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THESE DE DOCTORAT

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Extending the diversity of privileged natural product motifs: Synthesis of a library of resorcylic acid lactones and studies towards the guaianes and pseudoguaianes

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Résumé

Les protéines kinases sont des enzymes impliquées dans toutes les transductions de signaux, qui catalysent la phosphorylation des protéines et régulent ainsi leur fonction. Une kinase défectueuse pouvant être à l'origine de nombreuses pathologies telles que le cancer, les inflammations ou encore les maladies neurodégénératives,[1] les kinases sont devenues l'une des classes de protéines les plus prisées pour la découverte de nouveaux médicaments. Hormis l'intérêt thérapeutique, l'inhibition spécifique des kinases devrait permettre de déterminer individuellement la fonction exacte de chacune d'entre elles.

Les macrolides du résorcinol présentant une fonction *cis*-enone (Figure 1) se sont révélés être de puissants et irréversibles inhibiteurs de protéines kinases activées par les mitogènes (MAP kinases).[2] En cas de stress, ces kinases assurent la transmission du signal des récepteurs situés à la surface des cellules jusqu'aux molécules cibles intracellulaires en charge de la régulation, et ce par un système de phosphorelai composé de trois kinases activées successivement. L'activation et l'action de ces kinases est très spécifique.[3] L'inhibition irréversible de ces kinases par les macrolides du résorcinol présentant une fonction *cis*-énone a été attribuée à la formation d'une liaison covalente, par addition de type Michael, entre la cétone α,β-insaturée du macrocycle et un résidu cystéine se trouvant dans la poche ATP de certaines kinases. Ce résidu cystéine a été identifié dans 46 des 518 kinases que compte le kinôme.[4]

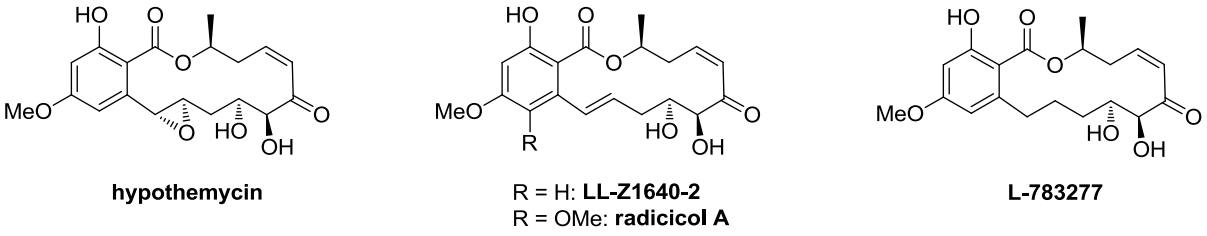


Figure 1. Exemples de membres de la famille des macrolides du résorcinol présentant une fonction *cis*-énone.

Attiré par l'activité biologique importante de ces composés, notre laboratoire a développé la première synthèse totale du radicicol A, dont la cible biologique précise était encore inconnue à l'époque, et a ainsi pu démontrer que ce produit naturel est en fait un puissant inhibiteur de VEGF-R2, VEGF-R3, FLT3 et PDGFR-β.[5] Dans le but de découvrir de nouvelles relations de structure-activité et de découvrir de nouveaux inhibiteurs spécifiques de kinases, il a été décidé d'appliquer la voie synthétique développée pour radicicol A à l'élaboration d'une chimiothèque de plus de 50 macrocycles.[6]

La première partie de ma thèse a consisté à mettre au point cette chimiothèque. Nous avons choisi d'utiliser la technologie des tags fluorés, développée par le Prof. Curran, permettant à la fois de purifier simplement les produits et de travailler avec des mélanges de composés (Schéma 1).[7-9] Vingt-huit des macrocycles ainsi préparés ont été testés sur un panel de dix-neuf kinases, et deux composés issus de cet échantillon ont ensuite été testés sur un plus large panel de 402 kinases ainsi que sur une série de mutations de FLT3 et de KIT. Ces tests ont permis d'identifier deux modifications

permettant d'accroitre l'activité biologique, à savoir l'ajout d'un carbone supplémentaire dans le macrocycle et l'ajout d'un groupement hydroxyl en position β du diol.

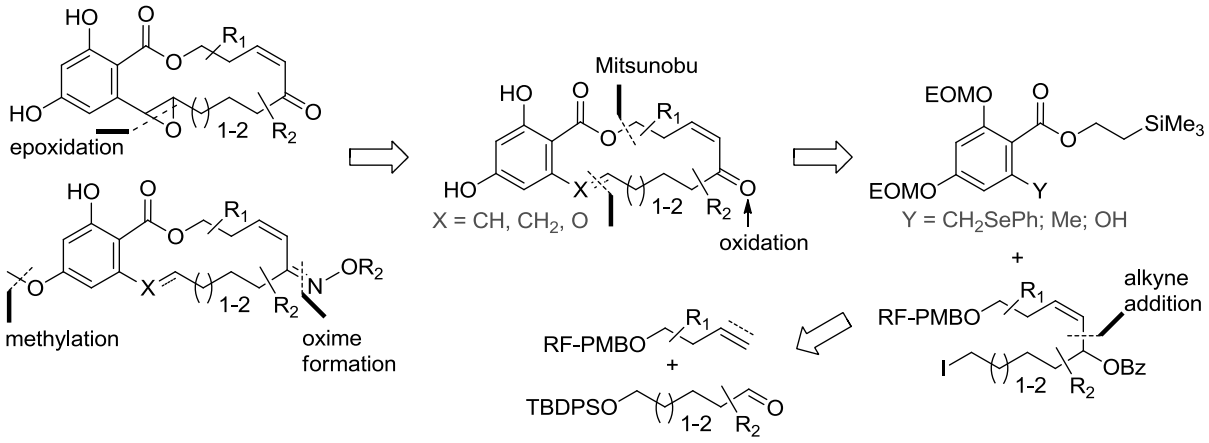


Schéma 1. Analyse rétrosynthétique de la chimiothèque de *cis*-énones.

La seconde partie de ma thèse a consisté à développer une voie de synthèse générale permettant d'accéder à certains membres d'une autre classe de puissants inhibiteurs irréversibles portant le nom de lactones sesquiterpéniques. Les lactones sesquiterpéniques sont une famille de produits naturels, généralement issus des racines et des fleurs des *Compositae*, pour laquelle plus de 3000 structures ont déjà été reportées. Ces composés sont classés, en fonction de leur squelette carboné, en quatre groupes principaux nommés germacranolides, eudesmanolides, guaianolides et pseudoguaianolides (Figure 2).

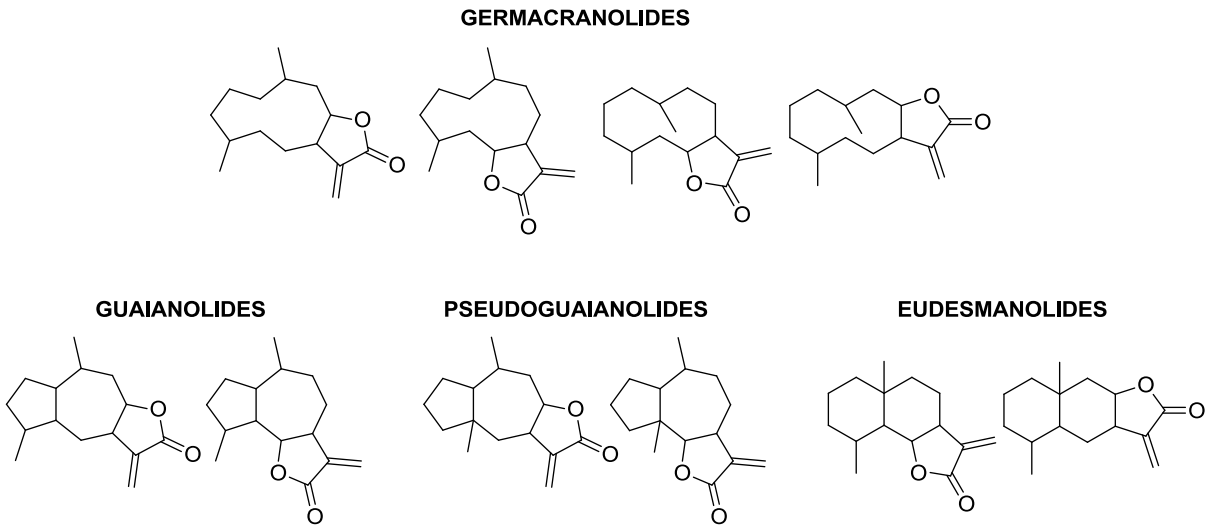


Figure 2. Squelette des quatre groupes principaux de lactones sesquiterpéniques.

Bien que la présence de ces produits naturels dans les plantes entraine l'intoxication du bétail, les lactones sesquiterpéniques ont été utilisées pendant des siècles en médecine traditionnelle et présentent un large spectre de propriétés biologiques comme des propriétés cytotoxiques, anti-tumorales, anti-inflammatoires, anti-microbiennes et anti-fongiques.[10] Les cibles biologiques et les mécanismes induisant la plupart de ces propriétés, à l'exception des propriétés anti-inflammatoires, n'ont pas encore été identifiés. Il a en effet été démontré que cette propriété est due à une inhibition du facteur de transcription NF-κB, un médiateur central de la réponse immunitaire chez l'homme, connu pour réguler la transcription de plus de 150 gênes et dont le mauvais fonctionnement implique entre autre des pathologies comme l'arthrite rhumatoïde, la maladie d'Alzheimer ou les chocs septiques. Il a été prouvé que les lactones sesquiterpéniques empêchent l'activation du NF-κB principalement en réagissant, par une addition de type Michael, avec le résidu cystéine 38 de sa sous-unité p65 (il a cependant été mis en évidence que d'autres cibles biologiques doivent être impliquées dans ce processus d'inactivation).[11-13] Le caractère irréversible et le mode d'action unique (en comparaison avec les inhibiteurs déjà reportés) de l'inhibition du NF-κB par les lactones sesquiterpéniques laisse apparaître cette famille de produits naturels comme une source prometteuse de nouveaux médicaments anti-inflammatoires.

Dans le but de développer des « composés outils » tels que des composés conjugués avec une biotine afin d'étudier encore plus en détail le mode d'action de ces composés, et convaincu de l'intérêt de préparer des analogues et d'étendre la diversité de ce pharmacophore au-delà de ce que la nature propose, notre laboratoire a décidé de développer une nouvelle voie de synthèse, à la fois efficace et flexible, pour accéder aux lactones sesquiterpéniques. Inspirés par la biosynthèse de ses produits, nous avons basé notre stratégie sur un intermédiaire simple (**A**), qui par le biais de différentes transformations chimiques (telles que des cyclisations et des oxydations) permettrait de préparer divers membres de la famille. Nous avons décidé de nous focaliser sur le squelette contenant un cycle à 5 et à 7 carbones, généralement plus actif, et avons choisi comme cible précise un membre de chacune des familles présentant ce squelette. La molécule d'hélénaline a été évidemment retenue pour la classe des pseudoguaianolides, ce composé étant l'un des membres les plus actifs et les plus étudiés de la famille des lactones sesquiterpéniques (utilisé très régulièrement comme modèle pour les tests biologiques), la molécule geigérine a ensuite été retenue pour la classe des guaianolides, principalement parce qu'elle présente une stéréochimie relative en C_1 et C_{10} identique à hélénaline (Schéma 2).

L'intermédiaire central **A** a pu être préparé avec succès en treize étapes, dont une addition de cuprate en position 1,4, une réduction de lactone, une réaction de Corey-Fuchs et une métathèse enyne domino. Bien que cette transformation ait déjà été réalisée sur des molécules similaires, le réarrangement de pinacol que nous avions envisagé pour fonctionnaliser l'hydroazulène **A** en hélénaline s'est révélé infructueux. Ce résultat n'est malgré tout pas si surprenant, la stabilité relative des carbocations s'étant révélée extrêmement dépendante de la structure et de la conformation de la molécule. Inversement, l'intermédiaire **A** a pu être converti de manière satisfaisante en geigérine (ainsi qu'en son analoque 6-deoxygeigérine) en quatre étapes, incluant une oxydation allylique, une addition conjuguée en position 1,6 et une époxydation, validant ainsi la stratégie développée.

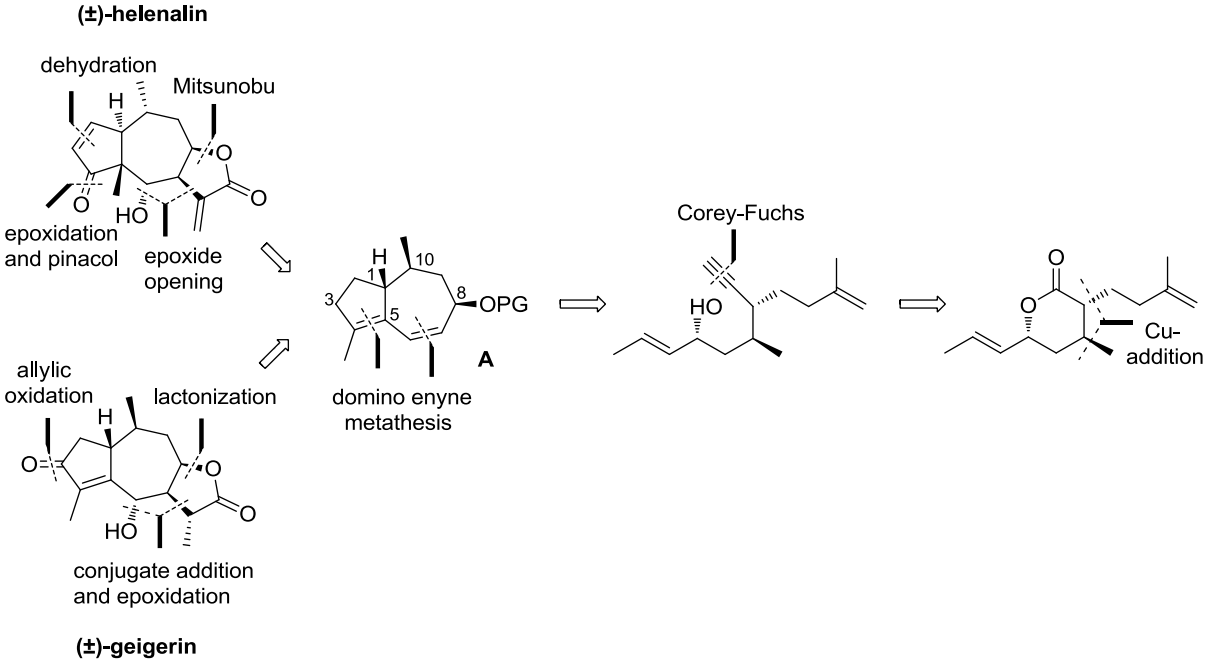


Schéma 2. Rétrosynthèse générale des guaianes et pseudoguaianes.

Summary

Protein kinases are enzymes implicated in every transduction pathways, which catalyze the phosphorylation of proteins and therefore participate to the regulation of their function. Their dysfunction being at the origin of a number of pathologies ranging from oncology to inflammation and neurodegenerative disease,[1] kinases have become one of the most intensively pursued classes of proteins for drug discovery. In addition to therapeutic benefit, their specific inhibition should also allow to individually determine the function of each kinase.

Natural *cis*-enone resorcylic acid lactones (RALs) have been shown to be potent and irreversible mitogen-activated protein (MAP) kinase inhibitors (Figure 1).[2] Under stress conditions, these kinases assure the transmission of the signal from the cell-surface receptors to the critical regulatory targets in the cell through a phosphorelay system composed of three sequentially activated kinases. Their activation, as well as their function, is very specific.[3] The irreversible inhibition of these kinases by the *cis*-enone RALs has been attributed to the formation of a covalent bound between the α,β-unsaturated ketone of the polyketide and a cysteine residue present in the adenosine triphosphate (ATP) binding pocket of a subset of kinases through a Michael-type addition. The targeted cysteine residue (Cys^{166}) has been identified in 46 of the 518 kinases of the kinome.[4]

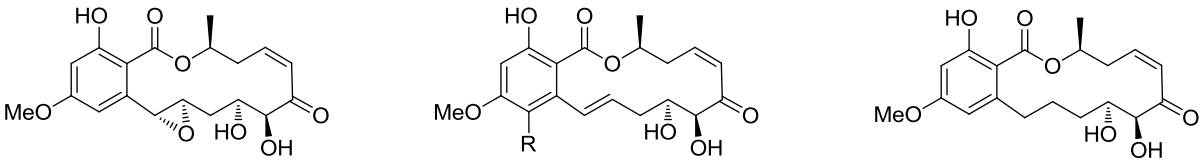
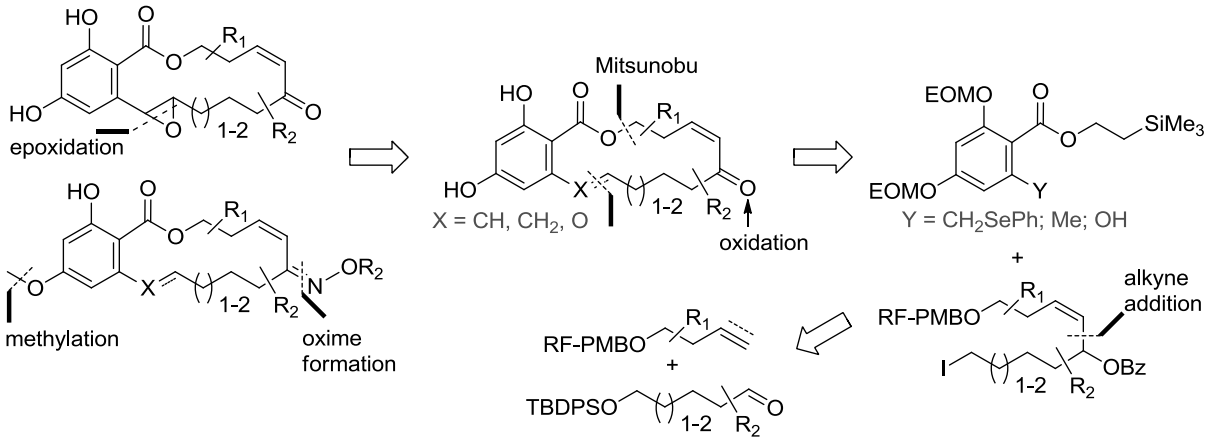


Figure 1. Selected members of the *cis*-enone RALs.

Attracted by the important biological activity of these pharmacophores, our laboratory developed the first total synthesis of radicicol A, whose precise biological target was at this time undetermined, and demonstrated that this compound is a potent inhibitor of vascular endothelial growth factor receptors VEGF-R2, VEGF-R3, FMS-related tyrosine kinase 3 (Flt3) and platelet-derived growth factor receptor PDGFR-β.[5] In the purpose of discovering new structure-activity trends and new specific kinase inhibitors, it was then decided to apply the strategy developed for radicicol A to the elaboration of a library of over fifty macrocycles.[6]

The synthesis of this library constituted the first part of my PhD. As shown in Scheme 1, the library was prepared using the fluorous tags technology developed by Curran *et al.* facilitating the isolation of the products and allowing to carry mixtures of products through a common synthetic pathway.[7-9] Twenty-eight of the macrocycles synthesized were evaluated against a panel of nineteen kinases, and two compounds representative of this subset were then screened against a larger panel of four-hundred-two kinases as well as against a series of mutations of FLT3 and tyrosine-protein kinase KIT. The biological evaluations allowed to identify two modifications as increasing the activity, namely the extra carbon and the additional hydroxyl in β position of the anti-diol moiety.



Scheme 1. Retrosynthetic analysis of the library of *cis*-enone RALs.

The second part of my PhD consisted in developing a general synthetic pathway to access some members of another class of potent and irreversible inhibitors called sesquiterpene lactones. The sesquiterpene lactones are a family of natural products, generally extracted from the leaves and flowerheads of the *Compositae*, with over 3000 different structures reported to date. They can, depending on their carbocyclic skeleton, be ordered in four major groups called germacranolides (most primitive class), eudesmanolides, guaianolides and pseudoguaianolides (Figure 2).

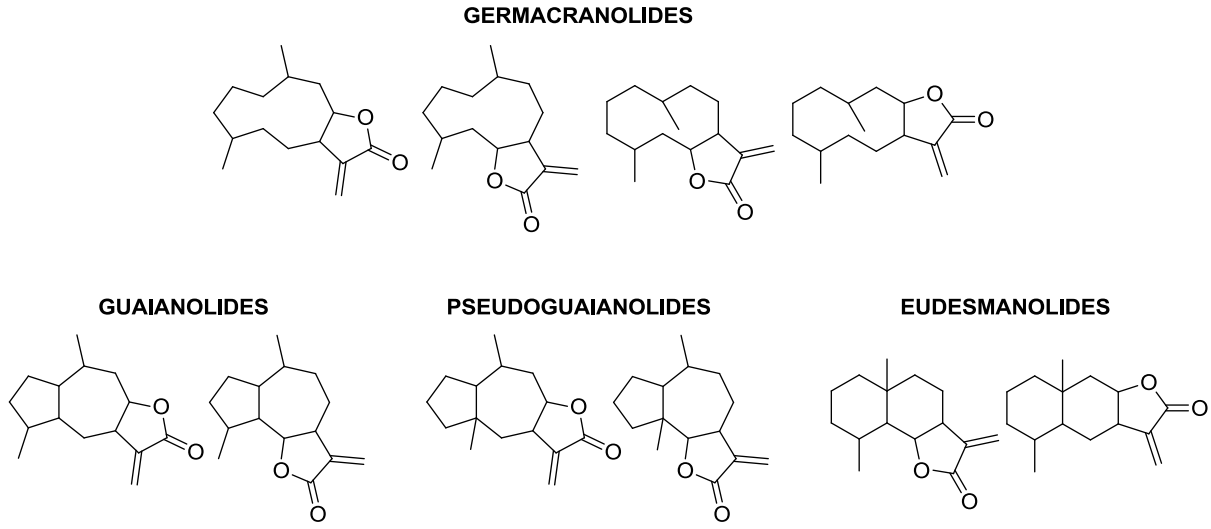
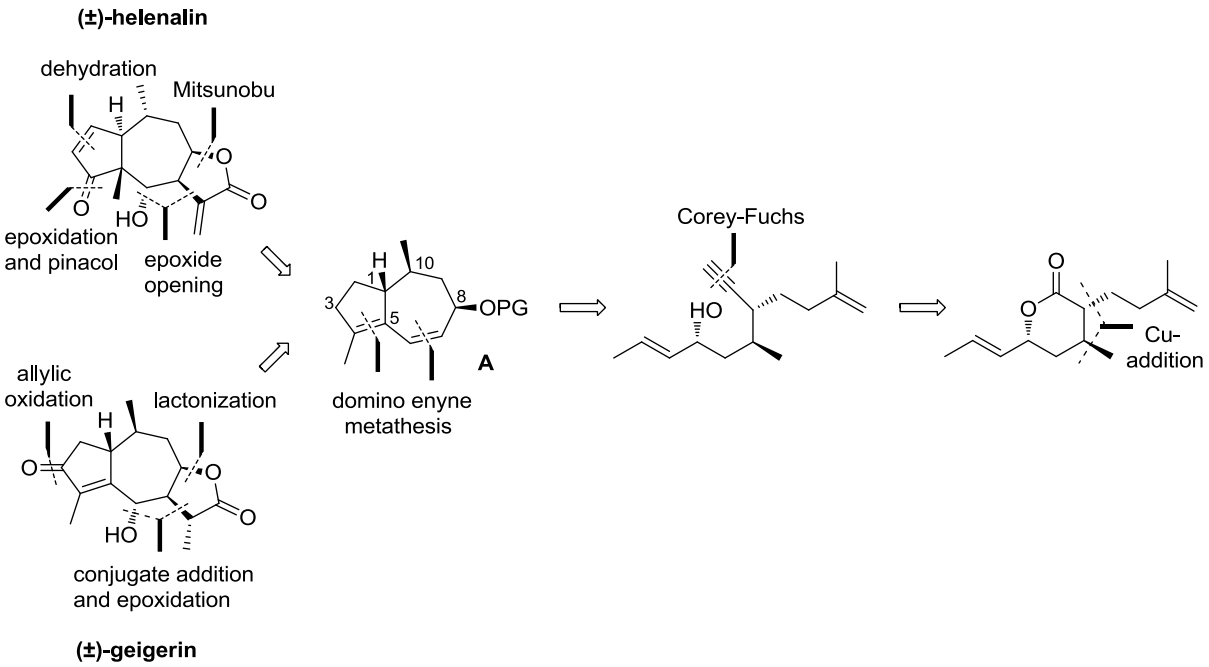


Figure 2. Skeletons of the four major groups of sesquiterpene lactones.

While their presence in plants is known to cause livestock intoxication, sesquiterpene lactones have been used in traditional medicine for centuries and proved to exhibit a wide spectrum of biological activity including cytotoxic/anti-tumor, anti-inflammatory, anti-microbial and anti-fungal properties.[10] The targets and mode of action implicated in most of these properties have not been identified, except for the anti-inflammatory activity, which has been attributed to nuclear factor

kappa-light-chain-enhancer of activated B cells (NF-κB) inhibition with well described mechanism. The NF-κB transcription factor is a central mediator of the human immune response, known to regulate the transcription of over 150 genes, and whose dysfunction is implicated among others in rheumatoid arthritis, Alzheimer's disease, or septic shocks. Sesquiterpene lactones have been proved to prevent its activation principally by reacting with the cysteine residue Cys^{38} of its p65 subunit through a Michael-type addition (there is however evidence that some other biological targets may be involved in this process).[11-13] The irreversible character and the unique level of action (compared to existing inhibitors) of NF-κB inhibition by the sesquiterpene lactones render this natural products family hardly promising for the discovery of new lead compounds for the development of anti-inflammatory drugs.

In the purpose of developing "tool compounds" such as biotin conjugates to investigate more in detail the mode of action of these compounds, and interested in preparing analogs and broadening the diversity of this pharmacophore beyond what nature provides, our laboratory decided to develop a new efficient and flexible synthetic pathway to sesquiterpene lactones. Inspired by the biogenesis, we based our strategy on a common and simple intermediate (**A**), which through various chemical transformations such as cyclizations and oxidations could lead to different members of the family. It was decided to focus on the 5/7-bicyclic framework, proved to be generally more active, and one member of each family presenting this skeleton was chosen as precise target. As shown in Scheme 2, helenalin was selected for the pseudoguaianolides and geigerin for the guaianolides. The choice of helenalin was obvious, this natural product being one of the most studied and active sesquiterpene lactones, almost every time selected as model for the biological tests. Geigerin was then selected especially because it presented the same relative stereochemistry at C_1 and C_{10} as helenalin.



Scheme 2. Retrosynthetic pathway towards the guaianes and pseudoguaianes.

Summary

Central intermediate **A** could be successfully prepared in thirteen steps, including a 1,4-cuprate addition, a reduction of the lactone, a Corey-Fuchs reaction and an enyne domino metathesis. Although such transformation had precedent, the pinacol rearrangement envisioned to functionalize the hydroazulene **A** into helenalin proved unsuccessful. This result is nevertheless not so surprising, relative stability of the carbocations having shown extremely dependant on the structure and conformation of the molecule. On the other hand, intermediate **A** could satisfyingly be converted into natural geigerin (as well as into its natural related analog 6-deoxygeigerin) in four steps, including an allylic oxidation, a one pot 1,6-conjugate addition-lactonization and an epoxidation, thus validating the strategy.

Irreversible inhibitors -

attractive candidates for drug discovery

During a screening, scientists are used to throw back hits which irreversibly bind to the target protein, these inhibitors being sometimes linked to adverse clinical events. In the case where the drug candidates are not specific, they can indeed collaterally bind to proteins other than the target of interest (target-off proteins), deoxyribonucleic acid (DNA) or glutathione (GSH), thus leading to toxicity issues such as allergic reactions, which are unfortunately difficult to predict and generally not detected before human clinical trials.[14] Covalent binding of the drug to a target-off protein can indeed be associated with conformational changes of the receptor, which because of the long duration of exposure to antigens, can be recognized by the immune system as foreign, and consequently induce an immune response. Due to the healthy debate around the irreversible inhibitors, these small molecules drug candidates are most of the time denigrated.

The irreversible inhibitors nevertheless present multiple advantages, which make them particularly attractive. First, these binders being non competitive with endogenous physiological effectors, such as the millimolar concentration of ATP (for inhibitors targeting the ATP binding pocket of kinases for example), they thus require a lower drug concentration as reversible inhibitors to achieve the same fraction of occupancy and the same response. They just require a drug concentration high enough to achieve target coverage. Then, these binders having a long residence time, they present an extended duration of efficacy.[15,16] Such molecules being not cleared by the systemic circulation, the pharmacological effects they induce can indeed only be overcome by *de novo* synthesis of new enzymes by the organism ("ultimate physiological inhibitors"). It is important to note that a long residence time of the drug on its molecular target was claimed by Copeland *et al.* to be one of the most crucial factors for sustained drug efficacy *in vivo*.[15] They among others proved the direct correlation between both parameters by taking data previously collected by Berezov *et al.* (Figure 3). The irreversible inhibitors inducing lower drug concentration, sustained effects through the dosing interval and a less frequent dosing, could then in one sense be considered as safer than reversible inhibitors.

A further attractive particularity of the irreversible binders is that they generally maintain activity against mutations. Most of the time, to protect itself from the inhibition caused by a drug, nature tends to increase the affinity of the enzyme for its primary substrate by bringing new specific interactions (by the way of mutations). Reversible inhibitors, which are in direct competition with the substrate, are destabilized by this narrow affinity and then require the use of higher drug concentrations. Inversely, irreversible inhibitors, due to their non competitiveness, are indeed insensitive to this changing. This concept can be exemplified by EGF receptor irreversible inhibitors, which proved to be as active on the mutant as on the wild type of the enzyme, both characterized by distinct affinities for ATP.[16] However, the potential benefit of irreversible inhibitors is not limited to mutations. They can also, due to their extremely long residence time, induce for the binding of a same target a completely different physiological response than reversible binders, thus resulting in different therapeutic indications. This is for example the case of aspirin (**10**, Figure 5), which targets the same enzyme (cyclooxygenase) as reversible ibuprofen inhibitor, but whose irreversible mechanism of inhibition allows in addition its use as an antiplatelet drug.[16]

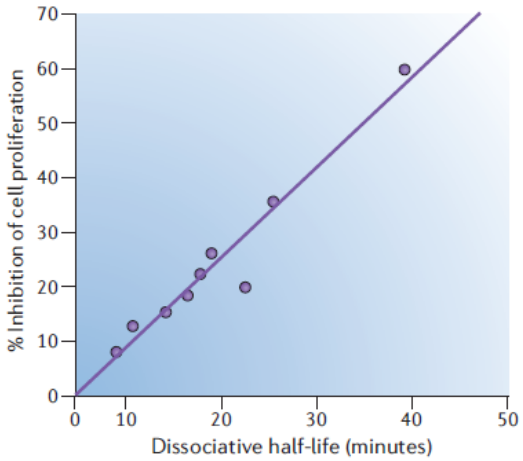


Figure 3. Correlation between the dissociative half-life of the peptide-HER2/*neu* receptor complexes and the percentage inhibition of T6-17 cell proliferation caused by addition of 1 µg/mL of the peptides. The line drawn through the data represents the least-square best fit to a simple linear equation.

Their unique characteristics render irreversible inhibitors particularly useful to identify proteins and to study their 3D structure (in particular their active site) or their cellular function.[17] The use of irreversible tagged analogs is notably a powerful method to discover new substrate-protein interactions. It among others allowed to discover the interaction of wortmannin (**5**, Figure 4) with the polo-like kinase, a kinase known to be over-expressed in various human cancers. The major application of the irreversible inhibitors nevertheless remains therapeutic. Their utility is particularly recognized in cancer or antibacterial therapeutics, for which a high target occupancy is required to be effective and prevent mutations.

It is extremely important to note that nature itself produces and uses in many ways a multitude of irreversible inhibitors. Several natural covalent binders have even been used for medicinal purposes for centuries. Examples of natural products, which irreversibly and specifically bind to proteins are depicted in Figure 4.[17] The covalent binding can engage diverse active sites in the inhibitor (carbonyl group, epoxide, electron-deficient alkene) as in the protein (serine, threonine, lysine, cysteine, histidine). Some of these natural products inhibit enzymes directly by modifying the key catalytic residue in their active site (lipstatin **1**, E-64 **2**, lactacystin **3**), some of them inhibit enzymes by modifying active-sites residues that are not essential for catalysis but whose modification results in enzyme inactivation (wortmannin **5**, fumagillin **6**, microcystin **7**), whereas the last one exceptionally targets a nonenzymatic protein (leptomycin B **4**). It is noteworthy that all these inhibitors are very specific. For example, lactacystin (**3**), which was identified as proteasome inhibitor, proved to be inefficient on other enzymes that degrade proteins: it indeed inhibits neither the serine proteases trypsin and chymotrypsin, nor the cysteine proteases papain, the calpains, or cathepsin B.

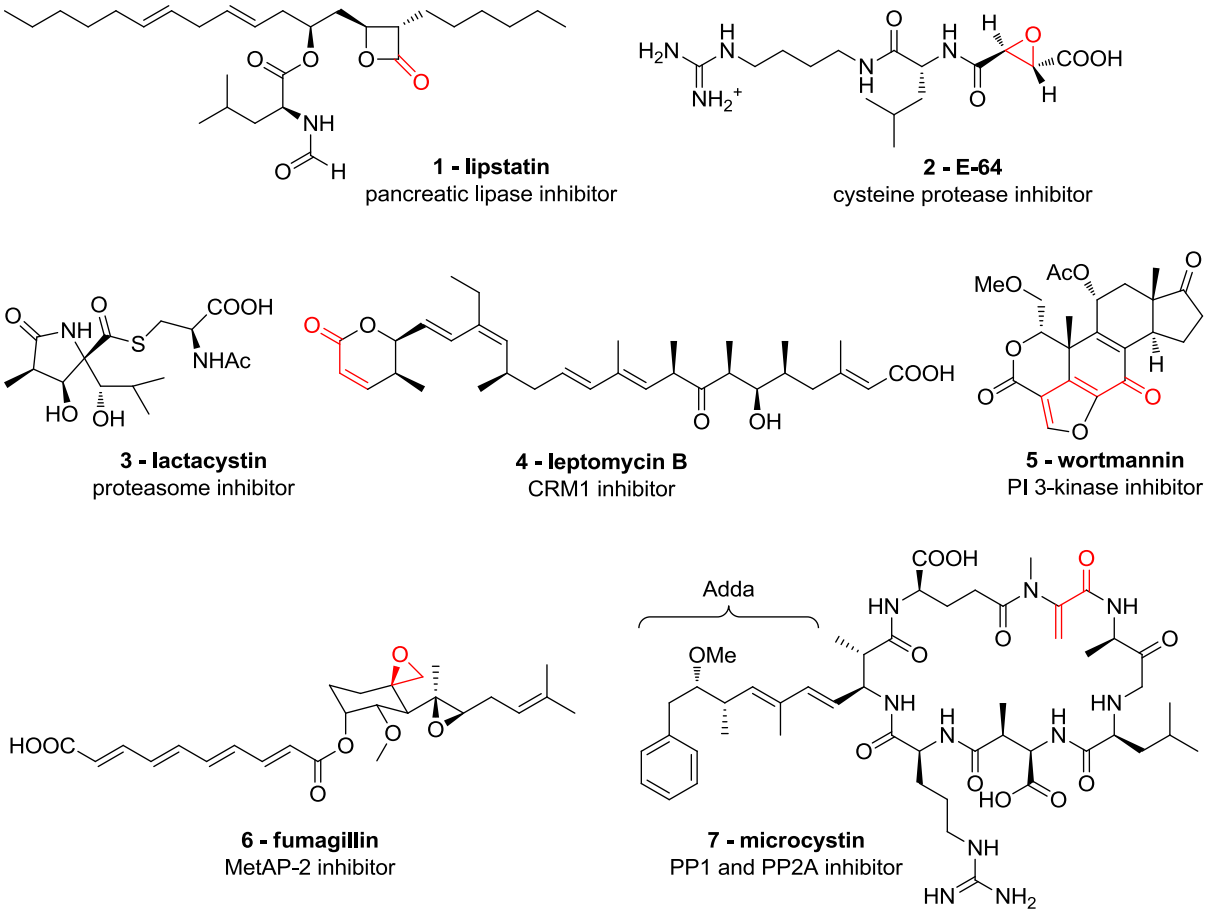


Figure 4. Natural irreversible inhibitors and their targeted protein. The reactive function of the inhibitor is indicated in red (except for the prodrug). CRM = chromosome maintenance region, MetAP = methionine aminopeptidase, PI = phosphatidylinositol, PP = serine/threonine phosphatase.

There are also numerous synthetic irreversible inhibitors being currently used as human drugs or in late stage clinical trials.[14] The most famous example is the semi-synthetic derivative of salicylic acid, aspirin (**10**), whose therapeutic benefits are known since Hippocrates (200 BC) and which is one of the most widely used remedy in the world. As shown in Figure 5, their structures are as diverse as their clinical indications. HKI-272 (**17**) is among others an inhibitor which has been shown to maintain its activity in the presence of mutations, confirming the theory evoked above.

The efficacy of the irreversible inhibitors does then no longer need to be proved. The only aspect that limits their extensive use is then their potential lack of specificity, which can as detailed above lead to allergic reactions. It is noteworthy that allergic issues are however likely to be a concern for drugs, whose off-targets are extracellular or presented on the surface of circulating cells only. Furthermore, although the broad toxicity of some irreversible inhibitors prevents their use as therapeutic agents, they remain particularly attractive for biologists to study the cell-biological activity of proteins. This is notably the case of microcystin (**7**, Figure 4), which was considered too toxic to be therapeutically prescribed (not because of a lack of specificity but because PP1 and PP2A are implicated in too many

essential functions), but which is nevertheless used to detect serine/threonine phosphatases in crude cell lysate samples, and which thus allowed for example to expand the list of this enzymes family.[17]

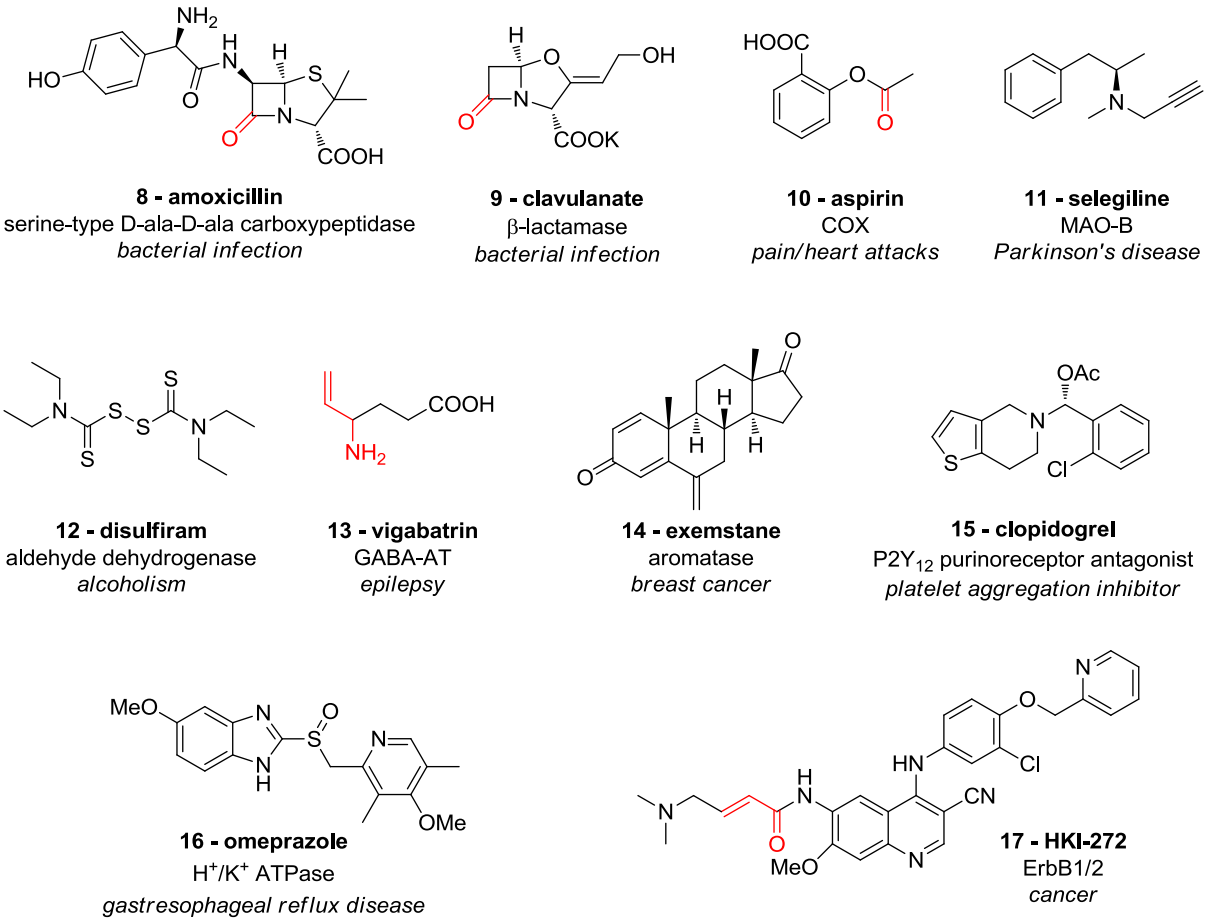
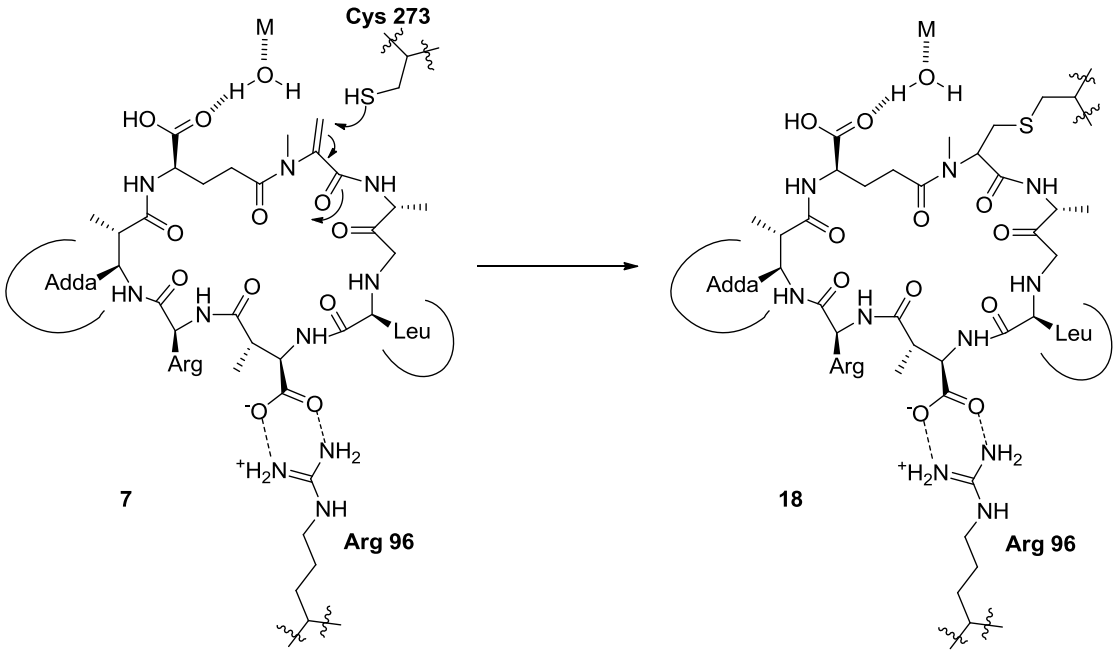


Figure 5. Structures, targets, and indications (italics) of some synthetic irreversible inhibitors currently used as drug or in late stage clinical trial. The reactive function of the inhibitor is indicated in red (except for the prodrugs). COX = cyclooxygenase, MAO = monoamine oxidase, GABA-AT = γ-aminobutyric acid aminotransferase, ErbB = epidermal growth factor receptor.

To exploit nevertheless the high clinical potential of the irreversible inhibitors, different strategies have been proposed to attenuate their toxicity. First, it has been obviously recommended to avoid the use of too reactive functionalities, such as epoxides and activated esters, which are prone to react with every nucleophilic residue. Then, it was proved that more target selectivity could be achieved by perfectly aligning the electrophile and the targeted nucleophile, *via* notably the induction of additional non covalent interactions. An optimal alignment should indeed increase the rate of inactivation of the primary target, thus favoring this interaction with regard to interactions with other solution nucleophiles. This concept was perfectly illustrated by Tauton et *al.*, who by judiciously positioning an electrophilic group on an otherwise promiscuous scaffold targeting the ATP binding site of kinases, could achieve exclusive inhibition of ribosomal S6 kinase (RSK) 1 and 2.[18] Microcystin (**7**) is a further example of how the existence of judicious non covalent interactions with

the primary enzyme (with an amino acid residue, a loop, a hydrophobic groove, and a metal) can facilitate one specific irreversible modification (Scheme 3).[17] The availability of detailed structural information such as X-ray crystallography and bioinformatics should enable the precise placement and the design in the future of selective irreversible binders.

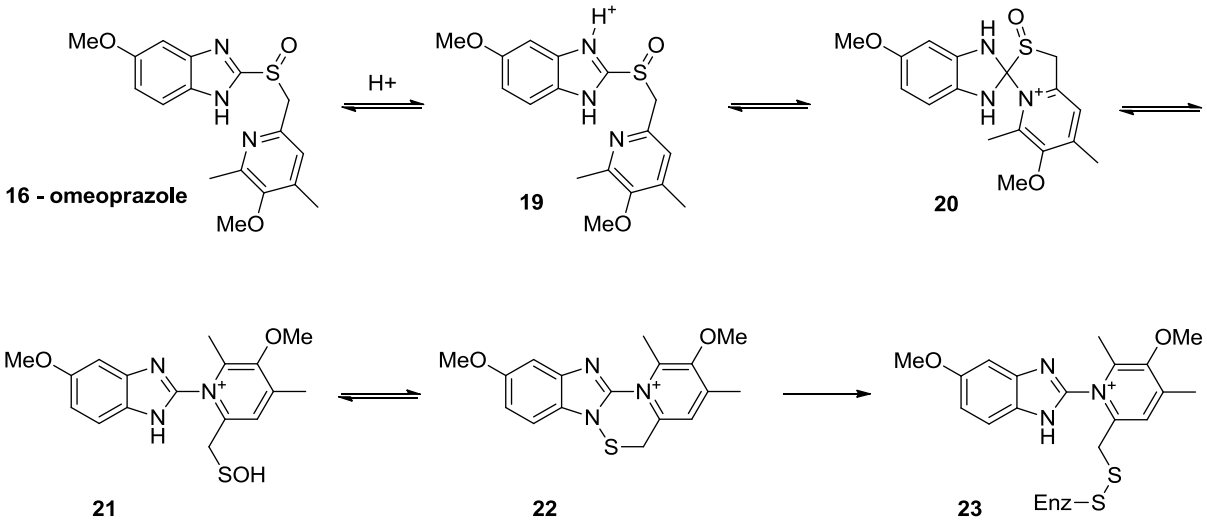


Scheme 3. Network of non covalent interactions essential for the effective conjugate addition of microcystin (**7**) to PP1.

The last strategy that is also very efficient, but more challenging, to promote selectivity is to induce the activation of the irreversible inhibitor only in the vicinity of its primary target, or only through the binding to the active site of this same target ("mechanism-based inactivators"). By this way, the activated form of the inhibitor is not exposed to the systemic circulation, thus reducing potential off-target toxicities, while maintaining the efficiency intact. This approach has been well illustrated by the use of prodrugs such as omeprazole (**16**). As depicted in Scheme 4, the electrophilic function of omeprazole (**16**) is masked until it is next to the acidic environment of the stomach, thus guarantying its exclusive interaction with the H^+/K^+ ATPase.[14]

Irreversible binders are then extremely effective inhibitors, with particularities that renders them promising as therapeutics agents, and which can contrary to the prejudices be safe if manipulated in a thoughtful way. Due to the significant role that the irreversible inhibitors played in the elucidation of proteins structure and function, Cravatt *et al.* "strongly advocate the sustained pursuit of the special pharmacological agents".[17] It is also noteworthy that there are still currently several covalent inhibitors in preclinical or early clinical investigations attesting of the potency of this drug discovery strategy.[14]

Irreversible inhibitors



Scheme 4. Inhibition of H^+/K^+ ATPase by the prodrug omeprazole (**16**).

In this manuscript, we will focus on two different families of irreversible inhibitors: the *cis*-enone resorcylic acid lactones (RALs) which are known as potent kinases inhibitors, and the sesquiterpene lactones, evaluated among others as effective transcription factor NF-κB inhibitors.

Chapter 1

Synthesis of a resorcylic acid lactones library

I. Introduction

1. Protein kinases - promising targets

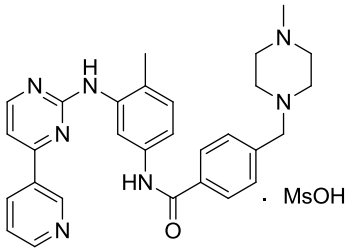
1. a. Generalities

Phosphorylation of serine, threonine and tyrosine residues is one of the most prevalent cellular mechanisms for regulating protein function. The enzymes that catalyze these phosphorylation reactions are the protein kinases: approximately 518 have been counted in the human kinome,[19] as well as a smaller set of protein phosphatases[20] which can work synergistically or concurrently at various levels in cellular pathways. Virtually every signal transduction pathway implicates kinases and as much as 30% of all human proteins may be modified by them.

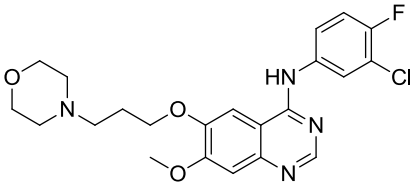
A number of pathologies ranging from oncology to inflammation and neurodegenerative diseases is attributed to a dysfunctional kinase,[1] protein kinases have thus emerged as important therapeutic targets. Several kinase inhibitors have then been proposed recently for the treatment of cancer, eleven of them having to date received FDA approval: nine are low-molecular-weight molecules presenting heteroaromatic or urea scaffold (Figure 6) and the two others, approved in 2004, are monoclonal antibodies named Bevacizumab (Avastin®, ImClone) and Cetuximab (Erbitux®, ImClone). Approximately thirty distinct kinase targets are also developed at the level of phase I clinical trials.

1. b. MAP kinases family

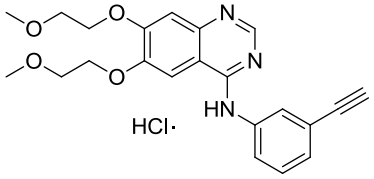
Due to its high implication in almost all cellular processes, one particularly targeted class of protein kinases is the mitogen-activated protein (MAP) kinases family. Under stress conditions (chemical and physical), MAP kinases relay and amplify signals delivered by the cell-surface receptors until the critical regulatory targets in the cells. The transmission of the signal is assured by a phosphorelay system composed of three sequentially activated kinases. In a generic fashion, a stimulus turns on the surface receptor which phosphorylates the first kinase (MAPKKK) which then phosphorylates the second kinase (MAPKK), which in turn phosphorylates the third kinase (MAPK) that finally phosphorylates regulatory targets.[21] In mammalian organisms, at least three subfamillies of MAP kinases have been identified which include the extracellular signal-regulated kinases (ERK); the c-JUN NH_2-terminal kinases (JNK); and the p38 proteins. Seven MAPKKs were counted (MEK1/2/5, MKK4/7 and MKK3/6) and at least seventeen MAPKKKs (each MAPKK can be activated by more than one MAPKKK). To allow a precise cellular response to the infinity of extracellular stimuli that exists by this comparatively small number of MAP kinases, the activation and the function of the MAPKs have to be very specific.[3]



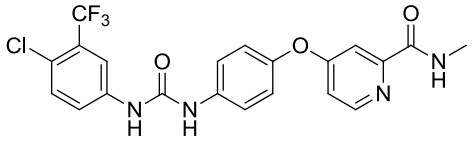
24 - Imatinib melisate (**Gleevec®**),
Novartis, 2001.
BCR-ABL, KIT, PDGFR



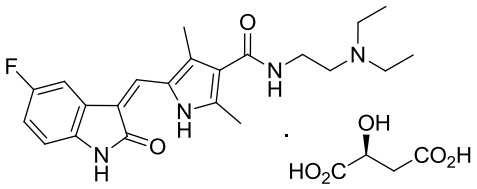
25 - Gefitinib (**Iressa®**),
Astra-Zeneka, 2003.
EGFR



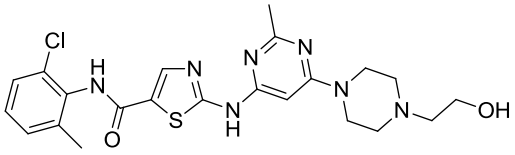
26 - Erlotinib hydrochloride (**Tarceva®**),
OSI Pharms, 2004.
EGFR



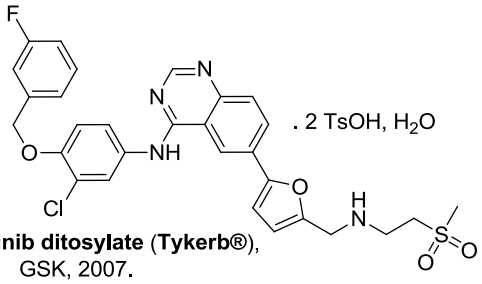
27 - Sorafenib (**Nexavar®**),
Bayer Pharms, 2005.
BRAF, KIT, PDGFR-β, VEGFR2



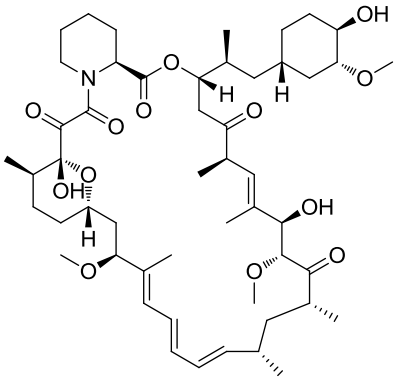
28 - Sunitinib malate (**Sutent®**),
Pfizer, 2006
KIT, PDGFR-β, VEGFR2



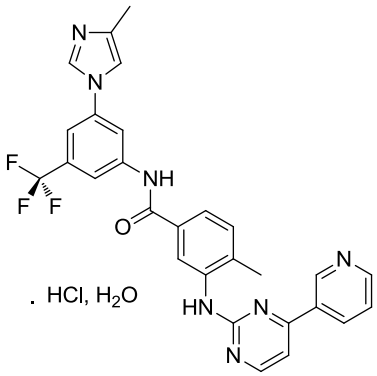
29 - Dasatinib (**Sprycel®**),
Bristol-Myers Squibb, 2006.
Src family, ABL1, KIT, PDGFR, Eph



30 - Lapatinib ditosylate (**Tykerb®**),
GSK, 2007.
EGFR, ErbB2



31 - Temsirolimus (**Torisel®**),
Wyeth Pharms, 2007.
mTOR



32 - Nilotinib hydrochloride monohydrate
(**Tasigna®**), Novartis, 2007.
BCR-ABL, PDGF-R, KIT

Figure 6. Food and drug administration (FDA)-approved small molecule kinase inhibitors.

The specificity during the activation is guaranteed among others by scaffolding proteins which organize and localize the three components of the cascade, or by the existence of sequential physical interactions between members of a given cascade. The specificity during the recognition of the target is then on one hand guaranteed by a bipartite enzyme-substrate interaction: MAPKs naturally

recognize the phosphoacceptor sites and the amino acids around but also a distinct site on the target thus limiting the phosphorylation of irrelevant substrates, and on the other hand by the fact that activating kinases and their substrates generally colocalize within the cell.

Phosphorylation of proteins by the MAP kinases induces important processes like genes expression, cell proliferation and cell survival or apoptosis.[3] To control genes expression, MAP kinases for example target nucleic transcription factors pre-bound to DNA or cytoplasmic proteins involved in post-transcriptional mechanisms like messenger ribonucleic acid (mRNA) stabilization, whereas to induce cell proliferation they generally stimulate DNA synthesis or promote cell-cycle progression by inactivating cell-cycle inhibitory kinases. However, although the functions of the MAPKs are globally known, the exact nature of their substrates (except for the transcription factors) remains undetermined. Identifying MAP kinases inhibitors is then not only interesting from a therapeutic point of view, but should also allow the dissection of these complex networks and the identification of individual MAP kinases regulatory target.

2. The *cis*-enone resorcylic acid lactones

2. a. Potent irreversible MAP kinases inhibitors

Resorcylic acid lactones (RALs) bearing a suitably positioned *cis*-enone such as hypothemycin (**33**), LL-Z1640-2 (**34**), L-783277 (**35**) (Figure 7) have been proved to be potent MAP kinases inhibitors.[2,22]

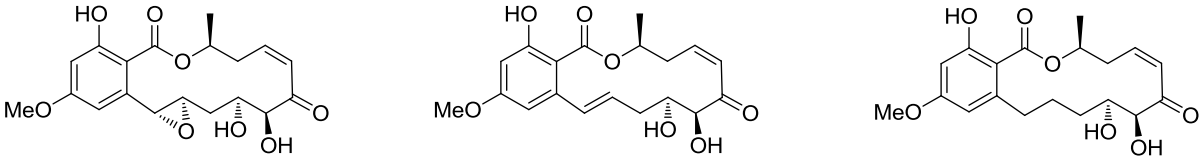


Figure 7. Selected members of the *cis*-enone RALs.

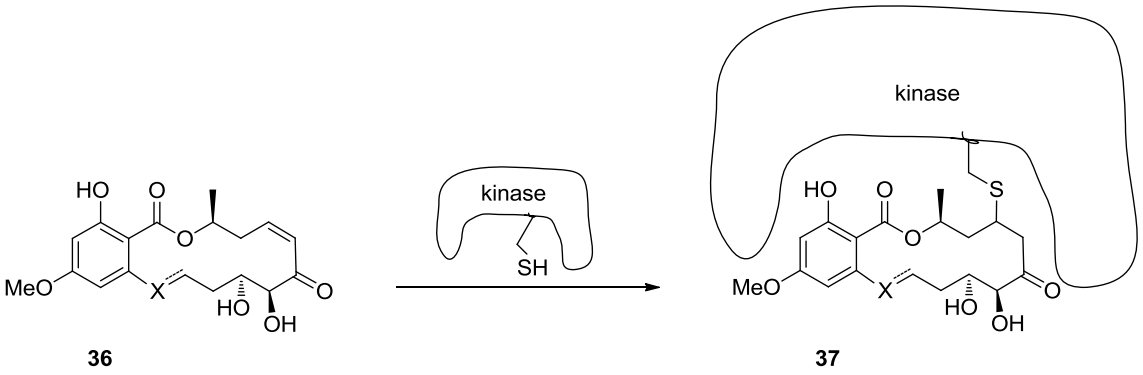
LL-Z1640-2 (**34**) was the first *cis*-enone RAL reported (1978) from an unidentified fungus named Lederle culture Z1640. Since the authors did not note any particularly interesting activity (devoid of anabolic and estrogen-like activity), this natural product was left aside for a while.[23] In 2003, it was rediscovered in a screen for transforming growth factor β-activated protein kinase 1 (TAK1) inhibition, by presenting an IC_{50} of 8.1 nM against this MAPKKK involved in the p38 signalling cascade for proinflammation signals such as cytokines.[24] In 2007, this compound was also proved to be a potent irreversible inhibitor of ERK2 (MAPK) with an IC_{50} of 80.0 nM and MKK7 (MAPKK), thus leading

to an effective inhibition of both activator protein 1 (AP-1) activation pathways, a transcription factor implicated in tumor promotion.[25]

L-783277 (**35**), reported first in 1999 from organic extracts of *Phoma sp*. (ATCC 74403) by researchers at Merck, was described as a potent and irreversible inhibitor of MEK (4 nM).[26] Only a weak inhibition against Lck kinase was reported (750 nM), whereas proto-oncogene serine/threonine protein kinase (RAF), protein kinases C and A (PKC, PKA) proved completely uninhibited.

Hypothemycin (**33**), initially reported in 1980 from a strain of *Hypomyces tricothecoides*, was in turn reported by the same authors as an inhibitor of MEK (15 nM). It was reported in parallel that this compound inhibits Rat sarcoma (*ras*)-signaling pathway and tumor growth in animal model[27] as well as the production of several cytokines.[28] It was later found to inhibit several oncogenic cell lines dependent on kinase activation.[4]

The high inhibitory activity of the *cis*-enone RALs is all the more attractive as, as evoked in the introduction, the inhibition induced by these compounds is irreversible, allowing thus a long and efficient inhibition using only small doses.[15] The inhibition of B-RAF V600E mutant cell line by 1 µM of hypothemycin (**33**) appeared for example to be still quite complete after 24 h.[4] This irreversible inhibition has been attributed to a Michael addition onto the α,β-unsaturated ketone of the polyketide by a cysteine residue present in the ATP binding pocket of a subset of kinases (Scheme 5).



36 **37**

Scheme 5. Irreversible inhibition of kinases by the *cis*-enone RALs.

The bases of this mechanism were first suggested thanks to a structure-activity relationship (SAR) study performed by researchers from Merck on L-783277 (**35**), in which they highlighted the crucial role played by the *cis*-enone funtionality on activity by demonstrating that the *trans*-isomer and the reduced form of the ketone were significantly less active.[26] They also introduced the concepts of time-dependent inhibition, competitiveness with ATP and irreversibility.

All these informations caught Santi *et al.* attention, who then suspected a covalent bound formation between the Michael acceptor and a cysteine residue.[4] By performing a structural-bioinformatics

study (alignment of the sequences), they could identify the targeted cysteine residue (Cys^{166}) within the ATP binding site.

The tool which undoubtedly confirmed the proposed mechanism is the resolution of the co-crystal structure by Nakajima *et al.* in 2007 of LL-Z1640-2 (**34**) bound in the nucleotide site of human ERK2 (Figure 8),[25] as well as the recent co-crystal structure by Rastelli *et al.* of hypothemycin (**33**) bound in the nucleotide site of rat ERK2 (Figure 9).[29] These crystals highlighted, in addition to the covalent bound to Cys^{166}, the significant presence for molecular recognition of four hydrogen bounds and van der Waals interactions.

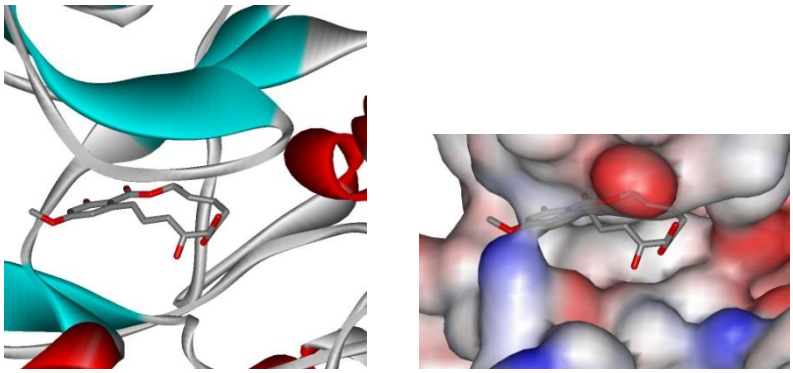


Figure 8. Co-crystal structure of LL-Z1640-2 (**34**) bound to human ERK2 (pdb ID: 2E14, 3.0 Å resolution crystal structure). [Images generated by Weblab from PDB data]

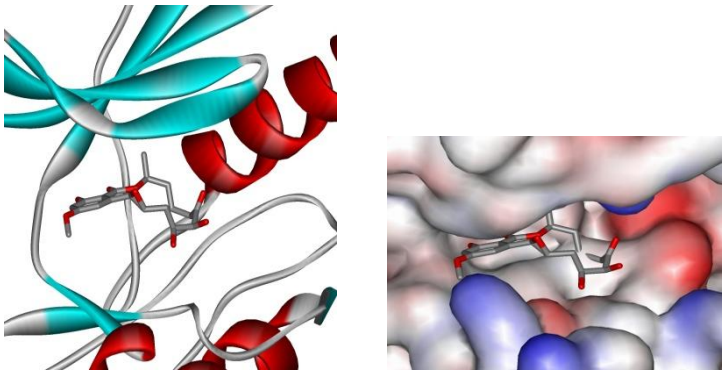


Figure 9. Co-crystal structure of hypothemycin (**33**) bound to rat ERK2 (pdb ID: 3C9W, 2.5 Å resolution crystal structure). [Images generated by Weblab from PDB data]

The other particularity which renders the *cis*-enone RALs attractive as kinase inhibitors is that they exhibit some levels of selectivity. For example, while LL-Z1640-2 (**34**) proved to be a potent inhibitor of TAK1, other MAP kinases such as MEK1 appeared to be 50 fold less inhibited by this compound (411nM), whereas MEKK1, ASNK and MKK4 proved unaffected at all.[24] The major cause of the *cis*-enone RALs selectivity is that only 46 of the 518 putative kinases contain the cysteine residue revealed by Santi *et al.* at the adequate position 166 (kinases which do not bear this residue, or

which bear a cysteine residue at another position proved incapable of reacting covalently with the inhibitor).[4] Owing to this filter, the number of kinases that may be inhibited by the *cis*-enone RALs compared to some multiple kinases inhibitors of current interest is small. It is noteworthy that several of the previous 46 kinases are implicated in very important pathways (like mitogen receptor tyrosine kinase, ERK and MEK), making their inhibition of high therapeutic interest. The reaction of the *cis*-enone RALs with the kinases bearing the Cys^{166} proved to be 10^5 to 10^7 faster than the reaction of RALs with small thiols and other thiols-containing proteins, attesting that these compounds can be used in biological environment. Interestingly, it appears that discrimination through the previous 46 kinases could even be achieved. Glycogen synthase kinase 3 (GSK3-α), which bears the Cys^{166} residue, proved for example uninhibited by hypothemycin. A non suitable juxtaposition of the *cis*-enone with the cysteine residue, induced by the replacement of the Met106 (methionine) residue by a proline in the peptide backbone, was evoked to justify the non-formation of the covalent bond. A wide range of k_{inact}/Ki values having been noted for diverse kinases in the presence of hypothemycin, selectivity through the 46 previous kinases could also be achieved by modulating the exposure time of the substrate to the inhibitor.[4]

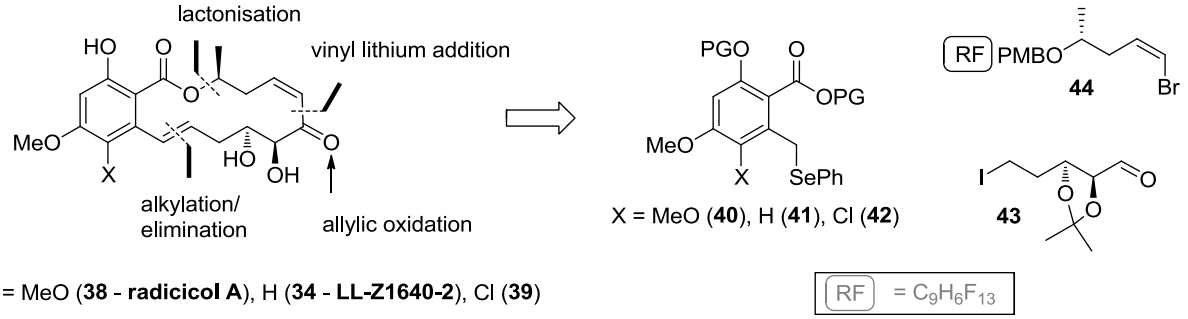
2. b. Modular total synthesis of radicicol A

Radicicol A (**38**, Scheme 6) is a *cis*-enone RAL reported in 1996 from the fungus strain F/87-2509.04 by researchers from Sandoz during a screen for interleukin-1 beta (IL-1β) inhibition. Following this discovery, the authors investigated the mode of action of this natural product. After observing a decrease of IL-1β mRNA levels and a significant reduction of mRNA half life in cells treated with radicicol A, they concluded that this compound accelerated mRNA degradation but revealed that only genes containing specific sequences including AU-rich elements (AREs) were affected.[30,31] They further demonstrated that this effect did not come from a direct disruption of protein/RNA binding or from the state of phosphorylation of protein/RNA complex at the AREs. Since radicicol A was found to inhibit tyrosine phosphorylation of a number of proteins, they finally proposed that radicicol A might influence post-translational phosphorylation level of proteins which interact with AU-binding proteins. Despite all these data, the precise molecular target of radicicol A could not be identified.

By analogy with the biological activities that have been previously reported for other *cis*-enone RALs, our laboratory anticipated radicicol A (**38**) to be an inhibitor of MAP kinases. A different selectivity profile than LL-Z1640-2 (**34**), L-783277 (**35**) or hypothemycin (**33**) was nevertheless expected. To be able to evaluate its kinase inhibitory activity, our laboratory elaborated the first total synthesis of radicicol A (**38**) and two related analogs (**34**, **39**).[5]

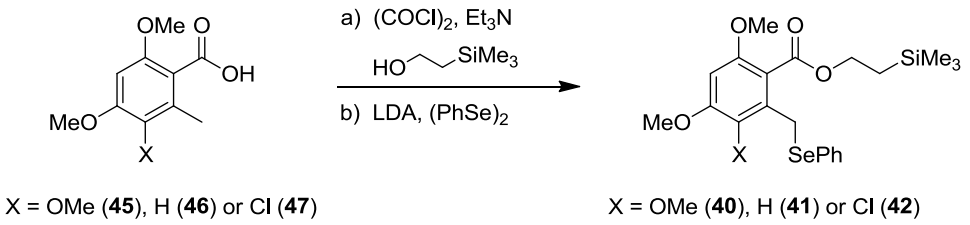
The disconnections that were chosen are summarized in the retrosynthetic Scheme 6. The challenge of this synthesis was to control the *cis*-geometry of the enone, investigations on the natural product having suggested that the *trans*-isomer, although significantly less active, was the thermodynamically favored one.[26] It had thus been decided to reveal the enone only at a late stage through a selective

allylic oxidation and the *cis*-alkene through a vinyl lithium addition onto an aldehyde. The molecule was disconnected into three fragments of same complexity: **40**-**42**, **43** and **44**. Although the order of coupling of these fragments could have been possible in all permutations, it had been decided to start the sequence with the coupling of **43** + **44** to allow the use of a fluorinated protecting group for the alcohol **44**, and thus the use of the fluorous isolation technology,[32,8] until the penultimate cyclization (this technology will be developed in a following section).



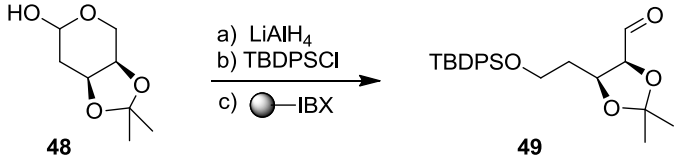
Scheme 6. Retrosynthetic disconnection of radicicol A and two related analogs.

As shown in scheme 7, the preparation of the aromatic fragments **40**-**42** was efficiently achieved in two steps from the different acids **45**-**47** by esterification with 2-trimethylsilylethanol followed by formation of the selenide via LDA deprotonation of the benzylic position and reaction with diphenydiselenide. Several protecting groups had been tested for the *ortho*-phenol (MOM, EOM, PMB), but although they all proved suitable in the case of the 2,4-dihydroxy substitution, they proved unstable in the case of the 2,4,5-trihydroxysubtituted aryl ring. The presence of the 5-methoxy substituent indeed renders any acid labile protecting group at the 2-position particularly sensitive to acids and more generally, makes this aryl moiety prone to oxidation. It was then decided to use a methyl ether, which appeared to be selectively cleavable using boron trichloride for all three aromatic systems.



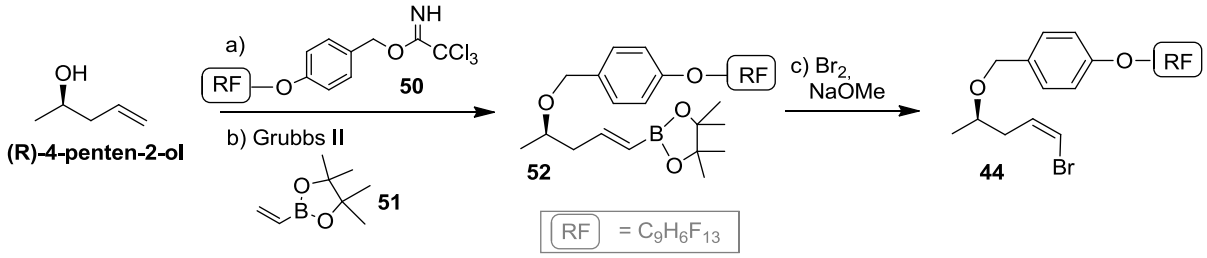
Scheme 7. Aryl moieties synthesis. a) $(COCl)_2$ (1.0 equiv), DMF (cat), CH_2Cl_2, 0 °C, 1 h; then TMSEOH (1.0 equiv), Et_3N (2.6 equiv), DMAP (cat), 23 °C, 1 h, 96-98%; b) LDA (2.0 equiv), $(PhSe)_2$ (1.0 equiv), THF, -78 ° C, 1 h, 89-91%. DMAP = 4-dimethylaminopyridine, DMF = N,N-dimethylformamide, LDA = lithium diisopropylamide, THF = tetrahydrofuran, TMSEOH = 2-trimethylsilylethanol.

Intermediate **49** with the iodide masked in the form of a silyl-protected hydroxyl was then conveniently obtained from acetal-protected 2-deoxy-D-ribose **48** in three steps (Scheme 8). The sequence started with the reduction using $LiAlH_4$ of protected 2-deoxy-D-ribose[33] (obtained in one step), the resulting crude reaction was then selectively silylated on the sterically less hindered alcohol using TBDPSCl (>15:1 selectivity) in the presence of imidazole before oxidizing the remaining alcohol with an immobilized version of IBX.[34] Thus obtained aldehyde **49** was used in the next reaction without workup or further purification.



Scheme 8. Anti-diol moiety synthesis. a) $LiAlH_4$ (1.4 equiv), THF, 0 to 23 °C, 2 h, 95%; b) TBDPSCl (1.0 equiv), imidazole (1.5 equiv), DMF, 23 °C, 2 h, 66%; c) PS-IBX (3.0 equiv), CH_2Cl_2, 23 °C, 2 h, quant. DMF = N,N-dimethylformamide, IBX = 2-iodobenzoic acid, PS = polystyrene, TBDPSCl = *tert*-butyldiphenylsilyl chloride, THF = tetrahydrofuran.

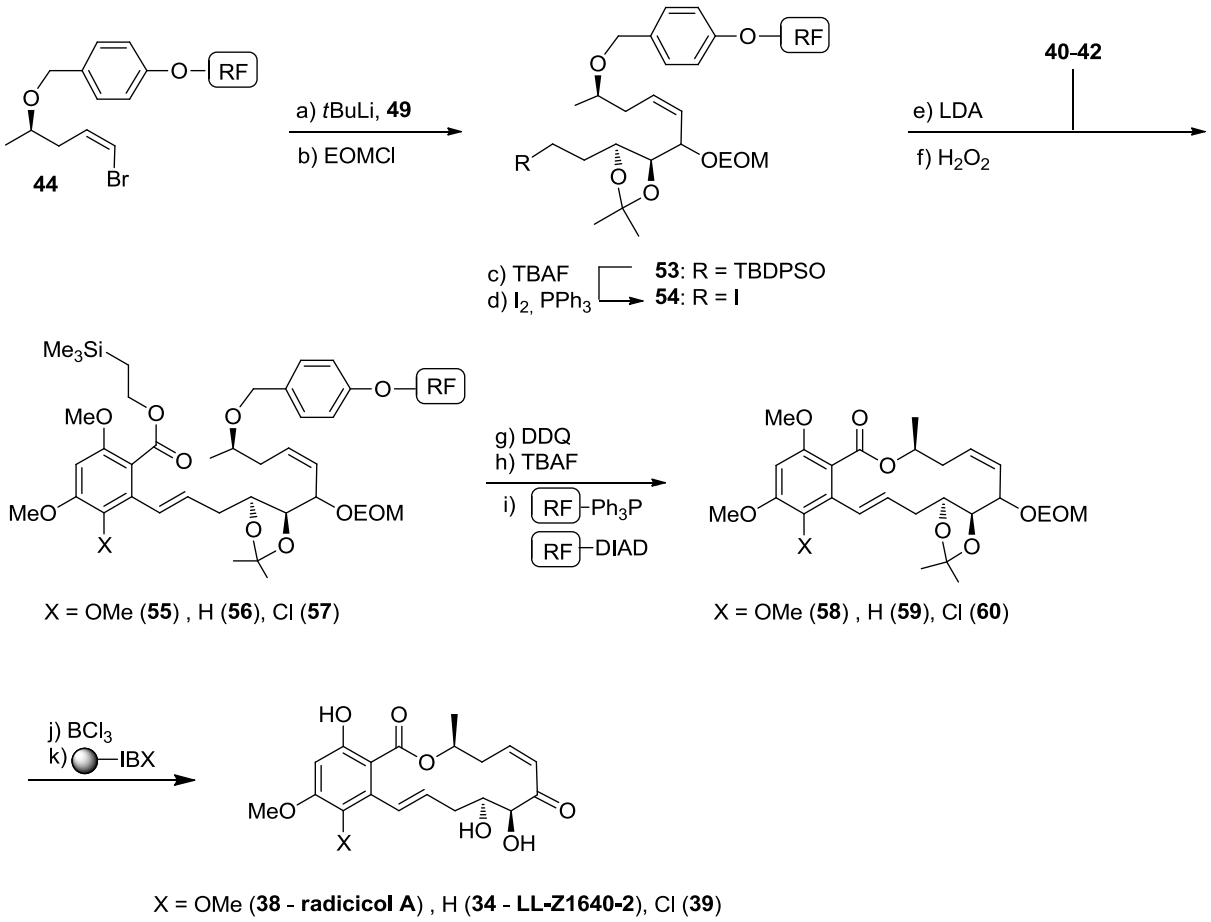
The last fragment, the vinyl halide **44**, was prepared in three steps from commercial (R)-4-penten-2-ol (Scheme 9). The alcohol was first protected with a fluorous version of PMB trichloroacetamidate **50**,[35,36] before being engaged in a cross metathesis reaction using vinyl borolane **51** and second-generation Grubbs catalyst to afford the *trans*-vinyl borolane **52**[37] in excellent yield and stereoselectivity (>20:1 *E*:*Z*). *Trans*-vinyl borolane **52** was finally stereospecifically converted to the desired *cis*-vinyl bromide **44** in excellent yield using Brown's protocol.[38]



Scheme 9. Vinyl halide synthesis. a) **50** (1.0 equiv), CSA (0.1 equiv), CH_2Cl_2, 23 °C, 12 h, 92%; b) **51** (2.0 equiv), Grubbs II (0.025 equiv), toluene, 80 °C, 12 h, 92%; c) Br_2 (1.0 equiv), Et_2O, -20 °C, 10 min; then NaOMe (2.2 equiv), -20 °C, 30 min, 89%. CSA = camphorsulfonic acid.

The three fragments in hand, the assembly started as explained above by the coupling of the *cis*-vinyl halide **44** with the crude aldehyde **49** through a transmetalation using *t*BuLi (Scheme 10). Thus recovered alcohol was protected using EOMCl to afford the intermediate **53** as a mixture of diastereoisomers in a 3:1 ratio; the lack of stereoselectivity was however inconsequential as this

center had to be ultimately oxidized to the ketone. Silyl-protected hydroxyl group was then converted to the iodide to afford compound **54** which was coupled in excellent yield with the three different aromatic fragments **40-42** by alkylation using LDA. Oxidation and *syn*-elimination of the selenide thus afforded compounds **55-57**. Thanks to the fluorinated protecting group, this reaction sequence did not require a single traditional work up, the crude reaction mixtures having simply been loaded on fluorous silica columns, eluted with 75% MeOH in H_2O to remove all non-fluorous tagged components and washed with MeOH to recover the desired compounds (**44**, **52-57**).



Scheme 10. Radicicol A (**38**) and its two related analogs (**34**, **39**) synthesis. a) *t*BuLi (2.0 equiv), THF/Et_2O, -100 °C, 15 min; then **49** (1.0 equiv), -100 °C, 15 min, 88%; b) EOMCl (8.0 equiv), iPr_2NEt (8.0 equiv), TBAI (cat), DMF, 23 °C, 12 h, 96%; c) TBAF (2.5 equiv), THF, 23 °C, 12 h, 92%; d) PPh_3 (1.5 equiv), I_2 (1.5 equiv), imidazole (2.5 equiv), THF, 0 °C, 1 h, 91%; e) **40-42** (1.0 equiv), LDA (2.0 equiv), THF/HMPA (10/1), -78 °C, 20 min, 88-91%, f) H_2O_2 (2.0 equiv), THF, 23 °C, 2 h, 79-82%; g) DDQ (1.2 equiv), CH_2Cl_2/H_2O (2/1), 23 °C, 2 h, 77-80%; h) TBAF (3.0 equiv), THF, 23 °C, 2 h, 87-88%; i) RF-Ph_3P (2.0 equiv), RF-DIAD (2.0 equiv), toluene, 23 °C, 2 h, 80-81%; j) BCl_3 (3.0 equiv), CH_2Cl_2, 0 °C, 15 min, 82-88%; k) PS-IBX (3.0 equiv), CH_2Cl_2, 23 °C, 1 h, 86-92%. DIAD = diisopropyl azodicarboxylate, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, EOMCl = chloromethyl ethyl ether, HMPA = hexamethylphosphoramide, IBX = 2-iodobenzoic acid, LDA = lithium diisopropylamide, PS = polystyrene, TBAF = tetrabutylammonium fluoride, TBAI = tetrabutylammonium iodide, TBDPS = *tert*-butyldiphenylsilyl, TMS = trimethylsilyl.

PMB group and 2-(trimethylsily)ethyl ester were then removed by successive treatment with DDQ and TBAF, thus affording the corresponding hydroxyacids, which were engaged in a Mitsunobu reaction using fluorous-tagged PPh_3 and DIAD to yield the macrocycles **58-60** (purification of PMB deprotection and Mitsunobu reactions were performed using fluorous solid phase extraction). Further deprotection of the *ortho*-phenol, the EOM and the acetonide groups in one step using BCl_3 afforded the fully deprotected allylic alcohols, which were finally oxidized to the α,β-unsaturated ketone using immobilized IBX.[34] Surprisingly, the outcome of this last reaction proved to be sensitive to the substitution pattern on the aryl ring. As a matter of fact, whereas radicicol A (**38**) and the chlorinated analog **39** were obtained as single product in nearly quantitative yield, the oxidation of the two different diastereoisomers of the allylic alcohol corresponding to LL-Z1640-2 (**34**) gave different outcomes. While the less polar minor isomer led cleanly to the desired LL-Z1640-2 (**34**) in 86% yield with a similar NMR profile that reported in the litterature,[39, 40] the major isomer afforded the mono-oxidized product resulting from the oxidation of the hydroxyl group γ to the alkene. Similar observations were noted by Altmann *et al.* during the first total synthesis of L-783277 (**35**).[41]

This first total synthesis of radicicol A (**38**), elaborated by the Dr. Pierre-Yves Dakas, allowed to prepare this natural product through a predominantly linear sequence of fourteen steps with an overall yield of 17%.

The motivation that led our laboratory to elaborate this synthesis was the evaluation of radicicol A's kinase inhibitory activity and its selectivity. Radicicol A (**38**), LL-Z1640-2 (**34**) and the chlorinated analog **39** as well as their corresponding allylic alcohols had then been tested *in vitro* against a panel of 24 kinases (Table 1). As expected, radicicol A (**38**) exhibited a potent inhibitory activity (low nM) against VEGFR2, VEGFR3, FLT3 and PDGFR-β. However, radicicol A's 5-methoxy aryl substitution appeared to make the 2-hydroxy aryl moiety prone to oxidation to the corresponding quinone, making this natural product less attractive from a therapeutic perspective. The same transformation has been observed for compounds related to LL-Z1640-2 (**34**) but using stronger oxidizing agents such as *m*CPBA. On the other hand, as for RALs such as pochonins C and D, substitution of the 5-methoxy by the chlorine atom proved to completely prevent the quinone formation. The chlorine analog **39**, although slightly less active, was then selected for a second evaluation on a huge panel of 127 kinases.

	AKT1	ARK5	Aurora-A	Aurora-B	B-RAF VE	CDK2/CycA	CDK4/CycD1	CK2-α1	FAK	EPHB4	ERBB2	EGF-R	IGF1-R	SRC	VEGF-R2	VEGF-R3	FLT3	INS-R	MET	PDGFRβ	PLK1	SAK	TIE2	COT
radicicol A **(38)**									9 100				9 600	26	66	110			210					
LL-Z1640-2 **(34)**				6 300									6 600	52	110	170			340					
Cl-analog **39**														90	210	1 800			370					

Table 1. IC_{50} proflile (nM) against a panel of 24 therapeutically relevant kinases (AKT1, ARK5, Aurora-A, Aurora-B, B-RAF VE, CDK2/CycA, CDK4/CycD1, CK2-α1, FAK, EPHB4, ERBB2, EGF-R, SRC, VEGF-R2, VEGF R3, FLT3, INS-R, MET, PDGFR-β, PLK1, SAK, TIE2, COT). Empty fields: IC_{50} > 100000 nM.

The activity of this analog thus appeared to be quite selective (nM range) for therapeutically important kinases such as MEK1, VGEFR2 and 3, and to a lesser extent PDGFR-α and -β (Figure 10).

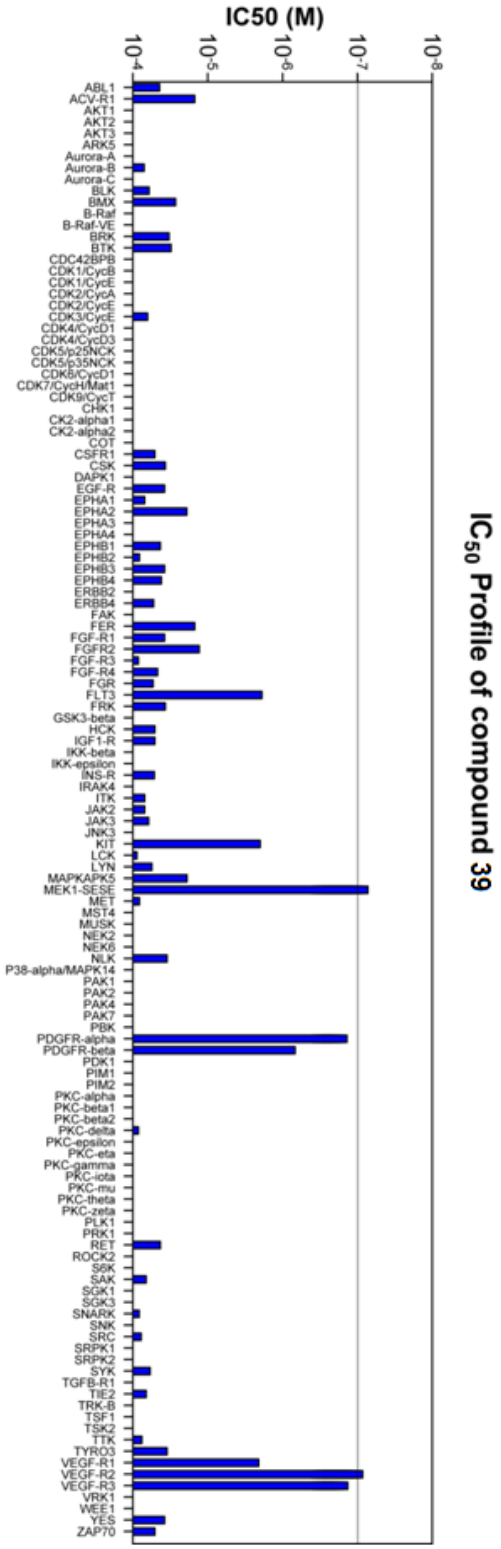


Figure 10. Half maximal inhibitory concentration (IC_{50}) profile of the chlorinated analog **39**.

Low µM inhibition was also observed to kinases such as FLT3, KIT and VEGF-R1 which bear a cysteine in the active site. It was noteworthy that while all inhibited kinases possessed a cysteine residue in their active site, not all of them were inhibited (for example GSK3-β), confirming the existence of a discrimination amongst the subset of potential kinases and the fact that unique interactions with the target are necessary for the Michael addition to proceed.

The potential efficacy of this compound had then been assessed in cell by measuring the level of VEGF-R2 autophosphorylation in the presence of its ligand ($VEGF_{165}$). Immortalized human umbilical vein endothelial cells (HUVECs) known to express high levels of VEGF-R2 had been incubated with inhibitor **39** for 90 min before being stimulated with $VEGF_{165}$ for 7 min. The level of autophosphorylation had been measured by enzyme-linked immunosorbent assay (ELISA) using anti-VEGF-R2 as capture antibody and anti-phosphotyrosine as detection antibody. As shown in Figure 11, compound **39** was found to have a cellular IC_{50} of 440 nM which is consistent with its inhibition at the enzymatic level (90 nM), whereas PDGFR-β autophosphorylation was mildly inhibited (IC_{50} =13 µM) and angiopietin receptor TIE2 autophosphorylation was unaffected.

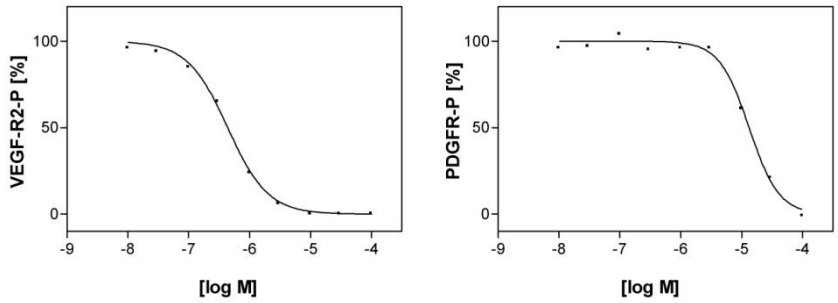


Figure 11. Cellular inhibition of VEGF-R2 and PDGFR-β autophosphorylation upon stimulation with their cognate ligand after preincubation with the chlorinated analog (the y-axis represents the percentage of phosphorylation compared to maximal phosphorylation in the absence of inhibitor).

Through a succession of biological evaluation tests, our laboratory has been able to demonstrate that radicicol A (**38**) is a potent inhibitor of key kinases involved in MAPK cascades. MAP kinases being know to play a role in the regulation of protein translation by controlling the stability of specific *m*RNAs,[42,43] this discovery rationalizes the decrease of Il-1β mRNA levels observed by researchers from Sandoz in the presence of radicicol A (**38**). These biological results showed especially that a significant level of selectivity can be achieved within the subset of 46 kinases bearing the cysteine residue at the right position in the active site, as already suggested by the works of Santi et *al.* showing the existence of kinetic differences of inactivation amongst this subset of kinases by hypothemycin (**33**),[4] or by the difference in activity inhibition observed between L-783277 (**35**)[26] and LL-Z1640-2 (**34**)[24] for the same kinase (MEK1, 100 folds).

In the purpose of enhancing the selectivity of these irreversible kinase inhibitors, promising as lead structure for the design of selective kinase inhibitors and as chemotherapeutic agents, our laboratory decided to extend this scaffold beyond what nature provides by elaborating a library of *cis*-enone RALs.

II. Diversity oriented synthesis of the *cis*-enone scaffold

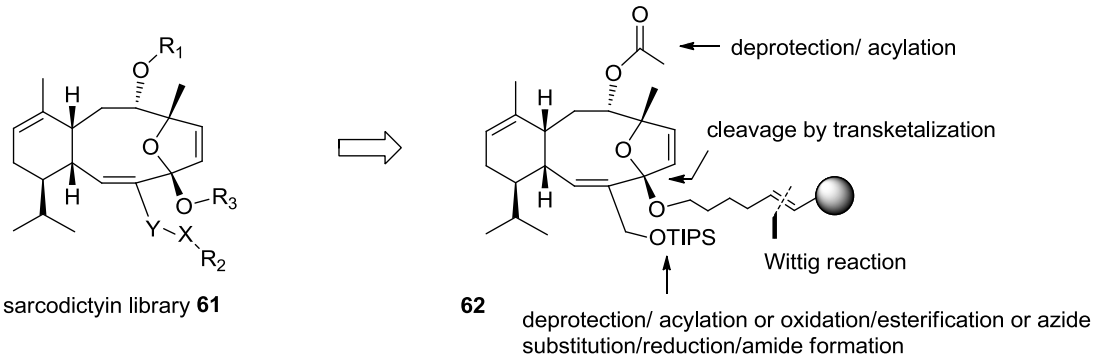
1. Main technologies available for the synthesis of libraries

1. a. Solid phase synthesis

Solid phase technique was originally developed to make the highly repetitive nature of amide bound formation and phosphoramidate couplings of peptides and oligonucleotides synthesis respectively less painful. However, the tremendous progresses made in this domain over the past ten years, such as the report of numerous new linkers, has encouraged chemists to apply it to the synthesis of complex natural products (ranging from alkaloids to polyketides and terpine derives secondary metabolites), as well as to the preparation of libraries. The main advantage of solid phase synthesis is its facile automation.

The elaboration of a library of compounds inspired by a natural scaffold on solid phase can be driven by various manners: by immobilizing a natural product core structure, by using immobilized reagents, or by performing the natural product total synthesis on solid phase.

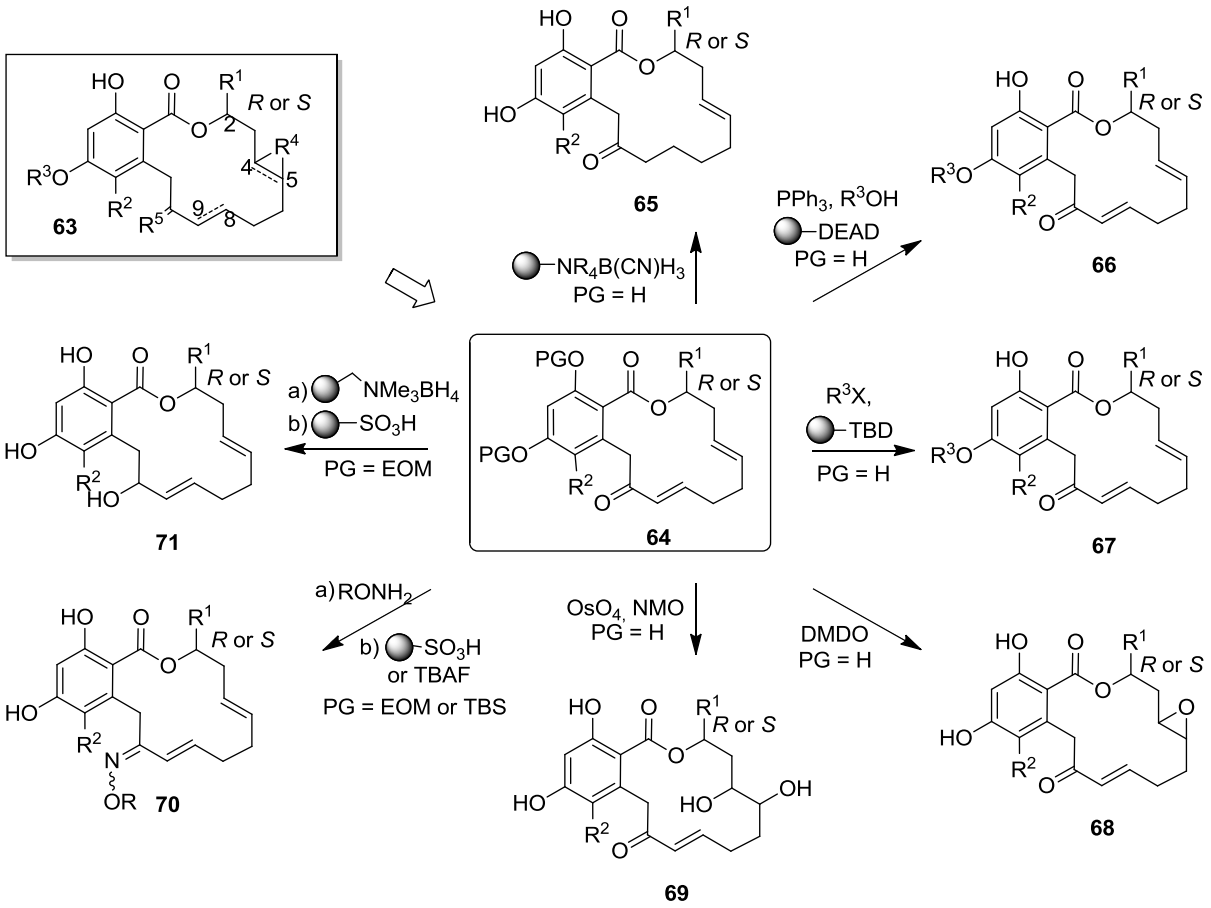
The immobilization of privileged core structure of natural products is generally retained when the natural scaffold is extremely complex, making a *de novo* combinatorial synthesis too demanding. In this case, only appendages or side chains are modified. An interesting example is the synthesis by Nicolaou *et al.* of a library of sarcodyctyin (**61**), a natural product proposed in the 90s as an alternative to Taxol for the stabilization of polymerized microtubules in the treatment of cancer. As shown in Scheme 11, they chose as starting point for diversification an advanced but still malleable sarcodictyin intermediate from their total synthesis program[44] that they immobilized on polystyrene (**62**).[45,46]



Scheme 11. Example of solid phase immobilization of important natural product scaffolds for diversification. TIPS = triisopropylsilyl.

The attachment to the resin was achieved via a Wittig reaction and three points of diversity were considered: the secondary alcohol, after acetate deprotection, was derivatized by esterification or reaction with isocyanates; the primary alcohol, after silyl deprotection, was elaborated in three different manners: simply by esterification or carbonate formation, by oxidation to the carboxylic acid and conversion to esters or amides or last but not least, by conversion into an azide which was reduced to the corresponding amine and further elaborated into amides. Finally, the library was released from the solid support *via* a transketalization in the presence of different alcohols thereby introducing the third point of diversity. This library offered a rapid structure activity profile of the important natural product sarcodyctyin, thus clearly identifying the areas that could lead to improved activity.

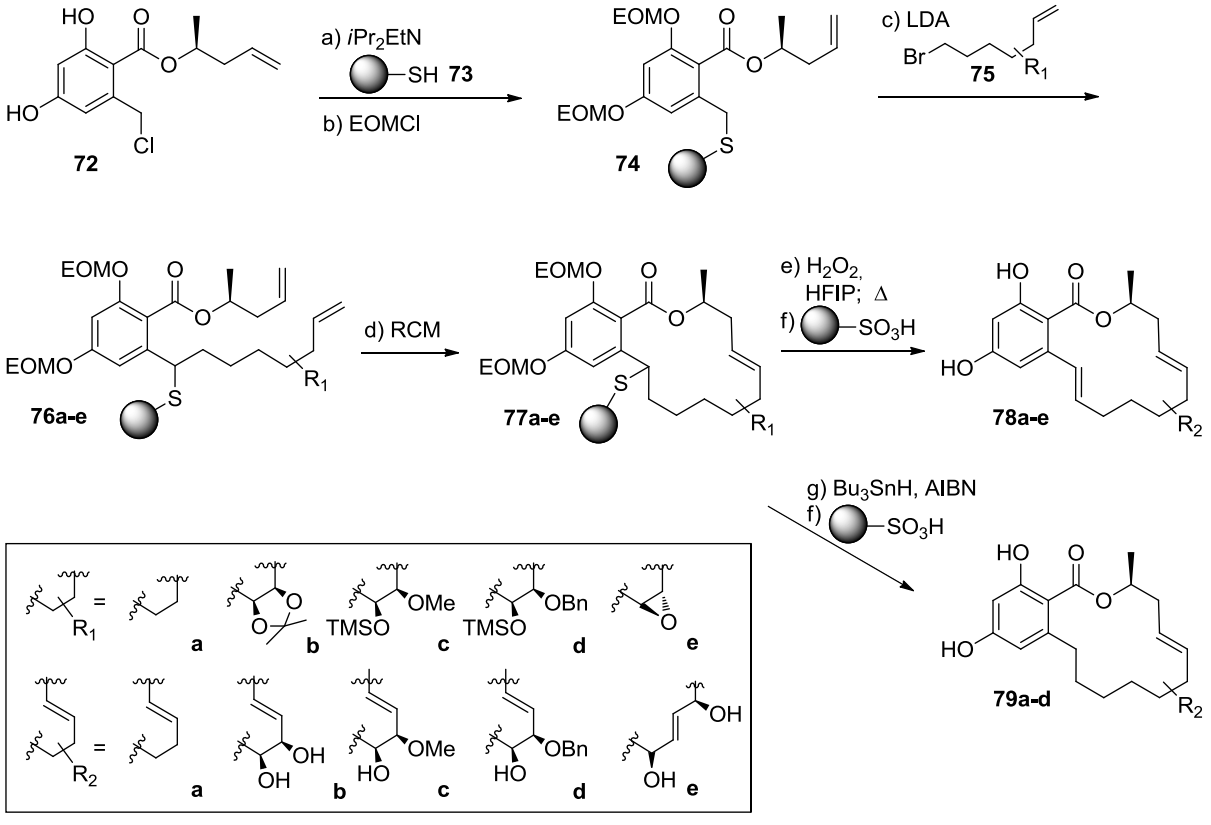
The use of immobilizied reagents, contrarily to classical solid phase synthesis, does not require extra steps to attach and release the product from the resin and allows the monitoring of the reactions, but still presents the advantage not to require traditional work-up and chromatography. One example of library elaborated following this technique, shown in Scheme 12, is the pochonin D library synthesized by our laboratory.[47]



Scheme 12. Example of library synthesis using immobilized reagents. DEAD = diethyl azodicarboxylate, DMDO = dimethyldioxirane, EOM = ethoxymethyl, TBAF = tetrabutylammonium fluoride, TBS = *tert*-butyldimethylsilyl, NMO = N-methylmorpholine-N-oxide.

This library, represented by the general structure **63** and starting from intermediate **64**, presents five points of diversification including: the group on C_2 (R^1); the *meta* position on the aryl ring (R^2); the substitution of the *para* phenol (R^3); the $C_{4\text{-}5}$ olefin (R^4) which was converted to a diol or an epoxide; the C_{10} carbonyl (R^5) which was reduced or converted to oximes and the olefin $C_{8\text{-}9}$ which was reduced. A total of 113 compounds were prepared using combinations of the chemistry. Screening of this library against heat shoock protein 90 (HSP90) led to the discovery of a compound with 100 fold higher efficacy than pochonin D in cellular assays and which was found to lead to tumor regression in a mouse xenograft bearing a breast tumor cell line.[48] Screening of a subset of this library for kinase inhibition also led to the identification of twelve compounds with greater than 50% inhibition for one kinase at 10 µM.

The last technique, which is the most commonly used, consists in elaborating the total synthesis on solid phase of the natural product and then exploiting the developed chemistry to prepare analogs. Here again, one example elaborated by our laboratory can be cited: the solid phase synthesis of aigialomycin D (**78b**).[49] A shown in Scheme 13, the sequence counts six steps, including the loading of the aryl moiety onto the thiophenol resin, the protection of the free phenols, the alkylation with an alkyl bromide, the ring closing metathesis (RCM), the release from the resin and the global deprotection.



Scheme 13. Example of natural product and its analogs synthesis on solid phase. AIBN = azobisisobutyronitrile, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMF = N,N-dimethylformamide, EOM = chloromethyl ethyl ether, HFIP = hexafluoro-2-propanol, HMPA = hexamethylphosporamide, LDA = lithium diisopropylamide, PS = polystyrene.

The repetition of the sequence using five different alkyl bromides and two different ways of cleavage allowed the preparation of 14 related analogs. A screening of aigialomycin D (**78b**) and its analogs against a panel of kinases showed among others the particular importance of the hydroxyls and the olefin moieties for the activity.

As illustrated by these diverse examples of application, solid phase synthesis is an extremely attractive strategy for library synthesis, particularly due to its simple automation and the absence of traditional work-up. However, this strategy still presents several limitations, such as the incompatibility of some reagents with the heterogeneous nature of the solid phase, the slower reaction rates compared to solution, the fact that complex transformations cannot always be driven to a clean product despite the excess of reagents utilized, the reduced reaction scope, the difficulty to monitor the reactions and to achieve long linear sequences (generally limited to ten to twelve steps for natural product synthesis). These later facts have then stimulated the development of alternative strategies such as the isolation tags.

1. b. Isolation tags

The use of isolation tags allows the preparation of libraries combining solid phase synthesis advantages, namely a rapid purification and the possibility of working with mixtures to prepare more compounds without more effort, with solution phase synthesis advantages (use of homogeneous and diverse conditions, simple analysis and identification of the products by all standard spectroscopic methods, suitable for large scale). Moreover, the tagged components being molecules and not materials, their reactivity is generally comparable to those of the non-tagged parent molecule, making the reaction features easily predictable.

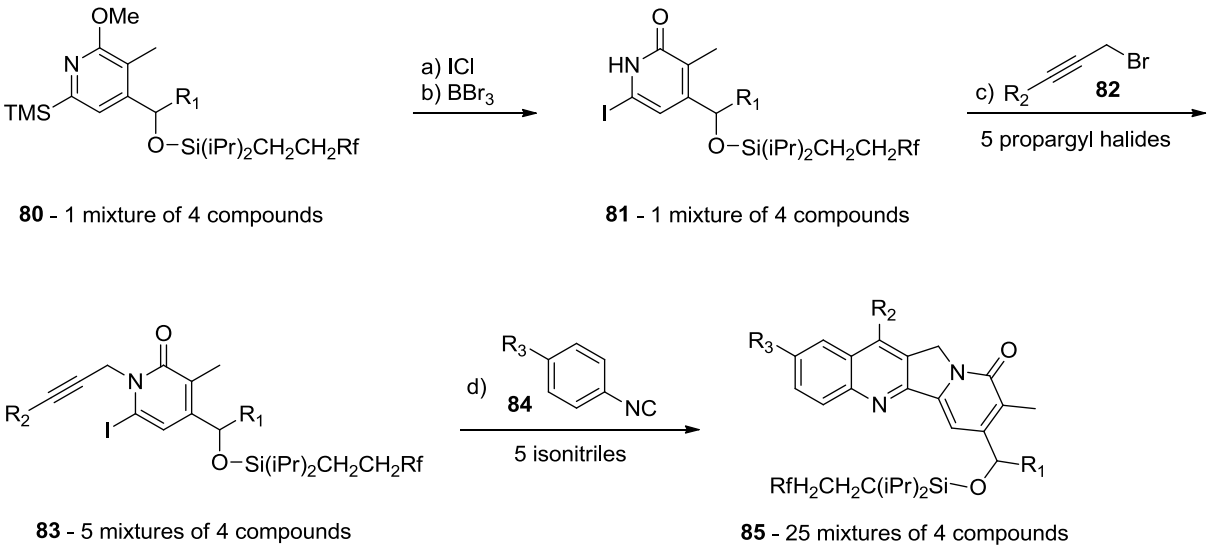
Different classes of tags have been developed: the long polyethylene glycol chains, the non-crossed linked polystyrene, and more recently the perfluoroalkyl tags.

The interest of the polyethylene glycol chains is that they are insoluble in ethers while being soluble in most other organic solvents, a molecule derivatized with such a chain can thus easily be precipitated in Et_2O and isolated. This fact was originally explored in the context of peptide synthesis.[50-52] The principle of the non-crossed linked polystyrene is globally the same, but with some differences in the solubility (precipitation is for example performed in methanol or water).[53]

The tagging of molecules with perfluroalkyl chains started to be explored in the mid 90s by Curran *et al.*.[54] They showed that molecules tagged with chains containing thirty-nine or more fluorine atoms are soluble in highly fluorinated solvents and can thus be easily purified by biphasic or triphasic liquid-liquid extraction (the fluorous phase being not miscible with either the aqueous or organic phase). On the other hand, molecules tagged with chains containing only nine to seventeen fluorine

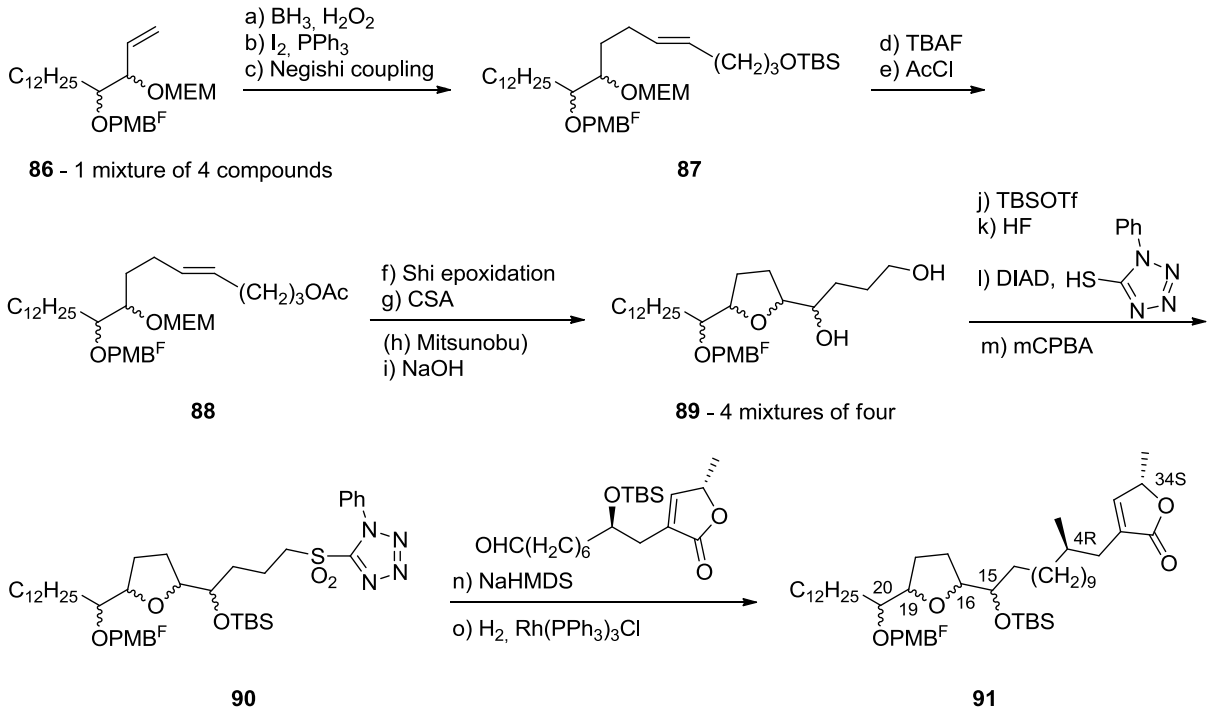
atoms, which are as a consequence more soluble in most organic solvents but less soluble in fluorous solvents, can be isolated using fluorous solid-phase extraction (F-SPE).[32] The F-SPE is based on the partitioning of molecules between a fluorous solid phase (silica gel with fluorocarbon bounded phase $–SiMe_2(CH_2)_2C_8F_{17}$) and a fluorophobic solvent: a first wash of the column using a fluorophobic solvent allows the collection of all non-tagged molecules, whereas a second fluorophilic pass delivers the tagged components. This separation technique is particularly attractive as it resembles more a filtration than a chromatography, requiring lower solvent volumes, no multiple fraction collection and enabling higher loading level.

