Application of Olefin Cross Metathesis in Natural Product Syntheses

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Abstract, Purnama Dewi-Wülfing

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Dank der Entwicklung von neuen Katalysatoren mit *N*-heterocyclischen Liganden, hat sich die Olefin Kreuzmetathese (CM) in den letzten Jahren zu einer sehr effizienten Kupplungsmethode entwickelt.

Im ersten Teil der vorliegenden Arbeit wurde eine sequentielle CM – reduktive Cyclisierungsmethode und deren Anwendung in den Synthesen von drei Naturstoffen präsentiert. Die CM zwischen Enonen bzw. Endionen und Allyl- bzw. Homoallylaminen führt zu *E*-substituierten Enonen, die unter Hydrierungsbedingungen und Stereokontrolle bereits zu gesättigten *N*-Heterocyclen cyclisieren.

Mit dieser Strategie wurde Xenovenin, ein biologisch aktives Pyrrolizidin, isoliert aus Ameisen der Gattung *Solenopsis xenovenum*, synthetisiert. Ausgehend von den leicht zugänglichem Benzyl-1-heptylallylcarbamat und Hept-6-ene-2,5-dion gelang die Synthese in zwei Stufen und mit einer Gesamtausbeute von 50%. Die Cyclisierung verlief stereoselektiv und ergab ausschließlich das *cis*-veknüpfte Produkt.

(+)-Hyacinthacin A_2, ein *cis*-verknüpftes polyhydroxyliertes Pyrolizidin aus Hyazinthen der Gattung *Muscari armeniacum*, wurde ebenfalls erfolgreich mit dieser Strategie synthetisiert. Die Synthese wurde in sechs Stufen, ausgehend von (-)-*N*-Cbz-Vinylgylcin und mit einer Gesamtausbeute von 12% durchgeführt. Als weiterer Schlüsselschritt diente die stereoselektive asymmetrische Sharpless-Dihydroxylierung.

(+)-Calvin, ein Piperidinlakton aus Marienkäfern von Gattung *Calvia guttata*, wurde in 9 Stufen ausgehend von (*R*)-Epichlorhydrin und mit einer Gesamtausbeute von 10% synthetisiert. Die Synthese beinhaltet die stereospezifische Epoxidöffnung, Substitutionsreaktion, CM-reduktive Cyclisierung und Laktonisierung.

Im zweiten Teil der Arbeit wurde die CM zwischen Butadienen und elektronarmen Olefinen untersucht. Reaktionen mit monosubstituierten Butadienen führten zu den Gemischen aus Produkt, Monoolefin, und dem Butadien-Dimer. Da der unselektive interne Angriff des Katalysators von einem zusätzlichen Substituent am Butadien vermieden wurde, ergaben Reaktionen von disubstituierten Butadienen höhere Produktausbeuten und Stereoselektivität. Das beste Ergebnis wurde mit Methylvinylketon als CM Partner erreicht, während elektronärmere Olefine wie Acrylnitril, Methylacrylat und Acrolein schlechtere Ausbeuten und Stereoselektivität lieferten.

The research project was conducted under the guidance of Prof. Dr. Siegfried Blechert from April 2002 to February 2005 in Institute of Chemistry, Faculty II of Mathematic and Natural Sciences, Technical University of Berlin.

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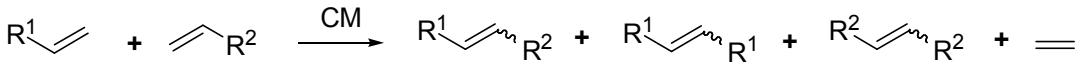
Contents

I Olefin Cross Metathesis

Olefin cross-metathesis (CM) is a mild, yet efficient method for the formation of carbon-carbon double bonds in organic synthesis (**Scheme 1**).[1] As an acyclic reaction, it has numerous advantages in comparison to other carbon-carbon coupling reactions, such as: (1) the substrates are generally easier to prepare, (2) the reaction is catalytic, mild, and pH neutral with high yields, (3) broad functional group tolerance, (4) the reaction is reversible, which leads to the most thermodynamically stable product, (5) in case of monosubstituted olefins, by-product is gaseous ethylene, which is advantageous for industrial application, and (6) the olefinic products are suitable for further modification, such as hydrogenation, epoxidation, and cycloaddition.[2]

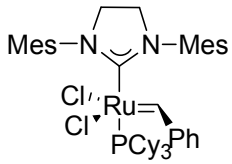


Scheme 1. Olefin cross metathesis.

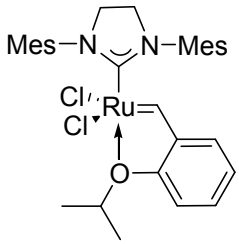
Because of its poor efficiency and selectivity, CM was initially not widely applied in laboratory, although it has been used in industrial processes, such as the Phillips Triolefin Process,[3] SHOP (Shell Higher Olefin Process),[4] and FEAST (Further Exploitation of Advanced Shell Technology) process. The breakthrough in this area was the development of new ruthenium catalysts bearing an *N*-heterocyclic carbene ligand.[5] The ligand is stable and bulky with strong σ-donor and poor π-acceptor properties, which stabilize the 14-electron ruthenium intermediate during metathesis. Two important new catalysts with high CM activity are the second generation Grubbs catalyst (Grubbs II)[5e] and the Hoveyda-Blechert catalyst ([**Ru**]).[5a,b] Both catalysts show remarkable reactivity, selectivity, and tolerance against various functional groups[6] in comparison to the Schrock catalyst[7] and the first generation Grubbs catalyst (Grubbs I)[8] (**Figure 1**).

Investigations of CM with various classes of olefins have led to a general empirical model useful for the prediction of product selectivity and stereoselectivity.[9] When an olefin of high reactivity is reacted with an olefin of lower reactivity (sterically bulky or electron-deficient), selective cross metathesis can be achieved. The slow rate of dimerization forces the olefin of lower reactivity to react with the CM partner to give high CM product/dimer ratio and

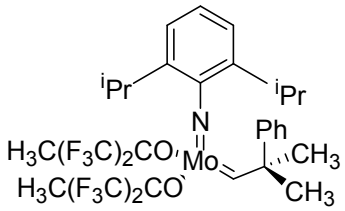
excellent *E*/*Z* selectivity (up to 95:5). The reaction is even possible with equimolar amounts of CM partners.



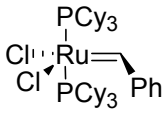
Grubbs II



Hoveyda-Blechert catalyst [Ru]



Schrock catalyst

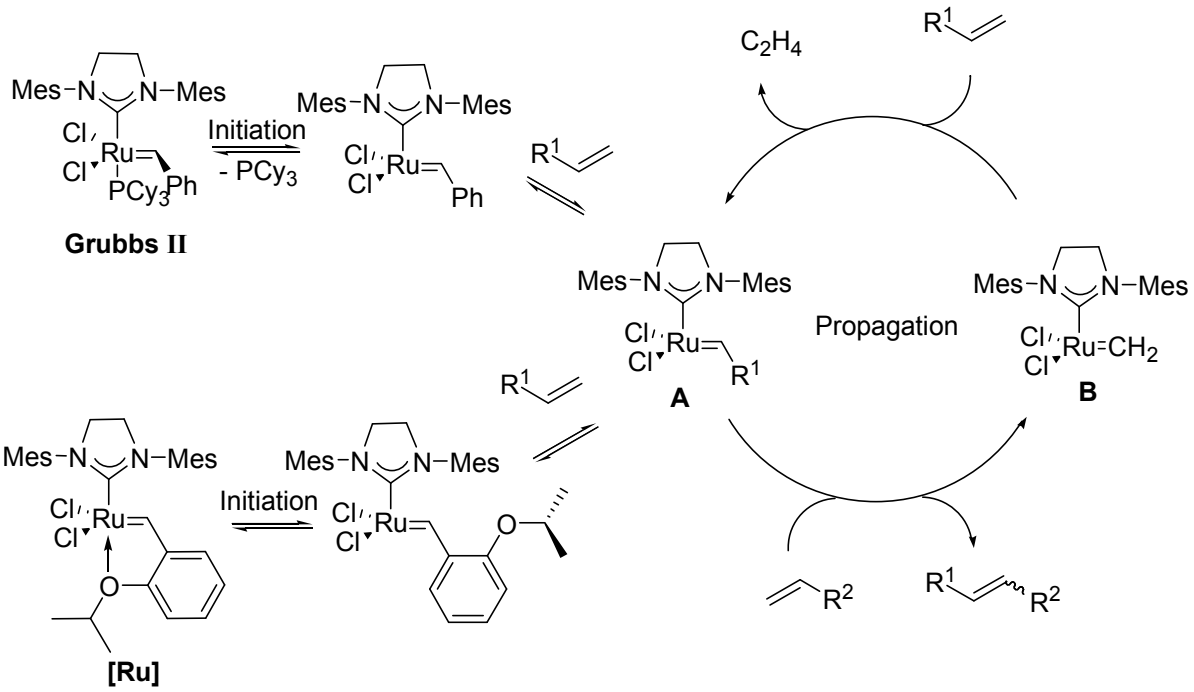


Grubbs I

Figure 1. Powerful catalysts for CM.

Although both Grubbs II and [**Ru**] are active in CM reactions, [**Ru**] shows its predominance in reactions involving fluorinated substrate[10] and acrylonitrile derivates.[11] It has also higher stability against water and oxygen, thus it can be stored under ambient atmosphere at room temperature.

The mechanism of CM is shown in **Scheme 2**. The initiation process is the dissociation of the PCy_3 ligand from Grubbs II or the ether ligand from [**Ru**]. The rates of dissociation and rebinding of the ligand determine the activity of the catalyst. Both catalysts have the same propagating species **A** and **B** after a single turnover. If either **A** or **B** is trapped by the ligand, the dissociation of it must occur before the catalysis can continue. The relative affinity of **A** or **B** for the olefin in preference to the ligand controls how long these species remain in the catalytic cycle. Consequently, by changing the nature of the ligand, the activity of the catalyst can be tuned.[12,13]

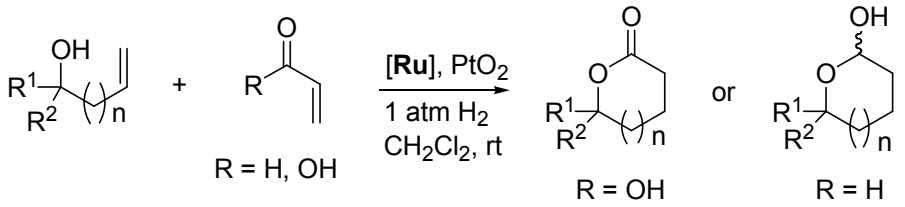


Scheme 2. Mechanism of CM.

II Application of Olefin Cross-Metathesis in Natural Product Syntheses

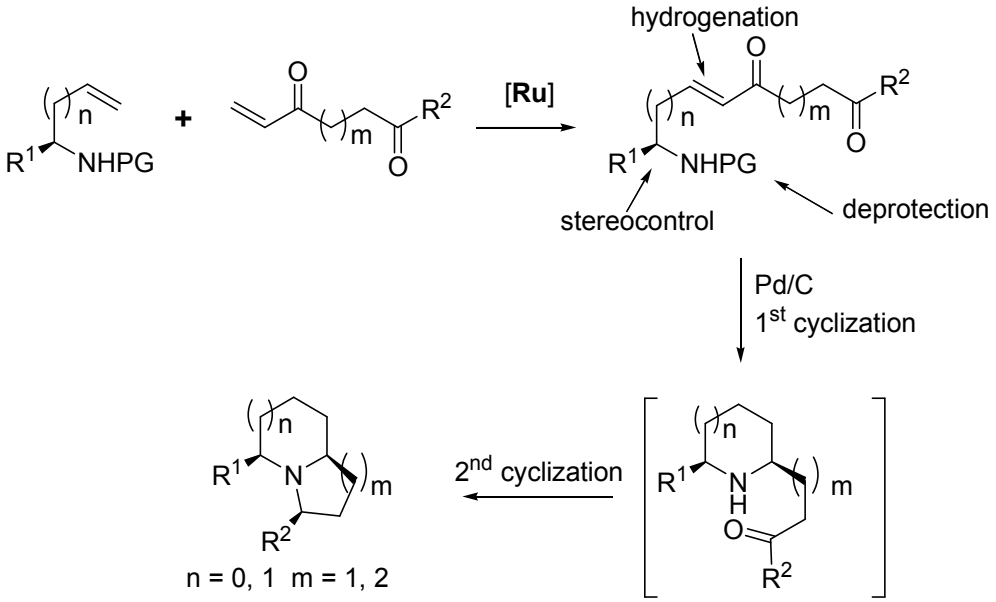
1. Sequential Cross Metathesis-Reductive Cyclization Reaction

Several sequential and tandem processes involving CM have been developed, which allow rapid construction of complex structures from relatively simple starting material, such as tandem ring closing-CM,[14] tandem CM-allyl boration,[15] and tandem CM-hydrogenation-cyclization.[16] The latter method, developed by Cossy, is a one-pot method in which [**Ru**] and PtO_2 work consecutively at room temperature under hydrogen atmosphere. Both catalysts are compatible to one another, with [**Ru**] reacting faster than the PtO_2, which leads to hydrogenated CM product. Subsequent intramolecular cyclization also occurs *in situ*. The reaction of unsaturated alcohols with acrylic acid or acrolein yields the substituted lactones or lactols respectively (**Scheme 3**).



Scheme 3. Cossy's one-pot CM-hydrogenation-cyclization method.

We have developed another sequential CM–reductive cyclization reaction, which is different from the one of Cossy.[17] CM between α,β-unsaturated ketones and *N*-protected allylic or homoallylic amines in the presence of a catalytic amount of [**Ru**] afford aminoenones in good to excellent yield and high *E*/*Z* selectivity. The corresponding CM products are then subjected to catalytic hydrogenation (Pd/C) and undergo a sequence of double-bond reduction, deprotection of amine, and reductive cyclization.[18] While simple reductive cyclization gives piperidines (n = 1) or pyrrolidines (n = 0), aminoenones with a second carbonyl group undergo a second cyclization to give bicyclic ring systems in one convenient step (**Scheme 4**).



Scheme 4. Sequential CM-reductive cyclization reaction.

The cyclization proceeds with high stereoselectivity, controlled by the stereogenic centre adjacent to the nitrogen atom. This tandem sequence therefore allows flexible and rapid access to *N*-heterocyclic compounds such as pyrrolidines, piperidines, pyrrolizidines, indolizidines and quinolizidines. The concept was successfully applied in the syntheses of indolizidine alkaloids (+)-monomorine I, (3*R*,5*S*,9*S*)-3-ethyl-5-methylindolizidine,[17b] and (+)-carpamic acid[17a] (**Figure 2**).

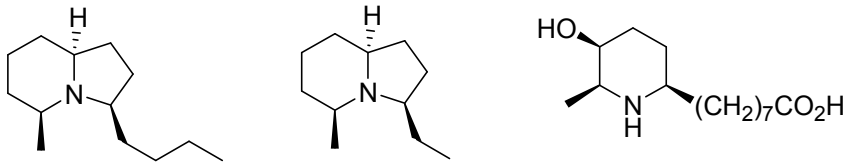


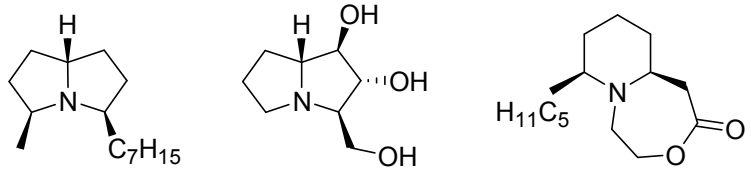
Figure 2. Natural products synthesized with sequential CM-reductive cyclization as key step.

The protection of the amino group is essential, since free amines bind strongly to the catalyst and inhibit the CM reaction. The suitable protection group should be compatible to the CM reaction conditions and easily removed during the hydrogenation. Fulfilling these criteria, benzyloxycarbonyl (Cbz) group was chosen.

One-pot tandem strategy with [**Ru**] and Pd/C is not applicable in this case, as the hydrogenation with Pd/C is faster than with PtO_2, giving hydrogenated starting materials and

product in low yield.[16c] Although PtO_2 is capable to reduce the double bond, it is not reactive enough to remove the Cbz group. Attempt to subject the crude CM product mixture directly to the hydrogenation conditions (by addition of methanol, Pd/C catalyst, and hydrogen atmosphere) failed, even after 48 hours of hydrogenation.[19]

The CM-reductive cyclization strategy offers further flexibility to the synthesis. The double bond obtained from CM reaction may be functionalized prior to hydrogenation. The high stereoselectivity of the reaction is shown by the *cis* configuration of the indolizidines and piperidine in **Figure 2**. We were therefore interested to apply this concept in the syntheses of xenovenine and two other 3,5-disubstituted pyrrolizidines, hyacinthacine A_2, and calvine (**Figure 3**).



xenovenine hyacinthacine A_2 calvine

Figure 3. Target molecules.

2. Syntheses of 3,5-Disubstituted Pyrrolizidines

2.1 Pyrrolizidine Alkaloids

Pyrrolizidine alkaloids (PAs) are a large family of natural products bearing an azabicyclo[3.3.0]octane structural core (**Figure 4**). The classification of the PAs is complicated, due to their structural diversities as shown in **Figure 5**.

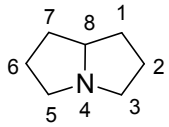


Figure 4. Structural core of PAs.

PAs are widely distributed in nature and display a broad range of biological and pharmacological activities. Most of the PAs have been found in flowering and leguminous plants, especially in the family *Asteraceae* (asters and sunflowers), *Boraginaceae* (forget-me-nots) and *Leguminaceae* (beans). Some PAs have also been found in ants, moths, frogs, butterflies and leaf beetles.[20,21]

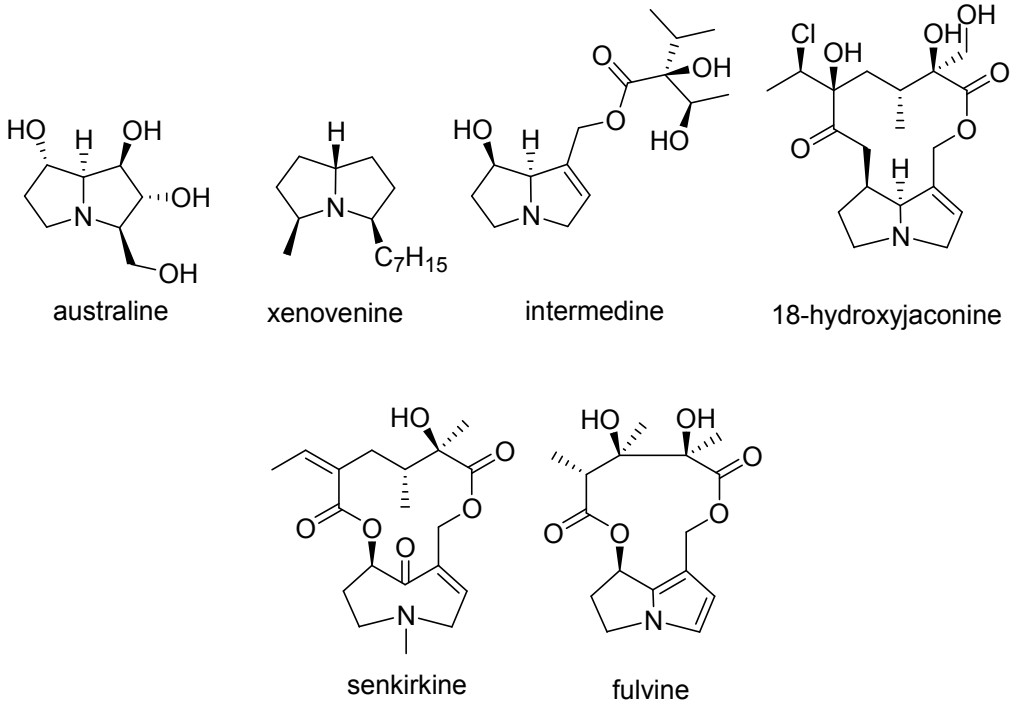


Figure 5. Structural diversity of PAs.

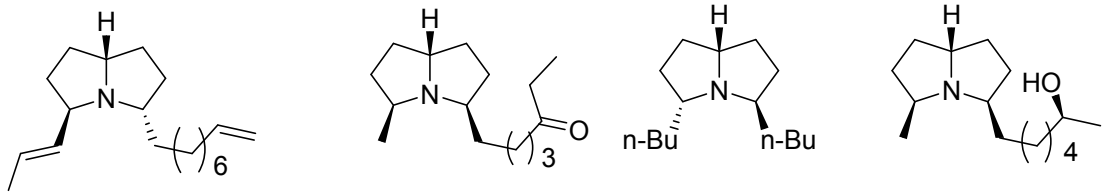
2.2 3,5-Disubstituted Pyrrolizidines

3,5-Disubstituted pyrrolizidines were first discovered in nature as constituent from ants. The first isolated and most renowned example is xenovenine (**Figure 5**), isolated in 1980 by Jones and Blum from thief ant *Solenopsis xenovenum*.[22] Other 3,5-disubstituted pyrrolizidines were also isolated from ants of genus *Monomorium* (*Chelaner*) and *Megalomyrex*[23] and in trace amounts from amphibian skin (frogs from genus *Dendrobates*, *Mantella*, and *Melanophryniscus*).[24] The frogs themselves produce none of the pyrrolizidines. Instead, they are taken up from dietary arthropods (including ants and beetles) and are sequestered unchanged into secretory skin glands.

Due to the great number of 3,5-disubstituted pyrrolizidines, only a few have been given common names. A nomenclature, which consists of a number and a letter, is used instead. The number corresponds to the nominal mass of the compound and the letter is to distinguish it from the compounds of the same mass. The configurational nomenclature for these pyrrolizidines follows the system devised by Sonnet *et al*.[25] for 3,5-disubstituted indolizidines, where the H-5 and H-8 configurations are related to that at H-3 and are either *cis* (*Z*) or *trans* (*E*). Xenovenine, for example, was found to be identical to pyrrolizidine (5*Z*,8*E*)-223H found in dendrobatid frogs.[23a] The bridgehead proton (H-8) is also referred as H-7a.

The stereochemistry of the pyrrolizidine ring junction is described as *cis*-fused, where the bridgehead proton (H-8) is *cis* to the nitrogen lone pair, or *trans*-fused, where the H-8 is *trans* to the nitrogen lone pair.[26] The *cis*-fused conformation of 3,5-disubstituted pyrrolizidines is less strained than its counterpart. Both conformations can be determined from the infrared (IR) and nuclear magnetic resonance (NMR) spectra. *Trans*-fused conformation shows strong Bohlmann bands in its IR spectrum in the region 2600-2800 cm^{-1}, while *cis*-fused does not.[27] The H-8 of *cis*-fused 3,5-dialkylpyrrolizidines resonates in the region of 3.59-3.66 ppm because of the deshielding effect of the nitrogen lone pair, while in the *trans*-fused counterpart the H-8 is found in the region of 2.53-2.72 ppm.[26] In the ^{13}C NMR spectra of dialkylsubstituted pyrrolizidines, the C-8 chemical shift greater than 70 ppm indicates a *trans*-fused conformation.[28]

The biological activity of 3,5-disubstituted pyrrolizidines has not been thoroughly studied. Xenovenine, for example, shows an affinity for nicotinic acetylcholine receptor, which affects neuronal functions, thus serves as venoms.[29] Several examples of 3,5-disubstituted pyrrolizidines are illustrated in **Figure 6**.



(5*E*,8*Z*)-3-(1-non-8-enyl)-5-((*E*)-1-prop-1-enyl)-pyrrolizidine

(5*Z*,8*E*)-**237G**

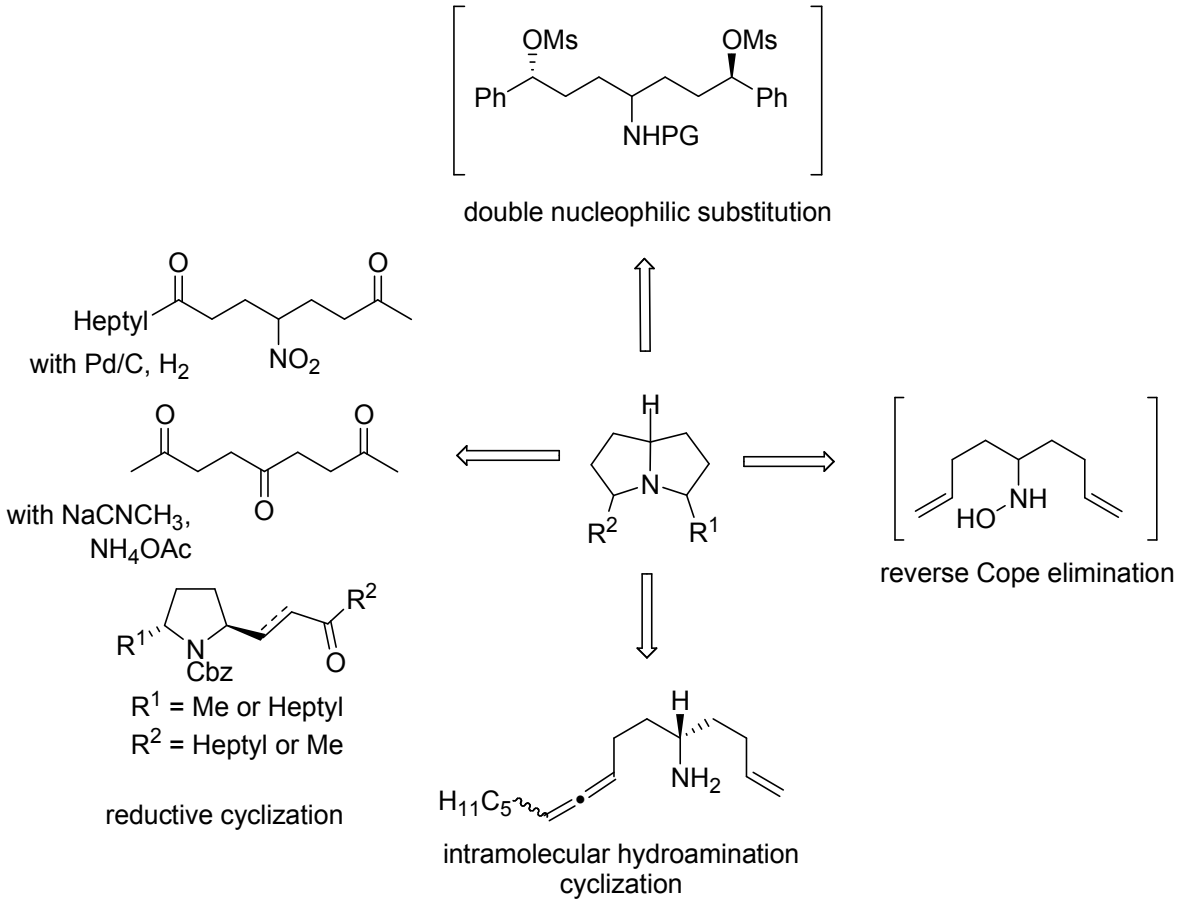
(5*E*,8*E*)-**223B**

239 K'

Figure 6. Various 3,5-disubstituted pyrrolizidines.

2.3 Synthetic Strategies of 3,5-Disubstituted Pyrrolizidines

Because of its scarcity, the optical rotation and absolute configuration of naturally occurring xenovenine have not been determined so far. However, it did not restrain chemists to synthesize both its enantiomers. Several synthetic strategies of 3,5-disubstited pyrrolizidines are categorized based on their cyclization methods (**Scheme 5**) and described briefly in this section.

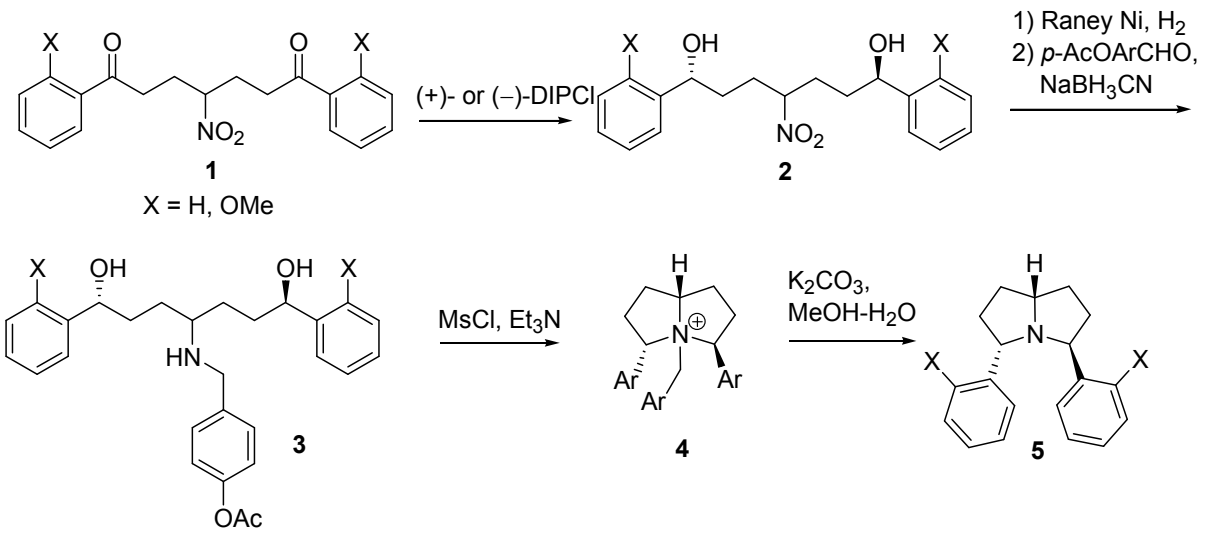


Scheme 5. Synthetic strategies of 3,5-disubstituted pyrrolizidines.

2.3.1 Double Nucleophilic Substitution

The double nucleophilic substitution strategy was developed by Guarna *et al*. to synthesize enantiopure 3,5-diarylpyrrolizidines.[26a] The short and efficient synthetic route to the product is presented in **Scheme 6**. The nitroketone **1** was reduced enantioselectively to nitrodiol **2** using (+)- or (-)-diisopinocampheylchloroborane (DIPCl).[30] Reduction of the nitro group by Raney nickel, followed by protection of the resulting amino group with *p*-acetoxybenzyl group gave the aminodiol **3**. The *N*-protection is necessary to avoid the mesylation of amino group and *p*-acetoxybenzyl was chosen, since it is readily removed by alkaline hydrolysis. Previous attempts to remove the protecting group by catalytic hydrogenation over Pd/C or $Pd(OH)_2$ were unsuccessful, as they resulted in the cleavage of the internal benzylic bonds, providing mixtures of α–branched *N*-benzyl pyrrolidines and *N*-benzyl amines. Mesylation of aminodiol **3** was followed *in situ* by the double nucleophilic substitution, giving the quaternary salt **4**, which was hydrolyzed further to afford the enantiopure 3,5-

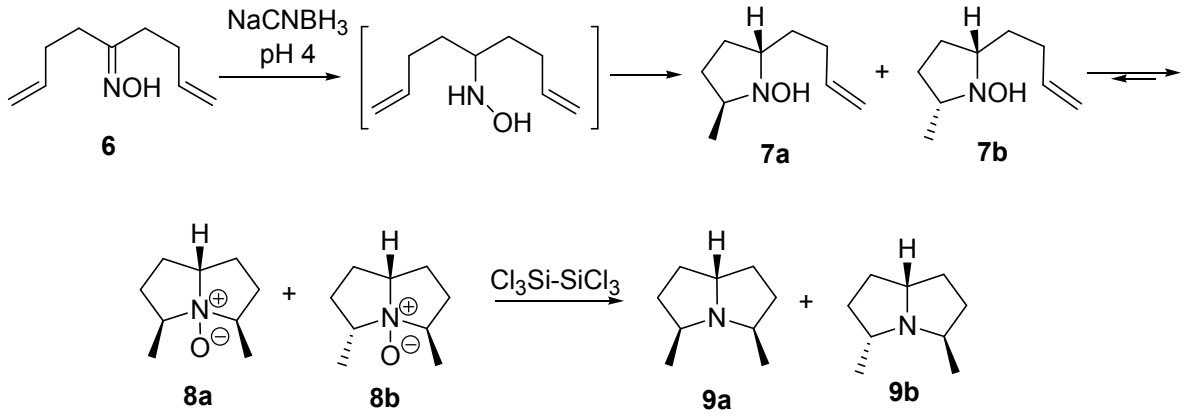
diarylpyrrolizidines **5**. This method is suitable to synthesize *cis*-fused, *trans*-3,5-diaryl pyrrolizidines.



Scheme 6. Enantioselective synthesis of (3*S*,5*S*,7a*S*)-(-)-3,5-Diphenylpyrrolizidine (**5a**) and (3*S*,5*S*,7a*S*)-(-)-3,5-bis(2-methoxyphenyl)pyrrolizidine (**5b**) by Guarna *et al*.

2.3.2 Reverse Cope Elimination

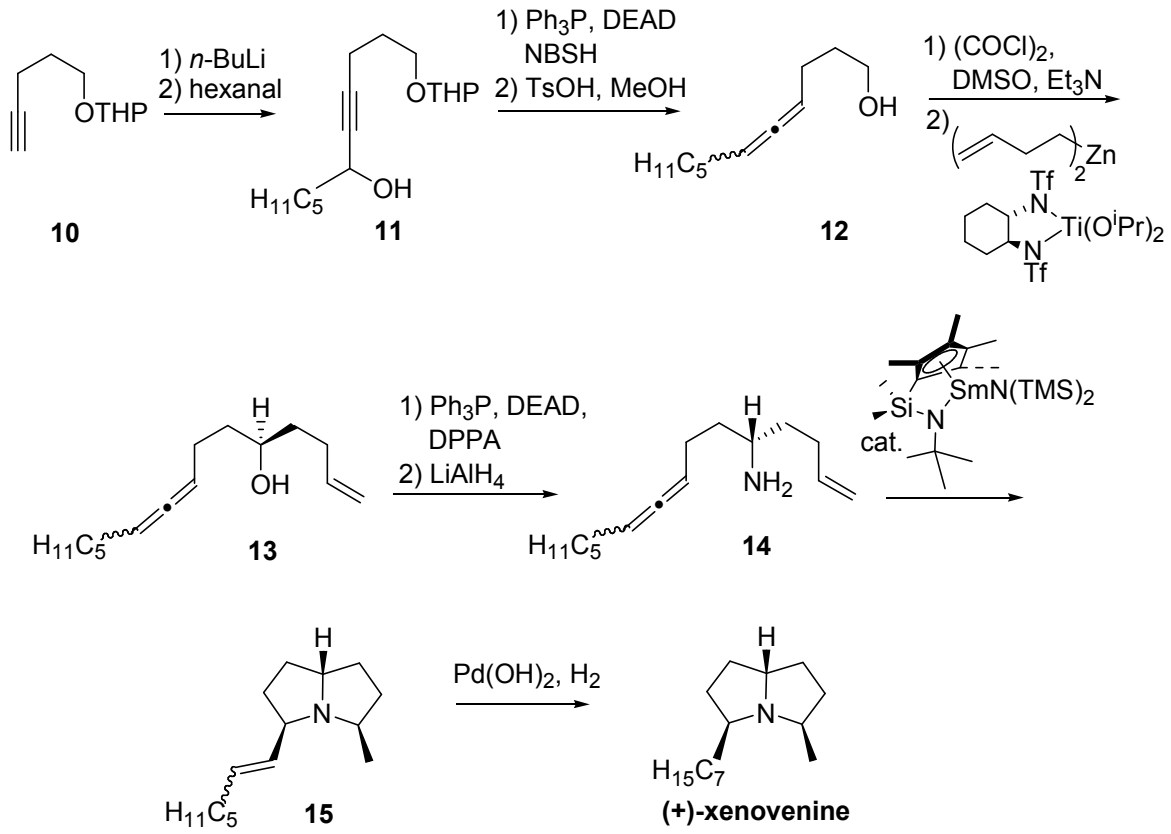
Ciganek developed the reverse cope elimination for the synthesis of racemic *cis*- and *trans*-3,5-dimethylpyrrolizidines outlined in **Scheme 7**.[31] The method involves an intramolecular addition of *N*-substituted hydroxylamine to an unactivated olefin. The short synthesis consisted of 2 steps, i.e. the reverse Cope elimination reaction and reduction of the pyrrolizidine oxide **8**. The oxime **6** was reduced with sodium cyanoborohydride at pH 4 to afford a mixture of hydroxylamines **7a**,**b** and *N*-oxides **8a**,**b**. Direct reduction of **8a**,**b** with hexachlorodisilane gave a 55:45 mixture of **9a** and **9b**, which were inseparable by distillation. Despite of the briefness of this method, its selectivity was quite low.



Scheme 7. Synthesis of racemic 3,5-dimethylpyrrolizidine by Ciganek.

2.3.3 Intramolecular Hydroamination Cyclization

A modern method to synthesize (+)-xenovenine was developed by Marks *et al.*, with organolanthanide-catalyzed intramolecular cyclohydroamination of allene as key reaction (**Scheme 8**).[32] Compound **10** was treated with *n*-BuLi and hexanal to afford the propargylic alcohol **11**. Its conversion to allene **12** was done according to a procedure of Myers and Zheng,[33] which involved a Mitsunobu reaction to convert the hydroxyl group to the corresponding *o*-nitrobenzenesulfonylhydrazine (NBSH) derivate. Spontaneous elimination of *o*-nitrobenzenesulfinic acid and nitrogen under mild acidic conditions yielded the allene **12**. Swern oxidation and enantioselective addition of dibut-3-enylzinc[34] in the presence of titan disulfonamide catalyst[35] furnished the allene **13**. Azide displacement of the hydroxyl group under Mitsunobu conditions with diphenylphosphorylazide (DPPA), followed by reduction with lithium aluminum hydride yielded the aminoallene **14**. The stereoselective tandem bicyclization was catalyzed by the "constrained geometry" organolathanide complex $Me_2Si(Me_4C_5)(^tBuN)SmN(TMS)_2$,[36] which provided the pyrrolizidine **15**. The final catalytic hydrogenation afforded (+)-xenovenine. The organolanthanide complex is however air sensitive and should be prepared freshly prior to use.



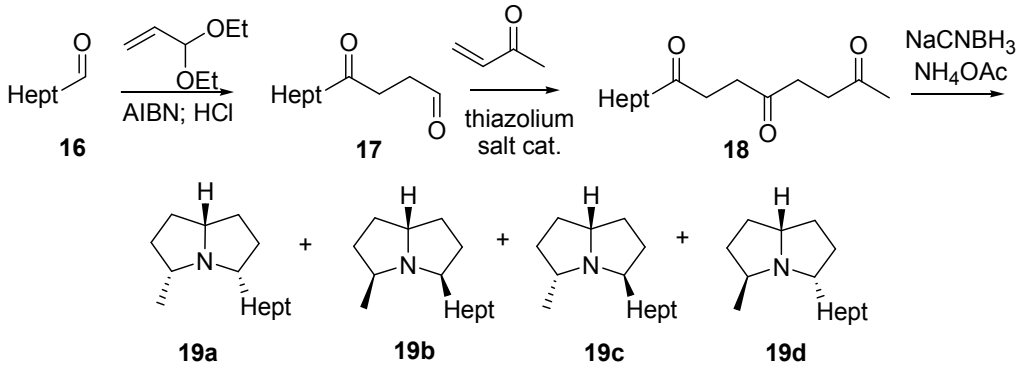
Scheme 8. Total synthesis of (+)-xenovenine by Marks *et al*.

2.3.4 Reductive Cyclization

Reductive cyclization is the most commonly applied method to synthesize 3,5-disubstituted pyrrolizidines. Triones and diones undergo tandem reductive cyclization to build the conjugated five-membered systems, as demonstrated by Jones *et al*. and Hesse *et al*. in their xenovenine syntheses.

