Synthetic studies towards tricyclic quinolizidine- or bicyclic decahydroquinoline-containing alkaloids.

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Abstract

The present investigations deal with two different topics, both related to the total synthesis of natural compounds.

In the first part of this work, two synthetic concepts towards cylindricines and related tricyclic natural compounds were investigated. The complex structures of these compounds combined with theirs interesting biological activities have made them highly attractive synthetic targets. Considering former group members' results, a synthetic route to the tricyclic core of the examined alkaloids was studied using transannular Mannich reactions on a suitable macrocyclic diketone. Numerous studies were performed on the way to the requisite macrocycle. The first challenge of this synthetic path was the construction of the central α,α'-chiral secondary amino group. An interesting two-step sequence, imine formation and Grignard addition, applied to the adequate amino alcohol was optimised and afforded the desired α,α'-chiral amine in a highly diastereoselective fashion. Despite various attempts to continue this synthetic route, the required macrocycle could not be obtained. Moreover, in 2009, during the realisation of the present work, Tanner and co-workers published the synthesis of the nude desired tricyclic core employing a similar model. As a consequence, to conserve the novelty of our synthetic concept, a modified route was developed. A new concept was developed, including the achievement of the desired tricyclic core through consecutive hydroamination reaction and Mannich reaction on an adequate triple bond and ketone containing macrocycle. Various synthetic ways towards suitable amino alcohols were first examined and afforded the different desired substrates in moderate to high yields. The previously developed two-step sequence, imine formation and Grignard addition, applied on these different amino alcohols afforded the corresponding requisite α,α'-chiral amines. Further studies on the following steps of the process led to traces of an interesting precursor which is expected to give the required macrocycle directly after an alkyne-alkyne ring closing metathesis, as it was demonstrated in another group member's current work.

In the second part of this work, a synthetic concept presented by a former group member for the total synthesis of pumiliotoxin CIII was taken into account and a generalisation to the synthesis of 2,5-disubstituted decahydroquinolines was investigated. Similarly to the previously reported studies, a synthetic route through a 2,5-disubstituted hexahydroquinoline obtained from a diastereoselective ring-rearrangement metathesis was developed. In the present work, the syntheses of the three required fragments for the achievement of the metathesis precursor were developed and optimised.

Zusammenfassung

Im ersten Teil der Arbeit wurden zwei totalsynthetische Konzepte zum Zugang zur Naturstoffklasse der Cylindricine und verwandten tricyclischen Naturstoffen untersucht. Sowohl die interessante pharmakologische Aktivität als auch die Strukturelle Komplexität machen diese Naturstoffklasse zu einem sehr attraktiven Syntheseziel. Zum Aufbau des gewünschten tricyclischen Kerns wurde basierend auf Vorarbeiten aus dieser Gruppe eine Synthesestrategie über eine transannulare Mannich-Reaktionen geeigneter makrocyclischer Diketone verfolgt. Eine effiziente, zweistufigen Sequenz aus Iminbildung und anschließender diastereoselektiver Grignard-Addition lieferte unter optimierten Bedingungen das gewünschte α,α'-chirale Amin mit einer hohen Diastereoselektivität und einer guten Ausbeute. Verschiedene Experimente haben jedoch gezeigt, dass der erforderliche Makrozyclus auf diesem Syntheseweg nicht erhalten werden kann. Basierend auf diesen Ergebnissen wurde ein modifiziertes Synthesekonzept entwickelt, welches den angestrebten Tricyclus in einer Reaktionsfolge aus Alkin-Alkin-Ringschlussmetathese entsprechender Dialkine, Hydroaminierung und transannularer Mannich-Reaktion zugänglich macht. Zur Darstellung entsprechend geeigneter α,α'-chiralen Amine wurde auch hier durch die zuvor erarbeitete zweistufigen Sequenz aus Iminbildung und Grignard-Addition anvisiert. Ersten Versuche zeigten, dass ein entsprechender Metathesevorläufer zur Bildung des Makrozyclusses zugänglich ist. Fortführende Untersuchungen auf dieser Syntheseroute sind Gegenstand aktueller Studien in dieser Gruppe.

Im zweiten Teil der Arbeit wurde ein synthetisches Konzept aus diesem Arbeitskreis, welches zuvor im Rahmen der Totalsynthese von Pumiliotoxin CIII Anwendung fand, auf die flexible Synthese von 2,5-disubstituirten Decahydrochinolinen erweitert. Basierend auf den zuvor berichteten Studien wurde eine Syntheseroute anvisiert, die als Schlüsselschritt zum Aufbau eine 2,5-disubstituirte Hexahydrochinolins eine diastereoselektive Ringumlagerungsmetathese beinhaltet. In der vorliegenden Arbeit wurden die Synthesen der drei benötigten Fragmente zur Darstellung des entsprechenden Methatesevorläufers entwickelt und optimiert.

Résumé

Deux sujets de recherche ont été abordés dans cette thèse, concernant tous deux la synthèse totale de composés naturels.

Dans la première partie de ces travaux, deux concepts de synthèse des cylindricines, produits naturels, et d'alcaloïdes tricycliques apparentés ont été étudiés. Les structures complexes de ces composés ainsi que leur intérêt biologique en ont fait des cibles synthétiques attractives. Prenant en compte des résultats obtenus par d'anciens membres du groupe, une voie de synthèse du noyau tricyclique de ces alcaloïdes utilisant des réactions de Mannich transannulaires sur une dicétone macrocyclique appropriée a tout d'abord été examinée. De nombreuses approches ont été considérées pour la synthèse de ce macrocycle. Le premier défi était la création de l'amine secondaire α,α'-chirale, au centre du squelette des molécules cibles. Une séquence en deux étapes, formation d'une imine puis addition d'un Grignard, appliquée à un amino-alcool approprié a été développée et optimisée, permettant l'obtention du composé souhaité avec une diastéréosélectivité importante. Cependant, malgré de nombreuses tentatives d'optimisation de cette voie de synthèse, le macrocycle requis n'a pu être obtenu. Par ailleurs, en 2009, durant la réalisation de ces travaux de recherche, le groupe du professeur Tanner a publié une synthèse du noyau tricyclique souhaité utilisant un modèle similaire. Par conséquent, pour préserver la nouveauté souhaitée de notre concept de synthèse, des modifications ont été apportées au modèle initialement développé. Un nouveau concept a été pensé, dans lequel le squelette tricyclique souhaité pourrait être obtenu par une hydroamination suivie d'une réaction de Mannich sur un macrocycle approprié contenant une triple liaison et une cétone. Dans un premier temps, des voies de synthèse variées des amino-alcools désirés ont été développées et ont permis leur obtention avec des rendements modérés à élevés. La séquence en deux étapes précédemment évoquée, formation d'une imine puis addition d'un Grignard, appliquée aux différents amino-alcools obtenus a conduit à l'obtention des amines α,α'-chirales nécessaires correspondantes. Des études supplémentaires sur les étapes suivantes de la synthèse ont mené à des traces d'un intermédiaire clé. En effet, l'obtention de ce dernier pourrait mener au macrocycle souhaité simplement après une métathèse alcyne-alcyne, comme cela a été récemment démontré dans les travaux d'un autre membre de notre groupe.

Dans la deuxième partie de ces travaux de recherche, la synthèse de décahydroquinoléines 2,5-disubstituées a été étudiée en utilisant le concept développé par un ancien membre du groupe pour la synthèse totale de la pumiliotoxine CIII. Une voie de synthèse comportant un intermédiaire hexahydroquinoléinique obtenu diastéréosélectivement par réarrangement de cycle par métathèse a été développée. Dans les travaux de recherche présentés ici, les synthèses des trois fragments nécessaires à l'obtention du précurseur de la réaction de métathèse ont été développées et optimisées.

A ma mère,

"All that I am, or hope to be,
I owe to my angel mother."

Abraham Lincoln

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1. Synthetic studies towards cylindricines and similar tricyclic alkaloids

1.1. Introduction

1.1.1. Cylindricines and related alkaloids

1.1.1.1. Isolation and structural determination

Ascidiacea, commonly known as ascidians or sea squirts, are sac-like marine invertebrates belonging to the phylum *Chordata*, subphylum *Tunicata*. They are characterized by a hard outer overlay made of the polysaccharide tunicin, making them the most rigid tunicates (**Figure 1**).

Figure 1. From the left to the right: ascidians *Clavelina cylindrica*,[1] *Clavelina lepadiformis* (Müller)[2] and *Clavelina moluccensis* (Sluiter).[3]

A large number of biologically active nitrogen containing second metabolites have been isolated from ascidians.[4] From the late 1980s, numerous alkaloids have been extracted from ascidians, approximately 165 between 1988 and 1992.[5] For example, the quinolizidines clavepictines **1**-**2**,[6] pictamine **3**[7] or the indolizidines piclavines **4**-**6**[8] were among the alkaloids isolated from the ascidian *Clavelina picta* (**Figure 2**).

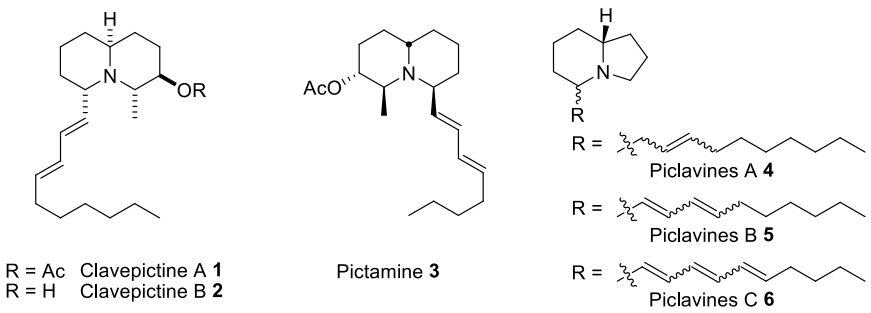


Figure 2. Structures of alkaloids clavepictines, pictamine and piclavines.

The natural compounds of interest for the presented work were also isolated from ascidians. They are, for example, cylindricine A **7**, lepadiformine (A) **8**, fasicularin **9** or polycitorol A **10** (**Figure 3**).

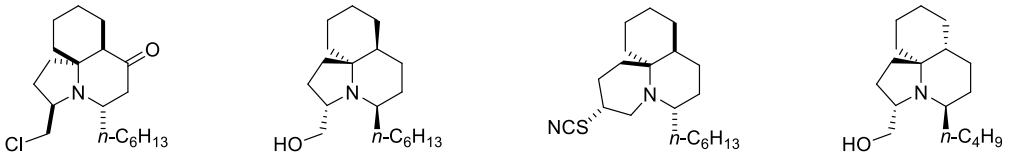
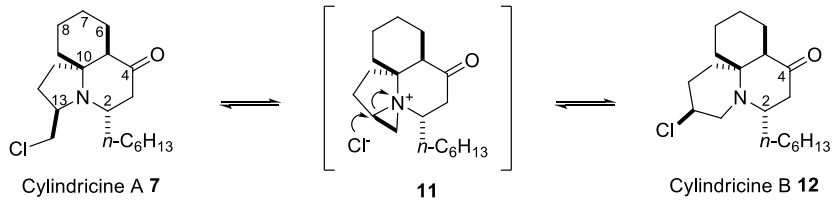


Figure 3. Examples of alkaloids which were studied in the present work

In the remaining of this section, isolation and structural determination of cylindricines, lepadiformines, polycitorols and fasicularin are detailed.

1.1.1.1.1. Cylindricines

In 1993, Blackman and co-workers investigated for the first time the ascidian *Clavelina cylindrica*, indigenous to Australia and collected in Tasmania at 10 meters depth. These studies allowed the isolation of cylindricines A **7** and B **12**.[9] Cylindricines A **7** and B **12** were respectively the first pyrrolo[2, 1-j]quinoline known from nature and the first pyrido[2, 1-j]quinoline ring system. EI-MS and NMR spectroscopy analyses of the compounds in addition to X-ray crystallography of their picrate salts were used, leading to the final structure of both alkaloids **7** and **12** (**Scheme 1**). Interestingly, a mixture of cylindricines A and B present as free bases in a solution will tend to give a 3 : 2 equilibrium mixture of **7** and **12**. This interconversion may be concerted or proceed through the aziridinium ion intermediate **11**.



Scheme 1. Structures of cylindricines A and B.

Both in 1994 and 1995, Blackman and co-workers reported the discovery of respectively five and four new cylindricines, cylindricines C-G **13**-**17** and cylindricines H-K **18**-**21**, which were isolated from the ascidian *Clavelina cylindrica* (**Figure 4**).[5,10] All these compounds were obtained as minor alkaloids, the major ones being cylindricines A and B. Further analysis and chemical interconversion tests lead to the structure and relative conformation of these new alkaloids. The structure of cylindricines C-F is closely related to cylindricine A. The chlorine atom in cylindricine A is replaced by a hydroxy group in cylindricine C, a methoxy group in cylindricine D, an acetoxy group in cylindricine E, and a thiocyanate group in cylindricine F. Cylindricine G only differs from cylindricine F in the length of the alkyl side chain at position C2. Cylindricines H-J contain an acetoxy group at position C4 instead of the ketone present in cylindricines A-G. Cylindricine I differs from cylindricine H by the presence of an isothiocyanate group instead of a thiocyanate group. Cylindricine J has a closer structure to cylindricine B; it varies from it in the length of the alkyl chain at position C2 and contains an isothiocyanate group at the place of the chlorine atom. Cylindricine K, structurally similar to cylindricine A, presents a keto group at position C8 instead of C4 and a C6-C7 double bond.

Interestingly, cylindricines F-H and cylindricines I and J were the first secondary metabolites obtained from an ascidian containing a thiocyanate and an isothiocyanate group, respectively.

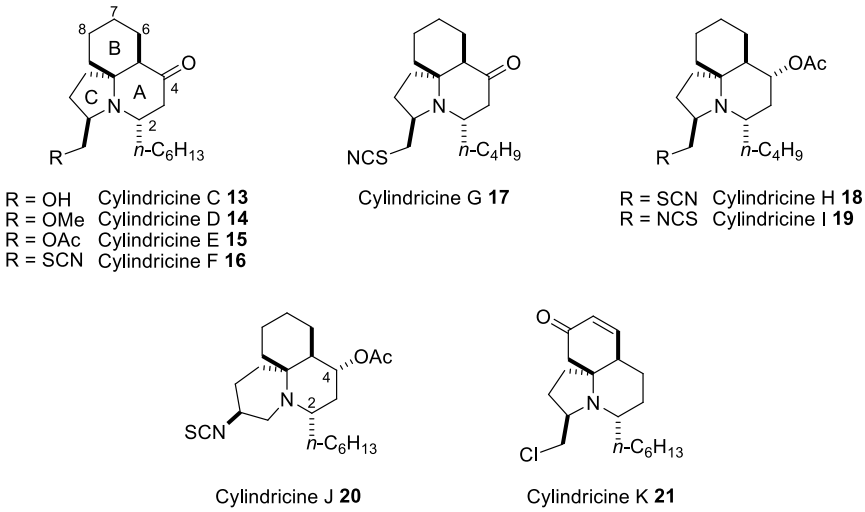


Figure 4. Structure of cylindricines C-K.

All of the cylindricines alkaloids possess a *cis*-fused 1-azadecalin A/B-ring system and prefer to exist in the conformations shown in **Figure 4** as evidenced by X-ray crystal structures and NMR spectroscopy data, as well as mechanics calculations. It is important to note that until now, it was impossible to compare the absolute configuration of synthetic compounds with the natural cylindricines as no optical rotation values are known for the natural products.

1.1.1.1.2. Lepadiformines

At the same period, in 1994, Biard and co-workers investigated *Clavelina lepadiformis* (Müller), also known as light-bulb sea squirt because of its transparent tunic and visible yellow to white internal organs.[11] During these investigations, lepadiformine, now also known as lepadiformine A, was isolated (**Figure 5**). For this new alkaloid, the reported structure **22** was containing an unprecedented vicinal zwitterionic amino alcohol moiety and led to the hypothesis of a new member of the cylindricine class due to its *cis*-1-azadecalin A/B ring system. However, unlike most of cylindricines, lepadiformine A is lacking of oxygenation at position C4. Based upon synthetic work, it was later shown that not only that the structure **22** is incorrect but also that lepadiformine A is not a zwitterion.[12,13] Moreover, it was proved that lepadiformine A is neither a C2 nor a C13 epimer of the structure **22**.[14] In 2000, Kibayashi and co-workers finally established the constitution and absolute configuration as shown in structure **8**.[15–17]

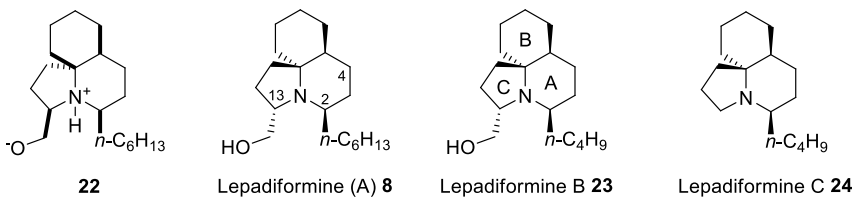
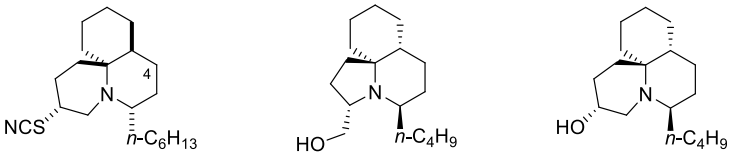


Figure 5. Structures of lepadiformines A-C.

In 2006, Sauviat and co-workers presented lepadiformines B **23** and C **24**, extracted from the ascidian *Clavelina moluccensis* (Sluiter).[18] Lepadiformine B differs from lepadiformine A in the presence of a butyl group instead of a hexyl group at position C2, and lepadiformine C is not bearing the hydroxymethyl group at position C1. Although it has not been proven yet, there are suspicions that lepadiformines B and C have the same absolute stereochemistry as lepadiformine A.

1.1.1.1.3. Polycitorols and fasicularin

In 1997, Patil and co-workers isolated fasicularin **9** from the ascidian *Nephteis fasicularis* which showed structural similarities with the cylindricine B series of pyridoquinolines.[19] However, further analyses evidenced a *trans*-1-azadecalin A/B-ring system and a lack of oxygenation at position C4 (**Figure 6**). As in the case of cylindricines, the lack of optical rotation value does not allow the comparison with the enantiopure synthetic products and the attribution of the natural compound absolute configuration.



Fasicularin **9** Polycitorol A **10** Polycitorol B **25**

Figure 6. Structures of fasicularin and polycitorols A and B.

Two other structurally similar tricyclic alkaloids, polycitorols A **10** and B **25**, were isolated in 2005 by Tanaka and co-workers from an ascidian of the family *Polycitoridae*.[20] They were found to bear a *n*-butyl side chain instead of the *n*-hexyl chain, which is more commonly observed in the other known related compounds. As members of the cylindricines and lepadiformines family, they contain a *cis*-fused A/B-ring system and as members of the lepadiformines family and fasicularin, they are lacking the common oxygenation of most of cylindricines at position C4.

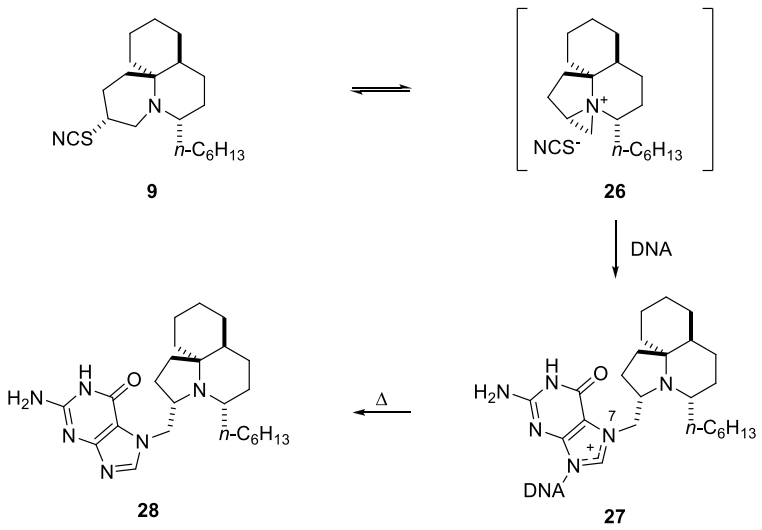
1.1.1.2. Biological activity

Like most of the alkaloids, cylindricines and related compounds are showing interesting biological properties. The toxicity of cylindricines A and B to brine shrimps was already reported in the first study published by Blackman and co-workers in 1993.[9] However, lepadiformines and fasicularin were the most investigated.

In 1994, Biard and co-workers described the moderate *in vitro* cytotoxicity of lepadiformine A on nasopharynx carcinoma (KB) and non-small-cell lung carcinoma (NSCLC-N6) cells, with an IC_{50} of respectively 9.2 and 6.1 µg/mL.[11] In later studies, they presented new results, while they were investigating the possible undesirable effects of lepadiformine A *in vivo*.[21] At first, carrying out studies about the acute toxicity of lepadiformine A on mice, they discovered that the injection of 15 mg/kg did not modify their behaviour. However, the injection of 30 mg/kg decreased motor

activity, producing respiratory weakness and cyanosis, and 40 mg/kg provoked muscular paralysis followed by death of the animal. In following tests on rat and frog hearts, they interestingly found out that with as less as 6 mg/kg, lepadiformine A had cardiovascular effects. It produced marked bradycardia and acted on the electrocardiogram intervals by significantly lengthening the repolarising phase of action potentials. These properties can be compared to the ones found in pharmacological substances like tacrine[22] or the antispasmodic agent terodiline.[23] Considering the properties shared between lepadiformine A and these drugs, and regarding the similarity between the effects of lepadiformine A and tacrine on the cardiovascular system, it also suggests that lepadiformine A may have antiarrythmic properties. Further studies were also performed on the mechanism of action of lepadiformine A on the cardiac muscle.[18] Lepadiformines B and C were reported to have similar properties.

In 1997, Patil and co-workers showed that fasicularin exhibits cytotoxic properties against Vero-cells with an IC_{50} of 14 μg/kg and acts as DNA-damaging agent in the assay using a DNA repair-deficient yeast strain.[19] In 2005, Gates and co-workers proposed a mechanism of action of fasicularin on DNA (**Scheme 2**).[24] They first based their research on the possibility that fasicularin could share with cylindricines A and B the ability to easily form an aziridinium intermediate, in this case the intermediate **26**, *via* intramolecular displacement of the thiocyanate group. To evidence this mechanism and the formation of the fasicularin-DNA adduct **27** by subsequent alkylation at position 7 of the guanine, they treated mixed-sequence duplex DNA with fasicularin and performed a thermal workup to release alkylated bases. The product **28** was found, supporting the hypothesis of the complete mechanism. Literature precedents, regarding the preferred site of nucleophilic attack on aziridinium ions structurally similar to **26**, explain the proposed regioselectivity for the attack of guanine on the intermediate **26**.[5,25,26]



Scheme 2. Mechanism of action of fasicularin on DNA.

In summary, the family of alkaloids studied presents strong and various biological properties, such as cytotoxicity against several tumour lines, cardiovascular activity or DNA damaging. These biological properties added to the synthetically challenging structural core of the cylindricine alkaloids confer them a significant interest for future synthetic studies.

1.1.2. State of the art in the total synthesis of cylindricines like alkaloids

Since their isolation, cylindricines and related tricyclic alkaloids have been increasingly studied, not only because of their interesting biological properties but also for the synthetic challenge they represent, especially in the construction of the quaternary centre at position C10. Numerous formal and total syntheses – 21 racemic and 28 enantioselective – have already been published, most of them being interestingly fixed on the construction of this particular centre and on obtaining the tricyclic core.[27–32]

In the published studies, natural compounds containing the specifically considered tricyclic backbone have been obtained using a broad scope of methods, including as key steps Michael addition[33–36] or Mannich-Michael cascade reaction,[37,38] rearrangements,[39–42] cycloadditions,[12–15,43–53] radical reactions,[54–62] metathesis,[63–65] ring-contractive cyclisation,[66] iminium[67,68] and *N*-acyliminium-ion reactions,[16,69–73] *N*-acylnitrenium-ion reactions,[74,75] metal-mediated alkylation/allylation of a chiral precursor,[76,77] Hajos-Parrish annulation,[78] nitrile anion double alkylation,[79] or finally transannular Mannich reactions.[80] Some other synthetic studies are proceeding through spirocyclic intermediates which have been formed using C-H insertion on carbene,[81] reductive lithiation[82] or oxidation of phenols.[83–86] In the remainder of this section, some of the most interesting syntheses in accordance with the topic of this work have been chosen to be detailed.

1.1.2.1. First total syntheses and use of double Michael additions

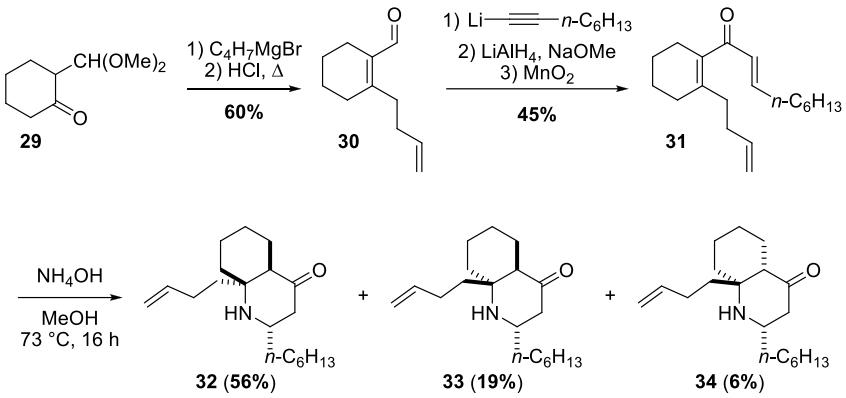
In this subsection, four different total syntheses are presented including the first racemic and the first enantioselective total syntheses of a member of the cylindricine alkaloids. These syntheses are sharing, as a key step, a similar double Michael addition to construct the required tricyclic skeleton.

1.1.2.1.1. First total synthesis of (±)-cylindricines A, D and E

The total synthesis of (±)-cylindricines A **7**, D **14** and E **15** achieved by Snider and Liu in 1997 was the first racemic total synthesis of a natural compound containing the tricyclic backbone of cylindricines.[33] This synthesis presents a double Michael addition of ammonia to a dienone to prepare the fused A/B-ring system and a copper catalyzed *N*-chloroamine/olefin radical cyclisation to form the C-ring, as the key steps.

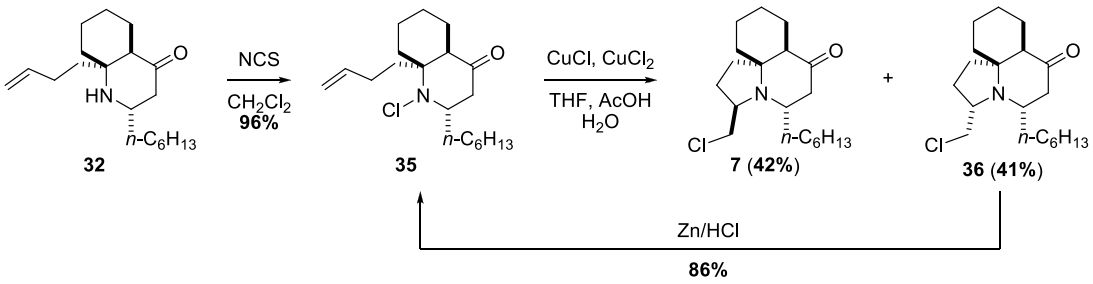
Starting with the known acetal ketone **29**, enal **30** was obtained in a 60% yield after addition of 3-butenylmagnesium bromide to **29** followed by hydrolysis of the acetal and dehydration (**Scheme** 3). Addition of 1-octynyllithium to aldehyde **30**, followed by reduction of the resulting propargylic alcohol, and allylic alcohol oxidation afforded the desired dienone **31** in a 45% yield. For the following reaction, various parameters were studied. It was interestingly found that the pH had the most important influence on the stereochemical ratio in the formation of 1-azadecalins by double Michael

addition of ammonia to dienones. At high pH, the desired stereoisomer **32** was mainly formed whereas lowering the pH by addition of ammonium chloride resulted in the formation of an increasing amount of undesired *trans*-fused 1-azadecalin system **33**. After optimisation of all parameters, heating the compound **31** in a 3 : 1 mixture of methanol and concentrated ammonium hydroxide in a sealed tube at 73 °C afforded the 1-azadecalins **32**, **33** and **34** in 56%, 19% and 6% yields.



Scheme 3. Synthesis of the fused A/B ring system by Snider and Liu.

To complete the synthesis, the *cis*-fused 1-azadecalin **32** was treated with *N*-chlorosuccinimide to give the *N*-chloroamine **35** in a 96% yield (**Scheme 4**). Subsequently, **35** underwent a nonstereoselective 5-*exo* cyclisation using the Stella conditions[87] for generating aminyl radicals. It provided after separation by flash chromatography 42% of the desired racemic cylindricine A **7** and 41% of its undesired epimer **36**. However, it was possible to recycle **36** by reduction with zinc and hydrochloric acid.



Scheme 4. Synthesis of 7 by Snider and Liu.

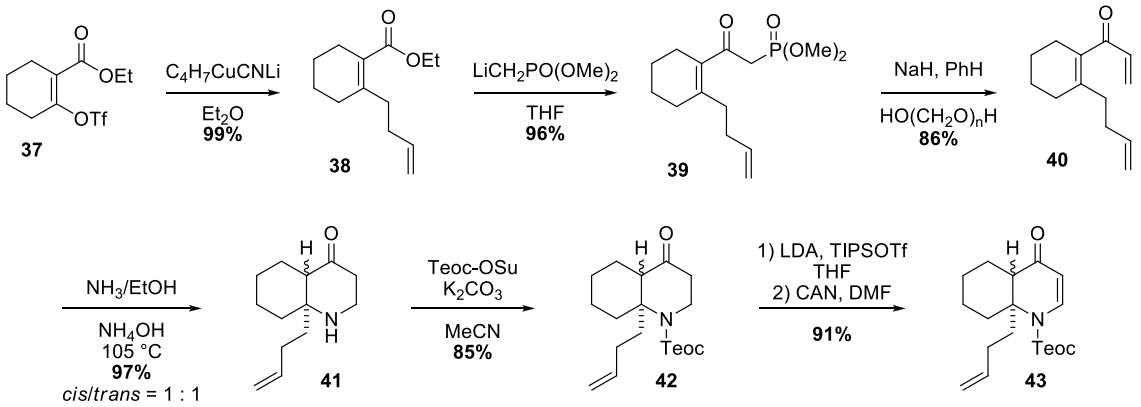
Snider and Liu were also able to use former procedures developed by Blackman and co-workers.[5] The treatment of (±)-cylindricine A **7** with sodium methoxide in methanol led to (±)-cylindricine D **14** and with sodium acetate in methanol to (±)-cylindricine E **15**.

1.1.2.1.2. Total synthesis of (±)-cylindricines A and B by Liu and Heathcock

The second racemic total synthesis of cylindricine alkaloids was the total synthesis of (±)-cylindricines **A** 7 and B **12** achieved by Liu and Heathcock in 1999.[34] The approach is very closely related to Snider

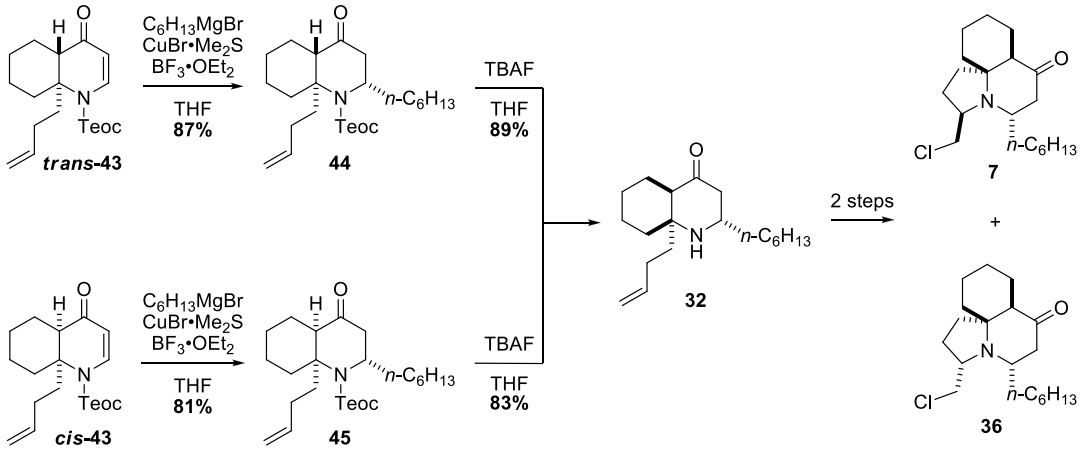
and Liu's synthesis as it includes a double Michael addition of ammonia to a dienone for the formation of the fused A/B-ring system and the construction of the C-ring is identical. However, the reaction conditions for the double Michael addition were optimised and an interesting addition of organocopper species to bicyclic vinylogous amide was used.

Heathcock and Liu explained that their initial approach regarding the double Michael addition was in fact identical to the one developed by Snider and Liu. Indeed, they obtained the same proportions of stereoisomers in the reaction of the dienone **31** with ammonia. Giving the low stereoselectivity of the process, they decided to examine other parameters and observed that the best results were obtained with the dienone **40**, which is lacking the *n*-hexyl chain present in the compound **31** (**Scheme 5**). The synthesis began with the enol triflate **37**, which was coupled with the second-order cuprate derived from 3-butenyllithium to give the ester **38**. This intermediate was converted into the corresponding β-ketophosphonate **39** by addition of the lithium anion of dimethyl methylphosphonate. The subsequent Horner-Emmons reaction of **39** with paraformaldehyde gave the dienone **40**. This compound was then heated with ammonia/ammonium hydroxide in ethanol, resulting in a double Michael addition of ammonia to the dienone, giving a 1 : 1 mixture of *cis* and *trans* isomers of the desired 1-azadecalin **41**. This mixture was *N*-acylated to give the corresponding Teoc-protected compound **42**. The triisopropylsilyl enol ether corresponding to the ketone **42** was subsequently formed and oxidized using cerium ammonium nitrate to afford the vinylogous amide **43**.



Scheme 5. Synthesis of the intermediate 43 on the way to the fused A/B-ring system by Liu and Heathcock.

The separation of the *cis* and *trans* isomers of the vinylogous amide **43** was achieved using HPLC. Subsequent alkylation following a method previously developed by Comins and co-workers provided 44 and 45 from respectively ***trans*-43** and ***cis*-43** (**Scheme 6**).[88,89] Considering the very good stereoselectivity of the previous examples of this method, it was not a surprise to obtain these products in a highly stereoselective manner, *via* axial attack of the organometallic reagent. The subsequent removal of the Teoc group, using tetrabutylammonium fluoride, from both isomers **44** and **45** afforded the more stable and desired *cis*-fused 1-azadecalin **32** in 83% and 89% yields. The conversion of the intermediate **32** to a 1 : 1 mixture of (±)-cylindricine A **7** and its epimer **36** was achieved using the same procedures as described previously by Snider and Liu (**Scheme 4**). Liu and Heathcock also reported that synthetic (±)-cylindricine A **7** equilibrated to a mixture of (±)-cylindricines A **7** and B **12**, when dissolved in C_6D_6, as described by Blackman and co-workers in the case of the natural molecules.[9]

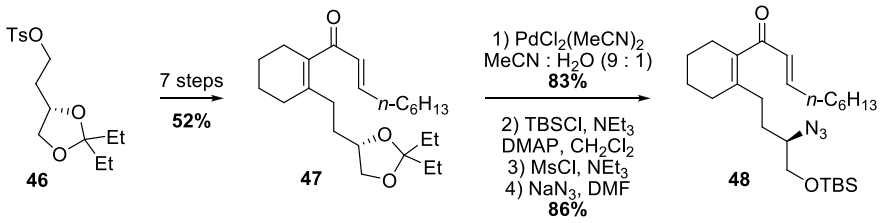


Scheme 6. Synthesis of 7 by Liu and Heathcock.

1.1.2.1.3. Total synthesis of (-)-cylindricine C by Molander and Rönn

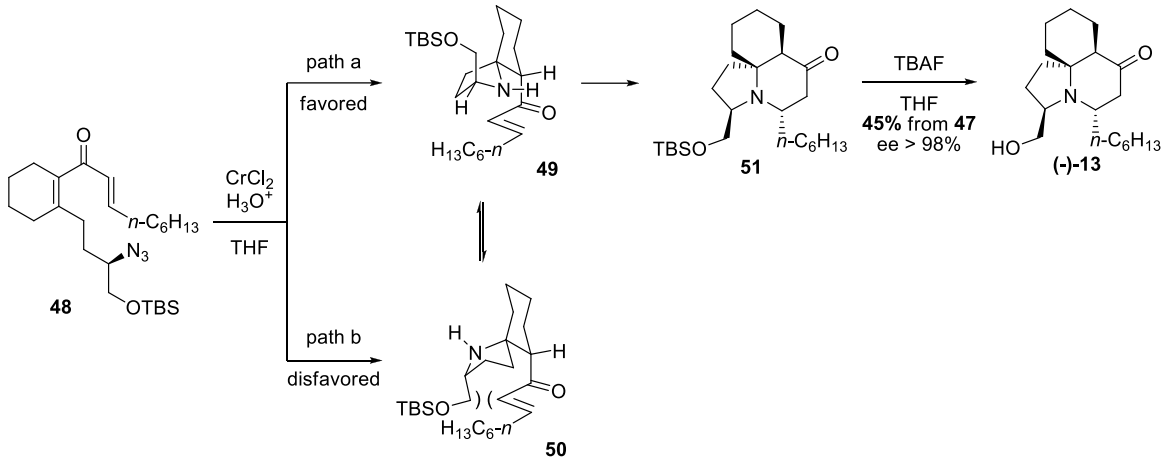
In 1999, the first enantioselective total synthesis of a cylindricine alkaloid, (-)-cylindricine C **(-)-13** was described by Molander and Rönn.[35] Following Snider and Liu pattern, the key step of this synthesis was the double Michael addition of an amine to a dienone.

The synthesis started with the known tosylate **46** which was used as source of absolute chirality for the synthesis. This derivate from (*S*)-1,2,4-butanetriol was converted in seven steps and 52% yield into the dienone **47** (**Scheme 7**). Hydrolysis of the ketal moiety in **47** using various acidic conditions provided the desired product only in low yield, most likely due to unwanted Michael addition of the secondary alcohol to the dienone. Further studies showed that the use of a palladium-mediated cleavage allow the avoidance of side reactions and led to the desired unprotected diol in a high 83% yield. This diol was then modified to afford the azide **48** in three steps and an 86% yield.



Scheme 7. Enantioselective total synthesis of (-)-13 by Molander and Rönn, synthesis of the intermediate 48.

The azide **48** was treated with chromium (II) chloride under acidic conditions to yield the *tert*-butyldimethylsilyl-protected (-)-cylindricine C **51**. (-)-cylindricine C **(-)-13** was obtained after deprotection in a moderate 45% yield over two steps (**Scheme** 8). The stereoselectivity of this cyclisation could partially be explained by the unfavourable steric interaction of the enone and the *tert*-butyldimethylsilyloxy group in the intermediate **50**. Additionally, this intermediate could be reversibly converted to intermediate **49**. It may also simply decompose in these particular reaction conditions, explaining the moderate yield of final product obtained.



Scheme 8. Enantioselective total synthesis of (-)-13 by Molander and Rönn.

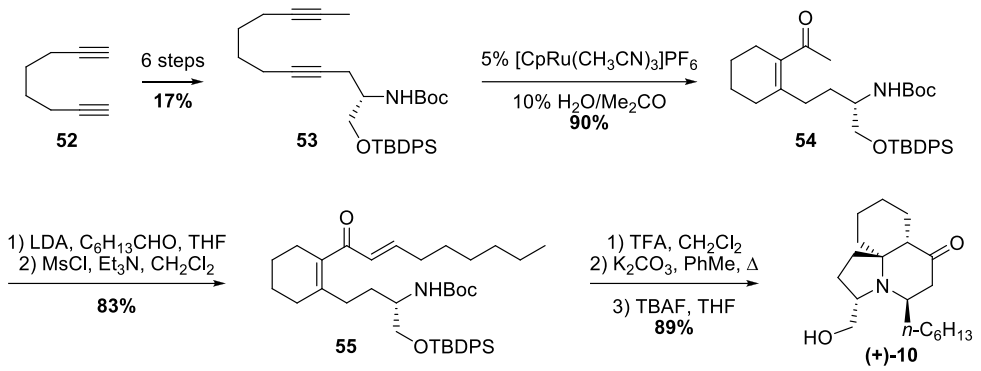
To summarize, this first enantioselective total synthesis of an alkaloid containing the tricyclic backbone of cylindricines was achieved by Molander and Rönn and afforded (-)-cylindricine C **(-)-13** in 13 steps, in a 17% overall yield from the tosylate **46** and with an enantiomeric excess greater than 98%.

1.1.2.1.4. Total synthesis of (+)-cylindricine C by Trost and Rudd

In 2003, Trost and Rudd described another enantioselective total synthesis of a cylindricine alkaloid, (+)-cylindricine C **(+)-13**, using as key steps a ruthenium-catalyzed hydrative diyne cyclisation and, as the three previously detailed syntheses, a double Michael addition of an amine to a dienone.[36]

Initially, 1,7-octadiyne **52** underwent a short series of modifications to afford the enantiomerically pure unsymmetrical diyne **53** in six steps and an overall yield of 17% (**Scheme 9**). Following a procedure previously developed in the Trost group,[90] this intermediate was engaged with 5% ruthenium catalyst in 10 vol% water/acetone to perform a chemoselective ruthenium-catalyzed hydrative diyne cyclisation, providing the enone **54** in a 90% yield. The product was then condensed with heptanal through an aldol reaction to afford, after subsequent dehydration, the dienone **55**. After cleavage of the *tert*-butoxycarbonyl group, double Michael addition of the amine to the dienone and *tert*-butyldiphenylsilyloxy group removal finally led to the desired product, (+)-cylindricine C **(+)-13**, in an 89% yield over three steps from the dienone **55**.

The enantioselective total synthesis of (+)-cylindricine C **(+)-13** was achieved in 9 steps from 1,7-octadiyne **52** with a moderate 14% overall yield mainly due to the difficult synthesis of the unsymmetrical diyne precursor **53**. In this study, as in the case of the one reported by Snider and Liu,[33] cylindricine C **13** was converted to cylindricine D **14** and E **15** using methylation or acetylation reactions. (+)-Cylindricine D **(+)-14** and (+)-Cylindricine E **(+)-15** were obtained in 90% and 99% yields from **(+)-13**.

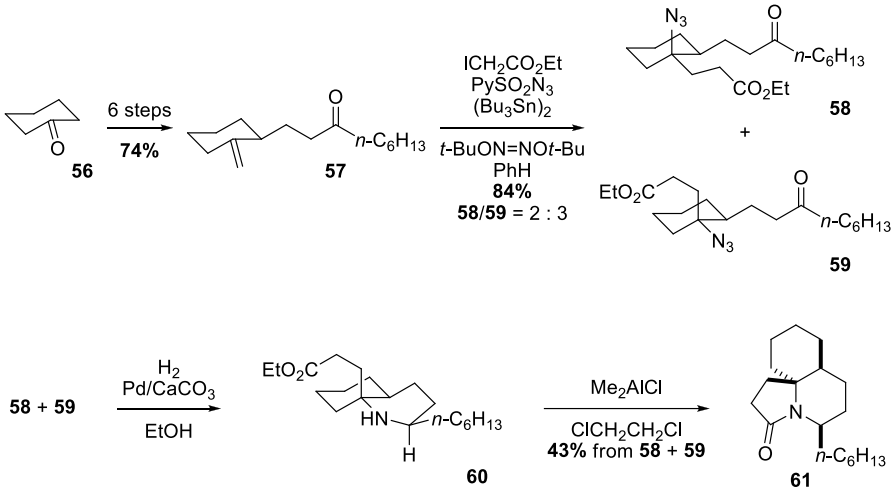


Scheme 9. Enantioselective total synthesis of (+)-13 by Trost and Rudd.

1.1.2.2. Total synthesis of 8 using radical carboazidation

In 2006, Schär and Renaud described a racemic total synthesis of (±)-lepadiformine A **8** including the use of an interesting free radical carboazidation methodology, developed by their group.[57]

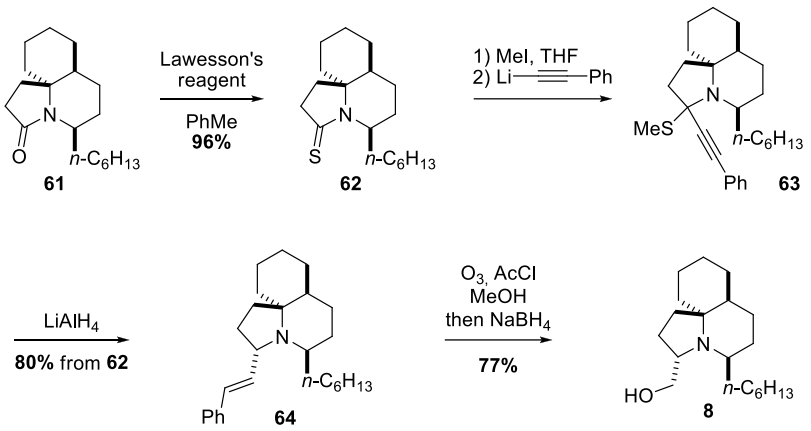
In the first part of the synthesis, methylenecyclohexane **57** was prepared in an effective manner in six steps and a 74% overall yield from cyclohexanone **56** (**Scheme 10**). The presented tin-mediated carboazidation led to a 3 : 2 mixture of the *trans* and *cis* isomers **59** and **58**. It was possible to separate the isomers at this stage but also to proceed with the mixture through the following reaction. The azido esters **58** and **59** were engaged in a catalytic hydrogenation. The ketone **59** afforded the corresponding amino ketone which directly underwent a stereoselective intramolecular reductive amination leading to the bicyclic azadecalin **60** whereas, in these conditions, **58** underwent an elimination due to the *anti* position of the azide with a proton, giving apolar side products. Subsequent cyclisation of the intermediate **60** then provided the tricyclic lactam **61** in a 43% overall yield from the mixture of *trans*/*cis* isomers **59** and **58** (72% yield from the pure *trans* isomer **59**).



Scheme 10. Total synthesis of 8 by Schär and Renaud, synthesis of the intermediate 61.

To complete the total synthesis of **8**, it was necessary to convert the γ-lactam **61** into a hydroxymethyl-substituted pyrrolidine (**Scheme 11**). The intermediate **61** was first converted into the

thiolactam **62** using the Lawesson's reagent.[91] The compound **62** was then *S*-methylated using methyl iodide. Subsequent treatment with lithium 2-phenylacetylide afforded the intermediate **63**, which was directly exposed to an excess of lithium aluminium hydride to give the alkene **64** in an 80% yield over three steps and with high diastereoselectivity. This intermediate **64** finally underwent an ozonolysis under acidic conditions and subsequent reduction with sodium borohydride afforded (±)-lepadiformine A **8** in a 77% yield.



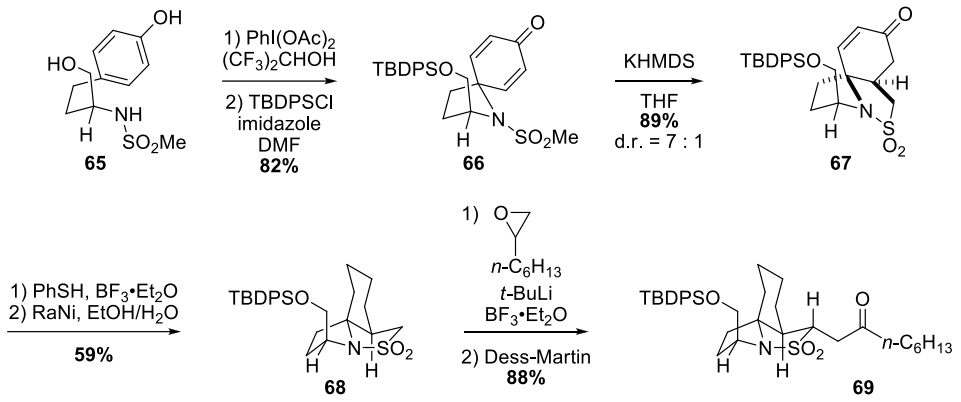
Scheme 11. Total synthesis of 8 by Schär and Renaud.

In this study, Schär and Renaud reported an efficient 10 steps total synthesis of racemic lepadiformine A **8**, in a 15% overall yield. More recently, using of the same radical carboazidation methodology, Renaud and co-workers published further total syntheses of natural compounds, including lepadiformine C **24**, and (±)-cylindricine C **13**.[58,59]

1.1.2.3. Total synthesis of (-)-13 using spirocyclisation through oxidation of phenols

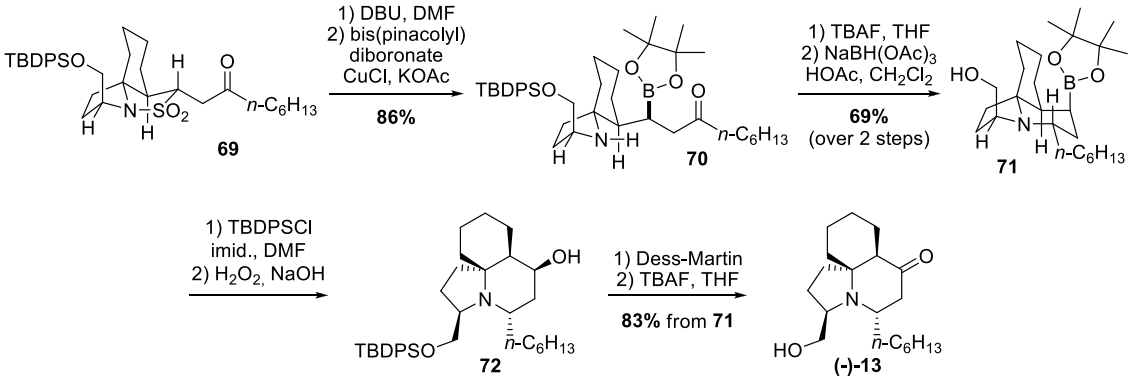
Ciufolini and co-workers reported in 2004 a total synthesis of (-)-cylindricine C **(-)-13** making use of an unusual method developed in their group, spirocyclisation through oxidation of phenols.[83]

The synthesis began with the sulfonamide **65**, D-homotyrosine derivative, which was oxidized using iodosobenzene diacetate in hexafluoro-2-propanol (**Scheme 12**). After subsequent alcohol protection, dienone **66** was obtained in an 82% yield over two steps. The intermediate **66** was then treated with potassium hexamethyldisilazane, to undergo conjugate addition of the derived sulfonamide anion, affording the adduct **67** in an 89% yield and with a diastereoselectivity of 7 : 1. The major isomer **67** was then reduced in two steps to give the intermediate **68** in a 59% yield. After deprotonation of the compound **68** using *tert*-butyllithium, the resulting anion was alkylated with 1-octene oxide leading to an alcohol which was directly treated with Dess-Martin periodinane[92] to give the corresponding ketone **69**.



Scheme 12. Enantioselective total synthesis of (-)-13 by Ciufolini and co-workers, synthesis of the intermediate 69.

In the following step, the ketone **69** was treated with 1,8-diazabicyclo(5.4.0)undec-7-ene, providing an isolable α,β-unsaturated ketone. This intermediate was directly subjected to the Miyaura borylation conditions[93] to afford the boronic ester **70** as a single stereoisomer in an 86% yield (**Scheme 13**). Subsequent cleavage of the silyl ether using tetrabutylammonium fluoride led to the corresponding primary alcohol. This intermediate directly underwent hydroxyl-directed reductive amination following Evans protocol[94] to afford the tricyclic intermediate **71** in a 69% yield over two steps. The primary alcohol in compound **71** was reprotected and the resulting silyl ether underwent oxidative conversion of the boronate to obtain the alcohol **72**. The subsequent oxidation of the intermediate **72** to the corresponding ketone afforded, after cleavage of the silyl group, (-)-cylindricine C **(-)-13** in an 83% yield over three steps.



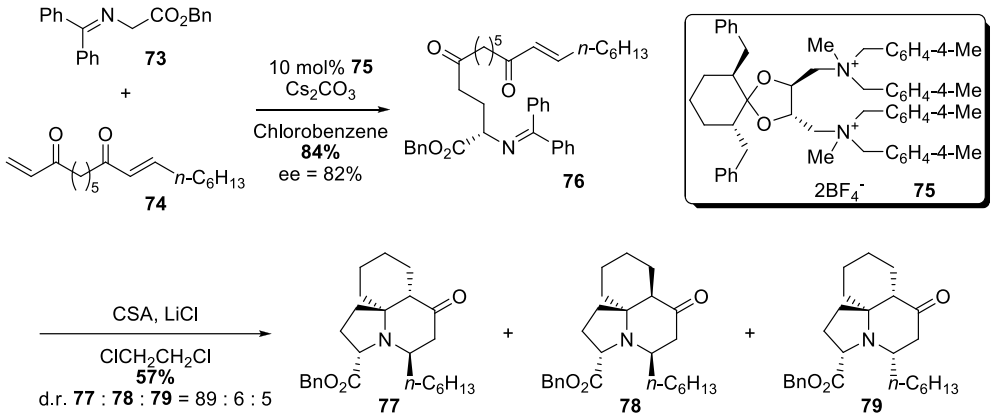
Scheme 13. Enantioselective total synthesis of (-)-13 by Ciufolini and co-workers.

In this study, Ciufolini and co-workers reported a unique and efficient enantioselective total synthesis affording (-)-cylindricine C **(-)-13** in a 19% overall yield from the sulfonamide **65**. Moreover, this publication also reports the enantioselective total synthesis of the unnatural C2-epimer from (-)-cylindricine C. More recently, Ciufolini and co-workers published several reviews, giving an overview of the broad synthetic applications of their method.[84–86]

1.1.2.4. Total synthesis of (+)-13 using catalytic asymmetric Michael addition and tandem cyclisation

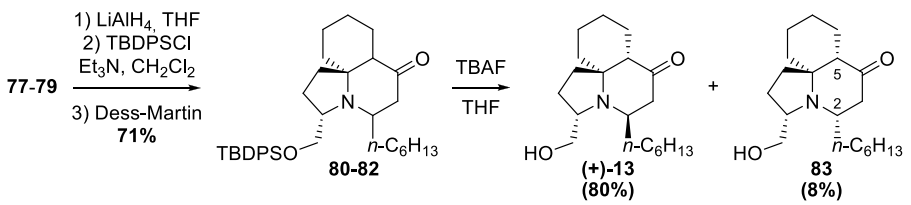
In 2006, Shibasaki and co-workers reported a novel and short enantioselective total synthesis of (+)-cylindricine C **(+)-13** involving a tandem cyclisation and a catalytic asymmetric Michael reaction using a newly designed two-centre organocatalyst.[37]

To begin the synthesis, the catalytic asymmetric Michael addition of the glycine Schiff base **73** to the dienone **74**, which was prepared in two steps from pimelic acid, was studied (**Scheme 14**). The reaction was successfully carried out using the two-centre catalyst **75**, previously developed in Shibasaki's group.[95] The intermediate **76** was obtained in an 84% yield and with an enantiomeric excess of 82%. Next, tandem cyclisation was examined. The treatment of **76** with camphorsulfonic acid and five different additives was studied. The best additive was found to be lithium chloride. In these conditions, a mixture of the tricyclic intermediates **77**, **78** and **79**, was obtained in a 57% yield and with high diastereoselectivity for the desired intermediate **77** (d.r. **77** : **78** : **79** = 89 : 6 : 5).



Scheme 14. Enantioselective total synthesis of (+)-13 by Shibasaki and co-workers, formation of the tricyclic core.

The obtained mixture of diastereomers **77**-**79** was treated with lithium aluminium hydride to afford a mixture of the corresponding primary alcohols. These intermediates were directly converted into the corresponding silyl ether and the obtained secondary alcohols were subsequently reoxidized to afford a mixture of diastereomers **80**-**82** in a 71% yield over three steps (**Scheme 15**). As the mixture was subsequently treated with tetrabutylammonium fluoride to cleave the silyl ether, it was noticed that the *trans*-fused A/B-ring system of **81** was isomerised at the C5 position to the desired *cis*-fused A/B-ring system under basic conditions. Under these conditions, (+)-cylindricine C **(+)-13** and its C2-epimer **83** were finally obtained respectively in 80% and 8% yields from the mixture of **80**-**82**.



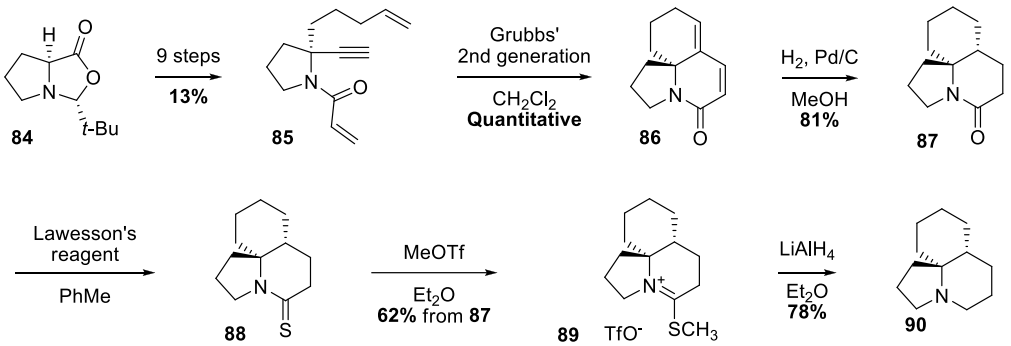
Scheme 15. Enantioselective total synthesis of (+)-13 by Shibasaki and co-workers.

Like in most of the syntheses using tandem reactions, time-cost efficiency had to be drastically improved. As a result, Shibasaki and co-workers obtained (+)-cylindricine C **(+)-13** in only six steps, which still represents the shorter total synthesis of a cylindricine alkaloid.

1.1.2.5. The use of metathesis in the synthesis of the tricyclic backbone

Only a few studies report the synthesis of a cylindricine alkaloid making use of metathesis as pivotal step. One of these approaches was published in 2010 by Mariano and co-workers.[64] They reported a synthesis of the cylindricine/lepadiformine tricyclic skeleton making use of a dienyne ring closing metathesis.

The synthesis began with the known bicyclic oxazolidinone **84** which was transformed in a fairly long nine-step sequence into the intermediate **85** in a moderate 13% yield (**Scheme 16**). Several sets of parameters were examined to perform a ring closing metathesis using the dienyne **85**. The best results were obtained when using Grubbs second generation ruthenium catalyst in refluxing dichloromethane.[96] Under these conditions, the tricyclic intermediate **86** was obtained quantitatively and a subsequent catalytic hydrogenation of **86** afforded exclusively the tricyclic lactam **87** in an 81% yield. After the compound **87** was converted into the corresponding tricyclic thiolactam **88** using the Lawesson's reagent,[91] treatment with methyl triflate gave the thioiminium salt **89** in a 62% yield over two steps. After reduction with lithium aluminium hydride, the known tricyclic amine **90** was obtained in a 78% yield.[54,56]



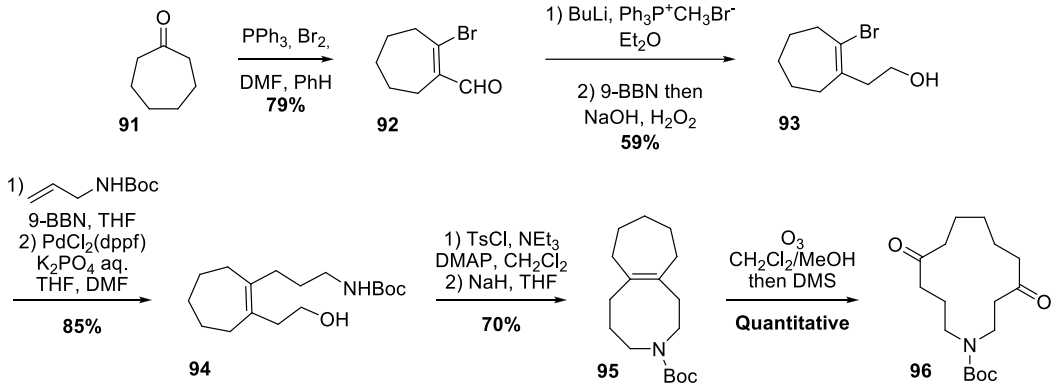
Scheme 16. Synthesis of the cylindricine/lepadiformine tricyclic skeleton by Mariano and co-workers.

In summary, Mariano and co-workers reported an interesting synthesis for the generation of the cylindricine/lepadiformine tricyclic backbone using an effective dienyne ring closing metathesis. However, the pathway leading to the metathesis substrate **84** was rather long and only afforded the product in a very moderate yield.

1.1.2.6. Tricyclic core synthesis via transannular Mannich reactions

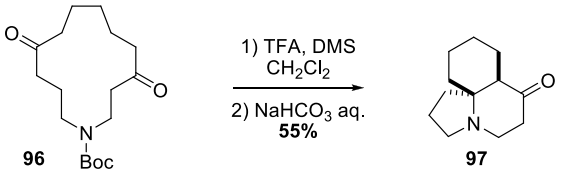
In 2009, Tanner and co-workers reported the first synthesis of the cylindricine tricyclic core proceeding through a macrocyclic intermediate.[80]

To begin the synthesis, cycloheptanone **91** was treated with triphenylphosphine, bromine and dimethylformamide to give bromoaldehyde **92** (**Scheme 17**). After Wittig reaction providing the corresponding diene, regioselective hydroboration and subsequent basic oxidation afforded the alcohol **93** in good yield. Subsequent hydroboration of *N*-Boc-allylamine, followed by a Suzuki-Miyaura cross coupling with the intermediate **93** led to the alcohol **94**. After conversion to the corresponding tosylate, treatment with sodium hydride provided the bicyclic intermediate **95**. The ozonolysis of this compound afforded quantitatively the macrocyclic diketoamine **96**.



Scheme 17. Synthesis of the macrocycle diketoamine 96 by Tanner and co-workers.

To complete the synthesis, the macrocycle **96** was treated with trifluoroacetic acid to cleave the *tert*-butoxycarbonyl protecting group and a subsequent basic work-up triggered the transannular Mannich reaction which led to the desired cylindricine tricyclic backbone **97** in a 55% yield (**Scheme 18**).



Scheme 18. Synthesis of the cylindricine tricyclic skeleton by Tanner and co-workers.

In summary, Tanner and co-workers reported an entirely new approach for the synthesis of the cylindricine tricyclic skeleton. They also claimed that this methodology may be applied in the future in enantioselective total synthesis of cylindricine alkaloids.

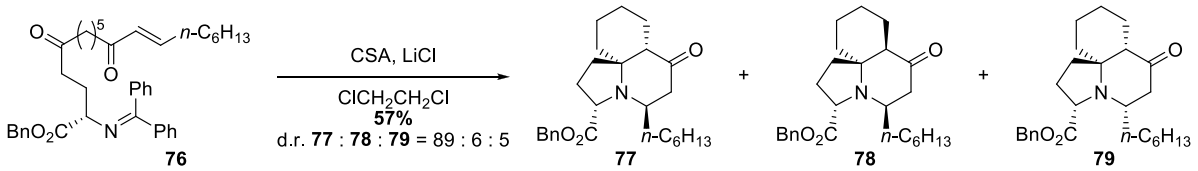
This methodology was published by Tanner and co-workers during the course of the present work and it used a concept similar to the one developed in our group.[97] However, our studies focus on the enantioselective total synthesis of natural products related to cylindricines whereas Tanner and co-workers only reported the synthesis of the nude tricyclic core. More details on our concept are given in the next sections (see **1.2**).

1.2. Motivation and synthetic concepts

1.2.1. Motivation

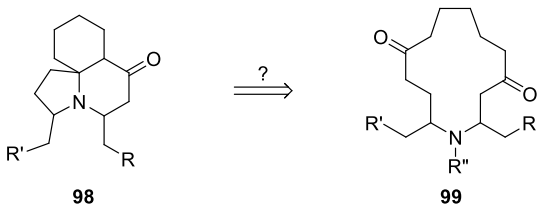
In the past couple of years, the interest in the total synthesis of cylindricine alkaloids strongly increased due to their challenging skeleton and substituent positions, especially the central quaternary asymmetric centre present in their tricyclic core. When Nicole Holub started studying this family of alkaloids in 2004, only a few studies had been reported concerning the total synthesis of cylindricine alkaloids.[97] Since then, various new methodologies to obtain their challenging tricyclic core have been published but still a few of the natural compounds have been studied. In fact, numerous racemic and enantioselective total syntheses of cylindricine C and lepadiformine A have been reported whereas only a few of cylindricines A, B, D and E, lepadiformines B and C and fasicularin; and none of cylindricines F-K and polycitorols.

Regarding the existing methods, the total synthesis of (+)-cylindricine C reported by Shibasaki and co-workers[37] in 2006 was unique. The acyclic precursor **76** led to the direct formation of the tricyclic backbone in one step. However, yields and diastereoselectivities presented for this transformation were moderate and the obtained mixtures needed to be epimerized and purified to separate the diastereomers. Indeed, the best result was obtained by treating the acyclic intermediate **76** with camphorsulfonic acid and lithium chloride in 1,2-dichloroethane, affording a 89 : 6 : 5 mixture of the tricyclic intermediates **77**, **78** and **79** in a 57% yield (**Scheme 19**).



Scheme 19. Formation of the cylindricine tricyclic backbone from an acyclic precursor by Shibasaki and co-workers.

Nicole Holub developed a new route, which would operate in a similar but intramolecular way, starting from a macrocycle **99**. Indeed, the extra-rigidity brought by the macrocycle should improve the yield and selectivity of the process (**Scheme 20**).[97]

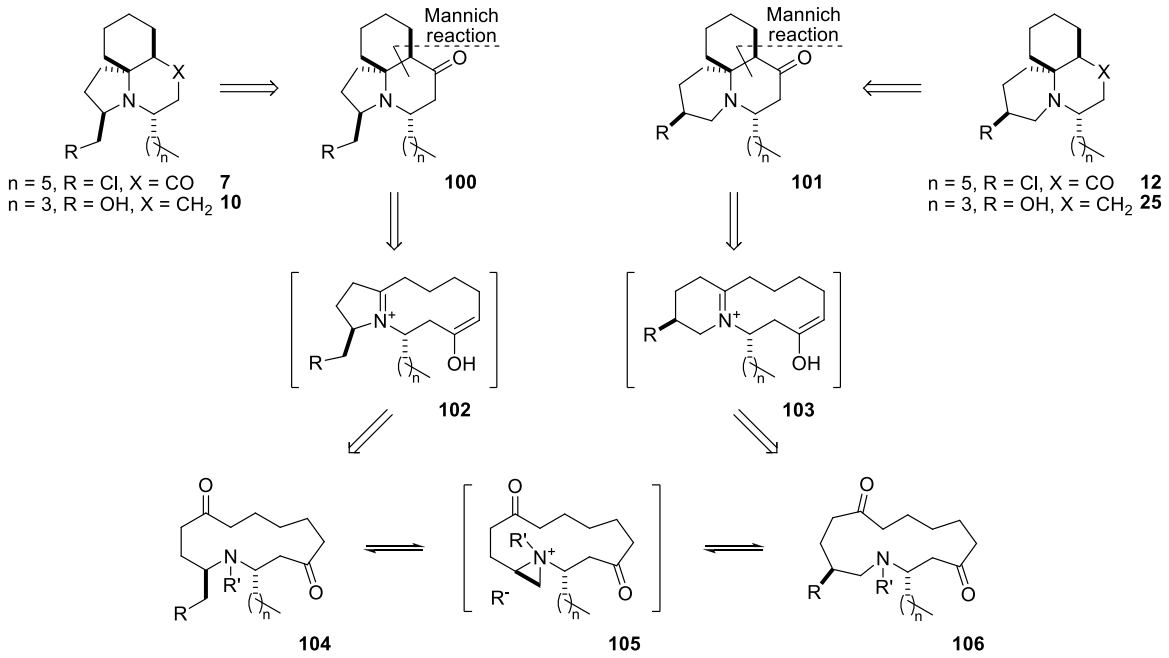


Scheme 20. Retrosynthetic analysis for the synthesis of the cylindricine tricyclic backbone by Nicole Holub.

Initial synthetic studies reported by Nicole Holub were encouraging, however, she did not obtain the tricyclic backbone of cylindricine alkaloids.[97] Thus, at the outset of this project, in 2008, given these promising results and the novelty of this approach, it was undoubtedly interesting to continue on the way of her investigations.

1.2.2. Synthetic concepts

Accordingly, the first part of the present work was dedicated to continue and deepen the initial synthetic concept developed by Nicole Holub. Cylindricine A **7** and polycitorol A **10** on the one side and cylindricine B **12** and polycitorol B **25** on the other side could be obtained from tricyclic ketones **100** and **101**, respectively (**Scheme 21**).[97] These last intermediates could be obtained from the diketones **104** and **106**, through the iminium ions **102** and **103** which could be engaged in an intramolecular Mannich reaction. Furthermore, in the particular case of R being a chloride, for example, the intermediates **104** and **106** should be transformable one into another through the aziridinium ion **105**.[98] As a consequence, the access to both kinds of tricyclic intermediates **100** and **101** could be allowed only from obtaining the diketone **104**.

