TECHNISCHE UNIVERSITÄT MÜNCHEN

FAKULTÄT FÜR CHEMIE

Synthesis of Furostemokerrin

Martin Erich Morgenstern

Vollständiger Abdruck der von der Fakultät für Chemie der Technischen Universität zur Erlangung eines Doktors der Naturwissenschaften genehmigten Dissertation.

Vorsitzender:		Prof. Dr. Michael Groll
Prüfer der Dissertation:	1.	Prof. Dr. Thorsten Bach
	2.	apl. Prof. Dr. Wolfgang Eisenreich

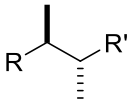
Die Dissertation wurde am 08.03.2022 bei der Technischen Universität München eingereicht und durch die Fakultät für Chemie am 22.03.2022 angenommen.

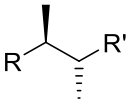
Die vorliegende Arbeit wurde in der Zeit von Dezember 2017 bis Dezember 2021 unter der Leitung von Prof. Dr. Thorsten Bach am Lehrstuhl für Organische Chemie I der Technischen Universität München angefertigt.

Teile dieser Arbeit wurden veröffentlicht:

M. Morgenstern, C. Mayer, C. Jandl, T. Bach, *Synthesis* **2022**, DOI: 10.1055/a-1777-2477

In dieser Arbeit wird von der Konvention Gebrauch gemacht, die Relativkonfiguration von Racematen durch gerade Balken (fett oder gestrichelt), die Absolut- und Relativkonfiguration von enantiomerenreiner oder enantiomerenangereicherter Verbindungen in Keilform (fett oder gestrichelt) darzustellen.

Racemat 

enantiomerenreine oder
enantiomerenangereicherte Verbindung 

Danksagung

Zuallererst möchte ich mich bei Prof. Dr. Thorsten Bach bedanken, der mich als externen Studenten so freundlich in seinen Arbeitskreis aufgenommen und mir dieses interessante und herausforderungsvolle Projekt gegeben hat. Dank seiner intensiven Betreuung in Form von Subgroup meetings, Übungen und Literaturseminaren konnte ich viel aus diversen Bereichen der Chemie lernen.

Prof. Dr. Michael Groll und apl. Prof. Dr. Wolfgang Eisenreich danke ich herzlich für die Übernahme des Prüfungsvorsitzes und des Koreferats.

Dr. Stefan Breitenlechner möchte ich danken für seine stetige Hilfe in sämtlichen Bereichen, angefangen von chemischen Fragestellungen, über organisatorische Dinge bis hin zur Wartung der Spülmaschinen. Auch Dr. Simone Stegbauer und Dr. Andreas Bauer waren mir stets hilfreich zur Seite gestanden bei Fragen zur photochemischen Ausrüstung.

Für die Messung meiner zahlreichen HPLC Proben und Loops sowie der tagtäglichen Versorgung mit Chemikalien und Verbrauchsgegenständen möchte ich mich herzlich bei Olaf Ackermann bedanken. Jürgen Kudermann gebührt mein Dank für die Hilfe bei der GC und IR Analytik. Für die pausenlose Hilfe im bürokratischen Dschungel, ihre unermesslichen Geduld und die netten Gespräche bedanke ich mich bei Kerstin Voigt.

Den Laboralltag angenehmer gestaltet durch zahlreiche fachliche Gespräche, musikalische Untermalung und generellem Smalltalk haben meine Laborkollegen Alena, Finn, Yao, Manu, Freya und Alba. Auch allen anderen, ehemaligen und gegenwärtigen Mitgliedern des AK Bach und des AK Storch haben für eine schöne Zeit im Labor gesorgt.

Für ihre fleissige und produktive Hilfe im Labor bedanke ich mich bei meinen Praktikanten Andi, Leo, Felicia und Markus und für die lustigen Geschichten bei meinen Praktikanten Senda und Ekatherina.

Bei Prof. Dr. Michael Groll bedanke ich mich für die Bereitstellung eines Laborplatzes während der Wartung im CRC und den netten, chemischen Gesprächen in dieser Zeit.

Und für Unterstützung, Hilfe, Rat oder einfach zum Frust ablassen oder lästern danke ich allen Freunden, im AK und außerhalb, sowie meinen Eltern, Peter und Johanna, meiner Schwester Steffi, meinem Schwager Flo, meinem Cousin Flori, seiner Freundin Ramona, meinem Onkel Erich, meiner Tante Ruppertine und allen ehemaligen Studienkolleginnen und Studienkollegen.

Für meine Familie

Abstract

Stemona alkaloids comprise a large class of nitrogen containing alkaloids isolated from plants of the *Stemonaceae* family. These alkaloids can be divided into eight different categories and so far, roughly 200 members are literature-known. Their diverse biological profiles and their complex structures make them interesting and challenging targets for natural product syntheses. Despite the plethora of different approaches to generate the core structures and total structures of Stemona alkaloids, one class has seen so far only little synthetic endeavors: The pyrido[1,2-*a*]azepines. Therefore, this work deals with synthetic studies towards to pyrido[1,2-*a*]azepines in general and the natural product stemokerrin specifically. We describe the successful synthesis of the common core structure of the pyrido[1,2-*a*]azepines consisting of rings *A*, *B* and *C*, and possessing six stereogenic center. Different tetronic acid derivatives were implemented in this framework, generating the entire carbon skeleton of stemokerrin and its derivatives. The ultimately harsh conditions for the last transformation led to a tautomerization and hence to the isolation of non-natural product which we named furostemokerrin.

Zusammenfassung

Stemona-Alkaloide bestehen aus einer großen Gruppe aus Stickstoff-haltigen Alkaloiden, welche aus Pflanzen der Familie *Stemonaceae* isoliert werden. Diese Alkaloide werden üblicherweise in acht verschiedene Kategorien unterteilt, und bis jetzt wurden etwa 200 verschiedene Mitglieder dieser Stoffklasse isoliert. Auf Grund ihrer diversen biologischen Aktivitäten und ihrer komplexen Struktur stellen die Stemona-Alkaloide interessante und komplexe Ziele für Totalsynthesen dar. Trotz der zahlreichen Ansätze zur Synthese von Stemona-Alkaloiden und deren Bausteinen gibt es für eine dieser Gruppen bislang nur wenige Berichte: die Pyrido[1,2-*a*]azepine. Aus diesem Grund beschäftigt sich diese Arbeit mit synthetischen Studien zu den Pyrido[1,2-*a*]azepinen im Allgemeinen, fokussiert sich aber vor allem auf den Naturstoff Stemokerrin. Im Folgenden wird die erfolgreiche Synthese der Kernstruktur der Pyrido[1,2-*a*]azepine mit ihren drei Ringsystemen *A*, *B* and *C* sowie den sechs stereogenen Zentren beschrieben. In dieses Strukturmotiv wurden verschiedene Tetronat-Körper eingebaut, wodurch das gesamte Kohlenstoffgerüst von Stemokerrin sowie weiterer Derivate entstand. Leider bewirkten die recht harschen Bedingungen für die letzte Transformation eine Tautomerisierung und führten damit ausschließlich zur Isolierung eines Derivates des Naturstoffs, welches wir Furostemokerrin nennen.

I. Theoretical part 1

1. Introduction 1

2. Stemona alkaloids 7

2.1. Classification 7

2.2. Biosynthesis 10

2.3. Bioactivity 14

2.4. Literature-reported synthetic approaches to Stemona alkaloids 15

3. Motivation and goals 27

4. Convergent synthesis to the Stille cross-coupling 28

4.1. Retrosynthetic analysis 28

4.2. Synthesis of the enamine triflate 29

4.3. Synthesis of the furan cross-coupling partner 42

5. Combination of the two fragments and synthesis of the diol 50

5.1. Synthesis of the tricyclic core structure 50

5.2. Synthesis of the 1,4-diol 53

6. Synthesis of tetronic acid derivatives 66

6.1. The tetronic acids 66

6.2. Functionalization of the methyl α-methyl tetronate 68

7. Assembly of the stemokerrin skeleton 73

7.1. Implementation of the unsubstituted tetronate 77

7.2. Assembly of the natural product skeleton with functionalized tetronates 83

8. Summary 98

II. Experimental 101

1. General experimental 101

1.1. Preliminary remarks 101

1.2. Solvents and reagents 101

1.3. Analytical methods and equipment 102

2. Synthetic procedures and analytical data 105

III. List of abbreviations 186

IV. Bibliography 188

I. Theoretical part

1. Introduction

Arguably one of the most fascinating philosophical questions in ancient times must have been the composition of matter. What is a tree, a stone or water made of? Many philosophers have pondered this question and there may have been just as many answers. Already 500 years before Christ some Greek philosophers like Leukippos, Demokritos and later Epikurus were on the right track.[1] They even went so far and established the very word still used today: atom. Although there were some inconsistencies, the general idea and notion was correct: all matter consists of atoms (from Greek atomos meaning indivisible).[2] The philosophical school of "atomism"[3] started out as a heuristic, one possible explanation to describe the world. Over the next centuries, the amount and the precision of scientific measurement devices grew, and so did our understanding of the universe. But it was not until the beginning of the 19th century that atomism was proven to be more than a philosophical idea. Many scientists, most notably Dalton,[4] found a linear correlation between compounds and the elements they were made of, resulting in the law of multiple proportions, also known as Dalton's Law.[5] From this general idea the atomic theory was established and, over time, the molecular structure of many compounds and the composition of living matter, including highly complex systems like the human genome,[6] was analyzed and understood.

All matter consists of atoms and these atoms undergo covalent bonds to form a near infinite number of molecules. In general, there are two types of interactions between molecules. Either molecules perform a chemical reaction, changing their covalent bonds and generating new compounds.[7] Or they merely undergo molecular interactions in the narrower sense, attracting or repelling each other without changing their composition.[8] Both of these types of interactions can be witnessed in our everyday lives. They explain why oil and water do not mix, why water drops are spheres, why wood burns, why table salt dissolves in water or how fish can breathe under water.

A more specific but highly interesting field is the biological area of molecular interactions. Overall, the human body, like any other animal, is a highly complex mixture of chemicals, all of them interacting with each other in a very regulated and precise way. Many different parameters move in only very small margins and the slightest change may lead to fatal consequences. A good example is the pH value of human blood, which has to be maintained at 7.4 by the many contributing compounds like CO_2, HCO_3^- and electrolytes like Na^+, K^+ or

Ca^{2+}.[9] Even more fascinating is the supply and demand of O_2 in the body. As the physical solubility of O_2 in human blood is too small to satisfy the demand by the living tissue, the well-known protein hemoglobin takes over the job of oxygen transport and increases the solubility in blood dramatically.[10] This protein, found in the red blood cells, the erythrocytes, binds molecular oxygen in the lungs, transports it to every cell in the body in need of oxygen and returns to the lungs for its next cargo. Providing fresh oxygen to the lungs by breathing is an event that occurs subconsciously and on average 20 times per minute.[11] But this oxygen transport is not as simple as it seems: If the binding to hemoglobin was thermodynamically so favored, it would not willingly part with the oxygen molecule when arriving in the tissue. This in turn would lead to a lack in oxygen and hence internal asphyxiation. Therefore, evolution had to design an intricate system for the affinity of hemoglobin to oxygen depending on external influences. Two of the major contributors to oxygen affinity are the cooperative binding of oxygen and the so called "*Bohr* effect", the sensitivity of hemoglobin's oxygen-affinity to the pH value.

The cooperative binding leads to hemoglobin more effectively binding oxygen at a high partial pressure of oxygen, primarily found in the lungs. In the oxygen-deficient tissue, the low partial pressure of oxygen leads to a strong dissociation of oxygen, resulting in hemoglobin acting as an efficient shuttle (Figure 1).

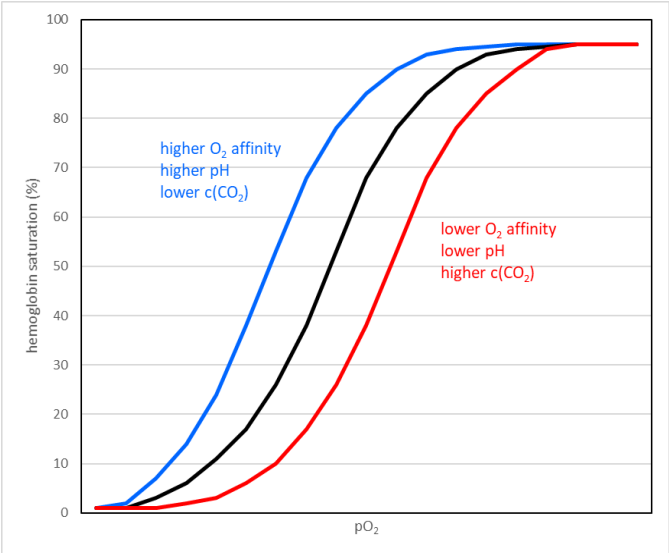


Figure 1. Cooperative binding of oxygen by hemoglobin. At a higher partial pressure of oxygen (pO_2), hemoglobin binds molecular oxygen more effectively. Lower blood pH value and higher concentration of CO_2 (red curve) decrease the O_2 affinity of hemoglobin while higher blood pH value and lower concentration of CO_2 (blue curve) increase the O_2 affinity.[12]

As the tissue not only consumes O_2 but also generates CO_2, which in turn forms carbonic acid by the enzyme carbonic anhydrase, the pH value decreases in the vicinity of oxygen-consuming tissue.[13] In this local acidic medium, specific basic histidine residues are protonated in the backbone of the hemoglobin molecule, changing its three-dimensional structure and decreasing its oxygen affinity.[14] The oxygen bound to hemoglobin in the lungs is hence released where it is needed the most. When returning to the lung, the normal pH restores the normal structure of hemoglobin along with its high affinity of oxygen, making it available for binding oxygen once more.

All this is just one example for the complexity and intricacy of living systems and understanding them requires knowledge from many different fields like chemistry, medicine, biology and physics. Even the most complex laboratory setups barely come close to the everyday molecular workings found in nature. It is to no surprise then, that the slightest irregularities can have a major impact on the normal functions of the body. And with the plethora of different components responsible for regulation, just as many possible alterations and hence diseases can exist. First, the normal functions have to be fully understood, only then is it possible to elucidate the flaws and faults in the machinery of living things.[15] This means the differences between a healthy person and one afflicted by a specific disease or a genetic alteration have to be found and understood on a molecular level. Only then is it possible to look for specific compounds or molecules that can interact with the faulty structures, be it directly or indirectly, and help restore the normal function.[16]

The gravity and importance of a disease can be linked to the number of people suffering or the global burden of the disease by the disability-adjusted life-years. An analysis of hundreds of diseases in over 200 countries over the last 30 years shows interesting trends.[17] Some of the prevailing examples of the 25 leading diseases are neonatal disorders, diarrhoeal diseases, stroke, malaria, depressive disorders and diabetes. Positive changes over the time period from 1990 to 2019 like the decreasing numbers in diseases like energy-malnutrition, measles, meningitis or whooping cough can be noted. Other diseases, commonly linked with the global increase of average age and body-mass index, like ischaemic heart diseases, stroke, low back pain or diabetes are gaining in importance.

A closer look into the irregularities of diabetes will exemplify the variety and complexity of diseases as well as their respective treatments. The medical term for the state after eating a meal is called the postprandial state and this state is associated with a short-term hyperglycaemia, meaning high concentrations of glucose in the blood. This in turn stimulates the β-cells of the pancreas to release the well-known hormone insulin, which induces a net

decrease of blood glucose, primarily by internalizing the glucose into muscle cells or adipose tissue and by decreasing the endogenous glucose production.[18] The antagonist of insulin, glucagon, has the opposite effect, hence leading to increased blood glucose levels, primarily *via* glycogenolysis or gluconeogenesis (Figure 2). Further influences and modulators on hepatic glucose production like allosteric modulation by metabolites, the influence of other hormones like catecholamines and corticosteroids or cellular redox states and especially complex signaling pathways *via* receptors, kinases or other enzymes shall not be discussed in detail.[19] But the rough understanding of insulin and glucagon is sufficient to comprehend both the origin as well as the treatment for type 1 and 2 diabetes mellitus.

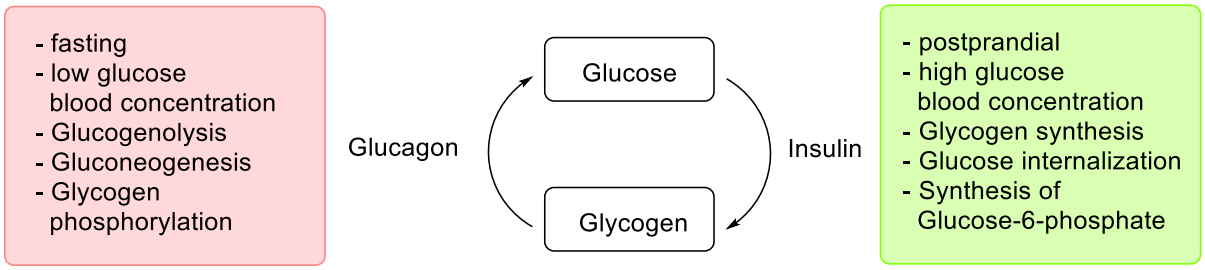


Figure 2. The influence of insulin and glucagon on the metabolism of glucose and glycogen and factors influencing the secretion of these hormones.[20]

Type 1 is defined by a hampered production of insulin by the patient, usually due to an autoimmune response of the body attacking its own β-cells of the pancreas.[21] Simply providing the body with external insulin is sufficient to restore the normal function and with regular doses, a normal life can usually be led. Since the discovery of insulin by Frederick Grant Banting and John James Rickard Macleod, awarded with the Nobel prize in medicine 1923, many optimizations to obtain a steady supply of insulin have taken place.[22] After its first isolation from canine pancreas, tremendous efforts resulted in a successful biosynthesis of human insulin in Escherichia coli and the approval as medication in 1982.[23]

However, supplementation of insulin is usually not an effective treatment option for type 2 diabetes mellitus, as this disease is characterized by an insulin resistance, meaning the body is less responsive to insulin secretion.[24] Therefore, treatment options have to target alternative signaling pathways. At this point, a little excursion is necessary to elucidate the path that led to the discovery of treatment options for type 2 diabetes, which are still valid today. This excursion shall act as an example for many similar medical discoveries.

Already early Egyptian physicians knew of several symptoms characterizing diabetes mellitus (from Greek diabetes = “flowing through” and Latin mellitus = “honey-sweet”).[25] One early

noted symptom was polyuria, the excess production of urine, which has, as indicated by the name of the disease, a sweet taste. This is due to the inefficient glucose metabolization, leading to the kidneys filtering the glucose out of the blood and excreting it *via* the urine. During medieval times it was noticed that the prescription of French lilac (*Galega officinalis*) was effective in relieving this symptom.[26] Later, the active compound galegine (**1**) was isolated and characterized from *Galega officinalis* and structurally related compounds were investigated as potential treatments. As the simple guanidine (**2**) was too toxic to be pharmacologically relevant, optimizations were performed which culminated in the compounds phenformin (**3**), buformin (**4**) and metformin (**5**) (Figure 3). Whereas the first two were withdrawn due to adverse effects, metformin remains one of the most common treatments for type 2 diabetes.[27]

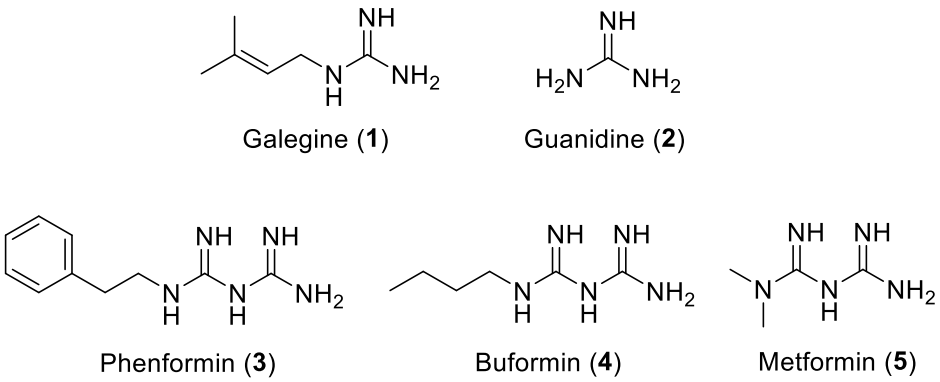


Figure 3. Structures of guanidine and the natural product galegine (top) and three examples of biguanides, a group of medication used against type 2 diabetes (bottom).

Hence, the primary treatment options for both type 1 and 2 diabetes historically started with compounds isolated from a natural source, namely mammalian pancreas and French lilac, respectively. This is of course by far not the only example. Myriad reviews point out the impact of natural products and one very extensive paper is discussed in the following. They report that in the time period from January 1981 to October 2019 a total of 1881 new drugs were approved all over the world by different agencies, most notably the FDA (food and drug administration). Not considering biological macromolecules and vaccines, 1394 molecules remain. Out of those, the group of natural products (NP) consists of 441 examples, the group of natural product inspired compounds (NPI) make up for another 489. On the other hand, the pure synthetic compounds (S) contain the leftover 464 drugs and hence only constitute roughly one third of the newly discovered, small molecule drugs (Figure 4).[28]

The authors therefore emphasize the continuous impact of natural products on drug design as well as the lack of successful drug candidates stemming solely from computation studies, of which they found only three examples. Although the rapid progress in the fields of computational chemistry, docking studies or virtual screenings might change this in the future, the recent history shows the relevance of natural product isolation and synthesis.

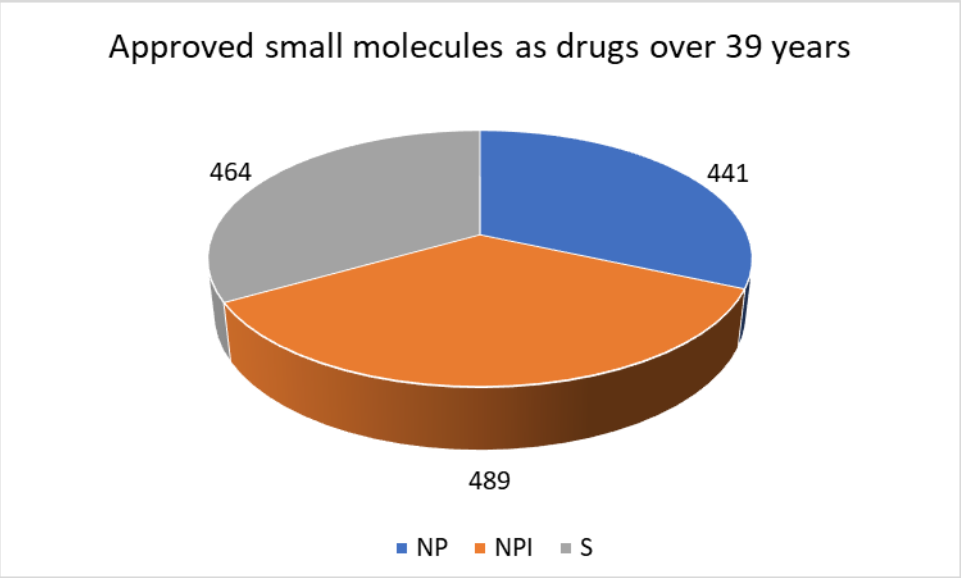


Figure 4. All 1394 newly approved small molecules and their chemical origins. (NP = natural products; NPI = natural product inspired compounds; S = synthetic compounds)

2. Stemona alkaloids

Alkaloids are a class of secondary organic compounds and are isolated from natural sources, most commonly plant material. Their biosynthetic pathway usually starts from amino acids, which explains the frequent, but not required, presence of basic amine functionalities.[29] The monocotyledonous family *Stemonaceae* contains roughly 37 species divided over the four genera *Stemona, Croomia*, *Pentastemona* and *Stichoneuron*.[30] This family is primarily found in Southern east Asia and has extensive applications in folk medicine for the treatment of respiratory problems, inflammation, the common cold and is used as an insect repellent. A majority of Stemona alkaloids features a prominent pyrrolo[1,2-*a*]azepine core structure with some exceptions containing a pyrido[1,2-*a*]azepine or a pyrido[1,3-*a*]azepine skeleton.[31]

2.1. Classification

Several classification systems for Stemona alkaloids have been proposed and had to be adopted over time, as new alkaloids were isolated and characterized. In the following, the two most commonly used classification systems are showcased.

One of the most commonly cited categorizations was developed by *Greger*.[32] This classification is strongly based on biosynthetic considerations and divides the Stemona alkaloids into three groups: croomine **6**, stichoneurine **8** and protostemonine **10** (Figure 5).[33] All classes are characterized by the presence of the pyrido[1,2-*a*]azepine core (rings A, B) and two α-methyl-γ-butyrolactone rings (rings C, D) on either side of the core. The main difference between those groups is the substitution pattern on C-9.

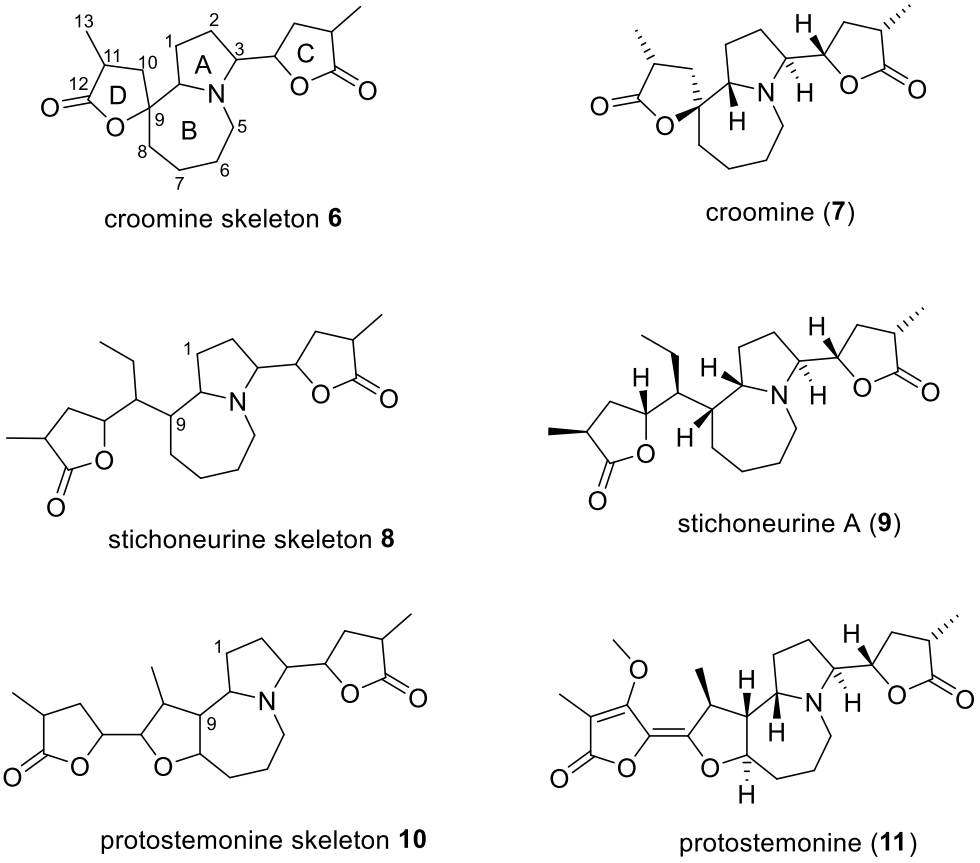


Figure 5. The three groups of Stemona alkaloids according to *Greger*, each shown with one example.[32]

In contrast, the classification system by *Pilli* and *Oliveira* comprises eight different groups, focusing on their structural differences and substitution patterns.[34] Six of the eight groups contain the established pyrido[1,2-*a*]azepine structure and one group contains the pyrido[1,2-*a*]azepine core compounds. All compounds deviating from these characteristic core features are found in the last, miscellaneous group (Figure 6). With a bigger set of groups, a more defined distinction is possible like the presence of a spirocycle at C-9 in the case of the tuberostemospironine-class alkaloids **16** or the lack of ring fusion at C-8 for the parvistemoline group **20**. This classification system also contains one separate group **22** for alkaloids exhibiting the highly complex cage structure of stemofoline (**23**), which has probably attracted the most synthetic interest of all Stemona alkaloids.[35,36] Lastly, one group consists of all pyrido[1,2-*a*]azepine Stemona alkaloids **24** and its individual members will be discussed in the following.

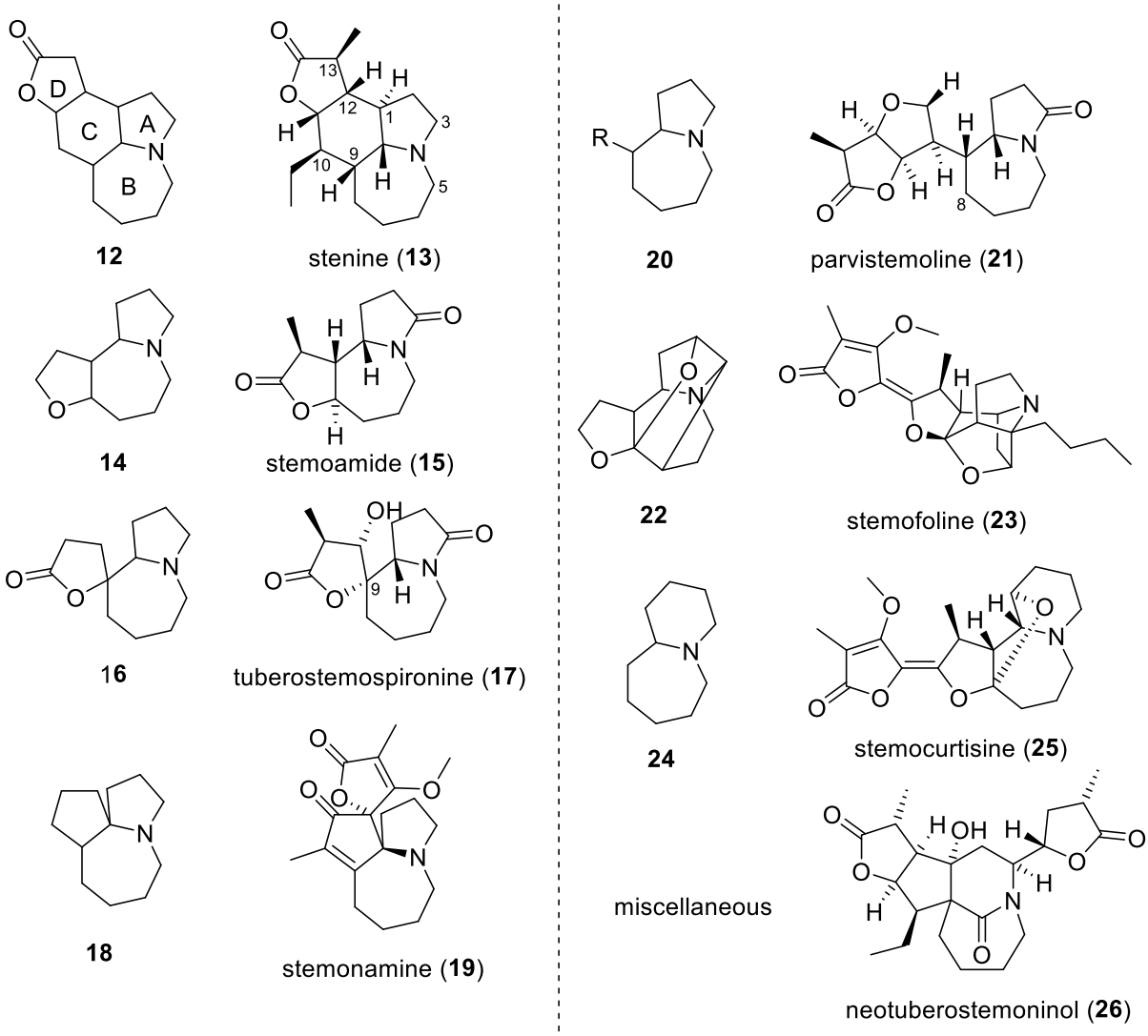


Figure 6. The eight groups of Stemona alkaloids according to *Pilli* and *Oliveira*, each shown with one example.[34]

Alongside its core structure, every member of the pyrido[1,2-*a*]azepine class shares the structural feature of a methyl α-methyl-tetronate unit, the five-membered lactone ring (Figure 7). The compounds stemokerrin (**27**), stemokerrin-*N*-oxide (**28**) and methoxystemokerrin-*N*-oxide (**29**) all contain a bis-enolether structure at C-8/C-9 and C-12/C-13 and a total of five stereogenic centers.[37] In the natural products oxystemokerrin (**30**) and oxystemokerrin-*N*-oxide (**31**) an ether bridge connects C-1 with the C-9 position to form a cyclic acetal. For both cochinchistemonine (**32**) and its closely related derivative cochinchistemoninone (**33**), the spirocycle between C-13 and C-9 is a defining structural motif. The three compounds stemocurtisine (**25**), stemocurtisine-*N*-oxide (**34**) and stemocurtisinol (**35**) contain the same tetrahydrofuran ring as oxystemokerrin (**30**), deviate however in the substituent at C-4. The

only difference between stemocurtisine (**25**) and the 6-hydroxy-5,6-seco-stemocurtisine (**36**) is the hydrolysis of the azepine ring at C-6.

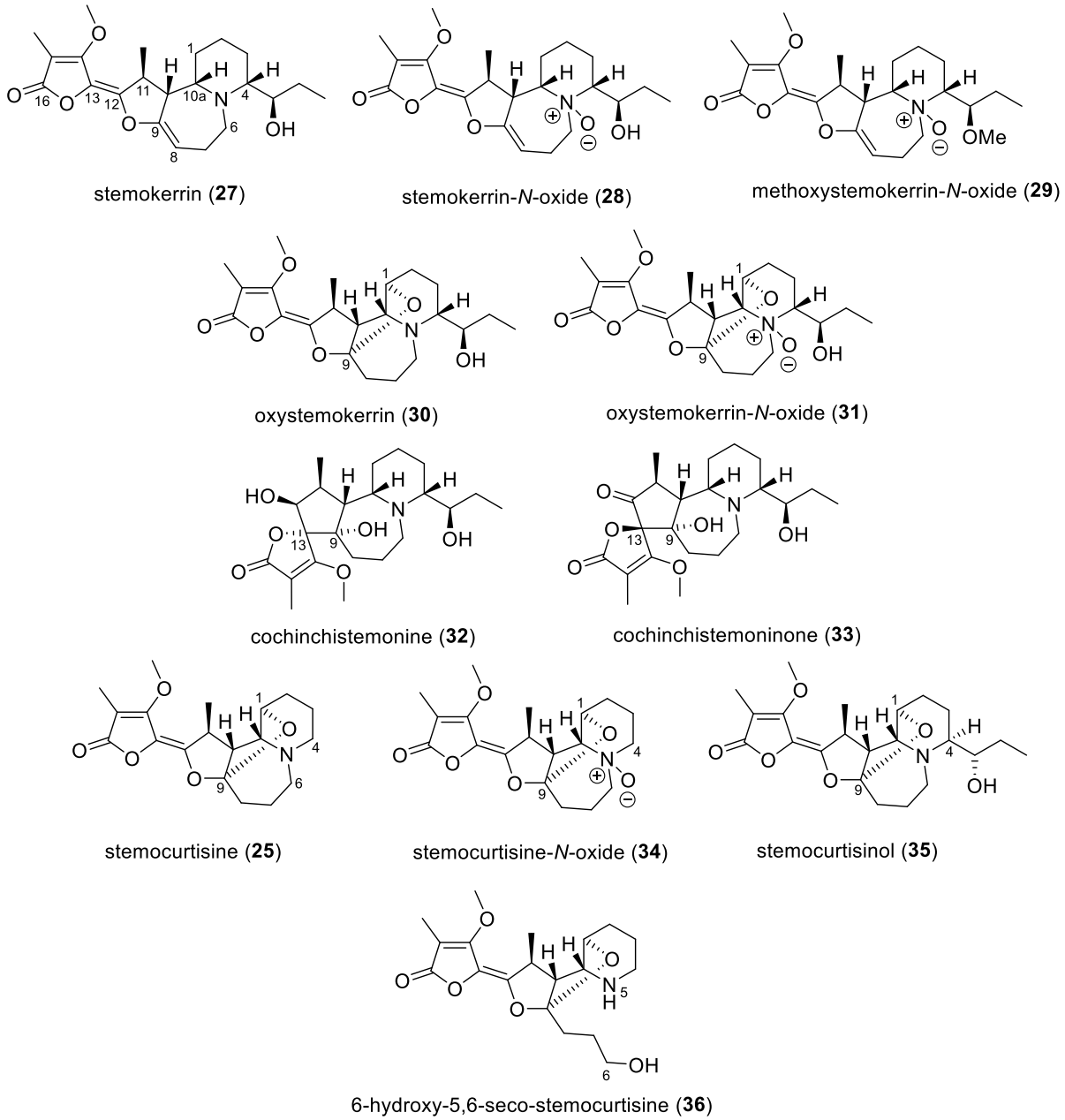


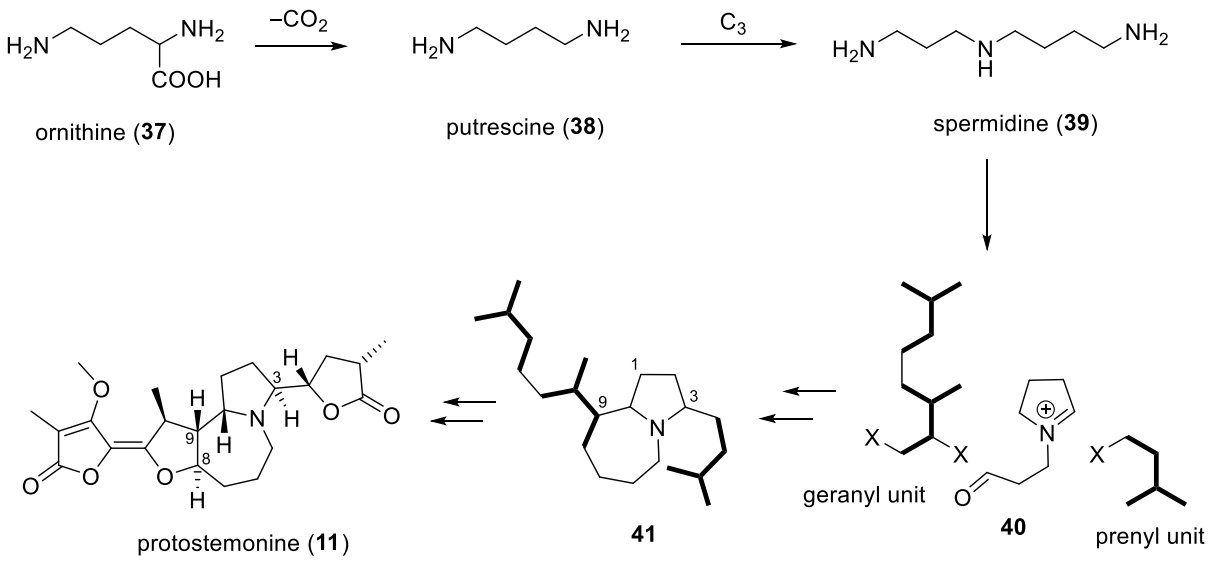
Figure 7. All members of the pyrido[1,2-*a*]azepine class of Stemona alkaloid as reported by *Greger*.[32]

2.2. Biosynthesis

Due to a lack of experimental evidence in form of isotope labeling or metabolites, the knowledge of the biosynthesis of Stemona alkaloids is limited. There are however several

tentative proposals based on compound similarities and logical pathways, out of which three are commonly mentioned and distinct from one another.

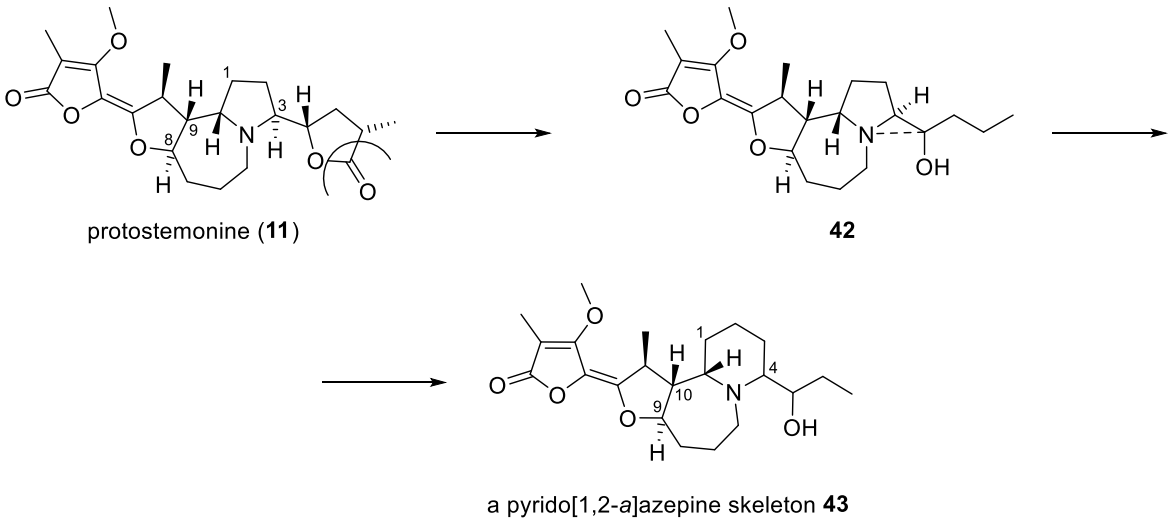
The first biosynthetic proposal by *Seger* and co-workers[38] draws several parallels to the pyrrolizidine-type natural products and starts with the amino acid ornithine (**37**) (Scheme 1).[39] After decarboxylation, the obtained diamine putrescine (**38**) is coupled with a C_3 building block to form spermidine (**39**). Oxidative deamination of both terminal amino groups yields a dialdehyde, which cyclizes to the thermodynamically favored iminium ion **40**. After consideration of typical substituents at C-9 and C-3 of the pyrrolo[1,2-*a*]azepine class alkaloids, suitable coupling partners were found in one C_{10} and one C_5 building block, which can be implemented as shown. With the entire carbon skeleton assembled in form of compound **41**, introduction of functional group and oxidations yield most Stemona alkaloids like the exemplary protostemonine (**11**).



Scheme 1. The biosynthetic pathway of Stemona alkaloids, starting from ornithine (**37**), as proposed by *Seger*.[38]

This biosynthetic approach has many strong suits and therefore seems quite intuitive. As the same route *via* iminium ion formation is established for the pyrrolizidine alkaloids, proposing the same intermediate for the synthesis of the pyrrolo[1,2-*a*]azepine core seems logical. Considering the residues at C-3, many Stemona alkaloids contain an α-methyl butyrolactone ring stemming from a C_5 building block like the prenyl unit. Decarboxylation would lead to a C_4 chain as shown for protostemonine (**11**) (Scheme 2) and consistently found in the stemofoline class **22**. Subsequent ring expansion of the pyrrole ring by implementation of one carbon atom of this side chain generates the pyrido[1,2-*a*]azepine structure of the

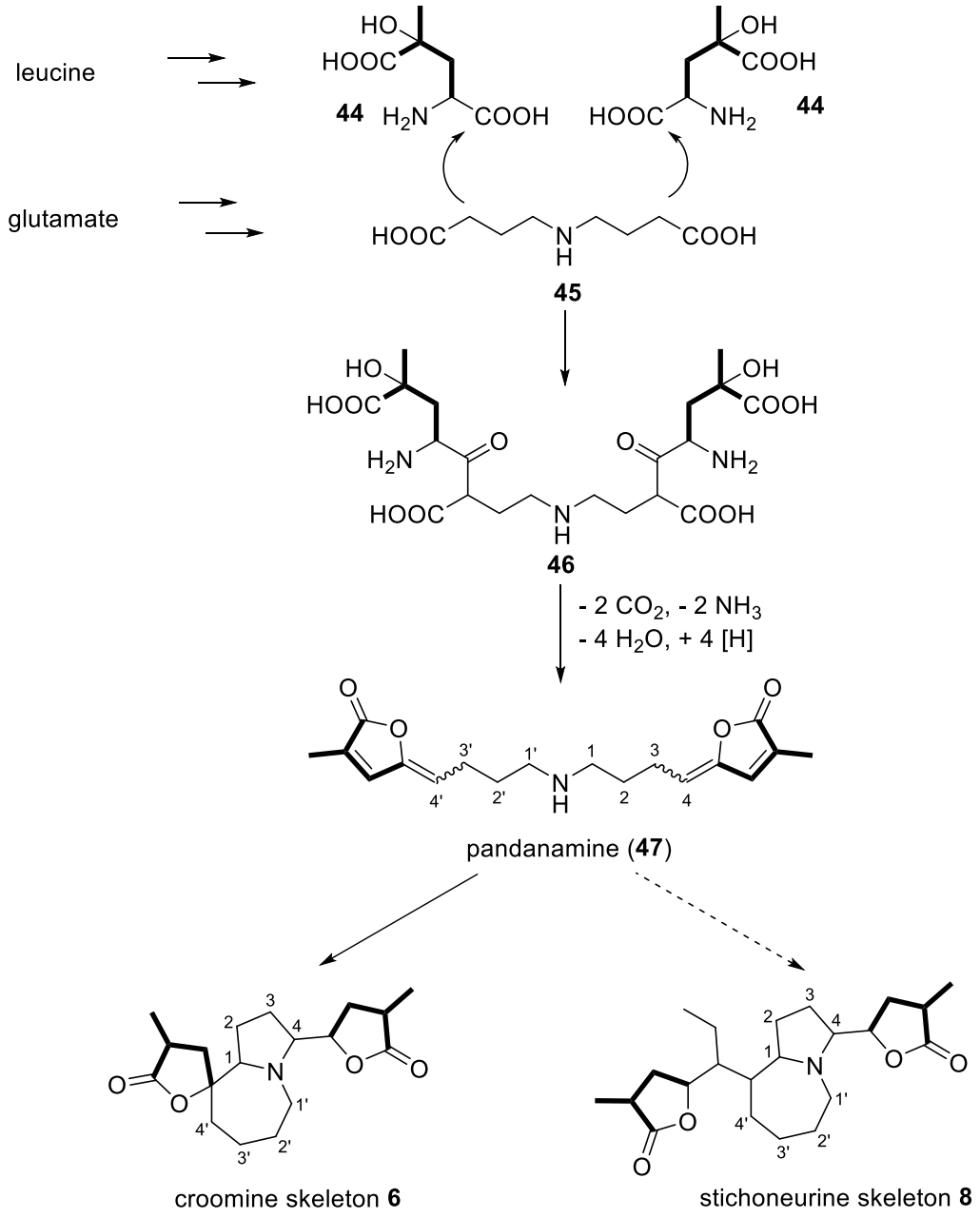
stemocurtisine class **24** along with the C_3 chain at C-4 encountered in most members of this class (Scheme 2). It has been separately proposed, that the biosynthesis of pyrido[1,2-*a*]azepine alkaloids could start from their pyrrole derivatives.[40]



Scheme 2. A potential biosynthetic conversion of a pyrrolo[1,2-*a*]azepine, in this case protostemonine (**11**), to a pyrido[1,2-*a*]azepine **43** *via* decarboxylation and ring expansion.[40]

The C-9 substituents consist mostly of C_8 entities for most pyrrolo[1,2-*a*]azepine Stemona alkaloids over different classes and even in the classification system of *Greger*, two of the three classes (stichoneurine **8** and protostemonine **10**) are defined by carrying such a C_8 substituent. Additionally, the proposed coupling of the geranyl unit to the aldehyde explains the common oxygenation at C-8.

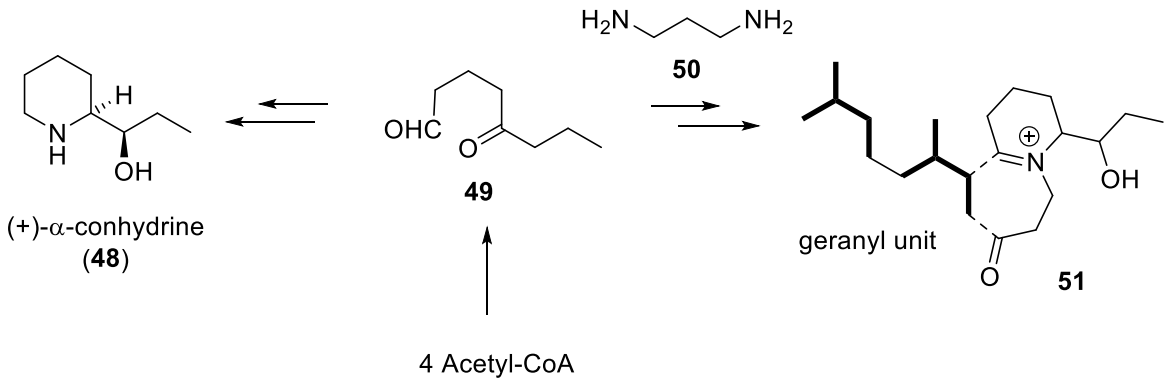
However, the existence of the croomine class **6** carrying a C_4 substituent at C-9 can, according to the first biosynthetic proposal, only be explained by a formal loss of C_4, possibly *via* hydrolysis. An alternative biosynthetic access to this last class has therefore been proposed by *Greger* (Scheme 3). He criticized the lack of postulated intermediates isolated from *Stemonaceae* and instead based his proposal on the alkaloid pandanamine (**47**), which was isolated from *Stichoneuron calcicola*. Starting from both glutamate and leucine, pandanamine is generated after several steps including a *Claisen*-type reaction, decarboxylation and hydrolysis. After cyclisation of the central secondary amine, the croomine type alkaloids **6** with their C_4 substituents at C-9 can be obtained. On the other hand, this proposal is lacking an explanation for the Stemona alkaloids carrying the C_8 substituents like the shown stichoneurine **8**.[41] Overall, both biosynthetic proposals have strengths and weaknesses and neither one can be ruled out so far.



Scheme 3. The proposed biosynthesis of the croomine-type Stemona alkaloids, starting from the amino acids leucine and glutamate.[41]

The last proposal by *Pyne* and co-workers sets a focus on the synthesis of pyrido[1,2-a]azepines (Scheme 4) and draws parallels to the hemlock alkaloid (+)-α-conhydrine (**48**)[42]. After combining four C_2 building blocks from acetyl-CoA, the polyketide derivative **49** is obtained. In contrast to the synthesis of (+)-α-conhydrine, this compound is coupled with 1,3-diaminopropane (**50**) to generate the cyclic iminium ion **51**. The implementation of a geranyl unit, similar to *Seger's* proposal, allows access to the pyrido[1,2-*a*]azepine class of Stemona

alkaloids. While this biosynthesis is rather limited, the similarities to hemlock alkaloids gives it credibility and makes it another potential option.



Scheme 4. Biosynthesis of the pyrido[1,2-*a*]azepine Stemona alkaloids and similarities to the hemlock alkaloids conhydrine.

2.3. Bioactivity

As previously mentioned, the biological activity profile of the *Stemonaceae* family is extensive and dates back thousands of years. In Asia several Stemona species have been used in traditional medicine to treat respiratory diseases like bronchitis or pertussis,[43] against the common cold, particularly because of its antitussive[44,45] and anti-inflammatory[46] properties, and the plant even finds application as a biological pesticide due to its insecticidal properties.[47,48] Notably, the three species *Stemona tuberosa*, *Stemona japonica* and *Stemona sessilifolia* can be found in the Chinese Pharmacopoeia as effective antitussive medicinal herbs.[49] Many of the traditional claims for its bioactivity have scientifically been proven.

The strong insecticidal effect of plant extracts of *Stemona collinsiae* was tested against the parasite *Parasarcophaga ruficornis* with mortality rates up to 94%.[50] Against the pest *Spodoptera littoralis*, assays revealed the insecticidal effect of both the crude plant extract (down to LC_{50} = 3 ppm) as well as the isolated alkaloids (didehydrostemofoline LC_{50} = 0.84 ppm).[51] Similarly, the antitussive effect of *Stemona tuberosa* and its constituents, particularly the croomine-type alkaloids, was proven by dose-dependent suppression of coughing induced by citric acid in guinea pigs.[52] Extracts of the same plant also exhibited anti-inflammatory properties after oral ingestion, protecting the lungs of mice from cigarette smoke as measured by lower levels of cytokines and chemokines.[53] Next to the commonly cited insecticidal, anthelmintic and antitussive properties, several more specific properties are

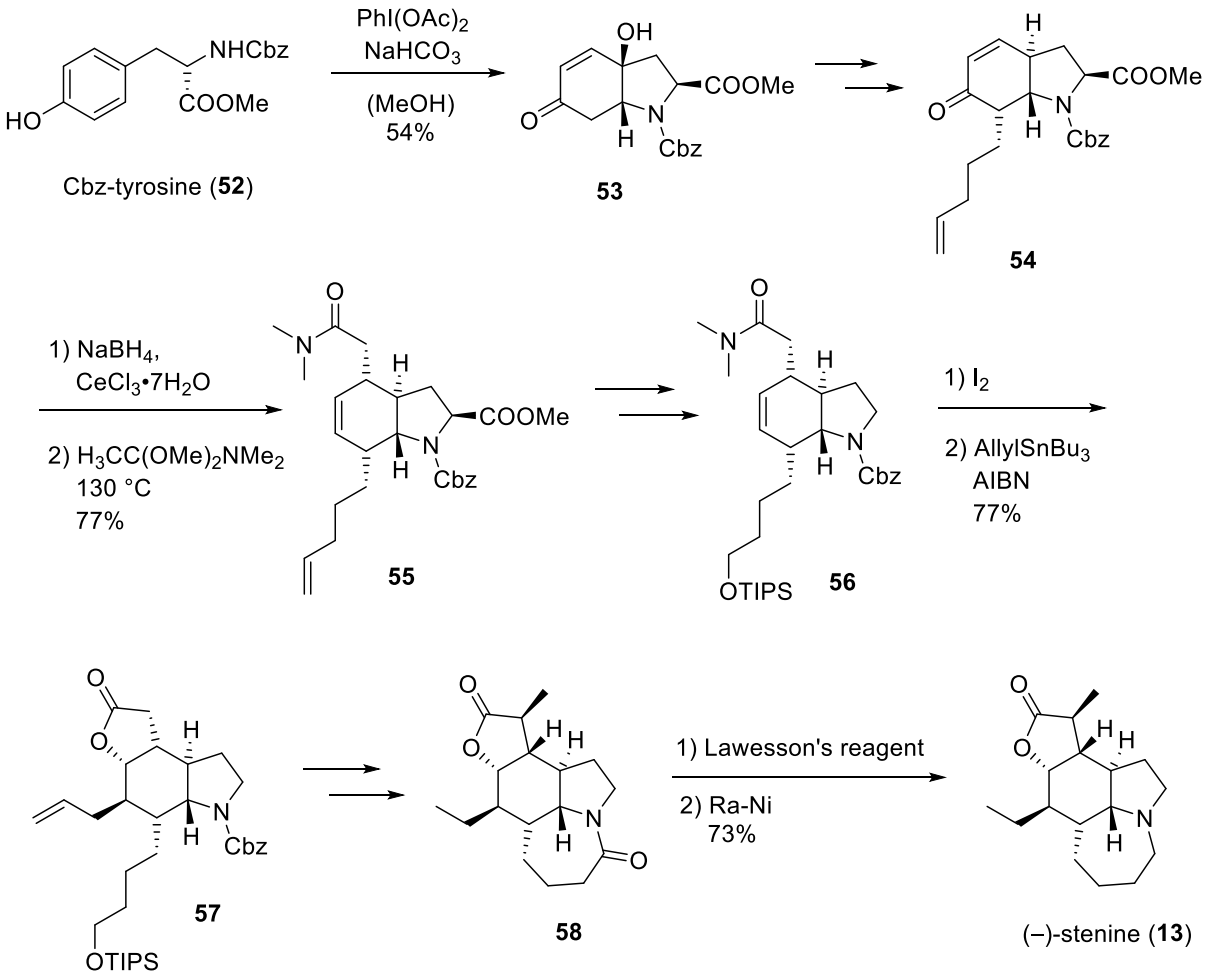
mentioned in literature as well. For the Stemona alkaloid tuberostemonine, antagonistic properties at glutamate receptors in the neuromuscular junction of crayfish was noted.[54] An inhibitory effect on oxytocin-induced contraction of rat uterus was measured for the natural product stemofoline.[55] The same natural product also exhibits another biological effect, which has probably attracted the most attention out of all Stemona alkaloids. Both the crude extract of *Stemona burkillii* as well as the purified compound stemofoline were able to enhance the sensitivity of MDR cervical carcinoma cells to chemotherapeutic agents. Multi drug resistant (MDR) cancer cell lines still pose the greatest problem to chemotherapy, making this recent discovery highly relevant.[56]

The pyrido[1,2-*a*]azepine class of Stemona alkaloids possess similar biological activities, including the antitussive or insecticidal properties, making them equally relevant for synthesis and testing. For example, several tests against mosquito larvae (*Anopheles minimus*) and larvae of *Spodoptera littoralis* were performed and showed promising results, making Stemona alkaloids potential biological and biodegradable pesticides.[57]

2.4. Literature-reported synthetic approaches to Stemona alkaloids

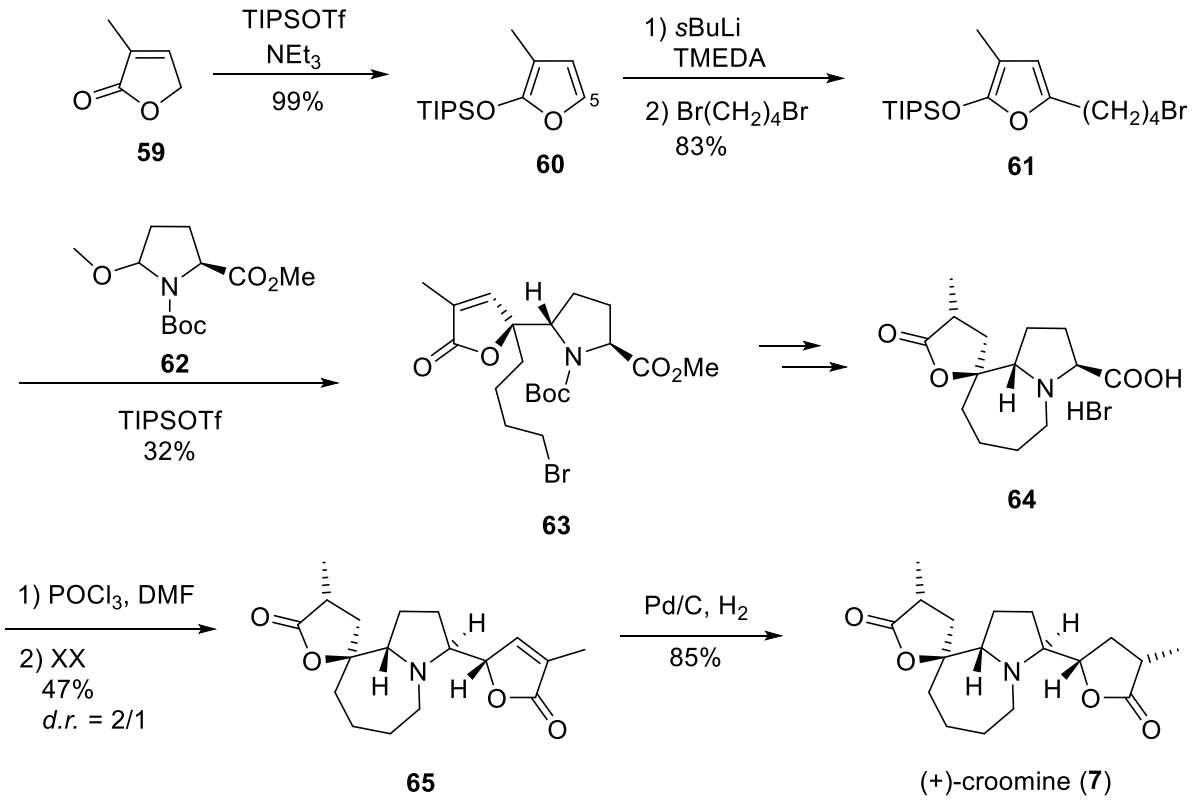
Due to the complex three-dimensional structures and their broad biological activities, the Stemona alkaloids have attracted much attention from organic chemists. So many successful syntheses have been published over the years that several reviews have been written.[58,59] This chapter shall only provide several examples and more classical approaches to the Stemona alkaloids and is by no means comprehensive.

The first asymmetric total synthesis of (−)-stenine (**13**) was reported by Wipf *et al*. in 1995 (Scheme 5).[60] Starting from Cbz-protected enantiopure tyrosine (**52**), a diastereoselective oxidation-cyclization cascade yielded the indoline-core **53**. After several transformations, the enone **54** was obtained and, after a *Luche* reduction, was subjected to an *Eschenmoser-Claisen* rearrangement to form the amide **55**. Further functionalization created the protected alcohol **56**, which underwent a smooth iodolactonization and *Stille* coupling sequence to generate lactone **57**. The compound was then transformed over several steps to the azepine lactam **58**. Finally, treatment with *Lawesson's* reagent and reduction with *Raney*-Nickel yielded the natural product (−)-stenine (**13**).



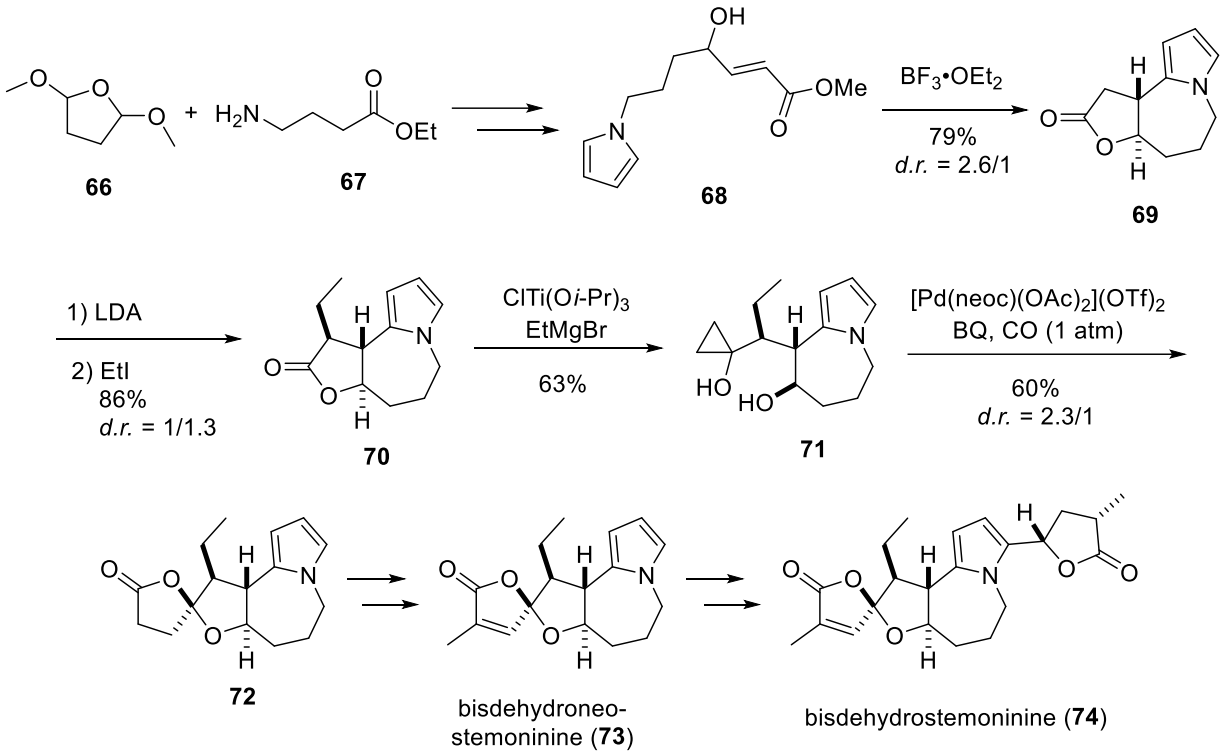
Scheme 5. Total synthesis of (−)-stenine (**13**) starting from the Cbz-protected amino acid tyrosine (**52**).

The pyrrolo[1,2-*a*]azepine core allows for an elegant construction *via* a vinylogous *Mannich* reaction as reported by *Martin et al*[61] in the synthesis of (+)-croomine (**7**) (Scheme 6). Starting from the commercial 3-methyl-2-(5*H*)-furanone (**59**), a facile synthesis of furan **60** and functionalization at C-5 to the alkyl bromide **61** was performed. This compound was coupled to the acyl iminium ion generated by *Lewis* acid catalysis from pyrrolidine **62**. While the *threo* coupling product **63** was obtained in 32% yield, less than 1% of the second *threo* compound was isolated and no *erythro* variant was detected, indicating an impressive diastereoselectivity. After a smooth cyclization and several transformations, azepine **64** was obtained. Subsequently, conversion to the acyl chloride led to a concomitant decarbonylation at room temperature, forming the iminium ion, which was coupled to furan **60** once more. An ultimate hydrogenation of unsaturated lactone **65** yielded (+)-croomine (**7**) after an efficient eleven step synthesis.



Scheme 6. Total synthesis of (+)-croomine (**7**) from the proline derivative **62**.

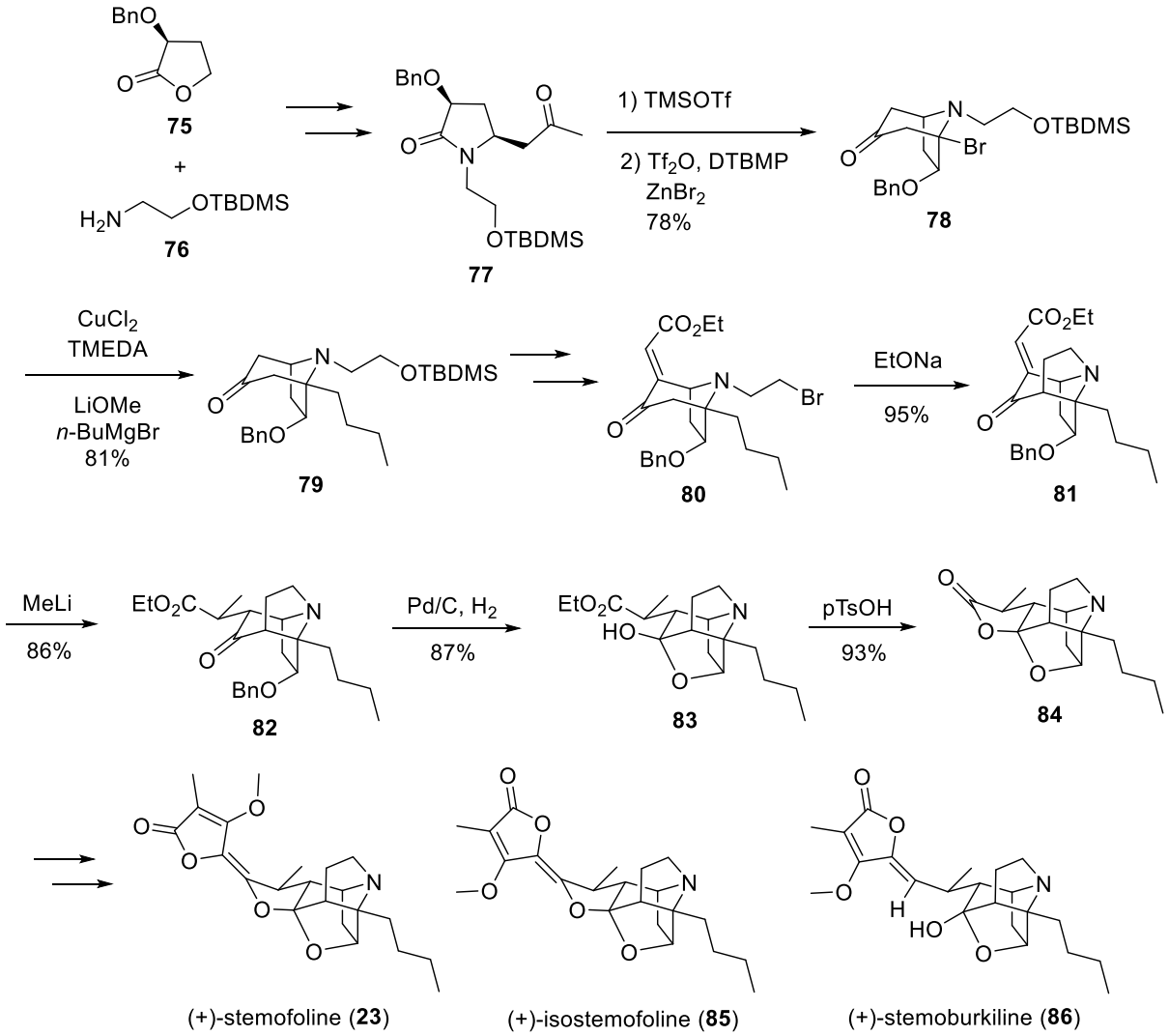
By employing their novel palladium catalyzed carbonylative spirolactonization, *Dai* and co-workers[62] managed to perform the first total synthesis of bisdehydroneostemoninine (**73**) and bisdehydrostemoninine (**74**) (Scheme 7). From commercially available acetal **66** and amine **67**, the route commenced with a *Clauson-Kaas* reaction to obtain the pyrrole **68**. A *Lewis* acid mediated tandem *Friedel-Crafts* cyclization and lactonization yielded the tricyclic compound **69**. After an alkylation to lactone **70**, a *Kulinkovich* reaction was performed to obtain cyclopropane **71**. The subsequent carbonylative key step gave spirocycle **72**. After applying *Eschenmoser's* protocol, bisdehydroneostemoninine (**73**) was obtained and after functionalization at the pyrrole ring, the synthetic route ended with the successful synthesis of bisdehydrostemoninine (**74**).



Scheme 7. Total synthesis of bisdehydroneostemoninine (**73**) and bisdehydrostemoninine (**74**).[62] (neoc = neocuproin = 2,9 dimethyl-1,10-phenanthroline; BQ = benzoquinone)

Among all Stemona alkaloids, the stemofoline class **22** arguably possesses the most complex structure due to their polycyclic cage-like core derived from tropane. Unsurprisingly, many studies have been published which gave access to this cage structure *via* different methods, including 1,3-dipolar cycloadditions of azomethine ylides,[63] intramolecular addition of silyl enol ethers on *in situ* activated lactams[64] or *Diels Alder* reactions.[65] The most recent addition to the collection of stemofoline-class total syntheses by *Huang* and co-workers will be discussed in the following.[66]

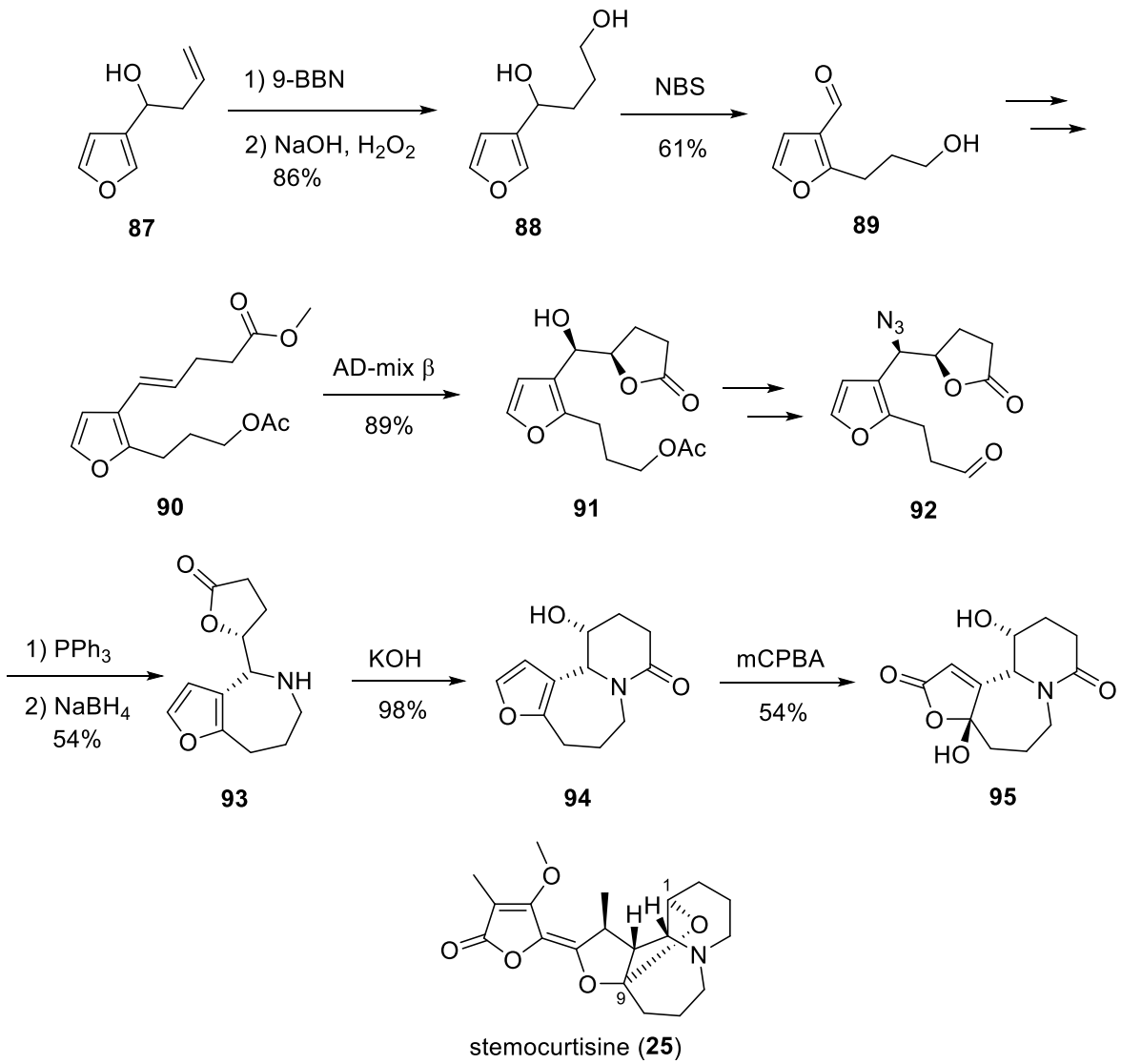
Starting from commercially available lactone **75** and β-aminoethanol **76**, the 2-pyrrolidone **77** was obtained over several steps. By employing a *Lewis* acid mediated keto-lactam cyclization and bromination cascade, the brominated tropane **78** was generated. Alkylation *via* nucleophilic substitution on an anti-*Bredt* iminium ion gave tropane **79**. After several transformations, the authors obtained the bromide **80**, which was subsequently converted to the tricyclic compound **81**. *Michael* addition of MeLi to form ketone **82** preceded the hydrogenation and formation of the hemiacetal **83**. Acid catalyzed lactonization assembled the key lactone **84**, which was, after extensive optimization, converted to a mixture of (+)-stemofoline (**23**), (+)-isostemofoline (**85**) and (+)-stemoburkiline (**86**).