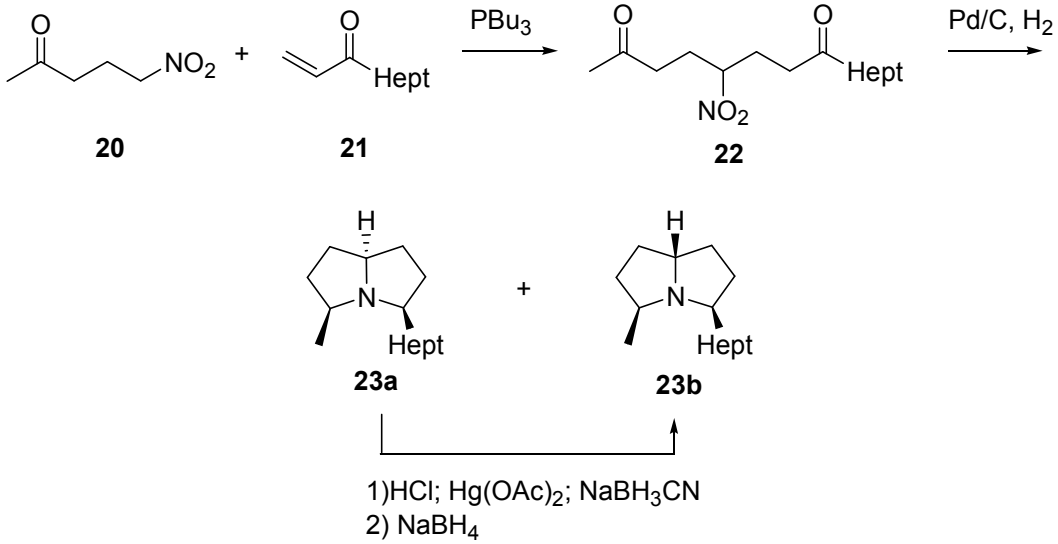
Jones *et al*. were the first to synthesize xenovenine (**Scheme 9**).[22] Treatment of a mixture of octanal and acrolein diethyl acetal with *N*,*N*-azobisisobutyronitrile (AIBN), followed by hydrolysis gave 4-oxoundecanal **17**. Stetter reaction between **17** and methyl vinyl ketone in the presence of thiazolium salt catalyst yielded 2,5,8-pentadecatrione **18**.[37] Reductive amination of the triketone with sodium cyanoborohydride and ammonium acetate afforded xenovenine, which according to gas chromatography analysis consisted of four isomers **19a-d** in a 2:14:2.2:1 ratio. NMR and IR spectra showed that the isomer **19a** has the *trans*-fused and the others have *cis*-fused configuration. The main isomer **19b** was found to be identical to the natural xenovenine, based on gas chromatography analysis. This first synthesis of

xenovenine is quite short and the low selectivity of the reductive amination was required to determine the structure of the natural product.



Scheme 9. First synthesis of xenovenine by Jones *et al*.

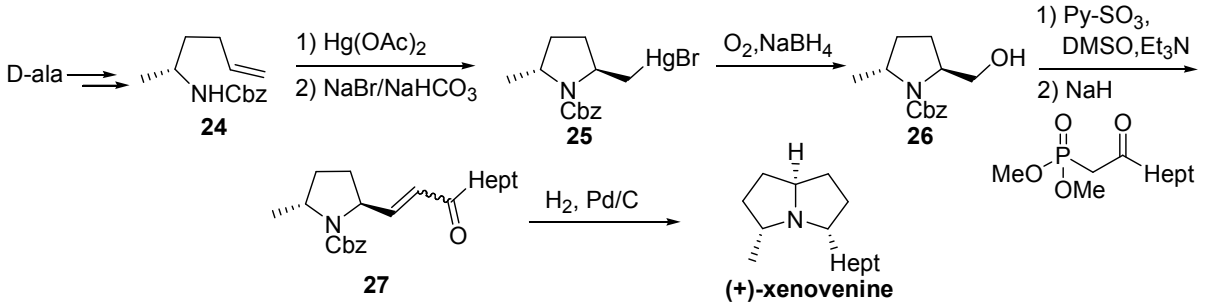
Hesse *et al*. utilized the nitrodiketone **22** as precursor for xenovenine synthesis (**Scheme 10)**.[26b] Michael reaction of **20** and **21** gave the nitrodiketone **22**, which cyclized under catalytic hydrogenation over Pd/C and 8-12 atm hydrogen to afford **23a**,**b** with a ratio of 12:1. After separation of both isomers, the HCl salt of the *trans*-fused isomer **23a** was oxidized with $Hg(OAc)_2$ and the resulting iminium salt was reduced with $NaBH_3CN$ and $NaBH_4$ to give *cis*-fused xenovenine (**23b**). The hydrogenation reaction gave a minor amount of **23b** presumably due to rearrangement of the intermediate on the catalyst surface.



Scheme 10. Synthesis of xenovenine by Hesse *et al*.

The main challenges in enantioselective synthesis of xenovenine are the *cis*-fused conformation of the ring and the stereochemistry of both alkyl substituents. The absence of stereo control gave racemic products in both presented tandem cyclization methods. Several research groups utilized the same concept i.e. the reductive cyclization of enantiopure *trans*-2,5-disubstituted ketopyrrolidine, differs only in its preparation.

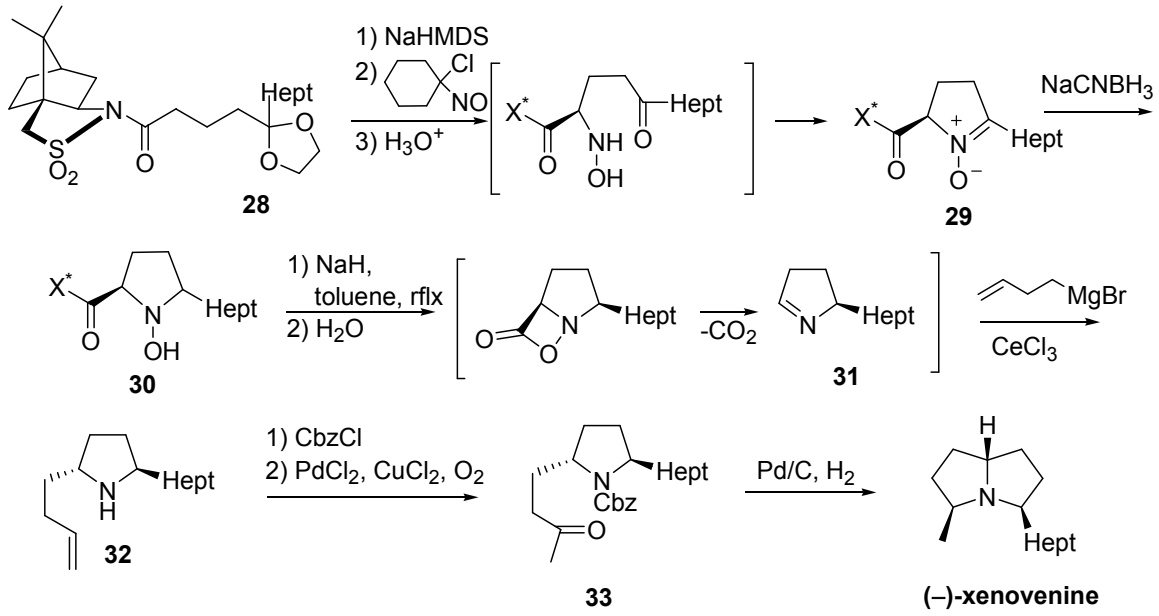
Starting with D-alanine, Takahata *et al*. utilized the kinetically controlled intramolecular amidomercuration as key reaction to synthesize (+)-xenovenine (**Scheme 11**).[38] The cyclization of unsaturated carbamate **24** followed by treatment with aqueous NaBr afforded the organomercurial **25**. Oxidative demercuration provided exclusively the *trans* diastereomer **26**. Subsequent oxidation and Horner-Wadsworth-Emmons reaction yielded α,β-unsaturated ketone **27** (*E*:*Z* 8:1). Final catalytic hydrogenation furnished the expected (+)-xenovenine. The synthesis is stereoselective, short, and efficient. The strategy was applied further by the same group to synthesize enantiopure 3,5-disubstituted pyrrolizidines **239K**, **265H**, and **267H**.[29a]



Scheme 11. Synthesis of (+)-xenovenine by Takahata *et al*.

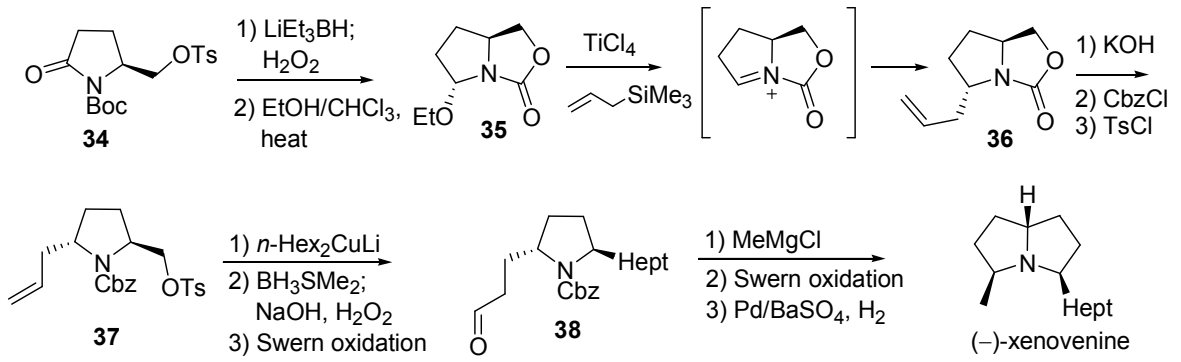
Oppolzer *et al*. prepared a chiral cyclic nitrone as key intermediate for the synthesis of (-)-xenovenine (**Scheme 12**).[39] Successive treatment of acylsultam **28** with sodium hexamethyldisilazide, 1-chloro-1-nitrosocyclohexane, and hydrochloric acid yielded the enantiopure nitrone **29**, which was reduced to give *N*-hydroxypyrrolidine **30**. Removal of the acylsultam auxiliary with simultaneous *N*,*O*-cleavage was achieved by heating **30** in toluene with sodium hydride. The reaction may involve an internal 'transesterification' and decarboxylation, which afforded the cyclic imine **31**. Addition of organocerium reagent gave the *trans*-disubstituted pyrrolidine **32**. Benzyloxycarbonylation, Wacker oxidation and catalytic hydrogenation of **32** yielded (-)-xenovenine. The strategy was flexible and modifiable to synthesize other classes of natural products. Several modifications, for example

1,3-dipolar addition of the nitrone intermediates and variation of organocerium reagents, were employed to prepare piperidines and polycyclic alkaloids.



Scheme 12. Synthesis of (-)-xenovenine by Oppolzer *et al*.

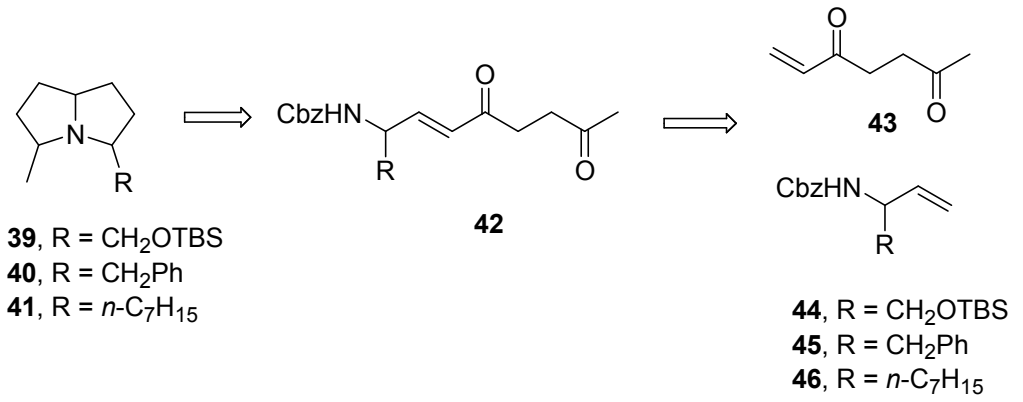
Lhommet *et al*. developed nucleophilic addition reaction to bicyclic *N*-acyliminium ion as key reaction to synthesize (-)-xenovenine (**Scheme 13**).[40] Reduction of tosylate **34** by lithium triethylborohydride yielded a hemiaminal, which was heated in an ethanol-chloroform mixture to afford the ethoxyoxazolidinone **35**. In the latter step, two transformations occurred: the intramolecular nucleophilic substitution of the tosylate by the *N*-Boc group to form an ethoxyoxazolidinone ring and etherification of the hemiaminal moiety. Elimination of the ethoxy group in the presence of $TiCl_4$ as Lewis acid yielded a bicyclic *N*-acyliminium ion, which was directly attacked by allyltrimethylsilane as nucleophil to give **36**. The *trans* attack is favored due to lower steric hindrance between the incoming nucleophile and the *N*-acyl group. Subsequent hydrolysis to open the oxazolidinone ring, protection of the amino and hydroxyl groups afforded pyrrolidine **37**. Substitution of the tosyl group by the Gilman cuprate reagent prolonged the alkyl chain with six carbon atoms. Oxidative hydroboration followed by Swern oxidation furnished the aldehyde **38**. Addition of Grignard reagent, Swern oxidation, and the final catalytic hydrogenation provided the desired (-)-xenovenine.



Scheme 13. Synthesis of (-)-xenovenine by Lhommet *et al*.

2.4 Retrosynthetic Analysis

The examples presented in previous section show the reliability of reductive cyclization method to synthesize the 3,5-disubstituted pyrrolizidines, in some cases even with high stereoselectivity. We were therefore interested to apply the sequential cross metathesis-reductive cyclization method to synthesize the target molecules **39**, **40**, and **41**. We envisaged the enedione **42** as the synthetic precursor, which should be prepared by CM reaction of two simple building blocks: 1,4-diketone **43** and allylamines **44-46** (**Scheme 14**). A certain prognosis about the conformation of the resulted pyrrolizidines could not be made. However, two important facts may be taken into account, i.e. the cyclization would proceed under thermodynamic control and the *cis*-fused product has the least strained conformation.

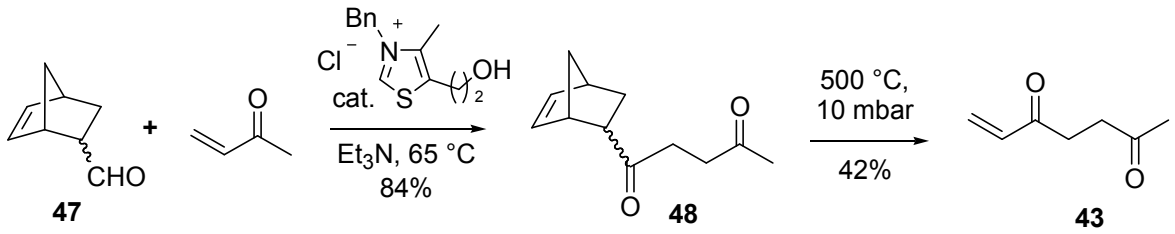


Scheme 14. Retrosyntheses of pyrrolizidines **39**-**41**.

2.5 Syntheses of 3,5-Disubstituted Pyrrolizidines

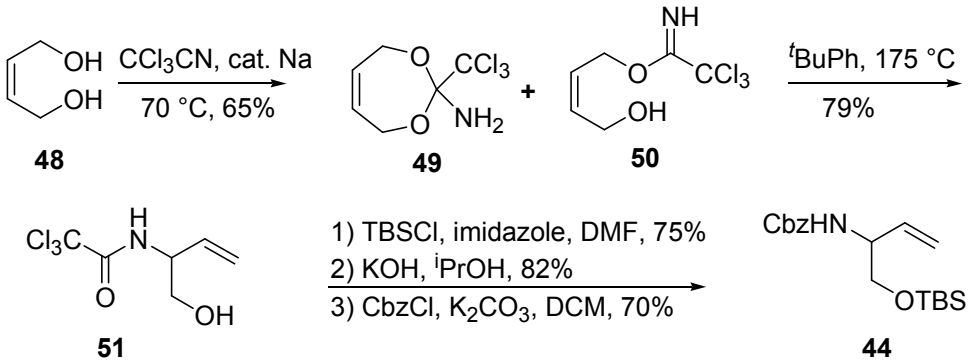
2.5.1 Syntheses of CM Partners

6-Hepten-2,5-dione **43** was prepared in two steps, starting with norbornene carbaldehyde **47** (endo/exo 1:1 mixture), as reported by Stetter and Landscheidt (**Scheme 15**).[41] The first step is the umpolung of norbornene catalyzed by thiazolium salt, followed by Michael addition to methyl vinyl ketone, yielding the diketone **48** (endo/exo 1:1) in 84% yield. Subsequent retro-Diels-Alder reaction at 500 °C and 10 mbar afforded cyclopentadiene and enedione **43** in 42% yield.



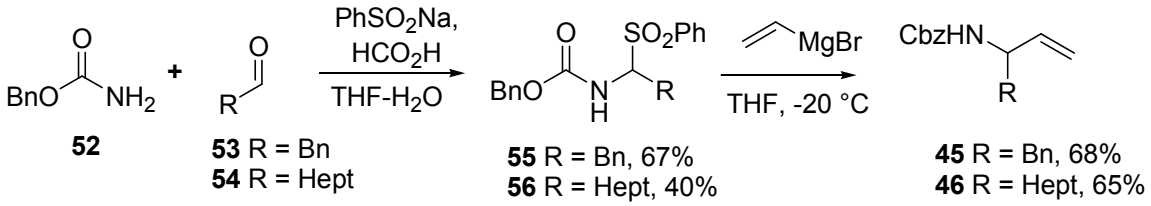
Scheme 15. Preparation of 6-hepten-2,5-dione **43**.

The preparation of allylamine **44** was achieved in five steps, starting from (*Z*)-2-butene-1,4-diol **48** (**Scheme 16**). The first two steps were reported by Vyas *et al*.,[42] which involved the imidation of the diol and subsequent thermal [3,3]-sigmatropic rearrangement. By the use of 1.1 equivalents of trichloroacetonitrile and a catalytic amount of sodium at 70 °C, the diol **48** reacted to afford dioxepine **49** together with mono imidation product **50** in 65% yield. This result differed from the original procedure, which claimed that dioxepine was the sole product. Subsequent [3,3]-sigmatropic rearrangement afforded allylalcohol **51** in 79% yield. The facts that the dioxepine and mono imidate rearranged under the same conditions and afforded the same product suggest the equilibrium between both intermediates. Based on our observations, the first two reactions should be done in multiple gram scale to obtain good yields. Reactions in smaller scale gave lower yield, especially the second step may give results in less than 20% yield due to an extensive decomposition of the adduct. Protection of the hydroxyl moiety by *tert*-butyl-dimethylsilyl (TBS) group, cleavage of the trichloroacetamide group, and protection of amino group with Cbz group furnished the allylamine **44** in good yield.



Scheme 16. Preparation of allylamine **44**.

Allylamines **45** and **46** were prepared according to Engberts method[43] with a procedure from Mecozzi and Petrini (**Scheme 17**).[44] The Mannich condensation of benzyl carbamate **52**, phenyl acetaldehyde **53** or octaldehyde **54**, and sodium benzenesulfinate in the presence of formic acid afforded α-amidoalkylsulfones **55** and **56** in moderate yield. The sulfones reacted with 2 equivalents of vinylmagnesium bromide to afford the allylamines **45** and **46**. The first equivalent of the organometallic reagent acted as base, converting the sulfone into imine, which reacted immediately with the second equivalent of the reagent to afford the addition product.



Scheme 17. Preparation of allylamines **45** and **46**.

2.5.2 Cross Metathesis

We studied and optimized the CM reaction conditions by utilizing the reaction between allylamine **44** and enone **43** as standard. Several factors were analyzed, i.e. the O-protecting group, solvent, temperature, time, and catalyst amount, with the results presented in **Table 1**.

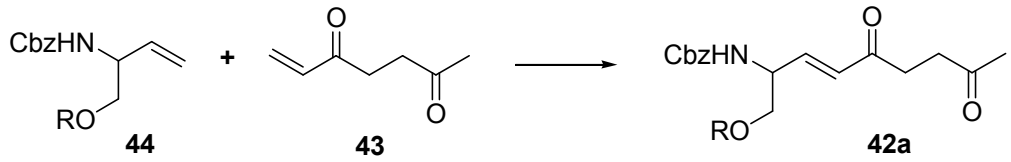


Table 1. CM conditions between **43** and **44**.

Entry	R	Solvent	Cat. mol%	Temp.(°C)	Time (h)	Yield (%)
1	H	CH_2Cl_2	[**Ru**] 5	40	24	17*
2	TMS	CH_2Cl_2	[**Ru**] 5	40	24	26*
3	TBS	CH_2Cl_2	[**Ru**] 5	40	24	39*
4	Ac	CH_2Cl_2	[**Ru**] 5	40	24	60% adduct + dimer
5	Ac	Toluene	[**Ru**] 5	80	24	16*
6	TBS	Toluene	[**Ru**] 7	80	24	54
7	TBS	Toluene	[**Ru**] 7	80	44	29*
8	TBS	$ClCH_2CH_2Cl$	[**Ru**] 7	80	44	27*
9	TBS	CH_2Cl_2	Grubbs II 10	40	24	39*
10	TBS	CH_2Cl_2	[**Ru**] 7	40	72	62
11	TBS	CH_2Cl_2	[**Ru**] 10	40	72	75

Reaction conditions: [**44**] = 0.05 M, **43** : **44** = 1:1, * unreacted educts not recovered

The first CM attempts were conducted in refluxing dichloromethane, with 1:1 ratio of **43** and **44**, and 5 mol% [**Ru**], which were the optimal conditions for CM between homoallylamine and enone precursors of monomorine I (see section **1**) giving over 80% yield.[17] On the contrary, the conditions was not optimal for CM between allylamine **44** and enone **43**, with only 39% yield as the best result (Entry 3). In comparison to trimethylsilyl, acetate and free hydroxyl group, TBS group proved to be the most suitable O-protecting group for the CM (Entry 1-4).

Elevated temperature increased the CM yield. For example, in entry 5 16% yield was achieved at 80 °C, in comparison to dimerization and recovered adduct at 40 °C (Entry 4). With the combination of increasing both the temperature and amount of catalyst, 15% more product could be obtained (Entry 6). Prolongation of the reaction time resulted in the

decrease of the isolated yield, both in toluene and 1,2-dichloroethane (Entry 7, 8). We presumed that at elevated temperature with prolonged reaction time, the decomposition of the catalyst was faster than the formation of CM product.

We focused our attempts on milder reaction conditions at 40 °C with dichloromethane as solvent with 7 and 10 mol% catalyst. Grubbs II gave quite similar results to [**Ru**] (Entry 9). Gratifyingly, with prolonged reaction time and catalyst amount, we managed to optimize the reaction giving up to 75% yield (Entry 10 and 11).

The sluggishness of allylamine compared to homoallylamine in CM reaction can be ascribed to the complexation of ruthenium by the carbonyl oxygen of Cbz group in the form of six-membered chelate, which was also observed in CM with homoallyl ester or homoallyl amide (**Figure 7**).[45]

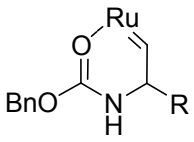


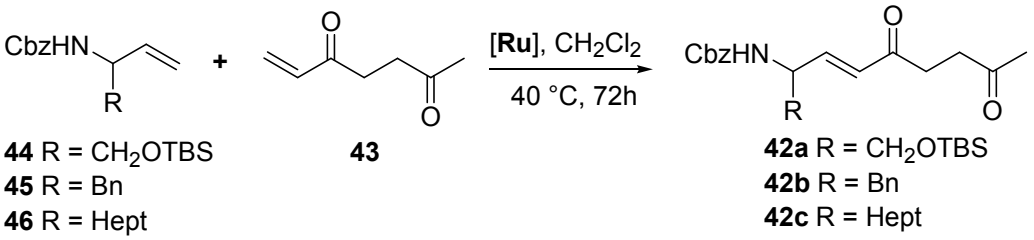
Figure 7. Six-membered chelate structure in CM.

Grubbs *et al*. observed that the degree of chelation depends on the electron density at the oxygen atom, the higher its electron density, the slower the reaction. The chelation effect slows down the metathesis activity by sequestering the catalyst in an unproductive form, thus lowering the catalytic turnover. Since CM is an intermolecular process, the chelation effects are more pronounced in comparison to intramolecular reaction such as the ring closing metathesis.[45b]

To destabilize the presumably unproductive chelate, Lewis acids such as $Ti(O^iPr)_4$, which may compete with the ruthenium carbene for coordination, can be added in a catalytic amount (30 mol%).[46] Following the procedure from Fürstner *et al*., CM with 5 mol% [**Ru**], 30 mol% $Ti(O^iPr)_4$, allylamine **44**, and enone **43** (1:1) in refluxing dichloromethane was conducted. After 24 hours, only 8% yield was isolated in comparison to 39% yield without the addition of Lewis acid (**Table 1**, Entry 3).

Our results in **Table 1** correspond to the results of other groups, who investigated CM involving allylamines with Grubbs II as catalyst.[47] Up to 20 mol% of catalyst was necessary to obtain the CM product in 64-82% yield. Using 10 mol% Grubbs II, equally good results could be obtained, however with extended reaction time (16 hours instead of 12 hours). Increasing the reaction temperature with 1,2-dichloroethane as solvent led also to significantly lower yields.

We apply the optimal conditions in CM between enone **43** and allylamines **45**,**46** (**Table 2**).



44 R = CH_2OTBS
45 R = Bn
46 R = Hept

43

42a R = CH_2OTBS
42b R = Bn
42c R = Hept

Table 2. CM results of enone and allylamines **44-46**.

Entry	Allylamine	[Ru] amount (mol%)	Yield (%)
1	**44**	10	75
2	**44**	7	62
3	**45**	10	70
4	**45**	7	56
5	**46**	10	69
6	**46**	7	48

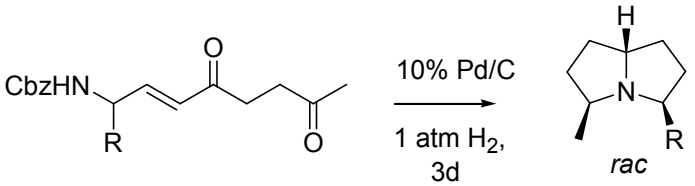
Conditions: in refluxing CH_2Cl_2 (0.05 M) for 72 hours, allylamine:enone 1:1

It is apparent that the amount of catalyst determines the isolated yield. The best yields were obtained when 10 mol% catalyst was employed. Allylamine **44** and **45** gave equally good results, but **46** gave lower CM yield, which may due to the steric factor of benzyl side chain.

2.5.3 Double Reductive Cyclization

The subsequent catalytic hydrogenation of aminoenones **42a-c** was performed in methanol at room temperature in the presence of 10 mol% Pd/C under 1 atm of hydrogen. The reactions

were relatively slow but could be monitored by TLC. The formation of two relatively polar imine intermediates was detected with R_f (MeOH) 0.6 and 0.7. The reaction finished after 3 days, with the formation of relatively polar product with R_f (MeOH) 0.02. The product was purified by column chromatography over basic aluminium oxide as silica gel is too acidic for this purpose. The results of double reductive cyclization are summarized in **Scheme 18**.



42a R = CH_2OTBS
42b R = Bn
42c R = Heptyl

39 R = CH_2OTBS, 73%
40 R = Bn, 68%
41 R = Heptyl, 73%

Scheme 18. Double reductive cyclization of **42a-c**.

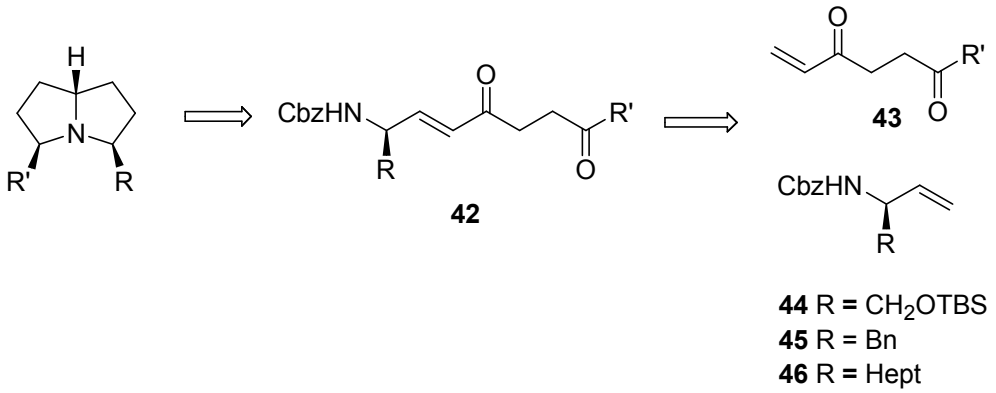
The structure and conformation of the products were determined by IR and NMR spectroscopy (see Section **2.2**). Compounds **39-41** did not show the Bohlmann band in their IR spectra. The chemical shifts of H-8 were 3.63, 3.67, and 3.56 ppm. The C-8 resonated at 65.53, 65.31, and 65.01 ppm, respectively. These facts assured the *cis*-fused conformation of the products. The spectra of xenovenine **41** were also identical to those reported for the natural product.[22]

The double reductive cyclization of enone **42a**,**b**,**c** gave the less strained *cis*-fused pyrrolizidines, resulted from *trans*-hydrogenation, which occurs occasionally by the use of Pd/C as catalyst. The two imine intermediates may rearrange on the surface of the catalyst, yielding the most thermodynamically stable product. These results were advantageous, as it provides an access to the more attractive class of naturally occurring (5*Z*,8*E*)-3,5-disubstituted pyrrolizidines.

Three examples presented in this section showed the effectiveness and efficiency of the CM-double reductive cyclization method to synthesize the *cis*-fused-*cis*-3,5-disubstituted pyrrolizidines. Starting from simple, easily accessible allylamines and enones, the products can be obtained in 2 steps with an overall yield of 48-55%.

2.6 Addendum

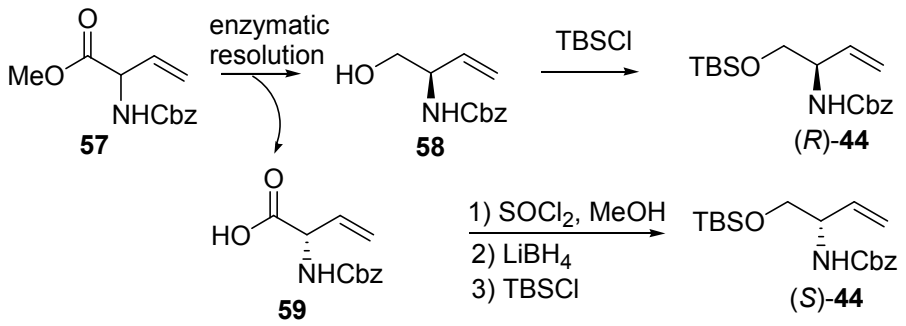
We have proved the capability of CM-double reductive cyclization to synthesize racemic 3,5-disubstituted pyrrolizidines. The development of new methods to synthesize enantiopure allylamines allows the application of our strategy for the synthesis of enantiopure products, with retrosynthetic analysis presented in **Scheme 19**.



Scheme 19. Retrosynthesis of enantiopure 3,5-disubstituted pyrrolizidines.

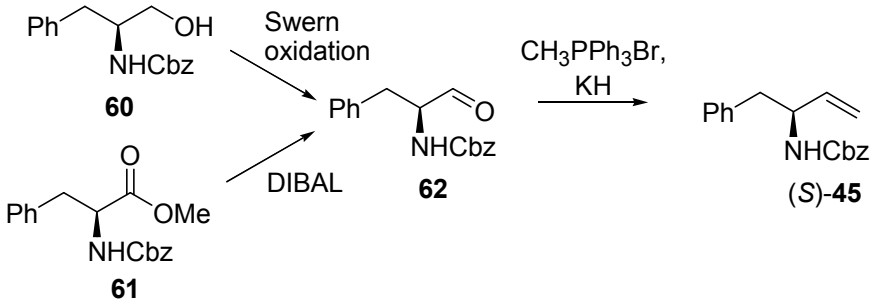
Stetter and Landscheidt reported the preparation of enediones **43** with methyl, ethyl, propyl, butyl, and hexyl side chains.[41] By the use of other alkyl vinyl ketones, enediones with various side chains can be prepared.

The preparation of enantiopure allylamine **44** was reported by Huwe und Blechert.[48] Enzymatic resolution of (±)-*N*-Cbz-vinyl glycine methyl ester **57** by *Subtilisin calsberg* yielded (+)-*N*-Cbz-vinyl gylycinol **58** and (-)-*N*-Cbz-vinyl glycine **59** with high enantiopurity (**Scheme 20**). This method is very flexible and provides after several transformations the allyl amine **44** in both enantiomeric forms.



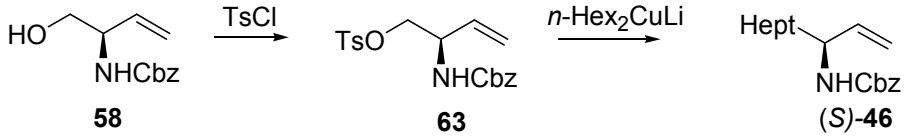
Scheme 20. Preparation of enantiopure allylamine **44**.

Sham *et al*. reported the preparation of enantiopure allylamine **45** from *N*-Cbz-*L*-phenylalaninol **60** by Swern oxidation and Wittig olefination.[49] The phenylalaninal **62** can also be prepared from *N*-Cbz-*L*-phenylalanine methyl ester **61** by reduction with diisobutylaluminiumhydride[50] (**Scheme 21**). Starting with *D*-phenylalaninol, the *R*-enantiomer can be prepared.



Scheme 21. Preparation of enantiopure allylamine **45**.

So far the preparation of enantiopure allylamine **46** has not been reported. A feasible preparation starts from enantiopure *N*-Cbz-vinylgylcinol **58**. Tosylation and replacement of it by Gilman cuprate reagent may lead to the enantiopure allylamine **46**, as outlined in **Scheme 22**.



Scheme 22. Feasible preparation of allylamine **43**.

Allylamines with various side chains can be prepared from amino acid based chiral pool with the procedures outlined in **Scheme 21**. It thus allows the syntheses of various enantiopure 3,5-disubstituted pyrrolizidines.

In the next section, we present the application of CM-double reductive cyclization method and the functionalization of the double bond resulted from CM to synthesize (+)-hyacinthacine A_2, a polyhydroxylated pyrrolizidine.

3. Synthesis of (+)-*Hyacinthacine* A_2

3.1 Polyhydroxylated Pyrrolizidines

According to the position of the hydroxymethyl substituents, polyhydroxylated pyrrolizidines can be classified into two classes: necine bases (with hydroxymethyl substituent at C-1) and 3-hydroxymethyl substituted pyrrolizidines. Necine bases occupy a larger class and are constituents of the complex pyrrolizidine alkaloids (**Figure 5**). One member of this class is rosmarinecine. The 3-hydroxymethylpyrrolizidines occupy a new class and were isolated from flowering and leguminous plants. The first examples of this family are alexine, which was isolated in 1988 from *Alexa leiopetala* by Nash *et al*.,[51] and australine, which was isolated in the same year from the seeds of *Castanospermum australe* by Molyneux *et al*.[52] Lately, more species of this class were isolated. Casuarine, for example, was isolated in 1994 from *Casuarina equisetifolia* L. by Nash *et al*.[53] A series of hyacinthacines were isolated from bluebells (*Hyacinthoides non-scripta*)[54] and grape hyacinths (*Muscari armeniacum*)[55] by Asano *et al*. (**Figure 8**).

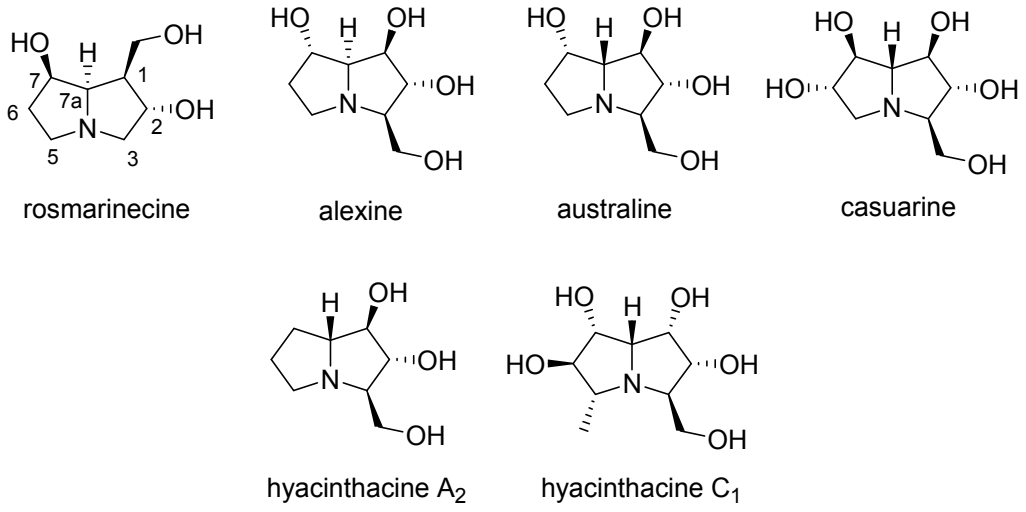


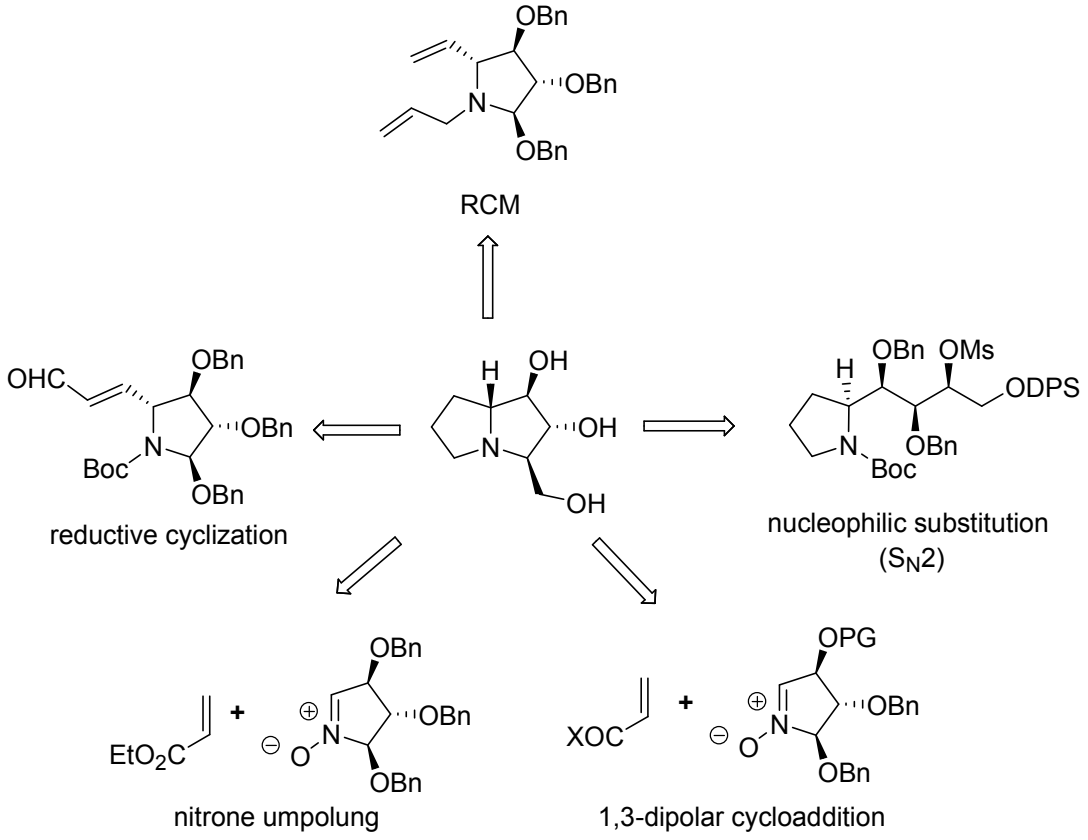
Figure 8. Various polyhydroxylated pyrrolizidines.

In contrast to the 3,5-disubstituted pyrrolizidines, the configuration of polyhydroxylated pyrrolizidines is more difficult to assign. X-ray crystallography and intensive nOe experiment are two important methods to determine the absolute and relative configuration of these alkaloids.

As sugar-mimics, many of these alkaloids possess potent gylcosidase inhibition activity, which makes them good candidates as new drugs for the treatment of many diseases such as viral infections, cancer, and diabetes.[56] Hyacinthacine A_2, for example, was found to be a selective inhibitor of amyloglucosidase (*Aspergillus niger*) with an IC_{50} value of 8.6 μM.[55,57]

3.2 Synthetic Strategies of Hyacinthacine A_2

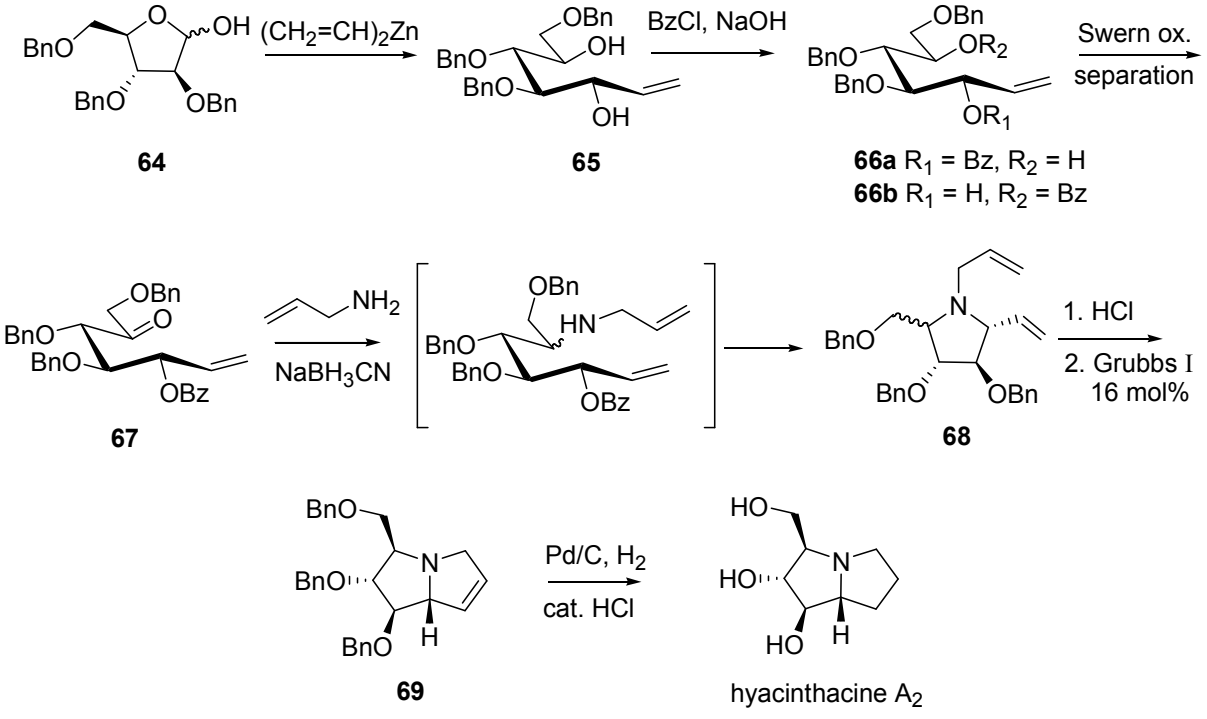
Several synthetic strategies of hyacinthacine A_2 and its diastereomers are categorized based on their cyclization methods (**Scheme 23**) and described briefly in this section. All the syntheses presented here started from the carbohydrate-based chiral pool.