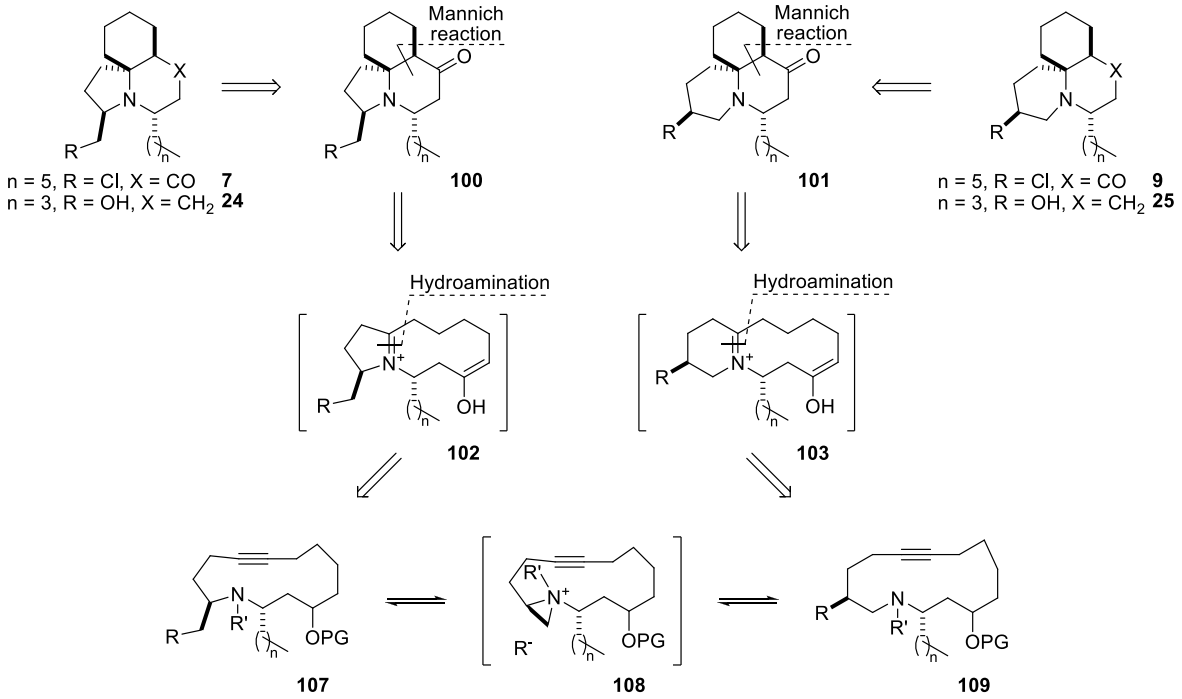


Scheme 21. Synthetic concept for the synthesis of cylindricine alkaloids using an intramolecular Mannich reaction.

This concept would have been the first example for the formation of the tricyclic backbone of cylindricine alkaloids in one step from a macrocycle. It also could have been a totally new synthetic route to tricyclic cylindricine alkaloids such as polycitorols A **10** and B **25** which had never been reported.

However in 2009, during the course of the present work, Tanner and co-workers published a similar concept (**Scheme 18**).[80] Nevertheless, they only reported the synthesis of the nude tricyclic backbone and no application to the synthesis of a natural product. Thus, our initial synthetic concept was slightly modified to deviate from their work and thus conserve the novelty of our approach. In fact, the initial idea using a macrocyclic diketone was put aside and instead a macrocycle containing an underlying ketone and a triple bond was used. Iminium intermediates **102** and **103** could effectively be obtained from a hydroamination reaction in macrocycles **107** and **109**, respectively (**Scheme 22**). As in the previous case, macrocycles **107** and **109** should be obtained, in particular cases, one from another through the aziridinium intermediate **108**.[98] Moreover, the idea emerged that the triple bond containing macrocycles **107** and **109** may be obtained through an alkyne-alkyne metathesis,

which could also represent a novelty of our concept as very few studies reported the synthesis of a cylindricine alkaloid using metathesis as pivotal step (see **1.1.2.5**).



Scheme 22. Synthetic concept for the synthesis of cylindricine alkaloids using a hydroamination.

1.2.3. Objectives

In the present work, new synthetic routes towards the synthesis of tricyclic cylindricine alkaloids were examined. As specified in the former sections and given the encouraging previous results obtained by Nicole Holub on this subject, the formation of the tricyclic core from a macrocyclic intermediate using an intramolecular Mannich reaction was investigated.

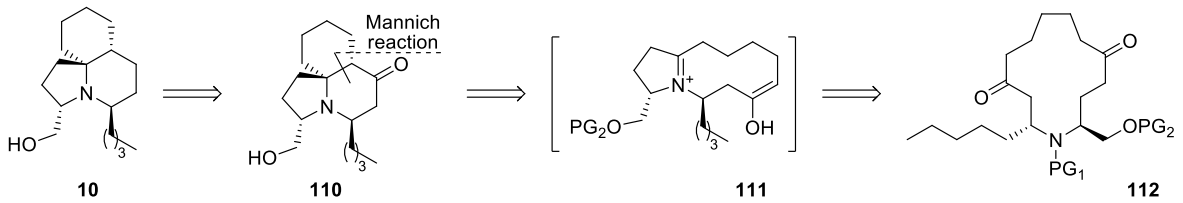
Firstly, various asymmetric synthetic ways to the macrocyclic diketone **104** have been examined in details and several already known steps on the way to this macrocycle have been optimised.

In a second part, the synthesis of the iminium intermediate **102** using a hydroamination reaction has been considered and various asymmetric synthetic ways have been developed on the way to the triple bond containing macrocyclic ketone **107**.

1.3. Results and discussion

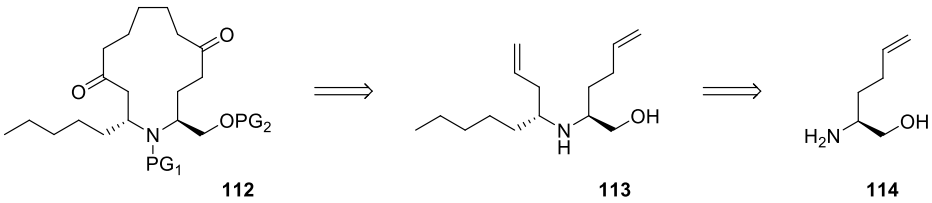
1.3.1. Synthetic ways to the macrocyclic diketone 112

As it was specified in the synthetic concepts (see **1.2.2**), the aim of our work has been to develop a new synthetic way towards the natural products of the cylindricine family and simultaneously a new method for the formation of the cylindricines tricyclic core, taking advantage of the extra-rigidity brought by a macrocyclic substrate. We reckon that the tricyclic core could be obtained from a macrocyclic diketone. Indeed, polycitorol A **10** for example, could be derived from the tricyclic ketone **110** (**Scheme 23**). The intermediate **110** could be obtained from the macrocyclic diketone **112**, through the iminium ion **111** which could be engaged in an intramolecular Mannich reaction.



Scheme 23. Retrosynthetic analysis for the synthesis of 10 from the macrocyclic diketone 112.

The macrocyclic diketone **112** could be obtained from the diene **113** after a double oxidation and metal organyl addition (**Scheme 24**). The diene **113** could finally be derived from the amino alcohol **114**, as such a transformation had been previously reported in our group.[97]

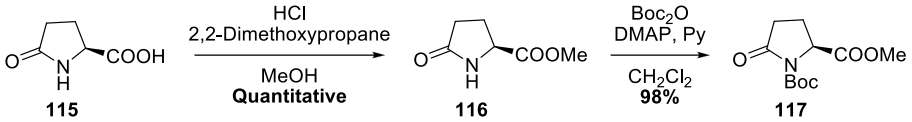


Scheme 24. Retrosynthetic analysis for the macrocyclic diketone 112.

In the present work, the syntheses developed in our group for obtaining the amino alcohol **114** and the diene **113** were first optimised. Further steps towards the synthesis of the desired macrocyclic diketone were then investigated.

1.3.1.1. Synthesis of the amino alcohol 114

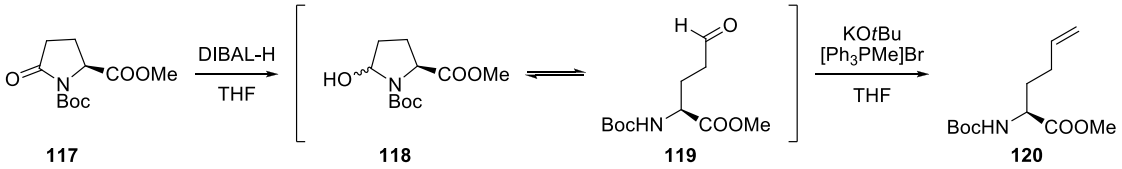
Starting from the commercial (*S*)-pyroglutamic acid **115** and using a protocol developed by Nicole Holub,[97] carbamate **117** was obtained in two steps and 98% yield (**Scheme 25**). In the first step, treating **115** with 2,2-dimethoxypropane and hydrochloric acid in methanol afforded quantitatively the esterification product **116**. A subsequent optimised protection reaction using di-*tert*-butyl dicarbonate, 4-dimethylaminopyridine and pyridine in dichloromethane provided the desired carbamate **117** in a 98% yield.



Scheme 25. Synthesis of the intermediate 117.

In the next step, the conversion of the carbamate **117** into the alkene **120** was investigated. Following procedures from Langlois and co-workers and Mendiola and co-workers, the desired product **120** was obtained in a moderate 25% yield (**Table 1**, **Entry 1**).[99–102] First, a reduction using a solution of di*iso*-butylaluminium hydride in toluene was achieved, affording the α-hydroxy carbamate **118**. The intermediate **118**, which was spectroscopically found to exist in a 9 : 1 ratio with the aldehyde **119**, subsequently underwent a Wittig reaction to provide the alkene **120**. Given the moderate yield of this process, an optimisation was required. The use of another reductive reagent was yet not examined as di*iso*-butylaluminium hydride had been described as the reductive agent of choice in this particular case.[99–103] Initially, the effect of decreasing the temperature of the reaction mixture for the reduction was studied. The product **120** was obtained in an improved yield – 34% and 45% – with temperatures of -91 °C and -104 °C, respectively (**Table 1**, **Entries 2 and 3**).

Table 1. Results of optimisation studies for the formation of the compound 120.



Ratio **118** : **119** = 9 : 1

Entry	DIBAL-H (Eq)	T (°C) add. DIBAL-H	$[Ph_3PMe]Br$ (Eq)	Other modifications	Yield (%)
1	1.5	-78 °C	2.1		25
2	1.5	-91 °C	2.1		34
3	1.5	-104 °C	2.1		45
4	1.2	-104 °C	2.1		51
5	1.2	-104 °C	2.1	Adduct columned a second time	38
6[a]	1.2	-104 °C	2.1	Adduct distilled	55
7[a]	1.2	-104 °C	1.2	Adduct distilled	27

Next, the quantity of di*iso*-butylaluminium hydride used for the reduction was decreased. It allowed a better isolation of the intermediate **118**, thanks to the lesser amount of aluminium salts present after the reduction, enhancing slightly the yield of the process to 51% (**Table 1**, **Entry 4**). As the ^{1}H-NMR spectrum of the reactant **117** showed an unknown impurity, even after purification by column chromatography, a second purification was performed. When the reactant was purified using a

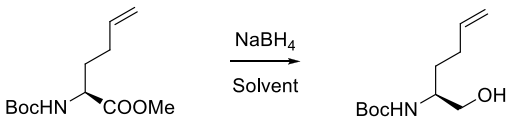
[a] This distillation was performed under very high vacuum – 10^{-5}-10^{-4} mbar – and at high temperature – 220 °C – as the carbamate **117** was crystalline at standard conditions for temperature and pressure, showing a very high stability of the compound.

second column chromatography, the quantity of impurities slightly increased, causing a reduction of the yield to 38% (**Table 1**, **Entry 5**). Nevertheless, the amount of impurities was still way too small to adequately identify them. To investigate if silica could be the cause of these impurities, the second purification was performed using distillation, which induced a slight increase of the yield to reach 55% (**Table 1**, **Entry 6**). A further experiment showed that decreasing the amount of Wittig reagent drastically decreased the yield to 27% (**Table 1**, **Entry 7**).

Regarding these results, the process for obtaining the alkene **120** has already been significantly optimised. Nevertheless, several parameters were not yet considered and may have a positive influence on the yield of this process. Indeed, an increase of the quantity of Wittig reagent used could be investigated but was not done because of a lack of time. Using a solution of di*iso*-butylaluminium hydride in hexanes, as it was described by Langlois and co-workers in the formation of the α-hydroxy carbamate **118**, was not investigated.[100] Indeed, in a more recent study reported by Mendiola and co-workers, a one molar solution of di*iso*-butylaluminium hydride in toluene, as used in the presented tests, was described to give the best yield.[102]

The ester **120** was then reduced into the alcohol **121** using sodium borohydride. The reaction was initially tried in methanol. As the completion of the reduction required four days and the addition of three further equivalents of sodium borohydride after two days, other solvent systems were investigated (**Table 2**, **Entry 1**). Ethanol or a 1 : 1 mixture of tetrahydrofuran and water allowed a completion of the reaction in a maximum of one day and only required three equivalents of reduction reagent (**Table 2**, **Entries 2 and 3**). In all cases, the desired alcohol **121** was obtained in very good yields, between 85% and 91%.

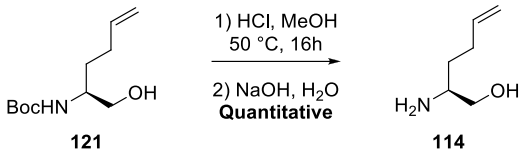
Table 2. Optimisation of the reduction conditions for obtaining the alcohol 121.



120 **121**

Entry	$NaBH_4$ (Eq)	Time to 100% conversion	Solvent	Yield (%)
1	3 + 3 after 2 d	4 d	MeOH	87
2	3	18 h	EtOH	91
3	3	1 d	THF/H_2O	85

In the next step, the alcohol **121** was treated with hydrochloric acid in methanol for the removal of the *tert*-butoxycarbonyl protecting group (**Scheme 26**). An aqueous solution of sodium hydroxide was subsequently added to neutralize the obtained ammonium chloride and thus afforded quantitatively the amino alcohol **114**.

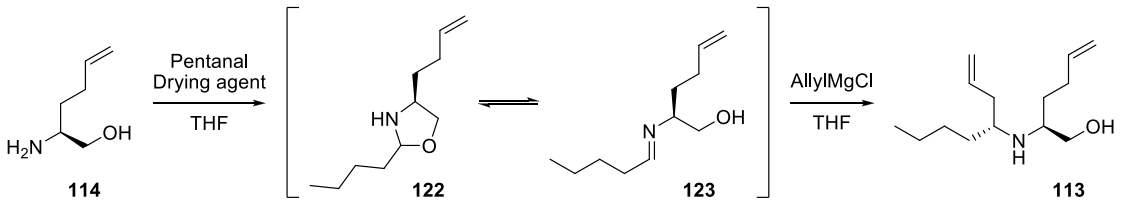


Scheme 26. Synthesis of the amino alcohol 114 from the protected intermediate 121.

After further studies and optimisations, the amino alcohol **114** was obtained in seven steps from commercial (*S*)-pyroglutamic acid **115**, in an overall 49% yield.[97]

1.3.1.2. Synthesis of the diene 113

The amino alcohol **114** was then engaged in a two-step reaction sequence, imine/oxazolidine formation and addition of an allyl Grignard, to afford the diene **113**.[97] In the first step, pentanal was added to the amino alcohol **114** in the presence of a drying agent to obtain the postulated imine/oxazolidine intermediates **122**/**123** (**Scheme 27**). After removal of both the drying agent and the excess of pentanal, this intermediate was treated with allylmagnesium chloride to give the desired diene **113**. Next, the reaction conditions of this two-step process were optimised. Separately, complementary studies were also performed to identify a predominant intermediate, imine or oxazolidine, with little success (see **Annex II**).

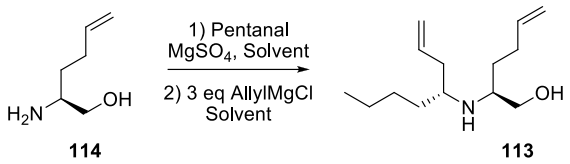


Scheme 27. Two-step process for the formation of the diene 113.

Following a known protocol, magnesium sulfate was used for the reaction of the amino alcohol **114** with pentanal, without further investigations.[97] The use of technical magnesium sulfate did not lead to the formation of the desired product. Only reactant **114** and unidentifiable decomposed reagents were recovered (**Table 3**, **Entry 1**). One reason for this decomposition might be an aldol addition of the aldehyde on itself in this slightly acidic medium (see **Annex II**). For the next set of experiments, magnesium sulfate was dried at 120 °C and 10^{-2} mbar over three hours. The same sequence, using the previously activated drying agent, afforded the desired product in a 17% yield (**Table 3**, **Entry 2**). The yield hardly increased when the drying agent was filtered between the two steps and the solvent used for the first step was replaced by fresh solvent for the second step. Indeed, the product was only obtained in a 19% yield (**Table 3, Entry 3**). Using 2-methyltetrahydrofuran instead of tetrahydrofuran for the imine formation reaction induced a slight increase of the yield to 24% whereas using chloroform or dichloromethane did not give better results (**Table 3**, **Entries 4-6**). Although tetrahydrofuran and 2-methyltetrahydrofuran share a lot of properties, the variation observed in yield can be attributed to the difference they present in their solvating properties or water-miscibility.[104] For the next set of experiments, freshly distilled 2-methyltetrahydrofuran was added and evacuated three times between the two steps, inducing a significant increase of the yield

to 33% (**Table 3**, **Entry 7**). Indeed, we believe that traces of water were removed thanks to the azeotrope formed by 2-methyltetrahydrofuran with water on distillation. Therefore, a last experiment was performed, where 2-methyltetrahydrofuran was evacuated and replaced three times and the reaction stirred each time for an additional hour. Afterwards, the solvent was evacuated and freshly added three further times before the second step was performed. Following this optimised protocol, the desired diene **113** was obtained in a 45% yield (**Table 3**, **Entry 8**).

Table 3. Synthetic optimisation results of the two-step process for the formation of the diene 113.



114 **113**

Entry	$MgSO_4$	Solvent for step 1/2	Yield (%)
1	Technical	THF/THF	0
2	Dried under vacuum at 120 °C during 3 h	THF/THF	17
3[b]	Dried under vacuum at 120 °C during 3 h	THF/THF	19
4**b**	Dried under vacuum at 120 °C during 3 h	$CHCl_3$/THF	12
5**b**	Dried under vacuum at 120 °C during 3 h	CH_2Cl_2/THF	13
6**b**	Dried under vacuum at 120 °C during 3 h	MeTHF/MeTHF	24
7[c]	Dried under vacuum at 120 °C during 3 h	MeTHF/MeTHF	33
8**c**,[d]	Dried under vacuum at 120 °C during 3 h	MeTHF/MeTHF	45

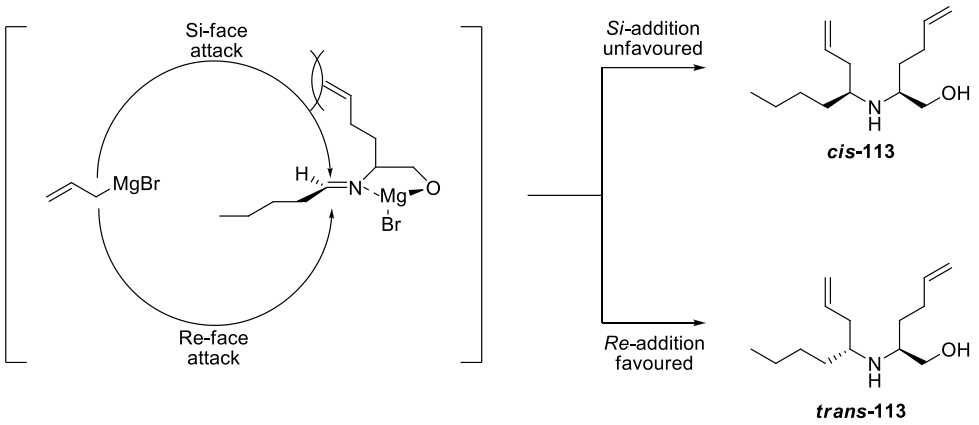
After optimisations of the two-step procedure, imine/oxazolidine formation and addition of an allyl Grignard, the diene **113** (which is also named ***trans*-113** when necessary for a better understanding) was obtained in a 45% yield from the amino alcohol **114**. The diastereoselectivity of the process was then examined. NMR-spectroscopy analysis revealed the presence of only one stereoisomer and the optical rotation was consistent with the one reported for ***trans*-113**. This result was concordant with our postulated mechanism of the allyl Grignard addition (**Scheme 28**).[97] Indeed, according to previous studies in our group, the high selectivity of the process could be explained by the formation of a five-ring chelated complex between the free electron pair of the imine nitrogen and the alkoxy

[b] Between the two steps, the drying agent was filtered, the solvent was evacuated and fresh solvent was added.

[c] Between the two steps, the drying agent was filtered, the solvent was evacuated and fresh solvent was added and evacuated three times.

[d] During the first step, the solvent was evacuated and replaced three times, the mixture being stirred each time for an additional hour.

magnesium bromide. The alkyl chain in α-position of the nitrogen is believed to create a steric hindrance favouring the attack on the *Re*-face and though leading predominantly to ***trans*-113**.

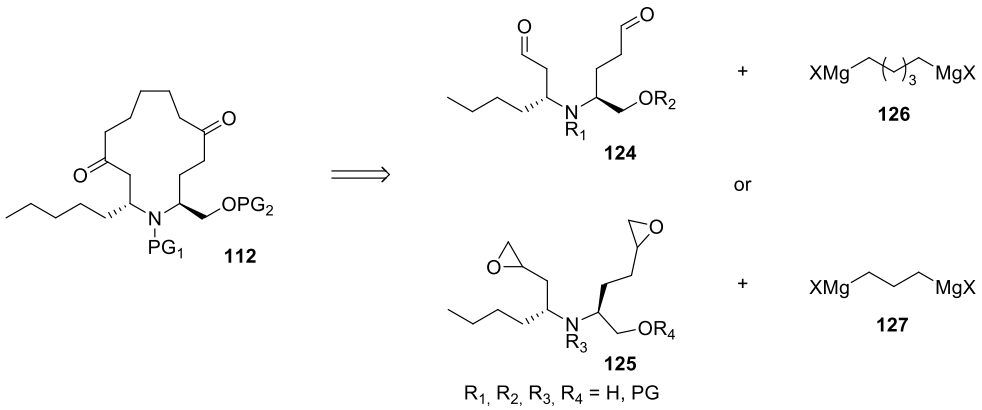


Scheme 28. Postulated mechanism for the allyl Grignard addition by Nicole Holub.[97]

To summarise, the two-step procedure, imine/oxazolidine formation and allyl Grignard addition, was optimised and afforded the desired diene ***trans*-113** in a 45% yield from the amino alcohol **114**. Moreover, ***trans*-113** was obtained in a very high diastereoselectivity as only this isomer was observed in ^{1}H-NMR spectroscopy. Given the possible margin of error due to the NMR-spectrometer, the diastereoselectivity was estimated to be higher than 97 to 3.

1.3.1.3. Towards the synthesis of a macrocycle starting from the diene 113

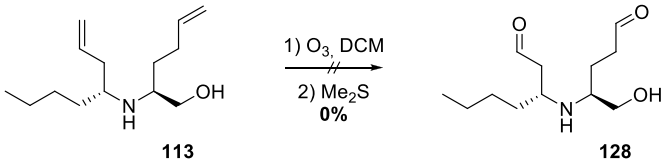
In the following section, studies concerning the tentative oxidations of diene **113** and protected analogues were first explored. Indeed, the desired macrocycle **112** could be derived from oxidized analogues of diene **113**, either an aldehyde **124** or an epoxide **125** (**Scheme 29**). These compounds reacted with Grignard reagents **126** or **127**, respectively, could easily conduct to a key intermediate on the way to macrocycle **112**.



Scheme 29. Retrosynthetic analysis on the way to macrocycle 112 through oxidized intermediates 124 or 125.

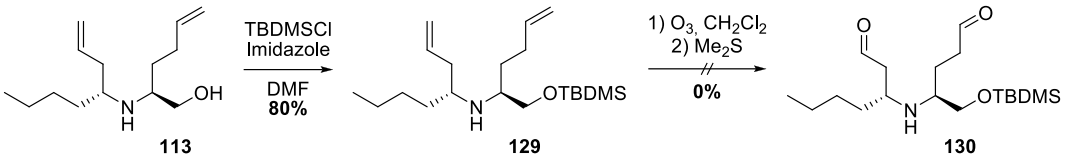
Initial ozonolysis reaction of the diene **113** did not led to the formation of the desired product **128** and the starting material **113** was predominantly recovered (**Scheme 30**). As previously reported, the

ozonolysis reaction could be disturbed by the presence of the free alcohol or the free amine in the compound **113**.[105–108] Therefore, protections of the alcohol and the amino functions were studied before any oxidation reaction.



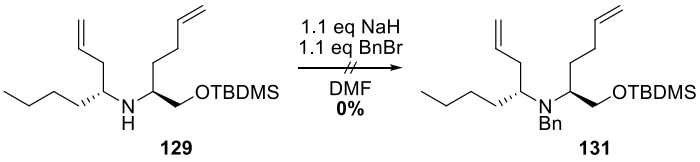
Scheme 30. Tentative ozonolysis of the diene 113.

Initially, the alcohol function of the diene **113** was protected using *tert*-butyldimethylsilyl chloride, affording the silyl ether **129** in an 80% yield (**Scheme 31**). The ozonolysis of the compound **129**, following a procedure reported by Matsuda and co-workers, did not lead to any desired product **130**, confirming that the free amino function could disturb the reaction and should be protected likewise.[106]



Scheme 31. Tentative synthesis of the oxidized intermediate 130.

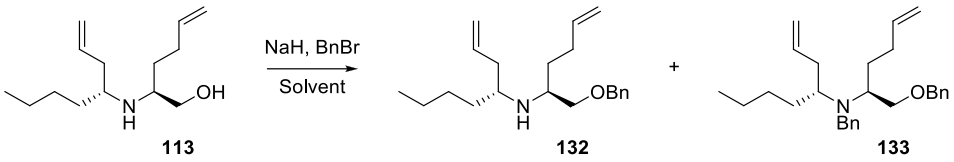
The silyl ether **129** was treated with benzyl bromide in order to obtain the *bis*-protected diene **131** (**Scheme 32**). No product was obtained and the reactant **129** was entirely recovered. This may be due to an excessive steric hindrance induced by the sterically demanding *tert*-butyldimethylsilyl group or by the alkyl substituents surrounding the amino function.



Scheme 32. Tentative protection reaction of the diene 129.

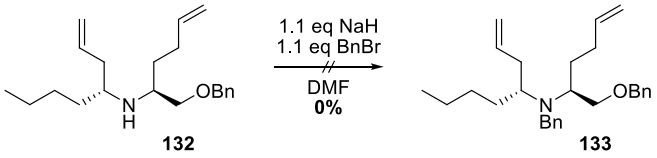
Given the impossibility to protect the amino function in the silyl ether **129** with a benzyl group, a protection test was directly performed on the amino alcohol **113**. Therefore, the amino alcohol **113** was treated with benzyl bromide and sodium hydride in the aim of obtaining the *bis*-protected diene **133**. The reaction was first carried out in dichloromethane, leading to the exclusive formation of *O*-protected product **132** (**Table 4**, **Entry 1**). The reaction was then tested in dimethylformamide, affording an 8 : 2 mixture of mono- and *bis*-protected products **132** and **133** and allowing the isolation of the desired product **133** in a 15% yield (**Table 4**, **Entry 2**).

Table 4. Studies towards the benzyl-protection of the diene 113.



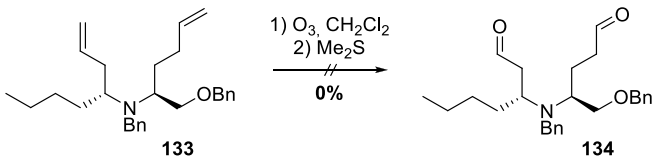
Entry	Solvent	Result
1	CH_2Cl_2	Only *O*-protected product **132**
2	DMF	**132**/**133** = 8 : 2 15% of *bis*-protected product **133** could be isolated

Despite the moderate success of the protection reaction, the mono-protected compound **132** was treated again with benzyl bromide but no *bis*-protected product **133** was obtained (**Scheme 33**). This result confirmed that an excessive steric hindrance around the amino function may simply be forbidding the *bis*-protection of the amino alcohol **113**.



Scheme 33. Tentative preparation of the *bis*-protected intermediate 133 starting from the compound 132.

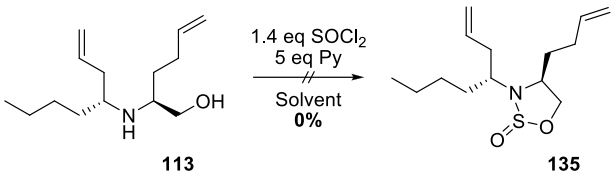
Although if very little *bis*-protected product **133** could be isolated from the reaction starting from **113**, an ozonolysis reaction test was performed on it (**Scheme 34**). However, the reaction did not lead to the desired *bis*-aldehyde **134** and various products were observed – but could not be identified due to the very low amounts obtained.



Scheme 34. Tentative ozonolysis of the diene 133.

To overcome the steric hindered protecting groups issue, the next experiments focused on an eventual joint protection from both alcohol and amino functions. Following a procedure reported by Ghosh and co-workers,[109] the first studies were performed on the reaction of the amino alcohol **113** with thionyl chloride in the presence of pyridine to obtain the *S*-oxidised oxathiazolidine **135**. For the first reaction, thionyl chloride was added dropwise, over 45 minutes, to a solution of reactant **113** and pyridine in dichloromethane previously brought to -50 °C (**Table 5**, **Entry 1**). As no product was traceable after 12 hours, the reaction was stopped and repeated in deuterated chloroform to be followed by ^{1}H-NMR. No formation of product and no transformation of the reactant were observed (**Table 5**, **Entry 2**). Two further tests were performed with an addition of thionyl chloride at higher temperatures and faster rates, but still no product formation could be observed (**Table 5**, **Entries 3 and 4**).

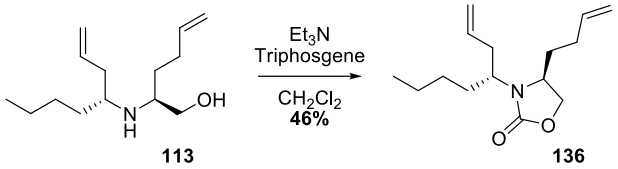
Table 5. Studies towards the formation of the protected intermediate 135.



113 135

Entry	Solvent	Addition from $SOCl_2$	Reaction Time	Yield (%)
1	CH_2Cl_2	At -50 °C over 45 min	12 h	0
2	$CDCl_3$	At -50 °C over 45 min	Checked every hour using ^{1}H-NMR spectroscopy	0
3	CH_2Cl_2	At -30 °C over 15 min	12 h	0
4	CH_2Cl_2	At 0 °C over 5 min	12 h	0

The unsuccessful attempt using thionyl chloride may, once more, be due to the excessive steric hindrance present around the amino function. Therefore, our attention next focused on the formation of an oxazolidinone, using phosgene, as this type of protection would be less sterically demanding. Given the extreme noxious properties of phosgene, the reaction was achieved with its crystalline and less dangerous substitute, triphosgene, in the presence of triethylamine in dichloromethane.[110,111] In these conditions, the desired product **136** was obtained in a 46% yield (**Scheme 35**).

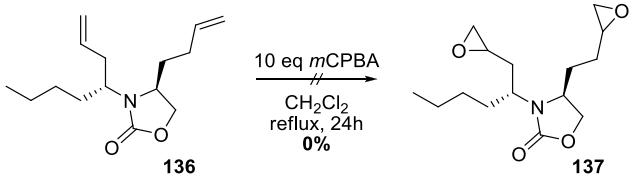


113 136

Scheme 35. Synthesis of the protected intermediate 136.

Pleased by these results, additional tests were performed and revealed the very complex behaviour of this protection group (see **Annex III**). Indeed, using a model molecule, it was very difficult even impossible to perform a deprotection reaction. Nevertheless, despite these results, this route was pursued – keeping in mind the deprotection reaction might cause some problems in the future.

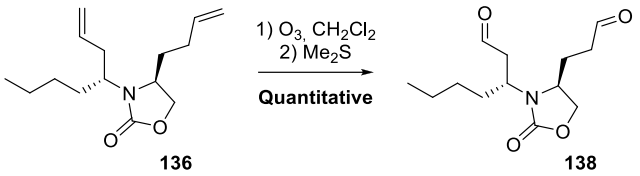
The oxidation of the intermediate **136** was examined, beginning with an epoxidation using *meta*-chloroperoxybenzoic acid (**Scheme 37**). The formation of the desired diepoxide **137** was not observed despite literature precedents on similar systems.[112–114]



136 137

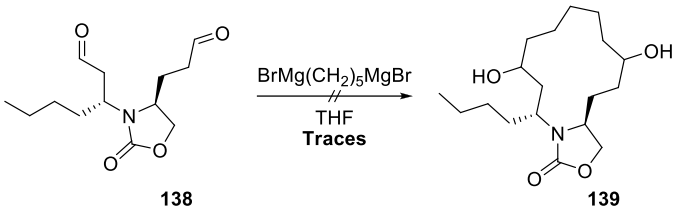
Scheme 36. Tentative epoxidation of the protected intermediate 136.

Meanwhile, the ozonolysis reaction was performed on the diene **136** and successfully led quantitatively to the desired dialdehyde **138** in a quantitative yield (**Scheme 37**).



Scheme 37. Ozonolysis of the protected intermediate 136.

The intermediate **138** was subsequently treated with pentamethylene*bis*(magnesium bromide) in tetrahydrofuran to synthesise the macrocycle **139**. In this single test, the product could only be seen in mass spectroscopy, being present in trace amounts. Too many products were present in the raw reaction mixture, thus any separation or spectroscopic identification were impossible. However, the mass spectrum allowed the identification of several compounds present in the mixture such as the reactant **138** and different oligomers formed from various combinations of the reactant **138** and the Grignard reagent.

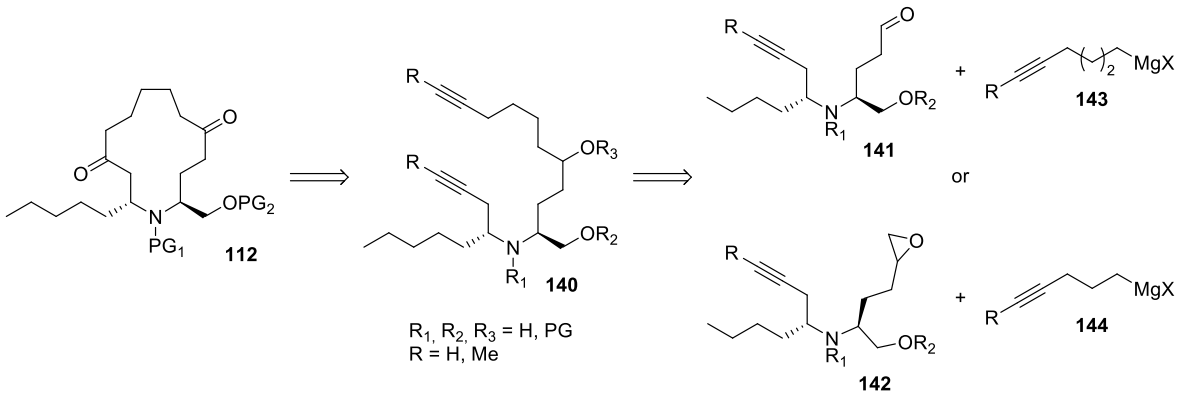


Scheme 38. Tentative synthesis of the macrocycle 139.

The results obtained in the previous experiment imply the existence of intermolecular reactions and thus the coupling of several molecules of reactant **138** through the reaction with pentamethylene*bis*(magnesium bromide). This effect may be reduced by performing the reaction in a more diluted environment or by studying the mode of addition of the Grignard reagent to try to control its mode of reaction. However, this method could also not be adequate because of a very difficult differentiation between the aldehydes in the synthesised compound **138**. The challenge will then be to develop a new substrate different from the diene **113**, differentiating both extremities and giving a different reactivity to each of them, which could facilitate the access to the desired macrocycle **139**.

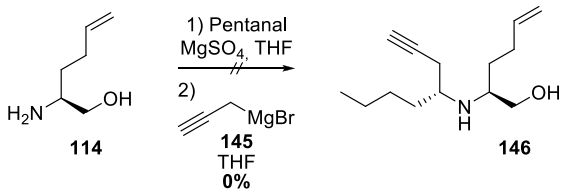
1.3.1.4. Synthetic studies using a different Grignard reagent in the two-step sequence, imine/oxazolidine formation and Grignard addition

In the aim of developing a new synthetic way using substrates with differentiated extremities instead of two aldehydes or two epoxides like in compounds **124** or **125**, oxidized intermediates such as **141** or **142** were considered (**Scheme 39**). Indeed, the desired macrocycle **112** could be obtained from the intermediate **140** after several steps, including an alkyne-alkyne ring closing metathesis. This intermediate **140** could be derived either from the reaction of aldehyde **141** with the Grignard reagent **143** or from the reaction of epoxide **142** with the Grignard reagent **144**.



Scheme 39. Retrosynthetic analysis on the way to macrocycle 112 through oxidized intermediates 141 or 142.

The previously developed imine/oxazolidine formation and Grignard addition sequence was used on the amino alcohol **114** with propargylmagnesium bromide **145** instead of allylmagnesium bromide (**Scheme 40**). Propargylmagnesium bromide **145** was first prepared from propargyl bromide, following Kobayashi and co-workers' procedure using magnesium and zinc bromide.[115] For the following steps, the amino alcohol **114** was engaged in the aforementioned sequence. No formation of the product **146** was observed. Identically to **113**'s synthesis, the intermediate after treatment of the amino alcohol **114** with pentanal was at this stage neither isolated nor analysed, which meant the problematic step could not be determined. As in the case of the realisation of this sequence with the amino alcohol **114** and allylmagnesium bromide, the kind of drying agent used in the first step might be problematic and would require further optimisation. The solvent used or the difference of reactivity between allylmagnesium bromide and propargylmagnesium bromide could also be considered as underlying causes for the failure of this sequence.



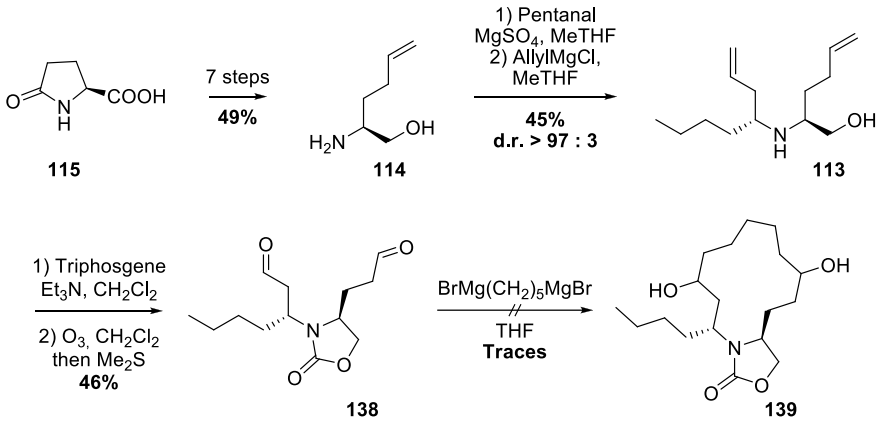
Scheme 40. Tentative two-step sequence, imine/oxazolidine formation and propargyl Grignard addition.

The first attempt using a different Grignard reagent in the sequence imine/oxazolidine formation and Grignard addition, in order to obtain a product **146** in which the extremities were already differentiated failed. Unfortunately a lot of possibilities could not be explored due to a lack of time. However, this synthetic route might be an interesting field of research in the future.

1.3.1.5. Summary and outlook

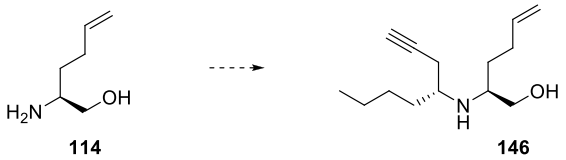
The present section describes numerous attempts performed to optimize the synthesis of the amino alcohol **114**. This compound was finally obtained in seven steps from commercial (*S*)-pyroglutamic acid **115**, in an overall 49% yield (**Scheme 41**). Secondly, the two-step process, imine/oxazolidine formation and allyl Grignard addition, was examined, to obtain the diene **113** from the amino alcohol **114**. A series of optimisations allowed to obtain the desired intermediate **113** in a 45% yield and with

a very high diastereoselectivity, as only the isomer ***trans*-113** was observed. After several studies on the following steps on the way to the desired macrocyclic diketone **139**, the dialdehyde **138** was obtained in two steps from the diene **113** in a 46% overall yield. This dialdehyde **138** was subsequently treated with a *bis*-Grignard reagent which led to a mixture of various oligomers derived from different combinations of additions of the dialdehyde **138** and the Grignard reagent. This result showed the necessity of differentiating both extremities of the diene **113**.



Scheme 41. Current development of the synthetic route to the macrocyclic diketone 139.

Bearing in mind the results described **Scheme 41**, our research focused on the development of a compound containing an alkyne and an alkene instead of two alkene functionalities to try to install a differentiation from the beginning of the synthetic way (**Scheme 42**).

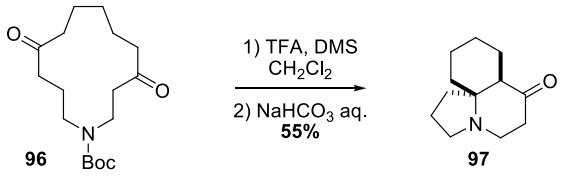


Scheme 42. Considered synthetic way to the intermediate 146.

Fortunately, this concept showed encouraging results. The dialdehyde **138**, which could be an intermediate towards the synthesis of the desired macrocycle **139**, was obtained in 11 steps in a 10% overall yield and with a high diastereoselectivity. However, in 2009, during our research work, Tanner and co-workers published a synthesis of the cylindricines tricyclic core **97** starting from a macrocyclic diketone **96** similar to the one forecasted in our retrosynthetic analysis (see **1.1.2.6**). For this reason, in a desire of conserving the novelty of the concept used in our total syntheses, this synthetic concept was abandoned and our efforts focused on another strategy.

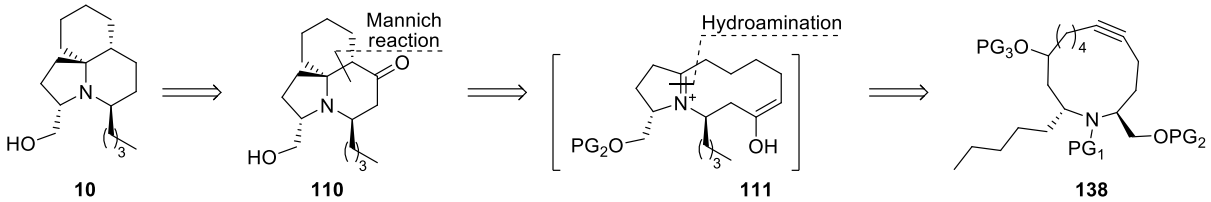
1.3.2. Synthetic ways to the triple bond containing macrocycle 138

As it was precised in the last section (**1.3.1**) and in the synthetic concepts (see **1.2.2**), Tanner and co-workers published in 2009, concomitant to the present work, a new synthetic method for the synthesis of the cylindricines tricyclic core showing strong similarities with the method we were trying to develop. Indeed, they reported the synthesis of the desired tricyclic skeleton **97** directly from the macrocyclic diketone **96** (**Scheme 43**).



Scheme 43. Synthesis of the cylindricine tricyclic skeleton by Tanner and co-workers.

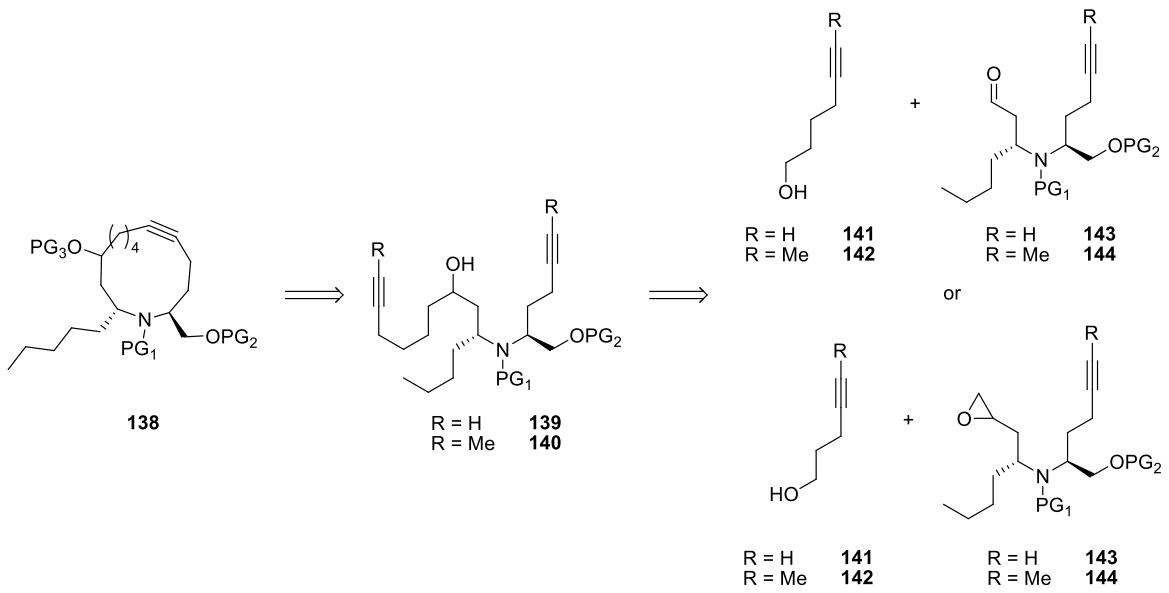
After this publication, the development of the concept seemed to be compromise even though Tanner and co-workers did not report any application of their method to the synthesis of a natural compound.[80] To conserve the novelty contained in our initial concept, it was though decided to modify it slightly. The aim was still to continue our development of a new synthetic way towards the natural products of the cylindricine family and, at the same time to develop a new method for the formation of the cylindricines tricyclic core taking advantage of the extra-rigidity brought by a macrocyclic substrate. It was thought that the tricyclic core could be obtained from a macrocycle containing a triple bond and an underlying ketone. Indeed, taking the example of polycitorol A **10**, this natural compound could be derived from the tricyclic ketone **110** (**Scheme 44**). This intermediate **110** could be obtained from an intramolecular Mannich reaction on the iminium ion **111**. Finally, the iminium intermediate could be obtained from a hydroamination reaction in the macrocycle **138**.



Scheme 44. Retrosynthetic analysis for the synthesis of 10 from the triple bond containing macrocycle 138.

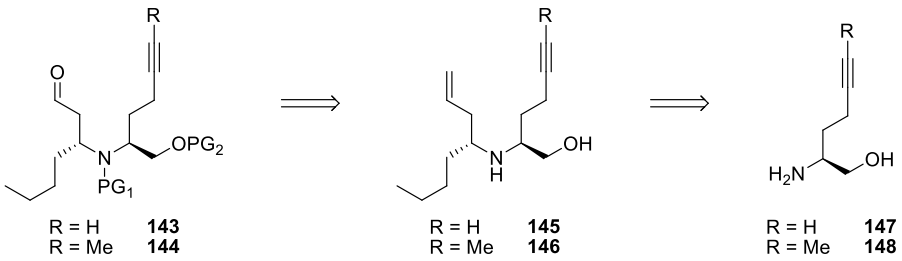
The macrocycle **138** could be obtained from an intramolecular alkyne-alkyne metathesis on the compound **139** or **140** as such macrocycle formation using alkyne-alkyne metathesis were already described by Fürstner and co-workers.[116–120] These intermediates **139** or **140** could be the product of the reaction of the aldehyde **143** or **144** with a metal organyl derived from the alcohol **141** or **142**.

At this stage, it is interesting to notice that a metal organyl derived from adapted alcohols similar to **145** or **146** could also be reacted with differently oxidized substrates such as, for instance, epoxides **147** and **148**, giving a larger range of possibilities for this synthetic way.



Scheme 45. Retrosynthetic analysis for the synthesis of the triple bond containing macrocycle 138.

The aldehydes **143** and **144** could be obtained from the corresponding alkenes **145** and **146** using ozonolysis, for example. Moreover, as described in literature, it was already proved that the ozonolysis of a double bond could be selectively achieved in the presence of a triple bond in the molecule.[121,122] The alkenes **145** and **146** could finally be derived from the triple bond containing amino alcohols **147** and **148** which could undergo the two-step process, imine/oxazolidine formation and addition of an allyl Grignard, and protection steps.



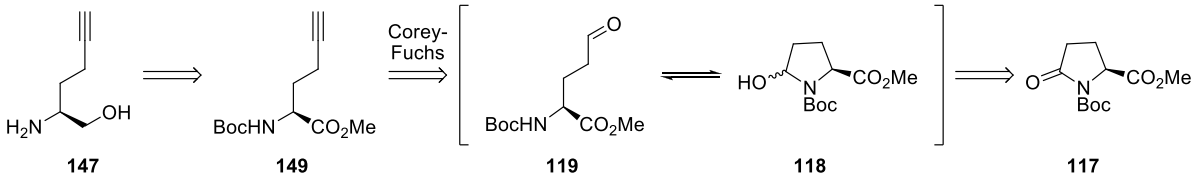
Scheme 46. Retrosynthetic analysis for the synthesis of the triple bond containing amino alcohols 147 and 148.

In the remaining part of this section, several synthetic routes for the synthesis of the enantiomerically pure amino alcohols **147** and **148** were examined. A synthetic method was also developed to obtain the racemic amino alcohol **147** (also named **rac-147**). Further steps towards the synthesis of a triple bond and ketone macrocycle were then investigated. Finally, a variation of this synthetic concept was considered and explored.

1.3.2.1. Tentative synthesis of the amino alcohol 147 starting from the 5-member ring intermediate 117

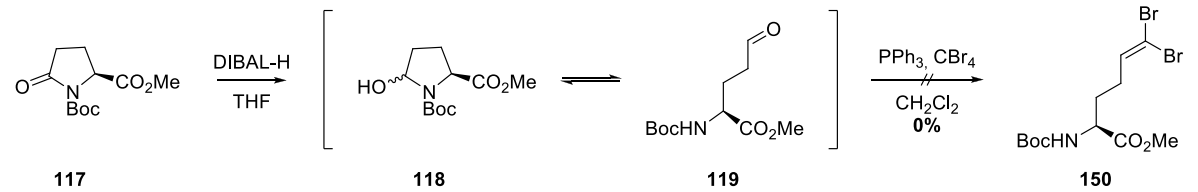
1.3.2.1.1. The use of a Corey-Fuchs reaction

Following our retrosynthetic analysis, we initially focused on the synthesis of a triple bond containing amino alcohol like **147** (**Scheme 47**). As the five-member ring intermediate **117** had already been synthesised and was available in gram amounts, a synthetic way starting from this compound was examined. It seemed possible that the amino alcohol **147** could be derived from the intermediate **149**. This intermediate could be obtained from the aldehyde **119** using a Corey-Fuchs reaction. This aldehyde **119** being in equilibrium with the intermediate **118**, this one could be obtained by reduction of the desired starting material **117**.



Scheme 47. Retrosynthetic analysis for the synthesis of the amino alcohol 147.

Initially, the previously synthesised five-member ring intermediate **117** was treated with di*iso*-butylaluminium hydride in tetrahydrofuran to form the intermediate **118** in equilibrium with the aldehyde **119** (**Scheme 48**). Following a known procedure, reported by Fürstner and co-workers,[123] the residue was subsequently engaged in a Corey-Fuchs reaction to obtain the 1,1-dibromoolefin **150**. Unfortunately, the reaction did not proceed as expected, possibly due to the very low availability in aldehyde **119** in the intermediary mixture. Indeed, after reduction with di*iso*-butylaluminium hydride, the ratio between intermediate **118** and aldehyde **119** in the residue was spectroscopically established to be of 9 : 1 respectively. Accordingly, other routes toward the synthesis of **147** were investigated.

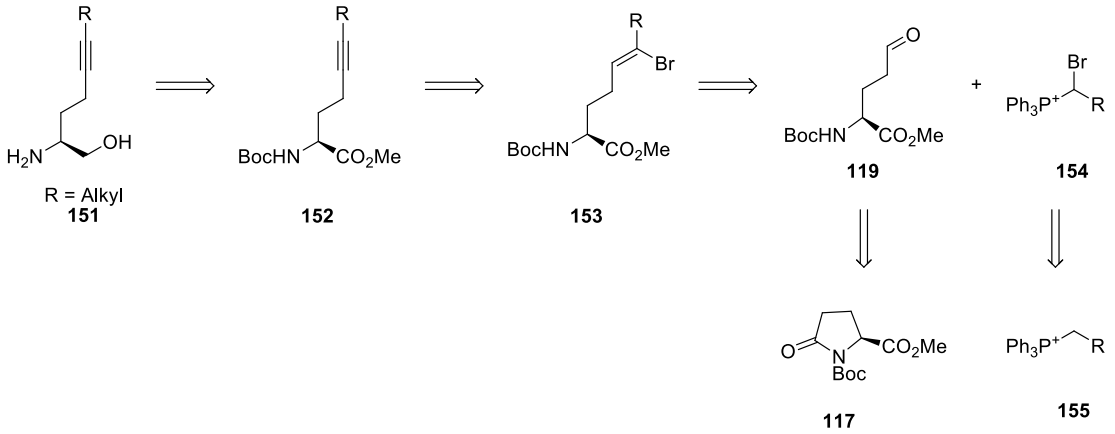


Scheme 48. Tentative synthesis of the intermediate 150.

1.3.2.1.2. Development of new phosphines for the synthesis of triple bond containing amino alcohols

As previously precised, the synthesis of the terminal triple bond containing amino alcohol **147** using a Corey-Fuchs reaction did not proceed. Our attention then focused on the synthesis of amino alcohols containing a substituted triple bond using a similar method. Indeed, amino alcohols **151** could be derived from the analogue **152** (**Scheme 49**). This compound could be obtained from the

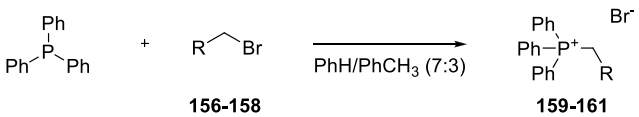
intermediate **153** which could be synthesised from the aldehyde **119** and the 1-bromoalkyltriphenylphosphonium salt **154**. As reported in the precedent section (see **1.3.2.1.1**), the aldehyde **119** existing in equilibrium with the intermediate **118** could be obtained by reduction of the five-member ring compound **117**. Regarding the bromoalkyltriphenylphosphonium salt **154**, it could be obtained from the corresponding alkyltriphenylphosphonium salt **155**.



Scheme 49. Retrosynthetic analysis for the synthesis of amino alcohols containing a substituted triple bond.

The synthesis of the alkyltriphenylphosphonium salts **155**, containing different alkyl chains, was initially studied. In accordance with a Dauben and co-workers' procedure,[124] triphenylphosphine was treated with ethyl bromide **156**, *n*-propyl bromide **157** or *n*-butyl bromide **158** in a 7 : 3 mixture of benzene and toluene. After two days of stirring at room temperature these reactions led to 33%, 12% and no conversion, respectively (**Table 6**, **Entries 1-3**). Following these results, our efforts then focused on the reaction of triphenylphosphine with ethyl bromide. The temperature was increased to 80 °C. After 16 h of stirring at this temperature, the reaction led to a 75% conversion and after 24 h of stirring, the desired product **Nr** was obtained in an 83% yield (**Table 6**, **Entries 4 and 5**).

Table 6. Studies towards the synthesis of alkyltriphenylphosphonium salts.



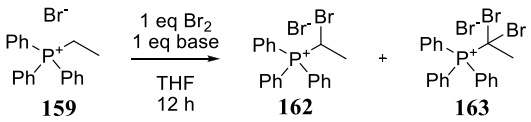
Entry	R	Reactant	Reaction conditions	Product	Result
1	$-CH_3$	**156**	RT, 2 days	**159**	33% conversion
2	$-CH_2CH_3$	**157**	RT, 2 days	**160**	12% conversion
3	$-(CH_2)_2CH_3$	**158**	RT, 2 days	**161**	No conversion
4	$-CH_3$	**156**	80 °C, 16 h	**159**	75% conversion
5	$-CH_3$	**156**	80 °C, 24 h	**159**	83% yield

Following these results and therefore the fact that ethyltriphenylphosphonium bromide **159** was obtained more easily than phosphonium salts containing longer alkyl chains,

ethyltriphenylphosphonium bromide **159** became our intermediate of choice to undergo the following bromination tests.

For our first attempt, the previously synthesised phosphonium salt **159** was dissolved in tetrahydrofuran and the solution was cooled down to -78 °C. After sodium hydride was added, a solution of bromine in tetrahydrofuran was added over fifteen minutes at the same temperature and the reaction was stirred during twelve hours. No conversion was observed and the starting material was entirely recovered (**Table 7**, **Entry 1**). The same result was obtained by using *n*-butyllithium instead of sodium hydride in the same conditions (**Table 7**, **Entry 2**). For the next attempts, the process was not cooled but kept at all times at room temperature, as described by Parker and Cao in the case of a similar halogenation.[125] Using sodium hydride in these conditions led to a 7 : 2 : 1 mixture of starting material **159**, monobromated **162** and dibromated **163** products (**Table 7**, **Entry 3**). Using *n*-butyllithium or phenyllithium afforded a similar 2 : 2 : 1 mixture of **159**, **162** and **163** (**Table** 7, **Entry 4 and 5**). A variation in the addition time of the bromine solution had a negative effect as it led to a smaller conversion. In the case of a faster addition, where a 7 : 2 : 1 mixture was obtained. This lower conversion may be due to the decomposition of the intermediate formed because of a highly exothermic process (**Table 7**, **Entry 6**). In the case of a slower addition, where a 8 : 1 : 1 mixture was obtained, a decrease in conversion may be simply due to a too slow addition compared to the stability time of the formed intermediate (**Table 7**, **Entry 7**). One test was also performed using *N*-bromosuccinimide in the conditions described by Huang and co-workers,[126] but the reaction did not give any bromated products **162** or **163**, only unidentified side-products and starting material **159** were recovered (**Table 7**, **Entry 8**).

Table 7. Bromination reactions on ethyltriphenylphosphonium bromide 159.



Entry	Base	Temperature	Bromine solution in THF added over:	**159**	**162**	**163**
1	NaH	-78 °C	15 min	100	0	0
2	*n*-BuLi	-78 °C	15 min	100	0	0
3	NaH	RT	15 min	67	22	11
4	*n*-BuLi	RT	15 min	38	40	22
5	PhLi	RT	15 min	39	39	22
6	*n*-BuLi	RT	< 1 min	69	17	14
7	*n*-BuLi	RT	1 h	81	11	8
8	none	-20 °C	15 min (NBS)	60	0	0

Given the obtained results and particularly the fact that only inseparabable mixtures of starting material **159**, monobromated and dibromated products, **162** and **163**, were obtained, this route was abandoned. Moreover, although these phosphonium salts could have been isolated and used,

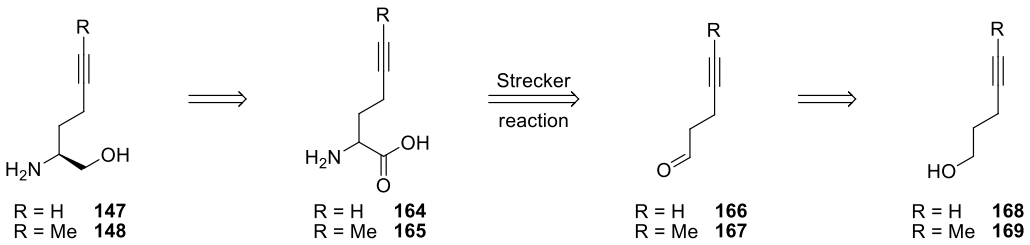
several examples of reactions of similar phosphonium salts with aldehydes described in the literature reported low yields, between 15 and 35%, which may simply confirm the non-efficiency of this synthetic way.[127]

1.3.2.2. Synthetic studies towards the amino alcohols 147 and 148 using a Strecker reaction

1.3.2.2.1. Retrosynthetic analysis

As the first attempts to synthesise triple bond containing amino alcohols like **147** or **148** using a Corey-Fuchs reaction or different phosphonium salts had a limited success, our attention focused on using an alcohol like **168** or **169** as a starting point, to be able to obtain the corresponding amino alcohol by Strecker reaction.[128,129] Moreover, numerous examples of asymmetric Strecker reactions had already been reported.[130–133]

The amino alcohols **147** and **148** could easily be derived from the corresponding amino acids **164** and **165** which could be obtained using the Strecker amino acid synthesis starting from the aldehydes **166** and **167**. The aldehydes **166** and **167** could also be derived from the corresponding alcohols **168** and **169**.



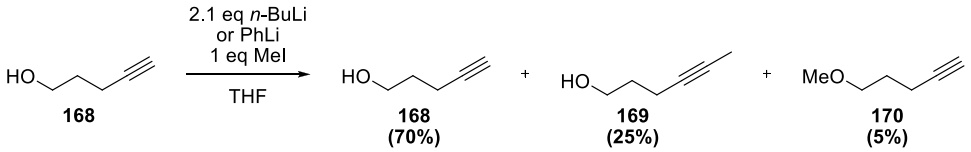
Scheme 50. Retrosynthetic analysis for the synthesis of the amino alcohols 147 and 148 using a Strecker reaction.

The syntheses of both alcohols **142** and **169** were first studied. Indeed, given the important similarities in structure and behaviour which should induce a high similarity on the synthetic way leading to their formation, it was interesting to try to obtain both alcohols using a similar method. Secondly, the oxidation of the alcohol **169** and the Strecker reaction on the aldehyde **167** were studied on the way to the synthesis of the amino alcohol **165**. Although numerous variations have been described in the literature, our attention focused only on classical racemic Strecker amino acid syntheses.

1.3.2.2.2. Synthesis of alcohols 142 and 169

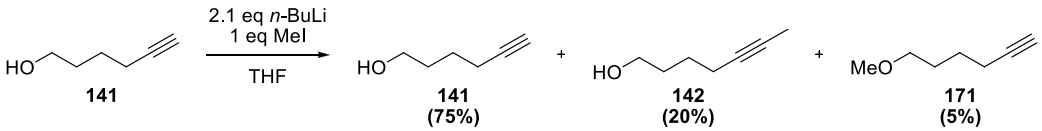
First and foremost, classic direct methylation reactions were tested on the commercially available 4-pentyn-1-ol **168** (**Scheme 51**). *n*-Butyllithium or phenyllithium were used as base and methyl iodide as methylating agent. Unfortunately, a large quantity of starting material was recovered and the

reaction led to the desired product **169** which was isolated in a 25% yield but also to the methylated alcohol **170** in a 5% yield.[e]



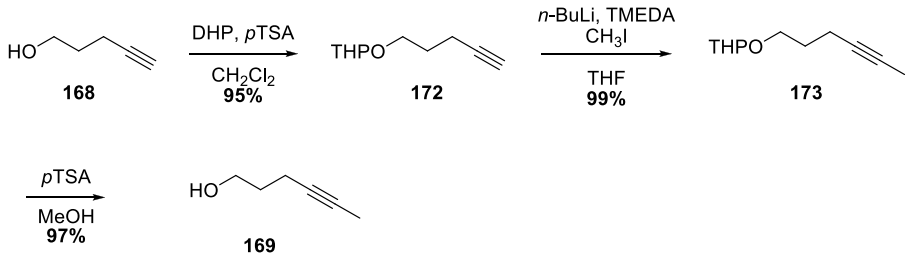
Scheme 51. Methylation of 4-pentyn-1-ol 168 using a lithium organyl and methyl iodide.

The same methylation method using *n*-butyllithium and methyl iodide was then tried on 5-hexyn-1-ol **141** (**Scheme 52**). Similar to the methylation trial of 4-pentyn-1-ol **168** previously described, the process led to a similar mixture of starting material **141**, product **142** and methylated alcohol **171**.[e]



Scheme 52. Methylation of 5-hexyn-1-ol 141 using a lithium organyl and methyl iodide.

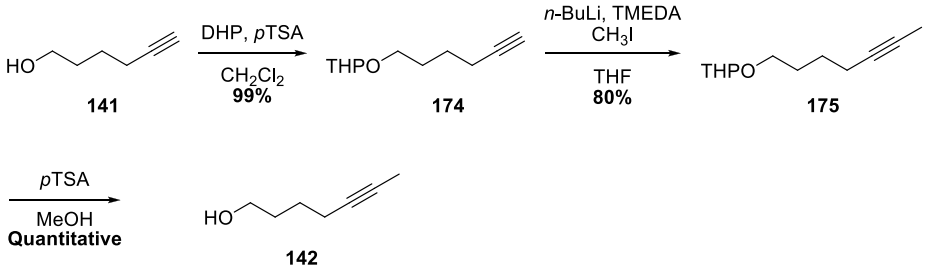
The direct methylation afforded the desired methylated product in a low yield as a mixture of starting material, product and methylated alcohol was recovered from the reaction. This result could be explained by the presence of the free alcohol function. To avoid the formation of methylated alcohol or any hindrance which could be caused by the alcohol group in the process, a procedure reported by Holmes and co-workers was optimised and a new sequence was thus developed including the use of a protecting group.[134] Initially, the sequence was performed on 4-pentyn-1-ol **168**. Indeed, we began with the protection of the alcohol group leading to the tetrahydropyranyl protected alcohol **172** in a 95% yield (**Scheme 53**). The subsequent methylation of **172** using methyl iodide gave the methylated alkyne **173** in a 99% yield. After acidic hydrolysis of **173**, the desired alcohol **169** was obtained in a 97% yield.



Scheme 53. Three-step sequence from 4-pentyn-1-ol 168 to 4-hexyn-1-ol 169.

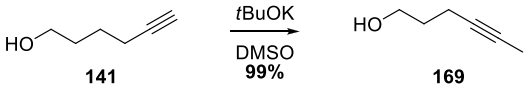
Given the successful use of the described reaction sequence on 4-pentyn-1-ol **168**, it was then applied to 5-hexyn-1-ol **141**. In the first step, the protected alcohol **174** was obtained in a 99% yield (**Scheme 54**). The subsequent methylation of **174** afforded the methylated alkyne **175** in an 80% yield. The final acidic hydrolysis of **175** gave quantitatively the desired alcohol **142**.

[e] All spectral data were in accordance with reported or known data.[134]



Scheme 54. Three-step sequence from 5-hexyn-1-ol 141 to 5-heptyn-1-ol 142.

The previous sequences afforded the desired alcohols **142** and **169** in three steps, in very good yields. However, the conversion of the commercially available 5-hexyn-1-ol **141** in 4-hexyn-1-ol **169** using an isomerisation reaction was also tested.[135] The alcohol **141** was treated with potassium *tert*-butoxide in dimethyl sulfoxide to afford the desired isomerised product **169** in a 99% yield (**Scheme 55**).



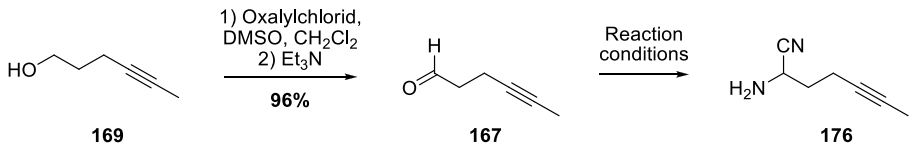
Scheme 55. Isomerisation reaction of 5-hexyn-1-ol 141 to 4-hexyn-1-ol 169.

This last method was not applied for the formation of 5-heptyn-1-ol **142** as 6-heptyn-1-ol which should have been used for the isomerisation reaction was not commercially available. The three-step sequence was though conserved for the formation of 5-heptyn-1-ol **142**.

1.3.2.2.3. Strecker reactions

Once the intermediate **169** had been synthesised, the first trials to obtain the corresponding α-aminonitrile **176** were performed (**Table 8**). Initially, the alcohol **169** was oxidized using the described Swern conditions to afford the aldehyde **167** in a 96% yield. The treatment of the aldehyde **167** with sodium cyanide and ammonium chloride in diethyl ether and water, following a protocol form Kendall and McKenzie,[136] afforded the desired aminonitrile **176** in 60% yield (**Table 8**, **Entry 1**). According to a protocol developed by Steiger,[137] ammonia was additionally used and diethyl ether was replaced by methanol, which led to the quantitative formation of the desired product **176** (**Table** 8, **Entry 2**).

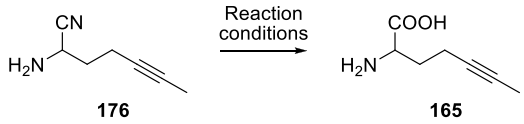
Table 8. Formation of the amino nitrile 176.



Entry	Reaction conditions	Yield
1	NaCN, NH_4Cl, Et_2O, H_2O	60%
2	NaCN, NH_4Cl, Ammonia, H_2O, MeOH	Quantitative

For the second part of the Strecker reaction and therefore the formation of the desired amino alcohol **165**, several hydrolysis conditions were tried. To perform this transformation, different acids were used, hydrochloric acid (**Table 9**, **Entries 1-3 and 5**) and sulfuric acid (**Table 9**, **Entries 4 and 6**), at different concentrations and temperatures without any success. Indeed, in all cases, only the starting material **176** was recovered.

Table 9. Tentative hydrolysis of the amino nitrile 176.