Scheme 8. Total synthesis of stemofoline (**23**), isostemofoline (**85**) and stemoburkiline (**86**).[66] (DTBMP = 2,6-di-*tert*-butyl 4-methyl pyridine; TMEDA = tetramethylethylene diamine; pTsOH = *para*-toluenesulfonic acid)

As a sharp contrast to the pyrrolo[1,2-*a*]azepines, their pyridine homologues have received less synthetic attention and, to our knowledge, not a single successful synthesis has been published. The only published studies, except for our own, were performed by *Pyne* and focused on the total synthesis of stemocurtisine (**25**). In their first publication on this topic,[67] the successful synthesis of the core structure **95** containing rings A, B and C was reported, starting from the known furan **87** (Scheme 9). After hydroboration, the diol **88** underwent an oxidative rearrangement to aldehyde **89**. Several steps, including a *Johnson-Claisen* rearrangement, were necessary to create ester **90**, which was subjected to a *Sharpless* dihydroxylation and immediately cyclized to the lactone **91**. Conversion to azide **92** was possible after much optimization and an *aza-Wittig* reaction followed by a reduction step yielded tricyclic compound **93**. Treatment with base led to the hydrolysis of the lactone and

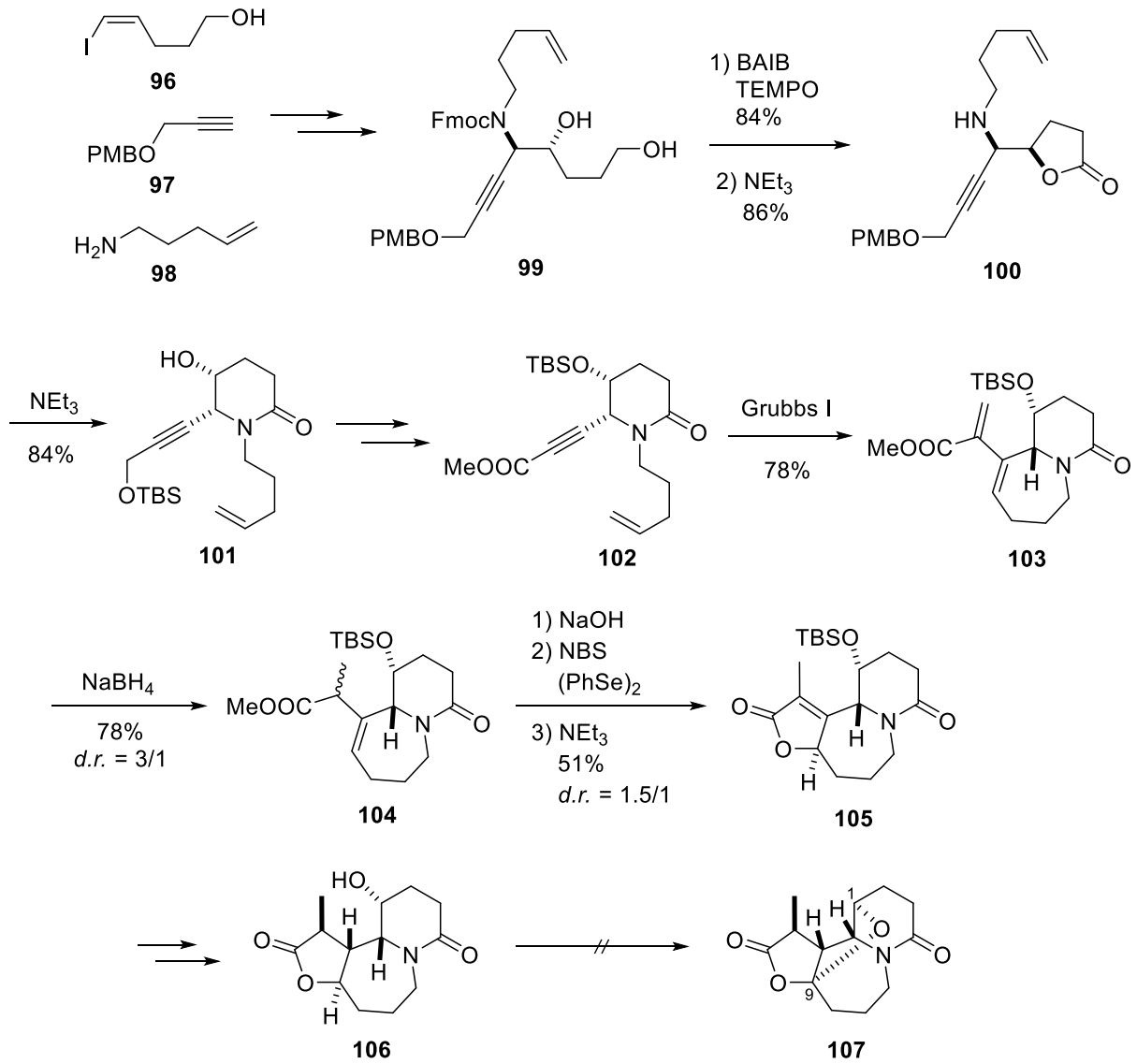
gave lactam **94**. The group was successful in oxidizing this and other furans with mCPBA, NBS or singlet oxygen reactions to form hydroxy-lactones like compound **95**. However, they were unable to form the intramolecular acetal between C-1 and C-9 with *Lewis* or *Brønsted* acidic conditions.



Scheme 9. Synthetic studies towards stemocurtisine (**25**), which failed as the cyclization to the tetrahydrofuran between C-1 and C-9 could not be achieved.[67]

The group subsequently changed their approach[68] to a linear compound assembled from alcohol **96**, alkyne **97** and amine **98** to form diol **99** (Scheme 10). Oxidation of the primary alcohol and lactonization was followed by base mediated deprotection to obtain secondary amine **100**. Basic hydrolysis in presence of triethylamine led to formation of lactam **101**. After several functional group interconversions, ester **102** was obtained and subsequently subjected to an enyne metathesis to generate bicyclic compound **103**. Conjugated reduction

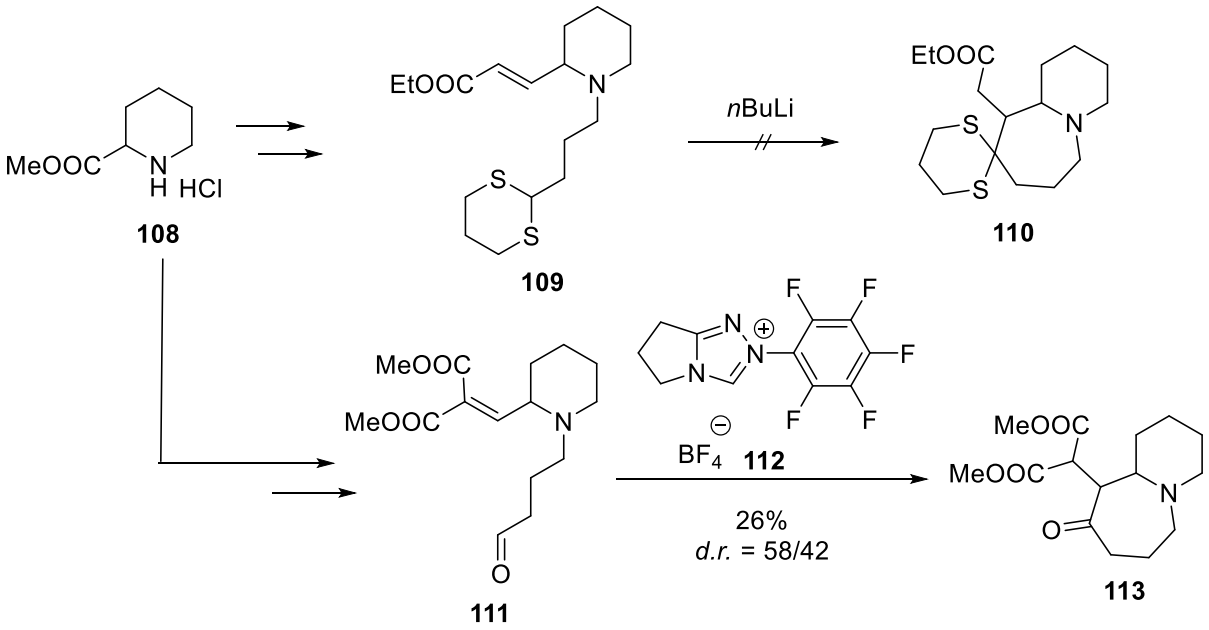
gave rise to the diastereomeric esters **104**, which were transformed in a bromolactonization reaction to the tricyclic unsaturated lactone **105**. Diastereoselective reduction and deprotection yielded the lactone **106**. As the previous acetalization strategy failed, the authors investigated the reported photochemical cyclization with iodine and BAIB.[69] Instead of the desired cyclization, they detected decomposition attributed to the fragmentation of the six membered ring. Neither optimization nor employing the corresponding amine variant of **106** solved the problem and this route was abandoned as compound **107** could not be obtained.



Scheme 10. Synthetic studies towards stemocurtisine (**25**) in a linear approach, culminating in the tricyclic compound **106**. Oxidative cyclization of the alcohol to C-9 failed.[68] [BAIB = Bis(acetoxy)iodobenzene; NBS = *N*-bromosuccinimide; PMB = *para*-methoxybenzyl]

Some recent work by *Duc* on the Stemona alkaloid stemocurtisine,[70] which heavily relies on the previous studies by *Pyne*, has been published as well.

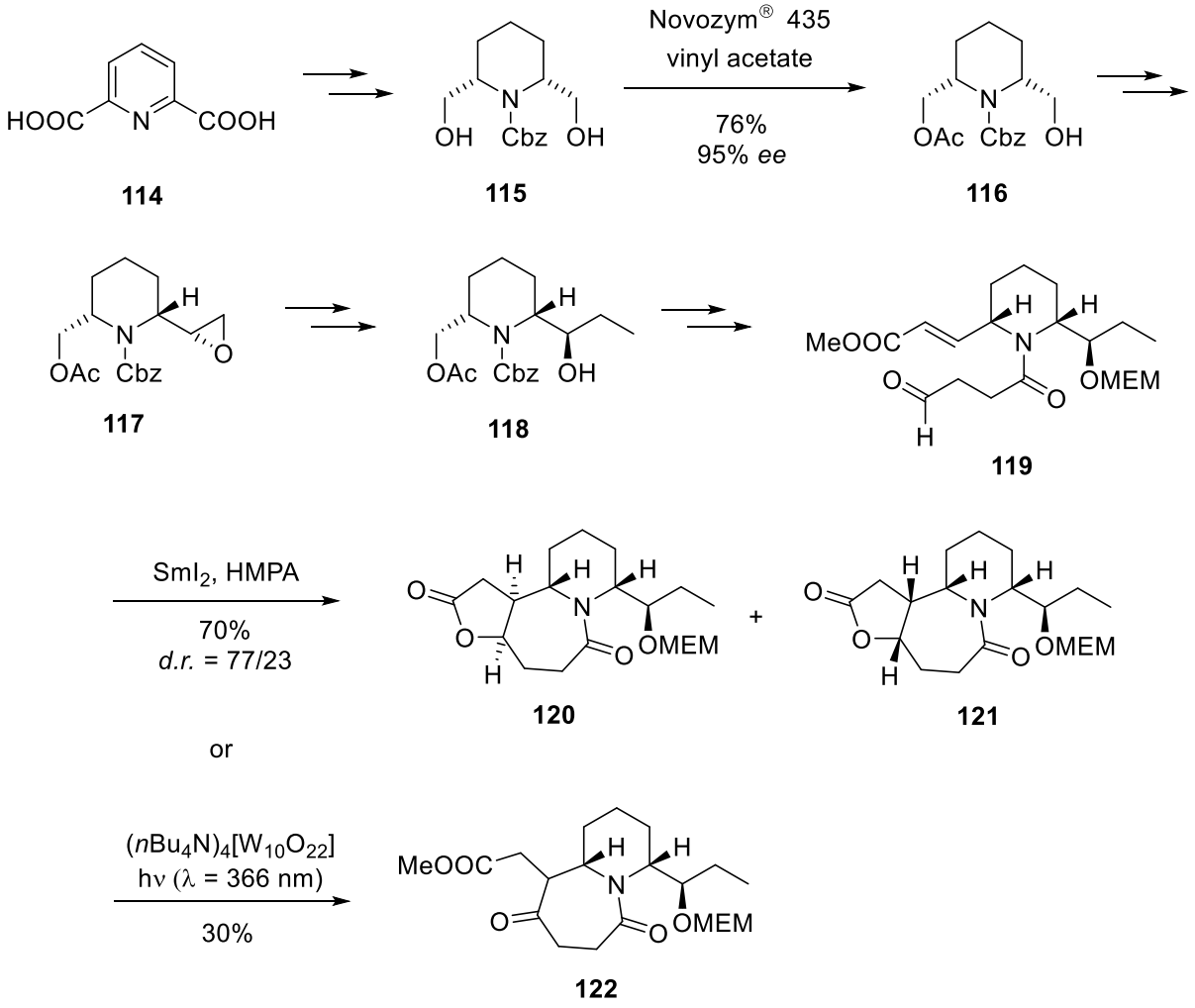
Already since 2007 attempts for the synthesis of pyrido[1,2-*a*]azepine Stemona alkaloids have been made in our group. *Tassel*[71] started from racemic pipecolic acid methyl ester hydrochloride (**108**) and tested two different routes (Scheme 11). The first proceeded *via* the dithiane **109** and employed a *Corey-Seebach* umpolung and *Michael* addition for the synthesis of the azepine ring, which failed to produce the azepane **110**. A second attempt was made with a similar strategy from the aldehyde **111**. A *Stetter* reaction with the triazole **112**[72] was successfully performed in the synthesis of azepine **113**. However, both the diastereoselectivity and the overall yield were unsatisfactory and an alternative route was developed.



Scheme 11. Synthetic studies towards pyrido[1,2-*a*]azepine alkaloids by *Tassel* involving two different umpolung strategies.[71]

A new route employing 2,6-pyridine dicarboxylic acid (**114**) was found by *Tassel* and optimized by *Romek*.[73] After reduction, the piperidine **115** was subjected to an enzymatic desymmetrization employing Novozym® 435, a commercial immobilized *Candida antarctica* lipase,[74] in vinyl acetate to obtain the monoacetylated alcohol **116** (Scheme 12). After some optimization, the propyl alcohol **118** was ultimately accessed *via* the methylation of oxirane **117**. Subsequently, *N*-functionalization and generation of a *Michael* acceptor gave rise to the key intermediate **119**. A SmI_2 mediated reduction of the aldehyde and subsequent cyclization delivered the diastereomeric lactones **120** and **121** in good yields.[75] However, the undesired

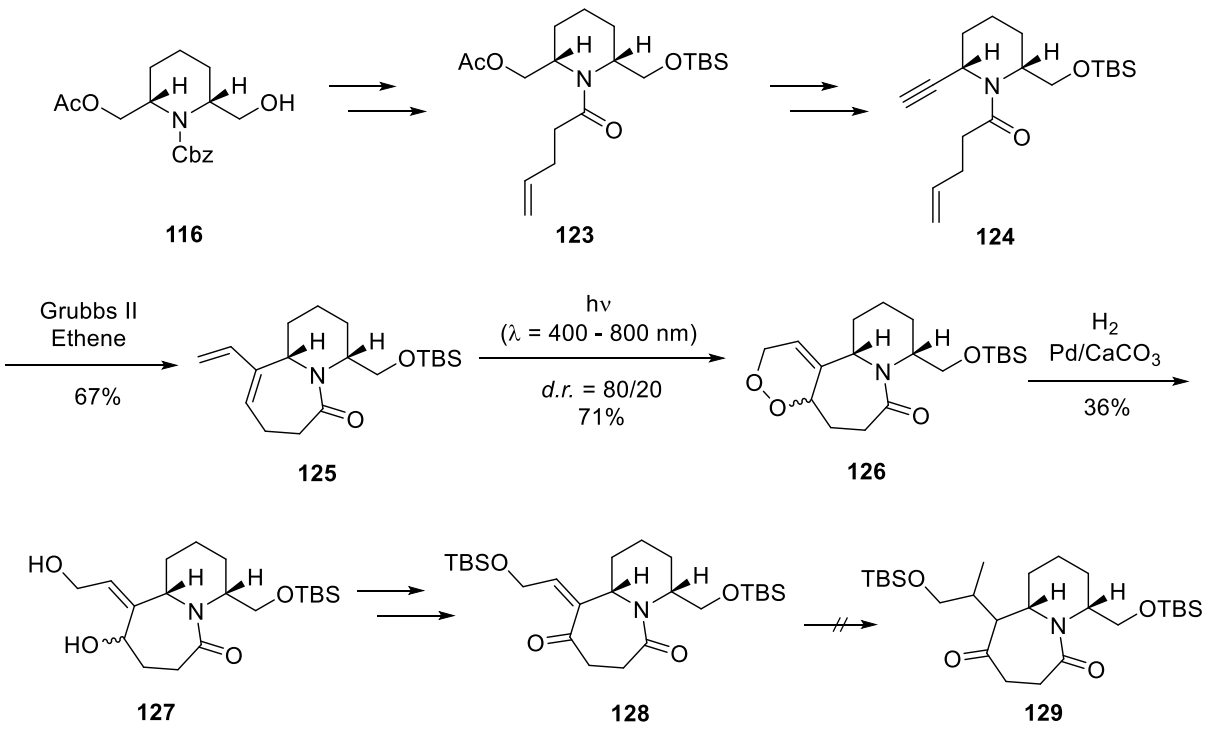
diastereomer was formed preferentially and neither optimization of the cyclization nor other subsequent transformations could increase the yield of the desired diastereomer **121**. Therefore, an alternative reaction using a photochemical radical cyclization was investigated. Irradiation of the same aldehyde **119** in presence of tetra-*n*butylammonium decatungstate[76] at a wavelength of 366 nm led to a successful cyclization to ketone **122**. But neither the optimizations of *Romek* nor further attempts by her successor, *Mayer*, were fruitful in increasing the overall yield of this transformation.



Scheme 12. Studies towards pyrido[1,2-*a*]azepine alkaloids employing a desymmetrization reaction and two different cyclization strategies.

The third student to work on the Stemona alkaloids, *Mayer*, started with the same enzymatic desymmetrization and aimed to apply an enyne metathesis as the key step (Scheme 13).[77] Her first approach involved the MEM-protected hydroxypropyl side chain, but this moiety turned out to be incompatible with the metathesis conditions. Instead, the alcohol **116** was protected

with a TBS group and *N*-alkylated with a C_5 building block to obtain alkene **123**. A *Seyferth-Gilbert* homologation yielded alkyne **124** as a precursor for the enyne metathesis. After much screening, the Grubbs II catalyst and an ethene atmosphere[78] proved optimal to obtain diene **125**. Using a singlet oxygen reaction under irradiation with a sodium vapor lamp, a [4+2] cycloaddition generated endoperoxide **126** as a mixture of two diastereomers.[79] Many different reductive conditions had to be tested to ultimately obtain diol **127** *via* hydrogenation. With the diol at hand, further transformations like the protection of the primary alcohol and oxidation of the secondary alcohol forming ketone **128** could be performed, although with low yields. Lastly, the route had to be abandoned as the long sequence with diminishing yields gave little product to work with and the envisioned *Michael* addition to product **129** failed.

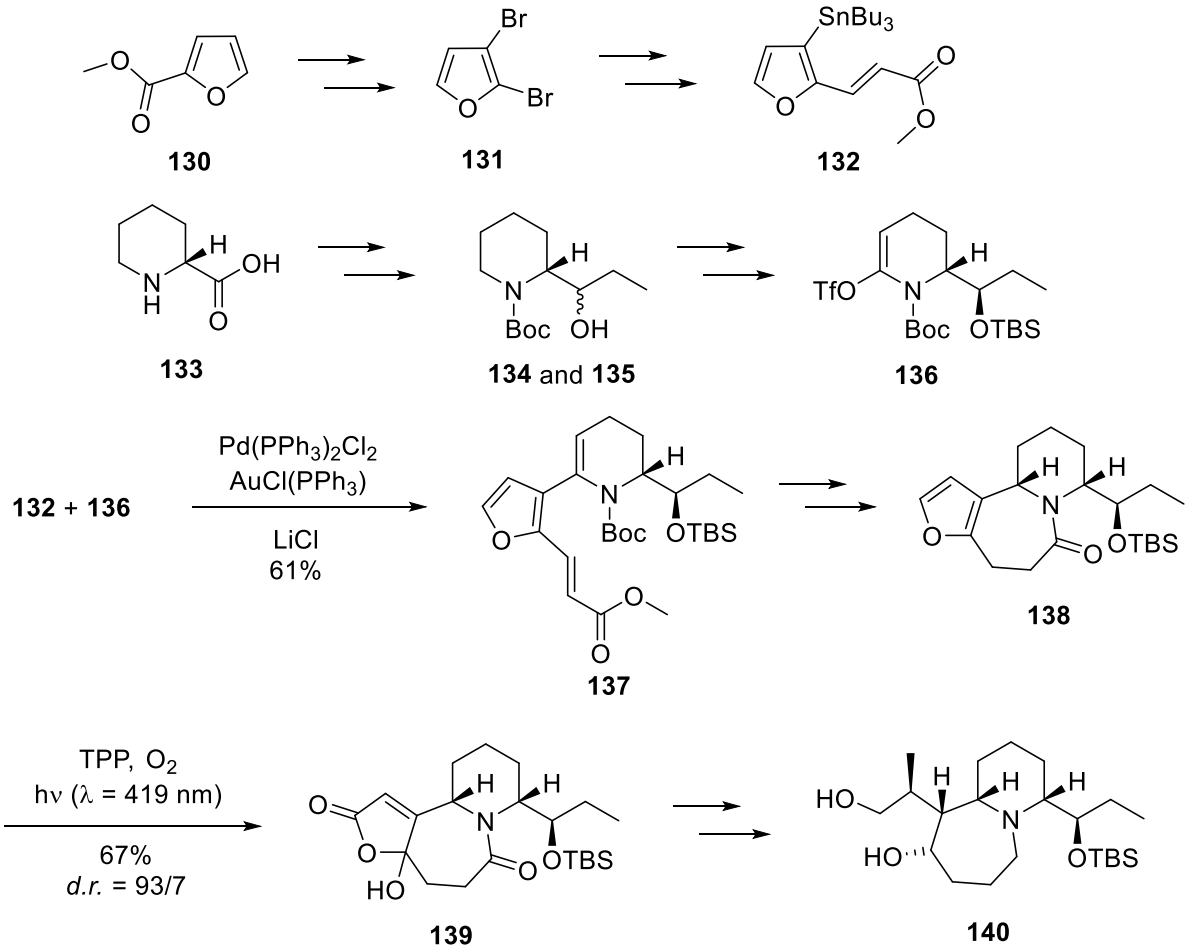


Scheme 13. Starting from the same piperidine **116**, the route by *Mayer* involved an enyne metathesis and a [4+2] cycloaddition with singlet oxygen. The route failed due to the overall low yields and the unsuccessful *Michael* addition.[77]

The generation of a furan side product during the reduction of endoperoxide **126** and the application of a singlet oxygen reaction inspired *Mayer* to a different synthetic route.[77] One half of this convergent strategy started from the commercially available 2-methyl furoate (**130**), which was converted to the known 2,3-dibromofuran (**131**). Subsequent reactions

formed the stannylated furan **132**, one of the partners for the convergent *Stille* cross-coupling reaction.

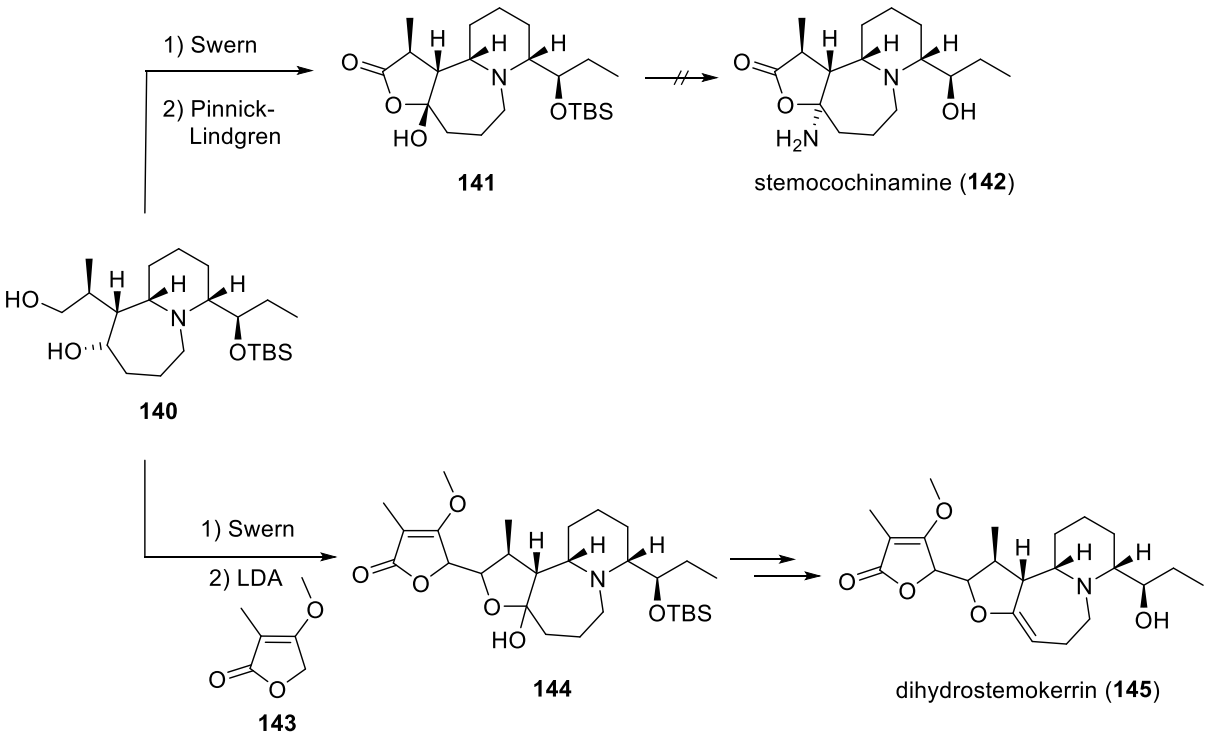
Secondly, the enantiopure, unnatural amino acid D-pipecolic acid (**133**) was converted to the Boc-protected hemlock alkaloid conhydrine **134** and **135** as a mixture of diastereomers. This part of the route resulted in the synthesis of the enamine triflate **136**, which was subjected to the *Stille* reaction with gold co-catalysis to generate the coupling product **137**. After several steps, the tricyclic azepine **138** was obtained. The second key step, the singlet oxygen reaction, generated the hydroxylactone **139** as a stabile compound. Subsequently, reduction and diastereoselective methylation yielded the diol **140** as a versatile building block for the potential synthesis of several pyrido[1,2-*a*]azepine Stemona alkaloids.



Scheme 14. Synthesis of the diol **140** in a convergent synthesis from furan **130** and amino acid **133**.[77]

The first attempted goal was the natural product stemocochinamine (**142**) with its uncommon hemiaminal structure. To this end, the diol **140** was readily converted to the hemiacetal **141** *via* a stepwise oxidation employing a *Swern* reaction followed by a *Pinnick-Lindgren*

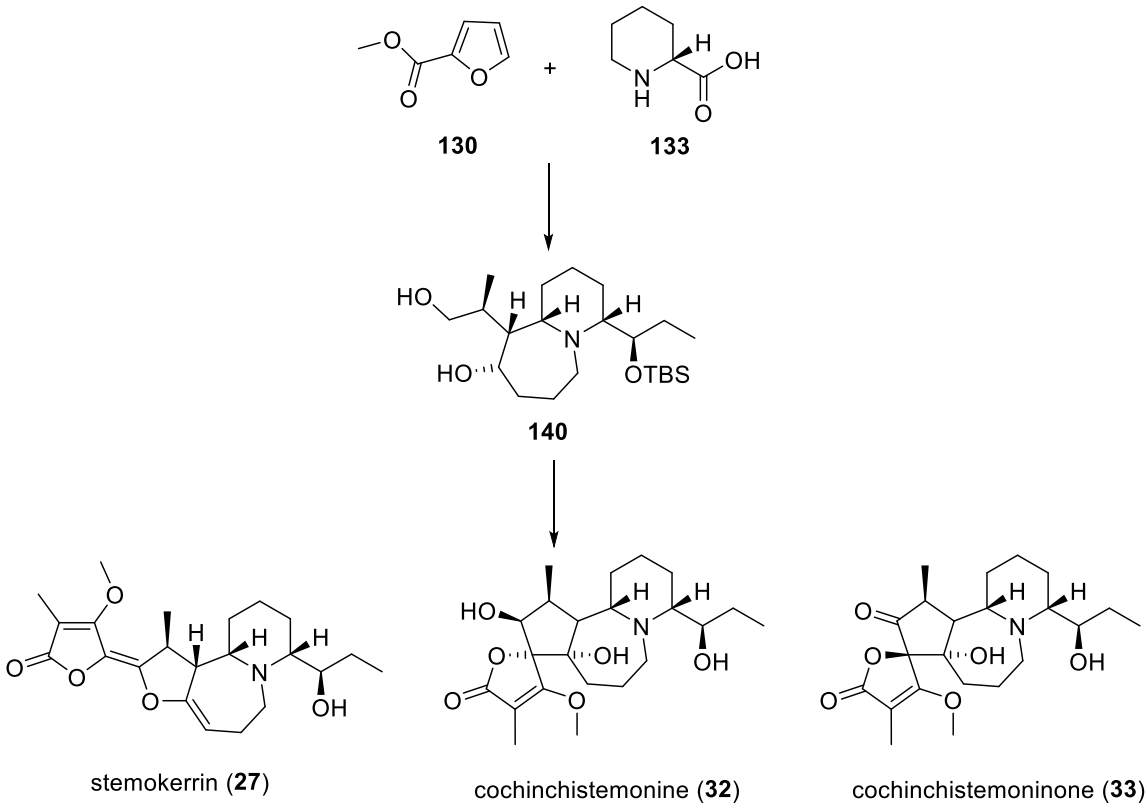
oxidation. Although some examples for the synthesis of the target functionality exist in literature, none of them were applicable to generate stemocochinamine. Among others, treatment with ammonia, benzylamine in combination with different acids and a dehydration with acetic anhydride were tested. As these attempts were unsuccessful, a different route involving new Stemona alkaloid targets was envisioned. After *Swern* oxidation of the diol **140**, the tetronate unit **143** was deprotonated and incorporated at the aldehyde to form hemiacetal **144**. Although the oxidation to the diketone would have been promising for the synthesis of cochinchistemonine (**32**), this transformation could not be achieved. On the other hand, to access stemokerrin (**27**), both the elimination as well as the deprotection were achieved to yield a potential precursor, dihydrostemokerrin (**145**). Ultimately, the dehydrogenation turned out to be impossible and stemokerrin was not obtained.



Scheme 15. Oxidation of diol **140** to hydroxy lactone **141** and failed attempts towards stemocochinamine (**142**) (top); Synthesis of hemiacetal **144** and conversion to dihydrostemokerrin (**145**) (bottom).

3. Motivation and goals

As illustrated, the Stemona alkaloids are quite large in number and, due to their complex structures and wide range of biological activities, they pose formidable targets for total synthesis. Especially the pyrido[1,2-*a*]azepine subclass of Stemona alkaloids is highly underexplored in literature and no successful total synthesis has been reported to the best of our knowledge. With the extensive preceding work of our group, further studies towards these alkaloids were promising. As a first step, both yield and selectivity for the synthesis of the key intermediate diol **140** should be optimized. Secondly, this versatile building block could be applied in the total synthesis many similar alkaloids like stemokerrin (**27**) and its two *N*-oxide derivatives as well as cochinchistemonine (**32**) and its closely related variant, cochinchistemoninone (**33**).



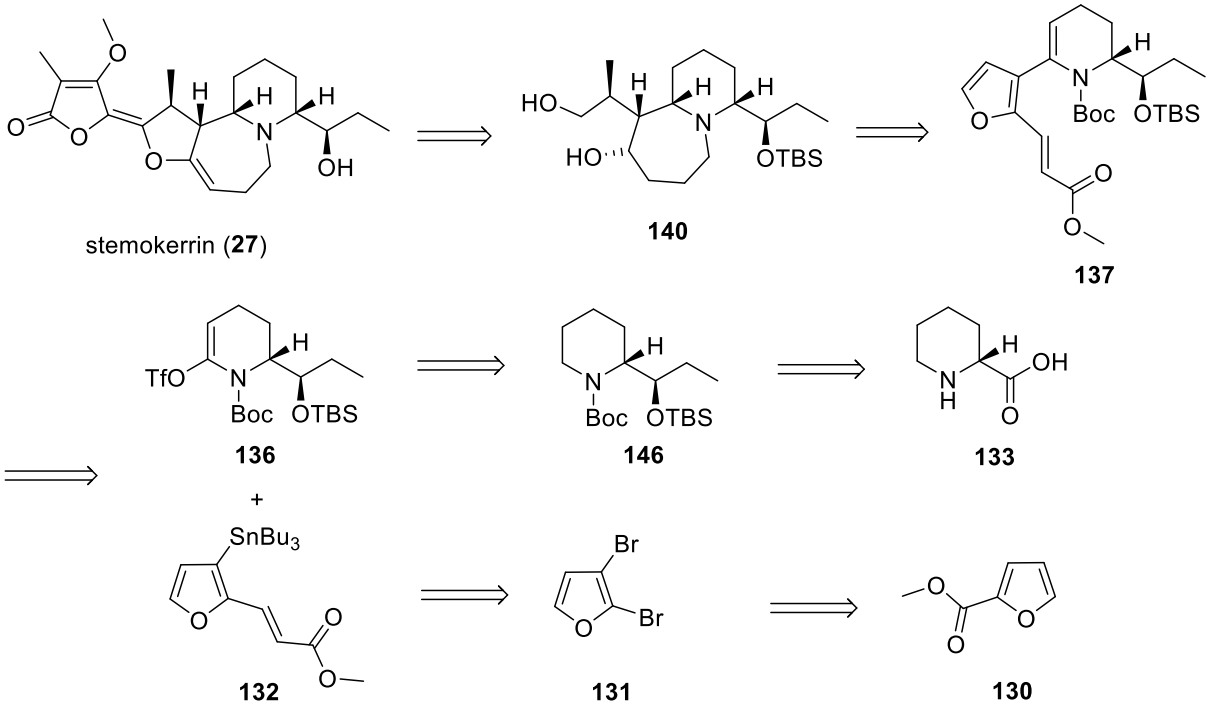
Scheme 16. Synthetic plan from furan **130** and D-pipecolic acid (**133**) to three Stemona alkaloids as potential synthetic targets.

4. Convergent synthesis to the Stille cross-coupling

4.1. Retrosynthetic analysis

Our envisioned retrosynthesis of stemokerrin (**27**) is closely related to the previous work performed by *Mayer*[77] and involves the synthesis of the versatile diol **140**. The synthesis of the γ-alkylidene-butenolide structure would undoubtedly be the biggest challenge of this route. Although many syntheses of conjugated diene-lactones are reported,[80,81] they are primarily found in endocyclic structures[82] or in a linear framework.[83,84] It is uncommon for this double bond to connect two ring structures and the exocyclic bis-enol ether structure of stemokerrin (**27**) similarly has very few examples.[85,86] The stability of this entity and the lack of tautomerization to the seemingly favorable furan comes to a surprise.

To obtain the carbon skeleton of the Stemona alkaloid stemokerrin, a twofold oxidation of the diol **140** and a chemoselective nucleophilic addition of a tetronate unit was required. Similar reactions are known[87] and have been performed in our laboratories as well. The synthesis of the diol in turn was envisioned from the ester **137**. The furan ring should act as a 1,4-diol synthon that can be liberated *via* a singlet oxygen reaction[88] or other oxidative transformations using *e.g.* mCPBA[89] or NBS.[90] The C_3 substituent at the furan allowed for the cyclization to the azepane ring structure. For the synthesis of coupling product **137**, a *Stille* coupling of the enamine triflate **136** with the *Michael* acceptor **132** was planed. Similar transformations using valerolactam triflate derivatives have been reported.[91] The synthesis of the triflate **136** from the protected conhydrine **146** necessitated a known α-oxidation and treatment with a triflating agent. Finally, selectively obtaining the desired (+)-β-conhydrine derivative out of the four existing conhydrine stereoisomers with high enantiopurity posed an interesting challenge. Many syntheses of these hemlock alkaloids are reported and some reviews exist on this topic.[92] However, these syntheses can include up to 15 steps and our strategy strongly relied on a quick, efficient and high yielding synthesis starting from amino acid **133**, as the conhydrine derivative **146** was a quite early building block. As a second building block of the convergent strategy, access to a 2,3-difunctionalized furan was required. This regioselectivity contradicts the inherent 2,5-selectivity of furans and explains the scarcity of these 2,3-substituted furans in literature. A possible route for the stannylated furan **132** could proceed *via* the 2,3-dibromofuran (**131**), which should be a reactive partner for halogen-metal exchange or palladium catalyzed cross-coupling reactions. Access to the literature-known 2,3-dibromofuran (**131**) from methyl 2-furoate (**130**) seemed possible.[93]



Scheme 17. Retrosynthetic analysis of stemokerrin (**27**) in a convergent synthesis.

4.2. Synthesis of the enamine triflate

As a first synthetic goal, the selective synthesis of (+)-β-conhydrine (**150**) was chosen. Next to coniine (**147**) and conhydrinone (**149**), the four stereoisomers of conhydrine are some of the most common hemlock alkaloids.[94] Many synthetic approaches have been published to access each of the stereoisomers of conhydrine with varying success and selectivity.[95] A short discussion about the most relevant syntheses is required to find an optimal route.

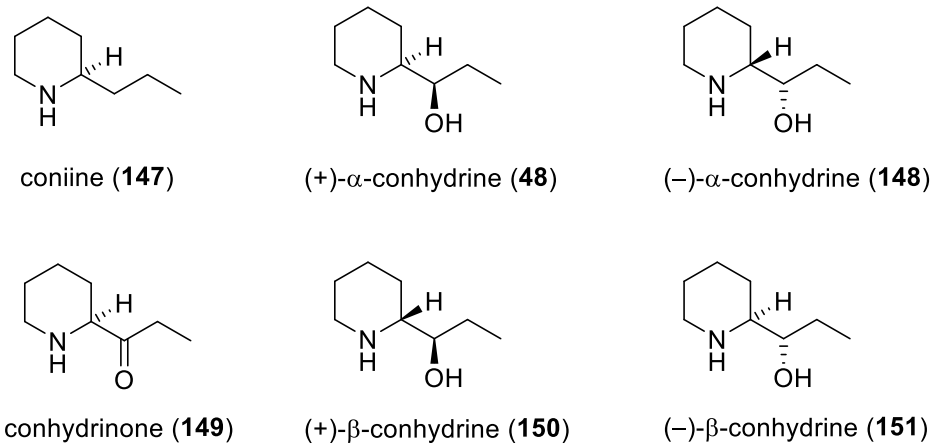
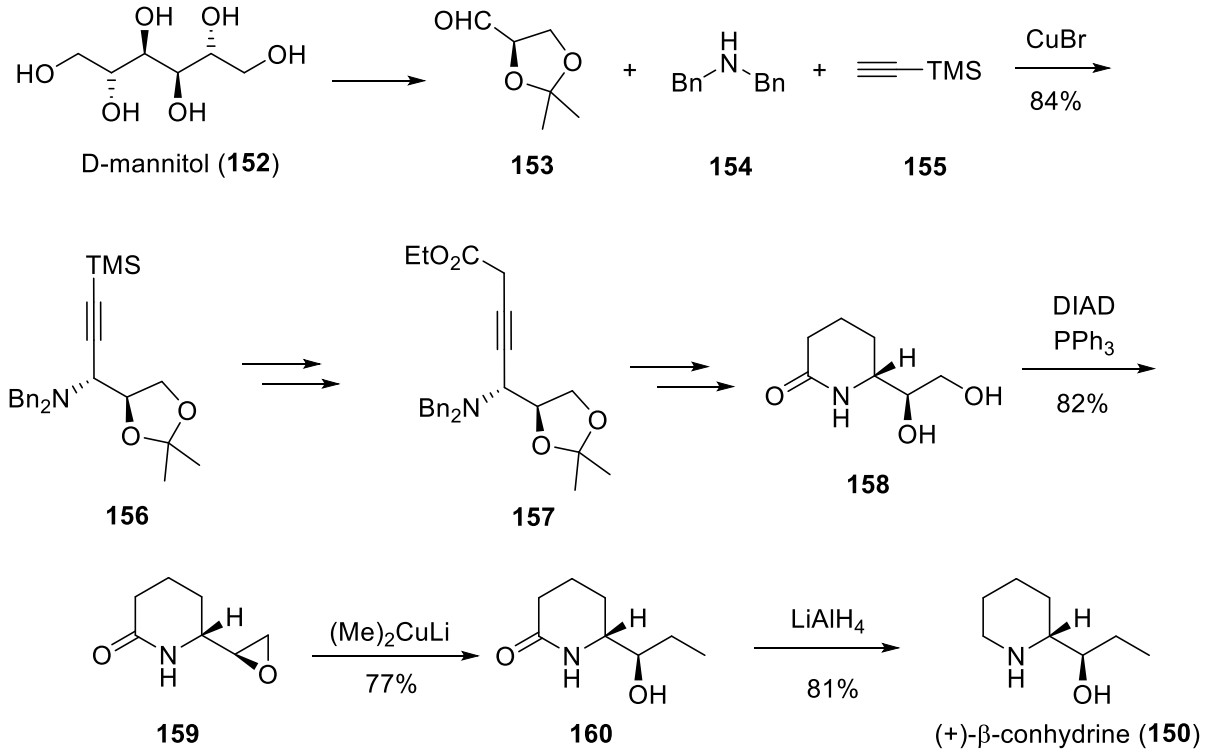


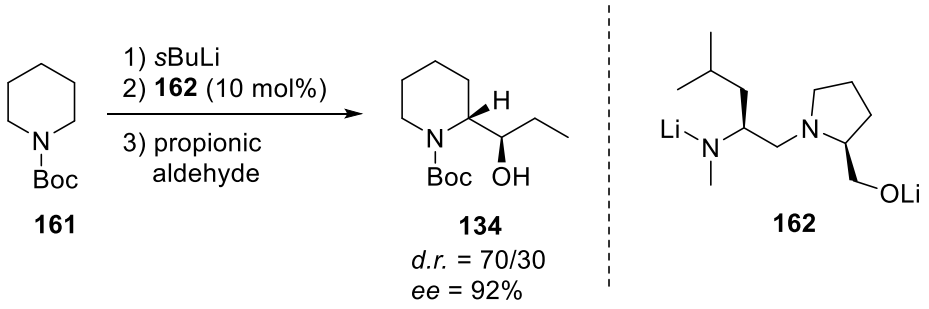
Figure 8. A selection of the most important piperidine-based hemlock alkaloids.

Three of the most commonly employed strategies for enantioselective synthesis include (a) starting from material of the chiral pool, (b) employing chiral auxiliaries or (c) using enantioselective catalysis. A major drawback of chiral auxiliaries on an early stage is the preparation of this reagent on large scale along with the necessity for reisolation. As the use of stochiometric amounts of chiral auxiliary would also complicate purification after cleavage, this strategy was ruled out. Using compounds available from the chiral pool however is rather common for the synthesis of natural products in general. For conhydrine, several routes have been published that employ chiral starting materials, for example a protected, chiral glycerin aldehyde derived from D-mannitol (**152**).[96] In the following example, the protected glycerin aldehyde **153** was converted in a three-component reaction with amine **154** and alkyne **155** under copper catalysis to the amine **156** (Scheme 18). After TMS deprotection and alkylation, the ester **157** was obtained. Cyclization and deprotection yielded the 2-piperidone **158**. A *Mitsunobu* reaction formed the oxirane **159**, which was subjected to a homologation using the *Gilman* reagent forming amide **160**, similarly to the side chain extension previously performed in our group. A final reduction step yielded conhydrine **150**. Despite the attempts for a short synthetic route by the authors, the overall yield of 12% over ten linear steps starting from D-mannitol was too inefficient for our purposes.



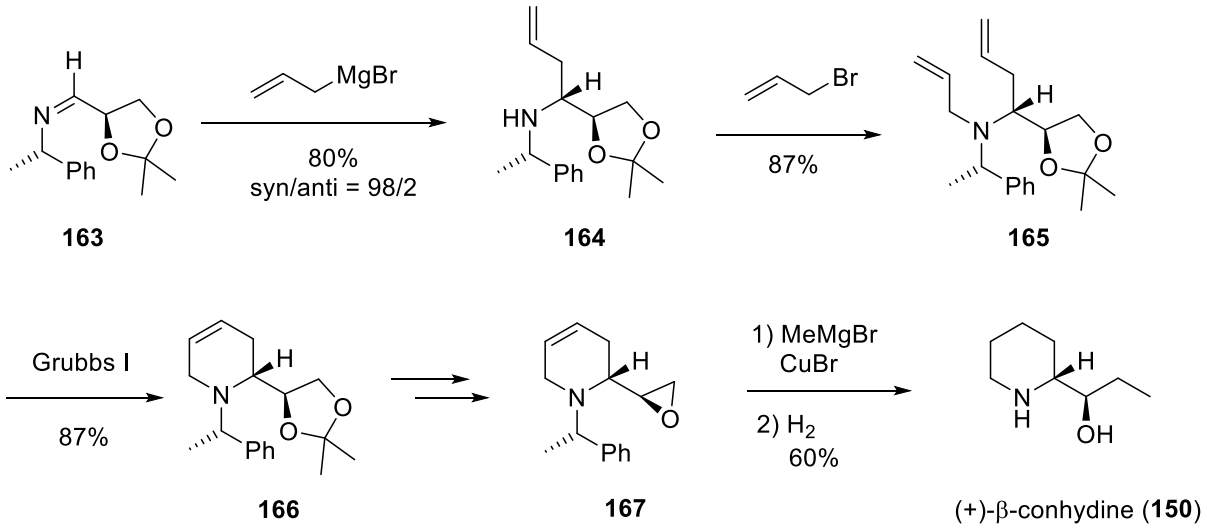
Scheme 18. Total synthesis of (+)-β-conhydrine (**150**) from D-mannitol (**152**).[96]

One of the most promising routes was the highly efficient synthesis by *Gawley* and co-workers.[97] They performed a deprotonation of Boc-protected piperidine (**161**) in the presence of chiral ligand **162** to obtain a chiral *N*-Boc-2-lithiopiperidine, which was subsequently quenched by a corresponding electrophile, in this case propionic aldehyde (Scheme 19). In only two steps starting from piperidine, the authors claimed to access the Boc-protected (+)-β-conhydrine (**134**) in high selectivities (*d.r.* = 70/30, *ee* = 92%) with low catalyst-loading of only 10 mol%. However, these results could not be reproduced in our laboratory[77] and this short and efficient route could not be applied.



Scheme 19. Enantioselective α-functionalization of Boc-piperidine (**161**).[97]

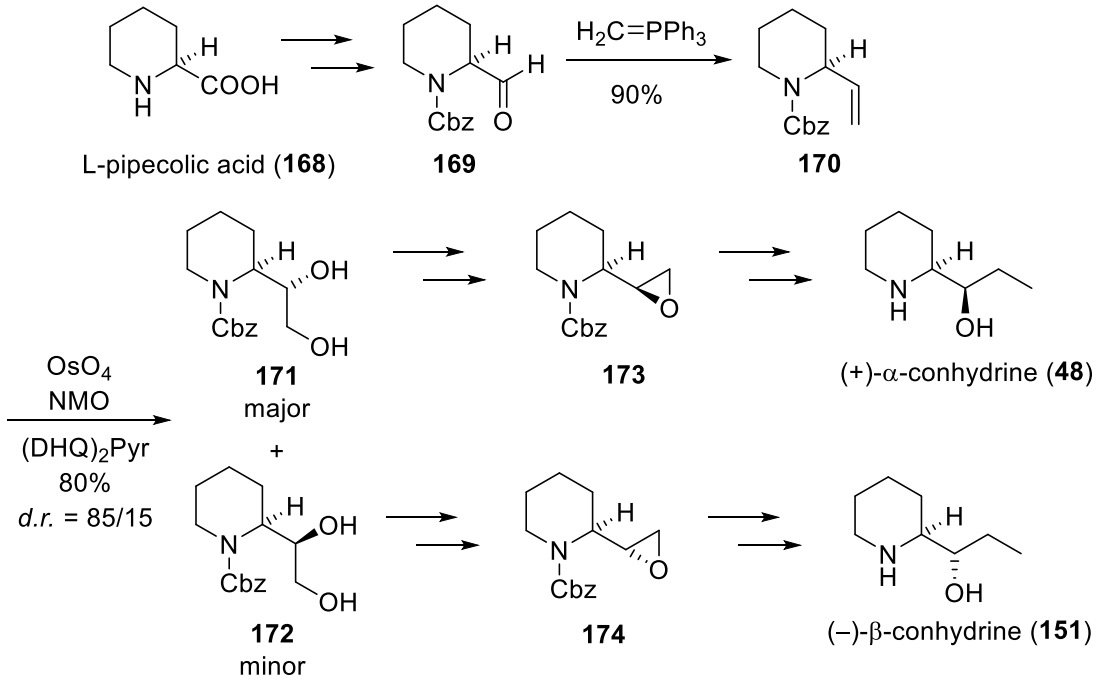
Several strategies, including the one shown below by *Galvez et al*[98] involve the generation of the six-membered ring *via* olefin metathesis (Scheme 20). The synthesis commenced from imine **163**, which was obtained from the condensation of D-mannitol-derived aldehyde **153** with a chiral amine as an auxiliary. Diastereoselective alkylation of the imine gave amine **164**. After an *N*-alkylation to form alkene **165**, the olefin metathesis to cyclic amine **166** was performed. Homologation was performed similar to the previous example by epoxidation to compound **167** and ring opening with a methyl nucleophile. Hydrogenation then led to reduction of the double bond and deprotection of the secondary amine, liberating (+)-β-conhydrine (**150**). Due to the use of highly expensive Grubbs catalysts and the use of a chiral auxiliary, this synthesis was not economical enough to be performed on a larger scale.



Scheme 20. Total synthesis of (+)-β-conhydrine (**150**) from a chiral aldehyde and a chiral amine auxiliary.[98]

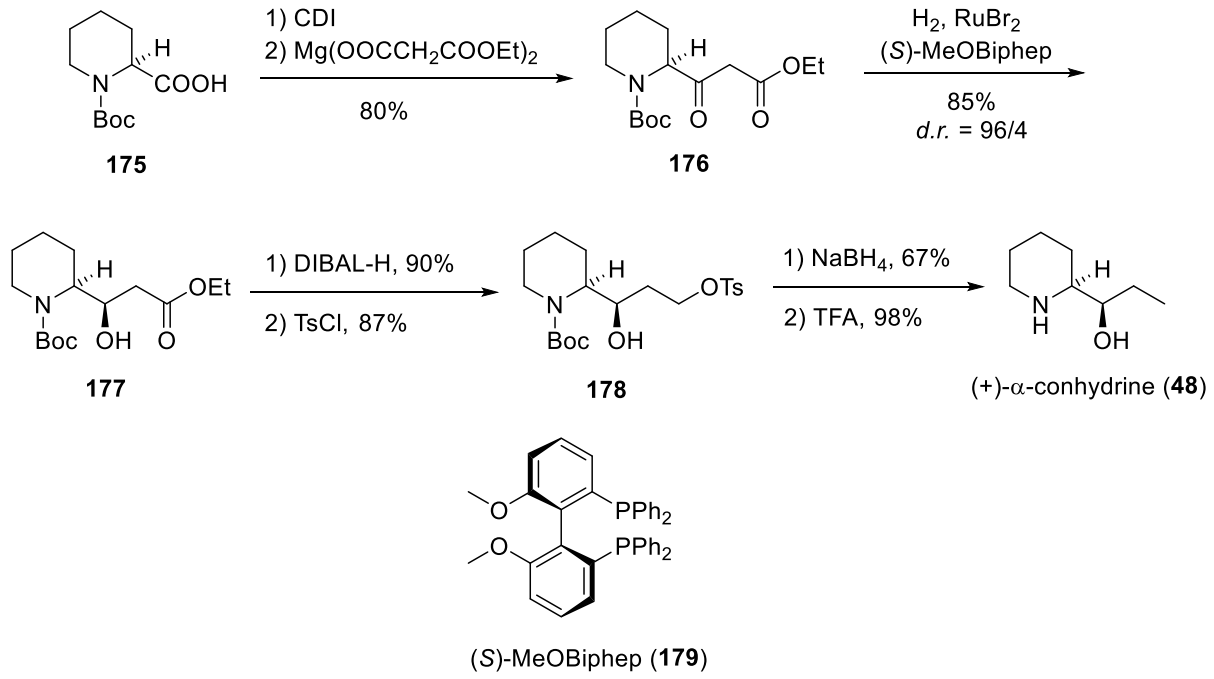
We were rather interested in a more direct approach lacking a linear precursor and subsequent cyclization strategies and focused therefore on pathways starting from piperidine derivatives. The unnatural amino acid pipecolic acid served as an ideal starting point, as it is an abundant and cheap source of chirality, only lacking a C_2 fragment in the side chain and already possessing one of the two stereogenic centers. By choosing either D- or L-pipecolic acid, all four conhydrine stereoisomers should in theory be obtainable by performing one diastereoselective transformation in the side chain. We therefore investigated similar transformations found in literature.

One approach by *Tilve* and co-workers[99] started from L-pipecolic acid (**168**) and proceeded *via* the protected amino aldehyde **169**, which was subjected to a *Wittig* reaction to form the alkene **170** (Scheme 21). Installation of the second stereogenic center by *Sharpless* oxidation was challenging as the reaction was high-yielding but lacked selectivity. The ligand-free dihydroxylation gave a diastereoselectivity of 60/40 and the same transformation employing a chiral ligand gave, after extensive screening, an increased selectivity of 85/15. After separation of the diastereomers, epoxidation and homologation, both conhydrine diastereomers were obtained separately.



Scheme 21. Synthesis of two conhydrine stereoisomers starting from L-pipecolic acid (**168**), employing an enantioselective *Sharpless* dihydroxylation.[99]

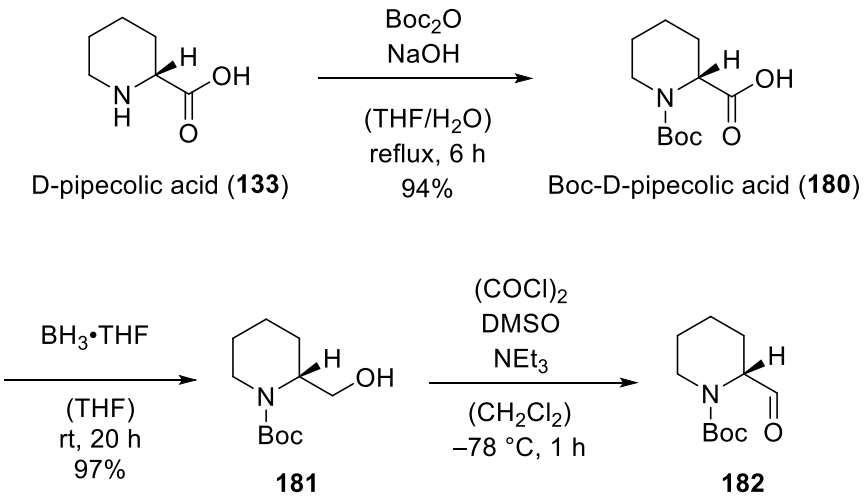
A more efficient route was reported by *Genet* and co-workers[100] starting from Boc-protected L-pipecolic acid (**175**), which was activated with carbonyl diimidazole (CDI) and treated with the magnesium salt of monoethyl maloric acid (Scheme 22). The obtained β-keto-ester **176** was diastereoselectively hydrogenated in presence of the chiral (*S*)-MeOBiphep ligand (**179**) and ruthenium to form alcohol **177**. Defunctionalization of the ester was performed by reduction and selective functionalization to the primary tosylate **178** followed by substitution with hydride and deprotection to obtain (+)-α-conhydrine (**48**).



Scheme 22. A highly diastereoselective synthesis of (+)-α-conhydrine (**48**) from Boc-protected L-pipecolic acid (**175**) using an enantioselective hydrogenation key-step.[100]

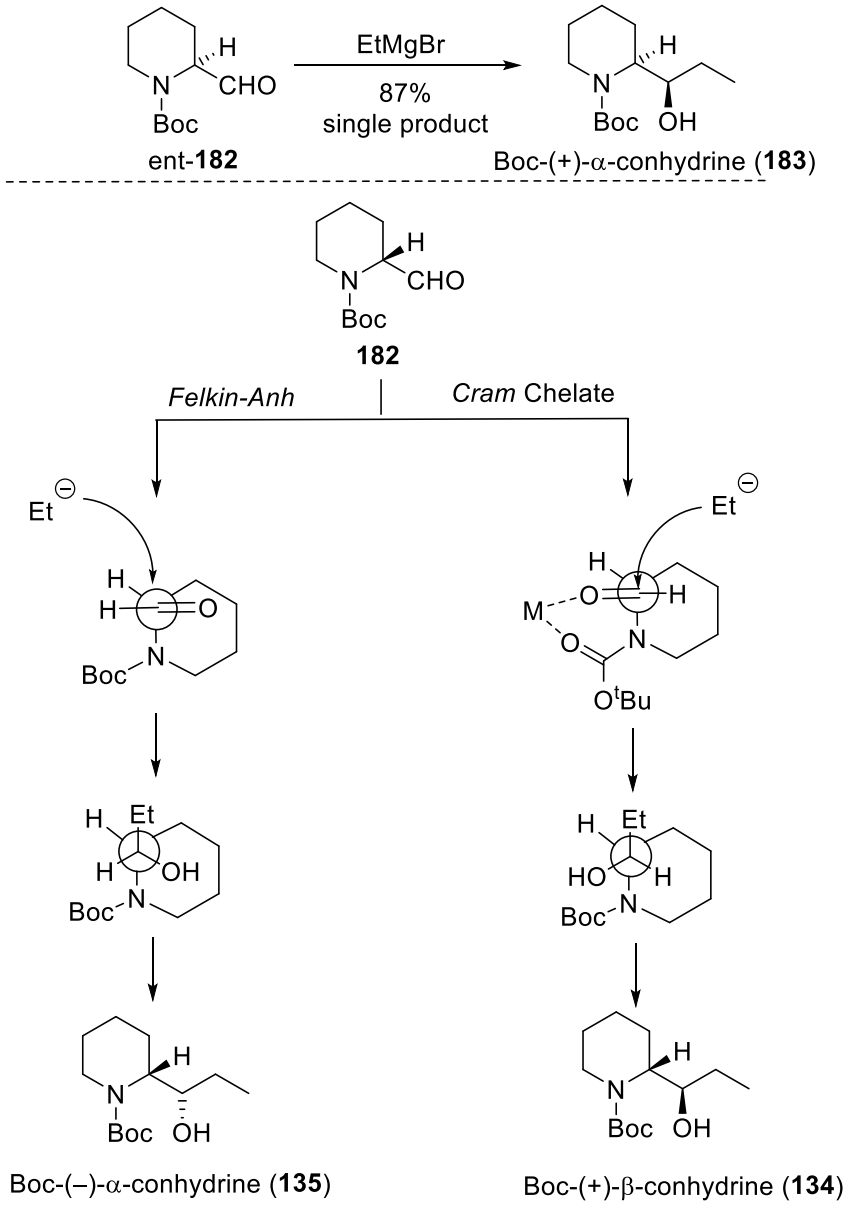
Both strategies necessitate the twofold employment of chirality, once in form of the chiral starting material L-pipecolic acid and a second time by performing a catalytic, chiral transformation, dihydroxylation or ketone reduction. Additionally, with a total of roughly ten steps, both appear unnecessary lengthy and we therefore undertook the endeavor to improve on these deficiencies.

Similarly to the strategy of *Tilve*, we sought to obtain the amino aldehyde of pipecolic acid, but instead to perform a diastereoselective addition of a nucleophilic C_2 building block. As we required (+)-β-conhydrine (**150**), our studies started from the corresponding D-pipecolic acid (**133**). Slight modifications of the literature-reported procedure for the protection of the secondary amine[101] gave quantitative yields for the Boc-protected amino acid **180** (Scheme 23). Employing sodium hydroxide as a base and acidification with hydrogen chloride after full conversion allowed for simple extraction of the product without the need for further purification. Reductions of carboxylic acid derivatives are commonly performed with borane and reported protocols could be applied for the synthesis of amino alcohol **181** without problems.[102] For the chemoselective oxidation to aldehyde **182**, a *Swern* protocol[103] was chosen over a toxic chromium-based oxidation or the expensive *Dess-Martin* oxidation. Due to the lability of the aldehyde, the subsequent nucleophilic addition was performed without prior purification.



Scheme 23. Synthesis of the known aldehyde **182** from chiral D-pipecolic acid (**133**).

A diastereoselective addition on the other enantiomer of the Boc-protected pipecolic aldehyde (ent-**182**) with ethyl magnesium bromide is reported.[104] The authors described the exclusive formation of the desired Boc-(+)-α-conhydrine (**183**) diastereomer in accordance with the *Felkin-Anh* model (Scheme 24, top). In contrast to this, the majority of studies on alkylation or arylation of 2-formylpiperidine report only negligible diastereoselectivities.[105] One publication in particular blames the Boc protecting group for the low diastereoselectivity and the authors were able to obtain a higher selectivity after switching to a trityl protecting group.[106]



Scheme 24. A reported nucleophilic addition on the Boc-L-pipecolic aldehyde (ent-**182**) forming a single diastereomer (top);[104] Nucleophilic addition onto the Boc-D-pipecolic aldehyde (**182**) following the *Felkin-Anh* and *Cram* chelate models (bottom).

With this information at hand, we proceeded with screening possible conditions. A first approach using easily accessible EtMgBr as the nucleophile gave promising results with high yield and *ee* (Table 1, entry 1). However, the desired diastereomer **134** was formed only with negligible preference over the second diastereomer **135** and an extensive optimization was necessary. Decreasing the reaction temperature led to lower conversion and yield but had little impact on the diastereoselectivity. As our desired product was formed according to the *Cram* chelate pathway, we subsequently screened different metal additives and ethyl sources. Neither $CeCl_3$ (entry 4) nor other metal additives like $Ti(OiPr)_4$ had the expected positive

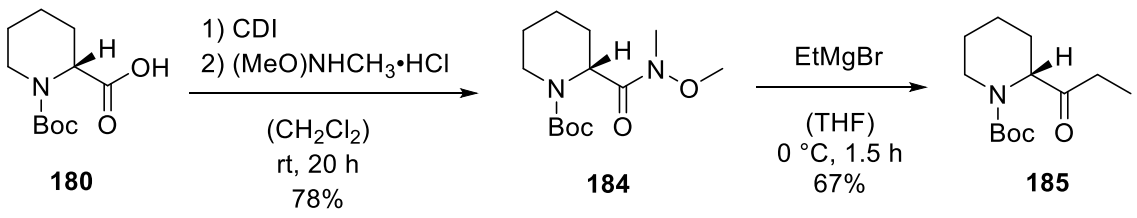
influence on the diastereoselectivity. In contrast to this, employing EtLi as the nucleophile resulted in a strong preference for the undesired *Felkin-Anh* product in accordance with the literature.[107] This was accompanied by pronounced racemization due to the higher basicity of organo-lithium reagents in comparison to *Grignard* reagents (entry 5). Finally, switching from the polar solvent THF to solvents with a lower polarity had a noticeable effect on the diastereoselectivity. As apolar solvents are less efficient at solubilizing and stabilizing cations, they facilitate the formation of *Cram* chelate products.[108] We therefore managed to shift the selectivity towards the desired diastereomer by changing to a less polar solvent like toluene (entry 7) or dichloromethane (entry 8).[109] Overall, the increase in diastereoselectivity was only modest and the new reaction conditions suffered from a concomitant decrease in yield. Additionally, the entire strategy led to an inconsistent loss of enantiopurity which was linked to the preceding *Swern* oxidation instead of the nucleophilic addition (see footnotes). The only exception of this trend was the pronounced racemization using EtLi, which can be easily explained by its higher basicity. Attempts to employ enantioselective alkylations of the aldehyde with Et_2Zn, $Ti(OiPr)_4$, and chiral ligands like BINOL were unsuccessful and no product could be isolated.[110] The overall failure to tune the diastereoselectivity accompanied with the inconsistent racemization forced us to explore an alternative route.

Table 1. Alkylation of the Boc-L-pipecolic aldehyde (**182**) with different C_2 nucleophiles.

entry	reagents	solvent	T [°C]	t [h]	yield [%]	*d.r.*[d]	*ee* [%]
1[a]	EtMgBr	THF	0	2.5	85	56/44	94
2[b]	EtMgBr	THF	−20	3.7	68	54/46	97
3[b]	EtMgBr	THF	−78	3.3	59	56/44	97
4[c]	EtMgBr + $CeCl_3$	THF	0	1	76	51/49	89
5[a]	EtLi	THF	0	2.5	25	9/91	82
6[b]	$Et_3ZnMgBr$	THF	−20	2.5	73	55/45	97
7[c]	EtMgBr	$PhCH_3$	0	1	53	70/30	89
8[c]	EtMgBr	CH_2Cl_2	0	1	45	77/23	87

[a, b, c] reactions starting from the same batch of aldehyde; [d] diastereomeric ratio: Boc-(+)-β-conhydrine (**134**) to Boc-(−)-α-conhydrine (**135**)

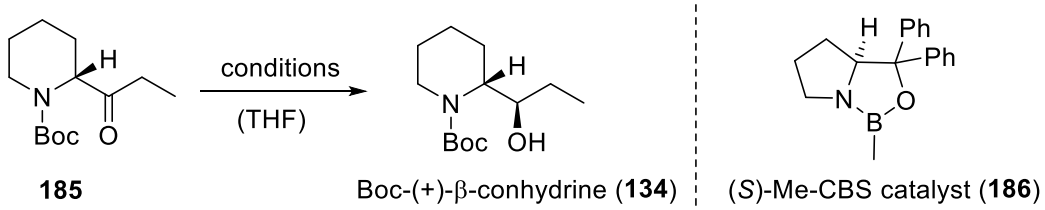
Access to ketone **185** and subsequent diastereoselective reduction was envisioned as an alternative strategy. With its small size, the delivery of a hydride should be more reagent-dependent and a higher diastereoselectivity was expected. Initial attempts to obtain the desired ketone **185** directly from Boc-protected acid **180** by using two equivalents EtLi (*Gilman* conditions) were disappointing.[111] The highest yield obtained was 21% when using 3.0 eq. EtLi with TMEDA in THF at −40 °C.[77] A less convenient but more established route *via Weinreb* amid **184** was explored instead (Scheme 25). For this literature-reported synthesis, several coupling reagents have been used and we chose the cheap carbonyl diimidazole (CDI) to efficiently obtain the product with 78% yield.[112] Initially, treatment of *Weinreb* amide with 1.2 eq. EtMgBr in THF at −78 °C led to a low yield of 33%. During screening, the yield could be increased to 45% by running the reaction at 0 °C instead and after applying a larger excess of 2.0 eq. EtMgBr, a satisfying yield of 67% was obtained.



Scheme 25. Synthesis of *Weinreb* amide **184** and conversion to ketone **185**.

Reduction of the ketone **185** turned out to be promising as an initial attempt employing $NaBH_4$ in a THF/MeOH mixture (2/1) at 0 °C (Table 2, entry 1) already gave similar diastereoselectivities as the optimized conditions of the aldehyde alkylation (*d.r.* = 3/1). A change of reducing agent was unnecessary because a decrease of the temperature to −40 °C (entry 3) led to excellent diastereoselectivities. However, a small erosion of enantiomeric excess was detected and blamed on the preceding *Weinreb* amide formation and not the reduction step, as the *ee* of all reduction attempts with $NaBH_4$ was similar. To increase the *ee*, we decided to apply an enantioselective reduction in form of the *Corey-Bakshi-Shibata* reaction.[113,114] The commercially available (*S*)-Me-CBS catalyst **186** and $BH_3{\cdot}SMe_2$ were chosen for the reduction. With 10 mol% catalyst, an excellent *ee* was achieved along with a high diastereoselectivity and short reaction times (entry 4), meaning a highly reproducible protocol had been found for the synthesis of sufficient quantities of enantiopure Boc-(+)-β-conhydrine (**134**) for further experiments.

Table 2. Optimization for the reduction of ketone **185**.

