universität wien

DISSERTATION

Titel der Dissertation

„Total Syntheses of Valerenic Acid and Lycoflexine“

Verfasser

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angestrebter akademischer Grad

Doktor der Naturwissenschaften (Dr.rer.nat.)

Wien, 2011

Studienkennzahl lt. Studienblatt:	A 091 419
Dissertationsgebiet lt. Studienblatt:	Dr.-Studium der Naturwissenschaften UniStG - Chemie
Betreuer:	Prof. Dr. Johann Mulzer

For my parents Frauke and Georg

And my girlfriend Lena

Acknowledgement

This PhD thesis would not have been possible without the help of many different people.

First of all, I would like to thank my supervisor Prof. Johann Mulzer for his guidance, his advice and last but not least for his permission to pursue some of my ideas independently. I have to admit that this part has probably been both the most fascinating and most challenging. Nonetheless, I am also thankful that he has always been the first to warn me, whenever I got carried away and the project has come to a deadlock.

I personally believe that solidarity and excellent teamwork are the two most important characteristics of the Mulzer group. More than once one of the discussions with my colleagues has resulted in vital ideas to solve a peculiar problem. Therefore, I would like to thank Harald Weinstabl, who has not only been involved in the total synthesis of lycoflexine, but also for numerous inspiring conversations. I would also like to thank my former colleague and soon-to-be Professor Thomas Magauer, as well as my other Oesi-labmates Martin Ariger, Nina Tölle, Johannes Preindl, Christian Leitner and Julien Gagnepain. Not to forget a long list of other colleagues, I have to thank Martin Himmelbauer, Jean-Baptiste Farcet, Peter Siengalewicz, Simon Baldauf, Ela Rosenbeiger, Uwe Rinner, Christoph Lentsch, Rita Fürst, Christian Aichinger, Petra Malova, Renzhe Qian, Anna Wieczorek, Katharina Schiessl, Tanja Gaich, Stefan Marchart, Konrad Tiefenbacher, Kathrin Höferl-Prantz, Andreas Gollner, Alexey Gromov, Katja Jantos, Roland Barth and Marion Kögl, who we will always remember.

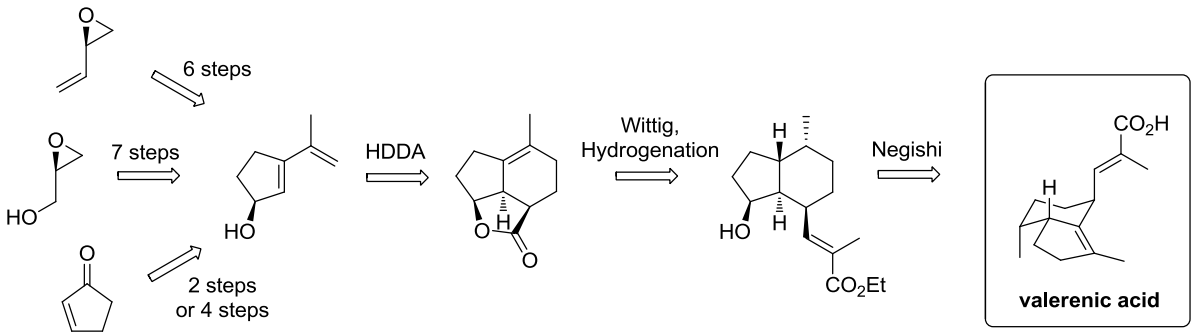
Because efficient synthetic chemistry would not be possible without the help of an excellent NMR-department, mass-department and HPLC-department, I am also indebted to Lothar Brecker, Hans-Peter Kählig (NMR), Peter Unteregger (HRMS), Alina Körner as well as Fikret Nasufi (HPLC) and Martina Drescher for technical support.

I also have to thank Sophia Khom, Barbara Strommer and Prof. Steffen Hering from the Department of Pharmacology and Toxicology, who have been responsible for testing the derivatives prepared during this PhD thesis.

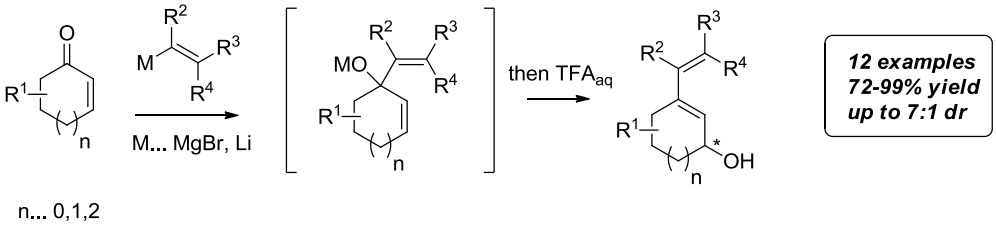
Finally and most of all, I would like to thank my family and my girlfriend Lena, who supported me wherever and whenever I needed help and encouragement.

Graphical Abstract

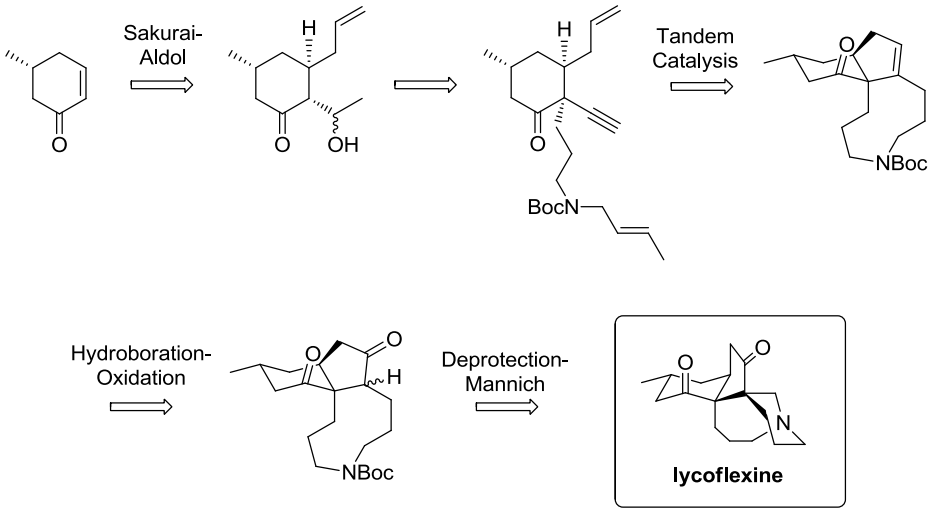
First Total Synthesis of Valerenic Acid:



Efficient and Scalable One-Pot Synthesis of 2,4-Dienols:



First Total Synthesis of Lycoflexine:



Abstract

This cumulative PhD thesis covers the first total synthesis of valerenic acid, the development of a new methodology to provide 2,4-dienols and the first total synthesis of lycoflexine.

The sesquiterpene valerenic acid belongs to the class of valerenanes and was recently subject of several pharmacological studies. Despite its interesting biological profile, no total synthesis had been completed before 2009. Both successful and unsuccessful approaches developed during this PhD thesis are discussed in detail. Eventually a very robust and concise total synthesis based on a novel one-pot sequence, a hydroxy directed Diels-Alder reaction and a regio- and stereoselective Crabtree hydrogenation has been established. This approach has provided the basis for derivatization and structure-activity relationship (SAR) studies. In these tests a series of easily accessible valerenic amides has displayed greater activity than the natural product itself.

During the optimization of the total synthesis of valerenic acid a very efficient one-pot protocol for the synthesis of 2,4-dienols has been developed. These compounds are important building blocks in synthetic organic chemistry. The second part of this cumulative thesis will describe the underlying concept of this methodology and its application in the synthesis of various substrates.

Finally the last part of this thesis summarizes the first total synthesis of lycoflexine. The structure of this Lycopodium alkaloid consists of an unprecedented tetracyclic skeleton, with four stereogenic centers. During this PhD thesis a very general approach towards Lycopodium alkaloids has been developed that culminates in the first total synthesis of lycoflexine and the unpublished shortest syntheses of fawcettimine and fawcettidine. A series of complex as well as straight forward one-pot and tandem reactions has been incorporated including a tandem catalyzed ene-yne-ene RCM and regioselective hydrogenation as keystep.

Kurzfassung

Diese kumulative Dissertation beschäftigt sich mit der ersten Totalsynthese von Valerensäure, der Entwicklung einer neuartigen Methodologie zur Herstellung von 2,4-Dienolen und der ersten Totalsynthese von Lycoflexine.

Das Sesquiterpen Valerensäure gehört zur Substanzklasse der Valerenane und wurde erst kürzlich in mehreren pharmakologischen Studien eingehend untersucht. Trotz des interessanten biologischen Profils war vor Beginn dieser Dissertation keine Totalsynthese bekannt. Sowohl erfolgreiche als auch missglückte Strategien, die im Laufe dieser Arbeit entwickelten wurden, werden ausführlich besprochen. Optimierung führte schlussendlich zu einer sehr robusten und kurzen Totalsynthese, die im Wesentlichen auf einer neuartigen One-Pot-Reaktion, einer Diels-Alder-Reaktion und einer regio- und stereoselektiven Crabtree Hydrierung basiert. Mit dieser neuentwickelten Syntheseroute war es möglich eine Reihe einfach zugänglicher Verbindungen in SAR-Studien zu testen. Im Zuge dieser Tests wurden verschiedene Valerensäureamide synthetisiert, die über eine größere Aktivität verfügen als Valerensäure selbst.

Während der Optimierung der Synthese von Valerensäure wurde eine sehr effiziente One-Pot-Reaktion entwickelt, die die einfache Herstellung von 2,4-Dienolen ermöglicht. Der zweite Teil dieser Dissertation beschäftigt sich sowohl mit den Grundlagen dieser neuartigen Methode, als auch mit der Synthese mehrerer Vertreter dieser wichtigen Substanzklasse.

Der abschließende Teil dieser Dissertation setzt sich mit der ersten Totalsynthese von Lycoflexine auseinander. Die Struktur dieses Lycopodium Alkaloids besteht aus einem bemerkenswerten Kohlenstoffskelett, dass sich aus vier Ringen mit vier Stereozentren aufbaut. Während dieser Arbeit wurde eine sehr allgemeine Synthesestrategie entwickelt, mit der es nicht nur möglich war die erste Totalsynthese von Lycoflexine zu bewerkstelligen, sondern auch die noch nicht veröffentlichten kürzesten Totalsynthesen von Fawcettimine und Fawcettidine abzuschließen. Die Synthese basiert auf einer Reihe von komplexen One-Pot- und Tandem-Reaktionen, wobei die tandem-katalysierte en-in-en Ringschlussmetathese und anschließende Hydrierung besonders hervorzuheben sind.

Publications and Presentations Resulting from this Thesis

Publications and Patents

- *"From Planning to Optimization: Total Synthesis of Valerenic Acid and some Bioactive Derivatives"*

  Ramharter, J.; Mulzer J. *Eur. J. Org. Chem.* submitted (21.12.2011)
- *"Efficient and Scalable One-Pot Synthesis of 2,4-Dienols from Cycloalkenones; Optimized Total Synthesis of Valerenic Acid"*

  Ramharter, J.; Mulzer J. *Org. Lett.* **2011**, *13*, 5310
- *"Synthesis of the Lycopodium Alkaloid (+)-Lycoflexine"*

  Ramharter, J.; Weinstabl, H.; Mulzer J. *J. Am. Chem. Soc.* **2010**, *132*, 14338
- *"Valerenic acid derivatives as novel subunit-selective $GABA_A$ receptor ligands"*

  Khom, S.; Strommer B.; Ramharter J.; Schwarz T.; Schwarzer C.; Erker T.; Ecker G. F.; Mulzer, J.; Hering S. *British J. Pharm.* **2010**, 161, 65
- *"Methods for making Valerenic Acid derivatives and their use as $GABA_A$ receptor ligands"*

  Mulzer J.; Ramharter J.; Khom S.; Hering, S. *PCT Int. Appl.* **2010** WO 2010/084182
- *"Total Synthesis of Valerenic Acid, a potent $GABA_A$ Receptor Modulator"*

  Ramharter, J.; Mulzer J. *Org. Lett.* **2009**, *11*, 1151

Media Response

Synthesis of Lycoflexine

- *Synfacts* **2011**, 2, 125
- *Totally Synthetic* http://totallysynthetic.com/blog/?p=2564

Synthesis of Valerenic Acid

- *Synfacts* **2009**, 10, 1062
- *Totally Synthetic* http://totallysynthetic.com/blog/?p=1448
- *Organic Chemistry Portal* http://www.organic-chemistry.org/Highlights/2010/30August.shtm

Oral and Poster Presentations

Oral Presentations

- *"Wie macht man eine Naturstoffsynthese effizient?"*

  Doktorandenworkshop Naturstoffchemie **2011** (Bayreuth, Germany)
- *"Hydroxy-dirigierte Totalsynthese von Valerensäure, Von der Planung zur Optimierung"*

  Doktorandenworkshop Naturstoffchemie **2010** (Jena, Germany)
- *"First Total Synthesis of Valerenic Acid"*

  Organic Chemistry Symposium **2009** (Paris, France)

Poster Presentations

- *"Synthesis of Natural Products applicable against CNS Dysfunctions"*

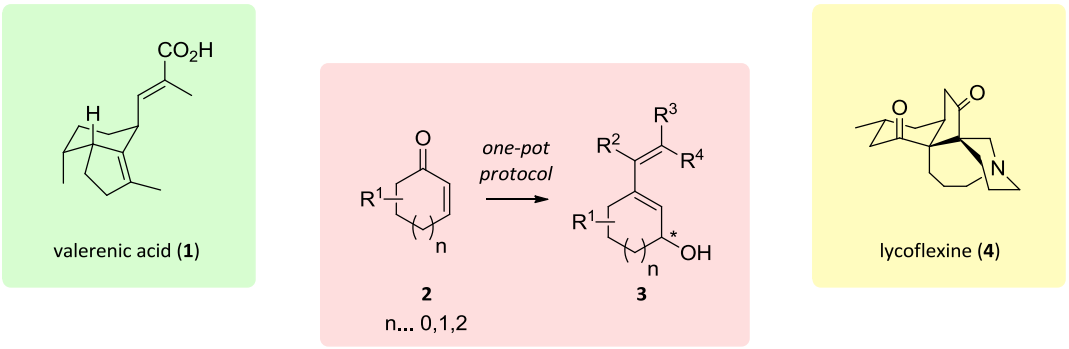
  Balticum Organicum Syntheticum **2010** (Riga, Latvia)
- *"First Total Synthesis of (-)-Valerenic Acid"*

  Münchner Naturstofftage **2009** (Munich, Germany)

Table of Contents

1 General Introduction and Overview

This cumulative PhD thesis covers the first total synthesis of valerenic acid (chapter 2), the development of a new methodology to provide 2,4-dienols (chapter 3) and the first total synthesis of lycoflexine (chapter 4).



Scheme 1: The three subtopics of this PhD thesis.

The sesquiterpene valerenic acid (**1**) belongs to the class of valerenanes and was recently subject of several pharmacological studies.[1,2,3] Despite its interesting biological profile, no total synthesis was completed before 2009. The first synthesis of this interesting substance is described in two publications.[4,5] Whereas the first describes the early efforts that have finally led to completion of the synthesis, the second summarizes both successful and unsuccessful approaches in more detail. Eventually a very robust and concise total synthesis based on a novel one-pot sequence, a hydroxy-directed Diels-Alder reaction and a regio- and stereoselective Crabtree hydrogenation has been established. This approach has provided the basis for derivatization and structure-activity relationship (SAR) studies. In these tests a series of easily accessible valerenic amides has displayed greater activity than the natural product itself. The results of *in vitro* and *in vivo* tests can be found in the third publication.[6]

During the optimization of the total synthesis of valerenic acid a very efficient one-pot protocol for the synthesis of 2,4-dienols **3** has been developed. These compounds are important building blocks in synthetic organic chemistry. The fourth publication of this cumulative thesis will describe the underlying concept of this methodology and its application in the syntheses of various substrates.[7]

Finally the last part of this thesis summarizes the first total synthesis of lycoflexine (**4**). The structure of this *Lycopodium* alkaloid consists of an unprecedented tetracyclic skeleton, with four stereogenic centers. During this PhD thesis a very general approach towards *Lycopodium* alkaloids has been

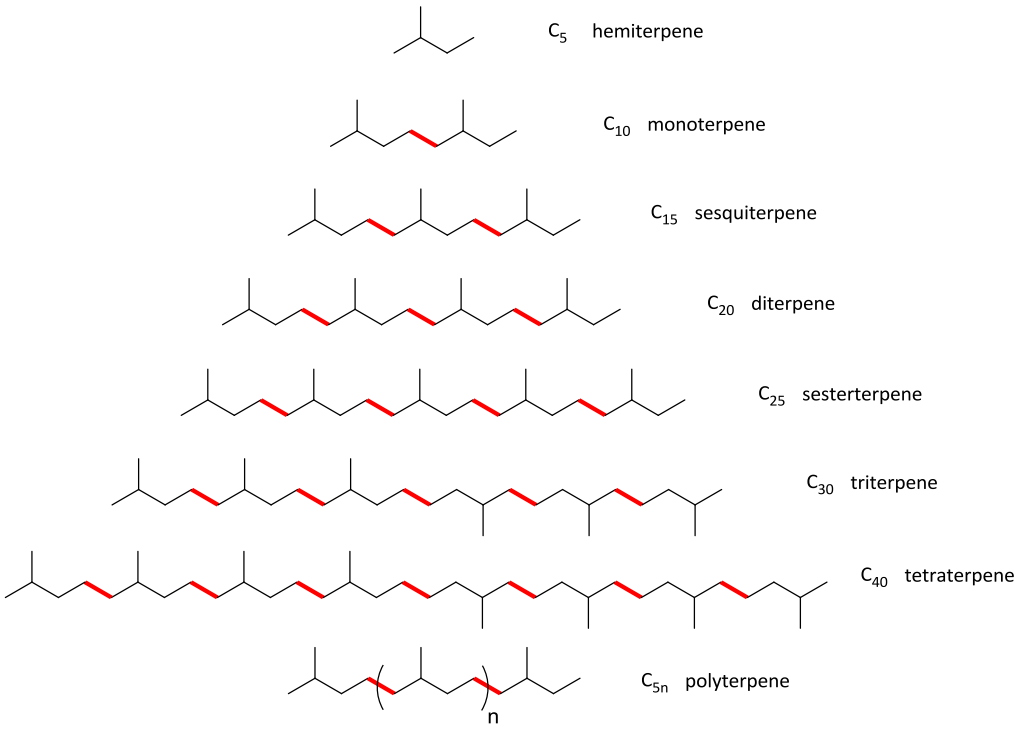
developed that culminates in the first total synthesis of lycoflexine (published in the fifth publication of this thesis)[8] and the unpublished and so far shortest syntheses of fawcettimine and fawcettidine. A series of complex as well as straight forward one-pot reactions has been incorporated including a tandem catalyzed ene-yne-ene RCM and regioselective hydrogenation as keystep.

2 Total Synthesis of Valerenic Acid

2.1 About Terpenes

2.1.1 Classification of Terpenes

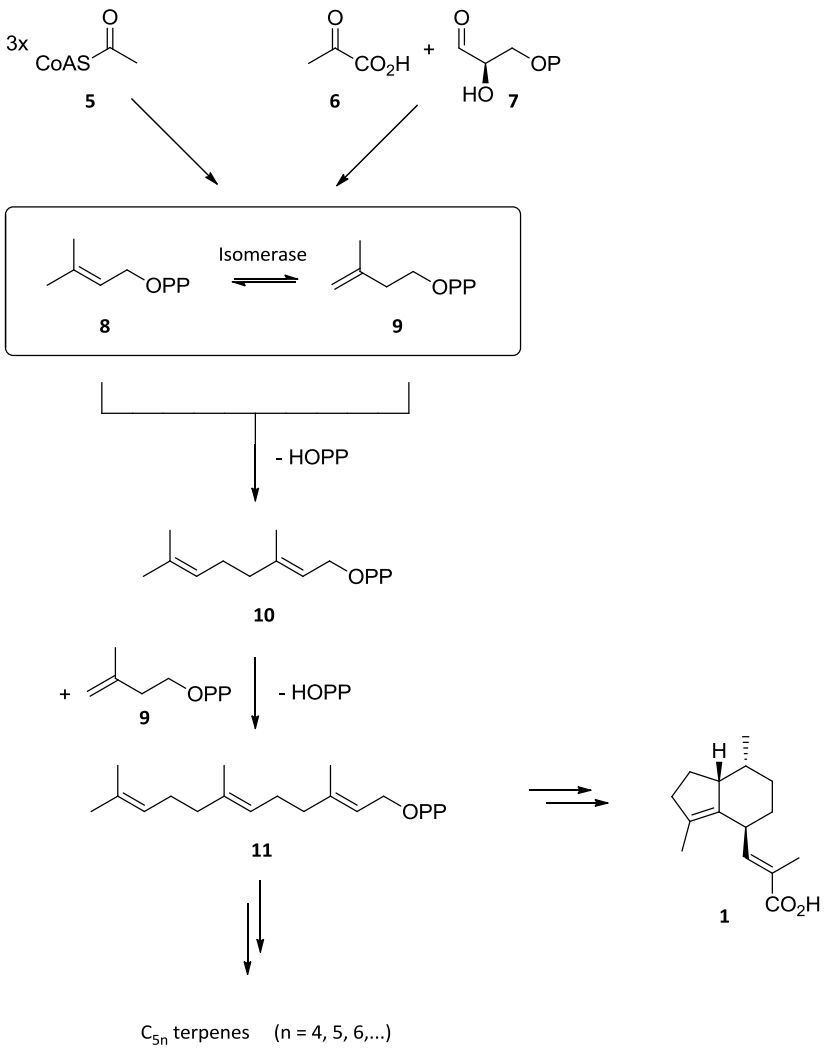
Terpenes represent an extremely large class of natural products with diverse structural and biological properties.[9] Depending on the corresponding biosynthesis, complex processes like cationic cyclizations, rearrangements and oxidation of comparatively simple isoprenoid precursors provide an impressive variety of natural products including more than 30.000 organic compounds. According to the so called “isoprene rule” the most common classification of terpenes refers to the number of isoprene units (C_5), that are needed to build up the carbon skeleton of the corresponding natural product (see Scheme 2).[10]



Scheme 2: Carbon skeletons of terpenes.

2.1.2 General Biosynthesis of Terpenes

The general precursors in the biosynthesis of terpenes are γ,γ-dimethylallylpyrophosphate (DMAPP, **8**) and isopentenylpyrophosphate (IPP, **9**). Both compounds are interconvertible and are either obtained by the acetate-mevalonate pathway starting with acetyl-coenzyme A (**5**) or by the Rohmer pathway starting with pyruvate (**6**) and glyceraldehyde-3-phosphate (**7**).[11,12]

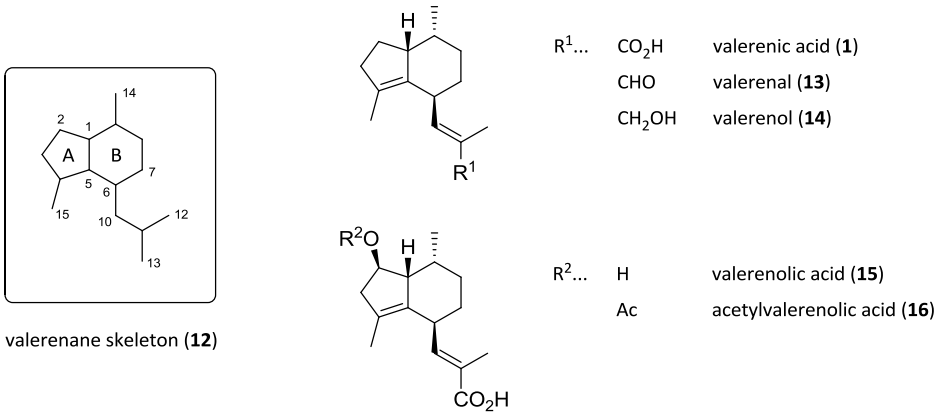


Scheme 3: General Biosynthesis of Terpenes.

As outlined in Scheme 3, coupling of electrophilic DMAPP with nucleophilic IPP leads to geranylpyrophosphate (**10**), which is the general precursor for monoterpenes (C_{10}). Consecutive coupling with a second IPP unit provides the chain-elongated farnesylpyrophosphate (**11**), which is the biosynthetic precursor for sesquiterpenes (C_{15}) like valerenic acid (**1**) (For a more detailed discussion of the biosynthesis of valerenic acid, see chapter 2.3.1). Geranylgeranylpyrophosphat is obtained in a similar fashion, whereas homologous pyrophosphates with more than four isoprene units are derived by coupling of two already chain-elongated terpene precursors.

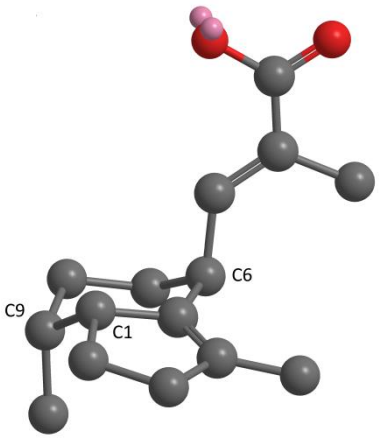
2.2 About Valerenanes

Valerenanes are a comparative small subgroup of bicyclic sesquiterpenes with interesting biological profiles and structural features (see Scheme 4).[9]



Scheme 4: Group of valerenanes.

Because all members of this group were isolated from the rhizome and roots of valerian (lat.: *valeriana officinalis*), this class of terpenes was called valerenanes. Structurally all compounds have an identical indanyl core as carbon skeleton, but differ in their oxidation state. Whereas valerenic acid (**1**), valerenal (**13**) and valerenol (**14**) have no substituent at C2 of the valerenane skeleton (**12**), valerenolic acid (**15**) as well as acetylvalerenolic acid (**16**) possess an additional hydroxy group in this position. However, the most remarkable feature about the valerenanes is their uncommon configuration of both onring substituents of the six-membered ring. Although a hypothetic diequatorial configuration would be thermodynamically much more stable, the three stereogenic centers C1, C6 and C9 of the valerenane skeleton fix the substituents at C6 and C9 in an axial position (For illustration the three dimensional structure of valerenic acid is depicted in Scheme 5).



Scheme 5: 3D model of valerenic acid (**1**).

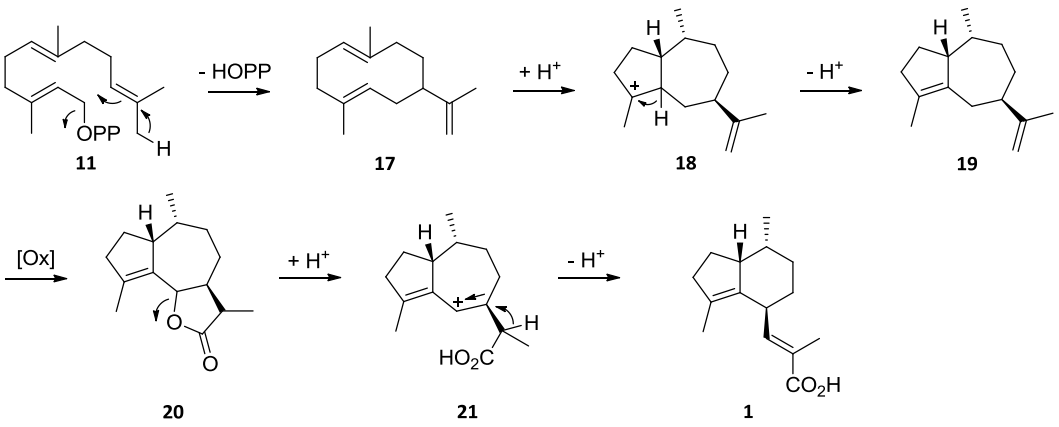
Interestingly, only valerenanes with this diaxial configuration have been isolated so far, whereas the corresponding epimers with the thermodynamically more stable diequatorial configuration remain unknown.

2.3 About Valerenic Acid

Due to its interesting biological activity (see also chapter 2.3.2) valerenic acid (**1**) is probably the most prominent member of the family of valerenanes. Valerenic acid was isolated by Stoll and Seebeck for the first time in 1957.[13] Shortly thereafter Büchi et al. proposed the correct isoprenoid structure, although both the relative and the absolute stereochemistry of all stereocenters and the configuration of the double bond of the side chain still remained unclear.[14] Eventually Birnbaum et al. confirmed the already proposed diaxial configuration of valerenanes by crystal structure analysis.[15] In the very same publications also the biosynthesis of valerenic acid was discussed, which led to the proposal of two different mechanisms.

2.3.1 Biosynthesis of Valerenic Acid

As key intermediate of the first proposal Büchi and coworkers suggested guaianolide **20**. A plausible mechanism towards this compound starts with farnesylpyrophosphate (**11**) derived germacrene A (**17**) (see Scheme 6).[14]

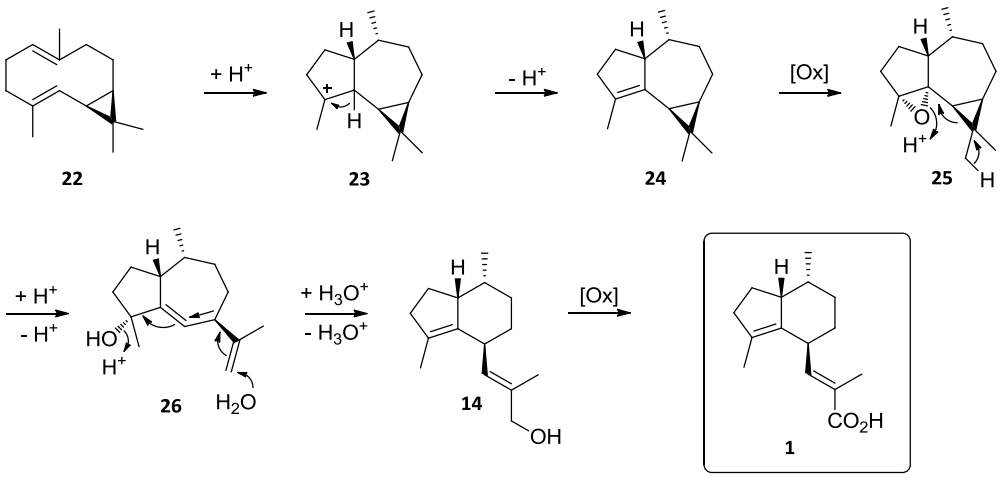


Scheme 6: Biosynthesis of valerenic acid proposed by Büchi *et al.*

In an acid catalyzed cyclization of germacrene A (**17**) the bicylic carbenium ion **18** is delivered, which rapidly forms guaiane **19**. After subsequent oxidation, Brønsted acid induced opening of the resulting lactone probably leads to the formation of allylic carbenium ion **21**. According to Büchi's proposal this species finally undergoes rearrangement with subsequent ring contraction to form the six-membered ring of valerenic acid (**1**).

A few years later Bates and Paknikar rationalized that it is more likely that valerenol (**14**) and valerenal (**13**) are found as precursors in the biosynthesis of valerenic acid.[16] All three compounds

could be isolated from the very same extract and it was reasoned that oxidation starting from valerenol would be more plausible than reduction of valerenic acid. Based on this suggestion an alternative biosynthesis was devised, which is depicted in Scheme 7.



Scheme 7: Biosynthesis of valerenic acid proposed by Bates and Paknikar.

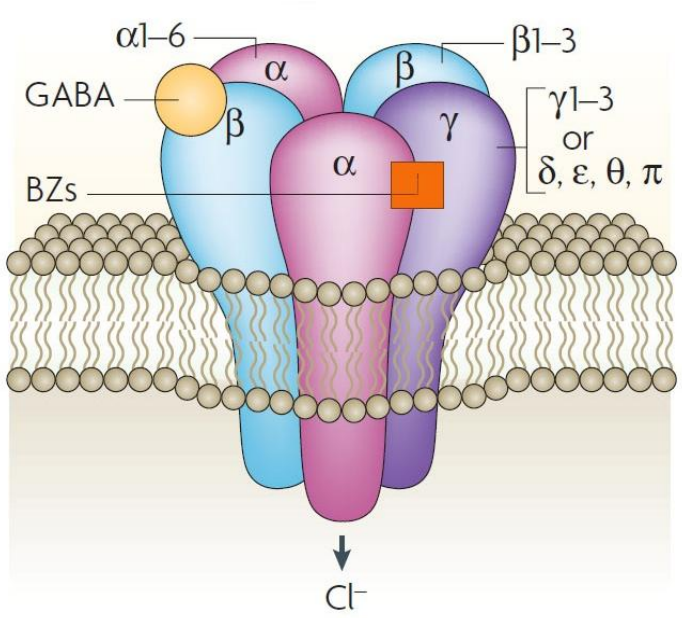
In contrast to the biosynthesis proposed by Büchi and coworkers, Bates and Paknikar related valerenic acid to terpene **22**. The first steps are very similar to the proposal of Büchi and lead to the acid catalyzed formation of α-gurjunene (**24**). After epoxidation of the double bond the resulting epoxide **25** is protonated, which leads to fragmentation of the cyclopropane ring to form intermediate **26**. Simultaneous dehydration of the tertiary alcohol and nucleophilic attack of water induces rearrangement and ring contraction to provide valerenol (**14**). After oxidation finally valerenic acid (**1**) is formed.

2.3.2 Biological Background

Already in ancient Greece and Rome valerian and extracts of valerian have been used to cure insomnia and sickness.[17] Nowadays valerian extracts are still popular medicinal products and sold at most pharmacies because of calming and soporific effects. Beginning in the late 20th century several scientific workgroups became interested in the mode of action of valerenic extracts. Interestingly, several constituents of valerian exhibit an affinity to $GABA_A$ receptors similar to benzodiazepines.[18] Because benzodiazepines are among the most important pharmaceuticals, studies to clarify the interaction of constituents of valerian and the GABA neurotransmitter receptor system have been intensified. Very recently the group of Hering at the University of Vienna identified valerenic acid (**1**) to be an allosteric modulator of $GABA_A$ receptor subtypes.[1]

GABA (γ-aminobutyric acid) is one of the most important inhibitory neurotransmitters of the CNS.[19] According to their structural and functional properties GABA receptors are divided into two major subgroups: The class of ionotropic receptors (ligand-gated ion channels) includes $GABA_A$ and $GABA_{A\text{-}\rho}$ (often also called $GABA_C$) receptors, whereas $GABA_B$ receptors belong to the class of metabotropic receptors (only indirectly linked with ion channels through G proteins).

As is depicted in Scheme 8 the $GABA_A$ receptor is a complex structure build up by five different subunits, which surround the central pore of the ion channel.



Jacob et al., Nature Reviews Neuroscience, 2008

Scheme 8: The $GABA_A$ receptor. The binding sites of GABA and benzodiazepines (BZs) are also displayed.[19]

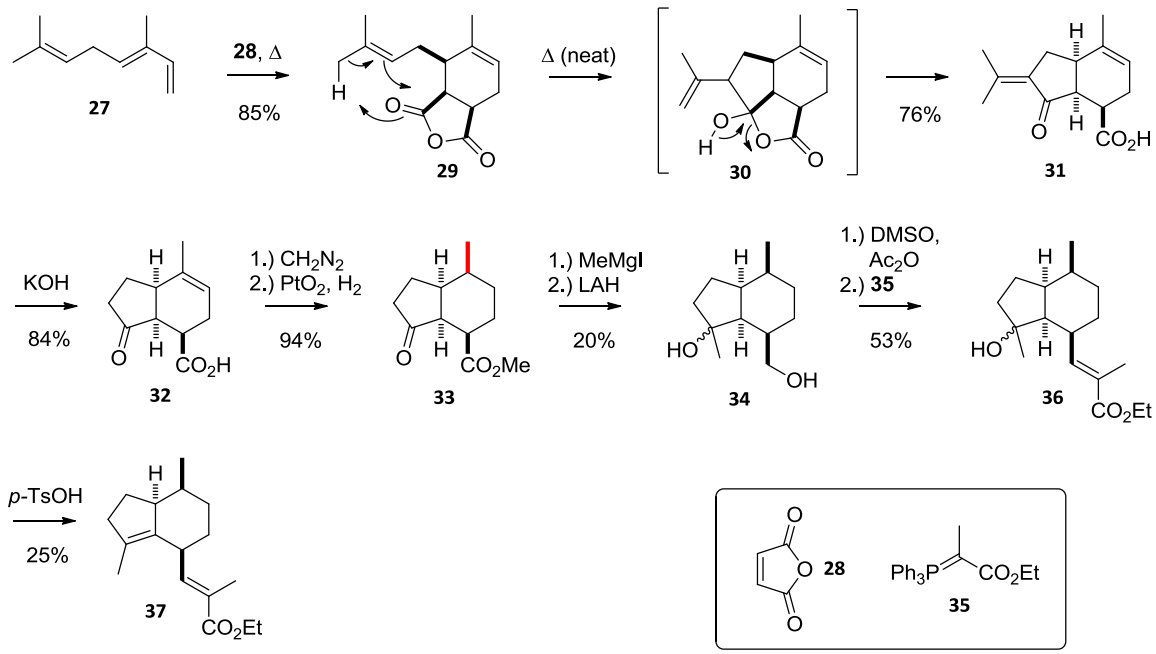
In the human brain seven different subunit families (α, β, γ, δ, ε, θ and π) are typically encountered. Combination of different subunits provides various receptor subtypes with different properties. In most cases two α-units, two β-units and a γ-unit assemble the pentameric ion channel. Whereas a general modulator activates receptors independent of the corresponding subunits, a specific modulator, like valerenic acid, stimulates only receptors with particular subunits. Interaction of GABA with the receptor leads to opening of the pore and causes influx of chloride ions into the neuron. If a modulator is also present the conformation of the receptor is alterated and the interaction of GABA and the active site is intensified. This leads to a prolonged opening of the pore and as result the membrane potential of the neuron is further lowered (hyperpolarization). The overall effect is an attenuation of central nervous activity, because it is more difficult to stimulate the neuron the lower the membrane potential.

2.4 Contributions by Other Groups

Although valerenic acid has been known for more than 50 years, no total synthesis of this molecule was completed until 2009. In 1967 an interesting but unsuccessful attempt towards valerenic acid was published by Joseph and Rao, which will be discussed in the following (see chapter 2.4.1).[20] Including other valerenanes two racemic syntheses of valerenol (**14**) and valerenal (**13**) by the groups of Bohlmann and Baudouy have been published in the early 1980s (see chapter 2.4.2 and 2.4.3).[21,22] Finally, the synthetic strategy developed during this PhD thesis has lead to the first total synthesis of valerenic acid.[4] Shortly thereafter the group of Prof. Altmann published the second total synthesis of the title compound (see chapter 2.4.4).[23]

2.4.1 Approach towards Valerenic Acid by Joseph and Rao

Ten years after its first isolation Joseph and Rao were the first to attempt the synthesis of valerenic acid.[20] Noteworthy, at this time both absolute and relative stereo configuration were still unknown, so eventually the devised strategy led to the synthesis of an epimer of valerenic acid (see Scheme 9).

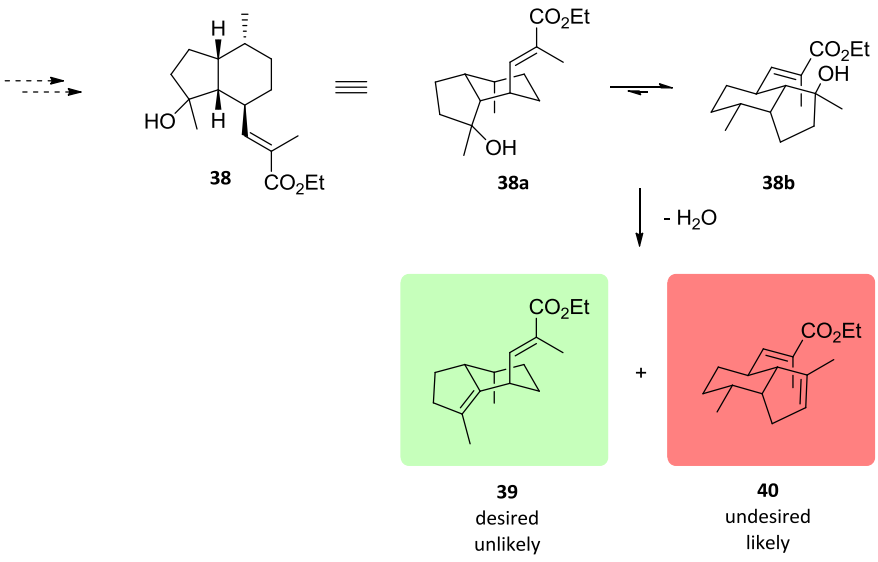


Scheme 9: Total Synthesis of *epi*-Valerenic acid ethyl ester **37**.

The sequence started with the Diels-Alder reaction of *trans*-ocimene **27** and maleic anhydride **28** to provide racemic substrate **29**. Simple heating of the neat Diels-Alder product caused a beautiful cascade reaction starting with an Alder-Ene reaction and subsequent fragmentation of intermediate

30 to furnish compound **31**.[24] In the next step the redundant isopropenylidene group was cleaved by means of a retro-aldol reaction. After esterification the authors had planned to introduce the final stereogenic center of valerenic acid *via* hydrogenation of the double bond. Unfortunately, the open-book effect of the substrate led to the formation of the wrong diastereomer and epimer **33** was obtained exclusively. However, because the configuration of valerenic acid was not established at that time the authors continued their investigations. In the next step treatment with methyl magnesium iodide and reduction provided diol **34**. After oxidation of the secondary alcohol and subsequent Wittig-olefination of the corresponding aldehyde the resulting compound **36** was dehydrated to yield *epi*-valerenic acid ethyl ester (**37**) in moderate yield. Although not mentioned in the publication, comparison of synthetic and authentic material (obtained by esterification of natural valerenic acid) most likely led to revelation of the unnatural configuration and the final saponification was not carried out.

In summary the strategy developed by Joseph and Rao incorporated several interesting transformations, but unfortunately it is not suitable for the synthesis of valerenic acid. Noteworthy, even if hydrogenation of compound **32** had led to the right configuration at C9 of the valerenane skeleton, the hypothetical endgame of this sequence would still have been extremely difficult (see Scheme 10).



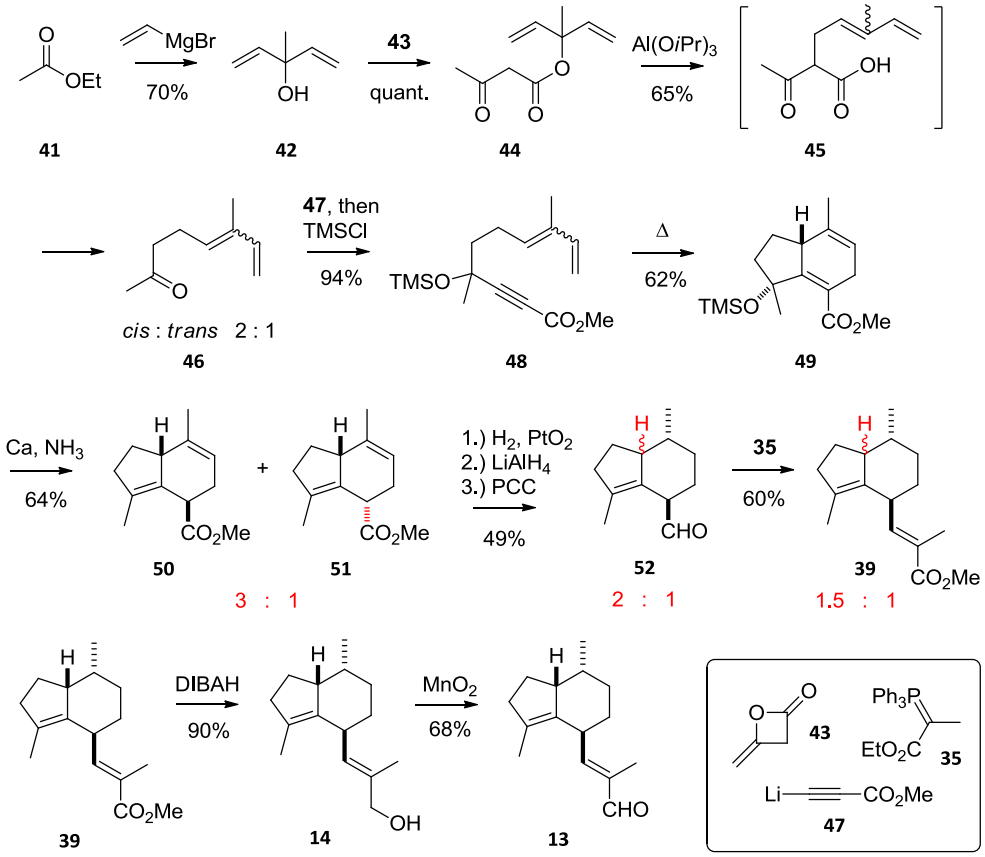
Scheme 10: Considerations about the hypothetically endgame devised by Joseph and Rao.

Bicyclic alcohol **38** would exist in two different chair conformations. Whereas in conformation **38b** only one single substituent is in an axial position, the second conformer **38a** has three axial substituents. Therefore conformation **38b** would be thermodynamically much more stable and

should clearly predominate. However, to generate the desired product **39** chair conformation **38a** would be needed. As result the formation of the undesired product **40** should clearly predominate.

2.4.2 Total Synthesis of (+/-) Valerenol and (+/-) Valerenal by Bohlmann

The first total synthesis of racemic valerenol **14** and valerenal **13** by Bohlmann and Lonitz in 1980 is outlined in Scheme 11.[21]

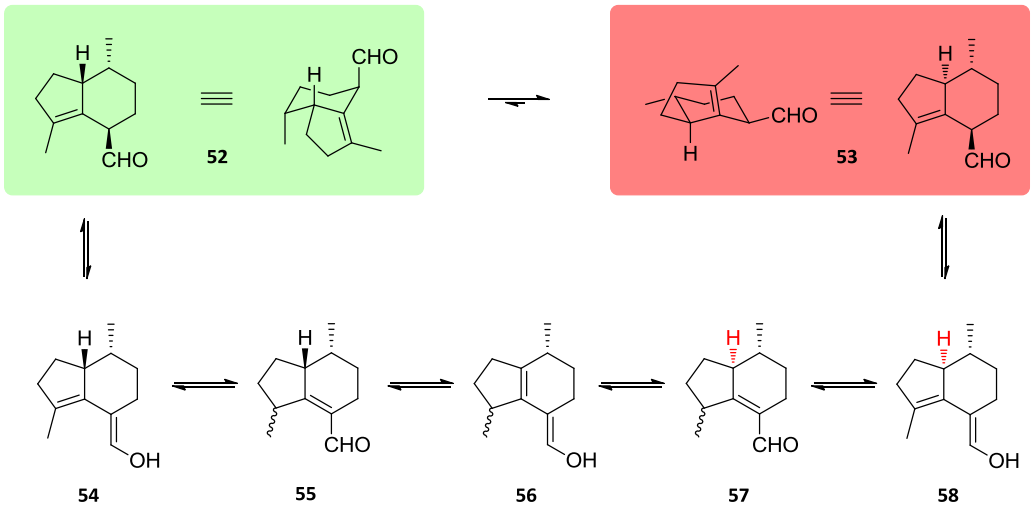


Scheme 11: Total Synthesis of racemic Valerenol and Valerenal.

The first step was the literature known preparation of diallylic alcohol **42** starting from ethyl acetate and an excess vinyl magnesium bromide. Alcohol **42** was then converted into the β-keto ester **44**, which underwent a Lewis acid catalyzed Claisen rearrangement into intermediate **45**. Under the applied conditions this substrate decarboxylated to yield keto compound **46**. After 1,2-addition of alkyne **47** the resulting alkoxide was treated with TMSCl to furnish silylether **48**. The silyl-protecting group was essential to block one site of the triple bond. Consequently the IMDA (intramolecular Diels-Alder) reaction was highly selective and only compound **49** was obtained. Birch reduction of the Diels-Alder product provided a three to one diastereomeric mixture of the desired ester **50** and its

epimer **51**. Hydrogenation and reduction of this mixture proceeded without incident, but the subsequent oxidation of the corresponding primary alcohol was problematic. According to intensive studies aldehyde **52** was unfortunately labile under both acidic and basic conditions and tended to epimerize (see also Scheme 12). Consequently after column chromatography a one to four ratio of the desired aldehyde and its epimer was obtained. This problem could partly be solved by avoiding purification (in this case a two to one ratio was obtained). However, epimerization was also observed during the subsequent Wittig olefination, so the ratio of both diastereomeric esters **39** further decreased to three to two. Nonetheless, these compounds were stable and could be separated. To complete the synthesis of racemic valerenal and valerenol, ester **39** was reduced to provide valerenol **14**, which was easily oxidized to yield valerenal **13**.

The sequence devised by the group of Bohlmann provided a general synthetic access to the class of valerenanes, so in principle also the synthesis of valerenic acid could be accomplished using this strategy. Although not enantioselective the applied strategy was straight forward and provided the bicyclic core in few steps. Nevertheless, the preparation of acid and base labile aldehyde **52** as one of the key intermediates seemed to be problematic, so epimeric mixtures could not be avoided even without isolation of this compound. A rationalization for its lability was provided by the authors (see Scheme 12).



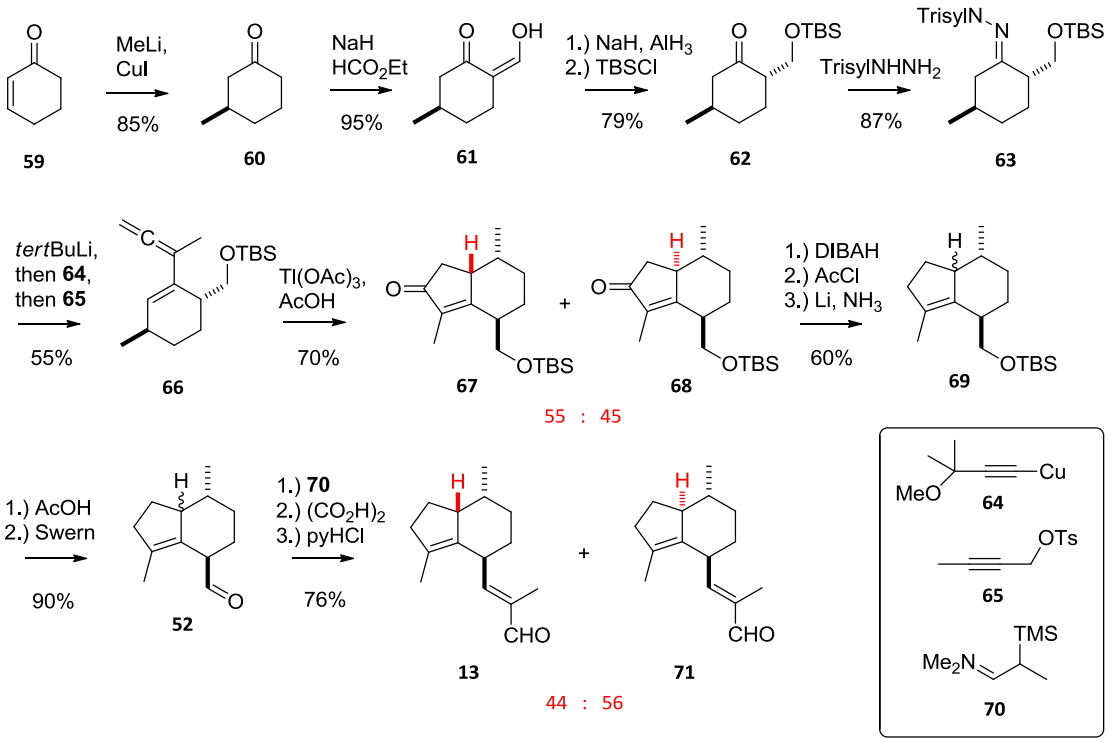
Scheme 12: Isomeric forms of aldehyde **52**.

Starting with enolization of aldehyde **52** several different isomers are accessible. As all isomers were in equilibrium, the most stable form was enriched. From a thermodynamic point of view the isomer with the desired diaxial configuration **52** is the least probably formed, whereas epimer **53** with a

diequatorial configuration is the most stable isomer. As result already a trace of acid or base led to enrichment of epimer **53**.

2.4.3 Total Synthesis of (+/-) Valerenal by Baudouy

In 1983, three years after the first racemic synthesis of valerenal (**13**), Baudouy and Sartoretti finished their approach towards the same target (see Scheme 13).[22]



Scheme 13: Total synthesis of valerenal by the group of Baudouy.

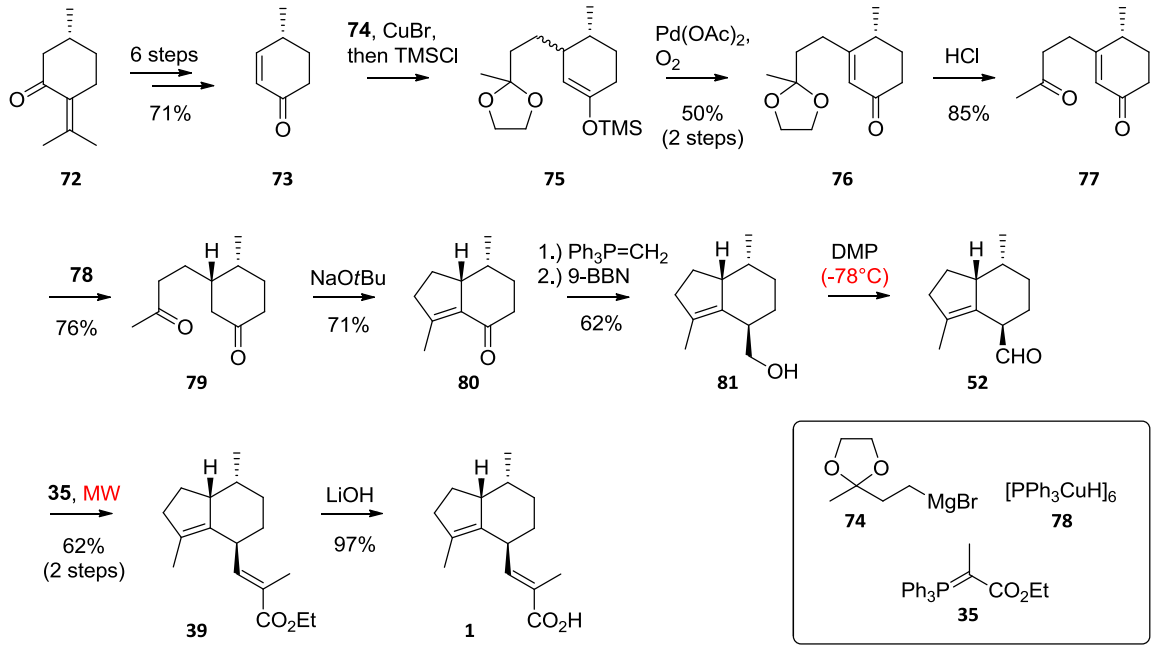
The sequence devised by the group of Baudouy started with literature known racemic methyl cyclohexanone **60**, which could be prepared from commercially available cyclohexenone **59** by simple cuprate addition. Enolization of **60** and addition of ethyl formate provided β-keto compound **61**, which was stereoselectively reduced and TBS protected. After formation of the trisylhydrazone **63**, a mixed cuprate was prepared by Shapiro reaction and subsequent addition of copper species **64**. Nucleophilic substitution of tosylate **65** by this compound provided allene **66**. In the keystep of the synthesis a thallium mediated cyclization of this substrate furnished a one to one mixture of the two diastereomers **67** and **68**. Unfortunately, attempted epimerization of this mixture into the desired isomer **67** was not possible, but led to the complete formation of the undesired epimer **68** instead. Without separation of both isomers this mixture was deoxygenated in a three step procedure including reduction of the keton, acetylation and Birch reduction. After deprotection of TBS ether **69**

oxidation yielded acid and base labile aldehyde **52**, which had already been known from the synthesis by Bohlmann and coworkers. Instead of a Wittig olefination a Peterson olefination with subsequent isomerization of the conjugated double bond with pyridinium hydrochloride finally provided valerenal (**13**). Noteworthy, because of the lability of the precursors the ratio decreased over the last steps, so eventually only a 44 to 56 ratio of valerenal and its epimer was obtained.

