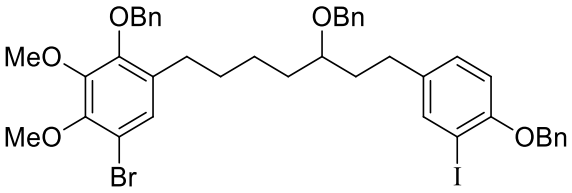
R_f = 0.5 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57-1.43 (m, 4H, C*H*$_2$ aliphatic chain); 2.32 (t, 2H, *J*=4.0Hz, COC*H*$_2$CH$_2$); 2.46 (t, 2H, *J*=4.0Hz, ArC*H*$_2$CH$_2$); 2.59 (t, 2H, *J*=4.0Hz, ArC*H*$_2$CH$_2$CO; 2.75 (t, 2H, *J*=4.0Hz, ArC*H*$_2$CH$_2$CO; 3.89 (s, 3H, OC*H*$_3$); 3.91 (s, 3H, OC*H*$_3$); 5.00 (s, 2H, C*H*$_2$-Bn); 5.11 (s, 2H, C*H*$_2$-Bn); 6.82 (d, 2H, *J*=8.3Hz, Ar-*H*); 7.00 (dd, 2H, *J*=8.3Hz, *J*=2.1Hz, Ar-*H*); 7.05 (s, 1H, Ar-*H*); 7.46-7.30 (m, 11H, 10Bn-*H,* 1Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.36 (COCH$_2$*C*H$_2$); 28.62 (Ar*C*H$_2$); 29.92 (Ar*C*H$_2$); 31.69 (ArCH$_2$*C*H$_2$); 42.64 (CO*C*H$_2$CH$_2$); 44.07 (CO*C*H$_2$CH$_2$); 61.05 (O*C*H$_3$); 61.06 (O*C*H$_3$); 70.91 (*C*H$_2$-Bn); 75.20 (*C*H$_2$-Bn); 111.35 (q, C-Br); 112.38 (q, C-Br); 113.94 (*C*H-Ar); 121.17 (q, C-Ar); 126.98 (*C*H-Ar); 127.26 (*C*H-Bn); 127.54 (*C*H-Bn); 127.88 (C*H*-Bn); 128.04 (C*H*-Bn); 128.24 (C*H*-Bn); 128.49 (C*H*-Bn); 128.53 (C*H*-Ar); 133.06 (q, *C*-Ar); 135.21 (q, *C*-Bn); 136.62 (q, *C*-Bn); 137.45 (q, *C*-Bn); 147.55 (q, *C*-OCH$_3$); 149.34 (q, *C*-OCH3); 150.35 (q, *C*-OBn); 153.35 (q, *C*-ArOBn); 209.64 (q, C=O).

anal. C 60.35, H 5.22 %, calcd for $C_{35}H_{36}Br_2O_5$, C 60.36, H 5.21 %

2-(benzyloxy)-1-(5-(benzyloxy)-7-(4-(benzyloxy)-3-iodophenyl)heptyl)-5-bromo-3,4-dimethoxybenzene (90)



Chemical Formula: $C_{42}H_{44}BrIO_5$
Exact Mass: 834.14 g mol
Molecular Weight: 835.60 g/mol

Di-halogenated product was prepared treating diarylheptanoid **85a** (1 equiv., 1.41mmol, 1.0g) with NBS (1.2 equiv., 1.69mmol, 0.30g). The product was obtained in **90% yield** (1.26mmol, 1.06g) Diarylheptanoid **88** (1 equiv., 1.41mmol, 1.0g) was treated with NIS (1.2 equiv., 1.69mmol, 0.38g) to give **90** in **77% yield** (1.08mmol, 0.90g).
For both reactions were followed the standard conditions reported in7.3.3and 7.3.4 for halogenation with NXS. The product was obtained pure as a yellow oil after a silica gel pad purification to remove the excess of succinimide.

Time = 18h

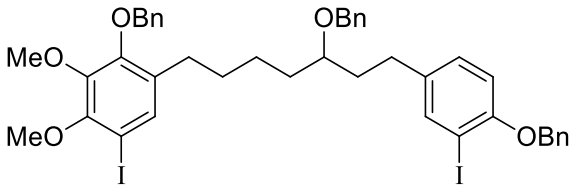
R_f = 0.55 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58-1.28 (m, 8H, CH_2); 2.52 (t, 2H, *J*=8.0Hz, ArCH_2); 2.56-2.50 (m, 1H, ArCH_2CH$_2$); 2.65-2.55 (m, 1H, ArCH_2CH$_2$); 3.45-3.35 (m, 1H, OC*H*-Bn); 3.92 (s, 3H, OCH_3); 3.93 (s, 3H, OCH_3); 4.46 (AB_{system}, 2H, *J*=12Hz, Δν=21Hz, CH_2-Bn, aliphatic chain); 5.04 (s, 2H, CH_2-Bn); 5.14 (s, 2H, CH_2-Bn); 6.77 (d, 1H, *J*=8.5Hz, Ar-*H*); 7.05 (dd, 1H, *J*=8.5Hz, *J*=2.1Hz, Ar-*H*); 7.09 (s, 1H, Ar-*H*); 7.52-7.31 (m, 15H, Bn-*H*); 7.62 (d, 1H, *J*=2.1Hz, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.05 (CH$_2$*C*H$_2$CH$_2$CH); 29.63 (Ar*C*H$_2$); 30.22 (ArCH$_2$*C*H$_2$); 30.61 (*C*H$_2$Ar); 33.41 (CH$_2$CH$_2$*C*H$_2$CH); 35.68 (*C*H$_2$CH$_2$Ar); 61.01 (O*C*H$_3$); 61.07 (O*C*H$_3$); 70.76 (*C*H$_2$-Bn); 70.98 (*C*H$_2$-Bn); 75.16 (*C*H$_2$-Bn); 77.91 (*C*HOH); 86.79 (q, *C*-I); 111.31 (q, C-Br); 112.69 (*C*H-Ar); 125.89 (CH-Ar), 126.97 (*C*H-Bn); 127.28 (*C*H-Bn); 127.50 (C*H*-Bn); 127.78 (C*H*-Bn); 127.97 (C*H*-Bn); 128.05 (C*H*-Bn); 128.34 (C*H*-Bn); 128.45 (C*H*-Bn); 128.49 (C*H*-Bn); 129.19 (C*H*-Ar); 133.44 (q, *C*-Ar); 136.68 (q, *C*-Bn); 137.08 (q, *C*-Bn); 137.49 (q, *C*-Bn); 139.20 (*C*H-Ar); 147.57 (q, *C*-OCH$_3$); 149.25 (q, *C*-OBn); 150.16 (q, *C*-OCH$_3$); 155.37 (q, *C*-ArOBn).

anal. C 60.40, H 5.33 %, calcd for $C_{42}H_{44}BrIO_5$, C 60.37, H 5.31 %

2-(benzyloxy)-1-(5-(benzyloxy)-7-(4-(benzyloxy)-3-iodophenyl)heptyl)-5-iodo-3,4-dimethoxybenzene (91)



Chemical Formula: $C_{42}H_{44}I_2O_5$
Exact Mass: 882.13 g mol
Molecular Weight: 882.60 g/mol

Di-iodinated product was prepared treating diarylheptanoid **85a** (1 equiv., 1.41mmol, 1.0g) with NIS (1.2 equiv., 1.69mmol, 0.38g). The product was obtained in **99% yield** (1.41mmol, 1.256g) after 18h.