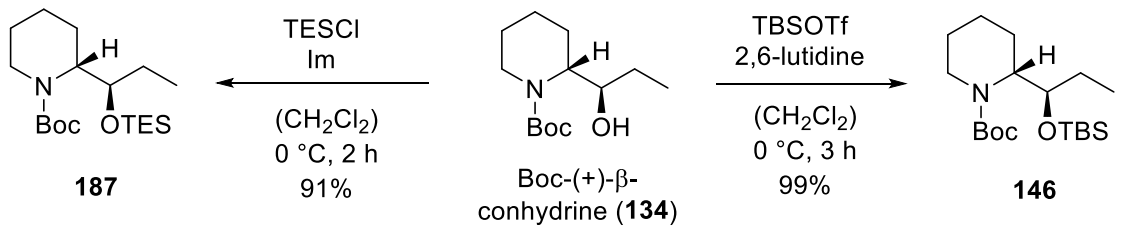


185 Boc-(+)-β-conhydrine (**134**) (*S*)-Me-CBS catalyst (**186**)

entry	conditions	T [°C]	t [h]	yield [%]	*d.r.*[a]	*ee* [%]
1	$NaBH_4$	0	2.5	81	78/22	96
2	$NaBH_4$	−20	4	75	92/8	97
3	$NaBH_4$	−40	24	72	94/6	96
4	(*S*)-Me-CBS + $BH_3 \cdot SMe_2$	0	5	97	91/9	99.9

[a] diastereomeric ratio: Boc-(+)-β-conhydrine (**134**) to Boc-(−)-α-conhydrine (**135**)

With both stereogenic centers established, a suitable protecting group for the secondary alcohol had to be found which was compatible with all future acidic, basic and oxidizing conditions and could be cleaved only in the last steps of the synthesis. As no other protecting groups were planned, a silyl ether seemed the most sensible choice. This kind of group should be orthogonal to all envisioned steps and could ultimately be cleaved with mild, fluoride-based reagents. Both the TES and TBS ethers were tested as possible protecting groups. The TES group was installed efficiently with standard reagents and the protected product **187** was obtained in high 91% yield (Scheme 26).[115] The protection with the more stable and sterically demanding TBS group proved more difficult and use of the commonly employed TBSCl was too low yielding. Applying the more reactive TBSOTf, the bulkier silyl group was efficiently introduced and the TBS ether **146** was isolated in 99% yield.[116]

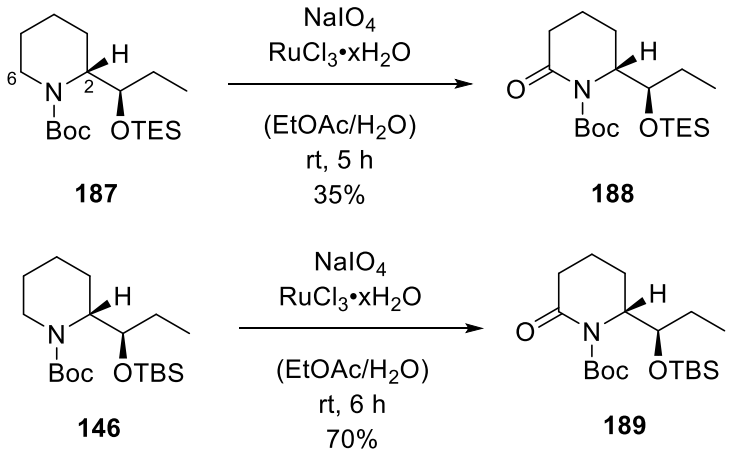


187 Boc-(+)-β-conhydrine (**134**) **146**

Scheme 26. Protection of the alcohol as a TES ether (left) and a TBS ether (right).

The next task was the α-functionalization of the piperidine to enable a coupling to a suitable furan derivative. At first, a direct coupling with the furan was considered, which is commonly performed by deprotonation at the α-position of the amine with *s*BuLi, followed by a potential transmetalation and coupling reaction with an appropriate partner. For example, a methylation of the lithiated species with MeI[117] and a *Negishi* coupling with aryl bromides after transmetalation with $ZnCl_2$[118] have been reported. An issue for our purpose arose from the substrate-induced diastereoselectivity. With an established stereocenter at the 2-position of the piperidine, a subsequent functionalization at the 6-position would inevitably lead to selective formation of the undesirable *trans*-substituted piperidine. As the selective inversion to the *cis*-diastereomer would prove troublesome, we opted for a different approach.

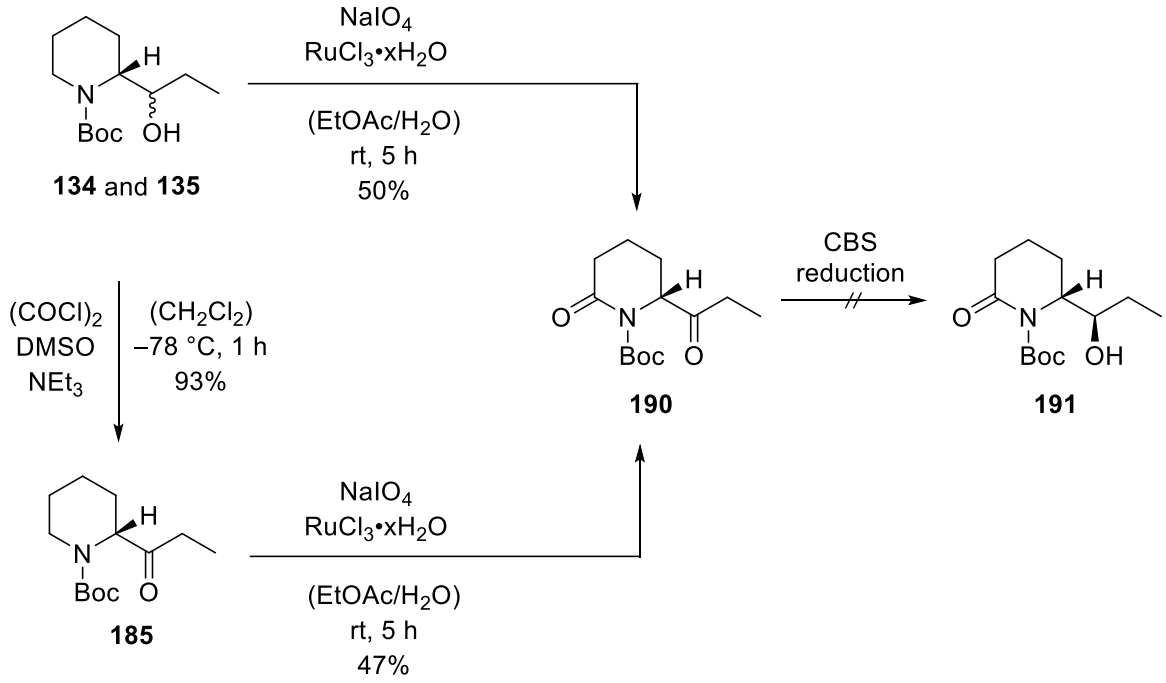
By oxidation of the piperidine to the lactam and subsequent conversion to the trifluoromethanesulfonate, a palladium catalyzed cross-coupling with a metalated furan entity would give rise to a planar intermediate. Diastereoselective reduction of the enamine from the sterically more accessible side should then provide the desired diastereomer. To this end, a ruthenium catalyzed oxidation of piperidine in a two-phasic mixture was employed (Scheme 27). Screening revealed, that the commonly used RuO_2 gave only traces of product and proved vastly inferior to $RuCl_3$ as a catalyst.[77] The use of the highly inert and hepatotoxic tetrachlorocarbon was unnecessary and good results were obtained with benign EtOAc.[119] Addition of $NaHCO_3$ to remove *in situ* generated HCl and prevent acid catalyzed Boc deprotection had no beneficial effect.[120] A strong impact of the alcohol protecting group on the overall performance of the reaction was noted. While the TBS-protected alcohol **146** gave good yields, applying the same conditions to the TES-protected counterpart **187** resulted in pronounced decomposition and little product was isolated.



Scheme 27. Ruthenium catalyzed α-oxidation of piperidines.

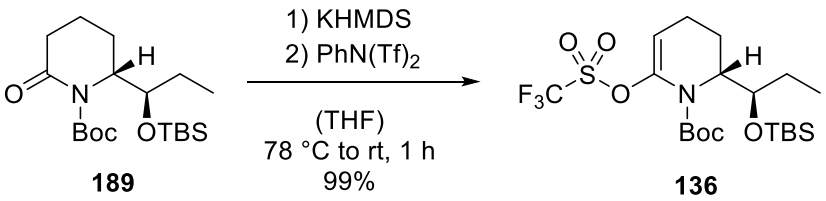
An alternative route to the lactam employing a diastereomeric mixture of the conhydrine derivatives was investigated. This would allow for recycling of the unused Boc-(−)-α-conhydrine (**135**) without a tedious inversion using a *Mitsunobu* reaction. To this end, a *Swern* oxidation was performed on the diastereomeric mixture to regenerate ketone **185** (Scheme 28). This obtained ketone could now be resubmitted to the CBS reduction.

Additionally, to investigate the reactivity of the ruthenium mediated oxidation, both alcohol and ketone were successfully employed in the oxidation of the piperidine to obtain the piperidone **190**. Subsequent reduction of the ketone and protection of the formed alcohol would provide an alternative access to the amide described above. However, CBS reduction to alcohol **191** suffered from low conversion, the reaction could not be optimized efficiently and this alternative route was discontinued.



Scheme 28. Oxidation of the diastereomeric mixture of Boc-(−)-α-conhydrine (**135**) and Boc-(+)-β-conhydrine (**134**) as well as ketone **185** to the lactam **190**.

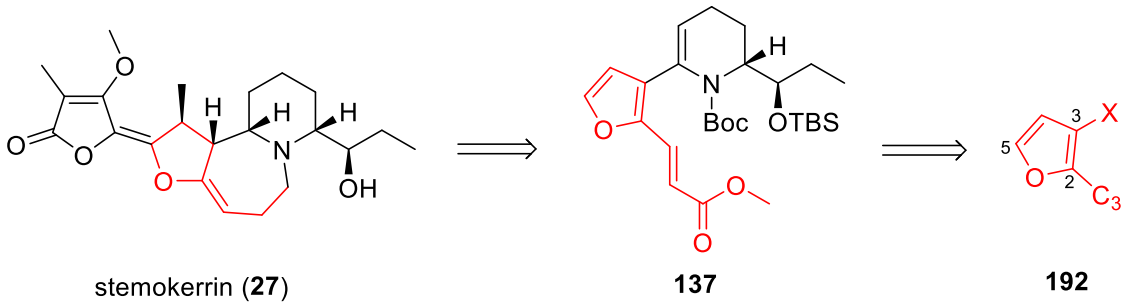
Research therefore continued with the TBS-protected amide **189**, which could be obtained in high yields. Inspired by preceding studies of *Comins*[121] and *Occhiato*,[122] we sought to employ a trifluoromethananesulfonyloxy enecarbamate as the electrophile in a palladium catalyzed cross-coupling. First, the amide **189** was selectively deprotonated at −78 °C with KHMDS. Treatment with $PhN(Tf)_2$ led to formation of the labile triflate **136** in quantitative yields (Scheme 29).[123]



Scheme 29. Conversion of the lactam **189** to the enamine triflate **136**.[77]

4.3. Synthesis of the furan cross-coupling partner

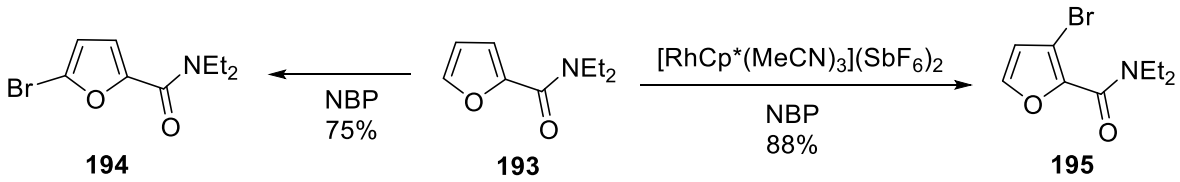
To accomplish the synthesis of the azepane ring and its annulated five-membered ring in stemokerrin (**27**), access to 2,3-difunctionalized furan **192** was necessary. A C_3 side chain at the 2-position of the furan would allow for a ring closure to the azepane ring later in the route, while a functional group at the 3-position was required for a regioselective coupling (Scheme 30) to the piperidine analogue **136**. This functional group should be some organometallic substituent (X = BOR_2, SnR_3, ZnR) to allow for a palladium catalyzed cross-coupling reaction. Overall, a selective 2,3-functionalization of a simple and commercially available furan was necessary. The desired regioselectivity could be difficult to achieve as it contradicts the natural reactivity of the furan, which prefers the functionalization at the 2- and 5-positions.[124]



Scheme 30. Retrosynthetic analysis of the furan building block.

Two different strategies for a potential regioselective functionalization of a cheap furan derivative came to mind. The first involved the selective C−H functionalization at the 3-position by using a directing group at the readily modifiable 2-position. Alternatively, a lengthier approach involved the blocking of the 5-position by some substituent and removing it after the desired functionalization at 2- and 3-position.

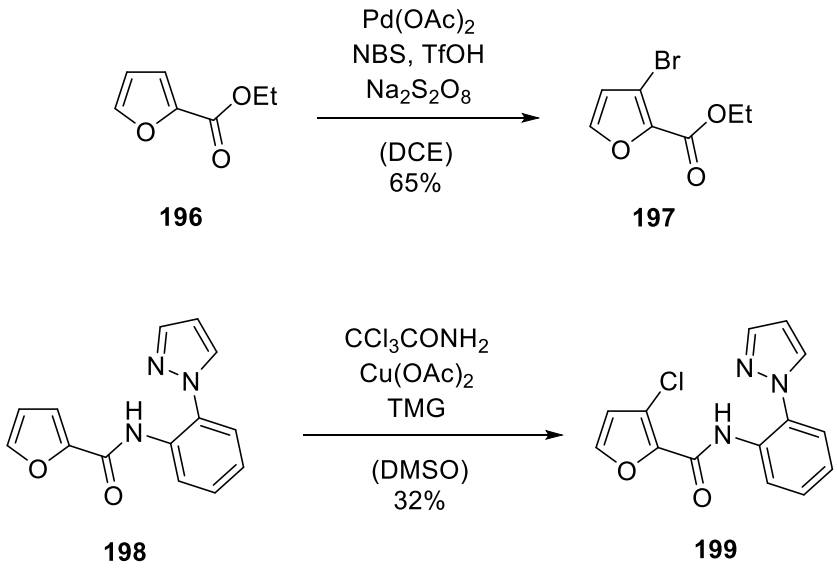
As direct C−H functionalization utilizing a directing group was seen as the superior, more elegant approach, it was investigated first. Literature on the C−H functionalization at the 3-position of furans is however quite scarce. One publication by *Glorius* and co-workers[125] reported a high-yielding and selective bromination at the 3-position forming compound **195** in presence of a rhodium catalyst (Scheme 31) while the 5-bromofuran **194** was formed without the catalyst. The authors found diethyl amide to be the most efficient directing group and *N*-bromophthalimide (NBP) the ideal bromine source.



Scheme 31. Bromination of furans like compound **193** with tuneable regioselectivity depending on the reaction conditions.

Similarly, *Rao* and co-workers[126] applied ethyl esters of different aromatic and heteroaromatic compounds in a palladium catalyzed bromination. Commercially available $Pd(OAc)_2$ as the transition metal catalyst, *N*-bromosuccinimide (NBS) as the bromine source and $Na_2S_2O_8$ as a co-oxidant were found to be most effective. Among several examples, they managed brominate ethyl 2-furoate (**196**) to obtain 3-bromo-2-ethyl furoate (**197)** in 65% yield (Scheme 32, top).

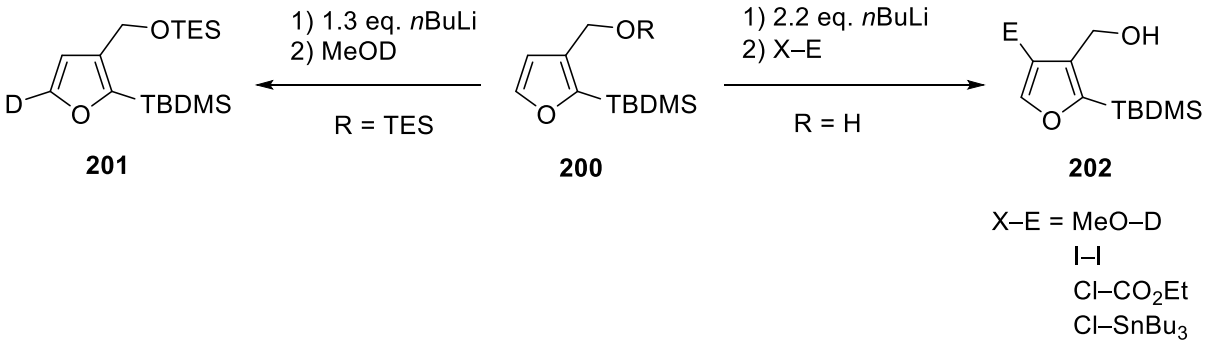
Another regioselective functionalization employing copper stems from *Li* and co-workers.[127] They used trichloroacetamide as a chlorine source along with a pyrazole-containing amide at the 2-position as a directing group, as illustrated for compound **198**. These optimized conditions still only led to disappointing 32% yield of the 3-chloro furan **199** (Scheme 32, bottom).



Scheme 32. Regioselective, palladium catalyzed bromination (top); Chlorination using a pyrazole-based directing group (bottom). (TMG = 1,1,3,3-tetramethylguanidine)

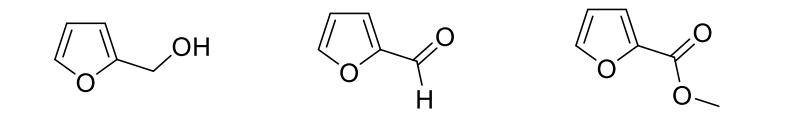
Overall, every strategy discussed so far proved unsuited for our purposes. Using a carboxylic acid derivative as a directing group would require several transformations to end up with the required C_3 building block. Employing high-cost transition metal catalysts was also undesirable. Instead, starting from commercially available furan derivatives and performing the regioselective C–H functionalization with stochiometric amounts of an organometallic reagent seemed more promising.

A similar strategy was published, proving the capabilities of a hydroxymethylene as a directing group.[128] With a free alcohol group, selective functionalization at the 4-position was reported (Scheme 33, right) whereas the electrophile ended up in the 5-position if the directing group was blocked as a TES ether (left).



Scheme 33. Regioselective functionalization of a furan. While the protected alcohol led to functionalization at the 5-position (left), the free alcohol group acted as a directing group, giving the 4-substituted product.[128]

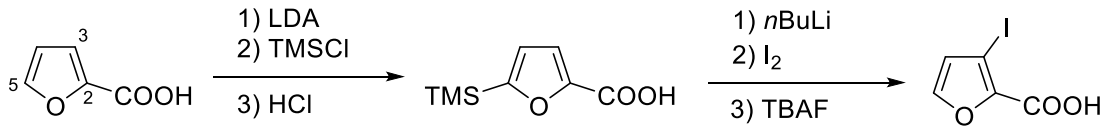
We began our own studies with the related furfuryl alcohol (**203**) and investigated the capabilities of the hydroxymethylene group as a directing group by deuterium incorporation after quantitative deprotonation. After addition of 2.2 eq. *n*BuLi at −78 °C in THF, the mixture was quenched with D_2O or MeOD and we observed exclusive deuterium incorporation at the 5-position in contrast to the previously mentioned publication. Similar attempts on methyl 2-furoate (**130**) gave addition to the tertiary alcohol with the base *n*BuLi and decomposition with *t*BuLi. Using milder bases like LiTMP or LDA on the other hand gave no deuterium incorporation for furfural (**204**) or methyl 2-furoate (**130**), despite similar reported procedures.[129]



furfuryl alcohol (**203**) furfural (**204**) methyl 2-furoate (**130**)

Figure 9. C−H functionalization was investigated on these commercially available furan derivatives.

As all attempts for a selective functionalization at the 3-position failed, the alternative strategy was investigated instead, utilizing a protecting group at the 5-position. Such a strategy has been reported for furoic acid (**205**),[130] which was protected with a TMS group after deprotonation with two equivalents LDA to form furan **206**. After a second deprotonation, this time at the 3-position, and quenching with elemental iodine, the TMS group was cleaved with TBAF to obtain the 2,3-difunctionalized furan **207**.



205 **206** **207**

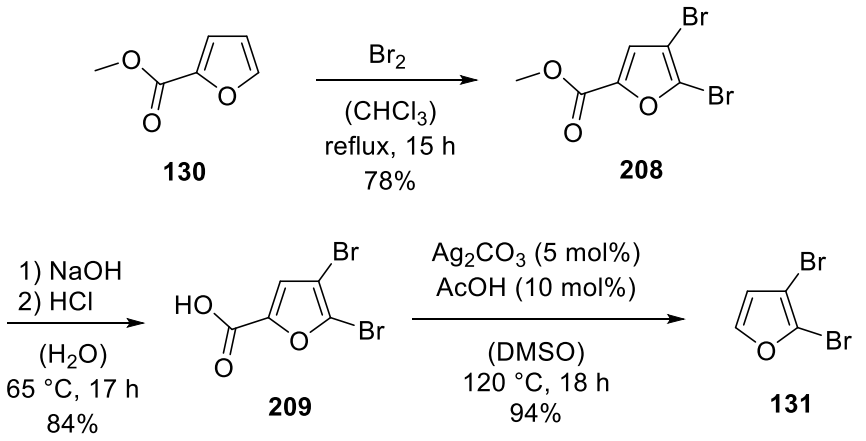
Scheme 34. Selective functionalization at the 3-position of a furoic acid by blocking the 5-position with a TMS group.

We tried to reproduce the deprotonation/TMS-protection/iodination sequence on both the reported furoic acid (**205**) and on methyl 2-furoate (**130**). However, we were unable to reproduce the reported results and observed no conversion upon treatment with LDA while *n*BuLi or *t*BuLi led to complex mixtures.

As both the directed ortho-metalation as well as the protection with the TMS group failed, we continued on a more reliable bromination procedure previously employed in our laboratory.[77] To this end, a twofold bromination of methyl 2-furoate (**130**) at the 4- and 5-position was performed. The methyl ester functional group plays a role as a protecting group, later to be cleaved by decarboxylation.

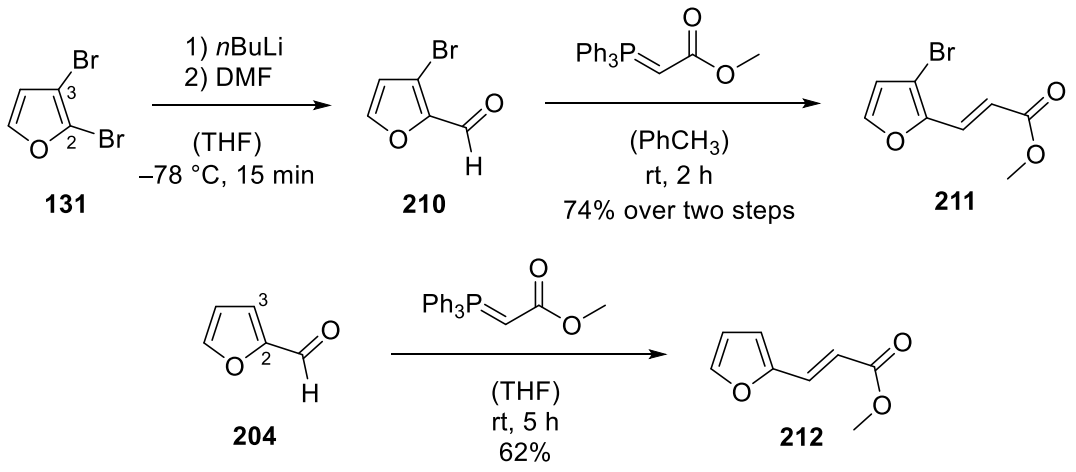
One reported bromination procedure using elemental bromine and stochiometric amounts of $AlCl_3$ was previously tested in our laboratory, but turned out to be poorly reproducible and highly dependent on the quality of the $AlCl_3$.[131] Instead, another procedure was successfully employed after some optimization.[93] Bromination of methyl 2-furoate (**130**) in chloroform with an excess of bromine gave the desired dibrominated furan **208** along with minor amounts of tribrominated side product. Subsequent hydrolysis of the methyl ester with 4 M NaOH at 65 °C led to precipitation of the sodium carboxylate and after filtration and acidification, the acid **209** was isolated (Scheme 35).

The carboxylic acid group played its role as a protecting group and defunctionalization would leave the desired 2,3-difunctionalized furan **131**. Most decarboxylation reactions on furans employ stochiometric amounts of copper powder in quinoline or other high-boiling solvents.[132] Applying these conditions to our substrate, however, gave only yields of 47% and the excess of copper resulted in a tedious work-up.[77] Instead, the silver catalyzed decarboxylation reported by *Larrosa* and co-workers[133] seemed promising and ultimately turned out superior. Applying the same conditions as reported resulted in a clean protodecarboxylation and the 2,3-dibromofuran (**131**) was obtained after purification by distillation in a yield of 94%.



Scheme 35. Synthesis of 2,3-dibromofuran (**131**).[77]

Due to the neighboring oxygen atom and thereby a higher reactivity at the 2-position, functionalization with a C_3 chain was attempted prior to modifications of the bromine at the 3-position. Previous studies towards a *Heck*-type coupling of the 2,3-dibromofuran with C_3 building blocks like methyl acrylate failed.[77] On the other hand, a selective halogen-metal-exchange with *n*BuLi delivered the expected 2-lithiated species and a subsequent reaction with DMF gave labile 3-bromo furfural (**210**) after work-up as reported.[132] A subsequent *Wittig* reaction gave *E* configured conjugated ester **211** as the sole product. Similarly, a *Wittig* reaction was performed on commercial furfural (**204**) to obtain the unfunctionalized methyl(furan-2-yl)acrylate (**212**).

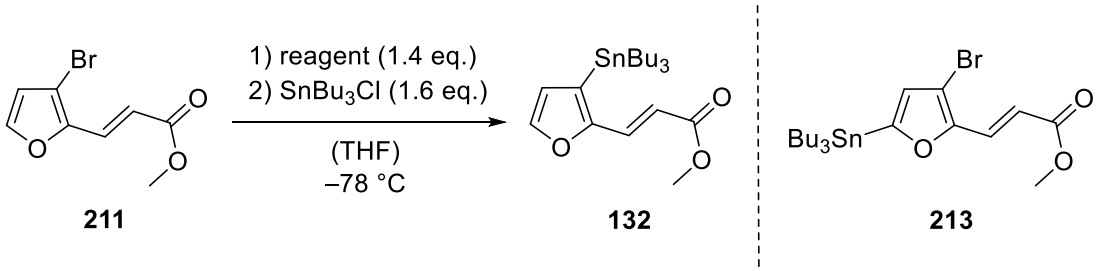


Scheme 36. *Wittig* reaction on 3-bromo-furfural (**210**) (top) and furfural (**204**) (bottom).

The unsubstituted ester **212** was a readily available compound but any attempts on the C−H functionalization at the 3-position with *n*BuLi, *t*BuLi or LiTMP remained as unsuccessful as it had been with the previously applied furan derivatives. Focus was therefore shifted to the brominated furan **211** and studies on a halogen-metal exchange at the 3-position were performed first. To this end, the compound was treated with different organometallic reagents and after 30 min, addition of tributyltin chloride was envisioned to form the stannylated furan **132** *via* transmetalation. In this reaction, the previously employed *n*BuLi gave complex product mixtures (Table 3, entry 1), presumably due to nucleophilic addition on the reactive methyl ester or ringopening reactions.[134] Unsurprisingly, similar results were obtained with the more reactive *t*BuLi. Typical transmetalation reagents like *i*PrMgCl (entry 3) and the "Turbo-Grignard" established by *Knochel*[135] (entry 4) gave no conversion at low temperatures and complex reaction mixtures were obtained after warming to 0 °C. Using the non-nucleophilic base LiTMP did not lead to the expected halogen-metal exchange but rather a

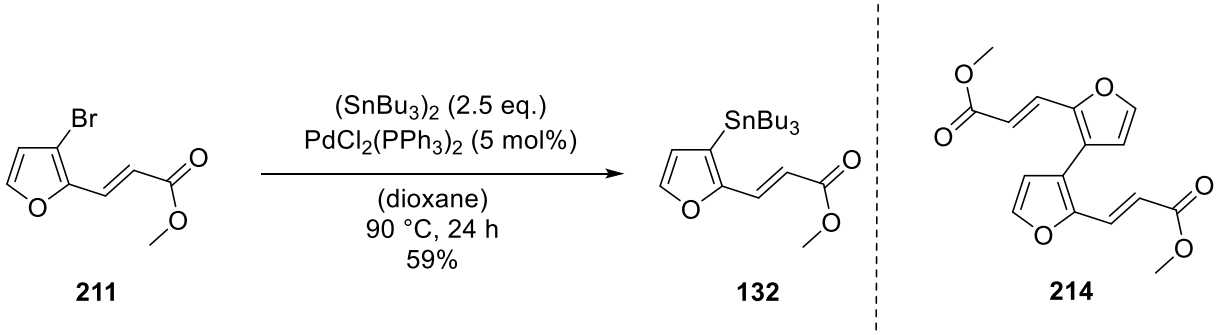
deprotonation at the acidic 5-position, giving, after treatment with $SnBu_3Cl$, the undesired furan **213** in low yields.

Table 3. Attempts towards the halogen-metal exchange at the 3-position to obtain stannylated furan **132**.



entry	reagent	result
1	*n*BuLi	complex mixture
2	*t*BuLi	decomposition
3	*i*PrMgCl	no conversion
4	*i*PrMgCl·LiCl	no conversion
5	LiTMP	16% **213**

The attempted transmetalation of furan **211** was presumably unsuccessful due to the lability of this electron-deficient aromatic ring. Analysis of the complex crude NMR spectra revealed the formation of compounds attributed to ringopening of the furan and addition onto the ester. Performing the transmetalation by a *Stille* reaction using a tin dimer as previously explored was instead investigated.[77] The reaction was performed in dioxane with $PdCl_2(PPh_3)_2$ as a palladium source at 90 °C. To decrease the likelihood of a detrimental dimerization, an excess of hexabutylditin had to be used. Still, the yield of this reaction reached 59% as large amounts of the dimer **214** were isolated. Nonetheless, the stannylated furan **132** could be successfully obtained as the major product and subsequent coupling reactions could be performed.



Scheme 37. *Stille* reaction with hexabutylditin to the stannylated furan **132**. Major side product was the formation of dimer **214**.

5. Combination of the two fragments and synthesis of the diol

5.1. Synthesis of the tricyclic core structure

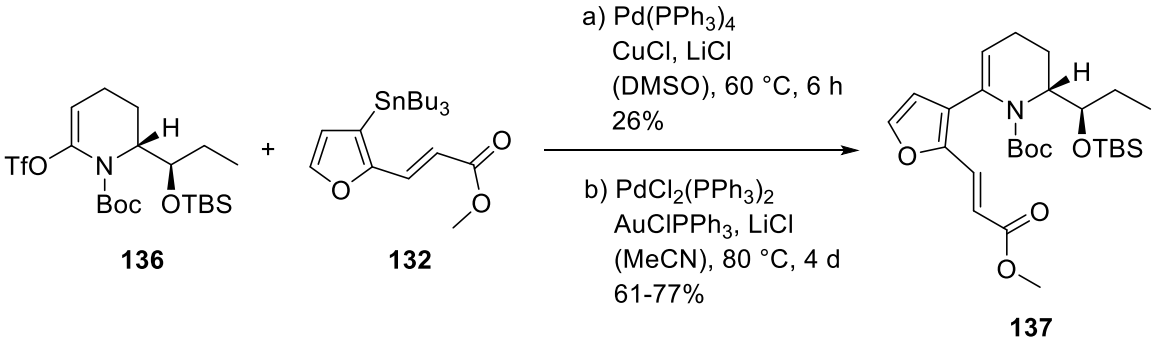
With synthetic access to both the enamine triflate **136** and the stannylated furan **132**, both building blocks could now be combined in a cross-coupling reaction. Extensive screening by *Mayer*[77] led from low conversion and traces of product **137** to optimized conditions and the major findings shall be repeated in the following. During the screening it became apparent that the reaction rate of the *Stille* coupling was extremely low and had to be enhanced to obtain a noticeable turnover. The use of LiCl as an additive is reported to increase the reaction rate by accelerating the oxidative addition.[136] In the presence of LiCl, an electron rich, anionic $[PdClL_2]^-$ complex can be formed, which is more reactive towards the oxidative addition than its electroneutral counterpart.[137] In our case, this reagent had a pronounced effect, as the yield increased from traces without LiCl to 26% of the coupling product in presence of 6.0 equivalents of LiCl (Scheme 38, conditions a).

Another strategy to enhance the rate of the *Stille* reaction is the employment copper(I) salts and this is so common that the term "copper-effect" has been coined.[138] The exact mechanism of this effect seems to be solvent dependent, with polar solvents leading to a transmetalation and the formation of a more reactive organo-copper species. On the other hand, in less polar solvent the copper acts as a scavenger of free ligands, therefore freeing a potential binding site at the palladium center for the substrates to bind.[139]

While copper is commonly employed in stochiometric quantities, catalytic amounts of Au(I) can also aid in the transmetalation. Due to the large size of the tributyltin group, the *Stille* coupling is very sensitive to steric hinderance and especially the transmetalation from the bulky organotin species to the sterically encumbered tetra-coordinated palladium complex poses a problem. The linear gold complexes only hold two ligands, are therefore less sterically demanding and can act as a shuttle of the organic residue from Sn to Pd.[140]

The optimized conditions therefore included the use of LiCl as an additive and $Au(PPh_3)Cl$ as a co-catalyst. Still, the reaction required four days at 80 °C for full conversion of the enamine triflate **136** proving the oxidative addition to be the kinetic bottleneck. Major decomposition pathways of the furan included the proto-destannylation and dimerization and the corresponding side products could be isolated. To further increase the yield, the excess of

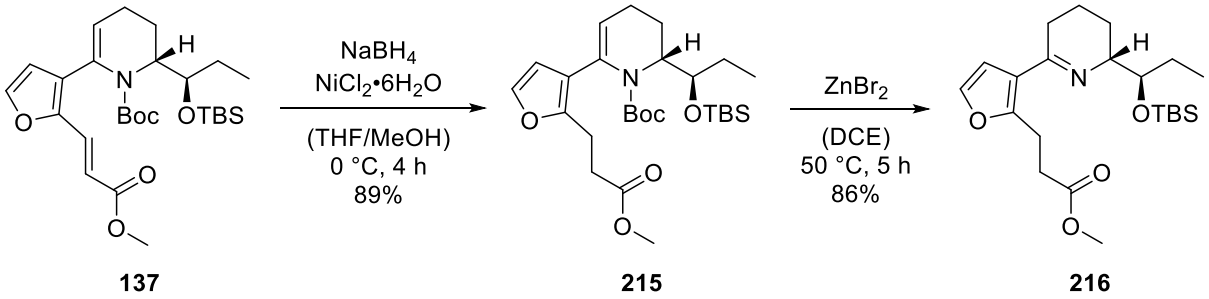
stannylated furan **132** was increased from 1.6 to 2.5 equivalents, leading from 61% to a satisfying 77% yield.



Scheme 38. Palladium catalyzed *Stille* cross-coupling reaction converging to product **137**.

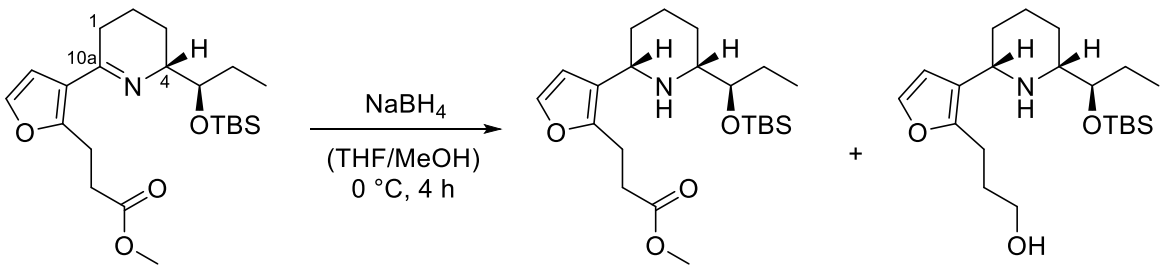
With the coupling product **137** at hand, the next steps envisioned were the reduction and deprotection to enable the lactamization. The selective reduction of an α,β-unsaturated ester is a common transformation and while the *Luche* reduction with $CeCl_3$ selectively reduces the ester, a soft hydride source is needed for the 1,4-reduction of the double bond to occur. In our case, using Ni_2B, *in situ* generated from $NaBH_4$ and $NiCl_2$,[141] gave selective reduction of the conjugated double bond to ester **215** without reduction of the enamine or the ester functionality.

For the removal of the Boc protecting group, treatment with typical *Brønsted* acids like HCl or TFA would be incompatible with our substrate. *Lewis* acid mediated deprotection with $ZnBr_2$ at 60 °C resulted in cleavage of the protecting group and immediate tautomerization to the corresponding imine **216**. The latter was stable enough to be purified by column chromatography.



Scheme 39. Conjugated reduction of the α,β-unsaturated ester and subsequent deprotection gave rise to imine **216**.

The following reduction of imine **216** to the amine generated a stereogenic center at C-10a. Due to the set stereoinformation at C-4, the hydride was expected to be delivered from the less congested side and accordingly, the required *cis*-product should form preferentially. Reductions of imines are usually performed with mild reagents like $NaBH_3CN$ or $NaBH(OAc)_3$.[142] In our case, however, the more sterically congested imine required the use of more reactive $NaBH_4$ to achieve turnover. Much to our delight, hydride delivery occurred exclusively from the sterically less hindered side and only the desired diastereomer **217** was formed (Scheme 40). However, yields were low for this simple reaction. It turned out that, despite using only 1.2 eq. $NaBH_4$ at 0 °C, these conditions were sufficient to concomitantly reduce the methyl ester forming the alcohol **218** as a side product. We saw in this over-reduction more of an opportunity than a problem and investigated both species for further applications.



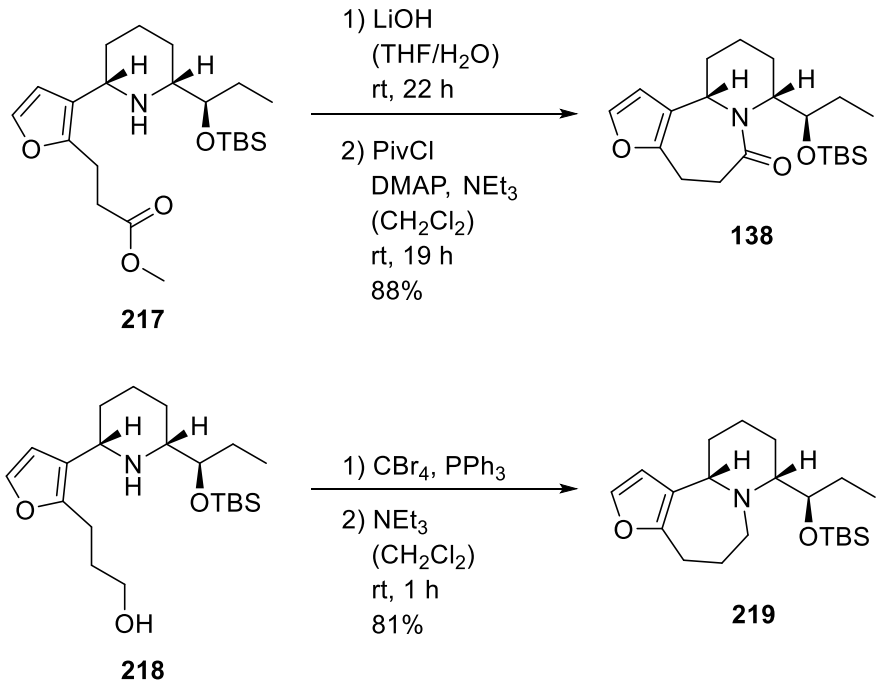
216 **217** 75% **218** 18%

Scheme 40. Diastereoselective reduction of imine **216** yielded both amine **217** and alcohol **218**.

For the formation of the azepine ring, hydrolysis of the methyl ester and subsequent lactamization was envisioned. Mild hydrolysis with LiOH in an emulsion of THF and water led to formation of the free acid.[143] Several peptide coupling reagents like DCC, EDC and the *Yamaguchi* reagent were unsuccessfully employed by *Mayer*[77] until pivalic acid chloride was found to enable the lactamization.[144] The cyclization proceeded presumably *via* the mixed anhydride to the seven-membered amide **138** (Scheme 41, top).

For the cyclization of alcohol **218**, activation of the hydroxy group and intramolecular nucleophilic substitution by the secondary amine was the most straightforward approach. Treatment with MsCl in the presence of an excess of NEt_3 is a commonly employed approach for the formation of azepine rings,[145] failed however in our case. Instead, the *Appel* reaction with CBr_4 and PPh_3 gave the envisioned cyclization to amine **219** after addition of NEt_3 in good yields.[146]

Overall, synthetic access to two variants of the tricyclic product, both amine **219** and amide **138**, was accomplished.



Scheme 41. Cyclization to the azepane ring as the amide (top) or amine variant (bottom).

5.2. Synthesis of the 1,4-diol

5.2.1. Furan oxidation of the tricyclic lactam

The next synthetic goal was the stereoselective synthesis of the 1,4-diol **140**, which possesses every stereogenic center found in stemokerrin (**27**). To this end, the new stereogenic centers at C-10 and C-11 in the furan ring had to be installed correctly. At first, the oxidation of the furan to liberate the protected 1,4-difunctionality was planned. The oxidation of the furan on the major amide **138** shall be discussed first and attempts on the minor amine **219** will be mentioned later.

A large library of conditions is reported for the oxidation of furans leading to different products with a range of oxidation states.[147] Most oxidations, like the treatment with singlet oxygen, peracids or quinones such as DDQ, lead to butenolides, a class of unsaturated five-membered ring lactones. Other conditions stop at an earlier oxidation stage *e.g.* the acetals formed in the *Achmatowicz* reaction.[148] And harsh conditions like the combination of $RuCl_3$

and $NaIO_4$ can degrade the furan to a simple carboxylic acid.[149] Not only were the right conditions required for the desired oxidation to the γ-hydroxy butenolide, but two other problems made matters more complicated. First, a new stereogenic center would be formed at C-9 and had to be established correctly. As for the reduction of imine **216**, a good diastereoselectivity due to the approach of the oxidant from the less hindered side of the rigid tricyclic structure was expected. A second issue would be the equilibrium of the oxidized compound, as both the closed γ-hydroxy butenolide **139** and the open keto-acid **220** could be formed.

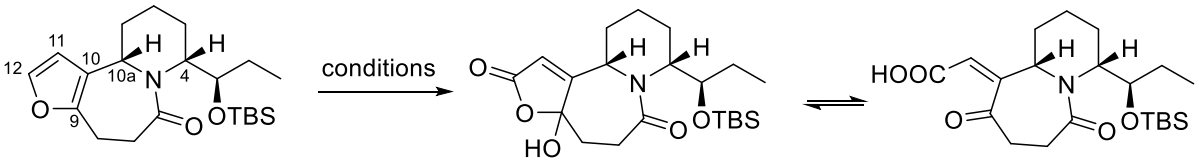
First, bromine-based oxidations were tested but both the *Achmatowicz* reaction and the treatment with NBS[90] led to complex product mixtures and no desirable product was detected (Table 4, entry 1 and 2). Potential bromination at C-12 by aromatic bromination could be a reason for the incompatibility of these conditions with the substrate, but the corresponding side product could not be detected. Utilizing peroxoacids, either as mCPBA[89] or generated *in situ* from hydrogen peroxide and acetic acid, failed to give any conversion (entry 3 and 4) and these reagents were disregarded. Using a *Pinnick-Lindgren*-derived oxidation with $NaClO_2$ led to full conversion, but only small amounts of rather impure product were obtained (entry 5). A major improvement was found upon switching to reactions employing light-generated singlet oxygen for the oxidation.

Most organic molecules exist in their thermodynamically preferred singlet state, having all their electrons spin paired. One exception to this is molecular oxygen, whose ground state has its two highest lying electrons in two separate orbitals in accordance with *Hund's* rule.[150] This lowest state of oxygen is called a triplet state and has the term symbol $^3\Sigma_g$. Already quite early this untypical state of oxygen was noted due to its paramagnetic properties.[151] Above its triplet ground state, the next two higher states of oxygen are both singlet states, one of them $^1\Delta_g$, lying 94 kJ/mol higher, and the energetically even higher $^1\Sigma_g$, lying a total of 157 kJ/mol higher than its ground state.[152] The latter, energetically higher state is rather irrelevant for synthetic purposes as it quickly deactivates to the lower singlet state. This $^1\Delta_g$ state on the other hand exhibits a very different chemistry of normal, ground-state triplet oxygen and is responsible for the three most common reactions performed with singlet oxygen, namely [4+2], ene and [2+2].[153]

Singlet oxygen can be either generated chemically, for example by combination of H_2O_2 and NaOCl,[154] or *via* sensitization by a photocatalyst. For the latter approach, only atmospheric or pure oxygen, sunlight and a sensitizer with a matching triplet energy are necessary. The photochemical generation of singlet oxygen and its application in chemistry therefore may be

regarded as one of the most ecological transformations. Oxidations with singlet oxygen are also typical in biological systems due to the presence of air and sunlight as well as the many possible sensitizers found in plants (chlorophylls, porphyrins, tannins etc.).[155] In a laboratory setting, typical sensitizers are rose bengal (RB), fluorescein, eosin blue, methylene blue or tetraphenylporphyrin (TPP).[156]

Table 4. Oxidation of the furan to the desired γ-hydroxy butenolide **139** and its potential open form acid **220**.



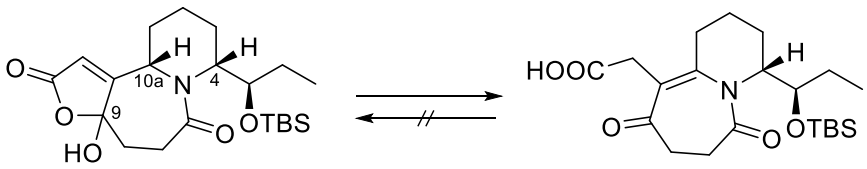
138 **139** **220**

entry	reagents	solvent	T [°C]	t [h]	yield **139**
1	Br_2	MeOH	20	16	decomposition
2	NBS, pyridine	THF	20	16	decomposition
3	mCPBA	CH_2Cl_2	0	5	no conversion
4	H_2O_2, AcOH	THF	0	5	no conversion
5	$NaClO_2$, NaH_2PO_4	*t*BuOH, H_2O	0	3	<20%
6[a,b]	TPP, DIPEA	CH_2Cl_2	−78	1	19-66%
7[a,b]	RB, DIPEA	MeOH	−78	1	61%
8[a,c]	RB, DIPEA	MeOH	−78	1	83%

[a] all singlet oxygen reactions were carried out with 1 mol% sensitizer, 5 eq. base, under irradiation with a 419 nm lamp. [b] the reaction solution was bubbled with pure O_2 during the reaction. [c] the reaction solution was bubbled with air instead.

Our first attempts, based on previous results,[77] employed 1 mol% TPP as a sensitizer in dichloromethane (Table 4, entry 6).[157] While some batches gave yields of up to 66%, other attempts were lower yielding and only 19% product were isolated. After several experiments, the inconsistency of the yield was found to be a tautomerization of the double bond, forming the open keto-acid **221**, which was isolated during column chromatography by flushing with ethyl acetate and acetic acid. Whereas the overall yield as the sum of both products was consistent, the product distribution varied a lot for different batches. Neither could the reason

for this tautomerization be clearly assigned nor were we able to prevent it from happening. Finding an application of tautomeric keto-acid **221** by regeneration of the hydroxy lactone **139** under a variety of acidic or basic conditions or reduction failed due to the high stability of the compound.



139 **221**

Scheme 42. Tautomerization of the γ-hydroxy lactone **139** during the singlet oxygen reaction with TPP in CH_2Cl_2 (Table 4, entry 6).

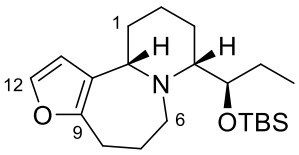
Instead, we continued screening other sensitizers and solvents and found a higher reproducibility by using RB in methanol (Table 4, entry 7).[158] Under these conditions, no tautomer **221** was formed, potentially due to the more polar solvent. As the yield of 61% still was unsatisfying for this commonly high-yielding reaction, further optimization was performed. Another break-through was achieved by applying air instead of pure oxygen, resulting in higher yields under otherwise identical reaction conditions (entry 8).
The singlet oxygen reaction exhibited a good diastereoselectivity (*d.r.* = 9/1), presumably forming the product preferentially, which has its hydroxy group at C-9 pointing up similarly to the protons at C-4 and C-10a. The presence of the minor diastereomer was however inconsequential, as the succeeding reaction step would converge the chiral center at C-9.

5.2.2. Studies on the tricyclic amine

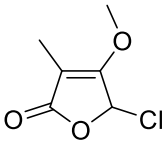
In contrast to the previously described amide **138**, amine **219** already exhibits the correct oxidation state of the azepane at position C-6 and therefore seemed a more promising compound. However, it turned out to be unstable and degraded rapidly at room temperature. Nonetheless, several attempts for further transformations were performed.
Hydrogenation of the furan[159] to obtain the saturated ether derivative failed and aside from decomposition, only starting material was reisolated (Table 5, entry 1). Functionalization at the C-12 position was attempted with the ultimate goal of coupling with a tetronate unit. A C−H activation by iridium catalyzed borylation with B_2pin_2 proposed by *Hartwig* gave no

conversion.[160] Generating the electrophilic coupling partner by bromination with NBS or elemental bromine[161] resulted in rapid decomposition (entry 3). As the proton at C-12 should be the most acidic, quantitative deprotonation with *n*BuLi in THF was performed.[162] Again, this led to complete decomposition and neither bromination nor nucleophilic substitution with the chlorinated tetronate unit **222** were successful (entry 5 and 6). Lastly, a direct coupling of the furan with a chlorinated tetronate unit *via Friedel-Crafts* alkylation with $ZnCl_2$ or $AlCl_3$ as *Lewis* acids[163,164] was attempted and led to rapid decomposition of the starting material.

Table 5. Attempts on the transformation of furan **219** and coupling with tetronate **222**. (dtbpy = 4,4'-di-*tert*-butyl bipyridine, cod = 1,5-cyclooctadiene)



219

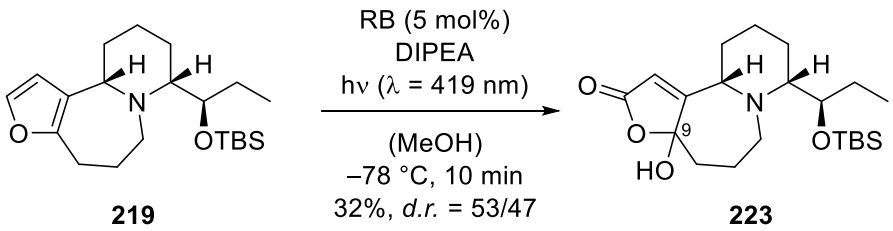


222

entry	reagents	solvent	T [°C]	t [h]	result
1	H_2, Pd/C	EtOAc	20	48	no conversion
2	$[Ir(cod)OMe]_2$, B_2pin_2, dtbpy/Me_4phen	THF	20	18	no conversion
3	NBS	$CHCl_3$	20	3	decomposition
4	Br_2	$CHCl_3$	20	3	decomposition
5	*n*BuLi, then Br_2	THF	−78	2	decomposition
6	*n*BuLi, then **222**	THF	−78	2	decomposition
7	**222**, $ZnCl_2$/$AlCl_3$	CH_2Cl_2	20	3	decomposition

With all attempts on the functionalization at C-12 failing, focus was laid on the oxidation of the furan. Bromine-based oxidations were ruled out due to the failure of these conditions for amide **138**. A *Pinnick-Lindgren*-derived oxidation with $NaClO_2$ also gave decomposition. Treatment with one equivalent mCPBA was expected to produce the *N*-oxide rather than an oxidized furan, resulted however in a complex mixture, from which no single characteristic compound could be isolated.

Interestingly, the previously optimized singlet oxygen conditions proved somewhat compatible. Amines are known to efficiently quench $^1O_2$,[165,166] nonetheless full conversion could be achieved with a higher catalyst loading of 5 mol%. Overall, the reactivity of amine **219** was higher than for the previously studied amide **138** and full conversion was obtained after ten minutes. Additionally, low diastereoselectivity was observed for this oxidation to the γ-hydroxylated lactone **223**, much unlike the singlet oxygen reaction of amide **138**.



Scheme 43. Successful singlet oxygen reaction on the amine **219**, giving the γ-hydroxy lactone **223** in low yield as a mixture of diastereomers.

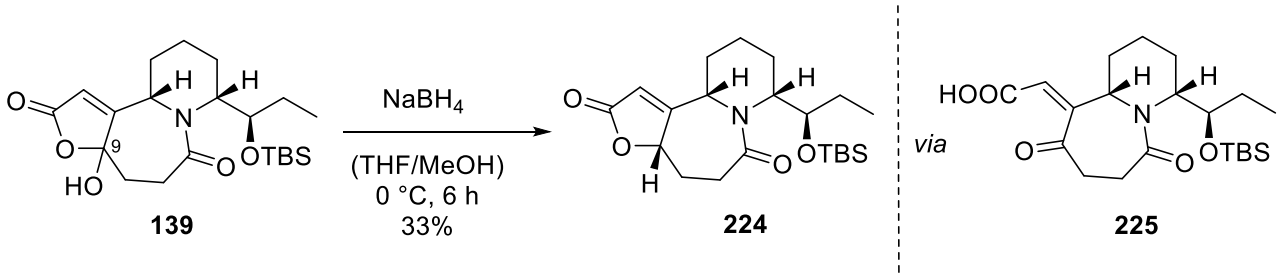
Due to the low stability of the intermediate amine **219** and its unsurprisingly low yields for the singlet oxygen reaction, further research seemed less promising. Several attempts for further transformations of lactone **223** were performed, trying to reduce the hemiacetal at C-9 or achieve an elimination to the enol ether. No conditions could be found to successfully convert the hydroxy lactone **223** and this alternative route was abandoned.

5.2.3. Conversion of the γ-hydroxy lactone to the 1,4-diol

After the efficient oxidation of lactam **138** with a singlet oxygen reaction to γ-hydroxy lactone **139**, further transformations were necessary to obtain a key intermediate towards stemokerrin (**27**). Primarily, a methyl group at the α-position of the lactone had to be installed in a diastereoselective fashion. To facilitate this, reduction of the hemiacetal and the α,β-unsaturated lactone was envisioned prior to methylation of the lactone *via* its enolate.

Initial studies for the reduction of the hemiacetal with $NaBH_4$ in a mixture of THF and MeOH were promising and gave the reduced lactone **224** (Scheme 44).[77] The formal deoxygenation reaction proceeded with excellent diastereoselectivity and a single diastereomer was isolated. Since a mixture of diastereomers has been employed in the reduction and only one diastereomer was isolated, a stereoconvergent pathway seemed logical. The reduction likely proceeds *via* the open form ketone **225** and the hydride is delivered from the sterically less

congested front side, leading, after cyclization, to selective formation of the drawn diastereomer.

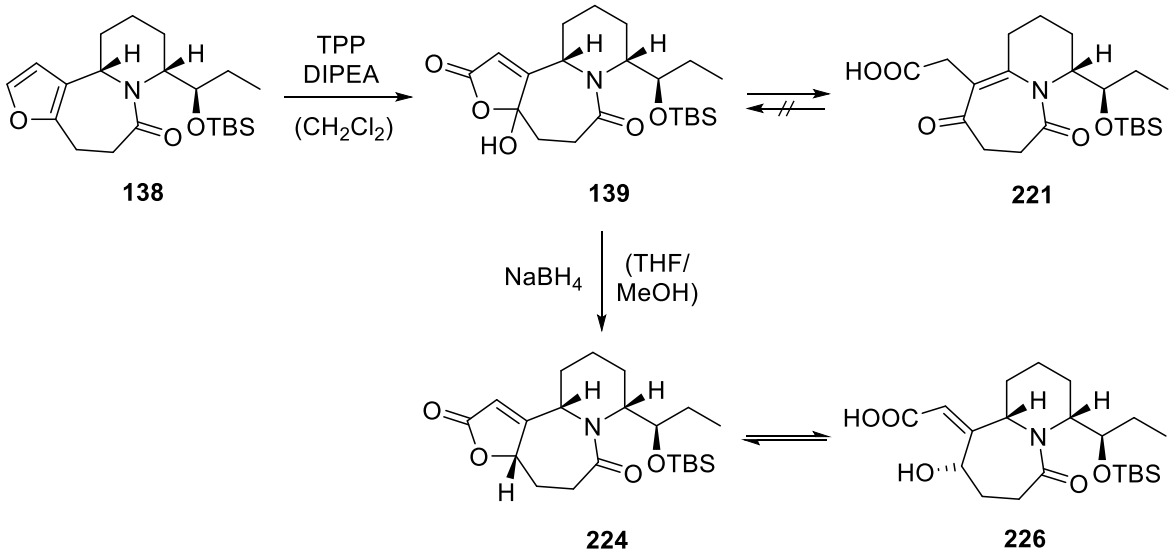


Scheme 44. Formal deoxygenation reaction *via* reduction of the hemiacetal at C-9.

However, the yield of the isolated product was consistently low despite the good crude yield, indicating problems during purification. Similar to the singlet oxygen reaction, a side product could be obtained by flushing the column with EtOAc and acetic acid which turned out to be the hydrolyzed hydroxy lactone **226** (Scheme 45).

On the one side, during the singlet oxygen reaction with TPP, hemiacetal **139** performed a concomitant and irreversible tautomerization to the inert keto-acid **221**. A potential driving force for this side reaction is the formation of a tetrasubstituted double bond and its conjugation to the ketone. The open form could not be recycled by ring closure.

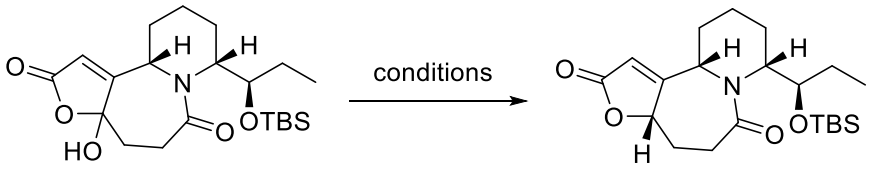
On the other hand, after diastereoselective reduction to lactone **224** a similar, open form acid **226** was isolated. In contrast to keto-acid **221**, no tautomerization was observed and the alcohol could be recycled by lactonization with AcOH or pTsOH (Table 6, entry 1).



Scheme 45. Irreversible tautomerization and ring opening during the singlet oxygen reaction of furan **138** with TPP. Reversible hydrolysis during the reduction of γ-hydroxy butenolide **139**.

To increase the yield of the reduction, conditions to prevent the hydrolysis were investigated. Reductions with $NaBH_4$[167] or Et_3SiH[168] in TFA were unsuccessful and gave no conversion (Table 6, entry 2 and 3). The use of $CeCl_3 \cdot 7H_2O$ as an additive in the standard $NaBH_4$ reduction showed great promise. Using 1.2 eq. of *Lewis* acid, the yield increased dramatically but the tedious work-up led to some losses and an overall yield of 61%. Lowering the amount of $CeCl_3 \cdot 7H_2O$ to 20 mol% gave better but somewhat inconsistent yields. The ideal conditions were found to be 50 mol%, leading to the lactone **224** in good yields with no formation of the open form acid **226**.

Table 6. Screening of conditions for the reduction of γ-hydroxy lactone **139** to the lactone **224** without hydrolysis to the open form acid **226**.



139 **224**

entry	reagents	solvent	t [h]	yield **224**
1	$NaBH_4$	THF/MeOH	6	33% + 8%[a]
2	$NaBH_4$	TFA	18	no conversion
3	Et_3SiH	TFA	18	no conversion
4	$NaBH_4$ + 1.2 eq. $CeCl_3 \cdot 7H_2O$	THF/MeOH	2	61%
5	$NaBH_4$ + 0.5 eq. $CeCl_3 \cdot 7H_2O$	THF/MeOH	2	83%
6	$NaBH_4$ + 0.2 eq. $CeCl_3 \cdot 7H_2O$	THF/MeOH	2	66-81%

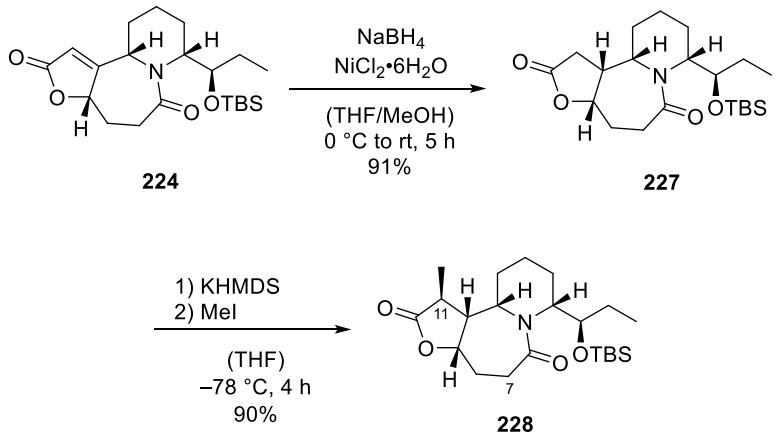
[a] another 8% product were isolated after flushing with EtOAc and AcOH (1%), spontaneous lactonization of the hydrolyzed acid **226** with residual AcOH over three days and a second purification.

Next, the reduction of the α,β-unsaturated lactone was necessary to subsequently install the methyl group at C-11. Just like the conjugated reduction of coupling product **137** (Scheme 39), employing a Ni_2B reduction on the unsaturated lactone **224** resulted in a smooth and clean formation of lactone **227**. Complete diastereoselectivity was observed in agreement with the previous experiments and only one diastereomer was isolated (Scheme 46).

Introduction of the methyl group proved to be rather troublesome due to large inconsistencies of yields. After quantitative deprotonation with KHMDS, the enolate was quenched by addition of MeI to obtain lactone **228**. While some batches gave yields of up to 90%, other times only 25% product alongside 20% reisolated starting material could be obtained. Extensive screening of different bases like LDA, LHMDS or NHMDS and different batches of MeI were performed but all proved inferior to the previously employed conditions using KHMDS and MeI.[77] The inconsistencies could ultimately be assigned to the quality of the base. Despite the same concentration and the same supplier, some batches of KHMDS (0.5 M in $PhCH_3$) led to quick decomposition of the starting material while others gave exclusive

deprotonation and no decomposition. Ultimately, these problems could be completely prevented by small-scale test reactions for each batch of KHMDS prior to up-scaling. This strategy led to consistently high yields for the methylation.

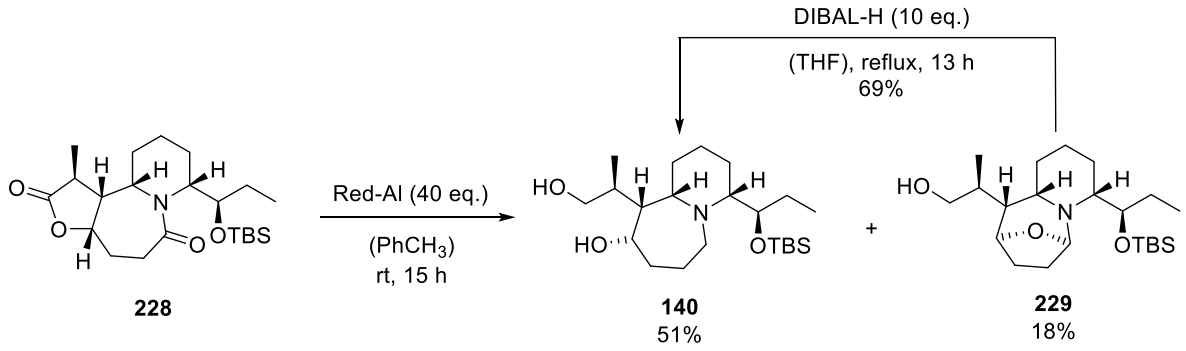
The overall reaction proceeded with excellent chemoselectivity, exclusively methylating the more acidic C-11 α to the lactone without any transformation occurring at the C-7 position α to the lactam. Additionally, only monomethylation was observed and formation of a single diastereomer occurred, similar to the previous transformations.



Scheme 46. Diastereoselective reduction and methylation to lactone **228**.

The tricyclic compound **228** already contained all stereogenic centers found in the target molecule stemokerrin (**27**) (C-1', C-4, C-10, C-10a, C-11) and a crystal structure ensured all centers were correctly assembled.[37,77] Subsequent reduction of the lactam to form the tertiary amine found in all pyrido[1,2-*a*]azepines was the next step. Attempts to selectively reduce the lactam in presence of the lactone moiety with BH_3·THF or transformation to the thioamide with *Lawesson's* reagent failed.[77] Instead, a global reduction to the 1,4-diol **140** and subsequent reoxidation of the hydroxy groups was envisioned.

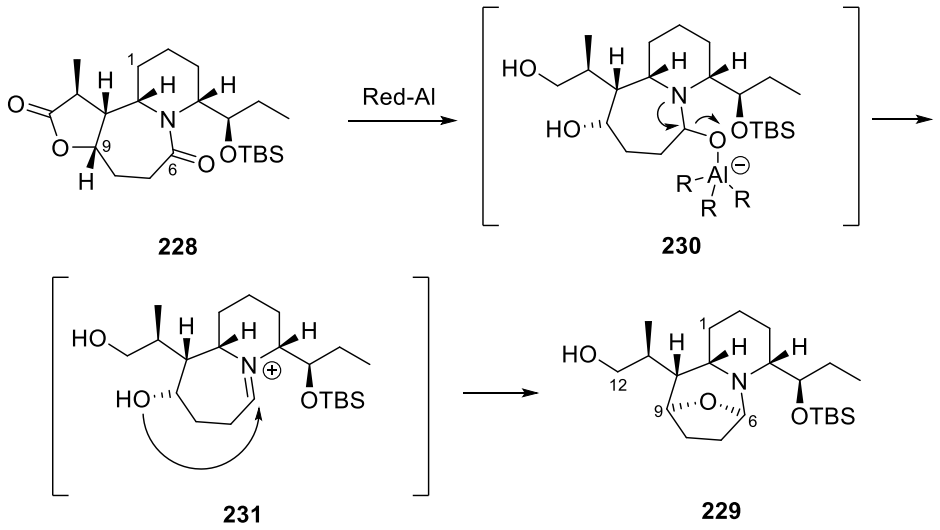
For the complete reduction, a total of four hydride equivalents had to be transferred and a large excess of reducing reagent was therefore employed. Only small amounts of desired diol **140** were isolated after reduction with $LiAlH_4$ whereas treatment with Red-Al gave higher yields and after optimization of temperature, equivalents and concentration, up to 51% product were obtained (Scheme 47). Still, the overall yield was surprisingly low and after some investigations, a side product was isolated in 18% yield. NMR analysis revealed this side product to be the cyclic ether **229**.



Scheme 47. Reduction of the lactam **228** to the 1,4-diol **140**. The cyclic ether **229**, formed as a side product, was successfully converted to the diol by DIBAL-H reduction.

A mechanistic proposal for the formation of the cyclic ether **229** is depicted in Scheme 48. If the reduction of the lactone occurs prior to the lactam reduction, the free hydroxy group at C-9 is already present during the hydride delivery onto the lactam. After attack of the first hydride equivalent onto the lactam moiety, an intermediate hemiaminal **230** is formed, which collapses into iminium ion **231** and aluminum alkoxide. In case of the iminium ion being reduced by a second hydride equivalent from Red-Al, the desired diol **140** is formed. Alternatively, an intramolecular cyclization on the iminium ion by the hydroxy group at C-9 can occur, instead leading to the ether side product **229**.

The formation and the structure of this cyclic ether is quite interesting. While no Stemona alkaloid with a C-6/C-9 ether bridge is known, several pyrido[1,2-*a*]azepine alkaloids possess a similar C-1/C-9 bridge, such as oxystemokerrin,[37] oxystemokerrilactone[169] or stemocurtisine (**25**).[170] Particularly the latter example has seen some previous attempts of synthesis and most failed to generate the aforementioned ether bridge. The isolation of cyclic ether **229** proves the potential for cyclization by *Lewis* acid mediated substitution of an oxygen-based leaving group. This knowledge might be extended to the synthesis of other Stemona alkaloids and help in the synthetic access of stemocurtisine among others.

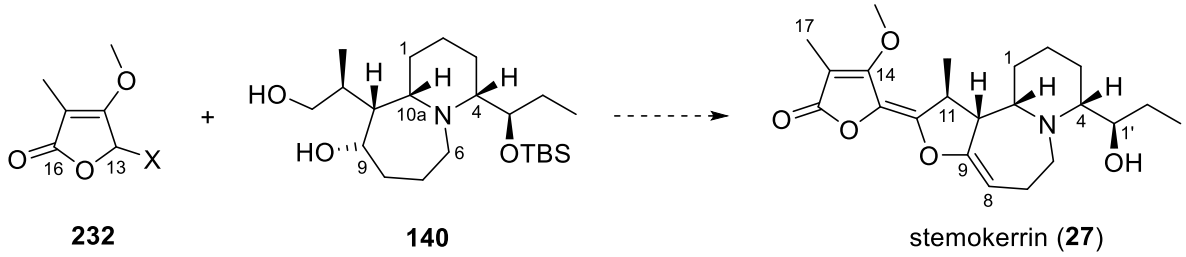


Scheme 48. Mechanistic proposal for the formation of cyclic ether **229** *via* intramolecular cyclization.

As the formation of ether **229** could not be prevented, potential applications were investigated. While a transformation of the free hydroxy group at C-12 and a late-stage liberation of the tertiary amine seemed promising at first, the ether bridge turned out to be exceptionally stable and harsh reduction conditions incompatible with other functional groups would be required. After many typical reducing reagents including Red-Al, $NaBH_4$, $LiAlH_4$, $NaBH(OAc)_3$ and $NaCNBH_3$ failed to give any conversion, some 1,4-diol **140** was isolated after treatment with DIBAL-H. To obtain full conversion, however, the reaction had to be stirred at reflux for 13 h (Scheme 47). This procedure proved too harsh for a late-stage transformation but it did allow for the recycling of the otherwise unusable ether side product and increased the overall yields of the diol.

In conclusion, a synthetic route was developed that gave access to the key intermediate diol **140** in a convergent synthesis starting from D-pipecolic acid (**133**) and methyl 2-furoate (**130**) in a sequence of 24 total steps and a longest linear sequence of 18 steps. The product of this sequence, the diol **140**, showcases all five stereogenic centers found in stemokerrin (**27**) and contains all carbon atoms except for a missing tetronate unit, which was planned to be installed as the next step.

The following chapter will deal with the synthesis of this butenolide fragment and its derivatives before a discussion of the coupling of both fragments to obtain the entire carbon skeleton of most pyrido[1,2-*a*]azepine alkaloids and finally attempts towards stemokerrin.



Scheme 49. The envisioned synthesis of stemokerrin by combining the diol **140** with tetronate derivative **232**.

6. Synthesis of tetronic acid derivatives

6.1. The tetronic acids

The group of tetronic acids, a subclass of the butenolides,[171] possess a 4-hydroxy-2(5*H*)-furanone core with up to two substituents at the 5-position and one at the 3-position. A second substituent would remove the ability of tautomerization from the keto form **234** to the enol form **233** and therefore dramatically change its chemistry.[172] The structural motif of a tetronic acid can be found in many different natural products of varying complexity, the most common examples being ascorbic acid (vitamin C, **235**)[173] and penicillic acid (**236**). Biological activity profiles of tetronic acid derivatives are broad and include, but are not limited to, antibiotic, anticoagulant, antifungal, insecticidal and anti-inflammatory properties.[174]

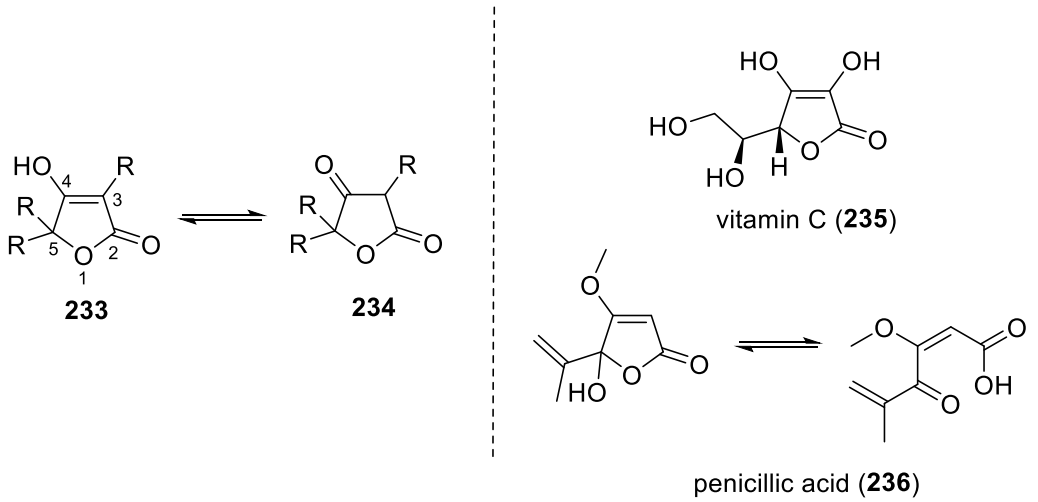
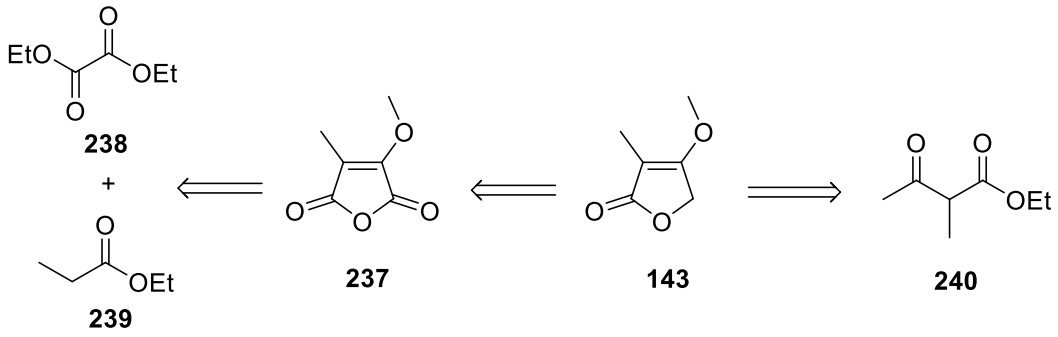


Figure 10. Tautomerization of the tetronic acid class from the enol to the keto form (left). Some examples for tetronic acid derivatives (right).