Scheme 23. Synthetic strategies of hyacinthacine A_2.

3.2.1 Ring-Closing-Metathesis

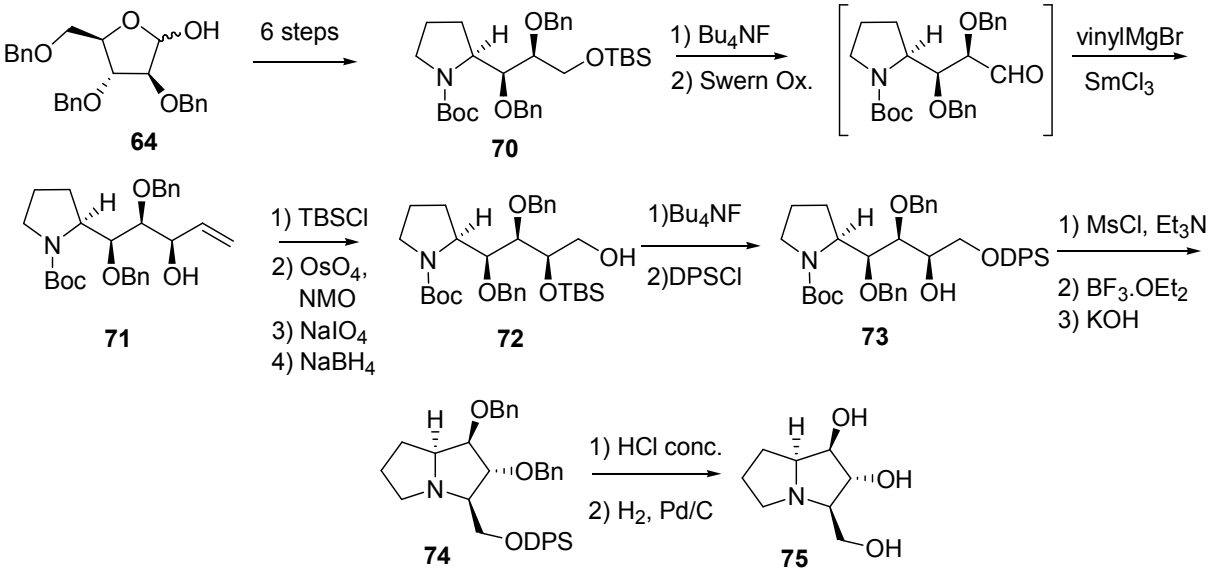
The first synthesis of hyacinthacine A_2 was reported by Martin *et al*. in 2001, who also confirmed the absolute configuration of hyacinthacine A_2 that had been proposed by Asano *et al*. as (1*R*,2*R*,3*R*,7a*R*)-1,2-dihydroxy-3-hydroxymethylpyrrolizidine.[58] The key step of the synthesis was the ring-closing-metathesis (RCM) reaction, as depicted in **Scheme 24**. The synthesis started by the addition of divinylzinc to the commercially available 2,3,5-tri-*O*-benzyl-D-arabinofuranose **64** to give **65**. Benzoylation of the allylic hydroxyl group gave the desired product **66a** together with the side product **66b** (3.5:1). The inseparable mixture was further oxidized and the ketone **67** was readily separable by flash chromatography. Reductive amination with allylamine and sodium cyanoborhydride gave an amine intermediate, which underwent intramolecular cyclization to form pyrrolidine **68**. RCM of the hydrochloride salt of **68** was conducted in the presence of 16 mol% of Grubbs I catalyst in toluene at 60 °C for 3 days. Despite of the rigorous reaction conditions, only 30% product was obtained. It presumably caused by the chelation of ruthenium by the amine group. The final hydrogenation step of **69** removed the benzyl group and reduced the double bond to give hyacinthacine A_2. The major drawbacks of the synthesis are the unselective benzoylation and the low yield of RCM.



Scheme 24. The first total synthesis of hyacinthacine A_2 by Martin *et al*.

3.2.2 Nucleophilic Substitution

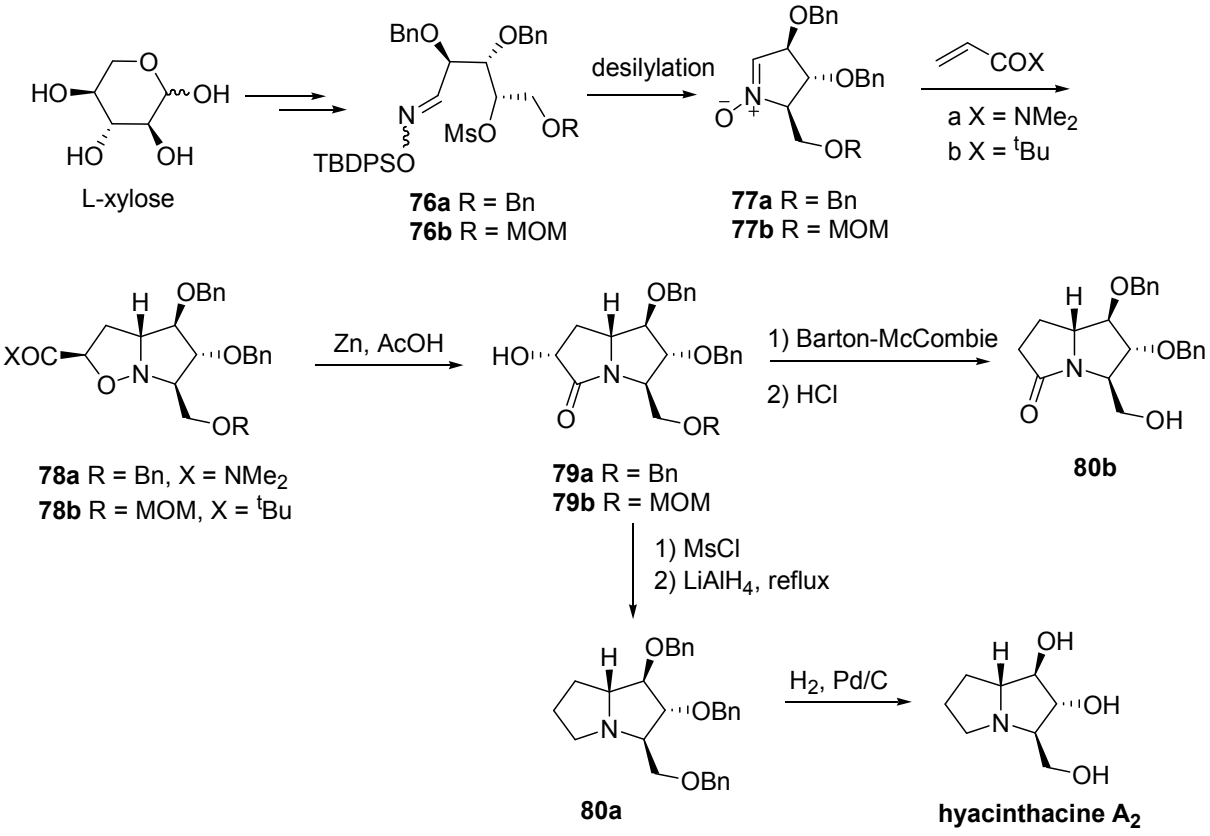
Yoda *et al*. utilized the nucleophilic substitution method to synthesize the unnatural 7-deoxyalexine (7a-*epi*-hyacinthacine A_2), as shown in **Scheme 25**.[59] The linear synthesis was conducted with the same starting material as that of Martin *et al*., i.e. the arabinofuranose derivate **64**, which was transformed into the pyrrolidine **70** after six steps. After desilylation and Swern oxidation, an aldehyde was obtained. It was then attacked by vinyl magnesium bromide in the presence of $SmCl_3$, to provide the allylalcohol **71** as the main product (68% *de*). The successive protection of the hydroxyl group, oxidative cleavage of the double bond, and reduction of the aldehyde intermediate by $NaBH_4$ gave the pyrrolidine **72**. The silyl protecting group was replaced from the secondary to primary alcohol with *tert*-butyldiphenylsilane (DPS) (**73**). Mesylation, removal of the Boc-group under acidic conditions, and simultaneous cyclization under basic conditions led to the pyrrolizidine **74**. The removal of the DPS group under acidic conditions and the benzyl groups by final hydrogenation step yielded the 7a-*epi*-hyacinthacine A_2. The synthesis was lengthy with 26 steps but with a remarkable overall yield of 25%.



Scheme 25. Total synthesis of 7a-*epi*-hyacinthacine A_2 by Yoda *et al*.

3.2.3 1,3-Dipolar Cycloaddition

Two quite similar syntheses of hyacinthacine A_2 with 1,3-dipolar cycloaddition as key reaction were reported by Tamura *et al.*[60] and Goti *et al.*[61] (**Scheme 26**).

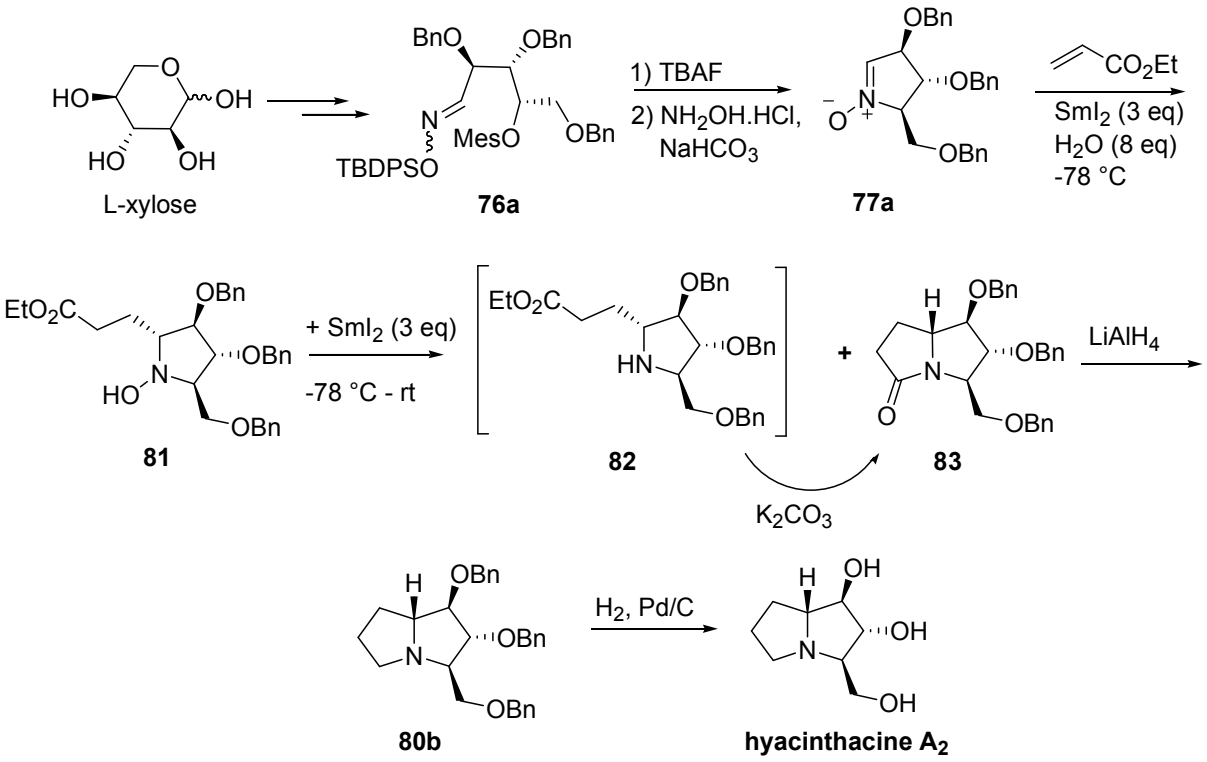


Scheme 26. Total synthesis of hyacinthacine A_2 by Goti *et al*. (**a**) and a formal synthesis by Tamura *et al*. (**b**)

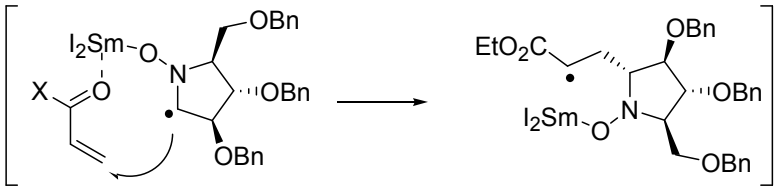
Both syntheses started with *L*-xylose, which was transformed to key nitrone intermediate **77a,b**. The 1,3-dipolar cycloaddition by Tamura *et al*. was conducted with *tert*-butyl acrylate as cycloaddition partner, yielding the desired *exo* product **78b** and the *endo* side product in 64 and 31% yields, respectively. Goti *et al*. chose the bulkier *N,N*-dimethylacrylamide as cycloaddition partner, leading exclusively to the *exo* product **78a** in 78% yield. Reductive cleavage of the N-O bond with zinc under acidic conditions afforded the lactam **79a,b**. The final steps of the formal synthesis by Tamura *et al*. consisted of the removal of hydroxyl group with Barton McCombie deoxygenation protocol and removal of the methoxymethyl (MOM) protecting group under acidic conditions yielded lactam **80b**. Goti *et al*. completed the total synthesis by mesylation of the hydroxyl group, reduction with lithium aluminium hydride, and final hydrogenation to afford the hyacinthacine A_2.

3.2.4 Nitrone Umpolung

A novel synthesis of hyacinthacine A_2 was reported by Py *et al*., in which nitrone **77a** also served as the key intermediate. Unlike the method of Tamura and Goti, the key reaction involved a samarium-diiodide induced umpolung of nitrone, which then undergoes a coupling reaction with ethyl acrylate at low temperature, as presented in **Scheme 27**.[62]



Plausible mechanism:



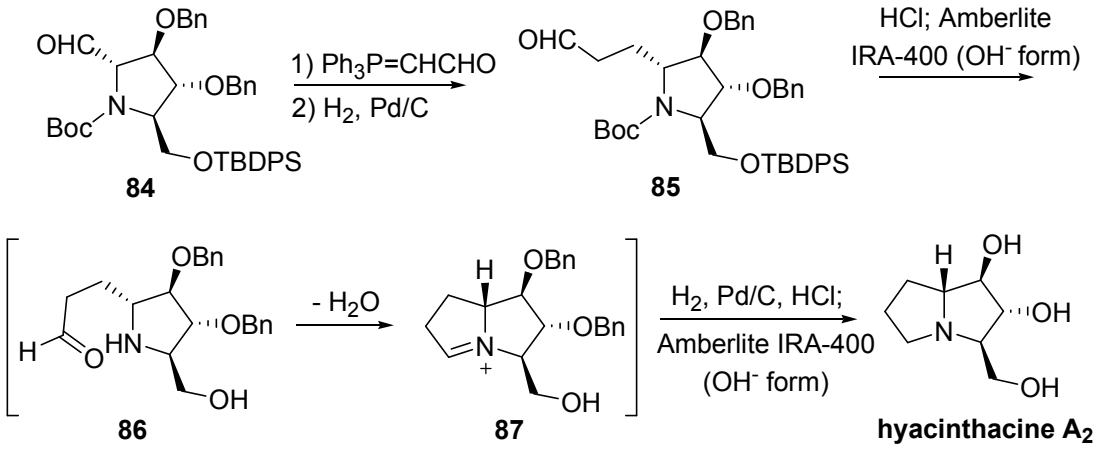
Scheme 27. Total synthesis of hyacinthacine A_2 by Py *et al*.

The nitrone **77a** was prepared according to Tamura's method with an additional step of heating the mesyloxy oxime in the presence of hydroxylamine hydrochloride and sodium hydrogen carbonate. The treatment of nitrone **77a** with samarium diiodide at -78 °C in the presence of water as proton source furnished the hydroxylamine **81**. Samarium diiodide reduces the C=N bond to generate an α-aza-nucleophilic species (radical or anion).

Activation of the ethyl acrylate by coordination of the lanthanide metal centre to the carboxyl group is followed by the 1,4-addition step, as illustrated in **Scheme 27**.[63] An addition of 3 equivalents of samarium diiodide to the reaction mixture resulted in the reduction of the *N*-hydroxylamine group (**81**) to amine (**82**), which cyclized partly to lactam **83**. A complete conversion was achieved by treating the crude product with potassium carbonate, which gave the product with diastereomeric ratio of 90:10. Reduction of lactam followed by hydrogenation furnished the natural product.

3.2.5 Reductive Cyclization

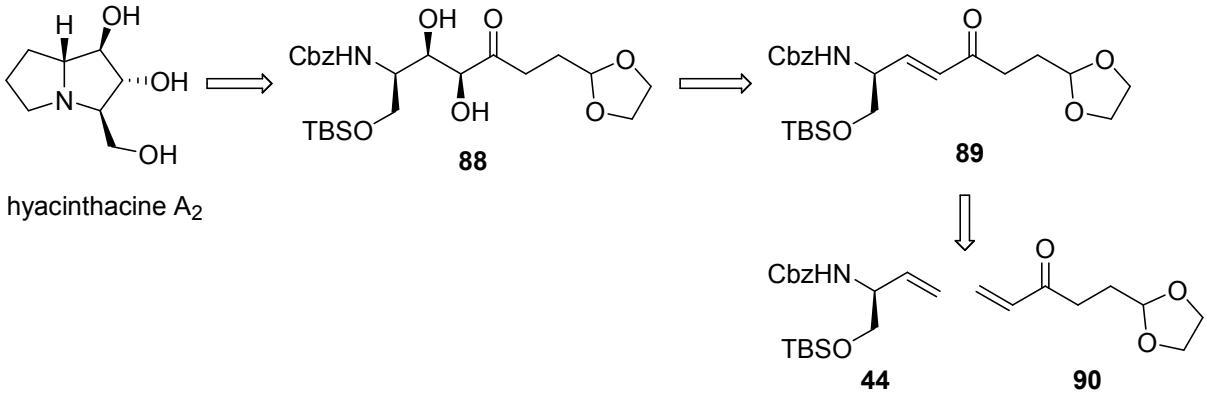
Izquierdo *et al*. prepared a series of hyacinthacines by reductive cyclization of the corresponding pyrrolidines.[64] The total synthesis of hyacinthacine A_2 started with pyrrolidine **84**, which was readily prepared from *D*-fructose,[65] as shown in **Scheme 28**.[64b] Wittig reaction with triphenylphosphoranylideneacetaldehyde followed by catalytic reduction prolonged the side chain by two carbon atoms to give pyrrolizidine **85**. Removal of Cbz and the silyl protecting group under acidic conditions gave **86**, which after neutralization readily cyclized to form **87**. Final hydrogenation in acidic medium and neutralization furnished the natural product. This synthesis is short and shows the effectiveness of the reductive cyclization method.



Scheme 28. Total synthesis of hyacinthacine A_2 by Izquierdo *et al*.

3.3 Retrosynthetic Analysis

We were eager to apply the sequential CM-reductive cyclization method to synthesize hyacinthacine A_2, especially since the strategy proved effective to build the *cis*-fused pyrrolizidines as described in Section **2.5**. We envisaged the diol **88** as the synthetic precursor for reductive cyclization, which should be prepared by Sharpless asymmetric dihydroxylation of CM product **89**, being prepared from two simple building blocks: enone **90** and enantiopure allyamine **44** (**Scheme 29**).

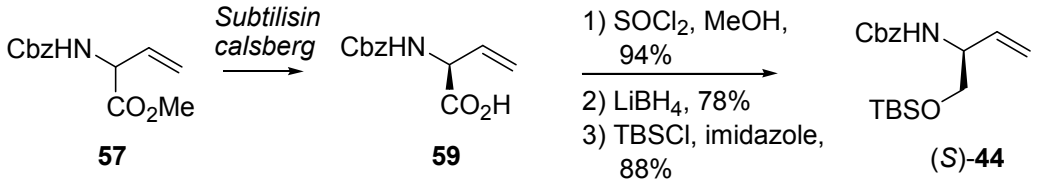


Scheme 29. Retrosynthesis of hyacinthacine A_2.

3.4 Synthesis of Hyacinthacine A_2

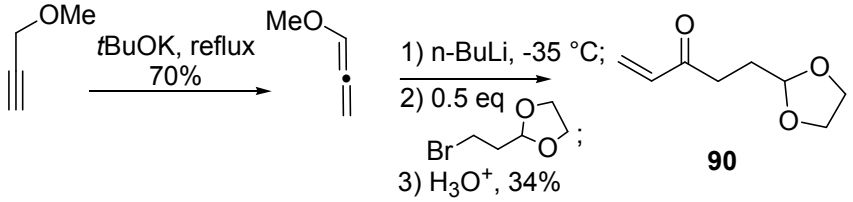
3.4.1 Preparation of CM Partners

The enantiopure allylamine **44** was prepared from (*S*)-*N*-Cbz-vinylglycine **59**, which was derived from the enzymatic resolution of *N*-Cbz-vinylglycine methyl ester **57** (see **Scheme 20**).[48b] Successive esterification, reduction of the ester group by $LiBH_4$, and protection of the hydroxyl group as TBS ether gave allylamine (*S*)-**44,** as outlined in **Scheme 30**. The optical rotation of the product ($[\alpha]_D^{20}$ -31.2 (c = 1.2, CH_2Cl_2)) was complementary to its *R*-counterpart [Lit.[48] $[\alpha]_D^{22}$ +31.8 (c = 1.2, CH_2Cl_2)].



Scheme 30. Preparation of allylamine (*S*)-**44**.

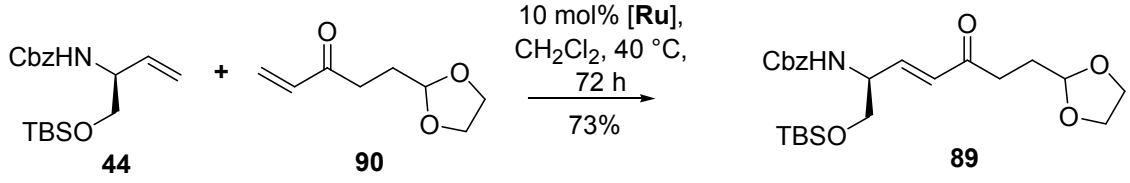
The alkylation of lithiated methoxyallene[66] with commercially available 2-(2-bromoethyl)-[1,3]-dioxolane yielded, after acidic workup, the enone **90**, as shown in **Scheme 31**.[67] According to TLC control, the alkylation reaction proceeded smoothly. However, some allene intermediate may decompose during the acidic work-up, yielding a moderate yield of 34%.



Scheme 31. Preparation of enone **90**.

3.4.2 Cross Metathesis

CM was conducted with the optimized condition described in Section **2.5.2**, in refluxing dichloromethane, enone **90** and allyl amine **44** in ratio of 1:1, and 10 mol% [**Ru**] for 3 days to afford enone **89** in 73% yield (**Scheme 32**). The high *E* selectivity of the CM reaction was a great advantage for the subsequent Sharpless asymmetric dihydroxylation reaction.



Scheme 32. Cross metathesis of allylamine **44** and enone **90**.

The catalyst should be freshly prepared prior to use, otherwise lower yields were obtained. The relatively high catalyst loading could be the result of the chelation effect between ruthenium and carbonyl oxygen of Cbz protecting group, as described in Section **2.5.2**.

3.4.3 Sharpless Asymmetric Dihydroxylation

To predict the enantiofacial selectivity and the ligand needed for the Sharpless dihydroxylation reaction, the mnemonic device was employed (**Figure 9**).

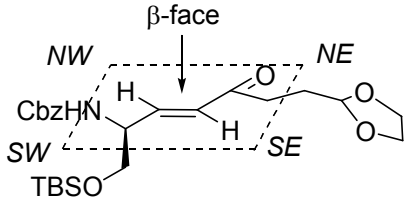


Figure 9. Mnemonic device of Sharpless dihydroxylation.

The alkyl substituent was placed on the southwest quadrant, which is well-suited to accommodate large substituents. The carbonyl group was placed on the northeast quadrant, which is suitable for substituents of moderate size. Both hydrogen atoms were placed on the northwest and southeast quadrants. To obtain the expected diol configuration, an attack from the top face was needed; in this case dihydroquinidine (DHQD) derivative was the ligand of choice.[68]

Since osmium tetroxide is an electrophilic reagent, the rate of osmylation of electron deficient olefins, such as α,β-unsaturated carbonyl compounds, is very low. The voluminous TBS group may play a role in controlling the enantioselectivity (substrate control), but it may also slow the reaction because of the steric hindrance. We studied both the substrate- and reagent controls and optimized the conditions, with the results summarized in **Table 3**.

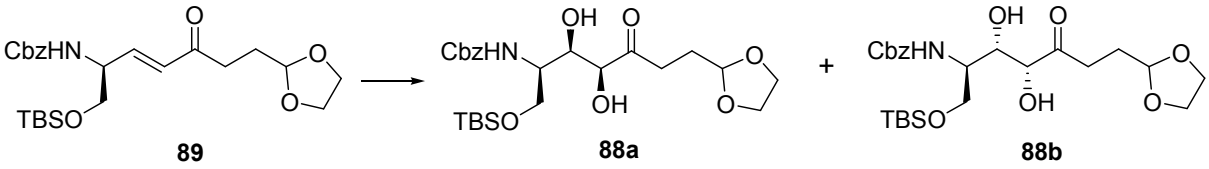


Table 3. Reaction conditions of Sharpless asymmetric dihydroxylation.

Entry	Conditions	Time	Conversion	Isolated yield* 88a:88b
1	Citric acid, NMO, K_2OsO_4 0.01 eq, rt	6 d	81%	42%, 1:2
2	$K_3Fe(CN)_6$, $MeSO_2NH_2$ 1eq, K_2OsO_4 0.05 eq, rt	14 d	84%	44%, 2:1
3	AD mix β, $MeSO_2NH_2$ 3eq, K_2OsO_4 0.01 eq, rt	8 d	79%	42%, 94:6
4	AD mix β, $MeSO_2NH_2$ 3.8 eq, K_2OsO_4 0.015 eq, rt	1 d	100%	67%, 94:6

*Determined by ^{1}H NMR

We first applied a variation of the Sharpless dihydroxylation, which was performed under acidic conditions (pH 4-6).[69] The citric acid maintains the pH during the reaction and neutralizes 4-methylmorpholine formed during the course of the reaction. Acting as a ligand for osmium, it also keeps the active Os(VI) in solution by stabilizing it against disproportionation to Os(VIII) and insoluble Os(IV) species. Under acidic conditions, the reaction rate and yields were improved. The new procedure is also suitable for electron poor olefin, such as α,β-unsaturated amide, esters, nitriles, ketones, and phosphonates with good yields and short reaction times. Applying the procedure to the enone **89**, 81% conversion was obtained after 6 days at room temperature. Along with recovered enone, the expected products **88a** and its diastereomer **88b** were isolated with a ratio of 1:2 and yield of 42%.

Sharpless *et al*. have also developed a particular procedure for α,β-unsaturated ketones with potassium hexaferricyanide as reoxidant and a buffer system (K_2CO_3/$NaHCO_3$) to avoid the epimerization of the α-center.[70] The procedure was applied in the absence of the chiral ligand to study the substrate effect (Entry 2). The reaction was also very slow, with 84% conversion after 14 days. Utilizing this method, the expected ketodiol **88a** was isolated as the main

product (ratio 2:1). These facts confirmed our assumption that the TBS group indeed showed a moderate substrate control but simultaneously retarded the reaction.

To study both reagent- and substrate controls, AD-mix β was employed. Three equivalents of methane sulphonamide were added to accelerate the reaction (Entry 3).[71] After 8 days at room temperature, ketodiol **88a** was isolated with high diastereoselectivity (94:6), which showed a matched case between reagent and substrate control.

The best results were achieved with the use of excess AD-Mix (2.1 g/mmol enone), methane sulphonamide (3.8 equivalents), and K_2OsO_4 (with a total of 0.015 equivalent).[72] Within one day, 100% conversion was achieved, providing **88a** in 67% yield and *dr* 94:6 (Entry 4). The methane sulphonamide accelerates the hydrolysis of the osmium (VI) glycolate, and thus improves the reaction rate. However, the whole amount should be added at one time, since successive addition is not as effective.

The ketodiol **88a** and **88b** differ in polarity and NMR spectra. The expected product is slightly more polar than its diastereomer. Although the chromatographic separation was difficult, most of **88a** could be separated from **88b**. The diastereoselectivity was determined by ^{1}H NMR and the diol configuration was determined after cyclization by nOe experiments.

3.4.4 Double Reductive Cyclization

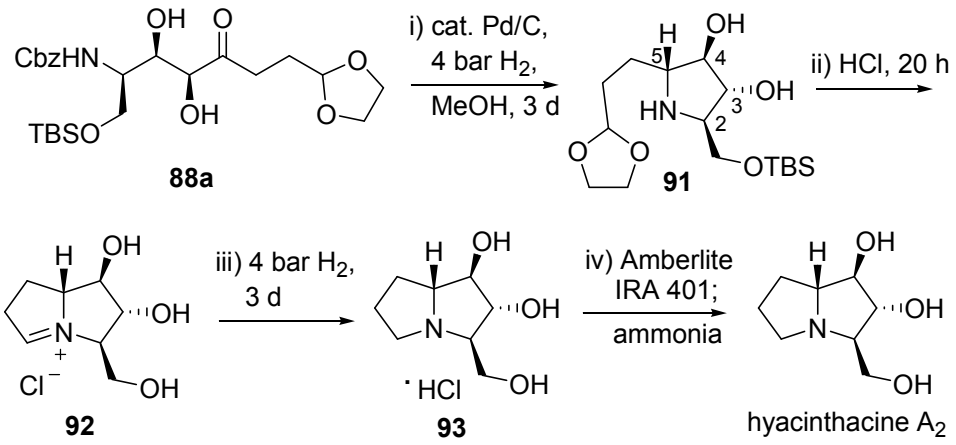
Initial attempts to conduct the double reductive cyclization in one pot failed, since the cyclization of the first five-membered ring was very slow, in comparison to that of the 3,5-disubstituted pyrrolizidines. The conditions used and the results are summarized in **Table 4**.

Table 4. Initial attempts of one pot double reductive cyclization.

Entry	Conditions	H_2 pressure & time	Results
1	MeOH, 10% Pd/C	1 bar, 3 d	imine
2	MeOH/THF/HCl, 10% Pd/C	1 bar, 9 d	trace of product
3	MeOH/HCl, 10% Pd/C	4 bar, 3 d	decomposed

We applied the optimal cyclization conditions of 3,5-disubstituted pyrrolizidines to the diol **88a** (Entry 1). After 3 days, only imine of the first five-membered ring was formed. Addition of a small amount of hydrochloric acid, which may accelerate the reaction, was not effective. After 9 days, only a trace of product was formed (Entry 2). Applying 4 bar hydrogen to the acidic reaction mixture led to the decomposition of adduct. Therefore, a sequential cyclization was required.

Our previous results showed that the first cyclization should be done in neutral yet under more rigorous conditions. Once the first five-membered ring was formed, the protecting group would be removed, followed by the second cyclization. **Scheme 33** showed the sequential transformations.



Scheme 33. Sequential reductive cyclization of diol **88a**.

The formation of the first five-membered ring was conducted under 4 bar hydrogen for 3 days to give pyrrolidine **91**.[73] Its configuration was determined based on the positive nOe observed between H-2 and H-4, and between H-3 and H-5. Without isolating the intermediate, hydrochloric acid was added and the mixture was stirred overnight to remove both dioxolane and TBS protecting groups. The mixture containing the iminium salt **92** was directly hydrogenated at 4 bar for 3 days without further addition of Pd/C. The hydrochloric salt of hyacinthacine A_2 **93** was isolated after removal of the catalyst. The mixture was neutralized with wet Amberlyte IRA 401 (OH form) to remove the chloride ions in the solution. After filtration, ammonia was added and the mixture was stirred for further 30 minutes to remove the chloride ions bonded to the product. The formation of a less polar product and the disappearance of the polar salt could be monitored by TLC. The final purification was done by preparative TLC which gave hyacinthacine A_2 in 39% yield.

3.4.5 Structure Determination

The nOe measurement confirmed the structure and configuration of the product as shown in **Figure 10**.

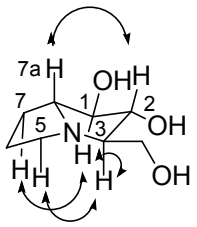


Figure 10. Correlation observed in the nOe spectrum of hyacinthacine A_2.

The nOe analysis of the product showed the enhancements of H-7a with H-2, H-1 with H-3 and H-7, and H-3 with H-5, which attribute only to hyacinthacine A_2. This also ensured the diol configuration and the *cis*-fused configuration of the product, which was in accordance with other results for 3,5-dialkyl pyrrolizidine syntheses. The IR spectrum supported this fact that no Bohlmann band was detected. The ^{13}C and the optical rotation of the product ($[\alpha]_D^{20}$ + 11.2 (*c* 0.52, H_2O)) was in agreement to the reported values. [Lit.[60] $[\alpha]_D^{25}$ + 12.5 (*c* 0.6, H_2O); Lit.[63] $[\alpha]_D^{25}$ + 12.7 (*c* 0.13, H_2O); Lit.[67] $[\alpha]_D^{25}$ + 10.5 (*c* 0.6, H_2O)].

(+)-Hyacinthacine A_2 was synthesized in 6 steps, starting from (-)-*N*-Cbz vinyl glycine with an overall yield of 12%. CM reaction yielded an enone in 73% yield with complete *E*-selectivity. The resulted double bond is very advantageous to introduce various functional groups into the molecule, such as the Sharpless asymmetric dihydroxylation, which gave the expected diol in 67% yield. The sequential double reductive cyclization, which is as effective as the one-pot tandem method, furnished the *cis*-fused hyacinthacine A_2 with a moderate yield of 39%.

In the next section, we describe the stereoselective synthesis of (+)-calvine. The CM-reductive cyclization method would be employed to prepare a 2,6-disubstituted piperidine intermediate, which after final lactonization was transformed to the expected natural product.

4. Synthesis of (+)-*Calvine*

4.1 Calvine

Substituted piperidines are abundant in nature and many of these exhibit important biological activities. Particularly 2,6-disubstituted piperidines are one of the most common piperidine skeletons and have been the subject of intensive studies and synthetic efforts.[74] One renowned example of this family is solenopsin A, the active ingredient in fire ants *Solenopsis*, which shows cytotoxic, hemolytic, necrotic, insecticidal, antibacterial, and antifungal activities.[75] Two examples of 2,6-disubstituted piperidines found in plants are lobeline from Indian tobacco (*Lobelia inflata*)[76] and dihydropinidine from pines, which was found later in the Mexican bean beetle (*Epilachna varivestis*)[77] (**Figure 11**).

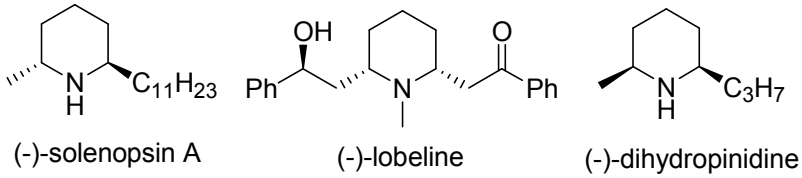


Figure 11. Examples of 2,6-disubstituted piperidines.

Ladybird beetles (Coccinellidae) are rarely exploited as food sources by predators, owing to toxic alkaloids produced in their hemolymph, which are released as yellow small droplets from their knee joints once they are disturbed or molested.[78] Calvine, a *cis*-2,6-disubstituted piperidine annulated with a seven-membered lactone, is the major alkaloid found in two ladybird beetles *Calvia 10-guttata* and *Calvia 14-guttata*. 2-Epicalvine, its corresponding *trans*-lactone was also found as the minor constituent (about 10%) (**Figure 12**). Braekman *et al*. isolated the alkaloids in 1999 and determined their absolute configuration by enantioselective syntheses in 2000.[79]

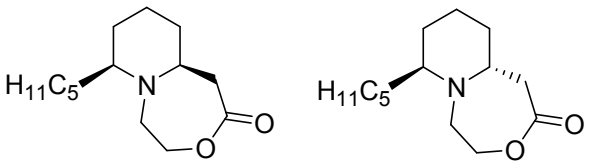


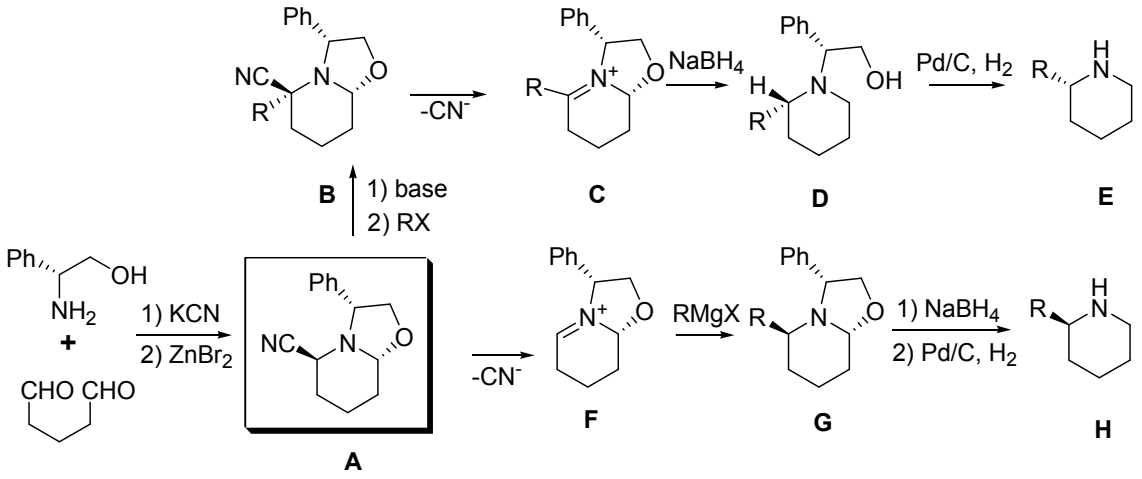
Figure 12. (+)-calvine and (+)-2-epicalvine.

4.2 Synthetic Strategies of Calvine

So far, only two enantioselective syntheses of calvine have been reported. The first total synthesis was done by Braekman *et al*. with CN(*R,S*) method as key step. Troin *et al*. reported a formal synthesis, which involved an intramolecular Mannich reaction.

