Studies on the defunctionalization of *Ouabain*, investigation of *bistriazol derivatives* decarboxylation and towards the synthesis of natural *Diarylheptanoids*

Dissertation

Zur Erlangung des Grades Dr. rer. nat.

Angefertigt im Fachbereich C, Mathematik und Naturwissenschaften

Der Bergischen Universität Wuppertal

Von **Federica Borghi**

geb. am. 22.07.1993 in Ozieri (SS) – Italien

The present work was carried out under the supervision of Prof. Dr. *Stefan F. Kirsch* at the University of Wuppertal from December 2018 to August 2022.

Published articles concerning this work:

F. Borghi, I. E. Çelik, P. Biallas, F. Mittendorf, S. F. Kirsch, Expanding the Versatile Reactivity of Diazido Malonic Acid Esters and Amides: Decarboxylation and Imine Formation*, Eur. J. Org. Chem*, **2020**, 11.

Vita brevis, ars longa, occasio volucris,
periculosa experimentia, judicium difficile.

La vita è breve, l'arte vasta, l'occasione fuggevole,
l'esperimento malcerto, il giudizio difficile.

Life is short, and art long, opportunity fleeting,
experimentations perilous, and judgment difficult

[Ippocrate, Coo, 460 a.C. circa – Larissa, 377 a.C.]

Acknowledgements

My first thanks go to my PhD supervisor, Prof. Dr. Stefan F. Kirsch, who gave me the opportunity to do my PhD abroad, in a field I was not familiar with before, as I graduated in pharmaceutical chemistry. Thanks to his encouragement and advice, I gained considerable experience and knowledge in organic chemistry and also grew personally.

Many thanks to the examiners of this thesis, Prof. Dr. Jürgen Scherkenbeck, Prof. Dr. Fabian Mohr and Prof. Dr. Julia Bornhorst, for their helpfulness.

Many thanks to all the employees of our working group, for their patience, helpfulness, advice and performed measurements: Dr. Hülya Aldemir, Dr. Andreas Kotthaus, Dr. Markus Roggel, Dr. Adrián Gómez Suárez, Christine Scheidereit, Andreas Siebert, Simone Bettinger, Ilka Polanz and Boris Ihmenkamp.

My thanks go to Khadijah Anwar, Kay Merkens and, in a special way, to Fran, the first international doctoral student with whom I managed the initially difficult period of working in a country other than our own.

I would like to thank the former PhD students: Torsten Cellnik, Marcel Jaschinski, Svenja Schlempp, Yasemin Özkaya, Phillip Biallas and Kristina Holzschneider.

I would like to thank my lab colleagues Anastasiia Krupka, My Linh Tong, Ibo and Frederic Ballaschk for their help and advice, as well as for the laughter and company, thanks to which time passed quickly, without forgetting the Master students Lukas, Fritz and Timo.

Thanks to my colleagues Kathrin Bensberg and Athanasios Savvidis for these years together.

A huge thank you to Kevin and Basti, who were initially colleagues but with whom a wonderful friendship and bond developed that made these years lighter and more fun.

One of the most important thanks goes to Fabia, who welcomed me in the beginning and helped me to face a new world with all its difficulties. She stood by me in the most difficult and darkest times, but also in the best ones, a friendship that is rare to find and that I will always carry in my heart.

Thank you to my international friends Dariyoush, Işil and Gokhan, whom I met during my German course and with whom I formed a deep bond. A special memory to Mohsen Rezaie.

Thank you to my parents who supported me in my decision to pursue a PhD far from home and from my all family. Thank you for spurring me on during the most difficult times and for your support. A big thank you also to grandparents, uncles and cousins.

Thanks to Davide, a wonderful man who, despite the distance, has always been close to me and has always listened to me.

Thanks to all my friends who have always been close to me, even those with whom we lost but found each other again: Mary, Antonio, Lucia, Cinzia, Serena, Giulia, Miriam M., Miriam D., Rosaria, Elettra, Silvia, Marta, Laura, Antonella, Roberta.

Thank you all!!!

Ringraziamenti

Il mio primo ringraziamento va al mio supervisore di dottorato Prof. Dr. Stefan F. Kirsch che mi ha dato la possibilità di poter svolgere un dottorato all'estero, in un campo che non mi apparteneva del tutto, essendo io laureata in chimica farmaceutica. Grazie ai suoi stimoli e consigli, ho maturato una notevole esperienza e conoscenza in chimica organica, oltre alla crescita personale.

Un sentito ringraziamento agli esaminatori di questa tesi, Prof. Dr. Jürgen Scherkenbeck, Prof. Dr. Fabian Mohr e Prof. Dr. Julia Bornhorst, per la loro disponibilità.

Un grazie a tutto il personale del nostro gruppo di lavoro, per la loro pazienza, disponibilità, per il loro aiuto, consigli e misurazioni effettuate: Dr. Hülya Aldemir, Dr. Andreas Kotthaus, Dr. Markus Roggel, Dr. Adrián Gómez Suárez, Christine Scheidereit, Andreas Siebert, Simone Bettinger, Ilka Polanz e Boris Ihmenkamp.

Un ringraziamento a Khadijah Anwar, Kay Merkens e, in maniera particolare, a Fran, primo dottorando internazionale insieme a me; assieme abbiamo affrontato l'iniziale difficoltoso periodo di lavoro in un paese diverso da quello d'origine.

Ringrazio gli ex dottorandi Torsten Cellnik, Marcel Jaschinski, Svenja Schlempp, Yasemin Özkaya, Phillip Biallas e Kristina Holzschneider.

Ringrazio i miei colleghi di laboratorio Anastasiia Krupka, My Linh Tong, Ibo e Frederic Ballaschk per avermi aiutato e dato consigli, oltre alle risate e alla compagnia grazie alla quale il tempo trascorreva velocemente, senza dimenticare gli studenti del master Lukas, Fritz e Timo.

Un ringraziamento ai miei colleghi Kathrin Bensberg, Athanasios Savvidis per questi anni insieme.

Un enorme grazie a Kevin e Basti, inizialmente colleghi ma con i quali si è instaurata una bella amicizia e un bel legame che ha reso questi anni più leggeri e divertenti.

Uno dei ringraziamenti più importanti va a Fabia, che mi ha accolto inizialmente e mi ha aiutato ad affrontare un nuovo mondo, con tutte le sue difficoltà. Mi è stata accanto nei periodi più difficili e bui ma anche in quelli più belli, un'amicizia rara da trovare e che porterò sempre nel cuore.

Grazie ai miei amici internazionali Dariyoush, Işil e Gokhan, incontrati durante il corso di tedesco e con i quali si è instaurato un profondo legame. Un ricordo speciale a Mohsen Rezaie.

Grazie ai miei genitori, che mi hanno appoggiato nella scelta di svolgere un dottorato lontano da casa e dalla famiglia, che mi hanno spronato nei periodi più complicati. Grazie per essere così orgogliosi di me.

Un grande ringraziamento anche a tutta la mia famiglia, nonni, zii e cugini.

Grazie a Davide, ragazzo splendido che nonostante la distanza, mi è sempre stato vicino e mi ha sempre ascoltato.

Grazie a tutti i miei amici che mi sono sempre stati vicini, anche a coloro con cui ci siamo persi ma ritrovati: Mary, Antonio, Lucia, Cinzia, Serena, Giulia, Miriam M., Miriam D., Rosaria, Elettra, Silvia, Marta, Laura, Antonella, Roberta.

Grazie a tutti!!

❖ Defunctionalization of Ouabain

1. Introduction

1.1. Discovery and structure of Ouabain

Ouabain **I-1**, also known as *g-Strophanthin*, is a natural product belonging to the cardenolides **I-2** class. Cardenolides are steroids characterized by an α,β-unsatured five- or six- membered lactone ring at C-17β position and a hydroxyl group at C-14β position, which causes the *cis* connection between C and D rings, and a linkage of the aglycone to carbohydrates (in this case the cardenolide is known as cardiac glycoside) or to acids at the hydroxyl group at C-3β position.[1] Ouabain's structure presents a five membered lactone ring at C-17 position, a rhamnose as a sugar linked to the hydroxyl group at C-3 position and two methyl groups at C-10 and C-13 positions (figure 1).

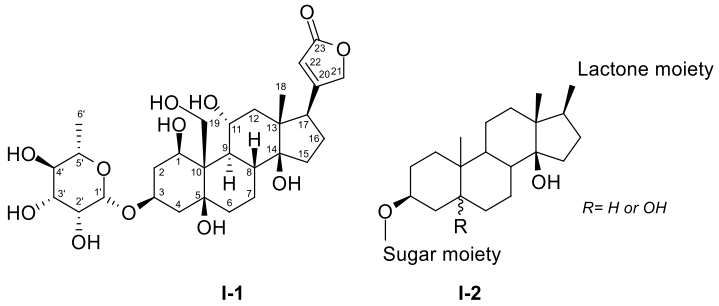
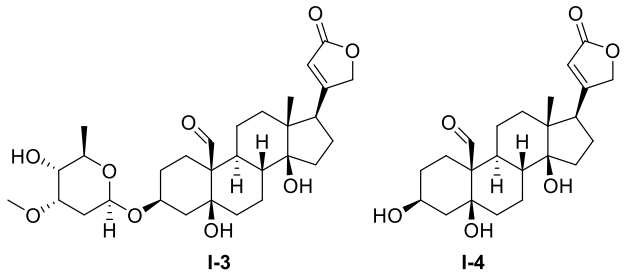


Figure 1. Ouabain **I-1** and general cardenolide **I-2** structures.

In 1888, Ouabain **I-1** was discovered by the French chemist *Léon-Albert Arnaud*,[2] who isolated an amorphous substance, that he identified as a glucoside,[3] from the bark and roots of the Ouabaio tree, a species of *Acocanthera* (*Acocanthera schimperi*). This glucoside was used by Somalis of East Africa as an arrow poison for hunting and warfare. *Arnaud* found the same glucoside in another arrow poison, which was prepared from the seeds of *Strophanthus gratus*.[2,4] The presence of those glycosides in the plants is extremely important as a defence against predators.[5] In 1904, *Herman Thoms* isolated pure glycosides from *S. kombé* and *S. gratus* and assigned them the name *k*- and *g-Strophanthin*, to distinguish Ouabain from the *Strophanthins* of other species (*h-Strophanthin* **I-3** or *k-Strophanthidin* **I-4**) (figure 2).[6,7]



I-3 **I-4**

Figure 2. *h-Strophanthin* **I-3** and *k-Strophanthidin* **I-4** structures.

1.1.1. From arrow poison to medicine

African healers knew the medical benefits of *Strophantus* plants very early on. Alcoholic extracts were produced by soaking the plant roots with subsequent fermentation and the bitter-tasting solutions were administered in small snips over a period of days or weeks. To avoid poisoning, the administered amount was carefully dosed by the healer and muscle pain, open wounds, constipation, food-poisoning, sexual and heart diseases were treated.[8]

Several researchers have rendered outstanding services in the clarification of the active substance contained in *Strophanthus* and its pharmacological properties[5] and, according to canonical explanations, Ouabain and other digitalis derivatives should have similar therapeutic effects.

However, clinical experience clearly indicated that Ouabain was different from other digitalis derivatives and one of the main differences was its fast start of action. It was showed in 1859 by the English botanist *John Kirk*, who discovered the fast activity of Ouabain by using a toothbrush contaminated with *Strophanthus* seeds.[9]

Since 1865, *Thomas Richard Fraser*, who taught pharmacognosy, pharmacy, pharmacology and therapy at the same time in Edinburgh, dealt most intensively with the *kombé* arrow poison and *Strophanthus kombé*. He isolated the pure cardio active ingredient from the seeds of *Strophanthus kombé* and characterized it as a glycoside in 1869. He also showed that this active ingredient had an important cardiac effect and was suitable for therapy in humans.

Indeed, in 1885 *Fraser* published his first experience with *Strophanthus* tincture in patients and recommended its use to treat all forms of *cardiac fatigue* and as a diuretic.[5,10]

In 1886, *Burroughs*, *Wellcome & Co* introduced a *S. kombè* extract called "Tincture of *Strophanthus*", based on the work of *Fraser*[7] and two years later, *Catillon* identified pure substances from *Strophanthus species gratus, hispidus, niger and kombé*. He isolated a crystalline product only from *Strophantus gratus*, while he identified only amorphous products from the others (*kombé* in particular).

Later, *Arnaud* identified the cardioactive principle from the *Strophanthus gratus* as Ouabain and this highlighted that the glycoside investigated by *Fraser* was referred to *k-Strophanthidin* **I-4** (figure 2).

After the First World War, in France, Ouabain **I-1**, which was identical to *g-Strophanthin*, largely replaced *k-Strophanthidin* **I-4** preparations in the therapy of heart patients as "*Ouabain Arnaud*".[5,10] Therefore, in 1904, *Schedel* reported on positive experiences with a *Strophantus gratus* tincture containing Ouabain and he highlighted the positive effects on respiratory distress and pulse in heart patients observed by other clinicians.[11]

In 1906, *Fraenkel* introduced in Germany *k-Strophanthidin* **I-4** into cardiac therapy for acute cardiac insufficiency by intravenous administration. He refused oral administration of *Strophanthin* preparations because of the known sensitivity of the *k-Strophanthidin* **I-4**, which led to the decomposition of the active ingredient in the stomach.

This was the first time that an arrow poison was used as medication, but it took more than three decades until intravenous *Strophanthin* therapy was generally accepted and used.[5,10,12]

1.2. Ouabain as endogenous hormone, its mechanism of action and pharmaceutical use

Many years of practical use of Ouabain **I-1** have shown benefits in prevention and treatment of acute heart attacks, and its prophylactic and therapeutic use has been recommended in insufficiency of the left ventricle.[13] Exceptionally, orally administered Ouabain has highlighted a biological activity for the treatment of cardiovascular diseases. [14]

In pharmacological research, Ouabain is used to investigate the multiple functions of the sodium-potassium ATPase pump (Na^+/K^+-ATPase). This pump is an omnipresent membrane-bound enzyme and it is involved in many physiological processes. It transports sodium ions from the cell and potassium ions into the cell, assuring the vital ion gradient between interior of cells and the extracellular fluid. This process requires energy that is obtained by hydrolysis of adenosine triphosphate (figure 3).[15]

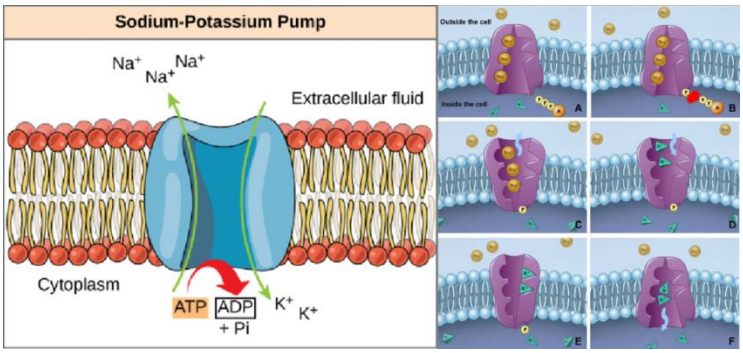


Figure 3. The sodium-potassium exchange pump mechanism. The Na^+/K^+-ATPase moves two potassium ions from outside to inside the cell and three sodium ions from inside to outside the cell by the hydrolysis of ATP molecules.[15]

In high concentration, Ouabain is able to inhibit the Na^+/K^+-ATPase pump, but not selectively.[16] Once Ouabain binds to this enzyme, the pump ends to function which leads to an increase of intracellular sodium, reducing the activity of the intracellular sodium-calcium exchanger (NCX) (which under normal conditions pumps one calcium ion out of the cell and three sodium ions into the cell), thus increasing intracellular calcium.[17] This results in higher cardiac contractility and an increase in cardiac vagal tone. The change in ionic gradients caused by Ouabain can also affect the membrane voltage of the cell and results in cardiac arrhythmias.

Despite the positive clinical experiences with Ouabain in humans, current research announces that several disease states seem to be associated with elevated levels of a compound into the human body that is claimed to be "endogenous Ouabain" (EO), a hormone originated or produced within an organism, tissue, or cell. It has been shown to be the main factor not only in the heart pathogenesis but in many common diseases, acting as a pro-hypertrophic and growth-promoting hormone, which might lead to cardiac remodelling affecting cardiovascular functions and structures.[18]

In the late 1970s, the concept of "EO" was originated when it was hypothesized that an endogenous inhibitor of vascular Na^+/K^+-ATPase could be a natriuretic hormone causing hypertension.[19]

Therefore, this EO concept suggested that Ouabain, as inhibitor of the Na^+/K^+-ATPase, could increase the blood pressure, in contrast to clinical experience, because in more than two centuries of clinical use with therapeutic concentrations of Ouabain, no hypertensinogenic effects have been observed but only a reduction of high blood pressure.[20]

In 1991, *Hamlyn et al.* cooperatively with scientists from *Upjohn* Laboratories in Kalamazoo (Michigan) reported the purification of a compound in human plasma indistinguishable from Ouabain by mass spectroscopy. Therefore, Ouabain was identified as an endogenous hormone and it was intensively re-examined as a drug, in particular its physiological functions and mechanism of action.[21,22,23,24] Subsequent work seemed to confirm this observation and indicated that mammalian Ouabain was present in multiple body fluids and tissues.[5]

In 1992, *Doursout and coworkers* and, a year later, *Yuan and colleagues* demonstrated that prolonged Ouabain administration induced hypertension in normal rats. These remarkable observations have been replicated in several laboratories.[25]

The mutually exclusive effects of Ouabain and the inhibitor activity of the sodium pump observed in mammalian tissues have not supported the hypothesis that this inhibitor is identical with Ouabain, but have highlighted that the natriuretic hormone is something different, which also is able to react with Ouabain antibodies. Indeed, some working group has showed that no endogenous Ouabain can be detected in human plasma with the help of chromatography methods, initially ignored.

Vogeser et al. developed a particular and extremely sensitive method (validated according to FDA guidelines) to detect Ouabain in human plasma that has showed

negative results. These results have confirmed that endogenous Ouabain is different from Ouabain, refuting the hypothesis of EO.[5,26]

Nowadays, there are still studies and contrasting ideas about endogenous Ouabain. New research has shown that Ouabain is an endogenous steroidal hormone of mammals, synthesized in the adrenal glands and the hypothalamus.[27]

However, over the years, there have been studies and research questioning what has been confirmed so far.

Based on the hypothesis that Ouabain could cause hypertension (inhibiting Na^+/K^+-ATPase pump), a research group at the University of Maryland, in cooperation with the Italian pharmaceutical company *Sigma-Tau*, has developed an Ouabain antagonist that in animal model is able to lower blood pressure, but has been shown to be ineffective during clinical trials in humans.[28]

In-depth research on possible mechanism of Ouabain's action has highlighted that low concentrations of this cardenolide can induce signalling cascades *via* Na^+/K^+-ATPase that regulates different cell functions, such as cell proliferation, apoptosis, metabolism and cell mobility, that are independent effects of the transport of sodium and potassium ions by sodium pump.

Other recent experimental studies indicate cardio-protecting effects of Ouabain, preventing hypertrophy of the heart and adrenal cortex in rats exposed to hypoxia, ischemia/reperfusion injury. In addition, Ouabain has showed promising effects in skeletal muscle motor dysfunction, immune-mediated diseases and neurodegenerative disorders, antiproliferative effects on various cancer cells including breast cancer, lung cancer, prostate cancer, colon cancer and leukemia by apoptosis, autophagy and immunogenic cell death (mechanism not fully elucidated), and protection of kidney development from adverse effects of malnutrition.[29,30,31,32,33,34,35,36]

Due to the pandemic situation of recent years, Ouabain has been one of several drugs studied and analyzed in the treatment against SARS-CoV-2 infection and its implications for COVID-19, showing interesting antiviral activity.[37,38,39]

1.3. Structure-Activity Relationship (SAR)

Crystallographic data together with in silico studies have been performed in order to study the Structure-Activity Relationship of Ouabain **I-1**.

The binding site of Ouabain within Na^+/K^+-ATPase pump resides on pump's extracellular loops, especially between specific transmembrane domains. There are important essential features for the inhibitory activity on sodium pump: the steroid nucleus **I-5** has to be in a chair configuration (**I-6**), with A/B and C/D ring bonds in a *cis* configuration and B/C bonds in a *trans* configuration. Furthermore, a hydroxyl group at C-14 position, a sugar at C-3 position and the unsaturated lactone are required (figure 4).

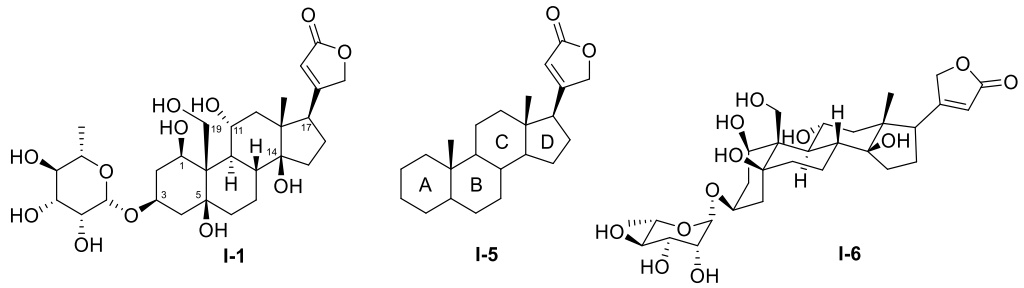


Figure 4. Structure with essential features for activity **I-1**, steroid nucleus **I-5** and chair configuration **I-6** of Ouabain.

The lactone ring at C-17 position is accommodated near to the residue Val329 and Ala330 in the transmembrane domain 4 displacing Gly326, essential for the K^+ coordination (figures 5, A). Modifying the lactone moiety, such as a saturation of double bond and the carbonyl's position, the Ouabain affinity is remarkably reduced.

The steroid nucleus interacts directly with the transmembrane. The key factor for a correct chair and a *cis* configuration of the A/B and C/D ring junctions is represented by three phenylalanine residues (Phe323, Phe790 and Phe793) (figures 5, A). These residues are able to create a close hydrophobic pocket that is replaced by the steroid nucleus, allowing for a better accommodation of this group.

The hydroxyl group at C-14 position forms a hydrogen bond with Thr804, and this proves that it is an important residue for the Ouabain binding (figures 5, A). On the contrary, the hydroxyl group at C-11 position is not involved with the interactions and could reduce the affinity because of a sterical hindrance.[40,41,42]

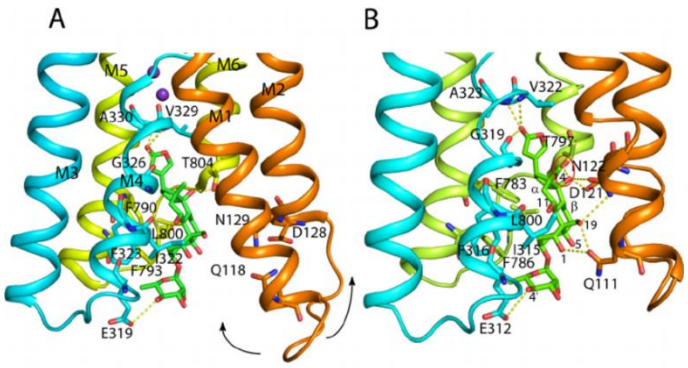
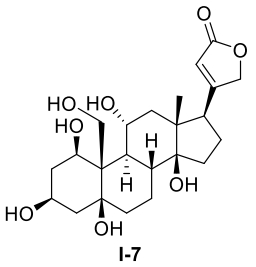


Figure 5. The Na^+/K^+-ATPase binding cavity for Ouabain. Residues of the Na^+/K^+-ATPase subunit important for coordination and Ouabain are shown in sticks. In **A**, residues important for Ouabain interaction in the low affinity Ouabain-bound crystal structure are shown; in **B**, the original high affinity Ouabain-bound structure is shown.[43]

The rhamnose residue at C-3 position can interact with Glu319 and Arg887 by hydrogen bonding (figures 5, B), giving the Ouabain an higher affinity than Ouabagenin **I-7** (figure 6), which doesn't present a sugar moiety.[44]



I-7

Figure 6. Ouabagenin

Some research present conflicting ideas and studies regarding the involvement of sugar for the inhibitory activity of Ouabain.[44]

1.4. Toxicology

Ouabain is a highly toxic compound with a LD_{50} (lethal dose, the amount of material, given all at once, which causes the death of 50% of a group of test animals) of 5 mg/kg, if orally administered to rodents.[45]

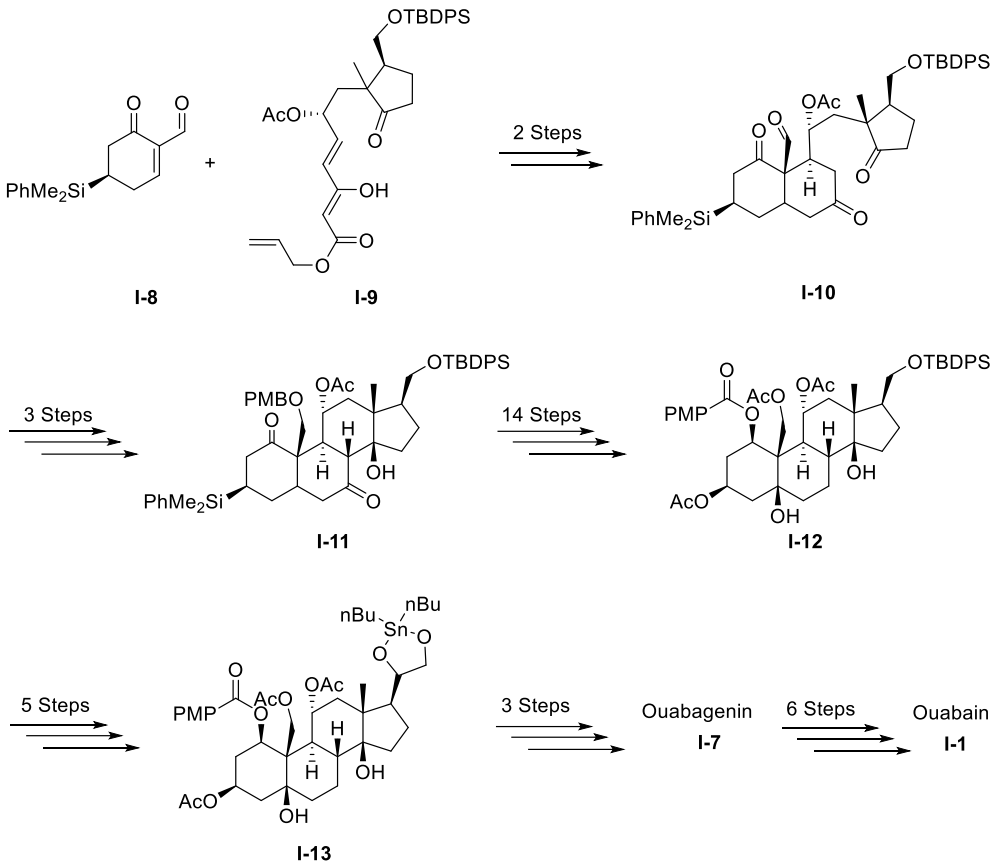
Nevertheless, it has a low bioavailability[16] because it is absorbed poorly from the alimentary tract, destroying the oral dose. Intravenous administration shows better available concentration, with a LD_{50} to 2.2 mg/kg, also in rodents.[45] Ouabain is eliminated by renal excretion, largely unchanged.

Since the lethal dose is very close to the pharmaceutical dose, an overdose of Ouabain can easily occur with the following symptoms: rapid twitching of the neck and chest musculature, respiratory distress, increased and irregular heartbeat, rise in blood pressure, convulsions, wheezing, clicking, and gasping rattling. Death is caused by cardiac arrest.[10]

1.5. Total synthesis

The total synthesis of Ouabain was a challenge for different research groups. The first total synthesis was published in 2008 by *Deslongchamps et al.* (scheme 1).[46]

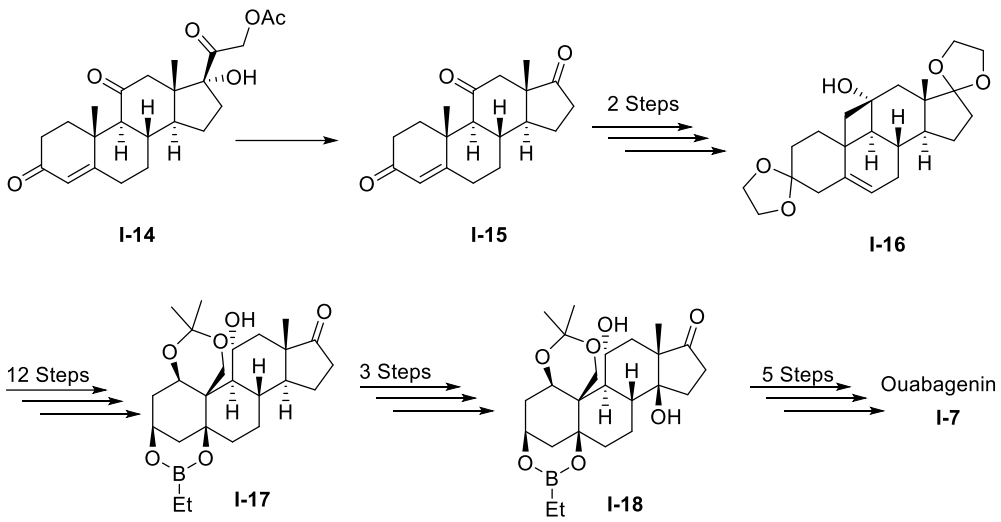
Their strategy was based on the initial construction of steroid skeleton which contains the functionalities required for Ouabagenin **I-7** (the aglycone of Ouabain isolated for the first time in 1942 by *Mannich* and *Siewert*[47]), and Ouabain **I-1**. Ouabagenin **I-7** was obtained after twenty-seven steps from cyclohexanone derivative **I-8** and Nazarov substrate **I-9** through a polyanionic cyclization (double-*Michael* addition followed by aldol condensation) strategy, allowing facile access to a tetracyclic intermediate with the desired A/B *cis* **I-10**, B/C *trans* and C/D *cis* **I-11** ring junctions and the formation of the key intermediate **I-12** in nineteen steps. This derivative led to the preparation of Ouabagenin **I-7** *via* eight-steps synthesis. Ouabain **I-1** was prepared from Ouabagenin **I-7** in six steps installing the rhamnose sugar successfully.



Scheme 1. Total synthesis of Ouabain by *Deslongchamps et al.*

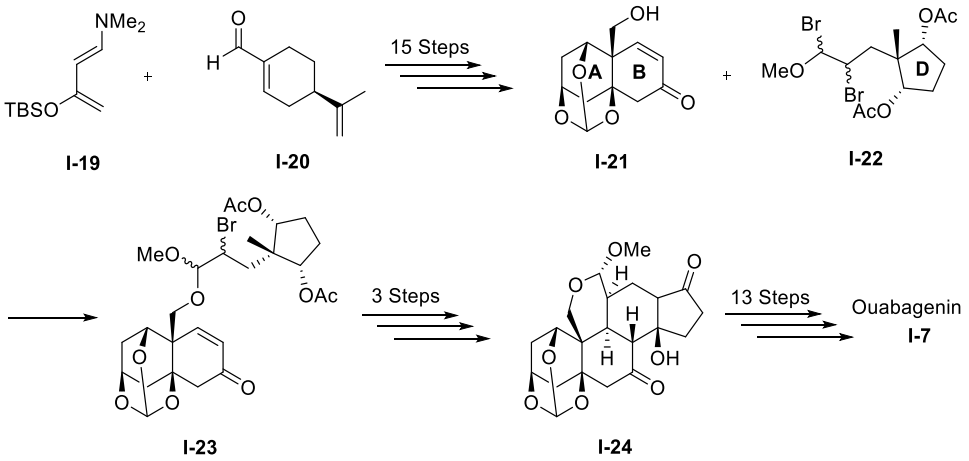
In 2013*, Baran at al.* reported the synthesis of Ouabagenin **I-7** with an unusual take on the age-old practice of steroid semi synthesis based on the strategic interplay of two relay elements: redox relay (rapid transfer of redox information from one site to another within a framework) and oxidative stereochemical relay (transfer of stereochemical information during an oxidative process).[48] Cortisone acetate **I-14** was chosen as an ideal starting material for its cheap price and was converted into adrenosterone **I-15** (more expensive) (scheme 2). This approach was focused on the evolution of synthetic strategy to access hydroxylation at C-19 position of cyclobutanol **I-16**, achieved *via* two-step synthesis from intermediate **I-15**.

After fifteen steps, protected Ouabageninone **I-18** was formed on a scale of >500 mg and few chromatographic purifications were required. Compound **I-18** was the ketonic core of the target molecule that would allow not only the synthesis of Ouabagenin **I-7** but also the versatile access to analogs carried at C-17 position, bearing a hydroxyl group at C-19 position. Then, Ouabagenin **I-7** was afforded *via* five-steps synthesis.



Scheme 2. Total synthesis of Ouabagenin by *Baran et al.* in 2013.

Two years later, *Inoue at al.* synthesized Ouabagenin **I-7** using a convergent synthesis based on assembly of the A/B rings, D ring and butenolide moiety. The A/B rings **I-21** were synthesized in fifteen steps using diene **I-19** and (*R*)-perillaldehyde **I-20** as starting materials, through *Diels-Alder* reaction and sequential oxidations. The steroidal skeleton **I-24** was obtained in selective way by intramolecular acetal formation of the A/B ring **I-21** and D-ring fragments **I-22** and a combination of intramolecular radical and aldol reactions. At the end, C-17 butenolide was connected by *Stille* coupling and hydrogenation, obtaining Ouabagenin **I-7** (scheme 3).[49]



Scheme 3. Total synthesis of Ouabagenin by *Inoue et al.*

1.6. Structural modifications of Ouabain

The structure of Ouabain presents attractive functional groups, allowing the possibility of being modified and of improving its biological activity. Its structure is rich in hydroxyl groups and it can be subjected to protection or deprotection, oxidation or dehydration,

elimination or deoxygenation reactions. As previously mentioned, the lactone moiety has a considerable importance for biological interaction, whereby Ouabain should undergoes modifications without losing its pharmacological activity.

1.6.1. Protection and deprotection of hydroxyl group (OH)

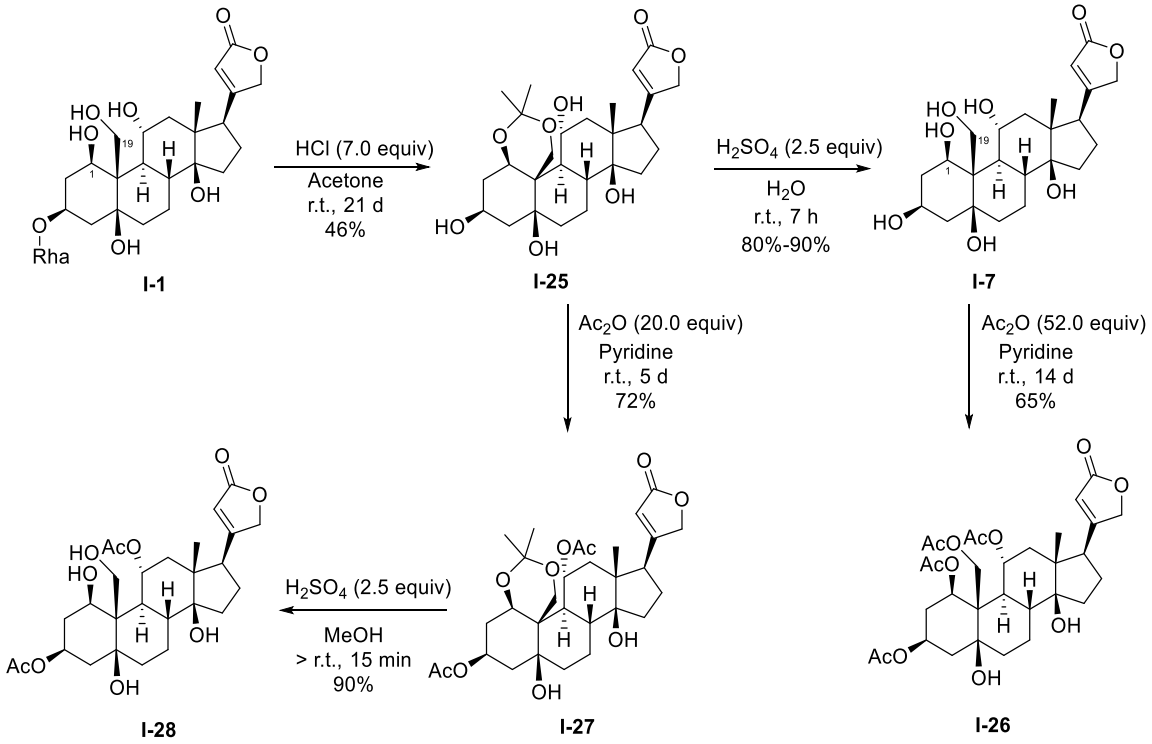
A protecting group is a molecular framework introduced into a molecule, by chemical modification of a functional group, to obtain chemoselectivity in a subsequent chemical reaction, especially in a multifunctional compound.[50]

In organic chemistry, there is a significant variety of protecting groups which are specific to each functional group, such as alcohols, amines, carbonyls, carboxylic acids, phosphates, terminal alkynes and so on. The structure of Ouabain contains six hydroxyl groups, and in order to selectively work on one of them, it is necessary to protect the others by using specific protecting groups, like acetonides, acetates, alkylating groups (*i.e.*, MOMCl) or silyl ethers.

In 1942, *Mannich* and *Siewert*[47] published their work on Ouabain, showing the possibility to protect the diol, formed by the secondary and primary alcohols at C-1 and C-19 positions (**I-25**), with an acetonide and to cleave the rhamnose moiety by using hydrochloric acid in acetone.

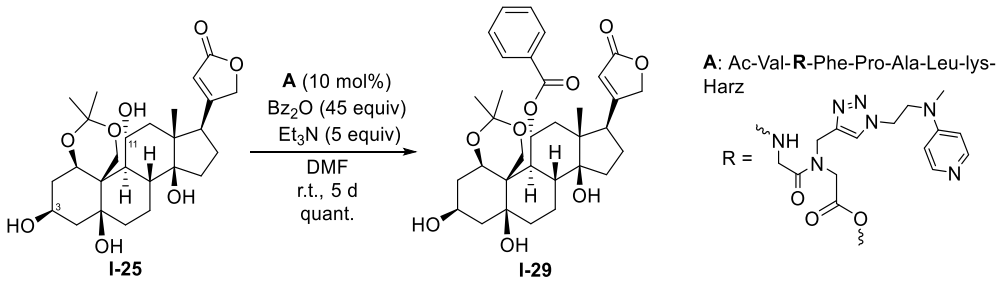
This protecting group was removed using sulfuric acid in water at low temperatures or refluxing in alcohol, obtaining Ouabagenin **I-7**, then converted into the tetra acetate compound **I-26** if treated with excess of acetic anhydride in pyridine (scheme 4).

If compound **I-25** was directly handled with acetic anhydride in pyridine, the diacetate compound **I-27** was afforded which was deprotected with sulfuric acid, furnishing compound **I-28**.[47]



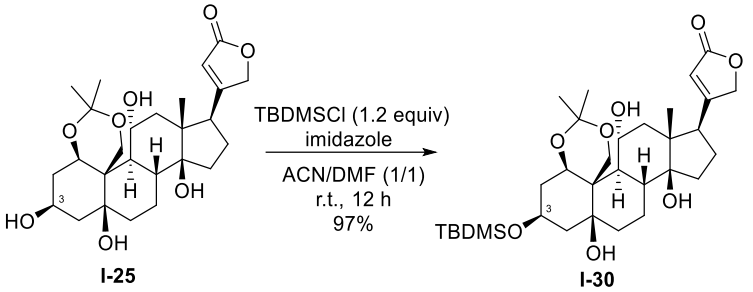
Scheme 4. Acetonide and acetate protection and deprotection of acetonide Ouabagenin **I-7**.

Recently, *Kirsch et al.* discovered a selective protection of the secondary alcohol at C-11 position of acetonide Ouabagenin **I-25**, in presence of the free secondary alcohol at C-3 position (scheme 5) by using a solid phase bound 4-Dimethylaminopyridine (DMAP). The sequence of the peptides, with which DMAP is linked to the resin, had a crucial role for preventing by-products (double benzoate protection), allowing only the synthesis of benzoate compound **I-29**.[51]



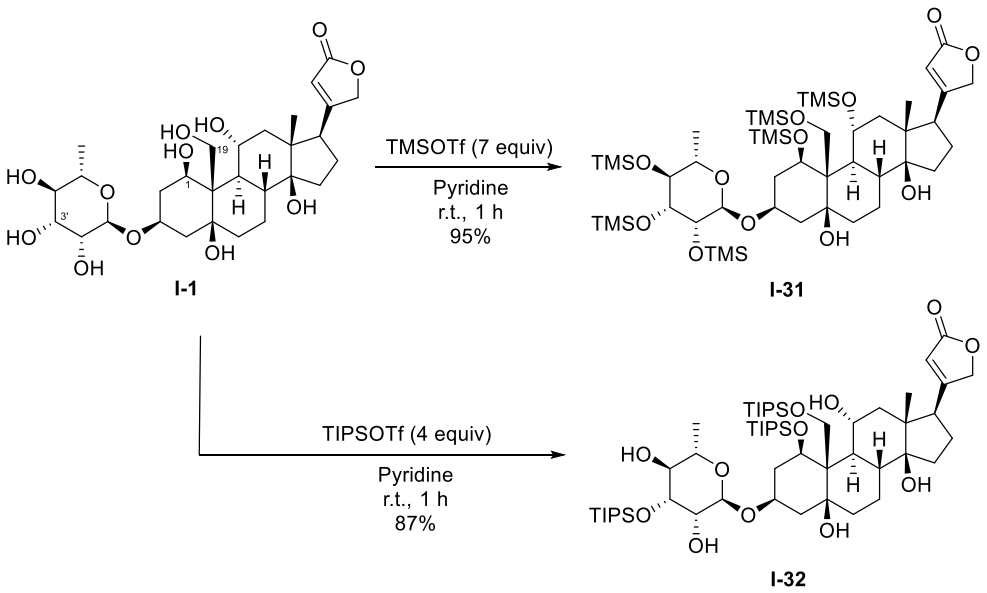
Scheme 5. Selective benzoate protection of acetonide Ouabagenin **I-25**.

The acetonide Ouabagenin **I-25** can also be protected using silyl protecting groups, such as trimethylsilyl ether (TMS), triethylsilyl ether (TES), *tert*-butyldimethylsilyl ether (TBS/TBDMS), *tert*-butyldiphenylsilyl ether (TBDPS) and triisopropylsilyl ether (TIPS).
Selective protection of the secondary alcohol at C-3 position is possible by employing TBDMSCl to generate silyl ether compound **I-30** (scheme 6).[52] This selectivity is due to the high steric bulk of the protecting group.



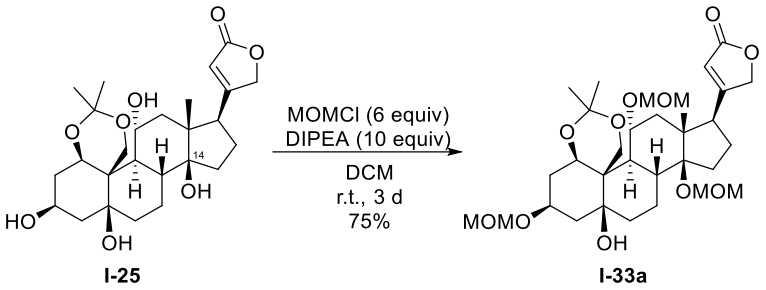
Scheme 6. Selective TBDMS protection of acetonide Ouabagenin.

In 2000, *Templeton et al*. studied the selective protection of free alcohols in Ouabain, including those in rhamnose. The primary alcohol at C-19 position, the most reactive one, was protected in all cases. The two tertiary alcohols didn't react and all secondary alcohols could be protected using seven equivalents of trimethylsilyltrifluoromethanesulfonate (TMSOTf) (**I-31**) (scheme 7).[53]
However, by using only four equivalents of triisopropylsilyltrifluoromethanesulfonate (TIPSOTf), only the alcohols at C-1, C-19 and C-3' positions were protected (**I-32**).



Scheme 7. TMS and TIPS protection of Ouabain.

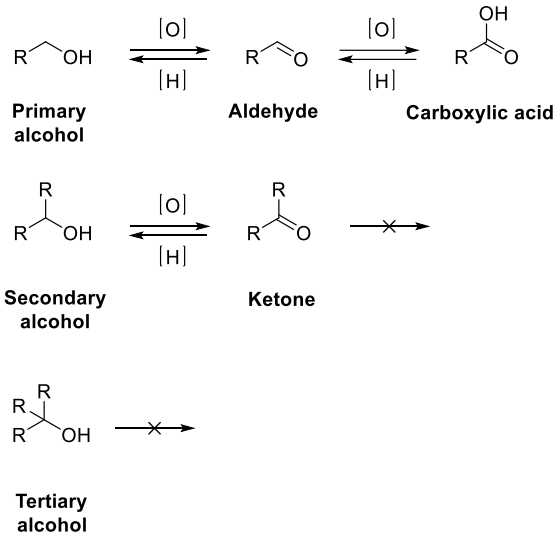
Another interesting protecting reagent is the chloromethyl methyl ether (MOMCl), by which it is possible to protect both secondary alcohols and the tertiary alcohol at C-14 position (**I-33a**) of compound **I-25** (scheme 8).[44]



Scheme 8. MOM protection of acetonide Ouabagenin **I-25**.

1.6.2. Oxidation of hydroxyl groups (OH)

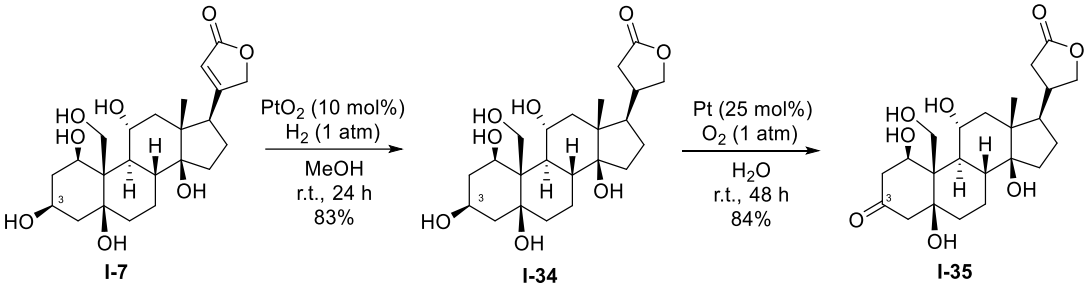
The oxidation of alcohols is a highly important reaction in organic chemistry, by which primary alcohols can be oxidized to aldehydes and carboxylic acids, secondary alcohols to ketones and tertiary alcohols, in contrast, can't be oxidized without breaking the molecule's C–C bond (scheme 9).



Scheme 9. Oxidation of alcohols.

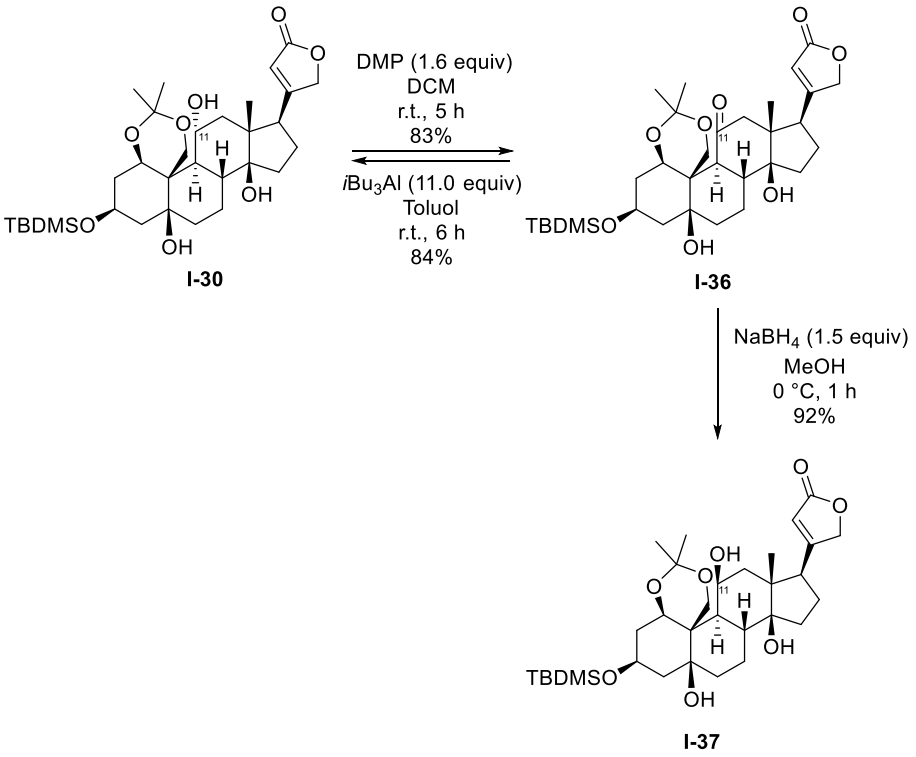
Several studies concerning Ouabain have shown the possibility of selective and non-selective oxidation of hydroxyl groups at C-3, C-11 and C-19 positions using different reaction conditions.

The hydroxyl group at C-3 position of Ouabagenin **I-7**, after reducing the unsaturated lactone (**I-34**), can be oxidized with platinum (Pt) under oxygen atmosphere, achieving ketone **I-35** (scheme 10).[54]



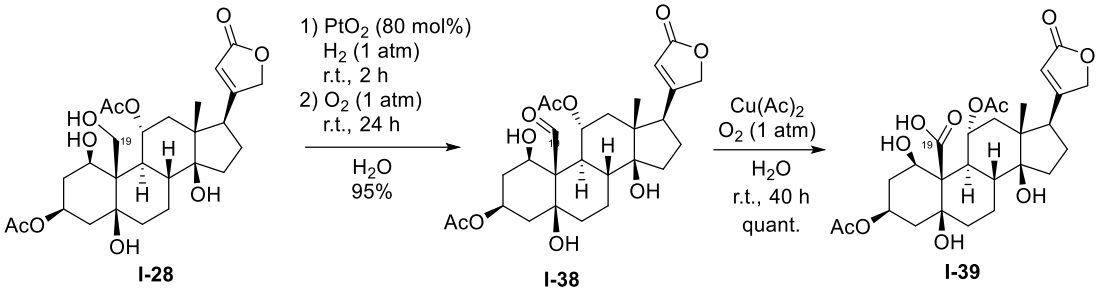
Scheme 10. Reduction of Ouabagenin's lactone and oxidation of OH at C-3 position.

For a selective oxidation of the secondary alcohol at C-11 position, the silyl compound **I-30** can be treated with *Dess-Martin* periodinane (DMP), obtaining the ketone derivative **I-36** which, in presence of sodium borohydride ($NaBH_4$), lead to the formation of the corresponding alcohol **I-37** with an inversion of the stereocenter. It has been shown that it is possible to re-synthesize the starting material **I-30** by reducing the intermediate **I-36** with triisobutylaluminium (TIBA) (scheme 11).[52]



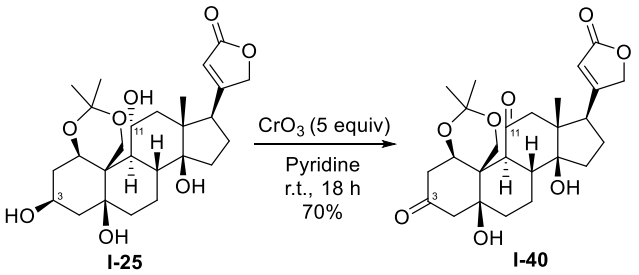
Scheme 11. Selective oxidation of secondary alcohol at C-11 position and subsequent inversion of stereocenter.

In 1967, *Reichstein et al*. oxidized selectively the primary alcohol at C-19 position of diacetate Ouabagenin **I-28** to aldehyde **I-38** with Pt under oxygen atmosphere and, subsequently, to carboxylic acid **I-39** using copper (II) acetate ($Cu(Ac)_2$) in water (scheme 12).[55]



Scheme 12. Selective oxidation of primary alcohol at C-19 position.

In 1964, *J. S. Baran* oxidized both secondary alcohols at C-3 and C-11 positions of acetonide Ouabagenin **I-25** using chromium (VI) oxide (CrO_3) to give diketone **I-40** (scheme 13).[56]



Scheme 13. Oxidation of secondary alcohols at C-3 and C-11 positions of acetonide Ouabagenin.

1.6.3. Deoxygenation of alcohols (OH)

1.6.3.1. Defunctionalization of hydroxyl groups

The deoxygenation of alcohol is a chemical reaction involving the removal of oxygen atoms from a molecule, important for the synthesis of natural product, with or without selectivity. There are disparate applicable methods to carry out the deoxygenation, compatible with different substrates and functional groups (figure 7).

Normally, the deoxygenation of alcohols employs a two-step procedure. One method consists in replacing the alcohol with a suitable leaving group which is removed in a second step: it can be converted into halide (**I**), followed by dehalogenation (**II**), or into ethers or esters (**III**) with *O*-thiocarbonyls, as typical derivative that can be reduced either by electron transfer (**IV**) with alkali metals or with stannanes in the known *Barton-Mc Combie* deoxygenation (**V**). However, undesired radical side reactions and the two-step procedure render this approach still disadvantageous and the direct deoxygenation (**VI**) and the use of catalysts are far more desirable. The problem of the direct deoxygenation is that requires specific reaction conditions and only few functional groups are tolerate. The most common two-step deoxygenation of alcohols is the elimination (**VII**), obtaining the alkene, followed by hydrogenation (**VIII**) to alkane.[57]

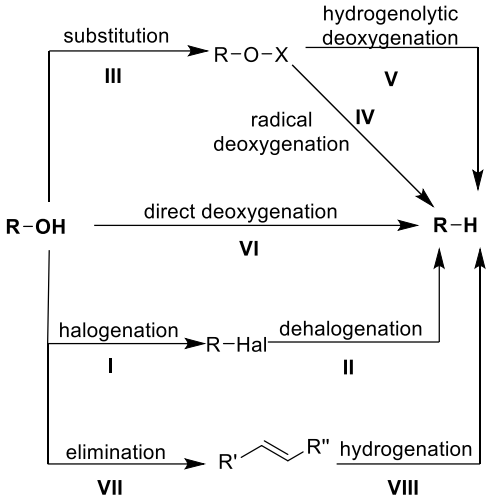
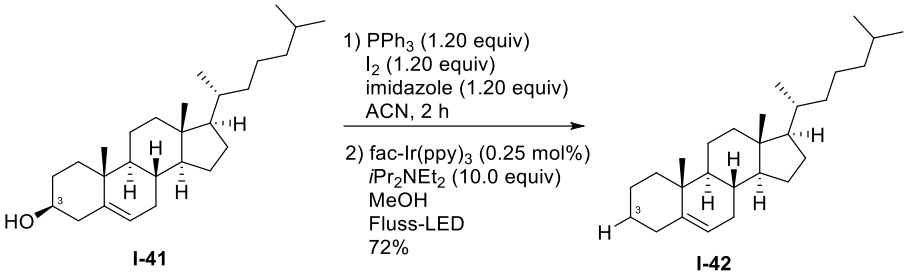


Figure 7. Different methods of alcohols deoxygenation.

Currently, in literature there are not many deoxygenation reactions applied to Ouabain, but mainly to structurally similar steroid compounds. For this reason, some examples of steroidal and non-steroidal compounds will be reported.

Regarding the halogenation reaction, one of the best-known is the *Appel* reaction, by which an alkyl chloride is generated using triphenylphosphine (PPh_3) and carbon tetrachloride (CCl_4).[58] The alkyl chloride can be removed *via* a radical reaction using a hydride source.

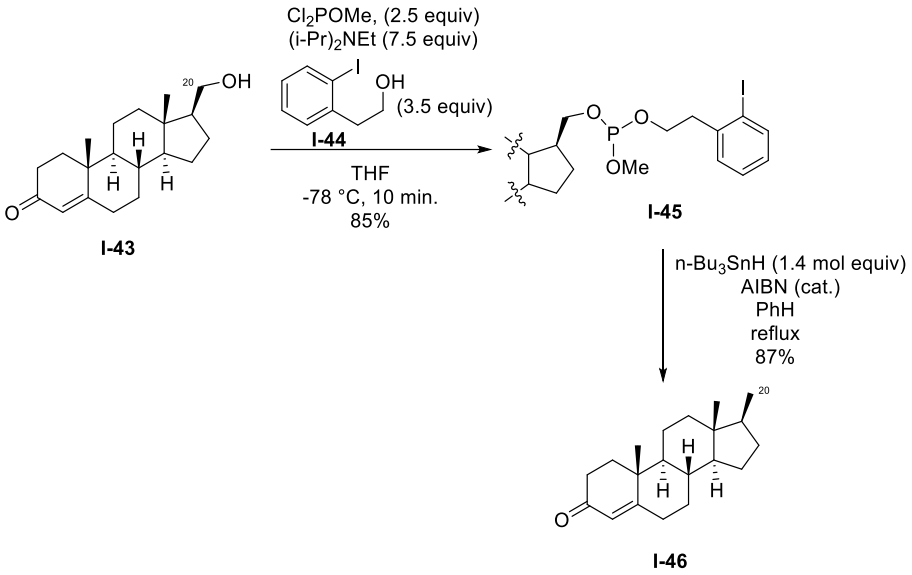
In 2018, *Stephenson et al.* discovered a photochemical approach obtaining *in situ* halogenation, followed by defunctionalization of alcohol. The reactions were carried out in a flow reactor and, combining the *Garegg-Samuelsson* reaction and photoredox catalysis, the alcohol at C-3 position of steroid **I-41** was deoxygenated (scheme 14).[59]



Scheme 14. Halogenation and defunctionalization *in situ* of secondary alcohol at C-3 position of steroid **I-41**.

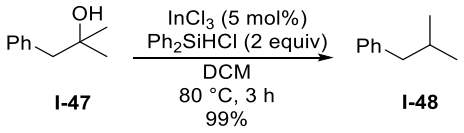
As mentioned above, the *Barton-Mc Combie* is one of the best-known reactions for the deoxygenation of alcohol. First, the alcohol is substituted by a xanthate and, then, radically defunctionalized.[60] Another plausible substituent, in place of xanthate, is the phosphorous which can be easily attached and defunctionalized in a similar way of xanthates.

In scheme 15, the primary alcohol at C-20 position of unsaturated ketone **I-43** is substituted and then radically removed (**I-46**) when phosphorylated intermediate **I-45** is treated with tributyltin hydride (*n*-Bu_3SnH) as hydride source.[61]



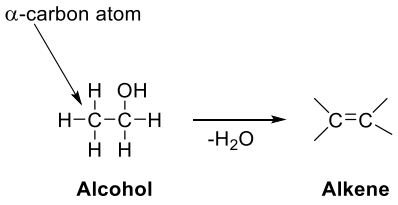
Scheme 15. Deoxygenation of primary alcohol at C-20 position of unsaturated ketone **I-43**.

By using indium (III) chloride ($InCl_3$) as catalyst and chlorodiphenylsilane (Ph_2SiHCl) as reducing agent, alcohols can be defunctionalized through a direct deoxygenation, as shown in scheme 16.[62]



Scheme 16. Direct deoxygenation of tertiary alcohol of 2-methyl-1-phenylpropan-2-ol **I-47**.

The dehydration or elimination of alcohols is an important reaction involving the elimination of a water's molecule from the structure to afford alkenes. This can be possible when the alcohol has a hydrogen atom on the α-carbon atom (scheme 17), *i.e.*, the carbon atom next to one carrying the hydroxyl group. When there is more than one hydrogen on the α-carbon atom, then isomeric alkenes may arise.[63]

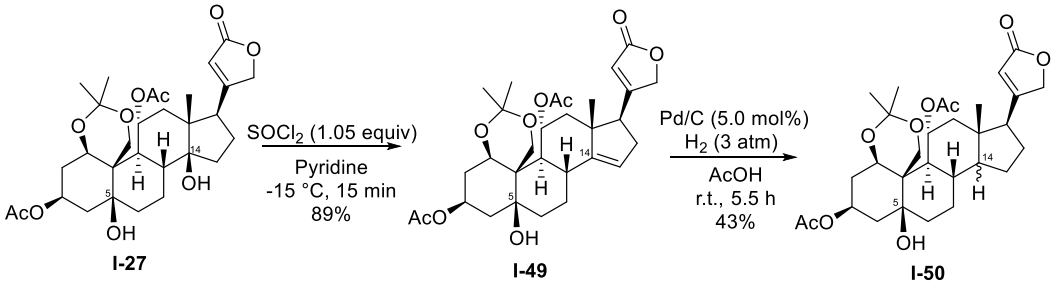


Scheme 17. Dehydration of an alcohol.

Many analyses on dehydration of Ouabagenin derivative's hydroxyl groups, have demonstrated the formation of alkenes or the breaking of the γ-lactone.

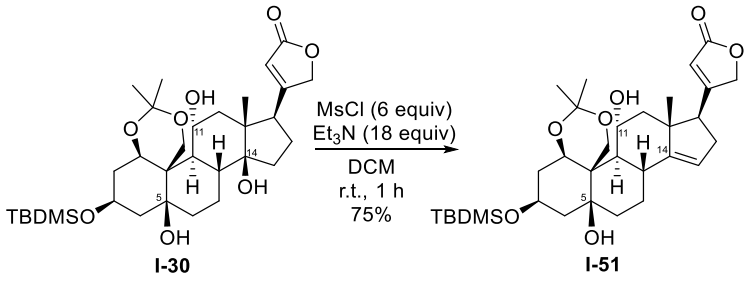
Obviously, the selective elimination of alcohols requires the presence of selective suitable protecting groups.

In 1961, *Baran et al.* discovered that the tertiary alcohol at C-14 position of diacetate acetonide Ouabagenin **I-27** could be eliminated using thionyl chloride ($SOCl_2$) in pyridine obtaining the alkene derivative **I-49** without involving the tertiary alcohol at C-5 position. The alkene **I-49** could be reduced with palladium on activated charcoal (Pd/C) catalyst in acetic acid to a diastereoisomer mixture **I-50** (scheme 18).[64]



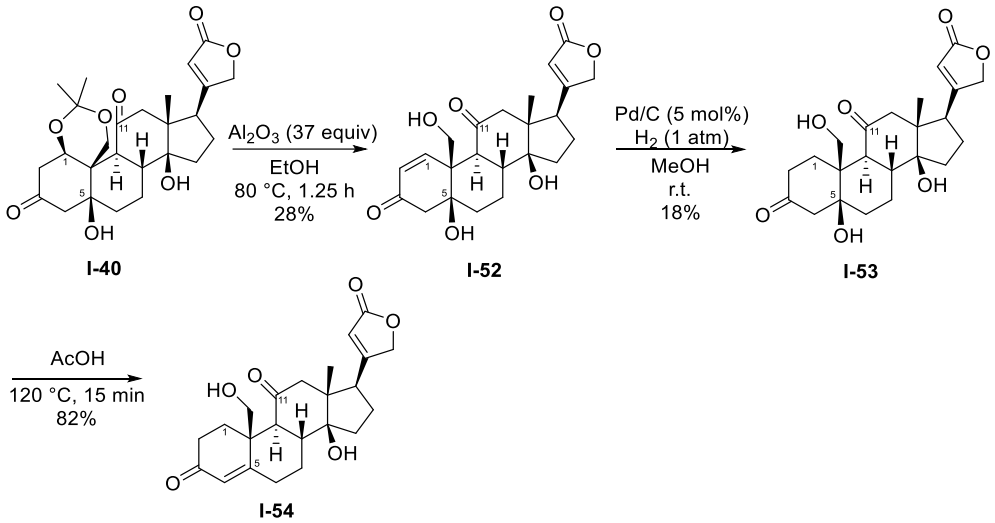
Scheme 18. Dehydration of tertiary alcohol at C-14 position of diacetate acetonide Ouabagenin **I-27** and subsequent hydrogenation.

The hydroxyl group at C-14 position can be also eliminated treating the silyl ether substrate **I-30** with methanesulfonyl chloride (MsCl) leading to the alkene **I-51**. Under this reaction condition, only this alcohol is eliminated, the others at C-11 and C-5 positions are not involved (scheme 19).[52]



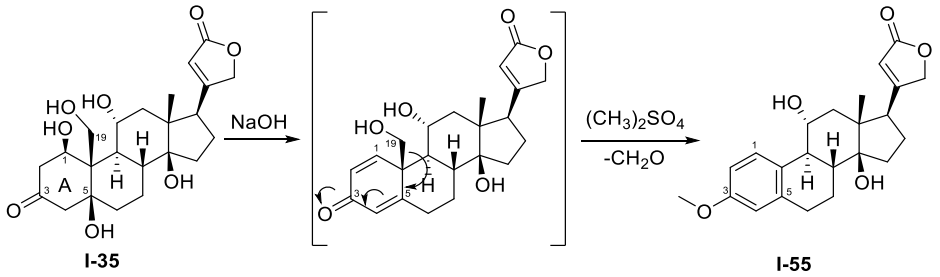
Scheme 19. Dehydration of tertiary alcohol at C-14 of sylil protected Ouabagenin.

Furthermore, the secondary alcohol at C-1 position has been selectively eliminated by treating the diketone **I-40** with basic alumina (Al_2O_3) in boiling ethanol. The unsaturated diketone **I-52** has been hydrogenated using Pd/C under H_2 pressure, obtaining the intermediate **I-53** which has lost the tertiary alcohol at C-5 position after treatment with acid (**I-54**) (scheme 20).[56]



Scheme 20. Dehydration of secondary and tertiary alcohols at C-1 and C-5 positions of diketone derivative.

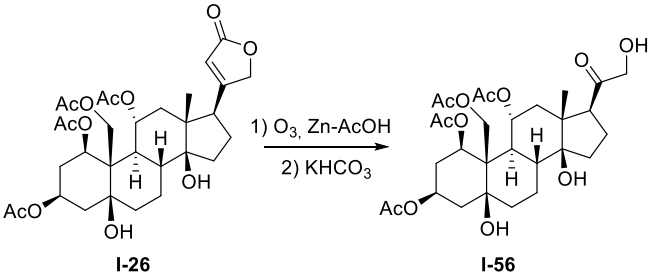
However, Ouabain may undergo aromatization of the ring A, as shown in scheme 21. Indeed, by treating ketone **I-35** with sodium hydroxide (NaOH), the two alcohols at C-1 and C-5 positions are eliminated by β-elimination. The subsequent retroaldolic reaction has resulted in the elimination of primary alcohol at C-19 position as formaldehyde and the reduction of ketone at C-3 position to alcohol that is methylated by dimethylsulfate ($(CH_3)_2SO_4$), obtaining the final aromatic compound **I-55**.[54]



Scheme 21. Aromatization of ring A of Ouabagenin's ketone derivative.

The opening of lactone can be generated by ozonolysis, thus if the tetracetate intermediate **I-26** is treated with zinc (Zn) in acetic acid and potassium hydrogen carbonate ($KHCO_3$), the α-hydroxyl ketone **I-56** is afforded (scheme 22).[65]

Recent reactions regarding the opening of the lactone with consequent modification date back to 2018.[44,65]

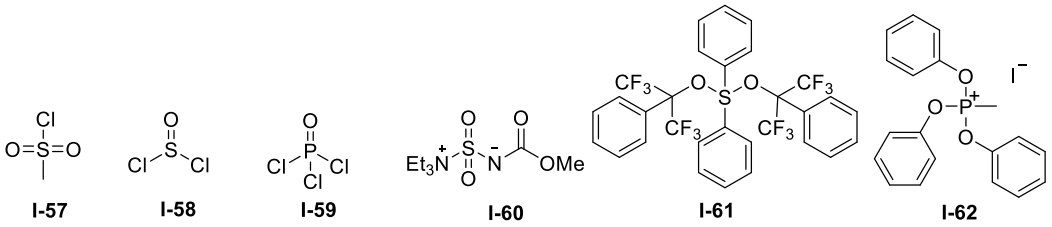


I-26 I-56

Scheme 22. Lactone opening by ozonolysis.

To summarize, in most cases the elimination of an alcohol and the subsequent formation of alkene is guaranteed by using dehydrating reagents, like methanesulfonyl chloride (MsCl) (**I-57**), thionyl chloride ($SOCl_2$) (**I-58**) and phosphoryl chloride ($POCl_3$) (**I-59**). They are the most easily accessible reagents but due to their high reactivity can origin other side products.

Other dehydrating reagent such as *Burgess* reagent (**I-60**),[66] *Martin's Sulfurane* (**I-61**)[67] and methyltriphenoxyphosphonium iodide (MTPI) (**I-62**)[68] can offer more selective methods (figure 8) because of their mechanism of action and steric bulk. The final alkene can be reduced using different hydrogenation methods (*i.e.,* Pd/C and H_2).

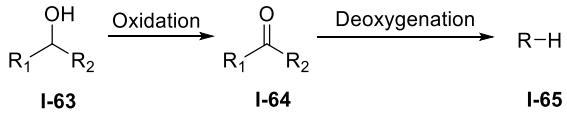


I-57 I-58 I-59 I-60 I-61 I-62

Figure 8. Dehydrating reagents.

1.6.3.2. Defunctionalization of carbonyl group

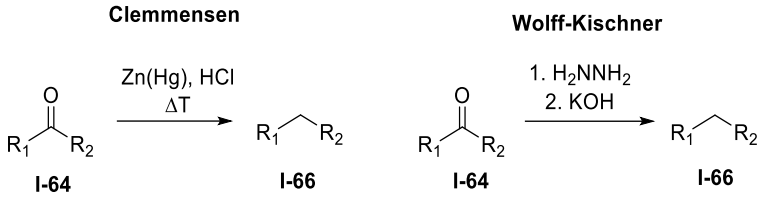
The deoxygenation can be carried out also involving a carbonyl group (scheme 23).



I-63 I-64 I-65

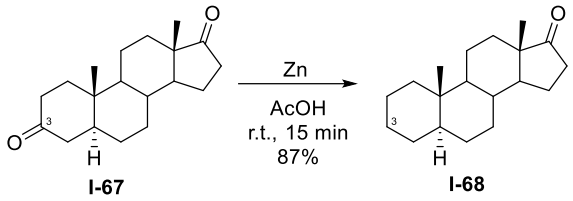
Scheme 23. Deoxygenation of ketone.

The most common reactions are the *Clemmensen* reduction,[69] which employs zinc in acidic conditions, and the *Wolff-Kischner* reduction,[70] which requires hydrazine and strongly basic conditions (scheme 24).



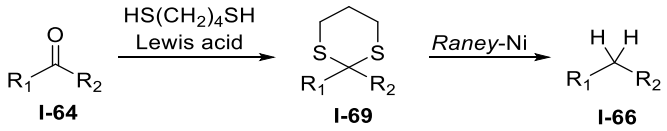
Scheme 24. *Clemmensen* and *Wolff-Kischner* reactions.

By using the *Clemmensen* reduction, selective deoxygenation of the ketone at C-3 position of steroid **I-67** can be obtained (scheme 25).[71]



Scheme 25. Selective deoxygenation of ketone at C-3 position of derivative **I-67**.

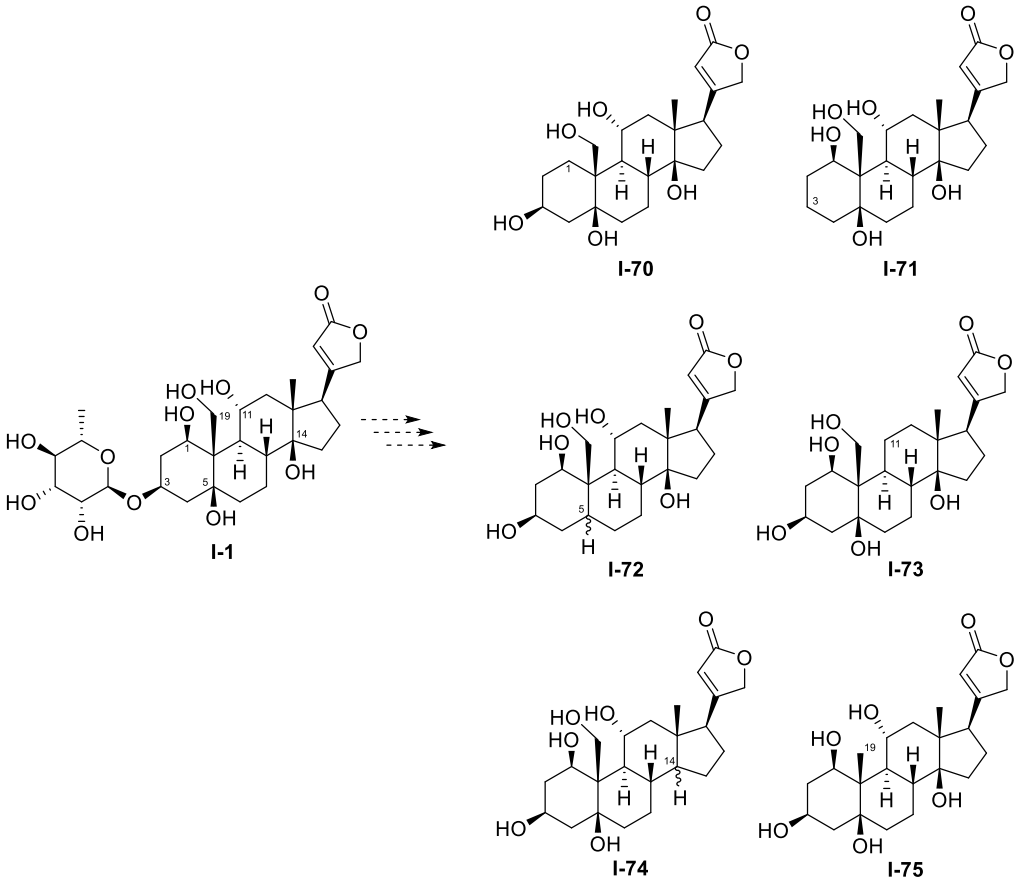
As an alternative method, the ketone can first be converted into a dithian derivative **I-69** and then desulfurized using *Raney* nickel as catalyst (scheme 26).[72]



Scheme 26. Ketone deoxygenation by using *Raney Nickel* catalyst.

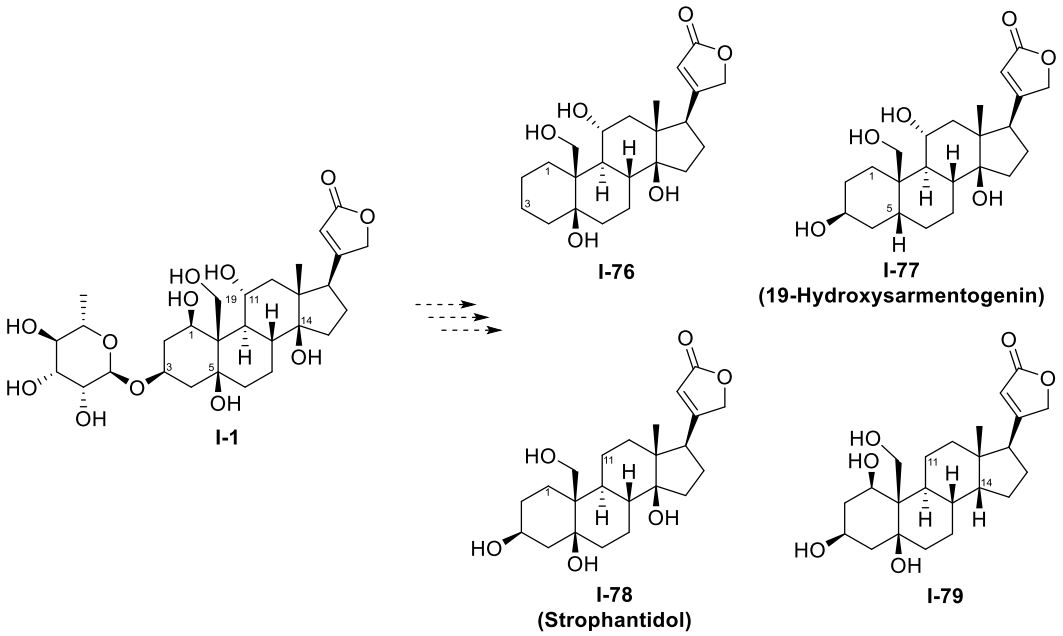
2. Task

The first aim of this project consists of selectively eliminating all six alcoholic functions present in Ouabain's structure, obtaining the final derivatives **I-70** to **I-75** shown in scheme 27, without changing the stereocenter of the remaining hydroxyl groups, the steroid structure and the γ-lactone.



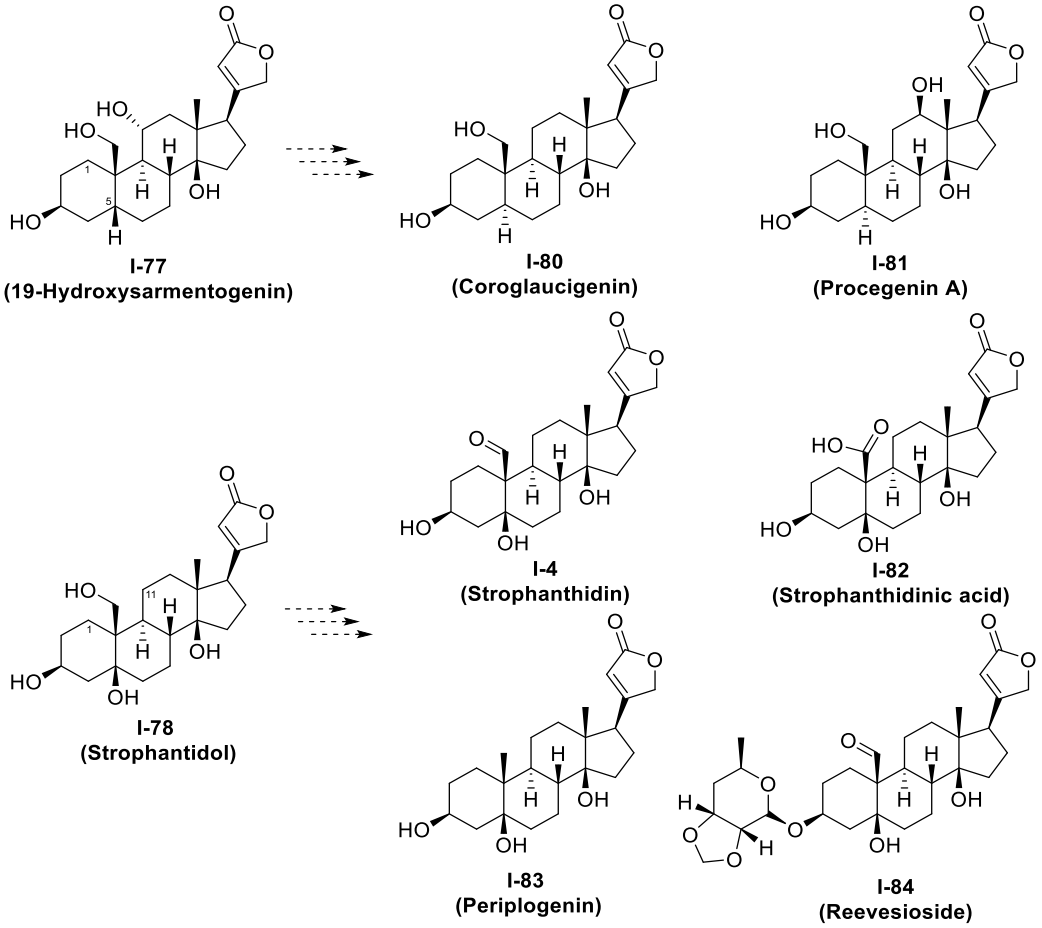
Scheme 27. Final desired products should be synthesized by selective defunctionalization of Ouabain.

The second goal of this project consists of selectively removing two of the six alcoholic functions present in Ouabain's structure, achieving the final derivatives **I-76** to **I-79** shown in scheme 28. In this case, it is also important not to change the stereocenter of the remaining hydroxyl groups, the steroid structure and the γ-lactone as well.



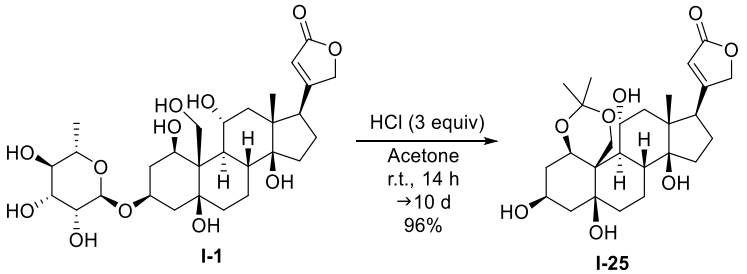
Scheme 28. Final desired products should be obtained by selectively elimination of two alcoholic functions.

The desired products **I-77** and **I-78** represent key molecules for the synthesis of well-known natural products **I-4** and **I-80** to **I-84**, highlighted in the scheme 29.



Scheme 29. Final desired natural products.

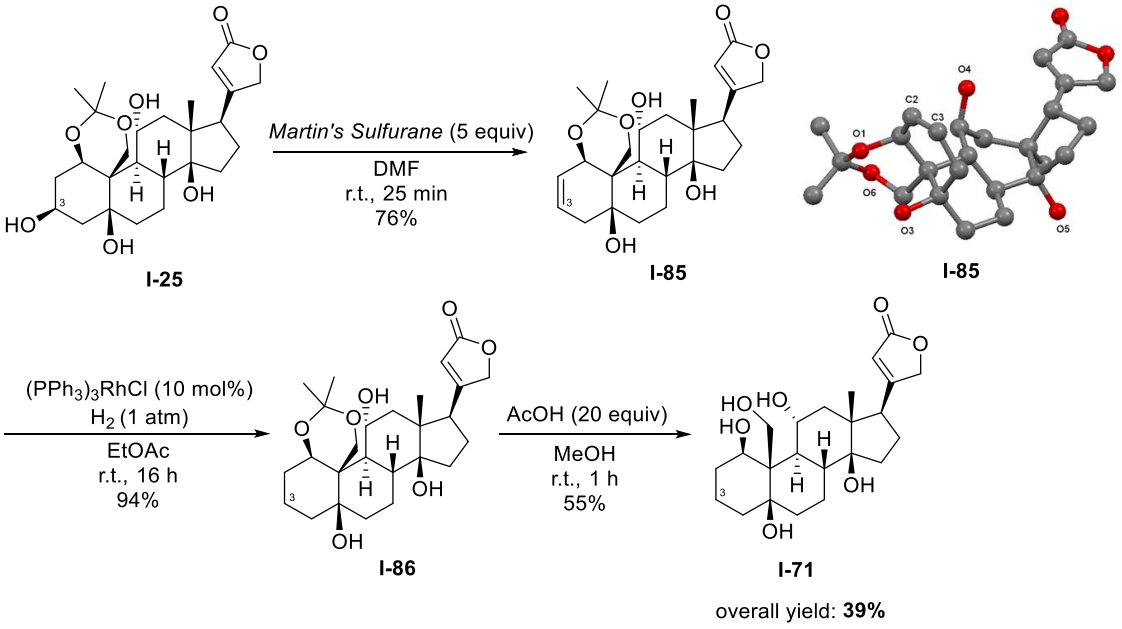
In order to reach the desired final products, the use of protecting groups and oxidation, elimination and deoxygenation reactions, generally described above, are required.
Before showing how these final products might be synthesized, it is necessary to specify that the starting material used for each pathway is represented by acetonide Ouabagenin **I-25**, achieved by treating the Ouabain **I-1** with hydrochloric acid (HCl) in acetone, in 96% yield (scheme 30).



Scheme 30. Synthesis of acetonide Ouabagenin **I-25.**

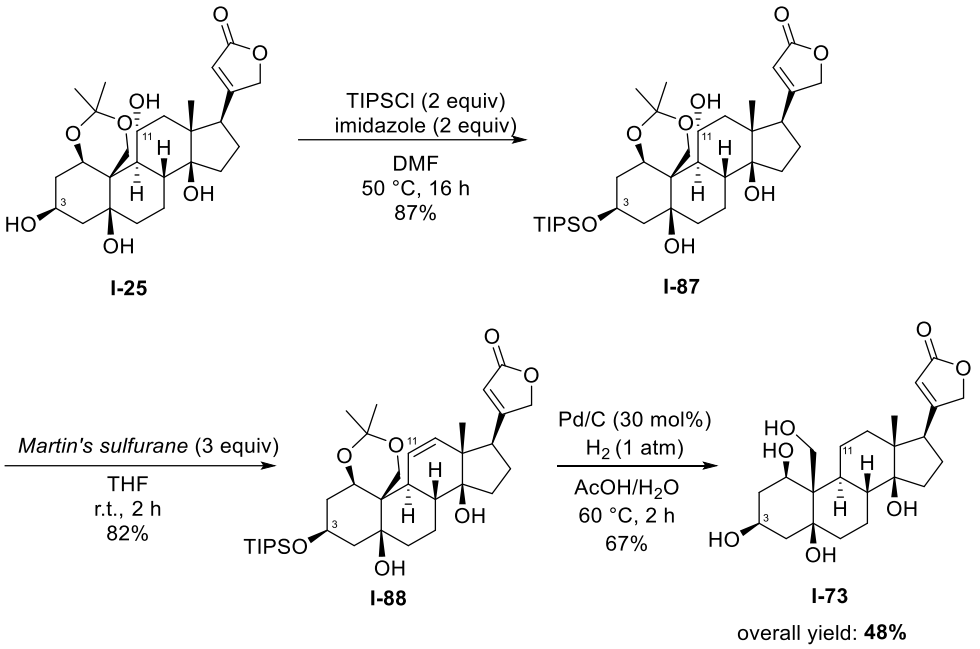
Specifically, derivatives **I-71, I-73** and **I-79** have been previously synthesized by Dr. *Torsten Cellnik*.[73]

The deoxygenated product **I-71** was obtained from acetonide Ouabagenin **I-25** *via* a three-step sequence in 39% overall yield (scheme 31). First, the alcohol at C-3 position was selectively eliminated, by using *Martin's Sulfurane* (**I-61**) dehydrating reagent, in 76% yield. The resulting alkene intermediate **I-85** (confirmed by a crystal structure) was hydrogenated with *Wilkinson*'s catalyst in 94% yield. In the last step, the deprotection of **I-86** with acetic acid in methanol gave the desired product **I-71** in 55% yield.



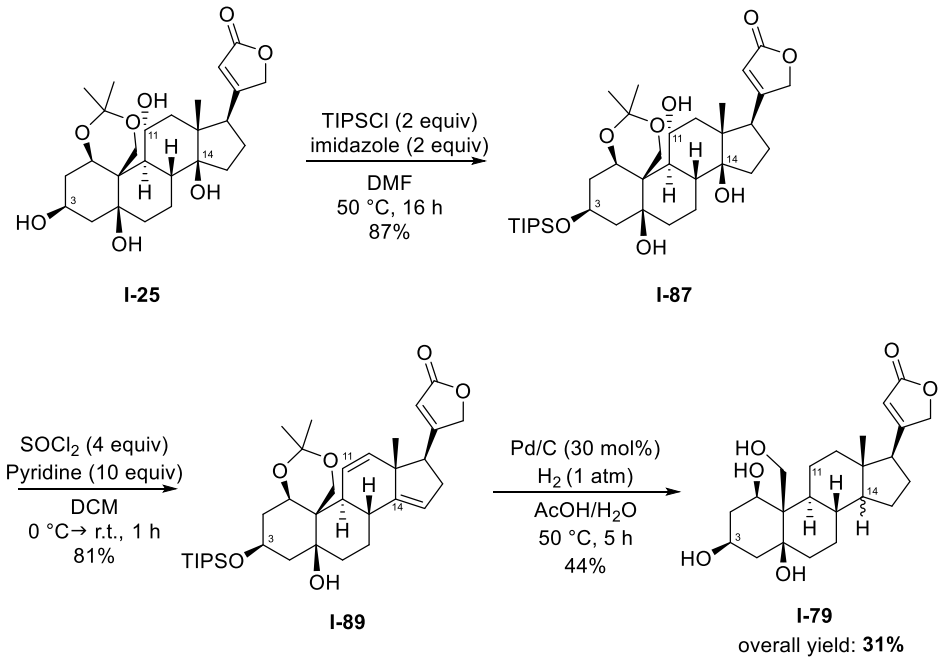
Scheme 31. Defunctionalization of acetonide Ouabagenin **I-25** at C-3 position (**I-71**).

Compound **I-73** was formed from acetonide Ouabagenin **I-25** by a three-step sequence in 48% overall yield (scheme 32). At the beginning, the secondary alcohol at C-3 position was protected with TIPSCl, obtaining intermediate **I-87** in 87% yield. Then, the hydroxyl group at C-11 position was eliminated using *Martin's Sulfurane* (**I-61**), achieving alkene **I-88** in 82% yield. The followed hydrogenation and deprotection led to final compound **I-73** in 67% yield.



Scheme 32. Defunctionalization of acetonide Ouabagenin at C-11 position (**I-73**).

The final product **I-79** was synthesized from acetonide Ouabagenin **I-25** through a three-step sequence in 31% overall yield (scheme 33). Initially, the secondary alcohol at C-3 position was protected with TIPSCl, obtaining intermediate **I-87** in 87% yield. Then, hydroxyl groups at C-11 and C-14 positions were eliminated using $SOCl_2$ and pyridine, achieving intermediate **I-89** in 81% yield, followed by a simultaneous hydrogenation and deprotection to final compound **I-79** in 44% yield.



Scheme 33. Defunctionalization of acetonide Ouabagenin at C-11 and C-14 position **I-79**.

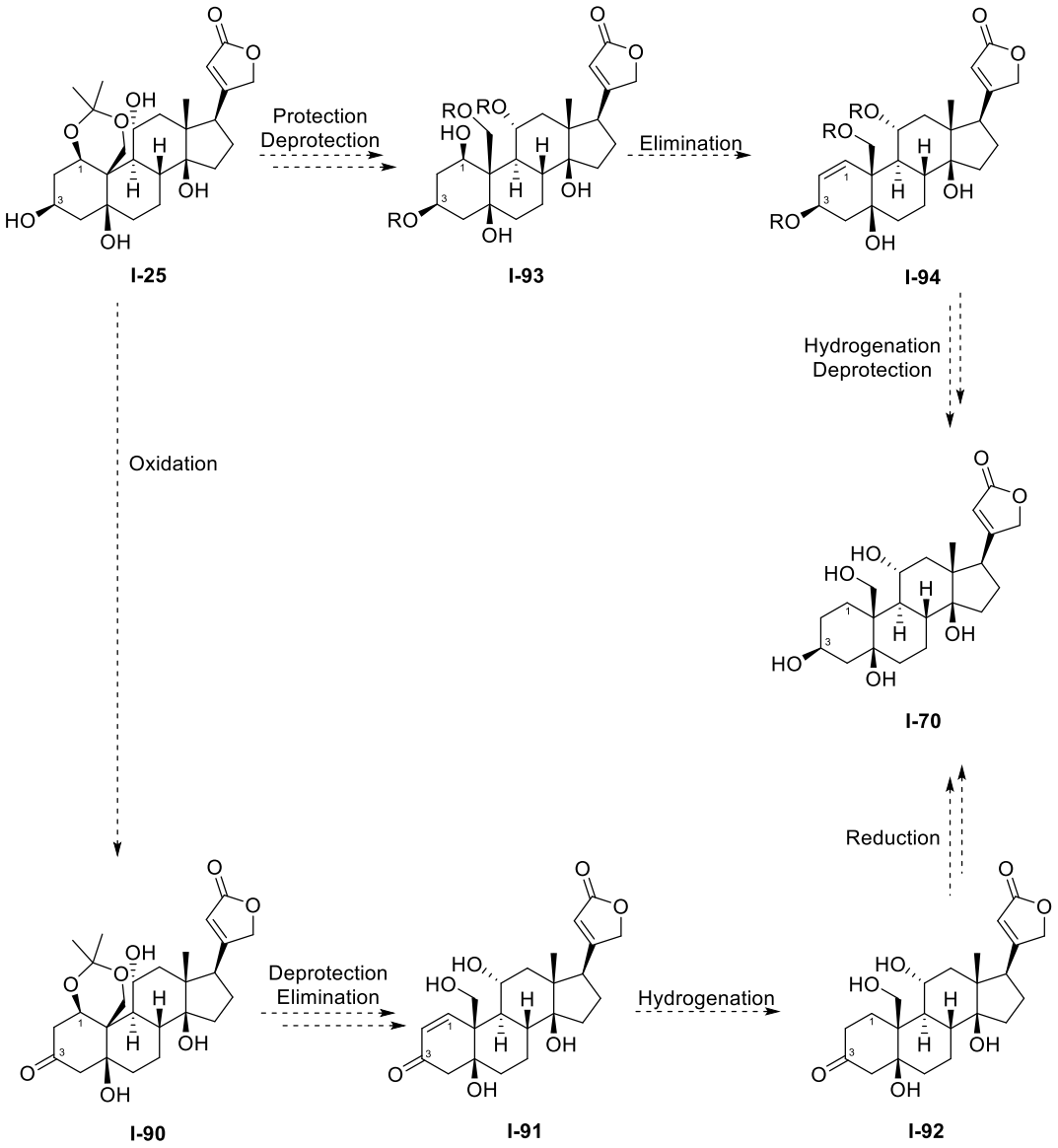
3. Results and discussion

3.1. Defunctionalization of Ouabain: *OH at C-1 position*

For the deoxygenation of the hydroxyl group at C-1 position, two different approaches have been applied, both using acetonide Ouabagenin **I-25** as starting material (scheme 34).

A first approach involved the oxidation of the secondary alcohol al C-3 position to ketone C-3 intermediate **I-90**, which should undergo dehydration and acetonide deprotection simultaneously, leading to unsaturated ketone **I-91**. Reduction of resulting alkene (**I-92**) and ketone should give the desired product **I-70**.

A second route implicated a triprotected intermediate **I-93** which should allow the elimination of the secondary alcohol at C-1 position to alkene **I-94**. Subsequent hydrogenation and deprotection should afford the final product **I-70**.[73]

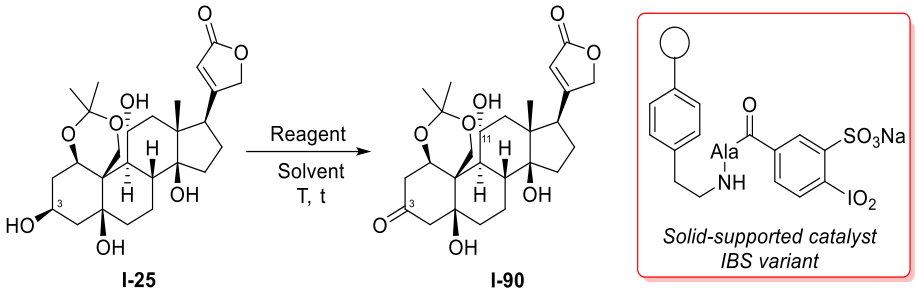


Scheme 34. Two different approaches to synthesize defunctionalized product **I-70**.

3.1.1. Deoxygenation of OH at C-1 position *via* ketone C-3 intermediate

The pathway to synthesize intermediate **I-92** has already been previously analyzed and studied.[73] The oxidation of the alcohol at C-3 position and formation of the corresponding ketone **I-90** represented one of the most problematic steps and different oxidation methods were applied to acetonide Ouabagenin **I-25** (table 1).

Table 1. Different oxidation conditions of hydroxyl group at C-3 position to achieve ketone **I-90**.



I-25 **I-90**

Entry	Reagent (equiv)	Solvent	T (°C)	t (h)	Product[a]
1	IBX (0.50-1.50)	DMSO	r.t.	4→24	- [d]
2	IBX (2.0)	EtOAc/H_2O (5:1)	70	2	- [d]
3	IBX (3.0)	DMSO/H_2O (1:1)	r.t.→40	24	- [d]
4	MnO_2 (5.0-10.0)	DCM	r.t.	4 →24	- [b, c]
5	MnO_2 (5.0-10.0)	Acetone	r.t.	24	- [b, c]
6	MnO_2 (15.0-50.0)	DCM/DMF	r.t.	24→72	- [b, c]
7	Ag_2CO_3 (5.0-15.0) Celite	DMF/Benzene (1:10)	reflux	24	- [d]
8	Oxone (1.20) solid-supported catalyst based on IBS (0.10)	ACN/H_2O	70	18	- [e, f]
9	Al(O-*i*-Pr)$_3$ (3.0)	Cyclohexanone/Toluene (1:6)	reflux	3→18	- [d]
10	Al(O-*i*-Pr)$_3$ (3.0)	Cyclohexanone/Toluene (1:1.5)	reflux	3	- [e]
11	Al(O-*i*-Pr)$_3$ (3.0)	Cyclohexanone/Toluene (1:2.5)	r.t.	20	- [e]
12	PDC (1.50)	DMF	r.t.	24	- [c, d]
13	PtO_2 (0.70)	EtOAc/H_2O (4:1)	50	6	- [d, g, i]
14	PtO_2 (1.50)	EtOAc/H_2O (4:1)	50	6	- [d, g, i]
15	PtO_2 (1.50)	EtOAc/H_2O (4:1)	r.t.	8	38% [g, i]
16	PtO_2 (0.70)	EtOAc/H_2O (1.5:1)	r.t.	8	60% [g, h]
17	PtO_2 (0.70)	EtOAc/H_2O (1.5:1)	r.t.	15	88% [g, h]

[a] Isolated yield after column chromatography. [b] No conversion. [c] Traces of impurities. [d] Product mixture. [e] No desired product. [f] Lactone degradation. [g] 1 atm O_2. [h] PtO_2 anhydrous. [i] PtO_2 hydrate.