For our purposes, a methyl α-methyltetronate (**143**) was required for the coupling with diol **140**. The alkylation of the oxygen atom at the 4-position prevented the potential tautomerization and simplified further steps after installation of the tetronate unit from its 5-position into the natural product.

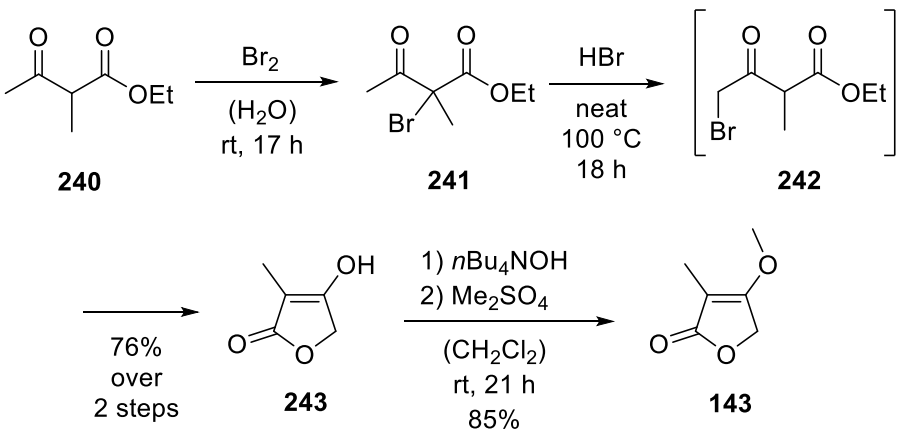
Two primary synthetic routes are reported in the literature for the synthesis of methyl α-methyltetronate (**143**). One of them proceeded *via* stereoselective reduction of the anhydride **237**, which itself was generated over several steps starting from a *Claisen* condensation of

ethyl propionate (**239**) with diethyl oxalate (**238**) (Scheme 50, left).[175] This route has the additional benefit that the stereoselective reduction of the anhydride can also lead to an interesting γ-hydroxylated tetronate as a product under different conditions.[176]



Scheme 50. Two possible routes for the retrosynthesis of the methyl α-methyltetronate (**143**).

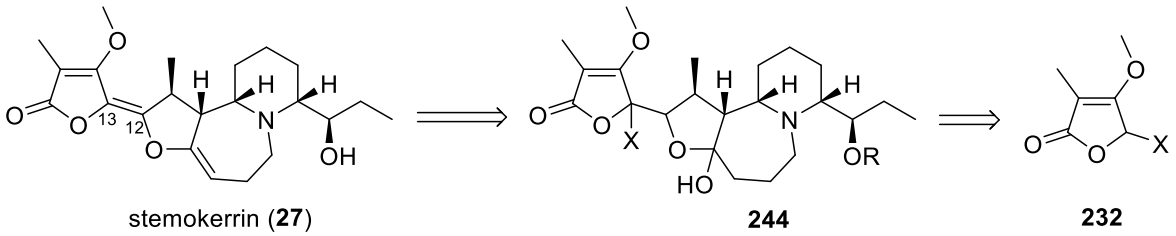
The second route on the other hand is very established and has been known for over 100 years (Scheme 50, right).[172] Due to its high yields, excellent reproducibility and the short and easy synthetic route, it was deemed superior and was reproduced. Starting from the commercially available ethyl 2-methyl acetoacetate (**240**), an autocatalytic bromination in water at the thermodynamically preferred 2-position was performed (Scheme 51).[177] The crude mixture of bromide **241** was subsequently mixed with catalytic amounts of HBr and heated to 100 °C to bring about a migration of the bromine atom, generating the intermediate **242**.[178] A spontaneous cyclization with concomitant loss of ethyl bromide gave the butenolide **243**, which exclusively existed as the drawn enol tautomer.[179] Lastly, quantitative deprotonation by tetrabutylammoniumhydroxide and subsequent methylation of the alkoxide salt with dimethyl sulfate[180] gave the methyl α-methyl tetronate (**143**) in 65% yield over three steps.



Scheme 51. Synthesis of the reported methyl α-methyl tetronate (**143**) from commercial β-ketoester **240**.

6.2. Functionalization of the methyl α-methyl tetronate

Implementation of the tetronate unit by γ-deprotonation and nucleophilic attack is an established procedure.[181,182] As stemokerrin exhibits a C-12/C-13 double bond, an additional substituent at the γ-position of the tetronate that could be eliminated later was considered beneficial (Scheme 52). Therefore, a small library of monosubstituted tetronates was synthesized to facilitate the late-stage generation of this double bond.



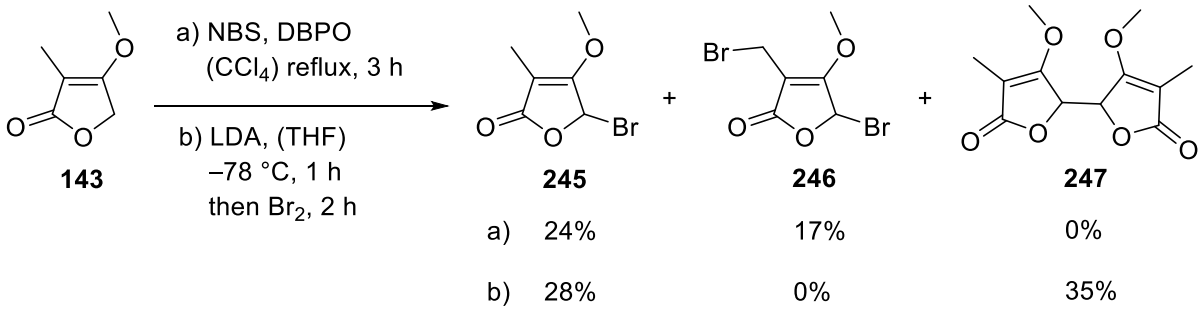
Scheme 52. Retrosynthesis of stemokerrin and the potential elimination of a substituent at the position C-13.

In a first step, pseudohalides were implemented as substituents, acting as potential leaving groups. These derivatives could either be directly implemented into the natural product or act as intermediates for further transformations of the tetronate. Due to its high reactivity towards substitution, a brominated tetronate **245** was opted as a starting point for diversification.

Bromination at the allylic position, the *Wohl-Ziegler* bromination, is quite established for tetronates[183] and even reported for methyl α-methyl tetronate (**143**).[184] Applying these conditions, NBS and DBPO in refluxing tetrachloromethane, did not lead to clean and exclusive formation of the monobrominated compound **245** (Scheme 53, conditions a). Instead, large quantities of the dibrominated product **246**, stemming from an additional bromination in the second available allylic position, were isolated. Optimization by applying different bromine sources, solvents or reaction times led to changes in the product distribution or incomplete conversion, but the overall yield of the desired monobrominated product could not be increased beyond 24%. Additionally, low reproducibility and the use of hepatotoxic tetrachloromethane discouraged the use of these conditions.

Alternatively, deprotonation of the tetronate **143** with LDA and reaction with a corresponding electrophile can also provide the brominated product.[185] While these conditions proved ideal for many other substituents discussed later, quenching with elemental bromine was not optimal (Scheme 53, conditions b). For one, the reaction never proceeded to full conversion despite the excess of base and bromine. Secondly, pronounced dimerization to compound **247**

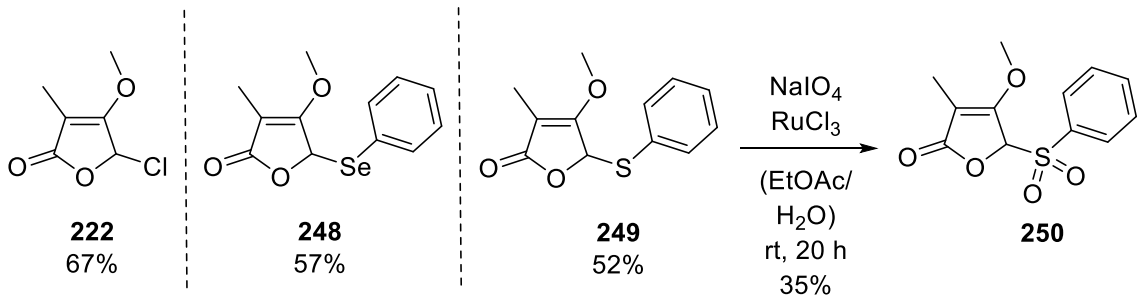
occurred. Lowering the concentration of the reaction or increasing the equivalents of bromine did not help to mitigate this problem. But as the standard tetronate **143** was readily available in large quantities, these low yields were ultimately accepted and the brominated tetronate **245** could subsequently be subjected to nucleophilic substitution to obtain other derivatives.



Scheme 53. Bromination of the tetronate to the desired product **245** and formation of side products.

The strategy of deprotonation of the tetronate with LDA and subsequent reaction with an electrophile was extended to other tetronate derivatives. The chlorinated compound **222** was obtained in good yields by treatment of the deprotonated tetronate with pTsCl (Scheme 54). In contrast to the low yield and pronounced dimerization of the brominated species, the chlorination gave no dimeric side product, indicating a higher stability but lower electrophilicity of the chlorine derivative.

Both the phenyl selenide **248** and the phenyl sulfide **249**, generated by reaction with PhSeBr and $(PhS)_2$ respectively, were obtained in good yields under standard conditions. Oxidation of the sulfide with mCPBA led to a mixture of sulfoxide and sulfone, while harsher conditions with $RuCl_3$ and $NaIO_4$ gave full oxidation to the sulfone **250**, albeit in lower yield.

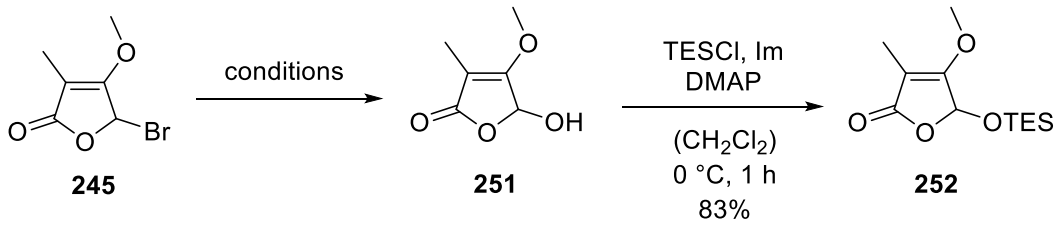


Scheme 54. Synthesis of γ-substituted tetronates by deprotonation of tetronate **143** with LDA and reaction with pTsCl, PhSeBr and $(PhS)_2$, respectively.

An oxygenated tetronate presented a good opportunity to modify the reactivity at later stages and was a promising substrate. Instead of the reduction protocol of the anhydride, γ-oxygenation of the unfunctionalized tetronate was attempted. The most common condition for the oxygenation at the γ-position of butenolides is the treatment with DBU in MeCN under an oxygen atmosphere.[186] Despite many attempts at different temperatures, no conversion for tetronate **143** was ever obtained under these conditions. Many other oxidative conditions like IBX[65] or the *Riley* oxidation[187] similarly failed to give any conversion.

Instead, highly electrophilic brominated tetronate **245** was employed for further substitution and at first, hydrolysis was attempted. Interestingly, mild basic conditions with LiOH (Table 7, entry 1) or $NaHCO_3$ (entry 2) in a mixture of water and THF only led to low yields while the harsher KOH conditions gave better results (entry 3). Treatment with AgOAc led to good yields, work-up was however sluggish due to the precipitated AgBr. A more convenient and superior procedure was the hydrolysis with TFA, giving the desired alcohol **251** in good yields (entry 5). Subsequent protection with a TES group to silyl ether **252** proceeded uneventfully.

Table 7. Optimization for the hydrolysis of brominated tetronate **245** and subsequent TES-protection.



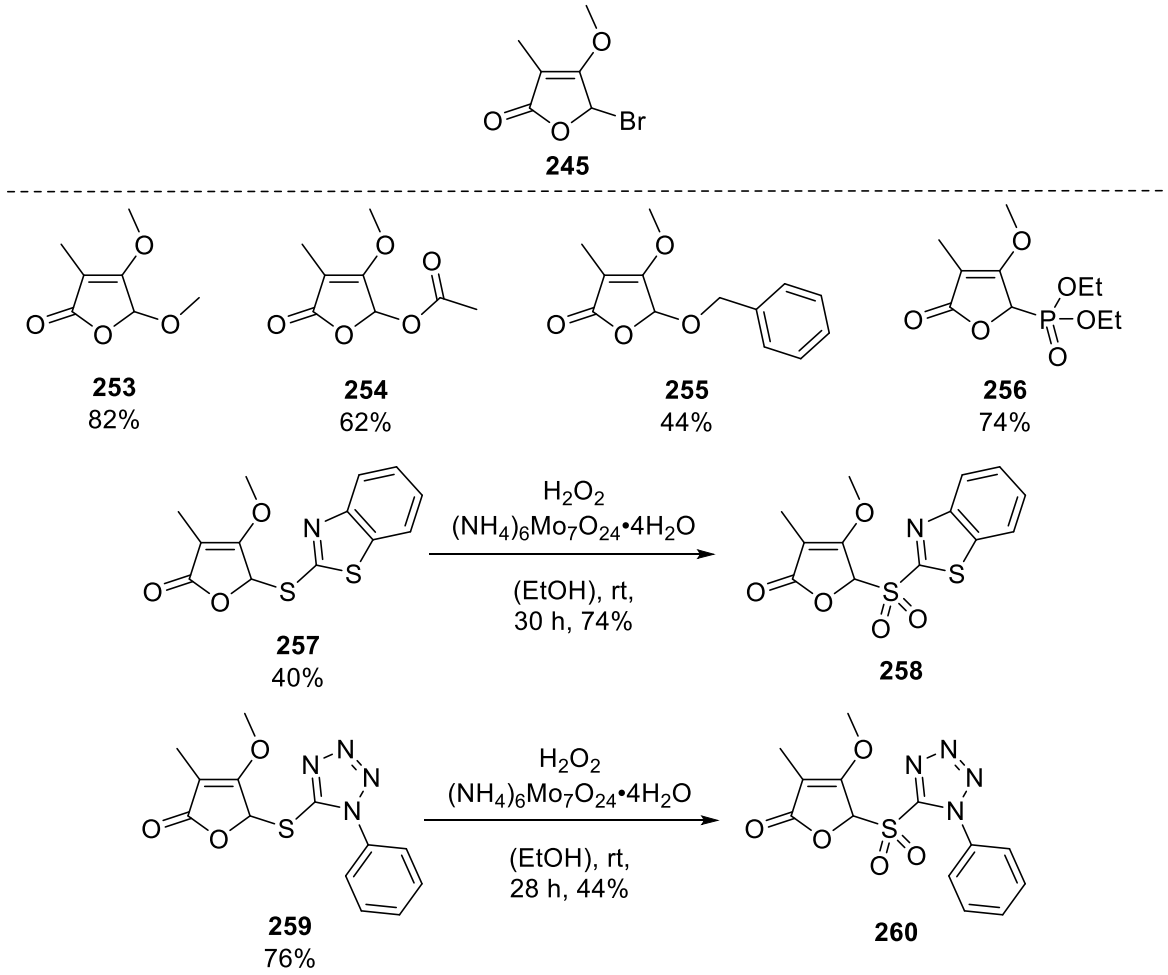
245 **251** **252**

entry	reagents	solvent	t [h]	yield **251**
1	LiOH	H_2O/THF	2.5	traces
2	$NaHCO_3$	H_2O/THF	4	<20%
3	KOH	H_2O/THF	1.5	42%
4	AgOAc	H_2O/ac	3	67%
5	F_3CCOOH	H_2O/THF	3	86%

Several other derivatives were generated by nucleophilic substitution starting from the brominated tetronate **245** (Scheme 55). Methanolysis was performed by dissolving the starting material in methanol in the presence of triethylamine and product **253** was obtained

after 46 h in 82% yield. Introduction of an acetoxy group was achieved with sodium acetate in DMF and after 4 h, 62% of product **254** were isolated. Deprotonation of benzyl alcohol with NaH in THF and subsequent substitution of brominated tetronate gave the benzyl ether **255** in 44% after 2 h.

Other substrates were prepared with subsequent olefination reactions in mind. The *Wittig* substrate was to be generated by substitution with PPh_3 and deprotonation to the ylide with NaOH[188] but instead, a complex mixture containing an unidentified dimer was obtained. The literature-reported *Michaelis-Arbuzov* reaction[66] with $P(OEt)_3$ on the other hand gave the phosphonate **256** for a subsequent *Horner-Wadsworth-Emmons* reaction in 74%. Treatment of the brominated tetronate **245** with 2-mercaptobenzothiazole and 5-mercapto-1-phenyl-1*H*-tetrazole in DMF with K_2CO_3 as base gave thioether **257** and thioether **259**, respectively. Oxidation to the sulfones **258** and **260** worked best with H_2O_2 and catalytic amounts of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ and both substrates for a *Julia-Kocienski* reaction were isolated in good yields.[189]



Scheme 55. Functionalization of the brominated tetronate **245** to an array of tetronate derivatives by nucleophilic substitution.

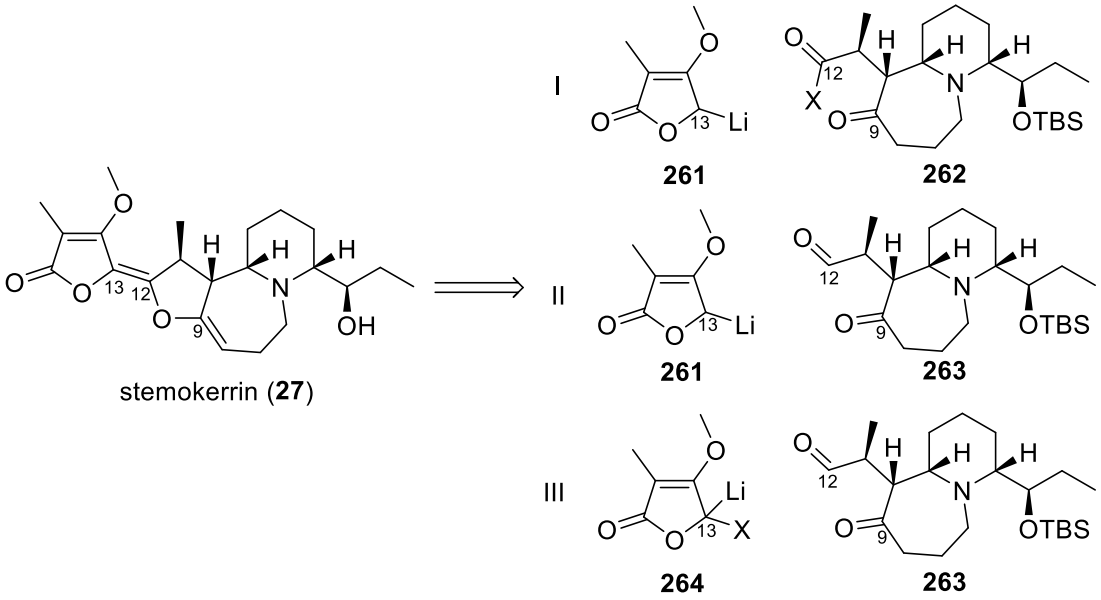
7. Assembly of the stemokerrin skeleton

Both the diol **140** and a selection of different tetronates were at hand and several potential routes presented themselves for further exploration and shall be discussed in the following section. Looking at the target structure of stemokerrin (**27**) and comparing it with intermediate diol **140** revealed, that the oxidation states at C-9 and C-12 together with the C-13 position of the tetronate had to be chosen suitably. Three different approaches were identified as the most promising (Scheme 56). As stemokerrin exhibits an enol ether at C-8/C-9, a ketone oxidation state was chosen accordingly for position C-9 for all three strategies.

The first strategy involved the coupling of an unsubstituted, deprotonated tetronate **261** onto carboxylic acid derivative **262**. Theoretically, in case of a chemoselective attack at C-12, the corresponding product would be a 1,4-diketone. Formal tautomerization of both ketone functionalities and etherification would lead to the required bis-enolether in stemokerrin.

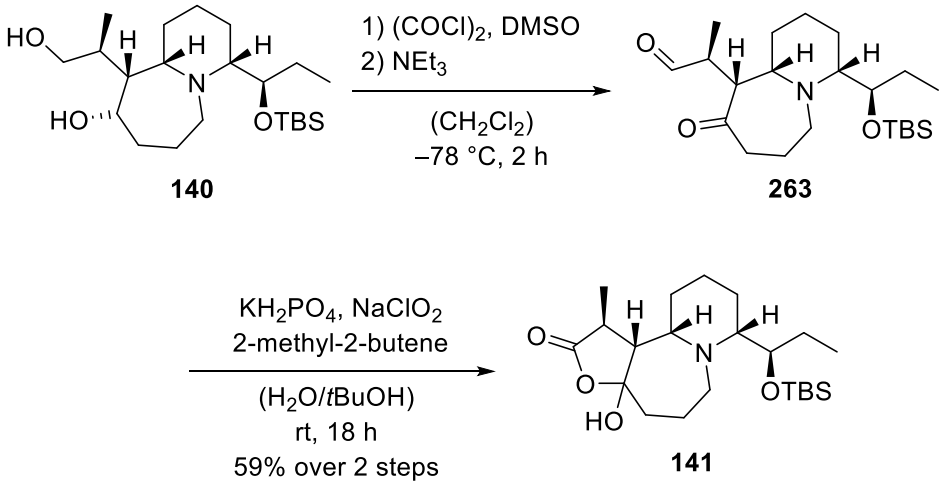
The selective attack on the carboxylic acid derivative was deemed unlikely and instead, a more promising aldehyde functionality was chosen for the following two strategies. For strategy II, the same unsubstituted tetronate **261** was envisioned to attack the aldehyde **263**, forming the previously prepared hemiacetal **144**.[77] The obtained product in turn would require a following oxidation reaction to generate the double bond at C-12/C-13.

Lastly, strategy III already employed an oxidized tetronate at C-13, circumventing the need for a late-stage oxidation. Nucleophilic attack of the deprotonated tetronate **264** at C-12 and formal elimination of HX would provide the enol ether. Problems of this strategy were seen in the lack of stability of the lithiated tetronate and its limited selectivity towards the nucleophilic attack at C-12.



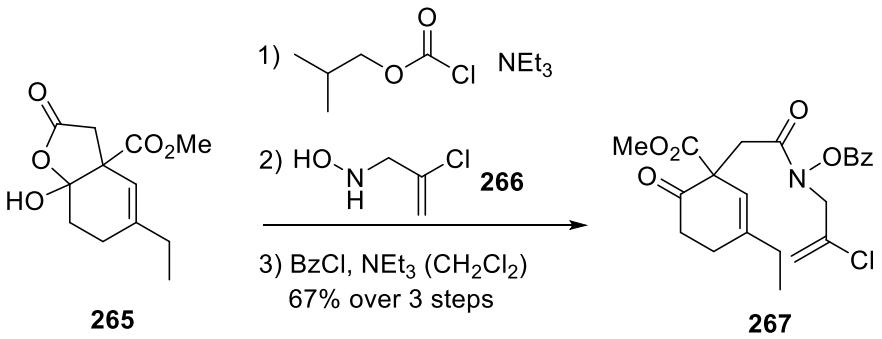
Scheme 56. Retrosynthetic analysis of stemokerrin (**27**) with three potential strategies to assemble the building blocks.

Strategy I was early deemed problematic due to the incompatibility of a ketone at C-9 and the acid derivative at C-12 towards a nucleophilic attack. Nonetheless, as the 1,4-diketo compound was a promising intermediate, some attempts were made and will be discussed briefly. Synthesis of the free acid derivative of **262**, the γ-hydroxy lactone **141**, was previously performed in our laboratories.[77] Starting from 1,4-diol **140**, a *Swern* oxidation was successfully employed to obtain the labile keto-aldehyde **263** (Scheme 57). For the first strategy, further oxidation of the aldehyde under *Pinnick-Lindgren* conditions to the carboxylic acid was performed and only the cyclized γ-hydroxy lactone **141** was isolated, while no open form acid could be detected.



Scheme 57. Oxidation of 1,4-diol **140** to γ-hydroxy lactone **141** *via* keto-aldehyde **263**.

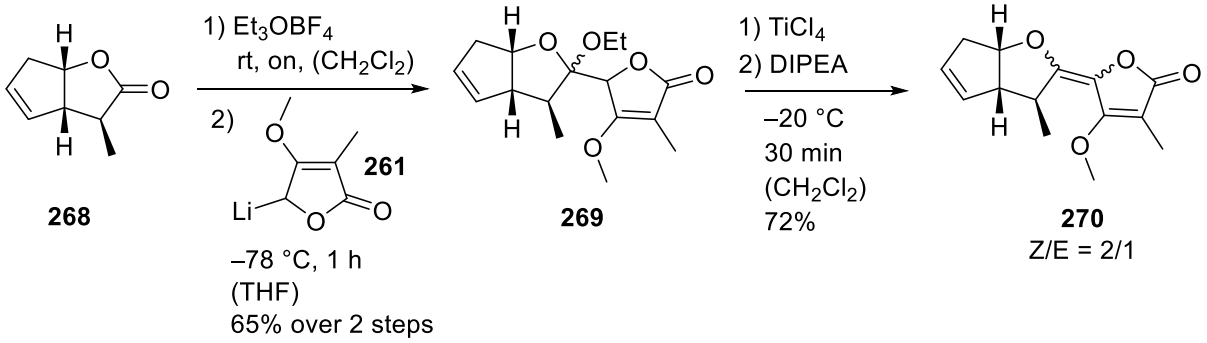
With the acid derivative **141** at hand, *Mayer*[77] tested two different methods to implement the tetronate at the C-12 position according to strategy I. The first route was inspired by a paper of *Zard* on the synthesis of aspidospermidine,[190] which employed a similar coupling onto a γ-hydroxy lactone. Activation of lactone **265** with isobutyl chloroformate and subsequent coupling with hydroxylamine **266** led, after protection with BzCl, to the coupling product **267**. Applying these conditions to lactone **141** and coupling with lithiated tetronate **261** however failed.



Scheme 58. Coupling of a hydroxylamine derivative onto the γ-hydroxy lactone **265** reported in the total synthesis of aspidospermidine.[190]

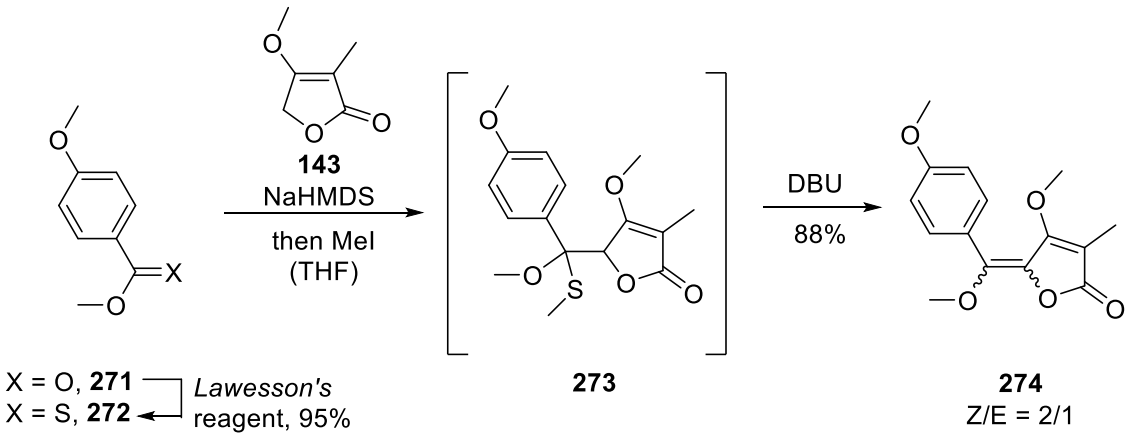
A second approach was based on studies of *Olivo*,[191] who investigated the synthesis of γ-alkylidene tetronates from lactones. In his studies he was able to obtain a broad scope of unsaturated tetronates by treating lactones like compound **268** with *Meerwein's* salt to form an intermediate oxonium species, which reacted with lithiated tetronate **261** to the mixed acetal **269**. Elimination with $TiCl_4$ and DIPEA led to the formation of the desired γ-ylidene

tetronate **270** as a mixture of configurational isomers. Application of these conditions to lactone **141** was unsuccessful.



Scheme 59. Synthesis of γ-alkylidene butenolides from lactones *via* synthesis of acetal derivatives and elimination.[191]

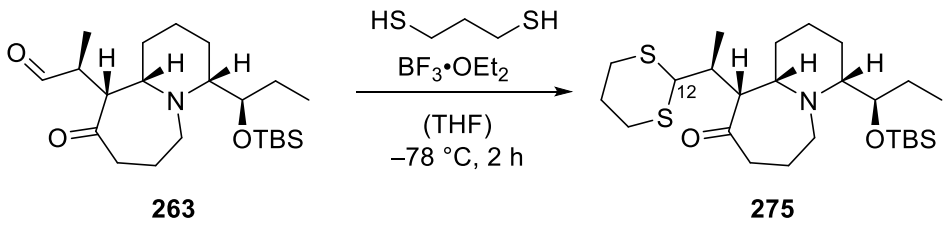
Another reported synthesis for γ-alkylidene butenolides stems from the laboratories of *Huang*.[192] A series of esters was successfully transformed to δ-oxygenated, unsaturated tetronates (Scheme 60). At first, conversion to the thiocarbonyl derivative of an ester, *e.g.* methyl ester **271** to compound **272**, with *Lawesson's* reagent was performed. Coupling with a deprotonated tetronate and treatment with methyl iodide yielded the labile *S,O*-Acetal **273**, which was immediately treated with DBU to induce an elimination and the formation of the double bond in a non-selective manner. The conjugated lactone **274** was obtained in good yields for a library of different substrates, saw however no application to the total synthesis of a Stemona alkaloid.



Scheme 60. Synthesis of δ-alkoxy-γ-alkylidene tetronates from thioesters.

Lastly, attempts towards a 1,4-diketoderivative in analogy to strategy I were made *via* an umpolung. Conversion of an aldehyde to a dithiane, deprotonation of the acidic C−H and coupling with halogenated alkanes, the *Corey-Seebach* umpolung, allows for an overall transformation of an aldehyde to a ketone. In contrast to the nucleophilic addition of a deprotonated tetronate to an aldehyde, which forms an alcohol, this strategy would leave the carbonyl group at C-12 intact and was therefore deemed another option for strategy I.

After oxidation of 1,4-diol **141** to labile keto-aldehyde **263**, conversion to a bis-dithiane was envisioned (Scheme 61). After some optimization, the optimal conditions were found in using 1,3-propanedithiol and $BF_3 \cdot OEt_2$ as a catalyst. It turned out that the ketone was too unreactive and only the aldehyde reacted to form a dithiane ring. Compound **275** was detected by ESI-MS, but intramolecular cyclization after deprotonation at C-12 was deemed an unavoidable side reaction. Additionally, initial studies of simple dithianes as test substrates for the coupling with chlorinated or brominated tetronates were discouraging and the route was discontinued.



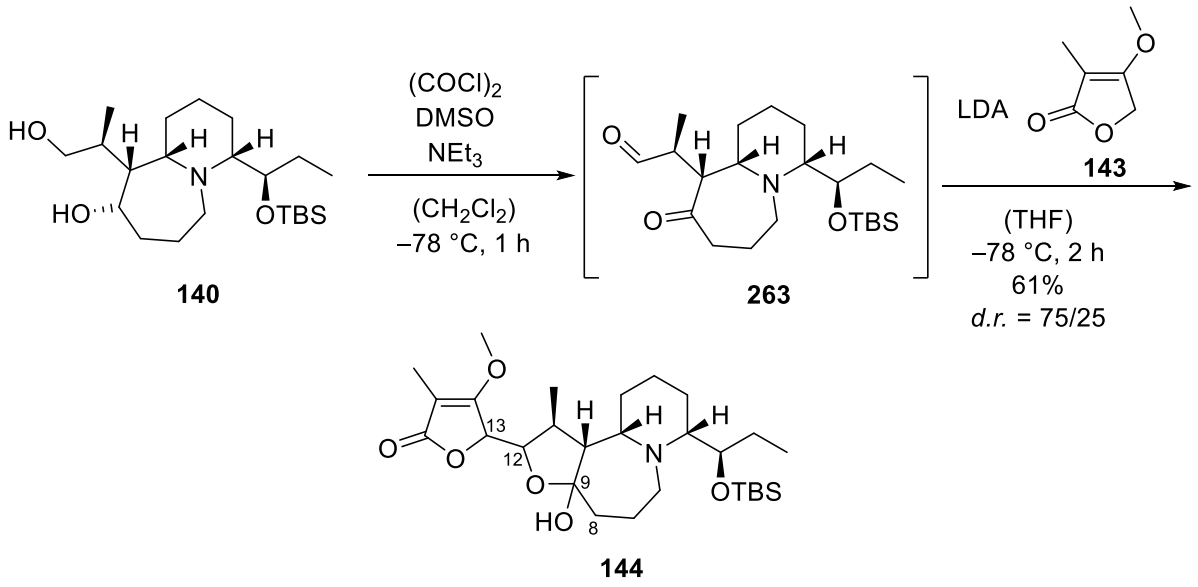
Scheme 61. Conversion of the keto-aldehyde **263** to a dithiane with no reaction of the ketone.

7.1. Implementation of the unsubstituted tetronate

This chapter deals with strategy II according to Scheme 56. At first, the implementation of the unsubstituted tetronate **143** into the keto-aldehyde **263** is discussed. This reaction assembles the complete carbon skeleton of stemokerrin. The rest of this chapter concerns the attempted oxidation reactions to ultimately generate the double bond between C-12 and C-13. Experiments with a functionalized tetronate and its implementation into the keto-aldehyde will then be addressed in the next chapter according to strategy III.

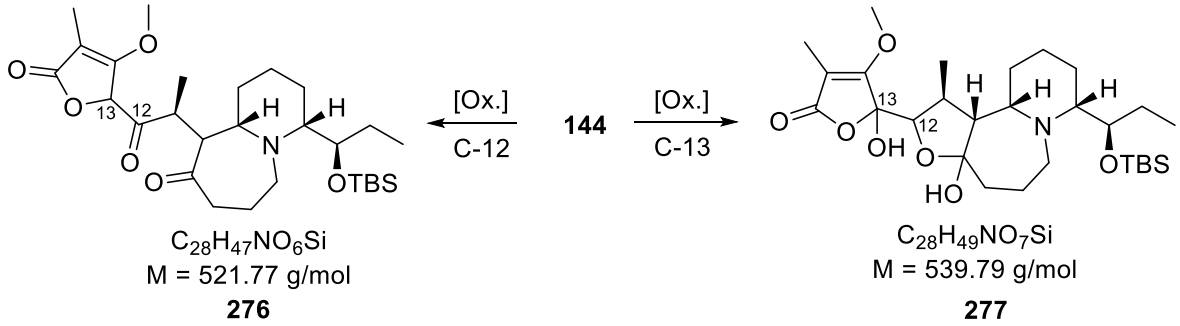
The *Swern* oxidation of 1,4-diol **140** generated the labile keto-aldehyde **263**, which was immediately subjected to the second reaction step. After deprotonation of unsubstituted tetronate **143** with LDA, it subsequently performed a nucleophilic attack at the C-12 aldehyde to generate the alcohol (Scheme 62). Only hemiacetal **144** was isolated after work-up and no

keto-alcohol could be detected in the NMR, indicating a high stability of the five-membered ring. Despite the formation of three new stereogenic centers (C-9, C-12, C-13) and hence the possibility for eight different diastereomers, the hemiacetal **144** was isolated solely as a mixture of two diastereomers (*d.r.* = 75/25).



Scheme 62. Synthesis of the carbon skeleton of stemokerrin by nucleophilic attack of the tetronate **143** on the keto-aldehyde **263**.

Although the elimination of water and the generation of an enol ether at C-8/C-9 was possible at this stage, the corresponding product was deemed too labile for the planed oxidative reactions. Initial attempts with iodine as an oxidant indeed resulted in addition to the electron-rich double bond of the enol ether but not in the desired oxidation at C-12/C-13. Instead, hemiacetal **144** was directly subjected to oxidative conditions and two different results were expected for the oxidation (Scheme 63). Either a ring opening and oxidation of the alcohol at C-12 to a ketone could occur, resulting in the formation of 1,4-diketone **276** of strategy I. Alternatively, a ring opening at C-13 and oxidation of this alcohol to a ketone would lead to a γ-hydroxylated tetronate derivative **277**.



$C_{28}H_{47}NO_6Si$
M = 521.77 g/mol
276

$C_{28}H_{49}NO_7Si$
M = 539.79 g/mol
277

Scheme 63. Two envisioned outcomes for the oxidation of hemiacetal **144**.

Typical γ-oxygenation reactions of tetronic acids are performed by oxidation with air or pure oxygen in acetonitrile in presence of DBU.[186] Some tetronates have even been oxidized by simply standing in contact with air.[193] Hemiacetal **144**, however, was not oxidized with molecular oxygen even at elevated temperatures and long reaction times and only starting material was isolated (Table 8, entry 1). A similar method for oxygenation is the quantitative deprotonation of the tetronate with a strong base at low temperatures under an oxygen atmosphere and reduction of the formed peroxide by triethylphosphite.[194] Likewise, no conversion was observed under these conditions (entry 2).

An oxidation of a tetronate with IBX has been reported and even successfully applied in the synthesis of the Stemona alkaloid didehydrostemofoline. The group of *Overman* performed a twofold oxidation of a secondary alcohol to a ketone and the oxygenation of a tetronate by treatment with IBX in DMSO at elevated temperatures.[65] Applying the reported conditions to hemiacetal **144** gave low conversion and prolonged reaction times resulted in a complex product mixture. Nonetheless, according to the ESI-MS, two defined products were forming. One of the products could be assigned to the enol ether **278**, stemming from the thermal elimination of water. The second product **279** with a *m/z* of 538 could result from the implementation of one oxygen atom and the loss of two hydrogen atoms, in line with a double oxidation. Despite several attempts, this product could not be isolated or detected in NMR.

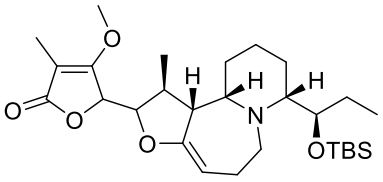
The *Riley* oxidation is an established reaction for the oxidation at allylic positions to generate allylic alcohols.[195] Treatment of hemiacetal **144** with SeO_2 in dioxane resulted in quick conversion, but the detected *m/z* of 522 matched an unexpected oxidation to 1,4-ketone **276** instead of the expected allylic alcohol **277** (Table 8, entry 4). However, no defined product could be isolated and the crude NMR showed decomposition.

Another reported allylic oxidation employed CrO_3 in combination with 3,5-dimethylpyrazole (3,5-DMP) as a ligand.[196] Applying these mild conditions at low temperatures on hemiacetal **144**, however, gave no conversion and only starting material was isolated. The *Jones*

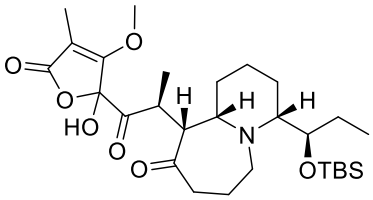
oxidation[197] (entry 6) on the other hand with its strongly acidic conditions due to sulfuric acid gave full conversion. According to the ESI-MS, no oxidation at C-12 or C-13 occurred but rather a deprotection of the alcohol at C-1' and partial oxidation to ketone **280**. While these results were irrelevant for the present study, they revealed the lability of the TBS group towards acidic conditions for the late-stage deprotection.

Lastly, oxidative conditions by *Ma* and co-workers[198] were tested. During the studies of an iodolactonization of allene carboxylic acids, the group observed γ-oxidation of the intermediate tetronates by iodine. Employing their conditions (entry 7) and screening different solvents gave little conversion for hemiacetal **144**, but some traces of compound **281** were detected, indicating an implementation of iodine into the molecule. This species was exclusively detected in the ESI-MS and no conversion was found according to NMR.

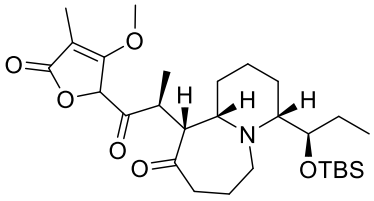
Table 8. Screening for the oxidation of hemiacetal **144**.



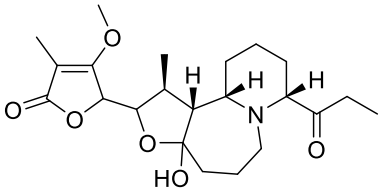
$C_{28}H_{47}NO_5Si$
M = 505.77 g/mol
278



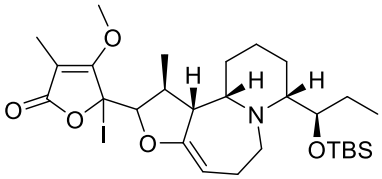
$C_{28}H_{47}NO_7Si$
M = 537.77 g/mol
279



$C_{28}H_{47}NO_6Si$
M = 521.77 g/mol
276



$C_{22}H_{33}NO_6$
M = 407.51 g/mol
280



$C_{28}H_{46}INO_5Si$
M = 631.67 g/mol
281

entry	reagents	solvent	T [°C]	t [h]	result [*m/z*][a]
1	DBU, O_2	MeCN	20-80	96	no conversion
2	LDA or KHMDS, O_2, then $P(OEt)_3$	THF	−78	4	no conversion
3	IBX	DMSO	55	8	506 (**278**), 538 (**279**)
4	SeO_2	Dioxane	60	2	522 (**276**)
5	CrO_3, 3,5-DMP	CH_2Cl_2	−20	4	no conversion
6	CrO_3, H_2SO_4	Acetone/H_2O	20	18	408 (**280**)
7	I_2, LiOAc, O_2	THF/DMF	20	16	traces 632 (**281**)

[a] all compounds were detected with ESI-MS but could not be isolated or characterized with NMR.

The failure of the desired oxidation to occur was partially blamed on the free hydroxy group at C-9 of the hemiacetal. Protection of this group was anticipated to prevent undesired side reactions and facilitate the desired oxidation. Silylation of the hydroxy group worked well with TBSOTf and lutidine whereas TBSCl was too unreactive. Initial oxidation reactions on the protected product **282** were discouraging, as the compound appeared extremely unreactive.

Switching to a smaller TMS protecting group seemed promising and the introduction by TMSCl and imidazole worked well. As expected, the compound **283** was more reactive but also more labile and optimized conditions utilized the crude product, as purification by column chromatography led to pronounced deprotection and reisolation of the starting material.

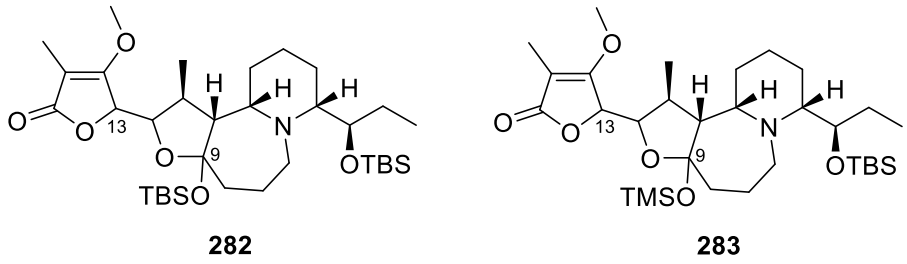
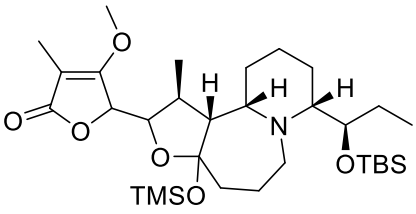


Figure 11. The silylated hemiacetals obtained from the protection of hemiacetal **144**.

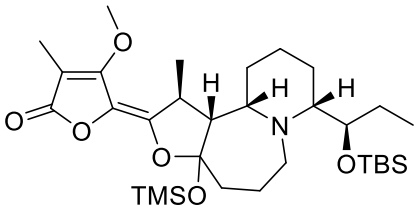
For TMS-protected alcohol **283**, the most acidic position should be at C-13, similar to the tetronate derivatives. The most logical approach was therefore a quantitative deprotonation followed by functionalization. While some bases like KHMDS led to complete decomposition, LDA once again proved compatible with the tetronate unit. Oxygenation attempts employing the previously used molecular oxygen and triethylphosphite combination as well as the reaction with *Davis* oxaziridine **285**[199] failed and gave no conversion (Table 9, entry 1 and 2). The promising oxidation with IBX led to cleavage of the silyl ether to hemiacetal **144** and subsequently to the thermal elimination of water to enol ether **278** (entry 3). Treatment with the peroxyacid mCPBA led to no conversion (entry 4). The oxidation employing elemental iodine behaved drastically different after protection of the hemiacetal. While the unprotected species **144** gave traces of a monoiodinated product **281** (Table 8, entry 7), the TMS-protected variant **283** indicated the formation of the desired dehydrogenated product **284** by a loss of two dalton according to MS. The reaction was initially plagued by low reproducibility but improvements were made by performing a work-up after the initial protection and switching the solvent of the second step from CH_2Cl_2 (Table 9, entry 5) to DMSO (entry 6). Still, the reaction gave complex TLCs and the crude NMRs were messy. Ultimately, the reaction was scaled up to 8 mg, the reaction mixture was purified by column chromatography and every fraction was analyzed. Frustratingly, the NMR spectra of every fraction showed decomposition and their mass spectra contained no defined product except starting material **283** and no trace of oxidized product **284**. The detected mass signal was

therefore ruled either an artefact or the compound too labile to be purified. Either way, the strategy II involving a dehydrogenation or late-stage functionalization at C-13 failed.

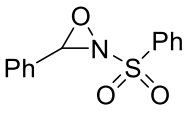
Table 9. Screening of conditions for the oxidation of the TMS-protected hemiacetal **283**.



$C_{31}H_{57}NO_6Si_2$
M = 595.97 g/mol
283



$C_{31}H_{55}NO_6Si_2$
M = 593.95 g/mol
284



Davis oxaziridine
285

entry	reagents	solvent	T [°C]	t [h]	result [*m/z*][a]
1	1) LDA 2) O_2, $P(OEt)_3$	THF	−78	6	no conversion
2	1) LDA 2) *Davis* oxaziridine	THF	−78	4	no conversion
3	IBX	DMSO	60	4	deprotection to **144**, elimination to **278**
4	mCPBA	CH_2Cl_2	20	18	no conversion
5	I_2	CH_2Cl_2	20	3	594 (**284**)
6	I_2	DMSO	20	1	594 (**284**)

[a] all compounds were detected with ESI-MS but could not be isolated or characterized with NMR.

7.2. Assembly of the natural product skeleton with functionalized tetronates

As illustrated in the previous chapter, the strategy of assembling the carbon skeleton of stemokerrin and a subsequent oxidation was unsuccessful. Therefore, synthetic efforts were switched to higher oxidized tetronates as shown in chapter 6.2 and their implementation into keto-aldehyde **263** in accordance with strategy III (Scheme 56). The most promising tetronate candidates for this coupling were compounds with a pre-installed leaving group. Due to their

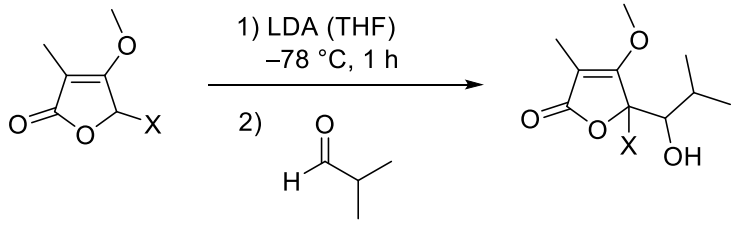
higher reactivity, issues with stability were suspected and a test substrate was designed. The substituted tetronates were first deprotonated with LDA for one hour before isobutanal was added as a model electrophile (Table 10).

As feared, the halogenated tetronates were incompatible with the standard coupling conditions. Brominated tetronate **245** gave complete decomposition after treatment with LDA for one hour (entry 1). For chlorinated tetronate **222**, pronounced degradation was observed and no coupling product could be isolated after addition of isobutanal (entry 2). Both the phenyl selenide **248** and phenyl sulfide **249** were efficiently coupled to the test aldehyde (entry 3 and 4). However, further oxidation and subsequent elimination, although reported for both the sulfoxide elimination[200] and the selenoxide elimination,[80] had been unsuccessfully applied in our laboratories.[77]

An elegant alternative was seen in the application of a γ-hydroxy substituted tetronate, which had to be protected due to the strongly basic conditions. After implementation and deprotection, the compound would possess two free hydroxy groups as hemiacetal derivatives, one at C-9 and one at C-13. The possibility for a twofold dehydration to form the C-8/C-9 and the C-12/C-13 double bonds concomitantly seemed both promising and elegant.

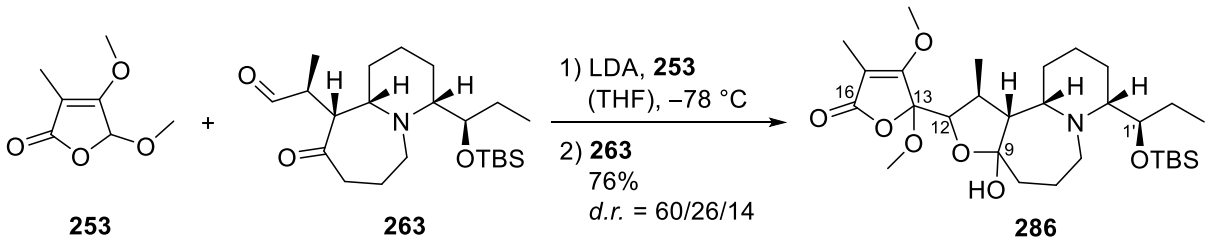
To this end, three different hydroxy protecting groups were installed and tested with isobutanal as a model substrate. Benzylated ether **255**, obtained from the reaction of brominated tetronate with benzyl alcohol, gave some decomposition and could not react with neither the test substrate isobutanal nor the real keto-aldehyde **263**. On the other hand, both methoxy derivative **253** and silyl ether **252** were stable under the basic conditions and successfully performed the nucleophilic attack on the aldehyde.

Table 10. Test reaction of different γ-substituted tetronate derivatives with isobutanal.



entry	substituent X	result
1	Br (**245**)	complete decomposition
2	Cl (**222**)	major decomposition, no coupling
3	SePh (**248**)	72% product
4	SPh (**249**)	73% product
5	OBn (**255**)	slight decomposition, no coupling
6	OMe (**253**)	76% product
7	OTES (**252**)	42% product

Some chemoselectivity issues were expected for the deprotection of the TES-protected alcohol at C-13 in presence of the TBS-protected alcohol at C-1'. Therefore, the methoxy-substituted tetronate **253** was first investigated in the reaction with keto-aldehyde **263**. Just like for the test reaction, the nucleophilic addition on the aldehyde worked well and the desired product **286** was obtained in 76% yield. The diastereoselectivity was lower than for the unsubstituted variant and an inseparable mixture of three diastereomers was obtained.



253 **263** **286**

Scheme 64. Nucleophilic addition of the γ-methoxy tetronate **253** on keto-aldehyde **263**.

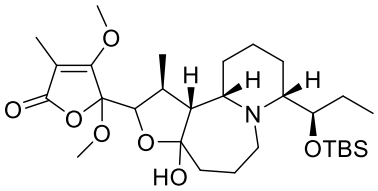
Whereas demethylation of methyl ethers is commonly difficult to achieve and requires harsh conditions,[201] the methoxy group at C-13 was expected to behave differently due to the

neighboring groups. The structural motif at C-13 is similar to an acetal, making it susceptible to acidic hydrolysis while the lactone at C-16 should allow for a basic hydrolysis and both conditions had been previously applied in similar hydrolysis reactions.

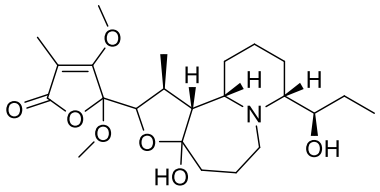
Treatment of acetal **286** with weak acids like AcOH[202] or TFA[203] gave no conversion according to ESI-MS even at higher temperatures up to 100 °C (Table 11, entry 1). Stronger acids like HCl[204] did result in a conversion but instead of the hydrolysis of the ether at C-13, a desilylation to alcohol **287** occurred. Higher concentrations of HCl[205] (entry 3) additionally gave a monodehydration, presumably forming enol ether **288**. As harsher conditions led to undesirable side reactions, the acetal **286** was simply stored in THF in presence of SiO_2 for seven days[206] but no conversion was observed (entry 4). Due to the difficulties to achieve the desired transformation under acidic conditions, basic hydrolysis was investigated instead.

Again, hemiacetal **286** exhibited surprisingly high stability towards basic conditions[207] as neither LiOH nor NaOH gave any conversion (entry 5 and 6). The more basic KOH produced a complex mixture of products after 24 h of reaction time and one of the detected species was indeed alcohol **277** according to ESI-MS. The desired product could however not be isolated from the complex mixture or detected in the NMR. As the methoxy-substituted compound showed an unexpected stability towards hydrolysis, we resorted to the alternative TES-protecting group.

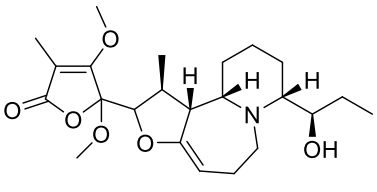
Table 11. Attempts on the demethylation of acetal **286** under acidic or basic conditions.



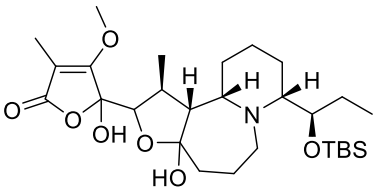
$C_{29}H_{51}NO_7Si$
M = 553.81 g/mol
286



$C_{23}H_{37}NO_7$
M = 439.55 g/mol
287



$C_{23}H_{35}NO_6$
M = 421.53 g/mol
288

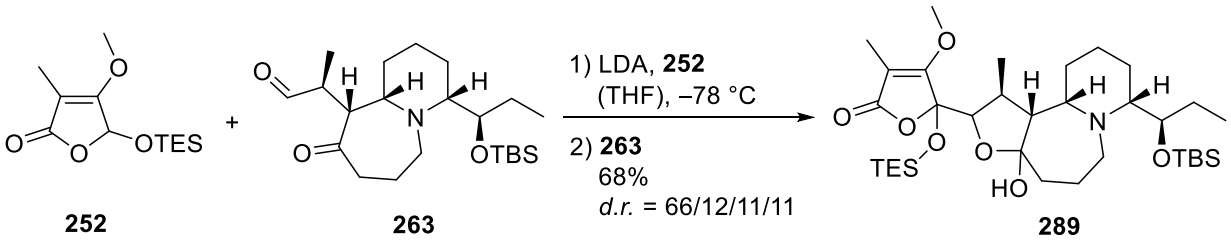


$C_{28}H_{49}NO_7Si$
M = 539.79 g/mol
277

entry	reagents	solvent	T [°C]	t [h]	result [*m/z*][a]
1	AcOH	H_2O	190	2	no conversion
2	0.025 M HCl	H_2O	50	216	440 (**287**), 422 (**288**)
3	3 M HCl	THF/H_2O	45	18	422 (**288**)
4	SiO_2	THF	20	168	no conversion
5	LiOH	THF/H_2O	20	48	no conversion
6	NaOH	THF/H_2O	20	24	no conversion
7	KOH	MeOH/H_2O	20	24	traces 540 (**277**)

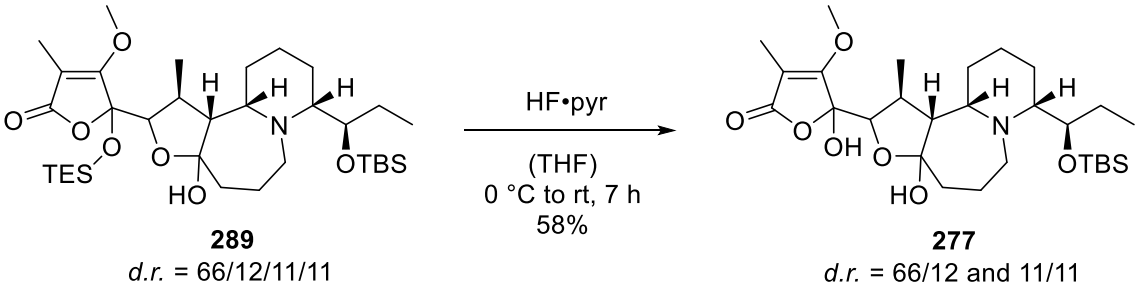
[a] all compounds were detected with ESI-MS but could not be isolated or characterized with NMR.

Once again, standard conditions for the coupling of the TES-protected tetronate **252** with keto-aldehyde **263** worked well and the desired product **289** was obtained in good 68% yield (Scheme 65). This time, an inseparable mixture of four different diastereomers was obtained with a preference for one isomer. As separation by column chromatography was impossible, the mixture was used directly for the subsequent deprotection.



Scheme 65. Nucleophilic addition of the TES-protected hydroxy tetronate **252** on keto-aldehyde **263**.

Luckily, selective deprotection of the tertiary alcohol in the presence of the secondary TBS ether was surprisingly facile. While the TBS group showed low stability towards acidic conditions, typical fluoride-based deprotection conditions gave no noticeable conversion. The commonly employed TBAF turned out to be incompatible with the compound **289** and only decomposition was observed after 2 h in THF. Instead, *Olah's* reagent worked well for the selective cleavage of the TES ether. Some optimization was required as full conversion was difficult to achieve but ultimately, the reaction performed best in a polyethylene flask with 20 equivalents of HF·pyridine complex (Scheme 66). At no point was a deprotection of the alcohol at C-1' observed. After successful deprotection, the four diastereomers of diol **277** could be separated into two sets of two diastereomers each. As their differing stereogenic centers would be destroyed upon successful synthesis of stemokerrin (**27**) and the compounds should therefore converge into one product, further studies towards the twofold dehydration were performed with a mixture of all four diastereomers.



Scheme 66. Chemoselective TES-deprotection with *Olah's* reagent forming diol **277**.

With diol **277** at hand, a large selection of dehydrating reagents was tested with varying results. The first conditions to be tested were the same as for the dehydration of the hemiacetal **144**. Treatment with TFAA and DMAP (Table 12, entry 1) gave exclusively monoelimination to form alcohol **290a**. While elimination to form the double bond between C-8 and C-9 proceeded quickly, the elimination from C-13 seemed more difficult to achieve.

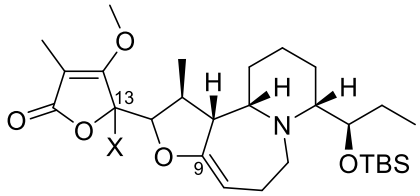
The same product **290a** was obtained with Tf_2O in the presence of a base (entry 2). On the other hand, treatment with pTs_2O not only gave the monoeliminated product **290a** but also a substituted variant **290b** (X = pTsO). The formation of this sulfonate proved, that the alcohol at C-13 did react with the dehydrating reagents but elimination to the exocyclic C-12/C-13 double bond seemed hindered. A similar result was obtained with Ac_2O as the dehydrating reagent and some of the acetylated product **290c** (X = OAc) was observed.

In contrast to the previous reagents, treatment with MsCl (entry 5) gave no signal for the monoeliminated product **290a**. Instead, two compounds were detected in the ESI-MS and were believed to be the desired bis-enol ether **291** and the mesylate **290d** (X = OMs). As this seemed the most promising result, further studies were performed and will be discussed later.

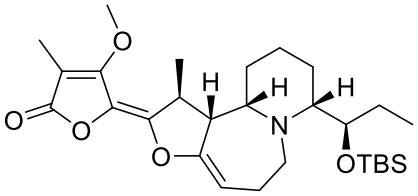
At first, further attempts for the dielimination were investigated. Treatment with HCl (entry 6) led again to monoelimination product **290a** as well as to some acid mediated TBS deprotection. The use of $SOCl_2$ gave a rather complex mixture containing, among others, the chlorinated product **290e** (X = Cl) and no desired elimination of the substituent at C-13 occurred (entry 7). Surprisingly, applying $SOBr_2$ led to formation of the dibrominated compound **292** according to ESI-MS and not even the monoelimination at C-9 was observed (entry 8). Despite the screening of different bases like pyridine, NEt_3, K_2CO_3 and Ag_2O, the bromine could not be forced to eliminate at either position.

The use of the common dehydrating reagent P_4O_{10} also gave interesting results. In the presence of an excess of base, low conversion and only monoelimination to **290a** was observed (entry 9). Omitting the base, however, led to acidic conditions due to the formation of phosphoric acid as a side product, which gave entirely different results (entry 10). The three products obtained according to ESI-MS were all characterized by TBS deprotection accompanied by elimination of one, two or three equivalents of water from the intermediate triol **293**. While stemokerrin (**27**) could theoretically be formed from triol **293** by loss of two molecules of water, the regioselectivity could not be determined and three regioisomers were possible. With this low selectivity, the overall reaction was unviable, the drastic increase of reactivity under acidic media was noteworthy, however.

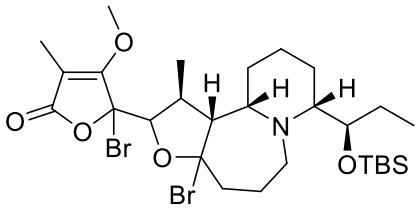
Table 12. Screening of conditions for the dielimination of diol **277**.



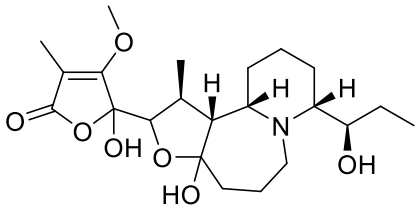
290a: X = OH
290b: X = OpTs
290c: X = OAc
290d: X = OMs
290e: X = Cl
290f: X = Br



$C_{28}H_{45}NO_5Si$
M = 503.76 g/mol
291



292



293

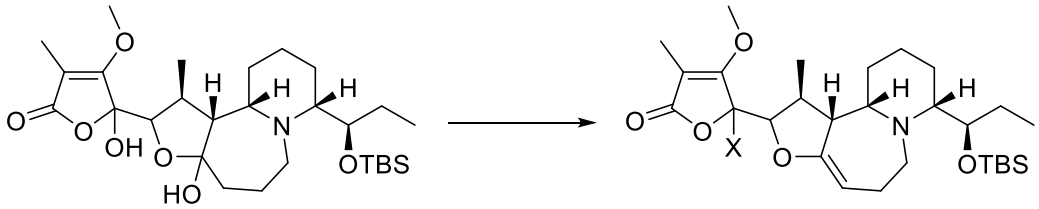
entry	reagents	solvent	T [°C]	t [h]	result
1	TFAA, DMAP	CH_2Cl_2/pyr	20	1	**290a**
2	Tf_2O, NEt_3	CH_2Cl_2	20	1	**290a**
3	pTs_2O, NEt_3	CH_2Cl_2	20	1	**290a**, **290b**
4	pTsOH	Ac_2O	20	2	**290a**, **290c**
5	MsCl, NEt_3	CH_2Cl_2	20	1	**291**[a], **290d**
6	1 M HCl	Dioxane	80	5	**290a**, **293** − $1H_2O$
7	$SOCl_2$, NEt_3	CH_2Cl_2	20	1	**290e**[b]
8	$SOBr_2$, pyr	CH_2Cl_2	20	1	**292**[c]
9	P_4O_{10}	$PhCH_3$/pyr	80	2	**290a**
10	P_4O_{10}	$PhCH_3$	80	2	**293** − $1/2/3H_2O$

[a] Subsequent studies revealed this signal to be an artefact produced by the ESI-MS, [b] isotope-distribution indicated the implementation of one chlorine atom, [c] isotope-distribution indicated the implementation of two bromine atoms.

In summary, most reaction conditions suffered from low selectivity and elimination from C-13 was difficult to achieve. While acidic conditions led to the cleavage of the TBS ether,

liberation of the third hydroxy group at C-1' made matters regarding chemoselectivity worse. Solely the use of MsCl gave the promising signal of *m/z* = 504 in the ESI-MS, which was at this point believed to be the desired product **291**. Additionally, mesylate **290d** was formed in this reaction. The following screening aimed to increase the amount of desired dieliminated product as detected in the ESI-MS and decrease the amount of mesylated product **290d**. Increasing the reaction time from 1 h (Table 13, entry 1) to 20 h (entry 2) led to the formation of the chlorinated compound **290e** as indicated by its isotope-distribution. Similar results were obtained at higher reaction temperatures (entry 3). The implementation of a chlorine atom can be explained by the nucleophilic substitution of the mesylate in compound **290d** by the chloride anion stemming from MsCl. Therefore, Ms_2O was applied in the reaction (entry 4) to prevent the substitution by the halogen and facilitate the elimination at higher temperatures. However, no dielimination could be observed and only monoelimination and mesylation was obtained. Lastly, the highly reactive MsBr was tested (entry 5) but only monoelimination and traces of brominated product **290f** (X = Br) were detected.

Table 13. Screening of conditions employing methanesulfonic acid derivatives for the elimination of diol **277**.



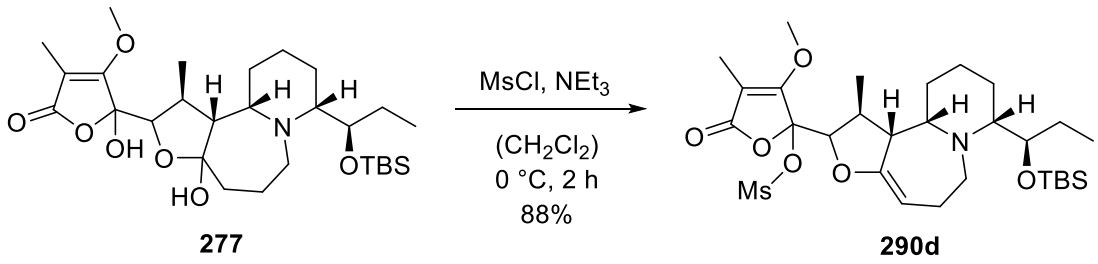
277

290a: X = OH
290d: X = OMs
290e: X = Cl
290f: X = Br

entry	reagents	solvent	T [°C]	t [h]	result
1	MsCl, NEt_3	CH_2Cl_2	20	1	**291**[a], **290d**
2	MsCl, NEt_3	CH_2Cl_2	20	20	**290e**[b]
3	MsCl, NEt_3	DCE	60	3	**290e**[b]
4	Ms_2O, NEt_3	DCE	60	2	**290a, 290d**
5	MsBr, NEt_3	THF	20	5	**290a**, **290f**[c]

[a] Subsequent studies revealed this signal to be an artefact produced by the ESI-MS, [b] isotope-distribution indicated the implementation of one chlorine atom, [c] isotope-distribution indicated the implementation of one bromine atom.

Overall, the tempting twofold elimination could not be achieved. As the treatment with MsCl (Table 13, entry 1) gave the most promising results, isolation of the two products, which had so far only been detected with ESI-MS, was attempted. Although a mixture of four different diastereomers was employed in the reaction, only one diastereomer of mesylate **290d** was isolated. While the minor two diastereomers of starting diol **277** gave decomposition under the reaction conditions, the major two diastereomers, presumably epimers at C-9, converged to product **290d**. However, no signals for the hypothesized **291** (*m/z* = 504) could be detected in the NMR. Measuring a pure sample of **290d** on the other hand gave signals for both compounds **290d** and **291**, suggesting the latter peak to be an artefact under the ionization conditions of the mass spectrometer. Much to our frustration, milder ionization conditions confirmed this theory. Still, the mesylated compound **290d** could be obtained in high yields as a single diastereomer and further studies towards the desired natural product stemokerrin (**27**) could be performed.



Scheme 67. Monoelimination and mesylation of the two major diastereomers of diol **277** gave mesylate **290d**.

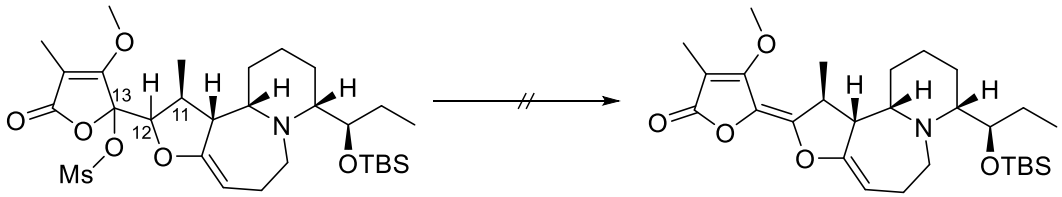
Arriving at this stage, only two transformations had to be performed to finish the total synthesis of stemokerrin. One would be the elimination of the methanesulfonic acid to generate the double bond between C-12 and C-13, the second would be the cleavage of the TBS ether at C-1'. As the former transformation seemed more difficult, it was investigated first.

As the elimination should proceed *via* an E2 mechanism, a variety of bases was screened to facilitate this process. Using Cs_2CO_3 as an inorganic base in acetonitrile gave no conversion even at higher temperatures (Table 14, entry 1). Triethylamine in conjunction with TBAI also failed to give any conversion (entry 2). Switching to LiBr and K_2CO_3 in DMF (entry 3) or NaI and NEt_3 in dioxane (entry 4) on the other hand gave rapid hydrolysis to **290a**. This hydrolysis presumably does not occur due to the reagents but rather due to traces water in the solvent. Both DMF as well as dioxane are rather hygroscopic and residual water led to hydrolysis at elevated temperatures while no such reaction occurred in acetonitrile. The use of

NEt_3 in DCE at 80 °C (entry 5) gave little conversion but traces of the desired bis-enolether **291** were detected. These conditions were repeated several times but at no point was an isolation of any characteristic compound possible.

As the treatment with weak bases, both organic and inorganic, failed to give the desired transformation, a stronger base was tested instead. Deprotonation at C-12 at low temperatures with a strong base like potassium *tert*-butoxide (entry 6) should lead to an elimination of methanesulfonic acid according to an E1cb mechanism. When applying these conditions, instead of the expected elimination of methanesulfonic acid at C-13 and generation of the double bond, the entire substituted tetronate left the molecule. Presumably, the reaction conditions lead to deprotonation at C-11 and a subsequent retro-aldol like reaction, regenerating the initially employed keto-aldehyde **263**. This result once again exhibited the unwillingness of the molecule to generate an exocyclic double bond between C-12 and C-13.

Table 14. Screening of basic conditions for the elimination of the mesylate at C-13.



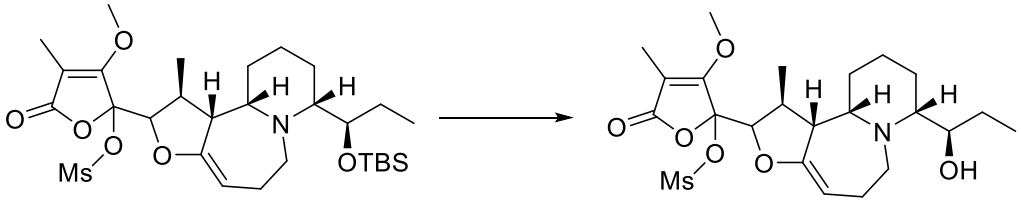
290d **291**

entry	reagents	solvent	T [°C]	t [h]	result
1	Cs_2CO_3	MeCN	80	20	no conversion
2	TBAI, NEt_3	MeCN	20	5	no conversion
3	LiBr, K_2CO_3	DMF	100	2	hydrolysis to **290a**
4	NaI, NEt_3	Dioxane	100	2	hydrolysis to **290a**
5	NEt_3	DCE	80	20	traces **291**
6	KOtBu	THF	−78	2	keto-aldehyde **263**

The low tendencies of the molecule to perform the elimination at C-13 was partially blamed on the bulky TBS protecting group. By changing the order of the reaction steps and cleaving the TBS ether first, the structure of alcohol **294** would come closer to stemokerrin (**27**). This in turn was hoped to bring about the ultimate elimination.