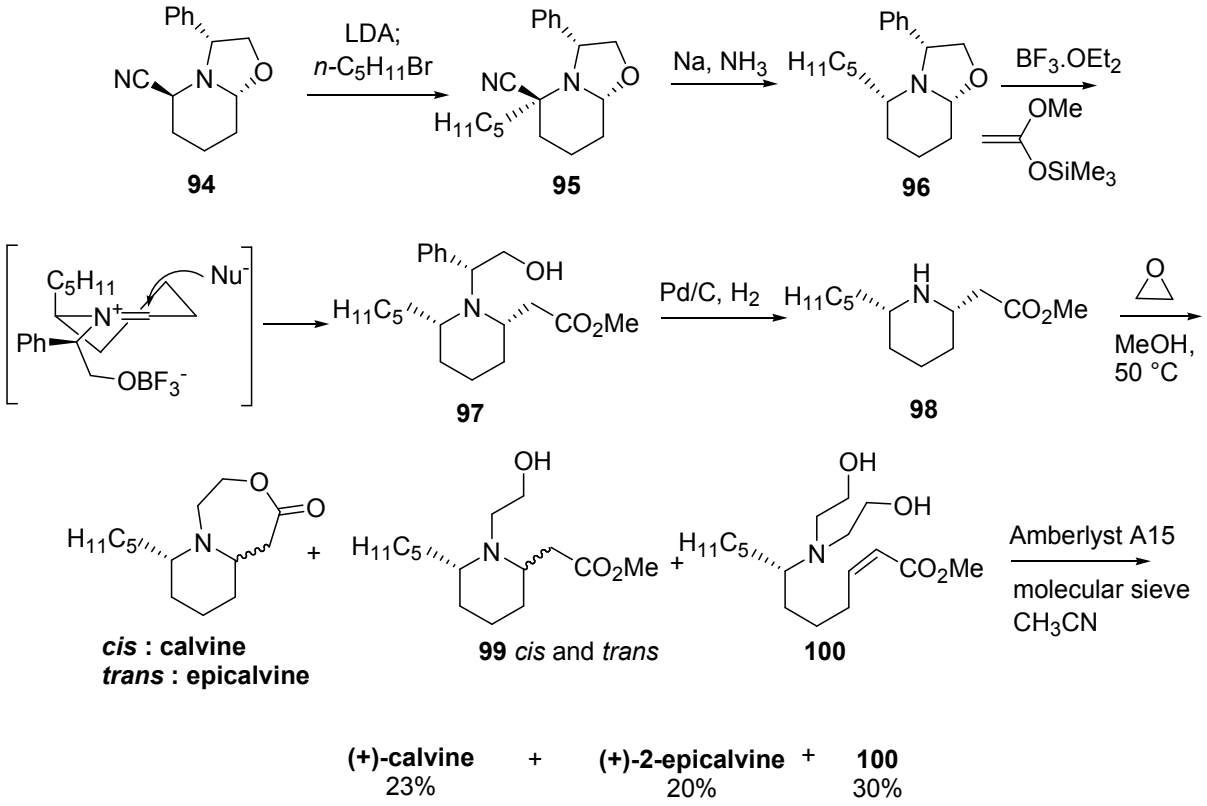
4.2.1 CN(*R*,*S*) Methodology

Husson and Royer developed a methodology known as CN(*R*,*S*), which based on a chiral *N*-cyanomethyloxazolidine intermediate. This method is flexible and allows the preparation of piperidines in both *R*- and *S*-configurations (**Scheme 34**).[80]



Scheme 34. CN(*R*,*S*) method.

Condensation of glutaraldehyde and phenyl gylcinol in the presence of KCN furnished the *N*-cyanomethyloxazolidine **A**. Its deprotonation and alkylation affords **B**, which after elimination of the cyano group gives the prochiral iminium **C**. Reduction and cleavage of the chiral moiety yield the piperidine **E**. On the other hand, elimination of the cyano group from **A** yields the prochiral iminium ion **F**, which reacts with a Grignard reagent to afford **G**. Cleavage of the chiral moiety leads to **H**, the enantiomer of **E**. The method was successfully applied, for example to synthesize both configurations of coniine.[81]

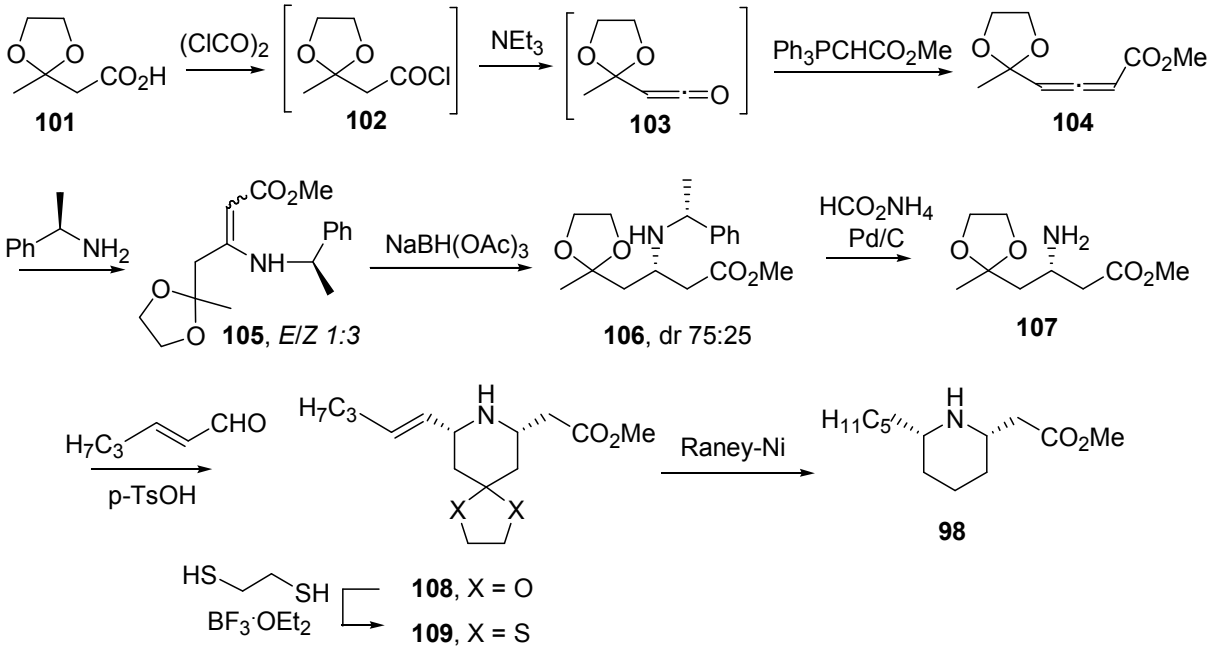


Scheme 35. Total synthesis of calvine by Braekman *et al*.

The total synthesis of calvine by Braekman *et al*. is outlined in **Scheme 35**.[79a] The CN(*R,S*) method furnished the aminoalcohol **96** after decyanation by sodium in liquid ammonia. Reaction of **96** with 1-methoxy-1-trimethylsilyloxyethene in the presence of $BF_3{\cdot}OEt_2$ led to piperidine **97** as single isomer.[82] The preferred formation of the *cis* isomer is ascribed to the stereoelectronically preferred axial approach of the nucleophile to the iminium intermediate, which is in a half-chair conformation with the pentyl substituents in a pseudo-axial disposition to relieve the $A^{(1,2)}$ strain.[83] Hydrogenolysis of the chiral appendage afforded the piperidine **98**. Introduction of the ethylhydroxyl group was conducted by treating **98** with an excess of ethylene oxide in methanol, which resulted in a crude mixture containing calvine, epicalvine, methylester **99** (*cis*:*trans* 1:1), and the *N*-dialkylated retro-Michael product **100**. Subjecting the crude product mixture to the lactonization conditions in the presence of Amberlyst A15 and molecular sieves in acetonitrile yielded calvine, epicalvine, and the by-product **100** in 23, 20, and 30% yield, respectively. The major drawback of the synthesis is the hydroxyethylation reaction, which gave low yield and selectivity. However, it was essential to prepare both calvine and 2-epicalvine for determination of their structures.

4.2.2 Intramolecular Mannich Reaction

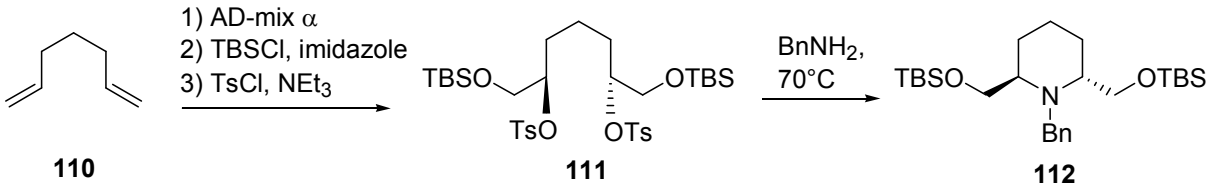
Troin *et al*. reported the synthesis of piperidine **98** from a chiral β-aminoester **107** and hex-2-enal *via* Mannich-type reaction as shown in **Scheme 36**.[84] The preparation of the aminoester started from acid **101**, which was transformed to the acylchloride **102**. Treatment of the crude mixture with triethylamine and methyl triphenylphosporanylidene acetate gave the conjugated allenic ester **104** *via* ketene intermediate **103** and subsequent Wittig reaction. Nucleophilic addition of (*R*)-methylbenzylamine provided an inseparable 3:1 *Z*/*E* mixture of chiral enaminoester **105**. The *Z*-isomer, which was stabilized by intramolecular hydrogen bond, formed predominantly.[85] Reduction of the product with sodium acetoxyborohydride yielded amine **106** (dr 75:25), which was readily separated from its diastereomer. Hydrogenation led to the chiral aminoester **107**, which reacted with hex-2-enal to give **108**. Transformation of the dioxolane to dithiolane derivative followed by the reaction with Raney nickel furnished the piperidine **98**. The synthetic route was lengthy and with moderate selectivity in the nucleophilic addition reaction.



Scheme 36. Formal synthesis of calvine by Troin *et al*.

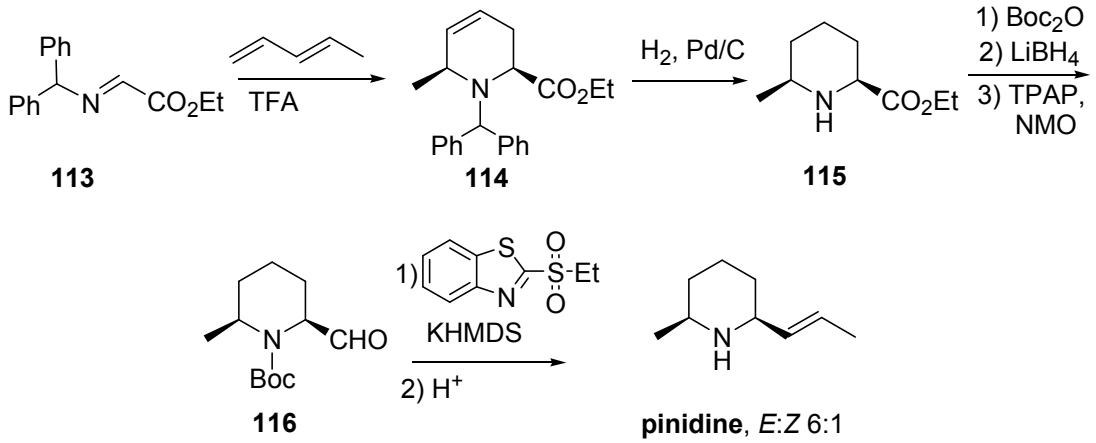
4.2.3 Several Synthetic Strategies of 2,6-Disubstituted Piperidines

Nucleophilic substitution of activated alcohol moiety (e.g. tosylate and mesylate) by an amine is a reliable method of preparing piperidines. It requires a synthesis of a linear chain, which already contains the substitution pattern and stereocenters. One example of its application is the synthesis of C_2-symmetric 2,6-dihydroxymethylpiperidine derivative by Takahata and Momose as summarized in **Scheme 37**.[86] Starting with 1,6-heptadiene **110**, a sequence of double Sharpless asymmetric dihydroxylation, protection of the primary alcohol groups and tosylation of secondary alcohol groups gave ditosylate **111**. The double nucleophilic substitution was conducted by heating the ditosylate with benzylamine to provide the piperidine **112** in 44% yield and 93% *ee*.



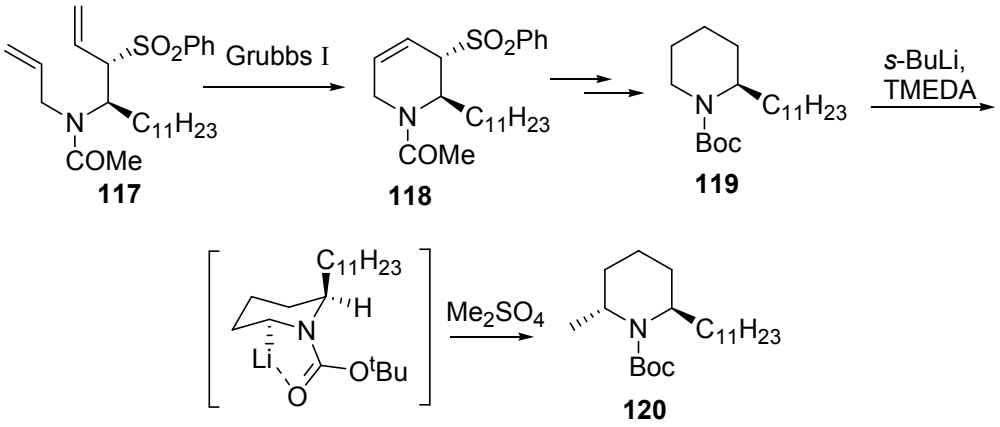
Scheme 37. Synthesis of 2,6-disubstituted piperidine by nucleophilic substitution reaction.

Aza Diels-Alder reaction is an important tool to synthesize piperidines as demonstrated by Bailey *et al*. in their synthesis of pinidine (**Scheme 38**).[87] Aza Diels-Alder reaction between benzhydryl imine **113** with penta-1,3-diene furnished the tetrahydropyridine **114**. Hydrogenation yielded 2,6-disubstituted piperidine **115**. Protection of the amino group and transformation of the ester group to aldehyde resulted in piperidine **116**. Julia olefination and removal of Cbz group afforded pinidine with *E*/*Z* 6:1.



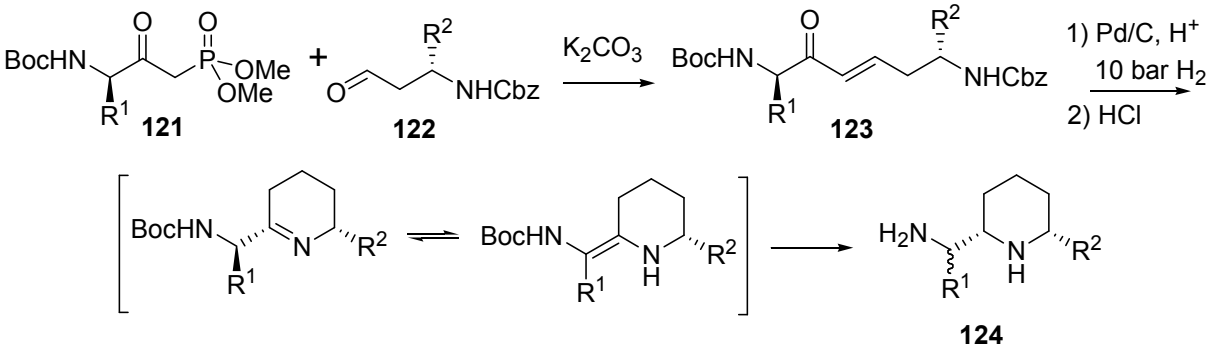
Scheme 38. Synthesis of pinidine by aza Diels-Alder.

Ring-closing metathesis (RCM) has become a powerful method for the preparation of unsaturated piperidines.[88] The resulted double bond can be easily functionalized. The amino group, however, should be protected with an electron withdrawing group (for example tosyl, nosyl, or carbamate) to avoid catalyst inhibition. Hassner and Kumareswaran utilized this method to synthesize a *trans*-solenopsin derivative (**Scheme 39**).[89] RCM of the acetamide **117** afforded the tetrahydropyridine **118**. Several transformations, which include the exchange of the *N*-protecting group, hydrogenation, and desulfonylation, yielded piperidine **119**. Lithiation and treatment with dimethylsulfate[90] afforded the *N*-Boc-*trans*-solenopsin **120**.



Scheme 39. Synthesis of *trans*-solenopsin by RCM.

Intramolecular reductive amination of chiral 1,5-aminoketone derivatives lead to 2,6-disubstituted piperidines. The reduction of the imine or enamine intermediate is thermodynamically controlled and gives very common *cis* products. Fehrentz *et al*. utilized this strategy to prepare a series of 2,6-disubstituted piperidines with various α-amino acid side chains, as shown in **Scheme 40**.[91] Horner-Wittig-Emmons reaction between β-ketophosphanate **121** and aldehyde **122** gave exclusively the *E*-enone **123**. Reductive amination and subsequent removal of the protecting group furnished the *cis*-2,6-disubstituted piperidine **124**. The equilibrium between imine and enamine intermediates resulted in the epimerization of the product.

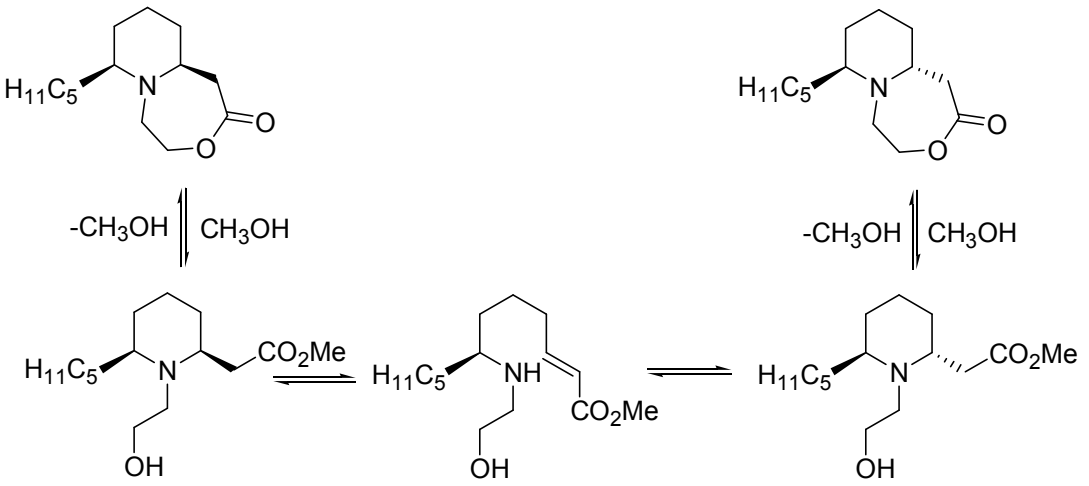


Scheme 40. Syntheses of 2,6-disubstituted piperidines by reductive amination.

4.3 Retrosynthetic Analysis

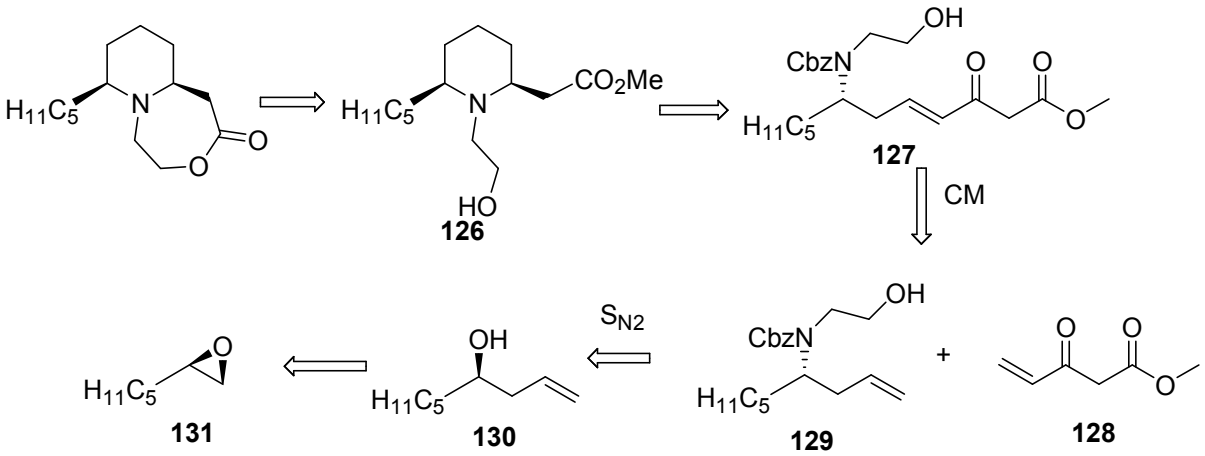
We would like to apply the CM-reductive cyclization method to synthesize calvine. In contrast to our results in five-membered ring cyclization, the sequential reaction gives exclusively *cis*-2,6-disubstituted piperidines. Taking the synthesis by Braekman *et al*. into account, two important aspects should be considered, i.e. to avoid the retro-Michael reaction which causes the epimerization and to find a more selective method to introduce the hydroxyethyl group.

The interconversion of calvine and 2-epicalvine occurs in protic solvent *via* transesterification, ring opening, and retro-Michael reactions as shown in **Scheme 41**. Interestingly, both lactones are stable in aprotic solvents such as THF or acetonitrile.[79b] A careful selection of solvents used in the reactions is therefore crucial.



Scheme 41. Interconversion of calvine and epicalvine.

The retrosynthesis of calvine is presented in **Scheme 42**. Our strategy was to introduce the hydroxyethyl group early in the synthesis. We envisaged the ester **126** as a synthetic precursor, which should result from the reductive cyclization of enone **127**, CM product of enone **128** and enantiopure homoallylamine **129**. The homoallylamine should be prepared *via* nucleophilic substitution reaction from homoallylalcohol **130**, prepared from oxirane **131**.

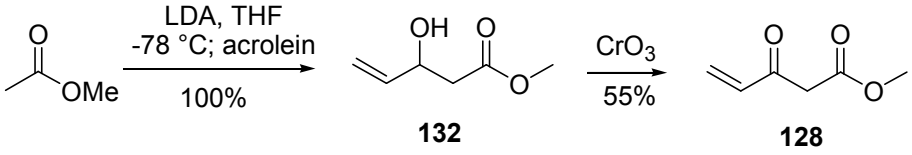


Scheme 42. Retrosynthetic analysis of calvine.

4.4 Synthesis of Calvine

4.4.1 Preparation of CM Partners

Methyl 3-oxo-4-pentanoate, **128** was prepared in 2 steps according to the procedure of Zibuck and Streiber (**Scheme 43**).[92]



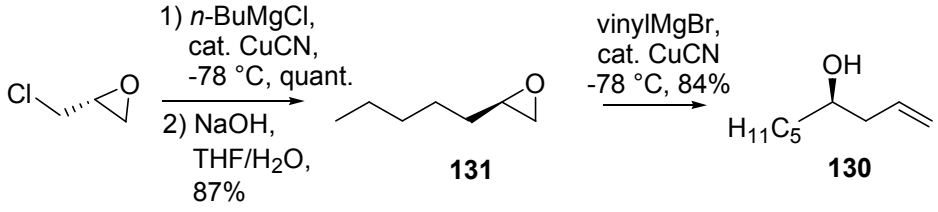
Scheme 43. Preparation of enone **128**.

The aldol reaction of methyl acetate and acrolein occurred smoothly to furnish the allyl alcohol **132**. The Jones oxidation yielded after Kugelrohr distillation the desired enone **128** in 55% yield. On smaller scale, however, Dess-Martin oxidation proved to be suitable,[93] in which 1.3 equivalents of the reagent were consumed. The enone is relatively unstable, that

flash chromatography technique was required to avoid its decomposition during purification. It was stored at -20 °C as a 2 M solution in anhydrous dichloromethane.

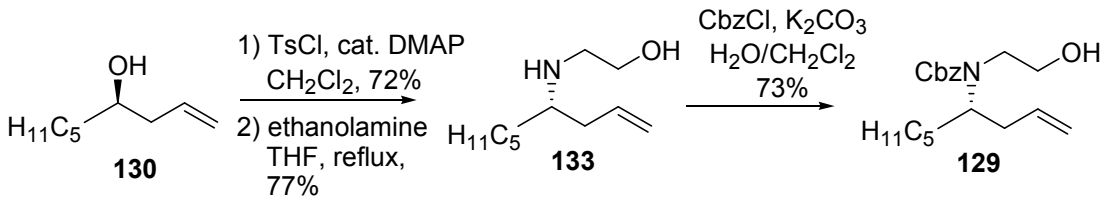
Several methods to prepare the homoallylalcohol have been reported. Brown *et al*. reported the reaction between allyldiisopinocampheylborane and *n*-butyraldehyde to furnish (*R*)-hept-1-en-4-ol in 72% yield, yet with moderate 87% *ee*.[94] Another approach was the Barbier reaction between allyltributyltin and hexanal in the presence of a catalytic amount (20 mol%) of a chiral BINOL-$TiCl_2$ complex to give (*R*)-non-1-en-4-ol in 75% yield and 98.4% *ee*. The reaction was reported on small scale (1.5 mmol of aldehyde) and an elaborate technique was required to prepare the chiral complex.[95] An alternative method was reported by Fürstner *et al*., which involved an oxirane opening by vinylmagnesium bromide in the presence of catalytic amounts of CuCl(COD) (COD = cyclooctadiene). This method is suitable for large scale and does not result in any erosion of *ee*.[96]

(*R*)-Non-1-en-4-ol (**130**) was prepared in 3 steps, starting with (*R*)-epichlorohydrine, as summarized in **Scheme 44**. The conversion of epichlorohydrine to pentyl oxirane **131** in 87% yield was conducted by copper-catalyzed oxirane ring opening with *n*-butyl magnesium chloride followed by ring closing reaction in basic conditions.[97] Successive oxirane ring opening with vinyl magnesiumbromide yielded the homoallylalcohol **130** in 84% yield. The optical rotation of the product ($[\alpha]_D^{20}$ + 8.7 (*c* 1.4, $CHCl_3$)) was in agreement to the reported value. [Lit.[98] $[\alpha]_D^{25}$ + 8.3 (*c* 1.4, $CHCl_3$)]. Copper cyanide works as well as CuCl(COD) in catalyzing the reaction.



Scheme 44. Preparation of homoallylamine **130**.

The transformation of homoallylalcohol **130** to homoallylamine **129** was accomplished in 3 steps, as depicted in **Scheme 45**.



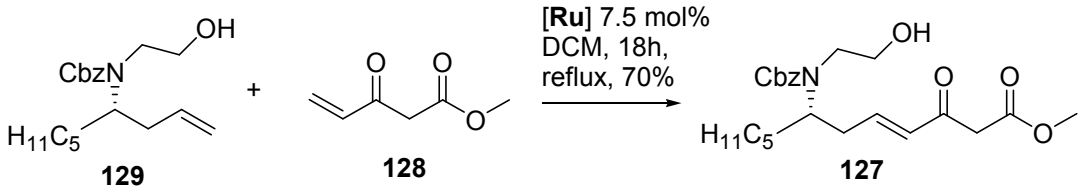
Scheme 45. Preparation of homoallylamine **129**.

Tosylation, nucleophilic substitution, and introduction of the protecting group gave the homoallylamine **129**. The tosylation proceeded slowly and was complete after 7 days. The tosyl group was chosen, since the substitution reaction with mesyl group was slower and the triflate group was too reactive, that the product decomposed readily during aqueous work-up. The substitution reaction was complete after 6 days yielding the volatile homoallylamine **133**. The introduction of Cbz group was done in a two-phase reaction system, which gave solely *N*-protected homoallylamine.

Attempts to determine the configuration of **129** and **133** *via* chiral HPLC and Mosher derivate[99] were unfortunately unsuccessful. Most HPLC-separable chiral compounds are UV active, with a heteroatom (with one hydrogen atom attached to it) and a bulky substituent adjacent to the chiral centre.[100] In this case, the pentyl group was not bulky enough. We then prepared the Mosher derivate of compound **133** and obtained only the Mosher ester, even with 3 equivalents of Mosher reagent. Hoye *et al*. reported similar observations with molecule containing secondary amine and primary alcohol. Attempts to prepare *bis*-Mosher derivative resulted in poor yields and mostly only Mosher ester was formed.[101] The Mosher ester was unfortunately too far from the chiral centre that it did not lead to the desired separation, either with reversed phase or chiral HPLC. However, further results showed that the nucleophilic substitution reaction occurred with complete inversion of configuration (S_N2 mechanism).

4.4.2 Cross Metathesis

CM between enone **128** and homoallylamine **129** was performed in refluxing dichloromethane, with enone **128** and amine **129** in ratio of 2:1 and 7.5 mol% [**Ru**] for 18 hours, to give enone **127** in 70% yield (**Scheme 46**).

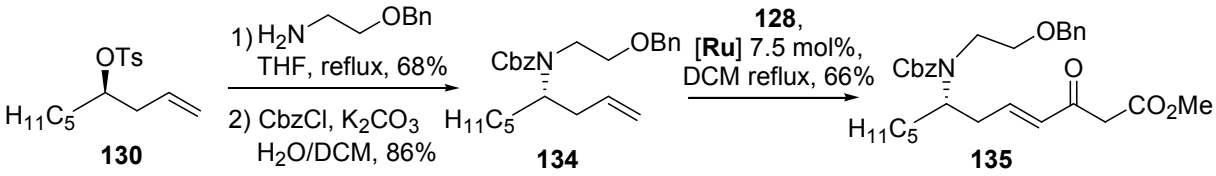


Scheme 46. CM between homoallylamine **129** and enone **128**.

The facts that less catalyst and time needed for the reaction suggest the absence of intramolecular chelation observed in the CM with allylamine (Section **2.5.2** and **3.4.2**). We were interested to explore, whether the free hydroxyl group plays a role in CM and if its protection would increase the reaction yield. An early attempt with TBS-protected adduct furnished the corresponding CM product in 79% yield. However, one additional reaction was required to remove it prior to lactonization. Therefore, we envisaged the benzyl group as the suitable protecting group, which would be removed in hydrogenation reaction.

4.4.3 Benzyl Group and its Effect

Since direct benzylation of the homoallylamine **129** failed, the benzyl protecting group should be introduced in nucleophilic substitution reaction *via O*-benzylated ethanolamine, which was prepared according to the procedure of Hu and Cassady.[102] The deprotonation of ethanolamine by sodium hydride followed by benzylation furnished the 2-benzyloxyethylamine in 67%, which was readily separated from minor by-products (dibenzylated and *N*-benzylated products) by acid-base extraction. Nucleophilic substitution and *N*-protection in two-phase system[103] led to the homoallylamine **134**. CM with enone **128** under the same reaction conditions gave enone **135** in a slightly lower yield as its unprotected analogue (**Scheme 47)**. Despite a higher yield in benzyloxycarbonylation, the benzyl group did not bring the expected effect in CM. It can be concluded that the free hydroxyl group did not interfere in the CM process.



Scheme 47. Preparation of homoallylamine **134** and its CM result.

4.4.4 Reductive cyclization

Further, we investigated the reductive cyclization reaction. Methanol, an effective solvent for catalytic hydrogenation, is unsuitable in this case, as it yielded in epimerization due to the retro-Michael reaction. A suitable aprotic solvent was required for the reaction. Hydrogenation in THF led only to the hydrogenated double bond with retention of the *N*-Cbz protecting group.[104] Maki *et al*. reported a hydrogenation reaction with various solvents, in which isopropyl ether proved to be as effective as methanol in hydrogenating benzyl ester moiety.[105] We employed the reaction conditions reported by González-Muñiz *et al*. for reductive cyclization of a β-ketoester with 10% Pd/C and 3 bar hydrogen at 40 °C for 7 hours as standard conditions[106] and optimized the reaction time, with the results summarized in **Table 5**.

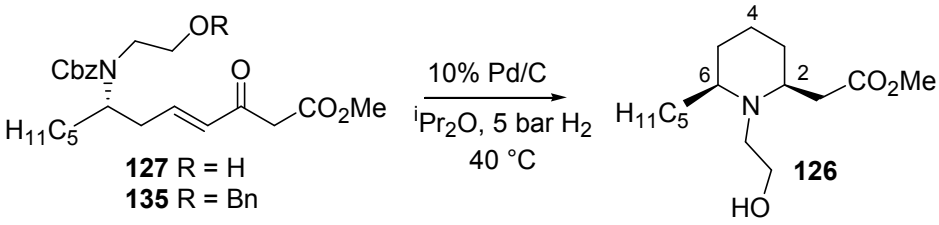


Table 5. Optimization of reductive cyclization.

R	Reaction time	Yield
H	7 h	49% enamine, 4% **126**
H	30.5 h	22% enamine, 44% **126**
H	3 d	60% **126**, 13% calvine
Bn	3 d	30% OBn product, 35% **126**

The reductive cyclization occurred *via* enamine intermediate, which was then reduced to furnish the piperidine. The best results were obtained with 3 days reaction time, which afforded *cis*-2,6-disubstituted piperidine **126** and calvine in 60 and 13% yield, respectively. The spectra and optical rotation of calvine were in agreement to the reported values $[\alpha]_D^{20}$ + 18.3 (*c* 0.35, CH_2Cl_2). [Lit.[79] $[\alpha]_D^{20}$ + 18 (*c* 0.66, CH_2Cl_2)]. Based on this fact, we can conclude that the nucleophilic substitution reaction occurred with complete inversion of the configuration. Reductive cyclization of **135**, on the other hand, yielded partially debenzylated product, which suggests the necessity of longer reaction time and rigorous reaction conditions

to obtain complete debenzylation. The benzyl group in the whole did not bring much advantage to the synthesis.

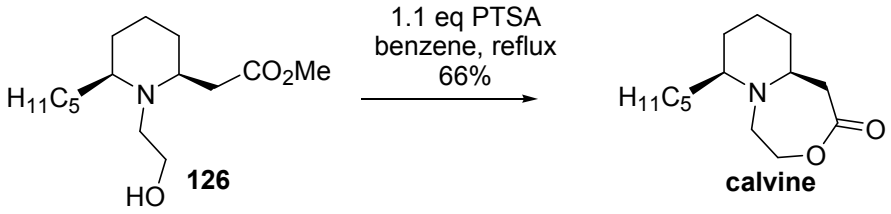
Reductive cyclization gave exclusively *cis*-products, based on their ^{1}H and ^{13}C spectra.[79] The assignment of the 2,6-*cis*-configuration and its *trans*-analogue was inferred from the comparison of the chemical shifts of C-2 and C-6, the signals of these atoms are more shielded in the *trans*- (53.7 and 55.3 ppm) than in the *cis*-product (59.4 and 62.8 ppm). The chemical shift of 2-H and 6-H are 3.10 and 2.55 ppm in *cis*- and 3.42 and 2.75 ppm in *trans*-configuration, respectively.

4.4.5 Lactonization

The lactonization procedure reported by Braekman *et al*. described the treatment of the crude mixture of hydroxyethylation in acetonitrile at 50 °C for 2 hours in the presence of Amberlyst A15 and 4Å molecular sieves. The work-up was done by addition of dilute ammonia and extraction with dichloromethane. The ratio of calvine/alkylation product/double alkylation product was 47.4:16.7:21.6 and after lactonization became 43:0:30.[79]

The first lactonization attempt was conducted with Amberlyst (0.3 g/mmol **126**) and molsieve (25 g/mmol **126**) in degassed anhydrous acetonitrile. After 4 hours TLC control showed the completion of the reaction. However, only 78% conversion and 48% yield of product isolated after work-up and column chromatography. Assuming that the problem might lay in the aqueous work-up, we changed the work-up procedure by adding acetonitrile, saturated with ammonia gas, instead of dilute ammonia to basify the crude mixture and wash the ion exchanger. The modified procedure gave a slight improvement of 76% conversion and 60% yield. We found out later that TLC detected only the substances in solution and not the adduct still attached on Amberlyst surface, which was released later during work-up.

A complete conversion was achieved by treating the piperidine **126** with a slight excess of *p*-toluene sulfonic acid in refluxing benzene, which furnished after 18 hours neat calvine in 66% yield (**Scheme 48**). The procedure is however suitable only for tertiary amine, otherwise lower yields were obtained.[107]



Scheme 48. Lactonization of **126**.

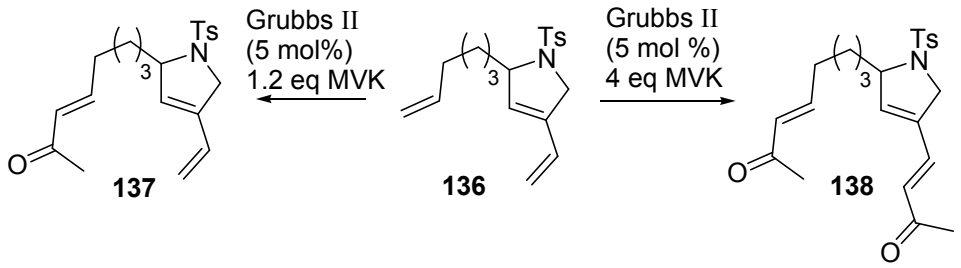
We have performed an enantiospecific synthesis of (+)-calvine in 9 steps starting from (*R*)-epichlorohydrine with an overall yield of 10%. The key strategies included the copper catalyzed oxirane opening, nucleophilic substitution, and CM-reductive cyclization method. Reactions of *O*-benzylated precursors provided quite similar overall yields with those of unprotected analogues.

III CM between Conjugated Dienes and Electron-Deficient Olefins

1. Introduction

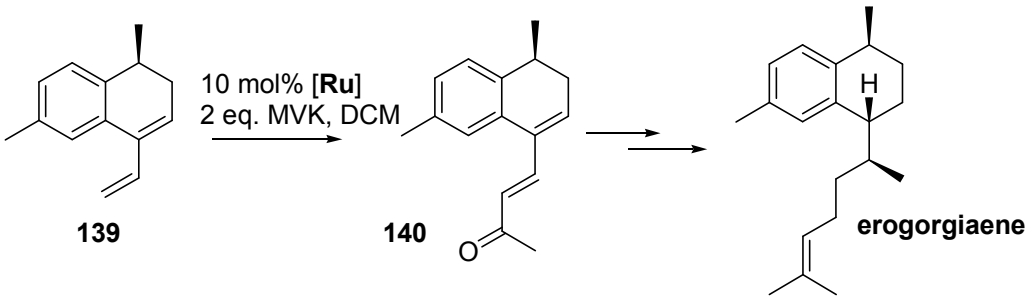
Conjugated dienes appear in a wide array of natural products and are useful synthetic building blocks. Olefin metathesis is a highly potential method to construct substituted conjugated dienes, especially because of its mild reaction conditions and the tolerance of the catalysts against various functional groups. The potential of ring-closing metathesis (RCM) between 1,3-dienes and unconjugated olefins has been recognized for some time and successfully employed in the synthesis of complex natural products.[108] Remarkably, CM reaction involving 1,3-dienes has not been applied extensively.

Our group reported the first example of CM between a 1,3-diene and methyl vinyl ketone (MVK) (**Scheme 49**).[109] Employing 1.2 equivalents MVK, the mono-CM product **137** was obtained and with 4 equivalents MVK the double-CM product **138** was isolated. It showed not only the higher reactivity of unconjugated olefin but also a possibility to differentiate between both types of double bond.



Scheme 49. First example of CM between a 1,3-diene and MVK.

Hoveyda *et al*. reported the application of CM between a conjugated diene and MVK in their synthesis of erogorgiaene, as depicted in **Scheme 50**. Reaction between **139** and MVK yielded the dienone **140**.[110] Snapper *et al*. have also described CM between substituted butadienes and electron-neutral olefins.[111,112]

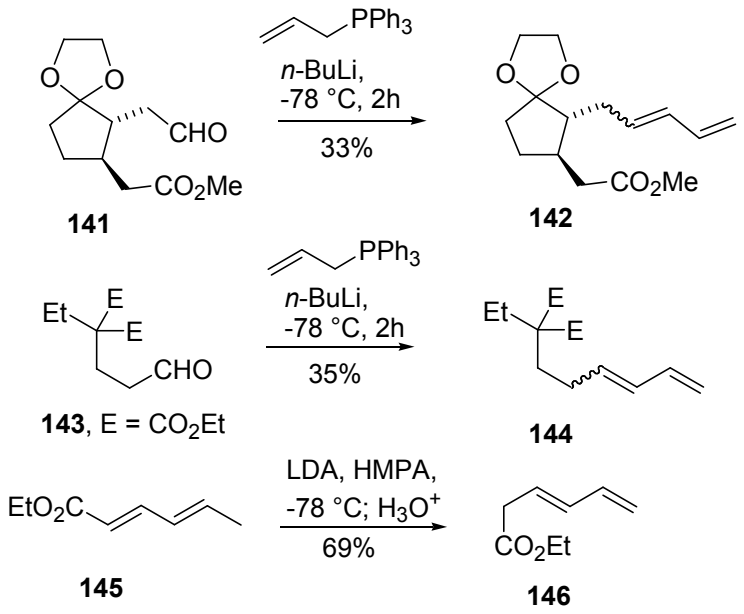


Scheme 50. Application of CM between conjugated diene and methylvinylketone.

Following our earlier work on CM reactions, we were interested in examining the general substrate scope of CM reactions between electron-deficient olefins and 1,3-dienes. As catalyst, we chose [**Ru**] for its superior activity towards electron-deficient olefins (see Chapter I).