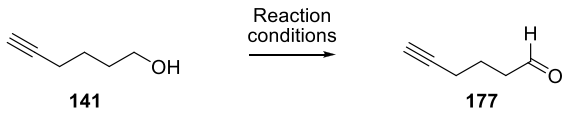


176 **165**

Entry	Reaction conditions	Result
1	Aqueous 1 N HCl, RT, 16 h	No product
2	Aqueous 1 N HCl, 60 °C, 16 h	No product
3	Aqueous 1 N HCl, 100 °C, 16 h	No product
4	Aqueous 10% H_2SO_4, 120 °C, 16 h	No product
5	Aqueous 37% HCl, dioxane, 100 °C, 16 h	No product
6	Aqueous 25% H_2SO_4, 120 °C, 16 h	No product

As the reaction had already been described by Budisa and co-workers on this substrate,[133] the same tests were performed on 5-hexyn-1-ol **141**, beginning with the oxidation to the corresponding aldehyde **177**. An oxidation test using TEMPO and trichloroisocyanuric acid was performed on the alcohol **141** and led to the desired product **177** in a 78% yield (**Table 10**, **Entry 1**). The same oxidation performed using Swern conditions afforded 5-hexynal **177** quantitatively (**Table 10**, **Entry 2**).

Table 10. Oxidation tests of 5-hexyn-1-ol 141 to 5-hexynal 177.

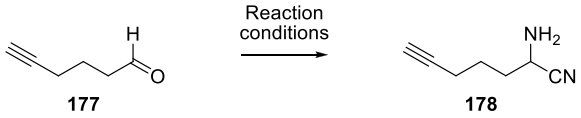


141 **177**

Entry	Reaction conditions	Yield
1	Trichloroisocyanuric acid, TEMPO, CH_2Cl_2	78%
2	1) Oxalylchloride, DMSO, CH_2Cl_2 2) Et_3N	Quantitative

For the formation of the corresponding aminonitrile **178**, the same conditions as for the formation of the aminonitrile **176** were tried (**Table 11**). As is the case for the intermediate **176** the conditions proposed by Kendall and McKenzie led to the desired product **178** in a moderate 56% yield (**Table 11**, **Entry 1**) whereas the conditions developed by Steiger afforded quantitatively the desired aminonitrile **178** (**Table 11**, **Entry 2**).[136,137]

Table 11. Formation of the aminonitrile 178.

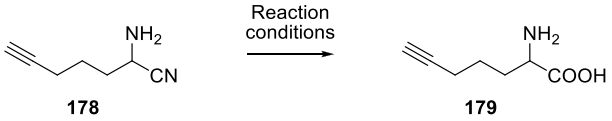


177 178

Entry	Reaction conditions	Result
1	NaCN, NH_4Cl, Et_2O, H_2O	56%
2	NaCN, NH_4Cl, Ammonia, H_2O, MeOH	Quantitative

For the second part of the attempted Strecker reaction, conditions for the hydrolysis of the aminonitrile **178** were studied (**Table 12**). As in the case of the hydrolysis of the aminonitrile **176** none of the considered conditions led to the desired product, only the harsher conditions were tried. However, neither the use of concentrated hydrochloric acid nor of sulfuric acid, at high temperature and for a relatively long stirring time, afforded the desired amino alcohol **179** (**Table 12**, **Entries 1-2**). As in the case of the tentative hydrolysis of the aminonitrile **176**, only the starting material **178** was recovered.

Table 12. Tentative hydrolysis of the amino nitrile 178.



178 179

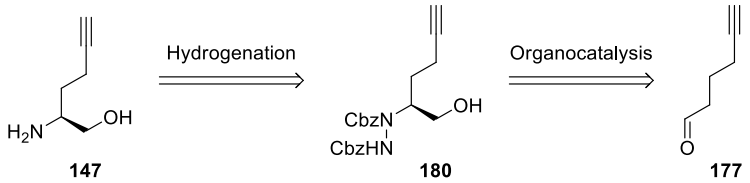
Entry	Reaction conditions	Result
1	Aqueous 37% HCl, dioxane, 100 °C, 16 h	No product
2	Aqueous 25% H_2SO_4, 100 °C, 16 h	No product

The syntheses of the aminonitriles **176** and **178** smoothly worked. These compounds **176** and **178** were obtained in two steps, respectively in a 96% yield and quantitatively from the alcohols **169** and **141**. However, despite the various methods examined to perform the hydrolysis of these aminonitriles, second part of the Strecker amino acid synthesis, it was not possible to obtain the desired amino acids **165** and **179**. Indeed, in all cases and for an inexplicable reason, only starting material was recovered. Although if the very same hydrolysis reaction was once reported,[133] given the consistent and repeatable results obtained in this work, this synthetic route seemed to be blocked at this stage and was thus abandoned in favour of a new one.

1.3.2.3. Synthesis of the amino alcohol 147 using organocatalysis

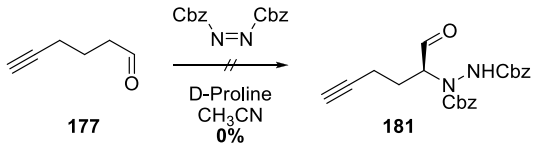
As the synthetic route to the amino acid **147** using a Strecker amino acid synthesis did not lead to the desired product, a new way was examined. In the following presented studies, the needed amino alcohol **147** was thought to be obtained using organocatalysis. Indeed, the amino alcohol **147** could

be obtained from the enantiomerically pure protected compound **180** (**Scheme 56**). This intermediate **180** could be synthesised from the aldehyde **177** as this reaction was already performed several times on various substrates.[138–140]



Scheme 56. Retrosynthetic analysis for the synthesis of the amino alcohol 147 using organocatalysis.

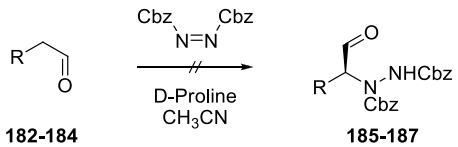
Following a procedure developed by List and later improved by Blackmond and co-workers, the aldehyde **177** was engaged with dibenzyl azodicarboxylate and D-proline in acetonitrile (**Scheme 57**).[138,140] The reaction did not afford the desired product **181**.



Scheme 57. Tentative organocatalytic reaction on the aldehyde 177.

First, it was thought that the triple bond could interfere in the reaction as this kind of substrate was never tried in this process. However, several other substrates were tested and the reactions did not give the expected products whereas these reactions were already described in the literature and gave the desired products in very high yields and enantiomeric excess (**Table 13**).[138–140] In our case, only the reaction using propanal led to the product and only in traces amounts (**Table 13**, **Entry 2**). Otherwise, in all cases, only starting materials were recovered. This could mean either that one of the used starting materials was from bad quality or that the conditions of the reaction described in the literature could not exactly be reproduced in our laboratory. Therefore, all the starting materials were then analysed using NMR-, infrared- and mass-spectroscopies and different reaction conditions were tested varying atmosphere, temperature and stirring time. The starting materials were proved to be pure and adapted for this process but repeating the reaction also using variations in the conditions did not led to the expected products.

Table 13. Studies on the considered organocatalytic reaction on different substrates.



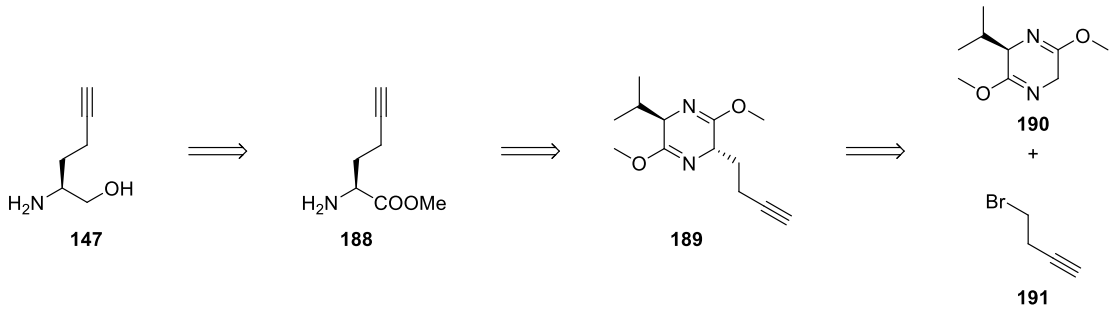
Entry	-R	Reactant	Product	Result
1	$-CH_2CH_3$	**182**	**185**	No product
2	$-CH_3$	**183**	**186**	Traces of product
3	$-(CH_2)_3CH_3$	**184**	**187**	No product

After numerous tests which did not lead to any positive result, this way was abandoned. Indeed, the process would have resulted in high costs in time, as it was still not possible at this stage to understand the behaviour of the reaction despite the numerous conducted tests and in money, as big amounts of the non-natural and though expensive D-proline would have been needed for an inevitable future scale-up of the reaction.

1.3.2.4. Synthesis of the amino alcohol 147 *via* a Schöllkopf auxiliary

1.3.2.4.1. Retrosynthetic analysis

For a new synthetic route to the enantiopure amino alcohol **147**, the possibility of using a Schöllkopf chiral auxiliary was examined. The desired amino alcohol **147** could be derived from the corresponding amino ester **188** (**Scheme 58**). This last compound **188** could be obtained from the intermediate **189** after cleavage of the chiral auxiliary. Finally, the intermediate **189** could be synthesised by alkylation of the Schöllkopf auxiliary **190** with 4-bromo-1-butyne **191**.[141–144]



Scheme 58. Retrosynthetic analysis for the synthesis of the amino alcohol 147 *via* a Schöllkopf auxiliary.

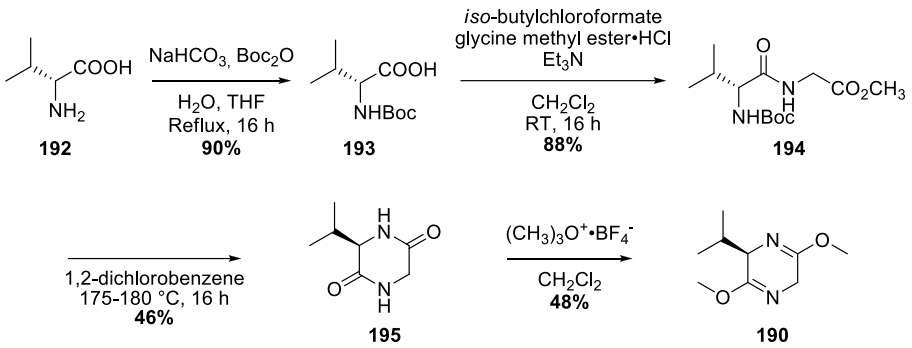
In the remaining of this section, studies upon the synthesis of the amino alcohol **147** *via* the Schöllkopf chiral auxiliary **190** together with the synthesis of this auxiliary **190** are thus reported.

1.3.2.4.2. Synthesis of the desired Schöllkopf auxiliary 190

For the synthesis of the desired Schöllkopf auxiliary **190**, several interesting synthetic processes were already published.[141,143–146] For this work, the protocol developed by Chen and co-workers was chosen because it presented a very efficient synthetic way which had already been proved to be convenient either for milligram and multi-gram scales.[145]

In a first step, D-valine **192** was converted to *tert*-butoxycarbonyl protected D-valine **193** in a 90% yield (**Scheme 59**). This intermediate **193** was subsequently treated with *iso*-butylchloroformate, glycine methyl ester hydrochloride and triethylamine in dichloromethane to give the protected dipeptide **194** in an 88% yield. The thermal cyclisation of the dipeptide **194** in 1,2-dichlorobenzene afforded the piperazinedione **195** in a moderate 46% yield. The following methylation of the

intermediate **195** using trimethyloxonium tetrafluoroborate led to the desired Schöllkopf auxiliary **190** in a 48% yield.[f]



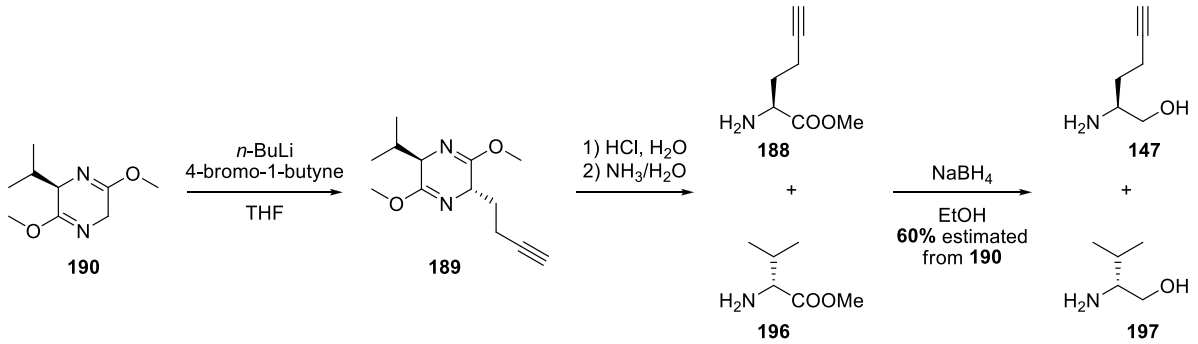
Scheme 59. Preparation of the desired Schöllkopf auxiliary 190.

In summary, using the protocol proposed by Chen and co-workers, the desired Schöllkopf auxiliary **190** was obtained in four steps and a moderate overall yield of 17%. The last step may be even more interesting for bigger scales. Indeed, in this work, for a one-gram scale, the purification of the auxiliary being a distillation under very high vacuum caused an important loss of material due to the high viscosity of the raw material. This loss could presumably be minored at a bigger scale, an example being reported by Chen and co-workers who obtained the auxiliary **190** in an 85% yield from the intermediate **195** for an hundred-gram scale reaction.

1.3.2.4.3. Preparation of the amino alcohol 147 *via* the Schöllkopf auxiliary 190

In the next part of the synthesis, following a procedure developed by Schöllkopf and Neubauer and optimised by Smith and co-workers, the considered Schöllkopf auxiliary was treated with *n*-butyllithium and 4-bromo-1-butyne to obtain the intermediate **189** (**Scheme 60**).[141,144] According to numerous reported examples, given the steric hindrance caused by the iso-propyl group in the Schöllkopf intermediate **190**, the compound **189** should present the drawn absolute configuration.[141,142,144,147] Without any further analyses or purification, the speculated chiral auxiliary **189** was cleaved, using dilute aqueous hydrochloric acid. After neutralization of the obtained mixture of hydrochlorides, using an aqueous solution of ammonia, a mixture of the corresponding amino esters **188** and **196** was obtained. At this stage, a separation using silica gel column chromatography was tried, but the separation was difficult and a 9 : 1 mixture of the desired amino ester **188** and of D-valine methyl ester **196** was obtained. Therefore, this 9 : 1 mixture of the compounds **188** and **196** was used without further purification for the next step. The treatment of these methyl esters with sodium borohydride in ethanol led to a 9 : 1 mixture of the desired amino alcohol **147** and D-valinol **197**. After another difficult purification, all spectral data were matched with known data and a 9 : 1 mixture of both amino alcohols **147** and **197** was still present. An estimation based on the obtained quantity of the mixture of **147** and **197** and on the spectroscopic data allowed approximating the yield of the desired amino alcohol to 60% from the Schöllkopf intermediate **190**.

[f] The absolute configuration of the product **190** was confirmed by measurement of the optical rotation and comparison of the specific rotation of the product with the literature known data.



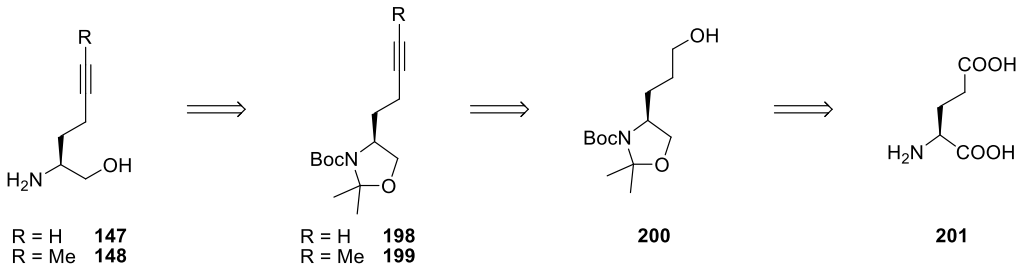
Scheme 60. Synthesis of the amino alcohol 147 *via* the Schöllkopf auxiliary 190.

In summary, it was difficult nay impossible at this stage to afford the pure amino alcohol **147** as an additional step could be necessary to isolate it out of the obtained mixture with D-valinol **197**. As the product **147** could not be isolated, it was also impossible to check the absolute configuration of the obtained amino alcohol. Moreover, the synthesis of this mixture demanded four steps for the preparation of the Schöllkopf auxiliary **190** and four additional steps for the formation of the mixture of the product **147** and D-valinol **197** in an overall 10% yield over eight steps. The efficiency of this process could not be considered as sufficient for this work as the amino alcohol **147** was one of the precursors of the project and a scale-up would have cost way too much money considering the amount of non-natural valine which would had been needed. As a consequence, this synthetic pathway was abandoned at this stage and a cheaper alternative was considered.

1.3.2.5. Development of a new synthetic route to the triple bond containing amino alcohols 147 and 148

1.3.2.5.1. Retrosynthetic analysis

The above results point to difficulties to afford the desired amino alcohols **147** or **148**, or to the impossibility to scale-up the syntheses of these ones. Indeed, for example in the cases of organocatalysis or synthesis *via* a Schöllkopf chiral auxiliary, the high amounts of non-natural starting material or catalyst needed to obtain the necessary big amounts of amino alcohols **147** or **148** for further studies, would result in very high costs (see **1.3.2.3** and **1.3.2.4**). For the next synthetic route, it was therefore decided to try to start from a product present in the chiral pool and already presenting the needed stereochemistry to avoid any additional costs for the creation of the asymmetric centre present in the desired amino alcohols **147** and **148**. L-Glutamic acid **201** was found to be a match for this situation. Indeed, the desired amino alcohols **147** and **148** could be derived from the corresponding protected intermediates **198** and **199** (**Scheme 61**). These last intermediates **198** and **199** could be obtained from the alcohol **200** from which a synthesis starting from L-glutamic acid **201** was already described by Suhartono and co-workers.[148]



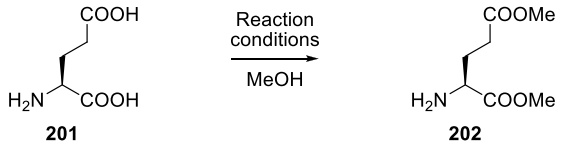
Scheme 61. Retrosynthetic analysis for the synthesis of the amino alcohols 147 and 148 starting from L-glutamic acid 201.

In the remaining of this section, the syntheses of the amino alcohols **147** and **148** are reported. Initially, the synthesis of the alcohol intermediate **200** described by Suhartono and co-workers was optimised.[148] The syntheses of the intermediates **198** and **199** and the transformation into the corresponding amino alcohols **147** and **148** was then examined. Finally, in an effort of further optimisation of the developed process, a variation in protecting groups was considered and the *tert*-butoxycarbonyl group was replaced by a benzyloxycarbonyl moiety.

1.3.2.5.2. Preparation of the alcohol intermediate 200

The desired protected intermediate **200** could be obtained from L-glutamic acid **201**, following a procedure described by Suhartono and co-workers.[148] In a first step, L-glutamic acid **201** was converted to the corresponding diester **202**. The esterification method described by Suhartono and co-workers, using trimethylsilyl chloride in methanol, only led to the desired product **202** in a 78% yield (**Table 14**, **Entry 1**). Other conditions were then examined for this reaction. The treatment of L-glutamic acid **201** with 2,2-dimethoxypropane and concentrated hydrochloric acid in methanol or with thionyl chloride in methanol both afforded the diester **202** in a quantitative way (**Table 14**, **Entries 2-3**).

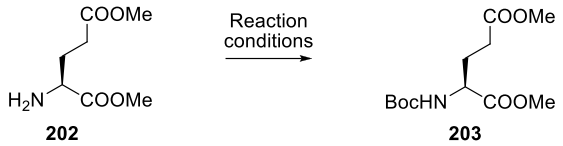
Table 14. Esterification reactions on L-glutamic acid.



Entry	Reaction conditions	Result
1	5 eq TMSCl	78%
2	37% HCl, 2,2-dimethoxypropane	Quantitative
3	2.4 eq $SOCl_2$	Quantitative

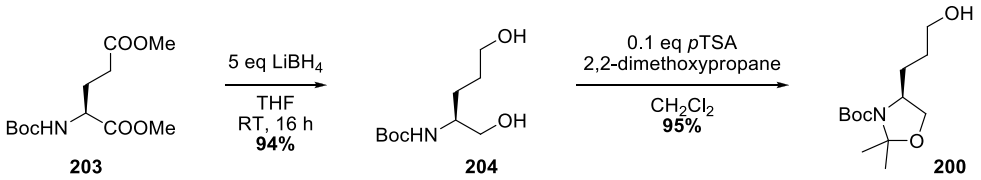
In a second step, the amino group of the obtained diester **202** was protected using di-*tert*-butyl dicarbonate to afford the intermediate **203**. This reaction was achieved with triethylamine in methanol or with pyridine and 4-dimethylamino pyridine in dichloromethane. The desired product **203** was obtained in a 71% and 75% yield, respectively (**Table 15**).

Table 15. Protection reactions on the diester 202.



Entry	Reaction conditions	Result
1	Boc_2O, Et_3N, MeOH	71%
2	Boc_2O, DMAP, pyridine, CH_2Cl_2	75%

The diester **203** was then treated with lithium borohydride in tetrahydrofuran to afford the diol **204** in a 94% yield (**Scheme 62**). For this reaction and the particularity of the substrate **203**, it is interesting to notice that the reducing power of lithium borohydride, being a stronger reducing agent than sodium borohydride but still milder than lithium aluminium hydride, was found to be perfectly adapted. Indeed, the same reduction reaction performed using sodium borohydride or lithium aluminium hydride led to the desired product **204** in lower yields, 30% and 73% respectively. A subsequent *N*,*O*-ketalization of the diol **204** with 2,2-dimethoxypropane afforded selectively, and in a very good 95% yield, the oxazolidine containing compound **200** which is thermodynamically favoured over acetonides with medium-sized rings.[149]



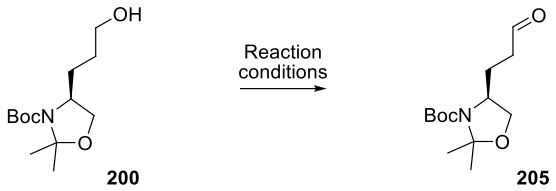
Scheme 62. Synthetic way from the diester 203 to the protected intermediate 200.

In summary, the desired protected intermediate **200** was obtained through an efficient and cheap synthetic pathway in only four steps and an overall 67% yield starting from L-glutamic acid **201**.

1.3.2.5.3. Preparation of the protected triple bond containing amino alcohols 147 and 148 using the Ohira-Bestmann reagent 210

On the way to the triple bond containing amino alcohols **147** and **148**, the protected intermediate **200** was first oxidized to the corresponding aldehyde **205**. Using a procedure reported by Quici and co-workers and optimised by Kinney and co-workers,[150,151] a first oxidation test performed with TEMPO afforded the desired aldehyde **205** in a 93% yield (**Table 16**, **Entry 1**). The same oxidation reaction performed in the Swern conditions with oxalyl chloride and dimethyl sulfoxide led to the compound **205** in an 88% yield (**Table 16**, **Entry 2**). However, in the modified Parikh-Doering conditions of the Swern reaction using sulfur trioxide pyridine complex and dimethyl sulfoxide, the aldehyde **205** was obtained in a 99% yield (**Table 16**, **Entry 3**).

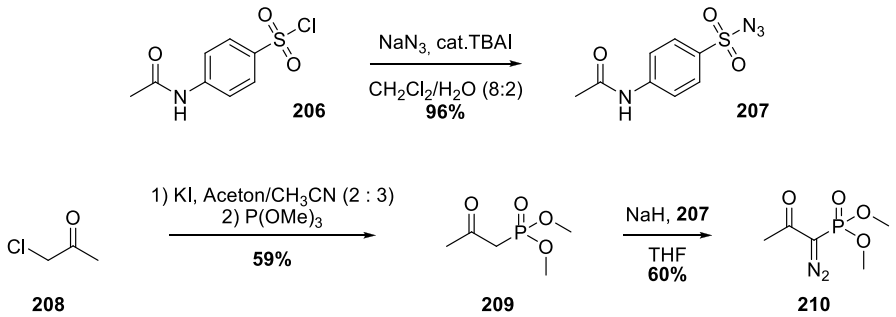
Table 16. Oxidation of the alcohol 200 to the aldehyde 205.



Entry	Reaction conditions	Result
1	TEMPO, KBr, $NaHCO_3$, NaClO, H_2O, CH_2Cl_2	93%
2	1) Oxalyl chloride, DMSO, CH_2Cl_2 2) Et_3N	88%
3	DMSO, Py•SO_3, Et_3N, CH_2Cl_2	99%

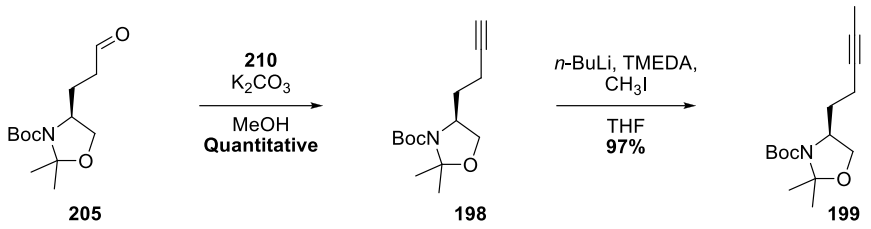
In order to introduce the triple bond present in the desired final amino alcohols **147** and **148**, the aldehyde **205** was engaged with the Ohira-Bestmann reagent **210** to undergo the Ohira-Bestmann modified version of the Seyferth-Gilbert homologation.[152,153]

To begin with, the Ohira-Bestmann reagent **210** was prepared. Following a procedure developed by Baum and co-workers, later optimised by Pietruszka and Witt,[154,155] 4-acetamidobenzenesulfonyl chloride **206** was first treated with sodium azide and a catalytic amount of tetrabutylammonium iodide to afford the corresponding azide **207** in a 96% yield (**Scheme 63**). Separately, trimethyl phosphite was added to iodoacetone, which was formed *in situ* from chloroacetone **208** and potassium iodide in acetone and acetonitrile,[156] to give the phosphonate **209** in a 59% yield. The compound **209** was then reacted with the azide **207** in the presence of sodium hydride in tetrahydrofuran to afford the Ohira-Bestmann reagent **210** in a 60% yield.



Scheme 63. Synthesis of the Ohira-Bestmann reagent 210.

Following a procedure reported by Ohira and optimised by Bestmann and co-workers,[152,153] the aldehyde **205** was treated with the Ohira-Bestmann reagent **210** in the presence of potassium carbonate in methanol to give quantitatively the desired alkyne **198** (**Scheme 64**). This intermediate was then treated with methyl iodide in tetrahydrofuran in the presence of *n*-butyllithium and *N*, *N*, *N'*, *N'*-tetramethylethylenediamine to afford the desired methylated alkyne **199** in a 97% yield.

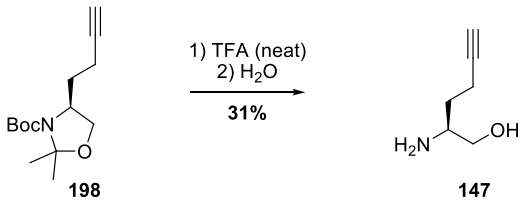


Scheme 64. Synthesis of the protected amino alcohols 198 and 199.

In summary, the desired protected amino alcohols **198** and **199** were obtained from the protected intermediate **200** through an efficient synthetic pathway in only two and three steps and overall yields of 99% and 96%, respectively.

1.3.2.5.4. Studies on the deprotection of the intermediates 198 and 199

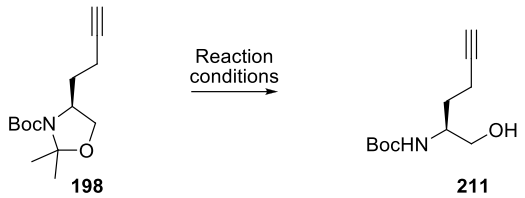
Following a procedure developed by Suhartono and co-workers and optimised by Kumar and co-workers,[148,157] the intermediate **198** was treated with neat trifluoroacetic acid to remove the *tert*-butoxycarbonyl protecting group, followed by the addition of water to remove the acetonide group protecting the vicinal amino alcohol (**Scheme 65**). Using this procedure, the desired amino alcohol **147** was obtained only once and in a low 31% yield, the reaction generally yielding to various unidentified side-products.



Scheme 65. Tentative deprotection of the intermediate 198.

Given the difficulties to obtain the amino alcohol **147** and the possible sensibility of the triple bond in highly acidic conditions, tests were performed to remove selectively, one after another, the protecting groups. First, following a procedure from Forsyth and co-workers,[158] the intermediate **198** was treated with *para*-toluenesulfonic acid in a mixture of water and acetone (**Table 17**, **Entry 1**). In this case, no deprotection was observed which may simply be due to the high concentration in acetone in the reaction mixture. Indeed, the presence of high amounts of acetone could have highly limited the inversion of the protective reaction. In the next trial, the same procedure was performed using ethanol instead of acetone. Using the same amount of acid, after two days, only a 36% conversion was observed for the deprotection process (**Table 17**, **Entry 2**). To try to improve the conversion, more equivalents of *para*-toluenesulfonic acid were used, yielding quantitatively to the desired *tert*-butoxycarbonyl protected amino alcohol **211** (**Table 17**, **Entry 3**). For this reaction, another method, developed by Singh and co-workers and optimised by Radha Krishna and Reddy, was tried.[159–161] The substrate **198** was treated with copper (II) chloride dihydrate in acetonitrile but the process did not afford the desired product **211** (**Table 17**, **Entry 4**). The removal of the acetonide was also not observed by using more equivalents of the complex (**Table 17**, **Entry 5**).

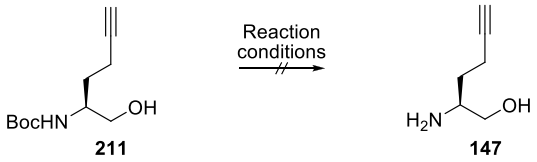
Table 17. Studies for the selective removal of the N,O-acetal group in the intermediate 198.



Entry	Reaction conditions	Result
1	1.5 eq *p*TSA•H_2O, water/acetone, 2 d	No conversion
2	1.5 eq *p*TSA•H_2O, water/ethanol, 2 d	36% conversion
3	5 eq *p*TSA•H_2O, water/ethanol, 2 d	Quantitative
4	1 eq $CuCl_2$•$2H_2O$, acetonitrile, 1 d	No conversion
5	3 eq $CuCl_2$•$2H_2O$, acetonitrile, 1 d	No conversion

After the desired intermediate **211** was obtained, the removal of the *tert*-butoxycarbonyl group was investigated but neither the use of trifluoroacetic acid in water nor of aqueous hydrochloric acid led to the desired amino alcohol (**Table 18**, **Entries 1 and 2**). As in the case of the deprotection tested on the substrate **198** using trifluoroacetic acid (**Scheme 65**), the deprotection reactions yielded various unidentified side-products.

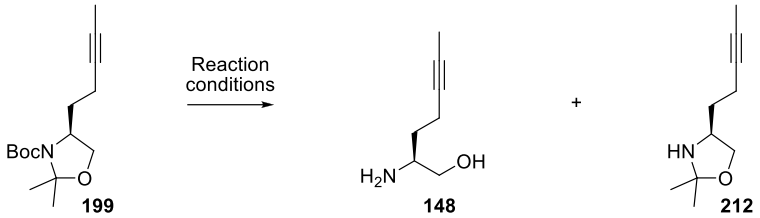
Table 18. Tentative removal of the *tert*-butoxycarbonyl moiety in the intermediate 211.



Entry	Reaction conditions	Result
1	5 eq TFA, water	Unidentified side-products
2	20 eq HCl, water	Unidentified side-products

At the same time, deprotection reactions were also tested on the other protected substrate **199**. To obtain complementary results, in this case, the selective removal of the *tert*-butoxycarbonyl group was first examined. The use of trimethylsilyl chloride, either on classic conditions or on optimised conditions described by Tam and co-workers, did not led to any conversion of the initial substrate **199** (**Table 19**, **Entries 1 and 2**).[162] The use of hydrochloric acid in dioxane in the conditions described by Ricci and co-workers afforded a 1 : 1 mixture of the products **148** and **212** (**Table 19**, **Entry 3**).[163] This result was also obtained when the substrate **199** was treated first with neat trifluoroacetic acid and then with water in the conditions described by Howell and co-workers (**Table 19**, **Entry 5**).[164] Finally, when the substrate was treated with sulfuric acid in dioxane, a 2 : 3 mixture of **148** and **212** was obtained (**Table 19**, **Entry 4**).

Table 19. Deprotection reactions of the substrate 199.

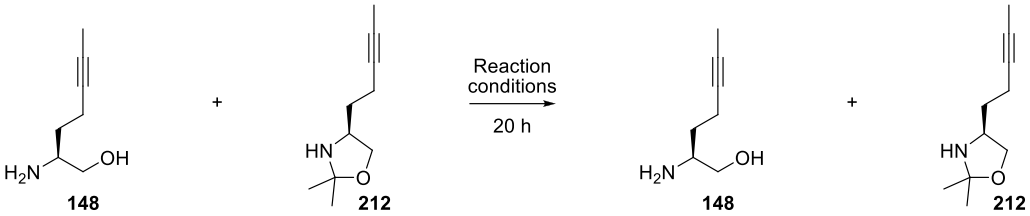


Entry	Reaction conditions	Result[g]
1	20 eq TMSCl, MeOH	No conversion
2	10 eq TMSCl, 30 eq Phenol, CH_2Cl_2	No conversion
3	50 eq HCl, dioxane	50% **148**, 50% **212**
4	50 eq H_2SO_4, dioxane	40% **148**, 60% **212**
5	TFA (neat) then water	50% **148**, 50% **212**

The tentative selective removal of the *tert*-butoxycarbonyl group led to a mixture of the desired product **212** and of the amino alcohol **148**. As it was not possible to separate both products **148** and **212** at this stage, several conditions were examined to complete the removal of the acetonide. The 1 : 1 mixture of **148** and **212** obtained from the treatment of the compound **199** with neat trifluoroacetic acid followed by the addition of water was directly used for these tests. The 1 : 1 mixture of **148** and **212** was treated with silica in chloroform leading to a 2 : 1 mixture of **148** and **212** after one day of stirring at room temperature (**Table 20**, **Entry 1**). In the same conditions but using a 4 : 1 mixture of acetonitrile and chloroform instead of pure chloroform, a 9 : 1 mixture was obtained (**Table 20**, **Entry 2**). Finally, using methanol instead of chloroform led completely to the desired amino alcohol (**Table 20**, **Entry 3**). These first results may simply be the reflection of the solubility properties of the initial mixture of **148** and **212** in the different solvents used. The use of copper (II) chloride dihydrate or boron trifluoride diethyl etherate in acetonitrile did not lead to any complementary conversion (**Table 20**, **Entries 4 and 6**). The treatment of the initial mixture with cerium(III) chloride heptahydrate in a 4 : 1 mixture of acetonitrile and chloroform afforded exclusively the desired amino alcohol **148** (**Table 20**, **Entry 5**) whereas using *para*-toluenesulfonic acid in ethanol afforded a 4 : 1 mixture of **148** and **212** (**Table 20**, **Entry 7**).

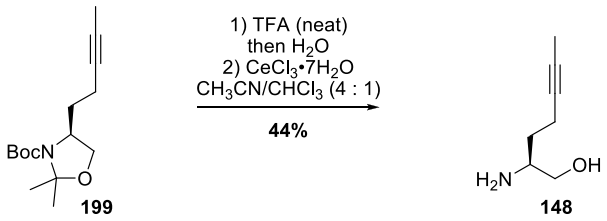
[g] All the mixtures compositions presented herein were determined from the analysis of their ^{1}H-NMR spectroscopic measurements.

Table 20. Studies upon the completion of the acetonide removal to obtain the amino alcohol 148.



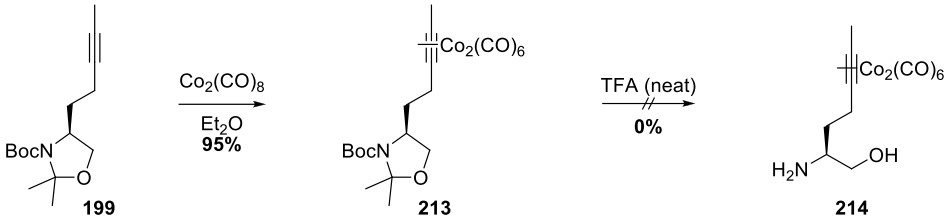
Entry	Reaction conditions	Result[g]
1	Silica, $CHCl_3$	65% **148**, 35% **212**
2	Silica, $CH_3CN/CHCl_3$ (4 : 1)	90% **148**, 10% **212**
3	Silica, MeOH	100% **148**
4	$CuCl_2 \bullet 2H_2O$, CH_3CN	50% **148**, 50% **212**
5	$CeCl_3 \bullet 7H_2O$, $CH_3CN/CHCl_3$ (4 : 1)	100% **148**
6	$BF_3 \bullet Et_2O$, CH_3CN	50% **148**, 50% **212**
7	*p*TSA$\bullet H_2O$, EtOH	80% **148**, 20% **212**

Considering all the results of the performed tests for the removal of the acetonide and *tert*-butoxycarbonyl moieties in the protected intermediate **199**, the best methods found were combined and as a consequence the deprotection process was optimised. The compound **199** was first treated with neat trifluoroacetic acid followed by the addition of water. After a work-up, the residue was treated with cerium(III) chloride heptahydrate in a 4 : 1 mixture of acetonitrile and chloroform to afford a brown paste, mixture of product and unidentified side-products. Before the desired amino alcohol **148** was isolated, both liquid-liquid continuous extraction and column chromatography were needed, showing once again the complex solubility behaviour of this kind of derivates. The amino alcohol **148** was finally obtained in a 44% yield from the protected intermediate **199**.



Scheme 66. Synthesis of the amino alcohol 148 from the protected intermediate 199.

Given the complexity of the process and the formation of unidentified side-products which could be attributed to the reactivity of the triple bond, a protection of the triple bond was performed. Following a procedure reported by Mukai and co-workers,[165] the intermediate **199** was first treated with dicobalt octacarbonyl in diethyl ether to give the protected triple bond containing substrate **213** (**Scheme 67**). A trial was then performed for the removal of the *tert*-butoxycarbonyl group and of the acetonide, using neat trifluoroacetic acid followed by addition of water. The reaction did not afford the desired product **214** but, as in the former case, unidentified side-products.



Scheme 67. Synthetic studies using triple bond protected derivates.

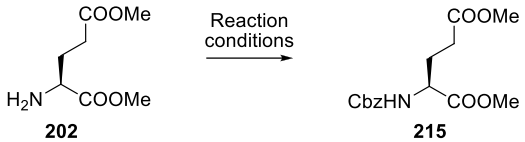
In summary, a lot of difficulties were encountered on the way to the desired amino alcohols **147** and **148**. The non-methylated amino alcohol **147** was obtained only once and in a low 31% yield whereas obtaining the methylated amino alcohol **148** required a complex reaction path followed by a complex isolation. As these difficulties could be partly imputed to the choice of the protecting groups, the use of another protecting group has been studied and is reported in the following section.

1.3.2.5.5. Towards the desired amino alcohol 147 *via* differently protected intermediates

As previously precised, given the difficulties on the developed synthetic way using a *tert*-butoxycarbonyl group and an acetonide as protecting groups, studies were performed on the use of another couple of protecting groups. A benzyloxycarbonyl group was used instead of the *tert*-butoxycarbonyl group.

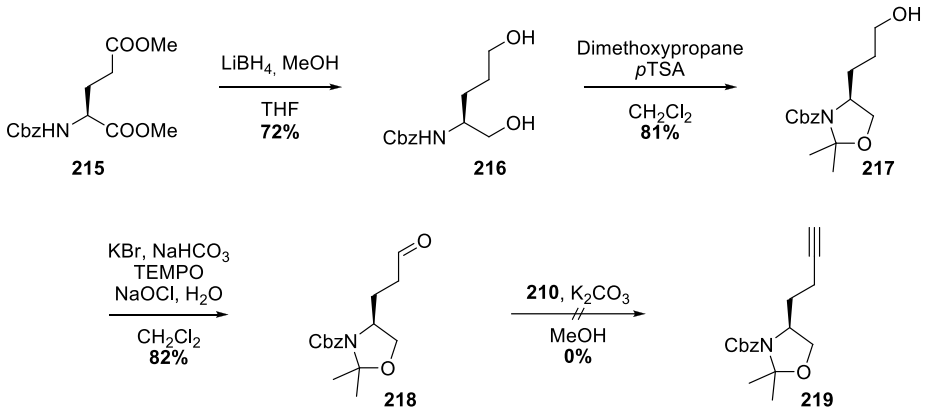
Initially, starting from the diester **202**, the benzyloxycarbonyl protected intermediate **215** was synthesised. Following a procedure by Fustero and co-workers,[166] the treatment of the diester **202** with benzyloxycarbonyl chloride and potassium carbonate in dioxane afforded the desired intermediate **215** in a 64% yield (**Table 21**, **Entry 1**). The use of dichloromethane instead of dioxane, in accordance with a variation of the previous method by Chavan and co-workers,[167] led to the product **215** in an 81% yield (**Table 21**, **Entry 2**). A third method, reported by Bremner and co-workers,[168] was also tested. The diester **202** was treated with benzyloxycarbonyl chloride and sodium hydrogen carbonate in a 1 : 1 mixture of tetrahydrofuran and water, affording the product **215** in an 83% yield (**Table 21**, **Entry 3**).

Table 21. Synthesis of the intermediate 215.



Entry	Reaction conditions	Yield
1	1.3 eq CbzCl, 3 eq K_2CO_3, Dioxane	64%
2	1.3 eq CbzCl, 3 eq K_2CO_3, CH_2Cl_2	81%
3	1.3 eq CbzCl, 3 eq $NaHCO_3$, THF/H_2O (1 : 1)	83%

In the following step, the synthesised *N*-benzyloxycarbonyl-protected diester **215** was treated with lithium borohydride and methanol in tetrahydrofuran to afford the diol **216** in a 72% yield (**Scheme 68**). The intermediate **216** was subsequently treated with 2,2-dimethoxypropane and *para*-toluenesulfonic acid in dichloromethane to give the desired alcohol **217** in an 81% yield. Using a procedure reported by Quici and co-workers and optimised by Kinney and co-workers,[152,153] the oxidation reaction of the compound **217** performed with TEMPO afforded the desired aldehyde **218** in an 82% yield.[150,151] As in the case of the *N*-*tert*-butoxycarbonyl-protected aldehyde **205**, following a procedure reported by Ohira and optimised by Bestmann and co-workers, the *N*-benzyloxycarbonyl-protected aldehyde **218** was treated with the Ohira-Bestmann reagent **210** in the presence of potassium carbonate in methanol. The reaction did not give the awaited product **219** but only starting material **218** and unidentified side-products.

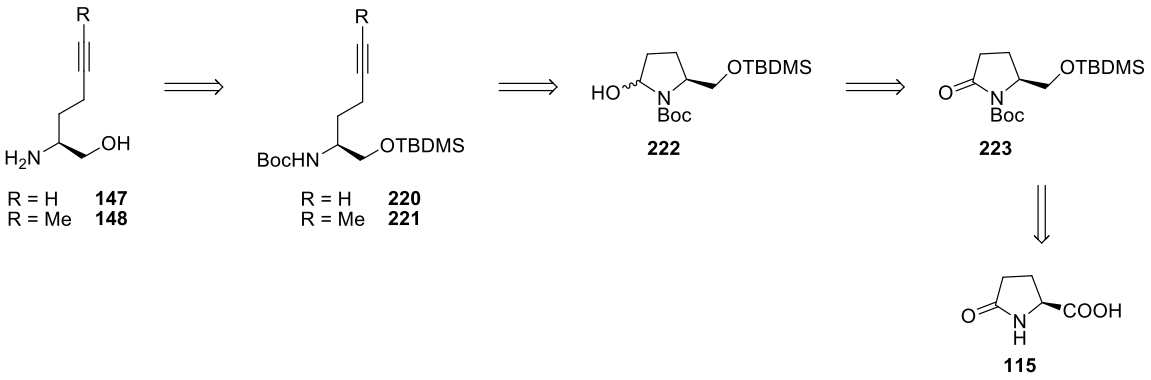


Scheme 68. Synthetic way to the triple-bond containing intermediate 219.

The desired intermediate **219** was finally not obtained whereas the reaction of the aldehyde **218** with the Ohira-Bestmann reagent **210** was repeated several times. This may be due to an incompatibility of both reactant **210** and **218** given their rich electronic environments and thus their reactivity behaviour. Furthermore, the synthetic way was not as efficient as the one using the *tert*-butoxycarbonyl group as the aldehyde **218** was obtained in five steps and a 40% overall yield from L-glutamic acid **201** whereas the *N*-*tert*-butoxycarbonyl-protected aldehyde **205** was obtained in five steps and a 66% overall yield from L-glutamic acid **201**. This synthetic route was thus abandoned and a new one developed.

1.3.2.6. Towards the amino alcohols 147 and 148 starting from (*S*)-pyroglutamic acid 115

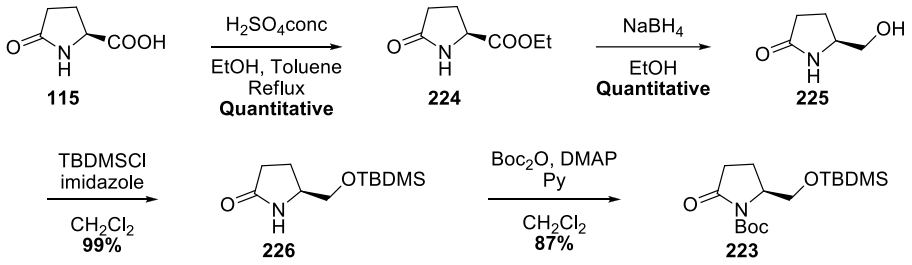
Considering the previous negative results and adapting an idea patented by Zeng and co-workers, a new synthetic route to the amino alcohols **147** and **148** was developed starting from (*S*)-pyroglutamic acid **115**.[169] The amino alcohols **147** or **148** could be obtained from the corresponding protected intermediate **220** or **221** (**Scheme 69**). As this process was reported by Zeng and co-workers on a quite similar substrate, the protected compounds **220** and **221** could be obtained from the intermediate **222** which could easily be derived from the compound **223**. The protected intermediate **223** could be obtained in several steps from (*S*)-pyroglutamic acid **115**.



Scheme 69. Retrosynthetic analysis for the synthesis of the amino alcohols 147 and 148 starting from (*S*)-pyroglutamic acid 115.

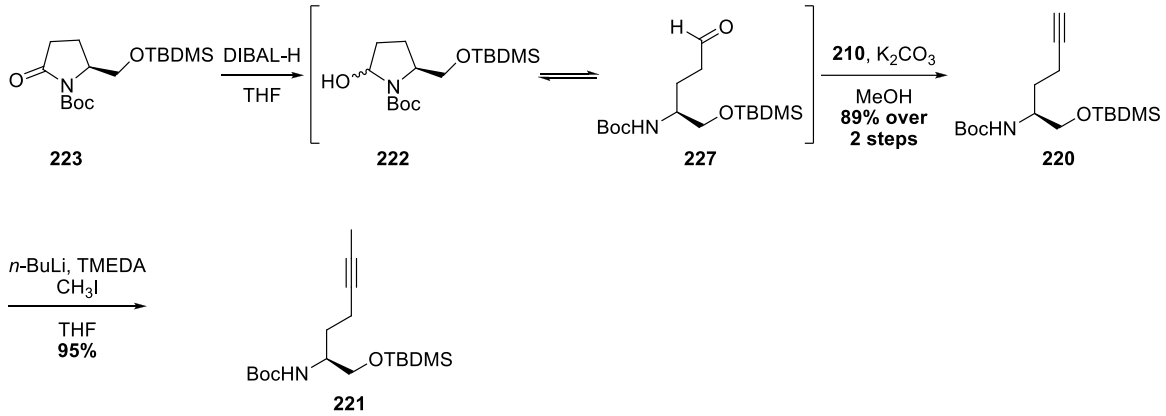
In the remaining of this section, the synthesis of the intermediate **223** was first studied. The transformation of the compound **223** into the triple bond containing intermediate **220** and the transformation into the methylated corresponding compound **221** were subsequently examined. Due to the reduced amount of time remaining to study this synthetic route, the following steps to the amino alcohols **147** and **148** were not investigated.

Following a procedure reported by Davies and co-workers, (*S*)-pyroglutamic acid **115** was first treated with sulfuric acid in ethanol and toluene to afford quantitatively the ester **224** (**Scheme 70**).[170] The compound **224** was subsequently reduced using sodium borohydride in ethanol and the alcohol **225** was obtained quantitatively. The alcohol **225** was then protected using *tert*-butyldimethylsilyl chloride and imidazole in dichloromethane to give the desired intermediate **226** in a 99% yield. Finally, the amino group of the intermediate **226** was protected using di-*tert*-butyl dicarbonate to afford the desired compound **223** in an 87% yield.



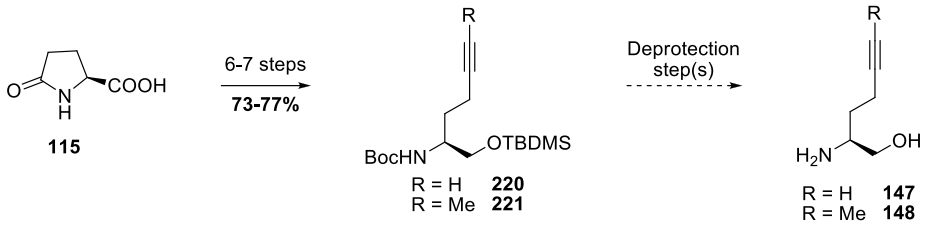
Scheme 70. Synthetic way to the intermediate 223.

The protected compound **223** was then treated with di*iso*-butylaluminium hydride in tetrahydrofuran to give the intermediate **222** in equilibrium with the aldehyde **227** (**Scheme 71**). According to a procedure reported by Zeng and co-workers on a quite similar substrate, after a common work-up, the residue was subsequently reacted with the Ohira-Bestmann reagent **210** and potassium carbonate in methanol to afford the alkyne **220** in an 89% yield over the two steps.[169] The compound **220** could also be methylated using *n*-butyllithium, *N*, *N*, *N'*, *N'*-tetramethylethylenediamine and methyl iodide in tetrahydrofuran, affording the alkyne **221** in a 95% yield.



Scheme 71. Synthesis of the alkynes 220 and 221.

In summary, in this section, a new synthetic way was develop on the way to the amino alcohols **147** and **148**. The corresponding protected intermediates **220** and **221** were obtained respectively in six and seven steps in 77% and 73% overall yields (**Scheme 72**). It should then be possible to obtain the corresponding amino alcohols **147** and **148** after removal of the protecting groups.

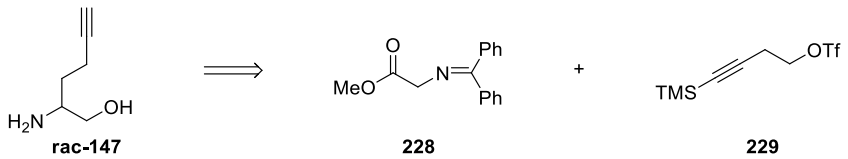


Scheme 72. Postulated synthetic route to the amino alcohols 147 and 148 starting from (*S*)-pyroglutamic acid 115.

In this work, due to the reduced amount of time remaining to study this synthetic route, the last steps on the way to the amino alcohols **147** and **148** were not investigated. However, the results obtained for the syntheses of the intermediates **220** and **221** are encouraging and this synthetic way should be further studied.

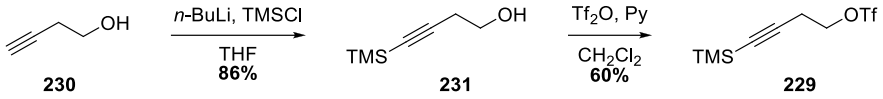
1.3.2.7. Synthetic studies towards the racemic amino alcohol rac-147

As it could eventually have been needed, for instance for analytical purposes, some synthetic studies were performed at the same time to obtain the racemic amino alcohol **147**, here named **rac-147**. As reported by Brummond and Yan, [171] it should be possible to obtain the desired racemic amino alcohol **rac-147** after three steps, starting from the protected methyl ester of glycine **228** and the alkyne **229** (**Scheme 73**).



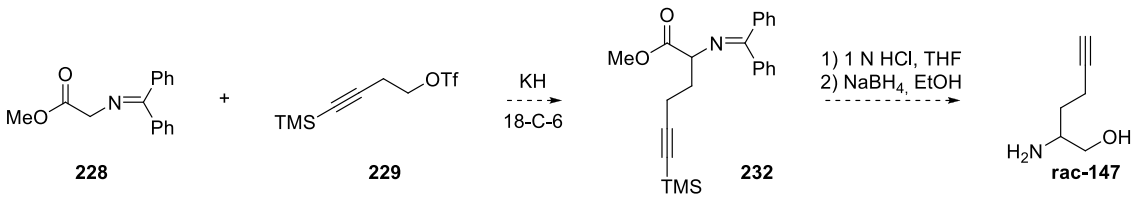
Scheme 73. Retrosynthetic analysis for the synthesis of the racemic amino alcohol rac-147.

The synthesis of the alkyne **229** was first examined. Following a procedure reported by Dieter and Chen, 3-butyn-1-ol **230** was treated with *n*-butyllithium and trimethylsilyl chloride in tetrahydrofuran to give the desired protected alcohol **231** in an 86% yield (**Scheme 74**).[172] The compound **231** was subsequently treated with trifluoromethanesulfonic anhydride and pyridine in dichloromethane to obtain the desired intermediate **229** in a 60% yield.



Scheme 74. Synthesis of the alkyne intermediate 229.

As numerous difficulties were encountered on the synthetic ways to obtain the enantiopure amino alcohol **147**, the racemic amino alcohol was not needed at this point. Moreover, the 18-crown-6 needed for the next step would have induced high costs. As a consequence, the studies concerning this racemic synthesis were discontinued. However, following the study reported by Brummond and Yan, it should be possible to obtain the desired racemic amino alcohol **rac-147** in three steps from the intermediates **228** and **229**. In this study, the alkyne **232** was obtained from the alkylation of the protected methyl ester of glycine **228** with the intermediate **229**. The protecting groups were then removed using hydrochloric acid and the methyl ester was reduced using sodium borohydride, to afford the desired racemic amino alcohol **rac-147**.

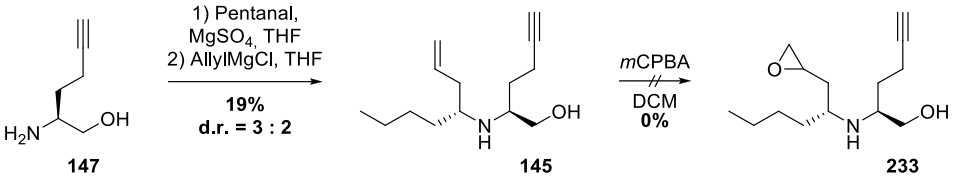


Scheme 75. Following reported steps for the synthesis of the racemic amino alcohol rac-147.

1.3.2.8. Towards the synthesis of a macrocycle starting from the triple bond containing amino alcohols 147 and 148

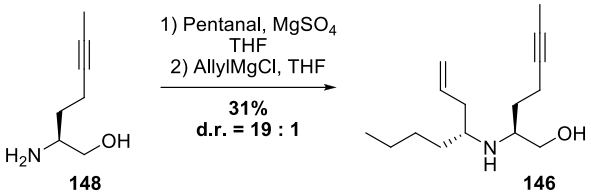
Although if their syntheses presented various difficulties, the amino alcohols **147** and **148** could be isolated in small amounts, sufficient to examine further steps, especially the formerly optimised two-step reaction sequence, imine/oxazolidine formation and addition of an allyl Grignard (see **1.3.1.2**).[97]

Initially, the sequence was applied to the amino alcohol **147**. It was first treated with pentanal in tetrahydrofuran in the presence of magnesium sulfate as drying agent (**Scheme 76**). After work-up, allylmagnesium chloride was added to the residue in tetrahydrofuran. The desired product **145** was obtained in a 19% yield and with a 3 : 2 diastereomeric ratio which was spectroscopically determined. The compound **145** was then treated with *meta*-chloroperoxybenzoic acid to try to obtain the epoxide **233** but the reaction did not run and the starting material was recovered.



Scheme 76. Tentative synthesis of the epoxide 233.

The previously described sequence was then applied to the amino alcohol **148**. The desired product **146** was obtained in a 31% yield and with a 19 : 1 diastereomeric ratio (**Scheme 77**). As in the case of the formation of the diene **113**, complementary studies were performed to identify a predominant intermediate in the process, without any success (see **Annex II**).



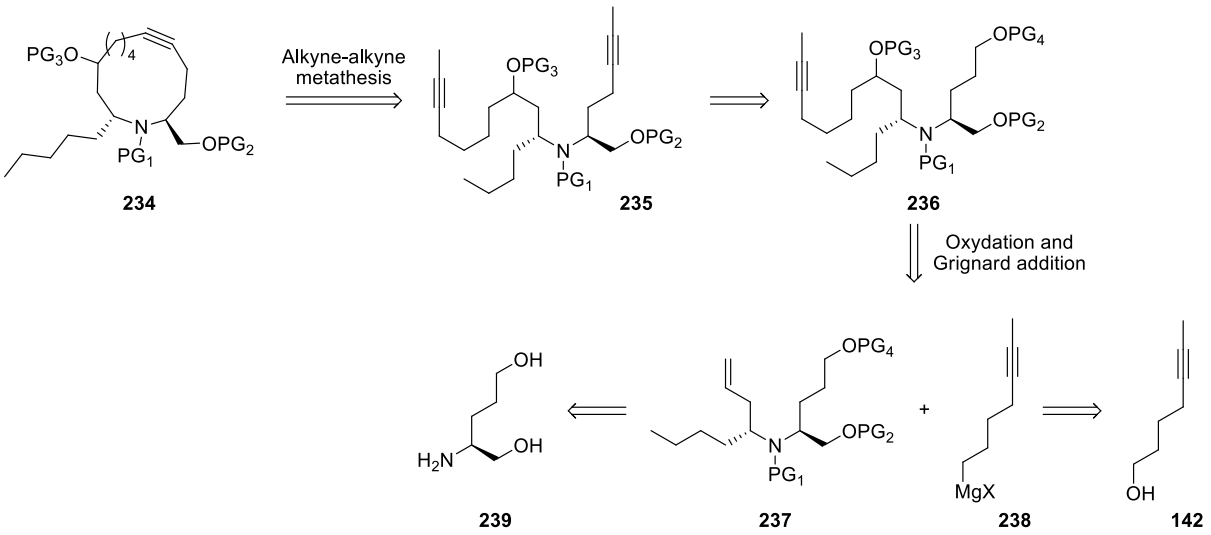
Scheme 77. Synthesis of the intermediate 146.

Considering the small amounts of amino alcohols obtained, it was not possible at this stage to examine this synthetic way any further. However, whereas the intermediate **145** was obtained in a low 19% yield and with a moderate 3 : 2 diastereomeric ratio, the corresponding methylated intermediate **146** was obtained in a 31% yield and a very good 19 : 1 diastereomeric ratio. This last result is quite encouraging and if a method is found to obtain the amino alcohol **148** in bigger amounts, it could be interesting to try to optimize the two-step process, imine/oxazolidine formation and addition of an allyl Grignard, and examine further steps on the way to the synthesis of the desired natural products.

1.3.2.9. Towards the synthesis of a macrocycle *via* an aminodiol

1.3.2.9.1. Retrosynthetic analysis

Given the numerous difficulties encountered in this work to find a suitable synthesis of the triple bond containing amino alcohols **147** and **148**, a slight modification of the initial retrosynthetic analysis was thought. A new synthetic route was therefore separately examined, starting from the aminodiol **239**. The desired macrocycle **234** could be obtained from the diyne **235** through an alkyne-alkyne metathesis (**Scheme 78**). Unlike in the initial retrosynthetic analysis, the intermediate **235** could be derived from the monoalkyne **236** and the second triple bond could be installed at this stage. This intermediate **236** could then be obtained from the protected intermediate **237** and the Grignard reagent **238**. Indeed, the addition of the Grignard reagent **238** on the product of the oxidation of the alkene **237** should lead to the desired intermediate **236**. The protected intermediate **237** could be obtained, after some protection steps, by applying the developed two-step sequence, imine/oxazolidine formation and addition of an allyl Grignard, to the aminodiol **239**. The Grignard reagent **238** could surely be derived from the corresponding alcohol **142**.



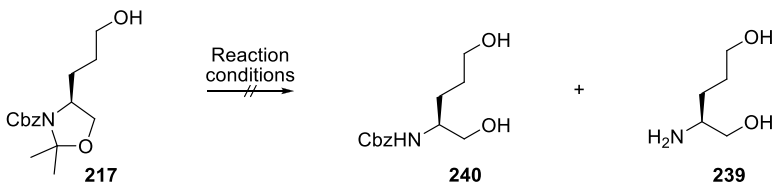
Scheme 78. Modified retrosynthetic analysis for the synthesis of a macrocycle 234 starting from the aminodiol 239.

In the remaining of this section, the synthesis of the aminodiol **239** was first examined. Then, further steps on the way to the macrocycle **234** were investigated. A study was also begun in order to try to optimize the diastereomeric ratio of the mixture obtained from the two-step process, imine/oxazolidine formation and addition of an allyl Grignard, especially by examining the effect of installing protecting groups on the aminodiol **239** before it underwent the process.

1.3.2.9.2. Synthesis of the aminodiol 239

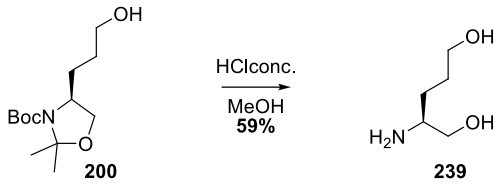
The desired aminodiol **239** was first synthesised. Deprotection reactions were first examined on the formerly obtained compound **217**. A first test, using dimethyl sulfide and trifluoroacetic acid did not led to the desired product **239** but to the protected intermediate **240** as only a removal of the acetonide was observed (**Table 22**, **Entry 1**). Following a procedure reported by Kiso and co-workers,[173] the compound **217** was treated with thioanisole and trifluoroacetic acid leading to the same result as the former trial, the exclusive formation of the protected intermediate **240** (**Table 22**, **Entry 2**).

Table 22. Synthetic way to the aminodiol 239 starting from the intermediate 217.



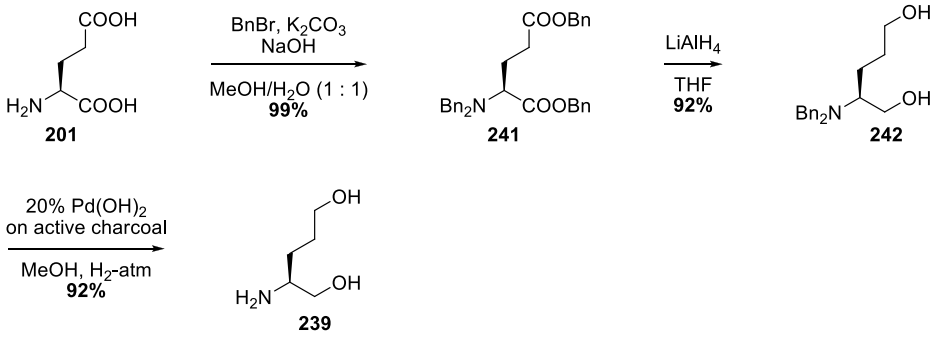
Entry	Conditions	Result
1	50 eq Me_2S, 270 eq TFA	Only **240** was observed
2	50 eq thioanisole, 270 eq TFA	Only **240** was observed

At the same time, deprotection reactions were examined on the formerly obtained protected intermediate **200**. This compound was treated with hydrochloric acid in methanol, leading to the desired aminodiol **239** in a 59% yield (**Scheme 79**). Considering this result and the important quantity of intermediate **200** which was available in our laboratory, this synthetic route was used and the studies upon the former one, starting from the intermediate **217**, were discontinued.



Scheme 79. Synthesis of the aminodiol 239 starting from the intermediate 200.

Separately, another synthetic route was also investigated. Following a procedure reported by Weigl and Wünsch and optimised by Nicole Holub, L-glutamic acid **201** was treated with benzyl bromide, potassium carbonate and sodium hydroxide in a 1 : 1 mixture of methanol and water, to afford the protected intermediate **241** in a 99% yield (**Scheme 80**).[97,174] The compound **241** was subsequently reduced to afford the diol **242** in a 92% yield. In a last step, the *N*-protecting benzyl groups were removed using 20% palladium hydroxide on charcoal in methanol under hydrogen atmosphere, giving the desired aminodiol **239** in a 92% yield.



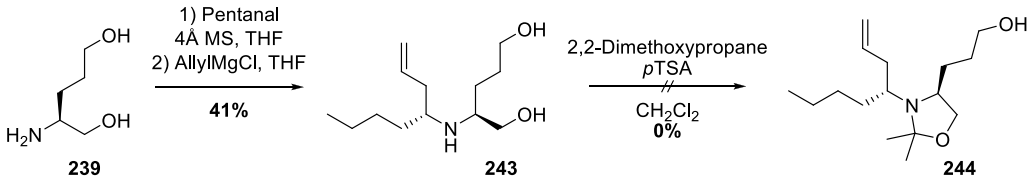
Scheme 80. Synthesis of the aminodiol 239 starting from L-glutamic acid 201.

In summary, the desired aminodiol **239** was obtained either in a 59% yield starting from the formerly synthesised intermediate **200** or in three steps and an 84% overall yield starting from L-glutamic acid **201**.

1.3.2.9.3. Towards the synthesis of a macrocycle starting from the aminodiol 239

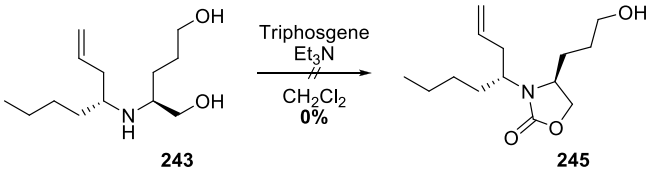
To continue on the way to a macrocycle, the formerly optimised two-step reaction sequence, imine/oxazolidine formation and addition of an allyl Grignard, was applied to the obtained aminodiol **239** (see **1.3.1.2**). In the first time, the aminodiol **239** was treated with pentanal in tetrahydrofuran in the presence of molecular sieves as drying agent (**Scheme 81**). After work-up, allylmagnesium chloride was subsequently added to the residue in tetrahydrofuran. The desired diol **243** was obtained in a 41% yield and with a 9 : 1 diastereomeric ratio. As in the case of the formation of the

diene **113**, complementary studies were performed to identify a predominant intermediate in the process, without any success (see **Annex II**). The compound **243** was then treated with 2,2-dimethoxypropane and *para*-toluenesulfonic acid in dichloromethane but the desired protected compound **244** was not obtained. Indeed, the reaction was not selective and a mixture of starting material, dimers and differently protected products was identified.



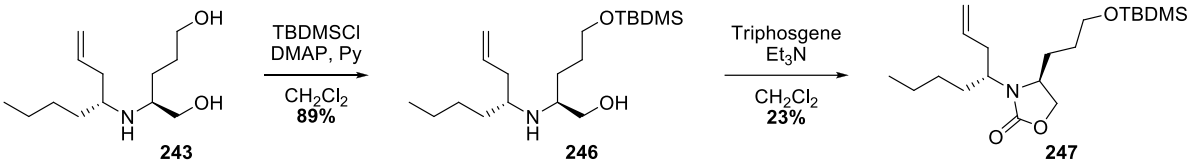
Scheme 81. Tentative synthesis of the protected intermediate 244.

As the acetonide protective reaction did not lead to the desired product **244**, another protective group was considered. The compound **243** was treated with triphosgene and triethylamine in dichloromethane (**Scheme 82**). The reaction did not afford the desired protected compound **245** but, as in the case of the formerly considered acetonide protective reaction, a mixture of starting material, dimers and differently protected products.



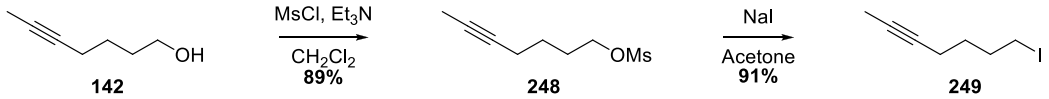
Scheme 82. Tentative synthesis of the protected intermediate 245.

The unsuccessful direct protections of the β-amino alcohol function in the compound **243** revealed the necessity of a previous protection of the second alcohol function present in the molecule. The diol **243** was treated with *tert*-butyldimethylsilyl chloride, affording selectively the desired protected alcohol **246** in an 89% yield (**Scheme 83**). The compound **246** was then treated with triphosgene and triethylamine in dichloromethane, leading to the desired intermediate **247** in a 23% yield.