Looking at the three isolation tags described above, the concept of the fluorous tags appears to be the most interesting for the elaboration of a library in the sense that it is most easily automatisable. The use of RapidTrace workstation for automatic F-SPE, allowing the completion of 100 SPEs in 1-2 h, was for example described by Zhang *et al.* in 2006.[55] Furthermore, Curran *et al.* demonstrated that a mixture of compounds tagged with different length of fluorinated alkyl chain could be resolved on fluorinated silica gel thus offering the possibility to carry out a synthesis using a mixture of compounds each labeled with a unique tag length which is ultimately resolved into its individual components.[7-9] This was for example elegantly applied to the synthesis of a mappicine analogs library **85** (Scheme 14).[7] After demixing and with no intermediate purifications, 99 of the expected 100 products could be identified by LC/MS with an average overall yield of 11% (comparable to reactions done serially) and 87 of them could be directly isolated in pure form.



Scheme 14. Synthesis of 100 mappicine analogs using fluorous tags technology. R_1(Rf): Pr (C_4F_9), Et (C_6F_{13}), *i*Pr (C_8F_{17}), $CH_2CH_2C_6H_{11}$ ($C_{10}F_{21}$); R_2: H, Me, Et, C_5H_{11}; R_3: H, F, Me, OMe, CF_3. TMS = trimethylsilyl.

This technology was also applied to the synthesis of pine sawfly sex pheromone[35] and (+)-murisolin[56,36] stereoisomers library. Assigning the exact structure of a natural product can be complicated when the compound presents symmetric subunits, remote stereocenters or is resistant to crystallization. However, a rigorous assignment is essential, isomers presenting sometimes radically opposite biological activities, as it is the case for murisolin isomers whose cell killing effects differ by factors of up to one billion. As depicted in Scheme 15, Curran *et al.* thus applicated the fluorous tags concept to prepare in parallel sixteen murisolin isomers **91** (evident stereocenters 4 and 34 were fixed). The synthesis was achieved in 39 steps, instead of the 156 required if every sample had been prepared individually, and allowed the confirmation of (+)-murisolin assignment by comparison of the NMRs spectra and HPLC co-injection.

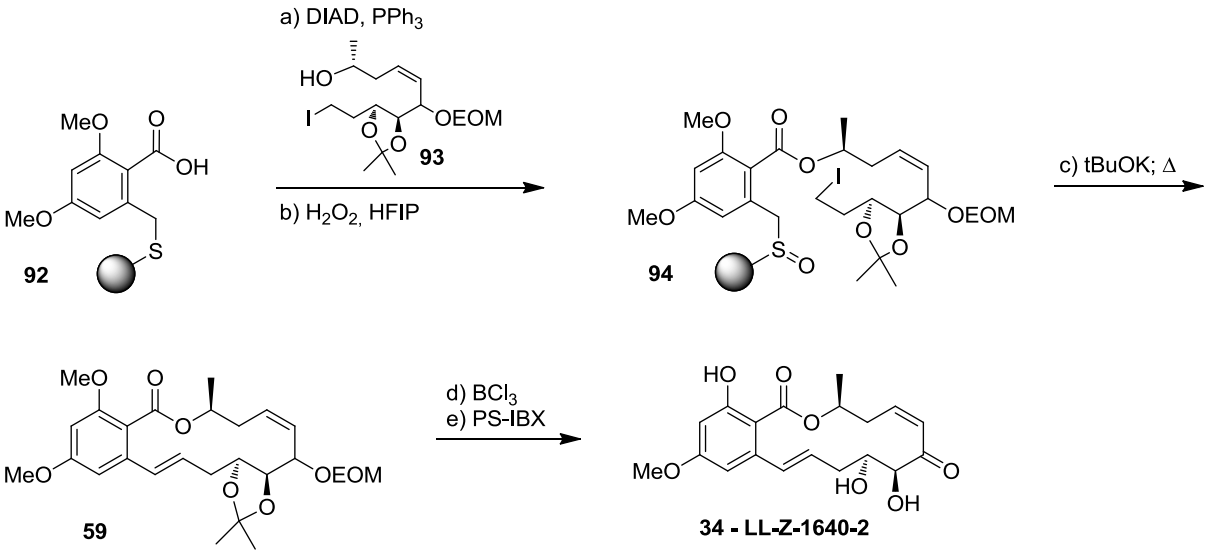


Scheme 15. Synthesis of (+)-murisolin and 15 of its isomers using fluorous tags technology. Ac = acetyl, mCPBA = *meta*-chloroperoxybenzoic acid, CSA = camphorsulfonic acid, DIAD = diisopropyl azodicarboxylate, MEM = methoxyethoxymethyl, NaHMDS = sodium bis(trimethylsilyl)amide, PMB = *para*-methoxybenzyl, TBAF = tetrabutylammonium fluoride, TBS = *tert*-butyldimethylsilyl.

2. Preliminary studies - adaptation of the radicicol A synthetic pathway

The compatibility of the strategy developed for the *cis*-enone resorcylides synthesis with solid phase was assessed. As shown in Scheme 16, it was decided to use as building blocks the intermediates **92** and **93**, respectively prepared from 2-(chloromethyl)-4,6-dimethoxy benzoyl chloride[57] and *cis*-

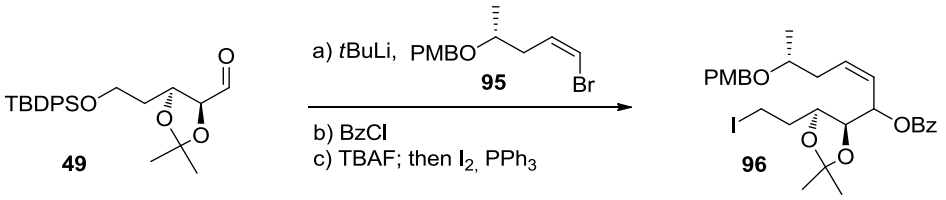
alkene **54**. The sequence began with the Mitsunobu reaction and the macrocyclization. Inducing a decomposition of the product over prolonged exposure to LDA and a disappointing yield when directly performed from the thiother, the macrocyclization was carried on the sulfoxide. The crude of the alkylation was directly suspended in toluene and irradiated with microwave to 120 °C to afford the desired alkene **59** in 34% overall yield (based on the loading of thiophenol resin). Macrocycle **59** was then treated with BCl_3 to deprotect selectively the *ortho*-phenol, the acetonide and the EOM group, thus affording the corresponding triol. The last remaining step was the oxidation of the allylic alcohol. Here again, as previously observed for the synthesis in solution, the outcome of the reaction proved sensitive to the substitution pattern on the aryl ring, and the use of immobilized IBX[34] afforded two different products.



Scheme 16. Adaptation of the *cis*-enone resorcylides synthesis on solid phase. a) **93** (2.0 equiv), DIAD (4.0 equiv), PPh_3 (4.0 equiv), toluene, 23 °C, 12 h; b) H_2O_2 (4.0 equiv), HFIP/CH_2Cl_2 (1/1), 23 °C, 12 h; c) *t*BuOK (10.0 equiv), DMSO, 23 °C, 12 h; then toluene, 120 °C, µwave, 25 min, 34% overall yield based on the loading of thiophenol resin; d) BCl_3 (6.0 equiv), CH_2Cl_2, 0 °C, 15 min, 82%; e) PS-IBX (3.0 equiv), CH_2Cl_2, 23 °C, 1 h, 86% for the less polar diastereoisomer. DIAD = diisopropyl azodicarboxylate, DMSO = dimethylsulfoxide, EOM = ethoxymethyl, HFIP = hexafluoro-2-propanol, IBX = 2-iodobenzoic acid, PS = polystyrene.

Looking at these results, the synthesis of the *cis*-enone RALs library could very well be carried out on solid phase. However, as it will be detailed below, we were interested in including in the library analogs bearing an oxygen at the benzylic position. While the thioether linker elegantly allows the access to the alkane and alkene functionalities at this position, it clearly precludes the formation of phenolic ethers. This element thus motivated the exclusive use of the fluorous isolation technology, whose numerous advantages and compatibility were already demonstrated above, for the purpose of the present library. The approach on solid phase nevertheless complemented the former two syntheses of LL-Z1640-2 (**34**) reported by Tatsuta's group[58] and Lett's group.[40]

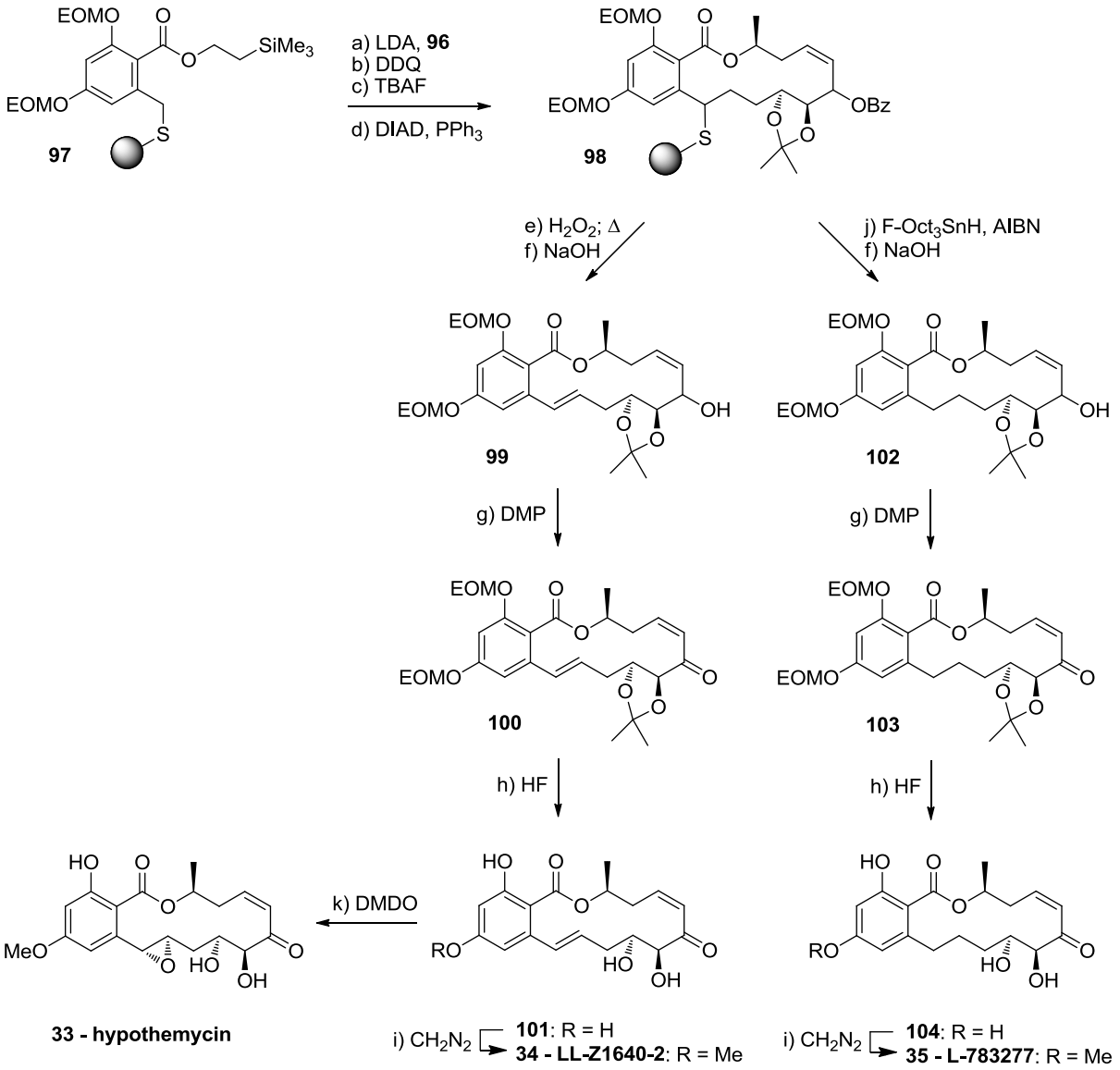
LL-Z1640-2 (**34**) appearing to be a good compromise between stability and activity (compared to radicicol A (**38**) and its chlorinated analog **39**), it was decided to focus on a library which would contain only macrocycles lacking substituents on the aryl moiety. Therefore, another pathway leading to a clean allylic oxidation without any discrimination between both diastereoisomeric alcohols needed to be envisioned. The best alternative seemed to be the use of an orthogonal protecting group for the allylic hydroxyl. The benzoate group was chosen (Scheme 17).



Scheme 17. a) **95** (1.0 equiv), *t*BuLi (2.0 equiv), Et_2O, -100 °C, 30 min, 88%; b) BzCl (2.5 equiv), pyridine (2.5 equiv), TBAI (cat), CH_2Cl_2, 0 to 23 °C, 6 h, 90%; c) TBAF (2.0 equiv), THF, 23 °C, 6 h, quant; then I_2 (1.5 equiv), PPh_3 (1.5 equiv), imidazole (2.5 equiv), THF, 0 °C, 30 min, 91%. Bz = benzoyl, PMB = *para*-methoxybenzyl, TBAF = tetrabutylammonium fluoride, TBAI = tetrabutylammonium iodide, TBDPS = *tert*-butyldiphenylsilyl, THF = tetrahydrofuran.

As shown in Scheme 18, the entire synthetic pathway was then reevaluated according to this protecting group. It was decided to start from the resin **97**, whose toluate position was thus alkylated with the Bz-protected intermediate **96** to afford after sequential cleavage of the PMB and silyl based protecting groups and Mitsunobu reaction, the polymer-bound macrocycle **98**. Two modes of cleavage were then applied in parallel to validate the sequence for both alcane and alkene functionalities at the benzylic position. Intermediate **98** was released from the resin on one hand under oxidative conditions thus affording after benzoate deprotection the macrocycle **99**, and on the other hand under reductive conditions thus affording after benzoate hydrolysis the macrocycle **102**. While the benzoate hydrolysis proceeded smoothly in solution using sodium hydroxide without any lactone opening, attempts to perform the same reaction on solid phase failed with a variety of nucleophiles (LiOH, NaOH, NaOMe, NaO*n*Bu, NaSMe, hydrazine), thus strengthening our preference for the fluorous tags technology. A number of alternative protecting groups for the allylic hydroxyl were investigated such as a PMB which would require a selective 14-membered *vs* 10-membered lactonization or a cinnamoyl which should allow hydrolysis under milder conditions but none of these resulted in pure final products. As expected, both diastereoisomers of **99** and **102** could now be oxidized to the desired *cis*-enone. Slightly more forceful conditions than immobilized IBX were required, namely DMP in refluxing CH_2Cl_2. To completely validate the method, appropriate conditions to deprotect the EOM and the acetonide groups without isomerizing the *cis*-enone had to be found. While Lett *et al.* had reported the use of TsOH with moderate success during the second total synthesis of LL-Z1640-2 (**34**),[59] the outcome of this reaction was too finicky to be used in the context of a library. Other acids such as TFA or HFIP were not suitable either. However, aqueous HF in acetonitrile[60] was found to give very clean deprotection without any isomerization and had the virtue that the crude mixture could be directly lyophilized at the end of the reaction. The *para*-EOM group was found to be the most resistant to acidic cleavage and it was found best not to drive the

reaction to completion but rather to stop it after 7 h which typically afforded 50% of the desired products **101** and **104** along with 50% of the corresponding mono-EOM analog.



Scheme 18. a) **96** (3.0 equiv), LDA (6.0 equiv), THF/HMPA (10/1), -78 °C, 20 min; b) DDQ (2.4 equiv), CH_2Cl_2/H_2O (2/1), 23 °C, 4 h; c) TBAF (10.0 equiv), THF, 23 °C, 6 h; d) DIAD (3.0 equiv), PPh_3 (3.0 equiv), toluene, 23 °C, 12 h; e) H_2O_2 (4.0 equiv), CH_2Cl_2/HFIP (1/1), 23 °C, 12 h; then toluene, 80 °C, 12 h, 62% (six steps); f) 1% NaOH/MeOH, 23 °C, 12 h, 76-80%; g) DMP (3.0 equiv), CH_2Cl_2, 65 °C, 6 h, 85%-quant; h) 40% HF/H_2O in CH_3CN (1/10), 23 °C, 7 h, 50%; i) CH_2N_2 (5.0-10.0 equiv), Et_2O, 23 °C, 6 h, 63-74%; j) F-Oct_3SnH (5.0 equiv), AIBN (cat), toluene, 150 °C, µwave, 10 min, 52% (five steps); k) DMDO (5.0 equiv), CH_3CN, 0 °C, 1 h, 25%. AIBN = azobisisobutyronitrile, Bz = benzoyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIAD = diisopropyl azodicarboxylate, DMDO = dimethyldioxirane, DMP = Dess-Martin periodinane, EOM = ethoxymethyl, HFIP = hexafluoro-2-propanol, HMPA = hexamethylphosphoramide, LDA = lithium diisopropylamide, F-Oct_3SnH = tris(1H,1H,2H,2H-perfluorooctyl)tin hydride, TBAF = tetrabutylammonium fluoride, THF = tetrahydrofuran.

The natural products LL-Z1640-2 (**34**) and L-783277 (**35**) could be obtained by straightforward diazomethane treatment of compounds **101** and **104** respectively (>90% conversion based on LC/MS, 63-74% isolated yield after HPLC purification). It should be noted that the final products isolated by HPLC were typically contaminated with small amounts (>5%) of a side product which is tentatively ascribed to the *trans*-enone isomer. It had been reported by Lett *et al.* that LL-Z1640-2 (**34**) could be regio- and stereoselectively converted to hypothemycin (**33**) using *m*CPBA.[59] Attracted by the fact that DMDO could provide the same selectivity while not requiring a work-up, we attempted the selective epoxidation of LL-Z1640-2 (**34**) with DMDO which afforded hypothemycin (**33**) in 25% isolated yield at 50% conversion. While the reaction appeared very clean when monitored by LC/MS and NMR of the crude reaction mixture, attempts to drive it to completion resulted in decomposition. Furthermore, it was found that the epoxide was quite sensitive to acidic conditions and partial degradation of the final product was observed upon isolation.

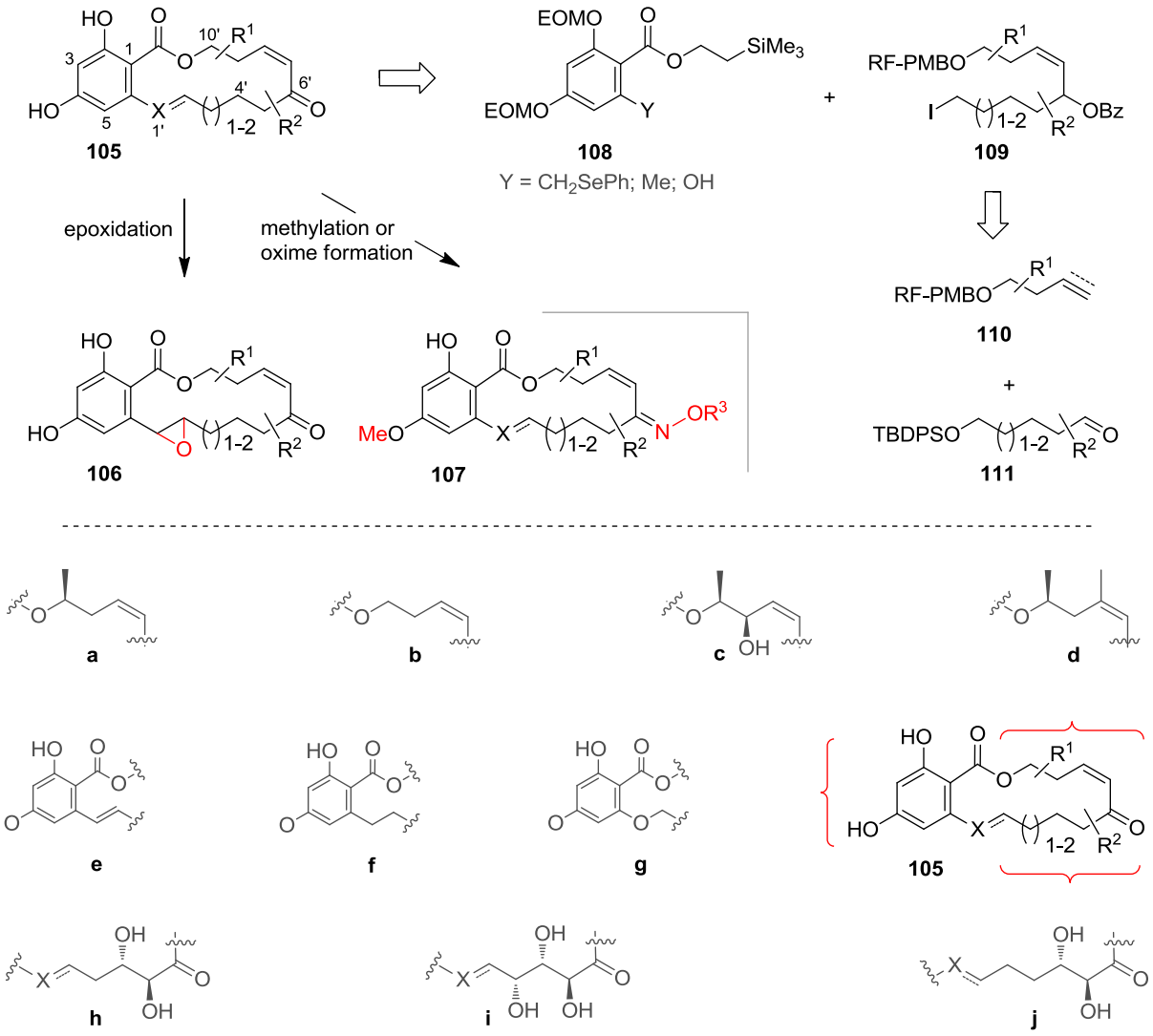
3. Synthesis of a library of over fifty *cis*-enone macrocycles

3. a. Synthetic planning and diversification points

As illustrated in Scheme 19, the library of general structure **105** was planned to be prepared applying the fluorous tags concept detailed above (compounds tagged with different length of fluorinated alkyl chain are carried out as mixtures[7-9]), and following the synthetic pathway developed for radicicol A taking the benzoate group modification in account. Macrocycles **105** were thus envisioned to result of the coupling of key fragment **109**, bearing a fluorous tag encoding its structure, with different aromatic moieties **108** bearing either the selenoether or methyl or hydroxyl at position Y to obtain respectively an alkene, an alkane or a phenolic ether at position X. Fragment **109** was itself envisioned to emanate from the coupling of aldehydes **111** with fragment **110**, this last fragment being either an alkyne which would be reduced to the *cis*-alkene with Lindlar catalyst or a *cis*-vinyl iodide. General structure **105** was eventually planned to be further diversified by epoxidation of the benzylic alkene (thus leading to hypothemycin related structure analogs **106**), by methylation of the more acidic phenol, and/or by oxime formation on the ketone to obtain analogs **107**.

It is known that natural products have been selected through evolutionary pressure for specific biological activities, their structure is then obviously a validated starting point for diversification.[61-63] Moreover, interesting biological activity was shown to be usually clustered on small islands within diversity space, it is thus not necessary to drastically differ from the natural products motifs to find biological hits. As a consequence, the *cis*-enone RALs basic scaffold has been conserved in all our analogs. The choice of the regions which would be modified, as well as the nature of the substituents, was based on our preliminary structure-activity data coupled to available structural information[24,25] and to structure-activity data obtained by semi-synthesis of hypothemycin.[64] In this

last study, Santi *et al.* demonstrated that the $C_{4'-8'}$ region is critical for activity (showing for example that methylation of the homoallylic diol leads to a significant reduction in activity), whereas the $C_{1'-2'}$ portion and the C_4 position tolerate modifications. It was thus decided to keep the diol function intact, to keep exploring diversification at the benzylic position, and to further study the influence of modifications at $C_{3'}$ position as well as at the $C_{9'-10'}$ portion.



Scheme 19. Diversification points and synthetic planning of a library of *cis*-enone RALs.

Concerning the $C_{1'-2'}$ portion, as shown in Scheme 19, three different functionalities were envisioned (**e**-**g**). We first felt important to include both of the alkene (fragment **e**) and the alkane (fragment **f**) functionalities in the library, the difference in activity between LL-Z1640-2 (**34**) and L-783277 (**35**) for MEK1 (411 nM vs 4 nM respectively) showing the influence that this modification could have on selectivity.[24,26] Although this modification may seem rather modest, preliminary modeling experiments have nevertheless suggested fairly different conformational landscape for both compounds. It was then decided to introduce an epoxide and an ether (fragment **g**) at the benzylic

position. While the epoxide at this position imparts a molecular conformation similar to an alkene, difference in dipoles may be significant. In the same way, the phenolic ether at that position should provide a conformational profile similar to the alkane but with different dipole moments. While structural information could rule out certain modifications, it should be noted that the crystal structures reported[25,29] are for the Michael adduct and the initial recognition event between the protein and the *cis*-enone may involve different macrocyclic and/or kinase conformations.

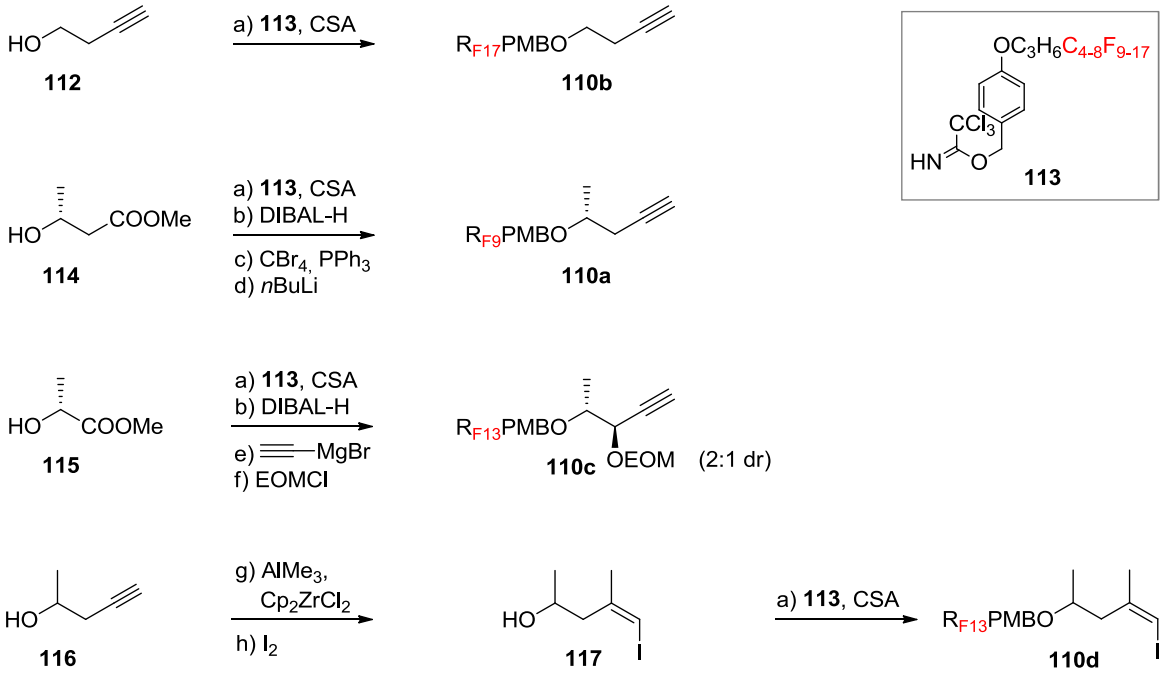
For the ester moiety ($C_{9'\text{-}10'}$ region), four different fragment R^1 (**a**-**d**) were considered. In natural *cis*-enone RALs, the chiral methyl substituent at $C_{10'}$ position points towards the surface of β-pleaded sheets (fragment **a**). Our prior investigation had shown that the *R*-chirality at that center dramatically attenuated activity. Nevertheless, we imagined that compounds lacking that methyl group (fragment **b**) may broaden specificity. An extra hydroxyl group at the adjacent $C_{9'}$ position (fragment **c**) was deemed interesting as it would probe whether additional interactions may be achieved and whether the chiral substituent imparts an important conformational bias on the macrocycle. Then, although Santi *et al.* suggested that the *cis*-enone moiety should be kept intact,[64] modification of the alkene (fragment **d**) was seen crucial in modulating the rate of conjugate addition (if the conjugate addition is catalyzed by a hydrogen bond to the carbonyl, the greater stability of a tertiary cation *vs* a secondary cation may favor the reaction). Furthermore, having a methyl substituent at that position could alleviate the issues related to *cis*/*trans* isomerization, the *trans*-enones being significantly less active.[26]

Eventually, three different fragments R^2 (**h**-**j**) were envisioned for the lower part of the macrocycle. The first one (fragment **h**) corresponds exactly to the natural product motif. Fragment **i**, presenting an additional hydroxyl group at $C_{3'}$ position, was selected for the same reasons as fragment **c** in the ester moiety. A larger macrocycle also appeared interesting in providing subtle changes in conformation profiles and was thus probed with fragment **j**.

While each of these modifications can be rationalized as providing a potential benefit, the combination of several modifications may provide unanticipated synergistic benefits.

3. b. Tagging - synthesis of fragments 110a-d

As shown in Scheme 20, fragments **110a-d** were obtained in one to five steps *via* well established chemistry. The first step to obtain **110a-c** involved the protection of the alcohols **112**, **114** and **115** with the trichloroacetimidate of the fluorous-PMB (**113**) bearing different length of fluorous tag encoding the structure of the starting alcohol. For the methoxy esters **114** and **115**, the alcohol protection was followed by a DIBAL-H reduction and a Corey-Fuchs reaction or a Grignard addition of acetylene (2:1 dr, inseparable mixture) followed by EOM-protection to afford the alkynes **110a** and **110c** respectively. Compound **110d** was prepared from the racemic 4-hydroxylpentyne **116** using a known procedure[65] to access the *Z*-vinyl iodide **117** which was protected with the fluorous tagged PMB. The product of each reaction was isolated by flash chromatography on fluorous silica gel.



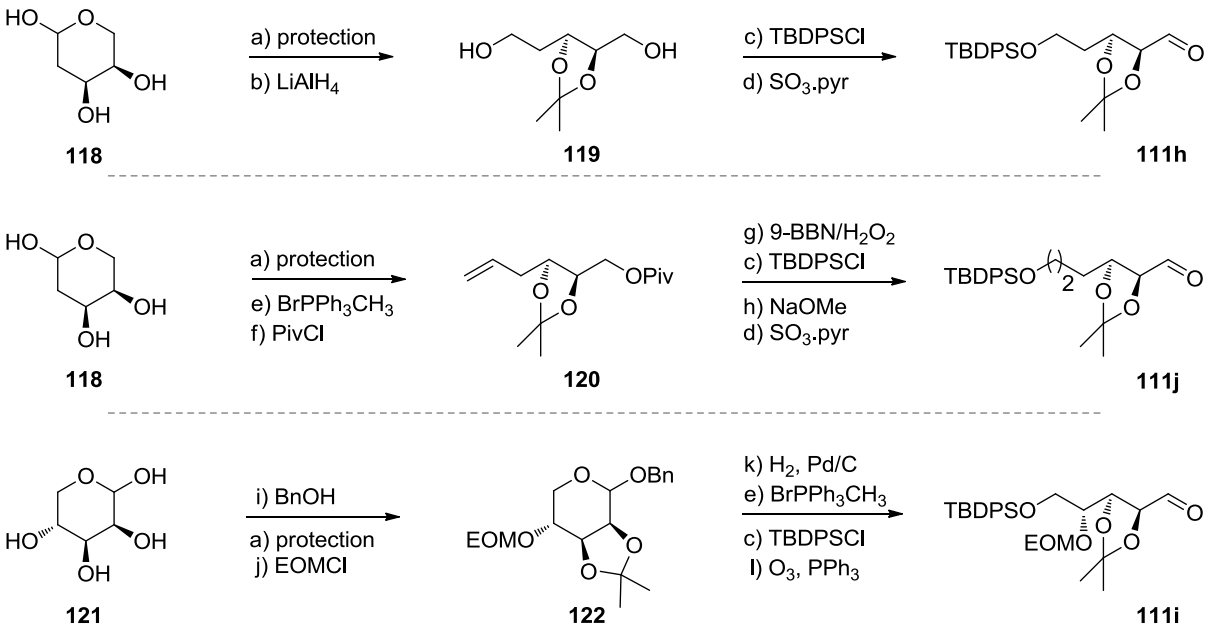
Scheme 20. a) **113** (1.0 equiv) , CSA (0.1 equiv), CH_2Cl_2, 23 °C, 12 h, 72-86%; b) DIBAL-H (1.1 equiv), toluene, -78°C, 1 h, 45-52%; c) CBr_4 (4.0 equiv), PPh_3 (8.0 equiv), CH_2Cl_2, 0 °C, 45 min, 63%; d) *n*BuLi (2.0 equiv), THF, -78 °C, 1 h, and 23°C, 1.5 h, 85%; e) HC_2MgBr (1.5 equiv), THF, -78 to 23 °C, 12 h, 88%; f) EOMCl (3.0 equiv), *i*Pr_2NEt (3.0 equiv), TBAI (cat), CH_2Cl_2, 23 °C, 12 h, 89%; g) Cp_2ZrCl_2 (0.25 equiv), $AlMe_3$ (3.0 equiv), CH_2Cl_2, 23 °C, 19 h and reflux, 5 days; h) I_2 (1.5 equiv), THF, -30 °C, 15 min, 60% (two steps). CSA = camphorsulfonic acid, Cp = cyclopentadienyl, DIBAL-H = diisobutylaluminium hydride, EOM = ethoxymethyl, PMB = *para*-methoxybenzyl, TBAI = tetrabutylammonium iodide, THF = tetrahydrofuran.

In general, a 10 to 20 fold ratio of silica to crude product weight was used for the isolation. The elutions were carried out systematically using a three steps gradient (7:3 MeOH:H_2O, 8:2 MeOH:H_2O and pure MeOH) and the product was collected from the MeOH fraction without further attempt to optimize individual isolation or to recover product from mixed fractions.

3. c. Synthesis of aldehydes 111h-j

The synthesis of fragments **111h-j** (Scheme 21) was leveraged on the naturally abundant chirality of 2-deoxy-D-ribose **118** and D-lyxose **121** using well established methodology. Thus, 2-deoxy-D-ribose **118** was selectively protected with an acetonide[33] and reduced with $LiAlH_4$ to obtain diol **119** which was selectively protected on the less hindered alcohol with TBDPSCl and oxidized to aldehyde **111h**. Starting with the same selective protection of ribose but engaging the resulting lactol in a Wittig olefination[66] rather than a reduction afforded alkene **120** after pivaloylation of the primary alcohol.

A sequence involving a hydroboration, silyl protection, pivaloyl deprotection and oxidation afforded fragment **111j** which has an additional carbon compared to **111h**.

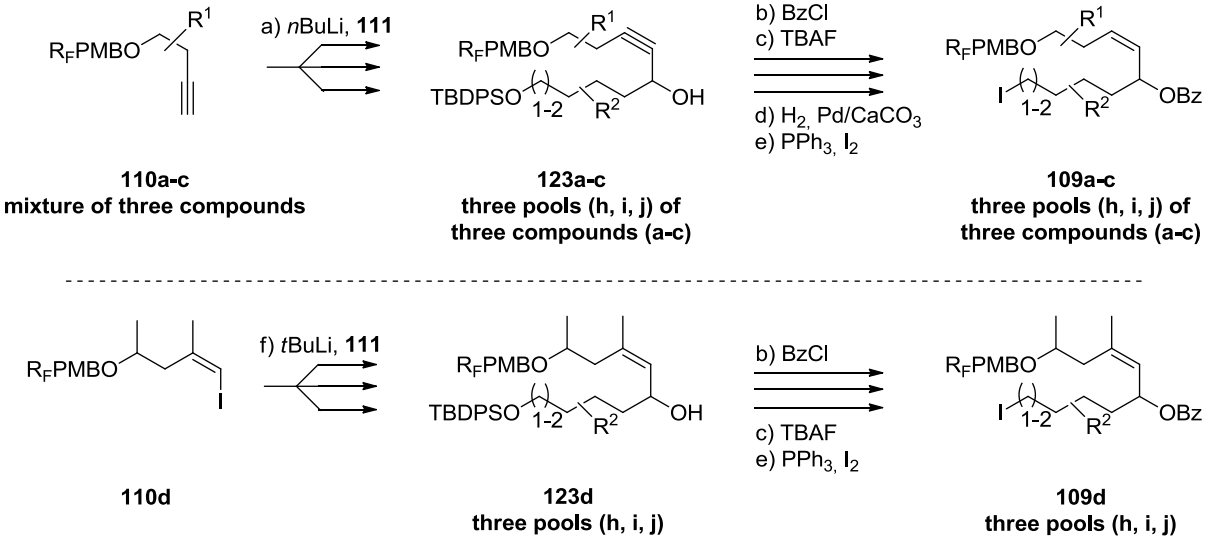


Scheme 21. a) 2-methoxypropene (2.0 equiv), *p*TSA (0.04 equiv), $CaSO_4$ (0.25 equiv), DMF, 0 °C, 3 h, 60% or 2,2-dimethoxypropane (3.5 equiv), *p*TSA (0.02 equiv), acetone, 23 °C, 12 h, 90%; b) $LiAlH_4$ (1.4 equiv), THF, 0 to 23 °C, 2 h, 95%; c) TBDPSCl (0.9 equiv), imidazole (1.5 equiv), DMF, 23 °C, 2-12 h, 66-99%; d) SO_3.pyr complex (3.5 equiv), Et_3N (4.9 equiv), CH_2Cl_2/DMSO (4/1), 0 to 23 °C, 30 min-1 h, 91-94%; e) $BrPPh_3CH_3$ (3.0 equiv), NaHDMS (2.8 equiv), THF, -78 to 23 °C, 1-12 h, 72-86%; f) PivCl (2.0 equiv), Et_3N (4.0 equiv), DMAP (0.2 equiv), CH_2Cl_2, 0 to 23 °C, 12 h, 93%; g) 9-BBN (2.2 equiv), THF, 0 to 23 °C, 3.5 h, then 3N NaOH/H_2O_2, 0 to 23 °C, 1.5 h, 94%; h) NaOMe (3.0 equiv), MeOH, 23 °C, 16 h, 83%; i) BnOH (7.2 equiv), 23 °C, 10 h, 96%; j) EOMCl (8.0 equiv), *i*Pr_2NEt (8.0 equiv), TBAI (cat), CH_2Cl_2, 23 °C, 12 h, 95%; k) H_2, Pd/C (0.05 equiv), MeOH, 23 °C, 5 h, 90%; l) O_3, PPh_3 (2.0 equiv), CH_2Cl_2, -78 °C, 1 h, 90%. Bn = benzyl, 9-BBN = 9-borabicylo[3.3.1]nonane, DMAP = 4-dimethylaminopyridine, DMF = N,N-dimethylformamide, DMSO = dimethylsulfoxide, EOM = ethoxymethyl, NaHDMS = sodium bis(trimethylsilyl)amide, Piv = pivaloyl, *p*TSA = *para*-toluenesulfonic acid, TBAI = tetrabutylammonium iodide, TBDPS = *tert*-butyldiphenylsilyl, THF = tetrahydrofuran.

The third fragment emanated from D-lyxose **121** by protection of the anomeric position followed by selective acetonide protection of the *cis*-diol, and EOM-protection of the remaining hydroxyl group. Deprotection of the anomeric position and conversion of the lactol to an alkene by Wittig olefination allowed protection of the unique hydroxyl group with TBDPSCl followed by ozonolysis of the alkene to obtain fragment **111i**. While a number of alternative strategies can be envisioned for each of these fragments, these procedures were found to be inexpensive, reliable and scalable.

3. d. Synthesis of *cis*-enol pools 109a-d

As shown in Scheme 22, the synthesis of key fragments **109** started with the deprotonation of the mixture of the three fluorous tagged alkynes **110** with *n*BuLi. The mixture was then added to three vessels containing the different aldehydes **111** affording three pools of **123**, each containing three compounds labeled with a unique fluorous tag. Benzoyl protection of the alcohols followed by desilylation, hydrogenation over Lindlar catalyst and iodination afforded the three pools of three compounds **109a**-**c**.

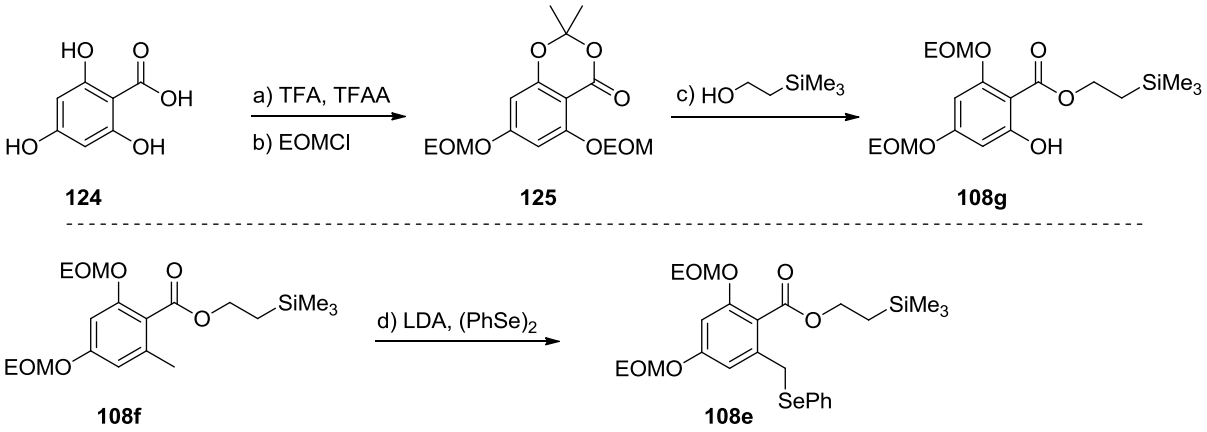


Scheme 22. a) **110a-c** (1.0 equiv), *n*BuLi (1.1 equiv), THF, -78 °C, 10 min; then **111** (1.2 equiv), -78 °C, 30 min-1 h, >80%; b) BzCl (2.5 equiv), pyridine (2.5 equiv), CH_2Cl_2, 0 to 23 °C, 4 h, >90%; c) TBAF (1.5 equiv), THF, 23 °C, 3 h, 86-94%; d) H_2, $Pd/CaCO_3$ (1.72 equiv), MeOH, 23 °C, 45 min, 90-96%; e) PPh_3 (1.5 equiv), imidazole (2.5 equiv), I_2 (1.5 equiv), THF, 0 °C, 30 min, 70-93%; f) **110d** (1.0 equiv), *t*BuLi (2.0 equiv), Et_2O, -78 °C, 20 min; then **111** (1.2 equiv), pentane, -78 to 0 °C, 7 h, 80%. Bz = benzoyl, PMB = *para*-methoxybenzyl, TBAF = tetrabutylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, THF = tetrahydrofuran.

All reactions were monitored by LC/MS and showed greater than 90% conversion. Although the isolated yield of the product following fluorous isolation was not optimized, acceptable yields were generally obtained. Vinyl iodide **110d** was transmetalated with *t*BuLi and similarly added to three different pools of aldehydes **111**. A similar sequence of benzoylation, desilylation, and iodination afforded three pools of **109d**.

3. e. Synthesis of aryl moieties 108e-g

As shown in Scheme 23, fragment **108g** was obtained starting from commercial 2,4,6-trihydroxy benzoicacid **124** by protection of the acid and *ortho*-phenol with an acetonide[67] followed by protection of the two remaining phenols with EOMCl to obtain **125** which was finally treated with the alkoxide of 2-trimethylsilylethanol. Compound **108f** was converted to **108e** by deprotonation using LDA and subsequent reaction with diphenyl diselenide.

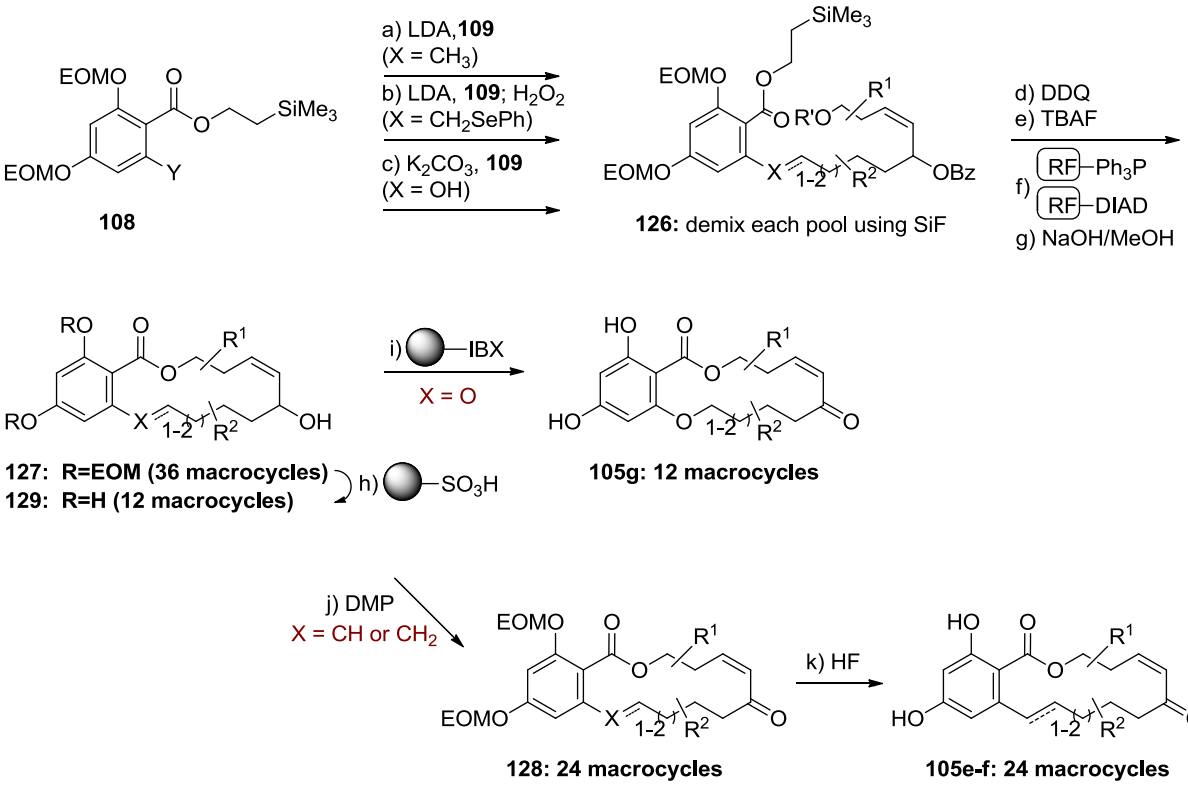


Scheme 23. a) TFA (20.0 equiv), TFAA (7.6 equiv), acetone, 23 °C, 12 h, 54%; b) EOMCl (4.0 equiv), *i*Pr_2NEt (4.0 equiv), TBAI (cat), CH_2Cl_2, 23 °C, 12 h, quant; c) TMSEOH (4.0 equiv), NaHDMS (4.4 equiv), THF, 0 to 23 °C, 12 h, 69%; d) LDA (2.0 equiv), THF, -78 °C, 30 min, $(PhSe)_2$ (0.9 equiv), THF, -78 °C, 2 h, 75%. EOM = ethoxymethyl, LDA = lithium diisopropylamide, NaHDMS = sodium bis(trimethylsilyl)amide, TBAI = tetrabutylammonium iodide, TFA = trifluoro acetic acid, TFAA = trifluoro acetic anhydride, THF = tetrahydrofuran, TMSEOH = 2-trimethylsilylethanol.

3. f. Coupling/demixing

As shown in Scheme 24, each aromatic fragment **108** was coupled to six pools of fragment **109**. Analysis of the reaction mixtures by LC/MS indicated good to excellent conversion for all reactions, with the phenol couplings being systematically the highest yield followed by the selenoether and alkyl couplings. Amongst the different pools of electrophiles, the pool containing the fragment **i** with an additional EOM-protected hydroxyl adjacent to the iodide being displaced gave the lowest coupling efficiency. However, the desired coupled product was obtained in all cases. Each pool was demixed to resolve the individual components which were then detagged (using DDQ) and deprotected (using TBAF) to be engaged in the Mitsunobu macrolactonization. We had previously observed that these reactions could be performed at 10 nM without dimerization or oligomerization. Treatment of each compound with fluorous-tagged PPh_3 and fluorous-tagged DIAD afforded high

yield in the lactonization (>85%) except for compounds containing the fragment **c** bearing a sterically more demanding alcohol for which 50% of conversion was achieved.

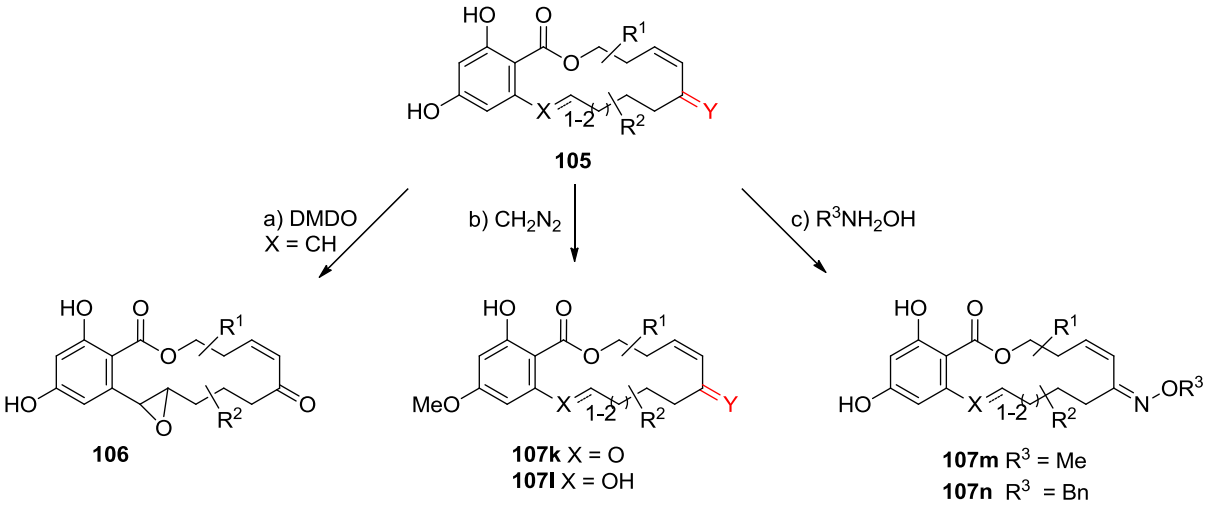


Scheme 24. a) LDA (2.0 equiv), THF, -78 °C, 10 min; then **109** (0.9 equiv), THF, -78 °C, 2 h, 60%; b) LDA (2.0 equiv), THF/HMPA (10/1), -78 °C, 10 min; then **109** (0.9 equiv), THF, -78 °C, 30 min; then H_2O_2 (2.0 equiv), THF, 23 °C, 2 h, 64-85%; c) K_2CO_3 (2.0 equiv), **109** (0.9 equiv), DMF, 100 °C, 12 h, 94%-quant; d) DDQ (1.2 equiv), CH_2Cl_2/H_2O (2/1), 23 °C, 2 h, 85-96%; e) TBAF (3.0 equiv), THF, 23 °C, 2 h, quant; f) RF-PPh_3 (2.0 equiv), RF-DIAD (2.0 equiv), toluene, 23 °C, 2 h, 50-85%; g) 1% NaOH in MeOH, reflux, 12 h, 80-90%; h) PS-SO_3H (5.0 equiv), MeOH, 50 °C, 2 h, >90%; i) PS-IBX (3.0 equiv), CH_2Cl_2/few drops of DMSO, 23 °C, 1-3 h (monitored by TLC), 50%; j) DMP (1.5 equiv), CH_2Cl_2, reflux, 4 h, 80-90%; k) 40% HF aq. solution in CH_3CN (1/10), 23 °C, 3-6 h, 50-70%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIAD = diisopropyl azodicarboxylate, DMF = N,N-dimethylformamide, DMP = Dess-Martin periodinane, DMSO = dimethylsulfoxide, EOM = ethoxymethyl, HMPA = hexamethylphophoramide, IBX = 2-iodoxybenzoic acid, LDA = lithium diisopropylamide, PS = polystyrene, TBAF = tetrabutylammonium fluoride, THF = tetrahydrofuran.

The allylic benzoate was removed in excellent yield for all macrocycles. Since we had previously noted that the selective allylic oxidation could be achieved on the macrocycles bearing an ether (X = O), these compounds were first fully deprotected and then treated with immobilized IBX. Inversely, for the macrocycles containing the alkane or alkene functionalities at the benzylic position, the oxidation was performed prior to deprotection using Dess-Martin periodinane in refluxing CH_2Cl_2, following the strategy developed in section II-2. Removal of the acetonide and EOM groups using aqueous HF afforded the desired macrocycles in moderate to good yields. As also explained in

section II-2, the reaction was never allowed to reach completion as prolonged reaction time led to product decomposition, and macrocycles **105e-f** bearing an EOM group on the *para*-phenol were also isolated from most reactions. All compounds were purified by preparative thin layer chromatography (TLC).

As described in section II-2, macrocycles **105e** could be further extended by epoxidation of the benzylic position using DMDO (Scheme 25), but the lability of the benzylic epoxide made isolation of the product challenging and pharmacologically undesirable. These macrocycles could be also further derivatized by selective methylation of the *para*-phenol with diazomethane. While being quite selective for the methylation of the *para*-phenol (**107k** and **107l**), the reactions were performed to ensure completion with a large excess of diazomethane, which led to the isolation of 10-40% of the bis-methylated product (not shown). The ketone could finally be converted to a methyl or benzyl oxime in high yield under standard conditions. In total, fifty-one macrocycles were isolated from these efforts.



Scheme 25. a) DMDO (4.0 equiv), CH_3CN, 0 °C, 1-2 h, 60-70%; b) CH_2N_2 (5.0-10.0 equiv), Et_2O, 23 °C, 3-12 h, 50-60%; c) $R^3NH_2OH.HCl$ (10.0 equiv), pyridine, 40 °C, 12 h, >50%. Bn = benzyl, DMDO = dimethyldioxirane.

3. g. Biological evaluations

Twenty-eight of these macrocycles (selected to have at least one example of each modification) and the related natural products hypothemycin (**33**), LL-Z1640-2 (**34**) and L-783277 (**35**), were first evaluated for their inhibitory activity against a panel of nineteen kinases. This panel included ten of the forty-eight kinases bearing the residue Cys^{166} (VEGFR1-3, PDGF-Rα, FLT3, MEK1, KIT, NLK, GSKα, MAP KAPK5), six kinases bearing a cysteine residue at a different position (EGFR-3, JNK3, NEK2, NIK, SRC, ZAP70), and finally three kinases which do not bear any cysteine residue within the ATP binding

pocket (PKCα, CK2α, INS-R). All the *cis*-enone analogs that were tested being expected to be irreversible inhibitors, comparison with data coming from other experiments should be made with caution, the value measured for the IC_{50} being indeed related to the procedure used. In the present case, to obtain an IC_{50} value which best reflects the rate of inactivation, substrate and inhibitor were added simultaneously to the kinase solution. Results are summarized in Table 2, where kinases have been ranked from the highest to the least inhibited.

The first comment that comes in mind looking at this Table is that, under these conditions, the *cis*-enone tested all have almost the same selectivity profile. VEGFR2 indeed appears to be the most highly inhibited kinase followed by PDGFR-α, VEGFR3, Flt3, VEGFR1, MEK1 SESE (which is a constitutively active form of MEK) and KIT.

		VEGF-R2*	PDGFR-α*	VEGF-R3*	FLT3*	VEGF-R1*	MEK1 (SESE)*	KIT*	NLK*	GSK-α*	MAP KAPK5*	EGFR-3**	JNK3**	NEK2**	NIK**	SRC**	ZAP70**	CK2 α	PKC-α	INS-R
1	hypothemycin	0,009	0,012	0,018	0,033	0,053	0,089	0,189	1,212	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
2	LL-Z1640-2	0,010	0,015	0,021	0,024	0,042	0,110	0,150	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
3	L-783277	0,169	0,227	0,253	0,369	2,113	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
4	105aej	0,016	0,022	0,035	0,026	0,058	>3	0,185	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
5	105afh	0,030	0,031	0,069	0,102	0,132	0,152	0,922	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
6	105afj	0,009	0,011	0,017	0,018	0,052	0,142	0,214	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
7	105agh	0,468	0,568	0,974	1,182	1,678	1,749	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
8	105agi	0,028	0,055	0,047	0,102	0,17	0,069	0,702	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
9	105agj	0,229	0,23	0,47	0,379	1,261	0,373	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
10	105bfj	0,044	0,152	0,11	1,271	0,198	1,511	0,676	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
11	105bgh	0,176	0,437	0,386	1,137	1,507	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
12	105bgi	0,208	0,647	0,379	2,213	1,279	0,75	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
13	105bgj	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
14	105cgh	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
15	105deh	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
16	105dfh	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
17	105dfj	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
18	105dgh	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
19	105dgj	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
20	106aj	1,142	1,565	1,66	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
21	107aejk	0,919	1,259	1,482	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
22	107aejkl	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
23	107aeim	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
24	107afjk	0,013	0,020	0,022	0,033	0,061	0,749	0,192	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
25	107aghl	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
26	107agil	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
27	107agjl	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
28	107bfjk	0,040	0,074	0,072	0,939	0,195	2,34	0,701	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
29	107dejk	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
30	129agh	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3
31	129dgh	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3	>3

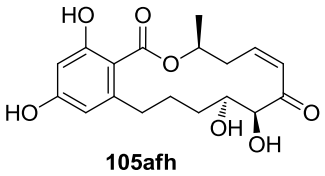
* part of the group of kinase described by Santi et al containing a cysteine in the same position as ERK2
** kinases containing a cysteine in the ATP-binding pocket but at a different site than ERK2

Table 2. IC_{50} values of the 28 selected macrocycles against a panel of 19 kinases (in µM).

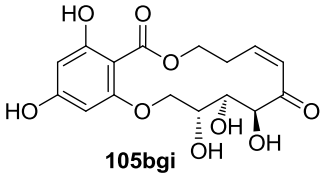
Nevertheless, important conclusions can be drawn concerning the influence of each structural modification on the activity. Concerning the $C_{9'\text{-}10'}$ portion, while not essential, the presence of the chiral methyl group seems to provide higher activity (entry 6 *vs* 10, 7 *vs* 11 and 8 *vs* 12). Inversely, substitution at the adjacent position with a hydroxyl group (entry 14 *vs* 7) or at the β-position of the enone with a methyl abrogated activity (entries 15, 19). Modifications brought to the $C_{1'\text{-}2'}$ portion, were not surprisingly well tolerated (phenolic ether included), confirming the observations done among others by Santi *et al.* from the natural products. The trend of activity for the three natural

products can be ranked as follows: alkene = epoxide >alkane, the ether being generally comparable to the alkane. Concerning the position $C_{3'}$, both modifications tested proved beneficial in certain combinations. The extra hydroxyl group (in fragment **i**), combined with fragment **a**, afforded for example a significant (10 fold) gain of activity (8 *vs* 7). Such improvement was however not observed in the presence of fragment **b** (entry 12 *vs* 11). In the same way, the larger macrocycle (fragment **j**) was particularly beneficial when conjugated with the alkane moiety at the benzylic position (fragment **f**): entry 6, macrocycle indeed affords a significant gain of activity *vs* 5, and entries 6, 10, 24 and 28, macrocycles are amongst the most potent compounds tested. Here again, no similar improvement was however observed with the benzylic alkene or ether: entry 21, the larger macrocycle representing LL-Z1640-2 (**34**) with one more carbon reduces significantly its activity (for the ether, see entries 9 and 13). As shown in entry 4, the activity of this last compound can nevertheless partially come back by removing the methyl group on the *para*-phenol position (but not at the original level of LL-Z1640-2). The rest of the time, methylation of the *para*-phenol to the ester appeared to have only a marginal influence on activity, while oxime formation clearly abolished activity. Finally, none of the alcohols **129** lacking the ketone showed significant inhibition attesting to the fairly low affinity of the macrocycle for the ATP-binding pocket and the importance of the Michael acceptor.

kinase	105afh	105bgi
AAK1	17	91
BIKE	26	76
CDKL2	83	87
CDKL3	69	52
CDKL5	100	100
ERK1	94	95
ERK2	85	100
FLT1	5,8	57
FLT3	7	40
FLT4	12	30
GAK	2,8	3,8
GSK3A	70	100
GSK3B	100	100
KIT	8,8	62
MAPKAPK	63	61
MEK1	0,35	5,6
MEK2	0,7	11
MEK3	49	73
MEK4	0	1
MEK6	28	19
MKNK1	4,4	23
MKNK2	0	4,4
NIK	100	100
NLK	87	100
PDGFRA	4,7	78
PDGFRB	0,65	37
PRP4	100	100
TAK1	3,4	27
TGFBR2	10	18
VEGFR2	20	77
ZAK	15	65



105afh



105bgi

Table 3. Residual activity as a percentage of control for thirty-one of the forty-six putative kinases inhibited by two resorcylides containing an alkane (**105afh**) or an ether (**105bgi**) at the benzylic position.

The inhibitory activity of two representative members of the library (**105afh** and **105bgi**) was then evaluated against a larger panel of 402 kinases, following the technology developed by Lockhart *et al.*.[68,69] The panel was constituted of thirty-one kinases presenting the well positioned cysteine residue (Cys^{166}), and numerous other kinases presenting a cysteine residue but at other positions.[1] Both compounds were screened at 1 µM (i.e. well above their IC_{50} concentration for the most potently inhibited kinases) to have a realistic perspective of their selectivity.

Only two kinases not bearing the cysteine residue at position 166 showed significant activity (STK36 and PRKD2), confirming that cysteine residues within the ATP-binding pocket can be used as selectivity filters.[18] As shown in Table 3, concerning **105afh**, through the thirty-one kinases bearing the suitably positioned cysteine, eleven had more than 50% residual activity, thirteen showed less than 10% residual activity (Flt1&3; GAK; KIT, MEK1,2,4; MKNK 1&2; PDGFRα&β; TAK1, TGFR2), and interestingly some were not inhibited (CDKL5, ERK1, GSK3β, NIK, NLK, PRP4). MEK4 was the most inhibited with 0% residual activity. For **105bgi**, nineteen out of the thirty-one kinases had over 50% residual activity, MEK4 being also the most highly inhibited kinase with 1% residual activity. While **105bgi** was overall less potent, it does appear to show subtle differences in reactivity compared to **105afh**. For example, while both compounds have similar activity against GAK, **105bgi** is ten times less active against Flt1 and PDGFRβ.

In a last experiment, the two previous compounds were evaluated against a series of mutations of FLT3 and KIT. Several mutations in FLT3 are known to lead to a gain of function or constitutive activity. An internal tandem duplication (ITD) in FLT3[70] is found in 20% of patients with acute myeloid leukemia (AML) while the most abundant mutation leading to a gain of function was found to be D835Y for which, as shown in Table 4, both compounds **105afh** and **105bgi** proved to be more active than against the wild type.[71] Other mutants (K663Q[72] and N841L[73]) leading to a gain of function remained equally sensitive to the inhibitors. Likewise, the compounds retained their activity against KIT mutants which results in a gain of function (D816V,[74] L576P[74] and V559D[75]); however, these compounds are not active against the dual mutations which confer resistance to imatinib (V559D, T670I; V559D, V654A).[76]

kinase	105afh	105bgi
FLT3	**7**	**40**
FLT3(D835H)	9	12
FLT3(D835Y)	0,4	2,8
FLT3(ITD)	3	26
FLT3(K663Q)	6	19
FLT3(N841I)	0	4,8
KIT	**8,8**	**62**
KIT(D816V)	0,9	13
KIT(L576P)	5,2	57
KIT(V559D)	7,8	38
KIT(V559D,T670I)	68	84
KIT(V559D,V654A)	66	100

Table 4. Residual activity as a percentage of control for mutations of kinases.

III. Conclusion

Following the synthetic pathway to radicicol A and its two related analogs developed in our laboratory (which allowed to demonstrate its kinases inhibitory activity), a library of fifty one macrocycles bearing a *cis*-enone function was elaborated. This library was based on the fluorous tags technology developed by Curran *et al.*, a powerful tool which facilitates products isolation and allows to carry mixtures of products through a common synthetic pathway.

Biological evaluations of the representative subset of twenty-eight macrocycles on a panel of nineteen kinases highlighted two important modifications which were found to independently and synergistically improve the activity of the *cis*-enone RALs. First, important benefits were observed in the case of the ring expansion: free phenols analog of L-783277 possessing the ring expension indeed exhibited the highest activity, exceeding even those of the three natural compounds tested (LL-Z1640-2 (**34**), L-783277 (**35**) and hypothemycin (**33**)). The second fruitful modification that proved beneficial for the activity is the extra hydroxyl group in β of the *anti*-diol moiety. Although the introduction of a hydroxyl function at the benzylic position did not increase the activity, it should be noted this modification proved to be well tolerated and thus remains interesting in the sense that it dramatically simplifies the synthetic accessibility of the compounds.

During this first screening, VEGFRs and PDGFRs appeared to be the most targeted kinases, whatever the inhibitor. The screening against a larger panel of 359 kinases (mutants excluded) then revealed a pattern similar to that of sunitinib, a reversible FDA-approved multitarget kinase inhibitor. By inhibiting the VEGF pathway, this small molecule inhibitor has been shown to hinder tumor growth. However, this beneficial outcome showed to be accompanied of undesired acceleration of metastasis invasiveness. Following these observations, the Pr. Winssinger decided in a further study to evaluate the *in vivo* antitumoral, antimetastatic and antiangiogenic efficacy of two previous *cis*-enone RAL analogs bearing some of the beneficial and tolerated modifications (**105agh** and **105aej**).[77] Both compounds showed to be good inhibitors of tumor growth with comparable efficacy to sunitinib. Whereas compound **105agh** proved to promote lung metastasis as sunitinib, compound **105aej** inversely proved to efficiently suppress them. Surprisingly, while compounds **105agh** and **105aej** showed a comparable profile of activity against 50 kinases, they showed a completely different behavior towards angiogenesis: compound **105agh** proved to strongly inhibit it, whereas compound **105aej** did not. Compound **105aej** having shown to be much faster inactivated than compound **105agh** by thiols such as dithiothreitol (DTT), it was hypothesized that both compounds may present a significant difference in the rate of kinase inhibition relative to inhibitor inactivation, and that this difference of kinetic could account for the previous stricking difference in selectivity.

Differences in kenetics of target inactivation versus inhibitor inactivation, as well as the presence of the residue cysteine 166 in only forty-eight kinases of the kinome, induce some selectivity in the kinases inhibited by the *cis*-enone RALs. Also these natural products have been shown to inhibit simultaneously multiple kinases (as all small molecule kinase inhibitors approved for therapeutic intervention or in clinical development[69]), all the kinases inhibited by the *cis*-enone RALs notably proved to be involved in the development, progression and aggressiveness of cancer. These irreversible inhibitors are then highly promising agents in oncology. Compound **105aej** is particularly interesting as, contrarily to sunitinib, it proved to inhibit metastasis which is at the origin of cancer

patient death (rather than primary tumor growth). However, due to the number of kinases inhibited along the MAP kinase cascade, a concerted evolution of several kinases to evade the growth inhibition of the resorcylic acid lactones is not inconceivable. An important question is then whether a mutation in the cysteine residue which is so important for the activity would be viable.

Chapter 2

Studies towards the synthesis of guaianes and pseudoguaianes

I. Introduction

1. Presentation of the sesquiterpene lactones family

Sesquiterpene lactones are a family of natural products with over 3000 different structures reported to date. They may be extracted from several plant families, generally from leaves and flowerheads of *Compositae* with a percentage per dry weight varying from 0.01% to 5%. Sesquiterpene lactones differ by their carbocyclic skeleton and the functionalities present on the cycles. As shown in Figure 12, they can be ordered in four major groups called germacranolides (10-membered ring), eudesmanolides ([4.4.0] bicyclic framework), guaianolides and pseudoguaianolides ([5.3.0] bicyclic frameworks).

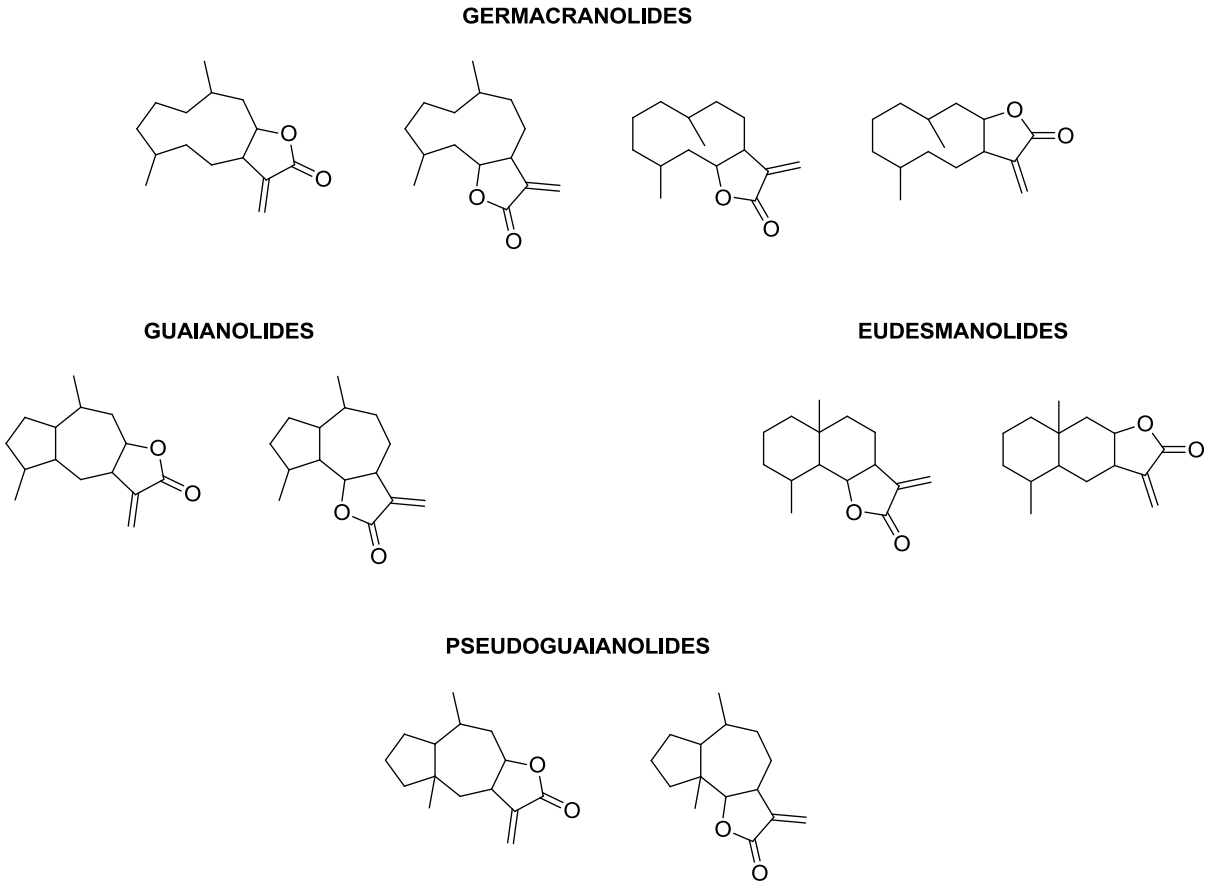


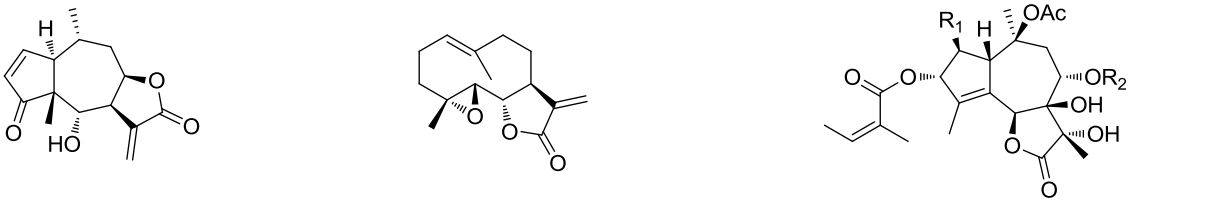
Figure 12. Skeletons of the four major groups of sesquiterpene lactones.

As it will be explained in the biosynthetic section, germacranolide subfamily is the first intermediate from which other sesquiterpene lactones are derived. Although different, the sesquiterpene lactones

all present commun features such as an α-methyl-γ-lactone, and generally contain further oxidation in the form of an epoxide, a hydroxyl or an esterified hydroxyl.

2. Biological activity and structural requirements

The presence of sesquiterpene lactones in plants is known to cause losses of livestock by intoxication, but they also exhibit a wide spectrum of biological activity including cytotoxic/anti-tumor, anti-inflammatory, anti-microbial and anti-fungal properties,[10] and have been used in traditional medicine for centuries. Helenalin (**130**) is for example the major ingredient of *Arnica montana*, a plant that is commonly used in anti-inflammatory preparations, principally to treat bruises, whereas parthenolide (**131**) is hardly associated to the therapeutic effects of feverfew, an herb widely used to relieve migraine, inflammation and arthritis, prevent blood clots and help digestion (Figure 13).[78] In the same way, thapsigargin (**132**) and its fifteen closely related analogs, have been elucidated as the main biologically active components of the plant *Thapsia*, whose root preparations have been used to treat rheumatic pains and pulmonary disorders.[79]



130 - helenalin **131 - parthenolide** **thapsigargins**

R_1 = octanoyl, R_2 = *n*-Butanoyl, **132 - thapsigargin**

Figure 13. Examples of sesquiterpene lactones used in traditional medicine.

2. a. Structure-activity relationship studies

An essential factor contributing to the pharmacological properties of these molecules is the presence of Michael acceptors which can react with targeted proteins. Concerning cytotoxicity, the importance of the α-methylene-γ-lactone or the cyclopentenone function was pointed out for the first time by Kupchan *et al.* in 1971 (Figure 14),[80] who observed that modifications such as saturation of the methylene group induced a loss of activity (analog **133** *vs* analog **134**, and analog **135** *vs* analog **136**).

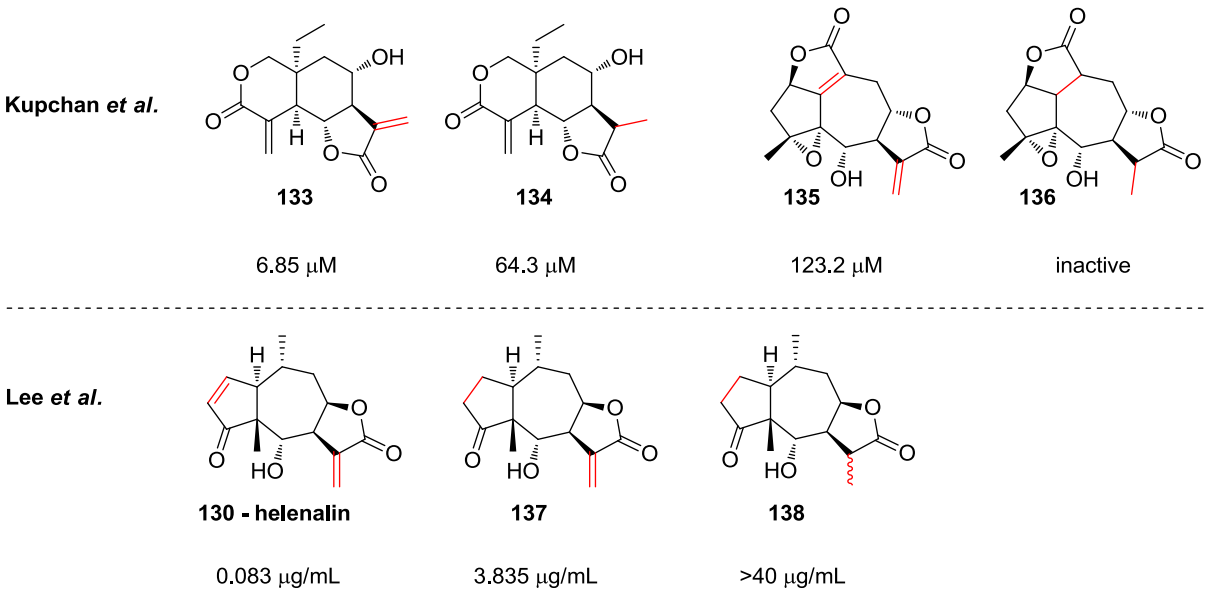


Figure 14. Influence of the α-methylene-γ-lactone and the cyclopentenone functions on cytotoxicity.

This result was directly demonstrated again by Lee *et al.* (who proved that helenalin (**130**) was more toxic than dihydrohelenalin (**137**), itself more toxic than tetrahydrohelenalin (**138**, Figure 14)),[81,82] or more recently by Woerdenbag *et al.* on different cell lines.[83] Several SAR studies were also published to highlight the crucial influence of these two functionalities on anti-inflammatory,[11] anti-microbial[84,85] and anti-fungal activities.[86,87]

In the case of cytotoxicity, Lee *et al.* however explained that, regardless of the α-methylene-γ-lactone or cyclopentenone, the real factor influencing the activity was the presence of a O=C-C=CH_2 system in the molecule.[65] They arrived to this conclusion following the observation that compounds **139** and **140** were both equally active (Figure 15).

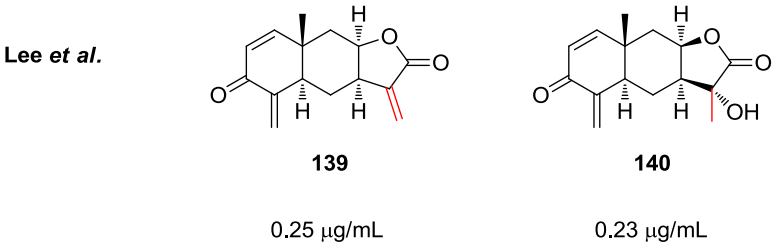


Figure 15. Influence of the O=C-C=CH_2 system on cytotoxicity.

Based on this postulate, it has been shown that adding conjugated ester side chains could promote a significant increase in the cytotoxic activity (Figure 16).[89] The addition of an aromatic nucleus in conjugation with the ester carbonyl appeared particularly efficient (helenalin **130** *vs* analog **142**).

Although such a correlation between the activity and the number of unsaturated ester was not observed in the case of anti-microbial[85] and anti-inflammatory[13] activities, the strong influence of the presence of the α-methylene-γ-lactone and the cyclopentenone on the diverse activities of the sesquiterpene lactones led to conclude that the reactivity of these molecules is due to the nucleophilic addition of thiol residues of the proteins on the Michael acceptors.

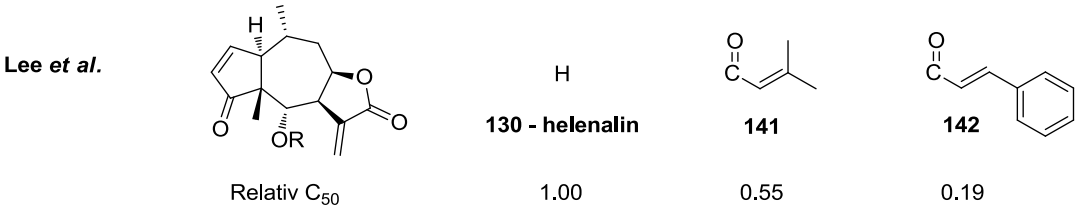


Figure 16. Influence of additional conjugated esters on cytotoxicity.

After the number of alkylating agents, the two parameters that were most often mentioned as influencing the biological activity are the lipophilicity and the molecular geometry.

The fact that activity increases when lipophilicitic character is enhanced is probably related to a question of transport process. This correlation was first illustrated for the cytotoxic activity by Kupchan *et al.*, who proposed an equation correlating these two data (Figure 17).[80]

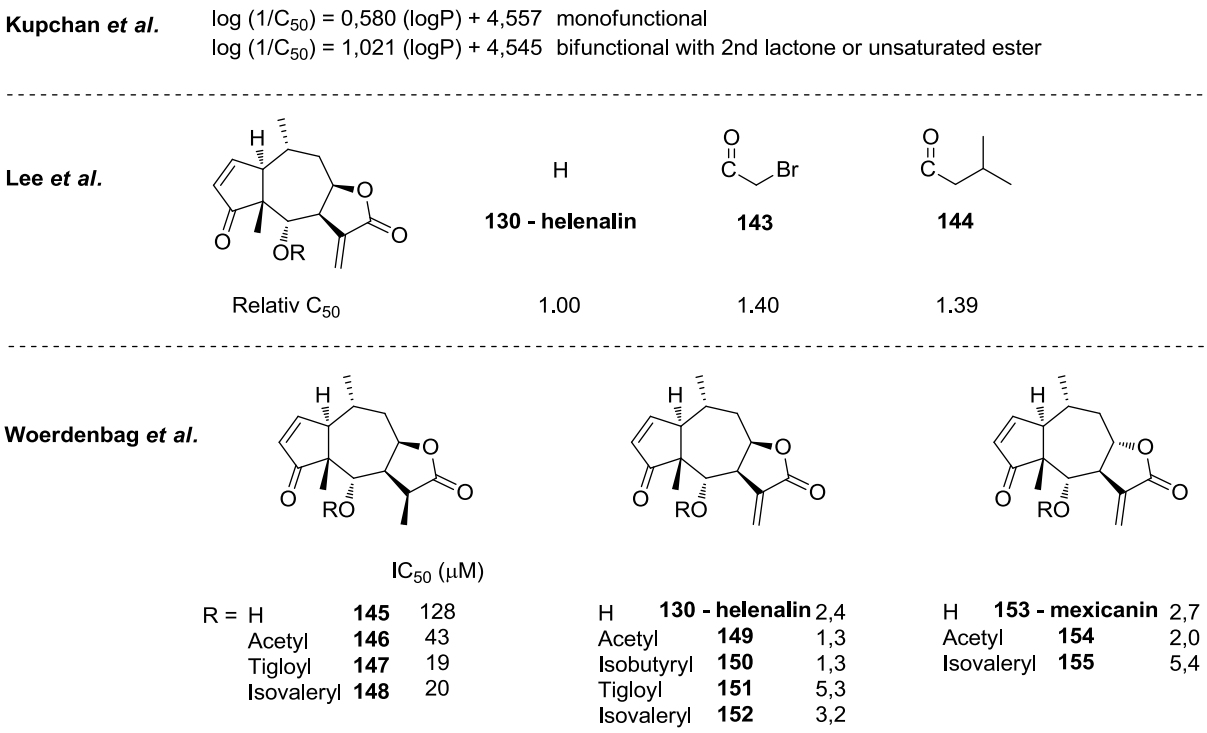


Figure 17. Influence of lipophilicity on cytotoxicity.

The idea was then taken over by Lee *et al.*[89] and more recently by Woerdenbag *et al.*,[90] who proved that incorporating a longer ester side chain induced stronger tumor inhibition (helenalin (**130**) *vs* analogs **143** and **144**, dihydrohelenalin **145** *vs* analogs **146**-**148**). Interestingly, in the case of helenalin and mexicanin series, cytotoxicity proved to decrease once the ester chain reached an optimal length. This regression could be explained by the fact that, when the ester chain becomes too large, the approach of the α-methylene-γ-lactone towards biological targets is prevented. In the dihydrohelenalin series, the alkylating agent being far away from the ester side chain, this phenomenon was not observed. Steric hindrance is thus another essential factor to consider for cytotoxicity. Similar influences of the lipophilicity and the molecular accessibility could be observed on the anti-microbial activity,[87] whereas anti-inflammatory proved unaffected.[11,13]

As evoked just above, molecular geometry also proved to induce dramatic changes in activity, and particularly on cytotoxicity (Figure 18).[90] For example, due to its 7,8-*cis* fused lactone helenalin (**130**) presents a high degree of flexibility (it possesses two conformers at room temperature), whereas its 7,8-*trans* fused lactone makes mexicanin (**153**) rigid, reducing its possibility of reacting with thiol residues and as a consequence less toxic. In the same way, arnifolin (**156**) proved to be five times more cytotoxic than the chamissonolide analog **157** by adopting completely different molecular conformations. Whereas chamissonolide analog **157** indeed adopts a twist boat conformation, inducing a strong hindrance of the exo-methylene group by the tigloyl group, arnifolin (**156**) adopts a twist chair conformation where the methylene group is more accessible and then more reactiv. Here again, it has been demonstrated that such a correlation does not exist in the case of the anti-inflammatory activity.[11]

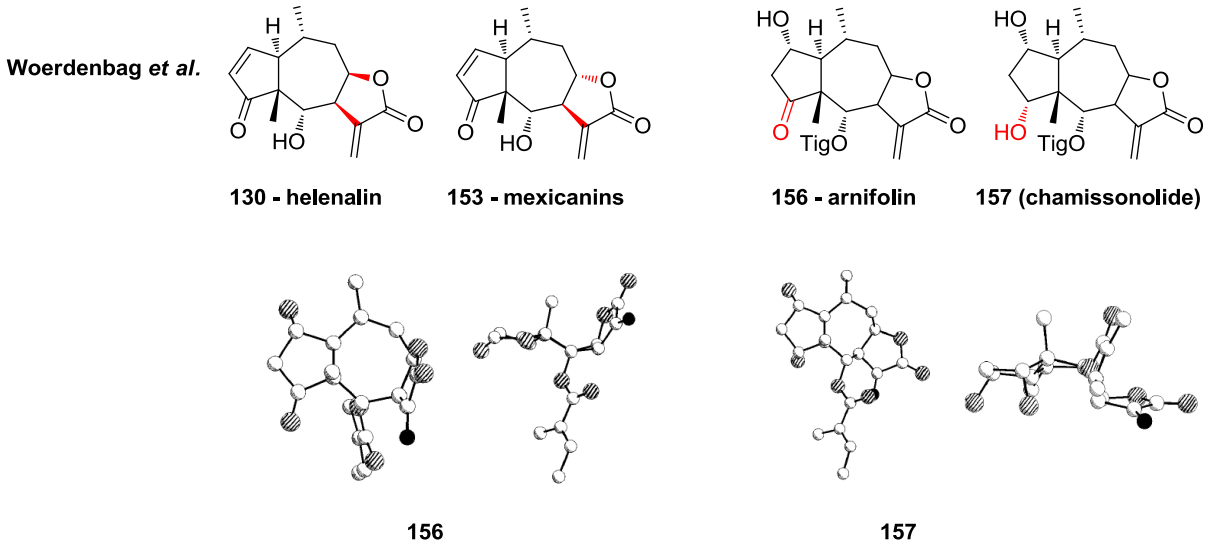


Figure 18. Influence of molecular geometry on cytotoxicity.

In view of the previous results, it appears clearly that the cytotoxicity is the biological activity which is the most logically influenced by structural changes, and for which it was easier to propose

classifications (similar classifications were also proposed for germacranolides[91,92] and eudesmanolides[92] classes), contrary to the anti-inflammatory activity which looks rather unpredictable[93]. Thus, although differences in cytotoxicity among individual sesquiterpene lactones could largely be explained by the three factors detailed above, many other parameters (more marginal) have been enumerated as having an influence on cytotoxicity.

The solubility of the molecule was for example cited as significant parameter. One reason evoked for the higher cytotoxicity of helenalin (**130**) compared with mexicanin (**153**) was indeed its greater solubility in polar and non-polar solvents.[90]

Another highlighted factor is the isomerism of the double bound of the lactone (Figure 19). To induce reactivity with biological targets, the methylene group has to be exo, reduction of the endo form inducing any loss of cytotoxicity (analog **158** appearing to be as active as analog **136**, and analog **159** as active as analog **160**).[80]

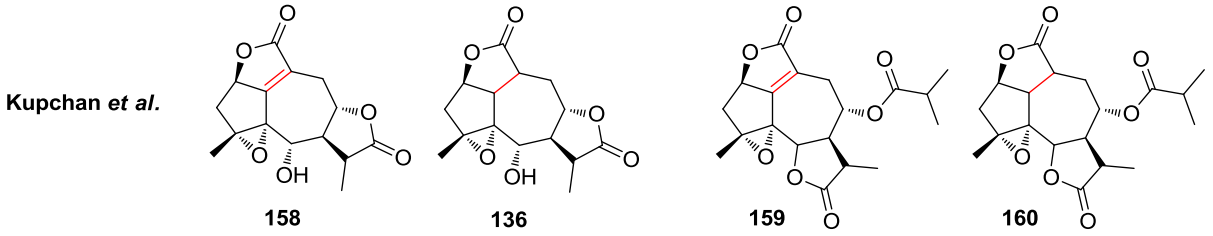


Figure 19. Influence of methylene group isomerism on cytotoxicity.

Another influencing parameter that has been cited is the presence of a hydroxyl group adjacent to the methylene group of the lactone. As shown in Figure 20, helenalin (**130**) proved to be significantly more cytotoxic than analog **161**, the same conclusion could be drawn by comparison on two different cell lines of analog **163** with analog **162**.[80] This observation was justified by the fact that the hydroxyl group may form hydrogen bounds with amino acid residues of the proteins.

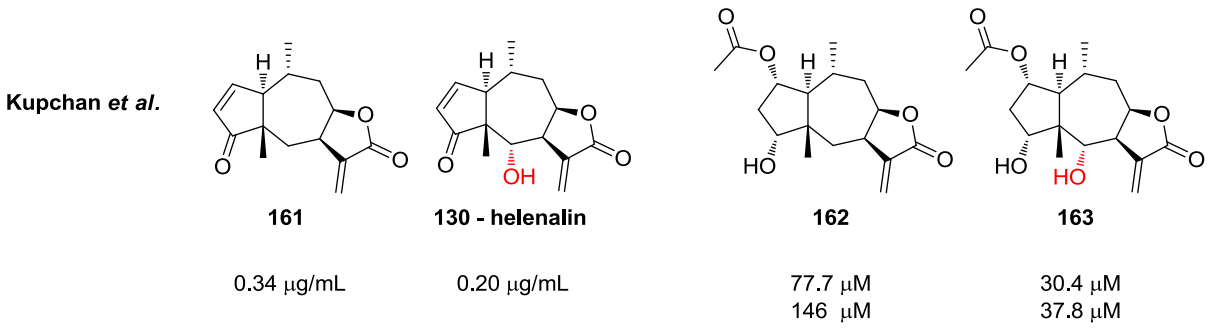


Figure 20. Influence of the hydroxyl group adjacent to the lactone on cytotoxicity.

Finally, a quantitative SAR (QSAR) study done recently by Emerenciano *et al.* on 37 sesquiterpene lactones coming from different classes (14 germacranolides, 6 elemanolides, 9 guaianolides, 8 pseudoguaianolides) highlighted the strong influence of four new factors on cytotoxicity.[94] The seven most active compounds that emerged from this study are depicted in Figure 21. By looking at them they concluded that to be highly cytotoxic, sesquiterpene lactones need to: have a double bound in the 5-membered ring at position 3 or in the 7-membered ring at position 10, possess a hydroxyl group at C_5, present a 6,12-lactonization (meaning no carbon between the cyclopentane and the α-methylene-γ-lactone), and have as skeletal the guaiane or pseudoguaiane.

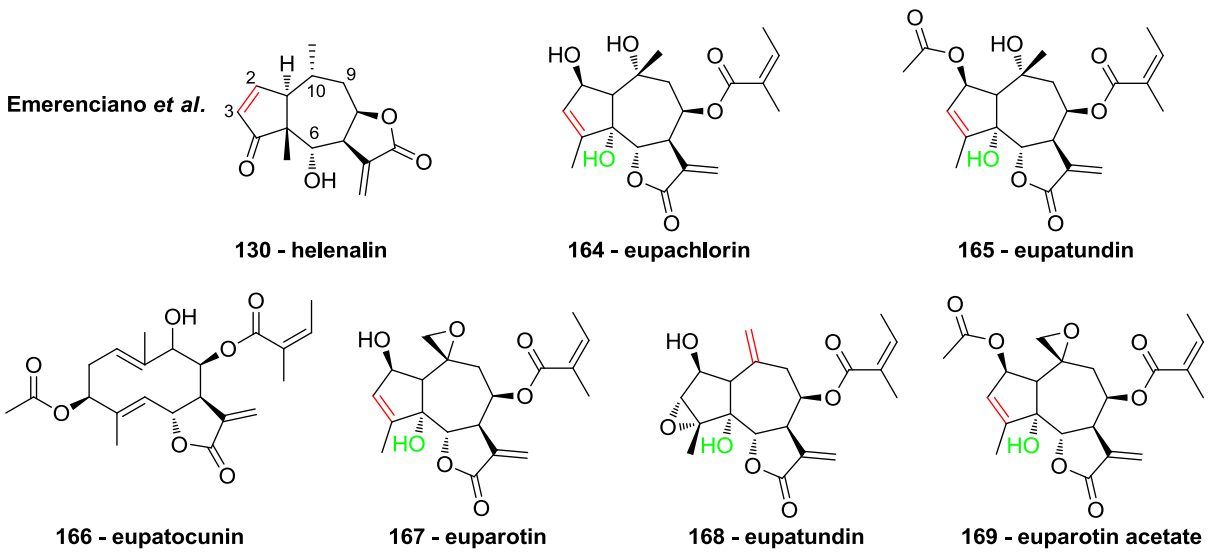


Figure 21. Most active compounds emerging from Emerenciano *et al.* SAR study.

Looking at the results of these SAR studies, it could be concluded, in a simplistic way, that the more Michael acceptors there is, the more reactive the molecules are, and it could consequently be feared that these natural products are going to react with every proteins bearing an accessible nucleophilic site, becoming thus a real poison or activating grave allergic reactions. However, some of these molecules have been shown to be highly selective, and the best counter-example to the previous theory is the guaianolide thapsigargin (**132**, Figure 13). This sesquiterpene lactone appeared to induce a potent sub-nanomolar inhibition of sarco/endoplasmic reticulum Ca^{2+} ATPases (SERCAs),[95,96] which besides being rapid and irreversible, indeed proved to be extremely selective.[97,98] While thapsigargin equally inhibits all the SERCAs isoforms, it indeed does not affect (even in large doses) the activities of the plasma membrane Ca^{2+} ATPase, the Na,K ATPase, channels that are dependent on Ca^{2+} plus ATP, phosphoinositide or protein kinase C. By inhibiting the SERCA pump, thapsigargin induces in few minutes a three to four fold rise of the cytosolic Ca^{2+} concentration, attributed to the depletion of the endoplasmic reticulum Ca^{2+} and the subsequent influx of extracellular Ca^{2+} consequently engaged by the plasma membrane Ca^{2+} ATPase.[99] This severe Ca^{2+} increase causes the arrest of the cells out of the progression cycle in G_0, and eventually leads to programmed cell death.[100] All these attractive properties have recently led to the development of a thapsigargin-derived prodrug for the treatment of androgen-independent prostate cancer, whose proliferation is too slow to apply standard chemotherapy (thapsigargin is linked to a

peptide residue, which is specifically recognized and cleaved extracellularly by a prostate-specific antigen (PSA), thus delivering the cell permeable and cytotoxic thapsigargin derivative in the vicinity of prostate tumors[101,102]).

2. b. Biological mechanism

While the cytotoxic properties of sesquiterpene lactones are well documented, the lack of identified targets and mode of action renders the interpretation of the SAR difficult. On the other hand, the anti-inflammatory properties of several sesquiterpene lactones have been attributed to NF-κB inhibition with well characterized mechanism. [103-105]

This protein, composed of two subunits called p50 and p65, is a central mediator of the human immune response (Figure 22).[106,107] It is generally retained in an inactive cytoplasmic complex by binding to IκB, an inhibitory subunit. Under inflammatory or infectious conditions, cells are stimulated by a variety of pathogenic agents, which lead to the generation of reactive oxygen intermediates (ROIs) and a cascade of signals causing the IκB-kinase complex (IKK) activation.

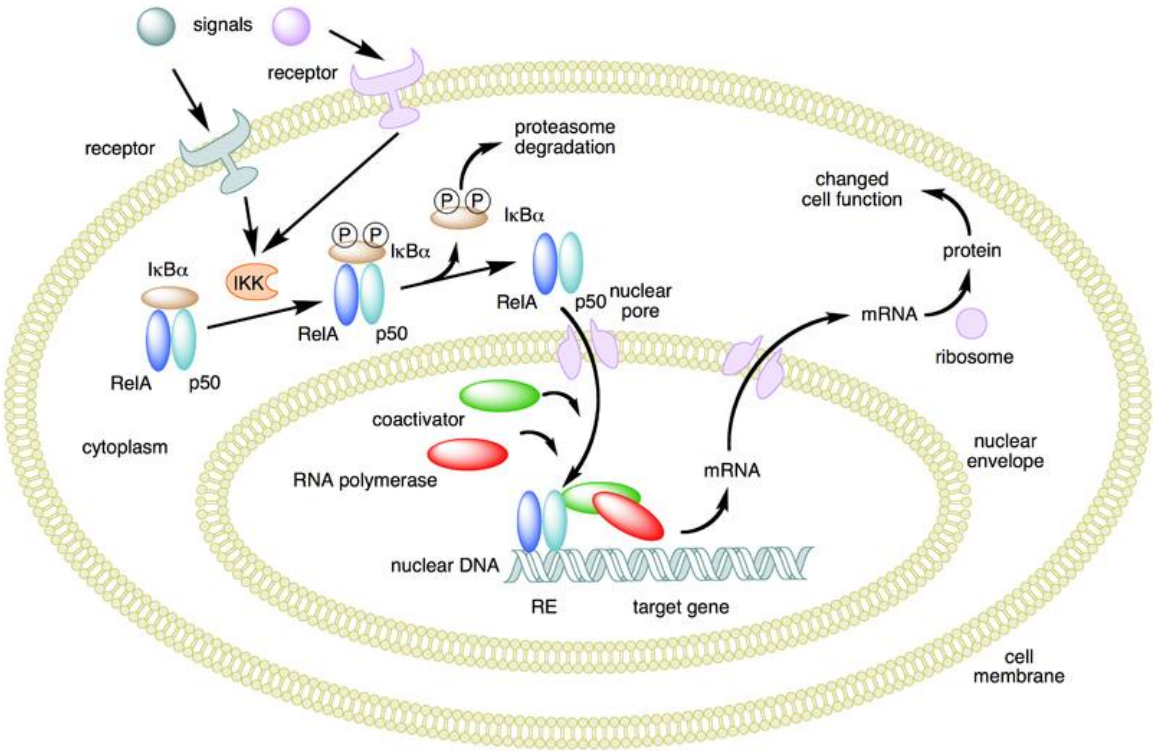


Figure 22. NF-κB mechanism of action.

The activated IKK then induces the phosphorylation of the two major forms of IκB protein (IκB-α and IκB-β) on serines 32 and 36, and their subsequent ubiquitinylation. The tagged inhibitory subunit can thus be degradated by the 26-S proteasome, which causes NF-κB translocation into the nucleus. Once in the nucleus, NF-κB binds to DNA sequence and stimulates the transcription of its target genes.

NF-κB is known to regulate the trancription of over 150 genes including genes encoding immunoreceptors, many cytokines, cell adhesion molecules, enzymes such as cyclooxygenase-II (COX-II) or inducible nitric-oxide synthase (iNOS). Its malfunction proved to be implicated among others in rheumatoid arthritis, Alzheimer's disease, or septic shocks.[108,109] These last one were indeed associated with a massive activation of the NF-κB, inducing a massive production of cytokines and subsequent failure of circulation as well as general organ function. It is therefore not surprising that strong interest is carried in its inhibition.

Different inhibitors of NF-κB,[109] interfering with activating processes at different levels in the signaling cascade, were already identified:

- The first group interferes with the generation of oxygen radicals just after the stimulation of the cell (anti-oxidative). This category includes for example *N*-acetyl-L-cysteine, pyrrolidine dithiocarbamate, acetylsalicylic acid, or curcumin.
- The second group interferes with the functioning of the 26-S proteasome, in charge of IκB degradation.
- The last group interferes in cell nucleus by preventing NF-κB, already bound to DNA, of transcripting its target genes.

Concerning the biological mechanism for the inhibition of NF-κB activation by the sesquiterpene lactones, two different theories have been proposed. On one hand, Merfort *et al.* advanced that sesquiterpene lactones directly target the NF-κB, thus preventing its binding to DNA.[11] On the other hand, Hehner *et al.* argued that the terpenoids only target the IκB-α and prevent its degradation.[109]

This second alternative was disproved in 2001 by Merfort *et al.* through simple experiments.

The first experiment consisted in staining with three different specific agents the cytoskeleton, the nuclei and the activated NF-κB p65 molecules of cells previously stimulated and treated with a sesquiterpene lactone (Figure 23A).[11] By combining the three resulting pictures, they could show that NF-κB molecules had translocated into the nuclei.

In a second experiment, they repeated the work performed by Hehner *et al.* comparing the amount of IκB present in cells pretreated or untreated with a sesquiterpene lactone (25 µM of parthenolide), but previously stimulated and treated the cells with cycloheximidine to avoid *de novo* IκB synthesis.[12] After 5 min, in the case of pretreated cells, NF-κB.DNA binding proved to be completely inhibited (data not shown). As shown in Figure 23B, no more IκB was detected after 120 min in untreated cells, whereas a small stable amount could still be detected in treated cells.

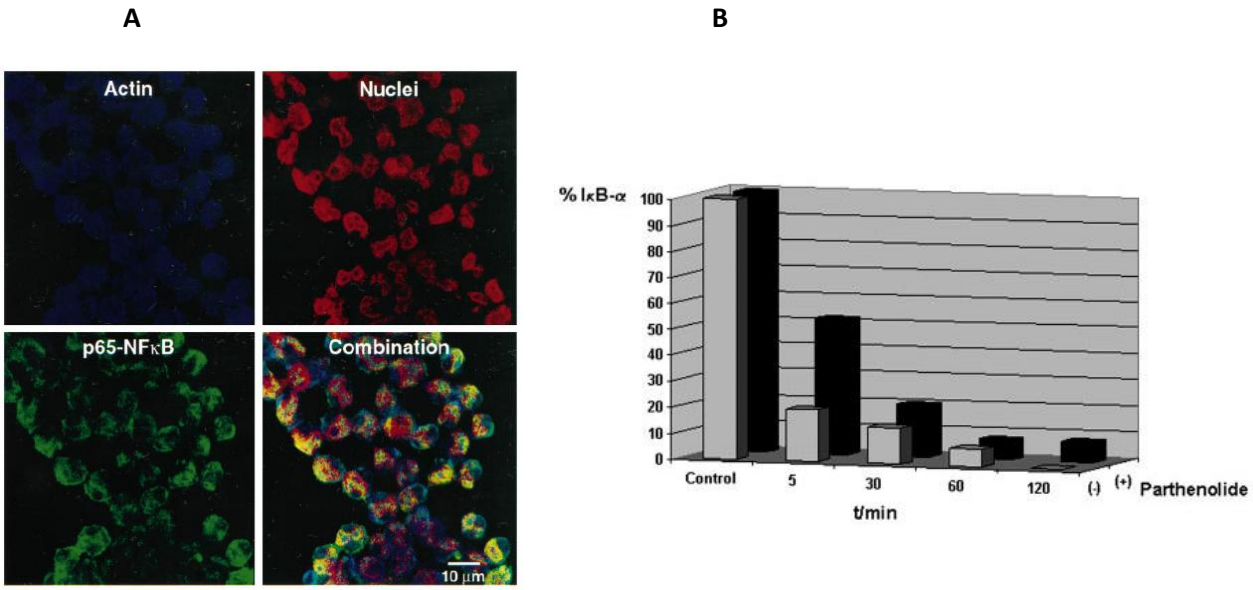


Figure 23. Non inhibition of IκB degradation by the sesquiterpene lactones. (**A**) Confocal scanning microscopy images of Jurkat T cells pretreated with 10 µM helenalin (**130**). Fixed samples were stained for filamentous actin with fluorescein isothiocyanate labeled phalloidin (blue label), for cell nuclei with TOTO-3 (red label) and for activated p65 NF-κB molecules using a mouse monoclonal anti-p65 NF-κB antibody biotin-conjugated anti-mouse IgG antibody and Cy3-labeled ExtrAvidin (green label, appears yellow when colocalizing with red cell nuclei). (**B**) Quantification of IκB-α. Cells were incubated with 100 µg/mL cycloheximide for 1 h before incubating with 25 µM parthenolide for 1 h and then stimulated with 200 units/mL TNF-α.

These results show that sesquiterpene lactones actually cause a partial inhibition of IκB degradation. It was suggested that this slight inhibition may be due to a partial inhibition of the IκB-kinase complex, by alkylation of the cysteine residues contained in both catalytic subunits IκB-α and IκB-β. However, the low level of this inhibition (5.6% of the total IκB present at the beginning in the cells) is clearly insufficient to explain, as suggested by Hehner *et al.*, the complete NF-κB inactivation. This model failed to consider *de novo* synthesis of IκB, and the delay of IκB degradation.

The theory of the IκB degradation inhibition being excluded, the theory of a direct targeting of the transcription factor NF-κB thus seemed the most plausible. Merfort *et al.* indeed proved, by treating cells transfected with a p65 subunit with increasing concentrations of helenalin (**130**), that the sesquiterpene lactones completely prevent p65.DNA binding (Figure 24).[11] The same experiment conducted using a p50 expressions vector showed no inhibition of p50.DNA binding (data not shown). These results clearly demonstrate that the privileged target of this natural products family is the p65 subunit of NF-κB.

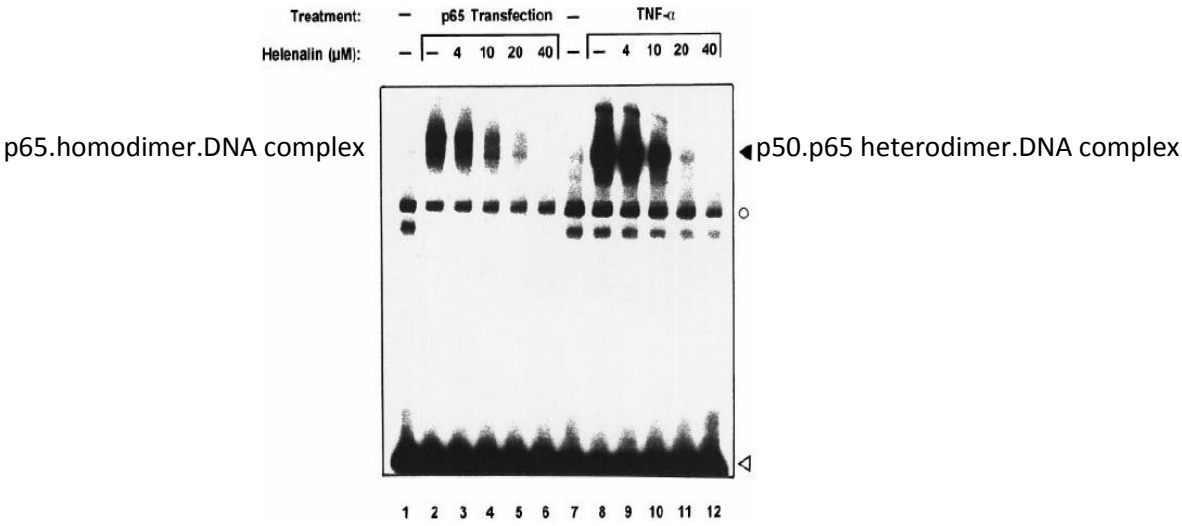


Figure 24. Inhibition of p65.DNA binding by helenalin (**130**). 293 cells were transiently transfected with 6 μg of a p65 expressions vector (lanes 2-6). 24 h after transfection, cells were treated with various concentrations of helenalin (**130**) for 1 h. Lanes 8-12 show 293 cells treated for 1 h with the indicated amounts of helenalin (**130**) and subsequently stimulated for 1 h with 200 units/mL TNF-α. Lanes 1 and 7 show untreated control cells. Total cell extracts were prepared and analyzed for NF-κB.DNA binding by EMSA. The open cycle denotes a nonspecific activity binding to the probe and the open arrowhead shows unbound oligonucleotide.