Diarylheptanoid **85** (1 equiv., 1.41mmol, 1.0g) was treated with NIS (5 equiv., 7.05mmol, 1.59g) to give **91** in **70% yield** (0.98mmol, 0.87g). In this reaction NIS was added portionwise in 36h, starting from 2.2 equivalents.

For both reactions were followed the standard conditions reported in 7.3.4 for halogenation with NIS. The product was obtained pure as a yellow oil after a silica gel pad purification to remove the excess of succinimide.

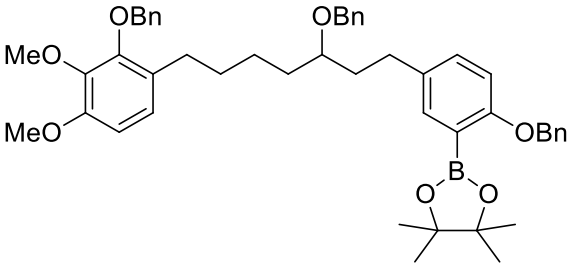
$\mathbf{R}_f$ = 0.55 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84-1.26 (m, 8H, CH_2); 2.48 (t, 2H, *J*=8.0Hz, ArCH_2); 2.55-2.46 (m, 1H, ArCH_2CH$_2$); 2.67-2.59 (m, 1H, ArCH_2CH$_2$); 3.95-3.33 (m, 1H, OC*H*-Bn); 3.88 (s, 3H, OCH_3); 3.90 (s, 3H, OCH_3); 4.46 (AB_{system}, 2H, *J*=12Hz, Δν=21Hz, CH_2-Bn, aliphatic chain); 5.02 (s, 2H, CH_2-Bn); 5.13 (s, 2H, CH_2-Bn); 6.76 (d, 1H, *J*=8.5Hz, Ar-*H*); 7.03 (dd, 1H, *J*=8.5Hz, *J*=2.1Hz, Ar-*H*); 7.51-7.29 (m, 16H, 15Bn-*H,* 1Ar-*H*); 7.60 (d, 1H, *J*=2.1Hz, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.08 (CH$_2$*C*H$_2$CH$_2$CH); 29.56 (Ar*C*H$_2$); 30.25 (ArCH$_2$*C*H$_2$); 30.68 (*C*H$_2$Ar); 33.42 (CH$_2$CH$_2$*C*H$_2$CH); 35.70 (*C*H$_2$CH$_2$Ar); 60.87 (O*C*H$_3$); 60.97 (O*C*H$_3$); 70.79 (*C*H$_2$-Bn); 71.02 (*C*H$_2$-Bn); 75.18 (*C*H$_2$-Bn); 77.94 (*C*HOH); 85.13 (q, *C*-I); 86.81 (q, *C*-I); 112.72 (*C*H-Ar); 127.00 (CH-Ar), 127.52 (q, C-Ar); 127.61 (*C*H-Bn); 127.77 (*C*H-Bn); 127.81 (C*H*-Bn); 127.98 (C*H*-Bn); 128.06 (C*H*-Bn); 128.37 (C*H*-Bn); 128.39 (C*H*-Bn); 128.47 (C*H*-Bn); 128.51 (*C*H-Ar); 129.21 (C*H*-Ar); 133.05 (q, *C*-Ar); 136.71 (q, *C*-Bn); 137.12 (q, *C*-Bn); 137.52 (q, *C*-Bn); 139.23 (*C*H-Ar); 146.72 (q, *C*-OCH$_3$); 151.34 (q, *C*-OBn); 151.86 (q, *C*-OCH$_3$); 155.40 (q, *C*-ArOBn).

anal. C 57.17, H 5.03 %, calcd for $C_{42}H_{44}I_2O_5$, C 57.15, H 5.02 %

2-(2-(benzyloxy)-5-(3-(benzyloxy)-7-(2-(benzyloxy)-3,4-dimethoxyphenyl)heptyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (92)



Chemical Formula: $C_{48}H_{57}BO_7$
Exact Mass: 756.42 g mol
Molecular Weight: 756.77 g/mol

A flame-dried flask was charged with $PdCl_2$dppf DCM (0,10 equiv., 0.01mmol, 0.01g). Vaccum/Argon cycle was again repeated in the flask and a solution of starting iodide **85a** (1 equiv., 0.12mmol, 0.09g)) in toluene (1 mL) was added. Pinacolborane (1.7equiv., 0.20mmol, 0.03mL) and Et_3N (0.13mL) were added under argon. The flask was sealed and heated to 110°C for 20h. After cooling to rt, the reaction mixture was hydrolyzed with aqueous saturated NH_4Cl (3mL) and extracted with EtOAc (3x5mL). The crude was purified by coloumn chromatography Cy/EtOAc (7/3 V/V) to eliminate the excess of pinacoloborane A second purification was made Cy/EtOAc (9/1) which afford the right product as a deliquescent white solid.

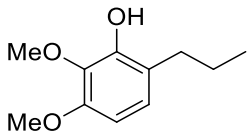
$\mathbf{R}_f$ = 0.3 (Cy/EtOAc = 9:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87-1.28 (m, 8H, CH_2); 1.38 (s, 12H, CH_3-pinacol); 2.56 (t, 2H, *J*=8.0Hz, ArCH_2); 2.71-2.52 (m, 2H, ArCH_2CH_2); 3.48-3.36 (m, 1H, OC*H*-Bn); 3.86 (s, 3H, OCH_3); 3.90 (s, 3H, OCH_3); 4.49 (s, 2H, CH_2-Bn, aliphatic chain); 5.06 (s, 2H, CH_2-Bn); 5.11 (s, 2H, CH_2-Bn); 6.64 (d, 1H, *J*=8.5Hz, Ar-*H*); 6.84 (d, 1H, *J*=8.5Hz, Ar-*H*); 6.87 (d, 1H, *J*=8.5Hz, Ar-*H*); 7.60-7.29 (m, 16H, 15Bn-*H,* 1Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.98 (CH_3, pinacol); 25.22 (CH_2CH_2CH_2CH); 29.74 (Ar*C*H_2); 30.79 (ArCH_2CH_2); 31.06 (*C*H_2Ar); 33.60 (CH_2CH_2*C*H_2CH); 35.96 (*C*H_2CH_2Ar); 56.05 (O*C*H_3); 60.90 (O*C*H_3); 70.23 (*C*H_2-Bn); 70.81 (*C*H_2-Bn); 75.16 (*C*H_2-Bn); 78.35 (*C*HOH); 83.45 (q, *C*$(CH_3)_2$ x2 pinacol); 107.43 (*C*H-Ar); 112.33 (CH-Ar), 123.84 (*C*H-Ar); 126.76 (*C*H-Bn); 127.21 (*C*H-Bn); 127.36 (*C*H-Bn); 127.77 (C*H*-Bn); 127.82 (C*H*-Bn); 128.02 (C*H*-Bn); 128.06 (C*H*-Bn); 128.26 (C*H*-Bn); 128.36 (C*H*-Bn); 128.86 (*C*H-Ar); 132.25 (C*H*-Ar); 134.36 (q, *C*B-pinacol); 136.48 (*C*H-Ar); 137.80 (q, *C*-Bn); 137.97 (q, *C*-Bn); 138.96 (q, *C*-Bn); 142.38 (q, *C*-OCH_3); 150.69 (q, *C*-OBn); 151.79 (q, *C*-OCH_3); 161.55 (q, *C*-ArOBn).