Like the synthesis of valerenal by Bohlmann also the synthesis of Baudouy and Sartoretti provides a general access to valerenanes. The number of steps and the overall yield are reasonable and, despite its toxicity, the novel thallium mediated cyclization highlighted the usefulness of such transformations. Contrary, again labile intermediates had to be used to provide the natural product. As result once more epimeric mixtures were obtained.

2.4.4 Total Synthesis of Valerenic Acid by Altmann

A few months after the completion of the first total synthesis of valerenic acid by our group, also the group of Altmann published a different approach towards this natural product (see Scheme 14).[23]



Scheme 14: Second total synthesis of valerenic acid by Altmann and coworkers.

The synthesis began with the literature known formation of enantiopure methylcyclohexenone **73** from readily available (+)-pulegone (**72**) in six steps. After 1,4-addition of cuprate **74** the *in situ* formed enolether was TMS protected to yield compound **75**. Because the cuprate addition

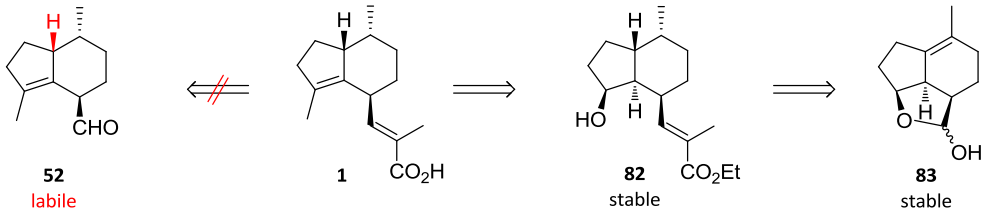
predominantly led to the undesired diastereomer, Wacker oxidation was used to form the α,β-unsaturated keto compound **76**. After deprotection of acetal **76**, stereoselective reduction of the double bond furnished diketo compound **79** with the desired configuration at C1. In the next steps the five-membered ring was closed by an aldol condensation and an *exo*-methylene group was installed by Wittig olefination, which was converted into an alcohol by hydroboration. To avoid epimerization, the subsequent Dess-Martin-periodinane oxidation was performed at very low temperature to yield aldehyde **52**, which has already been used by Bohlmann and Baudouy for their syntheses of valerenol and valerenal. Without purification of the aldehyde, Wittig olefination under microwave conditions gave the desired valerenic acid ethyl ester as single product with reasonable yield. After 16 steps finally saponification of the ester provided valerenic acid.

The synthetic strategy developed by Altman and coworkers once again rests upon the use of labile compounds, but oxidation with a mild oxidizing agent at very low temperature and the microwave assisted Wittig olefination provided effective tools to limit epimerization to a minimum.

2.5 First Total Synthesis of Valerenic Acid

2.5.1 Introduction

During this PhD thesis a completely different synthetic strategy was developed, which eventually led to publication of the first total synthesis of valerenic acid (see Scheme 15).



Scheme 15: Retrosynthetic considerations to avoid instable intermediates.

Instead of Wittig olefination of labile aldehyde **52**, installation of the endocyclic double bond was chosen as one of the last steps. To fix the crucial diaxial configuration of the two onring substituents *trans*-annulated bicyclic alcohol **82** was identified as key intermediate, which could be derived by Wittig olefination of lactol **83**. Based on the well-founded assumption that lactol **83** does not tend to epimerize, Wittig olefination of this substrate should proceed selectively and provide the desired epimer exclusively.

A more detailed retrosynthetic analysis and further details concerning the initially devised synthesis starting with commercially available (*R*)-glycidol can be found in the following communication.

2.5.2 Total Synthesis of Valerenic Acid, a Potent GABAA Receptor Modulator

Ramharter, J.; Mulzer J. *Org. Lett.* **2009**, *11*, 1151

The supporting information of this publication is omitted to avoid redundancy. For experimental and analytical data of all compounds see the supporting information of the full paper in chapter 5.1.

ORGANIC LETTERS

2009
Vol. 11, No. 5
1151−1153

Total Synthesis of Valerenic Acid, a Potent $GABA_A$ Receptor Modulator

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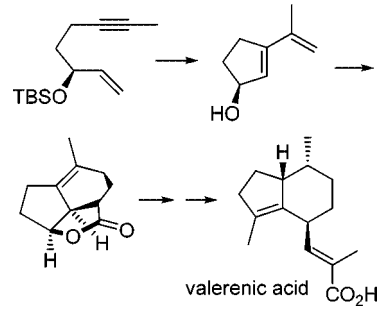
Received January 5, 2009

ABSTRACT



The first total synthesis of the sesquiterpenoid valerenic acid, a constituent of *Valeriana officinalis*, is described. The compound is a potent modulator of the $GABA_A$ receptor and may thus be useful in the treatment of various dysfunctions of the central nervous system. The synthesis is enantio-, diastereo-, and regiocontrolled and utilizes an enyne-RCM, a metal-coordinated Diels−Alder reaction, a hydroxy-directed Crabtree hydrogenation, and a Negishi methylation as key steps.

γ-Aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the mammalian brain and mediates its action by interaction with GABA type A ($GABA_A$) receptors representing a ligand-gated chloride channel, second messenger linked $GABA_B$ receptors that are coupled to Ca^{2+}- and K^+-channels via G-proteins and $GABA_C$ receptors.[1] There is clear evidence for specific expression of certain $GABA_A$ receptor subtypes (with different subunit compositions) in different regions in the central nervous system (CNS).[2] The subunit composition determines the GABA-sensitivity and the pharmacological properties of the $GABA_A$ receptor.[3] Searching for molecules selective for a certain $GABA_A$ receptor subtype is, therefore, a promising approach to develop new therapeutics.

Valerenic acid (**1**), isolated from the roots of *Valeriana officinalis*,[4] has recently been shown to selectively modulate $GABA_A$ receptor subtypes.[5] These data suggest that **1** is a subunit-specific allosteric modulator of $GABA_A$ receptors and as a drug, might be applicable against a variety of CNS dysfunctions, such as panic disorders, hyperactivity, poor motor coordination, learning deficits, spontaneous epileptic seizures, and abnormal facial development. Therefore, as more extensive and elaborate structural variations are envisaged, an efficient total synthesis of **1** appeared of importance. This intention seemed all the more worthwhile to us as, despite some fruitless efforts in the past,[6] no total synthesis of **1** has been reported so far.

(1) (a) Barnard, E. A.; Skolnick, P.; Olsen, R. W.; Mohler, H.; Sieghart, W.; Biggio, G.; Braestrup, C.; Bateson, A. N.; Langer, S. Z. *Pharmacol. Rev* **1998**, *50*, 291–313. (b) Bormann, J. *Trends Pharmacol. Sci.* **2000**, *21*, 16–19.

(2) (a) Korpi, E. R.; Grunder, G.; Luddens, H. *Prog. Neurobiol.* **2002**, *67*, 113–159. (b) Pirker, S.; Schwarzer, C.; Wieselthaler, A.; Sieghart, W.; Sperk, G. *Neuroscience* **2000**, *101*, 815–850.

(3) (a) Hevers, W.; Luddens, H. *Mol. Neurobiol.* **1998**, *18*, 35–86. (b) Sieghart, W.; Sperk, G. *Curr. Top. Med. Chem.* **2002**, *2*, 795–816. (c) Boileau, A. J.; Li, T.; Benkwitz, C.; Czajkowski, C.; Pearce, R. A. *Neuropharmacology* **2003**, *44*, 10031012.

(4) Stoll, A.; Seebeck, E. *Justus Liebigs Ann. Chem.* **1957**, *603*, 158–168.

(5) Khom, S.; Baburin, I.; Timin, E. N.; Hohaus, A.; Sieghart, W.; Hering, S. *Mol. Pharmacol.* **2002**, *69*, 640–649.

(6) (a) Joseph, K. T.; Krishna, R. G. S. *Tetrahedron* **1967**, *23*, 3215–3220. (b) Bohlmann, F.; Lonitz, M. *Chem. Ber.* **1980**, *113*, 2410–2423. (c) Baudouy, R.; Sartoretti, J.; Choplin, F. *Tetrahedron* **1983**, *39*, 3293–3305.

10.1021/ol9000137 CCC: $40.75
Published on Web 01/29/2009

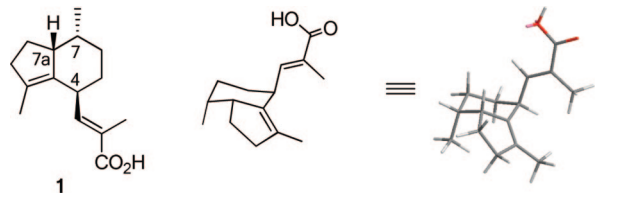
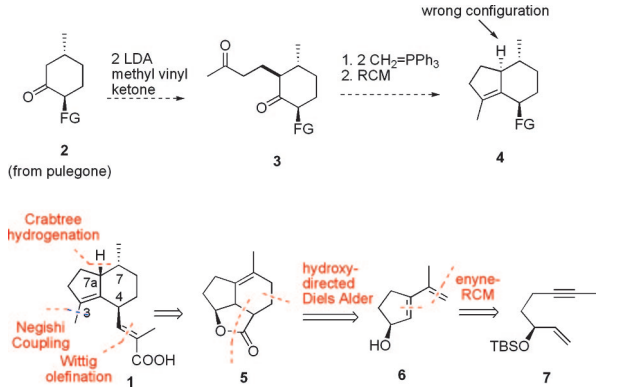


Figure 1. Structural features of valerenic acid (**1**).

Structurally, **1** is a sesquiterpene featuring an indanyl core with three stereogenic centers and two double bonds (Figure 1). A particular challenge in a total synthesis lies in the diaxial arrangement[7] of two onring substituents, which had to be installed without subsequent epimerization.[6b]

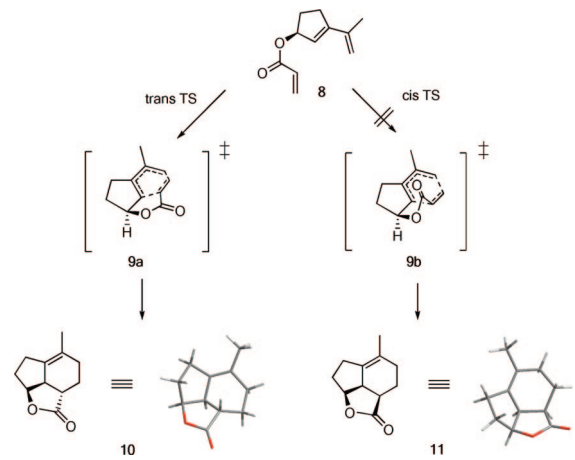
Scheme 1. Retrosynthetic Analysis of **1**



From the retrosynthetic perspective (Scheme 1), an obvious route to **1** might start from a pulegone-derived cyclohexanone such as **2** and attach the cyclopentene ring via alkylation to **3** and olefination/ring closing metathesis (RCM) to **4**. However, enolate additions to **2** are known[8] to favor the trans-diastereomer, which would generate **4** with the wrong configuration at the ring juncture. Therefore, we decided to prepare the bicyclic core from an acyclic precursor **7** via an enyne-RCM[9]-IMDA (IMDA = intramolecular Diels−Alder addition) sequence via **6** to generate lactone **5**. The relative configuration at C-7/7a should be created via hydroxy-directed catalytic hydrogenation. As the ultimate steps of our synthesis we considered a Negishi-coupling to introduce the methyl substituent at C-3, whereas the exocyclic enoate appendage at C-4 should be formed by an *E*-selective Wittig olefination. This plan had two main unknowns: (a) the stereochemical outcome of the IMDA reaction generating **5** and (b) the possibility to achieve the correct relative configuration at C-7/7a with respect to C-4.

(7) Cf. the crystal structure of valerenolic acid: Birnbaum, G. L.; Findlay, J. A.; Krepinsky, J. L. *J. Org. Chem.* **1978**, *43*, 272–276.
(8) Touriya, Z.; Santelli-Rouvier, C.; Santelli, M. *J. Org. Chem.* **1993**, *58*, 2686–2693.
(9) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317–1382.

Scheme 2. Stereochemical Implications of the IMDA Reaction of **8**



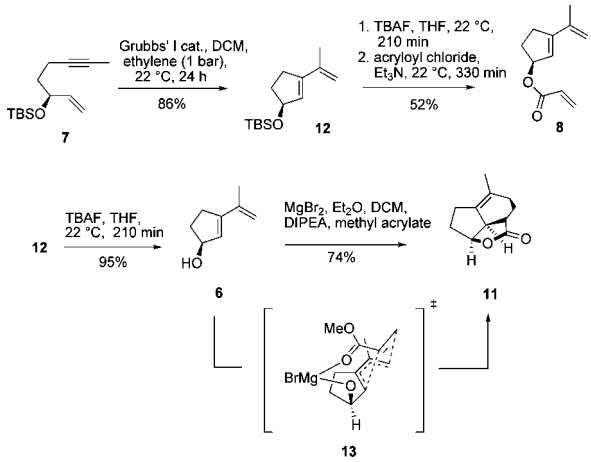
The IMDA reaction of ester-linked trienes such as **8** is known to proceed exclusively via the so-called trans (= exo) transition state **9a** (Scheme 2).[10,11] Because of great distortion and steric hindrance the electronically normally preferred cis (= endo) transition state **9b** is clearly disfavored and, thus, product **10** should be formed. On the other hand, this outcome would be *contra*-thermodynamic, as **10**, according to STO 3-21G calculations, is 13.2 kcal•mol^{-1} higher in energy than product **11**.

Our synthesis (Scheme 3) started with readily available racemic 3-OTBS-oct-1-en-6-yne (**7**),[12] which smoothly underwent RCM to cyclopentene **12** with Grubbs' first generation catalyst, if the reaction was carried out under an ethylene atmosphere (Mori's conditions).[13] Several other conditions such as using an argon atmosphere instead of ethylene or $PtCl_2$ as catalyst led to no conversion or decomposition. In situ deprotection and acylation furnished acrylic ester **8** as the envisaged IMDA substrate. However, all attempts to achieve cycloaddition under thermal conditions just led to decomposition. After this failure we switched to a metal-coordinated Diels−Alder reaction[14] of alcohol **6** and methyl acrylate with $MgBr_2$ as the template. This reaction furnished lactone **11** stereoselectively.[15] The transition state (**13**) of this Diels−Alder reaction now resembles the electronically favored *endo*-arrangement **9b** and furnishes lactone **11** as the thermodynamically more stable product, so that all disadvantages of the covalently tethered acrylate are now reversed.

The synthesis was continued (Scheme 4) by installing the side chain at C-4 via reduction to the lactol **14** (not isolated)

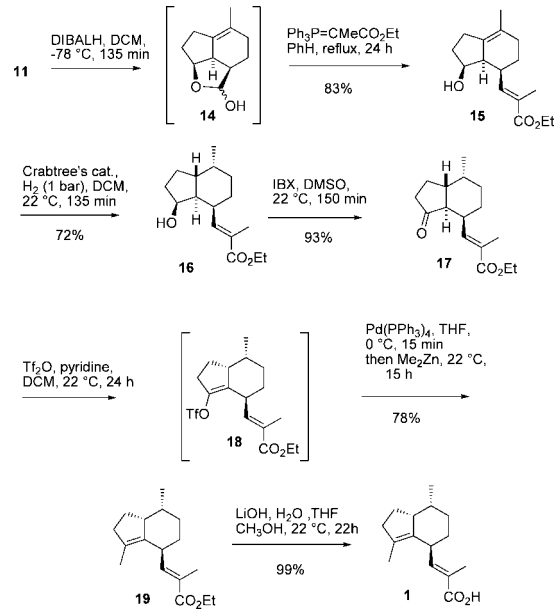
(10) Strekowski, L.; Kong, S.; Battiste, M. A. *J. Org. Chem.* **1988**, *53*, 901–904.
(11) Cayzer, T. N.; Paddon-Row, M. N.; Moran, D.; Payne, A. D.; Sherburn, M. S.; Turner, P. *J. Org. Chem.* **2005**, *70*, 5561–5570.
(12) Adrio, J.; Rodríguez Rivero, M.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2000**, *39*, 2906–2909.
(13) Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 12388–12389.
(14) Barriault, L.; Thomas, J. O. D.; Clement, R. *J. Org. Chem.* **2003**, *68*, 2317–2323.
(15) The relative configuration of **11** was secured via 2D NMR techniques (see the Supporting Information).

Scheme 3. Preparation of Lactone **11**[a]



[a] Abbreviations: DCM = dichloromethane, DIPEA = diisopropylethylamine.

Scheme 4. Completion of the Synthesis[a]



[a] Abbreviations: DCM = dichloromethane, IBX = 2-iodoxybenzoic acid.

and Wittig reaction to form enoate **15**. The free OH group was now used as an anchoring group for Crabtree's catalyst,[16] which delivered dihydrogen in a *syn* fashion to generate hydrindane **16** stereo- and chemoselectively. Oxidation to ketone **17** was followed by deprotonation to the thermodynamically more stable enolate, formation of vinyl triflate **18** (not isolated), and Negishi coupling[17] with dimethyl zinc. From this sequence the tetrasubstituted olefin **19** was obtained with >90% regioselectivity. Base-catalyzed ester hydrolysis led to *rac*-**1**. After that, the synthesis was repeated with enantiomerically pure (*S*)-**7**[18] to provide the natural enantiomer (−)-**1**. All analytical data of *rac*-**1** and (−)-**1** were in full agreement with those of an authentic sample (see the Supporting Information).

In conclusion we have achieved a concise stereo- and regiocontrolled synthesis of valerenic acid (**1**) in racemic (8 steps from **7**, 26% overall yield) and optically pure form (13 steps from (*R*)-glycidol, 8% overall yield). Remarkably, the initial stereochemical information introduced with the carbinol center in compound **7** is used in a relay-manner to control the stereogenic centers in the target molecule. After that it is discarded in favor of an endocyclic double bond. The route is flexible and should be applicable to a variety of derivatives, suitable for SAR investigations.

Acknowledgment. We thank Hanspeter Kählig, Susanne Felsinger, and Lothar Brecker, all at University of Vienna, Institute of Organic Chemistry, for NMR analysis, as well as Sophia Khom and Steffen Hering, both at University of Vienna, Department of Pharmacology and Toxicology, for fruitful discussions, and the Austrian Science Fund (FWF) for financial support (project P 21241-N19).

Supporting Information Available: Experimental data and analytical characterization for all new compounds provided. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9000137

(16) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655–2661.

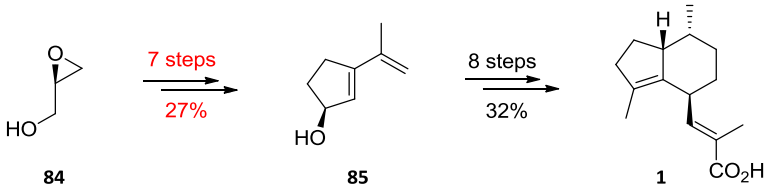
(17) (a) Marshall, J. A.; Zou, D. *Tetrahedron Lett.* **2000**, *41*, 1347–1350. (b) Review: Negishi, E.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. *Aldrichim. Acta* **2005**, *38*, 71–92.

(18) (*S*)-**7** was prepared via a stereo-unambiguous route from (*R*)-glycidol in five steps and 32% overall yield (see the Supporting Information).

2.6 Second Generation Approach

2.6.1 Introduction

To provide suitable amounts of valerenic acid **1** and its derivatives for SAR (structure-activity relationship) studies a short, flexible and scalable synthesis was required. While highly enantio- and diastereoselective the first generation synthesis starting from (*R*)-glycidol (**84**) suffered from three major disadvantages. First of all preparation of the Diels-Alder substrate **85** was rather lengthy. Although only of moderate complexity, its preparation took seven steps with an overall yield of 27 % (see Scheme 16).



Scheme 16: Analysis of the first generation synthesis of valerenic acid.

Secondly a rather pricy metathesis catalyst (Grubbs' first generation catalyst) was needed in an early stage of the synthesis and last but not least the starting material was derived from the chiral pool and quite expensive. As consequence only mg-quantities of valerenic acid were obtained from the first generation synthesis.

To optimize the devised synthesis several different approaches towards compound **85** have been developed, which are summarized together with all unsuccessful attempts concerning the total synthesis of valerenic acid in the following full paper.

2.6.2 From Planning to Optimization: Total Synthesis of Valerenic Acid

Ramharter, J.; Mulzer, J. *Eur. J. Org. Chem.* submitted (21.12.2011)

The supporting information of this full paper includes ^{1}H-NMR and ^{13}C-NMR spectra of all discussed compounds. These spectra are depicted in chapter 5.1.

DOI: 10.1002/ejoc.200((will be filled in by the editorial staff))

From Planning to Optimization:

Total Synthesis of Valerenic Acid and some Bioactive Derivatives

Juergen Ramharter and Johann Mulzer*[a]

Keywords: natural product synthesis / one-pot reaction / hydroxy-directed Diels-Alder / hydroxy-directed hydrogenation / Negishi coupling

A detailed study of the total synthesis of valerenic acid, a well known $GABA_A$ receptor subtype modulator, is described. Both successful as well as unsuccessful attempts towards the title compound are presented including four different strategies to synthesize one of the key intermediates of this synthesis. The first two strategies are based on epoxides provided from the chiral pool, whereas the last two approaches rest on stereocontrolled modifications of 2-cyclopentenone. The streamlined synthesis implements a novel one-pot reaction, which combines the addition of a Grignard species with an acid catalyzed isomerization of the intermediate allylic alcohol. Further highlights are a stereo- and regioselective hydroxy-directed Diels-Alder reaction, a hydroxy-directed hydrogenation and a final Negishi coupling. After optimization of our synthesis also the preparation of several easily available derivatives is discussed. Amides obtained by functionalization of the carboxyl group are more than twice as active as valerenic acid.

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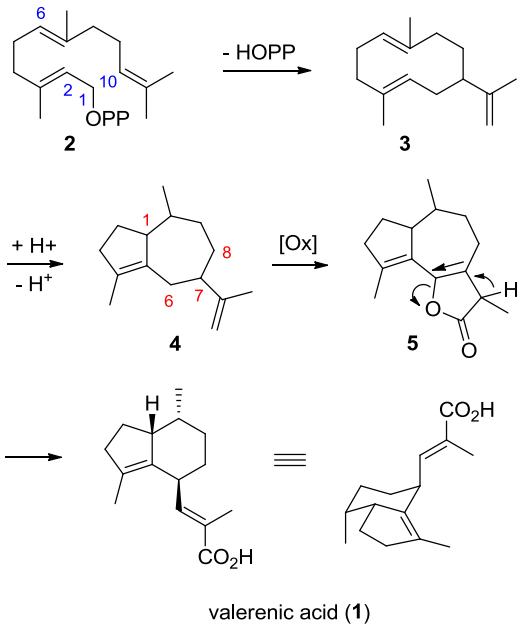
Supporting information for this article is available on the WWW under http://www.eurjoc.org/ or from the author.

Introduction

Valerenic acid (**1**) was isolated in 1957 by Stoll and Seebeck from the rhizome and roots of valerian (*valeriana officinalis*) and by now is probably the most prominent member of valerenanes.[1] Already known in ancient Greece valerian has been one of the oldest medicinal herbs in folk medicine and has been applied against various afflictions like insomnia, anxiety or pain.[2] Due to these interesting pharmacological effects valerian has attracted extensive studies to identify the bioactive target. It is now understood that several constituents of valerian interact with the GABA neurotransmitter receptor system and recently, valerenic acid (**1**) has been shown to act as subunit-specific allosteric modulator of $GABA_A$ subtype receptors.[3] Because of this selectivity and its overall activity, **1** is envisaged as a potential candidate in drug discovery and development.

Structurally **1** features an indanyl core with three stereogenic centers and two double bonds. As a sesquiterpene, it belongs to the class of guaianes, a group of more than five hundred natural products biogenetically derived from farnesyl pyrophosphate (**2**) by bond connections between C-1/C-10 and C-2/C-6 (Scheme 1).[4] After formation of the guaiane core **4**, isomerization and oxidation lead to guaianolide **5**, which undergoes a Wagner-Meerwein type ring contraction to **1**.[5] Most interestingly, both onring substituents of the six-membered ring are now fixed in an axial position. This unusual conformation has already been confirmed by X-ray crystallography in 1978.[6]

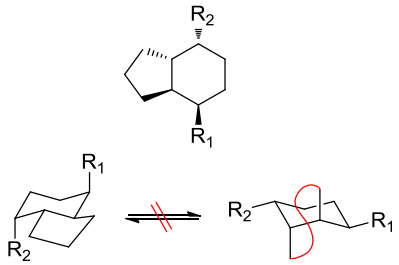


Scheme 1. Biosynthesis of Valerenic Acid (**1**).

The challenging architecture and the promising pharmacological profile prompted us, and shortly thereafter the group of Altmann to devise a concise and flexible total synthesis of **1**, which was extended to suitable derivatives and SAR studies thereof.[7] In this report we also disclose a considerably simplified and streamlined route and discuss the preparation of several derivatives, which are more active than the natural product itself.[8,9]

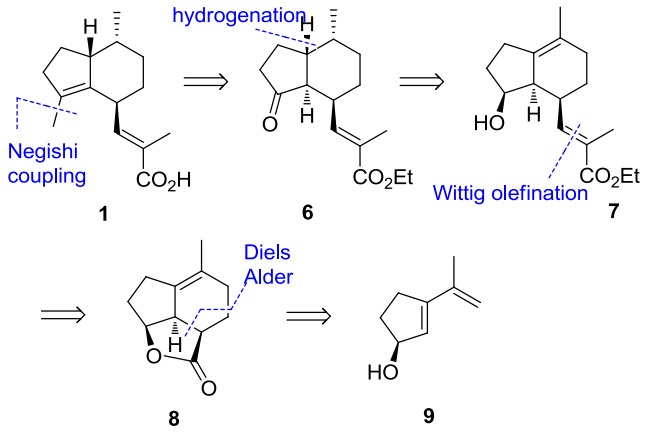
Results and Discussion

Many of the already known approaches towards valerenanes are based on intermediates which are moderately stable and prone to epimerization of the diaxial onring substituents, and/or include low yielding steps to install the substituents stereoselectively.[10] The key concept of our synthesis rests upon the construction of a *trans*-fused indane core for the following reason. A *trans*-annulated five-membered ring locks one of two chair conformations of the cyclohexane ring and thus allows us to fix both substituents in an axial position (see Scheme 2).



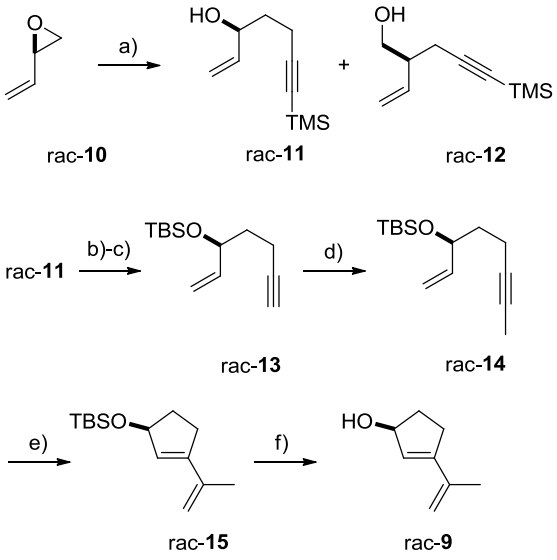
Scheme 2. Transannulated Indanyl Core as Key Concept.

As depicted in Scheme 3 our retrosynthetic analysis leads back to a Diels-Alder reaction of diene **9** with acrylic ester to generate the indane structure **8** stereoselectively. Further key steps are a Wittig reaction to introduce the side chain and a stereocontrolled hydrogenation to place the methyl group in the desired axial position.



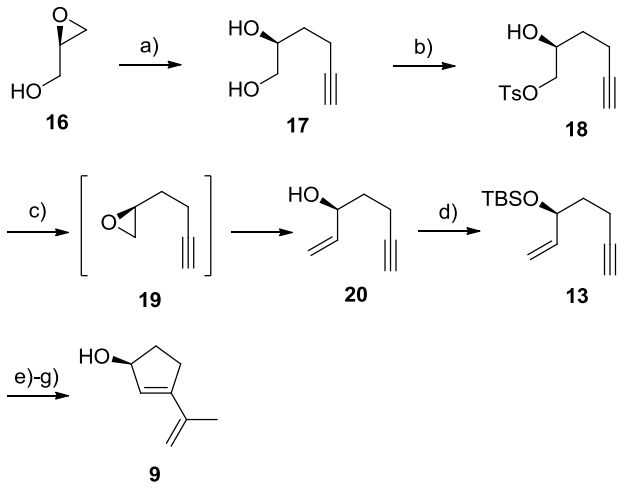
Scheme 3. Retrosynthetic Analysis.

Racemic approach: At the beginning of our project we needed a simple strategy to get enough material of hydroxydiene **9** to verify our retrosynthetic considerations. As depicted in Scheme 4 we devised a six step sequence starting with vinyloxirane (rac-**10**). Although **10** is available in both racemic and optically active forms only racemic material rac-**10** was used. In the first step oxirane rac-**10** was opened with 3-(trimethylsilyl)propargyllithium to furnish a separable mixture of the desired allylic alcohol rac-**11** and the undesired primary alcohol rac-**12** in a 2:1-ratio with a combined yield of 94%. Noteworthy, all attempts to use 3-(trimethylsilyl)propargylmagnesium bromide instead of the lithium compound only led to an increased amount of the undesired alcohol rac-**12**, whereas the use of the unsubstituted propargyllithium or 3-methylpropargyllithium predominantly afforded the corresponding allenes. The allylic alcohol of compound rac-**11** was protected as the TBS-ether, then the TMS-group was removed selectively and alkyne rac-**13** was methylated to provide enyne rac-**14** for the envisaged enyne-RCM reaction. Initially we planned to use platinum dichloride as catalyst for a skeletal rearrangement according to a protocol by Murai *et al.* [11] However, even though the cyclization of very similar substrates is known, all attempts failed and only led to isolation of the starting material, if an argon atmosphere was used, or to complete decomposition, if a carbon monoxide atmosphere was used instead. We rationalized that compared to other substrates the missing Thorpe-Ingold effect prevents the noble metal catalyzed rearrangement of our precursor. Therefore we switched to a Grubbs' I catalyzed enyne-RCM. Under an ethylene atmosphere (Mori's conditions) the reaction proceeded smoothly to furnish cyclopentene rac-**15** with excellent yield.[12] After deprotection of the alcohol the desired key intermediate rac-**9** for the envisaged Diels-Alder reaction was obtained in six steps from vinyloxirane (rac-**10**).



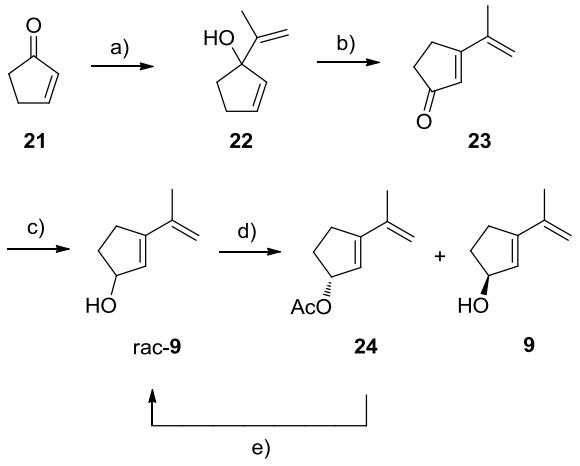
Scheme 4. Racemic Approach. a) $TMSC{\equiv}CCH_2Li$, Et_2O/THF = 5/1, -25 °C, 65% of rac-**11** and 29% of rac-**12**; b) TBSCl, imidazole, DMF, rt; c) K_2CO_3, MeOH/THF = 1/1, rt, 80% over two steps; d) n-BuLi, MeI, THF, -78 °C, 89%; e) ethylene atmosphere, Grubbs' I cat., rt, 86%; f) TBAF, THF, rt, 94%.

Glycidol approach: To obtain key compound **9** in optically pure form, we decided to avoid the expensive enantioenriched vinyloxirane (**10**). Therefore, our first enantioselective approach was based on (*R*)-glycidol (**16**), which can be used without protecting group in the first step (see Scheme 5). Regioselective opening of the epoxide with unsubstituted propargylmagnesium bromide led to diol **17**, whose primary alcohol was selectively tosylated with catalytic amounts of dibutyltin oxide in the next step.[13] Treatment of tosylate **18** with an excess of the basic Corey-Chaykovsky reagent afforded epoxide **19**, which was immediately opened by an additional equivalent of dimethylsulfonium methylide to furnish the slightly volatile allylic alcohol **20**.[14] Without purification the crude alcohol was protected as the TBS-ether **13** in enantiopure form. The last three steps were the same as in the racemic series and provided the optically active key intermediate **9** in seven steps from (*R*)-glycidol.



Scheme 5. Glycidol Approach. a) $HC{\equiv}CCH_2MgBr$, Et_2O, -78 °C, 97%; b) TsCl, NEt_3, cat. Bu_2SnO, DCM, rt, 80%; c) Me_3SI, n-BuLi then **19**, THF,-20 °C; d) TBSOTf, NEt_3, DCM, 0 °C, 58% over two steps; e) n-BuLi, MeI, THF, -78 °C, 89%; f) ethylene atmosphere, Grubbs' I cat., rt, 86%; g) TBAF, THF, rt, 94%.

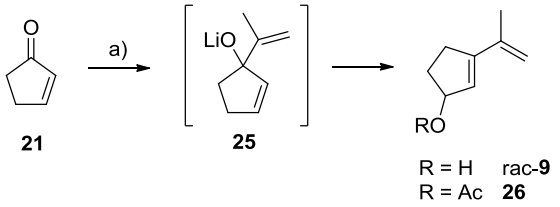
Oxidative rearrangement approach: The third approach towards compound **9** was developed to shorten our synthesis, and avoid costly starting materials and metathesis catalysts. As depicted in Scheme 6, this approach started with inexpensive cyclopentenone **21**.



Scheme 6. Oxidative Rearrangement Approach. a) isopropenyllithium, Et_2O, -78 °C; b) PDC, DCM, rt, 49% over two steps; c) DIBALH, DCM, -78 °C, 95%; d) vinyl acetate, Amano lipase PS, MTBE, rt, 45% of **9** with ee ≥ 95% and 46% of **24**; e) silica gel, THF, H_2O, rt, 95%.

Noteworthy, the 1,2-addition of an appropriate isopropenyl nucleophile proved more difficult than we had envisaged, because in most cases the yield was low and competitive 1,4-addition was observed. After screening different conditions, diethyl ether as solvent and isopropenyllithium as nucleophile was found to provide allylic alcohol **22** in satisfying yield. However, this compound turned out to be very sensitive to acids and therefore only of moderate stability, as well as slightly volatile. Therefore, without further purification, an oxidative rearrangement with PDC was performed to furnish dienone **23** in reasonable yield.[15] The reduction to the alcohol proceeded smoothly, and chiral resolution with Amano lipase PS and vinyl acetate gave enantiomerically enriched hydroxy diene **9** along with acetate **24**.[16] Interestingly chromatographic separation of both compounds had to be performed on aluminium oxide because the acetate was hydrolyzed on silica gel. This observation proved useful in the end, as simple treatment of the acetate with aqueous silica gel in THF reconverted it into the racemic hydroxy diene, which can be recycled in another chiral resolution.

One-pot reaction approach: The final and by far shortest method to provide sufficient amounts of **9** incorporates a novel one-pot reaction, which has been recently devised by our group (see Scheme 7).[8]

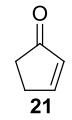
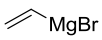
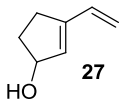
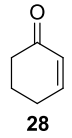
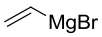
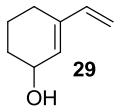
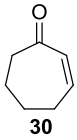
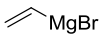
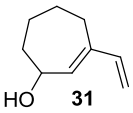
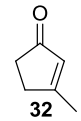
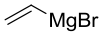
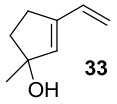
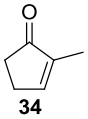
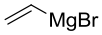
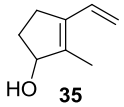
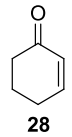
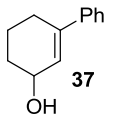


Scheme 7. One-Pot Reaction Approach. a) i) isopropenyllithium, Et_2O, -78 °C; then ii) TFA, H_2O, 0 °C, 81% (72% on gram scale).

The idea is based on the above mentioned acid lability of the allylic alcohol **22**. We rationalized, that this compound should be able to undergo an acid induced [1,3]-isomerization, which would lead to the formation of the thermodynamically more stable product.[17] To confirm this hypothesis the initially formed tertiary alkoxide **25** was protonated with aqueous acid to form the alcohol, which isomerizes to the more stable secondary hydroxy diene rac-**9**. If an inorganic acid such as sulphuric acid or hydrochloric acid was added, low yields were obtained, indicating that decomposition and side reactions seemed to be competitive with the [1,3]-isomerization. However, when acetic acid or trifluoroacetic acid was used, the yield considerably increased. Whereas isomerization induced by acetic acid took much longer and led to considerable amounts of 1-acetoxy-3-isopropenylcyclopent-2-ene (**26**) as a byproduct, treatment of **25** with trifluoroacetic acid resulted in the selective formation of 2,4-dienol rac-**9**. Finally with this scalable and high yielding one-pot reaction we were able to synthesize gram quantities of the racemic hydroxy diene rac-**9** in a single step. Combined with the chiral resolution, **9** is now accessible in just two steps.

To test the usefulness of this one-pot reaction we successfully expanded the scope of this reaction.[8] Fortunately the same principle could be applied on several other cycloalkenones as well, although depending on the substrates, slight alterations of the used conditions sometimes were necessary (see Table 1). As is depicted in table 1, the reaction is not restricted to the use of isopropenyllithium and smooth conversion is also observed with vinylmagnesium bromide (entries 1-5). Also substrates with larger ring size undergo selective isomerization (entries 2 and 3), as well as substituted cycloalkenones (entries 4 and 5). Noteworthy, the conversion of substrate **32** was much more acid-sensitive than of other substrates (entry 4). Therefore, the corresponding intermediate was treated with aqueous acetic acid instead of trifluoroacetic acid to provide the expected alcohol as sole product. Interestingly, in the isomerization of this substrate no other products were obtained. Finally, clean and selective isomerization was also observed for phenylmagnesium bromide (entry 6).

Table 1. Selected Examples of the Conversion of different Substrates.[a]

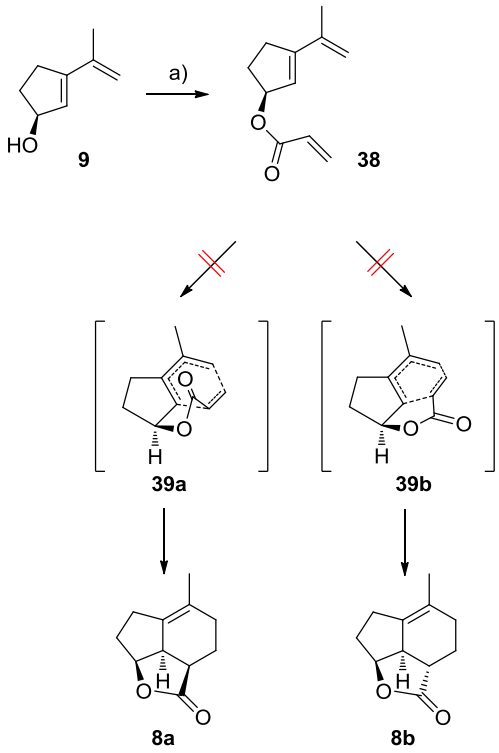
entry	substrate	nucleophile	conditions	product	yield
1	 **21**		TFA, 0 °C	 **27**	78% (73%)[b]
2	 **28**		TFA, 0 °C	 **29**	79%
3	 **30**		TFA, 25 °C	 **31**	80%
4	 **32**		AcOH, 0 °C	 **33**	99%
5	 **34**		TFA, 0 °C	 **35**	79%
6	 **28**	PhMgBr	TFA, 25 °C	 **37**	94%

[a] i) 0.1 M in Et_2O at 0 °C, 2.0 equiv nucleophile; ii) 0 °C or rt, H_2O, 2.5 equiv acid.

[b] Conducted on gram scale.

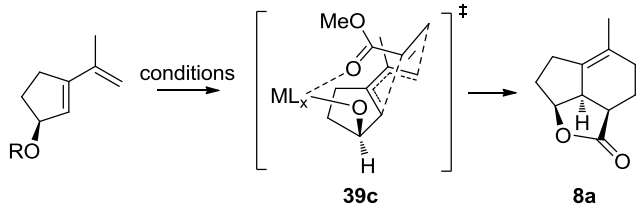
Hydroxy-directed Diels-Alder reaction: With both racemic as well as optically pure substrates in our hands, we proceeded with the remaining steps of our planned synthesis (see Scheme 8). Ester **38** was prepared by treatment of alcohol **9** with acryloyl chloride to get the precursor of the envisaged IMDA reaction. However, all attempts failed as either no conversion at all or decomposition was observed. According to literature precedence the IMDA reaction of compounds such as ester **38** should exclusively lead to the *exo* product **8b**.[18] The electronically preferred *endo* transition state **39a** is highly strained and should be disfavoured relative to the *exo* transition state **39b.** However, closer inspection and calculation of the predicted *exo* product **8b** reveal that such a compound would be extremely distorted, which makes its formation unlikely. In conclusion it seems that the *endo* product **8a** is not accessible because of kinetic reasons, whereas the *exo* product is not formed because of thermodynamic instability.

To solve this problem a hydroxy-directed Diels-Alder (HDDA) reaction was chosen, because in this case the esterification occurs after the Diels-Alder reaction.[19] Therefore the *endo* transition state **39c** lacks the distortion described above. The hydroxy function serves as anchoring group for the metal and allows enantio- and regioselective cyclization (see Table 2). Whereas all attempts to use phenyl magnesium bromide either with or without a scavanger alcohol to generate the alkoxide led to no conversion or complete decomposition (entries 1 and 2), deprotonation with triethylamine in the presence of magnesium dibromide etherate and addition of the dienophile according to a protocol of Barriault and coworkers provided lactone **8a** with 45% yield (entry 3).[20] Gratifyingly, the use of Huenig's base instead of triethylamine increased the yield to 81% (entry 4). Unfortunately, all attempts to deprotect racemic diene rac-**15** with boron trifluoride and to use the *in situ* formed boronate failed, probably because of the instability of rac-**15** under the conditions applied.



Scheme 8. Attempted IMDA. a) pyridine, acryloyl chloride, dichloromethane, 0 °C, 32%.

Table 2. Optimization of the HDDA.



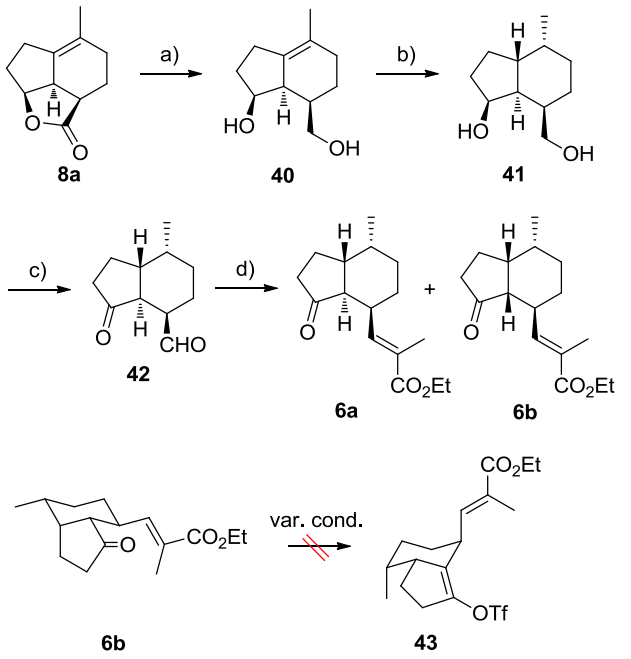
entry	R	conditions	yield
1	H	PhMgBr, toluene, rt to 50 °C	0%[a]
2	H	0.5 eq PhMgBr, $C_5H_{11}OH$, toluene, rt	0%[b]
3	H	$MgBr_2{\cdot}Et_2O$, NEt_3, rt	45%
4	H	$MgBr_2{\cdot}Et_2O$, DIPEA, rt	81%
5	TBS	$BF_3{\cdot}Et_2O$, DCM or CH_3CN, -15 °C	0%[a]

[a] Decomposition.

[b] No conversion of **9** observed.

Unsuccessful attempts: To introduce the *trans*-ring fusion in the hydroindane core and hence the two missing stereogenic

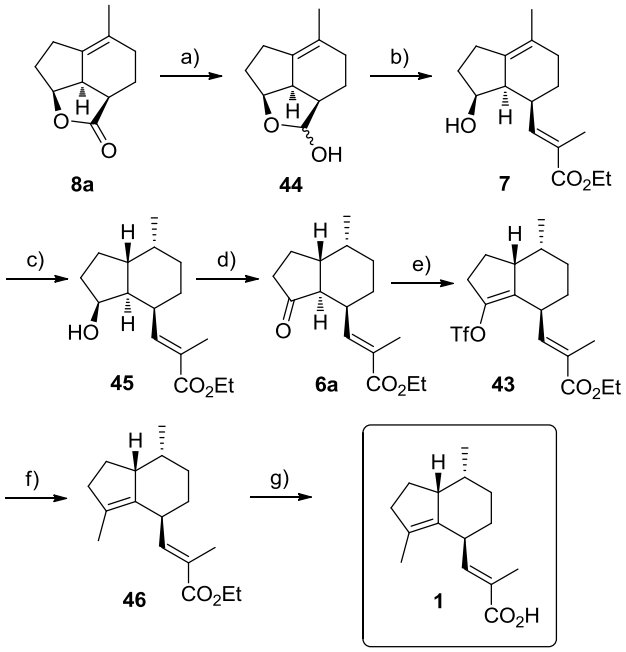
centers of valerenic acid, lactone **8a** was reduced to diol **40**, in which both hydroxy groups may serve as anchoring groups for a substrate directable hydrogenation (see Scheme 9). Indeed, Crabtree's catalyst furnished diol **41** stereoselectively with excellent yield.[21] After oxidation to ketoaldehyde **42** a Wittig olefination was used for introducing the enoate sidechain. However, although the desired compound **6a** was also obtained, the major product of this reaction was **6b**, resulting from epimerization of **6a** to its *cis*-fused diastereomer. Unfortunately, the consequences of this epimerization are crucial, because in **6b** both onring substituents are in equatorial positions of the six-membered ring. Therefore all attempts to convert **6b** into the desired enol triflate **43** failed, because this would place both substituents in axial positions. Only the formation of the less substituted enol triflate was observed.



Scheme 9. Envisaged Endgame. a) $LiAlH_4$, Et_2O, 0 °C to rt, 90%; b) cat. Ir(cod)(py)PCy_3, H_2, DCM, rt, 91%; c) IBX, DMSO, rt, 80%; d) Ph_3P=$CMeCO_2Et$, DCM, rfx, 14% of **6a** and 65% of **6b**.

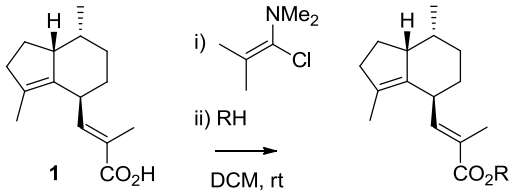
Completion of the synthesis: To prevent the detrimental epimerization lactone **8a** was reduced to lactol **44** instead (see Scheme 10). Gratifyingly, subsequent Wittig olefination led to the chain elongated product **7** without epimerization. Again the secondary alcohol was used to direct the chemo- and stereoselective Crabtree hydrogenation, which produced compound **45** with satisfying yield. Mild oxidation allowed us to isolate **6a** as sole product,[22] which was converted regioselectively into the tetrasubstituted enol triflate **43**. Negishi cross coupling with dimethylzinc furnished ethyl valerenate (**46**).[23] Small amounts of the undesired regioisomer were removed by column chromatography on silica gel (conditioned with silver nitrate) or by HPLC. Finally saponification furnished (-)-valerenic acid (**1**) with an overall yield of 13% (25% if compound **24** is fully recycled) over 10 steps (7 isolated intermediates) starting from commercially available cyclopentenone **21**.

Synthesis of derivatives: After completion and optimization of our synthesis we turned our attention to the preparation of suitable derivatives. Recently Rudolph and Altmann have demonstrated that functionalization of the carboxyl group has drastic consequences on the activity of valerenic acid.[24,25] Therefore we identified synthetic valerenic amides as potential targets. In an effort to learn more about the structure-activity relationship (SAR) of these compounds and their interaction with the $GABA_A$ receptor six simple amides with different substituents are chosen for a first series of derivatives. (see Table 3)



Scheme 10. Final Steps towards Valerenic Acid (**1**). a) DIBALH, DCM, -78 °C; b) Ph_3P=$CMeCO_2Et$, benzene, rfx, 83% over two steps; c) cat. Ir(cod)(py)PCy_3, H_2, DCM, rt, 72%; d) IBX, DMSO, rt, 93%; e) Tf_2O, pyridine, DCM, rt; f) cat. $Pd(PPh_3)_4$, Me_2Zn, THF, rt, 78% over two steps; g) LiOH, THF, H_2O, MeOH, rt, 99%.

Table 3. Preparation of Derivatives.



entry	R-H	product	yield
1	NH_3	**47**	96%
2	NH_2Me	**48**	95%
3	NH_2Et	**49**	94%
4	$NHEt_2$	**50**	94%
5	piperidine	**51**	91%
6	morpholine	**52**	90%

Although activation of valerenic acid with chloroformates or other coupling reagents and treatment with ammonia furnishes the desired unsubstituted amide **47**, unfortunately yields decrease when bulkier amines are used as nucleophiles. After testing several procedures eventually the use of Ghosez' reagent to form valerenic acid chloride under very mild conditions and subsequent addition of the corresponding amine provides the best yields. [26] In cooperation with the Department of Pharmacology and Toxicology, University of Vienna these substrates were both tested *in vitro* and *in vivo*.[9] To our delight all substances are highly active $GABA_A$ receptor modulators. Depending on the degree of substitution the activity of compound **47** to **52** decreases with growing substituents. As consequence the best results are obtained for unsubstituted valerenic amide **47**, which is more than twice as active as valerenic acid (**1**). To get a better understanding of this class of substances also a second series of derivatives with modified valerenane core has been synthesized. A more detailed discussion of these highly active and easily available substrates will be published in due course.

Conclusions

In conclusion we have developed a concise, protecting group free and highly stereoselective total synthesis of valerenic acid. Altogether four different approaches to provide key intermediate **9** are described, leading to gradual improvements. Both successful strategies as well as unsuccessful attempts are discussed to outline the difficulty to synthesize compounds with thermodynamically instable axial substituents and prevent irreversible epimerization. The final route incorporates a novel one-pot reaction, which allows the formation of key intermediate **9** in gram quantities. Further extension of this reaction underlines the scope and applicability of this reaction. The number of steps has been reduced from fifteen to ten steps, which makes this route suitable for the synthesis of a variety of derivatives and provides the basis for extensive SAR studies. In a first effort a series of derivatives has been prepared. Interestingly, easily available valerenic amides display a higher activity than valerenic acid both *in vitro* and *in vivo*.

Experimental Section

All reactions were carried out in oven-dried glassware under an argon atmosphere unless stated otherwise. Anhydrous CH_2Cl_2 was distilled under Argon from P_2O_5, diethyl ether, methanol and benzene from sodium, DMSO, triethylamine, and diisopropylethylamine from CaH_2 and anhydrous THF, DMF and MTBE were purchased from Aldrich. All other solvents were HPLC grade. Commercially available reagents were used without further purification besides stated otherwise. Reactions were magnetically stirred and monitored by thin layer chromatography. Flash column chromatography was performed with silica gel (0.04-0.063 mm, 240-400 mesh) under pressure besides stated otherwise. Yields refer to chromatographically and spectroscopically pure compounds unless stated otherwise. NMR-spectra were either recorded on 400 MHz or 600 MHz (^{1}H NMR) or 100 MHz or 150 MHz (^{13}C NMR) spectrometers. Besides stated otherwise all NMR spectra were measured in $CDCl_3$ solutions. The chemical shifts δ are reported relative to the residual solvent peaks. All ^{1}H and ^{13}C shifts are given in ppm (s = singulet; d = doublet; t = triplet; q = quadruplet; m = multiplet; bs = broad signal). If possible, assignments of proton resonances were confirmed by correlated spectroscopy. Optical rotations were measured at 20 °C. IR spectra were recorded of samples prepared as films on silicium plates. MS spectra were measured with a resolution of 10000.

7-(Trimethylsilyl)hept-1-en-6-yn-3-ol (rac-11): 1-(Trimethylsilyl)prop-1-yne (98%, 0.94 mL, 6.221 mmol, 2.0 eq) dissolved in anhydrous diethyl ether (30 mL) and anhydrous THF (6 mL) was cooled to -25 °C before 1.6 M n-BuLi (3.9 mL, 6.240 mmol, 2.0 eq) was added dropwise. After 15 minutes the solution was warmed to 0 °C and stirred for another 60 minutes. Then the resulting mixture was recooled to -25 °C and treated with racemic vinyloxirane (0.25 mL, 3.103 mmol, 1.0 eq). Stirring over night the solution was slowly warmed to room temperature. After quenching with saturated aqueous NH_4Cl, the aqueous phase was extracted with diethyl ether (4x), dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (pentane/diethyl ether 20/1 to 10/1) provided 370 mg of slightly impure alcohol rac-**11** as clear, slightly yellow oil with 65% yield. Analytical data is in agreement with the data reported in the literature.[27] ^{1}H-NMR (400MHz, $CDCl_3$, ppm): 5.87 (ddd, J=17.2 Hz, J=10.5 Hz, J=6.0 Hz, 1H), 5.27 (dt, J=17.2 Hz, J=1.4 Hz, 1H), 5.14 (dt, J=10.4 Hz, J=1.3 Hz, 1H), 4.27 (m, 1H), 2.35 (m, 2H), 1.84-1.70 (m, 3H), 0.15 (s, 9H). ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 140.5, 115.2, 106.9. 85.6, 72.3, 35.6, 16.3, 0.2. IR (film, cm^{-1}): 3345, 2958, 2927, 2175, 1426, 1249, 1122, 1043, 989, 923, 841, 760. HRMS (ESI, m/z): calcd for $C10H18NaOSi^+$: 205.1019; found: 205.1026.

