universität wien

DISSERTATION / DOCTORAL THESIS

Titel der Dissertation /Title of the Doctoral Thesis

„Synthesis of Natural Products and Analogues by Directed C-H Activation and Unified Synthesis of Cicutoxin and Virol A *via* Electrocyclic Cyclobutene Ring Opening“

verfasst von / submitted by

Martin Berger, BSc MSc

angestrebter akademischer Grad / in partial fulfilment of the requirements for the degree of

Doktor der Naturwissenschaften (Dr. rer. nat.)

Wien, 2019 / Vienna 2019

Studienkennzahl lt. Studienblatt / degree programme code as it appears on the student record sheet:	A 796 605 419
Dissertationsgebiet lt. Studienblatt / field of study as it appears on the student record sheet:	Chemie, DK: Molecular Drug Targets
Betreut von / Supervisor:	Univ.-Prof. Dr. Nuno Maulide

The work presented in this doctoral thesis was conducted between December 2014 and January 2019 at the University of Vienna (Austria) under the supervision of Univ. Prof. Dr. Nuno Maulide.

Referees:

Prof. Dr. Erick M. Carreira

Mag. Dr. Roman Lichtenecker, Privatdoz.

Written by Martin Berger, April 2019

Acknowledgement

First of all, I would like to thank Nuno for accepting me as a PhD student. His dedication and competence in teaching is certainly out of question and well known. Concerning the less known fact, he also is certainly the best boss one can have. No matter the incident, he always is the master of the situation and keeps calm when others would already go turbo. This faculty and all its people are certainly very lucky to have him and his vision around.

I thank my whole family for the support in my unusual career path, which would have not been possible without them. I could gather a lot of experience all my way from the carpenter´s apprentice to the PhD candidate. I hope I can return all of your devotion in this lifetime. I also thank my cat Zuko (aka Susu). He was a king amongst all cats and his character will remain unmatched in this world. Like many great minds he unfortunately passed away too early. May he rest in peace.

The practice of rock climbing was and always will be an important part of my life. To enumerate the number of individuals who shared this passion with me over the last 15 years would certainly exceed the boundaries of these pages. However, I would like to specifically express my gratitude to my main (former and present) comrades Daniel Maderthaner, Stefanie Pichler, Thomas Schmölz and Cornelia von Baeckmann (aka Schatz) for countless hours of belaying, cheering and fighting mosquitos in the forest.

I also thank my comrades-in-arms from my undergraduate studies, Christian Denner and Alanca Schmid, who spent significant time with me studying at the faculty or discussing other aspects of life in less educated places.

I thank all of my practical teachers during my studies. Special thanks to Jean-Baptiste Farcet, Afrooz Zirakzadeh, Tuvshinjargal Budragchaa and Ao. Prof. Walter Weissensteiner for their extensive supervision in the laboratory. I would also like to express my gratitude to Ao. Prof. Michael Widhalm who taught me how to work properly and who supervised my bachelor and master thesis.

Special thanks also to Martina Drescher. She is actually the person who professionally accompanied most of my time in this faculty, from being my lab-mate to become a good colleague in recent days. Although being often angry at the group I know that she likes all of us more than she would ever admit.

I am also greatly indepted to Prof. Erick Carreira and Dr. Roman Lichtenecker for reviewing this thesis. I hope it is entertaining and not too boring to read.

Although the Maulide-group-composition permanently changed over the last years, the atmosphere remained consistently great. From the large number of maulidians, I thank EVERYONE for these very

enjoyable years. I especially would like to thank Tona (il pesce della mia vita), Yong and Rik, who started with me at (more or less) the same time. I thank Christian Knittl-Frank for an amazing and memorable “Summer of WUK” and many more things which I prefer not to mention here. I thank Alberto Oppedisano for introducing us all to the harder stylez. I thank Antonio Misale for all the support in my early days. I thank all my co-workers in my projects I did not mention so far: Saad, Paul, Aurelién, Rajan, Catarina, Jing, Marwan and Wojciech. I thank Hsiang-Yu, Margaux, Marie and Wojciech for correcting parts of this thesis. I would like to further thank Guilhem, Pinto, Kaiser, Brinefalk, Immo, Gio, Bauer, Miran, Carlos, Tom (Stephens), Mirjam, Elena, Patricia, Iakovos, Mohan, Anais, Tobi, Eric, Boom, Jérémy, Harry, Kathi, Bogdan, John, ….

I thank all employees from the NMR-, mass- and x-ray department for measuring my samples.

I also thank Dirk Trauner and his group (especially Martin Maier and Giulio Volpin) for their support in Manhattan.

I would also like to thank the family of Schatz. I very much appreciate their kind welcoming into the family and their support.

Last but not least it is time to thank my Schatz. My further thoughts on Cornelia cannot be described by any common wording. I will however try to further elaborate with a more advanced tongue: Hananana, nadananamada. Nana hanananana? Nanahanana, hanananaaa dahananaa nanaaaaa! Nja:)

Abstract

In general, the work in this thesis is centered on the synthesis of biologically active natural products or structural analogues thereof.

Chapter 1 describes the preparation of several structurally diverse molecules by the utilization of C–H activation methodologies, which are briefly introduced in section 1.1. In section 1.2, the total synthesis of the anti-malarial alkaloid Quinine is presented. The C–H arylation of 3-aminoquinuclidine not only allowed the concise synthesis of the natural product itself but also the preparation of two C-3 aryl-analogues. One of these analogues was shown *in vivo* to have increased antimalarial activity when compared to the natural product itself. In section 1.3, an oxidative approach for the cleavage of the 8-aminoquinoline directing group is presented. Fragmentation of the quinoline moiety by ozonolysis was found to proceed readily, converting the stable amide bond into a labile imide intermediate. The method was found useful for the cleavage of particularly hindered substrates and was further demonstrated in the preparation of aryl-analogues of Dehydroabietic Acid. Section 1.4 describes the functionalization of ring B in the abundant feedstock Oleanolic Acid. By sequential C–H oxidation using a hydroxygroup at C-23 as a natural handle, the C–H oxidation at C-6 in this pentacyclic triterpenoid was achieved. The approach allowed the first synthesis of the polyhydroxylated natural products Uncargenin C and Protobassic Acid.

In chapter 2, the total synthesis of the polyacetylenic toxins Virol A and Cicutoxin is described. Both natural products were previously prepared by extensive use of cross coupling reactions. As described herein, the rapid construction of the common unsaturated motif has been realized by a cuprate addition/4π electrocyclic ring opening reaction. Further modification allowed the preparation of both natural products in a unified manner.

Kurzzusammenfassung

Diese Arbeit beschäftigt sich im Allgemeinen mit der Synthese von biologisch aktiven Naturstoffen oder strukturell ähnlichen Analoga.

Kapitel 1 beschreibt die Herstellung von mehreren strukturell verschiedenen Molekülen durch die Anwendung von Methoden zur C–H Aktivierung, welche kurz in Abschnitt 1.1 beschrieben werden. In Abschnitt 1.2 wird die Totalsynthese des Antimalaria-Alkaloids Chinin präsentiert. Die C–H Arylierung von 3-Aminochinuclidin erlaubte nicht nur eine kurze Synthese des Naturstoffes selbst sondern auch die Herstellung zweier C-3 Arylanaloga. Eines dieser Analoga zeigte *in vivo* eine erhöhte Aktivität gegen Malaria wenn verglichen zum Naturstoff selbst. In Abschnitt 1.3 wird ein oxidativer Zugang zur Spaltung der 8-Aminochinolin dirigierenden Gruppe präsentiert. Fragmentierung der Chinolingruppe durch Ozonolyse erfolgt sehr schnell und konvertiert die stabile Amidfunktionalität in ein labiles Imidintermediat. Die Methode ist besonders praktisch für die Spaltung von ausgesprochen gehinderten Substraten und wurde desweiteren in der Herstellung von Arylanaloga der Dehydroabietinsäure demonstriert. Abschnitt 1.4 beschreibt die Funktionalisierung von Ring B im reichlich vorhandenen Rohstoff Oleanolsäure. Durch eine C–H Oxidationssequenz unter Benutzung einer Hydroxygruppe an C-23 als natürlichem Ankerpunkt wurde die C–H Oxidation von C-6 in dem Triterpenoid erreicht. Dieser Zugang ermöglichte die erste Synthese der mehrfach hydroxylierten Naturstoffe Uncargenin C und Protobassic Acid.

In Kapitel 2 wird die Totalsynthese der mehrfach ungesättigten Gifte Virol A und Cicutoxin beschrieben. Beide Naturstoffe konnten früher durch mehrere Kreuzkupplungsreaktionen hergestellt werden. In dieser Arbeit wird die rasche Konstruktion des gemeinsamen ungesättigten Motives durch eine Kupprataddition/4π elektrozyklische Ringöffnung realisiert. Weitere Modifikationen erlaubten die Herstellung beider Naturstoffe in einer einheitlichen Weise.

TABLE OF CONTENTS

1 SYNTHESIS OF NATURAL PRODUCTS AND ANALOGUES BY DIRECTED C-H ACTIVATION

1.1 DIRECTED C(SP^3)–H ACTIVATION IN THE SYNTHESIS OF NATURAL PRODUCTS

C–H Activation ranks amongst the most powerful transformations in synthetic organic chemistry. This is easily comprehensible due to the fact that it allows the highly desirable direct functionalization of C–H bonds. Such transformation is not only of great importance for increasing the value of otherwise non-functionalized material, but also introduces a high-end toolbox for the synthesis of natural products. [1-3] From a mechanistic point of view, this family of reactions could not be more dissimilar. In this section, a brief overview of pioneering directed C–H activation methodologies with relevance to the presented work will be given. Section 1.2 describes the total synthesis of the antimalarial alkaloid Quinine and preparation of C-3 arylated analogues thereof by palladium catalyzed C–H arylation, utilizing a bidentate directing group. Section 1.3 discusses the synthesis of novel C–H arylated analogues of dehydroabietic acid, enabled by a newly developed protocol for the oxidative cleavage of the 8-aminoquinoline directing group in particularly hindered substrates. Section 1.4 elucidates a C–H oxidation sequence featuring a C–H acetoxylation reaction and the Suárez modification of the Hofmann Löffler Freytag reaction to enable the oxidation of ring B in Oleanolic Acid. This approach allowed the first synthesis of the highly oxygenated natural products Uncargenin C and Protobassic Acid.

1.1.1 Aliphatic C–H Activation by hydrogen atom transfer

The pioneering reactions for remote C–H functionalization operate *via* generation of a heteroatom-centered radical and subsequent hydrogen atom transfer (HAT). As such, the Hofmann-Löffler-Freytag (HLF) reaction is often considered the first contribution to the field of C–H activation. [4,5] This type of reaction has found numerous applications in the total synthesis of natural products. A pioneering work is the synthesis of Dihydroconessine **1.006** which was reported in 1958 by the group of Corey. [6] As shown in Figure 1, the classic HLF reaction is generally known for the synthesis of pyrrolidines from acyclic amines. After *N*-chlorination of amine **1.001** with *N*-chloro-succinimide (NCS), homolytic cleavage of the nitrogen-halide bond in **1.002** in acidic media leads to the formation of a *N*-centered radical **1.003**, which is prone to undergo hydrogen atom transfer (HAT) to give a carbon centered radical **1.004**. After radical recombination, nucleophilic substitution in **1.005** yields the cyclic product Dihydroconessine **1.006**.

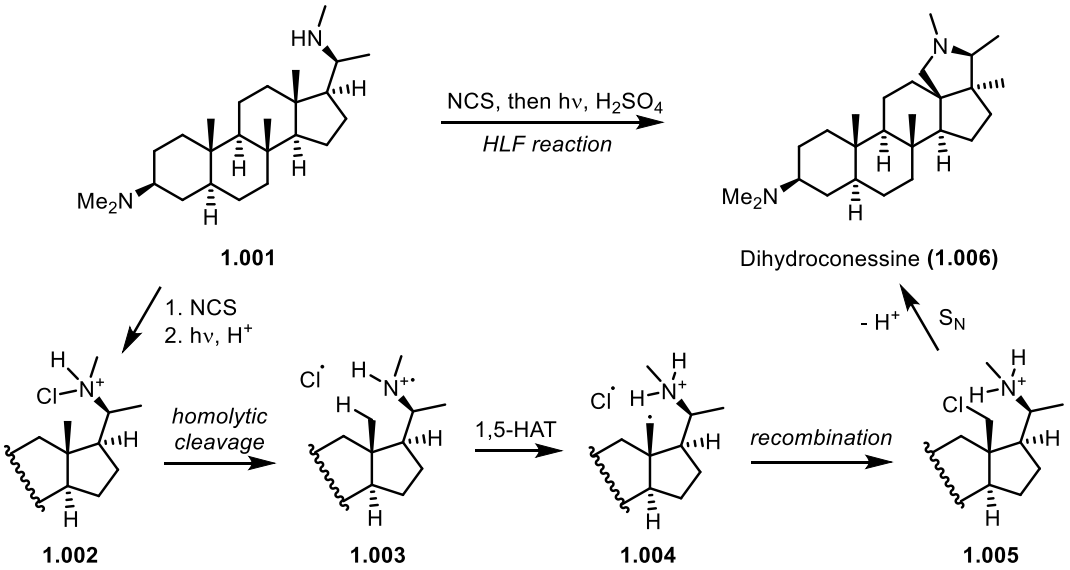


Figure 1. Proposed mechanism of the HLF reaction via 1,5-HAT as key step in Corey´s synthesis of Dihydroconessine

Besides the construction of cyclic pyrrolidine moieties, the HLF reaction can also be utilized for remote halogenation of C–H bonds. In 1978, Uskokovic and coworkers applied this reactivity for the remote C–H chlorination in a synthetic intermediate *via* an interrupted HLF reaction.[7] As shown in Figure 2, *N*-chlorination of piperidine derivative **1.007** with NCS and subsequent irradiation of **1.008** in trifluoroacetic acid afforded the desired chloride, which was isolated as its ammonium salt **1.009** and thereby allowed prevention of the undesired cyclization. *N*-Protection and elimination of HCl afforded

N-Benzoylmeroquinene **1.010**, which is an important key intermediate for many historical Quinine syntheses.

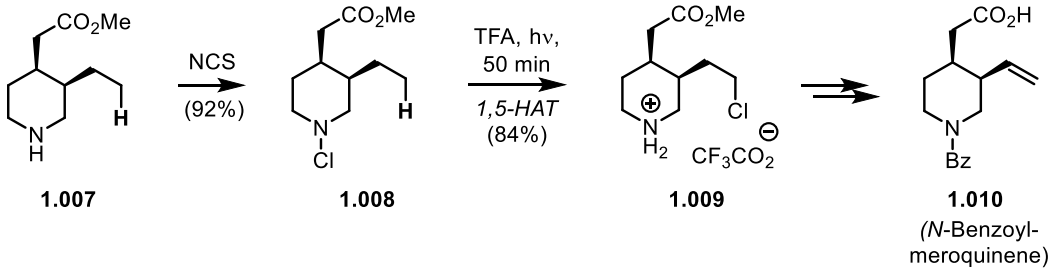


Figure 2. Interrupted HLF reaction in the synthesis of N-benzoyl-meroquinene by Uskokovic and coworkers.

In 1960, Barton *et al.* published another new photochemical reaction as an early entry for remote C–H functionalization. [8] The reaction is commonly known as Barton reaction and follows the same principle as the HLF reaction. Instead of *N*-halo-amines, this reaction utilizes nitrite esters and typically affords hydroxyoximes as products. The Barton reaction was applied in a short synthesis of Perhydrohistrionicotoxin **1.013** by the group of Corey in 1975, as shown in Figure 3. [9] The homolytic cleavage of nitrite ester **1.011** by irradiation with UV-light generated an alkoxyradical which is prone to undergo 1,5-HAT. In accordance with the HLF reaction, recombination of the nitrosyl- and the C-centered radical and subsequent tautomerization affords oxime **1.012**, a precursor of natural product **1.013**.

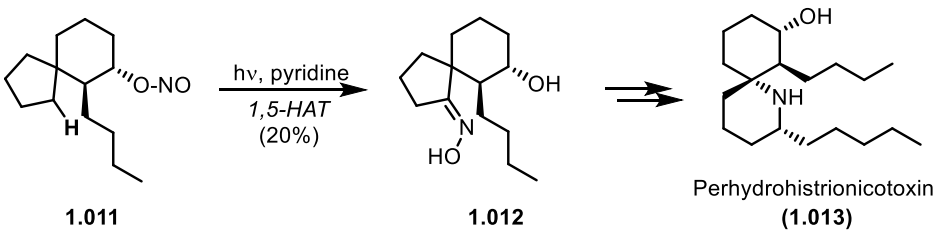


Figure 3. Corey´s synthesis of Perhydrohistrionicotoxin utilizing a Barton reaction

Analogous to the HLF and Barton reactions, HAT reactivity can also be applied to alcohols *via* the *in situ* formation and homolytic cleavage of the corresponding hypohalites by thermal heating or irradiation. Especially the homolytic cleavage of hypoiodites allows the efficient synthesis of tetrahydrofuran moieties *via* oxidative cyclization of alcohols, a process generally known as the hypoiodite reaction. [10] Formation of the alkoxyradicals was found to proceed in the presence of iodine and metal salts such as lead tetraacetate (LTA), silver acetate or mercury acetate upon

irradiation or heating. Iodination of the alcohols is believed to occur *via* the *in situ* formation of acetyl hypoiodite. In 1983, Suárez and coworkers reported the cyclization of alcohol **1.014** to Sarsasapogenin acetate **1.015** *via* 1,6-HAT by use of LTA/I_2 and irradiation in refluxing cyclohexane, as shown in Figure 4. [11] Although the formation of tetrahydrofuranes *via* 1,5-HAT is predominant in many cases, the position of the abstracted hydrogen atom (1,n-HAT) can vary and usually depends on the specific structure of the starting material. [12] The preference for the 1,6-HAT over a possible 1,5-HAT in this particular case can be explained by the formation of a very stable tertiary, α-oxygenated radical upon hydrogen atom transfer instead of a less favored secondary radical.

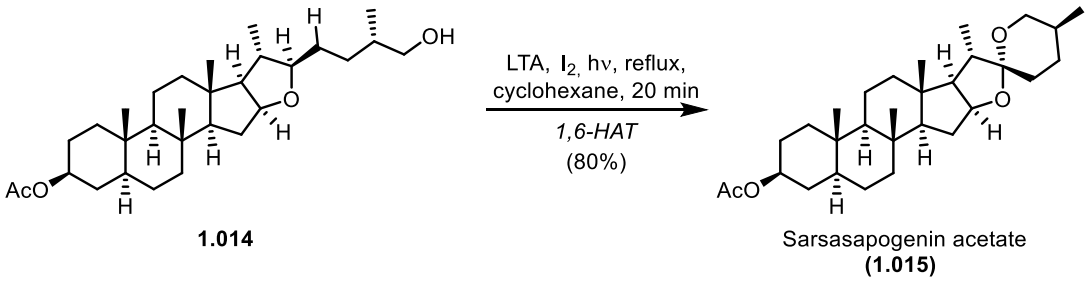


Figure 4. Synthesis of Sarsasapogenin acetate via the hypoiodite reaction by the group of Suárez

One year later, the same group reported the hypoiodite reaction to proceed by use of hypervalent iodine reagent phenyliodine(III) diacetate (PIDA) and iodine as much more convenient reagents for generation of alkoxyradicals by simultaneous irradiation with visible light. [13] This important contribution has found numerous applications in the synthesis of complex molecules and is generally known as the Suárez modification of the HLF reaction. Due to the exceptionally mild conditions, the transformation is still frequently applied. As shown in Figure 5a, the group of Trost utilized the Suárez modification at a late stage in their total synthesis of Siccanin **1.016**, as reported 2001. [14] More recent examples have been reported by Maimone and coworkers, utilizing the Suárez modification in the total synthesis of the sesquiterpenes Pseudoanisatin **1.017** [15] or Majucin **1.018**, as shown in Figure 5b. [16]

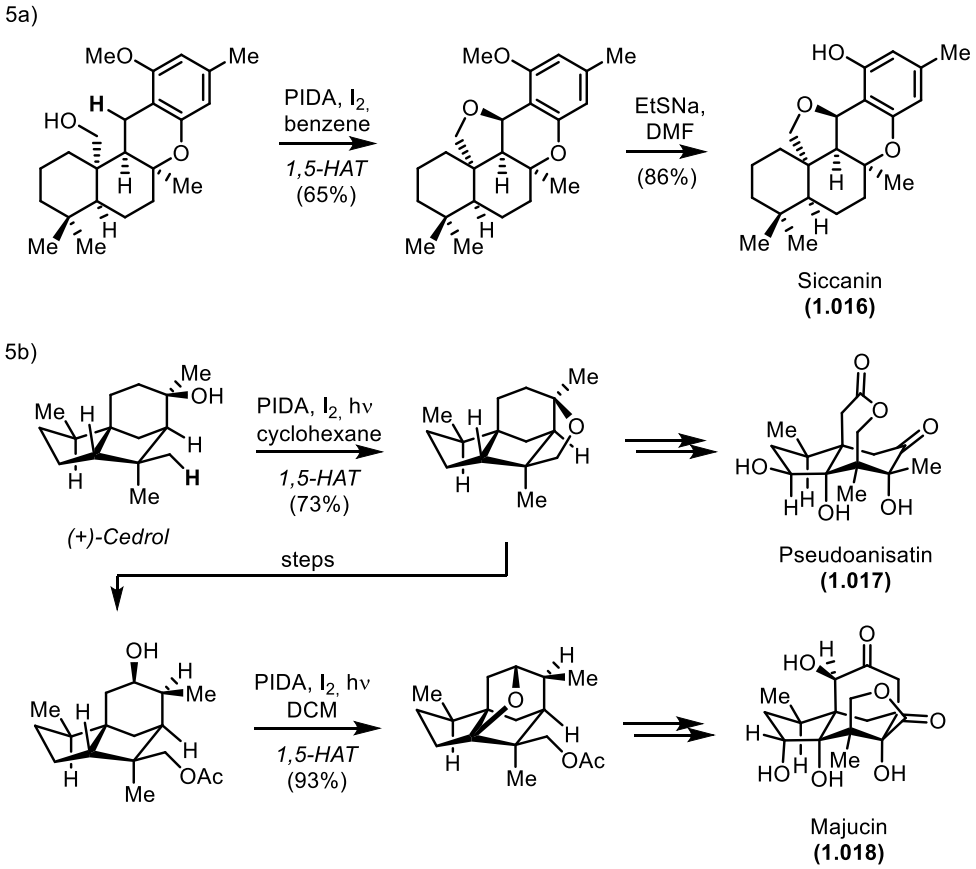


Figure 5. Selected examples for the Suárez modification in total synthesis by the groups of Trost (5a) and Maimone (5b)

1.1.2 Directed C(sp^3)–H functionalization by transition metal catalysis

In contrast to methods utilizing hydrogen atom abstraction, transition metal catalyzed C–H activation is a relatively young field but has already found numerous applications in natural product synthesis. The concept of directing groups drastically raised the applicability of the method, allowing the regioselective functionalization of even non-activated aliphatic positions in complex carbon frameworks.[17]

1.1.2.1 Cyclopalladation reactions

The ancestors of modern C–H activation reactions are cyclometallation reactions. An important seminal work in this field was published by Hartwell and coworkers in 1970 on the formation of palladium(II)- or platinum(II)-complexes of quinolines *via* a therein called ”proton abstracting process”.[18] The products were found to be chloride-bridged dimeric complexes with strong preference for the formation of 5-membered rings. As shown in Figure 6, the dimeric palladium complex **1.019** is a very early example of aliphatic C–H bond activation by use of a quinoline directing group. A few years later, Shaw and coworkers reported in 1978 on the cyclopalladation reactions of aliphatic hydrazones and oximes.[19] As derivatives of the carbonyl group, this class of substrates is particularly useful in preparative organic chemistry. That study not only comprised the isolation of similar dimeric Pd(II) complexes **1.020** but also the unambiguous identification of the palladacycles by x-ray analysis. The palladation of non-benzylic C–H bonds in pyridine substrates was reported later in 1983 by Fuchita and coworkers.[20] In that case, the complexes were reported to contain 6-membered palladacycles such as **1.021**, obviously simply achieved by substrate design. It should be noted that all palladacycles in Figure 6 are structurally unable to undergo β-hydride elimination as competing reaction pathway.

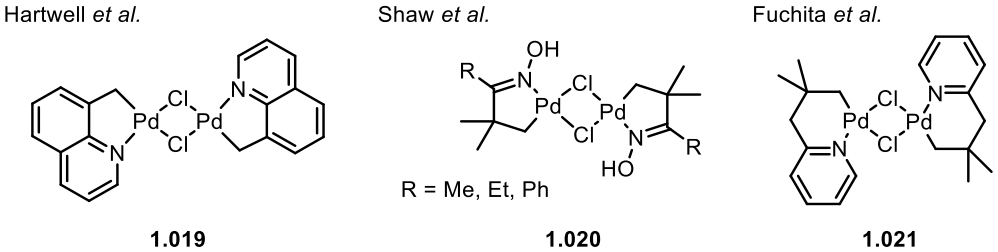


Figure 6. Dimeric palladacycles as early examples for activation of aliphatic C–H bonds by nitrogen directing groups

Baldwin and coworkers started to investigate the synthetic utility of these metallated methyl groups, obtained as described above.[21] With the dimeric palladium(II)-complexes **1.020** in hand, studies towards the reductive or oxidative functionalization of the activated methyl groups have been carried out. While the reduction of the complexes with $NaBD_3CN$ led to the deuterated product, treatment with Cl_2 in CCl_4 led to the overall C–H chlorinated product. Oxidation of the activated methyl group was attempted with lead tetraacetate (LTA). The monomeric complexes obtained by addition of pyridine gave the acetoxylated products in high yield, whereas the addition of LTA to the dimeric complexes only resulted in product mixtures. As shown in Figure 7, this method was applied to the modification of various substrates such as the hydrogenated lupane triterpenoid derivative **1.022**. While the oxidation of the monomeric pyridine complex in that case was found to be unsuccessful as well, the use of an *in situ* formed *O*-acetyl pyridine complex **1.023** gave a clean conversion. Final treatment with sodium borohydride was furthermore found necessary in order to remove palladium from the desired C–H acetoxylated product **1.024**.

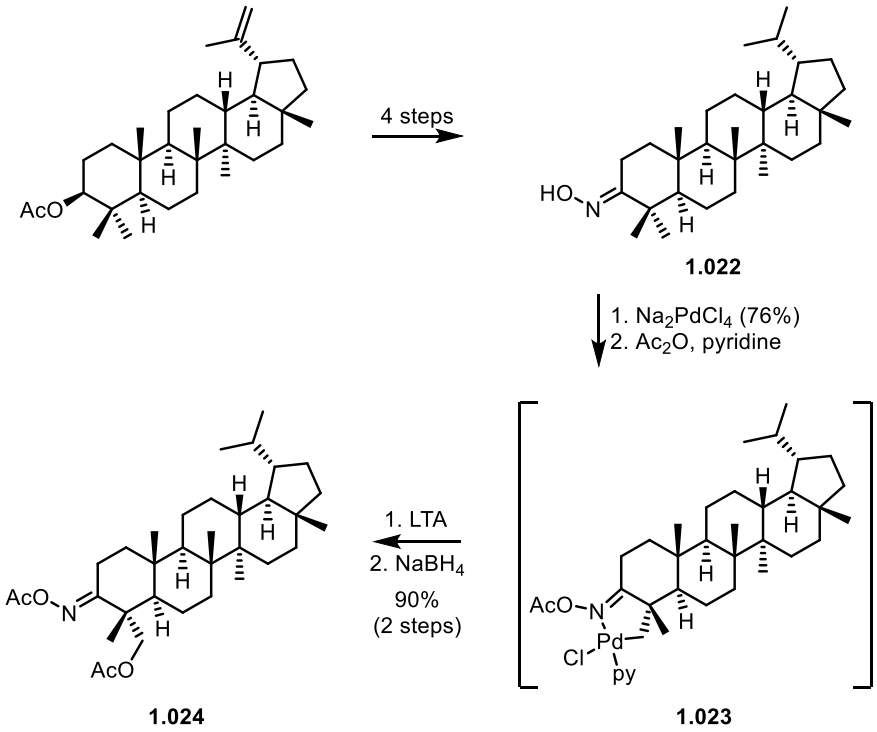


Figure 7. Acetoxylation of a monomeric Pd(II)-pyridine complex by Baldwin and coworkers

This multistep procedure is generally known as Baldwin´s method and has found multiple applications in the acetoxylation of pentacyclic triterpenes for the preparation of higher oxidized aglycons. An

illustrious example is the synthesis of the saponin Lobatoside E **1.026** as reported in 2008 by the group of Yu.[22] As shown in Figure 8, selective hydroxylation at C-23 in **1.025** was accomplished by cyclopalladation in a total of 9 steps, which corresponds nearly to one third of the total step count of the longest linear sequence.

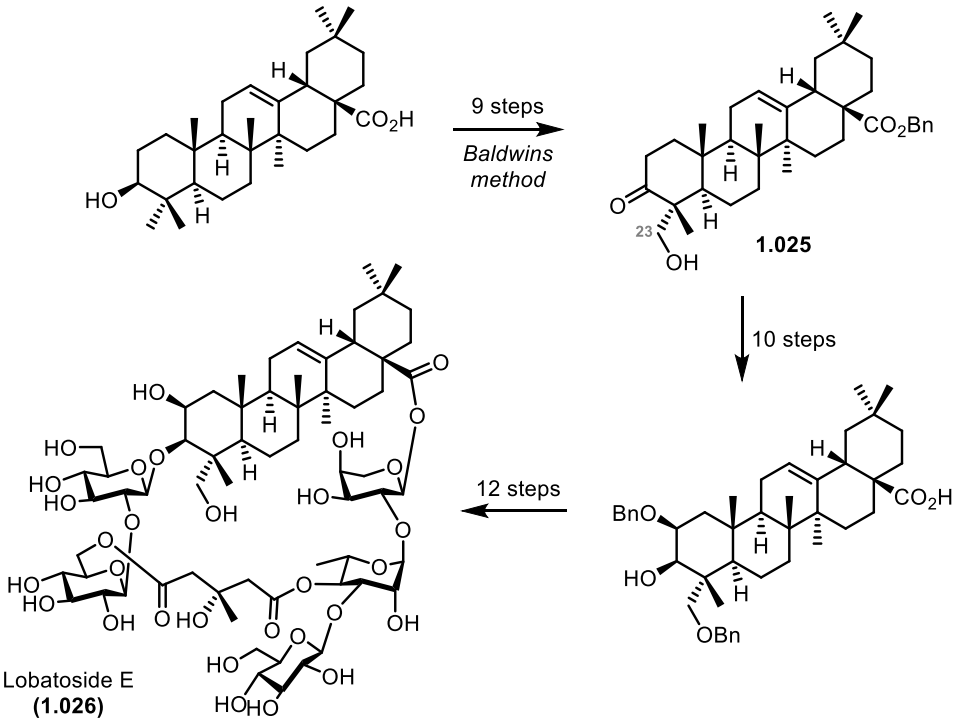


Figure 8. Synthesis of Lobatoside E by Yu and coworkers utilizing Baldwin´s method

1.1.2.2 Catalytic C–H activation

The functionalization of methyl groups in palladacycles comes at high cost, which is the requirement of stoichiometric palladium salts and numerous synthetic steps. No less than two decades after Baldwin´s pioneering work, the group of Sanford reported the catalytic version of the C–H acetoxylation reaction. Inspired by the previously isolated palladacycles (*vide supra*), a number of substrates containing nitrogen based monodentate directing groups were found suitable for the direct functionalization of aliphatic C–H bonds. As shown in Figure 9, treatment of various nitrogen-containing molecules with catalytic amounts of $Pd(OAc)_2$ and excess phenyliodine(III)-diacetate (PIDA) as co-oxidant led, upon heating, to the formation of the corresponding C–H acetoxylated products. While this transformation was initially investigated on quinoline substrates (Figure 9a),[23] *O*-methyl-oximes (Figure 9b)[24] or *in situ* formed *O*-acetyl-oximes (Figure 9c)[25] were also found to be suitable for this transformation. Protection of the OH group in oximes seems to be an absolute necessity, since unsubstituted oximes were otherwise found to simply undergo cleavage to the corresponding ketone starting materials under the oxidative conditions. It is further noteworthy that the oxime substrates could be applied as mixtures of E/Z isomers, since equilibration was found to occur fast under the reaction conditions.

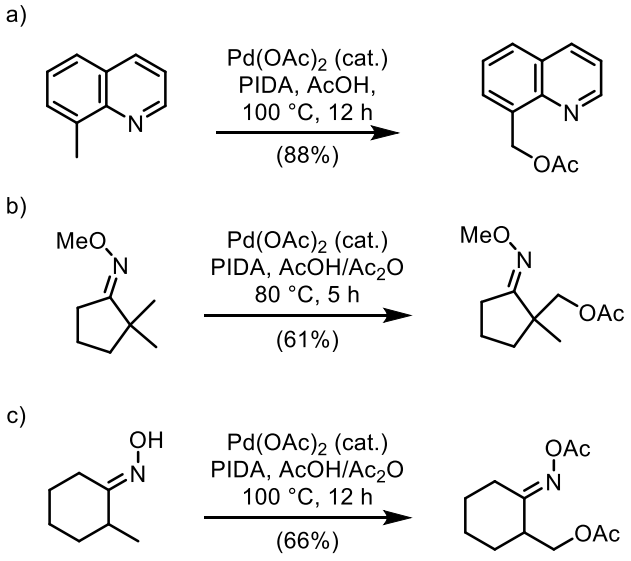


Figure 9. Pioneering examples of catalytic C–H activation by the group of Sanford

The proposed mechanism for this transformation follows the general catalytic cycle for C–H activation *via* a Pd(II)/Pd(IV) mechanism, as shown in Figure 10. Pre-coordination of Pd(II) to the substrate forms complex **A**, which then undergoes C–H activation *via* a concerted deprotonation/metalation process

[26] to form Pd(II) complex **B**. Oxidation of Pd(II) by PIDA generates the very reactive Pd(IV) complex **C**, which is prone to undergo reductive elimination to form the new C-O bond, releasing the product and regenerating the catalyst.

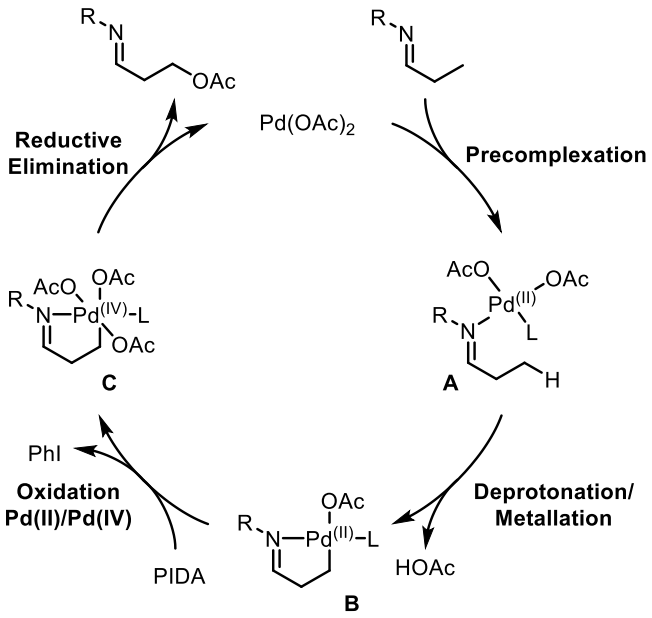


Figure 10. Proposed mechanism for C–H acetoxylation by a Pd(II)/Pd(IV) couple

The method was applied in 2014 in the total synthesis of Jiadifenolide **1.029** by the group of Sorensen, as shown in Figure 11.[27] C–H Acetoxylation at the geminal methylgroups in **1.027** proceeded well but unfortunately without any diastereoselectivity, yielding the products in a diastereomeric ratio of 1:1. The products however could be separated and the desired isomer **1.028** was obtained in 22% yield as precursor for Jiadifenolide **1.029**.

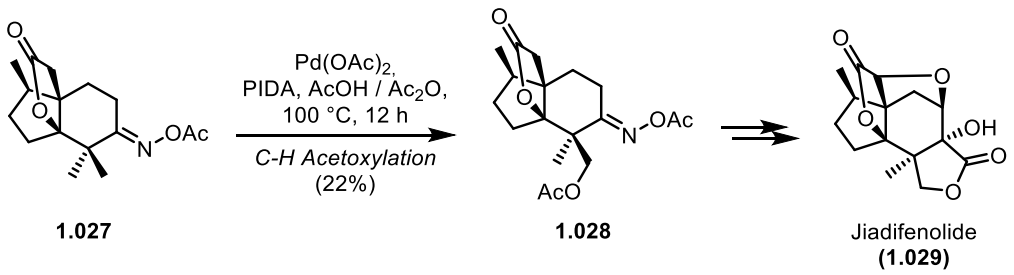
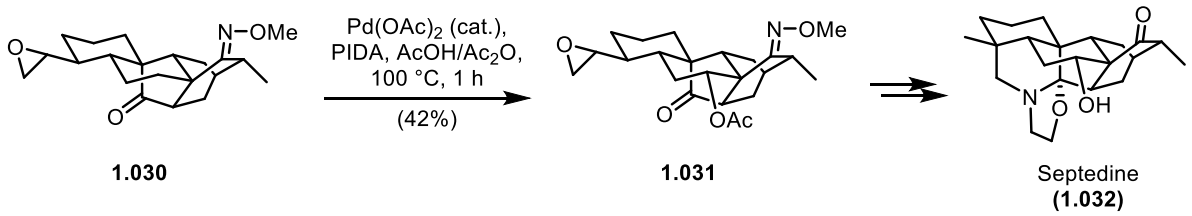


Figure 11. Total synthesis of Jiadifenolide by the group of Sorensen featuring C–H acetoxylation as key step.

More recently, this reaction also found application in the synthesis of Septedine **1.032** by the group of Li, as shown in Figure 12.[28] In general, C–H activation of methylene groups is considered to be much more challenging than gem-dimethyl groups. This is explained by the increased steric hindrance of methylene groups when compared to methyl groups and additionally the open possibility of β-hydride elimination as competing reaction pathway.[29] However, C–H acetoxylation of substrate **1.030** was achieved in 42% yield with high diastereoselectivity. Further functional group modifications on oxime **1.031** afforded the diterpenoid alkaloid Septedine **1.032**.



1.030 **1.031** Septedine **(1.032)**

Figure 12. Li´s total synthesis of Septedine employing C–H acetoxylation of a methylene group

Another milestone achievement in C–H activation was the introduction of bidentate directing groups, as developed for C–H arylation reactions by the group of Daugulis in 2005.[30] As a starting point, the 2-aminomethylpyridine moiety was found to decompose under C–H activation conditions due to the benzylic methylene group (Figure 13a). As an alternative, the 8-aminoquinoline (AQ) directing group was found to perform better in the attempted β-C–H arylation reaction using aryliodides as coupling partners. Surprisingly, this moiety was found particularly reactive in the case of non-activated methylene groups. While the latter can easily be installed by amide coupling to a carboxylic acid, picolinic amides were identified to be analogous directing groups for the attachment at amine substrates (Figure 13c). Although the picolinic amide (PA) directing group was found less effective when compared to the 8-aminoquinoline group (especially in the activation of methylene groups), it allowed the unprecedented direct γ-C–H arylation of amine substrates.

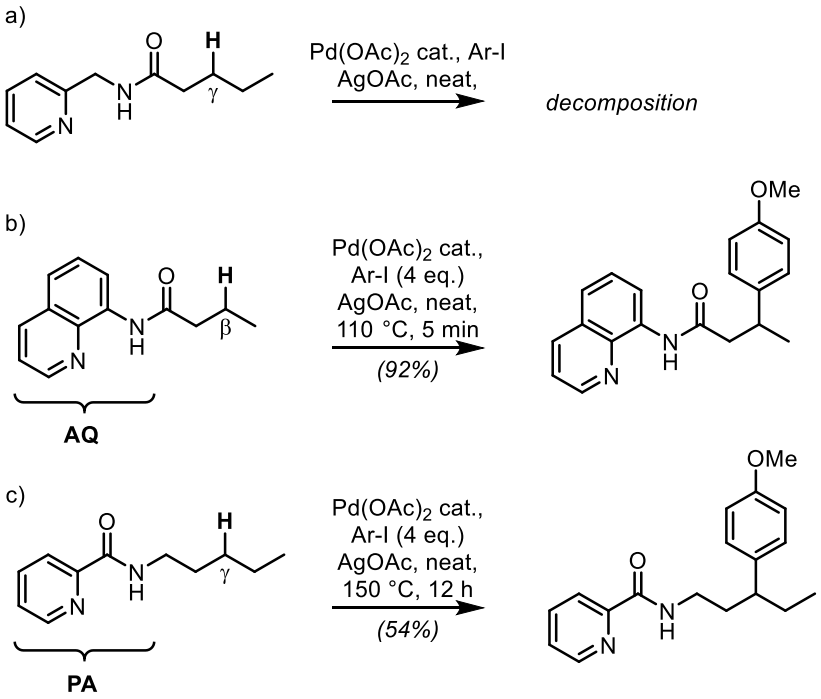


Figure 13. C–H arylation of aminoquinoline- and picolinic acid-derived bidentate directing groups, as reported by Daugulis.

The aminoquinoline directing group was shown to not only be applicable in C–H arylation but also in more challenging C–H alkenylation or C–H alkylation reactions. This was achieved using the corresponding organohalide coupling partners in presence of silver salts to capture the halides and facilitate the coupling process.[31] The mechanism is likely to be similar to the one presented for C–H acetoxylation involving a Pd(II)/Pd(IV) catalytic cycle (Figure 14). Pre-coordination of $Pd(OAc)_2$ with the AQ directing group affords complex **A**, which can undergo C–H activation with preference for the formation of 5-membered palladacycles such as complex **B**. Oxidative addition of the organohalide affords **C**, which is prone for reductive elimination to forge the new C-C bond.

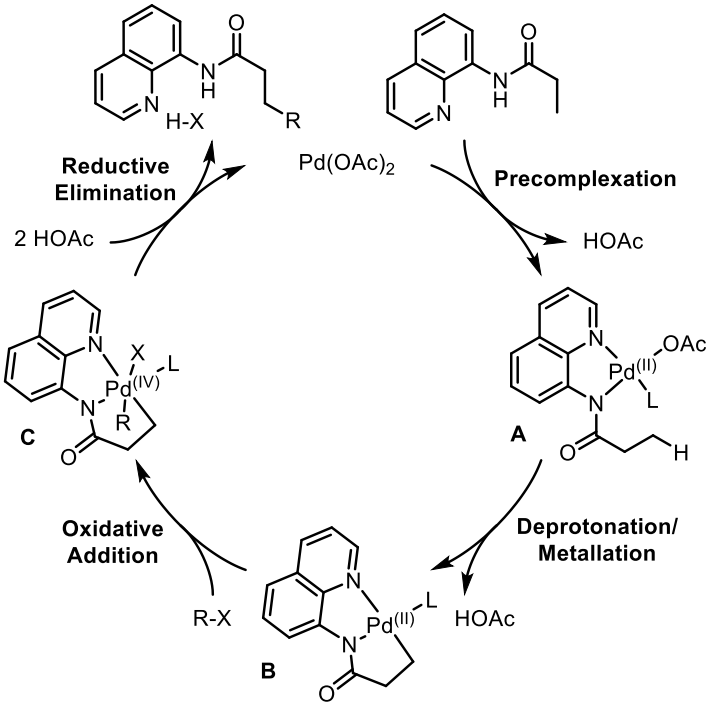


Figure 14. Proposed mechanism of C–H activation with organohalides and bidentate directing groups

An illustrative example for the high utility of the AQ directing group was demonstrated by the group of Baran in 2012 in their total synthesis of the proposed structure of Pipercyclobutanamide A **1.036** (Figure 15).[32] A sequential C–H functionalization strategy was pursued in order to decorate cyclobutene **1.033** with the required substituents. As envisioned, the AQ moiety successfully directed C–H arylation to yield intermediate **1.034** in 54% yield. Following a sequential strategy, another subsequent C–H alkenylation afforded *all-cis* cyclobutene **1.035**. Further manipulations including epimerization steps afforded the proposed structure of Pipercyclobutanamide A **1.036**. The NMR data was unfortunately found not to be in accordance with the isolated natural product.

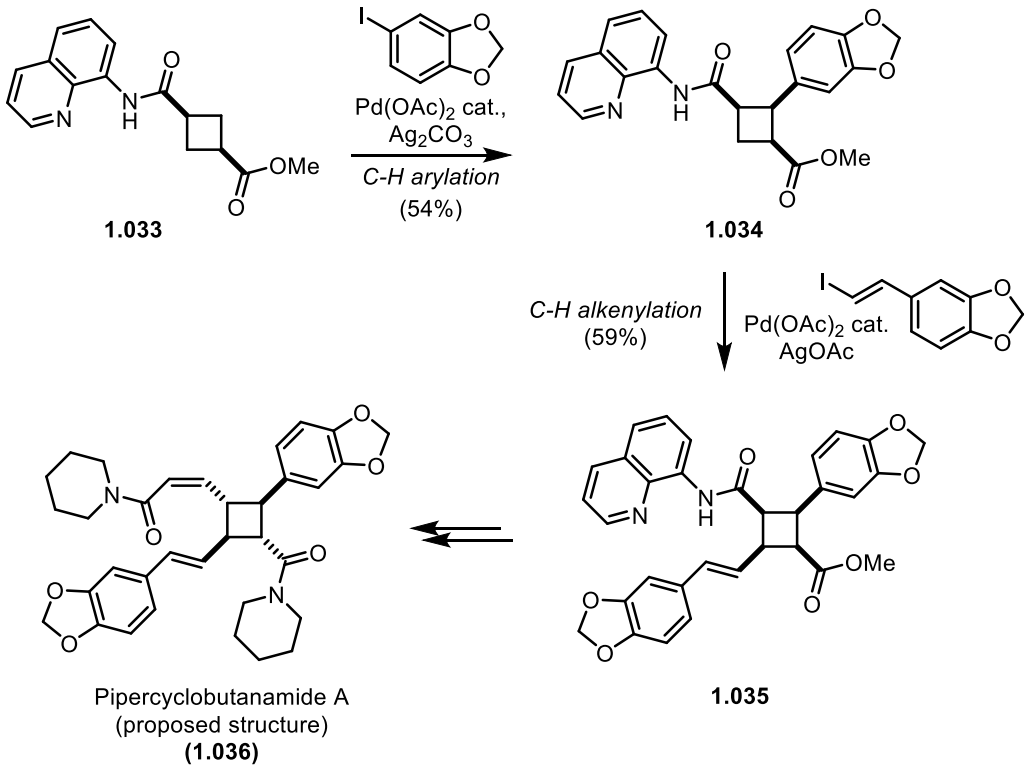


Figure 15. Use of the 8-aminoquinoline directing group in total synthesis by the group of Baran

The use of the aminoquinoline directing group has gained significant popularity in the field of C–H activation within the last decade [33] and found to be not limited to palladium catalysis. A plethora of applications utilizing various transition metal catalysts such as the third-row metals copper [34] or nickel [35] have been reported over the years, as shown in Figure 16. For example, Kanai and coworkers reported in 2014 the copper(II) acetate catalyzed intramolecular C-N bond formation, incorporating the nitrogen of the amide directing group into the β-lactam moiety (Figure 16a). [36] The mechanism is believed to proceed *via* Cu(I)/Cu(III) catalysis. Oxidation of copper(II) by Ag_2CO_3 generates a copper(III) species, which after complexation undergoes subsequent C–H activation and reductive elimination to form the C-N bond. Excess of silver salt operates as oxidant and regenerates the copper(III) catalyst. A representative example of nickel catalysis is the aliphatic C–H alkylation by use of 1,2-bis(diphenylphosphino)benzene (dppbz) as additional ligand, as reported by the group of Ge in 2014 (Figure 16b). [37] In contrast to copper, the present reaction is believed to proceed *via* the same oxidation levels than palladium catalysis (*via* a Ni(II)/Ni(IV) couple) and therefore follows a comparable catalytic cycle as shown before. Alternatively, also cobalt was found to be able to promote C–H activation. Utilizing again the AQ directing group, the group of Gaunt reported the aliphatic C–H

carbonylation in 2017. The use of cobalt(II) acetate and silver acetate under an CO-atmosphere enabled the synthesis of succinimide derivatives, as shown in Figure 16c.[38]

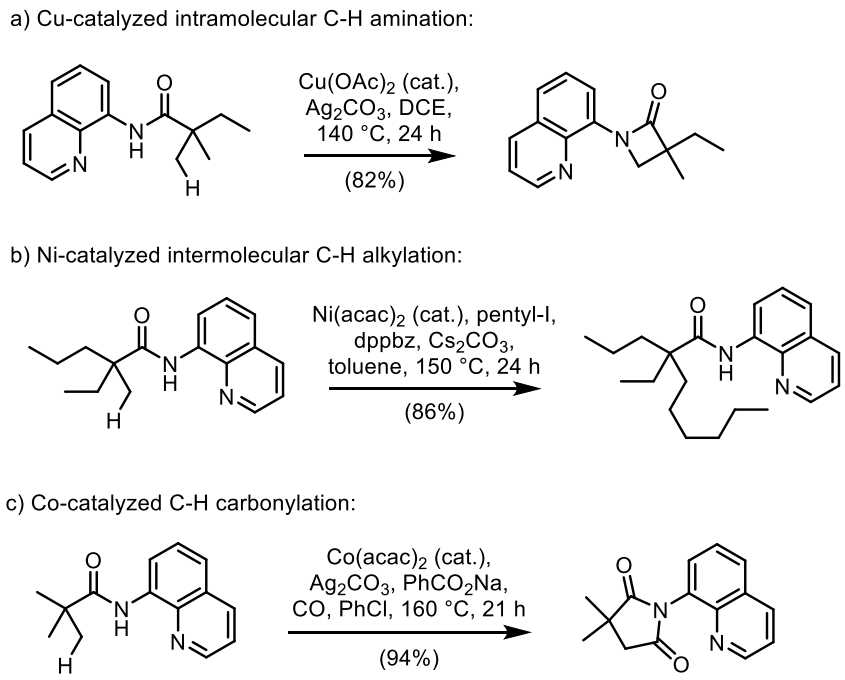


Figure 16. Selected examples of different metal catalysts and transformations utilizing the aminoquinoline directing group

The development of directing groups for C–H activation has been broadly pursued by numerous groups in organic synthesis leading to a plethora of variations.[39] Selected representative examples for the synthesis or modification of natural products using a variety of directing groups and transition metals are shown in Figure 17. In 2014, the group of Maimone reported the synthesis of Podophyllotoxin **1.039** by C–H arylation.[40] A bidentate amide directing group served well for the installation of the trimethoxyaryl-moiety by diastereoselective palladium-catalyzed C–H arylation in **1.037** in 58% yield (Figure 17a). Treatment of **1.038** with TFA in a last step led to cleavage of the directing group and concomitant lactonization to afford Podophyllotoxin **1.039**. In 2016, Sarpong and coworkers reported the formal synthesis of Herbindole B **1.042** utilizing a trifluoromethylsulfonamide functionality in **1.040** as monodentate directing group for overall C–H indolization.[41] The reaction is proposed to proceed by intramolecular C-N bond formation in **1.040** and subsequent oxidation to indole **1.041**. Although mechanistically distinct, several metal-mediated C–H functionalization reactions have been developed which utilize the concept of directing groups or elements but do not follow the classic C–H activation mechanism. One representative example was reported by Giannis

and coworkers utilizing a copper-catalyzed regioselective C–H hydroxylation of steroid derivative **1.043** as key step in the synthesis of Cyclopamine **1.045**.[42] The directing group is removed during the work-up of the reaction directly affording β-hydroxyketone **1.044**. This transformation was initially reported in 2003 by the group of Schönecker [43] and further optimized by the group of Baran in 2015.[44] Although the mechanism is not completely clear, evidence suggests that the reaction proceeds *via* a binuclear copper complex. Another recent example of C–H oxidation was utilized by the group of Brown in 2014 featuring a C–H lactonization reaction in the total synthesis of Gracilioether F **1.047**.[45] This iron catalyzed C–H oxidation was developed and reported by the group of White in 2012.[46] After coordination of the iron catalyst **1.048** to the carboxylic acid of **1.046** as directing element, a hydrogen atom abstraction reaction of the remote tertiary center is believed to take place. Subsequent oxidation of the resulting radical to a hydroxy group and condensation could yield the lactone product. It should be noted that the low yield of 9% (NMR) could be increased to 15% (isolated) by the use of copper salts instead, although the latter must be employed in stoichiometric amounts.

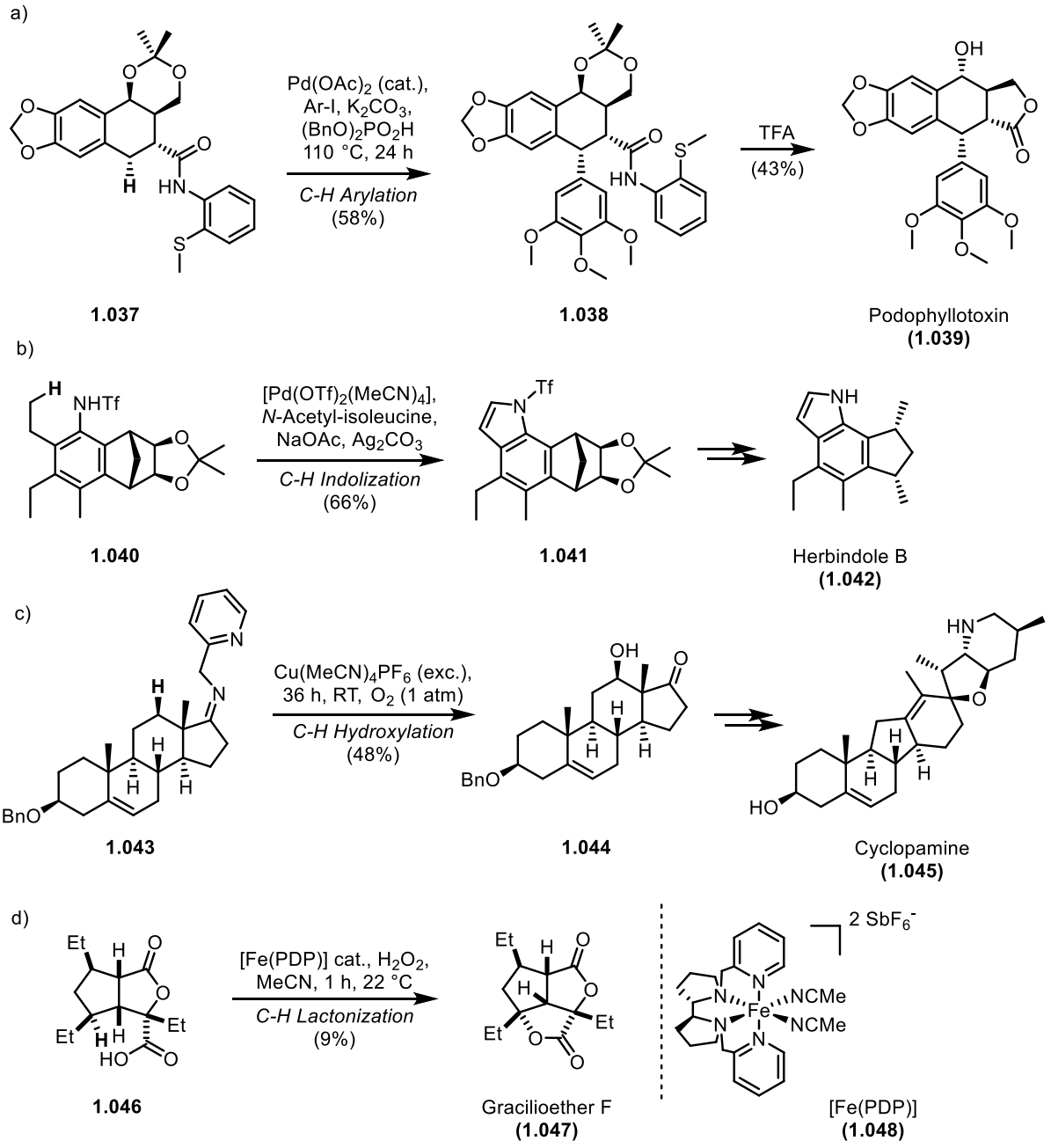


Figure 17. Selected examples for C–H functionalization in total synthesis using different directing groups

1.2 TOTAL SYNTHESIS OF QUININE AND ANALOGUES

1.2.1 Introduction

Quinine **1.101** is a cinchona alkaloid and can be isolated together with its pseudo enantiomer Quinidine **1.102** from the bark of cinchona trees. Figure 18 shows **1.101** and **1.102** together with their C-9 epimers epi-Quinine **1.103** and epi-Quinidine **1.104**. All contain a saturated quinuclidine, an unsaturated quinoline heterocycle and a total of five stereogenic centers. Quinine has become useful due to its antipyretic and antiinflammatory properties but gained fame for its potent antimalarial activity, since it has been the first effective treatment of the disease.[47] Besides their medicinal relevance, the cinchona alkaloids have been extensively used in organic synthesis as privileged chiral backbones in a plethora of organocatalysts or ligands for asymmetric induction.[48] Despite its apparent structural simplicity, Quinine has been a desirable synthetic target of many research groups for more than one century.[49]

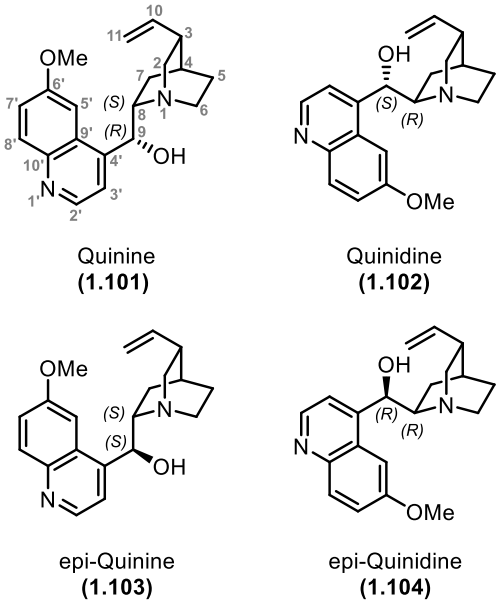


Figure 18. Quinine and its pseudoenantiomer Quinidine and their C-9 epimers

Although considerable efforts towards the synthesis of this alkaloid have been made, a fully stereo-controlled synthesis has not been reported before 2001. In the following section, a brief summary of the former Quinine syntheses will be given with focus on the construction of the quinuclidine skeleton.

1.2.2 Non-Stereoselective Syntheses of Quinine

Figure 19 shows an overview of the first synthetic sequence to Quinine, which was established by several partial syntheses.[50] In 1918, Rabe and Kindler succeeded in converting quinotoxine **1.107**, itself a degradation product of Quinine, back to the original structure of the natural product. The quinuclidine moiety was constructed by *N*-bromination of quinotoxine **1.107** with NaOBr to afford **1.108**. Subsequent ring closure by treatment with NaOEt afforded a mixture of Quininone **1.109** and its C-8 epimer Quinidinone. Reduction of **1.109** with aluminium powder afforded Quinine in a mixture together with quinidine **1.102** but also their corresponding C9 epimers, namely epi-Quinine **1.103** and epi-Quinidine **1.104**. (Figure 18) More than two decades later, Prelog and Prostenik reported the conversion of Homomeroquinene **1.106**, which is itself a degradation product of Quinotoxine **1.107**, back to the original structure of Quinotoxine. These reports are the basis for the first formal total synthesis of Quinine by Woodward and Doering, who achieved the synthesis of Homomeroquinene **1.106** from 3-hydroxybenzaldehyde **1.105**. [51,52]

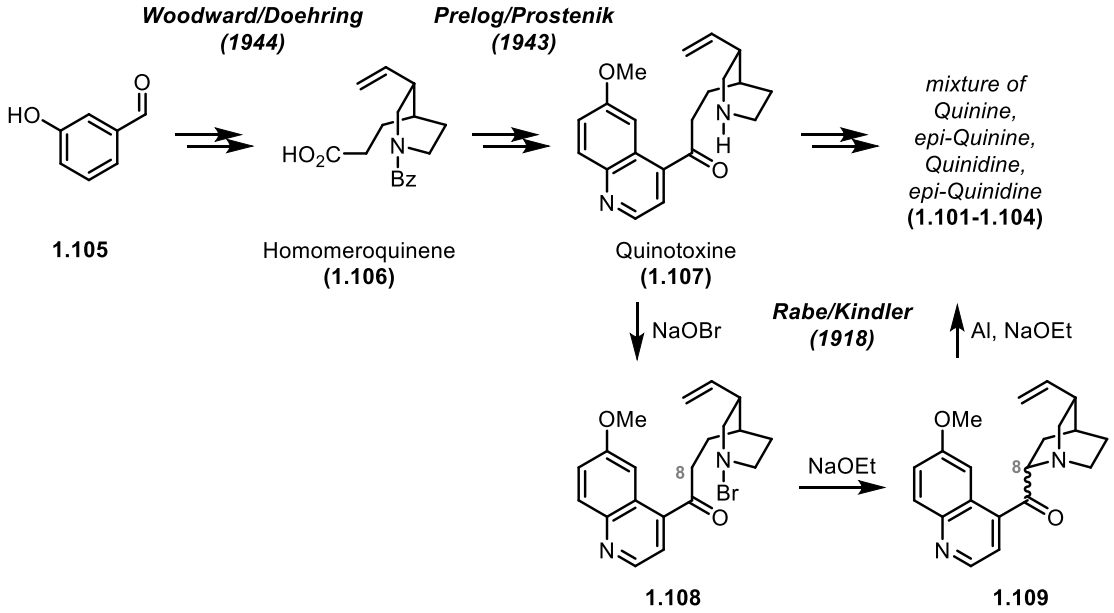


Figure 19. First complete synthetic sequence to Quinine by Woodward, Prelog and Rabe.

In 1970, Uskokovic and coworkers reported the synthesis of Quinine using a similar route for the construction of the quinuclidine moiety as described before *via* a C8-N1 disconnection.[53] As shown in Figure 20, meroquinene methyl ester **1.110** was treated with lithiated 6-methoxylepidine **1.111** to afford ketone **1.112**. Reduction and subsequent acetylation of the corresponding alcohol afforded

1.113, which allowed base-mediated elimination and formation of a vinylquinoline intermediate **1.114**. Direct cyclization of the latter afforded the quinuclidine moiety in desoxyquinine **1.115**, which was obtained as a mixture with C-8 epimeric desoxyquinidine. The last step is the base-catalyzed hydroxylation using KO^{t}Bu and an oxygen atmosphere to afford the desired mixture of the aminoalcohols Quinine and Quinidine. The hydroxylation proceeded with noticeable diastereoselectivity for the desired configuration as present in Quinine or Quinidine respectively. Attributed to electronic repulsion by the lone pair of the quinuclidine nitrogen, attack of the oxygen radical anion to the benzylic radical intermediate at C-9 in **1.115** occurs preferentially from the opposite side.

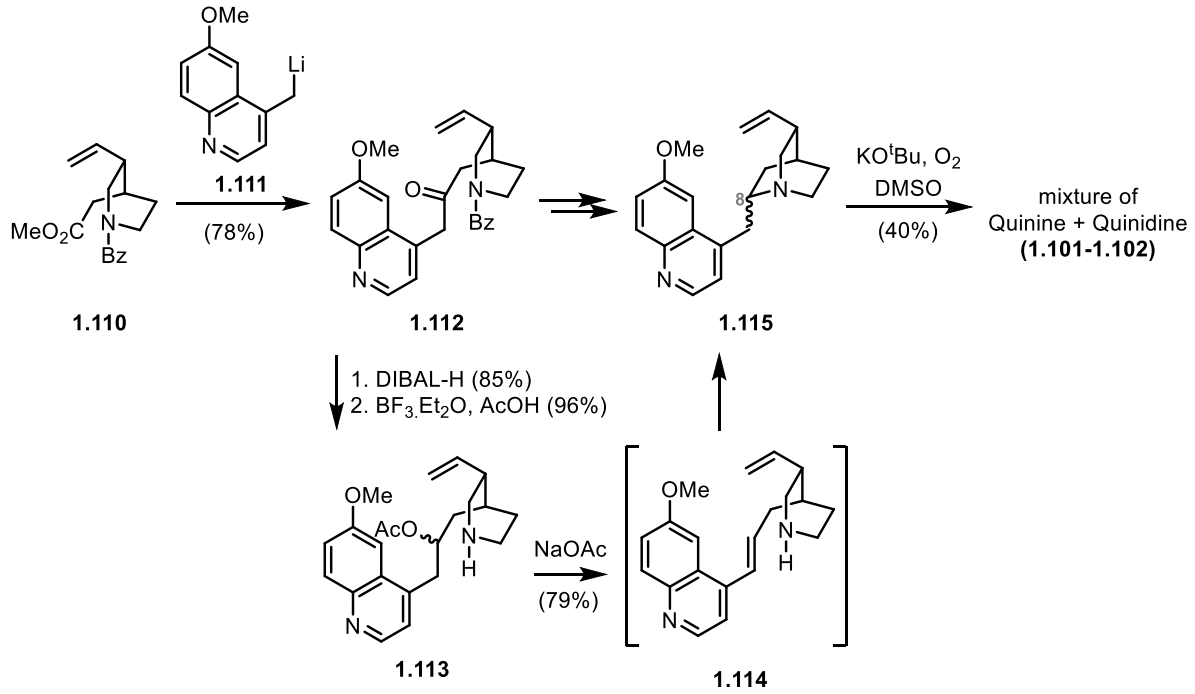


Figure 20. First approach for the synthesis of Quinine by Uskokovic and coworkers.

In the same publication, Uskokovic and coworkers reported another approach to the quinuclidine moiety, as shown in Figure 21a. However, this alternative remains non-stereoselective. Benzylic bromination of **1.112** with NBS and subsequent reduction with $NaBH_4$ afforded the C8-C9 epoxide as mixture of diastereomers. Reductive *N*-debenzoylation with DIBAL-H afforded epoxypiperidine **1.116**, which underwent the desired cyclization upon refluxing. Unfortunately, a mixture of all four possible diastereomers was obtained. In 1973, the same group reported another variant of C8-N1 bond formation (Figure 21b).[54] Cyclization of *N*-Chloro-quinotoxine **1.117** upon protonation with phosphoric acid afforded a mixture of Quininone **1.109** and Quinidinone. The reaction is believed to

proceed *via* formation of a α-chloroketone intermediate, which then undergoes nucleophilic displacement. It is important to note that the isolated ketones are configurationally unstable and prone to rapid epimerization to the corresponding epimer at C-8. Final reduction of the mixture containing **1.109** with DIBAL-H however proceeded quantitatively in high yield and diastereoselectivity, resulting in a mixture of quinine and quinidine. The stereoselectivity of this reduction is believed to originate in coordination of the Lewis-acidic DIBAL-H to the quinuclidine nitrogen prior to the reduction step. Five years later, another approach by Uskokovic was published for the construction of the quinuclidine moiety in **1.101** as shown in Figure 21c.[55] Treatment of dichlorohydrin **1.118** with $Ba(OH)_2$ led to the formation of a chloroepoxide, which directly underwent nucleophilic displacement to generate Quininone **1.109** again as a mixture with its C8 epimer Quinidinone. Final reduction of the mixture with DIBAL-H was utilized again yielding a mixture of quinine and quinidine. Another, but fundamentally completely distinct approach by Uskokovic *et al.* was reported in the same year (Figure 21d). The method utilizes a new C9-C4' disconnection *via* the addition of the lithiated quinoline **1.119** to a preformed quinuclidine building block.[56] **1.119** was prepared by a lithium-bromide exchange. Addition to an epimeric mixture of aldehyde **1.120** led to the formation of all 4 possible isomers. Since this approach again failed to give any stereoselectivity, addition to the corresponding ester **1.121** led to the formation of the corresponding ketones. As described before, the ketones were reduced with DIBAL-H to give a mixture of Quinine and Quinidine.

Despite all the synthetic efforts as described above, the stereospecific construction of the C-8 stereogenic center, and therefore a stereoselective synthesis of Quinine, remained elusive for the time being.

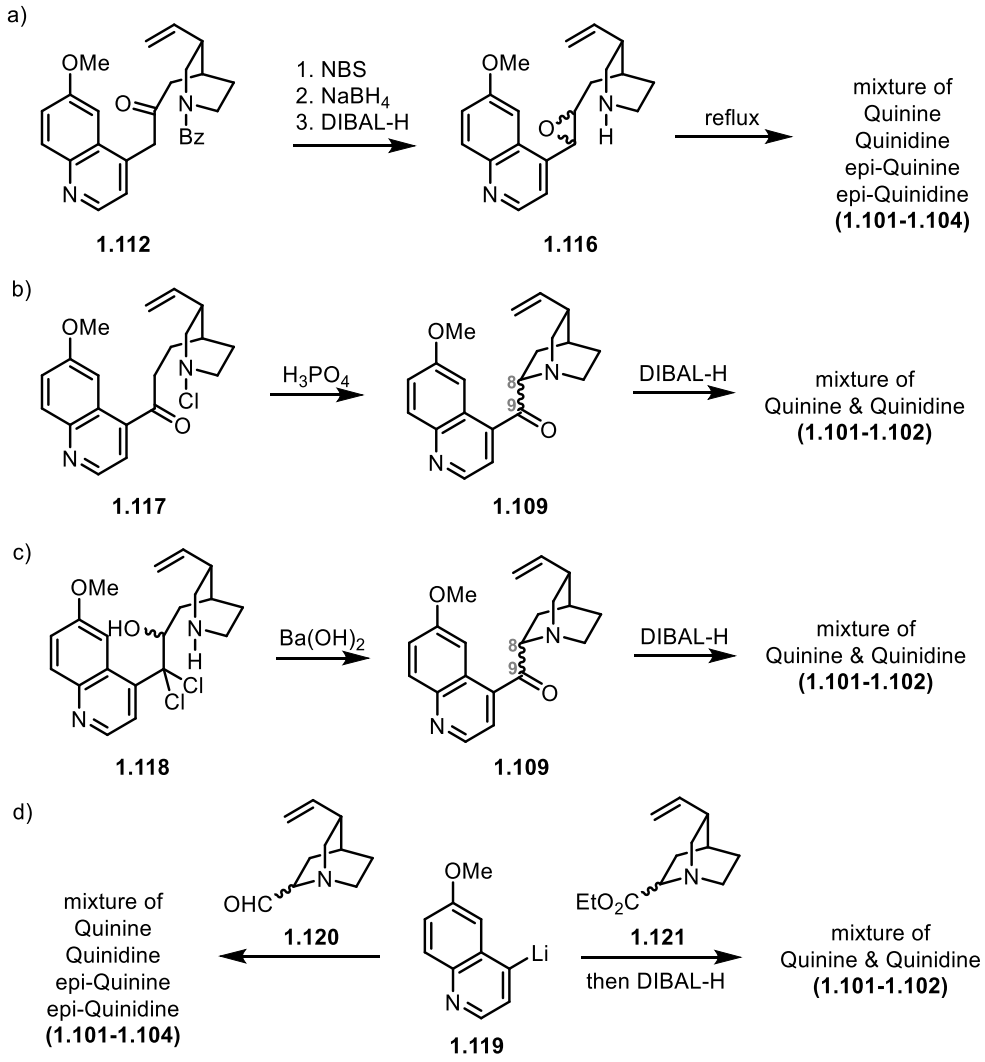


Figure 21. Additional non-stereoselective approaches to Quinine developed by Uskokovic and coworkers

1.2.3 Stereoselective Synthesis of Quinine

In 2001, the group of Stork published the first stereoselective synthesis of Quinine.[57] The chemists understood that the common C8-N1 disconnection for the construction of the quinuclidine moiety was best avoided, as it failed to provide any stereocontrol in previous syntheses. Instead, a novel C6-N1 disconnection was sought, again utilizing a substituted piperidine precursor. As shown in Figure 22, the required trisubstituted piperidine **1.125** was constructed by attachment of the quinoline moiety *via* the addition of lithiated 6-methoxylepidine **1.111** to aldehyde **1.122**, a reaction which has already been utilized by Uskokovic in his first synthesis of Quinine (*vide supra*). Functional group manipulations afforded tetrahydropyridine **1.124**, which was reduced by $NaBH_4$ to give the desired trisubstituted piperidine **1.125**. Stereoselectivity in this reaction arises from the presence of all substituents in equatorial position, when considering the product **1.125** in a chair-like conformation. C6-N1 bond formation was accomplished by nucleophilic substitution of a mesylate, affording desoxyquinine **1.115**. Utilizing a procedure adapted from the Uskokovic synthesis (*vide supra*), base-promoted hydroxylation reaction under oxygen atmosphere afforded Quinine in a diastereomeric ratio of 14:1.

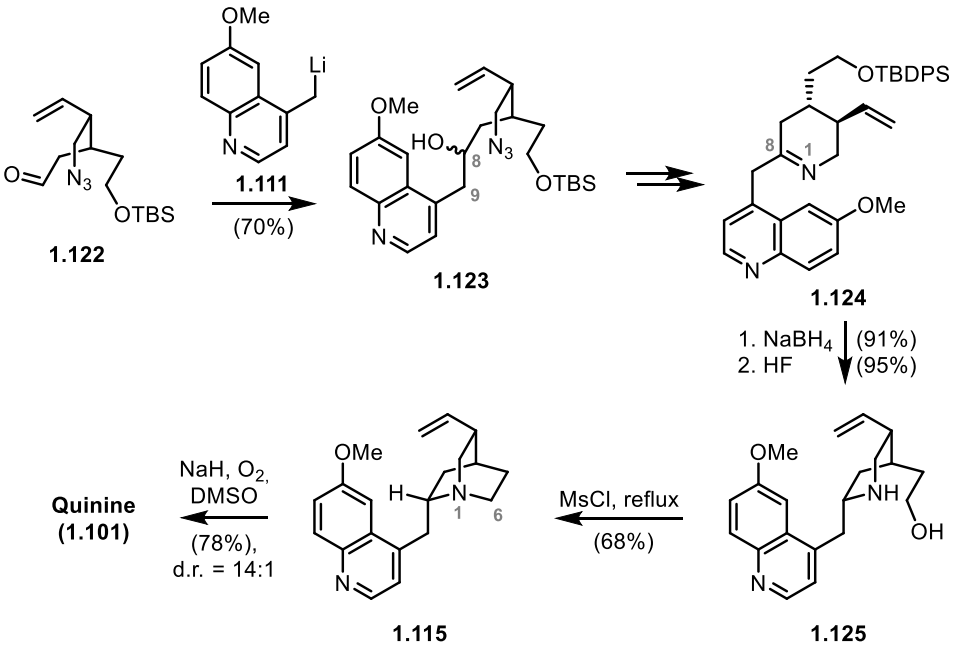


Figure 22. Construction of the quinuclidine by a C6-N1 disconnection in the first stereoselective synthesisof Quinine by Stork

In the following years, several other research groups published stereoselective syntheses of Quinine. Interestingly, all reported syntheses after Stork´s work turned back to the C8-N1 disconnection, as utilized in the earlier Quinine syntheses. In addition, all syntheses have been completed based on the

same epoxide intermediate for the construction of the quinuclidine moiety, as shown in Figure 23. The groups of Jacobsen [58] and Kobayashi [59] reported their stereoselective syntheses of Quinine and Quinidine in 2004. Inspired by the amino alcohol formation *via* epoxide ring opening, as reported by Uskokovic and coworkers (*vide supra*), a diastereoselective epoxidation and subsequent nucleophilic ring opening by the piperidine nitrogen was envisaged. While attempts at a direct asymmetric epoxidation of a vinylquinoline of general structure **1.126** led to unsuccessful results, a multistep sequence was realized utilizing Sharpless asymmetric dihydroxylation. It is ironic that this reaction itself is facilitated by dimeric cinchona alkaloid ligands. The dihydroquinine-derived ligand $(DHQ)_2PHAL$, as present in AD-mix-α, allows the formation of the epoxide precursor **1.127** for the synthesis of Quinidine. Use of the dihydroquinidine-derived ligand $(DHQD)_2PHAL$, as present in AD-mix-β, on the other hand led to the formation of the synthetic precursor **1.128** of Quinine. Deprotection of the piperidine nitrogen and subsequent heating afforded the desired alkaloids. In 2011, the group of Hatakeyama published another stereoselective synthesis of Quinine but again utilizing the dihydroxylation approach from their predecessors in 2004, as shown in Figure 23.[60]

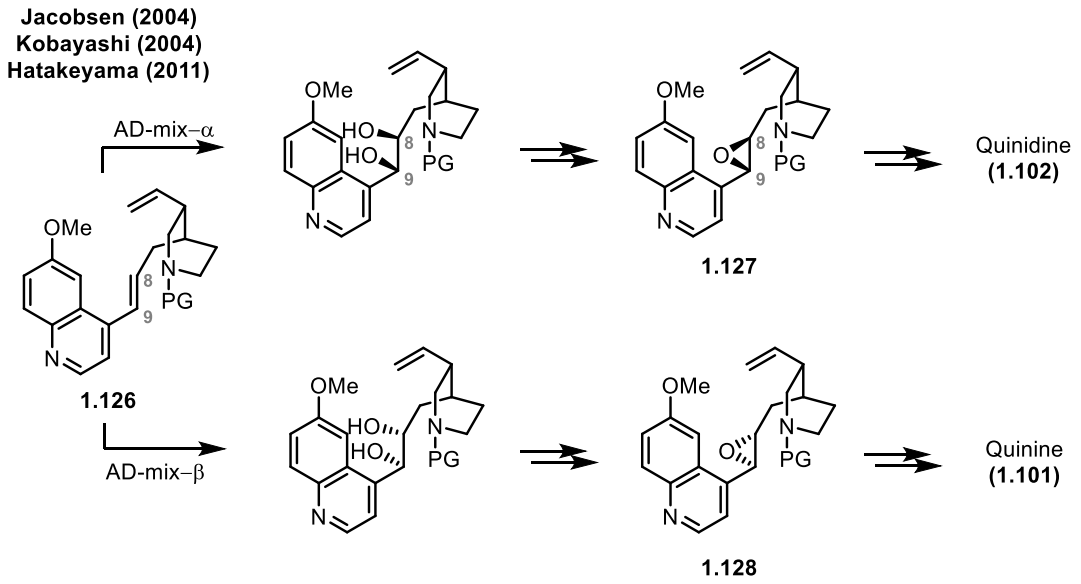


Figure 23. Consistent construction of the Quinuclidine moiety by C8-N1 disconnection in previous stereoselective synthesis of Quinine or Quinidine via synthesis of enantiopure epoxide precursors

In 2010, Aggarwal and coworkers applied their methodology for asymmetric epoxidation in a formal synthesis of Quinine.[61] (Figure 24) Addition of the enantiomerically pure sulfonium ylides (generated by deprotonation of **1.129** or **1.130**) to aldehyde precursor **1.131** led to the formation of

diastereomeric epoxides **1.132** or **1.133** respectively. Deprotection, cyclization and subsequent oxidation of the dihydroquinoline moiety led to the formation of Quinine or Quinidine respectively. However, it should be noted that Aggarwal and co-workers obtained their starting materials by degradation of quinine.

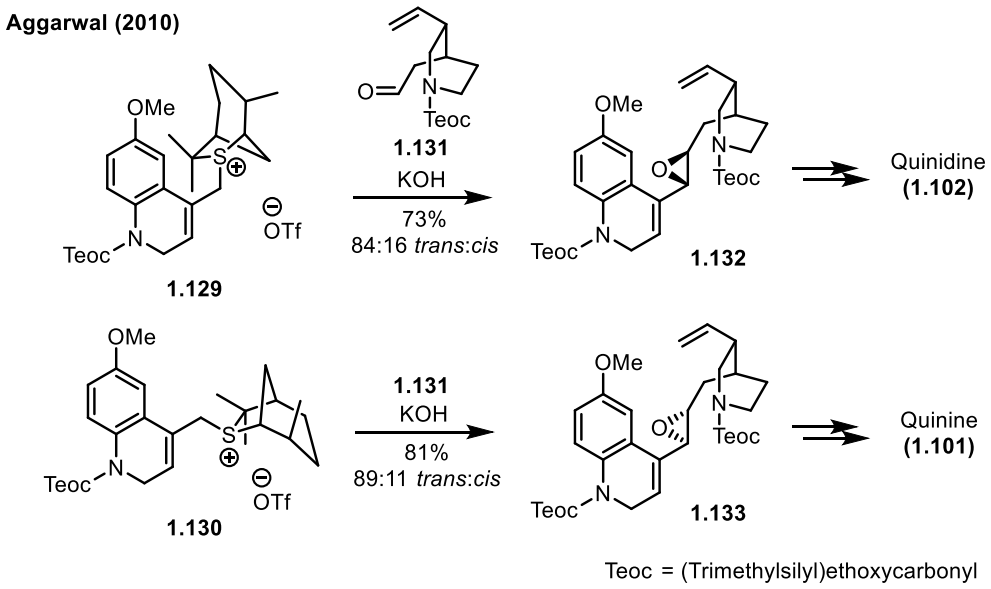


Figure 24. Synthesis of Quinine and Quinidine by asymmetric epoxidation as reported by Aggarwal et al.

1.2.4 An alternative strategy to quinine by a quinuclidinone percursor

In 1985, Stotter *et al.* reported model studies towards the total synthesis of Quinine.[62] Until that time, a general solution for the stereoselective construction of the C8 stereocenter in Quinine has not been found. Stotter envisaged a fundamentally completely different approach to this synthetic problem. As shown in Figure 25, utilization of a quinuclidinone as starting material in an Aldol addition with a lepidine aldehyde **1.135** was envisaged to proceed with high diastereoselectivity. Additionally, a suitable substituent, e.g. the vinyl group at C-3 in the specific case of **1.134**, might force the electrophile to approach from the opposite face, yielding the correct configuration at C-8 and C-9 as present in the Quinine scaffold. Deoxygenation of **1.136** would complete the plan.