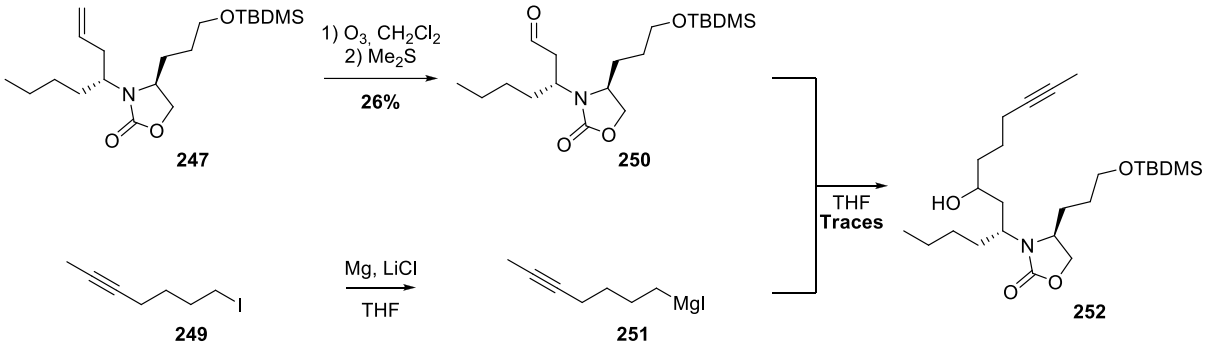
Scheme 83. Synthesis of the protected intermediate 247.

Separately, 7-iodohept-2-yne **249** was prepared from 5-heptyn-1-ol **142**. 5-heptyn-1-ol **142** was treated with methanesulfonyl chloride and triethylamine in dichloromethane to afford the protected alcohol **248** in an 89% yield (**Scheme 84**). In a second step, using a Finkelstein-type reaction, the mesylated compound **248** gave the desired 7-iodohept-2-yne **249** in a 91% yield.



Scheme 84. Synthesis of 7-iodohept-2-yne 249.

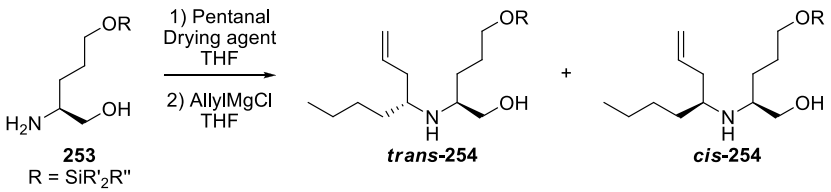
Due to time restrictions, only one test was performed for the next steps. In the first part, the alkene **247** underwent an ozonolysis reaction affording the aldehyde **250** in a moderate 26% yield (**Scheme 85**). Given the fact that only one test of this reaction was performed due to the small amounts of starting material available, it may be possible to optimize this ozonolysis reaction. Separately, the iodide **249** was reacted with magnesium and lithium chloride in tetrahydrofuran to afford the corresponding Grignard reagent **251**. The Grignard reagent **251** was subsequently titrated and engaged with the aldehyde **250** in tetrahydrofuran. Due to the small amounts engaged in the reaction, the desired intermediate **252** was only detected in mass spectroscopy, giving anyway an encouraging result for this synthetic way which should be further studied and optimised.



Scheme 85. Synthetic way to the intermediate 252.

1.3.2.9.4. Development of new protected substrates for selectivity studies

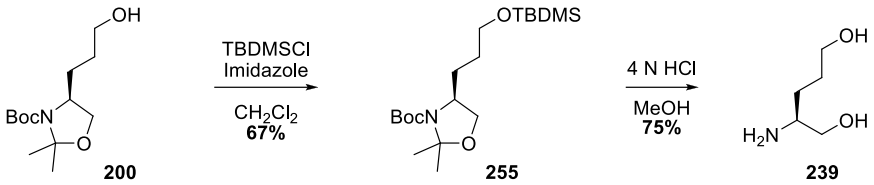
Given the moderate 9 : 1 diastereoselective ratio obtained in the two-step reaction sequence, imine/oxazolidine formation and addition of an allyl Grignard (see **1.3.1.2**), starting from the aminodiol **239**, the development of new intermediates containing a protected alcohol was examined. Moreover, Nicole Holub already reported that the presence of a free alcohol could have a negative influence on the diastereoselectivity of this sequence whereas the presence of a more apolar or of a smaller group could have a positive influence. In this work, the synthesis of new amino alcohols containing a silylated alcohol was thus examined to study the effect of this variation on the diastereoselectivity of the considered two-step sequence (**Scheme 86**).



Scheme 86. General scheme of the imine/oxazolidine formation and addition of allyl Grignard.

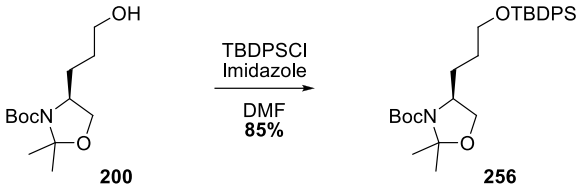
First, the formerly synthesised alcohol **200** was reacted with *tert*-butyldimethylsilyl chloride and imidazole in dichloromethane to obtain the corresponding protected alcohol **255** in a 67% yield (**Scheme 87**). A deprotection reaction using aqueous hydrochloric acid in methanol did only lead to the entirely deprotected aminodiol **239** in a 75% yield. Following the reaction using

NMR-spectroscopy, it was found that the *tert*-butyldimethylsilyl protecting group was the first being removed. As a consequence, it would be very difficult nay impossible to remove selectively the *tert*-butoxycarbonyl group and the acetonide from the substrate **200**.



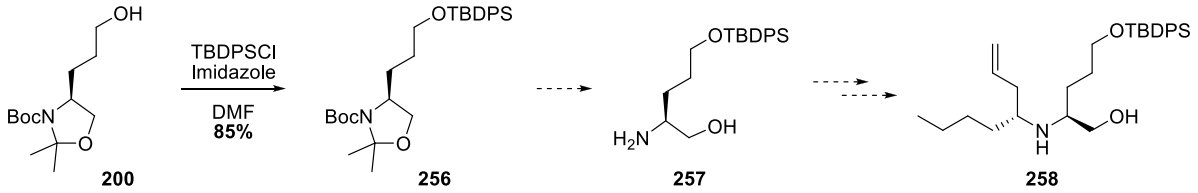
Scheme 87. Tentative protection of the alcohol 200.

As the *tert*-butyldimethylsilyl group was found to be too sensible in the acidic medium needed for the removal of the other protecting groups, a second test was begun using *tert*-butyldiphenylsilyl as protecting group. The alcohol **200** was treated with *tert*-butyldiphenylsilyl chloride, affording the corresponding protected alcohol **256** in an 85% yield (**Scheme 88**).



Scheme 88. Synthesis of the protected alcohol 256.

In this section, the synthesis of new protected substrates was examined. However, due to the limited time remaining for further studies, it was not possible to obtain any more results. It could be interesting to first complete the synthesis of protected substrates such as **257** and then to study the effect of this protection on the diastereoselectivity of the two-step sequence, imine/oxazolidine formation and Grignard addition (**Scheme 89**). To realize it, the sequence should be applied to a protected intermediate such as **257**, to obtain new substrates like **258** and maybe have a way to improve the selectivity of the entire process.

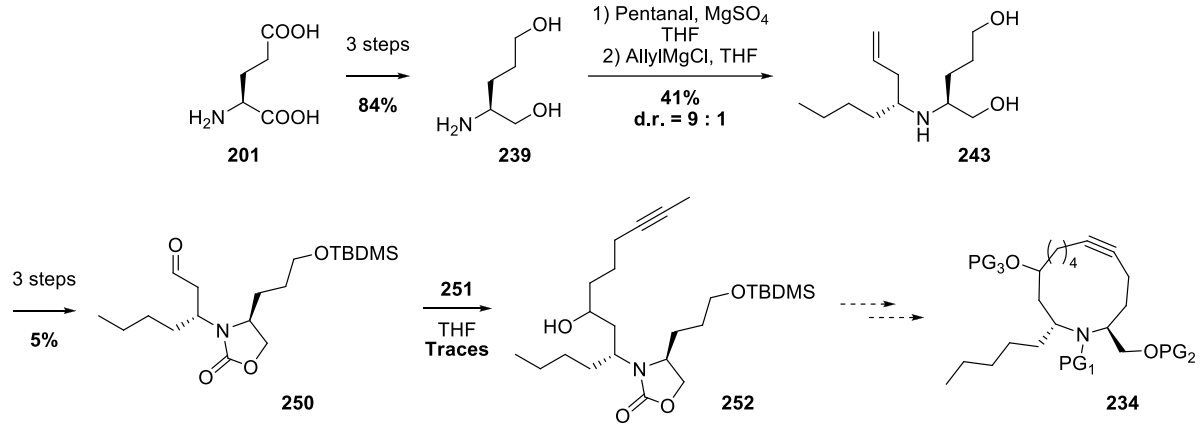


Scheme 89. Postulated synthetic way towards the new substrate 258.

1.3.2.9.5. Summary and synthetic potential

In this section, the beginning of a new methodology was developed for the synthesis of the desired macrocycle **234**, through the aminodiol **239**. Initially, synthetic ways to the aminodiol **239** were examined and it was finally obtained in three steps and an 84% overall yield from L-glutamic acid **201** (**Scheme 90**). Afterwards, the aminodiol **239** underwent the two-step sequence, imine/oxazolidine formation and allyl Grignard addition, leading to the desired intermediate **243** in a 41% yield and

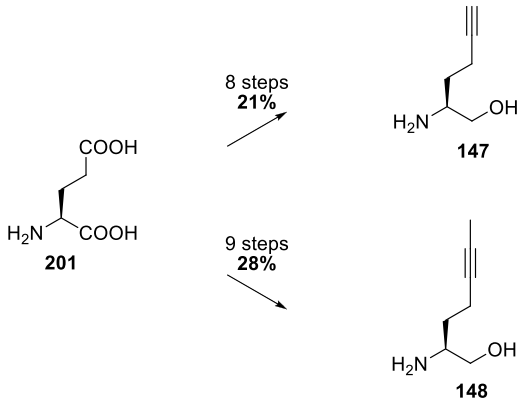
with a 9 : 1 diastereomeric ratio. Several studies were finally performed on further steps towards the synthesis of the macrocycle **234**. During these studies, the aldehyde **250** was obtained in three steps and a 5% overall yield from the intermediate **243**. In the next step, traces of the compound **252** were also identified. Starting from the intermediate **243**, the tests were performed on very small quantities and none of the steps were optimised. It means that all this process could be optimised and further developed, giving a good basis to a synthetic route to the macrocycle **234**. It would also be interesting to study the effect of using differently protected intermediates on the diastereoselectivity of the two-step sequence, imine/oxazolidine formation and Grignard addition, as it could allow an improvement in the global diastereoselectivity of the process by a better understanding of this sequence (see **1.3.2.9.4**).



Scheme 90. Synthetic way to the macrocycle 234 through the aminodiol 239.

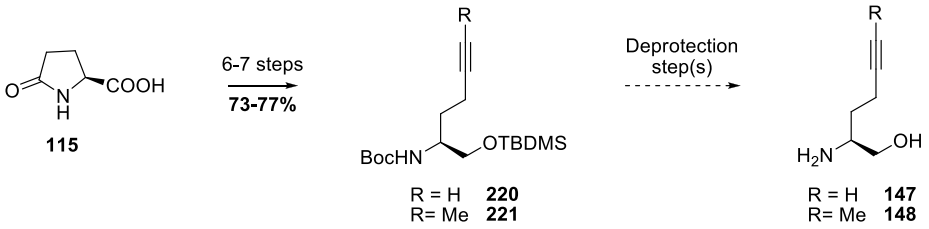
1.3.2.10. Summary and outlook

In this part, a lot of studies were performed to try to obtain the triple bond containing amino alcohols **147** and **148**. After numerous difficulties, in synthesis or isolation, the desired amino alcohols **147** and **148** were obtained respectively in 8 and 9 steps and in 21% and 28% overall yields starting from L-glutamic acid **201** (**Scheme 91**). However, both amino alcohols were only obtained in very small amounts and in a non reproducible manner.



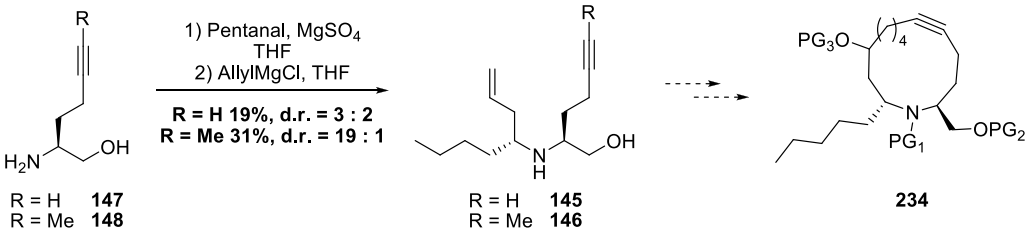
Scheme 91. Synthetic way to amino alcohols 147 and 148 from L-glutamic acid 201.

The last studied synthetic way for obtaining the amino alcohols **147** and **148** could be a new and effective route to obtain these substrates in high yields. Indeed, the compounds **220** and **221** were obtained respectively in 6 and 7 steps and in a 73% and 77% overall yields (see **1.3.2.6** and **Scheme 92**).



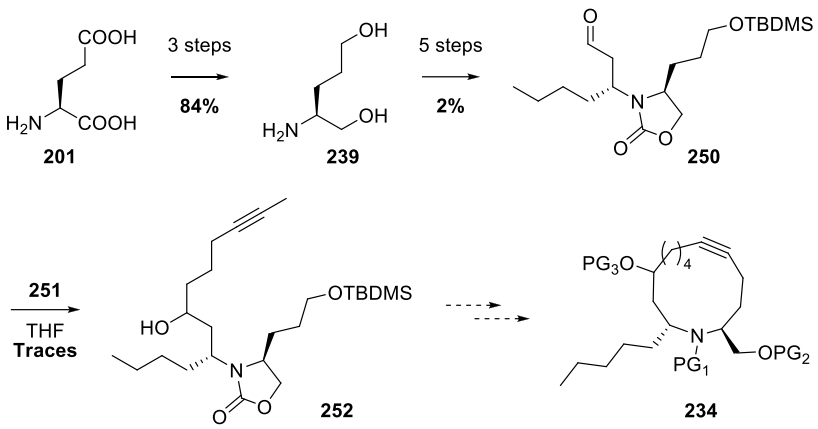
Scheme 92. New optimizable synthetic route to the amino alcohols 147 and 148.

Further studies then focused on the application of the two-step sequence, imine/oxazolidine formation and Grignard addition, on the small quantities of these amino alcohols obtained. The results of this sequence were moderate. Indeed, the substrates **145** and **146** were obtained respectively from **147** and **148** in a 19% and 31% yields (**Scheme 93**). However, the new substrate **146** was obtained with a good diastereoselective ratio of 19 : 1. This diastereoselectivity being encouraging, optimisation studies should be performed to improve the yield of this process and further steps on this synthetic route towards the desired macrocycle **234** should be examined.



Scheme 93. Synthetic way to the macrocycle 234 starting from the amino alcohols 147 and 148.

Separately, an alternative synthetic way was investigated, using the aminodiol **239** as an intermediate on the way to the desired macrocycle **234**. This aminodiol **239** was first obtained in three steps and an 84% overall yield starting from L-glutamic acid **201** (**Scheme 94**). The intermediate **250** was then obtained in five steps and a 2% overall yield. One coupling reaction test between the intermediate **250** and hept-5-ynylmagnesium iodide **251** afforded traces of the compound **252**. This result, quite encouraging, showed the high potential of this synthetic route which should be further developed and optimised on the way to the macrocycle **234**. It should also be possible to study and maybe optimize the diastereoselectivity of the process by testing differently protected intermediates for the two-step sequence, imine/oxazolidine formation and Grignard addition (see **1.3.2.9.4**).

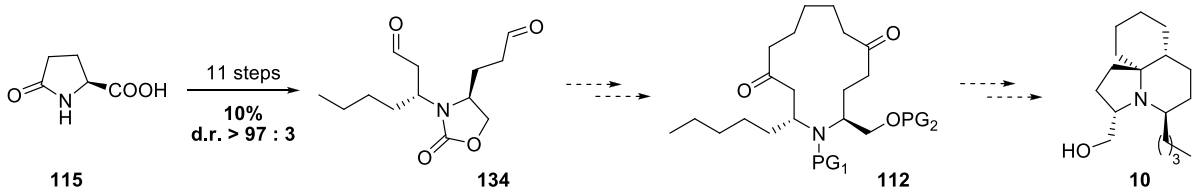


Scheme 94. Synthetic way to the macrocycle 234 through the aminodiol 239.

1.4. Summary and outlook

In the present work, the development of a new synthetic route towards the total syntheses of cylindricines and related natural compounds was examined. Two different routes were studied, both proceeding through a macrocyclic intermediate.

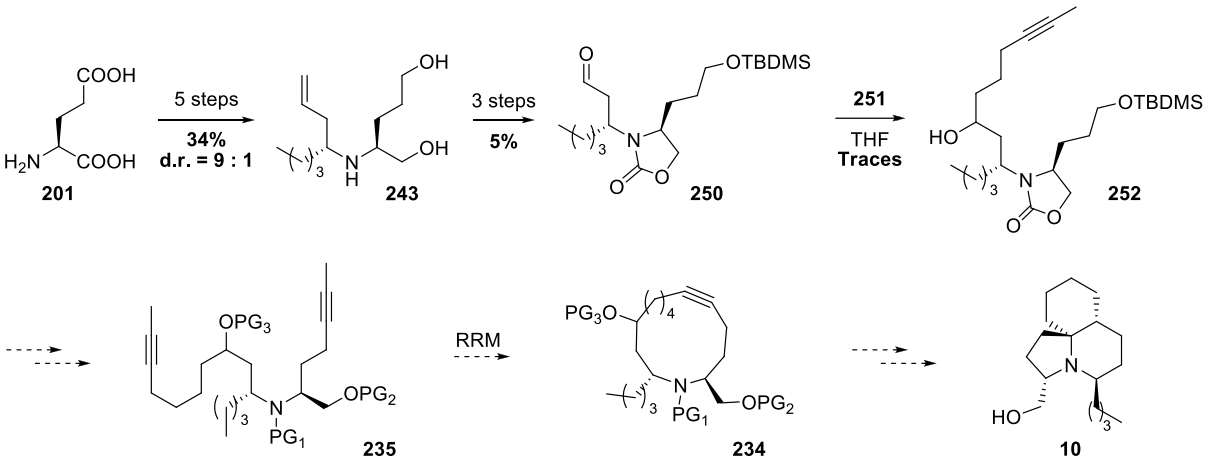
Initially, the synthesis of a macrocyclic diketone **112** as an intermediate was studied (**Scheme 95**). The compound **134** which could be used as a platform for synthetic studies towards the desired macrocycle **112** was obtained in 11 steps and a 10% overall yield from (*S*)-pyroglutamic acid **115**, with a diastereoselectivity exceeding 97 to 3. Several further steps could allow the formation of the macrocyclic diketone **112** on the way to, for example, polycitorol A **10**.



Scheme 95. Synthetic route to polycitorol A 10 through the macrocyclic diketone 112.

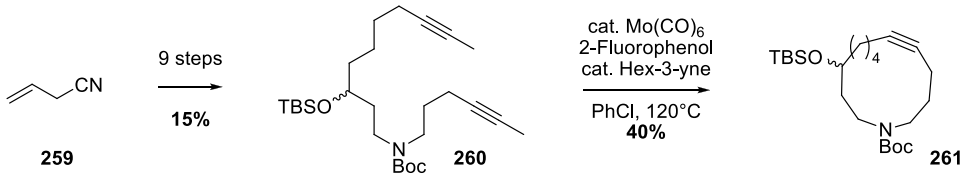
The previously described synthetic route gave encouraging results. However, given the synthesis of the nude cylindricines tricyclic core using a similar concept published by Tanner and co-workers in 2009,[80] a second synthetic way was considered in order to conserve the novelty of our approach for the access to the natural compounds. Therefore, the synthesis of a triple bond containing macrocycle **234** was examined (**Scheme 96**). The compound **243** was first obtained in 5 steps and a 34% overall yield from L-glutamic acid **201**, with a diastereoselectivity of 9 to 1. The intermediate **250** was then synthesised in 3 steps and a 5% overall yield, allowing a test of the coupling reaction with the Grignard reagent **251** which led to traces of the desired compound **252**. The synthesis of the compound **252** could surely be optimised as only one synthetic test was performed. This intermediate **252** could subsequently be converted into the metathesis substrate **235** in a few steps.

The compound **235** could then undergo a ring rearrangement metathesis to afford the desired macrocycle **234**. Several further steps could allow the formation of, for example, polycitorol A **10**.



Scheme 96. Synthetic route to polycitorol A 10 through the macrocyclic intermediate 234.

Such estimates can be supported by the recent studies which were performed in our group by J. Döbler.[175] Indeed, it has been shown that the metathesis substrate **260**, less substituted but similar to the substrate **235**, was able to be transformed into the desired corresponding macrocycle **261** in a 40% yield using ring rearrangement metathesis (**Scheme 97**). This gives an encouraging result for the ring rearrangement metathesis which should be realised on the substrate **235** on the way to the total synthesis of cylindricines and related natural compounds.



Scheme 97. Synthetic route to the macrocyclic intermediate 261 by J. Döbler.

2. Synthetic studies towards 2,5-disubstituted decahydroquinoline alkaloids

2.1. Introduction

In the past forty years, a great number of natural alkaloids containing a decahydroquinoline core were discovered. They were mostly extracted from amphibian skin which already represents the source of a collection of more than eight-hundred compounds from twenty different structural classes of biologically active alkaloids.[176–183] These decahydroquinoline alkaloids, exclusively present as 2,5-disubstituted, are commonly found in neotropical dendrobatig frogs with an occurrence which can attain 50 μg per frog. The skin extracts of Amazonian dendrobatig frogs of the genus *Ameerega*, for example *Ameerega picta* from Bolivia or *Ameerega bilinguis* from Ecuador, were found to be composed predominantly from 2,5-disubstituted decahydroquinoline alkaloids (**Figure 7**).[183]

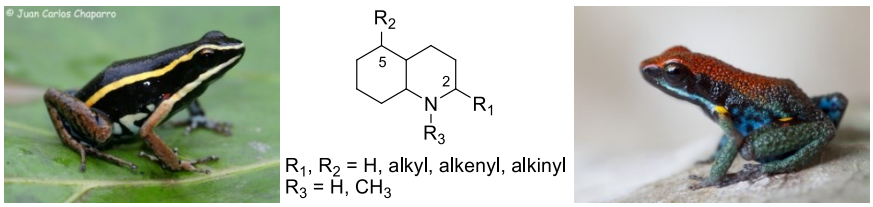


Figure 7. From the left to the right: the neotropical dendrobatig frog *Ameerega picta*,[184] the general form of 2,5-disubstituted decahydroquinolines and the neotropical dendrobatig frog *Ameerega bilinguis*.[185]

The studies on the toxicity of alkaloids containing a decahydroquinoline core are very limited. However, Daly reported that many of these alkaloids might be categorized as noxious or poisonous at high enough dosages and are used by the frogs as chemical defences.[186] Daly and co-workers specified in following studies that several of these compounds could have an activity as non competitive blockers of nicotinic receptors or an antimicrobial function, which may be beneficial to the frogs as it could represent a protection against skin infections.[187,188] Additionally, it could be interesting to note that the presence of a specific class of alkaloids in the skin of a specific frog has been reported to be dependent on its diet.[189]

Presently, more than fifty alkaloids are considered to be part of the 2,5-disubstituted decahydroquinoline class, including in some cases four stereoisomers. In addition to the alkaloids of this class previously reviewed, Daly and co-workers presented in 2009 twelve new compounds representing a new specific sub class, the 2,5-disubstituted *N*-methyldecahydroquinolines.[183] Representative members of the 2,5-disubstituted decahydroquinoline class are the parent member *cis*-**195A** former named Pumiliotoxin C, *cis* and *trans*-**243A** or the *N*-methylated *cis* and *trans*-**257A** (**Figure 8**). The isolation of these compounds and their first structural determination were reported by Daly and co-workers in 1968, 1986 and 2009, respectively.[176,179,183] The code designation for such alkaloids was first introduced in 1978 and consists of the nominal molecular weight and an identifying letter, both in bold face.[190]

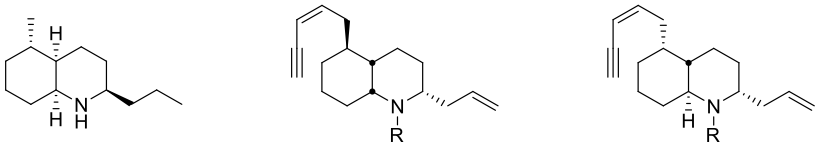


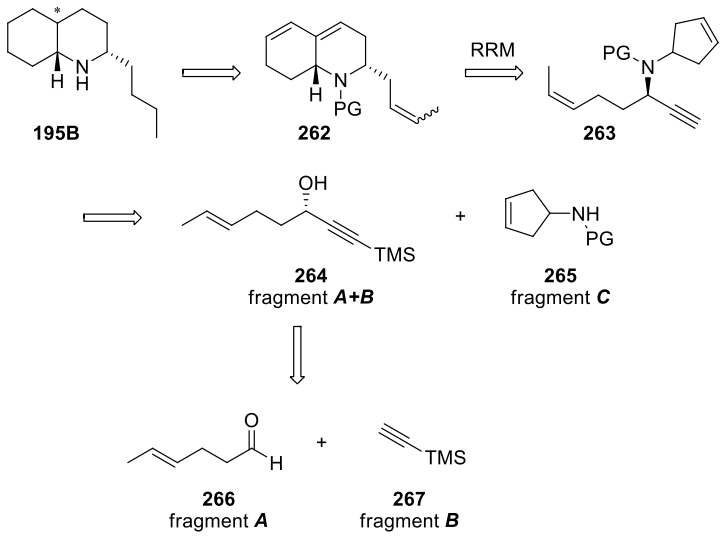
Figure 8. Representative members of the 2,5-disubstituted decahydroquinoline class.

Daly and co-workers presented reviews, regularly updated, containing structures, tentative structures and possible gross structures for the majority of amphibian skin alkaloids.[190–192]

2.2. Synthetic concepts and motivation

2.2.1. Background

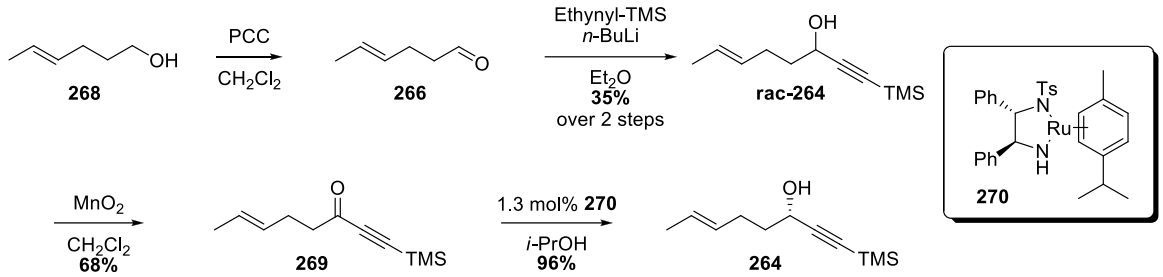
In 2010, Torsten Eichhorn presented in his PhD studies the total synthesis of the 2-substituted decahydroquinoline alkaloid **195B**, using ring rearrangement metathesis (RRM) as a key step (**Scheme 98**).[193] He initially proposed that the desired alkaloid **195B** could be derived from the bicyclic intermediate **262** using a hydrogenation reaction. The hexahydroquinoline **262** could be obtained from a ring rearrangement metathesis on the substrate **263**. The metathesis precursor could be synthesised starting from the enantiopure alcohol **264** and the cyclopentenamine derivate **265** through a Mitsunobu reaction. The alcohol **264** could be formerly obtained from the aldehyde **266** and the alkyne **267**.



Scheme 98. Retrosynthetic analysis for the synthesis of the alkaloid 195B by T. Eichhorn.

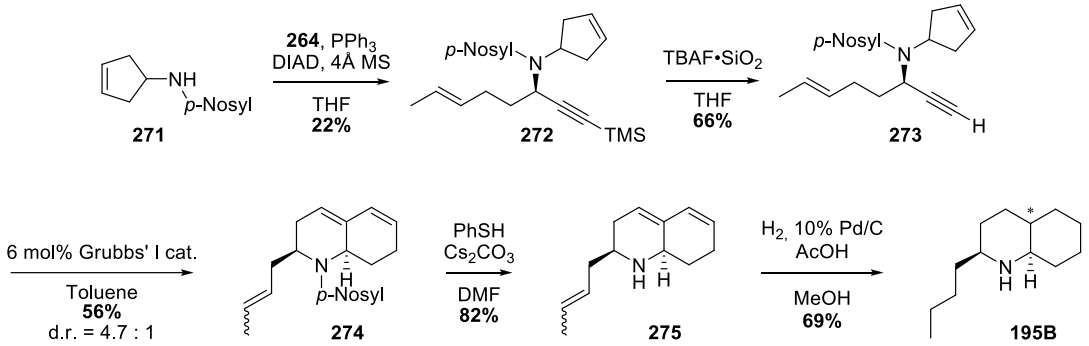
The compounds **266**, **267**, **264** and **265** and modifications on each of them were examined in this work. Therefore, for simplified analogies, these fragments are referred respectively as fragments ***A***, ***B***, ***A+B*** and ***C***.

The reported total synthesis from T. Eichhorn started from the alcohol **268**, which was first oxidized to give the aldehyde **266** (**Scheme 99**). After treatment of ethynyltrimethylsilane **267** with *n*-butyllithium, the aldehyde **266** was added to the mixture, affording the desired racemic propargylic alcohol **rac-264** in a 35% yield over two steps. The racemic alcohol **rac-264** was then oxidized to give the corresponding ketone **269** in a 68% yield. Afterwards, **269** underwent an enantioselective hydrogenation using the Noyori catalyst **270** to lead to the desired enantiopure alcohol **264**.



Scheme 99. Total synthesis of alkaloid 195B by T. Eichhorn, synthesis of the intermediate 264.

A Mitsunobu reaction between the alcohol **264** and the *p*-nosylamide **271**, prepared in six steps from cyclopentadiene, afforded the intermediate **272** in a moderate 22% yield (**Scheme 100**). The trimethylsilyl group was then removed using tetrabutylammonium fluoride supported on silica, giving the metathesis precursor **273** in a 66% yield. The ring rearrangement metathesis of the substrate **273** was examined under various conditions and the best results for selectivity and yield were obtained using first generation Grubbs catalyst in toluene. In these conditions, the desired hexahydroquinoline **274** was obtained in a 56% yield and with a high diastereoselectivity (d.r. = 4.7 : 1). The subsequent removal of the *p*-nosyl-protecting group led to the intermediate **275** which was successfully hydrogenated to afford the alkaloid **195B**.

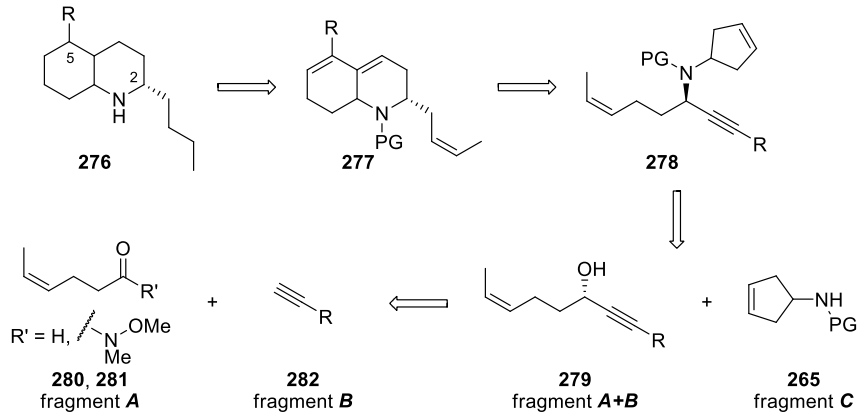


Scheme 100. Total synthesis of alkaloid 195B by T. Eichhorn.

The developed method is a new powerful tool for the total synthesis of decahydroquinoline alkaloids. As presented in this section, it already allowed the total synthesis of the 2-substituted decahydroquinoline alkaloid **195B** with a pretty good diastereoselectivity. However, the overall yield was quite low, around 1% although the synthesis counted only nine steps, letting open the possibility of an optimisation of the method and an eventual broadening to the syntheses of further decahydroquinoline alkaloids. For economical reason and as it should not disturb the process, our studies on fragment ***A*** started with *cis*-hexen-4-ol whereas T. Eichhorn used *trans*-hexen-4-ol. Moreover, S. Schmitt proved in a parallel study that the presence of a trans-substituted double bond should have a positive influence on the ring rearrangement metathesis.[194]

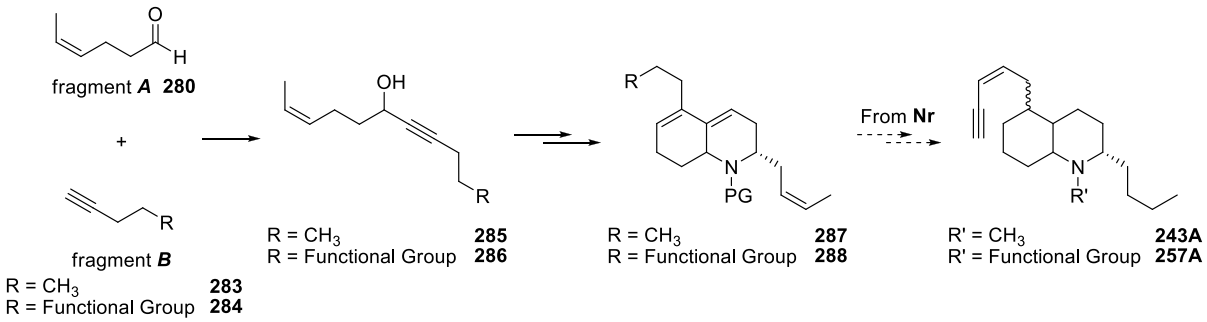
2.2.2. Motivation and objectives

In the presented work, investigations were carried out to optimize the previously presented concept and apply it more generally to the total synthesis of 2,5-disubstituted decahydroquinoline alkaloids. Indeed, considering and slightly modifying the retrosynthetic analysis proposed by T. Eichhorn, it could be possible to introduce new substituents by using differently substituted new fragments ***A***, ***B*** or ***C***. In the considered case of interest, the synthesis of 2,5-disubstituted decahydroquinoline alkaloids, it could be possible to insert the new substitution when using a substituted triple bond as fragment ***B*** (**Scheme 101**). It could also be interesting to study different fragments ***A*** for the coupling reaction with the fragments ***B*** to try to improve the process by using fragments presenting different reactivity properties.



Scheme 101. Retrosynthetic analysis for the synthesis of 2,5-disubstituted decahydroquinolines.

The assumption that it could be possible to insert a substituent at the C5 position results from a unique and successful try of this method by T. Eichhorn. Starting from the aldehyde **280** as the fragment ***A*** and pent-1-yne **283** as the fragment ***B***, he first synthesised the propargylic alcohol **285** (**Scheme 102**). The desired hexahydroquinoline **287** was then successfully obtained after a ring rearrangement metathesis on the substrate **285**. Therefore, it could be interesting to develop different metathesis precursors which could contain a functionalized substituting chain at the triple bond, allowing the access to alkaloids like, for example, **243A** and by extension **257A**.

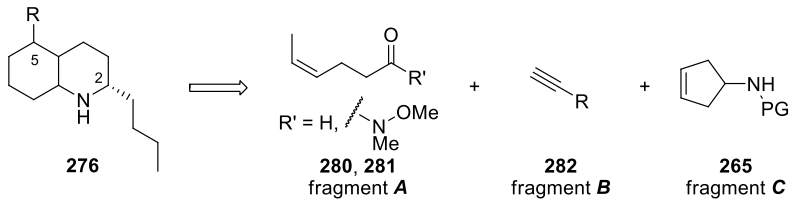


Scheme 102. Synthetic study on the way to 2,5-disustituted decahydroquinolines.

Given these promising results, the main focuses of this project were first to optimize the synthesis of the known metathesis substrates and secondly to develop new precursors, more functionalized, allowing the access to a broader range of alkaloids.

2.3. Results and discussion

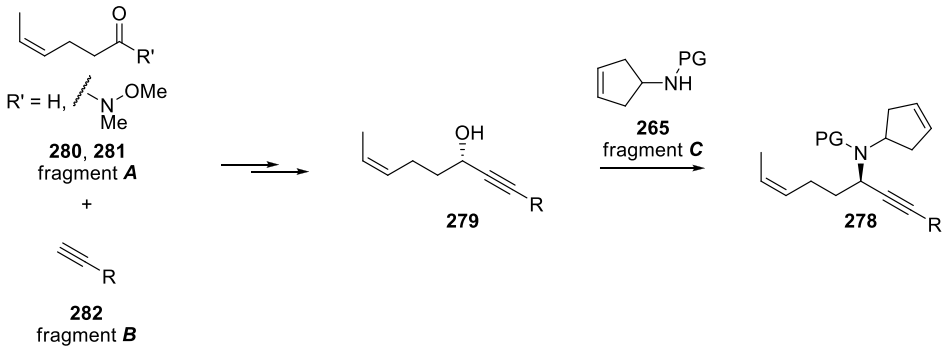
According to the objectives previously defined for this project, optimisation of the existing concept and its generalisation were studied and are presented in the remainder of this section. Most of this work was focusing on optimising the syntheses of fragments ***A*** and ***C*** and on developing and synthesising various functionalized fragments ***B*** (**Scheme 103**).



Scheme 103. Reminder presentation of fragments *A*, *B* and *C*.

Numerous modifications on each of these three fragments could be considered to broaden the range of target natural products which may be synthesised. However, limited modifications were operated on fragments ***A*** and ***C***. This work was more focused on the fragment ***B*** and consequently on the possibility to obtain 2,5-disubstituted decahydroquinoline with a flexible substituent at the C5 position.

Following the concept developed by T. Eichhorn, the reaction between fragments ***A*** and ***B*** to obtain, after few additional steps, enantiopure fragments ***A+B*** was examined (**Scheme 104**). The subsequent Mitsunobu reaction between the obtained fragments ***A+B*** and fragments ***C*** was also investigated.



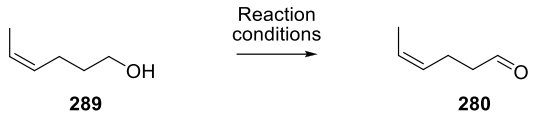
Scheme 104. Synthetic way to the metathesis precursor 278 from fragments *A*, *B* and *C*.

2.3.1. Synthetic studies on fragments *A*

In his PhD work, T. Eichhorn reported difficulties in the transformation of *cis*-4-hexen-1-ol **289** in the corresponding aldehyde **280** due to a complicated isolation process leading to the loss of an important amount of product.[193] Testing the oxidation of the alcohol **289** following his conditions, using pyridinium chlorochromate, led to the same result. As it was expected, *cis*-4-hexenal **280** was only obtained in a 60% yield due to isolation difficulties (**Table 23**, **Entry 1**). Several other reaction conditions were then examined to perform this oxidation. Despite the observation of rapid formation

of the aldehyde **280**, oxidation using TEMPO and trichloroisocyanuric acid in dichloromethane did not lead to a complete conversion (**Table 23**, **Entry 2**). Reactions using activated dimethyl sulfoxide gave better results. Indeed, when using the Swern conditions, the desired product **280** was isolated in a good 75% yield (**Table 23**, **Entry 3**).[195–197] Examining variations of the Swern conditions, **280** was obtained in an 87% yield using a modified Onodera procedure (**Table 23**, **Entry 4**),[198,199] and in a quantitative way using the Parikh-Doering procedure (**Table 23**, **Entry 5**).[200,201]

Table 23. Results of the oxidation of *cis*-4-hexen-1-ol 289 in *cis*-4-hexenal 280.



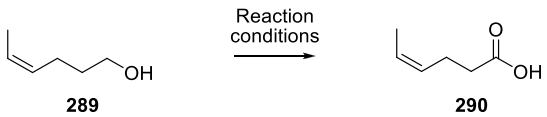
289 **280**

Entry	Reaction conditions	Yield
1	PCC, CH_2Cl_2	60%
2	TEMPO, Trichloroisocyanuric acid, CH_2Cl_2	No yield (reaction never completed)
3	1) Oxalylchloride, DMSO, CH_2Cl_2 2) Et_3N	75%
4	DMSO, P_2O_5, Et_3N, CH_2Cl_2	87 %
5	DMSO, Py•SO_3, Et_3N, CH_2Cl_2	Quantitative

To be able to perform some reactivity studies on the subsequent coupling reaction between fragments ***A*** and ***B***, another fragment ***A*** was synthesised. As a more reactive compound could undoubtedly be interesting, the Weinreb amide of *cis*-4-hexenoic acid **290** was prepared.

To begin with, the oxidation of *cis*-4-hexen-1-ol **289** in *cis*-4-hexenoic acid **290** was examined. The first test was conducted using Jones reagent and yielded the desired acid in a 76% yield (**Table 24**, **Entry 1**).[202,203] Two further tries using three and five equivalents of pyridinium dichromate in dimethylformamide led to the product in a 97% yield and quantitatively, respectively (**Table 24**, **Entries 2 and 3**), optimizing significantly the process.[204,205]

Table 24. Results of the oxidation of *cis*-4-hexen-1-ol 289 in *cis*-4-hexenoic acid 290.

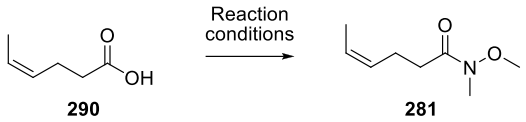


289 **290**

Entry	Reaction conditions	Yield
1	CrO_3, H_2SO_4, H_2O, Acetone (Jones reagent)	76%
2	3 eq PDC, DMF	97%
3	5 eq PDC, DMF	Quantitative

In the next step, *cis*-4-hexenoic acid **290** was converted into the corresponding *N*-methoxy-*N*-methylamide **281**. The acid **290** was first treated with oxalyl chloride to obtain the corresponding acyl chloride. Afterwards, the general procedure from Weinreb and Rahm for Weinreb amide formation was used, affording the desired product **281** in a very moderate 36% yield (**Table 25**, **Entry 1**).[206] Treating *cis*-4-hexenoic acid **290** with *N*,*O*-dimethylhydroxylamine and a peptide coupling agent, *N*,*N'*-dicyclohexylcarbodiimide, led to the product **281** in a 43% yield (**Table 25**, **Entry 2**). The best yield was obtained using another amidation procedure described by Weinreb and co-workers (**Table 25**, **Entry 3**).[207] The desired Weinreb amide **281** was then obtained in a 60% yield.

Table 25. Results of the formation of the Weinreb amide of *cis*-4-hexenoic Acid 281.



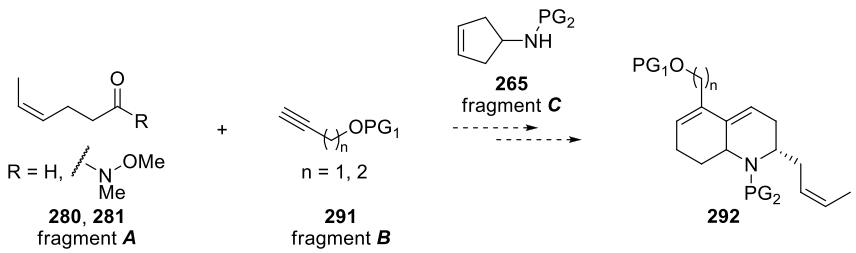
290 **281**

Entry	Reaction conditions	Yield
1	1) $(COCl)_2$, CH_2Cl_2 2) *N*,*O*-dimethylhydroxylamine hydrochloride, Pyridine, CH_2Cl_2	36%
2	*N*,*O*-dimethylhydroxylamine hydrochloride, Et_3N, DCC, CH_2Cl_2	43%
3	*N*,*O*-dimethylhydroxylamine hydrochloride, $AlMe_3$, CH_2Cl_2	60%

In summary, improvements have been achieved in the synthesis and chemical reactivity of the fragment ***A***. Indeed, not only 4-hexenal earlier obtained in a 60% yield was afforded quantitatively but also the corresponding Weinreb amide **281** was synthesised, providing a more powerful alkylating agent for the subsequent coupling with different fragments ***B***.

2.3.2. Synthetic studies on various fragments *B*

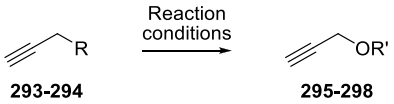
As it was detailed in the motivations and objectives of this work (see **2.2.2**), one of the most important point was to develop functionalized fragments ***B*** to be able to obtain flexible 2,5-disubstituted hexahydroquinolines **292** after ring rearrangement metathesis. This kind of intermediates could be an interesting platform on the way to the synthesis of numerous 2,5-disubstituted decahydroquinoline alkaloids (**Scheme 105**). In this work, different protected prop-2-yn-1-ol and but-3-yn-1-ol from the form **291** were considered as they may not only provide a flexibility of the substituent at C5 position but also allow a first study on the effects of the different protecting groups and of the chain length on the ring rearrangement metathesis efficacy and selectivity.



Scheme 105. From fragments *A* and *B* to the product of ring rearrangement metathesis.

Starting from prop-2-yn-1-ol **293**, the corresponding *tert*-butyldimethylsilyl, 2-tetrahydropyranyl and benzyl-protected compounds **295**, **296** and **297** were synthesised using common procedures and obtained in 98%, 49% and 60% yields, respectively (**Table 26**, **Entries 1-3**). For the preparation of 3-methoxy-1-propyne **298**, the used procedure starting from 3-bromoprop-1-yne **294** only partially processed and gave the product along with a non-negligible amount of starting material (**Table 26**, **Entry 4**).

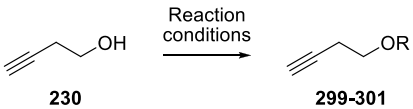
Table 26. Syntheses of protected prop-2-yn-1-ol.



Entry	-R	Reactant	Reaction conditions	-R'	Product	Yield
1	-OH	**293**	TBDMSCl, Imidazole, DMF	-TBDMS	**295**	98%
2	-OH	**293**	DHP, *p*TSA•H_2O, CH_2Cl_2	-THP	**296**	49%
3	-OH	**293**	NaH, BnBr, Et_2O	-Bn	**297**	60%
4	-Br	**294**	NaH, MeOH, THF	-Me	**298**	38% (84% brsm)

Similarly, starting from but-3-yn-1-ol **230**, the corresponding *tert*-butyldimethylsilyl, 2-tetrahydropyranyl and benzyl-protected compounds **299**, **300** and **301** were synthesised using common procedures and obtained in 99%, 56% and 98% yields, respectively (**Table 27**, **Entries 1-3**).

Table 27. Syntheses of protected but-3-yn-1-ol.



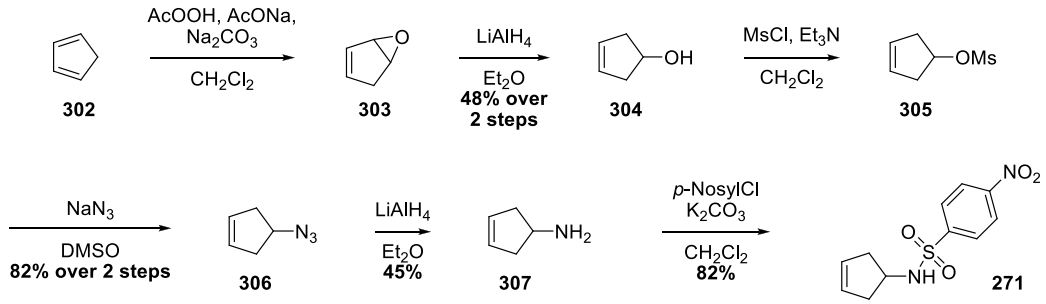
Entry	-OR	Reactant	Reaction conditions	Product	Yield
1	-OTBDMS	**230**	TBDMSCl, Imidazole, CH_2Cl_2	**299**	99%
2	-OTHP	**230**	DHP, *p*TSA•H_2O, CH_2Cl_2	**300**	56%
3	-OBn	**230**	NaH, BnBr, CH_2Cl_2	**301**	98%

Further optimisation studies on these syntheses were not performed at this stage as the quantities and panel of obtained compounds already allowed a diversity synthetic study for the subsequent steps.

2.3.3. Synthetic studies on fragment *C*

As some parts of the concept examined in this section had already been studied in the Blechert group, several tendencies were clearly defined. One of these involved the fragment ***C***, on which variations had been examined, in particular by T. Eichhorn and S. Schmitt, to know the possible effects on the subsequent Mitsunobu reaction between fragments ***A+B*** and ***C*** and on the ring rearrangement metathesis.[193,194] In these previous studies, the *p*-nosyl-protected cyclopent-3-enamine **271** was found to be the best fragment ***C*** for its behaviour in both Mitsunobu reaction and ring rearrangement metathesis. In addition, a multi-gram scale synthesis of the compound **271** had been developed by J. Neidhöfer.[208]

Initially, the protected cyclopent-3-enamine **271** was synthesised following the synthetic way developed by J. Neidhöfer. Using a procedure reported by Crandall and co-workers,[209] freshly cracked cyclopentadiene **302** was epoxidized and the resulting epoxide **303** was directly reduced to give the homoallylic alcohol **304** in a 48% yield over two steps (**Scheme 106**). The alcohol **304** was then mesylated and the corresponding mesylate **305** underwent an azidation to afford the azide **306** in an 82% yield over two steps. The reduction of the azide **306** led to the amine **307** in a 45% yield. Finally, the subsequent treatment of the amine **307** with *p*-nosylchloride in basic conditions afforded the desired *N*-(cyclopent-3-enyl)-4-nitrobenzenesulfonamide **271** in an 82% yield.

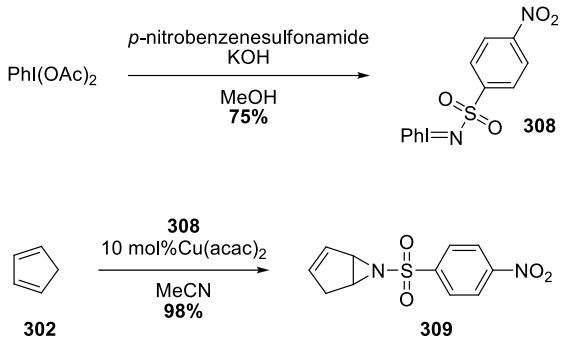


Scheme 106. Synthesis of 271 starting from cyclopentadiene 302.

This synthetic way is particularly convenient because it is applicable to multi-gram scale. However, the desired protected cyclopentenamine **271** was obtained in six steps and in a moderate 15% yield. From these results came the idea of developing a new, more effective, synthetic way to this intermediate.

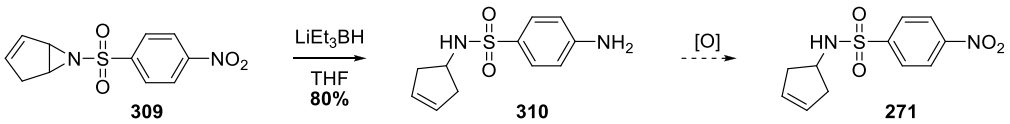
Following a strategy developed by Knight and Muldowney[210] and using the later improved procedure reported by O'Brien and co-workers for the monoaziridination of dienes,[211] cyclopentadiene **302** was engaged with (*N*-(*p*-nitrobenzenesulfonyl)imino)phenyliodinane **308** in the presence of 10 mol% copper(II) acetylacetonate to afford the aziridine **309** in a 98% yield (**Scheme 107**). The nitrenoid

precursor **308** was formerly freshly prepared from *p*-nitrobenzenesulfonamide and iodobenzene diacetate according to a procedure from Hutchings and co-workers.[212]



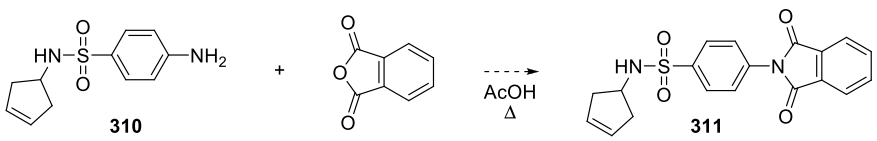
Scheme 107. Synthesis of the intermediate 309 using Knight and Muldowney's strategy.

As it would have been expected, nitro-groups being near the top of the list of reactivity towards hydrides, the subsequent opening of the aziridine using the conditions described by Knight and Muldowney did not lead to the desired compound **271** but to the amine **310**, because of a simultaneous reduction of the nitro-function of the nosyl-group (**Scheme 108**). Given the reactivity properties of the nitro-group, it could be difficult even impossible, to find aziridine opening conditions which would not affect the nosyl group. However, it is interesting to notice that in the performed test of aziridine opening using lithium triethylborohydride, the amine **310** was exclusively obtained and in a good 80% yield. Considering this result, we could think about oxidizing again this intermediate **310** to get the desired nosyl-protected compound **271**. The synthetic way to **271** could still be more competitive than the previously used procedure. The selected oxidation method should only be selective and not affect the double bond. Such procedures were already reported, for example using sodium perborate as described by McKillop and Tarbin for selective oxidation of substituted anilines.[213]



Scheme 108. Proposed new synthetic way to 271.

Another interesting possibility could be the development of a fragment ***C*** bearing a new protecting group, starting from the amine **310**. Condensing for example **310** with phthalic anhydride in acetic acid, following the procedure developed by Santos and co-workers,[214] would lead to the compound **311** (**Scheme 109**). This compound could allow a study of the effects of steric hindrance or of the difference between electron-withdrawing characters of the nitro group and the phtalimide derivate on the following Mitsunobu reaction and ring rearrangement metathesis.



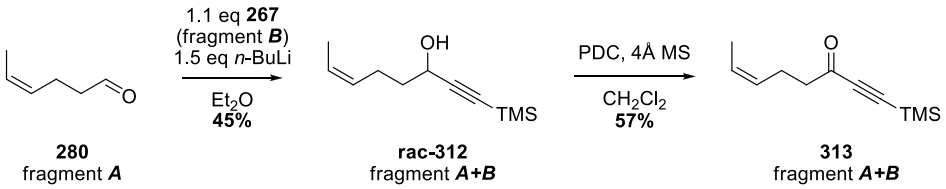
Scheme 109. Proposed condensation reaction between 310 and phthalic anhydride.

In the case of this work, due to the limited time dedicated to this project, the fragment ***C* 271** was synthesised using the procedure previously developed in Blechert group and further studies were not performed on the new presented way of synthesis. However, completing the development and optimisation of this proposed new synthetic way may give a powerful, way more competitive, synthesis of the desired *p*-nosyl-protected amine **271**. In addition, obtaining the amine **310** opens new possibilities, as it could be used as a platform on the way to the synthesis of new fragments ***C***.

2.3.4. Synthetic studies on the coupling of fragments *A* and *B*

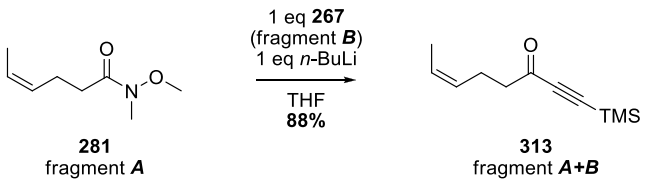
In the following section, studies were performed on the coupling reactions of fragments ***A*** and ***B***. The synthesis of the intermediate **313** was first optimised and the new synthetic procedure was then applied to newly developed substrates to afford the desired functionalized fragments ***A+B***.

The desired ketone **313** was first synthesised following the procedure reported by T. Eichhorn (**Scheme 110**).[193] The addition of ethynyltrimethylsilane **267** to *cis*-hex-4-enal **280** afforded the racemic alcohol **rac-312** in a 45% yield. The alcohol **rac-312** was then oxidized to give the corresponding ketone **313** in a 57% yield. As *cis*-hex-4-enal **280** was previously obtained quantitatively from *cis*-hex-4-en-1-ol **289**, this method led to the desired ketone **313** in three steps and a 26% overall yield from *cis*-hex-4-en-1-ol **289**.



Scheme 110. Synthesis of 313 following T. Eichhorn's procedure.

The addition of ethynyltrimethylsilane **267** to the Weinreb amide **281** afforded the same desired ketone **313** in only one step and in an 88% yield (**Scheme 111**). As the Weinreb amide **281** was obtained in two steps and 60% yield from *cis*-hex-4-en-1-ol **289**, the newly developed method led to **313** in three steps and a 53% overall yield from *cis*-hex-4-en-1-ol **289**, improving the previous method.

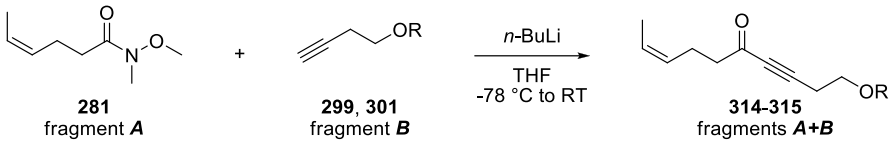


Scheme 111. New developed synthesis of 313 starting from the Weinreb amide 281.

Given the hopeful results previously obtained, the same method was used for the coupling reaction of the Weinreb amide **281** and fragments ***B*** containing a functionalized substituent. Following a protocol developed by Tanner and co-workers,[215] 2 equivalents of the fragment ***B* 299** and 2.2 equivalents of *n*-butyllithium were used, affording the desired fragment ***A+B* 314** in a moderate 48% yield due to a very difficult separation of the product **314** and the remaining excess of fragment ***B***

299 (**Table 28**, **Entry 1**). To avoid this purification problem, the reaction was then performed with only 1 equivalent of the fragment ***B*** **299** and 1.1 equivalents of *n*-butyllithium, giving the desired product **314** in a 92% yield (**Table 28**, **Entry 2**). The same method was then used with the fragment ***B*** **301** and led to the desired fragment ***A+B*** **315** in an 82% yield (**Table 28**, **Entry 3**).

Table 28. Synthetic studies on the way to new fragments *A+B*.



281
fragment ***A***

299, **301**
fragment ***B***

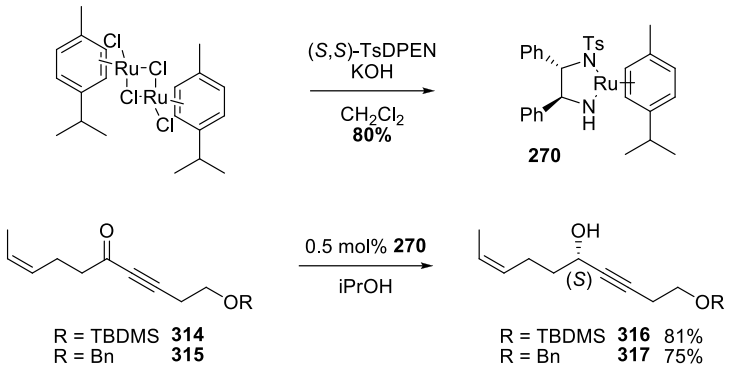
314-315
fragments ***A+B***

Entry	-R	Reactant ***B***	Eq ***B***	Eq *n*-BuLi	Product	Yield
1	-TBDMS	**299**	2	2.2	**314**	48%
2	-TBDMS	**299**	1	1.1	**314**	92%
3	-Bn	**301**	1	1.1	**315**	82%

The synthesis of the fragment ***A+B*** **313** was optimised by using a Weinreb amide instead of an aldehyde as fragment ***A*** in the coupling reaction with fragment ***B***. This method was further used for the synthesis of new fragments ***A+B***, containing a functionalized substituent at the triple bond, which could be used for studies towards the synthesis of 2,5-disubstituted decahydroquinolines. In the case of this work, due to the limited time dedicated to this project, only fragments ***A+B*** **314** and **315** were synthesised and used for further studies. Using the same procedure and the other fragments ***B*** obtained in this work, it could be possible to synthesise a broader range of fragments ***A+B***. Obtaining such compounds may allow a more complete study of the effects on the following steps of the type of functionalization and chain length of the substituent at the triple bond.

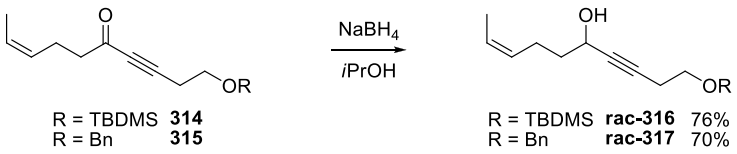
2.3.5. Studies on the enantioselective reduction of fragments *A+B*

In the next step, the enantioselective reduction of the obtained keto-fragments ***A+B***, **314** and **315**, was studied. Following concepts developed by Noyori and co-workers[216,217] and a procedure reported by Denmark and co-workers,[218] the requisite catalyst **270** was first prepared using dichloro(*p*-cymene)ruthenium(II) dimer and (*S*,*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine (**Scheme 112**). Afterwards, the ketones **314** and **315** were reduced using 0.5 mol% of the catalyst **270**, affording the corresponding alcohols **316** and **317** in 81% and 75% yields, respectively.



Scheme 112. Enantioselective reduction of keto-fragments *A+B*.

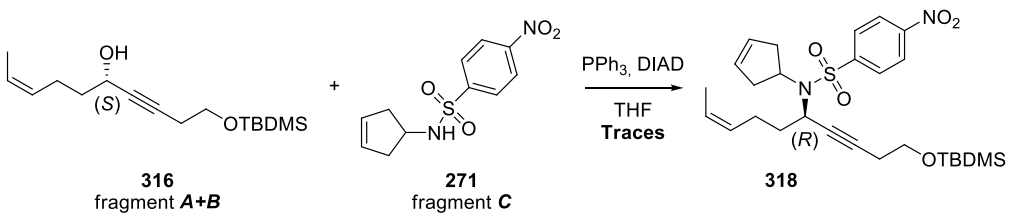
To determine the enantiomeric excess of the obtained alcohols **316** and **317** per HPLC analysis, small amounts of ketones **314** and **315** were also reduced using sodium borohydride in *iso*-propanol, leading to racemic alcohols **rac-316** and **rac-317** in 76% and 70% yields, respectively (**Scheme 113**). However, due to the impossibility to find separation conditions for chiral HPLC, the enantiomeric excess of the products were not determined at this stage and the compounds were engaged in the following step.



Scheme 113. Synthesis of the racemic alcohols rac-316 and rac-317.

2.3.6. Synthetic studies on the Mitsunobu reaction between fragments *A+B* and *C*

In the following step of the synthesis, the previously obtained enantioselectively reduced fragment ***A+B* 316** was engaged in a Mitsunobu reaction with a fragment ***C***. A test was performed using fragment ***A+B* 316** and fragment ***C* 271** and following a general procedure with triphenylphosphine and di*iso*-propyl azodicarboxylate in tetrahydrofuran (**Scheme 114**). The reaction did not afford the desired product **318** as only traces of it were identified using mass spectroscopy and starting materials were nearly fully recovered.



Scheme 114. Mitsunobu reaction between 316 and 271.

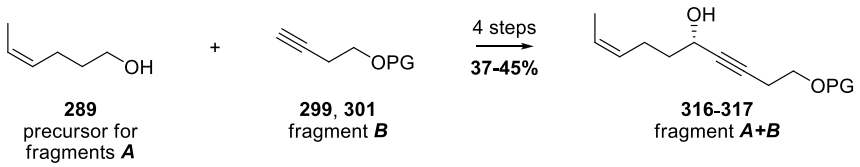
The synthesis of the ring rearrangement metathesis precursor **318** using a Mitsunobu reaction between fragments ***A+B* 316** and fragment ***C* 271** has not been successful yet, but only one test was

performed. Therefore, all the possibilities remain opened for an optimisation of the conditions and substrates used for this reaction.

2.4. Summary and outlook

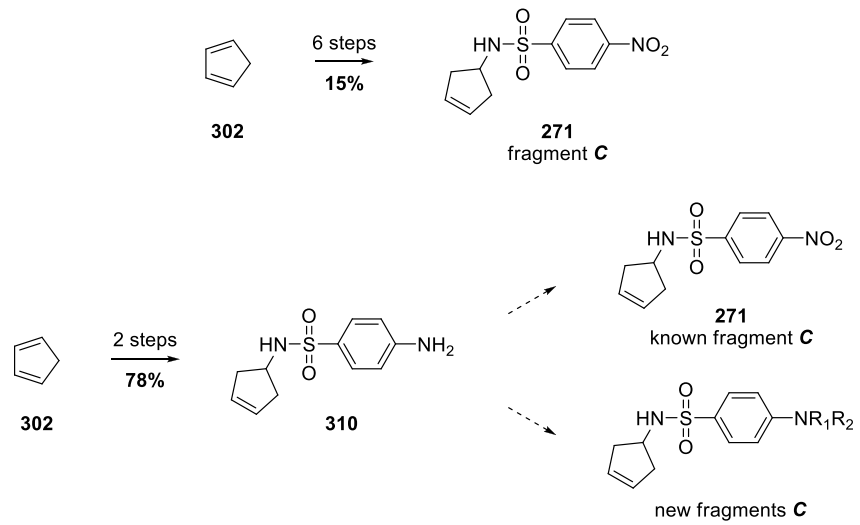
In the present work, synthetic optimisations and modifications on the precursors of the reported total synthesis of 2-substituted decahydroquinoline alkaloid *cis*-**195B** were performed. Our studies led to a partial improvement of the known synthesis and to the development of newly functionalized precursors, which could allow a generalisation of the known method for the synthesis of 2,5-disubstituted decahydroquinolines.

After the synthesis of reported precursor **313** was optimised by the use of a Weinreb amide as fragment ***A*** instead of an aldehyde, the overall yield of the three-step synthesis of the ketone **313** was improved from 26% to 53%. Given this good result, the same method was used for couplings of the Weinreb amide **281** with different fragments ***B***, containing a functionalized chain (**Scheme 105**, **Scheme 106**). After enantioselective reduction of the obtained products, the new fragments ***A+B*** **316**-**317** containing a newly substituted triple bond were afforded in 37% to 45% yields from *cis*-hex-4-en-1-ol **289** (**Scheme 115**). Various fragments ***B*** were obtained; this may allow a more complete study of the effects on the following steps of the substitution type at the triple bond.



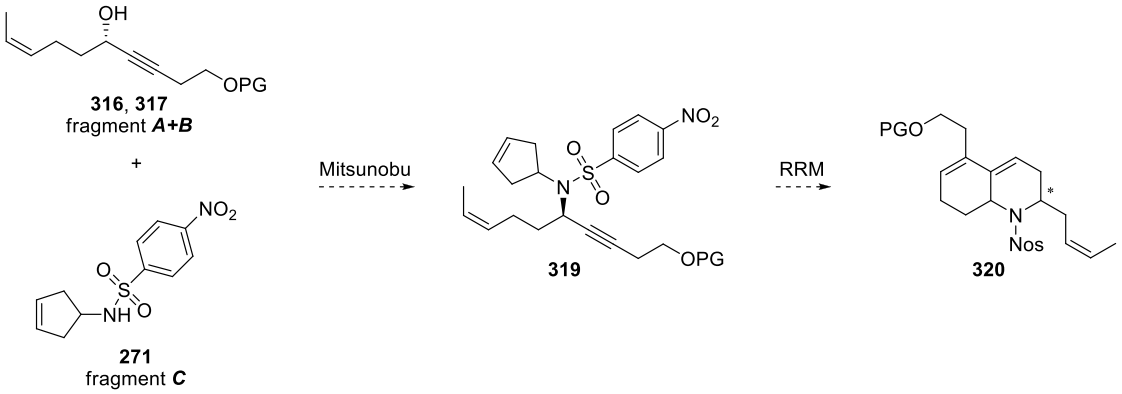
Scheme 115. Synthetic route to the fragments *A+B*.

Fragment ***C*** **271** was obtained in six steps from cyclopentadiene **302**, in a 15% overall yield (**Scheme 116**). A new synthetic way to differently protected fragments ***C*** was also partially developed, giving the intermediate **310** in two steps from cyclopentadiene in a 78% yield. The amine **310** could either allow a drastic optimisation of the synthesis of **271** or be a platform for the development of new fragments ***C***, with differently substituted amines. Obtaining such compounds may allow a synthetic study on several steric and electronic effects on the Mitsunobu reaction or on the ring rearrangement metathesis.



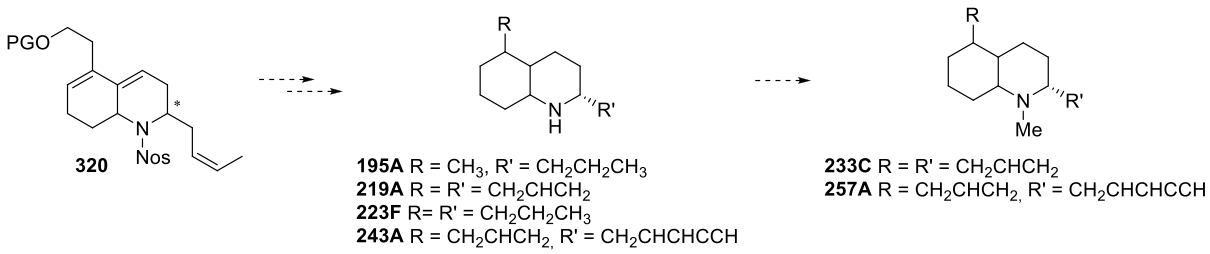
Scheme 116. Syntheses of fragments *A+B* and *C*.

The following steps had hardly been examined in the present work but we could already see that, given the first good results in the development of the new precursors, this method could be a very powerful new tool on the way to 2,5-disubstituted decahydroquinolines. From the obtained fragments ***A+B*** and ***C***, a Mitsunobu reaction followed by a ring rearrangement metathesis could lead to the 2,5-disubstituted hexahydroquinoline of the general form **320** (**Scheme 117**).



Scheme 117. From fragments *A+B* and *C* to the hexahydroquinoline 320.

The hexahydroquinoline intermediate **320** could then surely be a platform for the access to numerous 2,5-substituted decahydroquinoline alkaloids, *inter alia* **195A**, **219A**, **223F** or **243A** and obviously to several corresponding *N*-methylated alkaloids as **233C** or **257A** (**Scheme 118**).



Scheme 118. From the hexahydroquinoline intermediate 320 to 2,5-disubstituted decahydroquinolines alkaloids.