Deprotection of the alcohol at C-1' proved more difficult than expected. Nucleophilic solvents like methanol or ethanol were incompatible as they resulted in substitution of the mesylate at C-13. Employing *Lewis* acids like BF_3 (Table 15, entry 1) or $Sc(OTf)_3$ (entry 2) gave complex mixtures. Mild *Brønsted* acids like acetic acid were too weak and gave no conversion (entry 3). One of the most common ways to cleave silyl ethers are fluoride-based reagents. The prototypical TBAF (entry 4) exclusively gave decomposition under a variety of conditions using different solvents and temperatures. The previously employed *Olah's* reagent gave no conversion at short reaction times and prolonged exposure led to decomposition (entry 5). Even traces of water led to hydrolysis of the mesylate, so the resulting formation of alcohol **290a** after treatment with aqueous hydrogen fluoride was unsurprising (entry 6). Still, the TBS group was left intact even at longer reaction times. Exclusively the reaction with triethylamine trihydrofluoride ($3HF{\cdot}NEt_3$, TREAT-HF) gave traces of the desired product **294a** according to ESI-MS. Despite the excess of 20 equivalents TREAT-HF, the reaction proceeded very slowly and full conversion of the starting material was obtained only after five days at room temperature (entry 7). Luckily, the compound seemed stable under the reaction conditions and both the mass spectrum as well as the TLC looked promising. Indeed, the compound could be roughly characterized in a crude NMR. Alcohol **294a** however proved to be very labile and purification by column chromatography as well as full characterization turned out to be impossible. Several attempts to bring about the ultimate elimination from a crude mixture of alcohol **294a** with the previously described, basic conditions were unsuccessful.

Table 15. Deprotection of the secondary alcohol at C-1' to alcohol **294**.



290d **294a**

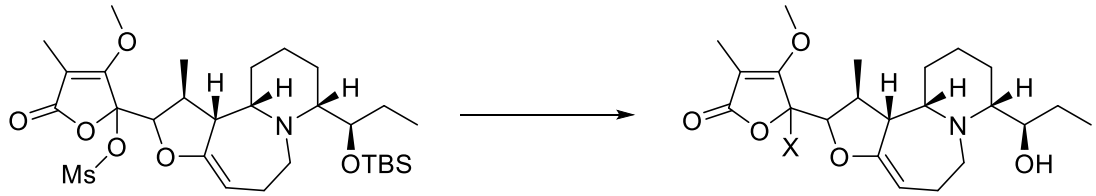
entry	reagents	solvent	T [°C]	t [h]	result
1	$BF_3 \cdot OEt_2$	CH_2Cl_2	20	2	decomposition
2	$Sc(OTf)_3$	MeCN	20	26	decomposition
3	AcOH	THF	20	16	no conversion
4	TBAF	THF	20	16	decomposition
5	HF·pyr	THF	20	50	decomposition
6	HF (aq.)	MeCN	20	26	hydrolysis to **290a**
7	3HF NEt_3	THF	20	102	**294a**

During the screening for the TBS deprotection, an interesting observation was made. As seen previously, strong *Brønsted* acids brought about the cleavage of the TBS ether. But when applying these conditions to the mesylate **290d**, additional substitution was observed according to mass spectrometry. For these deprotection reactions, even traces of moisture had to be excluded to prevent the hydrolysis to **290a**. Applying dry HCl in dioxane at high temperatures for 1 h (Table 16, entry 1) gave deprotected, chlorinated compound **294b**. Lower temperatures gave no reaction or incomplete conversion to a mixture of deprotected and chlorinated products. Using HBr in acetic acid only required room temperature and gave a mixture of acetylated compound **294c** and brominated compound **294d** after 2 h (entry 2). Both procedures gave promising results but isolation and purification of the products turned out to be impossible due to the lability of these species. Instead, a variety of quenching conditions to initiate the elimination was applied. While work-up with aqueous conditions like saturated $NaHCO_3$ led to hydrolysis, treatment with dry K_2CO_3, NEt_3, pyridine or AgOTf all led to decomposition.

To prevent the substitution, methanesulfonic acid was applied in the deprotection reaction. Instead of the expected deprotected mesylate **294a**, however, a mass signal of 390 was

detected, corresponding to the mass of the natural product stemokerrin (**27**). The conditions were optimized by pre-drying all reagents and quenching the reaction with flame-dried K_2CO_3. In contrast to the labile compounds obtained before, this species could be identified by crude NMR. Purification by employing the literature-reported conditions for stemokerrin was possible as well[37] and the compound showed no signs of decomposition. Analysis of the NMR data and comparison with the reported data for stemokerrin however revealed several differences.

Table 16. Acidic conditions employed to cleave the TBS ether at C-1'.



290d

294b: X = Cl
294c: X = OAc
294d: X = Br

entry	reagents	solvent	T [°C]	t [h]	result
1	HCl	dioxane	100	1	**294b**[a]
2	HBr in AcOH	$CHCl_3$	20	2	**294c**, **294d**[b]
3	MsOH	CH_2Cl_2	20	2	*m/z* = 390 (**295**)

[a] isotope-distribution indicated the implementation of one chlorine atom, [b] isotope-distribution indicated the implementation of one bromine atom.

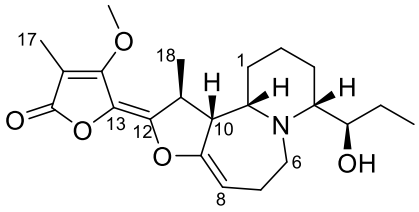
After treating the mesylate **290d**, which was employed as a single diastereomer, with methanesulfonic acid, the obtained product was a 1/1 mixture of diastereomers in a total yield of 76%. At first, these diastereomers were believed to be both the *E* and *Z* isomers at C-12/C-13[208] of the natural product stemokerrin (**27**), which itself exclusively exists as the *Z* isomer. After analysis of the NMR data however, the obtained compound turned out to be a tautomer of stemokerrin, which we named furostemokerrin (**295**).

In this section, a brief overview of the most characteristic NMR signals of both compounds is given and the major differences are pointed out. The most characteristic, low-field shifted proton of stemokerrin is the olefinic H-8. No such olefinic proton was detected in the new product and a methylene group was present at C-8 instead (Table 17). The most deshielded

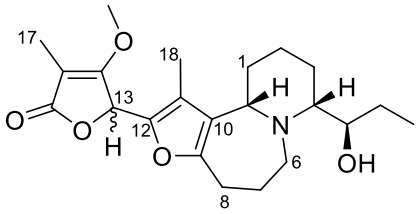
proton in product **295** turned out to be H-13, which existed as a quartet with a long range ^{5}J coupling to the methyl group C-17. Hence, the protons at C-17 gave a doublet similar to all other γ-monosubstituted tetronates, while in stemokerrin (**27**) the methyl group C-17 is a singlet. Additionally, the C-18 methyl group of stemokerrin is a doublet due to the coupling to the H-11 proton. For furostemokerrin, C-11 is a quaternary carbon atom and the methyl group at C-18 therefore is a singlet. Overall, both diastereomers obtained possess a tetrasubstituted furan ring and they only deviate from one another by the relative configuration at the C-13 carbon atom.

Mechanistically, the formation of furostemokerrin can be explained by an E1 elimination followed by an acid catalyzed tautomerization of the double bond. Similar tautomerization reactions under acid catalysis have been reported for exocyclic double bonds.[209,210,211] Although the thermodynamic driving force for aromatization is logical, it comes as a surprise that the natural product itself does not undergo a similar tautomerization.

Table 17. Comparison of the NMR data of stemokerrin and furostemokerrin.



stemokerrin (**27**)



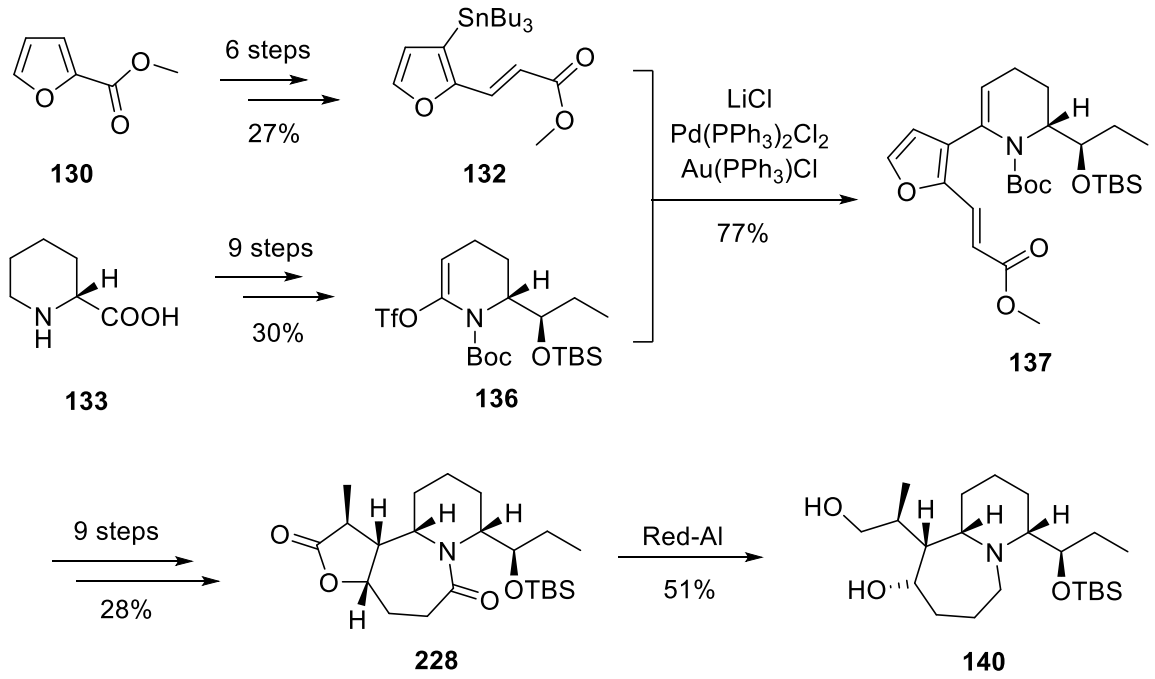
furostemokerrin (**295**)

Atom	stemokerrin (**27**)[a]		furostemokerrin (**295**)	
	^{1}H δ [ppm] (*J* [Hz])	^{13}C δ [ppm]	^{1}H δ [ppm] (*J* [Hz])	^{13}C δ [ppm]
8	5.48 ddd (9.0, 5.0, 2.0)	100.2	2.64 – 2.49 m[b], 2.36 – 2.30 m[b]	28.4[b]
11	2.92 dq (2.0, 7.1)	38.9	-	124.1[b]
13	-	123.2	5.30 q (1.3) 5.25 q (1.4)	71.1 70.5
17	2.08 s	9.2	1.77 d (1.4) 1.75 d (1.3)	8.2[b]
18	1.32 d (7.1)	22.1	1.65 s 1.64 s	7.8 7.9

[a] NMR data as reported from the isolation of stemokerrin,[37] [b] the signals of the two diastereomers were overlapping.

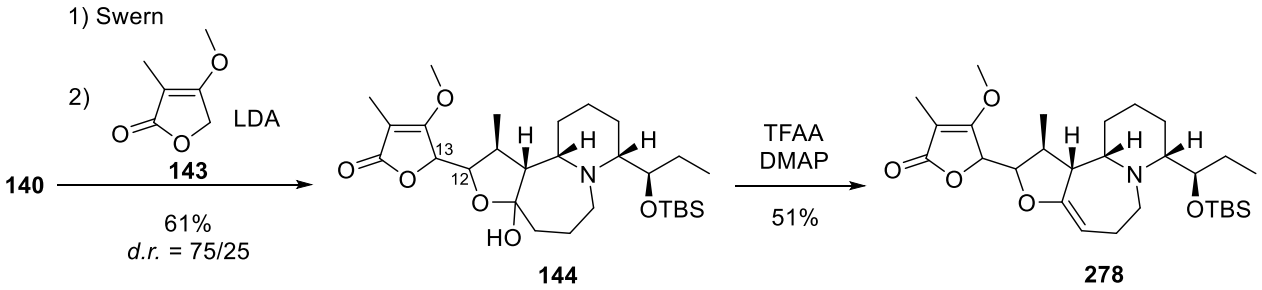
8. Summary

The overall goal of this thesis was the synthesis of the pyrido[1,2-*a*]azepine Stemona alkaloid stemokerrin. Based on previous work,[77] the tricyclic core was generated in a convergent synthesis starting from commercially available 2-methyl furoate (**130**) and the amino acid D-pipecolic acid (**133**) (Scheme 68). By subjecting the furan to a reaction sequence of, among others, bromination, decarboxylation, *Bouveault* aldehyde synthesis and *Stille* reaction, the stannylated furan **132** was obtained over a total of six steps in an overall yield of 27%. Chirality was introduced *via* enantiopure D-pipecolic acid (**133**) and in a total of nine synthetic steps, including a *Weinreb* amide formation, a *Corey-Bakshi-Shibata* reduction and a $RuCl_3$ catalyzed oxidation, enamine triflate **136** was obtained in 30% yield. Both compounds were combined in a *Stille* cross-coupling reaction to obtain intermediate **137**. Several reduction and oxidation steps had to be performed to assemble tricyclic compound **228** in 28% yield over nine steps, exhibiting all relevant stereogenic centers also found in stemokerrin. Simultaneous reduction of both lactam and lactone gave 1,4-diol **140**, on which several attempts towards stemokerrin (**27**) were made.



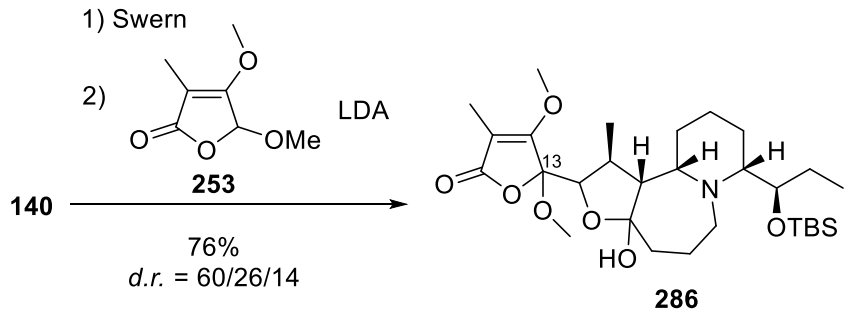
Scheme 68. Convergent synthesis of the two compounds furan **130** and amino acid **133** forming the 1,4-diol **140**.

The first approach towards stemokerrin involved the implementation of an unsubstituted tetronate **143** into keto-aldehyde **263**, obtained from a *Swern* oxidation of 1,4-diol **140**. After a successful nucleophilic attack of the tetronate, deprotonated by LDA, on the aldehyde, the entire carbon skeleton of stemokerrin was assembled as hemi-acetal **144** (Scheme 69). A subsequent elimination in an overall yield of 51% for both diastereomers gave enol ether **278**. Further studies to perform a formal dehydrogenation to generate the C-12/C-13 double bond failed and the use of a different tetronate builing block was investigated instead.



Scheme 69. Nucleophilic attack of the enolate of tetronate **143** on the aldehyde and subsequent elimination gave enol ether **278** as two separate diastereomers.

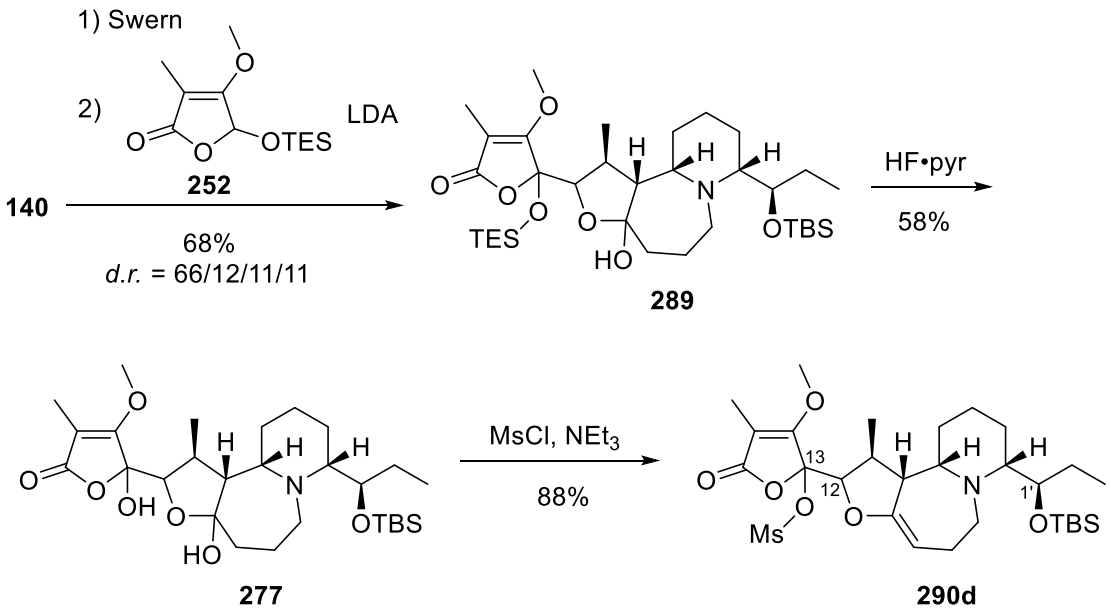
Implementation of a more highly oxidized tetronate was envisioned to facilitate the formation of the C-12/C-13 double bond. A methoxy-substituted tetronate **253** was successfully used as a nucleophile and acetal **286** was obtained in 76% yield (Scheme 70). The acetal functional group at C-13 turned out to be surprisingly stable and the desired hydrolysis could not be performed.



Scheme 70. Nucleophilic attack of the methoxy-substituted tetronate **253** gave rise to the hemiacetal **286**.

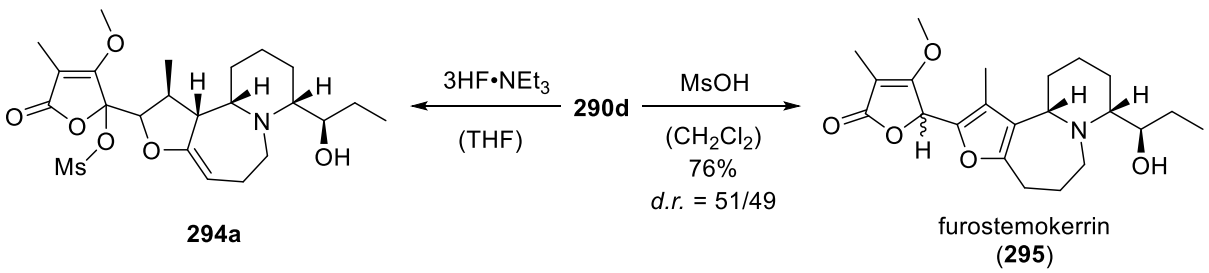
Investigations focused instead on a different protecting group for the γ-hydroxy group of the tetronate and triethylsilyl derivative **252** was chosen (Scheme 71). Again, the deprotonated tetronate could be used to generate hemiacetal **289** in 68% yield, this time as a mixture of four

different diastereomers. Treatment of the TES ether with *Olah's* reagent gave diol **277** in 58% yield as the same mixture of four diastereomers. After separation, the major two diastereomers were subjected to an elimination reaction with MsCl forming mesylate **290d** as a single compound in 88% yield.



Scheme 71. Synthesis of the hemiacetal **289** and subsequent deprotection and elimination.

Mesylate **290d** proved resistant to any attempts to eliminate methanesulfonic acid generating the double bond between C-12 and C-13. Deprotection of the alcohol at C-1' was successful by using triethylamine trihydrogenfluoride (Scheme 72), but free alcohol **294a** was too labile for an isolation and the desired elimination could not be performed, either. Acidic conditions on the other hand led to an impressive one-pot sequence of TBS deprotection, elimination and tautomerization to ultimately obtain the non-natural product furostemokerrin (**295**) as a mixture of two diastereomers.



Scheme 72. Deprotection of mesylate **290d** forming alcohol **294a** and furostemokerrin (**295**).

II. Experimental

1. General experimental

1.1. Preliminary remarks

All preparations and reactions with air or moisture sensitive compounds were carried out in flame-dried glassware under an argon atmosphere utilizing standard *Schlenk* techniques.
Given percentages are referring to mass percent unless stated otherwise. Saturated and x% solutions are aqueous solutions. Exempt of this are additions of triethylamine or acetic acid, which are given as % of the entire volume used.
The concentration of organometallic reagents was determined by titration against (−)-menthol with 1,10-phenantroline as indicator. All pH values were determined with universal indicator paper by *Merck*. Heating baths were filled with paraffin oil and regulated by electronic thermometers. Cooling baths contained ice and water (0 °C) or dry ice and acetone (−78 °C)

1.2. Solvents and reagents

The following solvents used for moisture-sensitive reactions were taken from a solvent purification system MB-SPS-800 by *M.Braun GmbH*.
Dichloromethane (CH_2Cl_2): *Merck* Emsure®, p.a., 99.8%, < 0.03% H_2O, column 2×MB-KOL-A.
Diethylether (Et_2O): *Merck* Emsure®, p.a., 99.7%, < 0.03% H_2O, column 1×MB-KOL-A, 1×MB-KOL-M type 2.
Tetrahydrofuran (THF): *Merck* Emsure®, p.a., 99.8%, < 0.03% H_2O, column 2×MB-KOL-M type 2.

The following solvents were purchased directly by the corresponding producer and used without prior purification.
Methanol (MeOH): *Acros Organics*, Extra Dry, 99.8% over molecular sieve, < 0.005% water
Ethanol (EtOH): *Acros Organics*, 99.5% over molecular sieve, absolute
Acetonitrile (MeCN): *Acros Organics*, Extra Dry, 99.9% over molecular sieve, < 0.005% water
1,2-Dichloroethane (DCE): *Sigma Aldrich*, 99.8% , < 0.003% water
Dimethylsulfoxide (DMSO): *Acros Organics*, puriss., 99.7% over molecular sieve, < 0.005% water

N,*N*-Dimethylformamide (DMF): *Acros Organics*, 99.8%, < 0.01% water

Pyridine (py): *Acros Organics*, 99.5%, < 0.005% water

Toluene (PhMe): *Acros Organics*, 99.8%, < 0.005% water

The following solvents for column or thin layer chromatography as well as for moisture-stable reactions were used after distillation: diethylether (Et_2O), tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), chloroform ($CHCl_3$), ethyl acetate (EtOAc), acetone (ac), methanol (MeOH), ethanol (EtOH).

Commercial reagents were used without prior purification unless stated otherwise.

1.3. Analytical methods and equipment

Irradiation experiments

The singlet oxygen reaction was carried out in a merry-go-round photoreactor (replica of a Rayonet RPR-100) with fluorescence lamps (cylindrical array of 16 *Luzchem* LZC-420 fluorescent light tubes, 8 W, λ_{max} = 420 nm). The reaction was performed in a duran glass phototube placed in the center of the illumination chamber. Cooling was established with a cryostat type CC 80 (*Huber*, Offenburg).

Ozonolysis

Ozone was generated by a 502 ozone generator by *FisherTechnology*.

Column- and thin layer chromatography

For the determination of the retention values (R_f), qualitative thin layer chromatography was performed on silica coated glass plates by *Merck* (0.25 mm silica 60, F_{254}). The compounds were detected by fluorescence at λ = 254 nm and, if specifically stated, at λ = 366 nm [UV] or by staining using a solution containing 3 g $KMnO_4$, 20 g K_2CO_3, 0.4 g NaOH in 300 mL water [$KMnO_4$] or a solution containing 2 g $Ce(SO_4)_2$, 50 g $(NH_4)_2MoO_4$ and 50 mL H_2SO_4 in 300 mL water [CAM].

For purification, column chromatography was performed on silica gel 40-63 µm (Si 60) by *Merck*. Solvent mixtures for column chromatography or thin layer chromatography are given in volumetric ratios v/v.

Gaschromatography (GC)

GC analyses were performed on a HP 6890 Series GC-System by *Agilent* with hydrogen gas at 160 kPa and a flame ionization detector. Achiral measurements were performed on a HP-5 column (Polydimethyl/diphenylsiloxane, 95/5) (temperature setting: 3 min. 60 °C, 15 °C/min. to 240 °C, 2 min. 240 °C).

Chiral measurements were performed on a column functionalized with 2,3-dimethyl-6-TBDMS-β-cyclodextrine.

High performance liquid chromatography (HPLC)

For achiral, analytical separations a stationary phase ODS-A 5µ by *YMC* and a 250 × 4.6 mm column were used. For chiral separations the following columns were used: Daicel ChiralCell OD (250 × 4.6 mm), Daicel ChiralCell AD (250 × 4.6 mm) and Daicel ChiralCell AD-H (250 × 4.6 mm). The HPLC setup by *Thermo-Fisher* consists of a SR3000 solvent rack, a LPG3400 SD pump, a WPS-3000 SL autosampler, a DAD-3000 UV/Vis detector and a LCQ Fleet mass spectrometer.

Nuclear magnetic resonance (NMR)

The NMR spectra were measured on AV-500cr, AVHD-300, AVHD-400 and AVHD-500 by *Bruker* at 300 K. The shift values are given in δ-values [ppm] and are referenced to the residual solvent peaks for ^{1}H-NMR-spectra ($CDCl_3$ δ = 7.26 ppm, benzene-d_6 δ = 7.16 ppm and DMSO-d_6 δ = 2.50 ppm). For ^{13}C-NMR-spectra, they are referenced to the deuterium coupled multiplets ($CDCl_3$ δ = 77.2 ppm, benzene-d_6 δ = 128.2 ppm and DMSO-d_6 δ = 39.5 ppm).

All signals are characterized by their chemical shift (δ) in [ppm] and by their coupling constants (*J)* in [Hz]. Following abbreviations were used for the assignment of the signals: s – singlet, d – doublet, t – triplet, q – quartet, quin – quintet, m – multiplet, *br* – broad, *virt*. – virtual. For coinicidentally equivalent coupling constants of magnetically non-equivalent protons the multiplets are marked as virtual.

Previously unreported compounds are fully characterized by DEPT-, HSQC-, HMBC-, ^{1}H-^{1}H-COSY- and NOESY-experiments. In the case of ambiguous signals, they are marked as interchangeably or not assignable. For mixtures of products, diastereomers or rotamers, the compounds ratio is given by the ratio of integrals of the respective best-defined peak.

Infrared spectroscopy (IR)

IR spectra were recorded on a *JASCO* IR-4100 spectrometer using the attenuated total reflection (ATR) technique. All bands are given in wave numbers [cm^{-1}]. The respective intensities are described by the following abbreviations: w (weak), m (medium), s (strong), vs (very strong), b (broad)

High resolution mass spectrometry

The mass spectra were recorded on a *Thermo Scientific* LTQ-TF Ultra (ESI) or a *Thermo Scientific* DFS-HRMS spectrometer (EI).

Melting points

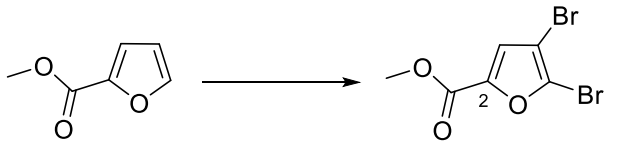
Melting points of solids were determined using a *Kofler* („Thermopan“, Fa. *Reichert*) and are not corrected.

Rotational values

Specific optical rotations were determined using a polarimeter 241 MC by *Perkin-Elmer* in a 1 dm cuvette or a polarimeter Stanley ADP400 by *Bellingham* in a 0.05 dm or a 0.5 dm cuvette at λ = 589 nm (Na-D-line) at room temperature. The rotational values are given in 10^{-1} grad cm^2 g^{-1}, with a concentration, following general convention, of g/100 mL. The optical purity is also given as the enantiomeric excess % *ee*, if it was determined by chiral GC or HPLC.

2. Synthetic procedures and analytical data

Methyl-4,5-dibromo-2-furoate (208)



$C_6H_4Br_2O_3$
M = 283.90 g/mol

In a 500 mL three-neck flask 41.0 g (35.5 mL, 325 mmol, 1.00 eq.) methyl-2-furoate (**130**) was diluted with 80 mL distilled chloroform. The three-neck flask was fitted with a dropping funnel and a reflux condenser, which was connected to four gas wash bottles (two protective bottles, one filled with 200 mL 2 M $Na_2S_2O_3$ solution and one filled with 200 mL 8 M NaOH solution). At first, the dropping funnel was filled with 156 g (50.0 mL, 976 mmol, 3.00 eq.) bromine and the solution was warmed to 50 °C. Next, the bromine was added slowly over the course of 1 h and after complete addition the mixture was heated under reflux for another 15 h. After having cooled to room temperature, the reaction mixture was quenched by addition of 300 mL 1 M $Na_2S_2O_3$ solution and 300 mL 1 M NaOH solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 120 mL). The combined organic fractions were washed iteratively with 300 mL 1 M $Na_2S_2O_3$ solution until no elemental sulfur precipitated. Subsequently, the organic fractions were washed with 300 mL brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure to obtain the crude product as an orange oil. After purification by column chromatography (h = 28 cm, Ø = 9 cm, pentane/diethylether = 60/1 → 40/1 → 20/1) ester **208** (60.0 g, 211 mmol, 78%) was obtained as a white solid.

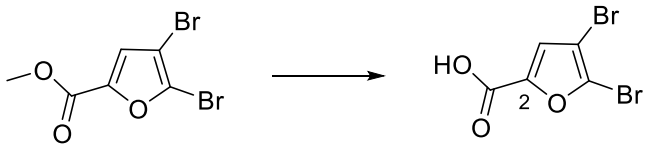
TLC: R_f = 0.68 (pentane/diethylether = 19/1) [UV, $KMnO_4$]

^{1}H-NMR (300 MHz, $CDCl_3$, 298 K): δ [ppm] = 7.16 (s, 1H, H-3), 3.89 (s, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$, 298 K): δ [ppm] = 157.5 (s, *C*OOMe), 146.0 (s, C-2), 128.5 (s, C-5), 122.0 (d, C-3), 103.9 (s, C-4), 52.5 (q, OCH_3).

The obtained analytical data matched with literature values.[212]

4,5-Dibromofuran-2-carboxylic acid (209)

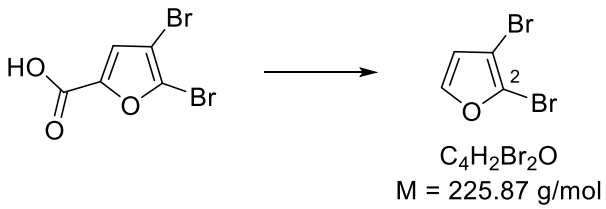


$C_5H_2Br_2O_3$
M = 269.88 g/mol

In a 1 L flask 56.1 g (197 mmol, 1.00 eq.) ester **208** was suspended in 400 mL 4 M NaOH solution and stirred for 17 h at 65 °C. After having cooled to room temperature, the precipitate was filtered and washed in portions with a total of 500 mL diethylether. The obtained white solid was suspended in 200 mL EtOAc and conc. HCl was added until the solid was fully dissolved (roughly 40 mL). Next, the mixture was diluted with 150 mL water and extracted with EtOAc (3 × 80 mL). The combined organic fractions were washed with 200 mL brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the acid **209** (44.9 g, 166 mmol, 84%) was obtained as a white solid.

^{1}H-NMR (500 MHz, DMSO-d_6, 298 K): δ [ppm] = 13.66 (s, 1H, COOH), 7.50 (s, 1H, CH)
^{13}C-NMR (126 MHz, DMSO-d_6, 298 K): δ [ppm] = 157.7 (s, COOH), 146.8 (s, C-2), 128.1 (s, C-5), 121.5 (d, C-3), 103.5 (s, C-4).
The obtained analytical data matched with literature values.[93]

4,5-Dibromofuran (131)



$C_4H_2Br_2O$
M = 225.87 g/mol

In a 250 mL flask 28.7 g (106 mmol, 1.00 eq.) acid **209** was dissolved in 45 mL DMSO. Next, 0.61 mL (0.64 g, 10.6 mmol, 0.10 eq.) AcOH and 1.46 g (5.31 mmol, 0.05 eq.) Ag_2CO_3 were added and the reaction mixture was stirred for 18 h at 120 °C. After having cooled to room temperature, the reaction mixture was diluted with 100 mL 3 M HCl and 100 mL diethylether. The layers were separated and the aqueous layer was extracted with diethylether (4 × 30 mL). The combined organic fractions were washed with water (50 mL) and brine (2 × 50 mL). After careful removal of the solvent under reduced pressure (max. 200 mbar) the crude product was obtained as a brown oil. The crude product was purified by fractional distillation to obtain the furan **131** (22.5 g, 99.9 mmol, 94%) as a colorless, clear liquid.

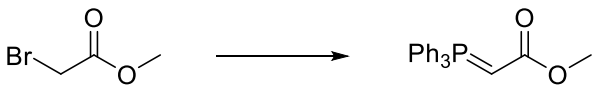
b.p. [°C] = 74 (80 mbar)

^{1}H-NMR (300 MHz, $CDCl_3$, 298 K): δ [ppm] = 7.41 (d, ^3J = 2.2 Hz, 1H, H-5), 6.47 (d, ^3J = 2.2 Hz, 1H, H-4).

^{13}C-NMR (75 MHz, $CDCl_3$, 298 K): δ [ppm] = 144.7 (d, C-5), 123.3 (s, C-2), 115.7 (d, C-4), 101.8 (s, C-3).

The obtained analytical data matched with literature values.[93]

Methyl-(triphenylphosphoranyliden)acetate



$C_{21}H_{19}O_2P$
M = 334.35 g/mol

Synthesis of the phosphonium salt

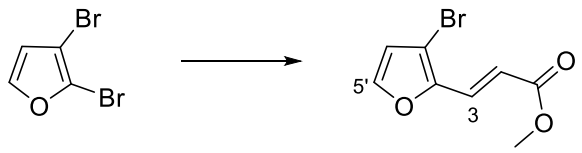
In a 1 L flask 80.8 g (50.5 mL, 528 mmol, 1.00 Eq) methyl-2-bromoacetate was dissolved in 830 mL EtOAc and 139 g (528 mmol, 1.00 eq) triphenylphosphine was added. The reaction mixture was stirred for 16 h before the solvent was removed under reduced pressure. The phosphonium salt (212 g, 511 mmol, 97%) was obtained as a white solid and used for the subsequent step without prior purification.

Synthesis of the ylid

In a 1 L flask 212 g phosphonium salt (511 mmol, 1.00 eq.) was dissolved in 400 mL CH_2Cl_2 and 400 mL H_2O. Next, 42.8 g (1.07 mol, 2.10 eq.) NaOH was added and the emulsion was stirred for 48 h at room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic fractions were washed with brine (300 mL), dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the pure ylide (167 g, 499 mmol, 98%) was obtained as a light-yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$, 298 K): δ [ppm] = 7.72 – 7.60 (m, 6H, $C_{ar}H$), 7.59 – 7.51 (m, 3H, $C_{ar}H$), 7.50 – 7.40 (m, 6 H, $C_{ar}H$), 3.52 (s, 3H, CH_3), 2.90 (br s, 1 H, CH).
^{13}C-NMR (75 MHz, $CDCl_3$, 298 K): δ [ppm] = 168.2 (s, COO), 133.2 (d, $C_{ar}H$), 132.5 (d, $C_{ar}H$), 129.1 (d, $C_{ar}H$), 128.9 (s, C_{ar}), 50.7 (q, CH_3), 30.5 (d, CH)
The obtained analytical data matched with literature values. [213]

Methyl-(*E*)-3-(3'-bromofuran-2'-yl)acrylate (211)



$C_8H_7BrO_3$
M = 231.05 g/mol

Bouveault Aldehyde synthesis

In a 1 L flask 10.2 mL (21.6 g, 95.5 mmol, 1.00 eq.) furan **131** was diluted with 210 mL THF under a protective atmosphere and cooled to −78 °C. Subsequently, 42.0 mL (2.5 M in hexane, 105 mmol, 1.10 eq.) *n*BuLi was added over 10 min and the reaction mixture was stirred for 10 min at this temperature. Next, 9.61 mL (9.07 g, 124 mmol, 1.30 eq.) DMF was added and after stirring for another 15 min the mixture was quenched with 300 mL saturated, aqueous NH_4Cl solution and the cooling bath was removed. After thawing, the layers were separated and the aqueous layer was extracted with diethylether (4 × 150 mL). The combined organic fractions were washed with 200 mL brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the crude product was obtained as a brown oil and used for the subsequent step without prior purification.

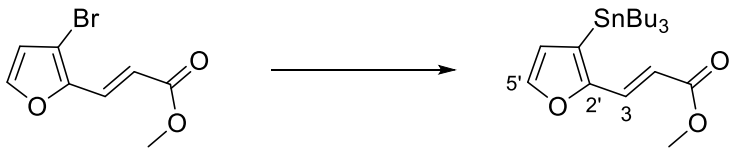
Wittig reaction

In a 1 L flask the crude product was diluted with 250 mL toluene and 31.9 g (95.5 mmol, 1.00 eq.) ylide was added. The reaction mixture was stirred for 2 h at room temperature and subsequently filtered over Celite®. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 24 cm, Ø = 9 cm, pentane/diethylether = 60/1 → 40/1 →20/1) to obtain the *Michael* acceptor **211** (16.4 g, 70.8 mmol, 74% over two steps) as a white solid.

TLC: R_f = 0.30 (pentane/diethylether = 19/1) [UV, $KMnO_4$]
^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 7.50 (d, ^3J = 15.9 Hz, 1H, H-3), 7.44 (d, ^3J = 2.0 Hz, 1H, H-5'), 6.54 (d, ^3J = 2.0 Hz, 1H, H-4'), 6.39 (d, ^3J = 15.9 Hz, 1H, H-2), 3.80 (s, 3H, OCH_3).

^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ [ppm] = 167.3 (s, C-1), 148.1 (s, C-2'), 144.8 (d, C-5'), 128.4 (d, C-3), 117.1 (d, C-2), 116.0 (d, C-4'), 105.7 (s, C-3'), 52.0 (q, CH_3).
The obtained analytical data matched with literature values.[214]

Methyl-(*E*)-3-(3'-(tributyltinfuran-2'-yl)acrylate (132)

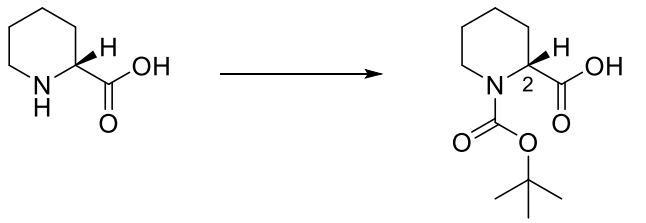


$C_{20}H_{34}O_3Sn$
M = 441.20 g/mol

In a 500 mL flask 8.00 g (34.6 mmol, 1.00 eq.) *Michael* acceptor **211** was dissolved in 90 mL dry dioxane under a protective atmosphere. Next, 43.8 mL (50.2 g, 86.6 mmol, 2.50 eq.) bis(tributyltin) and 1.22 g (1.73 mmol, 5 mol%) $PdCl_2(PPh_3)_2$ were added. After degassing the reaction mixture for 15 min in an ultrasonic bath under a constant argon flow, it was stirred at 90 °C for 24 h. Subsequently, the solvent was removed under reduced pressure. The excess bis(tributyltin) was removed by column chromatography with pure pentane. After column chromatography (h = 24 cm, Ø = 9 cm, pentane/diethylether = 80/1 → 60/1 → 40/1) the pure stannylated furan **132** (8.95 g, 20.3 mmol, 59%) was obtained as a clear, light-yellow oil.

TLC: R_f = 0.52 (pentane/diethylether = 19/1) [UV, $KMnO_4$]
IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2956 (m, C−H), 2924 (m, C−H), 2872 (m, C−H), 2853 (w, C−H), 1718 (s, C=O), 1632 (m, C=C), 1262 (s, C−H), 1162 (s, C−H).
^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 7.52 (d, ^3J = 1.7 Hz, 1H, H-5'), 7.33 (d, ^3J = 15.4 Hz, 1H, H-3), 6.44 (d, ^3J = 1.7 Hz, 1H, H-4'), 6.30 (d, ^3J = 15.4 Hz, 1H, H-2), 3.75 (s, 3H, OCH_3), 1.56 – 1.47 (m, 6H, $SnCH_2C\mathit{H}_2$), 1.39 – 1.25 (m, 6H, $C\mathit{H}_2CH_3$), 1.14 – 1.02 (m, 6H, $SnCH_2$), 0.87 (t, ^3J = 7.4 Hz, 9H, $CH_2C\mathit{H}_3$).
^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ [ppm] = 167.7 (s, C-1), 155.7 (s, C-2'), 144.4 (d, C-5'), 132.9 (d, C-3), 125.9 (s, C-3'), 118.5 (d, C-4'), 114.9 (d, C-2), 51.5 (q, OCH_3), 29.0 (t, $SnCH_2\mathit{C}H_2$), 27.3 (t, $\mathit{C}H_2CH_3$) 13.7 (q, $CH_2\mathit{C}H_3$) 10.1 (t, $SnCH_2$).
MS (ESI): *m/z* (%) = 443 (100) $[C_{21}H_{34}O_3Sn]^+$, 332 (29) $[C_{14}H_{28}OSn]^+$.
HRMS (ESI): $[C_{20}H_{35}O_3Sn]^+$ $[M+H]^+$ calculated: 443.1603; found: 443.1608.

(*R*)-1-(*tert*-Butoxycarbonyl)piperidine-2-carboxylic acid (180)



$C_{11}H_{19}NO_4$
M = 229.28 g/mol

In a 1 L flask 25.0 g (194 mmol, 1.00 eq.) D-pipecolic acid (**133**) was dissolved in 110 mL THF and 110 mL H_2O. Next, 50.7 g (232 mmol, 1.20 eq.) di-*tert*-butyldicarbonate and 7.82 g (196 mmol, 1.01 eq.) NaOH were added and the reaction mixture was heated under reflux for 6 h. After having cooled to room temperature, 100 mL hexane were added and the layers were separated. The aqueous layer was acidified with conc. HCl to a pH of roughly 1 and subsequently extracted with EtOAc (3 × 60 mL). The combined organic fractions were washed with brine (100 mL), dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the protected amino acid **180** (41.8 g, 182 mmol, 94%) was obtained as a white solid.

Rotameric ratio: R1/R2: 53/47

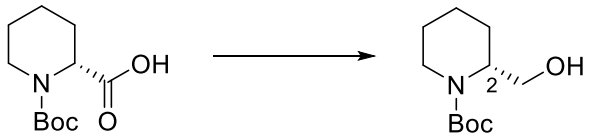
Specific rotation: $[\alpha]_D^{25}$ = +62 (c = 1.0, $CHCl_3$).

^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 4.93 (s, 0.53H, H-2 R1), 4.77 (s, 0.47H, H-2 R2), 4.01 (s, 0.47H, H-6 R2), 3.93 (s, 0.53H, H-6 R1), 3.05 – 2.94 (m, 0.53H, H-6 R1), 2.94 – 2.86 (m, 0.47H, H-6 R2), 2.30 – 2.15 (m, 1H, H-3), 1.75 – 1.57 (m, 3H, H-3, H-4, H-5), 1.46 [s, 9H, $C(CH_3)_3$], 1.45 – 1.37 (m, 1H, H-5), 1.37 – 1.24 (m, 1H, H-4).

^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ [ppm] = 177.9 (s, COOH R2), 177.5 (s, COOH R1), 156.4 (s, NCOO R1), 155.6 (s, NCOO R2), 80.5 [s, $C(CH_3)_3$], 54.8 (d, C-2 R2), 53.6 (d, C-2 R1), 42.3 (t, C-6 R1), 41.2 (t, C-6 R2), 28.5 [q, $C(CH_3)_3$], 26.8 (t, C-3 R2), 26.7 (t, C-3 R1), 24.9 (t, C-5 R1), 24.7 (t, C-5 R2), 20.9 (t, C-4).

The obtained analytical data matched with literature values.[215]

***N*-(*tert*-Butoxycarbonyl)-(*R*)-2-(hydroxymethyl)piperidine (181)**



$C_{11}H_{21}NO_3$
M = 215.29 g/mol

In a 1 L flask 32.8 g (143 mmol, 1.00 eq.) carboxylic acid **180** was dissolved in 100 mL dry THF under a protective argon atmosphere. The reaction mixture was cooled to 0 °C and 200 mL (1 M in THF, 200 mmol, 1.40 eq.) BH_3·THF complex was added over the course of 1 h. The cooling bath was subsequently removed and the reaction mixture was stirred for another 20 h before being quenched by slow addition of 100 mL 1 M HCl. The layers were separated and the aqueous layer was extracted with EtOAc (6 × 80 mL). The combined organic fractions were washed with 350 mL brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 21 cm, Ø = 9 cm, hexane/EtOAc = 2/1 → 1/1) to obtain the alcohol **181** (28.7 g, 138 mmol, 97%) as a colorless, viscous oil.

TLC: R_f = 0.43 (hexane/EtOAc = 1/1) [$KMnO_4$]

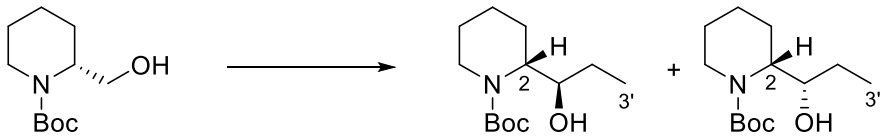
Specific rotation: $[\alpha]_D^{25}$ = +44 (c = 1.0, $CHCl_3$).

^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 4.30 – 4.25 (m, 1H, H-2), 3.96 – 3.88 (m, 1H, H-6), 3.79 (dd, ^2J = 11.0 Hz, ^3J = 9.0 Hz, 1H, CH_2OH), 3.59 (dd, ^2J = 11.0 Hz, ^3J = 5.9 Hz, 1H, CH_2OH), 2.90 – 2.80 (m, 1H, H-6), 2.19 (s, 1H, OH), 1.72 – 1.64 (m, 1H, H-3), 1.63 – 1.54 (m, 3H, H-3, H-4, H-5), 1.51 – 1.36 (m, 2H, H-4, H-5), 1.41 [s, 9H, C(CH_3)$_3$].

^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ [ppm] = 156.4 (s, NCOO), 80.0 [s, *C*(CH_3)$_3$], 61.8 (t, CH_2OH), 52.6 (d, C-2), 40.1 (t, C-6), 28.6 [q, C(*C*H_3)$_3$], 25.4 (t, C-3), 25.3 (t, C-5), 19.8 (t, C-4).

The obtained analytical data matched with literature values.[216]

_N_-(*tert*-Butoxycarbonyl)-(*R*)-2-[(*R*)-1'-hydroxypropyl]piperidine (134) and _N_-(*tert*-Butoxycarbonyl)-(*R*)-2-[(*S*)-1'-hydroxypropyl]piperidine (135)



$C_{13}H_{25}NO_3$
M = 243.35 g/mol

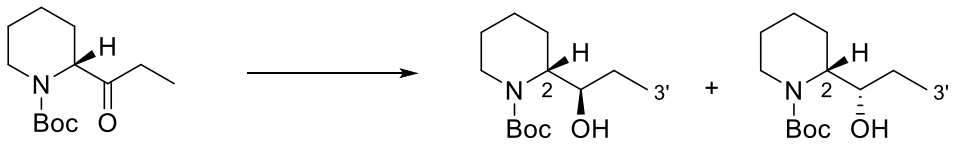
Swern oxidation

In a 1 L flask under protective argon atmosphere 11.0 mL (16.3 g, 129 mmol, 2.00 eq.) oxalyl chloride was dissolved in 300 mL dry CH_2Cl_2 and cooled to −78 °C. Subsequently, a solution of 13.7 mL (15.1 g, 193 mmol, 3.00 eq.) DMSO in 22 mL CH_2Cl_2 was added slowly over the course of 12 min. After stirring for 15 min at this temperature, a solution of 13.9 g (64.3 mmol, 1.00 eq.) alcohol **181** in 31 mL CH_2Cl_2 was added over 10 min. The reaction mixture was stirred for another 70 min at this temperature before 44.8 mL (32.6 g, 322 mmol, 5.00 eq.) triethylamine was added. After stirring for 10 min, the cooling bath was removed and the reaction mixture was warmed to room temperature. Next, the reaction was quenched by addition of 150 mL water. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic fractions were washed with brine (2 × 150 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the crude aldehyde was used for the subsequent reaction without prior purification.

Grignard reaction

In a 1 L flask the aldehyde was dissolved in 200 mL THF under a protective argon atmosphere and cooled to 0 °C. Next, 42.9 mL (3 M in THF, 129 mmol, 2.00 eq.) EtMgBr was added over the course of 20 min. The reaction mixture was stirred for 90 min at this temperature and subsequently quenched by addition of 100 mL saturated, aqueous NH_4Cl solution and 50 mL H_2O. The layers were separated and the aqueous layer was extracted with EtOAc (4 × 80 mL). The combined organic fractions were washed with 300 mL brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the diastereomers were purified and separated by column chromatography (h = 33 cm, Ø = 9 cm, pentane/diethylether = 8/1 → 6/1 → 4/1 → 2/1). The two diastereomeric compounds alcohol

134 (6.98 g, 28.7 mmol, 45%, 83% *ee*) and alcohol **135** (5.77 g, 23.7 mmol, 37%) were obtained separately as colorless, clear oils.



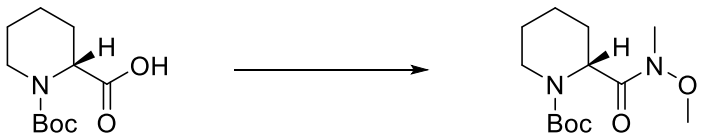
$C_{13}H_{25}NO_3$
M = 243.35 g/mol

Corey-Bakshi-Shibata reduction

In a 1 L flask 17.4 g (72.0 mmol, 1.00 eq.) ketone **185** was dissolved in 125 mL dry THF under a protective argon atmosphere and cooled to 0 °C. Next, 1.99 g (7.20 mmol, 10 mol%) Me-(*S*)-CBS-catalyst was added as a solid. Then, 86.4 mL (1 M in THF, 86.4 mmol, 1.20 eq.) $BH_3 \cdot SMe_2$ complex was added *via* a syringe pump over the course of 4 h. After complete addition, the reaction mixture was stirred for another 1 h at this temperature before being quenched by careful addition of 80 mL 1 M HCl. The layers were separated and the aqueous layer was extracted with EtOAc (4 × 30 mL). The combined organic fractions were washed with 100 mL brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the diastereomers were purified and separated by column chromatography (h = 32 cm, Ø = 9 cm, pentane/diethylether = 8/1 → 6/1 → 4/1 → 2/1). The alcohol **134** (15.4 g, 63.8 mmol, 88%, 99% *ee*) as well as the alcohol **135** (1.64 g, 6.74 mmol, 9%) were obtained separately as colorless, clear oils.

TLC: R_f = 0.18 and 0.13 (CH_2Cl_2/MeOH = 98/2) [$KMnO_4$]
Specific rotation: $[\alpha]_D^{25}$ = +40 (c = 1.0, $CHCl_3$).
^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 4.02 (m, 1H, H-2), 3.94 (m, 1H, H-6), 3.80 (ddd, ^3J = 10.3 Hz, 7.8 Hz, 2.9 Hz, 1H, H-1'), 2.89 (m, 1H, H-6), 1.84 (s, 1H, OH), 1.71 – 1.62 (m, 2H, H-2', H-3), 1.62 – 1.53 (m, 3H, H-3, H-4, H-5), 1.48 – 1.40 (m, 2H, H-4, H-5), 1.45 [s, 9H, $C(CH_3)_3$], 1.39 – 1.29 (m, 1H, H-2'), 1.01 (t, ^3J = 7.4 Hz, 3H, H-3').
^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ [ppm] = 157.6 (s, NCOO), 80.0 [s, $C(CH_3)_3$], 70.6 (d, C-1'), 55.7 (d, C-2), 40.7 (t, C-6), 28.5 [q, $C(CH_3)_3$], 27.4 (t, C-2'), 25.8 (t, C-5), 25.3 (t, C-3), 19.7 (t, C-4), 9.4 (q, C-3').
The obtained analytical data matched with literature values.[97]

***N*-(*tert*-Butoxycarbonyl)-(*R*)-2-[methoxy(methyl)carbamoyl]piperidine (184)**



$C_{13}H_{24}N_2O_4$
M = 272.35 g/mol

In a 1 L flask 32.4 g (141 mmol, 1.00 eq.) carboxylic acid **180** was dissolved in 360 mL dry CH_2Cl_2 under a protective argon atmosphere. Next, 29.8 g (184 mmol, 1.30 eq.) carbonyl diimidazole was added portion wise over 10 min to the reaction mixture. After stirring for 10 min, 16.5 g (170 mmol, 1.20 eq.) *N,O*-dimethyl hydroxylamine hydrochloride was added and the reaction mixture continued stirring for another 20 h. The reaction was quenched by addition of 200 mL water and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic fractions were washed with 1 M HCl (2 × 100 mL) and saturated, aqueous $NaHCO_3$ solution (3 × 100 mL). After drying over Na_2SO_4, filtration and removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 24 cm, Ø = 9 cm, pentane/diethylether = 3/1 → 2/1 →1/1) to obtain *Weinreb* amide **184** (30.0 g, 111 mmol, 78%) as a colorless, clear and viscous oil.

Rotameric ratio: R1/R2: 62/38

TLC: R_f = 0.41 (pentane/diethylether = 1/1) [$KMnO_4$]

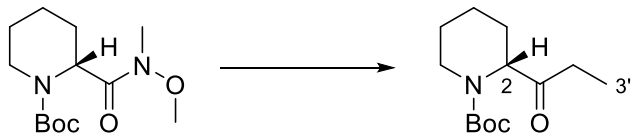
Specific rotation: $[\alpha]_D^{25}$ = +18 (c = 1.0, $CHCl_3$).

^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 5.06 (s, 0.62H, H-2 R1), 4.91 (s, 0.38H, H-2 R2), 4.00 (s, 0.38H, H-6 R2), 3.98 (s, 0.62H, H-6 R1), 3.76 (s, 3H, OCH_3), 3.54 – 3.35 (m, 1H, H-6), 3.17 (s, 3H, NCH_3), 2.01 – 1.95 (m, 1H, H-3), 1.73 – 1.63 (m, 2H, H-3, H-5), 1.62 – 1.56 (m, 1H, H-4), 1.44 [s, 9H, $C(CH_3)_3$], 1.44 – 1.28 (m, 2H, H-4, H-5).

^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ [ppm] = 173.7 [s, *C*ON$(CH_3)$$OCH_3$], 156.3 [s, NCOO], 79.8 [s, *C*$(CH_3)_3$], 61.4 (q, OCH_3), 52.3 (d, C-2 R2), 50.8 (d, C-2 R1), 42.5 (t, C-6 R1), 41.6 (t, C-6 R2), 32.2, (q, NCH_3), 28.6, [q, C(*C*$H_3)_3$], 26.6, (t, C-3), 25.1 (t, C-5), 19.8 (t, C-4).

The obtained analytical data matched with literature values.[217]

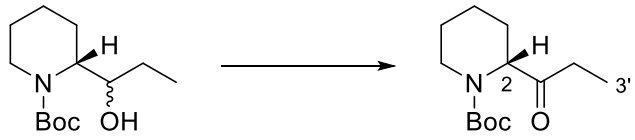
_N_-(_tert_-Butoxycarbonyl)-(_R_)-2-(1'-propionyl)piperidine (185)



$C_{13}H_{23}NO_3$
M = 241.33 g/mol

<u>*Grignard* reaction</u>

In a 1 L flask 20.1 g (73.7 mmol, 1.00 eq.) *Weinreb* amide **184** was dissolved in 200 mL dry THF under a protective argon atmosphere and cooled to 0 °C. Next, 49.1 mL (3 M in THF, 147 mmol, 2.00 eq.) EtMgBr were added over the course of 20 min. The ice bath was subsequently removed and after having stirred for another 90 min the reaction was quenched by addition of 300 mL saturated, aqueous NH_4Cl solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic fractions were washed with 300 mL brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the compound was purified by column chromatography (h = 29 cm, Ø = 8 cm, pentane/diethylether = 14/1 → 10/1) to obtain the ketone **185** (11.9 g, 49.3 mmol, 67%) as a colorless, clear oil.



$C_{13}H_{23}NO_3$
M = 241.33 g/mol

<u>*Swern* oxidation</u>

In a 500 mL flask under a protective argon atmosphere 240 mL dry CH_2Cl_2 and 11.0 mL (16.2 g, 128 mmol, 1.50 eq.) oxalyl chloride were mixed and the resulting solution was cooled to −78 °C. Subsequently, a solution of 10.9 mL (12.0 g, 153 mmol, 1.80 eq.) DMSO in 18 mL CH_2Cl_2 was added and the reaction mixture was stirred for 15 min. Afterwards a solution of 20.7 g (85.2 mmol, 1.00 eq.) of a diastereomeric mixture of alcohol **134** and alcohol **135** in

35 mL CH_2Cl_2 was added and the reaction mixture was stirred for 1 h. After addition of 35.6 mL (25.9 g, 256 mmol, 3.00 eq.) triethylamine and continued stirring for another 10 min the cooling bath was removed and the reaction mixture was warmed to room temperature. Then, the reaction was quenched by addition of 150 mL saturated, aqueous NH_4Cl solution and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 70 mL) and the combined organic fractions were washed with 150 mL brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 28 cm, Ø = 8 cm, pentane/diethylether = 14/1 → 10/1) to obtain the ketone **185** (19.2 g, 79.5 mmol, 93%) as a colorless, clear oil.

Rotameric ratio: R1/R2: 56/44

TLC: R_f = 0.40 (pentane/diethylether = 4/1) [$KMnO_4$]

Specific rotation: $[\alpha]_D^{25}$ = +84 (c = 1.0, $CHCl_3$).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2976 (m, C−H), 2940 (m, C−H), 2867 (w, C−H), 1720 (m, C=O), 1691 (s, C=O), 1410 (m, C−H), 1366 (m, C−H), 1163 (s).

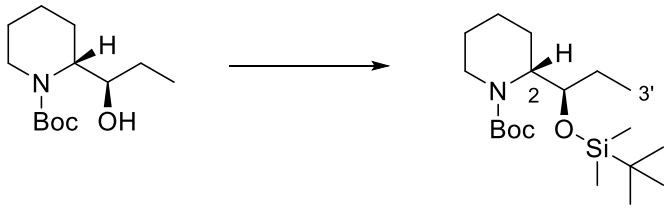
^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 4.72 (m, 0.56H, H-2 R1), 4.56 (m, 0.44H, H-2 R2), 4.06 (m, 0.44H, H-6 R2), 3.92 (m, 0.56H, H-6 R1), 2.86 (m, 0.56H, H-6 R1), 2.78 (m, 0.44H, H-6 R2), 2.48 – 2.38 (m, 2H, H-2'), 2.21 – 2.13 (m, 1H, H-3), 1.65 – 1.52 (m, 3H, H-3, H-4, H-5), 1.45 [s, 9H, C(CH_3)], 1.45 – 1.36 (m, 1H, H-5), 1.30 – 1.16 (m, 1H, H-4), 1.04 (t, ^3J = 7.3 Hz, 3H, H-3').

^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ [ppm] = 210.9 (s, C-1'), 155.9 (s, NCOO R1), 155.3 (s, NCOO R2), 80.1 [s, *C*(CH_3)], 61.1 (d, C-2 R2), 60.0 (d, C-2 R1), 42.8 (t, C-6 R1), 41.7 (t, C-6 R2), 32.2 (t, C-2'), 28.5 [q, C(*C*H_3)], 25.3 (t, C-3), 25.2 (t, C-5 R1), 24.9 (t, C-5 R2), 20.7 (t, C-4 R1), 20.6 (t, C-4 R2), 7.8 (q, C-3' R2), 7.8 (q, C-3' R1).

MS (ESI): *m/z* (%) = 242 (66) $[C_{13}H_{24}NO_3]^+$, 186 (100) $[C_{10}H_{20}NO_2]^+$, 142 (38) $[C_8H_{16}NO]^+$.

HRMS (ESI): $[C_{13}H_{24}NO_3]^+$ $[M+H]^+$ calculated: 242.1751; found: 242.1751.

***N*-(*tert*-Butoxycarbonyl)-(*R*)-2-[(*R*)-1'-(*tert*-butyldimethylsilyloxy)propyl]piperidine (146)**



$C_{19}H_{39}NO_3Si$
M = 357.61 g/mol

In a 250 mL flask 6.97 g (28.6 mmol, 1.00 eq.) alcohol **134** was dissolved in 80 mL dry CH_2Cl_2 under a protective argon atmosphere. The reaction mixture was cooled to 0 °C and subsequently, 7.96 mL (7.36 g, 68.7 mmol, 2.40 eq.) 2,6-lutidine and 7.89 mL (9.08 g, 34.4 mmol, 1.20 eq.) TBDMSOTf were added. The reaction mixture was stirred for 3 h at this temperature and was then quenched by addition of 80 mL water. After having warmed to room temperature, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic fractions were washed with 100 mL brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 15 cm, Ø = 6 cm, pentane/diethylether = 40/1 → 20/1) to obtain the protected alcohol **146** (10.1 g, 28.2 mmol, 99%) as a colorless, clear oil.

TLC: R_f = 0.29 (pentane/diethylether = 19/1) [$KMnO_4$]

Specific rotation: $[\alpha]_D^{25}$ = +22 (c = 1.0, $CHCl_3$).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2954 (w, C−H), 2930 (m, C−H), 2857 (w, C−H), 1688 (s, C=O), 1420 (m, C−H), 1364 (m), 1251 (s), 1149 (s), 833 (s), 772 (s).

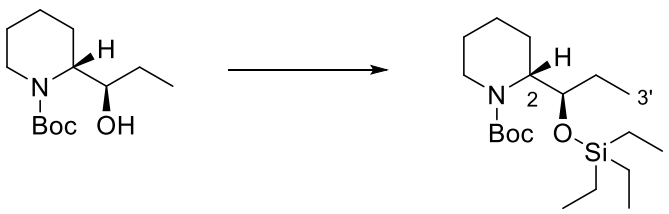
^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 4.20 – 4.14 (m, 1H, H-2), 4.06 – 3.99 (m, 1H, H-6), 3.96 (*virt*. dt, ^3J = 8.6 Hz, $^3J \approx {}^3J$ = 4.4 Hz, 1H, H-1'), 2.84 (*virt*. td, $^2J \approx {}^3J$ = 13.1 Hz, ^3J = 2.8 Hz, 1H, H-6), 1.65 – 1.46 (m, 8H, H-2', H-3, H-4, H-5), 1.44 [s, 9H, $OC(CH_3)_3$], 0.91 (t, ^3J = 6.9 Hz, 3H, H-3'), 0.87 [s, 9H, $SiC(CH_3)_3$], 0.05 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$).

^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ [ppm] = 155.5 (s, NCOO), 78.9 [s, $OC(CH_3)_3$], 70.7 (d, C-1'), 53.2 (d, C-2), 39.9 (t, C-6), 28.7 [q, $OC(CH_3)_3$], 26.9 (t, C-2'), 26.0 [q, $SiC(CH_3)_3$], 25.9 (t, C-3), 25.6 (t, C-5), 20.2 (t, C-4), 18.2 [s, $SiC(CH_3)_3$], 7.8 (q, C-3'), –4.3 (q, $SiCH_3$), –4.4 (q, $SiCH_3$).

MS (EI): *m/z* (%) = 244 (26) $[M-C_8H_{17}]^+$, 184 (15) $[C_{10}H_{18}NO_2]^+$, 128 (100) $[C_6H_{10}NO_2]^+$, 84 (54) $[C_5H_{10}N]^+$.

HRMS (ESI): $[C_{19}H_{40}NO_3Si]^+$ $[M+H]^+$ calculated: 358.2772; found: 358.2774.

***N*-(*tert*-Butoxycarbonyl)-(*R*)-2-[(*R*)-1'-(triethylsilyloxy)propyl]piperidine (187)**



$C_{19}H_{39}NO_3Si$
M = 357.61 g/mol

In a 250 mL flask 3.74 g (15.4 mmol, 1.00 eq.) alcohol **134** was dissolved in 150 mL CH_2Cl_2 and the mixture was cooled to 0 °C. Next, 1.36 g (20.0 mmol, 1.30 eq.) imidazole and 3.10 mL (2.78 g, 1.20 eq.) TESCl were added to the mixture. The reaction mixture immediately formed a white precipitate and was quenched after 2 h by addition of 60 mL saturated, aqueous NH_4Cl solution and 30 mL water. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic fractions were washed with 80 mL brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 17 cm, Ø = 4.5 cm, pentane/diethylether = 19/1 → 9/1) to obtain the protected alcohol **187** (5.02 g, 14.0 mmol, 91%) as a colorless, clear oil.

TLC: R_f = 0.54 (pentane/diethylether = 9/1) [$KMnO_4$]

Specific rotation: $[\alpha]_D^{25}$ = +40 (c = 1.0, $CHCl_3$).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2945 (m, C−H), 2878 (m, C−H), 1691 (s, C=O), 1417 (m, C−H), 1364, 1148 (s, C−O), 740 (s), 726 (s).

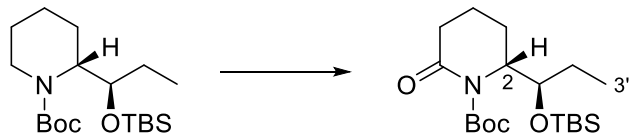
^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 4.18 – 4.11 (m, 1H, H-2), 4.05 – 3.98 (m, 1H, H-6), 3.96 (*virt*. dt, ^3J = 8.0 Hz, $^3J \approx {}^3J$ = 4.6 Hz, 1H, H-1'), 2.91 – 2.81 (m, 1H, H-6), 1.67 – 1.51 (m, 6H, H-2', H-3, H-4, H-5), 1.49 – 1.45 (m, 1H, H-2'), 1.44 [s, 9H, $C(CH_3)_3$], 1.43 – 1.33 (m, 1H, H-5), 0.95 [t, ^3J = 7.9 Hz, 9H, $Si(CH_2CH_3)_3$], 0.92 (t, ^3J = 7.4 Hz, 3H, H-3'), 0.58 [q, ^3J = 7.9 Hz, 6H, $Si(CH_2CH_3)_3$].

^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ [ppm] = 155.7 (s, NCOO), 78.9 [s, $C(CH_3)_3$], 71.4 (d, C-1'), 53.2 (d, C-2), 40.0 (t, C-6), 28.7 [q, $C(CH_3)_3$], 27.2 (t, C-2'), 26.0 (t, C-3), 25.5 (t, C-5), 20.2 (t, C-4), 8.2 (q, C-3'), 7.2 [q, $Si(CH_2CH_3)_3$], 5.3 [t, $Si(CH_2CH_3)_3$].

MS (EI): *m/z* (%) = 272 (28) $[C_{13}H_{26}NO_3Si]^+$, 184 (26) $[C_{10}H_{18}NO_2]^+$, 128 (100) $[C_6H_{10}NO_2]^+$, 84 (80) $[C_5H_{10}N]^+$.

HRMS (EI): $[C_{19}H_{39}NO_3Si]^{\cdot+}$ $[M]^{\cdot+}$ calculated: 357.2694; found: 357.2696.

_N_-(*tert*-Butoxycarbonyl)-(*R*)-2-[(*R*)-1'-(*tert*-butyldimethylsilyloxy)propyl]-6-oxo-piperidine (189)



$C_{19}H_{37}NO_4Si$
M = 371.59 g/mol

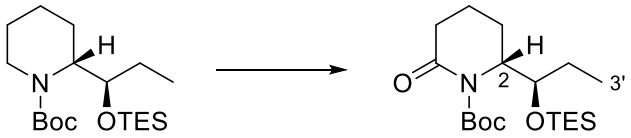
In a 500 mL flask 6.72 g (18.8 mmol, 1.00 eq.) protected alcohol **146** was dissolved in an emulsion of 70 mL EtOAc and 70 mL water. Next, 20.1 g (94.0 mmol, 5.00 eq.) $NaIO_4$ and 285 mg (1.13 mmol, 6 mol%) $RuCl_3 \cdot xH_2O$ were added and the suspension was stirred vigorously for 6 h. During this time, the dark orange suspensions discolored to bright yellow. Afterwards, 140 mL water was added, the layers were separated and the aqueous layer was extracted with EtOAc (4 × 50 mL). The combined organic fractions were washed with 150 mL 1 M Na_2SO_3 solution and 150 mL brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 20 cm, Ø = 5 cm, pentane/diethylether = 9/1 → 7/1 → 4/1 → 2/1) to obtain the lactam **189** (4.90 g, 13.2 mmol, 70%) as a colorless, clear oil.

TLC: R_f = 0.31 (pentane/diethylether = 4/1) [$KMnO_4$]
Specific rotation: $[\alpha]_D^{25}$ = +66 (c = 1.0, $CHCl_3$).
IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2957 (m, C−H), 2932 (m, C−H), 2858 (w, C−H), 1715 (m, C=O), 1670 (s, C=O), 1463 (w, C−H), 1391 (m), 1251 (s), 1151 (m), 1110 (m), 835 (s), 775 (s).
^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 4.19 (*virt*. td, $^3J \approx {}^3J$ = 6.8 Hz, ^3J = 5.1 Hz, 1H, H-2), 3.74 (ddd, ^3J = 8.4 Hz, 5.1 Hz, 3.3 Hz, 1H, H-1'), 2.48 (*virt*. dtd, ^2J = 17.5 Hz, $^3J \approx {}^3J$ = 5.5 Hz, ^4J = 1.6 Hz, 1H, H-5), 2.34 (ddd, ^2J = 17.5 Hz, ^3J = 9.4 Hz, 5.9 Hz, 1H, H-5), 2.00 – 1.91 (m, 1H, H-3), 1.91 – 1.81 (m, 1H, H-4), 1.81 – 1.70 (m, 1H, H-3), 1.70 – 1.59 (m, 1H, H-4), 1.51 [s, 9H, $OC(CH_3)_3$], 1.50 – 1.45 (m, 1H, H-2'), 1.42 – 1.33 (m, 1H, H-2'), 0.91 (t, ^3J = 7.4 Hz, 3H, H-3'), 0.88 [s, 9H, $SiC(CH_3)_3$], 0.08 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$).
^{13}C-NMR (75 MHz, $CDCl_3$, 298 K): δ [ppm] = 172.3 (s, C-6), 153.5 [s, *C*$OOC(CH_3)_3$], 83.0 [s, $COOC(CH_3)_3$], 74.5 (d, C-1'), 58.5 (d, C-2), 34.7 (t, C-5), 28.1 [q, $COOC(CH_3)_3$], 26.0 [q, $SiC(CH_3)_3$], 24.7 (t, C-2'), 22.5 (t, C-3), 18.9 (t, C-4), 18.1 [s, $SiC(CH_3)_3$], 10.7 (q, C-3'), -4.19 (q, $SiCH_3$), -4.62 (q, $SiCH_3$).

MS (EI): *m/z* (%) = 258 (17) $[C_{11}H_{20}NO_4Si]^+$, 214 (84) $[C_{10}H_{20}NO_2]^+$, 173 (100) $[C_9H_{21}OSi]^+$, 143 (20) $[C_6H_9NO_3]^+$.

HRMS (ESI): $[C_{19}H_{38}NO_4Si]^+$ $[M+H]^+$ calculated: 372.2565; found: 372.2568.

***N*-(*tert*-Butoxycarbonyl)-(*R*)-2-[(*R*)-1'-(triethyloxy)propyl]-6-oxo-piperidine (188)**

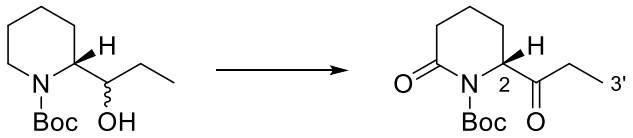


$C_{19}H_{37}NO_4Si$
M = 371.59 g/mol

In a 250 mL flask 4.90 g (13.7 mmol, 1.00 eq.) protected alcohol **187** was dissolved in an emulsion of 50 mL EtOAc and 50 mL water. Next, 14.6 g (68.5 mmol, 5.00 eq.) $NaIO_4$ and 208 mg (822 µmol, 6 mol%) $RuCl_3 \cdot xH_2O$ were added as solids and the suspension was stirred vigorously for 5 h at room temperature. The reaction mixture was subsequently diluted with 80 mL water and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL), the combined organic fractions were washed with 110 mL 1 M Na_2SO_3 solution and 130 mL brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 23 cm, Ø = 4.5 cm, pentane/diethylether = 6/1 → 4/1) to obtain the lactam **188** (1.78 g, 4.79 mmol, 35%) as a colorless, clear oil.