Further experiments were then performed to get more information about the way sesquiterpene lactones react with p65 subunit.[11] As shown in Figure 25A, when the cells were treated with an excess of DTT prior to incubation with helenalin (**130**), no more inhibition of the NF-κB.DNA binding was detected, suggesting a preferential reaction of helenalin (**130**) with the huge quantity of thiol groups brought by DTT. Inversely, when helenalin (**130**) was added prior to the excess of DTT (Figure 25B), the ability of helenalin (**130**) to completely inhibit NF-κB.DNA binding remained intact. Both observations confirmed that reaction of the sesquiterpene lactones with the p65 subunit takes place through a Michael-type addition on cysteine residues, and interestingly highlighted the irreversible character of this addition. As explained in the irreversible inhibitors section and in Chapter 1, this last characteristic is particularly interesting for a drug in the sense that it allows to reduce the required frequency of drug application.[14,15]

Finally, based on molecular modeling data and on all the previous observations (sesquiterpene lactones react with the cysteine residues of p65 subunit, p50 subunit is not targeted, bis-alkylating agents are more active than mono-alkylating), a first mechanism of action could be proposed.[13] This mechanism suggested that both cysteine residues of p65 subunit located in the DNA binding region, namely Cys^{38} and Cys^{120}, were simultaneously alkylated by one bifunctional sesquiterpene lactone. However, an experiment performed by the same group two years later revealed that this mechanism was not totally accurate, and had to be partially reviewed.

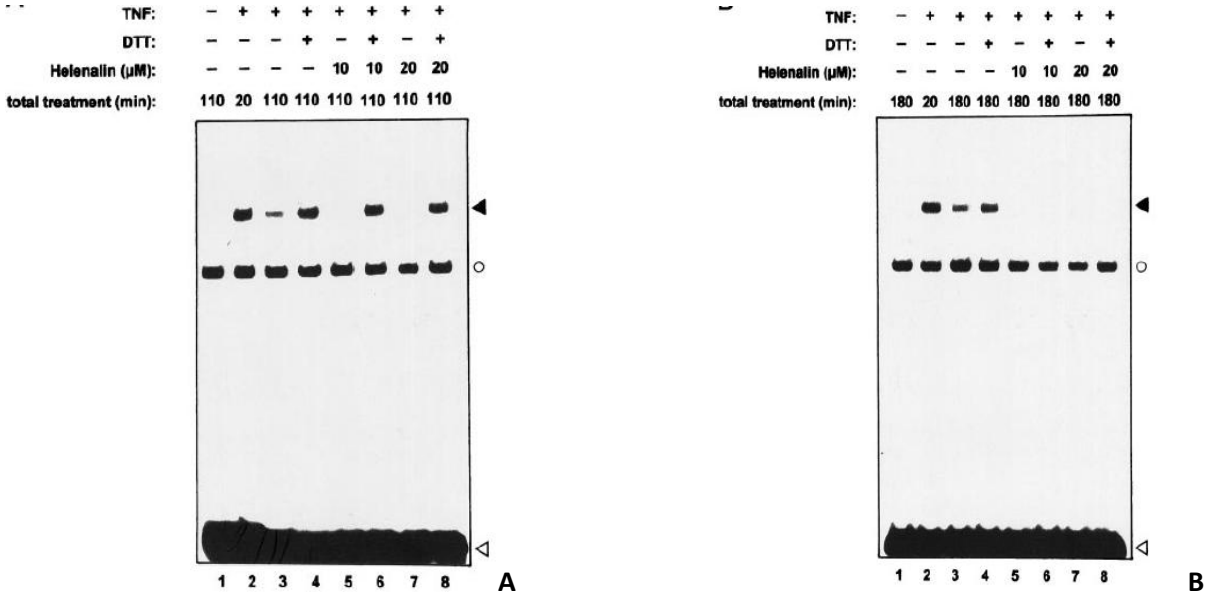


Figure 25. Irreversible addition of the sesquiterpene lactones on cysteine residues of p65 subunit. Lane 1 shows unstimulated cells. (**A**) In lane 2 cells were treated with 200 units/mL TNF-α alone for 20 min, in lane 3 for 110 min. In lanes 4-8, cells were stimulated with TNF-α. After 20 min, DTT was added to a final concentration of 5 mM (lanes 4, 6, and 8). 10 min after DTT addition, helenalin (**130**) was added at the concentrations indicated (lanes 5-8). After a total reaction of 20 (lane 2) or 110 min (lanes 1 and 3-8) cell extracts were prepared and analyzed for NF-κB activity by EMSA. (**B**) In lane 2 cells were treated with 200 units/mL TNF-α alone for 20 min, in lane 3 for 180 min. In lanes 4-8, cells were stimulated with TNF-α. After 20 min helenalin (**130**) was added at the concentrations indicated (lanes 5-8). 80 min after helenalin (**130**) addition, DTT was added to a final concentration of 5 mM (lanes 4, 6, and 8). After a total reaction time of 20 (lane 2) or 180 min (lanes 1 and 3-8) cell extracts were prepared and analyzed for NF-κB activity by EMSA. A filled arrowhead indicates the position of the NF-κB.DNA complex. The open circle denotes a nonspecific activity binding to the probe. The open arrowhead shows unbound oligonucleotide.

This experiment, depicted in Figure 26, involved p65 proteins containing mutations: cysteines at position 38 and/or 120 were replaced by a serine (except for Cys^{120}, which was replaced by an alanine, Cys^{120} → Ser no longer binding DNA), in which the thiol group is replaced by an alcohol and can thus no longer react with sesquiterpene lactones.[12] The observed order of affinity for DNA was: Cys^{38} → Ser > $Cys^{38, 120}$ → Ser > wild p65 > Cys^{120} → Ala. Cells were transfected with an excess of these mutants and treated with an increasing concentration of sesquiterpene lactone, before studying p65.DNA binding. Resulting gels show that Cys^{38} → Ser mutant.DNA complex was no longer inhibited by the sesquiterpene lactone whatever the concentration (Figure 26B), whereas Cys^{120} → Ala mutant.DNA complex was completely inhibited at a concentration even lower to that observed for wild p65 protein (Figure 26A). This last observation is not surprising: Cys^{120} → Ala having weaker affinity to DNA than wild p65, it is more sensitive to the perturbations of an inhibitor.

These results indeed prove that the mechanism proposed above is not totally correct and that only the cysteine at position 38 is alkylated by the sesquiterpene lactones. The only alkylation of Cys^{38} could actually justify the inhibition of NF-κB.DNA binding, this reaction inducing: the loss of the hydrogen bonding between Cys^{38} and DNA, dramatic changes in the position of the phenol group of

Tyr[36] whose interaction is essential for NF-κB.DNA binding (Figure 27B), and probable extension into spaces normally occupied by DNA (Figure 27C).

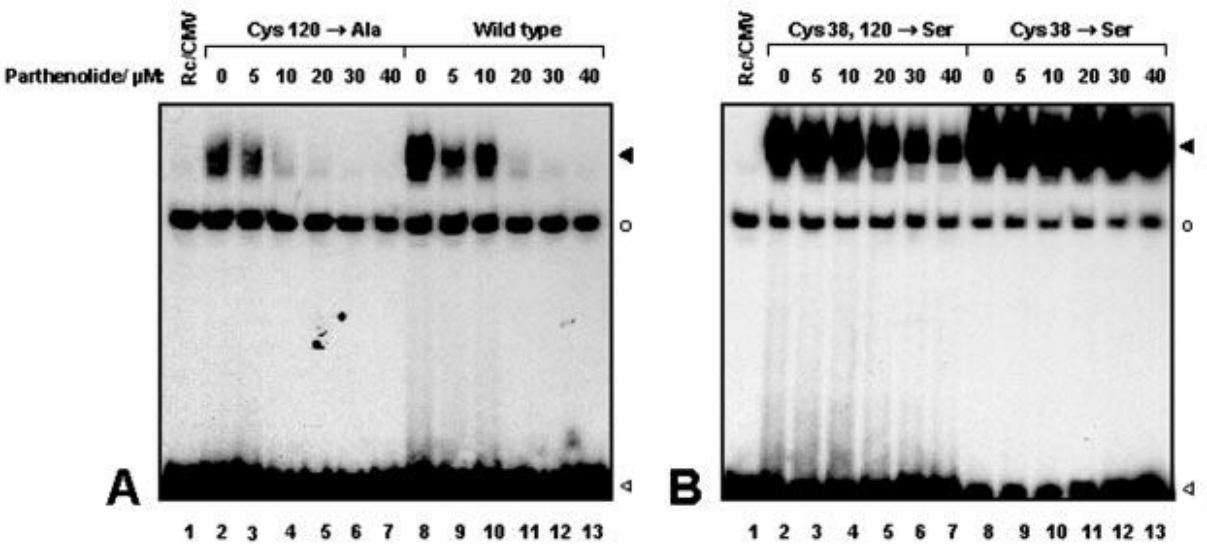


Figure 26. Inhibition of cysteine 38 in p65 subunit by the sesquiterpene lactones. 293 cells were transiently transfected with 3 µg of the corresponding expression vector. 48 h after transfection, cells were treated with the indicated concentrations of parthenolide for 2 h (**A** and **B**, lanes 3–7 and 9–13, respectively). In lanes 2 and 8, cells were not incubated with parthenolide after transfection. Total cell extracts were prepared and analyzed for NF-κB.DNA binding by EMSA. A filled arrowhead indicates the position of the p65 homodimer DNA complex. The open circle denotes a nonspecific activity binding to the probe, and the open arrowhead shows unbound oligonucleotide.

Nevertheless, even if Cys^{120} does not seem to be alkylated by the sesquiterpene lactones, this cysteine residue must play a crucial role in p65/DNA interactions. If Cys^{120} was unessential, p50 subunit, which presents a three dimensional structure similar to p65 with one cysteine residue at position 120 equivalent to Cys^{38} in p65 and as only real difference a hystidine at position 141 corresponding to Cys^{120} in p65, should have been alkylated in the same way as p65 by the sesquiterpene lactones family. Another observation underlying the significance of Cys^{120} is that, even if it did not prevent NF-κB.DNA binding inhibition, the mutation Cys^{120} → Ala made the system p65/DNA unstable (Figure 26). The first explanation coming in mind after this second experimental fact is that Cys^{120} may be implicated in DNA binding or recognition, but this explanation is in contraction with the fact that double mutant $Cys^{38, 120}$ → Ser was particularly stabilizing. It was thus finally suggested by Merfort *et al.* that Cys^{120} could be crucial for a question of optimal folder, but no evidence having been provided, the role of this cysteine residue still remains ambiguous.

As a conclusion, even if the principal molecular mechanism involved in sesquiterpene lactone anti-inflammatory activity is now globally elucidated (inhibition of NF-κB.DNA binding by alkylation of the Cys^{38} residue in p65 subunit), many gray areas still remain. As explained just above, the determination of Cys^{120} role would for example require further investigations.

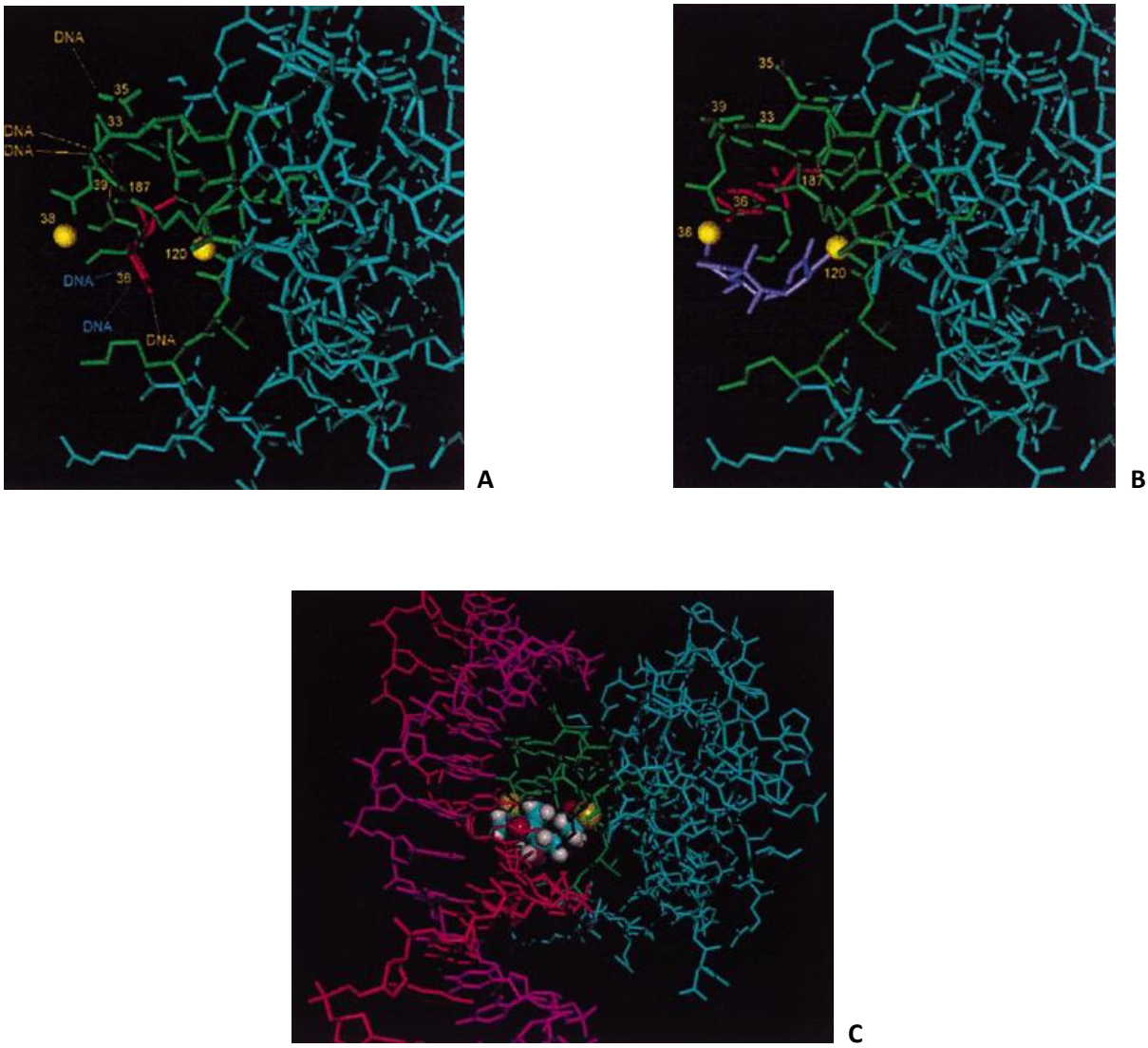


Figure 27. Dramatic geometrical changes induced by the alkylation of Cys^{38} by sesquiterpene lactones. (**A**) Native protein X-ray structure of NF-κB p65 homodimer subunit. (**B**) Energy minimized structure after linkage of cysteine residue by helenalin (**130**). (**C**) Overlay of the linked protein structure with DNA structure. Turquoise: protein portion kept rigid during energy minimization. Green: protein portion treated as flexible during energy minimization. Light blue: helenalin (**130**) molecule. Yellow spheres: cysteine sulfur atoms. Red: residue Tyr36. Red and purple: DNA strands. The other labeled residues Glu39, Arg33, Arg35 and Arg187 contribute to p65 DNA binding and recognition as indicated by yellow lines (hydrogen bounding) and light blue lines (van der Waals interactions with DNA).

Furthermore, several other undetermined biological molecules are hardly supposed to react, in a less significant but maybe interesting way, with the sesquiterpene lactones. For example, the inhibition of DNA binding with $Cys^{38,\ 120}$ → Ser double mutant (which no longer contains any reactive cysteine residues) being possible with high concentrations of sesquiterpene lactones suggested that amino acids of p65 subunit other than cysteine residues may also be targeted by the terpenoids.[12] In the same way, it could very well be imagined that one of the kinases implicated in the signaling cascade leading to NF-κB activation, unfortunately not all clearly determined to date, is at the origin of the partial IκB degradation inhibition (inhibition of the IKK being only a supposition). The hypothesis of

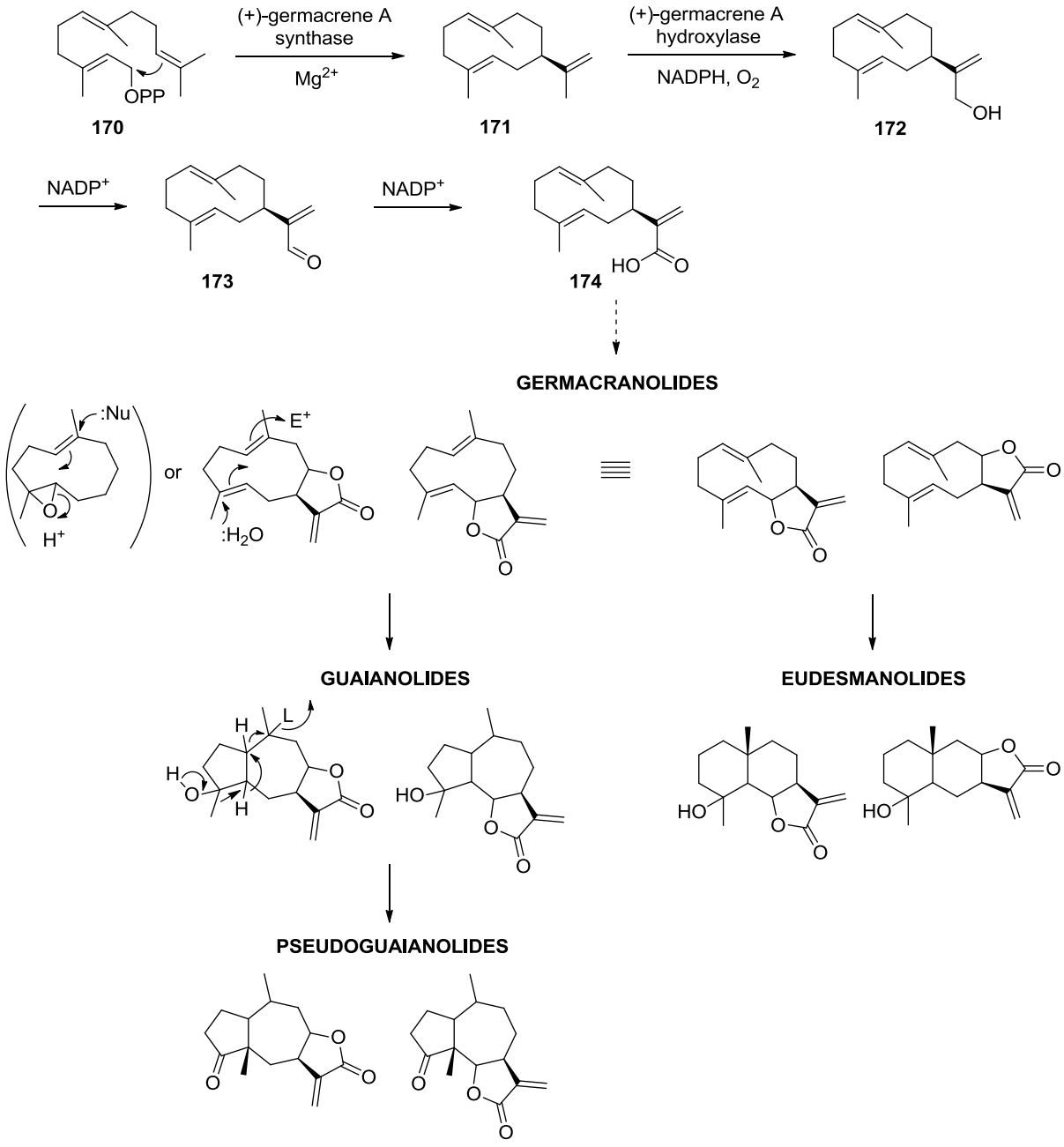
the existence of multi targets (other than Cys^{38}) is supported by the high concentrations of sesquiterpene lactones required to achieve the NF-κB activation inhibition.

Having efficient total syntheses of some sesquiterpene lactones available, allowing to prepare them in large quantities, should provide important "tool compounds" such as biotin conjugates to investigate their mode of action. Flexible total syntheses would also allow the preparation of analogs, for the purpose of discovering new lead compounds for the development of anti-inflammatory drugs. Sesquiterpene lactones should indeed become particularly interesting drugs due to their unique mode of inhibition of NF-κB activation (distinct from all the inhibitors listed above), their irreversibility, and their high degree of specificity[109] (no interference with the activity of other transcription factors). Futhermore, a synthetic access to these molecules could allow to broaden the diversity of this pharmacophore beyond biosynthetically available ones. Based on all these observations our laboratory decided to develop a new synthetic pathway to sesquiterpene lactones meeting these criteria. Before deciding of a strategy, the way nature prepares these natural products was consulted.

3. Biogenesis

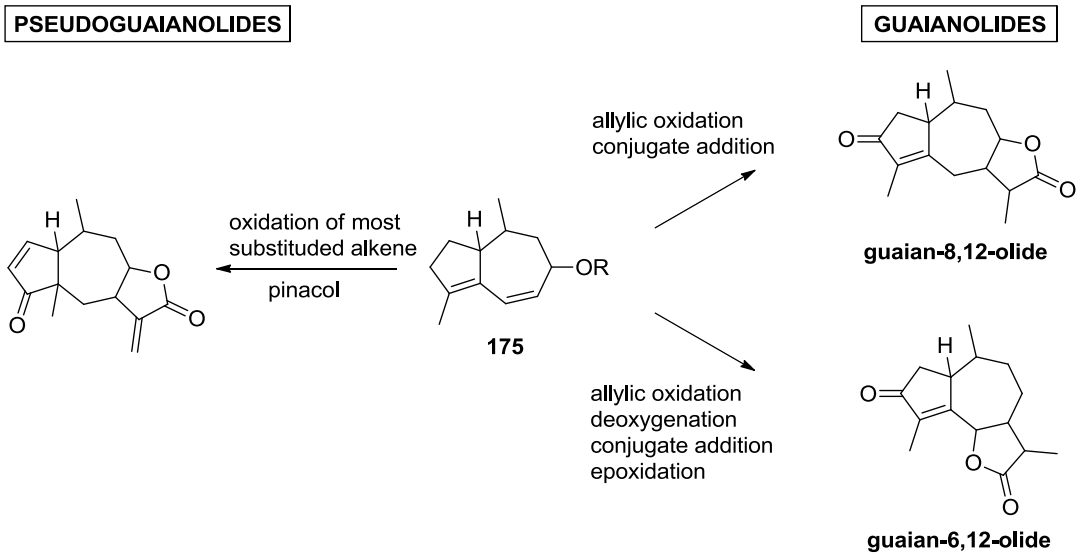
As indicated by their name, the sesquiterpene lactones all have for origin the assembly of three isoprene units. As illustrated in Scheme 26, they all appear to derive precisely from farnesyl diphosphate **170**, by a succession of cyclizations and oxidations.[110] This phosphate is first converted by an enzyme into (±)-germacrene A (**171**),[111] which by regioselective hydroxylation and two sequential oxidations affords (±)-germacrene A carboxylic acid (**174**).[112] Hydroxylation by a second enzyme then furnishes the germacranolide class, which is, as evoked above, the precursor of all the sesquiterpene lactones classes. Two different ways of cyclization, caused by water nucleophilic attack on this 10-membered skeleton, indeed result initially in the formation of guaianolides and eudesmanolides classes. These relatively simple 5/7- and 6/6-bicyclic compounds can then give access to the pseudoguaianolides class by pinacol rearrangement,[113] as well as to a broad variety of subfamilies by different transformations such as oxidations.

Inspired by the biosynthetic pathway our laboratory thus envisioned to base its strategy on a common and simple intermediate, which through various chemical transformations (notably oxidations) could lead to different members. Such a strategy should perfectly fulfill the criteria of efficiency and flexibility evoked above.



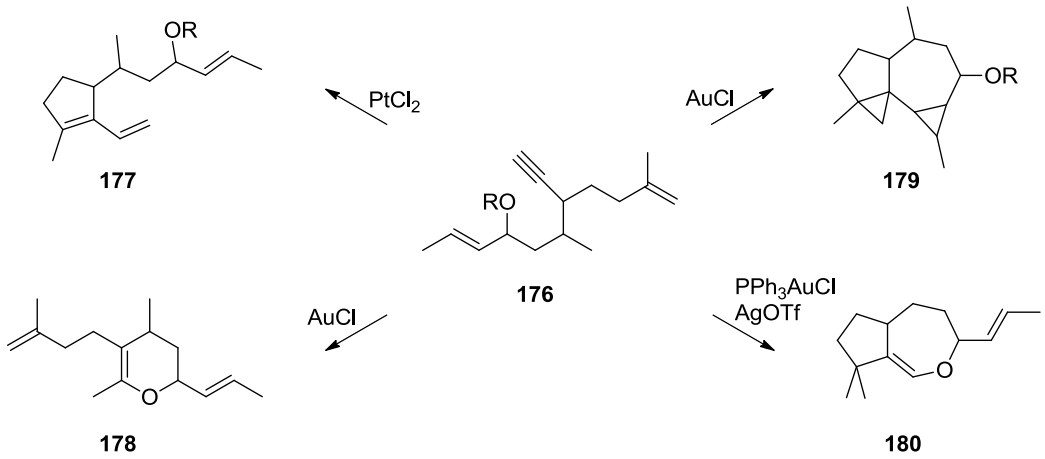
Scheme 26. Biogenesis of the sesquiterpene lactones.

It was decided to focus on the branch containing the 5/7-bicyclic framework, proved to be generally more active. As depicted in Scheme 27, a central intermediate like **175** could well be imagined to be transformed into pseudoguaianolides through a pinacol rearrangement (exactly as nature does), or into guaianolides through an allylic oxidation and conjugate addition.



Scheme 27. Synthesis of various sesquiterpene lactones from a common and simple intermediate.

Interestingly, as shown in Scheme 28, one coworker from the laboratory proved later that the synthetic precursor we chose for intermediate **175** (**176**) could also give access to carbocyclic scaffolds distinct of hydroazulene **175** just by changing the catalyst, then widening again the impact of the strategy.



Scheme 28. Other scaffolds accessible starting from the precursor of **175**.

A member of the two major classes containing the 5/7-bicyclic framework depicted in Scheme 27 was chosen as precise target to test the strategy: helenalin (**130**) was selected for the pseudoguaianolides and geigerin (**181**) for the guaianolides (Figure 28). The choice of helenalin (**130**) was obvious, this natural product being one of the most studied and active sesquiterpene lactones, almost every time selected as model for the biological tests. Geigerin (**181**) was selected subsequentially, due to the fact that it presented the same relative stereochemistry at C_1 and C_{10} as

helenalin (**130**). Three total syntheses have been proposed for (±)-helenalin (**130**) to date, and only one for (±)-geigerin (**181**).

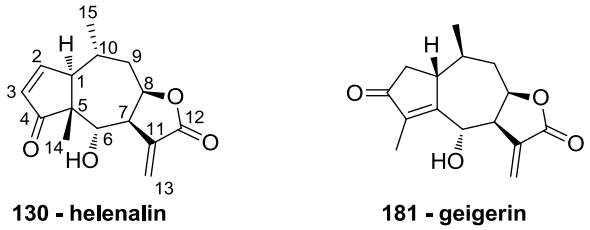
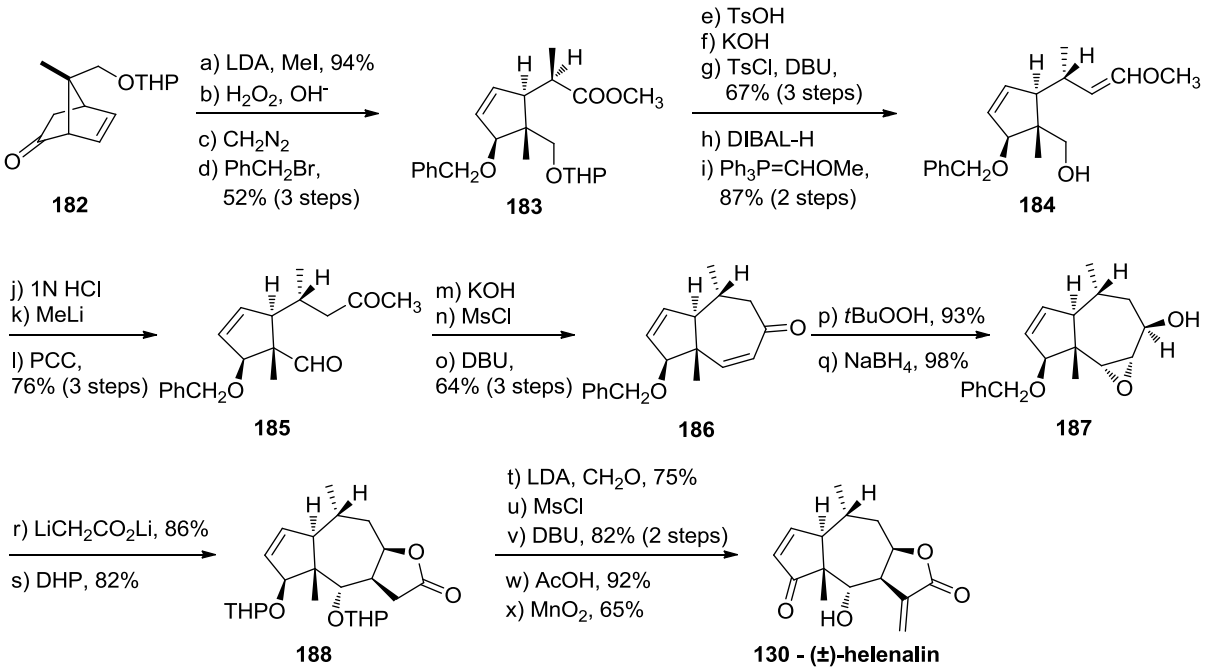


Figure 28. Structures of helenalin (**130**) and geigerin (**181**).

4. Previous total syntheses

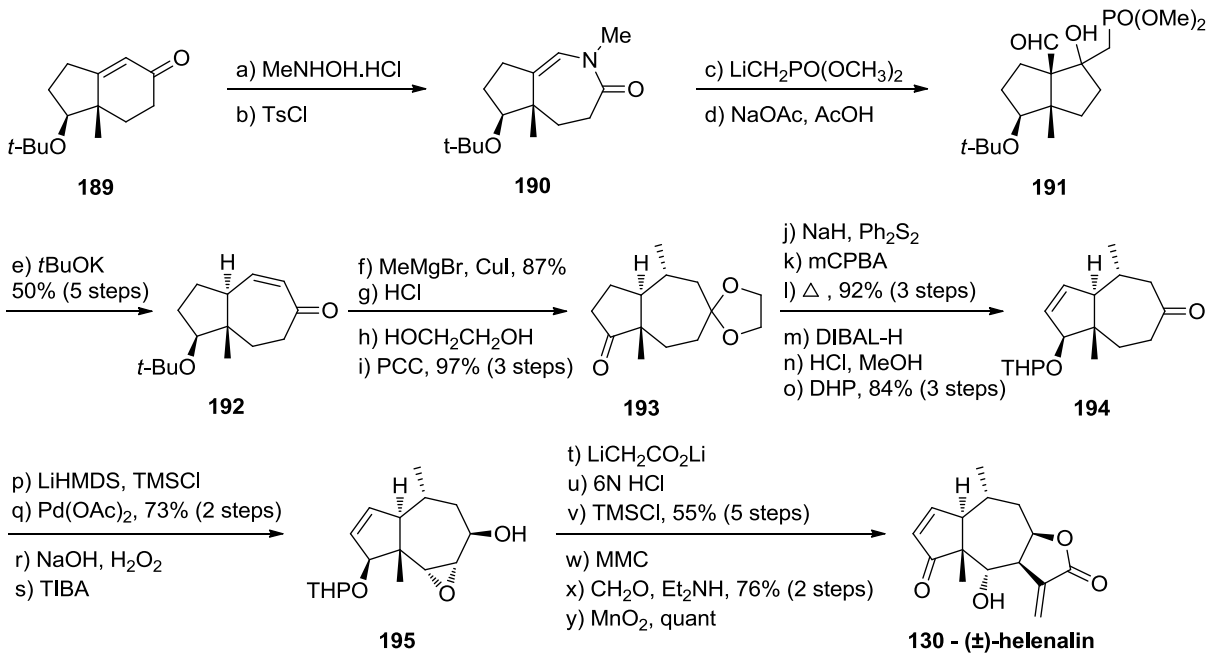
4. a. Previous total syntheses of (±)-helenalin

The first total synthesis of (±)-helenalin (**130**) was reported by Grieco *et al.* in 1978.[114] Some improvements have then been made in 1982 thus allowing the achievement of (±)-helenalin (**130**) total synthesis in twenty four steps starting from known bicyclo[2.2.1]heptenone **1** (Scheme 29).[115] Treatment of lithium enolate of bicyclic compound **182** with MeI, followed by Baeyer-Villiger oxidation under basic conditions, and subsequent protection of the resulting carboxylic acid and alcohol groups afforded intermediate **183**. Conversion of cyclopentenol **183** into enol ether **184** was achieved by sequential cleavage of the THP group and methyl ester, spontaneous lactonization and inversion of the methyl group configuration in the presence of TsCl and DBU, reduction of the resulting lactone in lactol using DIBAL-H and condensation with (methoxymethylene)-triphenylphosphorane. Hydrolysis of the methoxy group in enol ether **184**, followed by the treatment of the resulting aldehyde with MeLi and subsequent oxidation using PCC afforded keto aldehyde **185**. Intermediate **185** was converted by intramolecular aldol condensation and subsequent dehydration into bicyclo[5.3.0]compound **186**, which after epoxidation using bulky *t*BuOOH and reduction of the resulting epoxy ketone afforded alcohol **187**. Lactone **188** was then obtained by treatment of intermediate **187** with an excess of dilithioacetate and protection of both resulting alcohols using DHP. Desired (±)-helenalin (**130**) was finally isolated after hydroxymethylation, subsequent dehydration, deprotection of both THP groups, and allylic oxidation using MnO_2.



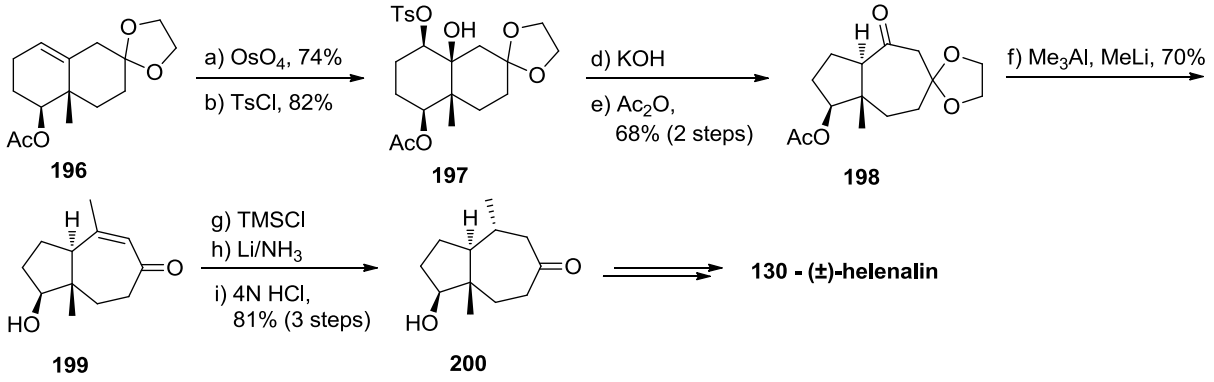
Scheme 29. Total synthesis of (±)-helenalin (**130**) by Grieco *et al*. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DHP = dihydropyran, DIBAL = diisobutylaluminium hydride, LDA = lithium diisopropylamide, Ms = mesyl, PCC = pyridinium chlorochromate, THP = tetrahydropyranyl, Ts = tosyl.

The second total synthesis of (±)-helenalin (**130**) has been described by Schlessinger *et al.* in 1979, and allowed to prepare (±)-helenalin (**130**) in twenty-five steps starting from readily available lactone **189** as illustrated in Scheme 30.[116] The sequence began with the conversion of lactone **189** following a protocol developed by Barton *et al.* into lactam **190**, which after reaction with lithio dimethyl methylphosphonate and hydrolysis of the resulting N-methyl imine afforded pentalene-derived aldehyde **191**. Enone **192** was then obtained from intermediate **191** using *t*BuOK by retro-aldol ring opening and subsequent intramolecular condensation between the resulting aldehyde and the β-ketophosphonate enolate. Conversion of enone **192** into ketal ketone **193** was achieved by sequential introduction of the methyl group using methylmagnesium bromide, *t*Bu-group deprotection using HCl, ketal formation using ethylene glycol, and final oxidation with PCC. Cyclopentanone in intermediate **193** was then converted by alkylation with dimethyl sulfide and subsequent oxidation/elimination into the corresponding cyclopentenone, which after reduction of the ketone using DIBAL-H, cleavage of the ketal and protection of the resultant alcohol using DHP afforded desired cycloheptanone **194**. Corresponding cycloheptenone was obtained by TMS-trapping of the enolate and treatment with $Pd(OAc)_2$, and was thus transformed into *trans*-epoxy alcohol **195** by epoxidation using H_2O_2 and reduction of the resulting epoxy ketone using TIBA. As in Grieco's synthesis, the lactone was introduced using dilithioacetate, whereas methylene group (after protecting groups manipulation) was introduced by formation of the lactone acid using MMC and subsequent treatment with CH_2O and Et_2NH. Final allylic oxidation using MnO_2 afforded racemic helenalin (**130**) in 6.6% overall yield.



Scheme 30. Total synthesis of (±)-helenalin (**130**) by Schlessinger *et al*. mCPBA = *meta*-chloroperoxy-benzoic acid, DHP = dihydropyran, DIBAL = diisobutylaluminium hydride, LiHMDS = lithium bis(trimethylsilyl)amide, MMC = methoxymagnesium carbonate, PCC = pyridinium chlorochromate, THP = tetrahydropyranyl, TIBA = triisobutylaluminium, TMS = trimethylsilyl, Ts = tosyl.

The last formal synthesis of (±)-helenalin (**130**) was achieved in 1982 by Heathcock *et al.* (Scheme 31),[117] the sequence from intermediate **200** to (±)-helenalin (**130**) being the same as that proposed by Schlessinger *et al*. The synthesis began with the dihydroxylation of know ketal acetate **196** using OsO_4, which after selective mono-tosylation of the resulting diol afforded intermediate **197**. Solvolysis of intermediate **197** in the presence of KOH and subsequent reprotection of the alcohol using Ac_2O afforded keto acetate **198** as an isomeric mixture in a ratio of 4:1, which could then be converted into enone **199** using $AlMe_3$ and an excess of MeLi.

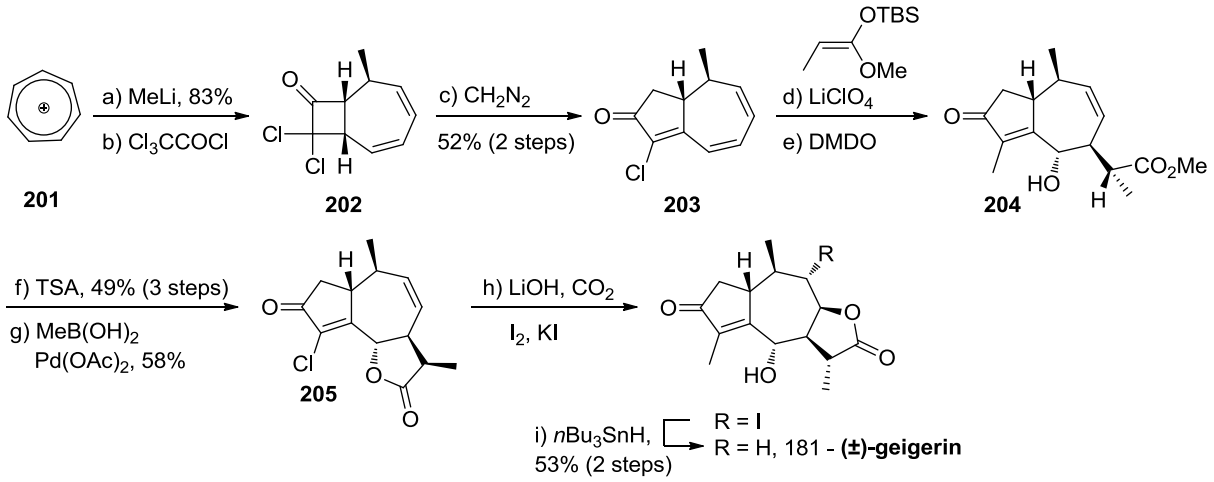


Scheme 31. Total synthesis of (±)-helenalin (**130**) by Heathcock *et al*. TMS = trimethylsilyl, Ts = tosyl.

Sequential protection of the resulting alcohol using TMSCl, Birch reduction of the double bond and TMS-group deprotection using HCl finally afforded hydroazulenone **200**.

4. b. Previous total synthesis of (±)-geigerin

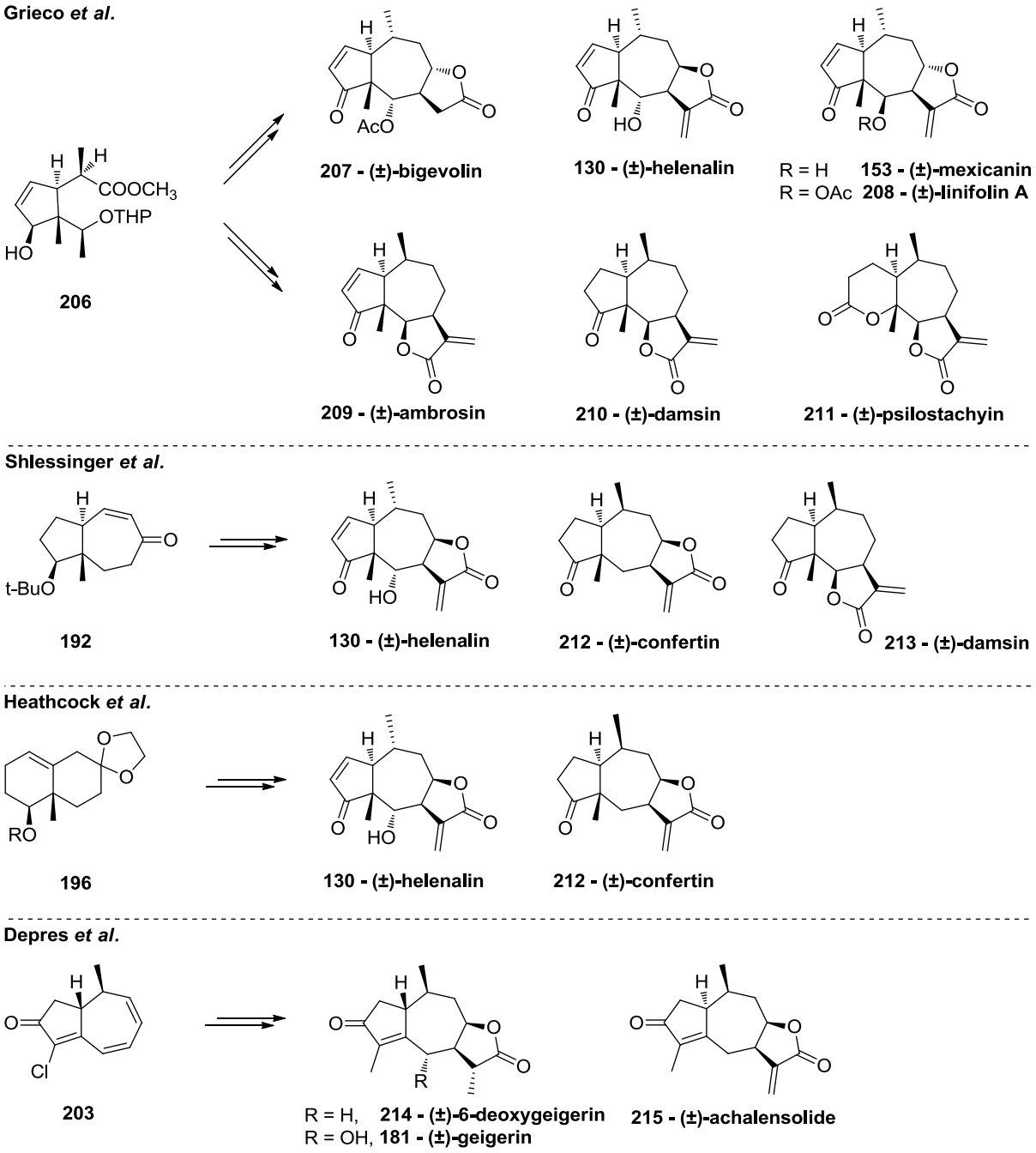
Concerning (±)-geigerin (**181**), only one total synthesis has been proposed to date by Deprés *et al.* in 2007 (Scheme 32).[118] The sequence began with the already known reaction of tropylium cation **201** with MeLi to obtain 7-methylcycloheptatriene, which could be selectively transformed into α,α-dichlorocyclobutanone **202** by using dichloroketene. Regioselective ring expansion and dehydrochlorination using diazomethane afforded hydroazulenone **203**, which could be converted into intermediate **204** by 1,6-conjugate addition using (*E*)-MeCH=C(OTBS)(OMe) enolate in the presence of $LiClO_4$ and subsequent epoxidation using DMDO. Lactonization induced by acid catalysis using TSA and methylation using Suzuki cross-coupling afforded the guaian-6,12-olide framework **205**, that was transformed into desired (±)-geigerin (**181**) by trans-iodolactonization in the presence of LiOH and I_2, and subsequent reduction of the iodide using nBu$_3$SnH. (±)-geigerin (**181**), which was obtained as a 4:1 mixture of diastereoisomers, could be isolated after purification in 4.9% overall yield in nine steps with no need of protecting groups.



Scheme 32. Total synthesis of (±)-geigerin (**181**) by Deprés *et al*. DMDO = dimethyldioxirane, TBS = *tert*-butyldimethyl, TSA = toluenesulfonic acid.

Although all these total syntheses are efficient and lead to the desired natural products, none of them proves flexible: functionalities on the cycles being installed at an early stage in the sequence prevents as a consequence the synthesis of other types of skeletons or the preparation of analogs to address biological issues. For example, as shown in Scheme 33, strategies and intermediates developed for helenalin (**130**) total synthesis by Grieco, Schlessinger, and Heathcock indeed allowed

to access to pseudoguaianolides only, the oxygen at C_4 as well as the methyl group at C_5 being present from the very first steps.[115-117, 119-122] In the same way, in the case of (±)-geigerin (**181**) total synthesis, the ketone at C_3 and the methyl group at C_4 already incorporated at the third step (Scheme 32) made the developed strategy only applicable to guaianolides synthesis.[118,123,124]



Scheme 33. Sesquiterpene lactones prepared using the same strategy as for helenalin (**130**) and geigerin (**181**).

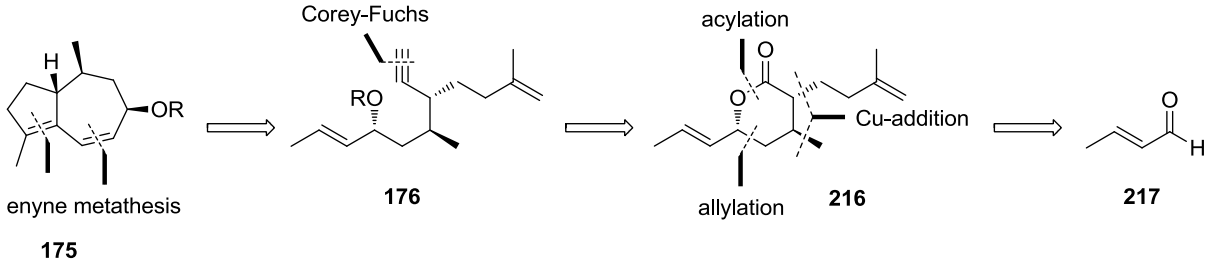
II. Towards the flexible total synthesis of (±)-helenalin and (±)-geigerin

1. Retrosynthetic pathway

1. a. Retrosynthesis of the common and simple intermediate hydroazulene

The different possibilities of cationic cyclization starting from a 10-membered ring being numerous and almost unpredictable (difficult to predict where the carbocation will be generated and how it will react), it was decided contrary to nature to prepare the common [5.3.0] bicyclic framework from an alkyne by enyne metathesis as shown in Scheme 34.

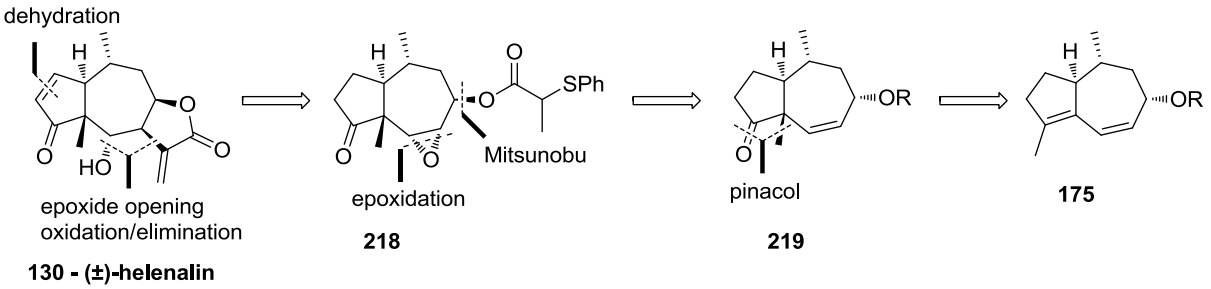
Hydroazulene **175** was expected to be prepared starting from commercial crotonaldehyde **217**, which after allylation using allylmagnesium bromide, acylation using acryloyl chloride, ring closing metathesis and 1,4-cuprate addition on the resulting α,β-unsaturated lactone should be converted into lactone **216**. Intermediate **216** could then be transformed into alkyne **176** through a Corey-Fuchs reaction, to finally afford the desired hydroazulene intermediate **175** by using a domino enyne metathesis reaction.



Scheme 34. Retrosynthetic pathway of the common intermediate hydroazulene **175**.

1. b. Functionalization towards (±)-helenalin

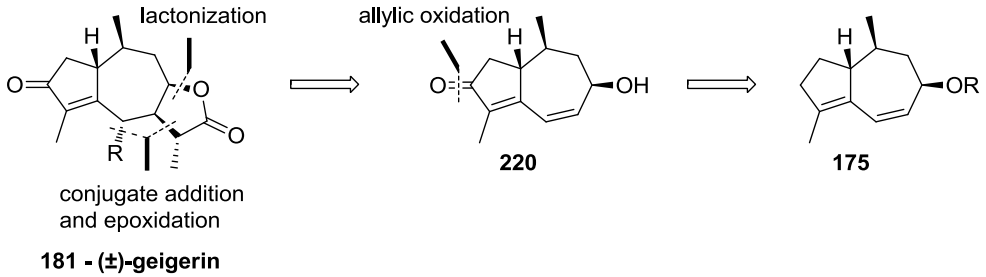
With the hydroazulene **175** in hand, functionalization into (±)-helenalin (**130**) was expected to take place as explained before through a pinacol rearrangement (Scheme 35), thus leading to cyclopentanone **219**, which could then be converted into intermediate **218** by epoxidation and subsequent Mitsunobu reaction to introduce the sulfide chain. (±)-helenalin (**130**) should finally be obtained by formation of the enolate in α-position of the ester, resulting opening of the epoxide, oxidation/elimination of the sulfide, and dehydration.



Scheme 35. Retrosynthetic pathway envisioned for (±)-helenalin (**130**) from hydroazulene **175**.

1. c. Functionalization towards (±)-geigerin

Hydroazulene **175** was also expected to be converted into (±)-geigerin (**181**) (Scheme 36), first by formation of hydroazulenone **220** through allylic oxidation and deprotection, and then by sequential 1,6-conjugate addition, epoxidation of the resulting intermediate and lactonization.



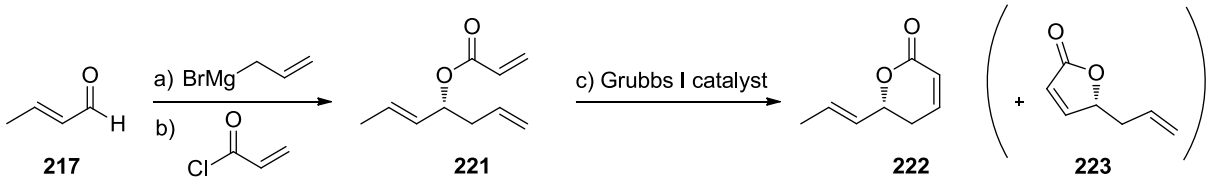
Scheme 36. Retrosynthetic pathway envisioned for (±)-geigerin (**181**) from hydroazulene **175**.

2. Efforts towards (±)-helenalin synthesis and (±)-geigerin total synthesis

2. a. Synthesis of the (±)-α,β-unsaturated lactone

As shown in Scheme 37, the synthesis of lactone **222** was achieved through a first strategy in only three steps. The sequence began with the reaction of crotonaldehyde **217** with allylmagnesium bromide, both commercially available, to afford the allylic alcohol as a racemic mixture.[125] The alcohol being sensitive to acid conditions was directly used in the subsequent reaction without

purification. Acylation of the alcohol performed using Et_3N and acryloyl chloride afforded the metathesis precursor **221** in quantitative yield for two steps.[126] Different reaction conditions (catalyst, solvent, temperature), summarized in Table 5, were tested for the ring-closing metathesis.[127]



Scheme 37. Synthesis of (±)-lactone **222**. a) Allylmagnesium bromide (1.5 equiv), Et_2O, from 0 °C to 23 °C, 12 h; b) acryloyl chloride (1.1 equiv), Et_3N (2.0 equiv), Et_2O, 23 °C, 12 h, quant (two steps); c) Grubbs I catalyst (20 mol%), CH_2Cl_2, 40 °C, 10 h, 70%.

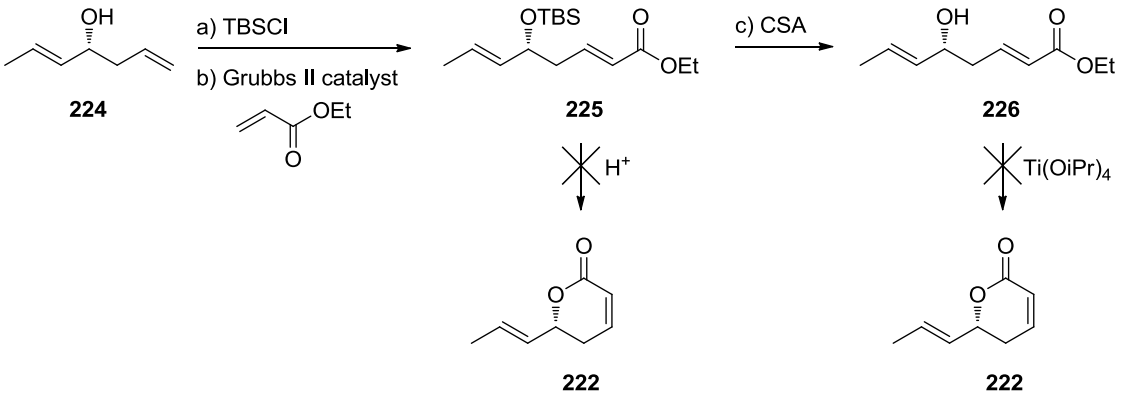
Ring-closing metathesis afforded lactone **222** in good yield and selectivity only by portionwise addition of 20 mol% of first-generation Grubbs catalyst in CH_2Cl_2 at 40 °C. Using less than 20 mol%, reaction never went to completion, probably due to the instability of the catalyst. The same argument could be suggested for the absence of reaction at 80 °C in toluene. Ring-closing metathesis with second-generation Grubbs or Hoveyda-Grubbs catalysts led to clearly different results. Lactone **222** was always obtained mixed with a by-product whatever the solvent or the temperature (increasing the temperature only increased a little bit the proportion of lactone **222** in the mixture). The by-product, having the same retention time as lactone **222**, could not be isolated and clearly analyzed but structure can be reasonably assigned to five-membered ring **223**.

Catalyst	Quantity	Solvent	Temperature	Results
Grubbs I	5 mol%	CH_2Cl_2	23 °C	no reaction
	5 mol%	CH_2Cl_2	40 °C	does not go to completion
	20 mol%	CH_2Cl_2	40 °C	**222** as single product
	5 mol%	toluene	80 °C	no reaction
Grubbs II	5 mol%	CH_2Cl_2	0 °C	no reaction
	5 mol%	CH_2Cl_2	23 °C	mixture **222** + **223**?
	5 mol%	CH_2Cl_2	40 °C	mixture **222** + **223**?
	5 mol%	toluene	80 °C	mixture **222** + **223**?
Hoveyda-Grubbs II	5 mol%	CH_2Cl_2	23 °C	mixture **222** + **223**?
	5 mol%	CH_2Cl_2	40 °C	mixture **222** + **223**?
	5 mol%	toluene	80 °C	mixture **222** + **223**?

Table 5. Conditions tested for ring-closing metathesis.

Through this first efficient synthetic pathway, synthesis of lactone **222** can be achieved in few steps with good yields. However, when done on large scale, using 20 mol% of first-generation Grubbs catalyst can be an economic issue. Moreover, the metathesis being done intramolecularly, a particularly high dilution is required, that can generate a significant loss of material during concentration of volatile compound **222**. For these reasons, another strategy had to be envisioned for big scales.

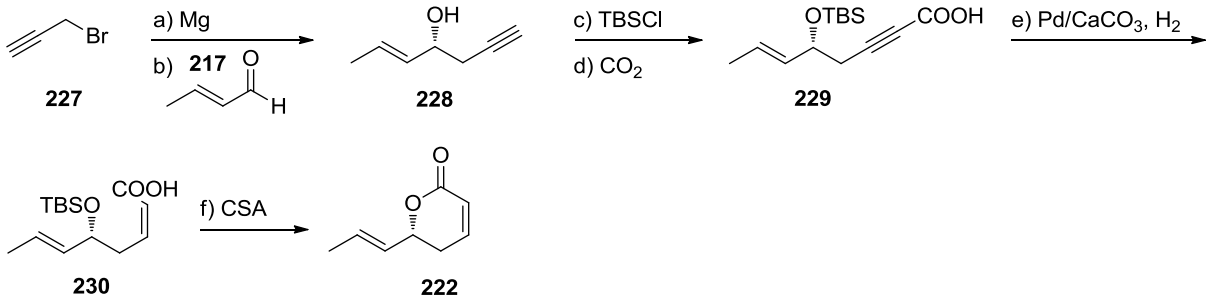
The first alternative envisioned was to reorder the steps in the sequence, and to perform the metathesis previous to esterification as illustrated in Scheme 38. The product recovered after metathesis being less volatile and the metathesis being done intermolecularly instead of intramolecularly, no more material would be lost by evaporation. The sequence started by the quantitative silylation of secondary alcohol in intermediate **224** by using TBSCl in the presence of imidazole in CH_2Cl_2. Cross-metathesis afforded as expected the non-volatile α,β-unsaturated ester **225** in very good yield using only 8 mol% of second-generation Grubbs catalyst, making this way more economic than the first one.[128,129] Unfortunately, all attempts to convert directly intermediate **225** into lactone **222** by acidic catalysis failed. All the acids tried (CSA,[130] HCl 1%,[131] $pTsOH.H_2O$[132]) only led to deprotected alcohol **226**. Attempts to induce the cyclization of intermediate **226** in presence of a Lewis acid were also disappointing. The *E*-conformation of the double bound built by metathesis clearly seemed to prevent lactonization.



Scheme 38. Alternative envisioned for the synthesis of (±)-lactone **222**. a) TBSCl (2.0 equiv), imidazole (2.0 equiv), CH_2Cl_2, 23 °C, 12 h, quant; b) ethyl acrylate (40.0 equiv), Grubbs II catalyst (8 mol%), CH_2Cl_2, 23 °C, 1 h, 82%; c) CSA (0.2 equiv), $MeOH/CH_2Cl_2$, 23 °C, 12 h, quant. CSA = camphorsulfonic acid, TBS = *tert*-butyldimethyl.

The strategy was then modified to be exclusively in the presence of a *Z*-conformation double bound (Scheme 39). The new sequence began with the formation of propargylmagnesium bromide from magnesium and commercial propargyl bromide **227**. The crude reaction product was added on crotonaldehyde **217** in Et_2O at -78 °C to yield intermediate **228** as a racemic mixture, which was silylated without further purification by using TBSCl and imidazole, thus affording the TBS-protected alcohol in quantitative yield for three steps. Carboxylation of the alkyne was achieved in the presence

of *n*BuLi and dry ice following the protocol of Danishefsky *et al.*[133] to yield the crude intermediate **229.** The alkyne was then reduced using hydrogen and Lindlar catalyst to afford carboxylic acid **230**, which presented exclusively the *Z*-double bound and could be used directly in the subsequent reaction.[134,135]

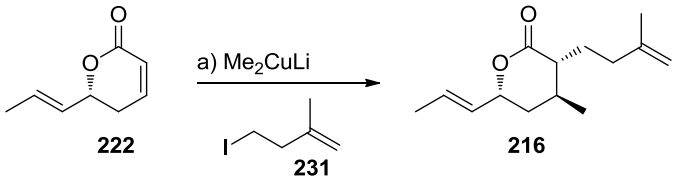


Scheme 39. Alternative for synthesis of (±)-lactone **222**. a) Mg (2.0 equiv), $HgCl_2$ (0.5 mol%), I_2 (small grain), **227** (1.9 equiv), 40 °C to 23 °C, 2 h; b) **217** (1.0 equiv), Et_2O, -78 °C to 23 °C, 12 h; c) TBSCl (2.0 equiv), imidazole (2.0 equiv), CH_2Cl_2, 23 °C, 12 h, quant (three steps); d) *n*BuLi (1.1 equiv), Et_2O, -78 °C, 45 min; then dry ice, -78 °C to 23 °C, 30 min; e) quinoline (1.0 equiv), Pd/$CaCO_3$ (0.4 equiv), H_2, EtOAc, 23 °C, 8 h; f) CSA (0.2 equiv), MeOH/CH_2Cl_2, 23 °C, 12 h, 70% (three steps). CSA = camphorsulfonic acid, TBS = *tert*-butyldimethyl.

As expected, lactone **222** could be obtained by acid catalysis using CSA, with 70% yield for the three last steps.[130] This sequence presents significant advantages: excellent yields, only two purifications required, inexpensive materials, any problem of volatility (most of the intermediates being carboxylic acids). However, with six steps, it counts twice more steps compared to the first strategy. Sequence depicted in Scheme 37 should then nevertheless be favored for small scales.

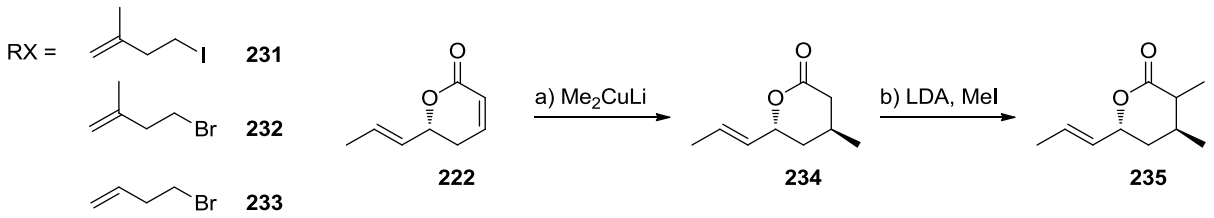
2. b. Introduction of the chirality

Introduction of the chiral centers on α,β-unsaturated lactone **222** was performed through a 1,4-cuprate addition using lithium dimethyl cuprate and 1-iodo-3-methyl-but-3-ene **231**[136] as shown in Scheme 40.[137,138] Lactone **216** was obtained with complete diastereoisomeric control in moderate yield, although conversion looked complete by TLC. Modifying the temperature (until -78 °C) or work up conditions did not cause any yield improvement. The unique parameter having an influence on the yield proved to be the nature of the halogen added at the end (Scheme 41). The yield for the 1,4-cuprate addition on α,β-unsaturated lactone **222** using 1-bromo-3-methyl-but-3-ene **232**[139] or 1-bromobut-3-ene **233** never exceeded 33%, whereas 41% yield could be achieved by using 1-iodo-3-methyl-but-3-ene **231**.[136] Addition of methyl iodide even allowed to isolate lactone **235** as a mixture of diastereoisomers in 73% yield.



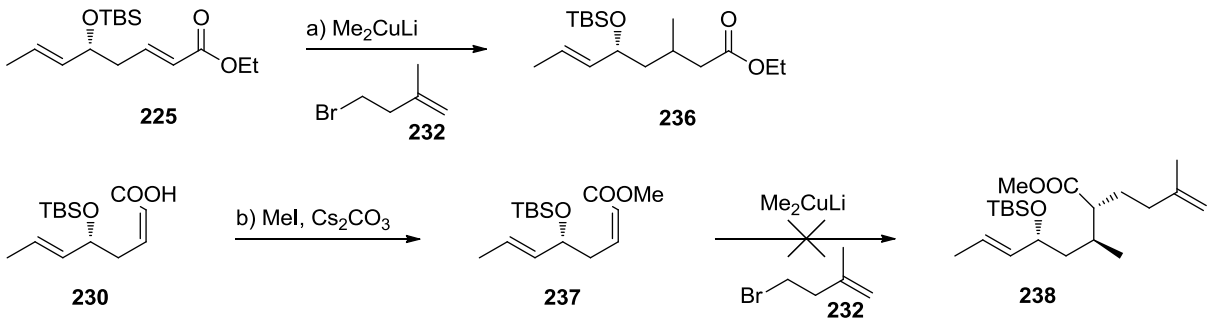
Scheme 40. Synthesis of (±)-lactone **216**. a) CuI (2.0 equiv), MeLi (4.0 equiv), Et_2O, 0 °C, 1 h; **9** (8.0 equiv), THF/HMPA, 23 °C, 12 h, 41%. HMPA = hexamethylphosphoramide, THF = tetrahydrofuran.

Nevertheless, moderate yield of the cuprate addition can not only be attributed to the halogen structure, the only addition of lithium dimethyl cuprate presenting also a moderate yield (isolation of volatile lactone **234** in 35% yield).



Scheme 41. Studies of the cuprate addition. a) CuI (2.0 equiv), MeLi (4.0 equiv), Et_2O, 0 °C, 1 h, 38%; b) LDA (3.0 equiv), MeI (5.0 equiv), THF, -78 °C, 2.5 h, 73%. LDA = lithium diisopropylamide.

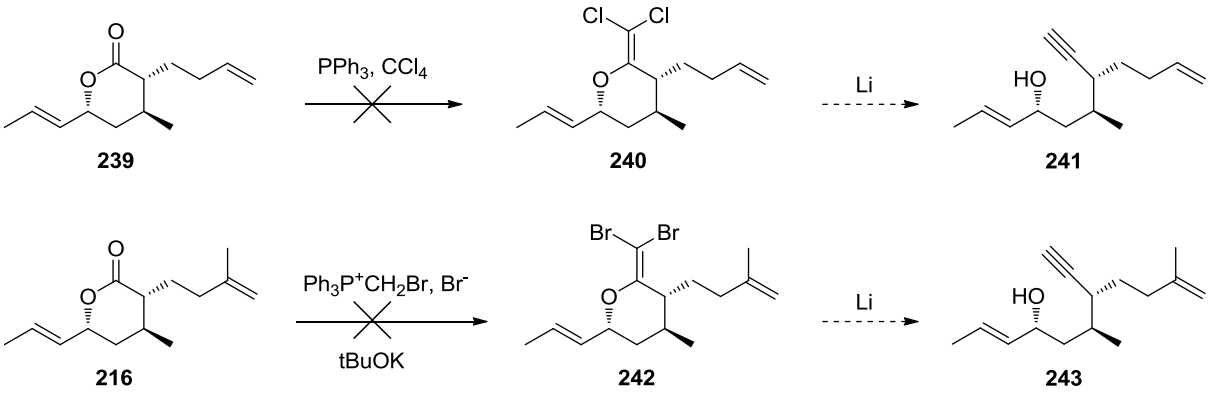
For the purpose of reducing the number of steps, 1,4-cuprate addition was also tested on the linear form of lactone **222** (Scheme 42). In the case of *E*-double bound analog **225**, only lithium dimethyl cuprate addition was observed affording methylated compound **236**. In the case of *Z*-double bound analog **237**, prepared by methylation of intermediate **230** using Cs_2CO_3 and MeLi,[140] the crude reaction was messy and no trace of desired compound **238** was detected.



Scheme 42. Cuprate addition on the opened form. a) CuI (2.0 equiv), MeLi (4.0 equiv), Et_2O, 0 °C, 1 h; then **11** (8.0 equiv), THF/HMPA, 23 °C, 12 h, 70%; b) MeI (1.5 equiv), Cs_2CO_3 (1.5 equiv), DMF, 23 °C, 9 h, 90%. DMF = *N*,*N*-dimethylformamide, HMPA = hexamethylphosporamide, TBS = *tert*-butyldimethyl, THF = tetrahydrofuran.

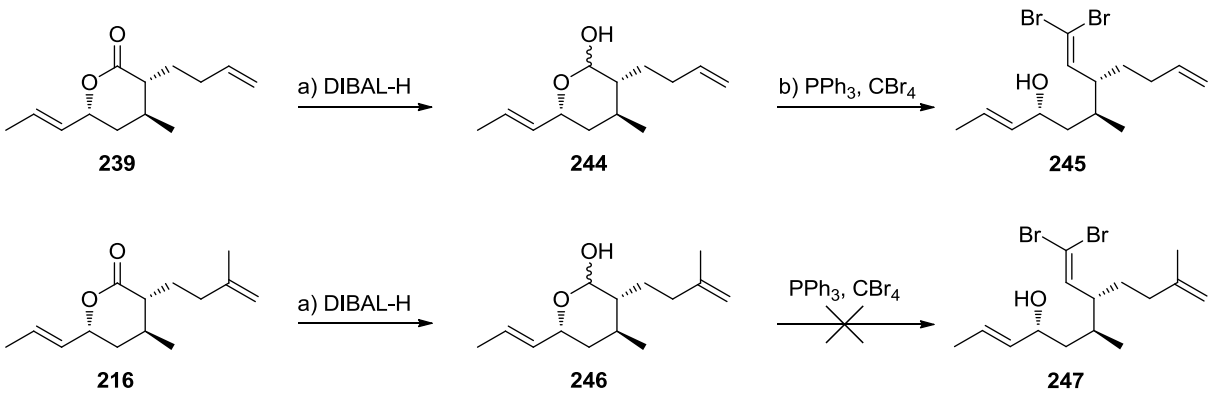
2. c. Synthesis of the (±)-alkyne

That synthesis of lactone **216** being established, synthesis of alkyne **243** could be envisioned. Most obvious synthetic pathway was to directly convert lactone **216** into its bis-halogenated analog before treating it with *n*BuLi (Scheme 43). For the tests, lactones **216** or **239** (missing the methyl group on terminal double bound) were used alternatively depending on the availabilities in the laboratory. Whatever the protocol used, bis-halogenated analog has never been obtained. Treatment of lactone **239** with PPh_3 and CCl_4 did not induce any reaction,[141] whereas treatment of lactone **216** with $Ph_3P^+CH_2Br,Br^-$ only caused insignificant conversion to a by-product of undetermined structure.[142,143] The conversion of lactone **216** into the corresponding bis-bromide **242** was investigated with $Ph_3P^+CH_2Br,Br^-$ rather than with PPh_3/CBr_4, usually used for the dibromination of carbonyl groups (and similar to the protocol used to form the bis-chloride), as these last conditions were claimed by Chapleur *et al.* to lead to unclean transformation when performed on poorly reactive ester carbonyl groups. Both procedures are nevertheless going through the same phosphorane intermediate ($Ph_3P=CBr_2$).[142]



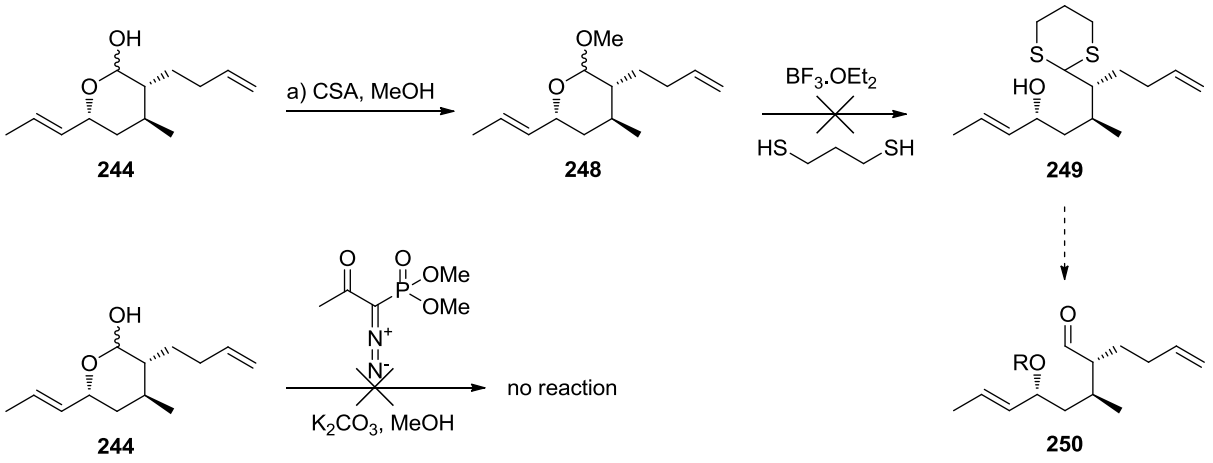
Scheme 43. Tests for synthesis of (±)-alkyne **243** directly from (±)-lactone **216**.

Another concise synthetic pathway that has been considered to convert lactone **216** into alkyne **243** was to form the bis-halogenated compound from the lactol instead of the lactone (Scheme 44). The reduction of lactones **239** and **216** into the corresponding lactols **244** and **246** proved to be successful using DIBAL-H at -78 °C, both lactols were obtained as a mixture of diastereoisomers in acceptable yield.[144] However, reactivity of these two lactols under Corey-Fuchs reaction conditions proved to be completely different. Whereas in the case of lactol **244** desired bis-brominated product **245** seems to have been obtained, lactol **246** could never be converted into bis-bromide **247**. Reaction of lactol **246** in the presence of PPH_3 and CBr_4 only afforded a mixture of two inseparable compounds whose structure could not be determined, but none of them presenting the signal characteristic of the olefinic proton attached to the bis-bromide at around 6 ppm on the ^1H NMR spectra, it can be asserted that expected reaction did not occur.



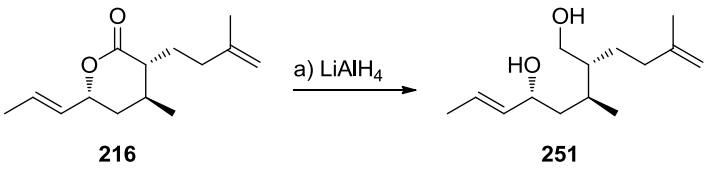
Scheme 44. Test for synthesis of (±)-alkyne **243** from (±)-lactol **246**. a) DIBAL-H (1.1 equiv), CH_2Cl_2, -78 °C, 1 h, 76% (**244**) and 94% (**246**); b) CBr_4 (1.0 equiv), PPh_3 (2.0 equiv), CH_2Cl_2, 45 min, 0 °C, 48%. DIBAL = diisobutylaluminium hydride.

As shown in Scheme 45, other possibilities starting from the lactol have been explored. One possibility was to mask the aldehyde function as a dithiane, thus allowing sequential protection of the hydroxyl group, deprotection of the aldehyde and Corey-Fuchs reaction. Unfortunately, even if methylation of lactol **244** using CSA in MeOH afforded desired O-methylated lactol **248** in quantitative yield,[145] protection of the aldehyde function in the presence of 1,3-dithiane and Lewis acid $BF_3.OEt_2$ was really messy and never succeeded.[146] Another proposal was to directly form the alkyne **243** from the lactol **244** in one step by using Bestmann reagent following the protocol of Pandey *et al*.[147] Unfortunately, no reaction was observed under these conditions, whatever the temperature (23 or 65 °C).



Scheme 45. Tests for synthesis of (±)-alkyne **241** from (±)-lactol **244**. a) CSA (cat), MeOH, 23 °C, 12 h, quant. CSA = camphorsulfonic acid.

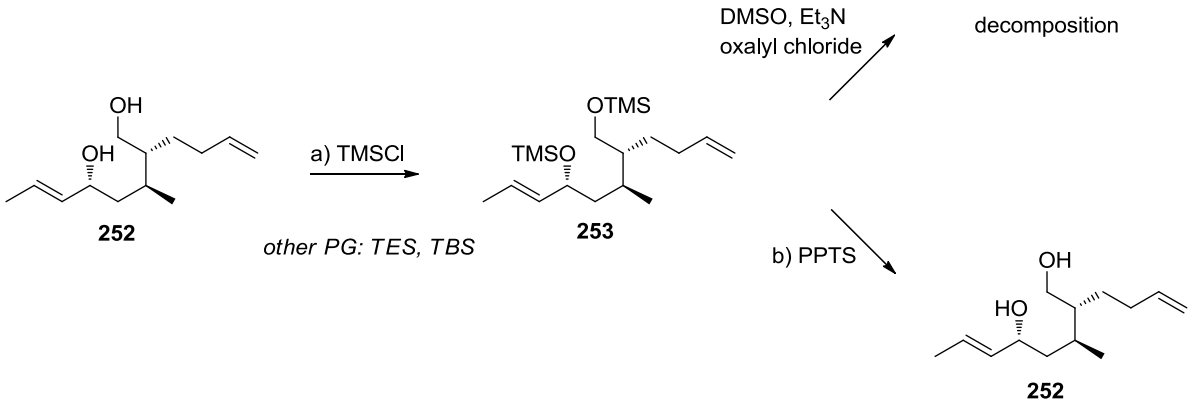
Last synthetic pathway that has been considered to convert lactone **216** into alkyne **243** was to go through the diol. In this purpose, lactone **216** was reduced using $LiAlH_4$ to afford the corresponding diol **251** in quantitative yield as illustrated in Scheme 46.[148]



Scheme 46. Synthesis of (±)-diol **251**. a) $LiAlH_4$ (3.0 equiv), Et_2O, 0 °C, 1 h, quant.

Synthesis of diol **251** (and **252**) being established, two synthetic pathways could be envisioned to go to the alkyne: through mono-deprotection or through mono-protection.

Mono-deprotection synthetic pathway had to start with the bis-protection of the diol (Scheme 47). Silylation of diol **252** using TMSCl in the presence of imidazole in CH_2Cl_2 afforded desired bis-silylated product **253** in 76% yield. To have protecting groups with different sensitivity to acidic conditions, analogs bis-protected with a TES or a TBS were prepared in the same way.

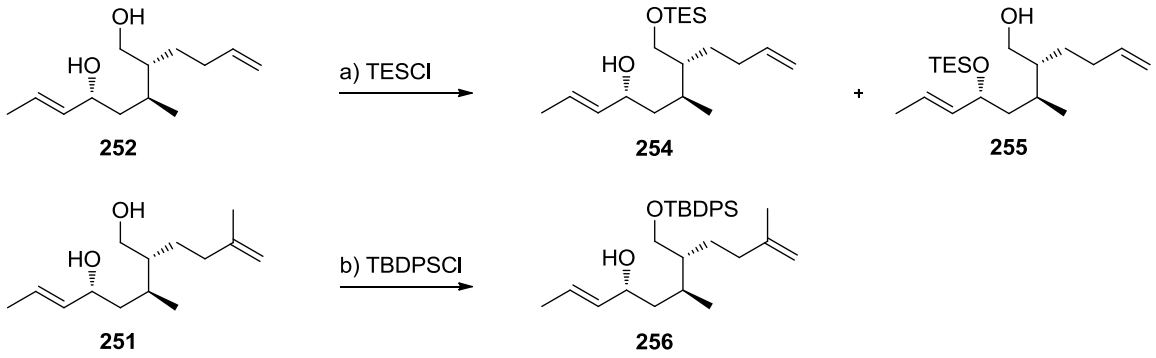


Scheme 47. Tests for selective mono-deprotection. a) TMSCl (4.2 equiv), imidazole (6.6 equiv), CH_2Cl_2, 23 °C, 12 h, 76%; b) PPTS (0.2 equiv), 1/3 MeOH/CH_2Cl_2, -10 °C, 10 min, quant. DMSO = dimethylsulfoxide, PPTS = pyridinium *para*-toluenesulfonate, TBS = *tert*-butyldimethyl, TES = triethylsilyl, TMS = trimethylsilyl.

One option for the mono-deprotection was to use Swern reaction conditions. Hydrochloric acid delivered during the reaction was expected to induce the selective deprotection of the primary alcohol, followed by its oxidation to afford exclusively the desired aldehyde.[149] Unfortunately, a decomposition of the starting material, just following the addition of Et_3N was observed, whatever the protecting group used.

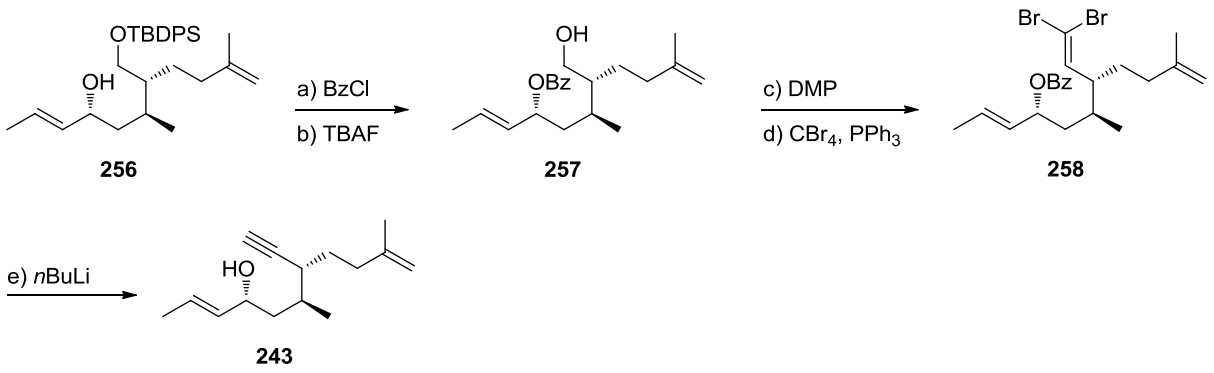
Another option, inducing one more step (deprotection and oxididation being done individually), was to mono-deprotect the primary alcohol using PPTS.[150] For TES-protected compound, as well as for TBS-protected analog, cleavage using PPTS afforded a mixture of the two mono-deprotected alcohols. On the contrary, reaction of PPTS with TMS-protected analog led to complete deprotection in less than 2 min affording exclusively the diol **252**.

Results of the mono-deprotection being disappointing, synthesis of alkyne **243** by mono-protection was explored. As shown in Scheme 48, different protecting groups were tested. Mono-protection using TESCl in the presence of imidazole in CH_2Cl_2 proved to be unselective, affording a mixture of inseparable mono-protected alcohols **254** and **255** in proportion 95/5.[151] Conversely, mono-protection of diol **251** could be achieved selectively using TBDPSCl to yield secondary alcohol **256** as single product. Using one equivalent of TBDPSCl, the reaction never went to completion, unreacted starting material thus had to be isolated and resubmitted to obtain desired compound **256** in excellent yield (99%).



Scheme 48. Selective mono-protection of (±)-diol **251** or **252**. a) TESCl (1.0 equiv), imidazole (1.3 equiv), CH_2Cl_2, -5 °C, 1 h, 61%; b) TBDPSCl (1.0 equiv), imidazole (1.3 equiv), CH_2Cl_2, -78 °C, 1 h, 99% (resubmitted two times). TBDPS = *tert*-butyldiphenylsilyl, TES = triethylsilyl.

Mono-protection of diol **251** being achieved successfully, the end of alkyne **243** synthesis looked obvious (Scheme 49). Protection of the secondary alcohol using BzCl and pyridine in CH_2Cl_2, followed by removal of the TBDPS group under the action of TBAF converted intermediate **256** in primary alcohol **257** with excellent yields. Other protecting groups tested to mask the secondary alcohol in compound **256** proved to be unsatisfactory: with PMB group the reaction was messy and never went to completion, whereas with EOM group, no reaction occurred. The free alcohol in intermediate **257** was then oxidized in good yield using DMP, thus affording the aldehyde, which was converted in bis-brominated compound **258** in 99% yield using PPh_3 and CBr_4. Conversion of intermediate **258** in alkyne using *n*BuLi afforded compound **243** but only in moderate yield (50%). Interestingly, when the analog of compound **258** lacking the methyl group on the terminal olefin was treated with *n*BuLi, the corresponding alkyne could be isolated in more than 90% yield. Direct conversion of the aldehyde into alkyne **243** was tested using Bestmann reagent and K_2CO_3 in MeOH, the yield was improved but epimerization was observed.

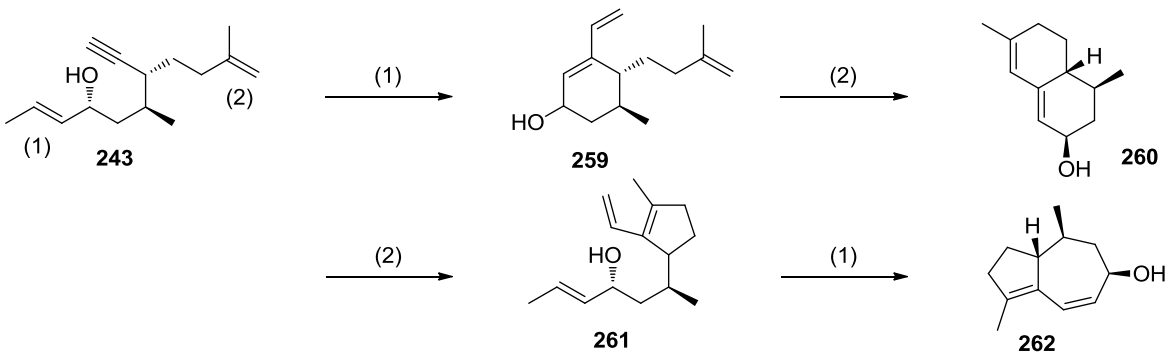


Scheme 49. Synthesis of (±)-alkyne **243**. a) BzCl (4.0 equiv), pyridine (4.0 equiv), CH_2Cl_2, 23 °C, 3 h, 97%; b) TBAF (2.0 equiv), THF, 23 °C, 12 h, quant; c) DMP (1.2 equiv), CH_2Cl_2, 23 °C, 12 h, 75%; d) CBr_4 (4.0 equiv), PPh_3 (8.0 equiv), CH_2Cl_2, 0 °C, 45 min, 99%; e) *n*BuLi (3.0 equiv), THF, from -78 °C to 23 °C, 2.5 h, 50%. Bz = benzoyl, DMP = Dess-Martin periodinane, TBAF = tetrabutylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, THF = tetrahydrofuran.

In conclusion, synthesis of alkyne **243** was achieved in seven steps from lactone **216**. The sequence is relatively long, but all the conditions used are simple and, except for last step, allowed the isolation of intermediates in excellent yield. All the other procedures tested (from lactone, from lactol, or from diol by mono-deprotection) failed.

2. d. Domino enyne metathesis – Access to the hydroazulene moiety

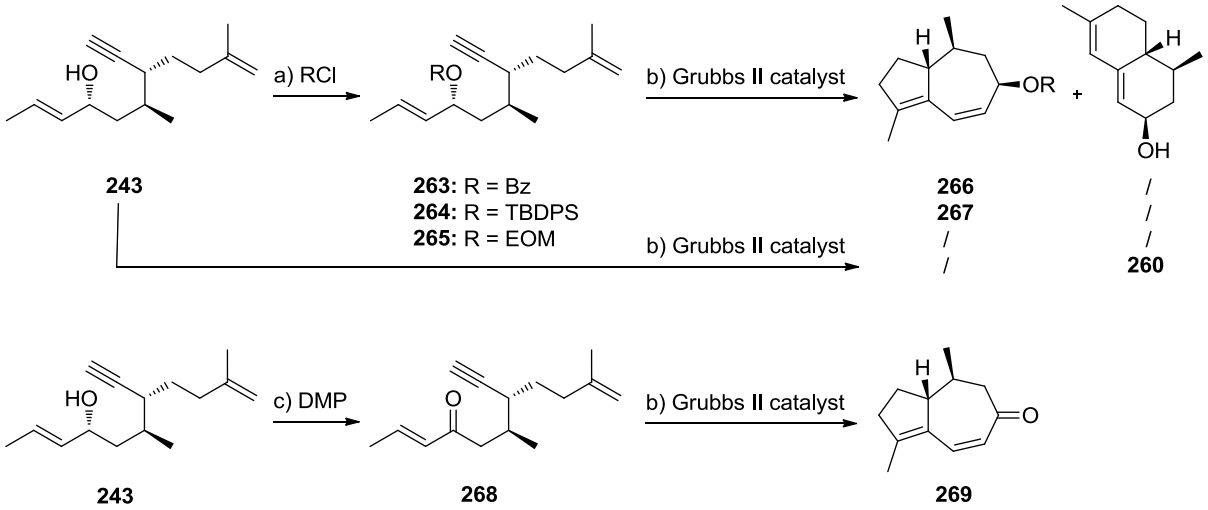
Synthesis of alkyne **243** having been achieved, next key step to address was the formation of the bicyclic framework by domino enyne metathesis.[152,153] After functionalization, the bicyclic intermediate was expected to give access to different members of the SLs family.



Scheme 50. Different ways of cyclization during enyne metathesis.

In the case of alkyne **243**, both double bounds being bis-substituted, two ways of cyclization are in competiton, making the domino enyne metathesis particularly challenging (Scheme 50). In the case where the activated alkyne function would react first with double bound (1), and then with double bound (2), only [4.4.0] bicyclic framework **261** should be obtained. On the contrary, if activated alkyne function first reacts with double bound (2), and only reacts in second with double bound (1), desired [5.3.0] bicyclic framework **263** should be isolated.

Domino enyne metathesis, when directly tried on unprotected alkyne **243** using second-generation Grubbs catalyst in toluene, only afforded undesired [4.4.0] bicyclic compound **260**. In the prospect of changing the outcome of the reaction, analogs of alkyne **243** protected with different groups like a Bz (**263**), a TBDPS (**264**) or an EOM (**265**) were then prepared. Oxidized analog **268** was also synthesized (Scheme 51). Changing the nature of the protecting group proved to completely change the way of cyclization (results are summarized in Table 6).



Scheme 51. Domino enyne metathesis. a) (**263**), (**264**): RCl (3.0 equiv), imidazole (3.0 equiv), CH_2Cl_2, 23 °C, 2 - 12 h, quant; (**265**): EOMCl (3.0 equiv), iPr_2NEt (3.0 equiv), CH_2Cl_2, 23 °C, 12 h, 97%; b) Grubbs II catalyst (7.5-10 mol%), toluene, 100 °C, 1 h - 3 d, 91%(**264**), 0% (**265**), 80%(**243**), 23%(**268**); c) DMP (1.2 equiv), CH_2Cl_2, 0 °C to 23 °C, 12 h, 95%. Bz = benzoyl, DMP = Dess-Martin periodinane, EOM = ethoxymethyl, TBDPS = *tert*-butyldiphenylsilyl.

For Bz-protected analog **263**, a large palette of conditions were tested. Whatever the solvent or the temperature, no reaction was observed using first-generation Grubbs catalyst.[152] This catalyst was however the one giving the best results on the alkyne analog lacking the methyl group on the terminal olefin. Using second-generation Grubbs catalyst[153] always afforded a mixture of desired [5.3.0] bicyclic compound **266** and a by-product, which having the same retention time could not be isolated and analyzed. Increasing the temperature allowed to slightly increase the proportion of desired compound **266** in the mixture, but up to 100 °C, decomposition was observed. Intermediate **266** even proved to be unstable at 23 °C, what made it inconvenient to use forward.

For TBDPS-protected analog **264**, [5.3.0] bicyclic compound **267** was obtained as single product in 91% using second-generation Grubbs catalyst added portionwise in toluene at 100 °C. Using these conditions, reaction proved to be clean and complete after three days, and recovered compound appeared stable even at high temperatures.

Substrate	Catalyst	Quantity	Solvent	Temp.	Results
243	Grubbs II	7.5 mol%	toluene	100 °C	**260**
263	Grubbs I	10 mol%	CH_2Cl_2	40 °C	no reaction
		10 mol%	toluene	50 °C	no reaction
		10 mol%	toluene	100 °C	no reaction
	Grubbs II	7.5 mol%	CH_2Cl_2	40 °C	mixture **266** + one by-product
		7.5 mol%	toluene	23 °C	mixture **266** + one by-product
		7.5 mol%	toluene	50 °C	mixture **266** + one by-product
		7.5 mol%	toluene	100 °C	**266** (not clean, decomposed)
	Hoveyda-Grubbs II	7.5 mol%	CH_2Cl_2	40 °C	mixture **266** + two by-products
264	Grubbs II	10 mol%	toluene	100 °C	**267**
265	Grubbs II	7.5 mol%	toluene	100 °C	no reaction
268	Grubbs II	7.5 mol%	toluene	100 °C	**269** (low yield)

Table 6. Conditions tested for the domino enyne metathesis.

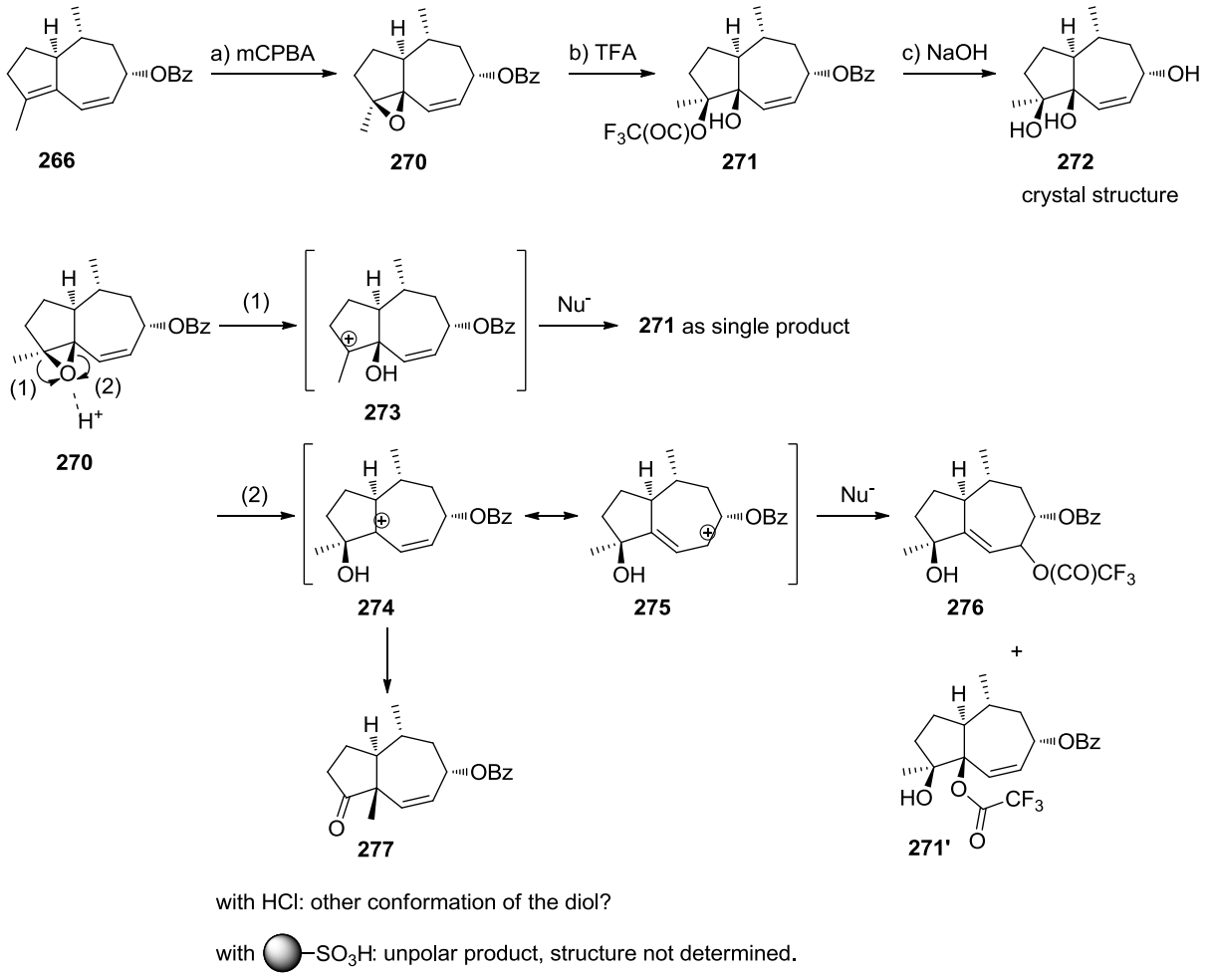
For EOM-protected analog **265**, no reaction was observed using the conditions that gave the best results for previous substrates. For oxidized analog **268**, using always the same conditions afforded desired bicyclic intermediate **269** as a single product in 23% yield. The crude NMR looking extremely clean, low yield may be due to volatility of the compound.

Best result in terms of yield and stability having been obtained using TBDPS-protected alkyne **264**, total synthesis of geigerin (**181**) was continued with [5.3.0] bicyclic intermediate **267**. However, influence of the protecting group on domino enyne metathesis having been realized relatively late, efforts through total synthesis of helenalin (**130**) had been performed with [5.3.0] bicyclic intermediate **266**.

2. e. Efforts towards the functionalization into (±)-helenalin

Synthesis of [5.3.0] bicylic intermediate being validated, functionalization of the cycles had to be achieved to access to members of the pseudoguainolides family, and particularly to helenalin (**130**). The first functionalization studied was the pinacol rearrangement.

Prior to the rearrangement, intermediate **266** had to be epoxidized (Scheme 52). By using one equivalent of mCPBA, epoxidation proved to be regio- and stereo-selective, epoxide **270** being obtained as single product. Epoxidation under the same conditions on Bz-deprotected bicyclic compound afforded a mixture of both mono-epoxides. In the purpose of inducing the opening of the epoxide and the subsequent pinacol rearrangement, epoxide **270** was subjected to acidic conditions using TFA. One single product was obtained, but flash chromatography allowing not to isolate perfectly clean intermediate **271**, the crude reaction product was directly treated with NaOH in MeOH, thus affording Bz- and trifluoroacetate-deprotected intermediate **272** as pure single product. No trace of compound **277** originating from the sought migration of the methyl group was detected. Structure of intermediate **272** could be determined by crystal structure (Figure 29, crystallization of **272** was achieved in pure EtOAc), whereas structure of intermediate **271** was confirmed by the presence of a second carbonyl signal in ^{13}C NMR spectra.



Scheme 52. Pinacol rearrangement. a) mCPBA (1.0 equiv), CH_2Cl_2, 0 °C, 1 h, 18% (two steps); b) TFA (1.0 equiv), CH_2Cl_2, 23 °C, 1 h; c) 1% NaOH in MeOH, 23 °C, 6 h, 60% (two steps). Bz = benzoyl, mCPBA = *meta*-chloroperoxybenzoic acid, TFA = trifluoroacetic acid.

Structure of triol **272** being undoubtedly established, mechanism of the reaction induced by TFA treatment could be determined. First, the two hydroxy groups on the 5-membered ring being both on the same side of the molecule, it looks clear that the addition of the nucleophile occurred through a SN_1 reaction. Generally speaking, in the presence of an acid, opening of epoxide **270** could take place in two different ways, (1) or (2), affording thus two different carbocations **273** and **274**. In the case of carbocation **273** no delocalization of the electrons or group migration being possible, only a nucleophilic addition (here CF_3COO^-) can take place to afford intermediate **271** as single product. In the case of carbocation **274**, migration of the methyl group (pinacol rearrangement) as well as delocalization of the double bound can occur, thus affording respectively ketone **277** and alcohol **276**. Any trace of intermediates **276** or **277** having been detected, it looks clear that the carbocation induced by TFA treatment was formed following pathway (1), suggesting a higher stability of carbocation **273** than carbocation **274**. To promote the desired pinacol, it will be important to introduce the right conformation for the 7-membered ring to stabilize the carbocation.

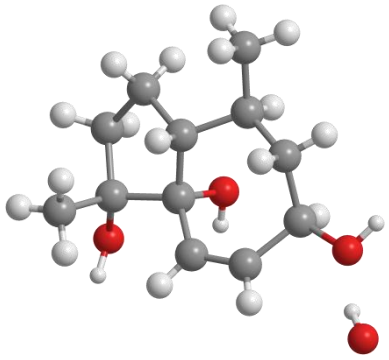
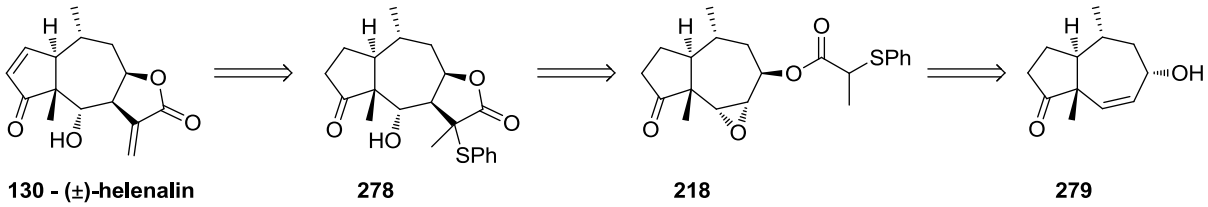


Figure 29. 3D structure of intermediate **272**.

Pinacol rearrangements were also tried using hydrochloric acid or Lewis acids. Reaction of intermediate **266** with hydrochloric acid afforded a really more polar product than TFA, whose structure was assumed to be an epimer of trifluoroacetate-deprotected intermediate **271**, this hypothesis could however never been confirmed. Reaction of intermediate **266** with $BF_3.OEt_2$ Lewis acid[154,155] afforded a really messy crude reaction.

It is noteworthy that the outcome of this reaction was not predictable. As shown in the biogenesis section, nature indeed uses exactly the same transformation to introduce the carbonyl of the α,β-unsaturated ketone into the pseudoguaianolides, then such pinacol rearrangement already proved successful in literature on similar substrates,[156] and it was logically supposed that the carbocation in intermediate **274** being allylic would be favored. We had then strong reasons for thinking that it would succeed. Nevertheless, relative stability of the carbocations having been proved to be extremely dependant on the structure and conformation of the molecule by Bordoloi *et al.*,[156] pinacol rearrangement should obviously be retried on other substrates later in the synthesis.

To this end the synthesis of the α-methylene-γ-lactone structure of (±)-helenalin (**130**) has been studied. As shown in Scheme 53, methylene group was expected to be obtained by oxidation/elimination of the sulfide in intermediate **278**, resulting itself of the epoxide opening induced by the formation of an enolate in α-position of the ester function in intermediate **218**. Finally, compound **218** was expected to be prepared from alcohol **279** by successive epoxidation and Mitsunobu reaction using 2-(phenylsulfanyl)propanoic acid.[157,158]



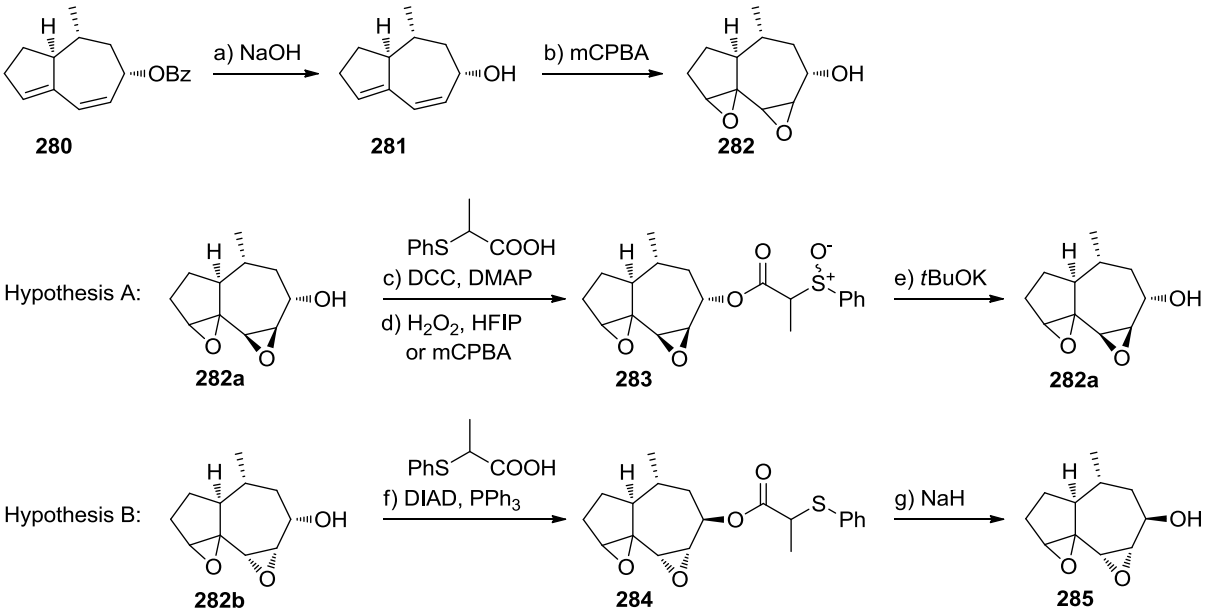
130 - (±)-helenalin **278** **218** **279**

Scheme 53. Retrosynthetic pathway envisioned for the introduction of the γ-lactone.

This strategy for the synthesis of the α-methylene-γ-lactone structure was studied starting from intermediate **280** (Scheme 54). Deprotection of the Bz group using 1% NaOH in MeOH afforded alcohol **281**, which was converted into bis-epoxide **282** in moderate yield using three equivalents of mCPBA. It was decided to push the epoxidation until the bis-epoxide simply for having more material to work with, mono-epoxidation of [5.3.0] bicyclic compounds with the alcohol deprotected affording, as explained previously, a mixture of both mono-epoxides.

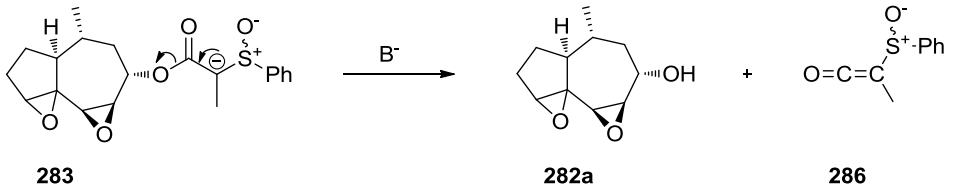
At this stage, the conformation of the epoxide close to the alcohol being unknown, the two possibilities had to be envisioned in parallel, keeping in mind that for the opening of the epoxide to occur epoxide and alcohol had to belong to opposite sides of the molecule.

In the case where the epoxide would be up (Hypothesis A), esterification of alcohol **282a** thus had to be performed using DCC and DMAP. The sulfide was then converted into the sulfoxide using indifferently H_2O_2 in HFIP[159] or mCPBA,[160] both affording intermediate **283** in excellent yield as a mixture of the four diastereoisomers. Oxidation of the sulfide prior to cyclization was expected to help for the enolate formation. Enolate in α-position of the ester could be obtained using as base *t*BuOK,[161] but instead of the expected opening of the epoxide, a breaking of the ester bound was observed restoring alcohol **282a**. Using the sulfide instead of the sulfoxide for the enolate formation led to the same result. A similar phenomenon had already been observed by Martin *et al.*, who attributed it to a basic elimination leading to the formation of a ketene (**286**) as illustrated in Scheme 55.[160] In the second case where the epoxide would be down (Hypothesis B), conformation of the alcohol having to be exchanged, a Mitsunobu reaction was performed on alcohol **282b** affording in 76% intermediate **284**, which was directly treated with NaH[160] to generate the enolate (sulfide oxidation having proved to be unnecessary for enolate formation).



Scheme 54. Tests for the synthesis of the γ-lactone in (±)-helenalin (**130**). a) 1% NaOH in MeOH, 23 °C, 12 h, 52%; b) mCPBA (3.0 equiv), CH_2Cl_2, 0 °C, 1 h, 69%; c) DMAP (0.1 equiv), DCC (1.1 equiv), 2-(phenylsulfanyl)propanoic acid (1.1 equiv), CH_2Cl_2, 23 °C, 12 h, 94%; d) H_2O_2 (2.0 equiv), HFIP, 23 °C, 1 h, 94%; or mCPBA (1.1 equiv), CH_2Cl_2, 0 °C, 15 min, 90%; e) *t*BuOK (1.0 equiv), DMSO, 23 °C, 24 h, 50%; f) DIAD (20.0 equiv), PPh_3 (20.0 equiv), 2-(phenylsulfanyl)propanoic acid (1.0 equiv), CH_2Cl_2, 23 °C, 1 h, 76%; g) NaH (1.0 equiv), DMF, -40 °C, 3 h, 60%;. Bz = benzoyl, mCPBA = *meta*-chloroperoxybenzoic acid, DCC = 1,3-dicyclocarbodiimide, DIAD = diisopropyl azodicarboxylate, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide , HFIP = hexafluoro-2-propanol.

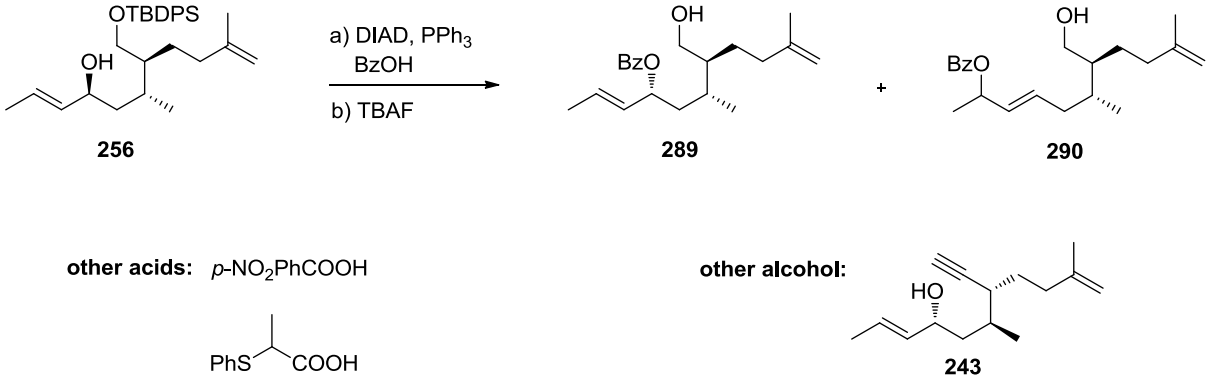
Unfortunately, as for previous hypothesis A, breaking of the ester bound instead of epoxide opening was observed, and only alcohol **285** was isolated. The strategy depicted in Scheme 53 is then not suitable to introduce α-methylene-γ-lactone structure in (±)-helenalin (**130**), confirming the work previously published by Grieco *et al*.[115]



Scheme 55. Basic elimination to the alcohol **282a**.