3. Experimental section

3.1. General methods and materials

For an improved information, all the analyses performed on the molecules used in this work are presented in an exhaustive manner.

^{1}H-NMR spectra were recorded on a spectrometer AV 400 (400.1 MHz), DRX 500 (500.1 MHz) or AV III (500.1 MHz) from the company *Bruker*. The solvent used is given for each molecule and if nothing different is specified, spectra were measured at 298.15 K. Deuterated benzene (C_6D_6), chloroform ($CDCl_3$), methanol (CD_3OD) and DMSO (DMSO-d_6) were used as solvents and internal standards. Chemical shifts δ are expressed in parts per million (ppm), without dimension, with a 0.01 precision and relative to the external standard TMS. Spectra were calibrated by setting the residual solvent signal according to its literature value.[219] For each determined peak, number of protons, multiplicity, coupling constants *J* in [Hz] and assignment of the specified protons to the structure are given. For the multiplicity, the following abbreviations and their suitable combinations are used: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), septet (sept), octet (oct), multiplet (m) and broad (b).

^{13}C-NMR spectra were recorded on a spectrometer AV 400 (100.6 MHz), DRX 500 (125.8 MHz) or AV III (125.8 MHz) from the company *Bruker*. The solvent used is given for each molecule and all spectra were measured at 298.15 K. Deuterated benzene (C_6D_6), chloroform ($CDCl_3$), methanol (CD_3OD) and DMSO (DMSO-d_6) were used as solvents and internal standards. Spectra were recorded proton decoupled. Chemical shifts δ are expressed in parts per million (ppm), without dimension, with a 0.1 precision and relative to the external standard TMS. Spectra were calibrated by setting the residual solvent signal according to its literature value.[219] The number of protons attached was determined using DEPT or APT and is given for each carbon. For quaternary carbons, the abbreviation C_q is used.

^{31}P-NMR spectra were recorded on a spectrometer AV III (212.6 MHz) from the company *Bruker*. Spectra were measured in chloroform ($CDCl_3$) at 298.15 K. Chemical shifts δ are expressed in parts per million (ppm), without dimension, with a 0.1 precision and relative to the external standard H_3PO_4.

2D-NMR spectra were recorded on a spectrometer AV 400 or AV III from the company *Bruker*. COSY (Correlation spectroscopy), HSQC (Heteronuclear single-quantum correlation spectroscopy), HMQC (Heteronuclear multiple-quantum correlation spectroscopy) and HMBC (Heteronuclear multiple-bond correlation spectroscopy) spectra were measured using field gradients.

IR spectra were obtained as ATR (Attenuated Total Reflectance) on a *Nicolet* Magna 750 FTIR-spectrometer. The absorption bands are given in wavenumber ν (cm^{-1}). The intensity of the bands is given relatively to the stronger peak (100%) and is indicated as follows: s (strong, 67%-100%), m (medium, 33%-67%), w (weak, < 33%), b (broad). The measurements were carried out by employees of the TU Berlin.

Mass spectra EI-MS and high resolution mass spectra **HR-MS** were obtained on a spectrometer MAT 95 from the company *Finnigan*. The samples were measured using a direct inlet and ionized at an ionization potential of 70 eV by electron ionization (EI). The vaporization temperature is given in each case. The intensities are given in percent, relatively to the highest peak (100). The measurements were carried out by employees of the TU Berlin. In each case, for HR-MS, the relative experimental error δ is given, in ppm, and was calculated as follow:

$$\delta = \frac{Experimental\ value - Calculated\ value}{Calculated\ value}$$

ESI-MS and **APCI-MS** spectra were obtained on a spectrometer LTQ XL FTMS from the company *Thermo Scientific*. The samples were dissolved in methanol or acetonitrile. The samples were ionized at a voltage from 4.5 kV or 5 kV, using electrospray ionization (ESI). For measurements using the auto sampler, the following conditions were used: methanol + 0.1% formic acid, flow rate 200 µL/ min. For measurements using a direct inlet, a flow rate from 5 µL/ min was used. The measurements were carried out by employees of the TU-Berlin.

Melting points were measured on a *Leica* Galen III hot-stage microscope with a heating regulator from the company *Wagner-Munz*. Values are uncorrected.

Optical rotations were measured on a *Perkin-Elmer* 341 polarimeter, at 20 °C, using a wavelength of 589 nm (sodium D-line). The solvent used and the concentration c (in g/ 100 mL) are given in each case. The value of the specific rotation is given as $[\alpha]_D^{20}$, with a formal unit in $deg.dm^{-1}.cm^3.g^{-1}$, calculated as follow:

$$[\alpha]_D^{20} = \frac{\alpha * 100}{c * d}$$

α: observed angle of optical rotation in deg, d: path length in dm, c: concentration in g/ 100 mL.

Thin layer chromatography (TLC) was carried out on aluminium foil with fluorescence indicator 254 from the company *Merck* (silica, Merck 60 F_{254} plates, coating thickness of 0.2 mm), from the company *Macherey-Nagel* (silica 60 with fluorescence indicator UV_{254}, coating thickness of 0.2 mm), or from the company *Sigma-Aldrich* (aluminium oxide TLC cards with fluorescent indicator 254, aluminium oxide matrix, coating thickness of 0.2 mm). Substances were detected by visualization under an UV lamp (λ = 254 nm) or revealed using a permanganate reagent (2.5% potassium permanganate in a 5% aqueous solution of sodium hydroxide). Solvents and retardation factor R_f are given in each case. R_f was calculated as follow:

$$R_f = \frac{migration\ distance\ of\ substance}{migration\ distance\ of\ solvent\ front}$$

Preparative thin layer chromatography (Preparative TLC) was carried out on glass plates Uniplate® with fluorescence indicator 254 from the company *Analtech* (silica, 20 x 20 cm, coating thickness of 1500 µm).

Column chromatography was carried out using silica gel from the company *Merck* (grain size 0.03-0.06 mm) or aluminium oxide from the company *Sigma-Aldrich* (activated, basic, Brockmann I, particle size 150 mesh, pH = 9.5 ± 0.5 in water). The solvents were distilled before use.

Solvents were distilled and if necessary dried before use. Diethyl ether, THF and toluene were dried using sodium. Dichloromethane was dried over calcium hydride. DMF, DMSO and pyridine were distilled over calcium hydride and stored over 4 Å molecular sieves.

Inert reactions were conducted under nitrogen atmosphere using Schlenk techniques or a Glovebox MB 120 BG from the company *MBraun*.

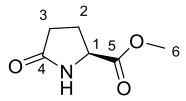
Ozonolyses were performed using an ozone generator OZ 500 from *Fischer Technology®* (i-Fischer Engineering GmbH), connected to a compressed gas cylinder of technical oxygen (O_2 > 99.5% from *Air Liquide*).

Microwave reactions were performed using an apparatus Discover from the company *CEM*.

Chemical names for all the synthesised substances were generated with the help of Cambridge Soft ChemBioDraw Ultra V.11.0.1, which is in accordance with Beilstein nomenclature. The atom numbers used for the attribution of the NMR signals are independent of the ones used in the name of the substances.

3.2. Experimental data for chapter 1

(*S*)-Methyl 5-oxopyrrolidine—carboxylate (116)



$C_6H_9NO_3$, MW = 143.1 g.mol^{-1}

(*S*)-5-Oxopyrrolidine-2-carboxylic acid **115** (12.9 g, 100 mmol, 1.00 eq) was dissolved in 25 mL methanol. After addition of concentrated hydrochloric acid (36% w/w solution, 0.21 mL, 2.50 mmol, 2.5 mol%) and 2,2-dimethoxypropane (25.0 mL, 204 mmol, 2.04 eq), the mixture was brought to 60 °C and stirred at this temperature for 6 h. The reaction was cooled down to room temperature and solvents were removed under vacuum. 50 mL ethyl acetate and 2.5 mL of an aqueous saturated solution of sodium hydrogen carbonate were added to the residue. Filtration followed by evaporation of the solvents under reduced pressure afforded **116** (14.3 g, 99.9 mmol, quantitative) as colourless oil.

R_f = 0.70 (dichloromethane : methanol = 8 : 2).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 6.42 (1H, bs, -NH), 4.26 (1H, dd, *J* = 8.6, 5.0 Hz, H-1), 3.77 (3H, s, H-6), 2.46 (1H, m, H-2), 2.40-2.29 (2H, m, H-2, H-3), 2.23 (1H, m, H-3).

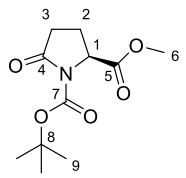
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 177.8 (C_q, C-4), 172.3 (C_q, C-5), 55.3 (CH_3, C-6), 52.6 (CH, C-1), 29.2 (CH_2, C-3), 24.8 (CH_2, C-2).

IR (ATR): ν (cm^{-1}) = 3523 (b), 3360 (b), 3240 (b), 2956 (w), 1732 (m), 1679 (s), 1458 (w), 1436 (m), 1422 (m), 1388 (w), 1342 (w), 1282 (m), 1257 (m), 1209 (s), 1182 (s), 1155 (m), 1109 (w), 1042 (w), 1021 (w), 983 (w), 788 (w), 696 (m).

HR-MS (ESI): for $C_6H_{10}NO_3$ $[M+H]^+$, calc.: 144.0655, found: 144.0654; δ = 0.7 ppm.

$[\alpha]_D^{20}$ = -1.2 (c = 0.85, dichloromethane).

(*S*)-1-*tert*-Butyl 2-methyl 5-oxopyrrolidine-1,2-dicarboxylate (117)



$C_{11}H_{17}NO_5$, MW = 243.3 g.mol^{-1}

116 (14.3 g, 99.9 mmol, 1.00 eq) was dissolved in 150 mL dichloromethane. After the mixture was brought to 0 °C pyridine (11.0 mL, 11.2 g, 137 mmol, 1.37 eq), DMAP (2.40 g, 20.0 mmol, 0.20 eq) and di-*tert*-butyl dicarbonate (28.4 g, 130 mmol, 1.30 eq) were added. The reaction was stirred for 18 h at

room temperature. The mixture was treated with 200 mL of a 1 N aqueous solution of hydrochloric acid, the layers were separated and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified by silica gel column chromatography (*c*-Hex : AcOEt = 3 : 2) to afford **117** (22.5 g, 92.5 mmol, 93%) as a brownish solid.

R_f = 0.23 (*c*-Hex : AcOEt = 3 : 2).

m_p = 73 °C.

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 4.61 (1H, dd, *J* = 12.0, 4.0 Hz, H-1), 3.78 (3H, s, H-6), 2.63 (1H, m, H-3), 2.49 (1H, m, H-3), 2.33 (1H, m, H-2), 2.04 (1H, m, H-2), 1.49 (9H, s, H-9).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 173.2 (C_q, C-5), 171.9 (C_q, C-4), 149.3 (C_q, C-7), 83.7 (C_q, C-8), 58.8 (CH, C-1), 52.6 (CH_3, C-6), 31.1 (CH_2, C-3), 27.9 (CH_3, C-9), 21.5 (CH_2, C-2).

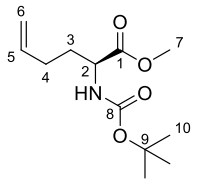
IR (ATR): ν (cm^{-1}) = 3537 (w), 3341 (b), 3248 (b), 3109 (w), 2957 (w), 1790 (w), 1739 (s), 1688 (s), 1458 (w), 1436 (m), 1374 (m), 1330 (m), 1282 (m), 1255 (s), 1207 (s), 1182 (s), 1151 (s), 1116 (m), 1042 (m), 1023 (m), 986 (m), 941 (w), 904 (w), 872 (w), 839 (m), 794 (m), 777 (m), 708 (m), 664 (m).

HR-MS (ESI): for $C_{11}H_{17}NNaO_5$ $[M+Na]^+$, calc.: 266.0999, found: 266.0998; δ = 0.4 ppm.

$[\alpha]_D^{20}$ = -37.8 (c = 1.10, dichloromethane).

The spectroscopic data are in full agreement with those published in the literature.[97]

(*S*)-Methyl-2-(*tert*-butoxycarbonylamino)hex-5-enoate (120)



$C_{12}H_{21}NO_4$, MW = 243.1 g.mol^{-1}

After a solution of **117** (6.19 g, 25.5 mmol, 1.0 eq) in 50 mL THF was brought to -104 °C, a solution of DIBAL-H (1.2 M solution in toluene, 25.5 mL, 30.6 mmol, 1.2 eq) was added dropwise and the mixture was stirred at this temperature for 1 h. Then, keeping the temperature under -60 °C, a 1 : 1 mixture of aqueous saturated solutions of sodium bicarbonate and ammonium chloride was slowly added and the reaction was warmed to room temperature over night. After filtration, layers were separated and the aqueous layer was extracted three times with MTBE. The combined organic layers were dried over $MgSO_4$, filtered and reduced under vacuum. After the residue was dissolved in 50 mL THF and cooled to 0 °C a premixed solution of methyltriphenylphosphonium bromide (10.9 g, 30.55 mmol, 1.2 eq) and potassium *tert*-butoxide (5.71 g, 50.9 mmol, 2.0 eq) in 200 mL THF was slowly added. The mixture was then stirred at room temperature for 18 h. After addition of 100 mL of an aqueous saturated solution of ammonium chloride to the reaction, the layers were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers

were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified by silica gel column chromatography (*c*-Hex : AcOEt = 20 : 1) to afford **120** (3.41 g, 14.0 mmol, 55%) as colourless oil.

R_f = 0.37 (*c*-Hex : AcOEt = 3 : 2).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 5.77 (1H, ddt, *J* = 17.2, 10.4, 8.0 Hz, H-5), 5.06-4.98 (2H, m, H-6), 4.31 (1H, m, H-2), 3.73 (3H, s, H-7), 2.11 (2H, btd, *J* = 8.4, 8.0 Hz, H-4), 1.91 (1H, m, H-3), 1.72 (1H, m, H-3), 1.41 (9H, s, H-10).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 173.3 (C_q, C-1), 158.3 (C_q, C-8), 137.0 (CH, C-5), 115.7 (CH_2, C-6), 79.9 (C_q, C-9), 53.0 (CH, C-2), 52.2 (CH_3, C-7), 32.0 (CH_2, C-3), 29.5 (CH_3, C-10), 28.3 (CH_2, C-4).

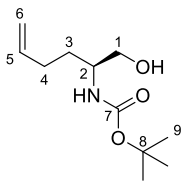
IR (ATR): ν (cm^{-1}) = 3656 (w), 3415 (b), 3240 (b), 3073 (w), 3056 (w), 2978 (w), 2917 (w), 2849 (w), 1740 (w), 1702 (m), 1641 (w), 1591 (w), 1532 (w), 1483 (w), 1436 (m), 1417 (w), 1387 (w), 1365 (w), 1332 (w), 1296 (w), 1252 (w), 1168 (s), 1118 (s), 1070 (w), 1049 (w), 1025 (w), 996 (w), 919 (w), 882 (m), 743 (s), 718 (s), 693 (s).

HR-MS (APCI): for $C_{12}H_{22}NO_4$ $[M+H]^+$, calc.: 244.1543, found: 244.1544; δ = 0.4 ppm.

$[\alpha]_D^{20}$ = +6.7 (c = 1.35, dichloromethane).

The spectroscopic data are in full agreement with those published in the literature.[97]

(*S*)-*tert*-Butyl 1-hydroxyhex-5-en-2-ylcarbamate (121)



$C_{11}H_{21}NO_3$, MW = 215.3 g.mol^{-1}

After **120** (400 mg, 1.65 mmol, 1.00 eq) was dissolved in 15 mL ethanol and the solution was brought to 0 °C sodium borohydride (188 mg, 4.97 mmol, 3.01 eq) was added portionwise. The mixture was stirred at room temperature for 18 h. The reaction was then quenched by addition of acetic acid and stirred for 1 h. The solvents were removed under reduced pressure, water and ethyl acetate were added to the residue, the layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified by silica gel column chromatography (*c*-Hex : MTBE = 8 : 2 to 6 : 4) to afford **121** (352 mg, 1.63 mmol, 99%) as slightly yellow oil.

R_f = 0.15 (*c*-Hex : MTBE = 1 : 1).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 5.81 (1H, ddt, *J* = 17.2, 10.4, 6.4 Hz, H-5), 5.03 (1H, bd, *J* = 17.2 Hz, H-6), 4.98 (1H, bd, *J* = 10.4 Hz, H-6), 4.63 (1H, bs, -NH), 3.72-3.51 (3H, m, H-1, H-2), 2.33 (1H, bs, -OH), 2.21-2.02 (2H, m, H-4), 1.66-1.39 (11H, m, H-3, H-9).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 156.1 (C_q, C-7), 137.0 (CH, C-5), 115.3 (CH_2, C-6), 77.2 (C_q, C-8), 64.2 (CH_2, C-1), 52.2 (CH, C-2), 32.0 (CH_2, C-3), 28.3 (CH_3, C-9), 28.0 (CH_2, C-4).

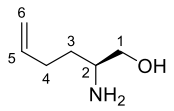
IR (ATR): ν (cm^{-1}) = 3341 (b), 3079 (w), 3003 (w), 2978 (m), 2931 (w), 2870 (w), 2361 (w), 2338 (w), 1696 (m), 1642 (w), 1501 (m), 1452 (m), 1390 (m), 1365 (s), 1248 (m), 1152 (s), 1049 (m), 1022 (m), 997 (m), 912 (m), 849 (m), 778 (m), 751 (w).

HR-MS (ESI): for $C_{11}H_{21}NNaO_3$ $[M+Na]^+$, calc.: 238.1414, found: 238.1413; δ = 0.4 ppm.

$[\alpha]_D^{20}$ = -13.5 (c = 1.10, methanol).

The spectroscopic data are in full agreement with those published in the literature.[97]

(*S*)-2-Aminohex-5-en-1-ol (114)



$C_6H_{13}NO$, MW = 115.2 g.mol^{-1}

After **121** (1.46 g, 6.78 mmol, 1.0 eq) was dissolved in 25 mL methanol, concentrated hydrochloric acid (25% w/w solution, 1.27 mL, 10.2 mmol, 1.5 eq) was added and the mixture was brought to 50 °C and stirred at this temperature for 18 h. The solution was then allowed to cool down to room temperature and solvents were removed under reduced pressure. The residue was neutralized by addition of a 2 M solution of sodium hydroxide and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered and reduced under vacuum to afford **114** (0.76 g, 6.59 mmol, 97%) as brown oil.

R_f = 0.10 (*c*-Hex : AcOEt = 1 : 1).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 5.83 (1H, m, H-5), 5.12-4.95 (2H, m, H-6), 3.57 (1H, dd, *J* = 10.4, 3.6 Hz, H-1), 3.26 (1H, dd, *J* = 10.4, 7.6 Hz, H-1), 2.83 (1H, m, H-2), 2.23-2.05 (2H, m, H-4), 1.54 (1H, m, H-3), 1.39 (1H, m, H-3).

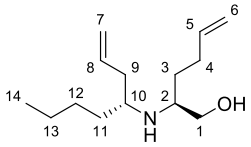
^{13}C-NMR (125.8 MHZ, $CDCl_3$): δ (ppm) = 138.0 (CH, C-5), 115.1 (CH_2, C-6), 66.1 (CH_2, C-1), 52.3 (CH, C-2), 33.1 (CH_2, C-3), 30.2 (CH_2, C-4).

IR (ATR): ν (cm^{-1}) = 3339 (b), 3278 (m), 3075 (m), 2999 (m), 2974 (m), 2921 (m), 2853 (m), 1739 (w), 1658 (m), 1640 (m), 1586 (m), 1555 (m), 1534 (m), 1449 (m), 1416 (m), 1370 (m), 1301 (m), 1254 (m), 1175 (w), 1134 (m), 1052 (s), 995 (s), 910 (s), 858 (m), 769 (m), 716 (m).

HR-MS (ESI): for $C_6H_{14}NO$ $[M+H]^+$, calc.: 116.1070, found: 116.1070; δ = 0.0 ppm.

$[\alpha]_D^{20}$ = +2.8 (c = 0.54, dichloromethane).

(*S*)-2-((*R*)-Oct-1-en-4-ylamino)hex-5-en-1-ol (113)



$C_{14}H_{27}NO$, MW = 225.4 g.mol^{-1}

After amino alcohol **114** (140 mg, 1.44 mmol, 1.0 eq) was dissolved in 5 mL THF, pentanal (0.17 mL, 1.58 mmol, 1.1 eq) and $MgSO_4$ (555 mg, 4.61 mmol, 3.2 eq) were added and the mixture was stirred at room temperature for 12 h. Solvents were then removed under vacuum, 5 mL THF were added again and once the residue was dissolved, the solution was transferred in another flask through a cannula in order to decant the $MgSO_4$. After the mixture was brought to -78 °C, allylmagnesium bromide (1.7 M solution in THF, 2.54 mL, 4.32 mmol, 3.0 eq) was added dropwise. The reaction was then allowed to reach room temperature over 6 h. After addition of 2 mL of an aqueous saturated solution of ammonium chloride, the layers were separated and the aqueous layer was extracted with MTBE. The combined organic layers were dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified by silica gel column chromatography (*c*-Hex : AcOEt = 7 : 3) to afford **113** (108 mg, 0.48 mmol, 33%) as slightly yellow oil. The diastereomeric ratio was spectroscopically determined and was found to be higher than 97 : 3.

R_f = 0.25 (*c*-Hex : AcOEt = 7 : 3).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 5.89-5.71 (2H, m, H-5, H-8), 5.15-4.92 (4H, m, H-6, H-7), 3.58 (1H, dd, *J* = 10.4, 4.0 Hz, H-1), 3.20 (1H, dd, *J* = 10.4, 5.6 Hz, H-1), 2.69 (1H, m, H-2), 2.62 (1H, quint, *J* = 5.8 Hz, H-10), 2.32-1.88 (4H, m, H-4, H-9), 1.63-1.09 (8H, m, H-3, H-11, H-12, H-13), 0.90 (3H, t, *J* = 6.6 Hz, H-14).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 138.2 (CH, C-5, C-8), 135.7 (CH, C-8, C-5), 117.1 (CH_2, C-6, C-7), 114.9 (CH_2, C-7, C-6), 63.4 (CH_2, C-1), 55.6 (CH, C-2), 54.5 (CH, C-10), 39.3 (CH_2, C-9), 34.4 (CH_2, C-11), 31.8 (CH_2, C-3), 30.3 (CH_2, C-4), 28.1 (CH_2, C-12), 22.9 (CH_2, C-13), 14.1 (CH_3, C-14).

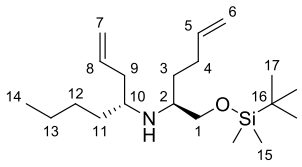
IR (ATR): ν (cm^{-1}) = 3350 (b), 3075 (w), 2954 (m), 2927 (s), 2858 (m), 1823 (w), 1727 (w), 1640 (w), 1554 (w), 1456 (m), 1438 (m), 1414 (m), 1377 (m), 1345 (w), 1295 (w), 1251 (w), 1202 (w), 1129 (m), 1101 (m), 1043 (m), 995 (m), 910 (s), 732 (m).

HR-MS (ESI): for $C_{14}H_{28}NO$ $[M+H]^+$, calc.: 226.2165, found: 226.2164; δ = 0.4 ppm.

$[\alpha]_D^{20}$ = +23.8 (c = 1.18, methanol).

The spectroscopic data are in full agreement with those published in the literature.[97]

(*R*)-*N*-((*S*)-1-(*tert*-Butyldimethylsilyloxy)hex-5-en-2-yl)oct-1-en-4-amine (125)



$C_{20}H_{41}NOSi$, MW = 339.6 g.mol^{-1}

Imidazole (7.50 mg, 0.11 mmol, 2.5 eq) and *tert*-butyldimethylsilyl chloride (8.60 mg, 57 µmol, 1.3 eq) were added to a solution of **113** (10.0 mg, 44 µmol, 1.0 eq) in 1 mL DMF previously brought to 0 °C. The mixture was stirred at room temperature for 18 h. Water and Et_2O were then added to the reaction, the layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified using preparative TLC (*c*-Hex : AcOEt = 8 : 2) to afford **125** (12 mg, 35 µmol, 80%) as colourless oil.

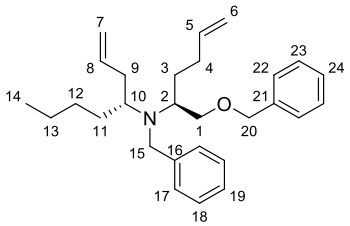
$\mathbf{R_f}$ = 0.35 (*c*-Hex : AcOEt = 3 : 7).

^{1}H-NMR (400.1 MHz, C_6D_6, 343.15 K): δ (ppm) = 5.91-5.63 (2H, m, H-5, H-8), 5.10-4.88 (4H, m, H-6, H-7), 3.47 (1H, dd, *J* = 10.5, 4.0 Hz, H-1), 3.18 (1H, dd, *J* = 10.5, 6.0 Hz, H-1), 2.68 (1H, m, H-2, H-10), 2.51 (1H, m, H-10, H-2), 2.25-1.91 (5H, m, H-4, H-9, -NH), 1.66-1.47 (2H, m, H-3), 1.47-1.08 (6H, m, H-11, H-12, H-13), 0.98-0.77 (12H, m, H-14, H-17), 0.06 (6H, s, H-15).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 138.1 (CH, C-6, C-7), 135.6 (CH, C-7, C-6), 117.2 (CH_2, C-5, C-8), 115.0 (CH_2, C-8, C-5), 63.3 (CH_2, C-1), 55.7 (CH, C-2, C-10), 54.6 (CH, C-10, C-2), 39.1 (CH_2, C-9), 34.3 (CH_2, C-11), 31.7 (CH_2, C-3, C-4), 31.5 (CH_2, C-4, C-3), 30.3 (C_q, C-16), 28.1 (CH_2, C-12), 25.9 (CH_3, C-17), 23.0 (CH_2, C-13), 14.1 (CH_3, C-14), -5.4 (CH_3, C-15).

HR-MS: for $C_{20}H_{42}NOSi$ $[M+H]^+$, calc.: 340.3030, found: 340.3025; δ = 1.5 ppm.

(*R*)-*N*-Benzyl-*N*-((*S*)-1-(benzyloxy)hex-5-en-2-yl)oct-1-en-4-amine (129)



$C_{28}H_{39}NO$, MW = 405.6 g.mol^{-1}

After **113** (10.0 mg, 44 µmol, 1.0 eq) and sodium hydride (75% in mineral oil, 3.10 mg, 97 µmol, 2.2 eq) were dissolved in 1 mL DMF, the mixture was brought to 0 °C and stirred for 30 min. Benzyl bromide (12 µL, 16.6 mg, 97 µmol, 2.2 eq) was then added dropwise and the reaction was stirred at room temperature for 16 h. 1 mL of saturated aqueous solution of ammonium chloride was added and the mixture was stirred for an additional 10 min. The aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with water and brine, dried over

$MgSO_4$, filtered and reduced under vacuum. The residue was purified using preparative TLC (*c*-Hex : AcOEt = 8 : 2) to afford **129** (3.00 mg, 7.0 µmol, 17%) as colourless oil.

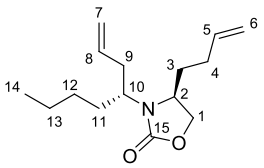
R_f = 0.60 (*c*-Hex : AcOEt = 1 : 1).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 7.35-7.23 (10H, m, H-Ar), 5.88-5.68 (2H, m, H-5, H-8), 5.04-4.86 (4H, m, H-6, H-7), 4.46 (2H, s, H-20), 3.79 (2H, s, H-15), 3.58 (1H, dd, *J* = 10.4, 5.4 Hz, H-1), 3.41 (1H, dd, *J* =10.4, 5.4 Hz, H-1), 2.80 (1H, m, H-2, H-10), 2.66 (1H, m, H-10, H-2), 2.31 (1H, m, H-9), 2.16-1.89 (3H, m, H-4, H-9), 1.40-1.16 (8H, m, H-3, H-11, H-12, H-13), 0.88 (3H, t, *J* = 6.8 Hz, H-14).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 141.0 (C_q, C-16, C-21), 138.3 (CH, C-5, C-8), 137.8 (CH, C-8, C-5), 137.5 (C_q, C-21, C-16), 129.1 (CH, C-Ar), 128.8 (CH, C-Ar), 128.8 (CH, C-Ar), 128.6 (CH, C-Ar), 128.6 (CH, C-Ar), 128.4 (CH, C-Ar), 127.9 (CH, C-Ar), 127.8 (CH, C-Ar), 127.7 (CH, C-Ar), 127.0 (CH, C-Ar), 115.8 (CH_2, C-6, C-7), 114.2 (CH_2, C-7, C-6), 73.4 (CH_2, C-1), 72.1 (CH_2, C-20), 65.3 (CH_2, C-15), 57.8 (CH, C-2, C-10), 56.4 (CH, C-10, C-2), 46.3 (CH_2, C-9), 33.6 (CH_2, C-11), 30.1 (CH_2, C-3, C-12), 29.7 (CH_2, C-12, C-3), 27.9 (CH_2, C-4), 22.7 (CH_2, C-13), 14.0 (CH_3, C-14).

HR-MS (APCI): for $C_{28}H_{40}NO$ $[M+H]^+$, calc.: 406.3104, found: 406.3096; δ = 2.0 ppm.

(*S*)-4-(But-3-enyl)-3-((*R*)-oct-1-en-4-yl)oxazolidin-2-one (132)



$C_{15}H_{25}NO_2$, MW = 251.4 g.mol^{-1}

To a solution of **113** (10.0 mg, 44 µmol, 1.0 eq) and triethylamine (31 µL, 0.22 mmol, 5.0 eq) in 0.5 mL dichloromethane at 0 °C was added dropwise a solution of triphosgen (6.60 mg, 22 µmol, 0.5 eq) in 0.5 mL dichloromethane. The mixture was then stirred at room temperature for 4 h. After addition of dichloromethane and water, the layers were separated and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were then washed with a 1 M aqueous solution of sodium hydroxide and with brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified using preparative TLC (*c*-Hex : AcOEt = 4 : 1) to afford **132** (4.00 mg, 16 µmol, 36%) as colourless oil.

R_f = 0.65 (*c*-Hex : AcOEt = 1 : 1).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 5.87-5.69 (2H, m, H-5, H-8), 5.15-4.99 (4H, m, H-6, H-7), 4.30 (1H, t, *J* = 8.6 Hz, H-1), 3.93 (1H, dd, *J* = 8.6, 6.0 Hz, H-1), 3.71 (1H, m, H-2), 3.46 (1H, m, H-10), 2.50 (1H, dtd, *J* = 14.0, 8.2, 1.2 Hz, H-9), 2.27 (1H, dtd, *J* = 14.0, 6.8, 1.2 Hz, H-9), 2.06 (1H, m, H-4), 1.97 (1H, m, H-4), 1.86 (1H, m, H-3), 1.73 (1H, m, H-3), 1.66-1.52 (2H, m, H-11), 1.37-1.18 (4H, m, H-12, H-13), 0.89 (3H, t, *J* = 7.0 Hz, H-14).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 145.1 (C_q, C-15), 136.6 (CH, C-5, C-8), 135.3 (CH, C-8, C-5), 117.7 (CH_2, C-6, C-7), 116.0 (CH_2, C-7, C-6), 67.2 (CH_2, C-1), 55.3 (CH, C-2, C-10), 54.8 (CH, C-10, C-2),

38.5 (CH_2, C-9), 33.0 (CH_2, C-3), 31.2 (CH_2, C-11), 29.0 (CH_2, C-4, C-12), 28.8 (CH_2, C-12, C-4), 22.5 (CH_2, C-13), 14.0 (CH_3, C-14).

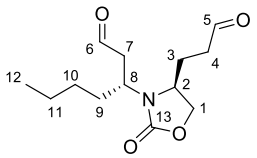
IR (ATR): ν (cm^{-1}) = 3077 (w), 2957 (m), 2929 (m), 2862 (w), 2344 (w), 1739 (s), 1641 (w), 1531 (w), 1415 (m), 1377 (m), 1253 (m), 1237 (m), 1187 (w), 1125 (w), 1049 (m), 995 (m), 913 (s), 788 (w), 765 (m), 734 (w), 697 (w).

HR-MS (APCI): for $C_{15}H_{26}NO_2$ $[M+H]^+$, calc.: 252.1958, found: 252.1957; δ = 0.4 ppm.

$[\alpha]_D^{20}$ = +27.0 (c = 0.95, chloroform).

The spectroscopic data are in full agreement with those published in the literature.[97]

(*R*)-3-((*S*)-2-Oxo-4-(3-oxopropyl)oxazolidin-3-yl)heptanal (134)



$C_{13}H_{21}NO_4$, MW = 255.3 g.mol^{-1}

132 (40.0 mg, 0.16 mmol) was dissolved in dichloromethane and the mixture was brought to -78 °C. At this temperature, after 5 min of a flux of oxygen, a flux of ozone is passed through the solution. The reaction was monitored with TLC and the reaction was completed after 20 min. The reaction was quenched with dimethylsulfide, slowly warmed to reach room temperature and stirred at this temperature for 12 h. The solvents were removed under vacuum and the residue was purified using preparative TLC (*c*-Hex : AcOEt = 4 : 6) to afford **134** (13.0 mg, 0.05 mmol, 32%) as colourless oil.

R_f = 0.30 (*c*-Hex : AcOEt = 3 : 7).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 9.83 (1H, s, H-6), 9.78 (1H, s, H-5), 4.30 (1H, t, *J* = 8.0 Hz, H-1), 3.99-3.83 (3H, m, H-1, H-2, H-8), 3.23 (1H, ddd, *J* = 18.4, 9.6, 1.4 Hz, H-7), 2.70 (1H, bdd, *J* = 18.4, 4.4 Hz, H-7), 2.61-2.44 (2H, m, H-4), 2.16 (1H, m, H-3), 1.88-1.68 (3H, m, H-3, H-9), 1.39-1.23 (4H, m, H-10, H-11), 0.92 (3H, t, *J* = 7.2 Hz, H-12).

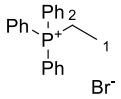
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 200.7 (CH, C-6), 199.8 (CH, C-5), 154.5 (C_q, C-13), 67.1 (CH_2, C-1), 55.4 (CH, C-2), 49.1 (CH, C-8), 47.2 (CH_2, C-7), 38.6 (CH_2, C-4), 32.1 (CH_2, C-9), 29.0 (CH_2, C-10), 25.4 (CH_2, C-3), 22.4 (CH_2, C-11), 14.0 (CH_3, C-12).

IR (ATR): ν (cm^{-1}) = 3075 (w), 2957 (m), 2925 (m), 2856 (m), 1727 (s), 1641 (w), 1599 (w), 1581 (w), 1459 (m), 1416 (w), 1378 (w), 1272 (s), 1122 (s), 1072 (s), 1040 (m), 993 (m), 969 (m), 914 (m), 838 (w), 793 (w), 764 (m), 742 (m), 702 (m).

HR-MS (APCI): for $C_{13}H_{22}NO_4$, $[M+H]^+$, calc.: 256.1543, found: 256.1546; δ = 1.2 ppm.

$[\alpha]_D^{20}$ = -4.0 (c = 0.65, methanol).

Ethyltriphenylphosphonium bromide (159)



$C_{20}H_{20}BrP$, MW = 371.3 g.mol^{-1}

After triphenylphosphine (262 mg, 1.00 mmol, 1.0 eq) was dissolved in 0.7 mL benzene and 0.3 mL toluene, bromoethane (0.15 mL, 2.00 mmol, 2.0 eq) was added and the mixture was stirred for 24 h at 80 °C. The solvents were removed under vacuum to afford **159** (310 mg, 0.83 mmol, 83%) as a brown solid.

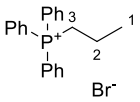
R_f = 0.80 (*c*-Hex : AcOEt = 1 : 1).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 7.98-7.89 (3H, m, H-Ar), 7.87-7.76 (12H, m, H-Ar), 3.45 (2H, dq, $^2J_{H,P}$ = 13.6 Hz, *J* = 7.6 Hz, H-2), 1.43 (3H, td, *J* = 7.6 Hz, $^3J_{H,P}$ = 0.8 Hz, H-1).

^{13}C-NMR (125.8 MHz, DMSO-d_6): δ (ppm) = 133.5 (CH, C-Ar), 133.5 (CH, C-Ar), 133.4 (CH, C-Ar), 133.2 (CH, C-Ar), 133.1 (CH, C-Ar), 129.0 (CH, C-Ar), 128.9 (CH, C-Ar), 128.9 (CH, C-Ar), 128.8 (CH, C-Ar), 128.7 (CH, C-Ar), 128.5 (CH, C-Ar), 118.6 (C_q, C-Ar), 117.9 (C_q, C-Ar), 20.9 (CH_2, C-2), 6.9 (CH_3, C-1).

HR-MS (ESI): for $C_{20}H_{21}P$ $[M+H]^+$, calc.: 291.1297, found: 291.1296; δ = 0.3 ppm.

Triphenyl(propyl)phosphonium bromide (160)



$C_{21}H_{22}BrP$, MW = 385.3 g.mol^{-1}

After triphenylphosphine (262 mg, 1.00 mmol, 1.0 eq) was dissolved in 0.7 mL benzene and 0.3 mL toluene, 1-bromopropane (0.18 mL, 2.00 mmol, 2.0 eq) was added and the mixture was stirred for 2 days. The solvents were removed under vacuum to afford a 7 : 1 mixture of triphenylphosphine and **160** (46.0 mg, 0.12 mmol, 12%) as a brown solid. The analytical results were deducted from the obtained mixture.

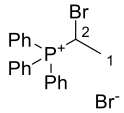
R_f = 0.80 (*c*-Hex : AcOEt = 1 : 1).

^{1}H-NMR (400.1 MHz, MeOD): δ (ppm) = 7.96-7.88 (3H, m, H-Ar), 7.86-7.72 (12H, m, H-Ar), 3.39-3.34 (2H, m, H-3), 1.76-1.61 (2H, m, H-2), 1.17 (3H, td, *J* = 7.4, 1.8 Hz, H-1).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 134.9 (CH, C-Ar), 134.7 (CH, C-Ar), 129.9 (CH, C-Ar), 129.7 (CH, C-Ar), 129.6 (CH, C-Ar), 129.3 (CH, C-Ar), 116.5 (C_q, C-Ar), 27.9 (CH_2, C-3), 16.0 (CH_2, C-2), 13.2 (CH_3, C-1).

HR-MS (ESI): for $C_{21}H_{22}P$ $[M]^+$, calc.: 305.1454, found: 305.1453; δ = 0.3 ppm.

(1-Bromoethyl)triphenylphosphonium bromide (162)



$C_{20}H_{19}Br_2P$, MW = 450.1 g.mol^{-1}

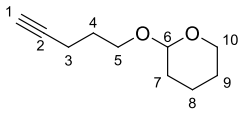
After **159** (200 mg, 0.54 mmol, 1.00 eq) was dissolved in 5 mL THF, *n*-butyllithium (2.5 M solution in hexanes, 0.21 mL, 0.53 mmol, 0.99 eq) was added at room temperature. The mixture was then brought to -78 °C and a solution of dibromine (0.03 mL, 86.1 mg, 0.54 mmol, 1.00 eq) in 10 mL THF was added. The reaction was stirred for 18 h at room temperature. 10 mL cyclohexane were added and the reaction mixture was filtered. The yellow precipitate was washed two times with 10 mL cyclohexane. The solvents were removed under vacuum to afford a 1 : 1.1 : 0.6 mixture of non-bromated **159**, bromated **162** and dibromated **163** products. The analytical results were deducted from the obtained mixture.

^{1}H-NMR (500.1 MHz, $CDCl_3$): δ (ppm) = 8.18-7.62 (15H, m, H-Ar), 3.87 (1H, m, H-2), 2.00 (3H, dd, $^3J_{H,P}$ = 18.0 Hz, $^3J_{H,H}$ = 7.0 Hz, H-1).

^{13}C-NMR (125.8 MHz, $CDCl_3$): δ (ppm) = 135.4 (CH, C-Ar), 135.3 (CH, C-Ar), 135.3 (CH, C-Ar), 135.2 (CH, C-Ar), 135.0 (CH, C-Ar), 134.6 (CH, C-Ar), 134.5 (CH, C-Ar), 133.8 (CH, C-Ar), 133.7 (CH, C-Ar), 130.5 (CH, C-Ar), 130.4 (CH, C-Ar), 130.3 (CH, C-Ar), 118.5 (C_q, C-Ar), 117.3 (C_q, C-Ar), 116.7 (C_q, C-Ar), 32.7 (CH, C-2), 19.9 (CH_3, C-1).

HR-MS (ESI): for $C_{20}H_{19}BrP$ $[M]^+$, calc.: 369.0402, found: 369.0396; δ = 1.6 ppm.

2-(Pent-4-ynyloxy)tetrahydro-2*H*-pyran (172)



$C_{10}H_{16}O_2$, MW = 168.2 g.mol^{-1}

After pent-4-yn-1-ol **168** (0.11 mL, 100 mg, 1.19 mmol, 1 eq) was dissolved in 2 mL dichloromethane, the mixture was brought to 0 °C and *p*TSA•H_2O (5.00 mg, 0.03 mmol, 2.5 mol%) and 3,4-dihydro-2*H*-pyran (0.32 mL, 300 mg, 3.57 mmol, 2 eq) were added. After the reaction was stirred at room temperature for 16 h, 10 mL ethyl acetate were added and the mixture was poured into 25 mL of a saturated aqueous solution of sodium hydrogen carbonate. The layers were separated and the organic layer was washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified by silica gel column chromatography (*c*-Hex : AcOEt = 95 : 5) to afford **172** (190 mg, 1.13 mmol, 95%) as colourless oil.

R_f = 0.50 (*c*-Hex : AcOEt = 8 : 2).

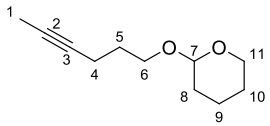
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 4.59 (1H, dd, *J* = 4.4, 2.8 Hz, H-6), 3.90-3.79 (2H, m, H-10), 3.53-3.44 (2H, m, H-5), 2.31 (2H, td, *J* = 6.8, 2.6 Hz, H-3), 1.94 (1H, *J* = 2.6 Hz, H-1), 1.81 (2H, quint, *J* = 6.8 Hz, H-4), 1.75-1.48 (6H, m, H-7, H-8, H-9).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 98.8 (CH, C-6), 84.0 (C_q, C-2), 68.4 (C_q, C-1), 65.8 (CH_2, C-5), 62.2 (CH_2, C-10), 30.7 (CH_2, C-7), 28.7 (CH_2, C-4), 25.5 (CH_2, C-9), 19.5 (CH_2, C-8), 15.3 (CH_2, C-3).

IR (ATR): ν (cm^{-1}) = 3446 (w), 3290 (w), 2940 (m), 2868 (w), 2848 (w), 1728 (w), 1696 (w), 1633 (w), 1466 (w), 1453 (w), 1441 (w), 1384 (w), 1364 (w), 1353 (w), 1345 (w), 1323 (w), 1283 (w), 1260 (w), 1200 (m), 1182 (w), 1158 (m), 1136 (s), 1120 (s), 1075 (s), 1061 (s), 1032 (s), 1019 (s), 991 (s), 968 (m), 945 (m), 901 (m), 881 (m), 868 (m), 814 (m).

HR-MS (ESI): for $C_{10}H_{16}NaO_2$ $[M+Na]^+$, calc.: 191.1043, found: 191.1040; δ = 1.6 ppm.

2-(Hex-4-ynyloxy)tetrahydro-2*H*-pyran (173)



$C_{11}H_{18}O_2$, MW = 182.3 g.mol^{-1}

After **172** (190 mg, 1.13 mmol, 1.0 eq) was dissolved in 10 mL THF, the mixture was brought to -10 °C and *n*-butyllithium (2.5 M solution in hexanes, 0.50 mL, 1.24 mmol, 1.1 eq) was added dropwise. The reaction was then stirred at the same temperature for 10 min, TMEDA (0.37 mL, 288 mg, 2.48 mmol, 2.2 eq) was added dropwise and the mixture was stirred for an additional 10 min. Methyl iodide (0.35 mL, 802 mg, 5.65 mmol, 5.0 eq) was added and the reaction was stirred at room temperature for 1 h. After the reaction mixture was poured into 25 mL water, the layers were separated and the aqueous layer was extracted three times with 10 mL ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified by silica gel column chromatography (*c*-Hex : AcOEt = 95 : 5) to afford **173** (205 mg, 1.12 mmol, 99%) as colourless oil.

R_f = 0.65 (*c*-Hex : AcOEt = 8 : 2).

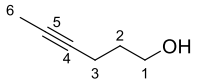
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 4.59 (1H, dd, *J* = 3.8, 3.0 Hz, H-7), 3.91-3.76 (2H, m, H-6, H-11), 3.53-3.42 (2H, m, H-11, H-6), 2.23 (2H, tq, *J* = 6.8, 2.4 Hz, H-4), 1.86-1.65 (4H, m, H-5, H-8), 1.76 (3H, t, *J* = 2.4 Hz, H-1), 1.62-1.46 (4H, m, H-9, H-10).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 98.8 (CH, C-7), 78.6 (C_q, C-3), 75.7 (C_q, C-2), 66.1 (CH_2, C-6, C-11), 62.1 (CH_2, C-11, C-6), 30.7 (CH_2, C-5, C-8), 29.2 (CH_2, C-8, C-5), 25.5 (CH_2, C-10), 19.5 (CH_2, C-9), 15.6 (CH_2, C-4), 3.4 (CH_3, C-1).

IR (ATR): ν (cm^{-1}) = 3470 (w), 2938 (m), 2869 (m), 2735 (w), 2657 (w), 1700 (w), 1465 (w), 1441 (w), 1382 (w), 1363 (w), 1353 (w), 1345 (w), 1322 (w), 1283 (w), 1260 (w), 1200 (m), 1182 (w), 1158 (w), 1136 (m), 1119 (s), 1076 (s), 1062 (s), 1032 (s), 1020 (s), 988 (s), 969 (m), 945 (w), 904 (m), 881 (m), 868 (m), 844 (w), 813 (m), 751 (w), 680 (w).

HR-MS (APCI): for $C_{11}H_{19}O_2$ $[M+H]^+$, calc.: 183.1380, found: 183.1379; δ = 0.5 ppm.

Hex-4-yn-1-ol (169)



$C_6H_{10}O$, MW = 98.1 g.mol^{-1}

*From **173***: After **173** (200 mg, 1.10 mmol, 1 eq) was dissolved in 10 mL methanol, *p*TSA•H_2O (5.00 mg, 0.03 mmol, 3.0 mol%) was added and the mixture was stirred at room temperature for 2 h. 3 mL of an aqueous saturated solution of sodium hydrogen carbonate were added, the suspension was poured into 10 mL water and the aqueous layer was extracted three times with 15 mL dichloromethane. The combined organic layers were then washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified by silica gel column chromatography (*c*-Hex : AcOEt = 8 : 2) to afford **169** (105 mg, 1.07 mmol, 97%) as colourless oil.

*From hex-5-yn-1-ol **141***: After potassium *tert*-butoxide (23.0 mg, 0.20 mmol, 0.2 eq) was dissolved in 2 mL DMSO, hex-5-yn-1-ol **141** (0.11 mL, 100 mg, 1.02 mmol, 1.0 eq) was added in one portion. After several minutes, an increase of the temperature from 20 to 30 °C was noticed and a white precipitate was formed. The mixture was heated to 80 °C and stirred at this temperature for 1 h. The reaction was then poured into 5 mL water. The aqueous layer was extracted six times with 5 mL of a mixture (1 : 1) of diethyl ether and pentane. The combined organic layers were washed two times with water, dried over $MgSO_4$, filtered, and reduced under vacuum to afford **169** (99.0 mg, 1.01 mmol, 99%) as colourless oil.

$\mathbf{R_f}$ = 0.25 (*c*-Hex : AcOEt = 8 : 2).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 3.75 (2H, q, *J* = 7.0 Hz, H-1), 2.25 (2H, tq, *J* = 7.0, 2.6 Hz, H-3), 1.77 (3H, t, *J* = 2.6 Hz, H-6), 1.73 (2H, quint, *J* = 7.0 Hz, H-2), 1.56 (1H, t, *J* = 7.0 Hz, -OH).

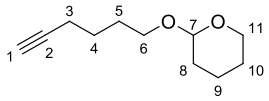
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 78.4 (C_q, C-4), 76.2 (C_q, C-5), 62.0 (CH_2, C-1), 31.5 (CH_2, C-2), 15.4 (CH_2, C-3), 3.4 (CH_3, C-6).

IR (ATR): ν (cm^{-1}) = 3612 (w), 3320 (b), 2943 (m), 2921 (m), 2872 (m), 2737 (w), 1703 (w), 1641 (w), 1474 (w), 1437 (m), 1382 (w), 1351 (w), 1330 (w), 1281 (w), 1227 (w), 1199 (w), 1178 (w), 1137 (w), 1120 (w), 1055 (s), 1034 (s), 970 (w), 950 (m), 931 (m), 909 (m), 870 (w), 852 (w), 794 (m), 757 (m), 695 (m), 664 (m).

HR-MS (ESI): for $C_6H_{11}O$ $[M+H]^+$, calc.: 99.0804, found: 99.0802; δ = 2.0 ppm.

The spectroscopic data are in full agreement with those published in the literature.[221]

2-(Hex-5-ynyloxy)tetrahydro-2*H*-pyran (174)



$C_{11}H_{18}O_2$, MW = 182.3 g.mol^{-1}

After hex-5-yn-1-ol **141** (0.11 mL, 100 mg, 1.02 mmol, 1.0 eq) was dissolved in 2 mL dichloromethane, the mixture was brought to 0 °C and *p*TSA•H_2O (5.00 mg, 0.03 mmol, 2.5 mol%) and 3,4-dihydro-2*H*-pyran (0.28 mL, 257 mg, 3.06 mmol, 3.0 eq) were added. After the reaction mixture was stirred at room temperature for 16 h, 10 mL ethyl acetate were added and the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified by silica gel column chromatography (*c*-Hex : AcOEt = 95 : 5) to afford **174** (185 mg, 1.01 mmol, 99%) as colourless oil.

R_f = 0.55 (*c*-Hex : AcOEt = 8 : 2).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 4.58 (1H, dd, *J* = 4.4, 2.8 Hz, H-7), 3.86 (1H, m, H-6), 3.76 (1H, dt, *J* = 10.0, 6.4 Hz, H-11), 3.50 (1H, m, H-6), 3.41 (1H, dt, *J* = 10.0, 5.8 Hz, H-11), 2.23 (2H, td, *J* = 7.0, 2.4 Hz, H-3), 1.94 (1H, t, *J* = 2.4 Hz, H-1), 1.87-1.48 (10H, m, H-4, H-5, H-8, H-9, H-10).

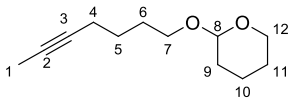
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 98.8 (CH, C-7), 84.4 (C_q, C-2), 68.3 (CH, C-1), 66.9 (CH_2, C-6), 62.3 (CH_2, C-11), 30.7 (CH_2, C-8), 28.8 (CH_2, C-5), 25.5 (CH_2, C-4, C-10), 25.4 (CH_2, C-10, C-4), 19.6 (CH_2, C-9), 18.3 (CH_2, C-3).

IR (ATR): ν (cm^{-1}) = 3614 (w), 3307 (b), 3261 (m), 2940 (m), 2866 (m), 1453 (m), 1439 (m), 1382 (m), 1349 (m), 1325 (m), 1280 (m), 1260 (m), 1201 (m), 1183 (m), 1155 (m), 1122 (s), 1074 (s), 1031 (s), 1018 (s), 987 (m), 966 (s), 926 (m), 905 (m), 869 (m), 813 (m), 728 (w), 688 (m).

HR-MS (APCI): for $C_{11}H_{19}O_2$ $[M+H]^+$, calc.: 183.1380, found: 183.1381; δ = 0.5 ppm.

The spectroscopic data are in full agreement with those published in the literature.[134]

2-(Hept-5-ynyloxy)tetrahydro-2*H*-pyran (175)



$C_{12}H_{20}O_2$, MW = 196.3 g.mol^{-1}

After **174** (186 mg, 1.02 mmol, 1.0 eq) was dissolved in 10 mL THF, the mixture was brought to -10 °C and *n*-butyllithium (2.5 M solution in hexanes, 0.45 mL, 1.12 mmol, 1.1 eq) was added dropwise. The reaction was stirred at the same temperature for 10 min, followed by dropwise addition of TMEDA (0.33 mL, 260 mg, 2.24 mmol, 2.2 eq). The mixture was stirred for an additional 10 min. Methyl iodide (0.32 mL, 724 mg, 5.10 mmol, 5.0 eq) was added and the reaction was stirred at room temperature for 1 h. After the reaction mixture was poured into 25 mL water, the layers were separated and the aqueous layer was extracted three times with 10 mL ethyl acetate. The combined

organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford a 4: 1 mixture of product **175** and reactant **174** (80% conversion). This mixture was purified by silica gel column chromatography (*c*-Hex : AcOEt = 95 : 5) to afford **175** (160 mg, 0.82 mmol, 80%) as colourless oil.

R_f = 0.70 (*c*-Hex : AcOEt = 8 : 2).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 4.58 (1H, dd, *J* = 4.4, 2.8 Hz, H-8), 3.87 (1H, m, H-7), 3.74 (1H, dt, *J* = 9.6, 6.8 Hz, H-12), 3.50 (1H, m, H-7), 3.40 (1H, dt, *J* = 9.6, 7.0 Hz, H-12), 2.16 (2H, tq, *J* = 7.2, 2.8 Hz, H-4), 1.86-1.65 (6H, m, H-9, H-10, H-11), 1.77 (3H, t, *J* = 2.4 Hz, H-1), 1.63-1.49 (4H, m, H-5, H-6, H-11, H-10).

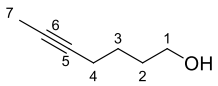
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 98.8 (CH, C-8), 79.0 (C_q, C-3), 75.8 (C_q, C-2), 67.1 (CH_2, C-12), 62.3 (CH_2, C-7), 30.8 (CH_2, C-10, C-11), 29.0 (CH_2, C-9), 25.9 (CH_2, C-5, C-6), 25.5 (CH_2, C-6, C-5), 19.6 (CH_2, C-11, C-10), 18.6 (CH_2, C-4), 3.5 (CH_3, C-1).

IR (ATR): ν (cm^{-1}) = 3447 (w), 2939 (m), 2920 (m), 2867 (m), 2736 (w), 2656 (w), 1728 (w), 1695 (w), 1675 (w), 1632 (w), 1453 (w), 1440 (w), 1409 (w), 1383 (w), 1365 (w), 1352 (m), 1323 (w), 1283 (w), 1275 (w), 1260 (w), 1201 (m), 1184 (m), 1176 (m), 1157 (m), 1136 (s), 1120 (s), 1075 (s), 1064 (s), 1033 (s), 1022 (s), 983 (m), 905 (m), 881 (w), 869 (m), 814 (m).

HR-MS (APCI): for $C_{12}H_{21}O_2$ $[M+H]^+$, calc.: 197.1536, found: 197.1531; δ = 2.5 ppm.

The spectroscopic data are in full agreement with those published in the literature.[134]

Hept-5-yn-1-ol (142)



$C_7H_{12}O$, MW = 112.2 g.mol^{-1}

After **175** (160 mg, 0.82 mmol, 1.0 eq) was dissolved in 7 mL methanol, *p*TSA•H_2O (3.00 mg, 0.02 mmol, 2.5 mol%) was added and the mixture was stirred at room temperature for 3 h. 2 mL of an aqueous saturated solution of sodium hydrogen carbonate were added, the suspension was poured into 5 mL water and the aqueous layer was extracted three times with 10 mL dichloromethane. The combined organic layers were then washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified by silica gel column chromatography (*c*-Hex : AcOEt = 8 : 2 to 1 : 1) to afford **142** (90.0 mg, 0.80 mmol, 98%) as colourless oil.

R_f = 0.20 (*c*-Hex : AcOEt = 8 : 2).

^{1}H-NMR (500.1 MHz, $CDCl_3$): δ (ppm) = 3.79 (2H, t, *J* = 7.0 Hz, H-1), 2.35 (2H, td, *J* = 7.0, 2.5 Hz, H-4), 1.80 (3H, t, *J* = 2.5 Hz, H-7), 1.76-1.54 (4H, m, H-2, H-3).

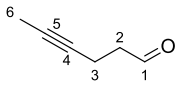
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 78.9 (C_q, C-5), 75.8 (C_q, C-6), 62.5 (CH_2, C-1), 31.1 (CH_2, C-2), 28.8 (CH_2, C-3), 18.5 (CH_2, C-4), 3.4 (CH_3, C-7).

IR (ATR): ν (cm^{-1}) = 3613 (w), 3292 (b), 2940 (m), 2868 (w), 1450 (w), 1433 (w), 1374 (w), 1331 (w), 1227 (b), 1113 (m), 1058 (s), 1035 (s), 985 (m), 927 (s), 907 (s), 879 (s), 860 (s), 815 (s), 764 (s), 716 (s).

HR-MS (APCI): for $C_7H_{13}O$ $[M+H]^+$, calc.: 113.0961, found: 113.0958; δ = 2.7 ppm.

The spectroscopic data are in full agreement with those published in the literature.[134]

Hex-4-ynal (167)



C_6H_8O, MW = 96.1 g.mol^{-1}

After DMSO (1.15 mL, 1.27 g, 16.2 mmol, 3.0 eq) in 10 mL dichloromethane was brought to -78 °C, oxalyl chloride (0.70 mL, 1.03 g, 8.10 mmol, 1.5 eq) was slowly added and the mixture was stirred at this temperature for 1 h. A solution of **169** (530 mg, 5.40 mmol, 1.0 eq) in 2 mL dichloromethane was added dropwise, over 20 min, keeping the temperature under -60 °C and the reaction was stirred for an additional 30 min. Triethylamine (3.74 mL, 2.73 g, 27.0 mmol, 5.0 eq) was added in one portion and the bath was removed, allowing the mixture to warm to room temperature. After 3 mL of a saturated aqueous solution of sodium hydrogen carbonate were added, the layers were separated and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford **167** (500 mg, 5.20 mmol, 96%) as colourless oil.

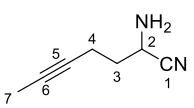
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 9.80 (1H, t, *J* = 1.4 Hz, H-1), 2.61 (2H, td, *J* = 6.8, 1.4 Hz, H-2), 2.49-2.42 (2H, m, H-3), 1.76 (3H, t, *J* =2.6 Hz, H-6).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 201.0 (CH, C-1), 77.2 (C_q, C-5), 75.7 (C_q, C-4), 42.9 (CH_2, C-2), 12.1 (CH_2, C-3), 3.4 (CH_3, C-6).

IR (ATR): ν (cm^{-1}) = 3351 (b), 2953 (w), 2920 (m), 2855 (m), 2733 (w), 1724 (m), 1714 (m), 1436 (m), 1411 (m), 1377 (m), 1329 (m), 1302 (m), 1261 (w), 1215 (w), 1187 (w), 1115 (m), 1026 (s), 953 (m), 933 (m), 914 (m), 851 (w), 840 (w), 731 (m), 705 (m), 682 (m).

HR-MS (ESI): for C_6H_8NaO $[M+Na]^+$, calc.: 119.0467, found: 119.0466; δ = 0.8 ppm.

2-Aminohept-6-ynenitrile (176)



$C_7H_{10}N_2$, MW = 122.2 g.mol^{-1}

After sodium cyanide (283 mg, 5.78 mmol, 1.7 eq) and ammonium chloride (309 mg, 5.78 mmol, 1.7 eq) were dissolved in 2 mL water and 2 mL ammonia (25% w/w solution in water), the mixture was stirred at room temperature for 1 h. A solution of **167** (327 mg, 3.40 mmol, 1.0 eq) in 1.5 mL methanol was then added and the reaction was stirred at room temperature for 16 h. After 3 mL of a saturated aqueous solution of sodium hydrogen carbonate were added, the layers were separated and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed with a saturated aqueous solution of sodium hydrogen carbonate and with brine, dried over $MgSO_4$, filtered and reduced under vacuum to obtain **176** (415 mg, 3.40 mmol, quantitative) as colourless oil.

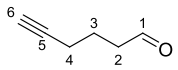
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 4.47 (1H, t, *J* = 5.6 Hz, H-2), 2.24-2.17 (2H, m, H-3), 1.83-1.72 (5H, m, H-4, H-7).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 121.9 (C_q, C-1), 77.6 (C_q, C-5), 76.4 (C_q, C-6), 42.2 (CH, C-2), 34.4 (CH_2, C-3), 15.2 (CH_2, C-4), 3.4 (CH_3, C-7).

IR (ATR): ν (cm^{-1}) = 3318 (b), 2957 (m), 2920 (s), 2857 (m), 2740 (w), 2231 (m), 2051 (w), 1668 (s), 1617 (m), 1526 (m), 1490 (m), 1438 (s), 1385 (m), 1353 (m), 1251 (w), 1215 (w), 1131 (s), 1034 (m), 979 (w), 927 (w), 877 (w), 832 (w), 812 (w), 763 (w), 705 (w).

HR-MS (ESI): for $C_7H_{11}N_2$ $[M+H]^+$, calc.: 123.0917, found: 123.0915; δ = 1.6 ppm.

Hex-5-ynal (177)



C_6H_8O, MW = 96.1 g.mol^{-1}

After DMSO (1.74 mL, 1.91 g, 24.5 mmol, 3.0 eq) in 10 mL dichloromethane was brought to -78 °C, oxalyl chloride (1.03 mL, 1.55 g, 12.2 mmol, 1.5 eq) was slowly added and the mixture stirred at this temperature for 1 h. A solution of hex-5-yn-1-ol **141** (0.90 mL, 0.80 g, 8.15 mmol, 1.0 eq) in 2 mL dichloromethane was added dropwise, over 20 min, keeping the temperature under -60 °C and the reaction was stirred for an additional 30 min. Triethylamine (5.65 mL, 4.12 g, 40.8 mmol, 5.0 eq) was added in one portion and the cold bath was removed, allowing the mixture to warm to room temperature. After 5 mL of a saturated aqueous solution of sodium hydrogen carbonate were added, the layers were separated and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford **177** (0.78 g, 8.12 mmol, quantitative) as colourless oil.

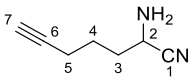
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 9.80 (1H, t, *J* = 1.4 Hz, H-1), 2.60 (2H, td, *J* = 7.2, 1.4 Hz, H-2), 2.27 (2H, td, *J* = 7.2, 2.8 Hz, H-4), 1.97 (1H, t, *J* = 2.8 Hz, H-6), 1.85 (2H, quint, *J* = 7.2 Hz, H-3).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 201.7 (C_q, C-1), 83.2 (C_q, C-5), 69.4 (CH, C-6), 42.6 (CH_2, C-2), 20.8 (CH_2, C-3), 17.8 (CH_2, C-4).

IR (ATR): ν (cm^{-1}) = 3729 (w), 3613 (w), 3318 (m), 3244 (m), 2961 (w), 2929 (w), 1668 (s), 1423 (m), 1335 (m), 1257 (m), 1227 (m), 1126 (m), 1096 (m), 970 (s), 923 (s), 873 (s), 821 (s), 737 (s), 694 (s), 681 (s), 672 (s), 666 (s).

HR-MS (APCI): for C_6H_9O $[M+H]^+$ calc.: 97.0648, found: 97.0646; δ = 2.0 ppm.

2-Aminohept-6-ynenitrile (178)



$C_7H_{10}N_2$, MW = 122.2 g.mol^{-1}

After sodium cyanide (339 mg, 6.92 mmol, 1.7 eq) and ammonium chloride (370 mg, 6.92 mmol, 1.7 eq) were dissolved in 2 mL water and 2 mL ammonia (25% w/w solution in water), the mixture was stirred at room temperature for 1 h. A solution of **177** (391 mg, 4.07 mmol, 1.0 eq) in 1.5 mL methanol was then added and the reaction was stirred at room temperature for 16 h. After 3 mL of a saturated aqueous solution of sodium hydrogen carbonate were added, the layers were separated and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed with a saturated aqueous solution of sodium hydrogen carbonate and with brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford **178** (495 mg, 4.05 mmol, quantitative) as colourless oil.

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 4.38 (1H, d, *J* = 5.6 Hz, H-2), 2.22 (2H, td, *J* = 7.0, 2.6 Hz, H-5), 1.95 (1H, t, *J* = 2.6 Hz, H-7), 1.76-1.65 (2H, m, H-3), 1.65-1.54 (2H, m, H-4).

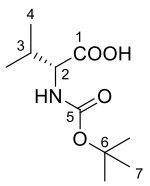
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 104.1 (C_q, C-1), 77.2 (C_q, C-6), 68.6 (CH, C-7), 52.7 (CH, C-2), 31.5 (CH_2, C-3), 23.6 (CH_2, C-4), 18.2 (CH_2, C-5).

IR (ATR): ν (cm^{-1}) = 3476 (b), 3379 (w), 3294 (m), 2937 (m), 2870 (m), 2833 (m), 2230 (w), 2116 (w), 1714 (w), 1636 (w), 1456 (m), 1434 (m), 1386 (m), 1366 (m), 1329 (m), 1267 (w), 1217 (m), 1191 (m), 1171 (m), 1127 (s), 1062 (s), 1000 (m), 954 (m), 930 (m), 845 (w), 833 (w), 806 (w).

HR-MS (ESI): for $C_7H_{11}N_2$ $[M+H]^+$, calc.: 123.0917, found: 123.0914; δ = 2.4 ppm.

The spectroscopic data are in full agreement with those published in the literature.[133]

(*R*)-2-(*tert*-Butoxycarbonylamino)-3-methylbutanoic acid (193)



$C_{10}H_{19}NO_4$, MW = 217.3 g.mol^{-1}

After D-valine **192** (2.50 g, 21.4 mmol, 1.00 eq) was dissolved in 32.5 mL water, sodium bicarbonate (3.59 g, 42.7 mmol, 2.00 eq) and a solution of di-*tert*-butyl dicarbonate (4.70 g, 21.6 mmol, 1.01 eq) in 32.5 mL THF were added. The mixture was refluxed and stirred for 16 h and THF was removed under vacuum. 50 mL ethyl acetate were added to the obtained aqueous solution and the mixture was brought to 0 °C. The pH was then adjusted to 3 by addition of aqueous saturated solution of sodium hydrogen sulfate. The layers were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were then washed with water and brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford **193** (4.18 g, 19.2 mmol, 90%) as colourless oil.

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 9.38 (1H, bs, -COOH), 4.98 (1H, d, *J* = 8.0 Hz, -NH), 4.25 (1H, m, H-2), 2.19 (1H, m, H-3), 1.45 (9H, s, H-7), 1.00 (3H, d, *J* = 6.8 Hz, H-4), 0.94 (3H, d, *J* = 6.8 Hz, H-4).

^{13}C-NMR (125.8 MHz, $CDCl_3$): δ (ppm) = 177.0 (C_q, C-1), 155.8 (C_q, C-5), 80.1 (C_q, C-6), 58.5 (CH, C-2), 31.0 (CH, C-3), 28.3 (CH_3, C-7), 19.0 (CH_3, C-4), 17.5 (CH_3, C-4).

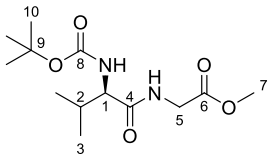
IR (ATR): ν (cm^{-1}) = 3440 (w), 3428 (w), 3317 (b), 3106 (w), 3006 (w), 2968 (m), 2934 (w), 2878 (w), 2606 (w), 1711 (s), 1661 (s), 1505 (m), 1469 (w), 1456 (w), 1393 (m), 1367 (s), 1306 (m), 1251 (m), 1157 (s), 1092 (m), 1044 (s), 1015 (m), 964 (w), 932 (w), 917 (w), 861 (w), 776 (w), 746 (w).

HR-MS (ESI): for $C_{10}H_{18}NO_4$ $[M-H]^-$, calc.: 216.1241, found: 216.1235; δ = 2.8 ppm.

$[\alpha]_D^{20}$ = +3.0 (c = 0.92, methanol).

The spectroscopic data are in full agreement with those published in the literature.[145]

(*R*)-Methyl 2-(2-(*tert*-butoxycarbonylamino)-3-methylbutanamido)acetate (194)



$C_{13}H_{24}N_2O_5$, MW = 288.3 g.mol^{-1}

After **193** (4.18 g, 19.2 mmol, 1.0 eq) and triethylamine (2.67 mL, 1.95 g, 19.2 mmol, 1.0 eq) were dissolved in 50 mL dichloromethane, *iso*-butyl chloroformate (2.5 mL, 2.63 g, 19.2 mmol, 1.0 eq) was slowly added (over 30 min) and the mixture was stirred at 0-5 °C for 30 min. Separately, a solution of glycine methylester hydrochloride (2.42 g, 19.2 mmol, 1.0 eq) and triethylamine (2.67 mL, 1.95 g, 19.2 mmol, 1.0 eq) in 50 mL dichloromethane was stirred at room temperature for 30 min. This solution was then slowly added (over 2 h) to the first one and the reaction was stirred at room temperature for 16 h. Water was added and the layers were separated. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford **194** (4.88 g, 16.9 mmol, 88%) as a white viscous paste.

^{1}H-NMR (500.1 MHz, $CDCl_3$): δ (ppm) = 6.61 (1H, bs, -NH), 5.09 (1H, bs, -NH), 4.13-3.96 (3H, m, H-1, H-5), 3.77 (3H, s, H-7), 2.19 (1H, m, H-2), 1.46 (9H, s, H-10), 1.00 (3H, d, *J* = 6.5 Hz, H-3), 0.94 (3H, d, *J* = 6.5 Hz, H-3).