TLC: R_f = 0.30 (pentane/diethylether = 4/1) [$KMnO_4$]
Specific rotation: $[\alpha]_D^{25}$ = +58 (c = 1.0, $CHCl_3$).
IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2956 (m, C−H), 2936 (m, C−H), 2878 (m, C−H), 1692 (s, C=O), 1418 (s), 1365 (m), 1150 (s, C−O).
^{1}H-NMR (400 MHz, $CDCl_3$, 298 K): δ [ppm] = 4.22 (*virt*. q, $^3J \approx {}^3J \approx {}^3J$ = 5.9 Hz, 1H, H-2), 3.73 (ddd, ^3J = 7.5 Hz, 5.9 Hz, 4.1 Hz, 1H, H-1'), 2.47 (*virt*. dtd, ^2J = 17.4 Hz, $^3J \approx {}^3J$ = 6.0 Hz, ^4J = 1.4 Hz, 1H, H-5), 2.37 (ddd, ^2J = 17.4 Hz, ^3J = 8.3 Hz, 5.9 Hz, 1H, H-5), 2.01 – 1.89 (m, 1H, H-3), 1.89 – 1.82 (m, 1H, H-4), 1.81 – 1.70 (m, 1H, H-3), 1.70 – 1.62 (m, 1H, H-4), 1.57 – 1.48 (m, 1H, H-2'), 1.51 [s, 9H, $OC(CH_3)_3$], 1.46 – 1.33 (m, 1H, H-2'), 0.94 [t, ^3J = 8.0 Hz, 9H, $Si(CH_2CH_3)_3$], 0.91 (t, ^3J = 7.5 Hz, 3H, H-3'), 0.61 [q, ^3J = 8.0 Hz, 6H, $Si(CH_2CH_3)_3$].
^{13}C-NMR (101 MHz, $CDCl_3$, 298 K): δ [ppm] = 172.2 (s, C-6), 153.5 (s, NCOO), 83.0 [s, $OC(CH_3)_3$], 74.7 (d, C-1'), 58.1 (d, C-2), 34.6 (t, C-5), 28.0 [q, $OC(CH_3)_3$], 25.3 (t, C-2'), 23.1 (t, C-3), 18.8 (t, C-4), 10.3 (q, C-3'), 7.0 [q, $Si(CH_2CH_3)_3$], 5.11 [t, $Si(CH_2CH_3)_3$].
MS (EI): *m/z* (%) = 242 (45) $[C_{12}H_{24}NO_2Si]^+$, 173 (98) $[C_9H_{21}OSi]^+$, 115 (100) $[C_6H_{15}Si]^+$.
HRMS (EI): $[C_{19}H_{37}NO_4Si]^{\cdot+}$ $[M]^{\cdot+}$calculated: 371.2486; found: 371.2482.

***N*-(*tert*-Butoxycarbonyl)-(*R*)-2-(1'-propionyl)-6-oxo-piperidine (190)**

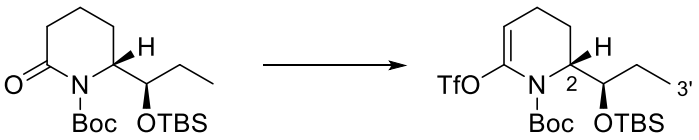


$C_{13}H_{21}NO_4$
M = 255.31 g/mol

In a 25 mL flask 161 mg (662 µmol, 1.00 eq.) of a mixture of diastereomeric alcohols **134** and **135** was dissolved in an emulsion of 3 mL EtOAc and 3 mL water. Next, 708 mg (3.31 mmol, 5.00 eq.) $NaIO_4$ and 10.0 mg (39.7 µmol, 6 mol%) $RuCl_3 \cdot xH_2O$ were added and the suspension was stirred vigorously for 5 h at room temperature. The reaction mixture was subsequently diluted with 10 mL water and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 4 mL) and the combined organic fractions were washed with 20 mL brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 18 cm, Ø = 2.5 cm, pentane/acetone = 7/1 → 5/1 → 3/1) to obtain the ketone **190** (84.4 mg, 328 µmol, 50%) as a colorless, clear oil.

TLC: R_f = 0.32 (hexane/EtOAc = 1/1) [$KMnO_4$]
Specific rotation: $[\alpha]_D^{25}$ = +71 (c = 1.0, $CHCl_3$).
IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2968 (m, C−H), 2935 (m, C−H), 2870 (m, C−H), 1710 (s, C=O), 1691 (s, C=O), 1418 (m, C−H), 1352 (m, C−H), 1163 (s).
^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 4.73 (dd, ^3J = 6.2 Hz, 4.3 Hz, 1H, H-2), 2.61 – 2.47 (m, 2H, H-2'), 2.56 – 2.42 (m, 2H, H-5), 2.11 – 1.94 (m, 2H, H-3), 1.79 – 1.62 (m, 2H, H-4), 1.48 [s, 9H, $OC(CH_3)_3$], 1.11 (t, ^3J = 7.3 Hz, 3H, H-3').
^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ [ppm] = 208.4 (s, C-1'), 170.7 (s, C-6), 153.0 (s, NCOO), 83.7 [$OC(CH_3)_3$], 63.8 (d, C-2), 34.6 (t, C-5), 32.2 (t, C-2'), 28.1 [$OC(CH_3)_3$], 24.9 (t, C-3), 18.1 (t, C-4), 7.7 (q, C-3').
MS (ESI): *m/z* (%) = 256 (100) $[C_{13}H_{22}NO_4]^+$, 200 (87) $[C_{10}H_{18}NO_3]^+$, 156 (42) $[C_8H_{14}NO_2]^+$.
HRMS (ESI): $[C_{13}H_{22}NO_4]^+$ $[M+H]^+$calculated: 256.1543; found: 256.1539.

_N_-(_tert_-Butoxycarbonyl)-(_R_)-2-[(_R_)-1'-(_tert_-butyldimethylsilyloxy)propyl]-6-[(trifluoromethylsulfonyl)oxy]-3,4-dihydropyridine (136)



$C_{20}H_{36}F_3NO_6SSi$
M = 503.65 g/mol

In a 500 mL flask 29.9 mL (0.5 M in $PhCH_3$, 15.0 mmol, 1.20 eq.) KHMDS and 130 mL dry THF were mixed under a protective argon atmosphere and the resulting solution was cooled to −78 °C. Next, a solution of 4.64 g (12.5 mmol, 1.00 eq.) lactam **189** in 16 mL dry THF was slowly added and the reaction mixture was stirred for 90 min at this temperature. Subsequently, 5.35 g *N*-phenyl-bis(trifluoromethane)sulfonylimide (15.0 mmol, 1.20 eq.) was added as a solid and the reaction mixture was stirred for 1 h at this temperature. Afterwards, the ice bath was removed and the reaction mixture was stirred at room temperature for 2 h before being quenched by addition of 70 mL water and 70 mL brine. The layers were separated and the aqueous layer was extracted with EtOAc (4 × 50 mL). The combined organic fractions were washed with 130 mL brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h =17 cm, Ø = 6 cm, pentane/diethylether = 50/1 → 40/1) to obtain the enamine **136** (6.22 g, 12.3 mmol, 99%) as a colorless, clear oil.

TLC: R_f = 0.48 (pentane/diethylether = 19/1) [UV, $KMnO_4$]

Specific rotation: $[\alpha]_D^{25}$ = +64 (c = 1.0, $CHCl_3$).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2960 (w, C−H), 2939 (w, C−H), 2915 (w, C−H), 2879 (w, C−H), 1721 (s, C=O), 1681 (s, C=C), 1423 (s), 1320 (s), 1206 (s), 1143 (s), 914 (m), 828 (m), 739 (s), 725 (s).

^{1}H-NMR (500 MHz, C_6D_6, 298 K): δ [ppm] = 5.02 (*virt*. t, $^3J \approx {}^3J$ = 3.9 Hz, 1H, H-5), 4.52 (ddd, ^3J = 7.7 Hz, 5.0 Hz, 3.5 Hz, 1H, H-2), 3.71 (ddd, ^3J = 7.7 Hz, 5.2 Hz, 4.0 Hz, 1H, H-1'), 1.48 [s, 9H, $OC(CH_3)_3$], 1.47 – 1.41 (m, 2H, H-2', H-4), 1.41 – 1.32 (m, 2H, H-3, H-4), 1.31 – 1.23 (m, 1H, H-3), 1.18 – 1.08 (m, 1H, H-2'), 1.01 [s, 9H, $SiC(CH_3)_3$], 0.88 (t, ^3J = 7.4 Hz, 3H, H-3'), 0.17 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$).

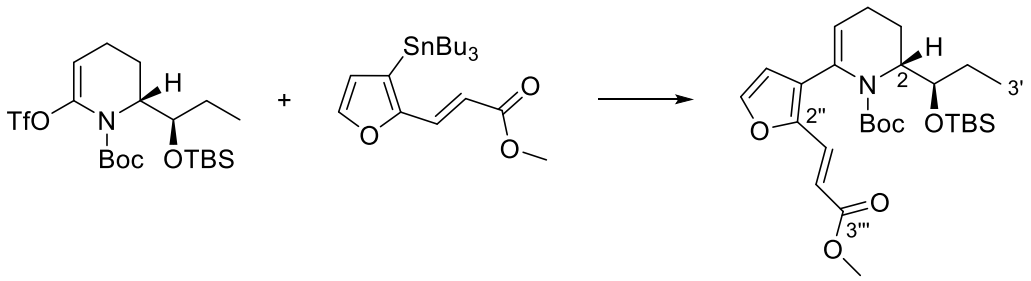
^{13}C-NMR (126 MHz, C_6D_6, 298 K): δ [ppm] = 153.2 (s, NCOO), 140.7 (s, C-6), 119.0 (q, ^2J = 319.8 Hz, CF_3), 105.0 (d, C-5), 83.2 [s, $COOC(CH_3)_3$], 71.0 (d, C-1'), 59.0 (d, C-2), 28.1

[q, COOC(CH_3)$_3$], 26.1 [q, SiC(CH_3)$_3$], 26.0 (t, C-2'), 23.62 (t, C-3), 20.0 (t, C-4), 18.4 [s, SiC(CH_3)$_3$], 8.4 (q, C-3'), -4.29 (q, SiCH_3), -4.76 (q, SiCH_3).

MS (ESI): *m/z* (%) = 504 (68) $[C_{20}H_{37}F_3NO_6SSi]^+$, 448 (100) $[C_{16}H_{29}F_3NO_6SSi]^+$, 404 (32) $[C_{15}H_{29}F_3NO_4SSi]^+$.

HRMS (ESI): $[C_{20}H_{37}F_3NO_6SSi]^+$ $[M+H]^+$ calculated: 504.2057; found: 504.2062.

_N_-(*tert*-Butoxycarbonyl)-(*R*)-2-[(*R*)-1'-(*tert*-butyldimethylsilyloxy)propyl]-6-{2''-[(*E*)-3'''-methoxy-3'''-oxoprop-1'''-en-1'''-yl]furan-3''-yl}-3,4-dihydropyridine (137)



$C_{27}H_{43}NO_6Si$
M = 505.73 g/mol

At first, two solutions were prepared separately by dissolving 3.76 g (7.47 mmol, 1.00 eq.) enamine **136** in 50 mL dry MeCN and 8.24 g (18.67 mmol, 2.50 eq.) stannylated furan **132** in 65 mL dry MeCN. In a third, 500 mL flask 1.90 g (44.8 mmol, 6.00 eq.) LiCl was rigorously dried under reduced pressure with a heating gun at 600 °C to remove any residual moisture. After having cooled to room temperature, the two previously prepared solutions were added. Lastly, 262 mg (374 µmol, 5 mol%) $PdCl_2(PPh_3)_2$ and 184 mg (374 µmol, 5 mol%) $AuClPPh_3$ were added as solids. The reaction mixture was degassed for 15 min in an ultrasonic bath under a constant argon flow and then stirred at 80 °C for 96 h. After having cooled to room temperature, the reaction mixture was filtered over a silica gel/K_2CO_3 mixture (9/1) and flushed with EtOAc. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 24 cm, Ø = 4.5 cm, pentane/diethylether = 19/1 → 14/1 → 9/1) to obtain the coupling product **137** (2.91 g, 5.75 mmol, 77%) as a colorless, clear oil.

TLC: R_f = 0.50 (pentane/diethylether = 7/1) [UV (254 nm, 366 nm), $KMnO_4$]
Specific rotation: $[\alpha]_D^{25}$ = +110 (c = 1.0, $CHCl_3$).
IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2956 (m, C−H), 2932 (m, C−H), 2857 (w, C−H), 1703 (s, C=O), 1629 (m, C=C), 1254 (s, C−N), 1165 (s, C−O), 836 (m), 774 (s).
^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 7.62 (d, ^3J = 15.7 Hz, 1H, H-1'''), 7.34 (d, ^3J = 1.8 Hz, 1H, H-5''), 6.42 (d, ^3J = 1.8 Hz, 1H, H-4''), 6.30 (d, ^3J = 15.7 Hz, 1H, H-2'''), 5.42 (*virt*. t, $^3J \approx {}^3J$ = 4.5 Hz, 1H, H-5), 4.45 (*virt*. dt, ^3J = 6.7 Hz, $^3J \approx {}^3J$ = 5.4 Hz, 1H, H-2), 3.86 (*virt*. td, $^3J \approx {}^3J$ = 5.4 Hz, ^3J = 4.6 Hz, 1H, H-1'), 3.76 (s, 3H, OCH_3), 2.20 – 2.07 (m, 2H, H-4), 2.06 – 1.95 (m, 1H, H-3), 1.94 – 1.84 (m, 1H, H-3), 1.60 (dqd, ^2J = 14.8 Hz, ^3J = 7.4 Hz,

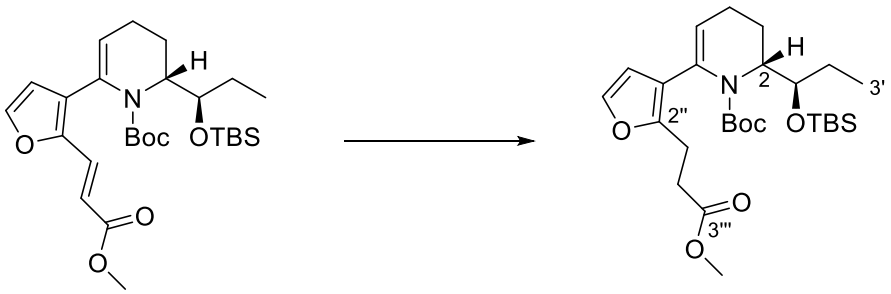
4.6 Hz, 1H, H-2'), 1.52 – 1.42 (m, 1H, H-2'), 1.17 [s, 9H, $OC(CH_3)_3$], 0.96 (t, ^3J = 7.4 Hz, 3H, H-3'), 0.86 [s, 9H, $SiC(CH_3)_3$], 0.08 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$).

^{13}C-NMR (75 MHz, $CDCl_3$, 298 K): δ [ppm] = 167.9 (s, C-3'''), 154.3 [s, *C*$OOC(CH_3)_3$], 146.3 (s, C-2''), 143.2 (d, C-5''), 131.5 (s, C-6), 131.2 (d, C-3''), 130.7 (d, C-1'''), 120.0 (d, C-5), 114.7 (d, C-2'''), 112.0 (d, C-4''), 80.5 [s, O*C*$(CH_3)_3$], 74.4 (d, C-1'), 55.6 (d, C-2), 51.6 (q, OCH_3), 28.0 [q, $OC(CH_3)_3$], 26.0 (t, C-2'), 26.0 [q, $SiC(CH_3)_3$], 25.0 (t, C-3), 21.5 (t, C-4), 18.2 [s, $SiC(CH_3)_3$], 9.7 (q, C-3'), -3.9 (q, $SiCH_3$), -4.31 (q, $SiCH_3$).

MS (EI): *m/z* (%) = 405 (40) $[C_{22}H_{35}NO_4Si]^+$, 346 (21) $[C_{20}H_{32}NO_2Si]^+$, 232 (100) $[C_{13}H_{14}NO_3]^+$, 214 (23) $[C_{14}H_{16}NO]^+$.

HRMS (ESI): $[C_{27}H_{44}NO_6Si]^+$ $[M+H]^+$ calculated: 506.2932; found: 506.2935.

_N_-(*tert*-Butoxycarbonyl)-(*R*)-2-[(*R*)-1'-(*tert*-butyldimethylsilyloxy)propyl]-6-[2''-(3'''-methoxy-3'''-oxoprop-1'''-yl)furan-3''-yl]-3,4-dihydropyridine (215)



$C_{27}H_{45}NO_6Si$
M = 507.74 g/mol

In a 250 mL flask 1.33 g (2.63 mmol, 1.00 eq.) coupling product **137** was dissolved in 9 mL dry THF and 63 mL dry MeOH under a protective argon atmosphere and the resulting mixture was cooled to 0 °C. Next, 313 mg (1.32 mmol, 0.50 eq.) $NiCl_2 \cdot 6H_2O$ was added as a solid and 697 mg (18.4 mmol, 7.00 eq.) $NaBH_4$ was added in portions. During the addition of $NaBH_4$ the color of the solution changed from green to black. After complete addition, the reaction mixture was stirred for 4 h at this temperature and was then quenched by addition of 70 mL saturated Rochelle salt solution and stirred for another 14 h. Afterwards, the mixture was filtered over Celite®, thoroughly washed with EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic fractions were washed with 100 mL brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 12 cm, Ø = 3.5 cm, pentane/diethylether = 19/1) to obtain the saturated ester **215** (1.19 g, 2.33 mmol, 89%) as a colorless, clear oil.

TLC: R_f = 0.50 (pentane/diethylether = 7/1) [UV, $KMnO_4$]

Specific rotation: $[\alpha]_D^{25}$ = +112 (c = 1.0, $CHCl_3$).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2955 (m, C−H), 2931 (m, C−H), 2857 (w, C−H), 1741 (m, C=O), 1696 (s, C=O), 1366 (m, C−H), 1252 (s, C−O), 1166 (s), 835 (s), 774 (s), 731 (s).

^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 7.20 (d, ^3J = 1.9 Hz, 1H, H-5''), 6.25 (d, ^3J = 1.9 Hz, 1H, H-4''), 5.30 (dd, ^3J = 5.2 Hz, 3.9 Hz, 1H, H-5), 4.43 (*virt*. dt, ^3J = 6.4 Hz, $^3J \approx {}^3J$ = 5.5 Hz, 1H, H-2), 3.87 (*virt*. td, $^3J \approx {}^3J$ = 6.4 Hz, ^3J = 4.1 Hz, 1H, H-1'), 3.70 (s, 3H, $COOCH_3$), 3.05 (*virt*. t, $^3J \approx {}^3J$ = 8.0 Hz, 2H, H-1'''), 2.75 – 2.61 (m, 2H, H-2'''), 2.17 – 2.03 (m, 2H, H-4), 2.01 – 1.93 (m, 1H, H-3), 1.91 – 1.82 (m, 1H, H-3), 1.65 – 1.53 (m, 1H, H-2'),

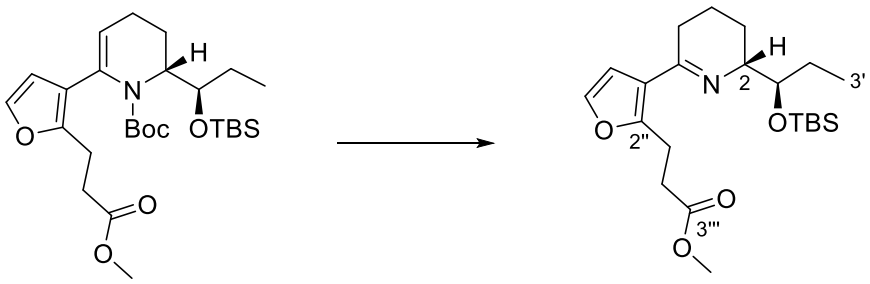
1.48 – 1.38 (m, 1H, H-2’), 1.21 [s, 9H, $OC(CH_3)_3$], 0.96 (t, ^3J = 7.4 Hz, 3H, H-3’), 0.88 [s, 9H, $SiC(CH_3)_3$], 0.10 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$).

^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ [ppm] = 173.4 (s, C-3’’’), 154.6 (s, NCOO), 148.7 (s, C-2’’), 139.7 (d, C-5’’), 132.2 (s, C-6), 121.9 (s, C-3’’), 116.3 (d, C-5), 110.7 (d, C-4’’), 80.1 [s, $OC(CH_3)_3$], 74.0 (d, C-1’), 56.1 (d, C-2), 51.9 (q, $COOCH_3$), 32.5 (t, C-2’’’), 28.0 [q, $OC(CH_3)_3$], 26.1 [q, $SiC(CH_3)_3$], 25.7 (t, C-2’), 25.0 (t, C-3), 22.6 (t, C-1’’’), 21.2 (t, C-4), 18.3 [s, $SiC(CH_3)_3$], 9.8 (q, C-3’), −3.9 (q, $SiCH_3$), −4.3 (q, $SiCH_3$).

MS (EI): *m/z* (%) = 406 (16) $[C_{22}H_{36}NO_4Si]^+$, 350 (21) $[C_{18}H_{28}NO_4Si]^+$, 234 (100) $[C_{13}H_{16}NO_3]^+$.

HRMS (ESI): $[C_{27}H_{46}NO_6Si]^+$ $[M+H]^+$ calculated: 508.3089; found: 508.3091.

(*R*)-2-[(*R*)-1'-(*tert*-Butyldimethylsilyloxy)propyl]-6-[2''-(3'''-methoxy-3'''-oxopropyl)furan-3''-yl]-2,3,4,5-tetrahydropyridine (216)



$C_{22}H_{37}NO_4Si$
M = 407.63 g/mol

In a 250 mL flask 2.50 g (4.92 mmol, 1.00 eq.) saturated ester **215** was dissolved in 100 mL dry DCE under a protective argon atmosphere. Next, 3.33 g (14.8 mmol, 3.00 eq.) $ZnBr_2$ was added as a solid and the reaction mixture was subsequently stirred at 50 °C for 5 h. After having cooled to room temperature, the reaction was quenched by addition of 65 mL saturated Rochelle salt solution and stirred for 1 h. The layers were subsequently separated and the aqueous layer was extracted with EtOAc (4 × 40 mL). The combined organic fractions were washed with 60 mL brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 18 cm, Ø = 6 cm, hexane/EtOAc = 20/1) to obtain the imine **216** (1.72 g, 4.22 mmol, 86%) as a light yellow, clear oil.

TLC: R_f = 0.49 (hexane/EtOAc = 6/1) [UV, $KMnO_4$]

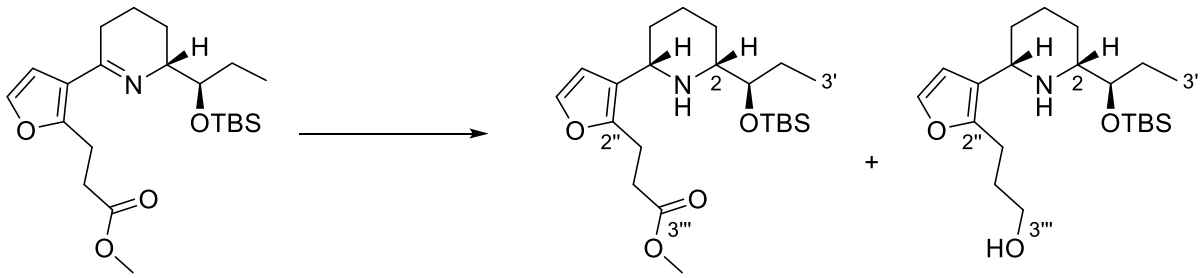
Specific rotation: $[\alpha]_D^{25}$ = +102 (c = 1.0, $CHCl_3$).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2953 (m, C−H), 2931 (m, C−H), 2858 (m, C−H), 1741 (s, C=O), 1635 (m, C=N), 1253 (m, C−N), 1106 (m, C−O), 1056 (m), 835 (s), 773 (s).

^{1}H-NMR (500 MHz, C_6D_6, 298 K): δ [ppm] = 6.95 (d, ^3J = 1.9 Hz, 1H, H-5''), 6.27 (d, ^3J = 1.9 Hz, 1H, H-4''), 4.07 (*virt*. dt, ^3J = 8.1 Hz, $^3J \approx {}^3J$ = 3.9 Hz, 1H, H-1'), 3.63 – 3.57 (m, 1H, H-2), 3.51 – 3.43 (m, 1H, H-1'''), 3.43 – 3.36 (m, 1H, H-1'''), 3.34 (s, 3H, OCH_3), 2.73 – 2.68 (m, 2H, H-2'''), 2.11 – 2.04 (m, 1H, H-5), 1.98 – 1.89 (m, 1H, H-5), 1.82 – 1.72 (m, 2H, H-3, H-2'), 1.61 – 1.54 (m, 1H, H-4), 1.54 – 1.46 (m, 1H, H-2'), 1.39 – 1.27 (m, 2H, H-3, H-4), 1.10 (t, ^3J = 7.4 Hz, 3H, H-3'), 1.02 [s, 9H, $SiC(CH_3)_3$], 0.16 (s, 3H, $SiCH_3$), 0.13 (s, 3H, $SiCH_3$).

^{13}C-NMR (126 MHz, C_6D_6, 298 K): δ [ppm] = 172.6 (s, C-3’’’), 160.9 (s, C-6), 154.5 (s, C-2’’), 140.1 (d, C-5’’), 121.9 (s, C-3’’), 110.1 (d, C-4’’), 78.6 (d, C-1’), 62.9 (d, C-2), 51.1 (q, OCH_3), 32.5 (t, C-2’’’), 29.0 (t, C-5), 26.2 [q, $SiC(CH_3)_3$], 25.4 (t, C-2’), 24.6 (t, C-1’’’), 22.0 (t, C-3), 20.0 (t, C-4), 18.4 [s, $SiC(CH_3)_3$], 11.7 (q, C-3’), −4.2 (q, $SiCH_3$), −4.3 (q, $SiCH_3$).
MS (EI): *m/z* (%) = 350 (89) $[C_{18}H_{28}NO_4Si]^+$, 235 (68) $[C_{13}H_{17}NO_3]^+$, 173 (100) $[C_9H_{21}OSi]^+$.
HRMS (ESI): $[C_{22}H_{38}NO_4Si]^+$ $[M+H]^+$ calculated: 408.2565; found: 408.2564

(*R*)-2-[(*R*)-1'-(*tert*-Butyldimethylsilyloxy)propyl]-(*S*)-6-[2''-(3'''-methoxy-3'''-oxopropyl)furan-3''-yl]-piperidine (217) and (*R*)-2-[(*R*)-1'-(*tert*-Butyldimethylsilyloxy)propyl]-(*S*)-6-[2''-(3'''-hydroxypropyl)furan-3''-yl]-piperidine (218)



$C_{22}H_{39}NO_4Si$
M = 409.64 g/mol

$C_{21}H_{39}NO_3Si$
M = 381.63 g/mol

In a 250 mL flask 2.35 g (5.77 mmol, 1.00 eq.) imine **216** was dissolved in 60 mL dry THF and 10 mL dry MeOH under a protective argon atmosphere and the resulting solution cooled to 0 °C. Next, 262 mg (6.92 mmol, 1.20 eq.) $NaBH_4$ was added and the reaction mixture was stirred for 4 h. The reaction was subsequently quenched by addition of 40 mL saturated, aqueous NH_4Cl solution and the layers were separated. The aqueous layer was extracted with EtOAc (4 × 30 mL) and the combined organic fractions were dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 22 cm, Ø = 4.5 cm, pentane/diethylether = 9/1 → 6/1 → 3/1) to obtain the ester **217** (1.78 g, 4.35 mmol, 75%) as well as the alcohol **218** (403 mg,1.06 mmol, 18%) as a colorless, clear oils.

Ester **217**:

TLC: R_f = 0.80 (pentane/diethylether = 1/1) [$KMnO_4$]

Specific rotation: $[\alpha]_D^{25}$ = −8.0 (c = 1.0, $CHCl_3$).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2951 (m, C−H), 2931 (m, C−H), 2856 (m, C−H), 1741 (s, C=O), 1437 (m, C−H), 1253 (C−O), 834 (s), 773 (s).

^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 7.21 (d, ^3J = 1.9 Hz, 1H, H-5''), 6.36 (d, ^3J = 1.9 Hz, 1H, H-4''), 3.68 (s, 3H, OCH_3), 3.58 – 3.52 (m, 1H, H-6), 3.48 (*virt*. dt, ^3J = 8.5 Hz, $^3J \approx {}^3J$ = 4.6 Hz, 1H, H-1'), 3.03 – 2.88 (m, 2H, H-1'''), 2.78 – 2.57 (m, 3H, H-2, H-2'''), 1.95 – 1.84 (m, 1H, H-4), 1.80 (s, 1H, NH), 1.67 – 1.55 (m, 3H, H-2', H-3, H-5), 1.51 (ddd, ^2J = 14.5 Hz, ^3J = 7.4 Hz, 4.6 Hz, 1H, H-2'), 1.46 – 1.36 (m, 2H, H-4, H-5), 1.16 – 1.00 (m, 1H,

H-3), 0.89 (t, ^3J = 7.4 Hz, 3H, H-3'), 0.84 [s, 9H, SiC(CH_3)$_3$], 0.05 (s, 3H, SiCH_3), 0.01 (s, 3H, SiCH_3).

^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ [ppm] = 173.3 (s, C-3'''), 148.7 (s, C-2''), 140.7 (d, C-5''), 124.0 (s, C-3''), 109.8 (d, C-4''), 77.4 (d, C-1'), 60.4 (d, C-2), 53.0 (d, C-6), 51.9 (q, OCH_3), 33.7 (t, C-5), 33.1 (t, C-2''''), 27.5 (t, C-3), 26.1 [q, SiC(*C*H_3)$_3$], 26.0 (t, C-2'), 25.1 (t, C-4), 21.9 (t, C-1'''), 18.3 [s, Si*C*(CH_3)$_3$], 8.5 (q, C-3'), –4.10 (q, SiCH_3), –4.34 (q, SiCH_3).

MS (EI): *m/z* (%) = 352 (11) [$C_{18}H_{30}NO_4Si$]$^+$, 236 (100) [$C_{13}H_{18}NO_3$]$^+$.

HRMS (ESI): [$C_{22}H_{40}NO_4Si$]$^+$ [M+H]$^+$ calculated: 410.2721; found: 410.2727.

Alcohol **218**:

TLC: R_f = 0.30 (pentane/diethylether = 1/1) [$KMnO_4$]

Specific rotation: $[\alpha]_D^{25}$ = +12 (c = 1.0, $CHCl_3$).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3310 (br s, O−H), 2930 (s, C−H), 2859 (m, C−H), 1440 (w, C−H), 1255 (m, C−O), 1000 (s), 835 (s), 774 (s).

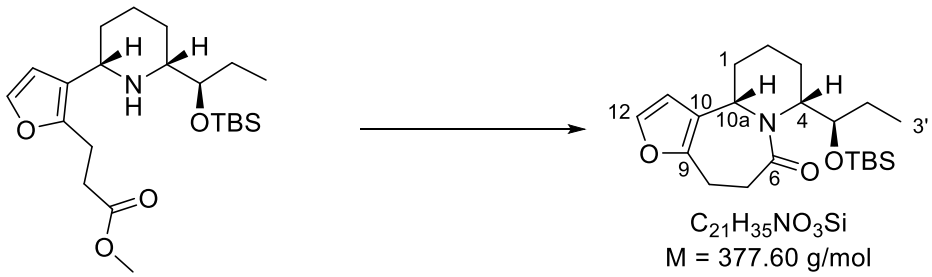
^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] =7.22 (d, ^3J = 1.9 Hz, 1H, H-5''), 6.23 (d, ^3J = 1.9 Hz, 1H, H-4''), 3.57 (dd, ^3J = 11.3 Hz, 2.8 Hz, 1H, H-6), 3.53 – 3.47 (m, 1H, H-1'), 3.44 – 3.36 (m, 1H, H-3'''), 3.36 – 3.25 (m, 1H, H-3'''), 2.83 (ddd, ^2J = 14.5 Hz, ^3J = 8.3 Hz, 5.8 Hz, 1H, H-1'''), 2.77 (*virt*. dt, ^2J = 14.6 Hz, $^3J \approx {}^3J$ = 6.1 Hz, 1H, H-1'''), 2.64 (ddd, ^3J = 11.6 Hz, 6.1 Hz, 2.6 Hz, 1H, H-2), 1.98 – 1.86 (m, 1H, H-4), 1.86 – 1.72 (m, 2H, H-2'''), 1.72 – 1.65 (m, 1H, H-5), 1.64 – 1.50 (m, 3H, H-2', H-3, H-5), 1.50 – 1.38 (m, 2H, H-2', H-4), 1.26 – 1.09 (m, 1H, H-3), 0.85 (t, ^3J = 7.5 Hz, 3H, H-3'), 0.85 [s, SiC(CH_3)$_3$], 0.04 (s, 3H, SiCH_3), 0.02 (s, 3H, SiCH_3).

^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ [ppm] = 150.4 (s, C-2''), 140.5 (d, C-5''), 123.2 (s, C-3''), 109.8 (d, C-4''), 76.4 (d, C-1'), 59.6 (d, C-2), 58.9 (t, C-3'''), 53.3 (d, C-6), 32.5 (t, C-5), 30.8 (t, C-2'''), 27.7 (t, C-3), 26.0 [q, SiC(*C*H_3)$_3$], 25.8 (t, C-2'), 24.9 (t, C-4), 22.4 (t, C-1'''), 18.2 [s, Si*C*(CH_3)$_3$], 8.7 (q, C-3'), –4.01 (q, SiCH_3), –4.61 (q, SiCH_3).

MS (EI): *m/z* (%) = 324 (5) [$C_{17}H_{30}NO_3Si$]$^+$, 208 (100) [$C_{12}H_{18}NO_2$]$^+$, 165 (20), [$C_{10}H_{15}NO$]$^+$.

HRMS (ESI): [$C_{21}H_{40}NO_3Si$]$^+$ [M+H]$^+$ calculated: 382.2772; found: 382.2776.

(4*R*,10a*S*)-4-[(*R*)-1'-(*tert*-Butyldimethylsilyloxy)propyl]-1,2,3,4,8,10a-hexahydrofuro[3,2-c]pyrido[1,2-a]azepin-6(7*H*)-one (138)



$C_{21}H_{35}NO_3Si$
M = 377.60 g/mol

Hydrolysis

In a 50 mL flask 717 mg (1.75 mmol, 1.00 eq.) ester **217** was dissolved in 5 mL THF and 5 mL water. Next, 367 mg (8.75 mmol, 5.00 eq.) $LiOH \cdot H_2O$ was added and the mixture was stirred at room temperature for 22 h. The reaction mixture was diluted with 5 mL water and 20 mL EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc (4 × 12 mL) and the combined organic fractions were dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the acid was obtained as a white foam and used for the subsequent step without prior purification.

Cyclization

In a 100 mL flask the acid was dissolved in 50 mL CH_2Cl_2 under a protective argon atmosphere and cooled to 0 °C. Next, 1.10 mL (797 mg, 7.88 mmol, 4.50 eq.) NEt_3 and 646 µL (633 mg, 5.25 mmol, 3.00 eq.) pivaloyl chloride were added and the reaction mixture was stirred for 10 min. Then, 21.4 mg (175 µmol, 10 mol%) DMAP was added, the ice bath was removed and the reaction mixture was stirred at room temperature for 19 h. The reaction mixture was subsequently quenched by addition of 20 mL saturated, aqueous NH_4Cl solution and 10 mL water and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic fractions were washed with 40 mL brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 18 cm, Ø = 2.5 cm, pentane/diethylether = 4/1 → 2/1) to obtain the lactam **138** (585 mg, 1.55 mmol, 88%) as a yellow oil.

TLC: R_f = 0.50 (pentane/diethlyether = 1/1) [$KMnO_4$]

Specific rotation: $[\alpha]_D^{25}$ = +14 (c = 1.0, $CHCl_3$).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2946 (s, C−H), 2938 (s, C−H), 2857 (m, C−H), 1641 (s, C=O), 1461 (w, C−H), 1391 (m, C−H), 1109 (m, C−O), 837 (s, C−H), 777 (s, C−H).

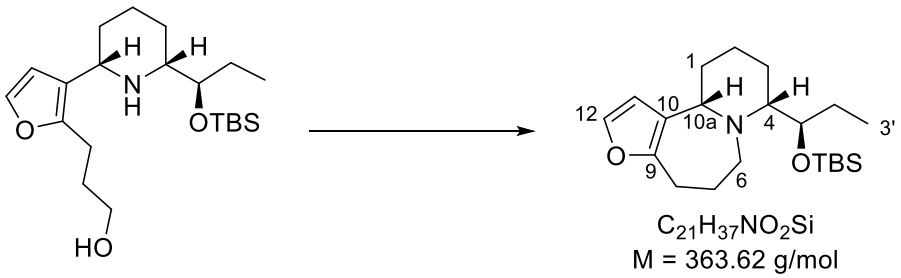
^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 7.21 (d, ^3J = 1.9 Hz, 1H, H-12), 6.21 (d, ^3J = 1.9 Hz, 1H, H-11), 5.01 – 4.84 (m, 1H, H-10a), 4.60 (*virt*. dt, ^3J = 10.4 Hz, $^3J \approx {}^3J$ = 5.3 Hz, 1H, H-4), 3.76 (ddd, ^3J = 10.1 Hz, 4.9 Hz, 2.5 Hz, 1H, H-1'), 3.22 (*virt*. dt, ^2J = 13.0 Hz, $^3J \approx {}^3J$ = 9.5 Hz, 1H, H-7), 3.04 – 2.90 (m, 2H, H-8), 2.71 (virt. dt, ^2J = 13.1 Hz, $^3J \approx {}^3J$ = 3.9 Hz, 1H, H-7), 2.40 – 2.04 (m, 1H, H-1), 1.95 – 1.81 (m, 3H, H-1, H-3), 1.81 – 1.71 (m, 1H, H-2), 1.46 – 1.32 (m, 1H, H-2), 1.21 – 1.14 (m, 1H, H-2'), 0.87 [s, 9H, $SiC(CH_3)_3$], 0.85 – 0.77 (m, 1H, H-2'), 0.69 (t, ^3J = 7.2 Hz, 3H, H-3'), 0.14 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$).

^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ [ppm] = 174.7 (s, C-6), 150.4 (s, C-9), 140.1 (d, C-12), 122.4 (s, C-10), 108.7 (d, C-11), 73.6 (d, C-1'), 53.6 (d, C-4), 49.7 (d, C-10a), 33.0 (t, C-7), 27.4 (t, C-1), 26.1 [q, $SiC(CH_3)_3$], 24.6 (t, C-2'), 23.8 (t, C-8), 21.8 (t, C-3), 18.7 (t, C-2), 18.2 [s, $SiC(CH_3)_3$], 11.4 (q, C-3'), –4.3 (q, $SiCH_3$), –4.6 (q, $SiCH_3$).

MS (EI): *m/z* (%) = 320 (29) $[C_{17}H_{26}NO_3Si]^+$, 204 (100) $[C_{12}H_{14}NO]^+$.

HRMS (ESI): $[C_{21}H_{36}NO_3Si]^+$ $[M+H]^+$ calculated: 378.2459; found: 378.2461.

(4*R*,10a*S*)-4-[(*R*)-1'-(*tert*-Butyldimethylsilyloxy)propyl]-1,2,3,4,5, 7, 8,10a-octahydrofuro[3,2-c]pyrido[1,2-a]azepine (219)



$C_{21}H_{37}NO_2Si$
M = 363.62 g/mol

In a 100 mL flask 339 mg (889 µmol, 1.00 eq.) alcohol **218** was dissolved in 35 mL dry CH_2Cl_2 under a protective argon atmosphere. Next, 354 mg (1.07 mmol, 1.20 eq.) CBr_4 and 583 mg (2.22 mmol, 2.50 eq.) PPh_3 were added as solids and the reaction mixture was stirred at room temperature for 1 h. Afterwards, 310 µL (225 mg, 2.22 mmol, 2.50 eq.) NEt_3 was added and the reaction mixture continued stirring for another 2 h. The reaction mixture was subsequently quenched by addition of 20 mL saturated, aqueous $NaHCO_3$ solution and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic fractions were washed with 20 mL brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 15 cm, Ø = 3.5 cm, pentane/diethylether = 9/1 → 5/1) to obtain the azepine **219** (260 mg, 716 µmol, 81%) as a colorless, clear oil.

TLC: R_f = 0.53 (pentane/diethylether = 4/1) [$KMnO_4$]

Specific rotation: $[\alpha]_D^{25}$ = −6 (c = 1.0, $CHCl_3$).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2931 (s, C−H), 2857 (m, C−H), 1463 (w, C−H), 1434 (w, C−H), 1255 (m, C−O), 1057 (m), 836 (s), 775 (s).

^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 7.22 (d, ^3J = 1.9 Hz, 1H, H-12), 6.37 (d, ^3J = 1.9 Hz, 1H, H-11), 3.60 – 3.53 (m, 1H, H-10a), 3.48 (ddd, ^3J = 9.0 Hz, 7.0 Hz, 4.5 Hz, 1H, 1'), 3.38 (*virt*. t, $^3J \approx {}^3J$ = 6.5 Hz, 2H, H-6), 2.97 – 2.72 (m, 2H, H-8), 2.70 – 2.59 (m, 1H, H-4), 2.24 – 2.10 (m, 2H, H-7), 1.96 – 1.84 (m, 1H, H-2), 1.72 – 1.56 (m, 3H, H-1, H-2', H-3), 1.51 (ddd, ^2J = 14.4 Hz, ^3J = 7.3 Hz, 4.7 Hz, 1H, H-2'), 1.47 – 1.38 (m, 2H, H-1, H-2), 1.15 – 1.03 (m, 1H, H-3), 0.89 (t, ^3J = 7.5 Hz, 3H, H-3'), 0.85 [s, 9H, $SiC(CH_3)_3$], 0.05 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$).

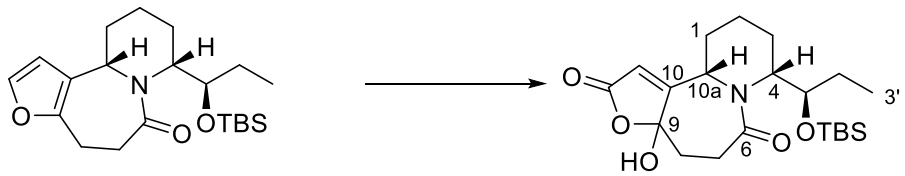
^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ [ppm] = 149.0 (s, C-9), 140.7 (d, C-12), 124.4 (s, C-10), 109.7 (d, C-11), 76.8 (d, C-1'), 60.4 (d, C-4), 53.0 (d, C-10a), 33.7 (t, C-1), 33.2 (t, C-6),

31.6 (t, C-7), 27.5 (t, C-3), 26.1 [q, SiC(*C*H_3)$_3$], 26.0 (t, C-2'),25.1 (t, C-2), 24.6 (t, C-8), 18.3 [s, Si*C*(CH_3)$_3$], 8.6 (q, C-3'), –4.1 (q, SiCH_3), –4.3 (q, SiCH_3).

MS (ESI): *m/z* (%) = 364 (8) [$C_{21}H_{38}NO_2Si$]$^+$.

HRMS (ESI): [$C_{21}H_{38}NO_2Si$]$^+$ [M+H]$^+$ calculated: 364.2666; found: 364.2671.

(4*R*,10a*S*)-4-[(*R*)-1'-(*tert*-Butyldimethylsilyloxy)propyl]-9-hydroxy-1,2,3,4,8,10a-hexahydrofuro[3,2-c]pyrido[1,2-a]azepin-6,12(7*H*,9*H*)-dion (139)



$C_{21}H_{35}NO_5Si$
M = 409.60 g/mol

In a 50 mL phototube a solution of 427 mg (1.13 mmol, 1.00 eq.) lactam **138** in 33 mL MeOH was added under a protective argon atmosphere. Next, 11.5 mg (11.3 µmol, 1 mol%) rose bengal and 962 µL (731 mg, 5.66 mmol, 5.00 eq.) DIPEA were added. A balloon filled with air and equipped with a long cannula was utilized to ensure a constant bubbling of air through the solution. The reaction mixture was cooled to –78 °C and subsequently irradiated at λ = 420 nm for 1 h. After removal of the light source and having warmed to room temperature the solvent was removed under reduced pressure. The compound was purified by column chromatography (h = 17 cm, Ø = 2.5 cm, hexane/EtOAc = 2/1) to obtain a diastereomeric mixture of hydroxylated lactones **139** (*d.r.* = 9/1, 391 mg, 956 µmol, 84%) as a white solid.

TLC: R_f = 0.53 (hexane/EtOAc = 1/2) [UV, $KMnO_4$]

Specific rotation: $[\alpha]_D^{25}$ = +70 (c = 1.0, $CHCl_3$).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3169 (br s, O−H), 2956 (s, C−H), 2934 (s, C−H), 2882 (m, C−H), 2857 (m, C−H), 1764 (s, C=O), 1733 (s, C=O), 1648 (m, C−H), 1614 (m, C−H), 1386 (m), 1256 (m), 1189 (m), 838 (m).

Smp. [°C]: 178

Major diastereomer:

^{1}H-NMR (300 MHz, $CDCl_3$, 298 K): δ [ppm] = 5.92 (s, 1H, H-11), 5.64 (s, 1H, OH), 4.70 (*virt*. dt, ^3J = 9.8 Hz, $^3J \approx {}^3J$ = 4.5 Hz, 1H, H-4), 4.48 (dd, ^3J = 11.3 Hz, 6.4 Hz, 1H, H-10a), 3.72 (*virt*. dt, ^3J = 7.8 Hz, $^3J \approx {}^3J$ = 4.5 Hz, 1H, H-1'), 3.02 (*virt*. t, $^2J \approx {}^3J$ = 14.5 Hz, 1H, H-7), 2.65 (dd, ^2J = 14.5 Hz, ^3J = 7.1 Hz, 1H, H-7), 2.51 (dd, ^3J = 14.5 Hz, 7.1 Hz, 1H, H-8), 2.17 – 1.96 (m, 2H, H-1, H-3), 1.95 – 1.73 (m, 4H, H-1, H-2, H-3, H-8), 1.42 – 1.22 (m, 2H, H-2, H-2'), 1.16 – 1.01 (m, 1H, H-2'), 0.91 [s, 9H, $SiC(CH_3)_3$], 0.85 (t, ^3J = 7.3 Hz, 3H, H-3'), 0.13 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$).

^{13}C-NMR (75 MHz, $CDCl_3$, 298 K): δ [ppm] = 175.8 (s, C-6), 170.5 (s, C-12), 166.6 (s, C-10), 116.6 (d, C-11), 105.9 (s, C-9), 75.5 (d, C-1'), 52.6 (d, C-4), 49.2 (d, C-10a), 34.4 (t, C-8), 32.7 (t, C-7), 26.2 [q, SiC(CH_3)$_3$], 26.0 (t, C-2'), 25.9 (t, C-1), 22.6 (t, C-3), 18.4 [s, SiC(CH_3)$_3$], 18.3 (t, C-2), 11.1 (q, C-3'), –4.2 (q, $SiCH_3$), –4.2 (q, $SiCH_3$).

Characteristic signals minor diastereomer:

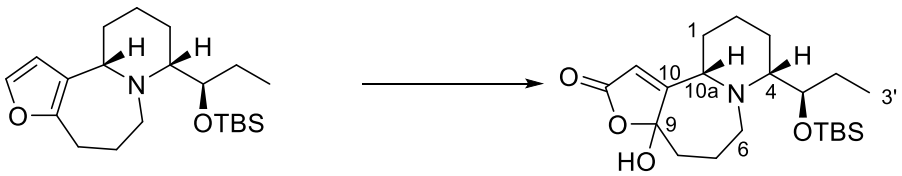
^{1}H-NMR (300 MHz, $CDCl_3$, 298 K): δ [ppm] = 5.86 (s, 1H, OH), 5.83 (d, ^{4}J = 2.4 Hz, 1H, H-11), 4.87 (dd, ^{3}J = 11.9 Hz, 5.0 Hz, 1H, H-4), 4.80 – 4.73 (m, 1H, H-10a), 3.47 (dd, ^{3}J = 10.7 Hz, 3.8 Hz, 1H, H-1'), 0.88 [s, 9H, SiC(CH_3)$_3$], 0.12 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$).

^{13}C-NMR (75 MHz, $CDCl_3$, 298 K): δ [ppm] = 175.3 (s, C-6), 169.5 (s, C-12), 167.2 (s, C-10), 116.1 (d, C-11), 106.1 (s, C-9), 82.1 (d, C-1'), 54.9 (d, C-10a), 48.6 (d, C-4), 26.2 [q, SiC(CH_3)$_3$], 18.4 [s, SiC(CH_3)$_3$].

MS (ESI): *m/z* (%) = 410 (100) $[C_{21}H_{36}NO_5Si]^+$, 278 (8) $[C_{15}H_{20}NO_4]^+$.

HRMS (ESI): $[C_{21}H_{36}NO_5Si]^+$ $[M+H]^+$ calculated: 410.2357; found: 410.2359.

(4*R*,10a*S*)-4-[(*R*)-1'-(*tert*-Butyldimethylsilyloxy)propyl]-9-hydroxy-1,2,3,4,8,10a-hexahydrofuro[3,2-c]pyrido[1,2-a]azepin-12(7*H*,9*H*)-on (223)



$C_{21}H_{37}NO_4Si$
M = 395.62 g/mol

In a flame dried 10 mL phototube a solution of 40.5 mg (111 µmol, 1.00 eq.) amine **219** in 4 mL MeOH was added under a protective argon atmosphere. Next, 5.7 mg (5.57 µmol, 5 mol%) rose bengal and 94.7 µL (72.0 mg, 555 µmol) DIPEA were added. A balloon filled with air and equipped with a long cannula was utilized to ensure a constant bubbling of air through the solution. The reaction mixture was cooled to –78 °C and subsequently irradiated at λ = 420 nm for 10 min. After removal of the light source and having warmed to room temperature, the solvent was removed under reduced pressure. The compound was purified by column chromatography (h = 22 cm, Ø = 1.5 cm, hexane/EtOAc = 5/1) to obtain the two diastereomeric hydroxylated lactones **223** (6.6 mg, 16.8 µmol, 15%) and (7.66 mg, 19.4 µmol, 17%) separately as clear oils.

First Diastereomer:

TLC: R_f = 0.41 (hexane/EtOAc = 3/1) [UV, $KMnO_4$]

Specific rotation: $[\alpha]_D^{25}$ = −34 (c = 1.0, $CHCl_3$).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3334 (br, O−H), 2953 (m, C−H), 2930 (m, C−H), 2857 (w, C−H), 1768 (s, C=O), 1463 (w, C−H), 1252 (m, C−O), 1095 (m, C−O), 835 (s, C−H), 773 (s, C−H).

^{1}H-NMR (500 MHz, C_6D_6, 298 K): δ [ppm] = 6.04 (d, ^4J = 1.3 Hz, 1H, H-11), 3.86 – 3.81 (m, 1H, H-6), 3.55 – 3.49 (m, 1H, H-6), 3.40 (*virt*. dt, ^3J = 6.6 Hz, $^3J \approx {}^3J$ = 4.8 Hz, 1H, H-1'), 3.14 – 3.08 (m, 1H, H-10a), 2.52 (ddd, ^3J = 11.1 Hz, 6.6 Hz, 2.5 Hz, 1H, H-4), 1.88 – 1.76 (m, 3H, H-1, H-7, H-8), 1.72 – 1.66 (m, 1H, H-8), 1.66 – 1.61 (m, 1H, H-2), 1.61 – 1.53 (m, 1H, H-2'), 1.48 – 1.41 (m, 1H, H-2'), 1.41 – 1.36 (m, 1H, H-7), 1.38 – 1.31 (m, 1H, H-3), 1.19 – 1.04 (m, 2H, H-1, H-2), 1.03 – 0.95 (m, 1H, H-3), 0.95 [s, 9H, $SiC(CH_3)_3$], 0.89 (t, ^3J = 7.5 Hz, 3H, H-3'), 0.06 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$).

^{13}C-NMR (126 MHz, C_6D_6, 298 K): δ [ppm] = 170.0 (s, C-10), 169.1 (s, C-12), 118.9 (d, C-11), 114.4 (s, C-9), 77.0 (d, C-1'), 70.2 (t, C-6), 59.6 (d, C-4), 54.6 (d, C-10a), 35.1 (t, C-8),

32.7 (t, C-1), 27.9 (t, C-3), 26.2 (t, C-2'), 26.1 [q, SiC(*C*H_3)$_3$], 24.9 (t, C-2), 24.5 (t, C-7), 18.4 [s, Si*C*(CH_3)$_3$], 8.8 (q, C-3'), −4.1 (q, SiCH_3), −4.4 (s, SiCH_3).

MS (ESI): *m/z* (%) = 338 (10) [$C_{17}H_{28}NO_4Si$]$^+$, 222 (100) [$C_{12}H_{16}NO_3$]$^+$.

HRMS (EI): [$C_{21}H_{37}NO_4Si$]$^+$ [M+H]$^+$ calculated: 395.2486; found: 395.2480.

Second Diastereomer:

TLC: R_f = 0.28 (hexane/EtOAc = 3/1) [UV, $KMnO_4$]

Specific rotation: $[\alpha]_D^{25}$ = −92 (c = 1.0, $CHCl_3$).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3337 (br, O−H), 2953 (m, C−H), 2930 (m, C−H), 2857 (w, C−H), 1766 (s, C=O), 1472 (w, C−H), 1251 (m, C−O), 1097 (m, C−O), 834 (s, C−H), 773 (s, C−H).

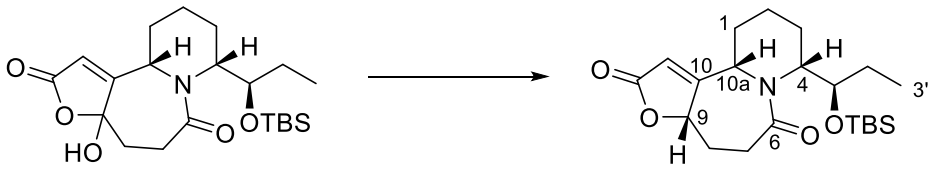
^{1}H-NMR (500 MHz, C_6D_6, 298 K): δ [ppm] = 5.96 (d, ^4J = 1.1 Hz, 1H, H-11), 3.88 – 3.81 (m, 1H, H-6), 3.63 – 3.56 (m, 1H, H-6), 3.38 (*virt*. dt, ^3J = 6.8 Hz, $^3J \approx {}^3J$ = 4.7 Hz, 1H, H-1'), 3.14 – 3.09 (m, 1H, H-10a), 2.48 (ddd, ^3J = 11.0 Hz, 6.8 Hz, 2.4 Hz, 1H, H-4), 1.87 – 1.74 (m, 2H, H-7, H-8), 1.72 – 1.66 (m, 1H, H-8), 1.66 – 1.61 (m, 1H, H-2), 1.60 – 1.49 (m, 1H, H-2'), 1.47 – 1.40 (m, 2H, H-2', H-7), 1.39 – 1.34 (m, 2H, H-1, H-3), 1.22 – 1.06 (m, 2H, H-1, H-2), 1.05 – 0.97 (m, 1H, H-3), 0.95 [s, 9H, SiC(CH_3)$_3$], 0.88 (t, ^3J = 7.5 Hz, 3H, H-3'), 0.06 (s, 3H, SiCH_3), 0.03 (s, 3H, SiCH_3).

^{13}C-NMR (126 MHz, C_6D_6, 298 K): δ [ppm] = 169.5 (s, C-10), 169.2 (s, C-12), 119.7 (d, C-11), 114.5 (s, C-9), 76.9 (d, C-1'), 70.1 (t, C-6), 59.7 (d, C-4), 54.2 (d, C-10a), 34.7 (t, C-8), 32.4 (t, C-1), 27.8 (t, C-3), 26.2 (t, C-2'), 26.1 [q, SiC(*C*H_3)$_3$], 24.8 (t, C-2), 24.5 (t, C-7), 18.4 [s, Si*C*(CH_3)$_3$], 8.8 (q, C-3'), −4.2 (q, SiCH_3), −4.3 (q, SiCH_3).

MS (ESI): *m/z* (%) = 338 (10) [$C_{17}H_{28}NO_4Si$]$^+$, 222 (100) [$C_{12}H_{16}NO_3$]$^+$.

HRMS (EI): [$C_{21}H_{37}NO_4Si$]$^+$ [M+H]$^+$ calculated: 395.2486; found: 395.2480.

(4*R*,9*S*,10a*S*)-4-[(*R*)-1'-(*tert*-Butyldimethylsilyloxy)propyl]-1,2,3,4,8,10a-hexahydrofuro[3,2-c]pyrido[1,2-a]azepin-6,12(7*H*,9*H*)-dion (224)



$C_{21}H_{35}NO_4Si$
M = 393.60 g/mol

In a 250 mL flask 331 mg (808 µmol, 1.00 eq.) hydroxylated lactone **139** as a mixture of diastereomers was dissolved in 30 mL THF and the resulting mixture was cooled to 0 °C. Next, 151 mg (404 µmol, 0.50 eq.) $CeCl_3 \cdot 7H_2O$ and 122 mg (3.23 mmol, 4.00 eq.) $NaBH_4$ were added and the mixture was diluted with 13 mL MeOH. The resulting mixture was stirred for 2 h at the same temperature, subsequently quenched by addition of 30 mL saturated Rochelle salt solution and stirred for another 1 h. Afterwards, the layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic fractions were dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 23 cm, Ø = 2.5 cm, hexane/EtOAc = 2/1 → 1/2) to obtain the unsaturated lactone **224** (260 mg, 661 µmol, 82%) as a colorless, viscous oil.

TLC: R_f = 0.38 (hexane/EtOAc = 1/2) [UV, $KMnO_4$]

Specific rotation: $[\alpha]_D^{25}$ = +66 (c = 1.0, $CHCl_3$).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2955 (m, C−H), 2933 (m, C−H), 2858 (w, C−H), 1752 (s, C=O), 1639 (s, C=C), 1458 (m, C−H), 1367, 1089 (m, C−O), 836 (m), 775 (s).

^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 5.99 (d, ^4J = 1.9 Hz, 1H, H-11), 4.89 (ddd, ^3J = 11.5 Hz, 6.5 Hz, ^4J = 1.9 Hz, 1H, H-9), 4.70 (*virt*. dt, ^3J = 10.1 Hz, $^3J \approx {}^3J$ = 4.6 Hz, 1H, H-4), 4.32 (dd, ^3J = 11.3 Hz, 6.4 Hz, 1H, 10a), 3.75 (*virt*. dt, ^3J = 8.6 Hz, $^3J \approx {}^3J$ = 4.6 Hz, 1H, H-1'), 2.79 – 2.70 (m, 2H, H-7), 2.65 – 2.54 (m, 1H, H-8), 2.20 – 2.08 (m, 1H, H-1), 2.05 – 1.96 (m, 1H, H-3), 1.96 – 1.90 (m, 1H, H-1), 1.88 – 1.75 (m, 2H, H-2, H-3), 1.69 – 1.54 (m, 1H, H-8), 1.40 – 1.28 (m, 2H, H-2, H-2'), 1.17 – 1.06 (m, 1H, H-2'), 0.91 [s, 9H, $SiC(CH_3)_3$], 0.85 (t, ^3J = 7.4 Hz, 3H, H-3'), 0.14 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$).

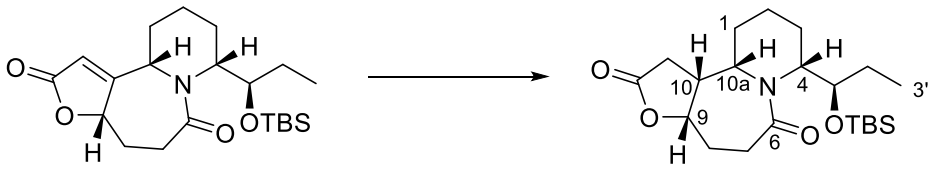
^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ [ppm] = 174.6 (s, C-6), 172.1 (s, C-12), 168.3 (s, C-10), 116.3 (d, C-11), 83.4 (d, C-9), 75.1 (d, C-1'), 52.8 (d, C-4), 50.9 (d, C-10a), 32.4 (t, C-7),

29.1 (t, C-8), 26.2 [q, SiC(*C*H_3)$_3$], 26.1 (t, C-1), 25.8 (t, C-2'), 22.5 (t, C-3), 18.5 [s, Si*C*(CH_3)$_3$], 18.3 (t, C-2), 11.1 (q, C-3'), –4.25 (q, SiCH_3), –4.25 (q, SiCH_3).

MS (EI): *m/z* (%) = 336 (100) $[C_{17}H_{26}NO_4Si]^+$, 220 (24) $[C_{12}H_{14}NO_3]^+$, 173 (43) $[C_9H_{21}OSi]^+$.

HRMS (EI): $[C_{12}H_{35}NO_4Si]^+$ $[M]^{\cdot+}$ calculated: 393.2330; found: 393.2328

(4*R*,9*S*,10*R*,10a*S*)-4-[(*R*)-1'-(*tert*-Butyldimethylsilyloxy)propyl]-octahydrofuro[3,2-c]pyrido[1,2-a]azepin-6,12(9*H*,11*H*)-dion (227)



$C_{21}H_{37}NO_4Si$
M = 395.62 g/mol

In a 250 mL flask 375 mg (952 µmol, 1.00 eq.) unsaturated lactone **224** was dissolved in 16 mL THF and the resulting mixture was cooled to 0 °C. Next, 113 mg (476 µmol, 0.50 eq.) $NiCl_2 \cdot 6H_2O$ and 288 mg (7.62 mmol, 8.00 eq.) $NaBH_4$ were added. To the reaction mixture was slowly added 7 mL MeOH and it was subsequently stirred for 3 h at 0 °C before warming to room temperature and stirring for another 2 h. The reaction was quenched by addition of 30 mL saturated Rochelle salt solution and stirred for 15 h. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic fractions were washed with 30 mL brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 18 cm, Ø = 3.5 cm, hexane/EtOAc = 2/1 → 1/2) to obtain the reduced lactone **227** (343 mg, 867 µmol, 91%) as a white solid.

TLC: R_f = 0.43 (hexane/EtOAc = 1/2) [$KMnO_4$]

Specific rotation: $[\alpha]_D^{25}$ = +44 (c = 1.0, $CHCl_3$).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2952 (m, C−H), 2934 (m, C−H), 2860 (w, C−H), 1776 (s, C=O), 1645 (s, C=O), 1311 (w, C−N), 1005 (s, C−O), 836 (m), 775 (s).

Smp. [°C]: 155

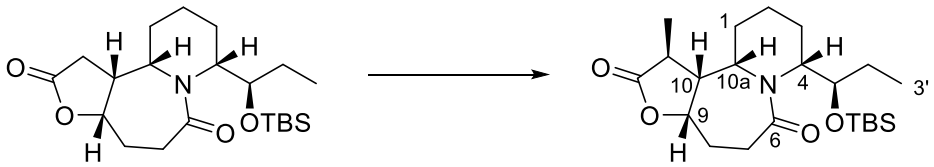
^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 4.90 (*virt*. dt, ^3J = 10.5 Hz, $^3J \approx {}^3J$ = 3.9 Hz, 1H, H-4), 4.59 (ddd, ^3J = 11.6 Hz, 7.5 Hz, 5.9 Hz, 1H, H-9), 3.90 (dd, ^3J = 12.6 Hz, 5.3 Hz, 1H, H-10a), 3.58 (*virt*. dt, ^3J = 7.7 Hz, $^3J \approx {}^3J$ = 3.9 Hz, 1H, H-1'), 2.82 (dd, ^2J = 17.2 Hz, ^3J = 13.7 Hz, 1H, H-11), 2.68 (ddd, ^3J = 13.7 Hz, 7.7 Hz, 7.5 Hz, 1H, H-10), 2.64 – 2.54 (m, 2H, H-7), 2.42 (dd, ^2J = 17.2 Hz, ^3J = 7.7 Hz, 1H, H-11), 2.30 – 2.21 (m, 1H, H-8), 2.11 – 2.02 (m, 1H, H-3), 2.01 – 1.92 (m, 1H, H-1), 1.80 – 1.72 (m, 1H, H-2), 1.72 – 1.62 (m, 3H, H-1, H-3, H-8), 1.52 – 1.41 (m, 1H, H-2'), 1.32 – 1.20 (m, 1H, H-2), 0.98 (t, ^3J = 7.4 Hz, 3H, H-3'), 0.93 [s, 9H, $SiC(CH_3)_3$], 0.14 (s, 3H, $SiCH_3$), 0.13 (s, 3H, $SiCH_3$).

^{13}C-NMR (75 MHz, $CDCl_3$, 298 K): δ [ppm] = 177.3 (s, C-6), 175.9 (s, C-12), 80.1 (d, C-9), 79.5 (d, C-1'), 54.3 (d, C-10a), 50.6 (d, C-4), 44.4 (d, C-10), 31.6 (t, C-7), 29.0 (t, C-1), 28.8 (t, C-11), 27.5 (t, C-2'), 26.4 [q, SiC(CH$_3$)$_3$], 26.2 (t, C-8), 24.2 (t, C-3), 19.7 (t, C-2), 18.6 [s, SiC(CH$_3$)$_3$], 11.3 (q, C-3'), –3.8 (q, $SiCH_3$), –4.3 (q, $SiCH_3$).

MS (EI): *m/z* (%) = 338 (100) $[C_{17}H_{28}NO_4Si]^+$, 222 (52) $[C_{12}H_{16}NO_3]^+$, 173 (21), $[C_9H_{21}OSi]^+$.

HRMS (ESI): $[C_{21}H_{38}NO_4Si]^+$ $[M+H]^+$ calculated: 396.2565; found: 396.2565.

(4*R*,9*S*,10*R*,10a*S*,11*S*)-4-[(*R*)-1'-(*tert*-Butyldimethylsilyloxy)propyl]-11-methyloctahydrofuro[3,2-c]pyrido[1,2-a]azepin-6,12(9*H*,11*H*)-dion (228)



$C_{22}H_{39}NO_4Si$
M = 409.64 g/mol

In a 250 mL flask 3.67 mL (0.5 M in PhMe, 1.84 mmol, 1.50 eq.) KHMDS was diluted with 28 mL THF and the resulting mixture was cooled to –78 °C. A solution of 484 mg (1.22 mmol, 1.00 eq.) reduced lactone **227** in 28 mL THF was added and the mixture was stirred at the same temperature for 1 h. Next, 610 µL (9.79 mmol, 8.00 eq.) MeI was added dropwise and the reaction mixture was stirred for another 4 h before being quenched by addition of 40 mL saturated, aqueous NH_4Cl solution. The layers were separated and the aqueous layer was extracted with EtOAc (5 × 15 mL). The combined organic fractions were washed with 25 mL brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 21 cm, Ø = 2.5 cm, hexane/EtOAc = 2/1) to obtain the methylated lactone **228** (451 mg, 1.10 mmol, 90%) as a white solid.

TLC: R_f = 0.54 (hexane/EtOAc = 1/2) [$KMnO_4$]

Specific rotation: $[\alpha]_D^{25}$ = +23 (c = 1.0, $CHCl_3$).

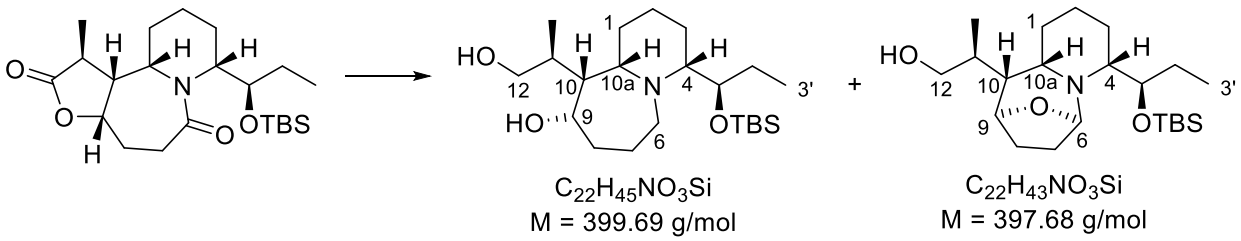
IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2954 (m, C−H), 2934 (m, C−H), 2873 (m, C−H), 2855 (w, C−H), 1775 (s, C=O), 1548 (s, C=O), 1088 (m), 1007 (s).

Smp. [°C]: 152

^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 4.61 – 4.49 (m, 2H, H-4, H-9), 3.99 (dd, ^3J = 12.5 Hz, 5.9 Hz, 1H, H-10a), 3.90 (*virt*. dt, ^3J = 7.0 Hz, $^3J \approx {}^3J$ = 4.7 Hz, 1H, H-1'), 2.81 (dq, ^3J = 11.5 Hz, 7.0 Hz, 1H, H-11), 2.68 – 2.55 (m, 2H, H-7), 2.31 (dd, ^3J = 11.5 Hz, 7.7 Hz, 1H, H-10), 2.27 – 2.17 (m, 1H, H-8), 2.08 – 1.98 (m, 1H, H-3), 1.97 – 1.84 (m, 1H, H-1), 1.83 – 1.72 (m, 2H, H-1, H-2), 1.72 – 1.65 (m, 1H, H-8), 1.65 – 1.53 (m, 1H, H-3), 1.51 – 1.37 (m, 2H, H-2'), 1.42 (d, ^3J = 7.0 Hz, 3H, H-18), 1.32 – 1.19 (m, 1H, H-2), 0.94 (t, ^3J = 7.4 Hz, 3H, H-3'), 0.90 [s, 9H, $SiC(CH_3)_3$], 0.15 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$).

^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ [ppm] = 179.1 (s, C-12), 177.2 (s, C-6), 78.4 (d, C-9), 76.2 (d, C-1'), 55.7 (d, C-4), 54.4 (d, C-10a), 51.3 (d, C-10), 34.0 (d, C-11), 32.1 (t, C-7), 30.0 (t, C-1), 26.2 [q, SiC(CH_3)$_3$], 26.1 (t, C-8), 25.6 (t, C-2'), 23.4 (t, C-3), 19.9 (t, C-2), 18.4 [s, SiC(CH_3)$_3$], 17.2 (q, C-18), 11.0 (q, C-3'), –4.0 (q, $SiCH_3$), –4.06 (q, $SiCH_3$).
MS (EI): *m/z* (%) = 352 (100) $[C_{18}H_{30}NO_4Si]^+$, 236 (79) $[C_{13}H_{18}NO_3]^+$, 173 (22) $[C_9H_{21}OSi]^+$.
HRMS (ESI): $[C_{22}H_{40}NO_4Si]^+$ $[M+H]^+$ calculated: 410.2721; found: 410.2724.

(4*R*,9*S*,10*R*,10a*S*)-4-[(*R*)-1'-(*tert*-Butyldimethylsilyloxy)propyl]-10-[(*S*)-12-hydroxypropan-11-yl]decahydropyrido[1,2-a]azepin-9-ol (140) and (4*R*,6*R*,9*S*,10*R*,10a*S*)-4-[(*R*)-1'-(*tert*-Butyldimethylsilyloxy)propyl]-10-[(*S*)-12-hydroxypropan-11-yl]decahydro-6,9-epoxypyrido[1,2-a]azepin (229)



$C_{22}H_{45}NO_3Si$
M = 399.69 g/mol

$C_{22}H_{43}NO_3Si$
M = 397.68 g/mol

Reduction of the lactam

In a 500 mL flask 334 mg (815 µmol, 1.00 eq.) methylated lactone **228** was dissolved in 330 mL $PhCH_3$. Next, 9.11 mL (3.5 M in $PhCH_3$, 9.43 g, 32.6 mmol, 40.0 eq.) sodium-bis-(2-methoxyethoxy)-aluminumhydride solution was added dropwise and the resulting reaction mixture was stirred for 15 h at room temperature. The reaction was subsequently quenched by careful addition of 150 mL saturated Rochelle salt solution and the mixture was stirred for another 8 h. The layers were separated and the aqueous layer was extracted with EtOAc (7 × 40 mL). The combined organic fractions were washed with brine (150 mL), dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 24 cm, Ø = 3.5 cm, hexane/EtOAc/MeOH = 5/1/0 → 2/1/0 → 0/50/1 → 0/20/1) to obtain tetrahydrofuran **229** (58.8 mg, 148 µmol, 18%) as a colorless, clear oil as well as diol **140** (165 mg, 413 µmol, 51%) as a white solid.