By treating the acetonide Ouabagenin **I-25** with different equivalents of the oxidizing agent 2-Iodoxybenzoic acid (IBX) (entries 1-3) in dimethyl sulfoxide, it was not possible to achieve selective oxidation of alcohol at C-3 position. Indeed, the desired product was detected in a mixture with diketone due to simultaneous oxidation of the secondary alcohol at C-11 position (**I-40**), also by changing the reaction time.

Same results were obtained by using silver carbonate (Ag_2CO_3) on celite[74,75] (entry 7) and pyridinium dichromate (PDC)[74,76](entry 12).

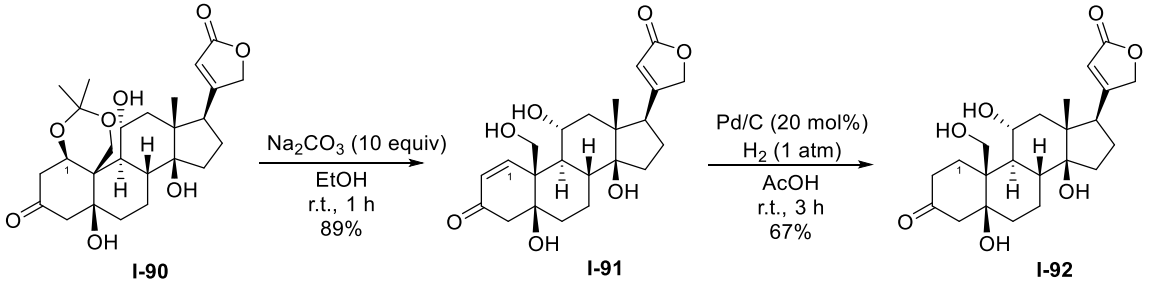
By employing the reaction condition of *Oppenauer* oxidation (entries 9-11),[74,77] the reaction time, temperature and solvent mixture played an important role, because by using aluminium isopropoxide Al(O-*i*-Pr)$_3$ in a solvent mixture of cyclohexanone:toluene (1:6) under reflux conditions from three to eighteen hours, a mixture of mono and diketone compounds was obtained (entry 9). In contrast, by using a solvent mixture cyclohexanone:toluene (1:1.5) at reflux conditions for three hours (entry 10) or cyclohexanone:toluene (1:2.5) at room temperature for twenty hours (entry 11), decomposition was detected.

Only starting material or some traces of impurities were achieved by employing manganese oxide (MnO_2)[74,78] under different reaction conditions (entries 4-6).

Unfortunately, oxidation and degradation of the lactone were observed by treating the acetonide Ouabagenin **I-25** with the solid-supported catalyst designed as a variant of IBS, in the presence of oxone (entry 8).[74,79]

By using PtO_2 hydrate as catalyst, no selectivity was detected by carrying out the reaction at high temperatures, forming a mixture of desired product and diketone (entries 13, 14). However, the same reaction at room temperature led to the desired ketone **I-90** in 38% yield (entry 15). The best results were achieved treating the starting material **I-25** with PtO_2 anhydrous (entries 16, 17) overnight, affording ketone **I-90** in 88% yield selectively. This highlighted that it was possible to obtain selectivity and good yield only by using anhydrous PtO_2 instead of the hydrated one.

After optimizing the oxidation conditions, the ketone intermediate **I-90** was treated with sodium carbonate (Na_2CO_3) in ethanol, losing the acetonide protecting group and, at the same time, eliminating the hydroxyl functionality at C-1 position to yield the unsaturated derivative **I-91** in 89% yield (scheme 35). Then, the double bond was reduced by hydrogenation with Pd/C in acetic acid to generate ketone **I-92** in 67% yield.



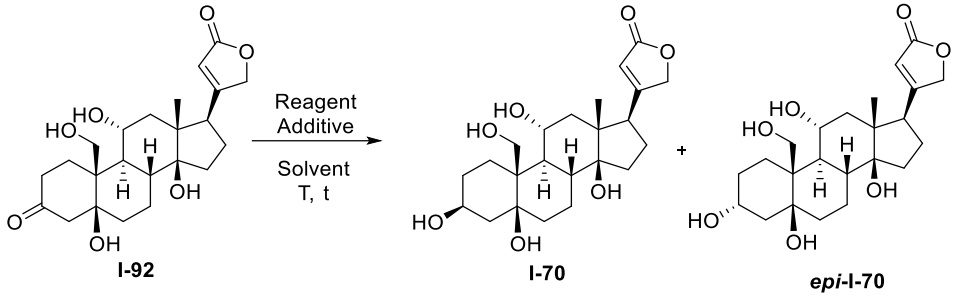
Scheme 35. Deprotection and elimination of hydroxyl group at C-1 position and subsequent hydrogenation of intermediate **I-91** to yield derivate **I-92**.

To achieve the desired final product **I-70**, another step was required: the stereoselective reduction of ketone **I-92** (table 2).

The two main problems of this step concerned both the limitation of the compatible reducing agent, because of the presence of the lactone, and the stereoselective reduction of ketone, avoiding a final mixture of epimers **I-70** and ***epi*- I-70**.

The most plausible reduction turned out to be the known *Luche* reduction,[80] empolying $NaBH_4$, compatible with the lactone moiety being a mild reducing reagent.

Table 2. Different reducing conditions to reduce ketone **1-92** to final compound **I-70**.



Entry	Reagent (equiv)	Additive (equiv)	Solvent	T (°C)	t (h)	Product[a]
1	$NaBH_4$ (1.50)	$CeCl_3$ (0.25)	MeOH	0 → r.t.	0.3	- [f]
2	$NaBH_4$ (1.0)	$CeCl_3$ (0.25)	MeOH	0	1	- [b]
3	$NaBH_4$ (2.0)	$CeCl_3$ (2.10)	MeOH	0	0.5	80% *d.r.* 2.7:1 [d]
4	$NaBH_4$ (1.0)	/	THF/MeOH (1:1)	0	48	- [c]
5	$NaBH_4$ (1.0)	$CeCl_3$ (0.20)	THF/MeOH (1:1)	0	72	- [b]
6	PtO_2 (0.50)	/	EtOH	r.t.	18	- [f, g]
7	*L-Selectride* solution (1.60)	/	THF	-78 → r.t.	2	- [e]
8	$Zn(BH_4)_2$/2NaCl	/	ACN	r.t.	18	- [b]
9	$NaBH_3CN$ (0.50)	/	MeOH	r.t.	18	- [f]

[a] Isolated yield after column chromatography. [b] No conversion. [c] Traces of desired product. [d] Product mixture. [e] No desired product. [f] Decomposition. [g] 1 atm H_2.

As shown in table 2, the reduction was carried out under different reaction conditions, causing decomposition with 1.5 equivalents of $NaBH_4$ in presence of 0.25 equivalents of cerium trichloride ($CeCl_3$) in methanol at 0 °C (entry 1) and any conversion was observed under the same conditions with only one equivalent of reducing reagent (entry 2).

By using a solvent mixture of tetrahydrofuran/methanol[81] and one equivalent of $NaBH_4$, after two days, only traces of conversion were detected (entry 4), but no conversion in the presence of $CeCl_3$ (entry 5).

The ketone intermediate **I-92** was converted into the desired product, by using two equivalents of $NaBH_4$, 2.10 equivalents of $CeCl_3$ in methanol at 0 °C, in 80% yield but as epimers mixture **I-70** and ***epi*-I-70** with a *d.r.* of 2.7:1 (entry 3).

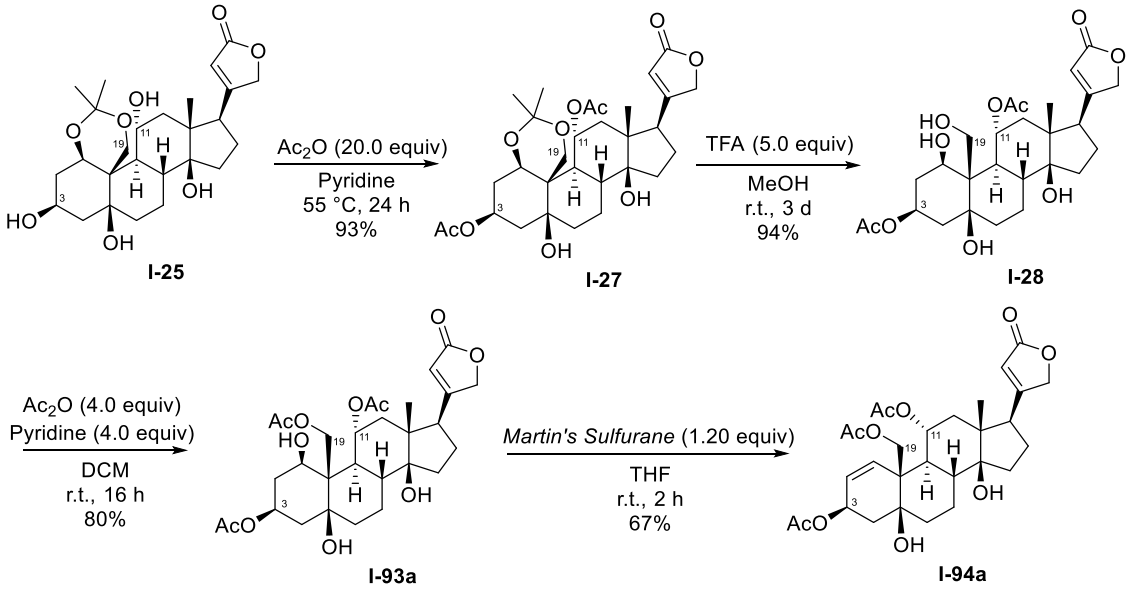
Decomposition was detected after reduction with PtO_2 in ethanol under H_2 pressure (entry 6).

By employing *L-selectride* and stirring the solution for two hours, still traces of ketone **I-92** and a new unknown compound were detected (entry 7).

A novel $Zn(BH_4)_2/2NaCl$[82] reducing system proved to be unsuccessful, resulting in no conversion of the starting material (entry 8).
Decomposition was detected in presence of sodium cyanoborohydride ($NaBH_3CN$) (entry 9).

3.1.2. Deoxygenation of OH at C-1 position *via* protected derivative I-93

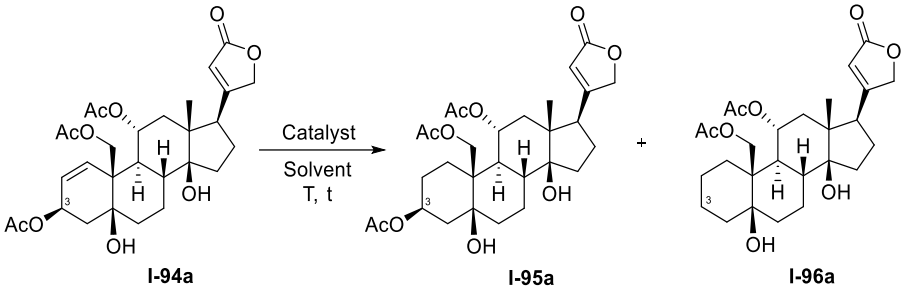
This second route involves intermediates in which the hydroxyl groups at C-3, C-11 and C-19 positions have been protected with different protecting groups as acetate, benzoate and silyl groups.
First, the secondary alcohols at C-3 and C-11 positions of acetonide Ouabagenin **I-25** were protected by using acetic anhydride in pyridine forming the tetra-protected Ouabagenin **I-27** in 93% yield, followed by treatment with trifluoracetic acid to deprotect the acetonide for achieving diol **I-28** in 94% yield.[73]
Subsequently, the primary alcohol at C-19 position was protected with acetic anhydride in pyridine affording the triacetate derivative **I-93a** in 80% yield. Treatment with *Martin's sulfurane* allowed the elimination of secondary alcohol at C-1 position, leading to the unsaturated intermediate **I-94a** in 67% yield (scheme 36).



Scheme 36. Pathway to obtain the unsaturated intermediate **I-94a** from acetonide Ouabagenin **I-25** through triacetate intermediate **I-93a**.

The project focused mainly on selective hydrogenation of the $\Delta^{1,2}$ double bond, applying different reduction condition (table 3).

Table 3. Different hydrogenation conditions to synthesize derivative **I-95a.**



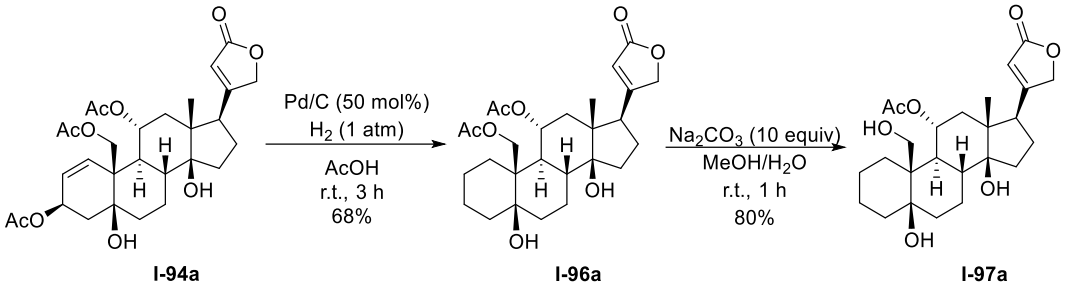
I-94a **I-95a** **I-96a**

Entry	Catalyst (equiv)	Additive (equiv)	Solvent	T (°C)	t (h)	Product[a]
1	$(PPh_3)_3RhCl$ (0.10)	/	Toluene	r.t.	24	- [b, c, e]
2	$(PPh_3)_3RhCl$ (0.10)	/	EtOAc	r.t.	24	- [e]
3	$[Ru(p\text{-cymene})Cl_2]_2$ (0.30)	Cs_2CO_3 (0.020)	*i*PrOH	70	16	- [d]
4	$RuCl_2(PPh3)_3$ (0.20)	Cs_2CO_3 (0.020)	*i*PrOH	70	16	- [d]
5	Pd/C (0.20-0.50)	/	EtOH	r.t.	5	- [b, c, e]
6	Pd/C (0.20 → 0.30)	/	AcOH	r.t.	24	- [b, e]
7	Pd/C (0.33)	/	EtOAc	r.t.	3	- [b, c, e]
8	Pd/C (0.50)	/	AcOH	r.t.	3	- [b, e]
9	$Pd/BaSO_4$ (0.33)	/	EtOAc	r.t.	3	- [b, c, e]
10	$Pd/BaSO_4$ (0.33)	/	AcOH	r.t.	3	- [b, c, e]

[a] Isolated yield after column chromatography. [b] I-96a formation. [c] Lactone reduction. [d] Decomposition. [e] 1 atm H_2.

By using the *Wilkinson*'s catalyst[83] for hydrogenation, the starting triacetate derivative **I-94a** also underwent the reduction of the lactone, without any selectivity (entries 1, 2).
In addition, by using ruthenium catalysts, compound **I-94a** was not converted into the desired compound but only decomposition was detected, probably because of the presence of the base at high temperatures (entries 3, 4).
Different results were achieved by employing Pd/C under different reaction conditions. Indeed, hydrogenation of derivative **I-94a** with 0.2 or 0.5 equivalents of Pd/C in ethanol at room temperature led to the corresponding double hydrogenated compound, also attacking the unsaturated lactone (entry 5).
Surprisingly, the lactone proved to be compatible with Pd/C in acetic acid or ethyl acetate at room temperature but derivative **I-94a** was fully (entry 8), slowly (entry 6) and in mixture (entry 7) converted into an unexpected new product **I-96a**, which didn't show the secondary alcohol at C-3 position in its structure. A mixture of products **I-96a** and the reduced unsaturated lactone were also obtained in presence of palladium on barium sulfate ($Pd/BaSO_4$) (entries 9, 10) in different solvents.
Treatment of the unexpected product **I-96a** with Na_2CO_3 in methanol/water for one hour at room temperature provided the partially deprotected intermediate **I-97a** (scheme 37), obtaining a useful intermediate for the synthesis of another desired

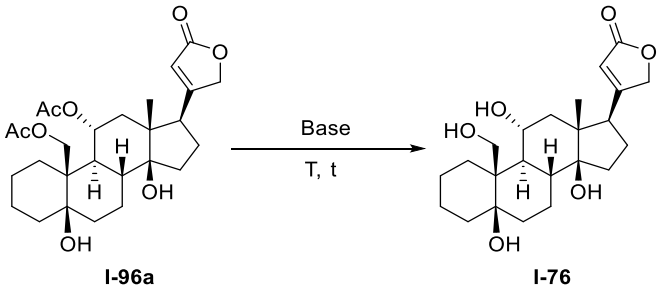
molecule (**I-76**) without two alcoholic functions and belonging to the second aim of this work (scheme 37).



Scheme 37. Unexpected hydrogenation of derivative **I-94a** followed by partial deprotection.

The total deprotection of compound **I-96a** has shown considerable difficulties, mainly due to the lactone, which is extremely sensitive to the required conditions for removing the acetate protecting group (table 4).

Table 4. Screening of fully acetate deprotection of compound **I-96a**.



Entry	Base (equiv)	Solvent	T (°C)	t (h)	Product[a]
1	Na_2CO_3 (2.20)	MeOH/H_2O	r.t.	16	- [d]
2	K_2CO_3 (3.0)	MeOH/H_2O	0 → r.t.	4	- [c]
3	K_2CO_3 (10.0)	MeOH/H_2O	0	48	- [b]
4	K_2CO_3 (20.0)	MeOH/H_2O	0	48	- [c]
5	K_2CO_3 (2.0)	MeOH	0 → r.t.	24	- [c]
6	Na_2CO_3 (10.0)	MeOH/H_2O	r.t. → 40	6	39%
7	Na_2CO_3 (10.0)	MeOH/H_2O	r.t.	16	50%
8	Sat. solut. Na_2CO_3	MeOH	r.t.	24	- [c]

[a] Isolated yield after column chromatography. [b] Dirty desired product. [c] Decomposition. [d] Unknown product.

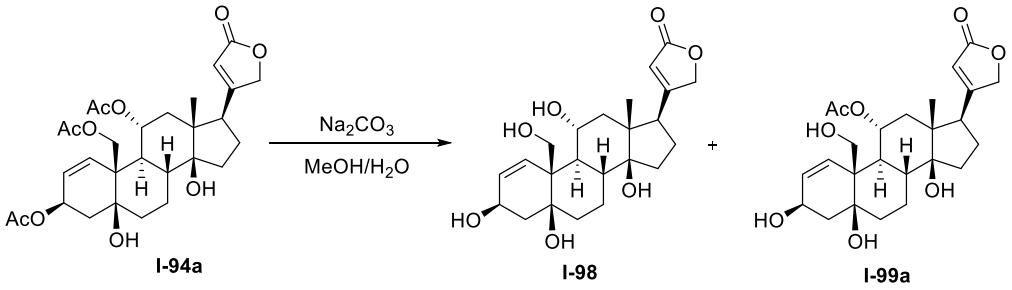
As shown in table 4, different reaction conditions were tested, always using weak bases due to the presence of the lactone. The two bases mainly involved are Na_2CO_3 and K_2CO_3.

By treating the starting material **I-96a** with K_2CO_3, decomposition or desired but extremely dirty product were detected (entries 2-5).

The use of a saturated Na_2CO_3 solution caused decomposition (entry 8) and by using fewer equivalents of this base, the desired product was not detected (entry 1).
The compound **I-76** was obtained only using about 10 equivalents of Na_2CO_3 in methanol/water in 39% yield at 40 °C for six hours (entry 6).
By carrying out the reaction at room temperature for sixteen hours, the desired product **I-76** was achieved in 50% yields (entry 7).

By analyzing this unexpected reduction (scheme 37) and assuming that the simultaneous elimination of hydroxyl group at C-3 position was promoted by the presence of the acetate protecting group as good leaving group, the reduction was also carried out using the completely deprotected derivative **I-98** as starting material (table 5).
Different reaction conditions were applied to deprotected the compound **I-94a** by using only Na_2CO_3 as a weak base because of the presence of the lactone.

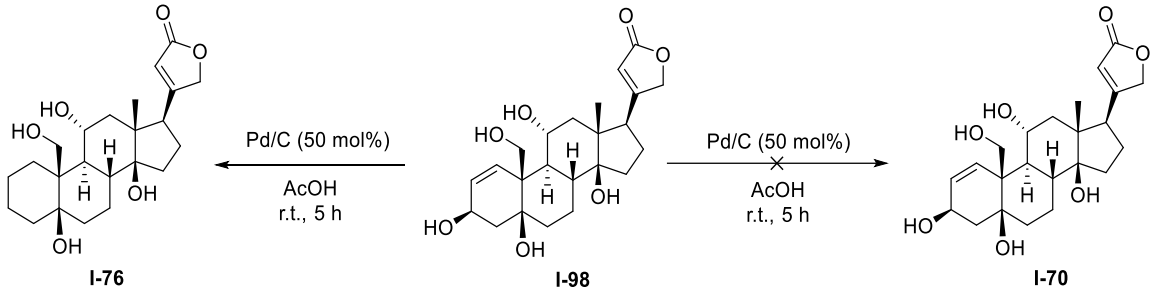
Table 5. Deprotection of triprotected intermediate **I-94a.**



Entry	Na_2CO_3 (equiv)	T (°C)	t (h)	Product[a]
1	3	40	24	32%
2	10	r.t.	24	82% [b]
3	10	r.t.	16	54%

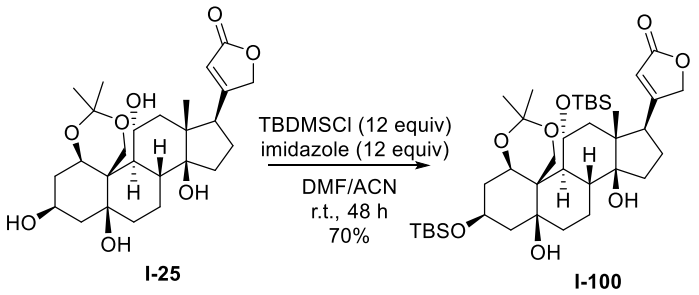
[a] Isolated yield after column chromatography. [b] Partial deprotection.

As shown in table 5, the desired product was obtained in a low yield of 32% using three equivalents of Na_2CO_3 in methanol/water at 40 °C (entry 1).
By increasing the equivalents to ten and carrying out the reaction at room temperature for one day, the yield improved to 54% (entry 3). Under the same conditions, the partially deprotected product **I-99a** was achieved after forty-five minutes in 82% yield (entry 2).
Nevertheless, this alternative route showed the same result as before, thus deoxygenation of two different hydroxyl groups (**I-76**) was achieved instead of the desired compound **I-70** (scheme 38).



Scheme 38. Alternative route to afford defunctionalized final product **I-70.**

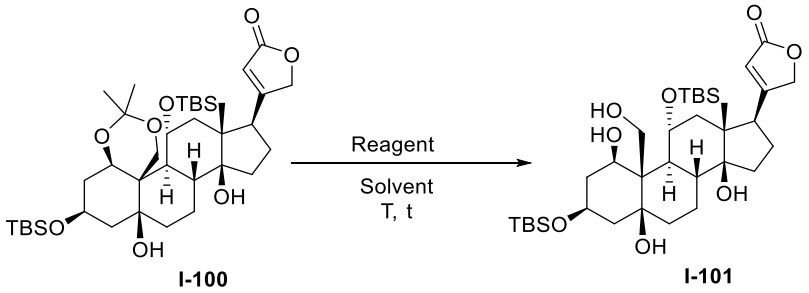
To avoid this problem, different protecting groups than acetate have been tried, initially choosing more stable ones as TBS,[73] achieving intermediate **I-100** (scheme 39).



Scheme 39. Acetonide Ouabagenin protection by using TBSCl.

The TBS protection was followed by acetonide deprotection to achieve diol **I-101**, but this showed to be the most limiting step of the route due to the difficult selective deprotection of the acetonide, since both protecting groups are sensitive to acidic conditions. For this reason, different reaction conditions were applied, resulting in unsatisfactory results (table 6).

Table 6. Acetonide deprotection of intermediate **I-100**.



Entry	Reagent (equiv)	Solvent	T (°C)	t (h)	Product[a]
1	/	H_2O	90	7	- [b]
2	/	DMSO/H_2O (10:1)	90	6	- [c]
3	$CeCl_3 \cdot 7H_2O$ (2.0) $(COOH)_2$ (0.05)	ACN	r.t.	5	53%

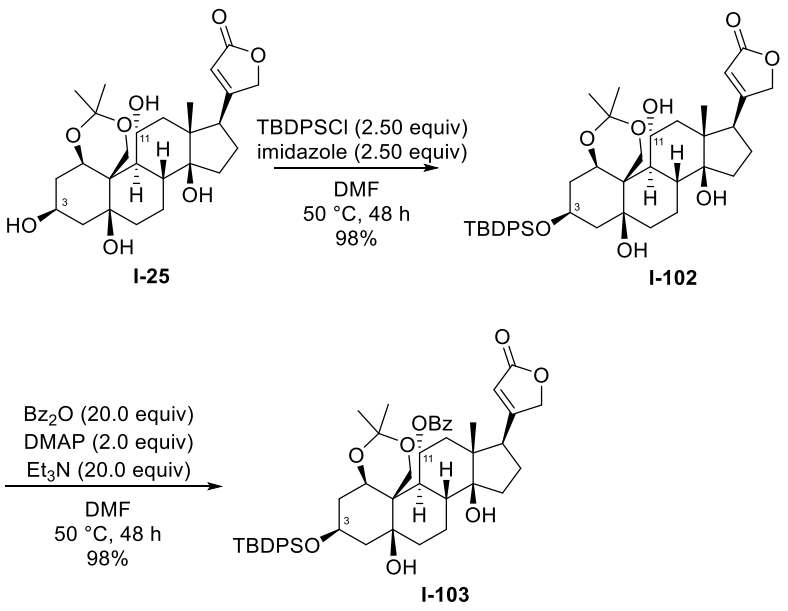
[a] Isolated yield after column chromatography. [b] No desired product. [c] No conversion.

A first approach consisted of treating compound **I-100** only with water (entry 1) at high temperatures,[84] obtaining a completely deprotected product, thus involving not only the acetonide but also the TBS group. By employing a mixture of water/dimethylsulfoxide 1:10 (entry 2),[73,84] no conversion of the starting product was noticed.

It was possible to synthesize the final product **I-101** by handling the acetonide product **I-100** with $CeCl_3$ heptahydrate and oxalic acid in acetonitrile at room temperature (entry 3).[85] Unfortunately, the final product proved to be extremely unstable, probably due to the TBS group jumping between the hydroxyl groups. Indeed, crude NMR and TLC showed several different products without acetonide but with TBS protecting group.

Subsequently, facing this obstacle, different protecting groups were employed, such as the TBDPS to protect the hydroxyl group at C-3 position and the benzoate for the hydroxyl group at C-11 position (**I-103**), as shown in scheme 40.

Thus, acetonide Ouabagenin **I-25** was, first, protected with TBDPSCl giving intermediate **I-102** that in presence of benzoic anhydride (Bz_2O) was converted to protected compound **I-103**.[73]

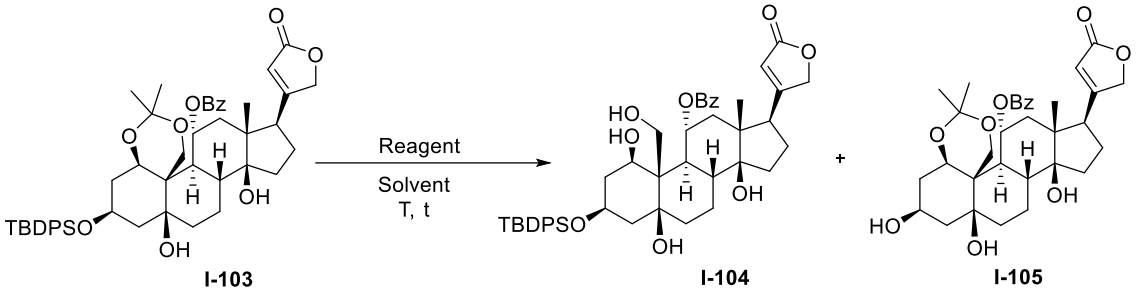


Scheme 40. TBDPS and Bz protection of acetonide Ouabagenin **I-25**.

Unfortunately, also in this case the selective deprotection of the acetonide protecting group represented a limiting step for the simultaneous deprotection of the TBDPS.

As shown in table 7, several reaction conditions were applied but with unsatisfactory results.

Table 7. Acetonide deprotection of derivative **I-103.**



I-103 **I-104** **I-105**

Entry	Reagent (equiv)	Solvent	T (°C)	t (h)	Product[a]
1	$CeCl_3 \cdot 7H_2O$ (2.0) $(COOH)_2$ (0.05)	ACN	r.t.	16	- [b]
2	/	H_2O	90	48	- [c]
3	/	H_2O/DMSO (1:10)	90	24	- [d]
4	TFA (2.42)	H_2O/THF (1:4)	r.t.	16	- [e]
5	$PdCl_2(CH_3CN)$ (0.10)	ACN/H_2O (3:1)	65	3	- [d]
6	$PdCl_2(CH_3CN)$ (0.10)	ACN/H_2O (3:1)	r.t.	24	- [c]
7	$PdCl_2(CH_3CN)$ (0.10)	ACN/H_2O (10:1)	65	6	31% [b]
8	$PdCl_2(CH_3CN)$ (0.10)	ACN/H_2O (6:1)	65	24	49% [b]
9	$PdCl_2(CH_3CN)$ (0.10)	ACN/H_2O (4:1)	65	6	73% [b]

[a] Isolated yield after column chromatography. [b] I-105 formation. [c] No conversion. [d] Decomposition. [e] Full deprotection.

Initially, the same reaction conditions, used previously on compound **I-100**, were applied for the synthesis of derivative **I-104**, without obtaining the desired results (entries 1-3). In case of entry 1, only deprotection of TBDPS was achieved, forming product **I-105**.

A non-selective deprotection of the acetonide but also of the TBDPS was achieved in presence of TFA in water/tetrahydrofuran (entry 4).[86]

After treatment of protected compound **I-103** with bis(acetonitrile)dichloropalladium (II) ($PdCl_2(CH_3CN)$) catalyst, different results by varying the reaction temperature and the *ratio* between acetonitrile and water as solvents were detected.[87]

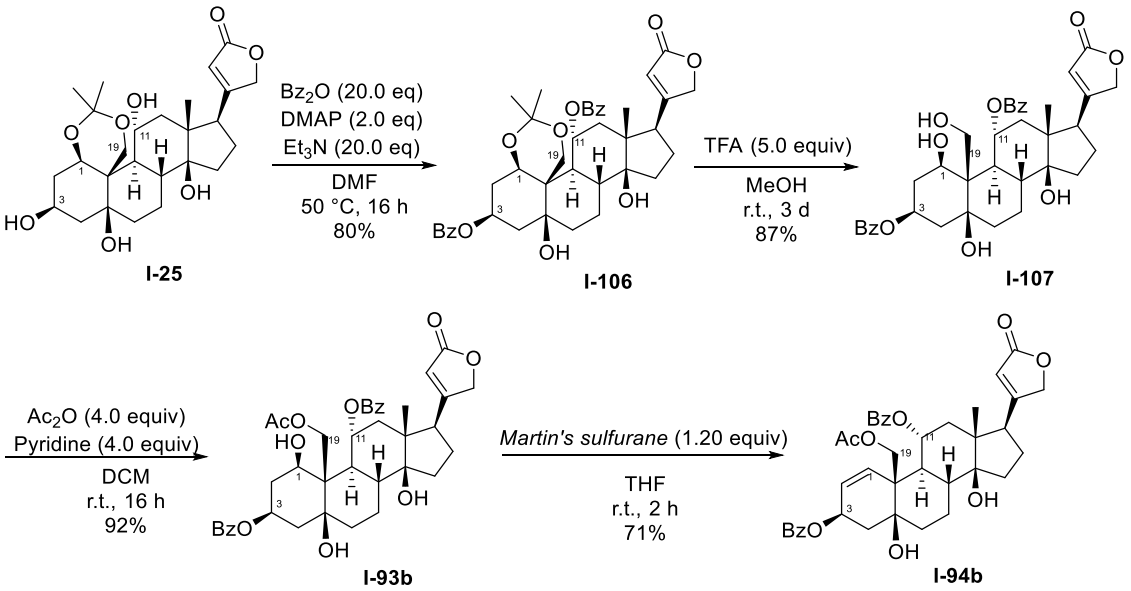
A selective deprotection of acetonide was not detected by using a 3:1 acetonitrile/water *ratio* both at room temperature (entry 6) for twenty-fours hours, which indicated no conversion, and at 65 °C (entry 5) for three hours after which decomposition was observed.

The desired derivative was synthesized and analyzed using a solvent *ratio* of 10:1, 6:1 and 4:1 at 65 °C in 31% (entry 7), 49% (entry 8) and 73% (entry 9) yields, respectively. The analysis of the final product showed a compound highly dirty and, in addition, this step turned out to be not easily reproducible, because whenever these reaction conditions were applied, the desired product was synthesized in a low yield due to the simultaneous deprotection of the TBDPS.

For this reason, a further pathway was developed (scheme 41) by using the benzoate protecting group that is not sensitive to acidic conditions, in order to selectively remove the acetonide, and it is bulkier than acetate so as to avoid the double elimination of alcohols at C-1 and C-3 positions, as in case of derivative **I-96a**.

This route is similar to the one analyzed above, involving the triacetate derivative (scheme 36). Therefore, acetonide Ouabagenin **I-25** was initially double protected with benzoate, achieving intermediate **I-106** which, if treated with TFA in methanol, underwent deprotection of acetonide achieving product **I-107** (scheme 41).

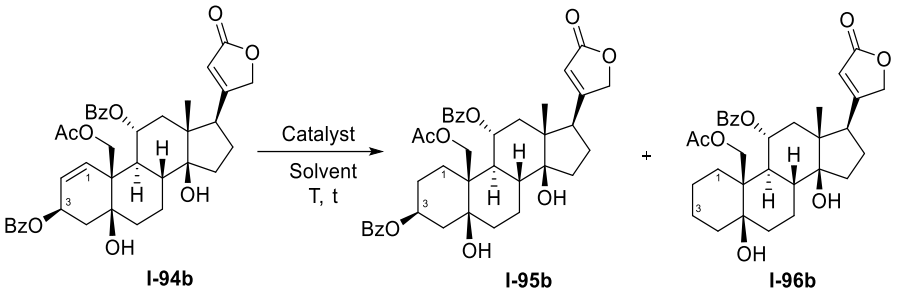
The primary alcohol at C-19 position was then further protected with acetic anhydride, thus obtaining the triprotected intermediate **I-93b**. By using *Martin's Sulfurane*, the secondary alcohol at C-1 position was eliminated with the formation of the unsaturated intermediate **I-94b**.



Scheme 41. Pathway to synthesize unsaturated intermediate **I-94b** from acetonide Ouabagenin **I-25**.

The next step, as previously analyzed (table 3), was based on the hydrogenation of the double bond of the unsaturated intermediate **I-94b** to synthesize compound **I-95b** which, following a deprotection, should allow the synthesis of the desired final product **I-70** (table 8).

Table 8. Hydrogenation of unsatured compound **I-94b.**



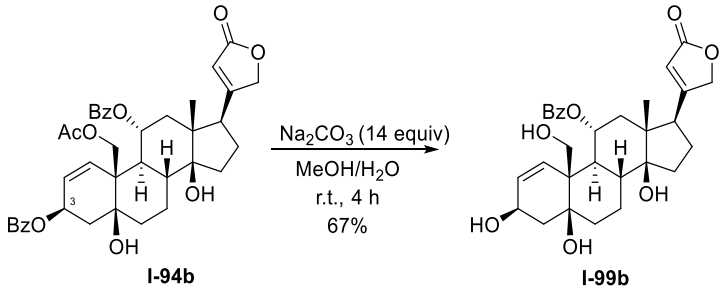
Entry	Catalyst (equiv)	Solvent	H_2 (atm)	T (°C)	t (h)	Product[a]
1	Pd/C (0.20)	AcOH	1	r.t.	3	- [d]
2	Pd/C (0.20)	AcOH	1	r.t.	5	- [b, c]
3	*Crabtree*'s catalyst (0.020)	DCM	50	r.t.	5	- [d]
4	*Crabtree*'s catalyst (0.050)	DCM	1	r.t.	2.5	- [d]

[a] Isolated yield after column chromatography. [b] I-96b formation. [c] No full conversion. [d] No conversion.

By treating the unsaturated compound **I-94b** with Pd/C in acetic acid at room temperature for three hours, only the starting material was detected (entry 1) but increasing the reaction time to five hours, beyond to the starting material **I-94b**, product **I-96b** was observed (entry 2).

In the presence of *Crabtree*'s catalyst,[88] the hydrogenation was carried out by using the autoclave and no conversion was obtained, despite an increase in catalyst equivalents and hydrogen pressure (entries 3, 4).

This difficult hydrogenation could be due to the steric bulk of the benzoate protecting group. Hence, before performing the hydrogenation with *Crabtree*'s catalyst, it was decided to completely deprotect this unsaturated compound with Na_2CO_3 in methanol/water, synthesizing the unexpected product **I-99b** with only partial deprotection of the acetate and the benzoate at C-3 position in 67% yield (scheme 42).

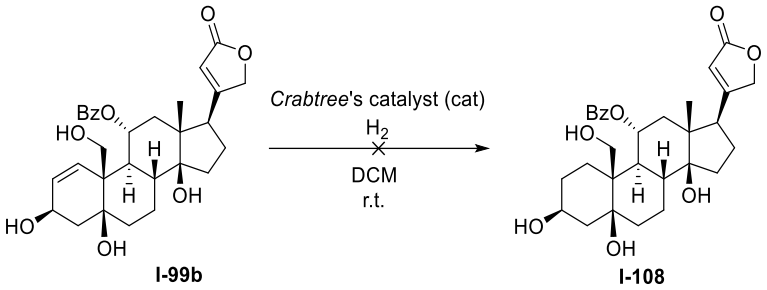


Scheme 42. Partial deprotection of unsatured intermediate **I-94b**.

Unfortunately, a total deprotection of compound **I-94b** was not possible to achieve. The increase of Na_2CO_3 equivalents or temperature did not lead to the desired compound and the addition of K_2CO_3 caused the opening of the lactone.

Despite this, hydrogenation of compound **I-99b** was carried out employing the *Crabtree*'s catalyst, without obtaining the desired result (table 9).

Table 9. Hydrogenation by using *Crabtree*'s catalyst



I-99b **I-108**

Entry	H_2 (atm)	t (h)	Product[a]
1	50	5	- [b]
2	10	2.5	- [b]

[a] Isolated yield after column chromatography. [b] No conversion.

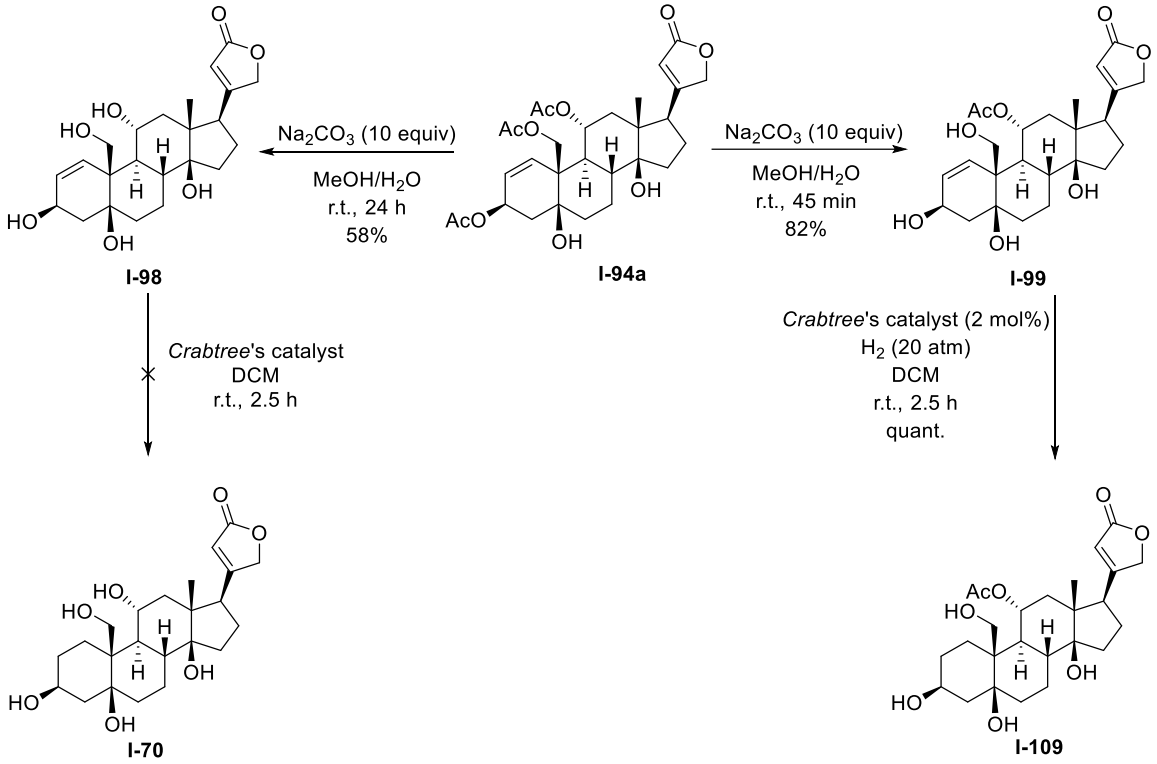
When a hydrogen pressure of 10 or 50 atm was used, the starting material **I-99b** did not show any change, only some impurities were detected.

Since the change in the protecting group did not help in the synthesis of the desired product, more attention was paid again on the triprotected intermediate **I-94a** to study and to search for the optimal conditions of hydrogenation with the *Crabtree*'s catalyst, a reagent extremely difficult to handle because of its extreme sensitivity to oxygen and water (scheme 43).

As shown previously in table 5, the protected product **I-94a** could be partially or completely deprotected using Na_2CO_3 and varying the reaction time.

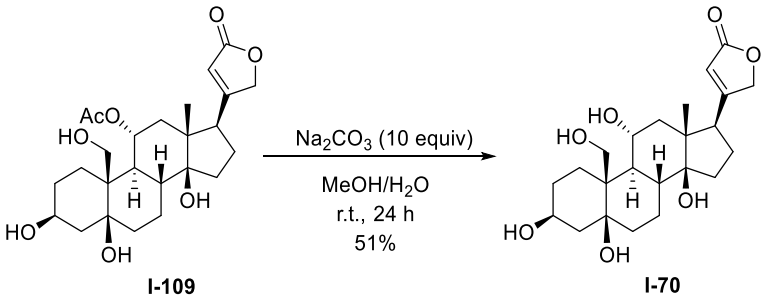
Both partially **I-99** or completely deprotected products **I-98** were treated with the *Crabtree*'s catalyst and hydrogenated under a hydrogen pressure of 20 atm, showing two different results: derivative **I-98** did not undergo any conversion while product derivative **I-99** was hydrogenated and transformed into the desired product **I-109**. This contrasting behavior is probably due to a different solubility in dichloromethane, which is in fact higher in the case of intermediate **I-99**.

It is also important to highlight the attention that this type of reaction requires: it should be carried out in extremely dry conditions, without any presence of oxygen and water (degassed and dry solvent) and with extremely long and repeated hydrogen washing, prior to the hydrogenation itself.



Scheme 43. Hydrogenation with *Crabtree*'s catalyst to reduce $\Delta^{1,2}$ double bond of intermediate **I-94a**.

The hydrogenated compound **I-109** was then deprotected with Na_2CO_3 and the desired final product **I-70** was finally afforded (scheme 44).
The desired product was confirmed by ^{1}H-NMR, ^{13}C-NMR and HRMS data. The analysis of these spectra is reported in the experimental part (*pp. 170-171*).

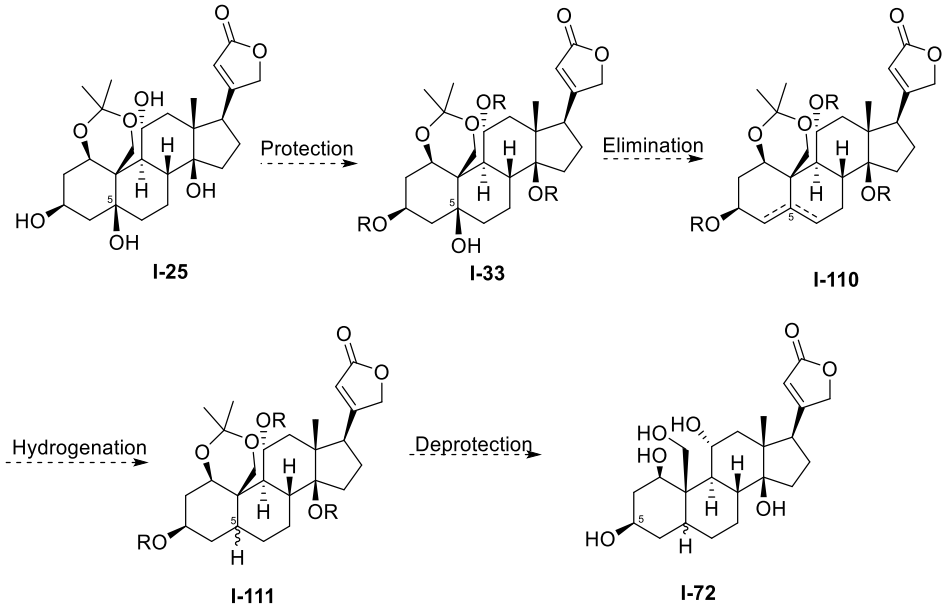


Scheme 44. Deprotection of hydrogenated compound **I-109** to obtain the final product **I-70**.

3.2. Defunctionalization of Ouabain: *OH at C-5 position*

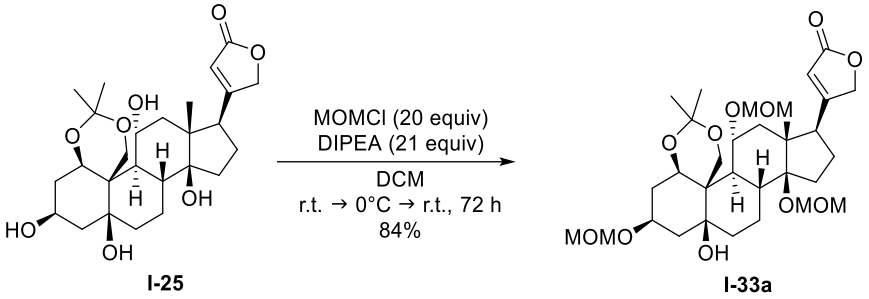
The elimination of hydroxyl at C-5 position encountered considerable obstacles, mainly being the most hindered alcohol compared to the others. The total protection of the alcohols presented at C-1, C-3, C-11, C-19 and C-14 positions should be required to obtain good selectivity.

The protected derivative **I-33** should be treated with dehydrating reagents to eliminate the alcohol, achieving the resulting alkene **I-110** which should be stereoselectively reduced by hydrogenation (**I-111**) to give the desired product **I-72** after global deprotection (scheme 45).



Scheme 45. Pathway for deoxygenation of OH at C-5 position.

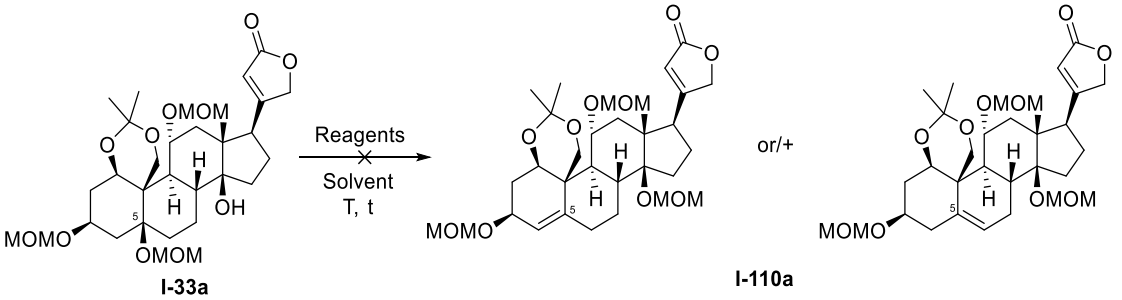
The total protection of alcohols to compound **I-33a** was achieved by treating acetonide Ouabagenin **I-25** with MOMCl protecting group, obtaining the desired protected product in 84% yield (scheme 46).[44]



Scheme 46. MOM protection of acetonide Ouabagenin **I-25.**

The protected derivative **I-33a** was subjected to several dehydration conditions in order to remove the alcohol at C-5 position, as shown in table 10.

Table 10. Elimination of alcohol at C-5 position.



I-33a **I-110a**

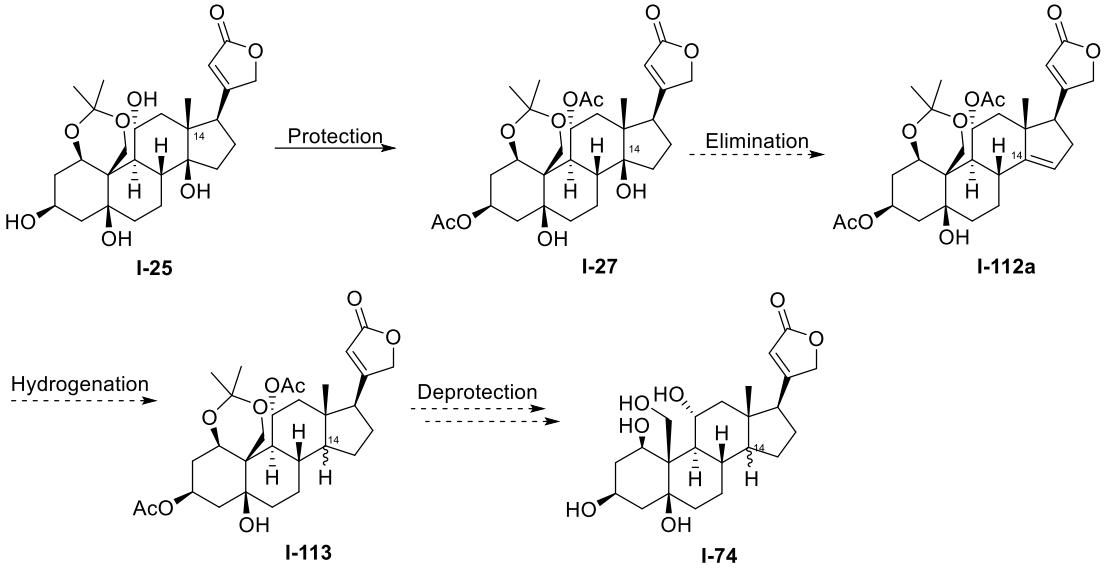
Entry	Reagents (equiv)	Solvent	T (°C)	t (h)	Product[a]
1	DAST (2.0)	DCM	r.t.	32	- [b]
2	DAST (4.0)	DCM	r.t. → 45	1.5 → 120	- [b]
3	$InCl_3$ (0.050) Ph_2SiHCl (2.0)	DCM	r.t. → 30 or 80	3 →19 or 2.15	- [e, f]
4	Ph_2SiH (1.20) TFA (2.0)	DCM	30/r.t.	3 → 18/65	- [e, f]
5	$SOCl_2$ (1.20 → 6.0) Pyr (5.0 → 10.0)	DCM	0	5 → 16	- [e]
6	$SOCl_2$ (3.0) Pyr (3.0) DMAP (4.0)	THF	0 → 50	5	- [e]
7	$SOCl_2$ (8.0 → 40.0)	Pyridine	0 → r.t.	16 → 48	- [e]
8	$SOCl_2$ (3.0) DMAP (4.0) Pyridine (3.0)	THF	0 → 50	24	- [e]
9	*p*-TsCl (3.0 →6.0) SiO_2 (1.0)	DCM	0 °C→ r.t.	30	- [e]
10	MsCl (1.50) Et_3N (3.0) DMAP (4 mol%)	DCM	0 → r.t.	16	- [b, e]
11	$POCl_3$ (1.20) Pyridine (5.0)	DCM	0	120	- [b]
12	$POCl_3$ (3.0 →10.0) Pyr (1.0 → 7.0)	DCM	0 → r.t. → 40	24 → 48	- [b]
13	*Martin's Sulfurane* (1.75 →5.0)	THF	r.t. → reflux	4 → 24	- [b, e]
14	Triphosgene (0.5.0) DMAP (2.0)	DCM/DCE	r.t./reflux	3/2	- [c, d, e]
15	*Burgess* reagent (5.0)	THF THF DCM 1,4-dioxane	reflux 50 r.t. reflux	24 24 6 6	- [c, e]

[a] Isolated yield after column chromatography. [b] No conversion. [c] Not full conversion. [d] Unknown product. [e] Decomposition. [f] Deoxygenation should be achieved

Several reagents were used for the desired elimination, but only starting material **I-33a**, impurities and little decomposition were possible to detect by TLC after treatment with diethylaminosulfur trifluoride (DAST), $POCl_3$ (**I-59**), MsCl (**I-57**) and *Martin's Sulfurane* (**I-61**) (entries 1, 2, 10-13).
In case of *Burgess* reagent (**I-60**), decomposition was always achieved, except for the treatment in THF at 50 °C, where a little conversion to the desired product was noted but then followed by decomposition, probably due to partial or complete deprotection of the MOM protecting group (entry 15).
By using $SOCl_2$ (**I-58**), *p*-TsCl or silyl reagent like Ph_2SiHCl or Ph_2SiH, the protected derivative **I-33a** was converted into several new compounds, thus highlighting decomposition (entries 3-9). The HRMS and LCMS showed the presence of the desired product, whereby a small part is formed during decomposition.
Similar decomposition was detected by treating intermediate **I-33a** with triphosgene and DMAP under reflux conditions for two hours. However, not full conversion to desired products was observed in presence of triphosgene and DMAP at room temperature for three hours (entry 14).[89]

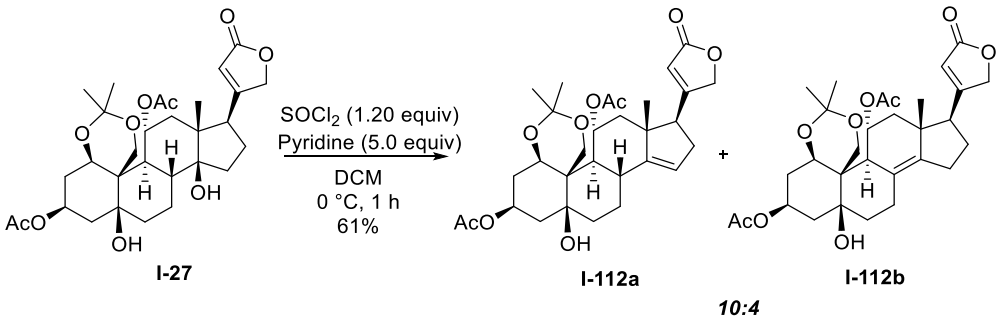
3.3. Defunctionalization of Ouabain: *OH at C-14 position*

The alcohol at C-14 position is a tertiary alcohol as the one at C-5 position, but since it is sterically less hindered, it should be eliminated easier.
In scheme 47, the general pathway to synthesize the desired product **I-74** is summarized. Initially, the acetonide Ouabagenin **I-25** was protected with acetic anhydride obtaining the diacetate compound **I-27**, as previously shown for the elimination of the alcohol at C-1 position (*See paragraph 3.1.2*), followed by the elimination of alcohol at C-14 position (**I-112a**) and subsequent hydrogenation of the double bond (**I-113**). The deprotection of protecting groups should lead to the final compound **I-74**.



Scheme 47. General pathway for synthesizing desired compound **I-74.**

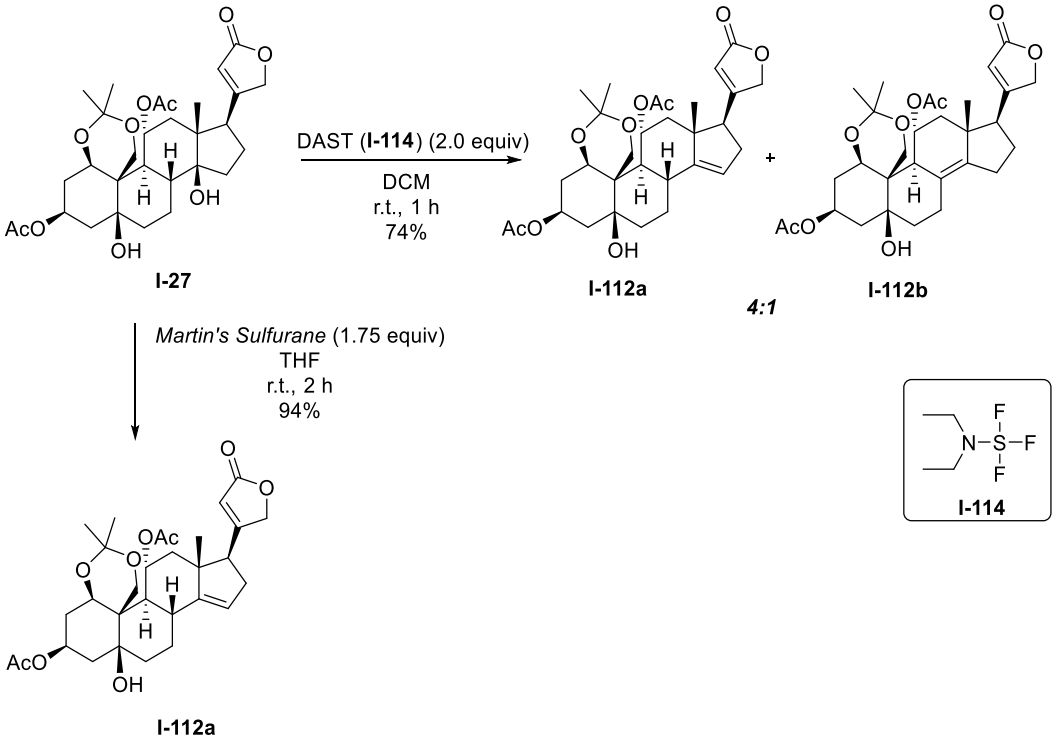
Initially, the elimination of alcohol at C-14 position was carried out by using $SOCl_2$ (**I-58**) and pyridine in dichloromethane, achieving the desired compound **I-112a** in a regioisomer mixture of **I-112a** and **I-112b** in a *ratio* of *10:4*: the desired $\Delta^{14\text{-}15}$ double bond and the undesired $\Delta^{14\text{-}8}$ double bond, which could not be separated by column chromatography (scheme 48). The reaction was also carried out at -15 °C, without any improvement.



Scheme 48. Conversion of diacetate starting material **I-27** to a regioisomer mixture **I-112a** and **I-112b**.

To avoid the formation of the regioisomer mixture, not necessary but desired to overpass further problems related to the subsequent diastereoselective reduction of the double bond, two other different dehydrating reagents were analyzed: DAST (**I-114**) and *Martin's Sulfurane* (**I-61**) (scheme 49).

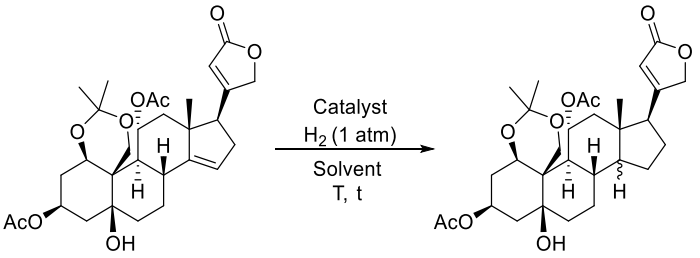
Using DAST, despite the full conversion of the compound **I-27** was observed quickly as in the case of $SOCl_2$ (**I-58**), a mixture of regioisomers was obtained in different *ratio* of *4:1*. *Martin's Sulfurane* proved to be the most suitable, guaranteeing a conversion of the starting material **I-27** into the unsaturated derivative **I-112a**, without any regioisomer mixture, in 94% yield.



Scheme 49. Optimization for a regioselective elimination of OH at C-14 position.

The diastereoselective reduction of the resulting alkene represented the most difficult step due to two main problems: the presence of the unsaturated lactone and the stereoselectivity, being the purpose to synthesize a final single diastereoisomer and not a mixture. Indeed, different reduction conditions were analyzed, as reported in table 11.

Table 11. Optimization of reaction conditions for diastereoselective alkene reduction.



Entry	Catalyst (equiv)	Solvent	T (°C)	t (h)	Product[a]
1	PtO_2 (0.50)	THF	r.t.	18	- [e]
2	Pd/C (0.50)	THF	r.t.	18	- [c, e]
3	Pd/C (0.50/1.0)	AcOH/ propionic acid	r.t./0	5/10	*d.r. 5:1* [d]
4	Pd/C (0.60)	EtOAc	r.t.	24	*d.r. 2:1* [d]
5	Pd/C (0.50)	EtOH	r.t.	24	- [e, g]

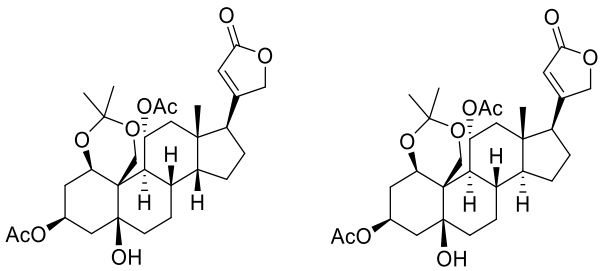
Entry	Catalyst (equiv)	Solvent	T (°C)	t (h)	Product[a]
6	$(PPh_3)_3RhCl$ (0.20)	THF	r.t.	24	- [b]
7	$(PPh_3)_3RhCl$ (0.30/2.76)	Toluene	r.t.	18	- [b]
8	$(PPh_3)_3RuCl_2$ (0.30)	EtOAc	r.t.	18	- [b]
9	$[Ru(p\text{-cymene})Cl_2]_2$ (0.30)	EtOAc	r.t.	18	- [b]
10	Rh/Al_2O_3(0.30)	AcOH	r.t.	48	- [b]
11	Rh/Al_2O_3(0.30)	EtOAc	r.t.	5	- [e]
12	Pt/C (0.30)	EtOAc/AcOH	r.t.	48	- [e]
13	$Pd/BaSO_4$ (0.30)	AcOH	r.t.	4	- [e]

[a] Isolated yield after column chromatography. [b] No conversion. [c] Not full conversion. [d] Product mixture. [e] No desired product. [f] Decomposition. [g] Hydrogenation of unsaturated lactone.

Under certain reaction conditions, some catalysts showed no selectivity in reducing the desired double bond, also causing the reduction or degradation of the lactone, such as Pd/C in ethanol (entry 5), Rh/Al_2O_3 in ethyl acetate (entry 11) and Pt/C in ethyl acetate or acetic acid (entry 12). By using $Pd/BaSO_4$ in acetic acid, only acetonide deprotection was detected (entry 13). However, a partial or complete conversion to an unknown product was obtained using PtO_2 and Pd/C in tetrahydrofuran (entries 1, 2).

Rhodium and ruthenium catalysts reported no interaction with the compound, thus detecting no conversion (entries 6-10). The desired product was detected by treating the alkene **I-112a** with Pd/C in presence of acids as solvents such as acetic or propionic acid both at room temperature and at 0 °C or in ethyl acetate (entries 3, 4).

Unfortunately, the reduction occurred without any diastereoselectivity, thus forming a mixture of the two diastereoisomers **I-113a** and **I-113b** (figure 9) with a *d.r.* equal to 5:1 in case of AcOH and propionic acid (entry 3) and to 2:1 in the case of ethyl acetate (entry 4).



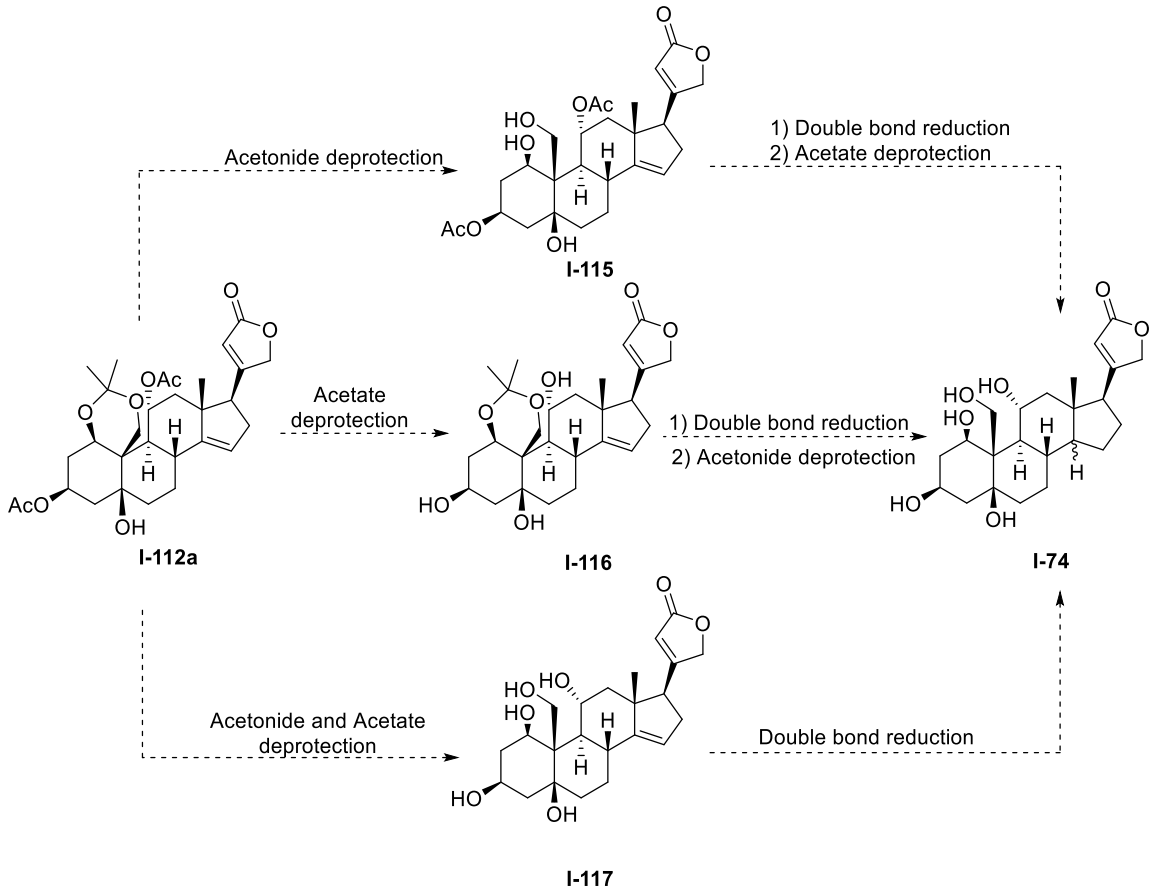
I-113a **I-113b**

Figure 9. Diastereoisomer mixture obtained after reduction of $\Delta^{14\text{-}15}$ double bond.

This proved that, despite the use of various catalysts, solvents or reaction temperatures, a stereoselective hydrogenation was not possible to achieved, hence it was necessary to change the route.

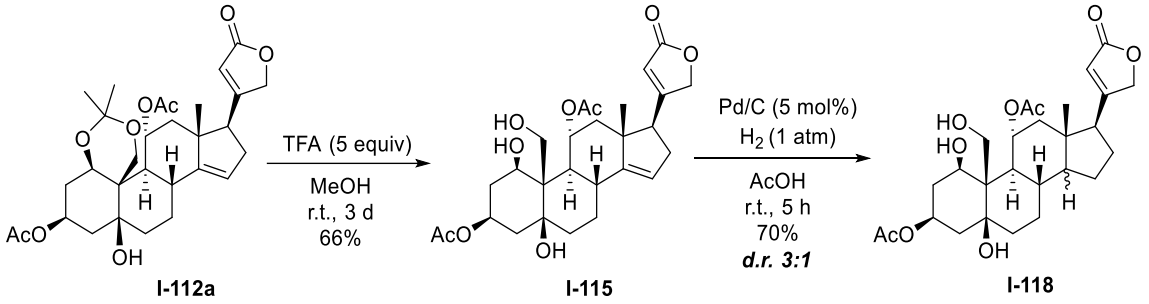
A second approach was based on a direct hydrogenation of the partially and totally deprotected compounds **I-115**, **I-116** and **I-117,** instead of the fully protected one **I-112a** (scheme 50).

Therefore, the starting material **I-112a** should undergo a partial acetonide (**I-115**) or acetate deprotection (**I-116**) or complete deprotection **I-117** to ultimately be treated with Pd/C in acetic acid, so that the double bond could be stereoselectively hydrogenated (scheme 50).



Scheme 50. New pathway to obtain stereoselective reduction and the final product **I-74**.

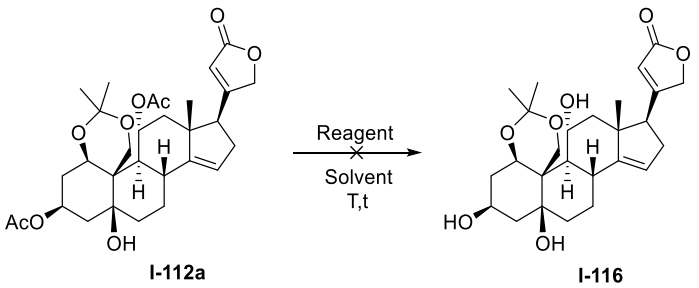
The acetonide deprotection was carried out as already highlighted before, using TFA in methanol, synthesizing compound **I-115** in 66% yield. The unsaturated intermediate **I-115** was treated with Pd/C in acetic acid, achieving product **I-118** in 70% yield as diastereoisomer mixture with a *d.r.* of 3:1 (scheme 51).



Scheme 51. Stereoselective hydrogenation *via* acetonide deprotection.

This route was less effective than the previous one in which the *d.r.* was equal to 5:1 (table 10), so the acetonide group proved not to be limiting for stereoselectivity. Acetate deprotection proved to be a difficult step because it was not possible to synthesize product **I-116**, as shown in table 12.

Table 12. Acetate deprotection of unsaturated compound **I-112a.**



Entry	Reagent (equiv)	Solvent	T (°C)	t (h)	Product[a]
1	Na_2CO_3 (10)	MeOH/H_2O (10:1)	r.t.	9	- [b]
2	K_2CO_3 (2)	MeOH	0	1	- [c]
3	K_2CO_3 (2)	MeOH	r.t.	5	- [d]

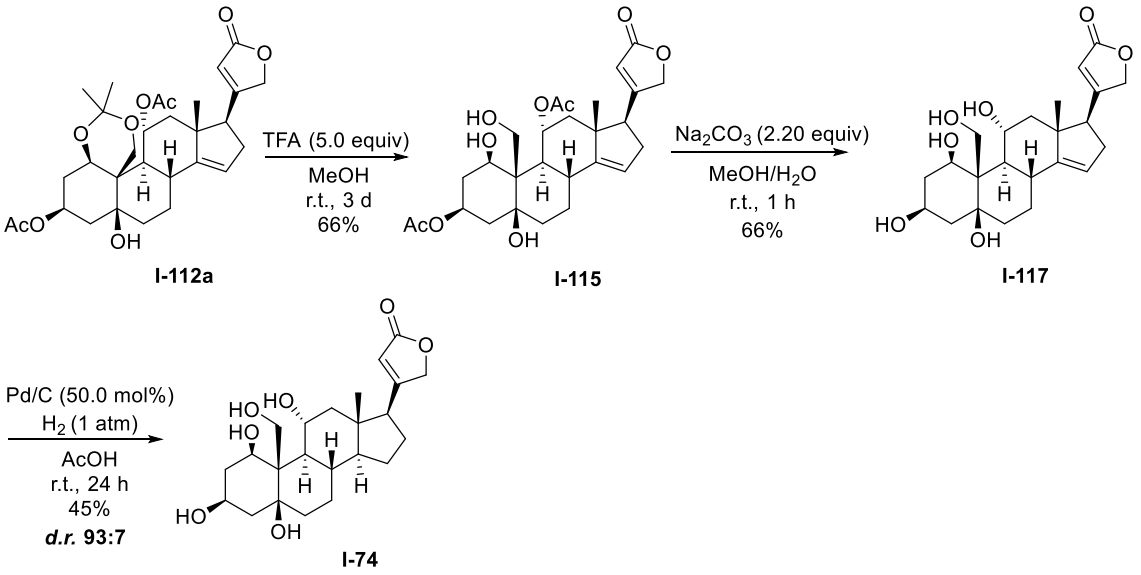
[a] Isolated yield after column chromatography. [b] Decomposition. [c] Unknown product. [d] No lactone.

Both Na_2CO_3 in water/methanol and K_2CO_3 in methanol did not give rise to compound **I-116** but only decomposition (entry 1), formation of unknown product (entry 2) and opening of the lactone (entry 3) were detected.

After performing a partial deprotection with no success, compound **I-112a** was fully deprotected before undergoing a hydrogenation (scheme 52), with an initial deprotection of the acetonide followed by acetate deprotection.

The acetonide was deprotected by using the reaction conditions previously described, synthesizing the intermediate **I-115** which was treated with Na_2CO_3 in water/methanol furnishing the totally deprotected unsaturated derivative **I-117** in 66% yield.

The hydrogenation with the Pd/C of alkene **I-117** gave satisfactory results, converting this intermediate to the final desired product **I-74** in 45% yield with a *d.r.* of 93:7.



Scheme 52. Stereoselective hydrogenation after fully deprotection of unsaturated starting material **I-112a.**

The major diastereoisomer was confirmed by crystal structure analysis, showing the proton at the C-14 position in *trans*-configuration compared to the methyl group at C-13 position (figure 10).

The analysis of crystal structure (performed by Prof. Dr. *F. Mohr*) is reported in the experimental part (*pp. 176-182*)

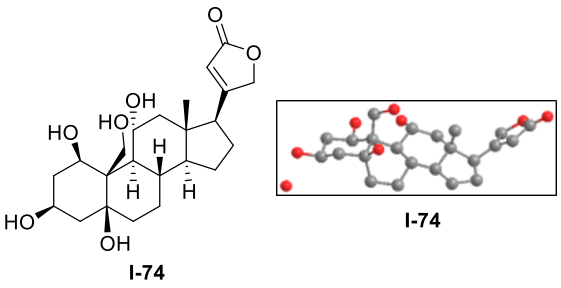


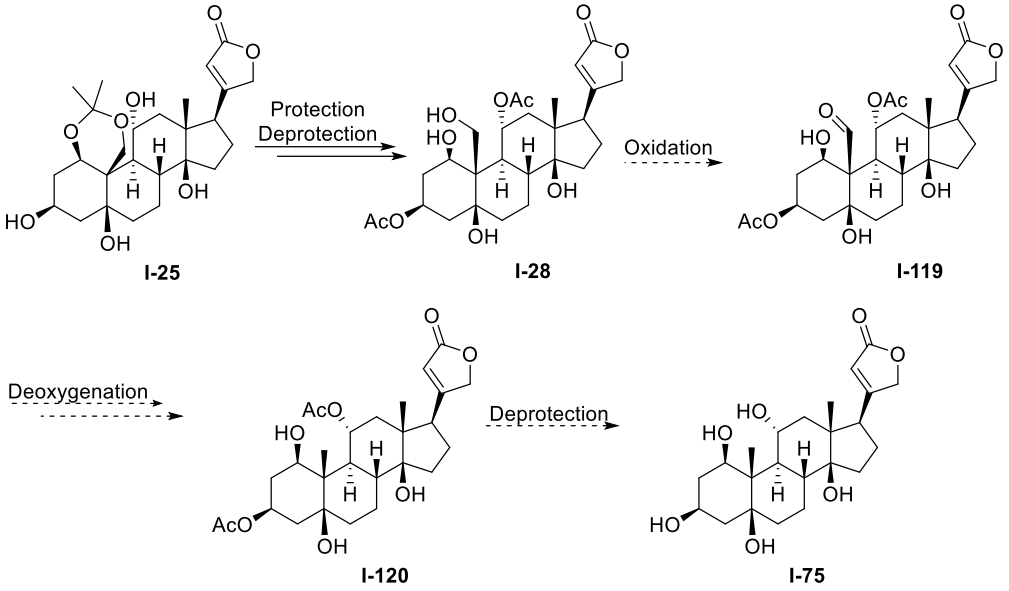
Figure 10. The major diastereoisomer and its crystal structure.

3.4. Defunctionalization of Ouabain: *OH at C-19 position*

In this section, the sole primary alcohol of Ouabain is analyzed requiring a different approach compared to the applied conditions to defunctionalize the secondary and tertiary alcohols.

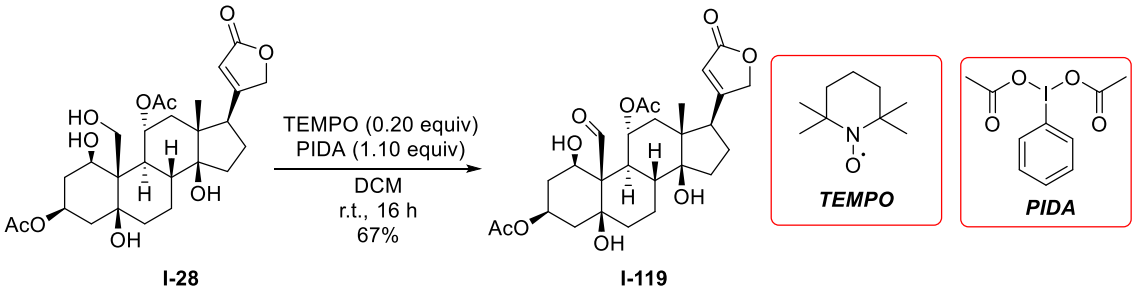
Initially, acetonide Ouabagenin **I-25** was protected by using acetic anhydride with followed deprotection of acetonide, obtaining compound **I-28**, in the same way shown for the elimination of secondary alcohol at C-1 position. (*See paragraph 3.1.2*)

The primary alcohol of intermediate **I-28** should be oxidized to the corresponding aldehyde **I-119** that should be reduced to alkane **I-120**. The subsequent deprotection should give the desired product **I-75** (scheme 53).



Scheme 53. General pathway to desired product **I-75**.

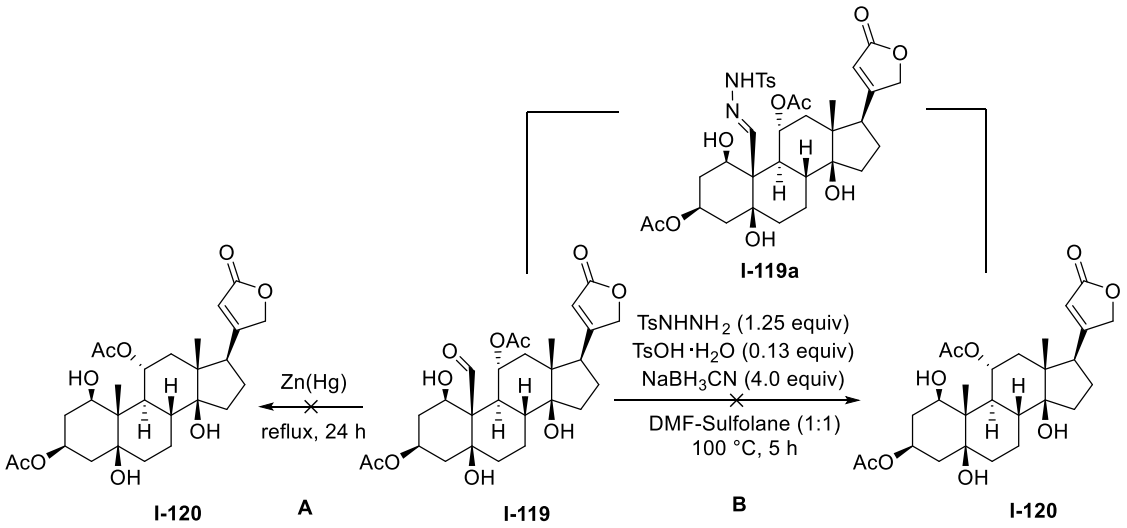
The selective oxidation of primary alcohol (**I-28**) was carried out by using the oxidizing agent 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) in presence of (diacetoxyiodo)benzene (PIDA),[74] achieving the corresponding aldehyde **I-119** in 67% yield (scheme 54).



Scheme 54. Oxidation of primary alcohol (**I-28**) to aldehyde (**I-119**).

By treating the aldehyde intermediate with zinc amalgam (Zn/Hg) (**A**)[90] under reflux conditions (*Clemmensen* reduction), decomposition was achieved and no desired result was obtained.

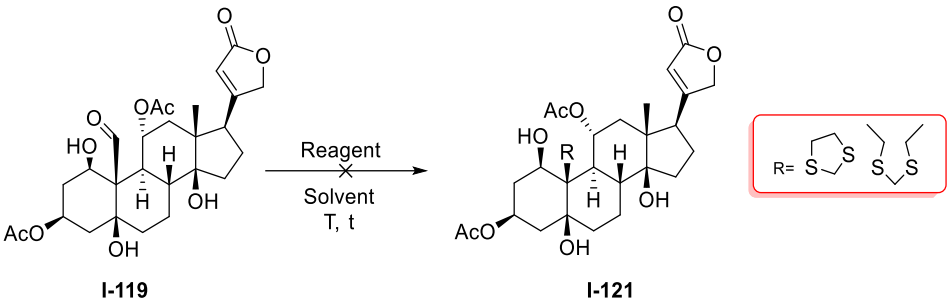
Same result was detected by employing the *Wolff-Kischner* reduction conditions (**B**),[91] by which the aldehyde **I-119** was treated with *p*-toluenesulfonylhidrazide and *p*-toluenesulfonic acid to form the tosylhydrazone intermediate **I-119a** to be subsequently reduced with $NaBH_3CN$ (scheme 55).[85]



Scheme 55. Unsuccessful reductions from aldehyde **I-119** to alkane **I-120**.

A further approach was opted for converting the aldehyde into a thioacetal derivative, to be subsequently reduced to alkane, for example by thioacetal (or thioketal) reduction with *Raney Nickel*.[92,86] Different reaction conditions were applied to synthesize the thioacetal derivatives resulting in decomposition or no conversion of the initial aldehyde (table 13).

Table 13. Different reaction conditions to synthesize thioacetal derivatives.

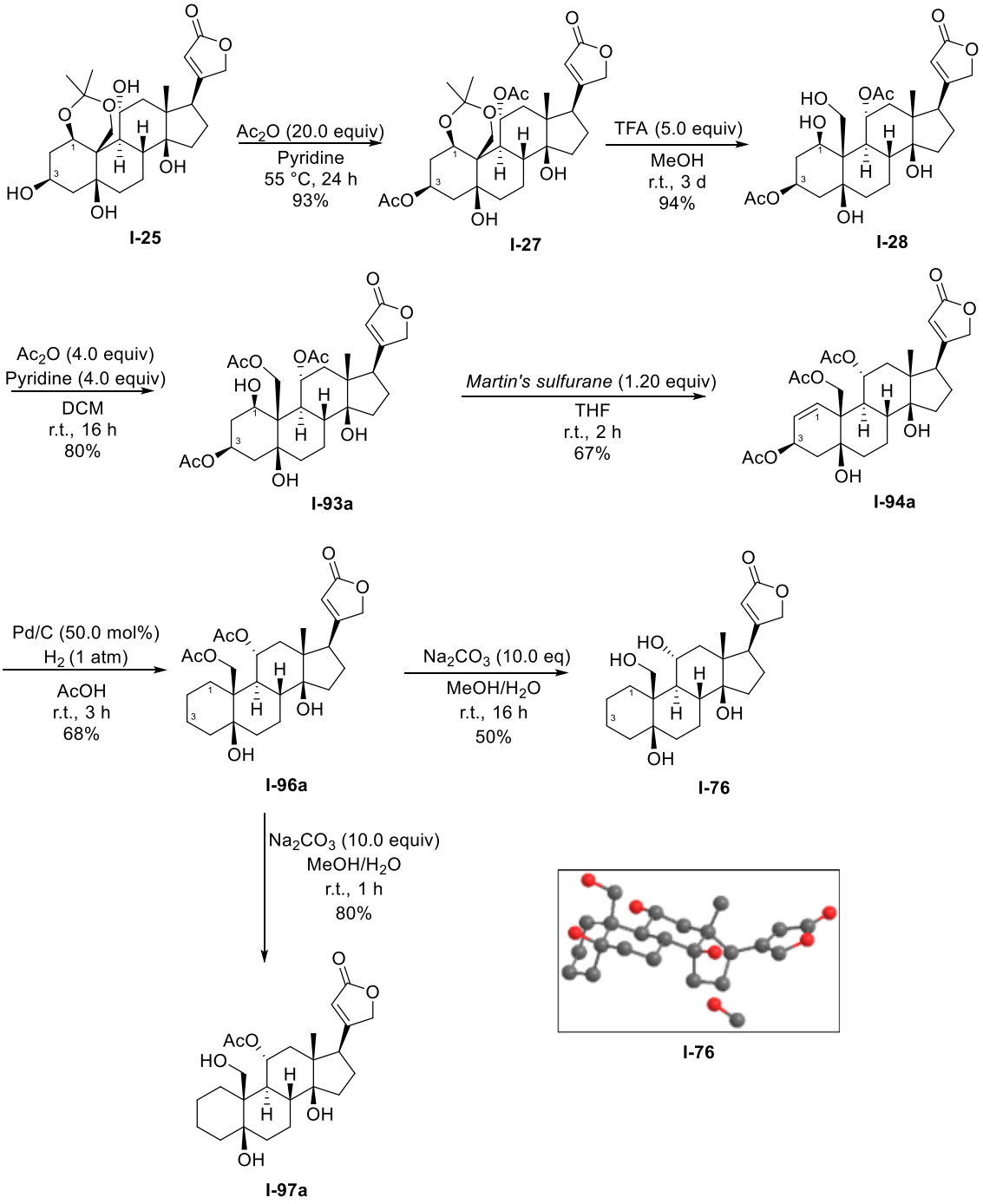


Entry	Reagents (equiv)	Solvent	T (°C)	t (h)	Product[a]
1	1,2-ethanedithiol (1.20) CuBr (0.050)	ACN	r.t. → 40	28	- [c]
2	1,2-ethanedithiol (1.0) $BF_3O(C_2H_5)_2$ (4.55)	AcOH	r.t.	16	- [b]
3	1,2-ethanedithiol or Ethanethiol (5.0) $BF_3O(C_2H_5)_2$ (9.0)	AcOH	r.t.	16	- [d]
4	1,2-ethanedithiol (10.0) CuBr (0.050)	ACN	r.t.	16	- [b]
5	1,2-ethanedithiol (1.10) Silica gel (27.0) TsOH	DCM	reflux	18	- [d]

[a] Isolated yield after column chromatography. [b] No conversion. [c] Unknown product. [d] Decomposition.

3.5. Defunctionalization of Ouabain: *OH at C-1 and C-3 positions*

As mentioned above (*See paragraph 3.1.2*), it is possible to selectively eliminate the hydroxy at C-1 and C-3 positions, thus, achieving the desired compound **I-76** (scheme 56), confirmed by crystal structure (performed by Prof. Dr. *F. Mohr*). The analysis of crystal structure is reported in the experimental part (*pp. 151-157*).

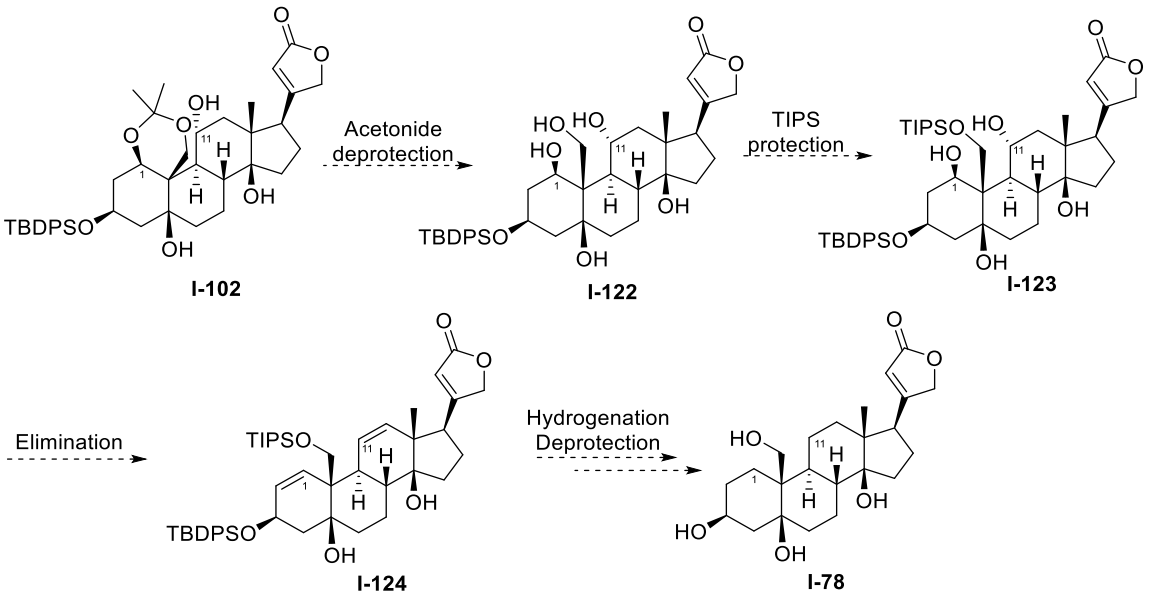


Scheme 56. Synthetic route for desired compound **I-76.**

3.6. Defunctionalization of Ouabain: *OH at C-1 and C-11 positions*

The elimination of the hydroxyl groups at C-1 and C-11 positions pointed out to be a challenge.

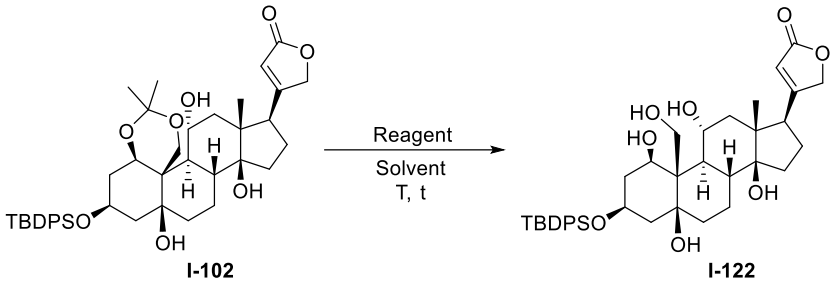
The first synthetic approach was based on a simultaneous elimination of the two secondary alcohols (scheme 57). The free secondary alcohol at C-3 position was protected with a silyl protecting group (**I-102**) followed by a selective deprotection of acetonide, protection of the primary alcohol and elimination of both secondary alcohols. A final hydrogenation and silyl deprotection should give the desired product **I-78**.



Scheme 57. Double elimination of OH at C-1 and C-11 positions.

The acetonide deprotection of intermediate **I-102**, which was synthesized as previously shown in scheme 40, presented some obstacles, essentially due to the presence of a protecting silyl group also sensitive to the acidic conditions, used for the deprotection of the acetonide. As shown in the following table 14, different reaction conditions were tested.

Table 14. Acetonide deprotection of compound **I-102.**



I-102 **I-122**

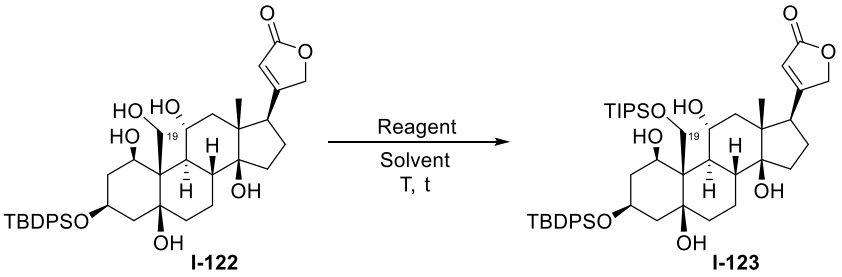
Entry	Reagents (equiv)	Solvent	T (°C)	t (h)	Product[a]
1	PPTS (0.25 → 0.50)	MeOH	r.t.	48	- [b]
2	TFA (2.40)	THF/H_2O	0 → r.t.	16	- [c]
3	$CeCl_3 \cdot 7H_2O$ (2.0) $(COOH)_2$ (0.050)	ACN	r.t.	45	- [c]
4	$Pd/Cl_2(CH_3ACN)$ (0.09)	ACN/H_2O	65	16	- [c]
5	$InCl_3$ (2.0)	ACN/H_2O	r.t.	2	90%

[a] Isolated yield after column chromatography. [b] Full deprotection. [c] Decomposition.

Decomposition was detected by TLC when silyl etherl **I-102** was treated with TFA in tetrahydrofuran/water (entry 2),[86] with $CeCl_3 \cdot 7H_2O$ in acetonitrile (entry 3)[85] and with $Pd/Cl_2(CH_3ACN)$ in acetonitrile/water (entry 4).[87] However, in presence of pyridinium *p*-toluenesulfonate (PPTS) in methanol, an incomplete conversion but direct double deprotection of the acetonide and the silyl group was achieved (entry 1). The desired product was achieved by treating the silyl derivative **I-102** with $InCl_3$ in a mixture of acetonitrile/water in 90% yield.[93]

Subsequently, the primary alcohol at C-19 position was protected as silyl ether intermediate **I-123**, to avoid problems regarding the formation of side products during the following elimination reaction (ethers, urethanes, or iodinated intermediates can be achieved by treating primary alcohol with *Martin's Sulfurane*, *Burgess* reagent or MTPI) (table 15).

Table 15. Tips protection of OH at C-19 position.



Entry	Reagents (equiv)	Base (equiv)	Solvent	T (°C)	t (h)	Product[a]
1	TIPSOTf (1.50)	2,6-Lutidine (5.0)	THF/DCM	0	0.1	- [b]
2	TIPSOTf (1.50)	2,6-Lutidine (5.0)	DCM	0	1	- [b]
3	TIPSCl (1.0 → 5.0) DMAP (0.080)	Et_3N (2.0)	DCM	0 → r.t.	120	68%
4	TIPSCl (1.50) DMAP (0.70)	Et_3N (5.0)	DCM/DMF	0 → 50	4	71%
5	TIPSCl (1.50) DMAP (0.70)	Et_3N (5.0)	DMF	0 → 50	8	89%

[a] Isolated yield after column chromatography. [b] No desired product.

By using TIPSOTf in the presence of 2,6-Lutidine, in different solvents, it was not possible to synthesize the desired product but different products were detected by TLC after few minutes (entries 1, 2). Probably, multiple protection occurred.

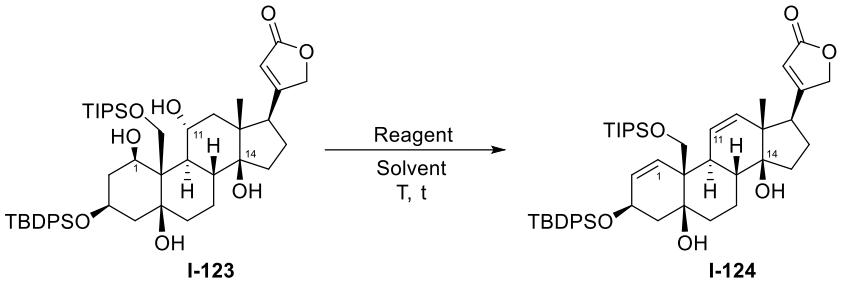
The desired product **I-123** was selectively obtained in the presence of TIPSCl, DMAP and Et_3N in 68% yield with dichloromethane as solvent at room temperature (entry 3). By carrying out the reaction in a dichloromethane/dimethylformamide solvent mixture at 50 °C, the yield was improved to 71% (entry 4).

An excellent yield of 89% was achieved by employing only DMF as solvent (entry 5).

The next step consisted in the selective elimination of the two secondary alcohols at C-1 and C-11 positions for obtaining the dehydrated compound **I-124**.

As shown in the following table 16, it was not possible to synthesize the desired product, no more than decomposition and mono-elimination of alcohol at the C-1 position were detected by crude NMR.

Table 16. Dehydration of OH at C-1 and C-11 positions.



I-123 **I-124**

Entry	Reagents (equiv)	Solvent	T (°C)	t (h)	Product[a]
1	*Martin's Sulfurane* (5.0)	THF	r.t.	0.5	- [c]
2	*Martin's Sulfurane* (3.0 → 10.0)	DCM/DMF	0 → r.t. → 40	72	- [c, e]
3	*Martin's Sulfurane* (8.0 → 11.0)	DMF	0 → r.t.	24	- [d]
4	*Burgess* reagent (4.0 → 5.0)	THF	reflux	2 → 24	- [e]
5	DEAD (4.0 → 8.0) PPh_3 (4.0 → 8.0) 3,3-dimethylglutarimid (4.0 → 8.0)	THF	0 → r.t.	18	- [e]
6	MTPI (2.0)	HMPA	75	24	- [b]
7	MTPI (2.70)	DMI	60	24	- [b]
8	MTPI (3.0)	DMF	r.t.	16	- [d]
9	MTPI (3.0) DMAP (3.0 → 5.0)	DMF	r.t.	16	- [d]
10	$SOCl_2$ (0.50) Pyridine (1.50)	DCM	-78	2	- [b]

[a] Isolated yield after column chromatography. [b] No conversion [c] Mono elimination. [d] Unknown product. [e] Decomposition.