^{11}B NMR (128 MHz, $CDCl_3$) δ 31.34 **anal**. C 76.20, H 7.60 %, calcd for $C_{48}H_{57}BO_7$, C 76.18, H 7.59 %

2,3-dimethoxy-6-propylphenol (93)



Chemical Formula: $C_{11}H_{16}O_3$
Exact Mass: 196.11 g mol
Molecular Weight: 196.24 g/mol

A mixture of starting phenol **48** (1equiv., 5.15mmol, 1.00g,), ammonium formate (5equiv., 25.5mmol, 1.60 g), Pd/C 10% (0,2equiv, 1.023mmol, 1.10 g) and MeOH (77mL) was refluxed for 30min. It was let to cool down to r.t.. The crude mixture was filtered over celite and evaporated to dryness to give a slightly pink solid. The residue was solubilize in water (20mL) and extracted with EtOAc (3x15mL). The organic layers were collected togheter, dried on Na_2SO_4, filtered and concentred under reduced pressure. Desired product was obtained as a transparent oil.

Time = 30min

Yield = (5.05mmol, 0.99g) 98%

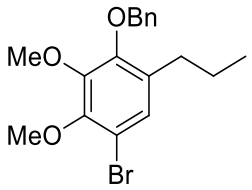
$\mathbf{R}_f$ = 0.5 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, 3H, *J*=7.5Hz, $CH_2CH_2CH_3$); 1.66-1.57 (m, 2H, $CH_2CH_2CH_3$); 2.62-2.48 (t, 2H, *J*=7.5Hz, $CH_2CH_2CH_3$); 3.85 (s, 3H, OCH_3); 3.91 (s, 3H, OCH_3); 5.84 (bs, 1H, O*H*); 6.41 (d, 1H, *J*=8.0Hz, Ar-*H*); 6.78 (d, 1H, *J*=8.0Hz, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.97 ($CH_2CH_2CH_3$); 23.05 ($CH_2CH_2CH_3$); 31.55 ($CH_2CH_2CH_3$); 55.79 (OCH_3); 60.88 (OCH_3); 103.21 (*C*H-Ar); 121.77 (q, C-Ar); 124.09 (*C*H-Ar); 135.32 (q, *C*-OCH_3); 147.29 (q, *C*-OH); 150.34 (q, *C*-OCH_3).

anal. C 67.33, H 8.23 %, calcd for $C_{11}H_{16}O_3$, C 67.32, H 8.22 %

4-bromo-2,3-dimethoxy-6-propylphenol (94)



Chemical Formula: $C_{11}H_{15}BrO_3$
Exact Mass: 274.02 g mol
Molecular Weight: 275.14 g/mol

The product was obtained performing the bromination as reported in the general procedure with NBS (see 7.3.3). Phenol **93** (1 equiv., 2.46mmol, 0.50g) was employed as strating material. The crude of reaction was purified on a silica gel pad to eliminate the succinimmide.

Time = 3h

Yield = (2.43mmol, 0.670g) 99%

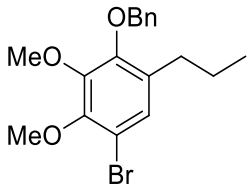
$\mathbf{R}_f$ = 0.4 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, 3H, *J*=7.4Hz, $CH_2CH_2CH_3$); 1.72-1.51 (m, 2H, $CH_2CH_2CH_3$); 2.55 (t, 2H, *J*=7.5Hz, $CH_2CH_2CH_3$); 3.87 (s, 3H, OCH_3); 3.95 (s, 3H, OCH_3); 5.76 (bs, 1H, O*H*); 7.03 (s, 1H, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.90 ($CH_2CH_2CH_3$); 22.73 ($CH_2CH_2CH_3$); 31.44 ($CH_2CH_2CH_3$); 60.65 (OCH_3); 61.08 (OCH_3); 106.26 (q, *C*-Br); 125.96 (q, *C*-Ar); 127.57 (*C*H-Ar), 140.33 (q, *C*-OCH_3); 146.81 (q, *C*-OH); 147.44 (q, *C*-OCH_3).

anal. C 48.05, H 5.53 %, calcd for $C_{11}H_{15}BrO_3$, C 48.02, H 5.50 %

2-(benzyloxy)-5-bromo-3,4-dimethoxy-1-propylbenzene (95)



Chemical Formula: $C_{18}H_{21}BrO_3$
Exact Mass: 364.07 g mol
Molecular Weight: 365.26 g/mol

Phenol **94** (1 equiv., 1.82mmol, 0.50g) was benzylated using K_2CO_3 base, as reported in the general procedure of paragraph 7.3.1. The crude of reaction was purified on a silica gel pad to eliminate the unreacted benzyl bromide (Rf = 0.9, Cy/EtOAc = 8:2)

Time = 5h

Yield = (1.78mmol, 0.650g) 98%

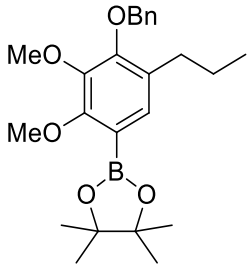
$\mathbf{R}_f$ = 0.6 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, 3H, *J*=7.4Hz, $CH_2CH_2CH_3$); 1.68-1.48 (m, 2H, $CH_2CH_2CH_3$); 2.51 (t, 2H, *J*=7.5Hz, $CH_2CH_2CH_3$); 3.92 (s, 3H, OCH_3); 3.94 (s, 3H, OCH_3); 5.03 (s, 2H, CH_2-Bn); 7.09 (s, 1H, Ar-*H*); 7.49-7.31 (m, 5H, Bn-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.95 ($CH_2CH_2CH_3$); 22.76 ($CH_2CH_2CH_3$); 31.48 ($CH_2CH_2CH_3$); 60.55 (OCH_3); 61.10 (OCH_3); 75.17 (CH_2-Bn); 105.98 (q, *C*-Br); 123.76 (q, *C*-Ar); 125.43 (*C*H-Ar), 127.32 (CH-Bn); 127.67 (CH-Bn), 128.85 (CH-Bn); 141.30 (q, *C*-OCH_3); 145.83 (q, *C*-OH); 149.34 (q, *C*-OCH_3).