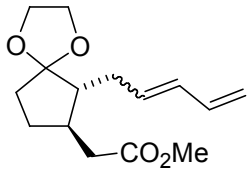
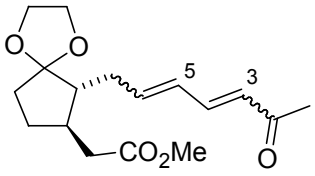
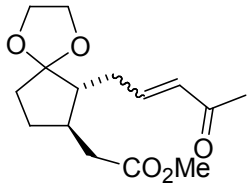
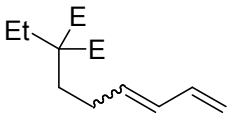
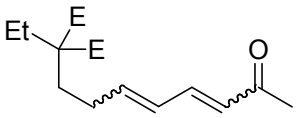
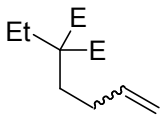
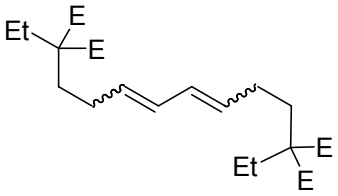
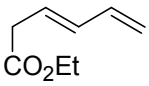
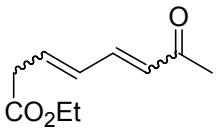
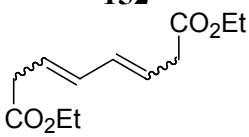
2. Reaction with Monosubstituted Terminal Butadienes

As substrates, three terminal conjugated butadienes **142**, **144**, and **146** were prepared as shown in **Scheme 51**. The reaction of aldehydes **141** and **143** with allyl triphenyl phosphonium bromide and *n*-BuLi gave the dienes **142** and **144** in yields of 33 and 35% as 1:1 *E/Z* mixture. Due to the presence of the ester groups and formation of semi-stabilized ylide, only moderate yields and stereoselectivity were obtained. The preparation of diene **146** was reported by Liu *et al*., which involved the isomerization of ethyl sorbate **145**.[113]



Scheme 51. Preparation of terminal 4-substituted 1,3-butadienes.

Table 6. CM reactions between terminal 4-substituted 1,3-dienes and MVK.

Entry	Substrate	Products	Yield (%)
1	 **142** (*E*/*Z* 1:1)	 **147**  **148**	35 (3*E*,5*E*)/(3*Z*,5*E*)/ (3*E*,5*Z*)/(3*Z*,5*Z*) 4:1:1:1[a] 38 (*E*/*Z*) 1:1[a]
2	 **144**	 **149**  **150**  **151**	38[b] 11 13[b]
3	 **146**	 **152**  **153**	24[b] 9[b]

Conditions: diene (1 equiv), MVK (3 equiv), [**Ru**] 5 mol% in refluxing CH_2Cl_2 (0.05 M) for 3h; [a] Determined by ^{1}H NMR, [b] *E*/*Z* not determined.

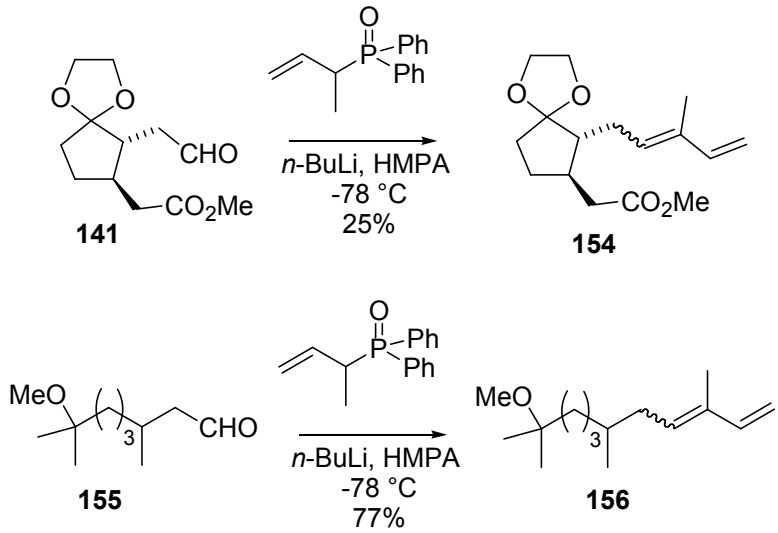
The CM results of butadienes **142**, **144**, and **146** with MVK are summarized in **Table 6**. The reaction was performed in refluxing dichloromethane (0.05 M) for 3 hours, with 3

equivalents MVK and 5 mol% [**Ru**]. The desired dienones **147**, **149**, and **152** were obtained in yields of less than 40%. In contrast to the complete *E*-stereoselectivity of CM of unconjugated alkenes and electron-deficient olefins, the newly formed double bonds were generated with moderate *E*/*Z*-stereoselectivity. In entry 1, for example, diene **142** were converted to a chromatographically inseparable 4:1:1:1 mixture of *E*/*Z*-stereoisomers of dienones **147**. Beside dienones, other products were also isolated, i.e. enone **148** (entry 1), dimers of adduct **151** and **153**, and also mono olefin **150** (entry 2 and 3). These facts indicate that the low yields were mainly due to unselective attack of the catalyst on the 1,3-diene system. The formation of the by-products can be rationalized by cleavage of the diene at the internal double bond. Attempts to optimize the product yield and selectivity by varying the amount of MVK, reaction time or temperature proved unsuccessful.

3. Reaction with 3,4-Disubstituted Terminal Dienes

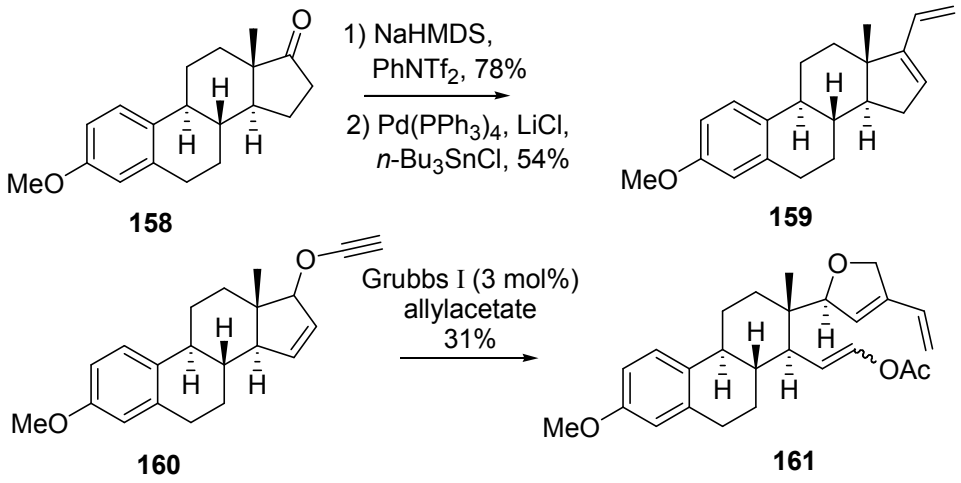
To suppress the competing catalyst attack on the internal double bond, we decided to employ 1,3-dienes with higher substituted internal double bond, which makes it less sterically accessible. Two types of dienes, i.e. acyclic and cyclic dienes, whose internal double bonds are incorporated in ring systems, were prepared and tested.

Wittig-Horner reaction of aldehydes **141** and **155** with lithio(1-methyl-2-propenyl) diphenylphosphine oxide yielded dienes **154** and **156** in 25 and 77% yield, with 4:1 *E*/*Z* selectivity (**Scheme 52**).[114]



Scheme 52. Preparation of acyclic 3,4-disubstituted terminal diene.

The preparation of *N*-tosyl-1-vinyl-2,4-dihydro-2*H*-pyrrole (**157**) was reported by Mori *et al*., which involved an enyne metathesis of *N*-allyl-*N*-prop-2-ynyl-*p*-toluenesulfonamide.[115] The diene **159** was prepared from *O*-methylestrone by Stille cross-coupling reaction,[116] while diene **161** was synthesized by enyne metathesis from the propargyl ether **160**, as outlined in **Scheme 53**.[117]



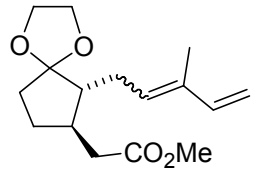
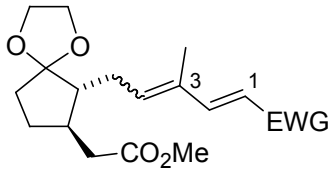
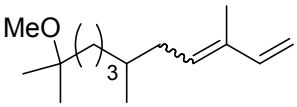
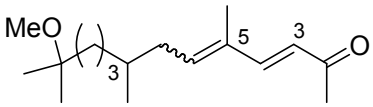
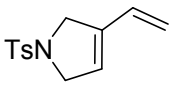
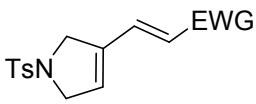
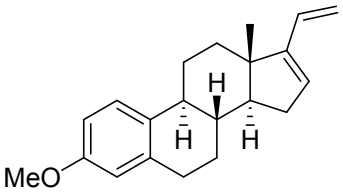
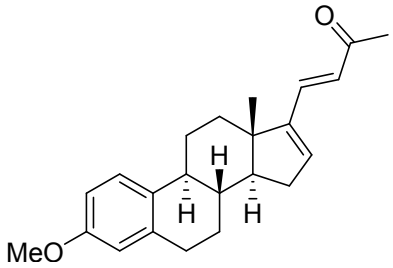
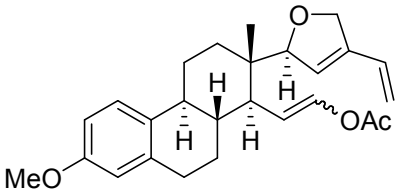
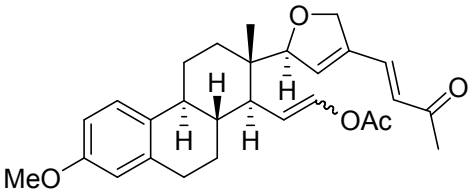
Scheme 53. Preparation of cyclic dienes **159** and **161**.

The CM results of 3,4-disubstituted dienes with MVK and other electron-poor olefins are summarized in **Table 7**. The reactions were conducted under the same conditions as the terminal monosubstituted dienes.

Introducing a substituent to the internal double bond indeed resulted in the expected chemoselectivity in both cyclic and acyclic substrates. The dienones were formed as the only product without the formation of the side product, which derived from the catalyst attack on the internal double bond. Reactions with MVK gave the desired products in moderate to good yields and with high stereoselectivity (*E*/*Z* > 20:1). The moderate yield of dienone **169** even after 24 hours reaction time may be resulted from the steric hindrance of the methyl group.

Whereas moderate yields were obtained with methyl acrylate, the more electron-deficient acrolein and acrylonitrile gave lower yields even at a higher reaction temperature. Instead of the formation of a side product, most of the starting material remained unreacted. Reactions with methyl acrylate and acrolein gave high stereoselectivity, as observed with MVK. Reaction with acrylonitrile, however, gave lower selectivity.

Table 7. CM reactions between terminal 3,4-disubstituted dienes and electron-poor olefins

Entry	Substrate	Product	Yield (%)
1	 **154** (*E*/*Z* 4:1)	 (3*E*/3*Z* 4:1) **162** EWG = COMe **163** EWG = CO_2Me **164** EWG = CHO **165** EWG = CN	 73 37 23 14[a]
2	 **156** (*E*/*Z* 4:1)	 **166** (5*E*/5*Z* 4:1)	77
3	 **157**	 **167** EWG = COMe **168** EWG = CO_2Me	 86 45
4	 **159**	 **169**	39[b]
5	 **161**	 **170**	70

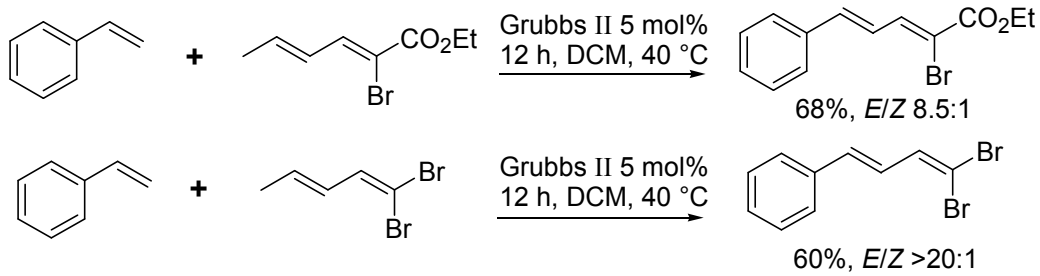
Conditions: diene (1 equiv), MVK (3 equiv), [**Ru**] 5 mol% in refluxing CH_2Cl_2 (0.05 M) for 3h; [a] (1*E*,3*E*)/(1*Z*:3*E*)/(1*E*,3*Z*)/(1*Z*,3*Z*) 4:12:1:3; [b] 24h reaction time.

In summary, we have investigated selective CM reactions between 1,3-dienes and electron-deficient olefins. High yield of the desired products is achieved only if the internal double bond is sterically congested, thus protected from catalyst attack. Methyl vinyl ketone proved to be the most effective coupling partner. With the exception of acrylonitrile, the products are provided with complete *E*-selectivity. Taking the well-known high functional group tolerance

of the Ru-catalysts into account, this reaction provides a valuable alternative for the preparation of dienones to existing methods, such as the Horner-Wadsworth-Emmons reaction, especially for base-sensitive substrates.

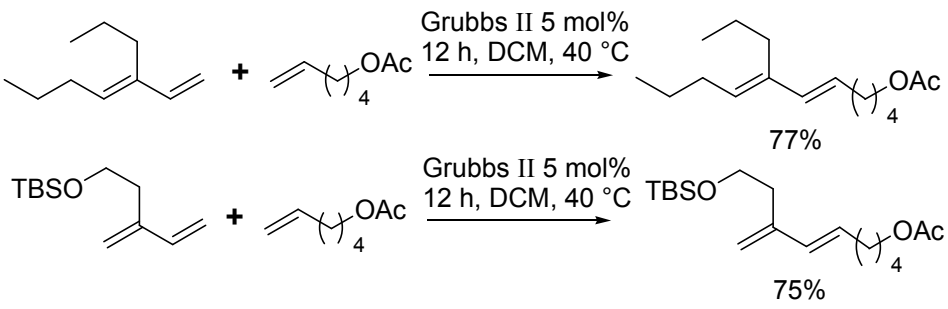
4. Addendum

Recently, Grubbs *et al*. reported further studies of CM reactions between substituted conjugated dienes and various olefins.[118] Similar to our observation, they also found out that the internal double bond should be electronically deactivated or sterically protected in order to obtain high chemo- and stereoselectivity. Two electron withdrawing groups (ethyl ester-bromine or dibromo groups) attached to the internal double bond reduce its electron density and increase the steric hindrance to give the products in moderate to good stereoselectivity and yields (**Scheme 54**).



Scheme 54. CM of electron-deficient dienes with styrene.

The steric hindrance, however, offers more efficient protection of the internal double bond. This was observed in CM of 1,2-disubstituted- and 2-substituted conjugated dienes with various olefins, which resulted in higher yields and stereoselectivity (**Scheme 55**).

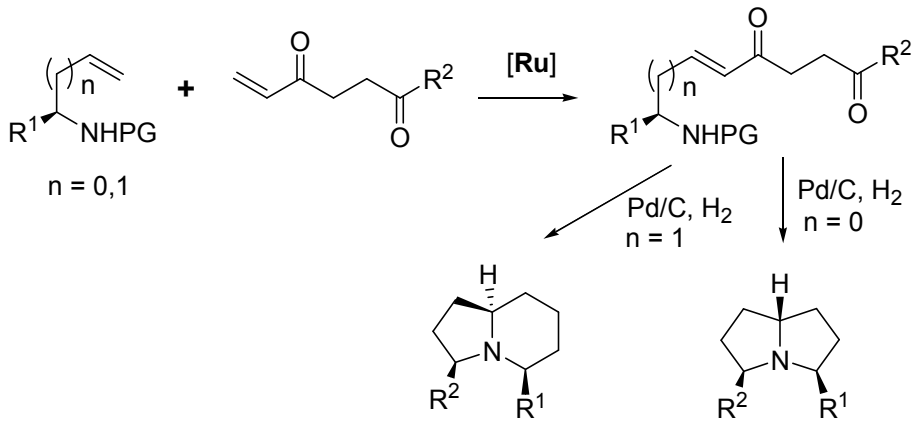


Scheme 55. CM of substituted butadienes.

These results, together with ours, showed that the protection of the internal double bond of conjugated dienes provide CM products in high chemo- and stereoselectivity. The comprehension of this method thus allows its application in the synthesis of complex molecules.

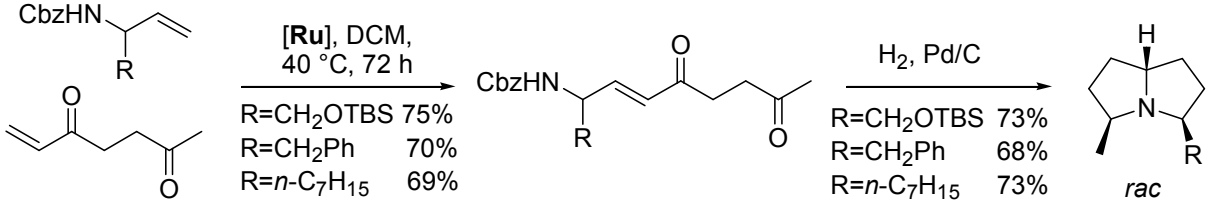
IV Summary

The highly stereoselective cross metathesis of allyl- or homoallylamines with enones or enediones combined with diastereoselective reductive amination provides an efficient method for preparing *N*-heterocycles, as summarized in **Scheme 56**.



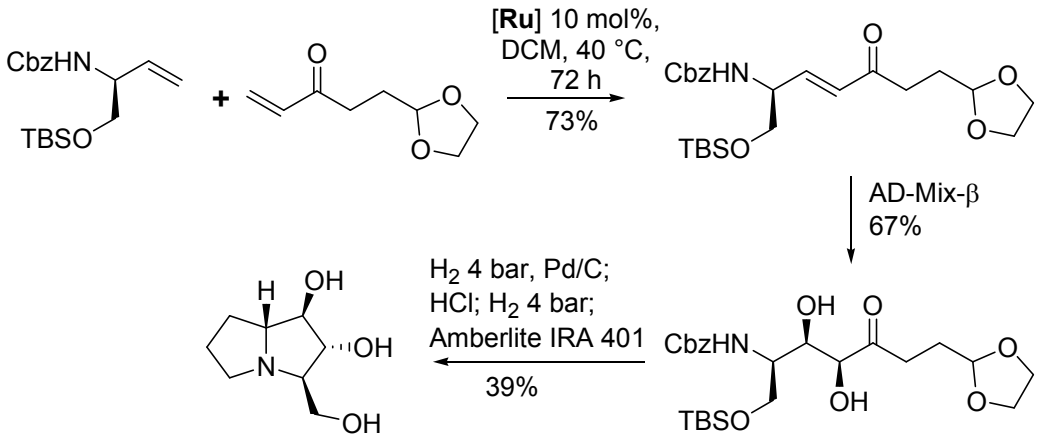
Scheme 56. Cross metathesis-reductive cyclization method.

The successful application of this strategy in the syntheses of piperidines and indolizidines motivated us to apply it in the synthesis of pyrrolizidines. This method was first applied to synthesize several 3,5-disubstituted pyrrolizidines, including xenovenine, as described in the first part of this work (**Scheme 57**). Due to the intramolecular chelation of ruthenium by the carbonyl oxygen of Cbz group, the CM was slow and required a higher amount of catalyst (10 mol%). The double reductive cyclization of enone gave the less strained *cis*-fused pyrrolizidines, as determined by NMR and IR spectra. Starting from simple, easily accessible allylamines and enones, the products can be obtained in 2 steps with an overall yield of 48-55%.



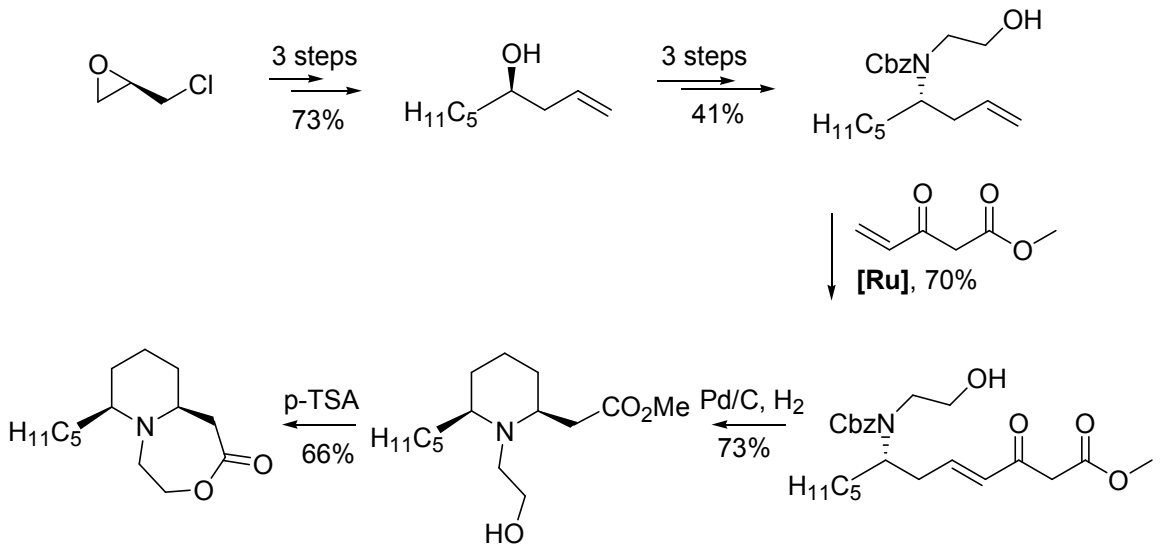
Scheme 57. Syntheses of 3,5-disubstituted pyrrolizidines.

The double bond obtained from the CM can be used to introduce various functional groups into the molecule. This concept was applied in the synthesis of (+)-hyacinthacine A_2 (**Scheme 58**). CM reaction gave exclusively *E*-product, which was advantageous for the following Sharpless asymmetric dihydroxylation. Utilizing AD-Mix-β, the matched product was obtained with high diastereoselectivity. The diol may hinder the double reductive cyclization, thus a sequential reaction was needed. (+)-Hyacinthacine A_2 was obtained exclusively in 6 steps, starting from (-)-*N*-Cbz vinyl glycine with an overall yield of 12%, as determined by nOe experiment and optical rotation.



Scheme 58. Synthesis of (+)-hyacinthacine A_2.

The third part of the work described the synthesis of (+)-calvine (**Scheme 59**). The homoallylalcohol was prepared in 3 steps from (*R*)-epichlorohydrine by copper catalyzed oxirane ring opening reaction. The nucleophilic substitution by aminoethanol occurred with complete inversion of the configuration. The absence of internal chelation in CM resulted in shorter reaction time and less catalyst required. Hydrogenation with isopropylether as solvent furnished the piperidine, which lactonized under acidic conditions to give (+)-calvine.



Scheme 59. Synthesis of (+)-calvine.

Further, the CM reaction between conjugated dienes and electron-deficient olefins was studied. Due to unselective catalyst attack on the monosubstituted conjugated dienes, a complex mixture of product, dimer of starting material, mono olefin, and enone were obtained. By introducing a substituent to the internal double bond as steric "protection", high yields and stereoselectivity were obtained with both acyclic and cyclic substrates. Methyl vinyl ketone proved to be the most suitable CM partner, whereas the more electron-deficient methyl acrylate, acrolein, and acrylonitrile gave lower yields.

V Experimental Section

1. Material and Method

Materials, unless otherwise specified, were purchased from commercial suppliers and used without further purification. (*R*)-Epichlorohydrine was donated by Daisho Ltd. All solvents were distilled prior to use. Ruthenium catalyst was prepared according to a published procedure[5a]. All reactions involving organometallic reagents were conducted under nitrogen atmosphere, with solvents in p.a. or absolute quality, except tetrahydrofuran, diethyl ether and dichloromethane, which were freshly distilled under anhydrous condition.

^{1}H NMR spectra were recorded on an AC 200 (200 MHz), AM 400 (400 MHz) or DRX 500 (500 MHz) spectrometer from *Bruker* in $CDCl_3$ or D_2O. Chemical shifts are reported in part per million (ppm) relative to the internal solvent peak. Multiplicities are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), or a suitable combination.

^{13}C NMR spectra were recorded on AC 200 (50 MHz) and DRX 500 (125.8 MHz) in $CDCl_3$ or D_2O. The number of directly bound protons was determined by DEPT spectra.

2D NMR spectra were recorded on DRX 500 (500 MHz).

IR spectra were recorded as ATR (Attenuated Total Reflectance) on a *Perkin-Elmer* 881 spectrometer. The bands are given in wave number (cm^{-1}) with intensities as abbreviated: vs (very strong), s (strong), m (medium), and w (weak).

MS and **HRMS** spectra were recorded on a *Finnigan* MAT 95 SQ or *Varian* MAT 711 and measured by EI (electron ionization) method at 70 eV and FAB (fast atom bombardment).

GC-MS spectra were recorded on a GC HP 5890 II, with a glass capillary column HP-1 (25 m, ID 0.25 mm, film thickness 0.3 mm) and MSD HP 5971 A detector from *Hewlett-Packard* with helium as carrier gas. The injection temperature was 250 °C and the detection temperature 280 °C.

Melting points were determined on a melting point microscope *Leica Galen* with control module from *Wagner Munz*. The values are not corrected.

Elemental micro analyses were conducted using an Elementar Vario EI from *Analytik Jena*.

Optical rotations were recorded on a *Perkin-Elmer* 341 polarimeter at 20 °C, with sodium-D-line of 589 nm, and are given as $[\alpha]_D$ (concentration in grams/100 mL of solvent).

Metathesis reactions with air labile catalysts were conducted in an inert gas box MB 120 GB from *MBraun* under nitrogen atmosphere.

Thin layer chromatography (TLC) was carried out on silica gel 60 F_{254} precoated plates (0.2 mm thickness) with fluorescent indicator. Components were detected by visualization under a UV lamp (254 nm) and/or using potassium permanganate reagent (2.5% $KMnO_4$ in 5% $NaHCO_3$ aqueous solution) or iodine chamber.

Preparative thin layer chromatography was carried out on a Silica-rapid-plates (F_{254}, 20x20 cm, 60 A) from *ICN Biomedicals*.

Column chromatography was performed with silica gel (40-63 μm) or in some cases with aluminium oxide basic grade III (contained 6% water).

The chemical names of the synthesized compounds were generated by *Beilstein* AutoNom programme version 4.0, which is in accordance with *Beilstein* nomenclature. In some cases, the numbers given in the figures correspond only to the NMR spectra and not to the generated name.

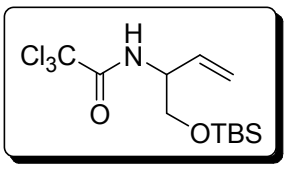
2 Procedures and Spectrometric Data

2.1 Compounds in Chapter II.2

General Procedure A: Cross metathesis reaction between allyl amine and enone
Ru-catalyst (10 mol %) was added to a solution of both coupling partners (1:1) in dry CH_2Cl_2 (0.05 M) under a nitrogen atmosphere in a carousel reaction station. The mixture was then refluxed for 3 d. The solvent was evaporated and the residue was purified by column chromatography (SiO_2, cyclohexane/ethyl acetate 3:1) to give the product.

General procedure B: Double reductive amination
Carbamate in methanol was hydrogenated at 1 atm over 10% Pd/C for 3 d. After filtration over celite, the solvent was evaporated and the residue was purified by column chromatography to furnish the product.

***N*-[1-(*tert*-Butyl-dimethyl-silanyoxymethyl)-allyl]-2,2,2,-trichloroacetamide**



To a solution of trichloro-oxoethylaminebutenol **51** (477 mg, 2 mmol) in dry DMF (5 mL), TBDMSCl (379 mg, 2.5 mmol) was added and the mixture was stirred at 0 °C for 10 min. Imidazole (350 mg, 5.1 mmol) was then added portionsweise. The reaction mixture was stirred at 0 °C for 30 min and at rt for 19 h. MTBE and 10% aqueous solution of $NaHCO_3$ were added and the layers were separated. The aqueous layer was extracted with MTBE (1 x 10 mL), the combined organic layers were dried over $MgSO_4$ and evaporated. Purification was done by column chromatography (SiO_2, cyclohexane/ethyl acetate 30:1) to furnish the TBS ether (536 mg, 75 %) as a clear oil.

R_f : 0.62 (SiO_2, cyclohexane/ethyl acetate 3:2)

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 0.05 (s, 6H, $SiMe_2$), 0.90 (s, 9H, *t*-Bu), 3.76 (dq, *J* = 10 and 3 Hz, 2H, C*H*$_2$O), 4.44 (br s, 1H, C*H*-N), 5.23 (d, *J* = 5 Hz, 1H, C*H*$_2$=CH), 5.30 (d, *J* = 12 Hz, 1H, C*H*$_2$=CH), 5.72-5.93 (m, 1H, C*H*=CH$_2$), 7.16 (br s, 1H, N*H*).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = -5.67 ($SiMe_2$), 17.99 (Si-*C*), 25.59 ((*C*H$_3$)$_3$C), 54.38 (*C*HN), 64.01 (*C*H$_2$O), 92.64 (*C*Cl$_3$), 117.12 (*C*H$_2$=CH), 134.05 (CH$_2$=*C*H), 161.04 (C=O).

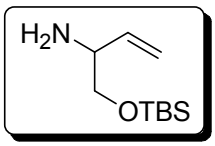
IR (ATR): υ (cm^{-1}) = 3421 (w), 3344 (w), 3088 (w), 2955 (m), 2929 (m), 2896 (m), 2885 (m), 2858 (m), 1721 (s), 1502 (s), 1472 (m), 1464 (m), 1362 (w), 1257 (s), 1114 (s), 1005 (m), 991 (m), 927 (m), 881 (m), 836 (vs), 778 (s).

MS (EI, 50 °C): m/z (%) = 346 ([M^+], <1%), 330 (2), 315 (1), 290 (76), 288 (75), 253 (4), 230 (1), 228 (13), 222 (16), 220 (44), 222 (46), 200 (1), 191 (7), 163 (7), 145 (8), 127 (40), 115 (15), 100 (9), 95 (15), 93 (38), 89 (69), 73 (100).

HRMS (M^+-CH_3, $C_{11}H_{19}Cl_3O_2NSi$): calcd: 330.0251, found: 330.0251.

CHN-Analytic ($C_{12}H_{22}Cl_3NO_2Si$): calcd. C 41.57, H 6.40, N 4.04.
found C 41.65, H 6.36, N 4.08.

1-(*tert*-Butyl-dimethyl-silanyoxymethyl)-allylamine



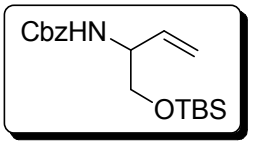
To a solution of KOH (0.5 g) in 2-propanol (5 mL), TBS-ether was added dropwise. The mixture was stirred at rt for 6 h and evaporated. The residue was diluted with water and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to give neat allyl amine (239 mg, 82 %) as a yellow oil.

R_f : 0.12 (SiO_2, cyclohexane/ethyl acetate 3:2).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = -0.02-0.10 (m, 6H, $SiMe_2$), 0.79-0.93 (m, 9H, *t*-Bu), 1.69 (br s, 2H, NH_2), 3.28-3.45 (m, 1H, CH_2O), 3.78 (dd, *J* = 3 and 7 Hz, 1H, C*H*N), 5.05 (td, *J* = 12 and 2 Hz, 1H, CH_2=CH), 5.18 (td, *J* = 16 and 2 Hz, 1H, CH_2=CH), 5.67-5.86 (m, 1H, C*H*=CH_2).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = -5.55 ($SiMe_2$), 18.10 (Si-*C*), 25.59 ((CH_3)$_3$C), 55.67 (*C*HN), 67.68 (*C*H_2O), 114.89 (*C*H_2=CH), 139.07 (CH_2=*C*H).

[1-(*tert*-Butyl-dimethyl-silanyoxymethyl)allyl]-carbamic acid benzyl ester (44)



To a solution of allyl amine (774 mg, 3.8 mmol) in CH_2Cl_2 (33 mL) K_2CO_3 (1.6 g, 11.6 mmol) and benzyl chloroformate (0.60 mL, 4.2 mmol) were added at 0 °C. After 1.5 h stirring at the same temperature,

the mixture was filtrated and evaporated. Purification was done with column chromatography (SiO_2, cyclohexane/ethyl acetate 30:1) to yield **44** (900 mg, 70 %) as a yellow solid.

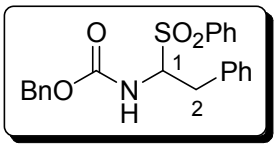
R_f : 0.15 (SiO_2, cyclohexane/ethyl acetate 3:2).

mp : 60-61 °C (Lit.[48] 59-61 °C).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 0.08 (s, 6H, $SiMe_2$), 0.90 (s, 9H, *t*-Bu), 3.55-3.80 (m, 2H, C*H*$_2$O), 4.25 (br s, 1H, C*H*N), 5.10 (s, 2H, C*H*$_2$Ph), 5.10 (m, 1H, C*H*$_2$CH), 45.23 (d, *J* = 17 Hz, 1H, C*H*$_2$=CH), 5.75-6.95 (m, 1H, CH_2=C*H*), 7.45 (m, 5H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = -5.58 ($SiMe_2$), 18.15 (Si-*C*), 25.70 ((*C*H_3)$_3$C), 54.64 (*C*HN), 65.07 (*C*H_2O), 66.58 (*C*H_2Ar), 115.78 (*C*H_2=CH), 128.36 (Ar), 128.36 (Ar), 136.05 (CH_2=*C*H), 136.43 (Ar), 155.77 (CO).

(1-Benzenesulfonyl-2-phenyl-ethyl)-carbamic acid benzyl ester (55)



Carbamate **52** (756 mg, 5 mmol) was dissolved in THF (2 mL), then water (5 mL), sodium phenylsulfinate (837 mg, 5 mmol), phenyl acetaldehyde **53** (649 mg, 5.4 mmol) and formic acid (1.2 mL) were added subsequently. The mixture was stirred at rt for 20 h. The resulting white precipitate was filtered and purified by crystallization (cyclohexane/ethyl acetate 3:1) to give **55** (1.33 g, 67%) as colorless needles.

mp : 126-127 °C.

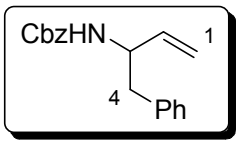
^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 3.00 (dd, *J* = 15 and 10 Hz, 1H, H-2), 3.62 (dd, *J* = 15 and 3 Hz, 1H, H-2), 4.73 (s, 2H, OC*H*$_2$Ar), 5.07-5.34 (m, 2H, H-1, NH), 7.00-7.96 (m, 15H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 32.37 (C-2), 66.99 (O*C*H_2Ar), 71.95 (C-1), 127.14, 127.79, 128.08, 128.33, 128.65, 128.92, 129.11, 129.15, 134.00, 134.50, 135.55, 136.26 (Ar), 154.58 (*C*OO).

IR (ATR): υ (cm^{-1}) = 3318 (m), 3089 (w), 3063 (w), 3032 (w), 2961 (w), 1729 (s), 1709 (s), 1603 (w), 1585 (w), 1528 (s), 1497 (m), 1455 (m), 1447 (s), 1396 (w), 1307 (vs), 1254 (s), 1230 (s), 1143 (vs), 1081 (s), 1045 (m), 1027 (m), 1002 (w), 740 (s), 696 (s), 688 (s).

MS (EI, 180 °C): m/z (%) = 355 (6), 327 (1), 264 ([M^+-SO_2Ph], 14), 220 (12), 209 (14), 191 (1), 167 (1), 142 (3), 118 (5), 91 (100).

***N*-(Benzyloxycarbonyl)-amino-1-phenylbut-3-ene (45)**



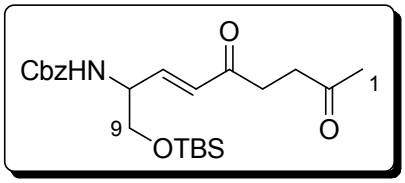
Sulfone **55** (0.7 g, 1.8 mmol) was dissolved in anhydrous THF (10 mL) and the solution was cooled to -20 °C. Vinyl magnesium bromide (3.54 mL, 3.5 mmol, 1M in THF) was added dropwise over 10 min. After 30 min stirring at -20 °C, the mixture was slowly warmed to 0 °C (3 h). Saturated aqueous NH_4Cl solution (3 mL) was added and the mixture was extracted with diethylether (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. Purification was done with column chromatography (cyclohexane/ethyl acetate 15:1) to furnish the allyl amine **45** (338 mg, 68%) as a clear oil.

R_f : 0.2 (SiO_2, cyclohexane/ethyl acetate 9:1).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 2.86 (d, *J* = 6 Hz, 2H, H-4), 4.42-4.59 (m, 1H, H-3), 4.61-4.80 (m, 1H, NH), 5.09 (s, 2H, PhC*H*$_2$O), 5.15 (dd, *J* = 6 and 1 Hz, 2H, H-1), 5.82 (ddd, *J* = 16, 10, and 5 Hz, 1H, H-2), 7.10-7.40 (m, 10 H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 41.21 (C-4), 53.92 (C-3), 66.57 (Ph*C*H$_2$O), 114.98 (C-1), 126.50, 127.93, 127.97, 128.29, 128.39, 129.41, 136.40, 136.99 (Ar), 137.60 (C-2), 155.58 (*C*OO).

[(*E*)-1-(*tert*-Butyl-dimethylsilanyloxymethyl)-4,7-dioxo-oct-2-enyl]-carbamic acid benzyl ester (42a)



Following the general procedure A, allyl amine **44** (63 mg, 0.19 mmol), enone **43** (26 mg, 0.20 mmol), and [**Ru**] (12 mg, 20 μmol) in CH_2Cl_2 (3.8 mL) were employed to afford after purification the enedione **42a** (61 mg, 75%) as a yellow oil.

R_f : 0.2 (SiO_2, cyclohexane/ethyl acetate 3:2).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 0.04 (s, 6H, $SiMe_2$), 0.84 (s, 9H, *t*-Bu), 2.20 (s, 3H, H-1), 2.69-2.90 (m, 4H, H-3, 4), 3.66-3.82 (m, 2H, H-9), 4.43 (br s, 1H, H-8), 5.11 (s, 2H, C*H*$_2$Ph), 5.20 (br s, 1H, NH), 6.25 (dd, *J* = 17 and 2 Hz, 1H, H-6), 6.78 (dd, *J* = 17 and 3 Hz, 1H, H-7), 7.38 (s, 5H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = -5.63 ($SiMe_2$), 18.10 (Si-*C*), 25.64 ((*C*H$_3$)$_3$C), 29.80 (C-1), 33.93, 36.63 (C-3, 4), 53.55 (C-8), 64.40 (C-9), 66.92 (*C*H$_2$Ph), 128.06, 128.09 (Ar), 129.76 (C-6), 136.08 (Ar), 143.69 (C-7), 155.58 (*C*OO), 197.76 (C-5), 206.82 (C-2).

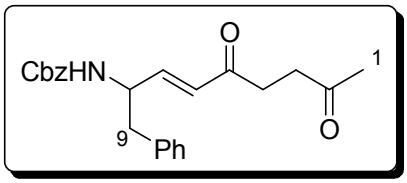
IR (ATR): υ (cm^{-1}) = 3445 (w), 3334 (w), 3066 (w), 3034 (w), 2954 (m), 2929 (m), 2900 (m), 2857 (m), 1718 (vs), 1701 (vs), 1678 (s), 1636 (m), 1525 (s), 1464 (m), 1399 (m), 1361 (m), 1253 (s), 1108 (s), 1051 (m), 980 (m), 838 (s), 777 (s), 697 (m).

MS (EI, 150 °C): m/z (%) = 433 ([M^+], 1%), 403 (2), 376 (11), 332 (4), 284 (2), 268 (1), 240 (4), 208 (2), 170 (1), 115 (4), 99 (2), 91 (100), 73 (15).

HRMS (M^+, $C_{23}H_{35}O_5NSi$): calcd: 433.2284, found: 433.2288.

CHN-Analytic ($C_{23}H_{35}NO_5Si$): calcd. C 63.71, H 8.14, N 3.23.
found C 63.35, H 7.95, N 3.11.

[(*E*)-1-Benzyl-4,7-dioxo-oct-2-enyl]-carbamic acid benzyl ester (42b)



Following the general procedure A, allyl amine **45** (52 mg, 0.18 mmol), enone **43** (24 mg, 0.19 mmol), and [**Ru**] (12 mg, 20 μmol) in CH_2Cl_2 (3.7 mL) were employed to give after purification the enedione **42b** (49 mg, 70%) as a light yellow solid.

R_f : 0.1 (SiO_2, cyclohexane/ethyl acetate 3:2).

mp : 90 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 2.20 (s, 3H, H-1), 2.54-3.00 (m, 6H, H-3, 4, 9), 4.69 (br s, 1H, H-8), 4.71 (br s, 1H, NH), 5.04 (s, 2H, OCH_2Ph), 6.13 (dd, *J* = 16 and 2 Hz, 1H, H-6), 6.79 (dd, *J* = 16 and 5 Hz, 1H, H-7), 7.06-7.42 (m, 10H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 29.82 (C-1), 34.05 (C-3), 36.64 (C-4), 40.54 (C-9), 52.89 (C-8), 66.78 (O*C*H_2Ph), 126.86 (C-6), 127.94, 128.06, 128.39, 128.53, 128.70, 129.20, 136.02, 136.10 (Ar), 145.09 (C-7), 155.43 (*C*OO), 197.94 (C-5), 207.00 (C-2).