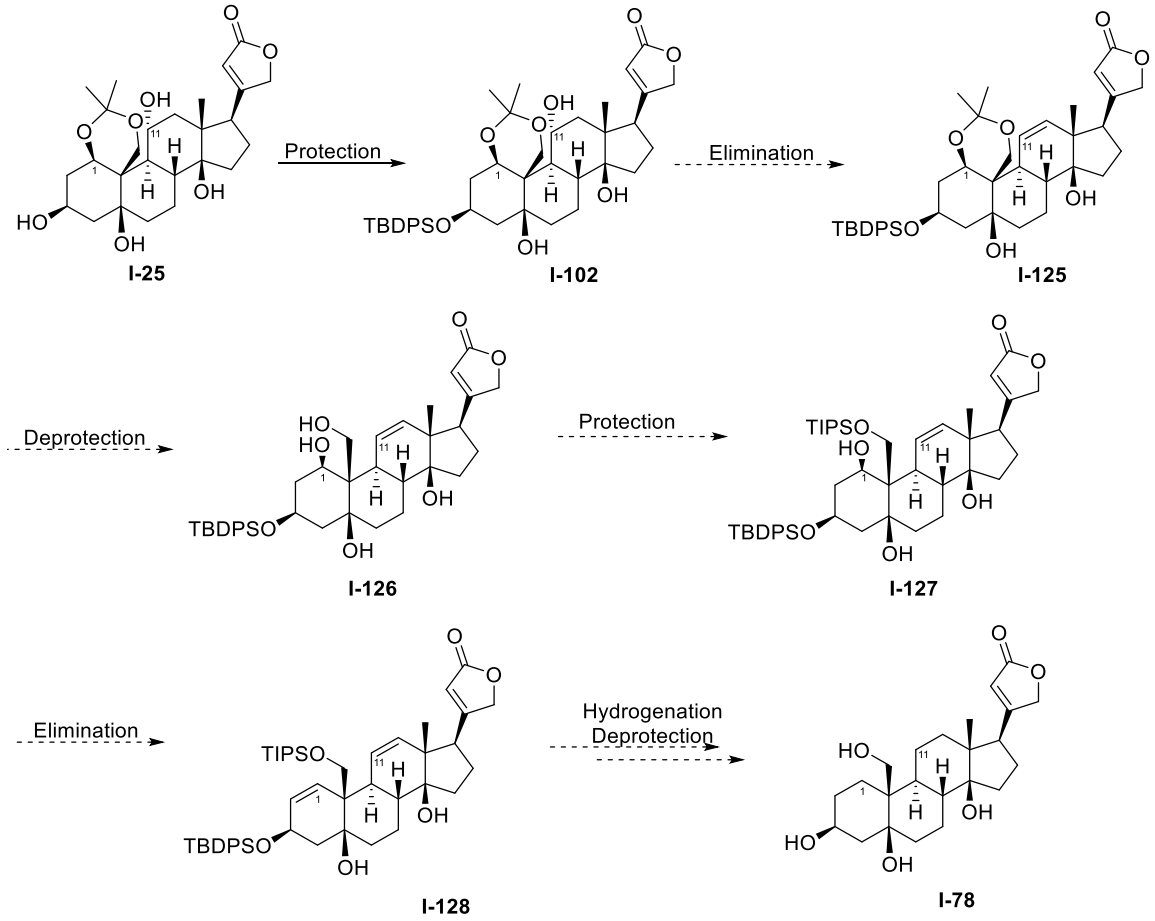
The use of *Martin's Sulfurane* as dehydrating reagent showed no succes in the formation of the desired product **I-124**, either using different equivalents, different temperatures and different solvents, only a mono dehydration or synthesis of no desired and not easily recognizable products were observed (entries 1-3).

Total decomposition was detected when treating starting material **I-123** with the *Burgess* reagent, by applying slightly modified *Mitsunobu* conditions[94] and with $SOCl_2$ in pyridine (entries 4, 5, 10).

The use of another dehydrating reagent such as MTPI (**I-62**), involved a non-conversion of the starting material or the formation of an undesired product which was not recognizable by analysis (entries 6-9).[95] Indeed, sylil compound **I-123** was isolated when the reaction was carried out in Hexamethylphosphoramide (HMPA) or 1,3-Dimethyl-2-imidazolidinone (DMI) as solvents at high temperatures, while formation of the undesired product was observed when dimethylformamide was used.

Therefore, the simultaneous elimination of the two secondary alcohols proved to be difficult and an alternative pathway was necessary.

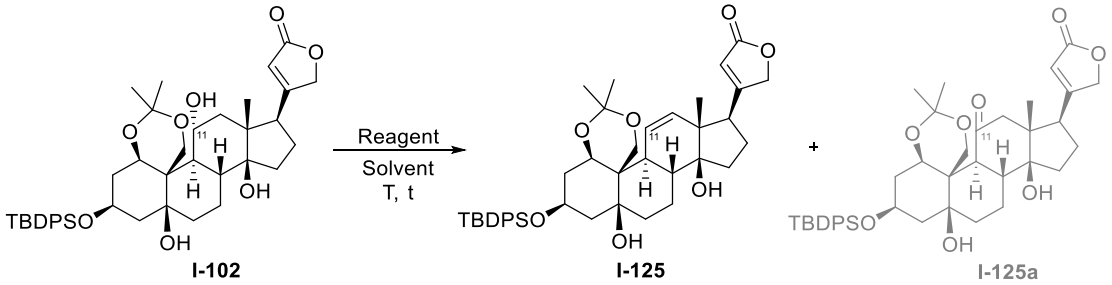
The new route consisted in the initial elimination of the secondary alcohol at C-11 position (**I-125**), followed by acetonide deprotection (**I-126**), protection of the primary alcohol with the TIPS protecting group (**I-127**) and elimination of the secondary alcohol at C-1 position (**I-128**). The final hydrogenation and deprotection should give the desired product **I-78** (scheme 58).



Scheme 58. Alternative route for the elimination of OH at C-1 and C-11 positions.

First, the secondary alcohol at C-11 position was dehydrated by using *Martin's sulfurane*. However, this elimination showed some difficulties due to the formation of the undesired ketone **I-125a**, with similar retention factor value to that of the desired product and extremely difficult to separate (table 17).

Table 17. Elimination of OH at C-11 position.



Entry	Reagents (equiv)	Solvent	T (°C)	t (h)	Product[a]
1	*Martin's Sulfurane* (3.0)	THF	r.t.	2	10% (**I-125**) [b, c]
2	*Martin's Sulfurane* (1.50)	THF	r.t.	3	37% (**I-125**) [b, c]
3	*Martin's Sulfurane* (2.0)	THF	r.t.	4	35% (**I-125**) [b, c]
4	*Martin's Sulfurane* (1.75 → 6.0)	THF	0 → 50	72	62% (**I-125**) [b, c]
5	*Martin's Sulfurane* (3.0)	THF	-30	24	48% (**I-125**) [b]
6	*Martin's Sulfurane* (3.0)	THF	-20	2	76% (**I-125**) [b]
7	MTPI (3.0) DMAP (3.0)	DMF	r.t.	16	98% (**I-125**)

[a] Isolated yield after column chromatography. [b] I-125a formation. [c] Double elimination (OH at C-11, C-14 positions).

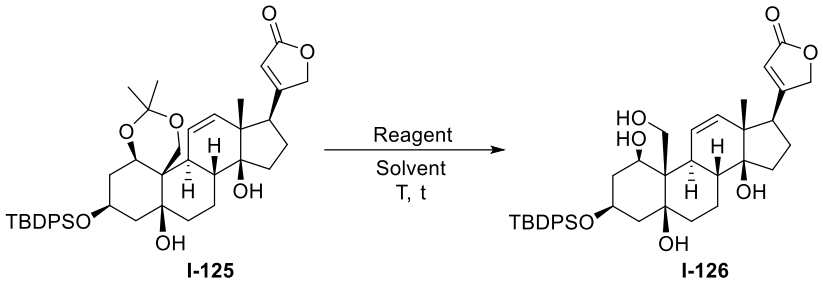
It was possible to synthesize the dehydrated product **I-125** by employing *Martin's Sulfurane*, but the yield proved to be extremely unpleasant (entry 1), due to the formation of the ketone derivative and a double elimination of the secondary alcohol at C-11 and the tertiary one at C-14 positions, as observed in the crude NMR. However, the yield was gradually improved by varying temperature and reaction time.

By carrying out the reaction at -20 °C for two hours, the product **I-125** was achieved in 76% yield, avoiding double elimination and obtaining the desired product as the main product.

The best yield of 95% was obtained after treatment of the starting material with MTPI in presence of DMAP.[95]

The following step consisted in the deprotection of the acetonide, a difficult step due to the presence of the TBDPS protecting group, which is also sensitive to the acidic conditions used for the deprotection.

Table 18. Acetonide deprotection of derivative **I-125**.

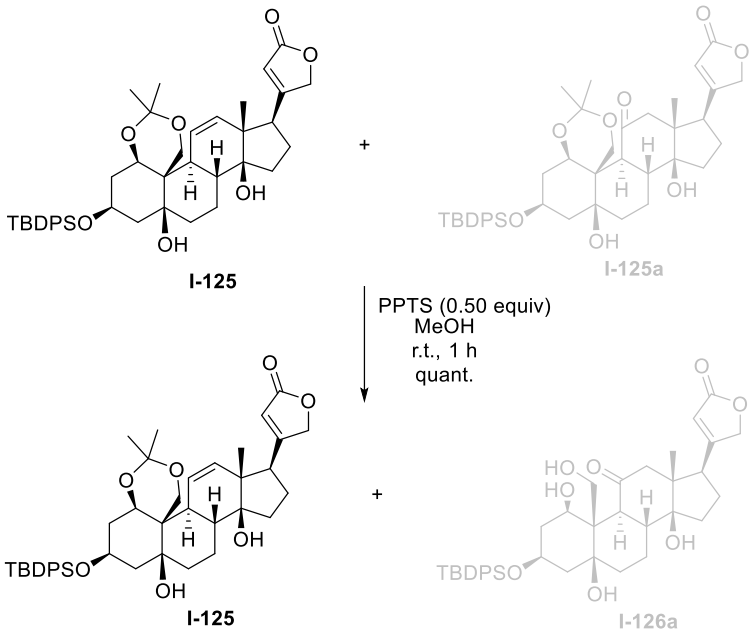


Entry	Reagents (equiv)	Solvent	T (°C)	t (h)	Product[a]
1	PPTS (0.25 → 0.50)	MeOH	r.t.	24	- [c]
2	$InCl_3$ (0.95)	ACN/H_2O	r.t.	24	- [d]
3	$InCl_3$ (2.0)	ACN/H_2O	r.t.	1.5	- [d]
4	$InCl_3$ (3.0)	ACN/H_2O	r.t.	7	20% [c, e]
5	$InCl_3$ (5.0)	ACN/H_2O	0 →50	16	21% [c, e]
6	$InCl_3$ (8.0)	ACN/H_2O	0 →50	18	37% [d]
7	$InCl_3$ (2.0 → 4.0)	MeOH	r.t. → 50	18	- [c]
8	$CeCl_3 \cdot 7H_2O$ (2.0) $(COOH)_2$ (0.050)	ACN	r.t.	45	- [c]
9	$Pd/Cl_2(CH_3ACN)$ (0.25 → 0.50)	ACN/H_2O	65	6	- [c]
10	TBHP (2.0)	t-BuOH/H_2O	reflux	24	- [d]
11	Et_3SiH (10.0) $BF_3 \cdot Et_2O$ (9.40)	DCM	r.t.	2	- [d]
12	CAN solution (quant.)	Acetone	68	96	- [b]
13	/	AcOH 80%	r.t.	7	- [d]
14	$FeCl_3 \cdot 6H_2O$	DCM	r.t.	2	- [d]
15	$FeCl_3 \cdot 6H_2O$	$CHCl_3$	r.t.	2	- [d]
16	$FeCl_3 \cdot 6H_2O$	ACN	r.t.	2	- [d]
17	$In(OTf)_3$ (0.010)	THF/H_2O	100 (MW)	0.05	- [e, f, g]
18	$In(OTf)_3$ (0.010)	THF/H_2O	100 (MW)	0.16	- [e, g]
19	$In(OTf)_3$ (0.010)	THF/H_2O	80 (MW)	0.16	- [d]
20	/	H_2O	100 (MW)	0.5	- [d]
21	Amberlyst-15 (21.0)	MeOH/H_2O	r.t. → 70	16	- [c]
22	Amberlyst-15 (11.0)	1,4-Dioxane/H_2O	70	16	- [c]
23	Dowex (8.0 → 13.0)	1,4-Dioxane/H_2O	r.t. → 70	72	- [c, e, f, g]
24	Dowex (4.0)	1,4-Dioxane/H_2O	80 → 90 (MW)	0.16	- [c, e, f, g]
25	$FeCl_3SiO_2$ (0.12)	DCM	r.t.	2	- [d]
26	$CuCl_2 \cdot 2H_2O$ (5.0)	*i*PrOH	r.t.	4	- [c, e, f, g]
27	$Yb(OTf)_3 \cdot 3H_2O$ (0.050)	ACN	r.t.	16	- [d]
28	TFA (4.0)	DCM	r.t.	4	- [d]

Entry	Reagents (equiv)	Solvent	T (°C)	t (h)	Product[a]
29	$Cu(NO_3)_2$ (1.0)	ACN	r.t.	24	- [c]
30	$ZnBr_2$ (20.0)	DCM	r.t.	24	87%

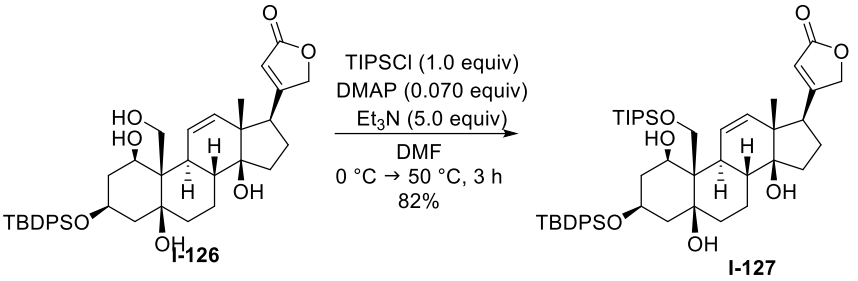
[a] Isolated yield after column chromatography. [b] No conversion. [c] Full deprotection. [d] Decomposition. [e] Desired product. [f] Starting material traces. [g] Impurities.

A total deprotection was obtained by treating the starting material **I-125** with PPTS in methanol (entry 1), $InCl_3$ in methanol (entry 7),[96] $CeCl_3 \cdot 7H_2O$ in acetonitrile (entry 8),[85] $Pd/Cl_2(CH_3ACN)$ in a mixture of acetonitrile/water (entry 9),[87] Amberlyst-15 in methanol/water[97] and 1,4-Dioxane/water[98] (entries 21, 22) and copper nitrate ($Cu(NO_3)_2$) in acetonitrile (entry 29).[99] The use of the CAN solution (solution of ammonium cerium (IV) nitrate in water and pyridine *pH* = 4.4) in acetone did not show any conversion of the derivative **I-125** (entry 12).[100] The desired product was gained with incomplete conversion of the acetonide compound **I-125** in an extremely low yield, because of the formation of the fully deprotected side product, after treatment with $InCl_3$ in acetonitrile/water[93] (entries 4, 5) and in an undetectable yield due to formation of other unknown impurities by using Dowex in 1,4-dioxane/water mixture (entries 23, 24) and with copper dichloride dihydrate ($CuCl_2 \cdot 2H_2O$) in isopropanol (entry 26).[101] All the other reaction conditions showed a total decomposition of the molecule (entries 2, 3, 10, 11, 13-16, 19, 20, 25, 27, 28).[102,103] Finally, the cleavage of the acetonide protecting group led to the formation of the desired product **I-126**, by employing the *Lewis* acid zinc bromide ($ZnBr_2$) in dichloromethane, in 87% yield.[104]
Unexpectedly, acetonide deprotection of compound **I-125a** was achieved by treating the mixture of alkene and ketone derivatives **I-125** and **I-125a** with PPTS in methanol. In this case, alkene **I-125** showed no conversion (scheme 59).



Scheme 59. Acetonide deprotection of ketone derivative **I-125a**.

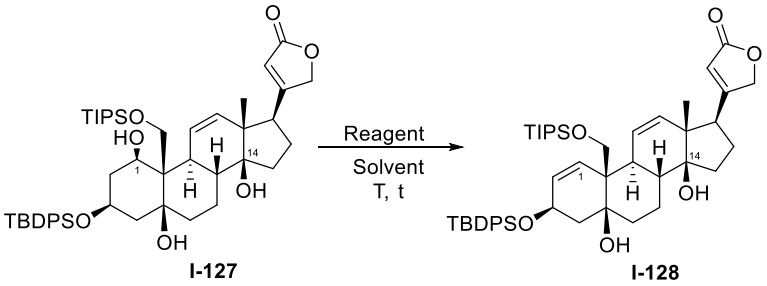
The next step consisted of protecting the primary alcohol with TIPS silyl group, obtaining intermediate **I-127** in 82% yield (scheme 60).



Scheme 60. TIPS protection of primary hydroxyl group (**I-126**)

Therefore, the subsequent elimination of the secondary alcohol at C-1 position to synthesize compound **I-128** was studied (table 19).

Table 19. Elimination of OH at C-1 position of intermediate **I-127** to achieve alkene **I-128**.



Entry	Reagents (equiv)	Solvent	T (°C)	t (h)	Product[a]
1	*Martin's Sulfurane* (3.0)	THF	-20 → 0	1.5	27% [b]
2	MTPI (3.0)	DMF	r.t.	16	- [d]
3	MTPI (3.0) DMAP (3.0)	DMF	r.t.	24	61%
4	MTPI (3.0) DMAP (3.0)	Pyridine	r.t.	6	- [d]
5	MTPI (3.0) DMAP (3.0)	Pyridine/DMF	r.t.	6	- [d]
6	MTPI (3.0) DMAP (3.0) Et_3N (5.0)	DMF	r.t.	6	- [c]
7	MTPI (2.0) 2,6 – Lutidine (5.0)	DMF	r.t.	16	- [c]
8	MTPI (2.0) 2,6 – Lutidine (5.0) DMAP (3.0)	DMF	r.t.	16	- [c]
9	MTPI (3.0) Imidazole (5.0) DMAP (3.0)	DMF	40	16	- [d]
10	MTPI (3.0) Imidazole (5.0)	DMF	40	16	- [d]

Entry	Reagents (equiv)	Solvent	T (°C)	t (h)	Product[a]
11	MTPI (3.0) Imidazole (5.0)	DMPU	r.t.	16	- [c]
12	MTPI (5.0)	DMPU	50	16	78%

[a] Isolated yield after column chromatography. [b] Elimination of tertiary alcohol at C-14 position. [c] No conversion. [d] Decomposition.

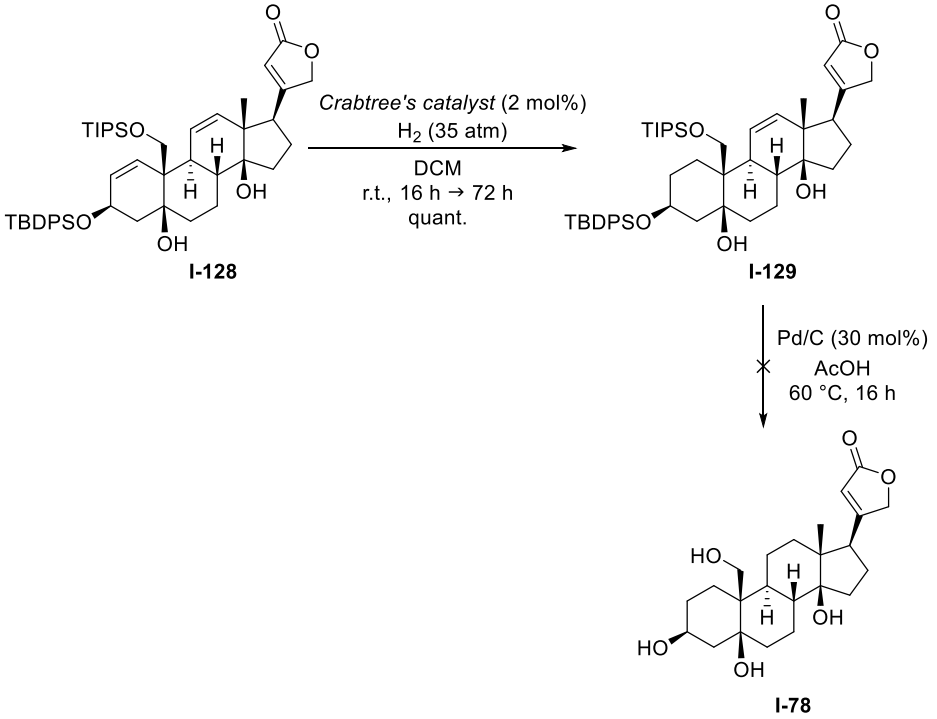
Desired alkene **I-128** was achieved using *Martin's Sulfurane* at low temperatures in 27% yield due to the formation of the side product as a result of the simultaneous elimination of the tertiary alcohol at C-14 position (entry 1). To avoid the formation of the side product, the MTPI was used because it is able to react only with primary alcohols (achieving iodinated compound) and with secondary alcohols (performing their elimination). In presence of this dehydrating reagent, decomposition was detected by treating the starting material **I-127** in dimethylformamide (entry 2), in association with DMAP in pyridine or pyridine/dimethylformamide mixture (entries 4, 5) and by employing imidazole in the presence or absence of DMAP in dimethylformamide (entries 9, 10).

No conversion was observed after treatment with Et_3N and 2,6-Lutidine as bases, in presence or absence of DMAP in dimethylformamide (entries 6-8) or imidazole in *N*,*N*'-Dimethylpropyleneurea (DMPU) (entry 11).

Desired product **I-128** was achieved by using MTPI and DMAP in dimethylformamide at room temperature in 61% (entry 3)[95] and MTPI in DMPU at 50 °C in 78% yield (entry 12).[105,106,107]

The first approach, for the hydrogenation of the Δ^{1-2} and Δ^{11-12} double bonds, consisted in using *Crabtree* as a homogeneous catalyst, but only hydrogenation of the Δ^{1-2} double bond (**I-129**) was detected by crude NMR, despite high hydrogen pressure and prolonged reaction time.

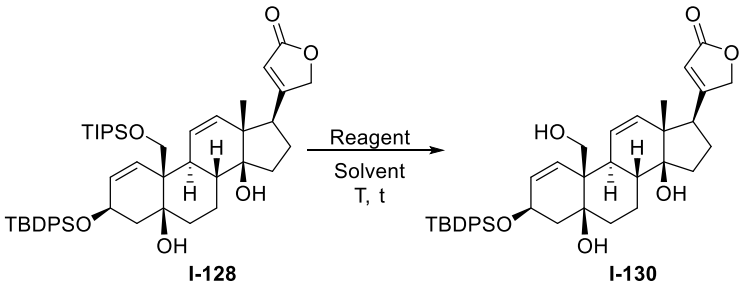
For this reason, a subsequent hydrogenation was tested by using Pd/C in acetic acid, in order that the desired hydrogenated and deprotected product could be achieved (**I-78**), but only a partial and total silyl deprotection were obtained, without hydrogenation of the Δ^{11-12} double bond (scheme 61).



Scheme 61. Hydrogenation of $\Delta^{1\text{-}2}$ double bond followed by partial and full deprotection.

A further strategy was based on the selective deprotection of the TIPS silyl group (**I-130**), in order to make the $\Delta^{11\text{-}12}$ double bond less hindered and more accessible for the hydrogenation (table 20). This deprotection proved to be a challenge due to the concomitant deprotection of the silyl TBDPS group.

Table 20. Selective TIPS deprotection of alkene **I-128**.



Entry	Reagents (equiv)	Solvent	T (°C)	t (h)	Product[a]
1	HF·pyridine (3.0)	THF	-5	3	- [b, c]
2	AcOH (3.0)	THF/H_2O	40	16	91%
3	TFA (5.0)	THF/H_2O	r.t.	2	- [c]
4	CSA (0.090)	MeOH	0	2	- [b, c]
5	*p*-TsOH (0.13)	MeOH	40	3	- [b, c]

[a] Isolated yield after column chromatography. [b] No full conversion. [c] Full deprotection.

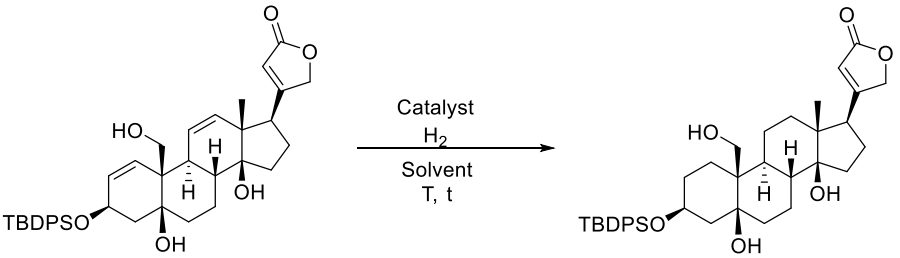
It was possible to observe a mixture of the unreacted starting material **I-128**, mono and fully deprotected products using HF·pyridine in tetrahydrofuran, camphorsulfonic acid (CSA) or *p*-TsOH in methanol (entries 1, 4, 5).

A conversion of the alkene **I-128** to a mixture of the mono and fully deprotected products was achieved in presence of TFA in tetrahydrofuran/water (entry 3).

Finally, a selective TIPS deprotection was yielded by treating the derivative **I-128** with acetic acid in tetrahydrofuran/water at 40 °C for sixteen hours in 91% yield (entry 2).

As already highlighted above, the hydrogenation of the $\Delta^{11\text{-}12}$ double bond proved to be extremely difficult and table 21 shows several reaction conditions carried out in order to obtain the desired hydrogenated product **I-131**.

Table 21. Hydrogenation of both double bonds.



I-130 **I-131**

Entry	Catalyst	Solvent	H_2 (atm)	T (°C)	t (h)	Product[a]
1	*Crabtree*'s catalyst	DCM	35	r.t.	72 → 120	- [e]
2	Rh/Al_2O_3	EtOAc	1-35	r.t.	4 →16	- [c, d]
3	Pd/C	EtOAc/MeOH	35	r.t.	16	- [c, d]
4	Pd/C	EtOH	35	r.t.	16	- [c, d]
5	$Pd(OH)_2/C$	EtOAc	35	r.t.	16	- [c, d]
6	Pd/C	EtOAc	1	r.t.	16	- [b]
7	$Pd(OH)_2/C$	EtOAc	1	r.t.	16	- [e]
8	$Pd(OH)_2/C$	EtOAc	7	r.t.	16	- [f]
9	Pd/C	EtOAc	7	r.t.	16	- [d, e, f]
10	*Wilkinson* catalyst	Toluene	70	r.t.	72	- [b, d]
11	$Pd/BaSO_4$	EtOAc	1	r.t.	16	- [d, e]
12	$Pd/CaCO_3$	EtOAc	1	r.t.	16	- [b, d]
13	Pd/C	THF	1	r.t.	4	- [e, f]
14	Pd/C	CH	1	r.t.	4	- [b]
15	Pd/C	MeOH	1	r.t.	4	- [c, d, f]
16	Pd/C	EtOH	1	r.t.	4	- [c, d, f]
17	Pd/C	CAN	1	r.t.	4	- [d, e, f]

[a] Isolated yield after column chromatography. [b] No conversion. [c] Full hydrogenation. [d] No unsaturated lactone. [e] $\Delta^{1\text{-}2}$ hydrogenation. [f] TBDPS deprotection.

Employing the *Crabtree*'s catalyst in dichloromethane under H_2 pressure (35 atm) or $Pd(OH)_2/C$ in ethylacetate (1 atm), only the Δ^{1-2} double bond hydrogenation was achieved (entries 1, 7). Similar results were observed in presence of Pd/C in tetrahydrofuran (1 atm) or $Pd(OH)_2/C$ in ethylacetate (7 atm), which also led to a partial TBDPS deprotection (entry 8, 13).

A total hydrogenation, also including the double bond of the lactone, was obtained by treating the starting material **I-130** with Rh/Al_2O_3 or $Pd(OH)_2/C$ in ethylacetate (35 atm), Pd/C in ethylacetate/methanol (35 atm) or Pd/C in ethanol (35 atm) (entries 2-5).

Similar results were observed with Pd/C in ethylacetate (7 atm) and Pd/C in ACN (1 atm), which products also presented a partial TBDPS deprotection (entries 9, 17).

A selective hydrogenation of the lactone was gained by treating the starting material **I-130** with the *Wilkinson* catalyst in toluene (70 atm) and $Pd/CaCO_3$ in ethylacetate (1 atm) (entries 10, 12).

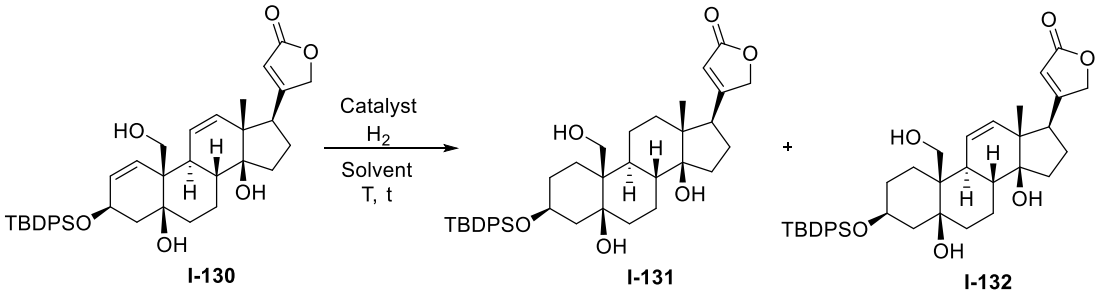
By employing $Pd/BaSO_4$ in ethylacetate (1 atm), the unsaturated lactone and Δ^{1-2} double bond were hydrogenated instead of the Δ^{11-12} one (entry 11).

The use of alcohol as solvent like methanol or ethanol in presence of Pd/C led to the hydrogenation of Δ^{1-2} double bond, almost full hydrogenation of unsaturated lactone and partial hydrogenation of Δ^{11-12} double bond (entries 15, 16).

No conversion was reached by using Pd/C in cyclohexane (1 atm), probably because of the low solubility of starting material in this solvent, and in ethylacetate (1 atm) (entries 6, 14).

Since the classical autoclave hydrogenation was unsuccessfull, this reaction was carried out *via* an *H-Cube* flow chemistry system, as shown in the table 22.

Table 22. New hydrogenation conditions employing a flow chemistry system.



Entry	Catalyst	Solvent	H_2 (atm)	T (°C)	Flow	Product[a]
1	Pd/C (10%)	THF	5	r.t.	2 mL/min	- [c]
2	Pd/C (10%)	THF	15	r.t.	2 mL/min	- [c]
3	Pd/C (10%)	THF	30	r.t.	2 mL/min	- [c]
4	Pd/C (10%)	THF	5	40	2 mL/min	- [c]
5	Pd/C (10%)	THF	5	50	2 mL/min	- [c]
6	Pd/C (10%)	THF	30	50	2 mL/min	- [d, f]
7	Pt/C (10%)	THF	5	50	2 mL/min	- [d, f]

Entry	Catalyst	Solvent	H_2 (atm)	T (°C)	Flow	Product[a]
8	Pt/C (sulfide) (20%)	THF	5	50	2 mL/min	- [d, f]
9	Pt/C (10%)	THF	15	r.t.	2 mL/min	- [d, f]
10	Pt/C (sulfide) (20%)	THF	15	r.t.	2 mL/min	- [d, f]
11	Ru/C (5%)	THF	5	r.t.	2 mL/min	- [b]
12	Rh/C (5%)	THF	5	r.t.	2 mL/min	- [b]
13	$Pd(OH)_2$/C (20%)	THF	5	r.t.	2 mL/min	- [c, d]
14	$Pd(OH)_2$/C (20%)	THF	15	r.t.	2 mL/min	- [e]
15	$Pd(OH)_2$/C (20%)	EtOAc	10	r.t.	2 mL/min	- [c]
16	$Pd(OH)_2$/C (20%)	EtOAc	15	15	2 mL/min	- [c]
17	Pd/C (10%)	EtOAc	15	50	2 mL/min	- [c, g]
18	Pt/C (10%)	EtOAc	10	50	2 mL/min	- [c, g]
19	Pt/C (sulfide) (20%)	EtOAc	20	50	2 mL/min	- [c]
20	Ru/C (5%)	EtOAc	10	50	2 mL/min	- [b]
21	Rh/C (5%)	EtOAc	5	r.t.	2 mL/min	- [b]
22	Rh/C (5%)	EtOAc	15	r.t.	2 mL/min	- [b]
23	$Pd(OH)_2$/C (20%)	EtOAc	30	50	2 mL/min	- [c]
24	Pd/C (10%)	EtOAc	35	60	2 mL/min	- [c]
25	Pt/C (10%)	EtOAc	30	50	2 mL/min	- [c, d]

[a] Isolated yield after column chromatography. [b] No conversion. [c] I-132 formation. [d] Aldehyde formation. [e] Decomposition [f] Aldehyde formation. [g] Partial hydrogenation of $\Delta^{1,2}$ double bond.

Initially, several catalysts were tested in tetrahydrofuran as a solvent, generally showing the hydrogenation of the Δ^{1-2} double bond (entries 1-5) or the unexpected formation of an aldehyde (entries 6-10, 13).

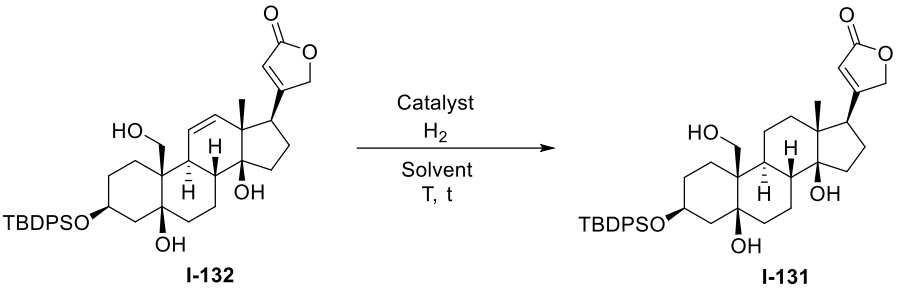
A non-conversion was noted employing Ru/C and Rh/C (entries 11, 12) and decomposition was detected in the presence of $Pd(OH)_2$/C under H_2 pressure of 15 atm.

By replacing the solvent with ethylacetate, the aldehyde formation was prevented but without achieving the desired product. Indeed, the starting material **I-130** showed no conversion to hydrogenated product **I-131** in presence of Ru/C and Rh/C (entries 20-22) and only Δ^{1-2} hydrogenation was obtained with the other catalysts (entries 15-19, 23-25).

A partial formation of the aldehyde was formed only by increasing temperature and H_2 pressure (entries 25), and an incomplete hydrogenation of the $\Delta^{11,12}$ double bond was detected with Pd/C and Pt/C (entries 17, 18).

Since no desired result was achieved so far, a further study was done using the monohydrogenated compound **I-132** as starting material (table 23).

Table 23. Screening for hydrogenation of $\Delta^{11\text{-}12}$ double bond.



I-132 **I-131**

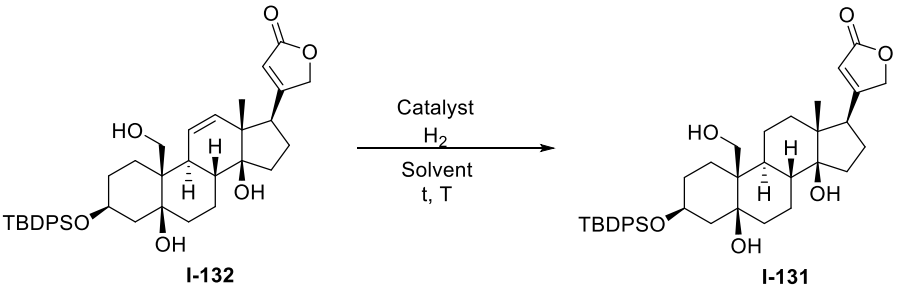
Entry	Catalyst (equiv)	Solvent	H_2 (atm)	T (°C)	t (h)	Product[a]
1	Pd/C	AcOH/H_2O	1	60	5	- [b, e]
2	Pd/C	AcOH/H_2O	1	60	24	- [c, e]
3	Pd/C	AcOH/H_2O	1	60	48	- [c, e]
4	Pd/C	AcOH/H_2O	7	r.t.	4	- [d]
5	Pd/C	AcOH/H_2O	1	75	16	- [c, e]
6	PtO_2	AcOH	1	r.t.	1	- [d]

[a] Isolated yield after column chromatography. [b] No conversion. [c] Partial hydrogenation of $\Delta^{11\text{-}12}$ duble bond. [d] No unsaturated lactone [e] TBDPS deprotection.

By using Pd/C in acetic acid/water mixture (1 atm), only partial TBDPS deprotection was achieved after five hours and partial hydrogenation of $\Delta^{11\text{-}12}$ double bond after one or two days at 60 °C or 75 °C (entries 1-3, 5). Hydrogenation of lactone was reached by employing Pd/C in acetic acid/water under higher H_2 pressure (7 atm) or in presence of PtO_2 in acetic acid (1 atm) (entries 4, 6).

Since all these reaction conditions also failed to result in the formation of the desired product, hydrogenation of monohydrogenated product **I-132** was once more studied using a flow chemistry system (*H-cube*), without any successful product **I-131** formation (table 24).

Table 24. New hydrogenation conditions of $\Delta^{11\text{-}12}$ double bond.



I-132 **I-131**

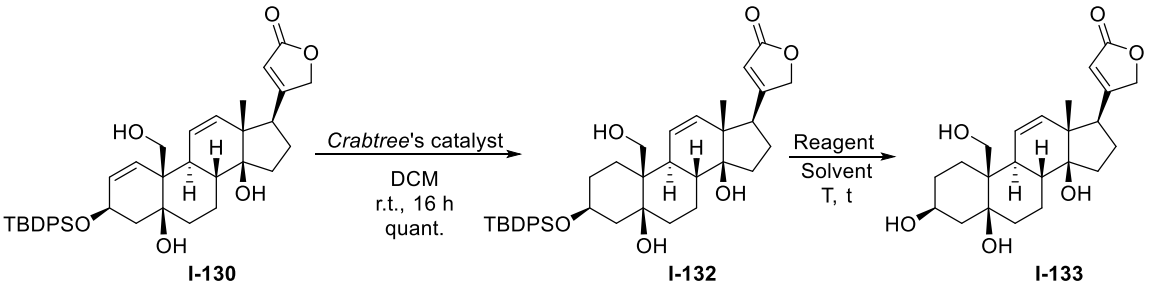
Entry	Catalyst	Solvent	H_2 (bar)	T (°C)	Flow	Product[a]
1	Pd/C (10%)	AcOH/H_2O	3	60	2 mL/min	- [b]
2	Pd/C (10%)	AcOH/H_2O	15	60	2 mL/min	- [b]

Entry	Catalyst	Solvent	H_2 (bar)	T (°C)	*Flow*	Product[a]
3	Pd/C (10%)	AcOH/H_2O	30	60	2 mL/min	- [b]
4	Pd/C (10%)	AcOH/H_2O	55	60	2 mL/min	- [b]

[a] Isolated yield after column chromatography. [b] No conversion.

As a result of this difficult hydrogenation, a second route was planned, based on an initial mono hydrogenation of intermediate **I-130** with *Crabtree*'s catalyst, followed by deprotection to achieve the final product **I-133**.

Table 25. Partial hydrogenation of alkene **I-130**, followed by TBDPS deprotection (**I-133**).



I-130 **I-132** **I-133**

Entry	Reagent (equiv)	Solvent	T (°C)	t (h)	Product[a]
1	*p*-TsOH (0.13)	MeOH	40	3	- [b]
2	TBAF (5.0)	THF	0 → r.t.	1	- [d]
3	HF·pyridine (20.0)	THF/MeOH/Pyridine	0 → r.t.	12	81%

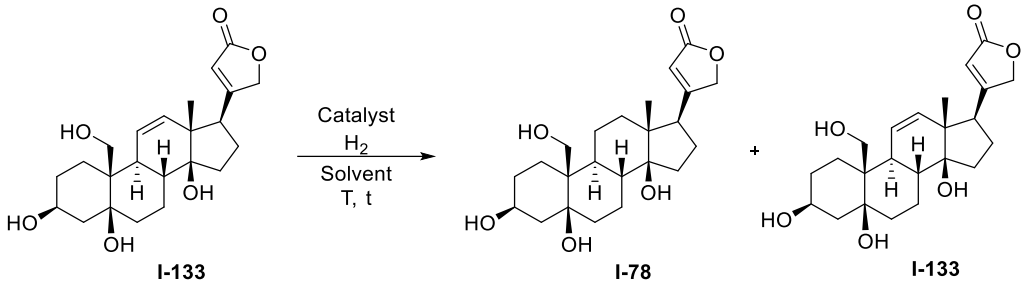
[a] Isolated yield after column chromatography. [b] Decomposition.

By using *p*-TsOH in methanol or tetrabutylammonium fluoride (TBAF) in tetrahydrofuran, decomposition was noticed (entries 1, 2). The fully deprotected product **I-133** was gained by employing HF·pyridine in tetrahydrofuran/methanol in 81% yield.

The subsequent hydrogenation was carried out using mainly Pd/C or *Crabtree* as catalysts and dichloromethane or a mixture of acetic acid and water as solvents (table 26).

This because the *Crabtree* showed to be one of the strongest catalysts and not to interact with the lactone moiety; the Pd/C in acetic acid/water represents the reaction condition that allowed the hydrogenation of the same double bond in previous pathway (scheme 30).

Table 26. Hydrogenation of deprotected compound **I-133**



I-133 **I-78** **I-133**

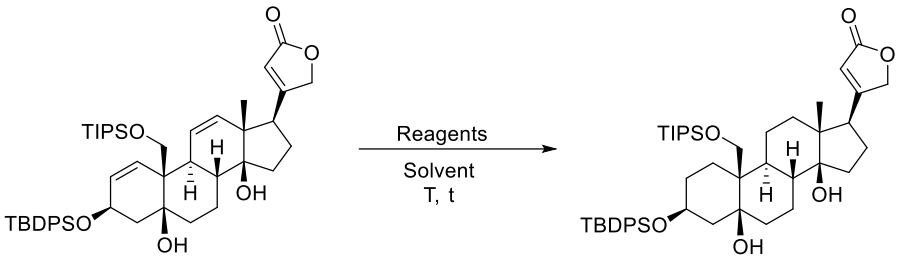
Entry	Catalyst (equiv)	Solvent	H_2 (atm)	T (°C)	t (h)	Product[a]
1	Pd/C (0.30)	AcOH (0.06 M) /H_2O (0.95 M)	1	60	16	- [b]
2	Pd/C (0.30)	AcOH (0.06 M) /H_2O (0.95 M)	1	60	3	- [c]
3	Pd/C (0.30)	AcOH (0.06 M) /H_2O (0.95 M)	35	r.t.	16	**I-133:I-78** *10:2.5* [d]
4	Pd/C (0.30)	AcOH (0.06 M) /H_2O (0.1 M)	35	r.t.	16	- [b]
5	Pd/C (0.01)	AcOH (0.06 M) /H_2O (0.95 M)	35	r.t.	16	- [c]
6	Pd/C (0.30)	AcOH (0.06 M) /H_2O (1 drop)	1	60	16	**I-133:I-78** *10:2.5* [d]
7	Pd/C (0.30)	AcOH (0.06 M) /H_2O (1 drop)	1	60	72	- [b]
8	Pd/C (0.5)	AcOH	1	60	16	- [b]
9	Pd/C (0.5)	AcOH	35	r.t.	16	- [e]
10	*Crabtree*'s catalyst (0.02)	DCM	35	r.t.	16	- [c]

[a] Isolated yield after column chromatography. [b] Lactone hydrogenation. [c] No conversion. [d] Mixture Sm and desired product [e] Unknown product (aromatic).

As shown in table 26, a non-conversion of the starting material **I-133** was observed using the *Crabtree* catalyst (entry 10) or the Pd/C in acetic acid/water at 60 °C for three hours under H_2 pressure (1 atm) (entry 2) and at room temperature for sixteen hours (35 atm).
By increasing the reaction temperature to 60 °C and stirring for sixteen hours, a full hydrogenation was detected under H_2 pressure (1 atm).
The lactone was hydrogenated also after variation of water concentration, hydrogen pressure, temperature and reaction time (entries 4, 7, 8).
An aromatization of the product **I-133** was observed in the crude NMR using Pd/C in acetic acid under high hydrogen pressure (entry 9).
A mixture of starting material **I-133** and desired product **I-78** was detected with Pd/C in acetic acid/water at room temperature for sixteen hours under H_2 pressure of 35 atm and by using acetic acid with a single drop of water at 60 °C for sixteen hours (entries 3, 6).
These results showed that water probably plays an important role in the reaction conditions, but without leading to the desired product **I-78**.

All these analyses have shown that it is not possible to obtain the desired product using a metal catalyst under hydrogen pressure, so new conditions have been employed, including the possibility of forming hydrogen *in situ via* a diimide hydrogenation.[109]
As shown in table 27, diimide hydrogenation was applied to the TIPS-protected intermediate **I-128** but without producing any desired product.

Table 27. Diimide hydrogenation.



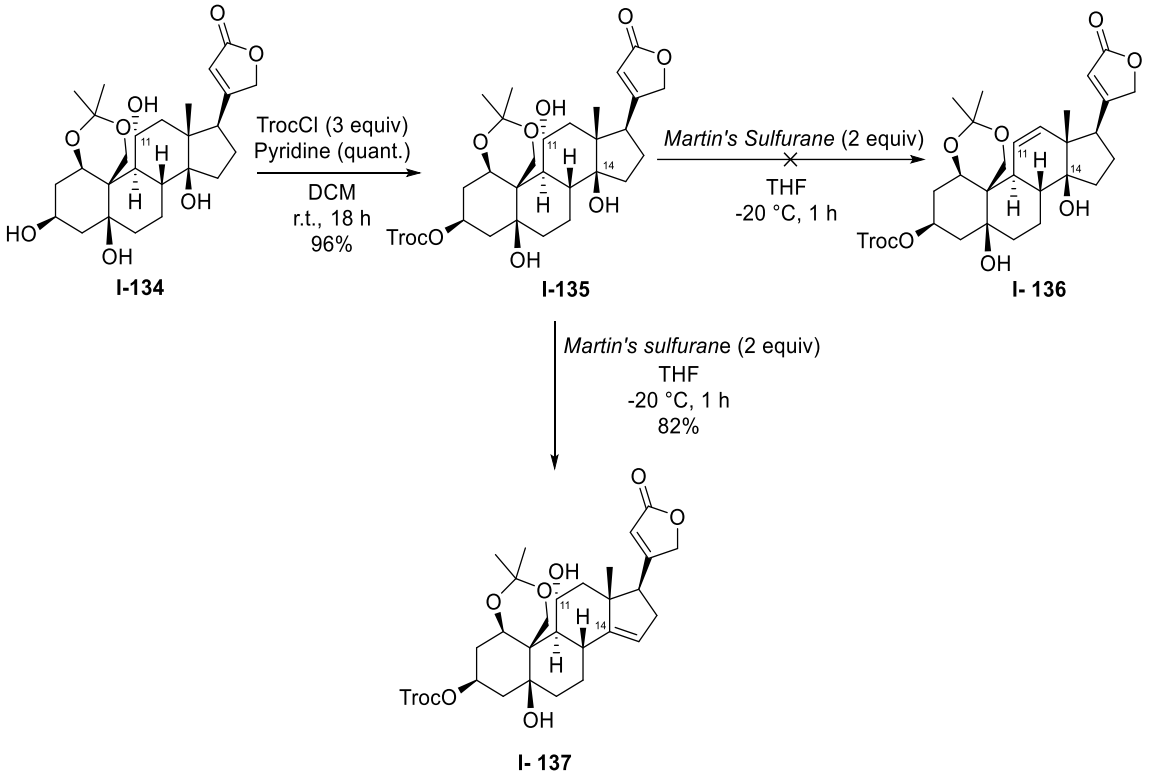
I-128 **I-134**

Entry	Reagent	Solvent	t (h)	T (°C)	Product[a]
1	N_2H_4 Propionic acid	EtOH	4	80	- [b]
2	N_2H_4 O_2	EtOH	4	35	- [b]
3	N_2H_4 H_2O_2 $CuSO_4$	EtOH	4	0	- [c]

[a] Isolated yield after column chromatography. [b] Lactone hydrogenation. [c] No conversion.

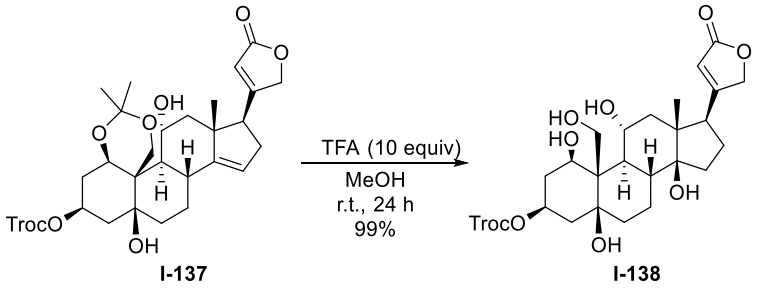
Analysis of the final products showed selective hydrogenation of the unsaturated lactone, without working on the other two double bonds (entries 1, 2). A non-conversion was determined following treatment with hydrazine hydrate (N_2H_4), hydrogen peroxide (H_2O_2) and aqueous copper sulfate solution ($CuSO_4$) (entry 3).[108]
The natural product **I-78** could be also obtained from the final product **I-73**, which was previously obtained (scheme 30), but reproduction did not yield the desired results.

Parallel to this route of synthesis, another approach was studied by protecting the alcohol at C-3 position with a Troc (2,2,2-Trichloroethoxycarbonyl) protecting group (**I-135**) (scheme 62).
The protection was carried out by using 2,2,2-Trichloroethyl chloroformate (TrocCl) and pyridine in dichloromethane and the protected product **I-135** was achieved in 96% yield.
The subsequent elimination in presence of *Martin's Sulfurane*, did not lead to the desired result **I-136** but to the dehydrated product **I-137** in 82% yield after elimination of tertiary hydroxyl group at C-14 position.



Scheme 62. Troc protection and unsuccessful C-11 hydroxy group elimination.

The subsequent deprotection of acetonide gave product **I-138** in 99% yield (scheme 63).

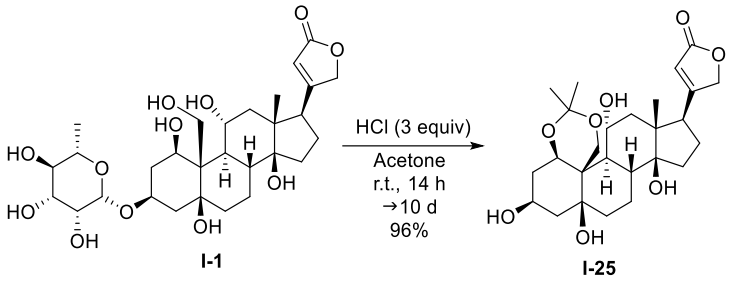


Scheme 63. Acetonide deprotection of intermediate **I-137.**

4. Summary

As previously mentioned, the purpose of this project is based on the selective deoxygenation of each hydroxyl group in the structure of the Ouabain (**I-1**). This has been made possible by using specific protecting groups and oxidizing, dehydrating and reducing reagents. The secondary alcohols at C-3 and C-11 positions have been previously selectively eliminated,[73] so this project is essentially based on the deoxygenation of the hydroxyl groups at C-1, C-5, C-14 and C-19 positions.

For each route that has been analyzed and carried out, Ouabain **I-1** was always converted to acetonide Ouabagenin **I-25** as first step in 96% yield. Therefore, the sugar at C-3 position was removed and the diol formed by the secondary alcohol at C-1 position and the primary alcohol at C-19 position was protected with an acetonide group (scheme 64).

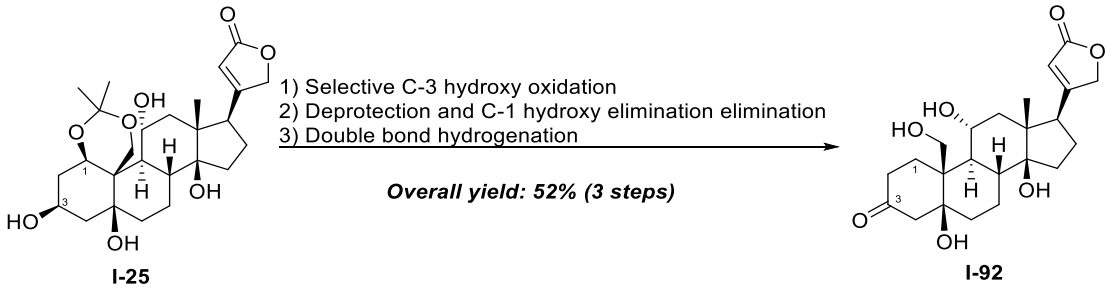


Scheme 64. Conversion of Ouabain **I-1** to acetonide Ouabagenin **I-25**.

Alcohol elimination at the C-1 position has been studied through two different approaches.

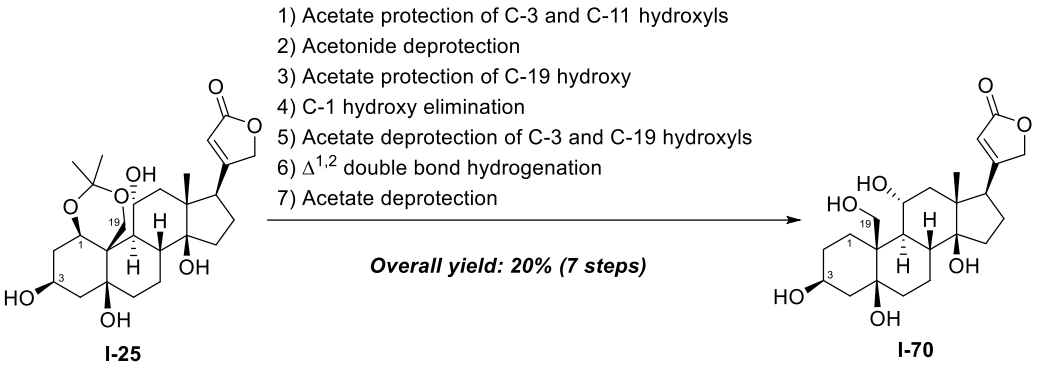
One was based on the formation of ketone at C-3 position *via* oxidation of hydroxy at C-3 position of acetonide Ouabagenin **I-25**, followed by acetonide deprotection and simultaneous β-elimination of alcohol at C-1 position. The corresponding $\Delta^{1\text{-}2}$ double bond was then hydrogenated to ketone intermediate **I-92** (scheme 65).

Currently, the diastereoselective reduction of the ketone is the main cause of failures. Derivate **I-92** has been synthesized in 52% overall yield (*See paragraph 3.1*).



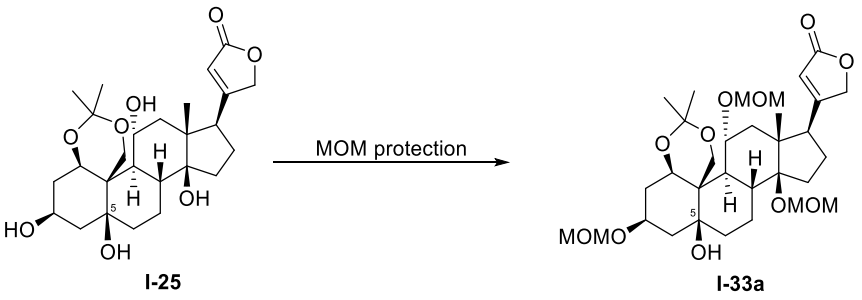
Scheme 65. Deoxygenation of hydroxyl group at C-1 position through C-3 ketone intermediate.

The second approach consisted of an initial diacetate protection of acetonide Ouabagenin **I-25** with subsequent acetonide deprotection and further acetate protection of primary alcohol at C-19 position. The secondary alcohol at C-1 position was eliminated using the *Martin's Sulfurane* reagent resulting in Δ^{1-2} double bond formation that was hydrogenated with *Crabtree*'s catalyst after a partial acetate deprotection. The last acetate deprotection achieved derivative **I-70** in 20% overall yield (scheme 66). (*See paragraph 3.1*)



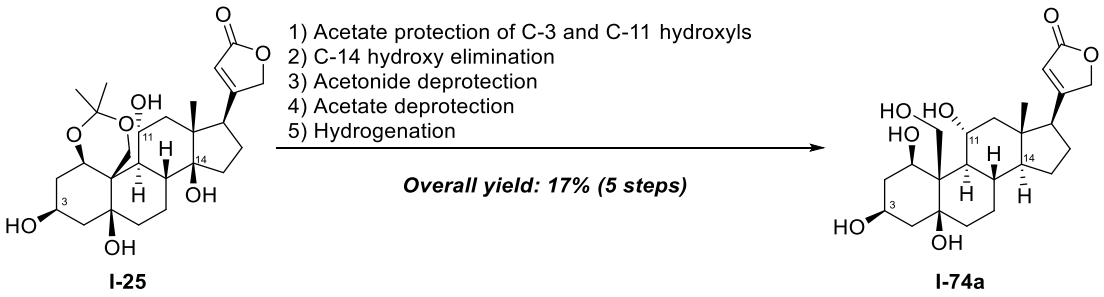
Scheme 66. Deoxygenation of OH at C-1 position through triacetate intermediate.

The deoxygenation of tertiary alcohol at C-5 position has not yet been completely developed, but the protection of secondary alcohols at C-3 and C-11 positions and of tertiary alcohol at C-14 position of acetonide Ouabagenin **I-25** is an adequate starting point to work on (**I-33a**) (scheme 67). (*See paragraph 3.2.*)



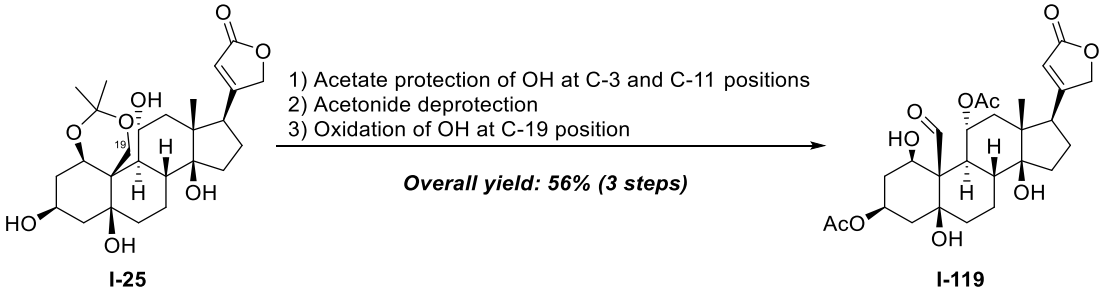
Scheme 67. Protection of acetonide Ouabagenin **I-25**.

The deoxygenation of tertiary alcohol at C-14 position has been successfully achieved. The pathway began with the acetate protection of the secondary hydroxyl group at C-3 and C-11 positions of Ouabagenin **I-25**, followed by elimination of tertiary alcohol at C-14. The subsequent hydrogenation of Δ^{14-15} double bond, after complete deprotection of the intermediate, led to the desired product **I-74** in 17% overall yield over 5 steps with a *d.r.* of *93:7* (scheme 68). The major diastereosomer presents the proton at the C-14 position in *trans*-configuration compared to the methyl group at C-13 position, confirmed by the crystal structure. (*See paragraph 3.3.*)



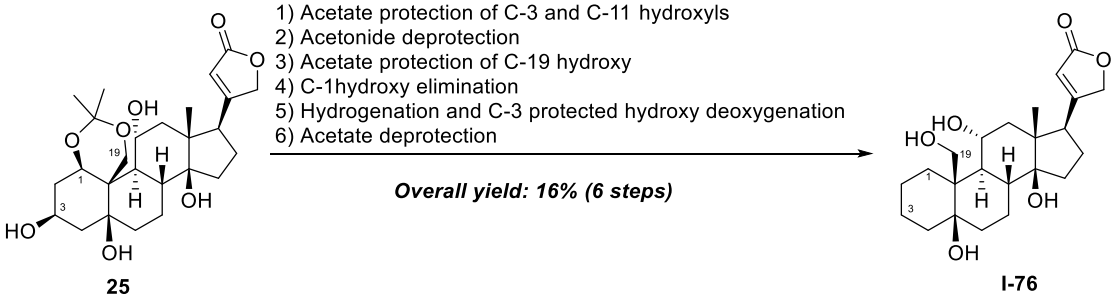
Scheme 68. Deoxygenation of C-14 hydroxy.

The defunctionalization of the primary alcohol at C-19 position has not yet been achieved. However, the analyzed route involved a first diacetate protection of hydroxy group at C-3 and C-11 positions of acetonide Ouabagenin **I-25**, followed by acetonide deprotection. The primary alcohol was then oxidized to form aldehyde **I-119** in 56% overall yield, an interesting intermediate for applying various deoxygenation reaction conditions (scheme 69). (*See paragraph 3.4.*)



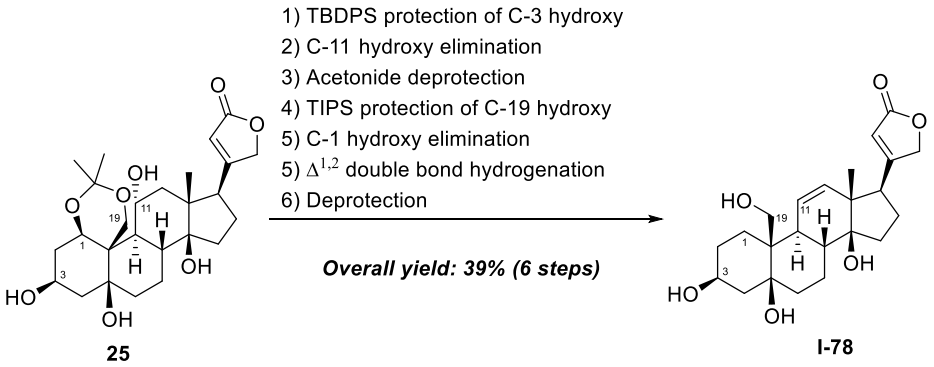
Scheme 69. Oxidation of primary alcohol at C-19 position.

The two hydroxyl groups at C-1 and C-3 positions have been satisfactorily deoxygenated with an initial diacetate protection of acetonide Ouabagenin **I-25** with subsequent acetonide deprotection and further acetate protection of primary alcohol at C-19 position. The elimination of the secondary alcohol at C-1 position resulted in a $\Delta^{1\text{-}2}$ double bond formation, then hydrogenated with Pd/C in acetic acid which also resulted in the deoxigenation of the C-1 protected hydroxy group. The last acetate deprotection afforded derivative **I-76** in 16% overall yield (scheme 70). (*See paragraph 3.5*)



Scheme 70. Deoxygenation of C-1 and C-3 hydroxyls.

The route for deoxygenation of the two alcohols at C-1 and C-11 positions has been deeply investigated. First, alcohol at C-3 position of acetonide Ouabagenin **I-25** was protected with TBDPS, followed by elimination of hydroxyl group at C-11 position and acetonide deprotection. Primary alcohol at C-19 position was protected with TIPS protecting group and subsequent elimination of secondary alcohol at C-1 position entailed a $\Delta^{1\text{-}2}$ double bond formation that was hydrogenated with *Crabtree*'s catalyst. Subsequent full deprotection achieved derivative **I-78** in 39% overall yield (scheme 71). (*See paragraph 3.6*)

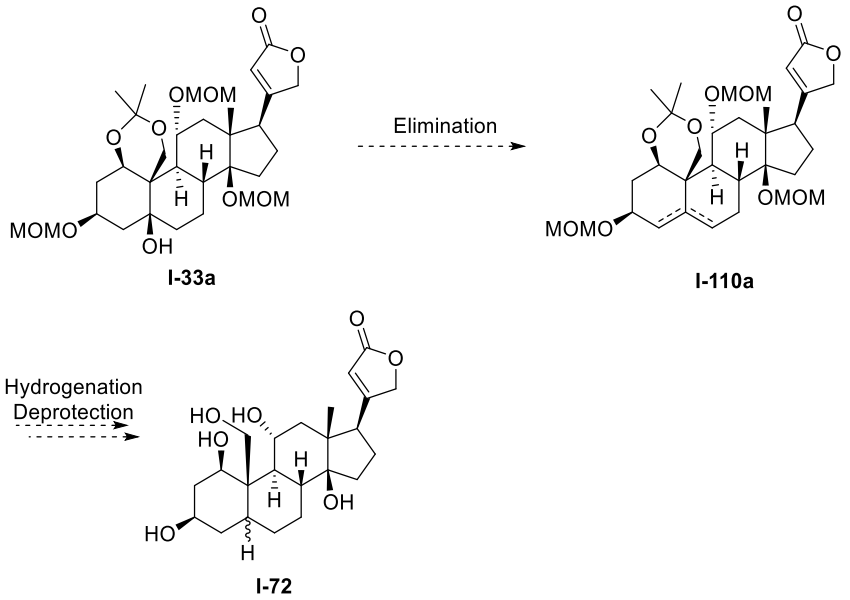


Scheme 71. Deoxygenation of OH at C-1 and C-11 positions.

5. Outlook

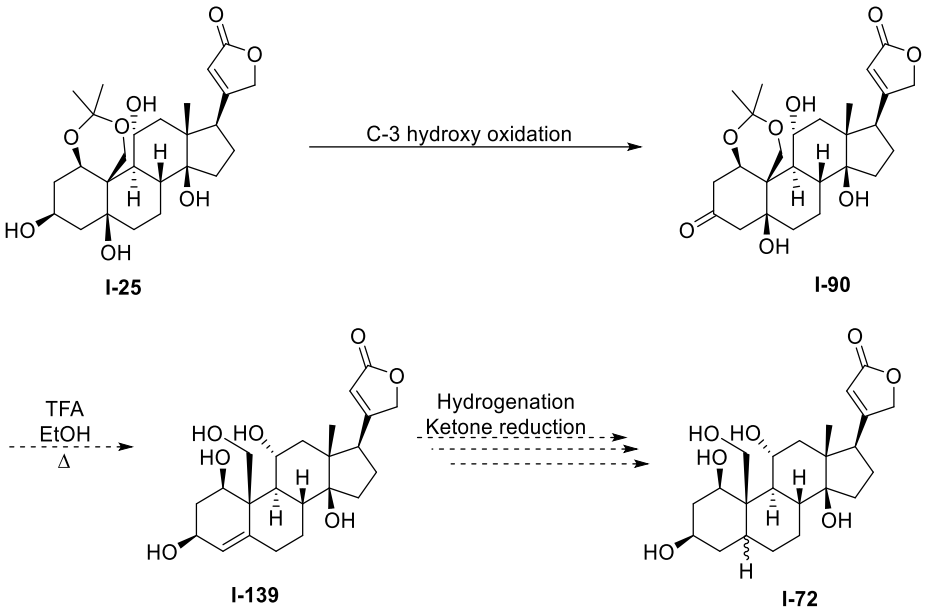
➢ **Defunctionalization of Ouabain: *OH* at C-5 position (I-72)**

The defunctionalization of tertiary alcohol at C-5 position should be studied and tested with different and stronger dehydrating reagents or reaction conditions.
Once the desired elimination will be achieved, it should be necessary to focus on a stereoselective reduction of the $\Delta^{4\text{-}5}$ or $\Delta^{5\text{-}6}$ double bond. This hydrogenation should be studied by applying a plethora of reaction conditions. The acetonide and MOM protecting groups should be simultaneously removed by using acidic conditions (*i.e.*, HCl in MeOH) (scheme 72).



Scheme 72. Towards the synthesis of derivative **I-72.**

A second approach could involve the elimination of tertiary alcohol from the ketone derivative **I-90**, under acidic conditions (scheme 73), achieving unsaturated ketone **I-139**.[73] Subsequent hydrogenation, diastereoselective ketone reduction and deprotection should give desired final product **I-72**.

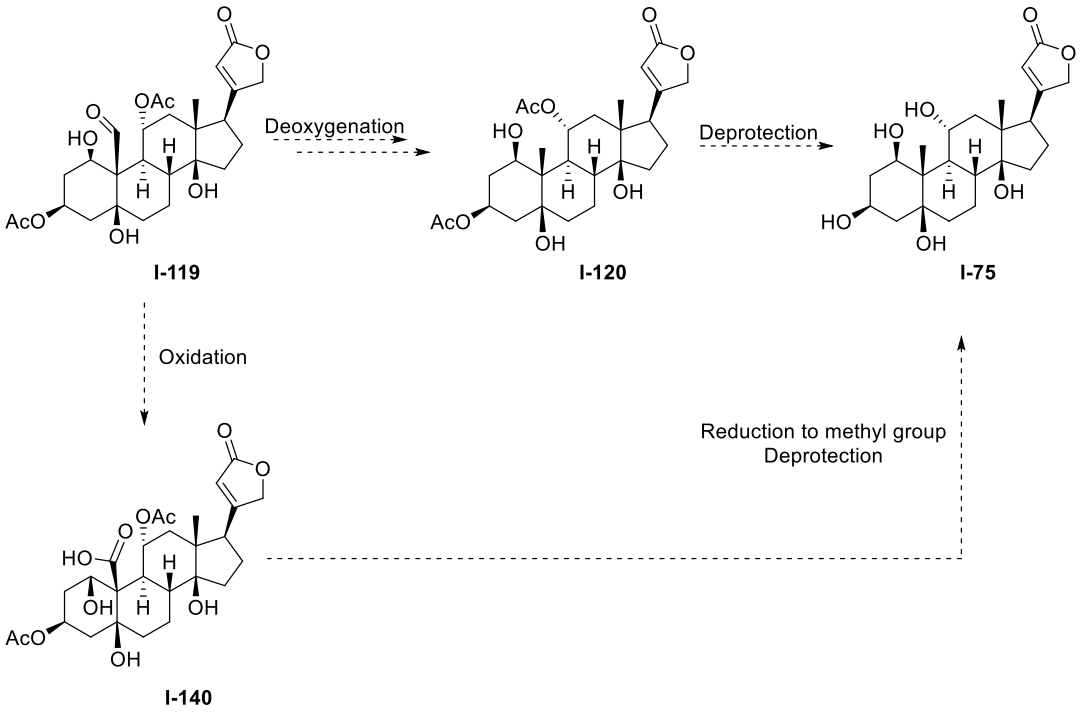


Scheme 73. A second approach for synthesizing derivative **I-72**

➢ Defunctionalization of Ouabain: *OH* at C-19 position (I-75)

In the case of primary alcohol, an appropriate reduction of aldehyde to alkane should be examined. Different reaction conditions should be tested in order to synthesize the thioacetal derivative which should be a good intermediate to obtain the corresponding alkane.

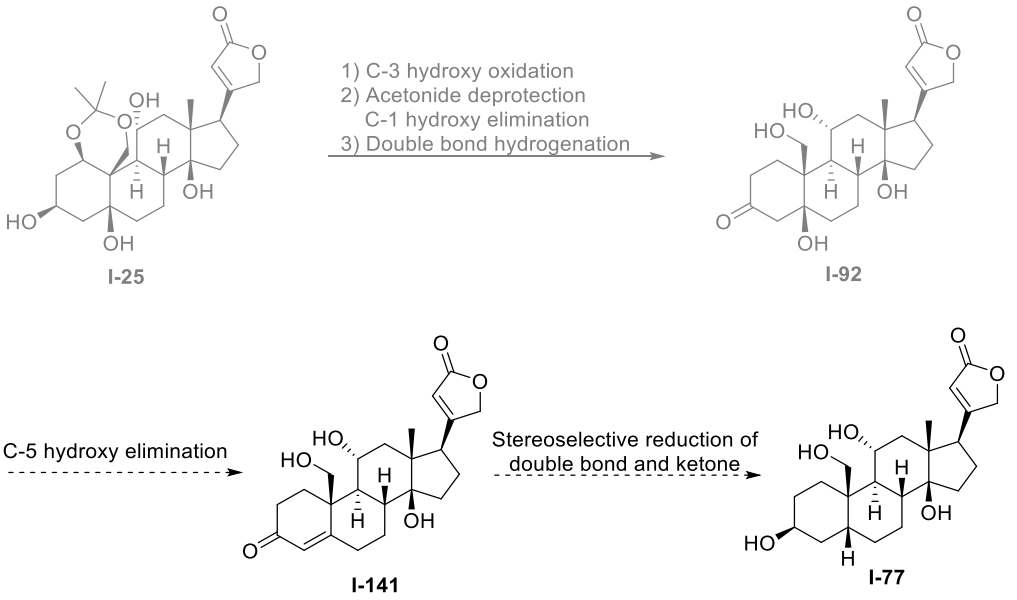
Furthermore, a direct deoxygenation of the primary alcohol to alkane compatible with the free secondary alcohol and with the lactone should be studied (scheme 74). The aldehyde **I-119** could also be further oxidized to carboxylic acid **I-140** which, through a reduction to a methyl group, should give the desired product **I-75**.



Scheme 74. Towards the synthesis of derivative **I-75.**

➢ *Defunctionalization of Ouabain: OH at C-1,5 position (***I-*77)

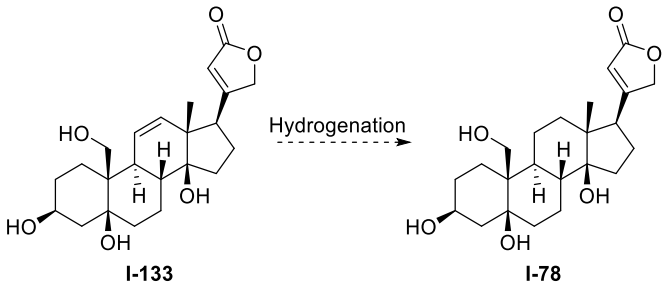
To synthesize desired product **I-77**, the same pathway considered for the synthesis of product **I-70** through a ketone intermediate can be used and optimized (*see paragraph 3.1*). The ketone derivative **I-92** should be treated with TFA in ethanol[73] to eliminate the tertiary alcohol at C-5 position and the subsequent stereoselective reduction of the Δ^{5-6} or Δ^{6-7} double bond and the ketone should give the desired product **I-77** (scheme 75).



Scheme 75. Towards the synthesis of compound **I-77.**

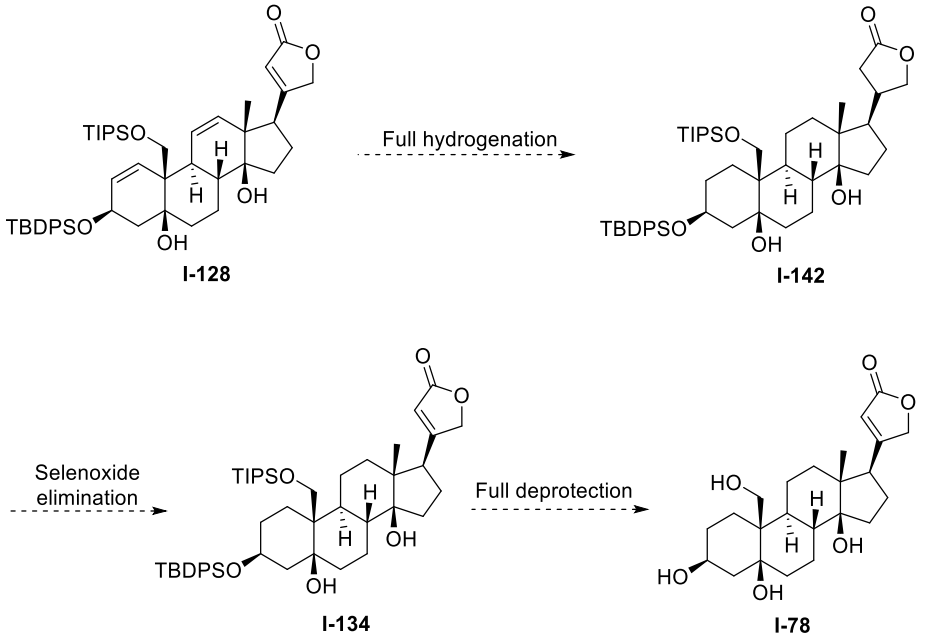
➢ Defunctionalization of Ouabain: *OH* at C-1,11 positions (I-78)

The desired product **I-78** should be synthesized by hydrogenating the $\Delta^{11\text{-}12}$ double bond of intermediate **I-133** (scheme 76).



Scheme 76. Towards the synthesis of final desired product **I-78**.

An in-depth study of hydrogenation was performed with nondesired result, so further catalysts should be analyzed or a different pathway should be carried out (scheme 77).
A total hydrogenation should be applied to the alkene **I-128**, followed by a selenoxide elimination to re-install the double bond within the lactone (**I-134**).[109] A subsequent total deprotection should lead to the desired product **I-78**.



Scheme 77. New pathway for synthesis of **I-78**.

➢ Towards the synthesis of *Coroglaucigenin* (I-80)

Coroglaucigenin (CGN) **I-80** is a natural product isolated from *Calotropis gigantean*, belonging to the cardenolide class.[110] This cardenolide showed excellent anti-cancer activities by a significant cytotoxicity against hepatoma carcinoma, gastric and lung cancer cells.[111,112]

CGN **I-80** has a special structure extremely similar to that of Ouabain **I-1**, as shown in figure 11.

Both have a methyl group at C-13 position, a primary alcohol at C-19 position, a secondary alcohol at C-3 position, a tertiary alcohol at C-14 position and a lactone at C-17 position, with the same stereogenity. Cardenolide **I-80** is characterized by the absence of the sugar moiety, both secondary alcohols at C-1 and C-11 positions and tertiary alcohols at C-5 position.

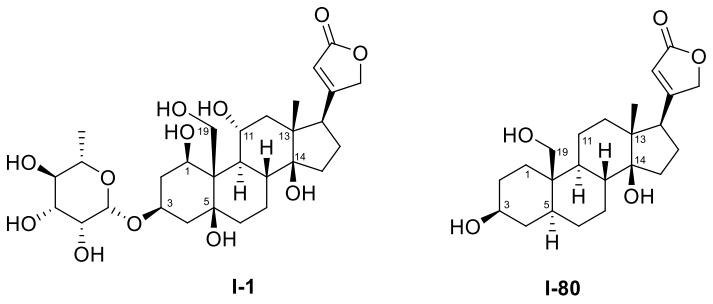


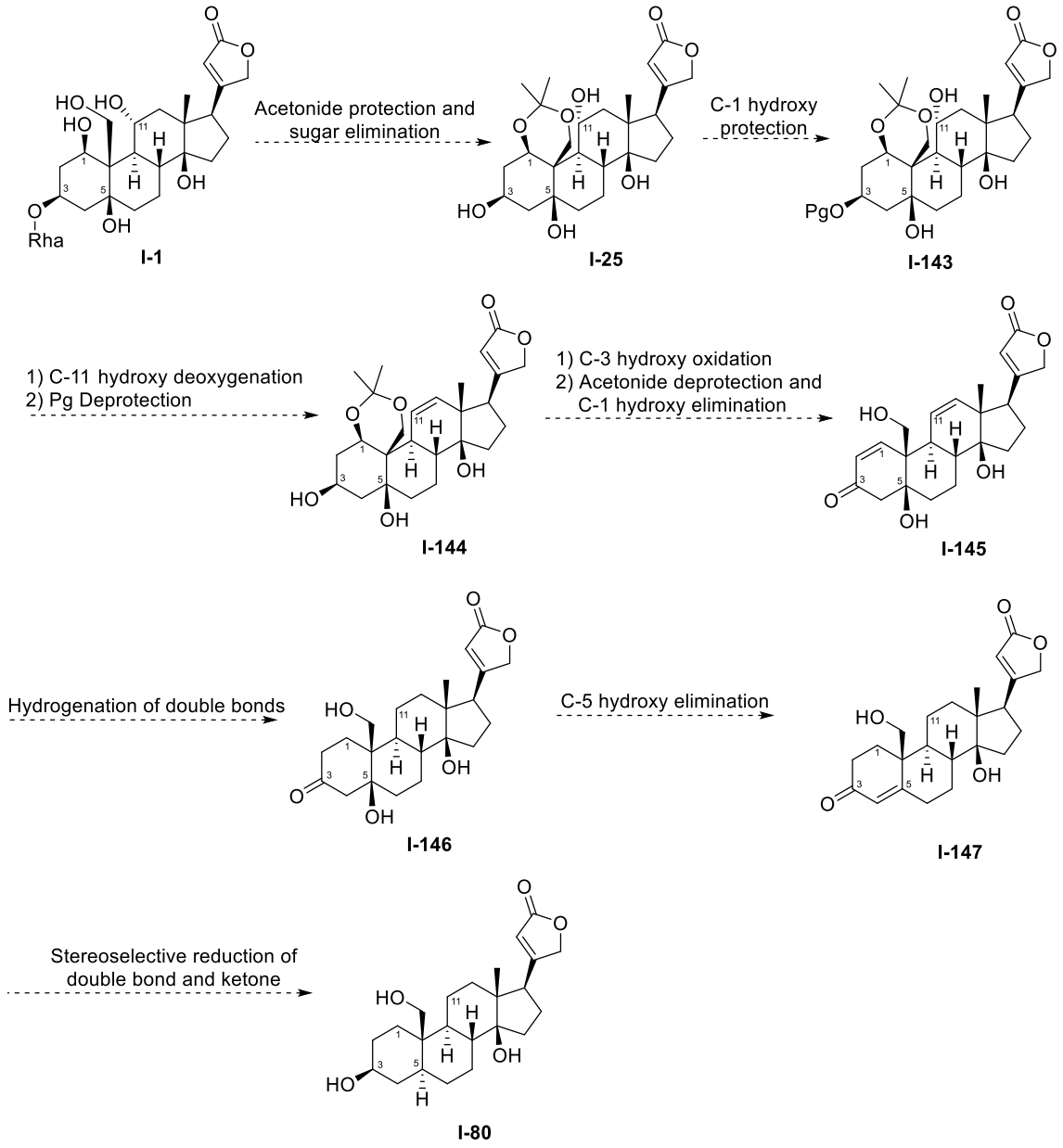
Figure 11. CGN **I-80** and Ouabain **I-1** structures.

This highlights the possibility to synthesize CGN **I-80** using Ouabain **I-1** as starting material. A general pathway is shown in scheme 78.

First, Ouabain should be converted into acetonide Ouabagenin **I-25**, as in all the previous cases. The most convenient alcohol to be eliminated first, by using dehydrating reagent such as *Martin's Sulfurane*, should be the secondary one at C-11 position after protection of the hydroxyl group at C-3 position (*i.e.*, silyl groups such as TIPS). A subsequent deprotection should afford the alkene intermediate **I-144**.

Afterward, the secondary hydroxyl group at C-1 position should be eliminated *via* the formation of the ketone derivative at C-3 position. The subsequent elimination, deprotection (**I-145**) and hydrogenation of the $\Delta^{1\text{-}2}$ and $\Delta^{11\text{-}12}$ double bonds should give the ketone **I-146**.

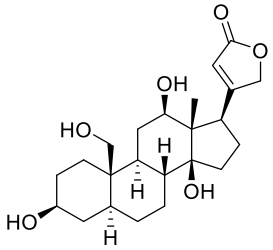
The tertiary alcohol at C-5 position should be eliminated by using TFA in ethanol at 50 °C,[73] forming the corresponding $\Delta^{5\text{-}6}$ or $\Delta^{6\text{-}7}$ double bond (**I-147**) which should be stereoselectively reduced, together with the ketone, giving the natural product **I-80**.



Scheme 78. General pathway to synthesize cardenolide **I-80.**

➢ Towards the synthesis of *Procegenin A* (I-81)

Procegenin A **I-81** (figure 12) is a natural product, in particular it is a secondary metabolite from the plant *Calotropi procera*, an evergreen, perennial shrub of the family Apocynaceae.[113]



I-81

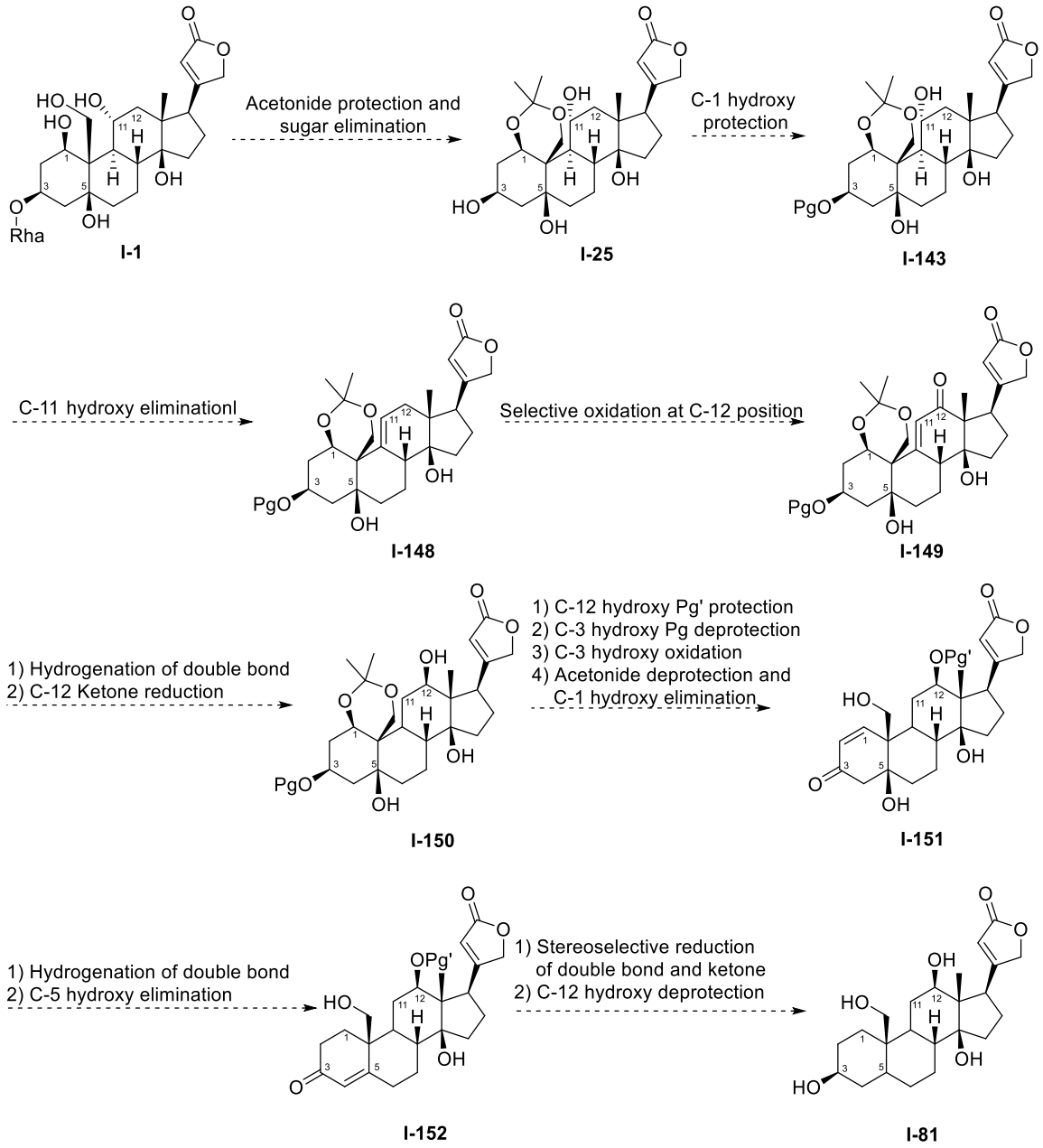
Figure 12. Structure of Procegenin A.

Several studies have shown that *C. procera* has important pharmacological activities, such as the treatment of cold, fever, leprosy, asthma, rheumatism, eczema, indigestion, diarrhoea, elephantiasis, skin diseases, and dysentery.[113]

As shown in scheme 79, the first two steps should be the same involved in the possible pathway for synthesis of Coroglaucigenin (CGN) **I-80**, obtaining the intermediate **I-143** which should undergo the elimination of secondary alcohol at C-11 position, leading to compound **I-148.**

A selective oxidation at C-12 position should achieve the ketone intermediate **I-149** that should be converted to compound **I-150** after hydrogenation of $\Delta^{9\text{-}11}$ double bond and ketone reduction. Next, secondary alcohol at C-12 position should be protected to allow the deprotection and subsequent selective oxidation of secondary alcohol at C-3 position, followed by acetonide deprotection and secondary alcohol elimination at C-1 position to afford unsaturated ketone **I-151**.

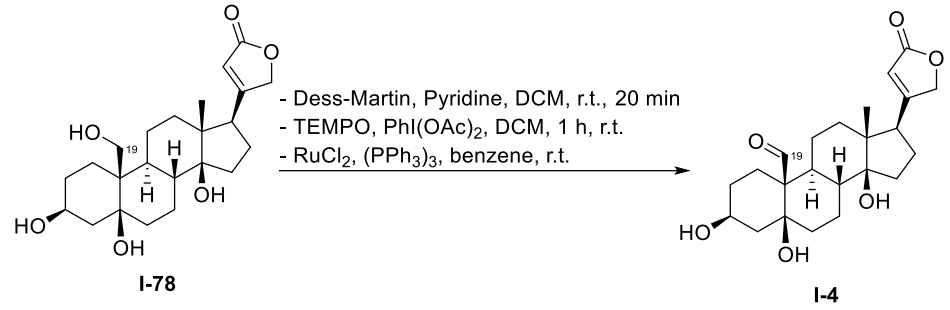
Reduction of the $\Delta^{1\text{-}2}$ double bond and elimination of tertiary alcohol at C-5 position should give alkene derivative **I-152**. The corresponding $\Delta^{5\text{-}6}$ or $\Delta^{6\text{-}7}$ double bond should be stereoselectively reduced, together with the ketone, to achieve the natural product **I-81** after the final deprotection of Pg'.



Scheme 79. Pathway for the synthesis of Procegenin A **I-81**.

➢ Towards the synthesis of *Strophanthidin* (I-4)

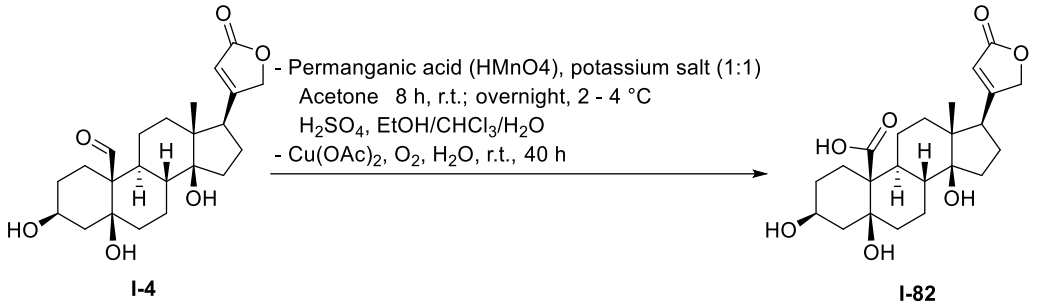
The natural compound *Strophanthidin* **I-4** should be easily synthesized, starting with the final product **I-78** because both molecules have a similar structure. *Strophantidin* should be obtained following a simple selective oxidation of the primary alcohol to aldehyde, involving an oxidant reagent (*i.e., Dess-Martin*,[114] TEMPO,[115] $RuCl_2$[116]).
Three different oxidation conditions that should be tested are shown in scheme 80.



Scheme 80. Synthesis of *Strophanthidin* by oxidation of primary alcohol at C-19 position of product **I-78**.

➢ Towards the synthesis of *Strophanthidinic acid* (I-82)

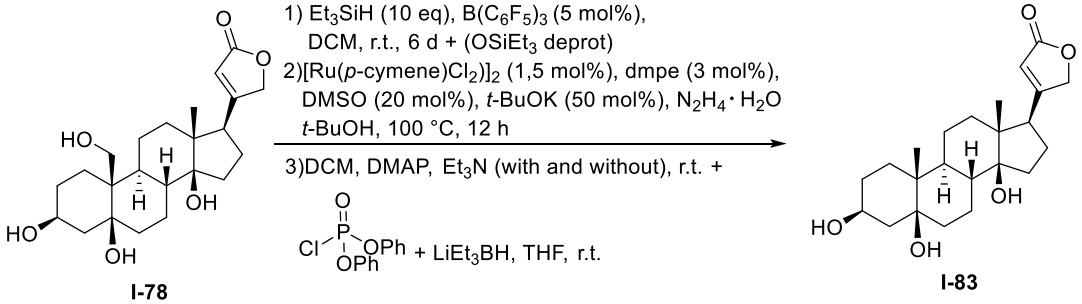
The natural product *Strophantidinic acid* **I-82** should be easily synthesized from the *Strophanthidin* **I-4**, because it should be achieved after aldehyde oxidation to carboxylic acid using copper (II) acetate under O_2 pressure[55] or permanganic acid in acetone in presence of potassium salt followed by treatment with sulfuric acid in a mixure of ethanol, chloroform and water (scheme 81).[117]



Scheme 81. Synthesis of *Strophanthidinic acid* by oxidation of compound **I-82**

➢ Towards the synthesis of *Periplogenin* (I-83)

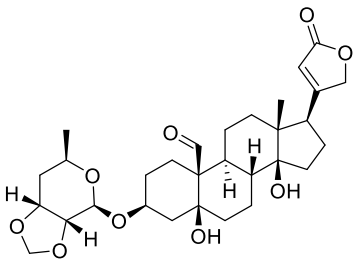
Periplogenin **I-83** is a natural compound with a similar structure to ones described above. In fact, it should also be obtained as a result of deoxygenation of aldehyde **I-4** to alkane by testing some different conditions showed in scheme 82.[118]



Scheme 82. Synthesis of *Periplogenin* by deoxygenation of compound **I-83**.

➢ Towards the synthesis of *Reevesioside A* (I-84)

Reevesioside A **I-84** (figure 13) is a cardenolide glycoside isolated from the root of *reevesia formosana*. Recent studies have shown it to display potent antiproliferative activity against human hormone-refractory prostate cancer.[119]



I-84

Figure 13. *Reevesioside A* structure **I-84**.

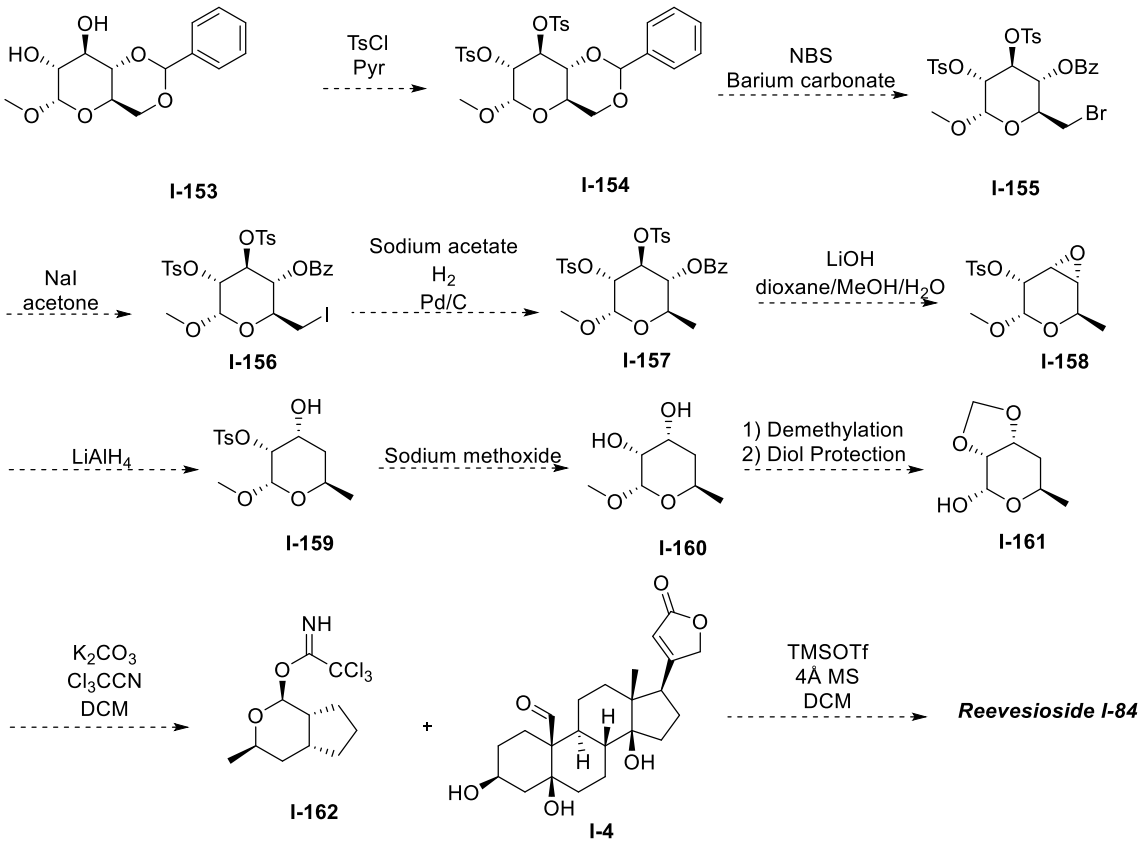
The synthesis of natural product **I-84** requires the synthesis of a carbohydrate moiety that should be then linked to the hydroxyl group at the C-3 position of *Strophanthidin* (**I-4**) (scheme 83).

The route should start with the commercially available reagent 4,6-benzylidene derivative of α-*D-methylglucopyranoside* **I-153** that should be first converted to the bis(tosylate) intermediate (**I-154**) and then to the bromobenzoate product (**I-155**).[120]

Deoxygenation should be achieved *via* a two-step procedure: conversion of bromide to iodide intermediate (**I-156**) and hydrogenolysis (**I-157**).

Subsequently, the cleavage of the benzoate with epoxide formation should achieve intermediate **I-158**, which ring should be opened by using lithium aluminum hydride and subsequent treatment with sodium methoxide should afford the tosylate cleveage.