anal. C 59.21, H 5.80 %, calcd for $C_{18}H_{21}BrO_3$, C 59.19, H 5.79 %

2-(4-(benzyloxy)-2,3-dimethoxy-5-propylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (96)



Chemical Formula: $C_{24}H_{33}BrO_5$
Exact Mass: 412.24 g mol
Molecular Weight: 412.33 g/mol

Boronic ester **96** was prepared following two procedure:

Procedure A: In a dried tube a solution of bromine **95** (1 equiv., 0,27mmol, 0.10g) in dried dioxane (1.20mL) was prepared. To this mixture were added $Pd(OAc)_2$ (0.05 equiv., 0.01mmol, 0.003g), S-Phos (0.2 equiv., 0.05mmol, 0.022g) and dry triethyilamine (4 equiv., 0.15mL). The resulting mixture solution was degassed with argon and pinacolborane (3 equiv., 0.80mmol, 0.11mL) was added dropwise. The reaction was heated to 85°C for 3h. The reaction was quenched with saturated solution of ammonium chloride and extracted with diethylether (3x5mL). The organic layers was treated with charcoal, dried on Na_2SO_4 and concentred under vacuum. The crude product was purified by column chromatography over silica gel (Cy/EtOAc 5:1) to afford the desired product in **55% yield** (0.15mmol, 0.061g).

Procedure B: A solution of bromine **95** (1 equiv., 0,22mmol, 0.08g) in dried toluene (1.2mL) was prepared. To this mixture were added $PdCl_2(dppf)_2$ (0.05 equiv., 0,01mmol, 0.008g), and dry triethyilamine (8 equiv., 1.77mmol, 0.25mL). The resulting mixture solution was degassed with argon and pinacolborane (1.2 equiv., 0,27mmol, 0.04mL) was added dropwise. The reaction is heated to 110°C for 3h. The reaction was quenched with saturated solution of ammonium chloride and extracted with diethylether (3x5mL). The organic layers was treated with charcoal, dried on Na_2SO_4 and concentred under vacuum. The crude product was purified by column chromatography over silica gel (Cy/EtOAc 5/1) in **52% yield** (0.11mmol, 0.047g).

$\mathbf{R}_f$ = 0.3 (Cy/EtOAc = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, 3H, *J*=7.4Hz, $CH_2CH_2CH_3$); 1.65-1.55 (m, 2H, $CH_2CH_2CH_3$); 2.52 (t, 2H, *J*=7.5Hz, $CH_2CH_2CH_3$); 3.89 (s, 3H, OCH_3); 3.92 (s, 3H, OCH_3); 5.08 (s, 2H, CH_2-Bn); 7.25 (s, 1H, Ar-*H*); 7.49-7.31 (m, 5H, Bn-*H*).

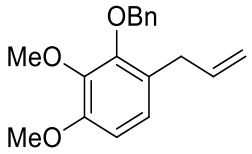
^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.17 ($CH_2CH_2CH_3$); 24.02 ($CH_2CH_2CH_3$); 24.83 (CH_3-pinacole); 31.90 ($CH_2CH_2CH_3$); 60.74 (OCH_3); 61.72 (OCH_3); 75. 17 (CH_2-Bn); 83.41 (q, $C(CH_3)_2$ pinacole); 127.91 (*C*H-

Bn), 128.42 (CH-Bn); 131.56 (CH-Ar), 132.25 (q, C-Bn); 146.00 (q, *C*-OCH_3); 153.51 (q, *C*-OH); 157.77 (q, *C*-OCH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 31.06

anal. C 69.90, H 8.05 %, calcd for $C_{24}H_{33}BrO_5$, C 69.91, H 8.07 %

1-allyl-2-(benzyloxy)-3,4-dimethoxybenzene (99)



Chemical Formula: $C_{18}H_{20}O_3$
Exact Mass: 284.14 g mol
Molecular Weight: 284.35 g/mol

Phenol **48** (1 equiv., 5.15mmol, 1.0g) was benzylated following the general procedure described in 7.3.1. The pure product was obtained as a yellow oil.

Time = 3h

Yield = (5.10mmol, 1.45g) 99%

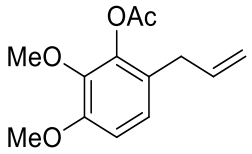
R_f = 0.6 (Cy/EtOAc = 8:2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 3,30 (d, 2H, *J*=10Hz, Ar-C*H*$_2$); 3,86 (s, 3H, OC*H*$_3$); 3,88 (s, 3H, OC*H*$_3$); 4,99 (d, 2H, *J*=10Hz, CH=C*H*$_2$); 5,03 (s, 2H, C*H*$_2$-Bn); 5,89 (m, 1H, C*H*=CH$_2$); 6,57 (d, 1H, *J* = 8.5Hz, Ar-*H*); 6,83 (d, 1H, *J*=8.5Hz, Ar-*H*); 7,45-7,31 (m, 5H, Bn-H)

^{13}C NMR (100 MHz, $CDCl_3$) δ: 33.65 (Ar-*C*H$_2$); 56.07 (O*C*H$_3$); 61.15 (O*C*H$_3$); 74.56 (*C*H$_2$-Bn); 103.57 (*C*H-Ar); 115.46 (*C*H$_2$-allyl); 120.13 (q, *C*-allyl); 124.67 (*C*H-Ar); 135.78 (*C*H-allyl); 142.45 (q, *C*OCH$_3$); 150.91 (q, *C*OCH$_3$); 151.98 (q, Ar-*C*OBn).

EIMS *m/z* 284 $[M]^+$(75), 243(10), 193 (50), 179(20), 91(100).

6-allyl-2,3-dimethoxyphenyl acetate (99a)



Chemical Formula: $C_{13}H_{16}O_4$
Exact Mass: 236.10 g mol
Molecular Weight: 236.26 g/mol

Phenol **48** (1 equiv., 2.72mmol, 0.50g) was dissolved in 2mL of acetic anhydride and 2mL of pyridine. The mixture was stirred for 2h at room temperature. The solution was quenched with water and extracted with EtOAc (3x10mL). Organic layer was dried on Na_2SO_4, filtered and concentered under reduced pressure. Pure compound was obtained as a yellow oil.