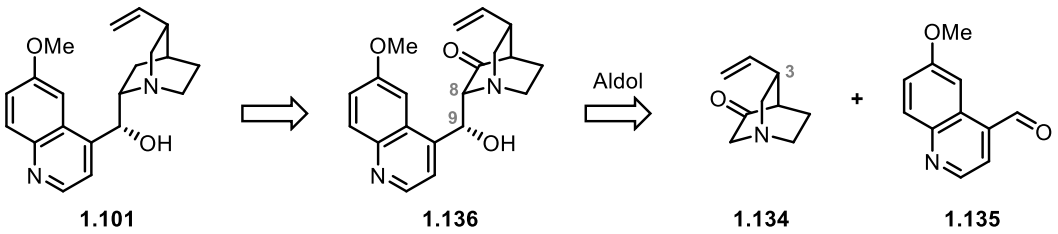


Figure 25. Stotter´s approach for the fully stereoselective construction of Quinine

In order to validate this approach, model studies without substitution at C-3 have been performed (Figure 26). In the event, subsequent treatment of unsubstituted quinuclidinone **1.137** with lithium diisopropylamide (LDA) and benzaldehyde yielded indeed the desired hydroxyketone **1.138** in high yield and diastereoselectivity. Unfortunately, that ketol was also found to be prone to rapid epimerization at C-8 (Quinine numbering) when kept in solution. In order to avoid this undesired erosion of diastereomeric excess, subsequent reduction of the carbonyl group in **1.138** and deoxygenation of diol **1.141** was attempted. While reduction of intermediate **1.139** with $NaBH_4$ or $LiAlH_4$ afforded an epimeric mixture of **1.141** at C-7, sodium bis(2-methoxyethoxy)aluminum dihydride (Red-Al) was found to perform the reduction step with high diastereoselectivity to afford diol **1.141** in 76% yield as single isomer, probably proceeding *via* adduct **1.140**. Although deoxygenation of C-7-OH should lead to the desired aminoalcohol **1.145** regardless of its configuration, only the shown isomer **1.141** was amenable to the following deoxygenation sequence. Selective acetylation of the less hindered benzylic alcohol yielded monoacetate **1.142**, which was then converted to xanthate **1.143**. Subjection of the latter to Barton-McCombie deoxygenation conditions afforded **1.144**. Deprotection with methyllithium finally gave the desired aminoalcohol **1.145** as single isomer in 5 steps from ketone **1.137**.

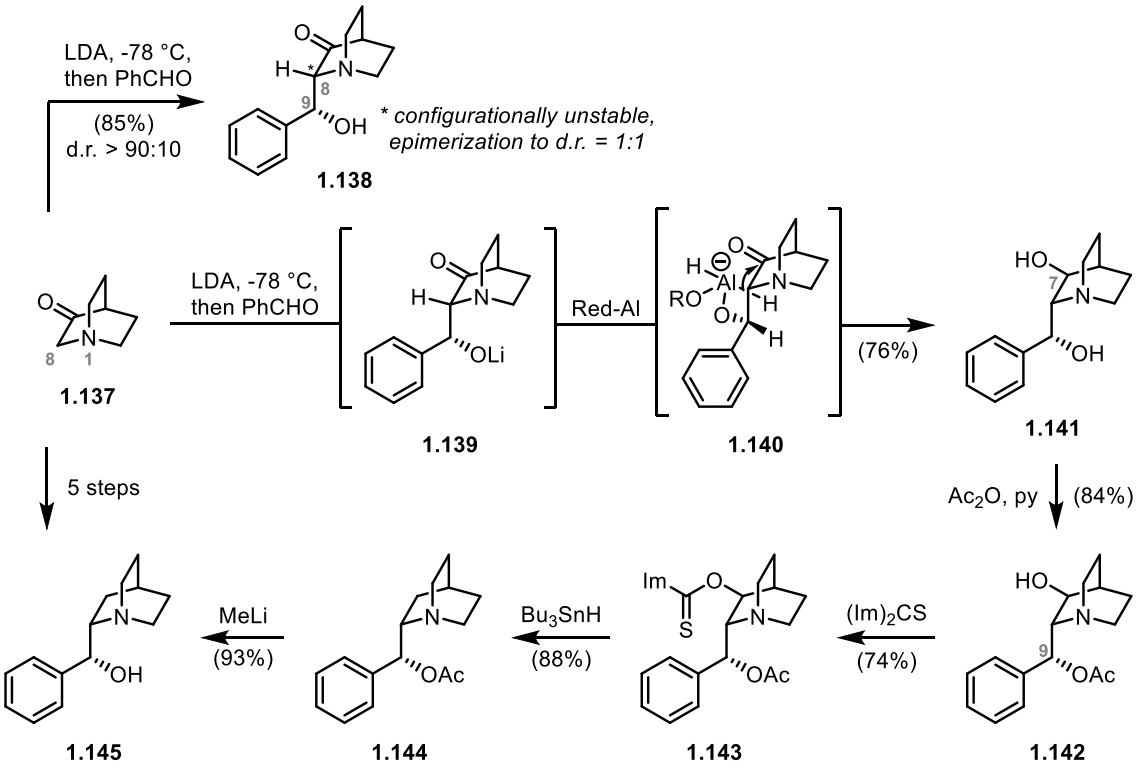


Figure 26. Stotter´s solution for the epimerization problem by subsequent deoxygenation

Although the fully stereoselective construction of substituted quinuclidine **1.145** was indeed achieved, application of this promising but lenghty C-8/C-9 disconnection to a total synthesis of Quinine was not successful. The authors further stated that application of lepidine aldehyde **1.135** (as required for Quinine) to this reaction sequence failed for several reasons.

In 2008, Krische and coworkers reported the synthesis of a 7-Hydroxyquinine analogue. [63] In accordance to previous stereoselective syntheses of Quinine, construction of the quinuclidine moiety was again envisaged by a diastereoselective epoxidation / cyclization sequence. In contrast to previous work, direct epoxidation of the allylic alcohol **1.146** *via* oxovanadium catalysis proceeded successfully to afford oxirane **1.147** in high yield and diastereoselectivity. Cyclization proceeded as expected to afford the desired 7-Hydroxyquinine **1.148**. However, the required deoxygenation of C-7-OH was met with failure despite extensive investigations. Important to note is that the diol was generally found to be resistant also towards a variety of electrophiles such as neat Ac_2O or AcCl, thwarting the total synthesis of Quinine by such an approach.

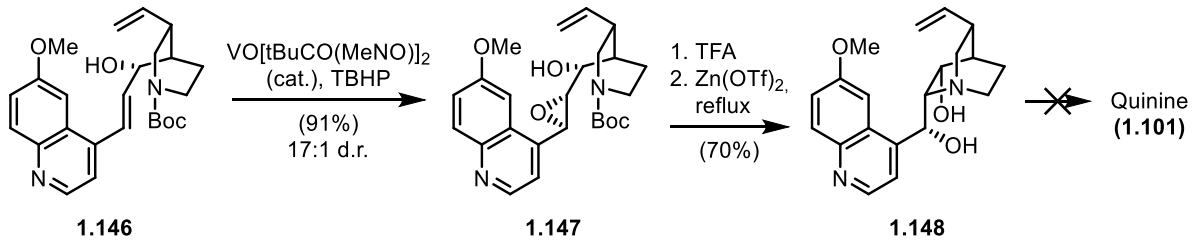


Figure 27. Synthesis of 7-Hydroxyquinine and unsuccessful deoxygenation by Krische et al.

1.2.5 Total synthesis of Quinine by C–H Activation

1.2.5.1 Objectives of this work

The formerly presented successful Quinine syntheses demonstrate clearly a unified trend in the prior total synthesis of the alkaloid. All prior reports focused on stereoselective synthesis by cyclization of a substituted piperidine precursor and the construction of the quinuclidine motif at a very late stage in the synthesis. However, these approaches proved to be challenging endeavors and required numerous steps for the establishment of the stereogenic center at C-8. (Figure 28a) With the rise of directed C–H activation methodology within the last decades, the tools for organic synthesis and therefore the possibilities for retrosynthetic disconnection in complex molecules have drastically increased. In this project, we envisaged a fundamentally distinct approach to Quinine as shown in Figure 28b. Inspired by the highly diastereoselective studies described before by Stotter *et al.*, functional group addition (FGA) to Quinine would give ketone **1.152**. Aldol addition should enable diastereoselective C8-C9 bond formation to afford lepidine aldehyde **1.135** and C-3 vinylated quinuclidinone intermediate **1.151**. The tools for its construction should be provided by C–H functionalization methodologies. Functional group interconversion (FGI) of ketone **1.151** to an enantiopure aminoquinuclidine **1.150** should permit directed regioselective C–H activation at C-3, yielding unsubstituted enantiopure 3-aminoquinuclidine **1.149** as commercially available precursor.

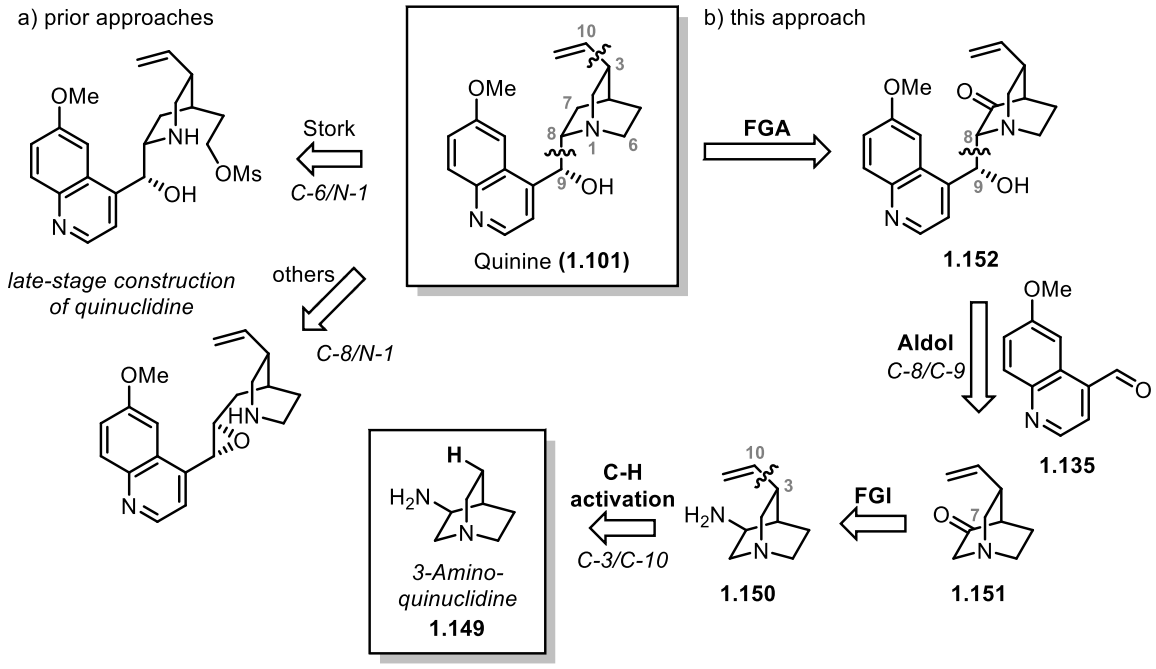


Figure 28. Summary of previous approaches to Quinine and retrosynthetic analysis of our approach

The total synthesis of Quinine was accomplished in collaboration with Daniel H. O´Donovan, Paul Aillard, Aurélien de la Torre, Desislava Petkova, Christian Knittl-Frank and Danny Geerdink. Biological testing has been coordinated by Marcel Kaiser at the Swiss Tropical and Public Health Institute (Switzerland). Complementary information can be found in the doctoral thesis of Desislava Petkova. [64] Substantial parts of the work as described herein have already been published.[65]

1.2.5.2 C–H Arylation of 3-Aminoquinuclidine

Based on Daugulis' pioneering work, the bidentate picolinic amide directing group was chosen as most promising for C–H activation in the aminoquinuclidine skeleton. 1,1'-Carbonyldiimidazole (CDI) proved to be particularly efficient for the coupling of 3-aminoquinuclidine dihydrochloride **1.153** and picolinic acid **1.154** to afford the desired amide **1.155** in 85% yield and in high purity without the need for column chromatography (Figure 29). Other coupling agents such as HATU afforded similar results but complicated the isolation of pure product due to the presence of numerous reaction byproducts. With the substrate **1.155** in hand, a direct C–H vinylation using $Pd(OAc)_2$ as most prominent C–H activation catalyst and vinyl iodide as coupling partner was attempted but did not yield the desired product **1.156**. Further experimentation indeed revealed picolinic amide **1.155** as an extraordinarily challenging substrate for this reaction class. A plethora of further C–H functionalization reactions, such as C–H alkenylation using styrene halides to yield alkenes **1.157** or C–H alkylation to yield saturated derivatives **1.158**, did not afford any of the desired C-3 functionalized products. Either no conversion or decomposition of the starting material was obtained. Figure 29 only shows a very general overview of numerous attempted C–H functionalization reactions.

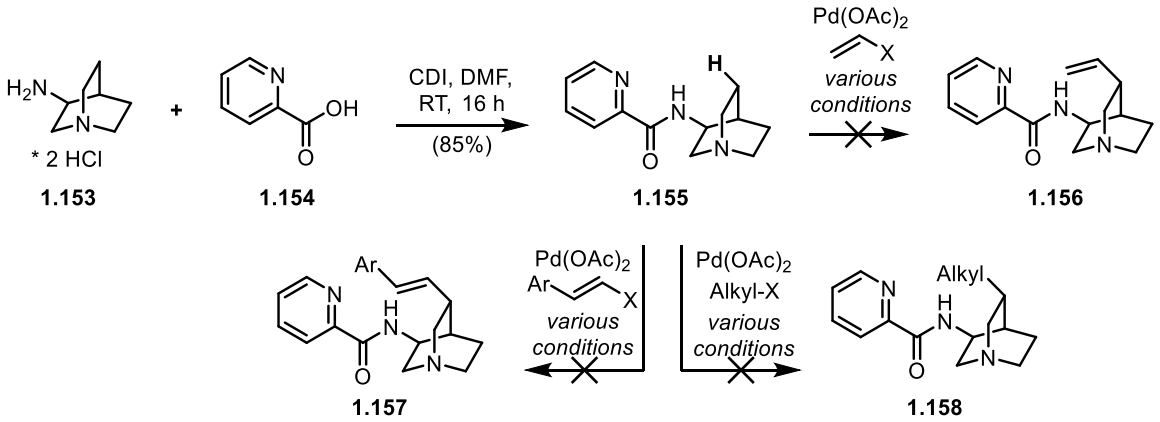


Figure 29. Initial attempts for C–H functionalization of the aminoquinuclidine skeleton

In contrast to the attempted C–H functionalization reactions as shown above, C–H arylation in **1.155** was found to be successful on this substrate almost from the very first attempts. Presumably following a Pd(II)/Pd(IV) cycle as described before, the reaction proceeded with high regioselectivity (Figure 30), indicating the formation of a five-membered palladacycle intermediate. In the presence of silver carbonate and pivalic acid as additive, the desired anisole product **1.159a** was obtained in 85% yield. Although direct vinylation was not successful, the synthesis of Quinine could nevertheless be achieved by an aryl-to-vinyl conversion, unfortunately resulting in a number of additional steps. However, such a sequence could be realized by oxidative degradation of the aryl moiety in **1.159a** leading to aldehyde **1.160**. Olefination of **1.160** could ultimately give the desired C-3 vinylated amide **1.161**. If a sequence for the conversion of **1.161** to Quinine were to be found, the arylated quinuclidine precursors could further be used as precursors for the synthesis of biologically interesting C-3 aryl-analogues of the natural product. In the case of quinuclidine **1.159a**, the synthesis of e.g. C-3 anisole analogue **1.162a** would be feasible.

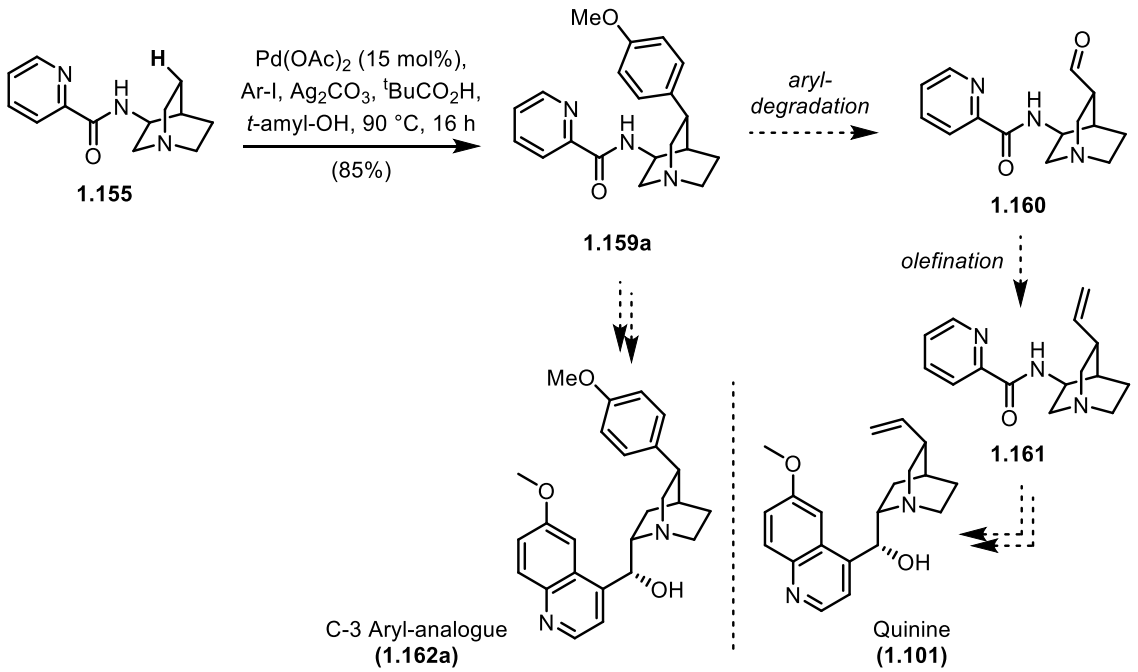


Figure 30. C–H Arylation of aminoquinuclidinone and revised strategy for the synthesis of Quinine by Aryl to Vinyl conversion

However, due to the poor solubility of the substrate **1.155** in *tert*-amylalcohol, further optimization of the initial conditions was attempted. The use of DMF as superior solvent was found to be compatible with the reaction conditions and additionally provided **1.159a** in 94% yield (Figure 31a). Further experimentation revealed this C–H arylation reaction to be a very general reaction on the quinuclidine

scaffold. To investigate the limitations of the method, a number of racemic arylated quinuclidines **1.159a-j** have been synthesized. The broad tolerance to various electron-rich and also electron-poor aryl iodide coupling partners was demonstrated. All products were obtained in generally moderate to very good yields with exception of structurally elaborate steroid derivative **1.159j**, which was obtained in only 26% yield. All aryl iodides, as used for the synthesis of quinuclidines **1.159a-i**, are commercially available. The preparation of the aryl iodide, as required for the synthesis of **1.159j**, is shown in Figure 31b. **1.164** was achieved from commercially available estradiol **1.163.**[66]

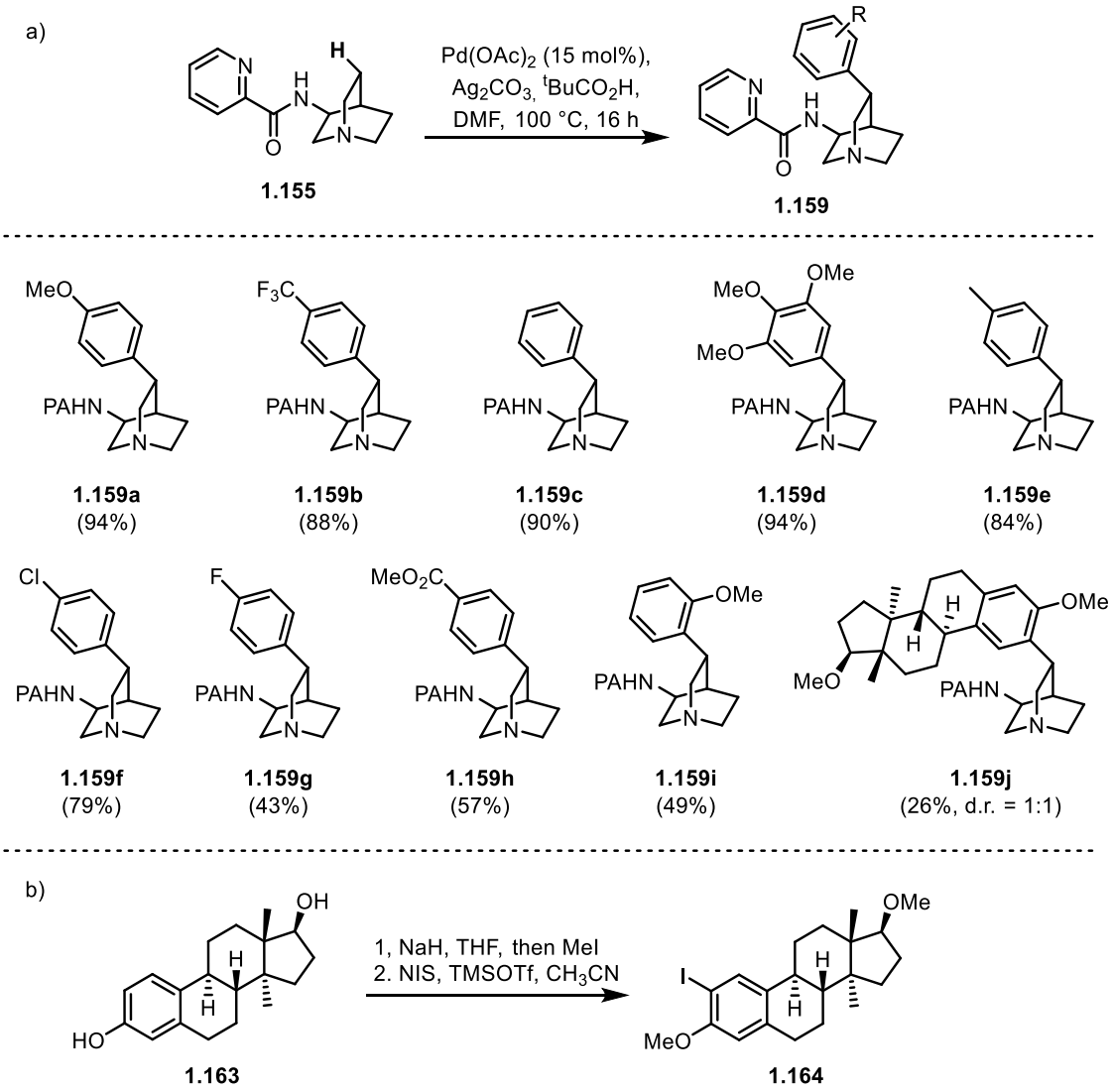


Figure 31. Synthesis of various C-3 arylated quinuclidines (a) and preparation of the estradiol coupling partner (b)

1.2.5.3 Aryl-to-Vinyl conversion

The RuO_4-mediated oxidative degradation of aryl moieties appears sparsely in the literature. In general, substrates for this reaction are preferentially electron-rich phenyl rings, usually bearing methoxysubstituents.[67,68] Common conditions for RuO_4-mediated oxidations entail an excess of $NaIO_4$ as co-oxidant and the reactions are performed in a biphasic mixture containing acetonitrile.[69] Degradation of the anisole moiety in **1.159a** using 40 mol% of $RuCl_3$ and 24 equivalents of $NaIO_4$ as co-oxidant proceeded well to afford the desired carboxylic acid, as shown in Figure 32. However, due to its zwitterionic character, isolation of **1.165** proved to be quite challenging. The preferential partition of the charged zwitterion in the aqueous layer allowed removal of non-polar impurities such as ruthenium salts by simple extraction with dichloromethane. Separation of inorganic periodate salts from the product was found feasible by use of the strong cation exchange resin Dowex 50WX8. Upon protonation of the zwitterion, **1.165** was absorbed as ammonium salt on the resin. Repeated washing of the resin with water was then performed in order to remove undesired inorganic impurities. The product was finally eluted with aqueous ammonia to afford **1.165** in 80% yield, which was used without further purification.

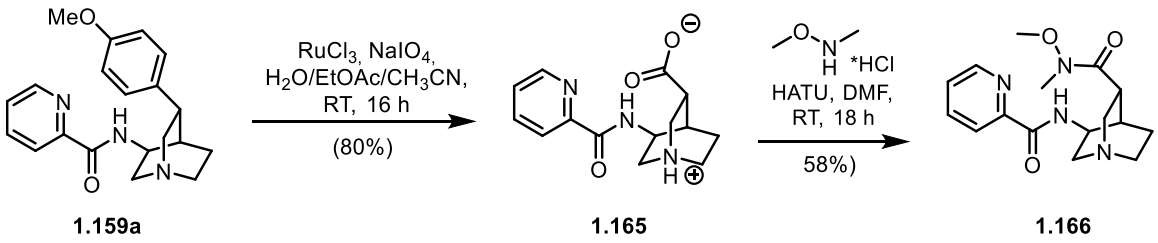


Figure 32. Oxidative degradation of the anisole moiety and Weinreb amide synthesis

In order to generate the desired aldehyde functionality, reduction of the corresponding Weinreb amide **1.166** was envisaged as reliable method. The poor solubility of **1.165** even in warm DMF required extensive mechanical dispersion. Consumption of eventually non-dissolved material however proceeded slowly upon subjecting **1.165** to the reaction conditions and stirring for 16 hours. Formation of Weinreb amide **1.166** proceeded smoothly using HATU as coupling agent in 58% yield (Table 1, entry 4). It should be mentioned that the yield of this reaction strongly depended on the purity of **1.165**. Ideally, pure **1.165** appears as dark red solid. Amide coupling as mediated by CDI instead led to a poor yield of **1.166** (Table 1, entry 1). As shown in entry 2, use of DMAP as additive did not yield any of the desired material. *In situ* generation of an acid chloride also met with failure.

Treatment of **1.165** as a suspension in DCM with oxalyl chloride and a catalytic amount of DMF simply led to sudden decomposition of material. (Table 1, entry 3)

Table 1. Selected attempted conditions for the formation of Weinreb amide 1.166.

entry	reagents	solvents	temperature	time	yield
1	CDI, imidazole hydrochloride	DMF	RT	1 day	24%
2	CDI, DMAP	DMF	RT	1 day	0%
3	$(COCl)_2$, Et_3N, DMF (1 drop)	DCM	0 °C	-	decomposition
4	**HATU, Et_3N**	**DMF**	**RT**	**2 days**	**58%**

As shown in Figure 33, reduction of the Weinreb amide **1.166** was found successful with DIBAL-H in dichloromethane (DCM) at -78 °C in 72% yield. In general, chlorinated solvents were found to be excellent solvents for polar quinuclidines such as **1.166**. However, care must be taken due to nucleophilic attack of the highly reactive quinuclidine nitrogen to solvents such as DCM or $CHCl_3$. If the compounds are stored in these solvents or if the solvents are not completely removed from the purified products, considerable loss of material due to quarternization of the amine is observed. The expected aldehyde **1.160** spontaneously cyclized to the hemiaminal **1.167** which could be isolated as a single stereoisomer in 72% yield. The spontaneous cyclization of **1.160** to **1.167** is of great benefit in this synthesis, since it locks the configuration at the C-3 position and prevents potential epimerization to the sterically relieved and synthetically less useful isomer **1.168**. The tendency of aldehyde **1.160** to undergo epimerization is supported by our results employing an alternative C–H acetoxylation sequence, as described in the next section. The prevention of such epimerization further demonstrates the importance of the picolinic amide moiety to this synthesis beyond its function as directing- and protecting-group. Fortunately, hemiaminal formation did not prevent the desired Wittig olefination to proceed. *In situ* ylide formation by deprotonation of phosphonium salt Ph_3PMeBr with lithium hexamethyldisilazide (LHMDS) in THF and DMSO as co-solvent followed by addition to **1.167** afforded vinylated quinuclidine **1.161** in 84% as single stereoisomer.

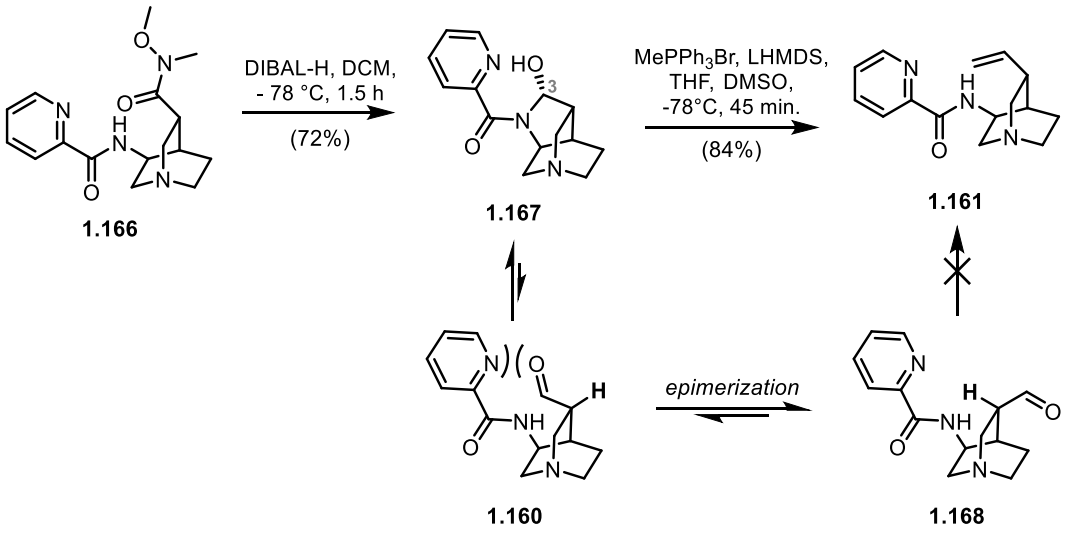


Figure 33. Reduction of Weinreb amide and Wittig reaction on the resulting masked aldehyde

Since the direct vinylation of the quinuclidine skeleton by C–H activation could not be achieved and the alternative sequence required a total of five steps as described above, a shorter synthetic sequence was highly desired. One such hypothetical reaction pathway could proceed *via* the direct conversion of an aryl moiety to an aldehyde by ozonolysis and subsequent reductive work-up. As shown in Figure 34, literature precedence for such transformations exist. An illustrative example can be found in the total synthesis of Coronafacic Acid **1.170** by the group of Jung (Figure 34a).[70] Oxidative degradation of the phenyl ring in **1.169** followed by oxidative work-up with hydrogen peroxide presumably yielded the corresponding lactone, which was subjected to saponification and esterification with diazomethane to afford methyl ester **1.170** in 40% overall yield. Another example for the direct conversion of an arene to an aldehyde is shown in Figure 34b. Ozonolysis of **1.171** and reductive quench with dimethylsulfide directly led to the formation of the desired aldehyde **1.172** in 47% yield.[71] Application of such protocol to our substrate **1.159a** would directly lead to hemiaminal **1.167** and would significantly shorten the previously developed reaction sequence.

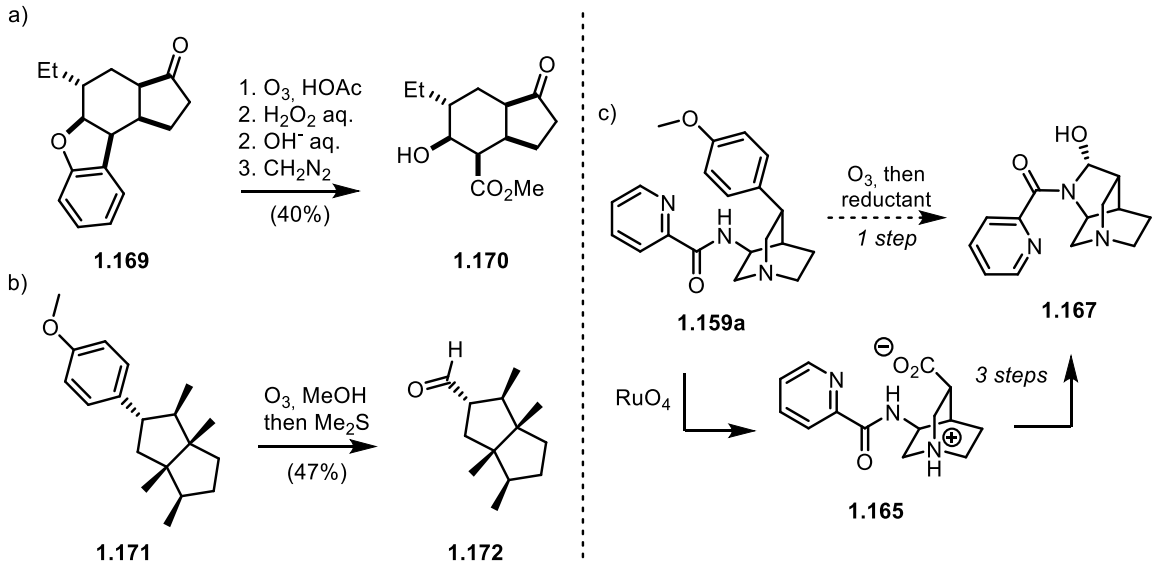


Figure 34. Examples for aryl degradation by ozonolysis (a,b) and hypothetical ozonolysis of our substrate (c)

As shown in Figure 35, ozonolysis of **1.159a** was attempted in DCM at -78 °C. The completeness of the reaction was simply determined by appearance of the blue color of unconsumed ozone. As expected, ozonolysis of anisole **1.159a** appeared to proceed much slower (> 1 hour) when compared to trimethoxylated **1.159d** (approximately 10 minutes). While MeOH as solvent afforded a very complex reaction mixture, use of DCM led to a significantly cleaner transformation and formation of a pale precipitate. However, upon filtration, the analysis of this solid proved to be quite problematic. Although NMR data clearly indicated the successful removal of the C-3 aryl substituent, the hypothetical hemiaminal product **1.167** did not appear in the reaction mixture. Mass spectroscopy analysis showed that the main products obtained are overoxidation products such as *N*-oxides **1.173** or **1.174** or mixtures thereof. This would be in accordance with the literature, since the readiness of the quinuclidine nitrogen to undergo oxidation by ozone to its *N*-oxide, even with preservation of the vinyl group, has already been reported.[72] Upon filtration of the bright solid, the tendency to quick decomposition of the obtained products thwarted any further identification or purification attempts.

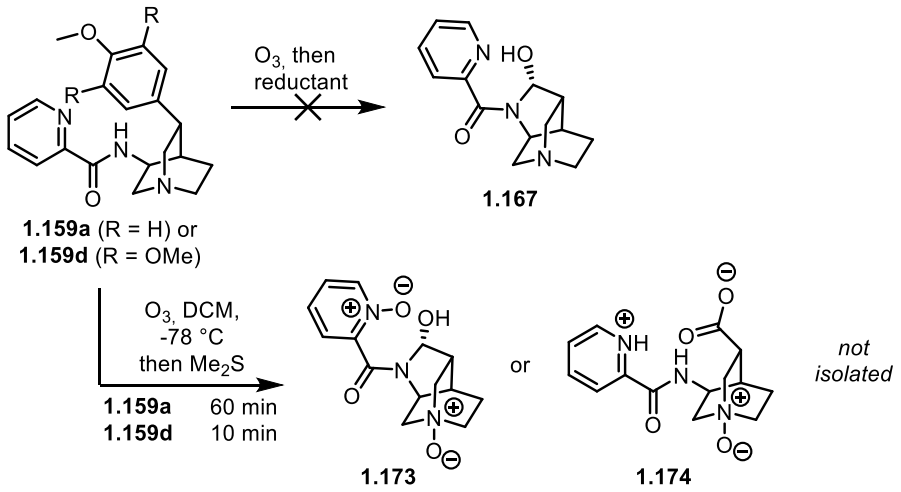


Figure 35. Hypothetical hemiaminal product (top) and probably obtained N-oxides (bottom) as obtained from ozonolysis

However, since the desired fragmentation of the aryl moiety in **1.159a** or **1.159d** seemed successful, further extensive experimentation was conducted in order to avoid this overoxidation problem. Direct subjection of the crude product gum, as obtained directly after filtration from the ozonolysis reaction mixture, to various reducing agents failed in our hands to give any stable and isolable compound in meaningful yields (Figure 36a). As obvious alternative, prior *N*-mono- or *N*-bis-protection of **1.159d** was attempted, unfortunately resulting in poorly soluble adducts and unsuccessful ozonolysis attempts of inhomogeneous mixtures (Figure 36b). This route was not further pursued.

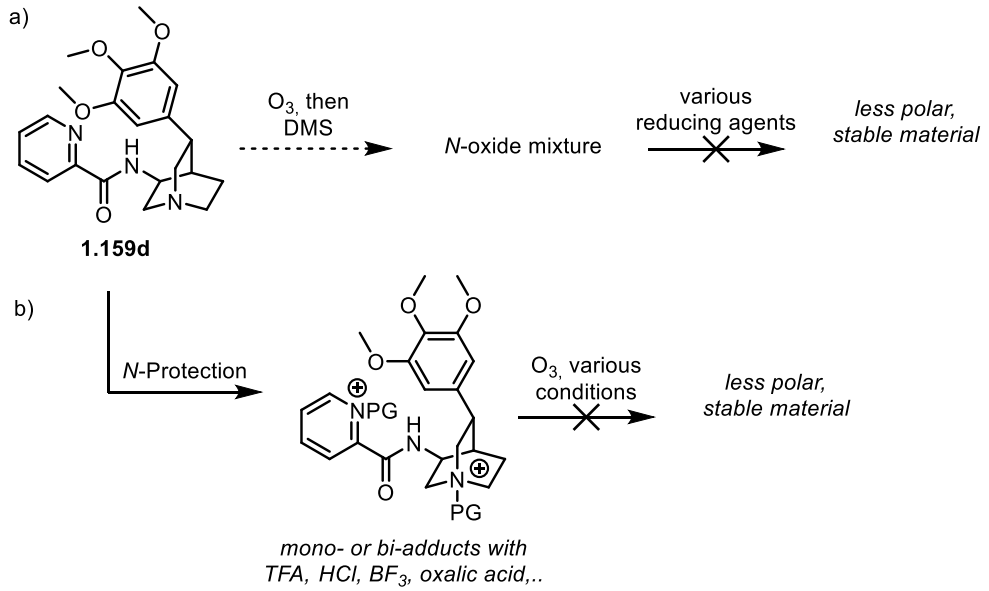


Figure 36. Alternative strategies to solve (a) or avoid (b) the overoxidation problem

1.2.5.4 Alternative route featuring C–H acetoxylation

As already mentioned before, only the C–H arylation of the quinuclidine skeleton was found successful. However, in order to reduce the number of steps, continuous efforts were made in search of alternative sequences to a desired vinylated quinuclidine intermediate. In 2014, the group of Chen reported a picolinic amide-directed acetoxylation of aliphatic C–H bonds.[73] C–H acetoxylation of methyl groups in substrates such as **1.175** was successful to give the desired products such as **1.176** (Figure 37). A crucial step in the optimization of this reaction was the addition of catalytic amounts of alkali salts, which proved essential for the suppression of 4-membered azetidine products such as **1.177** by intramolecular C-N bond formation. It was further stated that C–H acetoxylation of methylene groups generally failed to give the desired products, with norbornane derivative **1.178** as the sole exception. C–H acetoxylation proceeded in 89% yield to yield **1.179** as single isomer.

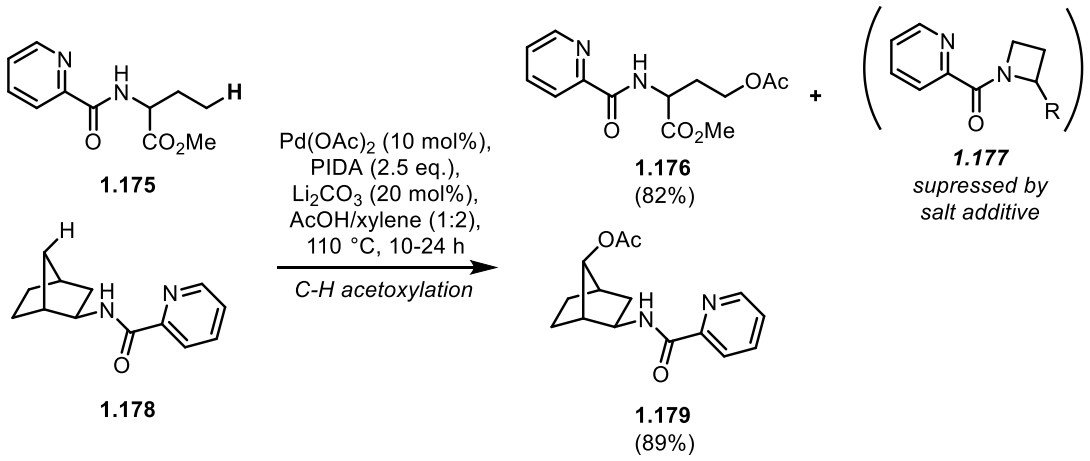
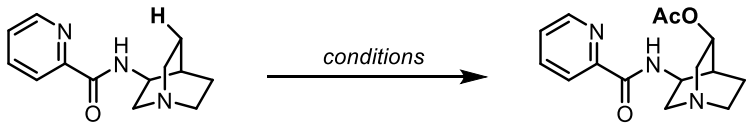


Figure 37. Picolinic acid directed C–H activation of aliphatic C–H bonds, as reported by the group of Chen

In accordance to Chen´s observation of the unsuccessful C–H acetoxylation reaction of methylene groups, subjection of our substrate **1.155** to analogous conditions only led to traces of product, as determined by HRMS. Even stoichiometric amounts of catalyst did not yield any of the desired product (Table 2, entry 1). In order to avoid the formation of a positively charged substrate formed upon protonation, further attempts without the presence of AcOH have been made. (Table 2, entries 2-5). The use of toluene as sole solvent finally afforded the desired product in 13% isolated yield, but with a required catalyst loading of 50 mol% (Table 2, entry 4). Unexpectedly, the product was obtained as mixture of isomers in a 70:30 ratio. Since decomposition of the palladium catalyst obviously hampered the reaction, iterative addition and prolonged reaction time were probed but did not change the

reaction outcome (Table 2, entry 5). Although AcOH was initially thought to hinder the reaction, addition of 5 equivalents of AcOH was found beneficial and increased the yield to 22% yield with a catalyst loading of 50 mol% (Table 2, entry 6).

Table 2. Optimization of C–H acetoxylation of aminoquinuclidine derivative 1.155



1.155 **1.180**

entry	$Pd(OAc)_2$	oxidant	solvent	additive	T (°C)	time	yield/comment
1	10-100 mol%	PIDA (2.5 eq.)	AcOH/xylene (1:2)	Li_2CO_3 (20 mol%)	90-110 °C	48-72 h	traces
2	50 mol%	PIDA (2.5 eq.)	DMF	-	100 °C	16 h	- / messy
3	30 mol%	PIFA (2.5 eq.)	toluene	-	100 °C	24 h	- / no conversion
4	50 mol%	PIDA (2.5 eq.)	toluene	-	100 °C	16 h	13% / d.r. = 70:30
5	2 x 30 mol%	PIDA (2.5 eq.)	toluene	-	100 °C	48 h	13% / d.r. = 70:30
6	**50 mol%**	**PIDA (2.5 eq.)**	**toluene**	**AcOH (5 eq.)**	**100 °C**	**48 h**	**22% / d.r. = 71:29**

As shown in Figure 38, 2D-NMR studies of the isolated product **1.180** revealed an unexpected reaction outcome. As already mentioned before, **1.180** was obtained as a mixture of 2 inseparable diastereomers. The expected product **1.180a** was found much to our surprise to be only the minor component, while the main product was determined to be its C-3 epimer **1.180b**. While **1.180a** clearly originates from reductive elimination of a Pd(IV)-complex, the formation of **1.180b** must be mechanistically distinct. In fact, the group of Sanford already proposed in their very first studies an alternative pathway for C-O bond formation by an S_N2-like nucleophilic substitution at the Pd(IV) species by an external acetate nucleophile.[23] However, such invertive C–H acetoxylation pathway has not been reported to the best of our knowledge and surely is attributable to the harsh conditions employed. Since cyclopalladation of **1.155** is known to proceed from our own results in successful C–

H arylation (*vide supra*), such behavior might be interpreted as deriving from an inability of the palladacycle intermediate to readily undergo reductive elimination.

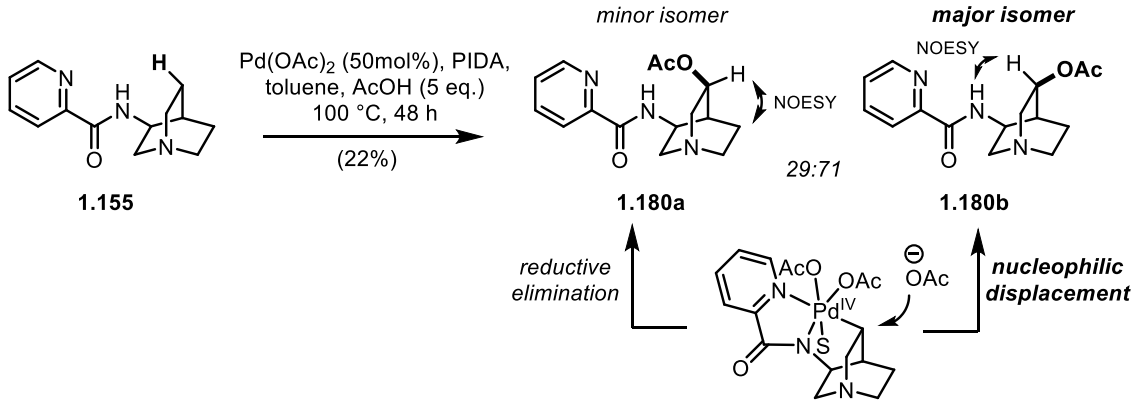


Figure 38. Unusual result as obtained from C–H acetoxylation of quinuclidine under harsh conditions.

With **1.180** in hand, a non-optimized route for its conversion to the hemiaminal **1.167**, a key intermediate in our own synthesis, was developed (Figure 39). Deacetylation of **1.180** with potassium carbonate in methanol afforded alcohol **1.181** again as an inseparable mixture of diastereomers with a ratio of 74:26. Oxidation of the alcohol with IBX in acetonitrile and simultaneous protection of the quinuclidine nitrogen with PTSA afforded the desired ketone **1.182**. Although sluggish at room temperature, the reaction proceeded upon heating to 60 °C to afford the product in 86% isolated yield. As can be seen, oxidation of **1.181** results in the loss of the C-3 stereogenic center and therefore renders the stereochemical outcome of the C–H acetoxylation reaction irrelevant. With synthetically useful ketone **1.182** in hand, Wittig homologation was realized to afford enol ether **1.183**. This reaction was found to be extraordinarily sluggish and a large excess of ylide (10 eq.) was required to obtain the product. When crude enol ether **1.183** was hydrolyzed by dilute aqueous hydrochloric acid, a clean transformation to hemiaminal **1.167** was observed, locking the stereogenic centers at C-3 and C-7 in an unfavorable 1,3-diaxial position by the hemiaminal. This observed diastereoconvergence further reinforces the role of the picolinic amide moiety as stereocontrolling element and its importance in avoiding C-3 epimerization in **1.167**, as already discussed in Figure 33.

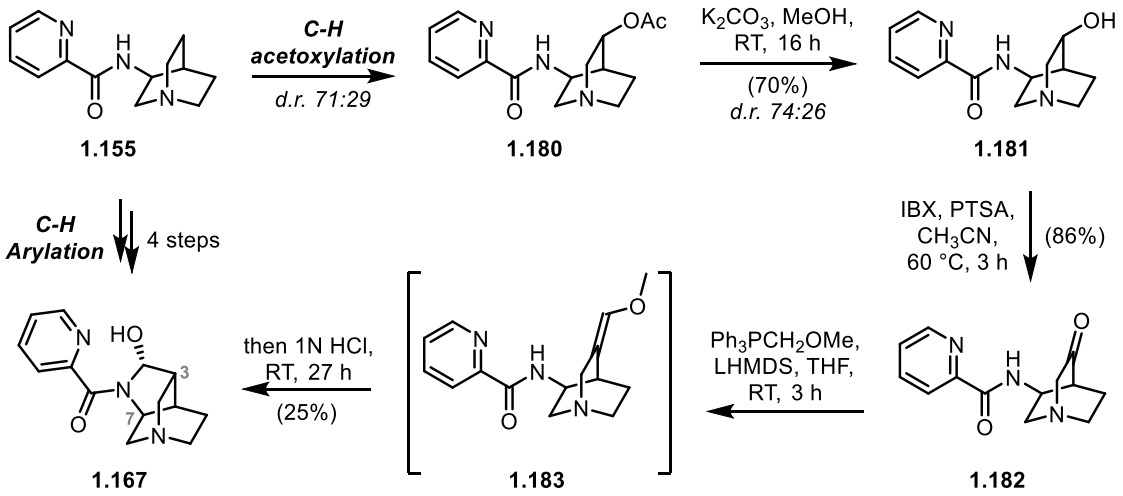


Figure 39. Alternative sequence to hemiaminal 1.167 enabled by C–H acetoxylation

The synthetic sequence as shown above is equally effective in terms of step count when compared to the C–H arylation sequence (*vide supra*). However, due to the low reactivity of **1.155** towards C–H acetoxylation, this approach was not further investigated or optimized.

1.2.5.5 Synthesis of quinuclidinone building blocks

The removal of the (meanwhile) redundant directing group in **1.161** was achieved by reductive cleavage of the amide functionality using zinc powder in hydrochloric acid.[74] As shown in Figure 40, addition of $Zn(OTf)_2$ was found to be beneficial to afford the desired amine. However, amine **1.150** appeared to be volatile and was found to be unstable, urging us to quickly convert it to ketone **1.151**

by oxidation. Initial attempts for the amine-to-ketone conversion were unfortunately met with resistance, as summarized in Figure 40.

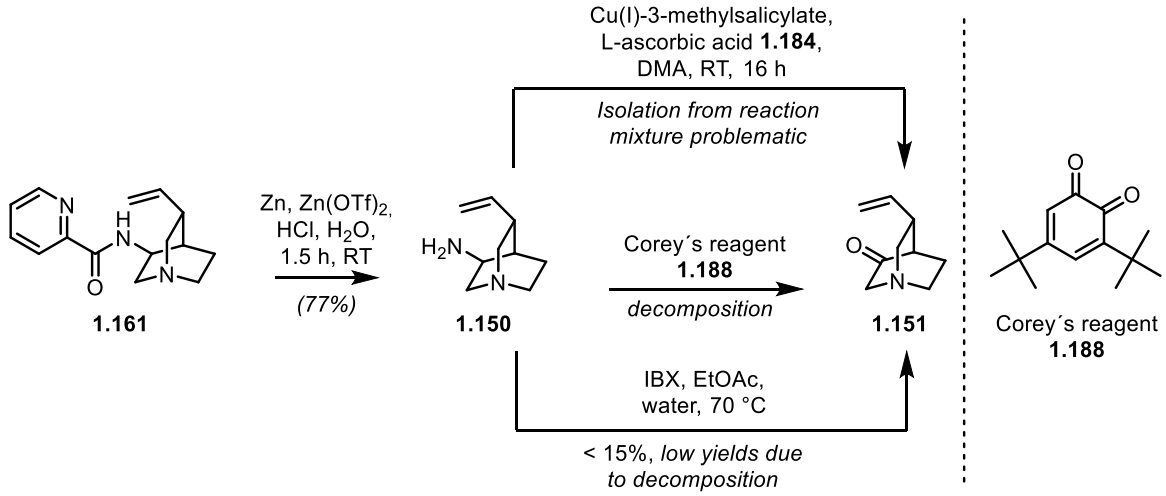


Figure 40. Initially investigated oxidants and resulting problems

While initial investigations towards the oxidation of **1.150** using Corey´s reagent **1.188** [75] mainly led to decomposed material, use of copper(I)-3-methylsalicylate and ascorbic acid **1.184** [76] was found to convert **1.150** to the desired ketone **1.151** (Figure 40, top). This is somehow surprising due to the fact that both reactions are proposed to proceed via an analogous mechanism, as outlined in Figure 41. The overall process is a transamination reaction from the amine starting material to the individual oxidant. After condensation of the amine with the effective oxidant dehydroascorbic acid **1.185** to form the corresponding Schiff base **1.186**, tautomerization (or prototropic shift) would result in the isomeric enol **1.187**, which would directly afford the desired ketone product upon hydrolysis.

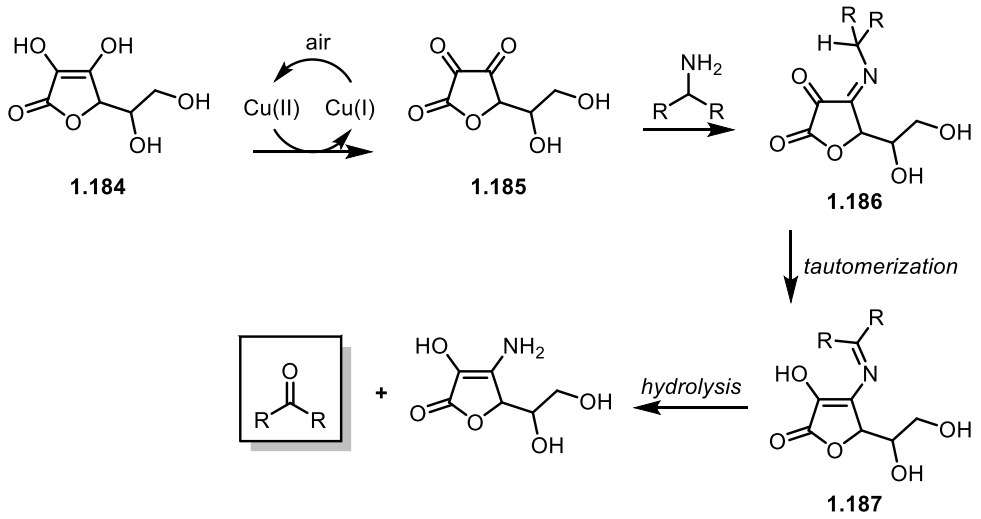


Figure 41. Proposed mechanism of the Cu(I)/ascorbic acid mediated oxidation of amines to ketones

Although the oxidation of **1.150** was found successful (Figure 40), the isolation of clean product **1.151** was unfortunately complicated by the inseparability of the product from the high boiling solvent dimethylacetamide (DMA). Replacement of DMA with other solvents such as DMF shut down the desired oxidation. In addition, the reaction was found to be unsuitable for upscale, as sufficient mixing by vigorous stirring under open air was absolutely essential for the reaction to proceed. Therefore, an alternative and more efficient oxidant was required. Oxidation with IBX yielded the desired ketone **1.151** as well, but only in very low yield and accompanied by considerable degradation of material. A possible explanation for the loss of material in the oxidation of **1.150** is shown in Figure 42. Upon condensation with the oxidation agent to yield an adduct similar to **1.188**, fragmentation of the quinuclidine moiety induced by donation of the lone-pair of the quinuclidine nitrogen could yield a highly reactive intermediate **1.189**, which is likely to undergo further reactions or decomposition. In order to prevent this C-C bond cleavage to proceed, protection of the lone pair of the quinuclidine nitrogen by protonation with para-toluenesulfonic acid (PTSA), as shown in structure **1.190**, was found to be essential to obtain ketone **1.151** in good yield.

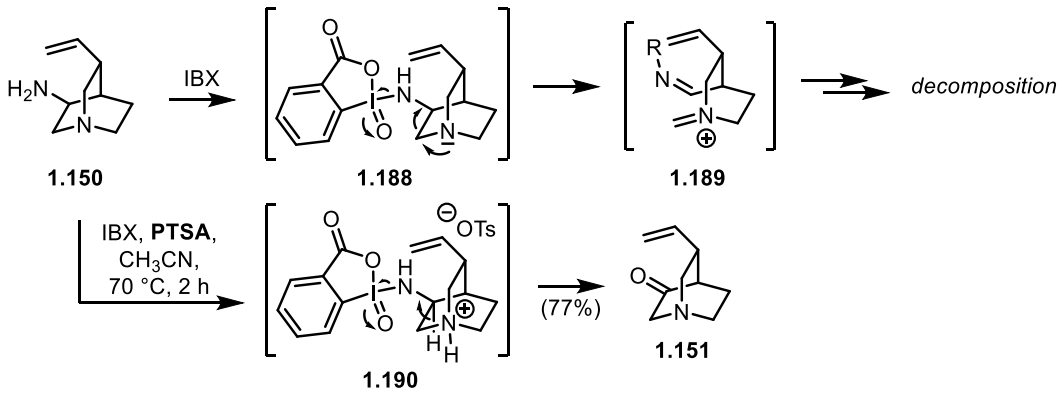


Figure 42. Proposed degradation of 1.150 by IBX and successful oxidation enabled by PTSA as additive

The possibility for modulation of the antimalarial activity of Quinine by modification of the C-3 vinyl group has already been demonstrated by Dinio and coworkers.[77] Considering the potential synthesis of novel C-3 arylated Quinine analogues, as suggested already in Figure 30, the arylated quinuclidine building blocks bearing an electron-rich *p*-OMe- (**1.192a**) and an electron withdrawing *p*-CF_3-substituent (**1.192b**) have been prepared, as shown in Figure 43. Since the preparation of the C-3 vinylated quinuclidinone **1.151** requires a total of eight steps, the arylated quinuclidinones **1.192** furthermore represent readily available material for model studies in the final steps of the synthesis. The oxidation of the amine precursors **1.191** has been successfully performed using the dehydroascorbic acid mediated oxidation conditions as described before, enabled by the superior chemical stability of the arylated ketones **1.192** when compared to vinylated **1.151**.

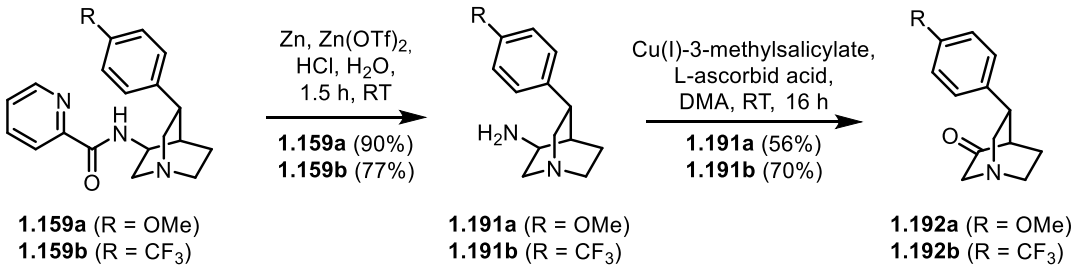


Figure 43. Synthesis of C-3 arylated quinuclidinone building blocks

1.2.5.6 Stereoselective assembly of quinuclidine and lepidine building blocks

In order to convert the quinuclidinone building blocks to the desired aminoalcohols, preparation of the lepidine aldehyde **1.135** was required, as shown in Figure 44. Although commercially available,

synthesis of its precursor 6-methoxy-lepidine **1.194** can be achieved for instance by a condensation reaction of aniline **1.193** with methyl vinyl ketone (Doebner-Miller quinoline synthesis).[78] Following a known procedure for the benzylic oxidation of **1.194** with selenium dioxide by the group of Williams, the desired aldehyde **1.135** can be prepared in 61% yield.[79]

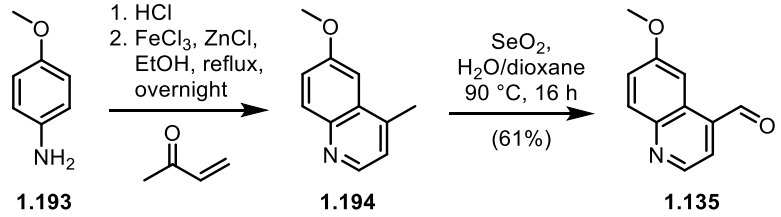


Figure 44.Synthesis of lepidine building block 1.135

The Aldol reaction of the lithium enolate of the arylated quinuclidinone **1.192a** and quinoline **1.135** proceeded smoothly and the desired ketol product **1.195** was isolated in 85% yield (Figure 45). Unfortunately and in accordance with the early model studies from Stotter *et al.* (see section 1.2.4),[62] the product was found to be a diastereomeric mixture with a ratio of 1.9:1 (^{1}H-NMR) as shown in Figure 46. This result can be attributed to epimerization at C-8, with **1.195** being the major isolated isomer. However, despite the configurational lability of **1.195**, this promising approach was found to deserve further investigation.

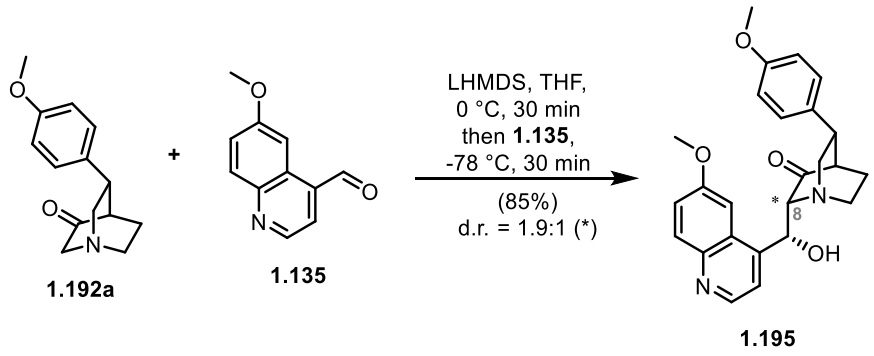


Figure 45. Aldol reaction with model substrate confirming the epimerization at C-8 position

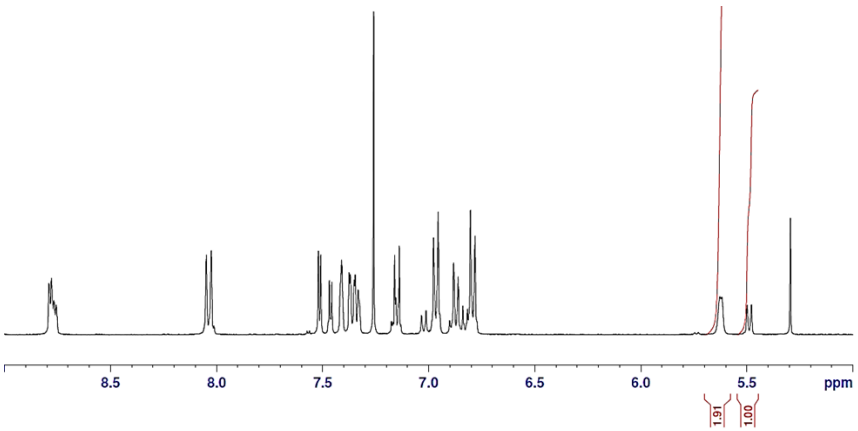


Figure 46. ^{1}H-NMR of Ketol 1.195 showing the mixture of isomers with benzylic C-9-H integrated

As described above, Stotter *et al.* prevented this undesired epimerization in their model studies by *in situ* reduction of the carbonyl functionality.[62] But when they used aldehyde **1.135** instead of benzaldehyde, the approach failed as stated for a variety of reasons. In order to probe the cause of their observations, the Red-Al reduction protocol was applied to our more elaborate substrates. However, *in situ* formation of ketol **1.195** according to Figure 45 and subsequent reduction yielded a very complex reaction mixture. Unfortunately, the desired diol **1.196** could not be detected. Instead, the aldol condensation product **1.197** was isolated in 21% yield (Figure 47).

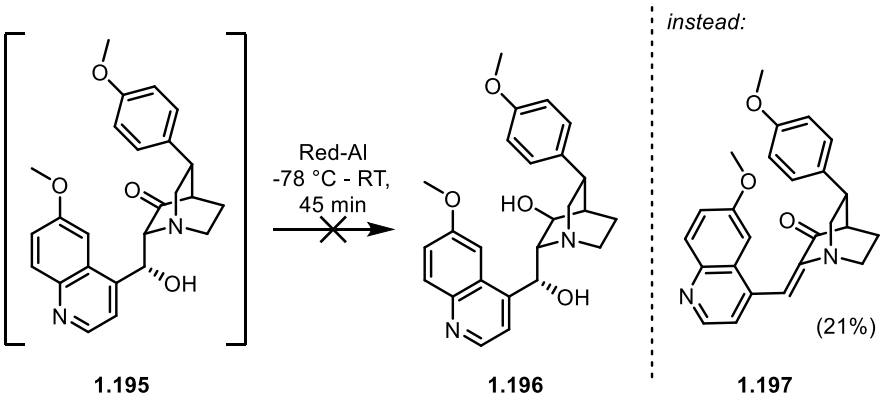


Figure 47. Attempted in situ reduction of ketol 1.195 to prevent epimerization

The isolated enone **1.197** can be interpreted as a result from unsuccessful reduction of the ketone in **1.195** by Red-Al. This might be due to the fact that both, quinuclidinone **1.192a** and the lepidine aldehyde **1.135**, are more sterically hindered building blocks in contrast to the simpler systems

investigated by Stotter.[62] In order to prevent this elimination to happen, *in situ* formation of a titanium alkoxide **1.198** to fix the benzylic alcohol in the substrate was attempted. At first, the reaction was investigated on ketol **1.198**, derived from unsubstituted quinuclidinone (Figure 48a). Despite the presence of the internal titanium lewis acid, reduction of the titaniumalkoxide **1.199** with $NaBH_4$ did not afford any of the desired product. Reduction with DIBAL-H on the other hand was found to yield the desired diol **1.200**, albeit in only 10% isolated yield. Reduction of the more sterically demanding **1.201** also led to the isolation of the desired diol **1.202** (Figure 48b). Unfortunately, the reaction was found to be sluggish and large amounts of inconvenient aluminium and titanium precipitates further complicated the isolation of the desired diol products from the reaction mixture.

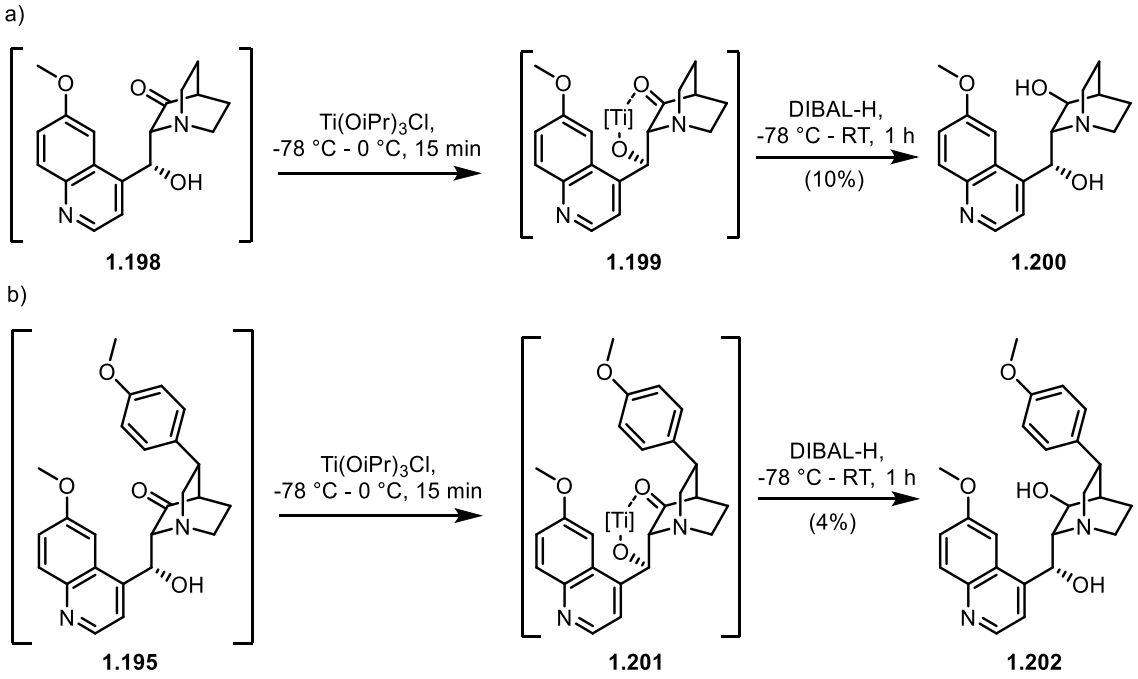


Figure 48. Prevention of the epimerization problem by reduction with DIBAL-H

As an alternative for the prevention of epimerization by reduction, conversion of *in situ* generated ketol **1.195** to the corresponding thioketal **1.203** was extensively investigated with various Lewis acids, but met with failure. Since classical methods were ineffective, chlorodithiaborolane **1.204** was prepared. **1.204**, described to be a very reactive reagent for the thioketalization of carbonyl compounds under mild conditions,[80] also failed on our substrate. Lawesson´s reagent **1.205** is a usually very reliable reagent for the conversion of ketones to the corresponding thioketones.[81]

However, treatment of **1.195** with Lawesson´s reagent did not result in the desired thioketone but yielded again enone **1.197** as the sole product in remarkable purity.

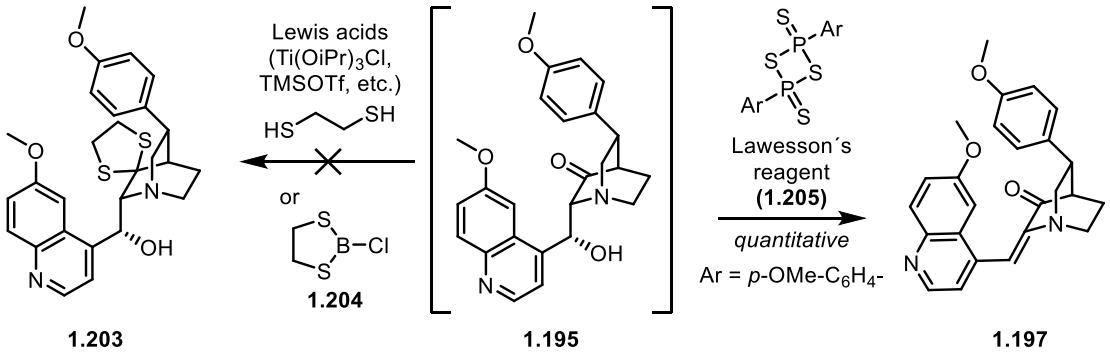


Figure 49. Unsuccessful attempts for thioketal or thioketone formation

It seems obvious that significant steric hindrance caused by the C-3 substituent and the quinoline moiety blocked the access to the ketone. A fundamentally different approach would be an alkylation reaction, as outlined in Figure 50. Due to the absence of the benzylic alcohol in the alkylation product, the system might gain flexibility and allow deoxygenation to afford **1.206**. Furthermore, this hypothetical intermediate could readily be oxidized at C-9 with high diastereoselectivity to afford the natural product, as already demonstrated by Uskokovic or Stork (*vide supra*).

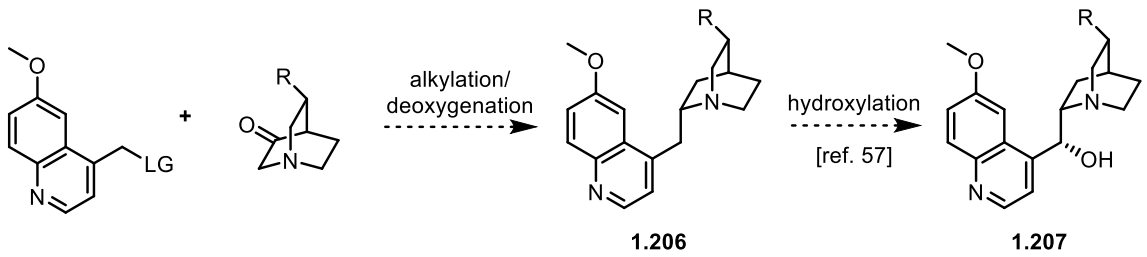


Figure 50. Alternative hypothetical quinuclidinone alkylation approach to Quinine

To confirm this theory, the synthesis of an appropriate (pseudo)halide coupling partner was required. As shown in Figure 51, reduction of aldehyde **1.135** with $NaBH_4$ afforded benzylic alcohol **1.208** in high yield.[61] While treatment of **1.208** with triflic anhydride did not afford the desired triflate **1.209** due to decomposition of the material, Appel reaction did proceed in nearly quantitative yield to give the

lepidine bromide **1.210**. This bromide was found to be particularly unstable and darkened upon exposure to air. Therefore, **1.210** was prepared fresh before use in the attempted alkylation reactions.

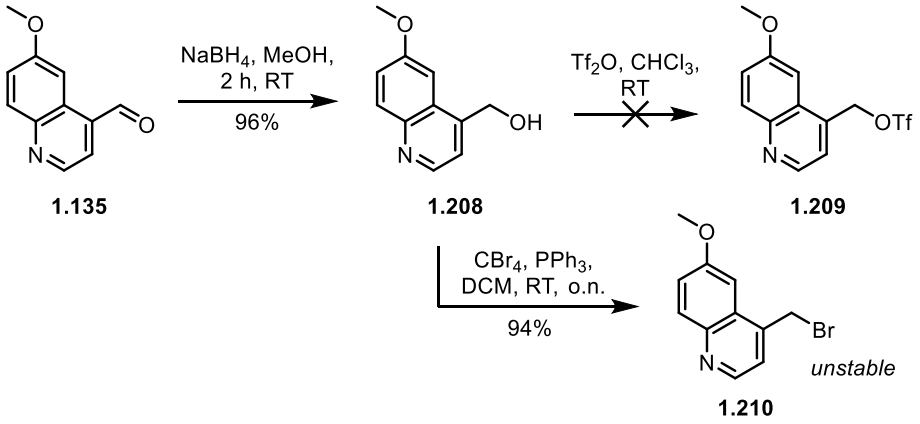


Figure 51. Synthesis of a lepidine bromide building block

The alkylation at C-8 in quinuclidinone **1.192a** could proceed *via* 2 pathways, as outlined in Figure 52a. These possible pathways are either *via* direct C-alkylation of the lithium enolate (pathway **a**) or *via* prior *N*-alkylation (pathway **b**) and subsequent Stephens-rearrangement of the obtained ammonium enolate **1.211** to afford the desired ketone **1.212**.[82] Unfortunately, alkylation did not yield any of the desired C-8 alkylated product **1.212**. Instead, the quaternary ammonium salt **1.213** was isolated in 71% yield (Figure 52b). This product could come either from the direct *N*-alkylation (pathway **c**) of the highly nucleophilic quinuclidine nitrogen or it could be obtained *via* a retro Stephens-rearrangement (pathway **d**) of the hypothetical intermediate **1.212**, as shown in Figure 52b. However, due to this unexpected result, further investigations towards the alkylation approach were abandoned.

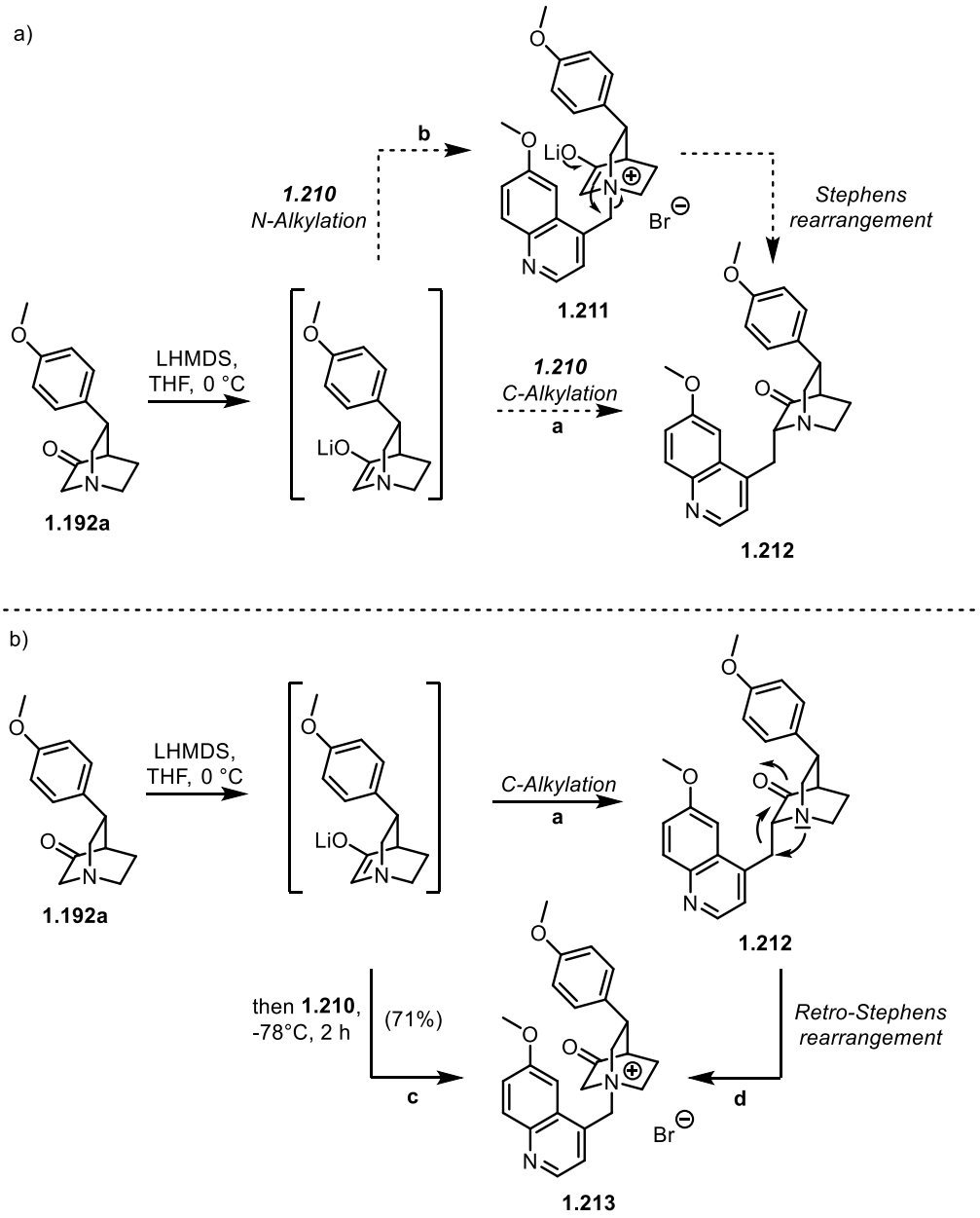


Figure 52. Possible pathways for the formation of the desired product 1.212 and the obtained product 1.213.

A successful solution for the epimerization problem was found by *in situ* conversion of the ketol **1.195** to the corresponding hydrazones. Employing model substrate **1.192a** and following the typical aldol reaction conditions described before, condensation of the *in situ* generated titanium alkoxide with hydrazines was found feasible. (Figure 53) The formation of trityl hydrazones **1.214** would be desirable since it would be susceptible for reductive halogenation.[83] However, although formation of **1.214** was observed, the product was found to be highly sensitive towards hydrolysis, preventing successful isolation of the material. The less bulky tosylhydrazone **1.215** on the other hand can be formed with

ease, and the desired product **1.215** was obtained in high yield and diastereoselectivity, since no epimerization at C-8 was observed.

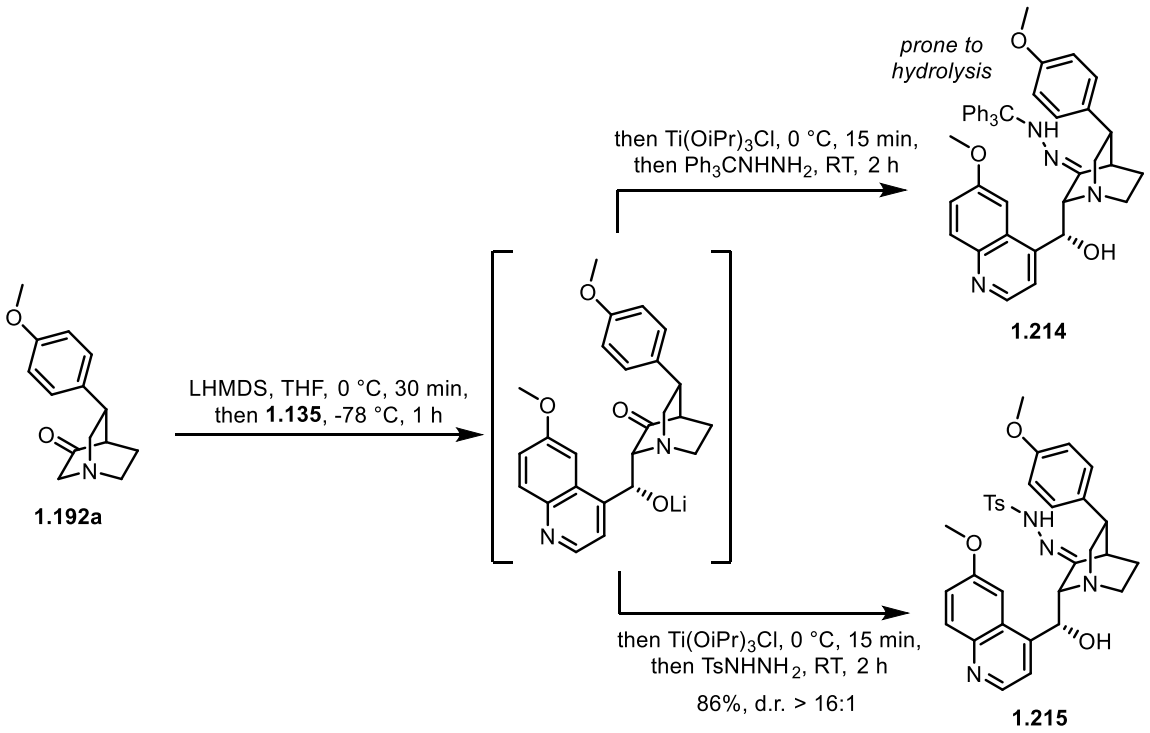


Figure 53. Unsuccessful trityl- and successful tosylhydrazone formation

The cleavage of tosylhydrazone in **1.215** could be achieved by its reduction to the corresponding hydrazide, which could then undergo decomposition to yield the desired methylene compounds upon elimination of *para*-toluenesulfinic acid and release of molecular nitrogen. This reaction is a very mild variant of the Wolff-Kishner reduction. The process is known with various hydride reducing agents and was first described by Caglioti and coworkers by use of lithium aluminium hydride.[84] However, despite extensive screening of a plethora of reducing agents, reduction of the tosylhydrazone **1.215** was not achieved and only gave decomposition of material when harsh conditions were used.