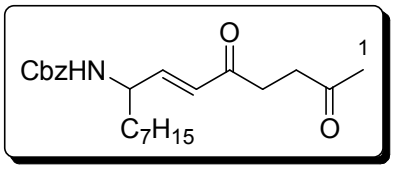
IR (ATR): υ (cm^{-1}) = 3325 (w), 3062 (w), 3030 (w), 2920 (w), 2856 (w), 1712 (vs), 1696 (vs), 1675 (s), 1632 (m), 1604 (w), 1522 (s), 1497 (s), 1454 (m), 1398 (m), 1357 (m), 1239 (s), 1161 (m), 1084 (m), 1027 (s), 977 (m), 745 (s), 698 (vs).

MS (EI, 175 °C): m/z (%) = 379 ([M^+], 1%), 288 (10), 270 (8), 244 (6), 236 (2), 99 (2), 92 (6), 91 (100).

HRMS (M^+, $C_{23}H_{25}NO_4$): calcd: 379.1784, found: 379.1788.

CHN-Analytic ($C_{23}H_{25}NO_4$): calcd. C 72.81, H 6.64, N 3.69.
found C 72.46, H 6.86, N 3.22.

[(*E*)-1-Heptyl-4,7-dioxo-oct-2-enyl]-carbamic acid benzyl ester (42c)



Following the general procedure A, allyl amine **46** (40 mg, 0.14 mmol), enone **43** (18 mg, 0.14 mmol), and [**Ru**] (9 mg, 14 μmol) in CH_2Cl_2 (2.5 mL) were employed to furnish after purification the enedione **42c** (37 mg, 69%) as a clear oil.

R_f : 0.12 (SiO_2, cyclohexane/ethyl acetate 3:2).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 0.86 (t, *J* = 7 Hz, 3H, H-15), 1.25 (br s, 12H, H-9-14), 2.20 (s, 3H, H-1), 2.69-2.90 (m, 4H, H-3, 4), 4.24-4.41 (m, 1H, H-8), 4.67-4.79 (m, 1H, NH), 5.11 (s, 2H, CH_2Ph), 6.18 (d, *J* = 16 Hz, 1H, H-6), 6.72 (dd, *J* = 16 and 6 Hz, 1H, H-7), 7.34 (s, 5H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 13.93 (C-15), 22.45 (C-14), 25.53 (C-13), 28.94 (C-12), 29.08 (C-11), 29.85 (C-1), 31.56 (C-10), 34.00 (C-3), 34.35 (C-9), 36.63 (C-4), 52.00 (C-8), 66.78 (*C*H_2Ph), 127.98 (C-6), 128.27, 128.41, 136.14 (Ar), 146.15 (C-7), 155.61 (*C*OO), 198.15 (C-5), 207.12 (C-2).

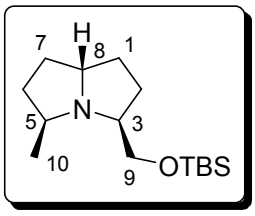
IR (ATR): υ (cm^{-1}) = 3327 (m), 3090 (w), 3065 (w), 3034 (w), 2954 (m), 2927 (s), 2856 (m), 1716 (vs), 1698 (vs), 1677 (s), 1633 (m), 1527 (s), 1455 (m), 1398 (m), 1359 (s), 1307 (m), 1235 (s), 1161 (m), 1108 (m), 1044 (m), 1028 (m), 979 (m), 776 (w), 753 (m), 738 (m), 698 (s).

MS (EI, 100 °C): m/z (%) = 387 ([M^+], 4%), 344 (<1), 296 (3), 288 (9), 252 (5), 244 (10), 238 (6), 215 (3), 194 (1), 99 (7), 91 (100).

HRMS (M^+, $C_{23}H_{33}NO_4$): calcd: 387.2410, found: 387.2420.

CHN-Analytic ($C_{23}H_{33}NO_4$): calcd. C 71.29, H 8.58, N 3.61.
found C 71.17, H 8.72, N 3.47.

3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-5-methyl-hexahydro-pyrrolizine (39)



Following the general procedure B, enedione **42a** (86 mg, 0.18 mmol) and Pd/C (10 mg, 10 μmol) in methanol (3.5 mL) were employed to afford after 3 d and column chromatography (Al_2O_3, CH_2Cl_2/cyclohexane 1:1) the pyrrolizidine **39** (35 mg, 73%) as a clear oil.

R_f : 0.08 (SiO_2, cyclohexane/ethyl acetate 3:2).

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.04 (s, 6H, $SiMe_2$), 0.87 (s, 9H, *t*-Bu), 1.07 (d, *J* = 7 Hz, 3H, H-10), 1.35-1.64 and 1.86-2.07 (m, 8H, H-1, 2, 6, 7), 2.83 (heptet, *J* = 7 Hz, 2H, H-3, 5), 3.35 (t, *J* = 9 Hz, 1H, H-9), 3.57 (quintet, *J* = 7 Hz, 1H, H-9), 3.63 (dd, *J* = 6 and 10 Hz, 1H, H-8).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = -5.20 ($SiMe_2$), 18.42 (Si-*C*), 21.81 (C-10), 26.04 ((*C*H_3)$_3$C), 29.77 (C-2 or 6), 31.71, 31.74 (C-1, 7), 34.61 (C-2 or 6), 62.17 (C-5), 65.53 (C-8), 67.57 (C-9), 67.72 (C-3).

IR (ATR): υ (cm^{-1}) = 3319 (w), 2954 (s), 2928 (vs), 2856 (s), 1715 (m), 1646 (w), 1564 (w), 1472 (m), 1463 (m), 1388 (w), 1361 (m), 1255 (s), 1108 (s), 836 (vs), 776 (s).

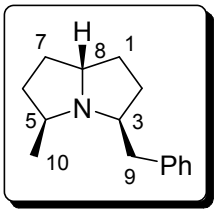
MS (EI, rt): m/z (%) = 269 ([M^+], <1%), 254 (2), 226 (1), 212 (4), 201 (<1), 182 (<1), 168 (<1), 156 (1), 138 (2), 125 (9), 124 (100), 108 (1), 94 (1), 81 (4), 73 (6).

HRMS (M^+, $C_{15}H_{31}NOSi$): calcd: 269.2175, found: 269.2175.

GC-MS retention time 19.05 min.

CHN-Analytic ($C_{15}H_{31}NOSi$): calcd. C 66.85, H 11.59, N 5.19.
found C 66.84, H 11.33, N 4.67.

3-Benzyl-5-methyl-hexahydro-pyrrolizine (40)



Following the general procedure B, enedione **42b** (65 mg, 0.17 mmol) and Pd/C (10 mg, 10 μmol) in methanol (3.4 mL) were employed to give after column chromatography (Al_2O_3, CH_2Cl_2/pentane 2:1) the pyrrolizidine **40** (25 mg, 68%) as a yellow oil.

R_f : 0.04 (SiO_2, cyclohexane/ethyl acetate 3:2).

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.10 (s, 3H, H-10), 1.25-1.60 and 1.74-2.01 (m, 8H, H-1, 2, 6, 7), 2.54 (dd, *J* = 10 and 13 Hz, 1H, H-9), 2.76 (sextet, *J* = 5 Hz, 1H, H-5), 2.85-2.92 (m, 1H, H-3), 2.95 (dd, *J* = 13 and 5 Hz, 1H, H-9), 3.67 (quintet, *J* = 7 Hz, 1H, H-8), 7.14-7.31 (m, 5H, Ar).

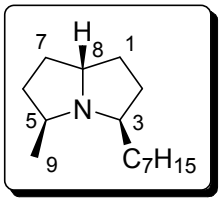
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 22.04 (C-10), 31.95 (C-1, 7), 32.36, 34.48 (C-2, 6), 43.69 (C-9), 61.77 (C-5), 65.31 (C-8), 68.57 (C-3), 125.92, 128.25, 129.23, 140.49 (Ar).

IR (ATR): υ (cm^{-1}) = 3084 (w), 3062 (w), 3026 (w), 2954 (s), 2924 (vs), 2855 (s), 1721 (w), 1691 (w), 1663 (w), 1603 (w), 1594 (w), 1496 (w), 1454 (m), 1375 (m), 1310 (w), 1288 (w), 1187 (w), 1163 (w), 1117 (w), 1091 (w), 1031 (w), 742 (w), 699 (m).

MS (EI, 50 °C): m/z (%) = 214 ([M^+-H], 1%), 200 (1), 186 (1), 169 (1), 162 (1), 151 (1), 142 (1), 131 (1), 125 (7), 124 (100), 108 (1), 91 (4), 82 (2), 81 (6).

HRMS (M^+-H, $C_{15}H_{20}N$): calcd: 214.1596, found: 214.1601.

3-Heptyl-5-methyl-hexahydro-pyrrolizine ((±)-xenovenine) (41)



Following the general procedure B, enedione **42c** (67 mg, 0.17 mmol) and Pd/C (13 mg, 12 μmol) in methanol (3.5 mL) were employed to yield after column chromatography (Al_2O_3, CH_2Cl_2/cyclohexane 1:1) xenovenine (28 mg, 73%) as a clear oil.

R_f : 0.05 (SiO_2, cyclohexane/ethyl acetate 3:2).

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.85 (t, *J* = 7 Hz, 3H, H-16), 1.08 (d, *J* = 8 Hz, 3H, H-9), 1.24 (br s, 12H, H-10-15), 1.35-1.57 and 1.86-1.99 (m, 8H, H-1, 2, 6, 7), 2.60 (quintet, *J* = 6 Hz, 1H, H-3), 2.75 (sextet, *J* = 6 Hz, 1H, H-5), 3.56 (quintet, *J* = 7 Hz, 1H, H-8).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 14.15 (C-16), 22.03 (C-9), 22.72 (C-15), 27.32 (C-14), 29.41 (C-13), 29.95 (C-12), 31.79 (C-11), 31.93 (C-10), 32.17, 32.49, 34.51, 37.23 (C-1, 2, 6, 7), 61.72 (C-5), 65.01 (C-8), 66.69 (C-3).

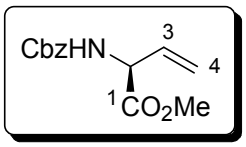
IR (ATR): υ (cm^{-1}) = 2954 (vs), 2924 (vs), 2856 (s), 1721 (w), 1457 (m), 1374 (m), 1354 (w), 1311 (w), 1180 (w), 1155 (w), 1132 (w), 1104 (m), 723 (w).

MS (EI, rt): m/z (%) = 223 ([M^+], 12%), 208 (16), 194 (6), 180 (6), 166 (8), 152 (8), 138 (8), 125 (26), 124 (100), 110 (8), 97 (8), 84 (8), 81 (11).

HRMS (M^+, $C_{15}H_{29}N$): calcd: 223.2299, found: 223.2300.

2.2 Compounds in Chapter II.3

(*S*)-2-Benzyloxycarbonylaminobut-3-enoic acid methyl ester



Anhydrous methanol (4 mL) was cooled to 0 °C under a nitrogen atmosphere. Thionyl chloride (0.37 mL, 5.1 mmol) was added slowly and after stirring for 15 min, (*S*)-*N*-Cbz-vinyl glycine **59** (1 g, 4.2 mmol) was added in small portions and the mixture was warmed to rt over 20 h. Water (5 mL) was added and the mixture was extracted with MTBE (4 x 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. Purification was done with column chromatography (SiO_2, hexane/ethyl acetate 9:1) to give the methyl ester (996 mg, 94 %) as a clear oil.

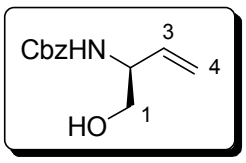
R_f : 0.71 (SiO_2, hexane/ethyl acetate 3:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.77 (s, 3H, CO_2Me), 4.86-4.98 (m, 1H, H-2), 5.13 (s, 2H, C*H*$_2$Ph), 5.28 (dd, *J* = 10 and 1 Hz, 1H, H-4), 5.37 (dd, *J* = 17 and 1 Hz, 1H, H-4), 5.46 (br d, *J* = 7 Hz, 1H, NH), 5.91 (ddd, *J* = 17, 10, and 5 Hz, 1H, H-3), 7.29-7.41 (m, 5H, Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 52.46 (CO_2CH_3), 55.99 (C-2), 66.86 (CH_2Ph), 117.55 (C-4), 127.90, 127.96 (Ar), 132.14 (C-3), 136.04 (Ar), 155.44 (N*C*O), 170.72 (C-1).

Optical rotation $[\alpha]_D^{20}$: -8.9 (c = 0.82, MeOH), Lit.[119] $[\alpha]_D^{20}$: -8.86 (c 1.84, MeOH).

(*S*)-(1-Hydroxymethylallyl)-carbamic acid benzyl ester



To a suspension of $LiBH_4$ (72 mg, 3.3 mmol) in anhydrous diethyl ether (7 mL), anhydrous methanol (0.13 mL) and ester **36** (411 mg, 1.7 mmol) in anhydrous diethyl ether (5 mL) were successively added and the mixture was stirred at rt for 2 h. Water (5 mL) was added and the mixture was extracted with MTBE (3 x 15 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. Purification was done with column chromatography (SiO_2, hexane/ethyl acetate 3:2) to afford the alcohol (285 mg, 78 %) as a white solid.

R_f : 0.24 (SiO_2, hexane/ethyl acetate 3:2)

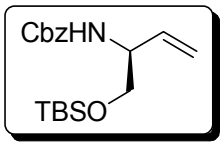
mp. : 47-48 °C

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.92 (br s, 1H, OH), 3.65-3.78 (m, 2H, H-1), 4.34 (s, 1H, H-2), 5.13 (br s, 3H, OC*H*$_2$Ph, NH), 5.21-5.34 (m, 2H, H-4), 5.91 (ddd, *J* = 17, 10, and 5 Hz, 1H, H-3), 7.30-7.41 (m, 5H, Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 54.94 (C-2), 64.47 (*C*H_2Ph), 66.77 (C-1), 116.42 (C-4), 127.92, 127.99, 128.37 (Ar), 135.11 (C-3), 136.15 (Ar), 156.44 (N*C*O).

Optical rotation $[\alpha]_D^{20}$: -27.4 (c = 1.54, $CHCl_3$), Lit. [120] $[\alpha]_D^{22}$ -29.6 (c 0.69, $CHCl_3$).

(*S*)-[1-(*tert*-Butyl-dimethyl-silanyoxymethyl)allyl] carbamic acid benzyl ester (44)

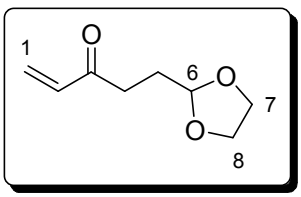


To a solution of alcohol (285 mg, 1.3 mmol) in anhydrous DMF (2 mL), *tert*-butylchlorodimethylsilane (233 mg, 1.55 mmol) was added and the mixture was stirred at 0 °C for 10 min. Imidazole (219 mg, 3.22 mmol) was added portionwise and the reaction mixture stirred further at 0 °C for 3 min and at rt for 18 h. MTBE was added and the mixture washed with 10% aqueous $NaHCO_3$ solution. The organic phase was dried over $MgSO_4$ and evaporated. Purification was done with column chromatography (SiO_2, hexane/ethyl acetate 9:1) to furnish **44** (405 mg, 88 %) as a white solid.

Spectral data and physical properties see compound **44** (rac) (Section **V.2.1**)

Optical rotation $[\alpha]_D^{20}$: -31.2 (c = 1.2, CH_2Cl_2), Lit.[48] (*R*-configuration): $[\alpha]_D^{22}$ +31.8 (c 1.2, CH_2Cl_2).

5-[1.3]-Dioxolan-2-yl-pent-1-en-3-one (90)



Methoxyallene (643 mg, 9 mmol) was dissolved in anhydrous THF (8 mL) and the solution was cooled to -35 °C. *n*-BuLi (5.5 mL, 9 mmol, 1.6 M in hexane) was added dropwise. After stirring for 1 h at the same temperature, 2-(2-bromoethyl)-[1,3]-dioxolane (0.83 g, 4.6 mmol) in anhydrous THF (4 mL) was added. The mixture was warmed to 0 °C while stirring for 3 h and hydrolyzed by addition of 1 M aqueous HCl solution (15 mL) and further stirring at 0 °C for 10 min. The mixture was extracted with diethyl ether (3 x 20 mL). The

combined organic layers were dried over $MgSO_4$ and carefully evaporated under reduced pressure (until 400 mbar). Purification was done with flash column chromatography (SiO_2, diethyl ether/pentane 1:1) to give enone **90** (246 mg, 34 %) as a yellow oil, which was stored as 1 M solution in anhydrous CH_2Cl_2 at -20 °C.

R_f : 0.37 (SiO_2, diethyl ether/pentane 1:1).

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 2.01 (dt, *J* = 4 and 7 Hz, 2H, H-5), 2.72 (t, *J* = 7 Hz, 2H, H-4), 3.83-4.00 (m, 4H, H-7, 8), 4.93 (t, *J* = 7 Hz, H-6), 5.83 (dd, *J* = 10 and 1 Hz, 1H, H-1), 6.23 (dd, *J* = 17 and 1 Hz, 1H, H-1), 6.36 (dd, *J* = 17 and 10, 1H, H-2).

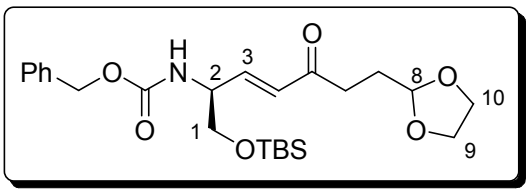
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 27.69 (C-5), 33.42 (C-4), 65.04 (C-7, 8), 103.40 (C-6), 128.14 (C-1), 136.21 (C-2), 199.86 (C-3).

IR (ATR): υ (cm^{-1}) = 3399 (m), 2956 (m), 2936 (m), 2892 (m), 1713 (vs), 1439 (m), 1408 (m), 1364 (m), 1262 (m), 1211 (m), 1139 (vs), 1032 (vs), 947 (s), 897 (m).

MS (EI, rt): m/z (%) = 155 ([M^+-H], 3%), 129 (4), 123 (1), 111 (1), 99 (4), 96 (7), 95 (2), 86 (12), 81 (4), 74 (4), 73 (100).

HRMS (M^+-H, $C_8H_{11}O_3$): calcd: 155.0708, found: 155.0710.

[(*E*)-(*S*)-1-(*tert*-Butyl-dimethyl-silanyloxymethyl)-6-[1,3]dioxolan-2-yl-4-oxo-hex-2-enyl]-carbamic acid benzyl ester (89)



Following the general procedure A, allyl amine **44** (54 mg, 0.16 mmol), enone **90** (0.16 mL, 0.16 mmol, 1M solution in anhydrous CH_2Cl_2), and [**Ru**] (10 mg, 16 μmol) in CH_2Cl_2 (3.2 mL) were employed to afford after 3 d at reflux temperature and column chromatography (SiO_2, hexane/ethyl acetate 3:1) the enone **89** (54 mg, 73%) as a yellow oil.

R_f : 0.6 (SiO_2, hexane/ethyl acetate 3:2).

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.03 (s, 6H, $SiMe_2$), 0.85 (s, 9H, *t*-Bu), 1.99 (dt, *J* = 7 and 4 Hz, 2H, H-7), 2.65 (m, 2H, H-6), 3.63-3.76 (m, 2H, H-2), 3.77-4.00 (m, 4H, H-9, 10), 4.40 (m, 1H, H-2), 4.90 (s, 1H, H-9), 5.10 (s, 2H, H-12), 5.19 (br s, 1H, NH), 6.23 (d, *J* = 16 Hz, 1H, H-4), 6.75 (dd, *J* = 16 and 4 Hz, 1H, H-3), 7.32 (m, 5H, Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = -5.42 ($SiMe_2$), 18.31 (Si-*C*), 25.85 ($(CH_3)_3C$), 27.73 (C-7), 34.37 (C-6), 53.66 (C-1), 64.66 (C-2), 65.03 (C-9, 10), 67.12 (CH_2Ph), 103.37 (C-8), 128.29, 128.64 (Ar), 130.16 (C-4), 136.30 (Ar), 143.64 (C-3), 155.81 (CO_2), 198.88 (C-5).

IR (ATR): υ (cm^{-1}) = 3441 (w), 3332 (m), 3065 (w), 3034 (w), 2954 (s), 2929 (s), 2885 (m), 2857 (s), 1723 (vs), 1701 (vs), 1678 (s), 1636 (m), 1587 (w), 1526 (s), 1499 (m), 1472 (m), 1464 (m), 1455 (m), 1390 (m), 1361 (m), 1253 (vs), 1111 (vs), 1028 (s), 980 (m), 837 (vs), 778 (s), 739 (m), 698 (m).

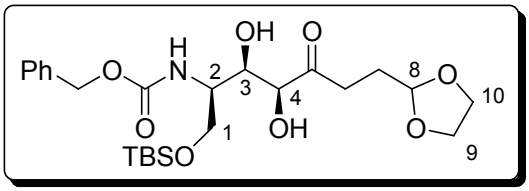
MS (EI, 120 °C): m/z (%) = 463 ([M^+], 2%), 433 (1), 406 (4), 386 (<1), 362 (2), 300 (1), 278 (4), 234 (4), 210 (2), 180 (2), 149 (3), 115 (4), 91 (100), 73 (32).

HRMS (M^+, $C_{24}H_{37}O_6NSi$): calcd: 463.2390, found: 463.2381.

CHN-Analytic ($C_{24}H_{37}NO_6Si$): calcd. C 62.17, H 8.05, N 3.02.
found C 62.04, H 7.95, N 3.15.

Optical rotation $[\alpha]_D^{20}$: -0.53 (c = 0.95, $CHCl_3$).

[(1*R*,2*R*,3*S*)-1-(*tert*-Butyl-dimethyl-silanyloxymethyl)-6-[1.3]dioxolan-2-yl-2,3-dihydroxy-4-oxo-hexyl]-carbamic acid benzyl ester (88a)



AD Mix β (768 mg), $NaHCO_3$ (97 mg), $MeSO_2NH_2$ (138 mg), and $K_2OsO_4{\cdot}2H_2O$ (1.5 mg) were dissolved in *t*-butanol-water (1:1, 1.8 mL) and stirred for 10 min. CM Product **89** (169 mg, 0.36 mmol) in *t*-butanol-water (1:1, 1.8 mL) was added, and the mixture was stirred at rt for 18 h. Na_2SO_3 (700 mg) and water (1 mL) were added, the mixture was stirred further for 1h, and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed subsequently with 1N aqueous NaOH solution (2 x 10 mL), water (2 x 10 mL), and brine,

dried over $MgSO_4$, and evaporated. Purification was done with column chromatography (SiO_2, hexane/ethyl acetate 3:1 → 3:2) to yield the diol **88a** and its diastereomer (total yield of 122 mg with 115 mg diol **88a**, dr 94:6, 67% yield) as a clear oil.

R_f : 0.2 (SiO_2, hexane/ethyl acetate 3:2)

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.05 (s, 6H, $SiMe_2$), 0.86 (s, 9H, *t*-Bu), 1.20-1.29 (m, 1H, OH), 1.96-2.09 (m, 2H, H-7), 2.55-2.82 (m, 2H, H-6), 3.70 (dd, *J* = 10 and 5 Hz, 1H, H-1), 3.74-4.00 (m, 5H, H-2, 9, 10), 4.05 (dd, *J* = 10 and 3 Hz, 1H, H-1'), 4.10 (t, *J* = 9 Hz, 1H, H-3), 4.19 (dd, *J* = 19 and 3 Hz, 1H, H-4), 4.92 (m, 1H, H-8), 5.10 (br s, 2H, CH_2Ph), 5.54 (d, *J* = 9 Hz, 1H, NH), 7.34 (m, 5H, Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = -5.48 ($SiMe_2$), 18.29 (Si-*C*), 25.91 ($(CH_3)_3C$), 27.19 (C-7), 32.52 (C-6), 54.07 (C-2), 62.10 (C-1), 65.07 (C-9, 10), 67.33 (CH_2Ph), 70.66 (C-3), 76.89 (C-4), 103.21 (C-8), 128.26, 128.66, 136.13 (Ar), 157.10 (CO_2), 210.44 (C-5).

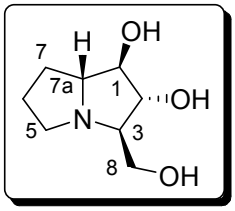
IR (ATR): υ (cm^{-1}) = 3432 (m), 3091 (w), 3065 (w), 3034 (w), 2954 (s), 2929 (s), 2885 (m), 2857 (m), 1715 (vs), 1587 (w), 1509 (s), 1471 (m), 1464 (m), 1406 (m), 1390 (m), 1361 (m), 1327 (m), 1305 (m), 1254 (s), 1219 (s), 1115 (s), 1087 (s), 1046 (s), 1028 (s), 837 (vs), 779 (s), 752 (m), 698 (m).

MS (EI, 130 °C): m/z (%) = 496 ([M^+-H], <1%), 482 (<1), 440 (4), 422 (1), 396 (1), 378 (8), 368 (4), 334 (3), 308 (6), 280 (2), 264 (9), 236 (3), 206 (2), 174 (2), 160 (3), 149 (6), 129 (10), 116 (8), 91 (100), 73 (26).

HRMS (M^+-H, $C_{24}H_{38}NO_8Si$): calcd: 496.2367, found: 496.2379.

Optical rotation $[\alpha]_D^{20}$: -10.1 (c = 0.9, $CHCl_3$)

(+)-Hyacinthacine A_2



Diol **88a** (30 mg, 60 μmol) in methanol (10 mL) was hydrogenated at 4 bar over 10% Pd/C (7 mg, 6 μmol) for 3 d. TLC (methanol) then showed that the first cyclization occured (R_f 0.47). Concentrated HCl (3 drops) was then added to the mixture, which was stirred further at rt for 1 d. The

heterogeneous mixture was again hydrogenated at 3 bar for 3 d. After filtration over celite, the filtrate was neutralized with Amberlite IRA 401 (wet, OH form). After filtration and evaporation, the residue containing HCl-salt was dissolved in methanol, ammonia (6 drops) was added, and the mixture was stirred for 30 min, evaporated, and purified by preparative TLC (SiO_2, methanol/ammonia 98:2) to give the hyacinthacine A_2 (4 mg, 39%) as a yellow oil.

R_f : 0.14 (SiO_2, methanol).

^{1}H-NMR (500 MHz, D_2O): δ (ppm) = 1.49-1.61 (m, 2H, H-6, 7), 1.62-1.69 (m, 1H, H-6), 1.69-1.75 (m, 1H, H-7), 2.46-2.49 (m, 1H, H-3), 2.49-2.57 and 2,64-2.42 (m, 1H, H-5), 2.90-2.96 (m, 1H, H-7a), 3.40-3.47 (dd, *J* = 11 and 6 Hz, 1H, H-8), 3.52 (br t, *J* = 8 Hz, 1H, H-1), 3.54-3.61 (m, 2H, H-2, 8').

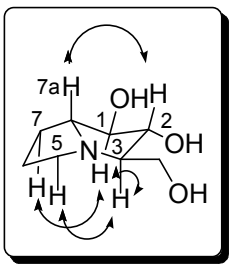
^{13}C NMR (125 MHz, D_2O): δ (ppm) = 25.24 (C-6), 30.50 (C-7), 55.55 (C-5), 63.75 (C-8), 66.72 (C-7a), 69.88 (C-3), 77.97 (C-2), 80.94 (C-1).

IR (ATR): υ (cm^{-1}) = 3313 (s), 2922 (s), 2868 (s), 1734 (w), 1701 (w), 1570 (w), 1446 (m), 1379 (m), 1334 (m), 1290 (m), 1261 (m), 1185 (m), 1115 (s), 1040 (vs), 988 (m), 912 (w), 862 (w), 799 (w).

MS (FAB): m/z (%) = 174 ([M^++H], 100%), 172 (20), 168 (9), 159 (11), 158 (24), 154 (30), 146 (54), 144 (26), 137 (32), 131 (22), 119 (31), 115 (38), 107 (23), 95 (26), 93 (88), 91 (54), 81 (56).

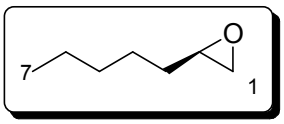
Optical rotation $[\alpha]_D^{20}$: +11.2 (c = 0.52, H_2O) (Lit. [60] $[\alpha]_D^{25}$ + 12.5 (*c* 0.6, H_2O); Lit.[63] $[\alpha]_D^{25}$ + 12.7 (*c* 0.13, H_2O); Lit.[67] $[\alpha]_D^{25}$ + 10.5 (*c* 0.6, H_2O))

nOe Correlation:



2.3 Compounds in Chapter II.4

(*R*)-2-Pentyl-oxirane (131)



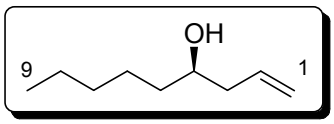
To a mixture of (*R*)-epichlorhydrin (2 g, 21.6 mmol, 98.2% ee) and CuCN (193 mg, 2.16 mmol) in anhydrous THF (25 mL), butylmagnesium bromide (16.2 mL, 32.4 mmol, 2M in THF) was added dropwise at -78 °C. The solution was warmed to -20 °C over 2.5 h and poured into a mixture of saturated aqueous NH_4Cl and diethyl ether with vigorous stirring. The layers were separated. The aqueous layer was extracted with diethyl ether (3 x 25 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. To the crude product (3.2 g) in THF/water mixture (25 + 15 mL) crushed NaOH (10 g, 0.22 mol) was added. The mixture was stirred vigorously at rt for 20 h and extracted with diethyl eter (3 x 25 mL). The combined organic layers were washed with saturated aqueous NH_4Cl solution, dried over $MgSO_4$ and carefully evaporated (bp. 50-52 °C, 20 mbar) to furnish the neat oxirane **131** (2.15 g, 87%) as a yellow oil.

R_f : 0.56 (SiO_2, cyclohexane/ethyl acetate 3:2).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 0.84 (t, *J* = 7 Hz, 3H, H-7), 1.12-1.59 (m, 8H, H-3-6), 2.41 (dd, *J* = 3 and 6 Hz, 1H, H-1), 2.70 (t, *J* = 5 Hz, 1H, H-1), 2.80-2.92 (m, 1H, H-2).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 13.78 (C-7), 22.39 (C-6), 25.47 (C-5), 31.44 (C-4), 32.27 (C-3), 46.89 (C-1), 52.18 (C-2)

(*R*)-Non-1-en-4-ol (130)



To a mixture of oxirane **131** (1 g, 8.8 mmol) and CuCN (78 mg, 0.9 mmol) in anhydrous THF (10 mL) at -78 °C, vinyl magnesium bromide (13.1 mL, 1M in THF) was added slowly dropwise. The mixture was warmed to rt over 24 h. Saturated aqueous NH_4Cl was added, followed by extraction with diethyl ether (3x10 mL). The combined organic layers were dried over $MgSO_4$, and carefully evaporated (bp. 88-90 °C, 20 mbar). Purification was done by column chromatography (SiO_2, pentane/diethyl ether 9:1) to afford the homoallyl alcohol **131** (1 g, 84%) as a clear oil.

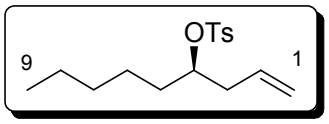
R_f : 0.42 (SiO_2, cyclohexane/ethyl acetate 3:1).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 0.90 (t, *J* = 7 Hz, 3H, H-9), 1.20-1.50 (m, 8H, H-5-8), 1.55 (d, *J* = 4 Hz, 1H, OH), 2.01-2.39 (m, 2H, H-3), 3.62 (br s, 1H, H-4), 5.01-5.20 (m, 2H, H-1), 5.70-5.94 (m, 1H, H-2).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 14.09 (C-9), 22.68 (C-8), 25.40 (C-7), 31.92 (C-6), 36.85 (C-5), 42.00 (C-3), 70.76 (C-4), 118.11 (C-1), 134.99 (C-2).

Optical rotation $[\alpha]_D^{20}$: +8.7 (c = 1.4, $CHCl_3$) Lit.[98] $[\alpha]_D^{25}$ +8.3 (c = 1.4, $CHCl_3$).

Toluene-4-sulfonic acid (*R*)-1-allyl-hexyl ester



Tosyl chloride (1.7 g, 9.5 mmol) was given in small portions to a mixture of nonenol **130** (900 mg, 6.33 mmol), triethylamine (1.35 mL, 9.5 mmol), and DMAP (87 mg, 0.6 mmol) in dichloromethane (10 mL) at 0 °C. The mixture was stirred at rt for 7 d, water (10 mL) was added and the mixture was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed subsequently with 1M aqueous HCl solution and saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and evaporated. Purification was done by column chromatography (SiO_2, cyclohexane/ethyl acetate 9:1) to give the product (1.4 g, 72%) as a clear oil.

R_f : 0.28 (SiO_2, cyclohexane/ethyl acetate 9:1).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 0.80 (t, *J* = 7 Hz, 3H, H-9), 1.01-1.31 (m, 6H, H-6-8), 1.52 (q, *J* = 7 Hz, 1H, H-5), 2.32 (t, *J* = 7 Hz, 2H, H-3), 2.43 (s, 3H, CH_3Ph), 4.52 (quintet, *J* = 6 Hz, 1H, H-4), 5.01 (dd, *J* = 13 and 1 Hz, 2H, H-1), 5.50-5.77 (m, 1H, H-2), 7.30 and 7.77 (d, *J* = 9 Hz, 4H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 13.93 (C-9), 21.66 (CH_3Ph), 22.45 (C-8), 24.40 (C-7), 31.39 (C-6), 33.66 (C-5), 38.83 (C-3), 83.14 (C-4), 118.64 (C-1), 127.84, 129.71 (Ar), 132.39 (C-2), 134.62, 144.51 (Ar).

IR (ATR): υ (cm^{-1}) = 3078 (w), 2955 (m), 2930 (m), 2872 (m), 2861 (m), 1643 (w), 1599 (m), 1496 (w), 1467 (m), 1457 (m), 1364 (s), 1306 (m), 1188 (vs), 1176 (vs), 1097 (m), 1020 (w), 995 (w), 898 (vs), 815 (m), 726 (w), 665 (s).

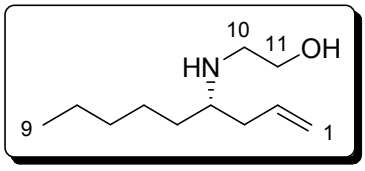
MS (EI, rt): m/z (%) = 296 ([M^+], <1%), 279 (<1), 257 (1), 255 (16), 225 (<1), 197 (<1), 172 (1), 155 (100), 139 (2), 124 (1), 107 (3), 91 (64), 83 (6).

HRMS (M^+, $C_{16}H_{24}O_3S$): calcd: 296.1446, found: 296.1451.

CHN-Analytic ($C_{16}H_{24}O_3S$): calcd. C 64.83, H 8.16.
found C 64.93, H 8.36.

Optical rotation $[\alpha]_D^{20}$: +18.8 (c = 1, $CHCl_3$).

2-((*S*)-1-Allyl-hexylamino)-ethanol (133)



A mixture of tosylated homoallyl alcohol (1.48 g, 5 mmol) and 2-aminoethanol (0.9 mL, 15 mmol) in anhydrous THF (10 mL) was refluxed under a nitrogen atmosphere for 6 d. The mixture was cooled to rt and saturated aqueous $NaHCO_3$ (10 mL) was added. The mixture was extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and carefully evaporated (until 100 mbar, 40 °C). Purification was done by column chromatography (SiO_2, cyclohexane/ethyl acetate 9:1 and methanol) to furnish homoallyl amine **133** (710 mg, 77%) as a yellow oil.

R_f : 0.36 (SiO_2, methanol).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 0.89 (t, *J* = 7 Hz, 3H, H-9), 1.16-1.48 (m, 8H, H-5-8), 1.92 (br s, 2H, NH, OH), 2.19 (octet, *J* = 7 Hz, 2H, H-3), 2.56 (quintet, *J* = 6 Hz, 1H, H-4), 2.77 (dt, *J* = 6 and 3 Hz, 2H, H-10), 3.60 (t, *J* = 7 Hz, 2H, H-11), 5.09 (dd, *J* = 13 and 1 Hz, 2H, H-1), 5.67-5.91 (m, 1H, H-2).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 14.09 (C-9), 22.67 (C-8), 25.56 (C-7), 32.08 (C-6), 34.06 (C-5), 38.46 (C-3), 48.28 (C-10), 56.85 (C-4), 61.16 (C-11), 117.37 (C-1), 135.52 (C-2).

IR (ATR): υ (cm^{-1}) = 3296 (w), 3076 (w), 2955 (s), 2928 (vs), 2858 (s), 1640 (w), 1466 (m), 1437 (m), 1378 (w), 1217 (w), 1141 (w), 1106 (w), 1058 (m), 995 (w), 912 (m), 726 (w).

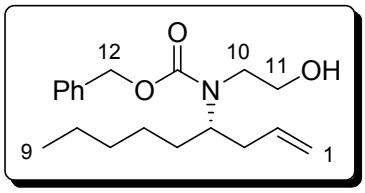
MS (EI, 70 °C): m/z (%) = 184 ([M^+-H], <1%), 170 (2), 154 (5), 145 (9), 144 (100), 135 (<1), 126 (1), 115 (1), 114 (14), 112 (1), 100 (2), 88 (<1), 84 (2).

HRMS (M^+-CH_3, $C_{10}H_{20}ONS$): calcd: 170.1545, found: 170.1545.

CHN-Analytic ($C_{11}H_{23}ONS$): calcd. C 71.29, H 12.51, N 7.56.
found C 68.66, H 12.13, N 7.03.

Optical rotation $[\alpha]_D^{20}$: +3.2 (c = 1, $CHCl_3$).

((*S*)-1-Allyl-hexyl)-(2-hydroxy-ethyl)-carbamic acid benzyl ester (129)



To a mixture of **133** (674 mg, 3.63 mmol) and K_2CO_3 (632 mg, 4.5 mmol) in water/dichloromethane (1:1, 35 mL) at 0 °C, benzyl chloroformate (0.63 mL, 4.5 mmol) was added dropwise. The mixture was stirred at rt for 4 h, after which 1M aqueous HCl solution was added to acidify the mixture (pH 1). The mixture was extracted with dichloromethane (3 x 25 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. Purification was done by column chromatography (SiO_2, cyclohexane/ethyl acetate 3:1) to afford **129** (843 mg, 73%) as a clear oil.

R_f : 0.36 (SiO_2, cyclohexane/ethyl acetate 3:2).

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.86 (t, *J* = 7 Hz, 3H, H-9), 1.26 (br s, 6H, H-6-8), 1.45 (br s, 2H, H-5), 2.10-2.40 (m, 2H, H-3), 3.20-3.43 (m, 2H, H-11), 3.72 (br s, 2H, H-10), 4.00 (quintet, *J* = 5 Hz, 1H, H-4), 4.95-5.08 (m, 2H, H-1), 5.15 (s, 2H, H-12), 5.60-5.91 (m, 1H, H-2), 7.25-7.40 (m, 5H, Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 13.82 (C-9), 22.41 (C-8), 26.14 (C-7), 31.65 (C-6), 33.12 (C-5), 38.05 (C-3), 46.54 (C-11), 57.45 (C-4), 62.74 (C-10), 67.33 (C-12), 116.96 (C-1), 126.98, 127.54, 127.92, 128.43 (Ar), 135.33 (C-2), 136.84 (Ar), 158.74 (*C*O_2).

IR (ATR): υ (cm^{-1}) = 3450 (w), 3067 (w), 3033 (w), 2956 (m), 2929 (s), 2859 (m), 1696 (vs), 1675 (vs), 1642 (w), 1498 (w), 1467 (m), 1456 (m), 1418 (s), 1379 (w), 1344 (m), 1276 (m), 1219 (m), 1109 (m), 1048 (m), 993 (m), 915 (m), 770 (m), 735 (m), 698 (m).

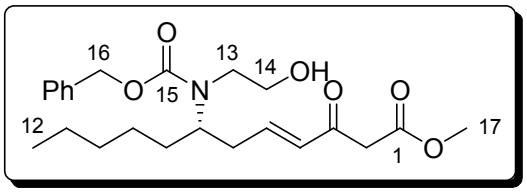
MS (EI, 80 °C): m/z (%) = 319 ([M^+], <1%), 288 (<1), 278 (24), 244 (2), 235 (8), 234 (49), 204 (2), 170 (10), 142 (1), 112 (2), 92 (13), 91 (100), 79 (4).

HRMS (M^+, $C_{19}H_{29}O_3N$): calcd: 319.2147, found: 319.2156.

CHN-Analytic ($C_{19}H_{29}O_3N$): calcd. C 71.44, H 9.15, N 4.38.
found C 71.07, H 9.15, N 4.07.

Optical rotation $[\alpha]_D^{20}$: -19.9 (c = 1, $CHCl_3$).