Tetrahydrofuran **229**:

TLC: R_f = 0.56 (hexane/EtOAc = 2/1) [$KMnO_4$]

Specific rotation: $[\alpha]_D^{25}$ = +54 (c = 1.0, $CHCl_3$).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3253 (br, O−H), 2956 (s, C−H), 2931 (s, C−H), 2859 (s, C−H), 1467 (w, C−H), 1254 (w, C−N), 1097 (s, C−O), 1040 (m), 774 (s).

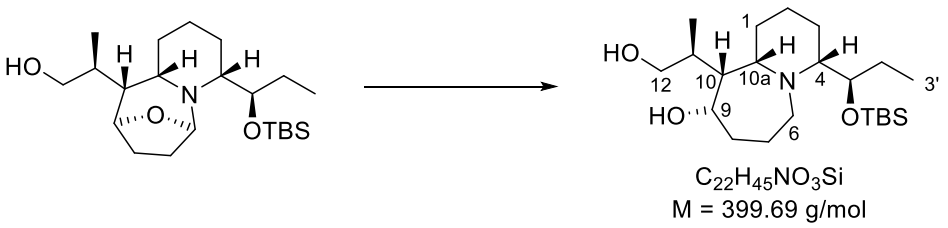
^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 6.43 (s, 1H, OH), 4.92 (d, ^3J = 5.7 Hz, 1H, H-6), 4.58 (d, ^3J = 7.1 Hz, 1H, H-9), 3.84 (*virt*. t, $^2J \approx {}^3J$ = 11.3 Hz, 1H, H-12), 3.80 – 3.75 (m, 1H, H-1'), 3.38 (*virt*. td, $^2J \approx {}^3J$ = 11.3 Hz, ^4J = 4.4 Hz, 1H, H-12), 2.57 – 2.50 (m, 1H, H-10a), 2.35 – 2.24 (m, 1H, H-11), 2.18 – 2.06 (m, 3H, H-4, H-7, H-8), 2.03 – 1.96 (m, 1H, H-1), 1.97 – 1.90 (m, 1H, H-3), 1.86 – 1.79 (m, 1H, H-2), 1.74 – 1.63 (m, 1H, H-7), 1.64 – 1.53

(m, 2H, H-2', H-8), 1.45 – 1.34 (m, 1H, H-2'), 1.33 – 1.22 (m, 2H, H-1, H-3), 1.21 – 1.15 (m, 2H, H-2, H-10), 0.93 – 0.87 [m, 15H, H-18, H-3', $SiC(CH_3)_3$], 0.04 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$).

^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ [ppm] = 86.5 (d, C-6), 74.9 (d, C-9), 71.9 (d, C-1'), 65.4 (t, C-12), 63.9 (d, C-4), 55.0 (d, C-10a), 48.6 (d, C-10), 33.1 (d, C-11), 29.3 (t, C-8), 29.1 (t, C-1), 26.0 [q, $SiC(CH_3)_3$], 24.6 (t, C-2), 23.8 (t, C-3), 23.0 (t, C-2'), 22.9 (t, C-7), 18.2 [s, $SiC(CH_3)_3$], 16.8 (q, C-18), 11.7 (q, C-3'), −4.3 (q, $SiCH_3$), −4.4 (q, $SiCH_3$).

MS (EI): *m/z* (%) = 224 (100) $[C_{13}H_{22}NO_2]^+$, 194 (11) $[C_{12}H_{20}NO]^+$.

HRMS (EI): $[C_{22}H_{43}NO_3Si]^+$; calculated: 397.3007; found: 397.2993.



$C_{22}H_{45}NO_3Si$
M = 399.69 g/mol

Reduction of the *N,O* acetal

In a 25 mL flask 39.0 mg (98.1 μmol, 1.00 eq.) tetrahydrofuran **229** was dissolved in 5 mL THF. Next, 981 μL (1 M in CH_2Cl_2, 981 μmol, 10.0 eq.) diisobutylaluminium hydride was added and the resulting reaction mixture was heated at reflux for 13 h. After having cooled to room temperature, the reaction was quenched by addition of 10 mL saturated Rochelle salt solution. The layers were separated and the aqueous layer was extracted with EtOAc (8 × 5 mL). The combined organic fractions were washed with 20 mL brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 20 cm, Ø = 1.5 cm, EtOAc/MeOH = 50/1 → 20/1) to obtain the diol **140** (27.1 mg, 67.8 μmol, 69%) as a white solid.

Diol **140**:

TLC: R_f = 0.37 (EtOAc/MeOH = 8/2) [$KMnO_4$]

Specific rotation: $[\alpha]_D^{25}$ = +62 (c = 1.0, $CHCl_3$).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3341 (br, O−H), 2955 (s, C−H), 2925 (s, C−H), 2848 (m, C−H), 1469 (w, C−H), 1251 (m, O−H), 1091 (s, C−O), 841 (s), 769 (s).

Smp. [°C]: 197

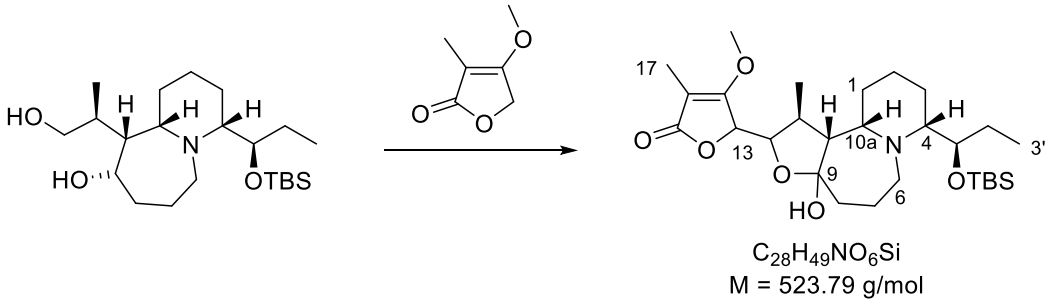
^{1}H-NMR (500 MHz, C_6D_6, 298 K): δ [ppm] = 4.32 (dd, ^{3}J = 5.4 Hz, 2.6 Hz, 1H, H-9), 3.87 (ddd, ^{3}J = 9.9 Hz, 3.6 Hz, 1.7 Hz, 1H, H-1'), 3.58 – 3.47 (m, 2H, H-12), 2.76 (*virt*. dt, ^{2}J = 14.8 Hz, $^{3}J \approx {}^{3}J$ = 3.9 Hz, 1H, H-6), 2.43 – 2.36 (m, 1H, H-10a), 2.35 – 2.29 (m, 2H, H-4, H-6), 2.12 – 2.01 (m, 1H, H-8), 2.00 – 1.89 (m, 1H, H-3), 1.86 – 1.81 (m, 1H, H-10), 1.80 – 1.71 (m, 4H, H-1, H-2', H-7, H-11), 1.71 – 1.66 (m, 1H, H-2), 1.52 – 1.42 (m, 2H, H-2', H-7), 1.38 – 1.31 (m, 1H, H-8), 1.30 – 1.21 (m, 1H, H-3), 1.05 – 0.97 (m, 1H, H-2), 0.99 [s, 9H, $SiC(CH_3)_3$], 0.98 (t, ^{3}J = 7.5 Hz, 3H, H-3'), 0.93 (d, ^{3}J = 6.7 Hz, 3H, H-18), 0.08 (s, 6H, $SiCH_3$).

^{13}C-NMR (126 MHz, C_6D_6, 298 K): δ [ppm] = 75.7 (d, C-1'), 70.7 (d, C-9), 68.5 (d, C-4), 66.6 (d, C-10a), 66.2 (t, C-12), 49.9 (t, C-6), 47.8 (d, C-10), 36.9 (t, C-8), 36.0 (d, C-11), 28.7 (t, C-1), 26.1 (t, C-7), 26.1 [q, $SiC(CH_3)_3$], 25.2 (t, C-3), 24.9 (t, C-2), 24.7 (t, C-2'), 18.3 [s, $SiC(CH_3)_3$], 18.2 (q, C-18), 12.3 (q, C-3'), –3.9 (q, $SiCH_3$), –4.2 (q, $SiCH_3$).

MS (EI): *m/z* (%) = 226 (100) $[C_{13}H_{24}NO_2]^+$, 210 (21) $[C_{13}H_{24}NO]^+$.

HRMS (ESI): $[C_{22}H_{46}NO_3Si]^+$ calculated: 400.3241; found: 400.3242.

13-{(4*R*,10*R*,10a*S*,11*S*)-4-[(*R*)-1'-(*tert*-Butyldimethylsilyloxy)propyl]-9-hydroxy-11-methyldodecahydrofuro[3,2-*c*]pyrido[1,2-*a*]azepin-12-yl}-14-methoxy-15-methylfuran-16(13H)-one. (144)



$C_{28}H_{49}NO_6Si$
M = 523.79 g/mol

Swern oxidation

In a 100 mL flask a solution of 67.1 µL (99.2 mg, 782 µmol, 5.00 eq.) oxalyl chloride in 3.3 mL CH_2Cl_2 was cooled to –78 °C. A solution of 83.3 µL (91.6 mg, 1.17 mmol, 7.50 eq.) DMSO in 1.2 mL CH_2Cl_2 was added and the mixture was stirred for 15 min. Next, a solution of 62.5 mg (156 µmol, 1.00 eq.) diol **140** in 3.0 mL CH_2Cl_2 was added and stirred for 1 h. Subsequently, 327 µL (237 mg, 2.35 mmol, 15.0 eq.) NEt_3 was added. The cooling bath was removed and the reaction was warmed to room temperature over the course of 1 h. The reaction was quenched by addition of 15 mL water. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic fractions were dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the keto-aldehyde was used in the next step without prior purification.

Aldol reaction

In a 50 mL flask the keto-aldehyde was dissolved in 5.9 mL THF and the resulting solution was cooled to –78 °C. Separately, in a 50 mL flask 370 mg (2.8 mmol, 18.5 eq.) tetronate **143** was dissolved in 5.9 mL THF and cooled to –78 °C. To this mixture, 5.62 mL (0.5 M in THF, 2.82 mmol, 18.0 eq.) freshly prepared LDA was added and the yellow solution was stirred for 1 h at this temperature. Then, the deprotonated tetronate solution was added to the keto-aldehyde solution *via* syringe and maintained at –78 °C for 2 h. The reaction was quenched by addition of 20 mL water. The layers were separated and the aqueous layer was extracted with EtOAc (5× 7 mL). The combined organic fractions were dried over Na_2SO_4 and filtered. After

removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 26 cm, Ø = 1.5 cm, hexane/EtOAc = 2/1 → 1/1 → 1/2) to obtain the hemiacetal **144** (49.7 mg, 94.9 µmol, 61%, *d.r.* = 75/25) as a colorless, clear oil.

TLC: R_f = 0.40 (hexane/EtOAc = 1/1) [UV, $KMnO_4$]

Specific rotation: $[\alpha]_D^{25}$ = −6 (c = 1.0, $CHCl_3$).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3227 (br, O−H), 2956 (s, C−H), 2931 (s, C−H), 2858 (m, C−H), 1754 (s, C=O), 1671 (s, C=C), 1459 (w, C−H), 1392 (m, O−H), 1334 (m, C−N), 1258 (m, C−N), 1089 (s, C=O), 836 (m), 799 (s), 775 (s).

Major diastereomer:

^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 4.51 – 4.47 (m, 2H, H-12, H-13), 4.11 (s, 3H, OMe), 3.81 – 3.74 (m, 1H, H-1'), 2.95 – 2.82 (m, 2H, H-6, H-11), 2.69 – 2.61 (m, 1H, H-10a), 2.58 – 2.46 (m, 1H, H-6), 2.43 (dd, ^3J = 12.2 Hz, 8.3 Hz, 1H, H-10), 2.36 – 2.28 (m, 1H, H-4), 1.99 (d, ^5J = 1.1 Hz, 3H, H-17), 1.91 – 1.82 (m, 2H, H-3, H-8), 1.80 – 1.75 (m, 1H, H-2), 1.71 – 1.64 (m, 1H, H-1), 1.63 –1.53 (m, 3H, H-2', H-3, H-7), 1.53 – 1.46 (m, 1H, H-8), 1.47 – 1.39 (m, 2H, H-1, H-7), 1.39 – 1.32 (m, 1H, H-2'), 1.15 –1.08 (m, 1H, H-2), 1.13 (d, ^3J = 6.8 Hz, 3H, H-18), 0.93 (t, ^3J = 7.4 Hz, 3H, H-3'), 0.88 [s, 9H, $SiC(CH_3)_3$], 0.06 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$).

^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ [ppm] = 175.8 (s, C-16), 171.8 (s, C-14), 108.8 (s, C-9), 98.2 (s, C-15), 78.3 (d, C-13), 78.0 (d, C-12), 74.9 (d, C-1'), 68.4 (d, C-4), 61.9 (d, C-10a), 59.1 (q, OCH_3), 53.3 (d, C-10), 51.5 (t, C-6), 39.2 (t, C-8), 36.2 (d, C-11), 28.5 (t, C-1), 26.0 [q, $SiC(CH_3)_3$], 25.5 (t, C-7), 24.6 (t, C-3), 24.4 (t, C-2'), 24.0 (t, C-2), 18.2 [s, $SiC(CH_3)_3$], 14.0 (q, C-18), 12.1 (q, C-3'), 8.7 (q, C-17), –3.9 (q, $SiCH_3$), –4.3 (q, $SiCH_3$).

Characteristic signals minor diastereomer:

^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 4.74 (dq, ^3J = 4.3 Hz, ^5J = 1.3 Hz, 1H, H-13), 4.39 (dd, ^3J = 8.0 Hz, 4.3 Hz, 1H, H-12), 4.11 (s, 3H, OCH_3), 2.95 – 2.83 (m, 1H, H-6), 2.80 – 2.70 (m, 1H, H-11), 2.59 – 2.46 (m, 1H, H-6), 2.39 – 2.27 (m, 2H, H-4, H-10), 2.09 – 2.04 (m, 1H, H-8), 1.97 (d, ^5J = 1.3 Hz, 3H, H-17), 1.73 – 1.68 (m, 1H, H-8), 1.25 (t, ^3J = 7.2 Hz, 3H, H-3'), 0.97 (d, ^3J = 7.1 Hz, 3H, H-18), 0.88 [s, 9H, $SiC(CH_3)_3$], 0.07 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$).

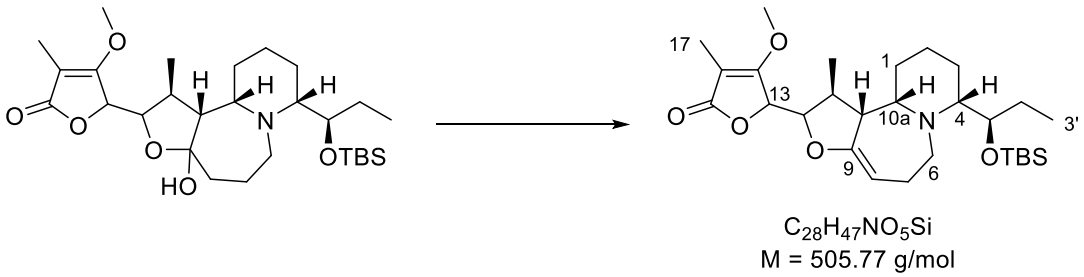
^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ [ppm] = 175.0 (s, C-16), 172.6 (s, C-14), 108.1 (s, C-9), 98.7 (s, C-15), 79.9 (d, C-12), 79.8 (d, C-13), 68.2 (d, C-4), 59.2 (q, OCH_3), 54.6 (d, C-

10), 51.1 (t, C-6), 39.7 (t, C-8), 37.2 (d, C-11), 26.0 [q, SiC(*C*H_3)$_3$], 14.3 (q, C-3'), 13.6 (q, C-18), 8.7 (q, C-17), –3.9 (q, SiCH_3), –4.3 (q, SiCH_3).

MS (EI): *m/z* (%): 396 (16) $[C_{22}H_{42}NO_3Si]^+$, 350 (100) $[C_{19}H_{28}NO_5]^+$, 332 (30) $[C_{19}H_{26}NO_4]^+$, 222 (13) $[C_{13}H_{20}NO_2]^+$.

HRMS (ESI): $[C_{28}H_{50}NO_6Si]^+$ $[M+H]^+$ calculated: 524.3402; found: 524.3393.

13-{(4*R*,10*R*,10a*S*,11*S*)-4-[(*R*)-1'-(*tert*-Butyldimethylsilyloxy)propyl]-11-methyl-1,2,3,4,6,7,10,10a,12,13-decahydrofuro[3,2-*c*]pyrido[1,2-*a*]azepin-12-yl}-14-methoxy-15-methylfuran-16(13H)-one. (278)



$C_{28}H_{47}NO_5Si$
M = 505.77 g/mol

In a 25 mL flask 25.1 mg (47.9 µmol, 1.00 eq.) hemiacetal **144** was dissolved in 3.2 mL CH_2Cl_2 and 2.2 mL pyridine and the resulting mixture was cooled to 0 °C. Next, 20.0 µL (30.2 mg, 144 µmol, 3.00 eq.) trifluoroacetic anhydride and 117 mg (958 µmol, 20.0 eq.) DMAP were added and the reaction mixture was stirred for 1 h at this temperature. The reaction was quenched by addition of 8 mL saturated, aqueous $NaHCO_3$ solution, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (5× 3 mL). The combined organic fractions were dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 20 cm, Ø = 1.5 cm, hexane/EtOAc = 7/1 → 3/1, 0.5% NEt_3) to obtain the two diastereomers of enol ether **278** (4.5 mg, 8.88 µmol, 19%) and (7.8 mg, 15.4 µmol, 32%) separately as colorless, clear oils.

First diastereomer:

TLC: R_f = 0.48 (hexane/EtOAc = 1/2) [UV, $KMnO_4$]

Specific rotation: $[\alpha]_D^{25}$ = −76 (c = 1.0, $CHCl_3$).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2937 (s, C−H), 2857 (m, C−H), 1759 (s, C=O), 1670 (s, C=C), 1461 (m, C−H), 1391 (m, O−H), 1334 (m, C−N), 1086 (m), 1056 (s), 836 (s), 775 (s).

^{1}H-NMR (500 MHz, C_6D_6, 298 K): δ [ppm] = 5.25 (ddd, ^3J = 8.9 Hz, 4.3 Hz, ^4J = 2.2 Hz, 1H, H-8), 4.30 (dd, ^3J = 7.1 Hz, ^5J = 1.3 Hz, 1H, H-13), 3.97 (*virt*. t, $^3J \approx {}^3J$ = 7.1 Hz, 1H, H-12), 3.44 (*virt*. dt, ^3J = 8.1 Hz, $^3J \approx {}^3J$ = 5.0 Hz, 1H, H-1'), 3.24 (s, 3H, OCH_3), 3.10 (ddd, ^2J = 13.1 Hz, ^3J = 6.6 Hz, 1.9 Hz, 1H, H-6), 2.96 – 2.92 (m, 1H, H-10), 2.82 – 2.77 (m, 1H, H-6), 2.66 – 2.58 (m, 2H, H-4, H-10a), 2.33 – 2.25 (m, 1H, H-7), 1.99 – 1.93 (m, 2H, H-7, H-11), 1.93 – 1.88 (m, 1H, H-2'), 1.81 – 1.74 (m, 2H, H-2, H-3), 1.73 – 1.67 (m, 1H, H-1), 1.69 (d, ^5J = 1.1 Hz, 3H, H-17), 1.58 – 1.47 (m, 1H, H-2'), 1.34 – 1.29 (m, 1H, H-3), 1.00 [s, 9H,

$SiC(CH_3)_3$], 0.98 – 0.93 (m, 6H, H-3', H-18), 0.92 – 0.87 (m, 1H, H-2), 0.84 – 0.78 (m, 1H, H-1), 0.07 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$).

^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ [ppm] = 173.2 (s, C-16), 173.0 (s, C-14), 159.4 (s, C-9), 99.4 (s, C-15), 96.7 (d, C-8), 83.9 (d, C-12), 77.3 (d, C-1'), 75.5 (d, C-13), 67.1 (d, C-4), 62.4 (d, C-10a), 58.2 (q, OCH_3), 54.7 (d, C-10), 43.1 (t, C-6), 39.5 (d, C-11), 28.0 (t, C-2'), 26.9 (t, C-7), 26.2 [q, $SiC(CH_3)_3$], 26.1 (t, C-3), 21.6 (t, C-2), 18.4 [s, $SiC(CH_3)_3$], 18.1 (t, C-1), 15.6 (q, C-18), 10.8 (q, C-3'), 8.4 (q, C-17), –4.1 (q, $SiCH_3$), –4.4 (q, $SiCH_3$).

MS (EI): *m/z* (%) = 448 (12) $[C_{24}H_{38}NO_5Si]^+$, 332 (100) $[C_{19}H_{26}NO_4]^+$, 251 (8) $[C_{14}H_{19}O_4]^+$.

HRMS (EI): $[C_{28}H_{47}NO_5Si]^{\cdot+}$ $[M+H]^{\cdot+}$calculated: 505.3218; found: 505.3218.

Second diastereomer:

TLC: R_f = 0.28 (hexane/EtOAc = 1/2) [UV, $KMnO_4$]

Specific rotation: $[\alpha]_D^{25}$ = −90 (c = 1.0, $CHCl_3$).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2938 (s, C−H), 2857 (m, C−H), 1760 (s, C=O), 1673 (s, C=C), 1460 (m, C−H), 1339 (m, C−N), 1055 (s, C−O), 1055 (s), 834 (s), 774 (s).

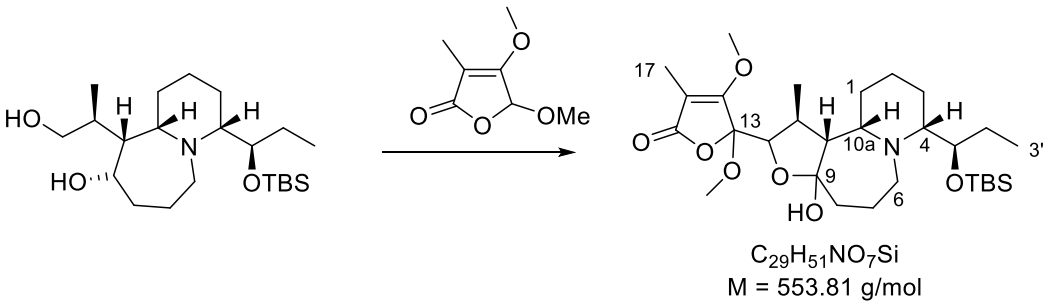
^{1}H-NMR (500 MHz, C_6D_6, 298 K): δ [ppm] = 5.21 (ddd, ^3J = 8.0 Hz, 4.4 Hz, ^4J = 2.4 Hz, 1H, H-8), 4.21 (dd, ^3J = 8.4 Hz, 1.4 Hz, 1H, H-12), 4.12 (dd, ^3J = 1.4 Hz, ^5J = 1.2 Hz, 1H, H-13), 3.46 (ddd, ^3J = 8.1 Hz, 5.4 Hz, 4.3 Hz, 1H, H-1'), 3.42 – 3.32 (m, 1H, H-10), 3.23 (s, 3H, OCH_3), 3.14 (ddd, ^2J = 13.4 Hz, ^3J = 7.1 Hz, 2.0 Hz, 1H, H-6), 3.02 – 2.92 (m, 1H, H-6), 2.76 (*virt*. dt, ^3J = 11.9 Hz, $^3J \approx {}^3J$ = 2.6 Hz, 1H, H-10a), 2.71 (ddd, ^3J = 11.9 Hz, 4.5 Hz, 2.4 Hz, 1H, H-4), 2.44 – 2.33 (m, 1H, H-7), 2.14 – 2.04 (m, 1H, H-11), 2.02 – 1.95 (m, 1H, H-7), 1.94 – 1.87 (m, 1H, H-2'), 1.98 – 1.81 (m, 3H, H-1, H-2, H-3), 1.71 (d, ^5J = 1.2 Hz, 3H, H-17), 1.51 (ddd, ^2J = 13.0 Hz, ^3J = 7.4 Hz, 5.5 Hz, 1H, H-2'), 1.43 – 1.34 (m, 1H, H-2), 1.14 – 1.05 (m, 1H, H-1), 1.01 – 0.94 (m, 1H, H-3), 0.98 [s, 9H, $SiC(CH_3)_3$], 0.97 (t, ^3J = 7.4 Hz, 3H, H-3'), 0.95 (d, ^3J = 7.1 Hz, 3H, H-18), 0.06 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$).

^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ [ppm] = 173.3 (s, C-16), 169.8 (s, C-14), 160.0 (s, C-9), 98.6 (s, C-15), 95.3 (d, C-8), 79.4 (d, C-12), 77.6 (d, C-1'), 77.6 (d, C-13), 67.2 (d, C-4), 61.6 (d, C-10a), 58.1 (q, OCH_3), 52.8 (d, C-10), 43.2 (t, C-6), 38.1 (d, C-11), 28.0 (t, C-2'), 27.1 (t, C-7), 26.3 (t, C-2), 26.2 [q, $SiC(CH_3)_3$], 22.5 (t, C-3), 18.4 [s, $SiC(CH_3)_3$], 18.0 (t, C-1), 14.1 (q, C-18), 10.9 (q, C-3'), 8.8 (q, C-17), –4.1 (q, $SiCH_3$), –4.5 (q, $SiCH_3$).

MS (EI): *m/z* (%) = 448 (12) $[C_{24}H_{38}NO_5Si]^+$, 332 (100) $[C_{19}H_{26}NO_4]^+$, 251 (8) $[C_{14}H_{19}O_4]^+$.

HRMS (EI): $[C_{28}H_{47}NO_5Si]^{\cdot+}$ $[M+H]^{\cdot+}$calculated: 505.3218; found: 505.3218.

13-{(4*R*,10*R*,10a*S*,11*S*)-4-[(*R*)-1'-(*tert*-Butyldimethylsilyloxy)propyl]-9-hydroxy-11-methyldodecahydrofuro[3,2-*c*]pyrido[1,2-*a*]azepin-12-yl}-13,14-dimethoxy-15-methylfuran-16(13H)-one. (286)



$C_{29}H_{51}NO_7Si$
M = 553.81 g/mol

Swern oxidation

In a 25 mL flask 32.5 µL (48.1 mg, 379 µmol, 5.00 eq.) oxalyl chloride and 3.2 mL CH_2Cl_2 were mixed and the resulting solution was cooled to –78 °C. A solution of 40.4 µL (44.4 mg, 569 µmol, 7.50 eq.) DMSO in 1.2 mL CH_2Cl_2 was added *via* syringe and the mixture was stirred at the same temperature for 15 min. Next, a solution of 30.3 mg (75.8 µmol, 1.00 eq.) diol **140** in 2.6 mL CH_2Cl_2 was added *via* syringe and the mixture was stirred for another 1 h. After addition of 158 µL (115 mg, 1.14 mmol, 15.0 eq.) NEt_3 the mixture was warmed to room temperature in the course of 1 h. The reaction mixture was subsequently quenched by addition of 10 mL water, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 5 mL). The combined organic fractions were dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the keto-aldehyde was used in the next step without prior purification.

Aldol reaction

The keto-aldehyde was dissolved in 2.9 mL THF and the resulting solution was cooled to –78 °C. Separately, 123 mg (780 µmol, 10.3 eq.) 5-methoxy-tetronate **253** was dissolved in 2.9 mL THF and the resulting solution was cooled to –78 °C. Next, 1.52 mL (0.5 M in THF, 758 µmol, 10.0 eq.) freshly prepared LDA was added to the tetronate and the resulting yellow solution was stirred for 1 h at the same temperature. After this time, the deprotonated tetronate solution was added to the keto-aldehyde solution *via* syringe and the reaction mixture was stirred for another 2 h. The reaction mixture was quenched by addition of 10 mL water and

after having warmed to room temperature, the layers were separated. The aqueous layer was extracted with EtOAc (5× 4 mL) and the combined organic fractions were dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 28 cm, Ø = 1.5 cm, hexane/EtOAc = 4/1 → 2/1 → 1/1) to obtain the hemiacetal **286** (31.7 mg, 57.3 μmol, 76%, *d.r.* = 60/26/14) as a mixture of three diastereomers as a colorless, clear oil.

TLC: R_f = 0.62 (CH_2Cl_2/MeOH = 9/1) [UV, $KMnO_4$]

Specific rotation: $[\alpha]_D^{25}$ = −30 (c = 1.0, $CHCl_3$).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3217 (br, O−H), 2964 (s, C−H), 2944 (s, C−H), 2858 (m, C−H), 1764 (s, C=O), 1676 (s, C=C), 1459 (w, C−H), 1391 (m, O−H), 1325 (m, C−N), 1086 (s, C−O), 1000 (m), 836 (s), 774 (s), 757 (s).

Diastereomer 1:

^{1}H-NMR (500 MHz, C_6D_6, 298 K): δ [ppm] = 4.72 (d, ^3J = 8.5 Hz, 1H, H-12), 3.80 – 3.70 (m, 1H, H-1'), 3.31 (s, 3H, C-14OCH_3), 2.95 (s, 3H, C-13OCH_3), 2.96 – 2.89 (m, 1H, H-11), 2.60 – 2.52 (m, 2H, H-6, H-10), 2.35 (ddd, ^3J = 11.4 Hz, 8.2 Hz, 2.9 Hz, 1H, H-10a), 2.32 – 2.24 (m, 1H, H-8), 2.23 – 2.17 (m, 1H, H-4), 2.06 – 1.95 (m, 1H, H-6), 1.98 – 1.93 (m, 1H, H-3), 1.91 – 1.85 (m, 1H, H-3), 1.81 (s, 3H, H-17), 1.76 – 1.67 (m, 1H, H-8), 1.62 – 1.55 (m, 2H, H-2, H-2'), 1.53 – 1.47 (m, 1H, H-1), 1.46 – 1.39 (m, 2H, H-1, H-7), 1.37 (d, ^3J = 7.1 Hz, 3H, H-18), 1.37 – 1.29 (m, 1H, H-2'), 0.97 [s, 9H, SiC(CH_3)$_3$], 0.99 – 0.91 (m, 1H, H-2), 0.88 (t, ^3J = 7.4 Hz, 3H, H-3'), 0.06 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3).

^{13}C-NMR (126 MHz, C_6D_6, 298 K): δ [ppm] = 172.4 (s, C-16), 168.4 (s, C-14), 108.7 (s, C-9), 107.3 (s, C-13), 100.8 (s, C-15), 80.0 (d, C-12), 75.3 (d, C-1'), 68.6 (d, C-4), 61.9 (d, C-10a), 58.2 (q, C-14O*C*H_3), 54.1 (d, C-10), 50.8 (t, C-6), 49.8 (q, C-13O*C*H_3), 40.3 (t, C-8), 37.5 (d, C-11), 28.4 (t, C-1), 26.2 [q, SiC(*C*H_3)$_3$], 26.1 (t, C-7), 24.9 (t, C-3), 24.7 (t, C-2'), 24.2 (t, C-2), 18.3 [q, Si*C*(CH_3)$_3$], 13.9 (q, C-18), 12.2 (q, C-3'), 8.1 (q, C-17), –4.0 (SiCH_3), –4.3 (SiCH_3).

Characteristic signals of diastereomer 2:

^{1}H-NMR (500 MHz, C_6D_6, 298 K): δ [ppm] =4.10 (d, ^3J = 8.8 Hz, 1H, H-12), 3.80 – 3.69 (m, 1H, H-1'), 3.63 (s, 3H, C-14OCH_3), 3.14 – 3.09 (m, 1H, H-11), 3.08 (s, 3H, C-13OCH_3), 2.71 – 2.63 (m, 1H, H-6), 2.32 – 2.24 (m, 2H, H-4, H-10a), 2.07 – 1.98 (m, 1H, H-6), 1.85 (s, 3H, H-17), 1.80 – 1.74 (m, 1H, H-10), 1.08 (d, ^3J = 6.3 Hz, 3H, H-18), 0.98 [s, 9H, SiC(CH_3)$_3$].

^{13}C-NMR (126 MHz, C_6D_6, 298 K): δ [ppm] = 171.2 (s, C-16), 166.6 (s, C-14), 108.0 (s, C-9), 106.8 (s, C-13), 103.1 (s, C-15), 86.4 (d, C-12), 75.3 (d, C-1'), 68.6 (d, C-4), 61.8 (d, C-

10a), 58.5 (q, C-14O*C*H$_3$), 57.3 (d, C-10), 51.9 (t, C-6), 50.5 (q, C-13O*C*H$_3$), 35.0 (d, C-11), 18.8 (q, C-18), 12.2 (q, C-3'), 8.6 (q, C-17).

Diastereomer 3:

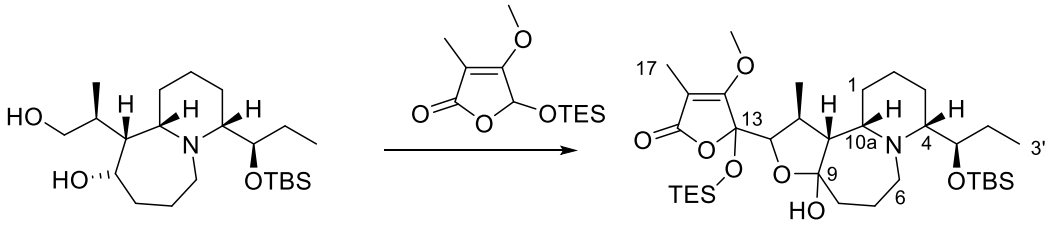
^{1}H-NMR (500 MHz, C_6D_6, 298 K): δ [ppm] = 4.24 (d, ^3J = 8.2 Hz, 1H, H-12), 3.84 – 3.77 (m, 1H, H-1'), 3.39 (s, 3H, C-14O*C*H$_3$), 2.96 (s, 3H, C-13O*C*H$_3$), 2.78 – 2.68 (m, 2H, H-6, H-11), 2.45 (dd, ^3J = 12.2 Hz, 8.1 Hz, 1H, H-10), 2.38 – 2.32 (m, 2H, H-8, H-10a), 2.29 – 2.24 (m, 1H, H-4), 2.23 – 2.16 (m, 1H, H-6), 1.87 – 1.78 (m, 1H, H-8), 1.72 (s, 3H, H-17), 1.71 – 1.64 (m, 1H, H-2'), 1.64 – 1.55 (m, 3H, H-2, H-3, H-7), 1.54 – 1.44 (m, 1H, H-1), 1.47 – 1.40 (m, 1H, H-7), 1.42 – 1.35 (m, 2H, H-3, H-2'), 1.27 (d, ^3J = 7.0 Hz, 3H, H-18), 0.99 – 0.93 (m, 1H, H-2), 0.98 [s, 9H, SiC(CH$_3$)$_3$], 0.94 (t, ^3J = 7.4 Hz, 3H, H-3'), 0.07 (s, 6H, SiCH$_3$).

^{13}C-NMR (126 MHz, C_6D_6, 298 K): δ [ppm] = 170.9 (s, C-16), 170.1 (s, C-14), 108.8 (s, C-9), 105.8 (s, C-13), 102.2 (s, C-15), 84.3 (d, C-12), 75.4 (d, C-1'), 68.5 (d, C-4), 62.2 (d, C-10a), 58.4 (q, C-14O*C*H$_3$), 54.1 (d, C-10), 50.7 (t, C-6), 50.3 (q, C-13O*C*H$_3$), 40.4 (t, C-8), 38.5 (d, C-11), 28.0 (t, C-1), 26.2 (t, C-7), 26.1 [q, SiC(*C*H$_3$)$_3$], 25.0 (t, C-2'), 24.7 (t, C-3), 24.3 (t, C-2), 18.3 [s, Si*C*(CH$_3$)$_3$], 14.0 (q, C-18), 12.3 (q, C-3'), 8.2 (q, C-17), –3.9 (q, SiCH$_3$), –4.3 (q, SiCH$_3$).

MS (ESI): *m/z* (%) = 554 (100) [$C_{29}H_{52}NO_7Si$]$^+$, 536 (92) [$C_{29}H_{50}NO_6Si$]$^+$.

HRMS (ESI): [$C_{29}H_{52}NO_7Si$]$^+$ [M+H]$^+$ calculated: 554.3508; found: 554.3497.

13-{(4*R*,10*R*,10a*S*,11*S*)-4-[(*R*)-1'-(*tert*-Butyldimethylsilyloxy)propyl]-9-hydroxy-11-methyldodecahydrofuro[3,2-*c*]pyrido[1,2-*a*]azepin-12-yl}-14-methoxy-15-methyl-13-[(triethylsilyl)oxy]furan-16(13*H*)-one. (289)



$C_{34}H_{63}NO_7Si_2$
M = 654.05 g/mol

Swern reaction

In a 100 mL flask 118 µL (175 mg, 1.38 mmol, 5.00 eq.) oxalyl chloride and 10.4 mL CH_2Cl_2 were mixed and the resulting solution was cooled to –78 °C. A solution of 147 µL (161 mg, 2.06 mmol, 7.50 eq.) DMSO in 5.6 mL CH_2Cl_2 was added *via* syringe at this temperature and the mixture was stirred for 15 min. A solution of 110 mg (275 µmol, 1.00 eq.) diol **140** in 11.0 mL CH_2Cl_2 was added *via* syringe and the reaction mixture was stirred at this temperature for another 1 h. After addition of 575 µL (418 mg, 4.13 mmol, 15.0 eq.) NEt_3 the reaction was warmed to room temperature over the course of 1 h. The reaction was quenched by addition of 40 mL saturated, aqueous $NaHCO_3$ and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (4 × 12 mL) and the combined organic fractions were washed with brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the keto-aldehyde was used in the next step without prior purification.

Aldol reaction

In a 100 mL flask the keto-aldehyde was dissolved in 22 mL THF and the resulting mixture was cooled to –78°C. Separately, 706 mg (2.73 mmol, 9.9 eq.) TES-protected tetronate **252** was dissolved in 22 mL THF and the resulting mixture was cooled to –78 °C. After addition of 5.23 mL (0.5 M in THF, 261 mmol) freshly prepared LDA, the yellow reaction mixture was stirred for another 1 h. Next, the deprotonated tetronate was added to the keto-aldehyde solution *via* syringe at the same temperature and the resulting mixture was stirred for another 2 h. The reaction was quenched by addition of 30 mL saturated, aqueous $NaHCO_3$ and

warmed to room temperature. After separation of the layers, the aqueous layer was extracted with EtOAc (5 × 6 mL). The combined organic fractions were dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 23 cm, Ø = 2.5 cm, hexane/EtOAc = 5/1) to obtain a mixture of four diastereomers of the protected alcohol **289** (120 mg, 187 μmol, 68%, *d.r.* = 66/12/11/11) as a colorless, clear oil.

TLC: R_f = 0.39 (hexane/EtOAc = 2/1) [UV, $KMnO_4$]

Specific rotation: $[\alpha]_D^{25}$ = −4 (c = 1.0, $CHCl_3$).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3288 (br, O−H), 2947 (s, C−H), 2928 (s, C−H), 2877 (m, C−H), 1766 (s, C=O), 1678 (s, C=C), 1460 (m, C−H), 1390 (m, O−H), 1332 (m, C−N), 1008 (s, C−O), 837 (s), 775 (s).

Major diastereomer:

^{1}H-NMR (500 MHz, C_6D_6, 298 K): δ [ppm] = 5.26 (br s, 1H, OH), 4.64 (d, ^3J = 8.5 Hz, 1H, H-12), 3.74 – 3.70 (m, 1H, H-1'), 3.39 (s, 3H, OCH_3), 2.96 – 2.86 (m, 1H, H-11), 2.57 – 2.51 (m, 2H, H-6, H-10), 2.35 (ddd, ^3J = 11.3 Hz, 8.1 Hz, 2.8 Hz, 1H, H-10a), 2.29 – 2.23 (m, 1H, H-8), 2.20 (*virt*. dt, ^3J = 11.7 Hz, $^3J \approx {}^3J$ = 3.4 Hz, 1H, H-4), 2.01 – 1.92 (m, 1H, H-6), 1.91 – 1.86 (m, 1H, H-3), 1.83 (s, 3H, H-17), 1.69 – 1.65 (m, 1H, H-8), 1.62 – 1.55 (m, 2H, H-2, H-2'), 1.55 – 1.51 (m, 1H, H-1), 1.50 – 1.38 (m, 3H, H-1, H-7), 1.37 (d, ^3J = 6.9 Hz, 3H, H-18), 1.35 – 1.26 (m, 1H, H-2'), 1.11 – 1.05 (m, 1H, H-3), 1.00 [t, ^3J = 7.9 Hz, 9H, $Si(CH_2CH_3)_3$], 0.99 – 0.92 (m, 1H, H-2), 0.96 [s, 9H, $SiC(CH_3)_3$], 0.87 (t , ^3J = 7.4 Hz, 3H, H-3'), 0.67 (q, ^3J = 7.9 Hz, 6H, $Si(CH_2CH_3)_3$], 0.05 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$).

^{13}C-NMR (126 MHz, C_6D_6, 298 K): δ [ppm] = 172.4 (s, C-16), 171.2 (s, C-14), 108.5 (s, C-9), 104.0 (s, C-13), 98.4 (s, C-15), 80.6 (d, C-12), 75.3 (d, C-1'), 68.6 (d, C-4), 61.9 (d, C-10a), 58.2 (q, OCH_3), 54.0 (d, C-10), 50.7 (t, C-6), 40.3 (t, C-8), 37.2 (d, C-11), 28.4 (t, C-1), 26.2 [q, $SiC(CH_3)_3$], 26.1 (t, C-7), 24.9 (t, C-3), 24.7 (t, C-2'), 24.3 (t, C-2), 18.3 [s, $SiC(CH_3)_3$], 14.2 (q, C-18), 12.2 (q, C-3'), 8.2 (q, C-17), 6.9 [q, $Si(CH_2CH_3)_3$], 5.9 [t, $Si(CH_2CH_3)_3$], –4.0 (q, $SiCH_3$), –4.3 (q, $SiCH_3$).

Characteristic signals minor diastereomer:

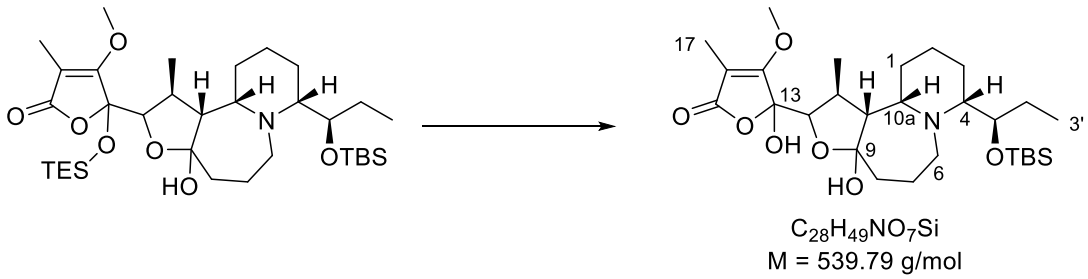
^{1}H-NMR (500 MHz, C_6D_6, 298 K): δ [ppm] = 4.01 (d, ^3J = 8.9 Hz, 1H, H-12), 3.78 – 3.75 (m, 1H, H-1'), 3.66 (s, 3H, OCH_3), 3.20 – 3.09 (m, 1H, H-11), 2.72 – 2.65 (m, 1H, H-6), 2.21 – 2.15 (m, 1H, H-8), 2.09 – 2.01 (m, 1H, H-6), 1.70 (s, 3H, H-17), 1.43 – 1.37 (m, 1H, H-8), 0.81 – 0.70 [m, 6H, $Si(CH_2CH_3)_3$], 0.07 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$).

^{13}C-NMR (126 MHz, C_6D_6, 298 K): δ [ppm] = 171.3 (s, C-16), 170.3 (s, C-14), 107.8 (s, C-9), 103.4 (s, C-13), 100.7 (s, C-15), 87.2 (d, C-12). 75.3 (d, C-1'), 58.7 (q, OCH_3), 51.8 (t, C-6), 40.6 (t, C-8), 8.2 (q, C-17), 7.0 [q, $Si(CH_2CH_3)_3$], 6.1 [t, $Si(CH_2CH_3)_3$], −3.9 (q, $SiCH_3$), −4.3 (q, $SiCH_3$).

MS (EI): *m/z* (%): 480 (51) $[C_{25}H_{42}NO_6Si]^+$, 462 (100) $[C_{25}H_{40}NO_5Si]^+$, 436 (34) $[C_{24}H_{42}NO_4Si]^+$, 348 (36) $[C_{19}H_{26}NO_5]^+$, 257 (29) $[C_{12}H_{21}O_4Si]^+$, 173 (25) $[C_9H_{21}OSi]^+$, 115 (72) $(C_6H_{15}Si]^+$.

HRMS (ESI): $[C_{34}H_{64}NO_7Si_2]^+$ $[M+H]^+$ calculated: 654.4216; found:654.4213.

13-{(4*R*,10*R*,10a*S*,11*S*)-4-[(*R*)-1'-(*tert*-Butyldimethylsilyloxy)propyl]-9-hydroxy-11-methyldodecahydrofuro[3,2-*c*]pyrido[1,2-*a*]azepin-12-yl}-13-hydroxy-14-methoxy-15-methylfuran-16(13*H*)-one. (277)



$C_{28}H_{49}NO_7Si$
M = 539.79 g/mol

In a 100 mL polyethylene flask, a solution of 74.3 mg (114 µmol, 1.00 eq.) protected alcohol **289** in 15 mL THF was cooled to 0 °C. Next, 78.0 µL (85.7 mg, 2.27 mmol, 20.0 eq.) hydrogenfluoride pyridine complex was added and the reaction was stirred at this temperature for 3 h. After this time, another 20.0 eq. hydrogenfluoride pyridine complex was added and the reaction mixture was stirred another 3 h. The reaction mixture was warmed to room temperature over 1 h and subsequently quenched by addition of 30 mL saturated, aqueous $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with EtOAc (7 × 9 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 25 cm, Ø = 2.5 cm, hexane/EtOAc = 5/1) to obtain a set of two diastereomeric alcohols (7.8 mg, 14.8 µmol, 13%, *d.r.* = 49/51) as a yellow oil as well as a second set of two diastereomeric alcohols (26.8 mg, 51.0 µmol, 45%, *d.r.* = 85/15) as a white solid.

Minor two diastereomers:

TLC: R_f = 0.60 (CH_2Cl_2/MeOH = 9/1) [UV, $KMnO_4$]

Specific rotation: $[\alpha]_D^{25}$ = +12 (c = 1.0, $CHCl_3$).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3249 (br, O–H), 2954 (m, C–H), 2931 (m, C–H), 2858 (w, C–H), 1756 (m, C=O), 1674 (s, C=C), 1462 (m, C–H), 1330 (m, O–H), 1087 (s, C–O), 1090 (m, C–O), 1003 (s, C–O), 751 (m).

Characteristic signals of both diastereomers:

^{1}H-NMR (500 MHz, C_6D_6, 298 K): δ [ppm] = 3.89 (d, ^3J = 6.9 Hz, 1H, H-12), 3.84 (d, ^3J = 6.9 Hz, 1H, H-12), 3.72 – 3.67 (m, 1H, H-1'), 3.67 – 3.62 (m, 1H, H-1'), 3.50 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3), 3.18 – 3.11 (m, 1H, H-11), 3.06 – 2.99 (m, 1H, H-11), 2.74 – 2.66 (m,

1H, H-6), 2.70 – 2.62 (m, 1H, H-6), 2.38 – 2.32 (m, 1H, H-8), 2.31 – 2.24 (m, 2H, H-8, H-10a), 2.23 – 2.13 (m, 3H, H-4, H-10a), 2.01 – 1.88 (m, 2H, H-6), 1.93 – 1.86 (m, 1H, H-10), 1.79 – 1.72 (m, 1H, H-10), 1.70 (s, 3H, H-17), 1.67 (s, 3H, H-17), 1.51 – 1.37 (m, 2H, H-8), 1.11 (t, ^3J = 7.0 Hz, 3H, H-3'), 1.06 (d, ^3J = 6.5 Hz, 3H, H-18), 0.97 [s, 18 H, SiC(CH_3)$_3$], 0.95 (t, ^3J = 7.5 Hz, 3H, H-3'), 0.89 (d, ^3J = 6.5 Hz, 3H, H-18), 0.07 (s, 3H, $SiCH_3$), 0.06 (s, 6H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$),

^{13}C-NMR (126 MHz, C_6D_6, 298 K): δ [ppm] = 173.3 (s, C-14), 171.6 (s, C-16), 171.5 (s, C-14), 168.3 (s, C-16), 109.7 (s, C-13), 108.3 (s, C-13), 101.4 (s, C-9), 101.2 (s, C-15), 100.7 (s, C-9), 98.6 (s, C-15), 90.2 (d, C-12), 88.7 (d, C-12), 75.2 (d, C-1'), 75.1 (d, C-1'), 69.2 (d, C-4), 69.0 (d, C-4), 61.8 (d, C-10a), 61.6 (d, C-10a), 58.6 (q, OCH_3), 58.4 (q, OCH_3), 58.1 (d, C-10), 57.0 (d, C-10), 53.7 (t, C-6), 53.4 (t, C-6), 39.4 (t, C-8), 37.0 (d, C-11), 35.7 (d, C-11), 26.1 [q, SiC(CH_3)$_3$], 26.0 [q, SiC(CH_3)$_3$], 20.5 (q, C-18), 19.5 (q, C-18), 18.3 [s, SiC(CH_3)$_3$], 18.2 [s, SiC(CH_3)$_3$], 15.6 (q, C-3'), 12.2 (q, C-3'), 8.6 (q, C-17), 7.9 (q, C-17), −3.9 (q, $SiCH_3$), −4.2 (q, $SiCH_3$), −4.3 (q, $SiCH_3$).

MS (EI): *m/z* (%) = 366 (17) $[C_{19}H_{28}NO_6]^+$, 348 (100) $[C_{19}H_{26}NO_5]^+$, 330 (41) $[C_{19}H_{24}NO_4]^+$, 312 (49) $[C_{19}H_{22}NO_3]^+$.

HRMS (EI): $[C_{28}H_{49}NO_7Si]^{\cdot+}$ $[M]^{\cdot+}$ calculated: 539.3273; found: 539.3258.

Major two diastereomers:

TLC: R_f = 0.55 (CH_2Cl_2/MeOH = 9/1) [UV, $KMnO_4$]

Specific rotation: $[\alpha]_D^{25}$ = –16 (c = 1.0, $CHCl_3$).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3285 (br, O–H), 2932 (s, C–H), 2955 (s, C–H), 2859 (s, C–H), 1759 (m, C=O), 1678 (s, C=C), 1462 (s, C–H), 1389 (s, O–H), 1330 (s, O–H), 1074 (s, C–O), 1042 (s, C–O), 1010 (s, C–O), 836 (s), 775 (s), 759 (s).

Smp. [°C]: 127

Major diastereomer:

^{1}H-NMR (500 MHz, C_6D_6, 298 K): δ [ppm] = 5.01 (br s, 1H, OH), 4.78 (d, ^3J = 8.5 Hz, 1H, H-12), 3.77 – 3.71 (m, 1H, H-1'), 3.50 (s, 3H, OCH_3), 3.06 – 2.87 (ddd, 1H, ^3J = 8.5 Hz, 6.9 Hz, 2.7 Hz, H-11), 2.63 – 2.58 (m, 1H, H-10), 2.60 – 2.52 (m, 1H, H-6), 2.36 (ddd, ^3J = 11.7 Hz, 8.2 Hz, 2.7 Hz, 1H, H-10a), 2.29 – 2.15 (m, 2H, H-4, H-8), 2.07 – 1.94 (m, 1H, H-6), 1.95 – 1.88 (m, 1H, H-3), 1.86 (s, 3H, H-17), 1.69 (ddd, ^2J = 12.9 Hz, ^3J = 8.4 Hz, 5.5 Hz, 1H, H-8), 1.66 – 1.61 (m, 1H, H-2), 1.61 – 1.55 (m, 2H, H-1, H-2'), 1.50 (d, ^3J = 6.9 Hz, 3H, H-18), 1.48 – 1.32 (m, 3H, H-1, H-2', H-7), 1.16 – 1.06 (m, 1H, H-3), 0.97 [s, 9H, SiC(CH_3)$_3$],

0.99 – 0.92 (m, 1H, H-2), 0.92 (t, ^{3}J = 7.4 Hz, 3H, H-3'), 0.06 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$).

^{13}C-NMR (126 MHz, C_6D_6, 298 K): δ [ppm] = 173.3 (s, C-16), 171.7 (s, C-14), 108.8 (s, C-9), 104.1 (s, C-13), 98.0 (s, C-15), 80.0 (d, C-12), 75.3 (d, C-1'), 68.6 (d, C-4), 61.9 (d, C-10a), 58.5 (q, OCH_3), 53.9 (d, C-10), 51.0 (t, C-6), 40.1 (t, C-8), 37.3 (d, C-11), 28.4 (t, C-1), 26.1 [q, $SiC(CH_3)_3$], 25.9 (t, C-7), 24.9 (t, C-3), 24.7 (t, C-2'), 24.2 (t, C-2), 18.3 [s, $SiC(CH_3)_3$], 14.0 (q, C-18), 12.3 (q, C-3'), 8.2 (q, C-17), –4.0 (q, $SiCH_3$), –4.3 (q, $SiCH_3$).

Characteristic signals minor diastereomer:

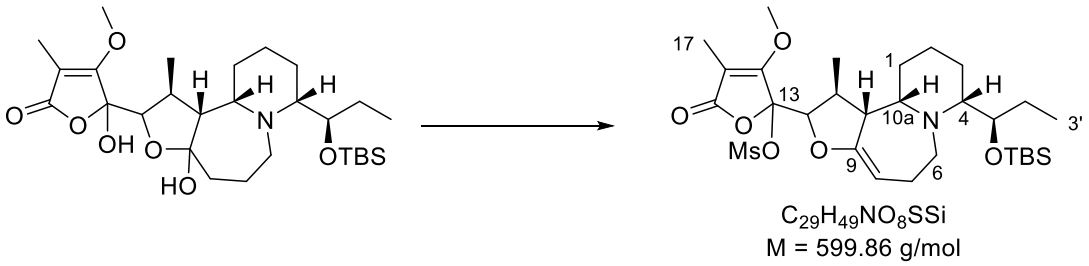
^{1}H-NMR (500 MHz, C_6D_6, 298 K): δ [ppm] = 4.58 (d, ^{3}J = 7.9 Hz, 1H, H-12), 3.79 – 3.74 (m, 1H, H-1'), 3.31 (s, 3H, OCH_3), 2.73 – 2.63 (m, 1H, H-11), 2.58 – 2.51 (m, 1H, H-6), 2.27 – 2.16 (m, 3H, H-4, H-8, H-10a), 2.08 – 2.03 (m, 1H, H-6), 1.94 – 1.88 (m, 1H, H-8), 1.63 (s, 3H, H-17), 0.08 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$).

^{13}C-NMR (126 MHz, C_6D_6, 298 K): δ [ppm] = 172.5 (s, C-16), 169.6 (s, C-14), 109.2 (s, C-9), 101.6 (s, C-13), 100.2 (s, C-15), 80.8 (d, C-12), 75.2 (d, C-1'), 68.2 (d, C-4), 61.3 (d, C-10a), 58.5 (q, OCH_3), 50.5 (t, C-6), 39.5 (t, C-8), 36.7 (d, C-11), 8.1 (q, C-17), −4.0(q, $SiCH_3$), −4.3 (q, $SiCH_3$).

MS (EI): *m/z* (%) = 366 (17) $[C_{19}H_{28}NO_6]^+$, 348 (100) $[C_{19}H_{26}NO_5]^+$, 330 (41) $[C_{19}H_{24}NO_4]^+$, 312 (49) $[C_{19}H_{22}NO_3]^+$.

HRMS (EI): $[C_{28}H_{49}NO_7Si]^{\cdot+}$ $[M]^{\cdot+}$ calculated: 539.3273; found: 539.3258.

13-{(4*R*,10*R*,10a*S*,11*S*)-4-[(*R*)-1'-(*tert*-Butyldimethylsilyloxy)propyl]-9-hydroxy-11-methyl-1,2,3,4,6,7,10,10a,12,13-decahydrofuro[3,2-*c*]pyrido[1,2-*a*]azepin-12-yl}-14-methoxy-15-methyl-16-oxo-13,16-dihydrofuran-13-yl methanesulfonate. (290d)



$C_{29}H_{49}NO_8SSi$
M = 599.86 g/mol

In a 50 mL flask 24.9 mg (46.1 µmol, 1.00 eq.) of the major two diastereomers of diol **277** was dissolved in 10 mL CH_2Cl_2 and the resulting mixture was cooled to 0 °C. Next, 64.3 µL (46.7 mg, 461 µmol, 10.0 eq.) NEt_3 and 17.9 µL (26.4 mg, 230 µmol, 5.00 eq.) methanesulfonylchloride were added and the reaction mixture was stirred at this temperature for 2 h. The reaction was quenched by addition of 10 mL saturated, aqueous $NaHCO_3$ solution and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic fractions were dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the compound was purified by column chromatography (h = 21 cm, Ø = 1.5 cm, pentane/acetone = 5/1) to obtain the mesylated alcohol **290d** (24.2 mg, 40.3 µmol, 88%) as a colorless oil.

TLC: R_f = 0.55 (CH_2Cl_2/MeOH = 9/1) [UV, $KMnO_4$]
Specific rotation: $[\alpha]_D^{25}$ = −68 (c = 1.0, $CHCl_3$).
IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2950 (m, C−H), 2929 (m, C−H), 2856 (m, C−H), 1787 (s, C=O), 1684 (s, C=C), 1462 (w, C−H), 1371 (s, S=O), 1327 (s, S=O), 1255 (w, C–O), 1173 (s, C–O), 1054 (s, C–O), 951 (s, C=C), 939 (s, C=C), 839 (s), 799 (s).
^{1}H-NMR (500 MHz, C_6D_6, 298 K): δ [ppm] = 5.16 (ddd, ^3J = 8.4 Hz, 4.2 Hz, ^4J = 2.2 Hz, 1H, H-8), 4.41 (d, ^3J = 7.4 Hz, 1H, H-12), 3.45 (*virt*. dt, ^3J = 8.2 Hz, $^3J \approx {}^3J$ = 4.9 Hz, 1H, H-1'), 3.39 (s, 3H, OCH_3), 3.34 – 3.27 (m, 1H, H-10), 3.13 (ddd, ^2J = 13.5 Hz, ^3J = 6.9 Hz, 2.0 Hz, 1H, H-6), 2.92 – 2.85 (m, 1H, H-6), 2.74 – 2.64 (m, 2H, H-4, H-10a), 2.37 (s, 3H, SO_2CH_3), 2.38 – 2.30 (m, 1H, H-7), 2.18 – 2.08 (m, 1H, H-11), 2.00 – 1.86 (m, 2H, H-2', H-7), 1.85 – 1.78 (m, 2H, H-2, H-3), 1.79 – 1.71 (m, 1H, H-1), 1.70 (s, 3H, H-17), 1.55 – 1.45 (m, 1H, H-2'), 1.40 – 1.31 (m, 1H, H-2), 1.10 (d, ^3J = 7.1 Hz, 3H, H-18), 0.98 [s, 9H,

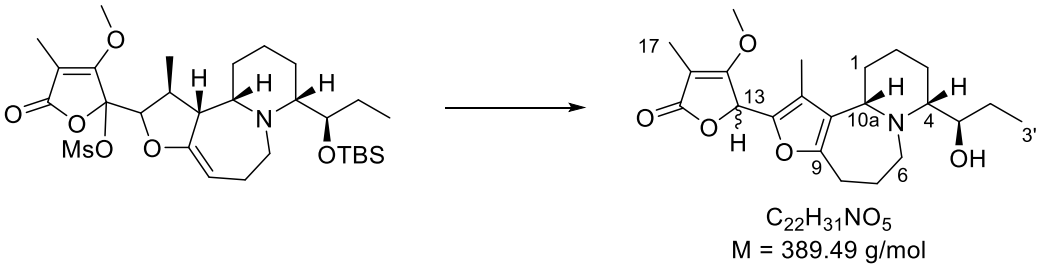
$SiC(CH_3)_3$], 0.99 – 0.91 (m, 2H, H-1, H-3), 0.96 (t, ^3J = 7.5 Hz, 3H, H-3'), 0.06 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$).

^{13}C-NMR (126 MHz, C_6D_6, 298 K): δ [ppm] = 170.0 (s, C-16), 167.9 (s, C-14), 158.8 (s, C-9), 105.9 (s, C-13), 100.1 (s, C-15), 97.2 (d, C-8), 79.8 (d, C-12), 77.5 (d, C-1'), 67.2 (d, C-4), 61.3 (d, C-10a), 58.9 (q, OCH_3), 53.3 (d, C-10), 42.8 (t, C-6), 40.8 (q, SO_2CH_3), 38.5 (d, C-11), 28.0 (t, C-2'), 26.9 (t, C-7), 26.3 [q, $SiC(CH_3)_3$], 26.2 (t, C-2), 22.1 (t, C-3), 18.4 [s, $SiC(CH_3)_3$], 17.6 (t, C-1), 14.5 (q, C-18), 10.9 (q, C-3'), 8.2 (q, C-17), −4.1 (q, $SiCH_3$), −4.4 (q, $SiCH_3$).

MS (EI): *m/z* (%) = 426 (13) $[C_{20}H_{28}NO_7S]^+$, 348 (10) $[C_{19}H_{28}NO_5]^+$, 330 (100) $[C_{19}H_{24}NO_4]^+$.

HRMS (ESI): $[C_{29}H_{50}NO_8SSi]^+$ $[M+H]^+$ calculated: 600.3021; found: 600.3021.

13-{(4*R*,10a*S*)-4-[(*R*)-1'-(*tert*-Butyldimethylsilyloxy)propyl]11-methyl-1,2,3,4,6,7,8,10a-octahydrofuro[3,2-*c*]pyrido[1,2-*a*]azepin-12-yl}-14-methoxy-15-methylfuran-16(13*H*)-one. (295)



$C_{22}H_{31}NO_5$
M = 389.49 g/mol

In a 25 mL flask 9.8 mg (16.3 μmol, 1.00 eq.) mesylate **290d** was dissolved in 4 mL dry CH_2Cl_2 under a protective argon atmosphere. Next, 53.0 μL (78.5 mg, 817 μmol, 50.0 eq.) methanesulfonic acid was added dropwise and the reaction mixture was stirred for 2 h at room temperature. The acid was subsequently neutralized with 271 mg (1.96 mmol, 120 eq.) K_2CO_3 and the mixture was stirred for another 30 min. Subsequently, 132 μL (129 mg, 1.63 mmol, 100 eq.) pyridine was added and stirring was continued for another 30 min. The reaction was quenched by addition of 4 mL saturated, aqueous $NaHCO_3$ and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic fractions were dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the compound was purified by column chromatography (h = 24 cm, Ø = 1.5 cm, EtOAc/CH_2Cl_2/MeOH/NEt_3 = 70/25/5/1) to obtain the two diastereomers of furostemokerrin **295** (4.8 mg, 12.3 μmol, 76%, *d.r.* = 51/49) as a colorless oil.

TLC: R_f = 0.31 (EtOAc/CH_2Cl_2/MeOH/NEt_3 = 70/25/5/1) [UV, $KMnO_4$]
Specific rotation: $[\alpha]_D^{25}$ = −24 (c = 1.0, $CHCl_3$).
IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3428 (br, O−H), 2929 (s, C−H), 2856 (m, C−H), 1757 (s, C=O), 1673 (s, C=C), 1461 (w, C−H), 1388 (w, C−H), 1337 (w, C−H), 1080 (w, C−O), 1018 (m, C−O).
^{1}H-NMR (500 MHz, C_6D_6, 298 K): δ [ppm] = 5.30 (q, ^5J = 1.3 Hz, 1H, H-13), 5.25 (q, ^5J = 1.4 Hz, 1H, H-13), 3.59 – 3.51 (m, 2H, H-10a, H-10a), 3.34 – 3.23 (m, 2H, H-1', H-1'), 3.12 (s, 3H, OCH_3), 3.07 (s, 3H, OCH_3), 2.64 – 2.49 (m, 6H, H-4, H-6, H-8, H-4, H-6, H-8), 2.36 – 2.30 (m, 2H, H-8, H-8), 2.30 – 2.24 (m, 2H, H-6, H-6), 1.77 (d, ^5J = 1.4 Hz, 3H, H-17), 1.75 (d, ^5J = 1.3 Hz, 3H, H-17), 1.65 (s, 3H, H-18), 1.64 (s, 3H, H-18), 1.59 – 1.46 (m, 6H, H-2, H-2', H-7, H-2, H-2', H-7), 1.46 – 1.39 (m, 4H, H-1, H-7, H-1, H-7), 1.39 – 1.32 (m, 2H, H-2', H-2'), 1.22 (t, ^3J = 7.3 Hz, 3H, H-3'), 1.20 (t, ^3J = 7.4 Hz, 3H, H-3'), 1.23 – 1.16 (m, 2H,

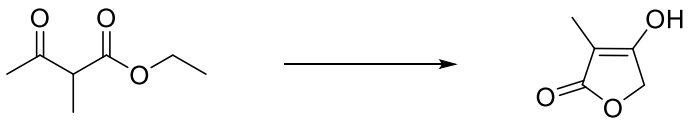
H-2, H-2), 1.13 – 1.07 (m, 1H, H-1), 1.10 – 1.04 (m, 1H, H-1), 1.05 – 0.98 (m, 2H, H-3, H-3), 0.93 – 0.85 (m, 2H, H-3, H-3).

^{13}C-NMR (126 MHz, C_6D_6, 298 K): δ [ppm] = 173. 5 (s, C-16), 173.4 (s, C-16), 169.4 (s, C-14, C-14), 151.6 (s, C-9), 151.4 (s, C-9), 139.7 (s, C-12), 139.6 (s, C-12), 124.1 (s, C-11, C-11), 121.5 (s, C-10), 121.3 (s, C-10), 99.6 (s, C-15), 99.3 (s, C-15), 71.1 (d, C-13), 71.1 (d, C-1', C-1'), 70.5 (d, C-13), 70.1 (d, C-4), 70.0 (d, C-4), 59.7 (d, C-10a), 59.6 (d, C-10a), 57.6 (q, OCH_3, OCH_3), 41.8 (t, C-6, C-6), 28.4 (t, C-8, C-8), 27.7 (t, C-7, C-7), 27.7 (t, C-2', C-2'), 25.4 (t, C-2), 24.7 (t, C-1), 24.5 (t, C-1), 20.2 (t, C-3, C-3), 10.6 (q, C-3'), 10.5 (q, C-3'), 8.2 (q, C-17, C-17), 7.9 (q, C-18, C-18).

MS (ESI): *m/z* (%) = 390 (100) $[C_{22}H_{32}NO_5]^+$.

HRMS (ESI): $[C_{22}H_{32}NO_5]^+$ $[M]^+$ calculated: 390.2275; found: 390.2263.

4-Hydroxy-3-methylfuran-2(5*H*)-one (243)



$C_5H_6O_3$
M = 114.10 g/mol

Bromination

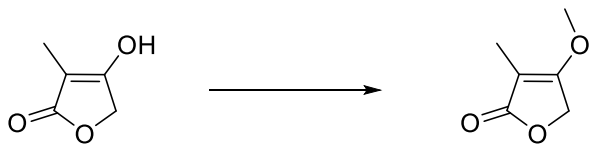
In a 100 mL flask 22.2 g (154 mmol, 1.00 eq.) ethyl 2-methyl-3-oxobutanoate (**240**) was emulsified in 45 mL water and the mixture was cooled to 0 °C. Next, 8.69 mL (27.1 g, 170 mmol, 1.10 eq.) Br_2 was slowly added and the ice bath was removed. After stirring for 17 h, the reaction was quenched by addition of 100 mL 1 M Na_2SO_3 solution and diluted with 100 mL CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic fractions were dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the brominated compound was obtained and used in the subsequent reaction without prior purification.

Cyclization

In a 50 mL flask the brominated compound was mixed with 20 drops aq. HBr (48%) and heated to 100 °C for 18 h. After having cooled to room temperature, the precipitated product was filtered off and washed with 40 mL EtOAc. The α-methyltetronate (**243**) (13.4 g, 118 mmol, 76% over two steps) was obtained as a white solid.

^{1}H-NMR (300 MHz, DMSO-d_6, 298 K): δ [ppm] = 11.76 (s, 1H, OH), 4.56 (q, ^5J = 1.3 Hz, 2H, CH_2), 1.57 (t, ^5J = 1.3 Hz, 3H, CH_3).
^{13}C-NMR (75 MHz, DMSO-d_6, 298 K): δ [ppm] = 175.3 (s, C-2), 173.0 (s, C-4), 94.4 (s, C-3), 66.5 (t, C-5), 6.0 (q, CH_3).
The obtained analytical data matched with literature values.[218]

4-Methoxy-3-methylfuran-2(5*H*)-one (143)



Chemical Formula: $C_6H_8O_3$
M = 128.13 g/mol

In a 500 mL flask 13.4 g (118 mmol, 1.00 eq.) α-methyltetronate (**243**) was mixed with 86.0 mL (130 mmol, 1.10 eq.) $(n\text{Bu})_4\text{NOH}$ (40% in H_2O) and the mixture was stirred for 30 min until fully dissolved. The water was subsequently removed under reduced pressure and the deprotonated compound was redissolved in 220 mL CH_2Cl_2. Next, 22.3 mL (29.7 g, 236 mmol, 2.00 eq.) Me_2SO_4 was added and the resulting mixture was stirred at room temperature for 21 h. The reaction was quenched by addition of 80 mL aqueous ammonia (25%) and stirred for another 24 h. The solution was then diluted with 100 mL water, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic fractions were dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 18 cm, Ø = 9 cm, hexane/EtOAc = 2/1 → 1/1) to obtain the methyl α-methyltetronate (**143**) (12.8 g, 99.6 mmol, 85%) as a colorless oil.

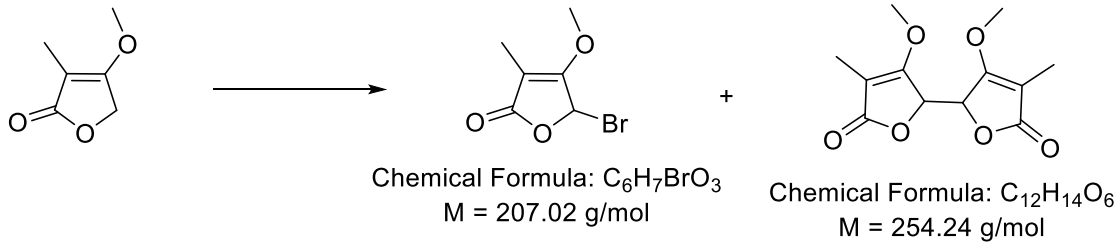
TLC: R_f = 0.46 (pentane/acetone = 3/1) [UV, $KMnO_4$]

^{1}H-NMR (300 MHz, $CDCl_3$, 298 K): δ [ppm] = 4.57 (q, ^5J = 1.5 Hz, 2H, CH_2), 3.93 (s, 3H, OCH_3), 1.75 (t, ^5J = 1.5 Hz, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$, 298 K): δ [ppm] = 175.4 (s, C-2), 172.3 (s, C-4), 98.4 (s, C-3), 65.7 (t, C-5), 57.8 (q, OCH_3), 7.1 (q, CH_3).

The obtained analytical data matched with literature values.[180]

5-Bromo-4-methoxy-3-methylfuran-2(5*H*)-one (245) and 3,3'-dimethoxy-4,4'-dimethyl-[2,2'-bifuran]-5,5'(2*H*,2'*H*)-dione (247)



Chemical Formula: $C_6H_7BrO_3$
M = 207.02 g/mol

Chemical Formula: $C_{12}H_{14}O_6$
M = 254.24 g/mol

In a 500 mL flask 2.76 g (21.6 mmol, 1.00 eq.) tetronate **143** was dissolved in 100 mL THF and the resulting mixture was cooled to –78 °C. Next, 51.8 mL (0.5 M in THF, 25.9 mmol, 1.20 eq.) freshly prepared LDA was added *via* syringe and the yellow solution was stirred for 1 h at this temperature. After this time, 1.66 mL (5.17 g, 32.4 mmol, 1.50 eq.) Br_2 was added and the reaction mixture stirred for 2 h. The reaction was quenched by addition of 70 mL 1 M $Na_2S_2O_3$ solution, warmed to room temperature and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 35 mL). The combined organic fractions were washed with 50 mL brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 21 cm, Ø = 4.5 cm, pentane/acetone = 6/1 → 4/1 → 2/1) to obtain the brominated tetronate **245** (1.25 g, 6.04 mmol, 28%) as a brown oil as well as the dimer **247** (974 mg, 3.83 mmol, 35%, *d.r.* = 78/22) as a brown solid.