^{13}C-NMR (125.8 MHz, $CDCl_3$): δ (ppm) = 171.9 (C_q, C-4), 170.1 (C_q, C-6), 156.8 (C_q, C-8), 79.5 (C_q, C-9), 59.3 (CH, C-1), 52.3 (CH_3, C-7), 41.1 (CH_2, C-5), 30.8 (CH, C-2), 28.3 (CH_3, C-10), 19.2 (CH_3, C-3).

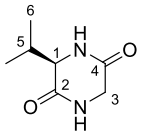
IR (ATR): ν (cm^{-1}) = 3312 (m), 3082 (w), 2957 (w), 2934 (w), 2871 (w), 1761 (m), 1750 (m), 1686 (m), 1655 (s), 1553 (m), 1524 (s), 1464 (w), 1447 (w), 1436 (m), 1417 (w), 1388 (m), 1364 (m), 1348 (w), 1297 (m), 1246 (m), 1210 (s), 1167 (s), 1117 (w), 1088 (w), 1045 (m), 1020 (m), 985 (m), 962 (w), 945 (w), 927 (w), 915 (m), 892 (w), 874 (w), 851 (w), 794 (w), 783 (w), 770 (w), 739 (w), 703 (m).

HR-MS (ESI): for $C_{13}H_{25}N_2O_5$ $[M+H]^+$, calc.: 289.1758, found: 289.1760; δ = 0.7 ppm.

$[\alpha]_D^{20}$ = +15.6 (c = 1.33, methanol).

The spectroscopic data are in full agreement with those published in the literature.[145]

(*R*)-3-*iso*-Propylpiperazine-2,5-dione (195)



$C_7H_{12}N_2O_2$, MW = 156.2 g.mol^{-1}

After **194** (4.88 g, 16.9 mmol) was dissolved in 45 mL 1,2-dichlorobenzene, the mixture was heated to 175-180 °C and stirred at this temperature for 16 h, allowing methanol to be removed by distillation. 1,2-dichlorobenzene was removed by vacuum distillation (15 mbar, 65 °C). When the residue reached 50 °C, 50 mL MTBE were added. The mixture was then cooled to room temperature and filtered. The solid was washed with MTBE and dried under vacuum at 100 °C to afford **195** (1.21 g, 7.75 mmol, 46%) as a white, slightly brown, powder.

m_p > 210 °C.

^{1}H-NMR (500.1 MHz, DMSO-d_6): δ (ppm) = 8.18 (1H, bs, -NH), 8.00 (1H, bs, -NH), 3.82 (1H, d, *J* = 17.5 Hz, H-3), 3.63 (1H, dd, *J* = 17.5, 3.0 Hz, H-3), 3.53 (1H, m, H-1), 2.12 (1H, m, H-5), 0.93 (3H, d, *J* = 7.0 Hz, H-6), 0.86 (3H, d, *J* = 7.0 Hz, H-6).

^{13}C-NMR (125.8 MHz, DMSO-d_6): δ (ppm) = 167.2 (C_q, C-2), 166.0 (C_q, C-4), 59.8 (CH, C-1), 44.1 (CH_2, C-3), 32.2 (CH, C-5), 18.5 (CH_3, C-6), 17.0 (CH_3, C-6).

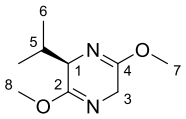
IR (ATR): ν (cm^{-1}) = 3322 (w), 3192 (b), 3049 (b), 2965 (m), 2921 (w), 2874 (w), 1662 (s), 1520 (w), 1471 (m), 1455 (m), 1421 (w), 1389 (w), 1370 (w), 1345 (m), 1331 (m), 1293 (w), 1269 (w), 1180 (w), 1114 (w), 1101 (w), 1080 (w), 1050 (w), 991 (w), 977 (w), 929 (w), 917 (w), 837 (m), 806 (m), 700 (w).

HR-MS (ESI): for $C_7H_{13}N_2O_2$ $[M+H]^+$, calc.: 157.0972, found: 157.0972; δ = 0.0 ppm.

$[\alpha]_D^{20}$ = -37.1 (c = 0.75, methanol).

The spectroscopic data are in full agreement with those published in the literature.[145]

(*R*)-2-*iso*-propyl-3,6-dimethoxy-2,5-dihydropyrazine (190)



$C_9H_{16}N_2O_2$, MW = 184.2 g.mol^{-1}

After **195** (1.21 g, 7.71 mmol, 1.0 eq) and trimethyloxonium tetrafluoroborate (4.1 g, 27.8 mmol, 3.6 eq) were dissolved in 20 mL dichloromethane, the reaction was stirred at room temperature for 5 days. The mixture was filtered under nitrogen atmosphere and the solid was washed three times with 10 mL dichloromethane. The solid was added slowly to 100 mL of a 3 : 2 mixture of an aqueous saturated solution of sodium hydrogen carbonate and dichloromethane, at 0 °C. The pH was maintained at 8-9 using sodium hydroxide. The layers were separated and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$ and reduced under vacuum. The residue was then distilled (1 mbar, 70 °C) to afford **190** (0.68 g, 3.69 mmol, 48%) as colourless oil.

^{1}H-NMR (500.1 MHz, $CDCl_3$): δ (ppm) = 4.05-3.99 (3H, m, H-1, H-3), 3.74 (3H, s, H-7, H-8), 3.70 (3H, s, H-8, H-7), 2.25 (1H, septd, *J* = 6.3, 3.5 Hz, H-5), 1.05 (3H, d, *J* = 6.3 Hz, H-6), 0.77 (3H, d, *J* = 6.3 Hz, H-6).

^{13}C-NMR (125.8 MHz, $CDCl_3$): δ (ppm) = 164.8 (C_q, C-2), 162.3 (C_q, C-4), 61.0 (CH, C-1), 52.5 (CH_3, C-7, C-8), 52.4 (CH_3, C-8, C-7), 46.6 (CH_2, C-3), 32.4 (CH, C-5), 19.0 (CH_3, C-6), 17.0 (CH_3, C-6).

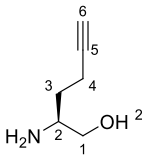
IR (ATR): ν (cm^{-1}) = 2961 (w), 2947 (w), 2904 (w), 2873 (w), 2845 (w), 1750 (w), 1697 (s), 1683 (s), 1665 (m), 1462 (m), 1437 (m), 1414 (w), 1392 (w), 1383 (w), 1366 (w), 1355 (m), 1312 (w), 1276 (w), 1236 (s), 1195 (m), 1142 (w), 1102 (m), 1053 (w), 1038 (w), 1009 (m), 967 (w), 929 (w), 913 (w), 839 (w), 776 (w), 756 (s), 671 (w).

HR-MS (ESI): for $C_9H_{17}N_2O_2$ $[M+H]^+$, calc.: 185.1285, found: 185.1280; δ = 2.7 ppm.

$[\alpha]_D^{20}$ = -107.2 (c = 0.95, ethanol).

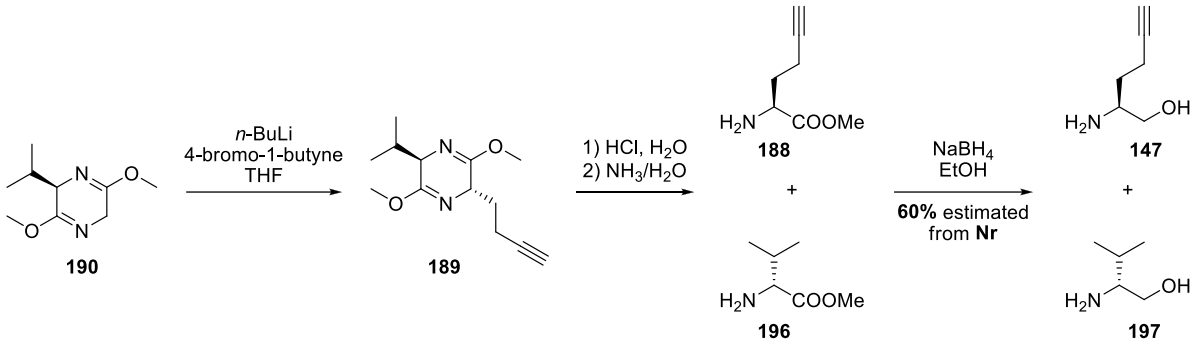
The spectroscopic data are in full agreement with those published in the literature.[145]

(*S*)-2-Aminohex-5-yn-1-ol (147)



$C_6H_{11}NO$, MW = 113.2 g.mol^{-1}

*From Schöllkopf auxiliary **190***:



Scheme 119: Reminder synthetic path from the Schöllkopf auxiliary 190 to (*S*)-2-Aminohex-5-yn-1-ol 147

After Schöllkopf auxiliary **190** (680 mg, 3.69 mmol, 1.0 eq) was dissolved in 8 mL THF, the mixture was brought to -78 °C and *n*-butyllithium (1.5 M solution in hexanes, 2.62 mL, 4.06 mmol, 1.1 eq) was added dropwise. The reaction mixture was stirred for 30 min and a solution of 4-bromo-1-butyne (0.60 mL, 835 mg, 6.28 mmol, 1.7 eq) in 22 mL THF was added over 45 min using a syringe pump. After 47 h of stirring at room temperature, the mixture was quenched with 100 µl methanol, stirred for 10 min and concentrated under vacuum. The residue was then added, without further purification or analysis, to a solution of hydrochloric acid (0.1 M in water, 73.8 mL, 7.38 mmol, 2.0 eq) and the mixture was stirred for 16 h. The aqueous solution was extracted three times with 20 mL diethyl ether and reduced under vacuum. The residue was dissolved in 5 mL water and 0.5 mL of a 10 M aqueous solution of ammonia. The obtained solution was extracted three times with 10 mL diethyl ether. The combined organic layers were then dried over $MgSO_4$, filtered and reduced under vacuum. At this stage, a purification of the residue using alumina column chromatography (*c*-Hex : AcOEt = 7 : 3) was attempted but a mixture was obtained. All spectral data were matched with reported or known data and the mixture was found to be a 9 : 1 mixture of the desired (*S*)-methyl 2-aminohex-5-ynoate **188** and D-valine methyl ester **196**. As the separation was very difficult nay impossible, this mixture was used for the next step without further purification. After the 9 : 1 mixture of **188** and **196** was dissolved in 30 mL ethanol and the solution was brought to 0 °C, sodium borohydride (700 mg, 18.5 mmol, 5.0 eq – compared with the quantity of **190** initially engaged) was added portionwise. The mixture was stirred at room temperature for 18 h. The reaction was then quenched by addition of acetic acid and stirred for 1 h. The solvents were removed under reduced pressure, water and ethyl acetate were added to the residue, the layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and reduced under vacuum. The residue was distilled (25 mbar, 200-220 °C), using a Kugelrohr distillation apparatus but the separation was very difficult and a mixture was obtained. All spectral data were matched with reported or known data and the mixture was found to be a 9 : 1

mixture of the desired product **147** and D-valinol **197**. An estimation based on the obtained quantity of mixture of **147** and **197** (250 mg) and on the spectroscopic data allowed approximating the yield of the product **147** to 60% from the Schöllkopf intermediate **190**.

*From **198***: A mixture of **198** (3.50 g, 13.8 mmol, 1.00 eq) and TFA (21.0 mL, 31.0 g, 272 mmol, 19.7 eq) was stirred at room temperature for 16 h. The reaction was then brought to 0 °C and 1 N sodium hydroxide solution was added until the pH value was between 9 and 10. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was distilled (25 mbar, 200-220 °C), using a Kugelrohr distillation apparatus to afford **147** (484 mg, 4.30 mmol, 31%) as colourless oil.

b_p = 200-220 °C (25 mbar)

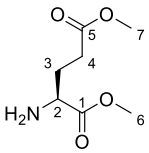
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 3.60 (1H, dd, *J* = 10.6, 3.9 Hz, H-1), 3.32 (1H, dd, *J* = 10.6, 7.6 Hz, H-1), 3.00 (1H, m, H-2), 2.31 (2H, td, *J* = 7.1, 2.5 Hz, H-4), 1.97 (1H, t, *J* = 2.6 Hz, H-6), 1.69 (1H, m, H-3), 1.47 (1H, m, H-3).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 83.7 (C_q, C-5), 68.9 (CH, C-6), 66.6 (CH_2, C-1), 51.8 (CH, C-2), 33.0 (CH_2, C-3), 15.3 (CH_2, C-4).

IR (ATR): ν (cm^{-1}) = 3373 (b), 3290 (m), 3113 (w), 2935 (w), 2876 (w), 2118 (w), 1592 (m), 1538 (m), 1432 (m), 1403 (m), 1376 (m), 1322 (m), 1268 (w), 1201 (s), 1180 (s), 1132 (s), 1093 (m), 1052 (m), 929 (w), 837 (m), 801 (s), 744 (m), 722 (s).

HR-MS (ESI): for $C_6H_{12}NO$ $[M+H]^+$, calc.: 114.0913, found: 114.0915; δ = 1.8 ppm.

(*S*)-Dimethyl 2-aminopentanedioate (202)



$C_7H_{13}NO_4$, MW = 175.2 g.mol^{-1}

After L-glutamic acid **201** (50.0 g, 340 mmol, 1.0 eq) was dissolved in 500 mL methanol, the mixture was brought to 0 °C. Thionylchloride (60.7 mL, 97.1 g, 816 mmol, 2.4 eq) was then added slowly. After the reaction was stirred at 80 °C for 18 h, the solvents were removed under vacuum to afford **202** (58.8 g, 336 mmol, 99%) as slightly yellow oil.

R_f = 0.10 (AcOEt).

^{1}H-NMR (400.1 MHz, MeOD): δ (ppm) = 4.10 (1H, t, *J* = 8.0 Hz, H-2), 3.82 (3H, s, H-6), 3.68 (3H, s, H-7), 2.67-2.50 (2H, m, H-4), 2.30-2.11 (2H, m, H-3).

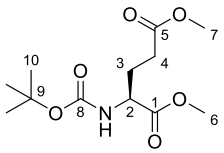
^{13}C-NMR (125.8 MHZ, $CDCl_3$): δ (ppm) = 172.9 (C_q, C-1, C-5), 169.6 (C_q, C-5, C-1), 53.4 (CH_3, C-6), 52.6 (CH, C-2), 52.0 (CH_3, C-7), 29.8 (CH_2, C-4), 25.3 (CH_2, C-3).

IR (ATR): ν (cm^{-1}) = 3367 (b), 2954 (s), 2919 (b), 2625 (m), 1718 (s), 1613 (s), 1503 (s), 1442 (s), 1415 (m), 1347 (m), 1311 (m), 1274 (m), 1233 (s), 1185 (m), 1147 (m), 1085 (m), 988 (w), 958 (w), 915 (w), 897 (w), 852 (w), 809 (w), 765 (w), 701 (w), 671 (w).

HR-MS (ESI): for $C_7H_{14}NO_4$ $[M+H]^+$, calc.: 176.0917, found: 176.0916; δ = 0.6 ppm.

$[\alpha]_D^{20}$ = +18.8 (c = 1.22, methanol).

(*S*)-Dimethyl 2-(*tert*-butoxycarbonylamino)pentanedioate (203)



$C_{12}H_{21}NO_6$, MW = 275.3 g.mol^{-1}

After **202** (42.0 g, 240 mmol, 1.00 eq) was dissolved in 560 mL dichloromethane, the mixture was brought to 0 °C and 105 mL pyridine were added. After DMAP (1.46 g, 12.0 mmol, 5 mol%) and di-*tert*-butyl dicarbonate (61.5 g, 281 mmol, 1.17 eq) were added consecutively, the mixture was stirred at room temperature for 18 h. 300 mL of an aqueous 1 N solution of hydrochloric acid were then added, the layers were separated and the aqueous layer was extracted three times with 100 mL dichloromethane. The combined organic layers were washed with a saturated aqueous solution of sodium hydrogen carbonate and with brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was filtered through a pad of silica (*c*-Hex : AcOEt = 1 : 1) to afford **203** (49.4 g, 179 mmol, 75%) as colourless oil.

R_f = 0.35 (*c*-Hex : AcOEt = 1 : 1).

^{1}H-NMR (400.1 MHz, MeOD): δ (ppm) = 4.15 (1H, m, H-2), 3.71 (3H, s, H-7, H-8), 3.66 (3H, s, H-8, H-7), 2.41 (2H, t, *J* = 7.4 Hz, H-4), 2.10 (1H, m, H-3), 1.88 (1H, m, H-3), 1.43 (9H, s, H-10).

^{13}C-NMR (100.6 MHz, MeOD): δ (ppm) = 174.8 (C_q, C-5, C-1), 174.3 (C_q, C-1, C-5), 158.1 (C_q, C-8), 80.7 (C_q, C-9), 54.3 (CH, C-2), 52.7 (CH_3, C-7, C-6), 52.2 (CH_3, C-6, C-7), 31.0 (CH_2, C-4), 28.7 (CH_3, C-10), 27.8 (CH_2, C-3).

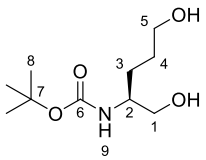
IR (ATR): ν (cm^{-1}) = 3367 (b), 2978 (m), 2955 (m), 2935 (s), 2848 (s), 1739 (s), 1715 (s), 1515 (m), 1438 (m), 1392 (s), 1367 (m), 1251 (s), 1211 (s), 1166 (s), 1050 (m), 1028 (m), 986 (s), 912 (s), 880 (s), 857 (s), 823 (s), 781 (s), 759 (s).

HR-MS (ESI): for $C_{12}H_{22}NO_6$ $[M+H]^+$, calc.: 276.1442, found: 276.1442; δ = 0.0 ppm.

$[\alpha]_D^{20}$ = -22.8 (c = 0.93, methanol).

The spectroscopic data are in full agreement with those published in the literature.[148]

(*S*)-*tert*-Butyl 1,5-dihydroxypentan-2-ylcarbamate (204)



$C_{10}H_{21}NO_4$, MW = 219.3 g.mol^{-1}

After lithium borohydride (7.54 g, 346 mmol, 2.5 eq) was added portionwise in 500 mL THF at 0 °C, the mixture was brought to -5 °C and a solution of **203** (38.1 g, 138 mmol, 1.0 eq) in 250 mL THF was added slowly, keeping the temperature under 0 °C. The reaction was stirred at room temperature for 16 h. Methanol was then added until the gas evolution stopped and the reaction mixture was reduced under vacuum. Water and ethyl acetate were added to the residue, the layers were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford **204** (26.0 g, 119 mmol, 86%) as a white solid.

R_f = 0.20 (*c*-Hex : AcOEt = 1 : 9).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 6.43 (1H, d, *J* = 8.4 Hz, H-9), 4.52 (1H, t, *J* = 4.8 Hz, -OH), 4.33 (1H, t, *J* = 5.2 Hz, -OH), 3.40-3.16 (5H, m, H-1, H-2, H-5), 1.58-1.31 (3H, m, H-3, H-4), 1.36 (9H, s, H-8), 1.18 (1H, m, H-4, H-3).

^{13}C-NMR (100.6 MHz, MeOD): δ (ppm) = 155.5 (C_q, C-6), 77.3 (C_q, C-7), 63.7 (CH_2, C-1), 59.8 (CH_2, C-5), 52.2 (CH, C-2), 29.3 (CH_2, C-4), 28.4 (CH_3, C-8), 27.7 (CH_2, C-3).

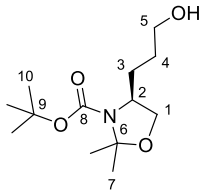
IR (ATR): ν (cm^{-1}) = 3329 (b), 2976 (m), 2935 (m), 2873 (w), 1686 (s), 1529 (m), 1392 (w), 1366 (m), 1250 (m), 1171 (s), 1051 (m).

HR-MS (ESI): for $C_{10}H_{21}NNaO_4$ $[M+Na]^+$, calc.: 242.1363, found: 242.1364; δ = 0.4 ppm.

$[\alpha]_D^{20}$ = -14.5 (c = 1.05, methanol).

The spectroscopic data are in full agreement with those published in the literature.[148]

(*S*)-*tert*-Butyl 4-(3-hydroxypropyl)-2,2-dimethyloxazolidine-3-carboxylate (200)



$C_{13}H_{25}NO_4$, MW = 259.3 g.mol^{-1}

After **204** (26.0 g, 119 mmol, 1.00 eq) was dissolved in 450 mL dichloromethane, *p*TSA•H_2O (2.30 g, 11.9 mmol, 0.10 eq) and 2,2-dimethoxypropane (165 mL, 140 g, 1.34 mol, 11.3 eq) were added respectively. The reaction was stirred at room temperature for 1.5 h. 100 mL of a saturated aqueous

solution of sodium hydrogen carbonate were added to the mixture, the layers were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford **200** (29.3 g, 113 mmol, 95%) as yellowish oil.

R_f = 0.70 (*c*-Hex : AcOEt = 1 : 1).

^{1}H-NMR (500.1 MHz, $CDCl_3$): δ (ppm) = 3.84 (1H, m, -OH), 3.80-3.64 (2H, m, H-5), 3.50-3.10 (3H, m, H-1, H-2), 1.70-1.15 (19H, m, H-3, H-4, H-7, H-10).

^{13}C-NMR (125.8 MHz, $CDCl_3$): δ (ppm) = 151.8 (C_q, C-8), 99.6 (C_q, C-6), 80.2 (CH, C-2), 79.4 (C_q, C-9), 67.0 (CH_2, C-1), 57.2 (CH_2, C-5), 29.7 (CH_2, C-4), 28.4 (CH_3, C-10), 26.9 (CH_2, C-3), 24.9 (CH_3, C-7), 24.4 (CH_3, C-7).

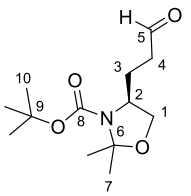
IR (ATR): ν (cm^{-1}) = 3500 (b), 2979 (m), 2937 (m), 2871 (m), 1696 (s), 1390 (s), 1366 (s), 1258 (m), 1175 (m), 1087 (m).

HR-MS (ESI): for $C_{13}H_{25}NNaO_4$ $[M+Na]^+$, calc.: 282.1676, found: 282.1680; δ = 1.4 ppm.

$[\alpha]_D^{20}$ = +31.1 (c = 1.30, methanol).

The spectroscopic data are in full agreement with those published in the literature.[148]

(*S*)-*tert*-Butyl 2,2-dimethyl-4-(3-oxopropyl)oxazolidine-3-carboxylate (205)



$C_{13}H_{23}NO_4$, MW = 257.3 g.mol^{-1}

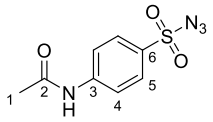
After **200** (6.04 g, 23.3 mmol, 1.0 eq) was dissolved in 110 mL dichloromethane, 22.2 mL DMSO and triethylamine (16.2 mL, 11.8 g, 117 mmol, 5.0 eq) were respectively added and the mixture was brought to 0 °C. At this temperature, Py•SO_3 (14.8 g, 93.2 mmol, 4.0 eq) was added portionwise and the reaction was stirred at room temperature for 16 h. 100 mL of a saturated aqueous solution of ammonium chloride and 100 mL dichloromethane were added, the layers were separated and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford **205** (5.93 g, 23.0 mmol, 99%) as colourless oil.

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 9.78 (1H, s, H-5), 4.01-3.90 (2H, m, H-1, H-2), 3.69 (1H, m, H-1), 2.52-2.49 (2H, m, H-4), 2.07-1.85 (2H, m, H-3), 1.68-1.40 (15H, m, H-7, H-10).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 201.3 (CH, C-5), 153.2 (C_q, C-8), 105.3 (C_q, C-6), 76.6 (C_q, C-9), 75.2 (CH, C-2), 68.7 (CH_2, C-1), 38.5 (CH_2, C-4), 28.5 (CH_3, C-10), 26.0 (CH_3, C-7), 21.1 (CH_2, C-3).

HR-MS (ESI): for $C_{13}H_{24}NO_4$ $[M+H]^+$, calc.: 258.1700, found: 258.1698; δ = 0.8 ppm.

4-Acetamidobenzenesulfonyl azide (207)



$C_8H_8N_4O_3S$, MW = 240.2 g.mol^{-1}

After 4-acetamidobenzenesulfonyl chloride **206** (100 g, 428 mmol, 1.00 eq) was dissolved in 800 mL dichloromethane, a catalytic amount of TBAI (0.40 g, 1.10 mmol, 0.25 mol%) was added. Sodium azide (42.0 g, 646 mmol, 1.51 eq) was dissolved in 200 mL water and added to the first solution. The reaction mixture was stirred at room temperature for 16 h. The layers were separated and the organic layer was washed two times with water, dried over $MgSO_4$, filtered and reduced under vacuum to afford **207** (98.8 g, 441 mmol, 96%) as a white, lightly yellow, crystalline solid.

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 7.91 (2H, m, H-5), 7.77 (2H, m, H-4), 7.46 (1H, s, -NH), 2.25 (3H, s, H-1).

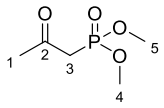
^{13}C-NMR (100.6 MHz, MeOD): δ (ppm) = 168.6 (C_q, C-2), 143.7 (C_q, C-3), 132.8 (C_q, C-6), 129.1 (CH, C-5), 119.5 (CH, C-4), 24.9 (CH_3, C-1).

IR (ATR): ν (cm^{-1}) = 3315 (b), 2128 (s), 1682 (m), 1590 (m), 1529 (m), 1404 (m), 1369 (m), 1318 (m), 1164 (s), 1088 (m), 754 (w).

HR-MS (ESI): for $C_8H_7N_4O_3S$ $[M-H]^-$, calc.: 239.0239, found: 239.0238; δ = 0.4 ppm.

The spectroscopic data are in full agreement with those published in the literature.[154]

Dimethyl 2-oxopropylphosphonate (209)



$C_5H_{11}O_4P$, MW = 166.1 g.mol^{-1}

After potassium iodide (232 g, 1.40 mol, 1 eq) was suspended in 280 mL freshly distilled acetone and 350 mL freshly distilled acetonitrile, 1-chloropropan-2-one **208** (112 mL, 130 g, 1.40 mol, 1 eq) was added and the reaction was stirred at room temperature for 1 h. The mixture was brought to -10 °C, trimethyl phosphite (166 mL, 1.40 mol, 1 eq) was added and the reaction was stirred at room temperature for 18 h. The reaction mixture was then filtered through a pad of Celite, the solvents were removed under vacuum and the residue was distilled (110 °C, 5 mbar) to afford **209** (114 g, 693 mmol, 50%) as slightly yellow oil.

b_p = 110 °C (5 mbar)

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 3.80 (3H, s, H-4, H-5), 3.77 (3H, s, H-5, H-4), 3.12 (2H, d, $^{3}J_{H,P}$ = 22.8 Hz, H-3), 2.31 (3H, s, H-1).

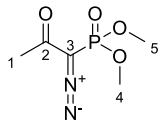
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 199.7 (C_q, d, $^{2}J_{C,P}$ = 6.4 Hz, C-2), 53.1 (CH_3, d, $^{2}J_{C,P}$ = 6.5 Hz, C-4, C-5), 42.3 (CH_2, d, $^{1}J_{C,P}$ = 127.9 Hz, C-3), 31.4 (CH_3, C-1).

IR (ATR): ν (cm^{-1}) = 2958 (b), 1711 (s), 1360 (m), 1253 (s), 1184 (m), 1021 (s), 826 (s).

HR-MS (ESI): for $C_5H_{12}O_4P$ $[M+H]^+$, calc.: 167.0468, found: 167.0463; δ = 3.0 ppm.

The spectroscopic data are in full agreement with those published in the literature.[154]

Dimethyl 1-diazo-2-oxopropylphosphonate (210)



$C_5H_9N_2O_4P$, MW = 192.1 g.mol^{-1}

After dimethyl 2-oxopropylphosphonate **209** (58.0 g, 349 mmol, 1.09 eq) was dissolved in 350 mL toluene, the solution was brought to 0 °C. At this temperature, sodium hydride (75% in mineral oil, 10.0 g, 315 mmol, 0.98 eq) was added portionwise added and subsequently, a solution of azide **207** (77.2 g, 322 mmol, 1.00 eq) in 110 mL THF was added dropwise. The reaction mixture was stirred at room temperature for 18 h, diluted with 300 mL diethyl ether and filtered through a pad of Celite. The organic layer was dried over $MgSO_4$, filtered and reduced under vacuum to afford **210** (37.1 g, 193 mmol, 60%) as slightly yellow oil.

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 3.84 (3H, d, $^{3}J_{H,P}$ = 2.0 Hz, H-4, H-5), 3.81 (3H, d, $^{3}J_{H,P}$ = 2.0 Hz, H-5, H-4), 2.25 (3H, s, H-1).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 189.9 (C_q, d, $^{2}J_{C,P}$ = 12.9 Hz, C-2), 128.4 (C_q, d, $^{1}J_{C,P}$ = 241.4 Hz, C-3), 53.6 (CH_3, d, $^{2}J_{C,P}$ = 5.6 Hz, C-4, C-5), 27.1 (CH_3, C-1).

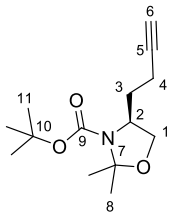
^{31}P-NMR (212.6 MHz, $CDCl_3$): δ (ppm) = 14.2.

IR (ATR): ν (cm^{-1}) = 2957 (b), 2925 (w), 2118 (s), 1655 (s), 1364 (m), 1266 (s), 1179 (m), 1015 (s), 833 (m), 780 (m).

HR-MS (APCI): for $C_5H_9N_2NaO_4P$ $[M+Na]^+$, calc.: 215.0192, found: 215.0191; δ = 0.5 ppm.

The spectroscopic data are in full agreement with those published in the literature.[154,223]

(*S*)-*tert*-Butyl 4-(but-3-ynyl)-2,2-dimethyloxazolidine-3-carboxylate (198)



$C_{14}H_{23}NO_3$, MW = 253.3 g.mol^{-1}

After **205** (5.45 g, 21.2 mmol, 1.0 eq) was dissolved in 200 mL methanol, the Ohira-Bestmann reagent **210** (3.81 mL, 4.88 g, 25.4 mmol, 1.2 eq) and potassium carbonate (5.85 g, 42.4 mmol, 2.0 eq) were added respectively. The reaction was stirred at room temperature for 1.5 h. The mixture was filtered to remove the potassium salts, 100 mL of a saturated aqueous solution of ammonium chloride and 100 mL of MTBE were added and the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified by silica gel column chromatography (*c*-Hex : AcOEt = 10 : 1) to afford **198** (3.58 g, 14.1 mmol, 67%) as colourless oil.

R_f = 0.67 (*c*-Hex : AcOEt = 2 : 1).

^{1}H-NMR (400.1 MHz, DMSO-d_6): δ (ppm) = 3.89-3.76 (3H, m, H-1, H-2), 2.78 (1H, t, *J* = 2.6 Hz, H-6), 2.25-2.08 (2H, m, H-4), 1.76 (1H, m, H-3), 1.60 (1H, m, H-3), 1.45 (3H, s, H-8), 1.40 (3H, s, H-8), 1.38 (9H, s, H-11).

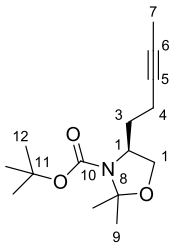
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 154.3 (C_q, C-9), 105.5 (C_q, C-7), 83.1 (C_q, C-5), 79.6 (C_q, C-10), 76.8 (CH, C-2), 69.2 (C_q, C-6), 67.1 (CH_2, C-1), 28.4 (CH_3, C-11), 26.8 (CH_3, C-8), 20.2 (CH_2, C-3), 16.4 (CH_2, C-4).

IR (ATR): ν (cm^{-1}) = 3310 (b), 3263 (b), 2979 (m), 2936 (w), 2874 (w), 2119 (w), 1739 (w), 1695 (s), 1538 (w), 1479 (w), 1455 (w), 1433 (w), 1388 (s), 1376 (s), 1366 (s), 1334 (w), 1307 (w), 1259 (m), 1207 (w), 1175 (m), 1149 (m), 1103 (m), 1085 (m), 1071 (m), 1043 (w), 1030 (w), 978 (w), 946 (w), 924 (w), 854 (w), 807 (w), 769 (w).

HR-MS (ESI): for $C_{14}H_{23}NNaO_3$ $[M+Na]^+$, calc.: 276.1570, found: 276.1569; δ = 0.4 ppm.

$[\alpha]_D^{20}$ = -23.7 (c = 0.63, methanol).

(*S*)-*tert*-Butyl 2,2-dimethyl-4-(pent-3-ynyl)oxazolidine-3-carboxylate (199)



$C_{15}H_{25}NO_3$, MW = 267.4 g.mol^{-1}

After **198** (200 mg, 0.79 mmol, 1.0 eq) was dissolved in 10 mL THF, the mixture was brought to -10 °C and *n*-butyllithium (2.5 M solution in hexanes, 0.35 mL, 0.87 mmol, 1.1 eq) was added dropwise. The reaction was stirred at the same temperature for 10 min, TMEDA (0.26 mL, 202 mg, 1.74 mmol, 2.2 eq) was added dropwise and the mixture was stirred for an additional 10 min. Methyl iodide (0.25 mL, 561 mg, 3.95 mmol, 5.0 eq) was added and the reaction was stirred at room temperature for 3 h. After the reaction mixture was poured into 10 mL water, the layers were separated and the aqueous layer was extracted three times with 20 mL ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was filtered through a pad of aluminium oxide (*c*-Hex : AcOEt = 9 : 1) to afford **199** (205 mg, 0.77 mmol, 97%) as colourless oil.

R_f = 0.65 (*c*-Hex : AcOEt = 9 : 1, aluminium oxide).

^{1}H-NMR (400.1 MHz, DMSO-d_6): δ (ppm) = 3.89-3.80 (2H, m, H-1), 3.76 (1H, m, H-2), 2.22-2.01 (2H, m, H-3), 1.74 (1H, m, H-4), 1.70 (3H, bs, H-7), 1.56 (1H, m, H-4), 1.45 (3H, s, H-9), 1.40 (9H, s, H-12), 1.37 (3H, s, H-9).

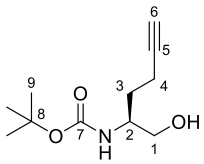
^{13}C-NMR (125.8 MHz, DMSO-d_6): δ (ppm) = 154.2 (C_q, C-10), 105.3 (C_q, C-8), 81.2 (C_q, C-5), 79.7 (C_q, C-11), 76.6 (CH, C-2), 75.2 (C_q, C-6), 66.7 (CH_2, C-1), 28.5 (CH_3, C-12), 27.0 (CH_3, C-9), 25.0 (CH_2, C-3), 15.9 (CH_2, C-4), 3.4 (CH_3, C-7).

IR (ATR): ν (cm^{-1}) = 3005 (w), 2978 (m), 2935 (w), 2872 (w), 1697 (s), 1479 (w), 1455 (w), 1388 (s), 1376 (s), 1365 (s), 1336 (w), 1306 (w), 1259 (m), 1207 (w), 1175 (m), 1150 (m), 1101 (m), 1084 (m), 1070 (m), 1029 (w), 947 (w), 853 (w), 807 (w), 769 (w).

HR-MS (ESI): for $C_{15}H_{25}NNaO_3$ $[M+Na]^+$, calc.: 290.1727, found: 290.1724; δ = 1.0 ppm.

$[\alpha]_D^{20}$ = -20.8 (c = 0.5, methanol).

(*S*)-*tert*-Butyl 1-hydroxyhex-5-yn-2-ylcarbamate (211)



$C_{11}H_{19}NO_3$, MW = 213.3 g.mol^{-1}

After **198** (50.0 mg, 0.20 mmol, 1.00 eq) was dissolved in 2.5 mL ethanol, water (0.13 mL, 125 mg, 6.94 mmol, 35.2 eq) and *p*TSA•H_2O (187 mg, 1.00 mmol, 5.00 eq) were added and the mixture was stirred at room temperature for 24 h. 2 mL of an aqueous saturated solution of sodium bicarbonate were added and the mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was then purified using column chromatography (*c*-Hex : AcOEt = 8 : 2, aluminium oxide) to afford the product **211** (42.0 mg, 0.20 mmol, quantitative) as colourless oil.

$\mathbf{R_f}$ = 0.40 (*c*-Hex : AcOEt = 7 : 3).

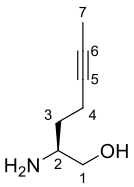
^{1}H-NMR (400.1 MHz, DMSO-d_6): δ (ppm) = 6.51 (1H, d, *J* = 8.4 Hz, -NH), 4.61 (1H, bs, -OH), 3.49-3.18 (3H, m, H-1, H-2), 2.71 (1H, t, *J* = 2.6 Hz, H-6), 2.20-2.06 (2H, m, H-4), 1.72 (1H, m, H-3), 1.43 (1H, m, H-3), 1.36 (9H, s, H-9).

^{13}C-NMR (100.6 MHz, DMSO-d_6): δ (ppm) = 156.7 (C_q, C-7), 84.3 (C_q, C-5), 79.7 (C_q, C-8), 68.8 (CH, C-6), 62.8 (CH_2, C-1), 54.9 (CH, C-2), 28.4 (CH_3, C-9), 19.8 (CH_2, C-3), 17.0 (CH_2, C-4).

IR (ATR): ν (cm^{-1}) = 3369 (b), 3291 (b), 2972 (w), 2928 (w), 2870 (w), 2252 (w), 2127 (w), 1694 (m), 1525 (m), 1452 (w), 1391 (m), 1365 (m), 1274 (w), 1248 (m), 1169 (s), 1050 (s), 1024 (s), 1005 (s), 863 (w), 823 (m), 762 (m).

HR-MS (ESI): for $C_{11}H_{19}NNaO_3$ $[M+Na]^+$, calc.: 236.1257, found: 236.1252; δ = 2.1 ppm.

(*S*)-2-Aminohept-5-yn-1-ol (148)



$C_7H_{13}NO$, MW = 127.2 g.mol^{-1}

After **199** (605 mg, 2.26 mmol, 1.0 eq) was brought to 0 °C, trifluoroacetic acid (1.74 mL, 2.58 g, 22.6 mmol, 10.0 eq) was added and the solution was stirred at room temperature for 16 h. Water was added and the mixture was stirred for an additional 30 min. A 1 M aqueous solution of sodium hydroxide was added until the pH was adjusted to 7. Ethyl acetate was added, the layers were separated and the aqueous layer was extracted two more times with ethyl acetate. The combined organic layers were washed with brine, dried and reduced under vacuum to afford a 1 : 1 mixture of

148 and **212** which were engaged in the following reaction without further purification. After the 1 : 1 mixture of **148** and **212** was dissolved in 25 mL of an 8 : 2 mixture of acetonitrile and chloroform, 0.6 mL water and cerium(III) chloride heptahydrate (84.2 mg, 0.23 mmol, 0.1 eq) were added and the reaction was stirred for 20 h at room temperature. The solvents were removed under vacuum. The reaction vessel was adapted with a liquid-liquid continuous extractor and water and chloroform were added to the residue. The continuous extraction water/chloroform was performed for 18 h. The layers were then separated and the organic layer was dried over $MgSO_4$ and reduced under vacuum. The residue was purified using column chromatography (dichloromethane : methanol : diethylamine = 88 : 10 : 2) to afford **148** (125 mg, 0.98 mmol, 44%) as yellowish oil.

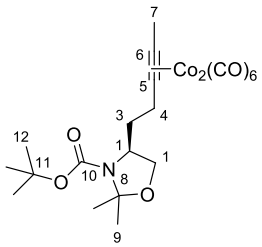
R_f = 0.50 (dichloromethane : methanol : diethylamine = 85 : 10 : 5).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 3.60 (1H, dd, *J* = 10.6, 4.0 Hz, H-1), 3.30 (1H, dd, *J* = 10.6, 7.6 Hz, H-1), 2.99 (1H, m, H-2), 2.25 (2H, tq, *J* = 7.0, 2.6 Hz, H-4), 1.81 (3H, bs, -OH, -NH2), 1.77 (3H, t, *J* = 2.6 Hz, H-7), 1.60 (1H, m, H-3), 1.42 (1H, m, H-3).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 77.6 (C_q, C-5, C-6), 76.9 (C_q, C-6, C-5), 63.4 (CH_2, C-1), 50.5 (CH, C-2), 31.2 (CH_2, C-3), 15.5 (CH_2, C-4), 3.5 (CH_3, C-7).

HR-MS (ESI): for $C_7H_{14}NO$ $[M+H]^+$, calc.: 128.1070, found: 128.1067; δ = 2.3 ppm.

Hexacarbonyl-μ-(η^4-(*S*)-*tert*-Butyl 2,2-dimethyl-4-(pent-3-ynyl)oxazolidine-3-carboxylate)dicobalt-(Co-Co) (213)



$C_{21}H_{25}Co_2NO_9$, MW = 553.3 g.mol^{-1}

After **199** (100 mg, 0.37 mmol, 1.0 eq) was dissolved in 4 mL diethyl ether, dicobalt octacarbonyl (141 mg, 0.41 mmol, 1.1 eq) was added and the mixture was stirred at room temperature for 20 h. The solvents were removed under vacuum and the residue was purified using column chromatography (*c*-Hex : AcOEt = 9 : 1, aluminium oxide) to afford **213** (197 mg, 0.36 mmol, 95%) as dark brown oil.

R_f = 0.60 (*c*-Hex : AcOEt = 1 : 1, aluminium oxide).

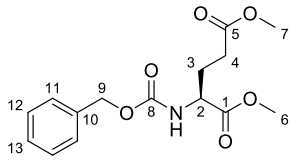
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 3.93 (2H, bs, H-1, H-2), 3.77 (1H, bs, H-2, H-1), 2.79 (2H, bs, H-3), 2.64 (3H, s, H-7), 1.84 (2H, bs, H-4), 1.43 (15H, bs, H-9, H-12).

IR (ATR): ν (cm^{-1}) = 3379 (b), 2978 (w), 2936 (w), 2973 (w), 2087 (m), 2044 (s), 2004 (s), 1694 (s), 1574 (w), 1478 (w), 1453 (w), 1384 (m), 1367 (m), 1308 (w), 1254 (m), 1207 (w), 1173 (m), 1148 (m), 1099 (m), 1077 (m), 1035 (w), 1015 (w), 944 (w), 853 (w), 806 (w), 767 (w).

HR-MS (APCI): for $C_{21}H_{25}Co_2NNaO_9$ $[M+Na]^+$, calc.: 576.0086, found: 576.0090; δ = 0.7 ppm.

Due to the ferromagnetism of the cobalt element, the ^{1}H-NMR spectrum of this compound was only composed of broad signals and it was not possible to analyse the ^{13}C-NMR spectrum.

(*S*)-Dimethyl 2-(benzyloxycarbonylamino)pentanedioate (215)



$C_{15}H_{19}NO_6$, MW = 309.3 g.mol^{-1}

After **202** (29.6 g, 125 mmol, 1.0 eq) was dissolved in a mixture of 150 mL of water and 150 mL of THF, sodium hydrogen carbonate (26.3 g, 313 mmol, 2.5 eq) and CbzCl (23.5 g, 138 mmol, 1.1 eq) were respectively added. The reaction was stirred at room temperature for 16 h. 150 mL of 1 N aqueous solution of hydrochloric acid were added, the layers were separated and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was filtered through a pad of silica (*c*-Hex : AcOEt = 1 : 1) to afford **215** (32.1 g, 104 mmol, 83%) as colourless oil.

R_f = 0.50 (*c*-Hex : AcOEt = 1 : 1).

^{1}H-NMR (400.1 MHz, MeOD): δ (ppm) = 7.36-7.30 (5H, m, H-Ar), 5.09 (2H, s, H-9), 4.25 (1H, m, H-2), 3.72 (3H, s, H-6), 3.65 (3H, s, H-7), 2.43 (2H, t, *J* = 7.2 Hz, H-4), 2.19 (1H, m, H-3), 1.92 (1H, m, H-3).

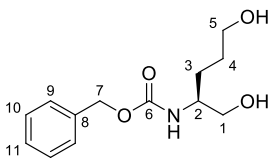
^{13}C-NMR (100.6 MHz, MeOD): δ (ppm) = 173.2 (C_q, C-1, C-5), 172.5 (C_q, C-5, C-1), 157.1 (C_q, C-8), 136.6 (C_q, C-10), 127.9 (CH, C-Ar), 127.8 (CH, C-Ar), 127.5 (CH, C-Ar), 127.3 (CH, C-Ar), 126.5 (CH, C-Ar), 66.2 (CH_2, C-9), 53.2 (CH, C-2), 51.2 (CH_3, C-6), 50.7 (CH_3, C-7), 29.4 (CH_2, C-4), 26.2 (CH_2, C-3).

IR (ATR): ν (cm^{-1}) = 3343 (b), 2953 (m), 1719 (s), 1524 (m), 1437 (m), 1334 (w), 1256 (m), 1210 (s), 1174 (m), 1050 (m), 777 (w), 740 (m), 698 (m).

HR-MS (ESI): for $C_{15}H_{20}NO_6$ $[M+H]^+$, calc.: 310.1285, found: 310.1290; δ = 1.6 ppm.

$[\alpha]_D^{20}$ = +4.8 (c = 1.45, chloroform).

(*S*)-Benzyl 1,5-dihydroxypentan-2-ylcarbamate (216)



$C_{13}H_{19}NO_4$, MW = 253.3 g.mol^{-1}

After **215** (23.2 g, 75.0 mmol, 1 eq) was dissolved in 400 mL THF, the mixture was brought to 0 °C and lithium borohydride (4.91 g, 225 mmol, 3 eq) was added portionwise followed by methanol (9.13 mL, 7.21 g, 225 mmol, 3 eq). The reaction was stirred at 0 °C for 4 h. A 1 N aqueous solution of hydrochloric acid was added until the gas evolution ceased and the reaction mixture was stirred for another 20 min. The layers were separated and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed two times with brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford **216** (13.6 g, 53.8 mmol, 72%) as a white solid.

R_f = 0.40 (AcOEt).

^{1}H-NMR (400.1 MHz, DMSO-d_6): δ (ppm) = 7.41-7.29 (5H, m, H-Ar), 6.95 (1H, d, *J* = 6.8 Hz, -NH), 5.01 (2H, s, H-7), 4.59 (1H, t, *J* = 4.4 Hz, -OH), 4.34 (1H, t, *J* = 4.4 Hz, -OH), 3.48-3.28 (4H, m, H-1, H-5), 3.24 (1H, m, H-2), 1.54 (1H, m, H-3), 1.48-1.30 (2H, m, H-, H-4), 1.24 (1H, m, H-4).

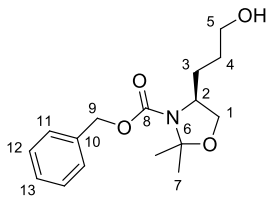
^{13}C-NMR (100.6 MHz, DMSO-d_6): δ (ppm) = 155.9 (C_q, C-6), 137.2 (C_q, C-8), 128.2 (CH, C-Ar), 127.6 (CH, C-Ar), 127.5 (CH, C-Ar), 64.9 (CH_2, C-7), 63.5 (CH_2, C-1), 60.6 (CH_2, C-5), 52.7 (CH, C-2), 29.0 (CH_2, C-4), 27.4 (CH_2, C-3).

IR (ATR): ν (cm^{-1}) = 3314 (b), 2953 (m), 2929 (m), 2876 (w), 1684 (s), 1543 (m), 1452 (w), 1290 (m), 1255 (m), 1073 (m), 1011 (m), 696 (w).

HR-MS (ESI): for $C_{13}H_{20}NO_4$ $[M+H]^+$, calc.: 254.1387, found: 254.1393; δ = 2.4 ppm.

$[\alpha]_D^{20}$ = -17.4 (c = 0.99, methanol).

(*S*)-Benzyl 4-(3-hydroxypropyl)-2,2-dimethyloxazolidine-3-carboxylate (217)



$C_{16}H_{23}NO_4$, MW = 293.4 g.mol^{-1}

After **216** (11.2 g, 44.3 mmol, 1.00 eq) was dissolved in 200 mL dichloromethane, *p*TSA•H_2O (0.84 g, 4.43 mmol, 0.10 eq) and 2,2-dimethoxypropan (81.8 mL, 69.2 g, 665 mmol, 15.0 eq) were added respectively. The reaction was stirred at room temperature for 1.5 h. 80 mL of a saturated aqueous solution of sodium hydrogen carbonate were added to the mixture, the layers were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford **217** (10.5 g, 35.8 mmol, 81%) as yellowish oil.

R_f = 0.35 (*c*-Hex : AcOEt = 1 : 1).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 7.55-7.35 (5H, m, H-Ar), 5.04 (2H, s, H-9), 4.39 (1H, t, *J* = 5.2 Hz, -OH), 3.98-3.80 (2H, m, H-1, H-2), 3.73 (1H, bd, *J* = 8.0 Hz, H-1), 3.36-3.26 (2H, m, H-5), 1.70-1.21 (10H, m, H-3, H-4, H-7).

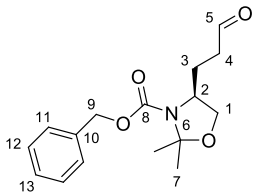
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 151.7 (C_q, C-8), 136.9 (C_q, C-10), 128.5 (CH, C-Ar), 127.9 (CH, C-Ar), 127.5 (CH, C-Ar), 93.1 (C_q, C-6), 66.7 (CH_2, C-1), 65.7 (CH_2, C-9), 60.7 (CH_2, C-5), 56.7 (CH, C-2), 29.0 (CH_2, C-4), 26.5 (CH_2, C-3), 24.4 (CH_3, C-7), 24.0 (CH_3, C-7).

IR (ATR): ν (cm^{-1}) = 3452 (b), 3112 (w), 3091 (w), 3065 (w), 3033 (w), 2984 (m), 2939 (m), 2873 (m), 1699 (s), 1587 (w), 1532 (w), 1498 (w), 1455 (m), 1407 (s), 1378 (m), 1351 (s), 1309 (m), 1257 (m), 1210 (m), 1182 (w), 1147 (m), 1088 (s), 1077 (s), 1029 (m), 959 (w), 910 (w), 859 (w), 838 (m), 766 (m), 751 (m), 738 (m), 698 (m).

HR-MS (APCI): for $C_{16}H_{24}NO_4$ $[M+H]^+$, calc.: 294.1700, found: 294.1694; δ = 2.0 ppm.

$[\alpha]_D^{20}$ = +23.7 (c = 0.94, dichloromethane).

(*S*)-Benzyl 2,2-dimethyl-4-(3-oxopropyl)oxazolidine-3-carboxylate (218)



$C_{16}H_{21}NO_4$, MW = 291.3 g.mol^{-1}

After **217** (1.00 g, 3.55 mmol, 1.00 eq) was dissolved in 17 mL dichloromethane, a solution of potassium bromide (44.3 mg, 0.37 mmol, 0.10 eq) and sodium bicarbonate (152 mg, 1.81 mmol, 0.50 eq) in 1.7 mL water was added. The mixture was brought to 0 °C, TEMPO (16.6 mg, 0.11 mmol, 3 mol%) and a solution of sodium hypochlorite (14.5% available chlorine, 2.40 mL, 5.53 mmol, 1.56 eq) were added and the reaction was stirred at room temperature for 16 h. 10 mL of an aqueous saturated solution of sodium thiosulfate were added and the layers were separated. The organic layer was washed three times with brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford **218** (842 mg, 2.89 mmol, 82%) as slightly pink oil.

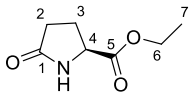
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 9.77 (1H, s, H-5), 7.40-7.30 (5H, m, H-11, H-12, H-13), 5.14 (2H, s, H-9), 4.08-3.92 (2H, m, H-1, H-2), 3.74 (1H, m, H-1), 2.56-2.37 (2H, m, H-4), 2.08-1.89 (2H, m, H-3), 1.63 (3H, s, H-7), 1.51 (3H, s, H-7).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 201.1 (CH, C-5), 148.7 (C_q, C-8), 137.2 (C_q, C-10), 128.6 (CH, C-11, C-12, C-13), 128.2 (CH, C-12, C-13, C-11), 128.1 (CH, C-13, C-11, C-12), 116.7 (C_q, C-6), 77.3 (CH, C-2), 67.4 (CH_2, C-1), 66.8 (CH_2, C-9), 41.0 (CH_2, C-4), 26.6 (CH_3, C-7), 26.1 (CH_3, C-7), 23.0 (CH_2, C-3).

IR (ATR): ν (cm^{-1}) = 3089 (w), 3064 (w), 3033 (w), 2982 (w), 2938 (w), 2876 (w), 2722 (w), 1695 (s), 1607 (w), 1586 (w), 1532 (w), 1498 (w), 1453 (w), 1404 (s), 1377 (m), 1350 (s), 1305 (m), 1253 (m), 1208 (m), 1147 (m), 1087 (s), 1075 (s), 1054 (s), 1028 (m), 958 (w), 908 (w), 860 (w), 836 (m), 766 (m), 748 (m), 737 (m), 698 (m).

HR-MS (ESI): for $C_{16}H_{21}NNaO_4$ $[M+Na]^+$, calc.: 314.1363, found: 314.1361; δ = 0.6 ppm.

(*S*)-Ethyl 5-oxopyrrolidine-2-carboxylate (224)



$C_7H_{11}NO_3$, MW = 157.2 g.mol^{-1}

After (*S*)-pyroglutamic acid **115** (15.0 g, 105 mmol, 1.0 eq) is suspended in 80 mL toluene, ethanol (31.6 mL, 25.0 g, 543 mmol, 5.2 eq) and 0.5 mL concentrated sulfuric acid were added. The reaction vessel was fitted with a Dean-Stark apparatus and the mixture refluxed with azeotropic removal of water for 6 h. While the reaction was cooling down to room temperature, 100 mL chloroform and potassium carbonate (10.0 g, 73.0 mmol) were added. After effervescence stopped, the mixture was filtered through a pad of Celite. The filtrate was then dried over $MgSO_4$ and reduced under vacuum to afford **224** (16.5 g, 105 mmol, quantitative) as colourless needles.

m_p = 50-52 °C.

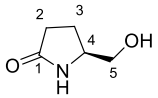
^{1}H-NMR (400.1 MHz, DMSO-d_6): δ (ppm) = 4.17-4.08 (3H, m, H-4, H-6), 2.32 (1H, m, H-3), 2.16-2.08 (2H, m, H-2), 1.95 (1H, m, H-3), 1.19 (3H, t, *J* = 7.2 Hz, H-7).

^{13}C-NMR (100.6 MHz, DMSO-d_6): δ (ppm) = 177.1 (C_q, C-1), 173.0 (C_q, C-5), 60.8 (CH_2, C-6), 54.8 (CH, C-4), 29.0 (CH_2, C-2), 24.6 (CH_2, C-3), 14.1 (CH_3, C-7).

HR-MS (ESI): for $C_7H_{12}NO_3$ $[M+H]^+$, calc.: 158.0812, found: 158.0809; δ = 1.8 ppm.

$[\alpha]_D^{20}$ = +2.7 (c = 0.95, ethanol).

(*S*)-5-(Hydroxymethyl)pyrrolidin-2-one (225)



$C_5H_9NO_2$, MW = 115.1 g.mol^{-1}

After **224** (16.5 g, 105 mmol, 1 eq) was dissolved in 150 mL ethanol, the mixture was brought to 0 °C and sodium borohydride (3.97 g, 105 mmol, 1 eq) was added portionwise. The reaction was stirred for 18 h at room temperature. 20 mL water were slowly added and the solvents were removed under vacuum. The residue was dissolved in 100 mL water, 50 mL ethyl acetate were added, the layers were separated and the aqueous layer was extracted three times with 50 mL ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford **225** (11.5 g, 100 mmol, 95%) as colourless oil which crystallized in the fridge (4 °C).

m_p = 93 °C.

R_f = 0.30 (dichloromethane : methanol = 8 : 2).

^{1}H-NMR (500.1 MHz, $CDCl_3$): δ (ppm) = 7.35 (1H, bs, -NH), 3.94-3.76 (2H, m, H-4, -OH), 3.69 (1H, dd, *J* = 11.5, 3.0 Hz, H-5), 3.47 (1H, dd, *J* = 11.5, 7.5 Hz, H-5), 2.45-2.31 (2H, m, H-2), 2.19 (1H, m, H-3), 1.81 (1H, m, H-3).

^{13}C-NMR (125.8 MHZ, $CDCl_3$): δ (ppm) = 179.5 (C_q, C-1), 65.8 (CH_2, C-5), 56.6 (CH, C-4), 30.3 (CH_2, C-2), 22.6 (CH_2, C-3).

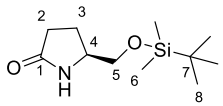
IR (ATR): ν (cm^{-1}) = 3607 (m), 3319 (b), 3241 (b), 2961 (m), 2925 (m), 2853 (w), 1665 (m), 1416 (m), 1326 (s), 1258 (m), 991 (s), 934 (s), 870 (s), 822 (s), 798 (s), 729 (s), 694 (s), 659 (s).

HR-MS (ESI): for $C_5H_9NNaO_2$ $[M+Na]^+$, calc.: 138.0525, found: 138.0524; δ = 0.7 ppm.

$[\alpha]_D^{20}$ = +29.0 (c = 1.01, ethanol).

The spectroscopic data are in full agreement with those published in the literature.[97,170]

(*S*)-5-((*tert*-Butyldimethylsilyloxy)methyl)pyrrolidin-2-one (226)



$C_{11}H_{23}NO_2Si$, MW = 229.4 g.mol^{-1}

After **225** (11.5 g, 100 mmol, 1.0 eq) was dissolved in 100 mL dichloromethane, the solution was brought to 0 °C. *tert*-Butyldimethylsilyl chloride (16.6 g, 110 mmol, 1.1 eq) and imidazole (7.50 g, 110 mmol, 1.1 eq) were added respectively. The mixture was then allowed to warm to room temperature and stirred for 20 h. 100 mL water were added, the layers were separated and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford **226** (22.8 g, 99.0 mmol, 99%) as colourless oil.

R_f = 0.20 (*c*-Hex : AcOEt = 1 : 1).

^{1}H-NMR (500.1 MHz, $CDCl_3$): δ (ppm) = 5.98 (1H, s, -NH), 3.68 (1H, m, H-4), 3.56 (1H, dd, *J* = 10.0, 4.0 Hz, H-5), 3.39 (1H, dd, *J* = 10.0, 7.5 Hz, H-5), 2.33-2.24 (2H, m, H-2), 2.11 (1H, m, H-3), 1.68 (1H, m, H-3), 0.83 (9H, s, H-8), 0.01 (6H, s, H-6).

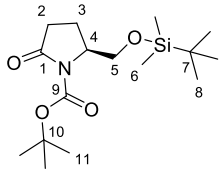
^{13}C-NMR (125.8 MHZ, $CDCl_3$): δ (ppm) = 178.0 (C_q, C-1), 66.9 (CH_2, C-5), 55.8 (CH, C-4), 29.8 (CH_2, C-2), 25.8 (CH_3, C-8), 22.8 (CH_2, C-3), 18.2 (C_q, C-7), -5.5 (CH_3, C-6).

IR (ATR): ν (cm^{-1}) = 3206 (b), 3101 (w), 2952 (m), 2929 (m), 2889 (m), 2856 (m), 1694 (s), 1545 (w), 1466 (m), 1424 (w), 1390 (w), 1363 (w), 1288 (w), 1252 (m), 1166 (w), 1111 (s), 1082 (m), 1033 (w), 1006 (w), 989 (w), 951 (w), 941 (w), 866 (m), 833 (s), 774 (s), 664 (m).

HR-MS (ESI): for $C_{11}H_{24}NO_2Si$ $[M+H]^+$, calc.: 230.1571, found: 230.1568; δ = 1.3 ppm.

$[\alpha]_D^{20}$ = +40.7 (c = 1.08, dichloromethane).

(*S*)-*tert*-Butyl 2-((*tert*-butyldimethylsilyloxy)methyl)-5-oxopyrrolidine-1-carboxylate (223)



$C_{16}H_{31}NO_4Si$, MW = 329.5 g.mol^{-1}

226 (500 mg, 2.18 mmol, 1.00 eq) was dissolved in 10 mL dichloromethane. After the mixture was brought to 0 °C, pyridine (0.50 mL, 509 mg, 6.43 mmol, 2.95 eq), DMAP (53.0 mg, 0.44 mmol, 0.20 eq) and di-*tert*-butyl dicarbonate (618 mg, 2.83 mmol, 1.30 eq) were added respectively. The reaction was then stirred for 18 h at room temperature. Afterwards, the mixture was treated with 5 mL of a 1 N aqueous solution of hydrochloric acid, the layers were separated and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified by silica gel column chromatography (*c*-Hex : AcOEt = 8 : 2) to afford **223** (620 mg, 1.88 mmol, 86%) as colourless oil.

$\mathbf{R_f}$ = 0.85 (*c*-Hex : AcOEt = 1 : 1).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 4.16 (1H, m, H-4), 3.90 (1H, dd, *J* = 10.4, 4.0 Hz, H-5), 3.68 (1H, dd, *J* = 10.4, 2.4 Hz, H-5), 2.70 (1H, ddd, *J* = 17.6, 11.2, 10.0 Hz, H-2), 2.36 (1H, ddd, *J* = 17.6, 9.6, 2.0 Hz, H-2), 2.16-1.96 (2H, m, H-3), 1.53 (9H, s, H-11), 0.87 (9H, s, H-8), 0.04 (3H, s, H-6), 0.03 (3H, s, H-6).

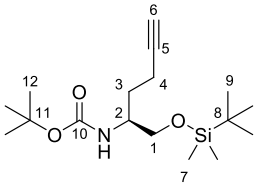
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 174.9 (C_q, C-1), 150.1 (C_q, C-9), 82.7 (C_q, C-10), 64.3 (CH_2, C-5), 58.9 (CH, C-4), 32.4 (CH_2, C-2), 28.1 (CH_3, C-11), 25.8 (CH_3, C-8), 21.1 (CH_2, C-3), 18.2 (C_q, C-7), -5.5 (CH_3, C-6), -5.6 (CH_3, C-6).

IR (ATR): ν (cm^{-1}) = 2954 (w), 2931 (w), 2887 (w), 2858 (w), 1788 (m), 1751 (m), 1711 (m), 1466 (w), 1416 (w), 1390 (w), 1365 (m), 1335 (w), 1309 (s), 1289 (m), 1235 (s), 1197 (m), 1153 (s), 1109 (s), 1077 (m), 1030 (m), 999 (m), 964 (w), 937 (w), 899 (m), 863 (s), 834 (s), 776 (s), 745 (m), 711 (w), 663 (m).

HR-MS (ESI): for $C_{16}H_{31}NNaO_4Si$ $[M+Na]^+$, calc.: 352.1915, found: 352.1905; δ = 2.8 ppm.

$\mathbf{[\alpha]_D^{20}}$ = -60.9 (c = 1.10, dichloromethane).

(*S*)-*tert*-Butyl 1-(*tert*-butyldimethylsilyloxy)hex-5-yn-2-ylcarbamate (220)



$C_{17}H_{33}NO_3Si$, MW = 327.5 g.mol^{-1}

After a solution of **223** (500 mg, 1.52 mmol, 1.0 eq) in 4 mL THF was brought to -78 °C, a solution of DIBAL-H (1.2 M solution in toluene, 1.52 mL, 1.81 mmol, 1.2 eq) was added dropwise, over 30 min, using a syringe pump, and the mixture was stirred at this temperature for 1 h. Then, keeping the temperature under -60 °C, a 1 : 1 mixture of saturated aqueous solutions of sodium bicarbonate and ammonium chloride was added slowly and the reaction was warmed to room temperature over night. After a filtration, the layers were separated, the aqueous layer was extracted with MTBE and the combined organic layers were dried over $MgSO_4$, filtered and reduced under vacuum. After the residue was dissolved in 15 mL methanol, Ohira-Bestmann reagent **210** (0.27 mL, 350 mg, 1.82 mmol, 1.2 eq) and potassium carbonate (386 mg, 3.04 mmol, 2.0 eq) were added respectively. The mixture was stirred at room temperature for 18 h. After the addition of 10 mL of an aqueous saturated solution of sodium bicarbonate and 20 mL MTBE, the layers were separated and the aqueous layer was extracted three times with MTBE. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford **220** (443 mg, 1.35 mmol, 89%) as colourless oil.

R_f = 0.35 (*c*-Hex : AcOEt = 1 : 1).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 4.68 (1H, bs, -NH), 3.76-3.54 (3H, m, H-1, H-2), 2.25 (2H, td, *J* = 7.0, 2.6 Hz, H-4), 1.95 (1H, t, *J* = 2.6 Hz, H-6), 1.82-1.63 (2H, m, H-3), 1.44 (9H, s, H-12), 0.89 (9H, s, H-9), 0.05 (6H, s, H-7).

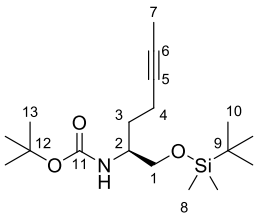
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 155.6 (C_q, C-10), 84.0 (C_q, C-5), 77.2 (C_q, C-11), 68.5 (CH, C-6), 64.6 (CH_2, C-1), 51.2 (CH, C-2), 30.8 (CH_2, C-3), 28.4 (CH_3, C-12), 25.9 (CH_3, C-9), 18.3 (C_q, C-8), 15.4 (CH_2, C-4), -5.5 (CH_3, C-7).

IR (ATR): ν (cm^{-1}) = 3449 (w), 3362 (w), 3314 (b), 2954 (w), 2931 (m), 2858 (w), 1697 (m), 1594 (w), 1498 (m), 1470 (m), 1389 (m), 1365 (m), 1252 (m), 1168 (s), 1116 (m), 1089 (m), 1052 (m), 1026 (m), 976 (w), 956 (w), 939 (w), 835 (s), 776 (s), 668 (m).

HR-MS (ESI): for $C_{17}H_{33}NNaO_3Si$ $[M+Na]^+$, calc.: 350.2122, found: 350.2123; δ = 0.3 ppm.

$[\alpha]_D^{20}$ = -33.0 (c = 1.02, dichloromethane).

(*S*)-*tert*-Butyl 1-(*tert*-butyldimethylsilyloxy)hept-5-yn-2-ylcarbamate (221)



$C_{18}H_{35}NO_3Si$, MW = 341.6 g.mol^{-1}

After **220** (1.00 g, 3.05 mmol, 1.0 eq) was dissolved in 50 mL THF, the mixture was brought to -10 °C and *n*-butyllithium (2.5 M solution in hexanes, 1.34 mL, 3.36 mmol, 1.1 eq) was added dropwise. The reaction was stirred at the same temperature for 10 min, TMEDA (1.00 mL, 0.78 g, 6.72 mmol, 2.2 eq) was added dropwise and the mixture was stirred for an additional 10 min. Methyl iodide

(0.95 mL, 2.17 g, 15.3 mmol, 5.0 eq) was added and the reaction was stirred at room temperature for 3 h. After the reaction mixture was poured into 50 mL water, the layers were separated and the aqueous layer was extracted three times with 50 mL ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was filtered through a pad of silica (*c*-Hex : AcOEt = 7 : 3) to afford **221** (0.99 g, 2.91 mmol, 95%) as colourless oil.

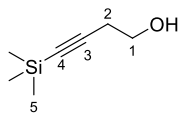
$\mathbf{R_f}$ = 0.50 (*c*-Hex : AcOEt = 1 : 1).

^{1}H-NMR (500.1 MHz, $CDCl_3$): δ (ppm) = 4.63 (1H, bs, -NH), 3.71-3.50 (3H, m, H-1, H-2), 2.20 (2H, bt, *J* = 7.5 Hz, H-4), 1.95 (3H, bs, H-7), 1.92-1.88 (2H, m, H-3), 1.40 (9H, s, H-13), 0.84 (9H, s, H-10), 0.00 (6H, s, H-8).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 155.6 (C_q, C-11), 84.0 (C_q, C-5), 79.6 (Cq, C-6), 77.3 (C_q, C-12), 63.8 (CH_2, C-1), 51.2 (CH, C-2), 30.8 (CH_2, C-3), 28.4 (CH_3, C-13), 25.9 (CH_3, C-10), 18.3 (C_q, C-9), 15.4 (CH_2, C-4), 3.4 (CH3, C-7), -5.5 (CH_3, C-8).

HR-MS (ESI): for $C_{18}H_{35}NNaO_3Si$ $[M+Na]^+$, calc.: 364.2278, found: 364.2278; δ = 0.0 ppm.

4-(Trimethylsilyl)but-3-yn-1-ol (231)



$C_7H_{14}OSi$, MW = 142.3 g.mol^{-1}

After but-3-yn-1-ol **230** (5.41 mL, 5.00 g, 71.4 mmol, 1.0 eq) was dissolved in 700 mL THF, the mixture was brought to -78 °C and *n*-butyllithium (1.9 M solution in hexanes, 82.7 mL, 157 mmol, 2.2 eq) was added. The reaction was stirred for 2 h at this temperature and trimethylsilyl chloride (19.9 mL, 17.1 g, 157 mmol, 2.2 eq) was added slowly, over 30 min, using a syringe pump. The mixture was allowed to reach room temperature and stirred for 18 h. After the reaction was brought to 0 °C, 50 mL of a 2 N aqueous solution of hydrochloric acid were added and the stirring was continued for an additional hour. The layers were separated and the aqueous layer was extracted three times with 200 mL diethyl ether. The combined organic layers were washed with an aqueous saturated solution of sodium bicarbonate and with brine, dried over $MgSO_4$, filtered and concentrated under vacuum to afford **231** (8.70 g, 61.2 mmol, 86%) as colourless oil.

$\mathbf{R_f}$ = 0.70 (*c*-Hex : AcOEt = 1 : 1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.71 (2H, t, *J* = 6.2 Hz, H-1), 2.51 (2H, t, *J* = 6.2 Hz, H-2), 0.15 (9H, s, H-5).