Still in the meantime, last point that has been raised concerning the total synthesis of (±)-helenalin (**130**), was the inversion of configuration of the hydroxyl group at a earlier stage in the sequence (prior to domino enyne metathesis) as shown in Scheme 56. Protecting and changing the

conformation of the secondary alcohol simultaneously would have shortened the sequence of two steps (Bz-protection+ Bz-deprotection+ Mitsunobu reaction being replaced simply by a Mitsunobu reaction), and would have avoid working with unstable intermediate like **281**. Unfortunately, applying Mitsunobu conditions directly on secondary alcohol **256** using BzOH in CH_2Cl_2, afforded an inseparable mixture of two compounds, which after TBDPS deprotection using TBAF were found to be intermediates **289** and **290**. Isolation of by-product **290** could be rationalized by the formation of a carbocation, through a SN_1 mechanism, during the Mitsunobu reaction. Using different acids (p-nitrobenzoic acid, 2-(phenylsulfanyl)propanoic acid), alcohol (intermediate **243**) or solvents (THF, toluene) did not avoid the formation of the carbocation, the inversion of configuration of the alcohol should then really be achieved after the domino enyne metathesis.



Scheme 56. Mitsunobu on the opened form. a) DIAD (2.0 equiv), PPh_3 (2.0 equiv), BzOH (1.0 equiv), CH_2Cl_2, 23 °C, 6 h, 68%; b) TBAF (2.0 equiv), THF, 23 °C, 12 h, 90%. Bz = benzoyl, DIAD = diisopropyl azodicarboxylate, TBAF = tetrabutylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, THF = tetrahydrofuran.

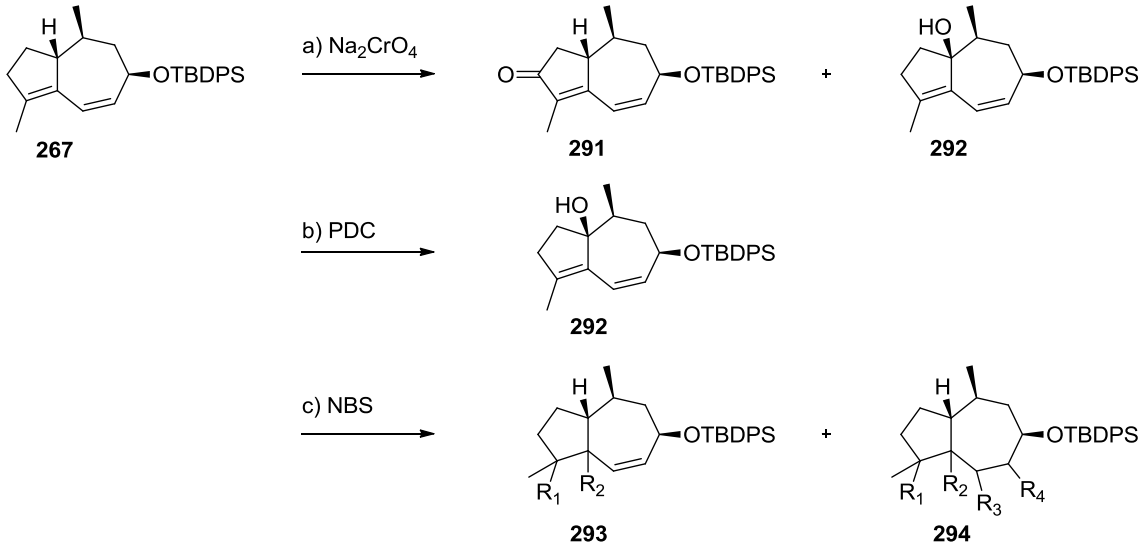
At this stage of my work, attention was shifted to geigerin (**181**) synthesis.

2. f. Total syntheses of (±)-6-deoxygeigerin and (±)-geigerin

Starting with [5.3.0] bicyclic intermediate **267**, first functionalization to study to access to members of the guaianolides family was the introduction of the carbonyl group on the 5-membered ring by allylic oxidation. As shown in Scheme 57, most conventional conditions for this kind of transformation were tested. Unfortunately, conversion of intermediate **267** into desired α,β-unsaturated ketone **291** could only be achieved in low yield using Na_2CrO_4 in the presence of NaOAc, AcOH and Ac_2O.[162,163] Using these conditions, intermediate **291** was obtained in 19% yield as a 1/1 mixture with tertiary alcohol **292**. Intermediate **292** could conversely be obtained as single product using PDC in $CHCl_3$ as oxidizing agent. Although having proved efficient on similar substrates,[164] NBS

only induced bromide addition on the double bounds affording a mixture of products **293** and **294**. Using *t*BuOOH in the presence of CuI[165,166] afforded a single product, whose structure could not be determined despite all the NMR analyses performed (^{1}H, ^{13}C, COSY). No reaction was observed using SeO_2[167] or CrO_3,[166] whereas oxidation in the presence of PCC and NaOAc[168] or Christina White's catalyst[169] afforded a messy crude reaction in which no trace of desired intermediate **291** was detected.

Aside from a kinetic selectivity which should favor oxidation of the secondary carbon, the selectivity will be a product of the relative transition state energy of the secondary *vs* tertiary carbon oxidation. The transition state will involve an intermediate with significant free radical character and its stability will be influenced by its alignment to the adjacent π system.

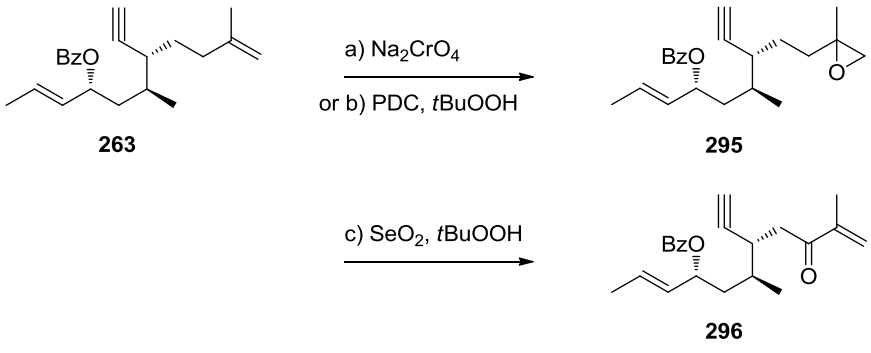


Scheme 57. Conditions tested for the allylic oxidation of the cyclic form. a) Na_2CrO_4 (5.7 equiv), AcOH, Ac_2O, NaOAc, benzene, 70 °C, 12 h, 19% (**291**) and 19% (**292**); b) PDC (30.0 equiv), $CHCl_3$, 70 °C, 12 h, 70%; c) NBS (1.9 equiv), THF/H_2O, 0 °C, 1 h, 13% (**293**) and 37% (**294**). NBS = *N*-bromosuccinimide, PCC =pyridinium chlorochromate, PDC = pyridinium chlorochromate, TBDPS = *tert*-butyldiphenylsilyl chloride, THF = tetrahydrofuran.

Expecting to improve the yield and the selectivity, allylic oxidation was also tried prior to domino enyne metathesis on opened intermediate **263**, even if it was feared that changing the electronics of the alkene would alter the domino enyne metathesis. Same oxidizing agents as for bicyclic intermediate were tested (Scheme 58). Only conditions which allowed the conversion of intermediate **263** into desired α,β-unsaturated ketone **296** were SeO_2 in the presence of *t*BuOOH,[170] but yield also proved very disappointing. Oxidizing agent Na_2CrO_4,[162,163] which gave the best results

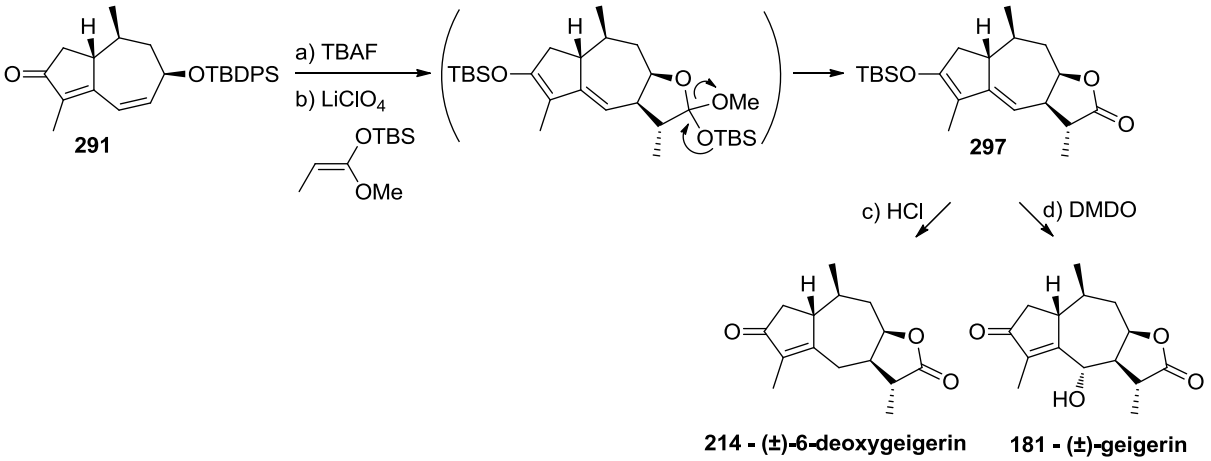
on the cyclic framework, only afforded epoxide **295**, whereas PDC and CrO_3[166] yielded a mixture of two compounds both missing the terminal olefin, but whose exact structure could not be determined. Finally the crude reaction obtained by using CuI and *t*BuOOH[165,166] or SeO_2[167] appeared so dirty that interpretation was impossible.

In conclusion, although the yield of the allylic oxidation on [5.3.0] bicyclic intermediate **267** using Na_2CrO_4 as oxidizing agent proved to be moderate, no better results could be obtained, total synthesis of (±)-geigerin (**181**) was thus continued in this way. An in-depth study should allow a significant improvement of the yield.



Scheme 58. Conditions tested for the allylic oxidation of the opened form. a) Na_2CrO_4 (5.7 equiv), AcOH, Ac_2O, NaOAc, benzene, 70 °C, 12 h, 50%; b) PDC (3.0 equiv), Celite, *t*BuOOH (3.0 equiv), CH_2Cl_2, 23 °C, 12 h, 10%; c) SeO_2 (4.2 equiv), *t*BuOOH (15.6 equiv), CH_2Cl_2, 0 °C to 23 °C, 12 h, 10%. Bz = benzoyl, PCC =pyridinium chlorochromate, PDC = pyridinium chlorochromate.

The carbonyl of the α,β-unsaturated ketone being introduced, few steps remained to be validated before achieving the total synthesis of (±)-geigerin (**181**). It was decided to use a methodology developed by Deprés *et al*,[118] applied to the total synthesis of guainolides family members, which consists in the 1,6-conjugate addition of (*E*)-MeCH=C(OTBS)(OMe) enolate[171] (Scheme 59). The sequence thus began with the TBDPS deprotection of intermediate **291** using TBAF (next step proving unsuccessful on the protected form), followed by the key 1,6-conjugate addition of the enolate (*E*)-MeCH=C(OTBS)(OMe) in the presence of $LiClO_4$[172,173] affording desired TBS-protected intermediate **297** which could be used in the subsequent reactions without further purification. The presence of $LiClO_4$ as a Lewis acid satisfactorily allowed the lactonization to occur simultaneously to the conjugate addition. Treating then intermediate **297** directly with 1N HCl yielded a first natural product called (±)-6-deoxygeigerin (**214**) in 95% (SiO_2 and NH_4Cl appeared not acidic enough to cleave the TBS group), whereas treating it with DMDO induced sequential epoxidation and TBS-deprotection affording the second expected natural product called (±)-geigerin (**181**) in 90% yield.



Scheme 59. Synthesis of (±)-6-deoxygeigerin (**214**) and (±)-geigerin (**181**). a) TBAF (2.0 equiv), THF, 23 °C, 12 h, 75%; b) $LiClO_4$ (0.1 mmol), (*E*)-MeCH=C(OTBS)(OMe) (4.0 equiv), CH_2Cl_2, 40 °C, 5 h; c) 1N HCl, EtOAc, 23 °C, 12 h, 95% (two steps); c) DMDO (1.5 equiv), acetone, -90 °C, 10 min, 90% (two steps). DMDO = dimethyldioxirane, TBAF = tetrabutylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethyl , THF = tetrahydrofuran.

It is important to note that, contrarily to Deprés *et al.*, although enolate MeCH=C(OTBS)(OMe) was used as a 3:1 *E*/*Z* mixture, (±)-6-deoxygeigerin (**214**) as well as (±)-geigerin (**181**) were obtained diastereomerically pure. As shown in Figure 30, the origin of the selectivity is believed to be dictated by the stereochemistry of the hydroxyl group which favors delivery of the enolate from the top face, in conjunction with the proton rather than methyl (irrespectively of the enolate geometry).

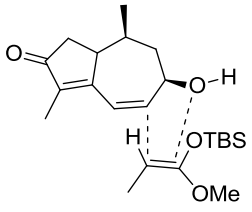


Figure 30. Explanation proposed for the diastereoselectivity observed during the 1,6-conjugate addition.

III. Conclusion

A new flexible synthetic strategy to access guaianolides and peudoguaianolides has then been developed by our laboratory. This methodoly is based on the construction of a central 5/7-bicyclic

core using domino enyne metathesis as a key step. The efficiency of this strategy has been validated by its application to the preparation of two natural products: (±)-geigerin and (±)-6-deoxygeigerin.

This new strategy allows, among others, to bypass the main limitation of the biosynthetic pathway leading to sesquiterpene lactones, namely its lack of specificity. The biosynthetic machine, as depicted in Scheme 26, is indeed not clean and leads generally to mixtures of numerous natural products from numerous classes (contrarily for example to the biosynthetic machine affording the RALs in fungi). Inversely, the proposed strategy allows to access specifically different individual members of the family.

The logic perspectives of the project are first to apply the later strategy to the preparation of other natural sesquiterpene lactones, by imagining new functionalizations of the 5/7-bicyclic framework or by epimerizing the proton in α position of the alkyne function in intermediate **243**. This last transformation should allow to access guaianes and pseudoguaianes bearing the proton at C_1 and the methyl group at C_{10} on opposite sides of the molecule, as it is the case for a large majority of the sesquiterpene lactones. The ultimate perspective is obviously to attach a tag to these natural irreversible inhibitors, such as a biotin, to study precisely their mode of action, which except for the inhibition of the transcription factor NF-κB by helenalin, remain almost unknown. The elucidation of the mechanism at the origin of their various biological properties should still increase the knowledge about individual protein function and should promote the design of extremely effective and selective therapeutic agents.

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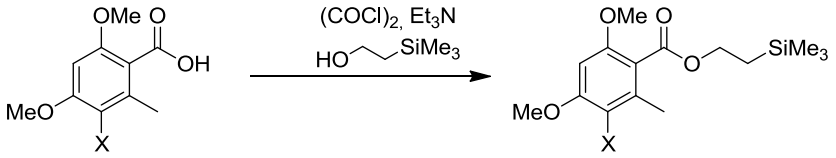
Experimental section

General Techniques. All reactions were carried out under a nitrogen atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Anhydrous solvents were obtained by passing them through commercially available alumina column (Innovative technology, Inc., VA). Reactions were monitored by LC/MS or by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and 10% ethanolic phosphomolybdic acid or vanillin solution and heat as developing agents. PTLC (preparative thin layer chromatography) were carried out on 0.25 mm E. Merck silica gel plates. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at highest available commercial quality and used without further purification unless otherwise stated. Substituted polystyrene resins (100-200 mesh, 1% DVB) were purchased from Novabiochem. All fluorous tags, reagents and silica gel were purchased from Florous Technologies Inc., PA (www.fluorous.com). E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash column chromatography. NMR spectra were recorded on Brucker Advance-400 instruments. Chemical shifts are given in parts per million (δ) and calibrated using residual un-deuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, m = multiplet, b = broad. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. LC/MS were recorded using an Agilent 1100 HPLC with a Bruker micro-TOF instrument (ESI). Unless otherwise stated, a Supelco C8 (5 cm x 4.6mm, 5 µm particules) column was used with a linear elution gradient from 100% H_2O (0.5% HCO_2H) to 100% MeCN in 13 min at a flow rate of 0.5 mL/min. The MALDI spectra were measured using Brucker Daltonics AutoflexII TOF/TOF spectrometer. Reactions performed under µwave irradiation were carried out in a CEM Discover instrument.

Experimental Chapter 1



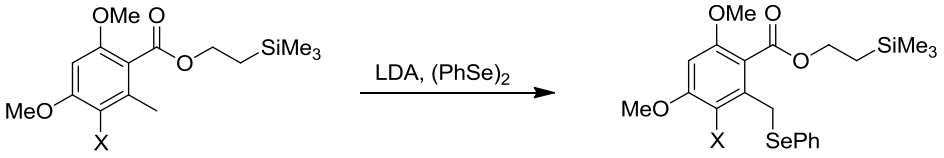
X = OMe (**45**), H (**46**) or Cl (**47**) X = OMe (**45'**), H (**46'**) or Cl (**47'**)

Esters 45', 46' and 47'. To a solution of acid **45**, **46** or **47** (1.0 equiv, **45:** 434 mg, 1.9 mmol, **46:** 377 mg, 1.9 mmol, or **47:** 433 mg, 1.9 mmol), in anhydrous CH_2Cl_2 (10 mL) and DMF (cat) at 0 °C was added oxalyl chloride (1.0 equiv, 165 µL, 1.9 mmol) and the reaction was stirred for 1 h at 23 °C turning progressively gold. Then the reaction was re-cooled to 0 °C, and treated sequentially with Et_3N (2.6 equiv, 700 µL, 5.0 mmol), 2-trimethylsilyl ethanol (1.0 equiv, 276 µL, 1.9 mmol) and DMAP (cat). The mixture was allowed to stir for 1 h at 23 °C, after which it was diluted with CH_2Cl_2, washed with sat. NH_4Cl aq. solution and dried over $MgSO_4$. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Hexane to Hexane/EtOAc 4/1) yielded esters **45'**, **46'**, and **47'** in 98%, 97% or 96% yield respectively (615 mg, 551 mg, 608 mg) as colorless solids.

45': *Rf* = 0.68 (Hexane/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.37 (s, 1H), 4.40-4.36 (m, 2H), 3.86 (s, 3H), 3.79 (s, 3H), 3.72 (s, 3H), 2.21 (s, 3H), 1.13-1.09 (m, 2H), 0.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) 168.2, 154.1, 153.2, 141.3, 130.4, 117.2, 95.3, 63.5, 60.54, 56.5, 56.0, 17.6, 12.9, -1.40 (x 3); HRMS (MALDI-TOF) *m/z* 327.1622 ([M+H$^+$], $C_{16}H_{26}O_5SiH$ requires 327.1628).

46': *Rf* = 0.78 (Hexane/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.30 (s x 2, 2H), 4.40-4.36 (m, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 2.29 (s, 3H), 1.13-1.08 (m, 2H), 0.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) 168.6, 161.3, 158.3, 138.1, 117.2, 106.7, 96.4, 63.3, 55.9, 55.5, 19.9, 17.6, -1.38 (x 3); HRMS (MALDI-TOF) *m/z* 297.1518 ([M+H$^+$], $C_{15}H_{24}O_4SiH$ requires 297.1522).

47': *Rf* = 0.75 (Hexane/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.38 (s, 1H), 4.41-4.36 (m, 2H), 3.89 (s, 3H), 3.81 (s, 3H), 2.30 (s, 3H), 1.12-1.10 (m, 2H), 0.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) 167.9, 156.5, 155.8, 135.4, 118.3, 115.0, 94.5, 63.8, 56.4, 56.3, 17.5, 17.4, -1.42 (x 3); HRMS (MALDI-TOF) *m/z* 331.1108 ([M+H$^+$], $C_{15}H_{23}ClO_4SiH$ requires 331.1132).



X = OMe (**45'**), H (**46'**) or Cl (**47'**) X = OMe (**40**), H (**41**) or Cl (**42**)

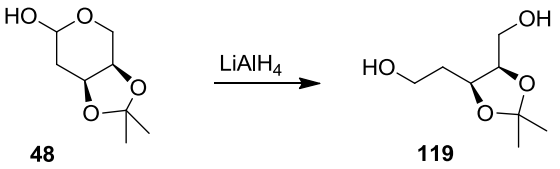
Selenoethers 40, 41 and 42. A solution of compound **45', 46'** or **47'** (1.0 equiv, **45':** 587 mg, 1.8 mmol, **46':** 532 mg, 1.8 mmol, or **47':** 595 mg, 1.8 mmol), in anhydrous THF (0.3 M) was treated at -78 °C with freshly made LDA in THF (2.0 equiv, 6.4 mL, 3.6 mmol). Immediately after, diphenyldiselenide (1.0 equiv, 562 mg, 1.8 mmol) was added, the reaction was stirred at this temperature for 1 h and quenched by addition of Amberlite resin (10.0 equiv, 4.5 g, 18.0 mmol, ~4.0 mmol/g). Upon warming up to 23 °C, the reaction was filtered. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Hexane to Hexane/EtOAc 4/1) yielded

esters **40**, **41** and **42** in 90%, 91% or 89% yield respectively (780 mg, 778 mg, and 776 mg) as colorless solids.

40: *Rf* = 0.40 (Hexane/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.56-7.54 (m, 2H), 7.28-7.25 (m, 3H), 6.44 (s, 1H), 4.35-4.31 (m, 2H), 4.30 (s, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 3.74 (s, 3H), 1.11-1.07 (m, 2H), 0.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) 167.7, 154.6, 154.1, 141.4, 133.5 (x 2), 132.2, 132.0, 129.2 (x 2), 127.3, 116.4, 97.1, 63.9, 61.0, 56.9, 56.3, 23.7, 17.7, -1.20 (x 3); HRMS (MALDI-TOF) *m/z* 483.1047 ([M+H$^+$], $C_{22}H_{30}O_5SeSiH$ requires 483.1106).

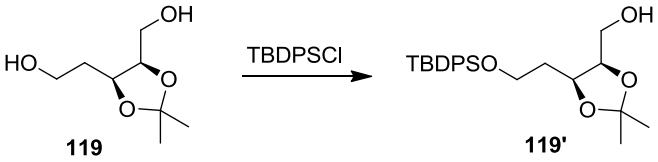
41: *Rf* = 0.56 (Hexane/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.54-7.51 (m, 2H), 7.29-7.26 (m, 3H), 6.36 (d, *J* = 2.4 Hz, 1H), 6.17 (d, *J* = 2.4 Hz, 1H), 4.42-4.38 (m, 2H), 4.14 (s, 2H), 3.82 (s, 3H), 3.69 (s, 3H), 1.17-1.12 (m, 2H), 0.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) 167.8, 161.3, 158.8, 139.8, 134.2 (x 2), 130.7, 129.1 (x 2), 127.6, 116.1, 106.2, 97.9, 63.6, 56.1, 55.4, 30.4, 17.7, -1.40 (x 3); HRMS (MALDI-TOF) *m/z* 475.0808 ([M+Na$^+$], $C_{21}H_{28}O_4SeSiNa$ requires 475.0820).

42: *Rf* = 0.45 (Hexane/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) 7.60-7.58 (m, 2H), 7.29-7.27 (m, 3H), 6.44 (s, 1H), 4.35 (s, 2H), 4.30-4.26 (m, 2H), 3.93 (s, 3H), 3.86 (s, 3H), 1.09-1.05 (m, 2H), 0.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) 167.1, 156.9, 156.5, 137.1, 134.2 (x 2), 131.0, 129.0 (x 2), 127.6, 117.5, 114.9, 95.6, 63.9, 56.5, 56.4, 27.3, 17.5, -1.40 (x 3); HRMS (MALDI-TOF) *m/z* 487.0518 ([M+H$^+$], $C_{21}H_{27}ClO_4SeSiH$ requires 487.0610).

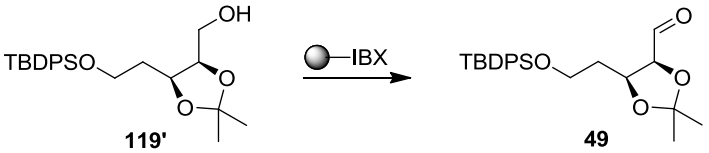


48 **119**

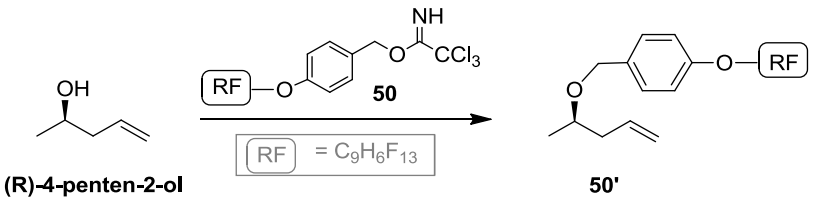
Diol 119. To a suspension of $LiAlH_4$ (1.4 equiv, 1.2 g, 31.4 mmol) in THF (100 mL) at 0 °C was added dropwise the protected sugar **48** (1.0 equiv, 3.9 g, 22.4 mmol) in THF (50 mL) and the mixture was stirred for 2 h at 23 °C. Then the reaction was quenched by careful addition of H_2O (1.2 mL), a 15% NaOH aq. solution (1.2 mL) and H_2O (3.6 mL) and stirred again for 15 min. The reaction was diluted with Et_2O (100 mL) and the precipitated was filtered through Celite and the solvents were evaporated under reduced pressure. Diol **119** was obtained in 95% yield as a colorless oil (3.7 g) and was used directly in the next step without further purification. *Rf* = 0.1 (Hexane/EtOAc 1/2); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 4.26 (dt, *J* = 7.9, 6.1 Hz, 1H), 4.12 (dt, *J* = 6.1, 6.1 Hz, 1H), 3.75 (dt, *J* = 10.4, 6.1 Hz, 1H), 3.66 (ddt, *J* = 10.9, 5.5, 1.8 Hz, 1H), 3.59 (dd, *J* = 11.6, 5.5 Hz, 1H), 3.53 (dd, *J* = 11.6, 6.7 Hz, 1H), 3.14 (bs, 2H), 1.77-1.73 (m, 2H), 1.38 (s, 3H), 1.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) 108.1, 77.9, 75.5, 61.2, 60.3, 31.5, 28.1, 25.5; HRMS (MALDI-TOF) *m/z* 177.1139 ([M+H$^+$], $C_8H_{16}O_4H$ requires 177.1127).



TBDPS-monoprotected alcohol 119'. To a solution of diol **119** (1.0 equiv, 3.7 g, 21.3 mmol) in DMF (21 mL) at 23 °C was added imidazole (1.5 equiv, 2.2 g, 32.0 mmol). The mixture was stirred for 15 min, and then TBDPSCl (1.0 equiv, 5.5 mL, 21.3 mmol) was added dropwise and stirred for 2 h. Then the reaction was diluted with Et_2O, washed with a 10% K_2CO_3 aq. solution, brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Hexane to Hexane/EtOAc 3/1) afforded TBDPS-monoprotected alcohol **119'** in 66% yield (5.8 g). In the crude NMR the selectivity of the reaction was calculated to be >15:1. *Rf* = 0.25 (Hexane/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.68-7.65 (m, 4H), 7.45-7.36 (m, 6H), 4.41 (dt, *J* = 7.3, 5.5 Hz, 1H), 4.16 (dt, *J* = 6.1, 5.0 Hz, 1H), 3.81 (dd, *J* = 7.3, 5.5 Hz, 2H), 3.60 (dd, *J* = 6.7, 5.0 Hz, 2H), 1.84-1.78 (m, 2H), 1.45 (s, 3H), 1.37 (s, 3H), 1.06 (s, 9H), OH signal is not visible; ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 135.6 (x 2), 135.5 (x 2), 133.6, 133.5, 129.6 (x 2), 127.7 (x 2), 127.6 (x 2), 107.9, 77.8, 73.8, 61.8, 61.0, 31.7, 28.2, 26.8 (x 3), 25.4, 19.1; HRMS (MALDI-TOF) *m/z* 437.2113 ([M+Na$^+$], $C_{24}H_{34}O_4SiNa$ requires 437.2124).

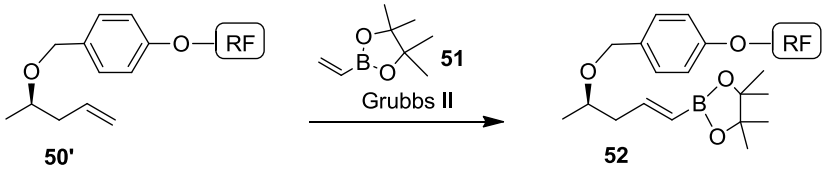


Aldehyde 49. To a solution of alcohol **119'** (1.0 equiv, 1.0 g, 2.4 mmol) in CH_2Cl_2 (21 mL) at 23 °C was added PS-IBX (3.0 equiv, 6.0 g, 7.2 mmol, 1.2 mmol/g) and the suspension was shaken for 2 h. Then the reaction was filtered and after removal of the solvents under vacuum aldehyde **49** was isolated in quantitative yield (990 mg). *Rf* = 0.45 (Hexane/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 9.68 (d, *J* = 3.0 Hz, 1H), 7.72-7.68 (m, 4H), 7.50-7.40 (m, 6H), 4.69-4.64 (m, 1H), 4.30 (dd, *J* = 7.3, 3.0 Hz, 1H), 3.87-3.84 (m, 2H), 1.99-1.91 (m, 1H), 1.72 (dddd, *J* = 7.5, 5.6, 3.9, 1.9 Hz, 1H), 1.60 (s, 3H), 1.45 (s, 3H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 202.1, 135.5 (x 2), 135.4 (x 2), 133.6, 133.5, 129.7, 129.6, 127.7 (x 2), 127.6 (x 2), 110.4, 81.8, 75.1, 60.4, 32.3, 27.6, 26.8 (x 3), 25.3, 19.2; HRMS (MALDI-TOF) *m/z* 413.2094 ([M+H$^+$], $C_{24}H_{32}O_4SiH$ requires 413.2148).

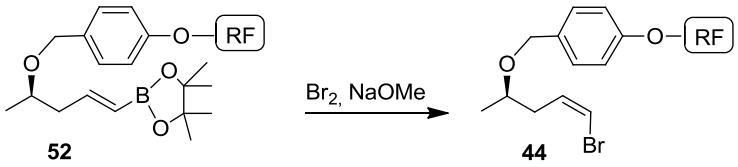


PMB-protected alcohol 50'. To a solution of RF-*para*-hydroxybenzylalcohol (1.0 equiv, 5.0 g, 10.6 mmol) in Et_2O (50 mL) was added NaH 60% (1.04 equiv, 440 mg, 11.0 mmol) and the suspension was stirred for 30 min at 23 °C. Then Cl_3CCN was added at 0 °C (5.0 equiv, 5.3 mL, 53.0 mmol) and the

reaction was allowed to warm up to 23 °C and stirred over 1 h at this temperature. The mixture was then quenched with sat. NH_4Cl aq. solution, extracted with EtOAc, dried over $MgSO_4$ and the solvents evaporated under reduced pressure to obtain acetimidate **50** as a white solid which was used directly in the next reaction. (*R*)-4-penten-2-ol (1.0 equiv, 1.1 mL, 10.6 mmol) was dissolved in CH_2Cl_2 (30 mL) at 23 °C and treated with the acetimidate **50** (1.0 equiv, 6.7 g, 10.6 mmol) and a catalytic amount of CSA (0.1 equiv, 230 mg, 1.06 mmol) and stirred at 23 °C for 12 h. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Hexane to Hexane/EtOAc 1/1) afforded the corresponding protected alcohol **50'** in 92% yield (5.4 g). *Rf* = 0.45 (Hexane/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.25 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 5.90-5.81 (m, 1H), 5.09 (d, *J* = 16.6 Hz, 1H), 5.06 (d, *J* = 8.6 Hz, 1H), 4.51 (d, *J* = 11.6 Hz, 1H), 4.46 (d, *J* = 11.3 Hz, 1H), 4.04 (t, *J* = 5.9 Hz, 2H), 3.60-3.52 (m, 2H), 2.38-2.22 (m, 4H), 2.10-2.05 (m, 2H), 1.21 (d, *J* = 6.5 Hz, 3H).

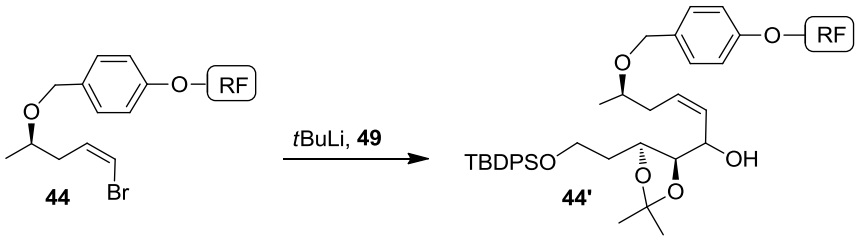


***Trans*-borolane 52.** To a solution of the terminal alkene **50'** (1.0 equiv, 1.5 g, 2.7 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,2,3-dioxaborolane **51** (1.0 equiv, 460 µL, 2.7 mmol) in degassed toluene (50 mL) warmed up to 80 °C was added Grubbs II catalyst (0.025 equiv, 57 mg, 0.07 mmol) and the mixture was stirred at this temperature for 12 h. Evaporation of the solvents under reduced pressure followed by fluorous chromatography using 100 g of fluorous silica, loading of the compound in DMF (1 mL) and eluting with 50% MeOH in H_2O (150 mL), then 80% MeOH in water (150 mL) and finally 100% MeOH (50 mL) afforded protected borolane **52** in 92% yield (1.7 g) which eluted at the solvent front in the 100% MeOH. *Rf* = 0.24 (Hexane/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.61 (dt, *J* = 18.2, 7.0 Hz, 1H), 5.49 (d, *J* = 18.2 Hz, 1H), 4.46 (d, *J* = 11.8 Hz, 1H), 4.42 (d, *J* = 11.3 Hz, 1H), 4.02 (t, *J* = 5.4 Hz, 2H), 3.60 (dq, *J* = 12.4, 5.9 Hz, 1H), 2.50-2.45 (m, 1H), 2.37-2.24 (m, 3H), 2.17-2.05 (m, 2H), 1.26 (s, 12H), 1.19 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 158.3, 150.7, 132.4, 131.8, 129.5 (x 2) , 120.3, 120-105 (m, C_6F_{13}) 114.7 (x 2), 83.4 (x 2), 74.1, 70.2, 66.9, 43.3, 27.8 (t, J_{CF} = 22.1 Hz), 25.1, 20.0 (x 4); HRMS (MALDI-TOF) *m/z* 701.2203 ([M+Na$^+$], $C_{27}H_{32}BF_{13}O_4Na$ requires 701.2084).

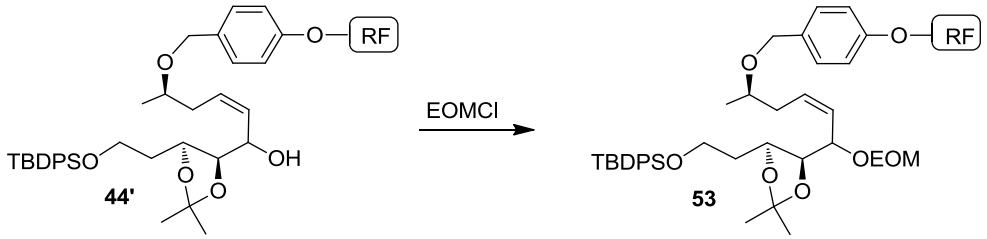


***Cis*-Bromide 44.** A solution of borolane **52** (1.0 equiv, 1.1 g, 1.6 mmol) in Et_2O (40 mL) was cooled to -20 °C. Then a 1.0 M solution of bromine in CH_2Cl_2 (1.0 equiv, 1.6 mL, 1.6 mmol) was added over 10 min. After stirring for 15 min, a 3.0 M solution of sodium methoxide in methanol (2.2 equiv, 1.2 mL, 3.5 mmol) was added. The mixture was then stirred 30 min at -20 °C and then brought up to 23 °C. The reaction was quenched with benzoic acid resin (20.0 equiv, 12.4 g, 32.0 mmol), diluted with

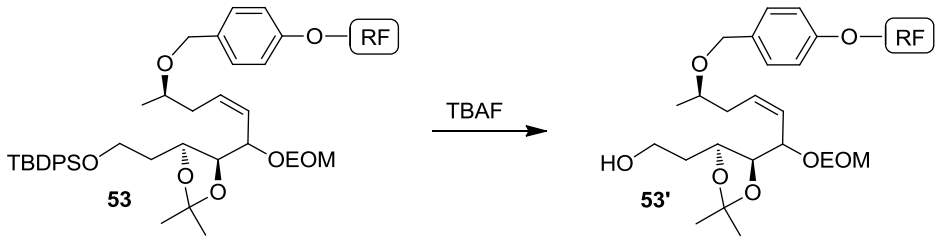
CH_2Cl_2 (50 mL), stirred for 2 h, filtered and washed with CH_2Cl_2. Evaporation of the solvents under reduced pressure followed by fluorous chromatography using the same conditions as for **52** afforded *cis*-bromide **44** in 89% yield (898 mg). *Rf* = 0.76 (Hexane/EtOAc 4/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.25-6.19 (m, 2H), 4.50 (d, *J* = 11.6 Hz, 1H), 4.44 (d, *J* = 11.6 Hz, 1H), 4.02 (t, *J* = 5.9 Hz, 2H), 3.67-3.62 (m, 1H), 2.45 (t, *J* = 6.4 Hz, 2H), 2.37-2.24 (m, 2H), 2.12-2.05 (m, 2H), 1.22 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 158.1, 131.3, 131.2, 129.2 (x 2), 122-105 (m, C_6F_{13}), 114.3 (x 2), 109.3, 73.2, 66.9, 66.3, 36.5, 27.9 (t, J_{CF} = 22.1 Hz), 20.5, 19.6; HRMS (MALDI-TOF) *m/z* 653.0301 ([M+Na$^+$], $C_{21}H_{20}BrF_{13}O_2Na$ requires 653.0336).



Alcohol 44'. To a solution of *cis*-bromide **44** (1.0 equiv, 1.5 g, 2.4 mmol) in THF/Et_2O 1/1 (15 ml) at -100 °C was carefully added a 1.7 M solution of *t*BuLi in pentane (1.0 equiv, 1.4 mL, 2.4 mmol). The resulting mixture was stirred for 15 min. Then, a solution of aldehyde **49** (1.0 equiv, 980 mg, 2.4 mmol) in THF/Et_2O 1/1 (5 mL) precooled to -78 °C was added. The resulting mixture was stirred, at -100 °C for 15 min. The reaction was then quenched with benzoic acid resin (10 equiv, 4.0 g 23.8 mmol), diluted with CH_2Cl_2 (50 mL), stirred for 1 h and then filtered, washed with brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by fluorous chromatography using the same conditions as for **52** afforded secondary alcohol **44'** as a mixture of diastereoisomers in a ratio 3/1 in 88% yield (2.0 g) as a colorless oil. *Rf* = 0.35 (Hexane/EtOAc 4/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.77-7.71 (m, 8H), 7.49-7.41 (m, 12 H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 4H), 5.82 (dd, *J* = 11.2, 8.0 Hz, 1H), 5.80-5.68 (m, 2H), 5.62 (dd, *J* = 11.3, 8.0 Hz, 1H), 4.60-4.40 (m, 8H), 4.10-3.97 (m, 6H), 3.92-3.87 (m, 4H), 3.74-3.67 (m, 1H), 3.64-3.59 (m, 1H), 2.60-2.52 (m, 2H), 2.41-2.22 (m, 6H), 2.06-2.15 (m, 4H), 1.85-1.81 (m, 4H), 1.50 (s, 3H), 1.49 (s, 3H), 1.42 (s x 2, 6 H), 1.27 (d, *J* = 5.9 Hz, 3H), 1.26 (d, *J* = 5.9 Hz, 3H), 1.07 (s, 18H), OH signal is not visible; ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 158.3, 158.2, 135.7 (x 4), 135.6 (x 4), 134.1, 134.0, 133.9, 133.8, 131.0, 130.9, 130.9, 130.6, 129.7, 129.7, 129.6, 129.6, 129.5 (x 4), 128.7, 128.6, 127.7 (x 4), 127.7 (x 4), 121-102 (m x 2, C_6F_{13}), 114.5 (x 2), 114.4 (x 4), 108.3, 107.8, 80.5, 79.8, 74.5, 74.1, 73.8, 73.7, 73.6, 73.3, 70.3, 70.2, 66.4, 66.3, 61.5, 61.0, 35.5, 34.4, 32.8, 32.6, 28.0 (x 2), 28.0 (t x 2, J_{CF} = 21.4 Hz), 25.6, 25.5, 26.9 (x 6), 20.6 (x 2), 19.5, 19.2 (x 2), 18.5; HRMS (MALDI-TOF) *m/z* 987.3646 ([M+Na$^+$], $C_{45}H_{53}F_{13}O_6SiNa$ requires 987.3301).

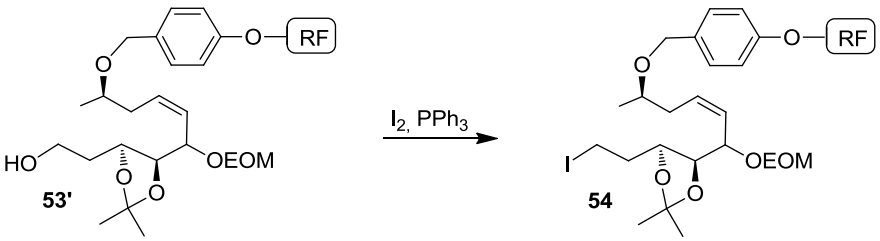


EOM-protected alcohol 53. To a solution of secondary alcohol **44'** (1.0 equiv, 2.0 g, 1.9 mmol) in DMF (4 mL) at 23 °C were added sequencially TBAI (cat), *i*Pr_2NEt (8.0 equiv, 2.5 mL, 15.4 mmol) and EOMCl (8.0 equiv, 1.5 mL, 15.4 mmol). The resulting mixture was stirred 12 h at 23 °C. Then, the reaction was diluted with H_2O (2 mL) and loaded directly on the fluorous silica. The column was eluted under the same conditions as for compound **52** to afforded protected alcohol **53** as a mixture of diastereoisomers in a ratio 3/1 in 96% yield (2.0 g) as a colorless oil. *Rf* = 0.77 (Hexane/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.70-7.68 (m, 8H), 7.41-7.39 (m, 12 H), 7.28-7.22 (m, 4H), 6.87 (d, *J* = 8.1 Hz, 4H), 5.85-5.82 (m, 2H), 5.46-5.36 (m, 2H), 4.72-4.64 (m, 3H), 4.53-4.39 (m, 9H), 4.16-4.10 (m, 1H), 4.07-3.99 (m, 1H), 4.01 (t, *J* = 5.4 Hz, 4H), 3.85-3.78 (m, 4H), 3.75-3.67 (m, 2H), 3.61-3.46 (m, 4H), 2.55-2.49 (m, 1H), 2.40-2.28 (m, 7H), 2.11-2.06 (m, 4H), 1.83-1.73 (m, 4H), 1.39 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3 H), 1.20-1.17 (m, 12H), 1.04 (s, 9H), 1.03 (s, 9H);^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 157.4, 157.3, 135.6 (x 2), 135.6 (x 2), 135.5 (x 2), 135.5 (x 2), 134.0, 133.9, 133.8, 133.8, 132.6, 132.0, 131.3, 130.9, 129.6 (x 2), 129.5 (x 2), 129.2 (x 2), 129.1 (x 2), 127.7, 127.7, 127.6 (x 4), 127.5 (x 4), 122-102 (m x 2, C_6F_{13}), 114.4, 114.4, 114.3, 114.3, 108.4, 107.8, 91.6, 91.5, 79.8, 78.8, 74.3, 74.0, 73.7, 73.4, 70.3, 70.2, 69.9, 69.6, 66.3 (x 2), 61.1, 61.0, 61.0, 60.9, 34.8, 34.7, 32.8, 32.5, 28.2, 28.1, 27.8, 27.7, 27.9 (t x 2, J_{CF} = 21.3 Hz), 26.8 (x 6), 20.6, 20.5, 19.6, 19.1, 15.3, 15.3 15.0, 14.9; HRMS (MALDI-TOF) *m/z* 1045.3903 ([M+Na$^+$], $C_{48}H_{59}F_{13}O_7SiNa$ requires 1045.3720).

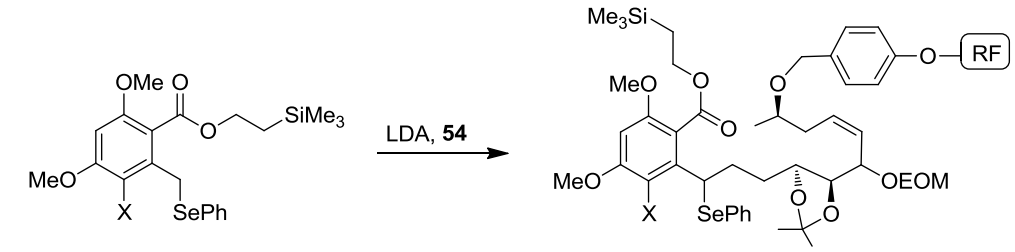


Alcohol 53'. To a solution of protected alcohol **53** (1.0 equiv, 1.9 g, 1.9 mmol) in THF (5 mL) at 23 ºC was added a 1.0 M solution of TBAF in THF (2.5 equiv, 4.7 mL, 4.7 mmol). The resulting mixture was stirred for 12 h then SiO_2 (1 g) and benzoic acid resin (5.0 equiv, 1.6 g, 9.3 mmol) were added and after 5 min, the crude sample was loaded directly on the fluorous column. The column was eluted as for compound **52** to afford the primary alcohol **53'** in 92% yield (1.4 g) as a colorless oil. *Rf* = 0.25 (Hexane/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.46 (d, *J* = 5.9 Hz, 4H), 7.05 (d, *J* = 5.9 Hz, 4H), 6.0-5.98 (m, 2H), 5.63-5.54 (m, 2H), 4.90 (d, *J* = 8.0 Hz, 1H), 4.89 (d, *J* = 7.5 Hz, 1H), 4.86 (d, *J* = 8.0 Hz, 1H), 4.85 (d, *J* = 7.5 Hz, 1H), 4.74-4.59 (m, 8H), 4.44-4.35 (m, 2H), 4.21 (t, *J* = 5.9 Hz, 4H), 4.02-3.66 (m, 10H), 2.76-2.69 (m, 2H), 2.65-2.43 (m, 6H), 2.31-2.24 (m, 4H), 2.18-1.97 (m, 4H), 1.86-1.83 (m, 2H), 1.69 (s, 3H), 1.61 (s, 3H), 1.57 (s, 3H), 1.52 (s, 3H), 1.41-1.37 (m, 12H);^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 158.1 (x 2), 132.8, 132.4, 131.5, 131.5, 129.2 (x 4), 127.9, 126.6, 121.9-105.2 (m x 2, C_6F_{13}), 114.39 (x 4), 108.6, 108.1, 91.8, 91.6, 80.1, 78.8, 76.7, 76.2, 74.3, 73.9, 70.0, 69.9, 69.5, 69.4,

66.4 (x 2), 64.0, 63.2, 61.1, 60.9, 34.9, 34.8, 32.1, 31.9, 27.9, 27.8, 27.7 (t x 2, J_{CF} = 21.3 Hz), 25.7, 25.3, 20.6, 20.5, 19.5, 19.4, 14.8, 14.7; HRMS (MALDI-TOF) *m/z* 807.2384 ([M+Na$^+$], $C_{32}H_{41}F_{13}O_7Na$ requires 807.2542).



Alkyliodide 54. To a solution of alcohol **53'** (1.0 equiv, 1.2 g, 1.5 mmol) in THF (5 mL) were added triphenylphosphine (1.2 equiv, 580 mg, 1.8 mmol) and imidazole (1.2 equiv, 252 mg, 1.8 mmol). The resulting mixture was cooled to 0 °C, followed by the addition of I_2 (1.2 equiv, 564 mg, 1.8 mmol). After 1 h at 0 °C, the reaction was loaded directly on the fluorous column and eluted as for compound **52** to afford alkyl iodide **54** in 91% yield (1.2 g) as a colorless oil. *Rf* = 0.85 (Hexane/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.55 (d, *J* = 8.0 Hz, 4H), 7.14 (d, *J* = 8.0 Hz, 4H), 6.16-6.10 (m, 2H), 5.69-5.59 (m, 2H), 4.98 (d, *J* = 7.0 Hz, 1H), 4.96 (d, *J* = 6.5 Hz, 1H), 4.95 (d, *J* = 7.0 Hz, 1H), 4.93 (d, *J* = 6.5 Hz, 1H), 4.81-4.69 (m, 8H), 4.56-4.51 (m, 1H), 4.47-4.43 (m, 1H), 4.37-4.29 (m, 2H), 4.30 (t, *J* = 6.0 Hz, 4H), 4.03-3.75 (m, 6H), 3.67-3.57 (m, 2H), 3.55-3.41 (m, 2H), 2.82-2.67 (m, 2H), 2.69-2.52 (m, 6H), 2.40-2.34 (m, 5H), 2.19-2.11 (m, 1H), 1.73 (s, 3H), 1.66 (s, 3H), 1.65 (s, 3H), 1.60 (s, 3H), 1.54-1.48 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 158.2 (x 2), 133.2, 132.7, 131.6, 131.6, 129.3 (x 2), 129.3 (x 2), 127.9, 126.3, 121.0-108.1 (m x 2, C_6F_{13}), 114.5 (x 2), 114.4 (x 2), 108.9, 108.4, 91.8, 91.7, 79.9, 79.2, 77.4, 76.9, 74.4, 74.0, 70.1, 70.0, 69.2, 69.5, 66.5 (x 2), 64.3, 63.4, 35.0, 34.8, 34.3, 34.1, 28.2 (t x 2, J_{CF} = 19.8 Hz), 28.1, 27.8, 25.9, 25.5, 20.7 (x 2), 19.8, 19.7, 15.3, 15.2, 3.20, 2.72; HRMS (MALDI-TOF) *m/z* 917.1313 ([M+Na$^+$], $C_{32}H_{40}F_{13}IO_6Na$ requires 917.1559).

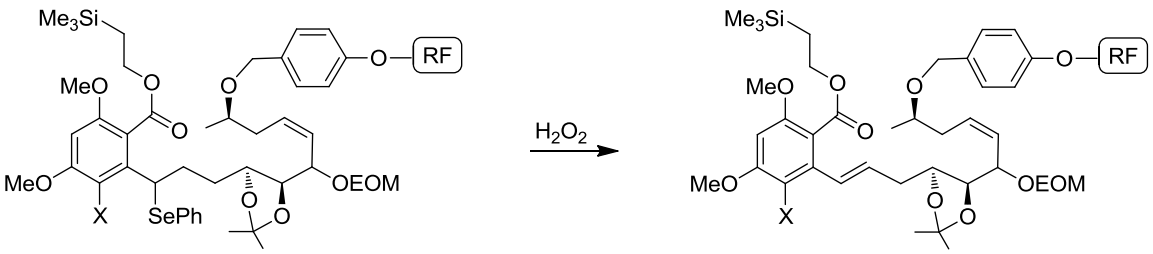


X = OMe (**40**), H (**41**) or Cl (**42**)

X = OMe (**40'**) , H (**41'**), Cl (**42'**)

Alkylated compounds 40', 41' and 42'. To a solution of selenoether **40**, **41** or **42** (1.0 equiv, **40:** 162 mg, 335 µmol, **41**: 152 mg, 335 µmol, **42:** 163 mg, 335 µmol) in THF/HMPA 10/1 (3 mL) cooled at -78 °C was added at once a freshly prepared solution of LDA in THF (2.0 equiv, 1.2 mL, 671 µmol) at -78 °C. The mixture immediately turned red. The reaction was stirred 10 min at -78°C and a solution of the precooled alkyl iodide **54** (1.0 equiv, 300 mg, 336 µmol) in THF (1 mL) was added very slowly along the side of the flask. After stirring at the same temperature for 10 min, the reaction was quenched with benzoic acid resin (5.0 equiv, 280 mg, 1.7 mmol) brought to 23 °C and loaded directly onto fluorous silica column (20 g) and eluted as for compound **52** to recover corresponding

selenoethers **40'**, **41'** or **42'** in 90%, 88% or 91% yield respectively (377 mg, 360 mg, 385 mg) as a mixture of 4 diastereoisomers. *Rf* = 0.30, 0.56 and 0.60 (Hexane/EtOAc 4/1).



X = OMe (**40'**) , H (**41'**), Cl (**42'**)

X = OMe (**55**) , H (**56**), Cl (**57**)

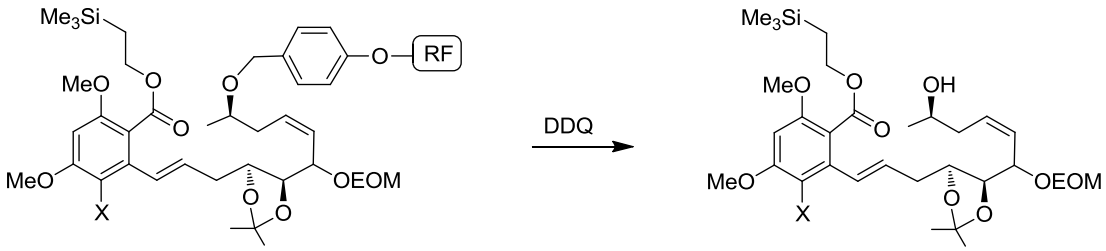
S*yn*-eliminated compounds 55, 56 and 57. To a stirred solution of previously prepared selenoether **40'**, **41'** or **42'** (1.0 equiv, **40':** 368 mg, 295 µmol, **41':** 360 mg, 295 µmol or **42':** 369 mg, 295 µmol) in THF (2 mL) at 23 °C was added a 35% H_2O_2 aq. solution (2.0 equiv, 51 µl, 590 µmol). After 2 h, the reaction was loaded directly on the fluorous silica and eluted as described above to afford compound **55**, **56** or **57** in 82%, 80% or 79% yield respectively (249 mg, 250 mg, 233 mg) as colorless oil.

55: *Rf* = 0.50 (Hexane/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.26 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.51 (bd, *J* = 16.1 Hz, 1H), 6.46 (d, *J* = 16.1 Hz, 1H), 6.41 (s x 2, 2 H), 6.32-6.19 (m, 2H), 5.89-5.79 (m, 2H), 5.42 (dd, *J* = 10.8, 10.8 Hz, 1H), 5.39 (dd, *J* = 9.6, 9.6 Hz, 1H), 4.77-4.65 (m, 4H), 4.55-4.41 (m, 8H), 4.36-4.31 (m, 4H), 4.26-4.21 (m, 2H), 4.08-4.00 (m, 4H), 3.87 (s x 2 , 6H), 3.80 (s x 2, 6H), 3.69 (s, 3H), 3.67 (s, 3H), 3.65-3.47 (m, 6H), 2.56-2.23 (m, 12H), 2.10-2.04 (m, 4H), 1.48 (s, 3H), 1.40 (s, 3H), 1.34 (s, 3H), 1.30 (s, 3H), 1.22-1.18 (m, 12H), 1.10-1.06 (m, 4H), 0.05 (s x 2, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 169.3, 169.2, 158.3, 158.2, 156.7, 156.1, 154.0, 153.2, 140.8, 140.6, 133.6, 133.2, 132.9, 132.6, 132.4, 132.1, 131.6, 131.6, 129.4, 129.3, 129.3, 129.2, 128.1, 127.8, 125.1, 124.7, 120-110 (m x 2, C_6F_{13}), 117.5, 117.4, 114.5, 114.5, 114.4, 114.4, 108.6, 108.1, 96.3, 93.9, 92.6, 91.9, 79.5, 78.9, 77.4, 77.3, 74.4, 74.1, 70.1, 70.0, 69.8, 69.6, 66.5 (x 2), 64.4, 64.2, 63.6, 63.6, 60.6, 60.5, 56.7, 56.6, 56.2, 56.2, 34.8, 34.6, 34.5, 33.9, 29.8 (x 2), 29.5 (x 2), 28.1 (t x 2, J_{CF} = 20.1 Hz), 20.8, 20.7, 19.7 (x 2), 17.4 (x 2), 15.3, 15.2, -1.36 (x 6); HRMS (MALDI-TOF) *m/z* 1097.3922 ([M+Na$^+$], $C_{48}H_{63}F_{13}O_{11}SiNa$ requires 1097.3881).

56: *Rf* = 0.45 (Hexane/EtOAc 4/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.55 (d, *J* = 8.1 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 8.6 Hz, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 6.93 (d, *J* = 2.2 Hz, 1H), 6.90 (d, *J* = 2.2 Hz, 1H), 6.78 (d, *J* = 16.1 Hz, 1H), 6.73 (d, *J* = 16.1 Hz, 1H), 6.63 (bs x 2, 2 H), 6.61-6.47 (m, 2H), 6.18-6.08 (m, 2H), 5.71 (dd, *J* = 9.7, 9.7 Hz, 1H), 5.68 (dd, *J* = 9.7, 9.7 Hz, 1H), 5.00 (d, *J* = 7.0 Hz, 1H), 4.98 (d, *J* = 7.0 Hz, 1H), 4.96 (d, *J* = 8.6 Hz, 1H), 4.95 (d, *J* = 8.6 Hz, 1H), 4.84-4.64 (m, 8H), 4.57-4.53 (m, 2H), 4.46-4.41 (m, 2H), 4.40-4.36 (m, 2H), 4.30-4.25 (m, 4H), 4.10 (s, 3H), 4.09 (s, 3H), 4.06 (s x 2, 6H), 4.04-3.76 (m, 6H), 2.86-2.51 (m, 10H), 2.38-2.32 (m, 6H), 1.78 (s, 3H), 1.71 (s, 3H), 1.70 (s, 3H), 1.65 (s, 3H), 1.56-1.48 (m, 12H), 1.40-1.30 (m, 4H), 0.34 (s, 9H), 0.33 (s, 9H) ; ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 168.4, 168.3, 161.4 (x 2), 158.2 (x 2), 158.1 (x 2), 137.4, 137.3, 132.5 (x 2), 131.6 (x 2), 135.5, 130.1, 129.3, 129.2 (x 4), 128.7, 128.0, 125.6, 120-110 (m x 2, C_6F_{13}), 116.4 (x 2), 114.5 (x 2) , 114.4 (x 2), 108.7, 108.2, 101.7, 101.6, 97.8, 97.7, 91.8, 91.7, 78.9, 78.9, 77.4, 77.0, 74.3, 74.0, 70.1, 70.0, 69.5, 69.4, 66.5 (x 2), 64.3, 64.2, 63.5, 63.4, 56.0 (x 2), 55.5 (x 2), 35.0, 34.8, 33.9, 33.8, 30.4 (x 2),

29.8 (x 2), 29.7 (x 2), 28.1 (t x 2, J_{CF} = 20.1 Hz), 20.7 (x 2), 19.7, 19.6, 17.5 (x 2), 15.2, 15.1, -1.46 (x 6); HRMS (MALDI-TOF) *m/z* 1083.3813 ([M+Na$^+$], $C_{47}H_{61}F_{13}O_{10}SiNa$ requires 1083.3724).

57: *Rf* = 0.54 (Hexane/EtOAc 2/1; ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.55 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.6 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 16.1 Hz, 1H), 6.81 (d, *J* = 16.1 Hz, 1H), 6.71 (s x 2, 2H), 6.40-6.27 (m, 2H), 6.18-6.09 (m, 2H), 5.70 (dd, *J* = 11.3, 11.3 Hz, 1H), 5.68 (dd, *J* = 11.8, 11.8 Hz, 1H), 5.00 (d, *J* = 7.0 Hz, 1H), 4.99 (d, *J* = 7.0 Hz, 1H), 4.97 (d, *J* = 7.0 Hz, 1H), 4.95 (d, *J* = 7.0 Hz, 1H), 4.84-4.68 (m, 8H), 4.64-4.58 (m, 4H), 4.56-4.48 (m, 2H), 4.38-4.28 (m, 4H), 4.18 (s x 2, 6 H), 4.11 (s x 2, 6 H), 4.00-3.96 (m, 2H), 3.90-3.85 (m, 2H), 3.81-3.77 (m, 2H), 2.92-2.83 (m, 2 H), 2.80-2.67 (m, 4H), 2.65-2.51 (m, 6 H), 2.38-2.32 (m, 4H), 1.71 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H), 1.54 (s, 3H), 1.50-1.47 (m, 12H), 1.37-1.32 (m, 4H), 0.33 (s x 2, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 167.6, 167.5, 158.1, 158.1, 156.4, 156.3, 155.9, 156.0, 136.2, 136.1, 134.1, 133.7, 132.9, 132.4, 131.6, 131.5, 129.3 (x 2), 129.2 (x 2), 128.1, 127.3, 127.2, 126.7, 120-110 (m x 2, C_6F_{13}), 117.5, 117.4, 114.5 (x 2), 114.4 (x 2), 113.7, 113.7, 108.6, 108.2, 95.3 (x 2), 91.9, 91.7, 78.9, 78.9, 77.4, 77.0, 74.3, 74.1, 70.1, 69.9, 69.6, 69.4, 66.5 (x 2), 64.2 (x 2), 63.4, 63.3, 56.5 (x 2), 56.3 (x 2), 34.9, 34.8, 34.2, 34.1, 30.4 (x 2), 29.8, 29.7, 28.1 (t, J_{CF} = 20.2 Hz), 28.0 (t, J_{CF} = 21.0 Hz), 20.7, 20.6, 19.7, 19.6, 17.4 (x 2), 15.2, 15.1, -1.43 (x 6); HRMS (MALDI-TOF) *m/z* 1117.3356 ([M+Na$^+$], $C_{47}H_{60}ClF_{13}O_{10}SiNa$ requires 1117.3334).



X = OMe (**55**) , H (**56**), Cl (**57**)

X = OMe (**55'**) , H (**56'**), Cl (**57'**)

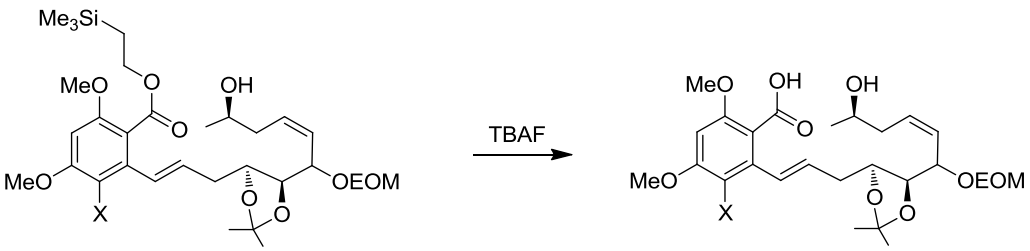
PMB-deprotected alcohols 55', 56' and 57'. To a solution of compound **55**, **56** or **57** (1.0 equiv, **55:** 251 mg, 230 µmol, **56:** 244 mg, 230 µmol or **57:** 252 mg, 230 µmol) in CH_2Cl_2/H_2O 2/1 (12 mL) at 23 °C was added DDQ (1.2 equiv, 63 mg, 276 µmol). The reaction mixture was stirred for 2 h and loaded directly on a fluorous column (20 g) then eluted as described for **52** to obtain compound **55'**-**57'** in the 80% MeOH fraction with a purity level of *ca.* 85%. Flash chromatography (SiO_2, Hexane/EtOAc 50/1 to 5/1) afforded desired alcohols **55'**, **56'** or **57'** in 77%, 80% and 80% respectively (111 mg, 109 mg, 101 mg) as a colorless oil.

55', less polar major isomer 55'a: *Rf* = 0.21 (Hexane/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.52 (d, *J* = 16.1 Hz, 1H), 6.41 (s, 1H), 6.27 (dt, *J* = 16.1, 7.0 Hz, 1H), 5.87 (dt, *J* = 10.8, 8.0 Hz, 1H), 5.49 (dd, *J* = 10.8, 10.2 Hz, 1H), 4.74 (d, *J* = 7.0 Hz, 1H), 4.57 (d, *J* = 7.0 Hz, 1H), 4.36-4.32 (m, 2H), 4.27-4.20 (m, 1H), 4.08 (d, *J* = 8.6 Hz, 1H), 4.05 (d, *J* = 8.6 Hz, 1H), 3.87 (s, 3H), 3.84-3.80 (m, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 3.67-3.52 (m, 2H), 2.53-2.47 (m, 2H), 2.33-2.29 (m, 2H), 1.44 (s, 3H), 1.31 (s, 3H), 1.25-1.20 (m, 6H), 1.10-1.06 (m, 2H), 0.05 (s, 9H), OH signal is not visible; ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 168.3, 154.0, 153.2, 140.8, 133.3, 132.6, 130.6, 130.3, 125.1, 116.1, 108.5, 96.3, 92.1, 78.5, 77.6, 69.3, 66.8, 64.3, 63.6, 60.5, 56.7, 56.2, 38.0, 34.6, 28.1, 25.9, 23.2, 17.4, 15.0, -1.35 (x 3); HRMS (MALDI-TOF) *m/z* 647.3322 ([M+Na$^+$], $C_{32}H_{52}O_{10}SiNa$ requires 647.3228).

55', more polar minor isomer 55'b: *Rf* = 0.20 (Hexane/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.47 (d, *J* = 16.1 Hz, 1H), 6.41 (s, 1H), 6.21 (dt, *J* = 16.1, 7.0 Hz, 1H), 5.83 (td, *J* = 10.2, 4.3 Hz, 1H), 5.44 (dd, *J* = 10.2, 10.2 Hz, 1H), 4.73 (d, *J* = 7.0 Hz, 1H), 4.71 (d, *J* = 7.0 Hz, 1H), 4.36-4.32 (m, 2H), 4.27-4.20 (m, 1H), 4.18-4.11 (m, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 3.69 (s, 3H), 3.70-3.69 (m, 2H), 3.67-3.52 (m, 2H), 2.73-2.67 (m, 1H), 2.64-2.60 (m, 1H), 2.48-2.39 (m, 1H), 2.36-2.32 (m, 1H), 1.51 (s, 3H), 1.35 (s, 3H), 1.25-1.21 (m, 6H), 1.10-1.06 (m, 2H), 0.05 (s, 9H), OH signal is not visible; ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 168.4, 154.0, 153.2, 140.7, 133.9, 132.9, 130.5, 130.3, 125.2, 116.0, 108.7, 96.4, 92.8, 79.9, 77.3, 70.0, 67.4, 64.4, 63.6, 60.5, 56.6, 56.2, 38.4, 34.5, 28.0, 26.1, 22.6, 17.4, 15.2, -1.35 (x 3); HRMS (MALDI-TOF) *m/z* 647.3169 ([M+Na$^+$], $C_{32}H_{52}O_{10}SiNa$ requires 647.3228).

56': *Rf* = 0.54 (Hexane/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.65 (d, *J* = 2.2 Hz, 1H), 6.61 (d, *J* = 2.2 Hz, 1H), 6.48 (d, *J* = 15.6 Hz, 1H), 6.44 (d, *J* = 16.2 Hz, 1H), 6.34 (s, 1H), 6.33 (s, 1H), 6.31-6.21 (m, 2H), 5.89-5.81 (m, 2H), 5.47 (dd, *J* = 10.8, 10.8 Hz, 1H) 5.45 (dd, *J* = 8.0, 8.0 Hz, 1H), 4.73-4.68 (m, 2H), 4.61-4.55 (m, 2H), 4.39-4.35 (m, 4H), 4.31-4.26 (m, 2H), 4.18-4.08 (m, 4H), 3.82 (s, 3H), 3.81 (S, 3H), 3.77 (s x 2, 6H), 3.72-3.64 (m, 3H), 3.59-3.50 (m, 3H), 2.64-2.54 (m, 4H), 2.48-2.45 (m, 4H), 1.46 (s, 3H), 1.42 (s, 3H), 1.37 (s, 3H), 1.33 (s, 3H), 1.20-1.19 (m, 12H), 1.17-1.08 (m, 4H), 0.05 (s, 18H), OH signal is not visible; ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 168.4, 168.3, 161.4, 161.3, 158.1, 158.0, 137.4, 137.3, 133.8, 132.7, 130.3, 130.2, 130.0, 129.9, 129.0, 128.9, 116.4 (x 2), 116.3 (x 2), 108.8, 108.6, 101.7, 101.6, 97.9, 97.8, 92.0, 91.9, 78.9, 78.7, 77.5, 77.1, 69.9, 69.1, 67.3, 66.8, 64.4, 64.3, 63.6, 63.5, 56.0, 56.0, 55.6, 55.5, 38.4, 38.0, 34.0, 33.9, 30.4 (x 2), 29.8, 29.7, 17.5 (x 2), 15.2, 15.1, -1.38 (x 6); HRMS (MALDI-TOF) *m/z* 617.3080 ([M+Na$^+$], $C_{31}H_{50}O_9SiNa$ requires 617.3122).

57': 0.21 (Hexane/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.57 (d, *J* = 16.1 Hz, 1H), 6.52 (d, *J* = 16.1 Hz, 1H), 6.42 (s x 2, 2H), 6.10-5.96 (m, 2H), 5.89-5.80 (m, 2H), 5.47 (dd, *J* = 10.8, 10.8 Hz, 1H), 5.42 (dd, *J* = 10.8, 10.8 Hz, 1H), 4.72 (d, *J* = 6.9 Hz, 1H), 4.70 (d, *J* = 7.5 Hz, 1H), 4.58 (d, *J* = 7.5 Hz, 1H), 4.55 (d, *J* = 6.9 Hz, 1H), 4.46 (dd, *J* = 9.7, 9.6 Hz, 1H), 4.37-4.28 (m, 4H), 4.27-4.21 (m, 2H), 4.16 (dd, *J* = 11.8, 5.9 Hz, 1H), 4.09 (dd, *J* = 9.7, 3.8 Hz, 1H), 4.05 (dd, *J* = 8.6, 5.4 Hz, 1H), 3.89 (s x 2, 6H), 3.82 (s x 2, 6H), 3.74-3.66 (m, 2H), 3.61-3.50 (m, 4H), 2.53-2.43 (m, 4H), 2.31-2.25 (m, 4H), 1.44 (s, 3H), 1.41 (s, 3H), 1.36 (s, 3H), 1.30 (s, 3H), 1.24-1.19 (m, 12H), 1.07-1.02 (m, 4H), 0.04 (s, 18H), OH signal is not visible; ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 167.7, 167.6, 156.3, 156.3, 155.9 (x 2), 136.3, 136.1, 134.0, 133.9, 133.6, 132.7, 130.3 (x 2), 127.4, 127.3, 117.5, 117.4, 113.8, 113.7, 108.8, 108.6, 95.5, 95.4, 92.1 91.9, 79.9, 78.7, 77.5, 76.7, 69.4, 69.2, 67.4, 66.7, 64.3 (x 2), 63.7, 63.6, 56.5 (x 2), 56.4 (x 2), 38.4, 38.0, 34.2, 34.1, 30.4 (x 2), 28.1, 28.1, 26.1, 26.0, 17.4 17.3, 15.2, 15.1, -1.39 (x 6); HRMS (MALDI-TOF) *m/z* 651.2772 ([M+Na$^+$], $C_{31}H_{49}ClO_9SiNa$ requires 651.2733).



X = OMe (**55'**) , H (**56'**), Cl (**57'**)

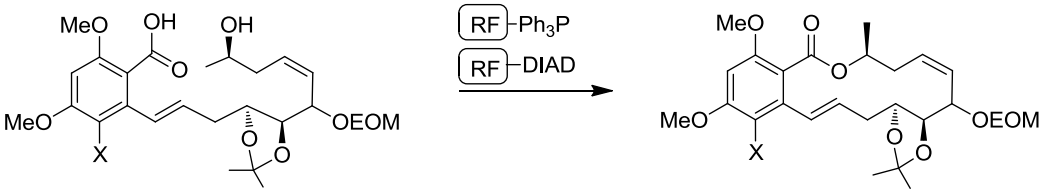
X = OMe (**55''**) , H (**56''**), Cl (**57''**)

Acids 55'', 56'' and 57''. To a solution of silyl-ester **55'**, **56'** or **57'** (1.0 equiv, **55':** 149 mg, 160 µmol, **56':** 93 mg, 160 µmol or **57':** 99 mg, 160 µmol) in THF (2 mL) at 23 °C was added a 1.0 M solution of TBAF in THF (3.0 equiv, 480 µl, 480 µmol). The reaction mixture was quenched after 30 min using sat. NH_4Cl aq. solution, extracted with EtOAc, dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (SiO_2, Hexane/EtOAc 10/1 to EtOAc/MeOH 50/1) provided desired acid **55''**, **56''** or **57''** in 87%, 87% and 88% yield respectively (73 mg, 69 mg, 74 mg) as colorless oil.

55'': *Rf* = 0.50 (EtOAc /MeOH 20/1); ^{1}H NMR ($(CD_3)_2CO$, 400 MHz, 25 °C) δ 6.69 (s x 2, 2H), 6.55-6.38 (m, 4H), 5.87-5.81 (m, 2H), 5.45 (dd, *J* = 9.7, 9.7 Hz, 1H), 5.39 (dd, *J* = 10.5, 10.5 Hz, 1H), 4.70 (d, *J* = 6.7 Hz, 1H), 4.63 (d, *J* = 7.0 Hz, 1H), 4.59 (d, *J* = 7.0 Hz, 1H), 4.57 (d, *J* = 6.7 Hz, 1H), 4.27-4.23 (m, 2H), 4.16-4.13 (m, 2H), 4.09-4.01 (m, 2H), 3.88 (s x 2, 6H), 3.81 (s x 2, 6H) 3.66 (s, 3H), 3.65 (s, 3H), 3.69-3.48 (m, 2H), 3.47-3.42 (m, 4H), 2.63-2.58 (m, 2H), 2.52-2.49 (m, 2H), 2.30 (dd x 2, *J* = 5.9, 5.9 Hz, 4H), 1.43 (s, 3H), 1.38 (s, 3H), 1.29 (s, 3H), 1.28 (s, 3H), 1.18-1.13 (m, 12H), OH and CO_2H signals are not visible; HRMS (MALDI-TOF) *m/z* 525.2722 ([M+H$^+$], $C_{27}H_{40}O_{10}H$ requires 525.2700).

56'': *Rf* = 0.45 (EtOAc /MeOH 20/1); ^{1}H NMR ($(CD_3)_2CO$, 400 MHz, 25 °C) δ 6.75 (d, *J* = 1.8 Hz, 1H), 6.73 (d, *J* = 1.8 Hz, 1H), 6.64 (d, *J* = 15.8 Hz, 2H), 6.50 (d, *J* = 1.8 Hz, 2H), 6.41 (dt x 2, *J* = 15.8, 7.3 Hz, 2H), 5.84 (dt x 2, *J* = 10.1, 7.9 Hz, 2H), 5.39 (dd, *J* = 9.7, 9.7 Hz, 1H), 5.38 (dd, *J* = 9.7, 9.7 Hz, 1H), 4.69 (d, *J* = 6.7 Hz, 1H), 4.62 (d, *J* = 9.0 Hz, 1H), 4.60 (d, *J* = 9.0 Hz, 1H), 4.57 (d, *J* = 6.7 Hz, 1H), 4.27 (ddd x 2, *J* = 9.6, 3.6, 3.0 Hz, 2H), 4.09 (dd x 2, *J* = 8.5, 6.0 Hz, 2H), 3.84 (s x 2, 6H), 3.81 (s x 2, 6H), 3.81-3.75 (m, 4H), 3.70-3.65 (m, 2H), 3.55-3.47 (m, 2H), 2.66-2.60 (m, 2H), 2.54-2.47 (m, 2H), 2.29 (dd, *J* = 6.7, 6.7 Hz, 4H), 1.38 (s x 2, 6H), 1.27 (s x 2, 6H), 1.78-1.12 (m, 12H), OH and CO_2H signals are not visible; HRMS (MALDI-TOF) *m/z* 517.2498 ([M+Na$^+$], $C_{26}H_{38}O_9Na$ requires 517.2414).

57'': *Rf* = 0.51 (EtOAc /MeOH 20/1); ^{1}H NMR ($(CD_3)_2CO$, 400 MHz, 25 °C) δ 6.78 (s x 2, 2H), 6.58 (d, *J* = 16.1 Hz, 1H), 6.56 (d, *J* = 16.1 Hz, 1H), 6.21 (dt, *J* = 16.1, 6.4 Hz, 1H), 6.15 (dt, *J* = 16.1, 6.9 Hz, 1H), 5.87-5.80 (m, 2H), 5.45 (dd, *J* = 9.7, 9.6 Hz, 1H), 5.39 (dd, *J* = 9.7, 9.6 Hz, 1H), 4.70 (d, *J* = 7.0 Hz, 1H), 4.60 (d, *J* = 9.1 Hz, 1H), 4.58 (d, *J* = 9.1 Hz, 1H), 4.57 (d, *J* = 7.0 Hz, 1H), 4.24 (ddd x 2, *J* = 9.6, 5.9, 4.3 Hz, 2H), 4.08 (dd x 2, *J* = 8.1, 5.9 Hz, 2H), 3.94 (s x 2, 6H), 3.87 (s x 2, 6H), 3.80-3.76 (m, 4H), 3.72-3.66 (m, 2H), 3.55-3.47 (m, 2H), 2.64 (ddd, *J* = 7.5, 3.7, 1.1 Hz, 1H), 2.61 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 2.54-2.47 (m, 2H), 2.33-2.29 (m, 4H), 1.42 (s, 3H), 1.37 (s, 3H), 1.29 (s, 3H), 1.28 (s, 3H), 1.18-1.14 (m, 12H), OH and CO_2H signals are not visible; HRMS (MALDI-TOF) *m/z* 551.1950 ([M+Na$^+$], $C_{26}H_{37}ClO_9Na$ requires 551.2024).



X = OMe (**55''**) , H (**56''**), Cl (**57''**)

X = OMe (**58**) , H (**59**), Cl (**60**)

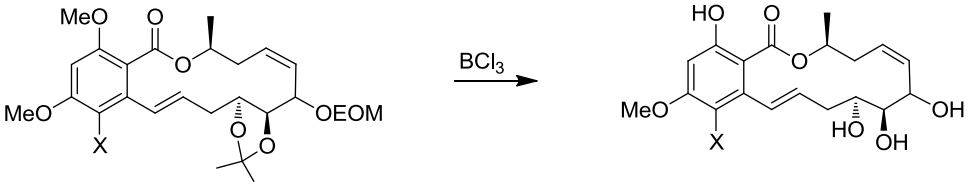
Macrocycles 58, 59 and 60. A solution of compound **55''**, **56''** or **57''** (1.0 equiv, **55'':** 52 mg, 100µmol, **56'':** 50 mg, 100 µmol or **57'':** 53 mg, 100 µmol) in toluene (10 mL) was treated with RF-DIAD (2.0 equiv, 168 mg, 200 µmol) and RF-Ph_3P (2.0 equiv, 142 mg, 280 µmol) and the mixture was stirred at 23 °C for 2 h. Then the solvents were evaporated, the crude dissolved in DMF (0.5 mL) and loaded onto a fluorous column (10 g) and eluted as described above. The desired compounds **58**, **59** or **60** were recovered in the 80% MeOH fractions with >80% purity in 81%, 80% and 81% yield respectively (41 mg, 38 mg, 41 mg) as white powder.

58: *Rf* = 0.44 (Hexane/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.62 (d, *J* = 16.4 Hz, 1H), 6.56 (d, *J* = 16.4 Hz, 1H), 6.42 (s, 1H), 6.39 (s, 1H), 6.15 (dt x 2, *J* = 15.6, 7.3 Hz, 2H), 5.99-5.87 (m, 2H), 5.69 (dd, *J* = 9.4, 9.4 Hz, 1H), 5.64 (dd, *J* = 10.7, 10.7 Hz, 1H), 5.35-5.29 (m, 2H), 4.75 (dd, *J* = 7.2, 0.8 Hz, 1H), 4.71 (d, *J* = 7.0 Hz, 1H), 4.65 (d, *J* = 7.0 Hz, 1H), 4.63 (d, *J* = 7.2 Hz, 1H), 4.44-4.40 (m, 2H), 4.32-4.30 (m, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.78-3.70 (m, 4H), 3.70 (s, 3H), 3.67 (s, 3H), 3.56-3.52 (m, 2H), 3.11 (ddd x 2, *J* = 16.1, 11.6, 4.6 Hz, 2H), 2.87-2.53 (m, 6H), 1.42 (s, 3H), 1.37 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H), 1.18-1.13 (m, 12H); HRMS (MALDI-TOF) *m/z* 529.2464 ([M+Na^+], $C_{27}H_{38}O_9Na$ requires 529.2413).

59: *Rf* = 0.25 (Hexane/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.63 (d x 2, *J* = 15.6 Hz, 2H), 6.48 (s, 1H), 6.47 (s, 1H), 6,37 (s, 1H), 6.35 (s, 1H), 6.23-6.11 (m, 2H), 5.95 (td, *J* = 11.8, 5.4 Hz, 1H), 5.87 (td, *J* = 11.3, 5.9 Hz, 1H), 5.65 (dd, *J* = 9.1, 9.1 Hz, 1H), 5.57 (dd, *J* = 9.7, 9.7 Hz, 1H), 5.39-5.31 (m, 2H), 4.80 (dd, *J* = 7.5, 7.5 Hz, 1H), 4.75-4.73 (m, 1H), 4.70 (d, *J* = 6.4 Hz, 1H), 4.69 (d, *J* = 7.0 Hz, 1H), 4.65 (d, *J* = 6.4 Hz, 1H), 4.64 (d, *J* = 7.0 Hz, 1H), 4.46-4.43 (m, 1H), 4.40-4.36 (m, 1H), 4.34-4.31 (m, 1H), 4.28-4.22 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.70-3.64 (m, 2H), 3.60-3.52 (m, 2H), 3.06 (ddd, *J* = 15.1, 11.3, 3.8 Hz, 1H), 2.87-2.74 (m, 1H), 2.67-2.53 (m, 4H), 2.31-2.23 (m, 2H), 1.41 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H), 1.20-1.14 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 166.8, 166.2, 160.5, 160.4, 156.9, 156.9, 137.2, 137.0, 131.0, 130.3, 129.5, 128.9, 128.3 (x 2), 128.1, 128.0, 115.2, 115.0, 107.1 (x 2), 102.4, 101.8, 96.8, 96.7, 92.1, 91.7, 79.9, 78.2, 76.4, 75.9, 74.9, 74.8, 69.8, 68.5, 62.9, 62.8, 55.1, 55.0, 54.6, 54.5, 34.9, 33.2, 32.6, 32.4, 26.0, 25.7, 24.5, 23.9, 17.2 (x 2), 14.2, 14.1; HRMS (MALDI-TOF) *m/z* 499.2310 ([M+Na^+], $C_{26}H_{36}O_8Na$ requires 499.2308).

60: *Rf* = 0.20 (Hexane/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.61 (d, *J* = 15.8 Hz, 2H), 6.42 (s, 1H), 6.41 (s, 1H), 6.32-6.26 (m, 2H), 6.04-5.94 (m, 2H), 5.70 (dd, *J* = 10.1, 10.1 Hz, 1H), 5.68 (dd, *J* = 10.5, 10.5 Hz, 1H), 5.38-5.33 (m, 2H), 4.73 (d, *J* = 9.0 Hz, 1H), 4.71 (d, *J* = 7.0 Hz, 1H), 4.64 (d, *J* = 9.0 Hz, 1H), 4.62 (d, *J* = 7.0 Hz, 1H), 4.45-4.41 (m, 2H), 4.32 (dd x 2, *J* = 6.4, 6.4 Hz, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.71-3.64 (m, 2H), 3.57-3.49 (m, 4H), 3.09-3.01 (m, 2H), 2.69-2.61 (m, 2H), 2.31-2.25 (m, 2H), 2.04-2.00 (m, 2H), 1.42 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H), 1.32 (s, 3H), 1.18-1.13 (m, 12 H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 167.6, 166.7, 156.4, 156.3, 155.7, 155.0, 136.1, 136.0, 133.6, 132.9, 130.9, 130.3, 129.4, 129.3, 128.0, 127.6, 117.0 (x 2), 113.8 (x 2), 108.7, 108.1, 95.6, 95.4, 92.5, 92.2, 80.4, 79.3, 77.4, 76.7, 71.3 (x 2), 70.3, 69.6, 63.9, 63.7, 56.5, 56.4, 56.4, 56.3,

35.8, 34.9, 33.2, 33.1, 26.6, 26.4, 25.8, 25.1, 18.9 (x 2), 15.2, 15.1; HRMS (MALDI-TOF) *m/z* 533.1922 ([M+Na$^+$], $C_{26}H_{35}ClO_8Na$ requires 533.1918).



X = OMe (**58**) , H (**59**), Cl (**60**)

X = OMe (**58'**) , H (**59'**), Cl (**60'**)

Deprotected compounds 58', 59' and 60'. To a solution of macrocycle **58**, **59** or **60** (1.0 equiv, **58**: 20 mg, 40 µmol, **59**: 19 mg, 40 µmol or **60**: 20 mg, 40 µmol) in CH_2Cl_2 (4 mL) at 0 °C was added a 1.0 M solution of BCl_3 in hexane (6.0 equiv, 240 µL, 240 µmol) and the reaction was monitored by LC/MS. The reactions were all complete within 15-30 min. The reaction was then quenched with sat. $NaHCO_3$ aq. (100 µL) and MeOH (200 µL) stirred for 5 min, further diluted with CH_2Cl_2 (4 mL), filtered through a pad of SiO_2 (150 mg) and washed with 20% MeOH in EtOAc. Evaporation of the solvents followed by PTLC (SiO_2, 2% MeOH in EtOAc) afforded deprotected compound **58'**, **59'** or **60'** as a mixture of two isomers in 88%, 82%, and 86% yield respectively (14 mg, 9 mg of the more polar isomer + 3 mg of the less polar one, 11 mg of the less polar isomer + 3 mg of the more polar one) as white powder.

58': *Rf* = 0.20 (EtOAc/MeOH 20/1); ^{1}H NMR (CD_3OD, 400 MHz, 25 °C) δ 6.77 (d, *J* = 16.6 Hz, 1H), 6.62 (d, *J* = 15.6 Hz, 1H), 6.53 (s x 2, 2H), 5.99-5.89 (m, 3H), 5.79 (dd, *J* = 9.6, 9.6 Hz, 1H), 5.73-5.61 (m, 2H), 5.40-5.31 (m, 2H), 4.78 (dd x 2, *J* = 8.0, 5.4 Hz, 2H), 4.71-4.64 (m, 2H), 3.93 (s x 2, 6H), 3.81 (bd, *J* = 5.4 Hz, 1H), 3.67 (bd, *J* = 6.4 Hz, 1H), 3.63 (s x 2, 6H), 3.11-3.03 (m, 1H), 2.97-2.90 (m, 1H), 2.79-2.64 (m, 3H), 2.57-2.49 (m, 1H), 2.46-2.40 (m 2H), 1.51 (d, *J* = 5.9 Hz, 3H), 1.47 (d, *J* = 5.9 Hz, 3H), 4 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 417.1567 ([M+Na$^+$], $C_{20}H_{26}O_8Na$ requires 417.1526).

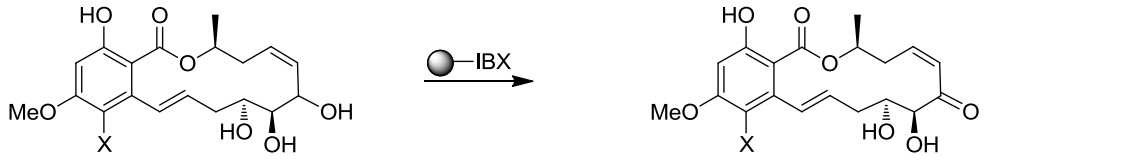
59', more polar major isomer 59a': *Rf* = 0.15 (2% MeOH in EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 12.35 (s, 1H), 7.20 (dd, *J* = 15.0, 2.2 Hz, 1H), 6.43 (d, *J* = 2.7 Hz, 1H), 6.40 (d, *J* = 2.7 Hz, 1H), 5.86 (ddd, *J* = 11.3, 11.3, 1.6 Hz, 1H), 5.72 (ddd, *J* = 15.0, 11.3, 3.2 Hz, 1H), 5.62 (td, *J* = 11.3, 4.3 Hz, 1H), 5.27-5.20 (m, 1H), 4.99 (d, *J* = 9.6 Hz, 1H), 4.11 (ddd, *J* = 10.8, 5.4, 2.7 Hz, 1H), 3.81 (s, 3H), 3.43 (d, *J* = 2.7 Hz, 1H), 3.06-2.97 (m, 1H), 2.86-2.80 (m, 1H), 2.59-2.50 (m, 1H), 2.30-2.25 (m, 1H), 1.45 (d, *J* = 5.9 Hz, 3H), 3 OH signals are not visible; ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) 166.4, 164.2, 157.9, 142.7, 133.9, 130.3, 130.1, 128.0, 119.4, 108.5, 100.4, 75.0, 72.5, 72.3, 64.5, 55.6, 39.0, 35.0, 21.6; HRMS (MALDI-TOF) *m/z* 387.1434 ([M+Na$^+$], $C_{19}H_{24}O_7Na$ requires 387.1420).

59', less polar minor isomer 59b': *Rf* = 0.28 (2% MeOH in EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 12.03 (s, 1H), 7.19 (d, *J* = 15.0 Hz, 1H), 6.45 (d, *J* = 2.2 Hz, 1H), 6.41 (d, *J* = 2.2 Hz, 1H), 6.09 (dd, *J* = 11.0 Hz, 8.6 Hz, 1H), 5.99 (dd, *J* = 11.0 Hz, 4.3 Hz, 1H), 5.68 (ddd, *J* = 15.0 Hz, 11.3, 2.7 Hz, 1H), 5.29-5.22 (m, 1H), 4.58-4.53 (m, 1H), 4.10-4.04 (m, 3H), 3.82 (s, 3H), 2.68-2.64 (m, 1H), 2.40-2.34 (m, 1H), 2.31-2.21 (m, 1H), 1.43 (d, *J* = 5.9 Hz, 3H), 3 OH signals are not visible; ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) 171.4, 166.0, 164.5, 143.1, 134.2, 133.7, 128.7, 127.3, 108.1, 103.4, 100.4, 75.6, 72.6, 72.0, 58.7, 55.6, 47.1, 37.3, 21.6; HRMS (MALDI-TOF) *m/z* 387.1390 ([M+Na$^+$], $C_{19}H_{24}O_7Na$ requires 387.1420).

60', less polar major isomer 60a': *Rf* = 0.30 (2% MeOH in EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 12.20 (s, 1H), 6.52 (dd, *J* = 15.4, 2.4 Hz, 1H), 6.47 (s, 1H), 5.84-5.81 (m, 2H), 5.61 (ddd, *J* = 15.4, 11.0,

3.0 Hz, 1H), 5.50-5.46 (m, 1H), 4.79-4.78 (m, 1H), 4.12 (dd, *J* = 11.0, 5.5 Hz, 1H), 3.91 (s, 3H), 3.68 (bd, *J* = 4.3 Hz, 1H), 2.98-2.89 (m, 2H), 2.66-2.58 (m, 1H), 2.46-2.42 (m, 1H), 1.43 (d, *J* = 6.1 Hz, 3H), 3 OH signals are not visible;[13]C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 171.1, 163.9, 160.5, 140.4, 132.7, 132.6, 132.5, 128.6, 125.1, 105.5, 99.8, 77.4, 73.1, 72.3, 71.5, 56.6, 38.6, 33.1, 19.0; HRMS (MALDI-TOF) *m/z* 421.1101 ([M+Na^+], $C_{19}H_{23}ClO_7Na$ requires 421.1030).

60', more polar minor isomer 60b': *Rf* = 0.25 (2% MeOH in EtOAc); [1]H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 12.14 (s, 1H), 6.69 (dd, *J* = 15.8, 1.2 Hz, 1H), 6.47 (s, 1H), 5.83-5.78 (m, 1H), 5.66-5.54 (m, 2H), 5.39-5.35 (m, 1H), 4.88 (bd, *J* = 9,1 Hz, 1H), 4.06-4.02 (m, 1H), 3.49 (s, 3H), 3.35 (bs, 1H), 3.02-2.83 (m, 2H), 2.63-2.50 (m, 1H), 2.31-2.25 (m, 1H), 1.38 (d, *J* = 6.1 Hz, 3H), 3 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 421.1084 ([M+Na^+], $C_{19}H_{23}ClO_7Na$ requires 421.1030).



X = OMe (**58'**) , H (**59b'**), Cl (**60'**)

X = OMe (**38 - radicicol A**) , H (**34 - LL-Z1640-2**), Cl (**39**)

Radicicol A (38), LL-Z1640-2 (34), chlorinated analog 39. To a solution of compound **58'**, **59b'** or **60'** (1.0 equiv, **58':** 10 mg, 25 µmol, **59b':** 9 mg, 25 µmol or **60':** 10 mg, 25 µmol, as single isomers or as a mixture) in CH_2Cl_2 at 23 °C was added PS- IBX (3.0 equiv, 68 mg, 75 µmol, 1.1 mmol/g). The reactions were monitored by LC/MS and found to go to completion within 1 h without overoxidation of the other alcohols. The reaction were filtered and loaded directly on PTLC (SiO_2, 2 or 3% MeOH in EtOAc) to afford deprotected **radicicol A (38)**, **LL-Z1640-2 (34)** or analog **39** in 90%, 86% and 92% respectively (8 mg, 7 mg, 9 mg).

Radicicol A (38): *Rf* = 0.56 (5% MeOH in EtOAc); [1]H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 12.07 (s, 1H), 6.46 (dd, *J* = 15.6, 1.3 Hz, 1H), 6.40 (s, 1H), 6.33 (dd, *J* = 11.6, 2.3 Hz, 1H), 6.19 (td, *J* = 11.6, 2.7 Hz, 1H), 6.10 (ddd, *J* = 15.6, 10.5, 3.5 Hz, 1H), 5.36-5.28 (m, 1H), 4.53 (bd, *J* = 2.4 Hz, 1H), 3.97-3.96 (m, 1H), 3.86 (s, 3H), 3.72 (bd, *J* = 5.4 Hz, 1H), 3.55 (s, 3H), 3.41 (dt, *J* = 17.5, 11.3 Hz, 1H), 2.52 (dq, *J* = 17.5, 2.4 Hz, 1H), 2.36-2.29 (m, 1H), 2.06 (ddd, *J* = 16.1, 10.8, 2.2 Hz, 1H), 1.42 (d, *J* = 6.1 Hz, 3H), OH signal is not visible; [13]C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 199.4, 171.5, 161.8, 159.0, 146.6, 140.2, 133.5, 132.8, 125.6, 125.2, 103.1, 99.5, 80.9, 73.6, 73.5, 60.2, 55.9, 37.8, 37.0, 20.8; HRMS (MALDI-TOF) *m/z* 415.1372 ([M+Na^+], $C_{20}H_{24}O_8Na$ requires 415.1369).

LL-Z1640-2 (34, from the less polar isomer 59b'): *Rf* = 0.44 (3% MeOH in EtOAc); [1]H NMR ($CDCl_3$, 500 MHz, 25 °C) δ 12.15 (s, 1H), 6.87 (d, *J* = 15.1 Hz, 1H), 6.40 (d, *J* = 2.4 Hz, 1H), 6.38 (d, *J* = 2.4 Hz, 1H), 6.33 (dd, *J* = 11.4, 2.6 Hz, 1H), 6.20 (td, *J* = 11.1, 2.6 Hz, 1H), 5.98 (ddd, *J* = 15.1, 8.4, 4.1 Hz, 1H), 5.27-5.21 (m, 1H), 4.50 (bs, 1H), 4.00-3.98 (m, 1H), 3.81 (s, 3H), 3.58 (dt, *J* = 17.0, 11.3 Hz, 1H), 2.50 (dq, *J* = 17.0, 2.1 Hz, 1H), 2.23-2.19 (m ,1H), 2.13 (ddd, *J* = 15.7, 10.8, 3.0 Hz, 1H), 1.47 (d, *J* = 6.1 Hz, 3H), 2 OH signals are not visible; [13]C NMR ($CDCl_3$, 125.75 MHz, 25 °C) δ 199.2, 171.5, 166.1, 164.4, 147.5, 143.1, 132.9, 130.2, 125.3, 108.2, 103.5, 100.4, 80.8, 73.8, 73.7, 55.6, 37.6, 37.2, 20.9; HRMS (MALDI-TOF) *m/z* 385.1260 ([M+Na^+], $C_{19}H_{22}O_7Na$ requires 385.1264).

(from the more polar isomer 59a'): oxidation slower and afforded a different mono-oxidation product. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C) δ 12.18 (s, 1H), 7.31 (d, *J* = 15.1 Hz, 1H), 6.46 (s, 1H), 6.45 (s, 1H), 5.95-5.87 (m, 2H), 5.78 (td, *J* = 10.7, 3.7 Hz, 1H), 5.31-5.25 (m, 1H), 4.92 (d, *J* = 8.8 Hz, 1H), 4.34 (bs, 1H), 3.90 (d, *J* = 2.4 Hz, 1H), 3.85 (s, 3H), 3.60-3.44 (m, 2H), 3.02 (ddd, *J* = 15.0, 11.8, 11.7 Hz, 1H), 2.35 (dm, *J* = 15.0 Hz, 1H), 1.49 (d, *J* = 6.7 Hz, 3H), 3 OH signals are not visible.

Radicicol chlorinated analog 39: *Rf* = 0.60 (2% MeOH in EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 12.12 (s, 1H), 6.45 (s, 1H), 6.40 (d, *J* = 16.1 Hz, 1H), 6.32 (dd, *J* = 11.3, 2.7 Hz, 1H), 6.18 (td, *J* = 11.3, 2.7 Hz, 1H), 5.83 (ddd, *J* = 16.1, 10.2, 3.2 Hz, 1H), 5.43-5.38 (m, 1H), 4.55 (bs, 1H), 3.96-3.94 (m, 1H), 3.91 (s, 3H), 3.37 (dt, *J* = 17.0, 10.8 Hz, 1H), 2.51 (dm, *J* = 17.0 Hz, 1H), 2.37-2.32 (m ,1H), 2.09 (ddd, *J* = 16.6, 10.8, 1.6 Hz, 1H), 1.39 (d, *J* = 6.5 Hz, 3H), 2 OH signals are not visible; ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 199.5, 171.1, 164.4, 163.9, 146.5, 140.1, 134.1, 127.5, 125.8, 114.4, 105.4, 99.7, 81.0, 73.8, 73.1, 56.6, 37.1, 37.1, 21.0; HRMS (MALDI-TOF) *m/z* 419.0875 ([M+Na^{+}], $C_{19}H_{21}ClO_7Na$ requires 419.0874).

Recombinant Protein Kinases

The following 24 protein kinases were used for determination of inhibitory profiles:

● AKT1	● ARK5	● Aurora-A	● Aurora-B
● B-RAF-VE	● CDK2/CycA	● CDK4/CycD1	● COT
● FAK	● EPHB4	● ERBB2	● EGF-R
● IGF1-R	● SRC	● VEGF-R2	● VEGF-R3
● FLT3	● INS-R	● MET	● PDGFR-β
● PLK1	● SAK	● TIE2	● CK2-α1

All protein kinases were expressed in Sf9 insect cells as human recombinant GST-fusion proteins or His-tagged proteins by means of the baculovirus expression system. Kinases were purified by affinity chromatography using either GSH-agarose (Sigma) or Ni-NTH-agarose (Qiagen). The purity of each kinase was checked by SDS-PAGE/silver staining and the identity of each kinase was verified by western blot analysis with kinase specific antibodies or by mass spectroscopy.

Protein Kinase Assay

A radiometric protein kinase assay (^{33}PanQinase® Activity Assay) was used for measuring the kinase activity of the 24 protein kinases. All kinase assays were performed in 96-well FlashPlates™ from Perkin Elmer (Boston, MA, USA) in a 50 µL reaction volume. The reaction cocktail was pipetted in 4 steps in the following order:

- 20 µL of assay buffer
- 5 µL of ATP solution (in H_2O)
- 5 µL of test compound (in 10 % DMSO)
- 10 µL of substrate / 10 µL of enzyme solution (premixed)

The assay for all enzymes contained 60 mM HEPES-NaOH, pH 7.5, 3 mM $MgCl_2$, 3 mM $MnCl_2$, 3 µM Na-orthovanadate, 1.2 mM DTT, 50 µg/ml PEG_{20000}, 1 µM [γ-^{33}P]-ATP (approx. 5 x 10^{05} cpm per well).

For the 24 kinase assays, the following amounts of enzyme and substrate were used per well:

#	Kinase	*Kinase Lot #*	*Kinase ng/50µL*	*Substrate*	*Substrate ng/50µL*
1	**AKT1**	SP007	100	GSK3(14-27), Lot 005	1000
2	**ARK5**	002	100	Autosphos.	-
3	**Aurora-A**	SP004	50	tetra(LRRWSLG)	500
4	**Aurora-B**	SP007	100	tetra(LRRWSLG)	250
5	**B-RAF-VE**	001	20	MEK1-KM(Lot 013)	250
6	**CDK2/CycA**	SP005	100	Histone H1	125
7	**CDK4/CycD1**	006	50	Rb-CTF, Lot 010	500
8	**COT**	017	400	Autophosphorylation	-
9	**EGF-R**	SP014	25	$Poly(Glu,Tyr)_{4:1}$	125
10	**EPHB4**	SP006	10	$Poly(Glu,Tyr)_{4:1}$	125
11	**ERBB2**	SP011	200	$Poly(Glu,Tyr)_{4:1}$	125
12	**FAK**	SP006	100	$Poly(Glu,Tyr)_{4:1}$	125
13	**IGF1-R**	012	20	$Poly(Glu,Tyr)_{4:1}$	125
14	**SRC**	004	10	$Poly(Glu,Tyr)_{4:1}$	125
15	**VEGF-R2**	011	50	$Poly(Glu,Tyr)_{4:1}$	125
16	**VEGF-R3**	SP011	100	$Poly(Glu,Tyr)_{4:1}$	125
17	**FLT3**	SP007	100	$Poly(Ala,Glu,Lys,Tyr)_{6:2:5:1}$	125

18 INS-R	SP005	25	$Poly(Ala,Glu,Lys,Tyr)_{6:2:5:1}$	125
19 MET	SP011	100	$Poly(Ala,Glu,Lys,Tyr)_{6:2:5:1}$	125
20 PDGFR-beta	SP012	50	$Poly(Ala,Glu,Lys,Tyr)_{6:2:5:1}$	125
21 PLK1	007	50	Casein	250
22 SAK	002	200	Autosphosphorylation	-
23 TIE2	SP006	200	$Poly(Glu,Tyr)_{4:1}$	250
24 CK2-alpha1	SP003	200	Casein	1000

The reaction cocktails were incubated at 30° C for 80 minutes. The reaction was stopped with 50 µL of 2 % (v/v) H_3PO_4, plates were aspirated and washed two times with 200 µL of 0.9 % (w/v) NaCl or 200 µL H_2O. Incorporation of $^{33}P_i$ was determined with a microplate scintillation counter (Microbeta Trilux, Wallac). All assays were performed with a BeckmanCoulter/Sagian robotic system.

Evaluation of Raw Data

The median value of the counts in column 1 (n=8) of each assay plate was defined as **"low control"**. This value reflects unspecific binding of radioactivity to the plate in the absence of a protein kinase but in the presence of the substrate. The median value of the counts in column 7 of each assay plate (n=8) was taken as the **"high control"**, i.e. full activity in the absence of any inhibitor. The difference between high and low control was taken as 100 % activity.

As part of the data evaluation the low control value from a particular plate was subtracted from the high control value as well as from all 80 "compound values" of the corresponding plate. The residual activity (in %) for each well of a particular plate was calculated by using the following formula:

Res. Activity (%) = 100 X [(cpm of compound – low control) / (high control – low control)]

The residual activities for each concentration and the compound IC_{50} values were calculated using *Quattro Workflow V2.1.0.0* (Quattro Research GmbH, Munich, Germany; www.quattro-research.com). The model used was "Sigmoidal response (variable slope)" with parameters "top" fixed at 100% and "bottom" at 0 %.

The detailed profile of activity for Cl-radicicol A **(113**) was carried out in a similar fashion with the following list of kinases:

1 ABL1	**33 CSFR1 ***	**65 JAK3**	**97 PKC-mu**
2 ACV-R1	**34 CSK**	**66 JNK3**	**98 PKC-theta**
3 AKT1	**35 DAPK1**	**67 KIT**	**99 PKC-zeta**
4 AKT2	**36 EGF-R**	**68 LCK**	**100 PLK1**
5 AKT3	**37 EPHA1**	**69 LYN**	**101 PRK1**
6 ARK5	**38 EPHA2**	**70 MAPKAPK5**	**102 RET**
7 Aurora-A	**39 EPHA3**	**71 MEK1 SESE**	**103 ROCK2**
8 Aurora-B	**40 EPHA4**	**72 MET**	**104 S6K**
9 Aurora-C	**41 EPHB1**	**73 MST4**	**105 SAK**
10 BLK	**42 EPHB2**	**74 MUSK**	**106 SGK1**
11 BMX *)	**43 EPHB3**	**75 NEK2**	**107 SGK3**
12 B-Raf-wt	**44 EPHB4**	**76 NEK6**	**108 SNARK**
13 B-Raf-VE	**45 ERBB2**	**77 NLK**	**109 SNK**
14 BRK	**46 ERBB4**	**78 P38-alpha**	**110 SRC**
15 BTK *)	**47 FAK**	**79 PAK1**	**111 SRPK1**
16 CDC42BPB	**48 FER *)**	**80 PAK2**	**112 SRPK2**
17 CDK1/CycB	**49 FGF-R1**	**81 PAK4**	**113 SYK**
18 CDK1/CycE	**50 FGF-R2 *)**	**82 PAK7**	**114 TGFB-R1**
19 CDK2/CycA	**51 FGF-R3**	**83 PBK**	**115 TIE2**
20 CDK2/CycE	**52 FGF-R4**	**84 PDGFR-alpha**	**116 TRK-B *)**
21 CDK3/CycE	**53 FGR**	**85 PDGFR-beta**	**117 TSF1**
22 CDK4/CycD1	**54 FLT3**	**86 PDK1**	**118 TSK2**
23 CDK4/CycD3	**55 FRK *)**	**87 PIM1**	**119 TTK**
24 CDK5/p25NCK	**56 GSK3-beta**	**88 PIM2**	**120 TYRO3**
25 CDK5/p35NCK	**57 HCK**	**89 PKC-alpha**	**121 VEGF-R1**
26 CDK6/CycD1	**58 IGF1-R**	**90 PKC-beta1**	**122 VEGF-R2**
27 CDK7/CycH/Mat1	**59 IKK-beta**	**91 PKC-beta2**	**123 VEGF-R3**
28 CDK9/CycT	**60 IKK-epsilon**	**92 PKC-delta**	**124 VRK1**
29 CHK1	**61 INS-R**	**93 PKC-epsilon**	**125 WEE1**
30 CK2-alpha1	**62 IRAK4**	**94 PKC-eta (m)**	**126 YES**
31 CK2-alpha2	**63 ITK**	**95 PKC-gamma**	**127 ZAP70**
32 COT	**64 JAK2 (m)**	**96 PKC-iota**	

All protein kinases were expressed in Sf9 insect cells as recombinant GST-fusion proteins or Histagged proteins by means of the baculovirus expression system. Except the kinases marked with (m), which are derived from mouse cDNA, all kinases are produced from human cDNA. Kinases were purified by affinity chromatography using either GSH-agarose (Sigma) or Ni-NTH-agarose (Qiagen). The purity of the protein kinases was examined by SDS-PAGE/coomassie staining. The identity of the protein kinases was checked by western blot analysis with specific antibodies or by mass spectroscopy. Kinases marked with *) were included from an external supplier.

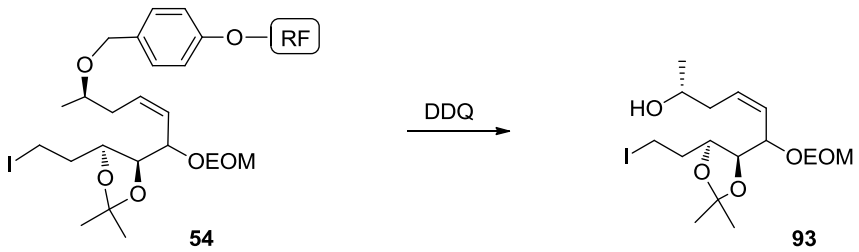
Cellular autophosphorylation assays for PDGFRβ, VEGF-R2 and TIE2

The test compound was serially diluted using 100% DMSO. The final assay concentration ranged from 1E-4M to 1E-8M, final DMSO concentration in the assay was 1%. In addition to 31 specific kinase inhibitors were used as reference compounds.

The assays to evaluate the inhibitory profile of test samples were performed using NIH3T3 cells, known to express high levels of PDGFR-beta, the spontaneously immortalized HUVEC clone (named HUE) for VEGF-R2 and a stably *trans*fected CHO-TIE2 cell line generated to constitutively express TIE2. Cells were plated in the apprpriate medium supplemented with 10% FCS with 35.000 cells/well in 48well cell culture dishes. After 24h the FCS-containing medium was exchanged against medium devoid of FCS and cells were starved 12 h.