***tert*-Butyl(hept-1-en-6-yn-3-yloxy)dimethylsilane (rac-13) (racemic approach):** A solution of alcohol rac-**11** (931 mg, 5.106 mmol, 1.0 eq) in anhydrous dimethylformamide (20 mL) was cooled to 0 °C and imidazole (869 mg, 12.76 mmol, 2.5 eq) and *tert*-butyldimethylsilyl chloride (927 mg, 6.150 mmol, 1.20 eq) were added. The solution was warmed to room temperature and stirred over night. The solution was quenched by the addition of water and the aqueous phase was extracted with diethyl ether (3x). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude yellow oil was dissolved in methanol (35 mL) and THF (35 mL) and K_2CO_3 (1065 mg, 7.706 mmol, 1.5 eq) was added. The resulting mixture was stirred over night, cooled to 0 °C and finally quenched by the addition of diluted aqueous NH_4Cl. The aqueous phase was extracted with diethyl ether/pentane 1/1 (3x) and the combined organic extracts were washed with brine, dried with Na_2SO_4 and the solvent evaporated. Column chromatography (hexane/ethyl acetate 100/1) furnishes 918 mg of the TBS-protected alcohol rac-**13** with 80% yield over two steps. ^{1}H-NMR (400 MHz $CDCl_3$, ppm): 5.78 (ddd, J=17.1 Hz, J=10.4 Hz, J=6.1 Hz, 1H), 5.21-5.03 (m, 2H), 4.23 (dd, J=12.2 Hz, J=6.2 Hz, 1H), 2.32-2.16 (m, 2H), 1.94 (t, J=2.7 Hz, 1H), 1.76-1.62 (m, 2H), 0.90 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 141.1, 114.5, 84.6, 72.4, 68.5, 36.8, 26.0, 18.4, 14.5, -4.2, -4.7; IR (film, cm^{-1}): 3314, 2929, 2857, 1939, 1645, 1472, 1362, 1251, 1091, 1027, 987, 923, 837, 776, 633; HRMS (ESI, m/z): calcd for $[M-C_4H_9]^+$, C9H15OSi: 167.0892; found: 167.0894.

(*S*)-Hex-5-yne-1,2-diol (17): A mixture of magnesium turnings (4.745 g, 195.2 mmol), mercury-(II)-chloride (269.1 mg, 0.991 mmol) and a single crystal of iodide in freshly distilled ether (100 mL) was carefully treated with propargyl bromide (80% in toluene, 10.5 mL, 11.59 g, 97.4 mmol) dissolved in freshly distilled ether (40 mL). After the reaction had started the mixture was cooled to 0 °C and the rest of the propargyl bromide solution was slowly added within 1 hour. The resulting mixture was stirred for another hour at 0 °C and one additional hour at room temperature. (*R*)-Glycidol (97%, 1.0 mL, 1.077 g, 14.53 mmol, 1.0 eq) dissolved in freshly distilled diethyl ether (290 mL) was cooled to -78 °C. Under vigorous stirring freshly prepared propargyl-magnesium bromide (112.5 mL, 72.788 mmol, 5.0 eq) was very slowly added within 1 hour. During the night the mixture was slowly warmed to room temperature. After 14 hours the reaction was quenched with saturated aqueous NH_4Cl. For a better phase separation potassium sodium tartrate was added and the solution was extracted with ether (4x) and ethyl acetate (4x). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by chromatography (hexane/ethyl acetate 10/1 to pure ethyl acetate) provided 1.560 g of compound **17** as clear yellow oil with 94% yield. ^{1}H-NMR (400MHz, $CDCl_3$, ppm): 3.89 (ddd, J=13.1 Hz, J=7.0 Hz, J=3.2 Hz, 1H),

3.68 (dd, J=11.1 Hz, J=3.2 Hz, 1H), 3.49 (dd, J=11.1 Hz, J=7.3 Hz, 1H), 2.47 (bs, 1H), 2.36 (dt, J=7.0 Hz, J=2.7 Hz, 2H), 2.16 (bs, 1H), 1.99 (t, J=2.7 Hz, 1H), 1.66 (dd, J=13.6 Hz, J=6.8 Hz, 2H); ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 83.9, 71.2, 69.2, 66.7, 31.7, 15.0; IR (film, cm^{-1}): 3296, 2924, 2853, 1654, 1437, 1099, 1044, 944, 890, 636; HRMS (ESI, m/z): calcd for [M], C6H10O2: 114.0681; found: 114.0680; $[\alpha]_D^{20}$ = -19.9 (c = 0.72 g/100mL, DCM).

(*S*)-1-Tosylhex-5-yne-1,2-diol (18): Diol **17** (1.560 g, 13.667 mmol, 1.0 eq) was dissolved in anhydrous DCM (140 mL) cooled to 0 °C and dibutyltin oxide (67.9 mg, 0.2728 mmol, 0.02 eq), triethylamine (2.08 mL, 1.518 g, 15.005 mmol, 1.1 eq) and toluenesulfonyl chloride (2.864 g, 15.022 mmol, 1.1 eq) were added. After 10 minutes the ice bath was removed and the reaction mixture was stirred for 22 hours. Then solids were removed by filtration and the filtrate concentrated in vacuo. Purification by chromatography (hexane/ethyl acetate 4/1) provided 2.95 g of compound **18** as clear colorless oil with 80% yield. ^{1}H-NMR (400 MHz $CDCl_3$, ppm): 7.81 (d, J=8.3 Hz, 2H), 7.36 (d, J=8.0 Hz, 2H), 4.10-3.99 (m, 2H), 3.94 (dd, J=9.6 Hz, J=6.4 Hz, 1H), 2.46 (s, 3H), 2.38-2.28 (m, 2H), 2.18 (d, J=4.6 Hz, 1H), 1.95 (t, J=2.7 Hz, 1H), 1.64 (dd, J=13.6 Hz, J=6.8 Hz, 2H); ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 145.3, 132.8, 130.1, 128.1, 83.3, 73.7, 69.4, 68.4, 31.3, 21.8, 14.7; IR (film, cm^{-1}): 3360, 2922, 2852, 1654, 1458, 1355, 1174, 965, 668, 554, 421, 416; HRMS (ESI, m/z): calcd for [M], C13H16O4S: 268.0769; found: 268.0764; $[\alpha]_D^{20}$ = -0.4 (c = 1.24 g/100mL, DCM).

(*S*)-*tert*-Butyl(hept-1-en-6-yn-3-yloxy)dimethylsilane (13) (glycidol approach): A suspension of trimethylsulfonium iodide (4.032 g, 19.758 mmol, 5.3 eq) in anhydrous THF (60 mL) was treated with 1.6 M n-BuLi (11.75 mL, 18.8 mmol, 5.0 eq) at -15 °C. After stirring for 30 minutes tosylate **18** (1.002 g, 3.733 mmol, 1.0 eq) dissolved in anhydrous THF (30 mL) was added dropwise within 45 minutes. The resulting reaction mixture was stirred at the same temperature for 1 hour, slowly warmed to room temperature during the night, before it was quenched by the addition of water. The solution was extracted with ether (4x), the combined organic phases were washed with brine, dried (Na_2SO_4) and due to the volatility of (*S*)-hept-1-en-6-yne-3-ol carefully concentrated in reduced vacuo. The crude (*S*)-hept-1-en-6-yne-3-ol was dissolved in anhydrous DCM (37 mL) and cooled to 0 °C. Triethylamine (1.55 mL, 1.132 g, 11.182 mmol, 3.0 eq) and *tert*-Butyldimethylsilyl triflate (2.15 mL, 2.475 g, 9.362 mmol, 2.5 eq) were added and the solution was stirred for 1 hour at 0 °C before it was warmed to room temperature. After stirring for another hour water was added and the solution was extracted with ether (4x). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Chromatography (pentane/ether 200/1) furnished 489 mg of compound **13** as clear colorless oil with 58% yield. Analytical data is consistent with the reported data for compound rac-**13**. $[\alpha]_D^{20}$ = -4.9 (c = 0.815 g/100mL, DCM).

(*S*)-*tert*-Butyl(oct-1-en-6-yn-3-yloxy)dimethylsilane (14): Compound **13** (1028 mg, 4.581 mmol, 1.0 eq) was dissolved in anhydrous THF (46 mL) and cooled to -78 °C before treated with 1.6 M n-BuLi (4.3 mL, 6.88 mmol, 1.5 eq) dropwise. The resulting solution was stirred 15 minutes at the same temperature and then methyl iodide (1.15 mL, 18.48 mmol, 4.0 eq) was added. During the night the mixture was slowly warmed to room temperature. The reaction was quenched with water. The solution was extracted with ether (3x), the combined extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by chromatography (hexane/ethyl acetate 100/1) provided 977 mg of compound **14** as clear colorless oil with 89% yield. ^{1}H-NMR (400 MHz $CDCl_3$, ppm): 5.78 (ddd, J=17.1 Hz, J=10.4 Hz, J=6.0 Hz, 1H), 5.20-5.01 (m, 2H), 4.21 (dt, J=6.8 Hz, J=5.8 Hz, 1H), 2.25-2.09 (m, 2H), 1.78 (t, J=2.6 Hz, 3H), 1.69-1.58 (m, 2H), 0.90 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 141.4, 114.1, 79.1, 75.8, 72.6, 37.4, 26.0, 18.4, 14.8, 3.6, -4.2, -4.8; IR (film, cm^{-1}): 2929, 2857, 1472, 1361, 1251, 1089, 989, 922, 837, 776; HRMS (ESI, m/z): calcd for [M-C_4H_9], C10H17OSi: 181.1049; found: 181.1052; $[\alpha]_D^{20}$ = -4.8 (c = 1.665 g/100mL, DCM).

(*S*)-*tert*-Butyldimethyl(3-(prop-1-en-2-yl)cyclopent-2-enyloxy)silane (15): A solution of compound **14** (263.8 mg, 1.106 mmol, 1.0 eq) and freshly distilled and degassed DCM (37 mL) was cooled to -78 °C. The flask was flushed with ethylene gas over a period of 10 minutes before ethylene gas was bubbled through the solution itself for 3 additional minutes. Grubbs' I catalyst (136.4 mg, 0.1657 mmol, 0.15 eq) was added and once again ethylene gas was bubbled through the resulting mixture for one minute. The dry ice bath was removed and the mixture stirred for 24 hours. The flask was flushed with argon and the solvent was evaporated. Chromatography of the residue (pentane/diethyl ether 200/1) furnished 226.6 mg of compound of **15** as clear colorless oil with 86% yield. ^{1}H-NMR (400 MHz $CDCl_3$, ppm): 5.68 (d, J=1.4 Hz, 1H), 5.00-4.94 (m, 3H), 2.69-2.59 (m, 1H), 2.39-2.25 (m, 2H), 1.93 (s, 3H), 1.80-1.69 (m, 1H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 146.0, 140.0, 129.9, 114.2, 78.5, 34.3, 30.7, 26.2, 20.7, 18.5, -4.3, -4.4; IR (film, cm^{-1}): 3360, 2927, 2855, 1661, 1634, 1600, 1464, 1361, 1251, 1108, 1051, 1005, 910, 835, 775; HRMS (ESI, m/z): calcd for [M], C14H26OSi: 238.1753; found: 238.1750; $[\alpha]_D^{20}$ = -98.6 (c = 1.96 g/100mL, DCM).

(*S*)-3-(Prop-1-en-2-yl)cyclopent-2-enol (9) (glycidol approach): A solution of compound **15** (402.8 mg; 1.689 mmol, 1.0 eq) in anhydrous THF (34mL) was cooled to 0 °C and treated with 1.0 M tetrabutylammonium fluoride (2.55 mL, 2.55 mmol, 1.5 eq). The next 3½ hours the reaction mixture was stirred at room temperature and then quenched with saturated aqueous NH_4Cl. The resulting solution was extracted with DCM (3x) and ethyl acetate (1x), dried (Na_2SO_4) and concentrated in vacuo. Purification by chromatography (pentane/ether 3/1 to 2/1) provided 190.4 mg of compound **9** as clear slightly yellow oil with 95% yield. ^{1}H-NMR (400 MHz $CDCl_3$, ppm): 5.80 (d, J=1.7 Hz, 1H), 5.02 (s, 2H), 4.96-4.89 (m, 1H), 2.73-2.63 (m, 1H), 2.45-2.31 (m, 2H), 1.94 (s, 3H), 1.80-1.73 (m, 1H), 1.44 (d, J=7.4 Hz, 1H); ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 147.7, 139.8, 129.0, 114.9, 78.1, 34.1, 30.6, 20.7; IR (film, cm^{-1}): 3324, 2924, 2854, 1599, 1458, 1032, 970, 888; HRMS (ESI, m/z): calcd for [M], C8H12O: 124.0888; found: 124.0884; $[\alpha]_D^{20}$ = -119.3 (c = 0.825 g/100mL, DCM).

3-(Prop-1-en-2-yl)cyclopent-2-enone (23): 2-Bromopropene (160 µL, 1.801 mmol, 1.5 eq) was dissolved in anhydrous diethyl ether (5.1 mL) and cooled to -78 °C. Then 1.7 M *tert*-BuLi (2.12 mL, 3.604 mmol, 3.0 eq) was added. After stirring for 2 hours the slightly turbid solution was warmed to ambient temperature. After 15 minutes the resulting 2-propenyllithium was slowly added to a solution of cyclopent-2-enone (100 µL, 1.194 mmol, 1.0 eq) and anhydrous diethyl ether (4.8 mL) at -78 °C. After 60 minutes the reaction was quenched by the addition of diluted aqueous NH_4Cl and warmed to room temperature. The aqueous phase was extracted with diethyl ether (3x), the combined organic phases were washed with brine and dried with Na_2SO_4, followed by careful concentration in reduced vacuo (Attention: The tertiary alcohol **22** is volatile). The crude alcohol was then dissolved in anhydrous DCM (12 mL), Celite (930 mg) was added and the resulting mixture treated with pyridinium dichromate (905 mg, 2.406 mmol, 2.0 eq). After stirring for 24 hours at room temperature solids were removed by filtration and the remaining solution was concentrated in vacuo. Purification by chromatography (pentane/diethyl ether 4/1 to 2/1) furnished 71.5 mg of compound **23** as yellow solid with 49% over two steps. ^{1}H-NMR (400MHz, $CDCl_3$, ppm): 6.10 (t, J=1.5 Hz, 1H), 5.55 (s, 1H), 5.32 (t, J=1.3 Hz, 1H), 2.79 (m, 2H), 2.48 (m, 2H), 2.02 (s, 3H). ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 210.1, 174.2, 139.8, 128.8, 119.8, 35.4, 27.8, 20.5. IR (film, cm^{-1}): 2925, 2362, 2341, 1707, 1693, 1673, 1622, 1576, 1441, 1253, 1232, 1183, 919, 866. HRMS (EI, m/z): calcd for [M], C8H10O: 122.0732; found: 122.0732.

3-(Prop-1-en-2-yl)cyclopent-2-enol (rac-9) (oxidative rearrangement approach): A solution of dienone **23** (22.8 mg, 0.1866 mmol, 1.0 eq) and

anhydrous DCM (0.93 mL) was cooled to -78 °C and was treated with 1.0 M diisobutylaluminium hydride (0.23, 0.230 mmol, 1.25 eq). After stirring for 1 hour the remaining DIBALH was quenched by the addition of methanol. After warming to room temperature a diluted potassium sodium tartrate solution was added and stirred over night. The aqueous phase was extracted with DCM (5x), the combined organic phases were dried with Na_2SO_4 and the solvent was evaporated. Purification of the residue by column chromatography (pentane/diethyl ether 3/1 to 1/1) provided 22.9 mg of racemic alcohol rac-**9** with 99% yield as slightly yellow oil. Analytical data is consistent with the reported data for compound 9 listed above.

(*S*)-3-(Prop-1-en-2-yl)cyclopent-2-enol (9) and (R)-3-(prop-1-en-2-yl)cyclopent-2-enyl acetate (24) (racemic resolution): To a solution of racemic dienol rac-**9** (520.5 mg, 4.191 mmol, 1.0 eq) and anhydrous MTBE (14.5 mL) were added Amano lipase PS (111.0 mg) and vinyl acetate (0.4 mL, 4.340 mmol, 1.0 eq). The resulting mixture was stirred at ambient temperature for 24 hours. After a small NMR-sample indicated conversion > 50% solids were removed by filtration and the resulting filtrate concentrated in vacuo. Purification of the residue by chromatography (H/EE = 10/1 to 1/1) using Merck aluminium oxide 90 (0.063-0.200 mm, 70-230 mesh) provided 321.0 mg of ester **24** with 46% yield and 234.8 mg of optically enriched alcohol **9** with 45% yield and an enantiomeric excess > 95% (Attention: Ester **24** is acid-labile and should be stored below 0 °C.). Analytical data for compound **9** is consistent with racemic alcohol rac-**9**, see above. $[\alpha]_D^{20}$ = - 124.9 (c = 1.175 g/100 ml, DCM). Analytical data for ester **24**: ^{1}H-NMR (400MHz, $CDCl_3$): 5.81-5.71 (m, 2H), 5.05 (s, 2H), 2.74-2.65 (m, 1H), 2.52-2.33 (m, 2H), 2.04 (s, 3H), 1.95 (s, 3H), 1.93-1.85 (m, 1H). ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 171.2, 150.0, 139.5, 124.9, 115.6, 81.0, 30.7, 30.3, 21.5, 20.6. IR (film, cm^{-1}): 2947, 2857, 1732, 1600, 1454, 1372, 1238, 1165, 1100, 1027, 962, 888. HRMS (ESI, m/z): calcd for [M], C10H14O2: 166.0994; found: 166.0995. $[\alpha]_D^{20}$ = + 213.7 (c = 1.110 g/100 ml, DCM).

3-(Prop-1-en-2-yl)cyclopent-2-enol (rac-9) (racemization): To a solution of acetate **24** (251.4 mg, 1.512 mmol, 1.0 eq) and THF (8 mL) cooled to 0 °C was added water (8 mL) and Merck silica gel (0.04-0.063 mm, 240-400 mesh) (256.5 mg). The resulting mixture was vigorously stirred for 36 hours at ambient temperature before solids were removed by filtration. The filtrate was treated with saturated aqueous $NaHCO_3$ and extracted with dichloromethane (4x). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by chromatography (H/EE = 4/1) provided 178.1 mg of 3-isopropenylcyclopent-2-enol (rac-**9**) with 95% yield. For analytical data, see above. $[\alpha]_D^{20}$ = 0.000 (c =1.05 g/100 ml, DCM).

3-(Prop-1-en-2-yl)cyclopent-2-enol (rac-9) (one-pot reaction approach): 2-Bromopropene (3.1 mL, 34.85 mmol, 2.0 eq) was dissolved in anhydrous diethyl ether (35.0 mL) and cooled to -78 °C. After treatment with 1.9 M *tert*-BuLi (36.0 mL, 68.4 mmol, 3.9 eq) the resulting slightly turbid solution was stirred for 2 hours at the same temperature before it was warmed to ambient temperature. After 15 minutes the clear yellow solution was transferred via canula to a solution of cyclopent-2-enone (98%, 1.5 mL, 17.55 mmol, 1.0 eq) and anhydrous diethyl ether (140 mL) precooled to -78 °C. The resulting turbid mixture was stirred for 60 minutes. Then it was warmed to 0 °C and water (175 mL) was added. The biphasic solution was slowly treated with trifluoroacetic acid (3.4 mL, 44.13 mmol, 2.5 eq) and then vigorously stirred for another hour at the same temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ and DCM was added. The aqueous phase was extracted with DCM (3x) and the combined organic phases were washed with brine, dried with Na_2SO_4 and reduced in vacuo. Column chromatography (hexane/ethyl acetate 5/1 to 3/1) furnished 1.57 g of racemic alcohol rac-**9** as colorless oil with 72% yield. Analytical data is consistent with the reported data for compound **9** listed above.

General procedure for the preparation of 2,4-dienols: A solution of cycloalkenone (1.0 eq) and anhydrous diethyl ether (0.1 M) was cooled to 0 °C and treated with 1.0 M vinylmagnesium bromide (2.0 eq). After TLC indicated full conversion (usually 1 hour) water (0.1 M) and trifluoroacetic or acetic acid (2.5 eq) were added. The biphasic solution was vigorously stirred at 0 °C or ambient temperature until full conversion was observed by TLC. Then saturated aqueous $NaHCO_3$ was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (3x) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by chromatography provided the corresponding 2,4-dienol.

3-Vinylcyclopent-2-enol (27): According to the general procedure described above reaction of 2-cyclopentenone (98%, 50 µL, 0.5853 mmol, 1.0 eq) with 1.0 M vinylmagnesium bromide (1.16 mL, 1.16 mmol, 2.0 eq) in anhydrous diethyl ether (5.9 mL) and subsequent treatment with water (5.9 mL) and trifluoroacetic acid (113 µL, 1.4668 mmol, 2.5 eq) for 1.0 hours at 0 °C provided 50.6 mg of 3-vinylcyclopent-2-enol as slightly yellow oil with 78% yield (column chromatography H/EE = 5/1). (Attention: Dienol **27** should be stored below 0 °C.) ^{1}H-NMR (400MHz, $CDCl_3$): 6.58 (dd, J=17.5 Hz, 10.6 Hz, 1H), 5.79-5.75 (m, 1H), 5.27-5.15 (m, 2H), 4.94-4.85 (bs, 1H), 2.70-2.57 (m, 1H), 2.42-2.30 (m, 2H), 1.83-1.72 (m, 1H), 1.43 (d, J=5.6 Hz, 1H). ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 146.1, 133.3, 132.1, 117.0, 77.6, 33.7, 29.2. IR (film, cm^{-1}): 3297, 2922, 2853, 2359, 1591, 1455, 1416, 1319, 1275, 1264, 1158, 1042, 986, 968, 905, 750. HRMS (EI, m/z): calcd for [M], C7H10O: 110.0732; found: 110.0728.

3-Vinylcyclohex-2-enol (29): According to the general procedure described above reaction of 2-cyclohexenone (95%, 20 µL, 0.1957 mmol, 1.0 eq) with 1.0 M vinylmagnesium bromide (0.40 mL, 0.40 mmol, 2.0 eq) in anhydrous diethyl ether (2.0 mL) and subsequent treatment with water (2.0 mL) and trifluoroacetic acid (38 µL, 0.4932 mmol, 2.5 eq) for 1.5 hours at 0 °C provided 19.2 mg of 3-vinylcyclohex-2-enol as colorless oil with 79% yield (column chromatography H/EE = 5/1). ^{1}H-NMR (400MHz, $CDCl_3$): 6.35 (dd, J=17.5 Hz, J=10.8 Hz, 1H), 5.80-5.74 (m, 1H), 5.21 (d, J=17.5 Hz, 1H), 5.05 (d, J=10.8 Hz, 1H), 4.35-4.26 (m, 1H), 2.24-2.04 (m, 2H), 1.97-1.76 (m, 2H), 1.69-1.54 (m, 2H), 1.53-1.42 (bs, 1H). ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 139.4, 138.9, 130.9, 113.1, 66.4, 32.3, 23.9, 19.0. IR (film, cm^{-1}): 3389, 2934, 2869, 1714, 1666, 1453, 1427, 1258, 1189, 1056, 995, 966, 912, 749. HRMS (EI, m/z): calcd for [M], C8H12O: 124.0888; found: 124.0884.

3-Vinylcyclohept-2-enol (31): According to the general procedure described above reaction of 2-cycloheptenone (50 µL, 0.4484 mmol, 1.0 eq) with 1.0 M vinylmagnesium bromide (0.90 mL, 0.90 mmol, 2.0 eq) in anhydrous diethyl ether (4.5 mL) and subsequent treatment with water (4.5 mL) and trifluoroacetic acid (87 µL, 1.1293 mmol, 2.5 eq) for 1.5 hours at ambient temperature provided 49.7 mg of 3-vinylcyclohept-2-enol as colorless oil with 80% yield (column chromatography H/EE = 5/1). ^{1}H-NMR (400MHz, $CDCl_3$): 6.30 (dd, J=17.4 Hz, J=10.7 Hz, 1H), 5.81-5.75 (m, 1H), 5.15 (d, J=5.15 Hz, 1H), 4.98 (dd, J=10.7 Hz, J=0.58 Hz, 1H), 4.56-4.47 (m, 1H), 2.54-2.43 (m, 1H), 2.10-2.00 (m, 1H), 2.00-1.89 (m, 1H), 1.89-1.79 (m, 1H), 1.77-1.59 (m, 4H), 1.32-1.22 (m, 1H). ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 140.2, 140.0, 139.3, 111.3, 71.8, 36.6, 27.8, 26.5, 25.7. IR (film, cm^{-1}): 3343, 2928, 2853, 1605, 1450, 1351, 1276, 1028, 989, 891, 839. HRMS (EI, m/z): calcd for [M], C9H14O: 138.1045; found: 138.1047.

1-Methyl-3-vinylcyclopent-2-enol (33): A solution of 3-methylcyclopent-2-enone (97%, 60 µL, 0.5879 mmol, 1.0 eq) and anhydrous diethyl ether (6.0 mL) was cooled to 0 °C. 1.0 M vinylmagnesium bromide (1.10 mL, 1.10 mmol, 2.0 eq) was slowly added and the resulting solution was stirred for 60 minutes. Then the solution was warmed to 0 °C and water (6.0 mL) was added. The biphasic solution was slowly treated with acetic acid (85 µL, 1.4863 mmol, 2.5 eq) and then

vigorously stirred for 45 minutes at the same temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ and DCM was added. The aqueous phase was extracted with DCM (3x) and the combined organic phases were washed with brine, dried with Na_2SO_4 and reduced in vacuo to provide 72.3 mg of racemic alcohol **33** as slightly yellow oil with 99% yield. (Purification by column chromatography was not necessary). (Attention: Dienol **33** should be stored below 0 °C.) ^{1}H-NMR (400MHz, $CDCl_3$): 6.53 (dd, J=17.5 Hz, J=10.6 Hz, 1H), 5.67-5.64 (m, 1H), 5.21 (dd, J=17.5 Hz, J=0.9 Hz, 1H), 5.16 (dd, J=10.6 Hz, J=1.3 Hz, 1H), 2.66-2.57 (m, 1H), 2.47-2.37 (m, 1H), 2.13-1.95 (m, 2H), 1.55-1.48 (bs, 1H), 1.40 (s, 3H). ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 143.8, 136.5, 133.4, 116.5, 83.3, 40.0, 29.3, 27.6. IR (film, cm^{-1}): 3354, 2967, 2928, 2855, 2346, 1600, 1452, 1368, 1304, 1180, 1133, 1084, 889, 851. HRMS (EI, m/z): calcd for [M-CH_3], C7H9O: 109.0653; found: 109.0651.

2-Methyl-3-vinylcyclopent-2-enol (35): According to the general procedure described above reaction of 2-methyl-2-cyclopentenone (98%, 50 µL, 0.5097 mmol, 1.0 eq) with 1.0 M vinylmagnesium bromide (1.02 mL, 1.02 mmol, 2.0 eq) in anhydrous diethyl ether (5.0 mL) and subsequent treatment with water (5.0 mL) and trifluoroacetic acid (98 µL, 1.2721 mmol, 2.5 eq) for 0.75 hours at 0 °C provided 49.8 mg of 2-methyl-3-vinyl-cyclopent-2-enol as colorless oil with 79% yield (column chromatography H/EE = 5/1). (Attention: Dienol **35** should be stored below 0 °C.) ^{1}H-NMR (400MHz, $CDCl_3$): 6.65 (dd, J=17.2 Hz, J=10.8 Hz, 1H), 5.21-5.13 (m, 2H), 4.71-4.60 (m, 1H), 2.65-2.53 (m, 1H), 2.38-2.26 (m, 2H), 1.83 (s, 3H), 1.71-1.62 (m, 1H), 1.45 (d, J=4.7 Hz, 1H). ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 138.9, 136.7, 131.3, 115.4, 81.6, 32.5, 29.4, 11.3. IR (film, cm^{-1}): 3345, 2960, 2936, 2912, 2854, 1443, 1421, 1276, 1261, 1198, 1049, 1005, 986, 900, 750. HRMS (APCI, m/z): calcd for $[M-H_2O+H]^+$, $C8H11^+$: 107.0855; found: 107.0850.

3-Phenylcyclohex-2-enol (37): According to the general procedure described above reaction of 2-cyclohexenone (95%, 50 µL, 0.4892 mmol, 1.0 eq) with 1.0 M phenylmagnesium bromide (0.98 mL, 0.98 mmol, 2.0 eq) in anhydrous diethyl ether (4.9 mL) and subsequent treatment with water (4.9 mL) and trifluoroacetic acid (95 µL, 1.2331 mmol, 2.5 eq) for 48 hours at ambient temperature provided 80.5 mg of 3-phenylcyclohex-2-enol as colorless oil with 94% yield (column chromatography H/EE = 3/1). ^{1}H-NMR (400MHz, $CDCl_3$): 7.44-7.39 (m, 2H), 7.36-7.30 (m, 2 H), 7.29-7.23 (m, 1H), 6.17-6.09 (m, 1H), 4.45-4.34 (bs, 1H), 2.53-2.43 (m, 1H), 2.43-2.32 (m, 1H), 2.01-1.86 (m, 2H), 1.82-1.63 (m, 2H), 1.55 (d, J=5.2 Hz, 1H). ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 141.5, 140.4, 128.5, 127.6, 126.7, 125.5, 66.5, 31.9, 27.7, 19.6. IR (film, cm^{-1}): 3336, 2934, 2862, 2358, 1494, 1446, 1344, 1276, 1053, 973, 907, 757, 695. HRMS (ESI, m/z): calcd for $[M+Na]^+$, $C12H14NaO^+$: 197.0937; found: 197.0938.

3-(Prop-1-en-2-yl)cyclopent-2-enyl acrylate (38): A solution of racemic hydroxyl-diene 9 (25.0 mg, 0.2013 mmol, 1.0 eq) and pyridine (0.28 mL, 3.469 mmol, 15 eq) in anhydrous DCM (2.0 mL) was cooled to 0 °C and treated with acryloyl chloride (0.19 ml, 2.339 mmol, 10 eq). After stirring for 2 hours saturated aqueous $NaHCO_3$ was added, the resulting solution diluted with diethyl ether and the aqueous phase extracted with DCM (3x). The combined organic phases were dried with Na_2SO_4 and reduced in vacuo. Chromatography using Merck aluminium oxide 90 (0.063-0.200 mm, 70-230 mesh) (hexane/ethyl acetate 30/1) afforded 12.9 mg of ester **38** as clear and colorless oil with 32% yield. ^{1}H-NMR (400MHz, $CDCl_3$, ppm): 6.39 (dd, J=17.3 Hz, J=1.5 Hz, 1H), 6.11 (dd, J=17.3 Hz, J=10.4 Hz, 1H), 5.86-5.76 (m, 3H), 5.06 (s, 2H), 2.80-2.65 (m, 1H), 2.53-2.36 (m, 2H), 1.99-1.90 (m, 4H). ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 166.4, 150.1, 139.6, 130.5, 129.0, 124.8, 115.6, 81.2, 30.8, 30.3, 20.6. IR (film, cm^{-1}): 2948, 1721, 1600, 1406, 1295, 1269, 1192, 1165, 1041, 1024, 984, 965, 890, 811. HRMS (EI, m/z): calcd for [M], C11H14O2: 178.0994; found: 178.0997.

(*2aR,7aS,7bR*)- 5-Methyl- 3,4,6,7,7a,7b-hexahydro-2a*H*-indeno[1,7-*bc*]furan-2-one (8a): Anhydrous $MgBr_2$•Et_2O (977 mg, 3.783 mmol, 2.0 eq) was suspended in anhydrous dichloromethane (4.5 mL), treated with diisopropylethylamine (1.3 mL, 7.644 mmol, 4.0 eq) and stirred for 15 minutes until the suspension turns magenta. Then compound **9** (234.8 mg, 1.891 mmol, 1.0 eq) dissolved in dichloromethane (14.5 mL) was added slowly via canula. After stirring for 1 hour methyl acrylate (0.34 mL, 3.776 mmol, 2.0 eq) was added dropwise. The resulting mixture was stirred for 6 hours before it was quenched with saturated aqueous NH_4Cl. For a better phase separation potassium sodium tartrate was added and the solution extracted with diethyl ether (2x) and dichloromethane (3x). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by chromatography (H/EE = 6/1) furnished 273.7 mg of compound **8a** as white solid with 81% yield. ^{1}H-NMR (400 MHz $CDCl_3$, ppm): 4.84 (dt, J=5.5 Hz, J=1.0 Hz, 1H), 3.02 (ddd, J=6.5 Hz, J=6.0 Hz, J=3.2 Hz, 1H), 2.88-2.80 (m, 1H), 2.63-2.51 (m, 1H), 2.32-2.18 (m, 1H), 2.15-1.87 (m, 6H), 1.65 (s, 3H); ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 178.7, 130.4, 129.3, 83.4, 43.8, 39.7, 29.1, 27.5, 27.2, 20.2, 20.0; IR (film, cm^{-1}): 2925, 1763, 1449, 1335, 1142, 1020, 985, 932, 877; HRMS (EI, m/z): calcd for [M], C11H14O2: 178.0994; found: 178.0997; $[\alpha]_D^{20}$ = -94.4 (c = 0.71 g/100mL, DCM).

(*1S,7R,7aR*)-7-(hydroxymethyl)-4-methyl-2,3,5,6,7,7a-hexahydro-1H-inden-1-ol (40): Racemic compound **8a** (19.6 mg, 0.1100 mmol, 1.0 eq) was dissolved in anhydrous diethyl ether (1.5 mL) and cooled to 0 °C before it was treated with $LiAlH_4$ (95%, 0.3304 mmol, 3.0 eq) in three portions. The resulting mixture was warmed to room temperature and stirred for 4 hours. After recooling to 0 °C the mixture was diluted with diethyl ether (1.5 mL) and the reaction was quenched with the subsequent addition of water (24 µL), 10% aqueous NaOH (24 µL) and again water (72 µL). Then the mixture was warmed to room temperature and vigorously stirred for 30 minutes. The clear colorless solution was removed and filtered over Celite, whereas the white residue was once again treated with diethyl ether (2 mL), water (56 µL) and 10% aqueous NaOH (14 µL). After stirring for another 30 minutes the white precipitate was removed by filtration and the combined organic filtrates were dried with Na_2SO_4 and concentrated in vacuo. Purification by chromatography (hexane/ethyl acetate 1/1) provided 18.0 mg of racemic diol **40** as clear, colorless oil with 90% yield. ^{1}H-NMR (400MHz, $CDCl_3$, ppm): 4.38 (t, J=3.6 Hz, 1H), 3.78 (t, J=10.2 Hz, 1H), 3.54 (dd, J=10.8 Hz, J=2.3 Hz, 1H), 3.48-3.01 (bs, 2H), 2.47 (m, 2H), 2.29 (m, 2H), 1.84 (m, 2H), 1.81-1.63 (m, 4H), 1.61 (s, 3H). ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 132.0, 124.8, 74.5, 63.5, 49.7, 37.5, 33.4, 28.4, 27.9, 26.0, 19.4. IR (film, cm^{-1}): 3234, 2925, 2333, 2158, 1439, 1164, 1110, 1056, 1012, 959, 786. HRMS (EI, m/z): calcd for [M], C11H18O2: 182.1307; found: 182.1304.

(*1S,3aR,4R,7R,7aS*)-7-(hydroxymethyl)-4-methyloctahydro-1H-inden-1-ol (41): A solution of racemic diol **40** (18.0 mg, 0.0988 mmol, 1.0 eq) and freshly distilled and degassed DCM (4 ml) was cooled to 0 °C. The flask was flushed with hydrogen over a period of 2 minutes before hydrogen was bubbled through the solution itself for one additional minute. After adding Crabtree's catalyst (5.2 mg, 0.00646 mmol, 0.065 eq) the flask was once again flashed with hydrogen for 3 minutes before hydrogen was bubbled through the solution for 2 minutes until it became colorless. The ice bath was removed and the mixture stirred for 24 hours. Argon was bubbled through the reaction mixture and the solvent was evaporated. Chromatography (hexane/ethyl acetate 3/2) of the residue affords 16.5 mg of racemic compound **41** as white solid with 91% yield. ^{1}H-NMR (400MHz, $CDCl_3$, ppm): 4.26 (s, 1H), 4.07 (t, J=10.7 Hz, 1H), 3.77-3.49 (bs, 2H), 3.46 (d, J=11.0 Hz, 1H), 2.33 (m, 1H), 2.15 (m, 2H), 1.88-1.52 (m, 5H), 1.49-1.29 (m, 4H), 0.87 (d, J=7.1 Hz, 3H). ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 74.8, 63.3, 45.4, 39.7, 36.4, 33.6, 30.0, 29.5, 25.9, 23.6, 12.0. IR (film, cm^{-1}): 3190, 2957, 2926, 2903,2882, 2861, 1460, 1439, 1371, 1340, 1276, 1049, 1009, 949, 764, 750. HRMS (EI, m/z): calcd for [M-H_2O], C11H18O: 166.1358; found: 166.1357.

(*3aS,4R,7R,7aR*)- 7-methyl- 3-oxooctahydro- 1H-indene- 4-carbaldehyde (42): Racemic diol **41** (16.5 mg, 0.0895 mmol, 1.0 eq) was dissolved in anhydrous DMSO (1.8 mL) and treated with a solution of IBX

(102.0 mg, 0.3643 mmol, 4.0 eq) in anhydrous DMSO (1.2 mL). After stirring for 5 hours water was added and the white precipitate removed by filtration. The precipitate was washed with DMSO/water 1/2 and pentane/diethyl ether 1/1. The filtrate was extracted with DCM (4x), the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. Purification by chromatography (hexane/ethyl acetate 5/1) provided 12.8 mg of racemic compound **42** as clear colorless oil with 80% yield (Attention: Compound **42** tends to epimerize and should be stored below 0 °C.). ^{1}H-NMR (400MHz, $CDCl_3$, ppm): 9.57 (s, 1H), 3.10 (m, 1H), 2.57-2.03 (m, 5H), 2.01-1.85 (m, 2H), 1.72 (m, 1H), 1.62-1.48 (m, 2H), 1.39 (m, 1H), 0.92 (d, J=7.0 Hz, 3H). ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 217.2, 201.9, 47.4, 47.3, 41.5, 37.9, 29.95, 29.85, 24.8, 19.6, 11.1. IR (film, cm^{-1}): 2934, 2877, 1738, 1458, 1389, 1306, 1262, 1161, 1142, 1082, 959, 878, 750. HRMS (EI, m/z): calcd for $[M-C_2H_4]^+$, C9H12O2$^+$: 152.0832; found: 152.0835.

(*E*)-Ethyl-2-methyl-3-((*3aR,4S,7R,7aR*)-7-methyl-3-oxooctahydro-1H-inden-4-yl)-acrylate (6b): A solution of racemic diketo compound **42** (12.8 mg, 0.0710 mmol, 1.0 eq) and anhydrous DCM (1.0 mL) was treated with (1-ethoxycarbonylethyliden)-triphenylphosphorane (94%, 54.6 mg, 0.1416 mmol, 2.0 eq) and refluxed for 24 hours. Then silica gel was added and the solvent evaporated. Purification of the residue by chromatography (hexane/ethyl acetate 7/1) furnished 12.2 mg of compound **6b** as white solid with 65% yield and 2.7 mg of slightly impure compound **6a** with 14% yield. Analytical data for **6b**: ^{1}H-NMR (400MHz, $CDCl_3$, ppm): 6.58 (dd, J=9.7 Hz, J=1.4 Hz, 1H), 4.18 (dq, J=7.1 Hz, J=4.2 Hz, 2H), 2.46-2.24 (m, 3H), 2.15 (m, 1H), 2.03 (m, 1H), 1.96-1.77 (m, 3H), 1.73 (d, J=1.4 Hz, 3H), 1.70-1.57 (m, 2H), 1.33-1.22 (m, 5H), 0.98 (d, J=6.9 Hz, 3H). ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 218.1, 168.1, 143.6, 128.2, 60.7, 54.0, 41.8, 36.7, 33.5, 31.1, 31.0, 28.3, 19.7, 19.2, 14.4, 12.9. IR (film, cm^{-1}): 2954, 2926, 2871, 1741, 1705, 1650, 1458, 1368, 1274, 1232, 1204, 1160, 1106, 1071, 748. HRMS (EI, m/z): calcd for [M], C16H24O3: 264.1725; found: 264.1723.

(*E*)-3-((*3S,3aR,4S*)-3-Hydroxy-7-methyl-2,3,3a,4,5,6-hexahydro-1*H*-inden-4-yl)-2-methyl-acrylic acid ethyl ester (7): A solution of compound **8a** (183.5 mg, 1.030 mmol, 1.0 eq) in DCM (10 mL) was cooled to -78 °C and 1.0 M diisobutylaluminium hydride (1.5 mL, 1.5 mmol, 1.5 eq) was added dropwise. After stirring the mixture for 2¼ hours the reaction was quenched by the addition of ethyl acetate (1 mL) and stirred for another 15 minutes. Saturated aqueous potassium sodium tartrate was added and the mixture warmed to room temperature. The aqueous layer was separated and extracted with DCM (5x). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. Filtration through a short pad of silica gel afforded a crude mixture of the two isomers of lactol **44** as clear slightly yellow oil. Lactol **44** was dissolved in benzene (10 mL), (1-ethoxycarbonylethyliden)-triphenylphosphorane (94%, 794.2 mg, 2.060 mmol, 2.0 eq) was added and heated under reflux for 24 hours. Saturated aqueous NH_4Cl was added and the solution extracted with DCM (4x). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by chromatography (hexane/ethyl acetate 10/1 to 5/1) furnished 226.9 mg of compound **7** as clear colorless oil with 83% yield. ^{1}H-NMR (400 MHz $CDCl_3$, ppm): 7.06 (dd, J=10.5 Hz, J=1.4 Hz, 1H), 4.29 (dd, J=6.0 Hz, J=3.4 Hz, 1H), 4.24-4.11 (m, 2H), 3.12 (ddd, J=10.2 Hz, J=8.8 Hz, J=5.0 Hz, 1H), 2.58-2.22 (m, 3H), 2.09-1.59 (m, 12H), 1.31 (d, J=3.4 Hz, 1H), 1.27 (t, J=7.1 Hz, 3H); ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 168.2, 143.5, 132.0, 127.6, 125.5, 75.3, 60.7, 50.2, 34.0, 33.1 29.3, 27.7, 26.0, 19.5, 14.4, 12.7; IR (film, cm^{-1}): 3480, 2926, 1704, 1645, 1447, 1367, 1246, 1110, 1033, 753; HRMS (ESI, m/z): calcd for [M-H_2O], C16H22O2: 246.1620; found: 246.1614; $[\alpha]_D^{20}$ = -5.4 (c = 0.895 g/100mL, DCM).

(*E*)-3-((*3S,3aS,4S,7R,7aR*)-3-Hydroxy-7-methyl-octahydro-inden-4-yl)-2-methyl-acrylic acid ethyl ester (45): A solution of compound **7** (223.8 mg, 0.8466 mmol, 1.0 eq) and freshly distilled and degassed DCM (34 mL) was cooled to 0 °C. The flask was flushed with hydrogen over a period of 2 minutes before hydrogen was bubbled through the solution itself for one additional minute. After adding Crabtree's catalyst (68.0 mg, 0.0845 mmol, 0.1 eq) the flask was once again flashed with hydrogen for 3 minutes before hydrogen was bubbled through the solution for 2 minutes until it became colorless. The ice bath was removed and the mixture stirred for 2¼ hours. Argon was bubbled through the reaction mixture and the solvent was evaporated. Chromatography (hexane/ethyl acetate 7/1 to 3/1) of the residue furnished 162.7 mg of compound **45** as white solid with 72% yield. ^{1}H-NMR (400 MHz $CDCl_3$, ppm): 7.38 (dd, J=10.7 Hz, J=1.4 Hz, 1H), 4.26-4.12 (m, 3H), 3.13-3.04 (m, 1H), 2.45-2.34 (m, 1H), 2.26-2.16 (m, 1H), 1.94-1.46 (m, 9H), 1.41-1.24 (m, 7H), 0.90 (d, J=7.2 Hz, 3H); ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 168.2, 144.0, 127.0, 75.5, 60.7, 46.7, 37.2, 35.3, 33.2, 29.8, 28.7, 27.0, 24.8, 14.5, 12.6, 12.1; IR (film, cm^{-1}): 3483, 2926, 1701, 1636, 1459, 1367, 1247, 1171, 1106, 1042, 750; HRMS (ESI, m/z): calcd for [M], C16H26O3: 266.1882; found: 266.1890; $[\alpha]_D^{20}$ = -118.7 (c = 0.715 g/100mL, DCM).

(*E*)-2-Methyl-3-((*3aS,4S,7R,7aR*)-7-methyl-3-oxo-octahydro-inden-4-yl)-acrylic acid ethyl ester (6a): Compound **45** (157.9 mg, 0.5928 mmol, 1.0 eq) was dissolved in anhydrous DMSO (2.4 mL) and treated with a solution of IBX (335.6 mg, 1.199 mmol, 2.0 eq) in anhydrous DMSO (4.8 mL). After stirring for 2½ hours water was added and the white precipitate removed by filtration. The precipitate was washed with DMSO/water 1/2 and a small amount of ethyl acetate. The filtrate was extracted with DCM (4x), the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. Purification by chromatography (hexane/ethyl acetate 7/1) provided 146.5 mg of compound of **6a** as clear pale yellow oil with 93% yield. ^{1}H-NMR (400 MHz $CDCl_3$, ppm): 6.83 (ddd, J=10.2Hz, J=2.8Hz, J=1.4Hz, 1H), 4.16 (dq, J=7.1Hz, J=1.4Hz, 2H), 3.24-3.16 (m, 1H), 2.32-2.21 (m, 3H), 2.14-1.86 (m, 6H), 1.79-1.68 (m, 2H), 1.63-1.39 (m, 3H), 1.27 (t, J=7.1Hz, 3H), 0.97 (d, J=6.9Hz, 3H); ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 217.4, 168.4, 139.9, 129.5, 60.6, 51.4, 40.1, 37.8, 32.6, 30.4, 28.4, 25.6, 24.5, 14.4, 13.0, 11.6; IR (film, cm^{-1}): 2925, 2855, 1743, 1713, 1465, 1366, 1312, 1246, 1210, 1157, 1111, 1043, 752; HRMS (ESI, m/z): calcd for [M], C16H24O3: 264.1725; found: 264.1727; $[\alpha]_D^{20}$ = -160.9 (c = 0.86 g/100mL, DCM).

Valerenic ethyl ester (46): A solution of compound **6a** (16.1 mg, 0.0609 mmol, 1.0 eq) and anhydrous DCM (2.4 mL) was cooled to 0 °C and treated with freshly distilled triflic anhydride (101 µL, 171.7 mg, 0.609 mmol, 10.0 eq) and pyridine (49 µL, 48.1 mg, 0.608 mmol, 10 eq) under vigorous stirring. The ice bath was removed after 15 minutes and the mixture stirred for 24 hours. The reaction mixture was cooled to 0 °C and washed consecutively with saturated aqueous $CuSO_4$ and saturated aqueous $NaHCO_3$. Both aqueous layers were extracted with DCM (1x). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Filtration through a short pad of silica gel afforded a crude mixture of the two isomers as clear colorless oil. The mixture of isomers was dissolved in THF (1.2 mL) and cooled to 0 °C before tetrakis(triphenylphosphine)palladium (6.9 mg, 0.00597 mmol, 0.1 eq) was added. After stirring for 15 minutes the resulting brown solution was treated with 1.0 M dimethylzinc (0.24 mL, 0.24 mmol, 4.0 eq). The mixture was allowed to warm to room temperature after another 15 minutes and was stirred for 15½ hours. After cooling to 0 °C water and saturated aqueous NH_4Cl were added and the solution was extracted with ether (3x). The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by chromatography (hexane/ethyl acetate 50/1) with silica gel treated with 10% $AgNO_3$ furnished 12.4 mg of compound **46** as clear colorless oil with 78%. ^{1}H-NMR (600 MHz $CDCl_3$, ppm): 7.01 (ddd, J=9.8 Hz, J=2.8 Hz, J=1.3 Hz, 1H), 4.18 (dq, J=7.1 Hz, J=1.1 Hz, 2H), 3.53 (dd, J=9.6 Hz, J=5.2 Hz, 1H), 2.96 (ddd, J=9.0 Hz, J=4.4 Hz, J=2.3 Hz, 1H), 2.19 (t, J=7.6 Hz, 2H), 2.02-1.96 (m, 1H), 1.90-1.71 (m, 6H), 1.63 (td, J=2.1 Hz, J=1.1 Hz, 3H), 1.57-1.51 (m, 1H), 1.45-1.36 (m, 2H), 1.29 (t, J=7.1 Hz, 3H), 0.78 (d, J=7.0 Hz, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$, ppm): 168.8, 143.4, 133.6, 131.0, 126.1, 60.6, 47.5, 37.6, 34.5, 33.2, 28.9, 25.6, 24.7, 14.5, 13.7, 12.5, 12.2; IR (film, cm^{-1}): 2926, 1712, 1645, 1455, 1379, 1238, 1131, 1104, 1061, 753; HRMS (ESI, m/z):

calcd for [M], C17H26O2: 262.1933; found: 262.1935; $[\alpha]_D^{20}$ = -106.1 (c = 0.70 g/100mL, DCM).

Valerenic acid (1): A solution of valerenic ethyl ester **46** (12.4 mg, 0.0473 mmol, 1.0 eq), methanol (0.5 mL) and THF (0.5 mL) was treated with 1.0 molar aqueous LiOH (0.36 mL, 0.36 mmol, 7.5 eq). After stirring 24 hours the resulting mixture was cooled to 0 °C, acidified with 10% citric acid and extracted with ethyl acetate (4x). The combined organic phases were washed with a small amount of brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by chromatography (hexane/ethyl acetate 5/1 to pure ethyl acetate) afforded 11.0 mg of valerenic acid with 99% yield. ^{1}H-NMR (600 MHz $CDCl_3$, ppm): 7.15 (ddd, J=10.0 Hz, J=2.7 Hz, J=1.3 Hz, 1H), 3.54 (dd, J=9.7 Hz, J=5.0 Hz, 1H), 2.95 (ddd, J=8.3 Hz, J=4.0 Hz, J=1.9 Hz, 1H), 2.20 (t, J=7.6 Hz, 2H), 1.99 (dt, J=7.2 Hz, J=3.7 Hz, 1H), 1.93-1.71 (m, 6H), 1.63 (td, J=2.0 Hz, J=1.0 Hz, 3H), 1.59-1.51 (m, 1H), 1.48-1.36 (m, 2H), 0.78 (d, J=7.0 Hz, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$, ppm): 173.0, 146.3, 133.3, 131.4, 125.2, 47.6, 37.6, 34.7, 33.2, 28.9, 25.5, 24.7, 13.6, 12.2, 12.2; IR (film, cm^{-1}): 2931, 1683, 1652, 1558, 1423, 1299, 1256, 904, 671, 575; HRMS (ESI, m/z): calcd for [M], C15H22O2: 234.1620; found: 234.1623; $[\alpha]_D^{20}$ = -159.9 (c = 0.76 g/100mL, DCM), authentic sample: $[\alpha]_D^{20}$ = -161.2 (c = 0.85 g/100mL, DCM); m.p.: 139-141 °C, authentic sample: m.p.: 140-142 °C.

Valerenic amide (47): Valerenic acid (104.3 mg, 0.4451 mmol, 1.0 eq) was dissolved in anhydrous dichloromethane (4.4 mL) cooled to 0°C and 1-Chloro-N,N,2-trimethylpropenylamine (0.21 mL, 212,1 mg, 1.587 mmol, 3.5 eq) was added dropwise. After 5 minutes the ice bath was removed and the reaction mixture stirred for 4 hours at room temperature before recooled to 0°C. 0.5M Ammonia in 1,4-dioxane (5.8 mL, 2.900 mmol, 6.5 eq) was rapidly added, the ice bath removed and the resulting mixture stirred over night. Diethyl ether was added and the white precipitate removed by filtration. The filtrate was concentrated in vacuo and chromatography (hexane/EtOAc 2/1 to 1/2) of the residue provided 99.8 mg of valerenic amide as white solid with 96% yield. ^{1}H-NMR (400MHz, $CDCl_3$, ppm): 6.67 (dq, J=9.3Hz, J=0.8Hz, 1H), 5.58 (s, 2H), 3.50 (dd, J=9.4Hz, J=4.7Hz, 1H), 2.93 (m, 1H), 2.19 (t, J=7.5Hz, 2H), 1.98 (m, 1H), 1.90 (d, J=3.3 Hz, 3H), 1.78 (m, 3H), 1.63 (m, 3H), 1.55 (m, 1H), 1.40 (m, 2H), 0.77 (d, J=7.0Hz, 3H). ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 171.8, 139.1, 133.7, 130.9, 128.3, 47.6, 37.6, 34.3, 33.2, 28.9, 25.7, 24.7, 13.6, 12.9, 12.2. IR (film, cm^{-1}): 3179, 3028, 2923, 2885, 2853, 1733, 1654, 1652, 1636, 1505, 1458, 1418, 1378. HRMS (ESI, m/z): calcd for [M], C15H21N: 215.1674; found: 215.1661. $[\alpha]_D^{20}$ = -119.2 (c = 0.775 g/100mL, DCM)

Valerenic N-methylamide (48): Using the same procedure as for the preparation of Valerenic amide Valerenic acid (49.7 mg, 0.2121 mmol, 1.0 eq) was treated with 1-Chloro-N,N,2-trimethylpropenylamine (98 µL, 99.0 mg, 0.7408 mmol, 3.5 eq) and methylamine (41% aqueous solution, 0.18 mL, 2.131 mmol, 10.0 eq) to afford 49.9 mg of valerenic N-methylamide as white solid with 95% yield. ^{1}H-NMR (400MHz, $CDCl_3$, ppm): 6.54 (dq, J=9.5Hz, J=1.3Hz, 1H), 5.71 (s, 1H), 3.48 (dd, J=9.2Hz, J=4.7Hz, 1H), 2.93 (m, 1H), 2.86 (d, J=4.9Hz, 3H), 2.19 (t, J=7.3Hz, 2H), 1.97 (m, 1H), 1.89 (d, J=1.4 Hz, 3H), 1.78 (m, 3H), 1.62 (m, 3H), 1.55 (m, 1H), 1.39 (m, 2H), 0.77 (d, J=7.0Hz, 3H). ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 170.7, 137.0, 134.0, 130.7, 129.5, 47.6, 37.6, 34.1, 33.3, 28.9, 26.7, 25.8, 24.7, 13.6, 12.9, 12.2. IR (film, cm^{-1}): 3326, 2925, 1655, 1616, 1539, 1456, 1379, 1311, 670, 667, 409. HRMS (ESI, m/z): calcd for [M], C16H25NO: 247.1936; found: 247.1932. $[\alpha]_D^{20}$ = -129.3 (c = 0.825 g/100mL, DCM)

Valerenic N-ethylamide (49): Using the same procedure as for the preparation of Valerenic amide Valerenic acid (20.9 mg, 0.0892 mmol, 1.0 eq) was treated with 1-Chloro-N,N,2-trimethylpropenylamine (35 µL, 35.4 mg, 0.2646 mmol, 3.0 eq) and 2.0M ethylamine in THF (0.45 mL, 0.9000 mmol, 10.0 eq) to afford 21.9 mg of valerenic N-ethylamide as slightly yellow solid with 94% yield. ^{1}H-NMR (400MHz, $CDCl_3$, ppm): 6.55 (dq, J=9.5Hz, J=1.3Hz, 1H), 5.66 (s, 1H), 3.49 (dd, J=9.3Hz, J=4.9Hz, 1H), 3.34 (dq, J=7.2Hz, J=5.6Hz, 2H), 2.95 (m, 1H), 2.19 (t, J=7.5Hz, 2H), 1.98 (m, 1H), 1.89 (d, J=1.4 Hz, 3H), 1.78 (m, 3H), 1.62 (m, 3H), 1.54 (m, 1H), 1.40 (m, 2H), 1.17 (t, J=7.3Hz, 3H), 0.78 (d, J=7.0Hz, 3H). ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 169.9, 136.9, 134.0, 130.6, 129.6, 47.6, 37.6, 34.8, 34.1, 33.3, 28.9, 25.8, 24.7, 15.1, 13.6, 12.9, 12.2. IR (film, cm^{-1}): 3308, 2925, 2884, 2855, 1653, 1639, 1616, 1533, 1456, 1379, 1309. HRMS (ESI, m/z): calcd for $[M]^+$, $C17H28NO^+$: 262.2165; found: 262.2161. $[\alpha]_D^{20}$ = -118.7 (c = 1.58 g/100mL, DCM).