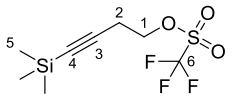
^{13}C-NMR (100.6 MHz, $CDCl_3$) = δ (ppm): 108.3 (C_q, C-3), 80.1 (C_q, C-4), 60.9 (CH_2, C-1), 24.3 (CH_2, C-2), 0.1 (CH_3, C-5).

IR (ATR): ν (cm^{-1}) = 3334 (b), 2956 (w), 2899 (w), 2175 (w), 1892 (w), 1468 (w), 1411 (w), 1378 (w), 1330 (w), 1249 (m), 1185 (w), 1053 (m), 1028 (m), 892 (m), 838 (s), 759 (s), 698 (m).

HR-MS (APCI): for $C_7H_{14}NaOSi$ $[M+Na]^+$, calc.: 165.0706, found: 165.0706; δ = 0.0 ppm.

The spectroscopic data are in full agreement with those published in the literature.[172]

4-(Trimethylsilyl)but-3-ynyl trifluoromethanesulfonate (229)



$C_8H_{13}F_3O_3SSi$, MW = 274.3 g.mol^{-1}

After a solution of pyridine (2.16 mL, 2.12 g, 26.8 mmol, 1.2 eq) in 25 mL dichloromethane was brought to -78 °C, trifluoromethanesulfonic anhydride (3.75 mL, 6.29 g, 22.3 mmol, 1.0 eq) was added and the mixture was stirred for 15 min. The alcohol **231** (3.17 g, 22.3 mmol, 1.0 eq) was added dropwise and the reaction was stirred for an additional 20 min. The mixture was then diluted with dichloromethane, washed with ice-cooled 1 N aqueous solution of hydrochloric acid and with water, dried over $MgSO_4$, filtered and reduced under vacuum (without heating). The residue was filtered through a pad of silica (*c*-Hex : Et_2O = 8 : 2) to afford **229** (4.65 g, 17.0 mmol, 76%) as slightly brown oil.

$\mathbf{R_f}$ = 0.40 (*c*-Hex : Et_2O = 8 : 2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.56 (2H, t, *J* = 6.8 Hz, H-1), 2.76 (2H, t, *J* = 6.8 Hz, H-2), 0.15 (9H, s, H-5).

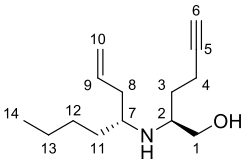
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 118.6 (C_q, q, $J_{C,F}$ = 320 Hz, C-6), 98.6 (C_q, C-3), 88.8 (C_q, C-4), 73.7 (CH_2, C-1), 21.1 (CH_2, C-2), -0.2 (CH_3, C-5).

IR (ATR): ν (cm^{-1}) = 3464 (b), 3307 (w), 2961 (w), 2929 (w), 2908 (w), 2864 (w), 2184 (w), 1719 (w), 1653 (w), 1463 (w), 1414 (s), 1340 (w), 1284 (w), 1245 (s), 1203 (s), 1145 (s), 1060 (m), 1028 (m), 954 (s), 917 (m), 843 (s), 784 (m), 759 (m), 700 (m).

HR-MS (APCI): for $C_8H_{17}OSi$ $[M-CF_3O_2S+CH_4O]^+$, calc.: 157.1043, found: 157.1039; δ = 2.5 ppm.

The spectroscopic data are in full agreement with those published in the literature.[222]

(*S*)-2-((*R*)-Oct-1-en-4-ylamino)hex-5-yn-1-ol (145)



$C_{14}H_{25}NO$, MW = 223.4 g.mol^{-1}

After amino alcohol **147** (100 mg, 0.88 mmol, 1.0 eq) was dissolved in 5 mL THF, pentanal (0.10 mL, 83.5 mg, 0.97 mmol, 1.1 eq) and $MgSO_4$ (150 mg, 1.25 mmol, 1.4 eq) were added and the mixture

was stirred at room temperature for 12 h. The solvents were removed under vacuum, 5 mL THF were added again and once the residue was dissolved, the solution was transferred in another flask through a cannula to decant the $MgSO_4$. After the mixture was brought to -78 °C, allylmagnesium chloride (2 M solution in THF, 1.32 mL, 2.64 mmol, 3.0 eq) was added dropwise. The reaction was allowed to reach room temperature over 6 h. After addition of 2 mL of an aqueous saturated solution of ammonium chloride, the layers were separated and the aqueous layer was extracted three times with 10 mL MTBE. The combined organic layers were dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified by silica gel column chromatography (*c*-Hex : AcOEt = 8 : 2) to afford **145** (38.0 mg, 0.17 mmol, 19%) as slightly yellow oil. The diastereomeric ratio was spectroscopically determined and was found to be 3 : 2.

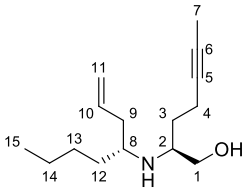
R_f = 0.35 (*c*-Hex : AcOEt = 8 : 2).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 5.82 (1H, m, H-9), 5.18-4.99 (2H, m, H-10), 3.89 (1H, dd, *J* = 8.4, 7.2 Hz, H-1), 3.56 (1H, dd, *J* = 8.4, 4.8 Hz, H-1), 3.25 (1H, m, H-2), 2.52 (1H, m, H-7), 2.35-2.22 (3H, m, H-4, H-8), 2.12 (1H, m, H-8), 1.94 (1H, t, *J* = 2.8 Hz, H-6), 1.53-1.26 (8H, m, H-3, H-11, H-12, H-13), 0.90 (3H, t, *J* = 7.0 Hz, H-14).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 134.9 (C_q, C-9), 118.0 (C_q, C-10), 82.5 (C_q, C-5), 70.7 (C_q, C-6), 63.2 (CH_2, C-1), 55.0 (CH, C-2, C-7), 54.4 (CH, C-7, C-2), 42.0 (CH_2, C-8), 36.5 (CH_2, C-11), 27.9 (CH_2, C-12), 22.9 (CH_2, C-3, C-13), 22.7 (CH_2, C-13, C-3), 15.4 (CH_2, C-4), 14.1 (CH_3, C-14).

HR-MS (ESI): for $C_{14}H_{26}NO$ $[M+H]^+$, calc.: 224.2009, found: 224.2006; δ = 1.3 ppm.

(*S*)-2-((*R*)-Oct-1-en-4-ylamino)hept-5-yn-1-ol (146)



$C_{15}H_{27}NO$, MW = 237.4 g.mol^{-1}

After amino alcohol **148** (50.0 mg, 0.39 mmol, 1.0 eq) was dissolved in 2.5 mL MeTHF, pentanal (0.05 mL, 37.3 mg, 0.43 mmol, 1.1 eq) and 150 mg 4 Å molecular sieves were added and the mixture was stirred at room temperature for 12 h. Solvents were then removed under vacuum, 2 mL THF were added and once the residue was dissolved again, the solution was transferred in another flask through a cannula in order to decant the molecular sieves. After the mixture was brought to -78 °C, allylmagnesium chloride (2 M solution in THF, 0.59 mL, 1.18 mmol, 3.0 eq) was added dropwise. The reaction was allowed to reach room temperature. After addition of 1 mL of an aqueous saturated solution of ammonium chloride the layers were separated and the aqueous layer was extracted three times with 10 mL MTBE. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified by silica gel column chromatography (*c*-Hex : AcOEt = 6 : 4) to afford **146** (29.0 mg, 0.12 mmol, 31%) as colourless oil. The diastereomeric ratio was spectroscopically determined and was found to be 19 : 1.

R_f = 0.20 (*c*-Hex : AcOEt = 7 : 3).

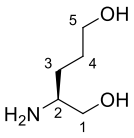
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 5.75 (1H, m, H-10), 5.08-5.01 (2H, m, H-11), 3.59 (1H, dd, *J* = 11.2, 4.0 Hz, H-1), 3.28 (1H, dd, *J* = 11.2, 3.6 Hz, H-1), 2.73 (1H, m, H-2), 2.28-2.10 (2H, m, H-8, H-9), 2.09-1.96 (2H, m, H-4), 1.85 (1H, m, H-9), 1.75 (3H, t, *J* = 2.6 Hz, H-7), 1.68-1.51 (2H, m, H-3), 1.48-1.29 (6H , m, H-12, H-13, H-14), 0.93 (3H, t, *J* = 7.6 Hz, H-15).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 135.0 (C_q, C-10), 115.3 (C_q, C-11), 79.5 (C_q, C-5), 76.6 (C_q, C-6), 62.3 (CH_2, C-1), 58.7 (CH, C-2, C-8), 57.9 (CH, C-8, C-2), 41.5 (CH_2, C-9), 34.0 (CH_2, C-12), 26.8 (CH_2, C-13), 22.9 (CH_2, C-14), 20.2 (CH_2, C-3), 14.3 (CH_2, C-4), 12.8 (CH_3, C-15), 3.4 (CH_3, C-7).

IR (ATR): ν (cm^{-1}) = 3397 (b), 3075 (w), 2956 (s), 2930 (s), 2871 (s), 2860 (m), 2735 (w), 1707 (w), 1640 (w), 1578 (w), 1466 (m), 1457 (m), 1414 (w), 1378 (w), 1260 (m), 1153 (w), 1097 (m), 1029 (m), 913 (w), 866 (w), 799 (m), 735 (w), 701 (w).

HR-MS (ESI): for $C_{15}H_{28}NO$ $[M+H]^+$, calc.: 238.2165, found: 238.2164; δ = 0.4 ppm.

(*S*)-2-Aminopentane-1,5-diol (239)



$C_5H_{13}NO_2$, MW = 119.2 g.mol^{-1}

*From **200***: After **200** (2.17 g, 9.90 mmol, 1.00 eq) was dissolved in 15 mL methanol, concentrated hydrochloric acid (32% w/w solution, 1.50 mL, 15.3 mmol, 1.55 eq) was added and the mixture was stirred at room temperature for 16 h. The solution was allowed to cool down to room temperature and the solvents were removed under reduced pressure after neutralization by addition of a 2 M solution of sodium hydroxide. The residue was distilled (140 °C, 1 mbar) to afford **239** (1.11 g, 9.31 mmol, 94%) as colourless oil.

*From **242***: After **242** (6.30 g, 21.0 mmol, 1 eq) was dissolved in 90 mL methanol, the mixture was degassed several times, palladium hydroxide (20% on active charcoal, 2.73 g, 5 mol%) was added and the reaction was stirred for 5 h under hydrogen atmosphere. The mixture was then filtered through a pad of Celite and the filtrate was reduced under vacuum. The residue was distilled (140 °C, 1 mbar) to afford **239** (2.30 g, 19.3 mmol, 92%) as colourless oil.

b_p = 140 °C (1 mbar).

^{1}H-NMR (400.1 MHz, MeOD): δ (ppm) = 3.79 (1H, dd, *J* = 9.4, 3.0 Hz, H-1), 3.67-3.55 (3H, m, H-1, H-5), 3.24 (1H, m, H-2), 1.82-1.59 (4H, m, H-3, H-4).

^{13}C-NMR (100.6 MHz, MeOD): δ (ppm) = 62.3 (CH_2, C-1, C-5), 54.7 (CH, C-2), 29.3 (CH_2, C-4), 27.5 (CH_2, C-3).

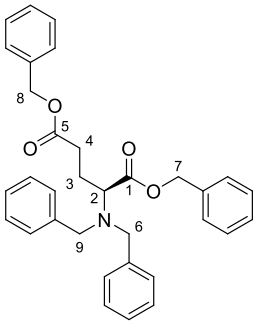
IR (ATR): ν (cm^{-1}) = 3339 (b), 3280 (b), 2926(m), 2862 (m), 1656 (w), 1587 (m), 1450 (m), 1369 (m), 1312 (w), 1240 (w), 1174 (w), 1048 (s), 968 (m), 907 (m), 876 (m), 815 (m).

HR-MS (APCI): for $C_5H_{14}NO_2$ $[M+H]^+$, calc.: 120.1019, found: 120.1018; δ = 0.8 ppm.

$[\alpha]_D^{20}$ = +1.2 (c = 1.20, methanol).

The spectroscopic data are in full agreement with those published in the literature.[97]

(*S*)-Dibenzyl 2-(dibenzylamino)pentanedioate (241)



$C_{33}H_{33}NO_4$, MW = 507.6 g.mol^{-1}

After L-glutamic acid **201** (14.7 g, 100 mmol, 1.00 eq) was dissolved in 75 mL methanol and 75 mL water, sodium hydroxide (9.10 g, 228 mmol, 2.28 eq), potassium carbonate (31.3 g, 228 mmol, 2.28 eq) and benzyl bromide (53.6 mL, 77.0 g, 450 mmol, 4.50 eq) were added respectively. The mixture was stirred and refluxed for 20 h. The reaction was cooled, and when reaching room temperature, 100 mL ethyl acetate were added, the layers were separated and the aqueous layer was extracted two times with 100 mL ethyl acetate. The combined organic layers were washed two times with brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford **241** (50.2 g, 99.0 mmol, 99%) as viscous colourless oil.

R_f = 0.70 (*c*-Hex : AcOEt = 1 : 1).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 7.44-7.08 (20H, m, H-Ar), 5.26 (1H, m, H-7), 5.19-5.12 (2H, m, H-7, H-8), 4.97 (1H, m, H-8), 3.87 (2H, dd, *J* = 13.6, 2.0 Hz, H-6, H-9), 3.49 (2H, dd, *J* = 13.6, 1.4 Hz, H-9, H-6), 3.35 (1H, m, H-2), 2.57-2.38 (2H, m, H-3, H-4), 2.16-2.02 (2H, m, H-4, H-3).

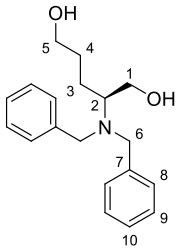
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 172.2 (C_q, C-1, C-5), 171.9 (C_q, C-5, C-1), 140.9 (C_q, C-Ar), 139.2 (C_q, C-Ar), 128.9 (CH, C-Ar), 128.7 (CH, C-Ar), 128.6 (CH, C-Ar), 128.6 (CH, C-Ar), 128.5 (CH, C-Ar), 128.5 (CH, C-Ar), 128.4 (CH, C-Ar), 128.3 (CH, C-Ar), 128.2 (CH, C-Ar), 128.1 (CH, C-Ar), 127.7 (CH, C-Ar), 127.0 (CH, C-Ar), 74.7 (CH, C-2), 66.2 (CH_2, C-7, C-8), 65.4 (CH_2, C-8, C-7), 59.6 (CH_2, C-6, C-9), 58.1 (CH_2, C-9, C-6), 30.4 (CH_2, C-4), 24.2 (CH_2, C-3).

IR (ATR): ν (cm^{-1}) = 3414 (b), 3086 (w), 3062 (w), 3029 (w), 2942 (w), 2885 (w), 2847 (w), 2811 (w), 1726 (m), 1597 (w), 1581 (w), 1569 (w), 1495 (w), 1453 (m), 1407 (w), 1377 (w), 1326 (w), 1305 (w), 1255 (m), 1205 (m), 1155 (m), 1129 (m), 1076 (w), 1025 (m), 961 (m), 912 (w), 843 (w), 823 (w), 733 (s), 695 (s).

HR-MS (ESI): for $C_{33}H_{34}NO_4$ $[M+H]^+$, calc.: 508.2482, found: 508.2482; δ = 0.0 ppm.

$[\alpha]_D^{20}$ = -53.1 (c = 0.95, methanol).

(*S*)-2-(Dibenzylamino)pentane-1,5-diol (242)



$C_{19}H_{25}NO_2$, MW = 299.4 g.mol^{-1}

After a suspension of lithium aluminium hydride (5.70 g, 150 mmol, 1.52 eq) in 450 mL THF was prepared, the mixture was brought to 0 °C and a solution of **241** (50.2 g, 99.0 mmol, 1.00 eq) in 100 mL THF was added dropwise. The reaction was stirred at 80 °C for 16 h. After the reaction mixture was brought to 0 °C, 6 mL water, 6 mL of an aqueous 15% solution of sodium hydroxide and 6 mL of water were added dropwise. The mixture was stirred at room temperature for 30 min, until it turned to a white colour, and was filtered through Celite. Celite was washed several times with MTBE and the combined organic layers were reduced under vacuum. The benzyl alcohol was then removed by distillation to afford **242** (27.2 g, 90.8 mmol, 92%) as colourless oil.

R_f = 0.60 (*c*-Hex : AcOEt = 1 : 1).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 7.30-7.21 (8H, m, H-8, H-9), 7.18-7.15 (2H, m, H-10), 3.82 (2H, d, *J* = 13.2 Hz, H-6), 3.64 (2H, bt, *J* = 5.2 Hz, H-5), 3.55-3.43 (2H, m, H-1), 3.47 (2H, d, *J* = 13.2 Hz, H-6), 2.81 (1H, m, H-2), 1.60-1.44 (2H, m, H-4), 1.40-1.23 (2H, m, H-3).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 140.5 (C_q, C-7), 129.1 (CH, C-9), 128.6 (CH, C-8), 127.7 (CH, C-10), 65.4 (CH_2, C-1), 61.2 (CH_2, C-5), 60.1 (CH, C-2), 53.2 (CH_2, C-6), 30.2 (CH_2, C-4), 21.3 (CH_2, C-3).

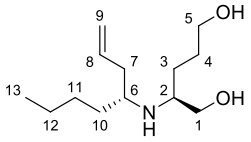
IR (ATR): ν (cm^{-1}) = 3344 (b), 3085 (w), 3061 (w), 3026 (w), 2934 (w), 2862 (w), 2804 (w), 2722 (w), 1602 (w), 1585 (w), 1494 (m), 1453 (m), 1413 (w), 1362 (w), 1326 (w), 1245 (w), 1208 (w), 1180 (w), 1131 (w), 1069 (m), 1051 (m), 1026 (s), 973 (m), 906 (w), 830 (w), 794 (w), 745 (s), 728 (s), 697 (s).

HR-MS (ESI): for $C_{19}H_{24}NO_2$ $[M-H]^+$, calc.: 298.1802, found: 298.1799; δ = 1.0 ppm.

$[\alpha]_D^{20}$ = +52.6 (c = 1.1, chloroform).

The spectroscopic data are in full agreement with those published in the literature.[97]

(*S*)-2-((*R*)-Oct-1-en-4-ylamino)pentane-1,5-diol (243)



$C_{13}H_{27}NO_2$, MW = 229.4 g.mol^{-1}

After amino alcohol **239** (539 mg, 4.24 mmol, 1.0 eq) was dissolved in 50 mL THF, pentanal (0.50 mL, 402 mg, 4.66 mmol, 1.1 eq) and 5.5 g molecular sieves (4 Å) were added and the mixture was stirred at room temperature for 12 h. The solvents were removed under vacuum, 50 mL THF were added and once the residue was dissolved, the solution was transferred in another flask through a cannula in order to decant the molecular sieves. After the mixture was brought to -78 °C, allylmagnesium chloride (2 M solution in THF, 6.36 mL, 12.7 mmol, 3.0 eq) was added dropwise. The reaction was allowed to reach room temperature. After addition of 15 mL of an aqueous saturated solution of ammonium chloride, the layers were separated and the aqueous layer was extracted three times with 50 mL MTBE. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified by silica gel column chromatography (AcOEt → dichloromethane → dichloromethane : methanol = 95 : 5 to 8 : 2) to afford **243** (398 mg, 1.73 mmol, 41%) as colourless oil. The diastereomeric ratio was spectroscopically determined and was found to be 9 : 1.

R_f = 0.60 (dichloromethane : methanol = 9 : 1).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 5.77 (1H, m, H-8), 5.15-5.06 (2H, m, H-9), 3.68-3.57 (3H, m, H-5, H-1), 3.41 (1H, dd, *J* = 10.4, 5.2 Hz, H-1), 2.74 (1H, m, H-2), 2.66 (1H, m, H-6), 2.24 (1H, m, H-7), 2.08 (1H, m, H-7), 1.72-1.50 (4H, m, H-3, H-4), 1.50-1.21 (6H, m, H-10, H-11, H-12), 0.90 (3H, t, *J* = 7.0 Hz, H-13).

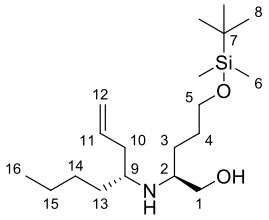
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 135.3 (CH, C-8), 117.9 (CH_2, C-9), 63.4 (CH_2, C-1), 62.8 (CH_2, C-5), 55.7 (CH, C-2), 54.0 (CH, C-6), 38.5 (CH_2, C-7), 33.9 (CH_2, C-10), 30.3 (CH_2, C-3, C-4), 29.7 (CH_2, C-4, C-3), 28.1 (CH_2, C-11, C-12), 22.9 (CH_2, C-12, C-11), 14.1 (CH_3, C-13).

IR (ATR): ν (cm^{-1}) = 3321 (b), 3076 (m), 2954 (s), 2929 (s), 2871 (s), 2860 (s), 2716 (m), 1832 (w), 1676 (w), 1640 (w), 1467 (m), 1458 (m), 1438 (m), 1378 (m), 1352 (w), 1240 (w), 1202 (w), 1183 (w), 1132 (w), 1057 (s), 997 (m), 913 (m), 800 (w), 731 (w).

HR-MS (ESI): for $C_{13}H_{28}NO_2$ $[M+H]^+$, calc.: 230.2115, found: 230.2113; δ = 0.9 ppm.

The spectroscopic data are in full agreement with those published in the literature.[97]

(*S*)-5-(*tert*-Butyldimethylsilyloxy)-2-((*R*)-oct-1-en-4-ylamino)pentan-1-ol (246)



$C_{19}H_{41}NO_2Si$, MW = 343.6 g.mol^{-1}

After **243** (187 mg, 0.82 mmol, 1.0 eq) was dissolved in 1 mL dichloromethane, pyridine (0.07 mL, 71.0 mg, 0.90 mmol, 1.1 eq) and DMAP (6.00 mg, 0.05 mmol, 6.0 mol%) were respectively added. A solution of *tert*-butyldimethylsilyl chloride (98.3 mg, 0.65 mmol, 0.8 eq) in 1 mL dichloromethane was then slowly added and the mixture was stirred at 0 °C for 16 h. Solvents were reduced under vacuum and the residue was purified by silica gel column chromatography (*c*-Hex: AcOEt = 3 : 2 → AcOEt) to afford **246** (250 mg, 0.73 mmol, 89%) as colourless oil.

R_f = 0.35 (*c*-Hex : AcOEt = 1 : 1).

^{1}H-NMR (500.1 MHz, $CDCl_3$): δ (ppm) = 5.75 (1H, m, H-11), 5.11-5.02 (2H, m, H-12), 3.61-3.54 (3H, m, H-1, H-5), 3.19 (1H, m, H-5, H-1), 2.69-2.56 (2H, m, H-2, H-9), 2.50 (2H, bs, -OH, -NH), 2.18-2.03 (2H, m, H-10), 1.55-1.19 (10H, m, H-3, H-4, H-13, H-14, H-15), 0.92-0.76 (12H, m, H-8, H-16), 0.01 (6H, s, H-6).

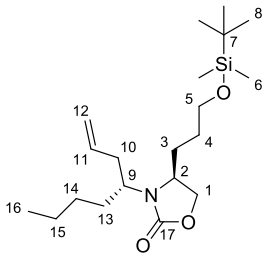
^{13}C-NMR (125.8 MHz, $CDCl_3$): δ (ppm) = 135.4 (CH, C-11), 117.2 (CH_2, C-12), 63.4 (CH_2, C-1, C-5), 63.0 (CH_2, C-5, C-1), 56.2 (CH, C-2, C-9), 54.6 (CH, C-9, C-2), 38.9 (CH_2, C-10), 34.2 (CH_2, C-3, C-4, C-13, C-14, C-15), 29.2 (CH_2, C-4, C-13, C-14, C-15, C-3), 28.5 (CH_2, C-13, C-14, C-15, C-3, C-4), 28.1 (CH_2, C-14, C-15, C-3, C-4, C-13), 25.9 (CH_3, C-8), 22.8 (CH_2, C-15, C-3, C-4, C-13, C-14), 18.3 (C_q, C-7), 14.0 (CH_3, C-16), -5.3 (CH_3, C-6).

IR (ATR): ν (cm^{-1}) = 3329 (b), 3077 (w), 2953 (m), 2929 (s), 2858 (m), 1643 (w), 1604 (w), 1589 (w), 1565 (w), 1464 (m), 1444 (m), 1407 (w), 1385 (w), 1362 (w), 1252 (m), 1218 (w), 1095 (m), 1055 (m), 999 (m), 934 (w), 919 (m), 875 (w), 832 (s), 774 (s), 723 (w), 715 (w), 663 (m).

HR-MS (ESI): for $C_{19}H_{42}NO_2Si$ $[M+H]^+$, calc.: 344.2979, found: 344.2979; δ = 0.0 ppm.

The spectroscopic data are in full agreement with those published in the literature.[97]

(*S*)-4-(3-*tert*-Butyldimethylsilyloxy)propyl)-3-((*R*)-oct-1-en-4-yl)oxazolidin-2-one (247)



$C_{20}H_{39}NO_3Si$, MW = 369.6 g.mol^{-1}

To a solution of **246** (46.0 mg, 0.13 mmol, 1.0 eq) and triethylamine (0.10 mL, 68.0 mg, 0.67 mmol, 5.0 eq) in 5 mL dichloromethane at -78 °C was added dropwise a solution of triphosgen (40.0 mg, 0.13 mmol, 1.0 eq) in 5 mL dichloromethane. The mixture was stirred at room temperature during 15 h. After addition of 5 mL dichloromethane and 5 mL water, the layers were separated and the aqueous layer was extracted three times with 5 mL dichloromethane. The combined organic layers were washed with 15 mL of a 1 M aqueous solution of sodium hydroxide and with brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford **247** (11.6 mg, 0.03 mmol, 23%) as colourless oil.

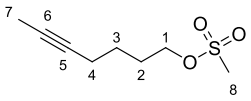
^{1}H-NMR (500.1 MHz, $CDCl_3$): δ (ppm) = 5.72 (1H, m, H-11), 5.08-5.00 (2H, m, H-12), 4.26 (1H, t, *J* = 8.5 Hz, H-1), 3.88 (1H, dd, *J* = 8.5, 6.0 Hz, H-1), 3.70 (1H, m, H-2), 3.68-3.53 (2H, m, H-5), 3.42 (1H, m, H-9), 2.49 (1H, m, H-10), 2.23 (1H, m, H-10), 1.83 (1H, m, H-13), 1.70 (1H, m, H-13), 1.60 (1H, m, H-3), 1.54-1.36 (2H, m, H-3, H-4), 1.35-1.16 (5H, m, H-4, H-14, H-15), 0.91-0.82 (12H, m, H-8, H-16), 0.02 (6H, s, H-6).

^{13}C-NMR (125.8 MHz, $CDCl_3$): δ (ppm) = 157.9 (C_q, C-17), 135.4 (CH, C-11), 117.6 (CH_2, C-12), 67.3 (CH_2, C-1), 62.4 (CH_2, C-5), 55.6 (CH, C-2), 54.8 (CH, C-9), 38.5 (CH_2, C-10), 31.2 (CH_2, C-13), 30.7 (CH_2, C-3, C-4, C-14, C-15), 29.1 (CH_2, C-4, C-14, C-15, C-3), 27.7 (CH_2, C-14, C-15, C-3, C-4), 25.9 (CH_3, C-8), 22.5 (CH_2, C-15, C-3, C-4, C-14), 18.3 (C_q, C-7), 14.0 (CH_3, C-16), -5.4 (CH_3, C-6).

IR (ATR): ν (cm^{-1}) = 3077 (w), 2956 (m), 2927 (m), 2857 (m), 1746 (s), 1642 (w), 1533 (w), 1471 (m), 1463 (m), 1412 (m), 1385 (m), 1361 (m), 1257 (s), 1092 (s), 1057 (s), 1007 (s), 940 (m), 916 (m), 835 (s), 797 (s), 778 (s), 731 (w), 702 (m), 668 (m), 661 (m).

HR-MS (ESI): for $C_{20}H_{39}NNaO_3Si$, $[M+Na]^+$, calc.: 392.2591, found: 392.2584; δ = 1.8 ppm.

Hept-5-ynyl methanesulfonate (248)



$C_8H_{14}O_3S$, MW = 190.3 g.mol^{-1}

After **142** (1.00 g, 8.98 mmol, 1.0 eq) was dissolved in 5 mL dichloromethane, the mixture was brought to 0 °C and triethylamine (1.63 mL, 1.18 g, 11.7 mmol, 1.3 eq) was added. Methanesulfonyl chloride (0.83 mL, 1.24 g, 10.8 mmol, 1.2 eq) was added dropwise, over 30 min, at the same temperature. The colourless solution was stirred at room temperature for 18 h. 50 mL of MTBE and

60 mL of water were added, the layers were separated and the aqueous layer was extracted three times with MTBE. The combined organic layers were washed three times with water, with brine, dried over $MgSO_4$ and reduced under vacuum to afford **248** (1.51 g, 7.93 mmol, 89%) as yellow oil.

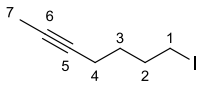
^{1}H-NMR (500.1 MHz, $CDCl_3$): δ (ppm) = 4.28 (2H, t, *J* = 6.5 Hz, H-1), 3.03 (3H, s, H-8), 2.25-2.18 (2H, m, H-4), 1.92-1.85 (2H, m, H-2), 1.79 (3H, t, *J* = 2.5 Hz, H-7), 1.65-1.57 (2H, m, H-3).

^{13}C-NMR (125.8 MHz, $CDCl_3$): δ (ppm) = 78.1 (C_q, C-5), 76.4 (C_q, C-6), 69.6 (CH_2, C-1), 37.4 (CH_3, C-8), 28.2 (CH_2, C-2), 24.8 (CH_2, C-3), 18.2 (CH_2, C-4), 3.4 (CH_3, C-7).

IR (ATR): ν (cm^{-1}) = 3021 (w), 2941 (w), 2919 (w), 2864 (w), 1455 (w), 1438 (w), 1416 (w), 1349 (s), 1333 (s), 1170 (s), 1085 (w), 1052 (w), 1036 (w), 1010 (w), 972 (m), 951 (m), 930 (s), 838 (m), 817 (m), 797 (m), 780 (w), 745 (w), 726 (w).

HR-MS (APCI): for $C_8H_{15}O_3S$ $[M+H]^+$, calc.: 191.0736, found: 191.0732; δ = 2.1 ppm.

7-iodohept-2-yne (249)



$C_7H_{11}I$, MW = 222.1 g.mol^{-1}

After **248** (1.35 g, 7.09 mmol, 1 eq) was dissolved in 50 mL acetone, sodium iodide (2.13 g, 14.2 mmol, 2 eq) was added and the solution was stirred at room temperature for 42 h. The mixture was filtered and the solvents were removed under vacuum. 25 mL of ethyl acetate and 30 mL of water were added, the layers were separated and the aqueous layer was extracted two times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and reduced under vacuum to afford **249** (1.43 g, 6.44 mmol, 91%) as yellow oil.

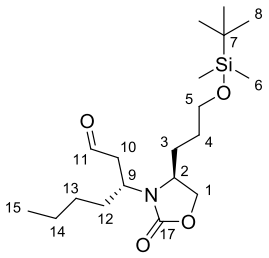
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 3.21 (2H, t, *J* = 7.0 Hz, H-1), 2.16 (2H, tq, *J* = 7.0, 2.6 Hz, H-4), 1.92 (2H, quint, *J* = 7.0 Hz, H-2), 1.77 (3H, t, *J* = 2.6 Hz, H-7), 1.58 (2H, quint, *J* = 7.0 Hz, H-3).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 78.3 (C_q, C-5, C-6), 76.2 (C_q, C-6, C-5), 32.5 (CH_2, C-2), 29.7 (CH_2, C-3), 17.7 (CH_2, C-4), 6.4 (CH_2, C-1), 3.5 (CH_3, C-7).

IR (ATR): ν (cm^{-1}) = 2922 (s), 2856 (m), 2221 (w), 1604 (w), 1446 (m), 1431 (m), 1360 (m), 1330 (m), 1286 (m), 1211 (s), 1172 (s), 1165 (s), 1117 (m), 1076 (m), 1054 (s), 1034 (m), 964 (m), 929 (m), 866 (w), 789 (w), 732 (m), 720 (w).

HR-MS (ESI): for $C_7H_{12}I$ $[M+H]^+$, calc.: 222.9978, found: 222.9979; δ = 0.4 ppm.

(*R*)-3-((*S*)-4-(3-(*tert*-Butyldimethylsilyloxy)propyl)-2-oxooxazolidin-3-yl)heptanal (250)



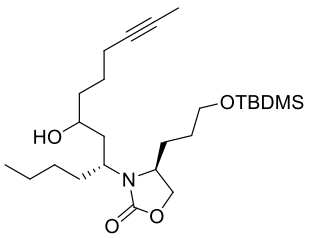
$C_{19}H_{37}NO_4Si$, MW = 371.6 g.mol^{-1}

247 (11.6 mg, 31 µmol) was dissolved in 2 mL dichloromethane and the mixture was brought to -78 °C. At this temperature, after 5 min of a flux of oxygen, a flux of ozone was passed through the solution. The reaction was monitored using TLC (*c*-Hex : AcOEt = 1 : 1) and the reaction was completed after 30 min. The reaction was quenched with dimethylsulfide, slowly warmed to reach room temperature and stirred at this temperature for 16 h. The solvents were removed under vacuum and the residue was purified using preparative TLC (*c*-Hex : AcOEt = 1 : 1) to afford **250** (3.00 mg, 8.1 µmol, 26%) as colourless oil. Given the small amount of product obtained, the compound **250** was only analysed using ^{1}H-NMR and mass spectroscopies and it was subsequently engaged in the next reaction.

^{1}H-NMR (500.1 MHz, $CDCl_3$): δ (ppm) = 9.72 (1H, s, H-11), 4.30-4.22 (1H, m, H-1), 3.92-3.76 (2H, m, H-1, H-2), 3.66-3.52 (3H, m, H-5, H-9), 2.60-2.48 (2H, m, H-10), 1.50-1.38 (6H, m, H-3, H-4, H-12), 1.30-1.14 (4H, m, H-13, H-14), 0.88-0.74 (12H, m, H-8, H-15), 0.01 (6H, s, H-6).

HR-MS (ESI): for $C_{19}H_{38}NO_4Si$, $[M+H]^+$, calc.: 372.2565, found: 372.2567; δ = 0.5 ppm.

(4*S*)-4-(3-(*tert*-Butyldimethylsilyloxy)propyl)-3-((5*R*)-7-hydroxytridec-11-yn-5-yl)oxazolidin-2-one (252)



$C_{19}H_{37}NO_4Si$, MW = 371.6 g.mol^{-1}

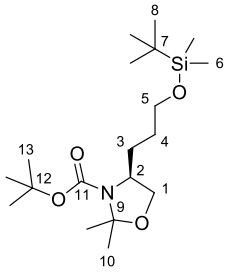
After magnesium (82.0 mg, 3.38 mmol, 1.5 eq) and lithium chloride (95.5 mg, 2.25 mmol, 1.0 eq) were dried under vacuum (1 mbar, 250 °C), the obtained mixture of solids was cooled down and 1 mL THF was added. A first portion of 7-iodohept-2-yne **249** (500 mg, 2.25 mmol, 1.0 eq) was added continuously until bubbles were seen, and the rest was added dropwise. The reaction mixture was then stirred at room temperature for 2 h. The obtained solution of the corresponding Grignard reagent hept-5-ynylmagnesium iodide **251** was then titrated using salicylaldehyde phenylhydrazone in accordance with the method developed by Love and Jones.[224] The concentration of the obtained

Grignard reagent solution in THF was found to be 1.8 M. The decanted solution was then directly used for the next step.

After a solution of **250** (3.00 mg, 8.1 µmol, 1.0 eq) in 1 mL THF was brought to -78 °C, hept-5-ynylmagnesium iodide **251** (1.8 M solution in THF, 5.0 µL, 9.0 µmol, 1.1 eq) was added dropwise. The reaction mixture was then allowed to reach room temperature over 6 h. After addition of 1 mL of an aqueous saturated solution of ammonium chloride, the layers were separated and the aqueous layer was extracted with MTBE. The combined organic layers were dried over $MgSO_4$, filtered and reduced under vacuum to afford a brown mixture. Only traces of **252** were identified in the mixture using HR-MS.

HR-MS (ESI): for $C_{19}H_{38}NO_4Si$, $[M+H]^+$, calc.: 372.2565, found: 372.2567; δ = 0.5 ppm.

(*S*)-*tert*-Butyl-4-(3-(*tert*-butyldimethylsilyloxy)propyl)-2,2-dimethyloxazolidine-3-carboxylate (255)



$C_{19}H_{39}NO_4Si$, MW = 373.6 g.mol^{-1}

After a solution of *tert*-butyldimethylsilyl chloride (1.74 g, 11.6 mmol, 1.5 eq) in 50 mL dichloromethane was brought to 0 °C, **200** (2.00 g, 7.71 mmol, 1.0 eq) and imidazole (788 mg, 11.6 mmol, 1.5 eq) were added respectively and the mixture was stirred 10 min at 0 °C and 18 hours at room temperature. After water and dichloromethane were added, the layers were separated and the aqueous layer was extracted three times with 50 mL dichloromethane. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified by column chromatography (*c*-Hex : AcOEt = 95 : 5, aluminium oxide) to afford **255** (1.93 g, 5.17 mmol, 67%) as colourless oil.

$\mathbf{R_f}$ = 0.35 (*c*-Hex : AcOEt = 9 : 1, aluminium oxide).

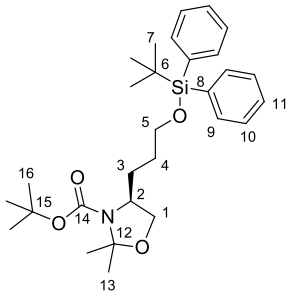
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 3.92 (1H, m, H-2), 3.84-3.72 (2H, m, H-1), 3.65-3.58 (2H, m, H-5), 1.68 (1H, m, H-3), 1.58-1.43 (18H, m, H-3, H-4, H-10, H-13), 0.88 (9H, s, H-8), 0.04 (6H, s, H-6).

^{13}C-NMR (125.8 MHz, $CDCl_3$): δ (ppm) = 152.8 (C_q, C-11), 105.3 (C_q, C-9), 79.0 (C_q, C-12), 77.6 (CH, C-2), 68.9 (CH_2, C-1), 62.5 (CH_2, C-5), 28.8 (C_q, C-7), 28.4 (CH_3, C-13), 28.3 (CH_2, C-4), 27.2 (CH_2, C-3), 25.6 (CH_3, C-8), 25.4 (CH_3, C-10), -3.6 (CH_3, C-6).

IR (ATR): ν (cm^{-1}) = 3440 (w), 3349 (b), 2976 (w), 2931 (m), 2870 (w), 1679 (s), 1520 (m), 1476 (w), 1454 (m), 1390 (s), 1376 (m), 1365 (s), 1247 (s), 1208 (w), 1168 (s), 1084 (s), 1050 (s), 1030 (m), 943 (w), 915 (w), 837 (m), 807 (w), 772 (m), 747 (w), 663 (w).

HR-MS (ESI): for $C_{19}H_{40}NO_4Si$ $[M+H]^+$, calc.: 374.2721, found: 374.2719; δ = 0.5 ppm.

(*S*)-*tert*-Butyl-4-(3-(*tert*-butyldiphenylsilyloxy)propyl)-2,2-dimethyloxazolidine-3-carboxylate (256)



$C_{29}H_{43}NO_4Si$, MW = 497.8 g.mol^{-1}

After **200** (500 mg, 1.93 mmol, 1.0 eq) was dissolved in 10 mL DMF, the mixture was brought to 0 °C, *tert*-butyldiphenylsilyl chloride (0.60 mL, 636 mg, 2.31 mmol, 1.2 eq) and imidazole (158 mg, 2.31 mmol, 1.2 eq) were added respectively and the reaction was stirred at room temperature for 16 h. Dichloromethane was added, the layers were separated and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified by column chromatography (*c*-Hex : AcOEt = 95 : 5, aluminium oxide) to afford **256** (815 mg, 1.64 mmol, 85%) as viscous colourless oil.

R_f = 0.50 (*c*-Hex : AcOEt = 1 : 1).

^{1}H-NMR (500.1 MHz, $CDCl_3$): δ (ppm) = 7.73 (4H, dd, *J* = 7.0, 1.5 Hz, H-9), 7.47-7.37 (6H, m, H-10, H-11), 3.74-3.56 (5H, m, H-1, H-2, H-5), 2.18-1.96 (4H, m, H-3, H-4), 1.74-1.50 (15H, m, H-13, H-16), 1.10 (9H, s, H-7).

^{13}C-NMR (125.8 MHz, $CDCl_3$): δ (ppm) = 155.6 (C_q, C-14), 135.3 (C_q, C-8), 129.6 (CH, C-9, C-10, C-11), 127.7 (CH, C-10, C-11, C-9), 127.6 (CH, C-11, C-9, C-10), 104.8 (C_q, C-12), 80.3 (C_q, C-15), 77.3 (CH, C-2), 67.1 (CH_2, C-1), 63.9 (CH_2, C-5), 29.4 (C_q, C-6), 28.5 (CH_3, C-16), 28.4 (CH_2, C-4), 26.9 (CH_3, C-7), 26.8 (CH_2, C-3), 26.6 (CH_3, C-13).

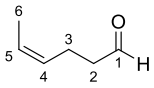
IR (ATR): ν (cm^{-1}) = 3424 (b), 3071 (w), 3050 (w), 2957 (m), 2931 (m), 2889 (w), 2858 (m), 1759 (w), 1694 (m), 1672 (m), 1589 (w), 1501 (w), 1470 (w), 1458 (w), 1426 (w), 1390 (m), 1367 (m), 1313 (w), 1254 (m), 1207 (w), 1172 (m), 1148 (w), 1107 (s), 1091 (s), 1057 (m), 1026 (w), 1010 (m), 974 (w), 943 (w), 846 (m), 821 (m), 769 (w), 739 (m), 702 (s).

HR-MS (ESI): for $C_{29}H_{44}NO_4Si$ $[M+H]^+$, calc.: 498.3034, found: 498.3026; δ = 1.6 ppm.

$[\alpha]_D^{20}$ = +11.5 (c = 1.54, methanol).

3.3. Experimental data for chapter 2

(*Z*)-Hex-4-enal (280)



$C_6H_{10}O$, MW = 98.1 g.mol^{-1}

After (*Z*)-hex-4-en-1-ol **289** (0.24 mL, 0.20 g, 2.00 mmol, 1.0 eq) was dissolved in 10 mL dichloromethane, 2 mL DMSO and triethylamine (1.40 mL, 1.00 g, 5.00 mmol, 2.5 eq) were added respectively and the mixture was brought to 0 °C. At this temperature Py•SO_3 (1.90 g, 12.0 mmol, 6.0 eq) was added portionwise and the reaction was stirred at room temperature for 16 h. Afterwards, 100 mL water and 50 mL diethyl ether were added, the layers were separated and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford **280** (196 mg, 2.00 mmol, quantitative) as colourless oil.

R_f = 0.40 (*c*-Hex : AcOEt = 1 : 1).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 9.78 (1H, t, *J* = 1.6 Hz, H-1), 5.50 (1H, m, H-4, H-5), 5.36 (1H, m, H-5, H-4), 2.55-2.49 (2H, m, H-2), 2.47-2.30 (2H, m, H-3), 1.64 (3H, d, *J* = 7.0 Hz, H-6).

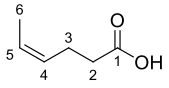
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 201.2 (C_q, C-1), 128.5 (CH, C-4), 125.6 (CH, C-5), 43.5 (CH_2, C-2), 20.1 (CH_2, C-3), 12.3 (CH_3, C-6).

IR (ATR): ν (cm^{-1}) = 3014 (m), 2923 (m), 2864 (m), 1658 (s), 1439 (m), 1403 (m), 1366 (w), 1299 (w), 1261 (w), 1193 (w), 1122 (s), 1065 (s), 1032 (s), 967 (m), 920 (m), 862 (w), 799 (w), 765 (w), 701 (s).

HR-MS (APCI): for $C_6H_{11}O$ $[M+H]^+$, calc.: 99.0804, found: 99.0802; δ = 2.0 ppm.

The spectroscopic data are in full agreement with those published in the literature.[193]

(*Z*)-Hex-4-enoic acid (290)



$C_6H_{10}O_2$, MW = 114.1 g.mol^{-1}

Pyridinium dichromate (94.0 g, 250 mmol, 5 eq) was added portionwise to a solution of (*Z*)-hex-4-enol **289** (5.83 mL, 50.0 mmol, 1 eq) in 300 mL DMF at 0 °C. The mixture was slowly warmed to room temperature and stirred for 18 h. The reaction was then cooled to 0 °C, water was slowly added and the mixture was extracted with ethyl acetate. The combined organic layers were washed with a saturated aqueous solution of potassium hydrogen sulfate, water and brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was distilled (150 °C, 25 mbar),

using a Kugelrohr distillation apparatus, to afford **290** (5.70 g, 50.0 mmol, quantitative) as yellowish oil.

R_f = 0.71 (*c*-Hex : AcOEt = 1 : 1).

b_p = 150 °C (25 mbar).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 11.46 (1H, m, -COOH), 5.51 (1H, m, H-4), 5.35 (1H, m, H-5), 2.47-2.31 (4H, m, H-2, H-3), 1.67-1.58 (3H, m, H-6).

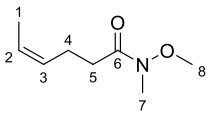
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 179.4 (C_q, C-1), 127.9 (CH, C-4), 125.7 (CH, C-5), 33.9 (CH_2, C-2), 22.1 (CH_2, C-3), 12.7 (CH_3, C-6).

IR (ATR): ν (cm^{-1}) = 3017 (m), 2972 (m), 2921 (m), 2865 (s), 2675 (s), 1737 (m), 1711 (s), 1659 (s), 1431 (s), 1413 (m), 1371 (s), 1339 (s), 1282 (m), 1250 (m), 1211 (m), 1167 (m), 1103 (s), 1009 (s), 996 (s), 929 (m), 823 (s), 705 (m).

HR-MS (ESI): for $C_6H_{11}O_2$ $[M+H]^+$, calc.: 115.0754, found: 115.0752; δ = 1.7 ppm.

The spectroscopic data are in full agreement with those published in the literature.[193]

(*Z*)-*N*-Methoxy-*N*-methylhex-4-enamide (281)



$C_8H_{15}NO_2$, MW = 157.2 g.mol^{-1}

After a solution of *N,O*-dimethylhydroxylamine (2.57 g, 26.3 mmol, 3.0 eq) in 20 mL dichloromethane was brought to -78 °C, trimethylaluminium (2 M solution in toluene, 13.2 mL, 26.4 mmol, 3.01 eq) was added dropwise and the reaction was warmed up and stirred at room temperature for 18 h. After the mixture was brought to 0 °C, acid **290** (1.00 g, 8.77 mmol, 1.0 eq) was added and the reaction was stirred for 1.5 h at 0 °C and 4 h at room temperature. Afterwards, a saturated aqueous solution of Rochelle salt was added, the mixture was filtered through celite, the layers were separated and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered and reduced under vacuum to afford **281** (830 mg, 5.28 mmol, 60%) as colourless oil.

R_f = 0.50 (*c*-Hex : AcOEt = 1 : 1).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 5.50 (1H, m, H-3), 5.39 (1H, m, H-2), 3.68 (3H, s, H-8), 3.18 (3H, s, H-7), 2.55-2.42 (2H, m, H-5), 2.42-2.35 (2H, m, H-4), 1.64 (3H, d, *J* = 6.4 Hz, H-1).

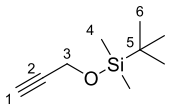
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 175.1 (C_q, C-6), 129.8 (CH, C-3), 125.0 (CH, C-2), 62.7 (CH_3, C-8), 32.5 (CH_3, C-7), 31.8 (CH_2, C-5), 23.2 (CH_2, C-4), 12.7 (CH_3, C-1).

IR (ATR): ν (cm^{-1}) = 3446 (b), 3014 (m), 2963 (m), 2933 (m), 2862 (m), 1775 (m), 1728 (s), 1659 (s), 1444 (s), 1418 (s), 1387 (s), 1316 (m), 1251 (m), 1173 (s), 1116 (m), 1044 (m), 988 (s), 924 (w), 708 (m).

HR-MS (ESI): for $C_8H_{15}NNaO_2$ $[M+H]^+$, calc.: 180.0995, found: 180.0997; δ = 1.1 ppm.

The spectroscopic data are in full agreement with those published in the literature.[193]

tert-Butyldimethyl(prop-2-ynyloxy)silane (295)



$C_9H_{18}OSi$, MW = 170.3 $g.mol^{-1}$

After a solution of imidazole (158 mg, 2.32 mmol, 1.3 eq) and *tert*-butylmethylsilyl chloride (350 mg, 2.32 mmol, 1.3 eq) in 3 mL DMF was brought to 0 °C, propargylic alcohol **293** (104 µL, 1.79 mmol, 1.0 eq) was added and the mixture was stirred at room temperature for 18 h. Water and diethyl ether were then added to the reaction, the layers were separated and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified by silica gel column chromatography (*c*-Hex : AcOEt = 8 : 2) to afford **295** (300 mg, 1.76 mmol, 98%) as colourless oil.

$\mathbf{R_f}$ = 0.55 (*c*-Hex : AcOEt = 1 : 1).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 4.23 (2H, d, *J* = 2.4 Hz, H-3), 2.42 (1H, t, *J* = 2.4 Hz, H-1), 0.89 (9H, s, H-6), 0.07 (6H, s, H-4).

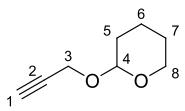
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 77.3 (C_q, C-2), 73.7 (CH, C-1), 50.8 (CH_2, C-3), 25.7 (CH_3, C-6), 18.3 (C_q, C-5), -3.6 (CH_3, C-4).

IR (ATR): ν (cm^{-1}) = 3398 (b), 2954 (m), 2929 (m), 2887 (w), 2856 (m), 2784 (w), 2456 (w), 1663 (s), 1596 (m), 1497 (w), 1467 (m), 1439 (w), 1409 (m), 1388 (m), 1363 (m), 1334 (m), 1321 (m), 1253 (m), 1176 (w), 1153 (w), 1095 (m), 1062 (w), 1025 (w), 1010 (w), 939 (w), 867 (s), 833 (s), 772 (s), 663 (s).

HR-MS (APCI): for $C_9H_{19}OSi$ $[M+H]^+$, calc.: 171.1200, found: 171.1199; δ = 0.6 ppm.

The spectroscopic data are in full agreement with those published in the literature.[225]

2-(Prop-2-ynyloxy)tetrahydro-2*H*-pyran (296)



$C_8H_{12}O_2$, MW = 140.2 $g.mol^{-1}$

After a solution of propargylic alcohol **293** (104 µL, 1.79 mmol, 1.0 eq) in 1 mL dichloromethane was brought to 0 °C, 3,4-dihydro-2*H*-pyran (163 µL, 1.79 mmol, 1.0 eq) and *p*TSA•H_2O (34.2 mg, 0.18 mmol, 0.1 eq) were added respectively and the reaction was stirred at room temperature for 18 h. After 2 mL of an aqueous saturated solution of sodium hydrogen carbonate were added, the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified by silica gel column chromatography (*c*-Hex : Et_2O = 7 : 3) to afford **296** (122 mg, 0.87 mmol, 49%) as yellowish oil.

R_f = 0.60 (*c*-Hex : AcOEt = 1 : 1).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 4.81 (1H, t, *J* = 3.4 Hz, H-4), 4.28 (1H, dd, *J* = 16.0, 2.4 Hz, H-3), 4.22 (1H, dd, *J* = 16.0, 2.4 Hz, H-3), 3.78 (1H, m, H-8), 3.53 (1H, m, H-8), 2.41 (1H, t, *J* = 2.4 Hz, H-1), 1.88-1.49 (6H, m, H-5, H-6, H-7).

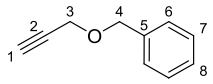
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 96.8 (CH, C-4), 79.8 (C_q, C-2), 74.0 (CH, C-1), 62.3 (CH_2, C-8), 54.0 (CH_2, C-3), 30.2 (CH_2, C-5), 25.3 (CH_2, C-7), 19.0 (CH_2, C-6).

IR (ATR): ν (cm^{-1}) = 3440 (w), 3261 (w), 2940 (m), 2868 (w), 1727 (m), 1632 (w), 1442 (w), 1380 (w), 1350 (w), 1322 (w), 1278 (w), 1260 (w), 1200 (m), 1176 (m), 1161 (m), 1133 (m), 1119 (s), 1074 (s), 1024 (s), 985 (s), 971 (s), 903 (m), 867 (m), 812 (m), 689 (w), 663 (w).

HR-MS (ESI): for $C_8H_{13}O_2$ $[M+H]^+$, calc.: 141.0910, found: 141.0909; δ = 0.7 ppm.

The spectroscopic data are in full agreement with those published in the literature.[226]

((Prop-2-ynyloxy)methyl)benzene (297)



$C_{10}H_{10}O$, MW = 146.2 g.mol^{-1}

At 0 °C, propargylic alcohol **293** (104 µL, 1.79 mmol, 1.0 eq) was added slowly to a solution of sodium hydride (75% in mineral oil, 144 mg, 4.48 mmol, 2.5 eq) and the reaction was stirred for 30 min followed by addition of benzyl bromide (218 µL, 1.79 mmol, 1.0 eq). The mixture was stirred for further 30 min at 0 °C and 18 h at room temperature. After the reaction was quenched by addition of water, the layers were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified by silica gel column chromatography (*c*-Hex : AcOEt = 98 : 2) to afford **297** (158 mg, 1.08 mmol, 60%) as colourless oil.

R_f = 0.70 (*c*-Hex : AcOEt = 9 : 1).

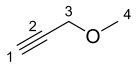
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 7.42-7.24 (5H, m, H-Ar), 4.49 (2H, s, H-4), 4.26 (2H, d, *J* = 2.4 Hz, H-3), 2.46 (1H, t, *J* = 2.4 Hz, H-1).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 137.8 (C_q, C-5), 129.0 (CH, C-Ar), 128.8 (CH, C-Ar), 128.5 (CH, C-Ar), 74.6 (CH_2, C-4), 73.8 (C_q, C-2), 71.5 (CH, C-1), 50.9 (CH_2, C-3).

IR (ATR): ν (cm^{-1}) = 3334 (b), 2955 (m), 2923 (s), 2856 (m), 1671 (w), 1654 (w), 1562 (w), 1456 (m), 1427 (m), 1378 (s), 1341 (s), 1276 (m), 1259 (m), 1131 (s), 1081 (m), 993 (s), 941 (s), 876 (s), 822 (s), 780 (s), 704 (s), 675 (s).

HR-MS (APCI): for $C_{10}H_{11}O$ $[M+H]^+$, calc.: 147.0804, found: 147.0801; δ = 2.0 ppm.

3-Methoxyprop-1-yne (298)



C_4H_6O, MW = 70.1 $g.mol^{-1}$

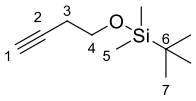
After a mixture of methanol (0.14 mL, 108 mg, 3.36 mmol, 5 eq) and 1 mL THF was brought to 0 °C, sodium hydride (70% in mineral oil, 23.0 mg, 0.67 mmol, 1 eq) and 3-bromoprop-1-yne **294** (80%, 100 mg, 0.67 mmol, 1 eq) were added respectively and the reaction was stirred at room temperature for 16 h. Water and dichloromethane were added, the mixture was stirred for an additional 30 min, the layers were separated and the aqueous layer was extracted two times with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum to obtain a mixture of 3-bromoprop-1-yne and product **298** (38% yield, 84% brsm) as yellowish oil.

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 4.10 (2H, d, *J* = 2.4 Hz, H-3), 3.40 (3H, s, H-4), 2.44 (1H, t, *J* = 2.4 Hz, H-1).

HR-MS (ESI): for C_4H_7O $[M+H]^+$, calc.: 71.0491, found: 71.0490; δ = 1.4 ppm.

The spectroscopic data are in full agreement with those published in the literature.[227]

(But-3-ynyloxy)(*tert*-butyl)dimethylsilane (299)



$C_{10}H_{20}OSi$, MW = 184.4 $g.mol^{-1}$

After a solution of *tert*-butyldimethylsilyl chloride (298 mg, 1.98 mmol, 1.5 eq) in 5 mL dichloromethane was brought to 0 °C, but-3-yn-1-ol **230** (0.10 mL, 92.4 mg, 1.32 mmol, 1.0 eq) and imidazole (135 mg, 1.98 mmol, 1.5 eq) were added respectively and the mixture was stirred 10 min at 0 °C and 18 h at room temperature. After water and dichloromethane were added, the layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and reduced under vacuum. The

residue was purified by silica gel column chromatography (*c*-Hex : AcOEt = 7 : 3) to afford **299** (360 mg, 1.95 mmol, 99%) as colourless oil.

R_f = 0.87 (*c*-Hex : AcOEt = 9 : 1).

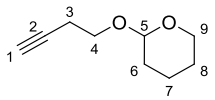
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 3.74 (2H, t, *J* = 7.1 Hz, H-4), 2.40 (2H, td, *J* = 7.1, 2.6 Hz, H-3), 1.96 (1H, t, *J* = 2.6 Hz, H-1), 0.90 (9H, s, H-7), 0.07 (6H, s, H-5).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 81.5 (C_q, C-2), 69.3 (CH, C-1), 61.8 (CH_2, C-4), 25.9 (CH_3, C-7), 22.9 (C_q, C-6), 18.3 (CH_2, C-3), -5.3 (CH_3, C-5).

IR (ATR): ν (cm^{-1}) = 3322 (b), 2925 (w), 2853 (w), 1662 (w), 1562 (w), 1425 (m), 1392 (m), 1328 (s), 1255 (m), 1126 (m), 988 (s), 933 (s), 870 (s), 825 (s), 700 (s).

HR-MS (ESI): for $C_{10}H_{21}OSi$ $[M+H]^+$, calc.: 185.1354, found: 185.1356; δ = 1.1 ppm.

2-(But-3-ynyloxy)tetrahydro-2*H*-pyran (300)



$C_9H_{14}O_2$, MW = 154.2 g.mol^{-1}

After a solution of but-3-yn-1-ol **230** (0.10 mL, 92.4 mg, 1.32 mmol, 1.0 eq) in 6 mL dichloromethane was brought to 0 °C, *p*TSA•H_2O (3.00 mg, 15 µmol, 1.0 mol%) and 3,4-dihydro-2*H*-pyran (0.16 mL, 1.72 mmol, 1.3 eq) were added and the reaction was stirred for 18 h at room temperature. 2.5 mL of an aqueous saturated solution of sodium hydrogen carbonate were added, the mixture was stirred for an additional 15 min, the layers were separated and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified by silica gel column chromatography (*c*-Hex : AcOEt = 1 : 1) to afford **300** (114 mg, 0.74 mmol, 56%) as colourless oil.

R_f = 0.60 (*c*-Hex : AcOEt = 1 : 1).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 4.64 (1H, t, *J* = 3.6 Hz, H-5), 3.93-3.79 (2H, m, H-4, H-9), 3.60-3.46 (2H, m, H-9, H-4), 2.49 (2H, td, *J* = 7.0, 2.6 Hz, H-3), 1.97 (1H, t, *J* = 2.6 Hz, H-1), 1.88-1.46 (6H, m, H-6, H-7, H-8).

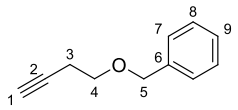
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 98.8 (CH, C-5), 81.4 (C_q, C-2), 69.2 (CH, C-1), 65.5 (CH_2, C-9), 62.2 (CH_2, C-4), 30.5 (CH_2, C-6), 25.4 (CH_2, C-8), 20.0 (CH_2, C-7), 19.4 (CH_2, C-3).

IR (ATR): ν (cm^{-1}) = 3290 (w), 2942 (m), 2873 (w), 1732 (w), 1439 (w), 1384 (w), 1350 (w), 1326 (w), 1279 (w), 1259 (w), 1202 (m), 1180 (m), 1156 (m), 1121 (s), 1070 (s), 1030 (s), 981 (s), 904 (m), 868 (m), 813 (m).

HR-MS (ESI): for $C_9H_{14}NaO_2$ $[M+Na]^+$, calc.: 177.0886, found: 177.0881; δ = 2.8 ppm.

The spectroscopic data are in full agreement with those published in the literature.[228]

((But-3-ynyloxy)methyl)benzene (301)



$C_{11}H_{12}O$, MW = 160.2 g.mol^{-1}

At 0 °C, but-3-yn-1-ol **230** (0.50 mL, 462 mg, 6.60 mmol, 1.0 eq) was added slowly to a solution of sodium hydride (75% in mineral oil, 528 mg, 16.5 mmol, 2.5 eq) and the reaction was stirred for 30 min, followed by slow addition of benzyl bromide (0.73 mL, 6.60 mmol, 1.0 eq). The mixture was stirred for further 30 min at 0 °C and 18 h at room temperature. After the reaction was quenched by addition of an aqueous saturated solution of ammonium chloride, the layers were separated and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified by silica gel column chromatography (*c*-Hex : AcOEt = 98 : 2) to afford **301** (1.04 g, 6.50 mmol, 98%) as colourless oil.

R_f = 0.64 (*c*-Hex : AcOEt = 9 : 1).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 7.30-7.26 (4H, m, H-Ar), 7.22 (1H, m, H-Ar), 4.57 (2H, s, H-5), 3.61 (2H, t, *J* = 7.2 Hz, H-4), 2.51 (2H, td, *J* = 7.2, 2.8 Hz, H-3), 2.00 (1H, t, *J* = 2.8 Hz, H-1).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 138.1 (C_q, C-6), 128.4 (CH, C-Ar), 127.7 (CH, C-Ar), 81.3 (C_q, C-2), 73.0 (CH_2, C-5), 69.3 (CH, C-1), 68.2 (CH_2, C-4), 19.9 (CH_2, C-3).

IR (ATR): ν (cm^{-1}) = 3295 (m), 3088 (w), 3064 (w), 3031 (w), 2936 (w), 2917 (w), 2862 (m), 2794 (w), 2120 (w), 1720 (w), 1493 (w), 1453 (m), 1362 (m), 1330 (m), 1315 (m), 1272 (m), 1207 (m), 1099 (s), 1025 (m), 1005 (m), 932 (m), 909 (m), 850 (m), 820 (m), 737 (s), 697 (s).

HR-MS (APCI): for $C_{11}H_{13}O$ $[M+H]^+$, calc.: 161.0961, found: 161.0957; δ = 2.5 ppm.

6-Oxabicyclo[3.1.0]hex-3-ene (303)

C_5H_6O, MW = 82.1 g.mol^{-1}

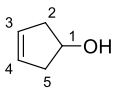
After freshly cracked cyclopentadiene **302** (100 mL, 79.0 g, 1.19 mol, 1 eq) and sodium carbonate (504 g, 4.76 mol, 4 eq) were dissolved in 1.2 L dichloromethane, the mixture was brought to -4 °C. A solution of sodium acetate (1.00 g, 0.01 mol, 1 mol%) and ethaneperoxoic acid (79.0 mL, 82.0 g, 1.18 mol, 1 eq) was slowly added while the temperature of the mixture was kept under 0 °C. After the reaction was stirred at room temperature for 18h, the solution was filtered and the filtrate was dried under vacuum to afford **303** (50.7 g, 618 mmol, 52%) as a colourless liquid.

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 6.15 (1H, m, H-3), 5.99 (1H, m, H-4), 3.91 (1H, m, H-2), 3.83 (1H, m, H-1), 2.64 (1H, m, H-5), 2.39 (1H, m, H-5).

HR-MS (APCI): for C_5H_7O $[M+H]^+$, calc.: 83.0491, found: 83.0491; δ = 0.0 ppm.

The spectroscopic data are in full agreement with those published in the literature.[193]

Cyclopent-3-enol (304)



C_5H_8O, MW = 84.1 g.mol^{-1}

After 250 mL diethyl ether were brought to -10 °C, lithium aluminium hydride (6.80 g, 179 mmol, 0.62 eq) was added in small portions. The epoxide **303** (23.7 g, 289 mmol, 1.00 eq) was dissolved in 80 mL diethyl ether and slowly added to the suspension, keeping the temperature under 0 °C. After the reaction was stirred at room temperature for 18 h, 100 mL water were slowly added, the suspension filtered through a pad of Celite and the filtrate washed with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered and reduced under vacuum. The residue was distilled (70-78 °C, 100 mbar) to afford **304** (22.5 g, 268 mmol, 93%) as a colourless liquid.

R_f = 0.55 (*c*-Hex : AcOEt = 1 : 1).

b_p = 75-78 °C (100 mbar).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 5.76-5.71 (2H, m, H-3, H-4), 4.52 (1H, m, H-1), 2.65 (2H, dd, *J* = 16.8, 6.0 Hz, H-2, H-5), 2.32 (2H, d, *J* = 17.2 Hz, H-5, H-2), 1.53 (1H, d, *J* = 6.0 Hz, -OH).

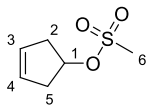
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 128.3 (CH, C-3, C-4), 71.6 (CH, C-1), 42.8 (CH_2, C-2, C-5).

IR (ATR): ν (cm^{-1}) = 3320 (b), 3060 (m), 2923 (m), 2841 (m), 1612 (w), 1428 (m), 1322 (m), 1284 (m), 1224 (w), 1192 (m), 1176 (m), 1107 (w), 1069 (m), 1045 (m), 946 (s), 872 (w), 829 (s), 779 (w), 670 (s).

HR-MS (APCI): for C_5H_9O $[M+H]^+$, calc.: 85.0648, found: 85.0648; δ = 0.0 ppm.

The spectroscopic data are in full agreement with those published in the literature.[193]

Cyclopent-3-enyl methanesulfonate (305)



$C_6H_{10}O_3S$, MW = 162.2 g.mol^{-1}

After **304** (21.5 g, 256 mmol, 1.0 eq) was dissolved in 80 mL dichloromethane, the mixture was brought to 0 °C and triethylamine (46.3 mL, 33.6 g, 332 mmol, 1.3 eq) was added. Methanesulfonyl chloride (23.8 mL, 35.2 g, 307 mmol, 1.2 eq) was added dropwise, over 1.5 h, at the same temperature. The colourless solution which slowly became white with formation of a precipitate was

stirred at 0 °C for 18 h. 150 mL of MTBE and 200 mL of water were added, the layers were separated and the aqueous layer was extracted three times with MTBE. The combined organic layers were washed three times with water, with brine, dried over $MgSO_4$ and dichloromethane is partly evaporated (around half of the volume). 140 mL DMSO, needed for the next step, were directly added and the rest of dichloromethane evaporated. This procedure was used because the product was known to have an explosive behaviour when dried. The product is then directly used for the next step without further purification.

R_f = 0.30 (*c*-Hex : AcOEt = 7 : 3).

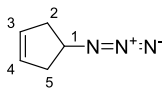
^{1}H-NMR (500.1 MHz, DMSO-d_6): δ (ppm) = 5.77-5.71 (2H, m, H-3, H-4), 5.31 (1H, tt, *J* = 6.5, 2.0 Hz, H-1), 3.17 (3H, s, H-6), 2.76 (2H, dd, *J* = 17.0, 6.5 Hz, H-2, H-5), 2.52 (2H, dd, *J* = 17.0, 2.0 Hz, H-5, H-2).

^{13}C-NMR (125.8 MHz, DMSO-d_6): δ (ppm) = 127.8 (CH, C-3, C-4), 81.3 (CH, C-1), 39.8 (CH_2, C-2, C-5), 37.6 (CH_3, C-6).

HR-MS (APCI): for $C_6H_{11}O_3S$ $[M+H]^+$, calc.: 163.0423, found: 163.0421; δ = 1.2 ppm.

The spectroscopic data are in full agreement with those published in the literature.[193]

4-Azidocyclopent-1-ene (306)



$C_5H_7N_3$, MW = 109.1 g.mol^{-1}

To the already prepared solution of **305** in 140 mL DMSO was added, sodium azide (83.1 g, 1.28 mol, 5 eq) at room temperature. The mixture was heated to 50 °C and stirred for 18 h. After the reaction was cooled to room temperature, 500 mL MTBE and 200 mL water were added, the layers were separated and the aqueous layer was extracted four times with MTBE. The combined organic layers were washed two times with water, two times with brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford **306** (22.9 g, 209 mmol, 82% over 2 steps) as brown oil.

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 5.75-5.66 (2H, m, H-3, H-4), 4.09 (1H, m, H-1), 2.67 (2H, dd, *J* = 16.0, 7.2 Hz, H-2, H-5), 2.44 (2H, dd, *J* = 16.0, 3.2 Hz, H-5, H-2).

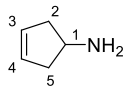
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 128.4 (CH, C-3, C-4), 60.2 (CH, C-1), 39.0 (CH_2, C-2, C-5).

IR (ATR): ν (cm^{-1}) = 3311 (w), 3048 (w), 2929 (m), 2901 (w), 2845 (m), 2495 (w), 2093 (s), 1740 (w), 1702 (w), 1666 (w), 1632 (m), 1612 (m), 1586 (m), 1571 (m), 1443 (m), 1350 (m), 1335 (m), 1254 (s), 1222 (m), 1138 (m), 1124 (m), 1075 (m), 1037 (m), 1020 (m), 946 (m), 863 (w), 847 (w), 786 (w), 772 (w), 737 (m), 702 (m), 676 (m).

HR-MS (APCI): for $C_5H_8N_3$ $[M+H]^+$, calc.: 110.0713, found: 110.0714; δ = 0.9 ppm.