Time = 2h

Yield = (2.23mmol, 0.53g) 82%

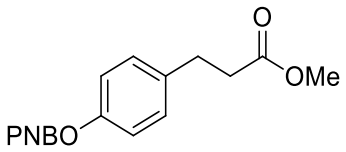
$\mathbf{R}_f$ = 0.55 (Cy/EtOAc = 8:2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.31 (s, 3H, acetyl); 3,21 (d, 2H, *J*=10Hz, Ar-CH_2); 3,81 (s, 3H, OCH_3); 3,84 (s, 3H, OCH_3); 5.02 (d, 2H, *J* =10Hz, C*H*=CH_2); 5,85 (m, 1H, C*H*=CH_2); 6,75 (d, 1H, *J* = 8.5Hz, Ar-*H*); 6,86 (d, 1H, *J* = 8.5Hz, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.21 (Ar-*C*H_2); 56.10 (O*C*H_3); 61.21 (O*C*H_3); 107.67 (*C*H-Ar); 115.86 (*C*H_2-allyl); 123.67 (*C*H-Ar); 128.75 (q, C-allyl); 136.57 (*C*H-allyl); 141.43 (q, Ar-*C*OAc); 141.32 (q, *C*OCH_3); 150.98 (q, *C*OCH_3); 151.98 (q, *C*=O).

EIMS *m/z* 236 $[M]^+$(25), 194(100), 43 (50).

4-(3-methoxy-3-oxopropyl)phenyl 4-nitrobenzoate (100)



Chemical Formula: $C_{17}H_{17}NO_5$
Exact Mass: 315.11 g mol
Molecular Weight: 315.32 g/mol

Ester **64** (1 equiv., 2.77mmol, 0.5g) was protected with para-nitrobenzylbromide following the general procedure described in 7.3.1. The crude of reaction was purified by column chromatography (EP/EtOAc = 8:2) and desired product was collected as very viscous oil.

Time = 1h

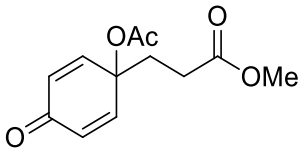
Yield = (2.74mmol, 0.90g) 99%

$\mathbf{R}_f$ = 0.45 (Cy/EtOAc = 8:2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.60 (t, 2H, *J*=7.5Hz, Ar-CH_2CH_2); 2.90 (t, 2H, *J*=7.5Hz, Ar-CH_2CH_2); 3.66 (s, 3H, $COOCH_3$); 5.15 (CH_2-Bn); 7.30 (d, 2H, *J* = 8.5Hz, Ar-*H*); 7.34 (d, 2H, *J*=8.5Hz, Ar-*H*); 8.43 (d, 2H, *J* = 8.3Hz, Ar-*H*); 8.45 (d, 2H, *J*=8.3Hz, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.12 (Ar-CH_2CH_2); 35.92 (Ar-CH_2CH_2); 51.62 (OCH_3); 68.74 (CH_2-Bn); 114.93 (*C*H-Ar); 123.82 (*C*H-Ar); 127.65 (*C*H-Ar); 129.45 (*C*H-Ar); 133.63 (q, *C*-Ar aliphatic chain); 144.64 (q, *C*-$ArNO_2$); 147.62 (q, *C*-$ArNO_2$); 156.73 (q, Ar-*C*OAr); 173.32 (q, C=O).

Methyl 3-(1-acetoxy-4-oxocyclohexa-2,5-dien-1-yl)propanoate (104)



Chemical Formula: $C_{12}H_{14}O_5$
Exact Mass: 238.08 g mol
Molecular Weight: 238.24 g/mol

Phenol **64** (1equiv., 1.1mmol, 0.20g) was dissolved in 8.8mL of AcOH. To this solution was added dropwise at room temperature a solution of (Diacetoxyiodo)benzene (PIDA) (1.1 equiv., 1.2mmol, 0.39g) in AcOH 5mL. A change of colour solution was observed from transparent to yellow. The reaction was stopped after 1h concentred the AcOH under reduced pressure. The residue was then quenched slowely with a saturated aqueous solution of $NaHCO_3$ (15mL). The aqueous phase was extracted with DCM (3x10mL). The organic layers were dried on Na_2SO_4, filtered and concentred under vacuum. The crude was purified by silica gel chromatography (EP/EtOAc 9/1) to afford desired product as a transparent oil.

Time = 1h

Yield = (0.12mmol, 0.03g) 11%

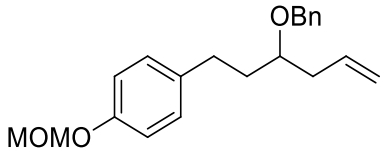
R_f = 0.4 (EP/EtOAc = 9:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.04 (s, 3H, OCOC*H*$_3$); 2.18 (t, 2H, *J*=7.5Hz, Ar-CH_2C*H*$_2$); 2.30 (t, 2H, *J*=7.5Hz, Ar-C*H*$_2CH_2$); 3.64 (s, 3H, COOC*H*$_3$); 6.27 (d, 2H, *J* = 8.5Hz, Ar-*H*); 6.77 (d, 1H, *J*=8.5Hz, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.10 (OCO*C*H_3); 28.05 (dienone-CH_2*C*H_2); 33.77 (dienone-*C*H_2CH_2); 51.87 (O*C*H_3); 75.88 (q, *C*-dienone); 129.34 (*C*H-dienone); 147.45 (*C*H-dienone); 123.82 (*C*H-Ar); 127.65 (*C*H-Ar); 129.45 (*C*H-Ar); 133.63 (q, *C*-Ar aliphatic chain); 144.64 (q, *C*-ArNO_2); 169.19 (q, C=O acetyl); 172.55 (q, C=OOCH_3); 184.87 (q, C=O dienone).

anal. C 60.52, H 5.93 %, calcd for $C_{12}H_{14}O_5$, C 60.50, H 5.92 %

1-(3-(benzyloxy)hex-5-en-1-yl)-4-(methoxymethoxy)benzene (106)



Chemical Formula: $C_{21}H_{26}O_3$
Exact Mass: 326.19 g mol
Molecular Weight: 326.43 g/mol

Homoallylic alcohol **72** (1 equiv., 0.98mmol, 0.230g) was protected with benzyl bromide (1.5 equiv.) using the general protocol of benzylation with NaH as base (see 7.3.1). Crude product showed that reaction was quantitative and because it appeared quasi-pure, crude was just characterized by ^{1}H-NMR and GC-MS and immediately use for successive reaction.