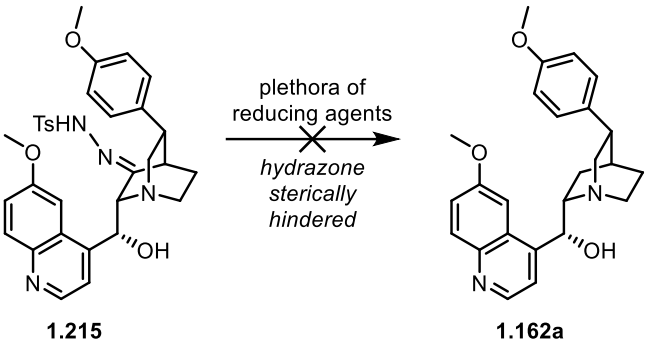


Figure 54. Exhaustive unsuccessful attempts for the reduction of tosylhydrazone 1.215

Considering the possible prevention of the Caglioti reaction in **1.215** by bulky substituents, the sterically less demanding mesyl hydrazone **1.216** bearing the C-3 vinyl substituent was prepared (Figure 55). As expected, **1.216** was formed in good yield and high diastereoselectivity by use of ketone **1.151** and conditions as used for the preparation of **1.215** (Figure 53). Using $LiAlH_4$ under harsh conditions, reduction of the mesyl hydrazone **1.216** was found successful and a small amount of Quinine was isolated.

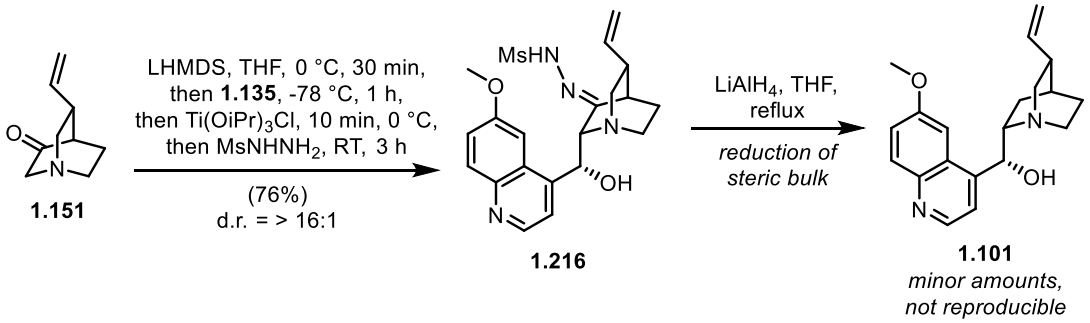


Figure 55. Preparation of mesylhydrazone and initially observed successful Caglioti reduction to afford Quinine

However, the reaction was unfortunately found to be irreproducible when other experimentators attempted this final reduction step. Therefore, the reaction was further investigated on the more readily available (but also more sterically hindered) anisole derivative **1.192a** in order to afford the C3- aryl analogues of Quinine. In analogy to **1.216**, the mesyl hydrazone **1.217a** bearing the C-3 anisole moiety could be readily synthesized following the established procedure (Figure 56).

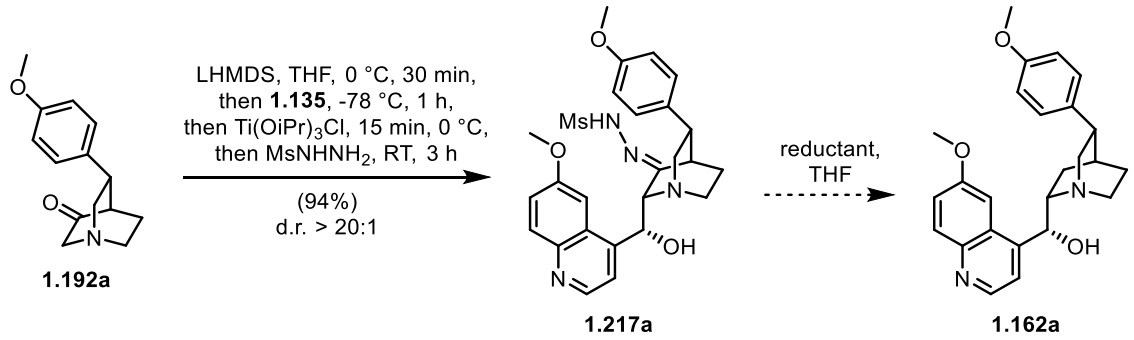
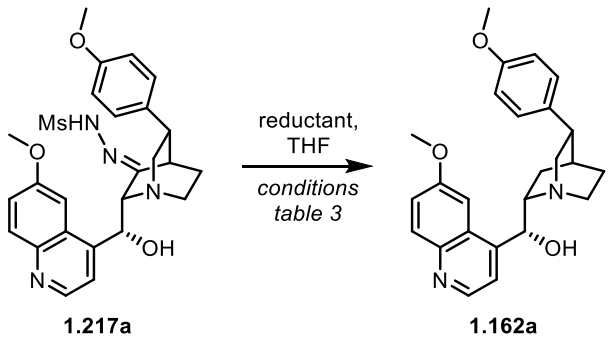


Figure 56. Preparation of C-3 anisol mesylhydrazone and attempted reduction

As shown in Table 3, reduction of the mesyl hydrazone **1.217a** proved to be a sophisticated endeavor. Treatment with $LiAlH_4$ and Red-Al did not yield any of the desired **1.162a** (Table 3, entry 1-6). Even an increase of amount of $LiAlH_4$ to 10 equivalents and heating to 60 °C in THF (entry 6) did not allow the desired reduction to take place and mainly starting material was recovered. When Quinine was first obtained (Figure 55), a quench of the reaction mixture with alcohol was performed. Indeed, quench of the hot reaction mixture with EtOH suddenly led to traces of product but mainly decomposition of material (Table 3, entry 7). Dropwise addition of MeOH (50 eq.) over 1 h or 15 equivalents of MeOH at once still was too harsh for the substrate yielding messy reaction mixtures (Table 3, entries 8-9). The optimal conditions were finally reached using 5 eq. of $LiAlH_4$ and 10 eq. MeOH without the necessity for any heating (Table 3, entry 10). In an upscale experiment, the aryl analogue **1.162a** could finally be isolated, albeit in a low yield of 17%.

Table 3. Reduction optimization of mesyl hydrazone 1.217a



entry	reductant	alcohol additive	T	time	yield	comment
1	Red-Al (2 eq.)	-	0 °C	180 min	-	no conversion
2	$LiAlH_4$ (1 eq.)	-	0 °C	180 min	-	no conversion

3	$LiAlH_4$ (1 eq.)	-	60 °C	180 min	-	no conversion
4	$LiAlH_4$ (3 eq.)	-	60 °C	120 min	-	no conversion
5	$LiAlH_4$ (10 eq.)	-	RT	120 min	-	no conversion
6	$LiAlH_4$ (10 eq.)	-	60 °C	60 min	-	no conversion
7	$LiAlH_4$ (15 eq.)	EtOH quench	60 °C	120 min	traces	decomposition
8	$LiAlH_4$ (10 eq.)	Drowise addition of MeOH (50 eq.)	60 °C	60 min	traces	decomposition
9	$LiAlH_4$ (5 eq.)	MeOH (15 eq.)	60 °C	30 min	traces	decomposition
10	**$LiAlH_4$ (5 eq.)**	**MeOH (10 eq.)**	**RT**	**23 min**	**17%**	**clean conversion**
11	$LiAlH_4$ (5 eq.)	MeOH (10 eq.)	RT	30 min	n.d.	complex mixture

It is important to point out that the reaction time must be carefully monitored. As demonstrated in Figure 57, the same reaction mixture after 30 minutes (instead of 23 minutes) already contained numerous byproducts (Table 3, entry 11). Although the product was detected in the crude mixture after 30 minutes, separation from numerous byproducts by chromatography to get pure **1.162a** was not successful.

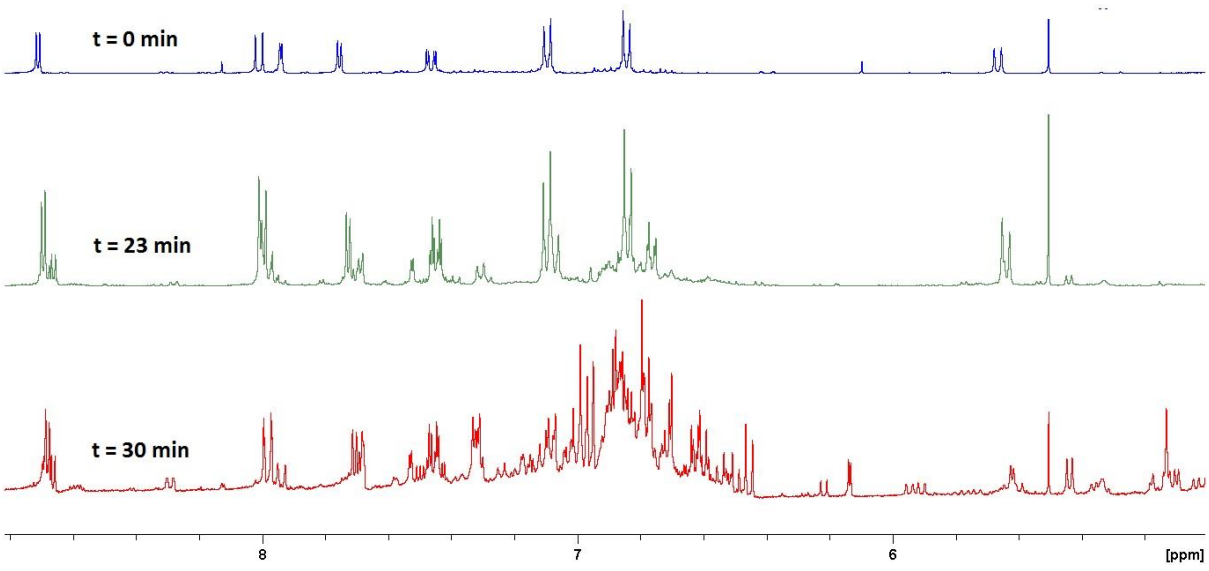


Figure 57. ^{1}H-NMR spectra of the starting material 1.217a (blue), clean reduction after 23 minutes (Table 3, entry 10) and noticeable degradation of material after 30 minutes (Table 3, entry 11)

Obviously, a prior reaction of the alcohol additive and lithium aluminium hydride generates the effective reducing agent. Similiar conditions were then applied to other mesylhydrazones, as shown in Figure 58. Reduction of **1.216** yielded Quinine **1.101** in 53% yield (Figure 58a). In analogy to the preparation of the anisole analogue **1.162a** as described before, another analogue **1.162b** containing an electronpoor p-CF_3-aryl moiety at C-3 was synthesized, as shown in Figure 58b. In contrast to the synthesis of Quinine, the yields for the reduction to the aryl analogues **1.162a** and **1.162b** were found to be consistently low, reflecting one more time the increased steric hindrance of their synthetic precursors.

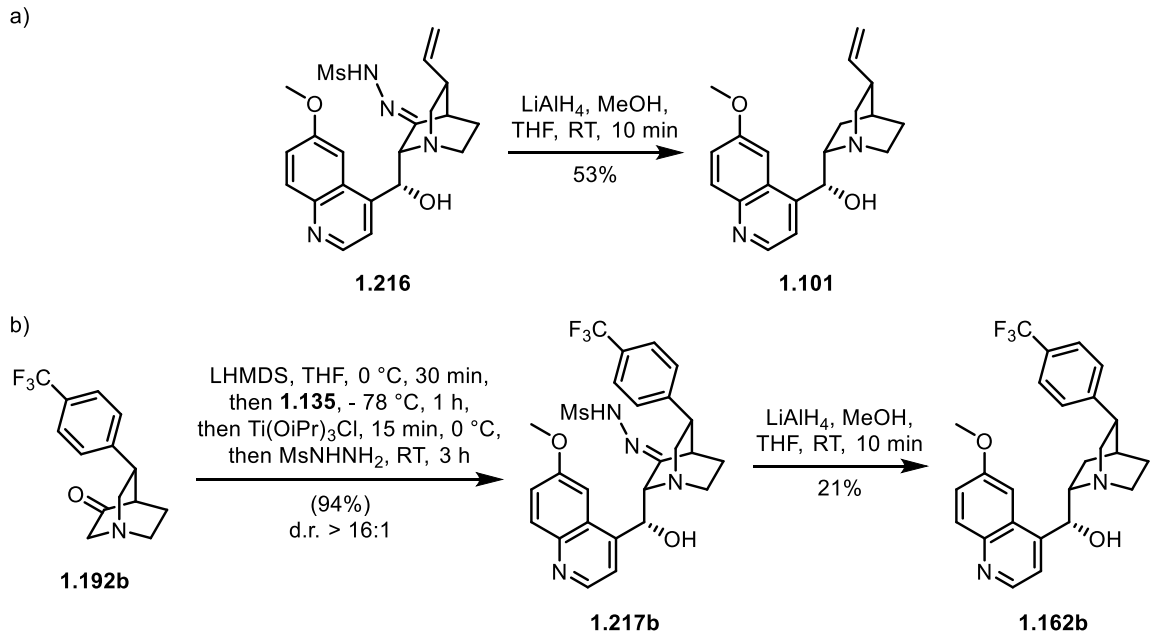


Figure 58. Synthesis of Quinine and aryl analogue 1.162b

In summary, the total synthesis of Quinine could be achieved in 10 steps (Figure 59). This remains the shortest reported synthesis to date despite the need of an aryl-to-vinyl reaction sequence. The key steps are a palladium-catalyzed C–H arylation reaction and a diastereoselective aldol reaction, enabling novel strategic disconnections in the synthesis of this classic target.

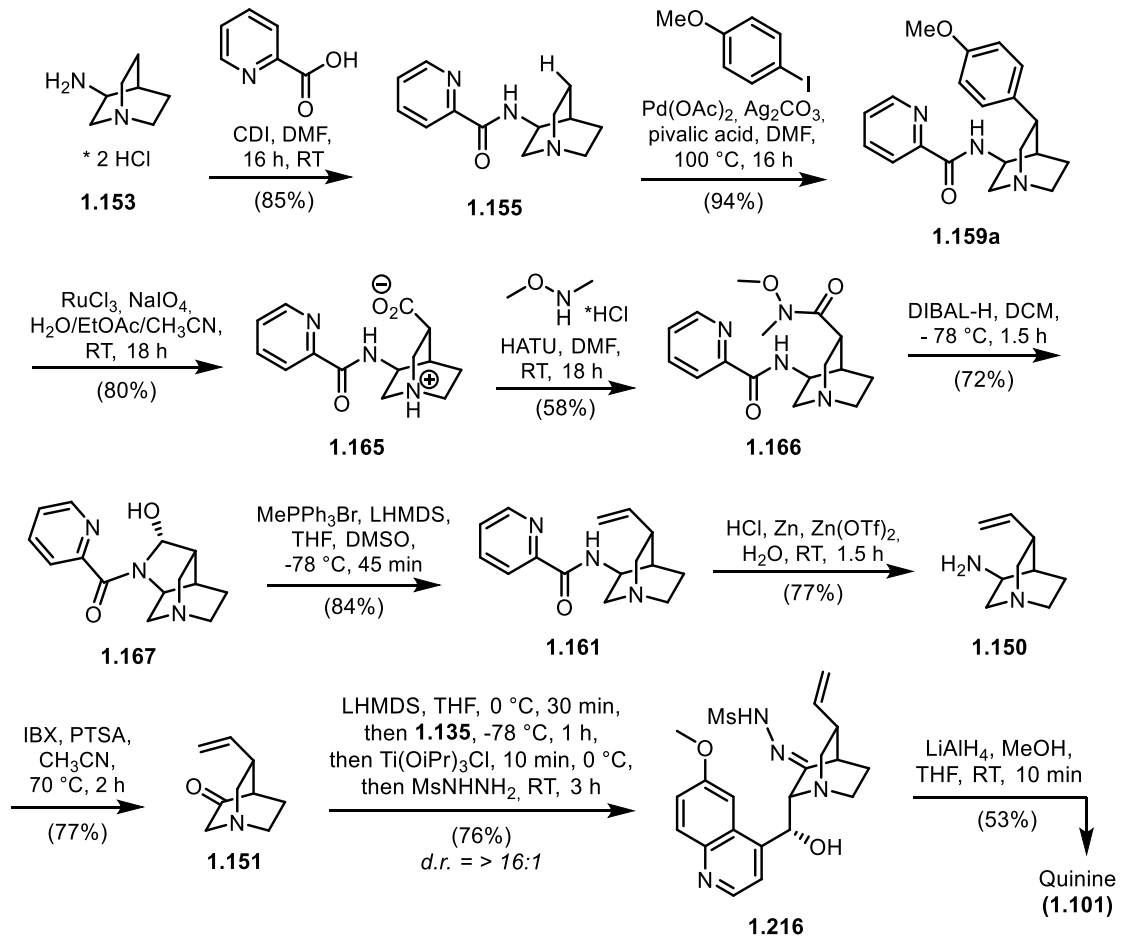


Figure 59. Complete reaction sequence for the synthesis of Quinine

1.2.5.7 Biological testing for antimalarial activity

Depending on the configuration of the 3-aminoquinuclidine starting material, both enantiomers of Quinine or the racemic compound can be obtained. In addition to the racemic aryl analogues **1.162a** and **1.162b**, the non-natural enantiomer (+)-Quinine has been prepared. The samples have been sent to the Swiss Tropical and Public Health Institute (Switzerland) and tested for their biological activity. The results for *in vitro* antimalarial activity of the tested compounds against the strain *P. falciparum* (strain NF54) are shown in Table 4. While the non-natural (+)-Quinine showed lower activity when compared to its commercially available enantiomer (applied as free base), both arylanalogues **1.162a** and **1.162b** showed increased antimalarial activity.

Table 4. Results for in vitro antimalarial testing of synthetic Quinine analogues. [a] 3 or [b] 2 replicates

	IC_{50} against P. falciparum (strain NF54, in µg/mL)	**IC_{50} for cytotoxicity (L6 rat cells, in µg/mL)**
Chloroquine	0.002 ± 0.001 [a]	-
Podophyllotoxine	-	0.004 ± 0.001 [a]
(-) Quinine	0.007 ± 0.001 [a]	36.15 ± 6.72 [b]
(+) Quinine	0.039 ± 0.001 [a]	46.15 ± 6.72 [b]
(±) **1.162a**	0.005 ± 0.006 [a]	6.53 ± 0.80 [b]
(±) **1.162b**	0.002 ± 0.002 [a]	3.13 ± 1.54 [b]

Encouraged by these positive results, *in vivo* experiments have been performed to confirm the increased activity of the aryl analogues. The compounds have been orally administered to groups of three mice 1 day after infection with malaria parasites of *P. berghei* (strain ANKA) as a single dose of 30 and 100 mg/kg respectively. After 3 days, the parasitaemia reduction in the blood was determined. As can be seen in Figure 60 (left chart), commercial quinine **1.101** (hydrochloride dihydride) and OMe-aryl-analogue **1.162a** were found to be poorly or not active at a low dose of 30 mg/kg, while the CF_3-aryl-analogue **1.162b** performed superior and effected a parasitaemia reduction of 98%. In the high dose of 100 mg/kg (Figure 60, right chart), the high activity of **1.162b** could be confirmed.

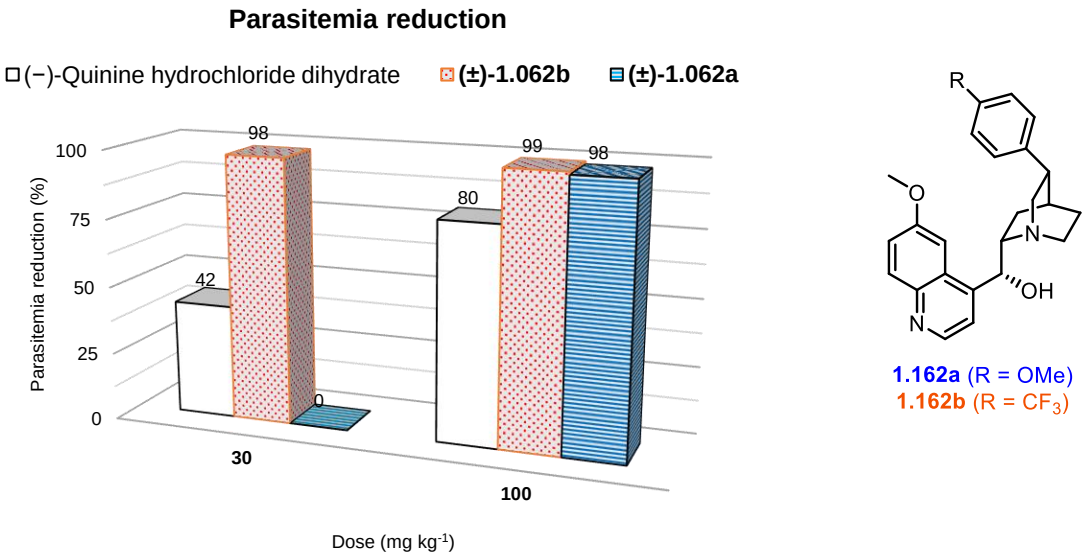


Figure 60. Parasitaemia reduction of Quinine, p-CF_3-arylanalogue 1.162b and p-OMe-arylanalogue 1.162a in low dose (left part) and high dose (right part).

Additionally, the time of survival was recorded in days, as shown in Figure 61 (including standard deviations). While the mice treated with Quinine and **1.162a** in low dose were euthanized to prevent death otherwise occurring latest on day 6 due to insufficient parasitaemia reduction (marked with *), mice treated with the CF_3-analogue **1.162b** survived an average of 8 days (Figure 61, left chart). A more significant effect can be seen in the days of survival upon administration of the high dose of 100 mg/kg (Figure 61, right chart). While the mice treated with Quinine or p-OMe-arylanalogue **1.162a** survived just an average of 7 days, treatment with p-CF_3-arylanalogue **1.162b** prolonged the average time of survival to 21 days.

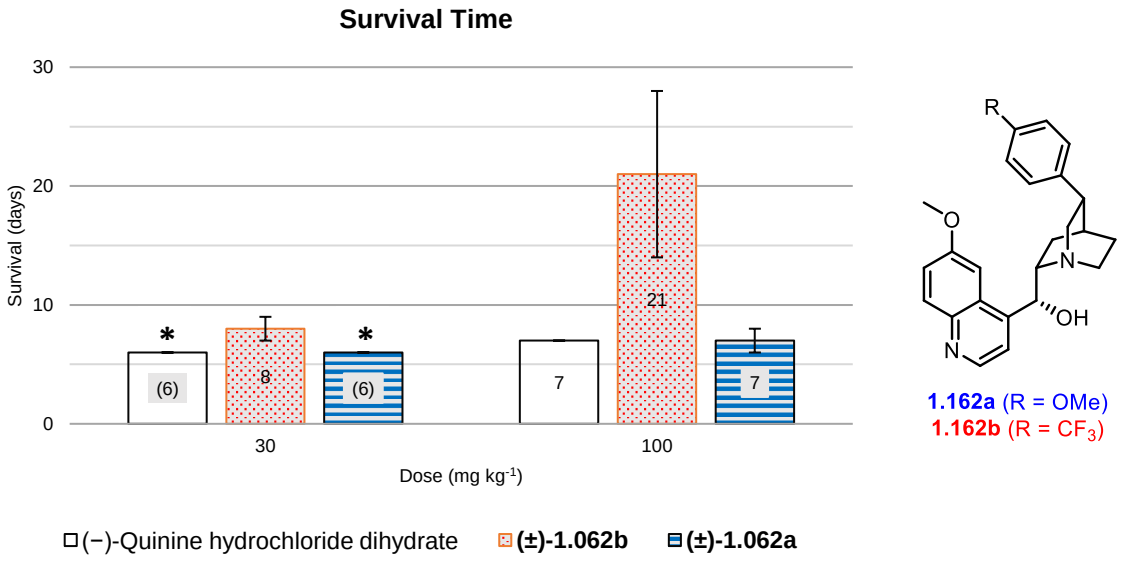


Figure 61. Survival time in days upon administration of Quinine, 1.162b and 1.162a in low dose (left chart) and high dose (right chart)

1.2.5.8 Conclusion

As described herein, the total synthesis of Quinine was achieved in a total of 10 steps starting from commercially available 3-aminoquinuclidine dihydrochloride. It is the shortest reported synthesis until the date of writing and utilizes palladium-catalyzed C–H arylation and a diastereoselective Aldol reaction as key steps. Furthermore, this approach enabled the short synthesis of C-3 arylanalogues of the natural product in only 6 steps. Biological activity of the latter was determined *in vitro* and *in vivo*, revealing significantly increased antimalarial activity when compared to the natural product. This finding clearly demonstrates the possibility for positive modulation of antimalarial activity of Quinine by modification of the substituent at C-3. It further highlights the value of tackling classical synthetic problems using modern methodology. Indeed, while the readily commercial availability of Quinine

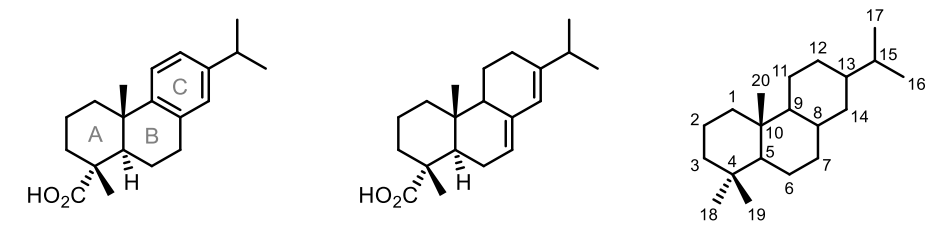
renders any total synthesis of that metabolite an academic endeavor, the fact that this exercise opened doors to C-3 analogues with increased potency showcases the value and societal and scientific relevance of total synthesis.

1.3 Oxidative Cleavage of the 8-Aminoquinoline Directing Group

1.3.1 Towards the Synthesis of DHAA Aryl-Analogues

1.3.1.1 Introduction

Dehydroabietanes are a large subfamily of diterpenoids consisting of around 200 isolated natural products to date. [85] The simplest representative is Dehydroabietic Acid (DHAA, **1.300**), which contains an aromatic C-ring and can be found alongside its saturated relative Abietic Acid (**1.301**) as major component in tree resins (Figure 62). Although differing in unsaturation, both structures share the abietane skeleton **1.302**. Naturally occurring derivatives of DHAA show a wide range of biological properties. However, the enzymatic derivatization of **1.300** seems to be mainly limited to functionalization of rings B and C. In particular, enzymatic modification in close proximity to the C-18 carboxylic acid in **1.300** is limited to a few examples. [85]



DHAA (Dehydroabietic Acid) **(1.300)** | Abietic Acid **(1.301)** | abietane skeleton **(1.302)**

Figure 62. Dehydroabietic Acid, Abietic Acid and the structure and numbering of the abietane skeleton

When compared to diene **1.301**, DHAA is considered more robust due to its aromaticity and therefore a popular scaffold in drug development. Mirroring the enzymatic panorama, its synthetic modification remains mostly limited to the aromatic or benzylic carbon atoms in the molecule, located in rings B and C.[86] Functionalization of ring A in **1.300** on the other hand is a challenging endeavor, due to the absence of functional handles. However, a suitable solution to diversify poorly functionalized molecules such as **1.300** would be based on methods enabling late-stage functionalization by C–H activation.[87]

Several derivatives of DHAA have already been prepared by C–H activation, as reported by the group of Yu. With the use of *O*-methyl hydroxamic acid as monodentate directing group, C–H alkylation at C-19 in substrate **1.303** was achieved and yielded e.g. amide **1.304** in 38% yield (Figure 63a).[88] When organometallic reagents such as alkyl boronic acids are utilized as coupling partners, the mechanism

often follows a Pd(II)/Pd(0) couple, as outlined in Figure 63b. Complexation of the Pd(II)-salt and subsequent C–H activation generates palladacycle **B**. Transmetalation and reductive elimination results in the observed product. The terminal formation of Pd(0) requires an additional co-oxidant in the reaction mixture to regenerate the Pd(II) species. As such, benzoquinone (BQ) is often used for this regeneration step but also to promote the typically sluggish reductive elimination event. [89]

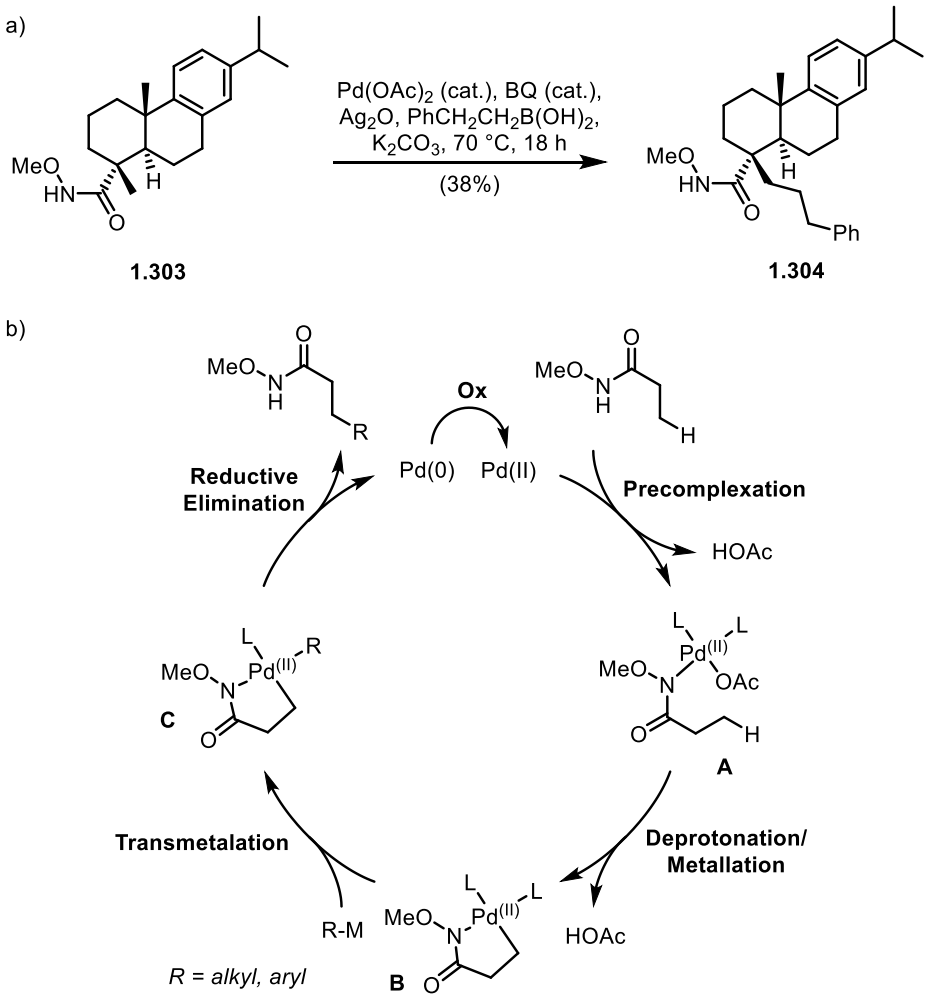


Figure 63. C–H Alkylation of a DHAA derivative (a) and mechanism involving a Pd(II)/Pd(0) couple (b)

Another example is the Pd-catalyzed C–H amination of DHAA derivative **1.305**, realized by the use of *N*-oxybenzoylated morpholine derivative **1.306** as coupling partner[90] (Figure 64a). In contrast to the examples described above, this reaction is proposed to proceed by a Pd(0)/Pd(II) cycle (Figure 64b). Oxidative addition of **1.306** to Pd(0) is proposed to generate adduct **A**, which affords after C–H activation palladacycle **C**. Reductive elimination of the product regenerates the Pd(0) catalyst.

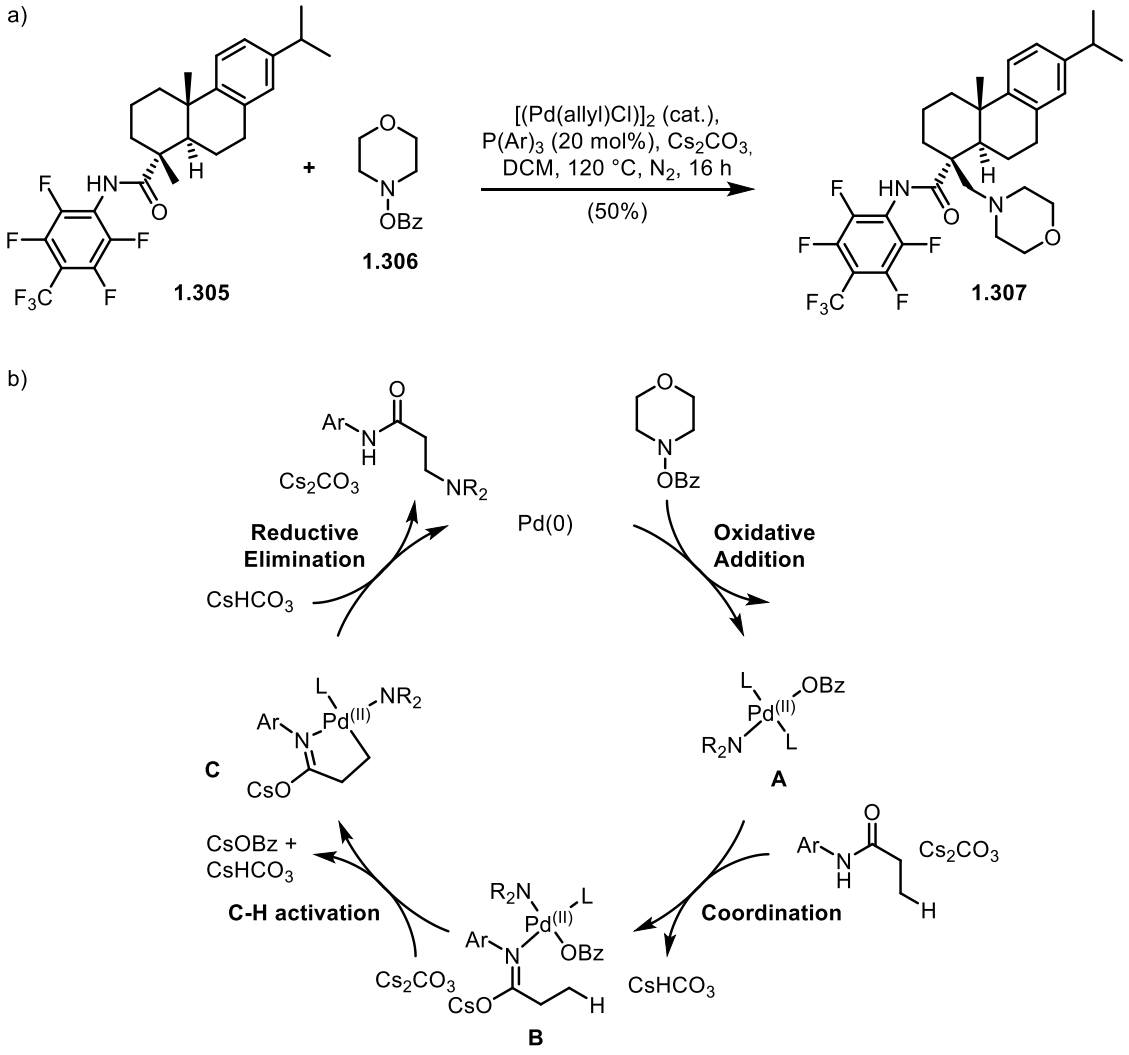


Figure 64. C–H Amination of a DHAA derivative (a) and proposed mechanism following a Pd(0)/Pd(II) couple (b)

The same substrate **1.305** was furthermore found to be susceptible to C–H borylation, as depicted in Figure 65.[91] The mechanism is believed to involve a Pd(II)/Pd(0) couple, similarly to that shown in Figure 63b. Instead of the transmetalation step, borylation of Pd(II) occurs by $(Bpin)_2$. An additional pyridine ligand was further required for reaction acceleration, by facilitating the otherwise slow reductive elimination. The borane intermediate was not isolated but directly converted to the alcohol **1.308**, which was isolated in 70% overall yield.

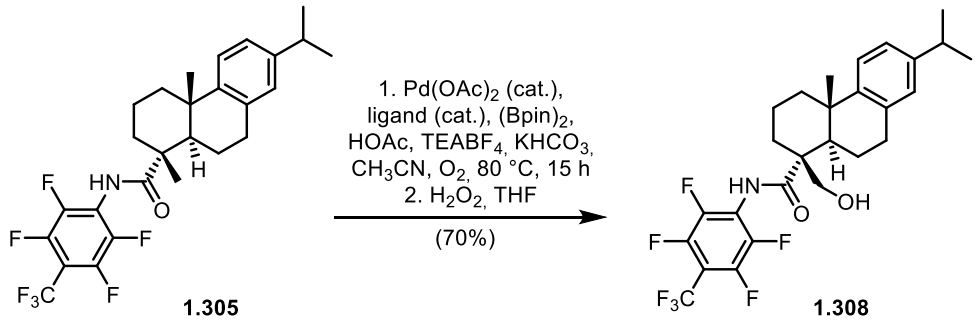


Figure 65. C–H Borylation and subsequent oxidation of a DHAA derivative as reported by Yu.

A complementary example for the C–H functionalization of C-19 in DHAA was reported by Rao and co-workers. [92] Various bidentate directing groups have been tested towards the desired C–H chlorination reaction by use of $Pd(OAc)_2$ as catalyst and *N*-chlorosuccinimide (NCS) as an oxidant. However, only the AQ directing group afforded the desired products, albeit in low yield. The reaction was hampered by chlorination of the AQ directing group itself as predominant side reaction. As a logical consequence, a C-5 chlorinated AQ-directing group was utilized, as shown in Figure 66. C–H Chlorination of **1.309** was eventually achieved and afforded the chlorinated DHAA derivative **1.310** in 56% yield.

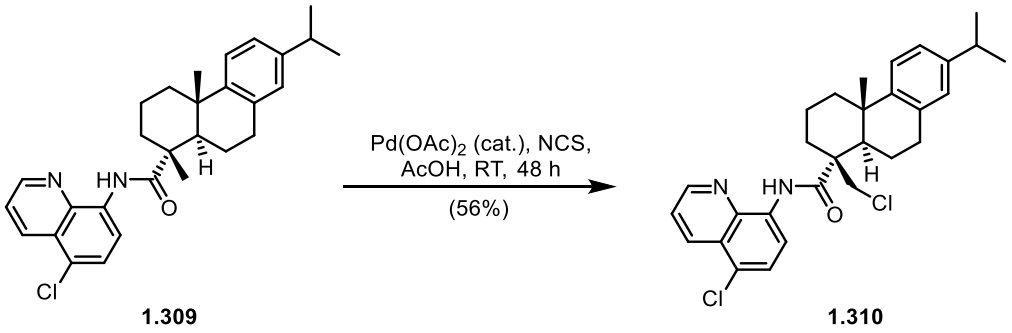


Figure 66. C–H Chlorination of a DHAA derivative facilitated by a C-5 chlorinated AQ directing group

However, the removal of the individual directing groups in all discussed C-19 modified DHAA derivatives to their free carboxylic acids (and therefore the actual DHAA analogues) have not been reported.

1.3.1.2 Objectives of this work

In 2015, derivatives of DHAA were shown to be potent openers of voltage-gated potassium channels.[93] Based on this work, the interest of novel DHAA-analogues as potential $GABA_A$-receptor modulators has been announced to us by other researchers working within the MOLTAG doctoral program. Our initial aim was the preparation of unprecedented C–H arylated derivatives of DHAA, as outlined in Figure 67. The resulting modification of the drug´s skeleton in close proximity to the carboxylic acid functionality in **1.300** and the overall change in lipophilicity was expected to greatly influence the biological activity. However, in contrast to the previous work, the sole C–H functionalization would not be sufficient. Since the carboxylic acid functionality in **1.311** was assumed to be essential for activity, the removal of the directing group was a prerequisite in order to obtain biologically active molecules.

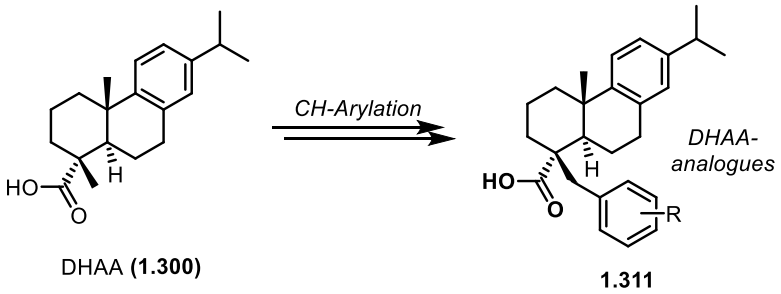


Figure 67. Preparation of DHAA aryl-analogues by C–H activation

The scope of the cleavage of the AQ directing group as discussed below was investigated together with Rajan Chauhan and Catarina A. B. Rodrigues. A substantial part of the following results has already been published.[94] Tanja Eder assisted in the early stage of the preparation of DHAA analogues.

Testing of the DHAA analogues on the GABA-A receptor has been performed by Marco Stadler (group of Prof. Steffen Hering, University of Vienna). The testing of the DHAA-analogues regarding antimicrobial activity has been coordinated by Alysha Elliott (CO-ADD initiative, University of Queensland). The work done on DHAA has also already been published.[95]

1.3.2 C–H Arylation of DHAA and attempted cleavage of the AQ auxiliary

We commenced our study with the prominent 8-Aminoquinoline (AQ) directing group, as shown in Figure 68. Initial experiments using Pd(II)-salts and aryliodides as coupling partners of amide **1.312** did not yield any of the desired products. We then turned our attention to the use of Ni(II) salts, as already successfully utilized for C–H arylation reactions, following a Ni(II)/Ni(IV) mechanism.[96] Instead of the common use of hygroscopic nickel catalysts such as $Ni(OTf)_2$ and exotic additives, we first investigated readily available and low-priced bulk chemical $Ni(OAc)_2 \cdot 4\ H_2O$ for this purpose, albeit in stoichiometric amount. Complete dehydration of the nickel salt was performed in the Schlenk tube by simple heating under vacuum with the flame torch. Then, subsequent addition of the substrate, Na_2CO_3 as base and DMF as solvent was conducted under argon. Upon heating to 140 °C overnight, introduction of several aryl entities was found successful at C-19 in **1.312**, as shown in Figure 68. Using our reaction conditions, electron-rich (as in **1.313a,b**) as well as electron poor aryl moieties (as in **1.313c,d**) have successfully been installed. Poor yields were obtained in the case of methylester **1.313d** and thiophene **1.313e**, which was found to readily undergo twofold C–H arylation. Since we were mainly interested in obtaining samples for biological evaluation, further optimization of the reaction conditions has not been conducted.

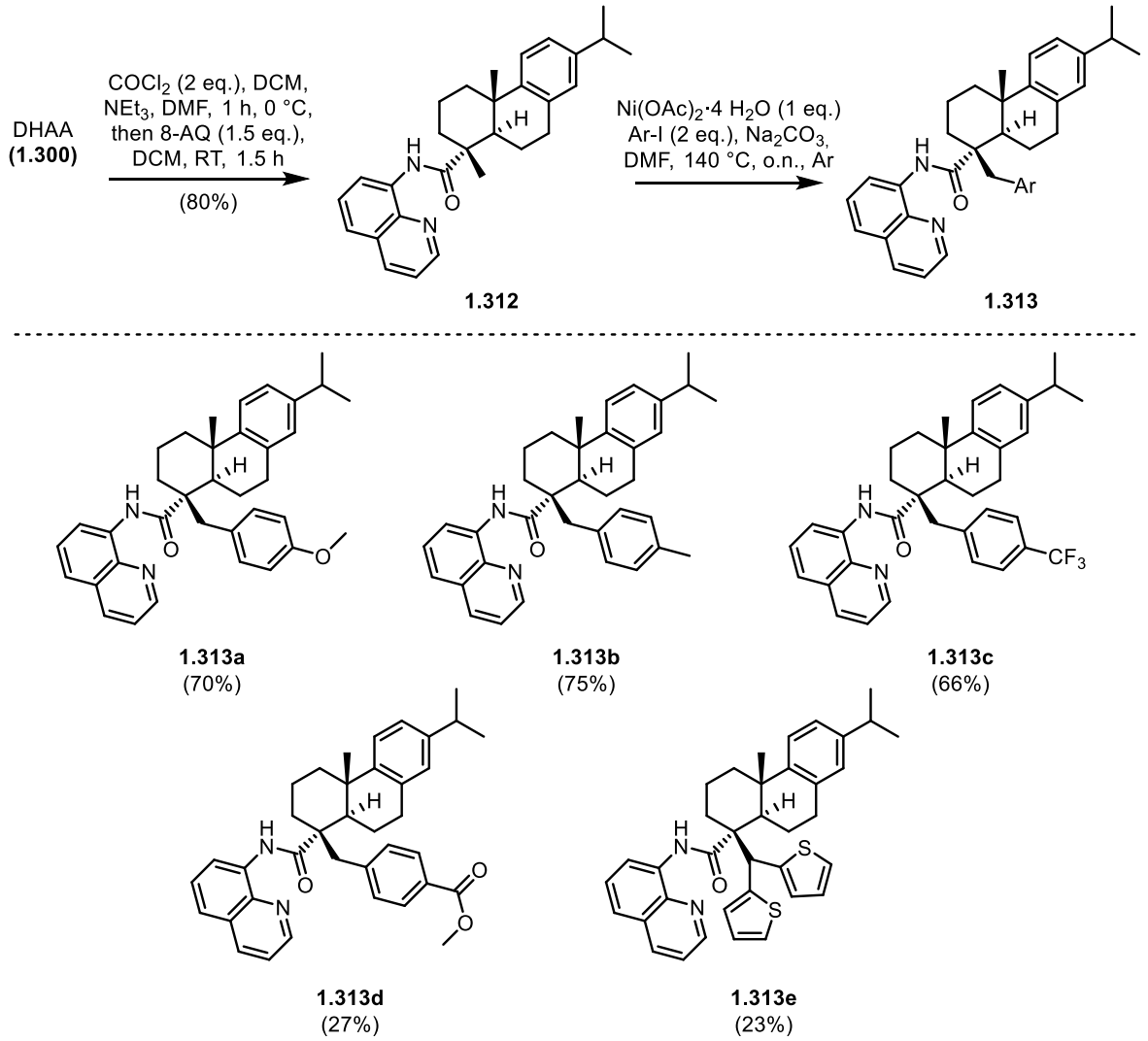
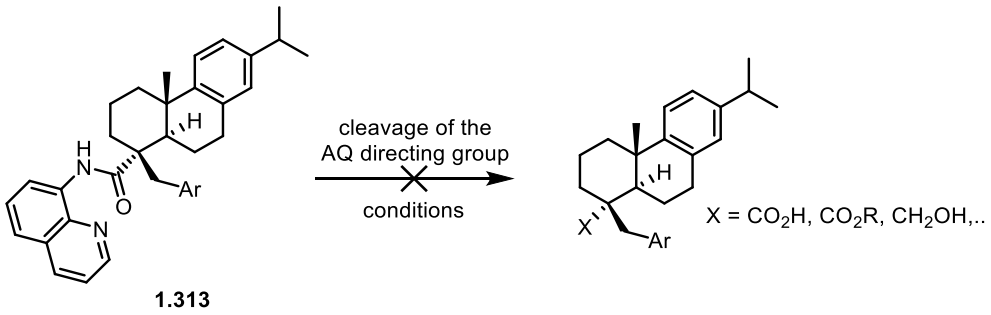


Figure 68. Preparation of C-19 arylated DHAA aminoquinoline derivatives

With the arylated derivatives **1.313** in hand, we next attempted removal of the redundant AQ directing group. Much to our surprise, this seemingly simple hydrolysis of the amide bond turned out to be a significant problem. As shown in Table 5, a plethora of reaction conditions aiming for the hydrolysis or reduction of the amide bond have been probed, but consistently met with failure. Mostly no conversion or decomposition of the material (as in the presence of boron trifluoride etherate) was observed (Table 5, entry 1).

Table 5. Unsuccessful conditions utilized for attempted cleavage of the AQ directing group



1.313

Entry	Conditions	Result
1	$BF_3{\cdot}OEt_2$ (10 eq.), THF/MeOH, 140 °C, o. n.	decomposition
2	Tf_2O (1.3 eq.), DCM, 0 °C, 1 day, then MeOH, RT, 1 h	no conversion
3	Me_3OBF_4 (1.3 eq.), HNa_2PO_4, CH_3CN, RT, 20 h, then 10% HCl	no conversion
4	KO^{t}Bu (30 eq.), DMSO, RT, 1 day	no conversion
5	NaOMe (30 eq.), MeOH, RT, 1 day	no conversion
6	6 N H_2SO_4/dioxane (1:1), reflux, 1 day	no conversion
7	Zn, HCl conc., water/^{i}PrO, RT, 2 days	no conversion
8	Zn, HCl conc., water/dioxane, RT, 2 days	no conversion
9	$(Boc)_2O$ (3 eq.), DMAP (2 eq.), CH_3CN, 70 °C, 28 h	no conversion
10	HBr (48%), 50 °C, 1 day	no conversion
11	LiOH (3 eq.), H_2O_2, THF/water, 50 °C	no conversion
12	$CuCl_2$, MeOH, 50 °C, 2 days	no conversion
13	SmI_2 (8 eq.), water/Et_3N, THF, RT, o.n.	clean reduction of quinoline
14	TfOH/water, toluene (1:1), RT, 30 h	no conversion
15	TfOH/water, toluene (1:1), 70 °C, 1 day	no conversion
16	TfOH/water, toluene (1:2), 110 °C, 1 day	messy mixture

Finally, boiling of the arylation products in toluene and water with excess of aqueous triflic acid led to some conversion of the product, but only a mixture of compounds was obtained (Table 5, entry 16). In order to confirm the presence of a potential cleavage product in the mixture, a scale-up experiment using similar conditions and substrate **1.313a** was performed, but revealed the main product to be the spiro compound **1.314**, which was isolated in 47% yield (Figure 69). The sterically congested AQ-amide

1.313a seems to preferentially undergo an unprecedented Friedel-Crafts-type cyclization instead of the desired AQ-amide bond cleavage under such harsh acidic conditions.

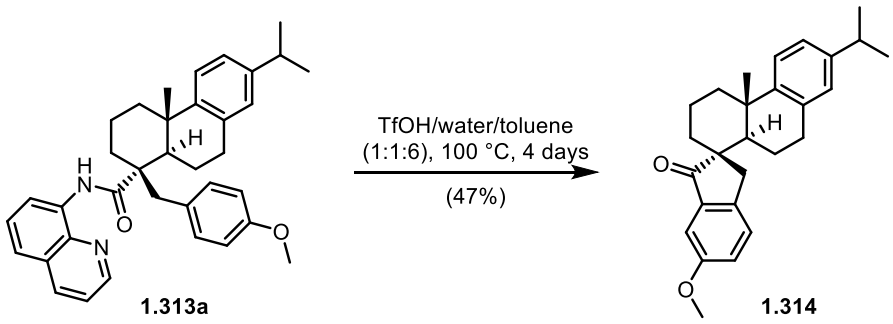


Figure 69. Friedel-Crafts-type cyclization of C-19 arylated DHAA-AQ under harsh acidic conditions

1.3.3 Common strategies for the removal of the AQ directing group

Since the AQ directing group is installed by an amide linkage, classic hydrolysis by basic or acidic conditions should be the most obvious approach for its removal. Although the cleavage of this moiety is often not demonstrated in numerous methodology publications, such simple hydrolysis has successfully been applied in numerous cases, but requiring quite high temperatures. An example of the cleavage of the auxiliary using basic conditions – at 130 °C for 3 days – was reported by Daugulis and co-workers, as shown in Figure 70.[97]

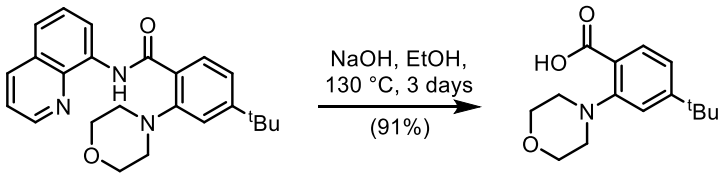


Figure 70. Removal of the AQ directing group under basic conditions

However, on more sterically congested substrates, such simple hydrolysis was already found to be troublesome. Figure 71 shows substrates where the cleavage of the AQ-amide by classic methods (concentrated HCl or NaOH) failed to give any conversion to the desired carboxylic acid, as reported by the groups of Babu or Padmavathi.[98-99] However, boiling of the substrates **1.315** and **1.317** in triflic acid as part of a solvent mixture with toluene and water was found necessary for the successful removal of the AQ moiety to afford the desired carboxylic acids **1.316** or **1.318**, respectively. As already

described before, these conditions where found not suitable for our substrates (carrying an all-carbon quarternary center next to the 8-AQ-carbonylgroup) and led to the spiro-cyclization to afford **1.314** (Figure 69).

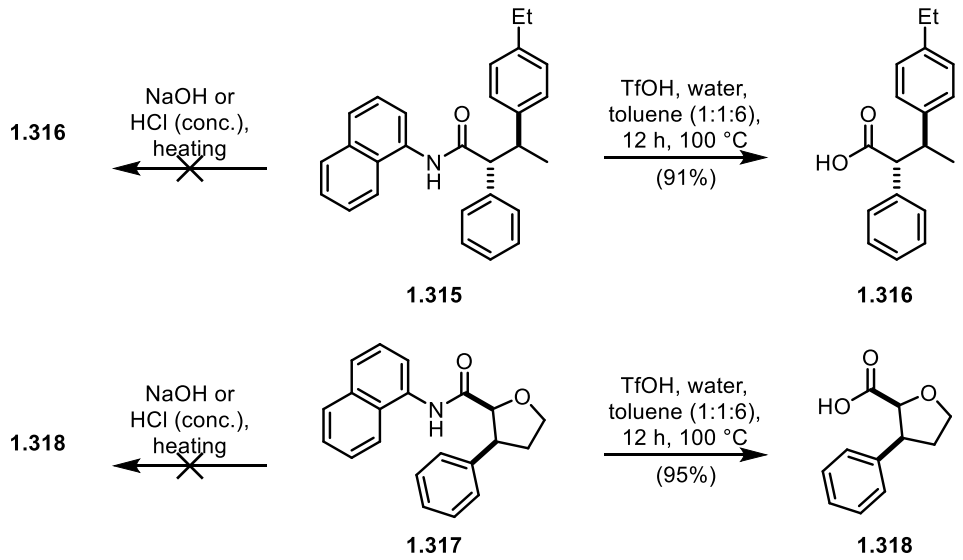


Figure 71. Failed AQ-removal under classic conditions requiring boiling in a solvent mixture containing TfOH

In 1983, Grieco and co-workers reported a mild two-step hydrolysis of secondary amides.[100] The method is based on prior *N*-Boc-protection of the amide starting material. The resulting imides were found much more susceptible towards basic hydrolysis. As a matter of fact, this approach has been successfully applied several times also in the cleavage of the AQ-directing group. The total synthesis of the peptide Celogentin C has independently been attempted by the research groups of Hutton[101] and Chen[102], both pursuing a similar strategy. As key step, they envisaged a diastereoselective AQ-directed C–H indolization reaction. For this transformation to proceed, the presence of the phthaloyl *N*-protecting group was found to be essential in the substrate **1.319** (Figure 72a). However, upon successful C–H indolization, the cleavage of the AQ directing group was met with enormous resistance. While the model substrate **1.319** was found to give the desired cleavage product **1.320** using Griego´s approach in quantitative yield, the actual C–H arylated product **1.321** failed to give the desired acid under all conditions tested. Severe steric hindrance in **1.321** was suggested by Hutton to be responsible for this failure. Chen and co-workers came to the same conclusion and doubted the AQ-directed C–H activation to be in general useful in natural product synthesis due to this problem. However, they eventually succeeded in the removal of the AQ-moiety by applying a 4 step sequence, as depicted in Figure 72b. It is important to note that *N*-Boc protection was not successful on our C–H arylated DHAA analogues (Table 5, entry 9).

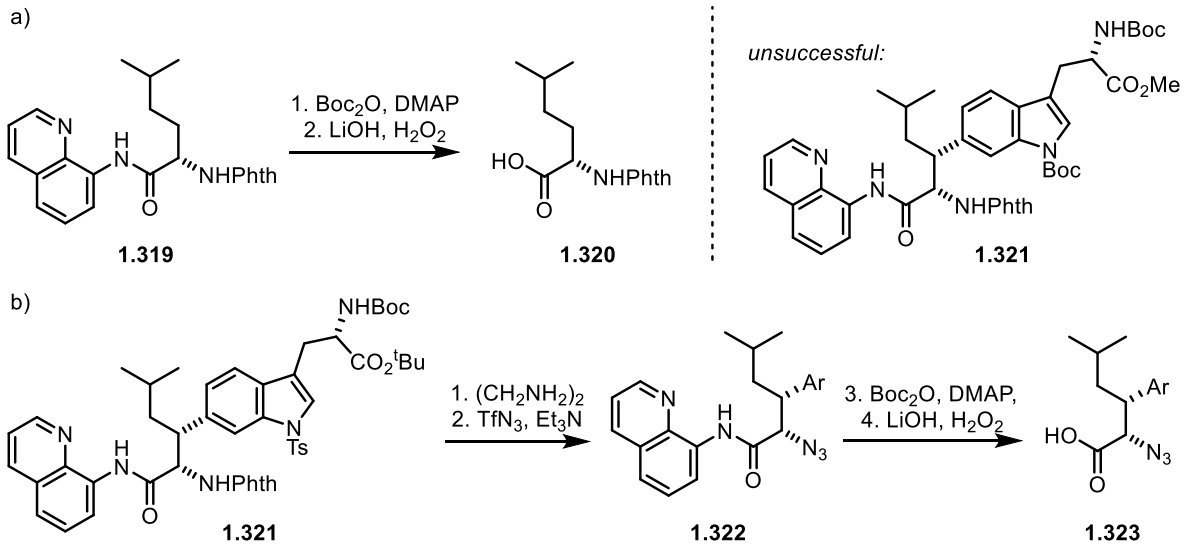


Figure 72. Failed cleavage of the AQ auxiliary by Hutton et al. and Chen´s successful deprotection by a 4-step sequence

In 2014, Baran and coworkers reported another case where the removal of the AQ directing group could not be achieved despite screening of various conditions and required the change to a different directing group.[103] Similar to our substrates, steric hindrance can presumably be attributed especially to the quarternary center next to the AQ-carboxamide functionality in cyclobutane **1.324**, as shown in Figure 73.

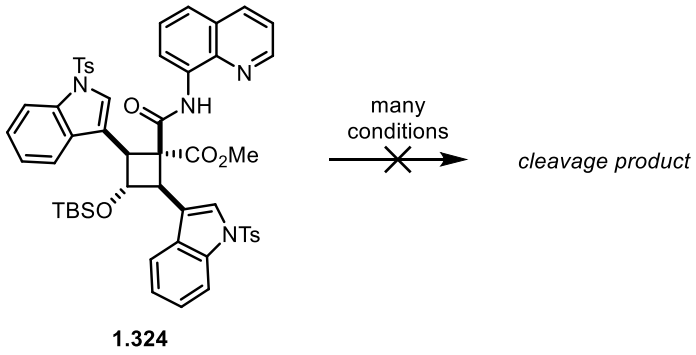


Figure 73. Failed removal of the AQ directing group, as reported by Baran and co-workers

An intriguing solution to this problem was found by the group of Chen by the introduction of the 8-amino-5-methoxyquinoline (MQ) directing group as a readily removable auxiliary.[104] Simple treatment with excess ceric ammonium nitrate (CAN) allows smooth removal of this modified quinoline directing group to afford the corresponding amides as final products. The method was found

particularly useful for the auxiliary cleavage of lactams, as obtained from intramolecular C–H activation, but was also found successful for the cleavage of acyclic substrates.

Despite the use of the AQ directing group for scope studies, the removal of the directing group is, in several reports, demonstrated on substrates bearing Chen´s MQ auxiliary instead of the actual AQ directing group. As shown in Figure 74, this strategy was necessary for deprotection of hindered substrates **1.325** [105] and **1.327** [106] due to the failed removal of the corresponding AQ-containing products. However, the use of the MQ auxiliary on large scale comes along with high costs when compared to abundant AQ.

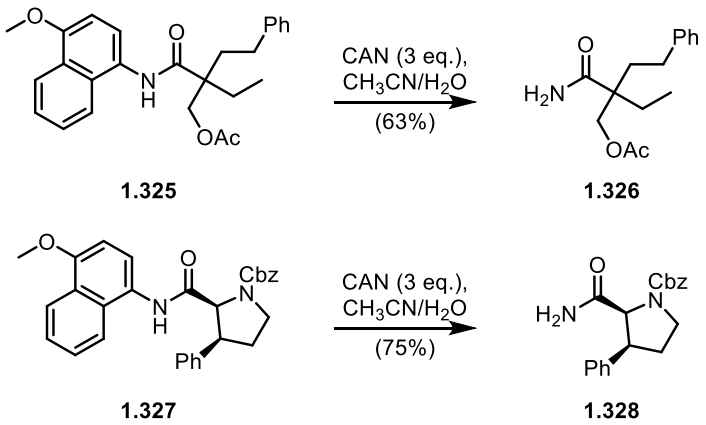


Figure 74. Oxidative removal of the MQ directing group as developed by Chen et al.

Although significant attempts for the cleavage of the AQ auxiliary have been made as described in this section, a general method for its cleavage in particularly hindered substrates remained elusive. However, instead of the change of the directing group in our DHAA derivatives **1.313**, we sought to find a solution to this general problem.

1.3.5 Oxidative cleavage of the 8-Aminoquinoline (AQ) directing group

Since the nucleophilic attack on the carbonyl group in our substrates **1.313** does not seem to be possible even under forcing conditions, we aimed for the removal of the AQ by a non-traditional approach. Inspired by the oxidative fragmentation of the anisole moiety in **1.159a** (Figure 34) in our Quinine synthesis, ozonolysis of DHAA derivative **1.313a** was performed in order to degrade the bulky anisole moiety, and as a result, reduce the steric bulk of the amide. In the event, a very clean and rapid reaction was found to take place. Its completion was indicated by the characteristic blue color of unconsumed ozone. After quenching with dimethylsulfide (DMS), column chromatography of the crude product was attempted but seemed not very promising in the first place due to an observed instability of the new product on silica gel. Much to our surprise, analysis of the collected material revealed the product to actually be the amide **1.329a**, with the AQ auxiliary successfully removed, albeit in only low amount (Figure 75a). This unexpected result was most intriguing, since it appeared that the AQ-removal occurred by cleavage of the *N*-quinoline bond rather than the amide bond (Figure 75b).

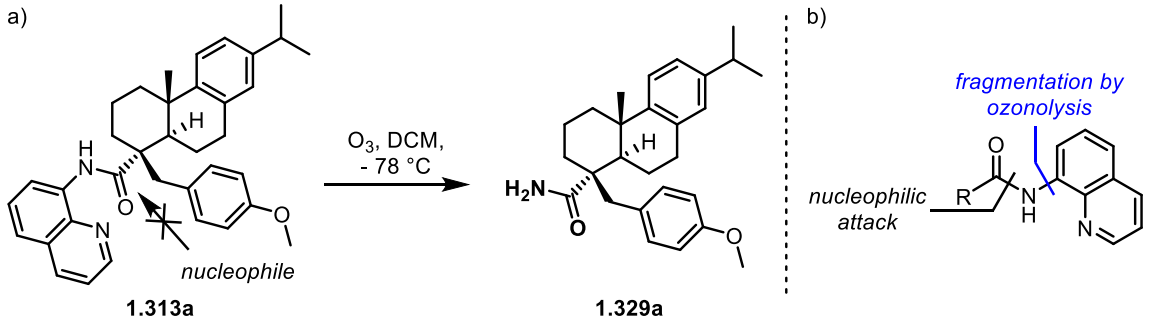


Figure 75. Unexpected removal of the AQ auxiliary by ozone (a) by N-quinoline bond cleavage (b)

According to the literature, the ozonolytic cleavage of quinolines is usually not an easy transformation to achieve. In 1989, O´Murchu reported the fragmentation of diversely substituted quinolines by ozonolysis with examples shown in Figure 76.[107] In general, one equivalent of H_2SO_4 was added, presumably for protection of the quinoline nitrogen. An oxidative work-up with H_2O_2 was utilized in order to obtain the desired carboxylic acid **1.332**. The required conditions seem very harsh, since (for ozonolysis) very high temperatures of 35 °C and a minimum of 20 hours reaction time (as for unsubstituted quinoline **1.330**) were required. The presence of an electron-donating hydroxy group at C-8 in **1.331** repuired an even longer reaction time of 25 hours. This is somehow surprising, since the readily cleaved AQ-moiety in **1.313a** (shown in Figure 75) bears its amide substituent in the same position.

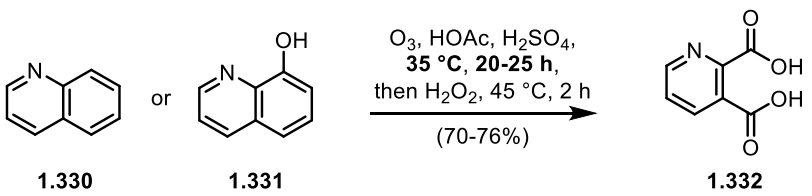


Figure 76. Ozonolysis of quinolines under harsh conditions, as reported by O´Murchu

In striking contrast to the quinolines shown above, ozonolysis of the AQ directing group proceeds within minutes at -78 °C without the need of an acid additive. This is an important fact, since most complex molecules would presumably not survive the harsh conditions required for quinolines **1.330** or **1.331**. The intermediates to this transformation are shown in Figure 77. Ozonolysis converted the robust amide bond in model substrate **1.333b** into the fragile imide **1.334**, which was found to be already partially hydrolyzed upon attempted purification by silica gel chromatography. Since a reductive work-up with DMS yields a carbaldehyde functionality, imide **1.334** cyclizes to give the cyclic product **1.335**, as unambiguously assigned by x-ray crystallography.

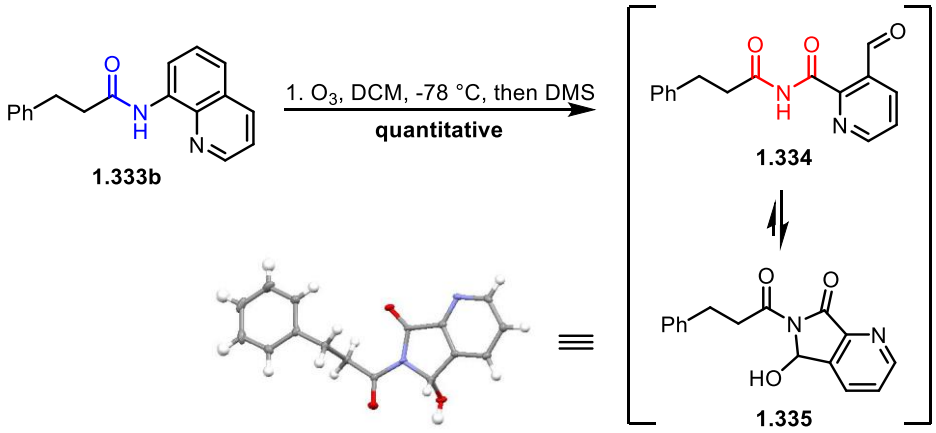


Figure 77. Fragmentation of the AQ directing group by ozonolysis, affording a labile imide moiety

The oxidation of **1.333b** furthermore proceeds with remarkable purity. Figure 78 shows the ^{1}H-NMR spectra of a sample of **1.333b** before (top, red) and after (bottom, blue) ozonolysis. **1.335** was obtained quite pure without any purification step and simple concentration of the crude reaction mixture to dryness.

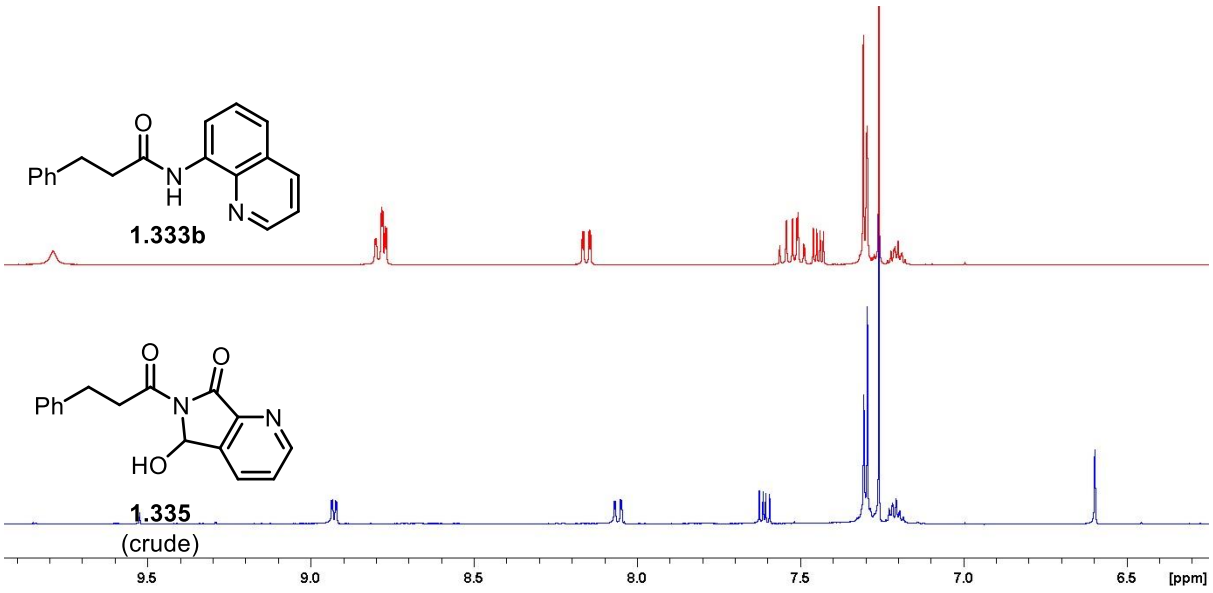


Figure 78. ^{1}H-NMR of a sample of substrate 1.333b before (top, red) and after (bottom, blue) ozonolysis

For the method to be generally useful, quantitative hydrolysis of the crude pyrrolidinone intermediates **1.336** must be achievable. In order to obtain the desired carboxylic acids **1.337**, nucleophilic attack at C-1 in **1.336** by a hydroxide is required, as shown in Figure 79 (left). As alternative reaction outcome, attack of any nucleophile on C-2 should give the primary amide **1.338** as product (Figure 79, right). Since the latter pathway is not desired, the carbaldehyde functionality (as obtained from reductive workup with DMS) was thought to be crucial in order to shield C-2 by enabling cyclization to give **1.336**.

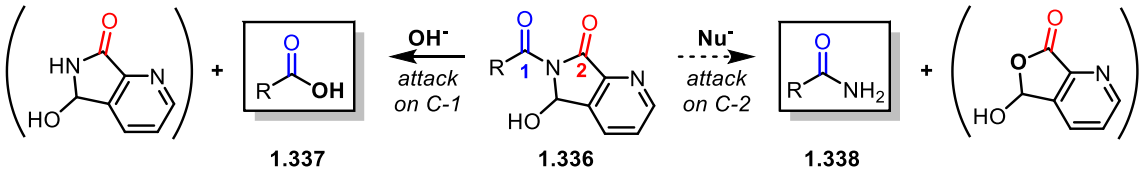


Figure 79. Possible pathways for the cleavage of the ozonolysis products

In order to provide a rough estimation on the efficiency of basic hydrolysis, a brief substrate scope has been performed, as shown in Figure 80. The crude imides (as obtained from ozonolysis) were subsequentially treated with LiOH/H_2O_2 in a mixture of THF and water in the same reaction vessel. As demonstrated on **1.337a-c**, cleavage of simple AQ substrates was found possible already at room

temperature. More sterically hindered and aromatic substrates required some warming of the reaction mixture in order to provide reasonable reaction times. Even highly hindered substrates **1.337k** and **1.337l** have been cleaved successfully, albeit in only moderate yield under prolonged reaction time. This can be attributed to the preferred nucleophilic attack at C-2 of the imide **1.336** due to sterical shielding of C-1 in particularly hindered substrates.

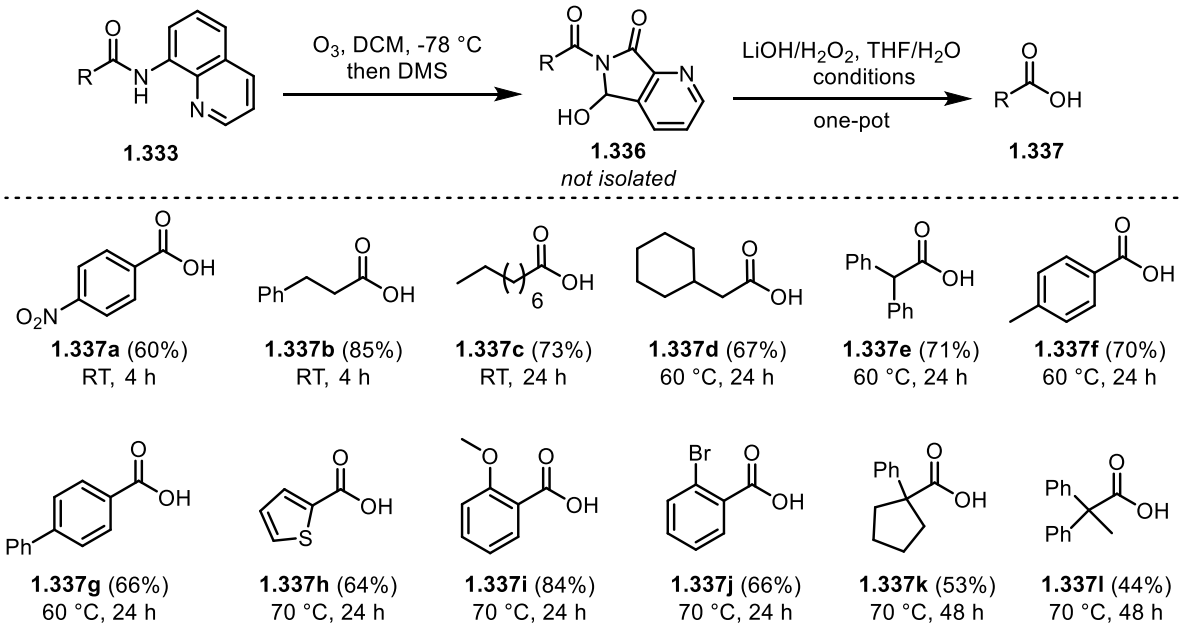


Figure 80. Scope of cleavage of AQ-amides to carboxylic acids

As alternative, cleavage of the AQ directing group to afford the primary amides can also be achieved by aminolysis, as shown in Figure 81. Attack of NH_3 at C-1 or C-2 affords the desired product. This degenerate reaction is therefore generally very clean and gives high yields, especially in the case of the hindered products **1.338c** and **1.338d**. In compound **1.338e**, the amide was cleaved in presence of an ester. Due to the rapid fragmentation of the AQ-moiety, a carbamate and an *N*-PMB group survived the ozonolytic cleavage to give product **1.338f** with an excellent yield of 89%.

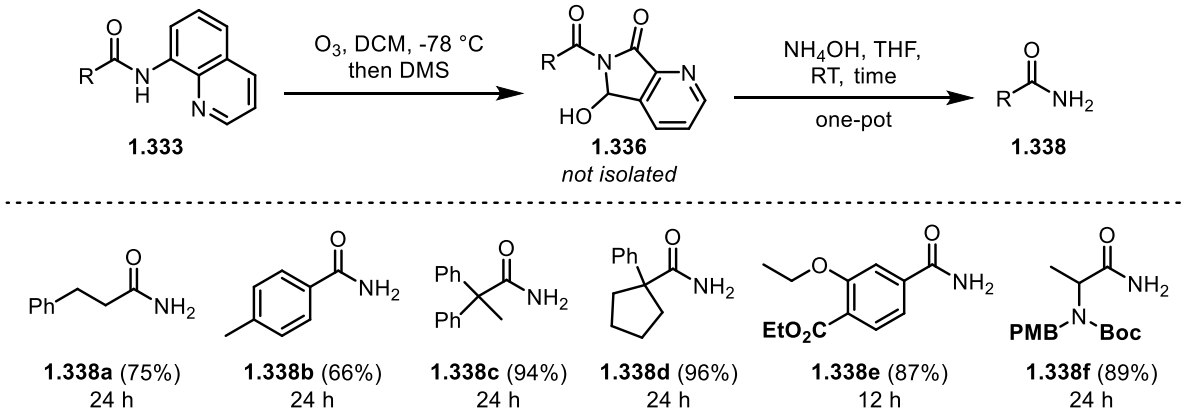


Figure 81. Scope of cleavage of AQ amides to primary carboxamides

If the hydrolysis of the robust AQ-amide bond in presence of comparable sensitive groups such as an ester or a nitrile is required, cleavage can be performed even under quasi-neutral conditions. Heating in a mixture of dioxane and water facilitated the desired hydrolysis of the imide intermediate **1.336**, as shown in Figure 82. Addition of $CuCl_2$ further led to an increase in yield, as shown in the formation of product **1.337b**. The overall hydrolysis of the robust amide bond was achieved with preservation of an ester in **1.337m** or a nitrile functionality in **1.337n**. The mode of action of the copper-salt may be explained either as Lewis acid or by chelation to the *N,N*-bidentate acyclic isomer of **1.336**.

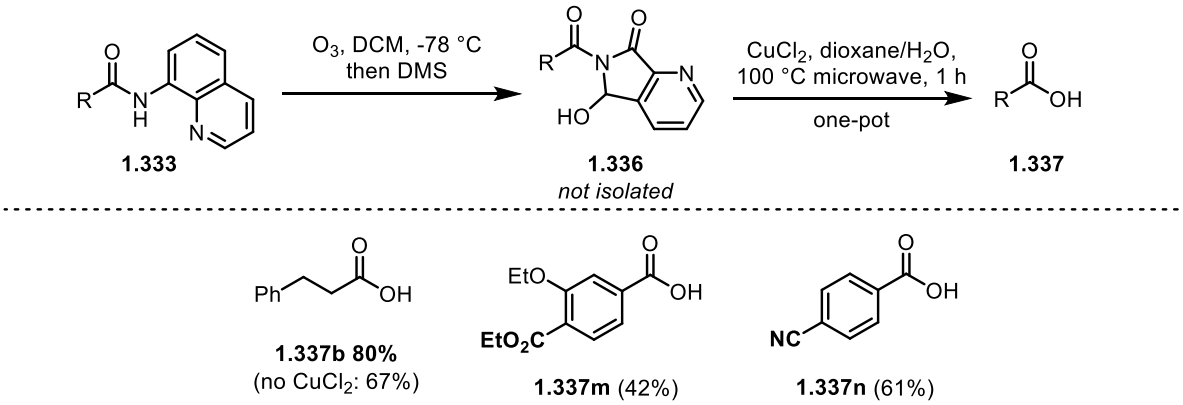
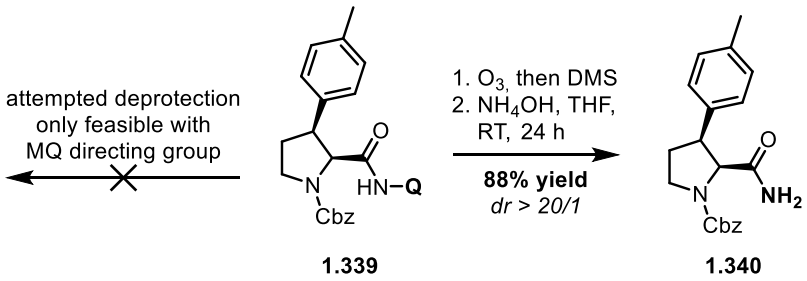


Figure 82. Hydrolysis of AQ amides under quasi-neutral conditions

A showcase study for the utility of the method is shown in Figure 83. Bull and co-workers developed the AQ-directed C–H arylation of proline derivatives.[106] As already described above in Figure 74, the cleavage of the directing group was unfortunately met with failure. The desired deprotection was only

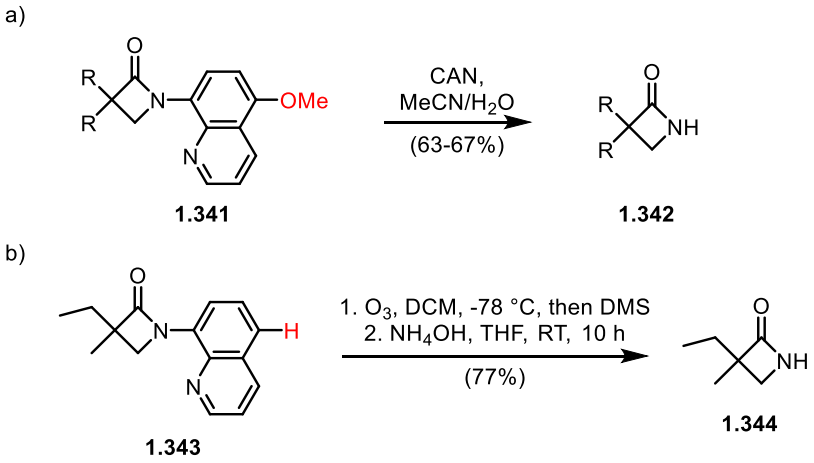
found possible when the MQ in **1.327** (Figure 74) was utilized. By following the reported procedure of Bull, AQ-derivative **1.339** was synthesized. Ozonolysis and aminolysis at room temperature smoothly afforded the desired product **1.340** in high yield without either epimerization or the need for the MQ auxiliary.