Valerenic N,N-diethylamide (50): Using the same procedure as for the preparation of Valerenic amide Valerenic acid (30.2 mg, 0.1289 mmol, 1.0 eq) was treated with 1-Chloro-N,N,2-trimethylpropenylamine (51 µL, 51.5 mg, 0.3855 mmol, 3.0 eq) and diethylamine (135 µL, 95.9 mg, 1.311 mmol, 10.0 eq) to afford 35.2 mg of Valerenic N,N-diethylamide as slightly yellow oil with 94% yield. ^{1}H-NMR (400MHz, $CDCl_3$, ppm): 5.75 (dq, J=7.6Hz, J=0.5Hz, 1H), 3.46 (dd, J=8.5Hz, J=3.9Hz, 1H), 3.34 (m, 4H), 2.85 (m, 1H), 2.17 (t, J=7.4Hz, 2H), 1.96 (m, 1H), 1.87 (d, J=1.5 Hz, 3H), 1.77 (m, 3H), 1.63 (m, 3H), 1.52 (m, 1H), 1.41 (m, 2H), 1.13 (t, J=7.1Hz, 6H), 0.77 (d, J=7.0Hz, 3H). ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 173.8, 134.3, 131.0, 130.3, 130.1, 47.7, 37.6, 33.5, 33.3, 29.0, 25.8, 24.8, 14.6, 13.6, 12.2. IR (film, cm^{-1}): 2926, 2866, 2855, 1628, 1458, 1396, 1380, 1333, 1291, 1221, 1097. HRMS (ESI, m/z): calcd for $[M]^+$, $C19H32NO^+$: 290,2478; found: 290,2488. $[\alpha]_D^{20}$ = -109.8 (c = 1.63 g/100mL, DCM).

Valerenic piperidine amide (51): A solution of Valerenic acid (43.5 mg, 0.1856 mmol, 1.0 eq) and anhydrous dichloromethane (1.8 mL) was cooled to 0°C and 1-Chloro-N,N,2-trimethylpropenylamine (86 µL, 86.9 mg, 0.6500 mmol, 3.5 eq) was added dropwise. After 5 minutes the ice bath was removed and the reaction mixture stirred for 4 hours at room temperature. Then the solvent and volatile byproducts were removed in vacuo (3 Torr for 1 hour) and the crude acid chloride was redissolved in dichloromethane (1.8 mL). After cooling to 0°C piperidine (74 µL, 63.6 mg, 0.7474 mmol, 4.0 eq) was added at once, the ice bath removed and the resulting mixture stirred for 1 hour. Diethyl ether was added and the white precipitate removed by filtration. The filtrate was concentrated in vacuo and chromatography (hexane/EtOAc 5/1 to 2/1) of the residue provided 50.7 mg of Valerenic piperidine amide as slightly yellow oil with 91% yield. ^{1}H-NMR (400MHz, $CDCl_3$, ppm): 5.78 (dq, J=9.1Hz, J=1.5Hz, 1H), 3.45 (m, 5H), 2.84 (m, 1H), 2.18 (t, J=4.9Hz, 2H), 1.96 (m, 1H), 1.85 (d, J=1.5 Hz, 3H), 1.77 (m, 3H), 1.63 (m, 5H), 1.54 (m, 5H), 1.40 (m, 2H), 0.77 (d, J=7.0Hz, 3H). ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 172.8, 134.3, 131.9, 130.0, 129.8, 47.7, 37.6, 33.5, 33.4, 29.0, 25.9, 24.9, 24.8, 14.5, 13.6, 12.2. IR (film, cm^{-1}): 2925, 2854, 1629, 1443, 1379, 1256, 425, 423, 420, 412. HRMS (ESI, m/z): calcd for [M], C20H31NO: 301.2406; found: 301.2398. $[\alpha]_D^{20}$ = -90.0 (c = 0.35 g/100mL, DCM).

Valerenic morpholine amide (52): Using the same procedure as for the preparation of Valerenic amide Valerenic acid (43.4 mg, 0.1852 mmol, 1.0 eq) was treated with 1-Chloro-N,N,2-trimethylpropenylamine (74 µL, 74.7 mg, 0.5593 mmol, 3.0 eq) and morpholine (160 µL, 160.0 mg, 1.837 mmol, 10.0 eq) to afford 50.4 mg of Valerenic morpholine amide as colorless oil with 90% yield. ^{1}H-NMR (400MHz, $CDCl_3$, ppm): 5.82 (dq, J=9.1Hz, J=1.5Hz, 1H), 3.66 (t, J=4.5Hz, 4H), 3.56 (m, 4H), 3.47 (dd, J=9.0Hz, J=2.8Hz, 1H), 2.82 (m, 1H), 2.18 (t, J=7.4Hz, 2H), 1.97 (m, 1H), 1.87 (d, J=1.5 Hz, 3H), 1.78 (m, 3H), 1.64 (m, 3H), 1.55 (m, 1H), 1.41 (m, 2H), 0.77 (d, J=7.0Hz, 3H). ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 172.9, 134.0, 133.6, 130.4, 128.9, 67.1, 47.8, 37.6, 33.6, 33.4, 29.0, 25.9, 24.8, 14.5, 13.6, 12.2. IR (film, cm^{-1}): 2923, 1654, 1652, 1628, 1420, 1393, 1379, 1245, 1116, 1028, 842. HRMS (ESI, m/z): calcd for [M], C19H29NO2: 303.2198; found: 303.2194. $[\alpha]_D^{20}$ = -110.5 (c = 0.8 g/100mL, DCM).

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H NMR and ^{13}NMR spectra of all compounds.

Acknowledgments

We thank S. Felsinger, L. Brecker and H. P. Kählig, all at the University of Vienna, Institute of Organic Chemistry, for NMR analysis, as well as S. Khom, B. Strommer and S. Hering, all at the University of Vienna, department of Pharmacology and Toxicology, for fruitful discussions and the Austrian Science Fund (FWF) for financial support (projects P21241-N19 and TRP 107-B11).

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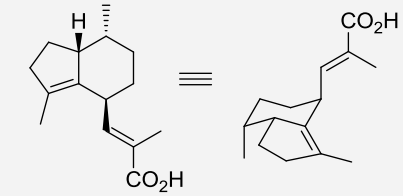
Entry for the Table of Contents

Layout 1:

((Key Topic))

Development and optimization of four different approaches towards valerenic acid (**1**) are described. Incorporating a novel one-pot reaction, a extremely stereo- and regioselective metal-coordinated DA reaction as well as a hydroxy-directed hydrogenation and a final Negishi coupling the shortest approach spans 10 steps and provides Valerenic Acid with 25% overall yield.



Valerenic Acid (**1**)

Jürgen Ramharter, Johann Mulzer*

…….. Page No. – Page No.

From Planning to Optimization: Total Synthesis of Valerenic Acid and some Bioactive Derivatives

Keywords: natural product synthesis / one-pot reaction / hydroxy-directed Diels-Alder / hydroxy-directed hydrogenation / Negishi coupling

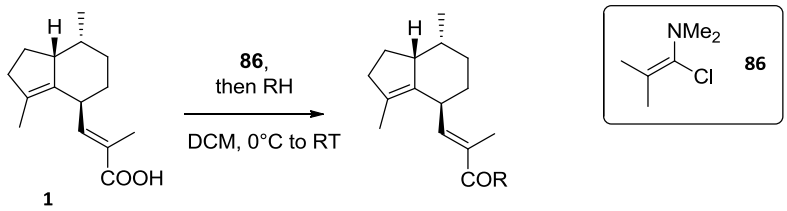
2.7 Derivatization of Valerenic Acid

2.7.1 Introduction

As potent modulator of the $GABA_A$ receptor subtype (see also chapter 2.3.2) valerenic acid has also attracted the interest of several pharmacological research groups.[1,2,3] In cooperation with the department of pharmacology and toxicology of the University of Vienna several derivatives of valerenic acid were tested.[6]

Immediately after completion of the synthesis of valerenic acid, several simple substrates based on derivatization of the carboxyl group were synthesized (see Table 1).

Table 1: Preparation of simple derivatives from valerenic acid.



RH	yield [%]	substance
NH_3	96	**87**
NH_2Me	95	**88**
NH_2Et	94	**89**
NH_2iPr [a]	78	**90**
NH_2nBu [a]	70	**91**
$NHMe_2$ [a]	85	**92**
$NHEt_2$	94	**93**
piperidine	91	**94**
morpholine	90	**95**
$H_2N\text{-}NH_2$	87	**96**
EtOH	91	**97**

[a] Key: Synthesized by T. Schwarz according to the procedure devised during this PhD thesis.

Interestingly, activation of the carboxylic acid with chloroformate or other coupling reagents failed or gave only moderate yields, so Ghosez' reagent (**86**) was used instead.[25] After preparation of valerenic acid chloride under mild conditions, various nucleophiles were added. Fortunately, in most cases

isolation of the acid chloride was not necessary, but the *in situ* formed intermediate was simply treated with an excess of the corresponding nucleophile to deliver the desired derivatives in excellent yield.

A summary and detailed discussion about the results of *in vitro* and *in vivo* SAR studies can be found in the following publication.

2.7.2 Valerenic Acid Derivatives as Novel Subunit-Selective GABAA Receptor Ligands

Khom, S.; Strommer B.; Ramharter J.; Schwarz T.; Schwarzer C.; Erker T.; Ecker G. F.; Mulzer, J.; Hering S. *British J. Pharm.* **2010**, 161, 65

Comment of the author: Please note, that both *in vitro* and *in vivo* tests were carried out by Sophia Khom and Barbara Strommer, who are also the principle authors of this manuscript, under the supervision of Prof. Steffen Hering in the Department of Pharmacology and Toxicology, University of Vienna.

BJP BRITISH JOURNAL OF PHARMACOLOGY

BPS BRITISH PHARMACOLOGICAL SOCIETY

BJP British Journal of Pharmacology

DOI:10.1111/j.1476-5381.2010.00865.x
www.brjpharmacol.org

RESEARCH PAPER

Valerenic acid derivatives as novel subunit-selective $GABA_A$ receptor ligands – *in vitro* and *in vivo* characterization

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*Both authors contributed equally to the paper.

Keywords
$GABA_A$ receptors; valerenic acid derivatives; 2-microelectrode voltage-clamp technique; behavioural pharmacology; structure–activity relationship

Received
23 December 2009
Revised
26 March 2010
Accepted
29 March 2010

BACKGROUND AND PURPOSE

Subunit-specific modulators of γ-aminobutyric acid (GABA) type A ($GABA_A$) receptors can help to assess the physiological function of receptors with different subunit composition and also provide the basis for the development of new drugs. Valerenic acid (VA) was recently identified as a $\beta_{2/3}$ subunit-specific modulator of $GABA_A$ receptors with anxiolytic potential. The aim of the present study was to generate VA derivatives as novel $GABA_A$ receptor modulators and to gain insight into the structure–activity relation of this molecule.

EXPERIMENTAL APPROACH

The carboxyl group of VA was substituted by an uncharged amide or amides with different chain length. Modulation of $GABA_A$ receptors composed of different subunit compositions by the VA derivatives was studied in *Xenopus* oocytes by means of the two-microelectrode voltage-clamp technique. Half-maximal stimulation of GABA-induced chloride currents (I_{GABA}) through $GABA_A$ receptors (EC_{50}) and efficacies (maximal stimulation of I_{GABA}) were estimated. Anxiolytic activity of the VA derivatives was studied in mice, applying the elevated plus maze test.

KEY RESULTS

Valerenic acid amide (VA-A) displayed the highest efficacy (more than twofold greater I_{GABA} enhancement than VA) and highest potency (EC_{50} = 13.7 ± 2.3 μM) on $\alpha_1\beta_3$ receptors. Higher efficacy and potency of VA-A were also observed on $\alpha_1\beta_2\gamma_{2s}$ and $\alpha_3\beta_3\gamma_{2s}$ receptors. Anxiolytic effects were most pronounced for VA-A.

CONCLUSIONS AND IMPLICATIONS

Valerenic acid derivatives with higher efficacy and affinity can be generated. Greater *in vitro* action of the amide derivative correlated with a more pronounced anxiolytic effect *in vivo*. The data give further confidence in targeting β_3 subunit containing $GABA_A$ receptors for development of anxiolytics.

Abbreviations

I_{GABA}, GABA-induced chloride currents; VA, valerenic acid; VA-A, valerenic acid amide; VA-BA, valerenic acid butylamide; VA-DEA, valerenic acid diethylamide; VA-DMA, valerenic acid dimethylamide; VA-EA, valerenic acid ethylamide; VA-EE, valerenic acid ethyl ester; VA-IPA, valerenic acid isopropylamide; VA-MA, valerenic acid methylamide; VA-MO, valerenic acid morpholine amide; VA-PIP, valerenic acid piperidine amide

Introduction

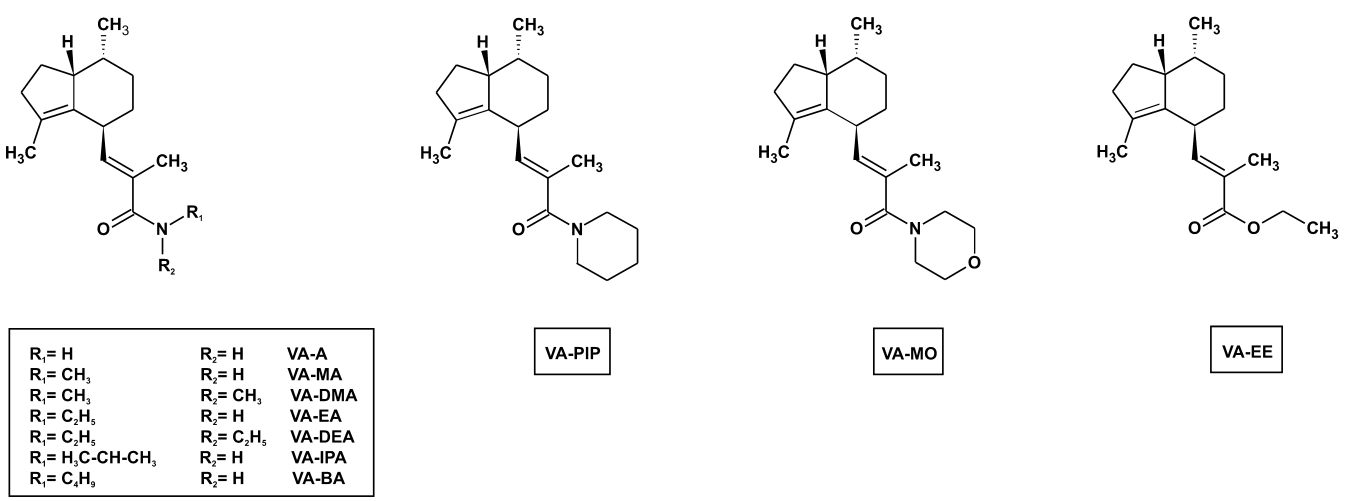
γ-Aminobutyric acid (GABA) mediates fast synaptic, inhibitory neurotransmission in the mammalian brain acting on GABA type A ($GABA_A$) receptors. $GABA_A$ receptors represent ligand gated chloride channels, assembled from different subunits forming a pentameric structure. Nineteen subunits of mammalian $GABA_A$ receptors have been cloned: α_{1-6}, β_{1-3}, γ_{1-3}, δ, ε, π, ρ_{1-3} and θ (Barnard *et al.*, 1998; Simon *et al.*, 2004; Olsen and Sieghart, 2008; receptor nomenclature follows Alexander *et al.*, 2009). The distribution of these subunits in the brain is highly distinct, suggesting differential functional roles for different $GABA_A$ receptors. The subunit composition determines the GABA sensitivity and the pharmacological properties of the $GABA_A$ receptor (Sieghart, 1995; D'Hulst *et al.*, 2009; Olsen and Sieghart, 2009).

γ-Aminobutyric acid type A receptors play a major role in controlling the excitability of the CNS. A disturbance of the balance between excitatory and inhibitory neurotransmission is associated with neurological disorders such as insomnia, anxiety disorders, epilepsy and schizophrenia (Sieghart and Sperk, 2002, Möhler, 2006a). Consequently, $GABA_A$ receptors represent the molecular target of many clinically important drugs such as benzodiazepines, barbiturates, general anaesthetics or the anticonvulsant loreclezole (see Sieghart 2006, Möhler, 2006b; Olsen and Sieghart, 2008). $GABA_A$ receptors are also modulated by natural compounds of plant origin (see Johnston *et al.*, 2006).

We have recently identified valerenic acid (VA), a major constituent of *Valeriana officinalis* L., as a subunit-specific modulator of $GABA_A$ receptors interacting exclusively with $GABA_A$ receptors comprising $\beta_{2/3}$ subunits, with no significant effect on GABA-induced chloride currents (I_{GABA}) through $GABA_A$ receptors containing β_1 subunits (Khom *et al.*, 2007). Moreover, enhancement of inhibitory, GABAergic neurotransmission by VA reduces anxiety-related behaviour *in vivo* (Benke *et al.*, 2009). Based on this subtype selectivity *in vitro* and anxiolytic effects *in vivo*, VA and its derivatives represent interesting drug candidates. In order to gain insight into the structure–activity relationship of these derivatives, we have synthesized 10 VA derivatives (Figure 1) and analysed their *in vitro* and *in vivo* effects. VA was converted into various amides with different lipophilicity and bulkiness. VA ethyl ester (VA-EE) emerged from the total synthesis described by Ramharter and Mulzer (2009).

The modulation of I_{GABA} by these VA derivatives through $GABA_A$ receptors expressed in *Xenopus* oocytes was analysed by means of the two-microelectrode voltage-clamp technique and a fast perfusion system. The behavioural effects of selected compounds were studied in the elevated plus maze test that allowed the identification of anxiolytic and sedative effects.

In vitro, short-chain VA amides such as VA amide (VA-A); VA methylamide (VA-MA) and VA ethylamide (VA-EA) revealed a stronger potentiation of I_{GABA} compared with VA itself, whereas side chain prolongation resulted in derivatives exhibiting a



R_1= H	R_2= H	VA-A
R_1= CH_3	R_2= H	VA-MA
R_1= CH_3	R_2= CH_3	VA-DMA
R_1= C_2H_5	R_2= H	VA-EA
R_1= C_2H_5	R_2= C_2H_5	VA-DEA
R_1= H_3C-CH-CH_3	R_2= H	VA-IPA
R_1= C_4H_9	R_2= H	VA-BA

Figure 1

Chemical structures of VA derivatives. VA-A, valerenic acid amide; VA-MA, valerenic acid methlyamide; VA-DMA, valerenic acid dimethylamide; VA-EA, valerenic acid ethylamide; VA-DEA, valerenic acid diethylamide; VA-IPA, valerenic acid isopropylamide; VA-BA, valerenic acid butylamide; VA-PIP, valerenic acid piperidine amide; VA-MO, valerenic acid morpholine amide; VA-EE, valerenic acid ethylate.

comparable or weaker enhancement of I_{GABA}. VA-A was more potent than VA *in vitro* and displayed the greatest anxiolytic effect *in vivo*.

Methods

Synthesis of VA derivatives

All reactions were carried out in oven-dried glassware under an argon atmosphere. Anhydrous CH_2Cl_2 was distilled under argon from P_2O_5. Commercially available reagents (purchased from Sigma, Vienna, Austria or Acros Organics, Vienna, Austria) were used without further purification. Reaction mixtures were magnetically stirred and monitored by thin layer chromatography with silica gel 60 F_{254} plates (E. Merck, Darmstadt, Germany). Flash column chromatography was performed with Merck silica gel (0.04–0.063 mm, 240–400 mesh) under pressure. Yields refer to chromatographically and spectroscopically pure compounds. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were either recorded on Bruker Avance 400, or DRX 400 spectrometers. All NMR spectra were measured in $CDCl_3$ solutions. The chemical shifts δ are reported relative to the residual solvent peaks. All ^{1}H and ^{13}C shifts are given in ppm (s = singlet; d = doublet; t = triplet; q = quadruplet; m = multiplet). If possible, assignments of proton resonances were confirmed by correlated spectroscopy. Optical rotations were measured at 20°C on a P 341 Perkin-Elmer polarimeter. IR spectra were recorded of samples prepared as films on silicium plates on a Perkin-Elmer Spectrum 1600 Series FTIR spectrometer. MS spectra were measured on a Finnigan MAT 8230 apparatus with a resolution of 10 000.

VA-A

Valerenic acid (104.3 mg, 0.4451 mM) was dissolved in anhydrous CH_2Cl_2 (4.4 mL) cooled to 0°C and 1-chloro-N,N,2-trimethylpropenylamine (0.21 mL, 212.1 mg, 1.587 mM) was added dropwise. After 5 min the icebath was removed and the reaction mixture stirred for 4 h at room temperature before being re-cooled to 0°C. Ammonia (0.5 M) in 1,4-dioxane (5.8 mL, 2.900 mM) was rapidly added, the icebath removed and the resulting mixture stirred overnight. Diethylether was added and the white precipitate removed by filtration. The filtrate was concentrated *in vacuo* and chromatography (hexane/EtOAc 2/1 to 1/2) of the residue provided 99.8 mg of VA-A as a white solid with 96% yield.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 6.67 (dq, 1 H, J = 0.8 Hz, J = 9.3 Hz), 5.58 (s, 2 H), 3.50 (dd, 1 H, J = 4.7 Hz, J = 9.4 Hz), 2.93 (m, 1 H), 2.19 (t, 2 H, J = 7.5 Hz), 1.98 (m, 1 H), 1.90 (d, 3 H, J = 3.3 Hz), 1.78 (m, 3 H), 1.63 (m, 3 H), 1.55 (m, 1 H), 1.40 (m, 2 H), 0.77 (d, 3 H, J = 7.0 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): 171.8, 139.1, 133.7, 130.9, 128.3, 47.6, 37.6, 34.3, 33.2, 28.9, 25.7, 24.7, 13.6, 12.9, 12.2

IR (film, cm^{-1}): 3179, 3028, 2923, 2885, 2853, 1733, 1654, 1652, 1636, 1505, 1458, 1418, 1378

HRMS (ESI, m/z): $[M]^+$ calc. 215.1674; found: 215.1661

$[\alpha]_D^{20}$ = –119.2 (c = 0.775 g per 100 mL, DCM)

VA-MA

Using the same procedure as for the preparation of VA-A, VA (49.7 mg, 0.2121 mM) was treated with 1-chloro-N,N,2-trimethylpropenylamine (0.098 mL, 99.0 mg, 0.7408 mM) and methylamine (41% aqueous solution, 0.18 mL, 2.131 mM) to afford 49.9 mg of VA-MA as a white solid with 95% yield.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 6.54 (dq, 1 H, J = 1.3 Hz, J = 9.5 Hz), 5.71 (s, 1 H), 3.48 (dd, 1 H, J = 4.7 Hz, J = 9.2 Hz), 2.93 (m, 1 H), 2.86 (d, 3 H, J = 4.9 Hz), 2.19 (t, 2 H, J = 7.3 Hz), 1.97 (m, 1 H), 1.89 (d, 3 H, J = 1.4 Hz), 1.78 (m, 3 H), 1.62 (m, 3 H), 1.55 (m, 1 H), 1.39 (m, 2 H), 0.77 (d, 3 H, J = 7.0 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): 170.7, 137.0, 134.0, 130.7, 129.5, 47.6, 37.6, 34.1, 33.3, 28.9, 26.7, 25.8, 24.7, 13.6, 12.9, 12.2

IR (film, cm^{-1}): 3326, 2925, 1655, 1616, 1539, 1456, 1379, 1311, 670, 667, 409

HRMS (ESI, m/z): $[M]^+$ calc. 247.1936; found: 247.1932

$[\alpha]_D^{20}$ = –129.3 (c = 0.825 g per 100 mL, DCM)

VA-EA

Using the same procedure as for the preparation of VA-A, VA (20.9 mg, 0.0892 mM) was treated with 1-chloro-N,N,2-trimethylpropenylamine (0.035 mL, 35.4 mg, 0.2646 mM) and 2.0 M ethylamine in THF (0.45 mL, 0.9000 mM) to afford 21.9 mg of VA EA as a slightly yellow solid with 94% yield.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 6.55 (dq, 1 H, J = 1.3 Hz, J = 9.5 Hz), 5.66 (s, 1 H), 3.49 (dd, 1 H, J = 4.9 Hz, J = 9.3 Hz), 3.34 (dq, 2 H, J = 5.6 Hz, J = 7.2 Hz), 2.95 (m, 1 H), 2.19 (t, 2 H, J = 7.5 Hz), 1.98 (m, 1 H), 1.89 (d, 3 H, J = 1.4 Hz), 1.78 (m, 3 H), 1.62 (m, 3 H), 1.54 (m, 1 H), 1.40 (m, 2 H), 1.17 (t, 3 H, J = 7.3 Hz), 0.78 (d, 3 H, J = 7.0 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): 169.9, 136.9, 134.0, 130.6, 129.6, 47.6, 37.6, 34.8, 34.1, 33.3, 28.9, 25.8, 24.7, 15.1, 13.6, 12.9, 12.2

IR (film, cm^{-1}): 3308, 2925, 2884, 2855, 1653, 1639, 1616, 1533, 1456, 1379, 1309

HRMS (ESI, m/z): $[M]^+$ calc. 262.2171; found: 262.2161

$[\alpha]_D^{20}$ = –118.7 (c = 1.58 g per 100 mL, DCM)

Valerenic N,N-diethylamide (VA-DEA)

Using the same procedure as for the preparation of VA-A, VA (30.2 mg, 0.1289 mM) was treated with 1-chloro-N,N,2-trimethylpropenylamine (0.051 mL, 51.5 mg, 0.3855 mM) and diethylamine (0.135 mL, 95.9 mg, 1.311 mM) to afford 35.2 mg of VA-DEA as a slightly yellow oil with 94% yield.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 5.75 (dq, 1 H, J = 0.5 Hz, J = 7.6 Hz), 3.46 (dd, 1 H, J = 3.9 Hz, J = 8.5 Hz), 3.34 (m, 4 H), 2.85 (m, 1 H), 2.17 (t, 2 H, J = 7.4 Hz), 1.96 (m, 1 H), 1.87 (d, 3 H, J = 1.5 Hz), 1.77 (m, 3 H), 1.63 (m, 3 H), 1.52 (m, 1 H), 1.41 (m, 2 H), 1.13 (t, 6 H, J = 7.1 Hz), 0.77 (d, 3 H, J = 7.0 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): 173.8, 134.3, 131.0, 130.3, 130.1, 47.7, 37.6, 33.5, 33.3, 29.0, 25.8, 24.8, 14.6, 13.6, 12.2

IR (film, cm^{-1}): 2926, 2866, 2855, 1628, 1458, 1396, 1380, 1333, 1291, 1221,1097

HRMS (ESI, m/z): $[M]^+$ calc. 290,2484; found: 290,2488

$[\alpha]_D^{20}$ = –109.8 (c = 1.63 g per 100 mL, DCM)

Valerenic acid morpholine amide (VA-MO)

Using the same procedure as for the preparation of VA-A, VA (43.4 mg, 0.1852 mM) was treated with 1-chloro-N,N,2-trimethylpropenylamine (0.074 mL, 74.7 mg, 0.5593 mM) and morpholine (0.160 mL, 160.0 mg, 1.837 mM) to afford 50.4 mg of VA-MO as a colourless oil with 90% yield.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 5.82 (dq, 1 H, J = 1.5 Hz, J = 9.1 Hz), 3.66 (t, 4 H, J = 4.5), 3.56 (m, 4 H), 3.47 (dd, 1 H, J = 2.8 Hz, J = 9.0 Hz), 2.82 (m, 1 H), 2.18 (t, 2 H, J = 7.4 Hz), 1.97 (m, 1 H), 1.87 (d, 3 H, J = 1.5 Hz), 1.78 (m, 3 H), 1.64 (m, 3 H), 1.55 (m, 1 H), 1.41 (m, 2 H), 0.77 (d, 3 H, J = 7.0 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): 172.9, 134.0, 133.6, 130.4, 128.9, 67.1, 47.8, 37.6, 33.6, 33.4, 29.0, 25.9, 24.8, 14.5, 13.6, 12.2

IR (film, cm^{-1}): 2923, 1654, 1652, 1628, 1420, 1393, 1379, 1245, 1116, 1028, 842

HRMS (ESI, m/z): $[M]^+$ calc. 303.2198; found: 303.2194

$[\alpha]_D^{20}$ = –110.5 (c = 0.8 g per 100 mL, DCM)

Valerenic N,N-dimethylamide (VA-DMA)

A solution of VA (117 mg, 0.5 mM) in anhydrous CH_2Cl_2 (5 mL) was cooled to 0°C and 1-chloro-N,N,2-trimethylpropenylamine (0.67 mL, 2 mM) was added dropwise. After 5 min the icebath was removed and the reaction mixture stirred for 4 h at room temperature. Then the solvent and volatile by-products were removed *in vacuo* (3 Torr for 1 h), and the crude acid chloride was redissolved in CH_2Cl_2 (5 mL). After cooling to 0°C, dimethylamine (0.51 mL, 5 mM) was added at once, the icebath removed and the resulting mixture stirred for 1 h. Diethylether was added and the white precipitate removed by filtration. The filtrate was concentrated *in vacuo* and chromatography (toluol/EtOAc 3/2) of the residue provided 111 mg of VA-DMA as a slightly yellow oil with 85% yield.

^{1}H-NMR (200 MHz, CDCl3, ppm): 5.83 (dd, 1 H, J = 1.5 Hz, J = 9.1 Hz), 3.48 (m, 1 H), 2.98 (s, 6 H), 2.86 (m, 1 H), 2.20 (t, 2 H, J = 7.2 Hz), 1.87 (m, 7 H), 1.49 (m, 5 H), 0.77 (dd, 3 H, J = 6.9 Hz)

^{13}C-NMR (50 MHz, CDCl3, ppm): 174.0, 134.0, 132.8, 129.9, 129.5, 47.5, 37.4, 33.3, 33.2, 28.8, 25.7, 24.6, 14.1, 13.4, 12.0

IR (film, cm^{-1}): 2926, 1627, 1496, 1448, 1390, 1091

HRMS (ESI, m/z): $[M]^+$ calc. 262.2171 found: 262.2189

$[\alpha]_D^{20}$ = –104.3 (c = 0.54 g per 100 mL, DCM)

Valerenic acid piperidine amide (VA-PIP)

A solution of VA (43.5 mg, 0.1856 mM) in anhydrous CH_2Cl_2 (1.8 mL) was cooled to 0°C and 1-chloro-N,N,2-trimethylpropenylamine (0.086 mL, 86.9 mg, 0.6500 mM) was added dropwise. After 5 min the icebath was removed and the reaction mixture stirred for 4 h at room temperature. Then the solvent and volatile by-products were removed *in vacuo* (3 Torr for 1 h), and the crude acid chloride was redissolved in CH_2Cl_2 (1.8 mL). After cooling to 0°C, piperidine (0.074 mL, 63.6 mg, 0.7474 mM) was added at once, the icebath removed and the resulting mixture stirred for 1 h. Diethylether was added and the white precipitate removed by filtration. The filtrate was concentrated *in vacuo* and chromatography (hexane/EtOAc 5/1 to 2/1) of the residue provided 50.7 mg of VA-PIP as a slightly yellow oil with 91% yield.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 5.78 (dq, 1 H, J = 1.5 Hz, J = 9.1 Hz), 3.45 (m, 5 H), 2.84 (m, 1 H), 2.18 (t, 2 H, J = 4.9 Hz), 1.96 (m, 1 H), 1.85 (d, 3 H, J = 1.5 Hz), 1.77 (m, 3 H), 1.63 (m, 5 H), 1.54 (m, 5 H), 1.40 (m, 2 H), 0.77 (d, 3 H, J = 7.0 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): 172.8, 134.3, 131.9, 130.0, 129.8, 47.7, 37.6, 33.5, 33.4, 29.0, 25.9, 24.9, 24.8, 14.5, 13.6, 12.2

IR (film, cm^{-1}): 2925, 2854, 1629, 1443, 1379, 1256, 425, 423, 420,412

HRMS (ESI, m/z): $[M]^+$ calc. 301.2406; found: 301.2398

$[\alpha]_D^{20}$ = –90.0 (c = 0.35 g per 100 mL, DCM)

Valerenic N-isopropylamide (VA-IPA)

A solution of VA (117 mg, 0.5 mM) in anhydrous CH_2Cl_2 (5 mL) was cooled to 0°C, and 1-chloro-N,N,2-trimethylpropenylamine (0.2 mL, 0.6 mM) was added dropwise. After 5 min the icebath was removed and the reaction mixture stirred for 4 h at room temperature. Then the solvent and volatile by-products were removed *in vacuo* (3 Torr for 1 h) and the crude acid chloride was redissolved in CH_2Cl_2 (5 mL). After cooling to 0°C n-isopropylamine (0.43 mL, 5 mM) was added at once, the icebath removed and the resulting mixture stirred for 1 h. Diethylether was added and the white precipitate removed by filtration. The filtrate was concentrated *in vacuo* and chromatography (toluole/EtOAc 3/2) of the residue provided 108 mg of VA-IPA as slightly yellow crystals with 78% yield.

^{1}H-NMR (200 MHz, CDCl3, ppm): 6.55 (dd, 1 H, J = 1.3 Hz, J = 9.5 Hz), 5.53 (m, 1 H), 4.12 (m, 1 H), 3.49 (m, 1 H), 2.95 (m, 1 H), 2.20 (t, 2 H, J = 7.4), 1.75 (m, 11 H), 1.39 (m, 2 H), 1.18 (d, 6 H, J = 6.6 Hz), 0.77 (d, 3 H, J = 6.9 Hz)

^{13}C-NMR (50 MHz, CDCl3, ppm): 168.9, 136.6, 133.8, 130.4, 129.4, 47.4, 41.4, 37.4, 33.9, 33.1, 28.7, 25.6, 24.5, 22.8, 13.4, 12.7, 12.0

IR (film, cm^{-1}): 3306, 2930, 1652, 1611, 1533, 1456

HRMS (ESI, m/z): [M]+ calc. 276.2327; found: 276.2332

$[\alpha]_D^{20}$ = –126.6 (c = 0.50 g per 100 mL, DCM)

Valerenic N-butylamide (VA-BA)

A solution of VA (117 mg, 0.5 mM) in anhydrous CH_2Cl_2 (5 mL) was cooled to 0°C and 1-chloro-N,N,2-trimethylpropenylamine (0.2 mL, 0.6 mM) was added dropwise. After 5 min the icebath was removed and the reaction mixture stirred for 4 h at room temperature. Then the solvent and volatile by-products were removed *in vacuo* (3 Torr for 1 h), and the crude acid chloride was redissolved in CH_2Cl_2 (5 mL). After cooling to 0°C, n-butylamine (0.28 mL, 5 mM) was added at once, the icebath removed and the resulting mixture stirred for 1 h. Diethylether was added and the white precipitate removed by filtration. The filtrate was concentrated *in vacuo* and chromatography (toluole/EtOAc 3/2) of the residue provided 102 mg of VA-BA as slightly yellow crystals with 70% yield.

^{1}H-NMR (200 MHz, CDCl3, ppm): 6.55 (dd, 1 H, J = 1.3 Hz, J = 9.3 Hz), 5.72 (s, 1 H), 3.48 (m, 1 H), 3.29 (q, 2 H, J = 6.82), 2.93 (m, 1 H), 1.86 (t, 2 H, J = 7.3), 1.86 (m, 7 H), 1.49 (m, 10 H), 0.93 (t, 3 H, J = 7.2), 0.77 (d, 3 H, J = 6.9)

^{13}C-NMR (50 MHz, CDCl3, ppm): 169.7, 136.7, 133.8, 130.4, 129.3, 47.4, 39.5, 37.4, 33.9, 33.1, 31.8, 28.7, 25.6, 24.5, 20.1, 13.8, 13.4, 12.8, 12.0

IR (film, cm^{-1}): 3306, 2929, 1652, 1616, 1538, 1380

HRMS (ESI, m/z): $[M]^+$ calc. 290.2484; found: 290.2488

$[\alpha]_D^{20}$ = –121.5 (c = 0.47 g per 100 mL, DCM)

Molecular modelling studies

Molecules used for the Free-Wilson analysis were built in MOE (version 2009.10) and energy minimized using standard conditions (MMFF94x force field, adjust H and LP, gradient = 0.01, calculate force field partial charges). A database was built and logP(o/w), TPSA and mr were calculated as descriptors. Correlation analyses were performed with the correlation plot tool implemented in MOE.

Pharmacological characterization of VA derivatives

For *in vitro* and *in vivo* experiments, stock solutions (100 mM) were prepared in dimethyl sulphoxide (DMSO; Sigma, Vienna, Austria). In voltage-clamp experiments equal amounts of DMSO were present in control and compound-containing solutions. The maximum DMSO concentration in the bath (0.3%) did not affect I_{GABA} (Khom *et al.*, 2007). For *in vivo* experiments, working concentrations were adjusted by dilution with 0.9% sodium chloride. pH was adjusted to 7.2–7.4 with NaOH. All solutions were freshly prepared every day prior to experiments.

Expression and functional characterization of $GABA_A$ receptors

Preparation of stage V–VI oocytes from *Xenopus laevis*, synthesis of capped off run-off poly(A^+) cRNA transcripts from linearized cDNA templates (pCMV vector) was performed as described (Khom *et al.*, 2006). Briefly, female *X. laevis* (NASCO, USA) were anaesthetized by exposing them for 15 min to a 0.2% solution of MS-222 (methane sulphonate salt of 3-aminobenzoic acid ethyl ester; Sigma) before surgically removing parts of the ovaries. Follicle membranes from isolated oocytes were enzymatically digested with 2 $mg \cdot mL^{-1}$ collagenase (Type 1A, Sigma). One day after isolation, the oocytes were injected with about 10–50 nL of DEPC-treated water (diethyl pyrocarbonate, Sigma) containing the different cRNAs at a concentration of approximately 150–3000 $ng \cdot \mu L^{-1} \cdot subunit^{-1}$. The amount of cRNA was determined by means of a NanoDrop ND-1000 (Kisker-biotech, Steinfurt, Germany).

To ensure expression of the gamma-subunit in the case of $\alpha_1\beta_2\gamma_{2S}$ and $\alpha_3\beta_3\gamma_{2S}$ receptors, cRNAs were mixed in a ratio of 1:1:10 and for receptors comprising only α- and β-subunits ($\alpha_1\beta_2$, $\alpha_1\beta_3$) in a ratio 1:1 (Khom *et al.*, 2007). cRNAs for $\alpha_1\beta_1$ channels were injected in a ratio of 3:1 to avoid formation of β_1

homo-oligomeric $GABA_A$ receptors (Krishek *et al.*, 1996). Oocytes were stored at 18°C in ND96 solution (Methfessel *et al.*, 1986). Electrophysiological experiments were done using the two-microelectrode voltage-clamp method at a holding potential of –70 mV making use of a TURBO TEC 01C amplifier (npi electronic, Tamm, Germany) and an Axon Digidata 1322A interface (Molecular Devices, Sunnyvale, CA). Data were acquired using pCLAMP v.9.2. The bath solution contained 90 mM NaCl, 1 mM KCl, 1 mM $MgCl_2 \cdot 6H_2O$, 1 mM $CaCl_2$ and 5 mM HEPES (pH 7.4). Microelectrodes were filled with 2 M KCl and had resistances between 1 and 3 MΩ (Khom *et al.*, 2007).

Perfusion system

γ-Aminobutyric acid and VA derivatives were applied by means of a fast perfusion system (see Baburin *et al.*, 2006 for details). Drug or control solutions were applied by means of a TECAN Miniprep 60 permitting automation of the experiments. To elicit I_{GABA} the chamber was perfused with 120 µL of GABA-containing solution at a rate of 300–1000 $\mu L \cdot s^{-1}$. The I_{GABA} rise time ranged between 100 and 250 ms (Baburin *et al.*, 2006; Khom *et al.*, 2006). Care was taken to account for possible slow recovery from increasing levels of desensitization in the presence of high GABA and drug concentrations. The duration of washout periods was therefore extended from 1.5 min (1–20 µM GABA, <10 µM drug) to 30 min (≥100 µM GABA, ≥10 µM drug) respectively. Oocytes with maximal current amplitudes >3 µA were discarded to exclude voltage-clamp errors (Khom *et al.*, 2007).

Analysing concentration–response curves

Stimulation of chloride currents by modulators of the $GABA_A$ receptor was measured at a GABA concentration eliciting between 3% and 5% of the maximal current amplitude (EC_{3-5}). The EC_{3-5} was determined at the beginning of each experiment.

Enhancement of the chloride current was defined as $[I_{(GABA+Comp)}/I_{GABA}] - 1$, where $I_{(GABA+Comp)}$ is the current response in the presence of GABA and a given compound (VA or VA derivative), and I_{GABA} is the control GABA current. To measure the sensitivity of the $GABA_A$ receptor for a given compound, it was applied for an equilibration period of 1 min before applying GABA (EC_{3-5}). Concentration–response curves were generated, and the data were fitted by non-linear regression analysis using Origin software (OriginLab Corporation, USA). Data were fitted to the equation: $\frac{1}{1+\left(\frac{EC_{50}}{[Comp]}\right)^{n_H}}$, where n_H is the Hill coefficient. Each data point represents the mean ± SE from at least four oocytes and ≥2 oocyte batches. Statistical significance was calculated using paired Student's *t*-test with a confidence interval of $P < 0.05$.

Animals

All animal care and experimental procedures were approved by the Austrian Animal Experimentation Ethics Board in compliance with the European convention for the protection of vertebrate animals used for experimental and other scientific purposes ETS no. 123. Every effort was taken to minimize the number of animals used. Male mice (c57Bl/6N) were obtained from Charles River Laboratories (Sulzfeld, Germany). For breeding and maintenance, mice were group-housed with free access to food and water. Temperature (23 ± 1°C) and humidity (60%) were fixed and the animals housed with a 12 h light–dark cycle (lights on 0700–1900 h). Male mice at 3–6 months age were tested in all experiments.

Elevated plus maze test

Explorative behaviour was tested over 5 min on an elevated plus maze 1 m above ground. The maze consisted of two closed and two open arms, each 50 × 5 cm in size as previously described by Wittmann *et al.* (2009). The test instrument was built from gray PVC; the height of closed arm walls was 20 cm. Illumination was set to 180 lx. Animals were placed in the centre, facing an open arm. Open and closed arm entries and time spent on open arm was automatically analysed using Video-Mot 2 equipment and software (TSE, Bad Homburg, Germany).

Statistical analysis of behavioural experiments

For comparison of control groups and compound-treated groups, the unpaired Student's *t*-test was used. Comparison of more than two groups was done by one-way ANOVA. *P*-values of <0.05 were accepted as statistically significant. All data are given as mean ± SEM (*n*).

Materials

Valerenic acid was obtained from Extrasynthese (Lyon, France) and DMSO was purchased from Sigma. VA-EE was an intermediate of the total VA synthesis described by Ramharter and Mulzer (2009). The other tested derivatives were synthesized as described above.

Results

We have synthesized a series of novel VA derivatives (for structures, see Figure 1) to study the structure–

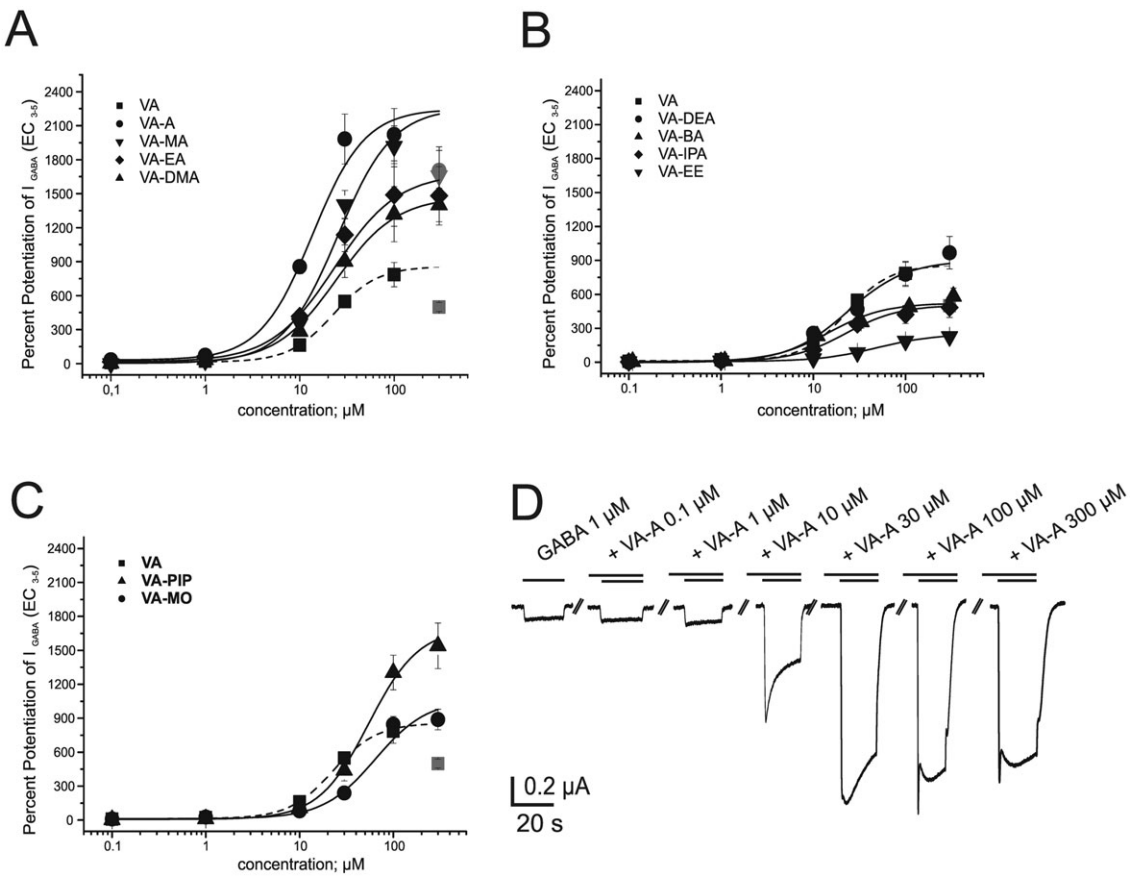


Figure 2

Concentration–effect curves for the enhancement of I_{GABA} through GABA$_A$ receptors composed of $\alpha_1\beta_3$ subunits by (A) VA, VA-A, VA-MA, VA-EA and VA-DMA; (B) VA, VA-DEA, VA-BA, VA-IPA and VA-EE; (C) VA, VA-PIP and VA-MO, using a GABA EC_{3-5} (EC_{50} and n_H values are given in Table 1). I_{GABA} at 300 µM (VA and VA-A) (Figure B) (grey symbols) were excluded from the fit. (D) Typical I_{GABA} recordings illustrating concentration-dependent modulation by VA-A of GABA elicited chloride currents through $\alpha_1\beta_3$ subunit-containing receptors. An open channel block at high VA-A concentrations was evident from the initial rapid current decay at 100 and 300 µM. GABA, γ-aminobutyric acid; I_{GABA}, GABA-induced chloride currents; VA, valerenic acid; VA-A, valerenic acid amide; VA-BA, valerenic acid butylamide; VA-DEA, valerenic acid diethylamide; VA-DMA, valerenic acid dimethylamide; VA-EA, valerenic acid ethylamide; VA-EE, valerenic acid ethyl ester; VA-IPA, valerenic acid isopropylamide; VA-MA, valerenic acid methylamide; VA-MO, valerenic acid morpholine amide; VA-PIP, valerenic acid piperidine amide.

activity relationship of these molecules on GABA$_A$ receptors composed of α_1 and β_3 subunits, expressed in *Xenopus* oocytes.

Modulation of I_{GABA} *by the VA derivatives*

We measured modulation of I_{GABA} by the VA derivatives by the two-microelectrode voltage-clamp technique. As shown in Figure 2A–C, all VA derivatives enhanced I_{GABA}. We observed, however, significant differences in efficacies and potencies.

Unsubstituted VA-A. VA-A was identified as the most effective and most potent VA derivative. Representative I_{GABA} modulated by VA-A are shown in Figure 2D. Relative to the parent compound, amidation resulted in an increased potency and a more than twofold enhanced maximal stimulation of I_{GABA} at GABA EC_{3-5} concentrations (see Figure 2A and Table 1).

Alkylated VA-amides. Introduction of aliphatic, alkyl residues resulted in a stronger modulation of I_{GABA} compared with VA. This effect was, however, less pronounced than for VA-A. Moreover, the nature of the alkyl residue significantly affected the efficacy of the amides: VA derivatives comprising residues such as monomethyl and monoethyl displayed a stronger I_{GABA} potentiation compared with VA. Bulkier residues such as dimethyl, diethyl, butyl and isopropyl, either decreased I_{GABA} enhancement or enhancement was not statistically different from VA (for details, see Figure 2 and Table 1).

Table 1

Summary of efficacies and potencies of tested VA derivatives

	EC_{50} (μM)	Maximum stimulation of I_{GABA} (EC_{3-5}) (%)	Hill coefficient (n_H)	Number of experiments (n)
VA	22.8 ± 5.6	858 ± 153	1.9 ± 0.3	5
VA-A	13.7 ± 2.3*	2247 ± 252*	1.6 ± 0.2	7
VA-MA	26.3 ± 6.6	2298 ± 312*	1.4 ± 0.1	6
VA-DMA	28.4 ± 7.1	1383 ± 211	2.1 ± 0.5	5
VA-EA	23.4 ± 6.9	1678 ± 258*	1.3 ± 0.3	5
VA-DEA	23.7 ± 6.3	901 ± 120	1.4 ± 0.1	6
VA-BA	18.8 ± 6.9	569 ± 57	1.1 ± 0.2	5
VA-IPA	22.5 ± 6.0	506 ± 76	1.5 ± 0.3	4
VA-PIP	54.6 ± 17.0*	1698 ± 266*	1.6 ± 0.3	6
VA-MO	64.2 ± 13.8*	1064 ± 132	1.6 ± 0.2	7
VA-EE	49.2 ± 26.3	250 ± 65*	1.4 ± 0.6	5

*$P < 0.05$, significantly different from corresponding values for VA.
GABA, γ-aminobutyric acid; I_{GABA}, GABA-induced chloride currents; VA, valerenic acid; VA-A, valerenic acid amide; VA-BA, valerenic acid butylamide; VA-DEA, valerenic acid diethylamide; VA-DMA, valerenic acid dimethylamide; VA-EA, valerenic acid ethylamide; VA-EE, valerenic acid ethyl ester; VA-IPA, valerenic acid isopropylamide; VA-MA, valerenic acid methylamide; VA-MO, valerenic acid morpholine amide; VA-PIP, valerenic acid piperidine amide.

Interestingly, introduction of cyclic residues on the amide nitrogen induced a significant loss of potency for VA-PIP and VA-MO (Table 1). Enhancement of I_{GABA} by VA-PIP was, however, comparable to that of VA-A, while potentiation of I_{GABA} by VA-MO was less pronounced, comparable to that of VA. VA-EE displayed the lowest efficacy and a reduced potency (Table 1).

β Subunit-specific modulation of I_{GABA} *by VA-A*

According to our previous study, VA selectively enhances I_{GABA} through $GABA_A$ receptors comprising either β_2 or β_3 subunits. Even high concentrations of VA (100 μM) induce no significant ($P < 0.05$) potentiation of I_{GABA} through receptors containing β_1 subunits. A similar study was performed with VA-A and I_{GABA} potentiation analysed for $GABA_A$ receptors composed of $\alpha_1\beta_1$, $\alpha_1\beta_2$ and $\alpha_1\beta_3$ subunits. VA-A displayed high selectivity for $\alpha_1\beta_2$ and $\alpha_1\beta_3$ receptors (Figure 3). Enhancement of I_{GABA} by VA-A was most pronounced through $GABA_A$ receptors composed of α_1 and β_3 subunits (maximal stimulation 2021 ± 231% at a concentration of 100 μM, EC_{50} = 13.7 ± 2.3 μM). VA-A also potentiated I_{GABA} through $GABA_A$ channels comprising β_2 subunits (maximal stimulation 1204 ± 270% at a concentration of 100 μM; EC_{50} = 8.2 ± 5.1 μM), but did not significantly enhance I_{GABA} through $\alpha_1\beta_1$ containing receptors even at 300 μM VA-A ($P < 0.05$).

Modulation of I_{GABA} *through* $\alpha_3\beta_3\gamma_{2S}$ *and* $\alpha_1\beta_2\gamma_{2S}$ *$GABA_A$ receptors by VA-A*

As shown in Figure 3, VA-A induced the most efficient I_{GABA} enhancement on receptors composed of $\alpha_1\beta_3$ receptors ($\alpha_1\beta_3 > \alpha_1\beta_2 >> \alpha_1\beta_1$, see similar data for VA in Khom *et al.*, 2007).