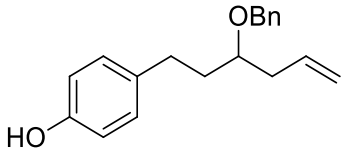
Time = 3h

$\mathbf{R}_f$ = 0.65 (EP/EtOAc = 9:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86-1.56 (m, 2H, $ArCH_2CH_2CHOBn$); 2.50-2.40 (m, 2H, $CHCH_2CH{=}CH_2$); 2.65-2.60 (m, 1H, $ArCH_2$); 2.83-2.78 (m, 1H, $ArCH_2$); 3.58-3.55 (s, 3H, OCH_3-MOM); 3.54 (m, 1H, CHOBn); 4.46 (AB_{system}, 2H, J=12Hz, $\Delta\nu$=21Hz, CH_2-Bn); 5.14 (dd, 2H, J=12Hz, J=2Hz, $CH{=}CH_2$); 5.20 (s, 2H, OCH_2-MOM); 5.90-5.80 (m, 1H, $CH{=}CH_2$); 7.00 (d, 2H, J = 8.5Hz, Ar-*H*); 7.13 (d, 2H, J = 8.5Hz, Ar-*H*); 7.44-7.34 (m, 5H, Bn-*H*).

EIMS *m/z* 326 $[M]^+$(5), 209(25), 91(100), 45(50).

4-(3-(benzyloxy)hex-5-en-1-yl)phenol (107)



Chemical Formula: $C_{19}H_{22}O_2$
Exact Mass: 282.16 g mol
Molecular Weight: 282.38 g/mol

106 (1 equiv., 6.13mmol, 0.2g) was dissolved in a mixture of THF/HCl(1M) (5mL/5mL). The solution was stirred at room temperature for 2h. The reaction was then diluited with water (2mL), extracted with Et_2O (3x5mL). The organic layers were dried on Na_2SO_4, filtered and concentred under vacuum pressure. The crude was purified by column chromatography (EP/Et_2O 7/3) to afford the pure product in a quantitative way.

Time = 3h

Yield = (6.06mmol, 0.17g) 99%

R_f = 0-4 (EP/Et_2 = 7:3)

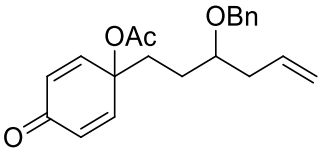
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96-1.76 (m, 2H, $ArCH_2CH_2CHOBn$); 2.50-2.30 (m, 2H, $CHCH_2CH{=}CH_2$); 2.63-2.56 (m, 1H, $ArCH_2$); 2.79-2.67 (m, 1H, $ArCH_2$); 3.58-3.55 (m, 1H, CHOBn); 4.55 (AB_{system}, 2H, *J*=12Hz, Δν=21Hz, CH_2-Bn); 5.12 (dd, 2H, *J*=12Hz, *J*=2Hz, $CH{=}CH_2$); 5.56 (bs, 1H, OH); 5.90-5.80 (m, 1H, $CH{=}CH_2$); 6.73 (d, 2H, *J* = 8.5Hz, Ar-H); 7.00 (d, 2H, *J* = 8.5Hz, Ar-H); 7.43-7.31 (m, 5H, Bn-H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.69 (Ar-CH_2); 35.81 ($ArCH_2CH_2CH$); 38.12 ($CHCH_2CH{=}CH_2$); 70.88 (CH_2-Bn); 77.73 (CHOBn); 115.15 (CH-Ar); 117.18 ($CH{=}CH_2$); 127.59 (CH-Bn); 127.90 (CH-Bn); 128.34 (CH-Bn); 129.37 (CH-Ar); 134.13 (q, C-Ar); 134.57 ($CH{=}CH_2$); 138.46 (q, C-Bn); 153.61 (q, C-OH).

EIMS *m/z* 282 $[M]^+$(5), 197(25), 133(30), 91(100).

anal. C 80.81, H 7.86 %, calcd for $C_{19}H_{22}O_2$, C 80.82, H 7.85 %

1-(3-(benzyloxy)hex-5-en-1-yl)-4-oxocyclohexa-2,5-dien-1-yl acetate (108)



Chemical Formula: $C_{21}H_{24}O_4$
Exact Mass: 340.17 g mol
Molecular Weight: 340.41 g/mol

Phenol **107** (1equiv., 0.20mmol, 0.06g) was dissolved in 1.6mL of AcOH. To this solution was added dropwise at room temperature a solution of (Diacetoxyiodo)benzene (PIDA) (1.1 equiv., 0.22mmol, 0.07g) in AcOH 2mL. A change of colour solution was observed from transparent to yellow. The reaction was stopped after 30min concentred the AcOH under reduced pressure. The residue was then quenched slowely with a saturated aqueous solution of $NaHCO_3$ (5mL). The aqueous phase was extracted with DCM (3x5mL). The organic layers were dried on Na_2SO_4, filtered and concentred under vacuum. The crude was purified by silica gel chromatography (EP/Et_2O 5/5) to afford desired product as a transparent oil.

Time = 30min

Yield = (0.13mmol, 0.04g) 65%

$\mathbf{R}_f$ = 0.4 (EP/Et_2O = 5/5)

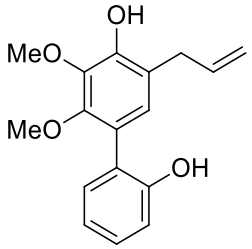
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60-1.48 (m, 2H, dienoneCH_2CH_2); 1.98-1,78 (m, 2H, dienoneCH_2CH_2); 2.13-1,97 (m, 1H, $CHCH_2CH{=}CH_2$); 2.06 (s, 3H, $COOCH_3$); 2.30-2.20 (m, 1H, $CHCH_2CH{=}CH_2$); 3.58-3.55 (m, 1H, CHOBn); 4.49 (AB_{system}, 2H, *J*=12Hz, Δν=21Hz, CH_2-Bn); 5.10 (dd, 2H, *J*=12Hz, *J*=2Hz, $CH{=}CH_2$); 5.89-5.81 (m, 1H, $CH{=}CH_2$); 6.26 (d, 2H, *J* = 8.5Hz, Ar-*H*); 6.79 (d, 2H, *J* = 8.5Hz, Ar-*H*); 7.38-7.31 (m, 5H, Bn-H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.28 (CH_3, acetyl); 27.20 (Ar-CH_2); 34.76 ($ArCH_2CH_2CH$); 37.99 ($CHCH_2CH{=}CH_2$); 71.03 (CH_2-Bn); 77.70 (CHOBn); 117.61 ($CH{=}CH_2$); 127.73 (C*H*-Bn); 128.34 (dienone-CH); 128.42 (CH-Bn); 129.10 (C*H*-Bn); 134.14 ($CH{=}CH_2$); 138.41 (q, *C*-Bn); 148.20 (dienone-CH); 169.42 (q, C=O, acetyl); 185.23 (q, *C*=O, dienone).