1.339 **1.340**

Figure 83. Previous unsuccessful removal of the AQ auxiliary and successful deprotection using pre-ozonolysis

In 2014, the groups of Ge [108-109] and Kanai [110] reported the intramolecular C–H bond formation of AQ-amides to construct the corresponding β-lactam moieties. However, the removal of the auxiliary required the cleavage of the *N*-quinoline bond. Although the scope was again performed using the AQ directing group, cleavage was demonstrated on MQ derivatives, as summarized in Figure 84a. Since ozonolysis should enable the same transformation on the actual AQ auxiliary, we prepared β-lactam **1.343**. As shown in Figure 84b, short ozonolysis facilitated aminolysis at room temperature to afford the desired product **1.344** in very good yield.



1.341 **1.342**

1.343 **1.344**

Figure 84. Previous deprotection of β-lactams by use of the MQ auxiliary (a) and deprotection of the AQ moiety by O_3 (b)

Besides the cleavage of the AQ moiety to the carboxylic or to the primary amide, the use of different nucleophiles should be applicable. Indeed, use of methanol or pyrrolidine as alternative nucleophiles and microwave irradiation afforded the corresponding ester **1.345** or tertiary amide **1.346**, respectively (Figure 85). The reaction proceeded in good yields, as determined by ^{1}H-NMR spectroscopy.

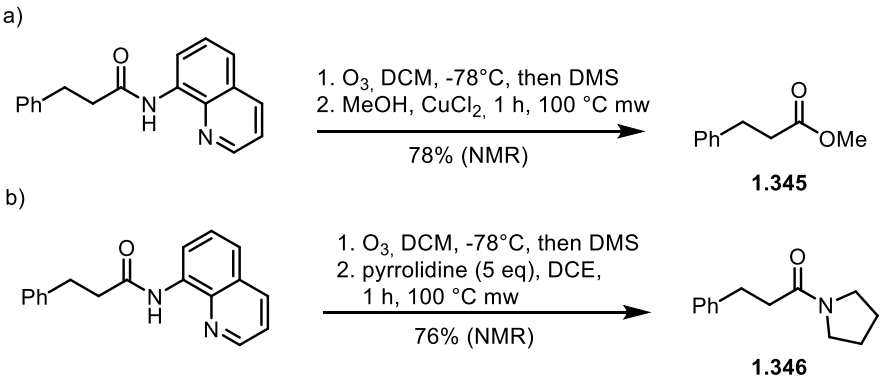


Figure 85. Methanolysis or transamidation of the AQ amide facilitated by pre-ozonolysis

1.3.6 Synthesis of DHAA-analogues

Application of this method to the cleavage of the AQ-dehydroabietamide **1.312** was found to be equally successful. However, regardless from the conditions used after ozonolysis, only the primary carboxamide **1.347** could be isolated. The result can be attributed to the significant steric bulk of the substrate and exclusive attack of the individual nucleophile at the distal imide carbonyl group in intermediate **1.336** (Figure 79). This behavior is in accordance with previous results on the particular resistance of dehydroabietic acid derivatives towards hydrolysis. In fact, the hydrolysis of structurally simple methyl dehydroabietate is known to be problematic, as reported by Wood [111] or Corey.[112] Ozonolysis and subsequent aminolysis of **1.312** however afforded the desired amide **1.347** in nearly quantitative yield and high purity, as shown in Figure 86.

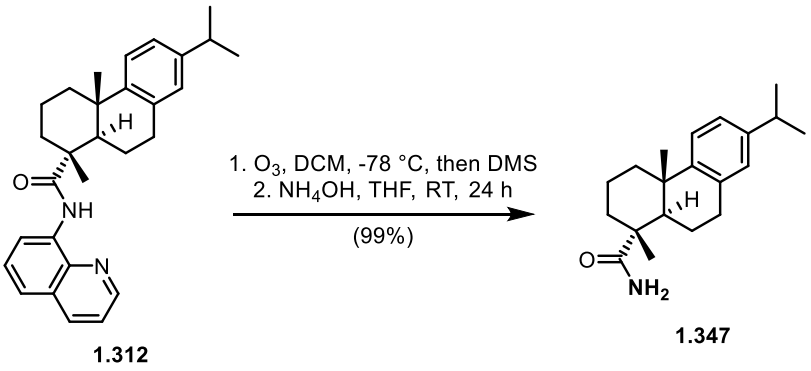


Figure 86. Ozonolytic cleavage of the highly hindered DHAA aminoquinoline amide

Ozonolytic cleavage of the more elaborate structures **1.313a-d** was found equally successful. In order to simultaneously hydrolyze the ester functionality in **1.313d** and apply a uniform procedure to all compounds, the imide intermediates were hydrolyzed with HCl to afford the desired amides **1.329a-d**, as shown in Figure 87. The structure of anisole **1.329a** was unambiguously assigned by x-ray crystallography.

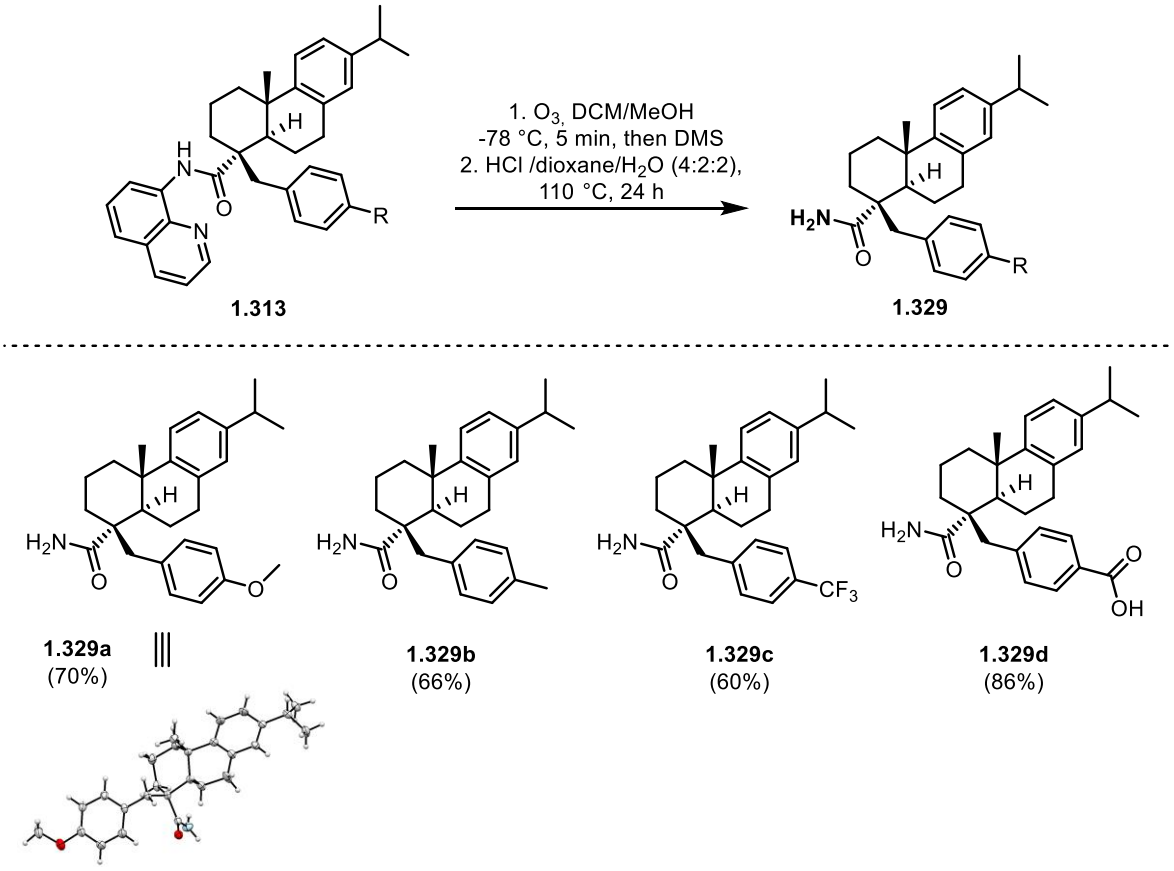


Figure 87. Successful deprotection of C-19 arylated DHAA derivatives

In order to prepare the carboxylic acid analogues from the hindered amides **1.329**, *N*-nitrosylation with $NOBF_4$ and subsequent hydrolysis of the diazonium intermediates was carried out. This method was successful and finally yielded the desired DHAA analogues **1.311** in low to very high yields (Figure 88).

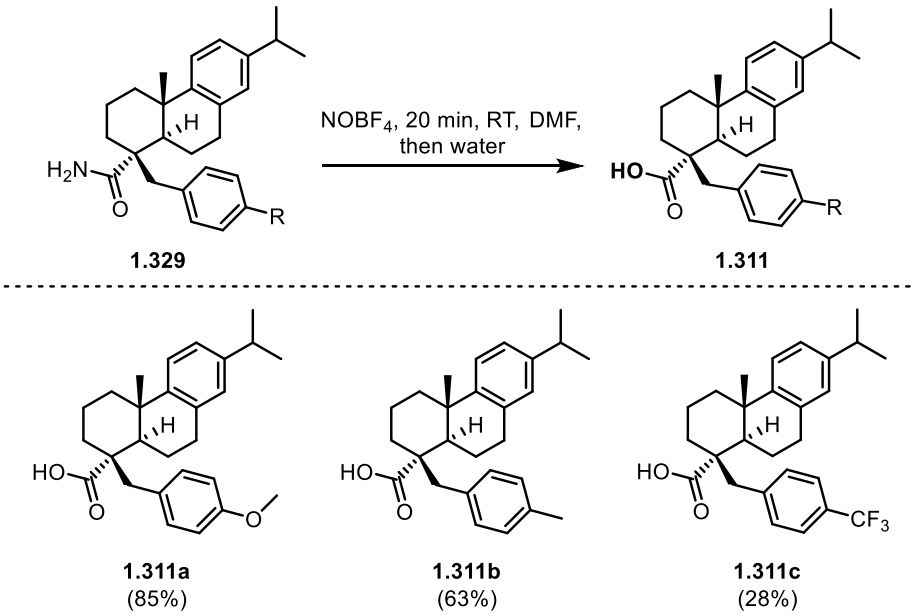


Figure 88. Hydrolysis of C-19 arylated DHAA carboxamides by $NOBF_4$

1.3.7 Biological activity of C-19-DHAA aryl analogues

The carboxylic acids **1.311** and the carboxamides **1.329** were screened as potential modulators of GABA-A receptors by the group of Steffen Hering at the University of Vienna (Department of Pharmaceutical Chemistry). Only the carboxylic acids **1.311a-c** and **1.329d** could be tested due to limited solubility. Prior experiments have shown that the carboxylic acid functionality at C-18 in DHAA **1.300** is essential for the compound to act as positive modulator of GABA-induced chloride currents. Although we had hypothesized that modification of the compound's lipophilicity might have a positive influence on the biological activity, arylation on C-19 was found to decrease the activity of DHAA, as clearly shown in Figure 89.

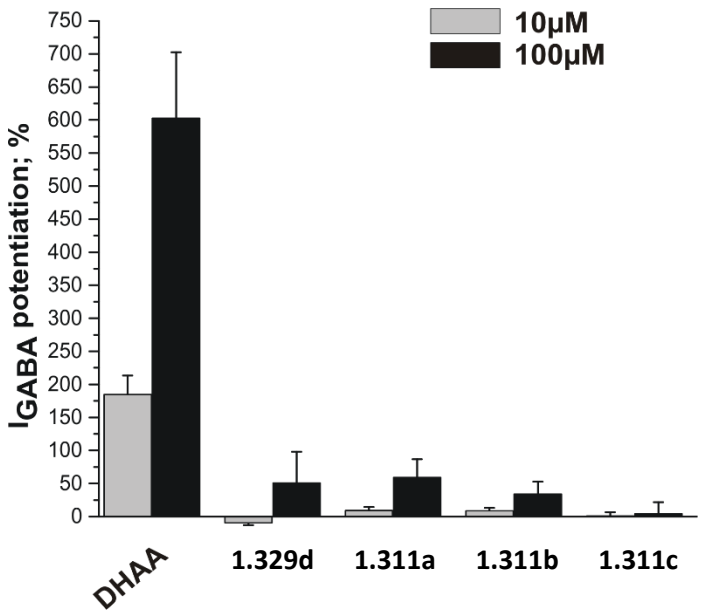


Figure 89. Results for the C-19 arylated DHAA analogues as potential GABA-A receptor modulators

The carboxylic acids **1.311a-c** and **1.329d** were further sent to the Institute for Molecular Bioscience at the University of Queensland in Australia and screened for their activity against multidrug-resistant bacteria strains (CO-ADD initiative, Community for Open Antimicrobial Drug Discovery). Screening by a whole cell inhibition assay revealed amide **1.329d** to have antibacterial activity against a methicillin- and oxacillin-resistant strain of *S. aureus* (MRSA, ATCC 43300), with an inhibitory concentration of 32 µg/mL.

1.3.8 Conclusion

The synthesis of DHAA aryl analogues proved to be a challenging endeavor. Although the C–H activation step itself was initially expected to be difficult it was the cleavage of the AQ directing group that proved most troublesome instead and brought the problematic removal of this popular auxiliary in hindered substrates to our attention. As described in this chapter, the fragmentation of the AQ directing group by ozonolysis is an effective approach for the removal of this auxiliary. Since this transformation affects primarily the quinoline moiety rather than the amide bond, resistance caused by sterical hindrance of the substrate is circumvented. The value of this method was not only demonstrated on the highly hindered C-19-aryl analogues **1.313** but has also already found use by other research groups by the time of writing. For instance, the diverse cleavage of the AQ directing group in C–H activation products derived from Pyroglutamic Acid by use of our protocol was achieved, as recently described by the group of Schreiber. [113] Using the procedure for aminolysis, quinoline **1.348** could be converted to the amide **1.349** (or **1.350** after epimerization) as shown in Figure 90. Alternatively, the carboxylic acid **1.351** could be prepared upon use of our hydrolysis conditions. In striking contrast, more classical hydrolysis conditions using LiOH caused epimerization to afford *trans*-isomer **1.352**.

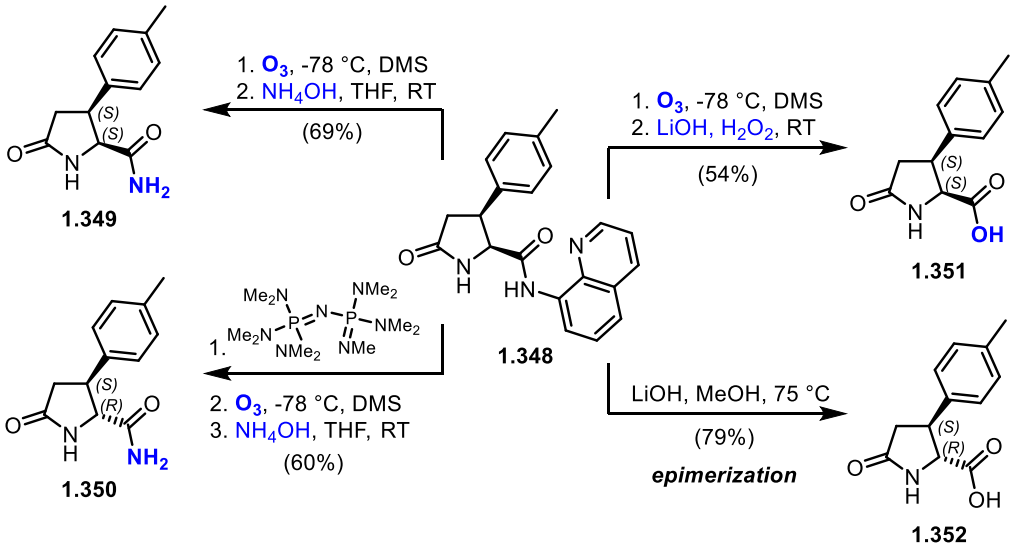
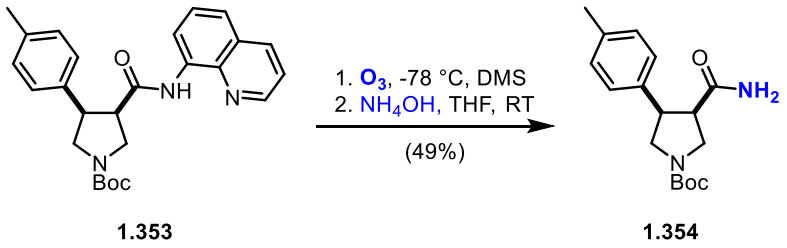


Figure 90. Utilization of our method by the group of Schreiber

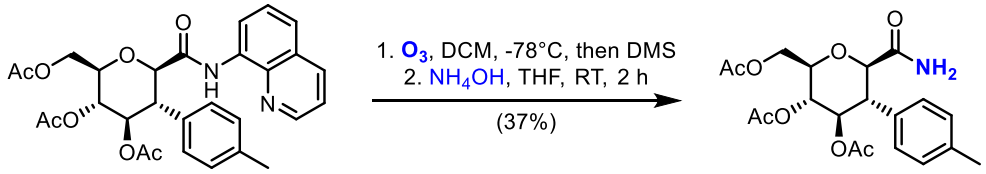
Furthermore, the group of Bull utilized our methodology for the deprotection of a pyrollidine derivative **1.353** (Figure 91).[114] Although cleavage to the carboxylic acid was also found possible using conventional conditions (*via* prior *N*-Boc activation), the primary amide **1.354** could be accessed by ozonolysis and subsequent aminolysis.



1.353 **1.354**

Figure 91. Utilization of our method by the group of Bull

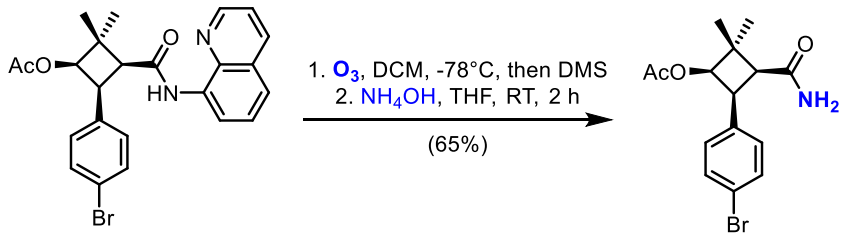
A more intriguing example for the application of our methodology is the successful ozonolytic cleavage of the AQ auxiliary in glycoside **1.355**, as reported recently by Messaoudi and coworkers (Figure 92).[115] Interestingly, it was stated that other methods failed to give the desired deprotected product.



1.355 **1.356**

Figure 92. Utilization of our method by the group of Messaoudi

A last demonstration of the exceptional mildness of our method was most recently reported by the group of Verho (Figure 93).[116] With the aim of preserving the delicate polysubstituted cyclobutane motif in **1.357**, the cleavage of the aminoquinoline moiety by our aminolysis conditions was their method of choice. Remarkably, cleavage of the amide was found possible with ease and most remarkably keeping the acetate untouched. The desired product **1.358** was isolated in respectable 65% yield without epimerization.



1.357 **1.358**

Figure 93. Utilization of our method by the group of Verho

Besides the examples as described above, our ozonolytic method has further been applied in other reports. [117-118] We hope that this method may serve also other research groups in the future for the removal of this important directing group.

1.4 Oxidation of Ring B in Pentacyclic Triterpenes by Sequential C–H Activation

1.4.1 Introduction

1.4.1.1 C–H Oxidation in natural product chemistry

Methods for the oxidation of unactivated C–H bonds are on the rise in synthetic organic chemistry. Such transformations do not only allow the rapid derivatization of a plethora of drug-like molecules [119] but also play an essential role in the synthesis of defined natural products. [120] A modern view on the synthesis of highly oxidized molecules is the introduction of molecular complexity by oxidation of readily available molecules in lower oxidation state. [121] Such semisynthetic approaches can allow more efficient routes to complex natural products when compared to classic strategies. Since the carbon skeleton of the individual target molecule is often already present to a large extent in the starting material, methods for the formation of C-C bonds fade from the spotlight by choosing this approach. Instead, the new challenge can be found in the selective oxidation of specific C–H bonds. [122] However, if methods for the site-selective oxidation of abundant hydrocarbons can successfully be identified, unprecedented access can be gained to several higher oxidized members of a natural product family or synthetic analogues in a divergent manner. [123] An example is the synthesis of the steroid Ouabagenin **1.402** from readily available protected andrenosterone **1.400**, as reported by the group of Baran in 2015 (Figure 94). [124] The hydroxylation of C-19 in **1.400** was identified as a key obstacle. The oxidation of this position has already been achieved by the group of Jeger by a Norrish type II reaction and subsequent oxidation with LTA. [125] Baran and coworkers utilized a modified approach to this reaction and achieved the synthesis of highly oxidized Oubagenin **1.402.**

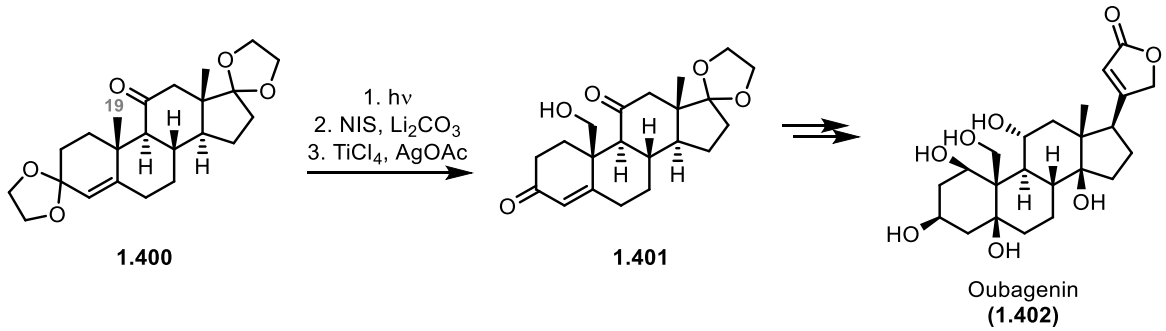


Figure 94. Baran´s synthesis of Oubagenin

1.4.1.2 Pentacyclic Triterpenoids

Naturally occurring triterpenoids are a very large family of natural products. They consist of more than one hundred different carbon skeletons and their individual members cover a wide range of biological activities. [126] One of the most famous triterpenes is squalene **1.403**, which together with 2,3-oxidosqualene is the precursor in the biosynthesis of many cyclic members of this family carried out by triterpene synthases (Figure 95a). [127] Cyclization and subsequent skeletal rearrangements of the latter generate a plethora of oligocyclic triterpene skeletons. Very prominent representative skeletons of pentacyclic triterpenes are the lupane **1.404**, ursane **1.405** and oleanane **1.406** skeletons. Specific representatives of each class are namely Betulinic Acid **1.407**, Ursolic Acid **1.408** and Oleanolic Acid **1.409**, as shown in Figure 95b.

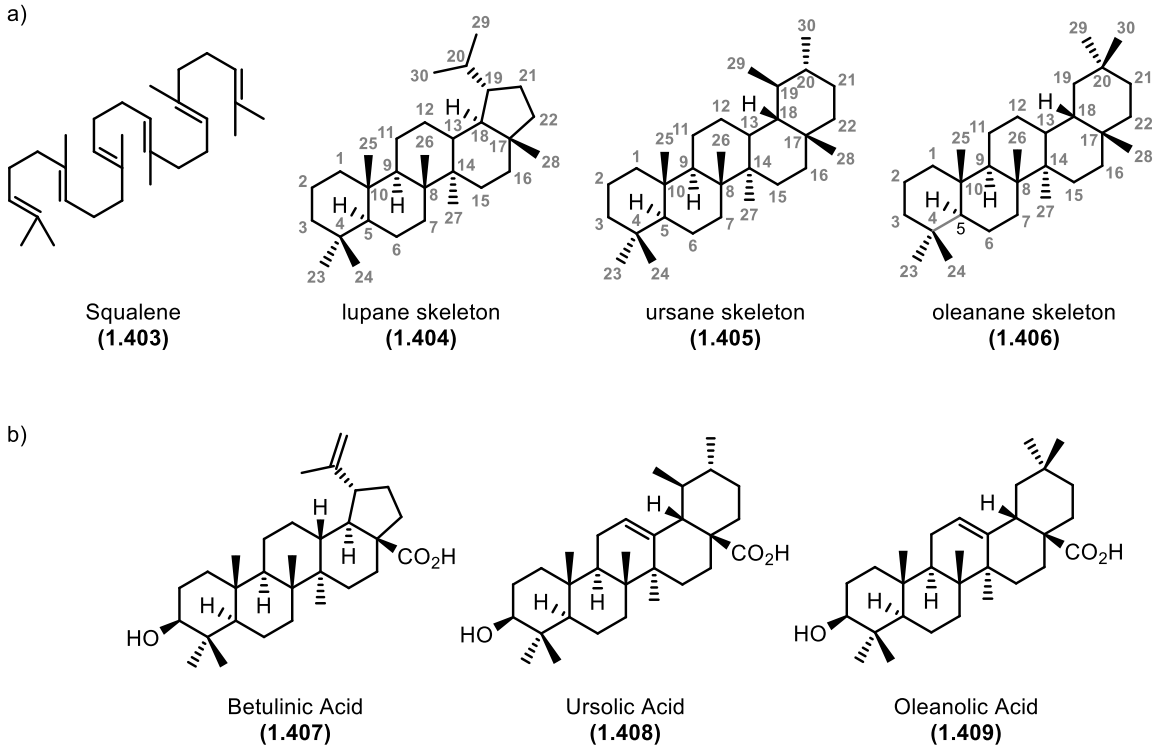


Figure 95. (a) Skeletons of selected pentacyclic triterpenes and (b) selected representatives of each class

Oleanolic Acid **1.409** and Ursolic Acid **1.408** are readily available abundant feedstock chemicals and have already been demonstrated to possess broad biological activity. [128] Nevertheless, despite their promising pharmacological properties, the application of these bulk chemicals as drugs is limited by their very poor solubility in aqueous media. This negatively effects the permeability and bioavailability

of the compounds. [129-130] This problem can be tackled by synthetic modification: indeed, significant research exists in the literature on the preparation of semisynthetic derivatives of pentacyclic triterpenoids such as Oleanolic Acid **1.409**. [131-133] However, chemical derivatization is only possible in the vicinity of the few functional handles already present. In Oleanolic Acid **1.409**, modification has therefore mainly been achieved in close proximity to the C-3 hydroxy group (located in ring A), the C12-C13 double bond (located in ring C) and the carboxylic acid at C-28.

Nature´s approach for increasing the solubility of pentacyclic triterpenes is the enzymatic C–H oxidation of their skeletons. This late-stage hydroxylation not only leads to structural diversification and consequent modulation of the biological activity but the additional hydroxy groups can also serve as additional anchor functionalities enabling the installation of sugar units in saponins. [134] However, due to the enormous molecular complexity in such triterpene saponins, their chemical synthesis is particularly challenging and has only been realized on few instances. [135] A prerequisite for the synthesis of saponins is the sufficient availability of their individually hydroxylated aglycons. However, the isolation of the latter from plant material is often highly limited due to, either their occurrence in only minor amounts or the requirement for laborious separation procedures of complex mixtures. [136]

The hydroxylation of pentacyclic triterpenoids such as **1.407**-**1.409** in plants is catalyzed by cytochrome P450 enzymes. Several monooxygenases, their individual substrates and the regioselectivity of their hydroxylation have already been identified. [137] The diversification of Oleanolic Acid **1.409** and the corresponding identified enzymes responsible for these transformations are shown in Figure 96a. As can be seen, enzymatic hydroxylation often occurs on C2 and C23 to yield products such as ring A - hydroxylated 2β-Hydroxyoleanolic Acid **1.410**, Maslinic Acid **1.411** and Hederagenine **1.413**. Oxidation at C-16 yields ring D - modified 16β-Hydroxyoleanolic Acid **1.414**. In 2017, Miettinen *et al.* reported that the CYP716 family is responsible for hydroxylation of C6 in ring B to yield 6β-Hydroxyoleanolic Acid **1.412**. [138] As shown in Figure 96b, CYP716E41 is not only capable of oxidizing ring B in Oleanolic Acid **1.409** but also in Ursolic Acid **1.408** to yield **1.415**. This is unsurprising, since pentacyclic triterpenes **1.408** and **1.409** share a uniform western carbon skeleton and chemical transformations on the western hemisphere of Oleanolic Acid **1.409** may therefore be extensible to related subfamilies of pentacyclic triterpenoids.

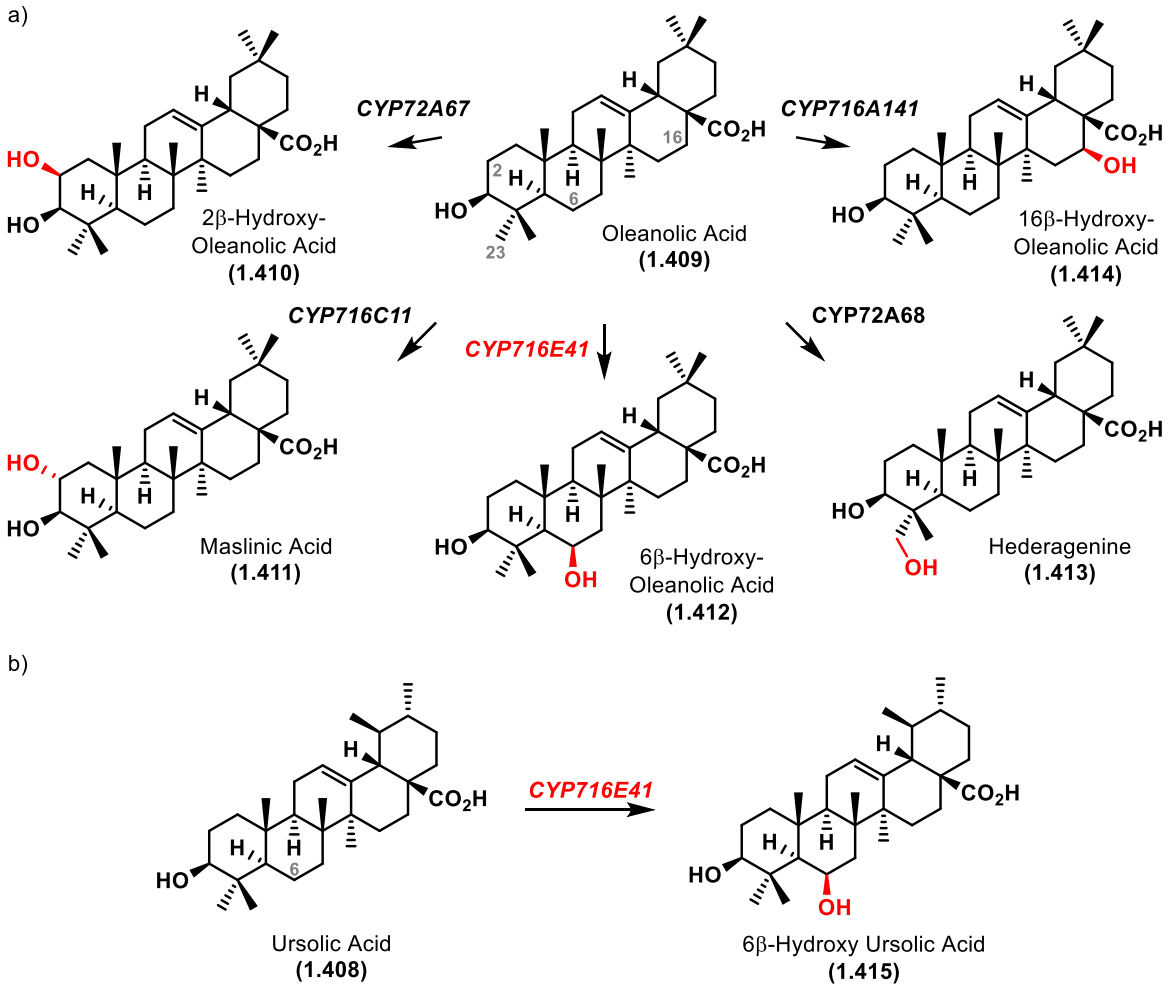


Figure 96. (a) Enzymatic hydroxylation of Oleanolic Acid by P-450 monooxygenases and (b) C-6 hydroxylation of Ursolic Acid by the same enzyme

1.4.1.3 Polyhydroxylated Oleanane Triterpenoids

In fact, the enzymatic hydroxylation of pentacyclic triterpenes not only takes place as a single event but can further lead to the production of polyhydroxylated aglycons with presumably better solubility. Representatives of such highly oxidized triterpenoids bearing a hydroxyl group at ring B are shown in Figure 97. These molecules are reported to have superior anti-inflammatory activity (values in italic) compared to their C-6 deoxy analogues (values indicated in brackets). The anti-inflammatory activity of Uncargenin C **1.416** was especially attributed to the presence of the C-6-OH group [139] and this observation is further reinforced by the reported superior activity of higher oxidized analogues Terminolic Acid **1.417** [140] or Protobassic Acid **1.418**. [141] Furthermore, **1.416** was reported to posess moderate activity against several cancer cell lines, whilst [142] saponins of Protobassic Acid **1.418** are further reported to have high antitrichomonas [143] and antitumor activity. [144]

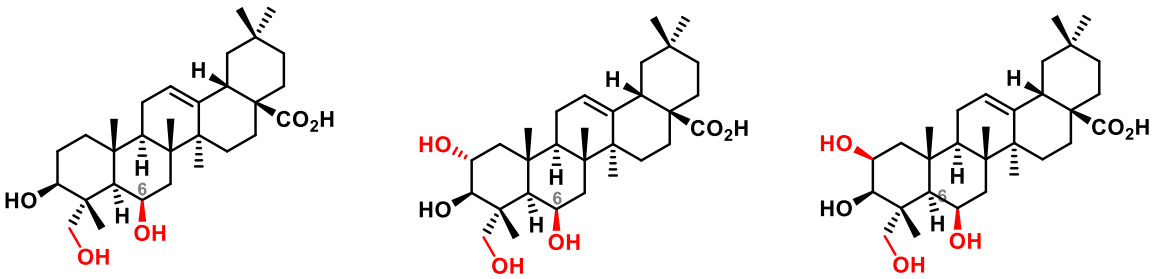


Figure 97. Highly anti-inflammatory polyhydroxylated oleanane triterpenoids

The isolation of Protobassic Acid **1.418** by hydrolysis from its saponins has been found problematic and revealed the chemical instability of the 6β-hydroxy group towards acidic conditions. In 1974, Yosioka and coworkers revealed that **1.418** is the genuine aglycon of numerous saponins instead of the previously reported Bassic Acid **1.419**, as shown in Figure 98. [145] Notably, **1.419** was previously obtained from acidic hydrolysis of sapogenins. Hydrolysis of a saponin mixture (obtained from seed kernels from *Madhuca longifolia L.*) by soil bacteria however led surprisingly only to isolation of **1.418**. Since then, Bassic Acid **1.419** has been considered to be an artefact of Protobassic Acid **1.418** and not a metabolite of plant origin. The 6β-hydroxy group in **1.418** was also found to be particularly hindered, as it resisted an attempt at global protection of the molecule (resulting in triacetylated ester **1.420**.)

A rationale for the dehydration of **1.418** can be found in the release of 1,3-diaxial interactions in Protobassic Acid **1.418**, as indicated in structure **1.421**. This theory also explains the formation of Mimusopic Acid **1.422**, which was isolated in 1993 by Mahatu and coworkers. [146] In this study, Bassic Acid **1.419** was found to be a highly strained intermediate and tends to further release more 1,3-diaxial strain (indicated in structure **1.423**) when subjected to acidic conditions. Rearrangement to the newly termed mimusopane skeleton allowed the isolation of Mimusopic Acid **1.422**.

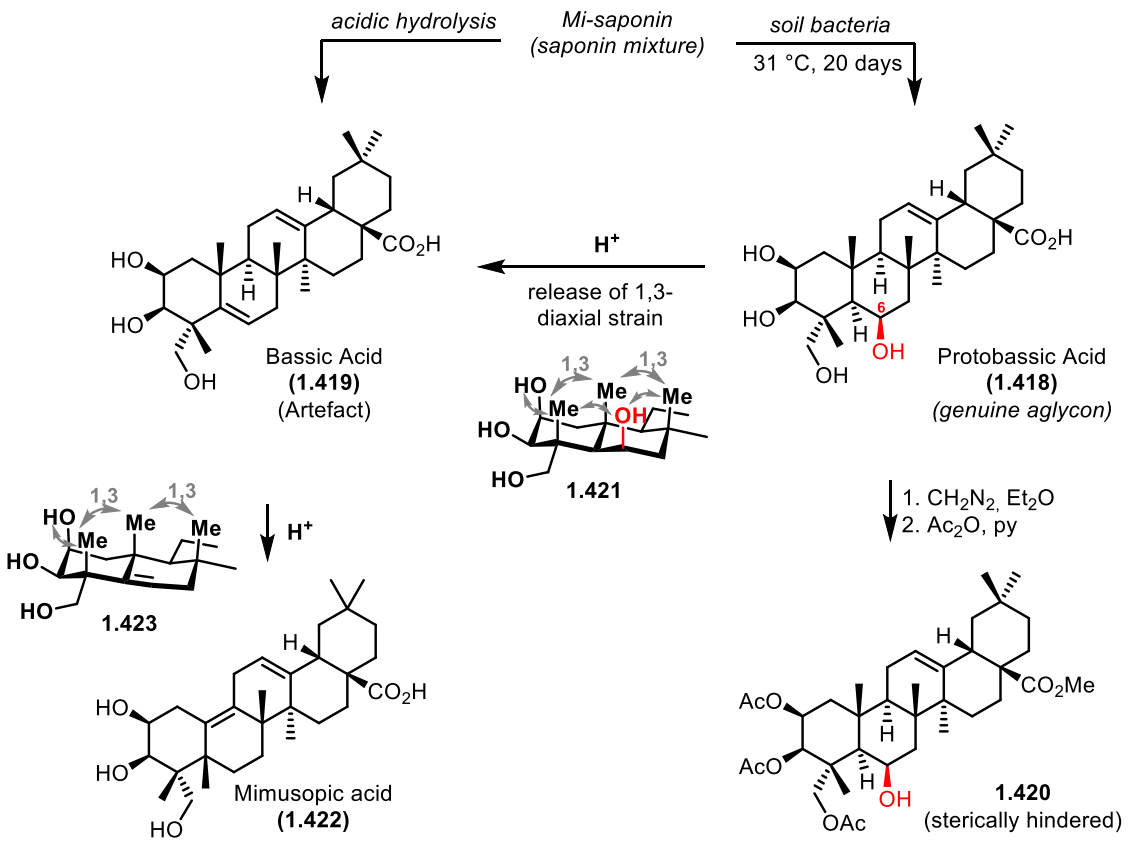


Figure 98. Isolation of the genuine aglycon Protobassic Acid and formation of its artefacts

1.4.2 C–H Oxidation in pentacyclic triterpenoids

The synthesis of highly oxidized oleanane triterpenoids **1.416**-**1.418** has not yet been reported. This might be due to the fact that, to the best of our knowledge, a serviceable protocol for the hydroxylation of C-6 in pentacyclic triterpenoids by C–H oxidation does not exist. Such a method would be highly desirable in order to allow the chemical modification of ring B in pentacyclic triterpenoids and therefore expand the chemical space in the synthesis of potential drug candidates.

Until today, only a few methods for the direct functionalization of C–H bonds in pentacyclic triterpenoids were reported. [147] As already described in the introduction, Baldwin´s method is one of the most popular reaction sequences for the hydroxylation of C-23 and did not only allow the synthesis of natural products such as Lobatoside A **1.026** (Figure 8) but was also utilized in the preparation of synthetic analogues of Oleanolic Acid **1.409**. [148] A more recent entry for the oxidation of C-23 was reported by Hartwig and co-workers in their synthesis of Hederagenine **1.413** from Methyl oleanate **1.424** by catalytic C–H silylation, as shown in Figure 99. [149] Using that protocol, **1.413** was prepared in only 4 steps from Oleanolic Acid, which is much more efficient than the previous preparation of

1.413 by Baldwin´s method in 10 steps. [150] The first step is an iridium-catalyzed silylation of the alcohol in Methyl oleanate **1.424** with Et_2SiH_2. Subsequently, intramolecular C–H silylation was found to take place when using the same iridium catalyst, tetramethyl phenanthroline as ligand and norbornene as hydrogen acceptor. Tamao-Fleming-oxidation afforded the desired diol Hederagenine **1.413** in an overall yield of 61% from **1.424**.

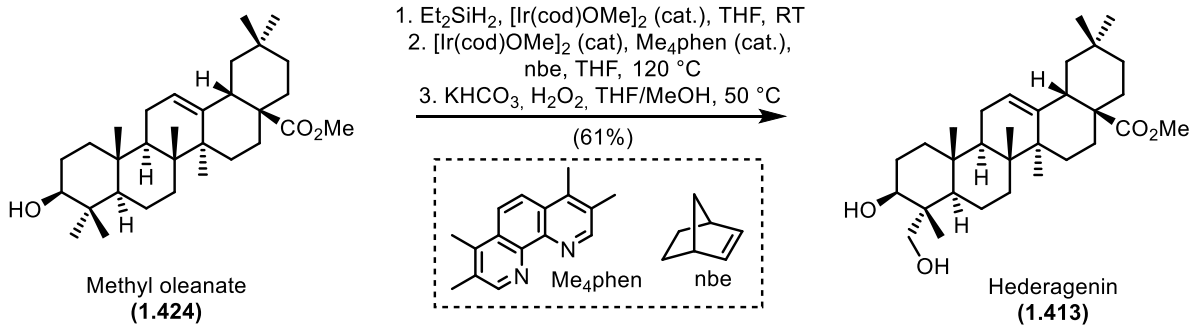


Figure 99. Synthesis of Hederagenin, as reported by Hartwig and coworkers

Baran and coworkers identified the problem of the extreme insolubility of pentacyclic triterpenes and that only a few positions of their carbon skeletons can be functionalized by synthetic means. [147] A survey of C–H oxidation methods has been carried out on the lupane skeleton in order to identify suitable conditions. However, as shown in Figure 100, only a few methods have been found applicable where the carbon skeleton stayed intact. While Betulinic Acid **1.407** was hydroxylated by use of Hartwigs method in 6 steps to yield **1.425** (Figure 100a), the Suaréz modification was found feasible when applied to a modified betuline derivative **1.426** to generate ether **1.427** in 30% yield (Figure 100b). Besides these directed methods, the non-directed oxidation of **1.426** has been attempted (Figure 100c). By NMR studies, C-6 has been identified to be the most electron-rich methylene group in **1.426** and, therefore, should undergo preferential oxidation. However, a screening of dozens of oxidants for direct C-6 oxidation failed, resulting in either no reaction or intractable mixtures. Finally, oxidation with methyl(trifluoromethyl)dioxirane (TFDO) provided the C-16 oxidized product **1.429** in 30% yield. Computational calculations revealed later a significant steric clash between the oxidant and the gem-dimethyl substituents at C-4 in the substrate to preclude successful oxidation at C-6.

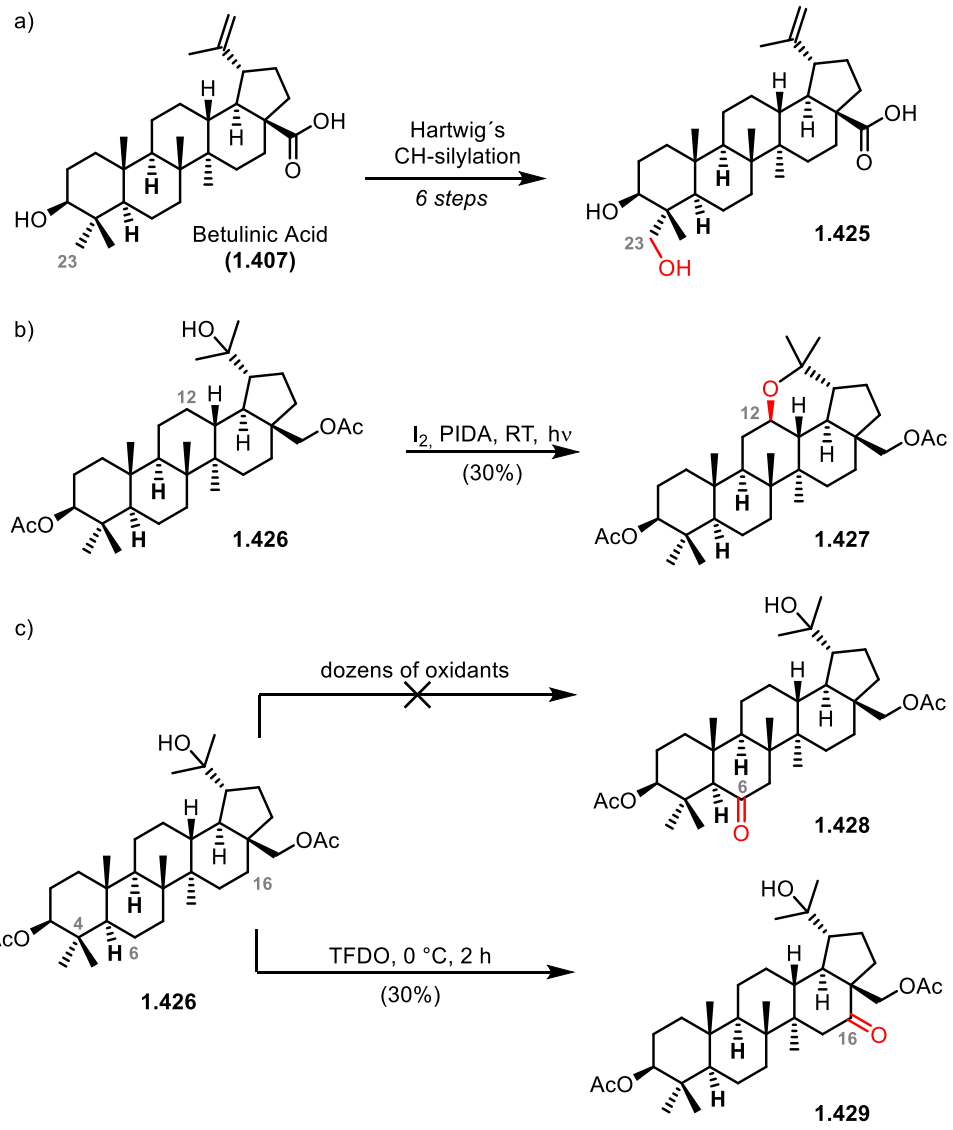


Figure 100. C–H Oxidation of Betulinic Acid and a Betuline derivative by Baran and coworkers

1.4.3 Objectives of this work

Oleanolic Acid **1.409** is one of the most abundant feedstock chemicals in the world. However, despite the large quantities, its use for medicinal purposes is hampered by the insolubility of the compound. In contrast, many polyhydroxylated oleananes such as Protobassic Acid **1.418** are commercially unavailable, preventing the exploration of their full pharmacological potential. Since hydroxylation at C-6 is a common feature of such metabolites, we sought a practical and efficient reaction sequence in order to oxidize ring B in Oleanolic Acid **1.409** and access several polyhydroxylated natural products of this family. Systematic screening of the compounds and intermediates will hopefully reveal some insight about the influence of C-6-hydroxylation on biological activity. Since several subfamilies such

as the lupanes **1.404** or the ursanes **1.405** share a uniform western carbon skeleton, the reaction sequence developed should furthermore be applicable to the synthesis of highly oxidized pentacyclic triterpenoids of related subfamilies. The synthesis as described below was partially conducted with Christian Knittl-Frank. Complementary information can be found in his master thesis, where the synthesis of Hederagonic Acid is described in detail. [151]

1.4.4 Synthetic approach

Since a straightforward and non-directed oxidation of C-6 was met with resistance as described before by Baran due to significant steric hindrance, we targeted a directed C–H oxidation to access this methylene group. However, due to the lack of functionality in Oleanolic Acid **1.409**, a sequence of C–H oxidation reactions will be required (Figure 101). Considering all functionalities in **1.409**, the C-3 hydroxy group in **1.430** is closest to C-6 and therefore the most logical starting point. Furthermore, significant literature precedence for the hydroxylation of C-23, directed by the C-3 hydroxylation, exists. Thereby, the newly introduced C-23-OH may further serve as a handle for the directed oxidation of C-6 as indicated in structure **1.431**. By such a sequence, the obstacle posed by the quaternary center at C-4 towards ring B should be conquerable. A protected key intermediate **1.432** would be desirable which may further be transformed to various natural products. Also desirable is a ketone oxidation state at C-3 for the late-stage diversification of C-2. Several polyhydroxylated triterpenoids, such as **1.416** or **1.418**, bearing multiple hydroxy groups might become accessible by this approach.

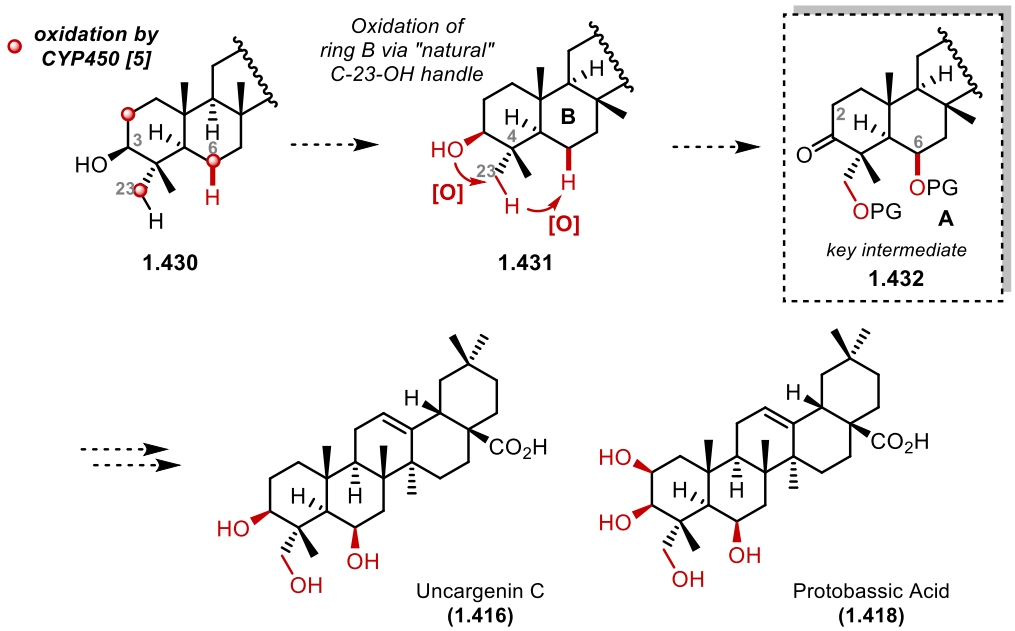


Figure 101. Sequential C–H oxidation to access ring B in Oleanolic Acid

1.4.5 Initial C–H oxidation attempts

A suitable candidate for the investigation of the C–H oxidation at C-6 would be Methyl hederagonate **1.439**, as shown later in Figure 104. The preparation of the free carboxylic acid (Hederagonic Acid) was already reported in 2010 by Sun and coworkers in 9 steps from Oleanolic Acid **1.409** using Baldwin´s method. [152] However, this long multi-step synthesis is synthetically not very practical. The most efficient approach to quickly establish the desired oxidation state in **1.439** was deemed to be Sanford´s catalytic C–H acetoxylation. In order to investigate this transformation on the oleanane skeleton, we prepared oxime **1.433** in three steps from **1.409** following modified procedures from the literature (Figure 102). [150]

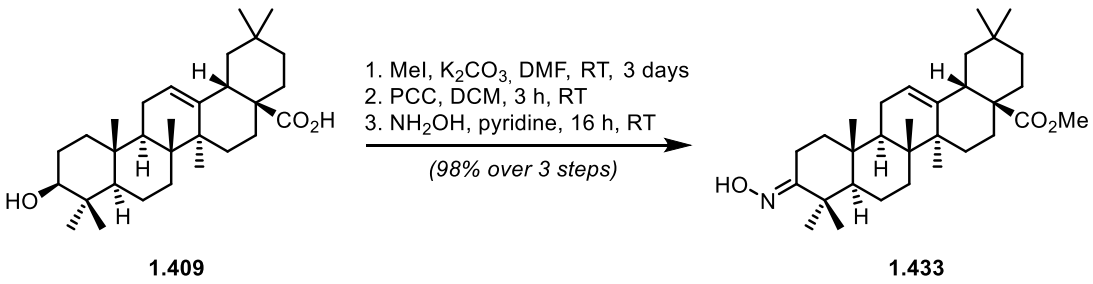
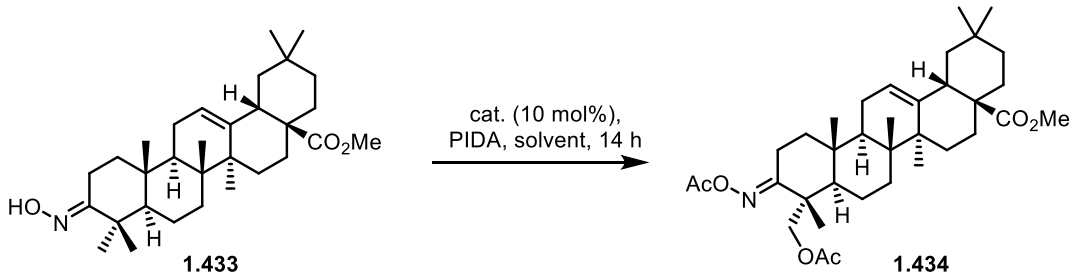


Figure 102. Preparation of the precursor for C–H Acetoxylation

With **1.433** in hand, we attempted C–H acetoxylation using $Pd(OAc)_2$/PIDA in a solvent mixture of Ac_2O and AcOH. A first attempt at 100 °C yielded the desired product **1.434**, albeit in only 15% yield (NMR) in a complex mixture. (Table 6, entry 1). In order to address potential overoxidation of the product, reducing the temperature was shown to be more beneficial than reducing the amount of oxidant (Table 6, entry 2-4). Pre-stirring of the starting material in the solvent before adding the reagents led to a slight improvement and isolation of **1.434** in 53% (Table 6, entry 5). In the event, the product was obtained in an inseparable mixture with its C-4 epimer in a consistent diastereomeric ratio of around 80:20. An analogous reaction using the more hindered pivalate-derived material indeed led to the formation of a single diastereomer, but in very low yield (Table 6, entry 7). Furthermore, when upscaling using the optimal conditions was attempted, the yield was significantly lower when compared to the small-scale experiment (Table 6, entry 9-10).

*Table 6. C–H Acetoxylation on C-23 (*prestirring in solvent for 1.5 h at RT)*



Entry	Scale (mmol)	catalyst	PIDA (eq)	T (°C)	solvent	yield	d.r.
1	0.1	$Pd(OAc)_2$	1.5	100	$AcOH/Ac_2O$	15% (NMR)	n.d.
2	0.1	$Pd(OAc)_2$	1.5	90	$AcOH/Ac_2O$	32% (isol.)	79:21
3	0.1	$Pd(OAc)_2$	1.0	90	$AcOH/Ac_2O$	29% (isol.)	75:25
4	0.1	$Pd(OAc)_2$	1.5	80	$AcOH/Ac_2O$	48% (isol.)	79:21
5	**0.1**	**$Pd(OAc)_2$**	**1.5**	**80**	**$AcOH/Ac_2O$**	**53% (isol.)***	**81:19**
6	0.1	$Pd(TFA)_2$	1.5	80	TFA/TFAA	-	-
7	0.1	$Pd(OPiv)_2$	1.5	80	$PivOH/(Piv)_2O$	10% (NMR)	>95:5
8	0.1	$Pd(OAc)_2$	1.2	80	$AcOH/Ac_2O$	45% (isol)*	81:19
9	0.6	$Pd(OAc)_2$	1.5	80	$AcOH/Ac_2O$	39% (isol.)*	80:20

10	1.1	$Pd(OAc)_2$	1.5	80	$AcOH/Ac_2O$	29% (isol.)*	80:20

In order to improve the diastereoselectivity of the reaction, various other bidentate directing groups were investigated, as shown in Figure 103. However, attempted installation of bulky imine directing groups such as **1.435** or **1.436** by condensation was in general not successful and led to recovery of starting material. The steric bulk at C-4 might be responsible for the observed instability. On the other hand, installation of an oxime directing group in **1.437** was accomplished, but this moiety was unsuccessful in the C–H acetoxylation reaction.

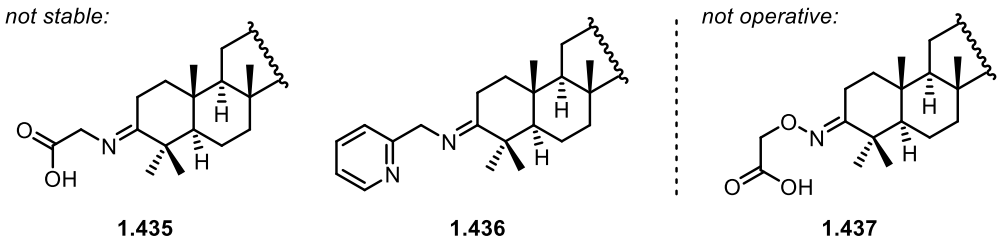


Figure 103. Bidentate directing groups investigated

With sufficient amounts of **1.434**, we next attempted a one-pot deprotection to directly afford methyl hederagonate **1.439**. Deacetylation of **1.434** with K_2CO_3 in methanol afforded oxime **1.438** in clean fashion. Without purification, crude **1.438** was directly subjected to mild hydrolysis using copper sulfate in a ternary solvent mixture, as shown in Figure 104. [153] Methyl hederagonate **1.439** could be isolated in 52% yield over 2 steps as a single stereoisomer. In order to decrease the overall number of steps, the reactions were attempted in one-pot to give **1.439** in 62% yield.

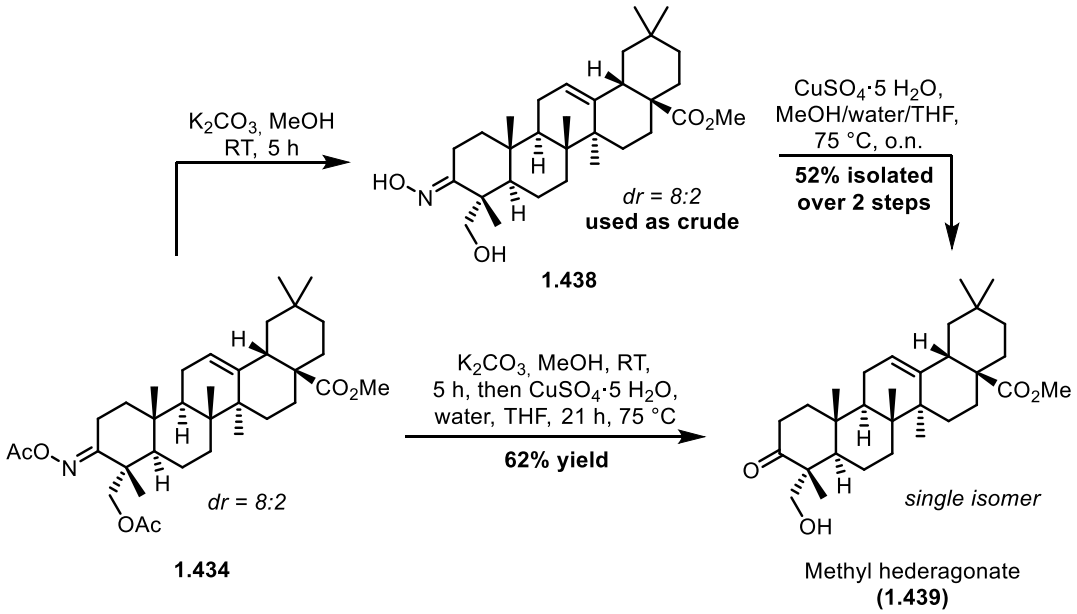


Figure 104. Deprotection of the C–H Acetoxylation product to afford Methyl hederagonate

With methyl hederagonate **1.439** in hand, we next investigated the oxidation of ring B by 1,5-HAT. However, preliminary experiments using the Suaréz modification of the HLF reaction on **1.439** did not yield any C-6 functionalized material but rather gave only inseparable mixtures (Figure 105). The use of oxime derivatives did not change this outcome. Analysis of the crude mixtures by mass spectrometry and ^{1}H-NMR indicated the presence of regioisomeric olefins **1.440**. The formation of **1.440** can be explained by assuming that the O-centered radical **1.441** preferentially undergoes β-fragmentation. The driving forces would be the release of 1,3-diaxial strain in **1.441** but also the formation of a stable (possibly resonance-stabilized) tertiary C-centered radical **1.442**.

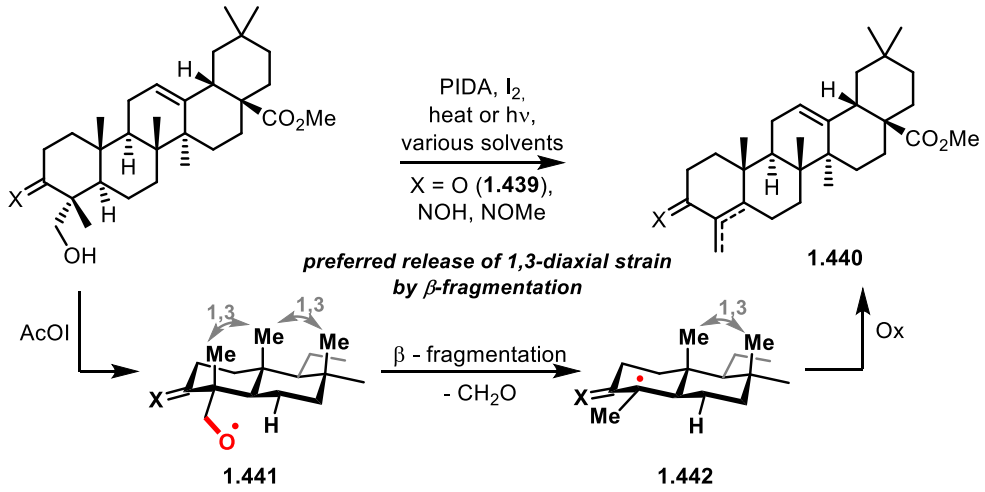


Figure 105. Release of 1,3-diaxial strain by β-fragmentation

The failure of hydrogen atom abstraction at C-6 due to preferred fragmentation is in accordance with the literature and has been observed on similar substrates. This fragmentation reaction is generally known as Suaréz reaction [154] and was for instance investigated by the group of Snyder on derivatives of betuline triterpenoids, as shown in Figure 106. [155] Similar to our case, fragmentation of the neopentylic alcohol **1.443** led to the formation of olefin **1.444** by fragmentation of ring A. Olefin formation is assumed to proceed by elimination of HI *via* a tertiary alkyl iodide intermediate.

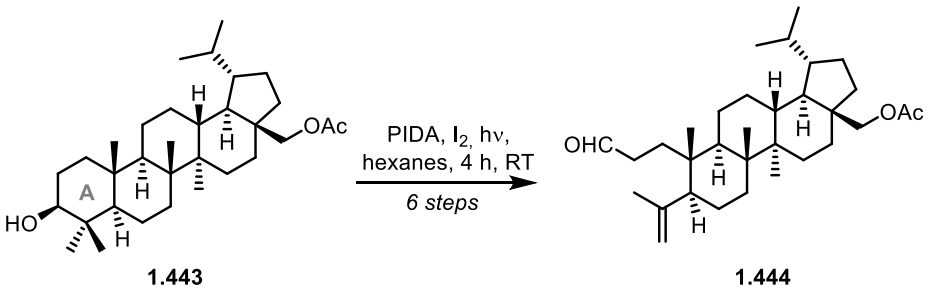


Figure 106. Snyder´s Suaréz reaction on a betuline derivative

As discussed above, first results indicated our substrate to be structurally unsuitable for the desired 1,5-HAT to proceed. However, further attempts were made to achieve the oxidation of ring B by modification of the substrate. In contrast to the substrates having sp^2-hybridization at C-3 as shown in Figure 105, ketal protection of **1.439** was envisaged to be less beneficial for the formation of a tertiary radical **1.442** at C-4. Therefore, the ketals **1.445a** and **1.445b** varying in ring size have been

prepared, as shown in Figure 107. Ketal formation proceeded smoothly without the need for purification. The bulky ketal group was envisaged to have a buttressing effect on the alkoxy radical intermediate and therefore facilitate the 1,5-HAT.

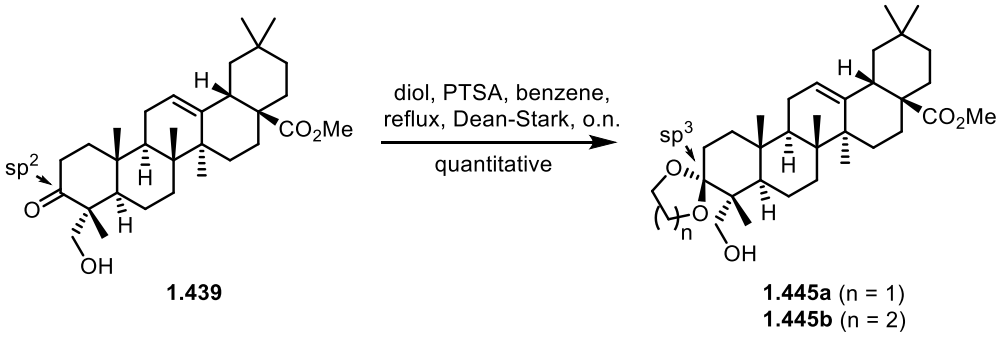
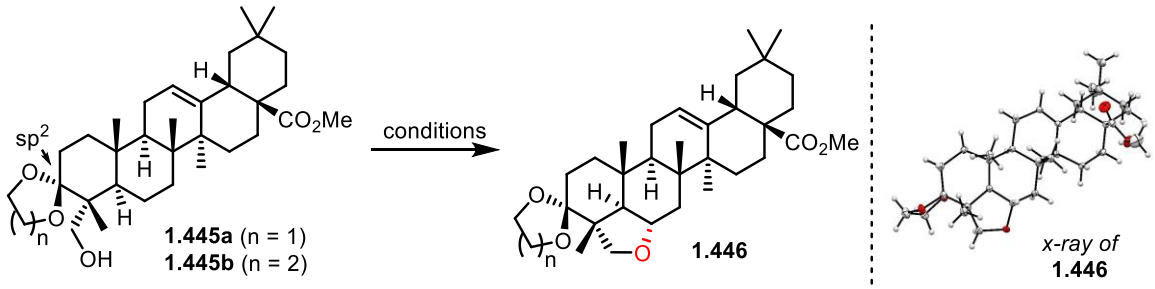


Figure 107. Installation of the ketal protecting group

Ketal **1.445a** was subjected to Suaréz modification and, much to our delight, the C–H etherification at C-6 was observed in 10% yield NMR (Table 7, entry 1). Use of 2 equivalents of LTA instead of PIDA surprisingly led to the formation of the product in 29% isolated yield (Table 7, entry 2). These conditions were shown to be quite close to optimal. Using the same conditions, change of oxidant (Table 7, entry 3) or ring-size of the ketal (Table 7, entry 4) led to no improvement. Subjecting the unprotected ketone **1.439** to the best conditions led again to complex fragmentation mixtures (Table 7, entry 5). These studies furthermore revealed the requirement for full conversion of the starting material, since alcohol **1.445a** and ether **1.446** were found to be inseparable by column chromatography. Other useful C-6 oxidized material has not been obtained.

Table 7. First successful C–H oxidation on C-6



entry	SM	oxidant	eq. I_2 / $CaCO_3$	solvent	condition	time	yield (ether)
1	**1.445a**	PIDA (1.1 eq)	1.1 / -	DCE	RT / hv	2 h	10% (NMR)
2	**1.445a**	**LTA (2 eq)**	**1.1 / 4**	**benzene**	**reflux**	**1 h**	**29% (isol.)**
3	**1.445a**	PIDA (2 eq)	1.1 / 4	benzene	reflux	1 h	18% (NMR)
4	**1.445b**	LTA (2 eq)	1.1 / 4	benzene	reflux	1 h	13% (NMR)
5	**1.439**	LTA (2 eq)	1.1 / 4	benzene	reflux	1 h	-

With the desired C-6 functionalized material in hand, we subjected **1.446** to various oxidants in order to convert the newly formed ether to a more synthetically useful lactone. However, as foreseeable and indicated in Figure 108, oxidation took preferentially place at the allylic position C-11 to yield **1.447**. This clearly showed the need for a more robust protection of the northern hemisphere of the molecule.

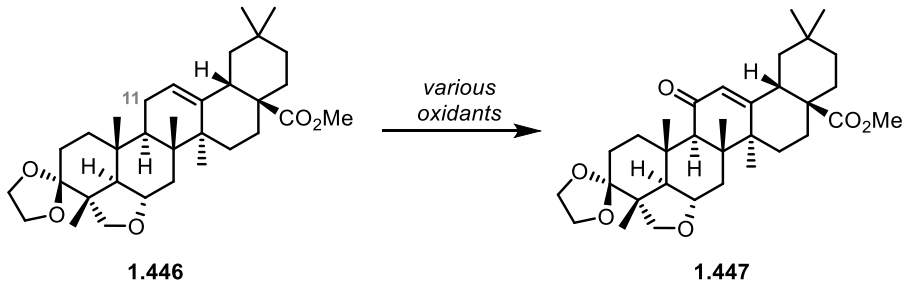
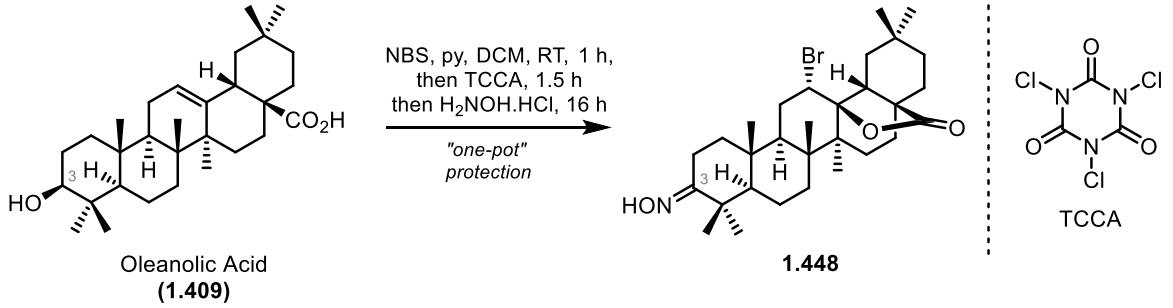


Figure 108. Allylic oxidation of C–H etherification product

1.4.6 Synthesis of polyhydroxylated oleanane triterpenoids

Encouraged by the knowledge of the possible oxidation at C-6 in protected Methyl hederagonate **1.445a**, we set out for the identification of more suitable protecting groups. In order to simultaneously protect the carboxylic acid and the olefin in **1.409**, halolactonization was found to be an attractive solution. [156] Initially, the chlorolactone protecting group was investigated but proved to be resistant to the reducing agents required for ultimate deprotection. Therefore, the bromolactone protecting group was used instead. The following reaction sequence was optimized by use of the bromolactone protecting group.

While the literature procedure to access the oxime derived from methyl oleanate **1.424** required three steps as shown in Figure 102, the synthesis was significantly shortened by the development of a one-pot procedure for the preparation of bromolactone **1.448** (Figure 109). Consecutive addition of *N*-bromosuccinimide (NBS), trichloroisocyanuric acid (TCCA) and hydroxylamine directly afforded the C–H acetoxylation substrate **1.448** in quantitative yield and high purity, without the need for further purification.



Oleanolic Acid
(1.409)

1.448

Figure 109 One-pot preparation of the C–H acetoxylation substrate

Oxime **1.448** could be converted further in a fashion similar as previously described (Figure 110). C–H acetoxylation proceeded smoothly to yield **1.449** but with a slight decrease in diastereoselectivity when compared to the use of methyl ester **1.434**. As already shown in Table 6 (entry 9-10), upscaling of this reaction was previously not successful due to formation of a black tar during the reaction. Indeed, such C–H oxidation typically proceeds at high temperatures (ca. 100 °C). However, the reaction was surprisingly found to take place already at room temperature, albeit with incomplete conversion. At 45 °C, the reaction was complete after 15 h. Notably, decreasing the temperature was key to solve the scalability issue as it prevented decomposition. On a 33 g scale, **1.449** was obtained in a respectable 56% isolated yield. Complete deprotection of the western hemisphere was again achieved using a one-pot procedure as described before to yield protected hederagonate **1.450** in only three steps from Oleanolic Acid **1.409**. Opening of the lactone moiety under these conditions did not occur to a noticeable extent. Since **1.450** can quantitatively be deprotected to yield Hederagonic Acid **1.451** by the use of zinc powder in acetic acid, this reaction sequence is the shortest reported synthesis of Hederagonic Acid **1.451** to date and allows the preparation of multigram quantities of the natural product. With **1.450** in hand, we aimed for the oxidation of C-6. Following again the reaction sequence developed before, ketal protection of **1.450** allowed successful C–H etherification. With the use of LTA, ether **1.452** was obtained in 48% yield (instead of 29% yield when substrate **1.445a** was used) over 2 steps. Further experimentation revealed the use of PIDA instead of LTA to be slightly superior,

yielding **1.452** in 53% yield without any requirement for heating or irradiation, as often required for the homolytic cleavage of the hypoiodite intermediate. [157]

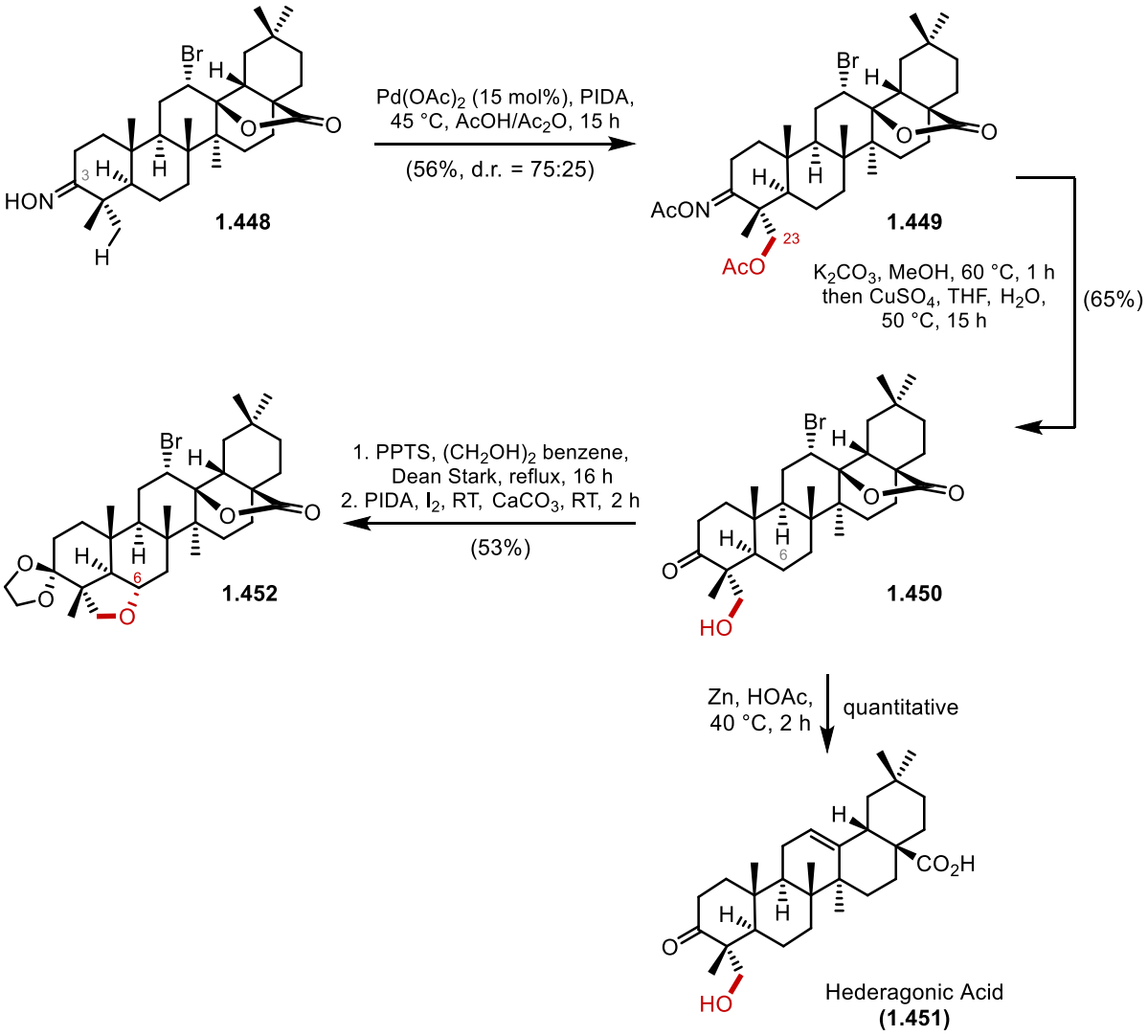


Figure 110. Sequence for oxidation of C-6 on the bromolactone substrate and concise synthesis of Hederagonic Acid

However, from many possible C-6 functionalized products, the THF-ether **1.452** is the synthetically least useful. As ether cleavage with boron trifluoride was not successful, oxidation of the ether to its lactone was envisaged. While chromium reagents such as PCC or the Jones reagent surprisingly did not give any conversion to the lactone, ruthenium tetroxide afforded a clean transformation. Prior deprotection of the ketal was found furthermore necessary to prevent preferential oxidation of the ketal protection group (Figure 111). However, due to the significant steric hindrance of the neopentylic ether methylene group in **1.453**, the reaction was found to be extraordinarily sluggish. Only stoichiometric amount of $RuCl_3$ and 10 equivalents of $NaIO_4$ led to full conversion after three days.

Although the reaction proceeded without the formation of byproducts in relevant amount, dilactone **1.454** was only obtained in 40% isolated yield. Despite extensive extraction of the crude reaction mixture with various organic solvents and mixtures, the yield could not be improved and the fate of the material remained uncertain. In order to avoid potential decomposition of material by the required high amount of oxidant, iterative addition of sodium periodate was found to generally increase the yield of the reaction. Dilactone **1.454**, which already corresponds to the desired intermediate **1.432** as described in Figure 101, was obtained in 69% yield over 2 steps and a total of 7 steps from Oleanolic Acid **1.409**.

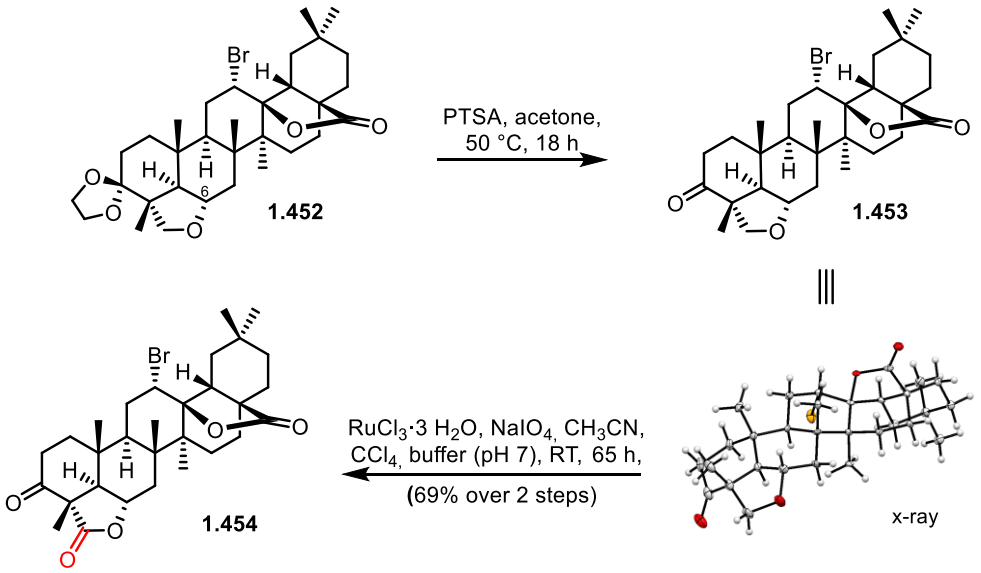


Figure 111. Synthesis of the synthetically useful dilactone by ether oxidation

Since introduction of the ketal protecting group (as mandatory for successful 1,5-HAT) results in additional steps, alternative methods for the functionalization at C-6 were probed as summarized in Figure 112. Attempted C–H lactonization of the carboxylic acid **1.455** by an iron-catalyzed oxidation as reported by the group of White, failed in our hands to give the desired lactone **1.454** (Figure 112a).[158] In order to exclude any potential mismatched effects, the chiral catalyst was employed in both configurations. A cerium-catalyzed C–H amination[159], as shown in Figure 112b failed to give any of the C-6 functionalized product **1.456** as well. Besides starting material, the fragmentation product **1.457** was isolated in 19% yield. The attempted amination reaction is reported to proceed by homolysis of Ce(IV)-alkoxide intermediates, which then undergo 1,5-HAT followed by addition of the C-centered radical to the azo-compound. The resulting *N*-centered radical then oxidizes the cerium(III)

to regenerate the active Ce(IV) catalyst.[159] However, β-fragmentation seems again to be the dominant fate of our substrate, judging from the missing carbon in **1.457**. As already indicated in the introduction, the Barton reaction is another reaction type operating *via* a 1,5-HAT. However, nitrite ester **1.458** was found not to be stable (Figure 112c).