Prediluted test samples were added 1:100 to the cell culture medium resulting in a final DMSO concentration of 1%. After 90min incubation at 37°C, cells were stimulated with 100ng/ml PDGF-BB, 100ng/ml VEGF165 and 10mM Sodium-Orthovanadate respectively. Stimulation was immediately followed by cell lysis.

Quantification of RTK-Phosphorylation was assessed in 96 well plates via sandwich ELISA using a respective receptor specific capture antibody and an anti-phosphotyrosine detection antibody. Raw data ($OD_{450nm-540nm}$) were converted into percent receptor autophosphorylation relative to stimulated controls, which were set to 100%. Graphical illustration and calculation of IC_{50} values were performed using GraphPad Prism 4.03 software.



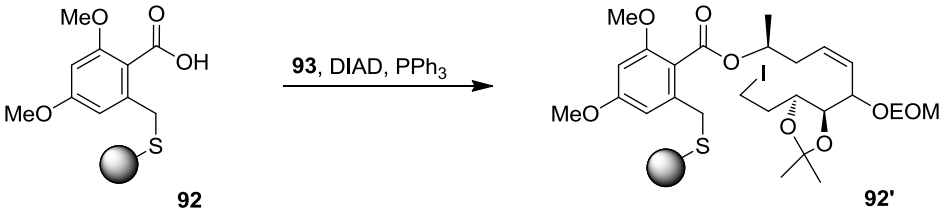
54 **93**

Alcohol 93. To a stirred solution of protected alcohol **54** (1.0 equiv, 733 mg, 0.8 mmol) in CH_2Cl_2/H_2O 2/1 (10 mL) was added DDQ (1.3 equiv, 243 mg, 1.1 mmol). The reaction mixture was stirred for 4 h and then quenched with sat. NH_4Cl aq. solution, diluted with CH_2Cl_2, washed with water and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 3/1) yielded alcohol **93** in 80% yield (282 mg).

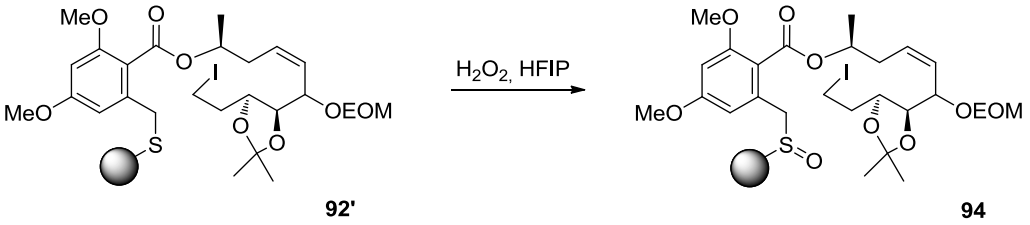
93a, less polar isomer: *Rf* = 0.29 (SiO_2, Hexane/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 5.86 (td, *J* = 10.8 Hz, 1H), 5.39 (t, *J* = 10.8 Hz, 1H), 4.85 (d, *J* = 6.8 Hz, 1H), 4.70 (d, *J* = 7.2 Hz, 1H), 4.40 (dd, *J* = 7.6 Hz, 1H), 4.18 (dd, *J* = 6.0 Hz, 1H), 4.12-4.07 (m, 1H), 3.91-3.83 (m, 1H), 3.78-3.70 (m, 1H), 3.63-

3.55 (m, 1H), 3.38-3.32 (m, 1H), 3.23-3.16 (m, 1H), 2.45-2.36 (m, 1H), 2.24-2.17 (m, 1H), 2.09-2.00 (m, 1H), 1.91-1.82 (m, 1H), 1.47 (s, 3H), 1.39 (s, 3H), 1.26-1.23 (m, 6H), OH signal is not visible.

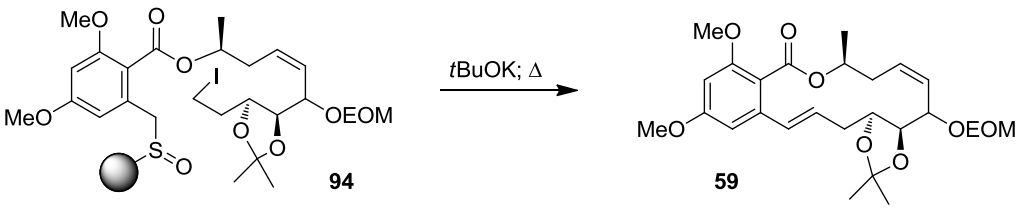
93b, more polar isomer: *Rf* = 0.15 (SiO_2, Hexane/EtOAc 2/1).



Ester 92'. To a stirred solution of resin **92** (1.0 equiv, 500 mg, 0.15 mmol, 0.3 mmol/g) in toluene (5 mL) were added alcohol **93** (2.0 equiv, 128 mg, 0.3 mmol) and PPh_3 (4.0 equiv, 157 mg, 0.6 mmol). The reaction mixture was then cooled at 0 °C and DIAD (4.0 equiv, 118 µL, 0.6 mmol) was added. After 12 h, the resin was filtered and washed using THF, MeOH, CH_2Cl_2, Et_2O and dried to constant mass under reduced pressure to afford the corresponding resin **92'** that was used directly in the next step.

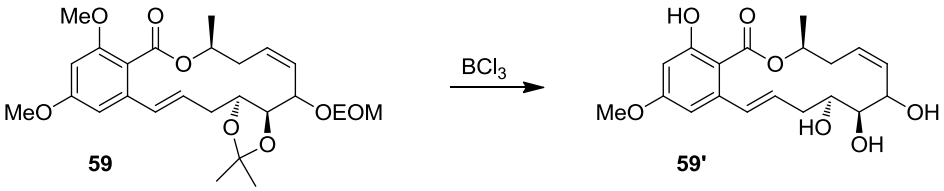


Sulfoxide resin 94. To a suspension of resin **92'** (1.0 equiv, 0.15 mmol) in HFIP/CH_2Cl_2 1/1 (6 mL) was added a 35% H_2O_2 aq. solution (4.0 equiv, 116 µL, 0.6 mmol) and the reaction mixture was stirred for 12 h at 23 °C. The resin was then washed using MeOH, CH_2Cl_2 and Et_2O to obtain sulfoxide resin **94**. The resin was dried to constant mass under reduced pressure before use.



Macrocycle 59. To a stirred suspension of resin **94** (1.0 equiv, 0.15 mmol) in DMSO (6 mL) was added *t*BuOK (10.0 equiv, 168 mg, 1.5 mmol). After 12 h, the reaction was filtered and the resin was then washed using MeOH, CH_2Cl_2 and Et_2O, and was directly suspended in toluene (5 mL) and heated up in a µwave (120 °C, 300W) for 25 min to yield macrocycle **59** in 34 % yield over 4 steps (24 mg). *Rf* = 0.25 (Hexane/EtOAc 1/1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 6.63 (d x 2, *J* = 15.6 Hz, 2H), 6.48 (s, 1H), 6.47 (s, 1H), 6,37 (s, 1H), 6.35 (s, 1H), 6.23-6.11 (m, 2H), 5.95 (td, *J* = 11.8, 5.4 Hz, 1H), 5.87 (td, *J* =

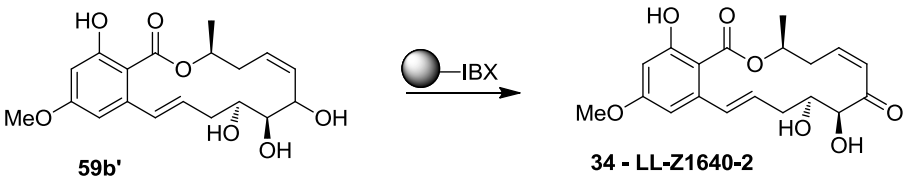
11.3, 5.9 Hz, 1H), 5.65 (dd, *J* = 9.1, 9.1 Hz, 1H), 5.57 (dd, *J* = 9.7, 9.7 Hz, 1H), 5.39-5.31 (m, 2H), 4.80 (dd, *J* = 7.5, 7.5 Hz, 1H), 4.75-4.73 (m, 1H), 4.70 (d, *J* = 6.4 Hz, 1H), 4.69 (d, *J* = 7.0 Hz, 1H), 4.65 (d, *J* = 6.4 Hz, 1H), 4.64 (d, *J* = 7.0 Hz, 1H), 4.46-4.43 (m, 1H), 4.40-4.36 (m, 1H), 4.34-4.31 (m, 1H), 4.28-4.22 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.70-3.64 (m, 2H), 3.60-3.52 (m, 2H), 3.06 (ddd, *J* = 15.1, 11.3, 3.8 Hz, 1H), 2.87-2.74 (m, 1H), 2.67-2.53 (m, 4H), 2.31-2.23 (m, 2H), 1.41 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H), 1.20- 1.14 (m, 12H); ^{13}C NMR (CDCl3, 100 MHz, 25 °C) δ166.8, 166.2, 160.5, 160.4, 156.9, 156.9, 137.2, 137.0, 131.0, 130.3, 129.5, 128.9, 128.3 (x 2), 128.1, 128.0, 115.2, 115.0, 107.1 (x 2), 102.4, 101.8, 96.8, 96.7, 92.1, 91.7, 79.9, 78.2, 76.4, 75.9, 74.9, 74.8, 69.8, 68.5, 62.9, 62.8, 55.1, 55.0, 54.6, 54.5, 34.9, 33.2, 32.6, 32.4, 26.0, 25.7, 24.5, 23.9, 17.2 (x 2), 14.2, 14.1; HRMS (MALDI-TOF) *m/z* 499.2310 ([M+Na$^+$], $C_{26}H_{36}O_8Na$ requires 499.2308).



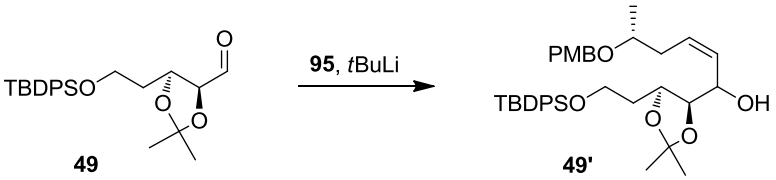
Deprotected alcohol 59'. To a solution of macrocycle **59** (1.0 equiv, 19 mg, 40 μmol) in CH_2Cl_2 (4 mL) at 0 °C was added a 1.0 M solution of BCl_3 in hexane (6.0 equiv, 240 μL, 240 μmol) and the reaction was monitored by LC/MS. After 15 min, the reaction was complete and was thus quenched with a sat. $NaHCO_3$ aq. solution (100 μL) and MeOH (200 μL), stirred for 5 min, further diluted with CH_2Cl_2 (4 mL), filtered through a pad of SiO_2 (150 mg) and washed with 20% MeOH in EtOAc. Evaporation of the solvents followed by PTLC (SiO_2, 2% MeOH in EtOAc) afforded corresponding deprotected compound **59'** in 82% yield (12 mg: 9 mg of the less polar isomer + 6 mg of the more polar one) as white powder.

59', more polar isomer 59a': *Rf* = 0.15 (2% MeOH in EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ12.35 (s, 1H), 7.20 (dd, *J* = 15.0, 2.2 Hz, 1H), 6.43 (d, *J* = 2.7 Hz, 1H), 6.40 (d, *J* = 2.7 Hz, 1H), 5.86 (ddd, *J* = 11.3, 11.3, 1.6 Hz, 1H), 5.72 (ddd, *J* = 15.0, 11.3, 3.2 Hz, 1H), 5.62 (td, *J* = 11.3, 4.3 Hz, 1H), 5.27-5.20 (m, 1H), 4.99 (d, *J* = 9.6 Hz, 1H), 4.11 (ddd, *J* = 10.8, 5.4, 2.7 Hz, 1H), 3.81 (s, 3H), 3.43 (d, *J* = 2.7 Hz, 1H), 3.06-2.97 (m, 1H), 2.86-2.80 (m, 1H), 2.59-2.50 (m, 1H), 2.30-2.25 (m, 1H), 1.45 (d, *J* = 5.9 Hz, 3H), 3 OH signals are not visible; ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ166.4, 164.2, 157.9, 142.7, 133.9, 130.3, 130.1, 128.0, 119.4, 108.5, 100.4, 75.0, 72.5, 72.3, 64.5, 55.6, 39.0, 35.0, 21.6; HRMS (MALDI-TOF) *m/z* 387.1434 ([M+Na$^+$], $C_{19}H_{24}O_7Na$ requires 387.1420).

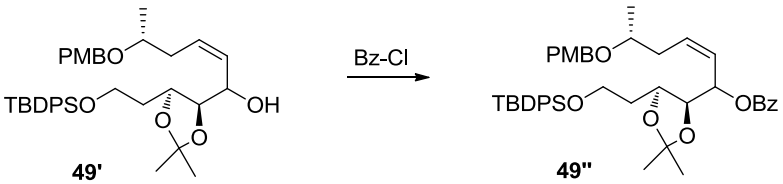
50', less polar isomer 50b': *Rf* = 0.28 (2% MeOH in EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ12.03 (s, 1H), 7.19 (d, *J* = 15.0 Hz, 1H), 6.45 (d, *J* = 2.2 Hz, 1H), 6.41 (d, *J* = 2.2 Hz, 1H), 6.09 (dd, *J* = 11.0 Hz, 8.6 Hz, 1H), 5.99 (dd, *J* = 11.0 Hz, 4.3 Hz, 1H), 5.68 (ddd, *J* = 15.0 Hz, 11.3, 2.7 Hz, 1H), 5.29-5.22 (m, 1H), 4.58-4.53 (m, 1H), 4.10-4.04 (m, 3H), 3.82 (s, 3H), 2.68-2.64 (m, 1H), 2.40-2.34 (m, 1H), 2.31-2.21 (m, 1H), 1.43 (d, *J* = 5.9 Hz, 3H), 3 OH signals are not visible; ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ171.4, 166.0, 164.5, 143.1, 134.2, 133.7, 128.7, 127.3, 108.1, 103.4, 100.4, 75.6, 72.6, 72.0, 58.7, 55.6, 47.1, 37.3, 21.6; HRMS (MALDI-TOF) *m/z* 387.1390 ([M+Na$^+$], $C19_9H_{24}O_7Na$ requires 387.1420).



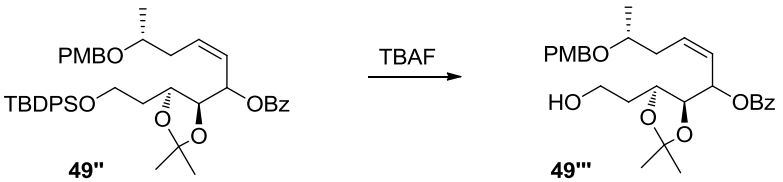
LL-Z1640-2 (34). To a solution of compound **59b'** (1.0 equiv, 9 mg, 25 µmol) in CH_2Cl_2 (1 mL) at 23 °C was added PS-IBX (3.0 equiv, 68 mg, 75 µmol, 1.1 mmol/g). The reaction was monitored by LC/MS and found to go to completion within 1 h without overoxidation of the other alcohols. The reaction was filtered and loaded directly on PTLC (SiO_2, 2 or 3% MeOH in EtOAc) to afford **LL-Z1640-2** (**34**) in 86% yield (7 mg). *Rf* = 0.44 (3% MeOH in EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C) δ 12.15 (s, 1H), 6.87 (d, *J* = 15.1 Hz, 1H), 6.40 (d, *J* = 2.4 Hz, 1H), 6.38 (d, *J* = 2.4 Hz, 1H), 6.33 (dd, *J* = 11.4, 2.6 Hz, 1H), 6.20 (td, *J* = 11.1, 2.6 Hz, 1H), 5.98 (ddd, *J* = 15.1, 8.4, 4.1 Hz, 1H), 5.27-5.21 (m, 1H), 4.50 (bs, 1H), 4.00-3.98 (m, 1H), 3.81 (s, 3H), 3.58 (dt, *J* = 17.0, 11.3 Hz, 1H), 2.50 (dq, *J* = 17.0, 2.1 Hz, 1H), 2.23-2.19 (m ,1H), 2.13 (ddd, *J* = 15.7, 10.8, 3.0 Hz, 1H), 1.47 (d, *J* = 6.1 Hz, 3H), 2 OH signals no visible; ^{13}C NMR ($CDCl_3$, 125.75 MHz, 25 °C) δ 199.2, 171.5, 166.1, 164.4, 147.5, 143.1, 132.9, 130.2, 125.3, 108.2, 103.5, 100.4, 80.8, 73.8, 73.7, 55.6, 37.6, 37.2, 20.9; HRMS (MALDI-TOF) *m/z* 385.1260 ([M+Na$^+$], $C_{19}H_{22}O_7Na$ requires 385.1264).



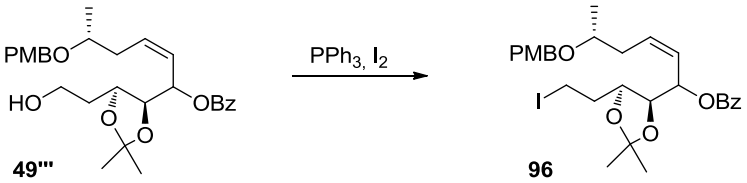
Secondary alcohol 49'. To a solution of *cis*-bromide **95** (1.0 equiv, 685 mg, 2.4 mmol) in Et_2O (15 ml) at -100 °C was carefully added a 1.7 M solution of *t*BuLi in pentane (2.0 equiv, 2.8 mL, 4.8 mmol) and the resulting mixture was stirred for 15 min. Then, a solution of aldehyde **49** (1.0 equiv, 990 mg, 2.4 mmol) in Et_2O (5 mL) precooled to -78 °C was added. The resulting mixture was stirred at -100 °C for 15min. The reaction was then quenched with sat. NH_4Cl aq. solution, diluted with EtOAc, washed with water, brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 10/1) afforded alcohol **49'** in 88% yield (1.3 g). *Rf* = 0.38 (Petroleum ether/EtOAc 4/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.74-7.68 (m, 4H), 7.45-7.37 (m, 6H), 7.30-7.25 (m, 2H), 6.91-6.86 (m, 2H), 5.85-5.80 (m, 0.5H), 5.77-5.61 (m, 1H), 5.58-5.52 (m, 0.5H), 4.58-4.34 (m, 4H), 4.05-4.09 (m, 0.3H), 4.05-3.98 (m, 0.7H), 3.90-3.82 (m, 2H), 3.80-3.78 (m, 3H), 3.70-3.52 (m, 1H), 3.02 (b, 0.3H), 2.74 (b, 0.7H), 2.60-2.49 (m, 0.5H), 2.46-2.32 (m, 1H), 2.20-1.94 (m, 1.5H), 1.90-1.75 (m, 1H), 1.48 (s, 1.8H), 1.46 (s, 1.2H), 1.39 (s, 1.8H), 1.36 (s, 1.2H), 1.26-1.22 (m, 3H), 1.09 (s, 6H), 1.08 (s, 3H).



Bz-protected alcohol 49''. To a stirred solution of alcohol **49'** (1.0 equiv, 1.3 g, 2.1 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added pyridine (2.5 equiv, 0.4 mL, 5.3 mmol), TBAI (>5 mg, cat), BzCl (2.5 equiv, 0.6 mL, 5.3 mmol). The reaction was slowly warmed up at 23 °C and after 6 h, it was quenched with sat. NH_4Cl aq. solution, diluted with EtOAc, washed with water, brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 10/1) yielded protected alcohol **49''** in 90% yield (1.4 g).

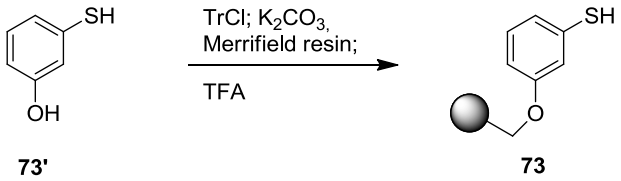


Primary alcohol 49'''. To a stirred solution of protected alcohol **49''** (1.0 equiv, 1.4 g, 1.9 mmol) in THF (10 mL) at 23 °C was added a 1.0 M solution of TBAF in THF (2.0 equiv, 3.8 mL, 3.8 mmol). After 6 h, the reaction was quenched with sat. NH_4Cl aq. solution, diluted with EtOAc, washed with water, brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 1/1) yielded alcohol **49'''** in quantitative yield (920 mg). *Rf* = 0.19 (Petroleum ether/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.05 (d, *J* = 7.2 Hz, 1.4H), 8.01 (d, *J* = 7.2 Hz, 0.6H), 7.57-7.51 (m, 1H), 7.46-7.40 (m, 2H), 7.27-7.23 (m, 2H), 6.87-6.83 (m, 2H), 5.86-5.74 (m, 2H), 5.66-5.53 (m, 1H), 4.51-4.39 (m, 2.5H), 4.38-4.32 (m, 0.5H), 4.30-4.25 (m, 1H), 3.78 (s, 2.2H), 3.77 (s, 0.8H), 3.77-3.70 (m, 2H), 3.68-3.49 (m, 1H), 2.65-2.56 (m, 1H), 2.54-2.45 (m, 1H), 2.09 (bs, 1H), 1.90-1.65 (m, 2H), 1.55 (s, 1.8H), 1.43 (s, 1.2H), 1.37 (s, 1.8H), 1.36 (s, 1.2H), 1.22 (s, 1.2H), 1.18 (s, 1.8H).



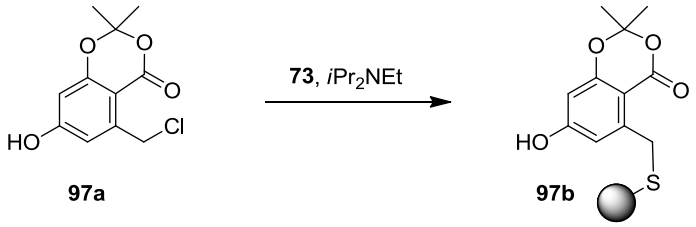
Alkyl iodide 96. To a stirred solution of alcohol **49'''** (1.0 equiv, 1.0 g, 2.1 mmol) in THF (10 mL) at 0 °C were added PPh_3 (1.5 equiv, 817 mg, 3.1 mmol) and imidazole (2.5 equiv, 353 mg, 5.2 mmol). Then, the resulting mixture was stirred for 5 min at 0 °C, followed by I_2 addition (1.5 equiv, 790 mg, 3.1 mmol). After 30 min, the reaction was quenched with sat. $NaHCO_3$ aq. solution, extracted with Et_2O and washed sequentially by sat. $Na_2S_2O_3$ aq. solution, brine and dried over Na_2SO_4. Concentration under reduced pressure, followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 2/1) afforded alkyl iodide **96** in 91% yield (1.1 g) as a colorless oil. *Rf* = 0.40

(Petroleum ether/EtOAc 4/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.06-8.01 (m, 2H), 7.57-7.52 (m, 1H), 7.46-7.41 (m, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.8 Hz, 2H), 5.85-5.74 (m, 2H), 5.62-5.53 (m, 1H), 4.51 (d, *J* = 11.6 Hz, 1H), 4.44 (d, *J* = 11.6 Hz, 1H), 4.36-4.28 (m, 1H), 4.21-4.16 (m, 1H), 3.79 (s, 3H), 3.69-3.59 (m, 1H), 3.34-3.28 (m, 1H), 3.24-3.14 (m, 1H), 2.68-2.58 (m, 1H), 2.56-2.48 (m, 1H), 2.10-2.00 (m, 1H), 1.98-1.87 (m, 1H), 1.51 (s, 3H), 1.37 (s, 3H), 1.23-1.19 (m, 3H).



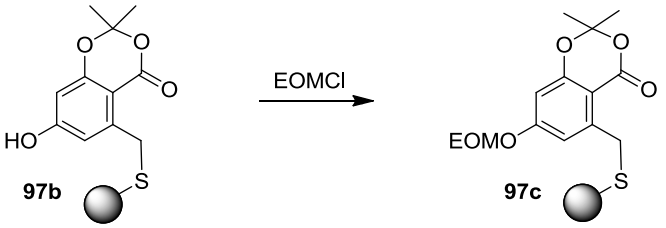
73' **73**

Thiophenol resin 73. To a solution of 3-hydroxythiophenol **73'** (1.0 equiv, 808 µL, 7.9 mmol) in CH_2Cl_2 (80 mL) were added trytil chloride (1.0 equiv, 2.2 g, 7.9 mmol) and pyridine (1.0 equiv, 640 µL, 7.9 mmol) and the resulting mixture was stirred at 23 °C for 4.5 h. The reaction was then quenched by sat. NH_4Cl aq. solution and extracted with EtOAc, washed with brine and dried over $MgSO_4$. Removal of the solvent provided the corresponding protected phenol, which was used without further purification in the next step. Thus, to a suspension of Merrifield resin (1.0 equiv, 6.0 g, 4.8 mmol, 0.8 mmol/g, 2% DVB, 100 mesh) in DMF (60 mL) were added K_2CO_3 (2.0 equiv, 1.3 g, 9.6 mmol) and the previously prepared protected thiophenol (1.0 equiv, 1.8 g, 4.8 mmol), and the mixture was stirred for 12 h at 50 °C. After that time the resin was filtered, washed using THF, MeOH, CH_2Cl_2 and Et_2O, and dried to constant mass under reduced pressure affording the corresponding resin in quantitative yield (8.0 g, 0.6 mmol/g). This resin (8.0 g, 0.6 mmol/g) was then suspended in a mixture of TFA/CH_2Cl_2/EtSiH (9/10/1), and stirred at 23 °C for 1 h. Then the resin was filtered, washed using EtOH, CH_2Cl_2 and Et_2O, and dried to constant mass under reduced pressure affording thiophenol resin **73** in quantitative yield (6.1 g, 0.792 mmol/g).

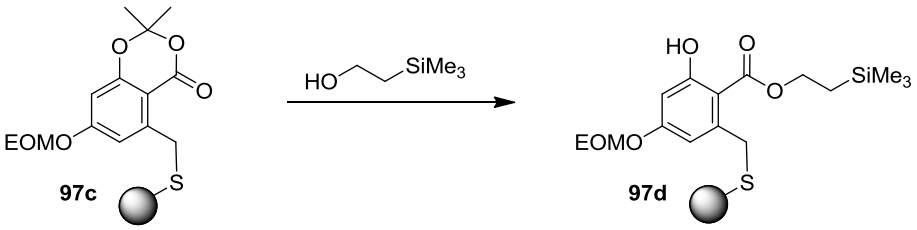


97a **97b**

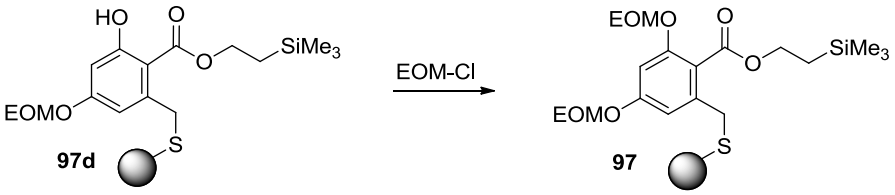
Resin 97b. To a stirred solution of thiophenol resin **73** (1.0 equiv, 2.5 g, 2.0 mmol, 0.792 mmol/g) in DMF (26 mL) were added benzyl chloride **97a** (1.5 equiv, 730 mg, 3.0 mmol) and *i*Pr_2NEt (1.0 equiv, 330 µL, 2.0 mmol). The reaction was heated up at 60°C for 12 h, then filtered and washed using THF, MeOH, CH_2Cl_2 and Et_2O, and dried to constant mass under reduced pressure to afford the corresponding resin **97b** in 99% yield (3.0 g, 0.657 mmol/g).



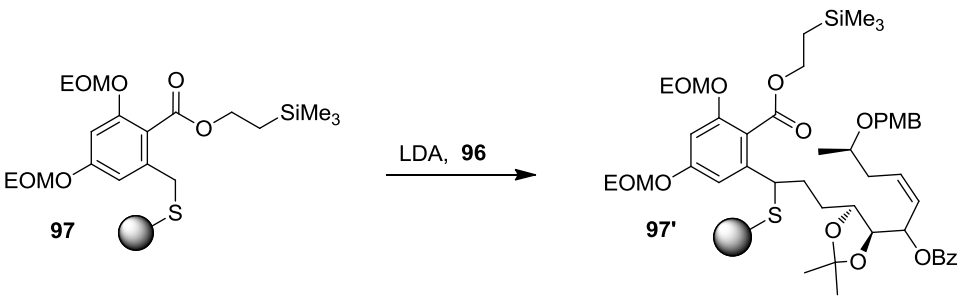
EOM-protected resin 97c. To a stirred suspension of resin **97b** (1.0 equiv, 3.0 g, 2.0 mmol, 0.657 mmol/g) in DMF (30 mL), were added subsequently EOMCl (2.0 equiv, 370 µL, 3.9 mmol), TBAI (cat), and DBU (2.0 equiv, 590 µL, 3.9 mmol). After 12 h, the resin was filtered, and washed using THF, MeOH, CH_2Cl_2 and Et_2O, and dried to constant mass under reduced pressure to yield resin **97c** in quantitative yield (3.2 g, 0.621 mmol/g).



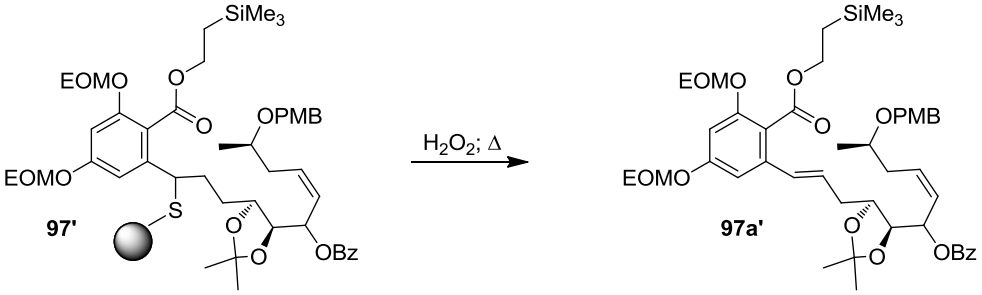
Ester resin 97d. Resin **97c** (1.0 equiv, 3.2 g, 2.0 mmol, 0.621 mmol/g) was suspended in THF (32 mL), cooled to 0°C and 2-(trimethylsilyl)ethanol (4.2 equiv, 1.2 mL, 8.3 mmol) followed by a 1.0 M solution of NaHMDS in THF (1.1 equiv, 8.6 mL, 8.6 mmol) were added. After 12 h, the resin was filtered, and washed using THF, MeOH, CH_2Cl_2 and Et_2O, and dried to constant mass under reduced pressure to yield the ester resin **97d** in 98% yield (3.3 g, 0.586 mmol/g).



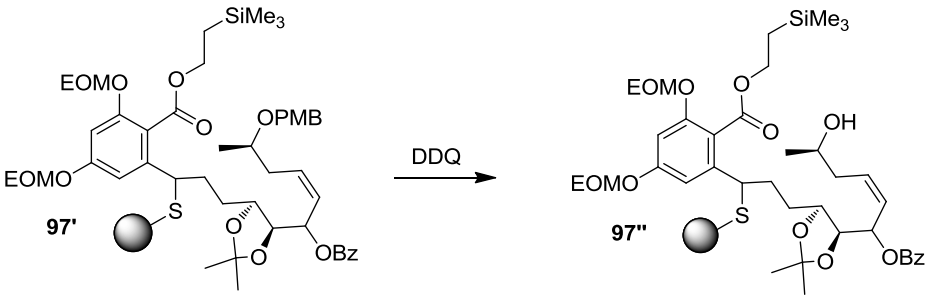
EOM-protected resin 97. To a suspension of resin **97d** (1.0 equiv, 288 mg, 170 µmol, 0.594 mmol/g) in DMF (3 mL) at 23 ^{o}C were added sequentially DBU (3.0 equiv, 76 µL, 510 µmol), EOM-Cl (3.0 equiv, 47 µL, 510 µmol) and TBAI (cat). The mixture was stirred at the same temperature for 12 h, then filtered and washed using THF, MeOH, CH_2Cl_2 and Et_2O, and dried to constant mass under reduced pressure to afford the corresponding resin **97** in quantitative yield (300 mg, 0.561 mmol/g).



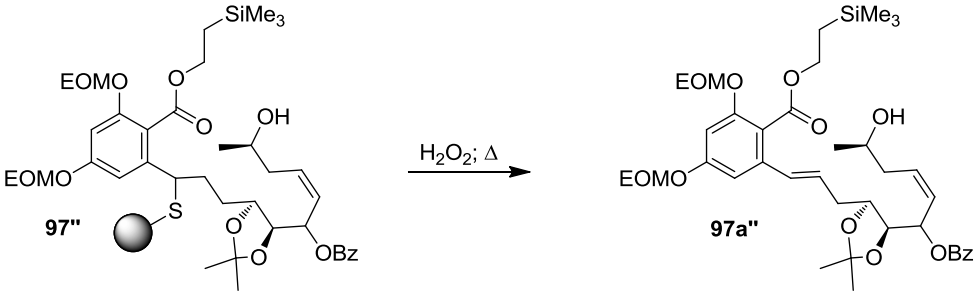
Resin 97'. To a stirred suspension of resin **97** (1.0 equiv, 300 mg, 170 µmol, 0.56 mmol/g) in THF/HMPA 10/1 (3 mL) cooled at -78 °C was added at once a freshly prepared solution of LDA in THF (6.0 equiv, 1.8 mL, 1.0 mmol). The reaction was stirred 10 min at -78 °C and a solution of precooled iodide **96** (3.0 equiv, 300 mg, 510 µmol) in THF (1 mL) was added. The mixture was further stirred another 10 min, and then the reaction was quenched by addition of AcOH (50.0 equiv). The resin was then washed using THF, MeOH, CH_2Cl_2 and Et_2O, and dried to constant mass under reduced pressure to afford the corresponding alkylated resin **97'** in quantitative yield (435 mg, 0.383 mmol/g)**.**



Alkylated compound 97a'. To a suspension of resin **97'** (1.0 equiv, 20 mg, 8 µmol, 0.383 mmol/g), in CH_2Cl_2/HFIP 1/1 (1 mL) was added a 30% H_2O_2 aq. solution (4.0 equiv, 0.9 µL, 31 µmol) and the mixture was stirred 12 h at 23 °C. The resin was then washed using THF, MeOH, CH_2Cl_2 and Et_2O, and dried to constant mass under reduced pressure. The previous sulfoxide resin was then suspended in toluene (2 mL) and the resulting mixture was heated up to 80 °C and stirred for 12 h. The corresponding eliminated compound **97a'** was recovered in pure form by filtration and evaporation of the solvents under reduced pressure in >77% yield suggesting the alkylation to be efficient (>5 mg). *Rf* = 0.65 (SiO_2, Petroleum ether/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.10-8.05 (m, 1.4H), 8.03-7.99 (m, 0.6H), 7.55 (m, 1H), 7.43 (m, 2H), 7.26-7.23 (m, 2H), 6.85-6.83 (m, 3H), 6.78-6.74 (m, 1H), 6.42 (d x 2, *J* = 16.0 Hz, 1H), 6.25-6.15 (m, 1H), 5.90-5.75 (m, 2H), 5.70-5.54 (m, 1H), 5.22-5.18 (m, 4H), 4.50-4.32 (m, 4.5H), 4.28-4.15 (m, 1.5H), 3.78-3.75 (m, 3H), 3.74-3.67 (m, 4H), 3.65-3.58 (m, 1H), 2.70-2.30 (m, 4H), 1.36 (s, 2.2H), 1.35 (s, 0.8H), 1.28-1.16 (m, 12H), 1.08 (t, *J* = 8.6 Hz, 2H), 0.07 (s, 2.4H), 0.05 (s, 6.6H).



PMB-deprotected resin 97''. To a suspension of the previously alkylated resin **97'** (1.0 equiv, 415 mg, 160 µmol, 0.383 mmol/g) in CH_2Cl_2/H_2O 2/1 (4.2 mL) was added DDQ (2.4 equiv, 87 mg, 384 µmol). The reaction mixture was stirred for 4 h and then washed with CH_2Cl_2/ H_2O, THF, MeOH, CH_2Cl_2 and Et_2O, and dried to constant mass under reduced pressure to afford the corresponding PMB-deprotected resin **97''** in quantitative yield (360 mg, 0.435 mmol/g)**.**

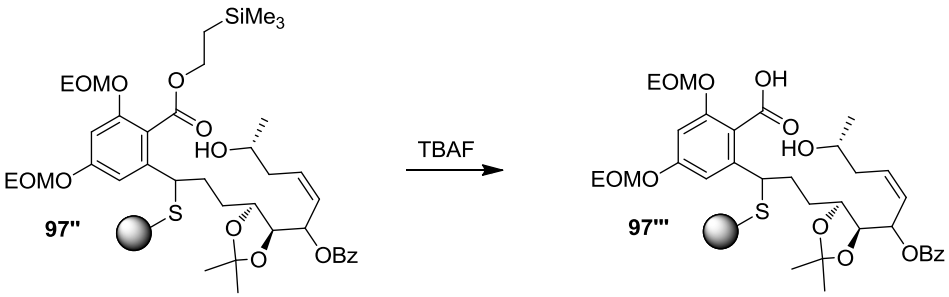


PMB-deprotected alcohol 97a''. To a suspension of resin **97''** (1.0 equiv, 20 mg, 8.7 µmol, 0.435 mmol/g) in CH_2Cl_2/HFIP 1/1 (1.0 mL) was added a 30% H_2O_2 aq. solution (4.0 equiv, 1 µL, 35 µmol,) and the mixture was stirred 12 h at 23 °C. The resin was then washed using THF, MeOH, CH_2Cl_2 and Et_2O, and dried to constant mass under reduced pressure. The previous sulfoxide resin was then suspended in toluene (2 mL) and the resulting mixture was heated up to 80°C and stirred for 12 h. The corresponding eliminated compound **97a''** was recovered in pure form by filtration and evaporation of the solvents under reduced pressure in quantitative yield suggesting the deprotection of the PMB was efficient (>5 mg).

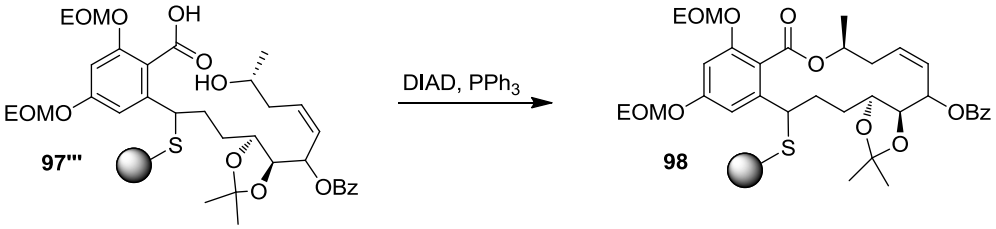
97aa'', less polar: *Rf* = 0.22 (SiO_2, Hexane/EtOAc 1/1).

97ab'', more polar: *Rf* = 0.21 (SiO_2, Petroleum ether/EtOAc 3/1).

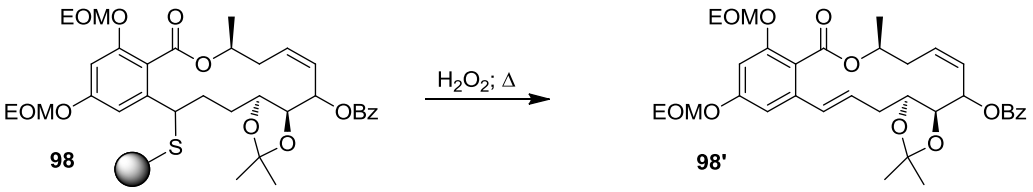
97aa'' + 97ab'': ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ8.10-8.04 (m, 1.4H), 8.01-7.95 (m, 0.6H), 7.58-7.52 (m, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 6.83 (d, *J* = 1.6 Hz, 1H), 6.76 (d, *J* = 2.0 Hz, 1H), 6.45 (d, *J* = 16.0 Hz, 0.7H), 6.38 (d, *J* = 16.0 Hz, 0.3H), 6.25-6.15 (m, 1H), 5.86-5.73 (m, 2H), 5.68-5.60 (m, 1H), 5.22-5.15 (m, 4H), 4.41-4.37 (m, 2H), 4.34-4.27 (m, 2H), 3.96-3.83 (m, 1H), 3.74-3.68 (m, 4H), 2.63-2.49 (m, 2H), 2.45-2.26 (m, 2H), 1.39-1.36 (m, 3H), 1.27-1.18 (m, 12H), 1.11-1.07 (m, 2H), 0.04 (s, 6H), 0.03 (s, 3H), OH signal is not visible.



TBAF-deprotected resin 97'''. To a suspension of resin **97''** (1.0 equiv, 340 mg, 150 µmol, 0.435 mmol/g) in THF (3.4 mL) was added a 1.0 M solution of TBAF in THF (10.0 equiv, 1.5 mL, 1.5 mmol). After 6 h, the resin was then washed using THF, MeOH, 1% AcOH in CH_2Cl_2 and Et_2O, and dried to constant mass under reduced pressure to afford the corresponding free carboxylic acid resin **97'''** in quantitative yield (305 mg, 0.483 mmol/g).



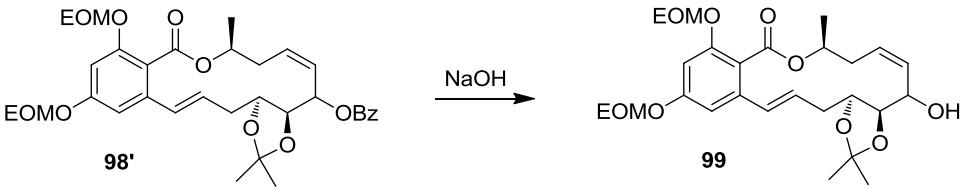
Resin 98. To a suspension of resin **97'''** (1.0 equiv, 305 mg, 150 µmol, 0.483 mmol/g) in toluene (3 mL) were added subsequently PPh_3 (3.0 equiv, 116 mg, 450 µmol) and DIAD (3.0 equiv, 87 µL, 450 µmol) at 23 °C. After 12 h, the resin was then washed using THF, MeOH, CH_2Cl_2 and Et_2O, and dried to constant mass under reduced pressure to afford the resin **98** in 97% yield (295 mg, 0.492 mmol/g).



Macrocycle 98'. To a suspension of resin **98** (1.0 equiv, 150 mg, 74 µmol, 0.492 mmol/g) in CH_2Cl_2/HFIP 1/1 (2 mL) was added a 30% H_2O_2 aq. solution (4.0 equiv, 8.8 µL, 0.3 mmol) and the mixture was stirred 12 h at 23 °C. The resin was then washed using THF, MeOH, CH_2Cl_2 and Et_2O, and dried to constant mass under reduced pressure. The previous sulfoxide resin was then suspended in toluene (2 mL), the resulting mixture was heated up to 80 °C and stirred for 12 h. After filtration and evaporation of the solvent, macrocycle **98'** was recovered pure in 62% yield based on the loading of the thiophenol resin (28 mg). The product was isolated as a diastereomeric mixture 2:1. *Rf* = 0.35 (SiO_2, Petroleum ether/EtOAc 3/1); as only the signal corresponding to the major isomer can be unambiguously assigned, only the major diastereoisomer is reported.

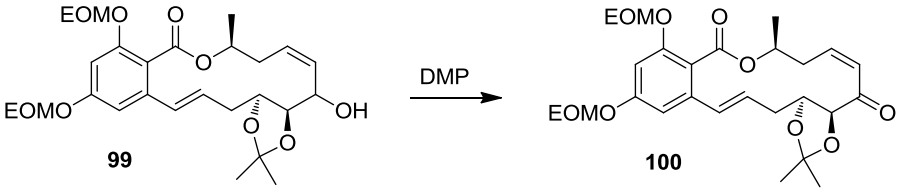
98', major diastereoisomer 98a': ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.01 (d, *J* = 7.2 Hz, 2H), 7.52-7.48 (m, 1H), 7.44-7.40 (m, 2H), 6.72 (d, *J* = 2.0 Hz, 1H), 6.60 (d, *J* = 2.0 Hz, 1H), 6.53-6.41 (m, 2H), 6.21-

6.00 (m, 1H), 5.82-5.60 (m, 2H), 5.22-5.16 (m, 5H), 4.54-4.44 (m, 1H), 4.40-4.36 (m, 0.4H), 4.28-4.22 (0.6H), 3.70-3.64 (m, 4H), 3.20-3.10 (m, 0.3H), 2.94-2.85 (m, 0.7H), 2.74-2.63 (m, 1H), 2.60-2.50 (m, 1H), 2.30-2.22 (m, 1H), 1.30-1.19 (m, 15H).

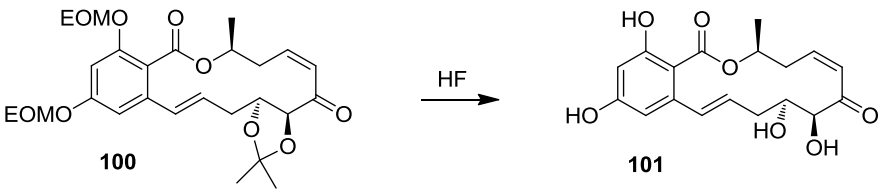


Bz-deprotected macrocycle 99. Macrocycle **98'** (1.0 equiv, 45 mg, 74 µmol) was added to a solution of 1% NaOH in MeOH (3 mL) and the resulting mixture was heated up to reflux for 12 h. The reaction was then quenched with sat. NH_4Cl aq. solution, diluted with EtOAc, washed with water, brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 1/1) yielded macrocycle **99** in 80% yield as a mixture of two unseparable diastereoisomers (29 mg). *Rf* = 0.20 (Petroleum ether/EtOAc 2/1); as only the signal corresponding to the major isomer can be unambiguously assigned, only the major diastereoisomer is reported.

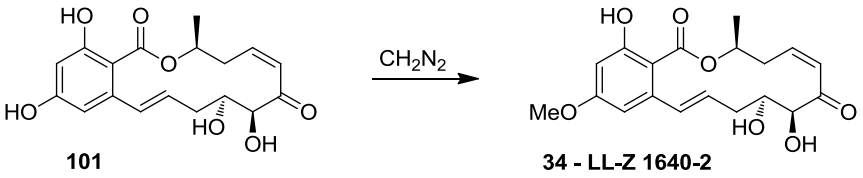
99, major diastereoisomer 99a: ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.75 (d, *J* = 1.6 Hz, 1H), 6.74 (m, 1H), 6.4 (d, *J* = 16.4 Hz, 1H), 6.22-6.08 (m, 1H), 5.88-5.74 (m, 2H), 5.54-5.50 (m, 1H), 5.20-5.10 (m, 4H), 4.52 (t, *J* = 6.8 Hz, 1H), 4.44 (t, *J* = 6.8 Hz, 1H), 4.21-4.08 (m, 1H), 3.72-3.67 (m, 4H), 2.99-2.90 (m, 1H), 2.82-2.74 (m, 1H), 2.68-2.64 (m, 1H), 2.59-2.53 (m, 1H), 1.45-1.14 (m, 15H), OH signal is not visible.



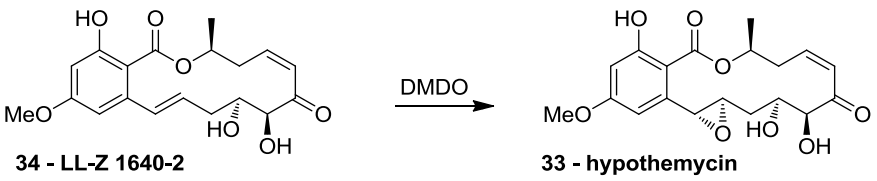
Oxidized macrocycle 100. To a solution of macrocycle **99** (1.0 equiv, 18 mg, 35 µmol) in CH_2Cl_2 (2.0 mL) was added DMP (3.0 equiv, 45 mg, 105 µmol) and the reaction was heated to reflux. After 6 h, the reaction was then quenched with MeOH (1 mL), diluted with EtOAc, washed with water, brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 2/1) yielded oxidized macrocycle **100** in quantitative yield (13 mg). *Rf* = 0.30 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) 6.73 (d, *J* = 2.0 Hz, 1H), 6.71 (d, *J* = 2.0 Hz, 1H), 6.56 (d, *J* = 11.6 Hz, 1H), 6.41-6.33 (m, 2H), 6.09-6.01 (m, 1H), 5.53-5.45 (m, 1H), 5.27-5.14 (m, 4H), 4.68-4.65 (m, 1H), 4.56 (d, *J* = 8.0 Hz, 1H), 3.69 (q, *J* = 7.2 Hz, 4H), 2.65 (d, *J* = 6.8 Hz, 2H), 1.55 (s, 3H), 1.46-1.31 (m, 2H), 1.41 (d, *J* = 6.8 Hz, 3H), 1.37 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 6H); HRMS (MALDI-TOF) *m/z* 505.2447 ($[M+H]^+$, $C_{27}H_{36}O_9H$ requires 505.2438).



Deprotected macrocycle 101. Macrocycle **100** (1.0 equiv, 3.4 mg, 6.7 µmol) was treated with a solution of 40% HF aq. solution/acetonitrile 1/10 (1 mL) at 23 ºC. After 7 h, H_2O (1 mL) was added, the reaction mixture was frozen by immersion in liquid N_2 and lyophilized to afford the deprotected macrocycle **101** in 50% yield (1.2 mg) and the corresponding macrocycle bearing an EOM on the *para*-phenol in 50% yield (1.3 mg). *Rf* = 0.21 (8% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 12.01 (s, 1H), 6.57 (s, 1H), 6.46-6.41 (m, 1H), 6.34-6.31 (m, 1H), 6.24-6.14 (m, 1H), 6.19 (s, 1H), 5.89-5.81 (m, 1H), 5.45-5.32 (m, 1H), 4.57-4.55 (m, 1H), 4.05-3.93 (m, 1H), 3.73-3.70 (m, 1H), 2.56-2.49 (m, 1H), 2.38-2.30 (m, 1H), 2.25-2.09 (m, 1H), 1.40 (d, *J* = 6.4 Hz, 3H). HRMS (MALDI-TOF) *m/z* 349.1224 ($[M+H]^+$, $C_{18}H_{20}O_7H$ requires 349.1287).

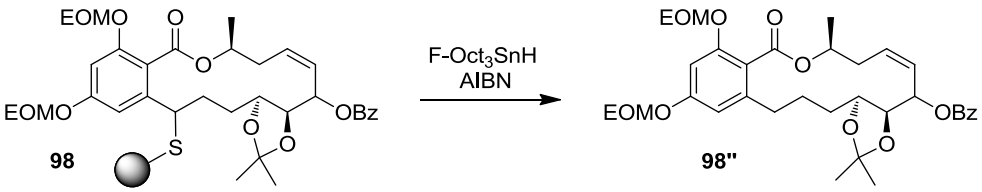


LL-Z1640-2 (34). To a solution of macrocycle **101** (1.0 equiv, 3.0 mg, 9 µmol) in Et_2O at 23 °C was added freshly prepared solution of CH_2N_2 in Et_2O (5.0 to 10.0 equiv). The reaction was monitored by LC/MS which indicated complete conversion after 6 h with less than 5% of bis-methylated product. The reaction mixture was concentrated and purified on HPLC (20-80% CH_3CN in H_2O in 50 min, flow: 2 mL/min, Discovery^R H C18, 5 µm, 5 cm x 10.0 mm) to afford **LL-Z1640-2** (**34**) in 74% yield (2.4 mg). *Rf* = 0.44 (3% MeOH in EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C) δ 12.15 (s, 1H), 6.87 (d, *J* = 15.1 Hz, 1H), 6.40 (d, *J* = 2.4 Hz, 1H), 6.38 (d, *J* = 2.4 Hz, 1H), 6.33 (dd, *J* = 11.4, 2.6 Hz, 1H), 6.20 (td, *J* = 11.1, 2.6 Hz, 1H), 5.98 (ddd, *J* = 15.1, 8.4, 4.1 Hz, 1H), 5.27-5.21 (m, 1H), 4.50 (bs, 1H), 4.00-3.98 (m, 1H), 3.81 (s, 3H), 3.58 (dt, *J* = 17.0, 11.3 Hz, 1H), 2.50 (dq, *J* = 17.0, 2.1 Hz, 1H), 2.23-2.19 (m ,1H), 2.13 (ddd, *J* = 15.7, 10.8, 3.0 Hz, 1H), 1.47 (d, *J* = 6.1 Hz, 3H), 2 OH signals are not visible; ^{13}C NMR ($CDCl_3$, 125.75 MHz, 25 °C) δ 199.2, 171.5, 166.1, 164.4, 147.5, 143.1, 132.9, 130.2, 125.3, 108.2, 103.5, 100.4, 80.8, 73.8, 73.7, 55.6, 37.6, 37.2, 20.9; HRMS (MALDI-TOF) *m/z* 385.1260 ($[M+Na]^+$, $C_{19}H_{22}O_7Na$ requires 385.1264).



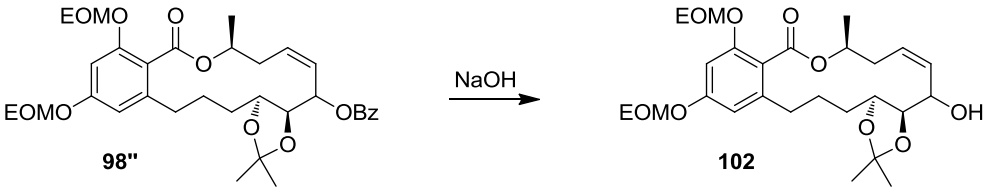
Hypothemycin (33). To a solution of **LL-Z1640-2** (**34**) (1.0 equiv, 2.0 mg, 5.2 µmol) in CH_3CN at 0 °C was added a 0.035 M freshly prepared solution of DMDO in acetone (5.0 equiv, 0.7 µl, 26 µmol). LC/MS analysis of the reaction mixture indicated a clean conversion of the starting material to a new

product. After 1 h, the reaction was stopped (~50% conversion). The reaction mixture was concentrated, followed by purification on HPLC (20-80% CH_3CN in H_2O in 50 min, flow: 2 mL/min, Discovery^R H C18, 5 µm, 5 cm x 10.0 mm) to afford **hypothemycin** (**33**) in 25% yield (0.5 mg). ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C) δ 12.07 (s, 1H), 6.43 (d, *J* = 2.5 Hz, 1H), 6.41 (d, *J* = 2.5 Hz, 1H), 6.37 (dd, *J* = 11.5, 2.9 Hz, 1H), 6.21 (td, *J* = 11.5, 2.5 Hz, 1H), 5.54-5.52 (m, 1H), 4.62 (d, *J* = 3.6 Hz, 1H), 4.41 (d, *J* = 1.6 Hz, 1H), 4.05-4.04 (m, 1H), 3.81 (s, 3H), 3.49 (s, *J* = 5.6 Hz, 1H), 3.13 (dt, *J* = 17.5, 11.5 Hz, 1H), 2.92 (d, *J* = 9.6 Hz, 1H), 2.60 (dm, *J* = 17.5 Hz, 1H), 2.00 (dd, *J* = 15.6, 9.6 Hz, 1H), 1.45 (d, *J* = 6.0 Hz, 3H), 1.14 (dd, *J* = 15.6, 9.6 Hz, 1H), OH signal is not visible; ^{13}C NMR ($CDCl_3$, 125.75 MHz, 25 °C) δ 199.5, 171.2, 166.2, 165.2, 145.5, 142.3, 126.3, 105.3, 103.6, 101.1, 80.9, 73.2, 70.8, 62.5, 57.9, 55.5, 36.9, 34.6, 21.1; HRMS (MALDI-TOF) *m/z* 401.1234 ([M+Na]$^+$, $C_{19}H_{22}O_8Na$ requires 401.1212).



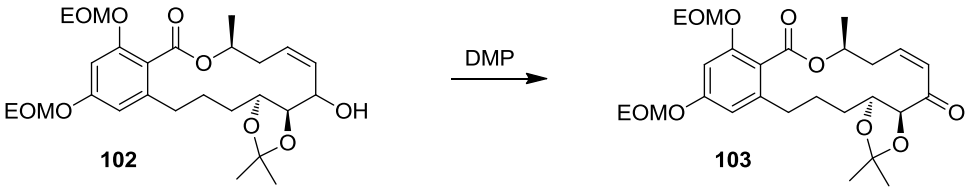
Macrocycle 98''. AIBN (cat) and F-Oct_3SnH (5.0 equiv, 414 mg, 357 µmol) were added to a suspension of resin **98** (1.0 equiv, 145 mg, 71 µmol, 0.492 mmol/g) in toluene (2 mL). The resulting mixture was irradiated with µwave at (150 °C, 300W) for 10 min. After filtration and evaporation of the solvent, followed by fluorous chromatography to remove the excess of organotin and its byproducts, macrocyle **98''** was recovered in 52% yield from thiophenol resin as an unseparable mixture of diastereosiomers (21 mg). *Rf* = 0.52 (Hexane/EtOAc 2/1); as only the signal corresponding to the major isomer can be unambiguously assigned, only the major diastereoisomer is report.

98'', major diastereoisomer 98a'': ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.02 (d, *J* = 7.2 Hz, 2H), 7.55-7.51 (m, 1H), 7.43-7.39 (m, 2H), 6.69 (d, *J* = 2.0 Hz, 1H), 6.52 (d, *J* = 2.0 Hz, 1H), 5.86 (t, *J* = 9.6 Hz, 1H), 5.82-5.75 (td, *J* = 11.6, 11.2 Hz, 1H), 5.55-5.48 (m, 1H), 5.36-5.27 (m, 1H), 5.21-5.17 (m, 4H), 4.32-4.29 (m, 1H), 4.18-4.04 (m, 1H), 3.77-3.66 (m, 4H), 3.22-3.17 (m, 1H), 2.72-2.68 (m, 1H), 2.47-2.39 (td, *J* = 12.4, 11.6 Hz, 1H), 2.27-2.22 (m, 1H), 1.83-1.46 (m, 4H), 1.44 (s, 2H), 1.43 (s, 2H), 1.42 (s, 1H), 1.40 (s, 1H), 1.32-1.21 (m, 9H), HRMS (MALDI-TOF) *m/z* 635.2869 ([M+Na]$^+$, $C_{34}H_{44}O_{10}Na$ requires 635.2833).

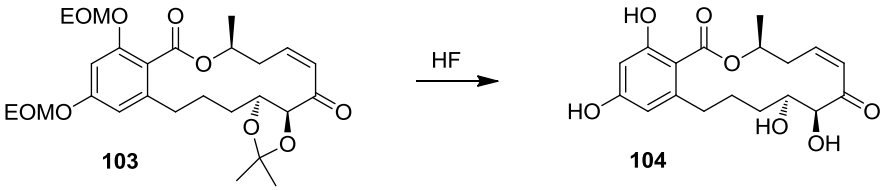


Bz-deprotected macrocycle 102. Compound **98''** (1.0 equiv, 40 mg, 65 µmol) was added to a 1% NaOH solution in MeOH (3 mL) and the resulting mixture was heated to reflux for 12 h. The reaction was then quenched with sat. NH_4Cl aq. solution, diluted with EtOAc, washed with water, brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 1/1) yielded macrocycle **102** in 76% yield (24 mg). *Rf* = 0.36 (Petroleum ether/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.67 (d,

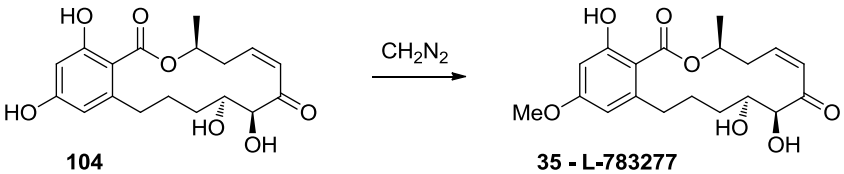
J = 2.0 Hz, 1H), 6.51 (d, *J* = 1.6 Hz, 1H), 5.83-5.77 (td, *J* = 11.6, 11.2 Hz, 1H), 5.44-5.39 (td, *J* = 11.2, 9.2 Hz, 1H), 5.35-5.27 (m, 1H), 5.20-5.14 (m, 4H), 4.34-4.28 (m, 1H), 4.05-4.01 (m, 1H), 3.95-3.90 (m, 1H), 3.72-3.68 (m, 4H), 2.92-2.83 (m, 1H), 2.70-2.65 (m, 1H), 2.47-2.40 (m, 1H), 2.30-2.23 (m, 1H), 1.56-1.38 (m, 10H), 1.33-1.18 (m, 9H), OH signal is not visible; HRMS (MALDI-TOF) *m/z* 509.2712 ($[M+H]^+$, $C_{27}H_{40}O_9H$ requires 509.2751).



Oxidized macrocycle 103. To a solution of macrocycle **102** (1.0 equiv, 8.0 mg, 16 µmol) in CH_2Cl_2 (0.5 mL) was added DMP (3.0 equiv, 20 mg, 48 µmmol) and the reaction was heated to reflux. After 6 h, the reaction was then quenched with MeOH (1 mL), diluted with EtOAc, washed with water, brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 2/1) yielded oxidized macrocycle **103** in 85% yield (6.6 mg). *Rf* = 0.70 (Petroleum ether/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.67 (d, *J* = 2.0 Hz, 1H), 6.50 (d, *J* = 2.0 Hz, 1H), 6.62-6.53 (m, 1H), 6.39-6.32 (m, 1H), 5.47-5.42 (m, 1H), 5.17 (s, 2H), 5.16 (s, 2H), 4.57 (d, *J* = 7.6 Hz, 1H), 4.46-4.42 (m, 1H), 3.77-3.66 (m, 4H), 2.53-2.50 (m, 2H), 1.57-1.37 (m, 12H), 1.33-1.20 (m, 9H).

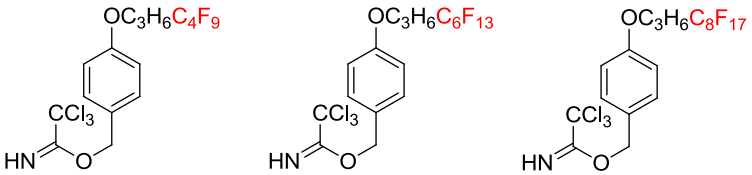


Deprotected macrocycle 104. Macrocycle **103** (1.0 equiv, 6.0 mg, 12 µmol) was added to a 40% HF aq. solution/acetonitrile 1/10 (1 mL) solution. After 7 h, H_2O (1.0 mL) was added and the reaction mixture was lyophilized to afford after PTLC purification (CH_2Cl_2/CH_3OH 20/1) macrocycle **104** in a 50% yield (2.0 mg) and the macrocycle with an EOM on the *para*-phenol also in 50% yield (2.4 mg). *Rf* = 0.29 (CH_2Cl_2/CH_3OH 10/1); ^{1}H NMR (CD_3OD, 400 MHz, 25 °C) δ 6.50 (dd, *J* = 11.6 Hz, 2.4 Hz, 1H), 6.31-6.23 (m, 2H), 6.18 (d, *J* = 2.4 Hz, 1H), 5.47-5.38 (m, 1H), 4.52 (d, *J* = 1.6 Hz, 1H), 3.95-3.92 (m, 1H), 3.03-2.89 (m, 1H), 2.64-2.46 (m, 2H), 1.78-1.69 (m, 1H), 1.65-1.52 (m, 2H), 1.42 (d, *J* = 6.4 Hz, 3H), 1.35-1.31 (m, 2H), 4 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 365.1475 ($[M+H]^+$, $C_{18}H_{22}O_7H$ requires 365.1425).



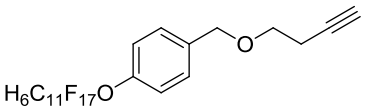
L-783277 (35). To a solution of macrocycle **104** (1.0 equiv, 1.0 mg, 3.0 µmol) in Et_2O at 23 °C was added freshly prepared solution of CH_2N_2 in Et_2O (5.0 to 10.0 equiv). After 8 h, LC/MS analysis indicated a complete consumption of the starting material with less than 10% of a bis-methylated product. The reaction mixture was concentrated and purified by HPLC (20-80% CH_3CN in H_2O in 50 min, flow: 2 mL/min, Discovery^R H C18, 5 µm, 5 cm x 10.0 mm) to afford **L-783277** (**35**) in 63% yield (0.6 mg). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 12.18 (s, 1H), 6.39 (dd, *J* = 11.6, 3.2 Hz, 1H), 6.36 (d, *J* = 2.4 Hz, 1H), 6.29 (dd, *J* = 11.6, 2.4 Hz, 1H), 6.28 (d, *J* = 2.4 Hz, 1H), 5.48-5.40 (m, 1H), 4.56-4.54 (m, 1H), 4.21 (ddd, *J* = 16.4, 12.0, 4.8 Hz, 1H), 3.93 (bs, 1H), 3.82 (s, 3H), 3.75 (d, *J* = 6.8 Hz, 1H), 3.68-3.65 (m, 2H), 3.37 (dt, *J* = 17.5, 11.5 Hz, 1H), 2.96 (tm, *J* = 12.0 Hz, 1H), 2.57 (dq, *J* = 16.8, 2.8 Hz, 1H), 2.52-2.44 (m, 1H), 2.04-2.00 (m, 1H), 1.45 (d, *J* = 6.0 Hz, 3H), 1.12 (m, 1H); HRMS (MALDI-TOF) *m/z* 365.1637 ([M+H]$^+$, $C_{19}H_{24}O_7H$ requires 365.1600).

1. Synthesis of fragments 110a-d

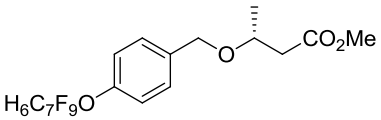


113$_{RF9}$ **113$_{RF13}$** **113$_{RF17}$**

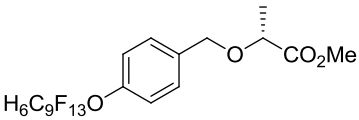
General procedure for the synthesis of trichloroacetimidates 113. To a solution of the fluorous-tagged alkoxybenzylalcohol $C_{4\text{-}8}$ $F_{9\text{-}17}$ (1.0 equiv) in anhydrous Et_2O (0.3 M) and THF (until homogenous solution is obtained) at 23 °C was added NaH 60% (0.25 equiv) and the reaction was stirred for 30 min. Then the reaction was cooled at 0 °C, and treated with Cl_3CCN (1.0 equiv). The mixture was allowed to stir for 1 h at 23 °C, after which it was quenched with sat. $NaHCO_3$ aq. solution, diluted with Et_2O, washed with brine and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure yielded trichloroacetimidates **113$_{RF9}$**, **113$_{RF13}$** and **113$_{RF17}$** which were used in the next step without any further purification. *Rf* = 0.55, 0.58 and 0.77 (Petroleum ether/EtOAc 3/1)



110b



114'



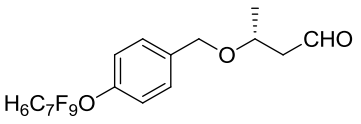
115'

General procedure for the R_FPMB protection of alcohols 112, 114 and 115. The alcohol (1.0 equiv) was dissolved in CH_2Cl_2 (0.25 M) at 23 ºC and treated with the corresponding acetimidate **113** (1.0 equiv). A catalytic amount of CSA (0.14 equiv) was added and the mixture was stirred at 23 °C for 12 h. The mixture was diluted with EtOAc, washed with sat. $NaHCO_3$ aq. solution and brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by fluorous chromatography (loading of the compound in DMF and eluting with 70% MeOH in H_2O, then 80% MeOH in H_2O and finally 100% MeOH) afforded the expected protected alcohols **110b**, **114'**, and **115'** in 72-86% yield.

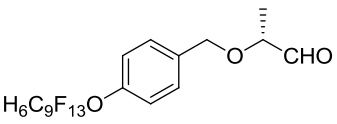
110b: *Rf* = 0.64 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.27 (d, *J* = 9.2 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.49 (s, 2H), 4.04 (t, *J* = 5.6 Hz, 2H), 3.58 (t, *J* = 6.8 Hz, 2H), 2.51-2.47 (m, 2H), 2.38-2.25 (m, 2H), 2.13-2.06 (m, 2H), 1.99-1.98 (m, 1H).

114': *Rf* = 0.38 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.25 (d, *J* = 11.2 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 4.50 (d, *J* = 11.2 Hz, 1H), 4.43 (d, *J* = 11.2 Hz, 1H), 4.03 (t, *J* = 6.0 Hz, 2H), 4.05-3.97 (m, 1H), 3.68 (s, 3H), 2.67-2.61 (m, 1H), 2.45-2.40 (m, 1H), 2.35-2.24 (m, 2H), 2.13-2.04 (m, 2H), 1.25 (d, *J* = 6.0 Hz, 3H).

115': *Rf* = 0.37 (Petroleum ether/EtOAc 5/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.29 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.62 (d, *J* = 11.2 Hz, 1H), 4.39 (d, *J* = 11.2 Hz, 1H), 4.08-4.02 (m, 3H), 3.76 (s, 3H), 2.36-2.24 (m, 2H), 2.13-2.08 (m, 2H), 1.42 (d, *J* = 6.8 Hz, 3H).



114"



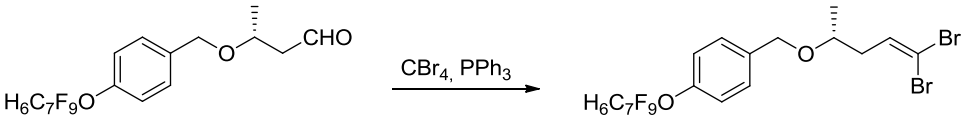
115"

General procedure for the DIBAL-H reduction of the ester functionality in compounds 114' and 115'. A 1.0 M solution of DIBAL-H in toluene (1.1 equiv) was added dropwise at -78 °C to the corresponding ester (1.0 equiv) in toluene (0.17 M). The reaction was stirred for 1 h at -78 °C. The mixture was then quenched with EtOAc and sat. NH_4Cl aq. solution, diluted with EtOAc, washed with potassium sodium tartrate aq. solution and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by fluorous chromatography (loading of the compound in DMF and eluting with 70% MeOH in H_2O, then 80% MeOH in H_2O and finally 100% MeOH) afforded the corresponding aldehydes **114''** and **115''** in 45-52% yield.

Aldehyde 114'': *Rf* = 0.53 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 9.78-9.77 (m, 1H), 7.24 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.54 (d, *J* = 11.6 Hz, 1H), 4.41 (d, *J* = 11.2 Hz, 1H), 4.13-4.02 (m, 3H), 2.72-2.65 (m, 1H), 2.53-2.48 (m, 1H), 2.37-2.24 (m, 2H), 2.13-2.05 (m, 2H), 1.29 (d, *J* = 6.0 Hz, 3H).

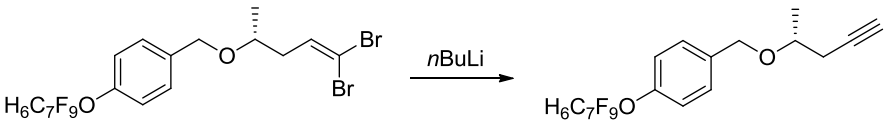
Aldehyde 115'': *Rf* = 0.40 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 9.64-9.63 (m, 1H), 7.29 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 4.58 (d, *J* = 11.2 Hz, 1H), 4.54 (d, *J* = 11.6 Hz, 1H), 4.04 (t, *J* = 6.0 Hz, 2H), 3.88-3.86 (m, 1H), 2.38-2.25 (m, 2H), 2.14-2.09 (m, 2H), 1.31 (d, *J* = 7.2 Hz, 3H).

Synthesis of fragment 110a.



114" **114'''**

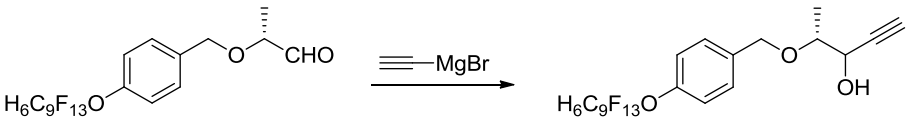
Dibromoalkene 114'''. CBr_4 (4.0 equiv, 41.2 g, 124.3 mmol) was dissolved in CH_2Cl_2 (426 mL) and cooled to 0 °C. The solution was treated with PPh_3 (8.0 equiv, 65.2 g, 248.6 mmol) and stirred for 5 min at 0 °C. A solution of the previously described aldehyde **114''** (1.0 equiv, 14.1 g, 31.1 mmol) in CH_2Cl_2 (20 mL) was added dropwise at 0 °C. The mixture was stirred for 45 min at 0 °C, and then diluted with Hexane and filtered. Evaporation of the solvents under reduced pressure followed by fluorous chromatography (loading of the compound in DMF and eluting with 70% MeOH in H_2O, then 80% MeOH in H_2O and finally 100% MeOH) afforded the corresponding dibromoalkene **114'''** in 63% yield (11.8 g). *Rf* = 0.55 (Petroleum ether/EtOAc 5/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.26 (d, *J* = 11.2 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.48 (t, *J* = 7.2 Hz, 1H), 4.50 (d, *J* = 11.6 Hz, 1H), 4.41 (d, *J* = 11.6 Hz, 1H), 4.04 (t, J = 6.0 Hz, 2H), 3.65-3.60 (m, 1H), 2.38-2.24 (m, 4H), 2.13-2.05 (m, 2H), 1.21 (d, *J* = 6.0 Hz, 3H).



114''' **110a**

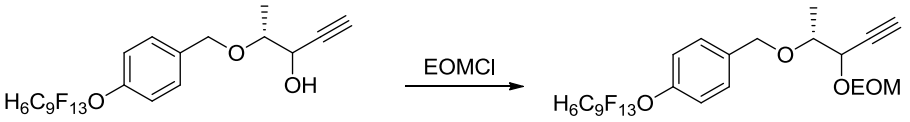
Alkyne 110a. The dibromoalkene **114'''** (1.0 equiv, 11.9 g, 19.4 mmol) was dissolved in THF (0.5 M, 40 mL), cooled at -78 °C and treated dropwise with a solution of *n*BuLi in hexane (2.0 equiv, 24.3 mL, 38.8 mmol) for 1 h at -78 °C and for 1.5 h at 23 °C. The reaction was quenched with a sat. NH_4Cl aq. solution, extracted with EtOAc and water, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by fluorous chromatography (loading of the compound in DMF and eluting with 70% MeOH in H_2O, then 80% MeOH in H_2O and finally 100% MeOH) afforded alkyne **110a** in a 85% yield (7.4 g). *Rf* = 0.50 (Petroleum ether/EtOAc 5/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.28 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.51 (s, 2H), 4.03 (t, *J* = 6.0 Hz, 2H), 4.68 (q, *J* = 6.0 Hz, 1H), 2.52-2.46 (m, 1H), 2.39-2.36 (m, 1H), 2.35-2.25 (m, 2H), 2.13-2.06 (m, 2H), 2.01 (t, *J* = 2.8 Hz, 1H), 1.30 (d, *J* = 6.0 Hz, 3H).

Synthesis of fragment 110c.



115" **115'"**

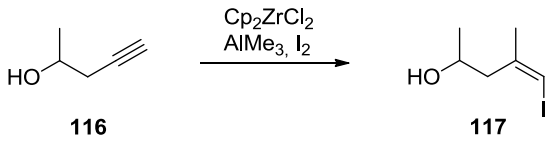
Alkyne 115'''. Aldehyde **115''** (1.0 equiv, 9.8 g, 18.1 mmol) was dissolved in THF (150 mL), cooled to -78 °C, and a 0.5 M solution of ethynylmagnesium bromide in THF (1.5 equiv, 54.3 mL, 27.2 mmol) was added slowly. The mixture was stirred for 12 h, diluted with EtOAc, washed with a sat. NH_4Cl aq. solution, brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by fluorous chromatography (loading of the compound in DMF and eluting with 70% MeOH in H_2O, then 80% MeOH in H_2O and finally 100% MeOH) afforded the corresponding alkyne **115'''** in 88% yield (9.0 g) as an unseparable mixture of diastereoisomers (2:1 dr). *Rf* = 0.31 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.27 (d, *J* = 10.4 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 4.65-4.46 (m, 2H), 4.41-4.21 (m, 1H), 4.04 (t, *J* = 6.0 Hz, 2H), 3.69-3.61 (m, 1H), 2.47 (s, 1H), 2.38-2.25 (m, 2H), 2.14-2.07 (m, 2H), 1.29-1.24 (m, 3H), OH signal is not visible.



115'" **110c**

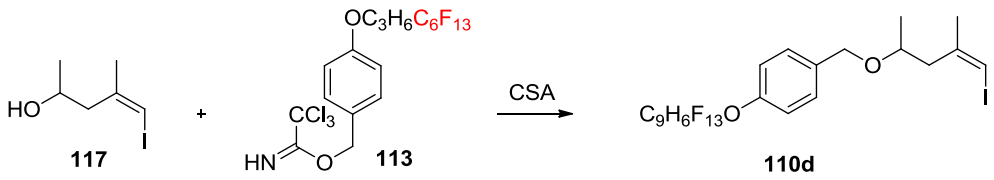
Alkyne 110c. To a solution of alcohol **115'''** (1.0 equiv, 9.0 g, 15.8 mmol) in CH_2Cl_2 (32 mL) at 23 °C were added sequentially TBAI (cat), *i*Pr_2NEt (3.0 equiv, 7.8 mL, 47.5 mmol), EOM-Cl (3.0 equiv, 4.6 mL, 47.5 mmol) and stirred 12 h at 23 °C. The mixture was diluted with EtOAc, washed with a sat. NH_4Cl aq. solution, water, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by fluorous chromatography (loading of the compound in DMF and eluting with 70% MeOH in H_2O, then 80% MeOH in H_2O and finally 100% MeOH) afforded building block **110c** in 89% yield (8.8 g). *Rf* = 0.52 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.31-7.28 (m, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 4.98-4.94 (m, 1H), 4.75-4.71 (m, 1H), 4.64-4.55 (m, 2H), 4.46-4.44 (m, 1H), 4.01 (t, *J* = 6.0 Hz, 2H), 3.73-3.64 (m, 2H), 3.59-3.54 (m, 1H), 2.44-2.43 (m, 1H), 2.37-2.24 (m, 2H), 2.12-2.05 (m, 2H), 1.29 (d, *J* = 6.4 Hz, 3H), 1.24-1.18 (m, 3H).

Synthesis of fragment 110d.



116 **117**

Vinyl iodide 117. To a suspension of Cp_2ZrCl_2 (0.25 equiv, 3.6 g, 12.5 mmol) in CH_2Cl_2 (100 mL) was added dropwise over a period of 1 h a 2.0 M solution of $AlMe_3$ in toluene (3.0 equiv, 74.8 mL, 150.0 mmol, 2M in toluene) followed by a solution of 4-hydroxylpentyne **116** (1.0 equiv, 4.2 g, 50.0 mmol) in CH_2Cl_2 (100 mL) in 2.5 h at 23 °C. After 19 h at 23 °C, the reaction mixture was refluxed for 5 days and subsequently quenched with I_2 (1.5 equiv, 19.0 g, 74.8 mmol) in THF (20 mL) at - 30 °C followed by the slow addition of K_2CO_3 aq. solution (10 mL) at 0 °C. Filtration and flash chromatography (SiO_2, Petroleum ether/EtOAc 4/1) provided vinyl iodide **117** in 60% yield (6.8 g) as a light yellow liquid. *Rf* = 0.35 (Petroleum ether/EtOAc 4/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 5.97 (s, 1H), 3.95-3.89 (m, 1H), 2.35-2.25 (m, 2H), 2.00 (d, *J* = 2.7 Hz, 1H), 1.83 (s, 3H), 1.15 (d, *J* = 6.2 Hz, 3H).



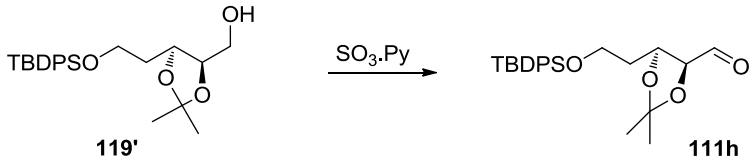
117 **113** **110d**

Vinyl iodide 110d. A solution of alcohol **117** (1.0 equiv, 5.9 g, 26.0 mmol) in CH_2Cl_2 (100 mL) was treated with freshly prepared fluorous tagged PMB trichloroacetimidate **113** (1.0 equiv, 16.3 g, 26.0 mmol) and CSA (0.1 equiv, 0.6 g, 2.6 mmol) at 23 °C and stirred at the same temperature for 19 h. Evaporation of the solvents under reduced pressure followed by fluorous chromatography (loading of the compound in DMF and eluting with 70% MeOH in H_2O, then 80% MeOH in H_2O and finally 100% MeOH) afforded protected vinyl iodide **110d** in 82% yield (14.8 g). *Rf* = 0.56 (Petroleum ether/EtOAc 4/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.24 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.96 (d, *J* = 0.8 Hz, 1H), 4.51 (d, *J* = 11.4 Hz, 1H), 4.38 (d, *J* = 11.3 Hz, 1H), 4.04 (t, *J* = 6.0 Hz, 2H), 3.68-3.60 (m, 1H), 2.52 (dd, *J* = 13.9, 7.2 Hz, 1H), 2.38-2.25 (m, 3H), 2.13-2.06 (m, 2H), 1.80 (d, *J* = 1.0 Hz, 3H), 1.17 (d, *J* = 6.1 Hz, 3H).

2. Synthesis of fragments 111i-j

Synthesis of fragment 111h.

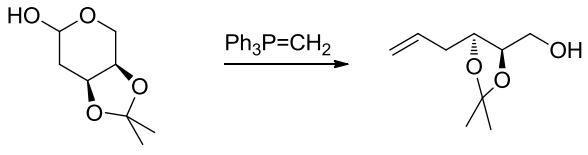
The three first steps are described (procedures and data) in radicicol A total synthesis section.



119' 111h

Aldehyde 111h. To a solution of mono-protected diol **119'** (1.0 equiv, 5.8 g, 14.0 mmol) and Et_3N (4.9 equiv, 9.6 mL, 68.6 mmol) in CH_2Cl_2/DMSO 4/1 (170 mL) at 0 °C was added SO_3.Py (3.5 equiv, 7.7 g, 48.6 mmol) and mixture was stirred for 30 min at 23 ºC. The reaction was diluted with EtOAc, washed sequentially with H_2O, sat. $NaHCO_3$ aq. solution, brine and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure provided the corresponding aldehyde **111h** in 94% yield (5.5 g). *Rf* = 0.45 (Hexane/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 9.68 (d, *J* = 3.0 Hz, 1H), 7.72-7.68 (m, 4H), 7.50-7.40 (m, 6H), 4.69-4.64 (m, 1H), 4.30 (dd, *J* = 7.3, 3.0 Hz, 1H), 3.87-3.84 (m, 2H), 1.99-1.91 (m, 1H), 1.72 (dddd, *J* = 7.5, 5.6, 3.9, 1.9 Hz, 1H), 1.60 (s, 3H), 1.45 (s, 3H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 202.1, 135.5 (x 2), 135.4 (x 2), 133.6, 133.5, 129.7, 129.6, 127.7 (x 2), 127.6 (x 2), 110.4, 81.8, 75.1, 60.4, 32.3, 27.6, 26.8 (x 3), 25.3, 19.2; HRMS (MALDI-TOF) *m/z* 413.2094 ([M + H]$^+$, $C_{24}H_{32}O_4SiH$ requires 413.2148).

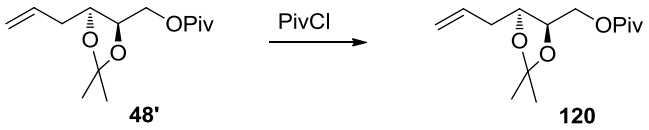
Synthesis of fragment 111j.



48 48'

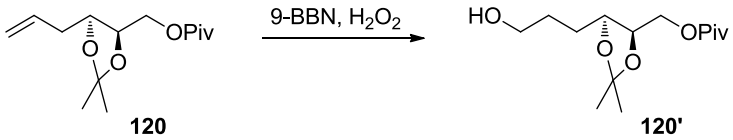
Alcohol 48'. A solution of NaHDMS in THF (2.8 equiv, 80.4 mL, 80.4 mmol) was added to a suspension of methyltriphenylphosphonium bromide (3.0 equiv, 30.7 g, 86.1 mmol) in THF (125 mL) at -78 °C. The mixture was stirred at 23 °C for 30 min before the addition of protected sugar **48** (1.0 equiv, 5.0 g, 28.7 mmol) in THF (15 mL) at -78 °C. The reaction mixture was stirred at 23 °C for 1 h, quenched with sat. NH_4Cl aq. solution, extracted with EtOAc, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Petroleum ether/EtOAc 5/1) to obtain alcohol **48'** in 72% yield (7.1 g) as a colorless liquid. *Rf* = 0.37 (Petroleum ether/EtOAc

1/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 5.81 (ddt, *J* = 17.3, 10.3, 6.8 Hz, 1H), 5.15-5.06 (m, 2H), 4.23 (dt, *J* = 8.3, 5.9 Hz, 1H), 4.16 (q, *J* = 5.9 Hz, 1H), 3.62 (d, *J* = 5.7 Hz, 2H), 2.41-2.22 (m, 2H), 2.20 (bs, 1H), 1.46 (s, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 134.1, 117.0, 108.0, 77.7, 76.1, 61.2, 33.5, 27.9, 25.2.



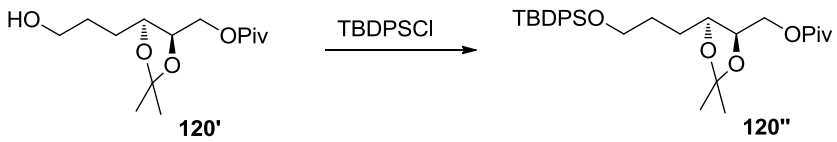
48' **120**

Piv-protected alcohol 120. To a solution of the previously described alcohol **48'** (1.0 equiv, 7.0 g, 40.6 mmol) in CH_2Cl_2 (75 mL) was added sequentially DMAP (0.2 equiv, 990 mg, 8.1 mmol), Et_3N (4.0 equiv, 22.5 mL, 162.4 mmol) and PivCl (2.0 equiv, 10.0 mL, 81.2 mmol) at 0 °C and the resulted mixture was slowly warmed up to 23 °C over 15 h. The reaction was quenched with sat. $NaHCO_3$ aq. solution, extracted with EtOAc, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Petroleum ether/EtOAc 5/1) to furnish pivolate **120** in 93% yield (9.7 g) as a colorless liquid. *Rf* = 0.30 (Petroleum ether/EtOAc 4/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 5.85 (ddt, *J* = 17.1, 10.3, 6.7 Hz, 1H), 5.17-5.09 (m, 2H), 4.28-4.21 (m, 2H), 4.12 (d, *J* = 5.4 Hz, 1H), 4.10 (d, *J* = 6.1 Hz, 1H), 2.40-2.27 (m, 2H), 1.46 (s, 3H), 1.35 (s, 3H), 1.21 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 178.2, 134.2, 117.3, 108.4, 76.4, 75.1, 62.7, 38.6, 33.7, 27.9, 27.1 (x 2), 26.5, 25.5; HRMS (MALDI-TOF) *m/z* 257.1739 ($[M + H]^+$, $C_{14}H_{24}O_4H$ requires 257.1753).

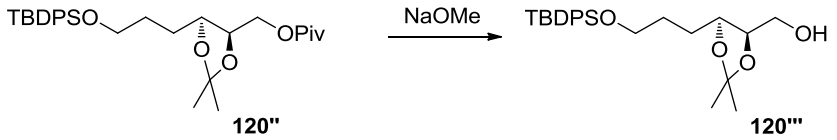


120 **120'**

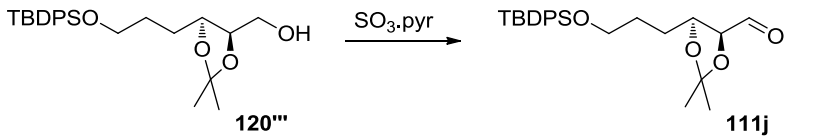
Alcohol 120'. To a solution of alkene **120** (1.0 equiv, 7.3 g, 28.4 mmol) in THF (64 mL) was added a 0.5 M solution of 9-BBN in THF (2.2 equiv, 125.0 mL, 62.5 mmol) at 0 °C. The reaction mixture was warmed to 23 °C and stirred for 3.5 h. After the flask was cooled to 0 °C and a 3N NaOH aq. solution (28.4 mL) followed by 30% H_2O_2 aq. solution (28.4 mL) were added very slowly, then the mixture was warmed to 23 °C and stirred for 1.5 h. The reaction mixture was quenched with H_2O, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Petroleum ether/EtOAc 4/1) to provide the corresponding alcohol **120'** in 94% yield (7.3 g) as a colorless liquid. *Rf* = 0.38 (Petroleum ether/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 4.24-4.14 (m, 2H), 4.07 (d, *J* = 5.4 Hz, 1H), 4.05 (d, *J* = 5.9 Hz, 1H), 3.65 (t, *J* = 6.0 Hz, 2H), 2.49 (bs, 1H), 1.79-1.51 (m, 4H), 1.42 (s, 3H), 1.32 (s, 3H), 1.18 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 178.2, 108.3, 77.1, 75.3, 62.8, 62.3, 38.6, 29.9, 27.9, 27.1 (x 3), 25.8, 25.5; HRMS (MALDI-TOF) *m/z* 275.1886 ($[M + H]^+$, $C_{14}H_{26}O_5H$ requires 275.1859).



TBDPS-protected alcohol 120''. To a solution of alcohol **120'** (1.0 equiv, 6.9 g, 25.0 mmol) in DMF (60 mL) were added imidazole (2.2 equiv, 3.7 g, 55.1 mmol) and TBDPSCl (1.1 equiv, 7.1 mL, 27.5 mmol) at 23 °C. The reaction mixture was stirred for 24 h, then diluted with EtO_2, washed with 10% K_2CO_3 aq. Solution, brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Petroleum ether/EtOAc 10/1) to provide TBDPS ether **120''** in 96% yield (12.3 g) as a colorless liquid. *Rf* = 0.36 (Petroleum ether/EtOAc 10/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.68-7.65 (m, 4H), 7.44-7.36 (m, 6H), 4.20 (q, *J* = 5.8 Hz, 1H), 4.17-4.12 (m, 1H), 4.08 (d, *J* = 5.9 Hz, 2H), 3.75-3.66 (m, 2H), 1.85-1.74 (m, 1H), 1.69-1.59 (m, 3H), 1.43 (s, 3H), 1.33 (s, 3H), 1.20 (s, 9H), 1.05 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 178.2, 135.5 (x 4), 133.8 (x 2), 129.5 (x 2), 127.6 (x 4), 108.2, 76.9, 75.2, 63.4, 62.9, 38.7, 29.5, 28.1, 27.1 (x 3), 26.8 (x 3), 25.6, 25.5, 19.2; HRMS (MALDI-TOF) *m/z* 513.3025 ($[M + H]^+$, $C_{30}H_{44}O_5SiH$ requires 513.3036).



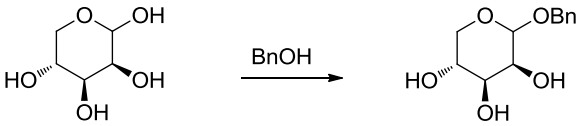
Alcohol 120'''. To a solution of pivolate **120''** (1.0 equiv, 12.4 g, 24.1 mmol) in MeOH (380 mL) was added NaOMe (3.0 equiv, 3.9 g, 72.3 mmol) and the mixture was stirred for 16 h at 23 °C. Then the reaction was quenched with sat. NH_4Cl aq. solution, extracted with EtOAc, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Petroleum ether/EtOAc 5/1) to provide alcohol **120'''** in 83% yield (8.5 g) as a colorless liquid. *Rf* = 0.21 (Petroleum ether/EtOAc 5/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.68-7.65 (m, 4H), 7.45-7.37 (m, 6H), 4.17-4.10 (m, 2H), 3.76-3.66 (m, 2H), 3.60 (d, *J* = 5.3 Hz, 2H), 1.95 (bs, 1H), 1.82-1.74 (m, 1H), 1.65-1.59 (m, 3H), 1.46 (s, 3H), 1.35 (s, 3H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 135.5 (x 4), 133.8 (x 2), 129.5 (x 2), 127.6 (x 4), 108.0, 77.9, 76.6, 63.4, 61.7, 29.4, 28.2, 26.8 (x 3), 25.5, 25.2, 19.1; HRMS (MALDI-TOF) *m/z* 429.2415 ($[M + H]^+$, $C_{25}H_{36}O_4SiH$ requires 429.2461).



Aldehyde 111j. To a solution of alcohol **120'''** (1.0 equiv, 4.4 g, 10.3 mmol) in CH_2Cl_2 (80 mL) and DMSO (20 mL) were added Et_3N (4.9 equiv, 7.0 mL, 50.5 mmol) and SO_3.pyr complex (3.5 equiv, 5.7 g, 35.7 mmol) at 0 °C. The reaction mixture was stirred for 20 min at 0 °C and 1 h at 23 °C before it was quenched with water, extracted with CH_2Cl_2, washed with water, brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Petroleum ether/EtOAc 4/1) to provide aldehyde **111j** in 91% yield (4.0 g) as a light yellow liquid. *Rf* = 0.38 (Petroleum ether/EtOAc 4/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 9.63 (d, *J* = 3.5 Hz, 1H), 7.66-

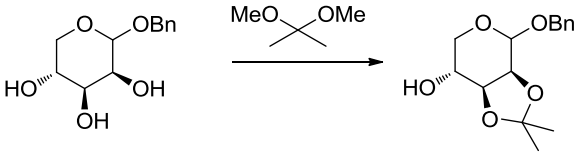
7.64 (m, 4H), 7.46-7.36 (m, 6H), 4.36-4.31 (m, 1H), 4.24 (dd, *J* = 7.0, 3.3 Hz, 1H), 3.68 (t, *J* = 5.6 Hz, 2H), 1.79-1.60 (m, 4H), 1.58 (s, 3H), 1.39 (s, 3H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 201.9, 135.5 (x 4), 133.7 (x 2), 129.5 (x 2), 127.6 (x 4), 108.1, 82.0, 78.3, 63.2, 29.2, 27.6, 26.8 (x 3), 26.2, 25.3, 19.2.

Synthesis of fragment 111i.



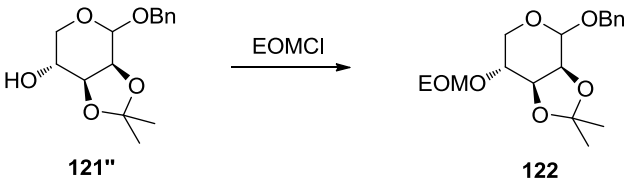
121 **121'**

Triol 121'. Benzyl alcohol (7.2 equiv, 50.0 ml, 480.2 mmol) was saturated with HCl(g) (prepared from NaCl and H_2SO_4) for 40 min at 0 °C, D-Lyxose **121** (1.0 equiv, 10.0 g, 66.7 mmol) was added and the mixture was stirred at 23 °C for 10 h. The precipitate was filtered and washed with EtOAc to give triol **121'** in 96% yield (15.4 g) as a white solid. *Rf* = 0.33 (CH_2Cl_2/MeOH 3.5/1); ^{1}H NMR (DMSO-d6, 400 MHz, 25 °C) δ 7.40-7.25 (m, 5H), 4.78 (d, *J* = 4.8 Hz, 1H), 4.7-4.6 (m, 2H), 4.43 (d, *J* = 4.8 Hz, 1H), 3.65-3.44 (m, 4H), 3 OH signals are not visible.

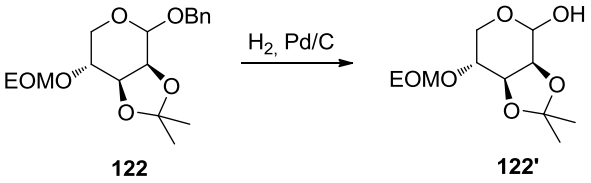


121' **121"**

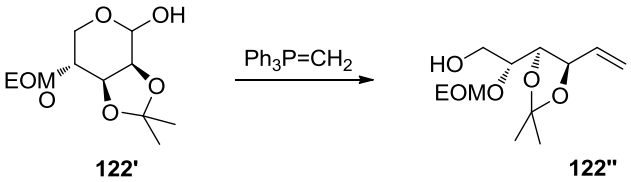
Acetal-protected sugar 121''. To a stirred solution of compound **121'** (1.0 equiv, 15.4 g, 64.1 mmol) in acetone (220 mL) were added dimethoxypropane (3.5 equiv, 28.0 mL, 225.0 mmol) and *p*-TSA (0.02 equiv, 240 mg, 1.3 mmol). After 12 h at 23 °C, the solution was diluted with EtO_2, washed with $NaHCO_3$ aq. solution, water and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 1/1) yielded ketal **121''** in 90% yield (16.2 g) as a colorless oil. *Rf* = 0.79 (CH_2Cl_2/MeOH 9/1), ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.33-7.26 (m, 5H), 4.81 (d, *J* = 2.7 Hz, 1H), 4.80-4.52 (q, *J* = 11.8 Hz, 2 H), 4.21-4.14 (m, 2H), 3.86-3.67 (m, 3H), 3.43-3.38 (m, 1H), 1.43 (s, 3H), 1.31 (s, 3H).



EOM-protected sugar 122. To a stirred solution of ketal **121''** (1.0 equiv, 16.2 g, 57.8 mmol) in CH_2Cl_2 (290 ml) were added sequentially TBAI (cat), *i*Pr_2NEt (8.0 equiv, 76.4 mL, 462.0 mmol) and EOMCl (8.0 equiv, 42.9 mL, 462.0 mmol). After 12 h at 23 °C, the reaction mixture was diluted with EtOAc, washed with sat. NH_4Cl aq. solution and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 5/1) yielded protected sugar **122** in 95% yield (18.6 g) as a white solid. *Rf* = 0.85 (Petroleum ether/EtOAc 2/1), ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.38-7.27 (m, 5H), 4.92 (d, *J* = 1.6 Hz, 1H), 4.82-4.75 (m, 3H), 4.54 (d, *J* = 11.8 Hz, 1H), 4.20-4.11 (m, 2H), 3.85-3.81 (m, 1H), 3.72-3.59 (m, 4H), 1.49 (s, 3H), 1.35 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 3H).

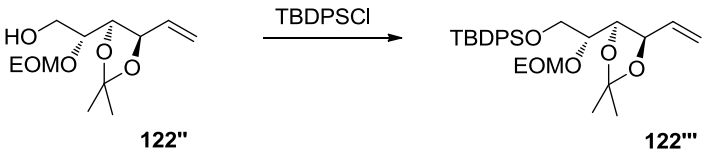


Sugar deprotected in anomeric position 122'. To a stirred solution of protected sugar **122** (1.0 equiv, 18.6 g, 55.0 mmol) in MeOH (550 ml) and under hydrogen was added palladium on activated charcoal (0.05 equiv, 41.8 g, 2.7 mmol). After 5 h at 23 °C, the reaction mixture was filtered on Celite and evaporated under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 3/1) to yield cyclic sugar **122'** as a white solid (12.3 g) in a 90% yield. *Rf* = 0.44 (Petroleum ether/EtOAc 2/1), ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 5.11 (m, 1H), 4.80 (d, *J* = 3.2 Hz, 2H), 4.27 (t, *J* = 4.8 Hz, 1H), 4.13 (m, 1H), 3.85-3.76 (m, 3H), 3.67-3.60 (m, 2H), 3.20-3.13 (b, 1H), 1.53 (s, 3H), 1.37 (s, 3H), 1.23 (t, *J* = 7 Hz, 3H).



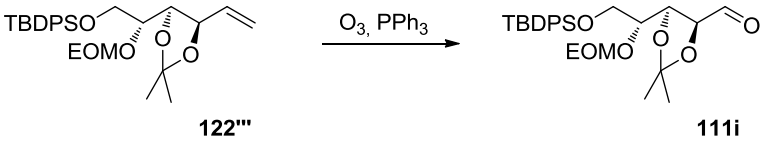
Alkene 122''. To a stirred solution of methyltriphenylphosphinium bromide (3.0 equiv, 53.1 g, 148.6 mmol) in THF (200 mL) at -78 °C was added 1.0 M solution of NaHMDS in THF (2.8 equiv, 139.0 mL, 139.0 mmol). The mixture was stirred for 30 min at 0 °C, cooled at -78 °C and the sugar **122'** (1.0 equiv, 12.3 g, 49.6 mmol), dissolved in THF, was added in dropwise fashion. After 12 h at 23 °C, the reaction mixture was diluted with EtOAc, washed with sat. NH_4Cl aq. solution and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 1/1) yielded alkene **122''** in 86% yield (10.5 g) as colorless

oil. *Rf* = 0.56 (Petroleum ether/EtOAc 1/1), ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 5.93-5.84 (m, 1H), 5.32 (d, *J* = 17.2 Hz, 1 H), 5.28 (d, *J* = 10.2 Hz, 1H), 4.89 (d, *J* = 7.5 Hz, 1H), 4.78 (m, 2H), 4.52 (t, *J* = 7 Hz, 1H), 4.24 (t, *J* = 6.5 Hz, 1H), 3.80 (m, 1H), 3.55-3.70 (m, 4H), 1.51 (s, 3H), 1.37 (s, 3H), 1.24-1.20 (t, *J* = 7 Hz, 3H); HRMS (MALDI-TOF) *m/z* 247.1572 ([M + H]$^+$, $C_{12}H_{22}O_5H$ requires 247.1545).



122" **122'"**

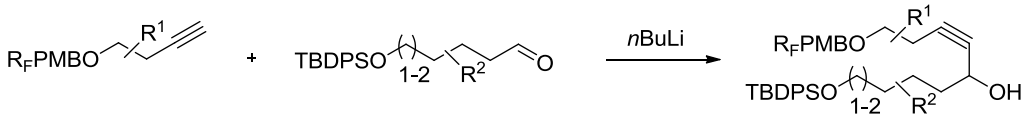
TBDPS-protected alcohol 122'''. To a stirred solution of alcohol **122''** (1.0 equiv, 10.5 g, 42.6 mmol) in CH_2Cl_2 (170 mL) at 0 °C was added imidazole (3.9 equiv, 11.3 g, 165.4 mmol) and *tert*-butyldiphenylchlorosilane (2.2 equiv, 22.1 mL, 85.2 mmol). After 1 h, the reaction mixture was diluted with EtOAc, washed with sat. NH_4Cl aq. solution and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 10/1) yielded protected alcohol **122'''** in 99% yield (20.4 g) as colorless oil. *Rf* = 0.78 (Petroleum ether/EtOAc 2/1), ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.66-7.23 (m, 4H), 7.44-7.35 (m, 6H), 5.90-5.80 (m, 1H), 5.12 (d, *J* = 10.8 Hz, 1H), 5.07 (d, *J* = 18.3 Hz, 1H), 4.80 (s, 2 H), 4.45-4.37 (m, 2H), 3.82-3.70 (s, 3H), 3.66-3.55 (m, 2H), 1.48 (s, 3H), 1.38 (s, 3H), 1.03-1.10 (m, 12H); HRMS (MALDI-TOF) *m/z* 485.2782 ([M + H]$^+$, $C_{28}H_{40}O_5SiH$ requires 485.2723).



122'" **111i**

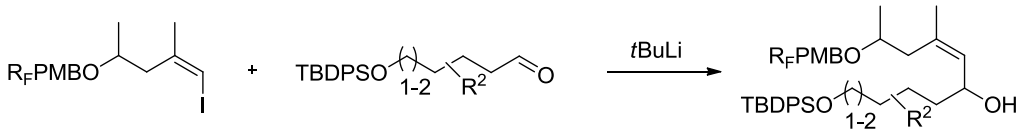
Aldehyde 169i. Ozone was flushed through a stirred solution of compound **177'''** (1.0 equiv, 20.4 g, 42.1 mmol) in CH_2Cl_2 (90 mL) at -78 °C. After removing the ozone excess, PPh_3 (2.0 equiv, 22.7 g, 84.2 mmol) was added and stirred for 1h, the solution was then warmed up to 23 °C and the solvent was removed under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 10/1) to yield aldehyde **169i** in 90% yield (18.6 g) as a colorless oil. *Rf* = 0.78 (Petroleum ether/EtOAc 4/1), ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 9.67 (d, *J* = 2.7 Hz, 1H), 7.72-7.66 (m, 4H), 7.46-7.36 (m, 6H), 4.85 (dd, *J* = 2.7 Hz, 8.0 Hz, 1H), 4.60 (d, *J* = 7 Hz, 1H), 4.47 (d, *J* = 7 Hz, 1H),4.35 (dd, *J* = 2.7 Hz, 8.1 Hz, 1H), 3.95 (m, 1 H), 3.84 (t, *J* = 8.1 Hz, 1H), 3.71 (m, 1 H), 3.53-3.45 (m, 1H), 3.42-3.34 (m, 1H), 1.60 (s, 3 H), 1.44 (s, 3H), 1.1 (s, 9H), 1.02 (t, *J* = 7 Hz, 3H).

3. Synthesis of compounds 109a-d



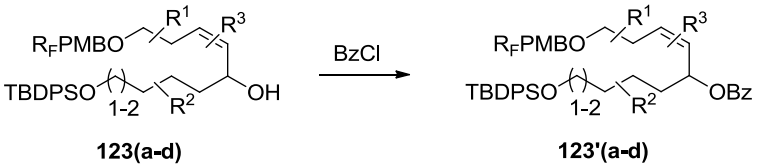
110(a-c) **111** **123(a-c)**

General procedure for the synthesis of pools 123(a-c). To a mixture of the three fluorous-tagged alkynes **110a-c** 1/1/1 (1.0 equiv) in THF at -78 °C was added a 1.6 M solution of *n*BuLi in hexane (1.1 equiv). The resulting mixture was stirred for 10 min. Then, a solution of the corresponding aldehyde **111** (1.2 equiv) in THF precooled to -78 °C was added. The resulting mixture was stirred at -78 °C for 30-60 min. The reaction was then quenched with sat. NH_4Cl aq. solution, diluted with EtOAc, washed with water, brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by fluorous chromatography (loading of the compound in DMF and eluting with 70% MeOH in H_2O, then 80% MeOH in water and finally 100% MeOH) afforded the corresponding pool (**h-j**) of three compounds each **123(a-c)** as mixtures of diastereoisomers for the newly generated chiral center. Analysis of crude reaction mixture by LC/MS indicated an overall conversion of >80% however, NMR analysis of these complex mixtures was not possible.



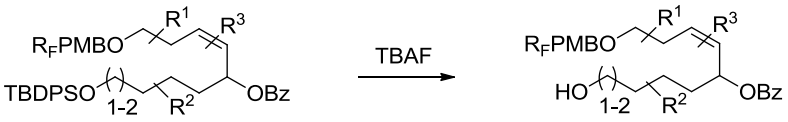
110d **111** **123(d)**

General procedure for the synthesis of alcohols 123(d). To a solution of *cis*-vinyl iodide **110d** (1.0 equiv) in Et_2O at -78°C was added a solution of *t*BuLi in pentane (2.0 equiv) dropwise over a period of 20 min and the resulted dark orange color solution was stirred for additional 20 min. Then a solution of the corresponding aldehyde **111** (1.2 equiv) in pentane was added dropwise and the resulted light orange yellowish solution was warmed slowly to 0 °C over a period of 7 h. Then, the reaction was quenched with sat. NH_4Cl aq. solution, warmed to 23 °C, extracted with EtOAc, washed with brine, dried over Na_2SO_4, and filtered. Evaporation of the solvents under reduced pressure followed by fluorous chromatography (loading of the compound in DMF and eluting with 70% MeOH in H_2O, then 80% MeOH in H_2O and finally 100% MeOH) afforded the corresponding diastereoisomeric mixtures of alcohols **123d** as light yellow oil. LC/MS analysis of the reaction mixture indicated a greater than 80% conversion.



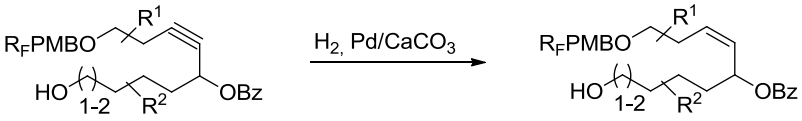
123(a-d) **123'(a-d)**

General procedure for the benzoate protection of alcohols 123(a-d). Synthesis of pools 123'(a-d). To a solution of the corresponding mixture of alcohols **123a-d** (1.0 equiv) in CH_2Cl_2 were added sequentially pyridine (2.5 equiv) and BzCl (2.5 equiv) at 0 °C. The mixture was stirred for 4 h at the same temperature. Then, the reaction was diluted with H_2O, extracted with CH_2Cl_2, washed with sat. NH_4Cl aq. solution, brine, dried over Na_2SO_4 and filtered. Evaporation of the solvents under reduced pressure followed by fluorous chromatography (loading of the compound in DMF and eluting with 70% MeOH in H_2O, then 80% MeOH in H_2O and finally 100% MeOH) afforded the corresponding pool of **123'a-d** in quantitative yield according to LC/MS analysis and >90% recovered yield.



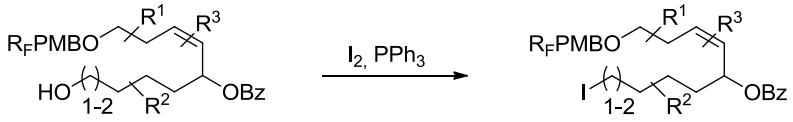
123'(a-d) **123''(a-d)**

General procedure for the TBDPS deprotection of mixtures 123'(a-d). Synthesis of pools 123''(a-d). To a solution of the corresponding pool **123'(a-d)** (1.0 equiv) in THF was added a 1.0 M solution of TBAF in THF (1.5 equiv) at 23 °C. The resulted mixture was stirred for 3 h at the same temperature. Then the reaction was quenched with sat. NH_4Cl aq. solution, extracted with EtOAc, dried over Na_2SO_4 and filtered. Evaporation of the solvent under reduced pressure followed by fluorous chromatography (loading of the compound in DMF and eluting with 70% MeOH in H_2O, then 80% MeOH in H_2O and finally 100% MeOH) afforded the corresponding pools **123''a-d** in 86-94% yields. LC/MS analysis of the reaction showed complete conversion for each pool.