(*E*)-(*S*)-7-[Benzyloxycarbonyl-(2-hydroxy-ethyl)-amino]-3-oxo-dodec-4-enoic acid methyl ester (127)



[**Ru**] (11 mg, 18 μmol) was added to a solution of homoallylamine **129** (76 mg, 0.2 mmol) and (*E*)-3-oxo-hex-4-enoic acid methyl ester **128** (60 mg, 0.4 mmol) in anhydrous CH_2Cl_2 (4.7 mL) under a nitrogen atmosphere. The mixture was then refluxed for 20 h. The solvent was evaporated and the residue was purified by column chromatography (SiO_2, cyclohexane/ethyl acetate 3:2) to give **127** (70 mg, 70%, as keto-enol mixture) as a brown oil.

R_f : 0.16 (SiO_2, cyclohexane/ethyl acetate 3:2).

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.81 (br s, 3H, H-12), 1.20 (m, 8H, H-9-11), 1.45-1.59 (m, 2H, H-8), 2.20-2.68 (m, 2H, H-6), 3.29 (m, 2H, H-13), 3.45 (s, H-2 keto), 3.50 (br s, 2H, H-14), 3.68, 3.70 (s, 3H, H-17), 4.05 (br s, 1H, H-7), 4.96 (s, H-2 enol), 5.12 (s, 2H, H-16), 5.69-5.85 and 6.05-6.20 (m, 1H, H-4), 6.45-6.62 and 6.69-6.86 (m, 1H, H-5), 7.21-7.41 (br s, 5H, Ar), 11.75 (s, OH enol).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 14.02 (C-12), 22.55 (C-11), 26.14 (C-10), 31.60 (C-9), 33.07, 33.41 (C-8), 36.50, 36.97 (C-6), 46.35, 46.69 (C-13), 51.32 (C-7), 52.44 (C-17),

61.64, 62.58 (C-14), 67.17, 67.76 (C-15), 90.52 (C-2), 126.60 (C-4), 1276.86, 128.13, 128.27, 128.65, 131.32, 136.81 (Ar), 145.93, 147.03 (C-5), 155.60 (C-16), 173.25 (C-1), 191.73 (C-3).

IR (ATR): υ (cm^{-1}) = 3451 (w), 3064 (w), 3032 (w), 2954 (m), 2930 (m), 2859 (m), 1744 (m), 1693 (vs), 1670 (vs), 1599 (m), 1498 (w), 1446 (s), 1414 (s), 1379 (m), 1339 (m), 1238 (vs), 1213 (s), 1149 (s), 1107 (m), 1046 (m), 1027 (m), 977 (m), 770 (m), 734 (m), 698 (m).

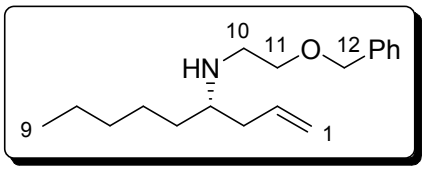
MS (EI, 150 °C): m/z (%) = 420 ([M^++H], <1%), 388 (<1), 344 (3), 328 (<1), 304 (2), 284 (1), 278 (25), 246 (1), 234 (55), 206 (1), 170 (1), 142 (1), 112 (2), 91 (100).

HRMS (M^++H, $C_{23}H_{34}O_6N$): calcd: 420.2386, found: 420.2390.

CHN-Analytic ($C_{23}H_{33}O_6N$): calcd. C 65.83, H 7.93, N 3.34.
found C 65.52, H 7.94, N 3.40.

Optical rotation $[\alpha]_D^{20}$: -8.0 (c = 1, $CHCl_3$).

((*S*)-1-Allyl-hexyl)-(2-benzyloxy-ethyl)-amine



A mixture of **130** (639 mg, 2.15 mmol) and 2-benzyloxy-ethylamine (0.98 g, 6.5 mmol) in anhydrous THF (5 mL) was refluxed under a nitrogen atmosphere for 3 d. The mixture was cooled and saturated aqueous $NaHCO_3$ (5 mL) was added. The mixture was extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. Purification was done by column chromatography (SiO_2, cyclohexane/ethyl acetate 9:1 → 3:2 and ethyl acetate) to yield the homoallyl amine (401 mg, 68%) as a yellow oil.

R_f : 0.23 (SiO_2, cyclohexane/ethyl acetate 3:2).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 0.90 (t, *J* = 7 Hz, 3H, H-9), 1.15-1.50 (m, 8H, H-5-8), 1.80 (br s, 1H, NH), 2.19 (d octet, *J* = 7 and 1 Hz, 2H, H-3), 2.56 (quintet, *J* = 6 Hz, 1H, H-4), 2.80 (t, *J* = 6 Hz, 2H, H-10), 3.59 (t, *J* = 5 Hz, 2H, H-11), 4.51 (s, 2H, H-12), 5.04 (d, *J*

= 10 Hz, 1H, H-1), 5.10 (dd, *J* = 7 and 1 Hz, 1H, H-1), 5.65-5.90 (m, 1H, H-2), 7.02-8.40 (m, 5H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 13.95 (C-9), 22.51 (C-8), 25.29 (C-7), 31.97 (C-6), 33.73 (C-5), 38.34 (C-3), 46.57 (C-10), 56.76 (C-4), 69.71 (C-11), 72.92 (C-12), 116.96 (C-1), 126.71, 127.42, 127.48, 128.20 (Ar), 135.67 (C-2), 138.23 (Ar).

IR (ATR): υ (cm^{-1}) = 3329 (w), 3066 (w), 3030 (w), 2954 (s), 2927 (vs), 2856 (s), 1639 (m), 1604 (w), 1586 (w), 1496 (m), 1467 (m), 1454 (s), 1356 (m), 1205 (m), 1096 (s), 1028 (m), 995 (m), 911 (s), 734 (vs), 697 (vs).

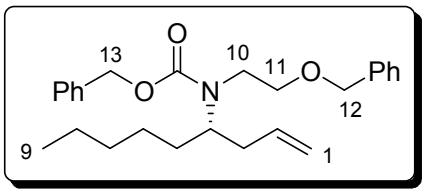
MS (EI, 100 °C): m/z (%) = 274 ([M^+-H], 1%), 235 (14), 234 (100), 204 (8), 184 (<1), 159 (2), 154 (12), 139 (4), 128 (1), 112 (1), 98 (1), 91 (90), 79 (3).

HRMS (M^+-H, $C_{18}H_{28}ON$): calcd: 274.2171, found: 274.2178.

CHN-Analytic ($C_{18}H_{29}ON$): calcd. C 78.48, H 10.62, N 5.08.
found C 77.41, H 10.71, N 4.90.

Optical rotation $[\alpha]_D^{20}$: -0.4 (c = 3, $CHCl_3$).

((*S*)-1-Allyl-hexyl)-(2-benzyloxy-ethyl)-carbamic acid benzyl ester (134)



To a mixture of homoallyl amine (100 mg, 0.36 mmol) and Na_2CO_3 (42 mg, 1.6 mmol) in water/THF (1:1, 2.4 mL), benzyl chloroformate (0.25 mL, 1.8 mmol) was added dropwise at 0 °C. The mixture was warmed to rt overnight and extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. Purification was done by column chromatography (SiO_2, cyclohexane/ethyl acetate 9:1) to give **134** (126 mg, 86%) as a clear oil.

R_f : 0.23 (SiO_2, cyclohexane/ethyl acetate 9:1)

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 0.85 (t, *J* = 7 Hz, 3H, H-9), 1.05-1.35 (m, 6H, H-6-8), 1.49 (br s, 2H, H-5), 2.11-2.41 (m, 2H, H-3), 3.35-3.47 (m, 2H, H-11), 3.50-3.73 (m, 2H, H-10), 3.86-4.23 (m, 1H, H-4), 4.51 (d, *J* = 14 Hz, 2H, H-12), 4.91-5.09 (m, 2H, H-1), 5.15 (s, 2H, H-13), 5.52-5.85 (m, 1H, H-2), 7.24-7.50 (m, 10H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 13.92 (C-9), 22.44 (C-8), 26.08 (C-7), 31.58 (C-6), 32.99 (C-5), 38.20 (C-3), 42.69 (C-10), 56.87 (C-4), 66.84 (C-11), 73.03 (C-12), 116.67 (C-1), 127.55, 127.77, 128.29, 128.46 (Ar), 135.40 (C-2), 137.96 (Ar), 156.67 (CO_2).

IR (ATR): υ (cm^{-1}) = 3065 (w), 3032 (w), 2955 (m), 2929 (m), 2858 (m), 1748 (w), 1697 (vs), 1641 (w), 1497 (w), 1454 (m), 1413 (m), 1347 (m), 1266 (m), 1223 (m), 1152 (m), 1111 (s), 1028 (w), 994 (m), 913 (m), 769 (m), 735 (m), 697 (s).

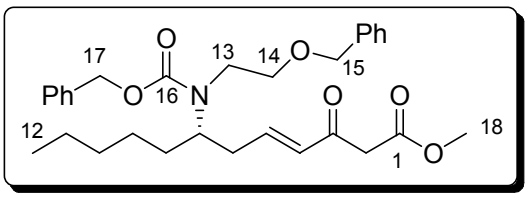
MS (EI, rt): m/z (%) = 410 ([M^++H], <1%), 368 (12), 324 (26), 318 (<1), 294 (1), 274 (<1), 244 (2), 216 (1), 196 (<1), 180 (10), 151 (12), 107 (21), 91 (100), 79 (10).

HRMS (M^++H, $C_{26}H_{36}O_3N$): calcd: 410.2695, found: 410.2700.

CHN-Analytic ($C_{26}H_{35}O_3N$): calcd. C 76.23, H 8.62, N 3.42.
found C 75.86, H 8.46, N 3.23.

Optical rotation $[\alpha]_D^{20}$: -12.9 (c = 1, $CHCl_3$)

(*E*)-(*S*)-7-[Benzyloxycarbonyl-(2-benzyloxy-ethyl)-amino]-3-oxo-dodec-4-enoic acid methyl ester (135)



[**Ru**] (4.6 mg, 7 μmol) was added to a solution of homoallylamine **134** (40 mg, 98 μmol) and (*E*)-3-oxo-hex-4-enoic acid methyl ester **128** (25 mg, 0.2 mmol) in anhydrous CH_2Cl_2 (1.9 mL) under a nitrogen atmosphere. The mixture was then refluxed for 19 h. The solvent was evaporated and the residue was purified by column chromatography (SiO_2, cyclohexane/ethyl acetate 9:1 → 3:1) to furnish **135** (33 mg, 66%, as keto-enol mixture) as a light red oil.

R_f : 0.37 (SiO_2, cyclohexane/ethyl acetate 3:1).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 0.80 (br s, 3H, H-12), 1.05-1.65 (m, 8H, H-8-11), 2.20-2.65 (m, 2H, H-6), 3.35-3.41 (m, 2H, H-13), 3.40 (s, H-2 keto), 3.49-3.59 (m, 2H, H-14), 3.54-3.69 (m, 1H, H-7), 3.70, 3.72 (s, 3H, H-18), 4.49 (d, *J* = 13 Hz, 2H, H-15), 4.90 (d, *J* = 3 Hz, H-2 enol), 5.10 (s, 2H, H-17), 5.70 (br t, *J* = 16 Hz, H-4 enol), 6.05 (dd, *J* = 16 and 9 Hz, H-4 keto), 6.55, 6.70 (2 x dt, *J* = 16 and 6 Hz, 1H, H-5), 7.21-7.45 (m, 10H, Ar), 11.75 (s, OH enol).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 13.95 (C-12), 22.48 (C-11), 26.11 (C-10), 31.53 (C-9), 32.85, 33.25 (C-8), 36.67, 37.08 (C-6), 46.24, 46.47 (C-13), 51.18, 52.27 (C-18), 56.84 (C-7), 66.79, 67.11 (C-14), 68.69, 69.09 (C-17), 73.15 (C-15), 90.14 (C-2), 126.10 (C-4), 1276.62, 127.82, 127.95, 128.11, 128.36, 128.47, 136.46, 136.66, 137.52, 137.96 (Ar), 146.42, 146.74 (C-5), 156.18 (C-16), 173.19 (C-1), 191.92 (3).

IR (ATR): υ (cm^{-1}) = 3089 (w), 3064 (w), 3031 (w), 2953 (m), 2928 (m), 2857 (m), 1745 (m), 1694 (vs), 1642 (m), 1598 (m), 1497 (w), 1453 (s), 1410 (s), 1348 (m), 1328 (m), 1236 (vs), 1142 (s), 1106 (s), 1028 (m), 1017 (m), 975 (m), 911 (w), 769 (m), 734 (s), 697 (s).

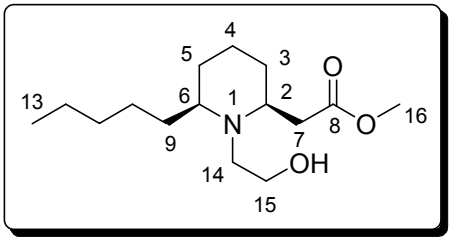
MS (EI, 60 °C): m/z (%) = 509 ([M^+], <1%), 478 (<1), 438 (<1), 418 (<1), 394 (1), 368 (17), 324 (34), 274 (1), 256 (1), 232 (1), 196 (1), 180 (8), 151 (8), 107 (13), 91 (100).

HRMS (M^+, $C_{30}H_{39}O_6N$): calcd: 509.2777, found: 509.2780.

CHN-Analytic ($C_{30}H_{39}O_6N$): calcd. C 70.69, H 7.72, N 2.75.
found C 70.49, H 7.49, N 2.79.

Optical rotation $[\alpha]_D^{20}$: +9.8 (c = 1, $CHCl_3$)

[(2*S*,6*S*)-1-(2-Hydroxy-ethyl)-6-pentyl-piperidin-2-yl]-acetic acid methyl ester (126)



CM Produkt **127** (270 mg, 0.64 mmol) in isopropylether (20 mL) was hydrogenated over 10% Pd/C (68 mg, 60 μmol) at 5 bar and 40 °C for 3 d. After filtration over celite and evaporation, the residue was purified by column chromatography (SiO_2, CH_2Cl_2/methanol/

ammonia 97:3:0.1) to afford piperidine **126** (105 mg, 61%) and calvine (20 mg, 13%) as light yellow oil.

R_f : 0.16 (SiO_2, CH_2Cl_2/methanol/ammonia 95:5:0.1).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 0.88 (t, *J* = 7 Hz, 3H, H-13), 1.10-1.80 (m, 14H, H-3-5, 9-12), 2.39 (dd, *J* = 15 and 9 Hz, 1H, H-7), 2.51-2.77 (m, 4H, H-6, 7, 14), 3.09-3.25 (m, 1H, H-2), 3.46 (t, *J* = 6Hz, 2H, H-15), 3.68 (s, 3H, H-16).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 14.12 (C-13), 21.69 (C-4), 22.71 (C-12), 26.15 (C-3), 27.01 (C-10), 27.27 (C-5), 32.11 (C-11), 34.07 (C-9), 39.28 (C-7), 48.35 (C-14), 51.73 (C-16), 58.32 (C-2), 60.45 (C-15), 61.93 (C-6), 172.97 (C-8).

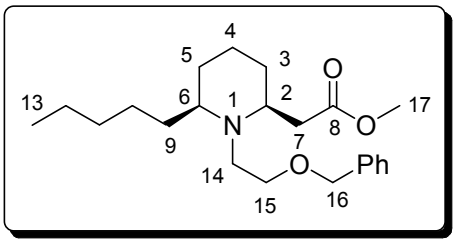
IR (ATR): υ (cm^{-1}) = 3442 (w), 2952 (s), 2930 (vs), 2858 (s), 1738 (vs), 1511 (w), 1459 (m), 1437 (m), 1377 (m), 1353 (m), 1289 (m), 1258 (m), 1192 (m), 1175 (m), 1120 (m), 1054 (m), 1020 (m), 882 (w).

MS (EI, 50 °C): m/z (%) = 271 ([M^+], 1%), 254 (1), 241 (13), 240 (88), 226 (5), 200 (100), 198 (30), 170 (12), 168 (19), 156 (4), 138 (3), 126 (18), 116 (3), 100 (3), 96 (4).

HRMS (M^+, $C_{15}H_{29}O_3N$): calcd: 271.2147, found: 271.2158.

Optical rotation $[\alpha]_D^{20}$: +8.5 (c = 1.3, CH_2Cl_2).

[(2*S*,6*S*)-1-(2-Benzyloxy-ethyl)-6-pentyl-piperidin-2-yl]-acetic acid methyl ester



CM Produkt **135** (75 mg, 0.15 mmol) in isopropylether (12 mL) was hydrogenated over 10% Pd/C (16 mg, 15 μmol) at 5 bar and 40 °C for 3d. After filtration over celite and evaporation, the residue was purified by column chromatography (SiO_2, CH_2Cl_2/methanol/ ammonia 97:3:0.1) to yield the *O*-benzylated piperidine (16 mg, 30%) and **126** (14 mg, 35%) as clear oil.

R_f : 0.59 (SiO_2, CH_2Cl_2/methanol/ammonia 95:5:0.1).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 0.89 (t, *J* = 7 Hz, 3H, H-13), 1.08-1.80 (m, 14H, H-3-5, 9-12), 2.25 (dd, *J* = 15 and 9 Hz, 1H, H-7), 2.40-2.80 (m, 4H, H-6, 7, 14), 3.03 (br s, 1H, H-2), 3.41 (t, *J* = 6Hz, 2H, H-15), 3.63 (s, 3H, H-17), 4.50 (s, 2H, H-16), 7.24-7.50 (m, 5H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 13.95 (C-13), 22.51 (C-12), 23.48 (C-4), 26.15 (C-10), 27.01 (C-5), 28.00 (C-3), 32.02 (C-11), 34.23 (C-9), 39.92 (C-7), 45.78 (C-14), 51.36 (C-17), 59.06 (C-2), 62.49 (C-6), 70.39 (C-15), 73.03 (C-16), 127.38, 127.45, 128.20, 138.26 (Ar), 172.69 (C-8).

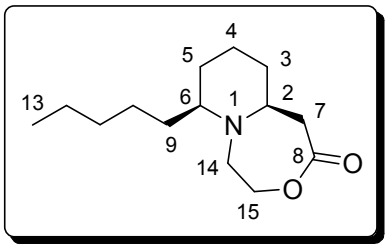
IR (ATR): υ (cm^{-1}) = 3088 (w), 3063 (w), 3029 (w), 2929 (s), 2857 (s), 1739 (vs), 1604 (w), 1586 (w), 1496 (w), 1454 (m), 1436 (m), 1364 (m), 1305 (m), 1287 (m), 1251 (m), 1197 (m), 1179 (m), 1157 (m), 1112 (s), 1103 (s), 1028 (m), 1020 (m), 735 (m), 698 (m).

MS (EI, 100 °C): m/z (%) = 361 ([M^+], 1%), 330 (<1), 318 (<1), 290 (56), 288 (14), 255 (1), 240 (100), 216 (2), 198 (1), 182 (1), 168 (11), 156 (4), 124 (2), 110 (4), 96 (5), 91 (28).

HRMS (M^+, $C_{22}H_{35}O_3N$): calcd: 361.2617, found: 361.2620.

Optical rotation $[\alpha]_D^{20}$: +3.3 (c = 0.6, CH_2Cl_2).

(+)-Calvine



To a solution of **126** (12 mg, 44 μmol) in benzene (3 mL), *p*-toluenesulfonic acid monohydrate (9.2 mg, 48 μmol) was added and the mixture was refluxed under a nitrogen atmosphere for 18 h. Dichloromethane (10 mL) and saturated aqueous $NaHCO_3$ solution (10 mL) were added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 x 10 mL), and the collected organic layers were evaporated to give neat calvine (7 mg, 66%) as a light yellow oil.

R_f : 0.39 (SiO_2, CH_2Cl_2/methanol/ammonia 95:5:0.1)

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 0.88 (t, *J* = 7 Hz, 3H, H-13), 1.15-1.81 (m, 14H, H-3-5, 9-12), 2.19-2.89 (m, 5H, H-6, 7, 14), 3.23-3.37 (m, 1H, H-2), 4.21-4.36 (m, 2H, H-15).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 14.11 (C-13), 21.51 (C-4), 22.67 (C-12), 24.62 (C-3), 25.21 (C-5), 32.27 (C-10, 11), 34.20 (C-9), 43.15 (C-7), 53.48 (C-14), 58.99 (C-2), 62.75 (C-6), 68.97 (C-15), 174.65 (C-8).

IR (ATR): υ (cm^{-1}) = 3954 (s), 2931 (s), 2859 (m), 2808 (w), 2770 (w), 1741 (vs), 1466 (m), 1435 (m), 1388 (m), 1378 (m), 1316 (m), 1283 (m), 1264 (m), 1216 (m), 1186 (m), 1154 (m), 1077 (m), 1063 (s), 904 (w).

MS (EI, 100 °C): m/z (%) = 240 ([M^++H], 2%), 226 (<1), 210 (<1), 196 (4), 182 (2), 168 (100), 166 (4), 154 (1), 138 (5), 126 (18), 108 (4), 96 (4).

HRMS (M^++H, $C_{14}H_{26}O_2N$): calcd: 240.1963, found: 240.1969.

Optical rotation $[\alpha]_D^{20}$: +18.3 (c = 0.35, CH_2Cl_2). Lit.[79] $[\alpha]_D^{20}$ + 18 (*c* 0.66, CH_2Cl_2)

2.4 Compounds in Chapter III

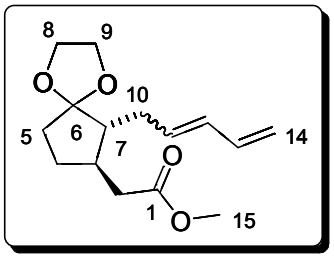
General Procedure C: Wittig reaction with allyl phosphonium bromide

To a suspension of allylphosphoniumbromide (0.78 g, 2 mmol) in 15 mL of anhydrous THF at -78 °C, *n*-BuLi (1.3 ml, 1.6 M in hexane) was added dropwise. After 1 h, aldehyde (2 mmol) in 4.0 mL of anhydrous THF was added dropwise and the mixture was stirred further at -78 °C. After completion of the reaction, as judged by TLC analysis, the mixture was hydrolyzed with saturated aqueous NH_4Cl solution, extracted with diethyl ether (3 x 20 mL), dried over $MgSO_4$, and evaporated. The crude product was purified by column chromatography (SiO_2, cyclohexane/ethyl acetate 9:1) to afford the desired product.

General procedure D: Cross metathesis of conjugated diene with electron deficient olefin

To a solution of diene (1 eq.) in anhydrous CH_2Cl_2 (0.05 M), electron deficient olefin (methyl vinyl ketone (MVK), methyl acrylate, acryl nitrile or acrolein) (3 eq.) and [**Ru**] (0.05 eq.) were added. The mixture was refluxed under a nitrogen atmosphere, cooled to rt, evaporated, and purified by preparative TLC or column chromatography to yield the desired product.

6-Penta-2,4-dienyl-1,4-dioxaspiro-[4.4]-non-7-yl acetic acid methyl ester (142)



Following the general procedure C, 6-(2-oxo-ethyl)-1,4-dioxaspiro [4.4]-non-7-yl-acetic acid methyl ester **141** (0.5 g, 2 mmol) was employed to give after 2 h reaction and purification the recovered aldehyde (149 mg) and diene **142** (126 mg, 33% according to the recovered aldehyde, 1:1 *cis*/*trans*) as a colorless oil.

R_f : 0.52 (SiO_2, cyclohexane/ethyl acetate 3:2).

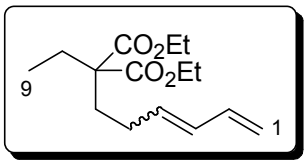
^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.21-1.50 and 1.62-2.62 (m, 10H, H-2-7, 10), 3.64 (s, 3H, H-15), 3.85 (s br, 4H, H-8, 9), 4.89-5.24 (m, 2H, H-14), 5.46 (q br, *J* = 7 and 11 Hz, H-11 *cis*) 5.66 (td, *J* = 15 and 7 Hz, H-11 *trans*), 5.92-6.14 (m, 1H, H-12), 6.29 (td, *J* = 17 and 10 Hz, H-13 *trans*), 6.65 (tdd, *J* = 17, 11 and 1 Hz, H-13 *cis*).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 19.67 (C-3), 27.83, 31.81 (C-4, 5), 35.03 (C-2), 38.9 (C-7), 39.60 (C-10), 51.30 (C-15), 64.02, 64.50 (C-8, 9), 114.75, 116.90 (C-14), 117.46 (C-6), 129.44, 131.21, 131.81, 132.11, 133.73, 137.01 (C-11, 12, 13), 173.01 (C-1).
IR (ATR): υ (cm^{-1}) = 3084 (w), 2952 (s), 2882 (m), 1731 (vs), 1650 (w), 1602 (w), 1436 (s), 1257 (m), 1206 (m), 1147 (s), 1037 (m), 1006 (s), 949 (m).

MS (EI, 45 °C): m/z (%) = 266 ([M^+], 20%), 251 (2), 235 (6), 204 (6), 193 (42), 151 (15), 144 (6), 130 (15), 127 (6), 99 (100), 86 (25).

HRMS (M^+, $C_{15}H_{22}O_4$): calcd: 226.1518, found: 226.1519.

2-Ethyl-2-hexa-3,5-dienyl-malonic acid diethyl ester (144)



Following the general procedure C, 2-ethyl-2-(3-oxo-propyl)-malonic acid diethyl ester **143** (0.5 g, 2 mmol) was employed to furnish after 1 h reaction at rt and purification the diene **144** (190 mg, 35%, 1:1 *trans*/*cis*) as a colorless oil.

R_f : 0.59 (SiO_2, cyclohexane/ethyl acetate 3:2).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 0.80 (dt, *J* = 7 and 1 Hz, 3H, H-9), 1.20 (dt, *J* = 7 and 1 Hz, 6H, OCH_2CH_3), 1.80-2.17 (m, 6H, H-5, 6, 8), 4.17 (dq, *J* = 7 and 1 Hz, 4H, OCH_2), 4.89-5.26 (m, 2H, H-1), 5.40 (q br, *J* = 8 and 11 Hz, H-4 *cis*) 5.66 (td, *J* = 15 and 7 Hz, H-4 *trans*), 5.90-6.13 (m, 1H, H-3), 6.25 (td, *J* = 17 and 10 Hz, H-2 *trans*), 6.55 (tdd, *J* = 17, 11 and 1 Hz, H-2 *cis*).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 8.23 (C-9), 13.95 (OCH_2CH_3), 22.35, 25.01, 25.27, 26.91 (C-6, 8), 30.89, 31.45 (C-5), 57.47, 57.59 (C-7), 60.09 (OCH_2), 115.31, 117.33 (C-1), 129.67, 130.97, 131.26, 131.68, 133.64, 136.82 (C-2, 3, 4), 171.48 (C-CO_2Et).

IR (ATR): υ (cm^{-1}) = 3086 (w), 2977 (s), 2940 (m), 2906 (m), 2882 (m), 1729 (vs), 1653 (w), 1603 (w), 1464 (s), 1447 (s), 1242 (vs), 1215 (vs), 1190 (vs), 1153 (vs), 1005 (s), 904 (m), 737 (w).

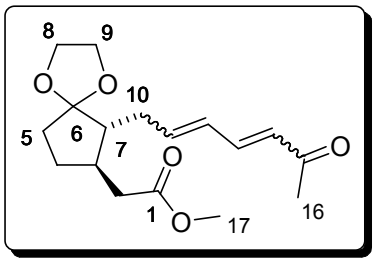
MS (EI, RT): m/z (%) = 268 ([M^+], 3), 223 (8), 188 (100), 173 (52), 142 (48), 99 (22), 80 (52), 67 (29).

HRMS (M^+, $C_{15}H_{24}O_4$): calcd. 268.1675, found: 268.1677.

GC-MS 2 peaks with retention time 19.20 and 19.37 min.

[6-(6-oxo-hepta-2,4-dienyl)-1,4-dioxaspiro[4.4]non-7-yl]-acetic acid methyl ester (147) and [6-(4-oxo-pent-2-enyl)-1,4-dioxaspiro[4.4]non-7-yl]-acetic acid methyl ester (148)
Following the general procedure D, diene **142** (20 mg, 75 μmol), MVK (19 μL, 0.23 mmol), and [**Ru**] (2.3 mg, 3.8 μmol) in CH_2Cl_2 (1.5 mL) were employed to give after 3 h reaction and preparative TLC (cyclohexane/ethylacetate 2:1) dienone **147** (8 mg, 35%, 4:1:1:1 (11*E*,13*E*)/(11*E*,13*Z*)/(11*Z*,13*E*)/(11*Z*,13*Z*) as determined by ^{1}H NMR) and enone **148** (8 mg, 38%, 1:1 *E*:*Z*) as yellow oil.

Dienone 147



R_f : 0.23 (SiO_2, cyclohexane/ethyl acetate 3:2).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.21-1.50 and 1.62-2.62 (m, 13H, H-2-7, 10, 16), 3.64 (s, 3H, H-17), 3.85 (s br, 4H, H-8, 9), 5.88-6.30 (m, 3H, H-11, 12 ,14), 6.57 (dd, *J* = 9 and 13 Hz, H-13 *E*,*Z*), 6.72-6.89 (m, H-13 *Z*,*Z*), 7.01-7.18 (m, H-13 *E*,*E*), 7.42-7.57 (dd, *J* = 11 and 15 Hz, H-13 *Z*,*E*).

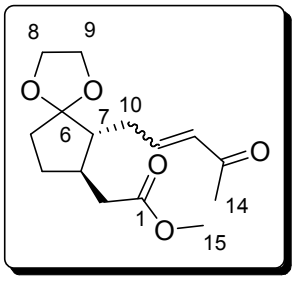
^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 19.67 (C-3), 27.86 (C-16), 27.85, 32.23 (C-4, 5), 34.97 (C-2), 38.81 (C-7), 39.38 (C-10), 51.39 (C-17), 64.01, 64.46 (C-8, 9), 117.28 (C-6), 128.71, 129.52 (C-12, 13), 143.63, 144.27 (C-11, 14), 172.86 (C-1), 199.02 (C-15).

IR (ATR): υ (cm^{-1}) = 2953 (s), 2888 (m), 1734 (vs), 1676 (s), 1631 (m), 1595 (w), 1437 (s), 1361 (s), 1255 (s), 1209 (m), 1152 (s), 1033 (m), 1002 (m), 950 (m).

MS (EI, 120 °C): m/z (%) = 308 ([M^+], 2), 265 (8), 251 (2), 241 (12), 225 (6), 213 (4), 181 (4), 169 (4), 137 (4), 125 (8), 99 (37), 55 (100).

HRMS (M^+, $C_{17}H_{24}O_5$): calcd: 308.1624, found: 308.1629.

Enone 148



R_f : 0.19 (SiO_2, cyclohexane/ethyl acetate 3:2).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.21-1.50 and 1.62-2.62 (m, 13H, H-2-7, 10, 14), 3.64 (s, 3H, H-15), 3.78-3.97 (m, 4H, H-8, 9), 6.00-6.13 (m, 1H, H-12), 6.83 (td, *J* = 7 and 16 Hz, 1H, H-11).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 19.67 (C-3), 26.56 (C-15), 27.83, 32.21 (C-4, 5), 34.96 (C-2), 38.79 (C-7), 39.23 (C-10), 50.27 and 51.39 (C-14), 63.99, 64.45 (C-8, 9), 117.27 (C-6), 131.84 (C-12), 147.68 (C-11), 172.85 (C-1), 198.68 (C-13).

IR (ATR): υ (cm^{-1}) = 2952 (m), 2886 (m), 1734 (vs), 1671 (vs), 1627 (s), 1594 (w), 1436 (s), 1360 (s), 1254 (vs), 1204 (s), 1148 (vs), 1033 (s), 998 (s), 949 (s).

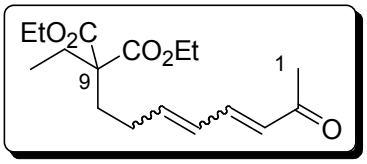
MS (EI, 70 °C): m/z (%) = 282 ([M^+], 10), 267 (>1), 251 (3), 239 (5), 224 (4), 209 (12), 155 (9), 125 (5), 99 (100), 86 (20).

HRMS (M^+, $C_{15}H_{22}O_5$): calcd: 282.1467, found: 282.1470.

2-Ethyl-2-(7-oxo-octa-3,5-dienyl)-malonic acid diethyl ester (149), 2-but-3-enyl-2-ethyl-malonic acid diethyl ester (150), and 2,11-bis-ethoxycarbonyl-2,11-diethyl-dodeca-5,7-dienoic acid diethyl ester (151).

Following the general procedure D, diene **144** (20 mg, 75 μmol), MVK (19 μL, 0.22 mmol), and [**Ru**] (2.3 mg, 3.7 μmol) in CH_2Cl_2 (1.5 mL) were employed to yield after 3 h reaction and column chromatography (cyclohexane/ethyl acetate 10:1) dienone **149** (9 mg, 38%), monoene **150** (2 mg, 11%), and dimer **151** (5 mg, 13%) as yellow oil.

Dienone 149



R_f : 0.31 (SiO_2, cyclohexane/ethyl acetate 10:1).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 0.81 (t, *J* = 7 Hz, 3H, H-11), 1.22 (t, *J* = 7 Hz , 6H, OCH_2CH_3), 1.82-2.17 (m, 6H, H-

7, 8, 10), 2.24 (d, *J* = 5Hz, 3H, H-1), 4.16 (q, *J* = 7 Hz, 4H, OC*H*$_2$), 6.00-6.20 (m, 3H, H-3, 5, 6), 6.76 (td, *J* = 16 and 6 Hz, H-4 *E*, *Z*), 7.06 (dd, *J* = 16 and 9 Hz, H-4 *E*, *E*).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 8.28 (C-11), 13.95 (OCH_2CH_3), 25.32 (C-10), 26.78, 27.07 (C-1), 27.00, 27.59 (C-8), 30.00, 30.49 (C-7), 57.37 (C-9), 61.00 (OCH_2), 129.12, 131.35, 143.28, 143.60, 146.63 (C-3, 4, 5, 6), 171.18 (*C*OO), 198.30, 198.54 (C-2).

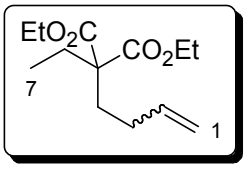
IR (ATR): υ (cm^{-1}) = 2978 (m), 2940 (m), 2907 (w), 2883 (w), 1727 (vs), 1677 (s), 1629 (m), 1465 (m), 1448 (m), 1366 (m), 1300 (m), 1249 (s), 1218 (s), 1191 (s), 1127 (s), 1113 (s), 1027 (s), 981 (m), 860 (m).

MS (EI, 70 °C): m/z (%) = 310 ([M^+], 2), 285 (2), 266 (1), 265 (4), 239 (10), 188 (100), 173 (64), 142 (44), 127 (48), 123 (37), 107 (34), 99 (67), 95 (58).

HRMS (M^+, $C_{17}H_{26}O_5$): calcd. 310.1780, found: 310.1801.

GC-MS 2 peaks with retention time 19.93 and 20.34 min.

Monoene 150

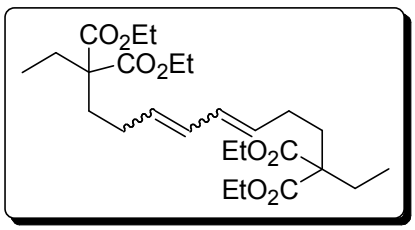


R_f : 0.80 (SiO_2, cyclohexane/ethyl acetate 10:1).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 0.82 (t, *J* = 7 Hz, 3H, H-7), 1.23 (t, *J* = 7 Hz, 6H, OCH_2CH_3), 1.83-2.00 (m, 6H, H-3, 4, 6), 4.18 (q, *J* = 7 Hz, 4H, OC*H*$_2$), 4.90-5.15 (m, 2H, H-1), 5.66-5.91 (m, 1H, H-2).

GC-MS retention time 17.7 min.

Dimer 151



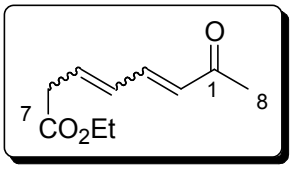
R_f : 0.56 (SiO_2, cyclohexane/ethyl acetate 10:1).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 0.79 (t, *J* = 7 Hz, 6H, CH_3), 1.20 (t, *J* = 7 Hz, 12H, OCH_2CH_3), 1.75-2.05 (m, 12H, CH_2), 4.15 (q, *J* = 7 Hz, 8H, OC*H*$_2$), 5.31-6.37 (m, 4H, H-olefin).

7-Oxo-octa-3,5-dienoic acid ethyl ester (152) and Octa-3,5-dienoic acid diethyl ester (153)

Following the general procedure D, (*E*)-hexa-3,5-dienoic acid ethyl ester **146** (40 mg, 0.28 mmol), MVK (70 µL, 0.85 mmol), and [**Ru**] (8 mg, 13 µmol) in CH_2Cl_2 (5.6 mL) were employed to give after 3 h reaction a complex mixture, which afforded after preparative TLC (cyclohexane/ethylacetate 2:1) 2 main products: dienone **152** (12 mg, 24%) and dimer **153** (6 mg, 9%) as yellow oil.

Dienone 152



R_f : 0.35 (SiO_2, cyclohexane/ethyl acetate 3:2)

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.25 (tt, *J* = 7 and 1 Hz, 3H, OCH_2CH_3), 2.15-2.42 (m, 3H, H-8), 3.11-3.38 (m, 2H, H-2), 4.13 (m, 2H, OCH_2), 5.79-6.36 (m, 3H, H-3, 4, 6), 6.50-7.19 (m, 1H, H-5).

^{13}C NMR (50 MHz, $CDCl_3$): 13.99 (OCH_2CH_3), 26.73, 27.03 (C-8), 37.46, 38.13 (C-2), 60.34, 61.08(OCH_2), 130.33, 131.73, 133.81, 134.87, 138.58, 139.51, 140.45, 142.36 (C-3-6), 169.74, 170.34 (C-1), 197.86, 198.41 (C-7).

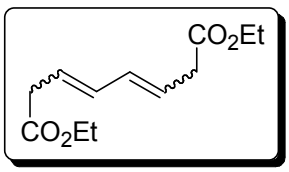
IR (ATR): υ (cm^{-1}) = 2980 (m), 2959 (m), 2925 (m), 2872 (w), 2852 (w), 1732 (vs), 1714 (vs), 1667 (s), 1639 (m), 1617 (m), 1598 (m), 1580 (m), 1465 (w), 1446 (w), 1367 (m), 1301 (m), 1252 (s), 1175 (s), 1158 (s), 1134 (s), 1096 (m), 1028 (s), 999 (s), 858 (w).

MS (EI, RT): m/z (%) = 182 ([M^+], 7), 167 (1), 153 (7), 147 (3), 140 (12), 137 (4), 135 (3), 111 (3), 109 (12), 108 (15), 95 (70), 93 (5), 67 (17), 66 (18), 58 (100).

HRMS (M^+, $C_{10}H_{14}O_3$): calcd. 182.0943, found: 182.0943.

GC-MS retention time 18.01 min.

Dimer 153



R_f : 0.54 (SiO_2, cyclohexane/ethyl acetate 3:2).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.25 (t, 6H, OCH_2CH_3), 3.01-3.25 (m, 4H, CH_2), 4.12 (q, *J* = 7 Hz, 4H, OCH_2CH_3), 5.50-6.42 (m, 4H, H-olefin).

^{13}C NMR (50 MHz, $CDCl_3$): 14.03 (OCH_2CH_3), 37.90 (CH_2), 60.71 (OCH_2CH_3), 124.77, 132.87 (C-olefin), 171.38 (CO_2).

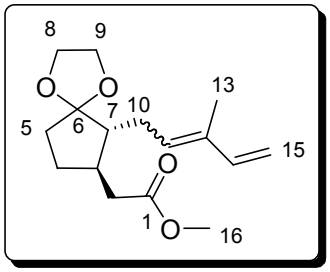
IR (ATR): υ (cm^{-1}) = 2981 (m), 2934 (w), 2908 (w), 1731 (vs), 1465 (w), 1446 (w), 1368 (m), 1300 (m), 1257 (s), 1174 (s), 1156 (vs), 1096 (m), 1026 (s), 989 (s), 939 (m), 857 (m).

MS (EI, 40 °C): m/z (%) = 226 ([M^+], 18), 180 (15), 167 (9), 153 (23), 134 (27), 111 (16), 107 (35), 83 (21), 80 (30), 79 (100), 67 (12).

HRMS (M^+, $C_{12}H_{18}O_4$): calcd. 226.1205, found: 226.1210.

GC-MS retention time 18.90 and 19.04 min.

[6-(3-Methyl-penta-2,4-dienyl)-1,4-dioxaspiro[4.4]non-7-yl]-acetic acid methyl ester (154)



To a solution of 1-methyl-allyldiphenylphosphine oxide (0.7 g, 2.7 mmol) in anhydrous THF (10 mL) at -78 °C, *n*-BuLi (1.7 mL, 1.6 M in hexane) was added dropwise. After further stirring for 20 min at the same temperature, anhydrous HMPA (0.96 mL, 5.48 mmol) was added, followed by slow addition of aldehyde **141** (0.5 g, 2 mmol) in anhydrous THF (2 mL), while temperature was kept below -72 °C. Stirring was continued at -78 °C for 2 h and water (5 mL) was added. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 20 mL). The combined organic layers were washed with saturated aqueous LiBr solution (2 x 20 mL), dried over $MgSO_4$, and evaporated. Purification was done with column chromatography (SiO_2, cyclohexane/ethyl acetate 9:1) to give diene **154** as a clear oil (147 mg, 25%, 4:1 *E*/*Z*).