The spectroscopic data are in full agreement with those published in the literature.[193]

Cyclopent-3-enamine (307)



C_5H_9N, MW = 83.1 g.mol^{-1}

In a three-necked 1 L round-bottom flask, adapted with a thermometer, a mechanical stirrer and an addition funnel of 500 mL, 300 mL diethyl ether were added and brought to 0 °C. Lithium aluminium hydride (16.5 g, 436 mmol, 2.08 eq) was added portionwise, forming a grey suspension. At the same temperature, a solution of **306** (22.9 g, 209 mmol, 1.00 eq) in 200 mL diethyl ether was added dropwise (over 2 h). The reaction was stirred at 0 °C for 30 min and at room temperature for 1 h. The mixture was brought to 0 °C and water was added slowly until the formation of a corn. After 30 min stirring, the mixture, which consisted of a clean white precipitate and a clear solution, was filtered through Celite and washed with diethyl ether. The organic layer was dried over $MgSO_4$, filtered and reduced under vacuum to afford **307** (7.84 g, 94.3 mmol, 45%) as an orange solid.

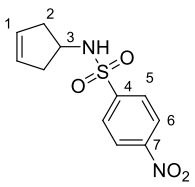
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 5.67-5.58 (2H, m, H-3, H-4), 3.63 (1H, m, H-1), 2.60 (2H, dd, *J* = 15.0, 7.0 Hz, H-2, H-5), 2.04 (2H, dd, *J* = 15.0, 4.6 Hz, H-5, H-2), 1.34 (2H, bs, -NH_2).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 128.8 (CH, C-3, C-4), 51.0 (CH, C-1), 43.1 (CH_2, C-2, C-5).

HR-MS (APCI): for $C_5H_{10}N$ $[M+H]^+$, calc.: 84.0808, found: 84.0808; δ = 0.0 ppm.

The spectroscopic data are in full agreement with those published in the literature.[193]

N-(Cyclopent-3-enyl)-4-nitrobenzenesulfonamide (271)



$C_{11}H_{12}N_2O_4S$, MW = 268.3 g.mol^{-1}

After potassium carbonate (3.99 g, 28.9 mmol, 1.2 eq) was added portionwise to a solution of **307** (2.00 g, 24.1 mmol, 1.0 eq) in 20 mL dichloromethane, the mixture was brought to 0 °C and 4-nitrobenzene-1-sulfonyl chloride (6.40 g, 28.9 mmol, 1.2 eq) was added portionwise. The reaction was stirred at room temperature for 18 h. After 50 mL dichloromethane were added, the mixture was washed with an aqueous saturated solution of potassium carbonate, water and brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford **271** (5.30 g, 19.8 mmol, 82%) as a white crystalline powder.

R_f = 0.86 (*c*-Hex : AcOEt = 9 : 1).

m_p = 96 °C.

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 8.38 (2H, d, *J* = 2.0 Hz, H-6), 8.08 (2H, d, *J* = 2.0 Hz, H-5), 5.71-5.62 (2H, m, H-1), 4.74 (1H, m, -NH), 4.06 (1H, m, H-3), 2.61 (2H, dd, *J* = 15.2, 7.6 Hz, H-2), 2.14 (2H, dd, *J* = 15.2, 4.0 Hz, H-2).

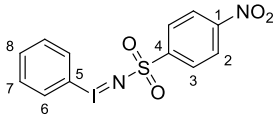
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 150.1 (C_q, C-7), 146.9 (C_q, C-4), 128.5 (CH, C-1), 128.4 (CH, C-5), 128.3 (CH, C-5), 125.0 (CH, C-6), 124.4 (CH, C-6), 53.5 (CH, C-3), 40.4 (CH_2, C-2).

IR (ATR): ν (cm^{-1}) = 3254 (b), 3109 (w), 3069 (w), 2925 (w), 2898 (w), 2843 (w), 1610 (w), 1528 (m), 1484 (w), 1442 (m), 1403 (w), 1343 (s), 1311 (m), 1289 (m), 1197 (w), 1158 (s), 1109 (w), 1089 (m), 1074 (m), 1010 (m), 943 (m), 899 (m), 851 (s), 825 (w), 809 (w), 736 (s), 677 (s).

HR-MS (APCI): for $C_{11}H_{13}N_2O_4S$ $[M+H]^+$, calc.: 269.0591, found: 269.0598; δ = 2.6 ppm.

The spectroscopic data are in full agreement with those published in the literature.[193]

(*N*-(*p*-Nitrobenzenesulfonyl)imino)phenyliodinane (308)



$C_{12}H_9IN_2O_4S$, MW = 404.2 g.mol^{-1}

After a solution of potassium hydroxide (7.00 g, 125 mmol, 2.5 eq) and *p*-nitrobenzenesulfonamide (10.1 g, 50.0 mmol, 1.0 eq) in 200 mL methanol was brought to 0 °C, iodophenyldiacetate (16.1 g, 50.0 mmol, 1.0 eq) was added and the reaction was stirred for 4 h. The creamy precipitate was filtered, washed with water and dried at room temperature under high vacuum to afford **308** (15.2 g, 37.6 mmol, 75%) as a white paste.

R_f = 0.60 (*c*-Hex : AcOEt = 1 : 1).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 8.05-7.99 (2H, m, H-2), 7.74-7.66 (4H, m, H-3, H-6), 7.39 (1H, tt, *J* = 7.4, 1.4 Hz, H-8), 7.27-7.21 (2H, m, H-7).

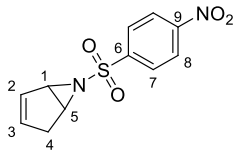
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 151.8 (C_q, C-4), 147.9 (C_q, C-1), 133.5 (CH, C-6), 130.8 (CH, C-7, C-8), 130.5 (CH, C-8, C-7), 130.2 (CH, C-7, C-8), 127.8 (CH, C-3), 123.7 (CH, C-2), 94.9 (C_q, C-5).

IR (ATR): ν (cm^{-1}) = 3312 (b), 3104 (m), 3070 (w), 3037 (w), 2967 (w), 2929 (w), 2858 (w), 1703 (w), 1605 (m), 1587 (w), 1565 (w), 1526 (s), 1471 (w), 1442 (w), 1402 (w), 1349 (s), 1311 (m), 1290 (m), 1270 (m), 1166 (s), 1134 (m), 1095 (m), 1082 (m), 1013 (w), 992 (w), 972 (w), 906 (m), 853 (s), 746 (m), 736 (s), 685 (m).

HR-MS (ESI): for $C_{12}H_{10}IN_2O_4S$ $[M+H]^+$, calc.: 404.9406, found: 404.9417; δ = 2.7 ppm.

The spectroscopic data are in full agreement with those published in the literature.[212]

6-(4-Nitrophenylsulfonyl)-6-azabicyclo[3.1.0]hex-2-ene (309)



$C_{11}H_{10}N_2O_4S$, MW = 266.3 g.mol^{-1}

After a solution of $Cu(acac)_2$ (59.0 mg, 0.23 mmol, 0.10 eq) and cyclopentadiene (300 mg, 4.55 mmol, 2.02 eq) in 2.5 mL acetonitrile was brought to 0 °C, **308** (909 mg, 2.25 mmol, 1.00 eq) was added portionwise, the reaction was stirred for 15 min at 0 °C and 1 h at room temperature. The mixture was poured in 50 mL of a 1 M solution of sodium hydroxide and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered and reduced under vacuum. The residue was kept under high vacuum for 4 h to afford **309** (585 mg, 2.20 mmol, 98%) as a brown solid.

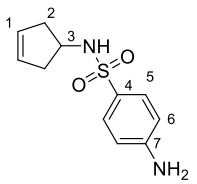
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 8.38 (2H, d, *J* = 9.0 Hz, H-8), 8.14 (2H, d, *J* = 9.0 Hz, H-7), 6.01-5.94 (2H, m, H-2, H-3), 3.96 (1H, dd, *J* = 5.2, 1.2 Hz, H-4), 3.84 (1H, t, *J* = 5.2 Hz, H-4), 2.71-2.55 (2H, m, H-1, H-5).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 150.5 (C_q, C-9), 144.2 (C_q, C-6), 138.8 (CH, C-2), 129.0 (CH, C-3), 127.7 (CH, C-7), 124.4 (CH, C-8), 51.8 (CH, C-1), 45.5 (CH, C-5), 35.8 (CH_2, C-4).

IR (ATR): ν (cm^{-1}) = 3504 (b), 3274 (b), 3104 (w), 3068 (w), 2926 (w), 2862 (w), 1712 (w), 1606 (w), 1571 (w), 1525 (s), 1471 (w), 1438 (w), 1402 (w), 1347 (s), 1307 (s), 1158 (s), 1107 (m), 1089 (s), 1057 (m), 1013 (m), 997 (m), 908 (w), 853 (s), 797 (w), 734 (s), 684 (s).

HR-MS (ESI): for $C_{11}H_{11}N_2O_4S$ $[M+H]^+$, calc.: 267.0434, found: 267.0432; δ = 0.7 ppm.

4-Amino-*N*-(cyclopent-3-enyl)benzenesulfonamide (310)



$C_{11}H_{14}N_2O_2S$, MW = 238.3 g.mol^{-1}

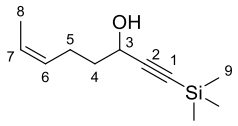
After a solution of **309** (300 mg, 1.12 mmol, 1 eq) in 40 mL THF was brought to 0 °C, lithium triethylborohydride (1 M solution in THF, 1.12 mL, 1.12 mmol, 1 eq) was added, and the reaction was stirred for 1 h at 0 °C and 30 min at room temperature. Water and ethyl acetate were added to the mixture and the aqueous layer was extracted two times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford **310** (213 mg, 0.89 mmol, 80%) as a brownish paste.

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 7.66 (2H, dd, *J* =8.0, 2.4 Hz, H-5), 6.75 (2H, dd, *J* = 8.0, 2.0 Hz, H-6), 6.10 (2H, bs, $-NH_2$), 5.70-5.58 (2H, m, H-1), 5.24 (1H, m, -NH), 3.19 (1H, m, H-3), 2.58 (2H, dd, *J* = 14.0, 7.0 Hz, H-2), 2.29 (2H, dd, *J* = 14.0, 3.6 Hz, H-2).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 150.4 (C_q, C-7), 137.5 (C_q, C-4), 130.2 (CH, C-1), 127.4 (CH, C-5), 106.9 (CH, C-6), 50.2 (CH, C-3), 41.8 (CH_2, C-2).

HR-MS (ESI): for $C_{11}H_{15}N_2O_2S$ $[M+H]^+$, calc.: 239.0849, found: 239.0845; δ = 1.6 ppm.

(±)-(*Z*)-1-(Trimethylsilyl)oct-6-en-1-yn-3-ol (rac-312)



$C_{11}H_{20}OSi$, MW = 196.4 g.mol^{-1}

After trimethylsilylacetylene **267** (0.14 mL, 101 mg, 1.10 mmol, 1.1 eq) was dissolved in 1 mL diethyl ether, the mixture was brought to -78 °C, *n*-butyllithium (2.5 M solution in hexanes, 0.61 mL, 1.50 mmol, 1.5 eq) was added slowly and the reaction was stirred at the same temperature for 1 h. Still at -78 °C, a solution of **280** (100 mg, 1.00 mmol, 1.0 eq) in 3.3 mL diethyl ether was dropwise added. After the reaction was stirred at room temperature for 4 h, 1 mL of a saturated aqueous solution of ammonium chloride was added and the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was distilled (150-160 °C, 25 mbar) to afford **rac-312** (88.0 mg, 0.45 mmol, 45%) as yellow oil.

R_f = 0.60 (*c*-Hex : AcOEt = 3 : 1).

b_p = 155 °C (25 mbar).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 5.51 (1H, m, H-6, H-7), 5.39 (1H, m, H-7, H-6), 4.37 (1H, dt, *J* = 6.4, 5.9 Hz, H-3), 2.29-2.20 (2H, m, H-5), 1.82-1.73 (2H, m, H-4), 1.63 (3H, d, *J* = 6.4 Hz, H-8), 0.17 (9H, s, H-9).

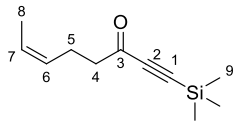
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 129.4 (CH, C-6), 125.2 (CH, C-7), 107.0 (C_q, C-2), 90.5 (C_q, C-1), 62.8 (CH, C-3), 36.6 (CH_2, C-5), 23.4 (CH_2, C-4), 12.0 (CH_3, C-8), 0.6 (CH_3, C-9).

IR (ATR): ν (cm^{-1}) = 3340 (b), 3019 (m), 2971 (s), 2940 (s), 2921 (m), 2898 (m), 2858 (m), 2203 (w), 1455 (m), 1380 (w), 1249 (s), 1065 (m), 1044 (m), 970 (s), 845 (s), 760 (m).

HR-MS (ESI): for $C_{11}H_{19}OSi$ $[M-H]^+$, calc.: 195.1205, found: 195.1208; δ = 1.5 ppm.

The spectroscopic data are in full agreement with those published in the literature.[193]

(*Z*)-1-(Trimethylsilyl)oct-6-en-1-yn-3-one (313)



$C_{11}H_{18}OSi$, MW = 194.3 g.mol^{-1}

*From **rac-312***: After **rac-312** (50.0 mg, 0.26 mmol, 1.0 eq) was dissolved in 2 mL dichloromethane, a suspension of pyridinium dichromate (145 mg, 0.39 mmol, 1.5 eq) and 0.2 g molecular sieves (4 Å) in 3 mL dichloromethane was added over 1 h. After the reaction was stirred at room temperature for 18 h, 4 mL diethyl ether were added and the mixture was filtered. The organic layer was reduced under vacuum and the residue was distilled (25 mbar, 155 °C) to afford **313** (29.0 mg, 0.15 mmol, 57%) as yellow oil.

*From **281***: After trimethylsilylacetylene **267** (0.20 mL, 144 mg, 1.40 mmol, 1 eq) was dissolved in 6.3 mL THF, the mixture was brought to -78 °C, *n*-butyllithium (2.4 M solution in hexanes, 0.60 mL, 1.40 mmol, 1 eq) was added slowly and the reaction was stirred at the same temperature for 1 h. Still at -78 °C, a solution of (*Z*)-*N*-methoxy-*N*-methylhex-4-enamide **281** (200 mg, 1.40 mmol, 1 eq) in 3 mL THF was dropwise added. After the reaction was stirred at room temperature for 16 h, it was brought to -78 °C and 1 mL of a saturated aqueous solution of NH_4Cl was added. The mixture was stirred for an additional 3.5 h, until it reached room temperature. Diethyl ether was added, the layers were separated and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford **313** (216 mg, 1.10 mmol, 88%) as yellow oil.

R_f = 0.71 (*c*-Hex : AcOEt = 3 : 1).

b_p = 155 °C (25 mbar)

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 5.50 (1H, m, H-6, H-7), 5.35 (1H, m, H-7, H-6), 2.61 (2H, t, *J* = 7.5 Hz, H-4), 2.48-2.37 (2H, m, H-5), 1.63 (3H, d, *J* = 6.6 Hz, H-8), 0.24 (9H, s, H-9).

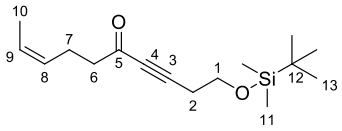
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 188.5 (C_q, C-3), 128.3 (CH, C-6), 125.6 (CH, C-7), 105.7 (C_q, C-2), 97.6 (C_q, C-1), 50.1 (CH_2, C-4), 21.5 (CH_2, C-5), 12.8 (CH_3, C-8), -0.1 (CH_3, C-9).

IR (ATR): ν (cm^{-1}) = 3367 (b), 3014 (w), 2957 (m), 2927 (m), 2862 (w), 1715 (s), 1657 (s), 1439 (m), 1405 (m), 1366 (m), 1251 (s), 1165 (s), 1099 (s), 1058 (s), 989 (s), 932 (m), 845 (s), 761 (w), 700 (m).

HR-MS (ESI): for $C_{11}H_{19}OSi$ $[M+H]^+$, calc.: 195.1200, found: 195.1198; δ = 1.0 ppm.

The spectroscopic data are in full agreement with those published in the literature.[193]

(*Z*)-1-(*tert*-Butyldimethylsilyloxy)dec-8-en-3-yn-5-one (314)



$C_{16}H_{28}O_2Si$, MW = 280.5 g.mol^{-1}

After a solution of **299** (105 mg, 0.57 mmol, 1.0 eq) in 3.5 mL THF was cooled to -78 °C, *n*-butyllithium (2.5 M solution in hexanes, 0.25 mL, 0.64 mmol, 1.1 eq) was added, the reaction was stirred for 1h at the same temperature and brought to 0 °C. **281** (90 mg, 0.57 mmol, 1.0 eq) was added, the mixture was stirred for 1 h at 0 °C and 4 h at room temperature. The solution was brought to -78 °C again and 5 mL of an aqueous saturated solution of ammonium chloride were added. The mixture was slowly warmed up, the layers were separated and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified by silica gel column chromatography (*c*-Hex : AcOEt = 99 : 1) to afford **314** (148 mg, 0.53 mmol, 92%) as colourless oil.

R_f = 0.70 (*c*-Hex : AcOEt = 9 : 1).

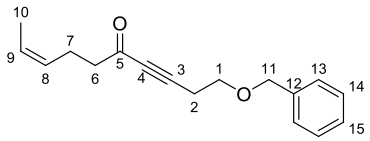
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 5.51 (1H, m, H-8), 5.33 (1H, m, H-9), 3.78 (2H, t, *J* = 6.8 Hz, H-1), 2.61-2.52 (4H, m, H-2, H-6), 2.39 (2H, dtd, *J* = 7.6, 7.4, 0.8 Hz, H-7), 1.62 (3H, bd, *J* = 6.4 Hz, H-10), 0.90 (9H, s, H-13), 0.07 (6H, s, H-11).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 187.2 (C_q, C-5), 128.0 (CH, C-8), 125.4 (CH, C-9), 105.6 (C_q, C-4), 91.3 (C_q, C-3), 60.8 (CH_2, C-1), 45.2 (CH_2, C-6), 25.8 (CH_3, C-13), 23.3 (CH_2, C-2), 21.6 (CH_2, C-7), 18.2 (C_q, C-12), 12.7 (CH_3, C-10), -5.4 (CH_3, C-11).

IR (ATR): ν (cm^{-1}) = 3016 (w), 2953 (m), 2929 (m), 2885 (m), 2858 (m), 2215 (m), 1675 (s), 1544 (w), 1468 (w), 1405 (w), 1387 (w), 1358 (w), 1330 (w), 1252 (m), 1222 (w), 1160 (m), 1106 (s), 1057 (m), 1006 (w), 936 (w), 910 (m), 835 (s), 811 (m), 777 (s), 708 (m), 663 (m).

HR-MS (ESI): for $C_{16}H_{29}O_2Si$ $[M+H]^+$, calc.: 281.1931, found: 281.1924; δ = 2.5 ppm.

(*Z*)-1-(Benzyloxy)dec-8-en-3-yn-5-one (315)



$C_{17}H_{20}O_2$, MW = 256.3 g.mol^{-1}

After a solution of **301** (102 mg, 0.64 mmol, 1.0 eq) in 3.5 mL THF was brought to -78 °C, *n*-butyllithium (2.5 M solution in hexanes, 0.28 mL, 0.70 mmol, 1.1 eq) was added and the mixture was stirred at the same temperature for 1 h. A solution of **281** (100 mg, 0.64 mmol, 1.0 eq) in 1.5 mL THF was added and the reaction was warmed to room temperature over 3 h and stirred for 16 h. The mixture was brought to -78 °C and 2 mL of a saturated aqueous solution of ammonium chloride were

added. The reaction was warmed to 0 °C, the layers were separated and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified by silica gel column chromatography (*c*-Hex : AcOEt = 95 : 5) to afford **315** (134 mg, 0.52 mmol, 82%) as colourless oil.

R_f = 0.70 (*c*-Hex : AcOEt = 9 : 1).

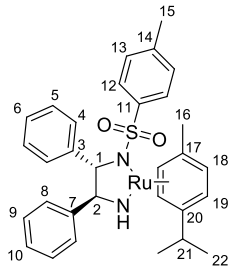
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 7.39-7.27 (5H, m, H-Ar), 5.49 (1H, m, H-9), 5.33 (1H, m, H-8), 4.56 (2H, s, H-11), 3.64 (2H, t, *J* = 6.8 Hz, H-1), 2.67 (2H, t, *J* = 6.8 Hz, H-2), 2.59 (2H, t, *J* = 6.8 Hz, H-6), 2.43-2.36 (2H, m, H-7), 1.62 (3H, dd, *J* = 6.8, 0.8 Hz, H-10).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 187.5 (C_q, C-5), 137.7 (C_q, C-12), 128.5 (CH, C-Ar), 128.0 (CH, C-8, C-Ar), 127.9 (CH, C-Ar, C-8), 127.7 (CH, C-Ar), 125.9 (CH, C-9), 90.8 (C_q, C-4), 81.4 (C_q, C-3), 73.1 (CH_2, C-11), 67.2 (CH_2, C-1), 45.2 (CH_2, C-6), 21.5 (CH_2, C-7), 20.5 (CH_2, C-2), 12.8 (CH_3, C-10).

IR (ATR) = ν (cm^{-1}): 3413 (b), 3062 (w), 3033 (w), 2961 (w), 2935 (w), 2241 (w), 2215 (w), 1713 (s), 1602 (w), 1584 (w), 1494 (w), 1452 (m), 1384 (m), 1362 (m), 1315 (m), 1269 (s), 1175 (s), 1098 (s), 1070 (s), 1026 (s), 939 (m), 804 (m), 734 (s), 713 (s), 702 (s), 689 (m), 677 (m).

HR-MS (APCI): for $C_{17}H_{21}O_2$ $[M+H]^+$, calc.: 257.1536, found: 257.1532; δ = 1.6 ppm.

Ru((*S*,*S*)-NTsCH(C_6H_5)CH(C_6H_5)NH)(*η*^{6}-cymene), Noyori catalyst (270)



$C_{31}H_{34}N_2O_2RuS$, MW = 600.1 g.mol^{-1}

Dichloro(*p*-cymene)ruthenium(II) dimer (50.0 mg, 0.08 mmol, 0.5 eq), *N*-((1*S*,2*S*)-2-amino-1,2-diphenylethyl)-4-methylbenzenesulfonamide (60.0 mg, 0.16 mmol, 1.0 eq) and potassium hydroxide (128 mg, 1.14 mmol, 7.0 eq) were dissolved in 1 mL dichloromethane and stirred at room temperature for 5 min. Afterwards, 1 mL water was added, the layers were separated and the organic layer was washed with water, dried over calcium hydride, filtered and reduced under vacuum to afford **270** (78.0 mg, 0.13 mmol, 80%) as a purple solid.

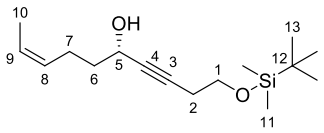
R_f = 0.60 (*c*-Hex : AcOEt = 8 : 2).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 7.64 (2H, d, *J* = 8.0 Hz, H-12, H-13), 7.42-6.98 (10H, m, H-4, H-5, H-6, H-8, H-9, H-10), 6.75 (2H, d, *J* = 8.0 Hz, H-13, H-12), 6.46 (bs, 1H, -NH), 5.24 (1H, d, *J* = 5.4 Hz, H-18, H-19), 5.12 (1H, d, *J* = 5.4 Hz, H-19, H-18), 5.09 (1H, d, *J* = 5.4 Hz, H-18, H-19), 4.97 (1H, d, *J* = 5.4 Hz, H-19, H-18), 4.84 (1H, bs, H-1), 3.97 (1H, d, *J* = 4.8 Hz, H-2), 2.41 (1H, m, H-21), 2.02 (3H, s, H-15), 1.89 (3H, s, C-16), 1.07 (3H, d, *J* = 7.0 Hz, H-22), 1.04 (3H, d, *J* = 7.0 Hz, H-22).

HR-MS: for $C_{31}H_{34}N_2O_2RuS$ $[M]^+$, calc.: 600.1384, found: 600.1387; δ = 0.5 ppm.

The spectroscopic data are in full agreement with those published in the literature.[216]

(*S*,*Z*)-1-(*tert*-Butyldimethylsilyloxy)dec-8-en-3-yn-5-ol (316)



$C_{16}H_{30}O_2Si$, MW = 282.5 g.mol^{-1}

Noyori catalyst **270** (0.20 mg, 0.27 µmol, 0.5 mol%) was added to a solution of **314** (15.0 mg, 53 µmol, 1 eq) in 0.5 mL *iso*-propanol and the reaction was stirred at room temperature for 6 h. The solvents were removed under vacuum and the residue was filtered through a pad of silica (AcOEt) to afford **316** (12.0 mg, 43 µmol, 81%) as colourless oil.

$\mathbf{R_f}$ = 0.12 (*c*-Hex : AcOEt = 95 : 5).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 5.52-5.33 (2H, m, H-8, H-9), 4.35 (1H, tt, *J* = 6.4, 1.8 Hz, H-5), 3.70 (2H, t, *J* = 7.2 Hz, H-1), 2.42 (2H, td, *J* = 7.2, 1.8 Hz, H-2), 2.20 (2H, dt, *J* = 8.8, 7.0 Hz, H-7), 1.75-1.68 (2H, m, H-6), 1.61 (3H, d, *J* = 6.4 Hz, H-10), 0.88 (9H, s, H-13), 0.06 (6H, s, H-11).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 129.4 (CH, C-8), 124.8 (CH, C-9), 82.4 (C_q, C-3, C-4), 82.3 (C_q, C-4, C-3), 62.3 (CH, C-5), 61.9 (CH_2, C-1), 37.7 (CH_2, C-7), 25.9 (CH_3, C-13), 23.1 (CH_2, C-6), 22.7 (CH_2, C-2), 18.3 (C_q, C-12), 12.7 (CH_3, C-10), -5.3 (CH_3, C-11).

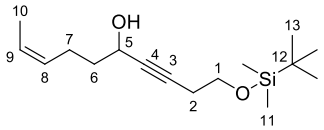
IR (ATR): ν (cm^{-1}) = 3322 (b), 3014 (w), 2951 (w), 2929 (m), 2858 (w), 1467 (w), 1437 (w), 1406 (w), 1386 (w), 1362 (w), 1335 (w), 1254 (m), 1220 (w), 1101 (s), 1058 (m), 1023 (m), 1007 (m), 936 (m), 913 (m), 835 (s), 813 (s), 775 (s), 705 (m), 662 (m).

HR-MS (APCI): for $C_{16}H_{31}O_2Si$ $[M+H]^+$, calc.: 283.2088, found: 283.2086; δ = 0.7 ppm.

$\mathbf{[\alpha]_D^{20}}$ = -8.2 (c = 0.085, methanol).

Due to technical and time limitations precised in the theoretical section, it was not possible to determine the enantiomeric excess at this point.

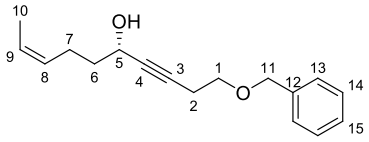
(±)-(*Z*)-1-(*tert*-Butyldimethylsilyloxy)dec-8-en-3-yn-5-ol (rac-316)



$C_{16}H_{30}O_2Si$, MW = 282.5 g.mol^{-1}

After **314** (20.0 mg, 0.07 mmol, 1.0 eq) was dissolved in 1 mL *iso*-propanol, the mixture was brought to 0 °C and sodium borohydride (4.00 mg, 0.11 mmol, 1.5 eq) was added. The reaction was stirred at room temperature for 4 days. Water was added to the mixture and the solvents were removed under vacuum. The residue was dissolved in water and ethyl acetate, the layers were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford **rac-316** (15.3 mg, 0.05 mmol, 76%) as colourless oil.

(*S*,*Z*)-1-(Benzyloxy)dec-8-en-3-yn-5-ol (317)



$C_{17}H_{22}O_2$, MW = 258.4 g.mol^{-1}

Noyori catalyst **270** (0.94 mg, 1.56 µmol, 2 mol%) was added to a solution of **315** (20.0 mg, 78 µmol, 1 eq) in 1 mL *iso*-propanol and the reaction was stirred at room temperature for 6 h. The solvents were removed under vacuum and the residue was filtered through a pad of silica (AcOEt) to afford **317** (15.0 mg, 58 µmol, 75%) as colourless oil.

R_f = 0.25 (*c*-Hex : AcOEt = 9 : 1).

^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 7.37-7.26 (5H, m, H-Ar), 5.55-5.29 (2H, m, H-8, H-9), 4.55 (2H, s, H-11), 4.37 (1H, tt, *J* = 6.4, 1.8 Hz, H-5), 3.59 (2H, t, *J* = 7.0 Hz, H-1), 2.54 (2H, td, *J* = 7.0, 1.8 Hz, H-2), 2.26-2.18 (2H, m, H-7), 1.79-1.70 (2H, m, H-6), 1.62 (3H, dd, *J* = 6.6, 1.0 Hz, H-10).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 137.9 (C_q, C-12), 130.2 (CH, C-15), 129.4 (CH, C-8), 129.0 (CH, C-14), 128.2 (CH, C-13), 125.3 (CH, C-9), 82.2 (C_q, C-4), 77.2 (C_q, C-3), 71.7 (CH_2, C-11), 62.3 (CH_2, C-1), 61.9 (CH, C-5), 35.6 (CH_2, C-7), 25.9 (CH_2, C-6), 21.5 (CH_2, C-2), 12.8 (CH_3, C-10).

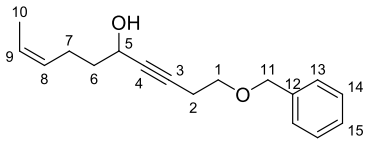
IR (ATR): ν (cm^{-1}) = 3428 (b), 3307 (w), 3086 (w), 3062 (w), 3015 (w), 2957 (m), 2859 (m), 1720 (w), 1647 (w), 1495 (w), 1453 (m), 1412 (m), 1385 (m), 1330 (w), 1314 (m), 1278 (m), 1176 (m), 1100 (m), 1028 (m), 987 (m), 930 (w), 912 (w), 846 (w), 821 (w), 739 (m), 699 (s), 680 (m).

HR-MS (APCI): for $C_{17}H_{23}O_2$ $[M+H]^+$, calc.: 259.1693, found: 259.1700; δ = 2.7 ppm.

$[\alpha]_D^{20}$ = +10.2 (c = 0.95, $CDCl_3$).

Due to technical and time limitations precised in the theoretical section, it was not possible to determine the enantiomeric excess at this point.

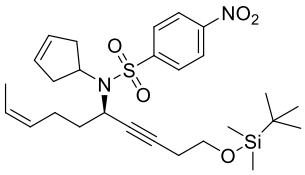
(±)-(*Z*)-1-(Benzyloxy)dec-8-en-3-yn-5-ol (rac-317)



$C_{17}H_{22}O_2$, MW = 258.4 g.mol^{-1}

After **315** (20.0 mg, 0.08 mmol, 1.0 eq) was dissolved in 1 mL *iso*-propanol, the mixture was brought to 0 °C and sodium borohydride (4.30 mg, 0.12 mmol, 1.5 eq) was added. The reaction was stirred at room temperature for 4 days. Water was added to the mixture and the solvents were removed under vacuum. The residue was dissolved in water and ethyl acetate, the layers were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford **rac-317** (14.0 mg, 0.05 mmol, 70%) as colourless oil.

(*R*,*Z*)-*N*-(1-(*tert*-Butyldimethylsilyloxy)dec-8-en-3-yn-5-yl)-*N*-(cyclopent-3-enyl)-4-nitrobenzenesulfonamide (318)



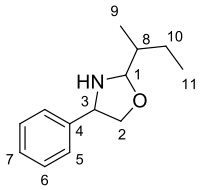
$C_{27}H_{40}N_2O_5SSi$, MW = 532.8 g.mol^{-1}

After **271** (13.4 mg, 0.05 mmol, 1.2 eq) and triphenylphosphine (27.5 mg, 0.11 mmol, 2.5 eq) were added respectively to a solution of **316** (12.0 mg, 0.04 mmol, 1.0 eq) in 0.3 mL THF, the mixture was brought to 0 °C. DIAD (16.5 µL, 17.0 mg, 0.08 mmol, 2.0 eq) was slowly added and the reaction was stirred at room temperature for 7 days. The solvents were removed under vacuum to afford a brown mixture. Only traces of **318** were identified in the mixture using HR-MS.

HR-MS (ESI): for $C_{27}H_{41}N_2O_5SSi$ $[M+H]^+$, calc.: 533.2500, found: 533.2493; δ = 1.3 ppm.

3.4. Experimental data for annex II and annex III

2-*sec*-Butyl-4-phenyloxazolidine (329)



$C_{13}H_{19}NO$, MW = 205.3 g.mol^{-1}

After phenylglycinol (100 mg, 0.73 mmol, 1 eq) was dissolved in 2 mL THF, 500 mg $MgSO_4$ and 2-methylbutanal (0.08 mL, 63.0 mg, 0.73 mmol, 1 eq) were added. The reaction was then stirred at room temperature for 6 h. The mixture was filtered through Celite which was washed several times with dichloromethane and the combined organic layers were reduced under vacuum to afford a mixture of *cis* and *trans* oxazolidines **329** (68.0 mg, 0.33 mmol, 45%) as colourless oil.

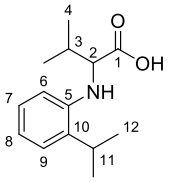
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 7.26-7.11 (5H, m, H-5, H-6, H-7), 4.49 (0.35H, td, *J* = 6.8, 3.6 Hz, H-1, H-2, H-3), 4.44-4.34 (1.65H, m, H-2, H-3, H-1), 4.26 (0.35H, ddd, *J* = 8.0, 7.6, 2.8 Hz, H-3, H-1, H-2), 4.12 (0.65H, t, *J* = 7.6 Hz, H-1, H-3, H-2), 3.63 (1H, m, H-3, H-2, H-1), 2.59 (1H, m, H-8), 1.78-1.59 (2H, m, H-10), 1.05-0.99 (3H, m, H-9), 0.99-0.92 (3H, m, H-11).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 142.0 (C_q, C-4), 141.2 (C_q, C-4), 129.0 (CH, C-5, C-6), 128.7 (CH, C-6, C-5), 127.9 (CH, C-5, C-6), 127.4 (CH, C-6, C-5), 127.0 (CH, C-7), 126.8 (CH, C-7), 98.9 (CH, C-1), 98.4 (CH, C-1), 72.8 (CH, C-3), 71.9 (CH, C-3), 62.4 (CH_2, C-2), 60.8 (CH_2, C-2), 33.5 (CH, C-8), 32.9 (CH, C-8), 22.5 (CH_2, C-10), 22.3 (CH_2, C-10), 13.6 (CH_3, C-9), 13.5 (CH_3, C-9), 11.5 (CH_3, C-11), 11.5 (CH_3, C-11).

IR (ATR): ν (cm^{-1}) = 3283 (b), 3088 (w), 3061 (w), 3032 (w), 2963 (m), 2932 (m), 2876 (m), 1656 (m), 1602 (m), 1534 (m), 1495 (m), 1453 (m), 1381 (m), 1309 (w), 1269 (w), 1183 (w), 1155 (w), 1070 (m), 1037 (m), 1027 (m), 1002 (w), 965 (w), 921 (w), 843 (w), 801 (w), 757 (m), 698 (s), 676 (m).

HR-MS (ESI): for $C_{13}H_{20}NO$ $[M+H]^+$, calc.: 206.1539, found: 206.1539; δ = 0.0 ppm.

2-(2-*iso*-Propylphenylamino)-3-methylbutanoic acid (331)



$C_{14}H_{21}NO_2$, MW = 235.3 g.mol^{-1}

After L-valine (3.29 g, 28.0 mmol, 1.0 eq), copper iodide (1.07 g, 5.61 mmol, 0.2 eq) and potassium carbonate (7.75 g, 56.1 mmol, 2.0 eq) were dissolved in 50 mL dimethyl sulfoxide, 1-iodo-2-*iso*-

propylbenzene (6.90 g, 28.0 mmol, 1.0 eq) was added and the reaction mixture was stirred at 100 °C for 75 h. The mixture was then cooled down to 0 °C and 50 mL of a 1 : 1 mixture of water and ethyl acetate were added. A 25% aqueous solution of hydrochloric acid was then slowly added until the pH reached the value of 3. The layers were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford **331** (4.85 g, 20.6 mmol, 74%) as brown oil.

R_f = 0.40 (*c*-Hex : AcOEt = 1 : 9).

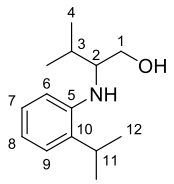
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 7.19 (1H, dd, *J* = 7.8, 1.4 Hz, H-9), 7.10 (1H, td, *J* = 7.8, 1.4 Hz, H-7), 6.80 (1H, td, *J* = 7.8, 1.4 Hz, H-8), 6.60 (1H, dd, *J* = 7.8, 1.4 Hz, H-6), 3.95 (1H, t, *J* = 5.4 Hz, H-2), 2.97 (1H, sept, *J* = 6.8 Hz, H-11), 2.24 (1H, septd, *J* = 6.8, 5.4 Hz, H-3), 1.30 (3H, d, *J* = 6.8 Hz, H-12), 1.27 (3H, d, *J* = 6.8 Hz, H-12), 1.12 (3H, d, *J* = 6.8 Hz, H-4), 1.10 (3H, d, *J* = 6.8 Hz, H-4).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 179.1 (C_q, C-1), 143.7 (C_q, C-5), 133.0 (C_q, C-10), 126.8 (CH, C-7, C-9), 125.3 (CH, C-9, C-7), 118.4 (CH, C-8), 111.0 (CH, C-6), 62.2 (CH, C-2), 31.5 (CH, C-3), 27.4 (CH, C-11), 22.4 (CH_3, C-12), 22.4 (CH_3, C-12), 19.3 (CH_3, C-4), 18.6 (CH_3, C-4).

HR-MS (ESI): for $C_{13}H_{22}N$ $[M+H-CO_2]^+$, calc.: 192.1747, found: 192.1746; δ = 0.5 ppm.

The spectroscopic data are in full agreement with those published in the literature.[220]

2-(2-*iso*-Propylphenylamino)-3-methylbutan-1-ol (332)



$C_{14}H_{23}NO$, MW = 221.3 g.mol^{-1}

After **331** (625 mg, 2.66 mmol, 1.0 eq) was dissolved in 10 mL diethyl ether, the mixture was brought to 0 °C. A 4 M solution of lithium aluminium hydride in diethyl ether (0.80 mL, 3.20 mmol, 1.2 eq) was slowly added and the reaction mixture was stirred at room temperature for 16 h. The mixture was then brought to 0 °C and 3 mL water were slowly added. The obtained suspension was filtered and the solid residue was washed with water and diethyl ether. Layers from the filtrate were separated and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified by silica gel column chromatography (*c*-Hex : AcOEt = 9 : 1) to afford **332** (254 mg, 1.15 mmol, 43%) as colourless oil.

R_f = 0.35 (*c*-Hex : AcOEt = 8 : 2).

^{1}H-NMR (500.1 MHz, $CDCl_3$): δ (ppm) = 7.08 (1H, d, *J* = 7.5 Hz, H-9), 7.01 (1H, td, *J* = 7.5, 1.5 Hz, H-7), 6.71-6.64 (2H, m, H-6, H-8), 3.73 (1H, dd, *J* = 11.0, 6.0 Hz, H-1), 3.54 (1H, dd, *J* = 11.0, 6.5 Hz, H-1), 3.33 (1H, m, H-2), 2.83 (1H, sept, *J* = 7.0 Hz, H-11), 1.90 (1H, oct, *J* = 7.0 Hz, H-3), 1.24 (3H, d,

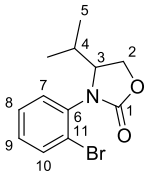
J = 7.0 Hz, H-12), 1.23 (3H, d, *J* = 7.0 Hz, H-12), 0.98 (3H, d, *J* = 7.0 Hz, H-4), 0.96 (3H, d, *J* = 7.0 Hz, H-4).

IR (ATR): ν (cm^{-1}) = 3729 (w), 3624 (w), 3598 (w), 3341 (b), 2961 (w), 2925 (w), 1680 (w), 1650 (w), 1560 (w), 1460 (m), 1417 (m), 1399 (m), 1336 (s), 1278 (m), 1257 (m), 1129 (m), 992 (s), 940 (s), 875 (s), 818 (s), 795 (s), 754 (m), 681 (s), 671 (s), 666 (s).

HR-MS (ESI): for $C_{14}H_{24}NO$ $[M+H]^+$, calc.: 222.1852, found: 222.1853; δ = 0.5 ppm.

The spectroscopic data are in full agreement with those published in the literature.[220]

3-(2-Bromophenyl)-4-*iso*-propyloxazolidin-2-one (335)



$C_{12}H_{14}BrNO_2$, MW = 284.1 g.mol^{-1}

To a solution of **334** (100 mg, 0.39 mmol, 1 eq) and triethylamine (0.27 mL, 197 mg, 1.94 mmol, 5 eq) in 5 mL dichloromethane at 0 °C was added dropwise, over 45 min, a solution of triphosgen (115 mg, 0.39 mmol, 1 eq) in 5 mL dichloromethane. The mixture was then stirred at room temperature for 4 h and refluxed for 2 d. After addition of dichloromethane and water, layers were separated and aqueous layer was extracted three times with dichloromethane. The combined organic layers were then washed with a 1 M aqueous solution of sodium hydroxide and with brine, dried over $MgSO_4$, filtered and reduced under vacuum. The residue was purified using preparative TLC (*c*-Hex : MTBE = 2 : 1) to afford **335** (57.0 mg, 0.20 mmol, 52%) as colourless oil.

R_f = 0.30 (*c*-Hex : MTBE = 2 : 1).

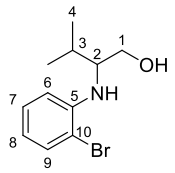
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ (ppm) = 7.64 (1H, m, H-Ar), 7.40-7.34 (2H, m, H-Ar), 7.22 (1H, m, H-Ar), 4.49 (1H, m, H-2), 4.35 (1H, m, H-2), 4.26 (1H, dt, *J*= 8.8, 5.2 Hz, H-3), 1.81 (1H, m, H-4), 0.96 (3H, d, *J* = 6.8 Hz, H-5), 0.84 (3H, d, *J* = 6.8 Hz, H-5).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 156.9 (C_q, C-1), 135.5 (C_q, C-6), 134.0 (CH, C-10), 130.8 (CH, C-Ar), 129.7 (CH, C-Ar), 128.4 (CH, C-Ar), 122.6 (C_q, C-11), 63.9 (CH, C-3), 61.7 (CH_2, C-2), 29.0 (CH, C-4), 18.0 (CH_3, C-5), 15.2 (CH_3, C-5).

IR (ATR) = ν (cm^{-1}): 3064 (w), 2961 (w), 2929 (w), 2876 (w), 1751 (s), 1586 (w), 1478 (s), 1443 (w), 1404 (m), 1370 (w), 1325 (w), 1252 (w), 1209 (s), 1141 (m), 1114 (m), 1079 (w), 1052 (m), 1026 (m), 991 (m), 962 (m), 929 (w), 863 (w), 835 (w), 757 (s), 722 (m), 691 (m).

HR-MS (ESI): for $C_{12}H_{14}BrNNaO_2$ $[M+Na]^+$, calc.: 306.0100, found: 306.0102; δ = 0.7 ppm.

2-(2-Bromophenylamino)-3-methylbutan-1-ol (334)



$C_{11}H_{16}BrNO$, MW = 257.0 g.mol^{-1}

To a solution of **335** (7.00 mg, 25 μmol, 1 eq) in 1 mL diethyl ether were added water (1 μL, 1.00 mg, 50 μmol, 2 eq) and potassium *tert*-butoxide (16.8 mg, 0.15 mmol, 6 eq). The reaction was then stirred at room temperature for 1 d and refluxed for 4 d. Diethyl ether and water were added and layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum to afford a mixture of reactant **335** and product **334** (ratio 1 : 0.4, 29% conversion). The product was isolated from the mixture using preparative TLC (*c*-Hex : MTBE = 1 : 1) and obtained as colourless oil.

R_f = 0.15 (*c*-Hex : MTBE = 1 : 1).

^{1}H-NMR (500.1 MHz, $CDCl_3$): δ (ppm) = 7.45 (1H, dd, *J* = 8.0, 1.5 Hz, H-9), 7.18 (1H, ddd, *J* = 9.0, 7.5, 1.5 Hz, H-7), 6.79 (1H, dd, *J* = 7.5, 1.5 Hz, H-6), 6.59 (1H, ddd, *J* = 9.0, 8.0, 1.5 Hz, H-8), 4.32 (1H, bs, -NH), 3.80 (1H, dd, *J* = 11.0, 3.5 Hz, H-1), 3.64 (1H, dd, *J* = 11.0, 7.0 Hz, H-1), 3.40 (1H, bs, H-2), 1.97 (1H, m, H-3), 1.90 (1H, bs, -OH), 1.03 (3H, d, *J* = 7.5 Hz, H-4), 1.00 (3H, d, *J* = 6.5 Hz, H-4).

^{13}C-NMR (125.8 MHZ, $CDCl_3$): δ (ppm) = 145.3 (C_q, C-5), 132.6 (CH, C-9), 128.5 (CH, C-7), 118.2 (CH, C-8), 112.6 (CH, C-6), 110.4 (C_q, C-10), 63.0 (CH_2, C-1), 61.3 (CH, C-2), 30.2 (CH, C-3), 19.3 (CH_3, C-4), 18.8 (CH_3, C-4).

IR (ATR): ν (cm^{-1}) = 3398 (b), 3067 (w), 3026 (w), 2957 (m), 2929 (w), 2873 (w), 1592 (m), 1507 (s), 1459 (m), 1431 (m), 1389 (w), 1368 (w), 1320 (m), 1284 (m), 1242 (w), 1163 (w), 1131 (w), 1064 (m), 1047 (m), 1016 (s), 924 (w), 831 (w), 808 (w), 739 (s), 705 (w), 666 (m).

HR-MS (ESI): for $C_{11}H_{17}BrNO$ $[M+H]^+$, calc.: 258.0488, found: 258.0488; δ = 0.0 ppm.

The spectroscopic data are in full agreement with those published in the literature.[220]

Annex

I. Abbreviations

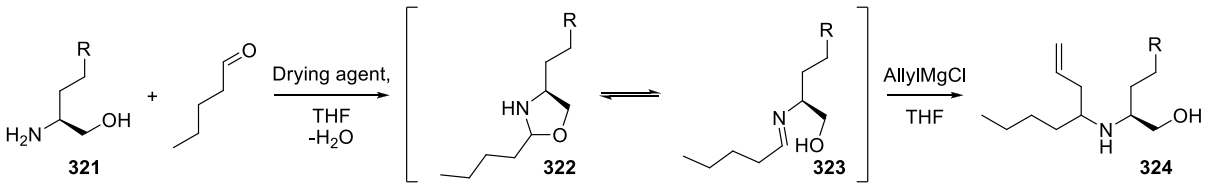
°C	Celsius degree
9-BBN	9-Borabicyclo(3.3.1)nonane
Å	Ångström
abs.	Absolute
Ac	Acetyl
acac	Acetylacetonate
AcOEt	Ethyl acetate
add.	Addition
APCI	Atmospheric-pressure chemical ionization
APT	Attached proton test
Ar	Aryl
ATR	Attenuated total reflectance
b	Broad (NMR, IR)
Boc	*tert*-Butoxycarbonyl
bp	Boiling point
brsm	Based on recovered starting material
c	Cyclo
calc.	Calculated
CAN	Ceric ammonium nitrate
Cbz	Benzyloxycarbonyl
COSY	Correlation spectroscopy
CSA	Camphorsulfonic acid
d	Day
d	Doublet (NMR)
d.r.	Diastereoselective ratio
δ	chemical shift (NMR)
δ	relative experimental error (MS)
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCC	*N*,*N'*-Dicyclohexylcarbodiimide
DEPT	Distortionless enhancement by polarization transfer
DHP	Dihydropyran, in this study 3,4-dihydro-2*H*-pyran
DIAD	Di*iso*-propyl azodicarboxylate
DIBAL-H	Di*iso*-butylaluminium hydride
DMAP	4-Dimethylamino pyridine
DMF	Dimethylformamide
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DPEN	1,2-Diphenyl-1,2-ethylenediamine

EI	Electronic ionization
eq	Equivalent
ESI	Electrospray ionisation
Et	Ethyl
h	Hour
Hex	Hexane
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HMDS	Hexamethyldisilazane
HMQC	Heteronuclear multiple-quantum correlation spectroscopy
HPLC	High-performance liquid chromatography
HR-MS	High resolution mass spectroscopy
HSQC	Heteronuclear single-quantum correlation spectroscopy
Hz	Hertz
IC_{50}	Half maximal inhibitory concentration
IR	Infra red
J	Coupling constant value in Hz (NMR)
KB cells	Sub line of tumour cell line HeLa (Henrietta Lacks' cells)
M	Molar
m	Medium (IR)
m	Multiplet (NMR)
Me	Methyl
MeTHF	2-Methyltetrahydrofuran
min	Minute
mL	Millilitre
mp	Melting point
MS	Mass spectroscopy
MS	Molecular sieves
MTBE	Methyl *tert*-butyl ether
n	*normal*
NCS	*N*-Chlorosuccinimide
NMR	Nuclear magnetic resonance
Nosyl	Nitrobenzenesulfonyl
NSCLC	Non-small-cell lung carcinoma
oct	Octet
p	Para
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
PG	Protecting group
ppm	Part per million
*p*TSA	*p*-Toluenesulfonic acid
Py	Pyridine
q	Quartet (NMR)
quint	Quintet (NMR)
rac	racemic
RaNi	Raney nickel

R_f	Retardation factor
s	Singlet (NMR)
s	Strong (IR)
sept	Septet (NMR)
t	Triplet (NMR)
*t*Bu	*tert*-Butyl
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDMS/TBS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Teoc	2-(Trimethylsilyl)ethoxycarbonyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Tri*iso*propylsilyl
TLC	Thin layer chromatography
TMEDA	*N*, *N*, *N'*, *N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	Toluene-4-sulfonyl
w	Weak (IR)

II. Studies upon the predominance of an intermediate in the imine/oxazolidine formation - Grignard addition two-step sequence

The imine/oxazolidine formation – Grignard addition two-step sequence developed by Nicole Holub and optimised in this work was studied separately in details to try to elucidate some of its mechanistic aspects.[97] The reaction between the general amino alcohol **321** and pentanal was postulated to lead to the equilibrium of the general oxazolidine and imine intermediates **322** and **323** which underwent a subsequent Grignard addition to give the general product **324**. In the remaining of this section, some studies are reported upon the tentative isolation of the process intermediate and the predominance of the intermediate **322** or **323**. No studies were here performed upon the process diastereoselectivity.



Scheme 120. General scheme of the imine/oxazolidine formation – Grignard addition two-step sequence.

Several tests and spectroscopic analyses were first performed on pentanal to study its stability in the desired reaction conditions. Initially, to have a reference ^{1}H-NMR spectrum, pentanal was simply diluted in deuterated chloroform and the sample was analysed using ^{1}H-NMR. The integration of the peak corresponding to the aldehyde proton was evaluated in comparison to the integration of the protons corresponding to the methyl group which was defined to be equal to 3. Considering this standard, the integration value of the aldehyde proton was equal to 0.72 (**Table 29**, **Entry 1**). The sample was then kept and a second measurement was performed after three days. The integration of the peak corresponding to the aldehyde proton, evaluated in the same conditions, was found to be equal to 0.45 showing a slight decomposition of the aldehyde in acidic medium which may simply be due to an aldol addition of the aldehyde on itself (**Table 29**, **Entry 2**). The same conclusions were noticed in the presence of magnesium sulfate (**Table 29**, **Entry 3**). For the next tests, the pentanal was diluted in tetrahydrofuran, either magnesium sulfate or 4Å molecular sieves were added and the mixtures were stirred during 12 hours. The reaction mixtures were then filtered through celite; the residues were dissolved in deuterated chloroform and analysed using ^{1}H-NMR. In the case of the presence of magnesium sulfate, only half of the aldehyde decomposed whereas only 20-25% of the aldehyde remained in the case of the presence of molecular sieves (**Table 29**, **Entries 4 and 5**).

These stability studies revealed an easy decomposition of pentanal, which may partly be due to intermolecular aldol reactions. In the presence of the drying agents which had to be used in the desired process, pentanal showed a difference in behaviour when stirred with magnesium sulfate or with 4Å molecular sieves. However, in both cases, a decomposition of pentanal was observed showing that the reaction time should be as short as possible to avoid losses in aldehyde. Also, to avoid any lack of aldehyde during the imine/oxazolidine intermediate formation, a large excess of aldehyde should be used.

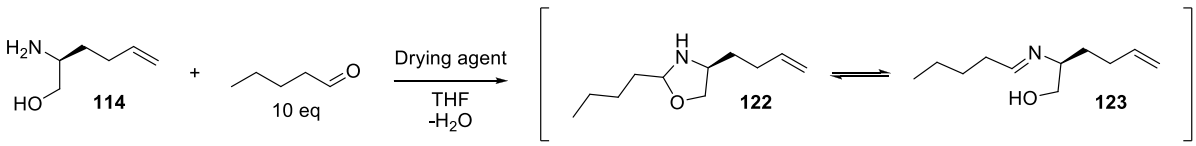
Table 29. Stability tests performed on pentanal.

Entry	Drying agent	Solvent	Stirring time	Result	^{1}H-NMR [Integration Value][h]
1	None	$CDCl_3$	0 min	OK	0.72
2	None	$CDCl_3$	3 days	Slight decomposition	0.45
3[i]	$MgSO_4$	$CDCl_3$	3 days	Slight decomposition	0.41
4**i**	$MgSO_4$	THF	12 h	Slight decomposition	0.35
5[j]	4Å MS	THF	12 h	Decomposition	0.15

In a second part, the amino alcohol obtained along our synthetic ways were reacted with an excess of pentanal in the presence of drying agents, which were previously activated, in tetrahydrofuran or deuterated tetrahydrofuran. For each amino alcohol, two reactions were directly monitored in deuterated tetrahydrofuran. In one case, magnesium sulfate was used as the drying agent and in the other case, 4Å molecular sieves were used. Depending on the substrate, the third test was performed in the conditions described as being the best either in the studies formerly performed by Nicole Holub or in this work.[97]

The imine/oxazolidine formation reaction was first studied on the alkene **114**. All monitored reactions, using magnesium sulfate or molecular sieves as drying agent, using tetrahydrofuran or deuterated tetrahydrofuran as solvent, led to unidentifiable mixtures. Neither the oxazolidine **122** nor the imine **123** was consequently identified in ^{1}H-NMR spectroscopy (**Table 30**).

Table 30. Reactions between the amino alcohol 114 and pentanal.



Entry	Conditions	Result
1**i**	10 eq $MgSO_4$, THF-d8	No intermediate was identified
2**j**	4Å MS, THF-d8	No intermediate was identified
3**i**	10 eq $MgSO_4$, THF	No intermediate was identified

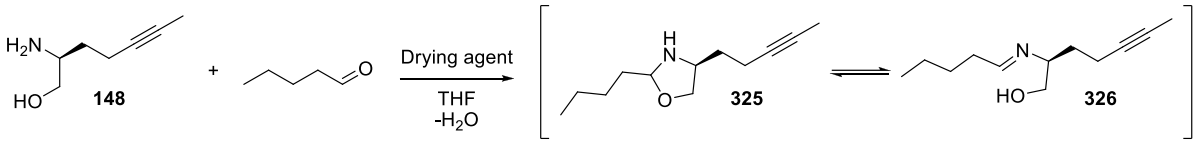
The same studies were performed using the amino alcohol **148**. As in the case of the amino alcohol **114**, all monitored reactions led to unidentifiable mixtures. None of the awaited intermediates **325** or **326** were consequently identified in ^{1}H-NMR spectroscopy (**Table 31**).

[h] ^{1}H-NMR integration value of the aldehyde proton is given relatively to the integration of the protons of the methyl group.

[i] $MgSO_4$ is dried at 120 °C, under vacuum (1 mbar), during 3 h.

[j] Molecular sieves are dried in a oven at 250 °C, under vacuum (1 mbar) during 16 h.

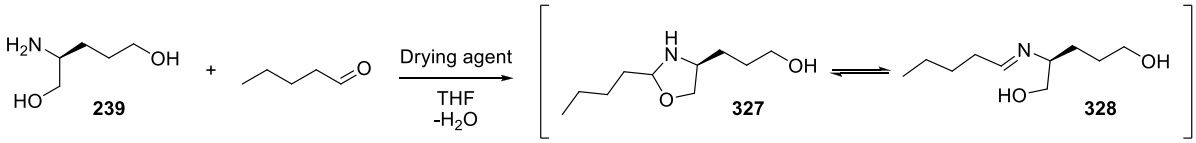
Table 31. Reactions between the amino alcohol 148 and pentanal.



Entry	Conditions	Result
1[k]	10 eq pentanal, 10 eq $MgSO_4$, THF-d8	No intermediate was identified
2[l]	10 eq pentanal, 4Å MS, THF-d8	No intermediate was identified
3k	1.5 eq pentanal, 12.5 eq $MgSO_4$, THF	No intermediate was identified

Identical studies were performed using the amino alcohol **239**. As in the case of the amino alcohols **114** and **148**, all monitored reactions led to unidentifiable mixtures. None of the awaited intermediates **327** or **328** were consequently identified in ^{1}H-NMR spectroscopy (**Table 32**).

Table 32. Reactions between the amino alcohol 239 and pentanal.

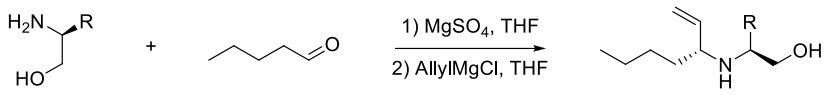


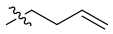
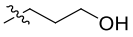
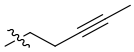
Entry	Conditions	Result
1k	10 eq pentanal, $MgSO_4$, THF-d8	No intermediate was identified
2l	10 eq pentanal, 4Å MS, THF-d8	No intermediate was identified
3l	1.1 eq pentanal, 4Å MS, THF	No intermediate was identified

As it was not possible to identify any of the awaited imine/oxazolidine intermediates, the two-step process was performed on the three amino alcohols **114**, **148** and **239**. In these cases, the imine/oxazolidine formation was performed in tetrahydrofuran and using magnesium sulfate as the drying agent. After a common work-up, the residue was dissolved in tetrahydrofuran, the solution was brought to -78 °C and the addition of a solution of allylmagnesium chloride in tetrahydrofuran was performed. After work-up and flash chromatography, the residues were analysed in ^{1}H-NMR spectroscopy. The first test was performed on the amino alcohol **114**. The desired product **113** was obtained in a 33% yield and 50% of amino alcohol **114** was recovered (**Table 33**, **Entry 1**). The test performed on the aminodiol **239** led to the product **243** in a 41% yield and to various unidentified side-products (**Table 33**, **Entry 2**). Finally, the test was performed on the amino alcohol **148** and afforded the product **146** in a 31% yield and various unidentified side-products (**Table 33**, **Entry 3**).

[k] $MgSO_4$ is dried at 120 °C, under vacuum (1 mbar), during 3 h.
[l] Molecular sieves are dried in a oven at 250 °C, under vacuum (1 mbar) during 16 h.

Table 33. Imine/Oxazolidine formation - Grignard addition two-step sequence on amino alcohols 114, 148 and 239.



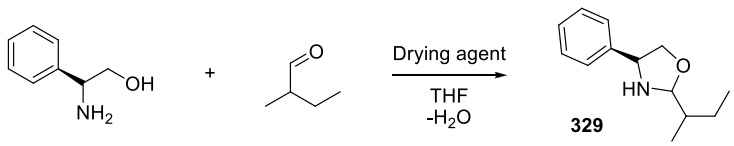
Entry	-R	Reactant	Product	Result
1		**114**	**113**	33% yield (66% brsm)
2		**239**	**243**	41% yield Various unidentified side-products
3		**148**	**146**	31% yield Various unidentified side-products

These last results point out the fact that although if the awaited imine/oxazolidine intermediates between the two-step of the used process could not be observed, the process is giving the final product in all cases. However, these results do not allow any speculation on the nature of the real intermediate in this process.

As one example of oxazolidine formation was described by Agami and co-workers and by Kuhnert and Danks starting from (2*S*)-phenylglycinol and using 2-methylbutanal as the aldehyde, further tests were performed using (2*S*)-phenylglycinol as the amino alcohol.[229,230]

Experiments were performed following the procedure reported by Agami and co-workers.[229] First, the experiment described was repeated using the same amino alcohol and aldehyde. Using thus (2*S*)-phenylglycinol and 2-methylbutanal, two tests were performed, one with magnesium sulfate as the drying agent and the other with 4Å molecular sieves. In both cases, the described intermediates were predominant in the mixture. Indeed, a mixture of *cis* and *trans* oxazolidines **329** was observed in the residue (**Table 34**, **Entries 1 and 2**).

Table 34. Oxazolidine formation starting from (2*S*)-phenylglycinol and 2-methylbutanal.



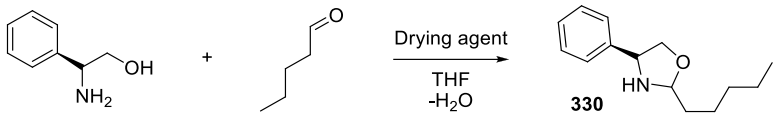
Entry	Drying agent	Result
1[m]	$MgSO_4$	**329** predominantly observed in the final mixture
2[n]	4Å MS	**329** predominantly observed in the final mixture

The same procedures were then applied using pentanal instead of 2-methylbutanal. As in the case of the other amino alcohols **114**, **148** and **239**, all monitored reactions led to unidentifiable mixtures. No oxazolidines **330** were identified in ^{1}H-NMR spectroscopy (**Table 35**, **Entries 1 and 2**).

[m] $MgSO_4$ is dried at 120 °C, under vacuum (1 mbar), during 3 h.

[n] Molecular sieves are dried in a oven at 250 °C, under vacuum (1 mbar) during 16 h.

Table 35. Oxazolidine formation starting from (2*S*)-phenylglycinol and pentanal.



Entry	Drying agent	Stirred [time]	Work-up	Result
1[o]	$MgSO_4$	6 h	Filtrated through Celite	No intermediate was identified
2[p]	4Å MS	6 h	Decantation and filtration	No intermediate was identified

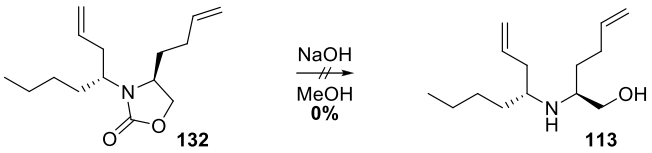
In summary, considering all the results obtained during these mechanistic studies, it was not possible to prove which intermediate was predominant in this two-step process. It is interesting to notice that the reaction of (2*S*)-phenylglycinol with 2-methylbutanal led to a mixture of *cis* and *trans* oxazolidines identifiable in ^{1}H-NMR spectroscopy whereas the reaction with pentanal, as for the reactions with other amino alcohols, led to a mixture of unidentifiable intermediates. However, it was separately proved that the two-step process in its entirety proceeded although if the final yield were sometimes moderate. It may simply be because these intermediary residues were composed of a complex mixture of *cis* and *trans* oxazolidines and of the corresponding imine rending thus difficult the interpretation of the results obtained in ^{1}H-NMR spectroscopy. As the final yields of the two-step process were found to be between 31% and 41%, it is also possible that other side-products were already formed in the first part of the process, inducing an additional difficulty for the analytical interpretation. In this work, no further studies were performed on this subject. However, to obtain complementary data, some additional analyses could be performed such as for example *in situ* infrared spectroscopy.

[o] $MgSO_4$ is dried at 120 °C, under vacuum (1 mbar), during 3 h.

[p] Molecular sieves are dried in a oven at 250 °C, under vacuum (1 mbar) during 16 h.

III. Studies upon the protection of the α-amino alcohol function of the diene 113 using triphosgene and the removal of the protecting group

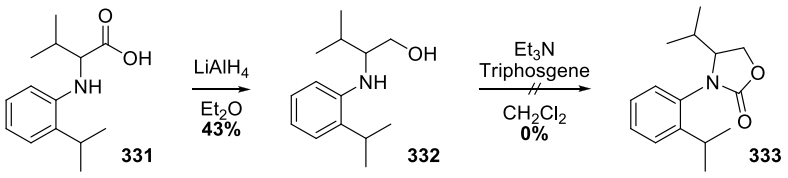
A single deprotection test was performed on the diene **132** using sodium hydroxide in methanol (**Scheme 121**).[231,232] In these conditions, the desired product **113** was not observed and the starting material entirely recovered.



Scheme 121. Tentative deprotection reaction of the diene 132.

Given the synthetic cost, in time and money, for obtaining the substrate **132**, and the apparent necessity of a study on the considered deprotection reaction, some tests were performed in parallel of this work on the carbamate protection reaction and on the removal of this protecting group on more affordable and common substrates of our group.

Initially, the amino alcohol **332** was considered for this study. The treatment of the amino acid **331**, available in big amounts in our group, with lithium aluminium hydride in diethyl ether afforded the desired substrate **332** in a 43% yield (**Scheme 122**). The subsequent treatment with triphosgene and triethylamine in dichloromethane did not lead to the desired protected product **333**. Only starting material **332** was recovered which may be due to the important steric hindrance induced by the *iso*-propyl groups.



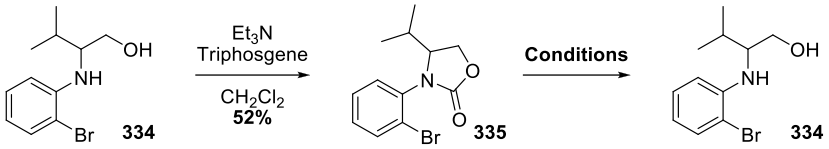
Scheme 122. Tentative synthesis of the protected substrate 333.

At the same time, a test was performed on the amino alcohol **334** which was also treated with triphosgene and triethylamine in dichloromethane. The protection reaction led to the desired corresponding protected substrate **335** in a 52% yield (**Table 36**). As the protection reaction worked in this case, the compound **335** was used for deprotection studies.

To begin with deprotection studies, the protected compound **335** was treated with sodium hydroxide in methanol. The reaction did not lead to any deprotection and only starting material **335** was recovered whereas the reaction mixture was stirred at room temperature and refluxed and additional equivalents of sodium hydroxide were added after two days of stirring (**Table 36**, **Entry 1**).[231,232] In the next test, the intermediate **335** was treated with lithium hydroxide in tetrahydrofuran leading to a 15% conversion (**Table 36**, **Entry 2**).[233] The use of potassium carbonate or caesium carbonate in methanol also did not afford any desired unprotected amino alcohol (**Table 36**, **Entries 3 and 4**).[234,235] The use of potassium *tert*-butoxide in a 1 : 1 mixture of *tert*-butanol and water did not afford any desired unprotected product **334** whereas the use of potassium tert-

butoxide in diethyl ether in the presence of small amounts of water led to a 29% conversion (**Table 36**, **Entries 5 and 6**).[236,237] Following a procedure developed by Weinreb and co-workers and optimised by Heiker and Schueller, the compound **335** was treated with barium hydroxide octahydrate in a 1 : 1 mixture of methanol and water.[238,239] The process did not give any deprotected product **334**, only starting material **335** was recovered (**Table 36**, **Entry 7**). A last test using methyllithium in tetrahydrofuran also did not led to the desired product **334** (**Table 36**, **Entry 8**).

Table 36. Protection/deprotection studies starting from the substrate 334.



Entry	Conditions	Result	Yield (%)
1	NaOH (6 eq), MeOH 1 d at RT, refluxed 15 d Additional NaOH (6 eq) added after 2 d	No deprotection	0
2	LiOH (24 eq), THF 1 d at RT, refluxed 4 d	15% conversion	15
3	K_2CO_3 (5 eq), MeOH 1 d at RT, refluxed 4 d	No deprotection	0
4	Cs_2CO_3 (5 eq), MeOH 1 d at RT, refluxed 4 d	No deprotection	0
5	*t*BuOK (4 eq), *t*BuOH/H_2O (1 : 1) 1d at RT, refluxed 4 d	No deprotection	0
6	*t*BuOK (6 eq), H_2O (2 eq), Et_2O 1 d at RT, refluxed 4 d	29% conversion	29
7	$Ba(OH)_2 \bullet 8H_2O$ (1.1 eq), MeOH/H_2O (1 : 1) 2 d at RT, 3 d at 70 °C	No deprotection	0
8	MeLi (1 eq), THF RT, 18 h	No deprotection	0

It is first important to notice that although if the substrate **335** on which the deprotection studies were performed is quite different of the actually used substrate **132** in our synthetic way, especially for electronic purposes, and is though not the perfect model for the needed deprotection reaction, both substrates **335** and **132** present a very hindered environment around the protected amino alcohol function. Some considerations are thus applicable for both substrates. This study confirmed for example the extreme complexity of protection and deprotection of an amino alcohol function using a phosgene derivate. Indeed, the protection reaction already showed a highly substrate dependent behaviour as it was for example impossible to obtain the protected product **333** whereas the quite similar compound **335** was obtained in a 52% yield. Then, the deprotection tests showed

that the method needed depends also highly on the substrate and although if most of these methods were reported to work for various substrates, they were also proved to fail in some cases.

In summary, it is important to notice the complexity of this deprotection reaction, above all in highly sterically hindered substrates such as **335** and **132**. This study, although if not performed using a perfect model, revealed the fact that it could have been difficult nay impossible to deprotect the amino alcohol later in our synthetic way due to high steric hindrance, stopping then our synthetic way.

IV. References

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