123''(a-c) **123'''(a-c)**

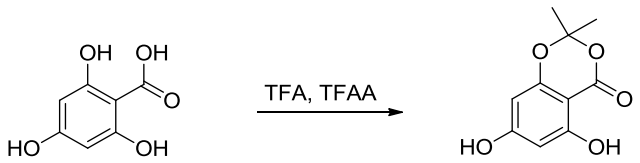
General procedure for the Lindlar reduction. Synthesis of pools 123'''(a-c). A solution of the corresponding pool **123''(a-c)** (1.0 equiv) in MeOH at 23 °C was treated with Lindlar catalyst (1.7 equiv) and a hydrogen atmosphere was introduced. The reaction was allowed to proceed for 45 min at 23 °C. After filtration on silica and Celite, the evaporation of the solvents under reduced pressure afforded the corresponding pools **123'''(a-c)** in 90-96% yields.



123'''(a-c), 123''d **109(a-d)**

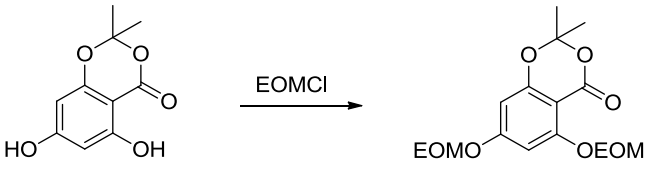
General procedure for the preparation of fragments 109(a-d). To a solution of the corresponding pool **123'''a-c** or **123''d** (1.0 equiv) in THF were added PPh_3 (1.5 equiv) and imidazole (2.5 equiv). The resulting mixture was cooled down to 0 °C, followed by the addition of I_2 (1.5 equiv). After 30 min at 0 °C, the reaction was treated with sat. NH_4Cl aq. solution and Na_2SO_3 aq. solution, diluted with EtOAc, washed with water and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by fluorous filtration (loading of the compound in DMF and eluting with 70% MeOH in H_2O, then 80% MeOH in H_2O and finally 100% MeOH) afforded the corresponding mixture of fragments **109(a-d)** in 70-93% yields. LC/MS analysis indicated greater than 95% conversion for all of these reactions.

4. Synthesis of fragments 108e-g



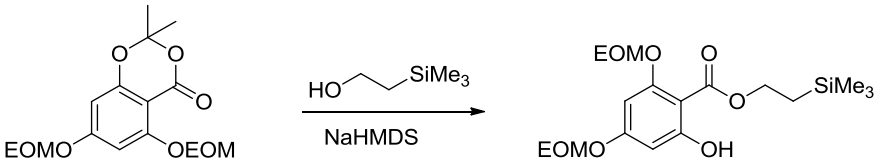
124 **124'**

Benzodioxinone 124'. To a suspension of **124** (1.0 equiv, 7.5 g, 40.0 mmol) in trifluoroacetic acid (60 mL) at 0 °C were added trifluoroacetic anhydride (37.5 mL) and acetone (7.5 mL). The mixture was warmed slowly to 23 °C and stirred for 12 h. After concentration under reduced pressure, the mixture was diluted with EtOAc, extracted with a sat. $NaHCO_3$ aq. solution, water, brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 1/1) yielded benzodioxinone **124'** in 54% yield (4.6 g). *Rf* = 0.56 (Petroleum ether/EtOAc 1/1); ^1H NMR ($(CD_3)_2CO$, 400 MHz, 25 °C) δ 10.44 (s, 1H), 9.73 (s, 1H), 6.06 (s, 1H), 5.99 (s, 1H), 1.71 (s, 6H).



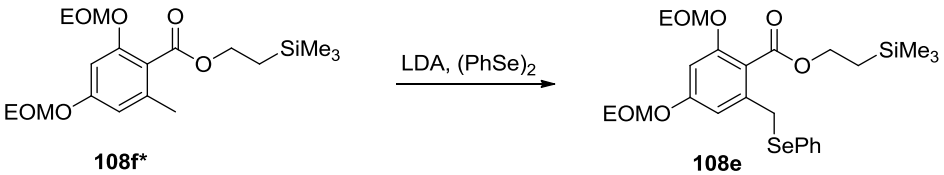
124' **125**

EOM-bisprotected alcohol 125. To a solution of alcohol **124'** (1.0 equiv, 4.6 g, 21.7 mmol) in CH_2Cl_2 (217 mL) at 23 °C were added sequentially TBAI (cat), *i*Pr_2NEt (4.0 equiv, 14.4 mL, 86.8 mmol) and EOMCl (4.0 equiv, 8.5 mL, 86.8 mmol). The resulting mixture was stirred 12 h at 23 °C. The mixture was diluted with EtOAc, washed with sat. NH_4Cl aq. solution, water, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 3/1) afforded EOM-protected alcohol **125** in quantitative yield (7.6 g). *Rf* = 0.56 (Petroleum ether/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.55 (s, 1H), 6.29 (s, 1H), 5.33 (s, 2H), 5.22 (s, 2H), 3.72 (2 x q, *J* = 7.2 Hz, 4H), 1.69 (s, 6H), 1.27-1.20 (m, 6H).



125 **108g**

Protected carboxylic acid 108g. To a solution of benzodioxinone **125** (1.0 equiv, 3.5 g, 10.8 mmol) in THF (41 mL) at 0 °C were added 2-(trimethylsilyl)ethanol (4.2 equiv, 6.7 mL, 46.0 mmol) and a solution of NaHMDS in THF (4.4 equiv, 48.0 mL, 47.7 mmol). The mixture was stirred for 12 h, quenched with a sat. NH_4Cl aq. solution, extracted with water and EtOAc, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 1/1) afforded phenol **108g** in 69% yield (2.8 g). *Rf* = 0.76 (Petroleum ether/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 11.88 (s, 1H), 6.32 (d, *J* = 2.4 Hz, 1H), 6.27 (d, *J* = 2.4 Hz, 1H), 5.21 (s, 2H), 5.20 (s, 2H), 4.43-4.38 (m, 2H), 3.76 (q, *J* = 7.3 Hz, 2H), 3.71 (q, *J* = 7.3 Hz, 2H), 1.24 (t, *J* = 6.9 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.14-1.10 (m, 2H), 0.07 (s, 9H).



108f* **108e**

Selenide 108e. Compound **108f*** (1.0 equiv, 220 mg, 630 µmol) in THF (1 mL) was cooled to -78 °C and added dropwise to a stirred solution of LDA in THF (2.0 equiv, 2.2 mL, 1.3 mmol). After 10 min, a precooled solution of $(PhSe)_2$ (0.9 equiv, 175 mg, 567 µmol) in THF (1 mL) was added dropwise. After 2 h, the reaction was quenched with sat. NH_4Cl aq. solution and extracted with EtOAc, washed with brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by flash chromatography (Petroleum ether to Petroleum ether/EtOAc 3/1) provided selenide **108e** in 75%

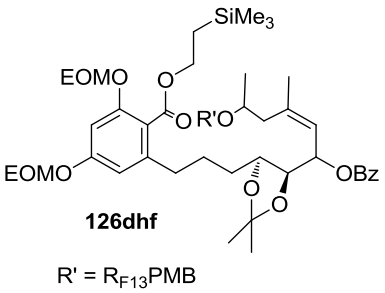
yield (255 mg). *Rf* = 0.63 (Hexane/EtOAc 5/1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.47 (m, 2H), 7.24 (m, 3H), 6.72 (d, *J* = 2.0 Hz, 1H,), 6.40 (d, *J* = 2.1 Hz, 1H), 5.19 (s, 2H), 5.08 (s, 2H), 4.38-4.33 (m, 2H), 4.11 (s, 2H), 3.72 (q, *J* = 7.2 Hz, 2H), 3.65 (q, *J* = 7.2 Hz, 2H), 1.22 (t, *J* = 6.9 Hz, 3H), 1.19 (t, *J* = 6.9 Hz, 3H), 1.11-107(m, 2H), 0.06 (s, 9H).

*From Winssinger *et al.*, *Chem. Eur. J.* **2005**, 11, 4935-4952.

5. Library synthesis

General procedure for the alkylation of 108f. Synthesis of pools 126f and demixing. To a solution of **108f** (1.2 equiv) in THF (0.3 M) cooled at -78 °C was added at once a freshly prepared solution of LDA in THF (2.4 equiv, 0.56 M). The mixture immediately turned red. The reaction was stirred 10 min at -78 °C and a solution of the corresponding precooled alkyl iodide pool **109** (1.0 equiv) in the minimum quantity possible of THF was added very slowly along the side of the flask. After stirring at the same temperature for 2 h, the reaction was quenched with sat. NH_4Cl aq. solution, diluted with EtOAc, washed with water, brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by fluorous chromatography (loading of the compound in DMF and eluting with 70% MeOH in H_2O, then 80% MeOH in H_2O and finally 100% MeOH) afforded the corresponding pools **126f** in 60% yield as estimated based on LC/MS analysis. Then, a second fluorous chromatography was performed loading the compound in DMF and eluting with an isocratic gradient (70% MeOH in H_2O) to isolate single components in 70-80% yields.

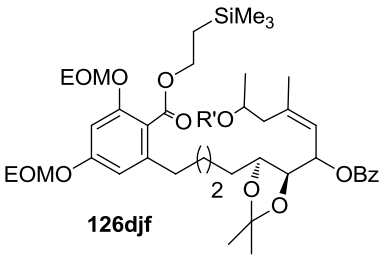
Selected examples of compounds 126f.



126dhf

R' = R_{F13}PMB

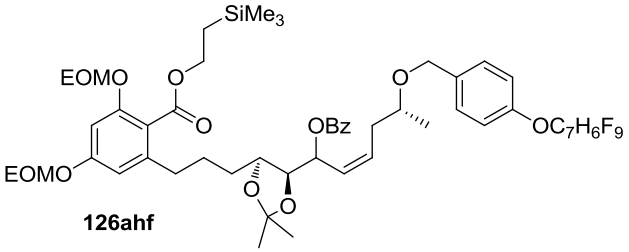
126dhf: *Rf* = 0.17 (Petroleum ether/EtOAc 4/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.02 (d, *J* = 7.1 Hz, 1H), 8.00 (d, *J* = 7.3 Hz, 1H), 7.56-7.35 (m, 3H), 7.32-7.14 (m, 2H), 6.82-6.43 (m, 4H), 5.82-5.70 (m, 1H), 5.46-5.31 (m, 1H), 5.21-5.13 (m, 4H), 4.42-4.09 (m, 6H), 4.02-3.91 (m, 1H), 3.76-3.57 (m, 6H), 3.13 (td, *J* = 14.0, 9.0 Hz, 0.6H), 2.54-2.23 (m, 5.4H), 2.16-2.02 (m, 2H), 1.86 (s, 3H), 1.65-1.54 (m, 4H), 1.48 (s, 1.5H), 1.42 (s, 0.75H), 1.40 (s, 0.75H), 1.36 (s, 3H), 1.25-1.04 (m, 11H), 0.06 (s, 6H) 0.04 (s, 3H).



126djf

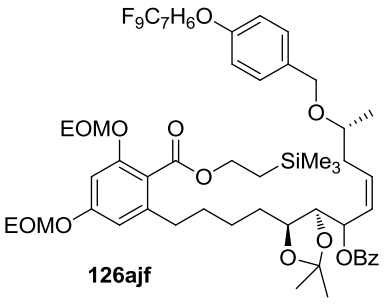
R' = R_{F13}PMB

126djf: *Rf* = 0.17 (Petroleum ether/EtOAc 4/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.04 (d, *J* = 7.1 Hz, 1H), 8.00 (d, *J* = 7.3 Hz, 1H), 7.58-7.38 (m, 3H), 7.30-7.13 (m, 2H), 6.84-6.42 (m, 4H), 5.80-5.71 (m, 1H), 5.46-5.31 (m, 1H), 5.21-5.13 (m, 4H), 4.43-4.08 (m, 6H), 4.01-3.92 (m, 1H), 3.76-3.57 (m, 6H), 3.11 (td, *J* = 14.0, 9.0 Hz, 0.6H), 2.55-2.25 (m, 5.4H), 2.16-2.02 (m, 2H), 1.86 (s, 3H), 1.66-1.53 (m, 4H), 1.49 (s, 1.5H), 1.43 (s, 0.75H), 1.41 (s, 0.75H), 1.36 (s, 3H), 1.25-1.04 (m, 13H), 0.06 (s, 6H) 0.04 (s, 3H). LC/MS *m/z* 1248.36 ([M + Na]$^+$, $C_{57}H_{73}F_{13}O_{12}SiNa$ requires 1248.23).



126ahf

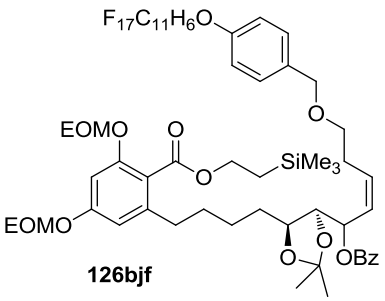
126ahf: *Rf* = 0.26 (Petroleum ether/EtOAc 4/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.04 (d, *J* = 7.5 Hz, 1.5H), 7.99 (d, *J* = 7.9 Hz, 0.5H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.56-7.52 (m, 1H), 7.45-7.40 (dd, *J* = 7.5 Hz, 2H), 7.25 (m, 2 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 6.70 (d, *J* = 2.2 Hz, 1H), 6.50 (d, *J* = 2.1 Hz, 1H), 5.85-5.72 (m, 2H), 5.65-5.53 (m, 1H), 5.17-5.15 (m, 4H), 4.50-4.40 (m, 2H), 4.37-4.32 (m, 2H), 4.26-4.16 (m, 1H), 4.12-4.00 (m, 1H), 4.00 (t, *J* = 5.9 Hz, 2H), 3.73-3.66 (m, 4H), 3.65-3.57 (m, 1H), 2.68-2.41 (m, 4H), 2.36-2.22 (m, 2H), 2.11-2.03 (m, 2H), 1.90-1.75 (m, 1H), 1.68-1.57 (m, 1H), 1.52 (s, 2H), 1.40 (s, 1H), 1.34 (s, 3H), 1.26-1.69 (m, 11H), 1.10-1.05 (m, 2H), 0.06 (s, 6H), 0.06 (s, 3H); LC/MS *m/z* 1119.33 ([M + Na]$^+$, for $C_{53}H_{69}F_9O_{12}SiNa$ requires 1119.44).



126ajf

126ajf: *Rf* = 0.41 (Petroleum ether/EtOAc 4/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.08-7.99 (m, 2H), 7.53 (t, *J* = 6.8 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.31-7.22 (m, 2H), 6.85-6.81 (m, 2H), 6.71-6.69 (m, 1H), 6.51 (d, *J* = 2.0 Hz, 1H), 5.83-5.70 (m, 2H), 5.65-5.49 (m, 1H), 5.18-5.15 (m, 4H), 4.46-4.31 (m, 4H),

4.21-4.18 (m, 1H), 4.13-3.95 (m, 3H), 3.73-3.67 (m, 4H), 3.47 (q, *J* = 6.8 Hz, 1H), 2.68-2.56 (m, 2H), 2.54-2.41 (m, 2H), 2.37-2.23 (m, 4H), 2.14-2.03 (m, 2H), 1.60-1.32 (m, 10H), 1.28-1.16 (m, 9H), 1.09-1.05 (m, 2H), 0.05 (s, 9H) ; LC/MS *m/z* 1133.37 ([M + Na]$^+$, for $C_{54}H_{71}F_9O_{12}SiNa$ requires 1133.45).

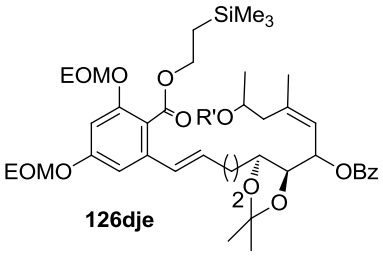


126bjf

126bjf: *Rf* = 0.41 (Petroleum ether/EtOAc 4/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.10-7.95 (m, 2H), 7.53 (m, 1H), 7.37-7.50 (m, 2H), 7.32-7.18 (m, 2H), 6.85-6.75 (m, 2H), 6.71 (d, J = 1.6 Hz, 0.6H), 6.69 (d, J = 2.1 Hz, 0.4H), 6.50 (d, J = 2.1 Hz, 0.6H), 6.42 (d, *J* = 2.1 Hz, 0.4H), 5.85-5.65 (m, 2H), 5.65-5.50 (m, 1H), 5.17 (m, 4H), 4.44-4.31 (m, 4H), 4.25-4.12 (m, 1H), 4.11-3.95 (m, 3H), 3.80-3.62 (m, 4H), 3.65-3.40 (m, 2H), 2.83-2.43 (m, 4H), 2.42-2.25 (m, 3H), 2.20-2.05 (m, 3H), 1.70-1.30 (m, 10H), 1.24-1.17 (m, 6H), 1.12-1.00 (m, 2H), 0.06 (s, 9H). LC/MS *m/z* 1319.27 ([M + Na]$^+$, for $C_{57}H_{69}F_{17}O_{12}SiNa$ requires 1319.42).

General procedure for alkylation of 108e followed by selenide oxidation/*syn*-elimination. Synthesis of pools 126e and demixing. To a solution of seleno-ether **108e** (1.1 equiv) in THF/HMPA 10/1 (0.15 M) cooled at -78 °C was added at once a freshly prepared solution of LDA in THF (2.0 equiv, 0.56 M) at -78 °C. The mixture immediately turned red. The reaction was stirred 10 min at -78 °C and a solution of precooled corresponding alkyl iodide mixture **109** (1.0 equiv) in THF (0.5 M) was added very slowly along the side of the flask. After stirring at the same temperature for 30 min, the reaction was quenched with a sat. NH_4Cl aq. solution, diluted with EtOAc, washed with water, brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by fluorous chromatography (loading of the compound in DMF and eluting with 70% MeOH in H_2O, then 80% MeOH in H_2O and finally 100% MeOH) afforded the corresponding seleno-ether pool. To a stirred solution of previously prepared mixture (1.0 equiv) in THF at 23°C was added a 30% H_2O_2 aq. solution (2.0 equiv). After 2 h, the reaction was quenched by adding 100 mL of 2.5% $NaHCO_3$ aq. solution followed by 10 mL of 5.0 % $Na_2S_2O_3$ aq., extracted with EtOAc, washed with brine and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by fluorous chromatography (loading of the compound in DMF and eluting with 70% MeOH in H_2O, then 80% MeOH in H_2O and finally 100% MeOH) afforded the corresponding pools **126e** in 64 to 85% yield. A second fluorous chromatography was performed, loading the mixture in DMF and eluting with an isocratic gradient (70% MeOH in H_2O) to isolate single compounds in 70-80% yield.

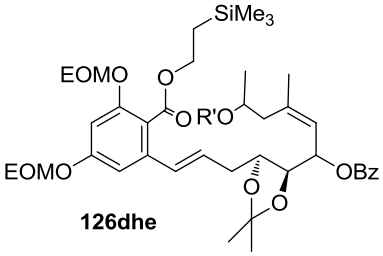
Selected examples of compounds 126e.



126dje

R' = R_{F13}PMB

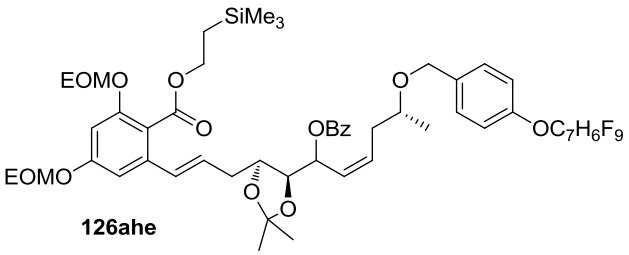
126dje: *Rf* = 0.31 (Petroleum ether/EtOAc 4/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.09 (d, *J* = 8.1 Hz, 1H), 8.05 (d, *J* = 8.3 Hz, 1H), 7.56-7.42 (m, 3H), 7.29-7.16 (m, 2H), 6.85-6.73 (m, 4H), 6.43 (d, *J* = 15.8 Hz, 0.5H), 6.39 (d, *J* = 15.9 Hz, 0.5H), 6.21-6.07 (m, 1H), 5.87-5.77 (m, 1H), 5.45-5.36 (m, 1H), 5.24 (s, 1H), 5.22 (s, 3H), 4.49-4.37 (m, 4H), 4.35-4.18 (m, 2H), 4.04-3.95 (m, 2H), 3.76-3.69 (m, 5H), 2.48-2.26 (m, 5H), 2.18-2.10 (m, 3H), 1.91 (s, 3H), 1.84-1.60 (m, 2H), 1.55 (s, 1.5H), 1.47 (s, 1.5H), 1.40 (s, 1.5H), 1.39 (s, 1H), 1.38 (s, 0.5H), 1.24-1.10 (m, 11H), 0.10 (s, 4H) 0.09 (s, 5H); LC/MS *m/z* 1245.75 ([M + Na]$^+$, for $C_{57}H_{71}F_{13}O_{12}SiNa$ requires 1245.98).



126dhe

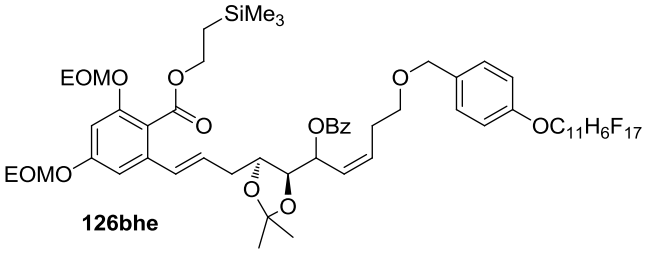
R' = R_{F13}PMB

126dhe: *Rf* = 0.32 (Petroleum ether/EtOAc 4/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.08-8.00 (m, 2H), 7.56-7.51 (m, 1H), 7.45-7.38 (m, 2H), 7.25-7.15 (m, 2H), 6.84-6.72 (m, 4H), 6.47-6.34 (m, 1H), 6.23-6.16 (m, 1H), 5.86-5.77 (m, 1H), 5.40 (d, *J* = 9.9 Hz, 0.5H), 5.37 (d, *J* = 9.7 Hz, 0.5H), 5.21 (s, 0.5H), 5.20 (s, 0.5H), 5.19 (s, 2H), 5.18 (s, 1H), 4.47-4.21 (m, 6H), 4.04-3.95 (m, 2H), 3.76-3.68 (m, 5H), 2.61-2.33 (m, 5H), 2.16-2.09 (m, 3H), 1.89 (d, *J* = 1.2 Hz, 1.5H), 1.89-1.88 (m, 1.5 H), 1.54 (s, 1.5H), 1.44 (s, 1.5H), 1.37 (s, 1.5H), 1.36 (s, 0.75H), 1.35 (s, 0.75H) 1.27-1.07 (m, 11H), 0.06 (s, 6H), 0.05 (s, 3H).



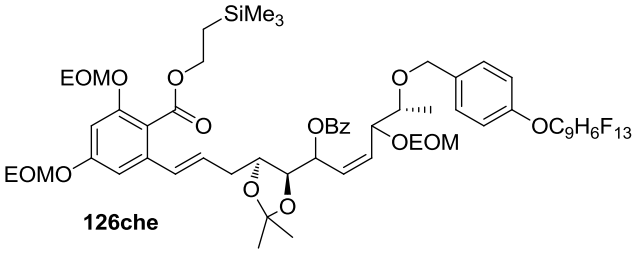
126ahe

126ahe: *Rf* = 0.51 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.07 (d, *J* = 7.2 Hz, 1.3H), 8.02 (d, *J* = 8.0 Hz, 0.7H), 7.59-7.51 (m, 1H), 7.48-7.39 (m, 2H), 7.30-7.20 (m, 2H), 6.89-6.80 (m, 3H), 6.80-6.73 (m, 1H), 6.49-6.38 (m, 1H), 6.27-6.15 (m, 1H), 5.90-5.75 (m, 2H), 5.70-5.54 (m, 1H), 5.23-5.17 (m, 4H), 4.52-4.28 (m, 5H), 4.28-4.22 (m, 0.5H), 4.22-4.15 (m, 0.5H), 4.05-3.95 (m, 2H), 3.78-3.67 (m, 4H), 3.67-3.59 (m, 1H), 2.69-2.58 (m, 1H), 2.58-2.43 (m, 2H), 2.42-2.20 (m, 3H), 2.14-2.00 (m, 2H), 1.58 (s, 1.8H), 1.44 (s, 1.2H), 1.37 (s, 1.8H), 1.35 (s, 1.2H), 1.30-1.14 (m, 9H), 1.13-1.02 (m, 2H), 0.06 (s, 6H), 0.05 (s, 3H); LC/MS *m/z* 1117.42 ([M + Na]$^+$, for $C_{53}H_{67}F_9O_{12}SiNa$ requires 1117.42).



126bhe

126bhe: *Rf* = 0.51 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.07 (d, *J* = 7.2 Hz, 1.4H), 8.02 (d, *J* = 7.2 Hz, 0.6H), 7.58-7.51 (m, 1H), 7.48-7.39 (m, 2H), 7.30-7.19 (m, 2H), 6.90-6.80 (m, 3H), 6.80-6.72 (m, 1H), 6.48-6.37 (m, 1H), 6.27-6.14 (m, 1H), 5.87-5.73 (m, 2H), 5.58-5.53 (m, 1H), 5.21 (s, 1.2H), 5.19 (s, 2.8H), 4.47-4.30 (m, 4.6H), 4.28-4.21 (m, 0.7H), 4.16-4.09 (m, 0.7H), 4.05-3.94 (m, 2H), 3.78-3.66 (m, 4H), 3.62-3.40 (m, 2H), 2.79-2.68 (m, 0.5H), 2.68-2.58 (m, 1.5H), 2.56-2.43 (m, 1H), 2.42-2.20 (m, 3H), 2.13-2.00 (m, 2H), 1.57 (s, 2H), 1.44 (s, 1H), 1.36 (s, 3H), 1.24-1.18 (m, 6H), 1.12-1.04 (m, 2H), 0.08-0.02 (m, 9H); LC/MS *m/z* 1303.29 ([M + Na]$^+$, for $C_{56}H_{65}F_{17}O_{12}SiNa$ requires 1303.39).



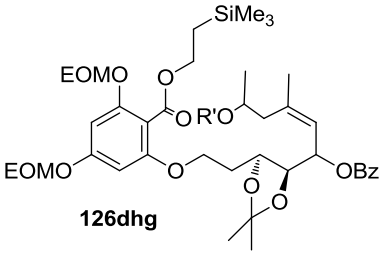
126che

126che: *Rf* = 0.51 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.10-7.96 (m, 2H), 7.59-7.50 (m, 1H), 7.48-7.38 (m, 2H), 7.32-7.28 (m, 2H), 6.88-6.78 (m, 3H), 6.78-6.72 (m, 1H), 6.48-6.38 (m, 1H), 6.28-6.16 (m, 0.6H), 6.12-6.02 (m, 0.4H), 5.99-5.90 (m, 1H), 5.84-5.74 (m, 1H), 5.69-5.59 (m, 0.8H), 5.54-5.58 (m, 0.2H), 5.20 (s, 2H), 5.18 (s, 2H), 4.90-4.76 (m, 1.2H), 4.76-4.68 (m, 1.5H),

4.68-4.61 (m, 0.3H), 4.60-4.50 (m, 2H), 4.48-4.41 (m, 0.6H), 4.40-4.28 (m, 3.4H), 4.04-3.97 (m, 1.3H), 3.97-3.94 (0.7H), 3.77-3.67 (m, 6H), 3.57-3.44 (m, 1H), 2.58-2.44 (m, 1H), 2.42-2.20 (m, 2.5H), 2.14-1.98 (m, 2H), 1.96-1.86 (m, 0.5H), 1.66-1.58 (m, 2.5H), 1.46 (s, 0.5H), 1.39 (s, 1.8H), 1.36 (s, 1.2H), 1.30-1.17 (m, 12H), 1.10-1.03 (m, 2H), 0.8-0.1 (m, 9H); LC/MS *m/z* 1291.32 ([M + Na]$^+$, for $C_{58}H_{73}F_{13}O_{14}SiNa$ requires 1291.45).

General procedure for alkylation of 108g. Synthesis of pools 126g and demixing. To a solution of phenol **108g** (1.1 equiv) in DMF (0.2 M) was added a solution of corresponding alkyl iodide mixture **109** (1.0 equiv) in DMF (0.2 M) at 23 °C. The mixture was treated with K_2CO_3 (2.0 equiv) and stirred for 12 h at 100 °C. The reaction was then quenched with a sat. NH_4Cl aq. solution, diluted with EtOAc, washed with water, brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by fluorous chromatography (loading of the compound in DMF and eluting with 70% MeOH in H_2O, then 80% MeOH in H_2O and finally 100% MeOH) afforded the corresponding pools **126g** in 94-100% yield. A second fluorous chromatography was performed to demix each pool loading the mixture in DMF and eluting with an isocratic gradient (70% MeOH in H_2O) to isolate single compounds in 70-80% yield.

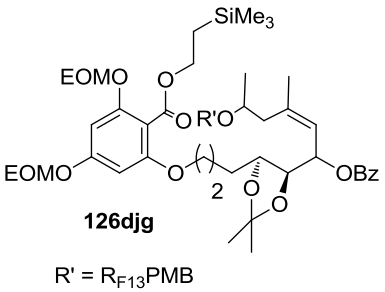
Selected examples of compounds 126g.



126dhg

R' = R_{F13}PMB

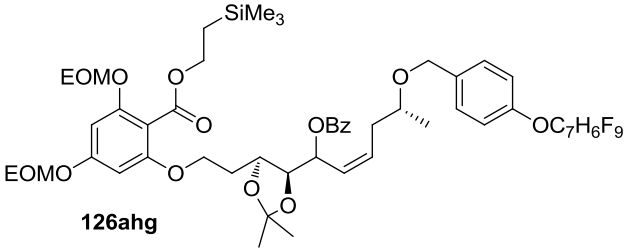
126dhg: *Rf* = 0.33 (Petroleum ether/EtOAc 5/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05 (d, *J* = 7.5 Hz, 1H), 7.99 (d, *J* = 7.6 Hz, 1H), 7.55-7.51 (m, 1H), 7.44-7.39 (m, 2H), 7.23 (d, *J* = 8.6 Hz, 0.5H), 7.20 (d, *J* = 8.9 Hz, 0.5H), 7.17 (d, *J* = 8.6 Hz, 0.5H), 7.14 (d, *J* = 8.6 Hz, 0.5H), 6.80 (d, *J* = 8.4 Hz, 0.5H), 6.78 (d, *J* = 8.4 Hz, 0.5H), 6.73 (d, *J* = 8.6 Hz, 0.5H), 6.70 (d, *J* = 8.6 Hz, 0.5H), 6.49 (d, *J* = 1.9 Hz, 0.5H), 6.46 (d, *J* = 1.9 Hz, 0.5H), 6.29 (d, *J* = 1.9 Hz, 0.25H), 6.27 (d, *J* = 1.9 Hz, 0.25H), 6.24 (d, *J* = 1.9 Hz, 0.5H), 5.83-5.72 (m, 1H), 5.37 (d, *J* = 10.5 Hz, 0.5H), 5.34 (d, *J* = 10.5 Hz, 0.5H), 5.18 (s, 1H), 5.17 (s, 1H), 5.16 (s, 1H), 5.14 (s, 1H), 4.53-4.28 (m, 6H), 4.09-3.93 (m, 4H), 3.73-3.65 (m, 5H), 2.45-2.23 (m, 3H), 2.15-2.03 (m, 3H), 2.01-1.91 (m, 2H), 1.89 (s, 1H), 1.88 (s, 1H), 1.87 (s, 1H), 1.51 (s, 1.5H), 1.43 (s, 0.5H), 1.42 (s, 0.5H), 1.41 (s, 0.5H), 1.36 (s, 1.5H), 1.35 (s, 0.75H), 1.34 (s, 0.75H), 1.27-1.05 (m, 11H), 0.06 (s, 3H) 0.05 (s, 3H), 0.04 (s, 3H) ; LC/MS *m/z* 1236.23 ([M + Na]$^+$, for $C_{55}H_{69}F_{13}O_{13}SiNa$ requires 1236.19).



126djg

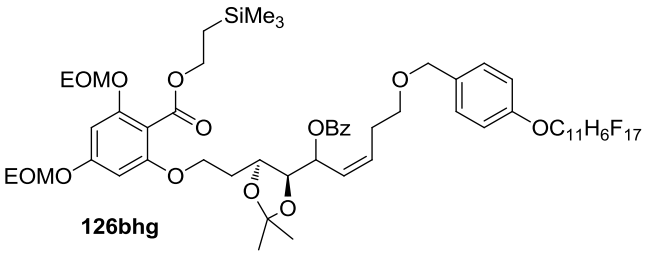
R' = R_{F13}PMB

126djg: *Rf* = 0.32 (Petroleum ether/EtOAc 5/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.02 (d, *J* = 7.8 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.48-7.42 (m, 1H), 7.37-7.29 (m, 2H), 7.20-7.09 (m, 2H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.67 (t, *J* = 9.0 Hz, 1H), 6.48 (bs, 0.5H), 6.45 (d, *J* = 1.8 Hz, 0.5H), 6.25 (d, *J* = 1.9 Hz, 0.5H), 6.16 (bs, 0.5H), 5.81-5.73 (m, 1H), 5.40-5.32 (m, 1H), 5.13 (s, 3H), 5.11 (s, 1H), 4.41-4.23 (m, 6H), 3.93-3.77 (m, 4H), 3.68-3.61 (m, 5H), 2.40-2.19 (m, 3H), 2.11-1.97 (m, 3H), 1.93-1.63 (m, 4H), 1.85 (d, *J* = 2.5 Hz, 3H), 1.47 (s, 0.75H), 1.46 (s, 0.75H), 1.39 (s, 1.5H), 1.33 (s, 1.5H), 1.31 (s, 1H), 1.30 (s, 0.5H), 1.20-1.03 (m, 11H), 0.03 (s, 4H) 0.02 (s, 2H), 0.01 (s, 3H). LC/MS *m/z* 1249.83 ([M + Na]$^+$, for $C_{56}H_{71}F_{13}O_{13}SiNa$ requires 1250.22).



126ahg

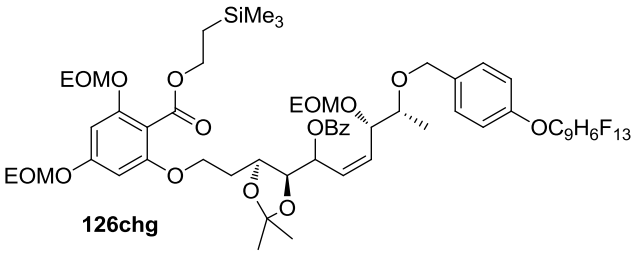
126ahg: *Rf* = 0.48 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.06 (d, *J* = 7.2 Hz, 1H), 8.00 (d, *J* = 7.2 Hz, 1H), 7.56-7.52 (m, 1H), 7.44-7.41 (m, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.82 (dd, *J* = 8.4, 1.6 Hz, 2H), 6.50 (d, *J* = 1.6 Hz, 0.6H), 6.47 (d, *J* = 1.6 Hz, 0.4H), 6.30 (d, *J* = 2.0 Hz, 0.6H), 6.26 (d, *J* = 2.0 Hz, 0.4H), 5.87-5.76 (m, 2H), 5.65-5.54 (m, 1H), 5.18-5.14 (m, 4H), 4.51-4.26 (m, 6H), 4.09-4.04 (m, 2H), 4.01-3.95 (m, 2H), 3.73-3.62 (m, 5H), 2.68-2.60 (m, 1H), 2.52-2.47 (m, 1H), 2.37-2.21 (m, 2H), 2.08-2.01 (m, 2H), 2.00-1.88 (m, 2H), 1.54 (s, 1.5H), 1.42 (s, 1.5H), 1.36 (s, 1.5H), 1.35 (s, 1.5H), 1.26-1.17 (m, 9H), 1.10-1.05 (m, 2H), 0.05 (s x 2, 9H); LC/MS *m/z* 1121.38 ([M + Na]$^+$, for $C_{52}H_{67}F_9O_{13}SiNa$ requires 1121.41).



126bhg

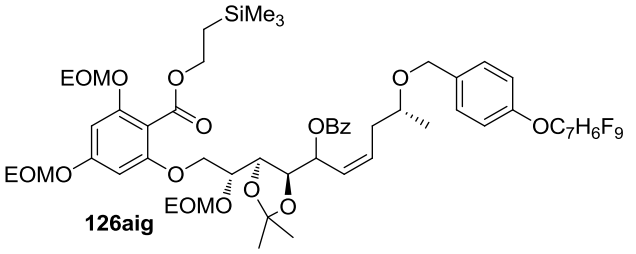
126bhg: *Rf* = 0.48 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.06 (d, *J* = 7.2 Hz, 1H), 7.99 (d, *J* = 7.2 Hz, 1H), 7.56-7.52 (m, 1H), 7.45-7.41 (m, 2H), 7.27-7.23 (m, 2H), 6.85 (d, *J* = 8.3 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 6.50 (d, *J* = 1.6 Hz, 1H), 6.47 (d, *J* = 1.6 Hz, 1H), 6.29 (d, *J* = 1.6 Hz, 1H),

6.26 (d, *J* = 1.6 Hz, 1H), 5.84-5.74 (m, 2H), 5.53-5.64 (m, 1H), 5.18-5.14 (m, 4H), 4.46-4.26 (m, 6H), 4.08-3.97 (m, 4H), 3.73-3.65 (m, 4H), 3.59-3.48 (m, 2H), 2.77-2.55 (m, 2H), 2.35-2.25 (m, 2H), 2.08-1.92 (m, 4H), 1.53 (s, 2H), 1.42 (s, 1H), 1.36 (s, 3H), 1.23-1.18 (m, 6H), 1.10-1.06 (m, 2H), 0.06 (s, 9H) ; LC/MS *m/z* 1307.25 ([M + Na]$^+$, for $C_{55}H_{65}F_{17}O_{13}SiNa$ requires 1307.38).



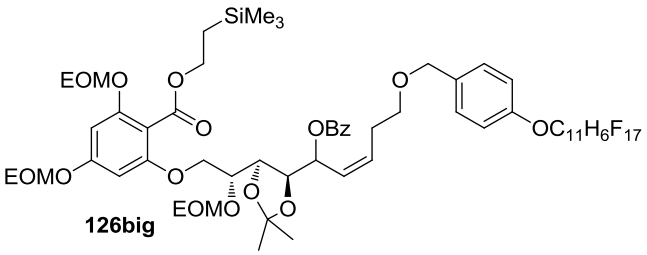
126chg

126chg: *Rf* = 0.48 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.09-7.98 (m, 2H), 7.59-7.53 (m, 1H), 7.47-7.42 (m, 2H), 7.32-7.23 (m, 2H), 6.90-6.77 (m, 2H), 6.53-6.48 (m, 1H), 6.33-6.29 (m, 1H), 6.02-5.91 (m, 1H), 5.85-5.78 (m, 1H), 5.72-5.65 (m, 1H), 5.28-5.17 (m, 4H), 4.88-4.84 (m, 1H), 4.76-4.65 (m, 2H), 4.62-4.53 (m, 2H), 4.48-4.32 (m, 3H), 4.13-4.07 (m, 2H), 4.02 (t, *J* = 5.6 Hz, 2H), 3.96-3.85 (m, 1H), 3.80-3.68 (m, 6H), 3.62-3.48 (m, 1H), 2.33-2.22 (m, 2H), 2.13-1.96 (m, 4H), 1.65-1.35 (m, 6H), 1.29-1.02 (m, 14H), 0.07-0.02 (m, 9H). LC/MS *m/z* 1295.35 ([M + Na]$^+$, for $C_{57}H_{73}F_{13}O_{15}SiNa$ requires 1295.44).



126aig

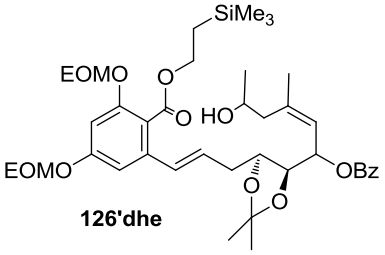
126aig: *Rf* = 0.39 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.06 (d, *J* = 7.5 Hz, 0.5H), 7.92 (d, *J* = 7.5 Hz, 1.5H), 7.50 (t, J = 8.6 Hz, 1H), 7.43-7.36 (m, 2H), 7.30-7.20 (m, 2H), 6.87-6.78 (m, 2H), 6.51 (d, *J* = 1.6 Hz, 0.3H), 6.39 (d, *J* = 1.6 Hz, 0.7H), 6.28 (d, *J* = 1.6 Hz, 0.3H), 6.24 (d, *J* = 1.6 Hz, 0.7H), 5.98-5.91 (m, 1H), 5.87-5.75 (m, 1H), 5.70-5.58 (m, 0.5H), 5.53-5.46 (m, 0.5H), 5.19-5.10 (m, 4H), 4.88-4.81 (m, 1H), 4.80-4.73 (m, 1H), 4.54-4.4.49 (m, 1H), 4.47-3.99 (m, 9H), 3.92-3.82 (m, 1H), 3.71-3.46 (m, 7H), 2.68-2.50 (m, 1.5H), 2.41-2.23 (m, 2.5H), 2.12-2.03 (m, 2H), 1.59 (s, 1H), 1.48 (s, 2H), 1.41 (s, 1H), 1.38 (s, 2H), 1.26-1.14 (m, 12H), 1.13-1.04 (m, 2H), 0.05 (s, 9H). LC/MS *m/z* 1195.43 ([M + Na]$^+$, for $C_{55}H_{73}F_9O_{15}SiNa$ requires 1195.45).



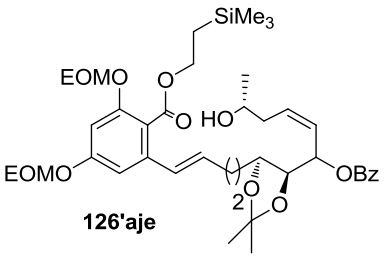
126big: *Rf* = 0.39 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.10-7.80 (m x 2, 2H), 7.55-7.45 (m, 1H), 7.44-7.33 (m, 2H), 7.28-7.14 (m x 2, 2H), 6.86-6.74 (m, 2H), 6.52-6.34 (m x 2, 1H), 6.33-6.18 (m x 2, 1H), 5.97-5.35 (m x 4, 3H), 5.28-5.04 (m, 4H), 4.86-4.65 (m, 2H), 4.56-4.14 (m, 7H), 4.13-3.94 (m, 3H), 3.92-3.78 (m, 1H), 3.76-3.32 (m, 8H), 2.69-2.42 (m, 1H), 2.40-2.20 (m, 2H), 2.12-2.01 (m, 2H), 2.01-1.71 (m, 1H), 1.52 (s, 1.5H), 1.47 (s, 1.5H), 1.40 (s, 2H), 1.38 (s, 1H), 1.22-1.12 (m, 8H), 1.12-0.98 (m, 3H), 0.03 (s, 9H); LC/MS *m/z* 1381.34 ([M + Na]$^+$, for $C_{58}H_{71}F_{17}O_{15}SiNa$ requires 1381.42).

General procedure for PMB deprotection of compounds 126. Synthesis of alcohols 126'. To a solution of PMB protected compounds **126** (1.0 equiv) in CH_2Cl_2/ H_2O 2/1 (0.3 M) at 23 °C was added DDQ (1.2 equiv). The reaction mixture was stirred for 2 h, quenched with sat. NH_4Cl aq. solution, extracted with water and CH_2Cl_2, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 3/1) afforded the corresponding alcohols **126'** in 85-96% yields.

Selected examples of compounds 126'.

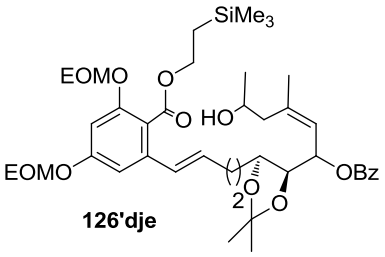


126'dhe: *Rf* = 0.20 (Petroleum ether/EtOAc 4/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.05-7.96 (m, 2H), 7.53-7.48 (m, 1H), 7.42-7.36 (m, 2H), 6.82-6.72 (m, 2H), 6.43 (d, *J* = 15.8 Hz, 0.7H), 6.39 (d, *J* = 15.3 Hz, 0.3H), 6.26-6.13 (m, 1H), 5.78-5.63 (m, 1H), 5.39-5.29 (m, 1H), 5.18 (s, 1H), 5.17 (s, 2H), 5.16 (s, 0.5H), 5.15 (s, 0.5H), 4.42-4.20 (m, 4H), 3.95-3.86 (m, 1H), 3.71-3.64 (m, 4H), 2.58-2.38 (m, 2H), 2.24-2.05 (m, 2H), 1.91 (s, 0.5H), 1.89 (s, 1.5H), 1.87 (s, 1H), 1.54 (s, 1H), 1.53 (s, 1H), 1.44 (s, 0.5H), 1.42 (s, 0.5H), 1.37 (s, 1H), 1.35 (s, 1H), 1.34 (s, 0.5H), 1.33 (s, 0.5H), 1.20-1.14 (m, 9H), 1.10-1.04 (m, 2H), 0.04 (s, 3H) 0.03 (s, 3H), 0.02 (s, 3H), OH signal is not visible; LC/MS *m/z* 743.31 ([M + H]$^+$, for $C_{40}H_{58}O_{11}SiH$ requires 743.96).



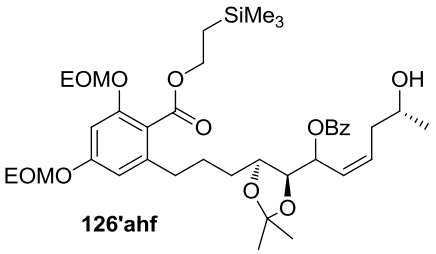
126'aje

126'aje: *Rf* = 0.21 (Petroleum ether/EtOAc 4/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ8.05 (d, *J* = 7.2 Hz, 1.5H), 7.99 (d, *J* = 7.3 Hz, 0.5H), 7.56-7.40 (m, 3H), 6.80 (d, *J* = 1.9 Hz, 0.5H), 6.74 (d, *J* = 2.1 Hz, 0.5H), 6.72 (s, 1H), 6.58-6.03 (m, 2H), 5.92-5.59 (m, 3H), 5.22-5.17 (m, 4H), 4.41-4.20 (m, 4H), 3.93-3.84 (m, 1H), 3.78-3.67 (m, 4H), 2.63-2.16 (m, 4H), 1.82-1.59 (m, 2H), 1.55 (s, 2H), 1.47 (s, 1H), 1.42 (s, 1H), 1.39 (s, 1H), 1.37 (s, 1H), 1.23-1.18 (m, 9H), 1.10-1.06 (m, 2H), 0.06 (s, 6H) 0.04 (s, 3H), OH signal is not visible; LC/MS *m/z* 743.34 ([M + H]$^+$, for $C_{40}H_{58}O_{11}SiH$ requires 743.96).



126'dje

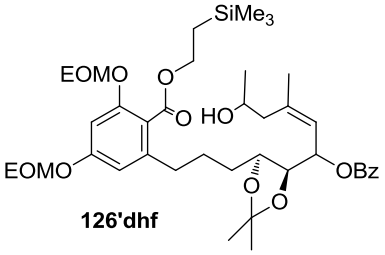
126'dje: *Rf* = 0.20 (Petroleum ether/EtOAc 4/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ8.03-7.96 (m, 2H), 7.56-7.36 (m, 3H), 6.79-6.69 (m, 2H), 6.39-6.30 (m, 1H), 6.17-6.01 (m, 1H), 5.75-5.60 (m, 1H), 5.35-5.29 (m, 1H), 5.18-5.15 (m, 4H), 4.37-4.22 (m, 4H), 3.93-3.75 (m, 1H), 3.70-3.65 (m, 4H), 2.45-2.09 (m, 4H), 1.89 (s, 1H), 1.87 (s, 1H), 1.86 (s, 1H), 1.77-1.57 (m, 2H), 1.50 (s, 1H), 1.42 (s, 1H), 1.41 (s, 0.5H), 1.39 (s, 0.5H), 1.35 (s, 1H), 1.34 (s, 1H), 1.33 (s, 1H), 1.20-1.03 (m, 11H), 0.04 (s, 5H) 0.03 (s, 4H), OH signal is not visible. LC/MS *m/z* 757.32 ([M + H]$^+$, for $C_{41}H_{60}O_{11}SiH$ requires 757.99).



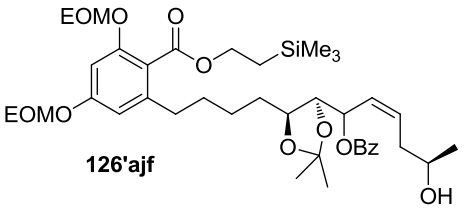
126'ahf

126'ahf: *Rf* = 0.70 (Petroleum ether/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ8.04 (d, *J* = 7.5 Hz, 1.5H), 7.98 (d, *J* = 7.0 Hz, 0.5H), 7.55 (m, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 6.70 (d, *J* = 2.2 Hz, 0.7H), 6.65 (d, *J* = 2.2 Hz, 0.3H), 6.50 (d, *J* = 2.2 Hz, 0.7H), 6.45 (d, *J* = 2.2 Hz, 0.3H), 6.51-6.45 (d x 2, 2.0 Hz, 1H), 5.86-5.56 (m, 3H), 5.18 (s, 1.5H), 5.17 (s, 1.5H), 5.16 (s, 0.5H), 5.15 (s, 0.5H), 4.38-4.33 (m, 2H), 4.24-4.21 (m, 1H), 4.36-4.14 (m x 2, 1H), 3.94-3.81 (m, 1H), 3.74-3.65 (m, 4H), 2.63-2.47 (m, 3H), 2.24-2.16 (m, 1H), 1.91-1.78 (m, 1H), 1.72-1.58 (m, 1H), 1.53 (s, 3H), 1.37 (s, 3H), 1.28-1.17 (m, 11H), 1.11-1.04 (m,

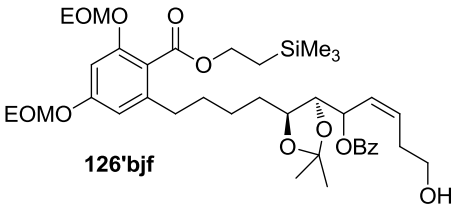
2H), 0.06 (s, 7H), 0.05 (s, 2H), OH signal is not visible; LC/MS *m/z* 753.34 ([M + Na]$^+$, $C_{39}H_{58}O_{11}SiNa$ requires 753.37).



126'dhf: *Rf* = 0.26 (Petroleum ether/EtOAc 4/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.04-7.96 (m, 2H), 7.54-7.38 (m, 3H), 6.71 (d, *J* = 1.8 Hz, 0.3H), 6.70 (d, *J* = 2.1 Hz, 0.3H), 6.67 (d, *J* = 1.9 Hz, 0.2H), 6.66 (d, *J* = 2.2 Hz, 0.2H), 6.52 (d, *J* = 2.2 Hz, 0.3H), 6.50 (d, *J* = 2.1 Hz, 0.3H), 6.44 (d, *J* = 2.1 Hz, 0.2H), 6.41 (d, *J* = 2.2 Hz, 0.2H), 5.68 (dd, *J* = 9.5, 6.8 Hz, 0.4H), 5.58 (dd, *J* = 9.3, 6.0 Hz, 0.6H), 5.37-5.25 (m, 1H), 5.23-5.12 (m, 4H), 4.37-4.06 (m, 4H), 3.94-3.75 (m, 1H), 3.72-3.66 (m, 4H), 2.69-2.42 (m, 2H), 2.28-1.98 (m, 3H), 1.89 (s, 0.5H), 1.87 (s, 0.5H), 1.82 (s, 1H), 1.77 (s, 1H), 1.68-1.53 (m, 3H), 1.49 (s, 1H), 1.48 (s, 1H), 1.41 (s, 0.5H), 1.39 (s, 0.5H), 1.35 (s, 1H), 1.34 (s, 1H), 1.33 (s, 0.5H), 1.31 (s, 0.5H), 1.22-1.12 (m, 9H), 1.11-1.05 (m, 2H), 0.06 (s, 3H) 0.05 (s, 3H), 0.04 (s, 3H), OH signal is not visible; LC/MS *m/z* 745.30 ([M + H]$^+$, $C_{40}H_{60}O_{11}SiH$ requires 745.98).

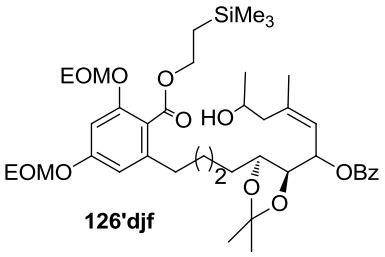


126'ajf: *Rf* = 0.60 (Petroleum ether/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.05 (d, *J* = 7.2 Hz, 1.5H), 7.99 (d, *J* = 7.2 Hz, 0.5H), 6.71 (d, *J* = 2.0 Hz, 0.7H), 6.69 (d, *J* = 2.0 Hz, 0.3H), 6.51 (d, *J* = 2.0 Hz, 0.7H), 6.43 (d, *J* = 2.0 Hz, 0.3H), 7.56-7.52 (m, 1H), 7.44-7.40 (m, 2H), 6.72-6.68 (d x 2, *J* = 2.0 Hz, 1H), 6.51-6.43 (d x 2, *J* = 2.0 Hz, 1H), 5.85-5.57 (m x 2, 3H), 5.19-5.16 (m, 4H), 4.37-4.15 (m x 2, 2H), 4.25-4.22 (m, 1H), 3.92-3.85 (m, 1H), 3.73-3.66 (m, 4H), 2.64-2.42 (m, 4H), 2.32-2.24 (m, 1H), 1.69-1.56 (m, 4H), 1.54 (s, 2H), 1.45 (s, 1H), 1.38 (s, 2H), 1.35 (s, 1H), 1.27-1.24 (m, 5H), 1.22-1.18 (m, 6H), 1.09-1.05 (m, 2H), 0.06 (s, 7H), 0.05 (s, 2H), OH signal is not visible; LC/MS *m/z* 767.36 ([M + Na]$^+$, $C_{40}H_{60}O_{11}SiNa$ requires 767.39).



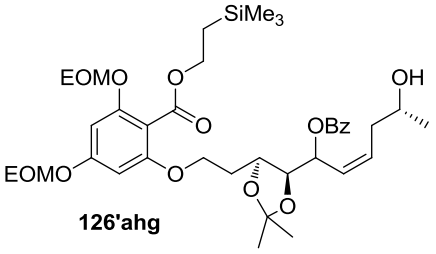
126'bjf

126'bjf: *Rf* = 0.64 (Petroleum ether/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.05 (d, *J* = 7.2 Hz, 1.5H), 7.99 (d, *J* = 7.2 Hz, 0.5H), 7.56-7.52 (m, 1H), 7.44-7.40 (m, 2H), 6.71 (d, *J* = 2.0 Hz, 0.6H), 6.69 (d, *J* = 2.0 Hz, 0.4H), 6.51 (d, *J* = 2.0 Hz, 0.6H), 6.42 (d, *J* = 2.0 Hz, 0.4H), 5.81-5.68 (m, 2H), 5.66-5.57 (m, 1H), 5.19-5.16 (m, 4H), 4.37-4.14 (m, 4H), 3.76-3.67 (m, 6H), 2.77-2.38 (m, 4H), 2.28-2.24 (m, 1H), 1.89-1.57 (m, 5H), 1.53 (s, 2H), 1.45 (s, 1H), 1.37 (s, 2H), 1.36 (s, 1H), 1.23-1.18 (m, 6H), 1.11-1.03 (m, 2H), 0.06 (s, 6H), 0.05 (s, 3H), OH signal is not visible ; LC/MS *m/z* 731.34 ($[M + H]^+$, $C_{39}H_{58}O_{11}SiH$ requires 730,37).



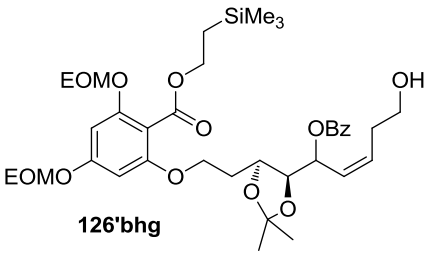
126'djf

126'djf: *Rf* = 0.26 (Petroleum ether/EtOAc 4/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.04-7.97 (m, 2H), 7.54-7.38 (m, 3H), 6.70 (d, *J* = 1.8 Hz, 1H), 6.51 (d, *J* = 1.9 Hz, 1H), 5.73-5.58 (m, 1H), 5.35 (d, *J* = 9.7 Hz, 0.8H), 5.34 (d, *J* = 9.6 Hz, 0.2H), 5.18 (s, 1H), 5.17 (s, 2H), 5.15 (s, 1H), 4.36-4.29 (m, 2H), 4.27-4.21 (m, 1H), 4.16-4.10 (m, 1H), 3.95-3.88 (m, 1H), 3.72-3.67 (m, 4H), 2.55-2.38 (m, 2H), 2.26-1.92 (m, 4H), 1.88 (s, 1H), 1.87 (s, 2H), 1.68-1.53 (m, 4H), 1.51 (s, 2H), 1.49 (s, 1H), 1.36 (s, 2H), 1.35 (s, 1H), 1.20-1.14 (m, 9H), 1.09-1.04 (m, 2H), 0.05 (s, 6H) 0.04 (s, 3H), OH signal is not visible; LC/MS *m/z* 781.33 ($[M + Na]^+$, $C_{41}H_{62}O_{11}SiNa$ requires 781.91).



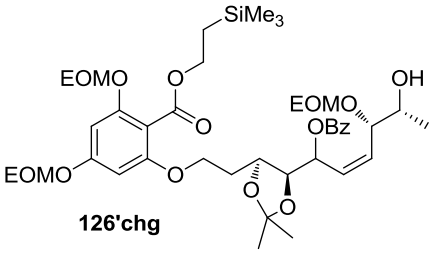
126'ahg

126'ahg: *Rf* = 0.44 (Petroleum ether/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.04 (d, *J* = 8.4 Hz, 1.3H), 7.95 (d, *J* = 8.4 Hz, 0.7H), 7.54-7.53 (m, 1H), 7.43-7.40 (m, 2H), 6.48 (s, 0.6H), 6.41 (s, 0.4H), 6.29 (s, 0.6H), 6.23 (s, 0.4H), 5.87-5.66 (m, 2H), 5.62-5.55 (m, 1H), 5.20-5.11 (m, 4H), 4.54-4.41 (m, 1H), 4.35-4.28 (m, 3H), 4.11-4.07 (m, 2H), 3.91-3.82 (m, 1H), 3.72-3.65 (m, 4H), 2.62-2.48 (m, 2H), 2.02-1.94 (m, 2H), 1.53-1.45 (m, 3H), 1.38-1.36 (m, 3H), 1.24 (d, *J* = 6.0 Hz, 3H), 1.22-1.16 (m, 6H), 1.08-1.02 (m, 2H), 0.04 (s, 9H), OH signal is not visible.



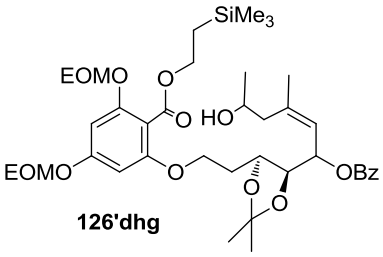
126'bhg

126'bhg: *Rf* = 0.38 (Petroleum ether/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ8.04 (d, *J* = 7.6 Hz, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 7.56-7.52 (m, 1H), 7.44-7.40 (m, 2H), 6.48 (s, 0.6H), 6.41 (s, 0.4H), 6.29 (s, 0.6H), 6.23 (s, 0.4H), 5.83-5.71 (m, 2H), 5.75-5.72 (m, 1H), 5.17-5.12 (m, 4H), 4.57-4.27 (m, 4H), 4.09-4.07 (m, 2H), 3.73-3.65 (m,6H), 2.70-2.66 (m, 1H), 2.58-2.43 (m, 1H), 2.09-1.91 (m, 2H), 1.53-1.45 (m, 3H), 1.38-1.36 (m, 3H), 1.22-1.17 (m, 6H), 1.09-1.03 (m, 2H), 0.05 (s, 9H), OH signal is not visible.



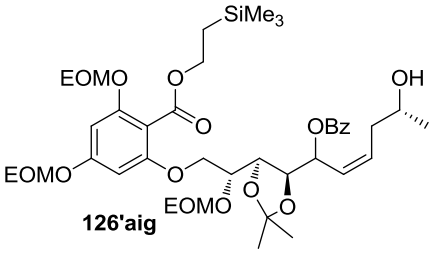
126'chg

126'chg: *Rf* = 0.46 (Petroleum ether/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ8.04 (d, *J* = 8.0 Hz, 2H), 7.58-7.52 (m, 1H), 7.46-7.42 (m, 2H), 6.49-6.41 (m, 1H), 6.29-6.24 (m, 1H), 5.89-5.81 (m, 1H), 5.75-5.68 (m, 1H), 5.64-5.56 (m, 1H), 5.18-5.13 (m, 4H), 4.91-4.83 (m, 1H), 4.72-4.70 (m, 1H), 4.64-4.49 (m, 2H), 4.35-4.30 (m, 2H), 4.43-4.24 (m, 1H), 4.15-4.09 (m, 2H), 3.88-3.76 (m, 1H), 3.73-3.46 (m, 6H), 2.12-1.92 (m, 2H), 1.62-1.60 (m, 3H), 1.40-1.36 (m, 3H), 1.28-1.15 (m, 12H), 1.08-1.03 (m, 2H), 0.05 (s, 3H), 0.04 (s, 6H), OH signal is not visible.

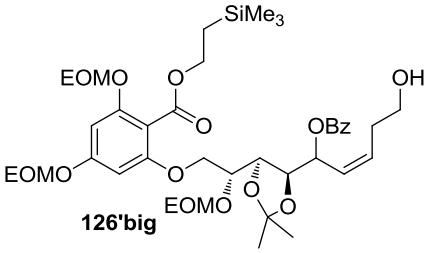


126'dhg

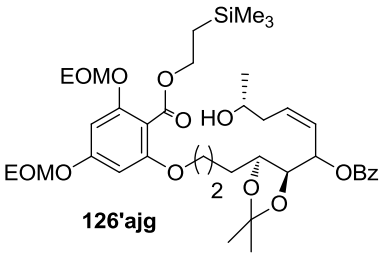
126'dhg: *Rf* = 0.24 (Petroleum ether/EtOAc 4/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ8.01-7.92 (m, 2H), 7.49-7.45 (m, 1H), 7.39-7.34 (m, 2H), 6.45 (d, *J* = 1.9 Hz, 0.3H), 6.44 (d, *J* = 1.9 Hz, 0.3H), 6.43 (d, *J* = 1.9 Hz, 0.2H), 6.42 (d, *J* = 1.9 Hz, 0.2H), 6.27 (d, *J* = 1.6 Hz, 0.6H), 6.21 (d, *J* = 1.9 Hz, 0.2H), 6.20 (d, *J* = 1.9 Hz, 0.2H), 5.74 (dd, *J* = 9.7, 7 Hz, 0.3H), 5.66-5.57 (m, 0.7H), 5.32 (d, *J* = 8.3 Hz, 0.4H), 5.27 (d, *J* = 10.2 Hz, 0.6H), 5.13 (s, 3H), 5.07 (s, 1H), 4.53-4.48 (m, 0.4H), 4.39-4.21 (m, 3.6H), 4.10-4.00 (m, 2H), 3.92-3.73 (m, 1H), 3.67-3.58 (m, 4H), 2.41 (bs, 1H), 2.18-1.94 (m, 4H), 1.87 (s, 1H), 1.85 (s, 0.5H), 1.84 (s, 1.5H), 1.47 (s, 0.75H), 1.44 (s, 0.75H), 1.39 (s, 0.75H), 1.37 (s, 0.75H), 1.33 (s, 1H), 1.31 (s, 1H), 1.30 (s, 1H), 1.17-0.99 (s, 11H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); LC/MS *m/z* 769.68 ([M + Na]$^+$, $C_{39}H_{58}O_{12}SiNa$ requires 769.96).



126'aig: *Rf* = 0.52 (Petroleum ether/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.05 (d, *J* = 7.5 Hz, 0.5H), 7.89 (d, *J* = 7.5 Hz, 1.5H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.42-7.36 (m, 2H), 6.51 (d, *J* = 1.9 Hz, 0.3H), 6.34 (d, *J* = 1.6 Hz, 0.7H), 6.28 (d, *J* = 1.9 Hz, 1H), 5.97 (t, *J* = 9.4 Hz, 1H), 5.88-5.71 (m, 1H), 5.60-5.51 (m, 1H), 5.12 (s, 1.5H), 5.08 (s, 1.5H), 4.92-4.76 (m, 2H), 4.55-4.02 (m, 7.5H), 3.88-3.80 (m, 1.5H), 3.70-3.49 (m, 6H), 2.62-2.25 (m, 2H), 1.58 (s, 1H), 1.50 (s, 2H), 1.41 (s, 1H), 1.38 (s, 2H), 1.24 (d, *J* = 5.9 Hz, 3H), 1.22-1.02 (m, 11H), 0.04 (s, 3H), 0.03 (s, 6H), OH signal is not visible; LC/MS *m/z* 829.37 ($[M + Na]^+$, $C_{41}H_{62}O_{14}SiNa$ requires 829.39).

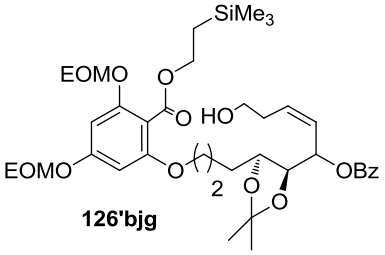


126'big: *Rf* = 0.25 (Petroleum ether/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.08-7.84 (m x 2, 2H), 7.54-7.43 (m, 1H), 7.42-7.31 (m, 2H), 6.52-6.31 (m x 2, 1H), 6.29-6.16 (m x 2, 1H), 5.98-5.32 (m x 4, 3H), 5.22-5.04 (m, 4H), 4.88-4.80 (m, 1H), 4.79-4.70 (m, 1H), 4.56-3.77 (m x 3, 7H), 3.68-3.40 (m, 8H), 2.68-2.36 (m, 1H), 1.98-1.70 (m, 1H), 1.51-1.44 (m, 3H), 1.41-1.34 (m, 3H), 1.18-0.98 (m, 11H), 0.04 (s, 3H), 0.03 (s, 6H), OH signal is not visible; LC/MS *m/z* 815.21 ($[M + Na]^+$, $C_{40}H_{60}O_{14}SiNa$ requires 815.37).



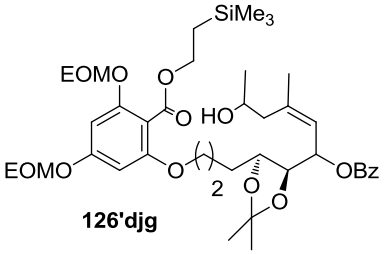
126'ajg: *Rf* = 0.23 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.04-7.95 (m, 2H), 7.51-7.46 (m, 1H), 7.41-7.33 (m, 2H), 6.46 (d, *J* = 1.9 Hz, 0.7H), 6.43 (d, *J* = 1.9 Hz, 0.3H), 6.24 (d, *J* = 1.9 Hz, 0.7H), 6.16 (d, *J* = 1.9 Hz, 0.3H), 5.80-5.54 (m, 3H), 5.15-5.12 (m, 4H), 4.37-4.16 (m, 4H), 3.97-3.81 (m, 3H), 3.69-3.64 (m, 4H), 2.58-2.23 (m, 1H), 2.03-1.58 (m, 5H), 1.49 (s, 1.5H), 1.42 (s, 1.5H),

1.35 (s, 1.5H), 1.33 (s, 1.5H), 1.19-1.03 (m, 11H), 0.02 (s, 6H) 0.01 (s, 3H), OH signal is not visible; LC/MS *m/z* 747.33 ($[M + H]^+$, $C_{39}H_{58}O_{12}SiH$ requires 747.95).



126'bjg

126'bjg: *Rf* = 0.20 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.02 (d, *J* = 7.6 Hz, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.52-7.46 (m, 1H), 7.41-7.34 (m, 2H), 6.46 (d, *J* = 1.6 Hz, 0.6H), 6.44 (d, *J* = 1.6 Hz, 0.4H), 6.25 (d, *J* = 1.9 Hz, 0.6H), 6.17 (d, *J* = 1.9 Hz, 0.4H), 5.79-5.70 (m, 2H), 5.59 (d, *J* = 10.0 Hz, 0.6H), 5.57 (d, *J* = 10.4 Hz, 0.4H), 5.15 (s, 3H), 5.13 (s, 1H), 4.36-4.14 (m, 4H), 3.99-3.78 (m, 2H), 3.69-3.63 (m, 1.5H), 3.67 (q, *J* = 6.7 Hz, 4H), 3.56 (t, *J* = 6.3 Hz, 0.5H), 2.69-2.40 (m, 2H), 1.97-1.91 (m, 1H), 1.81-1.62 (m, 3H), 1.49 (s, 2H), 1.42 (s, 1H), 1.35 (s, 2H), 1.32 (s, 1H), 1.18-1.14 (m, 6H), 1.09-1.03 (m, 2H), 0.03 (s, 6H) 0.01 (s, 3H), OH signal is not visible; LC/MS *m/z* 733.31 ($[M + H]^+$, $C_{38}H_{56}O_{12}SiH$ requires 733.93).



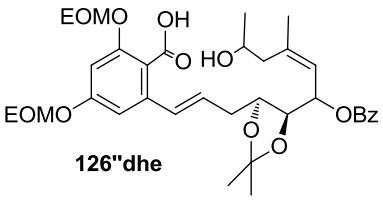
126'djg

126'djg: *Rf* = 0.18 (Petroleum ether/EtOAc 4/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ 8.00 (d, *J* = 7.5 Hz, 1H), 7.96 (d, *J* = 7.3 Hz, 0.5H), 7.95 (d, *J* = 7.2 Hz, 0.5H), 7.48-7.42 (m, 1H), 7.37-7.29 (m, 2H), 6.45 (s, 0.5H), 6.43 (s, 0.5H), 6.25 (d, *J* = 2.4 Hz, 0.5H), 6.16 (d, *J* = 1.1 Hz, 0.25H), 6.14 (d, *J* = 1.0 Hz, 0.25H), 5.73 (dd, *J* = 9.1, 7.0 Hz, 0.2H), 5.65-5.60 (m, 0.8H), 5.34-5.28 (m, 1H), 5.13 (s, 3H), 5.11 (s, 1H), 4.35-4.13 (m, 4H), 3.98-3.75 (m, 3H), 3.68-3.60 (m, 4H), 2.38 (bs, 1H), 2.15-2.00 (m, 2H), 1.94-1.90 (m, 1H), 1.88 (s, 1H), 1.85 (s, 1H), 1.84 (s, 1H), 1.80-1.63 (m, 3H), 1.47 (s, 0.75H), 1.45 (s, 0.75H), 1.39 (s, 0.75H), 1.38 (s, 0.75H), 1.33 (s, 1H), 1.31 (s, 2H), 1.20-1.01 (m, 11H), 0.02 (s, 4H) 0.01 (s, 5H); LC/MS *m/z* 783.27 ($[M + Na]^+$, $C_{40}H_{60}O_{12}SiNa$ requires 783.98).

General procedure for TBAF deprotection. Synthesis of acids 126''. To a solution of silyl-esters **126'** (1.0 equiv) in THF (0.3 M) at 23 °C was added a 1.0 M solution of TBAF in THF (3.0 equiv). The reaction mixture was quenched after 2 h with sat. NH_4Cl aq. solution, extracted with EtOAc, dried over Na_2SO_4 and concentrated under reduced pressure. Filtration through a short pad of SiO_2 with

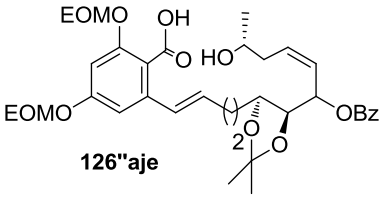
Petroleum ether/EtOAc 10/1 followed by EtOAc/MeOH 50/1 provided the desired acids **126''** in quantitative yields.

Selected examples of compounds 126''.



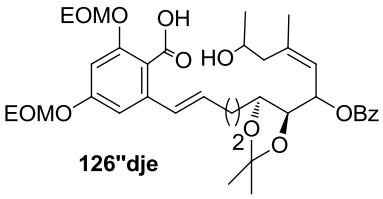
126''dhe

126''dhe: *Rf* = 0.12 (EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.05-7.93 (m, 2H), 7.54-7.47 (m, 1H), 7.42-7.34 (m, 2H), 6.84-6.68 (m, 3H), 6.25-6.08 (m, 1H), 5.80-5.64 (m, 1H), 5.35 (d, *J* = 9.4 Hz, 0.8H), 5.32 (d, *J* = 9.6 Hz, 0.2H), 5.20 (s, 3H), 5.15 (s, 0.5H), 5.13 (s, 0.5H), 4.41-4.23 (m, 2H), 3.99-3.89 (m, 1H), 3.73-3.66 (m, 4H), 2.61-2.35 (m, 2H), 2.27-2.09 (m, 2H), 1.91 (s, 0.5H), 1.89 (s, 2.5H), 1.54 (s, 1H), 1.53 (s, 1H), 1.45 (s, 0.5H), 1.43 (s, 0.5H), 1.37 (s, 1H), 1.35 (s, 1H), 1.34(s, 1H), 1.20-1.14 (m, 9H), OH and CO_2H signals are not visible; LC/MS *m/z* 665.70 ([M + Na]$^+$, $C_{35}H_{46}O_{11}SiNa$ requires 665.73).



126''aje

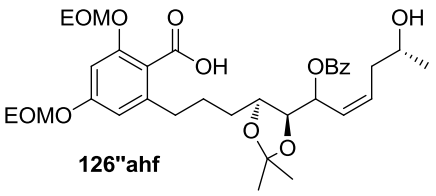
126''aje: *Rf* = 0.11 (EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.06 (d, *J* = 7.5 Hz, 1.5H), 7.99 (d, *J* = 7.7 Hz, 0.5H), 7.54-7.39 (m, 3H), 6.81 (d, *J* = 2.1 Hz, 1H), 6.75 (d, *J* = 2.1 Hz, 1H), 6.64-6.44 (m, 2H), 5.83-5.50 (m, 3H), 5.25 (s, 0.5H), 5.20 (s, 2.5H), 5.19 (s, 1H), 4.37-3.93 (m, 3H), 3.76-3.67 (m, 4H), 2.74-2.19 (m, 4H), 1.82-1.64 (m, 2H), 1.51 (s, 2H), 1.47 (s, 1H), 1.42 (s, 1H), 1.37 (s, 2H), 1.26-1.16 (m, 9H), OH and CO_2H signals are not visible; LC/MS *m/z* 643.42 ([M + H]$^+$, $C_{35}H_{46}O_{11}H$ requires 643.73).



126''dje

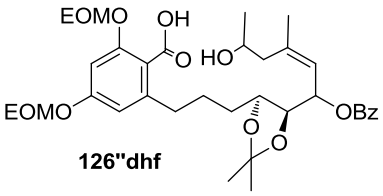
126''dje: *Rf* = 0.12 (EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.01-7.95 (m, 2H), 7.49-7.34 (m, 3H), 6.77-6.70 (m, 2H), 6.59-6.51 (m, 1H), 6.16-6.00 (m, 1H), 5.77-5.62 (m, 1H), 5.35-5.27 (m, 1H), 5.17 (s, 2H), 5.16 (s, 2H), 4.27-4.12 (m, 2H), 3.99-3.79 (m, 1H), 3.69-3.63 (m, 4H), 2.41-2.05 (m, 4H), 1.85 (s, 3H), 1.74-1.56 (m, 2H), 1.46 (s, 1H), 1.45 (s, 0.5H), 1.39 (s, 1H), 1.38 (s, 0.5H), 1.32 (s, 1H), 1.31 (s, 2H),

1.17-1.09 (m, 9H), OH and CO_2H signals are not visible; LC/MS *m/z* 679.28 ([M + Na]$^+$, $C_{36}H_{48}O_{11}Na$ requires 679.76).



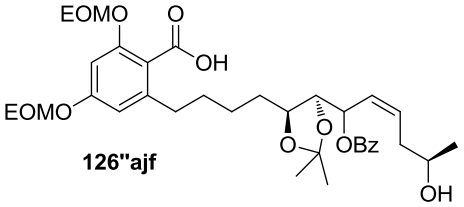
126''ahf

126''ahf: *Rf* = 0.07 (Petroleum ether/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.10-7.93 (m x 2, 2H), 7.60-7.52 (m, 1H), 7.48-7.39 (m, 2H), 6.75-6.65 (m, 1H), 6.54-6.46 (m, 1H), 5.92-5.50 (m, 3H), 5.27-5.08 (m, 4H), 4.38-4.18 (m, 2H), 4.00-3.60 (m, 5H), 2.90-2.46 (m, 3H), 2.43-2.25 (m, 1H), 1.90-1.69 (m, 2H), 1.65 (s, 1H), 1.62 (s, 2H), 1.39 (s, 2H), 1.35 (s, 1H), 1.33-1.10 (m, 11H), OH and CO_2H signals are not visible; LC/MS *m/z* 653.21 ([M + Na]$^+$, $C_{34}H_{46}O_{11}Na$ requires 653.30).



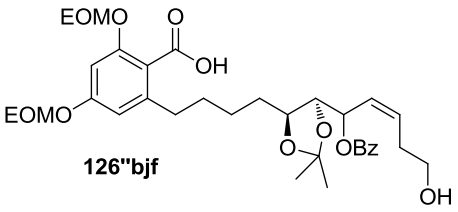
126''dhf

126''dhf: *Rf* = 0.12 (EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.02-7.96 (m, 2H), 7.53-7.37 (m, 3H), 6.72-6.67 (m, 1H), 6.55 (d, *J* = 2.1 Hz, 0.3H), 6.54 (d, *J* = 2.1 Hz, 0.3H), 6.49 (d, *J* = 2.2 Hz, 0.2H), 6.48 (d, *J* = 2.1 Hz, 0.2H), 5.71 (dd, *J* = 9.7, 7.3 Hz, 0.4H), 5.66-5.61 (m, 0.6H), 5.39-5.31 (m, 1H), 5.25-5.14 (m, 4H), 4.29-4.06 (m, 2H), 3.94-3.84 (m, 1H), 3.77-3.65 (m, 4H), 2.83-2.63 (m, 2H), 2.26-2.05 (m, 2H), 1.86 (s, 0.5H), 1.84 (s, 1.5H), 1.78 (s, 1H), 1.70-1.52 (m, 4H), 1.48 (s, 1H), 1.46 (s, 1H), 1.41 (s, 1H), 1.34 (s, 1.5H), 1.33 (s, 1.5H), 1.22-1.14 (m, 9H), OH and CO_2H signals are not visible; LC/MS *m/z* 667.93 ([M + Na]$^+$, $C_{35}H_{48}O_{11}SiNa$ requires 667.75).



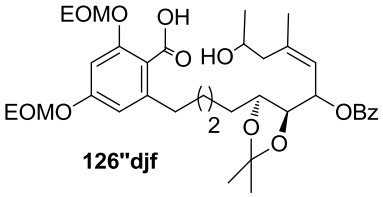
126''ajf

126''ajf: *Rf* = 0.07 (Petroleum ether/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.06 (d, *J* = 7.2 Hz, 1.3H), 8.01 (d, *J* = 7.2 Hz, 0.7H), 7.57-7.53 (m, 1H), 7.45-7.40 (m, 2H), 6.74-6.72 (m, 1H), 6.54 (d, *J* = 2.0 Hz, 0.7H), 6.52 (d, *J* = 7.2 Hz, 0.3H), 5.87-5.72 (m, 2H), 5.68-5.62 (m, 1H), 5.23 (s, 2H), 5.19 (s, 2H), 4.30-4.25 (m, 1H), 4.24-4.19 (m, 1H), 4.04-3.94 (m, 1H), 3.76-3.65 (m, 4H), 2.74-2.46 (m, 3H), 2.37-2.31 (m, 1H), 1.68-1.59 (m, 4H), 1.54 (s, 2H), 1.47 (s, 1H), 1.38 (s, 2H), 1.30 (s, 1H), 1.33-1.23 (m, 5H), 1.23-1.19 (m, 6H), OH and CO_2H signals are not visible; LC/MS *m/z* 667.29 ([M + Na]$^+$, $C_{35}H_{48}O_{11}Na$ requires 667.31).



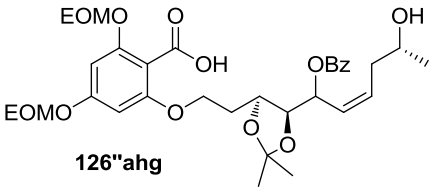
126''bjf

126''bjf: *Rf* = 0.07 (Petroleum ether/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.06 (d, *J* = 7.2 Hz, 1.3H), 8.01 (d, *J* = 7.2 Hz, 0.7H), 7.57-7.53 (m, 1H), 7.45-7.40 (m, 2H), 6.74-6.73 (m, 1H), 6.55 (d, *J* = 2.0 Hz, 0.7H), 6.51 (d, *J* = 2.0 Hz, 0.3H), 5.85-5.55 (m, 3H), 5.23 (s, 2H), 5.19 (s, 2H), 4.29-4.26 (m, 1H), 4.25-4.20 (m, 1H), 3.88-3.62 (m, 2H), 3.76-3.67 (m, 2H), 2.77-2.47 (m, 4H), 2.39-2.33 (m, 1H), 1.72-1.59 (m, 4H), 1.56 (s, 2H), 1.46 (s, 1H), 1.39 (s, 2H), 1.38 (s, 1H), 1.25 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 6H) OH and CO_2H signals are not visible; LC/MS *m/z* 653.23 ([M + Na]$^+$, $C_{34}H_{46}O_{11}Na$ requires 653.30).



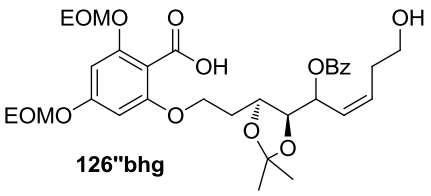
126''djf

126''djf: *Rf* = 0.12 (EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.05-7.99 (m, 2H), 7.54-7.38 (m, 3H), 6.74 (d, *J* = 2.2 Hz, 0.8H), 6.73 (d, *J* = 2.1 Hz, 0.2H), 6.56 (d, *J* = 2.1 Hz, 0.8H), 6.49 (d, *J* = 2.1 Hz, 0.2H), 5.80-5.65 (m, 1H), 5.39 (d, *J* = 9.4 Hz, 0.8H), 5.34 (d, *J* = 9.4 Hz, 0.2H), 5.23 (s, 1.5H), 5.22 (s, 0.5H), 5.20 (s, 1.5H), 5.18 (s, 0.5H), 4.30-4.10 (m, 2H), 4.04-3.89 (m, 1H), 3.75-3.67 (m, 4H), 2.71-2.53 (m, 2H), 2.26-2.01 (m, 2H), 1.90 (s, 0.5H), 1.89 (s, 1H), 1.88 (s, 1.5H), 1.68-1.51 (m, 6H), 1.49 (s, 1.5H), 1.47 (s, 0.5H), 1.42 (s, 1H), 1.36 (s, 2H), 1.34 (s, 1H),1.25-1.17 (m, 9H), OH and CO_2H signals are not visible; LC/MS *m/z* 681.34 ([M + Na]$^+$, $C_{36}H_{50}O_{11}Na$ requires 681.33).



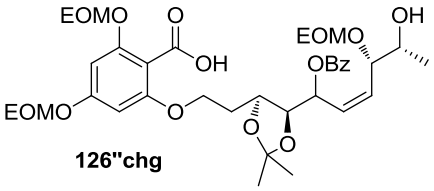
126''ahg

126''ahg: *Rf* = 0.07 (Petroleum ether/EtOAc 2/1); ^{1}H NMR ($(CD_3)_2CO$, 400 MHz, 25 °C) δ 8.07-7.99 (m, 2H), 7.85-7.83 (m, 1H), 7.51-7.47 (m, 2H), 6.52-6.36 (m, 1H), 6.24 (s, 1H), 5.87-5.81 (m, 2H), 5.70-5.57 (m, 1H), 5.48 (s, 1H), 5.30 (s, 1H), 5.26 (s, 0.5H), 5.24 (s, 0.5H), 5.23 (s, 1H), 4.66-4.57 (m, 1H), 4.53-4.40 (m, 2H), 4.34-4.10 (m, 1H), 3.91-3.80 (m, 1H), 3.77-3.62 (m, 4H), 2.50-2.45 (m, 2H), 2.50-2.40 (m, 2H), 1.47-1.27 (m, 6H), 1.17 (d, *J* = 6.8 Hz, 3H), 1.15-1.10 (m, 6H), OH and CO_2H signals are not visible; LC/MS *m/z* 655.24 ([M + Na]$^+$, for $C_{33}H_{44}O_{12}Na$ requires 655.27).



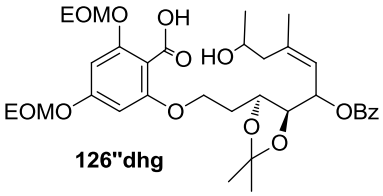
126"bhg

126''bhg: *Rf* = 0.07 (Petroleum ether/EtOAc 2/1); ^{1}H NMR ($(CD_3)_2CO$, 400 MHz, 25 °C) δ 8.06 (d, *J* = 7.6 Hz, 1.3H), 7.99 (d, *J* = 7.6 Hz, 0.7H), 7.62-7.60 (m, 1H), 7.52-7.48 (m, 2H), 6.52 (s, 0.6H), 6.48 (s, 0.4H), 6.41 (s, 0.6H), 6.36 (s, 0.4H), 5.90-5.74 (m, 2H), 5.66-5.59 (m, 1H), 5.26 (s, 1H), 5.24 (s, 1.5H), 5.23 (m, 1.5H), 4.64-4.49 (m, 1H), 4.45-4.40 (m, 1H), 4.19-4.08 (m, 2H), 3.70-3.59 (m, 6H), 2.57-2.58 (m, 2H), 1.77 (m, 2H), 1.48 (s, 1.5H), 1.40 (s, 1.5H), 1.32 (s, 2H), 1.27 (s, 1H), 1.16-1.13 (m, 6H), OH and CO_2H signals are not visible.



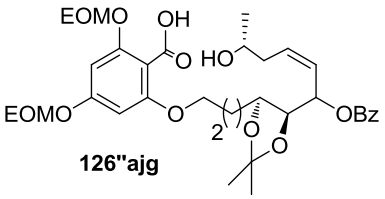
126"chg

126''chg: *Rf* = 0.25 (Petroleum ether/EtOAc 1/1); ^{1}H NMR ($(CD_3)_2CO$, 400 MHz, 25 °C) δ 8.07-7.98 (m, 2H), 7.63-7.61 (m, 1H), 7.53-7.49 (m, 2H), 6.50-6.45 (m 1H), 6.38-6.36 (m 1H), 5.99-5.87 (m, 1H), 5.84-5.78 (m, 1H), 5.67-5.56 (m, 1H), 5.21-5.18 (m, 4H), 4.87-4.78 (m, 1H), 4.71-4.48 (m, 3H), 4.42-4.38 (m, 1H), 4.18-4.08 (m, 2H), 3.89-3.83 (m, 1H), 3.71-3.62 (m, 6H), 2.20-2.11 (m, 1H), 1.89-1.78 (m, 1H), 1.56-1.53 (m, 2H), 1.41-1.40 (m, 1H), 1.32 (s, 3H), 1.18-1.08 (m, 12H), OH and CO_2H signals are not visible.



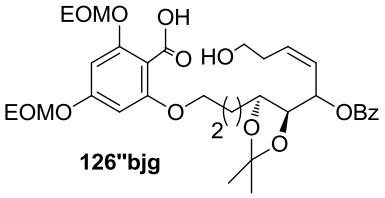
126"dhg

126''dhg: *Rf* = 0.12 (EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.71-7.64 (m, 2H), 7.21-7.16 (m, 1H), 7.10-7.05 (m, 2H), 6.15 (d, *J* = 1.6 Hz, 1H), 5.96 (s, 0.4H), 5.94 (s, 0.3H), 5.92 (s, 0.3H), 5.48-5.32 (m, 1H), 5.04-4.95 (m, 1H), 4.83 (s, 3H), 4.80 (s, 1H), 4.28-4.18 (m, 0.5H), 4.10-3.89 (m, 1.5H), 3.83-3.74 (m, 2H), 3.64-3.48 (m, 1H), 3.39-3.30 (m, 4H), 1.85-1.61 (m, 4H), 1.56 (s, 1.5H), 1.55 (s, 1H), 1.52 (s, 0.5H), 1.13 (s, 1H), 1.11 (s, 1H), 1.08 (s, 1H), 1.01 (s, 1H), 1.00 (s, 2H), 0.92-0.78 (m, 9H), OH and CO_2H signals are not visible; LC/MS *m/z* 669.53 ($[M + Na]^+$, for $C_{34}H_{46}O_{12}Na$ requires 669.72).



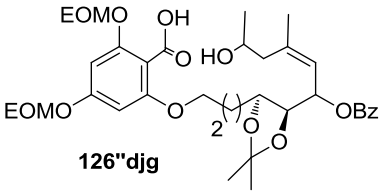
126''ajg

126''ajg: *Rf* = 0.12 (EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.04-7.94 (m, 2H), 7.54-7.48 (m, 1H), 7.41-7.36 (m, 2H), 6.46-6.44 (m, 1H), 6.27-6.22 (m, 1H), 5.81-5.53 (m, 3H), 5.16 (s, 3H), 5.13 (s, 1H), 4.39-4.15 (m, 2H), 3.96-3.84 (m, 2H), 3.71-3.62 (m, 5H), 2.74-2.29 (m, 2H), 2.25-2.06 (m, 1H), 1.97-1.79 (m, 3H), 1.49 (s, 1.5H), 1.46 (s, 1.5H), 1.39 (s, 1.5H), 1.34 (s, 1.5H), 1.22-1.14 (m, 9H). OH and CO_2H signals are not visible; LC/MS *m/z* 647.26 ([M + H]$^+$, for $C_{34}H_{46}O_{12}H$ requires 647.72).



126''bjg

126''bjg: *Rf* = 0.12 (EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.03 (d, *J* = 7.5 Hz, 1.5H), 7.98 (d, *J* = 7.3 Hz, 0.5H), 7.56-7.49 (m, 1H), 7.42-7.37 (m, 2H), 6.48 (d, *J* = 1.6 Hz, 1H), 6.27 (d, *J* = 1.6 Hz, 0.6H), 6.25 (d, *J* = 1.9 Hz, 0.4H), 5.83-5.54 (m, 3H), 5.17 (s, 2H), 5.15 (s, 2H), 4.40-4.16 (m, 2H), 4.05-3.81 (m, 2H), 3.75-3.63 (m, 6H), 2.67-2.52 (m, 1H), 1.98-1.65 (m, 5H), 1.51 (s, 2H), 1.48 (s, 1H), 1.37 (s, 1H), 1.35 (s, 2H), 1.20-1.15 (m, 6H), OH and CO_2H signals are not visible; LC/MS *m/z* 633.26 ([M + H]$^+$, for $C_{33}H_{44}O_{12}H$ requires 633.69).



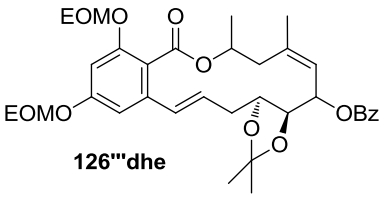
126''djg

126''djg: *Rf* = 0.12 (EtOAc); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.98-7.93 (m, 2H), 7.47-7.42 (m, 1H), 7.36-7.29 (m, 2H), 6.43 (bs, 1H), 6.23 (bs, 0.5H), 6.18 (bs, 0.25H), 6.16 (bs, 0.25H), 5.80-5.65 (m, 1H), 5.36-5.28 (m, 1H), 5.12 (s, 3H), 5.10 (s, 1H), 4.30-4.10 (m, 2H), 3.98-3.78 (m, 3H), 3.67-3.60 (m, 4H), 2.20-2.02 (m, 2H), 1.95-1.64 (m, 4H), 1.83 (s, 1H), 1.81 (s, 2H), 1.41 (s, 1H), 1.39 (s, 1H), 1.37 (s, 1H), 1.35 (s, 1H), 1.34 (s, 1H), 1.33 (s, 1H), 1.28 (d, *J* = 5.1 Hz, 3H), 1.16-1.11 (m, 6H), OH and CO_2H signals are not visible; LC/MS *m/z* 683.49 ([M + Na]$^+$, for $C_{35}H_{48}O_{12}Na$ requires 683.74).

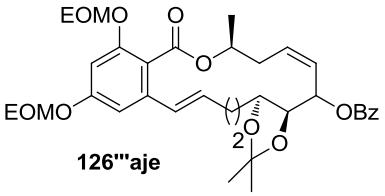
General procedure for the macrocyclization reaction. Synthesis of compounds 126'''. A solution of compound **126''** (1.0 equiv) in toluene (0.01 M) was treated with fluorous-DIAD (2.0 equiv) and fluorous-Ph_3P (2.0 equiv). The mixture was stirred at 23 °C for 2 h. The solvents were then

evaporated, the crude was dissolved in DMF (0.1 mL), loaded onto a fluorous column and eluted with 70% MeOH in H_2O, then 80% MeOH in H_2O and finally 100% MeOH. Compounds **126'''** were recovered in the 80% MeOH fractions in 50-85% yields with greater than 85% conversion for all reactions excepts reactions involving fragment "**c**" as estimated by LC/MS. Compounds requiring further purification were repurified by traditional silica gel chromatography.

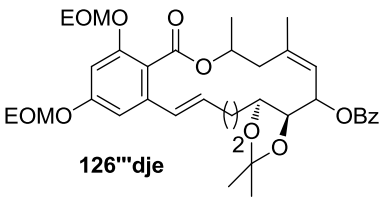
Selected examples of compounds 126'''.



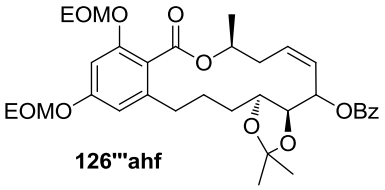
126'''dhe: *Rf* = 0.34 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.11 (d, *J* = 7.8 Hz, 1H), 8.06-8.03 (m, 1H), 7.59-7.51 (m, 1H), 7.48-7.39 (m, 2H), 6.77 (d, *J* = 2.1 Hz, 0.3H), 6.76 (d, *J* = 2.1 Hz, 0.3H), 6.74 (d, *J* = 2.2 Hz, 0.2H), 6.73 (d, *J* = 2.2 Hz, 0.2H), 6.64 (d, *J* = 2.1 Hz, 0.2H), 6.62 (d, *J* = 2.1 Hz, 0.2H), 6.59 (d, *J* = 2.2 Hz, 0.2H), 6.56 (d, *J* = 2.2 Hz, 0.4H), 6.53 (d, *J* = 16.1 Hz, 0.6H), 6.42 (d, *J* = 16.4 Hz, 0.2H), 6.36 (d, *J* = 16.1 Hz, 0.2H), 6.29-6.06 (m, 0.7H), 6.02-5.85 (m, 1.3H), 5.66-5.28 (m, 2H), 5.23-5.15 (m, 4H), 4.45-4.20 (m, 2H), 3.74-3.66 (m, 4H), 3.33-2.88 (m, 0.7H), 2.72-2.18 (m, 3.3H), 2.01 (s, 0.5H), 1.97 (s, 0.5H), 1.94 (s, 1H), 1.83 (s, 1H), 1.38-1.28 (m, 9H), 1.24-1.18 (m, 6H); LC/MS *m/z* 625.24 ($[M + H]^+$, for for $C_{35}H_{44}O_{10}H$ requires 625.71).



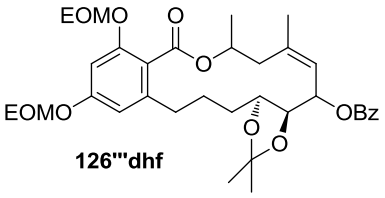
126'''aje: *Rf* = 0.36 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.11-8.04 (m, 2H), 7.59-7.41 (m, 3H), 6.80 (d, *J* = 1.9 Hz, 1H), 6.76 (d, *J* = 1.8 Hz, 0.7H), 6.72 (d, *J* = 1.9 Hz, 0.3H), 6.56-5.89 (m, 4H), 5.81-5.46 (m, 2H), 5.28-5.18 (m, 4H), 4.53-4.19 (m, 2H), 3.80-3.68 (m, 4H), 3.09-2.68 (m, 1H), 2.49-2.14 (m, 2H), 1.92-1.65 (m, 3H), 1.47-1.33 (m, 9H), 1.26-1.18 (m, 6H) ; LC/MS *m/z* 625.25 ($[M + H]^+$, for $C_{35}H_{44}O_{10}H$ requires 625.71).



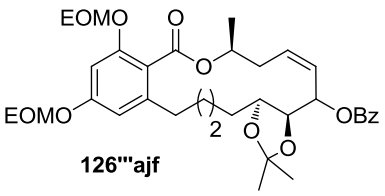
126'''dje: *Rf* = 0.35 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.08-8.03 (m, 2H), 7.59-7.40 (m, 3H), 6.84-6.70 (m, 2H), 6.45-6.27 (m, 1H), 6.25 (d, *J* = 16.4 Hz, 0.5H), 6.16 (d, *J* = 16.3 Hz, 0.5H), 6.02-5.86 (m, 1H), 5.59-5.51 (m, 1H), 5.22-5.14 (m, 5H), 4.48-4.13 (m, 2H), 3.74-3.66 (m, 4H), 2.50-2.27 (m, 4H), 2.07 (s, 1H), 1.98 (s, 1H), 1.82 (s, 1H), 1.79-1.52 (m, 2H), 1.49-1.33 (m, 9H), 1.24-1.19 (m, 6H) ; LC/MS *m/z* 639.32 ($[M + H]^+$, for $C_{36}H_{46}O_{10}H$ requires 639.74).



126'''ahf: *Rf* = 0.52 (Petroleum ether/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) (major diastereoisomer) δ 8.07 (d, *J* = 7.5 Hz, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.45-7.38 (m, 2H), 6.73 (d, *J* = 2.2 Hz, 1H), 6.53 (d, *J* = 1.9 Hz, 1H), 5.90 (d, *J* = 9.8 Hz, 1H), 5.83 (td, *J* = 11.3, 3.2 Hz, 1H), 5.55 (td, *J* = 10.5, 1.9 Hz, 1H), 5.38-5.27 (m, 1H), 5.20 (m, 4H), 4.34-4.29 (m, 1H), 4.10-4.04 (m, 1H), 3.79-3.66 (m, 4H), 3.24-3.13 (m, 1H), 2.79-2.66 (m, 1H), 2.49-2.39 (m, 1H), 2.31-2.21 (m, 1H), 1.90-1.74 (m, 1H), 1.73-1.50 (m, 3H), 1.44 (d, *J* = 6.5 Hz, 3H), 1.33 (s, 3H), 1.29 (s, 3H), 1.26-1.19 (m, 6H).

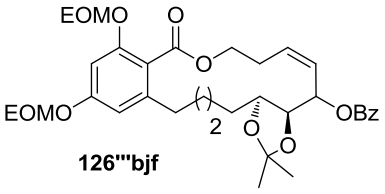


126'''dhf: *Rf* = 0.32 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ 8.02-7.96 (m, 2H), 7.53-7.37 (m, 3H), 6.72-6.67 (m, 1H), 6.55 (d, *J* = 2.1 Hz, 0.3H), 6.54 (d, *J* = 2.1 Hz, 0.3H), 6.49 (d, *J* = 2.2 Hz, 0.2H), 6.48 (d, *J* = 2.1 Hz, 0.2H), 5.71 (dd, *J* = 9.7, 7.3 Hz, 0.4H), 5.66-5.61 (m, 0.6H), 5.39-5.31 (m, 1H), 5.25-5.14 (m, 4H), 4.29-4.06 (m, 2H), 3.94-3.84 (m, 1H), 3.77-3.65 (m, 4H), 2.83-2.63 (m, 2H), 2.26-2.05 (m, 2H), 1.86 (s, 0.5H), 1.84 (s, 1.5H), 1.78 (s, 1H), 1.70-1.52 (m, 4H), 1.48 (s, 1H), 1.46 (s, 1H), 1.41 (s, 1H), 1.34 (s, 1.5H), 1.33 (s, 1.5H), 1.22-1.14 (m, 9H); LC/MS *m/z* 649.88 ($[M + Na]^+$, for $C_{35}H_{46}O_{10}Na$ requires 649.73).



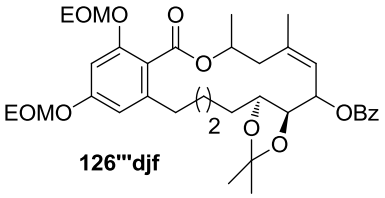
126'''ajf

126'''ajf: *Rf* = 0.78 (Petroleum ether/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.08-8.03 (m, 2H), 7.57-7.52 (m, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 6.72 (d, *J* = 2.2 Hz, 0.7H), 6.69 (d x 2, *J* = 2.2 Hz, 0.3H), 6.59 (d, *J* = 2.2 Hz, 0.7H), 6.55 (d, *J* = 2.2 Hz, 0.3H), 6.02-5.96 (m, 1H), 5.90-5.79 (m, 1H), 5.51-5.45 (m, 2H), 5.20 (s, 2H), 5.19 (s, 2H), 4.46-4.33 (m, 1H), 4.25-4.09 (m, 1H), 3.74-3.67 (m, 4H), 3.09-3.00 (m, 1H), 2.65-2.58 (m, 1H), 2.52-2.43 (m, 2H), 1.80-1.67 (m, 3H), 1.65-1.45 (m, 3H), 1.41 (s, 3H), 1.35 (s, 3H), 1.25 (s, 3H), 1.24-1.19 (m, 6H).



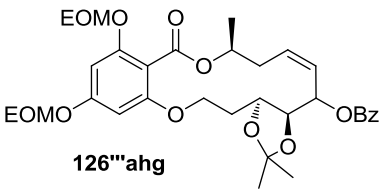
126'''bjf

126'''bjf: *Rf* = 0.74 (Petroleum ether/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.08-8.03 (m, 2H), 7.57-7.53 (m, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 6.72 (d, *J* = 1.6 Hz, 1H), 6.59 (d, *J* = 1.6 Hz, 0.6H), 6.57 (d, *J* = 1.6 Hz, 0.4H), 6.02 (t, *J* = 10.2 Hz, 0.4H), 5.90-5.77 (m, 2H), 5.48 (t, *J* = 10.2 Hz, 0.6H), 5.20 (s, 4H), 4.77-4.67 (m, 1H), 4.35-4.27 (m, 2H), 4.05-4.01 (m, 1H), 3.75-3.68 (m, 4H), 3.22-2.91 (m, 1H), 2.72-2.67 (m, 1H), 2.57 (t, *J* = 7.6 Hz, 2H), 1.88-1.53 (m, 6H), 1.50 (s, 1H), 1.42 (s, 2H), 1.35 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 6H).



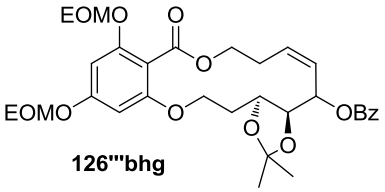
126'''djf

126'''djf: *Rf* = 0.32 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.08-8.02 (m, 2H), 7.55-7.40 (m, 3H), 6.69-5.55 (m, 2H), 5.95-5.82 (m, 1H), 5.67-5.26 (m, 2H), 5.21-5.14 (m, 4H), 4.37 (dd, *J* = 9.7, 5.3 Hz, 0.6H), 4.31 (dd, *J* = 9.6, 5.4 Hz, 0.4H), 4.21-4.13 (m, 1H), 3.73-3.67 (m, 4H), 2.75-2.16 (m, 4H), 1.99 (s, 1H), 1.98(s, 1H), 1.86 (s, 0.5H), 1.80 (s, 0.5H), 1.76-1.49 (m, 6H), 1.41 (s, 1.5H), 1.40 (s, 1.5H), 1.37-1.29 (m, 6H), 1.24-1.19 (m, 6H) ; LC/MS *m/z* 663.29 ([M + Na]$^+$, for $C_{36}H_{48}O_{10}Na$ requires 663.76).



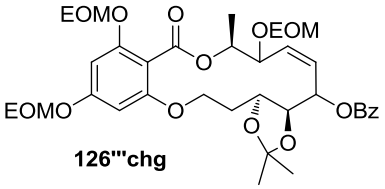
126'''ahg

126'''ahg: *Rf* = 0.45 (Petroleum ether/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.12-8.00 (m, 2H), 7.56-7.52 (m, 1H), 7.44-7.41 (m, 2H), 6.61-6.50 (m, 1H), 6.44-6.30 (m, 1H), 6.04-5.61 (m, 4H), 5.22 (s, 4H), 4.75-4.53 (m, 1H), 4.39-4.02 (m, 3H), 3.74-3.67 (m, 4H), 3.28-3.19 (m, 1H), 2.39-2.19 (m, 1H), 2.13-1.97 (m, 2H), 1.46-1.33 (m, 6H), 1.25-1.16 (m, 9H); LC/MS *m/z* 615.20 ([M + H]$^+$, for $C_{33}H_{42}O_{11}H$ requires 615.28).



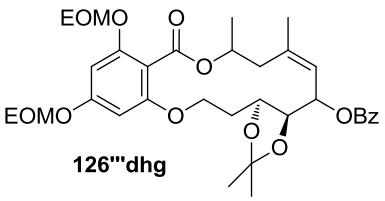
126'''bhg

126'''bhg: *Rf* = 0.44 (Petroleum ether/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.07 (d, *J* = 7.2 H, 2H), 7.57-7.52 (m, 1H), 7.44-7.40 (m, 2H), 6.57 (s, 0.3H), 6.52 (s, 0.7H), 6.39 (s, 0.3H), 6.37 (s, 0.7H), 5.89-5.75 (m, 3H), 5.19 (s, 4H), 4.63-4.54 (m, 1H), 4.32-4.14 (m, 5H), 3.74-3.67 (m, 4H), 3.39-3.01 (m, 1H), 2.46-2.43 (m, 1H), 2.31-2.18 (m, 1H), 2.11-2.07 (m, 1H), 1.59 (s, 1H), 1.46 (s, 2H), 1.37 (s, 1H), 1.33 (s, 2H), 1.25-1.18 (m, 6H); LC/MS *m/z* 601.21 ([M + H]$^+$, for $C_{32}H_{40}O_{11}H$ requires 601.26).



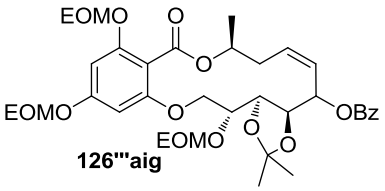
126'''chg

126'''chg: *Rf* = 0.42 (Petroleum ether/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.07 (d, *J* = 7.2 Hz, 2H), 7.62-7.53 (m, 1H), 7.45-7.41 (m, 2H), 6.30 (d, *J* = 2.0 Hz, 1H), 6.13 (d, *J* = 2.4 Hz, 1H), 6.05-6.02 (m, 1H), 5.94 (t, *J* = 10.8 Hz, 1H), 5.64-5.59 (m, 1H), 5.34-5.29 (m, 1H), 5.24-5.19 (m, 4H), 4.99 (t, *J* = 9.2 Hz, 1H), 4.75 (d, *J* = 6.4 Hz, 1H), 4.64 (d, *J* = 6.4 Hz, 1H), 4.27-4.21 (m, 2H), 4.17-4.13 (m, 1H), 4.03-4.01 (dd, *J* = 2.0 Hz, *J* = 6.4 Hz, 1H), 3.80-3.68 (m, 4H), 3.64-3.51 (m, 2H), 2.40-2.35 (m, 1H), 2.13-2.09 (m, 1H), 1.41-1.40 (m, 3H), 1.33 (s, 3H), 1.27-1.21 (m, 12H); LC/MS *m/z* 689.30 ([M + H]$^+$, for $C_{36}H_{48}O_{13}H$ requires 689.31).



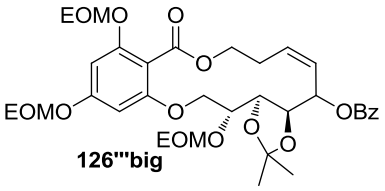
126'''dhg

126'''dhg: *Rf* = 0.35 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.05-7.97 (m, 2H), 7.51-7.44 (m, 1H), 7.40-7.25 (m, 2H), 6.46 (d, *J* = 1.6 Hz, 0.4H), 6.44 (d, *J* = 1.9 Hz, 0.2H), 6.42 (d, *J* = 1.6 Hz, 0.2H), 6.41 (d, *J* = 1.7 Hz, 0.2H), 6.35 (d, *J* = 1.6 Hz, 0.2H), 6.33 (d, *J* = 1.6 Hz, 0.2H), 6.29 (d, *J* = 1.9 Hz, 0.4H), 6.22 (d, *J* = 1.6 Hz, 0.2H), 6.14 (d, *J* = 7.2 Hz, 0.2H), 5.92 (d, *J* = 8.6 Hz, 0.3H), 5.82 (t, *J* = 9.5 Hz, 0.3H), 5.75 (t, *J* = 9.9 Hz, 0.2H), 5.42-5.25 (m, 2H), 5.13 (s, 2H), 5.11 (s, 2H), 4.45-3.89 (m, 4H), 3.66-3.61 (m, 4H), 2.43-2.07 (m, 3H), 1.97 (s, 0.75H), 1.96 (s, 0.75H), 1.92 (s, 0.75H), 1.91 (s, 0.75H), 1.84-1.67 (m, 1H), 1.38-1.11 (m, 15H); LC/MS *m/z* 630.01 ($[M + H]^+$, for $C_{34}H_{44}O_{11}H$ requires 629.99).