The following formation of diol intermediate (**I-159**) and its protection should lead to the desired product (**I-160**), then treated with potassium carbonate and thrichloroacetonitrile to form the acetimidate intermediate (**I-162**). The final coupling between *Strophanthidin* and carbohydrate should yield the desired final natural product (**I-84**).[46]



Scheme 83. Synthesis of *Reevesioside A* **I-84** from Strophanthidin **I-4.**

❖ Decarboxylation of bistriazol derivatives and synthesis of *N*-substituted imines from diazidated malonamides

1. Introduction

1.1. History and synthesis of geminal diazides

Organic azides have several applications in synthesis, despite their structure of three nitrogen atoms in linear arrangement attributes to them a potential thermal instability and sensitivity to impact or shock. Therefore, they are possible hazardous substances that belong to a very high-energy class of compounds. Introducing an azide group into a molecule, the compound's energy increases by around 290-355 kJ/mol, because of the easily polarization of N_3 bond that can dissociate in a highly exothermic process releasing nitrogen and reactive nitrenes.[121]

The chemistry of azides started with the preparation and discovery of the first aromatic organic azide **II-1**, in 1864 by *Peter Grieß*,[122,123] followed by the rearrangement of acyl azides **II-2** to the corresponding isocyanates **II-3**, with loss of nitrogen gas, reported in 1890 by *Theodor Curtius*, the grandseigneur of nitrogen chemistry (*Curtius* rearrangement **B**) (figure 14).[124,125] The isocyanates intermediate can then undergo attack by a variety of nuclephile (*i.e*., water, alcohols and amines) to afford carbamate **II-4**, amine **II-5**, or urea derivatives **II-6**.

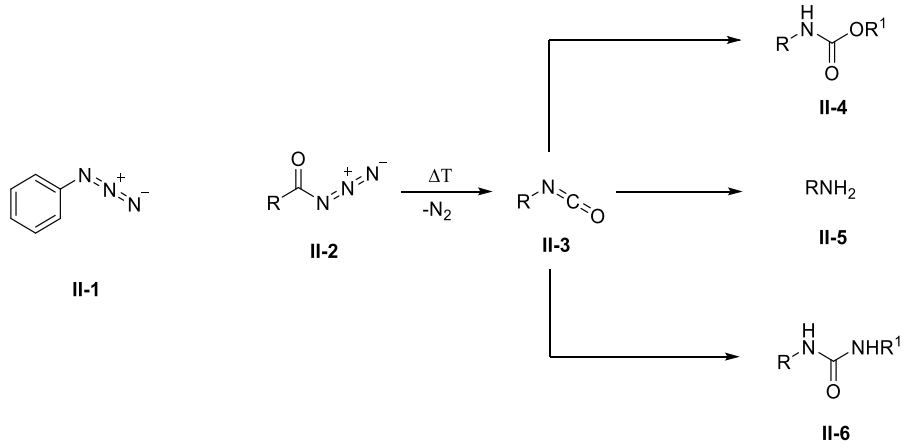
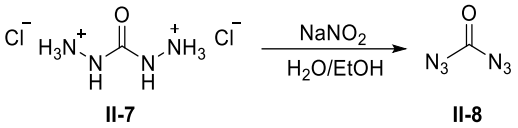


Figure 14. Phenyl azide's structure and *Curtius* rearrangement.

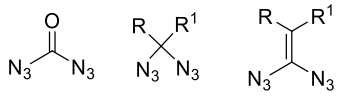
In 1894, *T. Curtius* and *K. Heidenreich* reported the synthesis and the stability of the first diazide derivative **II-8**, by treating an aqueous solution of carbonyl dihydrazide dihydrochloride **II-7** with sodium nitrite at low temperature (scheme 84).[126,127]



II-7 **II-8**

Scheme 84. Synthesis of the first carbonyl diazide.

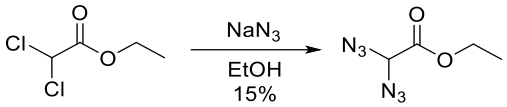
Nowadays, the class of geminal diazides is divided into three subclasses: carbonyl **II-9**, aliphatic **II-10** and vinyl **II-11** diazides (figure 15).



II-9 **II-10** **II-11**

Figure 15. Geminal diazides subclasses.

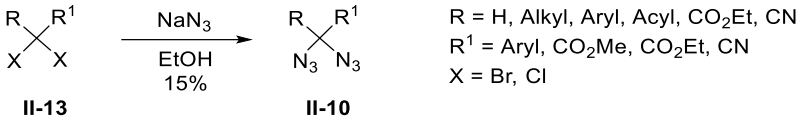
In 1908, the first aliphatic geminal diazide **II-10** was discovered by *Forster et al.*[128] who synthesized the 2,2-ethyldiazidoacetate **II-10a** derivative from the dichloride compound **II-12**, by using sodium azide in ethanol (scheme 85).



II-12 **II-10a**

Scheme 85. Synthesis of the first aliphatic geminal diazide.

This accessible method of synthesizing geminal diazides was used in subsequent years to produce several α-diazido esters,[129] α,α-diazido-β-ketoesters,[130] α,α-diazidoketone,[131] α,α-diazido-β-ketolactame,[132] 2,2-diazidomalonate,[133] heterocyclic[132,134] and benzylic[135] diazides (scheme 86).



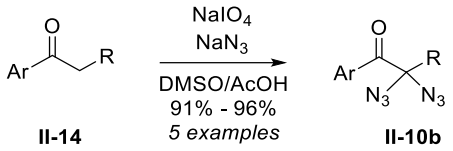
II-13 **II-10**

Scheme 86. Synthesis of diazido derivatives**.**

Being extremely substrate specific and having a limited range of applications, other methods to convert acetals and ketones into geminal diazide[136] with trimethylsilyl azide, with tin (IV) or tin (II) chloride to convert phosphorylides,[137] with tosyl azide to synthesize 2,2-diazido-1,3-diiodopropane from propanediene[138] using iodine azide, were employed sporadically.[139]

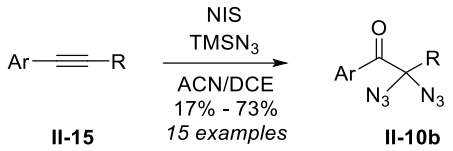
Currently, the newest and most used methods involve the use of oxidation conditions.

In 2012, *Sudalai et al.* synthesized the desired geminal diazides **II-10b** from different aryl ketones **II-14** by using sodium azide, sodium periodate in dimethylsulfoxide and acetic acid (scheme 87).[140]



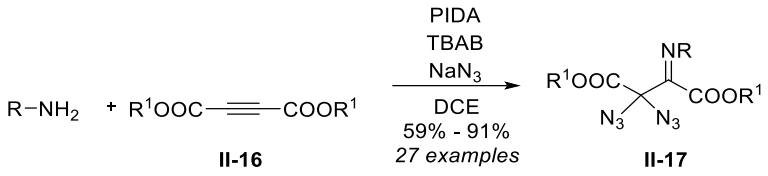
Scheme 87. Synthesis of geminal diazide **II-10b** from aryl ketones **II-14**.

Three years later, *Yanada et al.* demonstrated that geminal diazides **II-10b** could be also synthesized from alkynes **II-15** employing *N*-iodosuccinimide and trimethylsilyl azide (scheme 88).[141]



Scheme 88. Synthesis of geminal diazide from alkynes.

In 2018, *Sharada et al.* obtained various α,α-diazido-β-iminoesters **II-17** from electron poor alkynes **II-16** by hydroamination in presence of sodium azide, diacetoxyiodobenzene and tetrabutylammonium bromide (scheme 89).[142]



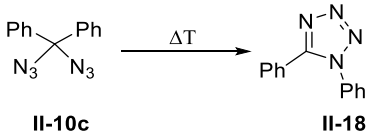
Scheme 89. Synthesis of α,α-diazido-β-iminoesters **II-17** from electron poor alkyne **II-16**.

1.2. Reactivity of geminal diazides

The reactivity of geminal diazides is not a common discussed topic in the literature given the limited number of publications. In most cases, diazides are only mentioned as by-products or proposed intermediates. Some reports examined thermodynamic and kinetic influences of the azido group on the stability of carbocations[143] and calculated structures of geminal diazides.[144]

Classic azide reactions, such as azide-alkine cycloadditions to bistriazole, thermal and photolysis reactions to synthesize other nitrogen-containing heterocyclic compounds, have been well investigated.[145,146,147,148,149,150]

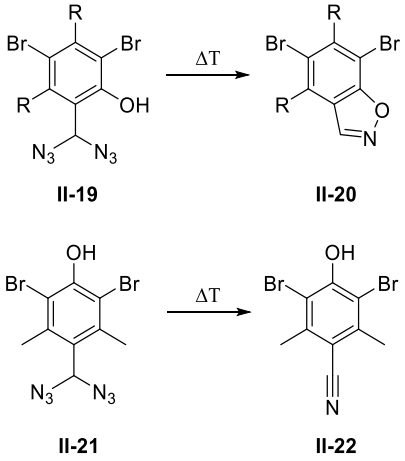
In 1909, *Schroeter* postulated that the thermal decomposition of diazidodiphenylmethane **II-10c** allowed the formation of the corresponding tetrazole **II-18** (scheme 90).[135]



II-10c **II-18**

Scheme 90. Thermal decomposition of diazidodiphenylmethane derivative.

In contrast, *Lindemann* and *Mühlhaus* found isoxazoles **II-20** and nitriles **II-22** applying the thermal decomposition to *ortho*-(**II-19**) and *para*-hydroxybenzylic diazides **II-21** (scheme 91). [135c]

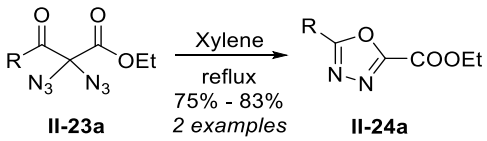


II-19 **II-20**

II-21 **II-22**

Scheme 91. Thermal decomposition of ortho- and para-hydroxybenzylic diazides.

Thermal decomposition of 2,2-diazidomalonates and 2,2-diazidomalonamides involved the formation of tetrazoles,[146] whereas 2,2-diazido-β-keto esters (**II-23a**) gave the corresponding 1,3,4-oxadiazoles (**II-24a**) (scheme 92).[130b]

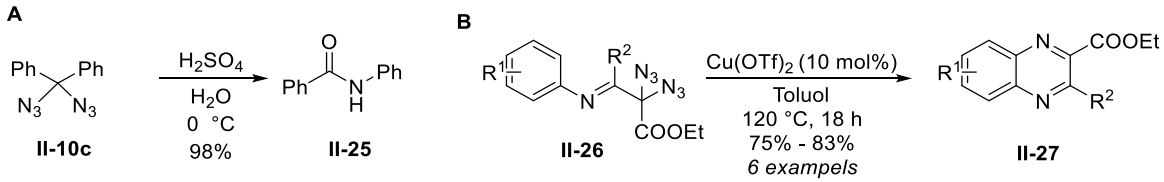


II-23a **II-24a**

Scheme 92. Thermal decomposition of 2,2-diazido-β-keto esters.

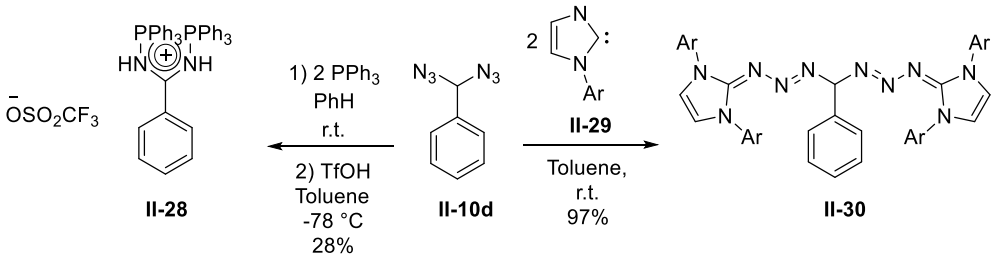
The photolysis can be involved in several different possible reaction pathways than thermolysis, leading to a large number of products. *Moriarty et al.* showed that heterocycles, such as tetrazoles,[146,147,148] oxadiazoles[147] and benzimidazoles,[148] were obtained as main products in ca. 50% yield.

In scheme 93, the different reactivity of geminal diazides is illustrated: diazidodiphenylmethane **II-10c** is converted into the amide **II-25** with strong acids following the hydrolysis of the diazide, subsequent nitrene formation and rearrangement (scheme 93, A).[135d]
This can also occur *via* a nitrene copper-catalyzed cycloamination of α,α-diazido-β-iminoesters **II-26** to the corresponding quinoxalines **II-27** (scheme 93, B).
This illustrates that in one case, azide function represents a source of nitrene, while, in the other, is splitted during the aromatization.[142]



Scheme 93. The diversity of the nitrene's chemistry of geminal diazides.

Another interesting reactivity of the diazide intermediated is shown in scheme 94, in which *N,N*-bis(phosphane) **II-28** and the geminal bis(triaza-1,3-butadiene) **II-30** can be obtained from (diazidomethyl)benzene **II-10d**.
After application of the well-known *Staudinger*[149] conditions to diazide **II-10d** and protonating the intermediate with trifluoromethanesulfonic acid, derivative **II-28** is synthesized. The derivative **II-30** is formed adding *N*-heterocyclic carbene **II-29** to the two azide functions (scheme 94).[150]



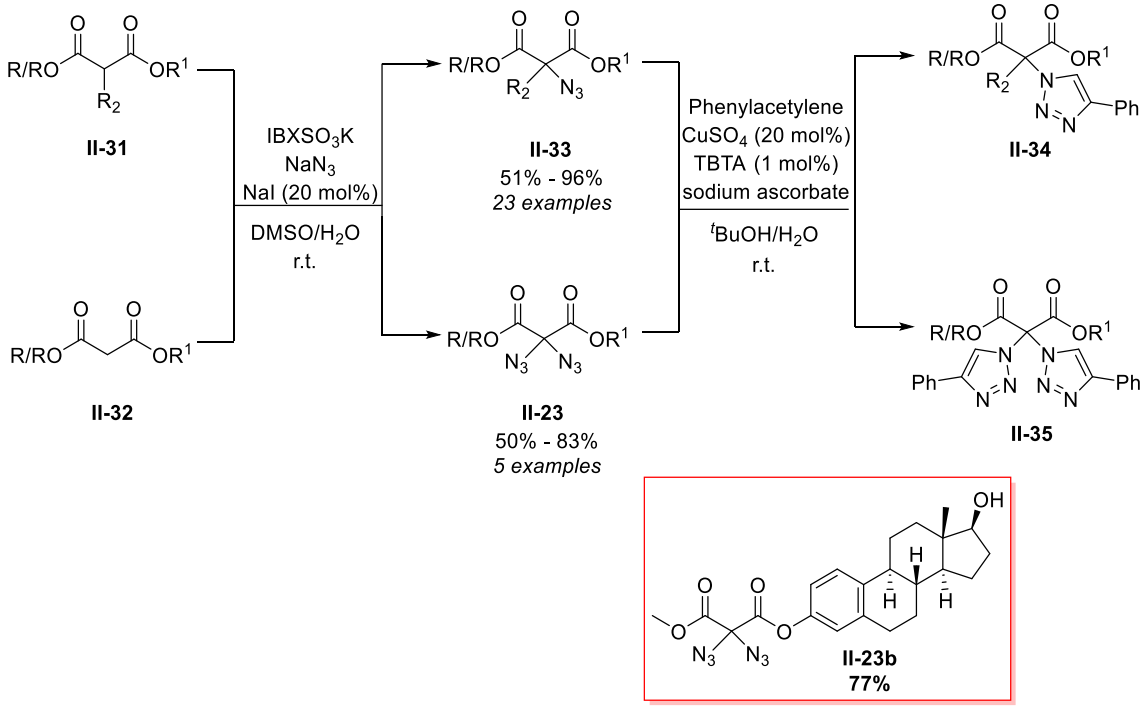
Scheme 94. Geminal diazide reactivities.

1.3. Synthesis and reactivity of geminal diazides by *Kirsch et al.*

In 2012, *Kirsch et al.* developed an oxidative method to convert both α-substituted **II-31** and unsubstituted 1,3-dicarbonyls **II-32** into the corresponding α-mono **II-33** or α,α-diazides **II-23**. This method included the use of the mild oxidizing agent IBX-SO_3K (compatible with several functional groups such as aromatics, olefins, epoxides, acetals, secondary and primary hydroxyl groups), sodium azide and catalytic amount of sodium

iodide (scheme 95).[151] An example was represented by the diazide of the β-estradiol derivative **II-23b**.

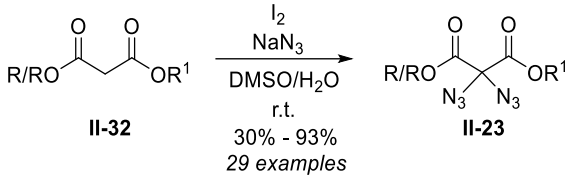
Using the established known conditions of *Click* reaction (*CuAAC*: copper(I)-catalyzed alkyne-azide cycloaddition)[152] with phenylacetylene as terminal alkyne, the azide intermediates were converted into the corresponding mono (**II-34**) and bistriazoles (**II-35**) (scheme 95).



Scheme 95. Oxidative method to synthesize α-mono or α,α-diazides derivatives and corresponding triazoles using *CuAAC* reaction condition.

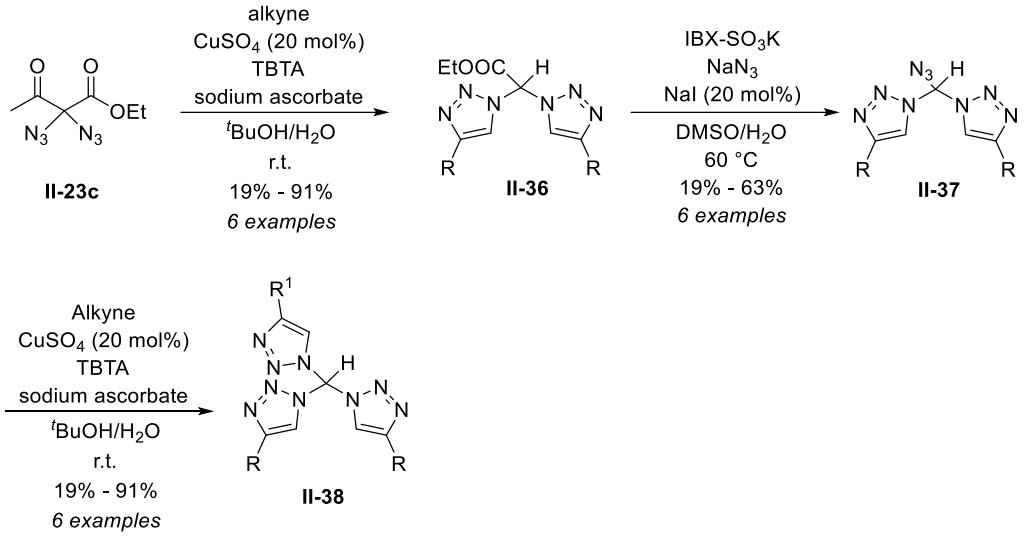
In 2014, by moderately modifying these conditions, triazidocarbonyl derivatives, a previously unknown class of geminal triazides, were prepared from 3-oxocarboxylic acids, iodomethyl ketones and terminal olefins.[153]

The year after, a new and straightforward route to achieve the diazidation of 1,3-dicarbonyl compounds **II-32** to generate the geminal diazides **II-23** was provided using mild reaction conditions with iodine and sodium azide in aqueous DMSO at room temperature (scheme 96). In this way, a plethora of compounds, belonging to this class, with a variety of functional groups were synthesized.[154] This method was also applied to cyclic systems, such as oxindoles, obtaining diazidated derivatives for the first time.[155]



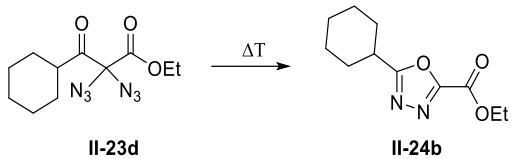
Scheme 96. Diazidation of 1,3-dicarbonyl compounds using mild conditions.

Nevertheless, not all geminal diazides could be converted into the bistriazole **II-36**. An example is showed in scheme 97, in which ethyl 2,2-diazido-3-oxobutanoate **II-23c**, under the same conditions of *CuAAC*, underwent an additional deacetylation achieving different classes of bistriazoles **II-36**. These unexpected bistriazoles were acidified to azidomethylene bistriazoles **II-37**, important intermediates that provided access to geminal tristriazole **II-38**.[156]



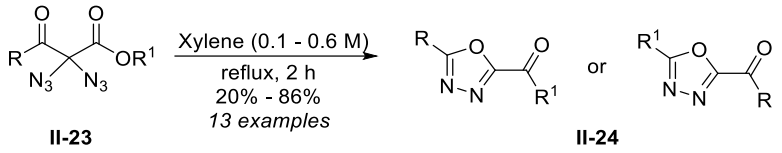
Scheme 97. Synthesis of geminal tristriazole.

In 2016, the reactivity of the geminal diazides under thermal conditions was investigated. *Rank et al.* published thermolysis of ethyl 2,2-diazido-3-oxobutanoate **II-23d** to 1,3,4-oxadiazole **II-24b** (scheme 98).[130]



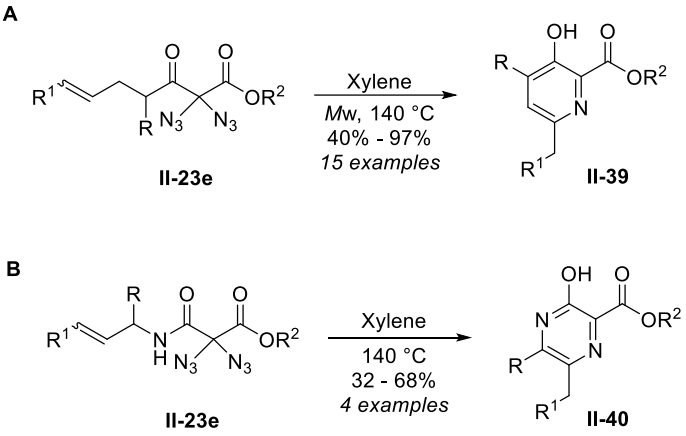
Scheme 98. Thermolysis of ethyl 2,2-diazido-3-oxobutanoate **II-23d**.

It was demonstrated that 2,2-diazido-β-keto esters **II-23** with aliphatic or aromatic substituent under diluted reaction conditions at ca. 140 °C, were converted into disubstituted 1,3,4-oxadiazoles **II-24** (scheme 99).[157]



Scheme 99. Conversion of 2,2-diazido-β-keto esters **II-23** to disubstituted 1,3,4-oxadiazoles **II-24**.

However, the formation of 3-hydroxypyridine **II-39**[158] (scheme 100, A) and 3-hydroxypyrazine **II-40**[159] (scheme 100, B), instead of the expected oxadiazole, was obtained in presence of olefinic side chains.

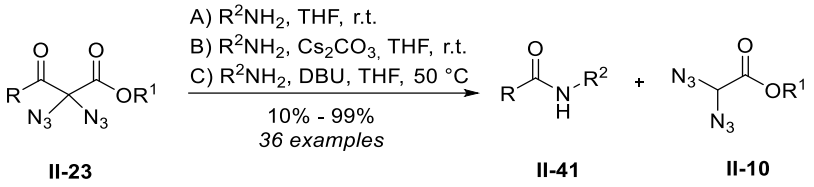


Scheme 100. Synthesis of 3-hydroxypiridine **II-39** and 3-hydroxypirazine **II-40** under thermolysis conditions.

These results illustrate that geminal diazides allow approach to a variety of highly substituted nitrogen-rich heterocycles, representing an alternative to other synthetic method such as transition-metal-catalyzed cyclization[160] or multicomponent reactions (often also transition metal catalyzed).[161]

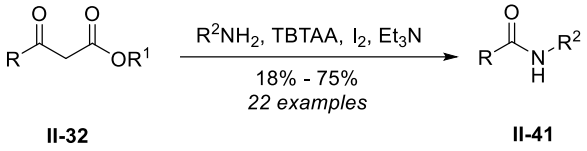
In 2017, the unknown reactivity of the α,α-diazido-β-ketoesters **II-23** towards nucleophile, in particular primary amines, was analyzed (scheme 101).[162]

The diazide **II-23** reacted with primary amines through a fragmentation to give 2,2-diazidoacetate **II-10**, transferring an acyl group to the amine and obtaining the amide derivative **II-41** as final product. This reaction required mild conditions such as a slight excess of amines or with base addition and was compatible with a large number of functional groups.



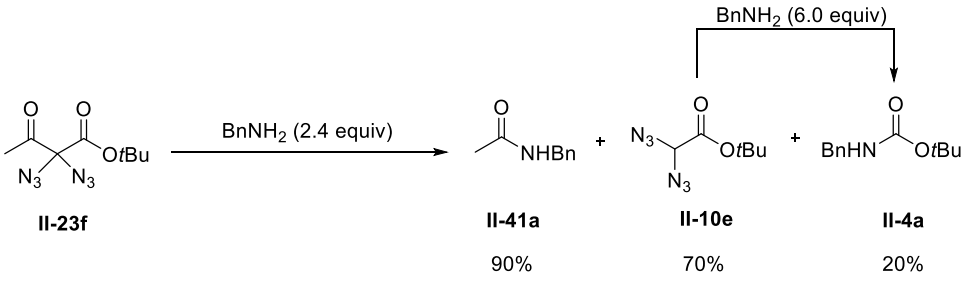
Scheme 101. Reactivity of α,α-diazido-β-ketoesters in presence of primary amines by using three different reaction conditions.

An alternative method consisting in a one-pot reaction was also developed, in order to not isolate the potentially explosive geminal diazide intermediate and directly obtain the final amide **II-41** from the β-ketoesters **II-32**. By using tetrabutylammonium azide, iodine and primary amines under basic conditions (scheme 102), the geminal diazide was generate *in situ*. [162]



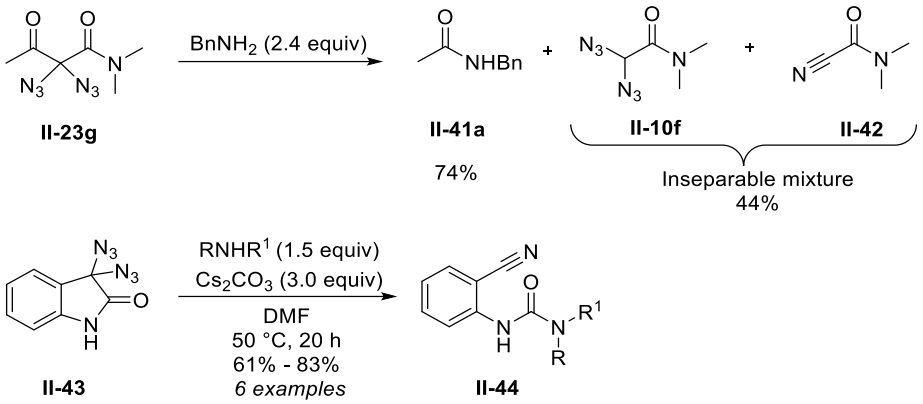
Scheme 102. Direct synthesis of final corresponding amide from β-ketoesters with the formation of geminal diazide *in situ*.

Regarding the side products after treatment of geminal azide **II-23** with primary amines, using the 2,2-diazido-β-keto esters **II-23f** as starting material and treating it with benzylamine, the 2,2-diazidoacetate **II-10e** was isolated in 70% yield and the carbamate **II-4a** in 20% yield (scheme 103). It was assumed that the diazidoacetate **II-10e**, in presence of a slight excess of amine, was slowly converted into the carbamate **II-4a**, because the *tert*-butyl-2,2-diazidoacetate **II-10e** reacted with a large excess of benzylamine to achieve the corresponding carbamate **II-4a** in 75% yield. [163]



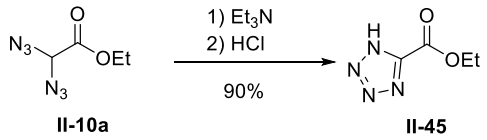
Scheme 103. Synthesis of carbamate **II-4a** as side product in presence of an excess of primary amine.

Based on these results, cyanides as intermediate step of this reaction were studied and detected in the reactions of 2,2-diazido-*N*,*N*-dimethyl-3-oxobutanamide **II-23g** and 3,3-diazidooxindoles **II-43** in presence of amines (scheme 104).[155,163]



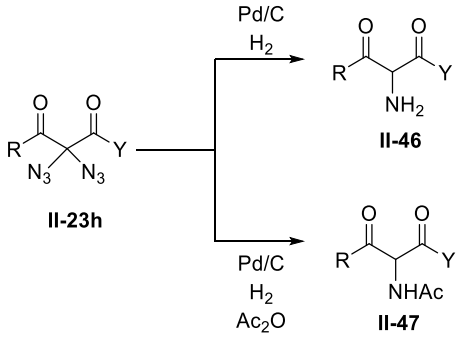
Scheme 104. Synthesis of cyanide intermediate by treating geminal diazide with amines.

Nevertheless, by treating the 2,2-diazidoacetate **II-10a** with non-nucleophilic bases, such as triethylamine, it was converted into the corresponding tetrazole **II-45** (scheme 105). [163]



Scheme 105. Tetrazole formation from **II-10a** in presence of non-nucleophilic bases.

In 2017, the reactivity of geminal azide under reduction conditions was studied. The diazide **II-23h** could be reduced, in presence of Pd/C under H_2 pressure, to amine **II-46** or to acetylated amine **II-47** after addition of acetic anhydride (scheme 106).[164]



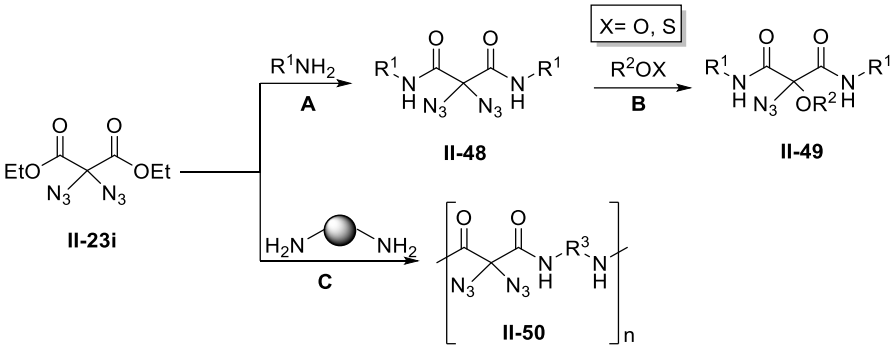
Scheme 106. Reduction of geminal azide.

Two years later, it was discovered that by treating diazidomalonates **II-23i** with primary amines, the diazidomalonamides **II-48** could be achieved (scheme 107, A). This new class of substance was turned out to be very interesting to perform new reactions and to obtain new different compounds.

Indeed, treating diazidemalonamide with lithiated or thiol alcohol, *N-O* acetals **II-49** could be built up after a nucleophilic substitution, in which the azide function acted as

leaving group (scheme 107, B).[165] The presence of another azide function in the structure can allow further functionalization and synthesis of highly functionalized derivatives.

In presence of diamines, geminal diazide **II-23i** underwent a polymerization reaction (scheme 107, C)[166] and generated polyamides with geminal diazide moiety **II-50** that could be used as high-energy materials.



Scheme 107. Synthesis of diazidomalonamides **II-48**, N-*O* acetals **II-49** and polyamides **II-50**.

1.4. Applications of azides

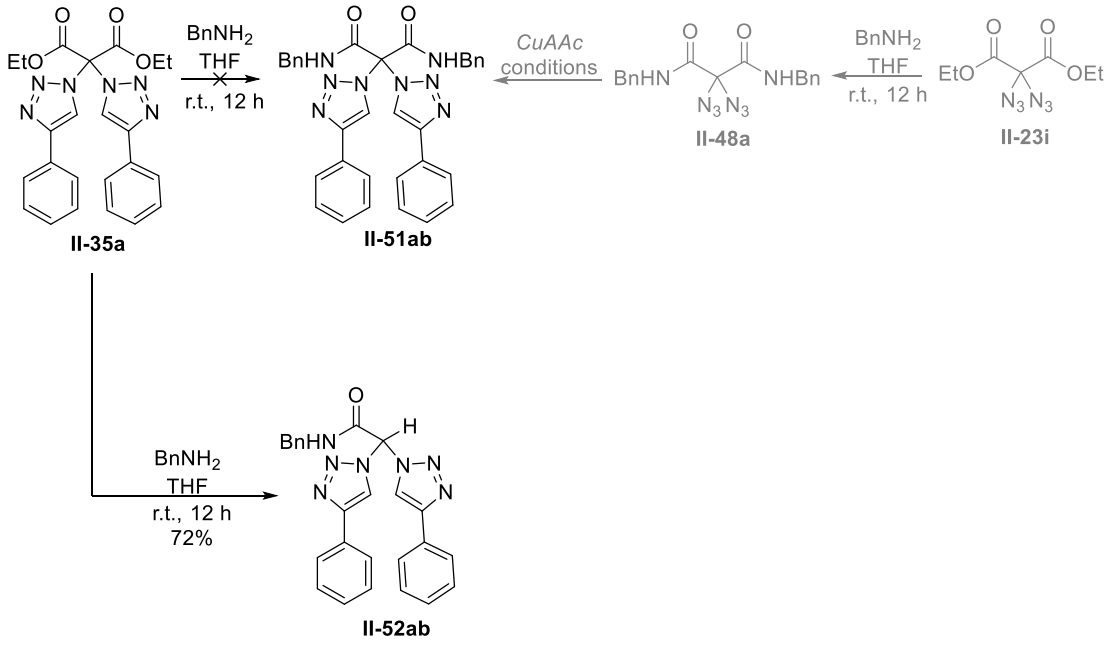
The incorporation of azides into organic molecules is of ever-growing interest, due to their great versatility in a broad range of applications like pharmaceutical,[167] medicinal,[168] chemical biology[169] and agricultural[170] areas.

2. Task

The work was based on the analysis of geminal diazides and mainly divided in two projects: 1) decarboxylation of bistriazole derivatives and 2) synthesis of *N*-substituted imines from diazidated malonamides.

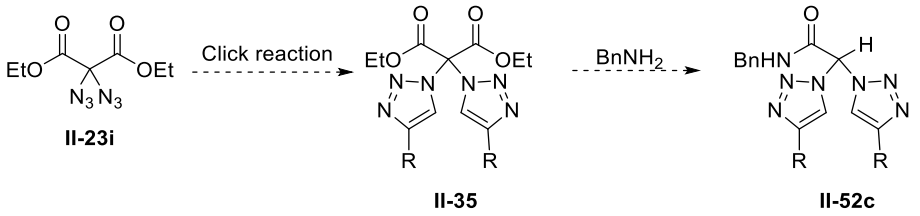
2.1. Decarboxylation of bistriazole derivatives

The goal of this project consisted of analyzing a decarboxylation reaction previously identified but not investigated by Dr. *Phillip Biallas*.[171]
Bistriazole **II-35a** was treated with a benzylamine to examinate a transamidation reaction for synthesizing the malonic acid-derived amide **II-51ab**. Nevertheless, this reaction led to the formation of the acetamide derivative **II-52ab** *via* a decarboxylation reaction. Consequently, the derivative **II-52ab** was studied and a scope, using different primary and secondary amines, was carried out (scheme 108).
The amide derivative **II-51ab** was previously synthesized using a further pathway which consisted first in the formation of the diazidomalonamide **II-48a** from geminal diazide **II-23i**. The intermediate **II-48a**[172] was converted to amide derivative **II-51ab** by applying standard *Click* chemistry (*CuAAC*).[173,174]



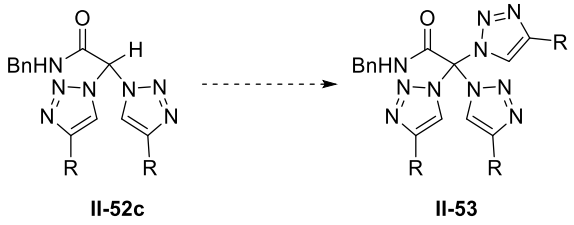
Scheme 108. Decarboxylation of bistriazole.

Previously, it was shown that bistriazole **II-35a** could be obtained from geminal diazide **II-23i** (scheme 95) by *CuAAC*. Therefore, different alkynes should also be tested to obtain different bistriazole derivatives **II-35**, then treated with benzylamine to analyze the flexibility of this decarboxylation reaction (scheme 109).



Scheme 109. Pathway for synthesizing bistriazole derivatives **II-35** and their acetamide derivatives **II-52c.**

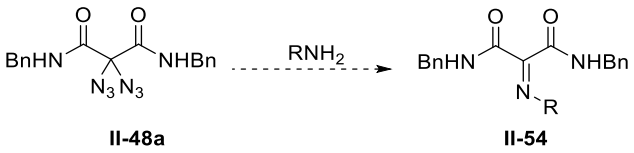
These acetamide derivatives proved to be extremely versatile, therefore the formation of triazole compound **II-53**, by employing acetamides **II-52c** as starting material, should be examined (scheme 110).



Scheme 110. Possible synthesis of triazoles derivatives**.**

2.2. Synthesis of *N*-substituted imines from diazidated malonamides

The aim of the second project was based on optimizing the reaction conditions, previously found by Dr. *Phillip Biallas* and analyzed by the PhD student *Fabia Mittendorf*, to synthesize substituted imines **II-54** (scheme 111) from diazidomalonamide **II-48a**. Subsequently, a scope with different primary amines was carried out.



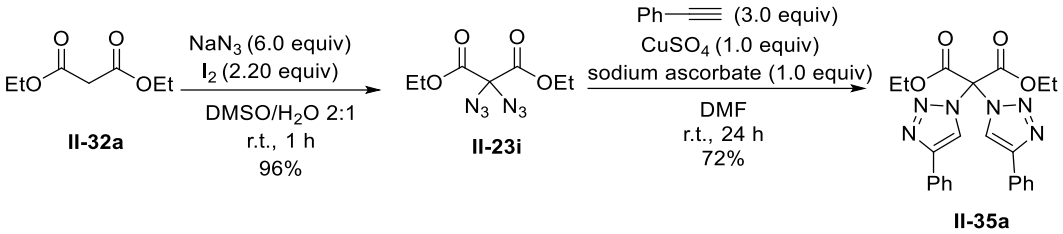
Scheme 111. Synthesis of *N*-substituted imines from diazidated malonamides.

3. Result and discussions

3.1. Decarboxylation of bistriazole derivatives

The synthesis of final acetammide **II-52ab** began with the preparation of starting geminal diazide **II-23i** from diethylmalonate **II-32a** by using NaN_3 and iodine in aqueous dimethylsulfoxide, as previously described (scheme 112).

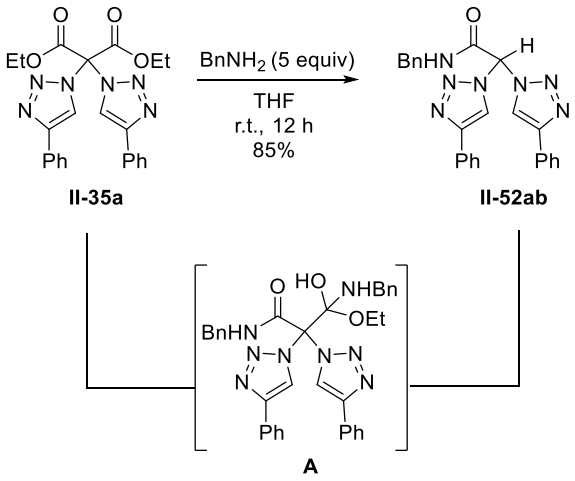
The azide functionality of **II-23i** was perfectly suited for additional linkages to alkynes under standard *Click* reaction conditions with phenylacetylene as alkyne, achieving intermediate **II-35a** in 72% yield.[175]



Scheme 112. Synthesis of bistriazole derivative **II-35a** from diethylmalonate **II-32a**.

Bistriazole **II-35a** proved to be sensitive to an excess of the benzylamine, undergoing a concomitant decarboxylation reaction at room temperature and resulting in the formation of acetamide compound **II-52ab** (scheme 113).

Presumably, upon transamidation with one ester unit of **II-35a**, steric repulsion with the bistrazole moiety may favor a carbon-carbon cleavage (*via* **A**), in analogy to a previous result with diazidated acyl acetates detected by *Kirsch et al*.[163]



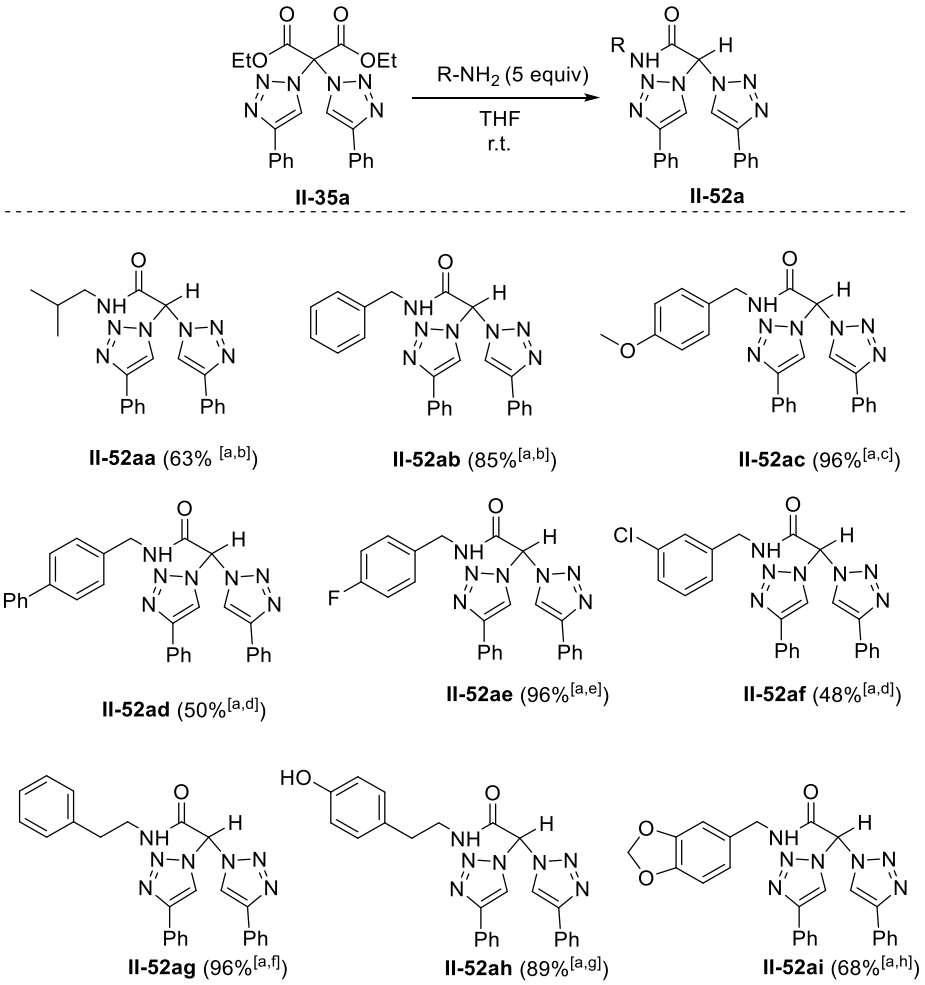
Scheme 113. Synthesis of acetamide derivative **II-52ab**.

This decarboxylative reaction was a rather slow reaction, because by treating compound **II-35a** with only two equivalents of benzylamine in tetrahydrofuran at room temperature, some product formation was observed overnight, however, complete conversion was not achieved under these conditions. A full conversion of **II-35a** into the product **II-52ab** was possible employing five equivalents of benzylamine, after three hours at room temperature.

A plethora of primary amines were successfully employed to convert the bistriazole **II-35a** into acetamide **II-52a**, with moderate to good yields reaching from 48% to 96%, as summarized in scheme 114.

The reaction time to achieve complete conversion of the starting material **II-35a** differed significantly, depending on the type of nucleophilic amine employed. First, the primary amine isobutylamine was tested obtaining **II-52aa** in 63% yield. Benzylamine variants bearing electron-donating groups (*i.e.*, methoxy) or phenyl furnished **II-52ac** and **II-52ad** in 96% and 50% yield, respectively, as did 4-fluorobenzylamine **II-52ae** and 3-chlorobenzylamine **II-52af**, although the formation of **II-52af** was surprisingly slow.

Furthermore, 2-phenylethylamine and tyramine were employed to produce the corresponding acetamides **II-52ag** and **II-52ah** in 96% and 89%, respectively. Acetamide **II-52ai** containing piperonylamine was also successfully obtained in 68% yield.

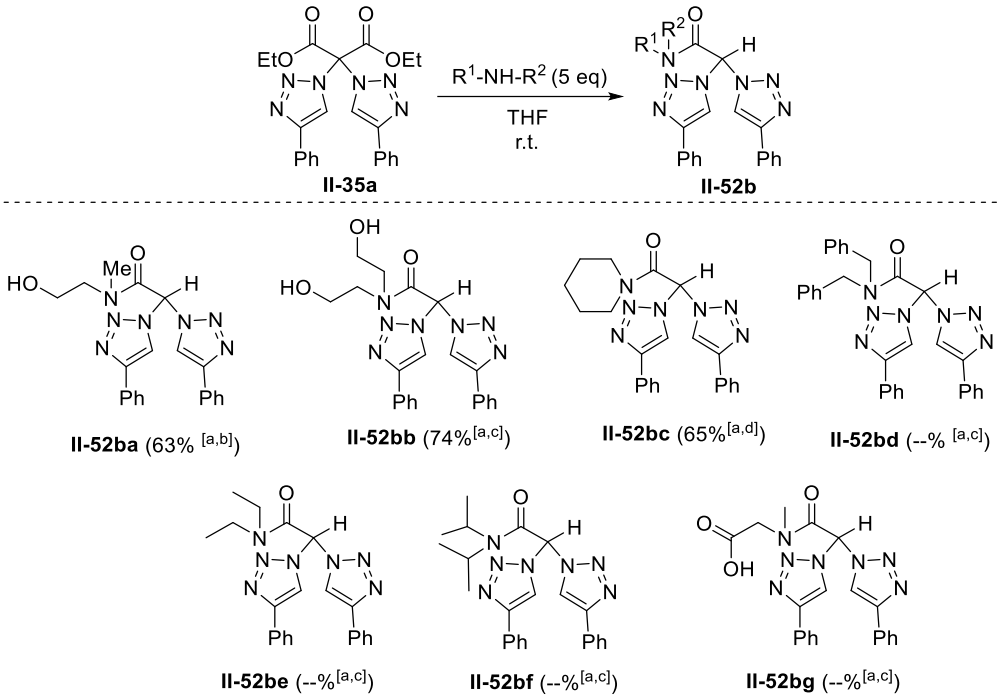


Scheme 114. Scope of the reaction leading to acetamide derivatives **II-52a** using primary amines;
[a] Isolated yield after column chromatography. [b] 5 h. [c] 3 h. [d] 19 h. [e] 7 h. [f] 1.5 h. [g] 75 h, 0.07 M. [h] 2.5 h.

After employing primary amine as nucleophiles, secondary amines were tested (scheme 115).

While most of the secondary amines or natural aminoacid derivatives tested proved to be poor substrates with slow or even no conversion (*i.e.*, dibenzylamine (**II-52bd**), diethylamine (**II-52be**), diisopropylamine (**II-52bf**) and sarcosine (**II-52bg**)), the sterically less demanding piperidine gave **II-52bc** in 65% yield, upon increasing the quantity to eight equivalents.

Surprisingly, 2-(methylamino)ethanol and diethanolamine were effective substrates providing **II-52ba** and **II-52bb** in good yields of 63% and 74%, with a considerable rate of conversion.



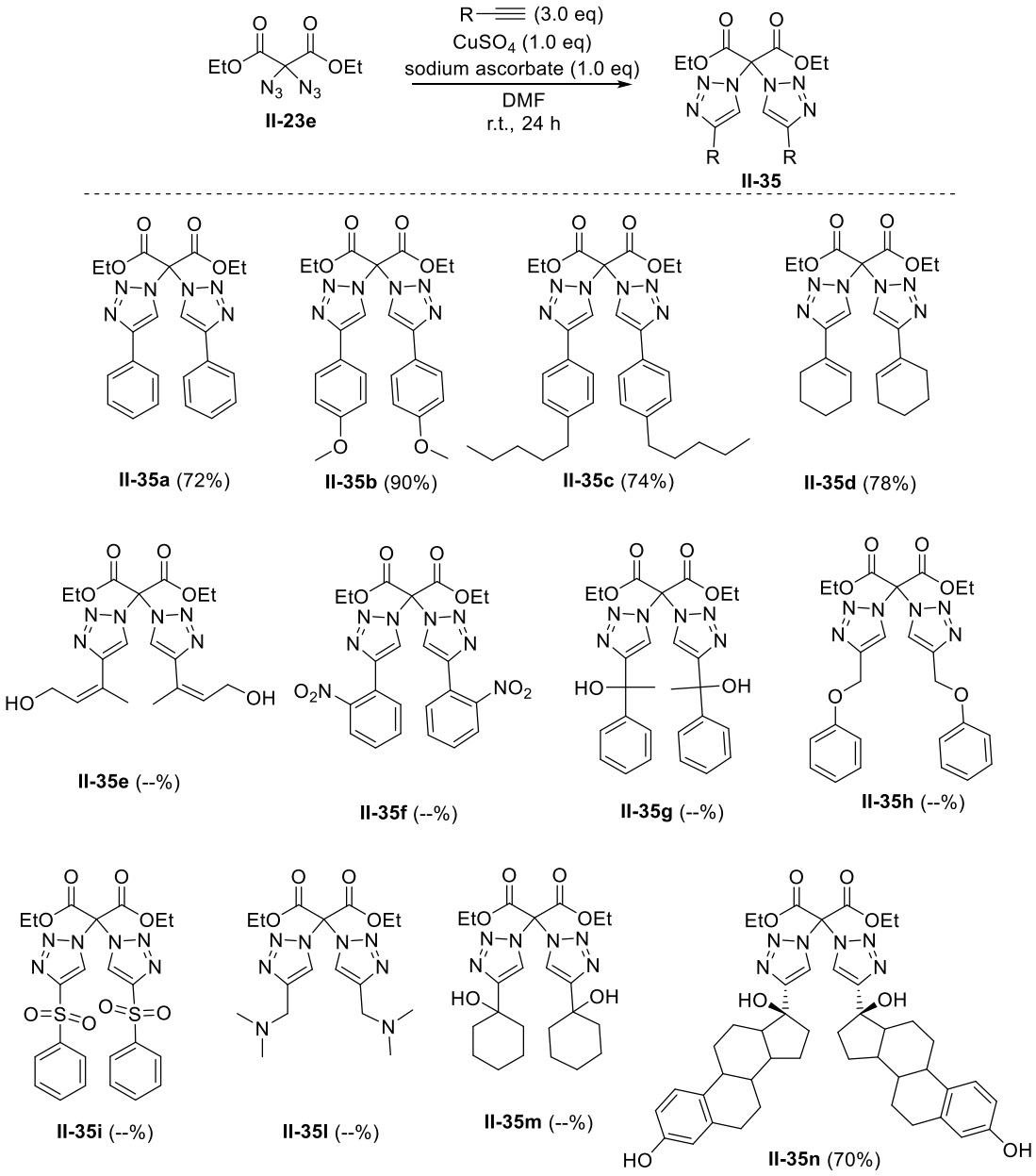
Scheme 115. Scope of the reaction leading to acetamide derivatives **II-52b** using secondary amines; **[a]Isolated yield after column chromatography. [b] 4 h. [c] 5 h. [d] R^1-NH-R^2 (8 equiv), 48 h.**

After testing different primary and secondary amines, the flexibility of the decarboxylation method was analyzed focusing on the triazole core. Therefore, various bistriazole diesters **II-35** were synthesized from diazide **II-23i**, using *Click* chemistry, with copper(II) sulfate pentahydrate (1 equiv.), sodium ascorbate (1 equiv.) and terminal alkynes (3 equiv.) in dimethylformamide at room temperature. Bistriazoles **II-35** were synthesized with moderate to good yields in a range between 70% and 90%, as summarized in scheme 116.

As described previously, the derivative **II-35a** was obtained in good yield by using phenylacetylene as terminal alkyne.

This has also been confirmed by phenylacetylene derivatives which have a methoxyl or pentyl group in *p*-position, furnishing **II-35b** and **II-35c** in 74% and 76% yield, respectively. However, nitrogroup in *o*-position (**II-35f**) and other aromatic alkynes as 2-phenyl-3-butyn-2-ol (**II-35g**) and phenylpropargyl ether (**II-35h**) were not compatible. With the use of tosylacetilene (**II-35i**), the formation of the desired product was observed, but it was not possible to isolate purely because of the increased side product's formation.

The intermediate **II-35d** was successfully achieved in 78% yield by using not an alkyne with an aromatic function but with a cyclic alkene. Non-aromatic alkynes such as 1-dimethylamino-2-propyne (**II-35l**) and 1-ethynilcyclohexanol (**II-35m**) have been shown to not be compatible but in case of 1-pentol (**II-35e**), an impure product was synthesized, like tosylacetilene. To great surprise, the treatment of geminal diazide **II-30b** with ethinylestradiol led to the formation of **II-35n** intermediate in 70% yield.

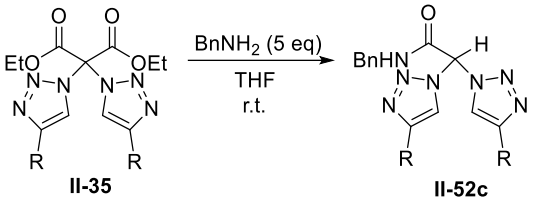


Scheme 116. Synthesis of bistriazoles **II-35**

The *CuAAC* reactions of diazidates **II-23i** were also successful using other two different conditions: one involved geminal diazide **II-23i** (1.0 equiv.), phenylacetylene (2.20 equiv.), tris(benzyltriazolylmethyl)amine (TBTA, 3 mol%), copper sulfate pentahydrate (20 mol%), sodium ascorbate (0.42 equiv.) in *tert*-butanol and water at room temperature; furnishing **II-35a** in 80% yield; the second one, employed geminal diazide **II-23i** (1 equiv.), phenylacetylene (3 equiv.), CuI (10 mol%), DIPEA (0.10 equiv.), in acetonitrile at room temperature, giving **II-35a** in 82% yield.

The bistriazoles **II-35b**, **II-35c** and **II-35d** were then treated with benzylamine to successfully obtain the final acetamides **II-52ca**, **II-52cb** and **II-52cc** in 82%, 78% and 55% yields. Unfortunately, the intermediate **II-35n** did not give any desired result (table 28).

Table 28. Synthesis of acetamides **II-52c** from different bistriazole intermediates.



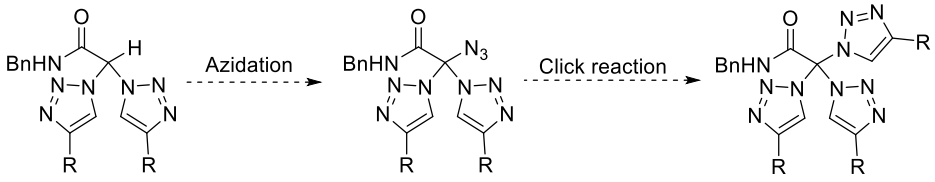
II-35 **II-52c**

Entry	Starting bistriazole	Final product	t (h)	Product[a]
1	**II-35b**	**II-52ca**	7	82%
2	**II-35c**	**II-52cb**	20	78%
3	**II-35d**	**II-52cc**	20	55%

[a]Isolated yield after column chromatography.

Once the acetamide derivatives **II-52** were synthesized, the possibility of converting them into tristriazole derivatives **II-53** was analysed (scheme 117), by employing two different approaches.

A first approach was based on the formation of the azide derivative **II-55** that should be, then, converted into tristriazole **II-53** through *Click* conditions.

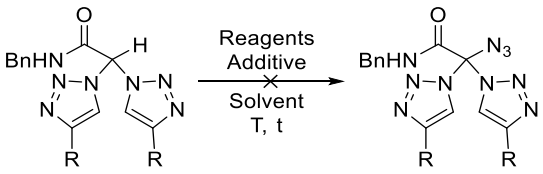


II-52c **II-55** **II-53**

Scheme 117. Pathway for the synthesis of tristriazoles **II-53**.

Unfortunately, the conversion of acetamide **II-52c** to azide derivative **II-55** did not show any interesting and expected result (table 29).

Table 29. Reaction conditions to synthesize azide derivative **II-55**.



II-52c **II-55**

Entry	Reagents (equiv)	Additive	Solvent	T (°C)	t (h)	Product[a]
1	I_2 (2.20) NaN_3 (6.0)	/	DMSO/H_2O	r.t. → 50	24 → 31	- [b, c]
2	I_2 (2.20) NaN_3 (6.0)	$NaHCO_3$ (3.0)	DMSO/H_2O	r.t. → 50	24 → 29	- [c]

Entry	Reagents (equiv)	Additive	Solvent	T (°C)	t (h)	Product[a]
3	NaI (0.20 → 0.70) NaN_3 (10.0) IBX-SO_3K (4.0)	/	DMSO/H_2O	r.t. → 60	18 → 48	- [b, c]
4	NaI (0.20) NaN_3 (10.0) IBX-SO_3K (4.0)	$NaHCO_3$ (3.0)	DMSO/H_2O	r.t.	18	- [b, c]

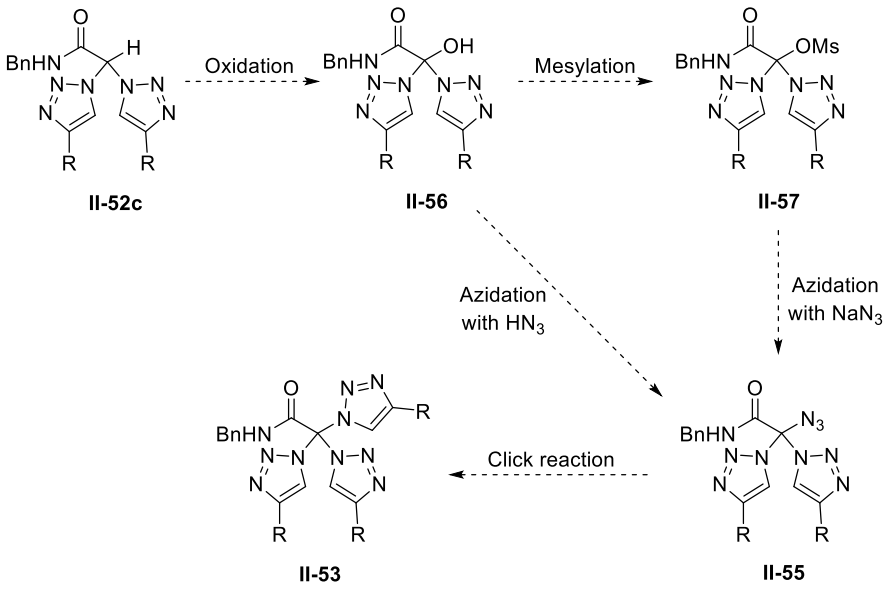
[a] Isolated yield after column chromatography. [b] No azide peak detected by IR [c] Unknown product.

By applying the azidation conditions reported above, full conversion of each reaction of the starting material **II-52c** was detected by TLC.

By employing iodine and NaN_3 (entry 1) or NaI, NaN_3 and IBX-SO_3K (entry 3), also in presence of sodium bicarbonate (entry 4), the final compounds did not show any azide characteristic peak in the infrared spectroscopy (IR).

An azide peak was detected by IR but an analysis of NMR highlighted the formation of an unknown product (entry 2).

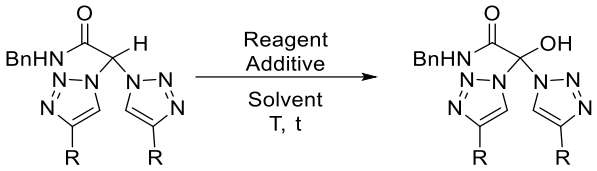
A second approach was based on the initial oxidation of acetamide **II-52c** to **II-56** and subsequent formation of the mesylated derivative **II-57**. The latter derivative should be converted into the azide intermediate **II-55** using NaN_3. The azide **II-55** should also be obtained from compound **II-56** *via Mitsunobu* reaction with hydrazoic acid and 1,1-(azodicarbonyl)dipiperidine (ADDP) (scheme 118).[176]



Scheme 118. Alternative approaches for the synthesis of derivative **II-55.**

Unfortunately, no oxidation reactions gave the desired results, as shown in table 30.

Table 30. Reaction conditions to oxidize acetamide **II-52c**.



II-52c **II-56**

Entry	Reagent (equiv)	Additive (equiv)	Solvent	T (°C)	t (h)	Product[a]
1	NBS (0.20)	/	DMSO	100	53	- [e]
2	NBS (0.20)	$NaHCO_3$ (2.0)	DMSO	100	80	- [c]
3	CS_2CO_3 (0.20)	$P(OEt)_3$ (2)	DMSO	r.t.	168	- [b, d]
4	$CuBr_2$ (0.20)	$P(OEt)_3$ (2.0) CS_2CO_3 (2.0)	DMSO	r.t.	168	- [b, e]
5	CS_2CO_3 (0.20)	$P(OEt)_3$ (2.0) TEMPO (2.0)	DMSO	r.t.	80	- [b, d]

[a] Isolated yield after column chromatography. [b] 1 atm O_2 [c] No conversion. [d] Unknown compound. [e] Decomposition.

By using the oxidizing agent *N*-Bromosuccinimide (NBS) in dimethylsulfoxide at high temperature,[177] decomposition was detected (entry 1) but no conversion was obtained in the presence of the base $NaHCO_3$ (entry 2). If the starting acetamide **II-52c** was oxidized with Cs_2CO_3 and $P(OEt)_3$, an unknown compound was achieved (entry 3) also in presence of TEMPO (entry 5), however, decomposition was observed by employing $CuBr_2$ as catalyst (entry 4).[178]

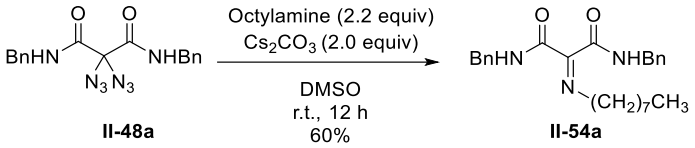
3.2. Synthesis of *N*-substituted imines from diazidated malonamides

The second task of this project is based on the analysis of a further reactivity of diazidated malonic acid amides **II-48a** in the presence of primary amines.

By treating the derivative **II-48a** with nucleophilic amines, it was expected to observe a reaction similar to the one previously developed with nucleophilic alcohols under basic conditions, by which one azide moiety was substituted with a suitable nucleophile.[165]

In contrast, in presence of an excess of primary amines, the diazide **II-48a** was converted into the *N*-alkyl-substituted imines **II-54**, probably formed through a sequence of substitution followed by elimination of HN_3.

In collaboration with other colleagues, the reaction conditions for synthesizing derivative **II-54a** have been optimized. At first, the initial product **II-48a** was treated with 2.2 equivalents of octylamine and two equivalents of Cs_2CO_3 as additive in dimethylsulfoxide, obtaining the imine derivative **II-54a** in 60% yield (scheme 119).

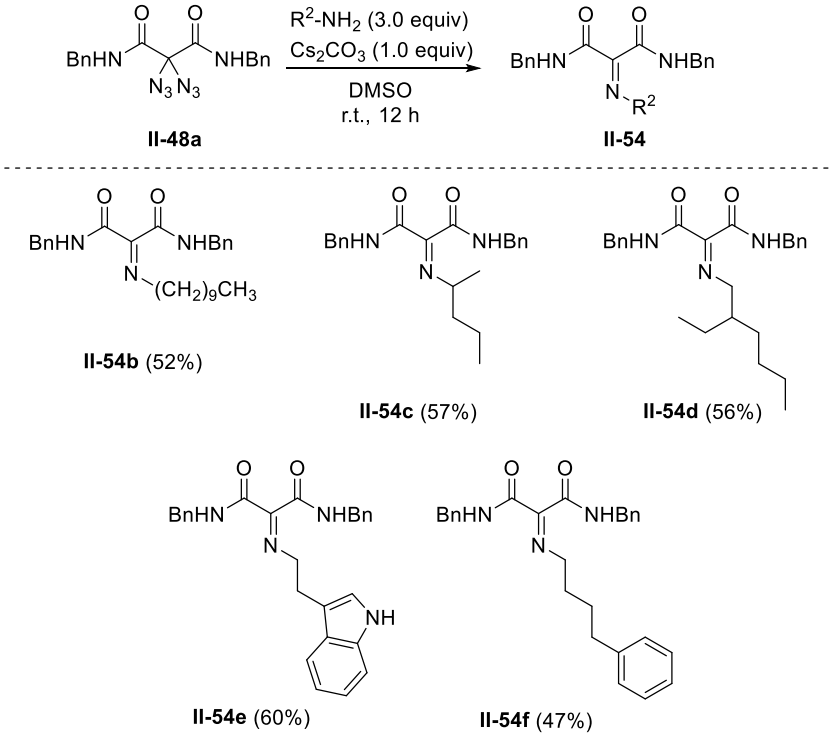


Scheme 119. Synthesis of *N*-alkyl-substituted imine **II-54a**.

During the optimization, it was noticed that the highest yield was obtained by using three equivalents of primary amine and one equivalent of the additive, synthesizing the final product **II-54a** in 65% yield.

Then, the scope of this imine formation by testing various primary amines was studied, as summarized in scheme 120.

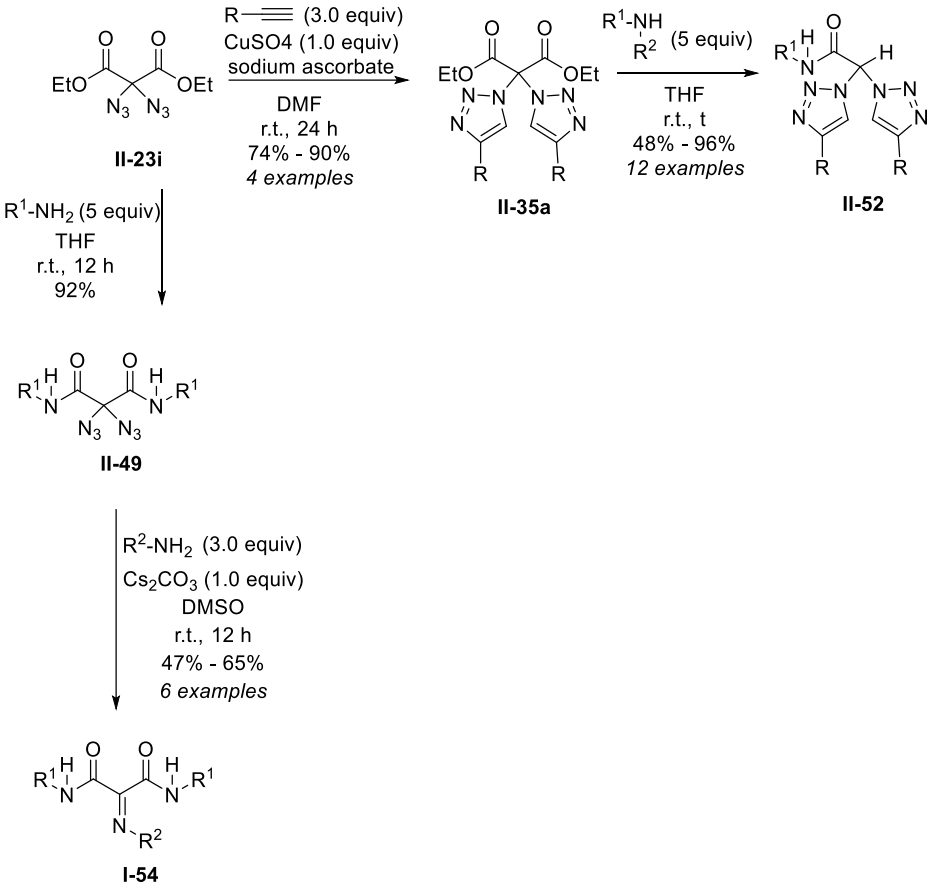
With decylamine, diazide **II-48a** was converted to imine **II-54b** in lower but still acceptable yield of 52%. Other simple amines, such as 2-aminopentane and 2-ethylhexylamine contributed well to the formation of **II-54c** and **II-54d** in 57% and 56% yields, respectively. Amines such as tryptamine and 4-phenylbutylamine were also reactive, furnishing **II-54e** and **II-54f** in 60% and 47% yields.



Scheme 120. Imine formation with diazide **II-48a** and primary amines**.**

4. Summary

To summarized, different reactions that further expand the reactivity of geminal diazides **II-23i** were examined (scheme 121).



Scheme 121. Synthetic routes from diazidated diethyl malonate **II-23i** to different final products**.**

After conversion of starting diazide **II-23i** into bistriazoles **II-35a** through *Click* chemistry, acetamides with bistriazole unit **II-52** were easily synthesized with amine nucleophiles. This decarboxylation reaction appeared to have a broad scope in combination with useful yield.

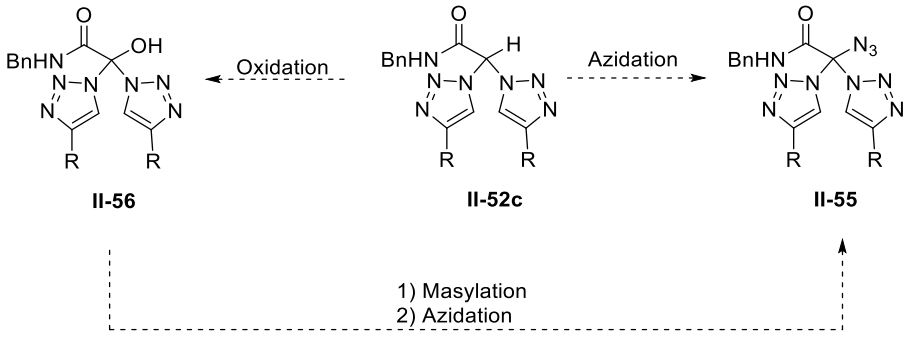
After transamidation of geminal diazide **II-23i** into diazidated malonic acid diamide **II-48**, this intermediate, if treated with an excess of amine in basic conditions, led to the *N*-alkyl substituted imine derivatives **II-54**.

5. Outlook

The formation of the tristriazole compounds could be interesting, to further highlight the versatility of these compounds.

This could be achieved by continuing the same pathway already started, with initial oxidation of amide **II-52c** followed by mesylation and azidation to achieve azide **II-55**. A direct azidation proved to be more complicated (scheme 122).

Further oxidation reactions to synthesize a tertiary alcohol should be tested.



II-56 **II-52c** **II-55**

Scheme 122. General pathway to synthesize the azide intermediate **II-55** for obtaining final tristriazoles**.**

❖ Synthesis of natural Diarylheptanoids

1. Introduction

1.1. General classification and structure of Diarylheptanoids

Diarylheptanoids belong to a small class of secondary plant metabolites and their structure consists of two aromatic rings connected by a seven membered aliphatic chain. They can be divided in cyclic and linear diarylheptanoids that can be subdivided into five different types: type I and type II differentiate between phenolic and non-phenolic linear diarylheptanoids, type III and type IV are distinguished by *meta,meta*-bridged biphenylic and *meta,para*-bridged diphenyl ether moiety and type V presents an additional tetrahydropyran ring (figure 16).[179,180,181,182]

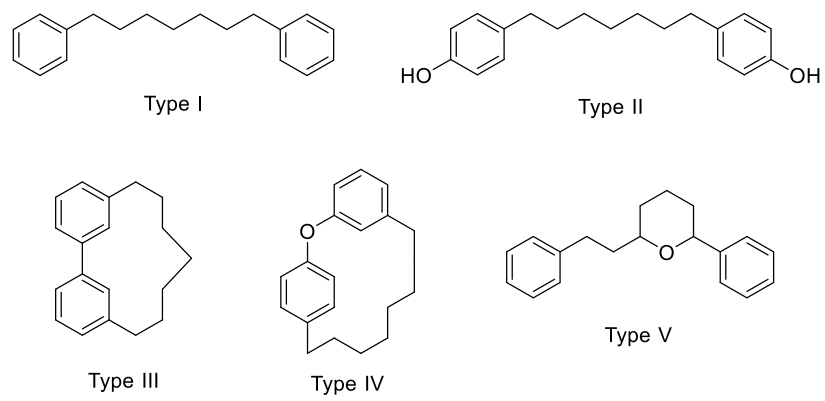


Figure 16. Diarylheptanoid classes type I-V.

Diarylheptanoids can be isolated from the extraction of the plant families of *Zingiberaceae*, *Betulaceae* and *Aceraceae*, in particular in the rhizomes of herbs, in the (inner) stem and root bark of parent trees and shrubs[183] but also in leaves and twings.[184]

Regarding the structural motifs, linear diarylheptanoids generally show hydroxyl and/or methoxy group on one or both aromatic rings, principally in meta and para, rarely in orto position (*i.e.*, *Curcuma, Alpinia*) (figure 17)[185] and different substituents on the aliphatic thethered chain (such as ketone or hydroxyl groups).

Diarylheptanoids without hydroxyl groups on the aromatic ring can rarely be found.[180]

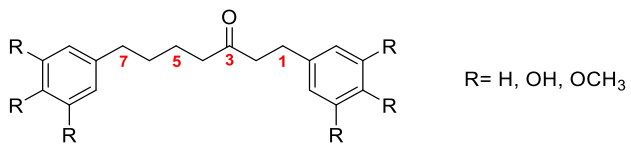
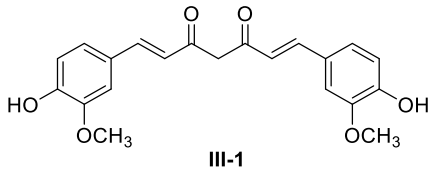


Figure 17. General structure of linear diarylheptanoids containing hydroxyl or methoxy substituent on aromatic group.

1.2. Biological activity

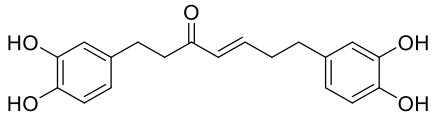
The diarylheptanoids are known for their powerful and interesting biological activity and they find a wide use in traditional medicines of Asia, South America and Africa.[181]
They are applied in traditional Chinese medicine for the treatment of biliary, skin and stomach disease[186] due to their antinflammatory,[184] hepatoprotective[187,188] and anticarcinogenic activity.[189]
One of the most diarylheptanoids used in the pharmaceutical field is Curcumin **III-1** (figure 18).



III-1

Figure 18. Structure of Curcumin **III-1**.

This is because several studies have demonstrated its interesting biological activity against the different cancer[190] like human colorectal,[191] melanoma, renal, breast[192] and fibrosarcoma cancer cell lines.
Diarylheptanoid **III-1** showed also an anti-inflammatory activity,[193] as Hirsutenone **III-2** (figure 19),[194] for arthritis, sepsis, asthma and gastritis treatment.[184] In addition, they manifested an important antioxidants activity.[195,196]



III-2

Figure 19. Structure of Hirsutenone **III-2**.

As a result of in-depth studies, diarylheptanoids, in particular Curcumin **III-1**, exhibited a significant antimicrobial activity, against *Candida* strains,[197] antiviral activity against *Coxsackievirus*,[198] antimalarial,[199] antiparasitic[200] and nematocidal[201] effects.
Hirsutenone **III-2** manifest activity against *Coronavirus* inducing severe acute respiratory syndrome (SARS).[202]
Cyclic diarylheptanoids, as Engelhardiols A (**III-3A**) and B (**III-3B**), displayed antitubercular properties (figure 20).[203]

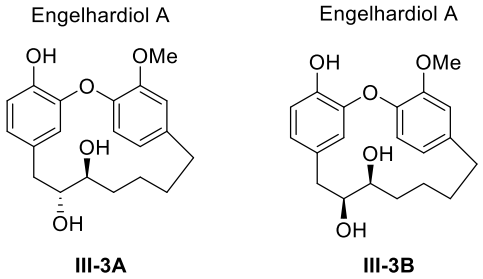


Figure 20. Structure of Engelhardiols A and B.

Curcumin **III-1** has also an important role also for preventing liver damage when acting against different inducers of liver injures (heavy metals,[204] chronic alcohol intake[205] and carbon tetrachloride[206]).
A further activity identified in Curcumin **III-1** has been to prevent and treat Alzheimer's syndrome, a widespread neurodegenerative disease. [207,208,209,210]

1.3. *Anti*-unsymmetrical Hannokinol and its derivatives

The following are examples of linear unsymmetrical diarylheptanoids, with their synthesis and biological activity information, which are of considerable importance in achieving the final goal of this project.

1.3.1. (*+*)-Hannokinol

(+)-Hannokinol **III-4** (figure 21) is a diarylheptanoid that was first isolated in 1996 by *Wu et al*.[211] It was also isolated from the seeds of *Alpinia blepharocalyx* in 2001 by *Kadota and co-workers* and its structure was confirmed on the basis of its spectroscopic data.[211]

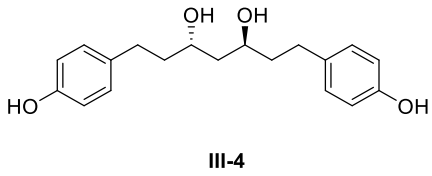


Figure 21. Structure of (*+*)-Hannokinol.

The biological and pharmaceutical activity of this natural product has not been deeply studied yet.
In 2011, *Seo et el.* highlight that Hannokinol has significant antiproliferative activity against murin colon *26-L5* carcinoma and human *HT-1086* fibrosarcoma.[212]

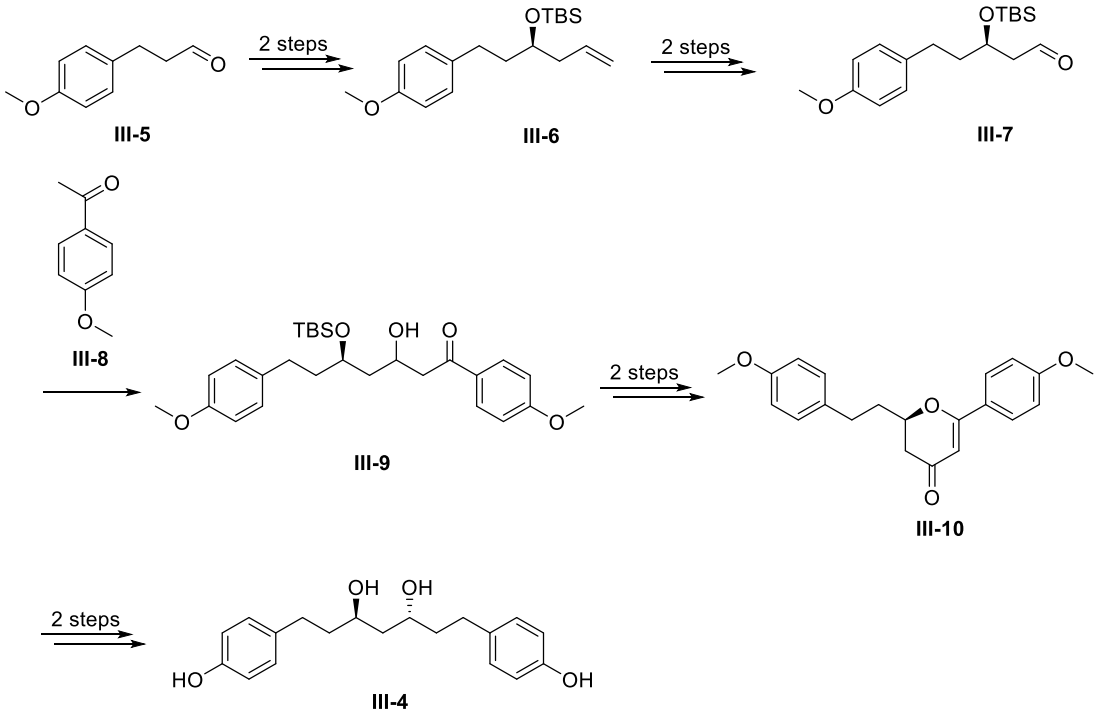
1.3.1.1. Total synthesis of (*+*)-Hannokinol

In 2015, two research groups studied and published two different pathways for the synthesis of Hannokinol **III-4**.

Yadav et al. synthesized (*+*)-Hannokinol **III-4** by using a substrate selective hydrogenation, ring cleavage of tetrahydropyran ring and *Keck-Maruoka* allylation as the key synthetic steps (scheme 123).[213]

The synthesis started from 3-(4-methoxyphenyl)propionaldehyde **III-5** that was converted to the homo allylic alcohol by *Keck-Muroka* allylation, then protected as its TBS ether **III-6**. *Upjihon* dihydroxylation, to obtain diol compound, and oxidative cleavage of diol led to the desired aldehyde **III-7**. The aldol reaction between aldehyde **III-7** and methoxyacetophenone **III-8** gave the β-hydroxy ketone **III-9**. The secondary alcohol was treated with DMP oxidation to get β-diketone that was easily converted into the key intermediate dihydropyranone **III-10**.

Under normal hydrogenation condition, the pyran ring was opened, the keto intermediate reduced and the following methoxy deprotection afforded (*+*)-Hannokinol **III-4**.



Scheme 123. Synthetic route for (*+*)-Hannokinol (**III-4**) *by Yadav et al***.**

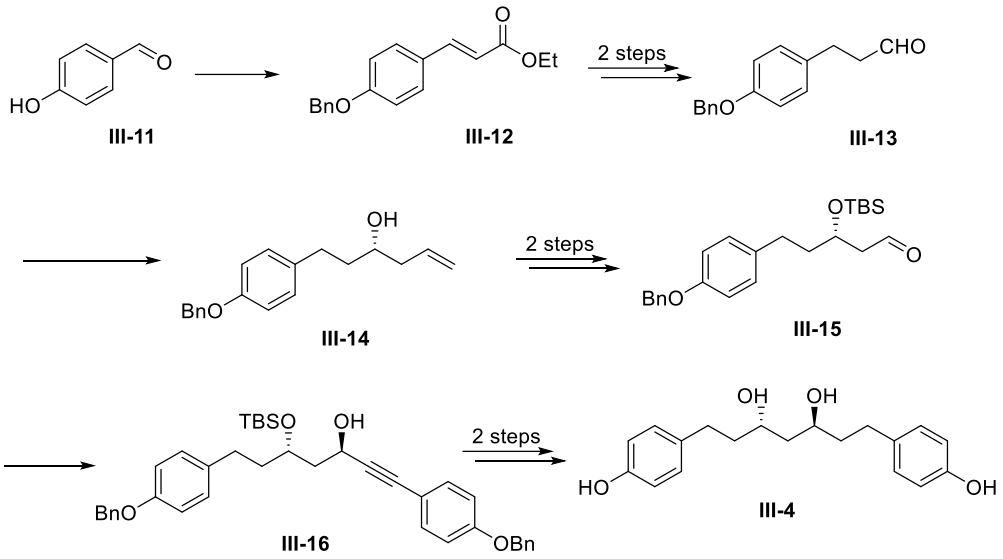
Babu at al.[214] envisaged the target molecule **III-4** from chiral homoallyl alcohol derivative which was prepared *via Brown*'s alkylation reaction of an aldehyde.

The synthesis of (*+*)-Hannokinol **III-4** began with the commercially available starting material 4-hydroxybenzaldehyde (**III-11**) (scheme 124). Aldehyde **III-11** was converted to

the unsaturated ester **III-12**, followed by reduction of double bond, afforded the saturated ester that was reduced one more time to furnish the respective aldehyde **III-13**. It was then converted to the chiral allylic alcohol **III-14** by *Brown*'s asymmetric allylation.

The homo allylic secondary alcohol (**III-14**) was protected as TBS ether and the terminal alkene was converted to the corresponding aldehyde **III-15** *via* catalyzed dihydroxylation and $NaIO_4$-mediated cleavage.

Aldehyde **III-15** reacted with 1-(benzyloxy)-4-ethynylbenzane affording alkyne **III-16** and subsequent debenzylation and TBS deprotection led to (*+*)-Hannokinol **III-4**.



Scheme 124. Synthetic route of (*+*)-Hannokinol by *Babu et al.*

1.3.2. Octahydrocurcumin

Octahydrocurcumin **III-17** (figure 22) is a metabolite (hydrogenated derivative) of Curcumin **III-4**, isolated from the rhizomes of *Curcuma Xanthorrhiza* (*Zingiberaceae*).[215]

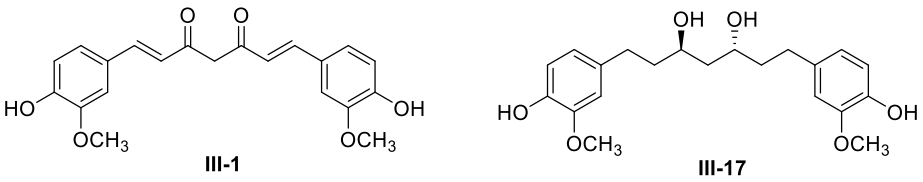


Figure 22. Structure of Curcumin **III-1** and Octahydrocurcumin **III-17**.

Several studies have shown that this diarylheptanoid has an important biological and pharmacological activities, whereby it is a natural product with very high pharmaceutical interest.

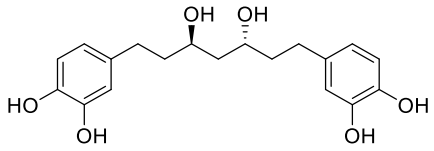
First of all, Octahydrocurcumin has been shown to have a better anti-cancer activity than curcumin (particularly hepatocellular carcinoma),[216] good anti-inflammatory[217,218] and antioxidant properties.[219]

It shows activity against the bacteria *B. subtilis*, *K. pneumoniae*, *E. coli*, *E. aerogenes*, *P. aeruginosa*, and *S. aureus*, as well as *C. albican*s and the plant pathogenic fungus *A. niger*, *in vitro*.[220]

Currently, there is no synthetic approach for Octahydrocurcumin. It is obtained by hydrogenation and reduction of Curcumin **III-1**, either chemically or by endophytic fungi.[221]

1.3.3. 4-[(3*R*,5*R*)-7-(3,4-dihydroxyphenyl)-3,5-dihydroxyheptyl]benzene-1,2-diol

This linear diarylheptanoid **III-18** (figure 23) is not deeply studied. It was isolated from rhizomes of *Tacca chantrieri* and exhibited interesting cytotoxic activity against leukaemia cells, human oral squamous carcinoma cells and normal human gingival fibroblasts.[222]

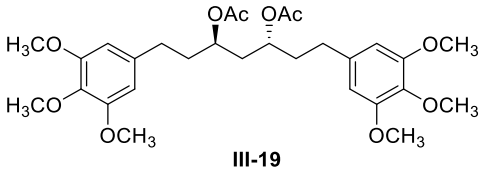


III-18

Figure 23. Structure of 4-[(3*R*,5*R*)-7-(3,4-dihydroxyphenyl)-3,5-dihydroxyheptyl]benzene-1,2-diol **III-18**.

1.3.4. (3*S*,5*S*)-3,5-diacetoxy-1,7-bis(3,4,5-trimethoxyphenyl)heptane

Regarding this diaryleptanoid, no-detailed research has been carried out yet. This product **III-19** (figure 24) was isolated from the rhizomes of *Zingiber mekongense,* belongs to the *Zingiberaceae* family and exhibited anti-*HIV*-1 activity.[223]



III-19

Figure 24. Structure of (3*S*,5*S*)-3,5-diacetoxy-1,7-bis(3,4,5-trimethoxyphenyl)heptane **III-19**.

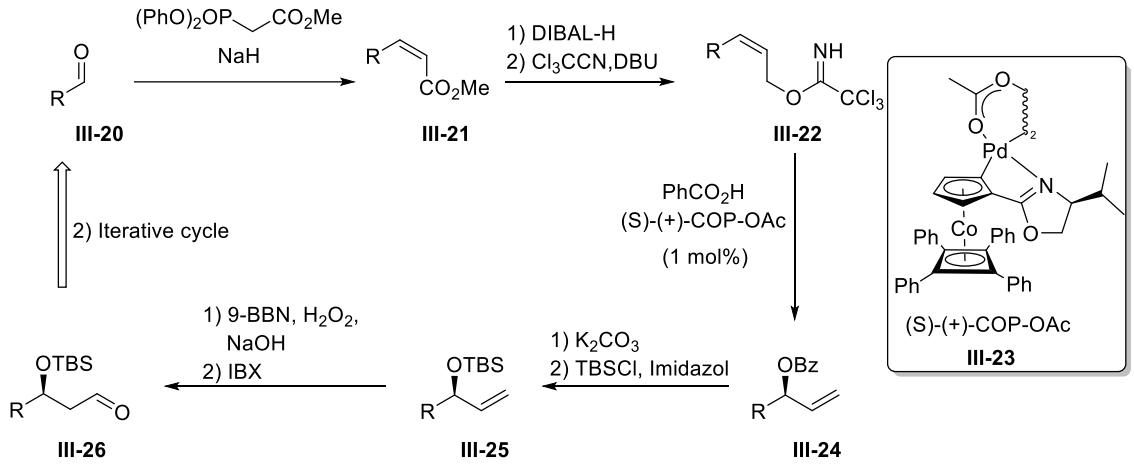
1.4. Stereoselective synthesis of asymmetric 1,3-diol moiety by *Kirsch et al.*

Kirsch group showed considerable interest in a strategic synthesis of polyketides.

The most widely used method for the synthesis of 1,3-diols involves an allyl addition sequence by using a stoichiometric amount of chiral boron and titanium reagents.[224,225]

In 2015, *Kirsch et al.* discovered a new method based on an eight-step iterative cycle to stereoselectively build up a 1,3-diol moiety (scheme 125).

The cycle started with aldehyde **III-20** that was converted to ester **III-21** *via Horner-Wadsworth-Emmons* reaction, which was then treated with DIBAL-H and trichloroacetonitrile to give trichloroacetimidate **III-22**. It was then reacted in an asymmetric *Overmann* rearrangement with benzoic acid and (*S*)-(+)-COP-OAc catalyst (**III-23**) to give alkene **III-24**. Subsequent saponification and TBS protection of the terminal alkene **III-24** led to the formation of intermediate **III-25**, which was then converted to aldehyde **III-26** by hydroboration and a new chiral centre was installed.

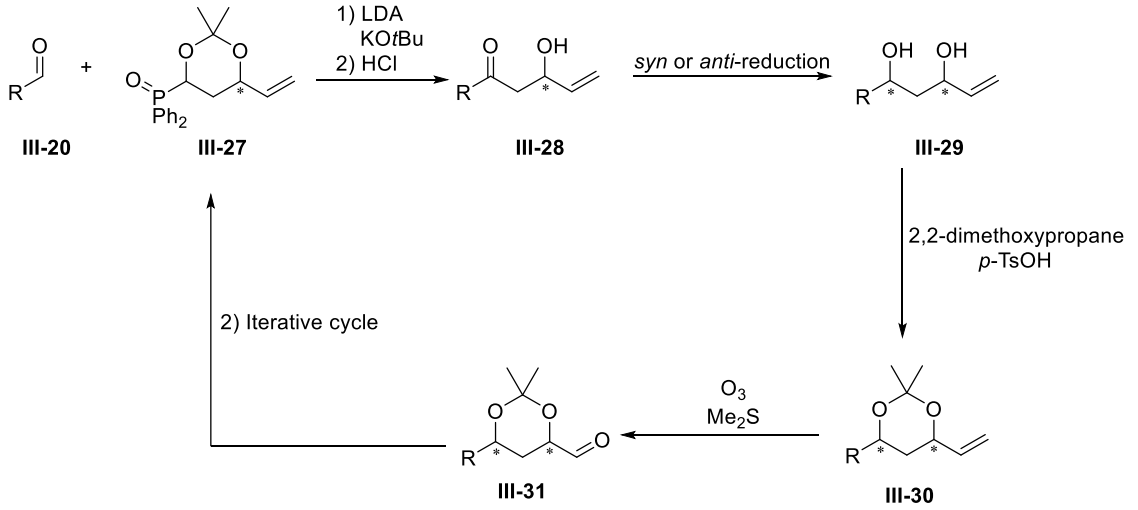


Scheme 125. Iterative polyolsynthesis *via* Overman rearrangement.

The year later, *Kirsch et al.* discovered a shorter synthetic route by which two chiral centres could be installed *via* four-step synthesis (scheme 126).[226]

Starting with aldehyde **III-20**, β-hydroxy ketone **III-28** with a new chiral centre was achieved following a *Horner-Wadsworth-Emmons* reaction with the chiral diphenylphosphane oxide building block **III-27**. The second chiral centre was installed during the following *syn* or *anti*-reduction, resulting in diol **III-29**.

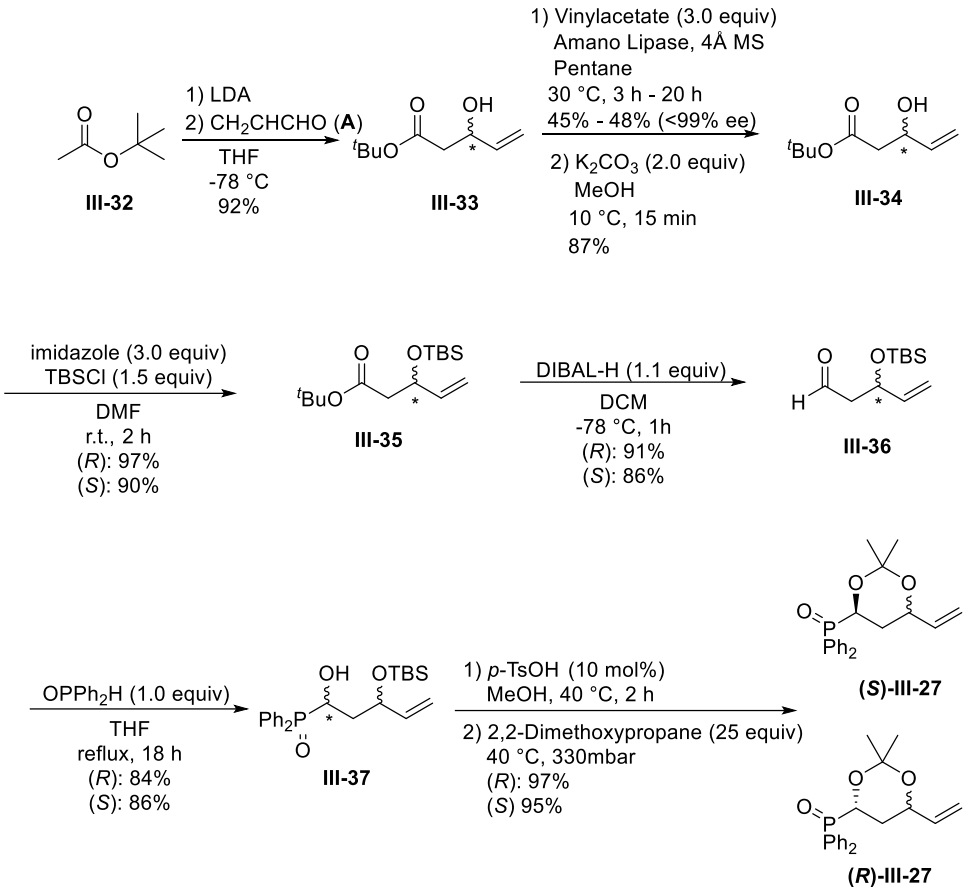
Subsequent diol protection (**III-30**) and alkene ozonolysis provided aldehyde **III-31** that could be used again in the iterative cycle.



Scheme 126. Iterative polyolsynthesis by using chiral Building Block.

The chiral diphenylphosphane oxide building block, involved in the *HWE* olefination, was first synthesized by Dr. *Angela Bredenkamp* (scheme 127).[226]

The synthesis started with the lithium enolate of *tert*-butyl acetate (**III-32**) that was treated with Acrolein (**A**) at –78 °C to give the allylic alcohol **III-33** as a racemic mixture in 92% yield. Kinetic resolution was easily achieved through enzymatic acetylation using vinyl acetate and Amano lipase PS in *n*-pentane and the enantiomers (*R*)-**III-34** and (*S*)-**III-34** were obtained with excellent enantiopurity. Subsequent protection as TBS ether (**III-35**) followed by partial reduction with DIBAL-H furnished intermediat **III-36**. Addition of diphenylphosphane oxide then led to the compound **III-37** in good yield as a diastereomeric mixture (ranging from 60:40 to 50:50); however, the stereogenic center at C-3 position remained fixed. Acid-catalyzed removal of the TBS group and diol protection achieved to the desired (*R*) or (*S*)-building block.



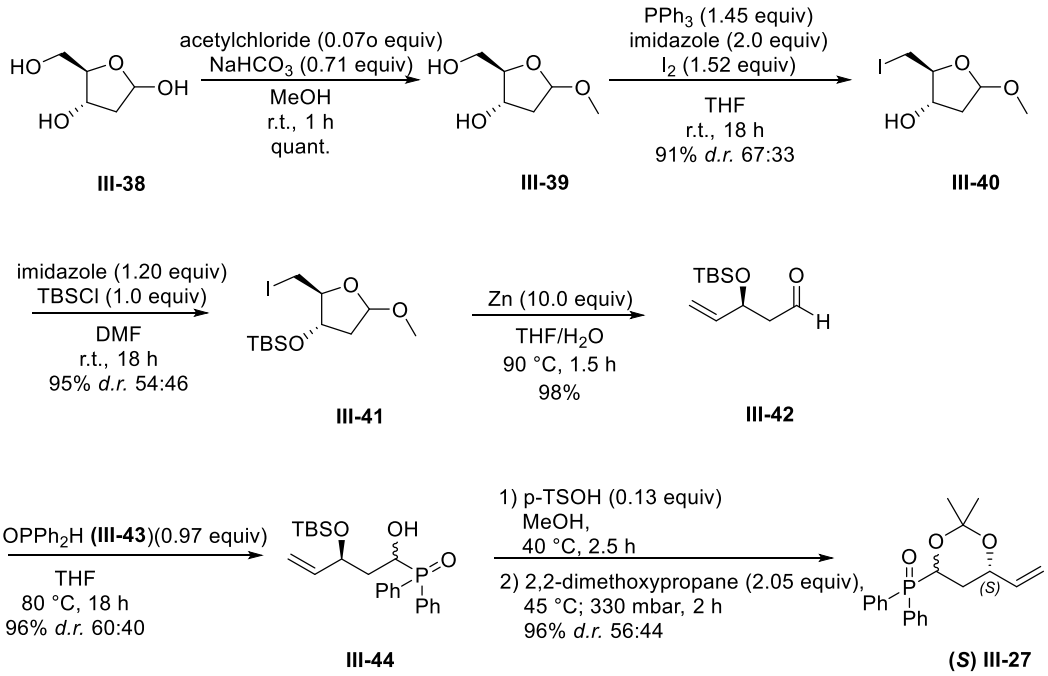
Scheme 127. Synthesis of Building Block **III-27** developed by *Angela Bredenkamp*.