R_f : 0.61 (SiO_2, cyclohexane/ethyl acetate 3:2).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.20-1.50 and 1.63-2.62 (m, 13H, H-2-7, 10, 13), 3.61 (s, 3H, H-16), 3.79-3.93 (m, 4H, H-8, 9), 4.96 (dd, *J* = 28 and 11 Hz, H-15 *E*), 5.01-5.23

(m, H-15 *Z*), 5.38 (t, *J* = 7 Hz, H-11 *Z*), 5.49 (t, *J* = 7 Hz, H-11 *E*), 6.34 (dd, *J* = 17 and 11 Hz, H-14 *E*), 6.78 (ddd, *J* = 17, 11 and 1 Hz, H-14 *Z*).

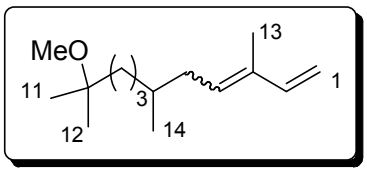
^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 11.58 (C-13), 19.67 (C-3), 27.86, 27.85 (C-4, 5), 35.59 (C-2), 39.13 (C-7), 39.63 (C-10), 51.29 (C-16), 64.02, 64.50 (C-8, 9), 110.28 (C-15 *E*), 113.28 (C-15 *Z*), 117.46 (C-6), 129.68 (C-11 *Z*), 131.79 (C-11 *E*), 133.55 (C-12 *Z*), 134.09 (C-12 *E*), 141.39 (C-14), 173.03 (C-1).

IR (ATR): υ (cm^{-1}) = 3088 (w), 2951 (s), 2882 (m), 1737 (vs), 1641 (w), 1606 (w), 1436 (s), 1306 (m), 1257 (m), 1203 (m), 1150 (s), 1034 (m), 991 (m), 949 (m), 895 (m).

MS (EI, 50 °C): m/z (%) = 280 ([M^+], 23%), 265 (2), 249 (7), 225 (4), 218 (14), 207 (47), 197 (6), 163 (13), 145 (30), 144 (34), 127 (20), 99 (100), 86 (25).

HRMS (M^+, $C_{16}H_{24}O_4$): calcd: 280.1674, found: 280.1677.

10-Methoxy-3,6,10-trimethyl-undeca-1,3-diene (156)



To a solution of 1-methyl-allyldiphenylphosphine oxide (0.91 g, 3.6 mmol) in anhydrous THF (15 mL) at -78 °C, *n*-BuLi (2.2 mL, 1.6 M in hexane) was added dropwise. After further stirring for 20 min at the same temperature, anhydrous HMPA (1.25 mL, 7.1 mmol) was added, followed by slow addition of 7-methoxy-3,7-dimethyl-octanal **155** (0.5 g, 2.7 mmol) in anhydrous THF (2 mL), while temperature was kept below -72 °C. After 2 h stirring at -78 °C and warming to rt, water (5 mL) was added. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with saturated aqueous LiBr solution (2 x 20 mL), dried over $MgSO_4$, and evaporated. Purification was done with column chromatography (SiO_2, cyclohexane/ethyl acetate 30:1) to yield diene **156** (462 mg, 77 %, 4:1 *E*/*Z*) as a clear oil.

R_f : 0.48 (SiO_2, cyclohexane/ethyl acetate 9:1).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 0.80-0.95 (d, *J* = 7 Hz, 3H, H-14), 1.05-1.60 (m, 12H, H-7, 8, 9, 11, 12), 1.72 (s, 3H, H-13), 1.75-1.21 (m, 3H, H-5, 6), 3.15 (s, 3H, OC*H*$_3$),

4.9 (dd, *J* = 30, 11 Hz, H-1 *E*), 5.05-5.25 (m, H-1 *Z*), 5.38 (t, *J* = 8 Hz, H-4 *Z*), 5.55 (t, *J* = 7 Hz, H-4 *E*), 6.37 (dd, *J* = 18 and 11 Hz, H-2 *E*), 6.75 (ddd, *J* = 17, 11 and 1 Hz, H-2 *Z*).

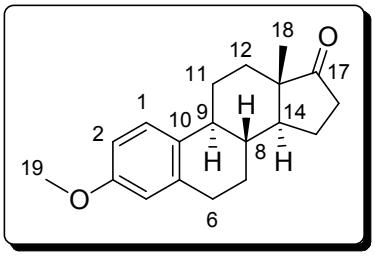
^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 11.64 (C-14), 19.52 (C-13), 21.21 (C-7), 24.83 (C-11, 12), 33.44 (C-6), 35.41, 37.09, 39.88 (C-5, 8, 9), 48.92 (O*C*H$_3$), 74.04 (C-10), 110.06 (C-1 *E*), 112.94 (C-1 *Z*), 130.04 (C-4 *Z*), 132.08 (C-4 *E*), 133.74 (C-3 *Z*), 134.32 (C-3 *E*), 141.57 (C-2).

IR (ATR): υ (cm^{-1}) = 3089 (w), 2969 (vs), 2938 (vs), 2902 (s), 2871 (s), 2847 (m), 2824 (m), 1642 (w), 1607 (m), 1462 (m), 1379 (s), 1363 (s), 1216 (m), 1196 (m), 1187 (m), 1154 (m), 1086 (vs), 988 (s), 891 (s).

MS (EI, 50 °C): m/z (%) = 224 ([M^+], 1%), 209 (2), 192 (8), 178 (2), 177 (10), 163 (2), 149 (10), 136 (10), 121 (10), 109 (14), 107 (18), 93 (10), 81 (23), 73 (100), 69 (30).

HRMS (M^+, $C_{15}H_{28}O$): calcd: 224.2140, found: 224.2143.

(8*R*,9*S*,13*S*,14*S*)-3-Methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-cyclopenta [α]phenanthren-17-one (*O*-methyl estrone) (158)



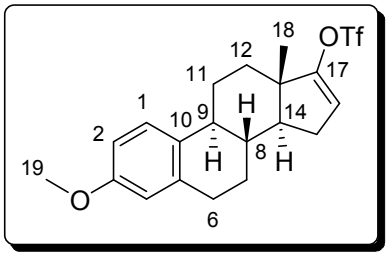
Estrone (400 mg, 4.48 mmol) was stirred in refluxing ethanol (20 mL) until it dissolved completely, then over a period of 8 min was treated 4 times alternately with 0.7 mL portions each of 50% aqueous KOH and dimethyl sulfate. The addition of KOH is exothermic and the first addition of dimethyl sulfate generates a white solid which dissolved under vigorous stirring. The mixture was refluxed for another 30 min, cooled to rt and evaporated. The residue was dissolved in water and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were filtrated through $MgSO_4$, washed with brine, dried over $MgSO_4$, and evaporated to furnish neat *O*-methyl estrone **158** (366 mg, 87%) as a white solid.

R_f : 0.53 (SiO_2, cyclohexane/ethyl acetate 3:2).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 0.91 (s, 3H, H-18), 1.30-1.72 (m, 7H), 1.90-2.52 (m, 6H), 2.92 (t, *J* = 5 Hz, 2H, H-6), 3.79 (s, 3H, H-19), 6.67 (d, *J* = 3 Hz, 1H, H-4), 6.73 (dd, *J* = 8 and 3 Hz, 1H, H-2), 7.22 (d, *J* = 9 Hz, 1H, H-1).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 13.70 (C-18), 21.42, 25.75, 26.39, 29.51, 31.41, 35.71 (C-6, 7, 11, 12, 15, 16), 38.23 (C-9), 43.83 (C-8), 47.88 (C-13), 50.26 (C-14), 55.06 (C-19), 111.41 (C-1), 113.73 (C-2), 126.19 (C-4), 131.88 (C-10), 137.61 (C-5), 157.44 (C-3), 220.81 (C-17).

Trifluoro-methanesulfonic acid (8*R*,9*S*,13*S*,14*S*)-3-methoxy-13-methyl-7,8,9,11,12,13,14, 15-octahydro-6H-cyclopenta[α]phenanthren-17-yl ester



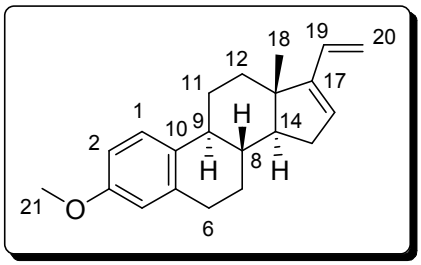
To a solution of NaHMDS (0.7 mL, 1M in THF) at -78 °C, *O*-methyl estrone **158** (99 mg, 0.34 mmol) in anhydrous THF (5 mL) was added. After 1h stirring, *N*-phenyltrifluoromethanesulfonimide (200 mg, 0.55 mmol) was added to the resulting enolate. After 20 min, the reaction mixture was slowly warmed to rt and stirred for 1 h. The reaction was quenched with water and extracted with diethyl ether (3 x 10 mL). The organic layer was washed subsequently with saturated aqueous solution of NH_4Cl and brine, dried over $MgSO_4$, and evaporated. The purification was done with column chromatography (SiO_2, cyclohexane/ethyl acetate 30:1) to afford vinyl triflate (113 mg, 78%) as a clear oil.

R_f : 0.59 (SiO_2, cyclohexane/ethyl acetate 3:2).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.01 (s, 3H, H-18), 1.30-2.50 (m, 11H), 2.92 (t, *J* = 5 Hz, 2H, H-6), 3.79 (s, 3H, H-19), 5.65 (s, 1H, H-16), 6.65 (m, 1H, H-4), 6.76 (dd, *J* = 8 and 3 Hz, 1H, H-2), 7.20 (d, *J* = 9 Hz, 1H, H-1).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 15.19 (C-18), 25.71, 26.64, 28.24, 29.32, 32.61 (C-6, 7, 11, 12, 15), 36.58 (C-8), 44.07 (C-9), 44.96 (C-13), 53.42 (C-14), 55.03 (C-19), 111.37 (C-1), 113.78 (C-2), 114.37 (C-16), 121.68 (*C*F$_3$),125.83 (C-4), 131.99 (C-10), 137.54 (C-5), 157.50 (C-3), 159.20 (C-17).

(8*R*,9*S*,13*S*,14*S*)-3-Methoxy-13-methyl-17-vinyl-7,8,9,11,12,13,14,15-octahydro-6H-cyclopenta[α]phenanthrene (159)



To a solution of vinyl triflate (113 mg, 0.27 mmol) in anhydrous THF (5 mL), $Pd(PPh_3)_4$ (9 mg, 8.1 μmol), LiCl (52 mg, 1.22 mmol), and tributyltin (95 mg, 0.3 mmol) were added subsequently. The reaction mixture was refluxed for 2h, quenched with water, and extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed subsequently with a 10% aqueous solution of NH_4OH and brine, dried over $MgSO_4$, and evaporated. The purification was done with column chromatography (SiO_2, cyclohexane/ethyl acetate 9:1) to yield diene **159** (43 mg, 54%) as a viscous oil.

R_f : 0.69 (SiO_2, cyclohexane/ethyl acetate 3:2)

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 0.95 (s, 3H, H-18), 1.32-2.49 (m, 11H), 2.80-3.01 (m, 2H, H-6), 3.81 (s, 3H, H-21), 5.00 (d, *J* = 11 Hz, 1H, H-20), 5.35 (d, *J* = 18 Hz, 1H, H-20), 5.72 (br s, 1H, H-16), 6.31 (dd, *J* = 18 and 11 Hz, 1H, H-19), 6.62 (s, 1H, H-4), 6.70 (dd, *J* = 8 and 3 Hz, 1H, H-2), 7.20 (d, *J* = 9 Hz, 1H, H-1).

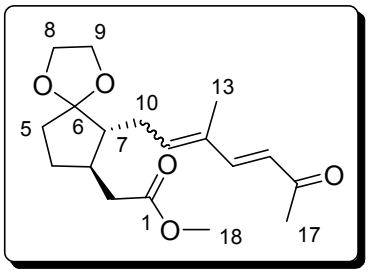
^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 15.93 (C-18), 26.55, 27.62, 29.62, 30.90, 35.26 (C-6, 7, 11, 12, 15), 37.08 (C-8), 44.15 (C-9), 46.38 (C-13), 55.06 (C-14), 56.38 (C-21), 111.28 (C-1), 112.81 (C-20), 113.72 (C-2), 125.91 (C-4), 129.17 (C-16), 132.29 (C-10), 132.79 (C-19), 137.84 (C-5), 153.23 (C-17), 157.32 (C-3).

IR (ATR): υ (cm^{-1}) = 3096 (w), 3082 (w), 3032 (w), 3010 (w), 2928 (vs), 2852 (m), 2833 (m), 1715 (m), 1609 (s), 1575 (m), 1499 (vs), 1464 (m), 1453 (m), 1371 (m), 1312 (m), 1281 (s), 1256 (vs), 1237 (vs), 1162 (m), 1154 (m), 1049 (s), 1037 (s), 992 (m), 962 (m), 889 (m), 817 (s), 781 (m).

MS (EI, 100 °C): m/z (%) = 294 ([M^+], 100%), 279 (30), 268 (6), 251 (2), 239 (2), 225 (3), 211 (4), 199 (9), 186 (34), 173 (43), 171 (20), 160 (16), 147 (24), 145 (6), 121 (7), 119 (10), 105 (22), 95 (4), 91 (16).

HRMS (M^+, $C_{21}H_{26}O$): calcd: 294.1984, found: 294.1985.

[6-((4*E*)-3-Methyl-6-oxo-hepta-2,4-dienyl)-1,4-dioxaspiro[4.4]non-7-yl]-acetic acid methyl ester (162)



Following the general procedure D, diene **154** (20 mg, 71 μmol), MVK (18 μL, 0.21 mmol), and [**Ru**] (2.2 mg, 3.6 μmol) in CH_2Cl_2 (1.4 mL) were employed to give after 3 h reaction and preparative TLC (cyclohexane/ethylacetate 3:2) dienone **162** (17 mg, 73%, 4:1 *E*,*E*/*Z*,*E*) as a clear oil.

R_f : 0.26 (SiO_2, cyclohexane/ethyl acetate 3:2).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.20-1.50 and 1.63-2.60 (m, 16H, H-2-7, 10, 13, 17), 3.63 (s, 3H, H-18), 3.72-3.93 (m, 4H, H-8, 9), 5.80 (t, *J* = 8 Hz, H-11, *Z*), 5.96 (t, *J* = 7 Hz, H-11, *E*), 6.05 (d, *J* = 15 Hz, H-15, *E*), 6.13 (d, *J* = 15 Hz, H-15, *Z*), 7.12 (d, *J* = 16 Hz, H-14, *E*), 7.60 (d, *J* = 15 Hz, H-14, *Z*).

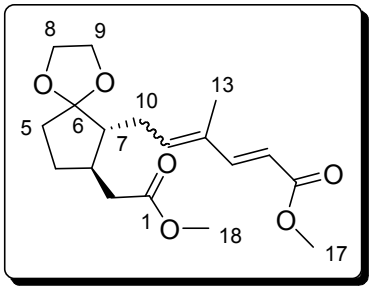
^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 12.06 (C-13), 19.95 (C-3), 27.77 (C-17), 27.86, 28.01 (C-4, 5), 34.99 (C-2), 39.14 (C-7), 39.40 (C-10), 51.36 (C-18), 63.96, 64.41 (C-8, 9), 117.26 (C-6), 124.88 (C-15 *E*), 127.18 (C-15 *Z*), 130.98 (C-12 *Z*), 133.12 (C-12 *E*), 139.28 (C-11 *Z*), 142.02 (C-11 *E*), 148.36 (C-14), 172.85 (C-1 *E*), 173.51 (C-1 *Z*), 198.36 (C-16 *Z*), 198.82 (C-16 *E*).

IR (ATR): υ (cm^{-1}) = 3446 (w), 2953 (s), 2888 (m), 1734 (vs), 1677 (s), 1628 (m), 1588 (w), 1437 (s), 1359 (s), 1306 (m), 1257 (s), 1207 (s), 1154 (s), 1034 (s), 984 (m), 949 (m), 890 (m).

MS (EI, 50 °C): m/z (%) = 322 ([M^+], 2%), 280 (8), 265 (2), 249 (4), 213 (28), 207 (14), 185 (5), 171 (5), 144 (6), 127 (8), 99 (100), 86 (14).

HRMS (M^+, $C_{18}H_{26}O_5$): calcd: 322.1780, found: 322.1788.

(4*E*)-6-(7-Methoxycarbonylmethyl-1,4-dioxaspiro[4.4]non-6-yl)-4-methyl-hexa-2,4-dienoic acid methyl ester (163)



Following the general procedure D, diene **154** (20 mg, 71 µmol), methyl acrylate (19 µL, 214 µmol), and [**Ru**] (2.2 mg, 3.6 µmol) in CH_2Cl_2 (1.4 mL) were employed to yield after 3 h reaction and preparative TLC (cyclohexane/ethylacetate 2:1) dienoic ester **163** (9 mg, 37%, 4:1 (*E*,*E*)/(*Z*,*E*)) as a clear oil.

R_f : 0.37 (SiO_2, cyclohexane/ethyl acetate 3:2).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.15-1.55 and 1.60-2.65 (m, 13H, H-2-7, 10, 13), 3.60-3.97 (m, 10H, H-8, 9, 17, 18), 5.78 (d, 1H, *J* = 16 Hz, H-15), 5.94 (t, 1H, *J* = 7 Hz, H-11), 7.30 (d, *J* = 16 Hz, H-14, *E*), 7.78 (d, *J* = 15 Hz, H-14, *Z*).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 12.04 (C-13), 19.92 (C-3), 27.98, 27.92 (C-4, 5), 35.08 (C-2), 39.28 (C-7), 39.44 (C-10), 51.03 (C-17), 51.32 (C-18), 64.01, 64.46 (C-8, 9), 114.86 (C-6), 117.29 (C-15 *E*), 117.51 (C-15 *Z*), 130.65 (C-12 *Z*), 132.79 (C-12 *E*), 138.41 (C-11 *Z*), 141.11 (C-11 *E*), 149.63 (C-14), 167.92 (C-16), 172.89 (C-1).

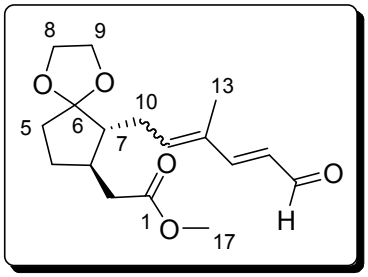
IR (ATR): υ (cm^{-1}) = 3412 (w), 2952 (m), 2885 (m), 1734 (vs), 1621 (m), 1436 (m), 1310 (s), 1274 (s), 1195 (s), 1169 (s), 1034 (m), 984 (m), 949 (m).

MS (EI, 140 °C): m/z (%) = 338 ([M^+], 5%), 307 (2), 278 (2), 265 (7), 233 (2), 225 (4), 213 (12), 189 (4), 169 (6), 125 (9), 99 (100), 86 (12).

HRMS (M^+, $C_{18}H_{26}O_6$): calcd: 338.1729, found: 338.1734.

GC-MS retention time 27.12 and 27.37 min.

[6-(4*E*)-3-Methyl-6-oxo-hexa-2,4-dienyl-1,4-dioxaspiro[4.4]non-7-yl)-acetic acid methyl ester (164)



Following the general procedure D, diene **154** (20 mg, 71 μmol), acrolein (16 μL, 214 μmol), and [**Ru**] (2.2 mg, 3.6 μmol) in CH_2Cl_2 (1.4 mL) were employed to afford after 3 h reaction and preparative TLC (cyclohexane/ethyl acetate 2:1) product **164** (5 mg, 23%, 4:1 (*E*,*E*)/(*Z*,*E*)) as a yellow oil together with recovered diene **154** (12 mg).

R_f : 0.30 (SiO_2, cyclohexane/ethyl acetate 3:2).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.15-1.57 and 1.60-2.70 (m, 13H, H-2-7, 10, 13), 3.67 (s, 3H, H-17), 3.75-4.00 (m, 4H, H-8, 9), 6.00-6.20 (m, 2H, H-11, 15), 7.11 (d, *J* = 16 Hz, 1H, H-14), 9.53 (d, *J* = 7 Hz, H-16, *E*), 9.75 (m, H-16, *Z*).

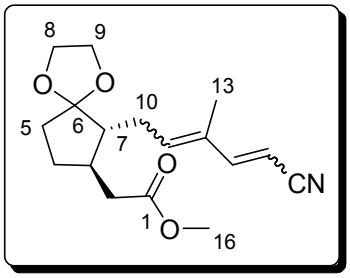
IR (ATR): υ (cm^{-1}) = 3434 (w), 2953 (m), 2888 (m), 1734 (vs), 1691 (s), 1623 (w), 1437 (m), 1307 (m), 1260 (s), 1207 (s), 1150 (s), 1033 (s), 984 (m), 949 (m).

MS (EI, 110 °C): m/z (%) = 309 ([M^+], 2%), 265 (2), 213 (10), 199 (2), 185 (6), 169 (6), 141 (5), 125 (5), 99 (100), 86 (7).

HRMS (M^+, $C_{17}H_{25}O_5$): calcd: 309.1702, found: 309.1712.

GC-MS retention time 25.21 min.

6-(5-Cyano-3-methyl-penta-2,4-dienyl)-1,4-dioxaspiro[4.4]non-7-yl-acetic acid methyl ester (165)



Following the general procedure D, diene **154** (20 mg, 71 μmol), acryl nitrile (14 μL, 214 μmol), and [**Ru**] (2.2 mg, 3.6 μmol) in CH_2Cl_2 (1.4 mL) were employed to furnish after 3 h reaction and preparative TLC (cyclohexane/ethylacetate 2:1) compound **165** (3 mg, 14%, 16:4:4:1 (11*E*,14*E*)/(11*E*,14*Z*)/(11*Z*,14*E*)/(11*Z*,14*Z*) as determined by ^{1}H NMR) as a clear oil together with recovered diene **154** (15 mg).

R_f : 0.37 (SiO_2, cyclohexane/ethyl acetate 3:2).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.25-2.55 (m, 13H, H-2-7, 10, 13), 3.65 (s, 3H, H-16), 3.70-3.95 (m, 4H, H-8, 9), 5.05 (d, *J* = 12 Hz, 1H, H-15, *E*,*Z*), 5.09 (d, *J* = 16Hz, H-15, *E*,*E*), 5.30 (d, *J* = 17 Hz, 1H, H-15, *Z*,*E*), 5.93 (t, *J* = 7 Hz, 1H, H-11), 6.60 (d, *J* = 12 Hz, H-14, *E*,*Z*), 7.03 (d, *J* = 16 Hz, H-14, *E*,*E*), 7.54 (d, *J* = 17 Hz, H-14, *Z*,*E*).

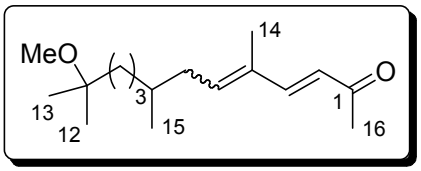
IR (ATR): υ (cm^{-1}) = 3421 (w), 2953 (m), 2927 (m), 2886 (m), 2224 (w), 1733 (vs), 1633 (w), 1437 (m), 1306 (m), 1263 (s), 1200 (s), 1150 (s), 1031 (s), 968 (m), 949 (m), 894 (w).

MS (EI, 110 °C): m/z (%) = 306 ([M^+], 1%), 290 (1), 279 (3), 260 (3), 248 (4), 213 (10), 185 (4), 169 (4), 149 (12), 125 (4), 99 (100), 95 (6).

HRMS (M^+-CH_3, $C_{16}H_{20}O_4N$): calcd: 290.1392, found: 290.1399.

GC-MS retention time 24.39, 25.42 and 25.98 min.

(3*E*)-12-Methoxy-5,8,12-trimethyl-trideca-3,5-dien-2-one (166)



Following the general procedure D, diene **156** (20 mg, 89 μmol), MVK (22 μL, 267 μmol), and [**Ru**] (2.8 mg, 4.5 μmol) in CH_2Cl_2 (1.8 mL) were employed to give after 3 h reaction and preparative TLC (cyclohexane/ethylacetate 2:1) dienone **166** (30 mg 77%, 4:1 (*E*,*E*)/(*E*,*Z*)) as a clear oil.

R_f : 0.51 (SiO_2, cyclohexane/ethyl acetate 3:2).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 0.78-0.95 (d, *J* = 7 Hz, 3H, H-15), 1.03-1.65 (m, 13H, H-7-13), 1.72 (s, H-14 *E*), 1.85 (s, H-14 *Z*), 1.92-2.40 (m, 5H, H-6, 16), 3.15 (s, 3H, OC*H*$_3$), 5.80 (t, *J* = 8 Hz, H-5 *Z*), 5.95 (t, *J* = 8 Hz, H-5 *E*), 6.05 (d, *J* = 17 Hz, H-2 *E*), 6.12 (d, *J* = 18 Hz, H-2 *Z*), 7.12 (d, *J* = 16 Hz, H-3 *E*), 7.55 (d, *J* = 16 Hz, H-3 *Z*).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 12.14 (C-15), 19.43 (C-14 *E*), 20.01 (C-14 *Z*), 21.14 (C-8), 24.77 (C-12, 13), 27.09 (C-16 *E*), 27.48 (C-16 *Z*), 33.27 (C-7), 36.11, 37.08, 39.91 (C-

6, 9, 10), 48.92 (O*C*H$_3$), 74.36 (C-11), 124.83 (C-2), 133.56 (C-4), 142.21 (C-5), 148.58 (C-3), 198.80 (C-1).

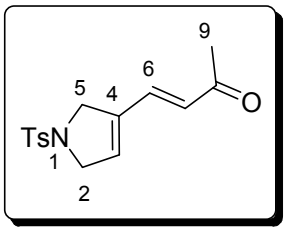
IR (ATR): υ (cm^{-1}) = 3413 (w), 3314 (w), 2969 (vs), 2939 (vs), 2873 (s), 2825 (m), 1720 (m), 1701 (m), 1679 (vs), 1628 (m), 1597 (w), 1463 (m), 1380 (s), 1363 (vs), 1254 (s), 1213 (m), 1186 (m), 1152 (m), 1084 (vs), 982 (m).

MS (EI, 80 °C): m/z (%) = 267 ([M+H$^+$], 1%), 250 (1), 234 (2), 219 (1), 195 (2), 177 (1), 163 (2), 147 (3), 137 (2), 123 (3), 109 (8), 96 (14), 81 (6), 73 (100), 69 (10).

HRMS (M$^+$+H, $C_{17}H_{31}O_2$): calcd: 267.2324, found: 267.2329.

GC-MS retention time 21.81 and 20.88 min.

(*E*)-4-[1-(Toluene-4-sulfonyl)-2,5-dihydro-1*H*-pyrrol-3-yl]-but-3-ene-2-one (167)



Following the general procedure D, 3-vinyl-2,5-dihydro-pyrrole-1-sulfonic acid *p*-tolyl ester **157** (20 mg, 80 µmol), MVK (20 µL, 240 µmol), and [**Ru**] (2.5 mg, 4 µmol) in CH_2Cl_2 (1.6 mL) were employed to furnish after 3 h reaction and column chromatography (SiO_2, cyclohexane/ethyl acetate 2:1) dienone **167** (20 mg, 86%) as a white solid.

R_f : 0.21 (SiO_2, cyclohexane/ethyl acetate 3:2).

mp : 130-132 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 2.28 (s, 3H, H-9), 2.42 (s, 3H, Ar-C*H*$_3$), 4.22 (br s, 4H, H-2, 5), 5.92 (d, *J* = 17 Hz, 1H, H-7), 6.15 (s, 1H, H-3), 7.12 (d, *J* = 16 Hz, 1H, H-6), 7.32 (d, *J* = 8 Hz, 2H, Ar), 7.72 (d, *J* = 8 Hz, 2H, Ar).

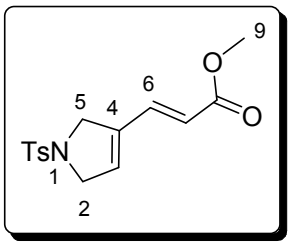
^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 21.36 (Ar*C*H$_3$), 27.64 (C-9), 53.05 (C-2), 55.27 (C-5), 127.27 (Ar), 128.95 (C-4), 129.64, 131.24 (Ar), 132.14 (C-7), 133.76 (C-3), 134.44 (C-6), 135.94, 143.68 (Ar), 197.56 (C-8).

IR (ATR): υ (cm^{-1}) = 3462 (w), 3065 (w), 3030 (w), 2971 (w), 2924 (w), 2865 (w), 1696 (s), 1671 (s), 1628 (s), 1596 (s), 1455 (m), 1420 (m), 1399 (m), 1343 (vs), 1306 (s), 1290 (s), 1254 (m), 1162 (vs), 1099 (s), 1066 (s), 1017 (m), 979 (m), 816 (s), 707 (m), 677 (s).

MS (EI, 120 °C): m/z (%) = 291 ([M^+], 35%), 289 (24), 274 (20), 264 (4), 249 (3), 226 (2), 210 (3), 198 (3), 184 (3), 155 (31), 139 (6), 136 (100), 134 (22), 120 (6), 118 (10), 108 (8), 94 (21), 91 (84), 65 (22).

HRMS (M^+, $C_{15}H_{17}O_3NS$): calcd: 291.0929, found: 291.0921.

(*E*)-3-[1-(Toluene-4-sulfonyl)-2,5-dihydro-1*H*-pyrrol-3-yl]-acrylic acid methyl ester (168)



Following the general procedure D, 3-vinyl-2,5-dihydro-pyrrole-1-sulfonic acid *p*-tolyl ester **157** (20 mg, 80 μmol), methyl acrylate (22 μL, 240 μmol), and [**Ru**] (2 mg, 4 μmol) in CH_2Cl_2 (1.6 mL) were employed to afford after 3 h reaction and column chromatography (SiO_2 cyclohexane/ethylacetate 4:1) ester **168** (11 mg, 45%) as a white solid together with the recovered diene **157** (2 mg).

R_f : 0.35 (SiO_2, cyclohexane/ethyl acetate 3:2).

mp : 143-145 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 2.61 (s, 3H, Ar-C*H*$_3$), 3.72 (s, 3H, H-9), 4.22 (br s, 4H, H-2, 5), 5.67 (d, *J* = 16 Hz, 1H, H-7), 6.02 (s, 1H, H-3), 7.24 (d, *J* = 3 Hz, 1H, H-6), 7.35 (d, *J* = 8 Hz, 2H, Ar), 7.72 (d, *J* = 8 Hz, 2H, Ar).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 21.36 (Ar*C*H$_3$), 51.64 (C-9), 53.05 (C-2), 55.18 (C-5), 120.39 (C-7), 127.27, 129.74 (Ar), 131.29 (C-3), 133.81 (C-4), 135.58 (Ar), 136.39 (C-6), 143.63 (Ar), 166.53 (C-8).

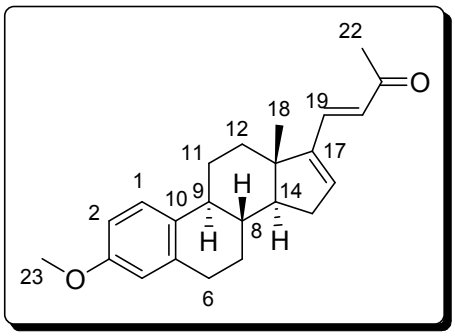
IR (ATR): υ (cm^{-1}) = 3065 (w), 3029 (w), 2992 (w), 2951 (w), 2923 (w), 2849 (w), 1718 (vs), 1641 (s), 1611 (m), 1597 (m), 1494 (w), 1457 (w), 1436 (m), 1398 (w), 1345 (vs), 1314

(s), 1289 (m), 1257 (m), 1206 (s), 1162 (vs), 1101 (s), 1069 (m), 1039 (m), 1017 (m), 985 (m), 815 (m), 709 (m), 673 (s), 661 (s).

MS (EI, 120 °C): m/z (%) = 307 ([M^+], 10%), 292 (1), 276 (5), 256 (1), 242 (1), 213 (1), 155 (14), 152 (81), 139 (2), 124 (4), 120 (100), 110 (4), 91 (56), 65 (29).

HRMS (M^+, $C_{15}H_{17}O_4NS$): calcd: 307.0878, found: 307.0878.

(*E*)-4-((8*R*,9*S*,13*S*,14*S*)-3-Methoxy-13-methyl-7,8,9,11,12,13,14,15-octahydro-6H-cyclopenta[α]phenanthren-17-yl)-but-3-en-2-one (169)



Following the general procedure D, diene **159** (20 mg, 68 μmol), MVK (17 μL, 204 μmol), and [**Ru**] (2.5 mg, 3.4 μmol) in CH_2Cl_2 (1.4 mL) were employed to give after 24 h reaction and column chromatography (SiO_2 cyclohexane/ethylacetate 20:1) dienone **169** (9 mg, 39%) as a clear oil.

R_f : 0.54 (SiO_2, cyclohexane/ethyl acetate 3:2).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 0.98 (s, 3H, H-18), 1.20-2.50 (m, 14H), 2.75-3.09 (m, 2H, H-6), 3.81 (s, 3H, H-23), 6.23 (s, 1H, H-16), 6.32 (d, *J* = 16 Hz, 1H, H-20), 6.61 (s, 1H, H-4), 6.71 (dd, *J* = 8 and 2 Hz, 1H, H-2), 7.10-7.40 (m, 2H, H-1, 19).

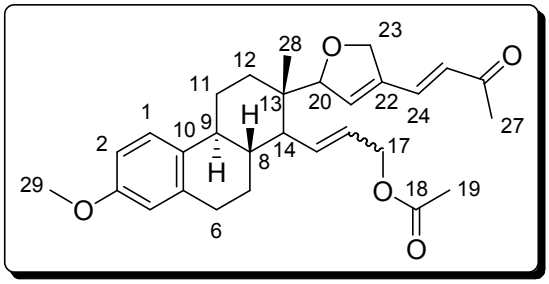
^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 15.93 (C-18), 26.92 (C-22), 26.35, 27.50, 29.49, 31.70, 35.11 (C-6, 7, 11, 12, 15), 36.96 (C-8), 43.99 (C-9), 46.36 (C-13), 55.06 (C-14), 56.28 (C-23), 111.31 (C-1), 113.72 (C-2), 125.93 (C-4), 130.71 (C-16), 132.38 (C-10), 137.67 (C-5), 139.05 (C-20), 140.31 (C-19), 151.89 (C-17), 157.37 (C-3), 198.95 (C-21).

IR (ATR): υ (cm^{-1}) = 3450 (w), 3031 (w), 2928 (s), 2855 (m), 2835 (m), 1665 (s), 1610 (vs), 1596 (s), 1576 (m), 1500 (vs), 1464 (m), 1453 (m), 1373 (m), 1359 (s), 1281 (s), 1255 (vs), 1240 (s), 1171 (m), 1163 (m), 1154 (m), 1047 (m), 1035 (m), 974 (m), 901 (w), 872 (w), 815 (m), 779 (m).

MS (EI, 170 °C): m/z (%) = 336 ([M^+], 98%), 324 (18), 309 (6), 281 (5), 265 (5), 251 (3), 227 (17), 215 (9), 199 (14), 186 (31), 173 (100), 160 (28), 147 (46), 135 (21), 115 (24), 91 (25).

HRMS (M^+, $C_{23}H_{28}O_2$): calcd: 336.2089, found: 336.2091.

Acetic acid 3-{(2*S*,4a*S*,10a*R*)-7-methoxy-2-methyl-2-[4-((*E*)-3-oxo-but-1-enyl)-2,5-dihydro-furan-2-yl]-1,2,3,4,4a,9,10,10a-octahydro-phenanthren-1-yl}-allyl ester (170)



Following the general procedure D, diene **161** (25 mg, 59 μmol), MVK (15 μL, 178 μmol), and [**Ru**] (1.8 mg, 3 μmol) in CH_2Cl_2 (1.2 mL) were employed to yield after 3 h reaction and column chromatography (SiO_2 cyclohexane/ethyl acetate 9:1) dienone **170** (20 mg, 70%) as a yellow oil.

R_f : 0.41 (SiO_2, cyclohexane/ethyl acetate 3:2).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 0.86 (s, 3H, H-28), 1.14-2.00 (m, 6H), 2.07 (s, 3H, H-19), 2.15-2.32 (m, 3H), 2.36 (s, 3H, H-27), 2.75-2.88 (m, 2H, H-6), 3.76 (s, 3H, H-29), 4.58 (d, *J* = 6 Hz, 2H, H-17), 4.72 (s, 3H, H-20, 23), 5.43 (dd, *J* = 16 and 10 Hz, 1H, H-15), 5.76 (td, *J* = 15 and 7 Hz, 1H, H-16), 5.87 (d, *J* = 16 Hz, 1H, H-21), 6.26 (s, 1H, H-25), 6.61 (d, *J* = 3 Hz, 1H, H-4), 6.70 (dd, *J* = 8 and 3 Hz, 1H, H-2), 7.19 (d, *J* = 9 Hz, 1H, H-1), 7.27 (d, *J* = 17 Hz, 1H, H-24).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 16.40 (C-28), 20.94 (C-19), 27.25 (C-27), 25.76, 27.25, 30.08, 31.73 (C-6, 7, 11, 12), 38.67 (C-8), 41.98 (C-13), 42.37 (C-9), 49.80 (C-14), 55.05 (C-29), 64.87 (C-17), 73.83 (C-23), 92.04 (C-20), 111.50 (C-1), 113.37 (C-2), 126.18 (C-4), 127.53 (C-15), 128.55 (C-21), 132.28 (C-10), 134.40 (C-25), 134.97 (C-16)**,** 136.12 (C-24), 137.82 (C-5), 138.01 (C-22)**,** 157.38 (C-3), 170.74 (C-18), 198.13 (C-26).

IR (ATR): υ (cm^{-1}) = 3506 (w), 2933 (m), 2858 (m), 2837 (m), 1736 (vs), 1692 (m), 1669 (s), 1626 (m), 1609 (m), 1590 (s), 1500 (s), 1464 (m), 1453 (m), 1382 (m), 1362 (s), 1283 (s), 1251 (vs), 1233 (vs), 1175 (s), 1072 (s), 1054 (m), 1037 (m), 1024 (m), 987 (s), 898 (m), 866 (w), 840 (w), 817 (m), 788 (w).

MS (EI, 150 °C): m/z (%) = 464 ([M^+], 20%), 404 (4), 355 (2), 327 (8), 273 (10), 267 (18), 239 (3), 226 (12), 211 (22), 199 (10), 173 (45), 160 (14), 147 (44), 138 (100), 137 (19), 121 (10), 109 (7), 93 (13), 81 (22).

HRMS (M^+, $C_{29}H_{36}O_5$): calcd: 464.2563, found: 464.2567.

VI Abbreviations

Ac	acetyl
Ar	aryl
atm	atmosphere
Boc	*tert*-butoxycarbonyl
bp	boiling point
br	broad
Bn	benzyl
Bu	butyl
Bz	benzoyl
calcd.	calculated
cat.	catalyst/catalytic
Cbz	benzyloxycarbonyl
CM	cross metathesis
Cy	cyclohexyl
d	days
DCM	dichloromethane
DEAD	diethylazodicarboxylate
DEPT	Distortionless Enhancement by Polarization Transfer
DMAP	4-dimethylamino pyridine
DMF	*N*, *N*-dimethyl formamide
DMSO	dimethylsulfoxide
EI	electronic ionization
eq.	equivalent(s)
Et	ethyl
GC	gas chromatography
h	hours
Hept	heptyl
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoric triamide
HRMS	high resolution mass spectroscopy
IR	infra red
LDA	lithium diisopropylamine

m	multiplett
Me	methyl
Mes	mesityl
MOM	methoxymethyl
mp	melting point
MS	mass spectroscopy
Ms	mesyl
MTBE	methyl *tert*-butyl ether
MVK	methyl vinyl ketone
NaHMDS	sodium hexamethyldisilazide
NMO	*N*-methyl-morpholine-*N*-oxide
NMR	Nuclear Magnetic Resonance
nOe	nuclear Overhauser effect
PG	protecting group
Ph	phenyl
Pr	propyl
PTSA	p-toluene sulfonic acid
q	quartett
rt	room temperature
[Ru]	Blechert-Hoveyda ruthenium catalyst
RCM	ring closing metathesis
s	singlet
t	triplett
TBAF	tetrabutyl ammonium floride
TBDMS, TBS	*tert*-butyl-dimethylsilyl chloride
TBDPS	*tert*-butyl diphenyl silyl
THF	tetrahydrofurane
TLC	thin layer chromatography
TMEDA	N, N, N', N'-tetra methyl ethylene diamine
TMS	trimethylsilyl
TPAP	tetra propyl ammonium peruthenate
Ts	toluene-4-sulfonyl
UV	ultra violet

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Publikationsliste

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