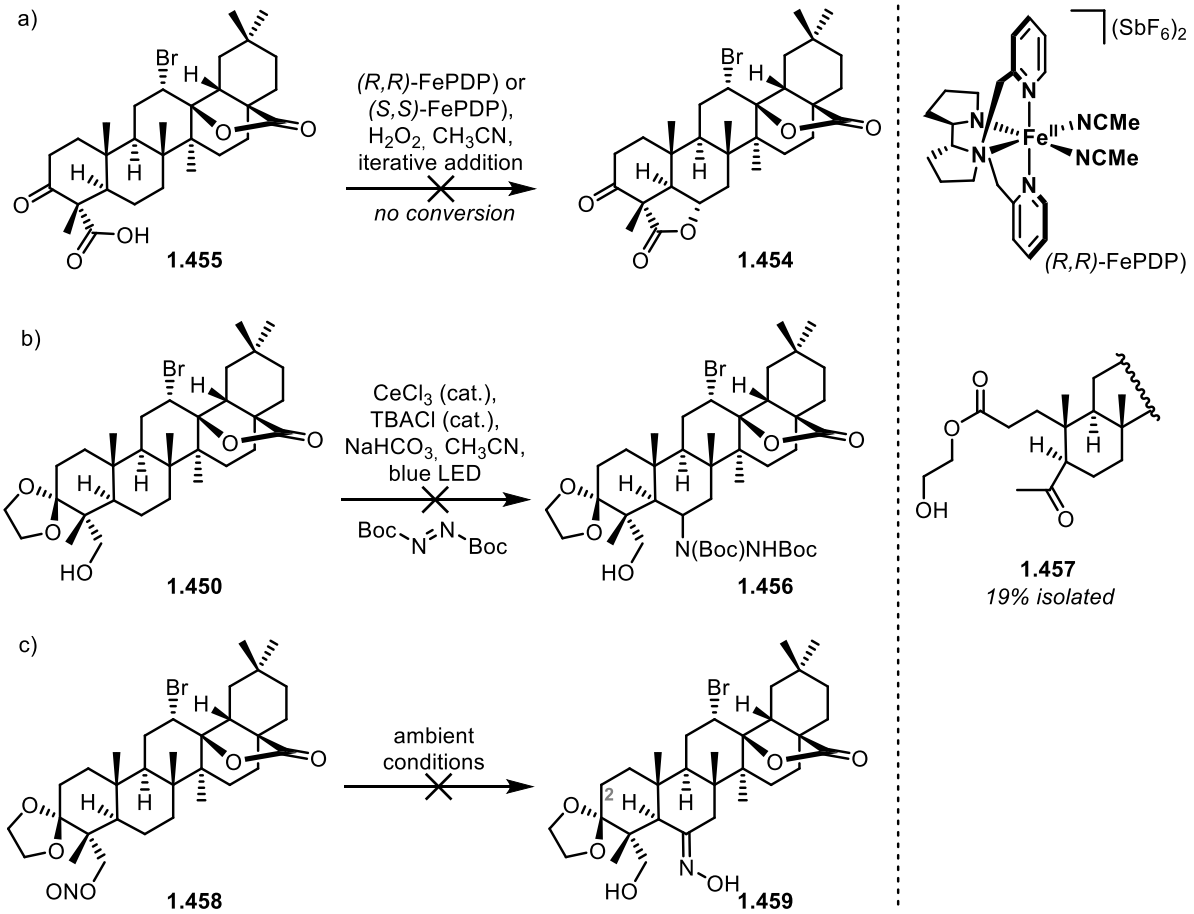


Figure 112. Selected examples for attempted alternative C-6-functionalization reactions

Although the desired C–H oxidation sequence of Oleanolic Acid **1.409** has been achieved, the conversion of dilactone **1.454** to the natural products (such as Uncargenin C **1.416** as shown in Figure 97) still requires diastereoselective reduction of the western part, inversion at C-6 and regeneration of the double bond.

In order to invert the stereogenic center at C-6, cleavage of the southern lactone in dilactone **1.454** was required in the first place. With two neopentylic lactones in **1.454**, some sort of differentiation was necessary. Initial results on the chlorolactone **1.460** are summarized in Figure 113. Direct

chlorolactone deprotection was met with resistance, as mentioned earlier. Upon refluxing with zinc powder, reduction of the C-3 ketone took place instead. Attempted regioselective reduction of **1.460** with defined amounts of reducing agents (DIBAL-H, $LiBH_4$, $LiAlH_4$) to yield a useful product such as **1.462** failed due to complete lack in regioselectivity by the reductants. Treatment with equimolar amounts of NaOMe (to presumably yield **1.463**) only led to partial decomposition, indicating some instability of **1.460** towards basic conditions. Surprisingly, treatment of **1.460** with excess of $LiAlH_4$ led to sudden formation of a voluminous precipitate. Work-up of the reaction revealed that incomplete reduction of the northern lactone in **1.460** to the very stable hemiacetal **1.464** had taken place. Additionally, reduction of the ketone at C-3 proceeded with complete diastereoselectivity to give the desired configuration. **1.464** was isolated in 94% yield as an inseparable (and ultimately irrelevant) mixture of C-28 epimers with a diastereomeric ratio of 83:17.

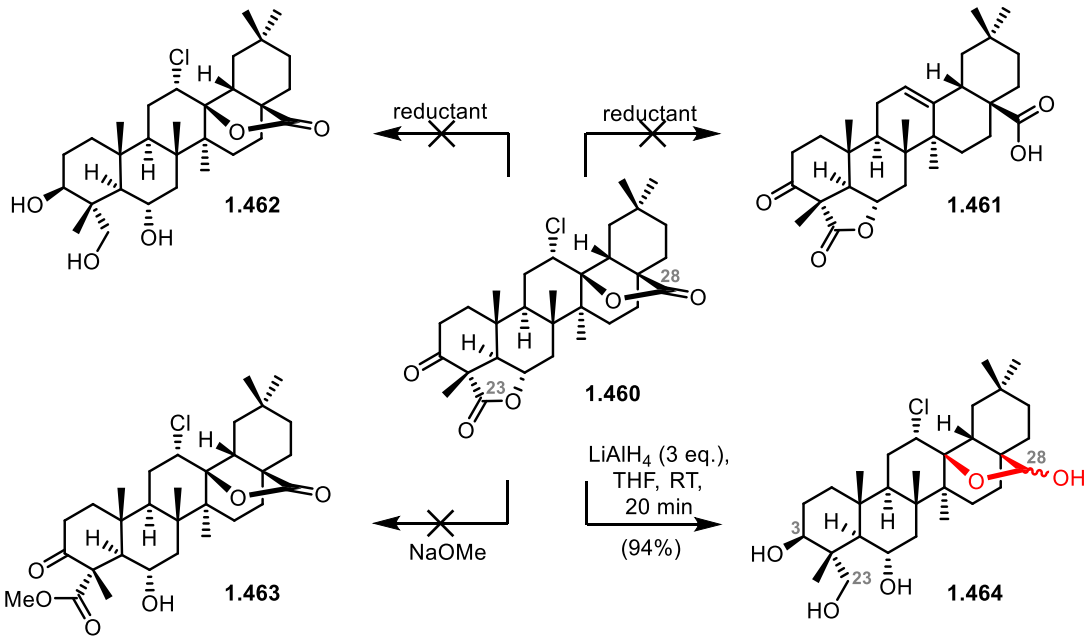


Figure 113. Attempts for differentiation of the neopentylic lactone moieties

In contrast to chlorolactone **1.160**, deprotection of the bromolactone with zinc powder in **1.454** was easily achieved, but led to the highly insoluble carboxylic acid **1.461** (Figure 114). Since reprotection of **1.461** would have been required but was not attractive, an alternative method for differentiation was sought. Since removal of the chloride was met with resistance, reduction to the hemiacetal-bromide **1.465** was attempted analogously to hemiacetal **1.464**. However, **1.465** was somewhat unstable upon attempted isolation, unfortunately yielding only impure material. In contrast to its

more stable chloro-analogue **1.464**, bromide **1.465** tends to eliminate HBr, since epoxy-aldehyde **1.466** was identified to be the main impurity.

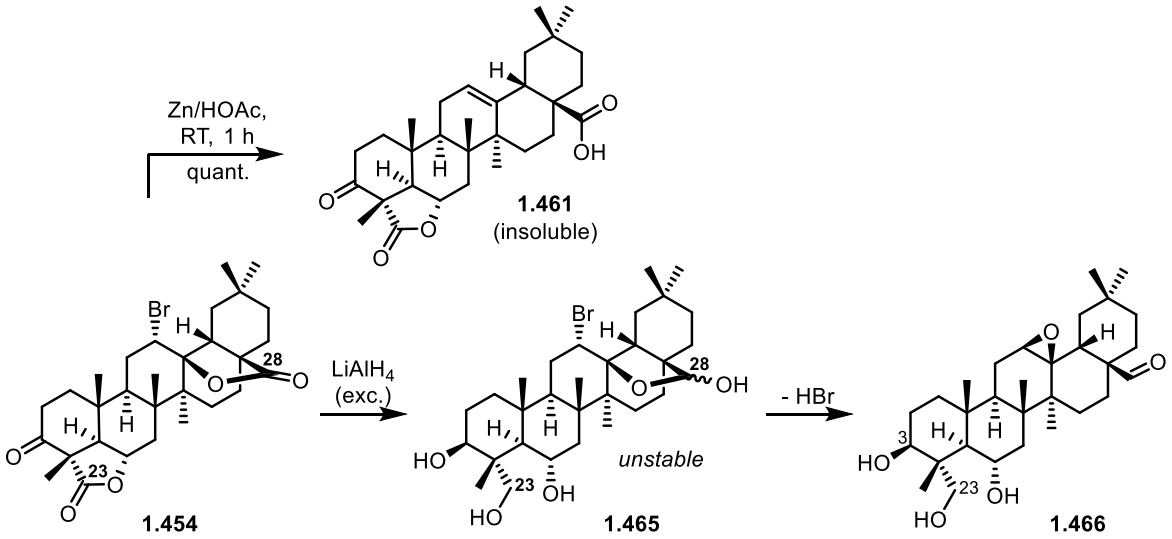


Figure 114. Reactivity of the bromo-dilactone 1.454 towards reduction

Since formation of the epoxide in **1.466** was best avoided, isolation of **1.465** was not performed. Instead, subsequent addition of zinc powder and acetic acid directly to the reaction mixture allowed regeneration of the double bond in the same pot. As shown in Figure 115, this one-pot reaction directly afforded aldehyde **1.467** and enabled the synthesis of Uncargenin C **1.416** to be envisaged.

With **1.467** in hand, a short sequence to the natural product **1.416** was attempted by inversion of C-6-OH and oxidation of C-28. Inversion of C-6 by S_N2-type reactivity (e.g. Mitsunobu) was not attempted due to expected significant steric shielding on the top face of the molecule. Conversely, this would mean that reduction of a C-6 ketone should proceed with high diastereoselectivity to give the desired 6β-hydroxy group exclusively. Since the hydroxyl groups at C3 and C-23 in **1.467** should be retained, simultaneous protection as acetonide was performed. Subsequently, oxidation of C-6-OH and the aldehyde at C-28 to regenerate the carboxylic acid on the crude acetonide was attempted, but found to be challenging. While PCC in DMF afforded small amounts of product **1.468** alongside with substantial decomposition, Ley oxidation conditions using *N*-Methylmorpholine *N*-oxide (NMO) as co-oxidant proved to be very clean but sluggish, attributable to the expected steric hindrance of both functionalities. Since the oxidation of aldehydes to carboxylic acids requires addition of water, NMO hydrate was used instead to avoid catalyst decomposition and to facilitate the reaction by formation of stabilized aldehyde hydrates. [160] Global oxidation afforded ketoacid **1.468** in 50% yield over 2 steps.

Deprotection of the acetonide in **1.468** with pyridinium para-toluenesulfonate (PPTS) and reduction of the ketone with $LiBH_4$ afforded Uncargenin C in 5 steps from dilactone **1.454**. It is worth to mention that the ketone at C-6 did not respond at all to treatment with excess of $NaBH_4$ in MeOH. The spectral data of isolated **1.416** was found to be in accordance with the literature. [161]

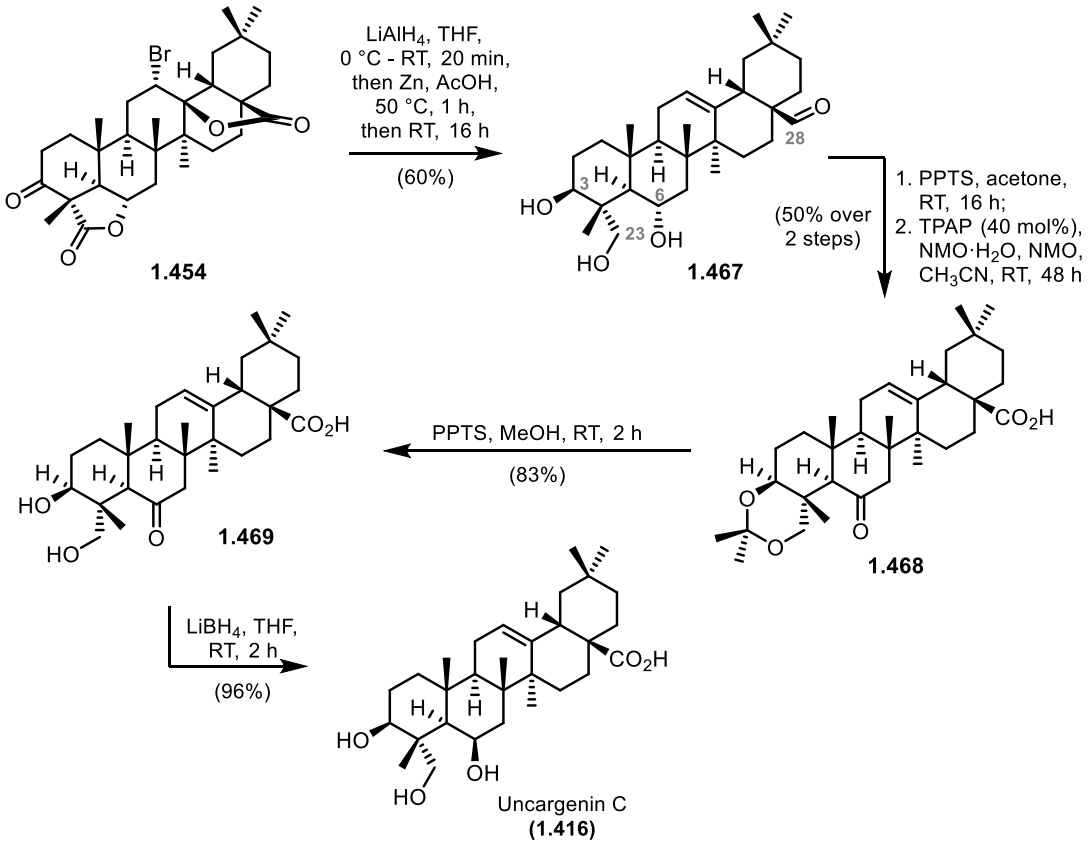
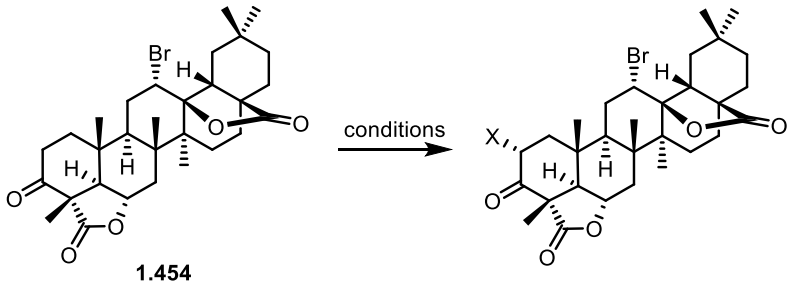


Figure 115. Synthesis of Uncargenin C

Next, we attempted conversion of **1.454** to obtain the tetrahydroxylated Protobassic Acid **1.418**. Therefore, diversification at C-2 was required but found problematic. Although a large number of methods for the α-hydroxylation of carbonyl compounds have been reported, the majority does not accommodate hindered aliphatic ketones as present in **1.454**. Selected attempts for the α-functionalization are summarized in Table 8. Hydroxylation of **1.454** using catalytic H_2SO_4 and mCPBA resulted not only in small amounts of desired product but also to several other species (Table 8, entry 1). [150] Riley oxidation of **1.454** with selenium dioxide led to decomposition of material (Table 8, entry 2). [162] Direct α-acyloxylation by condensation of **1.454** with *N*-methyl-*O*-benzoylhydroxylamine and subsequent [3,3]-sigmatropic rearrangement did not proceed although reported to proceed on

cyclohexanones at room temperature. [163] Even heating of the reaction mixture did not result in any conversion, which can simply be explained by the non-susceptibility of the hindered ketone in **1.454** towards condensation with the reagent in the first place. Alternatively, halogenation of the ketone **1.454** was another possible approach. While NBS did not afford any product, pyridinium hydrobromide perbromide (PHPB) resulted in remarkably clean bromination and afforded the product in quantitative yield (Table 8, entry 6). However, attempts for introducing an oxygen substituent by nucleophilic substitution of the bromide with various nucleophiles were met without success. Even refluxing in acetic acid in presence of 3 equivalents of silver acetate did not lead to any conversion, attributable to the steric shielding of the top face of the molecule.

*Table 8. Selected examples for attempted α-functionalization of **1.454***



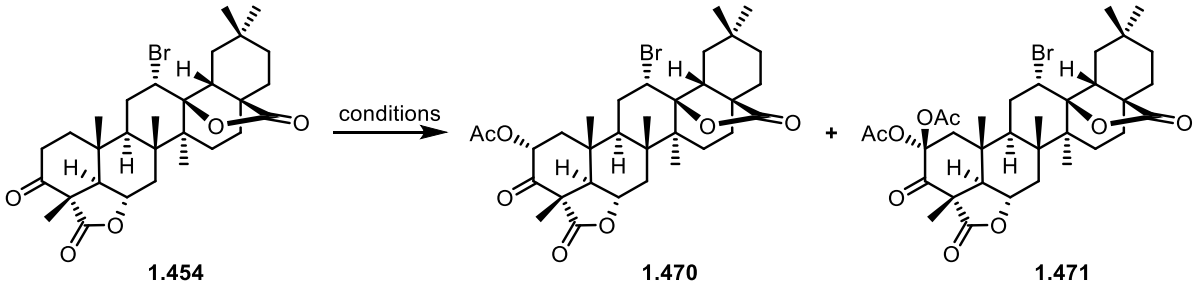
1.454

entry	conditions	X	yield
1	H_2SO_4 (cat.) mCPBA (1.2 eq.), THF/MeOH, RT	OH	several products
2	SeO_2 (1 eq.), AcOH, 90 °C, o. n.	O	decomposition
3	MeNHOAc (1 eq.), DMSO, RT, 3 days	OAc	no reaction
4	MeNHOAc (1 eq.), DMSO, 80 °C, 1 day	OAc	no reaction
5	NBS (1 eq.), 100 °C, 4 h	Br	no reaction
6	PHPB (1 eq.), RT, 3.5 h	Br	quantitative

Davis hydroxylation with an oxaziridine reagent failed already due to the decomposition of **1.454** upon attempted generation of the enolate with LHMDS. This fact excluded the use of methods operating *via* the generation of enolates from our list of possible methods. An approach to the acetoxylation of ketones at pH neutral conditions would be their oxidation with metal acetates, as initially reported by Fuson and coworkers by use of LTA. [164] After some experimentation with LTA on our substrate, some of the desired C-2 acetoxylated product **1.470** was indeed observed. Initially, the reaction was found unsuccessful when boiling in toluene (Table 9, entry 1). With acetic acid as solvent on the other hand, the reaction did not proceed upon warming to 50 °C (Table 9, entry 2). Heating to 90 °C with equimolar

amount of LTA finally afforded the desired acetate **1.470**. (Table 9, entry 3) However, formation of a byproduct was observed and **1.470** was found to be not separable from dilactone **1.454**. Concluding from this, full conversion of the starting material was required in order to obtain the clean product. Use of 2 equivalents of LTA at 80 °C finally led to the isolation of **1.470** in 23% yield and the main byproduct of the reaction in 13% yield, which was found to be the diacetoxylated dilactone **1.471** (Table 9, entry 4). This overreaction was found rather surprising, since considerable efforts to install a functionality at this position were met with resistance in the first place. To further increase the 23% yield of **1.470**, conditions were required which (a) keep the level of overoxidation to a minimum but (b) give also full conversion. Interestingly, when comparing entry 4 and entry 7 in Table 9, decrease by 5 °C and 0.2 equivalents of LTA dramatically improved the yield of **1.470**. Further attempts to milden the conditions led to incomplete consumption of starting material **1.454**.

*Table 9. C-2 Acetoxylation of dilactone **1.454***



1.454 **1.470** **1.471**

entry	reagent	solvent	time	T	conversion	1.470	1.471
1	LTA (2 eq.)	toluene	8 h	110 °C	no		
2	LTA (3 eq)	AcOH	4 h	50 °C	no		
3	LTA (1 eq)	AcOH	6 h	90 °C	incomplete		
4	LTA (2 eq.)	AcOH	16 h	80 °C	full	23%	13%
5	LTA (2 eq.)	AcOH	16 h	70 °C	incomplete	44% in mixture with 18% **1.454**	16%
6	LTA (2 eq.)	AcOH	16 h	75 °C	full	42%	17%
7	**LTA (1.8 eq.)**	**AcOH**	**16 h**	**75 °C**	**full**	**51%**	**n.d.**
8	LTA (1.6 eq.)	AcOH	16 h	75 °C	incomplete	n.d.	

With **1.470** in hands, we attempted the synthesis of Protobassic Acid **1.418**, following the same reaction sequence as utilized for the synthesis of Uncargenin C **1.416** (Figure 116). Global one-pot reduction to directly afford the aldehyde **1.472** was found successful despite the presence of the

additional functionality at C-2, albeit in lower yield. Aldehyde **1.472** was unfortunately obtained in a clean mixture with small amounts of the C-28 carboxylic acid. However, since re-oxidation of the aldehyde was required anyway at a later stage, this impurity was not of disturbance. To access the natural product **1.418**, two alcohols needed to be inverted. Therefore, regioselective and threefold oxidation of the two alcohols at C-2, C-6 and the aldehyde at C-28 in presence of the alcohols in C-3 and C-23 in **1.472** was required. Installation of the acetonide protecting group in tetraol **1.472** was found to be not as clean as observed before on triol **1.467**, but the desired diol seemed to be the main product. Subjecting the crude reaction mixture directly to Ley oxidation indeed afforded the desired diketone **1.473** in in 40% yield. Deprotection and reduction proved again to be successful and tetrahydroxylated Protobassic Acid **1.418** could be isolated. The analytical data was again found to be in accordance with the literature. [165]

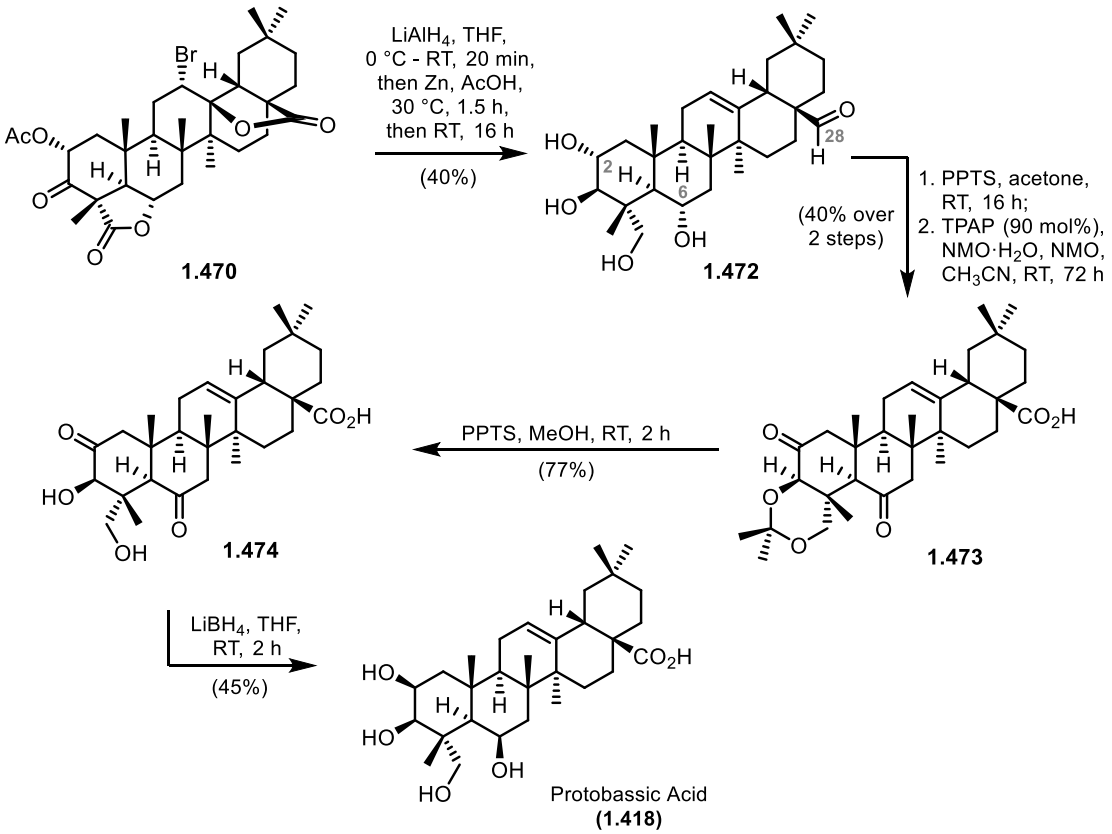


Figure 116. Synthesis of Protobassic Acid

The dilactone **1.454** could serve as intermediate for the synthesis of various other natural products. In 2006, Wang *et al.* isolated trace quantities of diol **1.475** from *C. hypoleucus*, which was shown to have broad anticancer properties in various cell lines. [166] Later, it was found that **1.475** was not only

cytotoxic but also inhibited proliferation of cervical cancer cells. [167] We envisioned the rapid synthesis of diol **1.475** by simultaneous deoxygenation of the aldehyde and the neopentylic alcohol at C-23 with preservation of both secondary alcohols, as shown in Figure 117. This seemed particularly ambitious but also feasible by a recently reported procedure for the selective reduction of primary alcohols in presence of secondary alcohols by Li and coworkers. [168] The reaction is proposed to proceed by dehydrogenation of the primary alcohols to aldehydes and subsequent Wolff-Kishner reduction. In the original report, successful demonstration on a hindered abietane alcohol, albeit requiring more reagent and prolonged reaction time, was achieved. In case of our substrate **1.467**, the reaction was found to produce a very complex mixture of numerous compounds. With the known ^{1}H-NMR data from the literature [166], isolation of the product **1.475** from the mixture could however be achieved, albeit requiring column chromatography and preparative thin layer chromatography. Pure diol **1.475** was obtained in only 4% yield, which could unfortunately not further be improved by optimization of the initial reaction conditions (Figure 117).

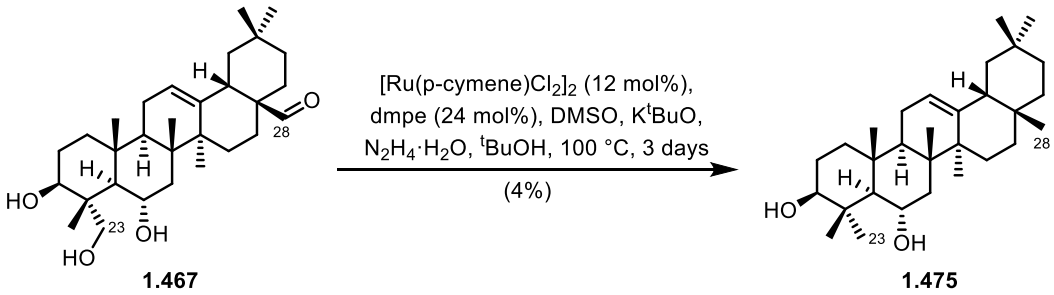


*Figure 117. Simultaneous deoxygenation of the neopentylic positions to afford anticancer diol **1.475***

1.4.7 Conclusion

The hydroxylation at C-6 in ring B of Oleanolic Acid has successfully been achieved by sequential C–H oxidation. This was possible by the use of C-23-OH as a natural handle. The synthetic utility of this transformation was further demonstrated by the first reported total synthesis of the highly oxygenated natural products Uncargenin C and Protobassic Acid. Due to the structural similarities in pentacyclic triterpenoids, our approach may further be useful for the synthesis of various other naturally occurring substances. At the time of writing, biological evaluation of the natural products and some intermediates as prepared herein is underway.

2 UNIFIED SYNTHESIS OF CICUTOXIN AND VIROL A VIA ELECTROCYCLIC CYCLOBUTENE RING OPENING

2.1 INTRODUCTION

2.1.1 Polyyne and polyene natural products

Polyyne [169-170] and polyene [171-172] natural products are a large class of structurally diverse molecules which can be isolated from terrestrial plants, bacteria or fungi, but can also be of marine origin. By definition, polyyne or polyene natural products share the common feature of a conjugated 1,3-diyne or 1,3-diene motif, respectively. However, the unsaturation of these systems can be often significantly extended by presence of additional conjugated (or non-conjugated) double or triple bonds. In fact, several natural products can be assigned to both families due to the simultaneous presence of polyyne and polyene moieties. In this thesis, such molecules will be termed polyenynes. Selected examples of conjugated polyenynes include Caryoynencin **(2.001**) or Xerulinic Acid (**2.002**), among other representatives of naturally occurring polyynes or polyenes depicted in Figure 118.

Polyynes or polyenes are often reported as unstable entities as a result of their high degree of unsaturation. The resulting chemical lability may pose a problem when isolation of such compounds is attempted or when such molecules are considered as targets for natural product synthesis. However, due to their versatile and promising biological activities, continuous efforts have been made towards their chemical synthesis over the last few decades. [179]

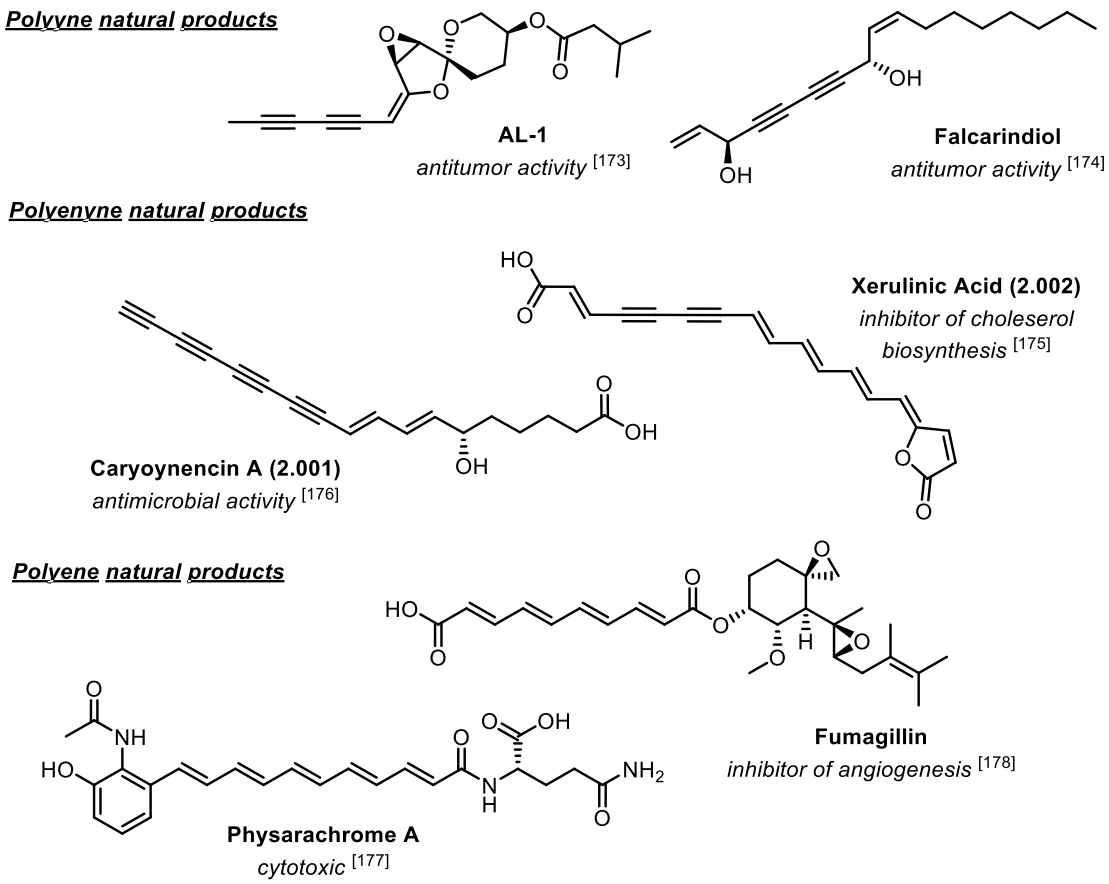


Figure 118. Selected examples of polyyne, polyenyne and polyene natural products

2.1.2 Polyenynes from Water Hemlock

Water Hemlock is a common name for various species of the Apicaceae family, which can be further divided into the genera of *Cicuta* and *Oenanthe*.[180] Several species of these plants (*C. douglasii, C. maculata, C. virosa* and *O. crocata*) notoriously rank among the most poisonous plants in Europe or Northern America. In Central Europe, *Ciguta virosa* is the most common representative. Due to their high toxicity, members of this plant family were given memorable names, such as “beaver poison”, “children´s bane” or “dead man´s fingers”. Although all parts of the plants contain toxins, the highest concentration of the latter can be found in their roots. Often confused with wild carrots, consumption of even small parts of the roots may lead to seizures and end fatally. Several cases of death by misidentification of these plants have been reported, and they still pose a danger to all forms of livestock. [181-184]

The molecules responsible for the toxicity are diols incorporanting a C-17 carbon chain, containing a highly unsaturated and conjugated central motif as a common feature. Furthermore, the toxins are

reported to be highly unstable and readily decompose upon exposure to heat, air and light. Compounds isolated from *C. virosa* are shown in Figure 119 with their absolute configuration and LD_{50} values. [185]

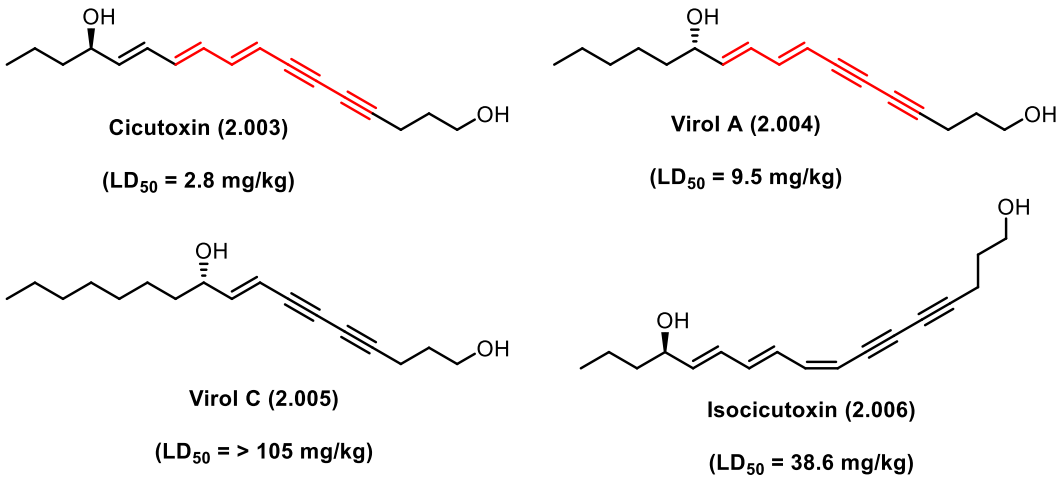


Figure 119. Polyacetylenic diols isolated from C. virosa and their LD_{50} values

Although several structurally similar compounds can be isolated from *C. virosa*, the by far most toxic entities are Cicutoxin **(2.003)** and Virol A **(2.004)**. Their common unsaturated central *all-trans* polyenyne motif is highlighted in red in Figure 119. These molecules are not an exception, since the same motif can be found in the structures of polyenynes **2.001** and **2.002** in Figure 118. Virol C **(2.005)** and Isocicutoxin **(2.006)** are compounds with significantly lower toxicity with respect to **2.003** or **2.004**. The small structural deviations reflect the structure-activity relationship of these compounds. [186] In general, shortening of the conjugated system (as in **2.005**) as well as double bond isomerization (as in **2.006**) results in reduction of toxicity. Virol A was found to inhibit GABA-induced chloride currents, which ultimately affects the central nervous system. [187] Besides its toxicity, Cicutoxin **2.003** was also reported to have potent antileukemic activity. [188]

All prior syntheses of **2.003** or **2.004** reflect the general trend for the synthesis of polyyne or polyene natural products, which is the assembly of several small linear fragments by means of cross-coupling chemistry. [189]

2.1.3 Synthesis of polyynes and polyenes by transition-metal-catalyzed coupling reactions

2.1.3.1 Polyyne synthesis by copper catalysis

The synthesis of diyne moieties is commonly achieved by copper-catalyzed coupling reactions of alkyne building blocks. [189] The first copper-mediated coupling of alkynes was reported as early as 1869 by Glaser (Figure 120a). [190] Treatment of terminal alkynes with CuCl was found to result in the precipitation of Cu(I)-acetylides. Upon exposure to air, oxidation of the latter resulted in homocoupling. However, the poor solubility of Cu(I)-acetylides in organic solvents and their explosive nature upon isolation limited the general utility of the method. Further modifications of the Glaser coupling conditions were necessary to improve its practicability (Figure 120b). A noteworthy contribution was the Eglinton modification utilizing the excess of Cu(II) salts. The Hay modification, on the other hand, increased the solubility of the Cu(I) acetylides by the use of TMEDA as a base or ligand.

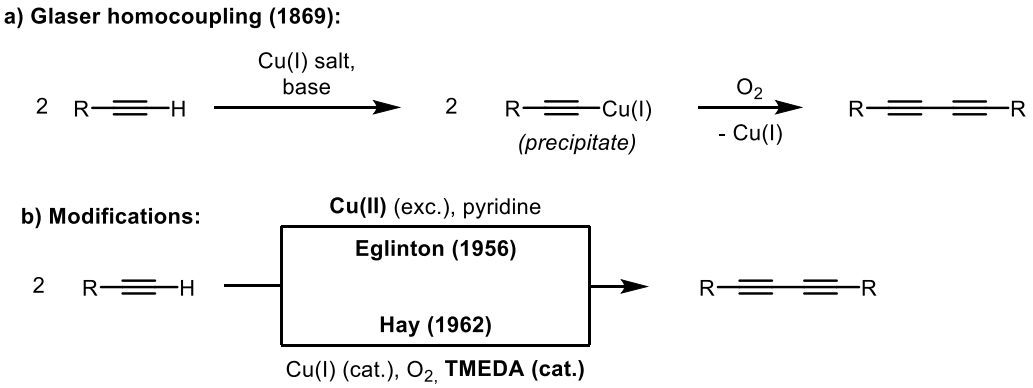


Figure 120. Overview of copper-mediated homocoupling reactions of terminal alkynes

The mechanism of the Glaser coupling is not fully understood yet. An initially proposed radical pathway was excluded upon a landmark study by Bohlmann and coworkers (Figure 121). [191] Activation of the alkyne by formation of a Cu(I)-π-complex (**A**) facilitates the deprotonation of the terminal alkyne by overall lowering of its pK_a to afford acetylide **B**. The homocoupling is believed to proceed *via* the formation of a dimeric Cu(II)-acetylide complex **C**, which eventually collapses to the diyne product.

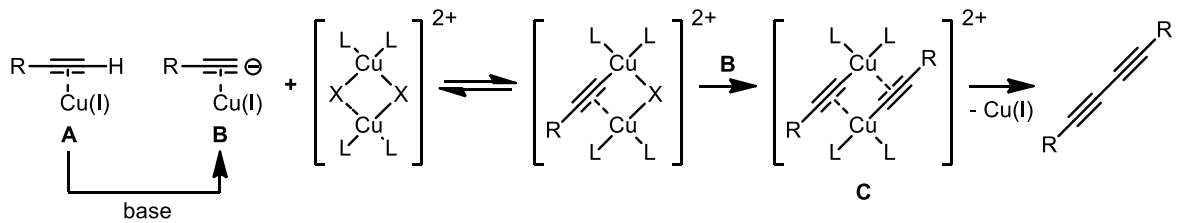


Figure 121. Proposed mechanism of the Glaser coupling via a binuclear Cu(II)-complex

Since the Glaser coupling is limited to the synthesis of symmetrical diynes, its utility in the synthesis of complex natural products is rather limited. A conceptually different and more useful approach would be the cross-coupling of two structurally diverse building blocks. This landmark achievement was the copper(I)-catalyzed cross-coupling of a terminal alkyne and a haloalkyne. The method allows access to non-symmetrical diynes with high selectivity and is known as the Cadiot-Chodkiewicz reaction (Figure 122). [192] Similarly to the Glaser coupling, activation of the alkyne via π-complex formation facilitates deprotonation by relatively weak amine bases. Upon formation of the Cu(I)-acetylide **A**, subsequent oxidative addition of the haloalkyne gives a Cu(III) species **B**, which is prone to reductive elimination of the diyne product.

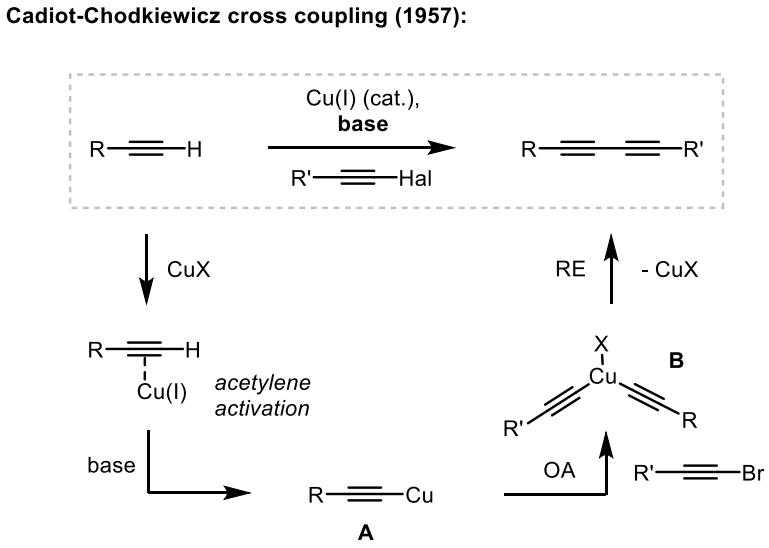


Figure 122. General scheme and mechanism of the Cadiot-Chodkiewicz cross coupling reaction

An example of the Cadiot-Chodkiewicz cross-coupling in natural product synthesis is shown in Figure 123. The group of Danishefsky utilized this reaction as a key step to unite the alkyne building blocks **2.007** and **2.008** delivering the anticancer natural product Panaxytriol **2.009**. [193]

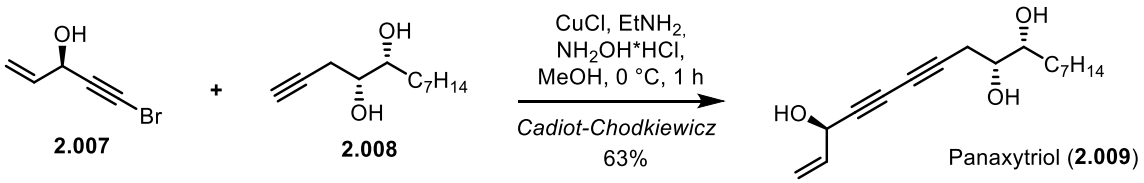


Figure 123. Danishefsky´s synthesis of Panaxytriol using a Cadiot-Chodkiewicz reaction as key step

2.1.3.2 Polyenyne and polyene synthesis by palladium catalysis

The cross-coupling of terminal alkynes with other electrophiles than haloalkynes usually requires additional transition metal co-catalysts. Palladium-catalyzed cross-coupling reactions are amongst the most powerful organic transformations. [194] The general reaction is the coupling of (pseudo)halides with a broad range of nucleophilic species. An overview of the most common types of reagents utilized is shown in Figure 124a. These reactions cover a broad scope of possible products, including polyenes prepared by sp^2-sp^2 coupling, but require the use of two pre-functionalized coupling partners. Fundamentally distinct are the Heck reaction [195] (Figure 124b) and the Sonogashira reaction [196] (Figure 124c), enabling the direct coupling of (pseudo)halides with non-functionalized alkenes or alkynes respectively.

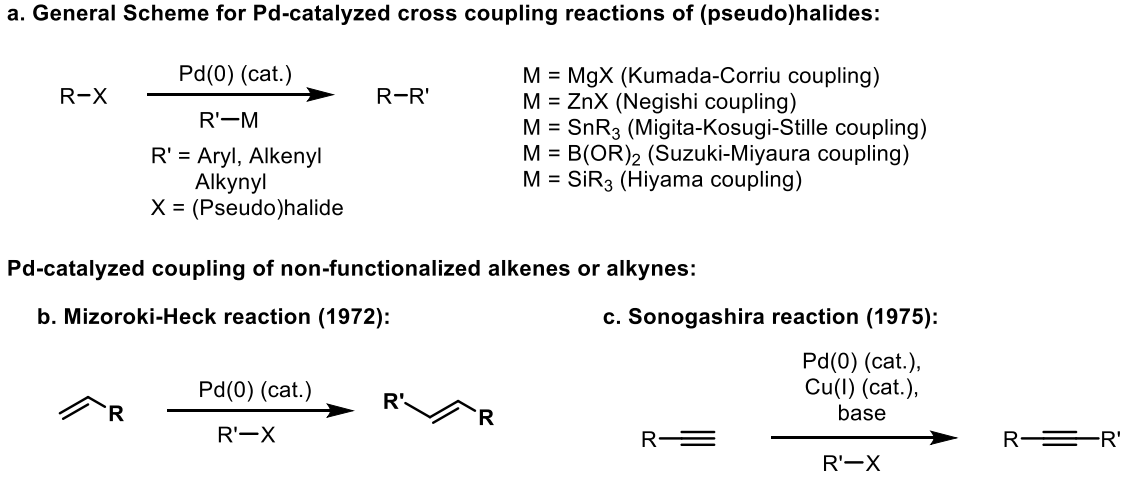


Figure 124. Common Pd-catalyzed cross-coupling reactions

The Suzuki-Miyaura reaction is, without a doubt, amongst the most commonly used palladium-catalyzed cross-coupling reactions. A prominent example is the formal total synthesis of Oximidine II **2.012** by the group of Molander, utilizing a sp^2-sp^2 Suzuki cross coupling for the macrocyclization of **2.010** (Figure 125). [197]

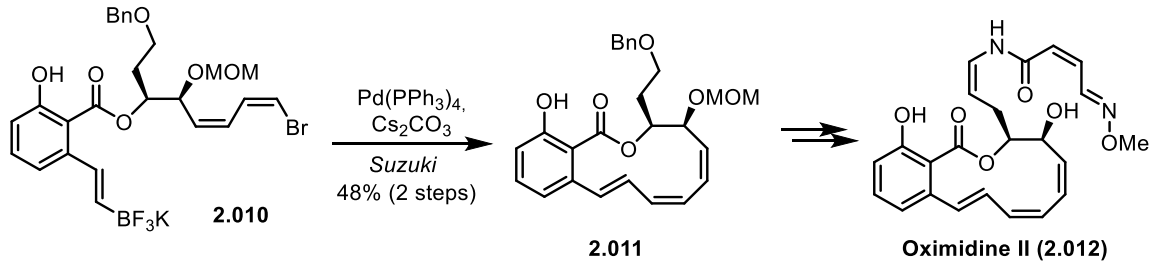


Figure 125. Suzuki cross-coupling as key step in Molander´s synthesis of Oximidine II

An intriguing, non-classical oxidative Heck coupling was utilized by the group of White [198] (Figure 126). The coupling of terminal alkene **2.013** and boronic ester **2.014** was accomplished for the construction of the diene moiety in Amphidinolide C (**2.016**).

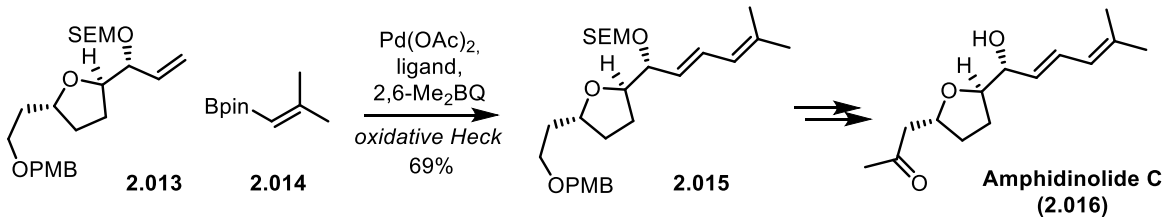


Figure 126. Synthesis of Amphidinolide C featuring an oxidative Heck coupling by the group of White.

The Sonogashira reaction combines the benefits of palladium and copper catalysis. The proposed mechanism is shown in Figure 127. [196] The palladium cycle is in accordance with the general mechanism proposed for Pd-catalyzed cross-coupling reactions. Oxidative addition of R'-X to the Pd(0)-catalyst yields complex **B**. Transmetallation of the nucleophile (**F**) from copper to the more "noble" palladium-species yields acetylide **C**. *Trans*/*cis*-isomerization to complex **D** is required to enable reductive elimination of the product. The copper cycle is believed to proceed via the formation of a π-complex (**E**) and subsequent deprotonation (*vide supra*) to afford **F** as a transmetallation agent.

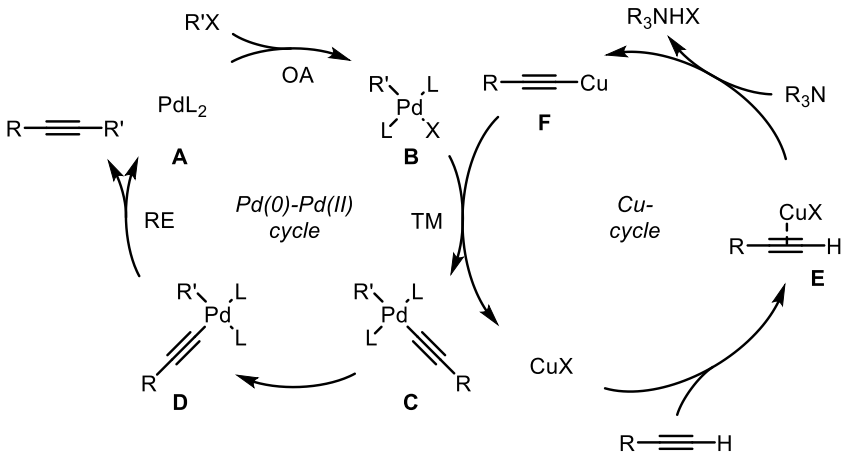


Figure 127. Proposed mechanism of the Sonogashira cross coupling reaction

However, it should be noted that Sonagashira reactions were also reported to proceed without copper co-catalysis, suggesting that the Pd(II)-species such as **B** might be able to participate in the alkyne activation step by itself. [199]

An example of the utility of the Sonogashira reaction is the total synthesis of Elansolid B1 reported by the group of Kirschning (Figure 128). [200] The coupling of terminal alkyne **2.017** with alkenyl bromide **2.018** afforded alkenyl iodide **2.019** following functional group manipulations**.** The subsequent Sonogashira coupling of **2.019** with alkyne **2.020** was applied to afford the elaborate intermediate **2.021**. Partial reduction of the alkyne functionalities finally afforded the *all-trans* triene moiety of the natural product Elansolid B1 (**2.022**).

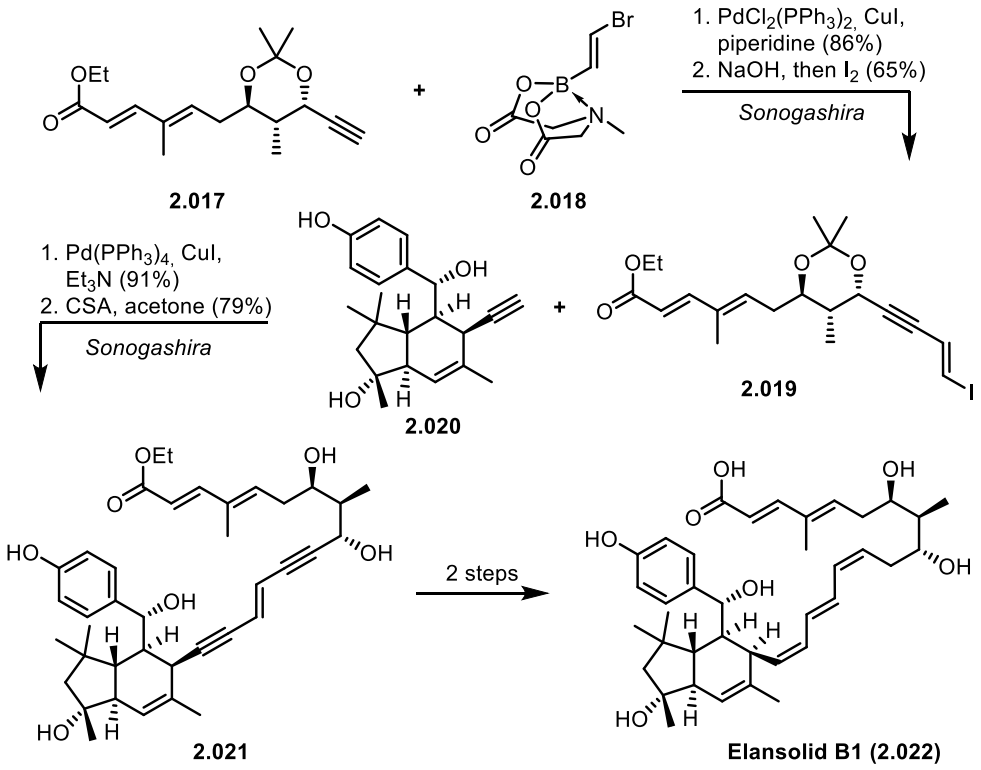


Figure 128. Total synthesis of Elansolid B1 by Kirschning et al.employing two Sonogashira cross coupling steps

2.1.4 Previous syntheses of Water Hemlock toxins by cross coupling methodologies

2.1.4.1 Previous syntheses of Virol A

The total synthesis of Virol A (**2.004**) was not achieved for a relatively long time, the first synthesis being reported by Uwai *et al.* no earlier than 1999. [2001] As shown in Figure 129, the synthesis makes extensive use of cross-coupling reactions utilizing building blocks containing single ethylene or acetylene units.

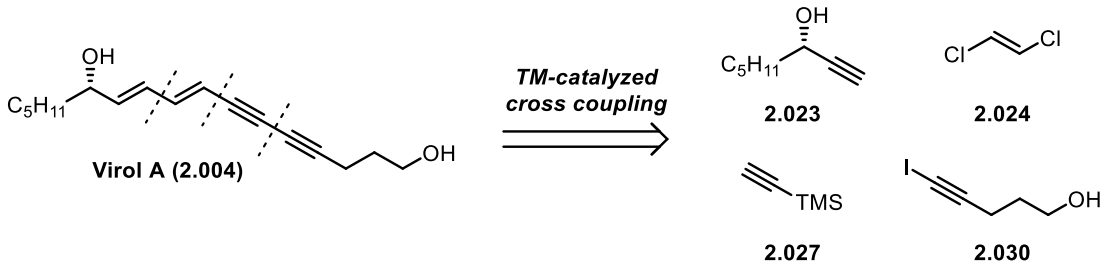


Figure 129. Synthesis of Virol A by Uwai et al. by iterative transition-metal-catalyzed cross-coupling of small fragments

The synthesis started from enantiomerically pure propargylic alcohol **2.023** (Figure 130). Sonogashira cross-coupling of the latter with *trans*-1,2-dichloroethene **2.024** afforded enyne **2.025.** Conversion to the diene moiety in **2.025** was achieved by hydroalumination of the alkyne functionality with Red-Al to afford, after hydrolysis, the *all-trans* diene **2.026**. Another Sonogashira cross-coupling with a diyne building block **2.034** (*vide infr*a) was found not to be suitable due to decomposition of the latter under cross-coupling conditions. Therefore, cross-coupling of **2.026** with silane **2.027** and subsequent desilylation afforded terminal alkyne **2.029**, predestined for another Sonogashira cross-coupling with iodide **2.030** (using Cadiot-Chodkiewicz conditions) to finally afford Virol A (**2.004**). Another synthesis of **2.004** was reported more recently in 2016 by the group of Yu, utilizing an approach similar to the one described here. [202]

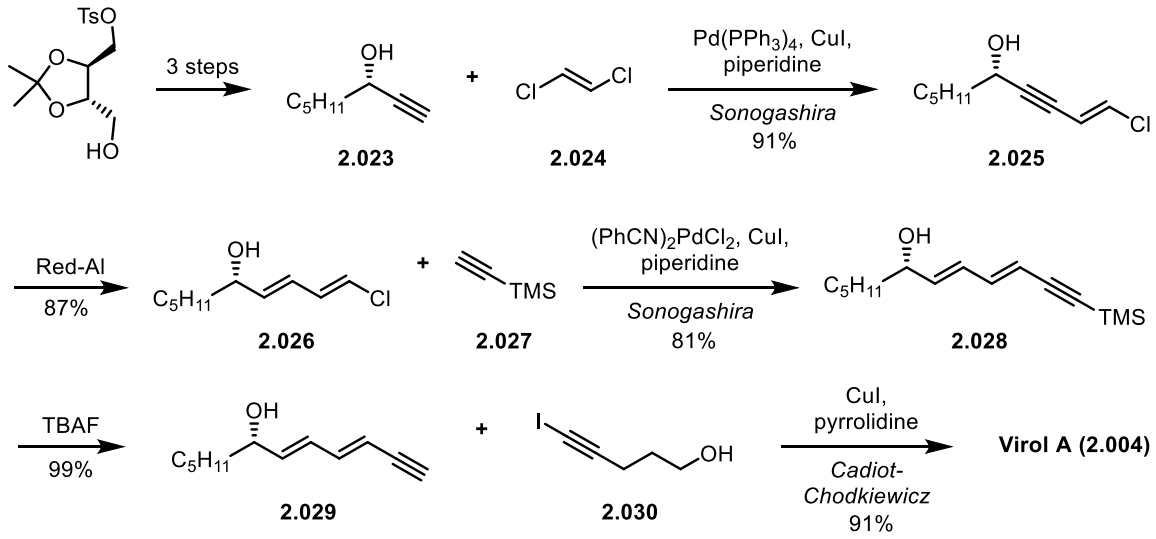


Figure 130. Detailed sequence of the total synthesis of Virol A by Gung et al.

2.1.4.2 Previous synthesis of Cicutoxin

Cicutoxin **2.003** was first isolated in 1915 by Jacobsen *et al*. [203] and its structural assignment followed in 1953 by Trippett *et al.* [204] The first racemic, but low-yielding synthesis was reported by the same group. [205] The first enantioselective synthesis of **2.003** was reported in 2009 by the group of Gung. [206] An initial attempt to furnish the enantiomerically pure material by enzymatic kinetic resolution as the last step met with failure, due to the instability of **2.003**. As an alternative approach, synthesis of **2.003** was achieved again by cross-coupling of linear fragments (Figure 131). In analogy to the synthesis of Virol A (**2.004**) by Uwai (*vide supra*, Figure 130), this synthesis started from enantiomerically pure propargyl alcohol **2.031** and utilized cross-coupling of linear fragments. Pd-

catalyzed linkage of **2.031** with *all-trans*-1,4-dichlorodiene **2.032** afforded alcohol **2.033**, which was subjected again to the Sonogashira cross-coupling conditions with diyne **2.034** to afford triyne **2.035**. Hydroalumination with Red-Al and subsequent THP-deprotection with TsOH directly afforded **2.003**. Noteworthy is the successful use of diyne **2.034** in the first cross-coupling step, which was found to be unsuitable in the synthesis of Virol A due to the chemical instability, requiring an additional coupling step to construct the diyne moiety.

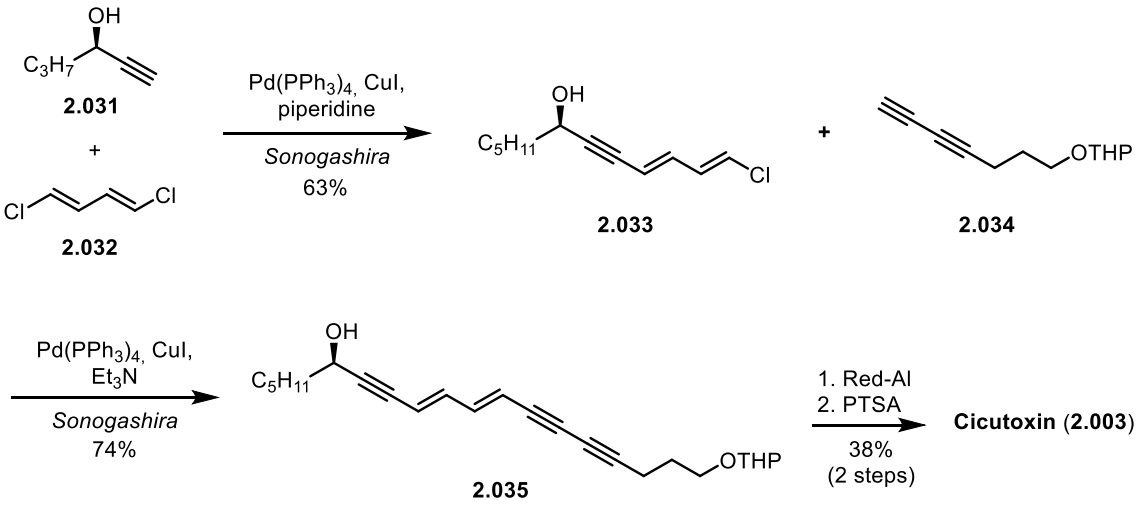


Figure 131. Synthesis of Cicutoxin by Gung et al. utilizing the Sonogashira cross-coupling

A different approach was reported by the group of Brückner in 2011 (Figure 132) [207] The previous syntheses of **2.003** or **2.004** utilized the Sonogashira cross-coupling for the assembly of the enyne moiety. In contrast, Brückner *et al.* used the Stille cross-coupling for the merger of bromide **2.037** and enantiomerically pure trienylstannane **2.038** in order to construct **2.003**. Dienylbromide **2.037** was prepared by the Cadiot-Chodkiewicz reaction.

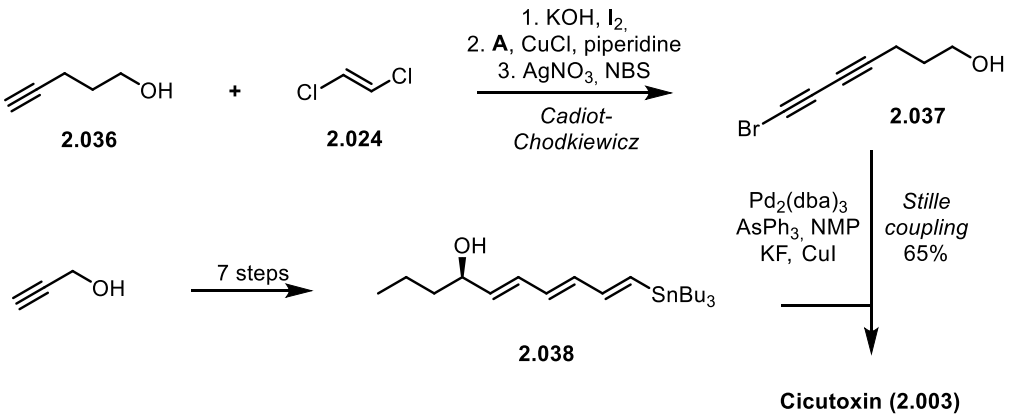


Figure 132. Synthesis of 2.003 by Brückner et al. utilizing the Cadiot-Chodkiewicz and Stille cross couplings

2.1.5 Cyclobutenes as precursors for diene synthesis

The Maulide group has a long-standing interest in the use of cyclobutenes as versatile precursors in organic synthesis. Bicyclic lactone **2.040** constitutes the foundation of this chemistry and was used as valuable starting material for different methodologies. [208] The highly reactive and labile cyclobutene **2.040** can be generated by photochemical 4π-electrocyclization of 2-pyrone **2.039**, as reported by Corey in 1964 (Figure 133). [209]

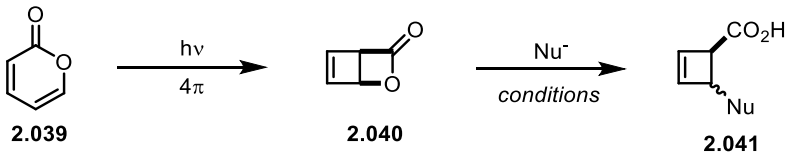


Figure 133. Lactone 2.040 as a precursor to disubstituted cyclobutenes prepared by 4π-electrocyclization of 2-pyrone

The reactivity of **2.040** towards nucleophiles for the generation of disubstituted cyclobutenes **2.041** offers very attractive synthetic perspectives. This is especially due to the proclivity of cyclobutenes (such as **2.041**) to undergo 4π-electrocyclic ring opening reactions. The resulting dienes are desirable building blocks due to their high occurrence of diene motifs in natural products. [170,210] According to the Woodward-Hoffmann rules, thermal electrocyclic ring opening of cyclobutenes proceeds in a conrotatory fashion (Figure 134). [211] Depending on the relative stereochemistry of **2.041**, access to various stereodefined dienes can be possible. *(E,E)*- or *(Z,Z)*-dienes would arise from *trans*-disubstituted cyclobutenes (Figure 134, left), while the *(Z,E)*- or *(E,Z)*-isomers are the possible products when starting from the corresponding *cis*-diastereomer (Figure 134, right).

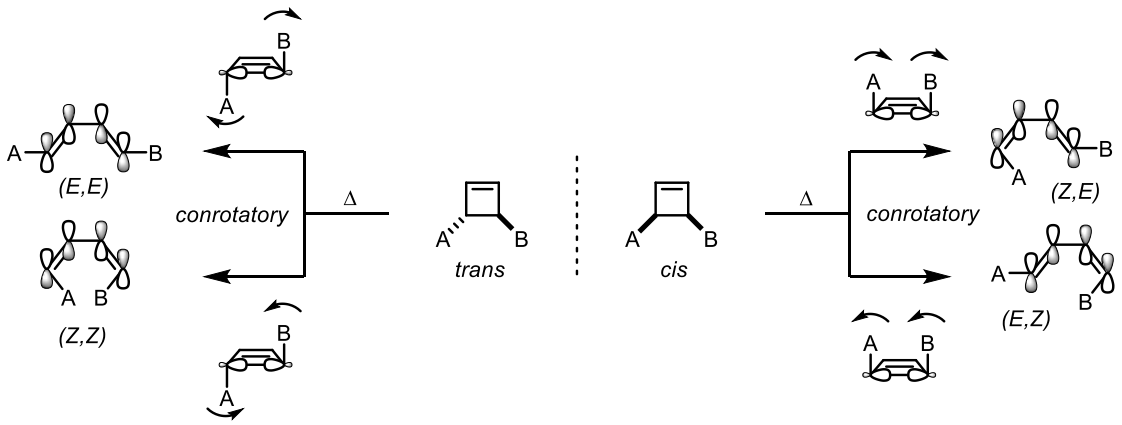


Figure 134. Accessible diene motifs from thermal electrocyclic ring opening of disubstituted cyclobutenes

Figure 135 shows examples of palladium-catalyzed allylation reactions of heteroatom nucleophiles with lactone **2.040**. The use of phenol nucleophiles with the aid of the corresponding sodium salts was initially expected to give the disubstituted cyclobutenes **2.042**. Surprisingly, *(Z,E)*-dienyl carboxylic acids **2.043** were isolated instead, probably *via* the *cis*-adduct **2.042** as an intermediate. [212] Introduction of an azide employing palladium-catalysis and $TMSN_3$ as nucleophile, on the other hand, afforded the *(E,E)*-carboxylic acid **2.045**, probably *via* the subsequent conrotatory electrocyclic ring opening of *trans*-cyclobutene **2.044**. [213] The thermal instability of cyclobutenes **2.042** and **2.044** was explained by the formation of a reactive push-pull system in donor-acceptor cyclobutenes **2.042** or **2.044**.

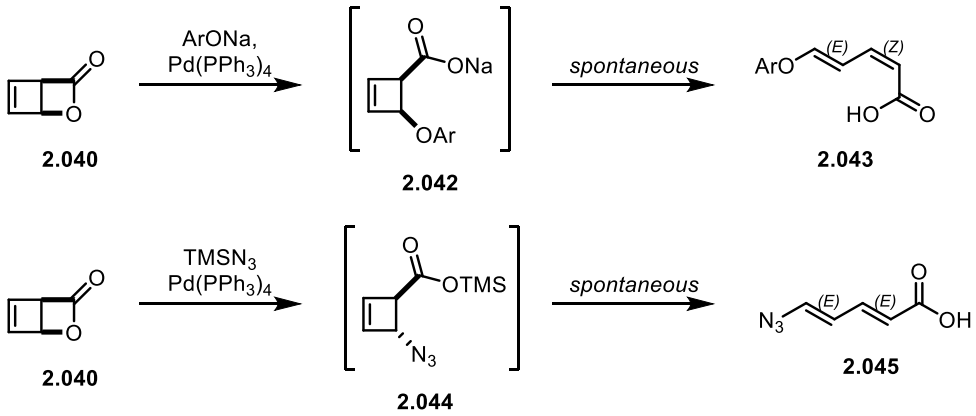


Figure 135. Domino allylic substitution/4π electrocyclic ring opening reactions

Importantly, the spontaneous domino-reactions shown in Figure 135 do not reflect the general behavior of cyclobutenes **2.041.** Simple treatment of **2.040** with lithium bromide affords the stable *trans*-adduct **2.046** (Figure 136). In order to convert the latter to the desired diene **2.047**, heating at 100 °C under microwave irradiation was required. [214] The same behavior was observed when direct alkylation of **2.040** with alkylcuprates was attempted. [215] The alkylated cyclobutenes proved to be very stable, as demonstrated since **2.048** did not decompose under acidic or basic conditions. However, microwave irradiation at 100 °C induced ring opening to afford the natural product Ieodomycin D **2.049**.

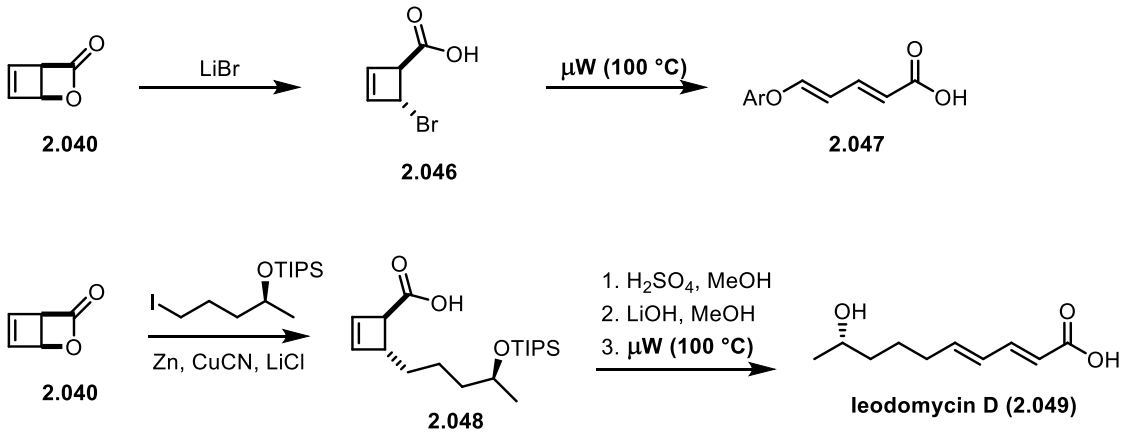


Figure 136. Synthesis of stable disubstituted cyclobutenes and thermal ring opening to afford (E,E)-dienyl carboxylic acids

2.1.6 Objectives of this work

The previously presented syntheses of polyenynes used extensively cross-coupling methodologies and often relied on single ethylene or acetylene units. As an alternative, we propose lactone **2.040** as a diene precursor in the synthesis of polyenyne natural products (Figure 137). As the starting point, the use of an alkyne nucleophile and the behavior of the resulting diene towards electrocyclic ring opening was investigated. This approach should be a powerful method for the rapid construction of polyenyne motifs (Figure 137). As suitable targets, the water hemlock toxins **2.003** or **2.004** were chosen. If successful, the method can be further extended to the synthesis of other polyenyne natural products containing this polyenyne motif, such as **2.001** or **2.002** shown in Figure 118.

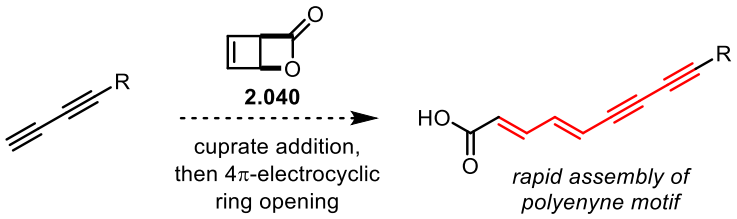


Figure 137. Proposed rapid construction of the polyenyne motif found in several natural products

The synthesis as described below was conducted in collaboration with Yong Chen. Complementary information can be found in his doctoral thesis. [216] The molecules have been tested by Konstantina Bampali in the group of Margot Ernst (Medical University of Vienna) and the results have already been published. [217]

2.2 UNIFIED SYNTHESIS OF CICUTOXIN AND VIROL A

2.2.1 Retrosynthesis

All previous reports on the synthesis of **2.003** or **2.004** share the common strategy of assembling linear building blocks (*vide supra*). Connection of the polyene and the diyne moiety in **2.003** or **2.004** has been achieved, without exception, by palladium-catalyzed cross-coupling. However, as shown in Figure 138, both toxins should be accessible from one common precursor, envisioned to be the Weinreb amide **2.050**. The carboxamide already contains the unsaturated central polyenyne motif present in both natural products. **2.050** should be accessible by 4π-electrocyclic ring opening of a *trans*-disubstituted cyclobutene such as **2.051**, which can be assembled by *trans*-addition of a protected metallated diyne precursor **2.052** to the lactone **2.040.**

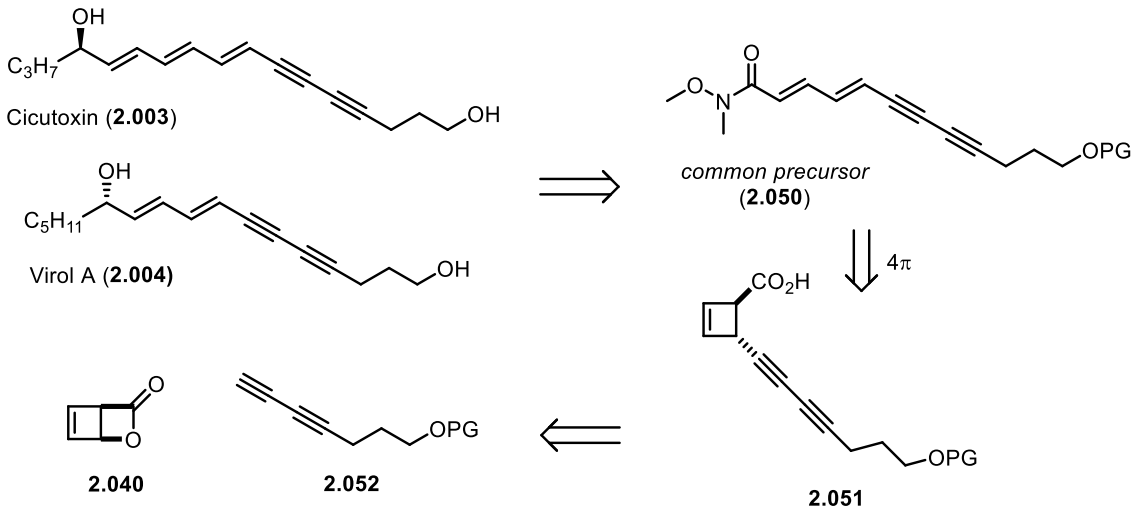


Figure 138. Retrosynthetic analysis of 2.003 and 2.004 from lactone 2.040 and diyne 2.052

2.2.2 Synthesis of Virol A

We started our investigations with the synthesis of Virol A (**2.004**), containing fewer unsaturated carbon-carbon bonds. As the diyne building block, we decided to use the known THP-protected alcohol **2.034**, prepared *via* a modified procedure (Figure 139). [218] Protection of iodoalcohol **2.053** with DHP and PPTS afforded **2.054** in high yield. Monodesilylation of diyne **2.055** with methyllithium generated the corresponding lithiumacetylide, set for nucleophilic substitution of iodide **2.054**. Subsequent desilylation with TBAF afforded the desired diyne building block **2.034**. This diyne was found to be

somewhat unstable, forming visible dark-red impurities upon concentration to dryness. However, the trace impurities did not prevent the further use of **2.034** in the synthesis. It should be noted that an alternative foregone attempt to prepare a TBDMS-analogue of **2.034** was found problematic due to the presence of inseparable byproducts. Diyne **2.034** can be prepared on multigram scale.

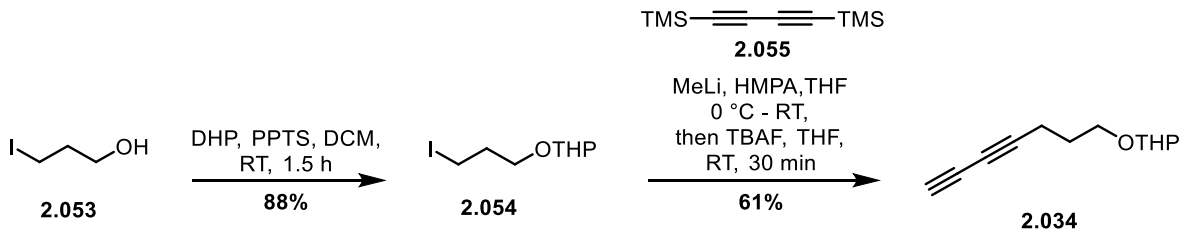


Figure 139. Preparation of the diyne starting material

With the starting material in hand, we attempted the synthesis of cyclobutene **2.056**. Lipschutz *et al.* reported the *in situ* formation of a mixed higher order cyanocuprate $R_2CuCNLi_2$, ideally suited for nucleophilic substitution of secondary halides. [219] Based on previous results by our group, [215] nucleophilic displacement in **2.040** by the cyanocuprate generated from **2.034** was attempted with lithium chloride as an additive (Figure 140, top). As can be seen, the ^{1}H-NMR spectra initially showed a mixture of compounds. The target cyclobutene **2.056** was found to be the major constituent in the crude mixture (signals in dashed boxes in Figure 140, bottom). However, upon standing in chloroform at room temperature for 40 h, the signals of **2.056** disappeared at the benefit of another product. This turned out to be the *all-trans* dienoic carboxylic acid **2.057**, which was isolated in 54% yield accompanied by small amounts of an inseparable impurity (identified as cyclobutenyl chloride **2.058**).