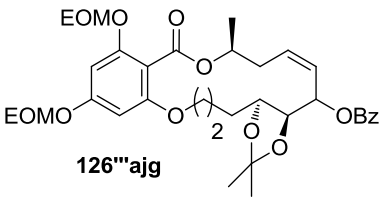
126'''aig

126'''aig: *Rf* = 0.69 (Petroleum ether/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.04 (d, *J* = 8.0 Hz, 2H), 7.50 (dd, *J* =7.5 Hz, 6.4 Hz, 1H), 7.37 (dd, *J* =8.0 Hz, 7.5 Hz, 2H), 6.49 (d, *J* =1.9 Hz, 0.4H), 6.48 (d, *J* =1.8 Hz, 0.4H), 6.38 (d, *J* =1.6 Hz, 0.6H), 6.31 (d, *J* = 1.6 Hz, 0.4H), 6.03-5.66 (m, 3H), 5.28-5.22 (m, 1H), 5.18-5.11 (m, 4H), 4.83 (d, *J* =7.0 Hz, 1H), 4.75 (d, *J* =7.0 Hz, 1H), 4.67-4.43 (m, 1.5H), 4.38-4.31 (m, 2H), 4.25-3.83 (m, 1.5H), 3.68-3.64 (m, 4H), 3.57-3.07 (m, 2H), 3.25-3.08 (m, 1H), 2.30-2.18 (m, 1H), 1.61 (s, 1H), 1.40 (s, 2H), 1.37 (s, 1H), 1.32 (s, 2H), 1.24-1.02 (m, 12H).



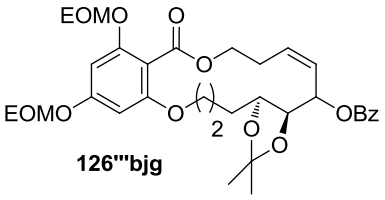
126'''big

126'''big: *Rf* = 0.66 (Petroleum ether/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.09-7.92 (m, 2H), 7.51-7.42 (m, 1H), 7.40-7.31 (m, 2H), 6.53-6.45 (m, 1H), 6.42-6.31 (m, 1H), 6.00-5.66 (m, 2H), 5.46-5.26 (m, 1H), 5.18-5.07 (m, 4H), 4.83-4.60 (m, 2H), 4.59-4.4.48 (m, 1H), 4.36-4.21 (m, 3H), 4.20-4.11 (m, 1H), 4.10-3.92 (m, 2H), 3.72-3.58 (m, 4H), 3.57-3.39 (m, 2H), 3.30-2.68 (m x 2, 1H), 2.36-2.20 (m, 1H), 1.53-1.41 (m, 3H), 1.36-1.26 (m, 3H), 1.20-1.10 (m, 9H).



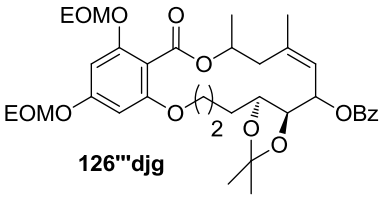
126'''ajg

126'''ajg: *Rf* = 0.35 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.01-7.96 (m, 2H), 7.49-7.45 (m, 1H), 7.39-7.33 (m, 2H), 6.43 (d, *J* = 1.9 Hz, 0.7H), 6.40 (d, *J* = 1.9 Hz, 0.3H), 6.24 (d, *J* = 1.9 Hz, 0.7H), 6.22 (d, *J* = 1.6 Hz, 0.3H), 5.93-5.77 (m, 2H), 5.41-5.27 (m, 2H), 5.16-5.08 (m, 4H), 4.40 (d, *J* = 6.2 Hz, 0.3H), 4.34 (d, *J* = 5.6 Hz, 0.3H), 4.30 (d, *J* = 5.4 Hz, 0.4H), 4.26-4.10 (m, 1H), 3.94-3.80 (m, 2H), 3.68-3.61 (m, 4H), 3.11-2.92 (m, 1H), 2.70-2.37 (m, 1H), 1.90-1.45 (m, 4H), 1.43 (s, 1H), 1.36 (s, 2H), 1.35 (s, 1H), 1.33 (s, 1H), 1.32 (s, 1H), 1.29 (d, *J* = 4.3 Hz, 2H), 1.27 (d, *J* = 4.6 Hz, 1H), 1.21-1.15 (m, 6H); LC/MS *m/z* 629.22 ($[M + H]^+$, for $C_{34}H_{44}O_{11}H$ requires 629.70).



126'''bjg

126'''bjg: *Rf* = 0.34 (Petroleum ether/EtOAc 3/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.05-8.01 (m, 2H), 7.54-7.49 (m, 1H), 7.43-7.38 (m, 2H), 6.48 (s, 1H), 6.27 (s, 1H), 5.97-5.75 (m, 2H), 5.41 (d, *J* = 10.2 Hz, 0.6H), 5.39 (d, *J* = 10.4 Hz, 0.4H), 5.18 (s, 1H), 5.17 (s, 3H), 4.83 (dt, *J* = 11.0, 3.8 Hz, 0.6H), 4.69 (dt, *J* = 11.0, 4.6 Hz, 0.4H), 4.44 (d, *J* = 6.7 Hz, 0.3H), 4.35 (d, *J* = 9.7 Hz, 0.4H), 4.32 (d, *J* = 9.7 Hz, 0.3H), 4.30-4.13 (m, 2H), 4.05-3.85 (m, 2H), 3.72-3.66 (m, 4H), 3.15-2.88 (m, 1H), 2.67-2.46 (m, 1H), 1.96-1.63 (m, 4H), 1.48 (s, 1H), 1.42 (s, 2H), 1.35 (s, 2H), 1.34 (s, 1H), 1.21-1.17 (m, 6H); LC/MS *m/z* 615.21 ($[M + H]^+$, for $C_{33}H_{42}O_{11}H$ requires 615.68).

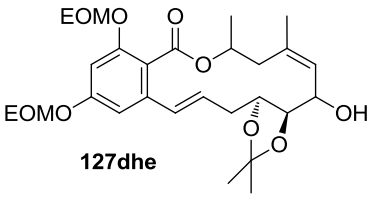


126'''djg

126'''djg: *Rf* = 0.35 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.03 (d, *J* = 7.7 Hz, 2H), 7.49 (d, *J* = 7.4 Hz, 1H), 7.41-7.35 (m, 2H), 6.45 (d, *J* = 1.6 Hz, 0.3H), 6.43 (d, *J* = 1.6 Hz, 0.4H), 6.42 (d, *J* = 1.6 Hz, 0.3H), 6.26 (d, *J* = 1.3 Hz, 0.4H), 6.25 (d, *J* = 1.9 Hz, 0.3H), 6.23 (d, *J* = 1.9 Hz, 0.3H), 5.87-5.79 (m, 1H), 5.63 (d, *J* = 9.7 Hz, 0.5H), 5.51-5.31 (m, 1H), 5.28 (d, *J* = 9.6 Hz, 0.5H), 5.20-5.12 (m, 4H), 4.43-6.31 (m, 1H), 4.26-4.10 (m, 2H), 4.05-3.92 (m, 1H), 3.68 (q, *J* = 7.1 Hz, 4H), 2.39-2.05 (m, 3H), 1.89 (s, 0.5H), 1.86 (s, 2H), 1.79 (s, 0.5H), 1.73-1.43 (m, 3H), 1.40 (s, 1H), 1.38 (s, 2H), 1.32 (s, 2H), 1.31 (s, 1H), 1.27 (d, *J* = 4.6 Hz, 2H), 1.23-1.15 (m, 7H); LC/MS *m/z* 643.27 ($[M + H]^+$, for $C_{35}H_{46}O_{11}H$ requires 643.73).

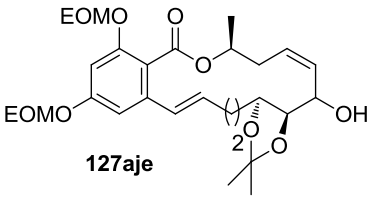
General procedure for the benzoate deprotection. Synthesis of compounds 127. Macrocycle **126'''** (1.0 equiv) was treated 12 h with a solution of 1% NaOH in MeOH at reflux. The reaction was quenched with sat. NH_4Cl aq. solution, extracted with EtOAc, dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 1/2) provided desired alcohols **127** in 80-90% yields.

Selected examples of compounds 127.



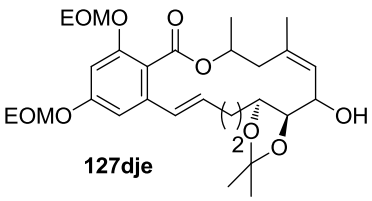
127dhe

126dhe: *Rf* = 0.20 (Petroleum ether/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.74 (d, *J* = 1.9 Hz, 0.3H), 6.73 (d, *J* = 1.9 Hz, 0.3H), 6.72 (d, *J* = 2.2 Hz, 0.2H), 6.71 (d, *J* = 2.2 Hz, 0.2H), 6.60 (d, *J* = 2.1 Hz, 0.2H), 6.59 (d, *J* = 2.2 Hz, 0.2H), 6.56 (d, *J* = 1.9 Hz, 0.2H), 6.54 (d, *J* = 2.2 Hz, 0.4H), 6.51 (d, *J* = 16.6 Hz, 0.4H), 6.46 (d, *J* = 15.8 Hz, 0.2H), 6.37 (d, *J* = 16.4 Hz, 0.2H), 6.32 (d, *J* = 16.2 Hz, 0.2H), 6.19 (dt, *J* = 16.1, 6.3 Hz, 0.2H), 6.13-5.99 (m, 0.5H), 5.85 (dt, *J* = 16.1, 6.9 Hz, 0.3H), 5.70-5.28 (m, 2H), 5.20-5.13 (m, 4H), 4.78 (d, *J* = 7.8 Hz, 0.2H), 4.72 (d, *J* = 7.8 Hz, 0.2H), 4.37 (d, *J* = 9.1 Hz, 0.3H), 4.33 (d, *J* = 8.9 Hz, 0.3H), 4.29-4.17 (m, 1H), 4.03 (dd, *J* = 9.5, 4.9 Hz, 0.4H), 3.93 (dd, *J* = 9.7, 4.8 Hz, 0.3H), 3.84 (dd, *J* = 9.4, 4.8 Hz, 0.3H), 3.74-3.65 (m, 4H), 2.65-2.15 (m, 4H), 1.87 (s, 1H), 1.83 (s, 1H), 1.80 (s, 0.5H), 1.69 (s, 0.5H), 1.54 (s, 0.5H), 1.52 (s, 0.5H), 1.51 (s, 1H), 1.50 (s, 1H), 1.41-1.30 (m, 6H), 1.21-1.17 (m, 6H), OH signal is not visible; LC/MS *m/z* 521.27 ($[M + H]^+$, for $C_{28}H_{40}O_9H$ requires 521.61).

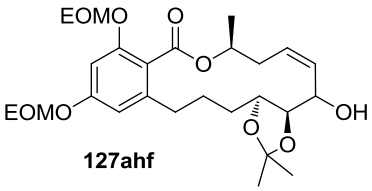


127aje

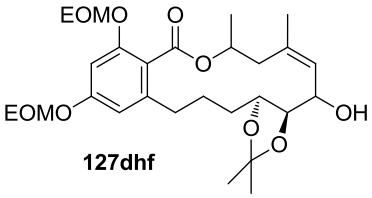
127aje: *Rf* = 0.20 (Petroleum ether/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.79 (d, *J* = 1.9 Hz, 0.4H), 6.77 (d, *J* = 2.1 Hz, 0.6H), 6.74 (d, *J* = 2.1 Hz, 0.6H), 6.71 (d, *J* = 2.1 Hz, 0.4H), 6.54-6.02 (m, 2H), 6.00-5.37 (m, 3H), 5.23-5.17 (m, 4H), 4.52-4.34 (m, 1H), 4.32-4.20 (m, 1H), 4.08-3.93 (m, 1H), 3.73-3.67 (m, 4H), 2.80-2.67 (m, 1H), 2.62-2.52 (m, 1H), 2.36-2.24 (m, 1H), 2.15-1.99 (m, 1H), 1.76-1.55 (m, 2H), 1.51-1.31 (m, 9H), 1.22-1.17 (m, 6H), OH signal is not visible; LC/MS *m/z* 521.28 ($[M + H]^+$, for $C_{28}H_{40}O_9H$ requires 521.61).



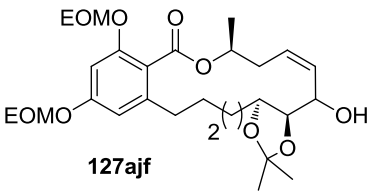
127dje: *Rf* = 0.21 (Petroleum ether/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.81 (d, *J* = 2.2 Hz, 0.3H), 6.79 (d, *J* = 2.1 Hz, 0.3H), 6.77 (d, *J* = 1.9 Hz, 0.4H), 6.71 (d, *J* = 2.1 Hz, 0.3H), 6.69 (d, *J* = 1.9 Hz, 0.4H), 6.67 (d, *J* = 1.9 Hz, 0.3H), 6.37-6.07 (m, 2H), 5.66-5.38 (m, 2H), 5.25-5.15 (m, 4H), 4.83-4.35 (m, 1H), 4.23-4.02 (m, 2H), 3.69 (q, *J* = 7.0 Hz, 4H), 2.53-2.21 (m, 4H), 1.91 (s, 0.75H), 1.86 (s, 0.75H), 1.84 (s, 0.75H), 1.81-1.57 (m, 2H), 1.71 (s, 0.75H), 1.50 (s, 1H), 1.47 (s, 1H), 1.46 (s, 1H), 1.41-1.33 (m, 6H), 1.21-1.17 (m, 6H), OH signal is not visible; LC/MS *m/z* 535.30 ($[M + H]^+$, for $C_{29}H_{42}O_9H$ requires 535.63).



127ahf: *Rf* = 0.36 (Petroleum ether/EtOAc 1/1) ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) (major diastereoisomer) δ 6.68 (d, *J* = 2.2 Hz, 1 H), 6.51 (d, *J* = 1.7 Hz, 1 H), 5.85-5.77 (m, 1H), 5.45-5.39 (m, 1H), 5.36-5.28 (m, 1H), 5.21-5.15 (m, 4H), 4.35-4.29 (m, 1H), 4.07-4.01 (m, 1H), 3.96-3.91 (m, 1H), 3.76-3.66 (m, 4H), 2.93-2.83 (m, 1H), 2.72-2.53 (m, 2H), 2.50-2.39 (m, 1H), 2.31-2.23 (m, 1H), 1.82-1.68 (m, 1H), 1.67-1.38 (m, 8H), 1.34 (m, 3H), 1.27-1.18 (m, 6H), OH signal is not visible; LC/MS *m/z* 531.22 ($[M + Na]^+$, for $C_{27}H_{40}O_9Na$ requires 531.26).

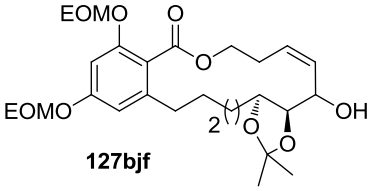


127dhf: *Rf* = 0.21 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.70 (d, *J* = 2.2 Hz, 0.3H), 6.68 (d, *J* = 2.2 Hz, 0.5H), 6.62 (d, *J* = 2.1 Hz, 0.2H), 6.54 (d, *J* = 2.1 Hz, 0.2H), 6.52 (d, *J* = 2.1 Hz, 0.5H), 6.48 (d, *J* = 2.1 Hz, 0.3H), 5.65-5.25 (m, 2H), 5.19-5.15 (m, 4H), 4.41-4.19 (m, 1H), 4.06-3.89 (m, 2H), 3.72-3.67 (m, 4H), 2.84-2.19 (m, 5H), 1.99-1.57 (m, 3H), 1.85 (s, 1.5H), 1.83 (s, 1H), 1.79 (s, 0.5H), 1.66 (s, 0.5H), 1.51 (s, 0.5H), 1.48 (s, 2H), 1.41-1.32 (m, 6H), 1.23-1.17 (m, 6H), OH signal is not visible; LC/MS *m/z* 545.41 ($[M + Na]^+$, for $C_{28}H_{42}O_9Na$ requires 545.62).



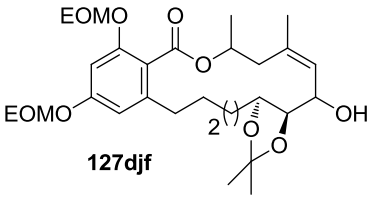
127ajf

127ajf: *Rf* = 0.14 (Petroleum ether/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.70 (d, *J* = 1.6 Hz, 1H), 6.56 (d, *J* = 1.9 Hz, 0.7H), 6.53 (d, *J* = 2.2 Hz, 0.3H), 5.97-5.90 (m, 1H), 5.49-5.39 (m, 2H), 5.18 (s, 4H), 4.36-4.28 (m, 1H), 4.20-4.05 (m, 1H), 3.96-3.92 (m, 1H), 3.73-3.67 (dq, *J* = 7.2 Hz, 2.4 Hz, 4H), 3.04-2.97 (m, 0.4H), 2.82 (dt, J = 17.2 Hz, 10.4 Hz, 0.6H), 2.62-2.38 (m, 3H), 1.75-1.70 (m, 2H), 1.67-1.54 (m, 4H), 1.47 (s, 1H), 1.45 (s, 2H), 1.40 (d, J = 7.0 Hz, 1.5H), 1.39 (d, J = 6.4 Hz, 1.5H), 1.36 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 6H), OH signal is not visible; LC/MS *m/z* 545.32 ([M + Na]$^+$, for $C_{28}H_{42}O_9Na$ requires 545.28).



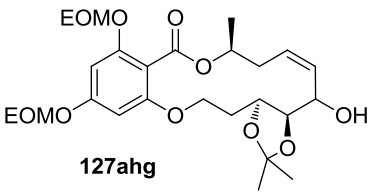
127bjf

127bjf: *Rf* = 0.33 (Petroleum ether/EtOAc 1/2); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.71 (d, *J* = 2.0 Hz, 1H), 6.59-6.55 (m, 1H), 5.92 (t, *J* = 9.6 Hz, 0.5H), 5.84-5.73 (m, 1H), 5.92 (t, *J* = 9.6 Hz, 0.5H), 5.19 (s, 4H), 4.73-4.58 (m x 2, 1H), 4.39-4.29 (m, 2H), 4.17-3.91 (m x 3, 2H), 3.71 (q, *J* = 7.2 Hz, 2H), 3.70 (q, *J* = 7.2 Hz, 2H), 3.04-2.84 (m, 1H), 2.57-2.50 (m, 3H), 1.74-1.51 (m, 4H), 1.48 (s, 1.5H), 1.47 (s, 1.5H), 1.36 (s, 1.5H), 1.35 (s, 1.5H), 1.25 (s, 2H), 1.21 (t, *J* = 7.2 Hz, 6H), OH signal is not visible; LC/MS *m/z* 531.18 ([M + Na]$^+$, for $C_{27}H_{40}O_9Na$ requires 531.26).



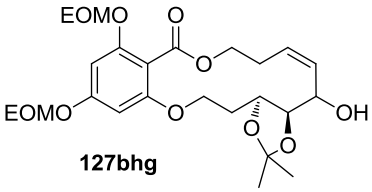
127djf

127djf: *Rf* = 0.10 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.68 (d, *J* = 2.1 Hz, 0.8H), 6.53 (d, *J* = 2.1 Hz, 0.2H), 6.57 (bs, 0.6H), 6.53 (d, *J* = 2.1 Hz, 0.4H), 5.60-5.29 (m, 2H), 5.20 (s, 2.5H), 5.17 (s, 1H), 5.14 (s, 0.5H), 4.41-4.30 (m, 1H), 4.27-4.03 (m, 1H), 3.97-3.85 (m, 1H), 3.71 (q, *J* = 7.0 Hz, 4H), 2.69-2.54 (m, 1H), 2.47-2.16 (m, 4H), 1.85 (s, 2H), 1.83 (s, 0.5H), 1.77 (s, 0.5H), 1.73-1.55 (m, 3H), 1.49 (s, 1.5H), 1.46 (s, 1.5H), 1.42-1.32 (m, 8H), 1.21 (t, *J* = 7.0 Hz, 6H), OH signal is not visible; LC/MS *m/z* 559.34 ([M + Na]$^+$, for $C_{29}H_{44}O_9Na$ requires 559.63).



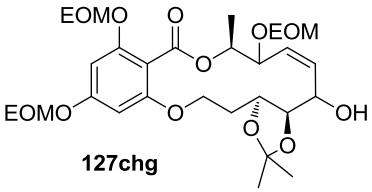
127ahg

127ahg: *Rf* = 0.47 (Petroleum ether/EtOAc 1/2); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.56 (d, *J* = 1.9 Hz, 1H), 6.39 (d, *J* = 1.7 Hz, 1H), 5.85-5.75 (m, 1H), 5.67-5.52 (m, 1H), 5.34-5.15 (m, 5H), 4.72-4.56 (m, 1H), 4.22-4.17 (m, 2H), 4.16-3.90 (m, 2H), 3.73-3.66 (m, 4H), 2.93-2.76 (m, 1H), 2.44-2.37 (m, 1H), 2.30-2.17 (m, 1H), 2.11-2.05 (m, 1H), 1.53-1.50 (m, 3H), 1.37-1.35 (m, 6H), 1.23-1.18 (m, 6H), OH signal is not visible; LC/MS *m/z* 511.23 ($[M + H]^+$, for $C_{26}H_{38}O_{10}H$ requires 511.25).



127bhg

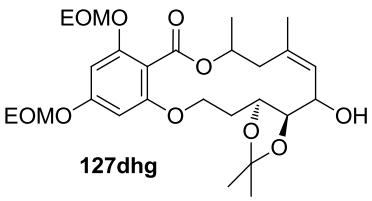
127bhg: *Rf* = 0.50 (Petroleum ether/EtOAc 1/2); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.52 (d, *J* = 1.9 Hz, 0.6H), 6.50 (d, *J* = 1.9 Hz, 0.4H), 6.37 (d, *J* = 1.9 Hz, 0.6H), 6.27 (d, *J* = 1.9 Hz, 0.4H), 5.75-5.68 (m, 2H), 5.18-5.15 (m, 4H), 5.82-4.60 (m, 2H), 4.28-4.11 (m, 4H), 3.98-3.96 (m, 1H), 3.73-3.66 (m, 4H), 3.04-2.69 (m, 1H), 2.53-2.43 (m, 1H), 2.34-2.07 (m, 2H), 1.51-1.43 (m, 3H), 1.36-1.33 (m, 3H), 1.22-1.18 (m, 6H), OH signal is not visible.



127chg

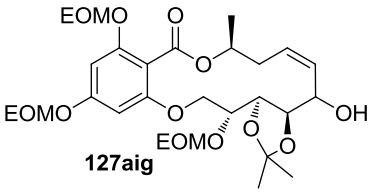
127chg, major diastereoisomer: *Rf* = 0.57 (Petroleum ether/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.54 (s, 1H), 6.38 (s, 1H), 5.82 (t, *J* = 11.2 Hz, 1H), 5.59 (t, *J* = 10.8 Hz, 1H), 5.33-5.28 (m, 1H), 5.23-5.16 (m, 4H), 4.84 (d, *J* = 7.2 Hz, 1H), 4.75-4.58 (m, 1H), 4.65 (d, *J* = 6.8 Hz, 1H), 4.44-4.38 (m, 1H), 4.21-4.02 (m, 4H), 3.77-3.55 (m, 6H), 2.22-2.13 (m, 1H), 2.05-1.96 (m, 1H), 1.49-1.36 (m, 6H), 1.25-1.20 (m, 12H), OH signal is not visible; LC/MS *m/z* 585.27 ($[M + H]^+$, for $C_{29}H_{44}O_{12}H$ requires 585.29).

127chg, minor diastereoisomer: *Rf* = 0.46 (Petroleum ether/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.26 (d, *J* = 2.0 Hz, 1H), 6.07 (d, *J* = 2.0 Hz, 1H), 5.92 (dd, *J* = 8.4 Hz, *J* = 11.2 Hz, 1H), 5.63 (t, *J* = 10.8 Hz, 1H), 5.33-5.30 (m, 1H), 5.21 (s, 4H), 4.83 (d, *J* = 7.2 Hz, 1H), 4.70 (d, *J* = 7.2 Hz, 1H), 4.53 (t, *J* = 7.2 Hz, 1H), 4.48-4.39 (m, 2H), 4.17 (t, *J* = 6.0 Hz, 1H), 4.012-4.08 (m, 2H), 3.76-3.57 (m, 6H), 2.03 (dt, *J* = 12.7, 6.1 Hz, 2H), 1.52 (s, 3H), 1.39 (s, 3H), 1.25-1.16 (m, 12H), OH signal is not visible; LC/MS *m/z* 585.27 ($[M + H]^+$, for $C_{29}H_{44}O_{12}H$ requires 585.29).



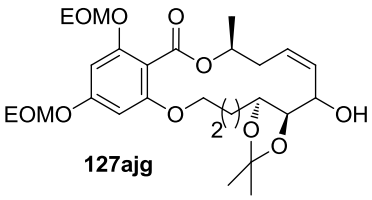
127dhg

127dhg: *Rf* = 0.22 (Petroleum ether/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.42 (d, *J* = 1.6 Hz, 0.6H), 6.40 (d, *J* = 1.9 Hz, 0.2H), 6.38 (d, *J* = 1.7 Hz, 0.2H), 6.34 (d, *J* = 1.6 Hz, 0.2H), 6.25 (d, *J* = 1.6 Hz, 0.6H), 6.19 (d, *J* = 1.6 Hz, 0.2H), 5.45-5.22 (m, 2H), 5.11 (s, 4H), 4.39-4.30 (m, 0.5H), 4.23-4.19 (m, 1H), 4.09-4.00 (m, 1.5H), 3.99-3.86 (m, 2H), 3.67-3.60 (m, 4H), 2.69-2.05 (m, 3H), 1.91-1.83 (m, 1H), 1.81 (s, 0.5H), 1.77 (s, 0.5H), 1.75 (s, 1H), 1.67 (s, 1H), 1.46 (s, 0.7H), 1.43 (s, 1.3H), 1.40 (s, 1H), 1.32 (d, *J* = 6.2 Hz, 1H), 1.29 (d, *J* = 6.4 Hz, 2H), 1.27 (s, 2.5H), 1.25 (s, 0.5H), 1.17-1.12 (m, 6H), OH signal is not visible; LC/MS *m/z* 547.53 ([M + Na]$^+$, for $C_{27}H_{40}O_{10}Na$ requires 547.60).



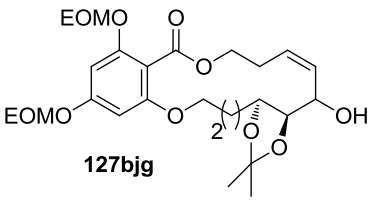
127aig

127aig: *Rf* = 0.69 (Petroleum ether/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.49 (d, *J* = 1.6 Hz, 0.4H), 6.44 (d, *J* = 1.6 Hz, 0.6H), 6.35 (d, *J* = 1.6 Hz, 0.4H), 6.32(d, *J* = 1.6 Hz, 0.6H), 5.90-5.58 (m, 2H), 5.27-5.21 (m, 1H), 5.18-5.04 (m, 4H), 5.05 (t, *J* = 7.3 Hz, 0.6H), 4.96-4.90 (m, 0.4H), 4.86-4.78 (m, 2H), 4.60 (dd, *J* = 9.4, 3.3 Hz, 0.4H), 4.46-4.39 (m, 1.6H), 4.28 (dd, *J* = 8.3, 6.4 Hz, 0.6H), 4.19-4.04 (m, 1.4H), 3.93 (ddd, *J* = 11.1, 10.3, 5.1 Hz, 1H), 3.68-3.53 (m, 6H), 2.77 (ddd, *J* = 15.6, 10.9, 8.2 Hz, 0.4H), 2.27-2.22 (m, 0.6H), 2.17-2.09 (m, 1H), 1.51 (s, 1H), 1.39 (s, 2H), 1.35 (s, 1H), 1.34 (s, 2H), 1.22 (d, *J* = 6.2 Hz, 2H), 1.20 (d, *J* = 6.2 Hz, 1H), 1.19-1.11 (m, 9H), OH signal is not visible; LC/MS *m/z* 607.37 ([M + Na]$^+$, for $C_{29}H_{44}O_{12}Na$ requires 607.28).



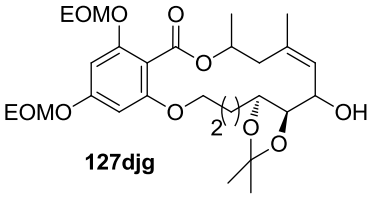
127ajg

127ajg: *Rf* = 0.25 (Petroleum ether/EtOAc 2/1); H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.44 (d, *J* = 1.9 Hz, 0.6H), 6.42 (d, *J* = 1.6 Hz, 0.4H), 6.23 (d, *J* = 1.6 Hz, 1H), 5.88-5.77 (m, 1H), 5.37-5.26 (m, 2H), 5.17-5.11 (m, 4H), 4.51-4.29 (m, 1H), 4.26-4.05 (m, 1H), 4.04-3.86 (m, 2H), 3.75-3.65 (m, 5H), 2.84-2.26 (m, 2H), 1.78-1.66 (m, 4H), 1.43 (s, 2H), 1.42 (s, 1H), 1.36 (d, *J* = 6.2 Hz, 3H), 1.33 (s, 2H), 1.32 (s, 1H), 1.23-1.15 (m, 6H), OH signal is not visible; LC/MS *m/z* 525.28 ([M + H]$^+$, for $C_{27}H_{40}O_{10}H$ requires 525.60).



127bjg

127bjg: *Rf* = 0.32 (Petroleum ether/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.46 (d, *J* = 1.6 Hz, 1H), 6.25 (d, *J* = 1.6 Hz, 1H), 5.87 (td, *J* = 9.9, 2.4 Hz, 0.4H), 5.73 (td, *J* = 9.9, 2.6 Hz, 0.6H), 5.38 (d, *J* = 10.1 Hz, 0.6H), 5.36 (d, *J* = 9.9 Hz, 0.4H), 5.17 (s, 2H), 5.16 (s, 2H), 4.77 (dt, *J* = 11.0, 3.8 Hz, 0.6H), 4.57 (dt, *J* = 11.0, 4.0 Hz, 0.4H), 4.43-3.77 (m, 5H), 3.72-3.65 (m, 5H), 2.97-2.82 (m, 1H), 2.47-2.41 (m, 1H), 2.15-1.98 (m, 1H), 1.94-1.79 (m, 1H), 1.75-1.50 (m, 2H), 1.46 (s, 3H), 1.35 (s, 2H), 1.34 (s, 1H), 1.23-1.16 (m, 6H), OH signal is not visible; LC/MS *m/z* 511.21 ($[M + H]^+$, for $C_{26}H_{38}O_{10}H$ requires 511.57).

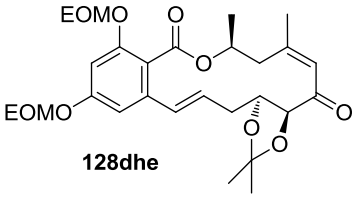


127djg

127djg: *Rf* = 0.35 (Petroleum ether/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.43 (d, *J* = 1.9 Hz, 0.3H), 6.42 (d, *J* = 1.9 Hz, 0.4H), 6.41 (d, *J* = 1.8 Hz, 0.3H), 6.24 (d, *J* = 1.6 Hz, 0.5H), 6.23 (d, *J* = 1.8 Hz, 0.25H), 6.22 (d, *J* = 1.9 Hz, 0.25H), 5.54-5.27 (m, 1H), 5.21-5.17 (m, 1H), 5.16-5.13 (m, 4H), 4.33-4.27 (m, 1H), 4.21-3.85 (m, 4H), 3.71-3.65 (m, 4H), 2.41-2.12 (m, 3H), 2.11-1.88 (m, 2H), 1.82 (s, 1H), 1.76 (s, 1H), 1.74 (s, 0.5H), 1.69 (s, 0.5H), 1.67-1.51 (m, 1H), 1.48 (s, 1H), 1.46 (s, 1H), 1.45 (s, 1H), 1.37 (d, *J* = 6.2 Hz, 1.5H), 1.34 (d, *J* = 6.5 Hz, 1.5H), 1.32 (s, 2H), 1.29 (s, 1H), 1.21-1.16 (m, 6H), OH signal is not visible; LC/MS *m/z* 539.25 ($[M + H]^+$, for $C_{28}H_{42}O_{10}H$ requires 539.62).

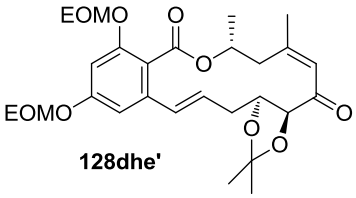
General procedure for the oxidation reaction with DMP. Synthesis of compounds 128. A solution of the corresponding compound **127** (1.0 equiv) in CH_2Cl_2 (0.05 M) was treated with DMP (1.5 equiv). The mixture was stirred for 4 h at reflux, diluted with Et_2O, washed with sat. $NaHCO_3$ aq. solution, sat. $Na_2S_2O_3$ aq. solution and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure and purification by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 2/1) afforded macrocycles **128** in 80-90% yields.

Selected examples of compounds 128.



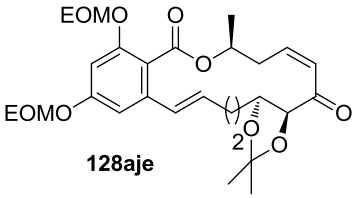
128dhe

128dhe: *Rf* = 0.31 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.75 (d, *J* = 2.1 Hz, 1H), 6.74 (d, *J* = 2.1 Hz, 1H), 6.44 (s, 1H), 6.31 (d, *J* = 16.1 Hz, 1H), 6.21-6.13 (m, 1H), 5.53-5.46 (m, 1H), 5.20 (s, 1H), 5.18 (s, 1H), 5.17 (s, 2H), 4.68-4.65 (m, 1H), 4.60 (d, *J* = 8.1 Hz, 1H), 3.73-3.66 (m, 4H), 2.47-2.36 (m, 4H), 2.34 (s, 3H), 1.47 (s, 3H), 1.42 (d, *J* = 6.4 Hz, 3H),1.33 (s, 3H), 1.23-1.17 (m, 6H); LC/MS *m/z* 541.43 ([M + Na]$^+$, for $C_{28}H_{38}O_9Na$ requires 541.59).



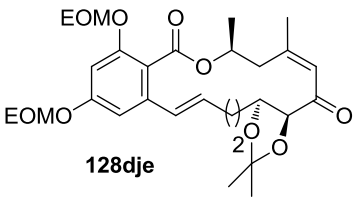
128dhe'

128dhe': *Rf* = 0.31 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.77 (d, *J* = 2.1 Hz, 1H), 6.76 (d, *J* = 2.1 Hz, 1H), 6.29 (dd, *J* = 15.6, 1.9 Hz, 1H), 6.13-6.09 (m, 2H), 5.53-5.45 (m, 1H), 5.22-5.14 (m, 4H), 4.57 (d, *J* = 6.7 Hz, 1H), 4.51-4.46 (m, 1H), 3.73-3.66 (m, 4H), 2.73-2.67 (m, 1H), 2.43-2.34 (m, 3H), 2.32 (s, 3H), 1.65 (s, 3H), 1.39 (s, 3H), 1.38 (d, *J* = 6.2 Hz, 3H), 1.23-1.18 (m, 6H); LC/MS *m/z* 541.43 ([M + Na]$^+$, for $C_{28}H_{38}O_9Na$ requires 541.59).



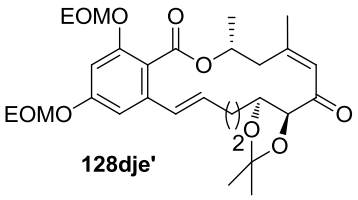
128aje

128aje: *Rf* = 0.30 (Petroleum ether/EtOAc 3/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.80 (d, *J* = 1.9 Hz, 1H), 6.78 (d, *J* = 2.2 Hz, 1H), 6.60-6.47 (m, 2H), 6.26-6.17 (m, 2H), 5.68-5.60 (m, 1H), 5.28-5.16 (m, 4H), 4.71 (d, *J* = 7.2 Hz, 1H), 4.43-4.38 (m, 1H), 3.70 (q, *J* = 7.0 Hz, 4H), 3.17-3.01 (m, 2H), 2.34-2.21 (m, 1H), 2.12-2.03 (m, 1H), 1.86-1.77 (m, 1H), 1.62 (s, 3H), 1.55-1.48 (m, 1H), 1.38 (s, 3H), 1.37 (d, *J* = 6.1 Hz, 3H), 1.23-1.18 (m, 6H); LC/MS *m/z* 519.26 ([M + H]$^+$, for $C_{28}H_{38}O_9H$ requires 519.59).



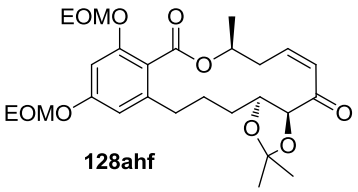
128dje

128dje: *Rf* = 0.31 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.81 (d, *J* = 2.1 Hz, 1H), 6.72 (d, *J* = 1.9 Hz, 1H), 6.52 (s, 1H), 6.26-6.19 (m, 1H), 6.09 (d, *J* = 15.9 Hz, 1H), 5.82-5.74 (m, 1H), 5.21-5.16 (m, 4H), 4.65 (d, *J* = 6.2 Hz, 1H), 4.40 (q, *J* = 6.4 Hz, 1H), 3.70 (q, *J* = 7.0 Hz, 4H), 2.67-2.48 (m, 2H), 2.34 (s, 3H), 2.27-2.05 (m, 2H), 1.71-1.60 (m, 2H), 1.52 (s, 3H), 1.39 (d, *J* = 6.1 Hz, 3H),1.34 (s, 3H), 1.22-1.18 (m, 6H); LC/MS *m/z* 555.36 ([M + Na]$^+$, for $C_{29}H_{40}O_9Na$ requires 555.62).



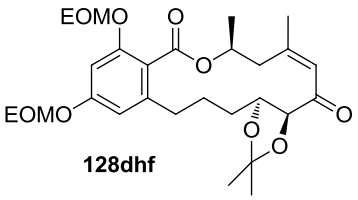
128dje'

128dje': *Rf* = 0.31 (Petroleum ether/EtOAc 3/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.82 (s, 1H), 6.72 (s, 1H), 6.55 (s, 1H), 6.34-6.16 (m, 2H), 5.54-5.48 (m, 1H), 5.52-5.15 (m, 4H), 4.75-4.66 (m, 1H), 4.47-4.38 (m, 1H), 3.73-3.65 (m, 4H), 2.65-2.34 (m, 4H), 2.30 (s, 3H), 1.75-1.64 (m, 2H), 1.58 (s, 3H), 1.42 (d, *J* = 6.4 Hz, 3H),1.35 (s, 3H), 1.25-1.18 (m, 6H); LC/MS *m/z* 555.32 ([M + Na]$^+$, for $C_{29}H_{40}O_9Na$ requires 555.62).



128ahf

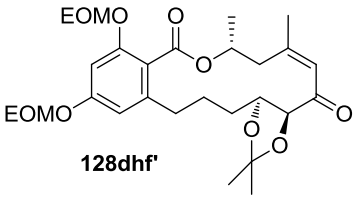
128ahf: *Rf* = 0.70 (Petroleum ether/EtOAc 1/1); NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.67 (d, *J* = 2.2 Hz, 1 H), 6.62-6.40 (m, 2H), 6.42-6.30 (m, 1H), 5.52-5.41 (m, 1H), 5.23-5.13 (m, 4H), 4.62-4.43 (m, 1H), 4.50-4.41 (m, 1H), 3.77-3.65 (m, 4H), 2.58-2.45 (m, 2H), 1.65-1.41 (m, 12H), 1.34 (s, 3H), 1.27-1.18 (m, 6H); LC/MS *m/z* 529.16 ([M + Na]$^+$, for $C_{27}H_{38}O_9Na$ requires 529.25).



128dhf

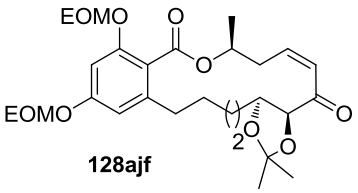
128dhf: *Rf* = 0.31 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.68 (d, *J* = 2.2 Hz, 1H), 6.54 (bs, 1H), 6.53 (d, *J* = 2.1 Hz, 1H), 5.55-5.47 (m, 1H), 5.18 (s, 2H), 5.17 (s, 2H), 4.53 (d, *J* = 7.3

Hz, 1H), 4.40 (dd, *J* = 7.2, 5.1 Hz, 1H), 3.74-3.66 (m, 4H), 2.57-2.38 (m, 5H), 2.29 (s, 3H), 1.62-1.53 (m, 3H), 1.43 (d, *J* = 6.2 Hz, 3H), 1.33 (s, 3H), 1.30 (s, 3H), 1.20 (t, *J* = 7.0 Hz, 6H); LC/MS *m/z* 543.87 ([M + Na]$^+$, for $C_{28}H_{40}O_9Na$ requires 543.61).



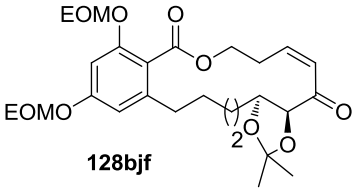
128dhf'

128dhf': *Rf* = 0.31 (Petroleum ether/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.71 (d, *J* = 2.1 Hz, 1H), 6.54 (d, *J* = 2.2 Hz, 1H), 6.06 (s, 1H), 5.52-5.43 (m, 1H), 5.20 (s, 2H), 5.17 (s, 2H), 4.56 (d, *J* = 6.6 Hz, 1H), 4.23-4.18 (m, 1H), 3.72 (q, *J* = 7.2 Hz, 2H), 3.71 (q, *J* = 7.0 Hz, 2H), 2.53-2.32 (m, 4H), 2.26 (s, 3H), 1.76-1.69 (m, 2H), 1.67 (s, 3H), 1.56-1.47 (m, 2H), 1.43 (d, *J* = 6.2 Hz, 3H), 1.35 (s, 3H), 1.22 (t, *J* = 7.0 Hz, 6H); LC/MS *m/z* 543.80 ([M + Na]$^+$, for $C_{28}H_{40}O_9Na$ requires 543.61).



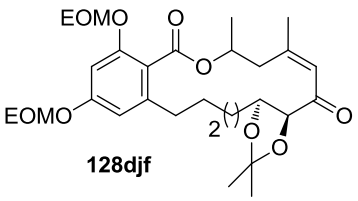
128ajf

128ajf: *Rf* = 0.63 (Petroleum ether/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.70-6.69 (m, 1H), 6.57-6.48 (m, 3H), 5.56-5.52 (m, 1H), 5.20-5.16 (m, 4H), 5.64 (d, *J* = 7.2 Hz, 1H), 4.38-4.34 (m, 1H), 3.72-3.67 (m, 4H), 3.10-3.07 (m, 2H), 2.46-2.42 (m, 2H), 1.71-1.40 (m, 10H), 1.36 (s, 3H), 1.27-1.24 (m, 2H), 1.21 (t, *J* = 7.2 Hz, 6H) ; LC/MS *m/z* 543.27 ([M + Na]$^+$, for $C_{28}H_{40}O_9Na$ requires 543.26).



128bjf

128bjf: *Rf* = 0.40 (Petroleum ether/EtOAc 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.70 (d, *J* = 2.0 Hz, 1H), 6.64 (d, *J* = 11.6 Hz, 1H), 6.52 (d, *J* = 2.0 Hz, 1H), 6.42-6.36 (m, 1H), 5.18 (s, 4H), 4.71-4.66 (m, 1H), 4.56 (d, *J* = 7.2 Hz, 1H), 4.45-4.34 (m, 2H), 3.74-3.67 (m, 4H), 3.44-3.36 (m, 1H), 2.93-2.85 (m, 1H), 2.44 (t, *J* = 8.2 Hz, 2H), 1.65-1.48 (m, 7H), 1.36 (s, 3H), 1.28-1.24 (m, 2H), 1.23-1.18 (m, 6H); LC/MS *m/z* 529.29 ([M + Na]$^+$, for $C_{27}H_{38}O_9Na$ requires 529.25).

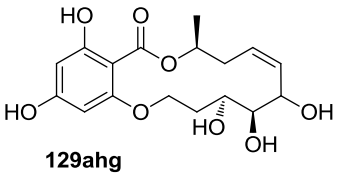


128djf

128djf: *Rf* = 0.30 (Petroleum ether/EtOAc 3/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, , 25 °C) δ 6.68 (d, *J* = 1.9 Hz, 0.5H), 6.66 (d, *J* = 1.9 Hz, 0.5H), 6.55 (bs, 1H), 6.49 (bs, 0.5H), 6.17 (bs, 0.5H), 5.54-5.38 (m, 1H), 5.20-5.14 (m, 4H), 4.62 (d, *J* = 6.7 Hz, 0.5H), 4.49 (d, *J* = 7.3 Hz, 0.5H), 4.39-4.23 (m, 1H), 3.73-3.68 (m, 4H), 2.61-2.35 (m, 5H), 2.26 (s, 1.5H), 2.25 (s, 1.5H), 1.73-1.66 (m, 5H), 1.57 (s, 1.5H), 1.43 (d, *J* = 6.2 Hz, 1.5H), 1.36 (s, 1.5H), 1.31 (d, *J* = 6.9 Hz, 1.5H), 1.25 (s, 3H), 1.23-1.19 (m, 6H); LC/MS *m/z* 557.35 ([M + Na]$^+$, for $C_{29}H_{42}O_9Na$ requires 557.63).

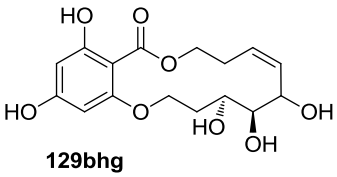
General procedure for the synthesis of compounds 129. To a solution of macrocycle **127** (1.0 equiv) in MeOH (10 mL/g of resin) was added sulfonic acid resin (5.0 equiv, 3 mmol/g). The suspension was warmed at 50 °C for 2 h. After filtration of the resin and evaporation of the solvents under reduced pressure, purification by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 2/1) afforded desired alcohols **129** in >90% yields.

Selected examples of compounds 129.



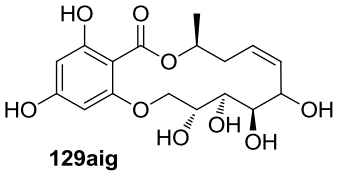
129ahg

129ahg: *Rf* = 0.26 (EtOAc/MeOH 10/1); ^{1}H NMR (CD_3OD, 400 MHz, 25 °C) δ 5.95 (d, *J* = 2.0 Hz, 1H), 5.91 (d, *J* = 2.4 Hz, 1H), 5.62 (t, *J* = 11.6 Hz, 1H), 5.43 (t, *J* = 10.8 Hz, 1H), 5.31-5.26 (m, 1H), 4.31-4.12 (m, 2H), 3.95-3.92 (m, 1H), 3.83-3.79 (m, 1H), 3.64 (d, *J* = 9.2 Hz, 1H), 2.94-2.84 (m, 1H), 2.36-2.27 (m, 1H), 1.94-1.92 (m, 2H), 1.33 (d, *J* = 6.0 Hz, 3H), 5 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 355.1400 ([M + H]$^+$, $C_{17}H_{22}O_8H$ requires 355.1393).



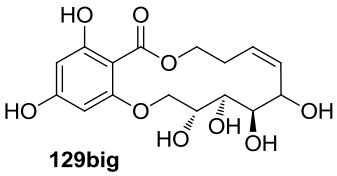
129bhg

129bhg: *Rf* = 0.38 (EtOAc/MeOH 10/1); ^{1}H NMR (CD_3OD, 400 MHz, 25 °C) δ 5.95 (dd, *J* = 8.4, 2.0 Hz, 1H), 5.90 (s, 1H), 5.70-5.58 (m, 1H), 5.70-5.42 (m, 1H), 4.59-4.46 (m, 2H), 4.28-4.12 (m, 2H), 3.97-3.92 (m, 1H), 3.87-3.85 (m, 1H), 3.62 (d, *J* = 9.2 Hz, 1H), 2.99-2.92 (m, 1H), 2.42-2.32 (m, 1H), 1.93-1.91 (m, 2H), 5 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 341.1270 ($[M + H]^+$, $C_{16}H_{20}O_8H$ requires 341.1236).



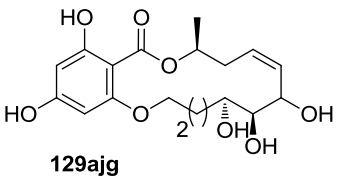
129aig

129aig: *Rf* = 0.46 (CH_2Cl_2/MeOH 4/1); ^{1}H NMR (CD_3OD, 400 MHz, 25 °C) δ 5.95-5.90 (m, 2H), 5.88-5.81 (m, 0.5H), 5.72 (dd, *J* = 19.0, 9.6 Hz, 0.5H), 5.61 (td, *J* = 11.3, 2.5 Hz, 0.5H), 5.40 (td, *J* = 11.2, 2.1 Hz, 0.5H), 5.38-5.24 (m, 1H), 4.60-4.53 (m, 1H), 4.42 (dd, *J* = 10.8, 9.4 Hz, 0.5H), 4.26 (dd, *J* = 9.7 Hz, 2.9 Hz, 0.5H), 4.18-4.02 (m, 2H), 3.76-3.67 (m, 2H), 2.90-2.78 (m, 1H), 2.67-2.56 (m, 0.6H), 2.31-2.24 (m, 0.4H), 1.40 (d, *J* = 6.5 Hz, 2H), 1.33 (d, *J* = 6.5 Hz, 1H), 6 OH signals are not visible. HRMS (MALDI-TOF) *m/z* 393.1195 ($[M + Na]^+$, $C_{17}H_{22}O_9Na$ requires 393.1161).



129big

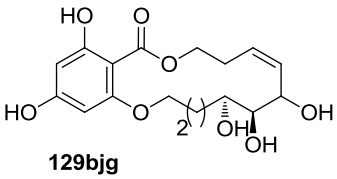
129big: *Rf* = 0.42 (CH_2Cl_2/MeOH 4/1); ^{1}H NMR (CD_3OD, 400 MHz, 25 °C) δ 6.40-5.98 (m, 1H), 5.96-5.90 (m, 1H), 5.68-5.40 (m x 2, 2H), 4.50-3.98 (m, 5H), 3.98-3.92 (m, 2H), 3.71-3.60 (m x 2, 1H), 3.04-2.90 (m, 1H), 2.44-2.30 (m, 1H), 6 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 357.1153 ($[M + H]^+$, $C_{16}H_{20}O_9H$ requires 357.1186).



129ajg

129ajg: *Rf* = 0.26 (8% MeOH/CH_2Cl_2); ^{1}H NMR (CD_3OD, 400 MHz, 25 °C) δ 6.00 (d, *J* = 1.9 Hz, 1H), 5.98 (d, *J* = 1.8 Hz, 0.5H), 5.97 (d, *J* = 1.9 Hz, 0.5H), 5.82-5.72 (m, 1H), 5.54-5.25 (m, 2H), 4.64 (dd, *J* = 7.8, 2.2 Hz, 0.4H), 4.34 (d, *J* = 9.5 Hz, 0.6H), 4.15-3.92 (m, 2H), 3.77-3.58 (m, 2H), 3.15-3.08 (m, 0.4H), 2.96

(dt, *J* = 16.3, 10.7 Hz, 0.6H), 2.53-2.44 (m, 1H), 2.04-1.83 (m, 3H), 1.78-1.66 (m, 1H), 1.49 (d, *J* = 6.5 Hz, 1H), 1.44 (d, *J* = 6.2 Hz, 2H). 5 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 369.1583 ([M + H]$^+$, $C_{18}H_{24}O_8H$ requires 369.1550).

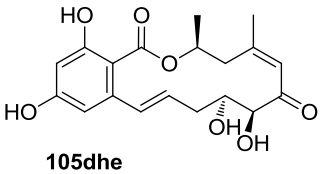


129bjg

129bjg: *Rf* = 0.24 (8% MeOH/CH_2Cl_2); ^{1}H NMR (CD_3OD, 400 MHz, 25 °C) δ 5.99 (s, 1H), 5.98 (s, 1H), 5.79-5.51 (m, 2H), 4.66-4.32 (m, 3H), 4.19-3.63 (m, 4H), 3.16-2.91 (m, 1H), 2.53-2.48 (m, 1H), 2.16-1.89 (m, 2H), 1.87-1.65 (m, 2H), 5 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 355.1326 ([M + H]$^+$, $C_{17}H_{22}O_8H$ requires 355.1393).

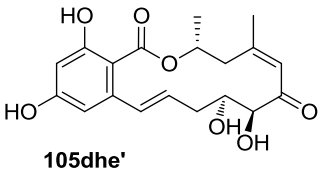
General procedure for the synthesis of compounds 105e-f. The corresponding ketone **128** (1.0 equiv) was dissolved with 40% HF in H_2O /MeCN (1/10) at 23 °C. The solution was stirred at 23 °C for 3-6 h, diluted with water, frozen by immersion into liquid N_2 and then dried by lyophilization. Compounds were isolated by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 2/1) affording desired macrocycles **105e-f** in 50-70% yields along with the corresponding *para*-mono-EOM compounds **130e-f** that were resubmitted for a second deprotection in the same conditions.

Selected examples of compounds 105e-f.



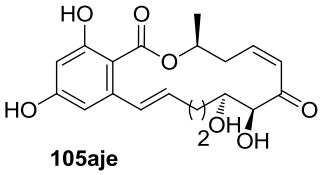
105dhe

105dhe: *Rf* = 0.22 (8% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 11.65 (s, 1H), 7.28 (d, *J* = 15.8 Hz, 1H), 6.48 (s, 1H), 6.39 (d, *J* = 1.9 Hz, 1H), 6.36 (d, *J* = 1.9 Hz, 1H), 5.86-5.80 (m, 1H), 5.41-5.39 (m, 1H), 4.26-4.16 (m, 2H), 2.92-2.81 (m, 1H), 2.64-2.55 (m, 2H), 2.44-2.35 (m, 1H), 2.19 (s, 3H), 1.47 (d, *J* = 5.9 Hz, 3H), 3 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 363.1485 ([M + H]$^+$, $C_{19}H_{22}O_7H$ requires 363.1444).



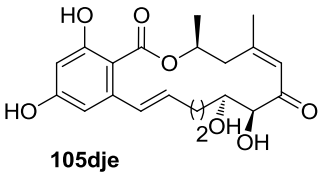
105dhe'

105dhe': *Rf* = 0.23 (8% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 11.57 (s, 1H), 6.93 (d, *J* = 15.1 Hz, 1H), 6.78 (s, 1H), 6.44 (d, *J* = 2.4 Hz, 1H), 6.36 (d, *J* = 2.4 Hz, 1H), 6.07 (ddd, *J* = 15.1, 10.2, 3.5 Hz, 1H), 5.50-5.46 (m, 1H), 4.33 (d, *J* = 2.7 Hz, 1H), 4.26-4.23 (m, 1H), 2.94 (d, *J* = 16.9 Hz, 1H), 2.73-2.69 (m, 1H), 2.46 (dd, *J* = 16.9, 5.3 Hz, 1H), 2.38-2.32 (m, 1H), 2.29 (s, 3H), 1.39 (d, *J* = 6.5 Hz, 3H), 3 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 363.1463 ([M + H]$^+$, $C_{19}H_{22}O_7H$ requires 363.1444).



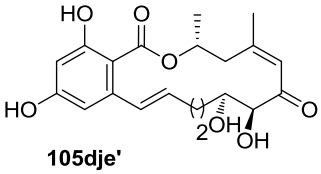
105aje

105aje: *Rf* = 0.22 (8% MeOH/CH_2Cl_2); ^{1}H NMR (CD_3OD, 400 MHz, 25 °C) δ 6.97 (d, *J* = 16.1 Hz, 1H), 6.47 (dd, *J* = 11.6, 2.7 Hz, 1H), 6.43 (d, *J* = 2.4 Hz, 1H), 6.27 (d, *J* = 2.4 Hz, 1H), 6.22-6.08 (m, 2H), 5.55-5.47 (m, 1H), 4.63 (d, *J* = 2.4 Hz, 1H), 4.15 (dt, *J* = 9.7, 2.8 Hz, 1H), 3.21-3.08 (m, 1H), 2.79-2.71 (m, 1H), 2.44-2.39 (m, 1H), 2.26-2.21 (m, 1H), 1.90-1.79 (m, 1H), 1.48 (d, *J* = 5.9 Hz, 3H), 1.45-1.38 (m, 1H), 4 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 363.1443 ([M + H]$^+$, $C_{19}H_{22}O_7H$ requires 363.1444).



105dje

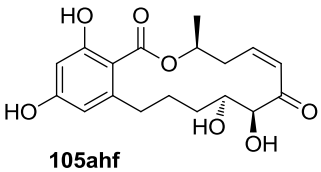
105dje: *Rf* = 0.20 (8% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 11.33 (s, 1H), 7.07 (d, *J* = 15.6 Hz, 1H), 6.47 (s, 1H), 6.32 (s, 1H), 6.28 (s, 1H), 6.13-5.82 (m, 1H), 5.68-5.51 (m, 1H), 4.48 (bs, 1H), 4.19-4.14 (m, 1H), 2.79-2.72 (m, 1H), 2.59-2.45 (m, 2H), 2.37 (s, 3H), 2.37-2.29 (m, 1H), 1.86-1.78 (m, 2H), 1.45 (d, *J* = 5.9 Hz, 3H), 3 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 377.1613 ([M + H]$^+$, $C_{20}H_{24}O_7H$ requires 377.1601).



105dje'

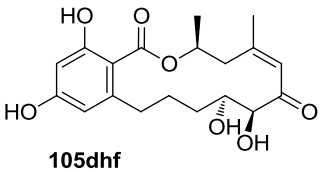
105dje': *Rf* = 0.20 (8% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 11.33 (s, 1H), 7.07 (d, *J* = 15.6 Hz, 1H), 6.47 (s, 1H), 6.32 (s, 1H), 6.28 (s, 1H), 6.13-5.82 (m, 1H), 5.68-5.51 (m, 1H), 4.48 (bs, 1H),

4.19-4.14 (m, 1H), 2.79-2.72 (m, 1H), 2.59-2.45 (m, 2H), 2.37 (s, 3H), 2.37-2.29 (m, 1H), 1.86-1.78 (m, 2H), 1.45 (d, *J* = 5.9 Hz, 3H), 3 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 377.1613 ($[M + H]^+$, $C_{20}H_{24}O_7H$ requires 377.1601).



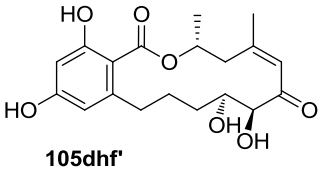
105ahf

105ahf: *Rf* = 0.29 (CH_2Cl_2/MeOH 10/1)); ^{1}H NMR (CD_3OD, 400 MHz, 25 °C) δ 6.47 (dd, *J* = 11.6 Hz, 2.4 Hz, 1H), 6.24 (td, *J* = 11.3 Hz, 2.4 Hz, 1H), 6.21 (d, *J* = 2.1 Hz, 1H), 6.15 (d, *J* = 2.4 Hz, 1H), 5.43-5.35 (m, 1H), 4.49 (d, *J* = 1.6 Hz, 1H), 3.93-3.87 (m, 1H), 3.04-2.92 (m, 1H), 2.69-2.49 (m, 2H), 1.85-1.72 (m, 1H), 1.70-1.56 (m, 2H), 1.39 (d, *J* = 6.4 Hz, 3H), 1.39-1.35 (m, 2H), 4 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 351.1429 ($[M + H]^+$, $C_{18}H_{22}O_7H$ requires 351.1444).



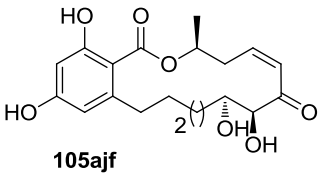
105dhf

105dhf: *Rf* = 0.24 (8% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 11.49 (s, 1H), 6.30 (d, *J* = 2.4 Hz, 1H), 6.26 (d, *J* = 2.4 Hz, 1H), 6.24 (bs, 1H), 5.59-5.53 (m, 1H), 4.34 (d, *J* = 3.5 Hz, 1H), 3.96-3.92 (m, 1H), 3.29-3.22 (m, 1H), 2.77-2.73 (m, 1H), 2.61-2.52 (m, 2H), 2.20 (s, 3H), 1.88-1.80 (m, 1H), 1.66-1.59 (m, 2H), 1.52-1.49 (m, 1H), 1.44 (d, *J* = 6.5 Hz, 3H), 3 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 365.1627 ($[M + H]^+$, $C_{19}H_{24}O_7H$ requires 365.1601).



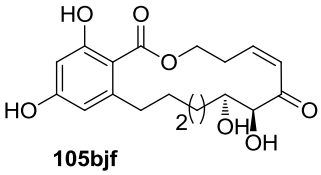
105dhf'

105dhf': *Rf* = 0.21 (8% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 11.07 (s, 1H), 6.27 (s, 2H), 6.24 (s, 1H), 5.50-5.45 (m, 1H), 4.44 (d, *J* = 2.7 Hz, 1H), 4.13-4.01 (m, 1H), 3.00-2.93 (m, 1H), 2.77-2.67 (m, 1H), 2.60 (d, *J* = 7.5 Hz, 2H), 2.23 (s, 3H), 1.88-1.76 (m, 1H), 1.57-1.52 (m, 3H), 1.45 (d, *J* = 5.9 Hz, 3H), 3 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 365.1612 ($[M + H]^+$, $C_{19}H_{24}O_7H$ requires 365.1601).



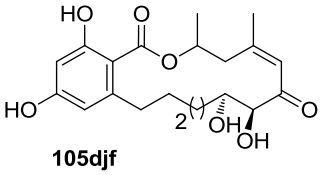
105ajf

105ajf: *Rf* = 0.26 (CH_2Cl_2/MeOH 10/1); ^{1}H NMR (CD_3OD, 400 MHz, 25 °C) δ 6.46 (dd, *J* = 11.6 Hz, 2.4 Hz, 1H), 6.29 (td, *J* = 10.4 Hz, 2.4 Hz, 1H), 6.22 (d, *J* = 2.4 Hz, 1H), 6.15 (d, *J* = 2.4 Hz, 1H), 5.55-5.49 (m, 1H), 4.48 (d, *J* = 1.6 Hz, 1H), 4.05-4.02 (m, 1H), 3.38-3.18 (m, 1H), 2.66-2.61 (m, 1H), 2.35-2.28 (m, 1H), 1.82-1.74 (m, 1H), 1.66-1.56 (m, 2H), 1.40 (d, *J* = 6.0 Hz, 3H), 1.36-1.29 (m, 4H), 4 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 351.1469 ($[M + H]^+$, $C_{19}H_{24}O_7H$ requires 351.1444).



105bjf

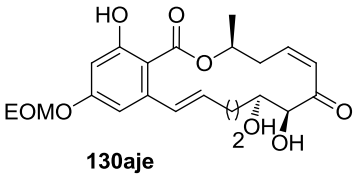
105bjf: *Rf* = 0.24 (CH_2Cl_2/MeOH 9/1); ^{1}H NMR (CD_3OD, 400 MHz, 25 °C) δ 6.61 (d, *J* = 12.0 Hz, 1H), 6.34-6.28 (m, 1H), 6.23 (d, *J* = 2.0 Hz, 1H), 6.14 (d, *J* = 2.4 Hz, 1H), 4.66-4.39 (m, 3H), 4.01-3.98 (m, 1H), 2.92-2.71 (m, 3H), 2.61-2.53 (m, 1H), 1.67-1.58 (m, 2H), 1.47-1.38 (m, 2H), 1.36-1.29 (m, 2H), 4 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 351.1469 ($[M + H]^+$, $C_{18}H_{22}O_7H$ requires 351.1444).



105djf

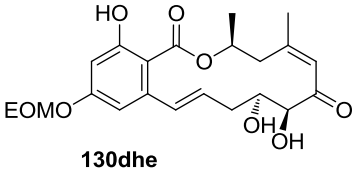
105djf: *Rf* = 0.29 (8% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 11.62 (s, 0.5H), 11.17 (s, 0.5H), 6.52 (d, *J* = 1.8 Hz, 0.5H), 6.33 (d, *J* = 1.9 Hz, 0.5H), 6.28 (d, *J* = 1.9 Hz, 0.5H), 6.26 (d, *J* = 2.4 Hz, 0.5H), 6.21 (d, *J* = 2.4 Hz, 0.5H), 6.20 (d, *J* = 2.4 Hz, 0.5H), 5.76-5.68 (m, 0.5H), 5.57-5.53 (m, 0.5H), 4.46 (d, *J* = 3.2 Hz, 0.5H), 4.42 (d, *J* = 2.9 Hz, 0.5H), 4.13-4.09 (m, 0.5H), 3.95-3.82 (m, 0.5H), 3.16-2.97 (m, 1H), 2.80-2.75 (m, 1H), 2.63-2.55 (m, 1H), 2.49-2.39 (m, 0.5H), 2.33 (s, 1.5H), 2.29 (s, 1.5H), 2.17-1.94 (m, 0.5H), 1.86-1.80 (m, 1H), 1.65-1.49 (m, 3H), 1.44 (d, *J* = 6.7 Hz, 1.5H), 1.43 (d, *J* = 5.9 Hz, 1.5H) 1.35-1.28 (m, 2H), 3 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 379.1766 ($[M + H]^+$, $C_{20}H_{26}O_7H$ requires 379.1757).

Selected examples of compounds 130e-f.



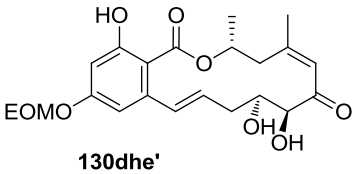
130aje

130aje: *Rf* = 0.31 (8% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.97 (s, 1H), 6.84 (d, *J* = 15.8 Hz, 1H), 6.55 (s, 2H), 6.29 (dd, *J* = 11.5, 2.7 Hz, 1H), 6.16-6.08 (m, 2H), 5.49-5.44 (m, 1H), 5.23 (s, 2H), 4.59 (bs, 1H), 4.04-3.99 (m, 1H), 3.71 (q, *J* = 7.0 Hz, 2H), 3.07-2.97 (m, 1H), 2.74-2.66 (m, 1H), 2.45-2.38 (m, 1H), 2.24-2.19 (m, 1H), 2.04-2.00 (m, 1H), 1.74-1.68 (m, 1H), 1.44 (d, *J* = 6.2 Hz, 3H), 1.23 (t, *J* = 7.0 Hz, 3H), 2 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 421.1896 ([M + H]$^+$, $C_{22}H_{28}O_8H$ requires 421.1863).



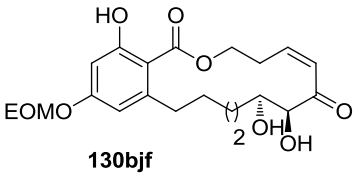
130dhe

130dhe: *Rf* = 0.33 (8% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 ºC) δ 11.59 (s, 1H), 7.28 (d, *J* = 16.1 Hz, 1H), 6.59 (d, *J* = 2.2 Hz, 1H), 6.56 (d, *J* = 2.2 Hz, 1H), 6.49 (s, 1H), 5.88-5.82 (m, 1H), 5.43-5.39 (m, 1H), 5.25 (s, 2H), 4.29-4.18 (m, 2H), 3.72 (q, *J* = 6.9 Hz, 2H), 2.89-2.85 (m, 1H), 2.64-2.54 (m, 1H), 2.48-2.35 (m, 2H), 2.19 (s, 3H), 1.47 (d, *J* = 6.2 Hz, 3H), 1.23 (t, *J* = 7.0 Hz, 3H), 2 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 443.1689 ([M + Na]$^+$, $C_{22}H_{28}O_8Na$ requires 443.1682).



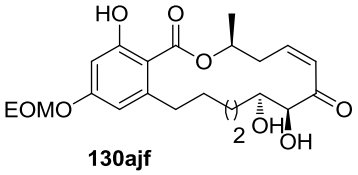
130dhe'

130dhe': *Rf* = 0.33 (8% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 11.51 (s, 1H), 6.94 (d, *J* = 15.3 Hz, 1H), 6.79 (s, 1H), 6.61 (d, *J* = 2.4 Hz, 1H), 6.59 (d, *J* = 2.4 Hz, 1H), 6.09 (ddd, *J* = 15.1, 10.5, 3.8 Hz, 1H), 5.51-5.47 (m, 1H), 5.25 (s, 2H), 4.32 (bs, 1H), 4.24-4.22 (m, 1H), 3.72 (q, *J* = 7.0 Hz, 2H), 2.95 (d, *J* = 17.0 Hz, 1H), 2.75-2.71 (m, 1H), 2.46 (dd, *J* = 16.9, 5.1 Hz, 1H), 2.38-2.32 (m, 1H), 2.29 (s, 3H), 1.39 (d, *J* = 6.2 Hz, 3H), 1.22 (t, *J* = 7.0 Hz, 3H), 2 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 443.1665 ([M + Na]$^+$, $C_{22}H_{28}O_8Na$ requires 443.1682).



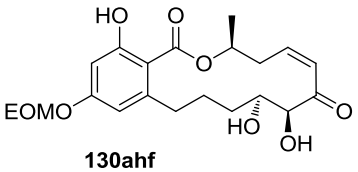
130bjf

130bjf: *Rf* = 0.37 (CH_2Cl_2/MeOH 9/1); ^{1}H NMR (CD_3OD, 400 MHz, 25 °C) δ 6.60 (d, *J* = 11.3 Hz, 1H), 6.43 (s, 2H), 6.334-6.29 (m, 1H), 5.22 (s, 2 H), 4.65-4.57 (m, 2H), 4.44 (d, *J* = 1.9 Hz, 1H), 4.01-3.98 (m, 1H), 3.70 (q, *J* = 7 Hz, 2H), 2.93-2.68 (m, 3H), 2.64-2.53 (m, 1H), 1.70-1.25 (m, 6H), 1.19 (t, *J* = 7.2 Hz, 3H) , 3 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 431.1674 ($[M + Na]^+$, $C_{21}H_{28}O_8Na$ requires 431.1682).



130ajf

130ajf: *Rf* = 0.39 (CH_2Cl_2/MeOH 10/1); ^{1}H NMR (CD_3OD, 400 MHz, 25 °C) δ 6.50-6.40 (m, 3H), 6.34 (td, *J* = 11.8 Hz, 2.2 Hz, 1H), 5.58-5.48 (m, 1H), 5.27 (s, 2H), 4.55 (d, *J* = 1.6 Hz, 1H), 4.13-4.09 (m, 1H), 3.76 (q, *J* = 7 Hz, 2H), 3.40-3.18 (m, 1H), 2.69-2.61 (m, 1H), 2.42-2.32 (m, 1H), 1.82-1.71 (m, 1H), 1.69-1.55 (m, 2H), 1.42 (d, *J* = 6.4 Hz, 3H), 1.36-1.28 (m, 4H), 1.26 (t, *J* = 7 Hz, 3H), 3 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 445.1852 ($[M + Na]^+$, $C_{22}H_{30}O_8Na$ requires 445.1838).

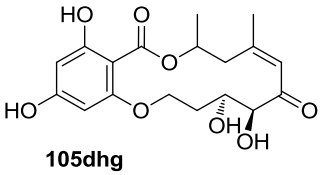


130ahf

130ahf: *Rf* = 0.42 (CH_2Cl_2/MeOH 10/1); ^{1}H NMR (CD_3OD, 400 MHz, 25 °C) δ 6.57-6.42 (m, 3H), 6.37-6.27 (m, 1H), 5.54-5.44 (m, 1H), 5.31 (s, 2H), 4.56 (s, 1H), 3.99-3.96 (m, 1H), 3.81-3.73 (q, *J* = 7.2Hz, 2H), 3.05-2.95 (m, 1H), 2.68-2.53 (m, 2H), 1.85-1.74 (m, 1H), 1.72-1.55 (m, 2H), 1.47 (d, *J* = 5.9 Hz, 3H), 1.39-1.34 (m, 2H), 1.26 (t, *J* = 7.0 Hz, 3H), 3 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 431.1678 ($[M + Na]^+$, $C_{21}H_{28}O_8Na$ requires 431.1682).

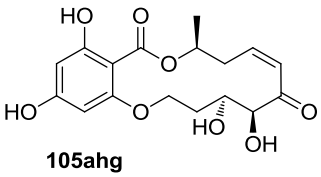
General procedure for the selective oxidation. Synthesis of compounds 105g. To a solution of the corresponding alcohol **129** (1.0 equiv) in CH_2Cl_2 (0.5 M) and DMSO (some drops to dissolve the alcohol) at 23 °C was added PS- IBX resin (3.0 equiv, 1.1 mmol/g). After 1-3 h the reaction was filtered and loaded directly on PTLC (SiO_2, 6 to 8% MeOH in EtOAc) to afford the corresponding ketone **105g** in greater than 50% yield.

Selected examples of compounds 105g.



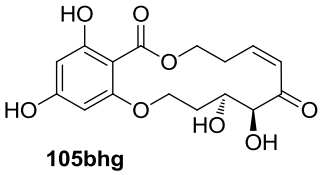
105dhg

105dhg: *Rf* = 0.29 (8% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 12.37 (s, 0.5H), 10.86 (s, 0.5H), 6.29 (s, 0.5H), 6.12 (s, 0.5H), 6.02 (s, 0.5H), 5.99 (s, 0.5H), 5.93 (s, 0.5H), 5.84 (s, 0.5H), 5.57-5.55 (m, 0.5H), 5.42-5.37 (m, 0.5H), 4.59 (bs, 0.5H), 4.55 (bs, 0.5H), 4.38-4.19 (m, 1H), 4.16-3.99 (m, 1H), 3.69-3.64 (m, 1H), 3.51-3.43 (m, 0.5H), 2.71-2.58 (m, 0.5H), 2.52-2.44 (m, 0.5H), 2.26-2.22 (m, 0.5H), 2.11 (s, 1.5H), 1.89 (s, 1.5H), 1.73-1.64 (m, 1H), 1.55-1.48 (m, 1H), 1.42 (d, *J* = 6.2 Hz, 1.5H), 1.28 (d, *J* = 5.9 Hz, 1.5H), 3 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 367.1359 ([M + H]$^+$, $C_{18}H_{22}O_8H$ requires 367.1393).



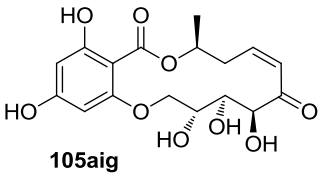
105ahg

105ahg: *Rf* = 0.36 (EtOAc/MeOH 10/1); ^{1}H NMR (CD_3OD, 400 MHz, 25 °C) δ 6.43 (dd, *J* = 11.6, 2.8 Hz, 1H), 6.14 (td, *J* = 11.2, 2.0 Hz, 1H), 5.93-5.89 (m, 2H), 5.37-5.31 (m, 1H), 4.59 (d, *J* = 6.8 Hz, 1H), 4.17-4.13 (m, 1H), 4.08-4.04 (m, 1H), 3.87-3.80 (m, 1H), 2.44- 2.37 (m, 1H), 1.84-1.77 (m, 1H), 1.64-1.58 (m, 2H), 6.14 (d, *J* = 7.0 Hz, 3H), 4 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 353.1243 ([M + H]$^+$, $C_{17}H_{20}O_8H$ requires 353.1237).



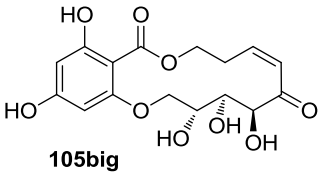
105bhg

105bhg: *Rf* = 0.51 (EtOAc/MeOH 10/1); ^{1}H NMR (CD_3OD, 400 MHz, 25 °C) δ 6.48 (dd, *J* = 11.6, 2.8 Hz, 1H), 6.15 (td, *J* = 11.2, 2.4 Hz, 1H), 5.94 (d, *J* = 2.0 Hz, 1H), 5.90 (d, *J* = 2.0 Hz, 1H), 4.63 (s, 1H), 4.56 (t, *J* = 11.6 Hz, 2H), 4.22-4.14 (m, 2H), 3.81-3.78 (m, 1H), 2.49-2.44 (m, 1H), 1.85-1.78 (m, 1H), 1.61-1.55 (m, 2H), 4 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 339.1056 ([M + H]$^+$, $C_{16}H_{18}O_8H$ requires 339.1080).



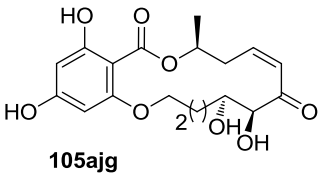
105aig

105aig: *Rf* = 0.6 (CH_2Cl_2/MeOH 4/1); ^{1}H NMR (CD_3OD, 400 MHz, 25 °C) δ 6.45 (dd, *J* = 11.8, 2.7 Hz, 1H), 6.15 (td, *J* = 11.8, 2.7 Hz, 1H), 5.93 (d, *J* = 2.54 Hz, 1H), 5.92 (d, *J* = 2.4 Hz, 1H), 5.36-5.29 (m, 1H), 4.74 (d, *J* = 1.3 Hz, 1H), 4.13-4.09 (m, 1H), 4.03 (d, *J* = 1.4 Hz, 1H), 3.82 (dd, *J* = 9.7, 2.7 Hz, 1H), 3.56 (dd, *J* = 8.6, 2.7 Hz, 1H), 3.31 (dt, *J* = 16.5, 11.3 Hz, 1H), 2.43 (dq, *J* = 16.6, 2.4 Hz, 1H), 1.38 (d, *J* = 5.9 Hz, 3H), 5 OH signals are not visible ; HRMS (MALDI-TOF) *m/z* 369.1180 ($[M + H]^+$, $C_{17}H_{20}O_9H$ requires 369.1186).



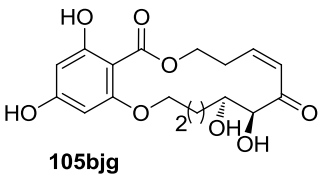
105big

105big: *Rf* = 0.64 (CH_2Cl_2/MeOH 4/1); ^{1}H NMR (CD_3OD, 400 MHz, 25 °C) δ 6.50 (dd, *J* = 11.8, 2.7 Hz, 1H), 6.17 (td, *J* = 11.3, 2.7 Hz, 1H), 5.95-5.92 (m, 2H), 4.77 (s, 1H), 4.62-4.52 (m, 2H), 4.20-4.12 (m, 2H), 3.88 (dd, *J* = 9.7, 2.7 Hz, 1H), 3.54 (dd, *J* = 8.0, 2.7 Hz, 1H), 2.54-2.45 (m, 1H), 1.99-1.85 (m, 1H), 5 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 355.1054 ($[M + H]^+$, $C_{16}H_{18}O_9H$ requires 355.1029).



105ajg

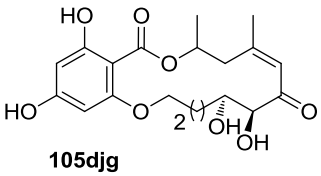
105ajg: *Rf* = 0.43 (15% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 12.24 (s, 1H), 6.26 (dd, *J* = 11.2, 2.9 Hz, 1H), 6.10 (td, *J* = 11.3, 2.1 Hz, 1H), 6.03 (s, 1H), 5.93 (d, *J* = 2.1 Hz, 1H), 5.49-5.43 (m, 1H), 4.57 (d, *J* = 3.5 Hz, 1H), 4.05-3.92 (m, 3H), 2.99-2.89 (m, 1H), 2.63-2.57 (m, 1H), 1.92-1.83 (m, 2H), 1.59-1.43 (m, 2H), 1.38 (d, *J* = 5.9 Hz, 3H), 3 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 367.1378 ($[M + H]^+$, $C_{18}H_{22}O_8H$ requires 367.1393).



105bjg

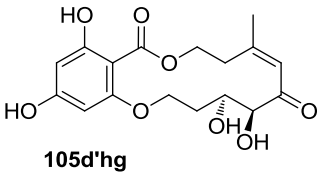
105bjg: *Rf* = 0.34 (8% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 11.94 (s, 1H), 6.37 (dd, *J* = 11.4, 2.3 Hz, 1H), 6.22 (td, *J* = 11.0, 2.5 Hz, 1H), 6.02 (d, *J* = 2.1 Hz, 1H), 5.91 (d, *J* = 2.1 Hz, 1H), 4.57 (d, *J* = 3.5 Hz, 1H), 4.48-4.40 (m, 2H), 4.02-3.92 (m, 3H), 3.33-3.23 (m, 1H), 2.67-2.55 (m, 1H), 1.97-1.75

(m, 3H), 1.54-1.43 (m, 1H), 3 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 353.1254 ([M + H]$^+$, $C_{17}H_{20}O_8H$ requires 353.1236).



105djg

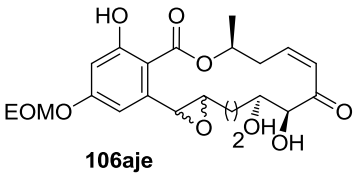
105djg: *Rf* = 0.26 (8% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 12.22 (s, 0.5H), 11.89 (s, 0.5H), 6.16 (s, 0.5H), 6.05 (s, 0.5H), 6.01 (d, *J* = 1.9 Hz, 0.5H), 5.98 (d, *J* = 2.2 Hz, 0.5H), 5.88 (d, *J* = 1.8 Hz, 0.5H), 5.85 (d, *J* = 1.8 Hz, 0.5H), 5.57-5.54 (m, 0.5H), 5.39-5.36 (m, 0.5H), 4.54 (d, *J* = 2.9 Hz, 0.5H), 4.40 (d, *J* = 2.9 Hz, 0.5H), 4.18-3.76 (m, 3H),3.31-3.23 (m, 1H), 2.67-2.39 (m, 2H), 2.13 (s. 1.5H), 2.07-1.87 (m, 1H), 1.78 (s. 1.5H), 1.75-1.44 (m, 1H), 1.39 (d, *J* = 5.9 Hz, 1.5H), 1.35 (d, *J* = 6.2 Hz, 1.5H), 1.33-1.29 (m, 1H), 3 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 381.1549 ([M + H]$^+$, $C_{19}H_{24}O_8H$ requires 381.1550).



105d'hg

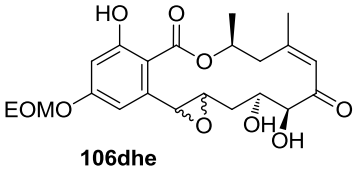
105d'hg: *Rf* = 0.21 (8% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ 11.85 (s, 1H), 6.31 (s, 1H), 5.98 (d, *J* = 1.9 Hz, 1H), 5.88 (d, *J* = 1.9 Hz, 1H), 4.70-4.58 (m, 2H), 4.45 (d, *J* = 9.9 Hz, 1H), 4.16 (t, *J* = 9.4 Hz, 1H), 3.95 (bs, 1H), 3.85-3.83 (m, 1H), 2.64-2.58 (m, 2H), 2.25 (s, 3H), 1.69-1.65 (m, 1H), 1.46-1.39 (m, 1H), 3 OH signals are not visible; HRMS (MALDI-TOF) *m/z* 353.1245 ([M + H]$^+$, $C_{17}H_{20}O_8H$ requires 353.1237).

General procedure for the epoxidation. Synthesis of compounds 106. To a solution of the macrocycle containing a benzylic alkene **105e** or **130e** (1.0 equiv, 1.0 mg) in CH_3CN (0.5 mL) at 0 °C was added a freshly prepared solution of DMDO in acetone (4.0 equiv, 0.1 M in acetone as titrated by PPh_3 oxidation). The reaction was monitored by LC/MS, after 1-2 h the reaction mixture was concentrated and the epoxide **106** was isolated by PTLC in 60-70% yield.



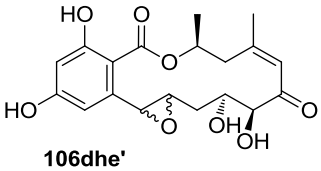
106aje

106aje: LC/MS *m/z* 435.23 ($[M + H]^+$, for $C_{23}H_{30}O_8H$ requires 435.20).



106dhe

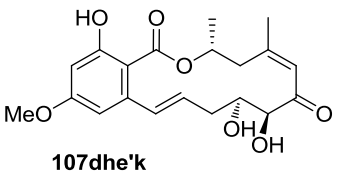
106dhe: LC/MS *m/z* 437.25 ($[M + H]^+$, for $C_{22}H_{28}O_9H$ requires 437.18).



106dhe'

106dhe': LC/MS *m/z* 379.13 ($[M + H]^+$, for $C_{19}H_{22}O_8H$ requires 379.13).

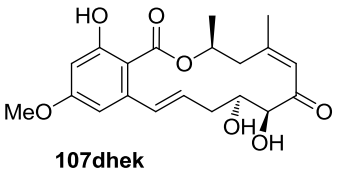
General procedure for the selective methylation of *para*-phenol, synthesis of compounds 107k-l. To a solution of macrocycle **105** (1.0 equiv, 1.0 mg) in Et_2O (0.5 mL) at 23 °C was added a freshly prepared solution of CH_2N_2 in Et_2O (0.5-1.0 mL). The reaction was monitored by TLC and LC/MS. Upon complete consumption of the starting material, the reaction mixture was concentrated and purified on HPLC (20-80% CH_3CN in H_2O gradient in 50 min, flow: 2 mL/min, Discovery^R H C18, 5µm, 5 cm x 10.0 mm) to afford the corresponding methylated macrocycle **107k-l** in 50-60% yield (bis methylated product was obtained in 20-30% yield).



107dhe'k

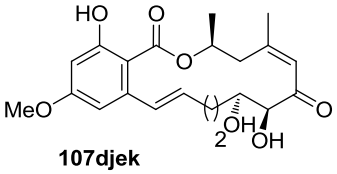
107dhe'k: *Rf* = 0.30 (8% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 11.63 (s, 1H), 6.96 (d, *J* = 15.2 Hz, 1H), 6.80 (s, 1H), 6.51 (d, *J* = 2.6 Hz, 1H), 6.45 (d, *J* = 2.5 Hz, 1H), 6.07 (ddd, *J* = 15.1, 10.4, 3.7 Hz, 1H), 5.52-5.45 (m, 1H), 4.32 (bs, 1H), 4.25-4.22 (m, 1H), 3.83 (s, 3H), 2.61 (d, *J* = 17.1 Hz, 1H), 2.74-2.70 (m, 1H), 2.46 (dd, *J* = 17.0, 5.2 Hz, 1H), 2.39-2.33 (m, 1H), 2.28 (s, 3H), 1.39 (d, *J* = 6.4 Hz,

3H), 2 OH signals not visible; LC/MS *m/z* 376.45 ([M + H]$^+$, for $C_{20}H_{24}O_7H$ requires 377.41) and *m/z* 399.35 ([M + Na]$^+$, for $C_{20}H_{24}O_7Na$ requires 399.39).



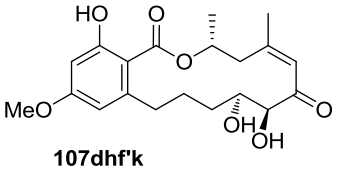
107dhek

107dhek: *Rf* = 0.29 (8% MeOH/CH_2Cl_2); LC/MS *m/z* 376.42 ([M + H]$^+$, for $C_{20}H_{24}O_7H$ requires 377.41) and *m/z* 399.38 ([M + Na]$^+$, for $C_{20}H_{24}O_7Na$ requires 399.38).



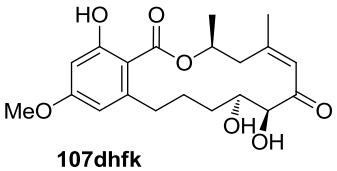
107djek

107djek: *Rf* = 0.34 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 9.49 (s, 1H), 6.60 (dt, *J* = 16.2, 1.3 Hz, 1H), 6.44 (s, 2H), 6.34 (s, 1H), 5.67-5.58 (m, 1H), 5.43-5.37 (m, 1H), 4.50-4.48 (m, 1H), 4.02 (ddd, *J* = 9.0, 6.0, 2.7 Hz, 1H), 3.90 (s, 3H), 2.67-2.64 (m, 2H), 2.35-2.31 (m, 1H), 2.29 (s, 3H), 2.25-2.23 (m, 1H), 2.04-1.93 (m, 2H), 1.46 (d, *J* = 6.1 Hz, 3H), 2 OH signals not visible; LC/MS *m/z* 391.25 ([M + H]$^+$, for $C_{21}H_{26}O_7H$ requires 391.43).



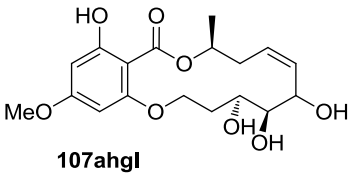
107dhf'k

107dhf'k: *Rf* = 0.30 (10% MeOH/CH_2Cl_2); LC/MS *m/z* 379.31 ([M + H]$^+$, for $C_{20}H_{26}O_7H$ requires 378.42) and *m/z* 401.18 ([M + Na]$^+$, for $C_{20}H_{26}O_7Na$ requires 401.40).



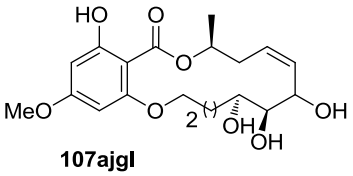
107dhfk

107dhfk: *Rf* = 0.30 (10% MeOH/CH_2Cl_2); LC/MS *m/z* 401.07 ([M + Na]$^+$, for $C_{20}H_{26}O_7Na$ requires 401.40).



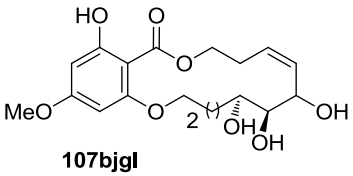
107ahgl

107ahgl: *Rf* = 0.25 (10% MeOH/CH_2Cl_2); LC/MS *m/z* 369.21 ($[M + H]^+$, for $C_{18}H_{24}O_8H$ requires 368.42) and *m/z* 391.24 ($[M + Na]^+$, for $C_{18}H_{24}O_8Na$ requires 391.36).



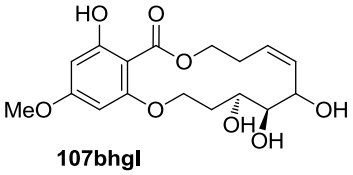
107ajgl

107ajgl: *Rf* = 0.27 (10% MeOH/CH_2Cl_2); LC/MS *m/z* 383.30 ($[M + H]^+$, for $C_{19}H_{26}O_8H$ requires 383.41) and *m/z* 405.32 ($[M + Na]^+$, for $C_{19}H_{26}O_8Na$ requires 405.39).



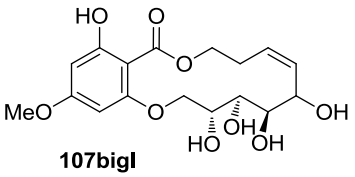
107bjgl

107bjgl: *Rf* = 0.26 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 12.20 (s, 0.6H), 11.86 (s, 0.4H), 6.36 (s, 2H), 5.60-5.46 (m, 2H), 4.63 (qd, *J* = 11.6, 2.6 Hz, 1H), 4.47-4.38 (m, 2H), 4.17-4.09 (m, 2H), 3.95 (s, 2H), 3.90 (s, 1H), 3.89-3.80 (m, 1H), 3.71 (dt, *J* = 9.1, 2.2 Hz, 1H), 3.02-2.89 (m, 2H), 2.58-2.45 (m, 1H), 2.33-2.23 (m, 1H), 2.10-2.02 (m, 1H), 1.87-1.78 (m, 1H), 3 OH signals are not visible; LC/MS *m/z* 369.19 ([M + H^+, for $C_{18}H_{24}O_8H$ requires 368.38).



107bhgl

107bhgl: *Rf* = 0.27 (10% MeOH/CH_2Cl_2); LC/MS *m/z* 355.23 ($[M + H]^+$, for $C_{17}H_{22}O_8H$ requires 355.36) and *m/z* 377.06 ($[M + Na]^+$, for $C_{17}H_{22}O_8Na$ requires 377.34).

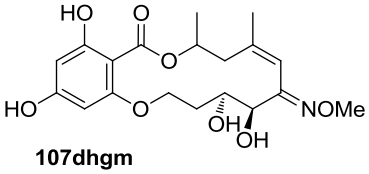


107bigl

107bigl: *Rf* = 0.18 (10% MeOH/CH_2Cl_2); LC/MS *m/z* 371.22 ($[M + H]^+$, for $C_{17}H_{22}O_9H$ requires 371.36) and *m/z* 393.20 ($[M + Na]^+$, for $C_{17}H_{22}O_9Na$ requires 393.34).

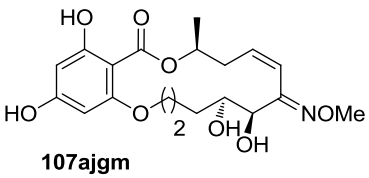
General procedure for the oxime formation, synthesis of compounds 107m-n. To a solution of the corresponding macrocycle **105** (1.0 equiv) in pyridine (0.5 M) at 23 °C was added corresponding hydroxyl amine derivative (5.0 equiv). The reaction was heated to 40 °C and stirred for 12 h at the same temperature. The solvent was removed at high vacuo and loaded directly on PTLC (SiO_2, 6 to 8% MeOH in CH_2Cl_2) to afford the corresponding oximes **107m-n** in over 50% yields.

Selected examples of oximes 107m-n.



107dhgm

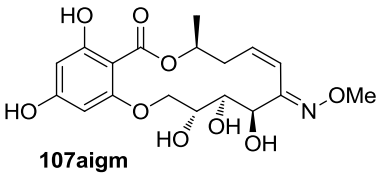
107dhgm: *Rf* = 0.29 (8% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 12.24 (s, 0.5H), 11.73 (bs, 0.5H), 8.61 (s, 0.5H), 8.21 (bs, 0.5H), 6.00 (d, *J* = 1.6 Hz, 0.5H) 5.97 (d, *J* = 1.6 Hz, 0.5H) 5.93 (s, 0.5H), 5.87 (s, 0.5H), 5.58 (s, 0.5H), 5.55-5.46 (m, 1H), 5.42-5.37 (m, 0.5H), 4.64 (bs, 0.5H), 4.46 (bs, 0.5H), 4.29-4.09 (m, 2H), 3.98-3.83 (m, 1H), 3.94 (s, 1.5H), 3.92 (s, 1.5H), 2.69-2.53 (m, 1H), 2.41-2.33 (m, 1H), 2.22-2.07 (m, 2H), 1.88 (s, 1.5H), 1.75 (s, 1.5H), 1.41 (d, *J* = 6.4 Hz, 1.5H), 1.31 (d, *J* = 6.2 Hz, 1.5H), 2 OH signals no visible; HRMS (MALDI-TOF) *m/z* 396.1628 ($[M + H]^+$, $C_{19}H_{25}NO_8H$ requires 396.1659).



107ajgm

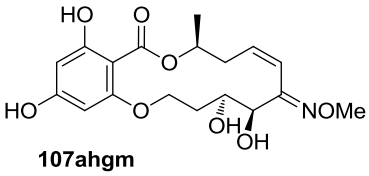
107ajgm: *Rf* = 0.34 (8%MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.38 (s, 0.5H), 12.17 (s, 0.5H), 6.01 (d, *J* = 1.1 Hz, 1H), 5.98-5.81 (m, 1H), 5.90 (s, 1H), 5.56 (dd, *J* = 11.3, 2.4 Hz, 0.5H), 5.49-5.35 (m, 1.5H), 4.56 (bs, 0.5H), 4.43 (bs, 0.5H), 4.25-3.81 (m, 3H), 3.96 (s, 1.5H), 3.95 (s, 1.5H), 2.96-2.72 (m,

1H), 2.45-2.25 (m, 1H), 2.04-1.70 (m, 4H), 1.42 (d, *J* = 6.2 Hz, 1.5H), 1.38 (d, *J* = 5.9 Hz, 1.5H), 3 OH signals no visible; HRMS (MALDI-TOF) *m/z* 418.1454 ($[M + Na]^+$, $C_{19}H_{25}NO_8Na$ requires 418.1478).



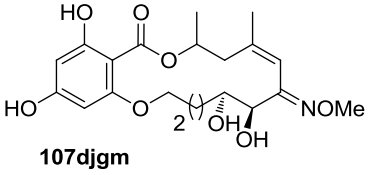
107aigm

107aigm: ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 5.96-5.82 (m, 4H), 5.37-5.28 (m, 1H), 5.54 (d, *J* = 4.9 Hz, 1H), 4.35 (dd, *J* = 10.2, 4.9 Hz, 1H), 4.14 (dd, *J* = 12.6, 5.1 Hz, 1H), 3.94 (s, 3H), 3.80 (dd, *J* = 8.1, 3.8 Hz, 1H), 3.57 (d, *J* = 5.6 Hz, 1H), 2.91-2.82 (m, 1H), 2.34-2.27 (m, 1H), 1.35 (d, *J* = 6.1 Hz, 3H), 5 OH signals no visible; HRMS (MALDI-TOF) *m/z* 420.1247 ($[M + Na]^+$, $C_{18}H_{23}NO_9Na$ requires 420.1271).



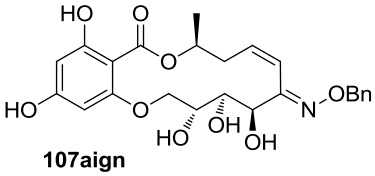
107ahgm

107ahgm: HRMS (MALDI-TOF) *m/z* 382.1524 ($[M + H]^+$, $C_{18}H_{23}NO_8H$ requires 382.1502).



107djgm

107djgm: HRMS (MALDI-TOF) *m/z* 432.1612 ($[M + Na]^+$, $C_{20}H_{27}NO_8Na$ requires 432.1635).



107aign

107aign: ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ 7.44-7.27 (m, 5H), 5.94 (d, *J* = 2.1 Hz, 0.5H), 5.92 (d, *J* = 2.1 Hz, 0.5H), 5.84 (s, 1H), 5.26-5.13 (m, 3H), 4.56 (d, *J* = 4.6 Hz, 1H), 4.32 (dd, *J* = 10.3, 3.6 Hz, 1H), 4.17 (dd, *J* = 11.3, 4.3 Hz, 1H), 4.11-4.06 (m, 2H), 3.84 (td, *J* = 10.5, 5.6 Hz, 1H), 3.77 (dd, *J* = 8.1, 3.7 Hz, 1H), 2.74-2.65 (m, 1H), 2.27-2.20 (m, 1H), 1.25 (d, *J* = 6.1 Hz, 3H), 5 OH signals no visible; HRMS (MALDI-TOF) *m/z* 496.1563 ($[M + Na]^+$, $C_{24}H_{27}NO_9Na$ requires 496.1584).

Kinase assay:

A radiometric protein kinase assay (33PanQinase® Activity Assay) was used for measuring the kinase activity of the 20 protein kinases. All kinase assays were performed in 96-well FlashPlatesTM from Perkin Elmer (Boston, MA, USA) in a 50 µL reaction volume. The reaction cocktail was pipetted in 4 steps in the following order:

- 20 µL of assay buffer
- 5 µL of ATP solution (in H_2O)
- 5 µL of test compound (in 10 % DMSO)
- 10 µL of substrate / 10 µL of enzyme solution (premixed)

The assay for all enzymes (except for the PKC-alpha assay, see below) contained 60 mM HEPES-NaOH, pH 7.5, 3 mM $MgCl_2$, 3 mM $MnCl_2$, 3 µM Na-orthovanadate, 1.2 mM DTT, 50 µg/ml PEG20000, 1 µM [γ-33P]-ATP (approx. 5 x 1005 cpm per well).

The PKC-alpha assay additionally contained 1 mM $CaCl_2$, 4 mM EDTA, 5 µg/mL Phosphatidyl-serine and 1 µg/ml 1.2-Dioleyl-glycerol.

For the 20 kinase assays the following amounts of enzyme and substrate were used per well:

Kinase		***Kinase (lot#)***	***Kinase ng/50µL***	***Substrate***	***Substrate ng/50µL***
1	**CK2-alpha1**	003	50	Casein	1000
2	**EGF-R**	015	10	$Poly(Glu,Tyr)_{4:1}$	125
3	**KIT**	008	100	$Poly(Glu,Tyr)_{4:1}$	125
4	**SRC**	004	10	$Poly(Glu,Tyr)_{4:1}$	125
5	**VEGF-R1**	SP009	50	$Poly(Glu,Tyr)_{4:1}$	125
6	**VEGF-R2**	016	50	$Poly(Glu,Tyr)_{4:1}$	125
7	**VEGF-R3**	011	100	$Poly(Glu,Tyr)_{4:1}$	125
8	**ZAP70**	001	20	$Poly(Glu,Tyr)_{4:1}$	125
9	**ERK2**	004	10	RBER-CHKtide, Lot 018	2000
10	**FLT3**	008	100	$Poly(Ala, Glu, Lys,Tyr)_{6:2:5:1}$	125
11	**INS-R**	SP005	25	$Poly(Ala, Glu, Lys,Tyr)_{6:2:5:1}$	125
12	**PDGFR-alpha**	SP007	100	$Poly(Ala, Glu, Lys,Tyr)_{6:2:5:1}$	125

13	**PKC-alpha**	SP004	40	Histone H1	250
14	**GSK3-alpha**	001	30	Myelin Basic Protein	1000
15	**NIK**	001	350	RBER-CHKtide, Lot 018	1000
16	**MAPKAPK5**	001	100	tetra(LRRWSLG)	250
17	**JNK3**	SP001	200	RB-CTF, Lot 012	1000
18	**NEK2**	SP002	100	RB-CTF, Lot 012	1000
19	**NLK**	SP001	25	RB-CTF, Lot 012	1000
20	**MEK1 SESE**	001	300	ERK2-KR, Lot 004	1000

The reaction cocktails were incubated at 30 °C for 80 min. The reaction was stopped with 50 µL of 2 % (v/v) H_3PO_4, plates were aspirated and washed two times with 200 µL of 0.9 % (w/v) NaCl. Incorporation of 33Pi was determined with a microplate scintillation counter (Microbeta Trilux, Wallac).

All assays were performed with a BeckmanCoulter/Sagian robotic system.
Each compound was screen at six serial dilutions starting from 3 µM to 1.4 nM.

As a parameter for assay quality, the **Z´-factor** (Zhang et al., *J. Biomol. Screen.* 2: 67-73, 1999) for the low and high controls of each assay plate (n = 8) was used. The Z´-factors for this screen did not drop below 0.51, indicating an excellent assay quality. (Iversen et al., *J. Biomol. Screen.* 3: 247-252, 2006).

The broad kinase profiling was performed by Ambitbioscience (http://www.ambitbio.com/).

The data for residual kinases is shown below:

Residual kinase activity as a percent of control following incubation with 1 µM of inhibitor.