Brominated tetronate **245**:

TLC: R_f = 0.65 (pentane/acetone = 3/1) [UV, $KMnO_4$]

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3002 (w, C−H), 2957 (w, C−H), 2868 (w, C−H), 1770 (s, C=O), 1661 (s, C=C), 1455 (m, C−H), 1390 (m, C−H), 1343 (s, C−O), 1299 (m, C−O), 1014 (s, C−O), 971 (s, C=C), 891 (m), 721 (s, C−Br).

^{1}H-NMR (300 MHz, $CDCl_3$, 298 K): δ [ppm] = 6.57 (q, ^5J = 0.9 Hz, 1H, CH), 4.15 (s, 3H, OCH_3), 1.97 (d, ^5J = 0.9 Hz, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$, 298 K): δ [ppm] = 171.4 (s, C-2), 171.1 (s, C-4), 99.8 (s, C-3), 72.2 (d, C-5), 59.0 (q, OCH_3), 8.1 (q, CH_3).

MS (EI): *m/z* (%) = 127 (100) $[C_6H_7O_3]^+$, 99 (15) $[(C_5H_7O_2)^+]$.

HRMS (EI): $[C_6H_7O_3{}^{79}Br]^{\cdot+}$ calculated: 205.9573; found: 205.9561.

$[C_6H_7O_3{}^{81}Br]^{\cdot+}$ calculated: 207.9553; found: 207.9537.

The obtained analytical data matched with literature values.[219]

Dimer **247**:

TLC: R_f = 0.15 (pentane/acetone = 3/1) [UV, $KMnO_4$]

Smp. [°C]: 178

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2999 (w, C−H), 2956 (w, C−H), 2867 (w, C−H), 1752 (s, C=O), 1666 (s, C=C), 1452 (m, C−H), 1392 (m, C−H), 1336 (s, C−O), 1079 (s, C−O), 982 (s, C=C), 755 (s).

Major diastereomer:

^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 4.82 (q, ^5J = 0.9 Hz, 2H, CH), 4.15 (s, 6H, OCH_3), 2.01 (d, ^5J = 0.9 Hz, 6H, CH_3).

^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ [ppm] = 174.1 (s, C-2), 169.1 (s, C-4), 98.8 (s, C-3), 74.1 (d, C-5), 59.4 (q, OCH_3), 8.8 (q, CH_3).

Minor diastereomer:

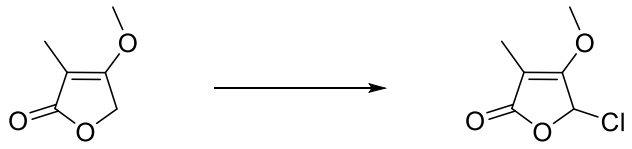
^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 4.96 (q, ^5J = 0.9 Hz, 2H, CH), 4.07 (s, 6H, OCH_3). 2.00 (d, ^5J = 0.9 Hz, 6H, CH_3).

^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ [ppm] = 174.1 (s, C-2), 168.7 (s, C-4), 99.2 (s, C-3), 75.9 (d, C-5), 59.4 (q, OCH_3), 8.8 (q, CH_3).

MS (EI): *m/z* (%) = 127 (100) $[C_6H_7O_3]^+$, 99 (47) $[C_5H_7O_2]^+$.

HRMS (EI): $[C_{12}H_{14}O_6]^{\cdot+}$ $[M]^{\cdot+}$ calculated: 254.0790; found: 254.0799.

5-Chloro-4-methoxy-3-methylfuran-2(5*H*)-one (222)



Chemical Formula: $C_6H_7ClO_3$
M = 162.57 g/mol

In a 50 mL flask 397 mg (3.10 mmol, 1.00 eq.) methyl α-methyltetronate (**143**) was dissolved in 8 mL THF and cooled to –78 °C. Next, 7.44 mL (0.5 M in THF, 3.72 mmol, 1.20 eq.) freshly prepared LDA was added and the yellow solution was stirred for 1 h. To this solution, 887 mg (4.65 mmol, 1.50 eq.) pTsCl was added and the reaction mixture was stirred for another 2 h. After this time, the reaction mixture was quenched by addition of 20 mL saturated, aqueous NH_4Cl solution and warmed to room temperature. The layers were subsequently separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic fractions were washed with 20 mL brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 21 cm, Ø = 4.5 cm, pentane/acetone = 6/1 → 4/1 → 2/1) to obtain the chlorinated tetronate **222** (337 mg, 2.07 mmol, 67%) as a clear, colorless oil.

TLC: R_f = 0.38 (pentane/acetone = 6/1) [UV, $KMnO_4$]

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2998 (w, C−H), 2959 (w, C−H), 2869 (w, C−H), 1776 (s, C=O), 1672 (s, C=C), 1460 (w, C−H), 1391 (m, C−H), 1344 (s, C−O), 1034 (m, C−O), 1021 (m, C−O), 978 (s, C=C), 713 (m, C−Cl).

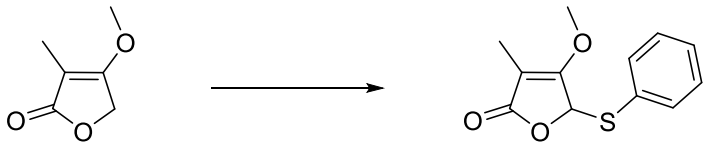
^{1}H-NMR (400 MHz, $CDCl_3$, 298 K): δ [ppm] = 6.27 (q, ^5J = 0.9 Hz, 1H, CH), 4.15 (s, 3H, OCH_3), 1.97 (d, ^5J = 0.9 Hz, 3H, CH_3).

^{13}C-NMR (101 MHz, $CDCl_3$, 298 K): δ [ppm] = 171.2 (s, C-2), 170.2 (s, C-4), 99.8 (s, C-3), 82.5 (d, C-5), 59.1 (q, OCH_3), 7.9 (q, CH_3).

MS (EI): *m/z* (%) = 162 (2) $[C_6H_7O_3Cl]^+$, 127 (100) $[C_6H_7O_3]^+$, 99 (36) $[C_5H_7O_2]^+$, 83 (58) $[C_5H_7O]^+$.

HRMS (EI): $[C_6H_7O_3{}^{35}Cl]^{\cdot+}$ calculated: 162.0079; found: 162.0070.
$[C_6H_7O_3{}^{37}Cl]^{\cdot+}$ calculated: 164.0049; found: 164.0041.

4-Methoxy-3-methyl-5-(phenylthio)furan-2(5*H*)-one (249)



Chemical Formula: $C_{12}H_{12}O_3S$
M = 236.29 g/mol

In a 50 mL flask 506 mg (3.95 mmol, 1.00 eq.) methyl α-methyltetronate (**143**) was dissolved in 9 mL THF and the resulting solution was cooled to −78 °C. Next, 8.68 mL (0.5 M in THF, 4.34 mmol, 1.10 eq.) freshly prepared LDA was added and the yellow solution was stirred for 1 h. Afterwards, 1.29 g (5.92 mmol, 1.50 eq.) diphenyl disulfide was added as a solid and the reaction mixture was stirred for another 3 h. The reaction was quenched by addition of 15 mL saturated, aqueous NH_4Cl solution and was subsequently warmed to room temperature. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 7 mL). The combined organic fractions were washed with 20 mL brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 24 cm, Ø = 3.5 cm, pentane/acetone = 8/1 → 6/1 → 4/1) to obtain the thioether **249** (488 mg, 2.07 mmol, 52%) as a white solid.

TLC: R_f = 0.47 (pentane/acetone = 4/1) [UV, $KMnO_4$]

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3059 (w, C−H), 2998 (w, C−H), 2952 (w, C−H), 1755 (s, C=O), 1664 (s, C=C), 1458 (m, C=C), 1387 (s, C−H), 1333 (s, C−O), 1068 (m, C−O), 1004 (m, C−O), 971 (s, C=C), 735 (s, C−H), 679 (s, C=C).

Smp. [°C]: 74

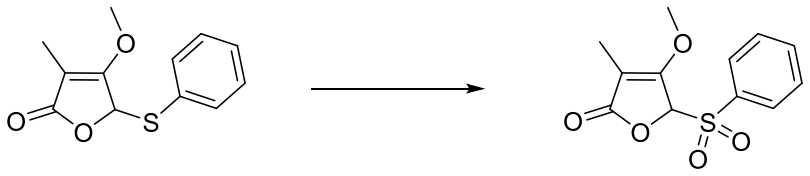
^{1}H-NMR (400 MHz, $CDCl_3$, 298 K): δ [ppm] = 7.54 – 7.49 (m, 2H, CH_o), 7.40 – 7.35 (m, 1H, CH_p), 7.35 – 7.29 (m, 2H, CH_m), 5.84 (q, ^5J = 1.2 Hz, 1H, H-5), 4.09 (s, 3H, OCH_3), 1.69 (d, ^5J = 1.2 Hz, 3H, CH_3).

^{13}C-NMR (101 MHz, $CDCl_3$, 298 K): δ [ppm] = 172.8 (s, C-2), 168.8 (s, C-4), 135.2 (d, C_o), 129.7 (d, C_p), 129.2 (d, C_m), 128.5 (s, C_i), 101.3 (s, C-3), 82.3 (d, C-5), 58.6 (q, OCH_3), 7.7 (q, CH_3).

MS (EI): *m/z* (%) = 236 (26) $[C_{12}H_{12}O_3S]^+$, 127 (100) $[C_6H_7O_3]^+$, 109 (16) $[C_6H_5S]^+$, 99 (34) $[C_5H_7O_2]^+$.

HRMS (EI): $[C_{12}H_{12}O_3S]^{\cdot+}$ $[M]^{\cdot+}$ calculated: 236.0502; found: 236.0500.

4-Methoxy-3-methyl-5-(phenylsulfonyl)furan-2(5*H*)-one (250)

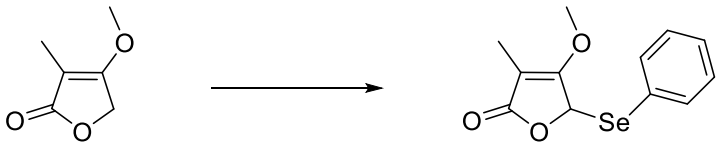


Chemical Formula: $C_{12}H_{12}O_5S$
M = 268.28 g/mol

In a 50 mL flask 133 mg (564 µmol, 1.00 eq.) thioether **249** was dissolved in a suspension of 7 mL EtOAc and 7 mL water. Next, 482 mg (2.23 mmol, 4.00 eq.) $NaIO_4$ and 14.2 mg (56.4 µmol, 10 mol%) $RuCl_3 \cdot xH_2O$ was added and the reaction mixture was vigorously stirred at room temperature for 20 h. The reaction mixture was diluted with 10 mL water and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 4 mL). The combined organic fractions were dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 17 cm, Ø = 2.5 cm, pentane/acetone = 3/1 → 1/1) to obtain the sulfone **250** (53.1 mg, 198 µmol, 35%) as a yellow solid.

TLC: R_f = 0.21 (pentane/acetone = 4/1) [UV, $KMnO_4$]
IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3060 (w, C−H), 2987 (w, C−H), 2948 (w, C−H), 1760 (s, C=O), 1657 (s, C=C), 1445 (m, C−H), 1339 (s, C−H), 1157 (s, C−O), 1042 (m, C−O), 977 (m, C=C), 755 (m, C−H), 725 (m, C−H).
Smp. [°C]: 192
^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 7.94 (dd, ^3J = 8.5 Hz, ^4J = 1.2 Hz, 2H, CH_o), 7.74 – 7.70 (m, 1H, CH_p), 7.65 – 7.57 (m, 2H, CH_m), 5.46 (q, ^5J = 1.2 Hz, 1H, H-5), 4.21 (s, 3H, OCH_3), 1.89 (d, ^5J = 1.2 Hz, 3H, CH_3).
^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ [ppm] = 171.7 (s, C-2), 165.5 (s, C-4), 135.2 (d, C_p), 135.0 (s, C_i), 129.9 (d, C_o), 129.5 (d, C_m), 103.0 (s, C-3), 88.3 (d, C-5), 60.1 (q, OCH_3), 8.6 (q, CH_3).
MS (EI): *m/z* (%): 127 (100) $[C_6H_7O_3]^+$, 99 (39) $[C_5H_7O_2]^+$.
HRMS (EI): $[C_{12}H_{12}O_5S]^{\cdot+}$ $[M]^{\cdot+}$ calculated: 268.0400; found: 268.0401.

4-Methoxy-3-methyl-5-(phenylselanyl)furan-2(5*H*)-one (248)

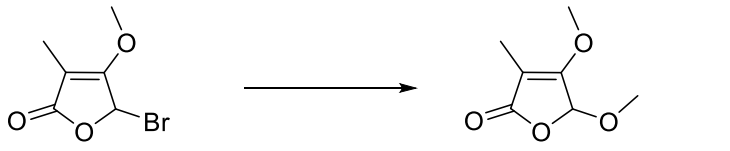


Chemical Formula: $C_{12}H_{12}O_3Se$
M = 283.20 g/mol

In a 50 mL flask 500 mg (3.91 mmol, 1.00 eq.) methyl α-methyltetronate (**143**) was dissolved in 9 mL THF and the resulting solution was cooled to −78 °C. Next, 8.60 mL (0.5 M in THF, 4.30 mmol, 1.10 eq.) freshly prepared LDA was added and the yellow solution was stirred at the same temperature for 1 h. After this time, 1.38 g (5.86 mmol, 1.50 eq.) phenylselenyl bromide was added as a solid and the reaction mixture was stirred for another 3 h. The reaction mixture was subsequently quenched by addition of 20 mL saturated, aqueous NH_4Cl solution and warmed to room temperature. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 9 mL). The combined organic fractions were dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 21 cm, Ø = 3.5 cm, pentane/acetone = 8/1 → 6/1) to obtain the selenium ether **248** (628 mg, 2.22 mmol, 57%) as a yellow solid.

TLC: R_f = 0.49 (pentane/acetone = 4/1) [UV, $KMnO_4$]
IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3057 (w, C−H), 2951 (w, C−H), 2863 (w, C−H), 1751 (s, C=O), 1656 (s, C=C), 1438 (m, C−H), 1386 (m, C−H), 1335 (s, C−O), 1008 (s, C−O), 974 (s, C=C), 741 (s, C−H), 691 (s, C−H).
Smp. [°C]: 68
^{1}H-NMR (400 MHz, $CDCl_3$, 298 K): δ [ppm] = 7.60 – 7.56 (m, 2H, CH_o), 7.39 – 7.33 (m, 1H, CH_p), 7.33 – 7.27 (m, 2H, CH_m), 6.12 (q, ^5J = 1.2 Hz, 1H, H-5), 4.05 (s, 3H, OCH_3), 1.61 (d, ^5J = 1.2 Hz, 3H, CH_3).
^{13}C-NMR (101 MHz, $CDCl_3$, 298 K): δ [ppm] = 172.9 (s, C-2), 170.3 (s, C-4), 137.0 (d, C_o), 129.6 (d, C_p), 129.2 (d, C_m), 124.5 (s, C_i), 100.7 (s, C-3), 76.0 (d, C-5), 58.4 (q, OCH_3), 7.6 (q, CH_3).
MS (EI): *m/z* (%) = 157 (8) $[C_6H_5Se]^+$, 127 (100) $[C_6H_7O_3]^+$, 99 (39) $[C_5H_7O_2]^+$, 83 (5) $[C_5H_7O]^+$.
HRMS (ESI): $[C_{12}H_{13}O_3Se]^+$ $[M]^+$ calculated: 285.0024; found: 285.0017.

4,5-Dimethoxy-3-methylfuran-2(5*H*)-one (253)



Chemical Formula: $C_7H_{10}O_4$
M = 158.15 g/mol

In a 50 mL flask 332 mg (1.60 mmol, 1.00 eq.) brominated tetronate **245** was dissolved in 9 mL MeOH. Next, 335 µL (243 mg, 2.40 mmol, 1.50 eq.) NEt_3 was added and the reaction mixture was stirred at room temperature for 46 h. The reaction mixture was diluted with 50 mL water and 15 mL EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. (5 × 10 mL). The combined organic fractions were dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 19 cm, Ø = 2.5 cm, pentane/acetone = 6/1 → 4/1) to obtain the methoxy tetronate **253** (207 mg, 1.31 mmol, 82%) as a yellow oil.

TLC: R_f = 0.70 (pentane/acetone = 3/1) [UV, $KMnO_4$]

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3005 (w, C−H), 2958 (m, C−H), 2872 (w, C−H), 1759 (s, C=O), 1676 (s, C=C), 1458 (m, C−H), 1395 (m, C−H), 1314 (s, C−O), 1070 (s, C−O), 962 (s, C=C), 754 (m, C−H).

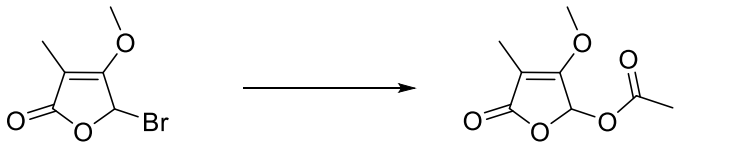
^{1}H-NMR (300 MHz, $CDCl_3$, 298 K): δ [ppm] = 5.58 (q, ^5J = 0.9 Hz, 1H, H-5), 4.06 (s, 3H, 4-OCH_3), 3.53 (s, 3H, 5-OCH_3), 1.87 (d, ^5J = 0.9 Hz, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$, 298 K): δ [ppm] = 172.4 (s, C-2), 168.0 (s, C-4), 101.3 (s, C-3), 98.1 (d. C-5), 58.5 (q, 4-OCH_3), 55.9 (q, 5-OCH_3), 7.4 (q, CH_3).

MS (EI): *m/z* (%) = 158 (36) $[C_7H_{10}O_4]^+$, 127 (32) $[C_6H_7O_3]^+$, 99 (84) $[C_5H_7O_2]^+$, 83 (100) $[C_5H_7O]^+$.

HRMS (EI): $[C_7H_{10}O_4]^{\cdot+}$ $[M]^{\cdot+}$ calculated: 158.0574; found: 158.0564.

4-Methoxy-3-methyl-2-oxo-2,5-dihydrofuran-5-yl acetate (254)

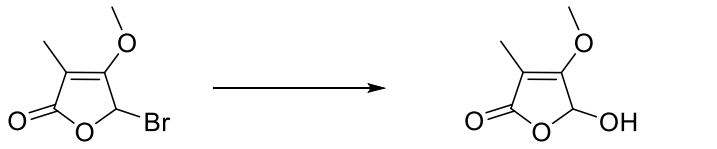


Chemical Formula: $C_8H_{10}O_5$
M = 186.16 g/mol

In a 25 mL flask 170 mg (821 µmol, 1.00 eq.) brominated tetronate **245** was dissolved in 6 mL DMF. Next, 202 mg (2.46 mmol, 3.00 eq.) NaOAc was added as a solid and the reaction mixture was stirred for 4 h at room temperature. The reaction was diluted with 30 mL water and 15 mL EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 12 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 24 cm, Ø = 3.5 cm, pentane/acetone = 6/1 → 4/1) to obtain the acetylated tetronate **254** (94.1 mg, 505 µmol, 62%) as a white solid.

TLC: R_f = 0.42 (pentane/acetone = 4/1) [UV, $KMnO_4$]
IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2960 (w, C–H), 2872 (w, C–H), 1762 (s, C=O), 1676 (s, C=C), 1463 (w, C–H), 1394 (m, C–O), 1360 (m, C–O), 1315 (m, C–O), 1207 (s, C–O), 1011 (s, C=C), 979 (s, C=C).
Smp. [°C]: 44
^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 6.70 (q, ^5J = 0.9 Hz, 1H, H-5), 4.07 (s, 3H, OCH_3), 2.17 (s, 3H, $OOCCH_3$), 1.96 (d, ^5J = 0.9 Hz, 3H, CH_3).
^{13}C-NMR (75 MHz, $CDCl_3$, 298 K): δ [ppm] = 171.9 (s, C-2), 169.2 (s, $OO\mathit{C}CH_3$), 167.7 (s, C-4), 100.7 (s, C-3), 88.6 (d, C-5), 58.9 (q, OCH_3), 20.8 (q, $OOC\mathit{C}H_3$), 7.9 (q, CH_3).
MS (EI): *m/z* (%) = 186 (22) $[C_8H_{10}O_5]^+$, 127 (40) $[C_6H_7O_3]^+$, 115 (100) $[C_5H_7O_3]^+$, 98 (36) $[C_5H_6O_2]^+$, 83 (95) $[C_4H_3O_2]^+$.
HRMS (EI): $[C_8H_{10}O_5]^{\cdot+}$ $[M]^{\cdot+}$ calculated: 186.0523; found: 186.0522.

5-Hydroxy-4-methoxy-3-methylfuran-2(5*H*)-one (251)

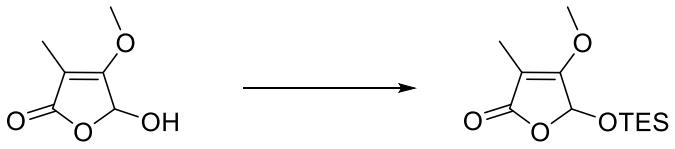


Chemical Formula: $C_6H_8O_4$
M = 144.13 g/mol

In a 50 mL flask 717 mg (3.46 mmol, 1.00 eq.) brominated tetronate **245** was dissolved in 10 mL THF and 20 mL water. Next, 398 µL (592 mg, 5.20 mmol, 1.50 eq.) trifluoroacetic acid was added and the reaction mixture was stirred at room temperature for 3 h. The mixture was diluted with 10 mL EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc (5 × 5 mL). The combined organic fractions were dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the compound was purified by column chromatography (h = 17 cm, Ø = 2.5 cm, pentane/acetone = 3/1 → 2/1) to obtain the hydroxylated tetronate **251** (427 mg, 2.96 mmol, 86%) as a white solid.

TLC: R_f = 0.23 (pentane/acetone = 3/1) [UV, $KMnO_4$]
IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3309 (br, O–H), 2959 (w, C–H), 2928 (w, C–H), 2871 (w, C–H), 1736 (m, C=O), 1670 (s, C=C), 1463 (w, C–H), 1332 (s, O–H), 1105 (m, O–H), 1059 (m, O–H), 962 (m, C=C), 756 (w).
Smp. [°C]: 89
^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 5.92 (q, ^5J = 0.9 Hz, 1H, H-5), 4.68 (br. s, 1H, OH), 4.10 (s, 3H, OCH_3), 1.84 (d, ^5J = 0.9 Hz, 3H, CH_3).
^{13}C-NMR (75 MHz, $CDCl_3$, 298 K): δ [ppm] = 173.3 (s, C-2), 170.2 (s, C-4), 100.5 (s, C-3), 92.8 (d, C-5), 58.6 (q, OCH_3), 7.2 (q, CH_3).
MS (EI): *m/z* (%) = 144 (45) $[C_6H_8O_4]^+$, 115 (10) $[C_5H_7O_3]^+$, 99 (72) $[C_5H_7O_2]^+$, 83 (100) $[C_5H_7O]^+$.
HRMS (EI): $[C_6H_8O_4]^{\cdot+}$ $[M]^{\cdot+}$ calculated: 144.0417; found: 144.0418.

4-Methoxy-3-methyl-5-[(triethylsilyl)oxy]furan-2(5*H*)-one (252)

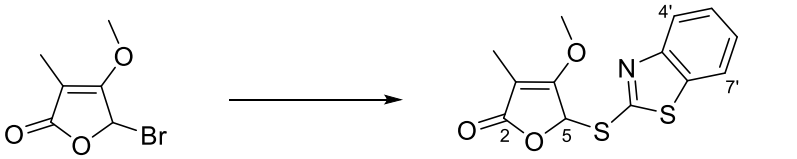


Chemical Formula: $C_{12}H_{22}O_4Si$
M = 258.39 g/mol

In a 100 mL flask 394 mg (2.73 mmol, 1.00 eq.) alcohol **251** was dissolved in 40 mL CH_2Cl_2 and the mixture was cooled to 0 °C. Next, 558 mg (8.20 mmol, 3.00 eq.) imidazole, 688 µL (618 mg, 4.10 mmol, 1.50 eq.) TESCl and 66.8 mg (547 µmol, 20 mol%) DMAP were added and the resulting reaction mixture was stirred for 1 h at the same temperature. Subsequently, the reaction was quenched by addition of 20 mL saturated, aqueous $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 12 mL). The combined organic fractions were dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 15 cm, Ø = 3.5 cm, pentane/acetone = 9/1) to obtain the TES-protected alcohol **252** (588 mg, 2.28 mmol, 83%) as a clear oil.

TLC: R_f = 0.42 (pentane/acetone = 9/1) [UV, $KMnO_4$]
IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2957 (m, C−H), 2914 (w, C−H), 2879 (m, C−H), 1767 (s, C=O), 1679 (s, C=C), 1459 (w, C−H), 1393 (m, C−H) 1317 (m, C−O), 1160 (m, C−O), 1069 (s), 1005 (s), 966 (s, C=C), 750 (s, C=C).
^{1}H-NMR (400 MHz, $CDCl_3$, 298 K): δ [ppm] = 5.82 (q, ^5J = 0.9 Hz, 1H, H-5), 4.05 (s, 3H, OCH_3), 1.85 (d, ^5J = 0.9 Hz, 3H, CH_3), 0.98 (t, ^3J = 7.8 Hz, 9H, $SiCH_2CH_3$), 0.70 (q, ^3J = 7.8 Hz, 6H, $SiCH_2CH_3$).
^{13}C-NMR (101 MHz, $CDCl_3$, 298 K): δ [ppm] = 172.7 (s, C-2), 170.5 (s, C-4), 99.5 (s, C-3), 92.7 (d, C-5), 58.4 (q, OCH_3), 7.4 (q, CH_3), 6.6 (q, $SiCH_2CH_3$), 4.9 (t, $SiCH_2CH_3$).
MS (EI): *m/z* (%) = 229 (100) $[C_{10}H_{17}O_4Si]^+$, 201 (78) $[C_9H_{17}O_3Si]^+$, 157 (35) $[C_8H_{17}OSi]^+$, 117 (25) $[C_5H_{13}OSi]^+$.
HRMS (EI): $[C_{12}H_{22}O_4Si]^{\cdot+}$ $[M]^{\cdot+}$ calculated: 258.1282; found: 258.1272.

5-(Benzo[*d*]thiazol-2-ylthio)-4-methoxy-3-methylfuran-2(5*H*)-one (257)



Chemical Formula: $C_{13}H_{11}NO_3S_2$
M = 293.36 g/mol

In a 50 mL flask 378 mg (1.82 mmol, 1.00 eq.) brominated tetronate **245** was dissolved in 10 mL DMF. Next, 397 mg (2.37 mmol, 1.30 eq.) 2-thiobenzothiazole and 504 mg (3.65 mmol, 2.00 eq.) K_2CO_3 were added and the resulting reaction mixture was stirred at room temperature for 4 h. The reaction mixture was subsequently diluted with 50 mL water and 20 mL EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc (4 × 10 mL) and the combined organic fractions were dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 17 cm, Ø = 2.5 cm, pentane/acetone = 6/1 → 3/1) to obtain the thioether **257** (215 mg, 732 µmol, 40%) as a yellow solid.

TLC: R_f = 0.63 (pentane/acetone = 3/1) [UV, $KMnO_4$]

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3000 (w, C−H), 2951 (w, C−H), 2861 (w, C−H), 1762 (s, C=C), 1665 (s, C=O), 1456 (m, C−H), 1426 (m, C−H), 1332 (m, C−H), 1030 (m, C−O), 1010 (m, C−O), 968 (s, C=C), 758 (m, C=C).

Smp. [°C]: 108

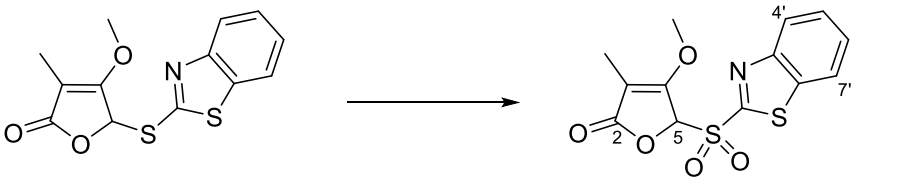
^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 7.94 (ddd, ^3J = 8.1 Hz, ^4J = 1.3 Hz, ^5J = 0.6 Hz, 1H, H-4'), 7.79 (ddd, ^3J =7.9 Hz, ^4J =1.3 Hz, ^5J = 0.6 Hz, 1H, H-7'), 7.45 (ddd, ^3J = 8.1 Hz, 7.3 Hz, ^4J = 1.3 Hz, 1H, H-5'), 7.35 (ddd, ^3J = 7.9 Hz, 7.3 Hz, ^4J = 1.3 Hz, 1H, H-6'), 6.75 (q, ^5J = 1.2 Hz, 1H, H-5), 4.13 (s, 3H, OCH_3), 1.91 (d, ^5J = 1.2 Hz, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$, 298 K): δ [ppm] = 172.3 (s, C-2), 168.6 (s, C-4), 160.2 (s, C-2'), 152.8 (s, C-3a'), 136.2 (s, C-7a'), 126.5 (d, C-5'), 125.3 (d, C-6'), 122.6 (d, C-4'), 121.3 (d, C-7'), 101.5 (s, C-3), 81.1 (d, C-5), 59.2 (q, OCH_3), 8.1 (q, CH_3)

MS (EI): *m/z* (%) = 293 (27) $[C_{13}H_{11}NO_3S_2]^+$, 165 (8) $[C_7H_4NS_2]^+$, 127 (100) $[C_6H_7O_3]^+$, 108 (12) $[C_6H_4S]^+$, 99 (39) $[C_5H_7O_2]^+$.

HRMS (EI): $[C_{13}H_{11}NO_3S_2]^{\cdot+}$ $[M]^{\cdot+}$ calculated: 293.0175; found: 293.0167.

5-(Benzo[*d*]thiazol-2-ylsulfonyl)-4-methoxy-3-methylfuran-2(5*H*)-one (258)



Chemical Formula: $C_{13}H_{11}NO_5S_2$
M = 325.35 g/mol

In a 25 mL flask 91.9 mg (313 µmol, 1.00 eq.) thioether **257** was dissolved in 5 mL EtOH. Next, 245 µL (30 % in H_2O, 107 mg, 3.13 mmol, 10.0 eq.) H_2O_2 and 38.7 mg (31.3 µmol, 10 mol%) $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ were added and the reaction mixture was stirred for 30 h at room temperature. The reaction mixture was subsequently diluted with 10 mL H_2O and 10 mL EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 3 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 23 cm, Ø = 2.5 cm, pentane/acetone = 4/1 → 2/1) to obtain the sulfone **258** (75.5 mg, 232 µmol, 74%) as a white solid.

TLC: R_f = 0.58 (pentane/acetone = 2/1) [UV]

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2955 (w, C−H), 2927 (w, C−H), 1777 (s, C=O), 1662 (s, C=C), 1463 (m, C−H), 1398 (m, C−H), 1347 (s, S=O), 1156 (s, C−O), 976 (s, C=C), 908 (m, C=C), 728 (s, C−H).

Smp. [°C]: 155

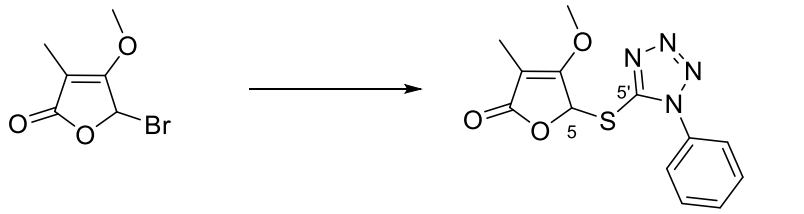
^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 8.27 – 8.22 (m, 1H, H-4'), 8.04 – 7.99 (m, 1H, H-7'), 7.67 – 7.58 (m, 2H, H-5', H-6'), 6.03 (q, ^5J = 1.2 Hz, 1H, H-5), 4.24 (s, 3H, OCH_3), 2.00 (d, ^5J = 1.2 Hz, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$, 298 K): δ [ppm] = 171.2 (s, C-2), 164.6 (s, C-4), 162.5 (s, C-2'), 152.7 (s, C-3a'), 137.7 (s, C-7a'), 128.7 (d, C-6'), 128.1 (d, C-5'), 125.8 (d, C-4'), 122.5 (d, C-7'), 103.6 (s, C-3), 87.9 (d, C-5), 60.2 (q, OCH_3), 8.8 (q, CH_3).

MS (EI): *m/z* (%) = 127 (100) $[C_6H_7O_3]^+$, 99 (55) $[C_5H_7O_2]^+$.

HRMS (EI): $[C_{13}H_{11}NO_5S_2]^{\cdot+}$ $[M]^{\cdot+}$ calculated: 325.0073; found: 325.0079.

4-Methoxy-3-methyl-5-[(1‘-phenyl-1*H*-tetrazol-5-yl)thio]furan-2(5*H*)-one (259)

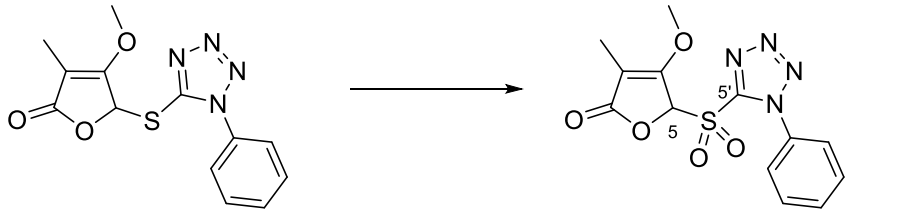


Chemical Formula: $C_{13}H_{12}N_4O_3S$
M = 304.32 g/mol

In a 25 mL flask 183 mg (883 µmol, 1.00 eq.) brominated tetronate **245** was dissolved in 5 mL DMF. Next, 205 mg (1.15 mmol, 1.30 eq.) 1-phenyl-1*H*-tetrazol-5-thiol and 244 mg (1.77 mmol, 2.00 eq.) K_2CO_3 were added and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was subsequently diluted with 40 mL water and 20 mL EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 19 cm, Ø = 2.5 cm, pentane/acetone = 6/1 → 3/1 → 1/1) to obtain the thioether **259** (203 mg, 0.67 µmol, 76%) as a white solid.

TLC: R_f = 0.26 (pentane/acetone = 3/1) [UV, $KMnO_4$]
IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3005 (w, C−H), 2956 (w, C−H), 2865 (w, C−H), 1766 (s, C=O), 1668 (s, C=C), 1499 (m, C−H), 1388 (m, C−H), 1334 (s, C−H), 975 (s, C=C), 763 (s, C=C).
Smp. [°C]: 142
^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 7.58 – 7.52 (m, 3H, C_pH, C_mH), 7.51 – 7.47 (m, 2H, C_oH), 6.68 (q, ^5J = 1.2 Hz, 1H, H-5), 4.13 (s, 3H, OCH_3), 1.93 (d, ^5J = 1.4 Hz, 1H, CH_3).
^{13}C-NMR (75 MHz, $CDCl_3$, 298 K): δ [ppm] = 171.7 (s, C-2), 167.9 (s, C-4), 150.1 (s, C-5’), 133.1 (s, C_i), 130.7 (d, C_p), 129.9 (d, C_o), 124.4 (d, C_m), 101.4 (s, C-3), 80.8 (d, C-5), 59.4 (q, OCH_3), 8.2 (q, CH_3).
MS (EI): *m/z* (%) = 275 (17) $[C_{13}H_{11}N_2O_3S]^+$, 127 (100) $[C_6H_7O_3]^+$, 99 (37) $[C_5H_7O_2]^+$, 83 (12) $[C_5H_7O]^+$.
HRMS (EI): $[C_{13}H_{12}N_4O_3S]^{\cdot+}$ $[M]^{\cdot+}$ calculated: 304.0625; found: 304.0629.

4-Methoxy-3-methyl-5-[(1‘-phenyl-1*H*-tetrazol-5-yl)sulfonyl]furan-2(5*H*)-one (260)



Chemical Formula: $C_{13}H_{12}N_4O_5S$
M = 336.32 g/mol

In a 25 mL flask 176 mg (579 µmol, 1.00 eq.) thioether **259** was dissolved in 9 mL EtOH. Next, 453 µL (30% in H_2O, 5.79 mmol, 10.0 eq.) H_2O_2 and 71.6 mg (57.9 µmol, 10 mol%) $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ were added and the reaction mixture was stirred at room temperature for 28 h. Subsequently, the reaction mixture was diluted with 20 mL water and 10 mL EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc (3 ×5 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure the compound was purified by column chromatography (h = 20 cm, Ø = 3.5 cm, pentane/acetone = 4/1 → 2/1) to obtain the sulfone **260** (86.4 mg, 257 µmol, 44%) as a white solid.

TLC: R_f = 0.51 (pentane/acetone = 2/1) [UV]

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3048 (w, C−H), 2957 (w, C−H), 2892 (w, C−H), 1781 (s, C=O), 1664 (s, C=C), 1497 (m, C−H), 1460 (m, C−H), 1370 (m, S=O), 1334 (s, S=O), 1159 (m, C−O), 975 (s, C=C), 764 (m, C−H), 689 (s, C−H).

Smp. [°C]: 159

^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 7.67 – 7.62 (m, 1H, C_pH), 7.61 – 7.56 (m, 4H, C_oH, C_mH), 6.04 (q, ^5J = 1.2 Hz, 1H, H-5), 4.21 (s, 3H, OCH_3), 2.01 (d, ^5J = 1.2 Hz, 3H, CH_3).

^{13}C-NMR (101 MHz, $CDCl_3$, 298 K): δ [ppm] = 170.4 (s, C-2), 163.4 (s, C-4), 151.7 (s, C-5’), 132.8 (s, C_i), 131.9 (d, C_p), 130.0 (d, C_m), 126.1 (d, C_o), 88.8 (d, C-5), 60.4 (q, OCH_3), 8.9 (q, CH_3).

MS (EI): *m/z* (%) = 243 (62) $[C_7H_7N_4O_4S]^+$, 127 (56) $[C_6H_7O_3]^+$, 99 (21) $[C_5H_7O_2]^+$, 83 (100) $[C_5H_7O_3]^+$.

HRMS (EI): $[C_{13}H_{12}N_4O_5S]^+$ $[M]^{\cdot+}$ calculated: 336.0523; found: 336.0514.

III. List of abbreviations

Ac	acetyl
AcOH	acetic acid
ac	acetone
AIBN	azobis(*iso*butyronitril)
9-BBN	9-borabicyclo[3.3.1]nonane
BAIB	bis(acetoxyiodo)benzene
bp	boiling point
BQ	1,4-benzoquinone
Bz	benzoyl
Cbz	benzyloxycarbonyl
cod	1,5-cyclooctadiene
DCC	*N*,*N'*-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
3,5-DMP	3,5-dimethylpyrazole
DMSO	dimethylsulfoxide
d.r.	diastereomeric ratio
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
eq.	equivalents
EtOAc	ethyl acetate
EtOH	ethanol
Fmoc	9-fluorenylmethoxycarbonyl
h	hour(s)
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
mCPBA	*meta*-chloroperoxybenzoic acid
MeCN	acetonitrile
MeOH	methanol
min	minute(s)

MDR	multi drug resistant
mp	melting point
Ms	methanesulfonate
NBP	*N*-bromophthalimide
NBS	*N*-bromosuccinimide
*n*BuLi	*n*-butyl lithium
neoc	neocuproine = 2,9-dimethyl-1,10-phenanthroline
NHMDS	sodium hexamethyldisilazide
NMR	nuclear magnetic resonance
NP	natural products
NPI	natural product-inspired compounds
Ph	phenyl
$PhCH_3$	toluene
PMB	*para*-methoxybenzyl
pTs	*para*-toluenesulfonate
py	pyridine
Ra-Ni	*Raney* nickel
RB	rose bengal
R_f	retardation factor
rt	room temperature
rr	rotameric ratio
S	synthetic compounds
SAM	*S*-adenosyl methionine
*s*BuLi	*sec*-butyl lithium
TBS, TBDMS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidinyloxyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	tri*iso*propylsilyl
TMEDA	tetramethylethylene diamine
TMG	1,1,3,3-tetramethylguanidine
TMS	trimethylsilyl
TPP	5,10,15,20-tetraphenylporphyrin

IV. Bibliography

[1] A. G. Drachmann, **1948**, Ktesibios, Philon and Heron: A Study in Ancient Pneumatics, Copenhagen: Munsksgaard.

[2] R. House, **2001**, Webster's Unabridged Dictionary, Random House Reference.

[3] S. Berryman, **2008**, The Stanford Encyclopedia of Philosophy.

[4] A. W. Thackray, *Isis* **1966**, *57*, 35-55.

[5] H. E. Roscoe, A. Harden, **1896**, A new view of the origin of Dalton's Atomic theory, London, Macmillan

[6] J. Schmutz, J. Wheeler, J. Grimwood, M. Dickson, J. Yang, C. Caoile, E. Bajorek, S. Black, Y. M. Chan, M. Denys, J. Escobar, D. Flowers, D. Fotopulos, C. Garcia, M. Gomez, E. Gonzales, L. Haydu, F. Lopez, L. Ramirez, J. Retterer, A. Rodriguez, S. Rogers, A. Salazar, M. Tsai, R. M. Myers, *Nature* **2004**, *429*, 365-368.

[7] P. Müller, *Pure Appl. Chem*. **1994**, *66*, 1077-1084.

[8] D. A. Micha, **2020**, Molecular Interactions: Concepts and Methods, Wiley.

[9] J. A. Kellum, *Crit. Care* **2000**, *4*, 6-14.

[10] R. N. Pittman, **2011**, Regulation of Tissue Oxygenation, Morgan & Claypool.

[11] J. Badawy, O. K. Nguyen, C. Clark, E. A. Halm, A. N. Makam, *BMJ Qual. Saf*. **2017**, *26*, 832-836.

[12] H. Mairbäur, R. E. Weber, *Compr. Physiol*. **2012**, *2*, 1463-1489.

[13] L. M. McManus, R. N. Mitchell, **2014**, Pathobiology of Human Disease, Elsevier.

[14] A. F. Riggs, *Annu. Rev. Physiol.* **1988**, *50*, 181-204.

[15] R. B. Silverman, *Technology and Innovation* **2016**, *17*, 153-158.

[16] L. L. Brunton, R. Hilal-Dandan, B. C. Knollman, **2011**, The Pharmacological Basis of Therapeutics, McGraw-Hill Education.

[17] GBD 2019 Diseases and Injuries Collaborators, *Lancet*, **2020**, *396*, 1204-1222.

[18] G. Dimitriadis, P. Mitrou, V. Lambadiari, E. Maratou, S. A. Raptis, *Diabetes Res. Clin. Pract.* **2011**, *93*, 52-59.

[19] M. C. Petersen, D. F. Vatner, G. I. Shulman, *Nat. Rev. Endocrinol*. **2017**, *13*, 572-587.

[20] R. Parrilla, M. N. Goodman, C. J. Toews, *Diabetes*, **1974**, *23*, 725-731.

[21] M. A. Atkinson, G. S. Eisenbarth, A. W. Michels, *Lancet*, **2014**, *383*, 69-82.

[22] C. Mathieu, P. J. Martens, R. Vangoitsenhoven, *Nat. Rev. Endocrinol*. **2021**, *17*, 715-725.

[23] R. E. Chance, B. H. Frank, *Diabetes Care* **1993**, *16*, 133-142.

[24] J. Boucher, A. Kleinridders, C. R. Kahn, *Cold Spring Harb. Perspect. Biol*. **2014**, *6*, a009191.

[25] A. M. Ahmed, *Saudi. Med. J.* **2002**, *23*, 373-378.

[26] L. A. Witters, *J. Clin. Invest*. **2001**, *108*, 1105-1107.

[27] C. J. Bailey, C. Day, *Practical Diabetes Int*. **2004**, *21*, 115-117.

[28] D. J. Newman, G. M. Cragg, *J. Nat. Prod*. **2020**, *83*, 770-803.

[29] R. Eguchi, N. Ono, A. H. Morita, T. Katsuragi, S. Nakamura, M. Huang, M. Altaf-Ul-Amin, S. Kanaya, *BMC Bioinformatics*, **2019**, *20*, 380.

[30] M. J. M. Christenhusz, J. W. Byng, *Phytotaxa*, **2016**, *261*, 201-217.

[31] F. Wang, Q. Chen, *Nat. Prod. Commun*, **2014**, *9*, 1809-1822.

[32] H. Greger, *Phytochem. Rev*. **2019**, *18*, 463-493.

[33] J. Schinnerl, B. Brem, P. P. H. But, S. Vajrodaya, O. Hofer, H. Greger, *Phytochemistry* **2007**, *68*, 1417-1427.

[34] R. A. Pilli, G. B. Rosso, M. C. F. Oliveira, *Nat. Prod. Rep*. **2010**, *27*, 1908-1937.

[35] B. K. Anderson, T. Livinghouse, *J. Org. Chem.* **2015**, *80*, 9847-9855.

[36] A. M. Baylis, M. P. H. Davies, E. J. Thomas, *Org. Biomol. Chem.* **2007**, *5*, 3139-3155.

[37] E. Kaltenegger, B. Brem, K. Mereiter, H. Kalchhauser, H. Kählig, O. Hofer, S. Vajrodaya, H. Greger, *Phytochemistry* **2003**, *63*, 803-816.

[38] C. Seger, K. Mereiter, E. Kaltenegger, T. Pacher, H. Greger, O. Hofer, *Chem. Biodivers*. **2004**, 1, 265-279.

[39] S. Schramm, N. Köhler, W. Rozhon, *Molecules*, **2019**, *24*, 498.

[40] H. Greger, *Planta Med*. **2006**, *72*, 99-113.

[41] H. Greger, J. Schinnerl, S. Vajrodaya, L. Brecker, O. Hofer, *J. Nat. Prod*. **2009**, *72*, 1708-1711.

[42] P. Mungkornasawakul, H. Matthews, A. T. Ung, S. G. Pyne, A. Jatisatienr, W. Lie, B. W. Skelton, A. H. White, *ACGC Chem. Res. Commun*. **2005**, *19*, 30-33.

[43] R. W. Jiang, P. M. Hon, P. P. H. But, H. S. Chung, G. Lin, W. C. Ye, T. C. W. Mak, *Tetrahedron*, **2002**, *58*, 6705-6712.

[44] Y. T. Xu, P. C. Shaw, R. W. Jiang, P. M. Hon, Y. M. Chan, P. P. H. But, *J. Ethnopharmacol.* **2010**, *128*, 679-684.

[45] Y. T. Xu, P. M. Hon, R. W. Jiang, L. Cheng, S. H. Li, Y. P. Chan, H. X. Xu, P. C. Shaw, P. P. H. But, *J. Ethnopharmacol.* **2006**, *108*, 46-53.

[46] K. H. Jung, Y. S. Kil, J. Jung, S. Park, D. Shin, K. Lee, E. K. Seo, H. Bae, *Phytomedicine* **2016**, *23*, 79-86.

[47] K. Sakata, K. Aoki, C. F. Chang, A. Sakurai, S. Tamura, S. Murakoshi, *Agric. Biol. Chem.* **1978**, *42*, 457-463.

[48] Y. Liu, Y. Shen, L. Teng, L. Yang, K. Cao, Q. Fu, J. Zhang, *J. Ethnopharmacol*. **2021**, *265*, 113112.

[49] H. S. Chung, P. M. Hon, G. Lin, P. P. H. But, H. Dong, *Planta Med*. **2003**, *69*, 914-920.

[50] A. Sakulpanich, S. Attrapadung, W. Gritsanapan, *Acta Trop*. **2017**, *173*, 62-68.

[51] B. Brem, C. Seger, T. Pacher, O. Hofer, S. Vajrodaya, H. Greger, *J. Agric. Food Chem*. **2002**, *50*, 6383-6388.

[52] L. G. Lin, H. P. H. Leung, J. Y. Zhu, C. P. Tang, C. Q. Ke, J. A. Rudd, G. Lin, Y. Ye, *Tetrahedron*, **2008**, *64*, 10155-10161.

[53] H. Lee, K. H. Jung, S. Park, Y. S. Kil, E. Y. Chung, Y. P. Jang, E. K. Seo, H. Bae, *BMC Complement. Altern. Med*. **2014**, *14*, 513.

[54] H. Shinozaki, M. Ishida, *Brain Res.* **1985**, *334*, 33-40.

[55] T. Sekine, F. Ikegami, N. Fukasawa, Y. Kashiwagi, T. Aizawa, Y. Fujii, N. Ruangrungsi, I. Murakoshi, *J. Chem. Soc. Perkin Trans. 1* **1995**, 391-393.

[56] S. Umsumarng, S. Mapoung, S. Yodkeeree, S. G. Pyne, P. L. Dejkriengkraikul, *Asian Pac. J. Cancer Prev*. **2018**, *19*, 3533-3543.

[57] S. G. Pyne, A. T. Ung, A. Jatisatienr, P. Mungkornasawakul, *Mj. Int. J. Sci. Tech*. **2007**, *1*, 157-165.

[58] R. Alibes, M. Figueredo, *Eur. J. Org. Chem*. **2009**, 2421-2435.

[59] X. Y. Liu, F. P.Wang, *Nat. Prod. Commun*. **2015**, *10*, 1093-1102.

[60] P. Wipf, Y. Kim, D. M. Goldstein, *J. Am. Chem. Soc*. **1995**, *117*, 11106-11112.

[61] S. F. Martin, K. J. Barr, *J. Am. Chem. Soc*. **1996**, *118*, 3299-3300.

[62] K. Ma, X. Yin, M. Dai, *Angew. Chem. Int. Ed.* **2018**, *57*, 15209-15212.

[63] M. T. Epperson, D. Y. Gin, *Angew. Chem. Int. Ed.* **2002**, *41*, 1778-1780.

[64] P. Q. Huang, S. Y. Huang, L. H. Gao, Z. Y. Mao, Z. Chang, A. E. Wang, *Chem. Commun*. **2015**, *51*, 4576-4578.

[65] M. Brüggemann, A. I. McDonald, L. E. Overman, M. D. Rosen, L. Schwink, J. P. Scott, *J. Am. Chem. Soc*. **2003**, *125*, 15284-15285.

[66] X. Z. Huang, L. H. Gao, P. Q. Huang, *Nat. Commun.* **2020**, *11*, 5314.

[67] S. R. Shengule, A. C. Willis, S. G. Pyne, *Tetrahedron* **2013**, *69*, 8042-8050.

[68] X. D. Dau, A. C. Willis, S. G. Pyne, *Eur. J. Org. Chem.* **2015**, 7682-7694.

[69] D. P. Furkert, M. A. Brimble, *Org. Lett*. **2002**, *4*, 3655-3658.

[70] X. D. Dau, *Lett. Org. Chem.* **2021**, *18*, 58-65.

[71] J. Tassel, *Dissertation*, Technische Universität München, **2010**.

[72] M. S. Kerr, J. R. de Alaniz, T. Rovis, *J. Org. Chem.* **2005**, 70, 5725-5728.

[73] A. Romek, *Dissertation*, Technische Universität München, **2013**

[74] R. Chenevert, M. Dickman, *J. Org. Chem.* **1996**, *61*, 3332-3341.

[75] T. Honda, T. Matsukawa, K. Takahashi, *Org. Biomol. Chem.* **2011**, *9*, 673-675.

[76] S. Esposti, D. Dondi, M. Fagnoni, A. Albini, *Angew. Chem. Int. Ed.* **2007**, *46*, 2531-2534.

[77] C. Mayer, *Dissertation*, Technische Universität München, **2017**.

[78] M. Mori, N. Sakakibara, A. Kinoshita, *J. Org. Chem.* **1998**, *63*, 6082-6083.

[79] M. Matsumoto, S. Dobashi, K. Kuroda, K. Kondo, *Tetrahedron* **1985**, *41*, 2147-2154.

[80] F. F. Paintner, G. Bauschke, M. Kestel, *Tetrahedron Lett*. **2000**, *41*, 9977-9980.

[81] T. Okada, K. Sakaguchi, T. Shinada, Y. Ohfune, *Tetrahedron Lett*. **2011**, *52*, 5740-5743.

[82] S. Qian, G. Zhao, *Chem. Commun*. **2012**, *48*, 3530-3532.

[83] M. Ito, T. Iwata, K. Tsukida, *Chem. Pharm. Bull*. **1984**, *32*, 1709-1716.

[84] T. Yamada, H. Hagiwara, H. Uda, *J. Chem. Soc. Chem. Commun*. **1980**, 838-839.

[85] T. Kusakabe, Y. Kawai, R. Shen, T. Mochida, K. Kato, *Org. Biomol. Chem.* **2012**, *10*, 3192-3194.

[86] Y. Fang, C. Li, *Chem. Commun.* **2005**, 3574-3576.

[87] J. Uenishi, R. Kawahama, O. Yonemitsu, *J. Org. Chem*. **1997**, *62*, 1691-1701.

[88] T. Montagnon, D. Kalaitzakis, M. Triantafyllakis, M. Stratakis, G. Vassilikogiannakis, *Chem. Commun*. **2014**, *50*, 15480-15498.

[89] T. Mitsui, R. Ishihara, K. Hayashi, M. Sunadome, N. Matsuura, H. Nozaki, *Chem. Pharm. Bull.* **2014**, *62*, 267-273.

[90] K. Isobe, K. Mohri, Y. Itoh, Y. Toyokawa, N. Takeda, J. Taga, Y. Tsuda, *Chem. Pharm. Bull*. **1987**, *35*, 2618-2621.

[91] E. G. Occiato, A. Trabocchi, A. Guarna, *J. Org. Chem*. **2001**, *66*, 2459-2465.

[92] C. Bhat, S. T. Bugde, S. G. Tilve, *Synthesis* **2014**, *46*, 2551-2573.

[93] P. Bury, G. Hareau, P. Kocienski D. Dhanak, *Tetrahedron* **1994**, *50*, 8793-8808.

[94] T. A. Lopez, M. S. Cid, M. L. Bianchini, *Toxicon* **1999**, *37*, 841-865.

[95] C. Bhat, S. T. Bugde, S. G. Tilve, *Synthesis* **2014**, *46*, 2551-2573.

[96] D. B. Ramachary, Y. V. Reddy, *J. Org. Chem*. **2010**, *75*, 74-85.

[97] T. K. Beng, R. E. Gawley, *J. Am. Chem. Soc*. **2010**, *132*, 12216-12217.

[98] J. A. Galvez, M. D. D. Villegas, R. Badorrey, P. Lopez-Ram-de-Viu, *Org. Biomol. Chem*. **2011**, *9*, 8155-8162.

[99] C. Bhat, S. G. Tilve, *Tetrahedron* **2013**, *69*, 10876-10883.

[100] P. Guerreiro, V. Ratovelomanana-Vidal, J. P. Genet, *Chirality*, **2000**, *12*, 408-410.

[101] G. Xia, L. Liu, H. Liu, J. Yu, Z. Xu, Q. Chen, C. Ma, P. Li, B. Xiong, X. Liu, J. Shen, *Chem. Med. Chem.* **2013**, *8*, 577-581.

[102] R. Alibes, M. Ballbe, F. Busque, P. March, L. Elias, M. Figueredo, J. Font, *Org. Lett.* **2004**, *6*, 1813-1816.

[103] A. D. Brosius, L. E. Overman, L. Schwink, *J. Am. Chem. Soc.* **1999**, *121*, 700-709.

[104] T. M. Shaikh, A. Sudalai, *Eur. J. Org. Chem.* **2010**, 3437-3444.

[105] K. Zhao, G. Seidler, R. R. Knowles, *Angew. Chem. Int. Ed.* **2021**, *60*, 20190-20195.

[106] L. G. J. Hammarström, R. K. Harmel, M. Granath, R. Ringom, Y. Gravenfors, K. Färnegardh, P. H. Svensson, D. Wennman, G. Lundin, Y. Roddis, S. S. Kitambi, A. Bernlind, F. Lehmann, P. Emfors, *J. Med. Chem.* **2016**, *59*, 8577-8592.

[107] S. M. Singh, A. C. Oehlschlager, *Can. J. Chem.* **1988**, *66*, 209-213.

[108] J. M. Wahl, M. L. Conner, M. K. Brown, *Angew. Chem. Int. Ed.* **2018**, *57*, 4647-4651.

[109] G. E. Keck, E. P. Boden, *Tetrahedron Lett.* **1984**, *25*, 265-268.

[110] F. Y. Zhang, A. S. C. Chan, *Tetrahedron Asymmetry* **1997**, *8*, 3651-3655.

[111] H. Gilman, P. R. van Ess, *J. Am. Chem. Soc.* **1933**, *55*, 1258-1261.

[112] C. Kong, N. Jana, T. G. Driver, *Org. Lett.* **2013**, *15*, 824-827.

[113] E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551-5553.

[114] E. J. Corey, S. Shibata, R. K. Bakshi, *J. Org. Chem.* **1988**, *53*, 2861-2863.

[115] P. G. M. Wuts, T. W. Greene, **2006**, Greene‘s Protective Groups in Organic Synthesis, John Wiley & Sons.

[116] G. Wu, S. Liu, T. Wang, Z. Jiang, K. Lv, Y. Wang, C. Sun, *Org. Lett.* **2018**, *20*, 3566-3569.

[117] D. L. Comins, N. R. Benjelloun, *Tetrahedron Lett.* **1994**, *35*, 829-832.

[118] I. Coldham, D. Leonori, *Org. Lett.* **2008**, *10*, 3923-3925.

[119] J. P. N. Papillon, R. J. K. Taylor, *Org. Lett.* **2000**, *2*, 1987-1990.

[120] J. Barbion, G. Sorin, M. Selkti, E. Kellenberger, R. Baati, S. Santoro, F. Himo, A. Pancrazi, M. I. Lannou, J. Ardisson, *Tetrahedron* **2012**, *68*, 6504-6512.

[121] C. J. Foti, D. L. Comins, *J. Org. Chem.* **1995**, *60*, 2656-2657.

[122] E. G. Occhiato, A. Trabocchi, A. Guarna, *J. Org. Chem.* **2001**, *66*, 2459-2465.

[123] T. Kurose, C. Tsukano, Y. Takemoto, *Org. Lett.* **2017**, *19*, 4762-4765.

[124] B. Y. Karlinskii, V. P. Ananikov, *ChemSusChem*, **2021**, *14*, 558-568.

[125] N. Schröder, F. Lied, F. Glorius, *J. Am. Chem. Soc.* **2015**, *137*, 1448-1451.

[126] X. Sun, G. Shan, Y. Sun, Y. Rao, *Angew. Chem. Int. Ed.* **2013**, *52*, 4440-4444.

[127] W. C. C. Lee, A. Tehrani, J. J. Li, *Synthesis* **2017**, *49*, 2865-2872.

[128] E. Bures, J. A. Nieman, S. Yu, P. G. Spinazze, J. L. J. Bontront, I. R. Hunt, A. Rauk, B. A. Keay, *J. Org. Chem.* **1997**, *62*, 8750-8759.

[129] Y. Kondo, M. Shilai, M. Uchiyama, T. Sakamoto *J. Am. Chem. Soc.* **1999**, *121*, 3539-3540.

[130] J. M. Duffault, F. Tellier, *Synth. Commun.* **1998**, *28*, 2467-2481.

[131] F. Brucoli, A. Natoli, P. Marimuthu, M. T. Borrello, P. Stapleton, S. Gibbons, A. Schätzlein, *Bioorg. Med. Chem.* **2012**, *20*, 2019-2024.

[132] Y. Zhang, J. W. Herndon, *J. Org. Chem.* **2002**, *67*, 4177-4185.

[133] P. Lu, C. Sanchez, J. Cornella, I. Larrosa, *Org. Lett.* **2009**, *11*, 5710-5713.

[134] J. T. Pinhey, E. G. Roche, *J. Chem. Soc. Perkin Trans. 1* **1988**, 2415-2421.

[135] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333-3336.

[136] R. Alvarez, M. Perez, O. N. Faza, A. R. Lera, *Organometallics* **2008**, *27*, 3378-3389.

[137] C. Cordovilla, C. Bartolome, J. M. Martinez-Ilarduya, P. Espinet, *ACS Catal.* **2015**, *5*, 3040-3053.

[138] V. Farina, S. Kapadia, B. Krishnan, C. Wang, L. S. Liebeskind, *J. Org. Chem.* **1994**, *59*, 5905-5911.

[139] S. P. H. Mee, V. Lee, J. E. Baldwin, *Angew. Chem. Int. Ed*. **2004**, *43*, 1132-1136.

[140] J. delPozo, D. Carrasco, M. H. Perez-Temprano, M. Garcia-Melchor, R. Alvarez, J. A. Casares, P. Espinet, *Angew. Chem. Int. Ed.* **2013**, *52*, 2189-2193.

[141] J. M. Khurana, A. Gogia, *Org. Prep. Proced. Int.* **1997**, *29*, 1-32.

[142] C. F. Lane, *Synthesis* **1975**, 135-146.

[143] C. Wu, P. A. Miller, M. J. Miller, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2611-2615.

[144] Merck Sharp & Dohme Corp. F. Xu, R. Desmond, R. S. Hoerrner, G. R. Humphrey, T. Itoh, M. Journet, N. Yoshikawa, M. J. Zacuto, **2010**, WO 2010/144293 A1, 35.

[145] N. Bogliotti, P. I. Dalko, J. Cossy, *J. Org. Chem.* **2006**, *71*, 9528-9531.

[146] K. B. Lindsay, S. G. Pyne, *Synlett*, **2004**, *5*, 779-782.

[147] A. S. Makarov, M. G. Uchuskin, I. V. Trushkov, *Synthesis* **2018**, *50*, 3059-3086.

[148] O. Achmatowicz, P. Bukowski, B. Szechner, Z. Zwierzchowska, A. Zamojski, *Tetrahedron* **1971**, *27*, 1973-1996.

[149] P. Merino, S. Anoro, S. Franco, F. L. Merchan, T. Tejero, V. Tunon, *J. Org. Chem.* **2000**, *65*, 1590-1596.

[150] D. B. Min, J. M. Boff, *Comp. Rev. Food Sci. Food Saf.* **2002**, *1*, 58-72.

[151] C. Schweitzer, R. Schmidt, *Chem. Rev.* **2003**, *103*, 1685-1758.

[152] R. D. Scurlock, B. Wang, P. R. Ogilby, *J. Am. Chem. Soc.* **1996**, *118*, 388-392.

[153] A. A. Ghogare, A. Greer, *Chem. Rev.* **2016**, *116*, 9994-10034.

[154] A. Greer, *Acc. Chem. Res.* **2006**, *39*, 797-804.

[155] T. Montagnon, M. Tofi, G. Vassilikogiannakis, *Acc. Chem. Res.* **2008**, *41*, 1001-1011.

[156] M. C. DeRosa, R. J. Crutchley, *Coord. Chem. Rev.* **2002**, *233-234*, 351-371.

[157] N. Furuichi, T. Hata, H. Soetjipto, M. Kato, S. Katsumura, *Tetrahedron* **2001**, *57*, 8425-8442.

[158] S. N. Patil, F. Liu, *Org. Lett.* **2007**, *9*, 195-198.

[159] B. H Wojcik, *Ind. Eng. Chem.* **1948**, *40*, 210-216.

[160] M. A. Larsen, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 4287-4299.

[161] Q. M. Dong, S. Dong, C. Shen, Q. H. Cao, M. Y. Song, Q. R. He, X. L. Wang, X. J. Yang, J. J. Tang, J. M. Gao, *Sci. Rep.* **2018**, *8*, 8372.

[162] D. L. Comins, M. O. Killpack, *J. Org. Chem.* **1987**, *52*, 104-109.

[163] H. Gilman, N. O. Calloway, *J. Am. Chem. Soc.* **1933**, *55*, 4197-4205.

[164] H. J. Anderson, C. W. Huang, *Can. J. Chem.* **1970**, *48*, 1550-1553.

[165] B. M. Monroe, *J. Phys. Chem.* **1977**, *81*, 1861-1864.

[166] E. L. Clennan, L. J. Noe, T. Wen, E. Szneler, *J. Org. Chem.* **1989**, *54*, 3581-3584.

[167] W. C. Patt, J. J. Edmunds, J. T. Repine, K. A. Berryman, B. R. Reisdorph, C. Lee, M. S. Plummer, A. Shahripour, S. J. Haleen, J. A. Keiser, M. A. Flynn, K. M. Welch, E. E. Reynolds, R. Rubin, B. Tobias, H. Hallak, A. M. Doherty, *J. Med. Chem.* **1997**, *40*, 1063-1074.

[168] K. Harada, K. Zaha, R. Bando, R. Irimaziri, M. Kubo, Y. Koriyama, Y. Fukuyama, *Eur. J. Med. Chem.* **2018**, *148*, 86-94.

[169] Y. Z. Wang, C. P. Tang, P. H. Dien, Y. Ye, *J. Nat. Prod.* **2007**, *70*, 1356-1359.

[170] P. Mungkornasawakul, S. G. Pyne, A. Jatisatienr, D. Supyen, W. Lie, A. T. Ung, B. W. Skelton, A. H. White, *J. Nat. Prod.* **2003**, *66*, 980-982.

[171] D. W. Knight, *Contemp. Org. Synth.* **1994**, *1*, 287-315.

[172] L. J. Haynes, J. R. Plimmer, *Q. Rev. Chem. Soc.* **1960**, *14*, 292-315.

[173] M. P. Bradshaw, C. Barril, A. C. Clark, P. D. Prenzler, G. R. Scollary, *Crit. Rev. Food Sci. Nutr.* **2011**, *51*, 479-498.

[174] M. M. Abdou, R. A. El-Saeed, M. A. Abozeid, M. G. Sadek, E. Zaki, Y. Barakat, H. Ibrahim, M. Fathy, S. Shabana, M, Amine, S. Bondock, *Arab. J. Chem.* **2019**, *12*, 464-475.

[175] M. M. Kayser, L. Breau, S. Eliev, P. Morand, H. S. Ip, *Can. J. Chem.* **1986**, *64*, 104-109.

[176] A. M. Baylis, M. Helliwell, A. C. Regan, E. J. Thomas, *J. Chem. Soc. Perkin Trans. 1* **1993**, 411-416.

[177] M. Conrad, *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 1042-1048.

[178] A. Hantzsch, *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 3168-3169.

[179] E. B. Reid, R. B. Fortenbaugh, H. R. Patterson, *J. Org. Chem.* **1950**, *15*, 572-582.

[180] A. S. Wengel, T. Reffstrup, P. M. Boll, *Tetrahedron* **1979**, *35*, 2181-2185.

[181] J. Uenishi, R. Kawahama, O. Yonemitsu, *J. Org. Chem.* **1997**, *62*, 1691-1701.

[182] T. Honda, A. Satoh, T. Yamada, T. Hayakawa, K. Kanai, *J. Chem. Soc. Perkin Trans. 1* **1998**, 397-406.

[183] P. March, J. Font, A. Gracia, Z. Qingying, *J. Org. Chem.* **1995**, *60*, 1814-1822.

[184] G. A. MacAlpine, R. A. Raphael, A. Shaw, A. W. Taylor, H. J. Wild, *J. Chem. Soc. Perkin Trans. 1* **1976**, 410-416.

[185] Y. Soda, Y. Sugiyama, M. Yoritate, H. Tajima, K. Shibuya, C. Ogihara, T. Oishi, T. Sato, N. Chida, *Org. Lett.* **2020**, *22*, 7502-7507.

[186] H. B. Borate, S. P. Sawargave, S. P. Chavan, M. A. Chandavarkar, R. Iyer, A. Tawte, D. Rao, J. V. Deore, A. S. Kudale, P. S. Mahajan, G. S. Kangire, *Bioorganic Med. Chem. Lett.* **2011**, *21*, 4873-4878.

[187] G. R. Waitkins, C. W. Clark, *Chem. Rev.* **1945**, *36*, 235-289.

[188] A. C. Campbell, M. S. Maidment, J. H. Pick, D. F. M. Stevenson, *J. Chem. Soc. Perkin Trans. 1* **1985**, 1567-1576.

[189] C. Aissa, *Eur. J. Org. Chem.* **2009**, 1831-1844.

[190] L. A. Sharp, S. Z. Zard, *Org. Lett.* **2006**, *8*, 831-834.

[191] F. Velazquez, H. F. Olivo, *Org. Lett.* **2002**, *4*, 3175-3178.

[192] Y. Q. Huang, X. Z. Huang, P. Q. Huang, *J. Org. Chem.* **2021**, *86*, 2359-2368.

[193] R. N. Lacey, *J. Chem. Soc.* **1954**, 822-826.

[194] K. C. Nicolaou, S. T. Harrison, *J. Am. Chem. Soc.* **2007**, *129*, 429-440.

[195] N. V. Kovganko, V. L. Survilo, *Chem. Nat. Compd.* **2002**, *38*, 340-343.

[196] W. G. Salmond, M. A. Barta, J. L. Havens, *J. Org. Chem.* **1978**, *43*, 2057-2059.

[197] A. C. Hunter, S. M. Priest, *Steroids*, **2006**, *71*, 30-33.

[198] S. Ma, B. Wu, Z. Shi, *J. Org. Chem.* **2004**, *69*, 1429-1431.

[199] F. A. Davis, L. C. Vishwakarma, J. G. Billmers, J. Finn, *J. Org. Chem.* **1984**, *49*, 3241-3243.

[200] T. Yamada, H. Hagiwara, H. Uda, *J. Chem. Soc., Chem. Commun.* **1980**, 838-839.

[201] E. H. Vickery, L. F. Pahler, E. J. Eisenbraun, *J. Org. Chem.* **1979**, *44*, 4444-4446.

[202] A. Dondoni, A. Marra, A. Boscarato, *Chem. Eur. J.* **1999**, *5*, 3562-3572.

[203] L. Vasamsetty, F. A. Khan, G. Mehta, *Tetrahedron Lett.* **2013**, *54*, 3522-3525.

[204] I. M. Reimer, D. L. Conley, D. L. Pompliano, J. W. Frost, *J. Am. Chem. Soc.* **1986**, *108*, 8010-8015.

[205] J. Ogikubo, E. Meehan, J. T. Engle, C. J. Ziegler, C. Brückner, *J. Org. Chem.* **2012**, *77*, 6199-6207.

[206] A. Nagatsu, R. Tanaka, M. Hashimoto, H. Mizukami, Y. Ogihara, J. Sakakibara, *Tetrahedron Lett.* **2000**, *41*, 2629-2632.

[207] K. Nishimura, Y. Hitotsuyanagi, N. Sugeta, K. Sakakura, K. Fujita, H. Fukaya, Y. Aoyagi, T. Hasuda, T. Kinoshita, D. H. He, H. Otsuka, Y. Takeda, K. Takeya, *Tetrahedron* **2006**, *62*, 1512-1519.

[208] R. Brückner, *Chem. Commun.* **2001**, 141-152.

[209] M. J. Kates, J. H. Schauble, *J. Org. Chem.* **1994**, *59*, 494-496.

[210] Y. Minami, K. Yamada, T. Hiyama, *Angew. Chem. Int. Ed.* **2013**, *52*, 10611-10615.

[211] W. T. Lambert, G. H. Hanson, F. Benayoud, S. D. Burke, *J. Org. Chem.* **2005**, *70*, 9382-9398.

[212] W. Zhan, L. Xu, X. Dong, J. Dong, X. Yi, X. Ma, N. Qiu, J. Li, B. Yang, Y. Zhou. Y. Hu, *Eur. J. Med. Chem.* **2016**, *117*, 47-58.

[213] M. Perez-Venegas, G. Reyes-Rangel, A. Neri, J. Escalante, E. Juaristi, *Beilstein J. Org. Chem.* **2017**, *13*, 1728-1734.

[214] M. Harmata, X. Hong, *J. Am. Chem. Soc.* **2003**, *125*, 5754-5756.

[215] I. Coldham, S. Raimbault, D. T. E. Whittaker, P. T. Chovatia, D. Leonori, J. J. Patel, N. S. Sheikh, *Chem. Eur. J.* **2010**, *16*, 4082-4090.

[216] H. Deng, T. Wel, R. J. B. H. N. Berg, A. M. C. H. Nieuwendijk, F. J. Janssen, M. P. Baggelaar, H. S. Overkleeft, M. Stelt, *Med. Chem. Commun.* **2017**, *8*, 982-988.

[217] D. L. Thai, M. T. Sapko, C. T. Reiter, D. E. Bierer, J. M. Perel, *J. Med. Chem.* **1998**, *41*, 591-601.

[218] U. K. Tambar, T. Kano, J. F. Zepernick, B. M. Stoltz, *J. Org. Chem.* **2006**, *71*, 8357-8364.

[219] G. Burton, S. C. M. Fell, J. H. Bateson, **1991**, US Patent 5064649A.