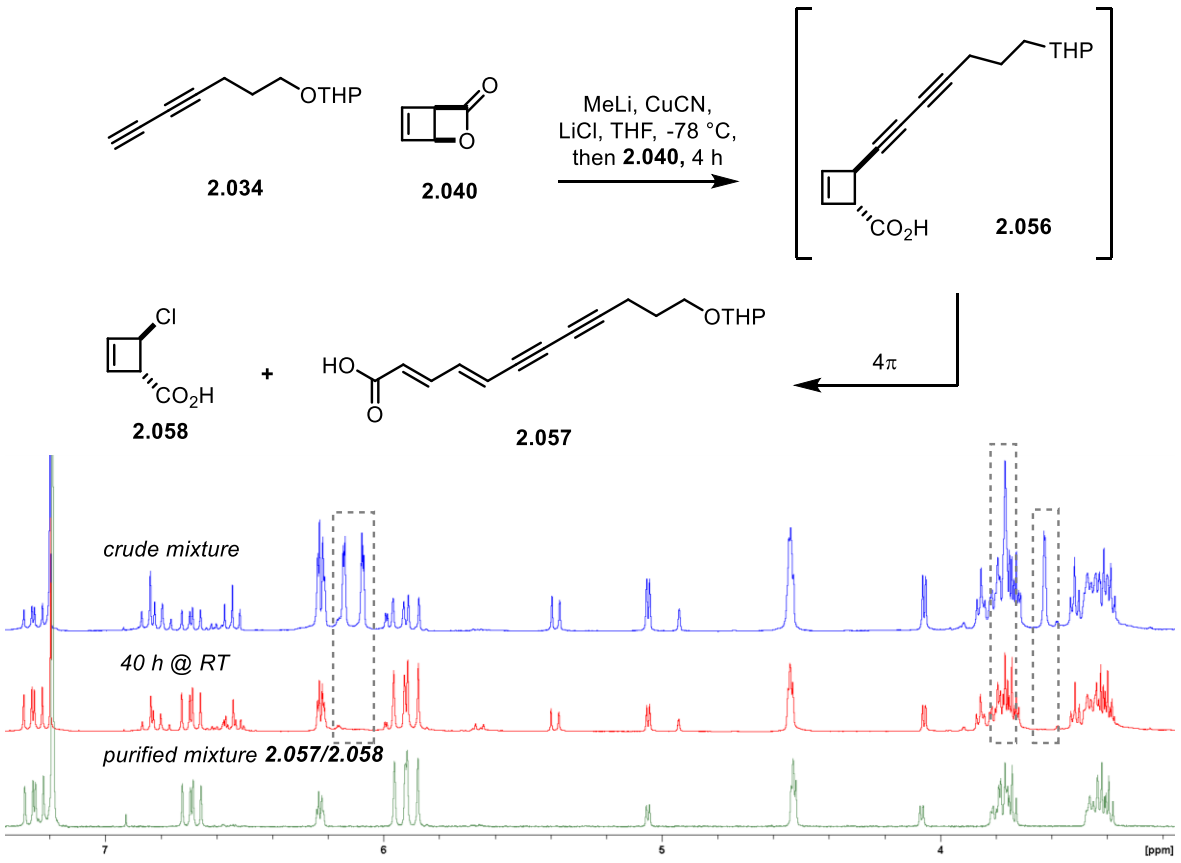


Figure 140. Initial attempt of the generation of cyclobutene 2.056 and identification of the domino reaction leading to the desired diene 2.057

Since lithium chloride as an additive seemed to be responsible for the formation of **2.058**, the same reaction was performed in the absence of the salt. The 4π-electrocyclic ring opening event was found to be complete after 12 h at room temperature, affording after minor optimization diene **2.057** in 82% yield (Figure 141, top). Conversion of the latter to its Weinreb amide **2.059** was straightforward. Initially conducted with CDI and Et_3N in 67% yield, the coupling conditions using EDCI and HOBt proved superior to yield 84% of the desired product. It should be noted that **2.059** was later found to be the last benchstable molecule in this synthetic route. As an alternative, the direct Sonogashira cross-coupling of chloride **2.060** with diyne **2.034** to afford Weinreb amide **2.059** was attempted but met with failure (Figure 141 bottom). Full consumption of **2.034** indicates decomposition of the diyne, which is in conclusion with prior reports. [201]

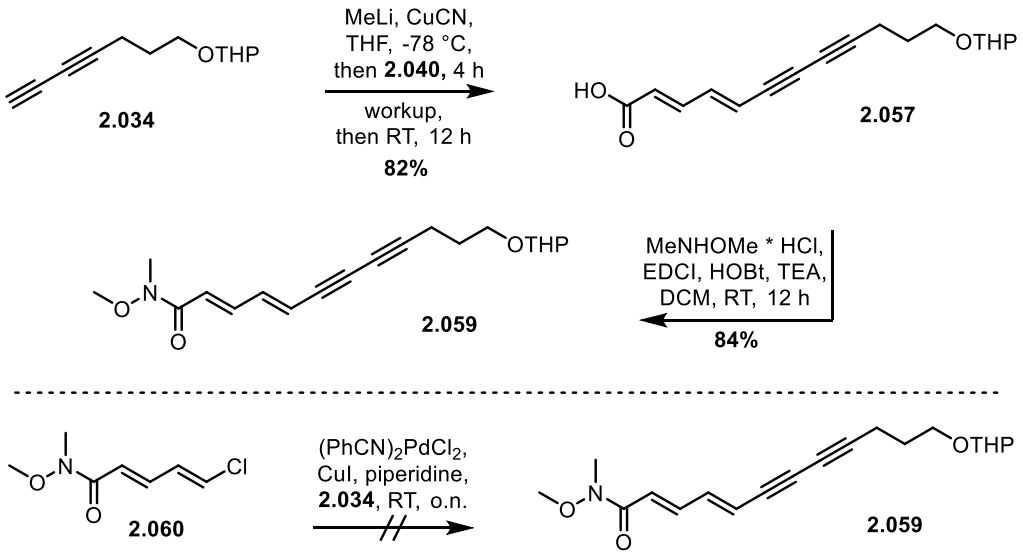


Figure 141. Synthesis of Weinreb amide 2.059 (top); attempting the synthesis by cross coupling with 2.060 was not successful (bottom).

For the synthesis of Virol A **2.004**, derivatization of **2.059** to afford highly conjugated enone **2.061** was attempted (Figure 142). Treatment of **2.059** with 3 equiv. of *n*-pentyl magnesium bromide indeed afforded the desired compound. However, attempted purification by column chromatography on silica gel afforded only a small amount of impure material, an observation attributed to the instability of **2.061** under even slightly acidic conditions. Column chromatography with aluminium oxide solved the problem of decomposition, but the enone was additionally found to undergo double bond isomerization upon exposure to light to give compound **2.062**. Despite the problems with chemical instability of **2.061**, addition of Grignard reagent *n*-pentyl magnesium bromide or *n*-pentyllithium to **2.059** seemed particularly sluggish. Only an excess (10 equiv.) of reagents led to full conversion but unfortunately affording mainly decomposed material. Further optimization revealed the presence of an excess of lithium chloride in the reaction mixture to be crucial for the reaction to proceed. With *n*-pentyllithium as a reagent and strict exclusion of light, the desired ketone **2.061** was afforded in 67% yield, but in an unavoidable *E*:*Z* ratio of 92:8.

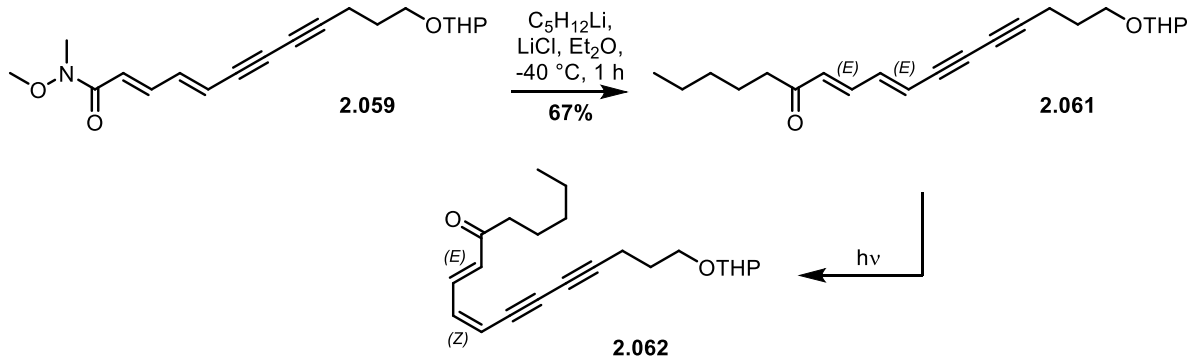


Figure 142. Synthesis of enone 2.061 and light-induced isomerization to 2.062.

In order to obtain enantiopure Virol A (**2.004**), enantioselective Corey-Bakshi-Shibata (CBS) reduction [220] with borane dimethylsulfide complex was found to be successful to obtain **2.063** in 76% yield (Figure 143). Fortunately, the latter compound was obtained as a single double bond isomer and exhibited lower propensity towards isomerization with respect to **2.061**. Alternatively, the racemic material can also be obtained by reduction with $NaBH_4$. Determination of the enantiomeric excess of **2.063** *via* HPLC-analysis of the deprotected material was unfortunately not possible due to complete decomposition. However, formation of a Mosher ester served this purpose, [221] revealing that **2.063** was a single stereoisomer. The distant stereogenic center of the THP group does not interact with the secondary alcohol and therefore **2.063** does not appear as diastereomers in NMR analysis. This simplifies the analysis *via* the Mosher ester method. Deprotection of **2.063** proceeded with PTSA in methanol to afford (*S*)-Virol A **2.004** in 72% yield. Since this compound is reported and was also found herein to be unstable, all operations are best carried out with the exclusion of light and the compounds should be stored in the freezer.

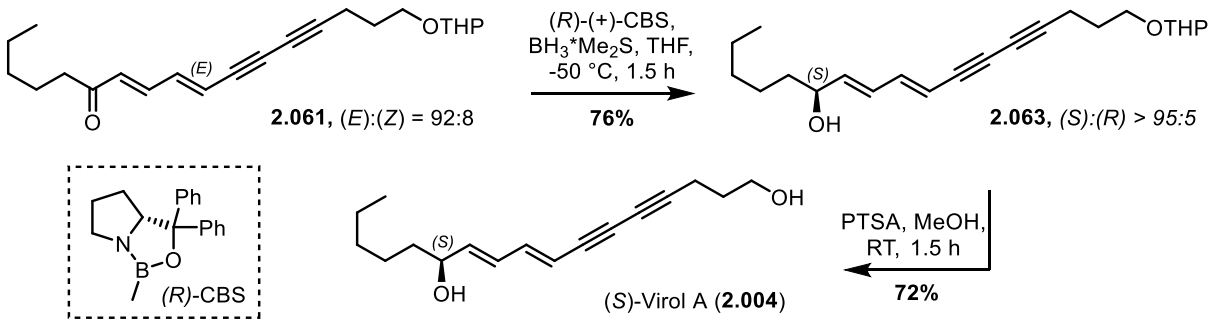


Figure 143. CBS-Reduction and deprotection to afford Virol A (2.004)

2.2.3 Synthesis of Cicutoxin

For the synthesis of Cicutoxin (**2.003**), elongation of the π-system by one *trans*-double bond is required with respect to the preparation of Virol A. With the Weinreb amide **2.059** in hand, partial reduction with DIBAL-H to aldehyde **2.064** and subsequent olefination seemed plausible (Figure 144, top). Considering the ease of light-induced isomerization of enone **2.061**, aldehyde **2.064** can be expected to be even more sensitive to light. Purification of **2.064** was therefore best avoided and all reactions were to be carried out in darkness. Reduction of **2.059** with DIBAL-H proceeded without noticeable problems. The crude aldehyde was directly subjected to Horner-Wadsworth-Emmons (HWE) olefination conditions to yield *all-trans* triene **2.065** in 52% yield over 2 steps. Surprisingly, we managed to isolate the compound as a single isomer. As shown in Figure 144 (bottom), **2.065** was found to be very unstable towards isomerization to **2.066**, induced as easily as by irradiation with ordinary ceiling light obtaining an E:Z ratio of 70:30 after 12 h.

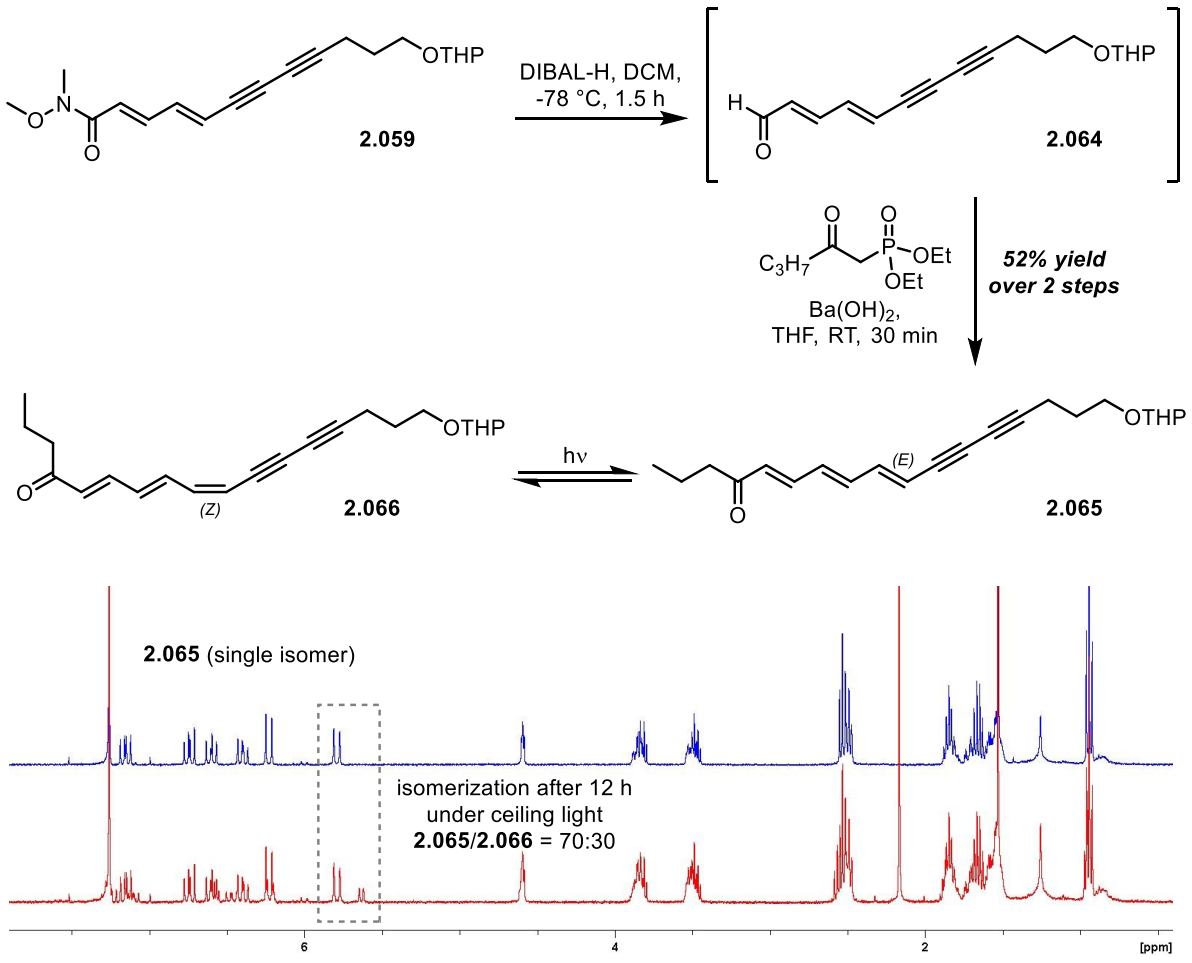


Figure 144. Elongation of the π-system in 2.059 towards the synthesis of Cicutoxin and observed isomerization of 2.065

In analogy to the synthesis of Virol A **2.004**, CBS reduction of **2.065** afforded the alcohol **2.067** in 76% yield as a single isomer (the remote stereogenic center of the THP protecting group could be ignored again in the analysis) according to ^{1}H-NMR analysis of the corresponding Mosher ester (Figure 145). In contrast to the deprotection of **2.063** (Figure 143), the deprotection step did not proceed as cleanly as expected in this case. Surprisingly, considerable amounts of a byproduct were observed, which turned out to be a racemic Cicutoxin analogue **2.068**, mono-methylated at the allylic oxygen atom. Such species were not obtained in the deprotection of **2.063** and can therefore be attributed to the extended π-system in **2.067**, which presumably facilitates the formation of an allylic carbenium intermediate. Using PTSA in methanol at room temperature afforded **2.003** in 53% yield. Since one of our aims was to perform biological studies, formation of the additional methoxy analogue **2.068** was a very welcome finding. Moderate heating in the presence of PPTS afforded analogue **2.068** as the main product in 60% yield.

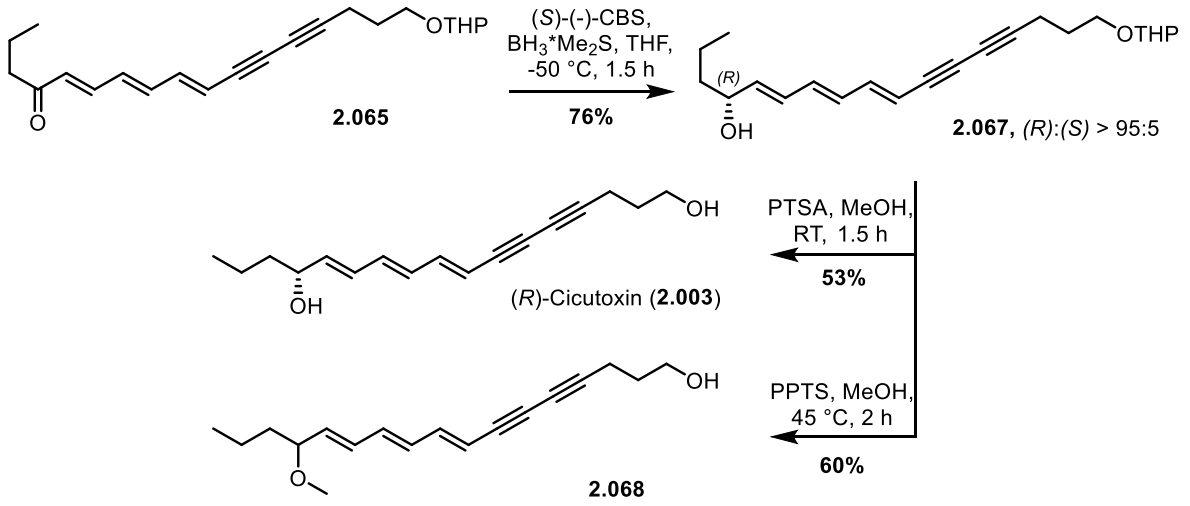


Figure 145. CBS-reduction and deprotection to afford Cicutoxin and monomethylated side product 2.068

Cicutoxin is reported to be highly unstable towards air, heat and light (*vide infra*). However, we observed that storage of a solution of **2.003** in chloroform (filtered over basic aluminium oxide) covered with aluminum foil did not lead to decomposition of this toxin at ambient temperature. However, upon irradiation with UV light (TLC detection lamp, 254 nm), significant decomposition was observed after 12 h and complete decomposition after another day (Figure 146). Interestingly, the methoxy analogue **2.068** seemed much less sensitive towards exposure to light when compared to **2.003**.

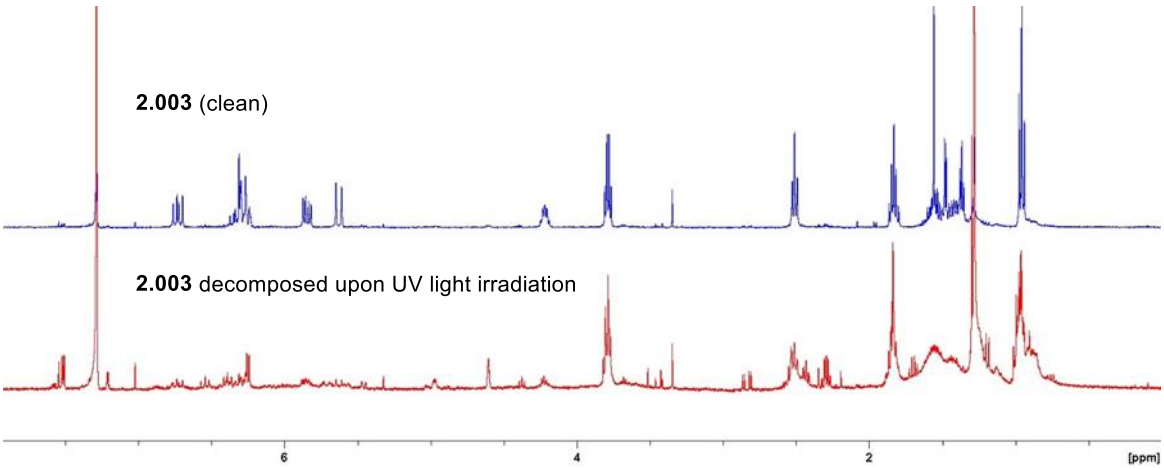


Figure 146. Decomposition of Cicutoxin upon exposure to UV light

2.2.4 Biological studies

The compounds **2.003**, **2.004** and **2.068** have been tested by the group of Dr. Margot Ernst (Medical University of Vienna) on α2β3γ2 $GABA_A$-receptors, which are the major isoforms in the adult mammalian brain. As shown in Figure 147, application of Virol A (**2.004**) resulted in the inhibition of $GABA_A$-induced chloride currents with similar values in the presence of racemic (left) or enantioenriched (right) material. This would suggest that the absolute configuration in **2.004** plays only a minor role in the compound's biological activity.

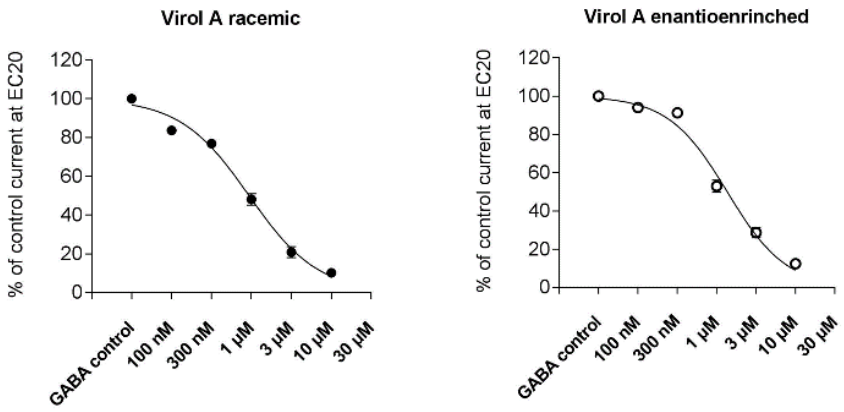


Figure 147. Inhibition of GABA-induced chloride currents by racemic (left) or enantioenriched (right) Virol A (2.004)

Similar behavior was found for the application of Cicutoxin (**2.003**), which is shown to inhibit chloride currents as found for **2.004**, again without being much influenced by the enantiopurity of the compound (Figure 148).

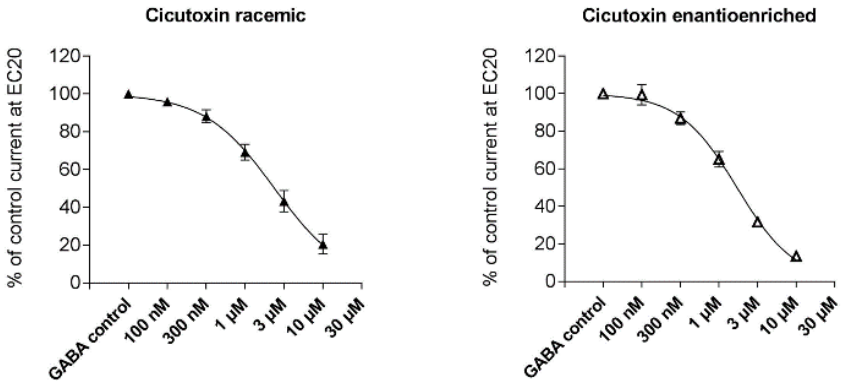


Figure 148. Inhibition of GABA-induced chloride currents by racemic (left) or enantioenriched (right) Cicutoxin (2.003)

Interestingly, application of monomethylated Cicutoxin analogue **2.068** did not result in inhibition of chloride currents, as shown in Figure 149. Hence, it may be concluded that the presence of the secondary hydroxyl group in these natural products is absolutely essential for the inhibition of chloride currents, suggestive of hydrogen bonding interactions of the compounds to this receptor isoform.

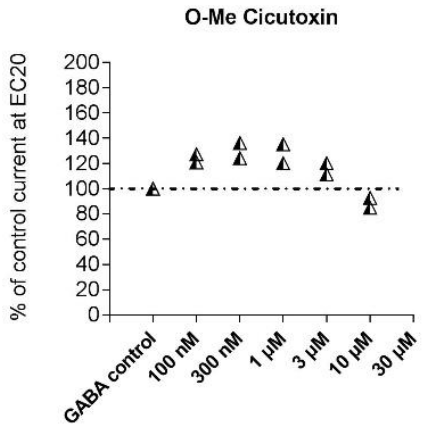


Figure 149. Absence of inhibition of GABA-induced chloride currents by O-methylated Cicutoxin analogue 2.068

2.2.5 Conclusion

The total synthesis of natural products Cicutoxin and Virol A has been achieved by rapid construction of their polyenyne motif *via* a cuprate addition/4π electrocyclic ring opening domino reaction. This methodology might be applicable to various other natural products sharing this motif. The synthesis also allowed the preparation of a methoxy analogue. Full characterization of activity on $GABA_A$ receptors shed more light on the mode of action of these fascinating toxins.

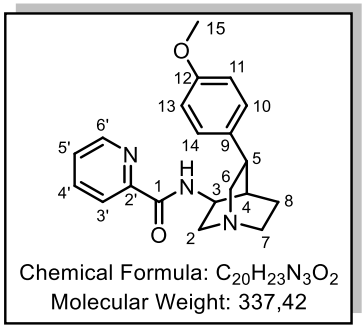
3 EXPERIMENTAL SECTION

3.1 GENERAL INFORMATION

All glassware was oven dried before use and the reactions were conducted under Argon atmosphere unless otherwise stated. All reagents were used as received from commercial suppliers unless otherwise stated. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminum plates coated with kieselgel F254 with 0.2 mm thickness. Visualization was achieved by a combination of UV light (254 nm) and acidic potassium permanganate, phosphomolybdic acid or bromocresol stain. Column chromatography was performed using silica gel 60 (230-400 mesh, Merck and co.). Ozonolysis was performed on an Anseros ozone generator COM-AD-02 and Anseros SEP-100 oxygen generator. Neat infra-red spectra were recorded using a Perkin-Elmer Spectrum 100 FTIR spectrometer. Mass spectra were obtained using a Finnigan MAT 8200 or (70 eV) or an Agilent 5973 (70 eV) spectrometer, using electrospray ionization (ESI). ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker AV 400, AV II 500, AV III 600 or AV III HD spectrometer at 300K (unless otherwise stated. Chemical shifts were given in parts per million (ppm, δ), referenced to the solvent peak. Coupling constants are quoted in Hz (*J*). ^{1}H NMR splitting patterns were designated as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p). Splitting patterns that could not be interpreted or easily visualized were designated as multiplet (m) or broad (b).

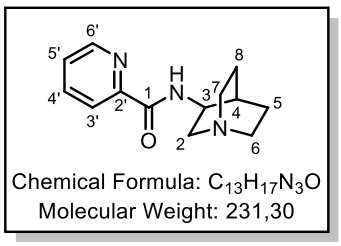
3.2 QUININE AND C-3-ARYL ANALOGUES

N-((1R,3S,4R)-Quinuclidin-3-yl)picolinamide **1.155**



Picolinic acid **1.154** (9.27 g, 75.3 mmol) was dissolved in dry DMF (300 mL). CDI (12.2 g, 75.3 mmol, 1 eq.) was added and the reaction was stirred for 90 min. Then, 3-aminoquinuclidine dihydrochloride **1.153** (15 g, 75.3 mmol, 1 eq.) was added at RT and the mixture was stirred at RT for 16 h. H_2O (50 mL) was added at 0 °C followed by 5 M NaOH (100 mL). The reaction mixture was poured into a separating funnel and extracted thrice with dichloromethane. The combined organic phases were washed twice with water, separated and dried over Na_2SO_4 and filtered. Solvents were evaporated *in vacuo* (rotary evaporator). The product was further purified by stirring in MTBE (400 mL) and removal of insoluble impurities by filtration. Solvents were removed *in vacuo* to afford the pure **1.155** (14.8 g, 85%) as a thick colorless oil. **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 8.49 (d, *J* = 4.7 Hz, 1H, $H_{6'}$), 8.20 (bs, 1H, NH), 8.12 (d, *J* = 7.8 Hz, 1H, $H_{3'}$), 7.78 (td, *J* = 7.8, 1.6 Hz, 1H, $H_{4'}$), 7.38–7.35 (m, 1H, $H_{5'}$), 4.14–4.06 (m, 1H, H_3), 3.42–3.34 (m, 1H, H_{2a}), 2.98–2.73 (m, 4H, $H_{7,6}$), 2.65–2.57 (m, 1H, H_{2b}), 2.01–1.96 (m, 1H, H_4), 1.82–1.703 (m, 1H, H_{8a}), 1.70–1.62 (m, 2H, H_5), 1.51–1.42 (m, 1H, H_{8b}) ppm. **^{13}C-NMR (125 MHz, $CDCl_3$)**: δ 164.2 (C_1), 150.0 ($C_{2'}$), 148.0 ($C_{6'}$), 137.4 ($C_{4'}$), 126.2 ($C_{5'}$), 122.1 ($C_{3'}$), 56.0 (C_2), 47.5 ($C_{6/7}$) 46.7 ($C_{6/7}$), 46.5 (C_3), 25.8 (C_4), 25.7 (C_5), 20.2 (C_8) ppm. **FT-IR (neat, cm^{-1}):** 3139, 2920, 2769, 1670, 1603, 1550, 1516, 1454, 1437, 1326, 1299, 1282, 1219, 1092, 1033, 992, 975, 944; **HRMS (ESI)** calcd. for $C_{13}H_{17}N_3ONa$ $[M+Na]^+$: 254.1264, found: 254.1262;

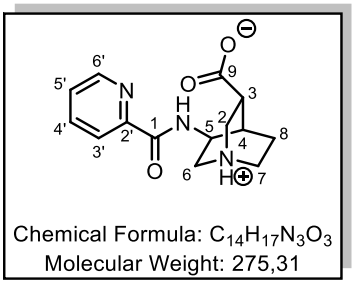
N-((1S,3S,4R,5S)-5-(4-Methoxyphenyl)quinuclidin-3-yl)picolinamide **1.159a**



To a solution of **1.155** (50 mg, 0.22 mmol) and *p*-iodoanisole (154.5 mg, 0.66 mmol, 3 eq.) in DMF (0.3 M) were added successively pivalic acid (22.5 mg, 0.22 mmol, 1 eq.), $Pd(OAc)_2$ (7.4 mg, 0.03 mmol, 15 mol%) and Ag_2CO_3 (60.6 mg, 0.22 mmol, 1 eq.). The resulting mixture was slowly heated to 100 °C and stirred at this temperature for 16 h. After 16 h, the reaction was cooled to room temperature, diluted with 5 M NaOH solution and extracted three times with dichloromethane. The combined organic phase were dried over Na_2SO_4, concentrated and purified by flash chromatography using a gradient of 10 to 30% DMA (CH_2Cl_2/MeOH/NH_4OH 80:20:3) in DCM to afford **1.159a** as a pale yellow solid (69 mg, 0.21 mmol, 94% yield). On a 2.4 mmol scale (555 mg), the product was obtained in 78% yield (629 mg, 1.86 mmol). **^{1}H-**

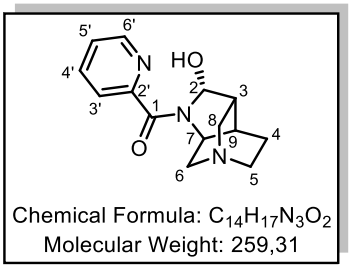
NMR (500 MHz, $CDCl_3$): δ 8.17 (d, J = 4.7 Hz, 1H, $H_{6'}$), 7.96 (d, J = 7.8 Hz, 1H, $H_{3'}$), 7.76–7.66 (m, 2H, NH, $H_{5'}$), 7.29–7.26 (m, 3H, $H_{4',10,14}$), 6.82 (d, J = 8.8 Hz, 2H, $H_{11,13}$), 4.19–4.13 (m, 1H, H_3), 3.73 (s, 3H, H_{15}) 3.52–3.36 (m, 3H, $H_{2a,6a,7a}$), 3.09 (t, J = 8.7 Hz, 1H, H_5), 2.95–2.88 (m, 2H, $H_{6b,7b}$), 2.77 (dd, J = 14.2, 5.0 Hz, 1H, H_{2b}), 2.52–2.50 (m, 1H, H_4), 1.92–1.78 (m, 2H, H_8). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ 163.6 (C_1), 157.9 (C_{12}), 149.5 ($C_{2'}$), 147.4 ($C_{6'}$), 136.9 ($C_{5'}$), 134.9 (C_9), 127.9 ($C_{10/14}$), 125.7 ($C_{4'}$), 121.6 ($C_{3'}$), 114.3 ($C_{11/12}$), 56.8 (C_2), 55.2 (C_{15}), 51.9 ($C_{6/7}$), 46.7 (C_3), 46.1 ($C_{6/7}$), 37.2 (C_5), 32.7 (C_3), 28.6 (C_8); **FT-IR (neat, cm^{-1}):** 3352, 2936, 2870, 1668, 1611, 1590, 1569, 1513, 1463, 1434, 1319, 1284, 1246, 1181, 1036, 997; **HRMS (ESI)** calcd. for $C_{20}H_{25}N_3O_2Na$ $[M+Na]^+$: 360.1682, found: 360.1681;

(1S,3R,4R,5S)-5-(Picolinamido)quinuclidin-1-ium-3-carboxylate **1.165**



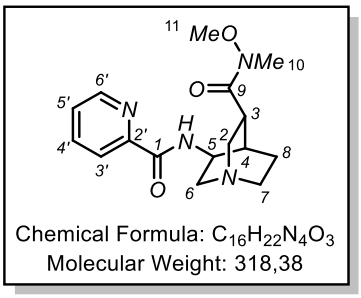
A 250 mL round bottom flask was charged with **1.159a** (1.35 g, 4.00 mmol), ruthenium(III) chloride (331 mg, 1.60 mmol) and sodium periodate (20.55 g, 96.03 mmol) to which H_2O was added (53 mL) followed by EtOAc (13.5 mL) and acetonitrile (13.5 mL). The flask was sealed with a septum pierced with a cannula to allow gases to escape and the reaction was stirred at room temperature overnight. After 18 h, the reaction was filtered through celite, and the pad was washed with 200 mL H_2O. The filtrate was transferred to a separating funnel and washed three times with DCM (3 × 50 mL). The halogenated phases were discarded, while the aqueous phase was collected and evaporated to a volume of *ca.* 20 mL *in vacuo*. To this residue was added 10 mL of 1 M HCl and the mixture was loaded onto a wet column of DOWEX–50WX8 (20 g) which had been pre-washed with 150 mL water. The column was washed with 4 × 500 mL portions of H_2O, during which time the $NaIO_4$ eluted. The column was then washed with 5 × 250 mL portions of 1 M NH_4OH; the product eluted in the first four fractions. Water was evaporated from the collected fractions *in vacuo* followed by drying under high vacuum to afford the zwitterionic **1.165** as a dark red solid (0.88 g, 80%). **^{1}H-NMR (500 MHz, D_2O):** δ 8.65 (br s, 1H, $H_{6'}$), 8.00 (m, 2H, $H_{3',4'}$), 7.62 (dd, J = 4.4, 4.3 Hz, 1H, $H_{5'}$), 4.54–4.46 (m, 1H, H_5), 3.87–3.74 (m, 2H, $H_{2a,6a}$), 3.57 (ddd, J = 10.9, 2.6, 2.6 Hz, 1H, H_{2b}), 3.39–3.32 (m, 3H, $H_{6b,7}$), 2.96 (t, J = 8.6 Hz, 1H, H_3), 2.87–2.84 (m, 1H, H_4), 2.17–2.08 (m, 2H, H_8); **^{13}C-NMR (125 MHz, D_2O):** δ 178.5 (C_9), 166.5 (C_1), 148.9 ($C_{6'}$), 148.0 ($C_{2'}$), 138.2 ($C_{4'}$), 127.3 ($C_{5'}$), 122.3 ($C_{3'}$), 52.6 (C_6), 49.5 (C_2), 42.5 (C_7), 44.5 (C_5), 39.0 (C_3), 27.5 (C_4), 22.8 (C_8); **FT-IR (neat, cm^{-1}):** 3240, 3059, 3015, 1655, 1586, 1568, 1509, 1464, 1434, 1376, 1292, 1088, 1043, 996, 911; **HRMS (ESI)** calcd. for $C_{14}H_{18}N_3O_3$ $[M+H]^+$: 276.1343, found: 276.1341.

(1S,3R,4R,5S)-N-Methoxy-*N*-methyl-5-(picolinamido)quinuclidine-3-carboxamide **1.166**



To a suspension of **1.165** (1.08 g, 3.92 mmol) in 30 mL DMF was added triethylamine (1.72 mL, 12.35 mmol) followed by *N,O*-dimethylhydroxylamine hydrochloride (401 mg, 4.11 mmol) and HATU (1.56 g, 4.11 mmol). The reaction was stirred overnight at room temperature. After 18 h, the reaction mixture was poured into 250 mL DCM to which 300 mL 1:1 5 M NaOH/brine was added, and the mixture was extracted three times with 250 mL DCM. The combined organic phase was dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude material was purified by chromatography over silica gel using a gradient of 10 to 30% DMA (CH_2Cl_2/MeOH/NH_4OH 80:20:3) in DCM, followed by evaporation of solvents to afford the Weinreb amide **1.166** as a pale pink gum (727 mg, 58%). **^{1}H-NMR (500 MHz, CD_2Cl_2):** δ 8.85 (br d, J = 6.2 Hz, 1H, NH), 8.61 (d, J = 4.8 Hz, 1H, $H_{6'}$), 8.08 (dt, J = 7.8, 1.1 Hz, 1H, $H_{3'}$), 7.81 (td, J = 7.8, 1.6 Hz, 1H, $H_{4'}$), 7.39 (ddd, J = 7.8, 4.8, 1.6 Hz, 1H, $H_{5'}$), 4.21–4.10 (m, 1H, H5), 3.63 (s, 3H, H_{11}), 3.44 (dd, J = 12.6, 4.5 Hz, 1H, H_{6a}), 3.30 (t, J = 12.5 Hz, 1H, H_{2a}), 3.04 (s, 3H, H_{10}), 3.01–2.71 (m, 5H, $H_{2b,6b,3,7}$), 2.36–2.30 (m, 1H, H_4), 1.84–1.62 (m, 2H, H_8); **^{13}C-NMR (125 MHz, CD_2Cl_2):** δ 177.0 (C_9), 164.2 (C_1), 150.8 ($C_{2'}$), 148.6 ($C_{6'}$), 137.4 ($C_{4'}$), 126.3 ($C_{5'}$), 122.3 ($C_{3'}$), 61.8 (C_{11}), 55.7 (C_2), 50.5 (C_6), 46.4 (C_7), 46.0 (C_5), 37.4 (C_3), 32.6 (C_{10}), 30.4 (C_4), 28.7 (C_8); **FT-IR (neat, cm^{-1}):** 3355, 2938, 2871, 1668, 1590, 1568, 1517, 1465, 1435, 1385, 1327, 1173, 1086, 1042, 997; **HRMS (ESI)** calcd. for $C_{16}H_{22}N_4O_3Na$ $[M+Na]^+$: 341.1584, found: 341.1586;

((2R)-2-Hydroxyhexahydro-3,6-methanopyrrolo[2,3-c]pyridin-1(2H)-yl)(pyridin-2-yl)methanone **1.167**

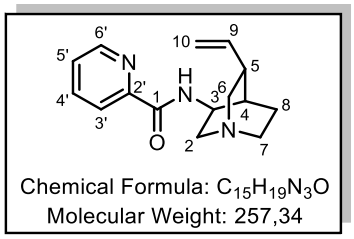


To a solution of **1.166** (550 mg, 1.73 mmol) in 11.5 mL DCM under argon at −78 °C was slowly added DIBAL-H as a 1 M solution in DCM (10.38 mL, 10.58 mmol) in one portion with stirring. The reaction was stirred at −78 °C for 1.5 h before quenching the excess DIBAL-H with 15 mL EtOAc. The cooling bath was then removed and 20 mL saturated Rochelle's salt solution in H_2O was added neat. 5 mL $CHCl_3$ and 5 mL H_2O were then added, and the reaction was stirred vigorously at room temperature for 1 h. The mixture was then transferred to a separating funnel and extracted from 150 mL 2 M NaOH/brine using three volumes of DCM (3 × 100 mL). The organic phase was dried over Na_2SO_4, filtered, and evaporated *in vacuo* to afford the product **1.167** as a dark green waxy solid (purity >90%, 357 mg, 72%) which could be used without further purification. **^{1}H-NMR (500 MHz, $CDCl_3$):** δ 8.56 (d, J = 4.9 Hz, 1H, $H_{6'}$), 8.16 (d, J = 7.8 Hz, 1H, $H_{3'}$), 7.95 (td, J = 7.8, 1.5 Hz, 1H, $H_{4'}$), 7.50 (ddd, J = 7.8, 4.9, 1.5 Hz, 1H,

$H_{5'}$), 7.18 (s, 1H, OH), 5.11 (s, 1H, H_2), 4.36 (t, *J* = 6.0 Hz, 1H, H_7), 3.21–3.08 (m, 2H, $H_{6a,8a}$), 3.06–2.96 (m, 2H, $H_{5a,8b}$), 2.91–2.80 (m, 2H, $H_{4,5b}$), 2.62 (br d, *J* = 14.0 Hz, 1H, H_{6b}), 2.39 (d, *J* = 9.0 Hz, 1H, H_9), 1.91–1.83 (m, 2H, H_4); **^{13}C-NMR (125 MHz, $CDCl_3$):** *δ* 165.8 (C_1), 152.6 ($C_{2'}$), 147.1 ($C_{6'}$), 138.2 ($C_{4'}$), 126.1 ($C_{5'}$), 126.0 ($C_{3'}$), 87.8 (C_2), 56.3 (C_7), 55.9 (C_8), 52.1 (C_6), 48.8 (C_5), 41.1 (C_9), 27.7 (C_3), 16.4 (C_4); **FT-IR (neat, cm^{-1}):** 3375, 3057, 2954, 2934, 2871, 1668, 1623, 1584, 1568, 1515, 1451, 1412, 1384, 1354, 1346, 1306, 1255, 1222, 1189, 1147, 1114, 1101, 1081, 1049, 998; **HRMS (ESI)** calcd. for $C_{14}H_{17}N_3O_2Na$ $[M+H]^+$: 282.1213, found: 282.1214;

The stereochemistry of **1.167** was determined *via* $^3J_{HH}$-coupling. The signal of the hemiaminal (CH) at 5.11 ppm, which appears as singlet, with a very small coupling constant corresponds, according to the Karplus equation, to a dihedral angle of approximately 90 degrees and, therefore, the shown diastereomer.

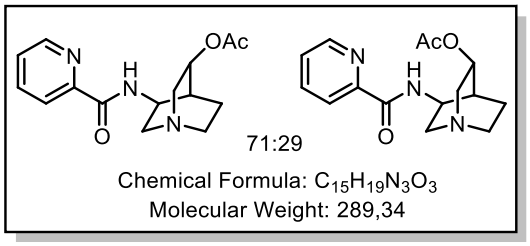
N-((1S,3S,4R,5R)-5-Vinylquinuclidin-3-yl)picolinamide **1.161**



Methyltriphenylphosphonium bromide (165 mg, 0.463 mmol) was placed in a dry argon-filled schlenk and evaporated for 5 min at 3 × 10^{-1} mbar, then filled again with argon. To this flask, 380 µL THF was added and the flask was cooled to −78 °C, followed by addition of LHMDS as a 1 M solution in THF (425 µL, 0.425 mmol). The solution was allowed to come to room temperature and stirred for 20 min to form the bright yellow ylid solution. Hemiaminal **1.167** (purity >90%, 30 mg, 0.105 mmol) was placed in a separate argon-filled schlenk, which was evaporated at 3 × 10^{-1} mbar for 5 min and refilled with argon. 60 µL dry DMSO was added in the same Schlenk and the rxn was stirred for 5 min, followed by the addition of 570 µL THF. The reaction was cooled to −78 °C and 650 µL of the freshly prepared ylid solution was introduced via syringe. The reaction was stirred at room temperature for 45 min and then quenched at 0 °C using 3 mL H_2O. The reaction mixture was then extracted using 1:1 2 M NaOH/brine and three volumes of DCM. The organic phases were dried over Na_2SO_4, then filtered and evaporated *in vacuo*. The crude residue was purified by chromatography over silica gel using a gradient of 15 to 30% DMA (CH_2Cl_2/MeOH/NH_4OH 80:20:3) in dichloromethane to afford the pure product **1.161** as a yellow oil (22 mg, 84%). On a 1.39 mmol scale (purity >90%, 400 mg), the product was obtained in 56% yield (200 mg, 0.78 mmol). **^{1}H-NMR (500 MHz, $CDCl_3$):** *δ* 8.53 (d, *J* = 4.9 Hz, 1H, $H_{6'}$), 8.43 (br d, *J* = 7.0 Hz, 1H, NH), 8.15 (d, *J* = 7.7 Hz, 1H, $H_{3'}$), 7.82 (td, *J* = 7.7, 1.7 Hz, 1H, $H_{4'}$), 7.50 (ddd, *J* = 7.7, 4.9, 1.7 Hz, 1H, $H_{5'}$), 6.06 (ddd, *J* = 17.2, 10.2, 5.6 Hz, 1H, H_9), 5.20–5.13 (m, 2H, H_{10}), 4.24–4.17 (m, 1H, H_3), 3.43 (ddd, *J* = 14.1, 9.7, 2.2 Hz, 1H, H_{2a}), 3.21 (ddd, *J* = 13.5, 10.2, 2.3 Hz, 1H, H_{6a}), 2.99 (dd, *J* = 13.5, 7.0 Hz, 1H,

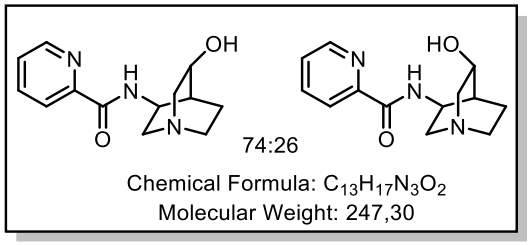
H_{6b}), 2.83 (t, *J* = 8.0 Hz, 2H, H_7), 2.67 (dd, *J* = 14.1, 4.8 Hz, 1H, H_{2b}), 2.48–2.42 (m, 1H, H_5), 2.17–2.13 (m, 1H, H_4), 1.75–1.70 (m, 2H, H_8); **^{13}C-NMR (125 MHz, $CDCl_3$):** *δ* 163.7 (C_1), 149.9 ($C_{2'}$), 148.1 ($C_{6'}$), 142.3 (C_9), 137.2 ($C_{4'}$), 126.0 ($C_{5'}$), 122.1 ($C_{3'}$), 114.5 (C_{10}), 56.8 (C_2), 52.7 (C_6), 46.7 (C_3), 46.0 (C_7), 37.6 (C_5), 32.4 (C_4), 28.2 (C_8); **FT-IR (neat, cm^{-1}):** 3373, 3058, 2934, 2865, 1667, 1590, 1569, 1513, 1464, 1434, 1321, 1290, 1243, 1168, 1087, 1062, 1042, 997; **HRMS (ESI)** calcd. for $C_{15}H_{19}N_3ONa$ $[M+Na]^+$: 280.1420, found: 280.1418;

Synthesis of **1.180**



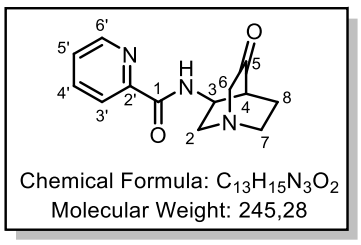
To a suspension of racemic **1.155** (1 eq., 1.754 g, 7.58 mmol) in dry toluene (37.9 mL) was added acetic acid (5 eq., 2.17 mL), $Pd(OAc)_2$ (0.5 eq., 851 mg, 3.79 mmol) and PIDA (2.5 eq., 6.106 mg, 19 mmol). The resulting mixture was stirred at 100 °C for 48 h. After cooling to room temperature, the mixture was filtered through a short pad of celite and was washed with EtOAc (100 mL). After concentration under reduced pressure, the crude mixture was purified by column chromatography (silica gel, DCM/MeOH/NH_4OH = 95/5/0.075 to afford 485 mg (22%) of the product **1.180** with a diastereomeric ratio of 70:30 as an orange foam. Characterization as a mixture of diastereomers: **^{1}H-NMR (600 MHz, $CDCl_3$):** δ 9.07 (d, *J* = 8.8 Hz, 1H-minor), 8.55 (d, *J* = 4.3 Hz, 1H-major), 8.51 (d, 1H, *J* = 4.3 Hz, 1H-minor), 8.22–8.14 (m, 2H-major, 1H-minor), 7.88–7.82 (m, 1H-major, 1H-minor), 7.47–7.41 (m, 1H-major), 1H-minor), 5.04–4.99 (m, 1H-major), 4.99 (m, 1H-minor), 4.35–4.29 (m, 1H-major, 1H-minor), 3.53 (bt, *J* = 11.7 Hz, 1H-minor), 3.47 (bdd, *J* = 14.4, 8.3 Hz, 1H-major), 3.43–3.23 (m, 1H-major, 1H-minor), 2.96–2.88 (m, 1H-major), 2.86–2.69 (m, 1H-major, 3H-minor), 2.67 (bd, *J* = 14.9 Hz, 1H-major), 2.58 (dd, *J* = 14.1, 3.4 Hz, 1H-major), 2.38 (bt, *J* = 2.9 Hz, 1H-major), 2.28 (s, 3H-minor), 2.21–2.18 (m, 1H-minor), 2.07 (s, 3H-major), 2.05–1.99 (m, 1H-major), 1.88–1.81 (m, 1H-minor), 1.69–1.61 (m, 1H-minor), 1.60–1.52 (m, 1H-major) ppm. **^{13}C-NMR (150 MHz, $CDCl_3$)**: δ 171.1 (C-major), 170.3 (C-minor), 164.5 (C-major), 163.6 (C-minor), 150.1 (C-minor), 149.5 (C-major), 148.2 (CH-major), 148.0 (CH-minor), 137.6 (CH-major), 137.6 (CH-minor), 126.5 (CH-major), 126.3 (CH-minor), 122.4 (CH-minor), 122.2 (CH-major), 71.1 (CH-minor), 67.6 (CH-major), 56.8 (CH_2-minor), 56.3 (CH_2-minor), 56.0 (CH_2-major), 55.2 (CH_2-major), 47.1 (CH-major), 46.5 (CH_2-major), 45.3 (CH_2-minor), 44.2 (CH-minor), 30.8 (CH-major), 30.3 (CH-minor), 24.7 (CH_2-minor), 21.4 (CH_3-minor), 21.3 (CH_3-major), 19.0 (CH_2-major) ppm. **FT-IR (neat, cm^{-1})**: 3382, 2938, 1725, 1669, 1569, 1520, 1435, 1367, 1324, 1246, 1031; **HRMS (ESI)** calcd. for $C_{15}H_{20}N_3O_3^+$ $[M+H]^+$: 290.1499, found: 290.1499.

Synthesis of **1.181**



To a solution of **1.180** (1 eq., 485 mg, 1.68 mmol) in dry methanol (33.6 mL) was added anhydrous K_2CO_3 powder (1 eq., 232 mg, 1.68 mmol). The mixture was stirred at room temperature for 16 h. The mixture was diluted with DCM (300 mL) and the organic layer were washed with aqueous NaOH (1 M, 100 mL). After separation, the aqueous layer was extracted again using DCM (2 × 300 mL). The combined organic layers were washed with brine (200 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product. Column chromatography (silica gel, DCM/MeOH/NH_4OH = 90/10/0.15) afforded 291 mg (70%) of **1.181** yellow solid with a d. r. of 74:26. Characterization as mixture of diastereomers: **^{1}H-NMR (700 MHz, $CDCl_3$)**: δ 9.41 (d, *J* = 8.8 Hz, 1H-minor), 8.52 (bd, *J* = 4.2 Hz, 1H-major, 1H-minor), 8.18–8.14 (m, 1H-major, 1H-minor), 8.13 (d, *J* = 6.9 Hz, 1H-major), 7.84 (td, *J* = 7.7, 1.3 Hz, 1H-major), 7.79 (td, *J* = 7.7, 1.4 Hz, 1H-minor), 7.42 (dd, *J* = 7.1, 5.4 Hz, 1H-major), 7.36 (dd, *J* = 7.1, 5.4 Hz, 1H-minor), 4.33–4.26 (m, 1H-major, 1H-minor), 4.18–4.14 (m, 1H-major), 4.06–4.02 (m, 1H-minor), 3.46 (bt, *J* = 12.0 Hz, 1H-minor), 3.56 (ddd, *J* = 14.0, 9.6, 1.7 Hz, 1H-major), 3.31 (ddd, *J* = 14.0, 8.5, 1.7 Hz, 1H-major), 3.21 (ddd, *J* = 14.0, 8.2,1.4 Hz, (1H-minor), 2.96–2.90 (m, 1H-major), 2.85 (bd, *J* = 14.2 Hz, 1H-minor), 2.78–2.70 m (1H-major, 2H-minor), 2.66 (bd, *J* = 13.7 Hz, 1H-major, 1H-minor), 2.52 (dd, *J* = 14.0, 3.8 Hz, 1H-major), 2.24 (bt, *J* = 3.0 Hz, 1H-major), 2.12–2.06 (m, 1H-major, 1H-minor), 1.79–1.73 (m, 1H-minor), 1.54–1.44 (m, 1H-major, 1H-minor) ppm. **^{13}C-NMR (175 MHz, $CDCl_3$)**: δ 164.4 (C-major), 163.9 (C-minor), 150.4 (C-minor), 149.6 (C-major), 148.4 (CH-minor), 148.2 (CH-major), 137.6 (CH-major), 137.3 (CH-minor), 126.4 (CH-major), 126.0 (CH-minor), 122.4 (CH-minor), 122.3 (CH-major), 68.4 (CH-minor), 63.3 (CH-major), 58.6 (CH_2-minor), 57.8 (CH_2-major), 56.8 (CH_2-minor), 55.1 (CH_2-major), 47.2 (CH-major), 46.7 (CH_2-major), 45.3 (CH_2-minor), 44.8 (CH-minor), 34.0 (CH-major), 32.7 (CH-minor), 24.4 (CH_2-minor), 18.4 (CH_2-major) ppm. **FT-IR (neat, cm^{-1})**: 3362, 2933, 1660, 1590, 1569, 1521, 1465, 1326, 1042, 997, 821, 751, 694; **HRMS (ESI)** calcd. for $C_{13}H_{18}N_3O_2^+$ $[M+H]^+$: 248.1394, found: 248.1393.

N-((1R,3S,4S)-5-Oxoquinuclidin-3-yl)picolinamide **1.182**



To a suspension of **1.181** (1 eq., 18.9 mg, 0.07 mmol) in dry acetonitrile (1.5 mL) was added PTSA (1 eq., 14.5 mg, 0.07 mmol) and the mixture was stirred for 10 min at room temperature. IBX (1.1 eq., 23.5 mg, 0.08 mmol) was added, and the mixture was stirred for 3 h at 60 °C. After cooling to room temperature, the mixture was

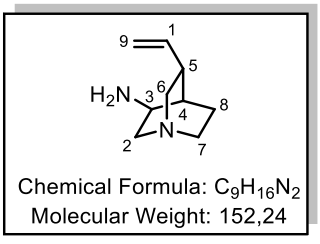
concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, DCM/MeOH/NH_4OH = 90/10/0.15) to afford 16.1 mg (86%) of **1.182** as yellow solid. **^{1}H-NMR (700 MHz, $CDCl_3$)**: δ 8.51 (d, *J* = 4.6 Hz, 1H, $H_{6'}$), 8.13 (d, *J* = 7.7 Hz, 1H, $H_{3'}$), 8.01 (bd, *J* = 5.7 Hz, 1H, NH), 7.83 (td, *J* = 7.7, 1.1 Hz, 1H, $H_{4'}$), 7.42 (ddd, *J* = 7.2, 4.8, 0.7 Hz, 1H, $H_{5'}$), 4.63–4.58 (m, 1H, H_4), 3.62 (dd, *J* = 14.5, 9.0 Hz, 1H, H_{2a}), 3.39 (bs, 2H, H_6), 3.03–2.92 (m, 2H, H_7), 2.77 (ddd, *J* = 14.5, 4.5, 1.9 Hz, 1H, H_{2b}), 2.73 (dd, *J* = 5.8, 2.7 Hz, 1H, H_3), 2.20–2.14 (m, 1H, H_{8a}), 2.11–2.05 (m, 1H, H_{8b}) ppm. **^{13}C-NMR (175 MHz, $CDCl_3$)**: δ 216.8 (C_5), 164.1 (C_1), 149.2 ($C_{2'}$), 148.3 ($C_{6'}$), 137.5 ($C_{4'}$), 126.6 ($C_{5'}$), 122.3 ($C_{3'}$), 63.2 (C_6), 56.2 (C_2), 49.5 (C_4), 46.1 (C_7), 45.3 (C_3), 24.1 (C_8) ppm. **FT-IR (neat, cm^{-1})**: 3297, 2946, 1728, 1666, 1591, 1569, 1517, 1466, 1435, 1308, 1056, 997, 751, 689; **HRMS (ESI)** calcd. for $C_{13}H_{16}N_3O_2^+$ $[M+H]^+$: 246.1237, found: 246.1240.

Conversion of **1.182** to **1.167** via Wittig homologation

To a suspension of Ph_3PCH_2OMeCl (10 eq., 1.168 g, 3.4 mmol) in dry THF in a flame-dried Schlenk under Argon was added a solution of LiHMDS (8 eq., 1 M in THF, 2.73 mL, 2.73 mmol) dropwise at room temperature over 5 min and the mixture was allowed to stir for another 30 min.

A separate flame-dried Schlenk tube under Argon was loaded with **1.182** (1 eq., 83.6 mg, 0.34 mmol), dry DMSO (240 µL) and dry THF (1.35 mL) in this order. After cooling to room temperature, the ylide solution prepared before was added, the ice bath was removed and the mixture was allowed to stir for 3 h at room temperature. Then, the reaction was quenched with aqueous HCl (1 M, 40 mL), and the mixture was stirred for 27 h. The slurry was diluted with aqueous KOH (3 M, 50 mL) and extracted with DCM (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, DCM/MeOH/NH_4OH 95/5/0.075) to afford **1.167** (>90% purity, 21.9 mg, 22%) as brown wax. The spectral data was found to be in full agreement with **1.167** as prepared by the C–H Arylation sequence (see above).

(1S,3S,4R,5R)-5-Vinylquinuclidin-3-amine **1.150**

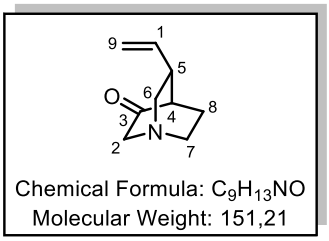


Chemical Formula: $C_9H_{16}N_2$
Molecular Weight: 152,24

1.161 (85 mg, 0.33 mmol) was suspended in 6 mL H_2O to which conc. HCl was added (0.23 mL), followed by $Zn(OTf)_2$ (120 mg, 0.33 mmol). After stirring at room temperature for 5 min, Zn dust (324 mg, 4.95 mmol) was added. After 1.5 h, the reaction mixture was filtered through celite and

the pad was washed with 50 mL H_2O. The filtrate was cooled in an ice-water bath and 40 mL DCM were added with stirring, followed by slow addition of 10 M aq. NaOH (20 mL). After 15 min, the mixture was poured into a separating funnel and extracted three times DCM (3 × 60 mL). The combined organic phases were dried over Na_2SO_4, filtered, and evaporated at 150 mbar/35 °C. The crude material was purified by chromatography over silica gel using a gradient of 30 to 50% DMA (CH_2Cl_2/MeOH/NH_4OH 80:20:3) in dichloromethane. After chromatography, solvents were removed under the same conditions as before, at 150 mbar/35 °C. The purified amine (clear oil, purity >90%, 43 mg, 77%) was stored under argon at −78 °C (in a sealed vessel immersed in dry ice) and used in the subsequent reaction within 36 h to minimize decomposition. On a 1.28 mmol scale (330 mg), the product was obtained in 35% yield (purity >90%, 75 mg, 0.44 mmol). Concerning the chemical instability of **1.150**, upscaling is not recommended as bigger scale setups require more time for work-up and purification. **^{1}H-NMR (500 MHz, CD_2Cl_2):** δ 6.24 (ddd, J = 17.3, 10.4, 6.4 Hz, 1H, H_1), 4.99 (d, J = 17.3 Hz, 1H, H_{9a}), 4.93 (d, J = 10.4 Hz, 1H, H_{9b}), 3.11 (ddd, J = 13.2, 9.4, 2.2 Hz, 1H, H_{2a}), 3.05 (ddd, J = 13.2, 10.2, 2.2 Hz, 1H, H_3), 2.95–2.91 (m, 1H, H_{7a}), 2.79 (ddd, J = 13.2, 7.0, 1.9 Hz, 1H, H_{7b}), 2.73–2.60 (m, 2H, H_6), 2.39–2.29 (m, 2H, $H_{6,2b}$), 1.79–1.75 (m, 1H, H_4), 1.66–1.42 (m, 4H, NH_2,H_8); **^{13}C-NMR (125 MHz, CD_2Cl_2):** δ 150.0 (C_1), 112.7 (C_9), 59.9 (C_2), 53.9 (C_6), 50.4 (C_7), 46.1 (C_3), 39.7 (C_5), 36.5 (C_4), 29.3 (C_8) ppm; **FT-IR (neat, cm^{-1}):** 3274, 3072, 2931, 2867, 1633, 1592, 1454, 1320, 1265, 1069, 1048, 998, 974, 907, 814, 732; **HRMS (ESI)** calcd. for $C_9H_{16}N_2$ $[M]^+$: 152.1313, found: 152.1312;

(1S,4R,5R)-5-Vinylquinuclidin-3-one **1.151**



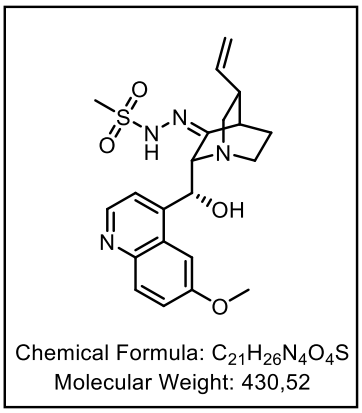
Chemical Formula: $C_9H_{13}NO$
Molecular Weight: 151,21

p-Toluenesulfonic acid monohydrate (137 mg, 0.72 mmol) was added to a solution of **1.150** (purity >90%, 110 mg, 0.65 mmol) in MeCN (7 mL) at RT. The reaction mixture was stirred at this temperature for 10 min then IBX (223 mg, 0.80 mmol) was added and the reaction was stirred at 70 °C for 2 h. The reaction was cooled to room temperature and then quenched with a 2 M NaOH solution. The mixture was poured into a separating funnel and extracted three times with dichloromethane (3 × 60 mL). The combined organic phases were dried over Na_2SO_4, filtered, and evaporated at 150 mbar/35 °C. The crude material was purified by chromatography over silica gel using a gradient of 1 to 4% MeOH in dichloromethane to afford the desired ketone **1.151** as a clear oil (75 mg, 77%). **^{1}H-NMR (400 MHz, CD_2Cl_2):** δ 5.65 (ddd, J = 17.2, 10.3, 7.6, 1H, H_1), 4.98 (ddd, J = 17.2, 1.4, 1.4 Hz, 1H, H_{9a}), 4.96 (ddd, J = 10.3, 1.4, 1.4 Hz, 1H, H_{9b}), 3.30–3.08 (m, 3H, $H_{2,6a}$), 2.99–2.78 (m, 3H, $H_{5,7}$), 2.62 (ddd, J = 13.8, 6.1, 2.2 Hz, 1H, H_{6b}), 2.39 (q, J = 3.0 Hz, 1H, H_4), 2.09–1.93 (m, 2H, H_8); **^{13}C-NMR (100 MHz, CD_2Cl_2):** δ 218.7 (C_3), 141.2 (C_1), 115.3 (C_9), 63.7 (C_2), 54.5 (C_6), 46.7 (C_7),

46.2 (C_4), 43.2 (C_5), 26.3 (C_8); **FT-IR (neat, cm^{-1}):** 2943, 2873, 1729, 1639, 1453, 1404, 1340, 1322, 1304, 1262, 1228, 1134, 1068, 1045, 991, 968, 918, 872, 812; **HRMS (ESI)** calcd. for $C_9H_{16}N_2$ $[M+H]^+$: 152.1070, found: 152.1070.

The following 2 reactions were carried out by Paul Aillard:

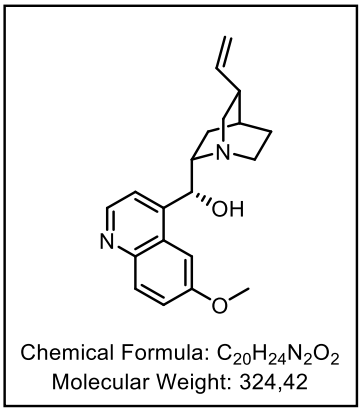
N'-((*1S,2S,4R,5R,Z*)-2-((R)-hydroxy(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidin-3-ylidene)methanesulfonohydrazide **1.216**



Chemical Formula: $C_{21}H_{26}N_4O_4S$
Molecular Weight: 430,52

1.151 (50 mg, 0.33 mmol) was dissolved in 3 ml of anhydrous THF under argon and cooled to 0 °C, followed by addition of LiHMDS (1.0 M in THF, 347 µl, 0.35 mmol). The reaction was stirred for 30 min at 0 °C, then cooled to −78 °C and 6-methoxyquinoline-4-carbaldehyde 12 (68 mg, 0.36 mmol) was added neat. After 1 h at −78 °C, Ti(O-i-Pr)$_3$Cl (202 mg, 0.78 mmol) was added and the reaction was brought to 0 °C and stirred for 5 min, followed by addition of methanesulfonyl hydrazide (73 mg, 0.66 mmol). After 5 min at 0 °C, the reaction was brought to room temperature and stirred for 3 h, then quenched at 0 °C using 1.0 ml sat. aq. $NaHCO_3$. The mixture was extracted from sat. aq. $NaHCO_3$ (30 ml) with DCM (3 × 30 ml). The combined organic phase was dried over Na_2SO_4 and filtered. The crude was purified by chromatography using a gradient of 10 to 30% DMA (CH_2Cl_2/MeOH/NH_4OH 80:20:3) in dichloromethane to afford the product **1.216** as a white solid (108 mg, 76%, dr > 16:1). **^{1}H-NMR (600 MHz, $CDCl_3$)**: δ 8.24 (d, *J* = 4.6 Hz, 1H), 7.77 (d, *J* = 9.2 Hz, 1H), 7.59 (d, *J* = 2.5 Hz, 1H), 7.28 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.20 (d, *J* = 4.6 Hz, 1H), 5.70–5.65 (m, 1H), 5.44 (d, *J* = 9.7 Hz, 1H), 4.97–4.95 (m, 1H), 4.94 (br s, 1H), 4.23 (d, *J* = 9.5 Hz, 1H), 3.91 (s, 3H), 3.08 (s, 3H), 3.03–2.91 (m, 2H), 2.66–2.63 (m, 1H), 2.60–2.56 (m, 1H), 2.52–2.47 (m, 1H), 2.19–2.15 (m, 1H), 2.05–1.99 (m, 1H), 1.89–1.84 (m, 1H); **^{13}C-NMR (150 MHz, $CDCl_3$)**: 161.8 (C), 158.2 (C), 146.8 (CH), 145.0 (C), 144.3 (C), 139.5 (CH), 131.1 (CH), 126.9 (C), 122.4 (CH), 120.1 (CH), 115.2 (CH_2), 101.9 (CH), 73.1 (CH), 66.1 (CH), 56.2 (CH_2), 56.0 (CH_3), 45.0 (CH), 41.0 (CH_2), 38.7 (CH), 38.4 (CH_3), 23.4 (CH_2); **FT-IR (neat, cm^{-1})**: 2933, 1739, 1509, 1473, 1432, 1323, 1241, 1158, 1087, 992, 849, 734; **HRMS (ESI)** calcd. for $C_{21}H_{27}N_4O_4S$ $[M+H]^+$: 431.1753, found: 431.1744.

Quinine **1.101**

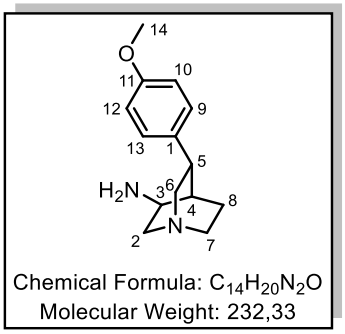


Chemical Formula: $C_{20}H_{24}N_2O_2$
Molecular Weight: 324,42

Lithium aluminium hydride solution (1.0 M in THF, 116 µl, 0.116 mmol) was diluted with THF (0.3 ml) in a Schlenk flask under argon. Methanol (14 µl, 0.348 mmol) was added dropwise at 0°C and stirred at this temperature for 10 min. In another Schlenk flask, a solution of hydrazone **1.216** (10 mg, 0.023 mmol) was diluted in THF (0.3 ml). The aluminium hydride solution was added dropwise to the solution of hydrazone at 0°C. The reaction mixture was then warmed to room temperature and stirred for an additionnal 10 min before being quenched by sat. aq. $NaHCO_3$ solution at 0 °C. The mixture was extracted from sat. aq. $NaHCO_3$ with three volumes of DCM. The combined organic phase was dried over Na_2SO_4 and filtered. The crude was purified by chromatography using a gradient of 10 to 30% DMA (CH_2Cl_2/MeOH/NH_4OH 80:20:3) in dichloromethane to afford the product 1.101 as a white powder (4 mg, 53%). **^{1}H-NMR (400 MHz, DMSO-d_6):** 8.67 (d, *J* = 4.5 Hz, 1H), 7.92 (d, *J* = 9.2 Hz, 1H), 7.49–7.52 (m, 2H), 7.39 (dd, *J* = 9.2, 2.8 Hz, 1H), 5.86 (dd, *J* = 17.5, 10.3, 7.6 Hz, 1H), 5.65 (br d, *J* = 4.7 Hz, 1H), 5.28–5.23 (m, 1H), 5.02–4.91 (m, 2H), 3.90 (s, 3H), 3.26–3.17 (m, 1H), 3.07 (q, *J* = 7.6 Hz, 1H), 2.93–2.84 (m, 1H), 2.48–2.40 (m, 1H), 2.25–2.17 (m, 1H), 1.77–1.60 (m, 4H), 1.49–1.38 (m, 1H). **$[\alpha]_D^{20}$** = -151.8° (c = 0.4, EtOH).

^{13}C-NMR data for **1.101** (bought) in DMSO-d_6	**^{13}C-NMR data** for **1.101** (prepared) in DMSO-d_6
156.7	156.7
149.3	149.3
147.5	147.4
143.9	143.9
142.6	142.6
131.1	131.1
127.1	127.1
120.9	120.9
119.1	119.1
114.0	114.0
102.5	102.5
71.0	71.0
60.6	60.7
55.9	55.9
55.5	55.4
41.8	41.7
39.6	39.6
27.5	27.5
27.4	27.4
24.1	24.2

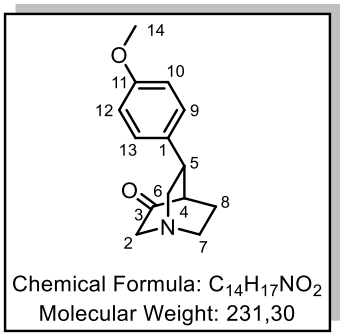
(1S,3S,4R,5S)-5-(4-Methoxyphenyl)quinuclidin-3-amine **1.191a**



Chemical Formula: $C_{14}H_{20}N_2O$
Molecular Weight: 232,33

Racemic **1.159a** (710 mg, 2.11 mmol) was suspended in 50 mL H_2O to which 5 mL conc. HCl were added slowly with stirring. The reaction was stirred at room temperature for 5 min, before Zn dust (2.07 g, 31.60 mmol) was added. After 16 h, 65 mL DCM were added, and the reaction mixture was cooled using an ice-bath followed by slow addition of 5 M NaOH (100 mL). The mixture was filtered through celite and the pad was washed with 30 mL H_2O and 30 mL DCM. The filtrate was extracted with DCM (3 × 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude was purified by chromatography using a gradient of 20 to 40% DMA (CH_2Cl_2/MeOH/NH_4OH 80:20:3) in dichloromethane to afford the free amine **1.191a** as a colorless oil (441 mg, 90%). **^{1}H-NMR (500 MHz, $CDCl_3$):** δ 7.27 (d, J = 8.0 Hz, 2H, $H_{9,13}$), 6.86 (d, J = 8.0 Hz, 2H, $H_{10,12}$), 3.78 (s, 3H, H_{14}), 3.39 (ddd, J = 13.5, 7.7, 1.8 Hz, 1H, H_{6a}), 3.30 (t, J = 13.5, 8.5, 1.8 Hz, 1H, H_{6b}), 3.22 (ddd, J = 14.0, 9.5, 2.2 Hz, 1H, H_{2a}), 3.00 (t, J = 8.5 Hz, 1H, H_5), 2.93–2.89 (m, 1H, H_3), 2.87–2.72 (m, 2H, H_7), 2.52 (ddd, J = 14.0, 5.4, 2.2 Hz, 1H, H_{2b}), 2.28–2.24 (m, 1H, H_4), 1.82–1.75 (m, 1H, H_{8a}), 1.63–1.56 (m, 1H, H_{8b}), 1.43 (br s, 2H, NH_2); **^{13}C-NMR (125 MHz, $CDCl_3$):** δ 157.7 (C_{11}), 136.2 (C_1), 127.8 ($C_{9,13}$), 114.0 ($C_{10,12}$), 59.3 (C_2), 55.3 (C_{14}), 52.2 (C_6), 50.0 (C_3), 45.9 (C_7), 37.7 (C_5), 36.1 (C_4), 29.4 (C_8); **FT-IR (neat, cm^{-1}):** 3367, 2934, 2868, 1667, 1610, 1581, 1513, 1456, 1320, 1282, 1247, 1181, 1118, 1034; **HRMS (ESI)** calcd. for $C_{14}H_{20}N_2ONa$ $[M+Na]^+$: 255.1468, found: 255.1466.

(1S,4R,5S)-5-(4-Methoxyphenyl)quinuclidin-3-one **1.192a**

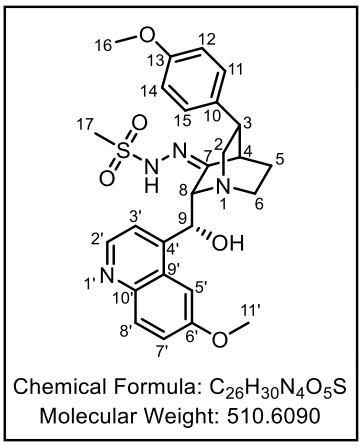


Chemical Formula: $C_{14}H_{17}NO_2$
Molecular Weight: 231,30

Due to scalability reasons, the following reaction has been carried out by running multiple reactions in parallel and combining the crude mixtures for purification. The yield is calculated by dividing by the number of individual reactions and therefore an average value of 20 reactions is given. **1.191a** (31 mg, 0.13 mmol) was dissolved in 266 µl of DMA. L-Ascorbic acid (71 mg, 0.40 mmol) and copper 3-methylsalicylate (29 mg, 0.13 mmol) were successively added and the reaction mixture was stirred in open air at room temperature. After 17 h the brown-purple viscous oil was poured into an ice/water mixture. 5 M NaOH was added and the biphasic system was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting crude material was purified by flash chromatography (silica gel, CH_2Cl_2/4% MeOH) to afford the quinuclidinone **1.192a** as an off-white solid (17 mg, 56%). **^{1}H-NMR (500 MHz, CD_2Cl_2):** δ 6.95 (d, J

= 8.6 Hz, 2H, $H_{9,13}$), 6.74 (d, *J* = 8.6 Hz, 2H, $H_{10,12}$), 3.68 (s, 3H, H_{14}), 3.43 (ddd, *J* = 13.0, 10.0, 1.9 Hz, 1H, H_{6a}), 3.30 (ddd, *J* = 11.8, 7.1, 1.8 Hz, 1H, H_5), 3.22 (m, 2H, H_2), 2.96–2.83 (m, 2H, H_7), 2.79-2.71 (m, 1H, H_{6b}), 2.45–2.42 (m, 1H, H_4), 2.11–2.03 (m, 1H, H_{8a}), 1.97–1.89 (m, 1H, H_{8b}); **^{13}C NMR (125 MHz, CD_2Cl_2):** *δ* 218.8 (C_3), 158.7 (C_{11}), 136.5 (C_1), 128.3 ($C_{9,13}$), 114.4 ($C_{10,12}$), 63.7 (C_2), 56.7 (C_6), 55.6 (C_{14}), 47.0 (C_4), 46.1 (C_7), 44.7 (C_5), 27.1 (C_8); **FT-IR (neat, cm^{-1}):** 2927, 2873, 1723, 1611, 1582, 1513, 1456, 1305, 1282, 1247, 1181, 1116, 1097, 1074, 1032; **HRMS (ESI)** calcd. for $C_{14}H_{17}NO_2Na$ $[M+Na]^+$: 254.1151, found: 254.1147.

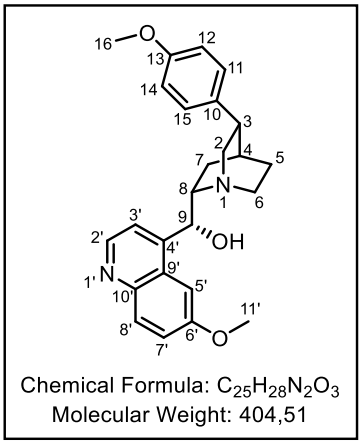
N'-((1S,2S,4R,5S,Z)-2-(*(R)*-Hydroxy(6-methoxyquinolin-4-yl)methyl)-5-(4-methoxyphenyl)quinuclidin-3-ylidene)methanesulfonohydrazide **1.217a**



A flame-dried Schlenk tube was charged with **1.192a** (1 eq., 92.5 mg, 0.40 mmol), dissolved in dry THF (1 mL). After cooling to 0 °C, LiHMDS (1.05 eq., 1 N in THF, 420 µL, 0.42 mmol) was added and stirred for 30 minutes. The red solution was cooled to -78 °C, and a solution of Quinolylaldehyde (1.05 eq., 78.6 mg, 0.42 mmol) in dry THF (0.5 mL) was added and stirred for 30 min. $Ti(OiPr)_3Cl$ (2.5 eq., 1 N in THF, 1.0 mL, 1.00 mmol) was added and stirred for another 5 min at -78 °C before stirring 10 minutes at 0 °C. After recooling to -78 °C, mesylhydrazone (3.0 eq., 132.0 mg, 1.20 mmol) was added neat and the mixture was stirred for 2 h at -78 °C, for another 2 h at 0 °C and finally overnight allowing the mixture to warm up to room temperature. A spatula of siliga gel was added, and the mixture was concentrated under reduced pressure. Column chromatography of the residue afforded 192 mg (94%, dr = 20:1) of the mesylhydrazone **1.217a** as a pale yellow solid. **^{1}H-NMR (600 MHz, $CDCl_3$):** δ = 8.30 (d, *J* = 4.5 Hz, 1H, $H_{2'}$), 7.79 (d, *J* = 9.2 Hz, 1 H, $H_{8'}$), 7.59 (d, *J* = 1.7 Hz, $H_{5'}$), 7.30–7.27 (m, 2 H, $H_{3',7'}$), 7.01 (d, *J* = 8.6 Hz, 2H, $H_{11,15}$), 6.79 (d, *J* = 8.6 Hz, 2H, $H_{12,14}$), 5.51 (d, *J* = 9.2 Hz, 1H, H_9), 4.29 (d, *J* = 9.2 Hz, 1H, H_8), 3.91 (s, 3H, $H_{11'}$), 3.75 (s, 3H, H_{16}), 3.23 (dd, *J* = 13.6, 9.9 Hz, 1H, H_{2a}), 3.19–3.14 (m, 1H, H_3), 3.02-2.93 (m, 4H, $H_{6a,17}$), 2.74 (bs, 1H, H_4), 2.62-2.55 (m, 1H, H_{6b}), 2.55–2.49 (m, 1H, H_{2b}), 2.12-2.04 (m, 1H, H_{5a}), 2.01–1.94 (m, 1H, H_{5b}) ppm. **^{13}C-NMR (150 MHz, $CDCl_3$):** δ = 160.9 (C_7), 158.5 (C_{13}), 158.2 ($C_{6'}$), 146.9 ($C_{2'}$), 145.1 ($C_{4'}$), 144.3 ($C_{10'}$), 134.9 (C_{10}), 131.2 ($C_{8'}$), 129.1 ($C_{11,15}$), 126.9 ($C_{9'}$), 122.3 ($C_{7'}$), 120.1 ($C_{3'}$), 113.8 ($C_{12,14}$), 101.9 ($C_{5'}$), 72.8 (C_9), 66.6 (C_8), 57.7 (C_2), 56.0 ($C_{11'}$), 55.4 (C_{16}), 46.3 (C_3), 41.0 (C_6), 39.9 (C_4), 38.5 (C_{17}), 24.5 (C_5) ppm. **FT-IR (neat, cm^{-1}):** 3056, 2936, 2836, 2172, 2041, 1621, 1592, 1512, 1473, 1433, 1325, 1286, 1246, 1181, 1155, 1109, 1084, 1031, 973, 919, 859, 829, 751, 735, 716, 620, 583, 568, 530. **HRMS (ESI) (m/z):** calculated for $[M + H^+]^+$ $(C_{26}H_{31}N_4O_5S)^+$: 511.2010, found: 511.2011.

(R)-((1S,2S,4S,5S)-5-(4-Methoxyphenyl)quinuclidin-2-yl)(6-methoxyquinolin-4-yl)methanol **1.162a**

Lithium aluminium hydride (1 N in THF, 5 eq, 597.0 µL, 0.60 mmol) was diluted with dry THF (1 mL) in a flame-dried Schlenk tube and cooled to 0 °C. Dry methanol (10 eq, 48.4 µL, 1.19 mmol) was added and the solution was stirred for 10 minutes. The mixture was transferred with a syringe to a solution of mesylhydrazone **1.217a** (1 eq, 61.0 mg, 0.12 mmol) in dry THF (1 mL) at 0 °C. The ice bath was removed, and the solution was stirred for 23 minutes while warming to room temperature. After recooling to 0 °C, the mixture was quenched dropwise with 1 N $NaHCO_3$ (5 mL) and extracted with DCM (3 x 5 mL). The solution was dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification by preparative thin layer chromatography (silica, DCM, MeOH, NH_4OH aq. = 94:6:0.05) afforded 7.3 mg (15%) of product **1.162a** as an off-white solid.