EIMS *m/z* 340 $[M]^+$(5), 297(30), 206(10), 91(100), 43(50).

anal. C 74.10, H 7.12 %, calcd for $C_{21}H_{24}O_4$, C 74.09, H 7.11 %

5'-allyl-2',3'-dimethoxy-[1,1'-biphenyl]-2,4'-diol (116)



Chemical Formula: $C_{17}H_{18}O_4$
Exact Mass: 286.12 g mol
Molecular Weight: 286.32 g/mol

In a dried tube were added **57** (1 equiv., 0.27mmol, 0.10g), commercial 2-hydroxyphenyl boronic acid (1.5equiv., 0.40mmol, 0.056g), $PdCl_2(PPh_3)_2$ (0.1 equiv., 0.027mmol, 0.02g), KF(5 equiv., 1.35mmol, 0.078g) and degassed solvent THF(2.5mL) and H_2O (0.25mL). The tube was purged under argon and sealed. The mixture was stirred at reflux for 15h. The solution was allowed to cool to room temperature and then quenched with an aqueous solution of HCl (0.1M, 2mL) which contemporary deprotected coupled compound from MOM. The crude was purified by column chromatography EP/EtOAc 9:1 to afford the desired product as a transparent oil.

Time = 15h

Yield = (0.13mmol, 0.039g) 50%

$\mathbf{R}_f$ = 0.5 (EP/EtOAc = 9:1)

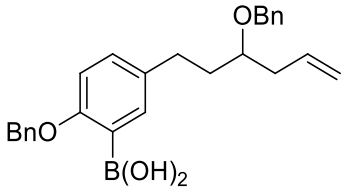
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.41 (d, 2H, J = 6.4Hz, Ar-*C*H_2); 3.69 (s, 3H, OC*H*$_3$); 4.01 (s, 3H, OC*H*$_3$); 5.09 (dd, 2H, J_{cis} = 10.4 Hz, J_{trans} = 17,0 Hz, C*H*$_2$-allyl); 5.93 (bs, 1H, O*H*); 6.18-5.95 (m, 1H, C*H*-allyl); 6.77 (bs, 1H, O*H*); 6.87 (s, 1H, Ar-*H*); 7.03 (m, 2H, Ar-*H*); 7.28 (m, 2H, Ar-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 33.88 (Ar-*C*H_2); 61.42 (O*C*H_3); 61.58 (O*C*H_3); 116.01 (*C*H_2-allyl); 117.78 (*C*H-Ar), 121.05 (*C*H-Ar), 123.13 (q, C-allyl); 123.49 (q, C Ar-Ar); 125.73 (q, C Ar-Ar); 127.11 (*C*H-Ar); 129.06 (*C*H-Ar); 130.99 (*C*H-Ar); 136.14 (CH-allyl); 136.15 (q, *C*OCH_3), 139.38 (q, *C*OCH_3); 147.15 (q, *C*OH), 153.29 (q, *C*-OH).

EIMS *m/z* 286 $[M]^+$(100), 239(25), 211(20), 165(10).

anal. C 71.32, H 6.35 %, calcd for $C_{17}H_{18}O_4$, C 71.31, H 6.34 %

(2-(benzyloxy)-5-(3-(benzyloxy)hex-5-en-1-yl)phenyl)boronic acid (117a)



Chemical Formula: $C_{26}H_{29}BO_4$
Exact Mass: 416.22 g/mol
Molecular Weight: 416.22 g/mol

Substrate **71c** (1equiv., 0.1mmol, 0,05g) was dissolved in 0.5mL of anhydrous THF under inert atmosphere. The mixture was stirred and allowed to -78°C. To this solution *i*-PrMgCl (1.5equiv., 0.15mmol, 0.075mL, solution 2M in THF) was added dropwise. The mixture was stirred for 1h at -78°C during which a change of colour solution from transparent to yellow was observed. After 1h, $B(OiPr)_3$ (6equiv., 0.60mmol, 0.141mL) was slowly added at -78°C. The mixture was stirred for 3h at same temperature after that the solution was allowed to warm to room temperature and stirred for 3d. The reaction was quenched with 5mL of HCl (0.1M) and the resultant solution was extracted three times with 5mL of diethyl ether. The collected organic layers were dried using Na_2SO_4, filtered and concentred under reduced pressure. The crude was purified by silica gel column chromatography (DCM/MeOH 100/1 V/V) to obtain the desired product as white butter.

Time = 3d

Yield = (0.024mmol, 0.010g) 24%

$\mathbf{R}_f$ = 0.7 (pure DCM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79-1.73 (m, 2H, $ArCH_2CH_2CH$); 2.41-2.36 (m, 2H, $CHCH_2CH{=}CH_2$); 2.62-2.45 (m, 1H, $ArCH_2$); 2.74-2.63 (m, 1H, $ArCH_2$); 3.55-3.50 (m, 1H, CHOBn); 4.46 (AB_{system}, 2H, *J*=12Hz, Δν=21Hz, CH_2-Bn); 4.57 (s, 2H, CH_2-Bn, aliphatic chain); 5.06 (m, 2H, $CH_2{=}CH_2$); 5.08 (s, 2H, CH_2-Bn); 5.95-5.78 (m, 1H, $CH{=}CH_2$); 6.67 (dd, 1H, J_{ortho} = 8.5Hz, J_{meta}=2.0Hz, Ar-*H*); 6.77 (d, 1H, J_{meta} = 2.0Hz, Ar-*H*); 6.82 (d, 1H, J_{ortho} = 2.1Hz, Ar-*H*).7.42-7.29 (m, 5H, Bn-*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.51 (Ar-CH_2); 36.23 ($ArCH_2CH_2CH$); 38.26 ($CHCH_2CH{=}CH_2$); 71.05 (CH_2-Bn); 71.96 (CH_2-Bn); 78.64 (CHOH); 113.43 ($CH{=}CH_2$); 117.54 (CH-Ar); 124.01 (q, *C*-$B(OH)_2$); 127.10 (CH-Bn); 127.54 (CH-Bn); 127.61 (CH-Bn); 128.15 (CH-Bn); 128.22 (CH-Bn); 128.48 (CH-Bn); 129.00 (CH-Ar); 133.61 (CH-Ar); 134.58 ($CH{=}CH_2$); 136.60 (q, *C*-Ar); 136.78 (q, *C*-Bn); 138.54 (CH-Ar); 155.53 (q, *C*-ArOBn).