Due to the toxicity of the acrolein, its commercial availability was highly limited, so an alternative route for the synthesis of the building block **III-27** was developed by PhD student *Fabia Mittendorf* (scheme 128).[227]

This method allowed the synthesis of the (*S*)-building block in five steps, starting from the cheap commercially available 2-deoxy-*D*-ribose **III-38**.

First, the sugar **III-38** was converted to acetal **III-39**, followed by iodination (**III-40**) and TBS protection of the primary alchol (**III-41**). The subsequent *Vasella*-fragmentation to aldehyde **III-42** was achieved by using zinc dust activated with 1M HCl.

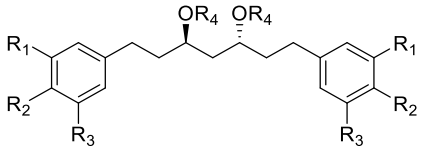
Phosphane oxide **III-44** was obtained after treatment with diphenylphosphane oxide (**III-43**) in 96% yield with *d.r.* of 60:40. Final TBS deprotection and acetal protection furnished the desired (*S*)-building block **III-127** in 78% overall yield.



Scheme 128. Synthesis of (*S*)-Building Block from 2-deoxy-*D*-ribose **III-38** developed by *Fabia Mittendorf*.

2. Task

The purpose of this project consists of the synthesis of unsymmetric diarylheptanoids **III-4**, **III-17**, **III-18** and **III-19** *via* the stereoselective route previously described, involving the use of a chiral *(S)*-building block **III-27** (figure 25).[227]

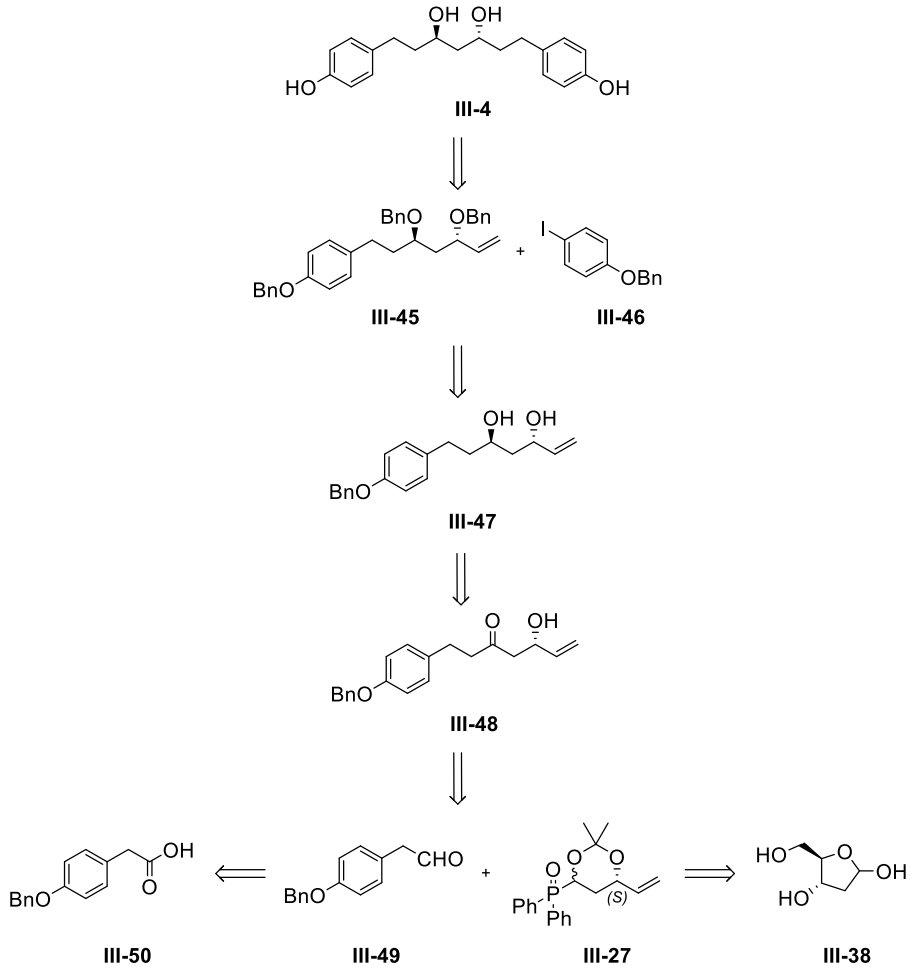


III-4: R_1=H R_2=OH R_3=H R_4=H
III-17: R_1=H R_2=OH R_3=OCH_3 R_4=H
III-18: R_1=H R_2=OH R_3=OH R_4=H
III-19: R_1=OCH_3 R_2=OCH_3 R_3=OCH_3 R_4=Ac

Figure 25. Structures of diarylheptanoid derivatives and (*S*)-Building block **III-27.**

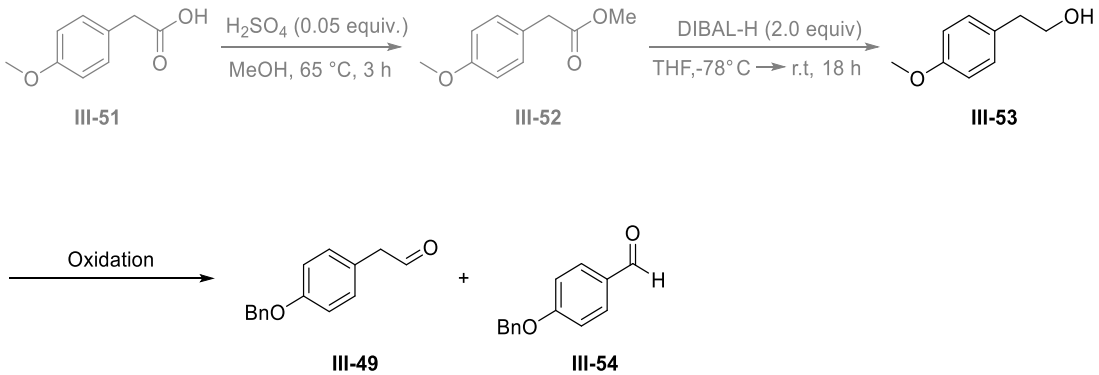
2.1 Towards the synthesis of (*+*)-Hannokinol

A possible pathway that could enable the synthesis of Hannokinol **III-4** was studied by student *Jan Mayer-Figge*,[228] starting from 2-(4-(benzyloxy)phenyl)acetic acid **III-50** (scheme 129).
By a *Wittig-Horner* olefination, the aldehyde **III-49**, that should be obtained from 2-(4-(benzyloxy)phenyl)acetic acid **III-50**, should be reacted with the (*S*)-building block **III-27** to achieve the β-hydroxyketone **III-48**. A subsequent *anti*-reduction (**III-47**), followed by benzyl protection of diol, should provide the benzyl ether **III-45**.
Via a Heck coupling with the benzyl-protected iodophenol **III-46**, the core structure of the natural product **III-4** should then be built up.
The last deprotection and double bonds reduction after hydrogenation should afford the natural product (*+*)-Hannokinol **III-4**.



Scheme 129. Retrosynthetic pathway for the synthesis of (*+*)-Hannokinol **III-4.**

The natural product (*+*)-Hannokinol **III-4** was synthesised *via* this route in a low yield due to the problems encountered during the synthesis of aldehyde **III-49** (scheme 130), because it could not be obtained completely pure. The NMR showed a mixture of the desired aldehyde **III-49** with aldehyde **III-54** due to fragmentation of the desired aldehyde **III-49**, even when applying different oxidation conditions.

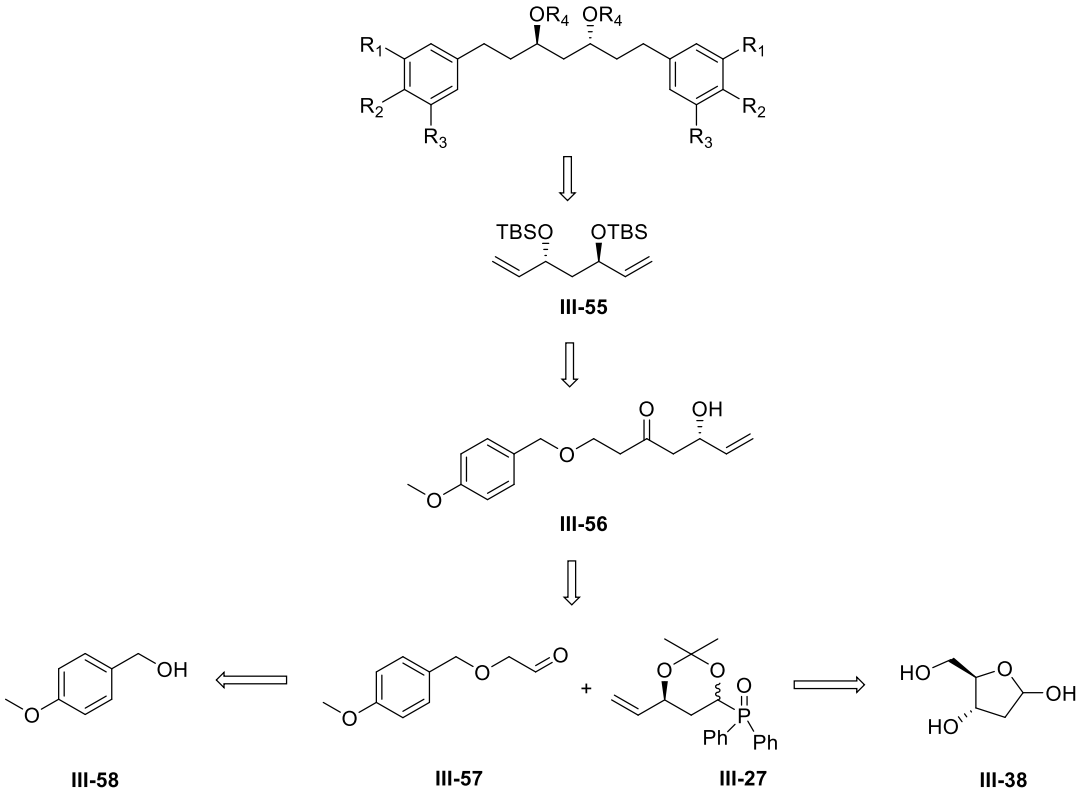


Scheme 130. Aldehyde fragmentation.

The use of this impure aldehyde in the followed *Wittig-Horner* olefination with (*S*)-Building Block **III-127** led to the synthesis of an impure β-hydroxyketone **III-48**, which could only be purified by preparative HPLC, resulting in an extremely low yield and loss of product.

2.2. Retrosynthesis

To attain the desired diarylheptanoids avoiding problems prescribed above, a new approach was employed, in which TBS protected diene **III-55** should be synthesized as the key intermediate molecule of the synthetic process.
It should be provided *via* the corresponding β-hydroxy-ketone intermediate **III-56**, achieved through the *Horner-Wittig* reaction between aldehyde **III-57**, reached *via* two-steps synthesis from 4-methoxybenzyl alcohol **III-58**, and *(S)*-building block **III-27**, obtained in five steps from commercially available 2-deoxy-*D*-ribose **III-38** (scheme 131).[227]

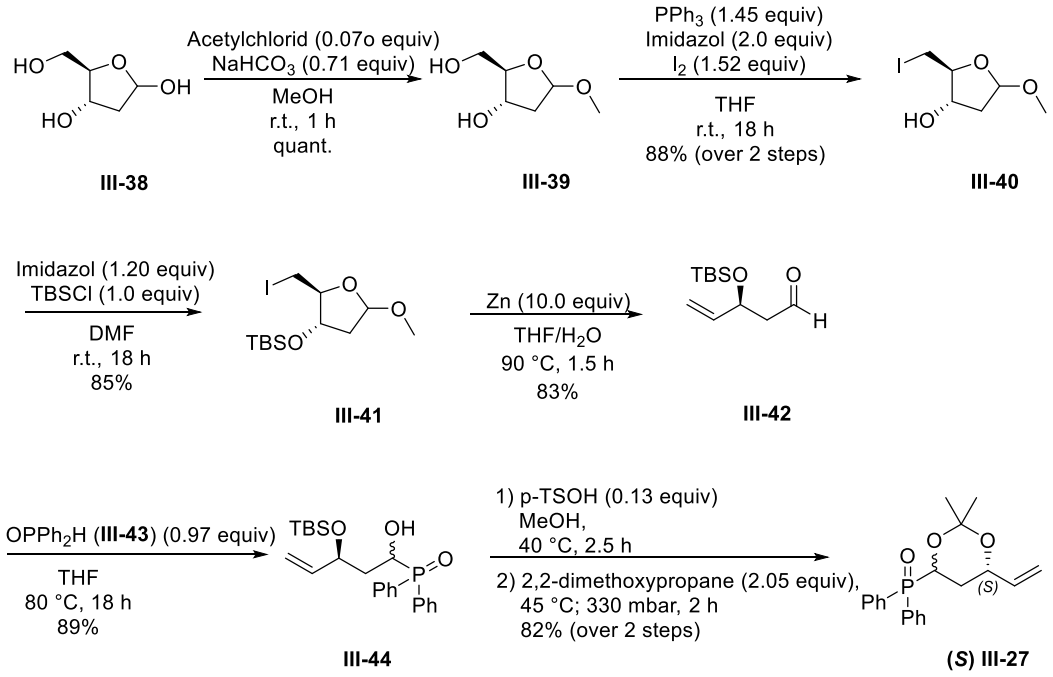


Scheme 131. Retrosynthesis of desired diarylheptanoids.

3. Result and discussion

3.1. Synthesis of *(S)*-building block III-27

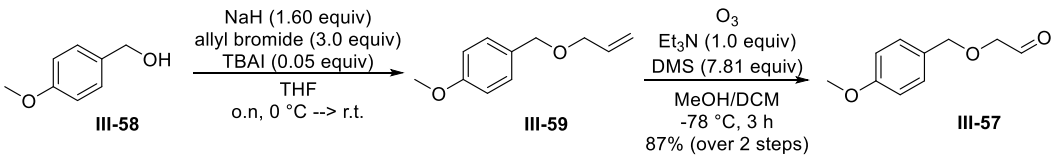
The (*S*)-Building Block **III-27** was synthesized from 2-deoxy-*D*-ribose **III-38** in 46% yield over seven steps with a *d.r.* of 56:44 as described above (scheme 132). (*See paragraph 1.4*)



Scheme 132. Synthesis of (*S*)-Building Block **III-27**.

3.2. Synthesis of diene III-55 as key intermediate molecule

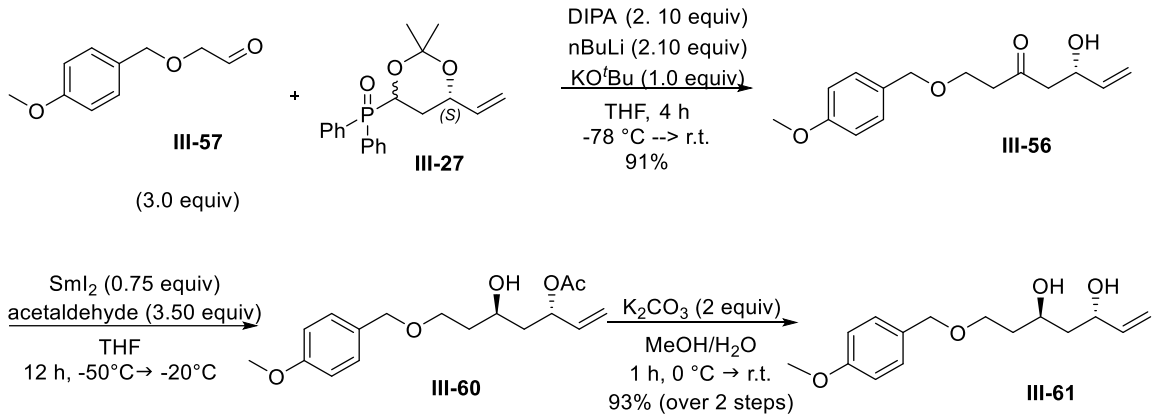
The route for the synthesis of the desired diene began with allylation of 4-methoxybenzyl alcohol **III-58**, followed by ozonolysis of alkene **III-59** to give aldehyde **III-57** in 87% over 2 steps (scheme 133).



Scheme 133. Synthesis of aldehyde **III-57** from alcohol **III-58.**

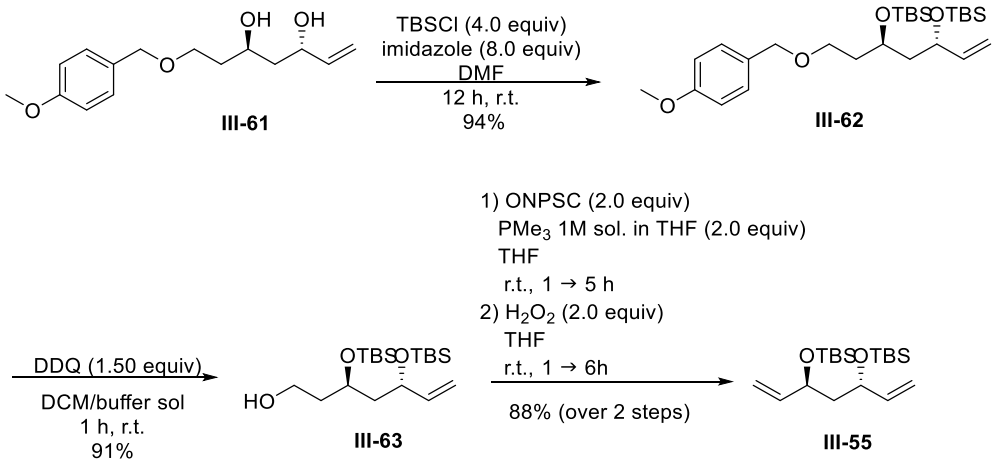
Aldehyde **III-57** and (*S*)-Building Block **III-27** represented important intermediates for the introduction of the first stereogenic center through the *Horner-Wittig* reaction,

mediated by LDA and potassium *tert*-butoxide. Subsequent acidic work-up, for acetal deprotection, achieved the β-hydroxy-ketone **III-56** in 91% yield (scheme 134).
The followed *anti*-reduction reaction by using samarium-(II)-iodide and acetaldehyde, to insert the second stereogenic center *via* a two-step *Evans-Tishchenko* reduction, gave intermediate **III-60**.
Successive acetate deprotection with K_2CO_3 furnished diol **III-61** in 93% yield over two steps and with excellent diastereoselectivity (*d.r.* > 99:1).



Scheme 134. Synthesis of diol **III-61** from aldehyde **III-57.**

Diol **III-61** was protected as *tert*-butyldimethylsilyl ether, obtaining intermediate **III-62** in 94% yield. It was then treated with DDQ, allowing deprotection of PMB protecting group and formation of primary alcohol **III-63** in 91% yield (scheme 135).
The primary alcohol was eliminated by *Grieco* elimination,[229] through a selenide intermediate, to a terminal alkene. The alcohol first reacted with *o*-nitrophenylselenocyanate and tributylphosphine to a selenide derivative and then was oxidized with hydrogen peroxide to a selenoxide moiety. Removal of the selenol furnished desired diene **III-55** in 88% yield.



Scheme 135. Synthesis of the diene **III-55** as key step.

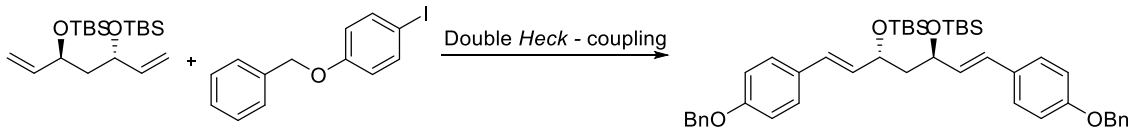
3.3. Synthesis of (+)-Hannokinol

The diene **III-55** highlighted an interesting starting point to obtain the desired diarylheptanoid. Its structure present two terminal alkene that could be involved in a double *Heck* coupling, allowing the synthesis of the structural skeleton of (+)-Hannokinol **III-4**.

Although *Heck* coupling is a well-known and broadly used reaction in organic and pharmaceutical chemistry, the double *Heck* coupling has shown to be not so common and, in some cases, a styrene with dihalogenated derivatives is involved.[230]

Therefore, a screening was carried out by using different bases, catalysts, ligands, additives and solvents, to find the best conditions for the double *Heck* coupling (table 31), in presence of 1-(benzyloxy)-4-iodobenzene **III-64**.[231]

Table 31. Double *Heck* - coupling screening



III-55 **III-64** **III-65**

Entry	Catalyst	Base	Ligand	Solvent	T (°C)	t (h)	Product[a]
1	$Pd(OAc)_2$	Et_3N	//	DMF	100 (MW)	12	-[c]
2	$Pd(OAc)_2$	K_2CO_3	dppe	DMF	90	16	-[c]
3	$Pd(OAc)_2$	Et_3N	tri-*o*-tolylphosphine	DMF	90	16	-[c]
4	$Pd(OAc)_2$	NaOAc	//	NMP	90	10	-[c]
5	$PdCl_2(PPh_3)_2$	2,6-lutidine	//	DMF	95	72	-[b]
6	Herrmann-Beller catalyst	*N,N*-dicyclohexylmethylamine	//	DMF	95	72	-[d]
7	$Pd(OAc)_2$ Bu_4NCl	Cs_2CO_3	//	DMF	90	16	-[d]
8	$Pd(OAc)_2$ Bu_4NBr	K_2CO_3	//	ACN	90	10	-[c]
9	$Pd(OAc)_2$	tributylamin	//	DMF	95	72	-[d]
10	$Pd(OAc)_2$ Bu_4NCl	K_2CO_3	//	DMF	90	16	77%
11	$Pd(OAc)_2$ Bu_4NCl	Ag_2CO_3	//	DMF	90	16	41%

[a] Isolated yield after column chromatography. [b] No conversion. [c] Decomposition. [d] Low conversion and impurities.

The most widely used catalyst was $Pd(OAc)_2$, but *Herrmann-Beller* catalyst and $PdCl_2(PPh_3)_2$ were also studied.

As shown in table 31, total decomposition was achieved by treating the diene with $Pd(OAc)_2$ in dimethylformamide at elevated temperatures, in the presence of Et_3N (entries 1, 3).

A similar result was afforded by using K_2CO_3, in the presence of dppe as ligand or without ligand but with tetrabutylammonium chloride (Bu_4NCl) as additive and using acetonitrile as solvent (entries 2, 8).

Further decomposition was noted by employing sodium acetate (NaOAc) as a base without using ligands and additives in *N*-methyl-2-pyrrolidone (NMP) as a solvent (entry 4).

No conversion of the starting material **III-55** was observed by employing $PdCl_2(PPh_3)_2$, in the presence of 2,6-lutidine as base and in absence of additive (entry 5).

Low or partial conversion was achieved by using $Pd(OAc)_2$ as a catalyst in the presence of cesium carbonate and tetrabutylammonium chloride or tributylamine (without ligands) (entries 6, 9).

By using *Herrmann-Beller* catalyst and *N,N*-dicyclohexylmethylamine as base, without additive, led to the same result (entry 5).

The desired product **III-65** was finally achieved by employing $Pd(OAc)_2$ in dimethylformamide at 90 °C in the presence of Bu_4NCl and K_2CO_3 or Ag_2CO_3 as bases, in 77% and 41% yields, respectively (entries 10, 11).

Hence, this screening showed that the desired product was achieved in the absence of ligands and in presence of additives.

A thorough analysis of the intermediate **III-65** by NMR and mass showed that the double *Heck* reaction led to the selective *E* product formation but resulted in a mixture consisting of regioisomers **III-65**, **III-65A** and **III-65B** in a *ratio* of 84:11:5 (figure 26).

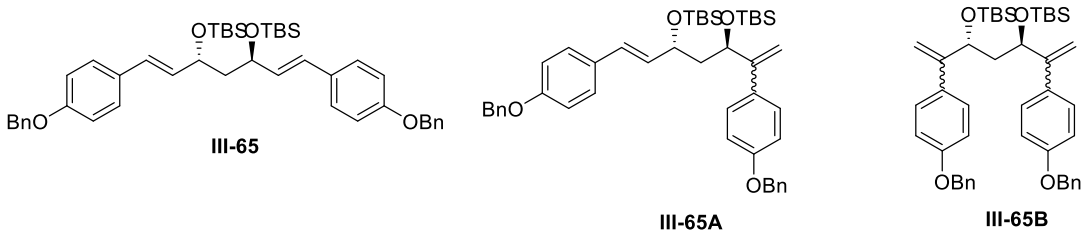
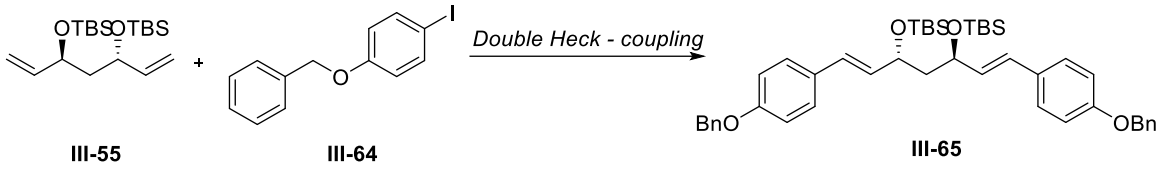


Figure 26. Desired product **III-65** and regioisomers **III-65A** and **III-65B**, after double *Heck* coupling.

For this reason, the conditions of double *Heck* coupling should be optimized, trying to decrease the temperature that might be responsible for non-regioselectivity in the reaction (table 32) and testing different bases and solvents.

Table 32. Further study of double *Heck* coupling



III-55 **III-64** **III-65**

Entry	Catalyst	Base	Additive	Solvent	T (°C)	t (h)	Product[a]
1	$Pd(OAc)_2$	K_2CO_3	Bu_4NCl	DMF	50	16	-[b]
2	$Pd(OAc)_2$	K_2CO_3	Bu_4NCl	DMF	60	48	-[c]
3	$Pd(OAc)_2$	K_2CO_3	Bu_4NCl	ACN	50	16	-[d]
4	$Pd(OAc)_2$	K_2CO_3	Bu_4NCl	ACN	60	48	-[d]
5	$Pd(OAc)_2$	NaOAc	Bu_4NCl	DMF	50	16	57%
6	$Pd(OAc)_2$	NaOAc	Bu_4NCl	DMF	40	16	66%
7	$Pd(OAc)_2$	NaOAc	Bu_4NCl	DMF	r.t.	16	42%

[a] Isolated yield after column chromatography. [b] No conversion. [c] Mixture. [d] III-55 + III-65 mixture

As pointed out in the table 32, no-conversion of the starting material could be achieved by applying the conditions previously found (table 31, entry 10) at 50 °C instead of 90 °C (entry 1). By raising the temperature to 60 °C, a mixture of starting material, desired product and impurities was obtained (entry 2).

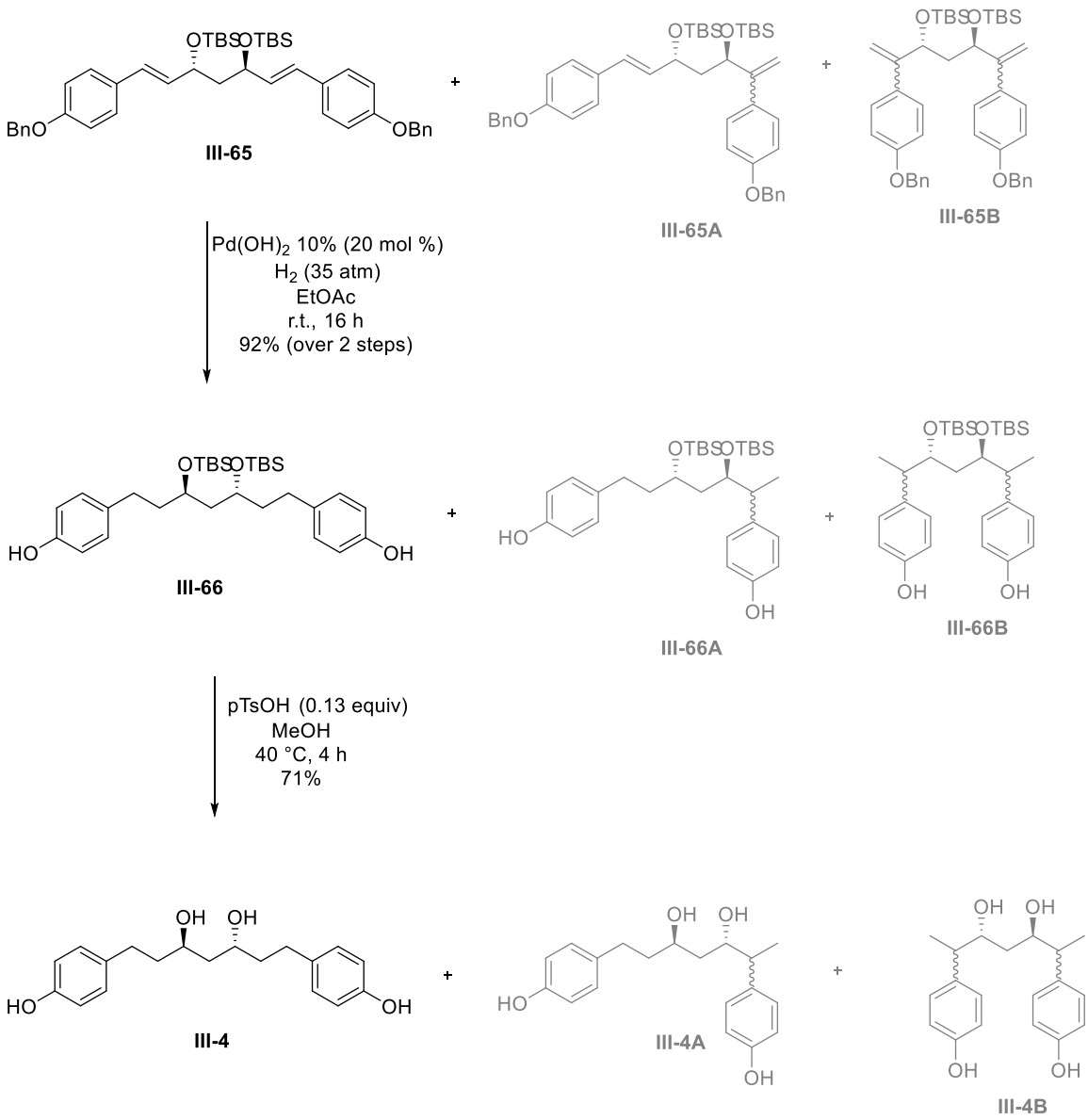
The same result was afforded by replacing the dimethylformamide with acetonitrile at 50 °C or 60 °C (entries 3, 4).

By employing sodium (NaOAc) instead of K_2CO_3 as a base, full conversion was obtained at 50 °C, 40 °C and room temperature, leading to the desired product **III-65** in 57%, 66% and 42% yields (entries 5, 6, 7), but the selectivity of the reaction did not change, indeed an analysis of the product showed the same mixture as previously obtained.

The purification of product **III-65** proved to be a difficult undertaking, even with the use of preparative HPLC, without any separation.

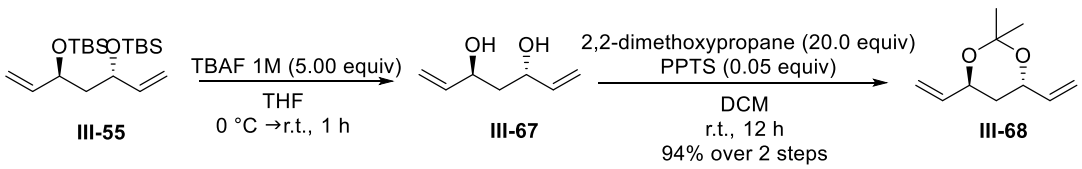
Therefore, the product mixture was used for the next steps. A hydrogenation was performed, to reduce the double bonds and to deprotect the benzyl groups, giving products **III-66** and side products **III-66A** and **III-66B** in 92% yield in a *ratio* of 86:9:5 (scheme 136).

Deprotection of the silyl groups with *p*-TSOH in methanol resulted in (*+*)-Hannokinol **III-4**, in a mixture containing impurities **III-4A** and **III-4B**, in 71% yield. The purity of (*+*)-Hannokinol **III-4** corresponds to 82% based on ^{1}H-NMR.



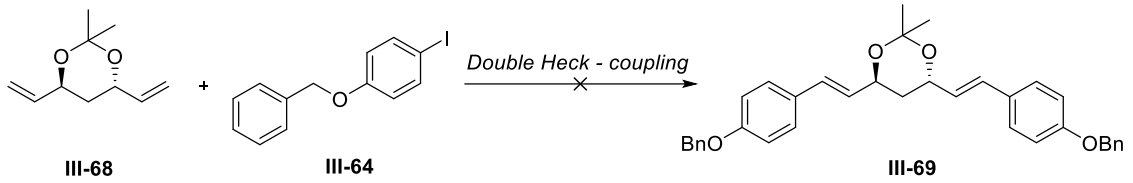
Scheme 136. Final synthesis of (+)-Hannokinol **III-4** and regioisomers.

To overcome this selectivity problem, the TBS protecting group was replaced with an acetonide (scheme 137). Then, diene **III-55** was treated with tetrabutylammonium fluoride in tetrahydrofuran, obtaining diol **III-67**, subsequently treated with 2,2-dimethoxypropane and pyridinium *p*-toluenesulfonic acid in dichloromethane, achieving desired product **III-68** in 94% yield over two steps.



Scheme 137. Synthesis of acetonide intermediate **III-68.**

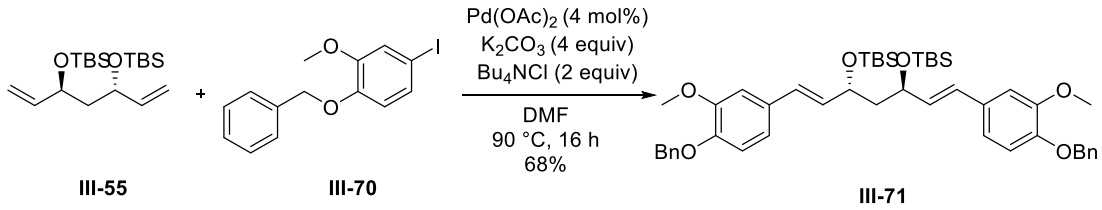
Unfortunately, this compound proved not to be stable under the conditions seen previously for a double *Heck* coupling, showing mainly decomposition (scheme 138).



Scheme 138. Unsuccessful *double Heck coupling*.

3.4. Octahydrocurcumin synthesis

For the synthesis of the Octahydrocurcumin **III-17**, the same conditions, as figured out previously for the double *Heck* coupling, were applied by employing diene **III-55** and 1-(benzyloxy)-4-iodo-2-methoxybenzene **III-70**[232] (scheme 139).



Scheme 139. Synthesis of **III-71** *via* double *Heck* coupling.

Despite using a different benzyl iodide reagent with different substituents, the double *Heck* coupling led to the formation of **III-71** as the major *E* product in a mixture of regioisomers **III-71**, **III-71A** and **III-71B** in 68% in a *ratio* of 84:11:5 (figure 27).

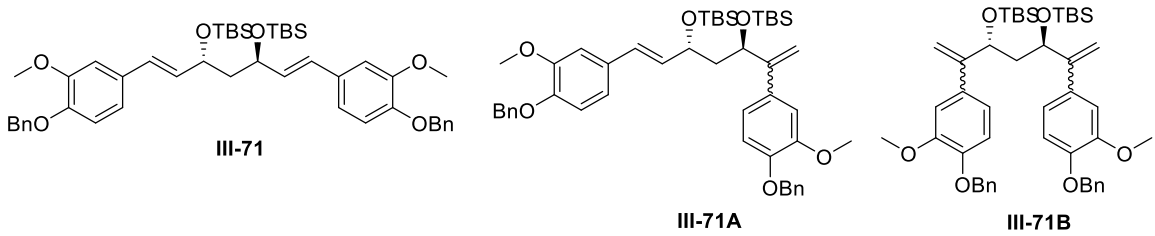
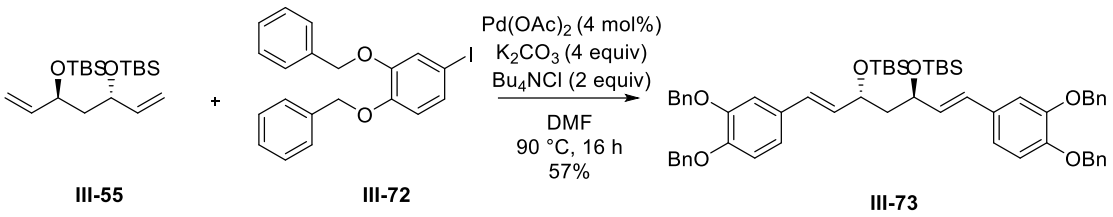


Figure 27. Regioisomers mixture after the double *Heck* coupling.

3.5. 4-[(3*R*,5*R*)-7-(3,4-dihydroxyphenyl)-3,5-dihydroxyheptyl]benzene-1,2-diol synthesis

For the synthesis of diarylheptanoid **III-18**, the double *Heck* coupling was carried out in the presence of diene **III-55** and (((4-iodo-1,2-phenylene)bis(oxy))bis(methylene))dibenzene **III-72**[233,234] (scheme 140), by applying the same reaction conditions discuss above.



Scheme 140. Synthesis of compound **III-73** via double *Heck* coupling.

The desired product **III-73** was obtained as *E* product in a mixture with regioisomers **III-73**, **III-73A** and **III-73B** in 57% yield in a *ratio* of 90:5:5 (figure 28).

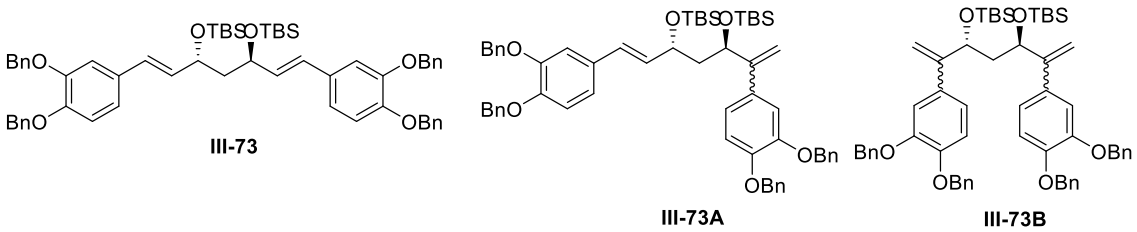
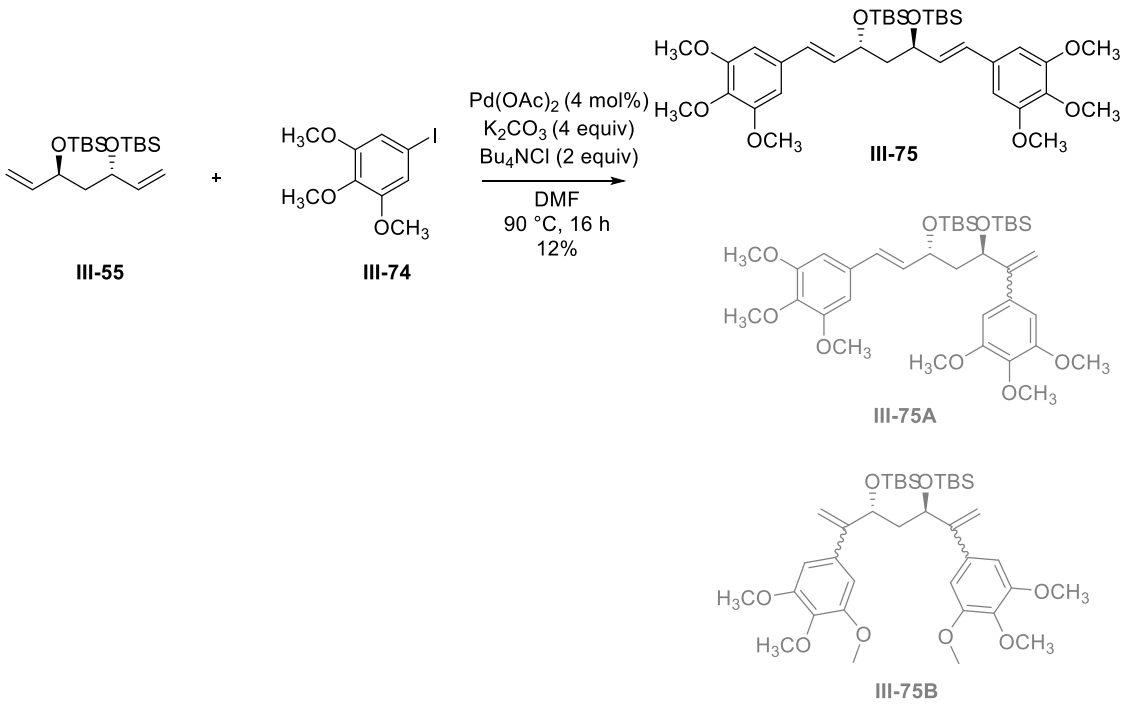


Figure 28. Regioisomers mixture after the double *Heck* coupling.

3.6. 3,5-diacetoxy-1,7-bis(3,4,5-trimethoxyphenyl)heptane synthesis

For the synthesis of the latter diarylheptanoid **III-19**, the double *Heck* coupling was carried out by using diene **III-55** and 5-iodo-1,2,3-trimethoxybenzene **III-74**,[235,236] obtaining the desired product **III-75** in a low yield of 12% and with no selectivity, thus in a mixture of regioisomers with no major product (scheme 141).

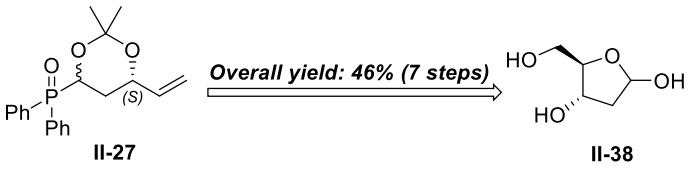


Scheme 141. Synthesis of **III-75** via double *Heck* coupling.

This highlighted that the presence of those three methoxyls on the benzyl iodide **III-74** derivative does not contribute to the selectivity of the reaction.

4. Summary

The stereoselective route for the synthesis of the four desired diaryleptanoid products involved the use of a chiral (*S*)-building block **III-27**, obtained from 2-deoxy-*D*-ribose *via* seven-steps synthesis in 46% overall yield, to insert two chiral centers during the synthesis of the natural products (scheme 142).

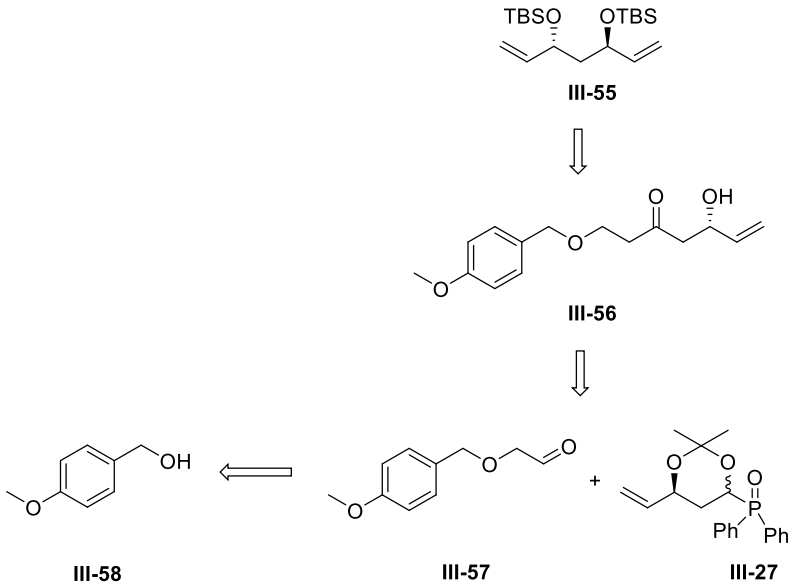


Scheme 142. Synthesis of (*S*)-building block **III-27**.

The key molecule in this process is represented by the diene **III-55**, which was obtained from 4-methoxy benzyl alcohol **III-27** *via* nine-steps synthesis in 51% overall yield (scheme 143).

One of the key steps is the *Horner-Wittig* olefination, between aldehyde **III-57** and (*S*)-building block **III-27**, because it allows the first chiral centre to be installed with the formation of β-hydroxyketone **III-56**.

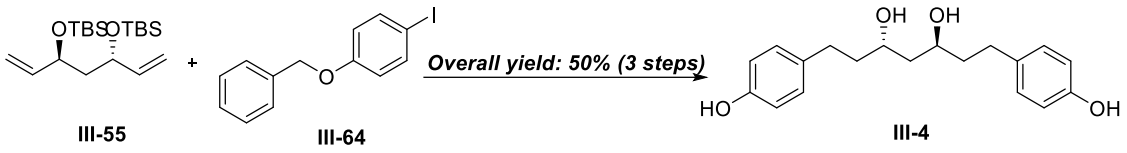
Another one is the *Grieco* elimination, which allows the elimination of the primary alcohol obtained after deprotection of PMB alcohol, furnishing diene **III-55**.



Scheme 143. Synthesis of diene **III-55**.

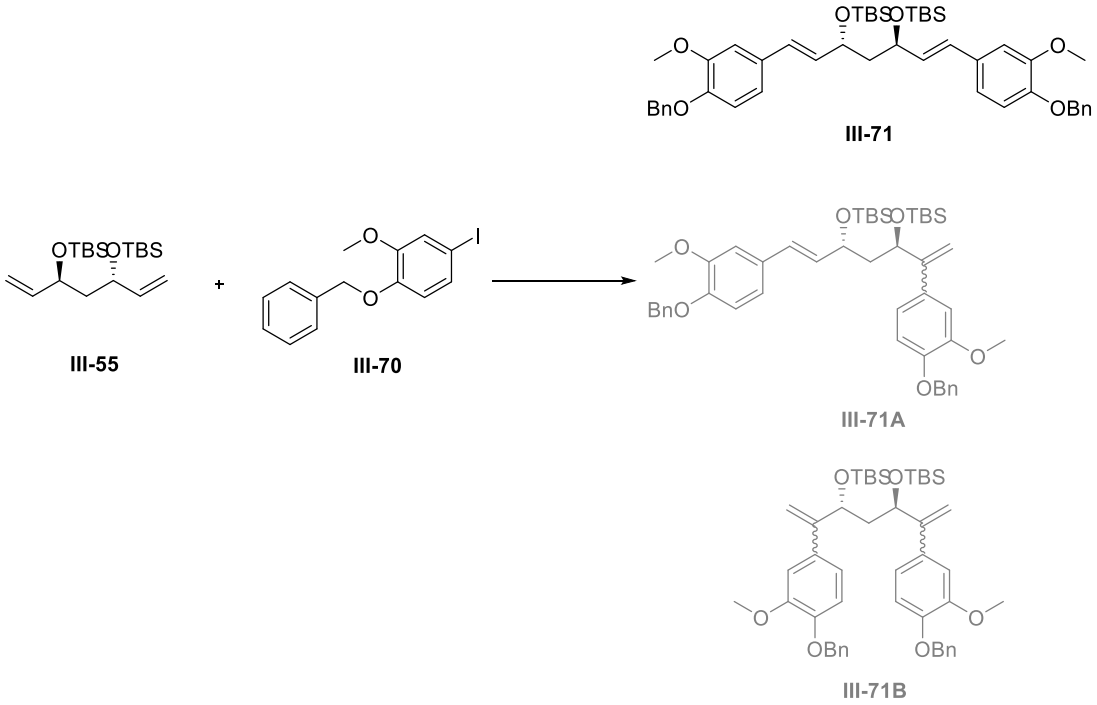
The diaryleptanoid (*+*)-Hannokinol **III-4** was obtained by employing diene **III-55** and 1-(benzyloxy)-4-iodobenzene **III-64** in a double *Heck* coupling with successive

hydrogenation and deprotection in 50% yield over 3 steps, in a mixture with regioisomers with 82% purity (scheme 144).



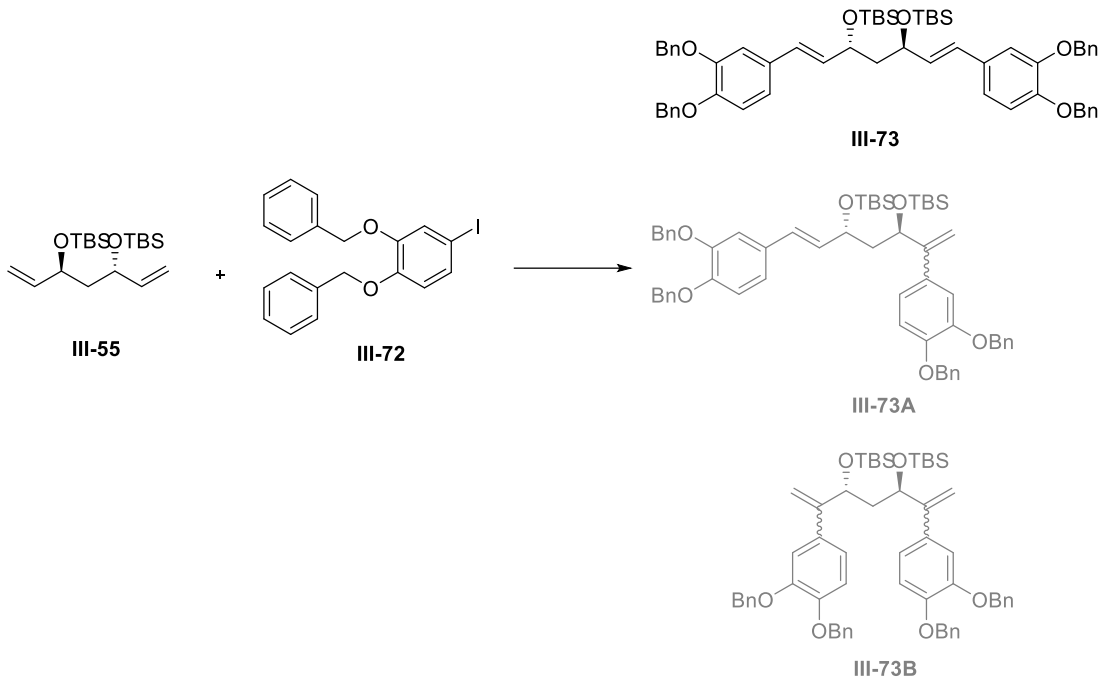
Scheme 144. Synthesis of (+)-Hannokinol **III-4**.

Octahydrocurcumin **III-17** was not fully synthesized but only the double *Heck* coupling was analyzed by using diene **III-55** and 1-(benzyloxy)-4-iodo-2-methoxybenzene **III-70**, obtaining the **III-71**, **III-71A** and **III-71b** in 68% yield in a *ratio* of 84:11:5 (scheme 145).



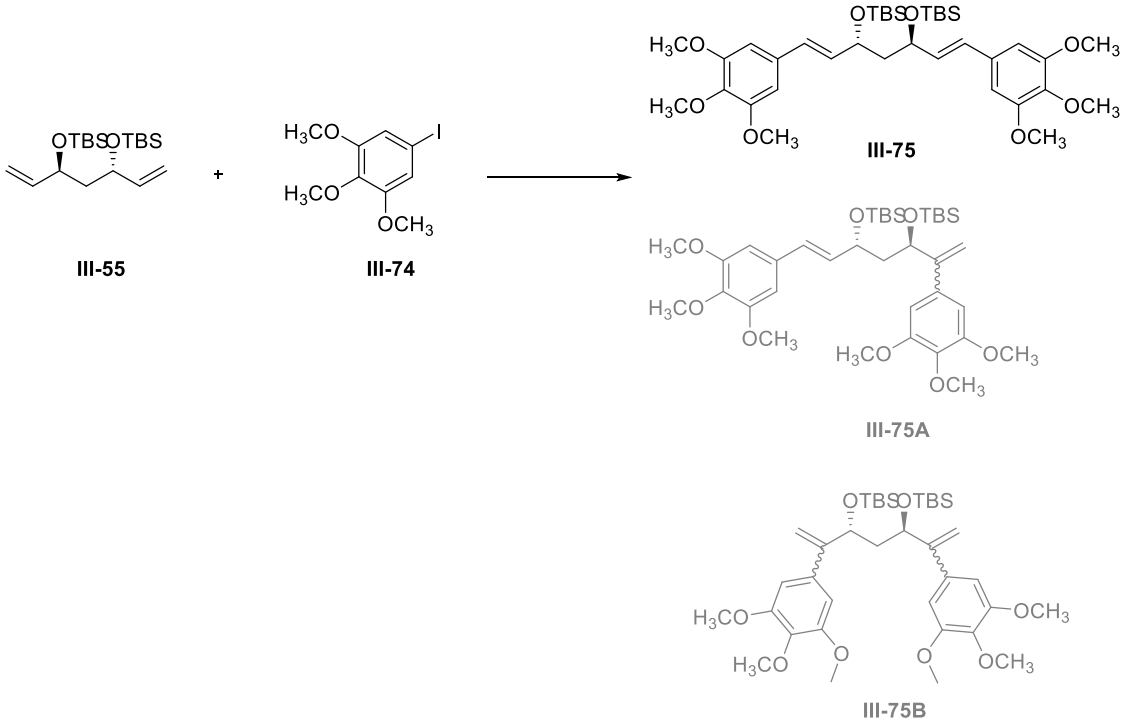
Scheme 145. Double *Heck* reaction for intermediate **III-71**.

The total synthesis of 4-[(3R,5R)-7-(3,4-dihydroxyphenyl)-3,5-dihydroxyheptyl]benzene-1,2-diol **III-18** has not been finished yet but only the double *Heck* coupling was studied by using diene **III-55** and (((4-iodo-1,2-phenylene)bis(oxy))bis(methylene))dibenzene **III-72**, obtaining the **III-73**, **III-73A** and **III-73B** derivative in 57% yield in a *ratio* of 90:5:5 (scheme 146).



Scheme 146. Double *Heck* reaction for intermediate **III-73**.

The diaryleptanoid 3,5-diacetoxy-1,7-bis(3,4,5-trimethoxyphenyl)heptane **III-19** has not been synthesized because the double *Heck* coupling with diene **III-55** and 5-iodo-1,2,3-trimethoxybenzene **III-74**, furnished the derivative **III-75** in 12% yield as a mixture of regioisomers and without any selectivity (scheme 147).



Scheme 147. Double *Heck* reaction for intermediate **III-75**.

5. Outlook

For all desired diarylheptanoids, the double *Heck* coupling has to be optimized to avoid the formation of regioisomers. This could be achieved by two routes: one implies a deeper analysis and study of the reaction conditions, the other one is based on the separation of the side products by further selective reaction with the terminal alkenes.
A thorough analysis and study of the *Heck* coupling reaction could include the use of additional different catalysts, different bases and reaction temperatures. It might also be useful to test different protecting groups instead of TBS (*i.e.*, TIPS **III-76**), or involve benzyl bromide derivatives (**III-77**) instead of iodide ones (figure 29).

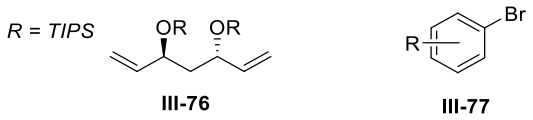
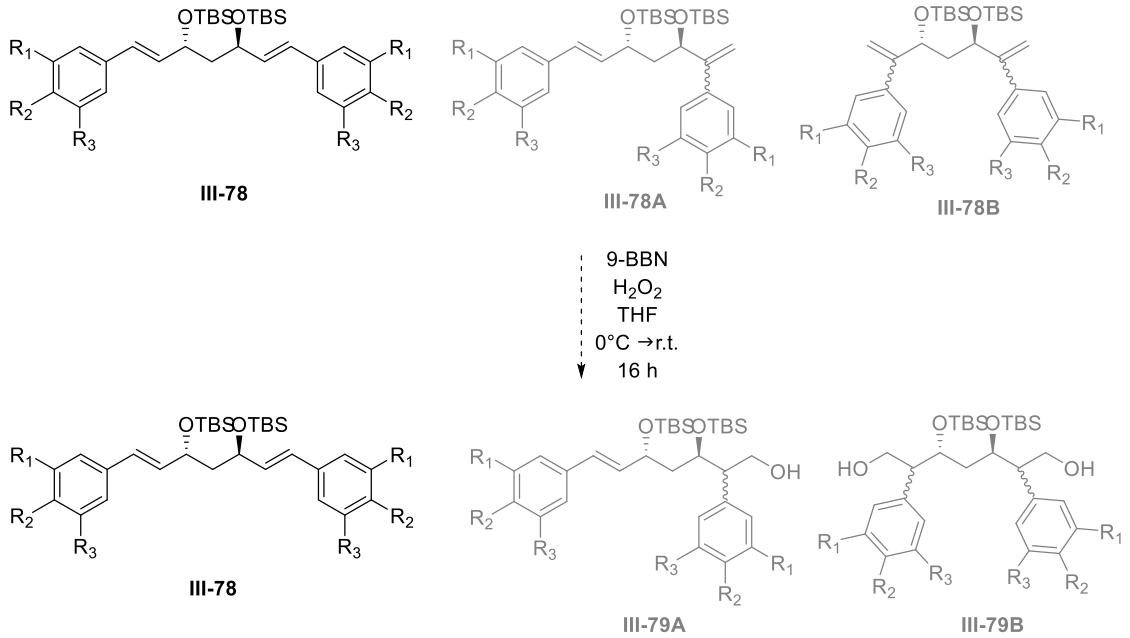


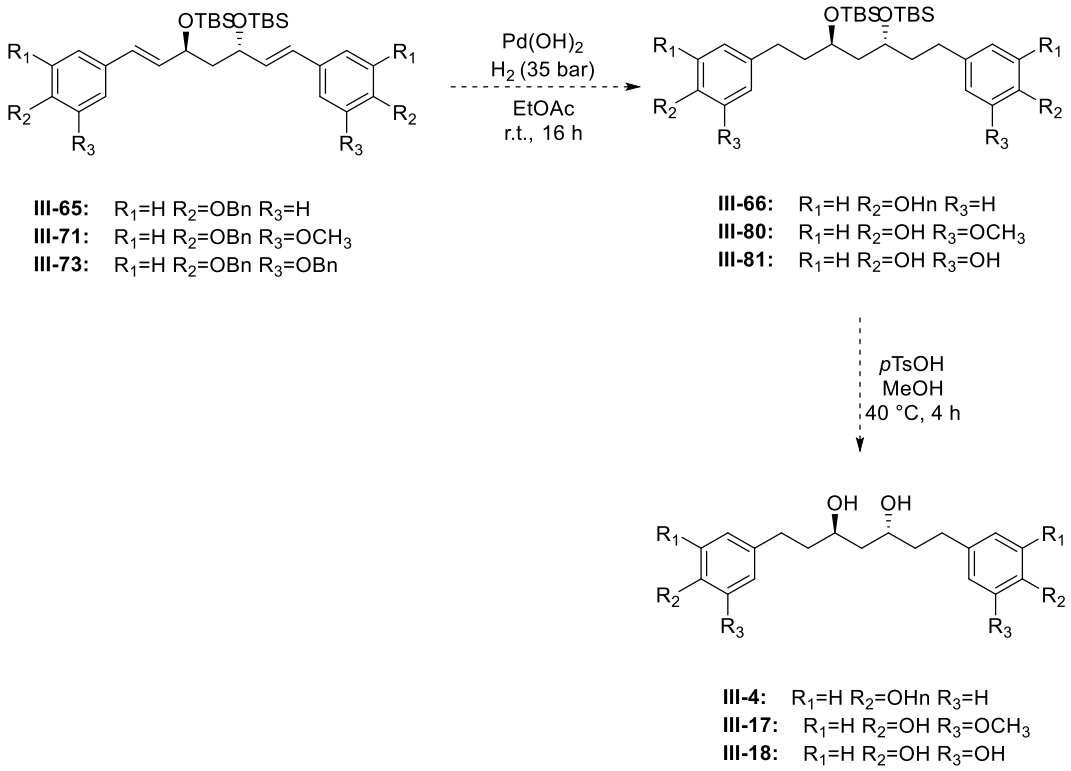
Figure 29. Different intermediates that should be tested.

About selective reactions for removing side products, the regioisomers **III-78A** and **III-78B** could be convert into primary alcohols intermediates **III-79A** and **III-79B** (i.e., *via* hydroboration reaction by using 9-BBN), which are more polar and easier to separate by purification (scheme 148).



Scheme 148. Selective hydroboration/oxidation to separate the regioisomers.

The pure products can then undergo hydrogenation to reduce the double bonds and for benzyl deprotection (scheme 149), leading to the desired products **III-4**, **III-17** and **III-18**.



III-65: R_1=H R_2=OBn R_3=H
III-71: R_1=H R_2=OBn R_3=OCH_3
III-73: R_1=H R_2=OBn R_3=OBn

III-66: R_1=H R_2=OHn R_3=H
III-80: R_1=H R_2=OH R_3=OCH_3
III-81: R_1=H R_2=OH R_3=OH

III-4: R_1=H R_2=OHn R_3=H
III-17: R_1=H R_2=OH R_3=OCH_3
III-18: R_1=H R_2=OH R_3=OH

Scheme 149. Subsequent hydrogenation and TBS deprotection to synthesize the final desired products.

❖ Experimental section

1. General informations

Technical quality solvents were used for the processing of reactions and chromatography. All nonaqueous reactions and with moisture sensitive reagents were carried out in heated glassware under nitrogen atmosphere with dry solvents. Reagents were either added under nitrogen or argon atmosphere by using syringes and cannulas through septa. Solvents such as THF, ACN, Et_2O and DCM were dried using a solvent purification system from M. Braun (Modell *SPS-800*). All other absolute solvents were commercially available from sigma-Aldrich, Acros Organics, Fluka and Merck. All non-absolute solvents, except DMF (Fischer Scientific) and DMSO (Roth), were distilled before using. Ethyl acetate, for extraction and chromatography steps, was also previously distilled. All reagents and chemicals were purchased from commercial sources and used without any further purification.
Reactions that required low temperature were cooled down with ice bath (0 °C), ice bath and salts NaCl (-20°C) or acetone/dry ice (-78°C). Reactions that required high temperatures were heated with oil bath and heating plate, the temperature was set and monitored by an external thermometer.
Reactions in a continuous flow system were carried out by using the flow reactor H-Cube® Mini Plus from ThalesNano.

Thin-layer chromatography was conducted with precoated aluminium sheets from Merck (TLC 100 µm silica gel 60 F_{254}) and visualized with UV light (λ = 254 nm, 366 nm) or stained with cerium ammonium molybdate (CAM or Hanessian's Stain: 10 g cerium (IV) sulfate, 25 g ammonium heptamolybdate tetrahydrate, 100 mL concentrated sulfuric acid, 1000 mL water) or basic potassium permanganate solutions (KMnO4: 3 g potassium permanganate, 20 g potassium carbonate, 5 g sodium hydroxide, 1000 mL water) and subsequent heating. Flash column chromatography was performed on VWR silica gel (40–63 µm), used as the stationary phase, applying medium pressure (0.5-1 bar, compressed air) and the eluent used is reported in the respective experiments.

Infrared spectroscopy (IR) was performed using ATR technology with an ALPHA FTIR spectrometer from Bruker in a range of 400–4000 cm^{-1}.

Nuclear magnetic resonance spectroscopy (NMR) was carried out using devices from Brucker (Avance III 600, Avance 4000). ^{1}H-NMR spectra were recorded at 400 MHz or 600 MHz instruments and ^{13}C NMR spectra at 101 MHz or 151 MHz. Chemical shifts have been reported in ppm (δ scale) and coupling constants *J* in Hz. The following abbreviations were used for the coupling multiplicities: s (singlet), d (doublet), dd

(doublet of doublets), ddd (doublet of doublet of doublets), dt (doublet of triplets), t (triplet), td (triplet of doublets), q (quartet), m (multiplet).

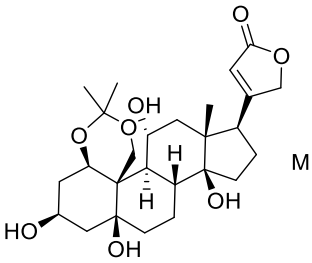
Low-resolution mass spectra (LRMS) were measured by using a device from Agilent Technologies (model 1260 infinity) on a 6120-quadrupole mass spectrometer and applying an electrospray ionization (ESI).
High-resolution mass spectra (HRMS) were either carried out using ESI ionization (positive) on micrOTOF mass spectrometer from Bruker with a liquid chromatograph from Agilent Technologies (1100) or by field desorption (FD) on an AccuTOF GCX from JEOL.

The specific rotation of the unknown chiral substances was measured on a *P8000-T* polarimeter from *Krüss Optronic GmbH*. The samples were measured in the specified solvent under the specified concentration (c = g/100 mL) at a fixed temperature. The concentration was rounded to one decimal place.

2. Experimental part

2.1. Defunctionalization of Ouabain

4-((3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*,14b*S*)-5,11,12a,14b-tetrahydroxy-3a,8,8-trimethylhexadecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-3-yl)furan-2(5*H*)-one (I-25)



$C_{26}H_{38}O_8$
M: 478,58 g/mol

A suspension of Ouabain octahydrate **I-1** 96% (5.13 g, 6.76 mmol, 1.0 equiv) in acetone (0.08 M) is treated with concentrated hydrochloric acid 37% (1.66 mL, 20.29 mmol, 3.0 equiv). The homogenous solution is stirred for 14 h at room temperature, followed by crystallization for 10 d.

The white crystalline precipitate is filtered off and washed with acetone and ethyl acetate. The remaining solvent is evaporated in vacuo and recrystallized to give, in total, **I-25** (3.09 g, 6.48 mmol) as pure white/pale pink solid in 96% yield.

Characterization:

R_f = 0.45 (EtOAc/MeOH 9/1 + 5% Et_3N) [CAM].

^{1}H NMR (600 MHz, DMSO-d_6): δ [ppm] = 5.93 (s, 1H), 5.08 (dd, *J* = 4.4, 2.5 Hz, 1H), 4.89 (dd, *J* = 4.6, 1.8 Hz, 2H), 4.27 (d, *J* = 11.9 Hz, 1H), 4.06 (t, *J* = 3.1 Hz, 1H), 3.95 (td, *J* = 8.3, 4.9 Hz, 1H), 3.64 (d, *J* = 11.9 Hz, 1H), 3.00 (t, *J* = 7.7 Hz, 1H), 2.05 – 1.84 (m, 4H), 1.80 – 1.72 (m, 3H), 1.56 (ddd, *J* = 33.5, 13.0, 6.4 Hz, 2H), 1.47 – 1.40 (m, 2H), 1.35 (dd, *J* = 12.5, 8.1 Hz, 1H), 1.30 – 1.26 (m, 2H), 1.25 (s, 3H), 1.24 (s, 3H), 1.19 (dd, *J* = 13.6, 4.3 Hz, 1H), 1.02 – 0.92 (m, 1H), 0.75 (s, 3H).

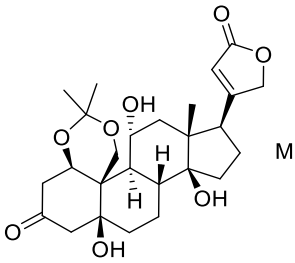
^{13}C-NMR (151 MHz, DMSO-d_6): δ [ppm] = 174.9, 173.7, 116.0, 99.3, 82.4, 73.2, 73.1, 66.6, 65.6, 65.4, 60.3, 49.0, 48.3, 46.9, 46.4, 45.7, 36.9, 36.6, 32.9, 31.8, 30.6, 26.0, 24.5, 24.0, 22.5, 17.5.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{26}H_{38}NaO_8$: 501.2460, found 501.2459.

LRMS (ESI) = *m/z* 479 (100%) $[M+H]^+$.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3495, 3424, 3364, 2944, 2924, 2864, 1733, 1625, 1225, 1154, 1093, 1074, 1026, 856, 528, 468.

(3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,12a*S*,14a*R*,14b*S*)-5,12a,14b-trihydroxy-3a,8,8-trimethyl-3-(5-oxo-2,5-dihydrofuran-3-yl)tetradecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-11(1*H*)-one (I-90)



$C_{26}H_{36}O_8$
M: 476,57 g/mol

Platin(IV)oxide hydrate (0.13 g, 0.59 mmol, 0.70 equiv) is initially charged in a round-bottom flask, degassed under aspirator vacuum and refilled with N_2 five times. Ethyl acetate (0.05 M) is added and the mixture is hydrogenated under H_2 (1 atm) for 30 min, whereupon the fine brown PtO_2 has become black and granular platinum. Subsequently, it is washed several times with nitrogen to remove hydrogen and 4-((3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*,14b*S*)-5,11,12a,14b-tetrahydroxy-3a,8,8-trimethylhexadecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-3-yl)furan-2(5*H*)-one **I-25** (0.40 g, 0.84 mmol, 1.0 equiv) and water (0.21 M) are added and the reaction mixture is charged with O_2. Under O_2 (1 atm), the mixture is strongly stirred for 24 h at room temperature. The suspension is filtered through celite to remove platinum, repeatedly washed with acetone and ethyl acetate. The solvent is evaporated in vacuo and the crude product is purified by column chromatography (DCM → DCM/MeOH 9/1) to give **I-90** (0.35 g, 0.73 mmol) as white crystalline product in 88% yield.

Characterization:

R_f = 0.45 (DCM/MeOH 9/1) [CAM].

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 5.92 (s, 1H), 5.58 (dd, *J* = 5.3, 2.4 Hz, 1H), 5.30 (s, 1H), 4.97 – 4.89 (m, 1H), 4.85 – 4.70 (m, 2H), 4.37 (d, *J* = 12.6 Hz, 1H), 4.22 (tt, *J* = 9.5, 4.4 Hz, 1H), 3.91 (d, *J* = 12.6 Hz, 1H), 2.95 (d, *J* = 14.3 Hz, 1H), 2.87 (dt, *J* = 15.9, 6.0 Hz, 2H), 2.49 (dt, *J* = 15.9, 2.6 Hz, 1H), 2.30 – 2.12 (m, 3H), 1.96 – 1.89 (m, 2H), 1.82 – 1.70 (m, 3H), 1.65 – 1.55 (m, 3H), 1.51 – 1.44 (m, 2H), 1.39 (s, 3H), 1.35 (s, 3H), 1.17 (qd, *J* = 13.0, 5.0 Hz, 1H), 0.97 (s, 3H).

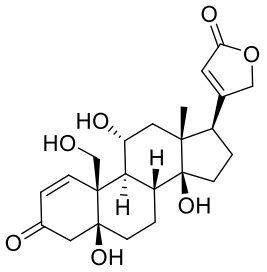
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 209.1, 174.4, 173.3, 118.4, 101.9, 84.0, 79.5, 73.5, 73.1, 67.3, 60.9, 50.3, 49.8, 49.6, 49.6, 46.9, 46.6, 42.8, 40.8, 36.7, 33.6, 26.8, 24.1, 23.5, 23.5, 17.1.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{26}H_{36}NaO_8$: 499.2304, found 499.2302.

LRMS (ESI) = *m/z* 494 (100%) $[M+H_2O]^+$, 477 (8%) $[M+H]^+$.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3422, 2936, 2360, 1714, 1621, 1378, 1220, 1116, 891, 731, 697.

4-((5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-5,11,14-trihydroxy-10-(hydroxymethyl)-13-methyl-3-oxo-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phenanthren-17-yl)furan-2(5*H*)-one (I-91)



$C_{23}H_{30}O_7$
M: 418,49 g/mol

(3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,12a*S*,14a*R*,14b*S*)-5,12a,14b-trihydroxy-3a,8,8-trimethyl-3-(5-oxo-2,5-dihydrofuran-3-yl)tetradecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-11(1*H*)-one **I-90** (35.0 mg, 73.4 µmol, 1.0 equiv) is dissolved in ethanol (0.04 M) and sodium carbonate is added (78.0 mg, 0.73 mmol, 10.0 equiv). The reaction is stirred for 1 h at room temperature. The suspension is filtered to remove sodium carbonate, washed with ethanol and the solvent is evaporated by Lyophilizer.
The crude product is purified by column chromatography (DCM → DCM/MeOH 9/1) to give **I-91** (27.5 mg, 65.7 µmol) as white solid in 89% yield.

Characterization:

R_f = 0.16 (DCM/MeOH 9/1) [UV, CAM].

^{1}H NMR (400 MHz, CD_3OD): δ [ppm] = 7.44 (d, *J* = 10.5 Hz, 1H), 5.96 – 5.88 (m, 2H), 5.02 (dd, *J* = 18.5, 1.9 Hz, 1H), 4.90 (dd, *J* = 18.3, 1.8 Hz, 1H), 4.35 (d, *J* = 11.1 Hz, 1H), 4.09 (d, *J* = 11.1 Hz, 1H), 3.88 (s, 1H), 3.10 (d, *J* = 17.1 Hz, 1H), 2.85 (dd, *J* = 9.3, 5.3 Hz, 1H), 2.27 – 2.10 (m, 2H), 2.11 – 1.98 (m, 3H), 1.81 – 1.61 (m, 5H), 1.46 (t, *J* = 12.3 Hz, 1H), 1.40 – 1.25 (m, 2H), 0.94 (s, 3H).

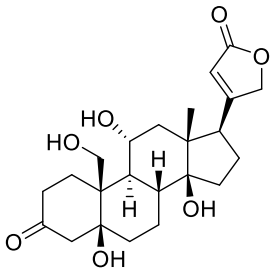
^{13}C-NMR (151 MHz, CD_3OD): δ [ppm] = 201.7, 177.6, 177.2, 160.3, 126.7, 118.4, 85.5, 79.8, 75.4, 68.0, 64.0, 54.6, 51.8, 51.3, 50.4, 48.7, 47.3, 41.5, 37.3, 33.4, 28.0, 25.8, 17.4.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{23}H_{30}NaO_7$: 441.1885, found 441.1884.

LRMS (ESI) = m/z 436 (100%) $[M+H_2O]^+$, 419 (68%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3454, 2923, 1752, 1645, 1369, 1167, 1016, 782, 529, 477, 448, 432.

4-((5*S*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-5,11,14-trihydroxy-10-(hydroxymethyl)-13-methyl-3-oxohexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)furan-2(5*H*)-one (I-92)



$C_{23}H_{32}O_7$
M: 420,50 g/mol

4-((5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-5,11,14-trihydroxy-10-(hydroxymethyl)-13-methyl-3-oxo-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phenanthren-17-yl)furan-2(5*H*)-one **I-91** (49.0 mg, 0.12 mmol, 1.0 equiv) and palladium on activated charcoal 10% (25.0 mg, 23.42 µmol, 20.0 mol%) are suspended in acetic acid (0.09 M) under N_2 atmosphere. The solution is hydrogenated with H_2 (1 atm) for 3 h at room temperature. The suspension is filtered by celite to remove palladium and the solvent evaporated in vacuo. The crude product is purified by column chromatography (DCM → DCM/MeOH 9/1) to give **I-92** (33.0 mg, 78.48 µmol) as white crystalline solid in 67% yield.

Characterization:

R_f = 0.16 (DCM/MeOH 9/1) [CAM].

^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 5.92 (s, 1H), 5.09 – 4.98 (m, 1H), 4.92 (dd, *J* = 18.3, 1.8 Hz, 1H), 4.31 (d, *J* = 11.1 Hz, 1H), 3.90 (d, *J* = 11.1 Hz, 2H), 3.06 (d, *J* = 15.0 Hz, 1H), 2.92 (dd, *J* = 9.0, 5.6 Hz, 1H), 2.82 – 2.69 (m, 2H), 2.50 – 2.36 (m, 1H), 2.29 – 2.14 (m, 3H), 2.13 – 2.00 (m, 2H), 1.99 – 1.84 (m, 3H), 1.81 – 1.68 (m, 2H), 1.59 (dd, *J* = 13.1, 11.2 Hz, 1H), 1.56 – 1.49 (m, 1H), 1.30 (qd, *J* = 13.6, 4.4 Hz, 2H), 0.94 (s, 3H).

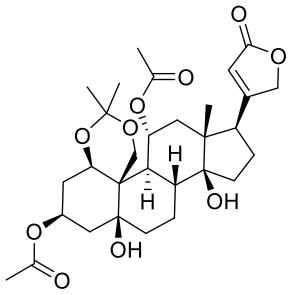
^{13}C-NMR (101 MHz, CD_3OD): δ [ppm] = 215.2, 177.5, 177.1, 118.1, 85.6, 80.9, 75.3, 68.5, 65.3, 51.7, 51.1, 50.7, 50.3, 45.9, 44.2, 40.9, 38.5, 37.3, 33.3, 28.8, 27.9, 25.6, 17.5.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{23}H_{32}NaO_7$: 443.2056, found 443.2040.

LRMS (ESI) = *m/z* 438 (100%) $[M+H_2O]^+$, 421 (47%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3329, 2922, 2851, 1699, 1621, 1435, 1346, 1259, 1169, 1023, 957, 888.

(3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*,14b*S*)-12a,14b-dihydroxy-3a,8,8-trimethyl-3-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxine-5,11-diyl diacetate (I-27)



$C_{30}H_{42}O_{10}$
M: 562,66 g/mol

4-((3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*,14b*S*)-5,11,12a,14b-tetrahydroxy-3a,8,8-trimethylhexadecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-3-yl)furan-2(5*H*)-one **I-25** (0.80 g, 1.68 mmol, 1.0 equiv) is dissolved in pyridine (0.09 M) followed by the addition of acetic anhydride (3.18 mL, 33.60 mmol, 20.0 equiv) at room temperature. The solution is stirred for 24 h at 55 °C, then quenched with water and extracted with dichloromethane. The combined organic phases are washed repeatedly with water and brine, dried over Na_2SO_4 and filtered. The solvent is evaporated in vacuo and the crude product is purified by column chromatography (EtOAc/CH 8/2 → 9/1) to give **I-27** (0.88 g, 1.57 mmol) as white solid in 93% yield.

Characterization:

R_f = 0.50 (DCM/MeOH 9/1) [CAM].

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 5.87 (s, 1H), 5.26 (td, *J* = 9.5, 5.1 Hz, 1H), 5.21 (tt, *J* = 4.4, 2.3 Hz, 1H), 4.88 – 4.82 (m, 1H), 4.77 (dd, *J* = 17.9, 1.8 Hz, 1H), 4.55 (d, *J* = 4.8 Hz, 1H), 4.45 (d, *J* = 12.4 Hz, 1H), 4.34 (t, *J* = 3.4 Hz, 1H), 3.75 (d, *J* = 12.4 Hz, 1H), 2.78 (ddd, *J* = 23.3, 9.0, 6.2 Hz, 1H), 2.15 – 2.05 (m, 5H), 2.04 (s, 3H), 2.02 (s, 3H), 1.96 – 1.86 (m, 3H), 1.82 (dt, *J* = 15.3, 2.4 Hz, 1H), 1.78 – 1.66 (m, 3H), 1.55 (dt, *J* = 14.0, 3.5 Hz, 1H), 1.47 – 1.39 (m, 3H), 1.38 (s, 3H), 1.24 (s, 3H), 1.13 (qd, *J* = 13.7, 3.9 Hz, 1H), 0.95 (s, 3H).

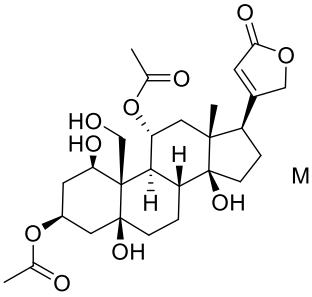
^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 174.1, 172.5, 170.5, 169.2, 118.3, 101.2, 83.7, 73.4, 72.9, 70.4, 68.7, 67.1, 60.5, 49.9, 48.9, 46.9, 44.0, 43.8, 41.0, 35.9, 35.4, 33.7, 28.8, 26.8, 24.4, 23.5, 23.3, 21.7, 21.6, 17.0.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{30}H_{42}NaO_{10}$: 585.2671, found 585.2670.

LRMS (ESI) = *m/z* 563 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3510, 2935, 1729, 1370, 1231, 1020, 956, 828, 705, 605, 501, 447.

(1*R*,3*S*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-1,5,14-trihydroxy-10-(hydroxymethyl)-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,11-diyl diacetate (I-28)



$C_{27}H_{38}O_{10}$
M: 522,59 g/mol

(3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*,14b*S*)-12a,14b-dihydroxy-3a,8,8-trimethyl-3-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxine-5,11-diyl diacetate **I-27** (0.72 g, 1.27 mmol, 1.0 equiv) is dissolved in methanol (0.07 M) and trifluoroacetic acid (0.49 mL, 6.37 mmol, 5.0 equiv) is added. The reaction is stirred for 3 days at room temperature. The solvent is evaporated in vacuo and the crude product is purified by column chromatography (DCM → DCM/MeOH 9/1) to give **I-28** (0.62 g, 1.19 mmol) as white crystalline compound in 94% yield.

Characterization:

R_f = 0.40 (DCM/MeOH 9/1) [CAM].

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 5.89 (s, 1H), 5.28 (s, 1H), 5.15 (dq, *J* = 10.2, 4.7 Hz, 1H), 4.90 – 4.85 (m, 1H), 4.77 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.64 (s, 1H), 4.57 (d, *J* = 11.9 Hz, 1H), 4.13 – 4.08 (m, 1H), 2.77 (dd, *J* = 9.3, 5.9 Hz, 1H), 2.25 (dd, *J* = 15.6, 4.3 Hz, 2H), 2.21 – 2.13 (m, 2H), 2.13 – 2.09 (m, 1H), 2.07 (s, 3H), 2.05 (d, *J* = 9.5 Hz, 1H), 2.00 (s, 3H), 1.92 (ddt, *J* = 13.2, 8.9, 4.7 Hz, 1H), 1.86 (dd, *J* = 13.5, 4.6 Hz, 1H), 1.82 – 1.74 (m, 4H), 1.68 (td, *J* = 13.9, 4.5 Hz, 2H), 1.56 – 1.52 (m, 2H), 1.39 – 1.34 (m, 1H), 1.26 (s, 3H), 0.99 (s, 3H).

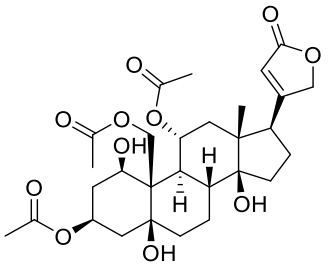
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 174.2, 172.8, 170.6, 169.6, 118.5, 84.4, 75.1, 73.5, 71.9, 70.6, 68.8, 63.0, 50.0, 49.4, 46.8, 44.9, 44.3, 40.5, 36.2, 35.9, 33.4, 31.0, 26.9, 23.5, 21.8, 21.7, 16.7.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{27}H_{38}NaO_{10}$: 545.2355, found 545.2357.

LRMS (ESI) = *m/z* 523 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3373, 2945, 1724, 1367, 1235, 1023, 800, 731, 697, 494.

(1*R*,3*S*,5*S*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-10-(acetoxymethyl)-1,5,14-trihydroxy-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,11-diyl diacetate (I-93a)



$C_{29}H_{40}O_{11}$
M: 564,63 g/mol

(1*R*,3*S*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-1,5,14-trihydroxy-10-(hydroxymethyl)-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,11-diyl diacetate **I-28** (0.35 g, 0.67 mmol, 1.0 equiv) is dissolved in dichloromethane (0.10 M) and pyridine (0.22 ml, 2.69 mmol, 4.0 equiv) and acetic anhydride (0.25 ml, 2.69 mmol, 4.0 equiv) are added. The solution is stirred for 16 h at room temperature. The solution is washed with HCl solution (1 M) and the aqueous phase extracted with dichloromethane. The combined organic phases are washed with brine, dried over Na_2SO_4, filtered and the solvent is evaporated in vacuo. The crude product is purified by column chromatography (EtOAc/CH 8/2 → 9/1) to give **I-93a** (0.30 g, 0. 54mmol) as white crystalline solid in 80% yield.

Characterization:

R_f = 0.46 (DCM/MeOH 9/1) [CAM].

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 5.89 (s, 1H), 5.27 (d, *J* = 4.6 Hz, 1H), 5.21 (d, *J* = 12.7 Hz, 1H), 4.95 – 4.87 (m, 1H), 4.77 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.61 (d, *J* = 12.7 Hz, 1H), 4.34 (s, 1H), 2.76 (dd, *J* = 9.2, 5.5 Hz, 1H), 2.31 (dd, *J* = 15.7, 4.3 Hz, 2H), 2.24 – 2.12 (m, 3H), 2.11 (s, 3H), 2.06 (s, 3H), 2.02 (s, 1H), 1.97 (s, 3H), 1.95 – 1.88 (m, 2H), 1.88 – 1.75 (m, 5H), 1.67 (td, *J* = 14.1, 4.7 Hz, 2H), 1.46 (d, *J* = 6.4 Hz, 2H), 1.35 – 1.24 (m, 3H), 0.99 (s, 3H).

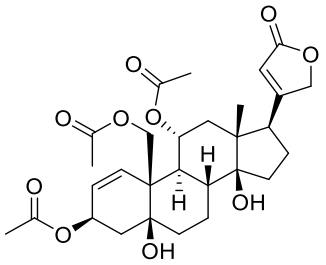
^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 174.2, 172.9, 172.6, 170.7, 169.4, 118.5, 84.4, 73.8, 73.5, 70.9, 68.7, 68.5, 62.6, 50.1, 49.4, 47.6, 44.9, 44.1, 40.6, 36.8, 35.2, 33.5, 30.4, 26.8, 23.9, 21.7, 21.6, 21.2, 16.2.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{29}H_{40}NaO_{11}$: 587.2463, found 587.2463.

LRMS (ESI) = *m/z* 565 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3459, 2937, 1723, 1619, 1431, 1376, 1237, 1023, 606, 500, 450.

(3*R*,5*S*,8*R*,9*S*,10R,11*R*,13*R*,14*S*,17*R*)-10-(acetoxymethyl)-5,14-dihydroxy-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phenanthrene-3,11-diyl diacetate (I-94a)



$C_{29}H_{38}O_{10}$
M: 546,61 g/mol

(1*R*,3*S*,5*S*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-10-(acetoxymethyl)-1,5,14-trihydroxy-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,11-diyl diacetate **I-93a** (0.40 g, 0.70 mmol, 1.0 equiv) is dissolved in dry tetrahydrofuran (0.035 M) and *Martin's Sulfurane* reagent (0.57 g, 0.84 mmol, 1.20 equiv) dissolved in tetrahydrofuran (0.035 M) is added dropwise under N_2 atmosphere. The solution is stirred for 2 h at room temperature. The solvent is evaporated under vacuo and the crude product is purified by column chromatography (EtOAc/CH 8/2 → 9/1) to give **I-94a** (0.26 g, 0.70 mmol) as white crystalline solid in 67% yield.

(Note: Martin's Sulfurane is handled and weighed inside the glove box)

Characterization:

R_f = 0.55 (DCM/MeOH 9/1) [CAM].

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 5.98 (dd*, J* = 10.5, 1.2 Hz, 1H), 5.89 (s, 1H), 5.81 (ddd*, J* = 10.5, 4.0, 1.5 Hz, 1H), 5.42 (t*, J* = 5.1 Hz, 1H), 5.12 (td*, J* = 10.9, 4.5 Hz, 1H), 4.90 (dd*, J* = 18.0, 1.9 Hz, 1H), 4.77 (dd*, J* = 18.0, 1.8 Hz, 1H), 4.56 (d*, J* = 12.2 Hz, 1H), 4.52 (s, 1H), 2.57 (dd*, J* = 15.8, 6.3 Hz, 1H), 2.21 – 2.14 (m, 2H), 2.07 (d*, J* = 2.0 Hz, 6H), 2.02 (s, 3H), 1.88 (dd*, J* = 13.0, 4.5 Hz, 2H), 1.85 – 1.79 (m, 3H), 1.77 (d*, J* = 11.2 Hz, 2H), 1.75 – 1.71 (m, 2H), 1.68 – 1.61 (m, 2H), 1.35 – 1.28 (m, 3H), 0.99 (s, 3H).

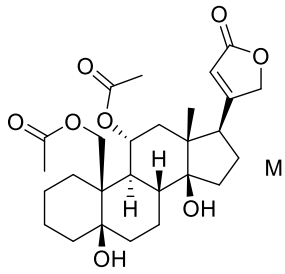
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 174.2, 173.1, 173.1, 170.1, 169.6, 135.7, 122.0, 118.5, 84.5, 73.5, 70.8, 70.5, 65.7, 63.5, 50.2, 49.7, 49.4, 45.4, 44.8, 40.3, 35.8, 34.4, 33.2, 26.9, 23.7, 21.8, 21.4, 21.2, 16.3.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{29}H_{38}NaO_{10}$: 569.2356, found 569.2357.

LRMS (ESI) = *m/z* 548 (7.8%) $[M+H]^+$, 564 (100%) $[M+H_2O]^+$.

IR (ATR): ṽ [cm^{-1}] = 3478, 2936, 2874, 1724, 1371, 1232, 1025, 973, 921, 893, 868, 605, 499.

((5*R*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-11-acetoxy-5,14-dihydroxy-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-10*H*-cyclopenta[*a*]phenanthren-10-yl)methyl acetate (I-96a)



$C_{27}H_{38}O_8$
M: 490,59 g/mol

(3*R*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-10-(acetoxymethyl)-5,14-dihydroxy-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phenanthrene-3,11-diyl diacetate **I-94a** (0.16 g, 0.30 mmol, 1.0 equiv) is dissolved in acetic acid (0.07 M) followed by the addition of palladium on activated charcoal 10% (0.16 g, 0.15 mmol, 50.0 mol%) under N_2 atmosphere. The solution is hydrogenated under H_2 atmosphere (1 atm) for 5 h at room temperature. The suspension is filtered by celite to remove palladium and the solvent evaporated in vacuo. The crude product is purified by column chromatography (DCM → DCM/MeOH 9/1) to give **I-96a** (0.10 g, 0.20 mmol) as white crystalline solid in 68% yield.

Characterization:

R_f = 0.47 (DCM/MeOH 9/1) [CAM].

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 5.88 (s, 1H), 5.19 (td, *J* = 10.7, 4.7 Hz, 1H), 4.95 – 4.82 (m, 1H), 4.77 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.39 (d, *J* = 12.0 Hz, 1H), 2.79 – 2.72 (m, 1H), 2.28 – 2.18 (m, 2H), 2.04 (s, 3H), 1.99 (s, 3H), 1.95 – 1.88 (m, 2H), 1.84 (ddd, *J* = 14.4, 7.9, 4.5 Hz, 3H), 1.78 – 1.71 (m, 2H), 1.66 – 1.47 (m, 9H), 1.39 (td, *J* = 12.9, 5.9 Hz, 2H), 1.28 – 1.15 (m, 2H), 0.96 (s, 3H).

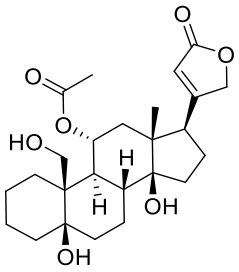
^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 174.2, 173.1, 171.5, 169.8, 118.4, 84.7, 73.5, 72.7, 71.0, 66.1, 50.2, 49.5, 45.0, 44.2, 41.7, 40.5, 36.4, 33.5, 33.4, 27.2, 26.9, 23.9, 21.6, 21.3, 21.2, 20.2, 16.5.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{27}H_{38}NaO_8$: 513.2444, found 513.2459.

LRMS (ESI) = *m/z* 491 (32%) $[M+H]^+$, 508 (100%) $[M+H_2O]^+$.

IR (ATR): ṽ [cm^{-1}] = 3450, 3112, 3005, 2934, 2867, 1731, 1703, 1620, 1450, 1363, 1242, 1027, 710, 579, 424.

(5*R*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-5,14-dihydroxy-10-(hydroxymethyl)-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-1*H*-cyclopenta[a]phenanthren-11-yl acetate (I-97a)



$C_{25}H_{36}O_7$
M: 448,56 g/mol

((5*R*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-11-acetoxy-5,14-dihydroxy-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-10*H*-cyclopenta[*a*]phenanthren-10-yl)methyl acetate **I-96a** (63.0 mg, 128.0 µmol, 1.0 equiv) is dissolved in methanol (0.05 M) and water (0.54 M) followed by the addition of sodium carbonate (0.14 g, 1.28 mmol, 10.0 equiv). The solution is stirred for 1 h at room temperature. The *pH* of the solution is neutralized with trifluoroacetic acid and the dry load is directly prepared. The crude product is purified by column chromatography (DCM → DCM/MeOH 9/1) to give **I-97a** (46.0 mg, 0.10 mmol) as white crystalline solid in 80% yield.

Characterization:

R_f = 0.40 (DCM/MeOH 9/1) [CAM].

^{1}H-NMR (400 MHz, CD_3OD): δ [ppm] = 5.91 (d, *J* = 1.9 Hz, 1H), 5.13 (td, *J* = 10.3, 4.7 Hz, 1H), 4.98 (dd, *J* = 18.4, 1.8 Hz, 1H), 4.90 (dd, *J* = 18.3, 1.8 Hz, 1H), 4.23 (s, 1H), 3.65 – 3.60 (m, 1H), 2.88 (t, *J* = 7.3 Hz, 1H), 2.32 (dd, *J* = 12.4, 10.3 Hz, 1H), 2.24 – 2.15 (m, 2H), 2.14 – 2.00 (m, 4H), 1.98 (s, 3H), 1.93 – 1.89 (m, 1H), 1.87 (q, *J* = 2.5 Hz, 1H), 1.85 – 1.79 (m, 1H), 1.78 – 1.70 (m, 4H), 1.59 – 1.44 (m, 6H), 1.41 – 1.29 (m, 2H), 1.18 – 1.12 (m, 1H), 0.93 (s, 3H).

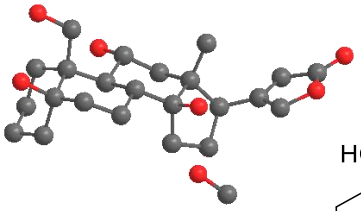
^{13}C-NMR (101 MHz, CD_3OD): δ [ppm] = 177.0, 177.0, 171.8, 118.1, 85.2, 76.0, 75.2, 71.8, 66.0, 51.3, 50.6, 45.7, 44.5, 42.7, 40.9, 37.8, 34.0, 33.4, 28.0, 27.8, 25.2, 22.6, 21.7, 21.5, 17.2.

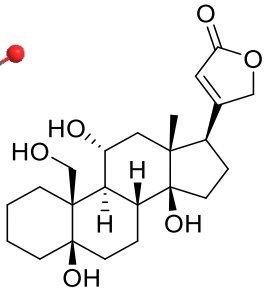
HRMS (ESI-TOF) = *m/z* calcd. for $C_{25}H_{36}NaO_7$: 471.2353, found 471.2354.

LRMS (ESI) = *m/z* 449 (48.5%) $[M+H]^+$, 466 (100%) $[M+H_2O]^+$.

IR (ATR): ṽ [cm^{-1}] = 3362, 2933, 2866, 1727, 1622, 1376, 1240, 1022, 891, 732, 606.

4-((3*R*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-3,5,11,14-tetrahydroxy-10-(hydroxymethyl)-13-methyl-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[a]phenanthren-17-yl)furan-2(5*H*)-one (I-76)





$C_{23}H_{34}O_6$
M: 406,52 g/mol

((5*R*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-11-acetoxy-5,14-dihydroxy-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-10*H*-cyclopenta[*a*]phenanthren-10-yl)methyl acetate **I-96a** (12.0 mg, 24.5 µmol, 1.0 equiv) is dissolved in methanol (0.05 M) and water (0.54 M) followed by the addition of sodium carbonate (24.0 mg, 0.23 mmol, 10.0 equiv). The solution is stirred for 24 h at room temperature. The *pH* of the solution is neutralized with trifluoroacetic acid and the solvent evaporated in vacuo. The crude product is purified by column chromatography (DCM → DCM/MeOH 9/1) to give **I-76** (5.0 mg, 12.3 µmol) as white crystalline solid in 50% yield.

Characterization:

R_f = 0.15 (DCM/MeOH 9/1) [CAM].

^{1}H-NMR (400 MHz, CD_3OD): δ [ppm] = *impossible to purify, crystalline structure*

^{13}C-NMR (101 MHz, CD_3OD): δ [ppm] =*impossible to purify, crystalline structure*

HRMS (ESI-TOF) = *m/z* calcd. for $C_{23}H_{34}NaO_6$: 429.2248, found 429.2259.

LRMS (ESI) = *m/z* 424 (100%) $[M+H_2O]^+$.

IR (ATR): ṽ [cm^{-1}] = 3350, 2937, 2865, 1723, 1622, 1451, 1253, 1025, 953, 855, 733, 541.

Crystal structure = C1-C2 bond length: (1.528 Å);
C2-C3 bond length: (1.520 Å);
C1-O and C3-O bonds: not present.