To gain insight into modulation of more physiological $GABA_A$ receptors (McKernan and Whiting, 1996; Olsen and Sieghart, 2008) we investigated the modulation of $\alpha_1\beta_2\gamma_{2S}$ and $\alpha_3\beta_3\gamma_{2S}$ receptors by VA-A. As illustrated in Figure 4A, $\alpha_1\beta_2\gamma_{2S}$ receptors were more efficiently modulated by VA-A than by VA. Co-expression of a γ_{2S} subunit had no significant effects on efficacy or on potency ($P > 0.05$; compare Figures 3A and 4A, see Khom *et al.*, 2006 for comparable data obtained with VA). VA-A displayed also a higher efficacy than VA on receptors composed of $\alpha_3\beta_3\gamma_{2S}$ subunits (Figure 4B, $P < 0.05$, see also Table 2). On this receptor subtype, only a trend towards a higher potency was observed for VA-A, compared with VA (Tables 2, $P > 0.05$).

In vivo *effects of selected VA derivatives*

In order to get insights into the *in vivo* effects of VA derivatives, the effect of selected compounds on anxiety-related behaviour in mice was studied in the elevated plus maze test. Thirty minutes after i.p. injection of either solvent (=control) or drug containing solution (3 mg drug·kg^{-1}), the mice were tested for 5 min in the elevated plus maze. Mice treated with VA spent significantly more ($P < 0.05$)

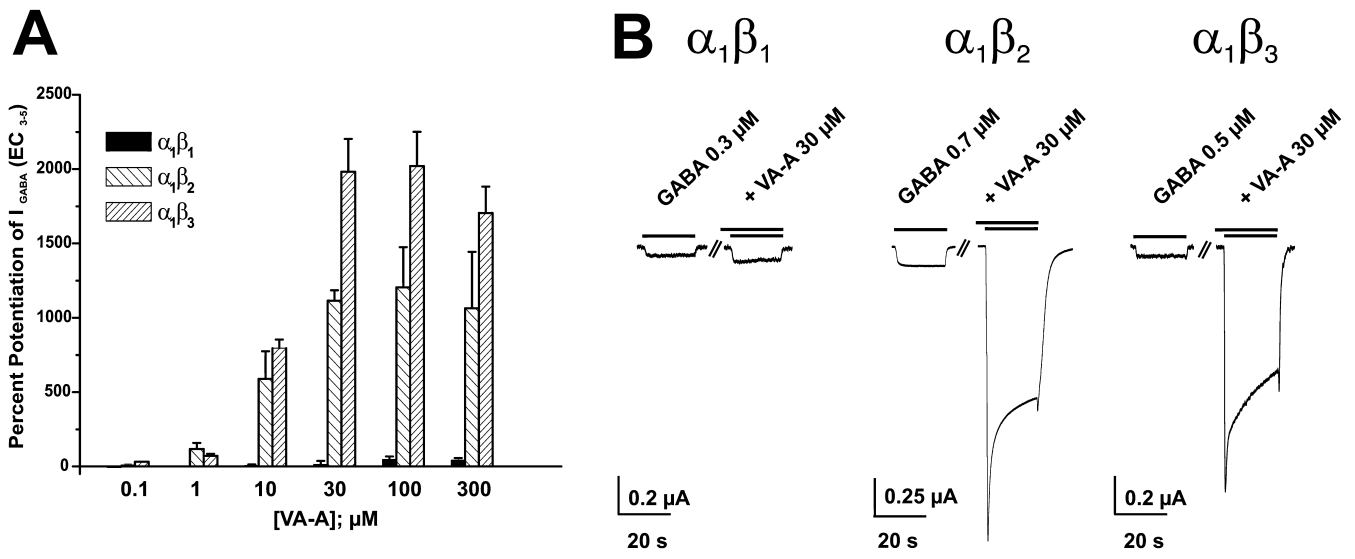


Figure 3

(A) Concentration-dependent effects for VA-A on $\alpha_1\beta_1$, $\alpha_1\beta_2$ and $\alpha_1\beta_3$ receptors using a GABA EC_{3-5} concentration. (B) Typical traces for modulation of chloride currents through $\alpha_1\beta_1$, $\alpha_1\beta_2$ and $\alpha_1\beta_3$ channels by 30 µM VA-A at GABA EC_{3-5}. Control currents (GABA, single bar) and corresponding currents elicited by co-application of GABA and the indicated VA-A concentration (double bar) are shown. GABA, γ-aminobutyric acid; I_{GABA}, GABA-induced chloride currents; VA-A, valerenic acid amide.

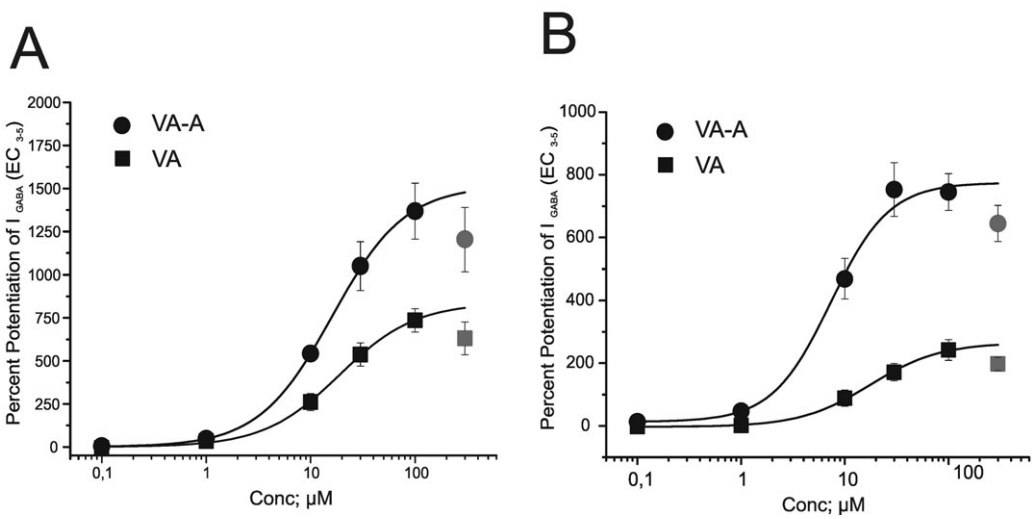


Figure 4

Concentration–effect curves for the enhancement of I_{GABA} through GABA$_A$ receptors composed of (A) $\alpha_1\beta_2\gamma_{2S}$ subunits and (B) of $\alpha_3\beta_3\gamma_{2S}$ subunits by VA-A and VA using a GABA EC_{3-5} (EC_{50} and maximal stimulation are given in Table 2). I_{GABA} at 300 µM (grey symbols) were excluded from the fit. GABA, γ-aminobutyric acid; GABA$_A$, GABA type A; I_{GABA}, GABA-induced chloride currents; VA, valerenic acid; VA-A, valerenic acid amide.

of the total time on the open arms, than the control littermates (injected with solvent), indicating anxiolytic potential of VA (Figure 5). More marked anxiolytic effects were observed after VA-A treatment ($P < 0.01$ vs. control and $P < 0.05$ vs. VA). Treatment with VA-EA, VA-DEA and VA-EE induced anxiolytic effects comparable to VA, while VA-MO did not show any anxiolytic response at the tested dose (Figure 5).

Dose-dependent reduction of anxiety in mice by VA and VA-A

Valerenic acid and VA-A were studied in more detail. As shown in Figure 6A,B, both compounds displayed similar anxiolytic activity at a dose of 1 mg·kg^{-1}. However, the anxiolytic effect was significantly more pronounced for VA-A at 3 mg·kg^{-1}. At higher doses, a reduction of the time spent in the open arms was observed for both compounds.

Table 2

Summary of potencies (as EC_{50}) and efficacies (as maximum stimulation of I_{GABA}) of VA and VA-A on different $GABA_A$ receptor subtypes

Subunit composition	Compound	EC_{50} (μM)	Maximum stimulation of I_{GABA} (%)	Number of experiments (*n*)
$\alpha_1\beta_2\gamma_{2S}$	VA-A	16.0 ± 4.4	1517 ± 234	5
$\alpha_1\beta_2\gamma_{2S}$	VA	18.9 ± 8.5	838 ± 157	4
$\alpha_3\beta_3\gamma_{2S}$	VA-A	7.3 ± 1.9	775 ± 62	6
$\alpha_3\beta_3\gamma_{2S}$	VA	17.6 ± 9.8	265 ± 68	4

GABA, γ-aminobutyric acid; $GABA_A$, GABA type A; I_{GABA}, GABA-induced chloride currents; VA, valerenic acid; VA-A, valerenic acid amide.

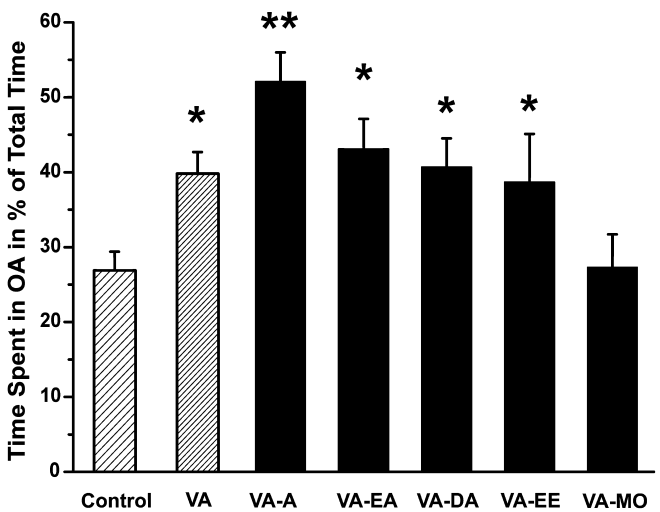


Figure 5

Behaviour in the elevated plus maze test for control and drug-treated mice at a dose of 3 mg·kg^{-1} of the indicated VA derivative. Bars indicate the time spent on the open arms (OA) in % of the total time. Bars represent means ± SEM from at least eight different mice. *P < 0.05; **P < 0.01, significantly different from control. VA, valerenic acid; VA-A, valerenic acid amide; VA-DEA, valerenic acid diethylamide; VA-EA, valerenic acid ethylamide; VA-EE, valerenic acid ethyl ester; VA-MO, valerenic acid morpholine amide.

Reduced exploratory drive after the highest dose of VA-A (30 mg·kg^{-1}) was accompanied by a reduction of closed arm entries and total distance. The number of closed arm entries and total distance of VA-treated mice were not significantly different from control values, at doses between 1 and 10 mg·kg^{-1}. At the highest dose (30 mg·kg^{-1} VA), the number of closed arm entries was reduced (see Figure 6C–F).

Discussion

Synthesis of high efficacy VA derivatives

We and others have recently identified VA (a major constituent of *V. officinalis* L.) as an allosteric modulator of $GABA_A$ receptors selectively enhancing I_{GABA} through channels comprising β_2 or β_3 (but not β_1) subunits (Khom *et al.*, 2007; Benke *et al.*, 2009). In the present study, we have analysed the structure–activity relationship of VA by modifying its carboxyl group (Figure 1). This approach allowed us to generate VA derivatives modulating $GABA_A$ receptors with higher efficacy than the natural parent compound. Significantly higher efficacies in the stimulation of I_{GABA} through $\alpha_1\beta_3$ receptors were observed for VA-A (2247 ± 252%), VA-MA (2298 ± 312%) and VA-EA (1678 ± 258%). All values were significantly different from those for VA ($P < 0.05$). VA-A was even more potent than VA ($P < 0.05$; Table 1). Introduction of bulkier residues or cyclic residues resulted in either a less efficient potentiation of I_{GABA} compared with VA or even a significantly reduced potency (for details, see Table 1 and Figure 2).

With respect to structure–activity relationships we observed no correlation between potency and efficacy of the compounds. The unsubstituted amide VA-A displayed the lowest EC_{50} (highest potency) at the $GABA_A$ receptors investigated. Notably, all mono- and dialkyl-substituted amides and VA itself exhibited almost identical EC_{50} values. This indicates, that, for this part of the molecule, neither charge nor H-bond donor properties nor lipophilicity influence drug receptor binding. In an activity ranking, this cluster of equally active compounds is followed by the ethyl ester, which was slightly less active than the respective ethyl amide. Interestingly, both the piperidine and the morpholine analogues wee significantly less potent than all the other compounds. This might either indicate a steric hindrance caused by the rigid six membered rings or an unfavourable entropic contribution caused by the greater rigidity of the amide substituent.

With respect to maximum stimulation, the differences are more pronounced with almost one order of magnitude difference (ester vs. unsubstituted amide). In addition, a different structure–activity relationship was observed. Open chain

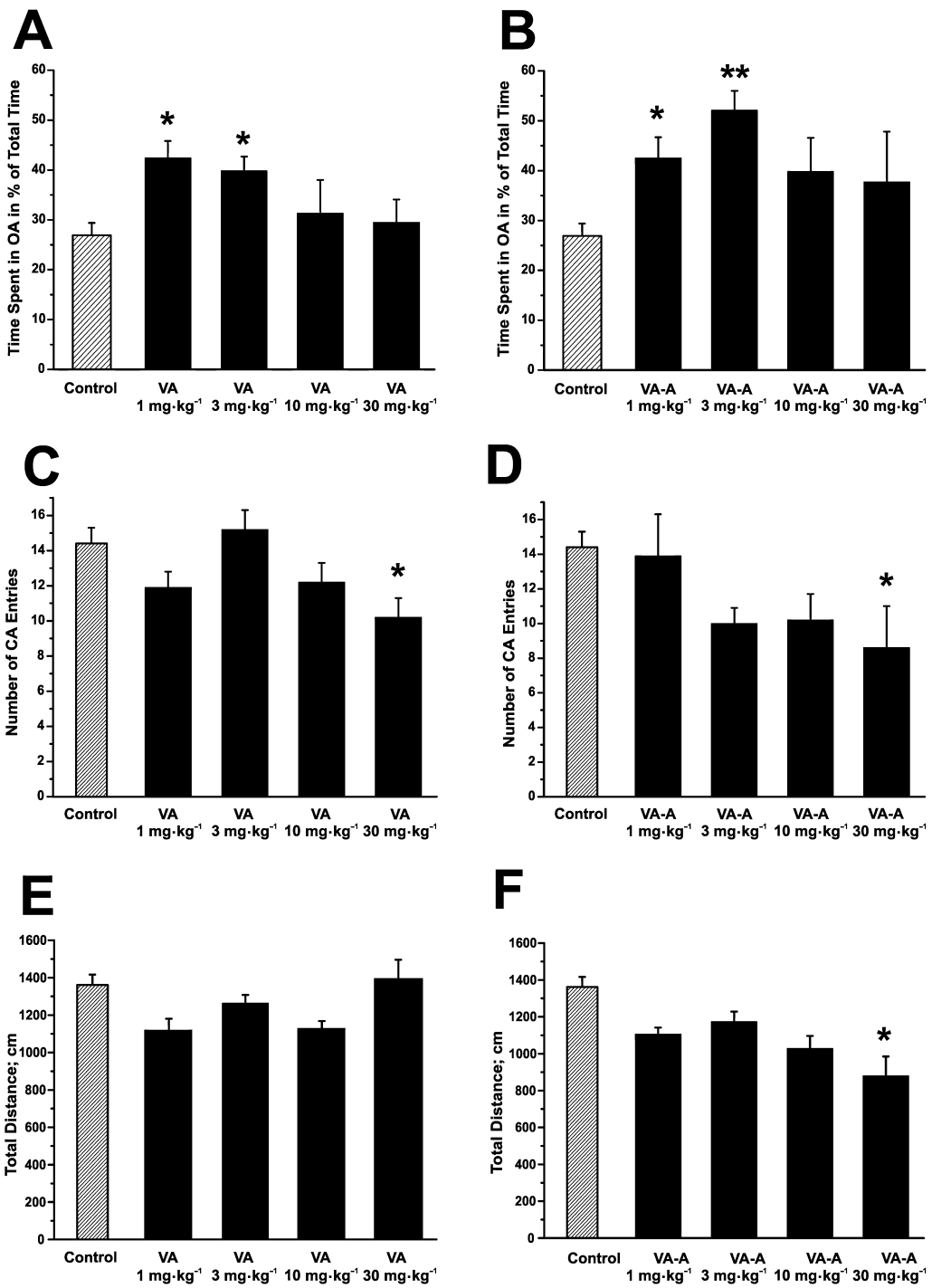


Figure 6

Behaviour in the elevated plus maze test for control (shaded bars in A–F) and drug-treated mice at the indicated dose and compound. Bars indicate in (A) time spent in open arms (OA), in % of the total time after application of the indicated dose of VA, (B) time spent in open arms in % of the total time after application of the indicated dose of VA-A, (C) number of closed arm (CA) entries after application of the indicated dose of VA, (D) number of closed arm entries after application of the indicated dose of VA-A, (E) total distance after application of the indicated dose of VA and (F) total distance after application of the indicated dose of VA-A. Bars represent means ± SEM from at least eight different mice. *$P < 0.05$; **$P < 0.01$, significantly different from control. VA, valerenic acid; VA-A, valerenic acid amide.

secondary and tertiary amides show a clear inverse correlation between logP values and maximum stimulation ($r^2 = 0.83$, $n = 7$), with the unsubstituted amide and the methylamide being the most active compounds. Pairwise comparison of mono- and di-substituted amides also reveals that the latter generally show lower maximum stimulation. This might point towards a potential importance of H-bond donor features in this region. Furthermore, the ethyl ester is almost one order of magnitude less efficient than the analogous ethyl amide, which might indicate that the carbonyl group functions as an H-bond acceptor. However, this data set needs to be interpreted very cautiously, as it is too limited to derive any quantitative (QSAR) models.

Derivatization preserves subunit specificity

Derivatization might influence the pharmacological properties of the compounds, which could lead to a loss of subunit specificity. We have therefore investigated the effects of VA-A (the most potent and effective derivative) on $\alpha_1\beta_1$, $\alpha_1\beta_2$ and $\alpha_1\beta_3$ receptors. Compared with VA, the selectivity for VA-A for $GABA_A$ receptors comprising β_2 or β_3 subunits was conserved. As shown in Figure 3, VA-A induced pronounced modulation of $\alpha_1\beta_3$ and $\alpha_1\beta_2$ receptors, and no significant effect was observed for $\alpha_1\beta_1$ receptors (300 μM; $P < 0.05$). Benke *et al*. (2009) reported, that $\alpha_1\beta_2$ receptors were not modulated by VA. This is in contrast to our previous data (Khom *et al*., 2007) and was also not observed for VA-A in the present study (see Figure 3).

VA-A efficiently enhances I_{GABA} through $\alpha_1\beta_2\gamma_{2S}$ and $\alpha_3\beta_3\gamma_{2S}$ receptors

In line with the data obtained on $\alpha_1\beta_3$ receptors (Figure 2), we found that I_{GABA} through $\alpha_1\beta_2\gamma_{2S}$ receptors were more effectively enhanced by VA-A than by VA (Figure 4A, Table 2). However, our data also show that VA-A was more potent on $GABA_A$ receptors comprising α_3 subunits than α_1 subunits ($P < 0.05$, see Table 2, Figure 4A,B) that could, by analogy with the effects of the benzodiazepines (Rudolph *et al*., 1999; McKernan *et al*., 2000; Atack, 2005; Dias *et al*., 2005), contribute to the anxiolytic action of VA-A (Figure 6).

VA-A showed the most marked anxiolytic effects in mice

Effects on anxiety were investigated in the elevated plus maze for five VA derivatives (VA-A, VA-EA, VA-DEA, VA-EE and VA-MO), selected on the basis of their *in vitro* properties.

In this test, all compounds except VA-MO induced significantly increased ambulation of the open arms. This anxiolytic effect was most pronounced for VA-A, as mice treated with VA-A spent about twice the time in the open arms of the elevated plus maze. Of note is the fact, that increasing lipophilicity did not directly translate into increased behavioural effects. VA-MO was inactive at the dose tested, but effects at higher doses cannot be excluded. Interestingly, VA-EE (the weakest modulator *in vitro*) displayed pronounced anxiolytic responses comparable to that of VA.

In vivo effects of VA and VA-A were compared over a broader range of doses. Both compounds induced comparable anxiolytic effects at 1 $mg \cdot kg^{-1}$. At doses of 10 and 30 $mg \cdot kg^{-1}$, VA treatment failed to increase time spent in the open arms (Figure 6). The lack of increased open arm ambulation after higher doses of VA or VA-A were paralleled by reduced motor activity as indicated by reduced closed arm entries and distance travelled (Figure 6). As this test depends on motor activity, any sedative effects may camouflage anxiolytic effects at higher doses of VA-A.

In conclusion, we report here the synthesis of novel VA derivatives that enabled to gain insights into the structure–activity relationship of this molecule. Amidation was found to increase potency and efficacy of VA. Greater I_{GABA} enhancement by VA-A through receptors comprising β_3 (β_2) subunits *in vitro* correlated with significantly stronger *in vivo* effects as compared with VA. Benke *et al*. (2009) have shown that the anxiolytic activity of VA is absent in β_3(N265M) point-mutated mice. It is therefore likely that the anxiolytic effect of the studied VA derivatives was caused by interaction with $GABA_A$ receptors containing β_3 subunits. Our data thus support the hypothesis that β_3 subunit containing $GABA_A$ receptors are interesting targets for the development of anxiolytics. We can not exclude, however, that the higher potency of VA-A on $GABA_A$ receptors comprising α_3 subunits (Figure 4B) contributes to its anxiolytic action. Some $\beta_{2/3}$-selective $GABA_A$ receptor ligands have also been shown to induce anticonvulsant (Wingrove *et al*., 1994; Groves *et al*., 2006) and anaesthetic effects (Li *et al*., 2006; Drexler *et al*., 2009). It will be interesting to study if such effects can be detected for VA or its derivatives.

Acknowledgements

This work was supported by FWF grant P15914 (SH) and FWF grant P21241 (JM).

Conflicts of interest

The University of Vienna has filed a European Patent Application, serial number EP09151278, with four inventors (S.K., J.R., J.M. and S.H.).

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Rudolph U, Crestani F, Benke D, Brunig I, Benson JA, Fritschy JM, *et al*. (1999). Benzodiazepine actions mediated by specific gamma-aminobutyric acid(A) receptor subtypes. Nature 401: 796–800.

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Simon J, Wakimoto H, Fujita N, Lalande M, Barnard EA (2004). Analysis of the set of GABA(A) receptor genes in the human genome. J Biol Chem 279: 41422–41435.

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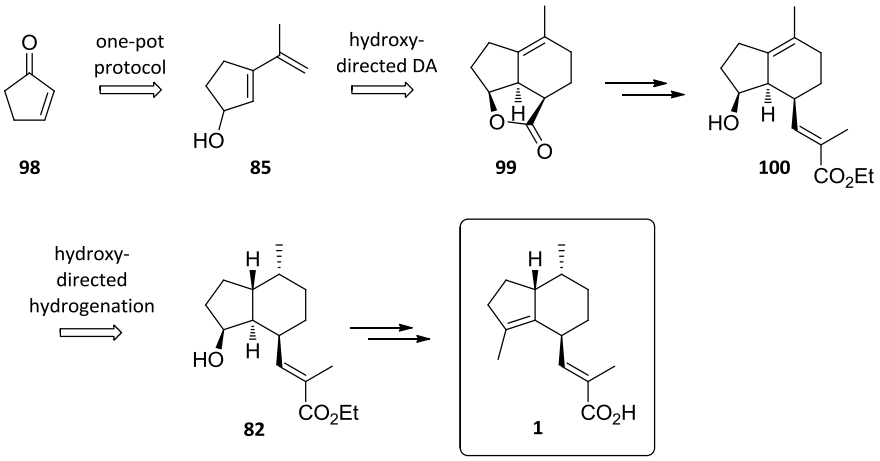
2.8 Summary

The synthetic strategy devised during this PhD thesis has led to the first total synthesis of valerenic acid. After optimization a ten step sequence has been elaborated, which utilized a novel one-pot reaction to provide key intermediate **85** and two hydroxy-directed reactions (HDDA, Crabtree hydrogenation) as further key steps to stereo- and regioselectively provide valerenic acid with an overall yield of 25 % (see Scheme 17).



Scheme 17: Keysteps of the synthesis of valerenic acid.

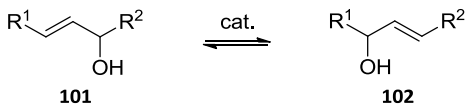
Importantly, in contrast to other approaches towards valerenanes, it was possible to avoid instable intermediates prone to epimerization. Up to date this approach represents the shortest total synthesis and delivers valerenic acid with the highest overall yield.

Based on this synthetic strategy also a series of simple derivatives has been synthesized and tested by the Department of Pharmacology and Toxicology. Both *in vitro* and *in vivo* tests have led to promising results, so both departments are confident that the results from this thesis will provide the basis for future developments.

3 [1,3]-Isomerization of Allylic Alcohols

3.1 Introduction to Anionotropic Isomerizations

Rearrangements based on migration of functional groups, which can also exist as stable anions or cations, are often referred to anionotropic or cationotropic reactions.[26] One well known example for an anionotropic rearrangement is the isomerization of allylic alcohols. Migration of the hydroxy group and simultaneous transposition of one or more π-bonds lead to another allylic alcohol in this transformation.

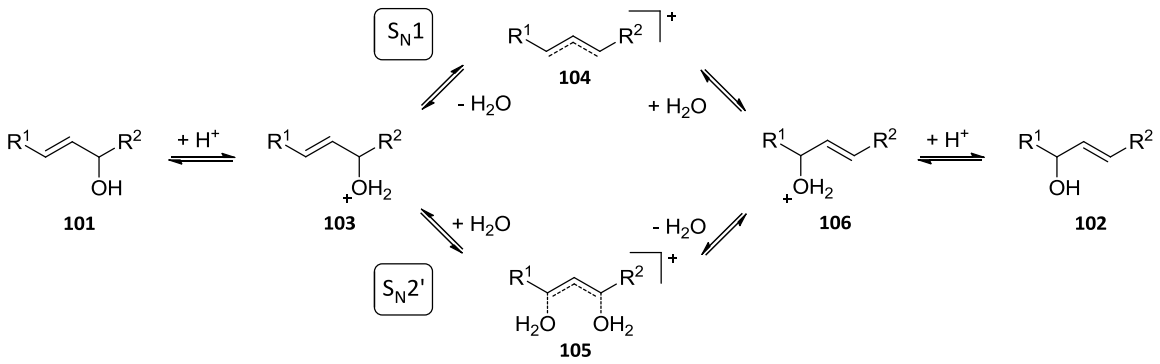


Scheme 18: [1,3]-Isomerization of allylic alcohols.

As outlined in Scheme 18, [1,3]-isomerizations are reversible processes, so product distribution is mainly dependent on the thermodynamic stability of both isomers. Often mixtures of starting material and product are obtained, but if substituents favor the formation of one of the isomers the equilibrium is shifted selectively. Nonetheless, because of a considerable activation barrier this type of anionotropic reaction requires a catalyst.

3.1.1 Brønsted Acid Induced Isomerizations

In pioneering studies mostly sulfuric acid was used to isomerize allylic alcohols.[27] However, the yields were often only moderate because the occurrence of cationic intermediates sometimes resulted in the formation of unwanted byproducts or decomposition. The Brønsted acid induced rearrangement was rationalized by two slightly different mechanisms.



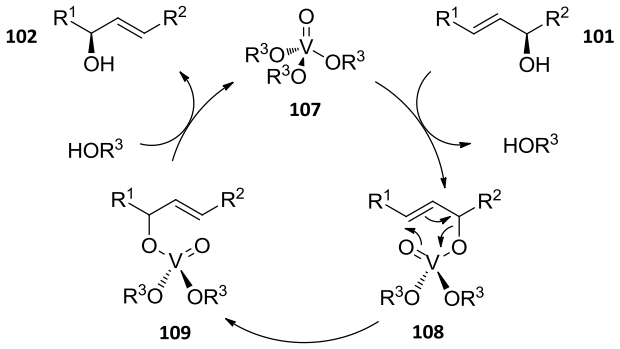
Scheme 19: Proposed mechanism for the acid induced allylic isomerization.

Because the initial protonation of alcohol **101** is very fast, the overall isomerization is a simple first order reaction and independent on the acid concentration.[27] After activation of the alcohol two different pathways seem plausible. Starting from **103** either carbenium ion **104** is formed (*via* an S_N1 mechanism), which immediately reacts with water to form the protonated isomeric alcohol **106**, or water substitutes the protonated hydroxy group according to a S_N2' mechanism.

Although most of the early investigations concentrated on mechanistic considerations, also some applications of sulfuric acid induced isomerizations in natural product synthesis have been published. The most prominent example was probably the total synthesis of vitamin A by Isler and coworkers.[28]

3.1.2 Metal Oxo Complex Catalyzed Isomerizations

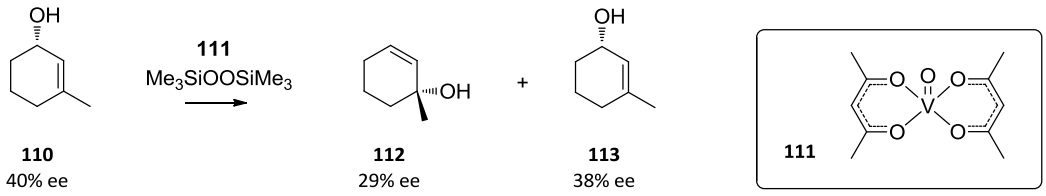
More recently metal oxo catalysts were used to carry out [1,3]-isomerizations.[29] In 1977 the group of Chabardes reported the first example for a metal oxo complex catalyzed rearrangement of unsaturated alcohols.[30] They observed that catalytic amounts of vanadate esters ($VO(OR)_3$) effectively catalyze [1,3]-isomerizations at elevated temperatures (see Scheme 20).



Scheme 20: Metal oxo complex catalyzed [1,3]-isomerization.

In the first substep transesterification of catalyst **107** with allylic alcohol **101** leads to formation of mixed vanadate ester **108**. In analogy to the [3,3]-sigmatropic Claisen rearrangement this substrate undergoes isomerization to afford intermediate **109**. After a second transesterification the isomerized alcohol **102** is obtained and the catalytic species regenerated. As in the acid induced isomerization all steps are reversible and a mixture of both isomers **101** and **102** is obtained. In agreement to the Woodward-Hoffmann rules this pericyclic reaction proceeds strictly suprafacial and is therefore stereoselective. Consequently formation of the new C-O bond proceeds from the hemisphere in which the original C-O bond is located. This mechanistic explanation is in agreement

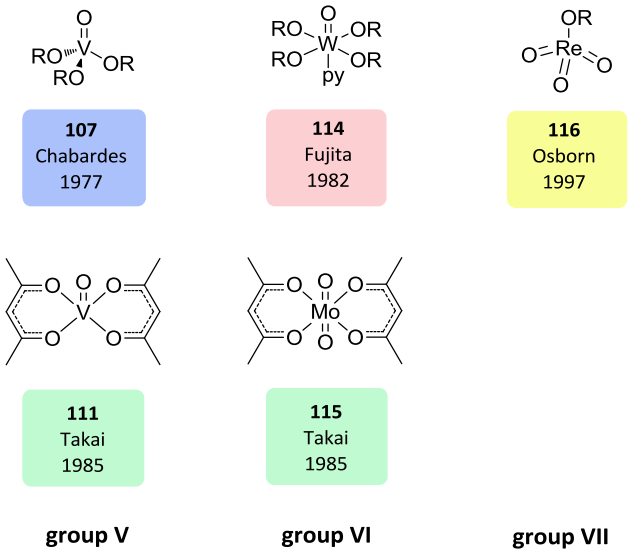
with the findings by Takai and coworkers, who used a slightly different vanadium catalyst ($VO(acac)_2$) to isomerize enantioenriched substrate **110**.[31]



Scheme 21: Conversion of a chiral substrate with catalytic amounts of $VO(acac)_2$.

As outlined in Scheme 21, the reaction proceeds mostly stereoselectively. Minor losses in the enantiomeric excess of both alcohols can be rationalized by competing reaction pathways involving allylic carbenium ions.

In the subsequent years several different catalysts have been developed (see Scheme 22).



Scheme 22: [1,3]-isomerization catalysts.

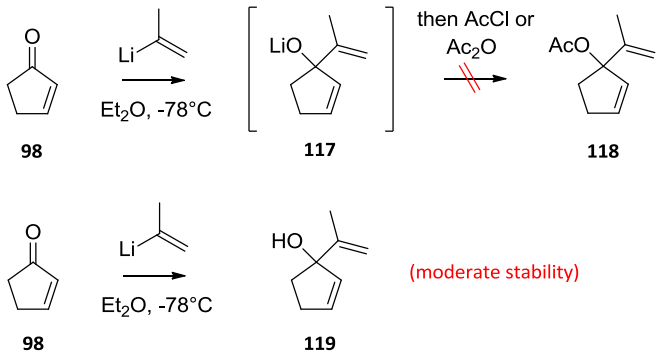
Shortly after introduction of vanadate ester **107** by Chabardes and coworkers, the groups of Fujita and Takai reported other catalytic species in the form of oxo vanadium, tungsten and molybdenum complexes.[31,32] Whereas the catalysts developed by Chabardes and Fujita need high temperature for suitable conversion, the vanadium and molybdenum acetylacetonate complexes used by Takai catalyze allylic isomerization already at room temperature. The last contribution on this field so far has been the oxo rhenium catalyst developed by Osborn and coworkers.[33] Noteworthy, this species was also used in natural product synthesis to provide galanthamine in the final step.[34] Although the

isomerization generally proceeds with good yields, sometimes also side reactions are observed. For example reduction of the highly oxidized catalysts leads to oxidation of the alcohol and more importantly to a loss of catalytic activity (Compare tungsten or molybdenum catalyzed isomerizations with the well known oxidation of tertiary allylic alcohols to enones by pyridinium dichromate or pyridinium chlorochromate.[35]).

3.2 One-Pot Synthesis of 2,4-Dienols

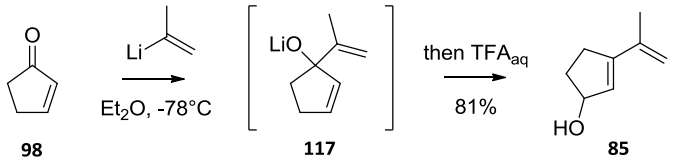
3.2.1 Introduction

During the efforts to optimize the first generation synthesis of valerenic acid (**1**) the preparation of two simple substrates has been envisaged (see Scheme 23).



Scheme 23: It began with an error…

To synthesize compound **118** enone **98** was converted with isopropenyl lithium and the *in situ* formed tertiary alkoxide was treated with acetyl chloride or acetic acid anhydride. However, all attempts to isolate any product failed and only a brown tarry residue was obtained, which smelled of acetic acid. Most likely autocatalytic generation of acetic acid led to decomposition. After this failure the synthesis of compound **119** was attempted. Although it was possible to isolate substrate **119**, the obtained yields were low and difficult to reproduce. Therefore, we rationalized that diallylic alcohol **119** was only of moderate stability. However, what might have been disadvantageous on first sight, became beneficially in the end, because we reasoned that the *in situ* formed tertiary alkoxide **117** should be an ideal substrate for a subsequent [1,3]-isomerization (see Scheme 24).



Scheme 24: One-pot synthesis of key intermediate **85**.

After several experiments, it eventually turned out, that not only isomerization of **117** was possible, but the same concept could be applied to a broad scope of different substrates. For a more detailed discussion, including also the conversion of chiral substrates, see the following communication.

3.2.2 Efficient and Scalable One-Pot Synthesis of 2,4-Dienols from Cycloalkenones

Ramharter, J.; Mulzer J. *Org. Lett.* **2011**, *13*, 5310

The supporting information of this communication includes experimental and analytical data of all discussed compounds. This data can be found in chapter 5.2.

ORGANIC LETTERS

2011
Vol. 13, No. 19
5310–5313

Efficient and Scalable One-Pot Synthesis of 2,4-Dienols from Cycloalkenones: Optimized Total Synthesis of Valerenic Acid

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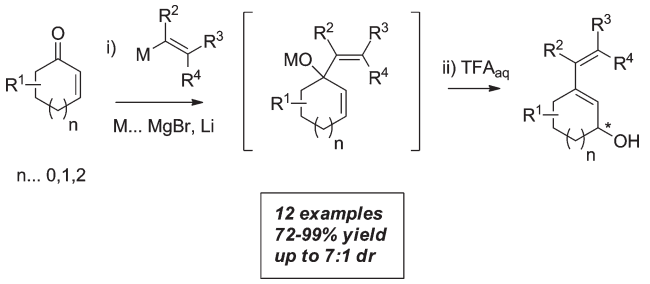
Received August 10, 2011

ABSTRACT



A mild and selective one-pot procedure to provide 2,4-dienols from simple cycloalkenones in high yields is described. This transformation is based on the in situ formation of acid-labile allylic alcohols, which on treatment with trifluoroacetic acid undergo a formal [1,3]-hydroxy migration to form diastereo- and enantiomerically enriched 2,4-dienols. The usefulness of this protocol is demonstrated in a short synthesis of valerenic acid.

2,4-Dienols are very important building blocks in natural product synthesis.[1] However, as even simple 2,4-dienols require several steps for their synthesis, a general and efficient access to these compounds would be welcome.

A straightforward access to 2,4-dienols is the [1,3]-hydroxy isomerization of tertiary allylic alcohols. This thermodynamically driven reaction has been known for several decades and has often been based on the use of metal−oxo catalysts,[2] although the pioneering investigations were carried out with sulfuric acid.[3] However, one of the disadvantages of this reaction type is the moderate stability of the required precursors. Therefore, we devised an effective and mild one-pot procedure that combines the preparation of the precursors with the [1,3]-hydroxy isomerization.[4,5]

As a proof of concept, 2-cyclopentenone (**1**) was chosen as a simple test substrate (see Table 1). After treatment with vinylmagnesium bromide, the in situ formed tertiary alkoxide **2** was treated with different aqueous Brønsted acids to trigger the transformation into 3-vinylcyclopent-2-enol (**3a**). The difference between sulfuric acid and hydrochloric acid was marginal, and at best, the isolated yields were only slightly higher than 40% (entries 1−3). After applying inorganic Brønsted acids, we switched to organic Brønsted acids instead (entries 4−6). Gratifyingly, when acetic acid or trifluoroacetic acid was used, decomposition and side reactions seemed to be much less competitive, in both cases, and much better results were obtained.

(1) For examples, see: (a) Corey, E. J.; Da Silva Jardine, P.; Rohloff, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 3672. (b) He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771. (c) Ramharter, J.; Mulzer, J. *Org. Lett.* **2009**, *11*, 1151.

(2) For a review, see: Bellemin-Laponnaz, S.; Le Ny, J.-P. *Compt. Rend. Chim.* **2002**, *5*, 217.

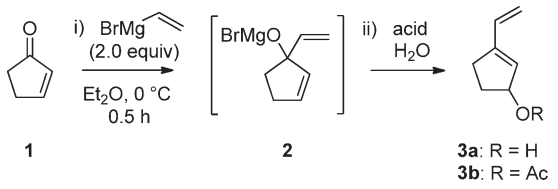
(3) For a review, see: Braude, E. A. *Q. Rev. Chem. Soc.* **1950**, *4*, 404.

(4) For reviews about one-pot reactions, see: (a) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831. (b) Albrecht, Ł.; Jiang, H.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* 2011, *50*, in press. (c) Vaxelaire, C.; Winter, P.; Christmann, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 3605.

(5) For a recent application of one-pot reactions in natural product synthesis from our group, see: Ramharter, J.; Weinstabl, H.; Mulzer, J. *J. Am. Chem. Soc.* **2010**, *132*, 14338.

10.1021/ol202170c
Published on Web 09/06/2011

Table 1. Screening of Different Brønsted Acids



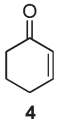
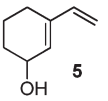
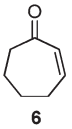
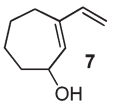
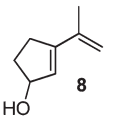
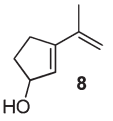
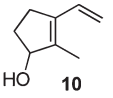
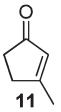
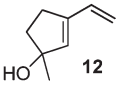
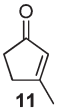
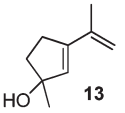
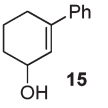
entry	acid (equiv)	temp (°C)	time (h)	product, yield (%)
1	H_2SO_4 (2.5)	25	1	**3a**, traces
2	H_2SO_4 (2.5)	0	1	**3a**, 45
3	HCl (2.5)	0	1	**3a**, 42
4	CH_3COOH (2.5)	25	24	**3a**, 68 + **3b**, 27
5	CF_3COOH (2.5)	0	1	**3a**, 78
6	CF_3COOH (2.5)	0	1.5	**3a**, 73 (gram scale)

Unfortunately, in the case of acetic acid, it took much longer to reach full conversion, and 1-acetoxy-2,4-dienol **3b** was isolated as side product (entry 4). Finally complete and selective isomerization to the desired 2,4-dienol **3a** was observed when trifluoroacetic acid was used (entry 5). The reaction was scalable, and nearly the same yield was obtained on a larger scale (entry 6).

After these initial results, the isomerization of other substrates was studied (see Table 2). The conversion of cycloalkenones with larger ring size was also highly selective (entries 1 and 2). Whereas treatment of 2-cyclopentenone (**1**) with 2-propenylmagnesium bromide led to the formation of considerable amounts of the 1,4-addition product, use of the corresponding organolithium compound and subsequent treatment with trifluoroacetic acid resulted in clean formation of the desired 2,4-dienol **8**. Scale up to gram scale did not reduce the yield (entry 4). Interestingly, while the substituent in 2-methylcyclopent-2-enone did not affect the transposition of the hydroxy group, the conversion of 3-methylcyclopent-2-enone was much more acid sensitive than most other substrates. As a consequence, better results were obtained when acetic acid was used instead of trifluoroacetic acid (entries 6 and 7). Remarkably, no other products were obtained in this case. Finally, also an aryl Grignard was used instead of an alkenyl Grignard (entry 8). Although the subsequent isomerization was much slower than before, a very selective formation of the expected 3-phenylhex-2-enol was observed in nearly quantitative yield.

Because metal−oxo-catalyzed 1,3-isomerizations of allylic alcohols often proceed stereoselectively,[6] the conversion of chiral substrates was investigated as well (see Table 3). According to our results, the limiting factor in the selectivity of the overall transformation appears to be the 1,2-addition. When a single intermediate was

Table 2. Conversion of Simple Substrates[a]

entry	substrate	nucleophile	cond.	product	yield
1	 **4**		TFA, 0 °C, 1.5 h	 **5**	79%
2	 **6**		TFA, 25 °C, 1.5 h	 **7**	80%
3	 **1**		TFA, 0 °C, 0.75 h	 **8**	81%
4	 **1**		TFA, 0 °C, 1 h	 **8**	72% (g-scale)
5	 **9**		TFA, 0 °C, 1 h	 **10**	79%
6	 **11**		AcOH, 0 °C, 0.75 h	 **12**	99%
7	 **11**		AcOH, 0 °C, 1 h	 **13**	78% (g-scale)
8	 **14**		TFA, 25 °C, 48 h	 **15**	94%

[a] Key: (i) 0.1 M in Et_2O at 0 °C or −78 °C, 2.0 equiv of nucleophile; (ii) 0 °C or rt, H_2O, 2.5 equiv of acid.

formed, high diastereomeric ratios were obtained for the resulting products (entries 2 and 3).[7] However, when the 1,2-addition was not selective, roughly the same diastereomeric ratio was observed for the rearranged dienols (entry 1).

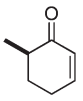
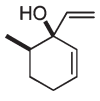
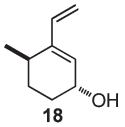
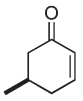
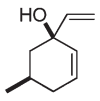
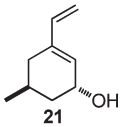
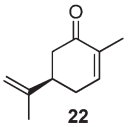
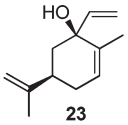
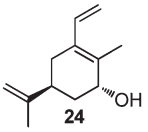
Interestingly, *cis* intermediates led to the formation of *trans* products, indicating that a different mechanism is operating than for metal−oxo catalyst mediated reactions.[8] To account for the observed stereoselectivity, we propose that trifluoroacetic acid does not only protonate the tertiary alcohol but also blocks the site of the molecule *syn* to the alcohol (see Figure 1). The interaction of acid and hydroxyl group may result either in the formation of an instable trifluoroacetate followed by S_N2 hydrolysis or

(6) (a) Matsubara, S.; Okazoe, T.; Oshima, K.; Takai, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 844. (b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 11262. (c) Morrill, C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 2842.

(7) Diastereomers were separated by means of HPLC. *cis*- and *trans*-configurations were assigned by NOE experiments.

(8) Bellemin-Laponnaz, S.; Le Ny, J.-P.; Dedieu, A. *Chem.—Eur. J.* **1999**, *5*, 57.

Table 3. Selective Conversion of Chiral Substrates[a]

entry	substrate	intermediate[b] (*cis* / *trans*)	product[b] (*trans* / *cis*)	yield[c]
1	 **16**	 **17** 2.2 / 1	 **18** 2.3 / 1	83%
2	 **19**	 **20** > 10 / 1	 **21** 7 / 1	82%
3[d]	 **22**	 **23** > 10 / 1	 **24** 6 / 1	79%

[a] Key: (i) 0.1 M in Et_2O at 0 °C, 2.0 equiv of vinylmagnesium bromide; (ii) rt, H_2O, 2.5 equiv of CF_3COOH. [b] Only the major isomer is depicted. [c] Combined yield of *cis* and *trans* products. [d] A 5-fold excess of CF_3COOH is used to speed up the reaction.

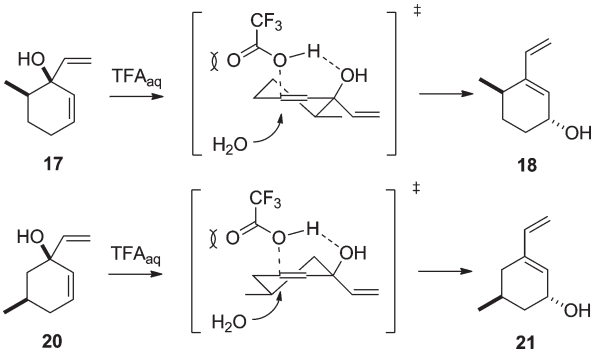
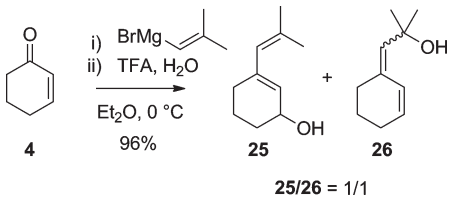


Figure 1. Proposed reaction mechanism for the diastereoselective [1,3]-hydroxy isomerization.

in the formation of a contact ion pair, which immediately is attacked by water from the opposite ring face.

Although, so far, all isomerizations have proven regioselective, some limitations must be taken into account. As outlined in Scheme 1, treatment of 2-cyclohexenone (**4**) with 2-methyl-1-propenylmagnesium bromide and subsequent addition of aqueous trifluoroacetic acid led to compounds **25** and **26** as a 1:1 mixture. This can be rationalized by assuming a significant carbenium character in the isomerization. Normally, a stereoelectronic preference for the endocyclic position is observed. If, however, the exocyclic position can stabilize a positive charge, nucleophilic attack can occur there too. A pronounced carbenium character also supports the proposed formation of a contact ion pair as intermediate (see discussion above).

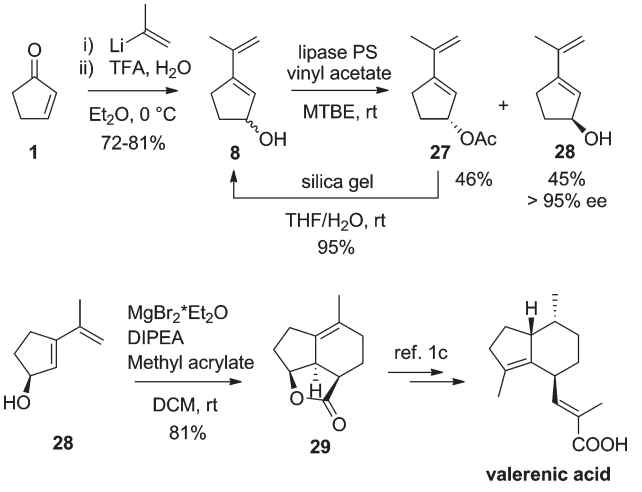
Scheme 1. Limitations[a]



[a] Key: (i) 0.1 M in Et_2O at 0 °C, 2.0 equiv of 2-methyl-1-propenylmagnesium bromide; (ii) 0 °C, H_2O, 2.5 equiv of CF_3COOH.

Finally, we highlight the usefulness of the described one-pot procedure by improving our previous synthesis of valerenic acid (see Scheme 2).[1c,9] We began with the one-pot synthesis of racemic dienol **8** (see Table 2, entries 3 and 4). Chiral resolution provided the optically enriched alcohol **28** and ester **27**.[10] The ester could easily be recycled to racemic dienol **8** by treatment with silica gel. Interestingly, during this reaction, the optical activity was completely lost,[11] indicating an S_N1 displacement of the acetate was occurring by water. With enantioenriched alcohol **28** in hand, a hydroxy-directed Diels–Alder reaction (HDDA), according to a modified protocol by the group of Barriault and co-workers, was conducted to provide tricyclic lactone **29**.[12] This compound is a

Scheme 2. Optimized Synthesis of Valerenic Acid[a]



[a] Abbreviations: TFA, trifluoroacetic acid; MTBE, methyl *tert*-butyl ether; DIPEA, diisopropylethylamine.

(9) For a different total synthesis of valerenic acid, see: Kopp, S.; Schweizer, W. B.; Altmann, K.-H. *Synlett* **2009**, *11*, 1769.

(10) Sumi, S.; Matsumoto, K.; Tokuyama, H.; Fukuyama, T. *Tetrahedron* **2003**, *59*, 8571.

(11) Proven by optical rotation: $[\alpha]^{20}_D = 0.000$.

(12) Barriault, L.; Thomas, J. D. O.; Clement, R. *J. Org. Chem.* **2003**, *68*, 2317.

key intermediate in our recently published synthesis of valerenic acid and only seven steps away from the target. The simplified access to dienol **8** shortens the route by five steps and increases the overall yield from 8% to 13% (25% if compound **27** is fully recycled).

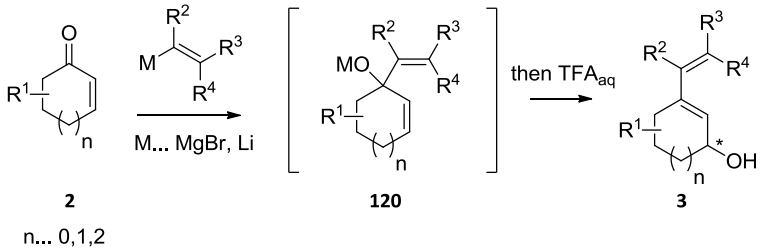
In conclusion, we have developed a selective, flexible, and scalable one-pot synthesis of optically enriched 2,4-dienols from simple cycloalkenones. The underlying [1,3]-hydroxy isomerization is simple and stereoselective. Stereochemically, it complements the well-known oxo-metal-catalyzed [1,3]-hydroxy isomerization. An application in the synthesis of valerenic acid has led to a significant reduction in the overall number of steps.

Acknowledgment. We thank H. P. Kählig and S. Felsinger for NMR analysis as well as A. Körner and F. Nasufi for HPLC analysis, all at the University of Vienna, and the Austrian Science Fund (FWF) for financial support (projects P21241-N19 and TRP 107-B11).

Supporting Information Available. Experimental procedures and analytical characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

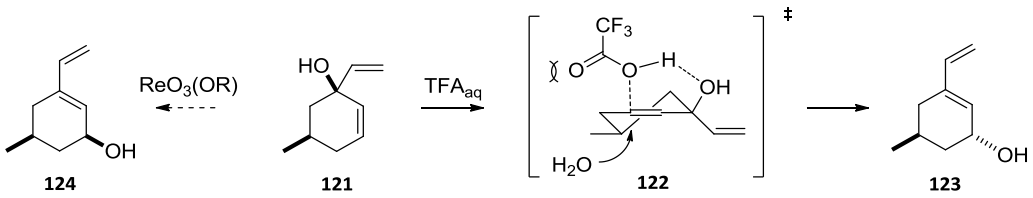
3.3 Summary

Attempts to optimize the synthesis of valerenic acid (see chapter 2) have led to the development of a novel one-pot reaction. Because of the anticipated impact of such transformations a series of simple substrates was converted in analogy to the preparation of 3-isopropenyl-2-cyclopentenol (**85**) (see also Scheme 25).



Scheme 25: Extension to other substrates.

Fortunately, the reaction was scalable and provided dienols **3** in good to excellent yields for a broad scope of substrates. Besides the conversion of non-chiral compounds, also the [1,3]-isomerization of chiral substrates has been studied. Interestingly, very selective transformations of the substrates were observed and products complementary to the metal oxo complex catalyzed isomerization were obtained (see Scheme 26).



Scheme 26: Comparison of metal oxo catalyzed and TFA catalyzed [1,3]-isomerization.

According to our proposal trifluoroacetic acid does not only protonate the tertiary alcohol, but also blocks nucleophilic attack from the *syn* hemisphere of the alcohol. Therefore the substitution of the alcohol proceeds in an anti selective S_N2' reaction.