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9 SCIENTIFIC PRODUCTIONS

9.1 ORAL COMMUNICATIONS

Toward the total synthesis of (+)-aR,11S-myricanol and its analogues
Bochicchio, A.; Chiummiento, L.; Funicello, M.; Lupattelli, P.; Hanquet, G.; Choppin, S.; Colobert, F.
"SECO51"
Port Lecate, 18-24 Mai 2014 (Abstract book, pag.49)

Metal catalyzed reactions for (+)-aR,11S-myricanol total synthesis.
Bochicchio, A.; Chiummiento, L.; Funicello, M.; Lupattelli, P.; Schiavo, L.; Hanquet, G.; Choppin, S.; Colobert, F.
"XXV CONGRESSO NAZIONALE DELLA SOCIETA' CHIMICA ITALIANA"
Arcavacata di Rende (CS)-7/12 September 2014 (Acts of congres, ORG-02, pag. 703)

[3,3]-sigmatropic Claisen rearrangement: a rapid access to Phenylpropenes and Lignans structures
Bochicchio, A.; Chiummiento, L.; Cefola, R.; Funicello, M.; Lupattelli, P.
"XVI CONVEGNO REAZIONI PERICICLICHE E SINTESI DI ETERO E CARBOCICLI"
Matera, 26-27 June 2015 (Acts of congress, O6, pag.10)

[7,0]-metacyclophanes from biaryl coupling/macrocylization
Bochicchio, A.; Chiummiento, L.; Funicello, M.; Lupattelli, P.; Hanquet, G.; Choppin, S.; Colobert, F.
"XXVI CONVEGNO NAZIONALE DELLA DIVISIONE DI CHIMICA ORGANICA"
Bologna-13/17 September 2015 (Act of congress, OC-52, pag. 102)

9.2 POSTERS

From pyrogallol derivatives to cyclic and linear diarylheptanoids: synthesis of (+)-aR,11S-myricanol
Bochicchio, A.; Chiummiento, L.; Funicello, M.; Lupattelli, P.; Choppin, S.; Colobert, F.
"ATTILIO CORBELLA' SUMMER SCHOOL ON ORGANIC SYNTHESIS"
Universita' degli Studi di MILANO-Gargnano-17/21 June 2013

Métathèse croisée et couplage intramoléculaire comme réactions clefs pour la synthèse d'arylheptanoïdes cycliques bioactifs
Bochicchio, A.; Chiummiento, L.; Funicello, M.; Lupattelli, P.; Hanquet, G.; Choppin, S.; Colobert, F.
"4ème SYMPOSIUM FRANCOPHONE DE SYNTHESE TOTALE"
Montpellier, 5-6 june 2014

Diarylheptanoids synthesis: small molecules, high activities
Bochicchio, A.; Chiummiento, L.; Funicello, M.; Lupattelli, P.; Schiavo, L.; Hanquet, G.; Choppin, S.; Colobert, F.
"IASOC 2014"(ISCHIA ADVANCED SCHOOL OF ORGANIC CHEMISTRY)
Università di Napoli-Ischia-21/25 September 2014 (Poster Abstract, P04)

Synthèse totale du Myricanol par macrocyclisation biarylique
Bochicchio, A.; Chiummiento, L.; Funicello, M.; Lupattelli, P.; Hanquet, G.; Choppin, S.; Colobert, F.
"5ème SYMPOSIUM FRANCOPHONE DE SYNTHESE TOTALE"
Strasbourg, 2-3 June 2014

Similar but different: natural products and analogues from phenylpropanoid derivatives
Bochicchio, A.; Chiummiento, L.; Funicello, M.; Lupattelli, P.; Cefola, R.; Schiavo, L.; P.; Hanquet, G.; Choppin, S.; Colobert, F.
"ISSNP 2015 (INTERNATIONAL SUMMER SCHOOL ON NATURAL PRODUCTS)"
Napoli, 06-10 July 2015 (Abstract book, P3, pag.67)

9.3 PUBLICATIONS

Antonella Bochicchio, Lucia Chiummiento, Paolo Convertini, Vittoria Infantino, Anna Santarsiero, Lucie Schiavo, Sabine Choppin, Gilles Hanquet and Françoise Colobert

Manuscript in preparation

9.4 PRIZE

17/09/2015

Reaxys SCI Young Researcher Award
1st prize for the field *Life Sciences, Medicinal and Organic Chemistry*

03/07/2014

Vinci Fellowship 2014

(Grant for mobility from Italy to France during cotutorship doctoral thesis)

Université Franco-Italienne/ Università Italo-Francese

Antonella BOCHICCHIO

TOWARDS THE ATROPO-STEREOSELECTIVE TOTAL SYNTHESIS OF MYRICANOL

Résumé

Le myricanol est un [7,0]-*meta*cyclophane naturel qui appartient à la famille des diarylheptanoïdes et qui possède des propriétés biologiques intéressantes. Ainsi le myricanol énantioenrichi possède un fort potentiel de réduction du niveau de protéines Tau dans les cellules (effet anti Alzheimer), et sous forme racémique, des propriétés anti-cancéreuses (cancer du poumon). Actuellement, seules deux synthèses racémiques du (+/-)-myricanol sont rapportées dans la littérature. L'objectif de ce travail de thèse est la préparation racémique puis stéréosélective du myricanol. Deux nouvelles approches rétrosynthétiques avec des étapes clés similaires ont été considérées pour la construction du [7,0]-*meta*cyclophane. D'une part, le diarylheptanoïde linéaire a été préparé par le biais d'une réaction-clé de métathèse croisée suivie d'une réaction de Suzuki-Miyaura domino intramoléculaire pour conduire au macrocycle avec un rendement de 2.55% en 11 étapes. Dans l'objectif d'une synthèse atropostéréosélective, un des partenaires de couplage énantiopur porteur d'un carbinol stéréogène a été synthétisé (transfert chiralité centrale vers axiale). D'autre part le noyau biarylique du myricanol a été envisagé par une réaction de couplage intermoléculaire (couplage de Suzuki-Miyaura ou couplage oxydant) qui sera suivie d'une réaction de métathèse cyclisante, encore jamais testée pour la préparation de cette molécule. Notons que de nouveaux composés diarylheptanoides linéaires ont également été préparés et pour lesquels une activité intéressante comme inhibiteur ROS et NO pour les cellules redox U937 et BV-2 a été mise en évidence.

Mots clés: myricanol, diarylheptanoïdes, métathèse croisée, couplage de Suzuki-Miyaura domino.

Abstract

The myricanol, a natural [7.0]-*meta*-cyclophane which belongs to the family of diarylheptanoids, possess interesting biological activities. Indeed the enantioenriched myricanol has a great potential to reduce the level of tau protein in cells (anti Alzheimer effect) and in its racemic form it was described as a potentiel candidate for the prevention and treatment of lung cancer. Actually only two synthesis of racemic (+/-) - myricanol have been reported in the literature. The goal of our research is the racemic and stereoselective preparation of myricanol. Two retrosynthetic approaches with similar key reactions have been investigated to build up the [7.0]-*meta*-cyclophane. On one side, the linear diarylheptanoid was prepared using an efficient cross-metathesis reaction followed by an intramolecular Suzuki-Miyaura domino reaction giving the desired cyclophane with 2.55% overall yield in 11 steps. On the other side, the biaryl core of myricanol was envisaged by an intermolecular coupling reaction (Suzuki-Miyaura coupling, oxidative coupling) between already highly functionalized fragments, followed by a ring closure metathesis, never tested for this type of compound. Noteworthy new linear diarylheptanoids have been achieved which revealed good ROS and NO inhibitor in U937 and BV-2 cell lines.

Keywords: myricanol, diarylheptanoides, cross metathesis, Suzuki-Miyaura domino coupling.