Crystal structure analysis of **4-((3R,5S,8R,9S,10R,11R,13R,14S,17R)-3,5,11,14-tetrahydroxy-10-(hydroxymethyl)-13-methyl-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3H-cyclopenta[a]phenanthren-17-yl)furan-2(5H)-one (I-76)**

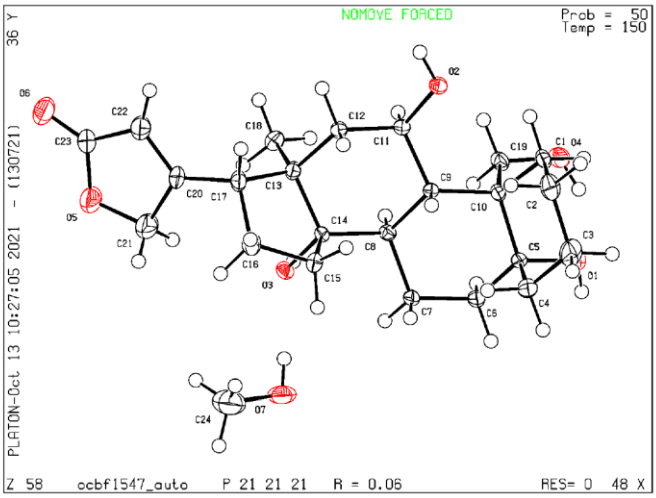


Table 1: Crystal data and structure refinement for I-76

Formula	$C_{24}H_{38}O_7$
Formula weight	438.54
Temperature/K	150
Crystal System	Orthorhombic
Space group	$P2_12_12_1$
a/ Å	7.9750(2)
b/ Å	10.7983(3)
c/ Å	25.9244(8)
α/°	90
β/°	90
γ/°	90
Volume/ Å	2232.52(11)
Z	4
$p_{calc}g/cm^3$	1.305
μ/mm-^{1}	0.094
F(000)	952.0
Crystal size/mm^3	0.15 x 0.03 x 0.02
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.91 to 59.314
Index ranges	-10 ≤ h ≤ 9, -14 ≤ k ≤ 8, -34 ≤ l ≤ 28
Reflections collected	8615
Independent reflections	4668 [R_{int} = 0.0282, R_{sigma} = 0.0504]
Data/restraints/parameters	4668/0/287
Goodness-of-fit on F^2	1.047
Final R indexes [I>2σ (I)]	R_1 = 0.0564, wR_2 = 0.1412
Final R indexes [all data]	R_1 = 0.0707, wR_2 = 0.1506
Largest diff. peak/hole / e Å^{-3}	0.71/-0.38
Flack parameter	0.3(6)

Table 2: Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for I-76. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*Y*	*z*	$U_{(eq)}$
O3	6330 (3)	6700 (2)	5475.2 (8)	16.5 (5)
O4	6452 (3)	11868 (2)	6890.2 (10)	23.6 (6)
O1	9531 (3)	11525 (2)	6579.6 (10)	22.5 (6)
O2	6021 (3)	8054 (3)	7568.6 (9)	27.5 (6)
O7	9071 (4)	6379 (3)	4814.1 (12)	37.4 (7)
O6	696 (4)	2517 (3)	5655.7 (12)	38.5 (7)
O5	2836 (4)	3399 (3)	5248.7 (11)	40.0 (8)
C9	7385 (4)	8393 (3)	6739.3 (12)	12.7 (6)
C14	6736 (4)	6785 (3)	6019.5 (12)	12.8 (6)
C8	7089 (4)	8156 (3)	6154.1 (12)	13.5 (6)
C12	5613 (4)	6513 (3)	6911.7 (12)	16.8 (7)
C5	9311 (4)	10200 (3)	6500.5 (13)	16.6 (7)
C10	7830 (4)	9792 (3)	6858.6 (12)	14.0 (6)
C6	8913 (5)	9994 (3)	5929.7 (13)	20.0 (7)
C13	5305 (4)	6196 (3)	6340.9 (13)	16.0 (7)
C15	8199 (4)	5901 (3)	6101.9 (14)	17.1 (7)
C1	8408 (4)	9992 (3)	7423.9 (13)	17.0 (7)
C19	6247 (4)	10582 (3)	6772.2 (13)	18.0 (7)
C18	3548 (4)	6627 (3)	6183.0 (14)	21.2 (7)
C7	8512 (4)	8645 (3)	5811.5 (13)	20.0 (7)
C17	5589 (5)	4752 (3)	6286.4 (13)	20.0 (7)
C11	5842 (4)	7894 (3)	7026.1 (12)	17.1 (7)
C16	7429 (4)	4601 (3)	6088.5 (15)	22.3 (8)
C20	4334 (5)	4095 (3)	5954.3 (15)	22.8 (8)
C23	2020 (5)	3041 (4)	5693.0 (15)	27.0 (8)
C2	10041 (5)	9334 (4)	7564.0 (15)	26.3 (8)
C4	10960 (4)	9565 (4)	6647.9 (15)	24.1 (8)
C3	11445 (5)	9762 (4)	7209.1 (16)	31.2 (9)
C22	2959 (5)	3494 (4)	6127.4 (16)	32.4 (9)
C21	4355 (6)	4049 (4)	5389.0 (16)	37.4 (10)
C24	9130 (7)	5105 (5)	4730.1 (19)	47.0 (12)

Table 3: Anisotropic Displacement Parameters (Å^2×10^3) for I-76. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O3	20.0 (11)	17.1 (11)	12.2 (11)	-0.6 (9)	0.0 (9)	-1.0 (10)
O4	27.9 (13)	13.4 (11)	29.4 (14)	-1.2 (11)	8.3 (11)	3.9 (11)
O1	29.6 (13)	14.9 (11)	23.1 (13)	-5.2 (10)	6.4 (11)	-8.1 (11)
O2	39.5 (16)	30.9 (14)	12.2 (11)	-5.4 (11)	9.6 (10)	-18.8 (13)
O7	43.4 (17)	32.0 (15)	36.6 (17)	0.8 (13)	24.6 (14)	-3.3 (14)
O6	42.6 (17)	37.2 (17)	35.6 (16)	-0.9 (14)	-0.1 (14)	-19.9 (15)
O5	45.9 (16)	47.3 (19)	26.8 (15)	-5.1 (14)	0.4 (13)	-23.2 (16)
C9	14.0 (14)	12.9 (14)	11.0 (13)	-0.1 (12)	1.3 (11)	-1.1 (12)
C14	14.7 (15)	13.2 (14)	10.4 (14)	-2.0 (12)	0.4 (11)	-1.4 (13)
C8	15.7 (14)	12.4 (14)	12.5 (14)	0.8 (13)	1.4 (12)	1.0 (13)
C12	23.2 (16)	15.9 (15)	11.2 (14)	0.6 (13)	1.9 (13)	-6.1 (14)
C5	19.0 (15)	13.6 (15)	17.3 (15)	-3.7 (13)	6.5 (13)	-3.9 (13)
C10	15.9 (15)	13.4 (15)	12.6 (14)	-2.3 (12)	-0.3 (12)	-0.3 (12)
C6	29.4 (19)	18.2 (16)	12.4 (15)	-1.1 (13)	6.1 (14)	-8.3 (15)
C13	17.3 (15)	15.8 (15)	14.8 (15)	-0.3 (13)	-1.0 (13)	-4.2 (13)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C15	17.4 (16)	15.7 (15)	18.2 (16)	-0.2 (13)	-2.4 (13)	-2.3 (13)
C1	22.1 (17)	15.4 (15)	13.6 (15)	-3.8 (13)	-1.2 (13)	-1.6 (14)
C19	20.1 (16)	15.2 (15)	18.7 (16)	-2.8 (14)	1.7 (13)	2.6 (13)
C18	17.1 (15)	23.6 (17)	22.8 (17)	-1.5 (15)	0.6 (14)	-3.5 (14)
C7	27.2 (17)	18.2 (16)	14.7 (15)	-4.1 (14)	8.0 (14)	-8.6 (15)
C17	27.1 (18)	15.8 (16)	17.0 (16)	-1.0 (13)	-1.2 (14)	-6.7 (15)
C11	20.6 (16)	18.1 (16)	12.7 (15)	-1.3 (13)	3.7 (13)	-5.2 (14)
C16	24.4 (18)	14.9 (15)	27.5 (19)	-0.9 (15)	-3.9 (15)	2.1 (14)
C20	25.1 (17)	15.7 (16)	27.6 (19)	-4.6 (15)	1.5 (16)	-6.5 (15)
C23	28.7 (18)	23.2 (18)	29 (2)	-6.7 (17)	0.6 (16)	-6.0 (16)
C2	26.5 (18)	28.6 (19)	23.8 (19)	-4.4 (16)	-10.8 (15)	0.4 (16)
C4	17.7 (16)	25.7 (18)	28.8 (19)	-7.1 (16)	5.6 (14)	-2.7 (15)
C3	19.4 (18)	37 (2)	38 (2)	-6.1 (19)	-8.4 (16)	-2.0 (17)
C22	41 (2)	32 (2)	24.0 (19)	-4.0 (17)	2.5 (18)	-15.2 (19)
C21	40 (2)	45 (3)	27 (2)	-4 (2)	1.1 (18)	-18 (2)
C24	55 (3)	46 (3)	40 (3)	2 (2)	18 (2)	3 (2)

Table 4: Bond Lengths for I-76.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O3	C14	1.451 (4)	C5	C10	1.566 (4)
O4	C19	1.431 (4)	C5	C6	1.530 (4)
O1	C5	1.456 (4)	C5	C4	1.531 (5)
O2	C11	1.424 (4)	C10	C1	1.551 (5)
O7	C24	1.394 (4)	C10	C19	1.540 (5)
O6	C23	1.202 (4)	C6	C7	1.523 (5)
O5	C23	1.378 (4)	C13	C18	1.532 (5)
O5	C21	1.446 (4)	C13	C17	1.583 (4)
C9	C8	1.556 (4)	C15	C16	1.533 (5)
C9	C10	1.583 (4)	C1	C2	1.528 (5)
C9	C11	1.535 (4)	C17	C16	1.563 (5)
C14	C8	1.546 (4)	C17	C20	1.499 (5)
C14	C13	1.549 (4)	C20	C22	1.350 (5)
C14	C15	1.523 (4)	C20	C21	1.467 (5)
C8	C7	1.535 (4)	C23	C22	1.438 (5)
C12	C13	1.538 (4)	C2	C3	1.520 (6)
C12	C11	1.532 (5)	C4	C3	1.520 (5)

Table 5: Bond Angles for I-76.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C23	O5	C21	108.7 (3)	C12	C13	C14	108.0 (3)
C8	C9	C10	112.4 (2)	C12	C13	C17	106.4 (3)
C11	C9	C8	107.0 (2)	C18	C13	C14	113.9 (3)
C11	C9	C10	114.8 (3)	C18	C13	C12	109.6 (3)
O3	C14	C8	108.7 (2)	C18	C13	C17	113.9 (3)
O3	C14	C13	109.5 (2)	C14	C15	C26	105.3 (3)
O3	C14	C15	105.5 (2)	C2	C1	C10	114.4 (3)
C8	C14	C13	113.9 (3)	O4	C19	C10	114.3 (3)
C15	C14	C8	115.4 (3)	C6	C7	C8	111.6 (3)
C15	C14	C13	103.4 (3)	C16	C17	C13	105.4 (3)
C14	C8	C9	113.9 (2)	C20	C17	C13	115.0 (3)
C7	C8	C9	113.3 (3)	C20	C17	C13	112.9 (3)
C7	C8	C14	109.5 (3)	O2	C11	C9	110.8 (3)

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C11	C12	C13	114.9 (3)	O2	C11	C12	108.7 (3)
O1	C5	C10	106.5 (3)	C12	C11	C9	110.1 (3)
O1	C5	C6	107.7 (3)	C15	C16	C17	105.9 (3)
O1	C5	C4	107.5 (3)	C22	C20	C17	125.4 (3)
C6	C5	C10	112.1 (3)	C22	C20	C21	109.0 (3)
C6	C5	C4	110.8 (3)	C21	C20	C17	125.6 (3)
C4	C5	C10	112.0 (3)	O6	C23	O5	118.6 (4)
C5	C10	C9	108.8 (2)	O6	C23	C22	132.9 (4)
C1	C10	C9	112.6 (3)	O5	C23	C22	108.3 (3)
C1	C10	C5	107.3 (3)	C3	C2	C1	110.0 (3)
C19	C10	C9	108.5 (3)	C3	C4	C5	113.2 (3)
C19	C10	C5	112.1 (3)	C4	C3	C2	110.5 (3)
C19	C10	C1	107.7 (3)	C20	C22	C23	109.0 (4)
C7	C6	C5	112.1 (3)	O5	C21	C20	105.0 (3)
C14	C13	C17	104.6 (3)				

Table 6: Torsion Angles for I-76.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
O3	C14	C8	C9	174.8 (2)	C6	C5	C10	C1	177.7 (3)
O3	C14	C8	C7	-57.2 (3)	C6	C5	C10	C19	-64.3 (3)
O3	C14	C13	C12	-169.7 (2)	C6	C5	C4	C3	178.7 (3)
O3	C14	C13	C18	-47.7 (3)	C13	C14	C8	C9	52.5 (3)
O3	C14	C13	C17	77.3 (3)	C13	C14	C8	C7	-179.6 (3)
O3	C14	C15	C16	-75.1 (3)	C13	C14	C15	C16	39.9 (3)
O1	C5	C10	C9	173.2 (2)	C13	C12	C11	O2	176.8 (3)
O1	C5	C10	C1	-64.8 (3)	C13	C12	C11	C9	-61.6 (4)
O1	C5	C10	C19	53.2 (3)	C13	C17	C16	C15	7.0 (3)
O1	C5	C6	C7	-175.2 (3)	C13	C17	C20	C22	-96.5 (5)
O1	C5	C4	C3	61.3 (4)	C13	C17	C20	C21	80.5 (5)
O6	C23	C22	C20	-175.8 (4)	C15	C14	C8	C9	-67.0 (3)
O5	C23	C22	C20	-1.1 (5)	C15	C14	C8	C7	61.0 (4)
C9	C8	C7	C6	-51.6 (4)	C15	C14	C13	C12	78.2 (3)
C9	C10	C1	C2	64.3 (4)	C15	C14	C13	C18	-159.8 (3)
C9	C10	C19	O4	177.2 (3)	C15	C14	C13	C17	-34.8 (3)
C14	C8	C7	C6	-179.9 (3)	C1	C10	C19	O4	55.1 (4)
C14	C13	C17	C16	17.0 (3)	C1	C2	C3	C4	-55.5 (4)
C14	C13	C17	C20	-108.0 (3)	C19	C10	C1	C2	-176.2 (3)
C14	C15	C16	C17	-29.1 (3)	C18	C13	C17	C16	142.0 (3)
C8	C9	C10	C5	-51.9 (3)	C18	C13	C17	C20	17.0 (4)
C8	C9	C10	C1	-170.6 (3)	C17	C20	C22	C23	176.9 (4)
C8	C9	C10	C19	70.3 (3)	C17	C20	C21	O5	-175.6 (3)
C8	C9	C11	O2	178.9 (3)	C11	C9	C8	C14	-55.8 (3)
C8	C9	C11	C12	58.6 (3)	C11	C9	C8	C7	178.2 (3)
C8	C14	C13	C12	-47.8 (3)	C11	C9	C10	C5	-174.6 (3)
C8	C14	C13	C18	74.2 (3)	C11	C9	C10	C1	66.7 (3)
C8	C14	C13	C17	-160.8 (3)	C11	C9	C10	C19	-52.4 (3)
C8	C14	C15	C16	164.9 (3)	C11	C12	C13	C14	53.5 (4)
C12	C13	C17	C16	-97.1 (3)	C11	C12	C13	C18	-71.1 (4)
C12	C13	C17	C20	137.9 (3)	C11	C12	C13	C17	165.2 (3)
C5	C10	C1	C2	-55.4 (4)	C16	C17	C20	C22	142.5 (4)
C5	C10	C19	O4	-62.6 (3)	C16	C17	C20	C21	-40.5 (5)
C5	C6	C7	C8	54.9 (4)	C20	C17	C16	C15	133.3 (3)
C5	C4	C3	C2	55.8 (4)	C23	O5	C21	C20	-2.5 (5)

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C10	C9	C8	C14	177.2 (3)	C4	C5	C10	C9	-69.6 (3)
C10	C9	C8	C7	51.2 (3)	C4	C5	C10	C1	52.4 (3)
C10	C9	C11	O2	-55.5 (4)	C4	C5	C10	C19	170.5 (3)
C10	C9	C11	C12	-175.8 (3)	C4	C5	C6	C7	67.5 (4)
C10	C5	C6	C7	-58.4 (4)	C22	C20	C21	O5	1.8 (5)
C10	C5	C4	C3	-55.4 (4)	C21	O5	C23	O6	177.8 (4)
C10	C1	C2	C3	58.1 (4)	C21	O5	C23	C22	2.3 (5)
C6	C5	C10	C9	55.7 (3)	C21	C20	C22	C23	-0.5 (5)

Table 7: Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for I-76.

Atom	*x*	*Y*	*z*	$U_{(eq)}$
H3	5676.53	7278.8	5394.61	25
H4	7419.54	12096.19	6804.01	35
H1	9829.57	11857.38	6301.46	34
H2	5215.98	7709.91	7720.63	41
H7	8213.65	6554.51	4987.75	56
H9	8368.07	7879.2	6846.72	15
H8	6059.73	8630.75	6057.2	16
H12A	4653.45	6202.41	7116.67	20
H12B	6627.08	6065.72	7029.17	20
H6A	7942.67	10515.56	5831.57	24
H6B	9885.23	10257.67	5719.3	24
H15A	8745.03	6058.42	6438.5	21
H15B	9043.3	5998.4	5824.85	21
H1A	8551.27	10891.42	7484.08	20
H1B	7511.99	9697.35	7658.02	20
H19A	5899.92	10503.06	6407.03	22
H19B	5329.4	10245.57	6988.03	22
H18A	3484.75	7531.18	6206.06	32
H18B	2714.92	6257.07	6414.23	32
H18C	3321.52	6366.63	5827.57	32
H7A	9528.59	8135.67	5866.81	24
H7B	8183.44	8566.54	5444.74	24
H17	5528.24	4382.1	6639.62	24
H11	4824.45	8353.81	6906.91	21
H16A	8064.56	4030.54	6314.58	27
H16B	7438.6	4267.26	5732.81	27
H2A	10339.48	9519.78	7926.54	32
H2B	9891.73	8427.69	7530.71	32
H4A	10857.74	8665.75	6581.48	29
H4B	11867.85	9888.6	6424.76	29
H3A	11675.23	10650.76	7269.89	37
H3B	12479.67	9291.02	7286.75	37
H22	2661.09	3387.38	6479.34	39
H21A	4361.92	4894.25	5241.51	45
H21B	5356.14	3597.36	5263.57	45
H24A	9873.95	4928.49	4438.48	71
H24B	8000.24	4799.73	4652.85	71
H24C	9556.41	4691.96	5039.99	71

Experimental

Single crystals of $C_{24}H_{38}O_7$ [**I-76**] were obtained by recrystallization from dichlomethane/methanol.
A suitable crystal was selected and [] on a Xcalibur, Eos, Gemini ultra diffractometer. The crystal was kept at 150 K during data collection. Using Olex2 [1], the structure was solved with the SHELXT [2] structure solution program using Intrinsic Phasing and refined with the SHELXL [3] refinement package using Least Squares minimisation.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2. Sheldrick, G.M. (2015). Acta Cryst. A71, 3-8.
3. Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

Crystal structure determination of I-76.

Crystal Data for $C_{24}H_{38}O_7$ (*M* =438.54 g/mol):
orthorhombic, space group $P2_12_12_1$ (no. 19), *a*7.9750(2) Å, *b* = 10.7983(3) Å, *c* = 25.9244(8) Å, *V* = 2232.52(11) Å^3, *Z* = 4, *T* = 150 K, μ(Mo Kα) = 0.094 mm^{-1}, *Dcalc* = 1.305 g/cm^3, 8615 reflections measured (4.91° ≤ 2Θ ≤ 59.314°), 4668 unique (R_{int} = 0.0282, R_{sigma} = 0.0504) which were used in all calculations. The final R_1 was 0.0564 (I > 2σ(I)) and wR_2 was 0.1506 (all data).

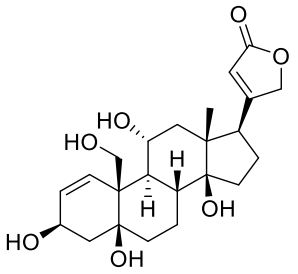
Refinement model description

Number of restraints - 0, number of constraints - unknown.

Details:

```
1. Fixed Uiso
 At 1.2 times of:
  All C(H) groups, All C(H,H) groups
 At 1.5 times of:
  All C(H,H,H) groups, All O(H) groups
2.a Ternary CH refined with riding coordinates:
 C9(H9), C8(H8), C17(H17), C11(H11)
2.b Secondary CH2 refined with riding coordinates:
 C12(H12A,H12B), C6(H6A,H6B), C15(H15A,H15B), C1(H1A,H1B), C19(H19A,H19B),
 C7(H7A,H7B), C16(H16A,H16B), C2(H2A,H2B), C4(H4A,H4B), C3(H3A,H3B), C21(H21A,
 H21B)
2.c Aromatic/amide H refined with riding coordinates:
 C22(H22)
2.d Idealised Me refined as rotating group:
 C18(H18A,H18B,H18C), C24(H24A,H24B,H24C)
2.e Idealised tetrahedral OH refined as rotating group:
 O3(H3), O4(H4), O1(H1), O2(H2), O7(H7)
```

4-((3*R*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-3,5,11,14-tetrahydroxy-10-(hydroxymethyl)-13-methyl-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[a]phenanthren-17-yl)furan-2(5*H*)-one (I-98)



$C_{23}H_{32}O_7$
M: 420,50 g/mol

(3*R*,5*S*,8*R*,9*S*,10R,11*R*,13*R*,14*S*,17*R*)-10-(acetoxymethyl)-5,14-dihydroxy-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phenanthrene-3,11-diyl diacetate **I-94a** (0.21 g, 0.38 mmol, 1.0 equiv) is dissolved in methanol (0.03 M) and water (0.33 M) followed by the addition of sodium carbonate (0.40 g, 0.38 mol, 3.0 equiv). The solution is stirred for 16 h at room temperature. The *pH* of the solution is neutralized with trifluoroacetic acid and the dry load is directly prepared. The crude product is purified by column chromatography (DCM → DCM/MeOH 9/1) to give **I-98** (85.0 mg, 47.6 µmol) as white crystalline solid in 54% yield.

Characterization:

R_f = 0.11 (DCM/MeOH 9/1) [CAM].

^{1}H-NMR (400 MHz, CD_3OD): δ [ppm] = 6.23 (d, *J* = 10.4 Hz, 1H), 5.90 (s, 1H), 5.78 (dd, *J* = 10.4, 2.9 Hz, 1H), 5.01 (dd, *J* = 18.4, 1.9 Hz, 1H), 4.90 (dd, *J* = 18.4, 1.8 Hz, 1H), 4.25 (d, *J* = 11.0 Hz, 1H), 4.18 (t, *J* = 4.6 Hz, 1H), 3.99 (d, *J* = 11.0 Hz, 1H), 3.85 (td, *J* = 10.9, 4.2 Hz, 1H), 2.85 (dd, *J* = 9.4, 5.4 Hz, 1H), 2.41 (dd, *J* = 14.8, 5.1 Hz, 1H), 2.22 – 1.99 (m, 3H), 1.87 (dtd, *J* = 17.5, 8.7, 8.2, 5.2 Hz, 1H), 1.70 (dtd, *J* = 13.3, 7.4, 6.9, 4.3 Hz, 4H), 1.64 – 1.59 (m, 1H), 1.55 – 1.40 (m, 2H), 1.34 – 1.21 (m, 2H), 0.92 (s, 3H).

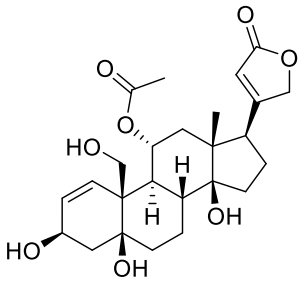
^{13}C-NMR (101 MHz, CD_3OD): δ [ppm] = 177.6, 177.1, 137.7, 126.7, 118.1, 85.5, 76.6, 75.3, 68.5, 65.2, 64.8, 53.6, 51.7, 51.1, 50.7, 46.9, 41.6, 38.7, 37.4, 33.2, 27.9, 24.9, 17.4.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{23}H_{32}NaO_7$: 443.2041, found 443.2040.

LRMS (ESI) = *m/z* 385 (100%) $[M\text{-}2OH]^+$.

IR (ATR): ṽ [cm^{-1}] = 3312, 2922, 1723, 1620, 1413, 1258, 1172, 1026, 822, 692, 569, 281.

(3*R*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-3,5,14-trihydroxy-10-(hydroxymethyl)-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[a]phenanthren-11-yl acetate (I-99a)



$C_{25}H_{34}O_8$
M: 462,54 g/mol

(3*R*,5*S*,8*R*,9*S*,10R,11*R*,13*R*,14*S*,17*R*)-10-(acetoxymethyl)-5,14-dihydroxy-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phenanthrene-3,11-diyl diacetate **I-94a** (0.23 g, 0.42 mmol, 1.0 equiv) is dissolved in methanol (0.03 M) and water (0.33 M) followed by the addition of sodium carbonate (0.45 g, 4.24 mmol, 10 equiv). The solution is stirred for 45 min at room temperature. The *pH* of the solution is neutralized with trifluoroacetic acid and the dry load is directly prepared with silica. The crude product is purified by column chromatography (DCM → DCM/MeOH 9/1) to give **I-99a** (0.16 g, 0.35 mmol) as white crystalline solid in 82% yield.

Characterization:

R_f = 0.32 (DCM/MeOH 9/1) [CAM].

^{1}H NMR (400 MHz, CD_3OD): δ [ppm] = δ 5.91 (td, *J* = 1.8, 0.6 Hz, 1H), 5.85 (ddd, *J* = 10.4, 4.2, 1.5 Hz, 1H), 5.74 (d, *J* = 10.4 Hz, 1H), 5.17 (td, *J* = 10.8, 4.5 Hz, 1H), 5.02 – 4.95 (m, 1H), 4.89 (dd, *J* = 18.4, 1.8 Hz, 1H), 4.20 (dd, *J* = 8.1, 3.6 Hz, 1H), 4.16 (s, 1H), 3.83 (d, *J* = 11.2 Hz, 1H), 2.83 (dd, *J* = 9.3, 5.3 Hz, 1H), 2.47 (dd, *J* = 14.9, 5.3 Hz, 1H), 2.21 – 2.12 (m, 2H), 2.11 – 2.04 (m, 2H), 2.02 (s, 3H), 1.92 – 1.86 (m, 1H), 1.83 (dq, *J* = 9.3, 3.1 Hz, 2H), 1.79 – 1.62 (m, 4H), 1.48 – 1.39 (m, 1H), 1.39 – 1.28 (m, 1H), 0.96 (s, 3H).

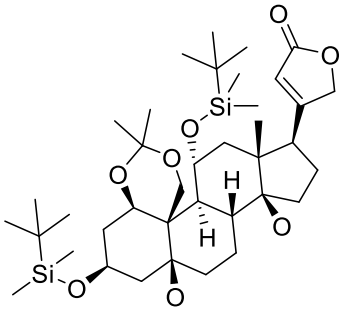
^{13}C-NMR (101 MHz, CD_3OD): δ [ppm] = 177.2, 177.0, 171.8, 135.9, 127.6, 118.3, 85.1, 76.0, 75.2, 71.3, 65.0, 64.4, 51.4, 51.0, 50.5, 46.6, 45.9, 41.4, 38.7, 37.2, 33.1, 27.8, 25.0, 21.7, 16.9.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{25}H_{34}NaO_8$: 485.2146, found 485.2151.

LRMS (ESI) = *m/z* 445 (%) $[M\text{-}OH]^+$.

IR (ATR): ṽ [cm^{-1}] = 3327, 2936, 1727, 1435, 1242, 1135, 1025, 823, 605, 469.

4-((3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*,14b*S*)-5,11-bis((tert-butyldimethylsilyl)oxy)-12a,14b-dihydroxy-3a,8,8-trimethylhexadecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-3-yl)furan-2(5*H*)-one (I-100)



$C_{38}H_{66}O_8Si_2$
M: 707,11 g/mol

4-((3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*,14b*S*)-5,11,12a,14b-tetrahydroxy-3a,8,8-trimethylhexadecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-3-yl)furan-2(5*H*)-one **I-25** (57.0 mg, 0.12 mmol, 1.0 equiv) is dissolved in dimethylformamide (0.12 M) and acetonitrile (0.12 M) followed by the addition of imidazole (41.0 mg, 0.60 mmol, 5.0 equiv) and *tert*-butyldimethylsilyl chloride (90.0 mg, 0.60 mmol, 5.0 equiv). The solution is stirred for 48 h at room temperature, then it is quenched by adding water and the mixture is diluted with ethylacetate. The phases are separated. The aqueous phase is extracted with ethylacetate and the combined organic phases are washed with brine, dried over Na_2SO_4 and filtered.

The solvent is evaporated in vacuo and the crude product is purified by column chromatography (EtOAc/CH 8/2 → 9/1) to give **I-100** (59.0 mg, 83.0 µmol) as white solid in 70% yield.

Characterization:

R_f = 0.60 (DCM/MeOH 9/1) [CAM].

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 5.89 (q, *J* = 1.5 Hz, 1H), 4.91 – 4.86 (m, 1H), 4.78 (dd, *J* = 17.8, 1.8 Hz, 1H), 4.64 (t, *J* = 3.3 Hz, 1H), 4.44 (dd, *J* = 11.9, 1.1 Hz, 1H), 4.33 (ddd, *J* = 8.0, 6.6, 4.8 Hz, 1H), 4.26 (p, *J* = 3.0 Hz, 1H), 3.64 (d, *J* = 12.1 Hz, 1H), 3.00 (t, *J* = 8.2 Hz, 1H), 2.14 (ddd, *J* = 13.1, 10.9, 8.7 Hz, 1H), 2.08 – 2.00 (m, 2H), 1.96 – 1.78 (m, 4H), 1.72 (dd, *J* = 14.1, 4.8 Hz, 1H), 1.67 – 1.55 (m, 4H), 1.54 – 1.47 (m, 2H), 1.37 (s, 3H), 1.30 (s, 3H), 1.22 (s, 1H), 0.91 (d, *J* = 3.4 Hz, 12H), 0.89 (s, 6H), 0.85 (s, 3H), 0.15 (d, *J* = 4.8 Hz, 6H), 0.10 (s, 3H), 0.07 (d, *J* = 2.4 Hz, 6H).

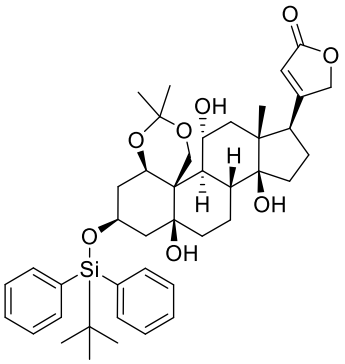
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 174.2, 172.6, 117.8, 100.4, 83.7, 73.5, 73.4, 68.5, 67.7, 66.9, 61.3, 50.1, 49.4, 48.9, 48.5, 47.4, 41.1, 38.1, 37.0, 33.6, 33.1, 27.0, 26.7, 26.3, 25.9, 25.8, 23.4, 18.6, 18.1, 17.9, -2.5, -3.2, -3.4, -4.8, -4.9.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{38}H_{66}NaO_8Si_2$: 729.4183, found 729.4188.

LRMS (ESI) = *m/z* 707 (100%).

IR (ATR): ṽ [cm^{-1}] = 3464, 2928, 1740, 1623, 1362, 1252, 1222, 1026, 868, 831, 772, 448.

4-((3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*,14b*S*)-11-((tert-butyldiphenylsilyl)oxy)-5,12a,14b-trihydroxy-3a,8,8-trimethylhexadecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-3-yl)furan-2(5*H*)-one (I-102)



$C_{42}H_{56}O_8Si$
M: 716,99 g/mol

4-((3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*,14b*S*)-5,11,12a,14b-tetrahydroxy-3a,8,8-trimethylhexadecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-3-yl)furan-2(5*H*)-one **I-25** (0.85 g, 1.78 mmol, 1.0 equiv) is dissolved in dimethylformamide (0.13 M) followed by the addition of imidazole (0.30 g, 4.46 mmol, 2.50 equiv). The mixture is cooled down to 0 °C and stirred for 15 min. Then, *tert*-butyldiphenylsilylchloride (1.16 mL, 4.46 mmol, 2.50 equiv) is added. The solution is stirred for 48 h at 50 °C. Subsequently, the solution is cooled down to room temperature, quenched by adding NH_4Cl and stirred for 30 min. The suspension is extracted with dichloromethane and the combined organic phases are washed with brine, dried over Na_2SO_4 and filtered.
The solvent is evaporated in vacuo and the crude product is purified by column chromatography (EtOAc/CH 7/3 → 8/2) to give **I-102** (1.25 g, 1.75 mmol) as white solid in 98% yield.

Characterization:

R_f = 0.57 (DCM/MeOH 9/1) [UV, CAM].

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.81 – 7.78 (m, 2H), 7.74 – 7.72 (m, 2H), 7.45 – 7.34 (m, 6H), 5.87 (q, *J* = 1.6 Hz, 1H), 5.31 (s, 1H), 5.02 (dd, *J* = 4.4, 2.6 Hz, 1H), 4.89 (dd, *J* = 18.3, 1.9 Hz, 1H), 4.77 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.21 (p, *J* = 3.0 Hz, 1H), 4.15 – 4.10 (m, 1H), 3.73 (d, *J* = 12.1 Hz, 1H), 2.90 – 2.83 (m, 1H), 2.17 (s, 1H), 2.08 (dtd, *J* = 12.5, 8.9, 8.4, 1.5 Hz, 1H), 2.04 (s, 1H), 2.01 – 1.89 (m, 2H), 1.88 – 1.80 (m, 2H), 1.81 – 1.73 (m, 2H), 1.73 – 1.69 (m, 2H), 1.63 (ddd, *J* = 13.5, 8.7, 1.8 Hz, 1H), 1.52 (ddd, *J* = 16.5, 11.8, 3.4 Hz, 2H), 1.47 (s, 3H), 1.36 (s, 3H), 1.35 – 1.23 (m, 4H), 1.06 (s, 9H), 0.92 (s, 3H).

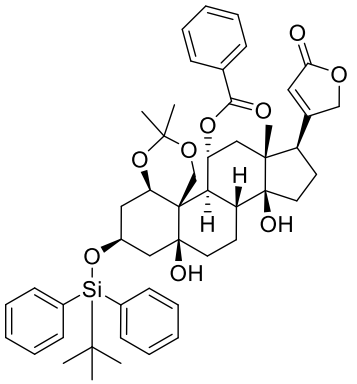
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 174.3, 173.2, 136.4, 136.1, 133.8, 133.5, 129.9, 129.8, 127.8, 127.6, 118.1, 101.4, 84.5, 73.5, 73.1, 68.8, 68.4, 67.3, 60.6, 50.2, 49.4, 48.9, 47.9, 46.3, 41.4, 37.7, 36.5, 33.8, 32.1, 27.0, 26.9, 25.0, 23.4, 22.6, 19.2, 17.7.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{42}H_{56}NaO_8Si$: 739.3637, found 739.3646.

LRMS (ESI) = *m/z* 717 (100%) $[M+ H]^+$.

IR (ATR): ṽ $[cm^{-1}]$ = 3445, 2930, 1732, 1427, 1222, 1052, 862, 742, 699, 612, 503.

(3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*,14b*S*)-11-((tert-butyldiphenylsilyl)oxy)-12a,14b-dihydroxy-3a,8,8-trimethyl-3-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-5-yl benzoate (I-103)



$C_{49}H_{60}O_9Si$
M: 821,10 g/mol

4-((3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*,14b*S*)-11-((tert-butyldiphenylsilyl)oxy)-5,12a,14b-trihydroxy-3a,8,8-trimethylhexadecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-3-yl)furan-2(5*H*)-one **I-102** (86.0 mg, 0.12 mmol, 1.0 equiv) is dissolved in dimethylformamide (0.01 M) followed by the addition of 4-(dimethylamino)pyridine (29.31 mg, 0.24 mmol, 2.0 equiv), triethylamine (0.33 mL, 2.40 mmol, 20 equiv) and benzoic anhydride (0.54 g, 2.40 mmol, 20 equiv). The solution is stirred for 48 h at 50 °C. Subsequently, the solution is cooled down to room temperature, extracted with dichloromethane and the combined organic phases are washed with water and brine, dried over Na_2SO_4 and filtered.
The solvent is evaporated in vacuo and the crude product is purified by column chromatography (EtOAc/CH 4/6 → 7/3) to give **I-103** (97.0 mg, 0.12 mmol) as white solid in 98% yield.

Characterization:

R_f = 0.51 (EtOAc/CH 9/1) [UV, CAM].

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.91 – 7.88 (m, 2H), 7.77 – 7.71 (m, 4H), 7.59 (tt, *J* = 7.3, 1.4 Hz, 1H), 7.44 – 7.36 (m, 6H), 7.32 (t, *J* = 7.6 Hz, 2H), 5.79 (d, *J* = 1.9 Hz, 1H), 5.64 (td, *J* = 8.6, 4.9 Hz, 1H), 4.69 (dd, *J* = 8.2, 1.8 Hz, 2H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.42 (t, *J* = 3.4 Hz, 1H), 4.24 (p, *J* = 3.0 Hz, 1H), 3.77 (d, *J* = 12.1 Hz, 1H), 2.82 (t, *J* = 7.6 Hz, 1H), 2.04 – 1.95 (m, 3H), 1.94 – 1.84 (m, 3H), 1.82 (dt, *J* = 10.1, 3.2 Hz, 2H), 1.80 – 1.73 (m, 3H), 1.71 (dd, *J* = 12.2, 8.0 Hz, 1H), 1.60 – 1.55 (m, 2H), 1.53 – 1.41 (m, 3H), 1.39 (s, 3H), 1.17 – 1.10 (m, 1H), 1.03 (s, 9H), 0.99 (s, 3H), 0.98 (s, 3H).

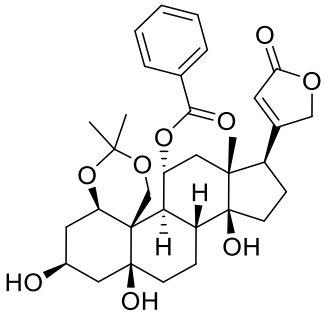
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 174.0, 172.1, 165.0, 136.4, 136.1, 133.8, 133.5, 133.4, 130.3, 130.2, 129.9, 129.8, 129.4, 128.8, 128.6, 128.6, 127.8, 127.6, 118.1, 101.2, 83.8, 73.4, 73.2, 71.4, 68.4, 66.7, 49.6, 48.6, 48.0, 43.9, 41.2, 37.6, 36.3, 34.0, 32.0, 26.9, 26.8, 24.7, 23.2, 22.8, 19.2, 17.6.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{49}H_{60}NaO_9Si$: 843.3899, found 843.3898.

LRMS (ESI) = *m/z* 821 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3493, 2930, 1715, 1621, 1377, 1266, 1107, 1065, 892, 741, 701, 608, 501, 442.

(3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*,14b*S*)-11,12a,14b-trihydroxy-3a,8,8-trimethyl-3-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-5-yl benzoate (I-105)



$C_{33}H_{42}O_9$
M: 582,69 g/mol

To a stirred solution of (3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*,14b*S*)-11-((tert-butyldiphenylsilyl)oxy)-12a,14b-dihydroxy-3a,8,8-trimethyl-3-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-5-yl benzoate **I-103** (82.0 mg, 99.8 µmol, 1.0 equiv) and cerium (III) chloride heptahydrate 98% (76.0 mg, 0.20 mmol, 2.0 equiv) in acetonitrile (0.2 M), oxalic acid (0.45 mg, 5.0 µmol, 0.05 equiv) is added at room temperature. The solution is stirred at room temperature for 16 h.
The mixture is cooled down to 0 °C and solid $NaHCO_3$ is added to neutralize the *pH* of the reaction and the solvent evaporated in vacuo. The residue is treated with ethylacetate and filtered. The filtrate is evaporated in vacuo and the crude product is purified by column chromatography (DCM → DCM/MeOH 9/1) to give **I-105** (13.0 mg, 22.3 µmol) as white solid in 22% yield.

Characterization:

R_f = 0.42 (DCM/MeOH 9/1) [UV, CAM].

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.98 – 7.96 (m, 2H), 7.63 – 7.59 (m, 1H), 7.50 – 7.46 (m, 2H), 5.84 (q, *J* = 1.6 Hz, 1H), 5.58 (td, *J* = 9.5, 4.9 Hz, 1H), 4.82 – 4.71 (m, 2H), 4.55 (t, *J* = 3.3 Hz, 1H), 4.47 (d, *J* = 12.5 Hz, 1H), 4.23 (p, *J* = 2.9 Hz, 1H), 4.01 (d, *J* = 12.5 Hz, 1H), 2.83 (t, *J* = 7.7 Hz,

1H), 2.18 – 2.09 (m, 4H), 2.00 – 1.87 (m, 6H), 1.87 – 1.74 (m, 3H), 1.71 – 1.65 (m, 2H), 1.64 – 1.50 (m, 3H), 1.33 (s, 3H), 1.25 (ddq, *J* = 12.8, 10.8, 7.2, 6.8 Hz, 1H), 1.12 (s, 3H), 1.00 (s, 3H).

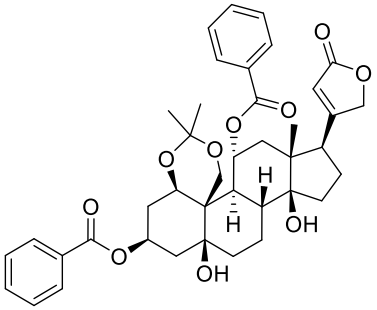
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 174.1, 172.4, 165.4, 133.8, 129.8, 129.5, 128.9, 118.3, 100.4, 83.9, 75.0, 73.4, 70.5, 68.3, 66.8, 61.3, 49.8, 48.8, 44.2, 44.1, 40.5, 37.6, 37.2, 33.8, 32.8, 26.8, 26.3, 23.8, 21.3, 17.1.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{33}H_{42}NaO_9$: 605.2721, found 605.2730.

LRMS (ESI) = *m/z* 583 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3407, 2933, 1739, 1623, 1379, 1266, 1221, 1024,856, 738, 526, 420.

(3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*,14b*S*)-12a,14b-dihydroxy-3a,8,8-trimethyl-3-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxine-5,11-diyl dibenzoate (I-106)



$C_{40}H_{46}O_{10}$
M: 686,80 g/mol

4-((3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*,14b*S*)-5,11,12a,14b-tetrahydroxy-3a,8,8-trimethylhexadecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-3-yl)furan-2(5*H*)-one **I-25** (0.43 g, 0.90 mmol, 1.0 equiv) is dissolved in dimethylformamide (0.02 M) followed by the addition of 4-(Dimethylamino)pyridine (0.22 g, 1.79 mmol, 2.0 equiv), triethylamine (2.48 mL, 17.92 mmol, 20.0 equiv) and benzoic anhydride (4.05 g, 17.92 mmol, 20 equiv). The solution is stirred for 24 h at 50 °C. Subsequently, the solution is cooled down to room temperature, extracted with dichloromethane and the combined organic phases are washed with water and brine, dried over Na_2SO_4 and filtered.
The solvent is evaporated in vacuo and the crude product is purified by column chromatography (EtOAc/CH 2/8 → 3/7) to give **I-106** (0.49 g, 0.71 mmol) as white solid in 80% yield.

Characterization:

R_f = 0.55 (DCM/MeOH 9/1) [UV, CAM].

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 8.00 (ddd, *J* = 8.4, 3.1, 1.3 Hz, 4H), 7.62 (ddt, *J* = 8.7, 7.2, 1.3 Hz, 1H), 7.55 – 7.53 (m, 1H), 7.50 – 7.48 (m, 2H), 7.43 – 7.39 (m, 2H), 5.89 (q, *J* = 1.5 Hz, 1H), 5.62 (td, *J* = 9.7, 4.9 Hz, 1H), 5.57 (dq, *J* = 4.0, 2.0 Hz, 1H), 4.86 – 4.84 (m, 2H), 4.79 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.61 (t, *J* = 3.3 Hz, 1H), 4.54 (d, *J* = 12.5 Hz, 1H), 3.89 (d, *J* = 12.5 Hz, 1H), 2.86 (t,

J = 7.5 Hz, 1H), 2.33 – 2.26 (m, 2H), 2.23 – 2.16 (m, 3H), 2.10 – 1.92 (m, 6H), 1.85 (dd, *J* = 11.8, 8.7 Hz, 1H), 1.67 – 1.58 (m, 2H), 1.53 (dtd, *J* = 39.7, 13.9, 13.0, 3.8 Hz, 2H), 1.36 (s, 3H), 1.29 – 1.20 (m, 1H), 1.07 (s, 3H), 0.93 (s, 3H).

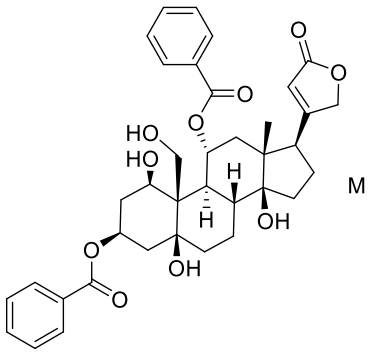
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 174.2, 172.8, 165.9, 165.1, 133.7, 133.1, 130.5, 130.0, 129.6, 129.4, 128.9, 128.5, 118.3, 101.4, 83.7, 73.4, 73.0, 71.1, 69.0, 67.0, 60.4, 49.9, 49.2, 47.2, 44.1, 44.0, 41.1, 35.8, 35.66, 33.7, 29.4, 26.9, 24.1, 23.3, 23.1, 17.0.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{40}H_{46}NaO_{10}$: 709.2983, found 709.2992.

LRMS (ESI) = *m/z* 687 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3499, 2933, 1744, 1711, 1601, 1450, 1380, 1267, 1108, 1059, 1024, 960, 869, 710, 498, 482.

(1*R*,3*S*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-1,5,14-trihydroxy-10-(hydroxymethyl)-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-1*H*-cyclopenta[a]phenanthrene-3,11-diyl dibenzoate (I-107)



$C_{37}H_{42}O_{10}$
M: 646,73 g/mol

(3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*,14b*S*)-12a,14b-dihydroxy-3a,8,8-trimethyl-3-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxine-5,11-diyl dibenzoate **I-106** (0.32 g, 0.47 mmol, 1.0 equiv) is dissolved in methanol (0.07 M) and trifluoroacetic acid (0.21 mL, 2.80 mmol, 5.0 equiv) is added. The reaction is stirred for 3 d at room temperature. The solvent is evaporated in vacuo and the crude product is purified by column chromatography (DCM → DCM/MeOH 9/1) to give **I-107** (0.26 g, 0.40 mmol) as white crystalline compound in 87% yield.

Characterization:

R_f = 0.39 (DCM/MeOH 9/1) [UV, CAM].

^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 8.00 (ddt, *J* = 10.8, 9.4, 1.7 Hz, 4H), 7.62 – 7.54 (m, 2H), 7.51 – 7.46 (m, 2H), 7.43 (dd, *J* = 8.4, 7.1 Hz, 2H), 5.91 (d, *J* = 1.9 Hz, 1H), 5.82 (td, *J* = 10.5, 4.4 Hz, 1H), 5.56 (dt, *J* = 4.8, 2.4 Hz, 1H), 5.01 – 4.87 (m, 2H), 4.81 (d, *J* = 3.1 Hz, 1H), 4.46 – 4.40 (m, 1H), 4.18 (d, *J* = 11.8 Hz, 1H), 2.92 – 2.87 (m, 1H), 2.66 – 2.57 (m, 2H), 2.38 – 2.03 (m, 6H), 2.03 – 1.79 (m, 4H), 1.73 – 1.52 (m, 2H), 1.47 – 1.26 (m, 2H), 1.09 (s, 3H).

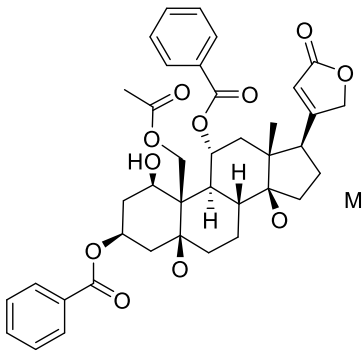
^{13}C-NMR (101 MHz, CD_3OD): δ [ppm] = 177.1, 177.0, 167.6, 166.5, 134.3, 134.0, 132.2, 132.1, 130.6, 130.4, 129.7, 129.4, 118.2, 85.2, 75.6, 75.2, 74.1, 71.3, 70.0, 59.9, 51.4, 50.8, 48.7, 45.6, 45.0, 41.4, 37.6, 36.9, 36.2, 33.7, 32.5, 31.7, 27.9, 24.5, 17.2.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{37}H_{42}NaO_{10}$: 669.2670, found 669.2672.

LRMS (ESI) = *m/z* 647 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3400, 2941, 1736, 1705, 1449, 1269, 1111, 1067, 879, 710, 494.

(1*R*,3*S*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-10-(acetoxymethyl)-1,5,14-trihydroxy-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-1*H*-cyclopenta[a]phenanthrene-3,11-diyl dibenzoate (I-93b)



$C_{39}H_{44}O_{11}$
M: 688,77 g/mol

(1*R*,3*S*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-1,5,14-trihydroxy-10-(hydroxymethyl)-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-1*H*-cyclopenta[a]phenanthrene-3,11-diyl dibenzoate **I-106** (0.43 mg, 0.40 mmol, 1.0 equiv) is dissolved in dichloromethane (0.08 M) and pyridine (0.22 ml, 2.66 mmol, 4.0 equiv) and acetic anhydride (0.25 mL, 2.66 mmol, 4.0 equiv) are added. The solution is stirred for 16 h at room temperature. The solution is washed with HCl solution (1 M) and the aqueous phase extracted with dichloromethane. The combined organic phases are washed with brine, dried over Na_2SO_4, filtered and the solvent is evaporated in vacuo. A pure white crystalline solid **I-93b** (0.42 g, 0.61 mmol) in 92% yield is obtained.

Characterization:

R_f = 0.50 (DCM/MeOH 9/1) [UV, CAM].

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.98 (q, *J* = 1.6 Hz, 2H), 7.93 – 7.90 (m, 2H), 7.60 – 7.56 (m, 1H), 7.52 – 7.48 (m, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.40 – 7.36 (m, 2H), 5.88 (t, *J* = 1.8 Hz, 1H), 5.60 (tt, *J* = 4.1, 2.1 Hz, 1H), 5.51 (td, *J* = 10.8, 4.4 Hz, 1H), 5.21 – 5.17 (m, 1H), 4.91 (dd, *J* = 18.2, 1.8 Hz, 1H), 4.78 (dd, *J* = 18.1, 1.8 Hz, 1H), 4.66 – 4.62 (m, 2H), 2.77 (dd, *J* = 8.8, 5.5 Hz, 1H), 2.43 (tdd, *J* = 15.8, 12.5, 7.5 Hz, 3H), 2.29 – 2.13 (m, 2H), 2.13 – 1.83 (m, 12H), 1.66 (td, *J* = 14.1, 4.6 Hz, 1H), 1.53 (ddd, *J* = 14.1, 4.5, 2.6 Hz, 1H), 1.50 – 1.44 (m, 1H), 1.43 – 1.22 (m, 2H), 1.07 (s, 3H).

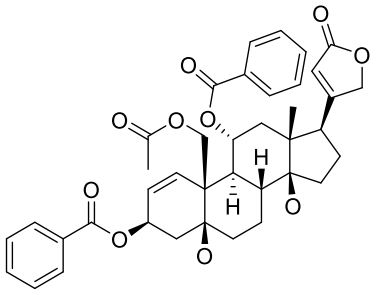
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 174.3, 173.2, 172.4, 166.2, 165.1, 133.7, 133.1, 130.5, 130.0, 129.7, 129.4, 129.0, 128.5, 118.4, 84.4, 73.7, 73.5, 71.9, 68.8, 68.8, 62.3, 50.2, 49.6, 47.5, 45.1, 44.3, 40.7, 36.8, 35.1, 33.5, 31.1, 26.9, 23.6, 21.1, 16.4.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{39}H_{44}NaO_{11}$: 711.2776, found 711.2784.

LRMS (ESI) = *m/z* 689 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3389, 2930, 2872, 1706, 1385, 1270, 1111, 1067, 1023, 713, 659, 513.

(3*R*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-10-(acetoxymethyl)-5,14-dihydroxy-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[a]phenanthrene-3,11-diyl dibenzoate (I-94b)



$C_{39}H_{42}O_{10}$
M: 670,76 g/mol

(1*R*,3*S*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-10-(acetoxymethyl)-1,5,14-trihydroxy-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-1*H*-cyclopenta[a]phenanthrene-3,11-diyl dibenzoate **I-93b** (0.25 g, 0.37 mmol, 1.0 equiv) is dissolved in dry tetrahydrofuran (0.07 M) and *Martin's Sulfurane* reagent (0.55 g, 0.97 mmol, 2.20 equiv) is added under N_2 atmosphere. The solution is stirred for 3 h at room temperature. The solvent is evaporated under vacuo and the crude product is purified by column chromatography (EtOAc/CH 3/7 → 6/4) to give **I-94b** (0.18 g, 0.26 mmol) as white crystalline solid in 71% yield.

(Note: Martin's Sulfurane is handled and weighed inside the glove box)

Characterization:

R_f = 0.48 (EtOAc/CH 9/1) [UV, CAM].

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 8.04 – 8.01 (m, 2H), 7.99 – 7.96 (m, 2H), 7.62 – 7.58 (m, 1H), 7.56 (ddt, *J* = 8.8, 7.2, 1.3 Hz, 1H), 7.50 – 7.46 (m, 2H), 7.44 – 7.40 (m, 2H), 6.10 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.96 (ddd, *J* = 10.4, 4.0, 1.5 Hz, 1H), 5.90 (d, *J* = 1.9 Hz, 1H), 5.76 (t, *J* = 5.1 Hz, 1H), 5.38 (dt, *J* = 11.1, 5.5 Hz, 1H), 4.93 (dd, *J* = 18.1, 1.8 Hz, 1H), 4.79 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.59 (q, *J* = 12.1 Hz, 2H), 2.79 – 2.72 (m, 2H), 2.20 (dp, *J* = 13.0, 10.3 Hz, 2H), 2.14 – 2.08 (m, 1H), 2.06 (dd, *J* = 6.2, 4.3 Hz, 1H), 2.04 – 1.96 (m, 5H), 1.96 – 1.81 (m, 6H), 1.71 (dt, *J* = 13.8, 3.5 Hz, 1H), 1.49 – 1.36 (m, 2H), 1.09 (s, 3H).

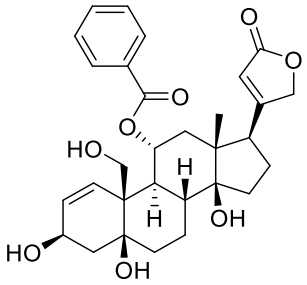
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 174.3, 173.2, 171.2, 165.8, 165.1, 136.9, 133.5, 133.5, 130.2, 129.8, 129.8, 129.7, 128.8, 128.7, 122.0, 118.5, 84.6, 73.5, 71.3, 70.8, 66.3, 63.2, 50.2, 50.0, 49.9, 45.6, 44.9, 40.4, 35.9, 34.2, 33.3, 27.0, 23.6, 21.1, 16.4.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{39}H_{42}NaO_{10}$: 693.2670, found 693.2671.

LRMS (ESI) = *m/z* 671 (1%) $[M+H]^+$, 549 (100%) $[M\text{-}OH\text{-}Bz]^+$.

IR (ATR): ṽ [cm^{-1}] = 3494, 2949, 1708, 1440, 1314, 1109, 1025, 931, 711, 509.

(3*R*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-5,11,14-trihydroxy-10-(hydroxymethyl)-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[a]phenanthren-3-yl benzoate (I-99b)



$C_{30}H_{36}O_8$
M: 524,61 g/mol

(3*R*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-10-(acetoxymethyl)-5,14-dihydroxy-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[a]phenanthrene-3,11-diyl dibenzoate **I-94b** (95.0 mg, 0.14 mmol, 1.0 equiv) is dissolved in methanol (0.04 M) and water (0.35 M) followed by the addition of sodium carbonate (0.15 g, 1.42 mmol, 10.0 equiv). The solution is stirred for 5 h at room temperature. The *pH* of the solution is neutralized with trifluoroacetic acid and the solvent evaporated in vacuo. The crude product is purified by column chromatography (DCM → DCM/MeOH 9/1) to give **I-99b** (50.0 mg, 95.3 µmol) as white crystalline solid in 67% yield.

Characterization:

R_f = 0.30 (DCM/MeOH 9/1) [UV, CAM].

^{1}H-NMR (600 MHz, CD_3OD): δ [ppm] = 8.05 – 8.01 (m, 2H), 7.63 (ddt, *J* = 8.8, 7.2, 1.2 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 2H), 5.92 (d, *J* = 1.9 Hz, 1H), 5.76 (ddd, *J* = 10.3, 4.2, 1.5 Hz, 1H), 5.70 (d, *J* = 10.4 Hz, 1H), 5.46 (td, *J* = 11.1, 4.4 Hz, 1H), 5.00 (dd, *J* = 18.4, 1.8 Hz, 1H), 4.91 (dd, *J* = 18.3, 1.8 Hz, 1H), 4.26 (t, *J* = 4.8 Hz, 1H), 4.21 (d, *J* = 11.2 Hz, 1H), 3.89 (d, *J* = 11.3 Hz, 1H), 2.86 (dd, *J* = 8.8, 5.6 Hz, 1H), 2.56 (dd, *J* = 14.9, 5.3 Hz, 1H), 2.24 – 2.15 (m, 2H), 2.12 – 2.01 (m, 3H), 1.90 (ddt, *J* = 17.7, 9.1, 3.9 Hz, 3H), 1.81 – 1.68 (m, 2H), 1.65 (d, *J* = 14.7 Hz, 1H), 1.57 (t, *J* = 12.2 Hz, 1H), 1.37 (qd, *J* = 13.3, 4.1 Hz, 1H), 1.04 (s, 3H).

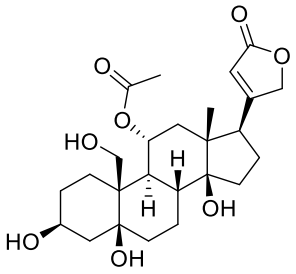
^{13}C-NMR (101 MHz, CD_3OD): δ [ppm] = 177.2, 177.0, 166.8, 136.7, 134.4, 131.7, 130.8, 129.6, 127.5, 118.3, 85.2, 76.0, 76.0, 71.9, 65.0, 64.4, 51.4, 51.1, 50.9, 49.8, 46.7, 45.9, 41.5, 38.6, 37.3, 33.2, 27.8, 25.08, 17.0.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{30}H_{36}NaO_8$: 547.2302, found 547.2304.

LRMS (ESI) = *m/z* 507 (100%) $[M\text{-}OH]^+$.

IR (ATR): ṽ [cm^{-1}] = 3360, 2938, 1707, 1449, 1270, 1023, 943, 712, 483.

(3*S*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-3,5,14-trihydroxy-10-(hydroxymethyl)-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-1*H*-cyclopenta[a]phenanthren-11-yl acetate (I-109)



$C_{25}H_{36}O_8$
M: 464,56 g/mol

(3*R*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-3,5,14-trihydroxy-10-(hydroxymethyl)-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[a]phenanthren-11-yl acetate **I-99** (23.0 mg, 50.0 µmol, 1.0 equiv) is loaded in a 4 mL vial and dry overnight under the high vacuum to remove all solvent and water traces. Then, it is washed with N_2 and the stir bar is added. The vial is insert into the gloves box and the catalyst (0.80 mg, 0.99 µmol, 2.0 mol%) is weighted and added to the starting material. Freshly dry degassed dichloromethane (0.11 M) under N_2 is added.
The hydrogenation is carried out by using the autoclave, first washed with N_2 and H_2 several times. Subsequently, the vial with the solution is placed inside and washed again for 25-30 min and the hydrogenation is performed under H_2 (20 atm) for 3 h at room temperature.
The orange crude product **I-109** (23.0 mg, 50.0 µmol) is obtained in quantitative yield and directly used for the next reaction.

Characterization:

R_f = 0.32 (DCM/MeOH 9/1) [CAM].

^{1}H NMR (400 MHz, CD_3OD): δ [ppm] = 5.90 (td, *J* = 1.8, 0.7 Hz, 1H), 5.25 (dt, *J* = 10.5, 5.3 Hz, 1H), 5.03 – 4.94 (m, 1H), 4.90 (dd, *J* = 18.3, 1.8 Hz, 1H), 4.13 (d, *J* = 1.5 Hz, 1H), 3.77 (d, *J* = 11.3 Hz, 1H), 2.87 (t, *J* = 7.3 Hz, 1H), 2.24 (t, *J* = 2.8 Hz, 1H), 2.21 (dd, *J* = 6.3, 3.0 Hz, 1H), 2.18 (d, *J* = 3.6 Hz, 1H), 2.16 – 2.07 (m, 1H), 2.06 – 2.01 (m, 1H), 1.99 (s, 3H), 1.96 – 1.84 (m, 3H), 1.84 –

1.79 (m, 1H), 1.78 – 1.71 (m, 3H), 1.71 – 1.60 (m, 2H), 1.57 – 1.41 (m, 4H), 1.29 (t, *J* = 3.4 Hz, 1H), 0.95 (s, 3H).

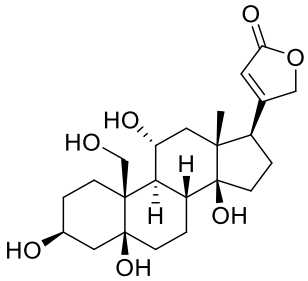
^{13}C-NMR (151 MHz, CD_3OD): δ [ppm] = 177.1, 177.0, 171.8, 118.2, 85.2, 77.9, 75.2, 72.3, 68.9, 65.5, 51.3, 50.8, 45.8, 45.1, 42.8, 40.7, 38.4, 36.6, 33.4, 28.9, 27.8, 24.9, 22.0, 21.6, 17.2.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{25}H_{36}NaO_8$: 487.2302, found 487.2301.

LRMS (ESI) = *m/z* 465 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3347, 2927, 1727, 1447, 1240, 1023, 839, 732, 697, 557.

4-((3*S*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-3,5,11,14-tetrahydroxy-10-(hydroxymethyl)-13-methylhexadecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)furan-2(5*H*)-one (I-70)



$C_{23}H_{34}O_7$
M: 422,52 g/mol

(3*S*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-3,5,14-trihydroxy-10-(hydroxymethyl)-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-1*H*-cyclopenta[a]phenanthren-11-yl acetate **I-99** (65.0 mg, 0.14 mmol, 1.0 equiv) is dissolved in methanol (0.05 M) and water (0.54 M) followed by the addition of sodium carbonate (0.15 g, 1.40 mmol, 10.0 equiv). The solution is stirred for 24 h at room temperature. The *pH* of the solution is neutralized with trifluoroacetic acid and the dry load is directly prepared. The crude product is purified by column chromatography (DCM → DCM/MeOH 9/1) to give **I-70** (30.0 mg, 71.0 µmol) as white crystalline solid in 51% yield.

Characterization:

R_f = 0.11 (DCM/MeOH 9/1) [CAM].

^{1}H-NMR (400 MHz, CD_3OD): δ [ppm] = 5.91 (s, 1H), 5.01 (dd, *J* = 18.3, 1.5 Hz, 1H), 4.91 (dd, *J* = 18.4, 1.6 Hz, 1H), 4.23 (d, *J* = 11.0 Hz, 1H), 3.93 – 3.83 (m, 2H), 3.81 (d, *J* = 11.1 Hz, 1H), 2.92 (t, *J* = 7.3 Hz, 1H), 2.20 – 2.13 (m, 4H), 1.92 – 1.87 (m, 2H), 1.84 (d, *J* = 4.5 Hz, 1H), 1.81 – 1.77 (m, 2H), 1.75 – 1.72 (m, 1H), 1.67 (dd, *J* = 13.4, 4.2 Hz, 2H), 1.56 (d, *J* = 11.0 Hz, 1H), 1.50 – 1.42 (m, 3H), 1.32 (d, *J* = 7.3 Hz, 1H), 1.10 – 1.04 (m, 1H), 0.91 (s, 3H).

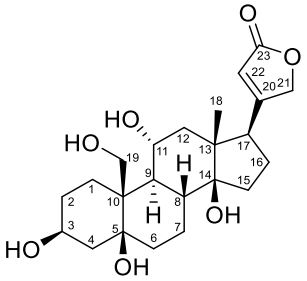
^{13}C-NMR (101 MHz, CD_3OD): δ [ppm] = 177.5, 177.1, 118.0, 85.7, 78.6, 75.3, 69.0, 69.0, 66.0, 51.6, 51.0, 50.6, 45.6, 44.8, 41.0, 38.8, 36.8, 33.4, 29.2, 27.9, 24.8, 19.8, 17.6.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{23}H_{35}O_7$: 423.2377, found 423.2382.

LRMS (ESI) = *m/z* 423 (100%) $[M+H]^+$.

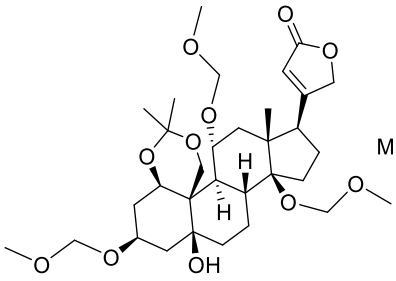
IR (ATR): ṽ [cm^{-1}] = 3359, 2927, 1676, 1440, 1136, 1027, 840, 723, 557.

Table 33. ^{1}H and ^{13}C NMR analysis of **I-70.**



Position	δ_C	δ_H (*J* in Hz)	Position	δ_C	δ_H (*J* in Hz)
1	29.2	2.20-1.42, m	**13**	51.0	-
2	24.8	2.20-1.42, m	**14**	85.7	-
3	69.0	3.93 - 3.83, m	**15**	33.4	2.20-1.42, m
4	38.8	2.20-1.42, m	**16**	27.9	2.20-1.42, m
5	78.6	-	**17**	51.6	2.92, t (7.3)
6	36.8	2.20-1.42, m	**18**	17.6	0.91, s
7	19.8	2.20-1.42, m	**19**	66.0	4.23, d (11.1) 3.81, d (11.1)
8	41.0	1.32, d (7.3)	**20**	177.1	-
9	44.8	1.10 - 1.04, m	**21**	75.3	5.01, dd (18.3, 1.5) 4.91, dd (18.4, 1.6)
10	45.6	-	**22**	118.0	5.91, s
11	69.0	3.93 - 3.83, m	**23**	177.5	-
12	50.6	2.20-1.42, m			

4-((3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*,14b*S*)-12a-hydroxy-5,11,14b-tris(methoxymethoxy)-3a,8,8-trimethylhexadecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-3-yl)furan-2(5*H*)-one (I-33a)



$C_{32}H_{50}O_{11}$
M: 610,74 g/mol

4-((3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*,14b*S*)-5,11,12a,14b-tetrahydroxy-3a,8,8-trimethylhexadecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-3-yl)furan-2(5*H*)-one **I-25** (1.0 g, 2.08 mmol, 1.0 equiv) is dissolved in dry dichloromethane (0.06 M) and diisopropylethylamine 99% (7.32 mL, 41.62 mmol, 20.0 equiv) is added at room temperature. After stirring 5 min, the suspension is cooled to 0 °C, and chloromethyl methyl ether (3.32 mL, 43.70 mmol, 21.0 equiv) is added. The mixture is warmed to room temperature, stirred for 72 h and then quenched with water. The organic phase is separated and the aqueous phase is extracted with additional dichloromethane. The combined organic phases are dried over Na_2SO_4, filtered and the solvent is evaporated in vacuo. The residue is purified by column chromatography (EtOAc/CH 9/1) to give **I-33a** (1.1 g, 1.75 mmol) as white crystalline solid in 84% yield.

Characterization:

R_f = 0.26 (CH/EtOAc 1/9) [CAM].

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 5.89 (d, *J* = 1.5 Hz, 1H), 4.84 (dd, *J* = 17.6, 1.8 Hz, 1H), 4.81 – 4.76 (m, 2H), 4.74 (dd, *J* = 12.9, 6.0 Hz, 2H), 4.72 – 4.66 (m, 2H), 4.65 – 4.60 (m, 2H), 4.55 (d, *J* = 12.2 Hz, 1H), 4.41 – 4.35 (m, 2H), 4.16 (s, 1H), 3.61 (d, *J* = 12.2 Hz, 1H), 3.44 (s, 2H), 3.42 (s, 2H), 3.41 (s, 4H), 3.39 (d, *J* = 2.2 Hz, 1H), 2.21 – 2.13 (m, 2H), 2.13 – 2.03 (m, 1H), 1.99 (dd, *J* = 14.8, 3.7 Hz, 1H), 1.95 – 1.72 (m, 7H), 1.64 (dt, *J* = 15.5, 5.2 Hz, 2H), 1.57 – 1.46 (m, 3H), 1.42 (d, *J* = 9.7 Hz, 3H), 1.38 (d, *J* = 6.6 Hz, 4H), 0.78 (s, 3H).

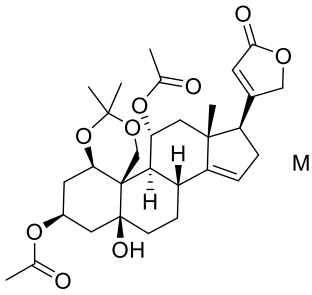
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 174.0, 171.0, 117.0, 101.4, 96.0, 94.9, 92.9, 90.8, 75.0, 73.7, 72.7, 71.1, 66.6, 61.1, 56.5, 56.3, 55.8, 48.5, 47.5, 46.9, 44.0, 40.8, 39.0, 35.1, 34.8, 30.4, 29.8, 28.1, 25.5, 23.3, 22.1, 21.1.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{32}H_{50}NaO_{11}$: 633.3246, found 633.3245.

LRMS (ESI) = *m/z* 611 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3510, 2929, 1747, 1625, 1448, 1376, 1223, 1145, 1018, 910, 784, 431.

(3*S*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*)-12a-hydroxy-3a,8,8-trimethyl-3-(5-oxo-2,5-dihydrofuran-3-yl)-2,3,3a,4,5,5a,9a,10,11,12,12a,13,14,14a-tetradecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxine-5,11-diyl diacetate (I-112a)



$C_{30}H_{40}O_9$
M: 544,64 g/mol

(3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*,14b*S*)-12a,14b-dihydroxy-3a,8,8-trimethyl-3-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxine-5,11-diyl diacetate **I-27** (0.20 g, 0.36 mmol, 1.0 equiv) is dissolved in dry tetrahydrofuran (0.05 M) and *Martin's Sulfurane* reagent (0.42 g, 0.62 mmol, 1.75 equiv) is added under N_2 atmosphere. The solution is stirred for 2 h at room temperature. The solvent is evaporated under vacuo and the crude product is purified by column chromatography (EtOAc/CH 7/3 → 9/1) to give **I-112a** (0.18 g, 0.33 mmol) as white crystalline solid in 94% yield.

(Note: Martin's Sulfurane is handled and weighed inside the glove box)

Characterization:

R_f = 0.60 (DCM/MeOH 9/1) [CAM].

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 5.89 (q, *J* = 1.7 Hz, 1H), 5.38 – 5.31 (m, 2H), 5.20 (dt, *J* = 4.0, 2.0 Hz, 1H), 4.77 (dd, *J* = 17.4, 1.8 Hz, 1H), 4.71 – 4.64 (m, 2H), 4.60 (dd, *J* = 4.0, 2.8 Hz, 1H), 4.44 (d, *J* = 12.4 Hz, 1H), 3.80 (d, *J* = 12.4 Hz, 1H), 2.82 (dd, *J* = 10.3, 7.9 Hz, 1H), 2.54 – 2.46 (m, 2H), 2.20 – 2.17 (m, 1H), 2.12 (dt, *J* = 11.2, 3.0 Hz, 2H), 2.07 (td, *J* = 3.7, 2.5 Hz, 1H), 2.05 – 2.03 (m, 7H), 1.97 – 1.78 (m, 4H), 1.62 – 1.52 (m, 3H), 1.39 (s, 3H), 1.25 (d, *J* = 1.3 Hz, 3H), 0.90 (s, 3H).

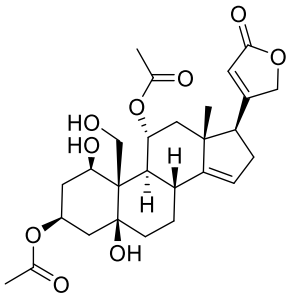
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 173.6, 170.6, 169.2, 150.1, 119.3, 117.2, 101.1, 73.4, 73.4, 73.2, 71.1, 68.7, 67.3, 60.1, 52.3, 52.0, 48.4, 47.3, 46.6, 46.6, 35.4, 34.0, 33.3, 28.9, 25.3, 24.4, 23.6, 21.8, 21.7, 19.1.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{30}H_{40}NaO_9$: 567.2569, found 567.2565.

LC-MS (ESI) = *m/z* 545 (100%) $[M+H]^+$.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3516, 2931, 2868, 1780, 1730, 1629, 1370, 1229, 1134, 1018, 960, 887, 604, 418.

(1*R*,3*S*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,17*S*)-1,5-dihydroxy-10-(hydroxymethyl)-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)-2,3,4,5,6,7,8,9,10,11,12,13,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthrene-3,11-diyl diacetate (I-115)



$C_{27}H_{36}O_9$
M: 504,58 g/mol

(3*S*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*)-12a-hydroxy-3a,8,8-trimethyl-3-(5-oxo-2,5-dihydrofuran-3-yl)-2,3,3a,4,5,5a,9a,10,11,12,12a,13,14,14a-tetradecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxine-5,11-diyl diacetate **I-112a** (0.43 g, 0.78 mmol, 1.0 equiv) is dissolved in methanol (0.20 M) and trifluoroacetic acid (0.30 mL, 3.91 mmol, 5.0 equiv) is added. The reaction is stirred for 3 d at room temperature. The solvent is evaporated in vacuo and the crude product is purified by column chromatography (DCM→ DCM/MeOH 9/1) to give **I-115** (0.26 g, 0.51 mmol) as white solid in 66% yield.

Characterization:

R_f = 0.49 (DCM/MeOH 9/1) [CAM].

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 5.89 (q, *J* = 1.7 Hz, 1H), 5.36 (q, *J* = 2.3 Hz, 1H), 5.27 (dq, *J* = 4.6, 2.2 Hz, 1H), 5.18 (td, *J* = 10.6, 4.1 Hz, 1H), 4.85 (t, *J* = 3.2 Hz, 1H), 4.76 (dd, *J* = 17.5, 1.8 Hz, 1H), 4.67 (ddd, *J* = 17.4, 1.9, 0.9 Hz, 1H), 4.57 (d, *J* = 11.9 Hz, 1H), 4.10 (d, *J* = 12.0 Hz, 1H), 3.65 (d, *J* = 4.1 Hz, 1H), 2.80 (t, *J* = 9.2 Hz, 1H), 2.51 (ddt, *J* = 10.4, 5.6, 2.3 Hz, 2H), 2.31 – 2.20 (m, 4H), 2.12 (dd, *J* = 5.8, 3.9 Hz, 1H), 2.10 – 2.08 (m, 1H), 2.07 (s, 3H), 2.03 (s, 3H), 1.96 – 1.91 (m, 1H), 1.82 – 1.79 (m, 1H), 1.78 (d, *J* = 3.7 Hz, 1H), 1.62 (dd, *J* = 11.8, 10.4 Hz, 1H), 1.57 – 1.52 (m, 2H), 1.34 (t, *J* = 11.5 Hz, 1H), 1.25 (s, 1H), 0.92 (s, 3H).

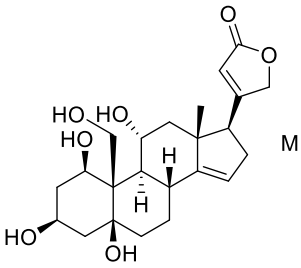
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 173.6, 170.6, 169.7, 169.1, 150.7, 119.4, 117.2, 75.5, 73.4, 72.3, 71.5, 68.8, 63.0, 52.3, 48.5, 47.9, 47.3, 46.8, 36.1, 35.5, 34.0, 33.3, 31.0, 25.6, 21.8, 21.8, 19.2.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{27}H_{36}NaO_9$: 527.2245, found 527.2252.

LRMS (ESI) = *m/z* 505 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3413, 2930, 1725, 1373, 1233, 1027, 732, 606.

4-((1*R*,3*S*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,17*S*)-1,3,5,11-tetrahydroxy-10-(hydroxymethyl)-13-methyl-2,3,4,5,6,7,8,9,10,11,12,13,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)furan-2(5*H*)-one (I-117)



$C_{23}H_{32}O_7$
M: 420,50 g/mol

(1*R*,3*S*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,17*S*)-1,5-dihydroxy-10-(hydroxymethyl)-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)-2,3,4,5,6,7,8,9,10,11,12,13,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthrene-3,11-diyl diacetate **I-115** (0.26 g, 0.51 mmol, 1.0 equiv) is dissolved in methanol (0.05 M) and water (0.53 M) followed by the addition of sodium carbonate (0.12 g, 1.13 mmol, 2.20 equiv). The solution is stirred for 1 h at room temperature. The *pH* of the solution is neutralized with trifluoroacetic acid and the dry load is directly prepared with silica. The crude product is purified by column chromatography (DCM → DCM/MeOH 9/1) to give **I-117** (0.14 g, 0.34 mmol) as white crystalline solid in 66% yield.

Characterization:

R_f = 0.11 (DCM/MeOH 9/1) [CAM].

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm] = 6.05 (q, *J* = 1.7 Hz, 1H), 5.22 (q, *J* = 1.7 Hz, 1H), 4.88 (dd, *J* = 5.8, 1.8 Hz, 2H), 4.77 (s, 1H), 4.48 – 4.42 (m, 1H), 4.18 (dd, *J* = 11.8, 6.0 Hz, 2H), 4.13 – 4.01 (m, 2H), 3.80 (s, 1H), 3.17 (d, *J* = 4.9 Hz, 1H), 2.86 – 2.77 (m, 1H), 2.40 – 2.30 (m, 1H), 2.06 – 1.72 (m, 6H), 1.60 (s, 3H), 1.43 (d, *J* = 7.9 Hz, 2H), 1.28 (dd, *J* = 23.1, 11.2 Hz, 2H), 1.16 (dd, *J* = 11.9, 9.5 Hz, 1H), 0.97 – 0.84 (m, 1H), 0.78 (s, 3H).

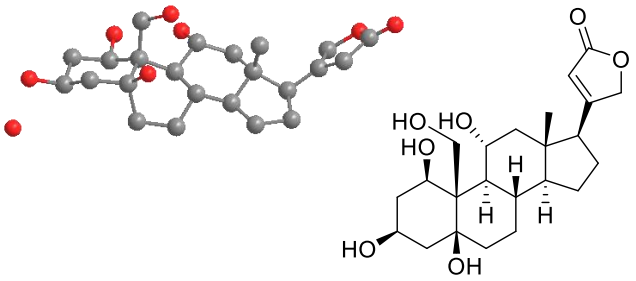
^{13}C-NMR (151 MHz, DMSO-d_6): δ [ppm] = 173.0, 171.1, 152.8, 116.4, 114.9, 114.8, 75.1, 72.8, 71.3, 67.3, 64.7, 60.6, 60.3, 54.4, 51.3, 50.1, 47.8, 47.2, 40.0, 33.0, 31.9, 24.6, 18.5.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{23}H_{32}NaO_7$: 443.2040, found 443.2045.

LRMS (ESI) = *m/z* 421 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3322, 2921, 2854, 1737, 1625, 1439, 1105, 1016, 891, 800, 687, 606, 580, 434.

4-((1*R*,3*S*,5*S*,8*S*,9*S*,10*R*,11*R*,13*S*,17*S*)-1,3,5,11-tetrahydroxy-10-(hydroxymethyl)-13-methylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)furan-2(5*H*)-one (I-74)



$C_{23}H_{34}O_7$
M: 422,52 g/mol

4-((1*R*,3*S*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,17*S*)-1,3,5,11-tetrahydroxy-10-(hydroxymethyl)-13-methyl-2,3,4,5,6,7,8,9,10,11,12,13,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)furan-2(5*H*)-one **I-117** (0.21 g, 0.50 mmol, 1.0 equiv) is dissolved in acetic acid (0.07 M) followed by the addition of palladium on activated charcoal 10% (0.27 g, 0.25 mmol, 50.0 mol%). The solution is then hydrogenated with H_2 atmosphere (1 atm) for 24 h at room temperature. The suspension is filtered by celite to remove the palladium and the solvent evaporated in vacuo.

The crude product is purified by column chromatography (DCM → DCM/MeOH 9/1) to give **I-74** (96.0 mg, 0.23 mmol) as white and crystalline compound in 45% yield (*d.r. 93:7*).

Characterization:

R_f = 0.10 (DCM/MeOH 9/1) [CAM].

^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 5.91 (q, *J* = 1.7 Hz, 1H), 4.94 (dd, *J* = 17.8, 1.8 Hz, 1H), 4.88 – 4.82 (m, 1H), 4.50 – 4.38 (m, 1H), 4.32 (d, *J* = 11.7 Hz, 1H), 4.23 (d, *J* = 11.7 Hz, 1H), 2.53 (t, *J* = 9.4 Hz, 1H), 2.11 – 2.01 (m, 4H), 1.96 – 1.89 (m, 1H), 1.80 (tdd, *J* = 14.1, 12.0, 9.4, 5.2 Hz, 4H), 1.73 – 1.64 (m, 1H), 1.56 (s, 3H), 1.40 – 1.14 (m, 6H), 0.72 (s, 3H).

^{13}C-NMR (101 MHz, CD_3OD): δ [ppm] = 180.2, 179.7, 176.7, 174.3, 116.3, 116.2, 78.5, 75.5, 75.2, 69.5, 68.8, 66.7, 62.8, 62.6, 57.9, 57.8, 55.2, 55.0, 54.8, 51.5, 50.9, 45.6, 45.4, 44.7, 44.4, 44.3, 43.9, 43.9, 35.0, 34.9, 29.3, 28.4, 28.0, 27.2, 27.0, 26.0, 25.5, 25.5, 25.3, 14.5, 14.1.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{23}H_{34}NaO_7$: 445.2197, found 445.2201.

LRMS (ESI) = *m/z* 423 (85%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3345, 2929, 1739, 1661, 1341, 1090, 1016, 951, 890, 798, 615, 540, 421.

Crystal structure = C14-C15 bond length: (1.531 Å);
C14-O bond: not present. Hydrogen bonded to C14 is in *trans*-configuration compared to the methyl group at C13 position.

Crystal structure analysis of **4-((1*R*,3*S*,5*S*,8*S*,9*S*,10*R*,11*R*,13*S*,17*S*)-1,3,5,11-tetrahydroxy-10-(hydroxymethyl)-13-methylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)furan-2(5*H*)-one (I-74)**

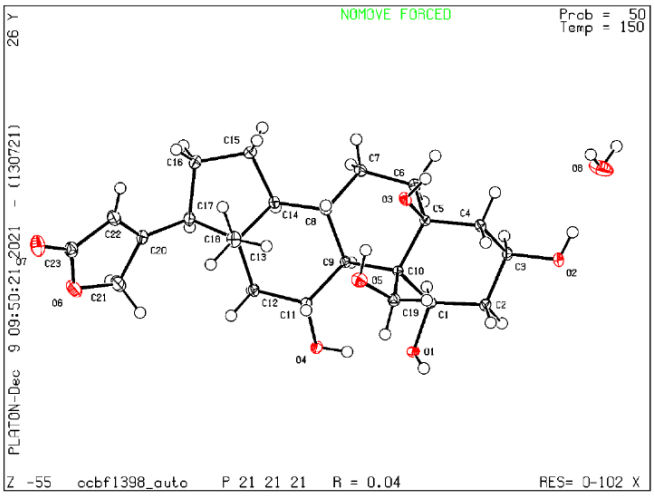


Table 1: Crystal data and structure refinement for I-74

Formula	$C_{23}H_{36}O_8$
Formula weight	440.52
Temperature/K	150
Crystal System	Orthorhombic
Space group	$P2_12_12_1$
a/ Å	8.0811(2)
b/ Å	10.7894(2)
c/ Å	24.5112(5)
α/°	90
β/°	90
γ/°	90
Volume/ Å	2137.14(8)
Z	4
p_{calc}g/cm^3	1.369
μ/mm-^{1}	0.102
F(000)	952.0
Crystal size/mm^3	0.14 x 0.05 x 0.03
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	5.03 to 65.146
Index ranges	-11 ≤ h ≤ 12, -15 ≤ k ≤ 8, -22 ≤ 1 ≤ 36
Reflections collected	14095
Independent reflections	6797 [R_{int} = 0.0316, R_{sigma} = 0.0461]
Data/restraints/parameters	6797/3/292
Goodness-of-fit on F^2	1.045
Final R indexes [I>2σ (I)]	R_1 = 0.0384, wR_2 = 0.0910
Final R indexes [all data]	R_1 = 0.0453, wR_2 = 0.0961
Largest diff. peak/hole / e Å^{-3}	0.30/-0.20
Flack parameter	0.6(4)

Table 2: Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for I-74. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*Y*	*Z*	$U_{(eq)}$
O5	3216.5 (16)	8714.6 (11)	3208.2 (5)	15.8 (2)
O2	5822.9 (15)	6021.5 (12)	5174.7 (5)	15.1 (2)
O3	5600.0 (14)	7029.6 (12)	3263.7 (5)	13.8 (2)
O1	543.9 (14)	6696.4 (12)	4357.3 (5)	13.2 (2)
O7	-1884.5 (19)	8416.5 (13)	17.3 (6)	24.5 (3)
O6	-3196.1 (16)	7491.8 (13)	712.9 (6)	21.9 (3)
O4	-1006.8 (15)	6847.4 (16)	3413.5 (5)	23.3 (3)
O8	8934.1 (19)	5001.9 (16)	5070.6 (7)	31.6 (4)
C23	-1819 (2)	7750.5 (16)	415.0 (7)	16.7 (3)
C20	-905 (2)	6511.2 (16)	1107.1 (7)	13.7 (3)
C5	4761.7 (19)	6248.2 (14)	3655.7 (6)	10.2 (3)
C1	2156.3 (19)	6176.8 (15)	4239.1 (6)	10.7 (3)
C14	1991 (2)	5433.4 (15)	2208.0 (6)	12.2 (3)
C3	4905.9 (19)	5780.9 (16)	4681.5 (6)	11.9 (3)
C13	720 (2)	6399.3 (15)	2019.0 (6)	10.6 (3)
C4	5717 (2)	6391.6 (16)	4193.8 (6)	12.4 (3)
C6	4822 (2)	4908.0 (16)	3452.3 (7)	14.3 (3)
C10	2895.0 (18)	6689.5 (14)	3691.6 (6)	9.2 (3)
C8	2985 (2)	5833.5 (15)	2701.3 (6)	11.5 (3)
C17	64 (2)	5733.0 (16)	1494.8 (7)	12.9 (3)
C19	2837 (2)	8118.3 (14)	3711.3 (7)	12.1 (3)
C11	308.1 (19)	6925.8 (16)	3020.1 (6)	12.3 (3)
C2	3207 (2)	6333.9 (16)	4753.7 (6)	12.5 (3)
C18	1498 (2)	7656.3 (16)	1871.9 (7)	16.4 (3)
C9	1845.3 (19)	6142.6 (15)	3192.6 (6)	9.9 (3)
C12	-515 (2)	6526.6 (17)	2483.9 (6)	13.4 (3)
C16	1642 (2)	5158.5 (17)	1234.5 (7)	17.7 (3)
C22	-404 (2)	7121.7 (18)	662.2 (7)	18.9 (3)
C15	2948 (2)	5097.2 (18)	1689.5 (7)	19.5 (4)
C7	4230 (2)	4811.4 (16)	2859.5 (7)	16.6 (3)
C21	-2733 (2)	6698.1 (19)	1165.2 (8)	20.5 (4)

Table 3: Anisotropic Displacement Parameters (Å^2×10^3) for I-74. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O5	14.3 (5)	16.0 (6)	17.1 (6)	4.8 (5)	4.2 (5)	0.1 (5)
O2	12.5 (5)	21.6 (6)	11.2 (5)	-1.2 (5)	-3.9 (4)	2.2 (5)
O3	6.5 (4)	22.2 (6)	12.6 (5)	3.7 (5)	1.1 (4)	-1.1 (5)
O1	8.1 (5)	20.6 (6)	10.8 (5)	-0.7 (4)	2.2 (4)	0.2 (5)
O7	27.9 (7)	23.5 (7)	22.1 (6)	6.0 (5)	-7.8 (6)	-0.4 (6)
O6	15.6 (6)	25.6 (7)	24.6 (7)	4.9 (5)	-3.5 (5)	5.4 (6)
O4	7.5 (5)	52.2 (9)	10.3 (5)	-2.5 (6)	0.9 (4)	3.3 (6)
O8	21.3 (7)	32.3 (8)	41.1 (9)	13.7 (7)	13.1 (6)	8.8 (7)
C23	18.5 (7)	14.8 (8)	16.9 (8)	-3.0 (6)	-5.2 (6)	0.9 (7)
C20	13.6 (7)	15.9 (7)	11.7 (7)	-2.1 (6)	-2.9 (6)	0.0 (7)
C5	7.9 (6)	13.9 (7)	8.9 (6)	-0.1 (6)	-0.2 (5)	1.1 (6)
C1	8.7 (6)	13.4 (7)	9.9 (7)	0.7 (5)	0.3 (5)	-0.4 (6)
C14	10.9 (7)	14.7 (7)	11.1 (7)	-1.8 (6)	-1.8 (6)	1.4 (6)
C3	10.5 (6)	15.6 (7)	9.5 (7)	-0.1 (6)	-2.5 (5)	-0.6 (6)
C13	10.0 (6)	13.1 (7)	8.7 (6)	0.2 (5)	-0.9 (5)	-0.1 (6)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C4	9.2 (6)	16.7 (7)	11.4 (7)	-0.3 (6)	-1.7 (5)	0.7 (6)
C6	14.2 (7)	16.4 (7)	12.2 (7)	-1.6 (6)	-2.8 (6)	4.0 (7)
C10	7.7 (6)	11.8 (6)	8.2 (6)	-0.5 (5)	0.6 (5)	0.4 (6)
C8	9.7 (6)	14.6 (7)	10.1 (7)	-2.1 (5)	-0.6 (5)	2.2 (6)
C17	12.9 (7)	15.4 (7)	10.4 (7)	0.4 (6)	-1.9 (6)	-0.2 (6)
C19	12.5 (7)	11.6 (7)	12.0 (7)	-0.3 (6)	-0.5 (6)	-0.1 (6)
C11	7.3 (6)	19.8 (8)	9.8 (7)	-1.1 (6)	0.6 (5)	1.5 (6)
C2	10.6 (6)	18.1 (7)	8.9 (6)	0.2 (6)	0.4 (5)	0.4 (6)
C18	18.5 (8)	13.9 (7)	16.7 (8)	2.2 (6)	-1.1 (6)	-1.5 (7)
C9	8.3 (6)	12.6 (7)	8.9 (6)	-0.3 (5)	-0.9 (5)	-0.7 (6)
C12	8.5 (6)	21.4 (8)	10.4 (7)	-0.5 (6)	-1.3 (5)	0.3 (6)
C16	19.8 (8)	21.8 (8)	11.6 (7)	-3.8 (6)	-2.8 (6)	6.5 (7)
C22	15.0 (7)	25.1 (9)	16.4 (8)	3.4 (7)	-1.4 (6)	2.8 (7)
C15	16.8 (8)	28.2 (9)	13.4 (7)	-8.0 (7)	-2.7 (6)	8.1 (8)
C7	17.4 (8)	18.3 (8)	14.2 (7)	-4.1 (6)	-3.6 (6)	8.5 (7)
C21	14.8 (7)	27.3 (9)	19.6 (9)	3.8 (7)	-0.4 (6)	3.8 (7)

Table 4: Bond Lengths for I-74.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O5	C19	1.4242 (19)	C14	C13	1.535 (2)
O2	C3	1.4414 (19)	C14	C8	1.514 (2)
O3	C5	1.4467 (19)	C14	C15	1.531 (2)
O1	C1	1.4478 (19)	C3	C4	1.514 (2)
O7	C23	1.212 (2)	C3	C2	1.507 (2)
O6	C23	1.360 (2)	C13	C17	1.565 (2)
O6	C21	1.450 (2)	C13	C18	1.538 (2)
O4	C11	1.4373 (19)	C13	C12	1.521 (2)
C23	C22	1.461 (2)	C6	C7	1.533 (2)
C20	C17	1.490 (2)	C10	C19	1.543 (2)
C20	C22	1.337 (2)	C10	C9	1.601 (2)
C20	C21	1.498 (2)	C8	C9	1.552 (2)
C5	C4	1.536 (2)	C8	C7	1.542 (2)
C5	C6	1.530 (2)	C17	C16	1.554 (2)
C5	C10	1.584 (2)	C11	C9	1.561 (2)
C1	C10	1.569 (2)	C11	C12	1.535 (2)
C1	C2	1.530 (2)	C16	C15	1.537 (2)

Table 5: Bond Angles for I-74.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C23	O6	C21	108.70 (14)	C3	C4	C5	114.63 (13)
O7	C23	O6	121.18 (17)	C5	C6	C7	111.29 (14)
O7	C23	C22	130.02 (19)	C5	C10	C9	110.56 (12)
O6	C23	C22	108.80 (15)	C1	C10	C5	107.68 (12)
C17	C20	C21	122.23 (15)	C1	C10	C9	108.77 (12)
C22	C20	C17	129.71 (17)	C19	C10	C5	109.32 (12)
C22	C20	C21	108.04 (16)	C19	C10	C1	108.30 (12)
O3	C5	C4	106.04 (12)	C19	C10	C9	112.09 (12)
O3	C5	C6	108.63 (13)	C14	C8	C9	111.48 (13)
O3	C5	C10	107.92 (12)	C14	C8	C7	110.05 (13)
C4	C5	C10	113.60 (12)	C7	C8	C9	110.23 (13)
C6	C5	C4	111.04 (13)	C20	C17	C13	116.28 (14)
C6	C5	C10	109.42 (12)	C20	C17	C16	113.19 (14)

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O1	C1	C10	112.14 (12)	C16	C17	C13	104.02 (13)
O1	C1	C2	106.95 (12)	O5	C19	C10	114.69 (13)
C2	C1	C10	117.05 (13)	O4	C11	C9	112.02 (13)
C8	C14	C13	113.72 (13)	O4	C11	C12	103.73 (12)
C8	C14	C15	117.56 (14)	C12	C11	C9	115.16 (13)
C15	C14	C13	104.38 (13)	C3	C2	C1	111.40 (13)
O2	C3	C4	111.18 (13)	C8	C9	C10	110.94 (12)
O2	C3	C2	107.37 (13)	C8	C9	C11	112.24 (12)
C2	C3	C4	108.33 (13)	C11	C9	C10	115.40 (12)
C14	C13	C17	99.36 (12)	C13	C12	C11	112.46 (13)
C14	C13	C18	113.35 (14)	C15	C16	C17	106.41 (13)
C18	C13	C17	110.55 (13)	C20	C22	C23	109.31 (17)
C12	C13	C14	105.94 (13)	C14	C15	C16	104.20 (13)
C12	C13	C17	115.73 (13)	C6	C7	C8	113.15 (13)
C12	C13	C18	111.36 (14)	O6	C21	C20	105.14 (15)

Table 6: Torsion Angles for I-74.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
O2	C3	C4	C5	-176.48 (13)	C6	C5	C10	C9	-37.88 (16)
O2	C3	C2	C1	177.47 (13)	C10	C5	C4	C3	53.80 (18)
O3	C5	C4	C3	172.15 (13)	C10	C5	C6	C7	66.91 (17)
O3	C5	C6	C7	-50.67 (17)	C10	C1	C2	C3	-55.20 (18)
O3	C5	C10	C1	-161.16 (12)	C8	C14	C13	C17	175.73 (13)
O3	C5	C10	C19	-43.71 (16)	C8	C14	C13	C18	58.43 (18)
O3	C5	C10	C9	80.14 (14)	C8	C14	C13	C12	-63.97 (17)
O1	C1	C10	C5	170.33 (12)	C8	C14	C15	C16	-162.08 (15)
O1	C1	C10	C19	52.23 (16)	C17	C20	C22	C23	179.74 (16)
O1	C1	C10	C9	-69.83 (16)	C17	C20	C21	O6	-179.58 (15)
O1	C1	C2	C3	178.06 (13)	C17	C13	C12	C11	167.59 (14)
O7	C23	C22	C20	178.24 (18)	C17	C16	C15	C14	8.98 (19)
O6	C23	C22	C20	-1.1 (2)	C19	C10	C9	C8	98.13 (15)
O4	C11	C9	C10	-71.92 (17)	C19	C10	C9	C11	-30.95 (18)
O4	C11	C9	C8	159.64 (14)	C2	C1	C10	C5	46.19 (17)
O4	C11	C12	C13	-173.36 (14)	C2	C1	C10	C19	-71.91 (17)
C23	O6	C21	C20	0.3 (2)	C2	C1	C10	C9	166.03 (13)
C20	C17	C16	C15	146.64 (16)	C2	C3	C4	C5	-58.72 (17)
C5	C6	C7	C8	-27.9 (2)	C18	C13	C17	C20	-45.61 (19)
C5	C10	C19	O5	72.67 (16)	C18	C13	C17	C16	79.56 (16)
C5	C10	C9	C8	-24.11 (17)	C18	C13	C12	C11	-65.06 (18)
C5	C10	C9	C11	-153.19 (13)	C9	C10	C19	O5	-50.27 (18)
C1	C10	C19	O5	-170.27 (12)	C9	C8	C7	C6	-35.7 (2)
C1	C10	C9	C8	-142.15 (13)	C9	C11	C12	C13	-50.60 (19)
C1	C10	C9	C11	88.77 (15)	C12	C13	C17	C20	82.15 (18)
C14	C13	C17	C20	-165.00 (14)	C12	C13	C17	C16	-152.68 (14)
C14	C13	C17	C16	-39.83 (15)	C12	C11	C9	C10	169.87 (13)
C14	C13	C12	C11	58.60 (17)	C12	C11	C9	C8	41.42 (18)
C14	C8	C9	C10	-174.47 (13)	C22	C20	C17	C13	94. 8(2)
C14	C8	C9	C11	-43.72 (18)	C22	C20	C17	C16	-25. 5(3)
C14	C8	C7	C6	-159.07 (15)	C22	C20	C21	O6	-0.9 (2)
C13	C14	C8	C9	57.62 (18)	C15	C14	C13	C17	46.35 (15)
C13	C14	C8	C7	-179.75 (14)	C15	C14	C13	C18	-70.95 (17)
C13	C14	C15	C16	-35.06 (17)	C15	C14	C13	C12	166.66 (14)
C13	C17	C16	C15	19.52 (18)	C15	C14	C8	C9	179.99 (14)

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C4	C5	C6	C7	-166.90 (14)	C15	C14	C8	C7	-57.4 (2)
C4	C5	C10	C1	-43.89 (16)	C7	C8	C9	C10	63.01 (17)
C4	C5	C10	C19	73.56 (16)	C7	C8	C9	C11	-166.24 (13)
C4	C5	C10	C9	-162.59 (13)	C21	O6	C23	O7	-178.95 (16)
C4	C3	C2	C1	57.31 (17)	C21	O6	C23	C22	0.5 (2)
C6	C5	C4	C3	-70.03 (17)	C21	C20	C17	C13	-86.8 (2)
C6	C5	C10	C1	80.82 (15)	C21	C20	C17	C16	152.80 (17)
C6	C5	C10	C19	-161.74 (13)	C21	C20	C22	C23	1.2 (2)

Table 7: Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for I-74.