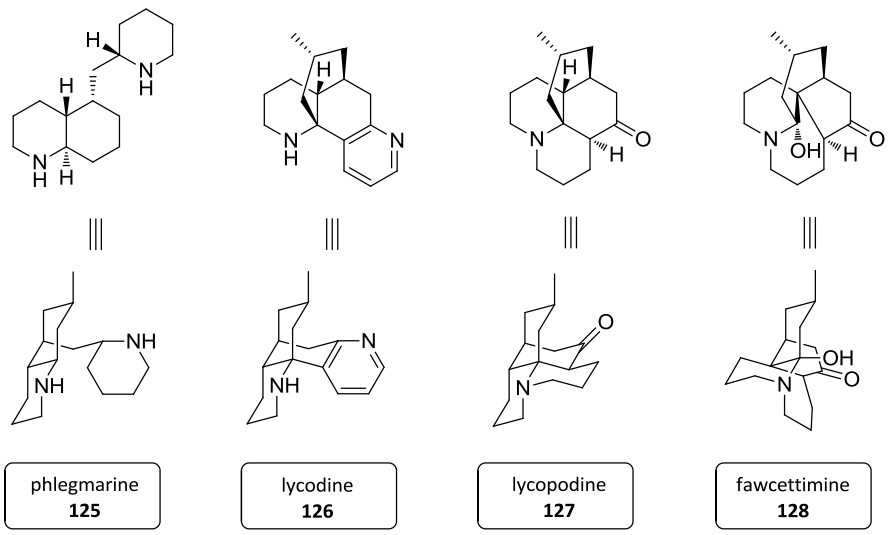
4 Total Synthesis of Lycoflexine

4.1 Introduction to Lycopodium Alkaloids

Lycopodium plants encompass a large group of nearly thousand species better known as club mosses.[36] Endemic to temperate subarctic climates they can only be found in very specialized habitats and seldom in abundance. Until today, no attempt to cultivate *Lycopodium* species has been successful. Nonetheless, *Lycopodium* species are well known because of their use in traditional folk medicine. Especially in China dried plants and extracts are applied against contusions, strains and swellings. More recently pharmacological investigations identified several constituents of *Lycopodium* to act as reversible acetyl cholinesterase inhibitor.[37,38] Eventually the most potent among them (huperzine A) has been approved as drug for treatment against Alzheimer disease.[39]

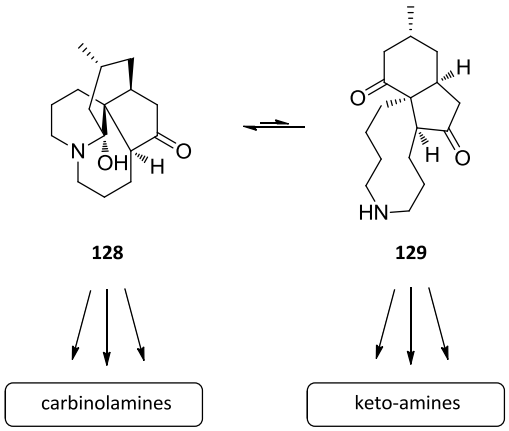
Because of their origin, nitrogen containing constituents of *Lycopodium* plants like huperzine A are called *Lycopodium* alkaloids.[40] This class of natural products includes a variety of different but structurally and biosynthetically related compounds. The first representative of this group is lycopodine (**127**), which has already been identified by Bödeker in 1881.[41] Until today more than two hundred natural products have been isolated from about fifty different species of *Lycopodium*. Despite the huge overall number nearly all of these compounds are built up by 16 or 32 carbons (monomeric / dimeric forms), respectively. They structurally feature a quinolizine, pyridine or α-pyridone based skeleton.

4.1.1 Classification of Lycopodium Alkaloids



Scheme 27: The four classes of *Lycopodium* alkaloids.

According to a proposal by Ayer *Lycopodium* alkaloids are divided into four subclasses with increasing structural complexity (see Scheme 27).[42] The group of phlegmarine related *Lycopodium* alkaloids covers the structurally simplest compounds, which cannot be placed in any other class. Pyridine or pyridone based compounds belong to the lycodine class and include the most potent acetyl cholinesterase inhibitors like the already mentioned huperzine A. The largest group, which spans more than 70 alkaloids, is named after its most important member lycopodine (**127**). Members of this group have a tetracyclic skeleton similar to lycodine (**126**), but lack the pyridine ring. The quinolizine core is annulated by an additional six membered ring instead. Finally the last group covers fawcettimine related compounds. Members of this class are formally derived by bond migration of lycopodine precursors to form a hemiaminal. As it has already been confirmed by Heathcock, fawcettimine (**128**) exists in two tautomeric forms (see Scheme 28).[43]



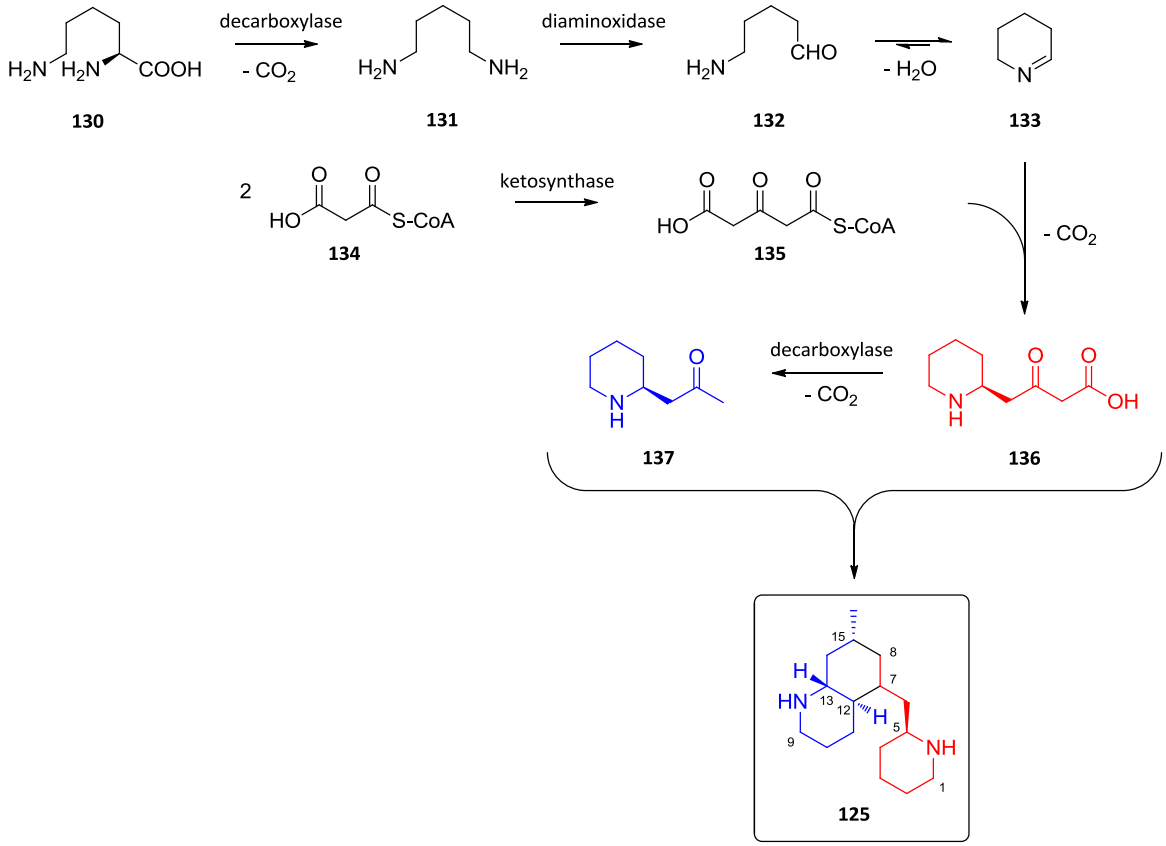
Scheme 28: The two different subclasses of fawcettimine related *Lycopodium* alkaloids.

Although the equilibrium is shifted to the left, both the carbinolamine form **128** and the keto-amine form **129** are observed. Therefore, further division of the fawcettimine class gives rise to another two different subclasses.

4.1.2 Biosynthesis of Lycopodium Alkaloids

Since more than 50 years the biosynthesis of *Lycopodium* alkaloids has been intensively studied and several revised biosyntheses have been proposed. Although most efforts concentrated on the formation of lycopodine (the most prominent member of *Lycopodium* alkaloids), the obtained results and gathered information can be easily extended to the biosynthesis of all other *Lycopodium* alkaloids as well. Already in 1968, Spenser and coworkers were able to prove by feeding experiments with ^{14}C-labeled substrates, that lysine serves as precursor of lycopodine.[44] In agreement with these

results they proposed a biosynthetic pathway, that has only slightly been alterated and extended in the following years (see Scheme 29 and Scheme 30).[45]

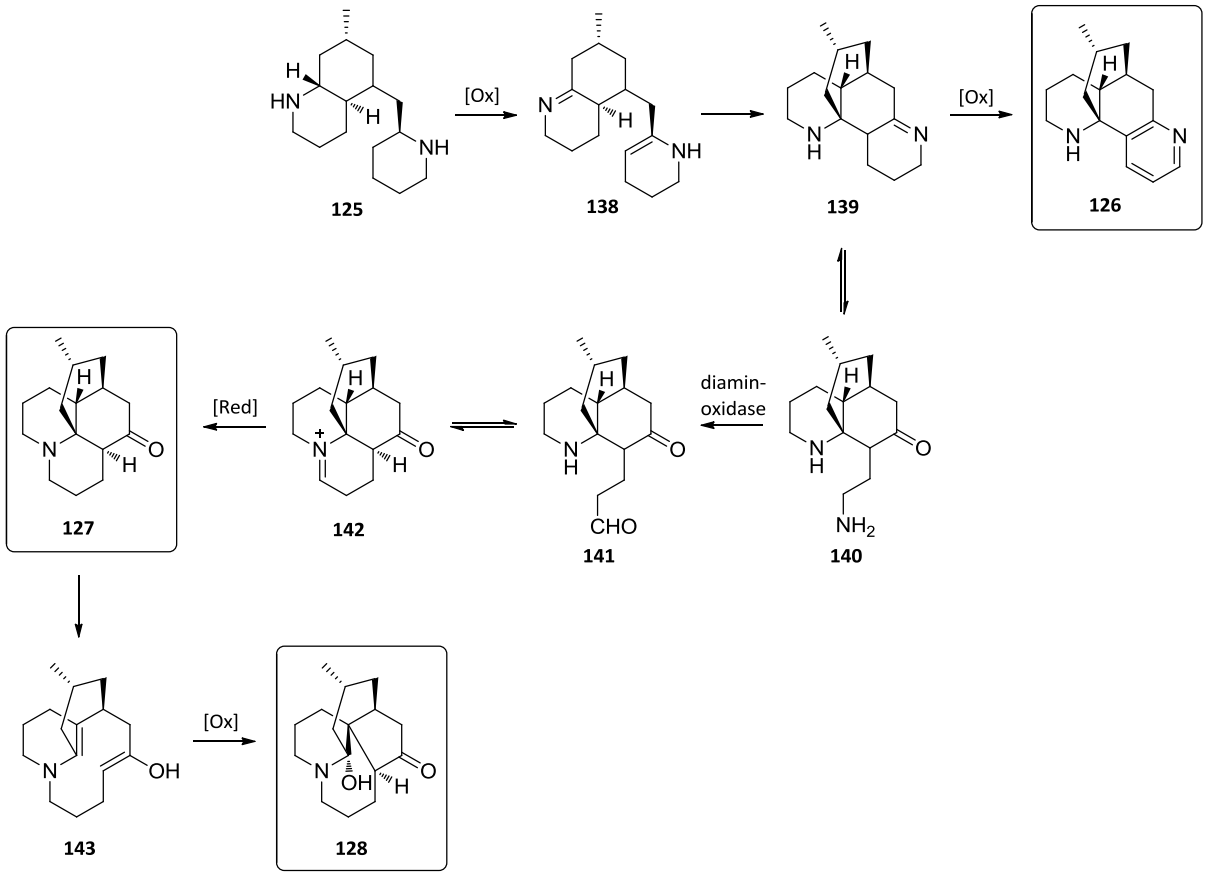


Scheme 29: Proposed biosynthesis of Phlegmarine.

As outlined in Scheme 29, the proposed biosynthesis of *Lycopodium* alkaloids starts with enzymatic decarboxylation of lysine (**130**) and oxidative degradation of one of the amino groups. The resulting aldehyde **132** is most likely labile and dehydrates to provide Δ^1-piperideine (**133**). In the next step electrophile **133** reacts with nucleophilic diketo acid **135**, which is derived by Claisen condensation of two equivalents of malonic acid derivative **134**. After decarboxylation coupling of pelletierene (**137**) with keto acid **136** provides phlegmarine (**125**) by bond formation between C7 and C12 as well as C8 and C15.

Whereas the first steps of the biosynthesis of *Lycopodium* alkaloids are well established, suggestions about the subsequent transformations to deliver lycodine, lycopodine and fawcettimine are comparatively vague (see Scheme 30).[44,46] Oxidation of phlegmarine most likely provides enamine **138**, which undergoes intramolecular nucleophilic addition to deliver the tetracyclic core of lycodine. In the next step the resulting imine **139** is either oxidized to lycodine (**126**) or transformed into amino aldehyde **141** by loss of ammonia. The latter compound undergoes dehydrative cyclization to form

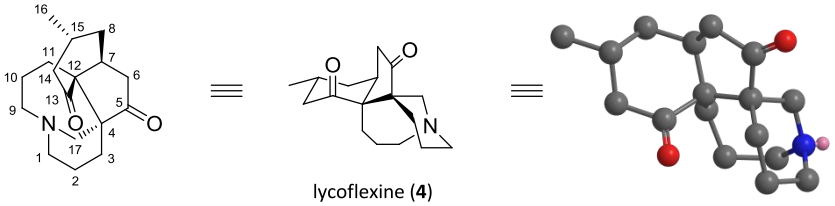
iminium cation **142**, which upon reduction provides lycopodine (**127**). Finally the formation of fawcettimine can be rationalized by fragmentation and subsequent oxidative enol enamine coupling of intermediate **143**.



Scheme 30: Proposed biosynthesis of Lycodine, Lycopodine and Fawcettimine.

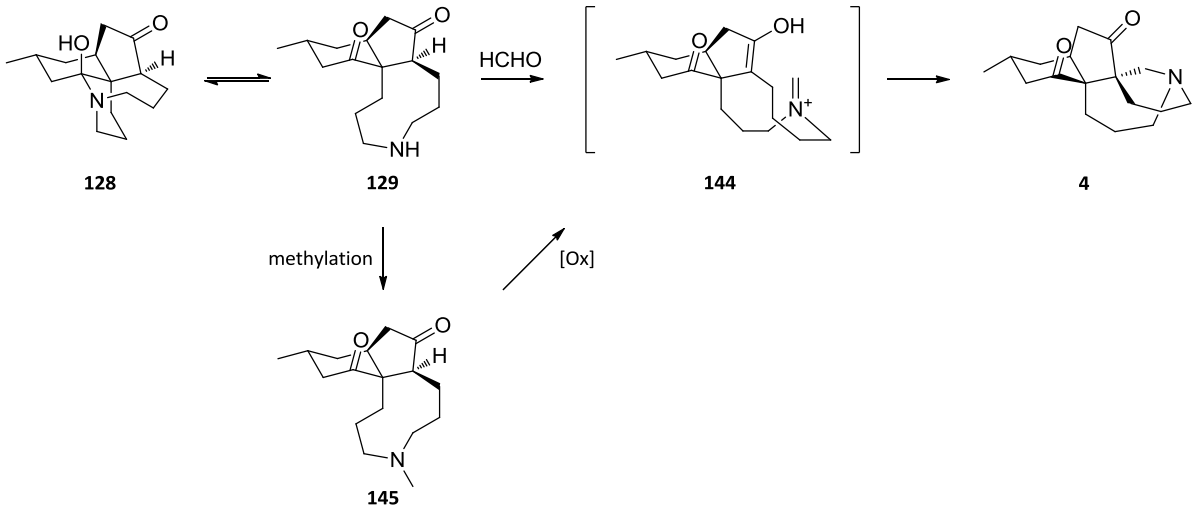
4.2 About Lycoflexine

Together with four other alkaloids (lycopodine, dihydrolycopodine, lycodoline and fawcettimine) lycoflexine (**4**) was isolated in 1973 by Ayer and coworkers from *Lycopodium clavatum* var. *inflexum*, which was collected in South Africa.[47]



Scheme 31: Structure of lycoflexine.

As depicted in Scheme 31 lycoflexine possesses an unprecedented tetracyclic core with four stereogenic centers. Noteworthy, two of them are adjacent quaternary carbons and one of the six-membered rings is spiro-annulated. Although at first sight lycoflexine and fawcettimine do not seem to be related, in fact the two compounds only differ in the methylene bridge C17. This apparent association to fawcettimine (**128**) also prompted Ayer and coworkers to propose the following biosynthesis, which is outlined in Scheme 32.[47]



Scheme 32: Proposed biosynthesis of lycoflexine.

They reasoned, that a transannular Mannich reaction of imminium species **144**, available by either oxidation of *N*-methylfawcettimine (**145**) or condensation of fawcettimine (**129**) with formaldehyde, leads to the formation of lycoflexine (**4**). This hypothesis was also supported by synthetic transformation of natural fawcettimine into lycoflexine, albeit the observed yield was only moderate.

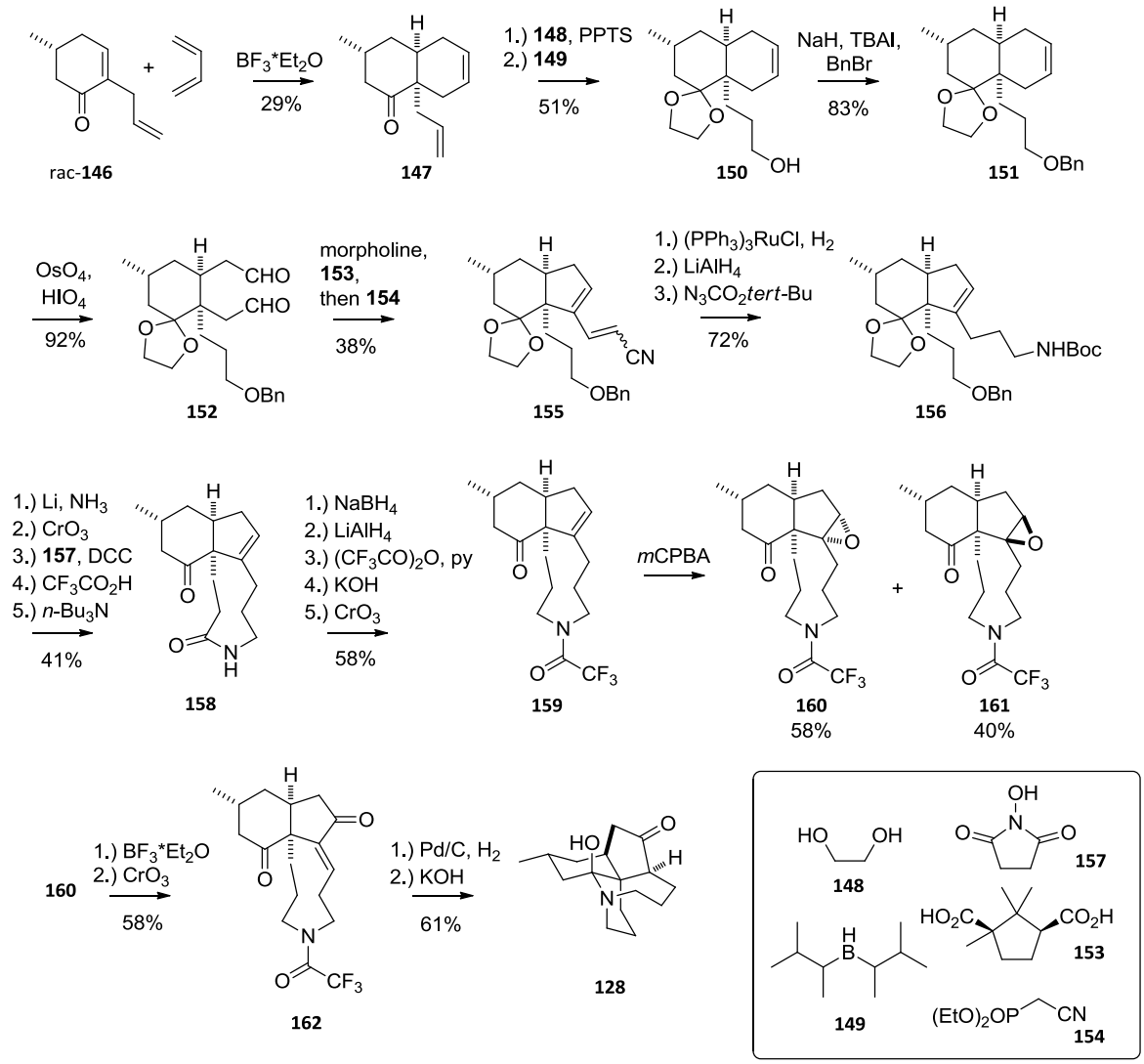
4.3 Contributions by Other Groups

Despite the unique and interesting structure of lycoflexine no total synthesis of this natural product was achieved before 2010.[8] One year after completion of the first total synthesis of lycoflexine (accomplished during this PhD thesis) a second one was published by Yang and coworkers in 2011 (see chapter 4.3.4).[48] Contrary to lycoflexine, three total syntheses and several formal total syntheses of fawcettimine, as well as the first total synthesis of fawcettidine have already been completed by the time this PhD thesis was begun. The first total synthesis of racemic fawcettimine was accomplished in 1979 by Inubushi and coworkers (see chapter 4.3.1).[49] Seven years later one of the classical *Lycopodium* alkaloid syntheses was published by the group of Heathcock[43,50] (see chapter 4.3.2) and in 2007 Toste[51] concluded the first asymmetric approach. Further syntheses of

fawcettimine were published by Mukai[52] in 2010 and Yang[48] and Lei[53] both in 2011. Also worth mentioning, the first total synthesis of fawcettidine, a *Lycopodium* alkaloid nearly identical to fawcettimine, was achieved by Dake and Kozak in 2008 (see chapter 4.3.3).[54] Very recently also a second successful approach was accomplished by Lei and coworkers.[53] Although not all of these syntheses can be discussed in detail, the following subchapters will provide an overview of the most significant contributions by other groups.

4.3.1 Total Synthesis of (+/-)-Fawcettimine by Inubushi

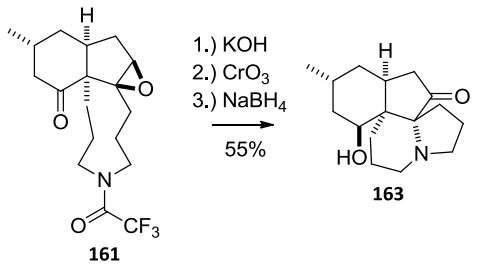
Already more than thirty years ago Inubushi and coworkers were able to complete the first total synthesis of fawcettimine (**128**).[49] An overview of the applied strategy is outlined in Scheme 33.



Scheme 33: First total synthesis of fawcettimine by Inubushi.

The sequence began with Diels-Alder reaction of racemic **146** with butadiene. Because the methyl substituent shielded the *syn* hemisphere of dienophile **146** effectively, compound **147** was obtained as single product, albeit in low yield. After protection of the carbonyl group *via* acetalization, hydroboration with disiamylborane provided the primary alcohol **150**, which was protected as benzyl ether before the double bond was cleaved to provide dialdehyde **152**. With this intermediate in hands an interesting one-pot protocol was applied to furnish cyano diene **155**. At first, aldol condensation with morpholine and camphoric acid led to an α,β-unsaturated aldehyde. Without isolation this intermediate was treated with **154** to yield compound **155.** After reduction of the less substituted double bond with Wilkinson's catalyst, treatment with $LiAlH_4$ and BOC azide afforded BOC-protected amine **156**. Macrocyclization was accomplished in a five step sequence including cleavage of the benzyl protecting group, subsequent oxidation with Jones' reagent, activation of the resulting carboxylic acid and finally intramolecular *N*-alkylation. After reduction of amide **158** the corresponding amino alcohol was treated with trifluoroacetic acid anhydride to protect the amine functionality. During the last step also esterification of the alcohol was observed, so it was treated with base to get the free alcohol again, which was oxidized with Jones' reagent to provide keto compound **159**. Unselective epoxidation of the double bond led to two diastereomers in a ratio of nearly one to one. Unfortunately, only transformation of epoxide **160** resulted in formation of an allylic alcohol, which was oxidized to get the α,β-unsaturated keto compound **162** in the next step. Finally stereoselective hydrogenation and deprotection furnished racemic fawcettimine (**128**).

Inubushi and coworkers accomplished the first total synthesis of fawcettimine in 24 steps starting from literature known **146**. Unfortunately, the yield of several steps was only moderate, so in summary the overall yield of this approach was below 1 %. Interestingly, the unselective epoxidation of **159** had also a positive side effect, because the side product **161** could be used to synthesize 8-deoxyserratinine (**163**), which is another *Lycopodium* alkaloid (see Scheme 34).[49]



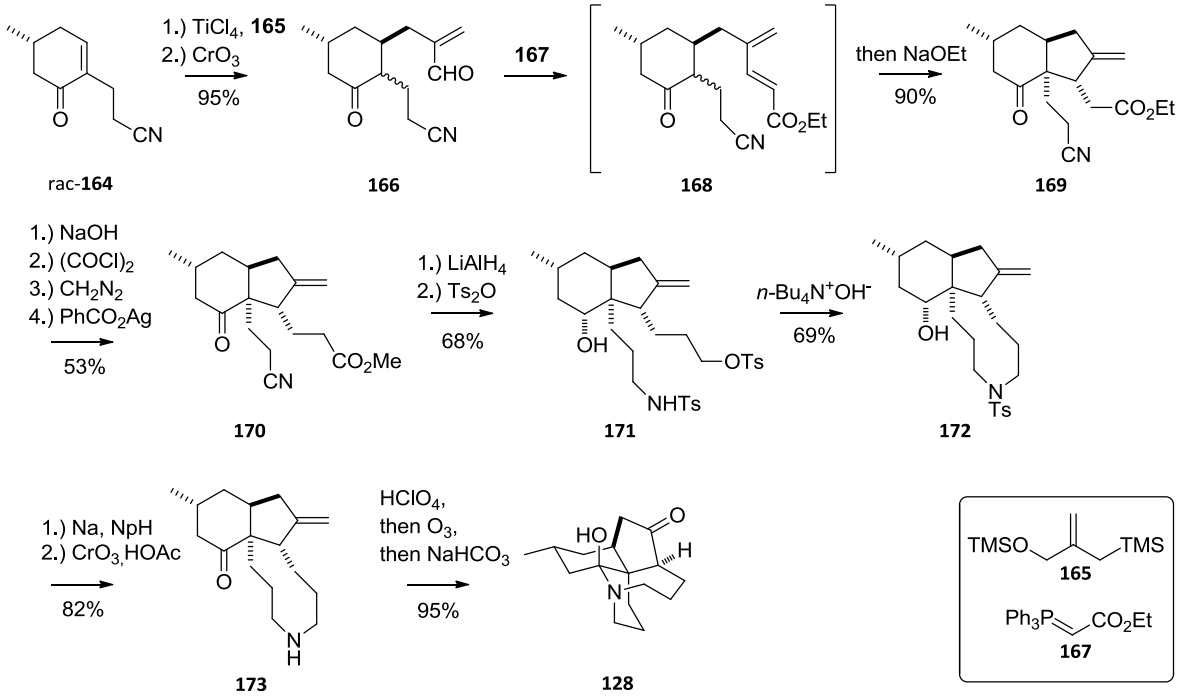
Scheme 34: Conversion of epoxide **161** to 8-deoxyserratinine.

Under basic conditions the protecting group was cleaved and an intramolecular opening of the epoxide induced. Oxidation of the alcohol and selective reduction of one carbonyl group eventually

delivered 8-deoxyserratinine (**163**). Noteworthy, this approach provided the first synthesis of 8-deoxyserratinine as well.

4.3.2 Total Synthesis of (+/-)-Fawcettimine by Heathcock

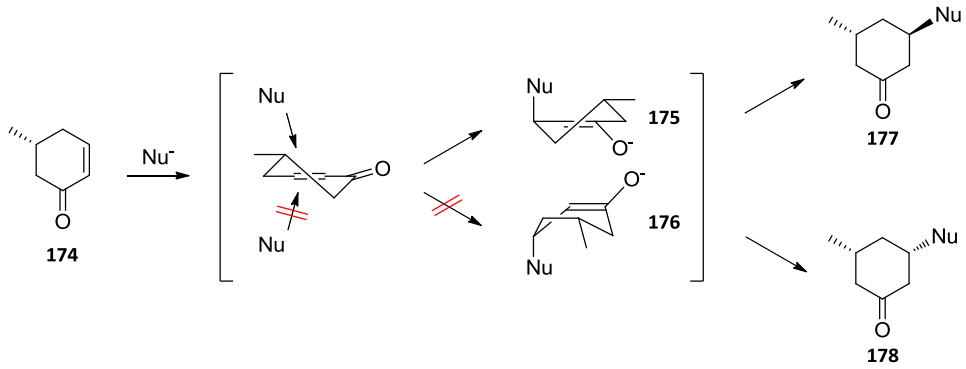
Several years later, also the group of Heathcock accomplished a straight forward synthesis of fawcettimine (see Scheme 35).[43,50]



Scheme 35: Total synthesis of fawcettimine by Heathcock.

The synthesis began with a Sakurai reaction of cyano enone **164** with allylsilane **165**. After oxidation of the resulting alcohol, Wittig olefination afforded unsaturated ester **168**, which was immediately treated with base to generate the five-membered ring in a one-pot operation. Sidechain-elongation was implemented in form of saponification of ester **169** and subsequent Arndt-Eistert homologation to provide cyano ester **170**. Threefold reduction and selective twofold tosylation of the resulting amino diol afforded ditosylate **171**, which was treated with base to generate the nine-membered macrocycle of **172**. After cleavage of the tosyl group and oxidation under acidic conditions, ozonolysis of the resulting amine **173** and epimerization under basic conditions finally provided racemic fawcettimine in a remarkably short sequence of 13 steps and an overall yield of 17 %.

In summary Heathcock and coworkers devised a very practical and high yielding strategy to provide fawcettimine. Although it was not the first total synthesis, this approach is one of the most significant synthetic contributions in this field by now. Worth mentioning, this group was also the first to apply the diastereoselective 1,4-addition to substituted α,β-unsaturated cyclohexenones.[55] In stark contrast to thermodynamics, cuprate or allylsilane addition afforded in most cases nearly exclusively the less stable product **177**, whereas the formation of the all equatorial product **178** was almost completely suppressed (see Scheme 36).



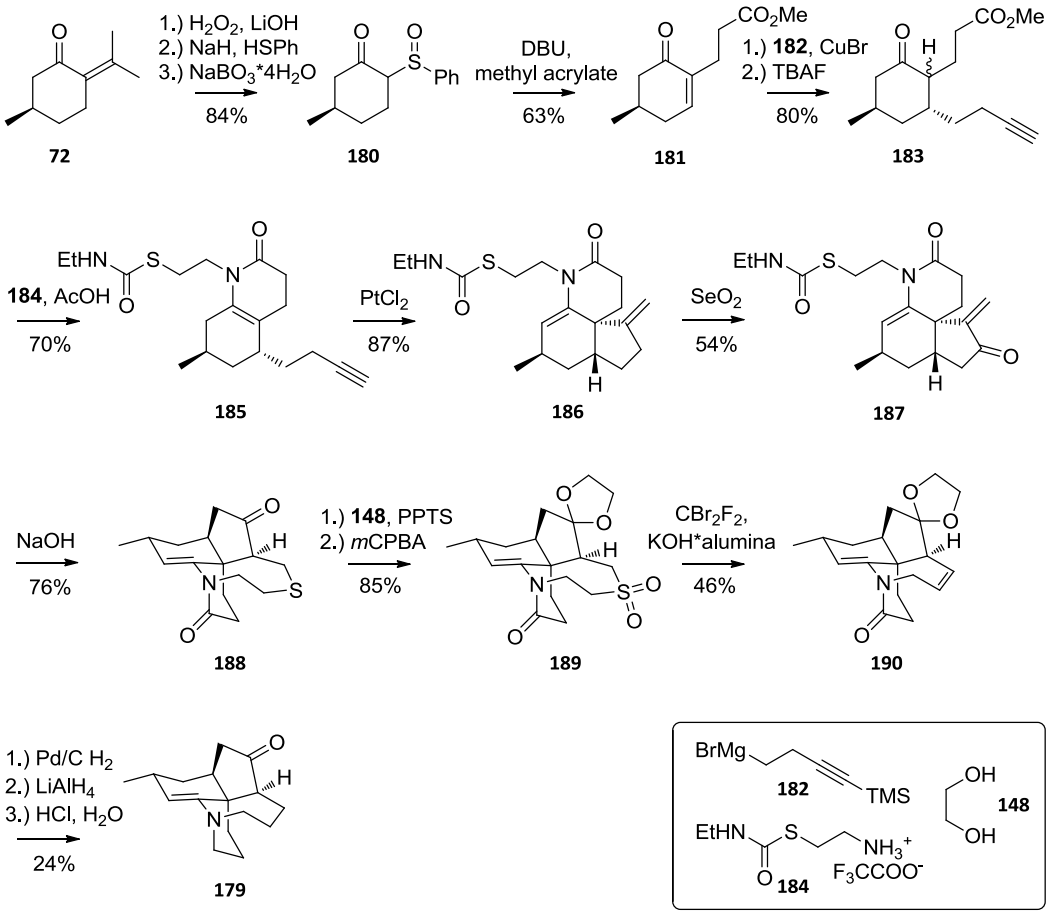
Scheme 36: Selective 1,4-addition.

This was rationalized by the unfavorable intermediate boat conformation **176**, which would lead to the thermodynamically more stable all equatorial product **178**. Because such transformations generally provide simple access to intermediates suitable for the synthesis of fawcettimine related *Lycopodium* alkaloids, similar strategies have been applied in various other approaches towards *Lycopodium* alkaloids (including the synthesis of lycoflexine developed during this PhD thesis).

4.3.3 Total Synthesis of Fawcettidine by Dake

In nature fawcettidine (**179**) is most probably derived by dehydration of fawcettimine. The first total synthesis of this interesting *Lycopodium* alkaloid was completed by Dake and Kozak in 2008.[54] Dake's approach started with epoxidation of commercially available pulegone (**72**) and subsequent treatment of the epoxide with thiophenol to afford acetone and the corresponding thiophenol ether, which was oxidized to provide sulfoxide **180**. Deprotonation and 1,4-addition to methyl acrylate, followed by heat induced elimination of the sulfoxide, delivered cyclohexenone **181**. In the next step regioselective cuprate addition and subsequent cleavage of the TMS group furnished alkyne **183**. After amide formation with fragment **184**, platinum dichloride catalyzed cyclization afforded the desired tricylic amide **186** in the first key step of this sequence. Allylic oxidation of **186** led to the

α,β-unsaturated keto compound **187**, which was used as Michael acceptor in the following macrocyclization. After protection of the carbonyl group, oxidation furnished sulfone **189**. Ramberg-Bäcklund reaction of this substrate provided compound **190**, which was converted into fawcettidine (**179**) in a three step sequence including hydrogenation reduction and removal of the protecting group. A detailed overview of the synthesis of fawcettidine is presented in Scheme 37.

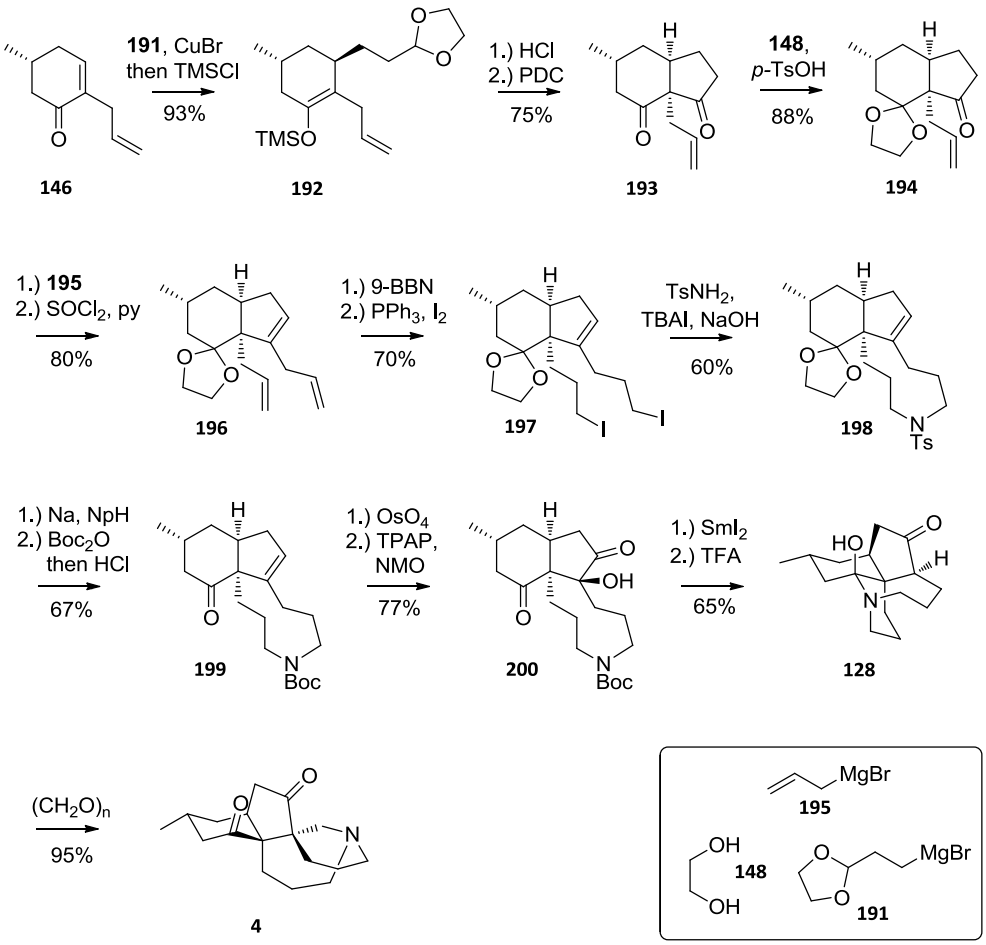


Scheme 37: First total synthesis of fawcettidine by Dake.

In conclusion, Dake and Kozak developed a very elegant synthetic strategy that applies modern methodology to approach a long known class of substances. Contrary to most of the other *Lycopodium* syntheses a remarkable thio-Michael/Ramberg-Bäcklund sequence was used instead of *N*-alkylation to provide the seven-membered ring of fawcettidine. Although the overall yield with about 1 % is only moderate, the number of steps starting from inexpensive pulegone is reasonable (16 steps).

4.3.4 Total Synthesis of Lycoflexine by Yang

One year after the completion of the first total synthesis of lycoflexine by our group, Yang and coworkers published a different approach to the same molecule. A detailed overview of the synthesis can be seen in Scheme 38.[48]



Scheme 38: Total synthesis of lycoflexine by Yang.

As starting material Yang and coworkers chose **146**, which had already been used by the group of Heathcock in their synthesis of fawcettimine.[43,50] Regioselective cuprate addition and subsequent treatment of the resulting enolate provided silyl enol ether **192**. By means of an intramolecular aldol reaction this substrate led to the formation of an alcohol that was further oxidized to yield diketo compound **193**. After selective protection of one carbonyl group, Grignard addition and subsequent dehydration furnished diene **196**. With this compound in hands, hydroboration of both double bonds and Appel reaction of the resulting hydroxy groups provided diiodide **197**. Treatment of this compound with tosylamide led to macrocyclization. Subsequent removal of the tosyl group was followed by protection of the resulting amine as carbamate and cleavage of the acetal furnished

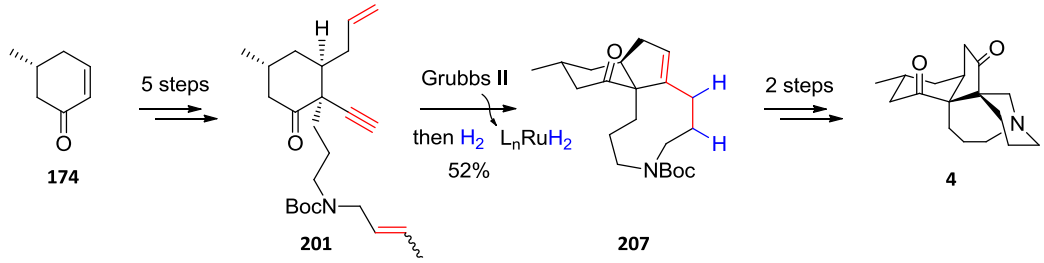
compound **199**. Probably to avoid an endgame that has been used by other groups, a rather lengthy four step sequence including dihydroxylation of the double bond, oxidation of the secondary alcohol and removal of the redundant alcohol by samarium diiodide was used to furnish fawcettimine (**128**). Finally fawcettimine was transformed into lycoflexine (**4**) in a way very similar to the final step of our synthesis and in agreement with the already discussed biosynthetic proposal by Ayer and coworkers.[8,47]

The strategy applied by Yang and coworkers has some similarities to known synthetic strategies towards *Lycopodium* alkaloids. Although mostly based on well known and long established methodologies, this approach appears robust and avoids pricey reagents to a great extent. A sequence of 16 steps was needed to provide lycoflexine from literature known compound **146** with 7 % overall yield.

4.4 First Total Synthesis of Lycoflexine

4.4.1 Introduction

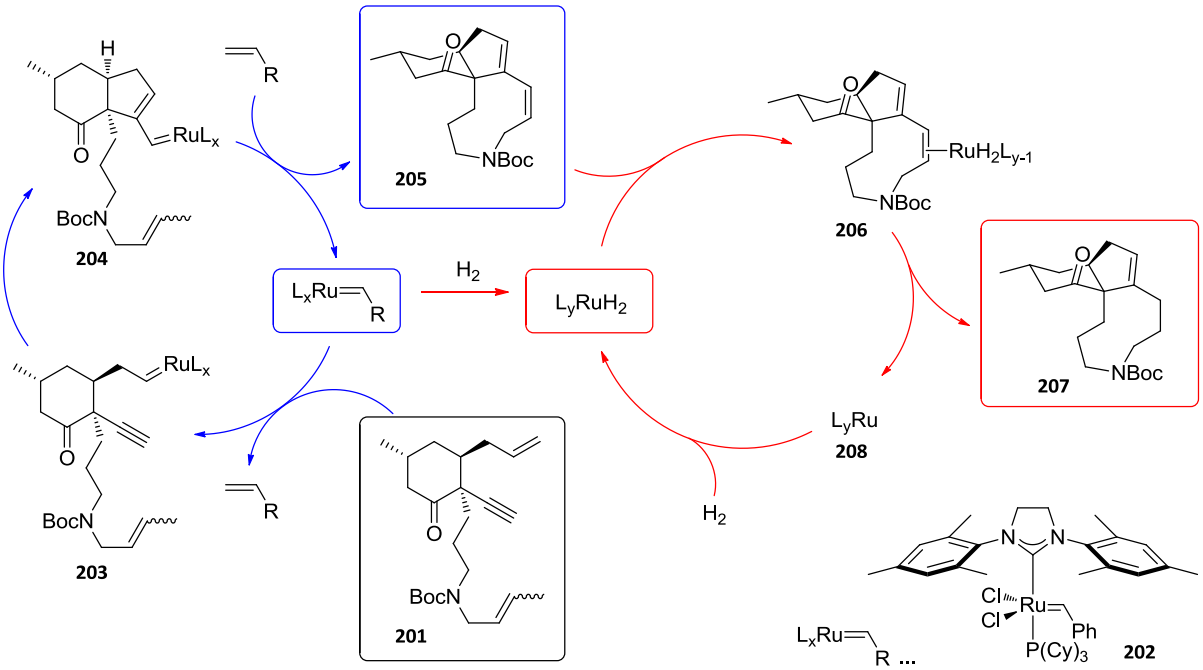
In 2010 the first total synthesis of lycoflexine developed during this PhD thesis was completed. This approach was focused on the step count and originality of the individual steps (see Scheme 39).



Scheme 39: First total synthesis of lycoflexine.

A highly concise sequence of five steps (discussed in more detail in the following publication) furnished key intermediate **201**. In the subsequent tandem catalyzed reaction, which combines an ene-yne-ene RCM and a selective hydrogenation, the latter compound was transformed into tricyclic carbamate **207** in a single step. As the following communication does not include an elaborate discussion of the keystep, an illustrative overview is given in Scheme 40. The first catalytic cycle starts with selective activation of the less substituted double bond of substrate **201** by Grubbs' second generation catalyst (**202**). For kinetic reasons the subsequent ene-yne reaction with the triple bond is much faster than the corresponding reaction with the second double bond, therefore intermediate

204 is formed exclusively.[56] Because the subsequent intramolecular metathesis reaction is preferred over cross metathesis of carbene **204** with starting material **201**, also the macrocycle of diene **205** is closed and the catalytic species regenerated. After complete conversion of precursor **201** into substrate **205** the argon atmosphere has to be exchanged for dihydrogen. This results in the formation of a new catalytic species (L_yRuH_2), which is a selective hydrogenation catalyst.[57] Consequently the catalyst binds to the less substituted double bond to form complex **206**, which finally is hydrogenated to form the desired product **207**.



Scheme 40: Keystep of the synthesis of lycoflexine.

With this compound in hands, just two steps were missing to complete the synthesis of lycoflexine.

For a more extensive description of the individual steps, specific reaction conditions and experimental details see the following communication.

4.4.2 Synthesis of the Lycopodium Alkaloid (+)-Lycoflexine

Ramharter, J.; Weinstabl, H.; Mulzer J. *J. Am. Chem. Soc.* **2010**, *132*, 14338

The supporting information of this communication includes experimental and analytical data of all discussed compounds. This data can be found in chapter 5.3.

J|A|C|S COMMUNICATIONS

Published on Web 09/24/2010

Synthesis of the Lycopodium Alkaloid (+)-Lycoflexine

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Abstract: The first total synthesis of (+)-lycoflexine (**1**), a constituent of *Lycopodium clavatum* var. *inflexum*, has been accomplished in eight steps with 13% overall yield. Our synthesis covers four one-pot reactions, including a tandem Sakurai/aldol sequence, a novel hydroboration/oxidation procedure, a deprotection/transannular Mannich reaction, and as a highlight, a tandem catalysis cascade combining an enynene ring-closing metathesis and a selective hydrogenation.

Lycopodium alkaloids[1] are a huge family of diverse but structurally related compounds (see Figure 1 for some examples) with impressive and challenging structures and interesting biological activities, such as acetylcholinesterase inhibition [e.g., huperzine A (**2**),[2] lycojapodine A (**3**),[3] or sieboldine A[4]].

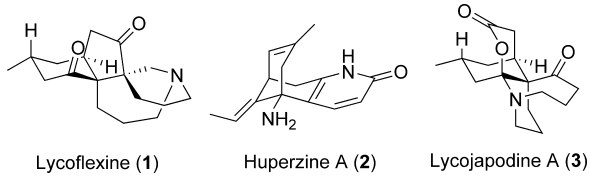
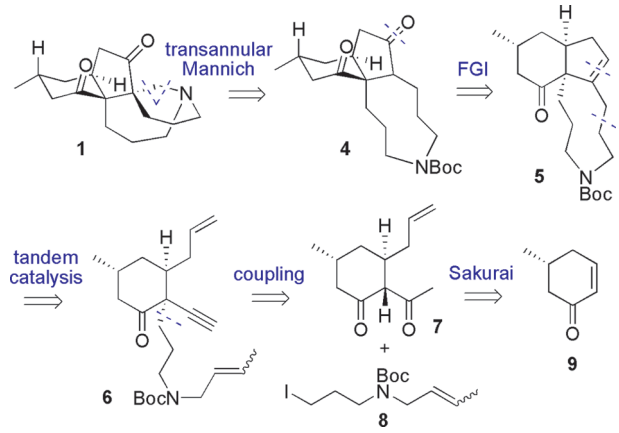


Figure 1. Selected *Lycopodium* alkaloids.

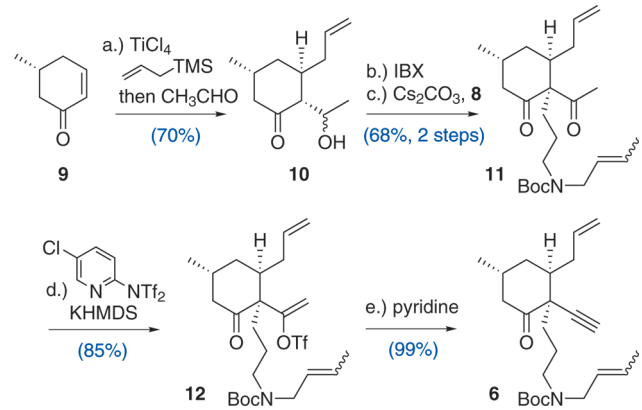
Lycoflexine (**1**) (also known as lycobergine) belongs to the class of fawcettimine-related alkaloids and was isolated by Ayer *et al.*[5] in the early 1970s by extraction of *Lycopodium clavatum* var. *inflexum* collected in the Eastern Transvaal (Republic of South Africa). Its structure consists of an exceptional tetracyclic carbon−nitrogen skeleton including a spiro-annulated six-membered ring and four stereogenic centers, of which two are adjacent quaternary carbons. Despite the interesting, complex molecular architecture of lycoflexine, no total synthesis has been reported to date.

Scheme 1. Retrosynthetic Analysis



Our retrosynthetic analysis of lycoflexine (**1**) is outlined in Scheme 1. The final step of our synthesis refers to the biosynthetic proposal of Ayer *et al.*[5] As a suitable substrate for such a conversion, we identified the tricyclic diketo compound **4**, which can be generated from substrate **5**.[6] The latter compound can be accessed via an enynene ring-closing metathesis (RCM) reaction of precursor **6**, which is easily obtained from diketone **7** derived from the well-known optically active enone **9**.[7]

Scheme 2. Synthesis of Precursor 6[a]



[a] Conditions: (a) (i) $TiCl_4$, allyltrimethylsilane, DCM, −78 °C; (ii) acetaldehyde, 70%. (b) IBX, EtOAc, reflux. (c) Cs_2CO_3, **8**, DMF, −15 °C, 68% (two steps). (d) Comins' reagent, KHMDS, THF, −78 °C, 85%. (e) Pyridine, 60 °C, 99%.

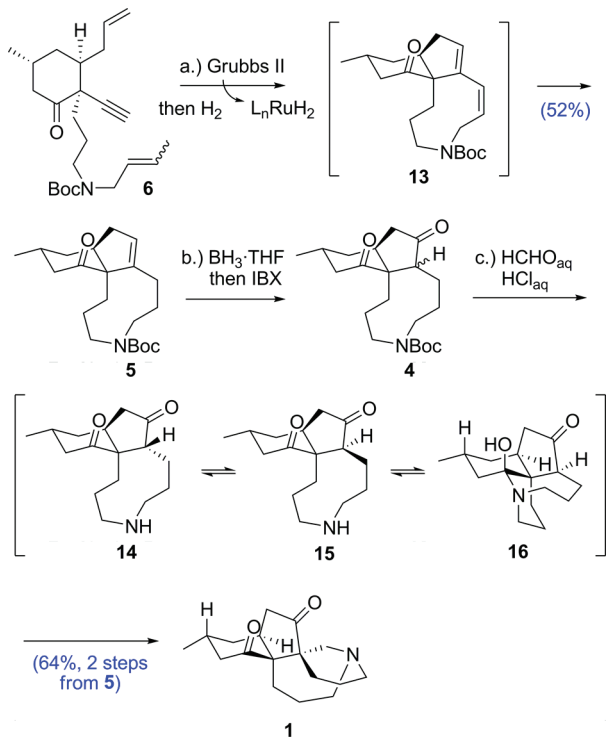
As is depicted in Scheme 2, the synthesis of key intermediate **6** started with a tandem Sakurai/aldol sequence that converted enone **9** into alcohol **10** as an inconsequential diastereomeric mixture.[8] After mild oxidation with IBX,[9] the resulting diketo compound **7** was alkylated with iodocarbamate **8**[10] to provide compound **11** with satisfying yield. After some optimization, triflation of the less-hindered carbonyl moiety was achieved with Comins' reagent.[11] Treatment of the resulting vinyl triflate **12** with pyridine at elevated temperature finally yielded dienyne **6**.[12]

In our first attempts, the envisaged enynene RCM was carried out under standard conditions with Grubbs' second-generation catalyst.[13] Although the formation of the desired tricyclic diene **13** was observed, the yield was only slightly higher than 30%. As no other byproducts could be isolated, we rationalized that the diene is probably of moderate stability and prone to decomposition. On the basis of Grubbs' findings that metathesis catalysts can be converted into active hydrogenation catalysts by treatment with dihydrogen,[14,15] we decided instead to attempt a tandem catalysis sequence and selectively hydrogenate the less-substituted double bond in situ. Gratifyingly, the desired tricyclic carbamate **5** was formed in 52% yield from **6** (Scheme 3).

To complete our synthesis, only two steps were missing. Direct oxidation of organoboranes to the corresponding ketones is known,

10.1021/ja107533m

Scheme 3. Final Steps toward Lycoflexine (**1**)[a]



[a] Conditions: (a) (i) Grubbs' second-generation (20 mol %), 1,2-dichloroethane, reflux; (ii) H_2, 10 atm, 70 °C, 52%. (b) (i) BH_3·THF, THF, 50 °C; (ii) IBX, EtOAc, reflux. (c) HCHO(aq), 0.5 M HCl, EtOH, reflux, 64% (two steps).

though mostly based on rather aggressive and toxic chromium reagents.[16] We thus developed a novel protocol that allowed us to oxidize the organoborane in situ with IBX to obtain an inconsequential diastereomeric mixture of diketo compounds **4**. It is noteworthy that both diastereomers also can be used to synthesize fawcettimine (**16**), another prominent member of the *Lycopodium* alkaloid family.[17] Our total synthesis of lycoflexine was concluded by a final tandem reaction. The *N*-Boc protecting group was removed using dilute aqueous HCl, and by analogy to the biomimetic conversion of fawcettimine to lycoflexine, excess formaldehyde was used to generate an iminium species, which smoothly underwent a transannular Mannich reaction to furnish (+)-lycoflexine (**1**).[18,19]

The identity of our compound with authentic lycoflexine was established by comparison with the spectroscopic data (^{1}H and ^{13}C NMR as well as CD) kindly provided by Professor Takayama, who had reisolated and characterized the compound.[20] In this way, the absolute configuration of **1** also was confirmed by total synthesis.

In conclusion, we have achieved the first total synthesis of (+)-lycoflexine. The extensive use of tandem and one-pot reactions (Sakurai/aldol, enynene RCM/hydrogenation tandem catalysis, hydroboration/oxidation, *N*-Boc deprotection/transannular Mannich cyclization) makes the sequence remarkably concise and efficient (eight steps from **9** with an overall yield of 13%). It is flexible and therefore should be suitable for the synthesis of several other *Lycopodium* alkaloids as well.

Acknowledgment. We are very grateful to Professor Hiromitsu Takayama of Chiba University for providing us spectroscopic data for authentic lycoflexine. We thank S. Felsinger, L. Brecker, and H. P. Kählig for NMR analysis, R. Konrat and G. Platzer for CD spectra, and R. Schuecker for technical support, all at the University of Vienna.