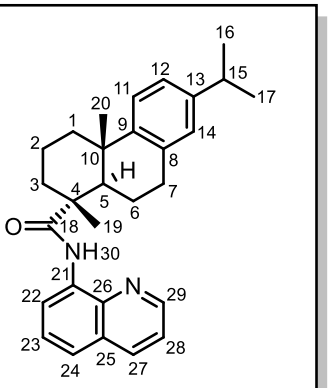
Chemical Formula: $C_{25}H_{28}N_2O_3$
Molecular Weight: 404,51

^{1}H-NMR (600 MHz, CD_3OD): δ = 8.65 (d, *J* = 4.6 Hz, 1H, $H_{2'}$), 7.96 (d, *J* = 9.2 Hz, 1 H, $H_{8'}$), 7.68 (d, *J* = 4.6 Hz, $H_{3'}$), 7.48 (d, *J* = 2.6 Hz, $H_{5'}$), 7.47 (dd, *J* = 9.2, 2.6 Hz, 1H, $H_{7'}$), 7.07 (d, J = 8.7 Hz, 2H, $H_{11,15}$), 6.76 (d, *J* = 8.7 Hz, 2H, $H_{12,14}$), 5.64 (d, *J* = 3.3 Hz, 1H, H_9), 4.01 (s, 3H, $H_{11'}$), 3.78–3.72 (m, 1H, H_{6a}), 3.69 (s, 3H, H_{16}), 3.40–3.35 (m, 1H, H_{2a}), 3.34–3.29 (m, 1H, H_8), 3.21–3.14 (m, 1H, H_{2b}), 3.06–3.00 (m, 1H, H_3), 2.89–2.82 (m, 1H, H_{6b}), 2.04–1.96 (m, 2H, $H_{5a,4}$), 1.92–1.86 (m, 1H, H_{7a}), 1.82–1.74 (m, 1H, H_{5b}), 1.40–1.34 (m, 1H, H_{7b}) ppm. **^{13}C-NMR (150 MHz, CD_3OD):** δ = 159.8 ($C_{6'}$), 159.5 (C_{13}), 150.2 ($C_{4'}$), 148.2 ($C_{2'}$), 144.8 ($C_{10'}$), 136.6 (C_{10}), 131.5 ($C_{8'}$), 129.3 ($C_{11,15}$), 128.1 ($C_{9'}$), 123.4 ($C_{7'}$), 120.3 ($C_{3'}$), 114.9 ($C_{12,14}$), 102.5 ($C_{5'}$), 72.0 (C_9), 61.4 (C_8), 57.7 (C_2), 56.5 ($C_{11'}$), 55.6 (C_{16}), 44.4 (C_6), 41.3 (C_3), 30.5 (C_4), 28.6 (C_5), 21.4 (C_7) ppm. **FT-IR (neat, cm^{-1}):** 3186, 2936, 2835, 1620, 1590, 1511, 1468, 1434, 1363, 1324, 1244, 1180, 1135, 1100, 1081, 1032, 855, 831, 752, 717, 642. **HRMS (ESI) (m/z):** calculated for $[M + H^+]^+$ $(C_{25}H_{29}N_2O_3)^+$: 405.2173, found: 405.2187.

3.3 Synthesis of DHAA-Analogues and Cleavage of the AQ-Directing Group

Synthesis of DHAA analogues

(1R,4aS)-7-Isopropyl-1,4a-dimethyl-N-(quinolin-8-yl)-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxamide **1.312**



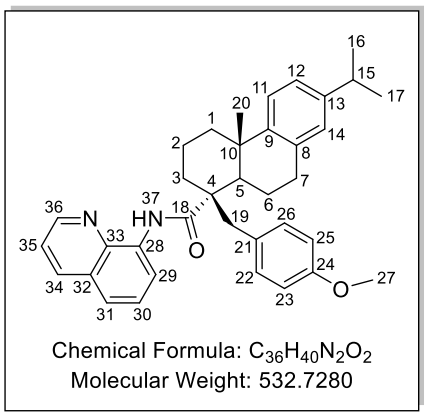
To a solution of DHAA (1.0 g, 3.3 mmol, 1 eq.) in DCM (20 ml), oxalyl chloride (0.6 ml, 6.7 mmol, 2 eq.) was added at 0 °C. After stirring overnight at room temperature, the mixture was concentrated under reduced pressure. The residue was redissolved in DCM (10 ml) followed by addition of 8-aminoquinoline (720 mg, 5.0 mmol, 1.5 eq.) and Et_3N (0.9 ml, 6.7 mmol, 2 eq.). After stirring for 1 h, the mixture was quenched at 0 °C with water (5 ml) and $NaHCO_3$ sat. (50 ml). The aqueous layer was extracted with DCM (3 x 50 ml), the combined organic layers were dried with $MgSO_4$ and concentrated *in vacu*o. Purification by flash-chromatography on silica gel (DCM) gave 1.1 g of **1.312** (78%) as a white foam. **^{1}H-NMR (700 MHz, $CDCl_3$):** δ = 10.42 (s, 1H, H_{30}), 8.83 (dd, *J* = 7.6, 1.1 Hz, 1H, H_{22}), 8.81 (dd, *J* = 4.3, 1.6 Hz, 1H, H_{29}), 8.16 (dd, *J* = 8.3, 1.4 Hz, 1H, H_{27}), 7.54 (t, *J* = 7.9 Hz, 1H, H_{23}), 7.49 (dd, *J* = 8.2, 1.0 Hz, 1H, H_{24}), 7.45 (dd, *J* = 8.2, 4.1 Hz, 1H, H_{28}), 7.22 (d, *J* = 8.2 Hz, 1H, H_{11}), 7.03 (dd, *J* = 8.2, 1.2 Hz, 1H, H_{12}), 6.87 (bs, 1H, H_{14}), 3.00-2.92 (m, 1H, H_{7a}), 2.87-2.79 (m, 2H, $H_{7b,15}$), 2.41-2.35 (m, 2H, $H_{1a,5}$), 2.01 (app. td, *J* = 13.6, 4.6 Hz, 1H, H_{3a}), 1.94-1.84 (m, 2H, $H_{6a,2a}$), 1.84-1.78 (m, 2H, $H_{2b,3b}$), 1.70-1.61 (m, 2H, $H_{6b,1b}$), 1.56 (s, 3H, H_{19}), 1.31 (s, 3H, H_{20}), 1.23 (app. dd, *J* = 7.0, 1.2 Hz, 6H, $H_{26,27}$) ppm. **^{13}C-NMR (700 MHz, $CDCl_3$):** δ = 177.4 (C_{18}), 148.4 (C_{29}), 147.1 (C_9), 145.8 (C_{13}), 139.1 (C_{26}), 136.4 (C_{27}), 135.0 (C_{21}), 134.9 (C_8), 128.1 (C_{25}), 127.6 (C_{23}), 127.1 (C_{14}), 124.3 (C_{11}), 124.0 (C_{12}), 121.7 (C_{28}), 121.4 (C_{24}), 116.5 (C_{22}), 49.1 (C_4), 46.0 (C_5), 38.2 (C_1), 37.5 (C_3), 37.5 (C_{10}), 33.6 (C_{15}), 30.3 (C_7), 25.6 (C_{20}), 24.4 (C_{16}), 24.1 (C_{17}), 21.5 (C_6), 19.1 (C_2), 16.9 (C_{19}) ppm. **FT-IR (neat, cm^{-1}):** 3366, 2957, 2929, 2868, 1671, 1526, 1484, 1423, 1384, 1325, 1259, 1127, 909, 825, 792, 756, 732, 685. **HRMS (ESI) (m/z):** calculated for $[M + H]^+$ ($C_{29}H_{35}N_2O^+$): 427.2744, found: 427.2737.

General procedure of CH-Arylation with $Ni(OAc_2)$ * 4 H_2O on the Schlenk line:

Nickel acetate tetrahydrate (1 eq.) and anhydrous sodium carbonate (2 eq.) was placed in a flame dried Schlenk under argon. After evacuating the tube, the reagents were heated under vacuum to 140 °C within 30 min by an oil bath (nickel acetate changes colour from turquoise to bright green when

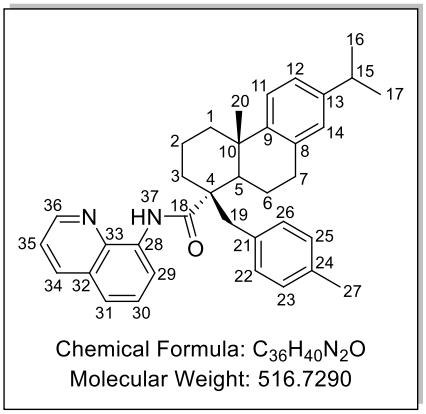
dehydrated). After cooling to room temperature, the tube was filled with argon and the starting material (1 eq.) and the aryliodide (2-3 eq.) were added. After addition of dry DMF (c = 0.5), the tube was sealed using a glass stopper, grease and clamp. The mixture was heated again to 140 °C, stirred for 16 h and allowed to cool down. The dark mixture was diluted with water (20 mL), extracted with EtOAc (3 x 20 mL), dried with $MgSO_4$ and concentrated under reduced pressure.

(1S,4aS)-7-Isopropyl-1-(4-methoxybenzyl)-4a-methyl-N-(quinolin-8-yl)-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxamide **1.313a**



Following the standart procedure, the reaction of nickel acetate tetrahydrate (23.5 mg, 0.1 mmol, 1 eq.), anhydrous sodium carbonate (20.0 mg, 0.2 mmol, 2 eq.), amide **1.312** (40.3 mg, 0.1 mmol, 1 eq.) and 4-iodoanisole (44.2 mg, 0.2 mmol, 2 eq.) in DMF (0.2 ml) afforded after purification by prepTLC (silica, 20% EtOAc in heptane) 35 mg **(70%)** of **1.313a** as yellow oil. **^{1}H-NMR (700 MHz, $CDCl_3$):** δ = 10.26 (s, 1H, H_{37}), 8.86 (dd, *J* = 7.7, 1.1 Hz, 1H, H_{29}), 8.69 (dd, *J* = 4.2, 1.6 Hz, 1H, H_{36}), 8.11 (dd, *J* = 8.2, 1.5 Hz, 1H, H_{34}), 7.54 (app.t, *J* = 8.0 Hz, 1H, H_{30}), 7.47 (dd, *J* = 8.3, 1.0 Hz, 1H, H_{31}), 7.39 (dd, *J* = 8.2, 4.2 Hz, 1H, H_{35}), 7.29 (bd, *J* = 8.7 Hz, 2H, $H_{22,26}$), 7.24 (d, *J* = 8.3 Hz, 1H, H_{11}), 7.02 (dd, *J* = 8.2, 1.5 Hz, 1H, H_{12}), 6.87 (bs, 1H, H_{14}), 6.73 (bd, *J* = 8.7 Hz, 2H, $H_{23,25}$), 3.71 (s, 3H, H_{27}), 3.62 (d, *J* = 14.6 Hz, 1H, H_{19a}), 3.15 (d, *J* = 14.6 Hz, 1H, H_{19b}), 2.92-2.88 (m, 2H, $H_{7a,b}$), 2.81 (hept, *J* = 6.9 Hz, 1H, H_{15}), 2.49 (bd, *J* = 12.9 Hz, H_{1a}), 2.28-2.24 (m, 1H, H_{6a}), 2.17 (dd, *J* = 12.6, 2.3 Hz, 1H, H_5), 2.09 (bd, *J* = 12.9 Hz, 1H, H_{3a}), 2.04-1.94 (m, 2H, $H_{2a,6b}$), 1.90-1.85 (m, 1H, H_{2b}), 1.81 (app. td, *J* = 13.2, 3.2 Hz, 1H, H_{3b}), 1.73 (app. td, *J* = 13.2, 3.4 Hz, 1H, H_{1b}), 1.49 (s, 3H, H_{20}), 1.21 (app. dd, *J* = 6.9, 1.7 Hz, 6H, $H_{16,17}$) ppm. **^{13}C-NMR** (700 MHz, $CDCl_3$): δ = 174.9 (C_{18}), 158.0 (C_{24}), 148.2 (C_{36}), 147.4 (C_9), 146.0 (C_{13}), 138.9 (C_{33}), 136.3 (C_{34}), 135.1 (C_8), 135.0 (C_{28}), 131.9 ($C_{22,26}$), 131.2 (C_{21}), 128.0 (C_{32}), 127.5 (C_{30}), 127.1 (C_{14}), 124.1 (C_{11}), 124.0 (C_{12}), 121.6 (C_{35}), 121.3 (C_{31}), 116.4 (C_{29}), 113.5 ($C_{23,25}$), 55.2 (C_{27}), 53.6 (C_4), 47.9 (C_5), 38.5 (C_1), 38.4 (C_{10}), 33.6 (C_{15}), 33.5 (C_{19}), 32.8 (C_3), 30.3 (C_7), 26.6 (C_{20}), 24.1 (C_{16}), 24.1 (C_{17}), 20.5 (C_6), 19.1 (C_2) ppm. **FT-IR (neat, cm^{-1}):** 3362, 2957, 2932, 2868, 1670, 1611, 1578, 1526, 1512, 1485, 1463, 1423, 1383, 1325, 1302, 1251, 1180, 1037, 907, 825, 792, 756, 733. **HRMS (ESI) (m/z):** calculated for $[M + H]^+$ ($C_{36}H_{41}N_2O_2^+$): 533.3163, found: 533.3153.

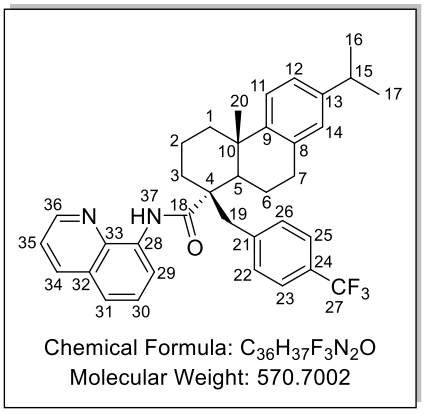
(1S,4aS)-7-Isopropyl-4*a*-methyl-1-(4-methylbenzyl)-*N*-(quinolin-8-yl)-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene-1-carboxamide **1.313b**



Following the standart procedure, the reaction of nickel acetate tetrahydrate (49.8 mg, 0.2 mmol, 1 eq.), anhydrous sodium carbonate (42.4 mg, 0.4 mmol, 2 eq.), amide **1.312** (85.3 mg, 0.2 mmol, 1 eq.) and 4-iodoanisole (131.0 mg, 0.6 mmol, 3 eq.) in DMF (0.4 ml) afforded after purification by prepTLC (silica, 20% EtOAc in heptane) 77 mg **(75%)** of **1.313b** as yellow oil. **^{1}H-NMR (700 MHz, $CDCl_3$):** δ = 10.26 (s, 1H, H_{37}), 8.86 (dd, *J* = 7.7, 1.0 Hz, 1H, H_{29}), 8.69 (dd, *J* = 4.2, 1.6 Hz, 1H, H_{36}), 8.11 (dd, *J* = 8.2, 1.4 Hz, 1H, H_{34}), 7.54 (app.t, *J* = 7.9 Hz, 1H, H_{30}), 7.47 (dd, *J* = 8.2, 0.8 Hz, 1H, H_{31}), 7.39 (dd, *J* = 8.2, 4.2 Hz, 1H, H_{35}), 7.28-7.25 (m, 2H, $H_{22,26}$), 7.24 (d, *J* = 8.4 Hz, 1H, H_{11}), 7.02 (dd, *J* = 8.2, 1.4 Hz, 1H, H_{12}), 6.99 (d, *J* = 7.9 Hz, 2H, $H_{23,25}$), 6.86 (bs, 1H, H_{14}), 3.65 (d, *J* = 14.3 Hz, 1H, H_{19a}), 3.16 (d, *J* = 14.3 Hz, 1H, H_{19b}), 2.92-2.88 (m, 2H, $H_{7a,b}$), 2.81 (hept, *J* = 6.9 Hz, 1H, H_{15}), 2.49 (bd, *J* = 12.9 Hz, H_{1a}), 2.30-2.25 (m, 1H, H_{6a}), 2.24 (s, 3H, H_{27}), 2.16 (dd, *J* = 12.6, 2.0 Hz, 1H, H_5), 2.08 (bd, *J* = 12.9 Hz, 1H, H_{3a}), 2.04-1.94 (m, 2H, $H_{2a,6b}$), 1.89-1.79 (m, 2H, $H_{2b,3b}$), 1.73 (app. td, *J* = 13.0, 3.3 Hz, 1H, H_{1b}), 1.49 (s, 3H, H_{20}), 1.21 (app. dd, *J* = 6.9, 1.5 Hz, 6H, $H_{16,17}$) ppm. **^{13}C-NMR** (700 MHz, $CDCl_3$): δ = 174.9 (C_{18}), 148.2 (C_{36}), 147.4 (C_9), 146.0 (C_{13}), 138.9 (C_{33}), 136.3 (C_{34}), 136.1 (C_{21}), 135.5 (C_{24}), 135.1 (C_8), 135.0 (C_{28}), 130.8 ($C_{22,26}$), 128.9 ($C_{23,25}$), 128.0 (C_{32}), 127.5 (C_{30}), 127.1 (C_{14}), 124.1 (C_{11}), 124.0 (C_{12}), 121.6 (C_{35}), 121.3 (C_{31}), 116.4 (C_{29}), 53.6 (C_4), 47.9 (C_5), 38.5 (C_1), 38.4 (C_{10}), 33.9 (C_{19}), 33.6 (C_{15}), 32.7 (C_3), 30.2 (C_7), 26.6 (C_{20}), 24.1 (C_{16}), 24.1 (C_{17}), 21.1 (C_{27}), 20.4 (C_6), 19.1 (C_2) ppm. **FT-IR (neat, cm^{-1})**: 3365, 2958, 2929, 2866, 1671, 1526, 1485, 1463, 1423, 1383, 1325, 1260, 1164, 906, 825, 791, 753, 735. **HRMS (ESI) (m/z):** calculated for $[M + H]^+$ ($C_{36}H_{41}N_2O^+$): 517.3213, found: 517.3204.

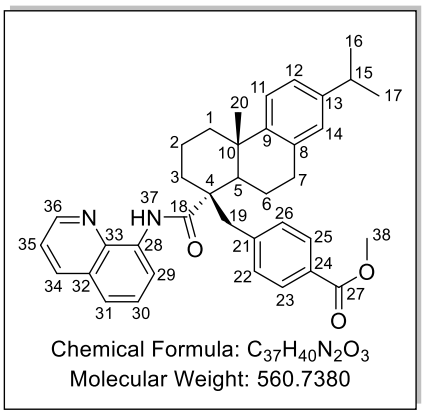
(1S,4aS)-7-isopropyl-4*a*-methyl-*N*-(quinolin-8-yl)-1-(4-(trifluoromethyl)benzyl)-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene-1-carboxamide **1.313c**

Following the standart procedure, the reaction of nickel acetate tetrahydrate (49.8 mg, 0.2 mmol, 1 eq.), anhydrous sodium carbonate (42.4 mg, 0.4 mmol, 2 eq.), amide **1.312** (85.3 mg, 0.2 mmol, 1 eq.) and 4-iodobenzotrifluoride (109.0 mg, 0.4 mmol, 2 eq.) in DMF (0.4 ml) afforded after purification by prepTLC (silica, 25% EtOAc in heptane) 75 mg **(66%)** of **1.313c** as yellow oil. **^{1}H-NMR (700 MHz, $CDCl_3$):** δ = 10.29 (s, 1H, H_{37}), 8.86 (dd, *J* = 7.7, 1.0 Hz, 1H, H_{29}), 8.69 (dd, *J* = 4.2, 1.6 Hz, 1H, H_{36}), 8.12 (dd, *J* = 8.3, 1.6 Hz, 1H, H_{34}), 7.55 (app.t, *J* = 8.0 Hz, 1H, H_{30}), 7.51 (d, *J* = 8.2 Hz, 2H, $H_{22,26}$), 7.49 (dd, *J* = 8.3, 0.9 Hz, 1H, H_{31}), 7.45 (d, *J* = 8.2 Hz, 2H, $H_{23,25}$), 7.40 (dd, *J* = 8.2, 4.2 Hz, 1H, H_{35}), 7.25 (d, *J* = 8.4 Hz, 1H,



H_{11}), 7.04 (dd, *J* = 8.2, 1.4 Hz, 1H, H_{12}), 6.88 (bs, 1H, H_{14}), 3.76 (d, *J* = 14.2 Hz, 1H, H_{19a}), 3.24 (d, *J* = 14.2 Hz, 1H, H_{19b}), 2.96-2.86 (m, 2H, $H_{7a,b}$), 2.82 (hept, *J* = 6.9 Hz, 1H, H_{15}), 2.53 (bd, *J* = 12.9 Hz, H_{1a}), 2.28-2.22 (m, 1H, H_{6a}), 2.19 (dd, *J* = 12.6, 1.9 Hz, 1H, H_5), 2.04-1.96 (m, 3H, $H_{2a, 3a, 6b}$), 1.93-1.88 (m, 1H, H_{2b}), 1.85 (app. td, *J* = 13.5, 3.0 Hz, 1H, H_{3b}) 1.77 (app. td, *J* = 12.9, 3.5 Hz, 1H, H_{1b}), 1.51 (s, 3H, H_{20}), 1.21 (app. dd, *J* = 7.0, 1.8 Hz, 6H, $H_{16,17}$) ppm. **^{13}C-NMR** (700 MHz, $CDCl_3$): δ = 174.4 (C_{18}), 148.4 (C_{36}), 147.1 (C_9), 146.2 (C_{13}), 143.7 (C_{21}), 138.9 (C_{33}), 136.4 (C_{34}), 134.9 (C_8), 134.7 (C_{28}), 131.3 ($C_{22,26}$), 128.4 (q, J = 32.2 Hz, C_{24}), 128.0 (C_{32}), 127.4 (C_{14}), 127.0 (C_{30}), 125.0 (q, J = 3.7 Hz, $C_{23,25}$), 124.5 (q, J = 271.8 Hz, C_{27}), 124.1 (C_{11}), 124.1 (C_{12}), 121.7 (C_{35}), 121.5 (C_{31}), 116.4 (C_{29}), 53.8 (C_4), 48.1 (C_5), 38.4 (C_1), 38.4 (C_{10}), 34.2 (C_{19}), 33.6 (C_{15}), 32.7 (C_3), 30.2 (C_7), 26.6 (C_{20}), 24.1 (C_{16}), 24.1 (C_{17}), 20.4 (C_6), 19.1 (C_2) ppm. **FT-IR (neat, cm^{-1})** = 2959, 2869, 1671, 1617, 1526, 1485, 1464, 1423, 1384, 1325, 1261, 1163, 1122, 1069, 1019, 908, 853, 825, 791, 752, 734, 645. **HRMS (ESI) (m/z):** calculated for $[M + H]^+$ ($C_{36}H_{38}F_3N_2O^+$): 571.2931, found: 571.2920.

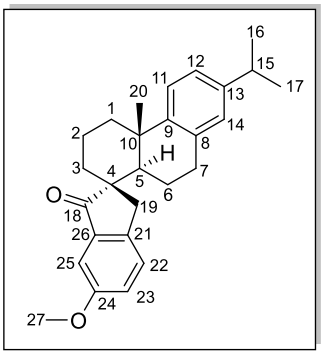
Methyl 4-((*(1S,4aS)*-7-isopropyl-4*a*-methyl-1-(quinolin-8-ylcarbamoyl)-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthren-1-yl)methyl)benzoate **1.313d**



According to the standart procedure, the reaction of nickel acetate tetrahydrate (49.8 mg, 0.2 mmol, 1 eq.), anhydrous sodium carbonate (42.4 mg, 0.4 mmol, 2 eq.), amide **1.312** (85.3 mg, 0.2 mmol, 1 eq.) and methyl 4-benzoate (105.0 mg, 0.4 mmol, 2 eq.) in DMF (0.4 ml) gave after purification by prepTLC (silica, 25% EtOAc in heptane) 30 mg **(27%)** of **1.313d** as yellow oil. **^{1}H-NMR (700 MHz, $CDCl_3$):** δ = 10.28 (s, 1H, H_{37}), 8.85 (dd, *J* = 7.6, 1.1 Hz, 1H, H_{29}), 8.69 (dd, *J* = 4.2, 1.6 Hz, 1H, H_{36}), 8.12 (dd, *J* = 8.2, 1.6 Hz, 1H, H_{34}), 7.86 (bd, *J* = 8.4 Hz, 2H, $H_{23,25}$), 7.54 (app.t, *J* = 8.1 Hz, 1H, H_{30}), 7.48 (dd, *J* = 8.3, 1.1 Hz, 1H, H_{31}), 7.46 (d, *J* = 8.4 Hz, 2H, $H_{22,26}$), 7.39 (dd, *J* = 8.2, 4.1 Hz, 1H, H_{35}), 7.24 (d, *J* = 8.2 Hz, 1H, H_{11}), 7.03 (dd, *J* = 8.2, 1.7 Hz, 1H, H_{12}), 6.87 (bs, 1H, H_{14}), 3.85 (s, 3H, H_{38}), 3.76 (d, *J* = 14.2 Hz, 1H, H_{19a}), 3.24 (d, *J* = 14.2 Hz, 1H, H_{19b}), 2.95-2.87 (m, 2H, $H_{7a,b}$), 2.81 (hept, *J* = 6.9 Hz, 1H, H_{15}), 2.51 (bd, *J* = 12.9 Hz, H_{1a}), 2.27-2.22 (m, 1H, H_{6a}), 2.18 (dd, *J* = 12.5, 2.0 Hz, 1H, H_5), 2.03-1.93 (m, 3H, $H_{2a, 3a, 6b}$), 1.90-1.81 (m, 2H, $H_{2b,3b}$), 1.75 (app. td, *J* = 12.7, 3.1 Hz, 1H, H_{1b}), 1.51 (s, 3H, H_{20}), 1.21 (app. dd, *J* = 7.0, 1.8 Hz, 6H, $H_{16,17}$) ppm. **^{13}C-NMR (700 MHz, $CDCl_3$)**: δ = 174.5 (C_{18}), 167.3 (C_{27}), 148.3 (C_{36}), 147.2 (C_9),

146.1 (C_{13}), 145.2 (C_{21}), 138.9 (C_{33}), 136.4 (C_{34}), 134.9 (C_8), 134.8 (C_{28}), 131.0 ($C_{22,26}$), 129.4 ($C_{23,25}$), 128.0 (C_{24}), 128.0 (C_{32}), 127.5 (C_{14}), 127.1 (C_{30}), 124.1 (C_{11}), 124.1 (C_{12}), 121.7 (C_{35}), 121.5 (C_{31}), 116.4 (C_{29}), 53.8 (C_4), 52.1 (C_{38}), 48.1 (C_5), 38.4 (C_1), 38.4 (C_{10}), 34.5 (C_{19}), 33.6 (C_{15}), 32.8 (C_3), 30.2 (C_7), 26.6 (C_{20}), 24.1 (C_{16}), 24.1 (C_{17}), 20.4 (C_6), 19.1 (C_2) ppm. **FT-IR (neat, cm^{-1})** = 2954, 2867, 1722, 1672, 1610, 1575, 1526, 1486, 1461, 1434, 1383, 1325, 1279, 1183, 1111, 1021, 905, 825, 792, 751, 705, 689. **HRMS (ESI) (m/z):** calculated for $[M + H]^+$ ($C_{37}H_{41}N_2O_3^+$): 561.3112, found: 561.3113.

(2S,4a'S)-7'-Isopropyl-6-methoxy-4*a'*-methyl-3',4',4*a*',9',10',10*a*'-hexahydro-2'H-spiro[indene-2,1'-phenanthren]-1(3H)-one **1.314**

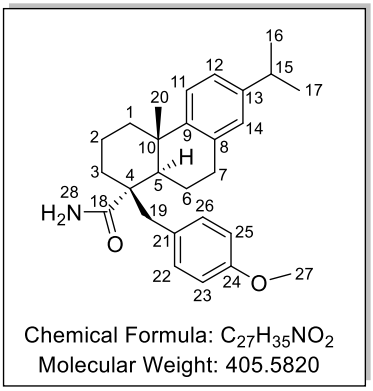


The amide **1.313a** (62.0 mg, 0.1 mmol) was dissolved in a mixture of toluene/water/triflic acid (2 mL, 6:1:1) and stirred for 4 days at 100 °C. The product was extracted from HCl (1 N, 10 mL) with DCM (3 x 10 mL), the combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. Purification by preparative TLC (25% EtOAc in heptane) afforded 21 mg (46%) of **1.314** as white solid. **^{1}H-NMR (700 MHz, $CDCl_3$):** δ = 7.34 (bd, *J* = 9.2 Hz, 1H, H_{22}), 7.22-7.19 (m, 3H, $H_{11,25,23}$), 7.01 (dd, *J* = 8.3, 1.6 Hz, 1H, H_{12}), 6.87 (bs, 1H, H_{14}), 3.84 (s, 3H, H_{27}), 3.23 (d, *J* = 16.8 Hz, 1H, H_{19a}), 2.94-2.87 (m, 2H, $H_{19b,7a}$), 2.82 (hept, *J* = 6.9 Hz, 1H, H_{15}), 2.75 (bdd, *J* = 16.8, 6.3 Hz, 1H, H_{7b}), 2.34-2.30 (m, 2H, $H_{1a,5}$), 1.85-1.77 (m, 2H, $H_{2a,b}$), 1.71-1.65 (m, 1H, H_{6a}), 1.65-1.56 (m, 2H, $H_{3a,1b}$), 1.43 (bd, *J* = 13.4 Hz, 1H, H_{3b}), 1.29-1.19 (m, 10H, $H_{6b,20,16,17}$) ppm. **^{13}C-NMR (700 MHz, $CDCl_3$)**: δ = 212.3 (C_{18}), 159.5 (C_{24}), 147.1 (C_{21}), 145.9 (C_{13}), 145.6 (C_9), 137.1 (C_{26}), 135.0 (C_8), 127.5 (C_{22}), 127.1 (C_{14}), 124.6 (C_{23}), 124.4 (C_{11}), 124.0 (C_{12}), 105.2 (C_{25}), 55.7 (C_{27}), 55.3 (C_4), 44.9 (C_5), 38.0 (C_1), 37.0 (C_{10}), 36.8 (C_3), 35.2 (C_{19}), 33.6 (C_{15}), 30.1 (C_7), 24.7 (C_{20}), 24.1 (C_{16}), 24.1 (C_{17}), 21.2 (C_6) 20.1 (C_2) ppm. **FT-IR (neat, cm^{-1})** = 2957, 2929, 2865, 1704, 1616, 1492, 1462, 1433, 1337, 1277, 1229, 1190, 1163, 1083, 1028, 823, 751. **HRMS (ESI) (m/z):** calculated for $[M + Na]^+$ ($C_{27}H_{32}NaO_2^+$): 411.2295, found: 411.2293.

General procedure for the oxidative cleavage of the directing group:

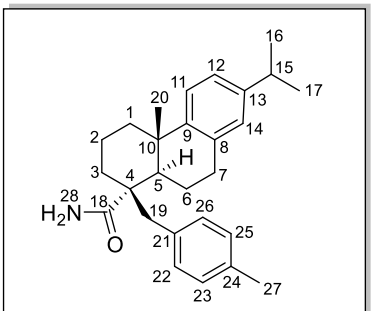
Aminoquinolinecarboxamide **1.313** (0.1 mmol) was dissolved in MeOH/DCM (1:1, c = 0.02) and cooled to – 78 °C. A stream of O_3 was bubbled through the stirring solution. After a few minutes, the solution turned blueish indicating accumulation of ozone and completion of the reaction. A stream of oxygen was passed through until decolorization of the solution occurred followed by reductive quench with excess of DMS. The solution was allowed to warm to room temperature and stirred for 2 h. Concentration *in vacuo* afforded a dark residue which was redissolved in 6 N HCl/dioxane (1:1, c = 0.02) and stirred at 110 °C for 16 h. The mixture was diluted with 1 N HCl (20 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried with $MgSO_4$ and concentrated. Purification by preparative TLC afforded the amides **1.329** in good yields.

(1S,4aS,10aR)-7-Isopropyl-1-(4-methoxybenzyl)-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxamide **1.329a**



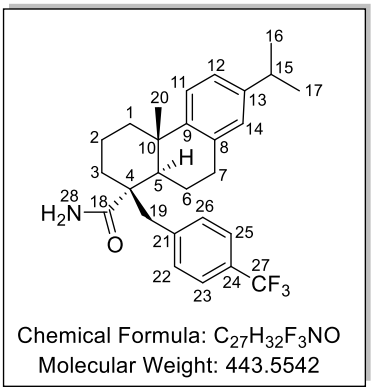
Ozonolytic cleavage was performed according to the general procedure with Quinolyl-carboxamide **3.313a** (93 mg, 0.18 mmol) and purified by chromatography (silica, 50% EtOAc in heptane) to afford 49 mg (70%) of the **1.329a**. **^{1}H-NMR (600 MHz, $CDCl_3$):** δ = 7.23 (bd, *J* = 8.7 Hz, 2H, $H_{22,26}$), 7.18 (d, *J* = 8.2 Hz, 1H, H_{11}), 7.01 (dd, *J* = 8.2, 1.6 Hz, 1H, H_{12}), 6.87 (bs, 1H, H_{14}), 6.81 (bd, *J* = 8.7 Hz, 2H, $H_{23,25}$), 5.49 (s, 1H, H_{28a}), 5.12 (s, 1H, H_{28b}), 3.79 (s, 3H, H_{27}), 3.35 (d, *J* = 14.3 Hz, 1H, H_{19a}), 2.99 (d, *J* = 14.3 Hz, 1H, H_{19b}), 2.97-2.86 (m, 2H, $H_{7a,b}$), 2.83 (hept, *J* = 6.9 Hz, 1H, H_{15}), 2.43 (bd, *J* = 13.0 Hz, H_{1a}), 2.27-2.21 (m, 1H, H_{6a}), 1.97-1.86 (m, 4H, $H_{5,3a,2a,6b}$), 1.76-1.70 (m, 1H, H_{2b}), 1.56 (app. td, *J* = 12.7, 3.1 Hz, 1H, H_{1b}), 1.41 (s, 3H, H_{20}), 1.34 (app. td, *J* = 13.9, 3.9 Hz, 1H, H_{3b}), 1.22 (app. d, *J* = 6.9, 6H, $H_{16,17}$) ppm. **^{13}C-NMR (150 MHz, $CDCl_3$):** δ = 178.9 (C_{18}), 158.1 (C_{24}), 147.3 (C_9), 146.1 (C_{13}), 135.0 (C_8), 131.9 ($C_{22,26}$), 131.0 (C_{21}), 127.1 (C_{14}), 124.1 (C_{11}), 124.0 (C_{12}), 113.6 ($C_{23,25}$), 55.3 (C_{27}), 51.9 (C_4), 47.6 (C_5), 38.5 (C_1), 38.1 (C_{10}), 33.6 (C_{15}), 33.1 (C_{19}), 32.8 (C_3), 30.2 (C_7), 26.4 (C_{20}), 24.1 (C_{16}), 24.1 (C_{17}), 20.2 (C_6), 18.9 (C_2) ppm. **FT-IR (neat, cm^{-1}):** 3473, 3353, 3187, 2957, 2931, 2868, 2835, 1659, 1609, 1511, 1460, 1364, 1301, 1250, 1179, 1037, 911, 849, 823, 733, 629. **HRMS (ESI) (m/z):** calculated for $[M + Na]^+$ ($C_{27}H_{35}NNaO_2^+$): 428.2560, found: 428.2560.

(1S,4aS,10aR)-7-Isopropyl-4a-methyl-1-(4-methylbenzyl)-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxamide **1.329b**



Ozonolytic cleavage was performed according to the general procedure with Quinolyl-carboxamide **3.313b** (75 mg, 0.15 mmol) and purified by chromatography (silica, 60% EtOAc in heptane) to afford 37 mg (66%) of the amide **1.329b** as yellow solid. **^{1}H-NMR (600 MHz, $CDCl_3$):** δ = 7.20 (bd, *J* = 8.0 Hz, 2H, $H_{22,26}$), 7.18 (d, *J* = 8.3 Hz, 1H, H_{11}), 7.07 (bd, *J* = 8.0 Hz, 2H, $H_{23,25}$), 7.01 (bd, *J* = 8.2 Hz, 1H, H_{12}), 6.90 (bs, 1H, H_{14}), 5.49 (s, 1H, H_{28a}), 5.13 (s, 1H, H_{28b}), 3.37 (d, *J* = 14.2 Hz, 1H, H_{19a}), 3.02 (d, *J* = 14.2 Hz, 1H, H_{19b}), 2.97-2.86 (m, 2H, $H_{7a,b}$), 2.83 (hept, *J* = 6.9 Hz, 1H, H_{15}), 2.42 (bd, *J* = 12.6 Hz, 1H, H_{1a}), 2.31 (s, 3H, H_{27}), 2.27-2.22 (m, 1H, H_{6a}), 1.99-1.88 (m, 4H, $H_{5,3a,2a,6b}$), 1.76-1.70 (m, 1H, H_{2b}), 1.59-1.53 (m, 1H, H_{1b}), 1.41 (s, 3H, H_{20}), 1.35 (m, 1H, H_{3b}), 1.22 (app. d, *J* = 6.9, 6H, $H_{16,17}$) ppm. **^{13}C-NMR (150 MHz, $CDCl_3$)**: δ = 178.9 (C_{18}), 147.3 (C_9), 146.1 (C_{13}), 136.0 (C_{21}), 135.8 (C_{24}), 135.0 (C_8), 130.8 ($C_{22,26}$), 129.0 ($C_{23,25}$), 127.1 (C_{14}), 124.0 (C_{11}), 124.0 (C_{12}), 51.8 (C_4), 47.6 (C_5), 38.5 (C_1), 38.1 (C_{10}), 33.6 (C_{19}), 33.6 (C_{15}), 32.8 (C_3), 30.2 (C_7), 26.4 (C_{20}), 24.1 (C_{16}), 24.1 (C_{17}), 21.2 (C_{27}), 20.3 (C_6), 18.9 (C_2) ppm. **FT-IR (neat, cm^{-1}):** 3479, 3359, 3189, 2957, 2928, 2867, 1659, 1599, 1513, 1498, 1459, 1376, 1324, 1124, 1068, 910, 821, 734, 626. **HRMS (ESI) (m/z):** calculated for $[M + Na]^+$ ($C_{27}H_{35}NNaO^+$): 412.2611, found: 412.2614.

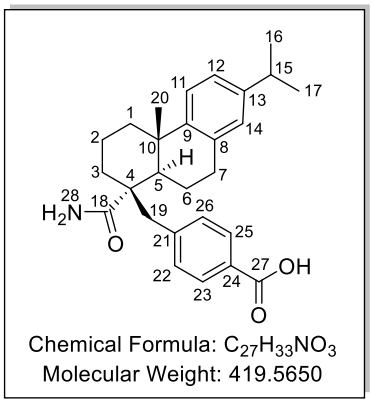
(1S,4aS,10aR)-7-Isopropyl-4a-methyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxamide **1.329c**



Ozonolytic cleavage was performed according to the general procedure with Quinolyl-carboxamide **1.313c** (73 mg, 0.13 mmol) and purified by chromatography (silica, 60% EtOAc in heptane) to afford 34 mg (60%) of the amide **1.313c**. **^{1}H-NMR (600 MHz, $CDCl_3$):** δ = 7.50 (bd, *J* = 8.2 Hz, 2H, $H_{23,25}$), 7.45 (bd, *J* = 8.2 Hz, 2H, $H_{22,26}$), 7.19 (d, *J* = 8.2 Hz, 1H, H_{12}), 7.03 (bd, *J* = 8.2 Hz, 1H, H_{11}), 6.90 (bs, 1H, H_{14}), 5.58 (s, 1H, H_{28a}), 5.40 (s, 1H, H_{28b}), 3.58 (d, *J* = 13.9 Hz, 1H, H_{19a}), 3.05 (d, *J* = 13.9 Hz, 1H, H_{19b}), 2.96 (dd, *J* = 16.3, 5.4 Hz, 1H, H_{7a}), 2.92-2.80 (m, 2H, $H_{7b,15}$), 2.46 (bd, *J* = 12.9 Hz, 1H, H_{1a}), 2.25-2.20 (m, 1H, H_{6a}), 1.97-1.85 (m, 3H, $H_{5,2a,6b}$), 1.81 (bd, J = 13.1 Hz, 1H, H_{3a}), 1.78-1.71 (m, 1H, H_{2b}), 1.59 (td, *J* = 13.1, 3.5 Hz, 1H, H_{1b}), 1.44 (s, 3H, H_{20}), 1.34 (td, *J* = 13.3, 3.2 Hz, 1H, H_{3b}), 1.23 (app. d, *J* = 6.9, 6H, $H_{16,17}$) ppm. **^{13}C-NMR (150 MHz, $CDCl_3$):** δ = 178.5 (C_{18}), 147.0 (C_9), 146.3 (C_{13}), 143.6 (C_{21}), 134.8 (C_8), 131.3 ($C_{22,26}$), 128.5 (q, J = 32.2

Hz, C_{24}), 127.1 (C_{14}), 125 (q, J = 3.7 Hz, $C_{23,25}$), 124.5 (q, J = 271.8 Hz, C_{27}), 124.2 (C_{12}), 124.0 (C_{11}), 52.1 (C_4), 48.1 (C_5), 38.4 (C_1), 38.1 (C_{10}), 33.7 (C_{19}), 33.6 (C_{15}), 32.6 (C_3), 30.1 (C_7), 26.3 (C_{20}), 24.1 (C_{16}), 24.1 (C_{17}), 20.0 (C_6), 18.8 (C_2) ppm. **FT-IR (neat, cm^{-1}):** 2958, 2868, 1655, 1616, 1497, 1460, 1417, 1364, 1322, 1261, 1230, 1162, 1118, 1067, 1019, 908, 887, 851, 824, 731, 648, 627. **HRMS (ESI) (m/z):** calculated for $[M + Na]^+$ ($C_{27}H_{32}F_3NNaO^+$): 466.2328, found: 466.2334.

4-(((*1S,4aS,10aR)*-1-carbamoyl-7-isopropyl-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl)methyl)benzoic acid **1.329d**

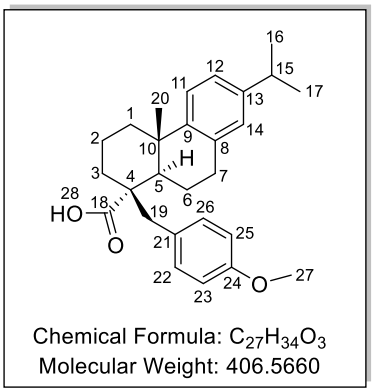


Ozonolytic cleavage was performed according to the general procedure with Quinolyl-carboxamide **1.313d** (28 mg, 0.05 mmol) and purified by chromatography (silica, EtOAc:AcOH:heptane, 9:1:10) to afford 18 mg (86%) of the amide 1.329 as colourless glass. **^{1}H-NMR (600 MHz, $CDCl_3$):** δ = 7.98 (bd, *J* = 8.3 Hz, 2H, $H_{23,25}$), 7.44 (bd, *J* = 8.3 Hz, 2H, $H_{22,26}$), 7.19 (d, *J* = 8.3 Hz, 1H, H_{11}), 7.02 (dd, *J* = 8.2, 1.5 Hz, 1H, H_{12}), 6.90 (d, *J* = 1.4 Hz, 1H, H_{14}), 6.07 (s, 1H, H_{28a}), 5.61 (s, 1H, H_{28b}), 3.57 (d, *J* = 13.9 Hz, 1H, H_{19a}), 3.09 (d, *J* = 13.9 Hz, 1H, H_{19b}), 3.00-2.86 (m, 2H, $H_{7a,b}$), 2.83 (hept, *J* = 6.9 Hz, 1H, H_{15}), 2.46 (bd, *J* = 12.9 Hz, 1H, H_{1a}), 2.29-2.21 (m, 1H, H_{6a}), 1.98-1.87 (m, 3H, $H_{5,2a,6b}$), 1.85 (bd, J = 13.2 Hz, 1H, H_{3a}), 1.79-1.72 (m, 1H, H_{2b}), 1.59 (td, *J* = 13.1, 3.5 Hz, 1H, H_{1b}), 1.44 (s, 3H, H_{20}), 1.35 (td, *J* = 13.2, 3.1 Hz, 1H, H_{3b}), 1.23 (app. d, *J* = 6.9, 6H, $H_{16,17}$) ppm. **^{13}C-NMR (150 MHz, $CDCl_3$):** δ = 179.4 (C_{18}), 170.0 (C_{27}), 147.0 (C_9), 146.3 (C_{13}), 145.7 (C_{21}), 134.8 (C_8), 131.2 ($C_{22,26}$), 130.0 ($C_{23,25}$), 127.1 (C_{24}), 127.1 (C_{14}), 124.2 (C_{12}), 124.0 (C_{11}), 52.1 (C_4), 48.1 (C_5), 38.5 (C_1), 38.1 (C_{10}), 34.1 (C_{19}), 33.6 (C_{15}), 32.7 (C_3), 30.1 (C_7), 26.4 (C_{20}), 24.1 (C_{16}), 24.1 (C_{17}), 20.1 (C_6), 18.9 (C_2) ppm. **FT-IR (neat, cm^{-1}):** 3352, 3181, 2957, 2928, 2869, 1690, 1610, 1575, 1498, 1459, 1418, 1380, 1314, 1277, 1232, 1181, 1104, 1020, 910, 822, 764, 750. **HRMS (ESI) (m/z):** calculated for $[M - H]^-$ ($C_{27}H_{32}F_3NO_3^-$): 418.2388, found: 418.2394.

General procedure for the hydrolysis of dehydroabietylamides

Amide **1.329** (1 eq.) was dissolved in dry DMF (c = 0.1) in a flame-dried Schlenk tube. $NOBF_4$ (2.2 eq.) was added at room temperature and stirred for 15 minutes. The mixture was quenched with 1 mL water, diluted with HCl aq. (1 N, 5 mL) and extracted twice with DCM (2 x 10 mL). The combined organic layers were dried with $MgSO_4$ and concentrated to give the crude acids **1.311**, which were purified by preparative TLC (silica gel, EtOAc/HOAc/heptane = 3/0.5/6.5).

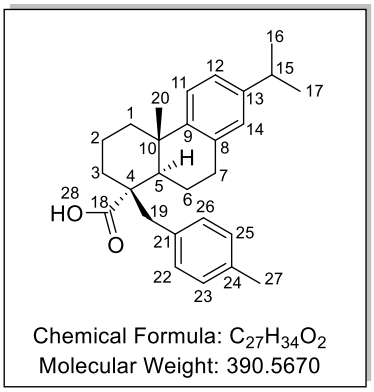
(1S,4aS,10aR)-7-isopropyl-1-(4-methoxybenzyl)-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxylic acid **1.311a**



Hydrolysis was performed according to the general procedure with Amide **1.329a** (32 mg, 0.08 mmol) in DMF (0.8 mL) and $NOBF_4$ (18.4 mg, 0.16 mmol) to give after purification 27 mg (84% yield). **^{1}H-NMR (600 MHz, $CDCl_3$):** δ = 7.24 (bd, *J* = 8.7 Hz, 2H, $H_{22,26}$), 7.19 (d, *J* = 8.2 Hz, 1H, H_{11}), 7.01 (dd, *J* = 8.1, 1.5 Hz, 1H, H_{12}), 6.89 (bs, 1H, H_{14}), 6.80 (bd, *J* = 8.7 Hz, 2H, $H_{23,25}$), 3.79 (s, 3H, H_{27}), 3.26 (d, *J* = 14.3 Hz, 1H, H_{19a}), 3.01 (d, *J* = 14.3 Hz, 1H, H_{19b}), 2.96-2.87 (m, 2H, $H_{7a,b}$), 2.83 (hept, *J* = 6.9 Hz, 1H, H_{15}), 2.39 (bd, *J* = 13.0 Hz, H_{1a}), 2.13-2.10 (m, 1H, H_5), 2.01-1.89 (m, 2H, $H6_{a,b}$), 1.89-1.74 (m, 3H, $H_{2a,3a,b}$), 1.74-1.68 (m, 1H, H_{2b}), 1.58 (app. td, *J* = 12.5, 3.5 Hz, 1H, H_{1b}), 1.41 (s, 3H, H_{20}), 1.23 (app. d, *J* = 6.9, 6H, $H_{16,17}$) ppm. **^{13}C-NMR (600 MHz, $CDCl_3$):** δ = 181.1 (C_{18}), 158.1 (C_{24}), 147.1 (C_9), 146.0 (C_{13}), 134.7 (C_8), 132.0 ($C_{22,26}$), 130.8 (C_{21}), 127.0 (C_{14}), 124.2 (C_{11}), 124.1 (C_{12}), 113.5 ($C_{23,25}$), 55.3 (C_{27}), 52.3 (C_4), 46.7 (C_5), 38.2 (C_1), 37.9 (C_{10}), 33.6 (C_{15}), 33.3 (C_{19}), 30.8 (C_3), 30.3 (C_7), 26.2 (C_{20}), 24.1 (C_{16}), 24.1 (C_{17}), 20.6 (C_6), 18.5 (C_2) ppm. **FT-IR (neat, cm^{-1}):** 2957, 2931, 2868, 1691, 1612, 1512, 1460, 1380, 1301, 1275, 1252, 1179, 1038, 910, 824, 764, 750. **HRMS (ESI) (m/z):** calculated for $[M + Na^+]^+$ ($C_{27}H_{34}NaO_3^+$): 429.2400, found: 429.2399.

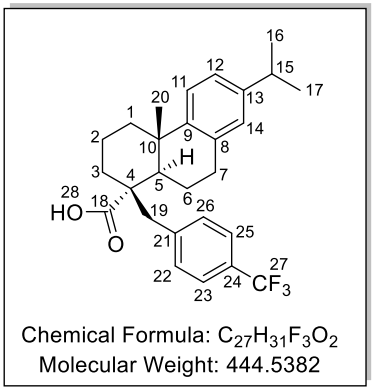
(1S,4aS,10aR)-7-isopropyl-4a-methyl-1-(4-methylbenzyl)-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxylic acid **1.311b**

Hydrolysis was performed according to the general procedure with Amide **1.329b** (33 mg, 0.08 mmol) in DMF (0.9 mL) and $NOBF_4$ (22.4 mg, 0.18 mmol) to give after purification 20.8 mg (63% yield). **^{1}H-NMR (600 MHz, $CDCl_3$):** δ = 9.43 (bs, 1H, H_{28}), 7.20 (app. t, *J* = 8.0 Hz, 3H, $H_{22,26,11}$), 7.07 (bd, *J* = 8.0 Hz,



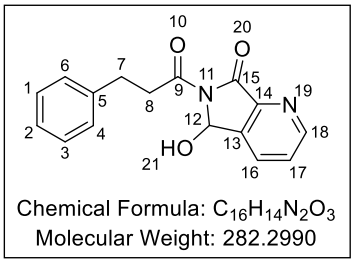
2H, $H_{23,25}$), 7.01 (dd, *J* = 8.1, 1.4 Hz, 1H, H_{12}), 6.89 (bs, 1H, H_{14}), 3.29 (d, *J* = 14.2 Hz, 1H, H_{19a}), 3.03 (d, *J* = 14.2 Hz, 1H, H_{19b}), 2.97-2.86 (m, 2H, $H_{7a,b}$), 2.83 (hept, *J* = 6.9 Hz, 1H, H_{15}), 2.39 (bd, *J* = 12.9 Hz, H_{1a}), 2.32 (s, 3H, H_{27}), 2.11 (dd, *J* = 12.4, 2.2 Hz, 1H, H_5), 2.03-1.90 (m, 2H, $H_{6a,b}$), 1.90-1.76 (m, 3H, $H_{3a,b,2a}$), 1.74-1.67 (m, 1H, H_{2b}), 1.58 (td, *J* = 12.7, 3.1 Hz, 1H, H_{1b}), 1.41 (s, 3H, H_{20}), 1.23 (app. d, *J* = 6.9, 6H, $H_{16,17}$) ppm. **^{13}C-NMR (150 MHz, $CDCl_3$):** δ = 180.4 (C_{18}), 147.1 (C_9), 146.0 (C_{13}), 135.7 (C_{21}), 135.7 (C_{24}), 134.7 (C_8), 130.9 ($C_{22,26}$), 128.8 ($C_{23,25}$), 126.9 (C_{14}), 124.2 (C_{11}), 124.1 (C_{12}), 52.1 (C_4), 46.7 (C_5), 38.2 (C_1), 37.9 (C_{10}), 33.8 (C_{19}), 33.6 (C_{15}), 30.7 (C_3), 30.2 (C_7), 26.2 (C_{20}), 24.1 (C_{16}), 24.1 (C_{17}), 21.2 (C_{27}), 20.5 (C_6), 18.5 (C_2) ppm. **FT-IR (neat, cm^{-1}):** 2958, 2927, 2868, 2657, 1691, 1514, 1498, 1459, 1415, 1379, 1274, 1207, 911, 885, 847, 820, 752, 551, 535, 526. **HRMS (ESI) (m/z):** calculated for $[M - H^+]^-$ $(C_{27}H_{33}O_2)^-$: 389.2486, found: 389.2490.

(1S,4aS,10aR)-7-isopropyl-4a-methyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxylic acid **1.311c**



Hydrolysis was performed according to the general procedure with Amide **1.329c** (23.5 mg, 0.05 mmol) in DMF (0.53 mL) and $NOBF_4$ (14 mg, 0.12 mmol) to give after purification 6.6 mg (28% yield). **^{1}H-NMR (600 MHz, $CDCl_3$):** δ = 9.17 (bs, 1H, H_{28}), 7.51 (bd, *J* = 8.2 Hz, 2H, $H_{23,25}$), 7.45 (bd, *J* = 8.2 Hz, 2H, $H_{22,26}$), 7.20 (d, *J* = 8.2 Hz, 1H, H_{12}), 7.03 (dd, *J* = 8.1, 1.6 Hz, 1H, H_{11}), 6.90 (bs, 1H, H_{14}), 3.37 (d, *J* = 14.1 Hz, 1H, H_{19a}), 3.12 (d, *J* = 14.1 Hz, 1H, H_{19b}), 2.99-2.87 (m, 2H, $H_{7a,b}$), 2.84 (hept, *J* = 6.9 Hz, 1H, H_{15}), 2.42 (bd, *J* = 11.1 Hz, H_{1a}), 2.19-2.14 (m, 1H, H_5), 1.97-1.90 (m, 2H, $H_{6a,b}$), 1.87-1.80 (m, 2H, $H_{3a,2a}$), 1.78-1.70 (m, 2H, $H_{3b,2b}$), 1.64-1.58 (m, 1H, H_{1b}), 1.42 (s, 3H, H_{20}), 1.23 (app. d, *J* = 6.9, 6H, $H_{16,17}$) ppm. **^{13}C-NMR (150 MHz, $CDCl_3$):** δ = 179.8 (C_{18}), 146.8 (C_9), 146.2 (C_{13}), 143.1 (C_{21}), 134.5 (C_8), 131.4 ($C_{22,26}$), 128.6 (q, J = 32.3 Hz, C_{24}), 127.0 (C_{14}), 125.0 (q, J = 3.7 Hz, $C_{23,25}$), 124.5 (q, J = 271.6 Hz, C_{27}), 124.3 (C_{12}), 124.2 (C_{11}), 52.2 (C_4), 46.7 (C_5), 38.1 (C_1), 37.8 (C_{10}), 34.1 (C_{19}), 33.6 (C_{15}), 30.6 (C_3), 30.2 (C_7), 26.1 (C_{20}), 24.1 (C_{16}), 24.1 (C_{17}), 20.6 (C_6), 18.4 (C_2) ppm. **FT-IR (neat, cm^{-1}):** 2959, 2930, 1693, 1618, 1498, 1461, 1417, 1380, 1325, 1275, 1164, 1124, 1069, 1020, 911, 851, 824, 764, 750. **HRMS (ESI) (m/z):** $[M + Na^+]^+$ $(C_{27}H_{31}F_3NaO_2)^+$: 467.2168, found: 467.2168.

3.4 OZONOLYSIS OF 8-AMINOQUINOLINE DIRECTING GROUP

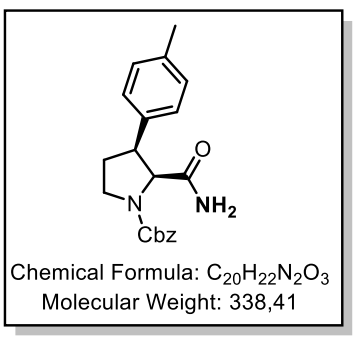


Amine **1.333b** (1 eq, 82.9 mg, 0.3 mmol) was dissolved in DCM/MeOH (1:1, 3 mL). At -78 °C, ozone was passed through until the characteristic blue color appeared. Oxygen was passed through until decolorization, followed by quenching with DMS (0.1 mL). After stirring overnight at room temperature, the mixture was concentrated under reduced pressure. The crude imide **1.335** proved to be instable on silica, characterization was therefore performed on the crude molecule. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 8.93 (dd, *J* = 4.7, 1.5 Hz, 1H, H_{18}), 8.06 (dd, *J* = 7.8, 1.5 Hz, 1H, H_{16}), 7.61 (dd, *J* = 7.8, 4.7 Hz, 1H, H_{17}), 7.23-7.28 (app. d, *J* = 4.5 Hz, 4H, $H_{1,3,4,6}$), 7.23-7.18 (m, 1H, H_2), 6.60 (s, 1H, H_{12}), 3.46 (dd, *J* = 7.6, 4.8 Hz, 2H, $H_{8a,b}$), 3.08 (t, *J* = 7.6 Hz, 2H, H_7) ppm. **^{13}C-NMR (150 MHz, $CDCl_3$):** δ = 175.2 (C_9), 164.1 (C_{15}), 153.8 (C_{18}), 148.4 (C_{14}), 140.4 (C_5), 137.3 (C_{13}), 133.0 (C_{16}), 128.7 ($C_{1,3,4,6}$), 128.7 ($C_{1,3,4,6}$),128.1 (C_{17}), 126.5 (C_2), 79.0 (C_{12}), 38.8 (C_8), 30.1 (C_7) ppm. **FT-IR (neat, cm^{-1}):** *not performed on crude sample.* **HRMS (ESI) (m/z):** calculated for $[M + Na^+]^+$ $(C_{16}H_{14}N_2NaO_3)^+$: 305.0898, found: 305.0897.

<u>Standard procedure for oxidative aminolysis</u>

The AQ-amide was dissolved in dry DCM (4 mL), cooled to -78 °C and a stream of ozone was passed through until the characteristic blue colour appeared after a few minutes. A stream of oxygen was passed through until decolorization and the mixture was quenched with DMS (0.05 mL). After stirring at room temperature for 2 h, the mixture was concentrated under reduced pressure. The residue was redissolved in NH_4OH (25%)/ THF (3 mL, 1:1) and stirred for the specified time at room temperature. The mixture was diluted with DCM (20 mL) and washed with 1N HCl (2x10 mL) and 1N NaOH (2x10 mL). The organic layer was dried with MgSO4 and concentrated to dryness to give the primary amides

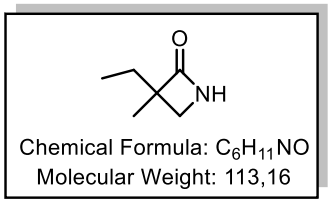
Benzyl (2S,3S)-2-carbamoyl-3-(p-tolyl)pyrrolidine-1-carboxylate **1.340**:



Ozonolysis was performed according to standard procedure on the amide (1 eq, 93.1 mg, 0.2 mmol). For aminolysis, the imide was stirred at RT for 24 h. Workup according to the standard procedure yielded 59.5 mg (88%) of primary amide. The spectral data is in accordance with the literature. [106] **^{1}H-NMR (500 MHz, DMSO-d_6, 373 K):** δ = 7.40-7.26 (m, 5H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.53 (bs,

2H), 5.09 (s, 2H), 4.44 (d, *J* = 8.3 Hz, 1H), 3.74 (t, *J* = 9.4 Hz, 1H), 3.63-3.55 (m, 1H), 3.49-3.42 (m, 1H), 2.28 (s, 3H), 2.07-2.00 (m, 1H) ppm.

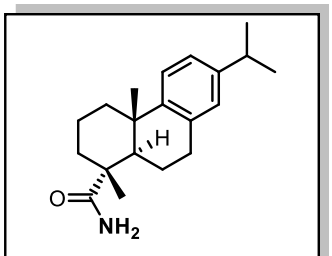
3-Ethyl-3-methylazetidin-2-one **1.344**:



Chemical Formula: $C_6H_{11}NO$
Molecular Weight: 113,16

N-Quinolyl lactam (1 eq, 36.0 mg, 0.15 mmol) was dissolved in dry DCM (4 mL). At -78 °C, a stream of ozone was passed through, until the characteristic blue colour appeared. A stream of oxygen was passed through until decolorization and the ozonides were quenched with DMS (0.05 mL). After stirring for 2 hours at room temperature, the mixture was concentrated under reduced pressure and dried properly on the pump under high vacuum for 3 hours. The dark red gum was suspended in NH_4OH (25%)/THF (1:1, 3 mL) and stirred for 10 hours at room temperature. After dilution with Na_2CO_3 sat. (15 mL), the product was extracted with DCM (2 x 15 mL). The combined organic layers were washed with 1 N HCl (20 mL), the aqueous layer was extracted with DCM (15 mL) and the combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure to afford 13.1 mg (77%) of the free lactam as yellow oil. The spectral data is in accordance with the literature. [222] **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 5.72 (bs, 1H), 3.17 (d, *J* = 5.3 Hz, 1H), 3.02 (d, *J* = 5.3 Hz, 1H), 1.74-1.59 (m, 2H), 1.31 (s, 3H), 0.98 (t, *J* = 7.5 Hz, 3H) ppm.

(1R,4aS,10aR)-7-Isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxamide **1.347**:

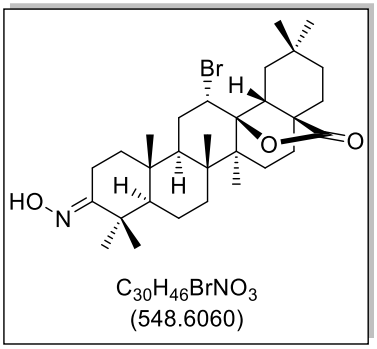


Chemical Formula: $C_{20}H_{29}NO$
Molecular Weight: 299,46

Ozonolysis was performed according to standard procedure on the amide (1 eq, 85.3 mg, 0.2 mmol). For aminolysis, the imide was stirred at RT for 24 h. Workup according to the standard procedure yielded 59.5.0 mg (99%) of primary amide. The spectral data is in accordance with the literature. [223] **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 7.16 (d, *J* = 8.2 Hz, 1H), 6.99 (dd, *J* = 8.1, 1.7 Hz, 1H), 6.87 (bs, 1H), 5.72 (bs, 1H), 5.27 (bs, 1H), 2.94-2.86 (m, 2H), 2.82 (hept, *J* = 6.9 Hz, 1H), 2.32 (bd, *J* = 13.0 Hz, 1H), 2.11 (dd, *J* = 12.5, 2.2 Hz, 1H), 1.88- 1.47 (m, 7H), 1.29 (s, 3H), 1.29 (s, 3H), 1.22 (m, 6H), 1.21 (s, 3H) ppm.

3.5 OXIDATION OF RING B IN PENTACYCLIC TRITERPENOIDS

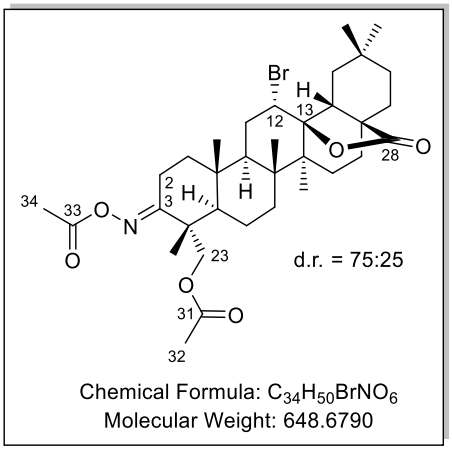
(*4aR,6aR,6bS,8aS,12aR,12bS,13S,14aR,14bR,E)*-13-Bromo-3-(hydroxyimino)-4,4,6a,6b,11,11,14b-heptamethyloctadecahydro-1H,9H-12b,8a-(epoxymethano)picen-16-one **1.448**



$C_{30}H_{46}BrNO_3$
(548.6060)

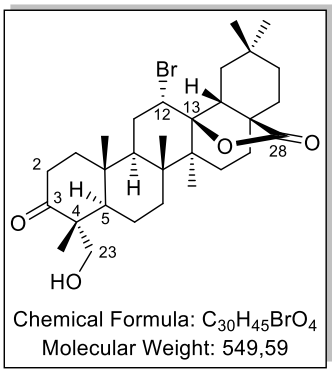
Oleanolic Acid **1.409** (1 equiv., 27.962 g, 60.0 mmol) was suspended in dry DCM (360 mL) and pyridine (15.2 equiv., 73.8 mL, 912 mmol) was added. The mixture was stirred at room temperature, resulting in a clear solution. NBS (1.03 equiv., 10.999 g, 61.8 mmol) was added and the mixture was stirred for 1 h at room temperature. Then, TCCA (0.8 equiv., 11.156 g, 48 mmol) was added and the mixture was stirred for 90 minutes at room temperature. In order to quench excess of oxidant, ^{i}PrOH (1.6 equiv., 5.769 g, 96 mmol) was added and the mixture was stirred for 30 minutes. Then, $NH_2OH{\cdot}HCl$ (3.2 equiv., 13.342 g, 192 mmol) was added and the mixture was stirred for 19 h at room temperature. After diluting with DCM (240 mL), the mixture was filtered from the sticky residue and after washed with DCM (160 mL). The mixture was washed with aqueous HCl (1 M, 960 mL) and the aqueous layer was back-extracted with DCM (360 mL). The combined organic layers were washed with aqueous NaOH (0.5M, 1000 mL) and brine (800 mL). After drying with $MgSO_4$ and filtration, the organic layer was concentrated under reduced pressure to give 33.010 g (100%) of **1.448** as pale-yellow solid which was used without further purification. Spectral data was found to be in accordance with the literature. [224] **^{1}H-NMR (600 MHz, $CDCl_3$)**: δ 7.83 (s, 1H, NOH), 4.30 (t, *J* = 2.9 Hz, 1H), 2.97 (ddd, *J* = 15.5, 6.1, 4.1 Hz, 1H), 2.44–2.29 (m, 3H), 2.16 (td, *J* = 13.4, 5.7 Hz, 1H), 2.05–1.92 (m, 3H), 1.84 (d, *J* = 15.2 Hz, 1H), 1.82–1.77 (m, 2H), 1.64 (dd, *J* = 9.3, 3.5 Hz, 2H), 1.61–1.44 (m, 3H), 1.43 (s, 3H), 1.39–1.31 (m, 2H), 1.31–1.19 (m, 7H), 1.19–1.14 (m, 4H), 1.06 (s, 3H), 0.99 (s, 3H), 0.98 (s, 3H), 0.90 (s, 3H) ppm.

((*4S,4aR,6aR,6bS,8aS,12aR,12bS,13S,14aR,14bR,Z*)-3-(Acetoxyimino)-13-bromo-4,6a,6b,11,11,14b-hexamethyl-16-oxooctadecahydro-1H,9H-12b,8a-(epoxymethano)picen-4-yl)methyl acetate **1.449**



Oxime **1.448** (33.010 g, 60 mmol, 1 eq.) was suspended in Ac_2O (151 mL) and AcOH (151 mL) and stirred for 1.5 h at 45 °C. Then, $Pd(OAc)_2$ (2.026 g, 9.03 mmol, 0.15 eq.) and PIDA (32.948 g, 102 mmol, 1.7 eq.) was added and the mixture was stirred for 16 h at 45 °C. After concentration under reduced pressure, the crude oil was purified by column chromatography (silica gel, 20-25% EtOAc in heptane) to afford 21.837 g (56%) of **1.449** as pale-yellow foam in a diastereomeric ratio of 75:25. **^{1}H-NMR (400 MHz, $CDCl_3$, major isomer)**: δ 4.31 (dd, *J* = 3.9, 2.3 Hz, 1H, H_{12}), 4.22 (d, *J* = 11.0 Hz, 1H, H_{23a}), 4.10 (d, *J* = 11.0 Hz, 1H, H_{23b}), 2.74-2.63 (m, 2H, H_2), 2.46-2.35 (m, 1H), 2.34-2.26 (m, 2H), 2.20–2.13 (m, 4H), 2.08 (s, 3H, H_{34}), 2.01-1.98 (m, 2H), 1.95 (td, *J* = 13.5, 5.6 Hz, 1H), 1.87-1.72 (m, 3H), 1.67-1.62 (m, 2H), 1.56-1.49 (m, 3H), 1.46-1.42 (m, 4H), 1.40-1.32 (m, 3H), 1.31-1.20 (m, 6H), 1.19 (s, 3H), 1.00 (s, 3H), 0.94 (s, 3H), 0.90 (s, 3H) ppm. **^{13}C-NMR (150 MHz, $CDCl_3$, major isomer)**: δ 178.9 (C_{28}), 171.1 (C_{33}), 170.4 (C_{31}), 169.7 (C_3), 91.6 (C_{13}), 68.4 (C_{23}), 56.3 (CH), 52.5 (CH), 48.3 (CH), 45.6 (CH), 44.9 (C), 44.1 (C), 43.6 (C), 42.3 (C), 40.1 (CH_2), 37.3 (CH_2), 36.2 (C), 34.0 (CH_2), 33.8 (CH_2), 33.4 (CH_3), 32.0 (C), 31.0 (CH_2), 29.2 (CH_2), 27.6 (CH_2), 23.7 (CH_3), 21.4 (CH_2), 21.2 (CH_3), 21.0 (CH_3), 20.3 (CH_2), 20.1 (CH_3), 19.0 (CH_2), 18.9 (CH_3), 18.8 (CH_3), 17.3 (CH_3) ppm. **FT-IR (neat, cm^{-1})** = 2928, 2863, 1770, 1743, 1465, 1387, 1366, 1213, 1132, 1040, 925, 906, 755. **HRMS (ESI)** (m/z): Calcd. for [M + Na]+ = $C_{34}H_{50}BrNNaO_6^+$: 670.2714; found 670.2712;

(*4R,4aR,6aR,6bS,8aS,12aR,12bS,13S,14aR,14bR*)-13-Bromo-4-(hydroxymethyl)-4,6a,6b,11,11,14b-hexamethyloctadecahydro-3H,9H-12b,8a-(epoxymethano)picene-3,16-dione **1.450**



Chemical Formula: $C_{30}H_{45}BrO_4$
Molecular Weight: 549,59

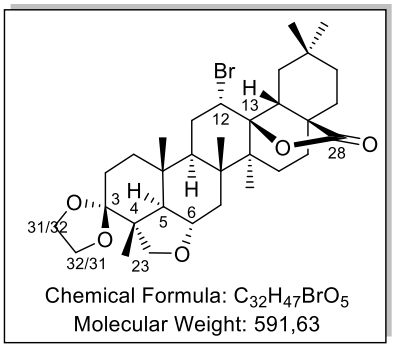
Oxime **1.449** (d.r. = 3:1, 1 equiv., 8.148 g, 12.6 mmol) was dissolved in MeOH (126 mL) and K_2CO_3 (868 mg, 6.28 mmol, 0.5 eq.) was added and the mixture was stirred for 90 minutes at 60 °C. Then, AcOH (0.72 mL, 12.6 mmol, 1 eq.) was added. The mixture was stirred until gas evolution deceased. Then, a solution of $CuSO_4$ * 5 H_2O (5 equiv., 15.681, 62.8 mmol) in water (126 mL) and THF (126 mL) was added. The mixture was stirred at 60 °C for 16 h. After cooling down, the product was extracted with DCM (3 x 500 mL), the organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (silica, 30% EtOAc in heptane) afforded 3.378 g (65%) of **1.450** as white solid and single isomer. **^{1}H-NMR (700 MHz, $CDCl_3$):** δ 4.31 (dd, *J* = 3.9, 2.3 Hz, 1H, H_{12}), 3.69 (dd, *J* = 11.2, 6.4 Hz, 1H, H_{23a}), 3.43 (dd, *J* = 11.3, 6.9 Hz, 1H, H_{23b}), 2.64 (ddd, *J* = 16.4, 12.4, 7.2 Hz, 1H, H_{2a}), 2.45 (ddd, *J* = 14.9, 12.3, 3.9 Hz, 1H), 2.37 (ddd, *J* = 16.4, 6.1, 2.9 Hz, 1H), 2.33 (dd, *J* = 10.1, 1.9 Hz, 1H), 2.23 (t, 1H, OH), 2.17 (td, *J* = 13.4, 5.8 Hz, 1H), 2.05–1.94 (m, 4H), 1.92 (dd, 1H), 1.88 (dt, 1H), 1.77 (dd, *J* = 12.1, 2.4 Hz, 1H), 1.67–1.63 (m, 3H), 1.57-1.49 (m, 2H), 1.46 (s, 3H), 1.44-1.39 (m, 1H), 1.39–1.32 (m, 2H), 1.32–1.21 (m, 6H), 1.09 (s, 3H), 1.01 (s, 3H), 1.00 (s, 3H), 0.91 (s, 3H) ppm; **^{13}C-NMR (175 MHz, $CDCl_3$)**: δ 218.5 (C_3), 178.9 (C_{28}), 91.7 (C_{13}), 67.0 (C_{23}), 56.2 (C_{12}), 52.6 (C_4), 52.5 (CH), 48.8 (C_5), 45.7 (C), 45.0 (CH), 43.7 (C), 42.5 (C), 40.1 (CH_2), 38.8 (CH_2), 36.3 (C), 35.3 (C_2), 34.1 (CH_2), 34.0 (CH_2), 33.4 (CH_3), 32.0 (C), 30.9 (CH_2), 29.3 (CH_2), 27.6 (CH_2), 23.7 (CH_3), 21.4 (CH_2), 21.2 (CH_3), 19.1 (CH_3), 18.7 (CH_2), 16.8 (CH_3), 16.8 (CH_3) ppm; **$[\alpha]^D_{20}$** = + 53.4 (c = 1, $CHCl_3$); **FT-IR (neat, cm^{-1})** = 3486, 2937, 2869, 1772, 1698, 1461, 1386, 1359, 1301, 1240, 1213, 1160, 1133, 1106, 1056, 1015, 926, 906, 877, 753. **HRMS (ESI) (m/z)**: Calcd. for $[M + Na]^+$ = $C_{30}H_{45}BrNaO_4^+$: 571.2393; found 571.2394;

(*4a'R,4b'S,5'S,6a'R,6b'R,6b1'R,9a'R,11a'S,12a'R,12b'S,14a'S*)-5'-Bromo-3',3',6b',9a',12a',12b'-hexamethyloctadecahydro-1'H,5'H-spiro[[1,3]dioxolane-2,9'-[4b,14a](epoxymethano)piceno[5,4-bc]furan]-15'-one **1.452**

Procedure for ketal protection:

Ketone **1.450** (1.040 g, 1.89 mmol, 1 eq.) was dissolved in dry benzene (94.5 mL). PPTS (476 mg, 1.89 mmol, 1 eq.) and ethylene glycol (9.4 mL) was added. The mixture was refluxed for 16 h using a Dean Stark apparatus. After cooling down, the mixture was diluted with EtOAc (300 mL) and extracted with aqueous $NaHCO_3$ (saturated, 100 mL), water (2 x 100 mL) and brine (100 mL). The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to afford the ketal as yellow solid, which was used without further purification.

Procedure for ether oxidation:



Chemical Formula: $C_{32}H_{47}BrO_5$
Molecular Weight: 591,63

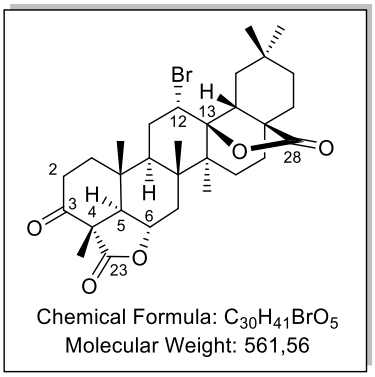
The crude ketal (1.187 g, 2.00 mmol, 1 eq.), I_2 (558 mg, 2.2 mmol, 1.1 eq.) and $CaCO_3$ (801 mg, 8.0 mmol, 4 eq.) were suspended in dry benzene (20 mL) and stirred at RT for 5 min. Then, PIDA (1085 mg, 3.3 mmol, 1.65 eq.) was added and stirred at RT for 2 h. The mixture was filtered and the solids were rinsed with EtOAc (2 x 30 mL). The combined organic layers were washed with a mixture of aqueous $Na_2S_2O_3$ (saturated, 10 mL) and water (10 mL). After separation of the organic layer, the aqueous layer was extracted with EtOAc (20 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. Purification by column (silica gel, 25-40% EtOAc in heptane) afforded 625 mg (53% over 2 steps) of **1.452** as colorless foam. **^{1}H-NMR (600 MHz, $CDCl_3$):** 4.29 (bs, 1H, H_{12}), 3.97 (ddd, *J* = 14.9, 12.6, 6.2 Hz, 2H, $H_{31a,32a}$), 3.90-3.83 (m, 2H, $H_{6,23a}$), 3.84-3.79 (m, 1H, $H_{31/32b}$), 3.79-3.76 (m, 1H, $H_{31/32b}$), 3.48 (d, *J* = 7.0 Hz, 1H, H_{23b}), 2.48-2.41 (m, 1H), 2.32 (d, *J* = 8.6 Hz, 1H), 2.17 (td, *J* = 13.5, 5.5 Hz, 1H), 2.03-1.94 (m, 4H), 1.86 (d, *J* = 12.8 Hz, 1H), 1.83 (dd, *J* = 11.9, 4.3 Hz, 1H), 1.80 (d, *J* = 15.5 Hz, 1H), 1.71-1.62 (m, 3H), 1.58 (bd, *J* = 14.4 Hz, 1H), 1.48-1.42 (m, 5H), 1.38-1.32 (m, 2H), 1.32-1.24 (m, 3H), 1.23 (s, 3H), 1.20 (s, 3H), 1.00 (s, 3H), 0.94 (s, 3H), 0.90 (s, 3H) ppm. **^{13}C-NMR (150 MHz, $CDCl_3$):** 178.9 (C_{28}), 111.6 (C_3), 91.9 (C_{13}), 76.4 (C_{23}), 71.6 (C_6), 65.6 ($C_{31/32}$), 64.6 ($C_{31/32}$), 58.1 (C_4), 55.8 (C_{12}), 52.5 (CH), 48.1 (C), 45.7 (C), 45.6 (C), 45.3 (CH), 45.3 (C), 43.7 (C), 40.6 (CH_2), 40.0 (CH_2), 39.4 (CH_2), 35.5 (C), 33.9 (CH_2), 33.4 (CH_3), 32.0 (C), 30.8 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 27.6 (CH_2), 23.7 (CH_3), 21.6 (CH_3), 21.4 (CH_2), 19.9 (CH_3), 18.4 (CH_3), 16.2 (CH_3) ppm. **$[\alpha]_D^{20}$** = + 48.6 (c = 1, $CHCl_3$); **FT-IR (neat, cm^{-1})** = 2930, 2886, 1776, 1464, 1391, 1275, 1260, 1214, 1158, 1145, 1131, 1102, 1090, 1030, 1013, 980, 928, 907, 751. **HRMS (ESI) (m/z):** Calcd. for $[M + Na]^+$ = $C_{32}H_{47}BrNaO_5^+$: 613.2499; found 613.2498;

(*4aR,4bS,5S,6aR,6bR,6b1R,9aS,11aS,12aR,12bS,14aS*)-5-Bromo-3,3,6b,9a,12a,12b-hexamethyloctadecahydro-1H,9H,10H-4b,14a-(epoxymethano)piceno[5,4-bc]furan-9,10,15-trione **1.454**

Procedure for ketal deprotection:

Ketal **1.452** (608 mg, 1.03 mmol, 1 eq.) and PTSA (196 mg, 103 mmol, 1 eq.) was dissolved in acetone (10.3 mL) and stirred for 18 h at 50 °C. The mixture was diluted with DCM (200 mL) and washed with a mixture of aqueous $NaHCO_3$ (saturated, 100 mL) and water (100 mL). After separation of the organic layer, the aqueous layer was extracted with DCM (200 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated to afford the ketone as yellowish solid, which was used without further purification.