Atom	*x*	*Y*	*z*	$U_{(eq)}$
H5	4143.53	8470.87	3096.28	24
H2	6734.46	5648.39	5161.91	23
H3	6624.09	7009	3321.76	21
H1	658.89	7398.05	4500.94	20
H4	-604.73	6835.97	3729.45	35
H8A	9490(40)	5470(20)	4844(11)	47
H8B	9530(30)	4390(20)	5126(12)	47
H1A	1992.98	5265.7	4186.98	13
H14	1355.1	4678.63	2317.69	15
H3A	4815.61	4867.14	4620.02	14
H4A	6836.17	6034.89	4146.32	15
H4B	5850.58	7286.25	4271.81	15
H6A	4112.48	4383.96	3687.19	17
H6B	5970.3	4594.01	3478.94	17
H8	3620.18	6596.85	2603.04	14
H17	-663.76	5035.05	1615.04	15
H19A	1716.53	8377.48	3827.74	14
H19B	3629.18	8409.09	3991.68	14
H11	653.49	7812.46	2986.25	15
H2A	3313.07	7226.88	4839.63	15
H2B	2646.06	5925.76	5064.62	15
H18A	2268.89	7547.92	1567.09	25
H18B	2095.57	7983.42	2188.59	25
H18C	624.06	8238.84	1766.36	25
H9	1397.43	5330.16	3321.99	12
H12A	-1080.37	5722.47	2539.88	16
H12B	-1365.02	7145.82	2382.1	16
H16A	1402.73	4318.21	1092.63	21
H16B	2039.69	5680.97	929.46	21
H22	697.87	7143.28	527.84	23
H15A	3425.01	4254.4	1717.4	23
H15B	3852.13	5696.92	1621.78	23
H7A	3705.83	3991.84	2803.85	20
H7B	5200.95	4862.25	2614.11	20
H21A	-3324.57	5895.86	1145.16	25
H21B	-2996.13	7099.75	1517.89	25

Experimental

Single crystals of $C_{24}H_{36}O_8$ [**I-74**] were obtained by recrystallization from dichlomethane/methanol.
A suitable crystal was selected and [] on a Xcalibur, Eos, Gemini ultra diffractometer. The crystal was kept at 150 K during data collection. Using Olex2 [1], the structure was solved with the SHELXT [2] structure solution program using Intrinsic Phasing and refined with the SHELXL [3] refinement package using Least Squares minimisation.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2. Sheldrick, G.M. (2015). Acta Cryst. A71, 3-8.
3. Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

Crystal structure determination of I-74.

Crystal Data for $C_{23}H_{36}O_8$ (M =440.52 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 8.0811(2) Å, b = 10.7894(2) Å, c = 24.5112(5) Å, V = 2137.14(8) Å^3, Z = 4, T = 150 K, μ(Mo Kα) = 0.102 mm^{-1}, *Dcalc* = 1.369 g/cm^3, 14095 reflections measured (5.03° ≤ 2Θ ≤ 65.146°), 6797 unique (R_{int} = 0.0316, R_{sigma} = 0.0461) which were used in all calculations. The final R_1 was 0.0384 (I > 2σ(I)) and wR_2 was 0.0961 (all data).

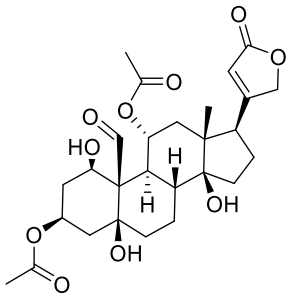
Refinement model description

Number of restraints - 3, number of constraints - unknown.

Details:

```
1. Fixed Uiso
 At 1.2 times of:
  All C(H) groups, All C(H,H) groups
 At 1.5 times of:
  All C(H,H,H) groups, All O(H) groups, All O(H,H) groups
2. Restrained distances
 O8-H8A = O8-H8B
 0.85 with sigma of 0.02
 H8A-H8B
 1.34 with sigma of 0.04
3.a Ternary CH refined with riding coordinates:
 C1(H1A), C14(H14), C3(H3A), C8(H8), C17(H17), C11(H11), C9(H9)
3.b Secondary CH2 refined with riding coordinates:
 C4(H4A,H4B), C6(H6A,H6B), C19(H19A,H19B), C2(H2A,H2B), C12(H12A,H12B),
 C16(H16A,H16B), C15(H15A,H15B), C7(H7A,H7B), C21(H21A,H21B)
3.c Aromatic/amide H refined with riding coordinates:
 C22(H22)
3.d Idealised Me refined as rotating group:
 C18(H18A,H18B,H18C)
3.e Idealised tetrahedral OH refined as rotating group:
 O5(H5), O2(H2), O3(H3), O1(H1), O4(H4)
```

(1*R*,3*S*,5*S*,8*R*,10*R*,11*R*,13*R*,14*S*,17*R*)-10-formyl-1,5,14-trihydroxy-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,11-diyl diacetate (I-119)



$C_{27}H_{36}O_{10}$
M: 520,58 g/mol

(1*R*,3*S*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-1,5,14-trihydroxy-10-(hydroxymethyl)-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,11-diyl diacetate **I-28** (95 mg, 182 µmol, 1.0 equiv) is dissolved in dichloromethane (0.06 M) containing (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO) (5.68 mg, 36.36 µmol, 0.20 equiv) and diacetoxyiodobenzene (64.0 mg, 198 µmol, 1.10 equiv) and the solution is stirred for 16 h at room temperature. The solution is washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and the solvent is evaporated in vacuo. The crude product is purified by column chromatography (DCM → DCM/MeOH 9/1) to give **I-119** (63.0 mg, 0.12 mmol) as white crystalline solid in 67% yield.

Characterization:

R_f = 0.27 (DCM/MeOH 9.5/0.5) [CAM].

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 10.13 (s, 1H), 5.87 (s, 1H), 5.22 (s, 2H), 4.88 (d, *J* = 17.7 Hz, 1H), 4.76 (d, *J* = 17.7 Hz, 1H), 4.63 (s, 1H), 2.73 (dd, *J* = 9.2, 5.2 Hz, 2H), 2.32 – 2.09 (m, 7H), 2.04 (s, 3H), 2.01 (s, 3H), 1.95 – 1.85 (m, 4H), 1.77 (p, *J* = 10.8, 10.2 Hz, 3H), 1.61 (t, *J* = 12.0 Hz, 1H), 1.38 – 1.20 (m, 3H), 0.90 (s, 3H).

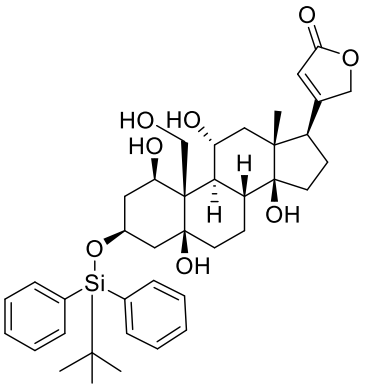
^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 207.6, 174.4, 173.1, 170.7, 169.4, 118.4, 83.7, 74.3, 73.6, 69.8, 69.4, 68.1, 58.0, 49.9, 49.3, 45.2, 44.3, 42.1, 37.1, 36.3, 32.8, 31.1, 26.7, 24.6, 21.7, 21.5, 16.3.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{27}H_{36}NaO_{10}$: 543.2203, found 543.2201.

LRMS (ESI) = *m/z* 538 (100%) $[M+H_2O]^+$, 521 (17.2%) $[M+H]^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3412, 2932, 1709, 1435, 1366, 1021, 953, 732, 604, 501, 439.

4-((1*R*,3*S*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-3-((tert-butyldiphenylsilyl)oxy)-1,5,11,14-tetrahydroxy-10-(hydroxymethyl)-13-methylhexadecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)furan-2(5*H*)-one (I-122)



$C_{39}H_{52}O_8Si$
M: 676,92 g/mol

4-((3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*,14b*S*)-11-((tert-butyldiphenylsilyl)oxy)-5,12a,14b-trihydroxy-3a,8,8-trimethylhexadecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-3-yl)furan-2(5*H*)-one **I-112** (0.49 g, 0.68 mmol, 1.0 equiv) and indium trichloride (0.30 g, 1.36 mmol) are dissolved in acetonitrile (0.07 M) and water (50.0 µL, 2.72 mmol, 4.0 equiv). The reaction is stirred for 1 h at room temperature. After addition of water and dichloromethane, the layers are separated and the aqueous layer is extracted two times with dichloromethane. The combined organic phases are dried with Na_2SO_4, filtered, the solvent is evaporated in vacuo and the crude product is purified by column chromatography (DCM → DCM/MeOH 95/5) to give **I-122** (0.42 g, 0.61 mmol) as white crystalline compound in 90% yield.

Characterization:

R_f = 0.15 (DCM/MeOH 95/5) [UV, CAM].

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.72 (dt, *J* = 6.8, 1.4 Hz, 2H), 7.70 – 7.67 (m, 2H), 7.49 – 7.45 (m, 2H), 7.43 – 7.39 (m, 4H), 5.88 (d, *J* = 1.9 Hz, 1H), 4.94 (s, 1H), 4.89 (dd, *J* = 18.2, 1.9 Hz, 1H), 4.75 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.34 (t, *J* = 3.4 Hz, 1H), 4.05 – 3.98 (m, 2H), 2.77 (dd, *J* = 9.4, 5.7 Hz, 1H), 2.16 – 2.04 (m, 2H), 2.01 – 1.93 (m, 2H), 1.91 – 1.80 (m, 3H), 1.73 – 1.51 (m, 6H), 1.44 (ddd, *J* = 13.2, 8.9, 4.5 Hz, 3H), 1.31 – 1.23 (m, 3H), 1.09 (s, 11H), 0.94 (s, 3H).

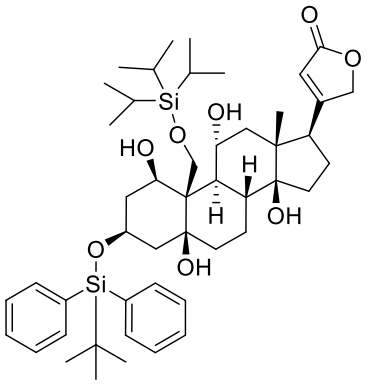
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 174.4, 173.6, 136.1, 136.0, 132.8, 132.8, 130.3, 130.3, 128.0, 118.1, 85.1, 75.7, 73.6, 71.3, 69.4, 69.1, 61.8, 50.4, 49.9, 49.1, 48.2, 47.6, 41.0, 38.7, 36.5, 35.0, 33.5, 27.2, 27.1, 23.0, 19.1, 17.5.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{39}H_{52}NaO_8Si$: 699.3324, found 699.3315.

LRMS (ESI) = *m/z* 677 (100%) $[M+H]^+$.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3380, 2929, 1731, 1426, 1109, 1026, 821, 701, 609, 503.

4-((1*R*,3*S*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-3-((tert-butyldiphenylsilyl)oxy)-1,5,11,14-tetrahydroxy-13-methyl-10-(((triisopropylsilyl)oxy)methyl)hexadecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)furan-2(5*H*)-one (I-123)



$C_{48}H_{72}O_8Si_2$
M: 833,27

4-((1*R*,3*S*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-3-((tert-butyldiphenylsilyl)oxy)-1,5,11,14-tetrahydroxy-10-(hydroxymethyl)-13-methylhexadecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)furan-2(5*H*)-one **I-122** (0.20 g, 0.29 mmol, 1.0 equiv), triethylamine (0.20 mL, 1.46 mmol, 5.0 equiv) and 4-dimethylaminopyridine (25.0 mg, 0.20 mmol, 0.70 equiv) are dissolved in dimethylformamide (0.05 M), the solution is cooled down to 0 °C and triisopropylsilyl chloride (92.0 µmL, 0.44 mmol, 1.50 equiv) is added dropwise. The solution is warmed up to 50 °C and stirred for 8 h. The reaction mixture is poured into water and extracted with ethylacetate. The combined organic phases are washed with brine, dried over Na_2SO_4, filtered, the solvent is evaporated in vacuo and the crude product is purified by column chromatography (CH/EtOAc 7/3→5/5) to give **I-123** (0.22 mg, 0.26 mmol) as white crystalline compound in 89% yield.

Characterization:

R_f = 0.59 (DCM/MeOH 95/5) [UV, CAM].

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.74 (ddd, *J* = 8.0, 3.5, 1.5 Hz, 4H), 7.46 – 7.42 (m, 2H), 7.39 (td, *J* = 7.2, 6.8, 1.6 Hz, 4H), 5.87 (d, *J* = 1.9 Hz, 1H), 5.07 (d, *J* = 36.3 Hz, 2H), 4.90 (dd, *J* = 18.1, 1.8 Hz, 1H), 4.80 – 4.72 (m, 2H), 4.29 (s, 1H), 4.21 (d, *J* = 10.3 Hz, 1H), 4.08 (ddd, *J* = 12.9, 9.8, 3.7 Hz, 1H), 2.80 (dd, *J* = 9.4, 5.9 Hz, 1H), 2.15 – 2.07 (m, 2H), 1.98 (dt, *J* = 13.5, 9.7 Hz, 1H), 1.92 – 1.78 (m, 5H), 1.72 – 1.56 (m, 5H), 1.54 – 1.38 (m, 3H), 1.37 – 1.31 (m, 2H), 1.23 (ddt, *J* = 13.4, 10.3, 6.3 Hz, 4H), 1.14 (d, *J* = 7.3 Hz, 18H), 1.08 (s, 9H), 0.94 (s, 3H).

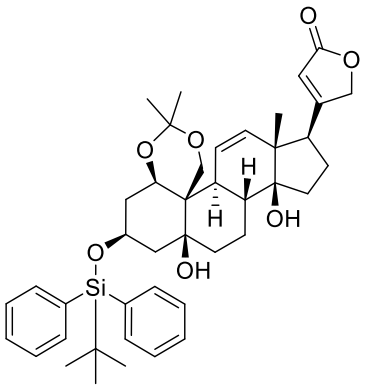
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 174.1, 173.3, 136.1, 136.0, 133.4, 133.4, 129.8, 127.7, 127.7, 117.9, 85.2, 73.8, 73.4, 69.8, 68.8, 62.2, 50.4, 49.6, 48.8, 48.6, 40.9, 33.5, 26.9, 22.5, 19.0, 18.2, 18.1, 17.7, 17.7, 17.5, 12.3, 12.1.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{48}H_{72}NaO_8Si_2$: 855.4660, found 855.4658.

LRMS (ESI) = *m/z* 833 (100%) $[M+H]^+$. *(Exact mass 832,48)*

IR (ATR): ṽ [cm^{-1}] = 3436, 2930, 2863, 1738, 1462, 1105, 1060, 883, 741, 702, 610, 503.

4-((3*R*,3a*R*,5a*S*,5bR,9a*R*,11S,12a*S*,14a*R*,14b*S*)-11-((tert-butyldiphenylsilyl)oxy)-12a,14b-dihydroxy-3a,8,8-trimethyl-1,2,3,3a,5a,9a,10,11,12,12a,13,14,14a,14b-tetradecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-3-yl)furan-2(5*H*)-one (I-125)



$C_{42}H_{54}O_7Si$
M: 698,97 g/mol

To a mixture of 4-((3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*,14b*S*)-11-((tert-butyldiphenylsilyl)oxy)-5,12a,14b-trihydroxy-3a,8,8-trimethylhexadecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-3-yl)furan-2(5*H*)-one **I-102** (0.85 g, 1.18 mmol, 1.0 equiv) and 4-dimethylaminopyridine (0.44 g, 3.56 mmol, 3.0 equiv), a solution of methyltriphenoxyphosphonium iodide (1.60 g, 3.55 mmol, 3.0 equiv) in dry dimethylformamide (0.06 M) is added. The solution is stirred for 16 h at room temperature. The solution is cooled down to 0 °C and quenched with aq. Na_2HCO_3 solution, then the product is extracted with ethylacetate. The combined organic phases are washed with brine, dried over Na_2SO_4, filtered, the solvent is evaporated in vacuo and the crude product is purified by column chromatography (CH → CH/EtOAc 7/3) to give **I-125** (0.81 g, 1.16 mmol) as white crystalline compound in 98% yield.

(Note: MTPI is handled and weighed inside the glove box)

Characterization:

R_f = 0.67 (EtOAc/CH 8/2) [UV, CAM].

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.83 – 7.80 (m, 2H), 7.74 (dt, *J* = 6.7, 1.5 Hz, 2H), 7.46 – 7.42 (m, 2H), 7.41 – 7.37 (m, 4H), 5.92 (q, *J* = 1.6 Hz, 1H), 5.79 (dd, *J* = 10.4, 1.5 Hz, 1H), 5.50 (dd, *J* = 10.3, 2.8 Hz, 1H), 5.10 (s, 1H), 4.93 – 4.89 (m, 1H), 4.79 – 4.75 (m, 1H), 4.47 (dd, *J* = 11.6, 1.2 Hz, 1H), 4.31 (dd, *J* = 4.4, 2.5 Hz, 1H), 4.21 (p, *J* = 2.9 Hz, 1H), 3.56 (d, *J* = 11.6 Hz, 1H), 2.75 (t, *J* = 7.3 Hz, 1H), 2.04 (s, 1H), 1.99 – 1.72 (m, 10H), 1.65 – 1.57 (m, 4H), 1.47 (s, 3H), 1.39 (s, 3H), 1.07 (s, 9H), 0.92 (s, 3H).

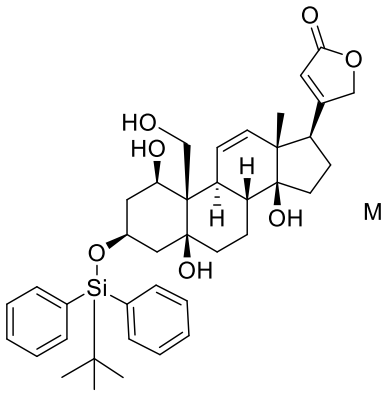
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 174.1, 172.2, 140.3, 136.4, 136.1, 133.8, 133.4, 129.9, 129.9, 127.8, 127.6, 123.3, 117.9, 100.7, 83.3, 73.5, 72.8, 68.3, 66.3, 60.7, 60.5, 51.5, 49.0, 45.2, 41.2, 41.0, 37.7, 36.7, 33.3, 32.2, 27.7, 26.9, 24.9, 23.9, 21.9, 21.2, 19.5, 19.2, 14.3.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{42}H_{54}NaO_7Si$: 721.3531, found 721.3532.

LRMS (ESI) = *m/z* 699 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3503, 2930, 2858, 1740, 1374, 1222, 1099, 865, 700, 609, 502.

4-((1*R*,3*S*,5*S*,8*R*,9*S*,10*R*,13*R*,14*S*,17*R*)-3-((tert-butyldiphenylsilyl)oxy)-1,5,14-trihydroxy-10-(hydroxymethyl)-13-methyl-2,3,4,5,6,7,8,9,10,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)furan-2(5*H*)-one (I-126)



$C_{39}H_{50}O_7Si$
M: 658,91 g/mol

4-((3*R*,3a*R*,5a*S*,5bR,9a*R*,11S,12a*S*,14a*R*,14b*S*)-11-((tert-butyldiphenylsilyl)oxy)-12a,14b-dihydroxy-3a,8,8-trimethyl-1,2,3,3a,5a,9a,10,11,12,12a,13,14,14a,14b-tetradecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-3-yl)furan-2(5*H*)-one **I-125** (0.54 g, 0.78 mmol, 1.0 equiv) is dissolved in dichloromethane (0.12 M) and zinc bromide (3.49 g, 15.51 mmol, 20.0 equiv) is added. The reaction is stirred for 72 h at room temperature.

The reaction is quenched by adding Na_2EDTA dissolved in water and the reaction is stirred for further 5 min.

The reaction mixture was poured into a brine and extracted with dichloromethane, the combined organic layers are dried over Na_2SO_4, filtered, the solvent is evaporated in vacuo and the crude product is purified by column chromatography (DCM → DCM/MeOH 95/5) to give **I-126** (0.45 g, 0.68 mmol) as white crystalline compound in 87% yield.

Characterization:

R_f = 0.47 (EtOAc/CH 8/2) [UV, CAM].

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.78 – 7.71 (m, 4H), 7.48 – 7.37 (m, 6H), 5.90 (q, *J* = 1.6 Hz, 1H), 5.55 – 5.50 (m, 1H), 5.38 (dd, *J* = 10.3, 2.5 Hz, 1H), 4.96 – 4.85 (m, 1H), 4.75 (dd, *J* = 17.9, 1.8 Hz, 1H), 4.53 (d, *J* = 12.3 Hz, 1H), 4.47 (t, *J* = 3.4 Hz, 1H), 4.32 (t, *J* = 3.1 Hz, 1H), 3.95 (d,

J = 12.3 Hz, 1H), 3.28 (s, 4H), 2.73 (t, *J* = 7.4 Hz, 1H), 2.13 – 1.99 (m, 2H), 1.99 – 1.89 (m, 2H), 1.89 – 1.74 (m, 5H), 1.74 – 1.65 (m, 3H), 1.65 – 1.55 (m, 2H), 1.09 (s, 9H), 0.90 (s, 3H).

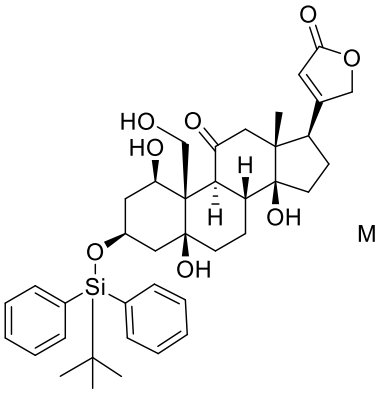
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 174.2, 172.6, 139.4, 136.2, 136.1, 133.2, 133.1, 130.1, 127.9, 122.7, 117.9, 83.4, 75.9, 73.6, 72.7, 69.1, 65.3, 51.5, 48.7, 45.2, 41.8, 39.3, 38.7, 37.0, 33.9, 32.6, 27.5, 27.1, 23.0, 19.3, 19.1.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{39}H_{50}NaO_7Si$: 681.3218, found 681.3216.

LRMS (ESI) = *m/z* 659 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3449, 2930, 2856, 1734, 1624, 1426, 1131, 1085, 861, 700, 610, 502.

4-((1*R*,3*S*,5*S*,8*R*,9*S*,10*R*,13*R*,14*S*,17*R*)-3-((tert-butyldiphenylsilyl)oxy)-1,5,14-trihydroxy-10-(hydroxymethyl)-13-methyl-11-oxohexadecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)furan-2(5*H*)-one (I-126a)



$C_{39}H_{50}O_8Si$
M: 674,91 g/mol

A mixture of 4-((3*R*,3a*R*,5a*S*,5bR,9a*R*,11S,12a*S*,14a*R*,14b*S*)-11-((tert-butyldiphenylsilyl)oxy)-12a,14b-dihydroxy-3a,8,8-trimethyl-1,2,3,3a,5a,9a,10,11,12,12a,13,14,14a,14b-tetradecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-3-yl)furan-2(5*H*)-one **I-125** (41.0 mg, 59.0 µmol, 1.0 equiv) and (3R,3aR,5aS,5bR,9aR,11S,12aS,14aR,14bS)-11-((tert-butyldiphenylsilyl)oxy)-12a,14b-dihydroxy-3a,8,8-trimethyl-3-(5-oxo-2,5-dihydrofuran-3-yl)tetradecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-5(5a*H*)-one **I-125A** (42.0 mg, 59.0 µmol, 1.0 equiv) is dissolved in dry methanol (0.03 M) and pyridinium *p*-toluenesulfonate (4.0 mg, 16.0 µmol, 0.5 equiv) is added. The reaction is stirred for 1 h at room temperature. The solvent is evaporated in vacuo and the crude product is purified by column chromatography (EtOAc/CH 2/8 → 7/3) to give **I-126a** (11.0 mg, 16.0 µmol) as white crystalline compound in 29% yield.

Characterization:

R_f = 0.34 (EtOAc/CH 8/2) [UV, CAM].

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.71 (dt, *J* = 6.8, 1.5 Hz, 2H), 7.65 – 7.61 (m, 2H), 7.49 – 7.44 (m, 2H), 7.42 – 7.37 (m, 4H), 5.88 (d, *J* = 1.9 Hz, 1H), 4.94 – 4.88 (m, 2H), 4.78 (d, *J* = 1.8 Hz, 1H), 4.75 (q, *J* = 5.4 Hz, 1H), 4.52 (q, *J* = 3.1 Hz, 1H), 4.39 (td, *J* = 11.1, 4.2 Hz, 1H), 4.00 (d, *J* = 12.4 Hz, 1H), 3.04 (dd, *J* = 13.4, 3.8 Hz, 1H), 2.76 (dd, *J* = 9.6, 5.3 Hz, 1H), 2.42 (dd, *J* = 15.0, 3.1 Hz, 1H), 2.29 (dt, *J* = 13.5, 2.8 Hz, 1H), 2.16 (dtd, *J* = 13.7, 9.9, 1.9 Hz, 1H), 2.09 – 1.98 (m, 4H), 1.89 (ddt, *J* = 13.4, 8.9, 4.7 Hz, 1H), 1.82 (td, *J* = 12.3, 4.2 Hz, 1H), 1.79 – 1.73 (m, 2H), 1.69 (dd, *J* = 13.2, 4.2 Hz, 1H), 1.62 (dtd, *J* = 12.1, 6.9, 6.0, 3.6 Hz, 2H), 1.57 (dd, *J* = 13.9, 4.6 Hz, 1H), 1.38 – 1.31 (m, 2H), 1.28 – 1.24 (m, 1H), 1.07 (s, 9H), 0.94 (s, 3H).

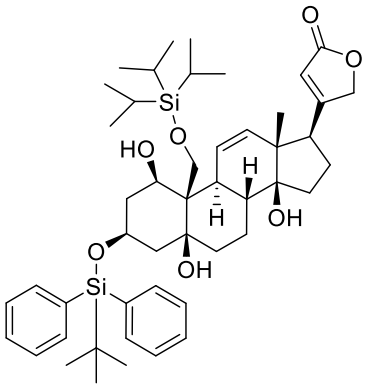
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 215.9, 174.4, 173.6, 136.2, 135.9, 132.3, 132.1, 130.5, 130.4, 128.1, 118.3, 85.0, 80.6, 73.6, 73.4, 67.3, 61.0, 60.0, 50.5, 50.3, 48.6, 45.7, 39.6, 37.6, 33.9, 33.2, 27.0, 27.0, 23.4, 19.1, 17.1.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{39}H_{50}NaO_8Si$: 697.3192, found 697.3265.

LRMS (ESI) = *m/z* 675 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3458, 2930, 1736, 1621, 1426, 1109, 1040, 890, 700, 609, 506, 435.

4-((1*R*,3*S*,5*S*,8*R*,9*S*,10*R*,13*R*,14*S*,17*R*)-3-((tert-butyldiphenylsilyl)oxy)-1,5,14-trihydroxy-13-methyl-10-(((triisopropylsilyl)oxy)methyl)-2,3,4,5,6,7,8,9,10,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)furan-2(5*H*)-one (I-127)



$C_{48}H_{70}O_7Si_2$
M: 815,25 g/mol

A solution of 4-((1*R*,3*S*,5*S*,8*R*,9*S*,10*R*,13*R*,14*S*,17*R*)-3-((tert-butyldiphenylsilyl)oxy)-1,5,14-trihydroxy-10-(hydroxymethyl)-13-methyl-2,3,4,5,6,7,8,9,10,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)furan-2(5*H*)-one **I-126** (0.45 g, 0.68 mmol, 1.0 equiv) in dimethylformamide (0.09 M) is treated with triethylamine (0.47 mL, 3.38 mmol, 5.0 equiv) and 4-dimethylaminopyridine (58.0 mg, 0.47 mmol, 0.70 equiv) at room temperature and then is cooled down to 0 °C and triisopropylsilyl chloride (0.14 mL, 0,68 mmol, 1.0 equiv) is added dropwise. The resulting mixture is stirred at room temperature for 30 min and then warmed up to 50 °C for 2 h.

The reaction mixture is cooled down to room temperature, quenched with water and extracted with ethylacetate. The combined organic phases are washed with brine, dried over Na_2SO_4, filtered, the solvent is evaporated in vacuo and the crude product is

purified by column chromatography (CH → CH/EtOAc 7/3) to give **I-127** (0.45 g, 0.56 mmol) as white crystalline compound in 82% yield.

Characterization:

R_f = 0.53 (CH/EtOAc 6/4) [UV, CAM].

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.82 – 7.71 (m, 4H), 7.41 (dq, *J* = 14.3, 7.2 Hz, 6H), 5.90 (s, 1H), 5.67 (d, *J* = 10.3 Hz, 1H), 5.27 (dd, *J* = 10.2, 2.3 Hz, 1H), 4.91 (dd, *J* = 17.9, 1.9 Hz, 1H), 4.82 – 4.71 (m, 2H), 4.59 (d, *J* = 10.3 Hz, 1H), 4.51 (d, *J* = 4.1 Hz, 1H), 4.31 – 4.25 (m, 1H), 4.12 (d, *J* = 10.3 Hz, 1H), 3.50 (s, 1H), 2.73 (t, *J* = 7.2 Hz, 1H), 2.13 (dt, *J* = 15.1, 2.8 Hz, 1H), 2.00 (dd, *J* = 15.0, 3.8 Hz, 1H), 1.93 – 1.55 (m, 12H), 1.51 – 1.40 (m, 2H), 1.27 (d, *J* = 6.2 Hz, 1H), 1.13 – 1.06 (m, 28H), 0.91 (d, *J* = 4.0 Hz, 3H).

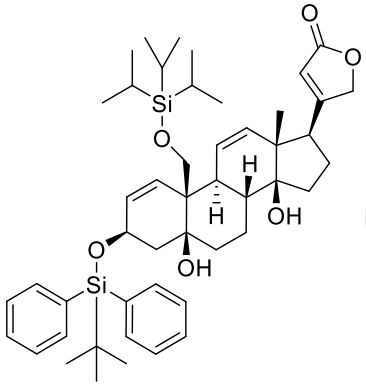
^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 174.1, 172.4, 137.4, 136.3, 133.7, 133.7, 129.9, 129.9, 127.8, 127.7, 124.8, 117.8, 83.8, 73.7, 73.6, 69.3, 68.7, 62.6, 51.4, 49.3, 47.2, 41.2, 40.4, 39.0, 35.8, 33.6, 33.3, 27.5, 27.1, 22.5, 19.4, 19.2, 18.4, 18.0, 12.1.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{48}H_{70}NaO_7Si_2$: 837.4541, found 837.4566.

LRMS (ESI) = *m/z* 815 (100%) $[M+H]^+$. (*Exact Mass: 814,47*)

IR (ATR): ṽ [cm^{-1}] = 3484, 2930, 2862, 1741, 1460, 1146, 1086, 882, 740, 700, 611, 501, 466.

4-((3*R*,5*S*,8*R*,9*S*,10*R*,13*R*,14*S*,17*R*)-3-((tert-butyldiphenylsilyl)oxy)-5,14-dihydroxy-13-methyl-10-(((triisopropylsilyl)oxy)methyl)-4,5,6,7,8,9,10,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[a]phenanthren-17-yl)furan-2(5*H*)-one (I-128)



$C_{48}H_{68}O_6Si_2$
M: 797,24 g/mol

A solution of methyltriphenoxyphosphonium iodide (0.70 g, 1.53 mmol, 4.70 equiv) in *N*,*N*'-dimethylpropyleneurea (0.08 M) is added to 4-((1*R*,3*S*,5*S*,8*R*,9*S*,10*R*,13*R*,14*S*,17*R*)-3-((tert-butyldiphenylsilyl)oxy)-1,5,14-trihydroxy-13-methyl-10-(((triisopropylsilyl)oxy)methyl)-2,3,4,5,6,7,8,9,10,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)furan-2(5*H*)-one **I-127** (0.27 g, 0.33 mmol, 1.0 equiv). The reaction is stirred for 16 h at 50 °C.

The solution is cooled down to 0 °C and quenched with saturated $NaHCO_3$ solution, then extracted with ethylacetate. The combined organic phases are washed with brine, dried

over Na_2SO_4, filtered, the solvent is evaporated in vacuo and the crude product is purified by column chromatography (CH → CH/EtOAc 7/3) to give **I-128** (0.20 g, 0.25 mmol) as white crystalline compound in 78% yield.

Characterization:

R_f = 0.18 (EtOAc/CH 2/8) [UV, CAM].

^{1}H NMR (400 MHz, C_6D_6): δ [ppm] = 7.84 – 7.76 (m, 4H), 7.26 (tq, *J* = 5.7, 2.2, 1.7 Hz, 6H), 6.21 (d, *J* = 10.4 Hz, 1H), 5.79 – 5.71 (m, 2H), 5.60 (dd, *J* = 10.1, 1.6 Hz, 1H), 5.00 (dd, *J* = 10.2, 2.7 Hz, 1H), 4.59 – 4.51 (m, 2H), 4.36 – 4.28 (m, 2H), 4.22 (td, *J* = 4.7, 1.5 Hz, 1H), 4.17 (d, *J* = 10.1 Hz, 1H), 2.26 (dd, *J* = 8.1, 5.5 Hz, 1H), 2.10 – 1.96 (m, 2H), 1.83 – 1.64 (m, 6H), 1.58 – 1.39 (m, 4H), 1.38 – 1.27 (m, 2H), 1.20 (dd, *J* = 5.6, 3.9 Hz, 18H), 1.15 (s, 9H), 0.88 (qd, *J* = 12.9, 3.4 Hz, 2H), 0.71 (s, 3H).

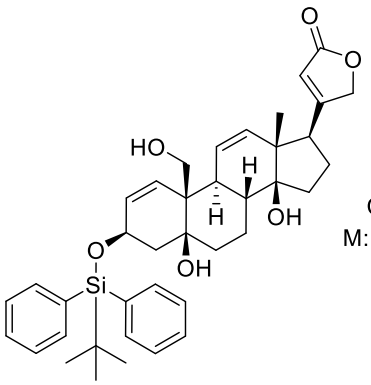
^{13}C-NMR (101 MHz, C_6D_6): δ [ppm] = 173.6, 172.5, 136.3, 136.3, 134.0, 133.6, 133.3, 130.3, 130.3, 118.0, 83.0, 73.1, 71.9, 66.4, 63.8, 51.4, 48.9, 47.2, 39.3, 32.4, 27.5, 27.0, 23.2, 19.3, 19.2, 18.5, 18.5, 18.2, 12.3.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{48}H_{68}NaO_6Si_2$: 819.4447, found 819.4457.

LRMS (ESI) = *m/z* 815 (100%) $[M+H_2O]^+$.

IR (ATR): ṽ [cm^{-1}] = 3494, 2930, 2862, 1741, 1622, 1460, 1058, 995, 796, 685, 609, 504, 485.

4-((3*R*,5*S*,8*R*,9*S*,10*R*,13*R*,14*S*,17*R*)-3-((tert-butyldiphenylsilyl)oxy)-5,14-dihydroxy-10-(hydroxymethyl)-13-methyl-4,5,6,7,8,9,10,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[a]phenanthren-17-yl)furan-2(5*H*)-one (I-130)



$C_{39}H_{48}O_6Si$
M: 640,32 g/mol

A suspension of 4-((3*R*,5*S*,8*R*,9*S*,10*R*,13*R*,14*S*,17*R*)-3-((tert-butyldiphenylsilyl)oxy)-5,14-dihydroxy-13-methyl-10-(((triisopropylsilyl)oxy)methyl)-4,5,6,7,8,9,10,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[a]phenanthren-17-yl)furan-2(5*H*)-one **I-128** (60.0 mg, 0.08 mmol, 1.0 equiv) in acetic acid (0.02 M), tetrahydrofuran (0.03 M) and water (0.03 M) is stirred overnight at 40 °C.

The reaction mixture is quenched and neutralize with saturated $NaHCO_3$ solution at 0 °C and the crude product extracted with dichloromethane.
The combined organic phases are washed with brine, dried over Na_2SO_4, filtered, the solvent is evaporated in vacuo. The crude product is purified by column chromatography (DCM → DCM/MeOH 95/5) to give **I-130** (44.0 mg, 68.6 µmol) as white crystalline compound in 91% yield.

Characterization:

R_f = 0.66 (EtOAc/CH 8/2) [CAM].

^{1}H NMR (400 MHz, C_6D_6): δ [ppm] = 7.76 (dt, *J* = 5.9, 3.7 Hz, 4H), 7.25 (dq, *J* = 5.5, 3.5, 2.7 Hz, 6H), 6.07 (d, *J* = 10.3 Hz, 1H), 5.79 – 5.71 (m, 2H), 5.38 (s, 1H), 5.25 (d, *J* = 10.2 Hz, 1H), 4.93 (dd, *J* = 10.1, 2.7 Hz, 1H), 4.56 – 4.45 (m, 1H), 4.39 (d, *J* = 11.4 Hz, 1H), 4.27 (dd, *J* = 17.7, 1.7 Hz, 1H), 4.20 (t, *J* = 3.8 Hz, 2H), 3.70 (d, *J* = 11.3 Hz, 1H), 2.12 (dt, *J* = 14.4, 8.4 Hz, 2H), 1.89 (dd, *J* = 14.9, 4.5 Hz, 1H), 1.72 – 1.63 (m, 3H), 1.61 (s, 1H), 1.54 (d, *J* = 11.5 Hz, 1H), 1.41 (dq, *J* = 14.3, 7.6, 6.1 Hz, 2H), 1.34 – 1.26 (m, 2H), 1.22 (dq, *J* = 10.2, 5.1, 4.6 Hz, 2H), 1.10 (s, 9H), 0.90 (dd, *J* = 22.4, 7.4 Hz, 1H), 0.73 (qd, *J* = 13.8, 13.4, 4.0 Hz, 2H).

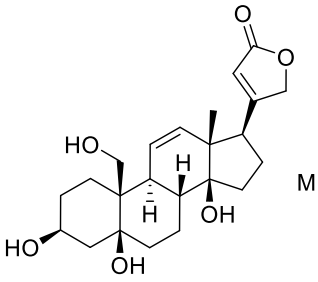
^{13}C-NMR (101 MHz, C_6D_6): δ [ppm] = 173.4, 171.9, 139.5, 136.3, 136.3, 135.6, 133.5, 133.2, 130.5, 130.5, 123.2, 118.3, 82.7, 75.7, 73.0, 66.7, 64.6, 51.4, 48.6, 47.2, 46.4, 39.0, 37.7, 36.9, 31.8, 27.5, 27.0, 23.4, 19.2, 19.0.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{39}H_{48}NaO_6Si$: 663.3112, found 663.3104.

LRMS (ESI) = *m/z* 641 (100%) $[M+H_2O]^+$.

IR (ATR): ṽ [cm^{-1}] = 3411, 2931, 2858, 1746, 1427, 1106, 1054, 993, 869, 801, 701, 596, 503.

4-((3*S*,5*S*,8*R*,9*S*,10*R*,13*R*,14*S*,17*R*)-3,5,14-trihydroxy-10-(hydroxymethyl)-13-methyl-2,3,4,5,6,7,8,9,10,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)furan-2(5*H*)-one (I-133)



$C_{23}H_{32}O_6$
M: 404,22 g/mol

4-((1*R*,3*S*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,14*S*,17*R*)-3-((tert-butyldiphenylsilyl)oxy)-1,5,11,14-tetrahydroxy-10-(hydroxymethyl)-13-methylhexadecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)furan-2(5*H*)-one **I-130** (78.0 mg, 0.12 mmol, 1.0 equiv) is loaded in a flask and dried overnight under the high vacuum to remove all solvent and water traces. Then, it is washed with N_2 and the stir bar is added. The vial is insert into

the gloves box and the catalyst (2.0 mg, 2.43 µmol, 2.0 mol%) is weighted and added to the starting material. Freshly dry degassed dichloromethane (0.04 M) under N_2 atmosphere is added.

The hydrogenation is carried out by using the autoclave, first washed with N_2 and H_2 several times. Subsequently, the vial with the solution is placed inside and washed again for 25-30 min and the hydrogenation is performed under H_2 (35 bar) for 16 h at room temperature.

The solvent is evaporated in vacuo and the orange crude product (80.0 mg, 0.12 mmol, 1.0 equiv) is dissolved in tetrahydrofuran (0.12 M) in a Teflon vial and the solution is cooled down to 0°C. In a second Teflon vial, pyridine (0.12 M) is cooled down to 0 °C and methanol (0.70 M) is added. HF·pyridine 70% (0.40 mL, 2.50 mmol, 20.0 equiv) is slowly added to the pyridine-methanol solution at 0 °C. This solution is then slowly transferred to the solution of sylil product in tetrahydrofuran at 0 °C. The reaction is allowed to stir overnight at room temperature.

The reaction is quenched at 0 °C with methoxytrimethylsilane (10.0 mL, 74.6 mmol, 600.0 equiv) and diluted with toluene. The solution is concentrated under reduced pressure, but not to dryness, and diluted again with toluene. This process is repeated 3 times to remove all pyridine. The crude product is purified by column chromatography (DCM → DCM/MeOH 9/1) to give **I-133** (41.0 mg, 0.10 mmol) as white crystalline compound in 81% yield.

Characterization:

R_f = 0.06 (EtOAc/CH 8/2) [UV, CAM].

^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 6.01 (s, 1H), 5.61 (d, *J* = 10.3 Hz, 1H), 5.55 – 5.52 (m, 1H), 5.07 (d, *J* = 18.1 Hz, 1H), 4.98 (dd, *J* = 18.2, 1.4 Hz, 1H), 4.29 (d, *J* = 11.5 Hz, 1H), 4.16 (s, 1H), 3.40 (d, *J* = 11.5 Hz, 1H), 2.94 (t, *J* = 7.0 Hz, 1H), 2.53 (tt, *J* = 13.1, 6.5 Hz, 1H), 2.35 (d, *J* = 11.5 Hz, 1H), 2.28 (dd, *J* = 15.0, 3.0 Hz, 1H), 2.09 – 1.91 (m, 6H), 1.88 (td, *J* = 12.3, 3.4 Hz, 1H), 1.81 – 1.71 (m, 4H), 1.64 – 1.53 (m, 4H), 1.30 (qd, *J* = 13.4, 3.8 Hz, 1H), 0.95 (s, 3H).

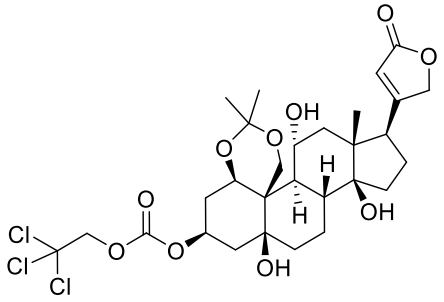
^{13}C-NMR (151 MHz, CD_3OD): δ [ppm] = 176.9, 176.6, 140.4, 123.8, 117.9, 84.5, 78.5, 75.4, 68.7, 66.2, 52.7, 50.0, 44.0, 40.5, 39.6, 38.6, 37.3, 32.7, 28.6, 28.1, 24.4, 19.8, 19.3.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{23}H_{32}NaO_6$: 427.2091, found 427.2090.

LRMS (ESI) = *m/z* 405 (100%) $[M+H_2O]^+$.

IR (ATR): ṽ [cm^{-1}] = 3444, 2931, 1731, 1446, 1137, 1026, 825, 732, 557.

Trichloromethyl ((3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*,14b*S*)-5,12a,14b-trihydroxy-3a,8,8-trimethyl-3-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-11-yl) carbonate (I-136)



$C_{29}H_{39}Cl_3O_{10}$
M: 653,97 g/mol

4-((3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*,14b*S*)-5,11,12a,14b-tetrahydroxy-3a,8,8-trimethylhexadecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-3-yl)furan-2(5*H*)-one **I-25** (0.98 g, 2.04 mmol, 1.0 equiv) is suspended in dichloromethane (0.06 M) and trichloroethyl chloroformate (0.84 mL, 6.12mmol, 3.0 equiv) and pyridine (in excess until **I-25** is completely dissolved) are added.

The solution is stirred at room temperature overnight, then quenched with saturated $NaHCO_3$ solution and extracting with dichloromethane. The combined organic phases are washed with brine, dried over Na_2SO_4 and filtered.

The solvent is evaporated in vacuo and the crude product is purified by column chromatography (CH → EtOAc/CH 7/3) to give **I-136** (1.28 g, 1.96 mmol) as white crystalline solid in 96% yield.

Characterization:

R_f = 0.53 (DCM/MeOH 9/1) [CAM].

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 5.89 (d, *J* = 1.9 Hz, 1H), 5.23 (td, *J* = 8.8, 5.1 Hz, 1H), 5.13 (s, 1H), 4.90 – 4.83 (m, 2H), 4.81 – 4.73 (m, 3H), 4.67 (d, *J* = 11.9 Hz, 1H), 4.50 (d, *J* = 12.5 Hz, 2H), 4.35 (t, *J* = 3.2 Hz, 1H), 3.73 (d, *J* = 12.6 Hz, 1H), 2.88 (t, *J* = 7.5 Hz, 1H), 2.35 – 2.23 (m, 1H), 2.15 – 2.04 (m, 3H), 1.97 (ddt, *J* = 25.9, 11.7, 4.6 Hz, 4H), 1.74 (dt, *J* = 12.4, 7.6 Hz, 2H), 1.62 (td, *J* = 18.6, 16.4, 11.3 Hz, 4H), 1.50 – 1.42 (m, 2H), 1.40 (s, 3H), 1.23 (s, 3H), 0.96 (s, 3H).

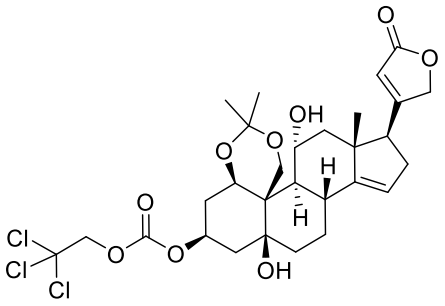
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 174.4, 172.6, 153.1, 152.6, 118.2, 101.6, 94.7, 94.3, 83.3, 76.7, 75.9, 74.0, 73.6, 72.6, 67.0, 60.4, 49.7, 48.8, 46.9, 43.8, 43.0, 40.9, 35.7, 35.1, 33.7, 31.0, 28.6, 26.8, 24.4, 23.1, 17.3.

HRMS (APCI) = *m/z* calcd. for $C_{29}H_{39}NaCl_3O_{10}$: 653.1682, found 653.1689.

LRMS (ESI) = *no detectable*

IR (ATR): ṽ [cm^{-1}] = 3488, 2937, 1745, 1380, 1236, 1053, 809, 723, 570, 431.

(3*S*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*)-5,12a-dihydroxy-3a,8,8-trimethyl-3-(5-oxo-2,5-dihydrofuran-3-yl)-2,3,3a,4,5,5a,9a,10,11,12,12a,13,14,14a-tetradecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-11-yl (3,3,3-trichloropropyl) carbonate (I-137)



$C_{29}H_{37}Cl_3O_9$
M: 635,96 g/mol

Trichloromethyl ((3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*,14b*S*)-5,12a,14b-trihydroxy-3a,8,8-trimethyl-3-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-11-yl) carbonate **I-136** (50.0 mg, 76.5 µmol, 1.0 equiv) is dissolved in tetrahydrofuran (0.05 M) and the solution is cooled down to -20 °C. *Martin's Sulfurane* reagent (0.10 g, 0.15 mmol, 2.0 equiv) dissolved in tetrahydrofuran (1.0 mL) is added dropwise to the solution under N_2. The reaction is stirred at -20 °C for 30 min. The solvent is evaporated in vacuo and the crude product is purified by column chromatography (CH → EtOAc/CH 7/3) to give **I-137** (40.0 mg, 62.89 µmol) as white crystalline solid in 82% yield.

(Note: Martin's Sulfurane is handled and weighed inside the glove box)

Characterization:

R_f = 0.59 (EtOAc/CH 9/1) [CAM].

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 5.90 (q, *J* = 1.7 Hz, 1H), 5.39 (q, *J* = 2.3 Hz, 1H), 5.22 (td, *J* = 10.1, 4.5 Hz, 1H), 5.10 (tt, *J* = 4.2, 2.1 Hz, 1H), 4.84 (dd, *J* = 11.9, 5.6 Hz, 2H), 4.77 (dd, *J* = 17.4, 1.9 Hz, 1H), 4.71 (d, *J* = 1.7 Hz, 1H), 4.67 (dd, *J* = 6.7, 3.5 Hz, 2H), 4.65 (d, *J* = 3.6 Hz, 1H), 4.49 (d, *J* = 12.5 Hz, 1H), 3.78 (d, *J* = 12.6 Hz, 1H), 2.90 – 2.82 (m, 1H), 2.57 – 2.44 (m, 2H), 2.34 – 2.22 (m, 2H), 2.17 – 2.06 (m, 2H), 2.05 – 2.02 (m, 1H), 2.00 – 1.86 (m, 3H), 1.62 – 1.55 (m, 3H), 1.51 (td, *J* = 13.8, 4.1 Hz, 1H), 1.39 (s, 3H), 1.25 (d, *J* = 2.1 Hz, 3H), 0.92 (s, 3H).

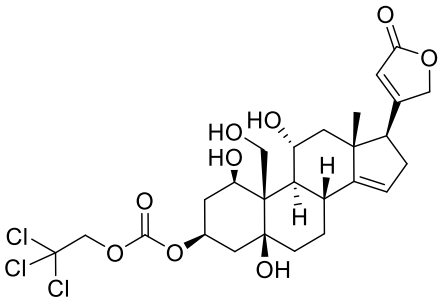
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 173.4, 168.8, 153.1, 152.4, 149.6, 119.6, 119.5, 117.2, 117.1, 101.5, 94.6, 94.1, 76.5, 73.9, 73.2, 72.6, 66.9, 59.7, 52.0, 51.8, 48.2, 47.3, 46.7, 46.1, 35.2, 35.1, 33.9, 33.4, 28.7, 24.8, 24.3, 22.9, 19.1, 19.0.

HRMS (APCI) = *m/z* calcd. for $C_{29}H_{36}Cl_3O_9$: 635.1576, found 635.1572.

LRMS (ESI) = *no detectable*

IR (ATR): ṽ [cm^{-1}] = 3503, 2933, 2868, 1748, 1380, 1237, 1045, 914, 807, 721, 569, 496.

2,2,2-trichloroethyl ((1*R*,3*S*,5*S*,8*R*,9*S*,10*R*,11*R*,13*R*,17*S*)-1,5,11-trihydroxy-10-(hydroxymethyl)-13-methyl-17-(5-oxo-2,5-dihydrofuran-3-yl)-2,3,4,5,6,7,8,9,10,11,12,13,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-3-yl) carbonate (I-138)



$C_{26}H_{33}Cl_3O_9$
M: 595,89 g/mol

Trichloromethyl ((3*R*,3a*R*,5*R*,5a*S*,5b*R*,9a*R*,11*S*,12a*S*,14a*R*,14b*S*)-5,12a,14b-trihydroxy-3a,8,8-trimethyl-3-(5-oxo-2,5-dihydrofuran-3-yl)hexadecahydro-6*H*-cyclopenta[7,8]phenanthro[4,4a-d][1,3]dioxin-11-yl) carbonate **I-137** (0.12 g, 0.18 mmol, 1.0 equiv) is dissolved in methanol (0.07 M) and trifluoroacetic acid (0.14 mL, 1.82 mmol, 10.0 equiv) is added. The mixture is stirred at room temperature for 20 h.
The solvent is evaporated in vacuo and the crude product is purified by column chromatography (DCM → DCM/MeOH 95/5) to give **I-138** (0.11 g, 0.18 mmol) as white crystalline solid in 99% yield.

Characterization:

R_f = 0.25 (EtOAc/CH 9/1) [CAM].

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 5.92 (q, *J* = 1.7 Hz, 1H), 5.39 (q, *J* = 2.2 Hz, 1H), 5.25 – 5.18 (m, 2H), 5.04 (q, *J* = 3.7, 3.2 Hz, 1H), 4.84 (d, *J* = 11.9 Hz, 1H), 4.77 (p, *J* = 1.6 Hz, 2H), 4.73 – 4.65 (m, 2H), 4.59 – 4.55 (m, 1H), 4.37 (s, 2H), 4.14 (d, *J* = 12.2 Hz, 1H), 2.90 – 2.81 (m, 1H), 2.60 – 2.48 (m, 2H), 2.47 – 2.40 (m, 1H), 2.34 (ddd, *J* = 16.6, 11.4, 6.2 Hz, 2H), 2.25 (dd, *J* = 12.1, 4.2 Hz, 1H), 2.21 – 2.13 (m, 1H), 2.01 – 1.93 (m, 2H), 1.74 (td, *J* = 14.6, 4.5 Hz, 1H), 1.64 (t, *J* = 11.1 Hz, 1H), 1.58 – 1.46 (m, 3H), 1.28 – 1.22 (m, 1H), 0.93 (d, *J* = 14.6 Hz, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 174.0, 169.2, 153.2, 152.5, 150.0, 119.7, 115.7, 94.4, 76.6, 76.6, 75.1, 73.9, 73.4, 70.1, 60.2, 52.1, 48.4, 47.7, 47.2, 46.7, 36.0, 35.0, 33.9, 32.9, 30.9, 25.2, 19.0.

HRMS (APCI) = *no detectable*

LRMS (ESI) = *no detectable*

IR (ATR): ṽ [cm^{-1}] = 3411, 2926, 2854, 1744, 1382, 1239, 1045, 807, 721, 568, 485.

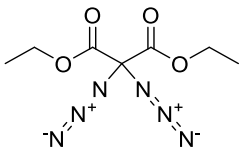
2.2. Decarboxylation of bistriazol derivatives and synthesis of N-substituted imines from diazidated malonamides

General Procedure A for the synthesis of bistriazole Intermediate II-35: Diethyl 2,2-diazidomalonate **II-23i** (1.0 equiv) is dissolved in dimethylformamide (0.15 M), followed by the addition of alkyne (3.0 equiv), sodium ascorbate (1.0 equiv) and copper(II) sulfate pentahydrate (1.0 equiv). The solution is stirred for 24 h at room temperature. The solvent is evaporated in vacuo and flash chromatography on silica gel afforded the correspondent bistriazole **II-35**.

General Procedure B for the synthesis of acetamides II-52: The bistriazole **II-35** (1.0 equiv) and primary or secondary amine (5.0 equiv) are dissolved in tetrahydrofuran (0.15 M) and the solution is stirred at room temperature for a time reported in the experimental details. The solvent is evaporated in vacuo and flash chromatography on silica gel afforded the correspondent acetamide **II-52**.

General Procedure C for the synthesis of *N*-substituted imine II-54: 2,2-diazido-*N*1,*N*3-dibenzylmalonamide **II-48a** (1.0 equiv) is dissolved in dimethylsulfoxide (0.10 M), primary amine (3.0 equiv) and cesium carbonate (1.0 equiv) are subsequently added. The solution is stirred for 12 h at room temperature. The reaction is quenched with water and extracted with ethyl acetate, washed with water, dried with Na_2SO_4 and filtered. The solvent is evaporated in vacuo and flash chromatography on silica gel afforded the correspondent *N*-substituted imine **II-54**.

Diethyl 2,2-diazidomalonate (II-23i)



$C_7H_{10}N_6O_4$
M: 242,20 g/mol

Diethylmalonate (1.0 mL, 6.56 mmol, 1.0 equiv) is dissolved in a solvent mixture of 43.70 mL of dimethylsulfoxide and 21.85 mL of water (2:1) followed by the addition of first sodium azide (2.55 g, 39.33 mmol, 6.0 equiv) and, then, iodine (3.66 g, 14.42 mmol, 2.20 equiv). The solution is stirred for 1 h at room temperature.
Saturated sodium thiosulfate is added until a discoloration is obtained. The final solution is extracted with diethylether, the organic phase is dried over Na_2SO_4, filtered and the solvent is evaporated in vacuo and flash chromatography on silica gel (PE → PE/EA 9/1) gives **II-23e** (1.53g, 6.32 mmol) as yellow oil in 96% yield.

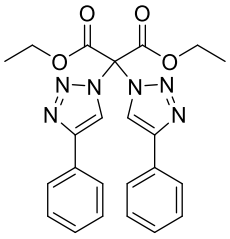
Characterization:

^{1}H NMR (400 MHz, DMSO-d6): δ [ppm] = 4.37 (q, *J* = 7.1 Hz, 4H), 1.26 (t, *J* = 7.1 Hz, 6H).

^{13}C-NMR (101 MHz, DMSO-d6): δ [ppm] = 163.0, 79.2, 64.3, 13.6.

The analytical data are consistent with the literature.[120]

Diethyl 2,2-Bis(4-phenyl-1*H*-1,2,3-triazol-1-yl)malonate (II-35a)



$C_{23}H_{22}N_6O_4$
M: 446,47 g/mol

According to the ***general procedure A*** using diethyl 2,2-diazido-malonate **II-23e** (2.90 g, 11.97 mmol, 1.0 equiv), phenylacetylene (3.95 mL, 35.92 mol, 3.0 equiv), sodium ascorbate (2.37 g, 11.97 mol, 1.0 equiv) and copper (II) sulfate pentahydrate (2.99 g, 11.97 mol, 1.0 equiv), **II-35a** (3.84 g, 8.60 mmol) is obtained after chromatography (PE/EtOAc 8/2 → 6/4) as white solid in 72% yield.

Characterization:

R_f = 0.58 (PE/EtOAc 6/4) [UV].

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 8.47 (s, 2H), 7.81 (d, *J* = 7.1 Hz, 4H), 7.41 (t, *J* = 7.3 Hz, 4H), 7.34 (t, *J* = 7.4 Hz, 2H), 4.57 (q, *J* = 7.2 Hz, 4H), 1.41 (t, *J* = 7.1 Hz, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 160.7, 148.4, 129.6, 129.0, 128.9, 126.1, 120.7, 79.7, 65.3, 13.9.

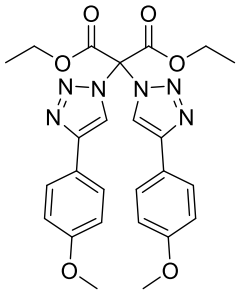
HRMS (ESI-TOF) = m/*z* calcd. for $C_{23}H_{22}N_6NaO_4$: 469.1597, found 469.1595.

LRMS (ESI) = *m/z* 447 (10.7%) $[M+H]^+$, 893 (100%) $[2M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3129, 2981, 1763, 1452, 1368, 1347, 1271, 1169, 1010, 764, 691, 641, 510, 458.

Mp = 150.3 – 151.0 °C.

Diethyl 2,2-Bis(4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)-malonate (II-35b)



$C_{25}H_{26}N_6O_6$
M: 506,52 g/mol

According to the ***general procedure A*** using diethyl 2,2-diazidomalonate **II-23e** (50.0 mg, 0.21 mmol, 1 equiv), 4-ethynylanisol (85.0 mg, 0.62 mmol, 3.0 equiv), sodium ascorbate (41.0 mg, 0.21 mmol, 1.0 equiv) and copper (II) sulfate pentahydrate (52.0 mg, 0.21 mmol, 1.0 equiv), **II-35b** (95.0 mg, 0.19 mmol) is obtained after chromatography (PE/EtOAc 8/2 → 6/4) as white solid in 90% yield.

Characterization:

R_f = 0.48 (PE/EtOAc 5/5) [UV].

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 8.35 (s, 2H), 7.73 (dd, *J* = 4.7, 2.2 Hz, 4H), 6.93 (dd, *J* = 4.7, 2.2 Hz, 4H), 4.56 (q, *J* = 7.1 Hz, 4H), 3.82 (s, 6H), 1.40 (t, *J* = 7.1 Hz, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 160.8, 160.2, 148.2, 127.4, 122.3, 119.7, 114.5, 79.7, 65.1, 55.5, 13.9.

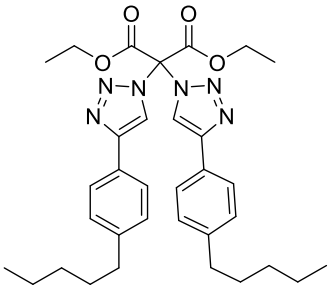
HRMS (ESI-TOF) = *m/z* calcd. for $C_{25}H_{26}N_6NaO_6$: 529.1807, found 529.1806.

LRMS (ESI) = *m/z* 507 (97.1%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3144, 2833, 1772, 1616, 1495, 1404, 1246, 1078, 803, 737, 659, 533.

Mp = 125.3 – 126.1 °C.

Diethyl 2,2-Bis(4-(4-pentylphenyl)-*1H*-1,2,3-triazol-1-yl)-malonate (II-35c)



$C_{33}H_{42}N_6O_4$
M: 586,74 g/mol

According to the ***general procedure A*** using diethyl 2,2-diazidomalonate **II-23e** (56.0 mg, 0.23 mmol, 1.0 equiv), 1-ethynyl-4-pentylbenzene (0.14 mL, 0.69 mmol, 3.0 equiv), sodium ascorbate (46.0 mg, 0.23 mmol, 1.0 equiv) and copper (II) sulfate pentahydrate (58.0 mg, 0.23 mmol, 1.0 equiv), **II-35c** (100.0 mg, 0.17 mmol) is obtained after chromatography (PE/EtOAc, 8/2 → 7/3) as yellow solid in 74% yield.

Characterization:

R_f = 0.62 (PE/EtOAc 4/6) [UV].

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 8.40 (s, 2H), 7.71 (dd, *J* = 4.7, 1.8 Hz, 4H), 7.21 (dd, *J* = 4.7, 1.8 Hz, 4H), 4.57 (q, *J* = 7.1 Hz, 4H), 2.61 (dd, *J* = 8.7, 6.7 Hz, 4H), 1.66 – 1.56 (m, 4H), 1.41 (t, *J* = 7.1 Hz, 6H), 1.36 – 1.27 (m, 8H), 0.90 – 0.84 (m, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 160.8, 148.4, 143.9, 129.1, 127.0, 126.0, 120.3, 79.8, 65.2, 35.8, 31.6, 31.1, 22.6, 14.1, 13.9.

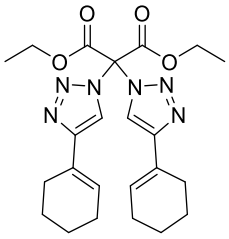
HRMS (ESI-TOF) = m/*z* calcd. for $C_{33}H_{42}N_6NaO_4$: 609.3159, found 609.3160.

LRMS (ESI) = *m/z* 587 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3163, 2928, 1765, 1400, 1208, 1167, 1075, 1012, 729, 665, 543.

Mp = 99.2 – 99.8 °C.

Diethyl 2,2-Bis(4-(cyclohex-1-en-1-yl)-1*H*-1,2,3-triazol-1-yl)-malonate (II-35d)



$C_{23}H_{30}N_6O_4$
M: 454,53 g/mol

According to the ***general procedure A*** using diethyl 2,2-diazidomalonate **II-23e** (56.0 mg, 0.23 mmol, 1.0 equiv), 1-ethynylcyclo-hexene (82.0 µL, 0.69 mmol, 3.0 equiv), sodium ascorbate (46.0 mg, 0.23 mmol, 1.0 equiv) and copper (II) sulfate pentahydrate (58.0 mg, 0.23 mmol, 1.0 equiv), **II-35d** (82.0 mg, 0.18 mmol) is obtained after chromatography (PE/EtOAc 9/1 → 8/2) as white solid in 78% yield.

Characterization:

R_f = 0.67 (PE/EtOAc 5/5) [UV].

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.98 (s, 2H), 6.57 (tt, *J* = 3.9, 1.8 Hz, 2H), 4.50 (q, *J* = 7.1 Hz, 4H), 2.31 (tq, *J* = 6.3, 2.4 Hz, 4H), 2.21 – 2.15 (m, 4H), 1.77 – 1.70 (m, 4H), 1.65 (ddt, *J* = 9.2, 5.5, 3.0 Hz, 4H), 1.36 (t, *J* = 7.1 Hz, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 160.8, 149.8, 126.6, 119.1, 79.6, 64.9, 26.3, 25.4, 22.5, 22.3, 13.9.

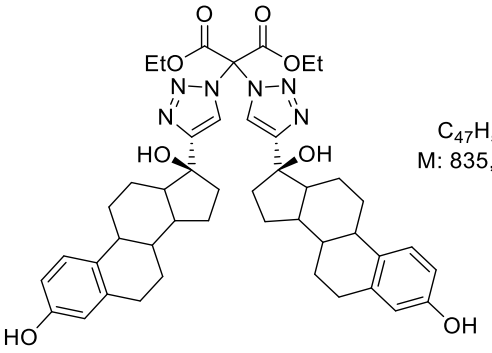
HRMS (ESI-TOF) = m/*z* calcd. for $C_{23}H_{30}N_6NaO_4$: 477.2218, found 477.2221.

LRMS (ESI) = *m/z* 455 (17.5%) $[M+H]^+$, 909 (100%) $[2M+H]^+$.

IR (ATR): ṽ [cm-1] = 3156, 2924, 2856, 1764, 1408, 1278, 1235, 1206, 1162, 1068, 929, 802, 726, 652, 469.

Mp = 137.8 – 138.5 °C.

Diethyl 2,2-bis(4-((8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-17-yl)-1*H*-1,2,3-triazol-1-yl)malonate (II-35e)



$C_{47}H_{58}N_6O_8$
M: 835,01 g/mol

According to the ***general procedure A*** using diethyl 2,2-diazidomalonate **II-23e** (54.0 mg, 0.22 mmol, 1.0 equiv), ethynylestradiol (0.20 g, 0.67 mmol, 3.0 equiv), sodium ascorbate (44.0 mg, 0.22 mmol, 1.0 equiv) and copper(II) sulfate pentahydrate (56.0 mg, 0.22 mmol, 1.0 equiv), **II-35e** (0.13 mg, 0.16 mmol) is obtained after chromatography (PE/EtOAc 4/6 → EtOAc) as yellow solid in 70% yield.

Characterization:

R_f = 0.60 (EtOAc) [UV].

^{1}H NMR (600 MHz, DMSO-d6): δ [ppm] = 8.94 (s, 2H), 8.12 (s, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 6.47 (dd, *J* = 8.4, 2.6 Hz, 2H), 6.41 (d, *J* = 2.6 Hz, 2H), 5.30 (s, 2H), 4.49 (q, *J* = 7.1 Hz, 4H), 3.17 (d, *J* = 5.2 Hz, 2H), 2.75 – 2.63 (m, 4H), 2.46 – 2.34 (m, 1H), 2.29 (ddd, *J* = 13.4, 9.5, 6.0 Hz, 2H), 1.86 – 1.75 (m, 7H), 1.71 – 1.63 (m, 2H), 1.46 – 1.31 (m, 7H), 1.28 (t, *J* = 7.1 Hz, 7H), 1.18 (t, *J* = 7.1 Hz, 4H), 0.90 (s, 6H).

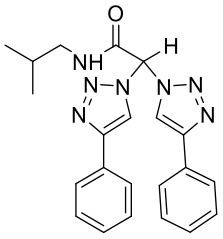
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 160.8, 154.5, 153.4, 138.4, 132.8, 126.5, 122.6, 115.4, 112.8, 82.6, 65.2, 48.7, 47.6, 43.5, 39.6, 38.2, 33.0, 29.8, 27.4, 26.3, 23.6, 14.4, 14.0.

HRMS (ESI-TOF) = m/*z* calcd. for $C_{47}H_{58}N_6NaO_8$: 857.4207, found 857.4208.

LRMS (ESI) = *m/z* 835 (100%) $[M+ H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3354, 2928, 1765,1249, 1043, 843, 651, 533.

_N_-Isobutyl-2,2-Bis(4-phenyl-1_H_-1,2,3-triazol-1-yl)acetamide (II-52aa)



$C_{22}H_{23}N_7O$
M: 401,47 g/mol

According to the ***general procedure B*** using diethyl 2,2-bis-(4-phenyl-1*H*-1,2,3-triazol-1-yl)malonate **II-35a** (30.0 mg, 70.0 µmol, 1.0 equiv) and isobutylamine (34.0 µL, 0.34 mmol, 5.0 equiv) and stirring for 5 h, **II-52aa** (17.0 mg, 40.0 µmol) is obtained after chromatography (PE/ EtOAc 8/2 → 6/4) as white solid in 63% yield.

Characterization:

R_f = 0.41 (PE/EtOAc 6/4) [UV].

^{1}H-NMR (600 MHz, DMSO-d_6): δ [ppm] = 8.95 – 8.91 (m, 3H), 8.21 (s, 1H), 7.91 (d, *J* = 7.1 Hz, 4H), 7.46 (t, *J* = 7.6 Hz, 4H), 7.36 (t, *J* = 7.4 Hz, 2H), 3.05 (t, *J* = 5.9 Hz, 2H), 1.78 (hept, *J* = 6.7 Hz, 1H), 0.84 (d, *J* = 6.7 Hz, 6H).

^{13}C-NMR (151 MHz, DMSO-d_6): δ [ppm] = 161.3, 147.0, 129.9, 128.9, 128.3, 125.4, 121.5, 71.0, 46.8, 27.7, 19.9.

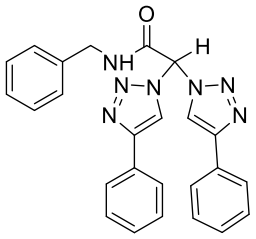
HRMS (ESI-TOF) = m/*z* calcd. for $C_{22}H_{23}N_7NaO$: 424.1827, found 424.1751.

LRMS (ESI) = *m/z* 402 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3284, 3139, 2961, 1673, 1578, 1459, 1185, 1077, 1022, 758, 691, 511.

Mp = 215.3 – 216.1 °C.

_N_-Benzyl-2,2-bis(4-phenyl-1_H_-1,2,3-triazol-1-yl)acetamide (II-52ab)



$C_{25}H_{21}N_7O$
M: 435,49 g/mol

According to the ***general procedure B*** using diethyl 2,2-bis-(4-phenyl-1*H*-1,2,3-triazol-1-yl)malonate **II-35a** (60.0 mg, 0.13 mmol, 1.0 equiv) and benzylamine (73.0 µL, 0.67 mmol, 5.0 equiv) and stirring for 5 h, **II-52ab** (50.0 mg, 0.11 mmol) is obtained after chromatography (PE/EtOAc 8/2 → 6/4) as white solid in 85% yield.

Characterization:

R_f = 0.35 (PE/EtOAc 6/4) [UV].

^{1}H-NMR (600 MHz, DMSO-d_6): δ [ppm] = 9.36 (t*, J* = 5.8 Hz, 1H), 8.94 (s, 2H), 8.31 (s, 1H), 7.92 (d*, J* = 1.5 Hz, 2H), 7.90 (d*, J* = 1.1 Hz, 2H), 7.46 (t*, J* = 7.5 Hz, 4H), 7.39 – 7.24 (m, 7H), 4.44 (d*, J* = 5.8 Hz, 2H).

^{13}C-NMR (151 MHz, DMSO-d_6): δ [ppm] = 161.4, 147.0, 137.9, 129.8, 128.9, 128.4, 127.4, 127.2, 125.4, 121.7, 71.1, 43.1.

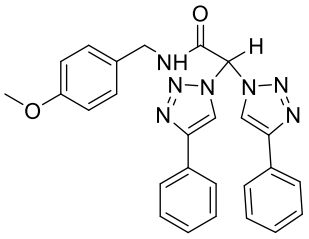
HRMS (ESI-TOF) = m/*z* calcd. for $C_{25}H_{21}N_7NaO$: 458.1713, found 458.1700.

LRMS (ESI) = *m/z* 436 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3274, 3152, 2968, 1667, 1566, 1455, 1234, 1185, 1076, 1023, 819, 758, 689.

Mp = 251.4 – 252.2 °C.

_N_-(4-Methoxybenzyl)-2,2-bis(4-phenyl-1_H_-1,2,3-triazol-1-yl)-acetamide (II-52ac)



$C_{26}H_{23}N_7O_2$
M: 465,52 g/mol

According to the ***general procedure B*** using diethyl 2,2-bis(4-phenyl-1*H*-1,2,3-triazol-1-yl)malonate **II-35a** (30.0 mg, 70.0 µmol, 1.0 equiv) and methoxybenzylamine (44.0 µL, 0.34 mmol, 5.0 equiv) and stirring for 3 h, **II-52ac** (30.0 mg, 60.0 µmol) is obtained after chromatography (PE/EtOAc 8/2 → 6/4) as white solid in 96% yield.

Characterization:

R_f = 0.32 (PE/EtOAc 6/4) [UV].

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm] = 9.31 (t*, J* = 5.6 Hz, 1H), 8.92 (s, 2H), 8.26 (s, 1H), 7.91 (d*, J* = 7.0 Hz, 4H), 7.46 (t*, J* = 7.5 Hz, 4H), 7.36 (tt*, J* = 4.2, 4.2, 1.4, 1.2 Hz, 2H), 7.23 (d*, J* = 8.6 Hz, 2H), 6.88 (d*, J* = 8.6 Hz, 2H), 4.36 (d*, J* = 5.7 Hz, 2H), 3.72 (s, 3H).

^{13}C-NMR (101 MHz, DMSO-d_6): δ [ppm] = 161.2, 158.5, 147.0, 129.8, 129.8, 128.9, 128.3, 125.4, 121.6, 113.8, 71.0, 55.0, 42.6.

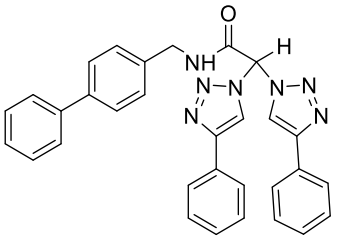
HRMS (ESI-TOF) = m/*z* calcd. for $C_{26}H_{23}N_7NaO_2$: 488.1824, found 488.1805.

LRMS (ESI) = *m/z* 466 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3273, 3142, 2960, 1664, 1514, 1457, 1364, 1248, 1175, 1030, 823, 759, 707, 528.

Mp = 217.3 – 218.1 °C.

_N_-([1,1′-Biphenyl]-4-ylmethyl)-2,2-bis(4-phenyl-1_H_-1,2,3-triazol-1-yl)acetamide (II-52ad)



$C_{31}H_{25}N_7O$
M: 511,59 g/mol

According to the ***general procedure B*** using diethyl 2,2-bis(4-phenyl-1*H*-1,2,3-triazol-1-yl)malonate **II-35a** (30.0 mg, 70.0 µmol, 1.0 equiv) and 4-phenylbenzylamine (62.0 mg, 0.34 mmol, 5.0 equiv) and stirring for 19 h, **II-52ad** (17.0 mg, 34.0 µmol) is obtained after chromatography (PE/EtOAc 8/2 → 6/4) as white solid in 50 % yield.

Characterization:

R_f = 0.27 (PE/EtOAc 6/4) [UV].

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm] = 9.40 (t*, J* = 5.6 Hz, 1H), 8.95 (s, 2H), 8.33 (s, 1H), 7.91 (dd*, J* = 7.1, 1.6 Hz, 4H), 7.65 – 7.61 (m, 4H), 7.46 (dddd*, J* = 7.7, 6.3, 2.4, 1.3 Hz, 6H), 7.41 (d*, J* = 1.9 Hz, 1H), 7.40 – 7.33 (m, 4H), 4.48 (d*, J* = 5.5 Hz, 2H).

^{13}C-NMR (101 MHz, DMSO-d_6): δ [ppm] = 161.4, 147.0, 139.8, 139.1, 137.1, 129.8, 128.9, 128.9, 128.3, 128.1, 127.4, 126.6, 126.5, 125.4, 121.7, 71.1, 42.9.

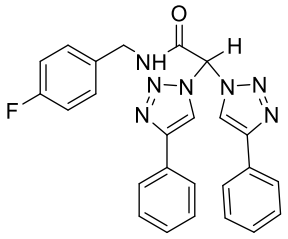
HRMS (ESI-TOF) = m*/z* calcd. for $C_{31}H_{25}N_7NaO$: 534.2016, found 534.2013.

LRMS (ESI) = *m/z* 512 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3299, 3132, 2923, 1696, 1531, 1360, 1017, 759, 689, 509.

Mp = 189.7 – 190.5 °C.

_N_-(4-Fluorobenzyl)-2,2-bis(4-phenyl-1_H_-1,2,3-triazol-1-yl)acetamide (II-52ae)



$C_{25}H_{20}FN_7O$
M: 453,48 g/mol

According to the ***general procedure B*** using diethyl 2,2-bis(4-phenyl-1*H*-1,2,3-triazol-1-yl)malonate **II-35a** (54.0 mg, 0.12 mmol, 1.0 equiv) and 4-fluorobenzylamine (69.0 µL, 0.60 mmol, 5.0 equiv) and stirring for 7 h, **II-52ae** (53.0 mg, 0.12 mmol) is obtained after chromatography (PE/EtOAc 8/2 → 6/4) as white solid in 96% yield.

Characterization:

R_f = 0.34 (PE/EtOAc 6/4) [UV].

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm] = 9.34 (t*, J* = 5.7 Hz, 1H), 8.92 (s, 2H), 8.31 (s, 1H), 7.91 (d*, J* = 7.0 Hz, 4H), 7.46 (t*, J* = 7.5 Hz, 4H), 7.38 –7.33 (m, 4H), 7.15 (tt*, J* = 4.6, 3.0, 2.1 Hz, 2H), 4.42 (d*, J* = 5.7 Hz, 2H).

^{13}C-NMR (101 MHz, DMSO-d_6): δ [ppm] = 161.4, 161.4 (d*, J* = 242.9 Hz), 147.0, 134.2 (d*, J* = 3.0 Hz), 129.8, 129.5 (d*, J* = 8.0 Hz), 128.9, 128.3, 125.4, 121.7, 115.1 (d*, J* = 21.4 Hz), 71.1, 42.4.

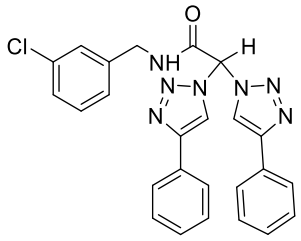
HRMS (ESI-TOF) = m/*z* calcd. for $C_{25}H_{20}FN_7NaO$: 476.1607, found 476.1606.

LRMS (ESI) = *m/z* 454 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3277, 3146, 2928, 1669, 1509, 1418, 1224, 1076, 819, 635, 550, 448.

Mp = 232.0 – 232.9 °C.

_N_-(3-Chlorobenzyl)-2,2-bis(4-phenyl-1_H_-1,2,3-triazol-1-yl)acetamide (II-52af)



$C_{25}H_{20}ClN_7O$
M: 469,93 g/mol

According to the ***general procedure B*** using diethyl 2,2-bis(4-phenyl-1*H*-1,2,3-triazol-1-yl)malonate **II-35a** (30.0 mg, 70.0 µmol, 1.0 equiv) and 3-chlorobenzylamine (48.0 mg, 0.34 mmol, 5.0 equiv) and stirring for 19 h, **II-52af** (15.0 mg, 30 µmol) is obtained after chromatography (PE/EtOAc, 8/2 → 6/4) as white solid in 48% yield.

Characterization:

R_f = 0.35 (PE/EtOAc 6/4) [UV].

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm] = 9.34 (t, *J* = 5.8 Hz, 1H), 8.94 (s, 2H), 8.37 (s, 1H), 7.91 (d, *J* = 7.2 Hz, 4H), 7.46 (t, *J* = 7.6 Hz, 4H), 7.39 – 7.26 (m, 6H), 4.45 (d, *J* = 5.5 Hz, 2H).

^{13}C-NMR (101 MHz, DMSO-d_6): δ [ppm] = 161.6, 147.0, 140.6, 133.0, 130.2, 129.8, 128.9, 128.3, 127.2, 127.0, 126.0, 125.4, 121.7, 71.1, 42.5.

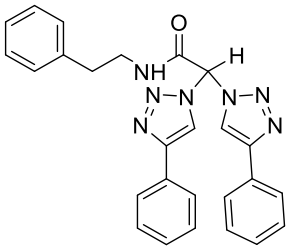
HRMS (ESI-TOF) = m/*z* calcd. for $C_{25}H_{20}ClN_7NaO$: 492.1323, found 492.1310.

LRMS (ESI) = *m/z* 470 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3283, 3153, 2924, 1671, 1556, 1434, 1368, 1182, 1077, 1030, 759, 679, 636, 510.

Mp = 229.7 – 230.2 °C.

_N_-Phenethyl-2,2-bis(4-phenyl-1H-1,2,3-triazol-1-yl)acetamide (II-52ag)



According to the ***general procedure B*** using diethyl 2,2-bis-(4-phenyl-1H-1,2,3-triazol-1-yl)malonate **II-35a** (60.0 mg, 0.13 mmol, 1.0 equiv) and 2-phenylethylamine (85.0 µL, 0.67 mmol, 5.0 equiv) and stirring for 1.5 h, **II-52ag** (58.0 mg, 0.13 mmol) is obtained after chromatography (PE/EtOAc 8/2 → 6/4) as white solid in 96% yield.

Characterization:

R_f = 0.34 (PE/EtOAc 6/4) [UV].

^{1}H-NMR (600 MHz, DMSO-d_6): δ [ppm] = 9.02 (t, *J* = 5.7 Hz, 1H), 8.90 (s, 2H), 8.17 (s, 1H), 7.91 (d, *J* = 7.0 Hz, 4H), 7.47 (t, *J* = 7.8 Hz, 4H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.20 (t, *J* = 7.5 Hz, 2H), 7.18 – 7.15 (m, 2H), 7.15 – 7.10 (m, 1H), 3.46 (td, *J* = 7.2, 5.6 Hz, 2H), 2.79 (t, *J* = 7.2 Hz, 2H).

^{13}C-NMR (151 MHz, DMSO-d_6): δ [ppm] = 161.2, 147.0, 138.8, 129.8, 128.9, 128.6, 128.3, 128.2, 126.1, 125.4, 121.4, 70.9, 40.9, 34.4.

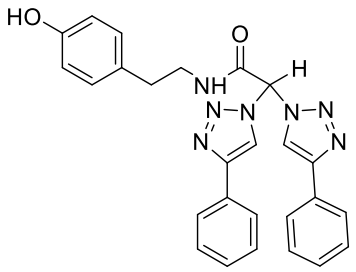
HRMS (ESI-TOF) = m/*z* calcd. for $C_{26}H_{23}N_7NaO$: 472.1857, found 472.1856.

LRMS (ESI) = *m/z* 450 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3294, 3148, 2974, 1666, 1548, 1456, 1366, 1179, 1076, 1022, 760, 689, 509.

Mp = 182.8 – 183.4 °C.

_N_-(4-Hydroxyphenethyl)-2,2-bis(4-phenyl-1_H_-1,2,3-triazol-1-yl)acetamide (II-52ah)



$C_{26}H_{23}N_7O_2$
M: 465,52

According to the ***general procedure B*** using di-ethyl 2,2-bis(4-phenyl-1*H*-1,2,3-triazol-1-yl)malonate **II-35a** (64.0 mg, 0.14 mmol, 1.0 equiv) and tyramine (98.0 mg, 0.71 mmol, 5.0 equiv) in tetrahydrofuran (0.07 M) and stirring for 75 h, **II-52ah** (59.0 mg, 0.13 mmol) is obtained after chromatography (PE/EtOAc, 8/2 → 6/4) as white solid in 89% yield.

Characterization:

R_f = 0.08 (PE/EtOAc 6/4) [UV].

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm] = 9.14 (s, 1H), 8.96 (t, *J* = 5.6 Hz, 1H), 8.90 (s, 2H), 8.16 (s, 1H), 7.91 (dd, *J* = 7.1, 1.5 Hz, 4H), 7.47 (t, *J* = 7.5 Hz, 4H), 7.37 (tt, *J* = 4.1, 1.2 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.62 (d, *J* = 8.4 Hz, 2H), 3.38 (q, *J* = 6.7 Hz, 2H), 2.67 (t, *J* = 7.2 Hz, 2H).

^{13}C-NMR (151 MHz, DMSO-d_6): δ [ppm] = 161.2, 155.7, 147.0, 129.8, 129.4, 128.9, 128.3, 125.4, 121.5, 115.1, 70.9, 41.4, 33.6.

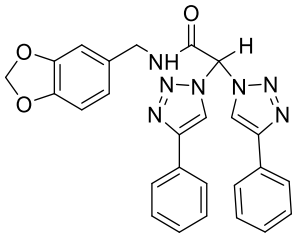
HRMS (ESI-TOF) = m/*z* calcd. for $C_{26}H_{23}N_7NaO_2$: 488.1806, found 488.1805.

LRMS (ESI) = *m/z* 466 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3294, 3148, 2974, 1666, 1548, 1456, 1366, 1179, 1076, 1022, 760, 689, 509.

Mp = 98.2 – 98.9 °C.

_N_-(Benzo[d][1,3]dioxol-5-ylmethyl)-2,2-bis(4-phenyl-1_H_-1,2,3-tri-azol-1-yl)acetamide (II-52ai)



$C_{26}H_{21}N_7O_3$
M: 479,50 g/mol

According to the ***general procedure B*** using diethyl 2,2-bis(4-phenyl-1*H*-1,2,3-triazol-1-yl)malonate **II-35a** (30.0 mg, 70.0 µmol, 1.0 equiv) and piperonylamine (42.0 µL, 0.34 mmol, 5.0 equiv) and stirring for 2.5 h, **II-52ai** (22.0 mg, 50.0 µmol) is obtained after chromatography (PE/EtOAc 8/2 → 6/4) as white solid in 68% yield.

Characterization:

R_f = 0.32 (PE/EtOAc 6/4) [UV].

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm] = 9.29 (t, *J* = 5.8 Hz, 1H), 8.93 (s, 2H), 8.29 (s, 1H), 7.91 (dd, *J* = 7.0, 1.4 Hz, 4H), 7.46 (t, *J* = 7.9 Hz, 4H), 7.36 (tt, *J* = 7.4, 7.3, 2.1, 1.3 Hz, 2H), 6.91 – 6.82 (m, 2H), 6.78 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.98 (s, 2H), 4.34 (d, *J* = 5.7 Hz, 2H).

^{13}C-NMR (151 MHz, DMSO-d_6): δ [ppm] = 161.3, 147.3, 147.0, 146.3, 131.7, 129.8, 128.9, 128.3, 125.4, 121.6, 120.8, 108.1, 108.0, 100.9, 71.0, 42.9.

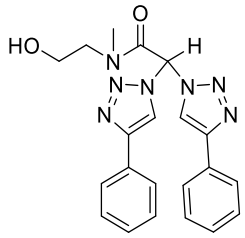
HRMS (ESI-TOF) = m/*z* calcd. for $C_{26}H_{21}N_7NaO_3$: 502.1598, found 502.1600.

LRMS (ESI) = *m/z* 480 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3270, 3151, 3064, 2967, 1665, 1549, 1486, 1444, 1370, 1246, 1181, 1023, 926, 809, 763, 692, 509.19.

Mp = 205.1 – 205.9 °C.

N-(2-Hydroxyethyl)-*N*-methyl-2,2-bis(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetamide (II-52ba)



$C_{21}H_{21}N_7O_2$
M: 403,45 g/mol

According to the ***general procedure B*** using diethyl 2,2-bis(4-phenyl-1*H*-1,2,3-triazol-1-yl)malonate **II-35a** (60.0 mg, 0.13 mmol, 1.0 equiv) and 2-(methylamino)ethanol (54.0 µL, 0.67 mmol, 5.0 equiv) and stirring for 4 h, **II-52ba** (34.0 mg, 80.0 µmol) is obtained after chromatography (PE/EtOAc 1/9) as white solid in 63% yield.

Characterization:

R_f = 0.18 (PE/EtOAc 1/9) [UV].

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm] = (mixture of rotamers) 8.90 (s, 1H), 8.83 (s, 1H), 8.79 (s, 0.5H), 8.78 (s, 0.5H), 7.95 – 7.87 (m, 4H), 7.50 – 7.41 (m, 4H), 7.40 – 7.33 (m, 2H), 5.20 (t, *J* = 4.9 Hz, 0.5H), 4.78 (t, *J* = 5.3 Hz, 0.5H), 3,62 – 3.55 (m, 1H), 3.54–3.44 (m, 2H), 3.41 – 3.35 (m, 1H) 3.01 (s, 1.5H), 2.91 (s, 1.5H).

^{13}C-NMR (151 MHz, DMSO-d_6): δ [ppm] = (mixture of rotamers) 161.5, 161.1, 147.2, 147.1, 129.8, 129.8, 128.9, 128.4, 125.4,7, 121.6, 69.9, 69.5, 60.4, 57.9, 57.7, 51.1, 51.0, 35.4, 34.2, 14.6.

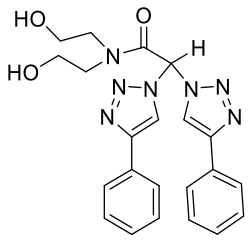
HRMS (ESI-TOF) = m/*z* calcd. for $C_{21}H_{21}N_7NaO_2$: 426.1633, found 426.1649.

LRMS (ESI) = *m/z* 404 (99.5%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3368, 3096, 2934, 1668, 1378, 1234, 1182.81, 1047, 837, 761, 688, 604, 512.

Mp = 149.7 – 151.9 °C.

_N_,_N_-Bis(2-hydroxyethyl)-2,2-bis(4-phenyl-1_H_-1,2,3-triazol-1-yl)acetamide (II-52bb)



$C_{22}H_{23}N_7O_3$
M: 433,47 g/mol

According to the ***general procedure B*** using diethyl 2,2-bis(4-phenyl-1*H*-1,2,3-triazol-1-yl)malonate **II-35a** (50.0 mg, 0.11 mmol, 1.0 equiv) and diethanolamine (54.0 µL, 0.56 mmol, 5.0 equiv) and stirring for 5 h, **II-52bb** (36.0 mg, 80.0 µmol) is obtained after chromatography (PE/EtOAc 2/8 → EtOAc) as white solid in 74% yield.

Characterization:

R_f = 0.71 (EtOAc) [UV].

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.88 (s, 2H), 8.81 (s, 1H), 7.91 (d, *J* = 7.0 Hz, 4H), 7.46 (t, *J* = 7.6 Hz, 4H), 7.36 (tt, *J* = 4.8, 4.0, 1.4 Hz, 2H), 5.25 (t, *J* = 4.9 Hz, 1H), 4.79 (t, *J* = 5.1 Hz, 1H), 3.60 (q, *J* = 5.7 Hz, 2H), 3.52 (dd, *J* = 8.8, 5.1 Hz, 4H), 3.41 (t, *J* = 5.0 Hz, 2H).

^{13}C-NMR (101 MHz, DMSO-d_6): δ [ppm] = 161.6, 147.1, 129.8, 128.9, 128.3, 125.4, 121.6, 69.5, 58.3, 58.0, 49.9, 48.9.

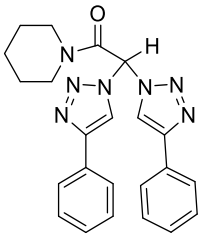
HRMS (ESI-TOF) = m/*z* calcd. for $C_{22}H_{23}N_7NaO_3$: 456.1757, found 456.1755.

LRMS (ESI) = *m/z* 434 (99.5%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3339, 3132, 2931, 1663, 1422, 1355, 1237, 1071, 1020, 760, 691, 508.

Mp = 79.4 – 80.1°C.

2,2-Bis(4-phenyl-1*H*-1,2,3-triazol-1-yl)-1-(piperidin-1-yl)ethan-1-one (II-52bc)



$C_{23}H_{23}N_7O$
M: 413,49 g/mol

According to the ***general procedure B*** using diethyl 2,2-bis(4-phenyl-1*H*-1,2,3-triazol-1-yl)malonate **II-35a** (50.0 mg, 0.11 mmol, 1.0 equiv) and piperidine (55.0 µL, 0.56 mmol, 5.0 equiv) and stirring for 24 h, **II-52bc** (30.0 mg, 70.0 µmol) is obtained after chromatography (CH/EtOAc 8/2 → 6/4) as white solid in 65% yield.

Characterization:

R_f = 0.76 (EtOAc) [UV].

^{1}H-NMR (600 MHz, DMSO-d_6): δ [ppm] = 8.88 (s, 1H), 8.84 (s, 2H), 7.92 (d, *J* = 6.8 Hz, 4H), 7.45 (t, *J* = 7.7 Hz, 4H), 7.36 (t, *J* = 7.4 Hz, 2H), 3.58 (d, *J* = 5.4 Hz, 2H), 3.34 (dd, *J* = 6.7, 4.1 Hz, 2H), 1.53 – 1.51 (m, 3H), 1.20 – 1.14 (m, 3H).

^{13}C-NMR (101 MHz, DMSO-d_6): δ [ppm] = 159.2, 147.0, 129.8, 128.9, 128.3, 125.4, 121.7, 69.6, 45.9, 43.6, 25.1, 24.9, 23.4.

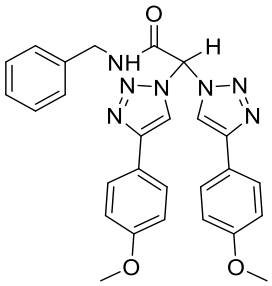
HRMS (ESI-TOF) = m/*z* calcd. for $C_{23}H_{23}N_7NaO$: 436.1857, found 436.1856.

LRMS (ESI) = *m/z* 414 (58.5%) $[M+H]^+$, 827 (100%) $[2M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3101, 2924, 2853, 1657, 1440, 1372, 1237, 1179, 1076, 1024, 825, 761, 691, 508.

Mp = 235.2 – 235.8°C.

_N_-Benzyl-2,2-bis(4-(4-methoxyphenyl)-1_H_-1,2,3-triazol-1-yl)acetamide (II-52ca)



$C_{27}H_{25}N_7O_3$
M: 495,54 g/mol

According to the ***general procedure B*** using diethyl 2,2-bis(4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)malonate **II-35b** (46.0 mg, 90.0 µmol, 1.0 equiv) and benzylamine (50.0 µL, 0.45 mmol, 5.0 equiv) and stirring for 7 h, **II-52ca** (37.0 mg, 70.0 µmol) is obtained after chromatography (PE/EtOAc 8/2 → 6/4) as white solid in 82% yield.

Characterization:

R_f = 0.22 (PE/EtOAc 5/5) [UV].

^{1}H-NMR (600 MHz, DMSO-d_6): δ [ppm] = 9.35 (t, *J* = 5.8 Hz, 1H), 8.82 (s, 2H), 8.25 (s, 1H), 7.83 (d, *J* = 8.8 Hz, 4H), 7.34 – 7.25 (m, 5H), 7.02 (d, *J* = 8.9 Hz, 4H), 4.43 (d, *J* = 5.8 Hz, 2H), 3.79 (s, 6H).

^{13}C-NMR (151 MHz, DMSO-d_6): δ [ppm] = 161.5, 159.3, 147.0, 137.9, 128.3, 127.4, 127.1, 126.8, 122.4, 120.5, 114.3, 71.0, 55.1, 43.1.

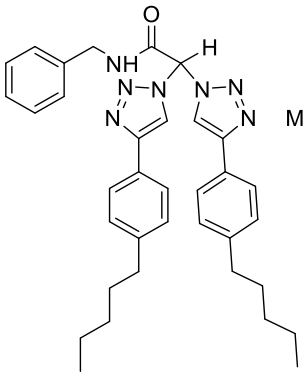
HRMS (ESI-TOF) = m/*z* calcd. for $C_{27}H_{25}N_7NaO_3$: 518.1912, found 518.1911.

LRMS (ESI) = *m/z* 496 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3101, 2924, 2853, 1657, 1440, 1372, 1237, 1179, 1076, 1024, 825, 761, 691, 508.

Mp = 199.1 – 200.1°C.

_N_-Benzyl-2,2-bis(4-(4-pentylphenyl)-1_H_-1,2,3-triazol-1-yl)acetamide (II-52cb)



$C_{35}H_{41}N_7O$
M: 575,76 g/mol

According to the ***general procedure B*** using diethyl 2,2-bis(4-(4-pentylphenyl)-1*H*-1,2,3-triazol-1-yl)malonate **II-35c** (46.0 mg, 80.0 µmol, 1.0 equiv) and benzylamine (43.0 µL, 0.39 mmol, 5.0 equiv) and stirring for 20 h, **II-52cb** (35.0 mg, 60.0 µmol) is obtained after chromatography (PE/EtOAc 7/3 → 6.5/3.5) as white solid in 78% yield.

Characterization:

R_f = 0.28 (PE/EtOAc 5/5) [UV].