Ambit Gene Symbol	**Entrez**	**163bgi**	**163afh**				
AAK1	AAK1	91	17	MAP3K1	MAP3K1	100	100
ABL1	ABL1	88	96	MAP3K15	MAP3K15	91	100
ABL1(E255K)	ABL1	86	100	MAP3K2	MAP3K2	100	100
ABL1(F317I)	ABL1	100	100	MAP3K3	MAP3K3	100	100
ABL1(F317L)	ABL1	89	82	MAP3K4	MAP3K4	88	100
ABL1(H396P)	ABL1	100	92	MAP4K2	MAP4K2	92	100
ABL1(M351T)	ABL1	100	81	MAP4K3	MAP4K3	100	89
ABL1(Q252H)	ABL1	83	93	MAP4K4	MAP4K4	100	100
ABL1(T315I)	ABL1	87	98	MAP4K5	MAP4K5	100	100
ABL1(Y253F)	ABL1	95	100	MAPKAPK2	MAPKAPK2	100	100
ABL2	ABL2	75	91	MAPKAPK5	MAPKAPK5	61	63
ACVR1	ACVR1	53	40	MARK1	MARK1	78	100
ACVR1B	ACVR1B	79	75	MARK2	MARK2	85	100

ACVR2A	ACVR2A	99	99	MARK3	MARK3	62	100
ACVR2B	ACVR2B	89	100	MARK4	MARK4	73	100
ACVRL1	ACVRL1	49	65	MAST1	MAST1	79	100
ADCK3	CABC1	77	96	MEK1	MAP2K1	5.6	0.35
ADCK4	ADCK4	100	79	MEK2	MAP2K2	11	0.7
AKT1	AKT1	100	100	MEK3	MAP2K3	73	49
AKT2	AKT2	81	100	MEK4	MAP2K4	1	0
AKT3	AKT3	84	97	MEK6	MAP2K6	19	28
ALK	ALK	74	100	MELK	MELK	58	100
AMPK-alpha1	PRKAA1	100	100	MERTK	MERTK	100	100
AMPK-alpha2	PRKAA2	100	100	MET	MET	100	100
ANKK1	ANKK1	100	100	MET(M1250T)	MET	100	100
ARK5	NUAK1	100	100	MET(Y1235D)	MET	100	98
ASK1	MAP3K5	74	100	MINK	MINK1	100	100
ASK2	MAP3K6	100	100	MKNK1	MKNK1	23	4.4
AURKA	AURKA	100	100	MKNK2	MKNK2	4.4	0
AURKB	AURKB	83	100	MLCK	MLCK	100	100
AURKC	AURKC	77	98	MLK1	MAP3K9	100	100
AXL	AXL	100	95	MLK2	MAP3K10	73	100
BIKE	BMP2K	76	26	MLK3	MAP3K11	100	98
BLK	BLK	62	100	MRCKA	CDC42BPA	97	100
BMPR1A	BMPR1A	84	73	MRCKB	CDC42BPB	100	100
BMPR1B	BMPR1B	60	70	MST1	STK4	100	100
BMPR2	BMPR2	100	100	MST1R	MST1R	83	100
BMX	BMX	100	100	MST2	STK3	100	100
BRAF	BRAF	100	100	MST3	STK24	100	94
BRAF(V600E)	BRAF	100	100	MST4	MST4	100	100
BRK	PTK6	82	96	MUSK	MUSK	100	90
BRSK1	BRSK1	100	100	MYLK	MYLK	76	100
BRSK2	BRSK2	72	100	MYLK2	MYLK2	88	100
BTK	BTK	93	100	MYO3A	MYO3A	85	93
CAMK1	CAMK1	100	100	MYO3B	MYO3B	100	100
CAMK1D	CAMK1D	100	100	NDR1	STK38	100	100
CAMK1G	CAMK1G	87	100	NDR2	STK38L	99	93
CAMK2A	CAMK2A	100	89	NEK1	NEK1	79	100
CAMK2B	CAMK2B	100	87	NEK2	NEK2	98	93
CAMK2D	CAMK2D	91	100	NEK5	NEK5	100	100
CAMK2G	CAMK2G	94	100	NEK6	NEK6	95	100
CAMK4	CAMK4	72	100	NEK7	NEK7	100	100
CAMKK1	CAMKK1	94	100	NEK9	NEK9	95	92
CAMKK2	CAMKK2	95	100	NIM1	MGC42105	100	100

CDC2L1	CDC2L1	88	100	NLK	NLK	100	87
CDC2L2	CDC2L2	99	100	OSR1	OXSR1	100	96
CDK11	CDC2L6	97	92	p38-alpha	MAPK14	88	100
CDK2	CDK2	100	100	p38-beta	MAPK11	91	100
CDK3	CDK3	100	100	p38-delta	MAPK13	85	100
CDK5	CDK5	95	100	p38-gamma	MAPK12	100	100
CDK7	CDK7	100	82	PAK1	PAK1	100	52
CDK8	CDK8	78	100	PAK2	PAK2	100	59
CDK9	CDK9	100	100	PAK3	PAK3	100	100
CDKL2	CDKL2	87	83	PAK4	PAK4	100	70
CDKL3	CDKL3	52	69	PAK6	PAK6	100	100
CDKL5	CDKL5	100	100	PAK7	PAK7	84	100
CHEK1	CHEK1	58	100	PCTK1	PCTK1	100	86
CHEK2	CHEK2	100	100	PCTK2	PCTK2	94	100
CIT	CIT	93	94	PCTK3	PCTK3	88	99
CLK1	CLK1	77	87	PDGFRA	PDGFRA	78	4.7
CLK2	CLK2	100	84	PDGFRB	PDGFRB	37	0.65
CLK3	CLK3	96	100	PDPK1	PDPK1	100	100
CLK4	CLK4	66	85	PFTAIRE2	PFTK2	91	100
CSF1R	CSF1R	100	87	PFTK1	PFTK1	94	100
CSK	CSK	100	100	PHKG1	PHKG1	100	100
CSNK1A1L	CSNK1A1L	100	97	PHKG2	PHKG2	100	87
CSNK1D	CSNK1D	100	89	PIK3C2B	PIK3C2B	100	100
CSNK1E	CSNK1E	100	98	PIK3C2G	PIK3C2G	100	88
CSNK1G1	CSNK1G1	100	100	PIK3CA	PIK3CA	100	91
CSNK1G2	CSNK1G2	93	100	PIK3CA(C420R)	PIK3CA	100	100
CSNK1G3	CSNK1G3	100	100	PIK3CA(E542K)	PIK3CA	100	100
CSNK2A1	CSNK2A1	99	100	PIK3CA(E545A)	PIK3CA	100	100
CSNK2A2	CSNK2A2	100	45	PIK3CA(E545K)	PIK3CA	100	100
CTK	MATK	88	92	PIK3CA(H1047L)	PIK3CA	100	100
DAPK1	DAPK1	100	100	PIK3CA(H1047Y)	PIK3CA	93	96
DAPK2	DAPK2	100	100	PIK3CA(M1043I)	PIK3CA	100	89
DAPK3	DAPK3	100	99	PIK3CA(Q546K)	PIK3CA	100	98
DCAMKL1	DCLK1	86	95	PIK3CB	PIK3CB	94	100
DCAMKL2	DCLK2	87	92	PIK3CD	PIK3CD	100	100
DCAMKL3	DCLK3	81	100	PIK3CG	PIK3CG	99	100
DDR1	DDR1	62	100	PIK4CB	PI4KB	74	100
DDR2	DDR2	82	79	PIM1	PIM1	100	66
DLK	MAP3K12	91	100	PIM2	PIM2	100	84
DMPK	DMPK	100	86	PIM3	PIM3	100	64

DMPK2	CDC42BPG	100	100	PIP5K1A	PIP5K1A	73	74
DRAK1	STK17A	100	100	PIP5K2B	PIP4K2B	94	100
DRAK2	STK17B	100	100	PKAC-alpha	PRKACA	100	100
DYRK1A	DYRK1A	65	100	PKAC-beta	PRKACB	95	99
DYRK1B	DYRK1B	76	90	PKMYT1	PKMYT1	96	89
DYRK2	DYRK2	75	96	PKN1	PKN1	100	100
EGFR	EGFR	96	100	PKN2	PKN2	100	100
EGFR(E746-A750del)	EGFR	93	87	PLK1	PLK1	61	100
EGFR(G719C)	EGFR	100	100	PLK2	PLK2	100	100
EGFR(G719S)	EGFR	84	88	PLK3	PLK3	100	100
EGFR(L747-E749del, A750P)	EGFR	94	100	PLK4	PLK4	87	87
EGFR(L747-S752del, P753S)	EGFR	100	100	PRKCD	PRKCD	86	98
EGFR(L747-T751del,Sins)	EGFR	48	100	PRKCE	PRKCE	100	100
EGFR(L858R)	EGFR	100	100	PRKCH	PRKCH	100	95
EGFR(L858R,T790M)	EGFR	95	100	PRKCQ	PRKCQ	100	100
EGFR(L861Q)	EGFR	100	98	PRKD1	PRKD1	74	37
EGFR(S752-I759del)	EGFR	96	80	PRKD2	PRKD2	100	7.8
EPHA1	EPHA1	100	100	PRKD3	PRKD3	52	22
EPHA2	EPHA2	89	100	PRKG1	PRKG1	100	97
EPHA3	EPHA3	81	100	PRKG2	PRKG2	100	100
EPHA4	EPHA4	60	100	PRKR	EIF2AK2	84	75
EPHA5	EPHA5	100	90	PRKX	PRKX	100	100
EPHA6	EPHA6	67	100	PRP4	PRPF4B	100	100
EPHA7	EPHA7	77	100	PYK2	PTK2B	100	87
EPHA8	EPHA8	84	100	QSK	KIAA0999	100	100
EPHB1	EPHB1	84	90	RAF1	RAF1	100	81
EPHB2	EPHB2	82	100	RET	RET	100	100
EPHB3	EPHB3	70	100	RET(M918T)	RET	98	100
EPHB4	EPHB4	69	100	RET(V804L)	RET	95	100
EPHB6	EPHB6	70	100	RET(V804M)	RET	96	100
ERBB2	ERBB2	100	100	RIOK1	RIOK1	89	73
ERBB3	ERBB3	86	100	RIOK2	RIOK2	92	100
ERBB4	ERBB4	100	100	RIOK3	RIOK3	82	72
ERK1	MAPK3	95	94	RIPK1	RIPK1	100	100
ERK2	MAPK1	100	85	RIPK2	RIPK2	100	100
ERK3	MAPK6	100	100	RIPK4	RIPK4	70	100
ERK4	MAPK4	94	98	ROCK1	ROCK1	100	86
ERK5	MAPk7	98	99	ROCK2	ROCK2	93	100

ERK8	MAPK15	45	65	ROS1	ROS1	96	81
ERN1	ERN1	65	100	RPS6KA1(Kin.Dom.1-N-terminal)	RPS6KA1	93	100
FAK	PTK2	100	100	RPS6KA1(Kin.Dom.2-C-terminal)	RPS6KA1	100	67
FER	FER	100	92	RPS6KA2(Kin.Dom.1-N-terminal)	RPS6KA2	99	100
FES	FES	75	100	RPS6KA2(Kin.Dom.2-C-terminal)	RPS6KA2	100	59
FGFR1	FGFR1	73	96	RPS6KA3(Kin.Dom.1-N-terminal)	RPS6KA3	95	100
FGFR2	FGFR2	77	100	RPS6KA4(Kin.Dom.1-N-terminal)	RPS6KA4	86	98
FGFR3	FGFR3	100	100	RPS6KA4(Kin.Dom.2-C-terminal)	RPS6KA4	93	99
FGFR3(G697C)	FGFR3	100	100	RPS6KA5(Kin.Dom.1-N-terminal)	RPS6KA5	100	100
FGFR4	FGFR4	100	100	RPS6KA5(Kin.Dom.2-C-terminal)	RPS6KA5	100	100
FGR	FGR	73	100	RPS6KA6(Kin.Dom.1-N-terminal)	RPS6KA6	100	100
FLT1	FLT1	57	5.8	RPS6KA6(Kin.Dom.2-C-terminal)	RPS6KA6	71	8.1
FLT3	FLT3	40	7	SBK1	SBK1	100	100
FLT3(D835H)	FLT3	12	9	SgK085	LOC340156	100	100
FLT3(D835Y)	FLT3	2.8	0.4	SgK110	SgK110	87	100
FLT3(ITD)	FLT3	26	3	SIK	SNF1LK	100	92
FLT3(K663Q)	FLT3	19	6	SIK2	SNF1LK2	100	89
FLT3(N841I)	FLT3	4.8	0	SLK	SLK	94	75
FLT4	FLT4	30	12	SNARK	NUAK2	76	82
FRK	FRK	85	100	SRC	SRC	91	100
FYN	FYN	100	99	SRMS	SRMS	99	97
GAK	GAK	3.8	2.8	SRPK1	SRPK1	100	100
GCN2(Kin.Dom.2,S808G)	EIF2AK4	100	78	SRPK2	SRPK2	97	100
GRK1	GRK1	100	100	SRPK3	SRPK3	100	98
GRK4	GRK4	100	91	STK16	STK16	92	100
GRK7	GRK7	100	100	STK33	STK33	60	100
GSK3A	GSK3A	100	70	STK35	STK35	100	95
GSK3B	GSK3B	100	100	STK36	STK36	15	2.8
HCK	HCK	100	100	STK39	STK39	100	89
HIPK1	HIPK1	92	100	SYK	SYK	100	77

HIPK2	HIPK2	76	100	TAK1	MAP3K7	27	3.4
HIPK3	HIPK3	100	96	TAO1	TAOK2	100	100
HIPK4	HIPK4	100	90	TAOK1	TAOK1	100	100
HPK1	MAP4K1	63	100	TAOK3	TAOK3	100	91
HUNK	HUNK	100	94	TBK1	TBK1	96	97
ICK	ICK	100	100	TEC	TEC	76	84
IGF1R	IGF1R	100	100	TESK1	TESK1	80	100
IKK-alpha	CHUK	89	77	TGFBR1	TGFBR1	92	77
IKK-beta	IKBKB	100	84	TGFBR2	TGFBR2	18	10
IKK-epsilon	IKBKE	100	100	TIE1	TIE1	100	95
INSR	INSR	100	97	TIE2	TEK	100	96
INSRR	INSRR	100	100	TLK1	TLK1	100	87
IRAK1	IRAK1	99	98	TLK2	TLK2	80	100
IRAK3	IRAK3	77	98	TNIK	TNIK	86	100
ITK	ITK	74	92	TNK1	TNK1	81	91
JAK1(JH1domain-catalytic)	JAK1	100	89	TNK2	TNK2	83	80
JAK1(JH2domain-pseudokinase)	JAK1	98	100	TNNI3K	TNNI3K	100	98
JAK2(JH1domain-catalytic)	JAK2	92	100	TRKA	NTRK1	89	100
JAK3(JH1domain-catalytic)	JAK3	81	100	TRKB	NTRK2	100	98
JNK1	MAPK8	95	100	TRKC	NTRK3	100	100
JNK2	MAPK9	95	89	TSSK1B	TSSK1B	71	92
JNK3	MAPK10	100	57	TTK	TTK	97	100
KIT	KIT	62	8.8	TXK	TXK	95	100
KIT(D816V)	KIT	13	0.9	TYK2(JH1domain-catalytic)	TYK2	72	87
KIT(L576P)	KIT	57	5.2	TYK2(JH2domain-pseudokinase)	TYK2	100	100
KIT(V559D)	KIT	38	7.8	TYRO3	TYRO3	96	100
KIT(V559D,T670I)	KIT	84	68	ULK1	ULK1	96	100
KIT(V559D,V654A)	KIT	100	66	ULK2	ULK2	100	100
LATS1	LATS1	96	100	ULK3	ULK3	88	100
LATS2	LATS2	74	100	VEGFR2	KDR	77	20
LCK	LCK	93	80	WEE1	WEE1	100	85
LIMK1	LIMK1	79	94	WEE2	WEE1B	100	90
LIMK2	LIMK2	100	100	YANK2	STK32B	100	100
LKB1	STK11	66	100	YANK3	STK32C	87	93
LOK	STK10	98	98	YES	YES1	83	100

LTK	LTK	100	100	YSK1	STK25	77	100
LYN	LYN	84	100	YSK4	YSK4	69	92
LZK	MAP3K13	100	94	ZAK	ZAK	65	15
MAK	MAK	94	100	ZAP70	ZAP70	100	100

List of kinases bearing a cysteine residue at the adequate position to participate in the Michael addition:

Analysis by Santi *et al.* (Santi *et al*., *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 4234-4239):

TK: FLT1 (VEGFR1), KDR (VEGFR2), FLT4 (VEGFR3), FLT3, KIT, PDGFRαβ

TKL: TAK1, TGF-BR2, ZAK

CMGC: CDKL1-5, GSKαβ, ERK1-2, MAPK15, NLK, PRP4K

CAMK: MAPKAP5, MNK1, MNK2, RSK1-4, PKD1-3, SPEG

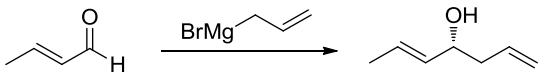
STE: MEK1-7, NIK1

Other AAK1, BMP2K, GAK, STK36, TOPK

Analysis by Gray *et al.* (N. S. Gray *et al.*, *Nat. Rev. Cancer* **2009**, *9*, 28-39):

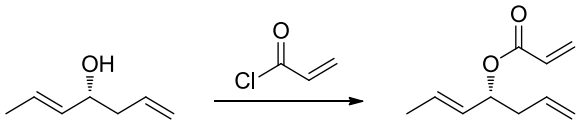
AAK1, BIKE, CDKL-1,2,3,4,5, Erk-1,2,7, FLT-1,3,4, Fused, GAK, GSK3-A,B, KDR, KIT, MAP2K-1,2,3,4,5,6,7, MAPKAPK5, MNK-1,2, NIK, NLK, Obscn, PBK, PDGR-α,β, PKD-1,2,3, PRP4, RSK-1,2,3,4, SPEG, TAK1, TGFβR2, ZAKα

Experimental Chapter 2



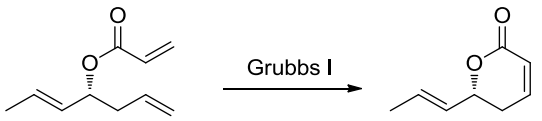
217 **224**

Secondary alcohol 224. To a solution of crotonaldehyde **217** (1.0 equiv, 822 μL, 10.0 mmol) in Et_2O (82 mL) at 0 °C was added dropwise a 1.0 M solution of allylmagnesium bromide in Et_2O (1.5 equiv, 15.0 mL, 15.0 mmol). The mixture was allowed to warm at 23 °C for 12 h. The reaction was quenched with a sat. NH_4Cl aq. solution, extracted with Et_2O, water and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the desired alcohol **224** as a crude. *Rf* = 0.50 (Petroleum ether/EtOAc 2/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 5.86-5.75 (m, 1H), 5.73-5.65 (m, 1H), 5.54-5.48 (m, 1H), 5.16-5.11 (m, 2H), 4.10 (dt, *J* = 6.0, 6.0 Hz, 1H), 2.35-2.22 (m, 2H), 1.70 (d, *J* = 6.4 Hz, 3H), OH signal is not visible; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 134.41, 133.30, 126.81, 117.82, 71.73, 41.88, 17.56.



224 **221**

Metathesis precursor 221. To a solution of secondary alcohol **224** (1.0 equiv, 1.1 g, 10.0 mmol) in Et_2O (228 mL) at 0 °C was added Et_3N (2.0 equiv, 2.8 mL, 20.0 mmol). The mixture was stirred for 10 min at 0 °C. Acryloyl chloride (1.1 equiv, 868 μL, 11.0 mmol) in Et_2O (14 mL) was added. The mixture was stirred 10 min at 0 °C and 12 h at 23 °C. The reaction was quenched with a sat. $NaHCO_3$ aq. Solution and stirred for 1 h. The reaction mixture was extracted Et_2O, water and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, Pentane to Pentane/Et_2O 50/1) yielded the metathesis precursor **221** in quantitative yield for 2 steps (1.7 g). *Rf* = 0.77 (Petroleum ether/EtOAc 2/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.39 (dd, *J* = 17.2, 1.2 Hz, 1H), 6.10 (dd, *J* = 17.2, 10.4 Hz, 1H), 5.81-5.71 (m, 3H), 5.49-5.43 (m, 1H), 5.33 (dt, *J* = 6.4, 6.4 Hz, 1H), 5.11-5.05 (m, 2H), 2.46-2.35 (m, 2H), 1.70 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 165.24, 133.22, 130.24, 129.34, 128.80, 128.75, 117.61, 73.94, 38.94, 17.57.



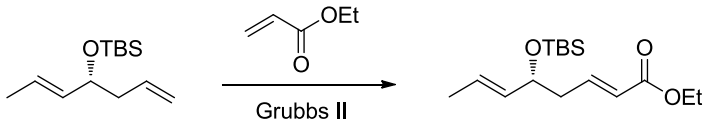
221 **222**

Lactone 222. To a solution of alkene **221** (1.0 equiv, 1.7 g, 10.0 mmol) in CH_2Cl_2 (1 L) at 40 °C was added Grubbs I catalyst (20 mol%, 1.6 g, 2.0 mmol). The catalyst was added each 2 h by portions (5 portions of 4 mol%), the mixture was then stirred 10 h at 40 °C. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Pentane to Pentane ether/Et_2O 2/1) yielded lactone **222** in a 70% yield (974 mg). *Rf* = 0.34 (Petroleum ether/EtOAc 2/1); ^{1}H-NMR ($CDCl_3$,

400 MHz, 25 °C) δ 6.86 (dt, *J* = 4.4, 9.6 Hz, 1H), 6.02 (d, *J* = 10.0 Hz, 1H), 5.84 (dq, *J* = 6.8, 15.6 Hz, 1H), 5.60 (dd, *J* = 15.6, 7.2 Hz, 1H), 4.85 (dt, *J* = 7.2 Hz, 1H), 2.42-2.39 (m, 2H), 1.73 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 164.04, 144.68, 130.50, 128.01, 121.47, 78.18, 29.68, 17.63.

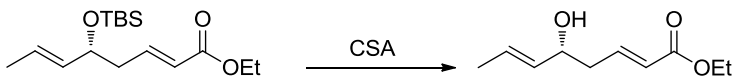
224 **224'**

TBS-protected alcohol 224'. To a solution of secondary alcohol **224** (1.0 equiv, 1.1 g, 10.0 mmol) and imidazole (2.0 equiv, 1.4 g, 20.0 mmol) in CH_2Cl_2 (97 mL) at 23 °C was added TBSCl (2.0 equiv, 3.0 g, 20.0 mmol). The resulting mixture was stirred 12 h at 23 °C. The reaction was then quenched with a sat. NH_4Cl aq. solution, extracted with EtOAc, water and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 50/1) yielded TBS-protected alcohol **224'** in quantitative yield (2.3 g). *Rf* = 0.82 (Petroleum ether/EtOAc 4/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 5.84-5.74 (m, 1H), 5.56 (dq, *J* = 6.4, 15.6 Hz, 1H), 5.46-5.40 (m, 1H), 5.05-5.00 (m, 2H), 4.07 (q, *J* = 6.4 Hz, 1H), 2.29-2.17 (m, 2H), 1.67 (d, *J* = 6.4 Hz, 3H), 0.88 (m, 9H), 0.04 (s, 3H), 0.02 (s, 3H).



224' **225**

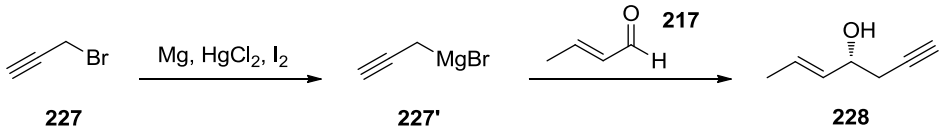
α,β-unsaturated ester 225. To a solution of TBS-protected alcohol **224'** (1.0 equiv, 2.3 g, 10.0 mmol) and ethyl acrylate (40.0 equiv, 43.5 mL, 400.0 mmol) in CH_2Cl_2 (118 mL) at 23 °C was added Grubbs II catalyst (8 mol%, 689 mg, 800 µmol). The resulting mixture was stirred 1 h at 23 °C. DMSO (2.86 mL) was added and the reaction was stirred for another 12 h. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 10/1) yielded α,β-unsaturated ester **225** in 82% yield (2.4 g). *Rf* = 0.80 (Petroleum ether/EtOAc 2/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.93 (dt, *J* = 7.6, 15.6 Hz, 1H), 5.82 (d, *J* = 15.6 Hz, 1H), 5.59 (dq, *J* = 6.4, 15.2 Hz, 1H), 5.45-5.39 (m, 1H), 4.21-4.13 (m, 3H), 2.40-2.32 (m, 2H), 1.67 (d, *J* = 6.4 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H).



225 **226**

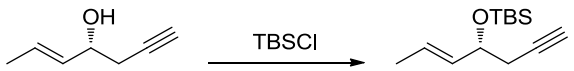
Secondary alcohol 226. To a solution of α,β-unsaturated ester **225** (1.0 equiv, 2.4 g, 8.2 mmol) in a CH_2Cl_2/MeOH mixture (92 mL/23 mL) at 23 °C was added CSA (0.24 equiv, 473 mg, 2.0 mmol). The reaction was stirred 12 h at 23 °C. The reaction was quenched with a sat. $NaHCO_3$ aq. solution, extracted with Et_2O, water and brine, and dried over Na_2SO_4. Evaporation of the solvent under

reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 1/1) yielded secondary alcohol **226** in quantitative yield (1.5 g). *Rf* = 0.32 (Petroleum ether/EtOAc 2/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.95 (dt, *J* = 7.2, 15.6 Hz, 1H), 5.89 (d, *J* = 15.6 Hz, 1H), 5.70 (dq, *J* = 6.4, 15.2 Hz, 1H), 5.51 (dd, *J* = 15.2, 7.2 Hz, 1H), 4.20-4.15 (m, 3H), 2.43-2.40 (m, 2H), 1.69 (d, *J* = 6.4 Hz, 3H), OH signal is not visible.



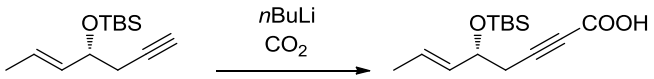
227 **227'** **228**

Alcohol 228. Magnesium (2.0 equiv, 517 mg, 21.6 mmol), mercuric chloride (0.5 mol%, 13 mg, 54 µmol), and a small grain of iodide were mixed together in Et_2O (123 mL) at 23 °C. The mixture was heated at reflux, and a 80% solution of propargyl bromide **227** in toluene (1.9 equiv, 3.1 mL, 20.5 mmol) was added in small portions. The resulting mixture was then left to cool and stirred for 2 h at 23 °C. This solution (**227'**) was transferred by canula into a flask containing a solution of crotonaldehyde **217** (1.0 equiv, 881 µL, 10.8 mmol) in Et_2O (60 mL) at -78 °C. The resulting solution was allowed to come back at 23 °C during 12 h. The reaction was quenched with a sat. NH_4Cl aq. solution, extracted with Et_2O, water and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the desired alcohol **228** as a crude. *Rf* = 0.46 (Petroleum ether/EtOAc 2/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 5.80-5.72 (m, 1H), 5.59-5.53 (m, 1H), 4.25-4.21 (m, 1H), 2.45-2.41 (m, 2H), 2.35 (s, 1H), 1.71 (d, *J* = 6.4 Hz, 3H), OH signal is not visible.



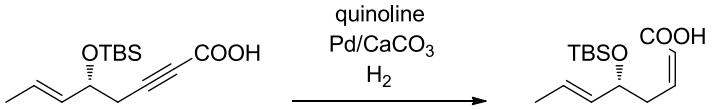
228 **228'**

TBS-protected alcohol 228'. To a solution of secondary alcohol **228** (1.0 equiv, 1.2 g, 10.8 mmol) in CH_2Cl_2 (104 mL) at 23 °C were added sequentially imidazole (2.0 equiv, 1.5 g, 21.6 mmol) and TBSCl (2.0 equiv, 3.2 g, 21.6 mmol). The resulting mixture was stirred 12 h at 23 °C. The reaction was quenched with a sat. NH_4Cl aq. solution, extracted with Et_2O, water and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, Pentane to Pentane/Et_2O 10/1) yielded the protected alcohol **228'** in quantitative yield for 3 steps (2.4 g). *Rf* = 0.85 (Petroleum ether/EtOAc 2/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 5.68-5.61 (m, 1H), 5.53-5.48 (m, 1H), 4.20 (dt, *J* = 6.4, 6.4 Hz, 1H), 2.42-2.27 (m, 2H), 1.97 (s, 1H), 1.69 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H).



228' **229**

Carboxylic acid 229. To a solution of TBS-protected alcohol **228'** (1.0 equiv, 2.4 g, 10.8 mmol) in Et_2O (48 mL) at -78 °C was added a 1.17 M solution of *n*-butyllithium in hexane (1.1 equiv, 10.0 mL, 11.9 mmol).The resulting mixture was stirred 45 min at -78 °C. Crushed dry ice was added and the reaction was allowed to warm to 23 °C. The reaction was quenched with a sat. NH_4Cl aq. solution, extracted with EtOAc, water and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the desired carboxylic acid **229** as a crude. *Rf* = 0.11 (Petroleum ether/EtOAc 2/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 5.64 (dq, *J* = 6.4, 15.2 Hz, 1H), 5.46 (dd, *J* = 15.2, 6.4 Hz, 1H), 4.23 (dt, *J* = 6.4, 6.4 Hz, 1H), 2.51-2.38 (m, 2H), 1.66 (d, *J* = 6.4 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H), CO_2H signal is not visible.



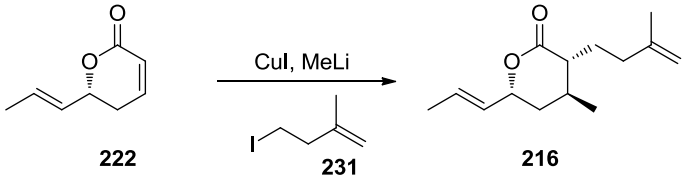
229 **230**

Carboxylic acid 230. A mixture of carboxylic acid **229** (1.0 equiv, 2.9 g, 10.8 mmol) and quinoline (1.0 equiv, 1.3 mL, 10.8 mmol) in EtOAc (107 mL) at 23 °C was treated with Lindlar catalyst (0.4 equiv, 460 mg, 4.3 mmol) and a hydrogen atmosphere was introduced. The reaction was allowed to proceed for 8 h at 23 °C. The mixture was filtered through Celite, wich was then washed with EtOAc. The recovered filtrate was washed with a 2.0 M solution of HCl, water and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the desired carboxylic acid **230** as a crude. *Rf* = 0.56 (Petroleum ether/EtOAc 2/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.43 (dt, *J* = 7.2, 11.6 Hz, 1H), 5.87 (d, *J* = 11.6 Hz, 1H), 5.59 (dq, *J* = 6.0, 15.2 Hz, 1H), 5.43 (dd, *J* = 15.2, 6.0 Hz, 1H), 4.22 (dt, *J* = 6.0, 6.0 Hz, 1H), 2.85-2.82 (m, 2H), 1.68 (d, *J* = 6.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), CO_2H signal is not visible.

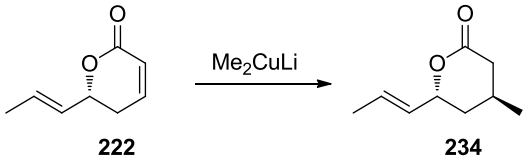
230 **222**

Lactone 222. To a solution of carboxylic acid **230** (1.0 equiv, 2.9 g, 10.8 mmol) in a CH_2Cl_2/MeOH mixture (122 mL/29 mL) at 23 °C was added CSA (0.24 equiv, 602 mg, 2.6 mmol). The reaction was stirred 12 h at 23 °C. The reaction was quenched with a sat. $NaHCO_3$ aq. solution, extracted with Et_2O, water and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 3/1) yielded the desired lactone **222** in 70% yield for 3 steps (974 mg). *Rf* = 0.34 (Petroleum ether/EtOAc 2/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.86 (dt, *J* = 4.4, 9.6 Hz, 1H), 6.02 (d, *J* = 10.0 Hz, 1H), 5.84 (dq, *J* = 6.8, 15.6 Hz, 1H), 5.60 (dd, *J* = 15.6, 7.2 Hz, 1H), 4.85 (dt, *J* = 7.2 Hz, 1H), 2.42-2.39 (m, 2H), 1.73 (d, *J* = 6.8

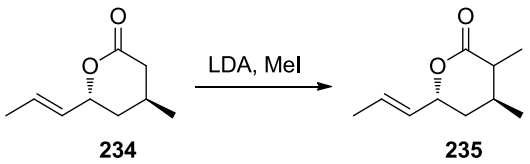
Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 164.04, 144.68, 130.50, 128.01, 121.47, 78.18, 29.68, 17.63.



Lactone 216. To a suspension of copper iodide (2.0 equiv, 2.7 g, 14.1 mmol) in Et_2O (69 mL) at 0 °C was added a 1.6 M solution of methyllithium in Et_2O (4.0 equiv, 17.6 mL, 28.2 mmol). The resulting mixture was stirred 30 min at 0 °C. A solution of lactone **222** (1.0 equiv, 974 mg, 7.0 mmol) in Et_2O (7 mL) was then added and the reaction was stirred for 1 h at 0 °C. A mixture of THF/HMPA (18 mL/18 mL) was added, followed by the quick addition of 1-iodo-3-methyl-but-3-ene **231** (8.0 equiv, 8.4 g, 56.4 mmol). The reaction was allowed to warm at 23 °C and stirred 12 h. The reaction was quenched with a 10% NH_4OH aq. solution, extracted with Et_2O, water and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, Pentane to Pentane/Et_2O 3/1) yielded the desired lactone **216** in 41% yield (643 mg). *Rf* = 0.68 (Petroleum ether/EtOAc 2/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 5.80-5.71 (m, 1H), 5.51-5.45 (m, 1H), 4.79-4.74 (m, 1H), 4.71 (bs, 1H), 4.67 (bs, 1H), 2.21-2.14 (m, 1H), 2.10-2.02 (m, 2H), 1.92-1.80 (m, 3H), 1.71 (s, 3H), 1.77-1.68 (m, 4H), 1.63-1.57 (m, 1H), 1.10 (d, *J* = 6.8 Hz, 3H)); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 174.26, 145.05, 129.13, 129.04, 110.28, 76.29, 45.72, 35.95, 35.07, 28.34, 27.11, 25.55, 22.27, 20.77, 17.52.

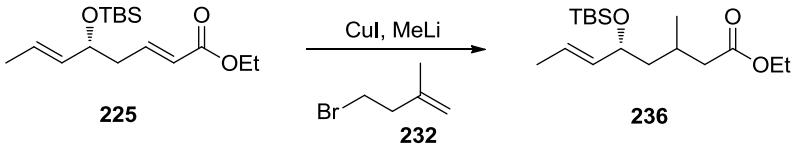


Lactone 234. To a suspension of copper iodide (2.0 equiv, 2.7 g, 14.1 mmol) in Et_2O (69 mL) at 0 °C was added a 1.6 M solution of methyllithium in Et_2O (4.0 equiv, 17.6 mL, 28.2 mmol). The resulting mixture was stirred 30 min at 0 °C. A solution of lactone **222** (1.0 equiv, 974 mg, 7.0 mmol) in Et_2O (7 mL) was then added and the reaction was stirred for 1 h at 0 °C. The reaction was quenched with a 10/1 sat. NH_4Cl aq. solution/25% NH_4OH aq. solution, extracted with Et_2O, water and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, Pentane to Pentane/Et_2O 3/1) afforded the desired lactone **234** in 38% yield (413 mg). *Rf* = 0.48 (Petroleum ether/EtOAc 2/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 5.76 (dq, *J* = 6.4, 14.8 Hz, 1H), 5.54-5.48 (m, 1H), 4.89 (q, *J* = 5.6 Hz, 1H), 2.60 (dd, *J* = 16.0, 4.8 Hz, 1H), 2.22-2.09 (m, 2H), 1.88-1.81 (m, 1H), 1.72 (d, *J* = 6.4 Hz, 3H), 1.66-1.59 (m, 1H), 1.07 (d, *J* = 6.4 Hz, 3H).



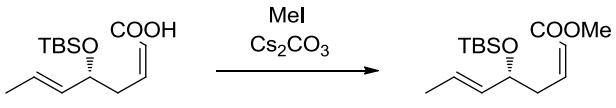
234 **235**

Lactone 235. To a solution of *i*Pr_2NH (3.0 equiv, 1.0 mL, 8.0 mmol) in THF (40 mL) at -78 °C was added a 1.6 M solution of *n*BuLi (3.0 equiv, 5.0 mL, 8.0 mmol). The resulting mixture was stirred 10 min at 0 °C, before being cooled down again at -78 °C. Lactone **234** (1.0 equiv, 413 mg, 2.7 mmol) was added dropwise and the reaction was stirred for another 30 min at -78 °C. Methyl iodide (5.0 equiv, 835 μL, 13.4 mmol) was then added, and the final mixture was stirred for 2 h at the same temperature. The reaction was quenched with water, extracted with Et_2O, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, Pentane to Pentane/Et_2O 1/1) yielded lactone **235** in 73% yield (329 mg). *Rf* = 0.40 (Petroleum ether/EtOAc 2/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 5.81-5.71 (m, 1H), 5.53-5.47 (m, 1H), 4.93-4.87 (m, 0.2H), 4.81-4.76 (m, 0.8H), 2.14 (dq, *J* = 6.8, 9.6 Hz, 1H), 1.94-1.69 (m, 2H), 1.72 (d, *J* = 6.8 Hz, 3H), 1.64-1.58 (m, 1H), 1.25 (d, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 6.4 Hz, 3H).



225 **232** **236**

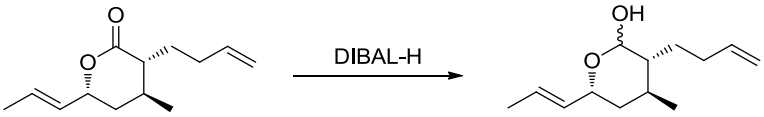
Methylated compound 236. To a suspension of copper iodide (2.0 equiv, 3.1 g, 16.4 mmol) in Et_2O (77 mL) at 0 °C was added a 1.6 M solution of methyllithium in Et_2O (4.0 equiv, 20.5 mL, 32.8 mmol). The resulting mixture was stirred 30 min at 0 °C. A solution of α,β-unsaturated ester **225** (1.0 equiv, 2.4 g, 8.2 mmol) in Et_2O (8 mL) was then added and the reaction was stirred for 1 h at 0 °C. A mixture of THF/HMPA (20 mL/20 mL) was added, followed by the quick addition of 1-bromo-3-methyl-but-3-ene **232** (8.0 equiv, 9.8 g, 65.6 mmol). The reaction was allowed to warm at 23 °C and stirred 12 h. The reaction was quenched with a sat. NH_4Cl aq. solution, extracted with Et_2O, water and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, Pentane to Pentane/Et_2O 3/1) yielded methylated compound **236** in 70% yield (1.8 g). *Rf* = 0.42 (Petroleum ether/EtOAc 8/1). ^{1}H NMR spectra was not clean enough to be completely interpreted.



230 **237**

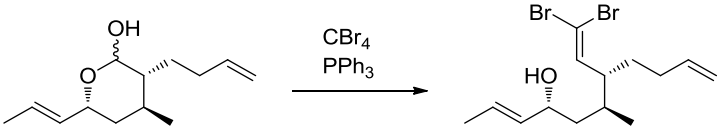
Methyl ester 237. To a solution of carboxylic acid **230** (1.0 equiv, 2.9 g, 10.8 mmol) in DMF (55 mL) at 23 °C were added sequentially cesium carbonate (1.5 equiv, 5.2 g, 16.2 mmol) and methyl iodide (1.5 equiv, 1.0 mL, 16.2 mmol). The mixture was stirred 9 h at 23 °C, and was then quenched by the addition of a 1N solution of HCl in water. The reaction mixture was extracted EtOAc, water and brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash

chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 80/1) yielded methyl ester **237** in 90% yield (2.8 g). *Rf* = 0.84 (Petroleum ether/EtOAc 2/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.32 (dt, *J* = 7.2, 11.6 Hz, 1H), 5.83 (d, *J* = 11.6 Hz, 1H), 5.59 (dq, *J* = 6.4, 15.6 Hz, 1H), 5.42 (dd, *J* = 15.6, 6.8 Hz, 1H), 4.20 (q, *J* = 6.4 Hz, 1H), 3.69 (s, 3H), 2.90-2.78 (m, 2H), 1.66 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).



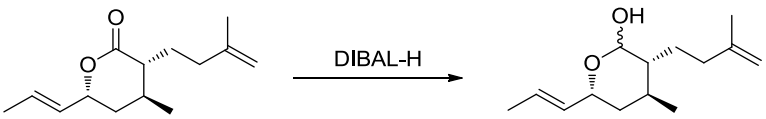
239 **244**

Aldehyde 244. To a solution of lactone **239** (1.0 equiv, 601 mg, 2.9 mmol) in CH_2Cl_2 (16 mL) at -78 °C was added dropwise a 1.0 M solution of DIBAL-H in toluene (1.1 equiv, 3.2 mL, 3.2 mmol). The mixture was then stirred 1 h at -78 °C. The reaction was quenched with a sat. sodium tartrate aq. solution, and stirred 12 h at 23 °C. The reaction mixture was extracted EtOAc, water and brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 1/1) yielded aldehyde **244** in 76% yield (461 mg). *Rf* = 0.35 (Petroleum ether/EtOAc 4/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 5.85-5.73 (m, 1H), 5.72-5.64 (m, 1H), 5.57-5.51 (m, 1H), 5.11-4.92 (m, 3H), 4.50 (dt, *J* = 6.4, 4.8 Hz, 0.6H), 4.17-4.15 (m, 0.4H), 2.16-2.05 (m, 2H), 2.03-1.99 (m, 1H), 1.77-1.65 (m, 5H), 1.55-1.50 (m, 1H), 1.43-1.34 (m, 1H), 1.30-1.25 (m, 1H), 1.12 (d, *J* = 6.8 Hz, 1.8H), 1.06 (d, *J* = 7.2 Hz, 1.2H), OH signal is not visible.



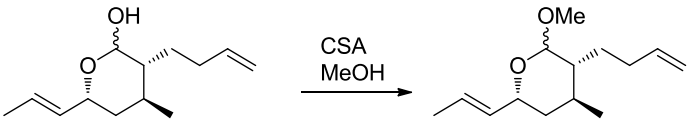
244 **245**

Dibromoalkene 245. To a stirred solution of CBr_4 (1.0 equiv, 730 mg, 2.2 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added PPh_3 (1.0 equiv, 578 mg, 2.2 mmol). After 30 min at this temperature, a solution of lactol **244** (1.0 equiv, 461 mg, 2.2 mmol) in CH_2Cl_2 (8 mL) was added. After 45 min at 0 °C, the reaction mixture was diluted with Petroleum ether and filtered on a pad of silica. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 50/1) yielded dibromoalkene **245** in a 48% yield (380 mg). *Rf* = 0.73 (Petroleum ether/EtOAc 3/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.19 (s, 1H), 5.84-5.71 (m, 2H), 5.57-5.51 (m, 1H), 5.02 (s, 0.5H), 4.98 (s, 0.5H), 4.95 (s, 0.5H), 4.93 (s, 0.5H), 4.21-4.17 (m, 1H), 2.18-2.11 (m, 2H), 2.09-2.01 (m, 2H), 1.96-1.91 (m, 1H), 1.77-1.70 (m, 1.5H), 1.71 (d, *J* = 6.4 Hz, 3H), 1.59-1.53 (m, 1.5H), 1.07 (d, *J* = 7.2 Hz, 3H), OH signal is not visible.



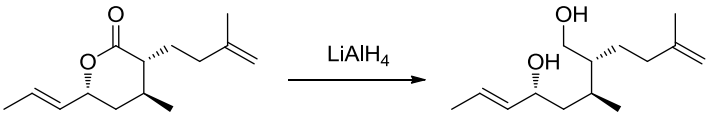
216 **246**

Lactol 246. To a solution of lactone **216** (1.0 equiv, 643 mg, 2.9 mmol) in CH_2Cl_2 (43 mL) at -78 °C was added dropwise a 1.0 M solution of DIBAL-H in toluene (1.1 equiv, 3.2 mL, 3.2 mmol). The mixture was then stirred 1 h at -78 °C. The reaction was quenched with a sat. sodium tartrate aq. solution, and stirred 12 h at 23 °C. The reaction mixture was extracted EtOAc, water and brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 1/1) yielded lactol **246** in 94% yield (609 mg). *Rf* = 0.60 (Petroleum ether/EtOAc 2/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 5.75-5.65 (m, 1.4H), 5.62-5.53 (m, 0.6H), 5.17-5.11 (m, 0.4H), 5.01-4.96 (m, 0.6H), 4.74-4.66 (m, 2H), 4.56-4.48 (m, 0.6H), 4.22-4.14 (m, 0.4H), 2.92-2.86 (d, *J* = 4.8 Hz, 0.4H), 2.74-2.67 (d, *J* = 4.4 Hz, 0.6H), 2.12-1.98 (m, 2.6H), 1.84-1.36 (m, 8.4H), 1.72 (s, 3H), 1.15 (d, *J* = 6.8 Hz, 1.8H), 1.08 (d, *J* = 7.2 Hz, 1.2H).



244 **248**

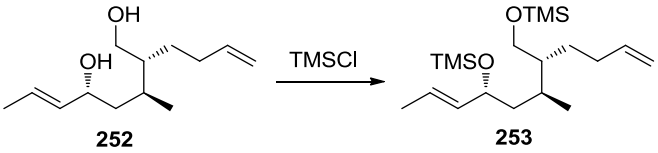
O-methylated lactol 248. To a solution of lactol **244** (1.0 equiv, 461 mg, 2.2 mmol) in MeOH (27 mL) at 23 °C was added CSA (cat). The resulting mixture was stirred 12 h at 23 °C. The reaction was quenched with a sat. $NaHCO_3$ aq. solution, extracted with EtOAc, water and brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 10/1) yielded O-methylated lactol **248** in quantitative yield (493 mg). *Rf* = 0.74 (Petroleum ether/EtOAc 4/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 5.85-5.65 (m, 2.4H), 5.54-5.48 (m, 0.6H), 5.03 (s, 0.6H), 4.98 (s, 0.6H), 4.96 (s, 0.4H), 4.94 (s, 0.4H), 4.58 (d, *J* = 2.8 Hz, 0.4H), 4.48 (d, *J* = 2.4 Hz, 0.6H), 4.30-4.26 (m, 0.6H), 4.17-4.13 (m, 0.4H), 3.39 (s, 1.2H), 3.35 (s, 1.8H), 2.10-2.04 (m, 2H), 1.75-1.44 (m, 7H), 1.39-1.28 (m, 2H), 1.15 (d, *J* = 6.8 Hz, 1.8H), 1.01 (d, J = 6.8 Hz, 1.2 H).



216 **251**

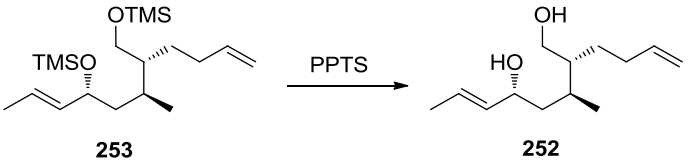
Diol 251. To a solution of lactone **216** (1.0 equiv, 643 mg, 2.9 mmol) in Et_2O (32 mL) at 0 °C was added a suspension of $LiAlH_4$ (3.0 equiv, 340 mg, 8.7 mmol) in Et_2O (9 mL). The resulting mixture was stirred for 1 h at 0 °C. The reaction was diluted with Et_2O at 0 °C, water was slowly added (340 µL), followed by a 15% solution of NaOH in water (340 µL), and water (1 mL). The mixture was allowed to warm at 23 °C during 15 min. The organic phase was then washed with water, brine, and dried over

Na_2SO_4. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAC 1/2) yielded the desired diol **251** in quantitative yield (654 mg). *Rf* = 0.09 (Petroleum ether/EtOAc 2/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 5.67 (dq, *J* = 6.4, 15.2 Hz, 1H), 5.48-5.42 (m, 1H), 4.71 (s, 1H), 4.68 (s, 1H), 4.13 (dt, *J* = 7.2, 7.2 Hz, 1H), 3.64-3.54 (m, 2H), 2.11-1.96 (m, 2H), 1.85-1.79 (m, 1H), 1.72 (s, 3H), 1.72-1.69 (m, 3H), 1.53-1.42 (m, 4H), 1.30-1.25 (m, 1H), 0.88 (d, *J* = 7.2 Hz, 3H), 2 OH signals are not visible; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 145.96, 134.20, 127.24, 110.03, 71.45, 63.77, 44.19, 41.47, 36.19, 28.98, 24.92, 22.37, 17.68, 16.01.



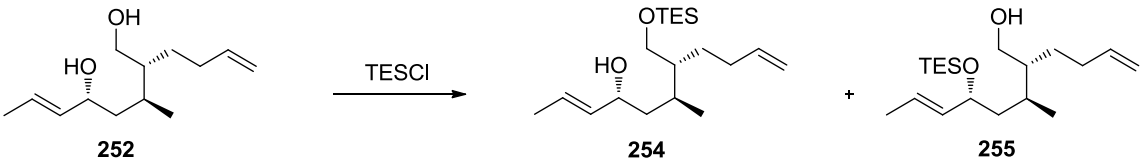
252 **253**

TMS-bisprotected diol 253. To a solution of diol **252** (1.0 equiv, 654 mg, 2.9 mmol) and imidazole (6.6 equiv, 1.3 g, 19.1 mmol) in CH_2Cl_2 (30 mL) at 23 °C was added TMSCl (4.2 equiv, 1.5 mL, 12.1 mmol). The resulting mixture was stirred 12 h at 23 °C. The reaction was then quenched with a sat. NH_4Cl aq. solution, extracted with EtOAc, water and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 10/1) yielded the TMS-bisprotected alcohol **253** in 76% yield (783 mg). *Rf* = 0.84 (Petroleum ether/EtOAc 2/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 5.84-5.74 (m, 1H), 5.54 (dq, *J* = 6.4, 15.2 Hz, 1H), 5.36 (dd, *J* = 15.2, 7.2 Hz, 1H), 4.99 (d, *J* = 17.2 Hz, 1H), 4.94 (d, *J* = 10.0 Hz, 1H), 4.05 (q, *J* = 7.2 Hz, 1H), 3.48 (d, *J* = 6.0 Hz, 2H), 2.14-1.95 (m, 2H), 1.81-1.72 (m, 1H), 1.68 (d, *J* = 6.4 Hz, 3H), 1.50-1.17 (m, 5H), 0.82 (d, *J* = 6.8 Hz, 3H), 0.10 (m, 9H), 0.09 (m, 9H).

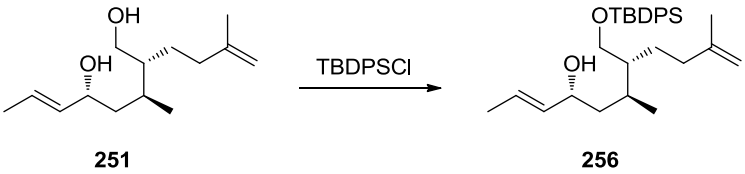


253 **252**

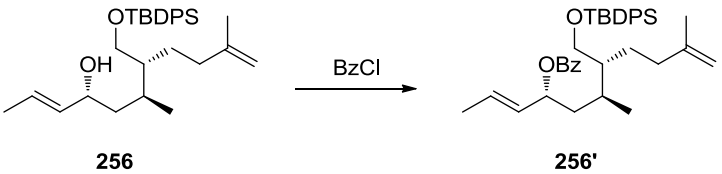
Diol 252. To a solution of TMS-bisprotected alcohol **253** (1.0 equiv, 783 mg, 2.2 mmol) in a 1/3 MeOH/CH_2Cl_2 mixture (3 mL/9 mL) at -10 °C was added PPTS (0.2 equiv, 112 mg, 440 µmol). The resulting mixture was stirred 10 min at -10 °C, quenched with a sat. NH_4Cl aq. solution, extracted with Et_2O, water and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 1/1) yielded diol **252** in quantitative yield (467 mg). *Rf* = 0.04 (Petroleum ether/EtOAc 5/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 5.85-5.74 (m, 1H), 5.67 (dq, *J* = 6.4, 15.2 Hz, 1H), 5.46 (dd, *J* = 15.2, 7.2 Hz, 1H), 5.01 (d, *J* = 17.2 Hz, 1H), 4.96 (d, *J* = 10.0 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 1H), 3.64-3.53 (m, 2H), 2.17-1.98 (m, 2H), 1.87-1.77 (m, 1H), 1.71 (d, *J* = 6.4 Hz, 3H), 1.55-1.35 (m, 4H), 1.31-1.21 (m, 1H), 0.87 (d, *J* = 7.2 Hz, 3H), 2 OH signals are not visible.



TES-monoprotected diols 254 and 255. To a solution of diol **252** (1.0 equiv, 654 mg, 2.9 mmol) and imidazole (1.3 equiv, 257 mg, 3.8 mmol) in CH_2Cl_2 (16 mL) at -5 °C was added dropwise a solution of TESCl (1.0 equiv, 473 µL, 2.9 mmol) in CH_2Cl_2 (14 mL). The resulting mixture was stirred 1 h at -5 °C. The reaction was then quenched with a sat. NH_4Cl aq. solution, extracted with EtOAc, water and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 6/1) yielded the TES-monoprotected alcohols **254** and **255** as an inseparable mixture in 61% yield (486 mg). *Rf* = 0.72 (Petroleum ether/EtOAc 2/1).

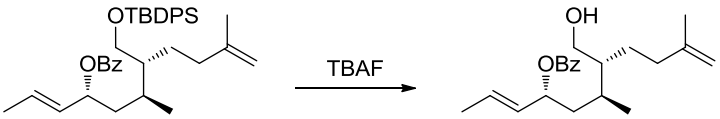


TBDPS-protected alcohol 256. To a solution of diol **251** (1.0 equiv, 654 mg, 2.9 mmol) and imidazole (1.3 equiv, 255 mg, 3.8 mmol) in CH_2Cl_2 (30 mL) at -78 °C was added dropwise a solution of TBDSCl (1.0 equiv, 761 µL, 2.9 mmol) in CH_2Cl_2 (18 mL). The resulting mixture was stirred 1 h at -78 °C. The reaction was then quenched with a sat. NH_4Cl aq. solution, extracted with EtOAc, water and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 8/1) yielded the mono-protected alcohol **256** (after resubmission of the unreacted diol **7**) in 99% yield (1.3 g). *Rf* = 0.60 (Petroleum ether/EtOAc 2/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.66 (d, *J* = 7.6 Hz, 4H), 7.42-7.36 (m, 6H), 5.67 (dq, *J* = 6.4, 15.2 Hz, 1H), 5.44 (dd, *J* = 15.2, 7.6 Hz, 1H), 4.66 (s, 1H), 4.58 (s, 1H), 4.13-4.07 (m, 1H), 3.60 (dd, *J* = 10.2, 5.2 Hz, 1H), 3.51 (dd, *J* = 10.2, 7.6 Hz, 1H), 1.96-1.89 (m, 2H), 1.87-1.82 (m, 1H), 1.69 (d, *J* = 6.4 Hz, 3H), 1.66 (s, 3H), 1.52-1.33 (m, 4H), 1.28-1.22 (m, 1H), 1.04 (s, 9H), 0.78 (d, *J* = 6.8 Hz, 3H), OH signal is not visible; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 146.04, 135.63 (x2), 165.61 (x2), 134.22, 133.86 (x2), 129.54 (x2), 127.59 (x4), 127.40, 109.81, 71.94, 64.48, 44.67, 41.97, 36.16, 29.02, 26.85 (x3), 24.61, 22.33, 19.21, 17.71, 15.36.



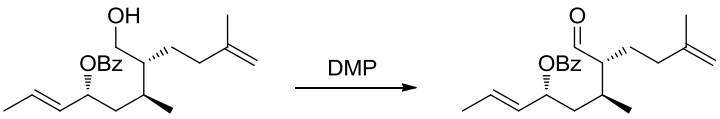
Bz-protected alcohol 256'. To a solution of mono-alcohol **256** (1.0 equiv, 1.3 g, 2.9 mmol) in CH_2Cl_2 (37 mL) at 0 °C were added sequentially pyridine (4.0 equiv, 899 µL, 11.4 mmol) and BzCl (4.0 equiv, 1.3 mL, 11.4 mmol). The resulting mixture was stirred 3 h at 23 °C. The reaction was then quenched

with a sat. NH_4Cl aq. solution, extracted with EtOAc, water and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 10/1) yielded the Bz-protected alcohol **256'** in 97% yield (1.5 g). *Rf* = 0.72 (Petroleum ether/EtOAc 4/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.04 (d, *J* = 8.0 Hz, 2H), 7.65-7.63 (m, 4H), 7.55-7.51 (m, 1H), 7.43-7.34 (m, 8H), 5.89-5.81 (m, 1H), 5.51-5.46 (m, 2H), 4.66 (s, 1H), 4.58 (s, 1H), 3.62 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.51 (dd, *J* = 10.0, 7.6 Hz, 1H), 2.01-1.96 (m, 1H), 1.93-1.80 (m, 2H), 1.71 (d, *J* = 6.4 Hz, 3H), 1.66 (s, 3H), 1.73-1.65 (m, 2H), 1.58-1.51 (m, 1H), 1.45-1.37 (m, 1H), 1.34-1.24 (m, 1H), 1.00 (s, 9H), 0.85 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 165.80, 145.99, 135.62 (x2), 135.60 (x2), 133.80, 133.79, 132.64, 130.89, 129.99, 129.61, 129.55 (x2), 169.52 (x2), 128.22 (x2), 127.58 (x4), 109.83, 74.88, 64.20, 44.89, 39.17, 36.12, 29.07, 26.79 (x3), 24.73, 22.38, 19.16, 17.81, 15.30.



256' **257**

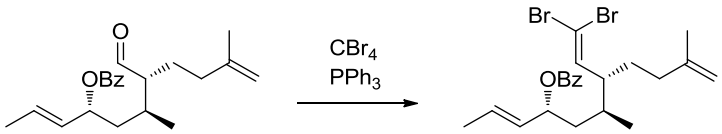
Primary alcohol 257. To a solution of bis-protected alcohol **256'** (1.0 equiv, 1.5 g, 2.8 mmol) in THF (67 mL) at 23 °C was added a 1.0 M solution of TBAF in THF (2.0 equiv, 5.5 mL, 5.5 mmol). The resulting mixture was stirred 12 h at 23 °C. The reaction was quenched with a sat. NH_4Cl aq. solution, extracted with EtOAc, water and brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 5/1) yielded the primary alcohol **257** in quantitative yield (876 mg). *Rf* = 0.30 (Petroleum ether/EtOAc 4/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.04 (d, *J* = 8.0 Hz, 2H), 7.56-7.52 (m, 1H), 7.45-7.41 (m, 2H), 5.84 (dq, *J* = 6.4, 13.2 Hz, 1H), 5.56-5.48 (m, 2H), 4.72 (s, 1H), 4.69 (s, 1H), 3.62 (dd, *J* = 10.8, 5.2 Hz, 1H), 3.53 (dd, *J* = 10.8, 7.2 Hz, 1H), 2.12-1.97 (m, 2H), 1.90-1.83 (m, 1H), 1.72 (s, 3H), 1.72-1.66 (m, 5H), 1.58-1.52 (m, 1H), 1.50-1.41 (m, 1H), 1.36-1.23 (m, 1H), 0.92 (d, *J* = 7.2 Hz, 3H), OH signal is not visible; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 166.10, 145.85, 132.77, 130.67, 129.85, 129.55 (x2), 129.51, 128.26 (x2), 110.07, 74.49, 63.61, 44.46, 39.03, 36.16, 29.00, 24.85, 22.38, 17.77, 15.75.



257 **257'**

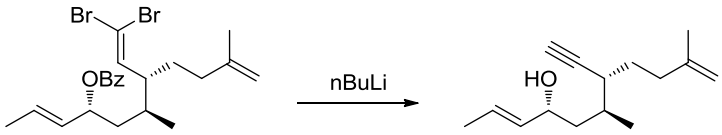
Aldehyde 257'. To a solution of primary alcohol **257** (1.0 equiv, 876 mg, 2.8 mmol) in CH_2Cl_2 (99 mL) at 0 °C was added DMP (1.2 equiv, 1.4 g, 3.3 mmol). The reaction was allowed to warm at 23 °C for 12 h. The resulting mixture was then diluted with hexane, and filtered on a pad of Celite and silica. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 5/1) yielded the aldehyde **257'** in 75% yield (653 mg). *Rf* = 0.55 (Petroleum ether/EtOAc 4/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 9.64-9.63 (m, 1H), 8.04 (d, *J* =

8.0 Hz, 2H), 7.58-7.54 (m, 1H), 7.46-7.42 (m, 2H), 5.91-5.83 (m, 1H), 5.54-5.46 (m, 2H), 4.74 (s, 1H), 4.67 (s, 1H), 2.32-2.29 (m, 1H), 2.10-2.03 (m, 2H), 1.98-1.80 (m, 2H), 1.77-1.72 (m, 4H), 1.71 (s, 3H), 1.54-1.46 (m, 2H), 0.97 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 204.65, 165.81, 144.94, 132.89, 130.53, 130.01, 129.55 (x2), 129.05, 128.34 (x2), 110.75, 74.02, 55.77, 39.04, 35.78, 29.22, 22.33, 22.30, 17.80, 16.50.



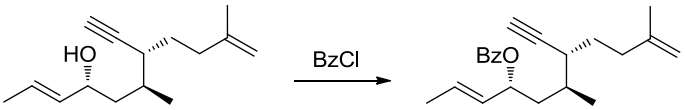
257' **258**

Dibromoalkene 258. To a stirred solution of CBr_4 (4.0 equiv, 2.7 g, 8.3 mmol) in CH_2Cl_2 (29 mL) at 0 °C was added PPh_3 (8.0 equiv, 4.4 g, 16.6 mmol). After 5 min at this temperature, a solution of aldehyde **257'** (1.0 equiv, 653 mg, 2.1 mmol) in CH_2Cl_2 (2 mL) was added. After 45 min at 0 °C, the reaction mixture was diluted with Petroleum ether and filtered on a pad of silica. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 50/1) yielded dibromoalkene **258** in 99% yield (968 mg). *Rf* = 0.68 (Petroleum ether/EtOAc 6/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.04 (d, *J* = 7.6 Hz, 2H), 7.57-7.53 (m, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 6.22 (d, *J* = 10.0 Hz, 1H), 5.90-5.82 (m, 1H), 5.50-5.44 (m, 2H), 4.73 (s, 1H), 4.68 (s, 1H), 2.39-2.32 (m, 1H), 2.01-1.93 (m, 2H), 1.79-1.66 (m, 5H), 1.72 (s, 3H), 1.64-1.57 (m, 2H), 1.48-1.38 (m, 1H), 0.99 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 165.80, 145.32, 141.31, 132.78, 130.73, 130.50, 129.55, 129.21, 128.29, 110.17, 89.20, 74.57, 48.41, 38.02, 35.33, 33.07, 28.53, 22.55, 17.82, 17.31.



258 **243**

Alkyne 243. To a solution of dibromoalkene **258** (1.0 equiv, 968 mg, 2.1 mmol) in THF (4 mL) cooled at -78 °C was added dropwise a 1.17 M solution of *n*-butyllithium in hexane (2.0 equiv, 3.5 mL, 4.1 mmol). The mixture was stirred for 1 h at -78 °C and for 1.5 h at 23 °C. The reaction was quenched with a sat. NH_4Cl aq. solution, extracted with EtOAc, water and brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 10/1) yielded alkene **243** in 50% yield (212 mg). *Rf* = 0.68 (Petroleum ether/EtOAc 4/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 5.67 (dq, *J* = 6.4, 15.2 Hz, 1H), 5.46-5.39 (m, 1H), 4.72 (s, 1H), 4.70 (s, 1H), 4.14-4.08 (m, 1H), 2.31-2.22 (m, 2H), 2.11-2.03 (m, 1H), 2.06 (d, *J* = 4.4 Hz, 1H), 1.72 (s, 3H), 1.70 (d, *J* = 6.4 Hz, 3H), 1.67-1.50 (m, 5H), 1.00 (d, *J* = 6.4 Hz, 3H), OH signal is not visible; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 145.27, 134.02, 127.65, 110.21, 86.21, 71.94, 70.38, 40.32, 37.32, 35.65, 33.13, 29.49, 22.44, 17.94, 17.66.

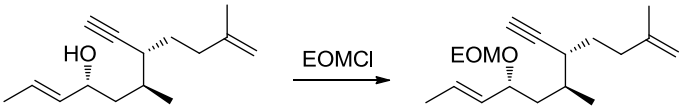


243 **263**

Bz-protected alcohol 263. To a solution of alkyne **243** (1.0 equiv, 212 mg, 1.0 mmol) in CH_2Cl_2 (13 mL) at 23 °C were added sequentially pyridine (4.0 equiv, 333 μL, 4.1 mmol) and BzCl (4.0 equiv, 478 μL, 4.1 mmol). The resulting mixture was stirred 12 h at 23 °C. The reaction was then quenched with a sat. NH_4Cl aq. solution, extracted with EtOAc, water and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 10/1) yielded the Bz-protected alcohol **263** in quantitative yield (320 mg). *Rf* = 0.64 (Petroleum ether/EtOAc 4/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.06-8.03 (m, 2H), 7.57-7.52 (m, 1H), 7.45-7.41 (m, 2H), 5.91-5.82 (m, 1H), 5.53-5.45 (m, 2H), 4.73 (s, 1H), 4.70 (s, 1H), 2.33-2.21 (m, 2H), 2.12-2.05 (m, 1H), 2.07 (d, *J* = 2.4 Hz, 1H), 1.92-1.87 (m, 1H), 1.83-1.54 (m, 7H), 1.73 (s, 3H), 1.07 (d, *J* = 6.0 Hz, 3H).

243 **264**

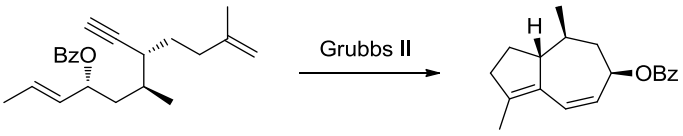
TBDPS-protected alcohol 264. To a solution of alkyne **243** (1.0 equiv, 212 mg, 1.0 mmol) in CH_2Cl_2 (13 mL) at 23 °C were added sequentially imidazole (5.0 equiv, 352 mg, 5.1 mmol) and TBDPSCl (5.0 equiv, 1.4 mL, 5.1 mmol). The resulting mixture was stirred 2 h at 23 °C. The reaction was then quenched with a sat. NH_4Cl aq. solution, extracted with EtOAc, water and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 10/1) yielded the TBDPS-protected alcohol **264** in quantitative yield (472 mg). *Rf* = 0.72 (Petroleum ether/EtOAc 4/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.69-7.65 (m, 4H), 7.43-7.33 (m, 6H), 5.34 (dd, *J* = 16.0, 8.0 Hz, 1H), 5.24-5.15 (m, 1H), 4.71 (s, 1H), 4.67 (s, 1H), 4.08-4.03 (m, 1H), 2.22-2.13 (m, 2H), 2.04-1.96 (m, 1H), 2.01 (d, *J* = 2.4 Hz, 1H), 1.70 (s, 3H), 1.64 (dd, *J* = 20.4, 10.4 Hz, 1H), 1.54 (d, *J* = 6.8 Hz, 3H), 1.56-1.40 (m, 4H), 1.06 (s, 9H), 0.71 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 145.40, 136.06 (x2), 135.95 (x2), 134.55, 134.52, 133.72, 129.44, 129.30, 127.40 (x2), 127.22 (x2), 126.64, 110.11, 86.36, 73.52, 70.08, 41.08, 37.39, 35.70, 32.43, 29.30, 27.07 (x3), 22.47, 19.24, 17.52, 17.47.



243 **265**

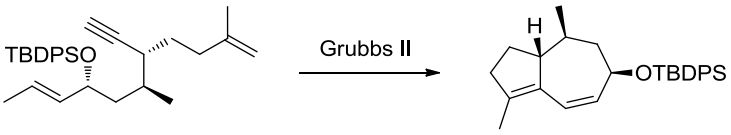
EOM-protected alcohol 265. To a solution of alkyne **243** (1.0 equiv, 212 mg, 1.0 mmol) in CH_2Cl_2 (13 mL) at 23 °C were added sequentially *i*Pr_2NEt (3.0 equiv, 497 μL, 3.1 mmol), EOMCl (3.0 equiv, 291

μL, 3.1 mmol), and TBAI (cat). The resulting mixture was stirred 12 h at 23 °C. The reaction was then quenched with a sat. NH_4Cl aq. solution, extracted with EtOAc, water and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 10/1) yielded the EOM-protected alcohol **265** in 97% yield (278 mg). *Rf* = 0.75 (Petroleum ether/EtOAc 4/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 5.66 (dq, *J* = 6.4, 15.2 Hz, 1H), 5.25-5.19 (m, 1H), 4.73-4.69 (m, 3H), 4.58 (d, *J* = 7.2 Hz, 1H), 4.05-4.00 (m, 1H), 3.70 (dq, *J* = 7.2, 9.6 Hz, 1H), 3.50 (dq, *J* = 7.2, 9.6 Hz, 1H), 2.33-2.28 (m, 1H), 2.26-2.20 (m, 1H), 2.11-2.03 (m, 2H), 1.72 (bs, 3H), 1.72-1.70 (m, 3H), 1.68-1.60 (m, 2H), 1.58-1.51 (m, 3H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H).



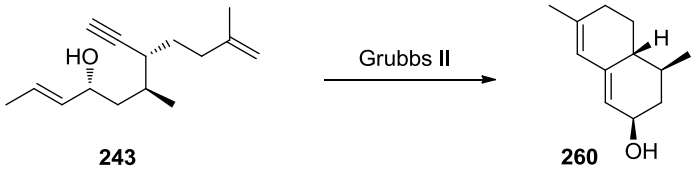
263 **266**

Hydroazulene 266. To a solution of alkene **263** (1.0 equiv, 320 mg, 1.0 mmol) in toluene (343 mL) at 100 °C was added Grubbs II catalyst (7.5 mol%, 65 mg, 75 μmol). The mixture was stirred 1 h at 100 °C. The reaction was then quenched by addition of DMSO (275 μL), and stirred for another 12 h. Evaporation of the solvents under reduced pressure followed by a simple filtration afforded hydroazulene **266** as a cude. *Rf* = 0.62 (Petroleum ether/EtOAc 4/1).



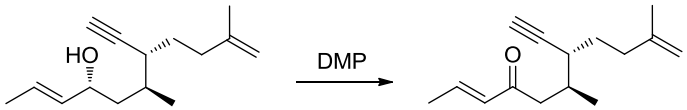
264 **267**

Hydroazulene 267. To a solution of alkene **264** (1.0 equiv, 472 mg, 1.0 mmol) in toluene (343 mL) at 100 °C was added Grubbs II catalyst (10 mol%, 88 mg, 100 μmol). The mixture was stirred 2 h at 100 °C. Four new portions of Grubbs II catalyst (5 mol%, 44 mg, 50 μmol) were added each 2 h. The reaction was then quenched by addition of DMSO (1.5 mL), and stirred for another 12 h. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 50/1) yielded hydroazulene **267** in 91% yield (390 mg). *Rf* = 0.73 (Petroleum ether/EtOAc 6/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.78-7.76 (m, 4H), 7.48-7.41 (m, 6H), 6.18 (d, *J* = 12.4 Hz, 1H), 5.79 (d, *J* = 12.4 Hz, 1H), 4.36 (d, *J* = 9.6 Hz, 1H), 2.31-2.16 (m, 3H), 2.08-2.01 (m, 1H), 1.80-1.73 (m, 1H), 1.77 (s, 3H), 1.65 (m, 1H), 1.29-1.07 (m, 2H), 1.17 (s, 9H), 0.86 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 140.56, 135.89 (x2), 135.86 (x2), 135.34, 134.51, 134.34, 134.27, 129.44 (x2), 127.39 (x4), 120.98, 73.41, 55.32, 46.10, 36.51, 35.63, 30.25, 27.04 (x3), 22.04, 19.18, 14.70.



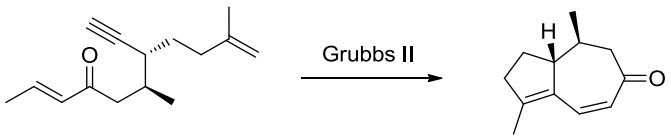
243 **260**

6/6-membered ring 260. To a solution of alkene **243** (1.0 equiv, 212 mg, 1.0 mmol) in toluene (343 mL) at 100 °C was added Grubbs II catalyst (7.5 mol%, 65 mg, 75 µmol). The mixture was stirred 2 h at 100 °C. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 4/1) afforded 6/6-membered ring **260** in 80% yield (147 mg). *Rf* = 0.26 (Petroleum ether/EtOAc 4/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.03 (s, 1H), 5.34 (s, 1H), 4.40-4.33 (m, 1H), 2.48-2.00 (m, 5H), 1.76 (s, 3H), 1.46-1.21 (m, 3H), 1.03 (d, *J* = 6.4 Hz, 3H), OH signal is not visible.



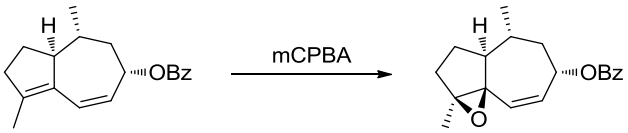
243 **268**

α,β-unsaturated ketone 268. To a solution of secondary alcohol **243** (1.0 equiv, 212 mg, 1.0 mmol) in CH_2Cl_2 (21 mL) at 0 °C was added DMP (1.2 equiv, 529 mg, 1.2 mmol). The reaction was allowed to warm at 23 °C for 12 h. The resulting mixture was then diluted with hexane, and filtered on a pad of Celite and silica. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 5/1) yielded the α,β-unsaturated ketone **268** in 95% yield (200 mg). ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.87 (dq, *J* = 6.8, 15.6 Hz, 1H), 6.14 (dd, *J* = 15.6, 1.6 Hz, 1H), 4.73 (s, 1H), 4.70 (s, 1H), 2.75 (dd, *J* = 15.6, 3.6 Hz, 1H), 2.47 (dd, *J* = 16.0, 9.6 Hz, 1H), 2.33-2.17 (mx2, 3H), 2.14-2.06 (m, 2H), 1.90 (dd, *J* = 6.8, 1.6 Hz, 3H), 1.72 (s, 3H), 1.64-1.50 (m, 2H), 0.99 (d, *J* = 6.8 Hz, 3H).



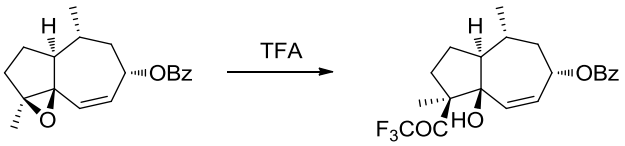
268 **269**

Hydroazulenone 269. To a solution of α,β-unsaturated ketone **268** (1.0 equiv, 200 mg, 1.0 mmol) in toluene (321 mL) at 100 °C was added Grubbs II catalyst (7.5 mol%, 64 mg, 75 µmol). The mixture was stirred 2 h at 100 °C, and was then quenched by addition of DMSO (271 µL), and stirred for another 12 h. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 20/1) yielded hydroazulenone **269** in 23% yield (42 mg). *Rf* = 0.37 (Petroleum ether/EtOAc 6/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.94 (d, *J* = 12.4 Hz, 1H), 5.80 (d, *J* = 12.4 Hz, 1H), 2.71-2.51 (m, 3H), 2.34 (d, *J* = 8.8 Hz, 2H), 2.18-2.09 (m, 2H), 1.91 (s, 3H), 1.88-1.80 (m, 1H), 1.00 (dd, *J* = 6.8, 1.6 Hz, 3H).



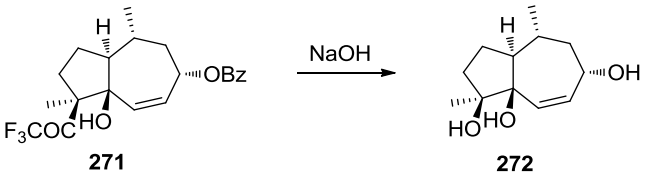
266 **270**

Epoxide 270. To a solution of bicyclic compound **266** (1.0 equiv, 291 mg, 1.0 mmol) in CH_2Cl_2 (17 mL) at 0 °C was added mCPBA (1.0 equiv, 236 mg, 1.0 mmol). The mixture was stirred 1 h at 0 °C. The reaction was quenched with a sat. $NaHCO_3$ aq. solution, extracted with EtOAc, water and brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 5/1) yielded epoxide **270** in 18% yield for 2 steps (55 mg). *Rf* = 0.52 (Petroleum ether/EtOAc 4/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.06 (d, *J* = 8.0 Hz, 2H), 7.58-7.54 (m, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 6.23-6.20 (m, 1H), 5.89-5.84 (m, 1H), 5.62 (dd, *J* = 12.0, 2.4 Hz, 1H), 2.07-1.98 (m, 2H), 1.92 (dd, *J* = 13.2, 8.0 Hz, 1H), 1.81-1.65 (m, 3H), 1.62-1.51 (m, 1H), 1.39 (s, 3H), 1.17-1.07 (m, 1H), 1.00 (d, *J* = 6.4 Hz, 3H).



270 **271**

Tertiary alcohol 271. To a solution of epoxide **270** (1.0 equiv, 55 mg, 180 µmol) in CH_2Cl_2 (9 mL) at 23 °C was added trifluoroacetic acid (1.0 equiv, 13 µL, 180 µmol). The mixture was stirred 1 h at 23 °C. The reaction was then quenched with a sat. $NaHCO_3$ aq. solution, extracted with EtOAc, water and brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 20/1) yielded tertiary alcohol **271** as a crude. *Rf* = 0.31 (Petroleum ether/EtOAc 4/1).

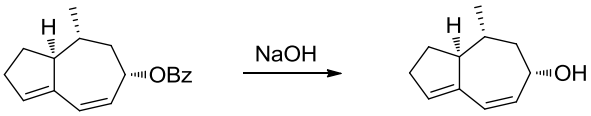


271 **272**

crystal structure

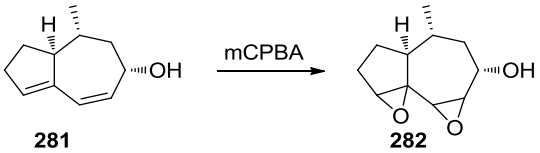
Triol 272. To alcohol **271** (1.0 equiv, 71 mg, 180 µmol) at 23 °C was added a 1% solution of NaOH in MeOH (4.9 mL). The mixture was stirred 6 h at 23 °C. The reaction was then quenched with a sat. NH_4Cl aq. solution, extracted with EtOAc, water and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 50/1) afforded triol **272** in 60% yield for 2 steps (23 mg). *Rf* = 0.11 (Petroleum ether/EtOAc 1/2); ^{1}H-NMR (Acetone-d6, 400 MHz, 25 °C) δ 5.87 (dd, *J* = 12.0, 1.2 Hz, 1H), 5.78 (dd, *J* = 12.0, 2.4 Hz, 1H), 4.69-4.65 (m, 1H), 3.70 (d, *J* = 4.8 Hz, 1H), 3.63 (s, 1H), 3.23 (s, 1H), 2.14-2.07 (m, 1H), 1.84-1.76 (m, 2H), 1.71-1.63 (m, 1H), 1.55-1.47 (m, 2H), 1.45-1.41 (m, 1H), 1.36 (q, *J* = 11.6 Hz,

1H), 1.18 (s, 3H), 0.88 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, Acetone-d6, 25 °C) δ 143.79, 129.33, 81.75, 80.86, 69.95, 50.22, 48.07, 36.94, 33.71, 26.13, 25.11, 21.78.



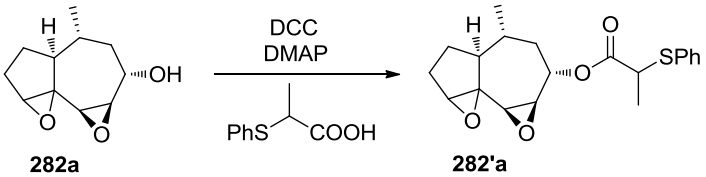
280 **281**

Secondary alcohol 281. To Bz-protected alcohol **280** (1.0 equiv, 276 mg, 1.0 mmol) at 23 °C was added a 1% solution of NaOH in MeOH (24.4 mL). The mixture was stirred 12 h at 23 °C. The reaction was then quenched with a sat. NH_4Cl aq. solution, extracted with EtOAc, water and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 1/1) yielded secondary alcohol **281** in 52% yield (88 mg). *Rf* = 0.32 (Petroleum ether/EtOAc 4/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.17 (d, *J* = 12.0 Hz, 1H), 5.77 (bs, 1H), 5.58 (d, *J* = 12.0 Hz, 1H), 4.26 (d, *J* = 10.8 Hz, 1H), 2.29-2.20 (m, 3H), 2.19-2.13 (m, 1H), 1.96-1.92 (mx2, 1H), 1.55 (dt, *J* = 10.8, 12.8 Hz, 1H), 1.45-1.32 (m, 2H), 1.01 (d, *J* = 6.8 Hz, 3H), OH signal is not visible.



281 **282**

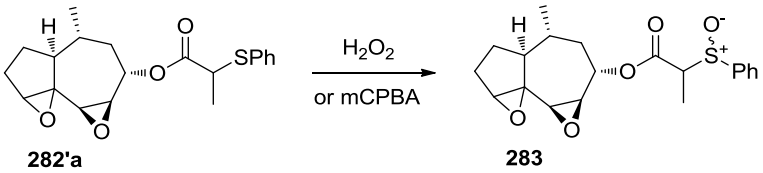
Bis-epoxide 282. To a solution of secondary alcohol **281** (1.0 equiv, 88 mg, 540 µmol) in CH_2Cl_2 (9 mL) at 0 °C was added mCPBA (3.0 equiv, 372 mg, 1.6 mmol). The mixture was stirred 1 h at 0 °C. The reaction was quenched with a sat. $NaHCO_3$ aq. solution, extracted with EtOAc, water and brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 1/1) yielded bis-epoxide **282** in 69% yield (73 mg). *Rf* = 0.24 (Petroleum ether/EtOAc 1/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 4.23-4.20 (m, 1H), 3.42 (s, 1H), 3.36 (d, *J* = 4.4 Hz, 1H), 2.88 (d, *J* = 4.4 Hz, 1H), 1.97-1.92 (m, 1H), 1.77-1.59 (m, 5H), 1.38-1.30 (m, 1H), 1.09-1.04 (m, 1H), 0.90 (d, *J* = 6.8 Hz, 3H), OH signal is not visible.



282a **282'a**

Esterified compound 282'a. To a solution of secondary alcohol **282a** (1.0 equiv, 73 mg, 370 µmol) in CH_2Cl_2 (10 mL) at 23 °C were added sequentially DMAP (0.1 equiv, 4.5 mg, 37 µmol) and DCC (1.1 equiv, 85 mg, 407 µmol). After 5 min, 2-(phenylsulfanyl)propanoic acid (1.1 equiv, 74 mg, 407 µmol) was added. The mixture was stirred 12 h at 23 °C. The reaction was filtered on Celite, which was

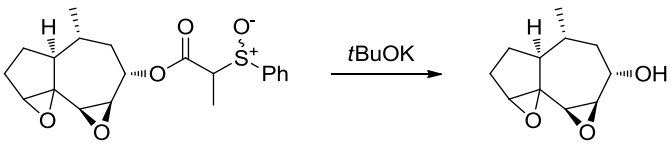
washed with EtOAc. The organic phase was then washed with a sat. $NaHCO_3$ aq. solution and brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 10/1) yielded esterified compound **282'a** in 94% yield (125 mg). *Rf* = 0.68 (Petroleum ether/EtOAc 1/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.49-7.47 (m, 2H), 7.33-7.27 (m, 3H), 5.26 (dt, *J* = 2.8, 11.6 Hz, 1H), 3.85 (q, *J* = 7.2 Hz, 0.4H), 3.84 (q, *J* = 7.2 Hz, 0.6H), 3.41 (s, 1H), 3.17 (d, *J* = 4.4 Hz, 0.4H), 2.97 (d, *J* = 4.8 Hz, 0.6H), 2.85 (d, *J* = 4.4 Hz, 0.4H), 2.82 (d, *J* = 4.8 Hz, 0.6H), 1.97-1.92 (m, 1H), 1.73-1.45 (m, 5H), 1.51 (d, *J* = 7.2 Hz, 3H), 1.38-1.03 (m, 2H), 0.94-0.83 (m, 3H).



282'a **283**

Sulfoxide 283. To a solution of esterified compound **282'a** (1.0 equiv, 125 mg, 340 µmol) in HFIP (1.7 mL) at 23 °C was added a 35% solution of H_2O_2 in water (2.0 equiv, 58 µL, 680 µmol). The mixture was stirred 1 h at 23 °C. The reaction was extracted with EtOAc and a 10/1 mixture of sat. $NaHCO_3$ aq. solution/sodium thiosulfate, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 1/3) yielded sulfoxide **283** in 94% yield (120 mg).

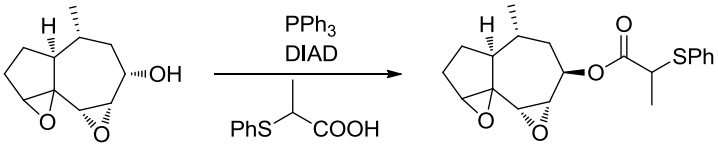
Sulfoxide 283. To a solution of esterified compound **282'a** (1.0 equiv, 125 mg, 340 µmol) in CH_2Cl_2 (6 mL) at 0 °C was added mCPBA (1.1 equiv, 85 mg, 374 µmol). The mixture was stirred 15 min at 0 °C. The reaction was quenched with potassium fluoride, stirred for another 30 min and filtered through Celite, which was washed with Et_2O. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 1/3) yielded sulfoxide **283** in 90% yield (115 mg). *Rf* = 0.19 (Petroleum ether/EtOAc 2/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.68-7.63 (m, 2H), 7.53-7.52 (m, 3H), 5.30-5.23 (m, 1H), 3.82 (q, *J* = 7.2 Hz, 0.2H), 3.80 (q, *J* = 7.2 Hz, 0.2H), 3.55 (q, *J* = 7.2 Hz, 0.3H), 3.55 (q, *J* = 7.2 Hz, 0.3H), 3.41 (s, 1H), 3.17 (d, *J* = 4.4 Hz, 0.3H), 3.13 (d, *J* = 4.4 Hz, 0.2H), 3.05 (d, *J* = 4.4 Hz, 0.2H), 2.88-2.81 (m, 1.3H), 1.98-1.92 (m, 1H), 1.73-1.13 (m, 6H), 1.53 (d, *J* = 7.2 Hz, 0.9H), 1.52 (d, *J* = 7.2 Hz, 0.9H), 1.39 (d, *J* = 7.2 Hz, 0.6H), 1.38 (d, *J* = 7.2 Hz, 0.6H), 1.09-1.03 (m, 1H), 0.94-0.84 (m, 3H).



283 **282a**

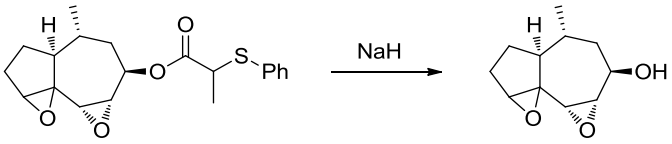
Secondary alcohol 282a. To a suspension of *t*BuOK (1.0 equiv, 36 mg, 320 µmol) in DMSO (30 mL) at 23 °C was added a solution of sulfoxide **283** (1.0 equiv, 120 mg, 320 µmol) in DMSO (15 mL). The reaction was stirred 12 h at 23 °C and another portion of *t*BuOK (1.0 equiv, 36 mg, 320 µmol) was added. The reaction was stirred for another 12 h at 23 °C. The reaction was then quenched with a

sat. NH_4Cl aq. solution, extracted with EtOAc, water and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 1/2) yielded secondary alcohol **282a** in 50% yield (31 mg). *Rf* = 0.43 (Petroleum ether/EtOAc 1/2); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 4.23-4.20 (m, 1H), 3.42 (s, 1H), 3.36 (d, *J* = 4.4 Hz, 1H), 2.88 (d, *J* = 4.4 Hz, 1H), 1.97-1.92 (m, 1H), 1.77-1.59 (m, 5H), 1.38-1.30 (m, 1H), 1.09-1.04 (m, 1H), 0.90 (d, *J* = 6.8 Hz, 3H), OH signal is not visible.



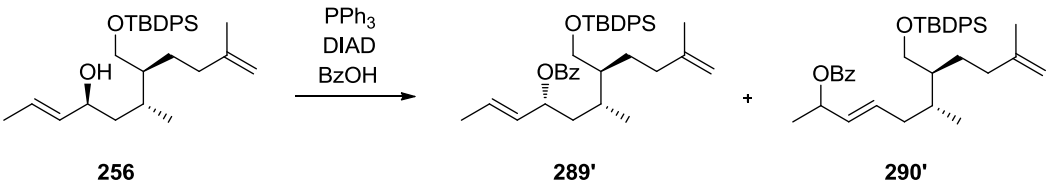
282b **284**

Esterified compound 284. To a solution of secondary alcohol **282b** (1.0 equiv, 73 mg, 370 µmol) in CH_2Cl_2 (37 mL) at 23 °C were added PPh_3 (20.0 equiv, 1.9 g, 7.4 mmol) and 2-(phenylsulfanyl)propanoic acid (1.0 equiv, 68 mg, 370 µmol). The reaction was cooled at 0 °C and DIAD (20.0 equiv, 1.5 mL, 7.4 mmol) was added. The mixture was stirred 1 h at 23 °C. The solvent was then evaporated under reduced pressure, followed by flash chromatography (SiO2, Petroleum ether to Petroleum ether/EtOAc 10/1) to afford the corresponding ester **284** in 76% yield (101 mg). *Rf* = 0.64 (Petroleum ether/EtOAc 1/1); 7.49-7.45 (m, 2H), 7.32-7.26 (m, 3H), 5.56 (t, *J* = 5.6 Hz, 1H), 3.95-3.89 (m, 1H), 3.41 (s, 1H), 3.29 (t, *J* = 4.6 Hz, 0.5H), 3.12 (t, *J* = 4.6 Hz, 0.5H), 2.85 (d, *J* = 4.0 Hz, 0.5H), 2.80 (d, *J* = 4.0 Hz, 0.5H), 2.05-1.95 (m, 1H), 1.87-1.01 (m, 7H), 1.55 (d, *J* = 7.2 Hz, 1.5H), 1.53 (d, *J* = 7.2 Hz, 1.5H), 0.82 (d, *J* = 5.6 Hz, 1.5H), 0.76 (d, *J* = 6.8 Hz, 1.5H).

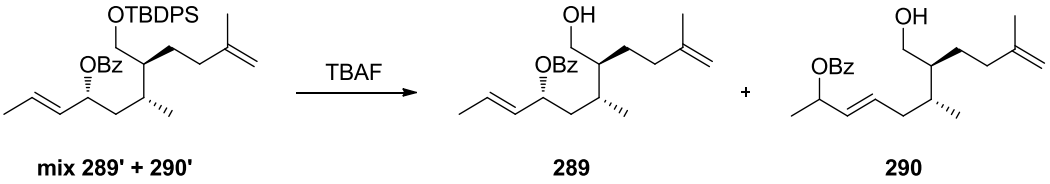


284 **285**

Secondary alcohol 285. To a suspension of NaH 60% in oil (1.0 equiv, 6.7 mg, 280 µmol) in DMF (20 mL) at -40 °C was added dropwise a solution of bis-epoxide **284** (1.0 equiv, 101 mg, 280 µmol) in DMF (10 mL). The reaction was stirred 3 h at -40 °C. The reaction was quenched with a sat. NH_4Cl aq. solution, extracted with Et_2O, washed with a sat. $NaHCO_3$ aq. solution and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 1/2) yielded secondary alcohol **285** in 60% yield (33 mg). *Rf* = 0.25 (Petroleum ether/EtOAc 1/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 4.57-4.55 (m, 1H), 3.51 (s, 1H), 3.32 (t, *J* = 4.4 Hz, 1H), 2.92 (d, *J* = 4.4 Hz, 1H), 2.04-1.99 (m, 1H), 1.83-1.20 (m, 6H), 1.14-1.10 (m, 1H), 0.91-0.86 (m, 3H), OH signal is not visible.



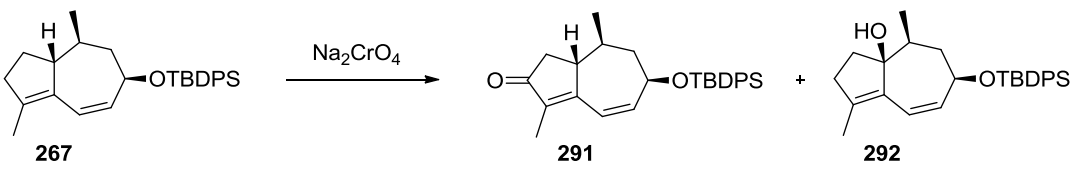
Esterified compound 289'. To a solution of secondary alcohol **256** (1.0 equiv, 1.3 g, 2.9 mmol) in CH_2Cl_2 (66 mL) at 23 °C were added PPh_3 (2.0 equiv, 1.5 g, 5.7 mmol) and para-nitrobenzoic acid (1.0 equiv, 352 mg, 2.9 mmol). The reaction was cooled at 0 °C and DIAD (2.0 equiv, 1.2 mL, 5.7 mmol) was added. The mixture was stirred 6 h at 23 °C. The solvent was then evaporated under reduced pressure, followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 50/1) yielded esterified compounds **289'** and **290'** as an inseparable mixture in 68% yield (1.1 g). *Rf* = 0.68 (Petroleum ether/EtOAc 4/1).



Primary alcohol 289. To a solution of mixture **289' + 290'** (1.0 equiv, 1.1 g, 1.9 mmol) in THF (47 mL) at 23 °C was added a 1.0 M solution of TBAF in THF (2.0 equiv, 3.9 mL, 3.9 mmol). The resulting mixture was stirred 12 h at 23 °C. The reaction was quenched with a sat. NH_4Cl aq. solution, extracted with EtOAc, water and brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 5/1) yielded the primary alcohols **289** and **290** in 90% yield (577 mg).

289: *Rf* = 0.49 (CH_2Cl_2/Acetone 20/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.04 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 5.82 (dq, *J* = 6.8, 14.0 Hz, 1H), 5.57-5.50 (m, 2H), 4.71 (bs, 1H), 4.68 (bs, 1H), 3.61 (t, *J* = 4.8 Hz, 2H), 2.08-1.99 (m, 2H), 1.93-1.86 (m, 2H), 1.71 (s, 3H), 1.72-1.69 (m, 3H), 1.49-1.15 (mx2, 4H), 0.94 (d, *J* = 6.8 Hz, 3H), OH signal is not visible.

290: *Rf* = 0.42 (CH_2Cl_2/Acetone 20/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.04 (d, *J* = 8.0 Hz, 2H), 7.56-7.53 (m, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 5.80-5.71 (m, 1H), 5.61-5.52 (m, 2H), 4.67 (bs, 1H), 4.64 (bs, 1H), 3.66-3.50 (mx2, 2H), 2.15-2.07 (m, 1H), 2.05-1.90 (m, 3H), 1.86-1.81 (m, 1H), 1.68 (s, 3H), 1.50-1.42 (m, 5H), 1.36-1.22 (m, 1H), 0.85 (d, *J* = 7.2 Hz, 3H), OH signal is not visible.

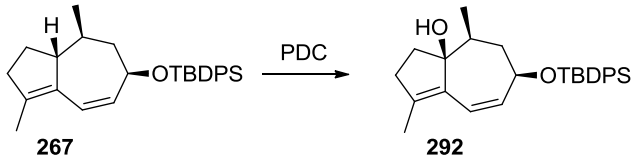


Hydoazulenone 291. To a solution of hydroazulene **267** (1.0 equiv, 390 mg, 940 µmol) in benzene (20 mL) at 23 °C were added sequentially AcOH (1.8 mL), Ac_2O (2.6 mL), NaOAc (648.9 mg) and Na_2CrO_4 (5.7 equiv, 886.4 mg, 5.4 mmol). The resulting mixture was stirred for 12 h at 70 °C. After

evaporation of the solvent under reduced pressure, the mixture was diluted with a sat. $Na_2S_2O_3$ aq. solution, extracted with EtOAc, water and brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 1/1) yielded the hydroazulenones **291** and **292** in 19% yield each (77 mg and 77 mg).

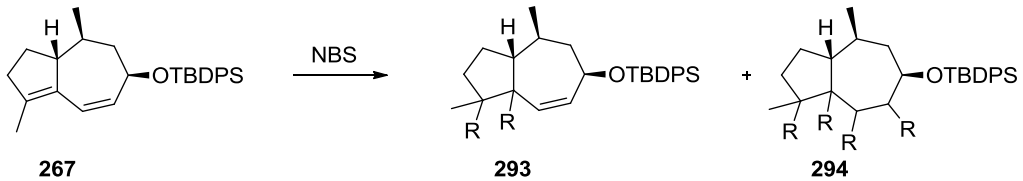
291: *Rf* = 0.39 (Petroleum ether/EtOAc 4/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.69-7.65 (m, 4H), 7.46-7.37 (m, 6H), 6.30 (d, *J* = 12.0 Hz, 1H), 6.19 (d, *J* = 12.0 Hz, 1H), 4.39-4.34 (m, 1H), 2.55 (dd, *J* = 18.0, 6.4 Hz, 1H), 2.50-2.42 (m, 1H), 2.01 (dd, *J* = 18.0, 3.6 Hz, 1H), 1.79-1.75 (m, 2H), 1.67 (bs, 3H), 1.40-1.22 (m, 1H), 1.09 (m, 9H), 0.89 (d, *J* = 6.4 Hz, 3H).

292: *Rf* = 0.35 (Petroleum ether/EtOAc 4/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.74-7.62 (m, 4H), 7.47-7.38 (m, 6H), 6.24 (dd, *J* = 12.8, 2.0 Hz, 1H), 5.75 (dd, *J* = 12.8, 2.0 Hz, 1H), 4.24-4.32 (m, 1H), 2.36-2.27 (m, 2H), 2.18-2.12 (m, 1H), 2.07 (s, 3H), 1.82-1.63 (m, 2H), 1.54-1.21 (m, 2H), 1.06 (s, 9H), 0.93 (d, *J* = 6.8 Hz, 3H), OH signal is not visible.



267 **292**

Tertiary alcohol 292. To a solution of hydroazulene **267** (1.0 equiv, 390 mg, 940 µmol) in $CHCl_3$ (98 mL) at 23 °C was added PDC (30.0 equiv, 10.6 g, 28.2 mmol). The mixture was stirred 12 h at 70 °C, and was then filtered through a short pad of Celite and SiO_2. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 4/1) yielded the tertiary alcohol **292** in 70% yield (285 mg). *Rf* = 0.35 (Petroleum ether/EtOAc 4/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.74-7.62 (m, 4H), 7.47-7.38 (m, 6H), 6.24 (dd, *J* = 12.8, 2.0 Hz, 1H), 5.75 (dd, *J* = 12.8, 2.0 Hz, 1H), 4.24-4.32 (m, 1H), 2.36-2.27 (m, 2H), 2.18-2.12 (m, 1H), 2.07 (s, 3H), 1.82-1.63 (m, 2H), 1.54-1.21 (m, 2H), 1.06 (s, 9H), 0.93 (d, *J* = 6.8 Hz, 3H), OH signal is not visible.

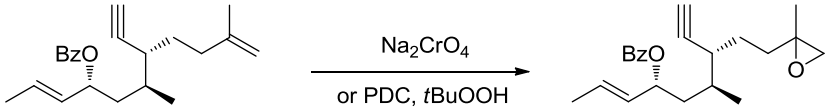


267 **293** **294**

Compounds 293 and 294. To a solution of hydroazulene **267** (1.0 equiv, 390 mg, 940 µmol) in a 4/1 mixture of THF/H_2O (14 mL) cooled at 0 °C in the dark, was added NBS (1.9 equiv, 319 mg, 1.8 mmol). The mixture was stirred 1 h at 0 °C and was then quenched with a sat. $NaHCO_3$ aq. solution, extracted with Et_2O, water and brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, toluene) yielded compounds **293** and **294** in 13% and 37% yield (63 mg and 212 mg).

293: *Rf* = 0.41 (Toluene); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.72-7.62 (m, 4H), 7.44-7.26 (m, 6H), 6.29 (dd, *J* = 12.0, 1.6 Hz, 1H), 5.40 (dd, *J* = 12.0, 2.4 Hz, 1H), 4.62-4.56 (m, 1H), 1.84-1.78 (m, 1H), 1.68-1.61 (m, 2H), 1.60-1.52 (m, 1H), 1.50-1.39 (m, 3H), 1.32 (s, 3H), 1.07 (m, 9H), 0.96-0.81 (m, 1H), 0.73 (d, *J* = 6.8 Hz, 3H), 2 OH signals are not visible; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 147.84, 135.83 (x4), 129.61 (x2), 127.61 (x2), 127.56 (x2), 121.06, 72.72, 68.83, 66.99, 48.84, 46.36, 33.78, 29.69, 27.02 (x2), 25.69, 21.54, 19.15, 16.01.

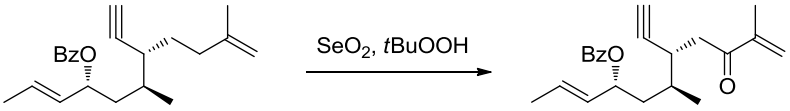
294: *Rf* = 0.49 (Toluene); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.73-7.68 (m, 4H), 7.46-7.37 (m, 6H), 4.54-4.50 (m, 1H), 4.48-4.46 (m, 1H), 4.07 (d, *J* = 6.4 Hz, 1H), 2.13-2.02 (m, 2H), 1.82-1.70 (m, 4H), 1.67-1.52 (m, 2H), 1.34 (s, 3H), 1.09 (s, 9H), 0.77 (d, *J* = 6.8 Hz, 3H), 2 OH signals are not visible; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 135.89 (x2), 135.86 (x2), 133.86, 133.52, 129.91, 129.78, 127.78 (x2), 127.67 (x2), 74.14, 73.05, 70.97, 60.02, 52.25, 51.80, 44.18, 32.69, 32.01, 30.66, 26.93 (x3), 22.29, 19.27, 17.68.



263 **295**

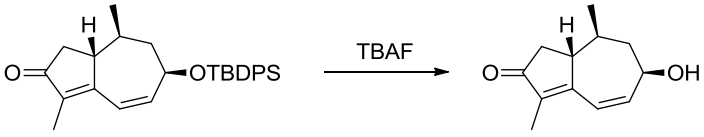
Epoxide 295. To a solution of alkyne **263** (1.0 equiv, 320 mg, 1.0 mmol) in benzene (22 mL) at 23 °C were added sequentially AcOH (1.9 mL), Ac_2O (2.9 mL), NaOAc (711 mg) and Na_2CrO_4 (5.7 equiv, 998 mg, 5.9 mmol). The resulting mixture was stirred for 12 h at 70 °C. After evaporation of the solvent under reduced pressure, the mixture was diluted with a sat. $Na_2S_2O_3$ aq. solution, extracted with EtOAc, water and brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 4/1) yielded the epoxide **295** in 50% yield (175 mg).

Epoxide 295. To a solution of alkyne **263** (1.0 equiv, 320 mg, 1.0 mmol) in CH_2Cl_2 (8 mL) at 23 °C were added sequentially PDC (3.0 equiv, 1.2 g, 3.1 mmol), Celite (767 mg), and a 70% *t*BuOOH aq. solution (3.0 equiv, 464 μL, 3.1 mmol). The mixture was stirred for 12 h at 23 °C and filtered. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 4/1) yielded the epoxide **295** in 10% yield (35 mg). *Rf* = 0.44 (Petroleum ether/EtOAc 4/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.05 (d, *J* = 8.0 Hz, 2H), 7.56-7.53 (m, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 5.91-5.80 (m, 1H), 5.55-5.42 (m, 2H), 2.64 (dd, *J* = 13.2, 4.8 Hz, 1H), 2.58 (dd, *J* = 8.0, 4.8 Hz, 1H), 2.32-2.25 (m, 1H), 2.07 (t, *J* = 2.4 Hz, 1H), 1.96-1.82 (m, 2H), 1.80-1.62 (m, 2H), 1.72 (d, *J* = 6.0 Hz, 3H), 1.62-1.49 (m, 3H), 1.32 (s, 3H), 1.07 (d, *J* = 6.0 Hz, 3H).



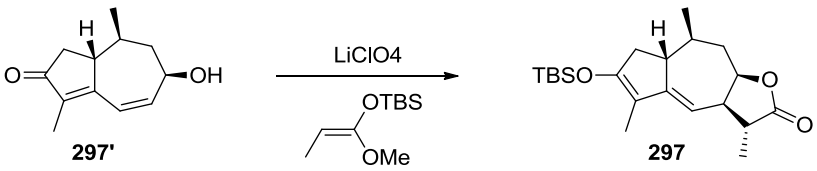
263 **296**

α,β-unsaturated ketone 296. To a suspension of SeO_2 (4.2 equiv, 480 mg, 4.3 mmol) in CH_2Cl_2 (124 mL) at 0 °C was added a 70% *t*BuOOH aq. solution (15.6 equiv, 2.2 mL, 16.1 mmol). The mixture was stirred 10 min at 0 °C and 20 min at 23 °C. The reaction was then cooled at 0 °C and alkyne **263** (1.0 equiv, 320 mg, 1.0 mmol) in CH_2Cl_2 (69 mL) was added. The mixture was stirred for 12 h at 23 °C, and was then quenched with a sat. $Na_2S_2O_3$ aq. solution, extracted with CH_2Cl_2 and water, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether to Petroleum ether/EtOAc 4/1) yielded the α,β-unsaturated ketone **296** in 10% yield (35 mg). *Rf* = 0.59 (Petroleum ether/EtOAc 4/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.03 (d, *J* = 7.2 Hz, 2H), 7.56-7.52 (m, 1H), 7.45-7.41 (m, 2H), 5.95 (bs, 1H), 5.85 (dd, *J* = 14.4, 6.4 Hz, 1H), 5.79 (d, *J* = 0.8 Hz, 1H), 5.52-5.41 (m, 2H), 3.00 (bs, 1H), 3.02-2.95 (m, 1H), 2.80-2.73 (m, 1H), 2.07-2.03 (m, 1H), 1.87 (bs, 3H), 1.89-1.82 (m, 1H), 1.77-1.65 (m, 2H), 1.70 (d, *J* = 5.6 Hz, 3H), 1.10 (d, *J* = 6.0 Hz, 3H).



291 **297'**

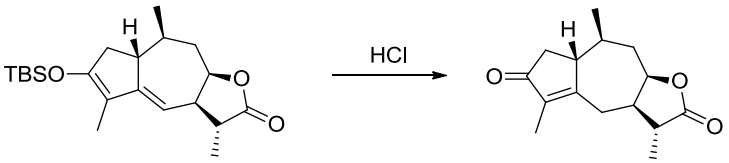
Secondary alcohol 297'. To a solution of hydrozulenone **291** (1.0 equiv, 77 mg, 180 µmol) in THF (4 mL) at 23 °C was added a 1.0 M solution of TBAF in THF (2.0 equiv, 360 µL, 360 µmol). The resulting mixture was stirred 12 h at 23 °C. The reaction was quenched with a sat. NH_4Cl aq. solution, extracted with EtOAc, water and brine, and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, Petroleum ether/EtOAc 10/1 to 1/3) yielded the secondary alcohol **297'** in 75% yield (26 mg). *Rf* = 0.22 (Petroleum ether/EtOAc 1/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.43 (d, *J* = 12.4 Hz, 1H), 6.15 (d, *J* = 12.4 Hz, 1H), 4.42 (d, *J* = 10.4 Hz, 1H), 2.64 (dd, *J* = 18.4, 6.4 Hz, 1H), 2.48-2.56 (m, 1H), 2.14 (dd, *J* = 18.4, 3.6 Hz, 1H), 2.05-1.99 (m, 1H), 1.80-1.76 (m, 1H), 1.74 (bs, 3H), 1.71-1.63 (m, 1H), 1.11 (d, *J* = 6.8 Hz, 3H), OH signal is not visible; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 207.41, 165.59, 143.08, 138.18, 122.45, 71.29, 48.14, 46.36, 41.49, 35.64, 22.86, 8.17.



297' **297**

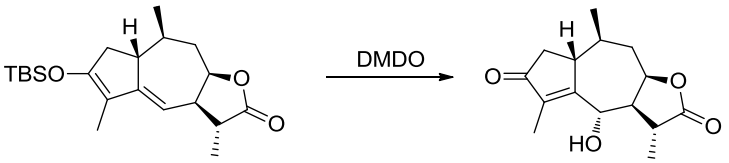
TBS-protected intermediate 297. To a solution of secondary alcohol **297'** (1.0 equiv, 2.0 mg, 10 µmol) in CH_2Cl_2 (500 µL) at 23 °C were added sequentially (*E*)-MeCH=C(OTBS)(OMe) (4.0 equiv, 8.4 mg, 42 µmol) and $LiClO_4$ (0.1 equiv, 0.11 mg, 1 µmol). The resulting suspension was stirred 5 h at 40

°C. The mixture was quenched with a sat. $NaHCO_3$ aq. solution, extracted with Et_2O/pentane (1/1) and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure yielded TBS-protected intermediate **297**, which was used without further purification.



297 **214 - (±)-6-deoxygeigerin**

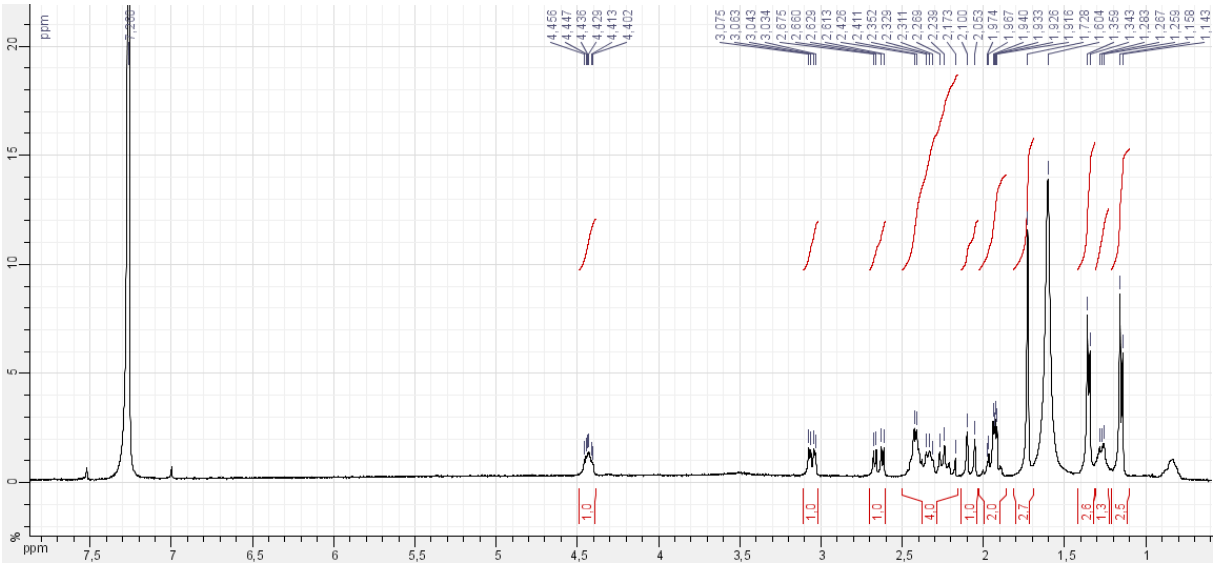
(±)-6-deoxygeigerin (214). To a solution of TBS-protected intermediate **297** (1.0 equiv, 3.8 mg, 10 µmol) in EtOAc (500 µL) at 23 °C was added a 1.0 N solution of HCl in water (few drops). The suspension was stirred 2 h at 23 °C and filtered. Evaporation of the solvent under reduced pressure followed by PTLC (CH_2Cl_2/Acetone 15/1) yielded **(±)-6-deoxygeigerin** (**214**) in 95% yield for 2 steps (2.4 mg). *Rf* = 0.51 (CH_2Cl_2/Acetone 10/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 4.46-4.40 (m, 1H), 3.05 (m, 1H), 2.64 (dd, *J* = 18.8, 6.4 Hz, 1H), 2.47-2.37 (m, 2H), 2.37-2.30 (m, 1H), 2.29-2.20 (m, 1H), 2.08 (d, *J* = 18.8 Hz, 1H), 2.00-1.88 (m, 2H), 1.73 (bs, 3H), 1.35 (d, *J* = 6.4 Hz, 3H), 1.32-1.23 (m, 1H), 1.15 (d, *J* = 6.0 Hz, 3H).



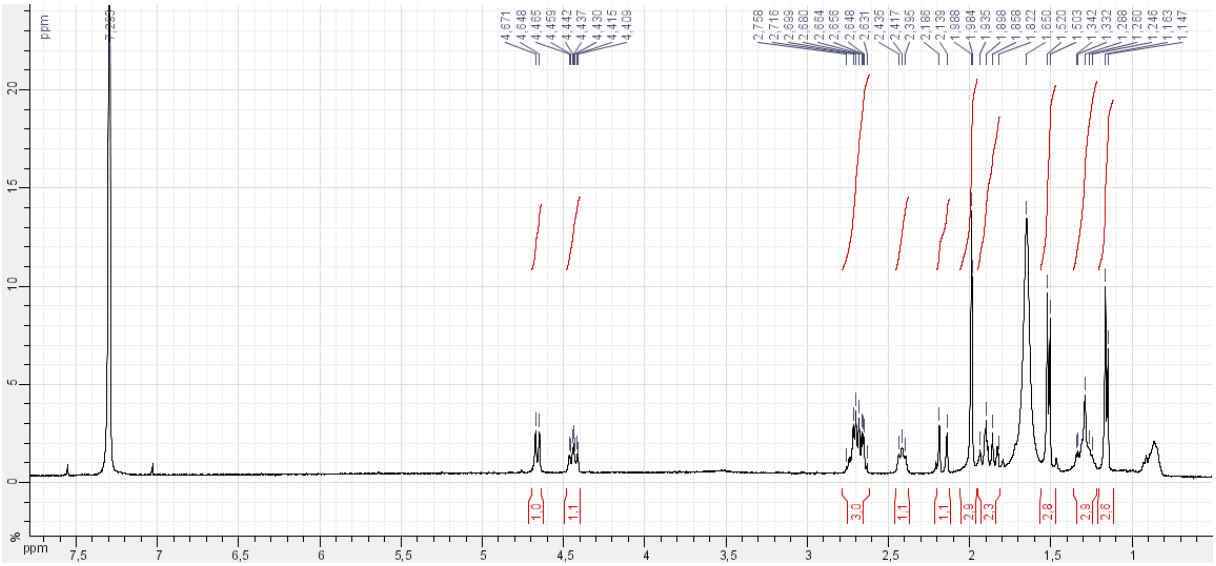
297 **181 - (±)-geigerin**

(±)-geigerin (181). To a solution of TBS-protected intermediate **297** (1.0 equiv, 3.8 mg, 10 µmol) in acetone (500 µL) at -90 °C was added a 0.047 M freshly prepared solution of DMDO in acetone (1.5 equiv, 448 µL, 21 µmol). The mixture was stirred 10 min at -90 °C, treated with water, extracted with EtOAc/pentane (2/1), and dried over Na_2SO_4. After evaporation of the solvents under reduced pressure, the mixture was dissolved in EtOAc and treated for 12 h at 23 °C with SiO_2. The solution was the filtered and purified by PTLC (Petroleum ether/EtOAc 1/1) to yield **(±)-geigerin** (**181**) in 90% yield for 2 steps (2.4 mg). *Rf* = 0.19 (CH_2Cl_2/Acetone 10/1); ^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C) δ 4.63 (d, *J* = 9.2 Hz, 1H), 4.43-4.38 (m, 1H), 2.72-2.60 (m, 3H), 2.42-2.35 (m, 1H), 2.13 (d, *J* = 18. Hz, 1H), 1.95 (bs, 3H), 1.92-1.76 (m, 2H), 1.48 (d, *J* = 6.4 Hz, 3H), 1.31-1.19 (m, 1H), 1.12 (d, *J* = 6.4 Hz, 3H), OH signal is not visible; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 208.10, 178.27, 171.28, 138.29, 78.51, 75.35, 49.26, 48.40, 42.01, 40.60, 40.12, 37.96, 22.63, 16.48, 9.06.

Annexes



Annexe 1. ^{1}H NMR spectra of (±)-6-deoxygeigerin.



Annexe 2. ^{1}H NMR spectra of (±)-geigerin.