Supporting Information Available: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Iodocarbamate **8** was prepared from *N*-Boc-protected allylamine in two steps and 52% overall yield (see the Supporting Information for more details).
(11) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.
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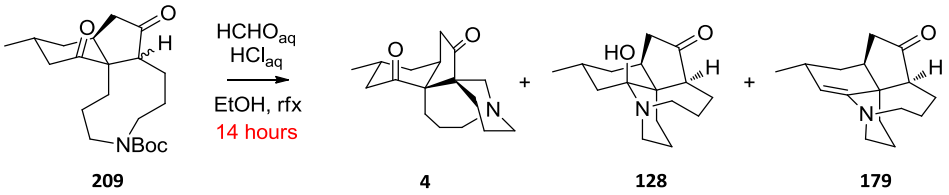
JA107533M

4.5 Total Syntheses of Fawcettimine and Fawcettidine

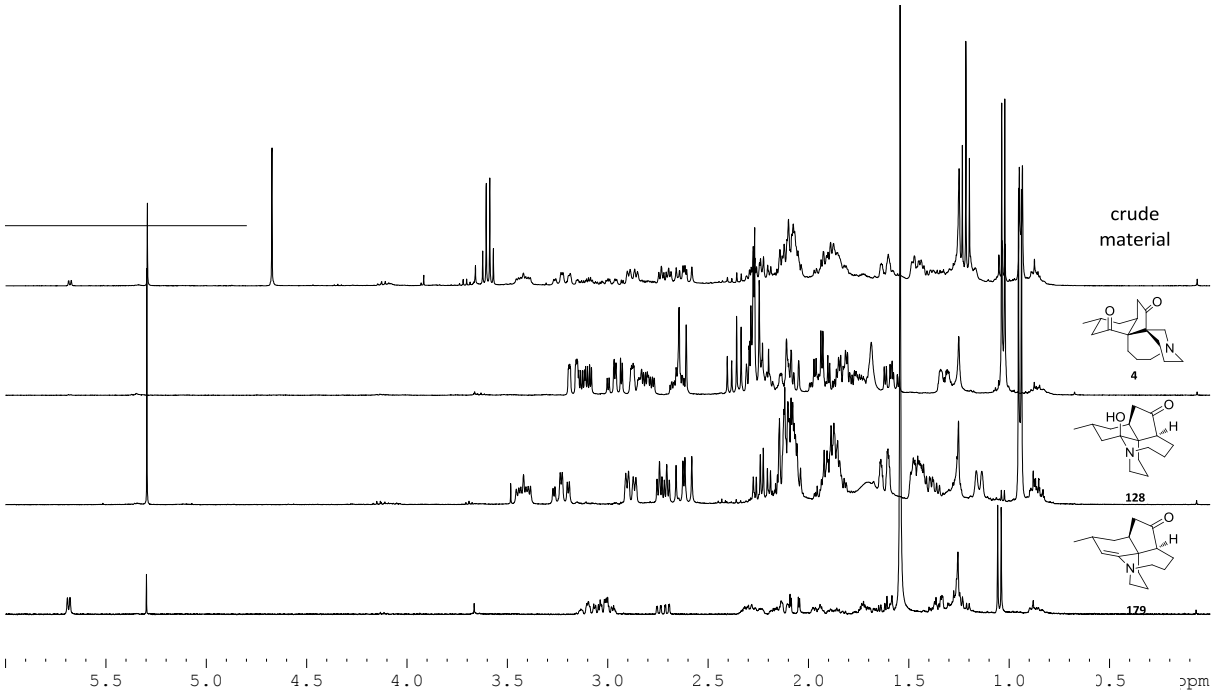
To extend the scope of the synthetic strategy presented in chapter 4.4, also two other *Lycopodium* alkaloids were synthesized. As those results have not been published yet, a short summary is given in this chapter.

During optimization of the last step of the synthesis not only lycoflexine was obtained, but also the formation of two other *Lycopodium* alkaloids was observed (see Scheme 41).



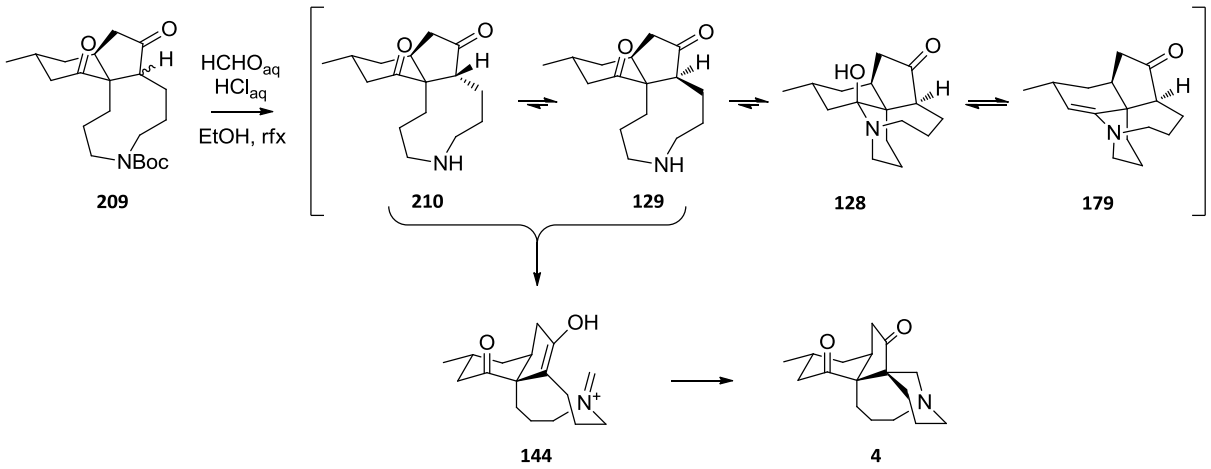
Scheme 41: Three *Lycopodium* alkaloids from the same precursor.

To achieve full conversion of carbamate **209** into lycoflexine (**4**), a prolonged reaction time of about 48 hours was needed. However, when the reaction was quenched after 14 hours, a complex mixture was obtained. After careful purification and separation by column chromatography, three different *Lycopodium* alkaloids were isolated. ^{1}H-NMR spectra of the crude material and the individual *Lycopodium* alkaloids are depicted in Scheme 42.



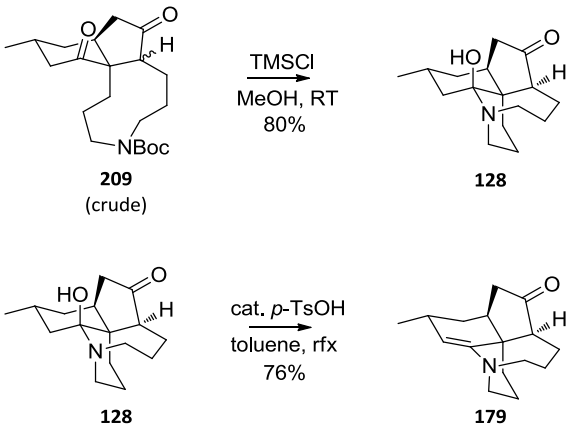
Scheme 42: ^{1}H-NMR reveals lycoflexine, fawcettimine and fawcettidine.

As expected, one of them was lycoflexine, but also fawcettimine and small amounts of fawcettidine were obtained. A mechanistic rationalization for the formation of the latter two compounds is depicted in Scheme 43.



Scheme 43: Mechanistic considerations about the formation of lycoflexine.

Obviously, acid induced cleavage of the BOC-group provides a diastereomeric mixture of amines **210** and **129**. As Heathcock has already noticed, diastereomer **210** is thermodynamically less stable than the keto-amine form of fawcettimine **129**.[43] Consequently, intermediate **210** is rapidly epimerized under acidic conditions to provide the keto-amine form of fawcettimine (**129**). In the next step of this cascade the resulting natural product is either converted in a biomimetic Mannich reaction to deliver lycoflexine (**4**) or dehydrated to furnish fawcettidine (**179**). Noteworthy, also the dehydration of fawcettimine seems to be reversible, if an aqueous acid is used. Therefore, all intermediates are in equilibrium and only the final transannular Mannich reaction is irreversible. Consequently, a prolonged reaction time leads to the formation of lycoflexine (**4**) as sole product.



Scheme 44: Synthesis of fawcettimine and fawcettidine.

Nonetheless, the temporary formation of two other natural products encouraged us to attempt the selective synthesis of fawcettimine (**128**) and fawcettidine (**179**) as well (see Scheme 44). To achieve the synthesis of both compounds TMSCl was added to a methanolic solution of carbamate **208**. The *in situ* generated hydrochloric acid caused deprotection and epimerization to furnish fawcettimine (**128**) in good yield. Treatment of this natural product with sulfonic acid and removal of water eventually provided fawcettidine (**179**) as single product in a final biomimetic transformation.

4.6 Summary

In conclusion, we have accomplished the first total synthesis of (+)-lycoflexine in eight steps starting from literature known (*R*)-5-methyl-2-cyclohexenone with an overall yield of 13 %. Incorporation of several tandem and one-pot reactions has provided a highly concise and flexible general approach towards *Lycopodium* alkaloids, which has led to the total synthesis of two additional *Lycopodium* alkaloids (fawcettimine and fawcettidine). With eight and nine steps, respectively, we have developed by far the shortest approach towards fawcettimine related *Lycopodium* alkaloids up to date (see also Table 2).

Table 2: Comparison of known total syntheses of lycoflexine, fawcettimine and fawcettidine.

	year	selectivity	lycoflexine	fawcettimine	fawcettidine	steps	overall yield
PhD thesis	2010	(+)	x			8	13%
Yang	2011	(+)	x			16	7%
Inubushi	1979	(+/-)		x		24	<1%
Heathcock	1983	(+/-)		x		13	17%
Toste	2007	(+)		x		13	15%
Mukai	2010	(+)		x		27	1%
Yang	2011	(+)		x		15	7%
Lei	2011	(+)		x		12	6%
PhD thesis	2011	(+)		x		8	13%
Dake	2008	(+)			x	16	1%
Lei	2011	(+)			x	12	11%
PhD thesis	2011	(+)			x	9	10%

Besides the advantageous number of steps, the synthetic strategy developed during this PhD thesis also ranges among the highest yielding syntheses of these three *Lycopodium* alkaloids. Remarkably,

Heathcock's total synthesis of fawcettimine in 1983 is still ranking highest with respect to its overall yield of 17 %.

5 Supporting Information

5.1 Total Synthesis of Valerenic Acid, SI

^{1}H-NMR and ^{13}C-NMR spectra of all compounds discussed in chapter 2.6.2 (*From Planning to Optimization: Total Synthesis of Valerenic Acid and some Bioactive Derivatives*) are depicted in the following supporting information.

From Planning to Optimization:

Total Synthesis of Valerenic Acid and some Bioactive Derivatives

Supporting Information

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Austria

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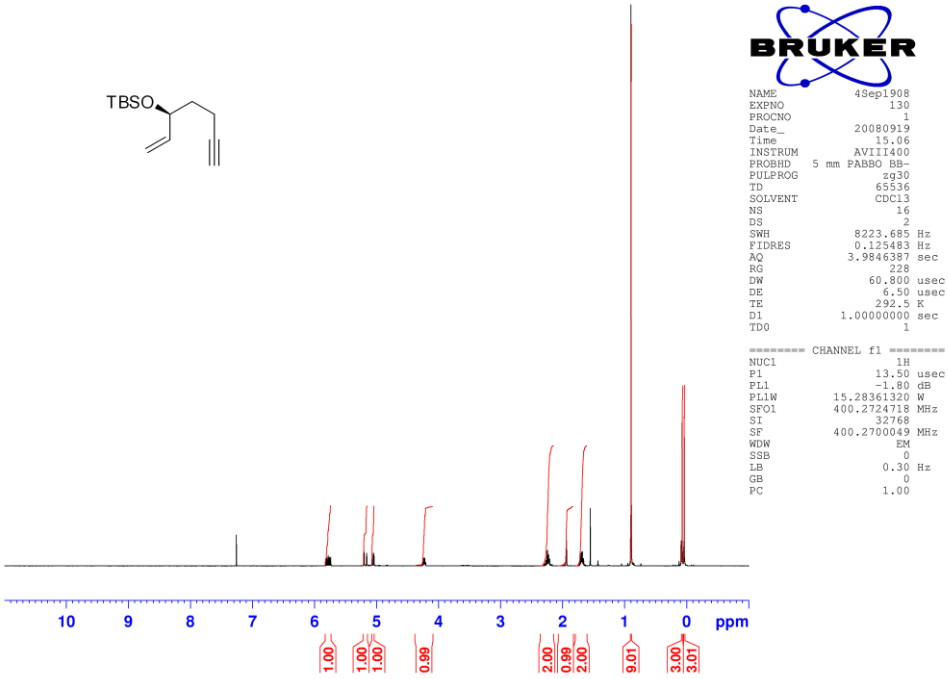
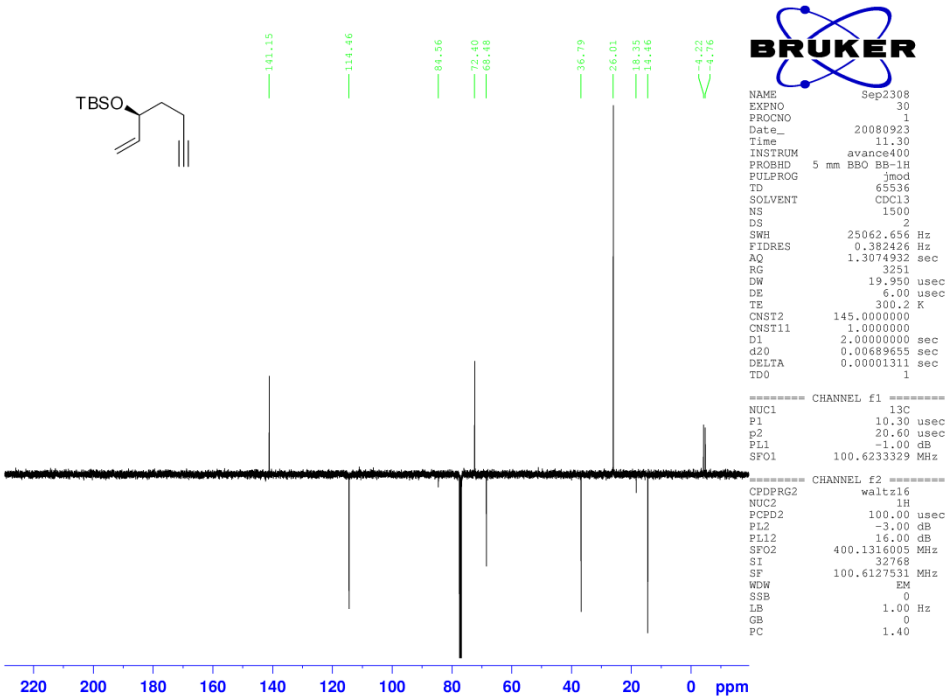
Table of Contents:

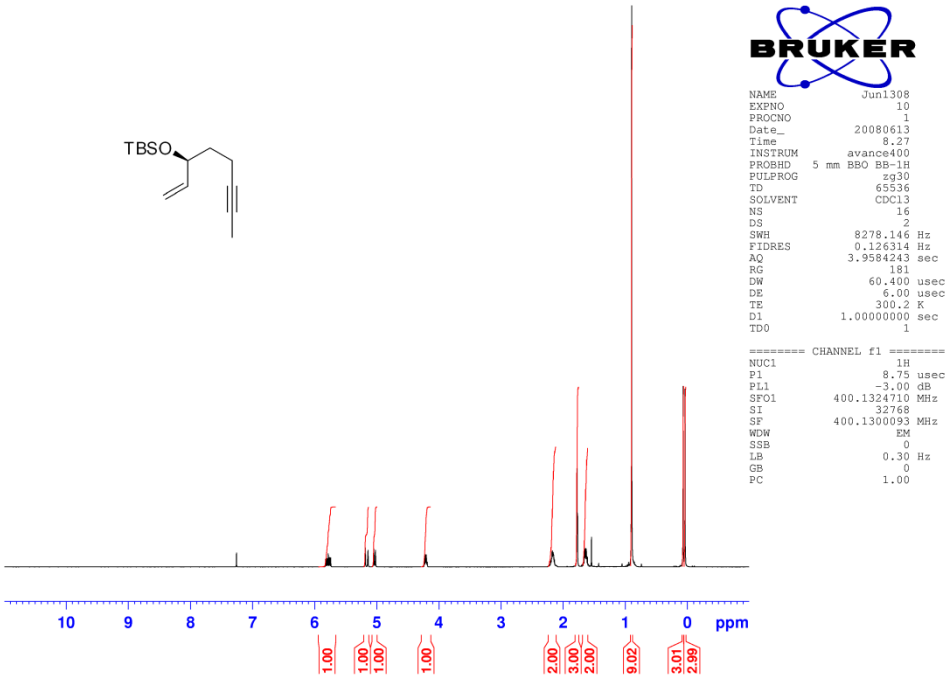
1. NMR Spectra

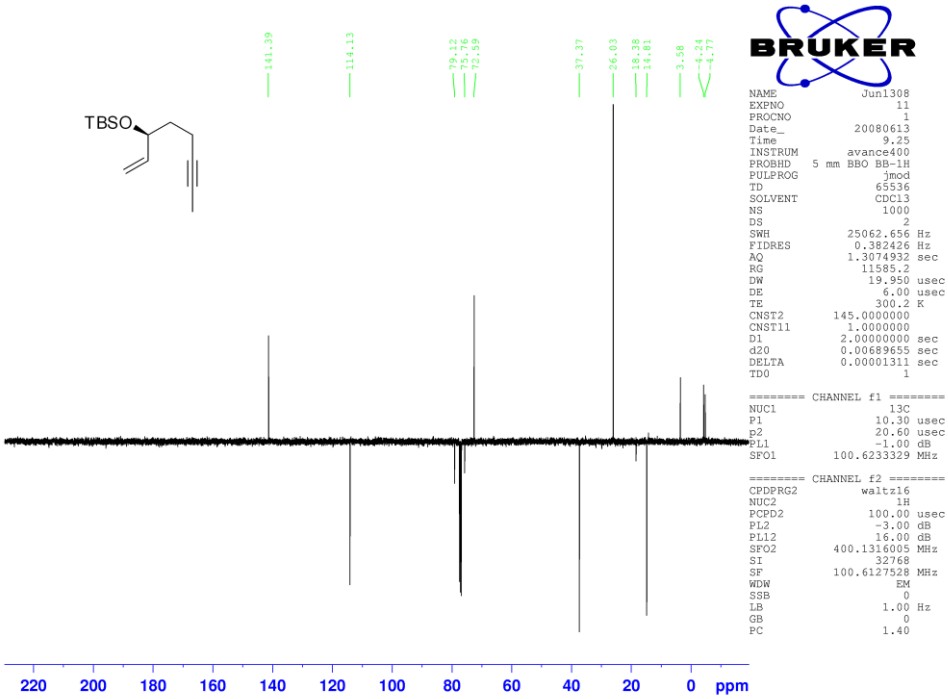
(*S*)-*tert*-Butyl(hept-1-en-6-yn-3-yloxy)dimethylsilane (13)



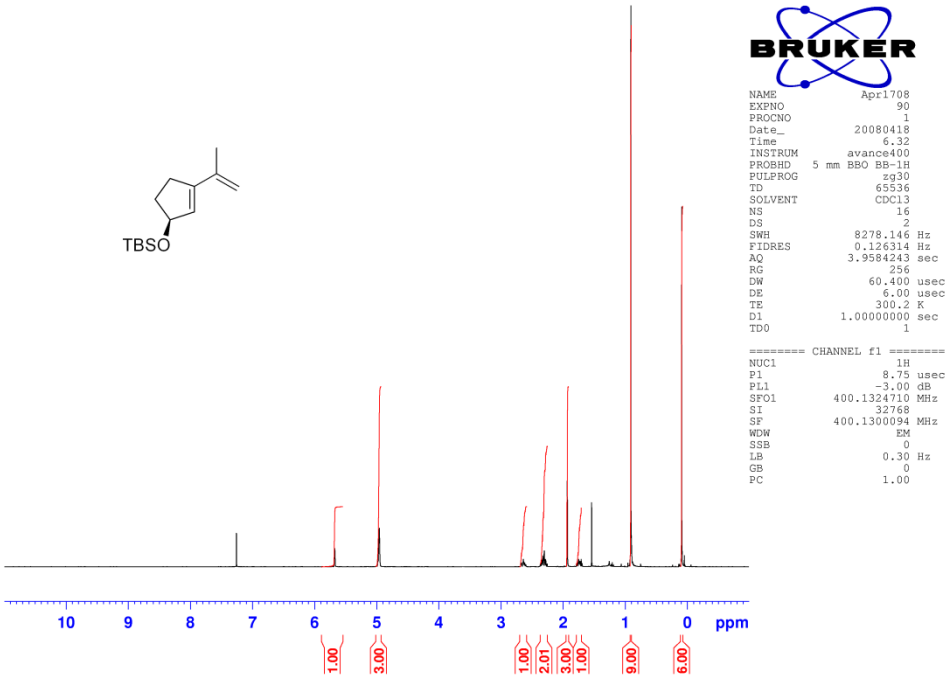


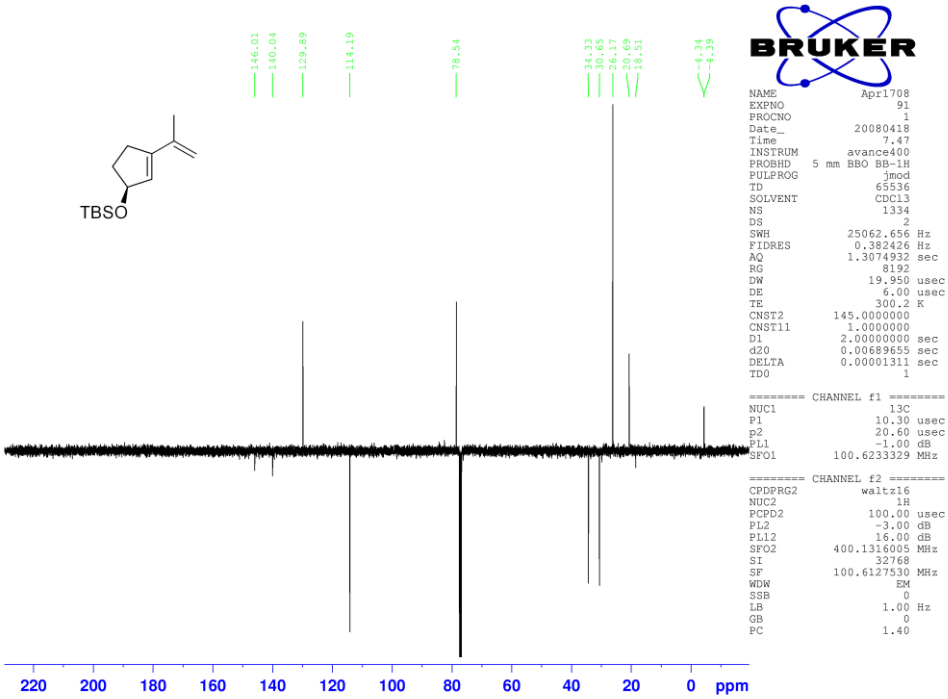
(*S*)-*tert*-Butyl(oct-1-en-6-yn-3-yloxy)dimethylsilane (14)



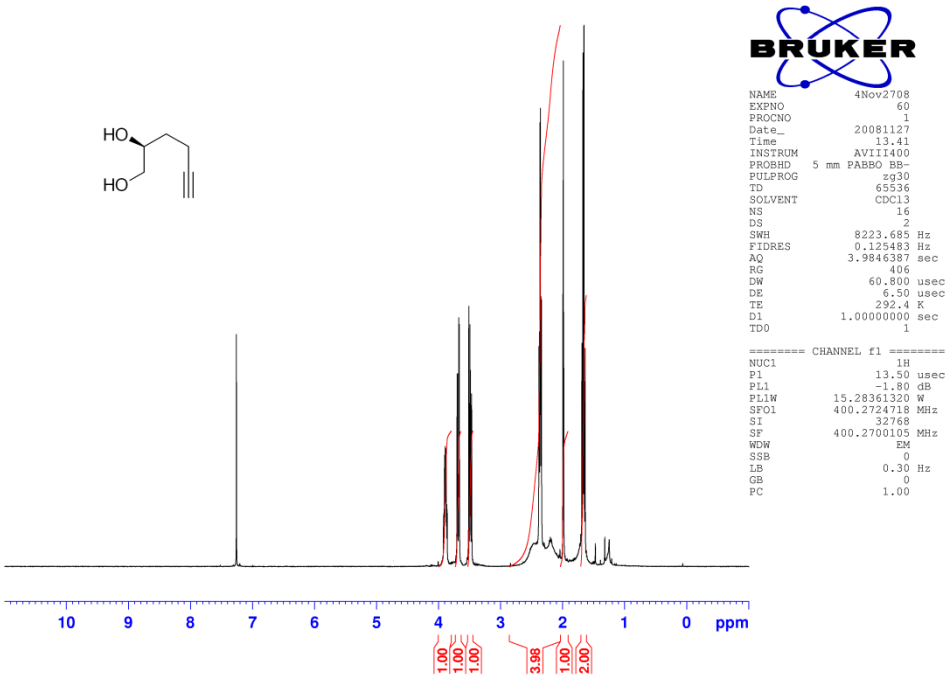


(*S*)-*tert*-Butyldimethyl(3-(prop-1-en-2-yl)cyclopent-2-enyloxy)silane (15)





(*S*)-Hex-5-yne-1,2-diol (17)



BRUKER

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RG                        406
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DE                      6.50 usec
TE                     292.4 K
D1                1.00000000 sec
TD0                         1

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SI                      32768
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LB                       0.30 Hz
GB                          0
PC                       1.00
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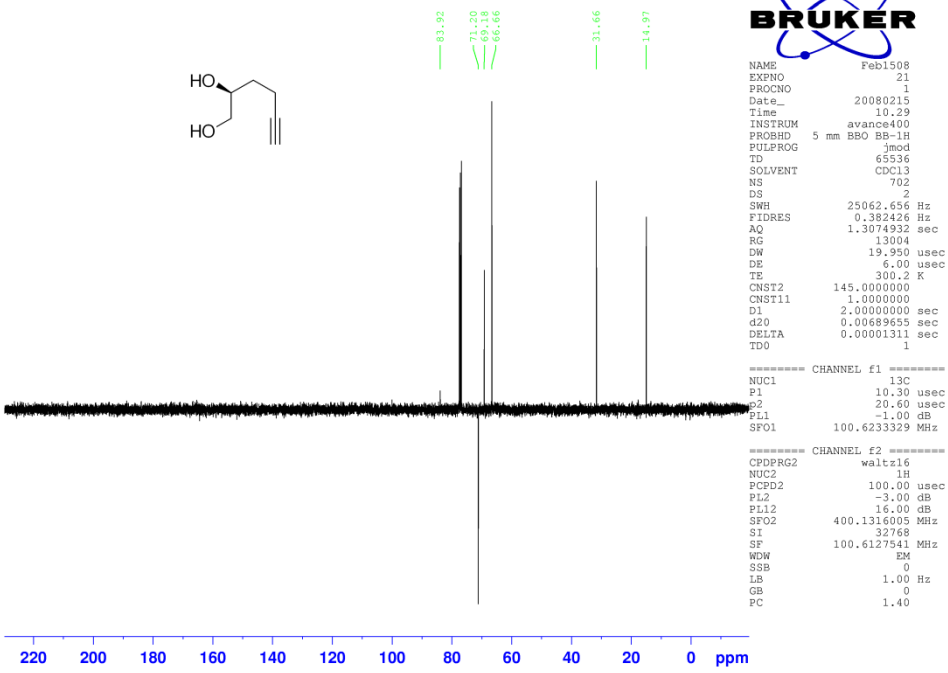

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RG                        13004
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DE                      6.00 usec
TE                     300.2 K
CNST2               145.0000000
CNST11                1.0000000
D1                    2.00000000 sec
d20                   0.00689655 sec
DELTA                 0.00001311 sec
TD0                         1

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p2                      20.60 usec
PL1                     -1.00 dB
SFO1            100.6233329 MHz

======== CHANNEL f2 ========
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NUC2                       1H
PCPD2                  100.00 usec
PL2                     -3.00 dB
PL12                    16.00 dB
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SI                      32768
SF              100.6127541 MHz
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LB                       1.00 Hz
GB                          0
PC                       1.40
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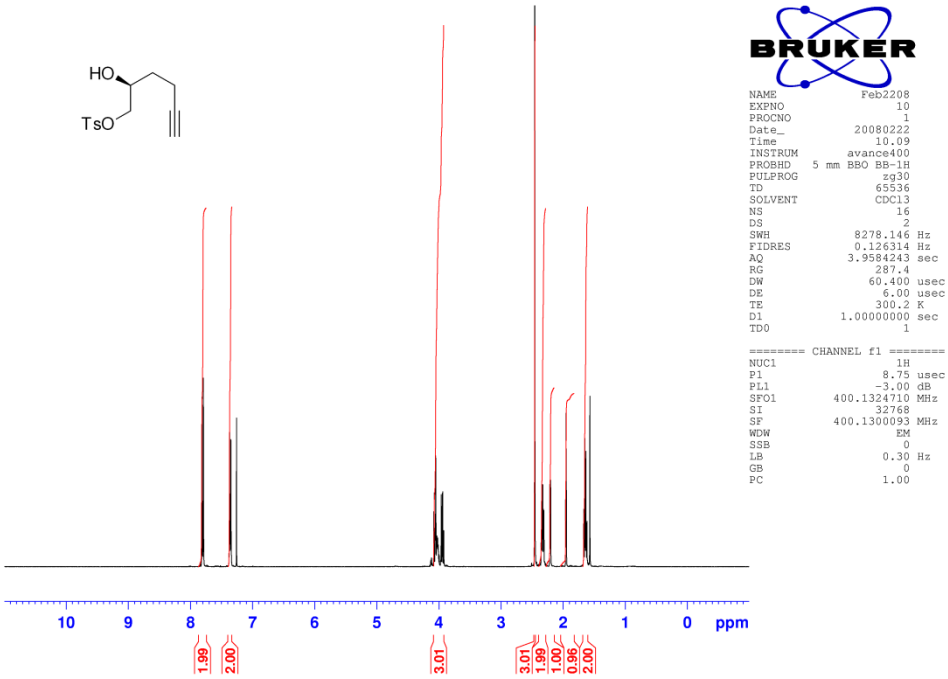
(S)-1-Tosylhex-5-yne-1,2-diol (18):



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SWH                 8278.146 Hz
FIDRES              0.126314 Hz
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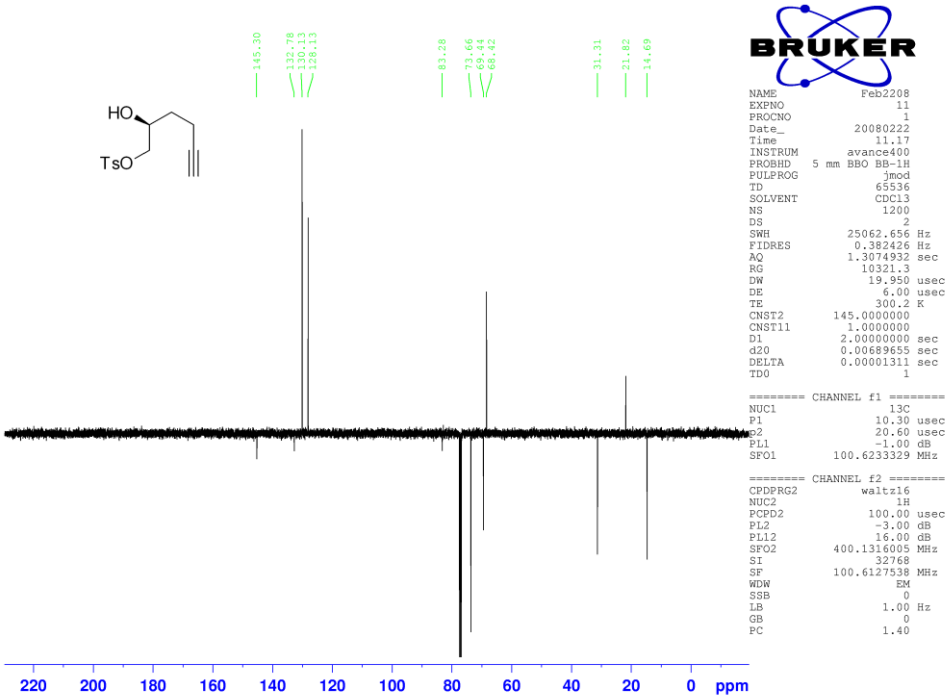

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DS                         2
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FIDRES              0.382426 Hz
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RG                    10321.3
DW                     19.950 usec
DE                      6.00 usec
TE                     300.2 K
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CNST11               1.0000000
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DELTA                0.00001311 sec
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======== CHANNEL f1 ========
NUC1                      13C
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p2                     20.60 usec
PL1                    -1.00 dB
SFO1             100.6233329 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -3.00 dB
PL12                   16.00 dB
SFO2             400.1316005 MHz
SI                     32768
SF               100.6127538 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
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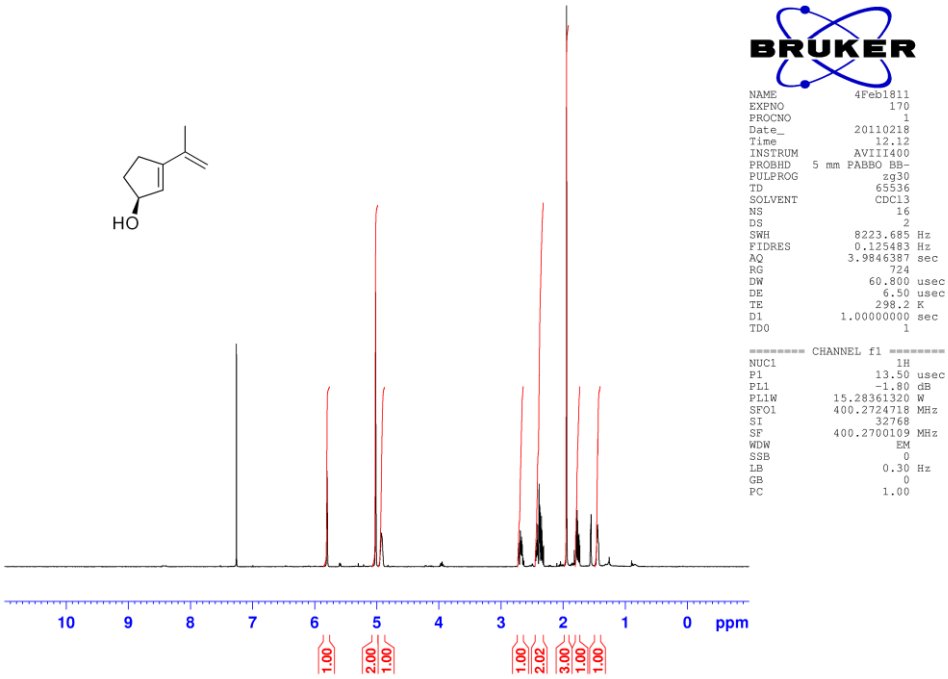
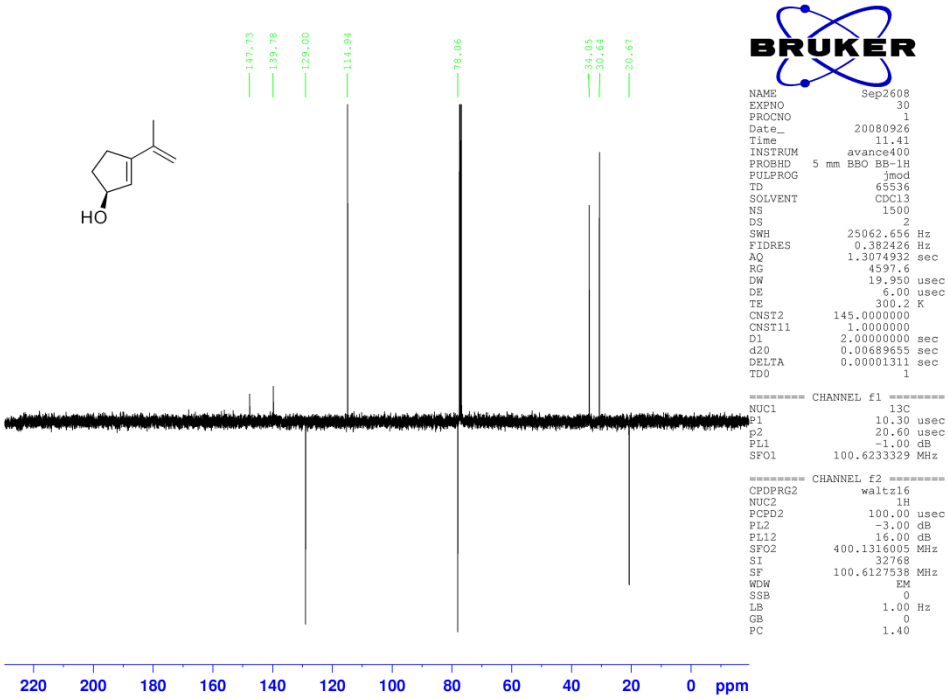
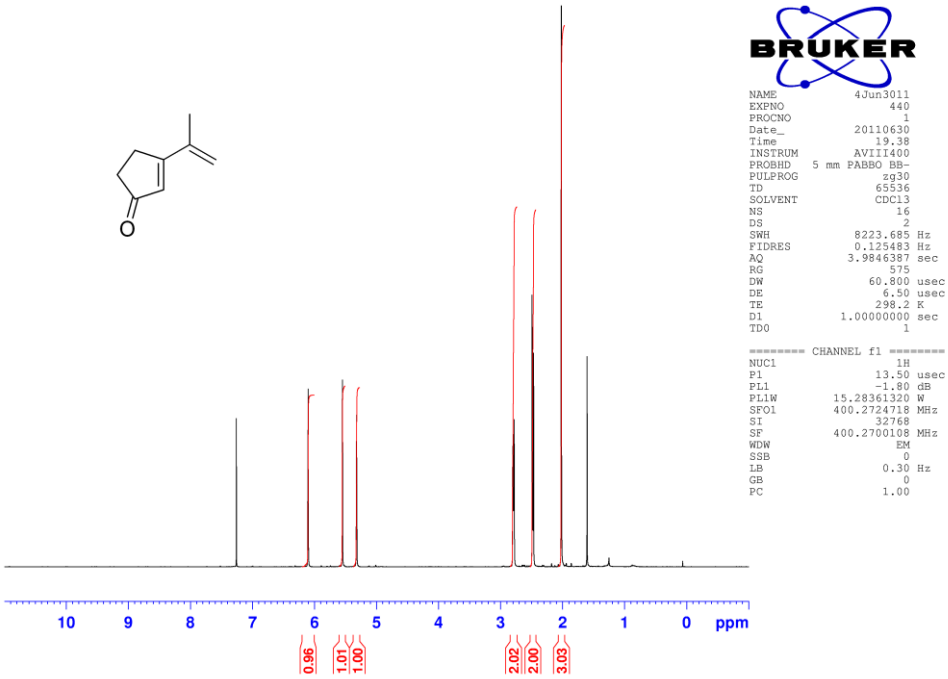
(*S*)-3-(Prop-1-en-2-yl)cyclopent-2-enol (9)





3-(Prop-1-en-2-yl)cyclopent-2-enone (23)

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PULPROG                 zg30
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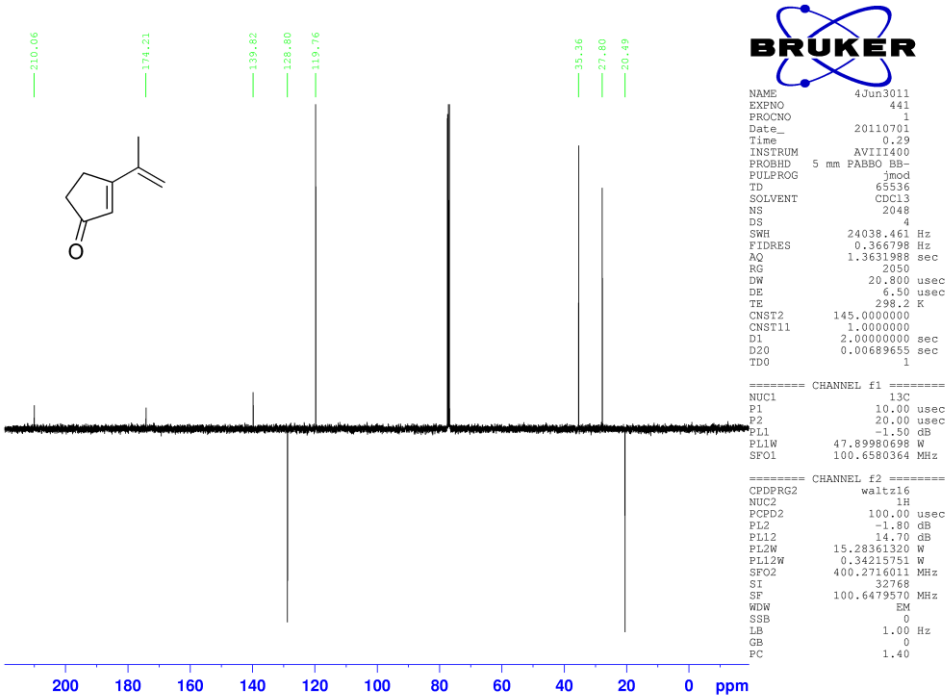
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                       575
DW                    60.800 usec
DE                     6.50 usec
TE                   298.2 K
D1                  1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PL1                    -1.80 dB
PL1W             15.28361320 W
SFO1            400.2724718 MHz
SI                     32768
SF              400.2700108 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```

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PULPROG                jmod
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NS                      2048
DS                         4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                      2050
DW                    20.800 usec
DE                     6.50 usec
TE                   298.2 K
CNST2           145.0000000
CNST11            1.0000000
D1                2.00000000 sec
D20               0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                     10.00 usec
P2                     20.00 usec
PL1                    -1.50 dB
PL1W             47.89980698 W
SFO1            100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -1.80 dB
PL12                   14.70 dB
PL2W             15.28361320 W
PL12W             0.34215751 W
SFO2            400.2716011 MHz
SI                     32768
SF              100.6479570 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```
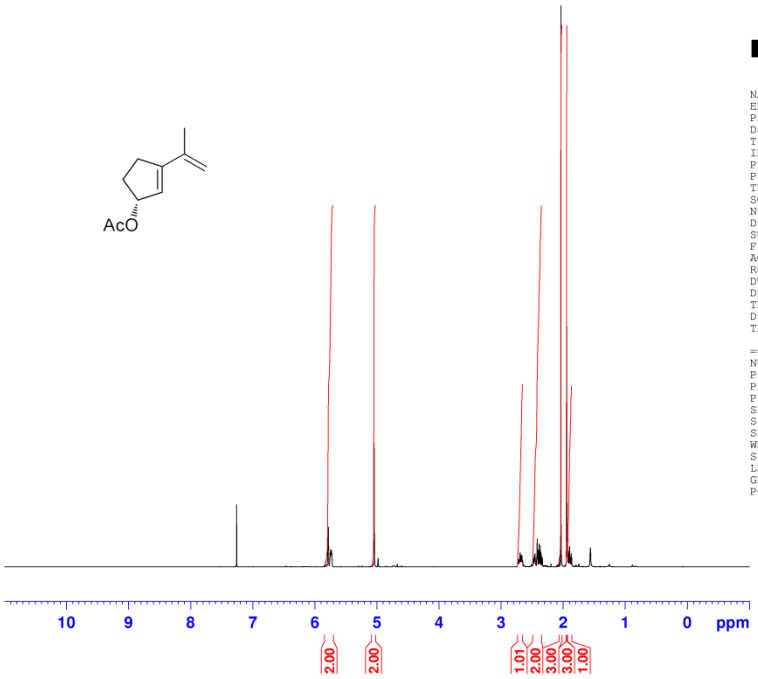

(R)-3-(prop-1-en-2-yl)cyclopent-2-enyl acetate (24)

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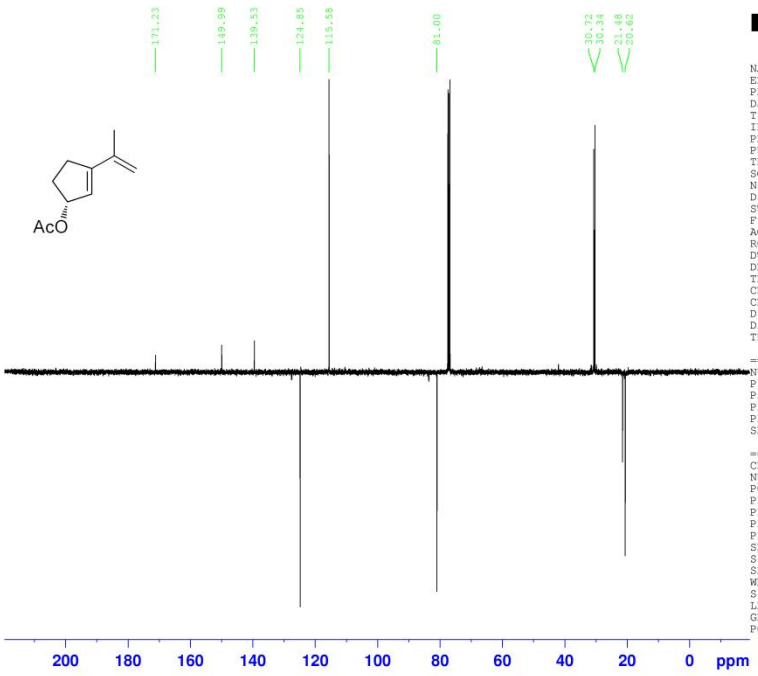
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                       512
DW                    60.800 usec
DE                     6.50 usec
TE                    298.2 K
D1                 1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PL1                    -1.80 dB
PL1W            15.28361320 W
SFO1           400.2724718 MHz
SI                     32768
SF             400.2700108 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```

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PULPROG                jmod
TD                     65536
SOLVENT                CDCl3
NS                       4096
DS                         4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                      2050
DW                    20.800 usec
DE                     6.50 usec
TE                    298.2 K
CNST2             145.0000000
CNST11              1.0000000
D1                  2.00000000 sec
D20                 0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                     10.00 usec
P2                     20.00 usec
PL1                    -1.50 dB
PL1W            47.89980698 W
SFO1           100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -1.80 dB
PL12                   14.70 dB
PL2W            15.28361320 W
PL12W            0.34215751 W
SFO2           400.2716011 MHz
SI                     32768
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WDW                       EM
SSB                        0
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GB                         0
PC                      1.40
```
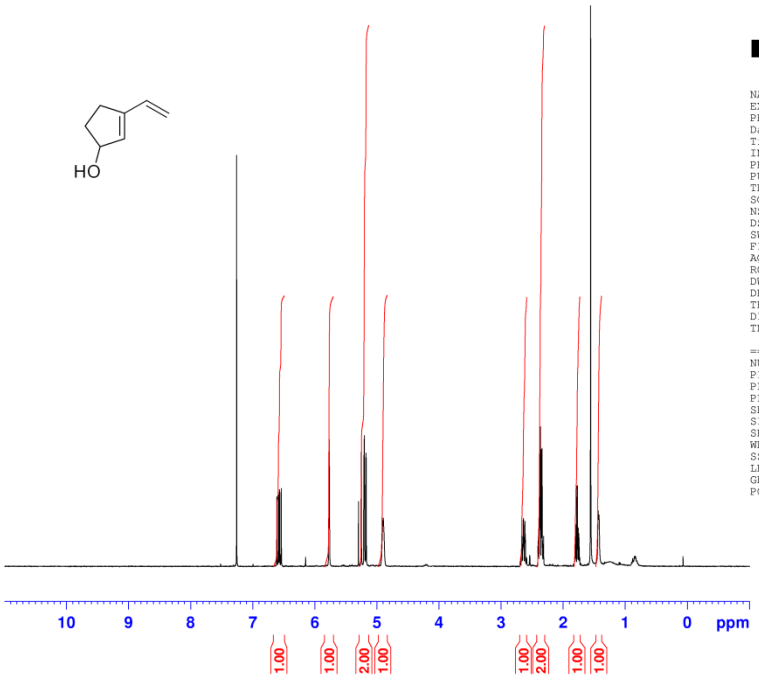

3-Vinylcyclopent-2-enol (27)

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PROCNO                     1
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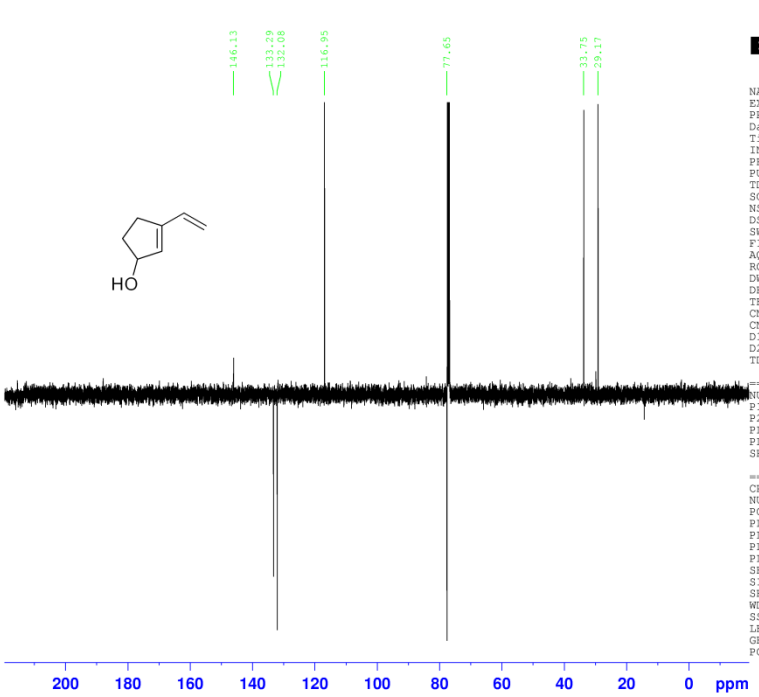
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                       812
DW                    60.800 usec
DE                     6.50 usec
TE                   298.2 K
D1                  1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PL1                    -1.80 dB
PL1W            15.28361320 W
SFO1           400.2724718 MHz
SI                     32768
SF             400.2700108 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```

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PULPROG                jmod
TD                     65536
SOLVENT                CDCl3
NS                      6000
DS                         4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                      2050
DW                    20.800 usec
DE                     6.50 usec
TE                   298.2 K
CNST2              145.0000000
CNST11               1.0000000
D1                   2.00000000 sec
D20                  0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                     10.00 usec
P2                     20.00 usec
PL1                    -1.50 dB
PL1W            47.89980698 W
SFO1           100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -1.80 dB
PL12                   14.70 dB
PL2W            15.28361320 W
PL12W            0.34215751 W
SFO2           400.2716011 MHz
SI                     32768
SF             100.6479562 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
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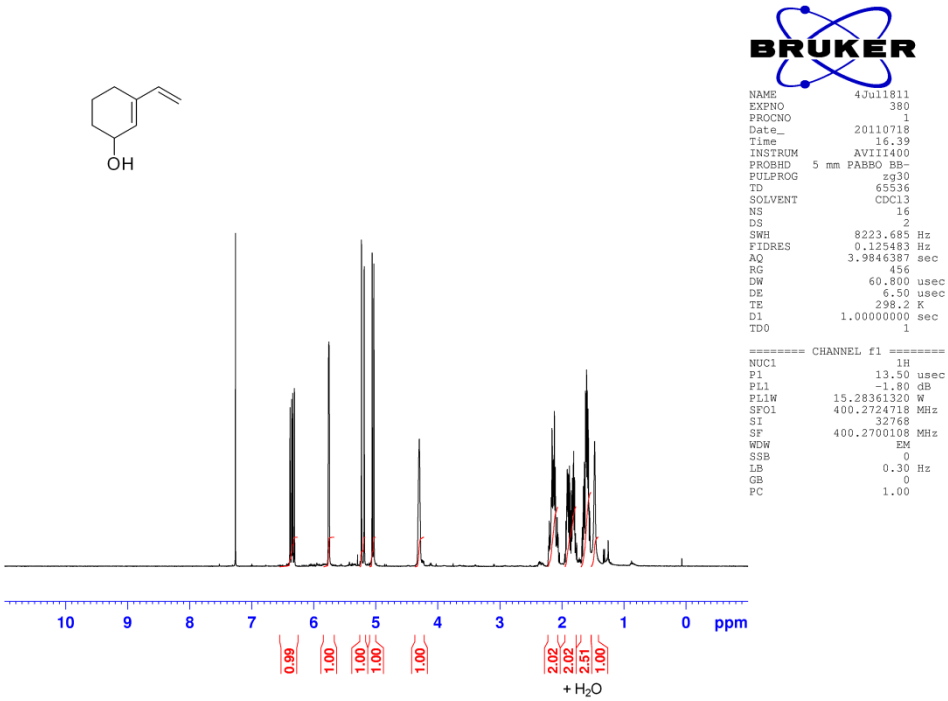
3-Vinylcyclohex-2-enol (29)

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PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                       456
DW                    60.800 usec
DE                     6.50 usec
TE                    298.2 K
D1                  1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PL1                    -1.80 dB
PL1W            15.28361320 W
SFO1           400.2724718 MHz
SI                     32768
SF             400.2700108 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```
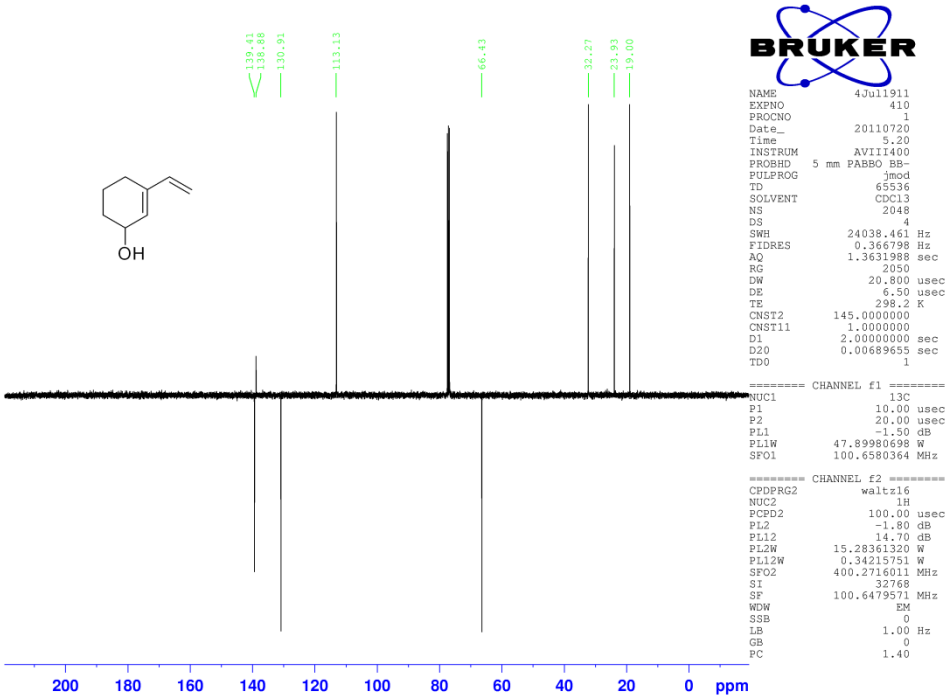
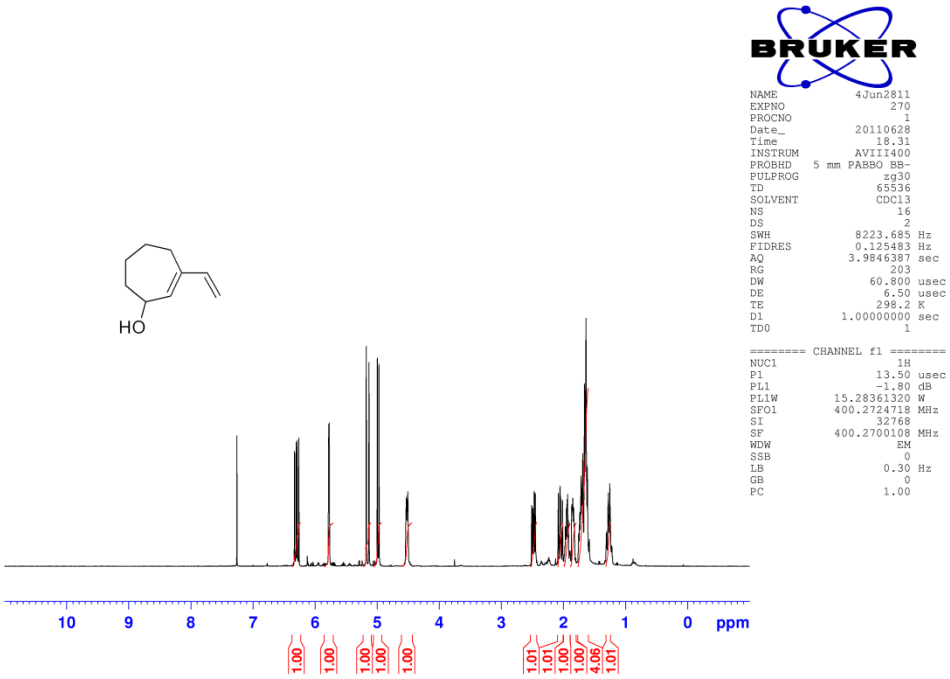
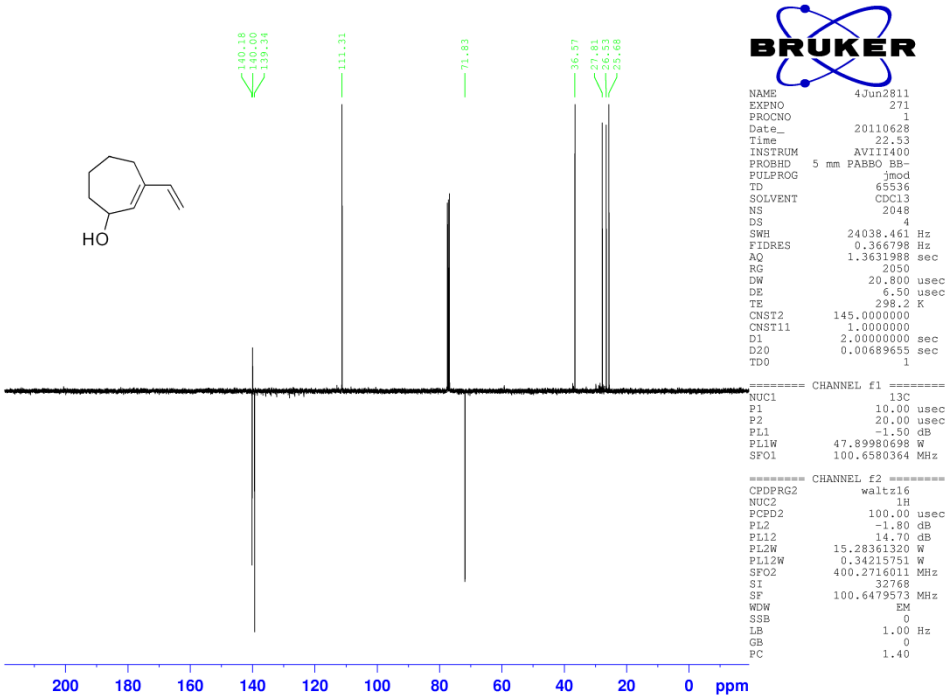