^{1}H-NMR (600 MHz, DMSO-d_6): δ [ppm] = 9.36 (t, *J* = 5.8 Hz, 1H), 8.87 (s, 2H), 8.28 (s, 1H), 7.80 (d, *J* = 8.2 Hz, 4H), 7.34 – 7.29 (m, 4H), 7.29 – 7.24 (m, 5H), 4.43 (d, *J* = 5.8 Hz, 2H), 2.59 (t, *J* = 7.7 Hz, 4H), 1.58 (p, *J* = 7.3 Hz, 4H), 1.34 – 1.24 (m, 8H), 0.85 (t, *J* = 7.1 Hz, 6H).

^{13}C-NMR (151 MHz, DMSO-d_6): δ [ppm] = 161.5, 147.1, 142.6, 137.9, 128.8, 128.3, 128.2, 127.4, 127.3, 127.1, 126.9, 126.6, 125.3, 121.1, 71.0, 43.1, 34.8, 30.8, 30.4, 21.9, 13.8.

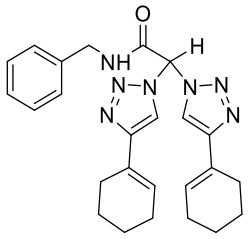
HRMS (ESI-TOF) = m/*z* calcd. for $C_{35}H_{41}N_7NaO$: 598.3263, found 598.3265.

LRMS (ESI) = *m/z* 576 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3101, 2924, 2853, 1657, 1440, 1372, 1237, 1179, 1076, 1024, 825, 761, 691, 508.

Mp = 170.8 – 171.5°C.

_N_-Benzyl-2,2-bis(4-(cyclohex-1-en-1-yl)-1_H_-1,2,3-triazol-1-yl)-acetamide (I-52cc)



$C_{25}H_{29}N_7O$
M: 443,55 g/mol

According to the ***general procedure B*** using diethyl 2,2-bis(4-(cyclohex-1-en-1-yl)-1*H*-1,2,3-triazol-1-yl)malonate **II-35d** (52.0 mg, 0.11 mmol, 1.0 equiv) and benzylamine (62.0 µL, 0.57 mmol, 5.0 equiv) and stirring for 20 h, **II-52cc** (28.0 mg, 60.0 µmol) is obtained after chromatography (PE/EtOAc 8/2 → 6/4) as white solid in 55% yield.

Characterization:

R_f = 0.41 (PE/EtOAc 5/5) [UV].

^{1}H-NMR (600 MHz, DMSO-d_6): δ [ppm] = 9.25 (t, *J* = 5.8 Hz, 1H), 8.35 (s, 2H), 8.11 (s, 1H), 7.32 (t, *J* = 7.9, 6.9 Hz, 2H), 7.26 (t, *J* = 7.2 Hz, 3H), 6.48 (tt, *J* = 3.9, 1.8 Hz, 2H), 4.38 (d, *J* = 5.7 Hz, 2H), 2.34 – 2.28 (m, 4H), 2.15 (td, *J* = 6.1, 3.1 Hz, 4H), 1.71 – 1.66 (m, 4H), 1.62 – 1.58 (m, 4H).

^{13}C-NMR (151 MHz, DMSO-d_6): δ [ppm] = 161.6, 148.6, 137.9, 128.3, 127.4, 127.1, 126.8, 124.7, 119.8, 70.8, 43.0, 25.7, 24.6, 21.9, 21.7.

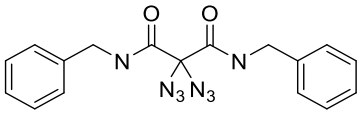
HRMS (ESI-TOF) = m/*z* calcd. for $C_{25}H_{29}N_7NaO$: 466.2356, found 466.2326.

LRMS (ESI) = *m/z* 444 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3276, 3125, 2927, 1670, 1564, 1433, 1232, 1171, 1024, 848, 757, 696, 658, 464.

Mp = 232.3 – 233.1°C.

2,2-diazido-*N*^{1},*N*^{3}-dibenzylmalonamide (II-48a)



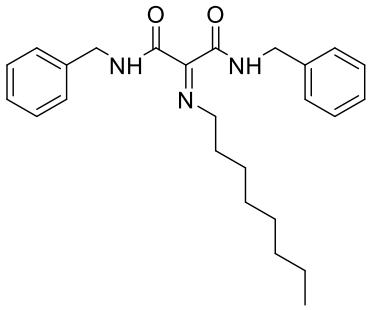
$C_{17}H_{16}N_8O_2$
M: 364,14 g/mol

Diethyl 2,2-diazidomalonate **II-23i** (1.0 g, 4.13 mmol, 1.0 equiv) is dissolved in tetrahydrofuran (1.0 M), followed by the addition of benzylamine (1.14 mL, 10.32 mmol, 2.50 equiv). The solution is stirred overnight and, then, the solvent is evaporated in vacuo.
The crude product is purified by column chromatography (PE/EA 9/1 → 7/3) to give a white crystalline solid in 80% yield.

Characterization:

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.37 – 7.34 (m, 3H), 7.33 (dt, *J* = 4.9, 1.6 Hz, 4H), 7.31 – 7.27 (m, 3H), 7.25 – 7.23 (m, 2H), 4.49 (d, *J* = 5.8 Hz, 4H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 163.6, 136.7, 129.1, 128.1, 127.8, 44.5.
The analytical data are consistent with the literature.[131]

N^1,N^3-dibenzyl-2-(octylimino)malonamide (I-54a).



$C_{25}H_{33}N_3O_2$
M: 407,56 g/mol

According to the ***general procedure C*** using 2,2-diazido-N^1,N^3-dibenzylmalonamide **II-48a** (0.10 g, 0.27 mmol, 1.0 equiv), octylamine (0.14 mL, 0.82 mmol, 3.0 equiv) and cesium carbonate (89.0 mg, 0.27 mmol, 1.0 equiv), **II-54a** (73.0 mg, 0.18 mmol) is obtained after chromatography (PE/EtOAc 8:2) as yellowish solid in 65% yield.

Characterization:

R_f = 0.46 (CH/EtOAc 8/2) [UV].

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.06 (t, *J* = 5.9 Hz, 1H), 7.70 (t, *J* = 6.0 Hz, 1H), 7.36 – 7.32 (m, 6H), 7.31 – 7.27 (m, 4H), 4.57 (d, *J* = 5.8 Hz, 2H), 4.49 (d, *J* = 6.1 Hz, 2H), 3.90 (t, *J* = 7.1 Hz, 2H), 1.67 (p, *J* = 7.2 Hz, 2H), 1.31 – 1.24 (m, 10H), 0.88 (t, *J* = 7.0 Hz, 3H).

^{13}C-NMR (101 MHz, DMSO-d_6): δ [ppm] = 163.3, 160.9, 153.3, 137.6, 128.9, 128.9, 128.8, 127.9, 127.8, 127.8, 127.7, 54.4, 43.6, 43.4, 32.0, 30.9, 29.5, 29.4, 27.6, 22.8, 14.2.

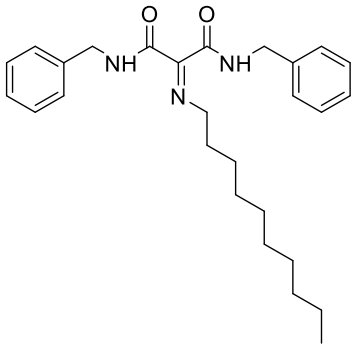
HRMS (ESI-TOF) = m/*z* calcd. for $C_{25}H_{34}N_3O_2$: 408.2646, found 408.2650.

LRMS (ESI) = *m/z* 408 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3385, 3292, 2953, 2854, 1678, 1641, 1518, 1454, 1242, 1140, 1079, 728, 696, 457.

Mp: 60.1 - 61.8 °C.

N[1],*N*[3]-Dibenzyl-2-(decylimino)malonamide (II-54b)



$C_{27}H_{37}N_3O_2$
M: 435,61 g/mol

According to the ***general procedure C*** using 2,2-diazido-*N*[1],*N*[3]-dibenzylmalon-amide **II-48a** (51.0 mg, 0.14 mmol, 1.0 equiv), decylamine (84.26 µL, 0.42 mmol, 3.0 equiv) and cesium carbonate (46.0 mg, 0.14 mmol, 1.0 equiv), **II-54b** (32.0 mg, 70.0 µmol) is obtained after chromatography (CH/EtOAc 8/2) as yellow oil in 52% yield.

Characterization:

R*f* = 0.39 (CH/EtOAc 8/2) [UV].

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm] = 9.01 (t, *J* = 6.0 Hz, 1H), 8.69 (t, *J* = 6.5 Hz, 1H), 7.37 – 7.33 (m, 3H), 7.32–7.27 (m, 5H), 7.26 – 7.21 (m, 2H), 4.39 (d, *J* = 6.0 Hz, 2H), 4.36 (d, *J* = 6.4 Hz, 2H), 3.41 (t, *J* = 7.2 Hz, 2H), 1.56 (q, *J* = 7.2 Hz, 2H), 1.29 – 1.22 (m, 14H), 0.86 (t, *J* = 7.1, 6.6 Hz, 3H).

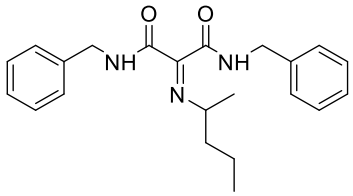
^{13}C-NMR (101 MHz, DMSO-d_6): δ [ppm] = 163.6, 162.0, 159.5, 139.2, 138.7, 128.2, 127.4, 127.2, 53.4, 42.1, 41.5, 31.2, 29.7, 28.9, 28.7, 28.6, 26.7, 22.0, 13.9.

HRMS (ESI-TOF) = m/*z* calcd. for $C_{27}H_{37}N_3NaO_2$: 458.2778, found 458.2778.

LRMS (ESI) = *m/z* 436 (87.4%) $[M+H]^+$, 872 (100%) $[2M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3362, 3288, 2951, 2850, 1677, 1645, 1524, 1430, 1249, 1134, 727, 694, 608, 450.

N[1],*N*[3]-Dibenzyl-2-(pentan-2-ylimino)malonamide (II-54c)



$C_{22}H_{27}N_3O_2$
M: 365,48 g/mol

According to the ***general procedure C*** using 2,2-diazido-*N*[1],*N*[3]-dibenzyl-malonamide **II-48a** (50.0 mg, 0.14 mmol, 1.0 equiv), 2-aminopentane (48.7 µL, 0.41 mmol, 3.0 equiv) and cesium carbonate (45.0 mg, 0.14 mmol, 1.0 equiv), **II-54c** (29.0 mg, 80.0 µmol) is obtained after chromatography (CH/EtOAc 8/2) as yellow oil in 57% yield.

Characterization:

R_f = 0.34 (CH/EtOAc 8/2) [UV].

^{1}H-NMR (600 MHz, DMSO-d_6): δ [ppm] = 8.99 (t, *J* = 6.0 Hz, 1H), 8.63 (t, *J* = 6.5 Hz, 1H), 7.37–7.29 (m, 8H), 7.24 (ddt, *J* = 8.5, 5.0, 1.4 Hz, 2H), 4.42 – 4.33 (m, 4H), 3.50 – 3.44 (m, 1H), 1.53–1.37 (m, 2H), 1.22 – 1.13 (m, 2H), 1.10 (d, *J* = 6.2 Hz, 3H), 0.81 (t, *J* = 7.4 Hz, 3H).

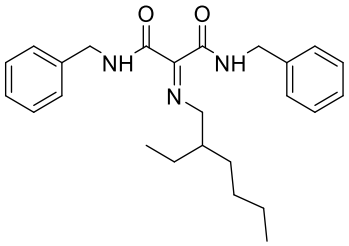
^{13}C-NMR (101 MHz, DMSO-d_6): δ [ppm] = 163.7, 162.2, 157.7, 139.2, 138.7, 128.2, 128.2, 127.5, 127.2, 126.8, 58.3, 42.1, 41.6, 21.3, 18.9, 13.8.

HRMS (ESI-TOF) = m/*z* calcd. for $C_{22}H_{27}N_3NaO_2$: 388.1999, found 388.1995.

LRMS (ESI) = *m/z* 366 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3388, 3293, 2926, 1737, 1640, 1517, 1454, 1239, 1144, 1044, 730, 697, 600, 491.

N[1],*N*[3]-Dibenzyl-2-((2-ethylhexyl)imino)malonamide (II-54d)



$C_{25}H_{33}N_3O_2$
M: 407,56 g/mol

According to the ***general procedure C*** using 2,2-diazido-*N*[1],*N*[3]-dibenzyl-malonamide **II-48a** (50.0 mg, 0.14 mmol, 1.0 equiv), 2-ethylhexylamine (67.44 µL, 0.41 mmol, 3.0 equiv) and cesium carbonate (45.0 mg, 0.14 mmol, 1.0 equiv), **II-54d** (31.0 mg, 80.0 µmol) is obtained after chromatography (CH/EtOAc 8/2) as yellow oil in 56% yield.

Characterization:

R*f* = 0.39 (CH/EtOAc 8/2) [UV].

^{1}H-NMR (600 MHz, DMSO-d_6): δ [ppm] = 9.02 (t, *J* = 6.0 Hz, 1H), 8.62 (t, *J* = 6.4 Hz, 1H), 7.36 (d, *J* = 7.5 Hz, 2H), 7.34 – 7.27 (m, 6H), 7.27 – 7.22 (m, 2H), 4.38 (dd, *J* = 10.5, 6.2 Hz, 4H), 1.63 – 1.54 (m, 1H), 1.37 (tdd, *J* = 14.5, 7.6, 4.2 Hz, 1H), 1.30 – 1.16 (m, 9H), 0.85 (t, *J* = 7.1 Hz, 3H), 0.81 (t, *J* = 7.4 Hz, 3H).

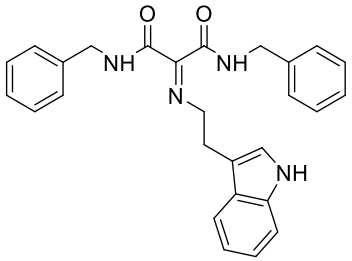
^{13}C-NMR (101 MHz, DMSO-d_6): δ [ppm] = 163.6, 162.0, 159.6, 139.2, 138.7, 128.2, 128.1, 127.3, 127.2, 126.8, 126.7, 56.4, 42.0, 41.6, 30.7, 28.3, 24.0, 22.4, 13.9, 10.7.

HRMS (ESI-TOF) = m/*z* calcd. for $C_{25}H_{33}N_3NaO_2$: 430.2463, found 430.2465.

LRMS (ESI) = *m/z* 408 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3388, 3303, 2923, 2130, 1680, 1642, 1518, 1454, 1239, 1079, 1044, 728, 696, 602, 492.

2-((2-(1*H*-Indol-3-yl)ethyl)imino)-*N*^{1},*N*^{3}-dibenzylmalonamide (II-54e)



$C_{27}H_{26}N_4O_2$
M: 438,53 g/mol

According to the ***general procedure C*** using 2,2-diazido-*N*^{1},*N*^{3}-dibenzylmalonamide **II-48a** (51.0 mg, 0.14 mmol, 1.0 equiv), tryptamine (68.0 mg, 0.42 mmol, 3.0 equiv) and cesium carbonate (46.0 mg, 0.14 mmol, 1.0 equiv), **II-54e** (37.0 mg, 80.0 µmol) is obtained after chromatography (CH/EtOAc 8/2) as white solid in 60% yield.

Characterization:

R$_f$ = 0.13 (CH/EtOAc 8/2) [UV].

^{1}H-NMR (600 MHz, DMSO-d_6): δ [ppm] = 10.79 (s, 1H), 9.26 (t, *J* = 6.5 Hz, 1H), 8.81 (t, *J* = 6.0 Hz, 1H), 7.57 (dq, *J* = 8.0, 1.0 Hz, 1H), 7.39 – 7.28 (m, 5H), 7.28 – 7.17 (m, 5H), 7.16 (d, *J* = 2.4 Hz, 1H), 7.06 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 2H), 6.97 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 1H), 4.51 – 4.16 (m, 4H), 3.48 – 3.40 (m, 2H), 2.90 (t, *J* = 7.5 Hz, 2H).

^{13}C-NMR (151 MHz, DMSO-d_6): δ [ppm] = 163.6, 162.0, 159.7, 139.1, 138.6, 136.2, 128.2, 128.2, 127.4, 127.2, 126.8, 122.7, 120.9, 118.3, 118.2, 111.8, 111.3, 54.5, 42.1, 41.6, 26.0.

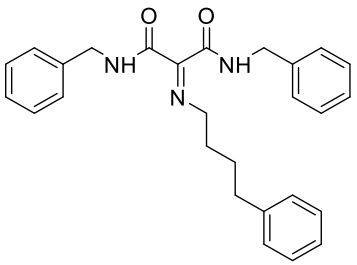
HRMS (ESI-TOF) = m/*z* calcd. for $C_{27}H_{26}N_4NaO_2$: 461.2034, found 461.1952.

LRMS (ESI) = *m/z* 439 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3311, 2925, 1732, 1643, 1519, 1454, 1239, 1079, 1042, 739, 697, 605, 480.

Mp = 191.8 – 192.5 °C.

N[1],*N*[3]-Dibenzyl-2-((4-phenylbutyl)imino)malonamide (II-54f)



$C_{27}H_{29}N_3O_2$
M: 427,55 g/mol

According to the ***general procedure C*** using 2,2-diazido-*N*[1],*N*[3]-dibenzyl-malonamide **II-48a** (50.0 mg, 0.14 mmol, 1.0 equiv), 4-phenylbutylamine (65.08 µL, 0.41 mmol, 3.0 equiv) and cesium carbonate (45.0 mg, 0.14 mmol, 1.0 equiv), **II-54f** (27.5 mg, 60.0 µmol) is obtained after chromatography (CH/EtOAc 8/2) as yellow oil in 47% yield.

Characterization:

R*f* = 0.32 (CH/EtOAc 8/2) [UV].

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 9.03 (t, *J* = 6.0 Hz, 1H), 8.70 (t, *J* = 6.4 Hz, 1H), 7.36 – 7.23 (m, 12H), 7.20 – 7.15 (m, 3H), 4.40 (d, *J* = 6.0 Hz, 2H), 4.35 (d, *J* = 6.5 Hz, 2H), 3.44 (d, *J* = 6.5 Hz, 2H), 2.58–2.53 (m, 2H), 1.61 (p, *J* = 3.7 Hz, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 163.6, 162.0, 159.6, 142.0, 139.2, 138.7, 128.2, 128.2, 128.2, 127.4, 127.2, 126.8, 126.8, 125.6, 53.2, 42.0, 41.6, 34.7, 29.3, 28.5.

HRMS (ESI-TOF) = m/*z* calcd. for $C_{27}H_{29}N_3NaO_2$: 450.2153, found 450.2152.

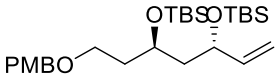
LRMS (ESI) = *m/z* 428 (100%) $[M+H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3381, 3290, 3027, 2923, 2852, 1640, 1517, 1359, 1238, 1133, 731, 695, 599, 491.

2.3. Synthesis of natural Diarylheptanoids

Compounds **III-27**, **III-38**, **III-39**, **III-40**, **III-41**, **III-42**, **III-43**, **III-44**, **III-56**, **III-57**, **III-58**, **III-59**, **III-60**, **III-61** are synthesized in accordance with the experimental section of the literature[227] and the analytical data are consistent with the literature.[227]
Iodinated compound **III-64**,[231] **III-70**,[232] **III-72**[233][234] and **III-74**[235][236] are synthesized in accordance with the experimental section of the literature and the analytical data are consistent with the literature.

(5*R*,7*S*)-5-(2-((4-methoxybenzyl)oxy)ethyl)-2,2,3,3,9,9,10,10-octamethyl-7-vinyl-4,8-dioxa-3,9-disilaundecane (III-62)



$C_{27}H_{50}O_4Si_2$
M: 494,86 g/mol

(3*S*,5*R*)-7-((4-methoxybenzyl)oxy)hept-1-ene-3,5-diol (1.72 g, 6.46 mmol, 1.0 equiv) **III-61** is dissolved in dimethylformamide (1.0 M) and treated with imidazole (3.5 g, 51.6 mmol, 8.0 equiv) and *tert*-butyldimethylsilylchloride (3.89 g, 25.83 mmol, 4.0 equiv). The solution is stirred for 16 h at room temperature, then quenched with water and extracted with dichloromethane.
The combined organic phases are dried over Na_2SO_4 and filtered. The solvent is evaporated in vacuo and the crude product is purified by column chromatography (CH → CH/EtOAc 9/1) to give **III-62** (3.01 g, 6.08 mmol) as colorless liquid in 94% yield.

Characterization:

R_f = 0.69 (CH/EtOAc 9/1) [$KMnO_4$].

[α]^{20}D = 10.7 (c = 1.0, DCM)

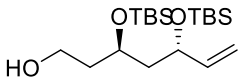
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.30 – 7.27 (m, 2H), 6.92 – 6.88 (m, 2H), 5.82 (ddd, *J* = 17.2, 10.3, 7.0 Hz, 1H), 5.16 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.06 (ddd, *J* = 10.2, 1.8, 0.8 Hz, 1H), 4.45 (d, *J* = 3.4 Hz, 2H), 4.19 (q, *J* = 6.7 Hz, 1H), 3.92 (tt, *J* = 6.4, 3.2 Hz, 1H), 3.84 (d, *J* = 0.6 Hz, 3H), 3.56 – 3.52 (m, 2H), 1.86 (dtd, *J* = 14.1, 7.2, 4.7 Hz, 1H), 1.76 (ddt, *J* = 15.8, 13.5, 6.7 Hz, 2H), 1.65 (dt, *J* = 13.6, 6.1 Hz, 1H), 0.92 – 0.89 (m, 18H), 0.09 (d, *J* = 2.4 Hz, 6H), 0.06 (d, *J* = 2.3 Hz, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 159.2, 142.0, 130.9, 129.3, 114.3, 113.9, 72.8, 71.9, 67.3, 66.9, 55.4, 46.9, 37.8, 26.1, 26.0, 18.3, 18.2, -3.8, -4.0, -4.2, -4.5.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{27}H_{50}NaO_4Si_2$: 517.3140, found 517.3166.

IR (ATR): ṽ [cm^{-1}] = 2953, 2855, 1513, 1247, 1091, 1038, 832, 772, 512.

(3*R*,5*S*)-3,5-bis((tert-butyldimethylsilyl)oxy)hept-6-en-1-ol (III-63)



$C_{19}H_{42}O_3Si_2$
M: 374,71 g/mol

(5*R*,7*S*)-5-(2-((4-methoxybenzyl)oxy)ethyl)-2,2,3,3,9,9,10,10-octamethyl-7-vinyl-4,8-dioxa-3,9-disilaundecane **III-62** (4.35 g, 8.79 mmol, 1.0 equiv) is dissolved in a mixture of dichloromethane (0.15 M) and *pH* 7 buffer (0.50 M) and 2,3-dichloro-5,6-dicyano-p-benzoquinone (3.08 g, 13.19 mmol, 1.5 equiv) is added. The reaction is stirred vigorously for 1 h (changes colour from black to red) and the suspension is filtered through celite, washed several times with dichloromethane and then water is added to the filtrate.
The two phases are separated and the aqueous phase is extracted with dichloromethane, the combined organic phases are washed with brine, dried over Na_2SO_4 and filtered. The solvent is evaporated in vacuo and the crude product is purified by column chromatography (CH → CH/EtOAc 95/5) to give **III-63** (3.0 g, 8.01 mmol) as colorless liquid in 91% yield.

Characterization:

R_f = 0.61 (CH/EtOAc 8/2) [$KMnO_4$].

[α]^{20}D = 13.1 (c = 1.0, DCM)

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 5.78 (ddd, *J* = 17.3, 10.3, 7.1 Hz, 1H), 5.12 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.05 (ddd, *J* = 10.3, 1.6, 0.9 Hz, 1H), 4.10 (dd, *J* = 7.4, 6.2 Hz, 1H), 3.97 (ddt, *J* = 7.9, 6.0, 4.5 Hz, 1H), 3.84 (ddd, *J* = 10.9, 8.3, 4.5 Hz, 1H), 3.72 (ddd, *J* = 10.9, 5.8, 5.1 Hz, 1H), 1.92 – 1.79 (m, 2H), 1.75 – 1.63 (m, 2H), 0.89 (d, *J* = 3.2 Hz, 18H), 0.09 (d, *J* = 2.1 Hz, 6H), 0.06 (s, 3H), 0.04 (s, 3H).

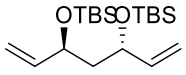
^{13}C-NMR (MHz, $CDCl_3$): δ [ppm] = 141.6, 114.7, 72.1, 69.5, 60.3, 45.7, 38.5, 26.0, 26.0, 18.3, 18.18, -3.9, -4.2, -4.4, -4.5.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{19}H_{42}NaO_3Si_2$: 397.2565, found 397.2580.

LRMS (ESI) = *m/z* 375 (42%) $[M+ H]^+$.

IR (ATR): ṽ [cm^{-1}] = 3380, 2929, 2856, 1471, 1252, 1077, 922, 832, 771, 679.

(5*S*,7*S*)-2,2,3,3,9,9,10,10-octamethyl-5,7-divinyl-4,8-dioxa-3,9-disilaundecane (III-55)



$C_{19}H_{40}O_2Si_2$
M: 356,70 g/mol

To a stirred solution of (3*R*,5*S*)-3,5-bis((tert-butyldimethylsilyl)oxy)hept-6-en-1-ol **III-63** (0.27 g, 0.72 mmol, 1.0 equiv) in tetrahydrofuran (0.06 M), *ortho*-nitrophenylselenocyanate (0.33 g, 1.43 mmol, 2.0 equiv) and trimethylphosphine solution 1 M in tetrahydrofuran (0.13 mL, 1.43 mmol, 2.0 equiv) are added under Ar at room temperature. The reaction is stirred for 1 h at room temperature. Silica is then added to the solution and the solvent is evaporated under vacuo. The crude product (0.40 g, 0.71 mmol) is purified by colomn chromatography (CH) to give a yellow solid directly solved in tetrahydrofuran (0.11 M) and treated with aqueous hydrogen peroxide 35% (0.12 mL, 1.42 mmol, 2.0 equiv) that it is added dropwise at 0 °C. The solution is stirred at room temperature for 1 h.
The solvent was removed under vacuo and the crude product purified by column chromatography (CH/EtOAc 99/1) to give **III-55** (0.23 g, 0.63 mmol) as colorless oil in 88% yield over 2 steps.

(*Note: when necessary, the oxidation could be induced by heating the reaction mixture for 10 min at 50 °C with reaction flask open to the air*.)

Characterization:

R_f = 0.61 (CH/EtOAc 8/2) [$KMnO_4$].

$[\alpha]^{20}D$ = 6.9 (c = 1.0, DCM)

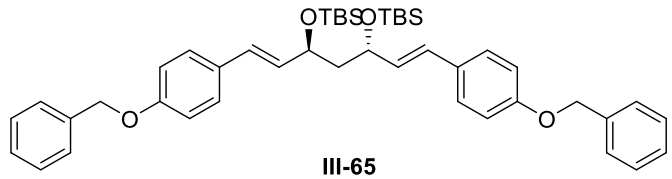
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 5.81 (ddd, *J* = 17.2, 10.3, 7.0 Hz, 2H), 5.12 (ddd, *J* = 17.1, 1.7, 1.1 Hz, 2H), 5.03 (ddd, *J* = 10.2, 1.7, 0.9 Hz, 2H), 4.18 (tdd, *J* = 6.5, 5.4, 1.1 Hz, 2H), 1.69 (t, *J* = 6.4 Hz, 2H), 0.89 (s, 18H), 0.06 (s, 6H), 0.03 (s, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 142.0, 114.3, 71.5, 47.5, 26.1, 18.4, -3.7, -4.5.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{19}H_{40}NaO_2Si_2$: 379.2459, found 379.2459.

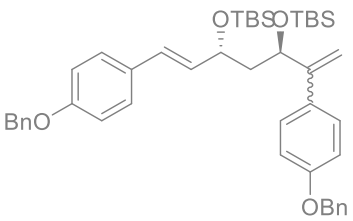
IR (ATR): ṽ [cm^{-1}] = 2955, 2857, 1251, 1070, 832, 772, 679.

(5*S*,7*S*)-5,7-bis((E)-4-(benzyloxy)styryl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (III-65)

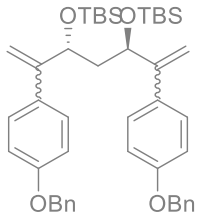


III-65

$C_{45}H_{60}O_4Si_2$
M: 721,14 g/mol



III-65A



III-65B

To a stirred suspension of 1-(benzyloxy)-4-iodobenzene **III-64** (0.41 g, 1.33 mmol, 5.0 equiv), potassium carbonate (0.15 g, 1.07 mmol, 4.0 eq), tetrabutylammonium chloride (0.15 g, 0.53 mmol, 2.0 equiv), $Pd(OAc)_2$ (10.0 mg, 10.6 µmol, 0.04 equiv) in dimethylformamide (0.03 M), (5*S*,7*S*)-2,2,3,3,9,9,10,10-octamethyl-5,7-divinyl-4,8-dioxa-3,9-disilaundecane **III-55** in dimethylformamide (0.03 M) is added dropwise at 95 °C and the reaction is stirred at 95 °C for 5 h.

The mixture is cooled down, filtered through a long pad of silica and washed several times with CH/EtOAc 99/1 mixture.

The solvent is evaporated under vacuo and the crude product purified by column chromatography (Pentane/Et_2O 99/1) to give **III-65** as white solid (0.15 g, 0.21 mmol) in 77% yield in a mixture of **III-65A** and **III-65B** regioisomers (84:11:5).

(Note: potassium carbonate, tetrabutylammonium chloride, $Pd(OAc)_2$ and are handled and weighed inside the glove box. NMR spectra report the peaks of the desired main molecule.)

Characterization:

R_f = 0.44 (CH/EtOAc 98/2) [UV, $KMnO_4$].

$[\alpha]^{20}D$ = -20.3 (c = 1.0, DCM)

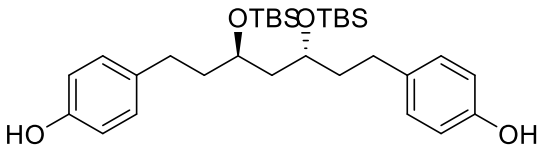
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.43 (d, *J* = 7.2 Hz, 5H), 7.39 (t, *J* = 7.5 Hz, 5H), 7.33 (d, *J* = 7.2 Hz, 2H), 7.27 (s, 2H), 6.92 (d, *J* = 8.7 Hz, 4H), 6.40 (d, *J* = 15.8 Hz, 2H), 6.06 – 6.01 (m, 2H), 5.07 (s, 4H), 4.41 (q, *J* = 6.4 Hz, 2H), 1.85 (t, *J* = 6.2 Hz, 2H), 0.92 (d, *J* = 3.7 Hz, 18H), 0.08 (s, 6H), 0.04 (s, 6).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 158.5, 137.2, 131.7, 130.3, 129.0, 128.7, 128.1, 127.7, 127.6, 115.1, 71.2, 70.2, 26.2, 18.4.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{45}H_{60}NaO_4Si_2$: 743.3922, found 743.3921.

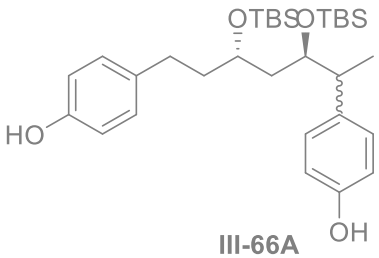
IR (ATR): ṽ [cm^{-1}] = 3090, 2952, 2854, 1606, 1509, 1247, 1105, 832, 773, 733, 694.

4,4'-((3*R*,5*R*)-3,5-bis((tert-butyldimethylsilyl)oxy)heptane-1,7-diyl)diphenol (III-66)

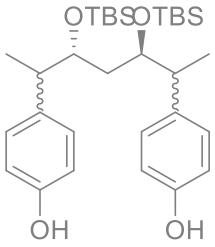


III-66

$C_{31}H_{52}O_4Si_2$
M: 544,92 g/mol



III-66A



III-66B

(5*S*,7*S*)-5,7-bis((E)-4-(benzyloxy)styryl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane **III-65** in a mixture of regioisomers (65.0 mg, 90.0 µmol, 1.0 equiv) is dissolved in ethylacetate (0.03 M) and and $Pd(OH)_2$ 20% (13.0 mg, 18.5 µmol, 0.21 equiv) is added under N_2. The reaction is stirred under H_2 (35 atm) for 16 h.
The mixture is filtered by celite, washed with ethylacetate and the solvent is evaporated under vacuo. The crude product purified by column chromatography (CH/EtOAc 8/2) to give **III-66** as colourless oil (45.0 mg, 80.0 µmol) in 91% yield in a mixture of **III-66A** and **III-66B** regioisomers (86:9:5).

(Note: NMR spectra report the peaks of the desired main molecule.)

Characterization:

R_f = 0.71 (CH/EtOAc 6/4) [UV, $KMnO_4$].

$[\alpha]^{20}D$ = 1 (c = 1.0, DCM)

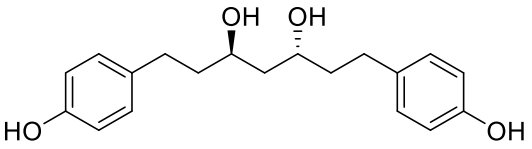
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.03 (d, *J* = 8.4 Hz, 4H), 6.76 (d, *J* = 8.4 Hz, 4H), 4.90 (s, 2H), 3.80 (dq, *J* = 9.7, 4.8, 3.7 Hz, 2H), 2.58 (dddt, *J* = 30.2, 14.0, 10.7, 5.1 Hz, 4H), 1.72 (dq, *J* = 15.3, 5.9, 4.4 Hz, 6H), 0.91 (s, 18H), 0.07 (dd, *J* = 6.2, 2.9 Hz, 12H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 153.7, 134.9, 129.5, 129.5, 115.4, 69.9, 45.4, 40.0, 30.6, 26.2, 26.1, 18.3.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{31}H_{52}NaO_4Si_2$: 567.3296, found 567.3290.

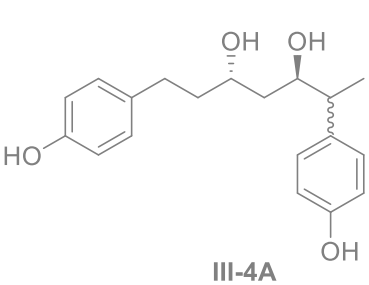
IR (ATR): ṽ [cm^{-1}] = 3386, 2928, 2855, 1513, 1249, 828, 771.

(3*R*,5*R*)-1,7-bis(4-hydroxyphenyl)heptane-3,5-diol (III-4)

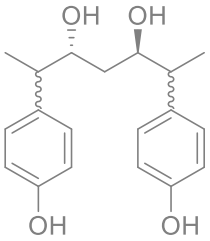


III-4

$C_{19}H_{24}O_4$
M: 316,40 g/mol



III-4A



III-4B

4,4'-((3R,5R)-3,5-bis((tert-butyldimethylsilyl)oxy)heptane-1,7-diyl)diphenol **III-66** in a mixture of regioisomers (70.0 mg, 0.13 mmol, 1.0 equiv) and *p*-toluenesulfonic acid 95% (3.0 mg, 20.0 µmol, 0.13 equiv) are dissolved in methanol (0.024 M) and the reaction is stirred at 40 °C for 3 h.

The solution is cooled down to room temperature, quenched with saturated $NaHCO_3$ solution, extracted with ethylacetate and the combined organic phases are washed with brine, dried over Na_2SO_4 and filtered. The solvent is evaporated in vacuo and the crude product purified by column chromatography (CH/EtOAc 5/5) to give **III-4** as white solid (29.0 mg, 90.0 µmol) in 71% yield in a mixture of **III-4A** and **III-4B** regioisomers (purity: 82%)

(Note: NMR spectra report the peaks of the desired main molecule.)

Characterization:

R_f = 0.31 (CH/EtOAc 4/6) [UV, $KMnO_4$].

$[\alpha]^{20}D$ = 2.6 (c = 1.0, DCM)

^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 7.04 (d, *J* = 8.4 Hz, 4H), 6.74 – 6.71 (m, 4H), 3.85 (p, *J* = 6.5, 6.1 Hz, 2H), 2.70 (ddd, *J* = 14.8, 8.7, 6.6 Hz, 2H), 2.59 (dt, *J* = 13.8, 8.0 Hz, 2H), 1.72 (qd, *J* = 8.4, 4.7 Hz, 4H), 1.60 – 1.56 (m, 2H).

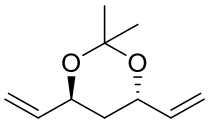
^{13}C-NMR (151 MHz, CD_3OD): δ [ppm] = 156.3, 134.5, 130.3, 116.1, 68.7, 45.6, 41.3, 41.2, 32.1.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{19}H_{23}O_4$: 315.1602, found 315.11605.

m/z calcd. for $C_{19}H_{24}NaO_4$: 339.1567, found 339.1570.

IR (ATR): ṽ [cm^{-1}] = 3278, 2938, 2912, 1511, 1237, 1054, 828, 511.

2,2-dimethyl-4,6-divinyl-1,3-dioxane (III-68)



$C_{10}H_{16}O_2$
M: 168,24 g/mol

To a solution of (5*S*,7*S*)-2,2,3,3,9,9,10,10-octamethyl-5,7-divinyl-4,8-dioxa-3,9-disilaundecane **III-55** (0.70 g, 1.97 mmol, 1.0 equiv) in tetrahydrofuran (0.46 M) tetrabutylammonium fluoride solution 1 M in tetrahydrofuran (9.85 mL, 9.85 mmol, 5.0 equiv) is added at 0 °C. The reaction mixture is quenched by the addition of saturated NH_4Cl solution, then extracted with ethylacetate, washed with water and brine, dried over Na_2SO_4 and filtered.

The solvent is evaporated under vacuo and the crude product (0.25 mg, 1.97 mmol) is dissolved in dichloromethane (0.30 M) and 2,2-dimethoxypropane (4.95 mL, 39.42 mmol, 20.0 equiv) and pyridinium *p*-toluenesulfonate (25.0 mg, 0.10 mmol, 0.05 equiv) are added. The reaction is stirred for 16 h at room temperature, then diluted with dichloromethane and washed with saturated $NaHCO_3$ solution. The aqueous phase is extracted with dichloromethane and all combined organic phases are dried over Na_2SO_4, filtered and the solvent is evaporated under vacuo.

The crude product is purified by column chromatography (CH/EtOAc 9/1) to give a yellowish oil (0.31 g, 1.85 mmol) in 94% yield over 2 steps.

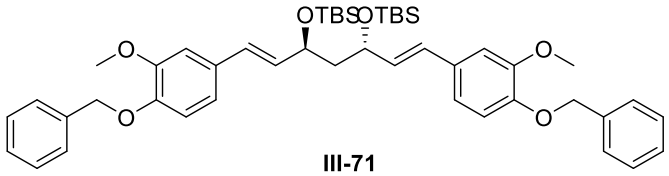
Characterization:

R_f = 0.50 (CH/EtOAc 8/2) [$KMnO_4$].

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 5.90 (ddd, *J* = 16.9, 10.5, 5.8 Hz, 2H), 5.23 (d, *J* = 17.3 Hz, 2H), 5.13 (d, *J* = 10.5 Hz, 2H), 4.38 (q, *J* = 7.2 Hz, 2H), 1.84 (t, *J* = 7.5 Hz, 2H), 1.41 (s, 6H).

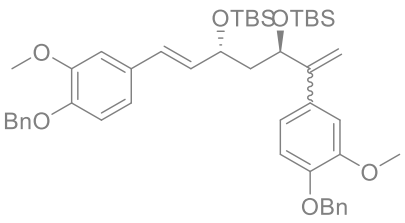
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 138.8, 115.3, 100.5, 67.8, 36.5, 25.7.

(5*S*,7*S*)-5-((E)-4-(benzyloxy)-3-ethoxystyryl)-7-((E)-4-(benzyloxy)-3-methoxystyryl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (III-71)

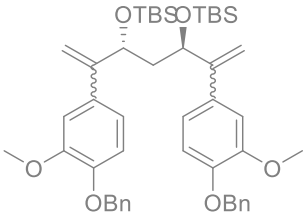


III-71

$C_{47}H_{64}O_6Si_2$
M: 781,19 g/mol



III-71A



III-71B

To a stirred suspension of 1-(benzyloxy)-4-iodo-2-methoxybenzene **III-70** (0.48 g, 1.40 mmol, 5.0 equiv) potassium carbonate (0.16 g, 1.12 mmol, 4.0 equiv), tetrabutylammonium chloride (0.16 g, 0.56 mmol, 2.0 eq), $Pd(OAc)_2$ (11.0 mg, 11.2 µmol, 0.04 equiv) in dimethylformamide (0.03 M), (5*S*,7*S*)-2,2,3,3,9,9,10,10-octamethyl-5,7-divinyl-4,8-dioxa-3,9-disilaundecane **III-55** in dimethylformamide (0.03 M) is added dropwise at 90 °C and the reaction is stirred at 90 °C for 16 h. The mixture is cooled down to room temperature, filtered through a long pad of silica and washed several times with CH/EtOAc 9/1. The solvent is evaporated under vacuo and the crude product purified by column chromatography (CH/EtOAc 9/1) to give a colourless oil (0.15 mg, 0.19 mmol) in 68% yield in a mixture of **III-71A** and **III-71B** regioisomers (84:11:5)

(Note: potassium carbonate, tetrabutylammonium chloride, $Pd(OAc)_2$ and is handled and weighed inside the glove box. NMR spectra report the peaks of the desired main molecule.).

Characterization:

R_f = 0.2 (CH/EtOAc 9/1) [UV, $KMnO_4$].

$[\alpha]^{20}D$ = -31.6 (c = 1.0, DCM)

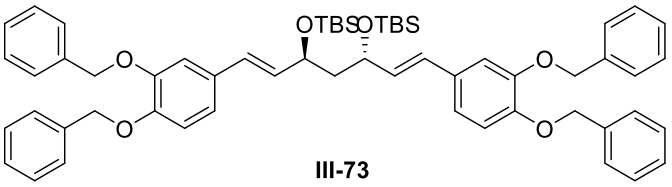
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.43 (s, 3H), 7.37 (s, 4H), 7.31 (d, *J* = 7.2 Hz, 3H), 6.91 (s, 2H), 6.82 (s, 4H), 6.38 (d, *J* = 15.8 Hz, 2H), 6.04 (dd, *J* = 15.8, 7.4 Hz, 2H), 5.15 (s, 4H), 4.43 (q, *J* = 6.5 Hz, 2H), 3.86 (s, 6H), 1.87 (t, *J* = 6.2 Hz, 2H), 0.92 (s, 18H), 0.09 (s, 6H), 0.05 (s, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 149.9, 148.1, 137.3, 132.0, 130.9, 129.3, 128.7, 128.7, 128.0, 127.4, 127.4, 119.5, 114.2, 109.7, 71.4, 60.5, 56.1, 48.1, 26.2, 18.4, 14.3.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{47}H_{64}NaO_6Si_2$: 803.4134, found 803.4132.

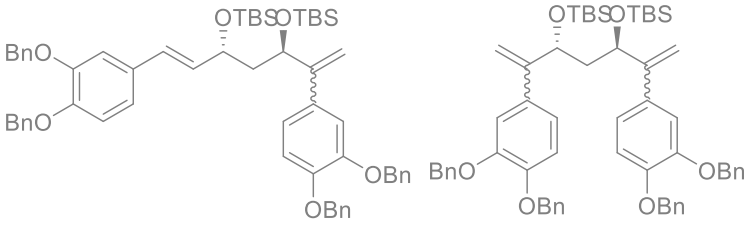
IR (ATR): ṽ [cm^{-1}] = 2952, 2854, .1509, 1250, 1025, 833, 773, 695.

(5*S*,7*S*)-5,7-bis((*E*)-3,4-bis(benzyloxy)styryl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (III-73)



III-73

$C_{59}H_{72}O_6Si_2$
M: 933,39 g/mol



III-73A **III-73B**

To a stirred suspension of (((4-iodo-1,2-phenylene)bis(oxy))bis(methylene))dibenzene **III-72** (0.41 g, 0.98 mmol, 5.0 equiv) potassium carbonate (0.11 g, 0.78 mmol, 4.0 equiv), tetrabutylammonium chloride (0.11 g, 0.39 mmol, 2.0 eq), $Pd(OAc)_2$ (7.0 mg, 7.85 µmol, 0.04 equiv) in dimethylformamide (0.03 M), (5*S*,7*S*)-2,2,3,3,9,9,10,10-octamethyl-5,7-divinyl-4,8-dioxa-3,9-disilaundecane **III-55** in dimethylformamide (0.03 M) is added dropwise at 90 °C and the reaction is stirred at 90 °C for 16 h.

The mixture is cooled down to room temperature, filtered through a long pad of silica and washed several times with CH/EtOAC 9/1 mixture.

The solvent is evaporated under vacuo and the crude product purified by column chromatography (CH/EtOAc 9/1) to give a colourless oil (0.10 mg, 0.11 mmol) in 57% yield in a mixture of **III-73A** and **III-73B** regioisomers (90:5:5).

(Note: potassium carbonate, tetrabutylammonium chloride, $Pd(OAc)_2$ and is handled and weighed inside the glove box. In case of no full conversion after 16 h, K_2CO_3, Bu_4NCl and $Pd(OAc)_2$ are added again and the reaction is stirred for a further 16 h. NMR spectra report the peaks of the desired main molecule.)

Characterization:

R_f = 0.59 (CH/EtOAc 9/1) [UV, $KMnO_4$].

$[\alpha]^{20}D$ = -18.3 (c = 1.0, DCM)

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.50 – 7.46 (m, 8H), 7.39 (td, *J* = 6.4, 5.7, 2.8 Hz, 8H), 7.35 – 7.31 (m, 6H), 7.02 (s, 2H), 6.89 (s, 2H), 6.39 (d, *J* = 15.8 Hz, 2H), 6.02 (dd, *J* = 15.8, 7.4 Hz, 2H), 5.15 (d, *J* = 5.9 Hz, 8H), 4.45 (q, *J* = 6.4 Hz, 2H), 1.89 (t, *J* = 6.2 Hz, 2H), 0.96 (s, 18H), 0.12 (s, 6H), 0.07 (s, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 149.2, 149.2, 137.4, 132.1, 131.0, 129.1, 128.6, 127.9, 127.6, 127.4, 127.39, 121.8, 120.3, 115.2, 113.0, 71.5, 48.02, 26.2, 18.4.

HRMS (ESI-TOF) = *m/z* calcd. for $C_{59}H_{72}NaO_6Si_2$: 955.4760, found 955.4763.

IR (ATR): ṽ [cm^{-1}] = 2952, 2884, 1508, 1249, 1004, 833, 773, 731, 694.

❖ List of abbreviations

9-BBN	9-Borabicyclo(3.3.1)nonane
[α]D	Specific rotation
Å	Ångström
Ac	Acetyl
ACN	Acetonitrile
AcOH	Acetic acid
ATR	Attenuated total reflection
Equiv.	Equivalent
Bn	Benzyl
Bz	Benzoyl
°C	Celsius degree
CAM	Ceric Ammonium Molybdate
CH	Cyclohexane
CSA	Camphorsulfonic acid
CuAAC	Copper(I)-catalyzed azide-alkyne cycloaddition
Δ	Delta
δ	Chemical shift
DAST	Diethylaminosulfur trifluoride
DMPU	N,N'-Dimethylpropyleneurea
TLC	Thin-layer chromatography
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DIPA	Diisopropylamine
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess-Martin-Periodinan
DMSO	Dimethylsulfoxide
d.r.	diastereomeric ration
ESI	Electrospray ionization
EtOAc	Ethylacetate
et al.	and others
EtOH	Ethanol
g	Gramm
h	Hours

HMPA	Hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectroscopy
Hz	Hertz
IBS	2-iodoxybenzenesulfonic acid
IBX	2-Iodoxybenzoic acid
IC_{50}	Half-maximal inhibitory concentration
IR	Infrared spectroscopy
J	coupling constants
Cat.	Catalyst
LA	Lewis acid
LC_{50}	Half-maximal letal dose
LDA	Lithium diisopropylamide
LRMS	low resolution mass spectrometry
M	Molarity
MeOH	Methanol
mg	Milligramm
MHz	Megahertz
min	Minuten
mL	Milliliter
mmol	Millimol
mol	Mol
mol%	Mol percent
µ	micro
MOM	Methoxymethyl
Mp	Melting point
Na_2EDTA	Ethylenedinitrilotetraacetic acid disodium salt
NBS	N-Bromosuccinimide
NMR	Nuclear magnetic resonance spectroscopy
p	Para
Pd/C	Palladium on carbon
PE	Petrolether
PG	Protecting group
pH	quantitative measure of the acidity or basicity of aqueous or other liquid solutions
PhH	Benzene
PMB	4-Methoxybenzyl
Ppm	parts per million
PPTS	Pyridinium p-toluenesulfonate
pTsOH	p-Toluenesulfonic acid

Rf	Retention Factors
r.t.	Room temperature
T	Temperature
t	time
TBAF	Tetra-n-butylammonium fluoride
TBDPS	tert-Butyldiphenylsilyl
TBS	tert-Butyldimethylsilyl Ethers
TEA	Triethylamine
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
Tol	Toluene
Troc	2,2,2-Trichlorethylformiat
UV	ultraviolett

❖ References

[1]. a) H. R. El-Seedi, S. A. M. Khalifa, E. A. Taher, M. A. Farag, A. Saeed, M. Gamal, M. E. F. Hegazy, D. Youssef, S. G. Musharraf, M. M. Alajlani, J. Xiao, T. Efferth, *Pharmacol. Res. Comm.*, **2019**, 14, 123; b) M. Luckner, B. Diettrich, *Phytochemicals in Plant Cell Cultures*, **1988**, 5, 193.

[2]. a) L. F. Fieser, M. Fieser, *Steroids*, **1959**, 62, 196; b) A. Arnaud, *CR. Hebd. Seances Acad. Sci.*, **1888**, 106, 1011; c) A. Arnaud, *C. R. Hebd. Seances. Acad. Sci.*, **1888**, 107, 1162.

[3]. J. S. Miller, *J. Nat. Prod*., **1999**, 62, 1077.

[4]. W. A. Jacobs, N. M. Bigelow, *J. Biol. Chem*., **1932**, 96, 647.

[5]. H. Fürstenwerth, *Ouabain, a gift from paradise*, **2018**.

[6]. H. Thoms, *Ber. Pharm. Ges*., **1904**, 14, 114.

[7]. H. Fürstenwerth, *Int. J. Mol. Sci*., **2019**, 20, 505.

[8]. A. D. Osseo-Asare, *Bitter Roots: The Search for Healing Plants in Africa*, **2014**.

[9]. H. Fürstenwerth, *Int. J. Clin. Pract*., **2010**, 64, 1591.

[10]. H. D. Neuwinger, *African Ethnobotany: Poison and drugs*, **1996**.

[11]. H. Schedel, E. Ginlg, H. Thoms, *Die Strophanthus-frage*, **1904**.

[12]. a) R. Thauer, *Albert Fraenkel*; *The 50th Anniversary of the Introduction of Intravenous Strophanthin Therapy,* **1956**, 485; b) A. Fraenkel, *Von der empirischen zur experimentellen Digitalistherapie, Schweizerische Medizinische Wochenschrift,* **1936**, 18, 434.

[13]. a) R. Dohrmann, M. Dohrmann, *Erfahrungsheilkunde,* **1984**, 33, 183; b) R. Dohrmann, H. Janisch, M. Kessel, *Cardiol. Bull.* **1977**, 14/15, 183.

[14]. M. Halhuber, T. Lantscherat, K. Meusburger, *Med. Klein.*, **1954**, 36, 1440.

[15]. a) C. H. Williams, *Adv. Biosci. Biotechnol.*, **2014**, 05, 197; b) M. A. Crepalde, A. C. Faria-Campos, S. Campos, *BMC Genomics*, **2011**, 12, S14.

[16]. Pubchem.ncbi.nlm.nih.gov,. 'Ouabain | C29H44O12 - Pubchem'. N.p., **2015**;

[17]. S. P. Yu, D. W. Choi, *Eur. J. Neurosci.*, **1997**, 9, 1273.

[18]. a) M. Blaustein, *Am. J. Physiol. Cell. Physiol.*, **2018**, 314, C3-C26; b) M. Simonini, P. Casanova, L. Citterio, E. Messaggio, C. Lanzani, P. Manunta, *Int. J. Mol. Sci.*, **2018**, 19, 1948.

[19]. V. M. Buckalew, *Front. Endocrinol.*, **2015**, 6, 1.

[20]. H. Fürstenwerth, *Br. J. Med. Med. Res.*, **2015**, 8, 477.

[21]. A. Bagrov, J. Shapiro, O. Fedorova, *Pharmacol. Rev.*, **2009**, 61, 9.

[22]. W. Schoner, G. Scheiner-Bobis, *Am. J. Physiol.*, **2007**, 293, C509.

[23]. M. Nesher, U. Shpolansky, H. Rosen, D. Lichtstein, *Life Sci.*, **2007**, 80, 2093.

[24]. J. M. Hamlyn, M. P. Blaustein, S. Bova, D. W. DuCharme, D. W. Harris, F. Mandel, W. R. Mathews, J. H. Ludens, *Proc. Natl. Acad. Sci.*, **1991**, 88, 6259.

[25]. a) M. F. Doursout, J. E. Chelly, Y. Y. Liang, J. P. Buckley, *Clin. Exp. Hypertens*., **1992**, A 14, 393; b) C. M. Yuan, P. Manunta, J. M. Hamlyn, S. Chen, E. Bohen, J. Yeun, F. J. Haddy, M. B. Pamnani, *Hypertens.*, **1993**, 22, 178; c) P. Manunta, A. C. Rogowski, B. P. Hamilton, J. M. Hamlyn, *Hypertens.*, **1994,** 12, 549; d) M. P. Blaustein, F. H. Leenen, L. Chen, V. A. Golovina, J. M. Hamlyn, T. L. Pallone, J. W. Van Huysse, J. Zhang, W. G. Wier*, Am J. Physiol. Heart Circ. Physiol*., **2012**, 302, H1031; e) B. S. Huang, X. Huang, E. Harmsen, F. H. Leenen, *Hypertens.*, **1994**, 23, 1087; f) T. Kurashina, K. A. Kirchner, J. P. Granger, A. R. Patel, *Clin. Sci.*, **1996**, 91, 497–502; g) H. Wang, Z. Lu, W. Yuan, *Chin. Med. J.*, **1997**, 110, 911.

[26]. S. Baecher, M. Kroiss, M. Fassnacht, M. Vogeser, *Clin. Chim. Acta.*, **2014**, 431, 87.

[27]. W. Schoner, G. Scheiner-Bobis, *Semin. Nephrol.*, **2005**, 25, 343; b) W. Schoner, *Eur. J. Biochem.*, **2002**, 269, 2440.

[28]. J. A Staessen, L. Thijs, K. Stolarz-Skrzypek, A. Bacchieri, J. Barton, E. Degli Espositi, P. W De Leeuw, M. Dłużniewski, N. Glorioso, A. Januszewicz, P. Manunta, V. Milyagin, Y. Nikitin, M.

Souček, C. Lanzani, L. Citterio, M. Timio, A. Tykarski, P. Ferrari, G. Valentini, K. Kawecka-Jaszcz, G. Bianchi, *Trials.*, **2011**, 12.

[29]. V. V. Kravtsova, I. I. Paramonova, N. A. Vilchinskaya, M. V. Tishkova, V. V. Matchkov, B. S. Shenkman, I. I. Krivoi*, Int. J. Mol. Sci.*, **2021**, 22, 3920.

[30]. A. Leite, L. H. A. Cavalcante-Silva, M. R. Ribeiro, G. de Morais Lima, C. Scavone, S. Rodrigues-Mascarenhas, *Front. Pharmacol.*, **2022**, 13,1.

[31]. J. Du, L. Jiang, F. Chen, H. Hu, M. Zhou, *Front. Oncol.*, **2021**, 11, 1.

[32]. L. Wang, W. Cai, B. Han, J. Zhang, B. Yu, M. Chen, *OncoTargets and Therapy*, **2021**, 14, 1261.

[33]. E. Silva, P. Soares-da-Silva, *Int. Rev. Cell Mol. Biol*., **2012**, 294, 99.

[34]. a) J. Wu, D. Li, L. Du, M. Baldawi, M. E. Gable, A. Askari, L. Liu, *Cell Biosci*., **2015**, 5, 64; b) N. Buzaglo, M. Golomb, H. Rosen, R. Beeri, H. Cohen-Ben Ami, F. Langane, S. Pierre, D. Lichtstein*, J. Cardio. Pharm. Ther.*, **2018**, 1, 78; c) P. V. Marck, S. V. Pierre, *Int. J. Mol. Sci.*, **2018**, 19, 2336.

[35]. L. Liu, J. Wu, D. J. Kennedy, *Front. Physiol*., **2016**, 7, 382.

[36]. a) J. Li, G. R. Khodus, M. Kruusmägi, P. Kamali-Zare, X. Liu, A. C. Eklöf, S. Zelenin, h. Brismar, A. Aperia, *Nat. Commun.*, **2010**, 1, 42; b) G. R. Khodus, M. Kruusmägi, J. Li, *Pediatr. Nephrol*., **2011**, 26, 149.

[37]. K. Sroka, *J. Cardiol. Clin. Pract*., **2020**, 3, 1.

[38]. J. Cho, Y. J. Lee, J. h. Kim, S. il Kim, S. S. Kim, B. S. Choi, J. H. Choi, *Nature*, **2020**, 10.

[39]. H. Caohuy, O. Eidelman, T. Chen, Q. Yang, A. Bera, N. Walton, H. B. Pollard, *Nature*, **2021**, 11.

[40]. S. Paula, M. R. Tabet, W. J. Ball, *Biochemistry* **2005**, 44, 498-510

[41]. H. Ogawa, T. Shinoda, F. Cornelius, C. Toyoshima, *PNAS*, **2009**, 106, 13742.

[42]. A. Rahman, *Studies in Natural products Chemistry,* **2018**.

[43]. F. Cornelius, R. Kanai, C. Toyoshima, *Journal of Biol. Chem.,* **2013**, 288, 6602.

[44]. S. S. Syeda, G. Sánchez, K. Ho Hong, J. E. Hawkinson, G. I. Georg, G. Blanco, *J. Med. Chem.*, **2018**, 61, 1800.

[45]. Guidechem.com, 'Ouabain (Cas 630-60-4) Msds'. N.p., **2015**.

[46]. H. Zhang, M. S. Reddy, S. Phoenix, P. Deslongchamps, *Angew. Chem. Int. Ed.*, **2008**, 47, 1272;

[47]. C. Mannich, G. Siewert, *Ber. Dtsch. Chem. Ges.*, **1942**, 75, 737.

[48]. H. Renata, Q. Zhou, G. Dünstl, J. Felding, R. R. Merchant, C. H. Yeh, P. S. Baran, *J. Am. Chem. Soc.*, **2015**, 137, 1330.

[49]. K. Mukai, S. Kasuya, Y. Nakagawa, D. Urabe, M. Inoue, *Chem. Sci.*, **2015**, 6, 3383.

[50]. T. W. Greene, P. G. M. Wuts, *Protecting Groups in Organic Synthesis,* **1999**.

[51]. M. L. Tong, F. Huber, E. S. T. Kaptouom, T. Cellnik, S. F. Kirsch, *Chem. Commun.*, **2017**, 53, 3086.

[52]. L. E. Overman, P. V. Rucker, *Heterocycles*, **2000**, 52, 1297.

[53]. a) M. B. Smith, *March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure,* **2013**; b) H. Beyer, W. Walter, W. Francke, *Hirzel Lehrbuch der Organischen Chemie*, **2004**.

[54]. R. P. A. Sneeden, R. B. Turner**,** *J. Am. Chem. Soc.*, **1954**, 77, 130.

[55]. U. P. Geiger, E. Weiss, T. Reichstein, *Helv. Chim. Acta.*, **1967**, 50, 194.

[56]. J. S. Baran, *J. Org. Chem.*, **1964**, 29, 527.

[57]. B. Champman, A. Jarvis, *Organic Chemistry, Energetics, Kinetics and Equilibrium*, **2000**.

[58]. R. Appel, *Angew. Chem. Int. Ed.*, **1975**, *14*, 801.

[59]. J. D. Nguyen, B. Reiß, C. Dai, C. R. J. Stephenson, *Chem. Commun.*, **2013**, 49, 4352.

[60]. D. H. R. Barton, S. W. McCombie*, J. Chem. Soc. Perkin Trans.*, **1975**, 16, 1574.

[61]. L. Zhang, M. Koreeda*, J. Am. Chem. Soc*., **2004**, 126, 13190.

[62]. M. Yasuda, Y. Onishi, M. Ueba, T. Miyai, A. Baba, *J. Org. Chem.*, **2001**, 66, 7741.

[63]. J. M. Herrmann, *Reductive Deoxygenation of Alcohols & Synthesis of Novel Natural Products isolated from Ruscus aculeatus L*., **2013**.

[64]. J. S. Baran, *Tetrahedron Lett.*, **1961**, 425, 527.

[65]. C. Tamm, G. Volpp, G. Baumgartner, *Helv. Chim. Acta*, **1957**, 40, 1469.
[66]. E. M. Burgess, h. R. Penton, E. A. Taylor, *J. Org. Chem.,* **1973**, *38*, 26.
[67]. J. C. Martin, R. J. Arhart, *J. Am. Chem. Soc.*, **1971**, *93*, 2341.
[68]. R. O. Hutchins, M. G. Hutchins, C. A. Milewski, *J. Org. Chem.,* **1972**, 37, 25, 4190.
[69]. E. Clemmensen, *Ber. deu. Chem. Gesell.,* **1913**, 46, 1837.
[70]. a) N. Kishner, *J. Russ. Phys. Chem. Soc.,* **1911**, 43, 582; b) L. Wolff, *Liebigs Ann. Chem.,* **1912**, 394, 86.
[71]. J. A. R. Salvador, M. L. S. Melo, *Tetrahedron Lett.,* **1993**, 34, 361.
[72]. R. Mozingo, D. E. Wolf, S. A. Harris, K. Folkers, *J. Am. Chem. Soc.*, **1943**, *65*, 1013.
[73]. T. Cellnik, *Defunktionalisierung von Ouabain*, *Dissertation*, **2019**.
[74]. G. Tojo, M. Fernández, *Oxidation of Alcohols to aldehydes and Ketones*, **2006**.
[75]. a) H. Rapoport, H. N. Reist, *J. Am. Chem. Soc.*, **1955**, 77, 490; b) H. Rapoport, D. R. Baker, H. N. Reis, *J. Org. Chem.*, **1957**, 22, 1489; c) W. King, W. G. Penprase, M. C. Kloetzel, *J. Org. Chem.*, **1961**, 26, 3558; d) M. Fétizon, M. Golfier, *C. R. Acad. Sc. Paris*, **1968**, 267, 900.
[76]. a) E. J. Corey, G. Schmidt, *Tetrahedron Lett.*, **1979**, 5, 399; b) J. Salmon, *Chem. Br.*, **1982**, 25, 703; c) W. M. Coates, J. R. Corrigan, *Chem. And Ind.*, **1969**, 44, 1594.
[77]. R. V. Oppenauer, *Rec. Trav. Chim. Pays-Bas*, **1937**, 56, 137.
[78]. a) L. Canonica, *Gazz. Chim. Ital.*, **1947**, 77, 92; b) A. J. Fatiadi, *J. Chem. Soc.*, **1971**, 889.
[79]. F. Ballaschk, S. Kirsch, *Green Chem.*, **2019**, 21, 5896.
[80]. J. L. Luche, *J. Am. Chem. Soc*., **1978**, 100, 2226.
[81]. K. Soai, K. Ohi, *Bull. Chem. Soc. Jpn.*, **1985**, 58, 1601.
[82]. D. Setamdideh, L. Khaledi, *S. Afr. J. Chem.*, **2013**, 66, 150.
[83]. J. A. Osborn, F. h. Jardine, J. F. Young, G. Wilkinson, *J. Chem. Soc. A*, **1966**, 1711.
[84]. S. Mukherjee, A. Sengupta, S. C. Roy*, J. Chem. Sci,* **2013**, 125, 1493.
[85]. X. Xiao, D. Bai, *Synlett*., **2001**, 4, 535.
[86]. Y. Leblanc, B. J. Fitzsimmons, J. Adams, F. Perez, J. Rokach*, J. Org. Chem*., **1986**, 51, 789.
[87]. C. Schmeck, L. S. Hegedus*, J. Am. Chem. Soc.*, **1994**, 116, 9927; Y. G. Wang, X. X. Wu, Z. Y. Jiang, *Tetrahedron Lett.*, **2004**, 45, 2973.
[88]. R. Liffert, J. Hoecker, C. K. Jana, T. M. Woods, P. Burch, H. J. Jessen, M. Neuburgerb, K. Gademann, *Chem. Sci.*, **2013**, 4, 2851–2857.
[89]. M. O. Ganiu, A. H. Cleveland, Jarrod L. Paul, and R. Kartika*, Org. Lett.*, **2019**, 21, 5611.
[90]. A. P. Marchand, W. R. Weimer, *J. Org. Chem.*, **1969**, 34, 1109.
[91]. R. O. Hutchins, C. A. Milewski, B. E. Maryanoff, *J. Am. Chem. Soc.,* **1973**, 3662
[92]. R. B. Woodward, W. J. Brehm*, J. Am. Chem. Soc.*, **1948**, 70, 2107.
[93]. F. Pfrengle, V. Dekaris, L. Schefzig, R. Zimmer, H. Reissig, *Synlett*, **2008**, 19, 2965.
[94]. R. K. Wolfram, *Synthese von Triterpenderivaten und ihre biologische Evaluierung*, *Dissertation*, **2019**.
[95]. a) P. N. Rao, Z. Wang, *Steroids*, **1997**, 62, 487; b) C. W. Spangler, D. P. Kjell, L. L. Wellander, M. A. Kinsella, *J. C. S. Perkin*, **1981**, 2287.
[96]. S. M. Mahalingam, I. S. Aidhen, *Z. Naturforsch,* **2005**, 60b, 962.
[97]. J. Zhu, D. Ma, *Angew. Chem. Int. Ed.*, **2003**, 42, 5348.
[98]. B. M. Trost, J. J. Cregg*, J. Am. Chem. Soc.*, **2015**, 137, 620.
[99]. A. Dalla Cort, *Synthetic communications*, **1990**, 20, 757.
[100]. G. Barone, E. Bedini, A. Iadonisi, E. Manzo, M. Parrilli, *Synlett.*, **2002**, 10, 1645.
[101]. M. Iwata, H. Ohrui, *Bull. Chem. Soc. Jpn.*, **1981,** 54, 2837.
[102]. M. R. Maddani, K. R. Prabhu, *Synlett.*, **2011**, 6, 821.
[103]. G. J. Eqing, M. J. Robins, *Org. Lett.*, **1999**, 1, 635.
[104]. C. Ribes, E. Falomir, J. Murga, *Tetrahedron*, **2006**, 62, 1239.

[105]. T. P. Ofman, F. Küllmer, G. A. van der Marel, J. D. C. Codée, H. S. Overkleeft, *Org. Lett.*, **2021**, 23, 9516.

[106]. T. D. Cushing, J. F. Sanz-Cervera, R. M. Williams, *J. Am. Chem. Soc.*, **1996**, 118, 3, 557.

[107]. J. P. h. Verheyden, J. G. Moffatt, *J. Org. Chem.*, **1970**, 35, 7.

[108]. Miller E. C., *J. Chem. Educ.*, **1965**, 42, 254.

[109]. K. Blaszczyk, H. Koenig, Z. Paryzek, *Eur. J. Org. Chem*., **2005**, 749.

[110]. H. T. A. Cheung, C. J. Nelson*, J. Chem. Soc., Perkin Trans.*, **1989**, 1, 1563.

[111]. Y. H. Huang, J. Lei, G. H. Yi, F. Y. Huang, Y. N. Li, C. C. Wang, Y. Sun, H. F. Dai, G. H. Tan., *Cell prolif.*, **2018**, 51, e12451.

[112]. a) M. Y. Wang, W. L. Mei, Y. Y. Deng*, Modern Pharm Res*., **2008**, 1, 4; b) M. Sun, D. Pan, Y. Chen, *Oncotarget*., **2017**, 8, 32807.

[113]. a) A. Kaur, D. R. Batish, S. Kaur, B. S. Chauhan, *Front Plant Sci*, **2021**, 12, 690806; b) S. L. Al-Rowaily, A. M. Abd-ElGawad, A. M. Assaeed, A. E. N. G. El Gendy, T. A. Mohamed, *Molecule*, **2020**, 25, 5203.

[114]. D. A. Evans, J. R. Gage, J. L. Leighton, *J. Am. Chem. Soc.*, **1992**, 114, 9434.

[115]. I. Paterson, G. J. Florence, K. Gerlach, J. P. Scott, N. Sereinig, *J. Am. Chem. Soc.*, **2001**, 123, 9535.

[116]. A. Arefolov, J. S. Panek, *Org. Lett.*, **2002**, 4, 2397.

[117]. I. Gubin Yu, I. F. Makarevich, S. N. Kovalenko, T. I. Savchenko, S. Yu. Povstenko, E. M. Bezchasnyuk, *Zhurnal Organichnoi ta Farmatsevtichnoi Khimii*, **2011**, 9, 70.

[118]. a) S. Chowdhury, R. F. Standaert, *J. Org. Chem.*, **2016**, 81, 9957; b) X. J. Dai, C- J. Li, *J. Org. Chem*., **2016**, 138, 5433; c) M. Denancé, Michèle Guyot, M. Samadi, *Steorids*, **2006**, 71, 599.

[119]. W. J. Leu, H. S. Chang, S. H. Chan, J. L. Hsu, C. C. Yu, L. C. Hsu, I. S. Chen, J. H. Guh, *PLoS One*, **2014**, 9, e87323.

[120]. G. E. Keck, E. P. Boden, M. R. Wiley, *J. Org. Chem.*, **1989**, 54, 896.

[121]. a) F. D. Tropper, F. O. Andersson, S. Braun, R. Roy, *Synthesis*, **1992**, 7, 618; b) R. Kumar, P. Tiwari, P. R. Maulik, A. K. Misra, *Eur. J. Org. Chem.*, **2006**, 1, 74.

[122]. a) E. F. V. Scriven, K. Turnbull, *Chem. Rev.*, **1988**, 88, 297; b) G. L'Abbé, *Chem. Rev.*, **1969**, 69, 345.

[123]. a) P. Grieß, *Proc. R. Soc. London*, **1864**, 13, 375; b) P. Grieß, *Liebigs Ann. Chem.*, **1866**, 137, 3.

[124]. T. curtius, *Ber. Dtsch. Chem. Ges.*, **1890**, 23, 3023.

[125]. S. Bräse, K. Banert, *Organic Azides Syntheses and Applications*, **2010**.

[126]. T. Curtius, K. Heidenreich, *Ber. Dtsch. Chem. Ges.*, **1894**, 27, 2684.

[127]. T. Curtius, K. Heidenreich, *J. Prakt. Chem.*, **1895**, 52, 454.

[128]. M. O. Forster, H. E. Fierz, W. P. Joshua, *J. Chem. Soc.*, *Trans.*, **1908**, 93, 1070.

[129]. a) M. B. Sohn, M. Jones, M. E. Hendrick, R. R. Rando, W. V. E. Doerin, *Tetrahedron Lett.*, **1972**, 13, 53; b) Y. Takeuchi, K. Takagi, T. Yamaba, M. Nabetani, T. J. Koizumi, *Fluorine Chem.*, **1994**, 68, 149.

[130]. a) M. O. Forster, S. H. Newman, *J. Chem. Soc.,* **1910**, 97, 1360; b) W. Ogilvie, W. Rank, *Can. J. Chem.*, **1987**, 65, 166.

[131]. V. A. Zapolskii, J. C. Namyslo, M. Gjikaj, D. E. Kaufmann, *Synlett*, **2007**, 1507.

[132]. G. Lande, H. W. Moore, *Tetrahedron Lett.*, **1976**, 17, 2513.

[133]. M. O. Forster, R. Müller, *J. Chem. Soc. Trans.*, **1910**, 97, 126

[134]. a) E. S. A. M. Badawey, S. M. Rida, F. S. G. Soliman, T. Kappe, *Monatsh. Chem.*, **1989**, 120, 1159; b) E. Malle, W. Stadlbauer, G. Ostermann, B. Hofmann, H. J. Leis, G. M. Kostner, *Eur. J. Med. Chem.*, **1990**, 25, 137; c) C. O. Kappe, *Liebigs. Ann. Chem.*, **1990**, 5, 505.

[135]. a) E. E. Gilbert, *J. Energ. Mater.*, **1987**, 5, 77; b) G. Schroeter, *Ber. Dtsch. Chem. Ges*., **1909**, 42, 2336; c) H. Lindemann, A. Mühlhaus, *Justus Liebigs Ann. Chem.*, **1926**, 446, 1; d) S. Götzky, *Ber. Dtsch. Chem. Ges.*, *A/B* **1931**, 64, 1555; e) L. Barash, E. Wasserman, W. A. Yager, *J. Am. Chem.*

Soc., **1967**, 89, 3931; f) M. Wieland, K. Su, G. Wagner, U. H. Brinker, V. B. Arion, *Acta Crystallogr. Sect. C Struct. Chem.*, **2009**, 65, 240.

[136]. a) K. Nishiyama, T. Yamaguchi, *Synthesis*, **1988**, 106; b) K. Nishiyama, M. Oba, A. Watanabe, *Tetrahedron*, **1987**, *43*, 693; c) K. Nishiyama, A. Watanabe, *Chem. Lett.*, **1984**, *13*, 455; d) S. Kirchmeyer, A. Mertens, G. A. Olah, *Synthesis*, **1983**, 500.

[137]. D. A. Evans, T. C. Britton, J. A. Ellman, R. L. Dorow, *J. Am. Chem. Soc.*, **1990**, 112, 4011.

[138]. A. Hassner, J. Keogh, *J. Org. Chem*., **1986**, 51, 2767.

[139]. A. P. Häring, S. F. Kirsch, *Molecules*, **2015**, 20, 20042.

[140]. D. A. Kamble, P. U. Karabal, P. V. Chouthaiwale, A. Sudalai, *Tetrahedron Lett.*, **2012**, 53, 4195.

[141]. N. Okamoto, T. Sueda, H. Minami, Y. Miwa, R. Yanada, *Org. Lett.*, **2015**, 17, 1336.

[142]. S. Arepally, V. N. Babu, A. Polu, D. S. Sharada, *Eur. J. Org. Chem.*, **2018**, 5700.

[143]. a) T. L. Amyes, J. P. Richard, *J. Am. Chem. Soc.* **1991**, 113, 1867; b) T. L. Amyes, J. P. Richard, I. W. Stevens, *J. Org. Chem.*, **1993**, 58, 6057; c) T. L. Amyes, J. P. Richard, Y. G. lee, *J. Am. Chem. Soc.*, **1994**, 116, 10833; d) T. L. Amyes, J. P. Richard, V. Jagannadham, Y. G. Lee, D. J. Rice, *J. Am. Chem. Soc.*, **1995**, 117, 5198.

[144]. Y. Liang, N. Li, *J. Phys. Chem.*, **2014**, 118, 248.

[145]. a) A. Hassner, M. Stern, h. E. Gottlieb, F. Frolow, *J. Org. Chem.*, **1990**, 55, 2304; b) K. Banert, Y.-H. Joo, T. Ruffer, B. Walfort, H. Lang, *Tetrahedron Lett.*, **2010**, *51*, 2880; c) G.-C. Kuang, H. A. Michaels, J. T. Simmons, R. J. Clark, L. Zhu, *J. Org. Chem.*, **2010**, *75*, 6540; d) J. E. Hein, J. C. Tripp, L. B. Krasnova, K. B. Sharpless, V. V. Fokin, *Angew. Chem. Int. Ed.*, **2009**, 48, 8018; e) J. A. Castro-Osma, A. Lara-Sanchez, A. Otero, A. M. Rodriguez, M. C. de la Torre, M. A. Sierra, *Eur. J. Org. Chem.*, **2016**, 682.

[146]. R. M. Moriarty, P. Serridge, *J. Am. Chem. Soc.*, **1971**, 93, 1534.

[147]. R. M. Moriarty, J. M. Kliegman, C. J. Shovlin, *J. Am. Chem. Soc.*, **1967**, 89, 5958.

[148]. R. M. Moriarty, J. M. Kliegman, *J. Am. Chem. Soc.*, **1967**, 89, 5959.

[149]. a) Y. G. Gololobov, *Tetrahedron,* **1981**, 3, 437; b) Y. G. Gololobov, L. F. Kasukhin, *Tetrahedron*, **1992**, 48, 1353.

[150]. P. P Samuel, S. Kundu, C. Mohapatra, A. George, S. De, P. Parameswaran, H. W. Roesky, *Eur. J. Org. Chem.*, **2017**, 2327.

[151]. T. Harschneck, S. Hummel, P. Klahn, S. F. Kirsch, *Chem. Eur. J.*, **2012**, 18, 1187.

[152]. a) R. Huisge*, Proceedings of the Chemical Society of London*, **1961**, 357; b) H. C. Kolb, B. K. Sharpless, *Drug Discov. Today*, **2003**, 8, 112.

[153]. P. Klahn, H. Erhardt, A. Kotthaus, S. F. Kirsch, *Angew. Chem. Int. Ed.*, **2014**, 53, 7913.

[154]. H. Erhardt, A. P. Häring, A. Kotthaus, M. Roggel, M. L. Tong, P. Biallas, M. Jübermann, F. Mohr, S. F. Kirsch, *J. Org. Chem.*, **2015**, 80, 12460.

[155]. K. Holzschneider, F. Mohr, S. F. Kirsch, *Org. Lett.*, **2018**, 20, 7066.

[156]. H. Erhardt, F. Mohr, S. F. Kirsch, *Chem. Commun.*, **2016**, 52, 545.

[157]. H. Erhardt, F. Mohr, S. F. Kirsch, *Eur. J. Org. Chem.*, **2016**, 5629.

[158]. H. Erhardt, K. A. Kunz, S. F. Kirsch, *Org. Lett.*, **2017**, 19, 178.

[159]. F. Ballaschk, h. Erhardt, S. F: Kirsch, *RSC Adv*., **2017**, 7, 55594.

[160]. a) G. Zeni, R. C. Larock, *Chem. Rev.* **2004**, 104, 2285; b) N. T. Patil, Y. Yamamoto, *Chem. Rev.*, **2008**, 108, 3395; c) G. Zeni, R. C. Larock, *Chem. Rev.*, **2006**, 106, 4644; d) X. X. Guo, D. W. Gu, Z. Wu, W. Zhang, *Chem. Rev.*, **2015**, 115, 1622; d) X. F. Wu, H. Neumann, M. Beller, *Chem. Rev.*, **2013**, 113, 1; e) M. Alvarez-Corral, M. Munoz-Dorado, I. Rodriguez-Garcia, *Chem. Rev.*, **2008**, 108, 3174; f) M. Rudolph, A. S. K. Hashmi, *Chem. Commun.*, **2011**, 47, 6536; g) S. R. Chemler, P. H. Fuller, *Chem. Soc. Rev.*, **2007**, 36, 1153; h) H. Villar, M. Frings, C. Bolm, *Chem. Soc. Rev.*, **2007**, 36, 55.

[161]. a) J. Zhu, *Eur. J. Org. Chem.*, **2003**, 1133; b) B. Jiang, T. Rajale, W. Wever, S. J. Tu, G. Li, *Chem. Asian J.*, **2010**, 5, 2318; c) G. Balme, E. Bossharth, N. Monteiro, *Eur. J. Org. Chem*., **2003**, 4101;

d) S. Sadjadi, M. M. Heravi, N. Nazari, *RSC Adv.* **2016**, 6, 53203; e) T. J. J. Müller, *Applied Homogeneous Catalysis with Organometallic Compounds*, **2018**, 4, 1463; f) D. M. D`Souza, T. J. J. Müller, *Chem. Soc. Rev.*, **2007**, 36, 1095; g) B. Willy, T. J. J. Müller, *Curr. Org. Chem.*, **2009**, 13, 1777; h) B. Willy, T. J. J. Müller, *ARKIVOC*, **2008**, 1, 195; i) S. Hassan, T. J. J. Müller, *Adv. Synth. Catal.*, **2015**, 357, 617; j) C. F. Gers-Panther, T. J. J. Müller, *Adv. Heterocycl. Chem.*, **2016**, 120, 67.

[162]. A. P. Häring, P. Biallas, S. F. Kirsch, *Eur. J. Org. Chem*., **2017**, 1526.

[163]. K. Holzschneider, A. P. Häring, A. Haack, D. J. Correy, T. Benter, S. F. Kirsch, *J. Org. Chem.*, **2017**, 82, 8242.

[164]. P. Biallas, S. F. Kirsch, *Tetrahedron Lett.*, **2017**, 58, 4209.

[165]. P. Biallas, T. M. Mensak, K. A. Kunz, S. F. Kirsch*, J. Org. Chem.*, **2019**, 84, 1654.

[166]. P. Biallas, J. Heider, S. F. Kirsch, *Polym. Chem.*, **2019**, 10, 60.

[167]. a) H. Tanimoto, K. Kakiuchi, *Nat. Prod. Commun.*, **2013**, 8, 1021; Selected examples: b) S. Guo, B. Chen, D. Zhao, W. Chen, G. Zhang, *Adv. Synth.Catal*., **2016**, 358, 3010; c) C. Pan, A. Abdukader, J. Han, Y. Cheng, C. Zhu, *Chem. Eur. J.*, **2014**, 20, 3606; d) A. G. O'Brien, F. Lévesque, P. H. Seeberger, *Chem. Commun.*, **2011**, 47, 2688; e) Q. Wang, W. Hu, S. Wang, Z. Pan, L. Tao, X. Guo, K. Qian, C. H. Chen, K. H. Lee, J. Chang, *Eur. J. Med. Chem.*, **2011**, 46, 4178.

[168]. Selected examples: a) F. Kamali, A. Gescher, J. A. Slack, *Xenobiotica*, **1988**, 18, 1157; b) D. Nicholls, A. Gescher, R. J. Griffin, *Xenobiotica*, **1991**, 21, 935; c) T. S. Lin, M. S. Chen, C. Mclaren, Y. S. Gao, I. Ghazzouli, W. h. Prusoff, *J. Med. Chem.*, **1987**, 30, 440; d) K. G. Pinney, M. P. Mejia, V. M. Villalobos, B. E. Rosenquist, G. R. Pettit, P. Verdier-Pinard, E. Hamel, *Bioorg. Med. Chem*., **2000**, 8, 2417.

[169]. a) C. I. Schilling, N. Jung, M. Biskup, U. Schepers, S. Bräse, *Chem. Soc. Rev*., **2011**, 40, 4840; b) S. K. Mamidyala, M.G. Finn, *Chem. Soc. Rev*., **2010**, 39, 1252; c) V. Hong, N. F. Steinmetz, M. Manchester, M. G. Finn, *Bioconjugate Chem.*, **2010**, 21, 1912; d) T. Pathak, *Chem. Rev.*, **2002**, 102, 1623; e) S. X. Cai, D. J. Glenn, K. R. Gee, M. D. Yan, R. E. Cotter, N. L. Reddy, E. Weber, J. F. W. Keana, *Bioconjugate Chem.*, **1993**, 4, 545; f) M. S. Platz, *Photochem. Photobiol.*, **1997**, 65, 193; g) H. Bayley, J. V. Staros, *Azides and Nitrenes-Reactivity and Utility*, **1984**, 433; h) A. Radominska, R. R. Drake, *Methods Enzymol.*, **1994**, 230, 330; i) J. S. Fedan, G. K. Hogaboom, J. P. O'Donnell, *Biochem. Pharmacol.*, **1984**, 33, 1167.

[170]. a) D. Ichinari, A. Nagaki, J. I. Yoshida, *Bioorg. Med. Chem.*, **2017**, 25, 6224; b) R. Rodriguez-Kabana, P. A. Backman, P. S. King, *Plant Disease Reporter*, **1975**, 59, 528; c) M. A. Awan, C. F. Konzak, J. N. Rutger, R. A. Nilan, *Crop Sci.*, **2000**, 20, 663; d) X. Cheng, M. Gao, *Environ. Exp. Bot.*, **1988**, 28, 281; e) H. W. Rines, *Environ. Exp. Bot.*, **1985**, 25, 7; f) S. Voltrová, M. Muselli, J. Filgas, V. Matoušek, B. Klepetářová, P. Beier, *Org. Biomol. Chem.*, **2017**, 15, 4962.

[171]. P. Biallas, Über die Reaktivität geminaler Diazide und Studien zur Totalsynthese von Tetrafibricin, *Dissertation*, **2019**.

[172]. E. Hellmuth, Synthese von polyazidierten organischen Verbindungen und deren Anwendung in der Darstellung von stickstoffhaltigen Heterozyklen, *Dissertation*, **2016**.

[173]. For pioneering examples of CuI-catalyzed 1,3-dipolar cycloaddition reactions of azides, see: a) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem*., **2002**, 114, 2708; b) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.*, **2002**, 67, 3057; For selected reviews, see: c) M. Meldal, C. W. Tornøe, *Chem. Rev.*, **2008**, 108, 2952; d) F. Amblard, J. H. Cho, R. F. Schinazi, *Chem. Rev.*, **2009**, 109, 4207; e) S. K. Mamidyala, M. G. Finn, *Chem. Soc. Rev.*, **2010**, 39, 1252; f) L. Casarrubios, M. C. de la Torre, M. A. Sierra, *Chem. Eur. J.*, **2013**, 19, 3534; g) E. Haldón, M. C. Nicasio, P. J. Pérez, *Org. Biomol. Chem.*, **2015**, 13, 9528.

[174]. For reviews on CuI-catalyzed 1,3-dipolar cycloaddition reactions, see: a) J. E. Moses, A. D. Moorhouse, *Chem. Soc. Rev.*, **2007**, 36, 1249; b) C. Spiteri, J. E. Moses *Angew. Chem.*, **2010**, 122, 33; *Angew. Chem. Int. Ed.*, **2010**, 49, 31; c) J. F. Lutz, *Angew. Chem.*, **2007**, 119, 1036; d) H. C.

Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.*, **2001**, 40, 2004; e) E. Haldón, M. C. Nicasio, P. J. Pérez, *Org. Biomol. Chem.*, **2015**, 13, 9528; f) K. Kacprzak, I. Skiera, M. Piasecka, Z. Paryzek, *Chem. Rev.*, **2016**, 116, 5689; g) V. K. Tiwari, B. B. Mishra, K. B. Mishra, N. Mishra, A. S. Singh, X. Chen, *Chem. Rev.*, **2016**, 116, 3086; h) P. Thirumurugan, D. Matosiuk, K. Jozwiak, *Chem. Rev.*, **2013**, 113, 4905; i) X. Jiang, X. Hao, L. Jing, G. Wu, D. Kang, X. Liu, P. Zhan, *Expert Opin. Drug Discov.*, **2019**, 14, 779.

[175]. F. Borghi, I. E. Çelik, P. Biallas, F. Mittendorf, S. Kirsch*, Eur. J. Org. Chem.*, **2020**, 4389.

[176]. J. E. Green, D. M. Bender, S. Jackson, M. J. O'Donnell, J. R. McCarthy, *Org. Lett*., **2009**, 11, 4, 804.

[177]. Y. F. Liang, K. Wu, S. Song, X. Li, X. Huang, N. Jiao, *Org. Lett.*, **2015**, 17, 876.

[178]. N. Jiao, Y. F. Liang, *Angew. Chem. Int. Ed*., **2014**, 53, 548.

[179]. G. M. Keserü, M. Nógrádi, *The chemistry of natural diarylheptanoids*, **1995**.

[180]. P. Claeson, U. P. Claeson, P. Tuchinda, V. Reutrakul, *Studies in Natural Products Chemistry*, **2002**, 26, 881.

[181]. P. Jirásek, *Synthesis of natural and non-natural diarylheptanoids and evaluation of their neuroprotective activity*, *Dissertation*, **2014**.

[182]. P. Claeson, P. Tuchinda, V. Reutrakul, *J. Indian Chem. Soc*., **1994**, 509.

[183]. H. N. Lv, G. M. She, *Nat. Prod. Commun*., **2010**, 5, 1687.

[184]. H. Yang, S. h. Sung, J. Kim, Y. C. Kim, *Planta Med*., **2011**, 77, 841.

[185]. H. N. Lv, G. M. She, *Rec. Nat. Prod*., **2012**, 6, 321.

[186]. S. Shishodia, G. Sethi, B. B. Aggarwal, N. Y. Ann., *Acad. Sci.*, **2005**, 1056, 206.

[187]. M. E. Egan, M. Pearson, S. A. Weiner, V. Rajendran, D. Rubin, J. Glöckner-Pagel, S. Canny, K. Du, G. L. Lukacs, M. J. Caplan, *Science*, **2004**, 304, 600.

[188]. S. Nagumo, S. Ishizawa, M. Nagai, T. Inoue, *Chem. Pharm. Bull.*, **1996**, 44, 1086.

[189]. R. J. Anto, J. George, K. V. Babu, K. N. Rajasekharan, R. Kuttan, *Mutat. Res*., **1996**, 370, 127.

[190]. J. S. Cha, S. S. Kwon, *J. Org. Chem*., **1987**, 52, 5486.

[191]. V. Mshvildadze, J. Legault, S. Lavoie, C. Gauthier, A. Pichette, *Phytochemistry*, **2007**, 68, 2531.

[192]. C. M. n-Cordero, M. López-Lázaro, M. A. A. Agudo, E. Navarro, J. Trujillo, M. A. Jesús Ayuso, *Phytochemistry*, **2001**, 58, 567.

[193]. T. Esatbeyoglu, P. Huebbe, I. M. A. Ernst, D. Chin, A. E. Wagner, G. Rimbach, *Angew. Chem.*, **2012**, 51, 5308.

[194]. C. S. Lee, E. R. Jang, Y. J. Kim, M. S. Lee, S. J. Seo, M. W. Lee, *Int. Immunopharmacol*., **2010**, 10, 520.

[195]. A. T. Dinkova-Kostova, P. Talalay, *Mol. Nutr. Food Re*s., **2008**, 52, S128-S138.

[196]. K. I. Priyadarsini, D. K. Maity, G. h. Naik, M. S. Kumar, M. K. Unnikrishnan, J. G. Satav, H. Mohan, *Free Radic. Biol. Med*, **2003**, 35, 475.

[197]. K. Neelofar, S. Shreaz, B. Rimple, S. Muralidhar, M. Nikhat, L. A. Khan, J. Can., *Microbiol*., **2011**, 57, 204.

[198]. X. Si, Y. Wang, J. Wong, J. Zhang, B. M. McManus, H. J. Luo, *Virol*., **2007**, 81, 3142.

[199]. a) H. F. Ji, L. Shen, *Bioorg. Med. Chem. Lett.*, **2009**, 19, 2453; b) R. C. Reddy, P. G. Vatsala, V. G. Keshamouni, G. Padmanaban, P. N. Rangarajan, *Biochem. Biophys. Res. Commun*., **2005**, 326, 472.

[200]. M. Nose, T. Koide, Y. Ogihara, Y. Yabu, N. Ohta, *Biol. Pharm. Bull.*, **1998**, 21, 643.

[201]. F. Kiuchi, Y. Goto, N. Sugimoto, N. Akao, K. Kondo, Y. Tsuda, *Chem. Pharm. Bull*., **1993**, 41, 1640.

[202]. J. Y. Park, h. J. Jeong, J. H. Kim, Y. M. Kim, S. J. Park, D. Kim, K. H. Park, W. S. Lee, Y. B. Ryu, *Biol. Pharm. Bull*., **2012**, 35, 2036.

[203]. J. G. Choi, M. W. Lee, S. E. Choi, M. H. Kim, O. H. Kang, Y. S. Lee, H. S. Chae, B. Obiang-Obounou, Y. C. Oh, M. R. Kim, D. W. Shin, J. h. Lee, D. Y. Kwon, *Eur. Rev. Med. Pharmacol. Sci*., **2012**, 16, 853.

[204]. W. R. García-Niño, J. Pedraza-Chaverrí, *Food Chem. Toxicol*., **2014**, 69, 182.
[205]. H. I. Lee, R. A. McGregor, M. S. Choi, K. I. Seo, U. J. Jung, J. Yeo, M. J. Kim, M. K. Lee, *Life Sci*., **2013**, 93, 693.
[206]. C. Girish, S. C. Pradhan, *J. Pharmacol. Pharmacother*., **2012**, 3, 149.
[207]. C. Mancuso, T. E. Bates, D. A. Butterfield, S. Calafato, C. Cornelius, A. D. Lorenzo, A. T. Dinkova Kostova, V. Calabrese, *Expert Opin. Investig. Drugs*, **2007**, 16, 1921.
[208]. G. P. Lim, T. Chu, F. S. Yang, W. Beech, S. A. Frautschy, G. M. Cole, *J. Neurosci*., **2001**, 21, 8370.
[209]. Q. Wang, A. Y. Sun, A. Simonyi, M. D. Jensen, P. B. Shelat, G. E. Rottinghaus, R. S. MacDonald, D. K. Miller, D. E. Lubahn, G. A. Weisman, G. Y. Sun, *J. Neurosci. Res*., **2005**, 82, 138.
[210]. N. Braidy, R. Grant, S. Adams, G. J. Guillemin, *FEBS J*., **2010**, 277, 368.
[211]. a) F. J. Wu, J. D. Su, *Zhongguo Nongye Hauxue Huizhi*, **1996**, 34, 438; b) M. S. Ali, Y. Tezuka, S. Awale, A. H. Banskota, S. Kadota, *J. Nat. Prod*., **2001**, 64, 289.
[212]. a) K. Venkatesham, S. P. Reddy, B. Chinnababu, K. S. Babu, *Helv. Chim. Acta*, **2015**, 98, 1307; b) J. W. Nam, G. Y. Kang, A. R. Han, D. Lee, Y. S. Lee, E. K. Seo, *J. Nat. Prod.*, **2011**, 74, 2109.
[213]. J. S. Yadav, E. Gyanchander, S. Bujaranipalli, S. Das, *Tetrahedron Lett.*, **2015**, 1360.
[214]. K. Venkatesham, S. Purushotham Reddy, B. Chinnababu, K. Suresh Babu, *HCA*, **2015**, 1307.
[215]. S. I. Uehara, I. Yasuda, K. Akiyama, h. Morita, K. Takeia, H. Itokawa, *Chem. Pharm. Bull*., **1987**, 35, 3298.
[216]. Z. Zhang, D. Luo, J. Xie, G. Lin, J. Zhou, W. Liu, h. Li, T. Yi, Z. Su, J. Chen, *Food Funct*., **2018**, 9, 2005.
[217]. S. Goenka, S. R. Simon, *Cells. Cosmetics*, **2021**, 8, 1.
[218]. F. Zhao, Y. Gong, Y. Hu, et al., *Mol. Med. Rep*., **2015**, 11, 3087.
[219]. M. Deters, h. Knochenwefel, D. Lindhorst, *Pharm. Res*., **2008**, 25, 1822.
[220]. R. P. Singh, *Pharm. Res*., **2012**, 5, 3650.
[221]. S. Maehara, I. Michiteru, h. Hiroyuki, K. Chinami, N. Tetsuro, O. Kazuyoshi, S. Hirotaka, *Chem. Pharm. Bull.*, **2011**, 59, 1042.
[222]. A. Yokosuka, Y. Mimaki, h. Sakagami, Y. Sashida, *J. Nat. Prod*., **2002**, 65, 283.
[223]. A. Chareonkla et al., *Fitoterapia*, **2011**, 82, 534.
[224]. A. B. Garcia, T. Lessmann, J. D. Umarye, V. Mamane, S. Sommer, H. Waldmann, *Chemical communications*, **2006**, 3868.
[225]. J. T. Binder, S. F. Kirsch, *Chemical Commun.*, **2007**, 4164.
[226]. a) A. Bredenkamp, Z. B. Zhu, S. F. Kirsch, *Eur. J. Org. Chem.*, **2016**, 252; b) A. Bredenkamp, M. Wegener, S. Hummel, A. P. Häring, S. F. Kirsch, *Chem. Commun*., **2016**, 52, 1875.
[227]. F. Mittendorf, I. E. Celik, S. Kirsch, *J. Org. Chem*., **2022**, **ASAP**.
[228]. Jan Mayer-Figge, *Studien zur Totalsynthese von (+)-Hannokinol*, *Bachelor Thesis*, **2021.**
[229]. J. M. Winne, B. Guang, J. D'herd, P. J. De Clercq, *Org. Lett.*, **2006**, 21, 4815.
[230]. A. Ali, M. Hussain, I. Malik, A. Villinger, C. Fischer, P. Langer, *Helv. Chim. Acta*, **2010**, 93, 1764.
[231]. J. S. Sarie, C. Thiehoff, R. J. Mudd, C. G. Daniliuc, G. Kehr, R. Gilmour, *J. Org. Chem*., **2017**, 82, 11792.
[232]. L. Guo, F. Zhang, W. Hu, L. Li, Y. Jia, *Chem. Comm.*, **2014**, 50, 3299.
[233]. W. L. Wang, S. C. Chai, Q. Z. Ye, *Bioorg. Med. Chem.*, **2009**, 19, 1080.
[234]. a) J. L. C. Sousa, C. Proença, M. Freitas, E. Fernandes, A. M. S. Silva, *Eur. J. Med. Chem.*, **2016**, 119, 250; b) A. S. Castanet, F. Colobert, P. E. Broutin, *Tetrahedron Lett*., **2002**, 5047.
[235]. S. S. Moleele, J. P. Michael, C. B. de Koning, *Tetrahedron*, **2006**, 62, 2831.
[236]. J. J. Molloy, K, M. O'Rourke, C. P. Frias, N. L. Sloan, M. J. West, S. L. Pimlott, A. Sutherland, A. J. B. Watson, *Org. Lett.*, **2019**, 21, 2488.