Procedure for ether oxidation:

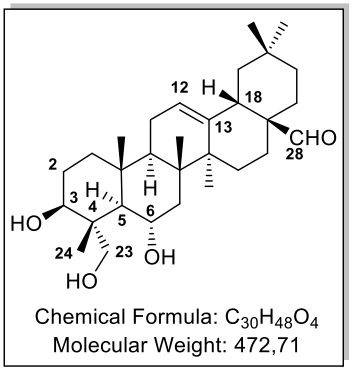


Chemical Formula: $C_{30}H_{41}BrO_5$
Molecular Weight: 561,56

The crude ether (560 mg, 1.02 mmol, 1 eq.) was dissolved in CH_3CN (10.2 mL) and CCl_4 (10.2 mL). Then, potassium phosphate buffer (1 M, pH = 7, 10.2 mL) was added followed by $RuCl_3$ * 3 H_2O (267 mg, 1.02 mmol, 1eq.) and $NaIO_4$ (656 mg, 3.07 mmol, 3 eq.) and the mixture was stirred vigorously at RT. After 11 h, another portion of $NaIO_4$ (2 eq.) was added and the mixture was stirred for 24 h. This was repeated once, then another portion of $NaIO_4$ (2 eq.) was added and stirred for another 6 h (9 equivalents of $NaIO_4$ and 65 h in total). Then ethylene glycol (0.57 mL, 10.2 mmol, 10 eq. was added and stirring remained until the mixture turned black. The mixture was diluted with water (200 mL) and extracted with DCM (3 x 200 mL). The combined organic layers were dried with $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (silica, 50% EtOAc in heptane) to afford 394 mg (69%) of **1.454** as white solid. **^{1}H-NMR (600 MHz, $CDCl_3$):** 4.49 (ddd, *J* = 11.3, 10.4, 4.7 Hz, 1H, H_6), 4.29 (dd, *J* = 3.3, 2.4 Hz, 1H, H_{12}), 2.81 (ddd, *J* = 15.4, 13.4, 6.6 Hz, 1H, H_{2a}), 2.54 (ddd, *J* = 15.1, 12.9, 3.9 Hz, 1H), 2.37 (ddd, *J* = 15.5, 4.8, 1.6 Hz, 1H, H_{2b}), 2.31 (bd, *J* = 8.4 Hz, 1H), 2.19 (td, *J* = 13.4, 5.7 Hz, 1H), 2.08 (bdd, *J* = 13.3, 6.9 Hz, 1H), 2.05-1.98 (m, 5H), 1.84-1.80 (m, 2H), 1.70-1.60 (m, 4H), 1.54 (s, 3H), 1.47 (s, 3H), 1.37-1.31 (m, 5H), 1.31-1.27 (m, 2H), 1.23 (s, 3H), 1.00 (s, 3H), 0.91 (s, 3H) ppm. **^{13}C-NMR (150 MHz, $CDCl_3$):** 203.5 (C_3), 178.5 (C_{28}), 172.9 (C_{23}), 91.3 (C_{13}), 72.7 (C_6), 60.5 (C_5), 54.7 (C_{12}), 52.5 (CH), 51.7 (C_4), 45.5 (C), 45.3 (CH), 45.3 (C), 43.7 (CH_2), 40.0 (CH_2), 38.5 (CH_2), 35.5 (C), 35.2 (C2), 33.8 (CH_2), 33.4 (CH_3), 32.1 (C), 30.9 (CH_2), 29.6 (C), 29.5 (CH_2), 27.5 (CH_2), 23.6 (CH_3), 21.6 (CH_3), 21.2 (CH_2), 19.8 (CH_3), 16.5 (CH_3), 16.1 (CH_3) ppm. **$[\alpha]_D^{20}$** = +18.9 (c = 1, $CHCl_3$); **FT-IR (neat, cm^{-1})** = 2926, 2855, 1778, 1720, 1463, 1215,

1140, 1106, 1047, 969, 926, 906, 758, 734. **HRMS (ESI) (m/z):** Calcd. for $[M + Na]^+ = C_{30}H_{41}BrNaO_5^+$: 583.2030; found 583.2031;

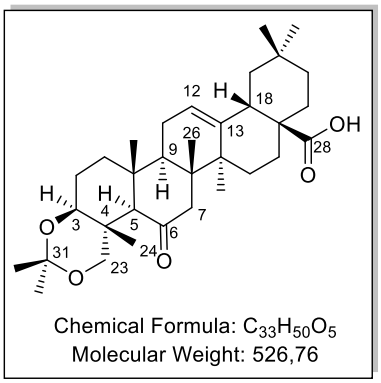
(*4aS,6aS,6bR,8S,8aR,9R,10S,12aR,12bR,14bS*)-8,10-dihydroxy-9-(hydroxymethyl)-2,2,6a,6b,9,12a-hexamethyl-1,3,4,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-4a(2H)-carbaldehyde **1.467**



Chemical Formula: $C_{30}H_{48}O_4$
Molecular Weight: 472,71

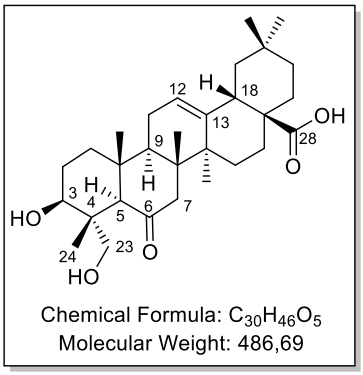
Diketone **1.454** (356 mg, 0.634 mmol, 1 eq.) was dissolved in THF (dry, 31.7 mL) in a flame-dried flask under Argon. After cooling to 0 °C, $LiAlH_4$ (96.2 mg, 2.54 mmol, 4 eq.) was added and stirred for 5 minutes. The ice bath was removed and the mixture was allowed to stir for 20 minutes at RT before cooling again to 0 °C. Excess of reducing agent was quenched dropwise with minimum of AcOH (amount taken from 31.7 mL) until gas evolution ceased. Then, zinc powder (1.244 g, 19 mmol, 30 eq.) was added and the rest of AcOH (31.7 mL in total). The mixture was sonicated for 1 minute, stirred 1 h at 50 °C and overnight at RT. The solvents were removed *in vacuo*, then ^{i}PrOH (10 mL) and Rochelle´s salt (saturated, 50 mL) was added and the mixture was vigorously stirred for 4 h at RT. After addition of EtOAc (40 mL) and stirring for another hour, the organic layer was separated and the aqueous layer was extracted with EtOAc (4 x 50 mL). The combined organic layers were dried with $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (silica gel, EtOAc) to afford 180 mg (60%) of **1.467** as white solid. **^{1}H-NMR (600 MHz, $CDCl_3$):** 9.38 (s, 1H, H_{28}), 5.35 (t, *J* = 2.5 Hz, 1H, H_{12}), 4.00 (td, *J* = 10.2, 4.3 Hz, 1H, H_6), 3.76 (d, *J* = 11.2 Hz, 1H, H_{23a}), 3.69 (d, *J* = 11.2 Hz, 1H, H_{23b}), 3.48 (dd, *J* = 11.5, 5.1 Hz, 1H, H_3), 2.63 (dd, *J* = 13.5, 3.8 Hz, 1H, H_{18}), 1.98 (td, *J* = 13.9, 4.0 Hz, 1H), 1.92-1.84 (m, 2H), 1.71-1.62 (m, 4H), 1.62-1.49 (m, 5H), 1.45 (td, *J* = 13.5, 4.6 Hz, 1H), 1.31 (td, *J* = 13.3, 3.7 Hz, 1H), 1.27-1.17 (m, 4H), 1.16 (s, 3H), 1.08, (bd, *J* = 13.5 Hz, 1H), 1.01 (td, *J* = 13.4, 8.9, 1H), 0.97 (s, 3H), 0.92 (s, 3H), 0.91 (s, 3H), 0.88 (s, 3H), 0.79 (s, 3H) ppm. **^{13}C-NMR (150 MHz, $CDCl_3$):** 207.4 (C_{28}), 142.5 (C_{13}), 123.1 (C_{12}), 73.3 (C_3), 68.8 (C_{23}), 67.4 (C_6), 53.7 (C_5), 49.1 (C), 45.8 (C_9), 45.5 (CH_2), 44.3 (CH_2), 43.0 (C_4), 41.8 (C), 40.5 (C), 40.1 (C_{18}), 38.6 (C), 38.0 (CH_2), 33.1 (CH_2), 33.0 (CH_3), 30.6 (C), 27.6 (CH_2), 26.7 (CH_2), 26.7 (CH_2), 25.5 (CH_3), 23.4 (CH_2), 23.4 (CH_3), 21.9 (CH_2), 18.1 (CH_3), 16.6 (CH_3), 12.6 (C_{24}) ppm. **$[\alpha]_D^{20}$** = + 85.3 (c = 1, $CHCl_3$); **FT-IR (neat, cm^{-1}):** 3373, 2929, 2862, 1721, 1462, 1388, 1364, 1261, 1086, 1033, 989, 956, 754. **HRMS (ESI) (m/z):** Calcd. for $[M + Na]^+ = C_{30}H_{48}NaO_4^+$: 495.3445; found 495.3442.

(*4aR,4bR,6aR,6bS,8aS,12aS,14aR,14bR,16aS*)-2,2,4a,6a,6b,11,11,14b-Octamethyl-5-oxo-4a,5,6,6a,6b,7,8,9,10,11,12,12a,14,14a,14b,15,16,16a-octadecahydro-4H-piceno[3,4-d][1,3]dioxine-8a(4bH)-carboxylic acid **1.468**



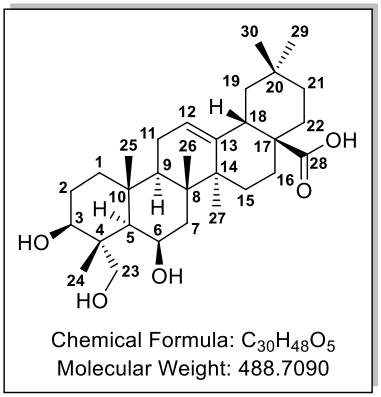
1.467 (107 mg, 0.226 mmol, 1 eq.) and PPTS (56.9 mg, 0.226 mmol, 1 eq.) were combined in acetone (dry, 2.26 mL) and stirred overnight at RT. The mixture was poured in aqueous $NaHCO_3$ (saturated, 20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried with $MgSO_4$ concentrated and dried under reduced pressure. The residue was combined with TPAP (23.8 mg, 0.068 mmol, 0.3 eq.), NMO·H_2O (397 mg, 2.94 mmol, 13 eq.) and anhydrous NMO (185 mg, 1.58 mmol, 7 eq.) in a flame dried Schlenk under Argon. Acetonitrile (dry, 2.26 mL) was added and the mixture was stirred for 48 h at RT. The mixture was filtered over a short silica pad with EtOAc and concentrated. The crude was purified by column chromatography (silica gel, column packed with 1% Et_3N in EtOAc/heptane 2:8; elute first impurities with 20% EtOAc in heptane, then elute product with NMO impurities with EtOAc). The product containing fractions were concentrated and filtered again over a short pad of silica gel with 20% EtOAc in heptane) to afford 59.8 mg (50%) of **1.468** as white solid. **^{1}H-NMR (600 MHz, $CDCl_3$):** 5.33 (t, *J* = 3.6 Hz, 1H, H_{12}), 3.79 (d, *J* = 10.6 Hz, 1H, H_{23a}), 3.41 (dd, *J* = 11.7, 3.6 Hz, 1H, H_3), 3.32 (d, *J* = 10.6 Hz, 1H, H_{23b}), 2.85 (dd, *J* = 13.7, 4.1 Hz, 1H, H_{18}), 2.39 (d, *J* = 13.4 Hz, 1H, H_{7a}), 2.17 (dd, *J* = 10.8, 6.8 Hz, 1H, H_9), 2.05-1.92 (m, 4H), 1.88 (d, *J* = 13.3 Hz, 1H, H_{7b}), 1.80-1.58 (m, 6H), 1.56 (td, *J* = 13.6, 3.3 Hz, 1H), 1.47-1.42 (m, 4H), 1.41 (s, 3H), 1.40 (s, 3H), 1.33 (td, *J* = 13.8, 4.0 Hz, 1H), 1.30-1.20 (m, 5H), 1.67 (ddd, *J* = 13.9, 4.6, 2.0 Hz, 1H), 0.98 (s, 3H), 0.95 (bd, *J* = 14.2 Hz, 1H), 0.93 (s, 3H), 0.92 (s, 3H), 0.75 (s, 3H) ppm. **^{13}C-NMR (150 MHz, $CDCl_3$):** 210.9 (C_6), 183.7 (C_{28}), 143.2 (C_{13}), 122.4 (C_{12}), 99.2 (C_{31}), 76.7 (C_3), 71.2 (C_{23}), 61.7 (C_5), 49.8 (C_7), 47.8 (C_9), 46.6 (C), 45.7 (CH_2), 45.7 (C), 43.0 (C), 42.0 (C), 41.0 (C_{18}), 39.0 (CH_2), 35.9 (C), 33.8 (CH_2), 33.2 (CH_3), 32.4 (CH_2), 30.8 (C), 29.9 (CH_3), 27.6 (CH_2), 26.7 (CH_3), 23.7 (CH_2), 23.7 (CH_3), 23.3 (CH_2), 22.7 (CH_2), 19.3 (CH_3), 18.1 (C_{26}), 17.9 (CH_3), 12.6 (C_{24}) ppm. **$[\alpha]_D^{20}$** = +33.1 (c = 1, $CHCl_3$). **FT-IR (neat, cm^{-1}):** 2988, 2942, 2862, 1708, 1365, 1276, 1261, 1195, 1105, 764, 750. **HRMS (ESI) (m/z):** Calcd. for $[M - H]^-$ = $C_{33}H_{49}O_5^-$: 525.3585; found 525.3603.

(4aS,6aS,6bR,8aR,9R,10S,12aR,12bR,14bS)-10-hydroxy-9-(hydroxymethyl)-2,2,6a,6b,9,12a-hexamethyl-8-oxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-4a(2H)-carboxylic acid **1.469**



1.468 (42.8 mg, 0.081 mmol, 1 eq.) and PPTS (10.2 mg, 0.041 mmol, 0.5 eq.) were dissolved in MeOH (3.24 mL) and stirred at RT for 8 h. The product was directly adsorbed on silica gel and purified by column chromatography (dryload, silica gel, 40-60% EtOAc in heptane) to give 32.8 mg (83%) of **1.469** as colorless solid. **^{1}H-NMR (600 MHz, CD_3OD):** 5.31 (t, *J* = 3.6 Hz, 1H, H_{12}), 3.54 (dd, *J* = 11.7, 4.-6 Hz, 1H, H_3), 3.52 (d, *J* = 10.7 Hz, 1H, H_{23a}), 3.38 (d, *J* = 10.7 Hz, 1H, H_{23b}), 2.89 (dd, *J* = 13.9, 4.2 Hz, 1H, H_{18}), 2.69 (d, *J* = 12.6 Hz, 1H, H_{7a}), 2.62 (s, 1H, H_5), 2.23 (dd, *J* = 11.2, 6.5 Hz, 1H, H_9), 2.09-1.95 (m, 3H), 1.79 (d, *J* = 12.6 Hz, 1H, H_{7b}), 1.77-1.58 (m, 7H), 1.56 (td, *J* = 13.5, 3.2 Hz, 1H), 1.41 (td, *J* = 13.9, 4.0 Hz, 1H), 1.33-1.26 (m, 4H), 1.24-1.20 (m, 1H), 1.16 (ddd, *J* = 13.6, 4.5, 2.2 Hz, 1H), 1.07 (s, 3H), 1.02-0.96 (m, 4H), 0.95 (s, 3H), 0.93 (s, 3H), 0.84 (s, 3H) ppm. **^{13}C-NMR (150 MHz, CD_3OD):** 215.4 (C_6), 181.6 (C_{28}), 144.8 (C_{13}), 123.3 (C_{12}), 72.3 (C_3), 66.0 (C_{23}), 58.9 (C_5), 51.3 (C_7), 49.0 (C_9), 47.6 (C), 47.5 (C), 47.0 (CH_2), 44.0 (C), 43.2 (C), 42.6 (C_{18}), 42.4 (C), 39.8 (CH_2), 34.8 (CH_2), 33.7 (CH_2), 33.5 (CH_3), 31.6 (C), 28.7 (CH_2), 27.1 (CH_2), 26.8 (CH_3), 24.9 (CH_2), 24.0 (CH_3), 23,9 (CH_2), 18.1 (CH_3), 17.4 (CH_3), 12.8 (C_{24}) ppm. **FT-IR (neat, cm^{-1}):** 3436, 2954, 1710, 1436, 1340, 1010, 962. **$[\alpha]_D^{20}$** = + 62.8 (c = 1, MeOH). **HRMS (ESI) (m/z):** Calcd. for $[M + Na]^+$ = $C_{30}H_{46}NaO_5^+$: 509.3237; found 509.3229.

Uncargenin C 1.416



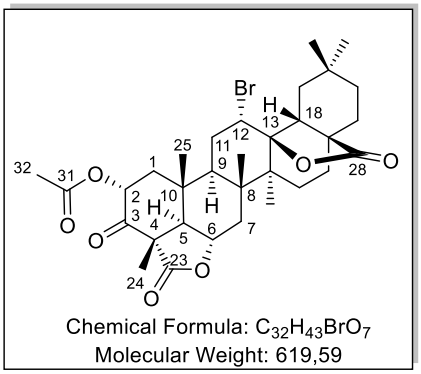
1.469 (25 mg, 0.051 mmol, 1 eq.) was dissolved under Argon in a flame-dried Schlenk in THF (dry, 2.04 mL). $LiBH_4$ (2 M in THF, 0.128 mL, 5 eq.) was added dropwise at RT and the mixture was stirred 2 h at RT. Excess of reducing agent was quenched with a mixture of 10% AcOH in MeOH (0.3 mL) and allowed to stir for 10 min. The mixture was filtered over a short silica pad with 10% MeOH in DCM and concentrated. The crude mixture was purified by column chromatography (dryload, 3-8% MeOH in DCM) to afford 24.1 mg (96%) of **1.416** as white solid.

$[\alpha]_D^{20}$ = + 40.4 (c = 1, MeOH) (Lit. $[\alpha]_D^{20}$ = + 40.3 (c = 3.25, MeOH)

^{13}C-NMR data for **1.416** (isolated) in C_5D_5N[161]	**^{13}C-NMR data** for **1.416** (herein prepared) in C_5D_5N
180.2 (C_{28})	180.2 (C)
144.2 (C_{13})	144.2 (C)
122.9 (C_{12})	123.0 (CH)
73.3 (C_3)	73.3 (CH)
67.5 (C_6)	67.6 (CH)
67.1 (C_{23})	67.2 (CH_2)
49.3 (C_5)	49.4 (CH)
48.7 (C_9)	48.7 (CH)
46.6 (C_{17})	46.7 (C)
46.4 (C_{19})	46.5 (CH_2)
44.0 (C_4)	44.0 (C)
42.7 (C_{14})	42.7 (C)
42.0 (C_{18})	42.1 (CH)
41.1 (C_7)	41.1 (CH_2)
41.1 (C_1)	41.1 (CH_2)
39.2 (C_8)	39.2 (C)
36.9 (C_{10})	37.0 (C)
34.2 (C_{21})	34.2 (CH_2)
33.2 (C_{22})	33.2 (CH_2)
33.2 (C_{30})	33.2 (CH_3)
30.9 (C_{20})	31.0 (C)
28.3 (C_{15})	28.3 (CH_2)
28.**3** (C_2)	28.**0** (CH_2)
26.2 (C_{27})	26.3 (CH_3)
23.9 (C_{16})	23.9 (CH_2)
23.7 (C_{11})	23.8 (CH_2)
23.7 (C_{29})	23.8 (CH_3)
18.6 (C_{26})	18.6 (CH_3)
17.4 (C_{25})	17.5 (CH_3)
14.7 (C_{24})	14.7 (CH_3)

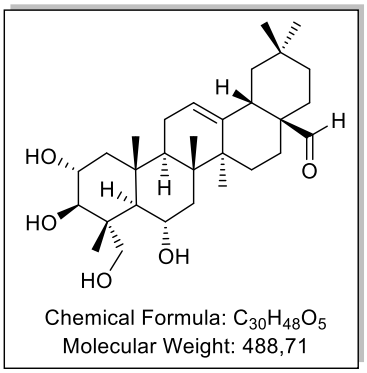
(*4aR,4bS,5S,6aR,6bR,6b1R,8R,9aS,11aS,12aR,12bS,14aS*)-5-Bromo-3,3,6b,9a,12a,12b-hexamethyl-9,10,15-trioxooctadecahydro-1H,5H,7H-4b,14a-(epoxymethano)piceno[5,4-bc]furan-8-yl acetate

1.470



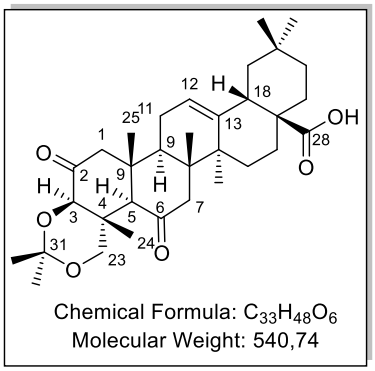
1.454 (300 mg, 0.534 mmol, 1 eq.) was dissolved in AcOH (glacial, 10.7 mL) and LTA (449 mg, 0.962 mmol, 1.8 eq.) was added and stirred for 16 h at 75 °C. After cooling down, the mixture was poured into aqueous $Na_2S_2O_3$ (saturated, 100 mL) and extracted with DCM (3 x 100 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 30-50% EtOAc in heptane) to afford 167 mg (51%) of **1.470** as white solid. **^{1}H-NMR (600 MHz, $CDCl_3$):** 5.69 (dd, *J* = 12.2, 6.6 Hz, 1H, H_2), 4.52 (ddd, *J* = 11.1, 10.3, 4.7 Hz, 1H, H_6), 4.29 (dd, *J* = 3.5, 2.4 Hz, 1H, H_{12}), 2.56 (ddd, *J* = 15.2, 12.8, 3.9 Hz, 1H, H_{11a}), 2.38 (dd, *J* = 12.6, 6.6 Hz, 1H, H_{1a}), 2.32 (dd, *J* = 9.8, 1.3 Hz, 1H), 2.22-2.15 (m, 4H), 2.08 (dd, *J* = 12.6, 1.5 Hz, 1H, H_9), 2.05-1.96 (m, 4H), 1.88 (d, *J* = 11.5 Hz, 1H, H_5), 1.82 (dt, *J* = 14.8, 1.2 Hz, 1H, H_{11b}), 1.76 (t, *J* = 12.4 Hz, 1H, H_{1b}), 1.68-1.59 (m, 6H), 1.47 (s, 3H), 1.39-1.26 (m, 10H), 1.01 (s, 3H), 0.91 (s, 3H) ppm. **^{13}C-NMR (150 MHz, $CDCl_3$):** 197.0 (C_3), 178.3 (C_{28}), 171.6 (C_{23}), 167.0 (C_{31}), 91.1 (C_{13}), 72.3 (C_6), 71.3 (C_2), 61.1 (C_5), 54.5 (C_{12}), 52.5 (C_{18}), 52.0 (C), 49.5 (C_1), 45.5 (C), 45.5 (C), 45.4 (C_9), 43.8 (C), 40.0 (CH_2), 38.5 (C_7), 35.3 (C), 33.9 (CH_2), 33.3 (CH_3), 32.1 (C), 31.0 (CH_2), 29.5 (CH_2), 27.5 (CH_2), 23.7 (CH_3), 21.6 (CH_3), 21.2 (CH_2), 20.7 (C_{32}), 19.8 (CH_3), 17.6 (C_{25}), 15.8 (C_{24}) ppm. **FT-IR (neat, cm^{-1}):** 2944, 2361, 2338, 1795, 1276, 1261, 1239, 1132, 1112, 974, 927, 764, 750. **HRMS (ESI) (m/z):** Calcd. for $[M + Na]^+ = C_{32}H_{43}BrNaO_7^+$: 641.2084; found 641.2073. **$[\alpha]_D^{20}$** = +19.7 (c = 1, $CHCl_3$).

(4aS,6aS,6bR,8S,8aR,9R,10R,11R,12aR,12bR,14bS)-8,10,11-trihydroxy-9-(hydroxymethyl)-2,2,6a,6b,9,12a-hexamethyl-1,3,4,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-4a(2H)-carbaldehyde **1.472**



1.470 (153 mg, 0.247 mmol, 1 eq.) was dissolved in a flame-dried flask under argon in THF (dry, 12.3 mL). After cooling to 0 °C, $LiAlH_4$ (46.9 mg, 1.23 mmol, 5 eq.) was added and stirred for 5 minutes. The ice bath was removed and the mixture was allowed to stir for 20 minutes at RT before cooling again to 0 °C. Excess of reducing agent was quenched dropwise with minimum of AcOH (amount taken from 12.3 mL) until gas evolution ceased. Then, zinc powder (484 mg, 7.41 mmol, 30 eq.) was added and the rest of AcOH (12.3 mL in total). The mixture was sonicated for 1 minute, stirred for 70 min at 40 °C. The solvents were removed *in vacuo*, then iPrOH (5 mL), aqueous Rochelle´s salt (saturated, 20 mL) and $CHCl_3$ (15 mL) was added and the mixture was vigorously stirred overnight. After addition of water (30 mL), the mixture was extracted with $CHCl_3$/iPrOH (3:1, 4 x 50 mL). The combined organic layers were dried with $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (silica gel, 2-6% MeOH in DCM) to afford 47.6 mg of **1.472** (*80% in an inseparable mixture with the C-28 carboxylic acid*). **HRMS (ESI) (m/z):** Calcd. for $[M + Na]^+ = C_{30}H_{48}NaO_5^+$: 511.3394; found 511.3378.

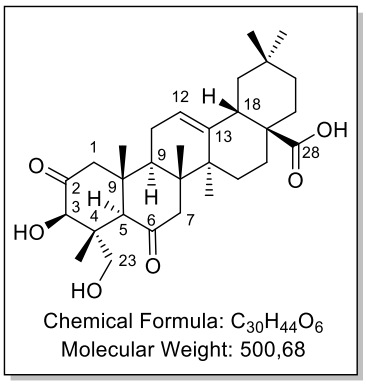
(*4aR,4bR,6aR,6bS,8aS,12aS,14aR,14bR,16aR*)-2,2,4a,6a,6b,11,11,14b-octamethyl-5,16-dioxo-4a,5,6,6a,6b,7,8,9,10,11,12,12a,14,14a,14b,15,16,16a-octadecahydro-4H-piceno[3,4-d][1,3]dioxine-8a(4bH)-carboxylic acid **1.473**



A mixture containing **1.472** (80%, 45 mg, 0.074 + 0.018 mmol, total 1 eq.) and PPTS (23.1 mg, 0.092 mmol, 1 eq.) were combined in acetone (dry, 3.68 mL) and stirred overnight at RT. The mixture was poured in aqueous $NaHCO_3$ (saturated, 20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried with $MgSO_4$ concentrated and dried under reduced pressure. The residue was combined with TPAP (29.1 mg, 0.083 mmol, 0.9 eq.), NMO*H_2O (294 mg, 1.840 mmol, 20 eq.) and anhydrous NMO (108 mg, 0.921 mmol, 10 eq.) in a flame dried Schlenk under argon. Acetonitrile (dry, 0.92 mL) was added and the mixture was stirred for 72 h at RT. The mixture was filtered over a short silica pad with EtOAc and concentrated. The crude was purified by column chromatography (silica gel, 20% EtOAc in heptane) to afford 19.5 mg (40% over 2 steps or

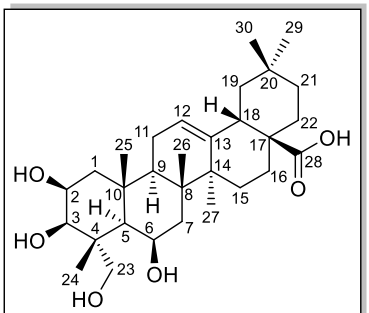
16% over 3 steps from **1.470**) of **1.473** as white solid. **^{1}H-NMR (600 MHz, $CDCl_3$):** 5.34 (t, *J* = 3.4 Hz, 1H, H_{12}), 4.32 (s, 1H, H_3), 3.86 (d, *J* = 10.6 Hz, 1H, H_{23a}), 3.56 (d, *J* = 10.7 Hz, 1H, H_{23b}), 2.87 (dd, *J* = 13.9, 4.3 Hz, 1H, H_{18}), 2.62 (s, 1H, H_5), 2.51 (d, *J* = 13.6 Hz, 1H, H_{7a}), 2.46 (d, *J* = 13.0 Hz, 1H, H_{1a}), 2.44 (dd, *J* = 11.0, 6.8 Hz, 1H, H_9), 2.31 (d, *J* = 13.0 Hz, 1H, H_{1b}), 2.04-1.90 (m, 3H), 1.76 (td, *J* = 13.8, 4.4 Hz, 1H), 1.73-1.56 (m, 4H), 1.52 (s, 3H), 1.44 (c, 3H), 1.37 (s, 3H, H_{24}), 1.36-1.15 (m, 6H), 1.05 (s, 3H, H_{25}), 1.00 (bd, *J* = 13.9 Hz, 1H), 0.93 (s, 3H), 0.93 (s, 3H), 0.83-0.79 (m, 1H), 0.73 (s, 3H) ppm. **^{13}C-NMR (150 MHz, $CDCl_3$):** 208.8 (C_6), 203.1 (C_2), 182.3 (C_{28}), 143.5 (C_{12}), 121.7 (C_{13}), 100.1 (C_{31}), 80.8 (C_3), 70.2 (C_{23}), 61.1 (C_5), 54.4 (C_1), 49.7 (C_7), 48.3 (C), 48.0 (C_9), 46.5 (C), 45.8 (C_{11}), 45.5 (C), 42.2 (C), 41.1 (C_{18}), 40.9 (C), 33.8 (CH_2), 33.2 (CH_3), 32.3 (CH_2), 30.9 (C), 29.7 (CH_3), 27.6 (CH_2), 26.7 (CH_3), 23.7 (CH_3), 23.7 (CH_2), 22.8 (CH_2), 19.2 (C_{25}), 18.8 (CH_3), 17.7 (CH_3), 13.6 (C_{24}) ppm. **FT-IR (neat, cm^{-1}):** 2925, 2360, 1711, 1462, 1367, 1219, 1117, 1064, 968, 849, 772, 667, 620. **HRMS (ESI) (m/z):** Calcd. for $[M + Na]^+ = C_{33}H_{48}NaO_6^+$: 563.3343; found 563.3344. **$[\alpha]_D^{20}$** = +43.4 (c = 1.0, $CHCl_3$).

(*4aS,6aS,6bR,8aR,9R,10R,12aR,12bR,14bS*)-10-hydroxy-9-(hydroxymethyl)-2,2,6a,6b,9,12a-hexamethyl-8,11-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-4a(2H)-carboxylic acid **1.474**



1.473 (16 mg, 0.030 mmol, 1 eq.) and PPTS (7.5 mg, 0.030 mmol, 1 eq.) were dissolved in MeOH (1.18 mL) and stirred at RT for 12 h. The product was directly absorbed on silica gel and purified by column chromatography (dryload, silica gel, 0-40% MeOH in DCM) to give 11.4 mg (77%) of **1.474** as colorless solid. **^{1}H-NMR (600 MHz, CD_3OD):** 5.33 (t, *J* = 3.6 Hz, 1H, H_12), 4.35 (d, *J* = 0.9 Hz, 1H, H_3), 3.51 (d, *J* = 10.9 Hz, 1H, H_{23a}), 3.44 (d, *J* = 10.9 Hz, 1H, H_{23b}), 3.36 (s, 1H, H_5), 2.91 (dd, *J* = 13.9, 4.1 Hz, 1H, H_{18}), 2.83 (d, *J* = 12.7 Hz, 1H, H_7), 2.59 (t, *J* = 8.8 Hz, 1H, H_9), 2.51 (d, *J* = 12.6 Hz, 1H, H_{1a}), 2.41 (d, *J* = 12.6 Hz, 1H, H_{1b}), 2.11-1.99 (m, 3H), 1.89 (d, *J* = 12.8 Hz, 1H, H_7), 1.82-1.72 (m, 3H), 1.64 (bd, *J* = 13.7 Hz, 1H), 1.57 (dt, *J* = 13.5, 3.2 Hz, 1H), 1.46-1.35 (m, 4H), 1.27-1.13 (m, 2H), 1.04 (dt, *J* = 13.5, 3.0 Hz, 1H), 0.96 (s, 3H), 0.94-0.92 (m, 9H), 0.84 (s, 3H) ppm. **^{13}C-NMR (150 MHz, CD_3OD):** 213.3 (C_6), 212.2 (C_2), 181.6 (C_{28}), 145.0 (C_{13}), 122.9 (C_{12}), 77.3 (C_3), 65.2 (C_{23}), 57.5 (C_5), 54.3 (C_1), 51.2 (C_7), 48.7 (C_9), 48.6 (C), 48.3 (C), 47.6 (C), 47.1 (CH_2), 47.0 (C), 43.4 (C), 43.7 (C_{18}), 34.8 (CH_2), 33.6 (CH_2), 33.5 (CH_3), 31.6 (C), 28.7 (CH_2), 26.8 (CH_3), 24.8 (CH_2), 24.0 (CH_3), 23.9 (CH_2), 18.7 (CH_3), 17.9 (CH_3), 13.7 (C_{24}) ppm. **$[\alpha]_D^{20}$ =** +50.6 (c = 0.5, MeOH) **FT-IR (neat, cm^{-1}):** 3728, 3705, 3626, 3602, 2927, 2360, 2341, 1711, 669, 651. **HRMS (ESI) (m/z):** Calcd. for $[M + Na]^+ = C_{30}H_{44}NaO_6^+$: 523.3030; found 523.3035.

Protobassic Acid **1.418**

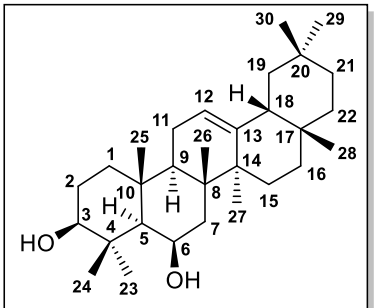


1.474 (8.5 mg, 0.017 mmol, 1 eq.) was dissolved under argon in a flame-dried Schlenk in THF (dry, 1.18 mL). $LiBH_4$ (2 M in THF, 0.0849 mL, 10 eq.) was added dropwise at 0 °C and the mixture was stirred 4 h at RT. Excess of reducing agent was quenched with a mixture of 10% AcOH in MeOH (0.5 mL) at 0 °C and allowed to stir for 10 min at RT. The mixture was filtered over a short silica pad with 1% AcOH in MeOH/DCM (1:9) and concentrated. The crude mixture was purified by column chromatography (dryload, 0-9% MeOH in DCM) to afford 5.0 mg (58%) of **1.418** as white solid.

$[\alpha]_D^{20}$ = + 48.0 (c = 0.5, pyridine)

^{13}C-NMR data for **1.418** (isolated) in C_5D_5N[165]	**^{13}C-NMR data** for **1.418** (herein prepared) in C_5D_5N
180.4 (C_{28})	180.4 (C)
144.4 (C_{13})	144.4 (C)
123.2 (C_{12})	123.2 (CH)
73.4 (C_3)	73.2 (CH)
72.0 (C_2)	72.0 (CH)
67.9 (C_6)	67.8 (CH)
67.6 (C_{23})	67.4 (CH_2)
49.4 (C_5)	49.3 (CH)
49.3 (C_9)	49.3 (CH)
47.5 (C_1)	47.5 (CH_2)
46.9 (C_{17})	46.8 (C)
46.7 (C_{19})	46.6 (CH_2)
43.6 (C_4)	43.7 (C)
43.1 (C_{14})	43.0 (C)
42.3 (C_{18})	42.3 (CH)
41.2 (C_7)	41.3 (CH_2)
39.5 (C_8)	39.4 (C)
37.2 (C_{10})	37.3 (C)
34.4 (C_{21})	34.4 (CH_2)
33.4 (C_{29})	33.4 (CH_3)
33.3 (C_{22})	33.4 (CH_2)
31.1 (C_{20})	31.1 (C)
28.4 (C_{15})	28.4 (CH_2)
26.5 (C_{27})	26.5 (CH_3)
24.2 (C_{11})	24.2 (CH_2)
24.0 (C_{16})	23.9 (CH_2)
24.0 (C_{30})	23.9 (CH_3)
19.1 (C_{25})	19.1 (CH_3)
18.7 (C_{26})	18.7 (CH_3)
16.2 (C_{24})	16.3 (CH_3)

(3S,4aR,5R,6aR,6bS,8aR,12aR,14aR,14bR)-4,4,6a,6b,8a,11,11,14b-octamethyl-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,14,14a,14b-icosahydropicene-3,5-diol **1.475**



Chemical Formula: $C_{30}H_{50}O_2$
Molecular Weight: 442,73

A dry Schlenk tube was charged with $[Ru(p\text{-cymene})Cl_2]_2$ (7.35 mg, 0.012 mmol, 0.12 eq.), KO^{t}Bu (44.9 mg, 0.4 mmol, 4 eq.) and 1,2-Bis(dimethylphosphino)ethane (3.6 mg, 0.024 mmol, 0.24 eq.) in the glove box. Then, **1.467** (0.1 mmol, 47.3 mg, 1 eq.), DMSO (5.68 µL, 0.08 mmol, 0.8 eq.), 0.8 mL *tert*-BuOH and hydrazine monohydrate (73.6 mg, 1.44 mmol, 14.4 eq.) have been added. The mixture was heated to 100 °C for 3 days. After cooling to RT, the mixture was quenched with MeOH. The crude reaction mixture was adsorbed on celite and filtered with EtOAc through a short silica gel column with EtOAc. After concentration under reduced pressure, the mixture was purified by column chromatography (silica gel, 10-60% EtOAc in heptanes) The product containing fractions where combined and separated by preparative TLC (silica gel, EtOAc:heptane = 4:3) to afford 1.9 mg (4%) of **1.475** as white solid.

^{13}C-NMR data for **1.475** (isolated) in $CDCl_3$[166]	**^{13}C-NMR data** for **1.475** (herein prepared) in $CDCl_3$
145.1 (C_{13})	145.1 (C)
121.9 (C_{12})	121.8 (CH)
79.0 (C_3)	78.9 (CH)
69.2 (C_6)	69.1 (CH)
60.5 (C_5)	60.4 (CH)
47.4 (C_9)	47.3 (CH)
47.3 (C_{18})	47.3 (CH)
47.0 (C_{18})	46.9 (CH_2)
45.2 (C_7)	45.2 (CH_2)
42.1 (C_8)	42.0 (C)
41.5 (C_{14})	41.4 (C)
39.3 (C_{10})	39.2 (C)
39.3 (C_4)	39.2 (C)
38.6 (C_1)	38.5 (CH_2)
37.3 (C_{22})	37.2 (CH_2)
34.9 (C_{21})	34.9 (CH_2)
33.6 (C_{29})	33.5 (CH_3)
32.7 (C_{17})	32.7 (C)
31.3 (C_{20})	31.2 (C)
31.2 (C_{23})	31.1 (CH_3)
28.6 (C_{28})	28.5 (CH_3)
27.1 (C_2)	27.0 (CH_2)
27.0 (C_{16})	26.9 (CH_2)
26.4 (C_{15})	26.3 (CH_2)
26.2 (C_{27})	26.1 (CH_3)
23.9 (C_{30})	23.8 (CH_3)
23.9 (C_{11})	23.8 (CH_2)

18.4 (C_{26})	18.3 (CH_3)
16.6 (C_{25})	16.5 (CH_3)
15.9 (C_{24})	15.9 (CH_3)

3.7 SYNTHESIS OF CICUTOXIN AND VIROL A

Synthesis of Weinreb Amide

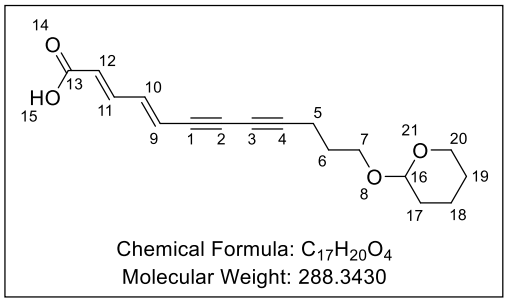
2-(3-Iodopropoxy)tetrahydro-2H-pyran (**2.054**)

3-Iodopropan-1-ol (1.0 equiv., 0.48 mL, 5.0 mmol), pyridinium p-toluenesulfonate (PPTS) (0.15 equiv., 188.0 mg, 0.75 mmol) and 3, 4-Dihydro-2H-pyrane (DHP) (1.5 equiv., 0.68 mL, 7.5 mmol) were dissolved in dry DCM (10 mL) in a 25 mL round bottom flask. After purging with Argon, the mixture was stirred for 1.5 h at room temperature while covered with aluminium foil. The mixture was concentrated under reduced pressure and loaded directly on a column (silica gel, 0-3 % Et_2O in heptane) to give the product **2.054** in 88% yield. The procedure was adapted[225] and the spectral data is in accordance with the literature. [226] **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 4.62-4.59 (m, 1H), 3.91-3.84 (m, 1H), 3.81 (dt, *J* = 10.0, 5.9 Hz, 1H), 3.56-3.49 (m, 1H), 3.54 (dt, *J* = 10.0, 5.9 Hz, 1H), 3.30 (td, *J* = 6.9, 1.1 Hz, 2H), 2.13-2.06 (m, 2H), 1.86-1.76 (m, 1H), 1.76-1.66 (m, 1H), 1.62-1.48 (m, 4H) ppm.

2-(Hepta-4,6-diyn-1-yloxy)tetrahydro-2H-pyran (**2.034**)

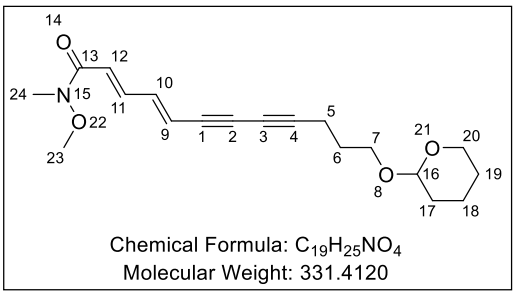
1,4-Bis-(trimethylsilyl)-1,3-budadiyne (1.0 equiv., 5.15 g, 5.3 mL, 26.5 mmol) was dissolved in dry THF (50 mL) in a flame-dried Schlenk tube. MeLi (1.6 M in ether, 1.0 equiv., 16.6 mL, 26.5 mmol) was added dropwise at 0 °C and stirred for 3.5 hours at room temperature. Iodide **2.054** (1.0 equiv., 7.16 g, 26.5 mmol), dissolved in hexamethylphosphoramide (HMPA) (2.0 equiv., 9.2 mL, 53 mmol), was added dropwise and stirred overnight at room temperature. The mixture was quenched with brine (50 mL) and extracted with DCM (2 x 100 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was redissolved in dry THF (50 mL), and tetra-n-butylammonium fluoride (TBAF) (1 M in THF, 3.0 equiv., 79.5 mL, 79.5 mmol) was added slowly at room temperature and stirred for 30 min. After removal of the solvent *in vacuo*, the crude product was dissolved in DCM (100 mL) and washed with water (100 mL). After extracting the aqueous layer with DCM (100 mL), the combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. Column chromatography (silica gel, 0-3% EtOAc in heptane) afforded 3.67 g (72%) of the product **2.034** as a red oil. The spectral data is in accordance with the literature. [201] **^{1}H-NMR (600 MHz, $CDCl_3$):** δ = 4.61-4.57 (m, 1H), 3.91-3.78 (m, 2H), 3.56-3.44 (m, 2H), 3.40 (bt, *J* = 7.0 Hz, 2H), 1.95 (t, *J* = 1.2 Hz, 1H), 1.87-1.79 (m, 3H), 1.75-1.62 (m, 1H), 1.61-1.48 (m, 4H) ppm.

(2E,4E)-12-((Tetrahydro-2H-pyran-2-yl)oxy)dodeca-2,4-dien-6,8-diynoic acid (**2.057**)



Diyne **2.034** (2 eq, 700 mg, 3.64 mmol) was dissolved in dry THF (4.0 mL) in a flame-dried Schlenk tube and cooled to -40 °C. MeLi (1.6 M in ether, 2 eq, 2.43 mL, 3.64 mmol) was added and the mixture was stirred for 30 minutes, before added *via* canula to a solution of CuCN (1 eq, 163.0 mg, 1.82 mmol) dry THF (4.0 mL) at -78 °C, which was stirred for 1 h at -78 °C. Lactone **2.040** (0.1 M in ether, 1 eq, 18.2 mL, 1.82 mmol) was added dropwise and the mixture was allowed to slowly warm up to room temperature. The slurry was quenched after warming to room temperature with water (80 mL), acidified to pH 2 with 1 M HCl and extracted with DCM (2 x 100 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The crude mixture was allowed to stay at room temperature for 1 day. Purification by column chromatography (silica, EtOAc/heptane/HOAc = 20:77:3) afforded 429 mg (82%) of **2.057** as white solid. **^{1}H-NMR (600 MHz, $CDCl_3$):** δ = 7.23 (dd, *J* = 15.3, 11.6 Hz, 1H, H_{11}), 6.76 (dd, *J* = 15.4, 11.5 Hz, 1H, H_{10}), 6.01 (d, *J* = 15.5 Hz, 1H, H_9), 5.97 (d, *J* = 15.3 Hz, 1H, H_{12}), 4.60 (m, 1H, H_{16}), 3.89-3.79 (m, 2H, $H_{7a,20a}$), 3.54-3.50 (m, 1H, H_{20b}), 3.48 (dt, *J* = 9.9, 6.1 Hz, 1H, H_{7b}), 2.50 (bt, *J* = 7.0 Hz, 2H, $H_{5a,b}$), 1.88-1.78 (m, 3H, $H_{6a,b,18a}$), 1.74-1.68 (m, 1H, H_{17a}), 1.62-1.49 (m, 4H, $H_{19a,b,17b,18b}$) ppm. **^{13}C-NMR (150 MHz, $CDCl_3$):** δ = 169.7 (C_{13}), 144.9 (C_{11}), 140.9 (C_{10}), 122.4 (C_{12}), 119.7 (C_9), 99.0 (C_{16}), 88.0 (C_4), 81.7 (C_2), 73.4 (C_1), 65.8 (C_7), 65.4 (C_3), 62.4 (C_{20}), 30.8 (C_{17}), 28.5 (C_6), 25.6 (C_{19}), 19.7 (C_{18}), 16.9 (C_5) ppm. **FT-IR (neat, cm^{-1}):** 2950, 2925, 2854, 1673, 1618, 1344, 1275, 1263, 1138, 1075, 1034, 1001, 764, 751, 528. **HRMS (ESI) (m/z):** calculated for $[M - H^+]^-$ $(C_{17}H_{19}O_4)^-$: 287.1289, found: 287.1281.

(*2E,4E*)-*N*-Methoxy-*N*-methyl-12-((tetrahydro-2H-pyran-2-yl)oxy)dodeca-2,4-dien-6,8-diynamide (**2.059**)

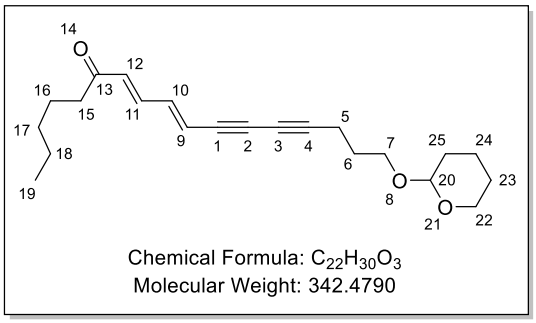


Carboxylic acid **2.057** (1.0 equiv., 270 mg, 0.936 mmol) was dissolved in dry DCM (5 mL) in a flame-dried Schlenk tube. N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDCI) (1.2 equiv., 215 mg, 1.12 mmol) and 1-Hydroxybenzotriazole hydrate (HOBt) (88% w/w, 1.2 equiv., 172 mg, 1.12 mmol) was added at room temperature and the mixture stirred for 30 min. After addition of *N,O*-Dimethylhydroxylamine hydrochloride (1.5 equiv., 137 mg, 1.40 mmol) and triethylamine (TEA) (2.0 equiv., 0.26 mL, 1.87

mmol), the mixture was kept stirring for 12 hours and quenched with sat. $NaHCO_3$ (aq.) (15 mL). The mixture was extracted with DCM (2 x 15 mL), the combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (silica gel, 50% EtOAc in heptane) afforded 245 mg (79%) of the Weinreb amide **2.059** as a yellow oil. **^{1}H-NMR (600 MHz, $CDCl_3$):** δ = 7.31 (dd, *J* = 15.1, 11.4 Hz, 1H, H_{11}), 6.80 (dd, *J* = 15.5, 11.5 Hz, 1H, H_{10}), 6.55 (d, *J* = 15.2 Hz, 1H, H_{12}), 5.96 (d, *J* = 15.5 Hz, 1H, H_9), 4.61-4.58 (m, 1H, H_{16}), 3.89-3.79 (m, 2H, $H_{7a,20a}$), 3.71 (s, 3H, H_{23}), 3.54-3.50 (m, 1H, H_{20b}), 3.48 (dt, *J* = 9.9, 6.1 Hz, 1H, H_{7b}), 3.26 (s, 3H, H_{24}), 2.49 (bt, *J* = 7.0 Hz, 2H, $H_{5a,b}$), 1.88-1.78 (m, 3H, $H_{6a,b,18a}$), 1.74-1.68 (m, 1H, H_{17a}), 1.61-1.49 (m, 4H, $H_{19a,b,17b,18b}$) ppm. **^{13}C-NMR (150 MHz, $CDCl_3$):** δ = 166.5 (C_{13}), 142.0 (C_{10}), 141.6 (C_{11}), 121.8 (C_{12}), 117.7 (C_9), 99.0 (C_{16}), 87.2 (C_4), 80.5 (C_2), 73.8 (C_1), 65.8 (C_7), 65.5 (C_3), 62.4 (C_{20}), 62.1 (C_{23}), 32.6 (C_{24}), 30.8 (C_{17}), 28.6 (C_6), 25.6 (C_{19}), 19.7 (C_{18}), 16.9 (C_5) ppm. **FT-IR (neat, cm^{-1}):** 2938, 2871, 2225, 1651, 1607, 1462, 1440, 1416, 1380, 1261, 1202, 1179, 1136, 1120, 1075, 1034, 996, 869, 816. **HRMS (ESI) (m/z):** calculated for $[M + Na^+]^+$ $(C_{19}H_{25}NNaO_4)^+$: 354.1679, found: 354.1676.

Synthesis of Virol A

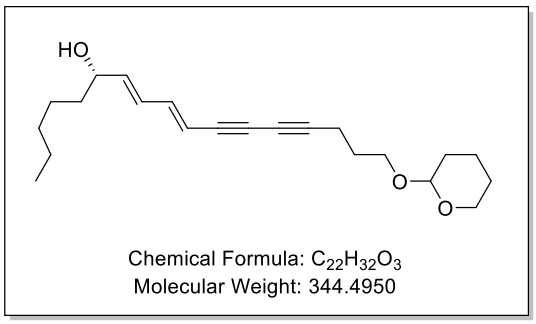
(7E,9E)-17-((Tetrahydro-2H-pyran-2-yl)oxy)heptadeca-7,9-dien-11,13-diyn-6-one (**2.061**)



A flame-dried Schlenk flask was charged with 1-Iodopentane (3 eq, 26.1 µL, 0.2 mmol) and dry Et_2O (1 mL). After cooling to -78 °C, tert-BuLi (1.7 M in pentane, 6 eq, 0.235 mL, 0.4 mmol) was added dropwise, and the mixture was stirred for 1 h at -78 °C. A separate flame-dried Schlenk was charged with Weinreb amide **2.059** (1 eq, 22.1 mg, 0.067 mmol), LiCl (5 eq, 14.1 mg, 0.333 mmol) and dry Et_2O (0.5 mL) and cooled to -40 °C. The Penzyllithium solution was added via canula and the mixture was stirred for 45 minutes. The mixture was quenched with brine and water (5 mL, 1:1) and extracted with DCM (2 x 10 mL). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. Purification by prepTLC (Alox, 30% EtOAc in heptane) afforded 15.2 mg (67%) of desired ketone, containing 8% of isomerization product. **^{1}H-NMR (major isomer) (600 MHz, $CDCl_3$):** δ = 7.12 (dd, *J* = 15.5, 11.3 Hz, 1H, H_{11}), 6.74 (dd, *J* = 15.4, 11.3 Hz, 1H, H_{10}), 6.23 (bd, *J* = 15.4 Hz, 1H, H_{12}), 6.00 (d, *J* = 15.5 Hz, 1H, H_9), 4.61-4.58 (m, 1H, H_{20}), 3.88-3.78 (m, 2H, $H_{7a,22a}$), 3.54-3.45 (m, 2H, $H_{7b,22b}$), 2.55 (t, J = 7.44 Hz, 2 H, H_{15}), 2.47 (bt, J = 6.84 Hz, 2H, H_5), 1.89-1.78 (m, 3 H, $H_{6,24a}$), 1.74-1.68 (m, 1H, H_{25a}), 1.65-1.48 (m, 6H, $H_{16,23,24b,25b}$), 1.36-1.24 (m, 4H, $H_{17,18}$), 0.89 (t, *J* = 7.1 Hz, 3H, H_{19}) ppm. **^{1}H-NMR (only clear signals of minor isomer) (600 MHz, $CDCl_3$):** δ = 7.57 (ddd,

J = 15.6, 11.4, 0.8 Hz, 1H), 6.58 (app. t, *J* = 11.1 Hz, 1H), 5.83 (d, *J* = 10.5 Hz, 1H) ppm. **^{13}C-NMR (major isomer) (150 MHz, $CDCl_3$):** δ = 200.5 (C_{13}), 141.9 (C_{10}), 140.2 (C_{11}), 131.6 (C_{12}), 119.0 (C_9), 99.0 (C_{20}), 87.8 (C_4), 81.2 (C_2), 73.7 (C_1), 65.8 (C_7), 65.4 (C_3), 62.4 (C_{22}), 41.3 (C_{15}), 31.6 (C_{17}), 30.8 (C_{25}), 28.5 (C_6), 25.6 (C_{23}), 24.0 (C_{16}), 22.6 (C_{18}), 19.6 (C_{24}), 16.9 (C_5), 14.1 (C_{19}) ppm. **^{13}C-NMR (only clear signals of minor isomer) (150 MHz, $CDCl_3$):** δ = 201.2,140.6, 137.7, 132.7, 116.7, 88.1, 84.3, 71.3, 40.7 ppm.

(6S,7E,9E)-17-((Tetrahydro-2H-pyran-2-yl)oxy)heptadeca-7,9-dien-11,13-diyn-6-ol (**2.063**)



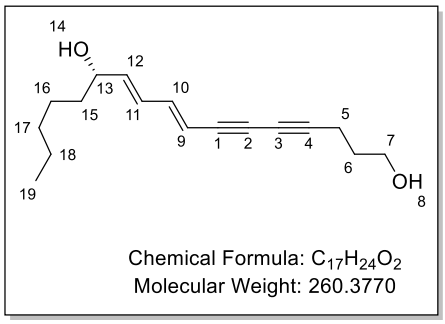
A flame-dry Schlenk tube was charged with a solution of *(R)-(+)*-2-Methyl-CBS-oxazaborolidine [(*R*)-CBS] (2.0 equiv., 1 M in THF, 76 µL, 0.076 mmol), then a solution of ketone **2.061** (*(E):(Z)* = 9:1, 1.0 equiv., 13.0 mg, 0.038 mmol) in dry THF (0.5 mL) was added. The mixture stirred at -50 °C for 10 min. Then BH_3-Me_2S complex (2.0 equiv., 7 µL, 0.076 mmol) was added. The mixture was stirred vigorously at -50 °C for 1.5 hours. After quenching with sat. NH_4Cl (aq.) (1 mL), the aqueous layer was extracted with DCM (2 x 4 mL), the combined organic layers were dried with $MgSO_4$ and filtered. Concentration under reduced pressure and column chromatography (silica gel, 50% EtOAc in heptane) afforded 10.0 mg (76%) of the desired product **2.063** as a colourless oil. The spectral data is in accordance with the literature. [201] **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 6.67 (dd, *J* = 15.6, 10.9 Hz, 1H), 6.29 (dd, *J* = 15.3, 10.9 Hz, 1H), 5.84 (dd, *J* = 15.2, 6.4 Hz, 1H), 5.61 (d, *J* = 15.4 Hz, 1H), 4.61-4.58 (m, 1H), 4.21-4.14 (m, 1H), 3.90-3.78 (m, 2H), 3.55-3.43 (m, 2H), 2.47 (bt, *J* = 7.0 Hz, 2H), 1.90-1.65 (m, 4H), 1.64-1.19 (m, 13H), 0.89 (t, *J* = 6.8 Hz, 3H) ppm. Specific rotation is in accordance with the literature: $[\alpha]_D$ = +9.6 (c = 0.5, $CHCl_3$), $[\alpha]_D$ (Lit.) [201] = +10.8 (c = 1.1, $CHCl_3$);

Determination of enantiomeric excess using Mosher ester method:

A dry schlenk tube was charged with *(R)-(+)*-α-Methoxy-α-(trifluoromethyl)phenylacetic acid (9.9 mg, 41.8 µmol) and dissolved in dry pentane (1.5 mL). $(COCl)_2$ (697 mmol, 59 µL) was added, followed by addition of dry DMF (1 drop). The mixture was stirred for 30 minutes at room temperature and filtered through a plug of cotton. Removal of the solvent to 100 mbar (40 °C waterbath) afforded the acid chloride, which was redissolved in $CDCl_3$ (0.7 mL). After addition of triethylamine (5.8 µL, 41.8 µmol), the solution was added to 3.6 mg of crude alcohol. Addition of DMAP (8.5 mg, 0.7 µmol) led to completion of the ester formation within 15 minutes. ^{1}H-NMR data of olefinic signals of Mosher ester:

^{1}H NMR (700 MHz, $CDCl_3$): δ = 6.56 (dd, *J* = 15.6, 10.9 Hz, 1H), 6.14 (dd, *J* = 15.2, 10.9 Hz, 1H), 5.64 (dd, *J* = 15.2, 7.1 Hz, 1H), 5.54 (d, *J* = 15.6 Hz, 1H) ppm.

Virol A (**2.004**)



THP-protected alcohol **2.063** (1.0 equiv., 8.7 mg, 25.3 µmol) and PPTS (1.0 equiv., 6.4 mg, 25.3 µmol) were dissolved in MeOH (1 mL) in a glass vial and stirred at 35 °C for 2 h. After removing most of the methanol under reduced pressure, the mixture was diluted with ether (5 mL) and washed with NH_4Cl sat. (5 mL). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (silica prewashed with 5% Et_3N in DCM, elute remaining starting material (2.1 mg) with DCM, elute product with EtOAc) affords 4.7 mg (72%) of Virol A **(2.004)** as a colourless oil. The spectral data is in accordance with the literature. **^{1}H-NMR (600 MHz, $CDCl_3$):** δ = 6.68 (dd, *J* = 15.6, 10.9 Hz, 1H), 6.27 (dd, *J* = 15.2, 11.0 Hz, 1H), 5.84 (dd, *J* = 15.2, 6.3 Hz, 1H), 5.60 (d, *J* = 15.6 Hz, 1H), 4.20-4.14 (m, 1H), 3.78-3.74 (m, 2H), 2.48 (t, *J* = 6.8 Hz, 2 H), 1.80 (app. pent, *J* = 6.5 Hz, 2H), 1.56 (s, 2H), 1.55-1.48 (m, 2H), 1.39-1.26 (m, 6H), 0.88 (t, J = 6.9 Hz, 3H) ppm. **FT-IR (neat, cm^{-1}):** 3343, 3319, 2954, 2929, 2859, 1463, 1426, 1348, 1292, 1219, 1054, 984, 772. **HRMS (ESI) (m/z):** calculated for $[M + Na^+]^+$ $(C_{17}H_{24}ONa)^+$: 283.1669, found: 283.1665. **$[\alpha]_D^{20}$** = +12.5° (c = 0.25, MeOH), **$[\alpha]_D^{20}$** (Lit.) = +15.4 (c = 1.1, MeOH) [201]

^{13}C-NMR (125 MHz, $CDCl_3$) (isolated)[185]	**^{13}C-NMR (150 MHz, $CDCl_3$) (synthetic)**
143.8 (C10)	144.0
140.1 (C12)	140.2
129.0 (C11)	129.1
110.5 (C9)	110.3
84.7 (C4)	84.8
77.4 (C2)	76.9
72.5 (C1)	74.7
72.3 (C13)	72.4
65.8 (C3)	65.9
61.4 (C7)	61.6
37.2 (C15)	37.3
31.7 (C17)	31.8
30.9 (C6)	31.0
25.0 (C16)	25.1
22.6 (C18)	22.7
16.2 (C5)	16.3
14.0 (C19)	14.2

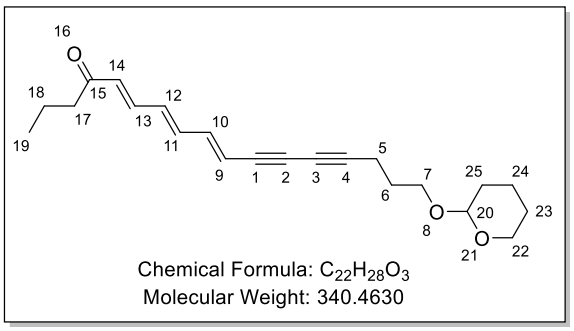
(7E,9E)-17-((Tetrahydro-2H-pyran-2-yl)oxy)heptadeca-7,9-dien-11,13-diyn-6-ol (**2.063** rac.)

Mg powder (20 eq, 54.3 mg, 2.23 mmol) was covered in a flame-dried Schlenk tube with dry Et_2O (0.2 mL). Dropwise addition of 1-bromopentane (10 eq, 138 µL, 1.12 mmol), dissolved in 0.5 mL Et_2O), at room temperature led to an exothermic reaction. After subsiding, dry Et_2O (0.5 mL) was added and the mixture was kept at reflux for 15 min. The metallic solution was added to a solution of weinreb amide **2.059** (1 eq, 17 mg, 0.05 mmol) in dry Et_2O (0.5 mL) at 0 °C and kept stirring for 15 min followed by 30 minutes at room temperature. The paste-like residue was suspended in NH_4Cl sat. (10 mL) and extracted with DCM (2 x 10 mL). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. The crude ketone was redissolved in ethanol (abs., 2 mL) in a flame-dried Schlenk tube. $NaBH_4$ was added and the mixture was stirred for 2 h at room temperature. The mixture was quenched with NH_4Cl sat. (5 mL) and extracted with DCM (2 x 10 mL). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. Purification by preparative TLC (Alox, 40% EtOAc in heptane) afforded 8.7 mg (23%) of racemic alcohol (**2.063 rac.**) as a colorless oil.

Racemic Virol A (**2.004**) was prepared from **(rac)-2.063** according to the procedure described for (*S*)-Virol A.

Synthesis of Cicutoxin

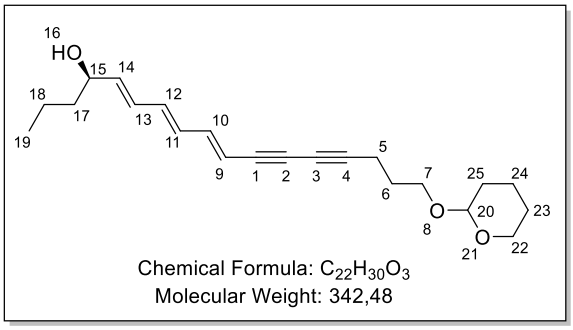
(5E,7E,9E)-17-((Tetrahydro-2H-pyran-2-yl) oxy) heptadeca-5,7,9-trien-11,13-diyn-4-one (**2.065**)



The following reaction was performed in the shadows, since light may cause double bond isomerization of the following intermediates: A flame-dried Schlenk was charged with Weinreb amide **2.059** (1.0 equiv., 38.3 mg, 0.116 mmol) and dry DCM (1 mL). After cooling to -78 °C, a solution of diisobutylaluminum hydride (DIBAL-H) in DCM (2.0 equiv., 1 M in DCM, 0.23 mL, 0.23 mmol) was added and the mixture was stirred for 1.5 h at -78 °C. After quenching with EtOAc (0.5 mL), the solution was allowed to warm up to room temperature. Na-K-tartrate sat. (10 mL) and water (5 mL) was added, and the aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated to give the crude aldehyde as yellow oil. A flame-dried Schlenk tube was charged with phosphonate (2.0 equiv., 51.6 mg, 0.232 mmol) in dry THF (0.5 mL). Anhydrous barium hydroxide (4.0 equiv., 79.5 mg, 0.464 mmol) was added and the mixture was stirred for 30 minutes at room

temperature. A solution of crude aldehyde in THF (1 mL) and water (25 µL) was added dropwise and stirred for 30 minutes at room temperature. Water (10 mL) was added and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel prewashed with Et_3N/EtOAc/heptane 5:20:80, elution with 20% EtOAc in heptane) afforded 20.6 mg (52%) of product **2.065** as a yellow oil and single isomer. **^{1}H-NMR (600 MHz, $CDCl_3$):** δ = 7.15 (dd, *J* = 15.5, 11.3 Hz, 1H, H_{13}), 6.74 (dd, *J* = 15.4, 11.3 Hz, 1H, H_{10}), 6.60 (dd, *J* = 14.8, 11.4 Hz, 1H, H_{11}), 6.40 (dd, *J* = 14.8, 11.3 Hz, 1H, H_{12}), 6.23 (bd, *J* = 15.4 Hz, 1H, H_{14}), 5.79 (d, *J* = 15.4 Hz, 1H, H_9), 4.60-4.58 (m, 1H, H_{20}), 3.88-3.79 (m, 2H, $H_{7a,22a}$), 3.54-3.44 (m, 2H, $H_{7b,22b}$), 2.53 (t, J = 7.4 Hz, 2 H, H_{17}), 2.47 (bt, J = 7.1 Hz, 2H, H_5), 1.87-1.78 (m, 3 H, $H_{6,24a}$), 1.74-1.68 (m, 1H, H_{25a}), 1.65 (aqq. hex, *J* = 7.4 Hz, 2H, H_{18}), 1.60-1.49 (m, 4H, $H_{23,24b,25b}$), 1.25 (bs, 2H, OH), 0.94 (t, *J* = 7.4 Hz, 3H, H_{19}) ppm. **^{13}C-NMR (150 MHz, $CDCl_3$):** δ = 200.5 (C_{15}), 143.1 (C_{10}), 141.1 (C_{13}), 139.6 (C_{11}), 133.4 (C_{12}), 131.1 (C_{14}), 114.5 (C_9), 99.0 (C_{20}), 87.2 (C_4), 80.3 (C_2), 74.4 (C_1), 65.8 (C_7), 65.7 (C_3), 62.4 (C_{22}), 43.0 (C_{17}), 30.8 (C_{25}), 28.6 (C_6), 25.6 (C_{23}), 19.6 (C_{24}), 17.9 (C_{18}), 16.9 (C_5), 14.0 (C_{19}) ppm. **FT-IR (neat, cm^{-1})**: 2932, 2873, 1682, 1661, 1602, 1563, 1366, 1261, 1201, 1183, 1156, 1136, 1121, 1062, 1035, 1020, 1001. **HRMS (ESI) (m/z):** calculated for $[M + Na^+]^+$ $(C_{22}H_{28}O_3Na)^+$: 363.1931, found: 363.1931.

(4R, 5E, 7E, 9E)-17-((Tetrahydro-2H-pyran-2-yl) oxy) heptadeca-5, 7, 9-trien-11, 13-diyn-4-ol (**2.067**)



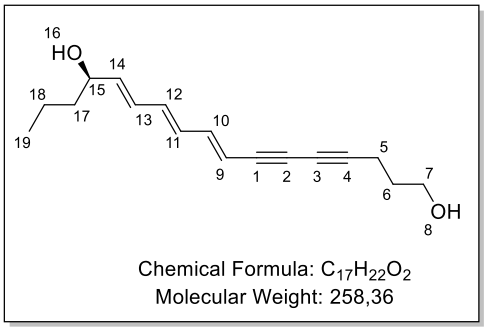
A flame-dry Schlenk tube was charged with a solution of *(S)*-2-Methyl-CBS-oxazaborolidine [(*S*)-CBS] (2.0 equiv., 21.2 mg, 0.076 mmol), then a solution of ketone **2.065** (1.0 equiv., 13.0 mg, 0.038 mmol) in dry THF (0.5 mL) was added. The mixture stirred at -50 °C for 10 min. Then BH_3-Me_2S complex (2.0 equiv., 7.0 µL, 0.076 mmol) was added. The mixture was stirred vigorously at -50 °C for 1.5 hours. After quenching with sat. NH_4Cl (aq.) (1 mL), the aqueous layer was extracted with DCM (2 x 4 mL), the combined organic layers were dried with $MgSO_4$ and filtered. Concentration under reduced pressure and column chromatography (silica gel, 50% EtOAc in heptane) afforded 10.0 mg (76%) of the desired product **2.067** as a colourless oil. **^{1}H-NMR (600 MHz, $CDCl_3$):** δ = 6.70 (dd, *J* = 15.4, 10.6 Hz, 1H, H_{10}), 6.33-6.21 (m, 3H, $H_{11,12,13}$), 5.81 (dd, *J* = 15.2, 6.5 Hz, 1H, H_{14}), 5.60 (d, *J* = 15.4 Hz, 1H, H_9), 4.60-4.58 (m, 1H, H_{20}), 4.22-4.16 (m, 1H, H_{15}), 3.88-3.79 (m, 2H, $H_{7a,22a}$), 3.54-3.45 (m, 2H, $H_{7b,22b}$), 2.47 (btd, *J* = 7.1, 3.1 Hz, 2 H, H_5), 1.87-1.78 (m, 3 H, $H_{6,24a}$), 1.74-1.67 (m, 1H, H_{25a}), 1.61-1.49 (m, 6H, $H_{23,24b,25b,17}$), 1.47 (d, *J* = 4.2 Hz, OH), 1.46-1.31 (m,

2H, H_{18}), 0.93 (t, *J* = 7.3 Hz, 3H, H_{19}) ppm. **^{13}C-NMR (150 MHz, $CDCl_3$):** δ = 144.3 (C_{10}), 139.3 (C_{14}), 135.4 (C_{12}), 131.7 (C_{11}), 129.9 (C_{13}), 110.2 (C_9), 99.0 (C_{20}), 85.7 (C_4), 77.9 (C_2), 75.0 (C_1), 72.4 (C_{26}), 65.9 (C_7), 65.8 (C_3), 62.4 (C_{22}), 39.5 (C_{28}), 30.8 (C_{25}), 28.7 (C_6), 25.6 (C_{23}), 19.7 (C_{24}), 18.7 (C_{29}), 16.8 (C_5), 14.1 (C_{30}) ppm. **FT-IR (neat, cm^{-1}):** 3422, 2954, 2930, 2871, 1455, 1441, 1354, 1287, 1200, 1157, 1136, 1121, 1073, 1063, 1034, 1022, 995. **HRMS (ESI) (m/z):** calculated for $[M + Na^+]^+$ $(C_{22}H_{30}O_3Na)^+$: 365.2087, found: 365.2096.

Determination of enantiomeric excess using Mosher ester method:

A dry schlenk tube was charged with *(S)*-α-Methoxy-α-(trifluoromethyl)phenylacetic acid (5.0 equiv., 12.0 mg, 51.1 µmol) and dissolved in dry pentane (1.5 mL). $(COCl)_2$ (25 equiv., 22 µL, 0.255 mmol) was added, followed by addition of dry DMF (1 drop). The mixture was stirred for 30 minutes at room temperature and filtered through a plug of cotton. Removal of the solvent to 100 mbar (40 °C waterbath) afforded the acid chloride. Then the above alcohol **2.067** (1.0 equiv., 3.5 mg, 10.2 µmol) which was dissolved in DCM (0.7 mL) was added to the acid chloride, followed by the addition of DMAP (1.0 equiv., 1.2 mg, 10.2 µmol) and triethylamine (6.0 equiv., 8.6 µL, 61.3 µmol). The mixture stirred vigorously at room temperature for 30 min leading to the complete consumption of alcohol **11**. Then the solvent was removed, flash column chromatography (silica gel, 20% EtOAc in heptane) gave the mosher ester (5.0 mg, 88%) as a colorless oil. (NMR-data of olefinic signals of Mosher ester: **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 6.71-6.64 (m, 1H), 6.28-6.16 (m, 3H), 5.66-5.61 (m, 2H), 5.50 (dd, *J* = 13.7, 7.0 Hz, 1H) ppm.

(R)-Cicutoxin (**2.003**)



To a solution of alcohol **2.067** (1.0 equiv., 7.0 mg, 20.4 µmol) in MeOH (2.0 mL) in a glass vial covered by aluminium foil was added p-toluenesulfonic acid (PTSA) (0.5 equiv., 1.8 mg, 10.2 µmol) and the mixture was stirred for 1.5 hours at RT. The crude mixture was quenched by sat. $NaHCO_3$ (aq.) (1.0 mL), after concentrating, the water phase was extracted by EtOAc (3 x 10 mL), the combined organic phase was washed by brine, dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel prewashed with Et_3N/EtOAc/heptane 5:20:80, elution with 20% EtOAc in heptane) afforded 2.8 mg (53%) Cicutoxin as a colourless oil. **^{1}H-NMR (600 MHz, $CDCl_3$):** δ = 6.70 (dd, *J* = 15.4, 10.7 Hz, 1H, H_{10}), 6.37-6.21 (m, 3H, $H_{11,12,13}$), 5.82 (dd, *J* = 15.2, 6.6 Hz, 1H, H_{14}), 5.60

(d, *J* = 15.4 Hz, 1H, H_9), 4.22-4.16 (m, 1H, H_{15}), 3.76 (bq, *J* = 5.8 Hz, 2H, H_7), 2.49 (bt, *J* = 7.0 Hz, 2 H, H_5), 1.81 (app. pent., J = 6.5 Hz, 2 H, H_6), 1.60-1.48 (m, 2H, H_{17}), 1.46 (d, *J* = 4.2 Hz, OH_{16}), 1.45-1.33 (m, 3H, $H_{18,}$ OH_8), 0.93 (t, *J* = 7.3 Hz, 3H, H_{19}) ppm. **^{13}C-NMR (150 MHz, $CDCl_3$):** δ = 144.4 (C_{10}), 139.4 (C_{14}), 135.4 (C_{12}), 131.7 (C_{11}), 129.9 (C_{13}), 110.1 (C_9), 85.3 (C_4), 77.7 (C_2), 75.2 (C_1), 72.4 (C_{15}), 66.0 (C_3), 62.4 (C_7), 39.5 (C_{17}), 31.1 (C_6), 18.7 (C_{18}), 16.4 (C_5), 14.1 (C_{19}) ppm. **FT-IR (neat, cm^{-1}):** 3348, 2956, 2930, 2871, 1061, 995, 751. **HRMS (ESI) (m/z):** calculated for $[M + Na^+]^+$ $(C_{17}H_{22}O_2Na)^+$: 281.1512, found: 281.1512. $[\alpha]_D$ = -17.1 (c = 0.17, MeOH), $[\alpha]_D$ (Lit.) = -14.9° (c = 1.12, MeOH)[17]

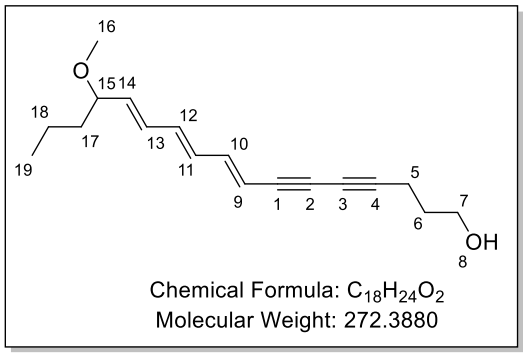
^{13}C-NMR (125 MHz, $CDCl_3$) (isolated)[185]	**^{13}C-NMR (150 MHz, $CDCl_3$) (synthetic)**
144.4 (C10)	144.4
139.3 (C14)	139.3
135.4 (C12)	135.4
131.6 (C11)	131.7
129.8 (C13)	129.9
110.0 (C9)	110.1
85.3 (C4)	85.3
77.7 (C2)	77.7
75.1 (C1)	75.2
72.3 (C15)	72.4
65.9 (C3)	66.0
61.4 (C7)	62.4
39.4 (C17)	39.5
31.0 (C6)	31.1
18.7 (C18)	18.7
16.3 (C5)	16.4
14.0 (C19)	14.1

(5E,7E,9E)-17-((Tetrahydro-2H-pyran-2-yl)oxy)heptadeca-5,7,9-trien-11,13-diyn-4-ol (**2.003 rac.**)

To a solution of ketone **2.065** (1.0 equiv., 17.0 mg, 50 µmol) in MeOH (1 mL) in a glass vial, covered with aluminium foil, was added $NaBH_4$ (1.5 equiv., 2.8 mg, 0.26 mmol) and the mixture was stirred for 15 minutes at 0 °C. Then the mixture was carefully quenched by addition of sat. NH_4Cl (aq.) (2 mL), and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed by brine and dried with $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel prewashed with Et_3N/EtOAc/heptane 5:20:80, elution with 30% EtOAc in heptane) afforded **2.067 rac.** (14.2 mg, 83%) as a colorless oil.

Racemic Cicutoxin was prepared according to the procedure described for (R)-Cicutoxin.

(8E,10E,12E)-14-Methoxyheptadeca-8,10,12-trien-4,6-diyn-1-ol (**2.068**)



To a solution of alcohol **2.067** (1.0 equiv., 2.1 mg, 6.1 µmol) in MeOH (0.5 mL) in a glass vial covered by aluminium foil was added pyridinium p-toluenesulfonate (PPTS) (1.0 equiv., 1.5 mg, 6.1 µmol) and the mixture was stirred for 2 hours at 45 °C. The crude mixture was quenched by sat. $NaHCO_3$ (aq.) (1.0 mL), after concentrating, the water phase was extracted by EtOAc (3 x 10 mL), the combined organic phase was washed by brine, dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel prewashed with Et_3N/EtOAc/heptane 5:20:80, elution with 20% EtOAc in heptane) afforded **2.068** 1.0 mg (60%) as a colorless oil. **^{1}H-NMR (600 MHz, $CDCl_3$):** δ = 6.71 (dd, *J* = 15.4, 10.8 Hz, 1H, H_{10}), 6.33 (dd, *J* = 14.8, 10.6 Hz, 1H, H_{12}), 6.24 (dd, *J* = 14.8, 11.0 Hz, 1H, H_{11}), 6.20 (dd, *J* = 15.2, 10.7 Hz, 1H, H_{13}), 5.65 (dd, *J* = 15.2, 7.9 Hz, 1H, H_{14}), 5.61 (d, *J* = 15.4 Hz, 1H, H_9), 3.78-3.74 (bq, *J* = 5.8 Hz, 2H, H_7), 3.59 (bq, J = 7.0 Hz, 1H, H_{15}), 3.26 (s, 3H, H_{16}), 2.49 (td, *J* = 7.0, 0.7 Hz, 2 H, H_5), 1.81 (app. pent., *J* = 6.5 Hz, 2 H, H_6), 1.62-1.55 (m, 1H, H_{17a}), 1.48-1.41 (m, 1H, H_{17b}), 1.40-1.29 (m, 3H, $H_{18,}$ OH_8), 0.90 (t, *J* = 7.3 Hz, 3H, H_{19}) ppm. **^{13}C-NMR (150 MHz, $CDCl_3$):** δ = 144.5 (C_{10}), 137.6 (C_{14}), 135.4 (C_{12}), 131.8 (C_{13}), 131.6 (C_{11}), 110.0 (C_9), 85.3 (C_4), 81.9 (C_{15}), 77.7 (C_2), 75.2 (C_1), 66.0 (C_3), 61.6 (C_7), 56.5 (C_{16}), 37.8 (C_{17}), 31.1 (C_6), 18.7 (C_{18}), 16.4 (C_5), 14.2 (C_{19}) ppm. **FT-IR (neat, cm^{-1}):** 3366, 2958, 2930, 2871, 1111, 1084, 996, 764, 750. **HRMS (ESI) (m/z):** calculated for $[M + Na]^+$ $(C_{18}H_{24}O_2Na)^+$: 295.1669, found: 295.1662.

4 LIST OF ABBREVIATIONS

acac	Acetylacetonate
AQ	8-Aminoquinoline
BQ	Benzoquinone
CAN	Ceric ammonium nitrate
CBS	Corey-Bakshi-Shibata
CDI	1,1'-Carbonyldiimidazole
cod	Cyclooctadiene
CSA	Camphorsulfonic acid
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DHAA	Dehydroabietic acid
DHP	2,3-Dihydropyrane
DIBAL-H	Diisobutylaluminium hydride
DMA	*N,N*-Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
dmpe	1,2-Bis(dimethylphosphino)ethane
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
dppbz	1,2-Bis(diphenylphosphino)benzene
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
FGI	Functional group interconversion
FGA	Functional group addition

GABA	gamma-Aminobutyric acid
HAT	Hydrogen atom transfer
HATU	Hexafluorophosphate azabenzotriazole tetramethyl uronium
HLF	Hofmann Löffler Freytag
HMPA	Hexamethylphosphoramide
HOBt	1-Hydroxybenzotriazole
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectroscopy
HWE	Horner-Wadsworth-Emmons
IBX	2-Iodoxybenzoic Acid
LDA	Lithium disopropylamide
LHMDS	Lithium hexamethyldisilazide
LTA	Lead tetraacetate
mCPBA	meta-Chloroperoxybenzoic acid
MQ	8-Amino-5-methoxyquinoline
nbe	Norbornene
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NIS	*N*-Iodosuccinimide
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
PA	Picolinic amide
PCC	Pyridinium chlorochromate
PHPB	Pyridinium hydrobromide perbromide
PIDA	Phenyliodine(III)-diacetate

PPTS	Pyridinium paratoluenesulfonate
PTSA	para-Toluenesulfonic acid
py	Pyridine
RT	Room temperature
TBACl	Tetrabutylammonium chloride
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBHP	*tert*-Butylhydroperoxide
TCCA	Trichloroisocyanuric acid
TEA	Triethylamine
TFA	Trifluoroacetic acid
TFDO	Trifluoromethyl-methyldioxirane
THF	Tetrahydrofurane
THP	Tetrahydropyrane
TLC	Thin layer chromatography
TMEDA	*N,N,N',N'*-Tetramethylethylendiamine
TPAP	Tetrapropylammonium perruthenate

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