```
NAME                4Jul1911
EXPNO                    410
PROCNO                     1
Date_               20110720
Time                    5.20
INSTRUM             AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                 jmod
TD                     65536
SOLVENT                CDCl3
NS                      2048
DS                         4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                      2050
DW                    20.800 usec
DE                     6.50 usec
TE                    298.2 K
CNST2           145.0000000
CNST11            1.0000000
D1                2.00000000 sec
D20               0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                     10.00 usec
P2                     20.00 usec
PL1                    -1.50 dB
PL1W            47.89980698 W
SFO1           100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -1.80 dB
PL12                   14.70 dB
PL2W            15.28361320 W
PL12W            0.34215751 W
SFO2           400.2716011 MHz
SI                     32768
SF             100.6479571 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```

3-Vinylcyclohept-2-enol (31)

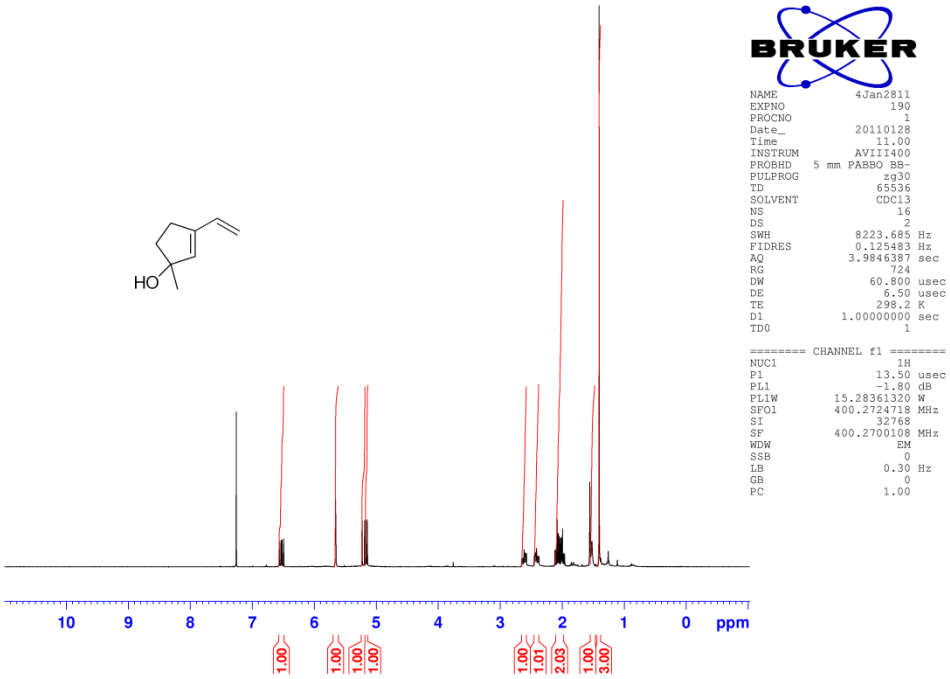



```
NAME                4Jun2811
EXPNO                    270
PROCNO                     1
Date_               20110628
Time                   18.31
INSTRUM              AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                       203
DW                    60.800 usec
DE                     6.50 usec
TE                   298.2 K
D1                  1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PL1                    -1.80 dB
PL1W             15.28361320 W
SFO1            400.2724718 MHz
SI                     32768
SF              400.2700108 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```

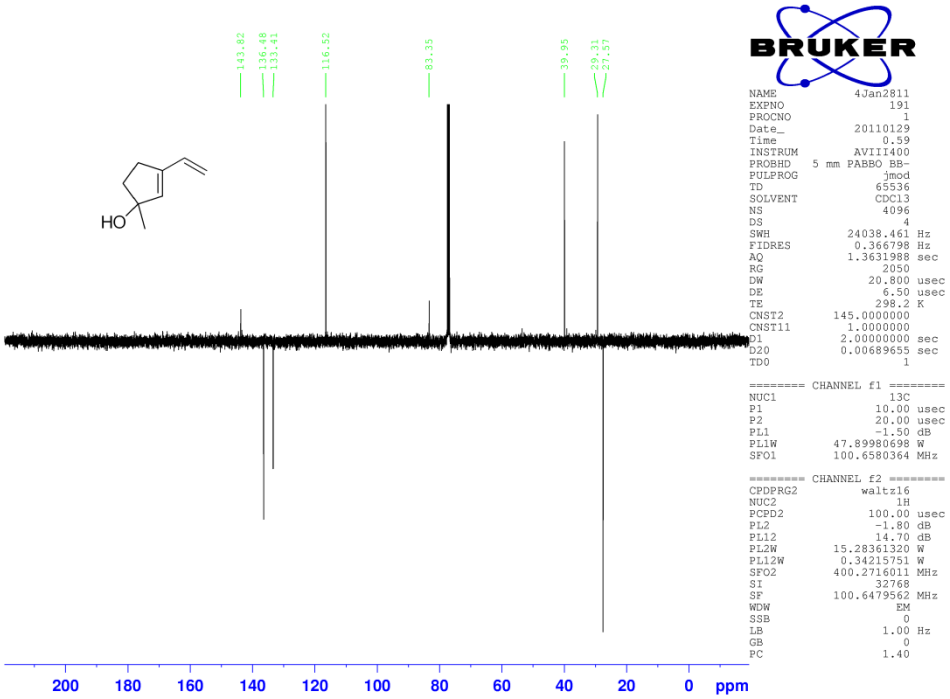



```
NAME                4Jun2811
EXPNO                    271
PROCNO                     1
Date_               20110628
Time                   22.53
INSTRUM              AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                jmod
TD                     65536
SOLVENT                CDCl3
NS                      2048
DS                         4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                      2050
DW                    20.800 usec
DE                     6.50 usec
TE                   298.2 K
CNST2           145.0000000
CNST11            1.0000000
D1                2.00000000 sec
D20               0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                     10.00 usec
P2                     20.00 usec
PL1                    -1.50 dB
PL1W             47.89980698 W
SFO1            100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -1.80 dB
PL12                   14.70 dB
PL2W             15.28361320 W
PL12W             0.34215751 W
SFO2            400.2716011 MHz
SI                     32768
SF              100.6479573 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```

1-Methyl-3-vinylcyclopent-2-enol (33)

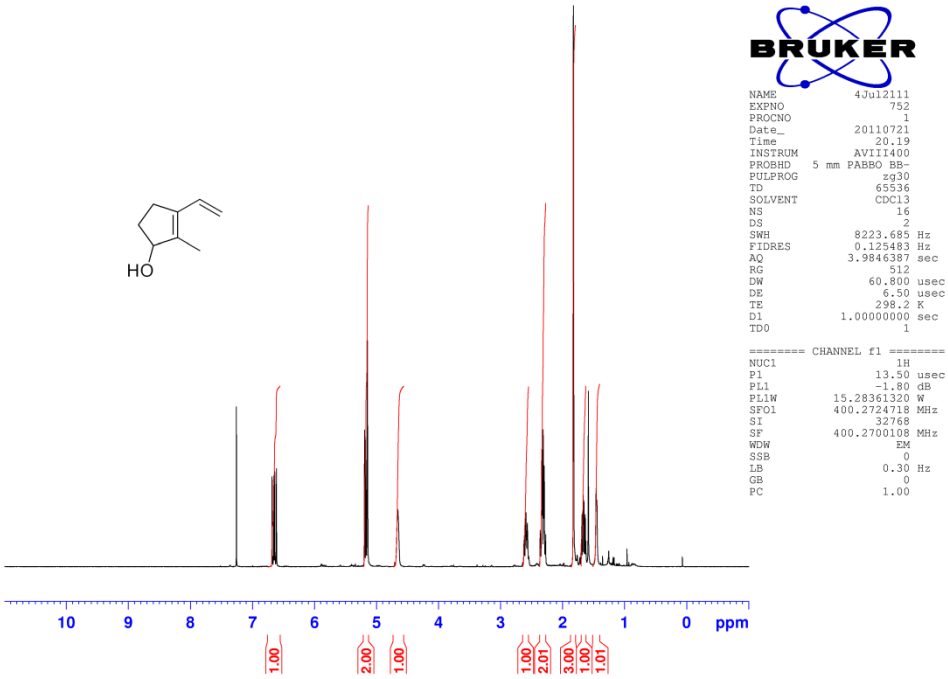



```
NAME                4Jan2811
EXPNO                    190
PROCNO                     1
Date_               20110128
Time                   11.00
INSTRUM              AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                       724
DW                    60.800 usec
DE                     6.50 usec
TE                   298.2 K
D1                  1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PL1                    -1.80 dB
PL1W            15.28361320 W
SFO1           400.2724718 MHz
SI                     32768
SF             400.2700108 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```

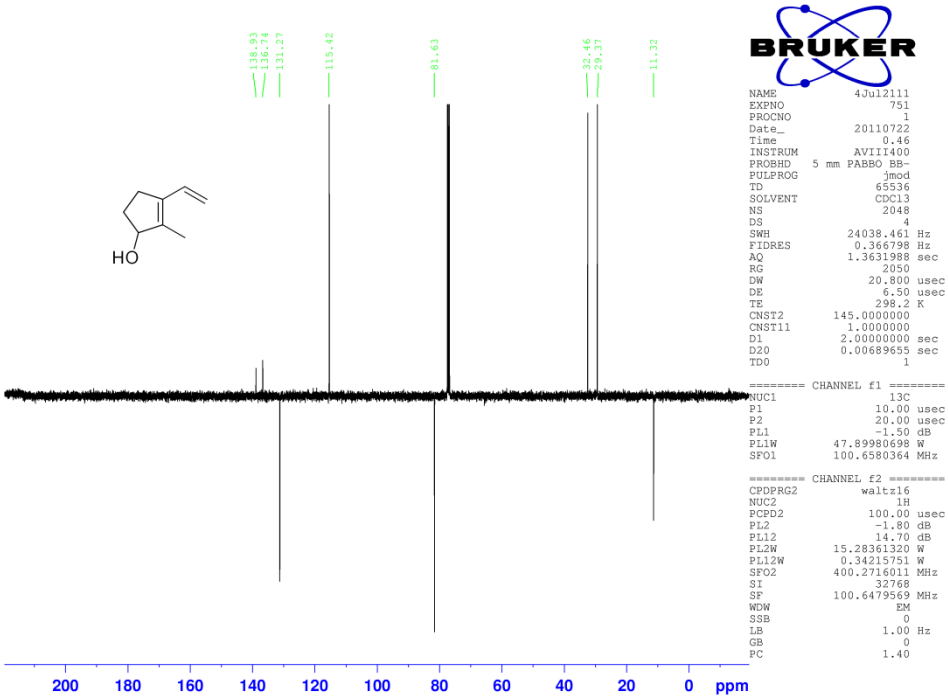



```
NAME                4Jan2811
EXPNO                    191
PROCNO                     1
Date_               20110129
Time                   0.59
INSTRUM              AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                jmod
TD                     65536
SOLVENT                CDCl3
NS                      4096
DS                         4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                      2050
DW                    20.800 usec
DE                     6.50 usec
TE                   298.2 K
CNST2              145.0000000
CNST11               1.0000000
D1                   2.00000000 sec
D20                  0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                     10.00 usec
P2                     20.00 usec
PL1                    -1.50 dB
PL1W            47.89980698 W
SFO1           100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -1.80 dB
PL12                   14.70 dB
PL2W            15.28361320 W
PL12W            0.34215751 W
SFO2           400.2716011 MHz
SI                     32768
SF             100.6479562 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```

2-Methyl-3-vinylcyclopent-2-enol (35)

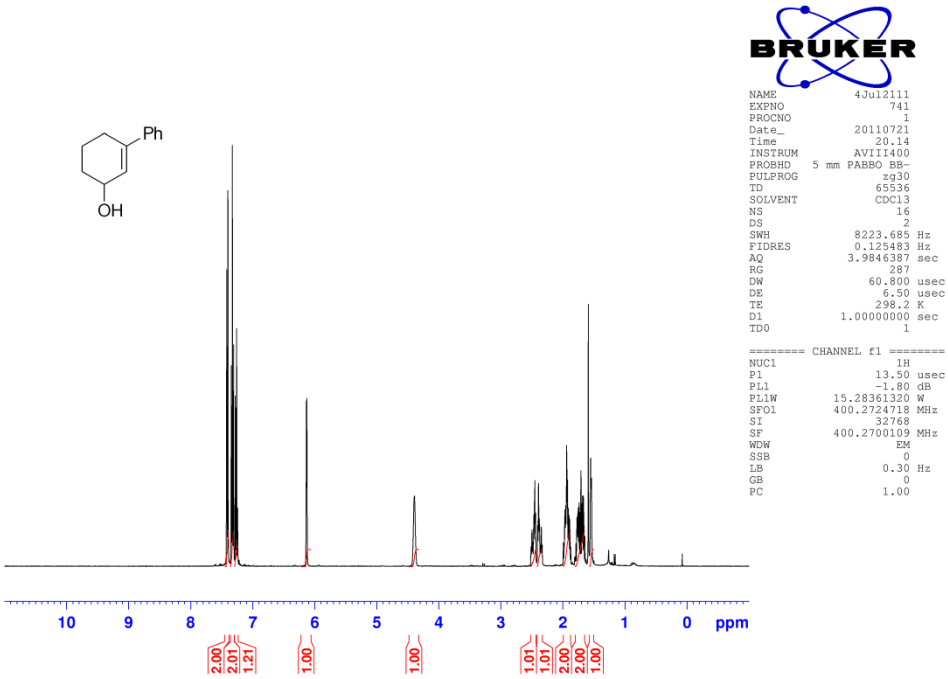



```
NAME                4Jul2111
EXPNO                    752
PROCNO                     1
Date_               20110721
Time                   20.19
INSTRUM              AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                       512
DW                    60.800 usec
DE                     6.50 usec
TE                    298.2 K
D1                 1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PL1                    -1.80 dB
PL1W            15.28361320 W
SFO1           400.2724718 MHz
SI                     32768
SF             400.2700108 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```

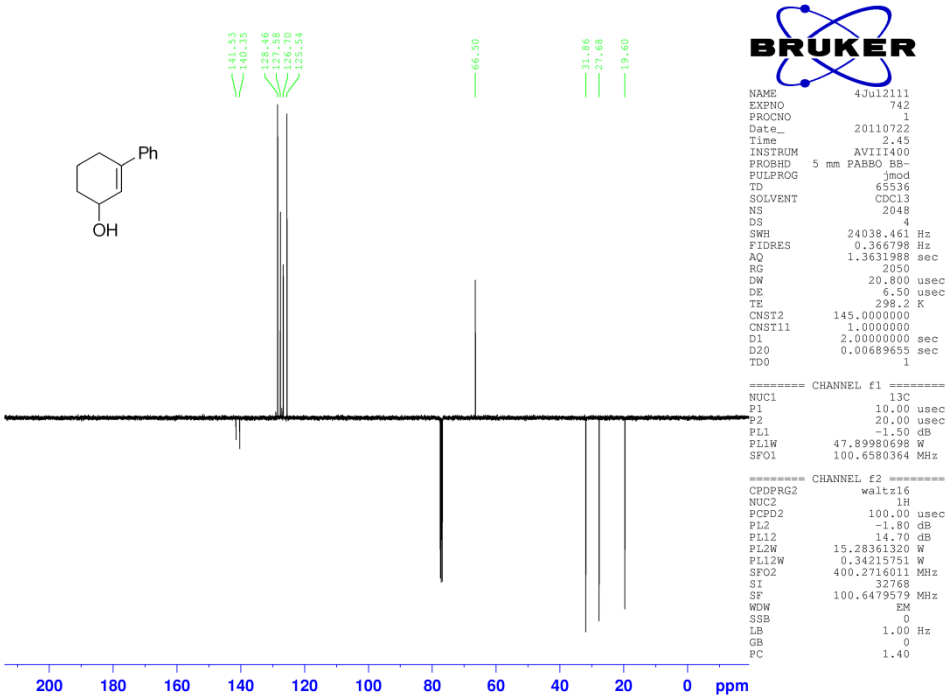



```
NAME                4Jul2111
EXPNO                    751
PROCNO                     1
Date_               20110722
Time                   0.46
INSTRUM              AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                 jmod
TD                     65536
SOLVENT                CDCl3
NS                      2048
DS                         4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                       2050
DW                    20.800 usec
DE                     6.50 usec
TE                    298.2 K
CNST2              145.0000000
CNST11               1.0000000
D1                 2.00000000 sec
D20                0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                     10.00 usec
P2                     20.00 usec
PL1                    -1.50 dB
PL1W            47.89980698 W
SFO1           100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -1.80 dB
PL12                   14.70 dB
PL2W            15.28361320 W
PL12W            0.34215751 W
SFO2           400.2716011 MHz
SI                     32768
SF             100.6479569 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```

3-Phenylcyclohex-2-enol (37)

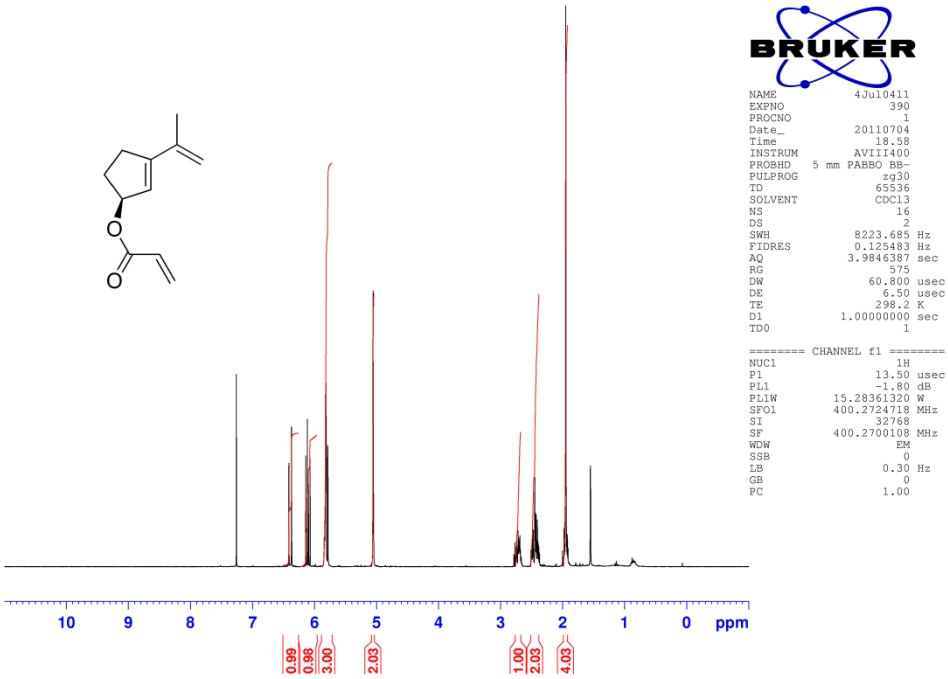


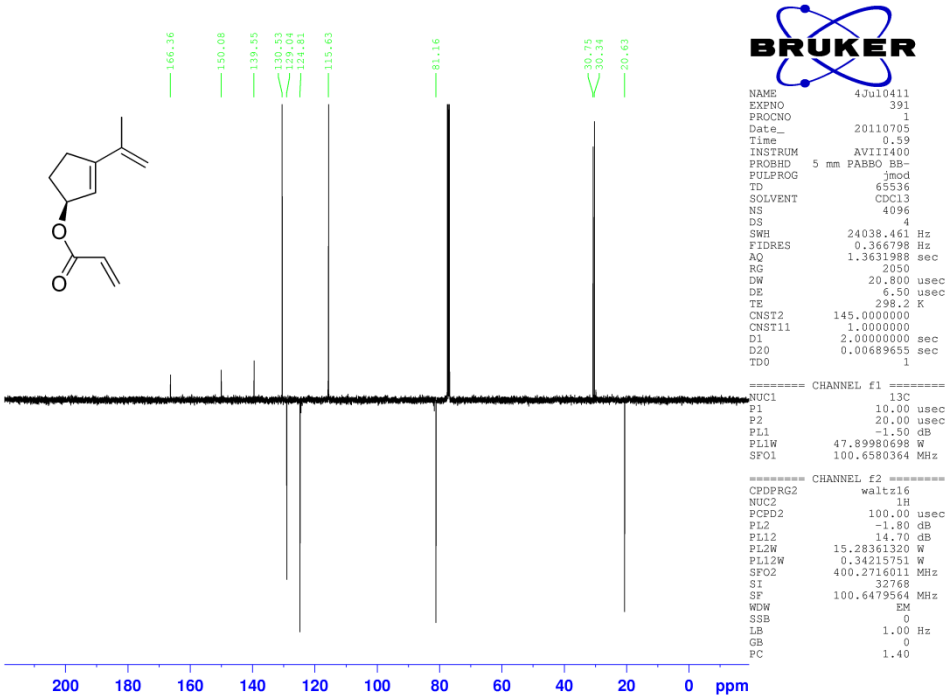

```
NAME                4Jul2111
EXPNO                    741
PROCNO                     1
Date_               20110721
Time                   20.14
INSTRUM             AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                       287
DW                    60.800 usec
DE                     6.50 usec
TE                    298.2 K
D1                  1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PL1                    -1.80 dB
PL1W             15.28361320 W
SFO1            400.2724718 MHz
SI                     32768
SF              400.2700109 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```



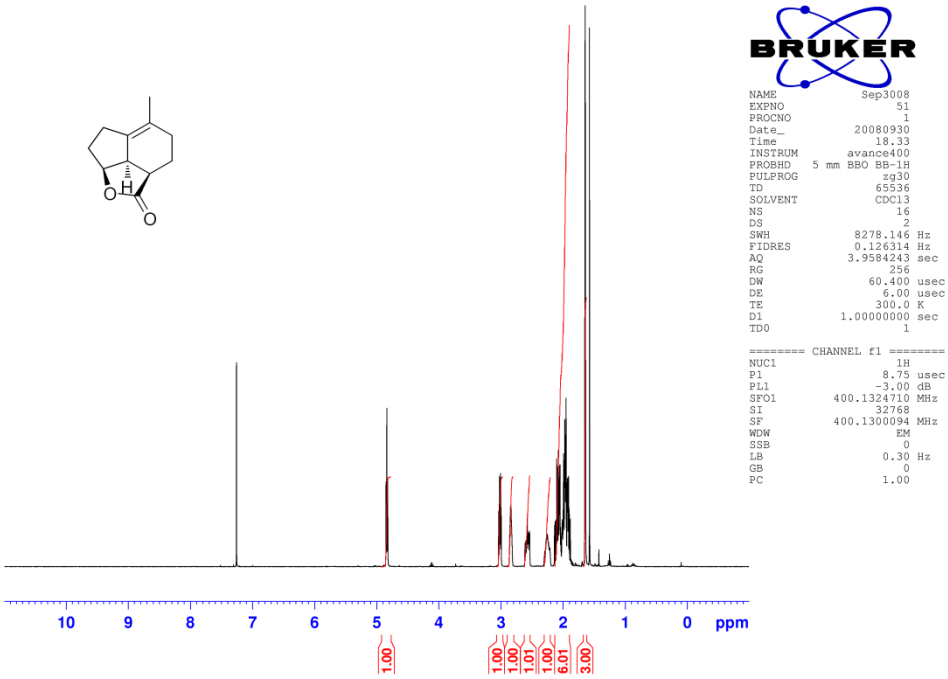

```
NAME                4Jul2111
EXPNO                    742
PROCNO                     1
Date_               20110722
Time                    2.45
INSTRUM             AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                jmod
TD                     65536
SOLVENT                CDCl3
NS                      2048
DS                         4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                      2050
DW                    20.800 usec
DE                     6.50 usec
TE                    298.2 K
CNST2             145.0000000
CNST11              1.0000000
D1                  2.00000000 sec
D20                 0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                     10.00 usec
P2                     20.00 usec
PL1                    -1.50 dB
PL1W             47.89980698 W
SFO1            100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -1.80 dB
PL12                   14.70 dB
PL2W             15.28361320 W
PL12W             0.34215751 W
SFO2            400.2716011 MHz
SI                     32768
SF              100.6479579 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```

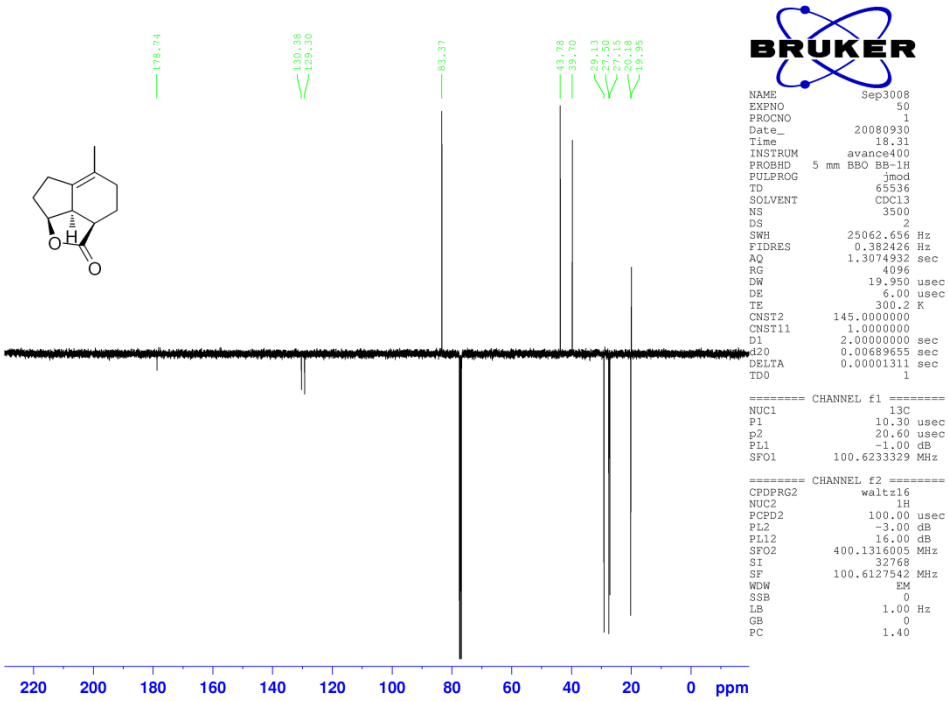
3-(Prop-1-en-2-yl)cyclopent-2-enyl acrylate (38)



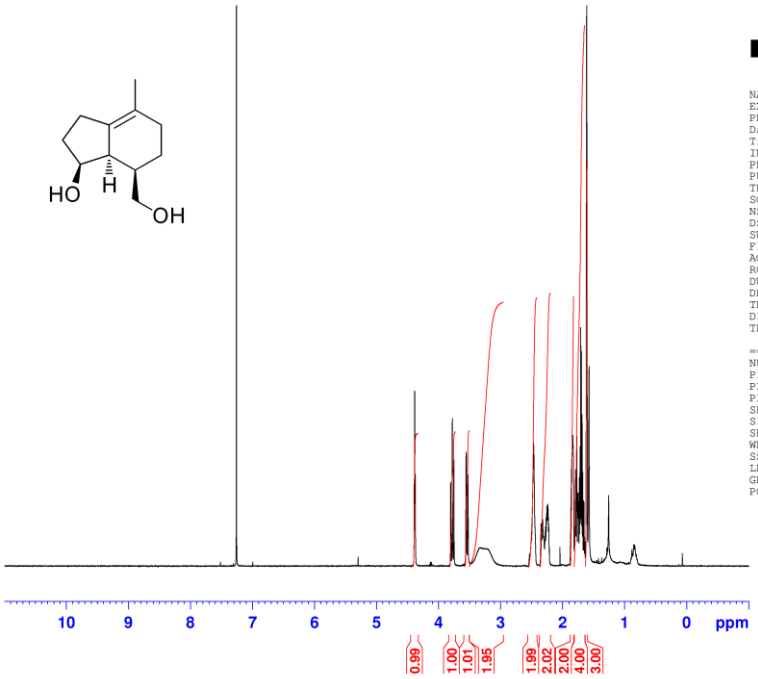


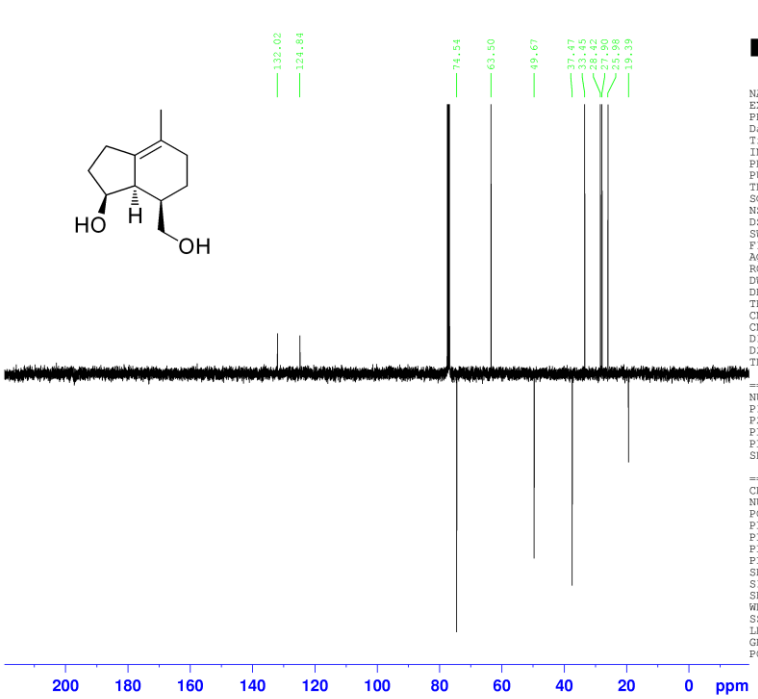
(*2aR,7aS,7bR*)- 5-Methyl- 3,4,6,7,7a,7b-hexahydro-2a*H*-indeno[1,7-*bc*]furan-2-one (8a)





(*1S,7R,7aR*)-7-(hydroxymethyl)-4-methyl-2,3,5,6,7,7a-hexahydro-1H-inden-1-ol (40)





BRUKER

NAME 4Mar2311
EXPNO 390
PROCNO 1
Date_ 20110323
Time 19.28
INSTRUM AVIII400
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 724
DW 60.800 usec
DE 6.50 usec
TE 298.2 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 13.50 usec
PL1 -1.80 dB
PL1W 15.28361320 W
SFO1 400.2724718 MHz
SI 32768
SF 400.2700107 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

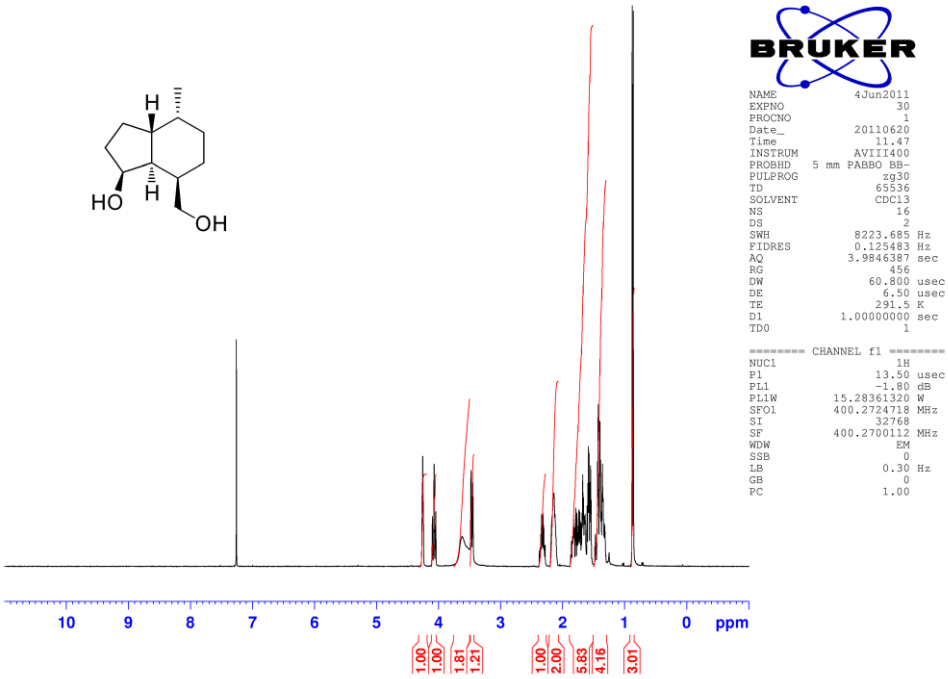
BRUKER

NAME 4Mar2311
EXPNO 391
PROCNO 1
Date_ 20110324
Time 6.11
INSTRUM AVIII400
PROBHD 5 mm PABBO BB-
PULPROG jmod
TD 65536
SOLVENT CDCl3
NS 3072
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 2050
DW 20.800 usec
DE 6.50 usec
TE 298.2 K
CNST2 145.0000000
CNST11 1.0000000
D1 2.00000000 sec
D20 0.00689655 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 10.00 usec
P2 20.00 usec
PL1 -1.50 dB
PL1W 47.89980698 W
SFO1 100.6580364 MHz

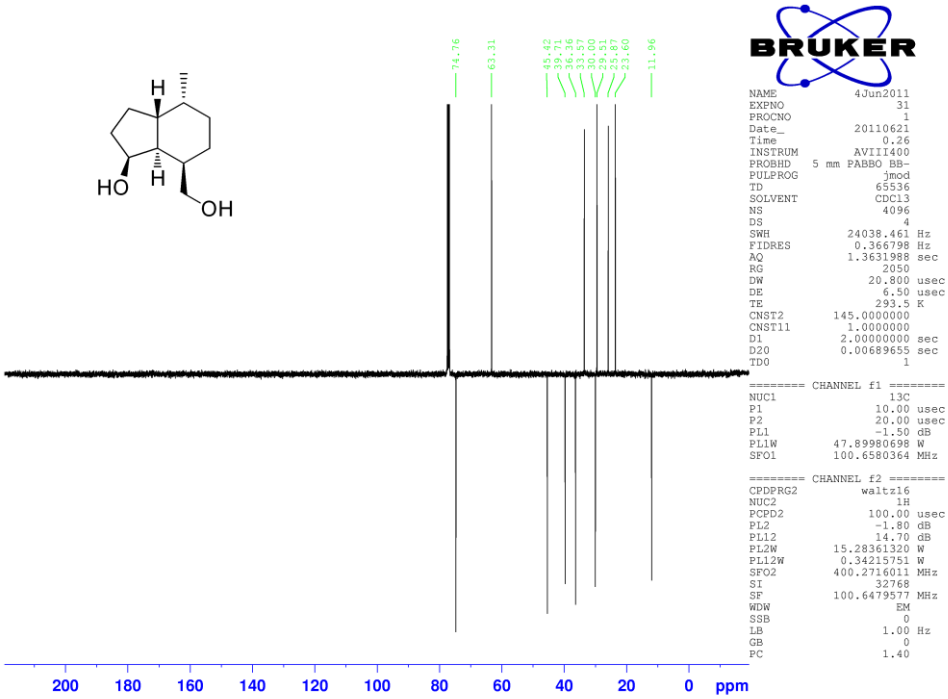
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -1.80 dB
PL12 14.70 dB
PL2W 15.28361320 W
PL12W 0.34215751 W
SFO2 400.2716011 MHz
SI 32768
SF 100.6479562 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

(*1S,3aR,4R,7R,7aS*)-7-(hydroxymethyl)-4-methyloctahydro-1H-inden-1-ol (41)



BRUKER

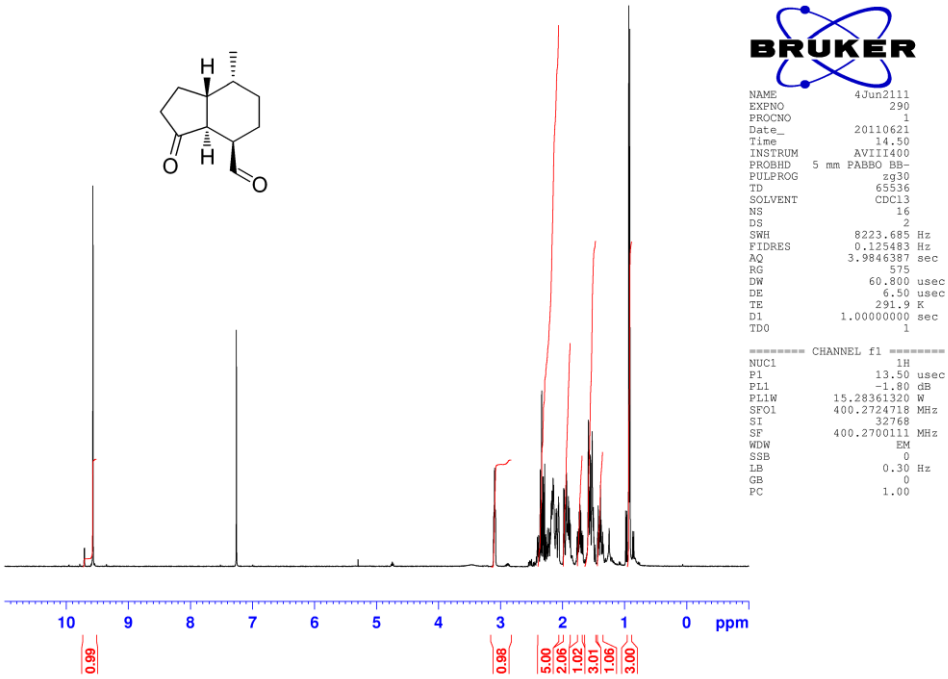
NAME	4Jun2011
EXPNO	30
PROCNO	1
Date_	20110620
Time	11.47
INSTRUM	AVIII400
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	456
DW	60.800 usec
DE	6.50 usec
TE	291.5 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	13.50 usec
PL1	-1.80 dB
PL1W	15.28361320 W
SFO1	400.2724718 MHz
SI	32768
SF	400.2700112 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



BRUKER

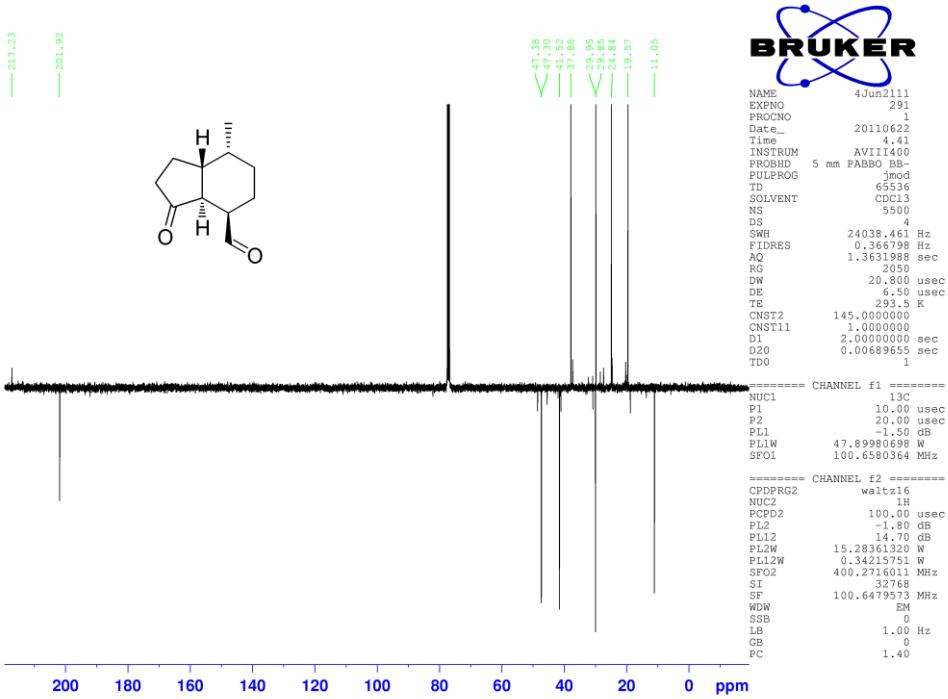
NAME	4Jun2011
EXPNO	31
PROCNO	1
Date_	20110621
Time	0.26
INSTRUM	AVIII400
PROBHD	5 mm PABBO BB-
PULPROG	jmod
TD	65536
SOLVENT	CDCl3
NS	4096
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	2050
DW	20.800 usec
DE	6.50 usec
TE	293.5 K
CNST2	145.0000000
CNST11	1.0000000
D1	2.00000000 sec
D20	0.00689655 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
P2	20.00 usec
PL1	-1.50 dB
PL1W	47.89980698 W
SFO1	100.6580364 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	-1.80 dB
PL12	14.70 dB
PL2W	15.28361320 W
PL12W	0.34215751 W
SFO2	400.2716011 MHz
SI	32768
SF	100.6479577 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

(*3aS,4R,7R,7aR*)- 7-methyl- 3-oxooctahydro- 1H-indene-4-carbaldehyde (42)



BRUKER

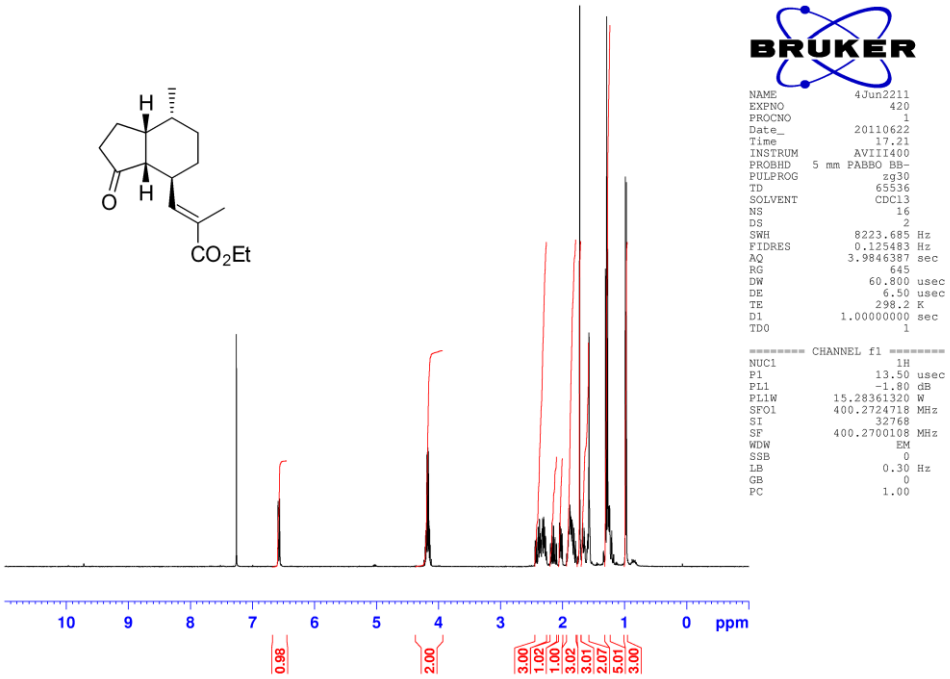
```
NAME                4Jun2111
EXPNO                    290
PROCNO                     1
Date_               20110621
Time                   14.50
INSTRUM             AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                       575
DW                    60.800 usec
DE                     6.50 usec
TE                    291.9 K
D1                 1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PL1                    -1.80 dB
PL1W            15.28361320 W
SFO1           400.2724718 MHz
SI                     32768
SF             400.2700111 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```



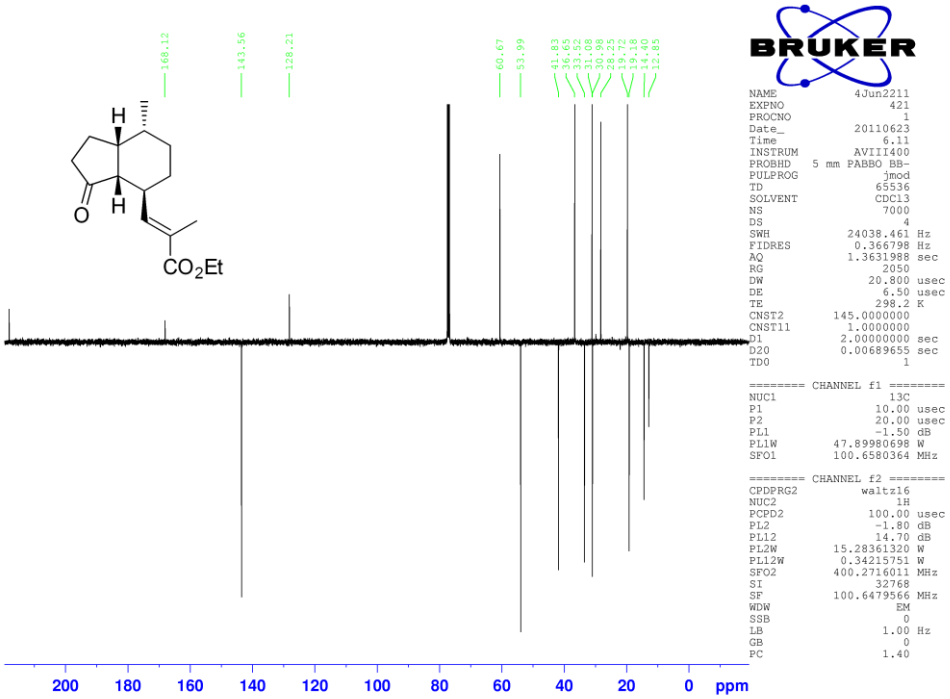
BRUKER

```
NAME                4Jun2111
EXPNO                    291
PROCNO                     1
Date_               20110622
Time                    4.41
INSTRUM             AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                 jmod
TD                     65536
SOLVENT                CDCl3
NS                       5500
DS                         4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                      2050
DW                    20.800 usec
DE                     6.50 usec
TE                    293.5 K
CNST2           145.0000000
CNST11            1.0000000
D1                2.00000000 sec
D20               0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                     10.00 usec
P2                     20.00 usec
PL1                    -1.50 dB
PL1W            47.89980698 W
SFO1           100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -1.80 dB
PL12                   14.70 dB
PL2W            15.28361320 W
PL12W            0.34215751 W
SFO2           400.2716011 MHz
SI                     32768
SF             100.6479573 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```

(*E*)-Ethyl-2-methyl-3-((*3aR,4S,7R,7aR*)-7-methyl-3-oxooctahydro-1H-inden-4-yl)-acrylate (6b)

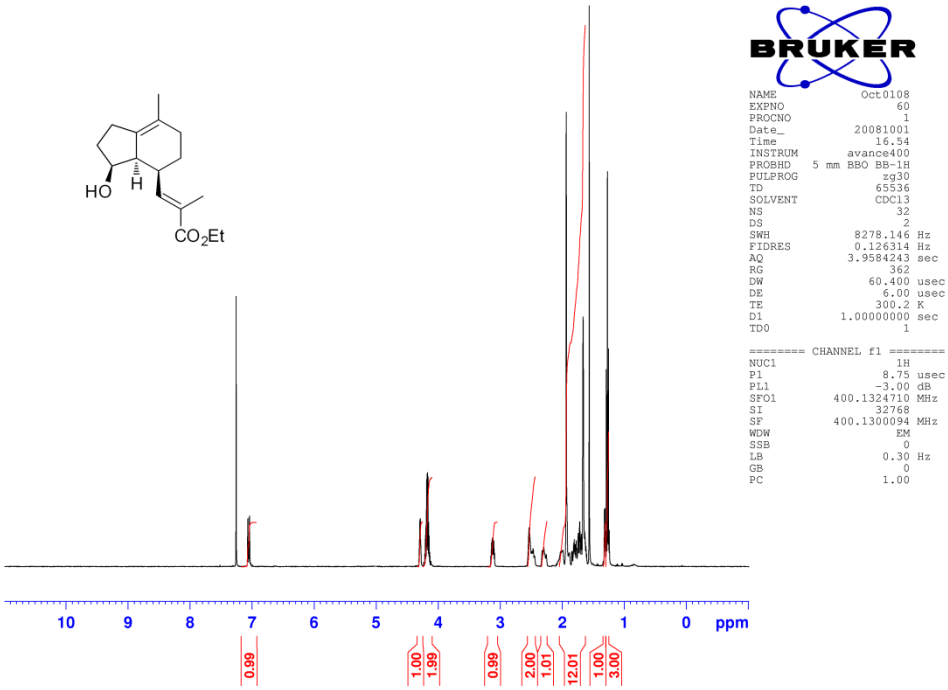



```
NAME                4Jun2211
EXPNO                    420
PROCNO                     1
Date_               20110622
Time                   17.21
INSTRUM             AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                CDC13
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                       645
DW                    60.800 usec
DE                     6.50 usec
TE                    298.2 K
D1                 1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PL1                    -1.80 dB
PL1W            15.28361320 W
SFO1           400.2724718 MHz
SI                     32768
SF             400.2700108 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```

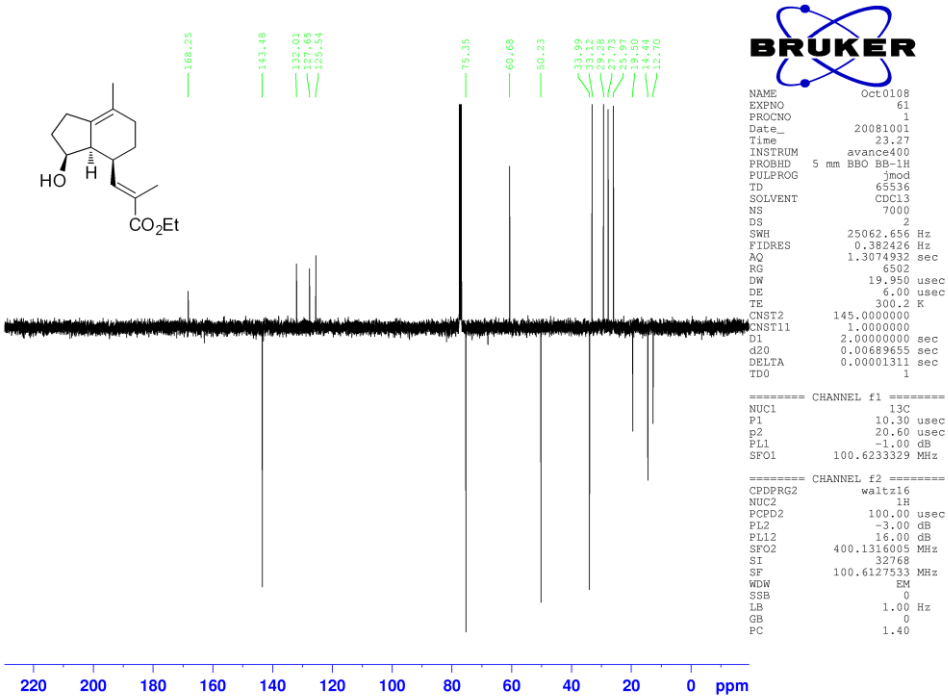



```
NAME                4Jun2211
EXPNO                    421
PROCNO                     1
Date_               20110623
Time                    6.11
INSTRUM             AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                jmod
TD                     65536
SOLVENT                CDC13
NS                      7000
DS                         4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                      2050
DW                    20.800 usec
DE                     6.50 usec
TE                    298.2 K
CNST2              145.0000000
CNST11               1.0000000
D1                   2.00000000 sec
D20                  0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                     10.00 usec
P2                     20.00 usec
PL1                    -1.50 dB
PL1W            47.89980698 W
SFO1           100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -1.80 dB
PL12                   14.70 dB
PL2W            15.28361320 W
PL12W            0.34215751 W
SFO2           400.2716011 MHz
SI                     32768
SF             100.6479566 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```

(*E*)-3-((*3S,3aR,4S*)-3-Hydroxy-7-methyl-2,3,3a,4,5,6-hexahydro-1*H*-inden-4-yl)-2-methyl-acrylic acid ethyl ester (7)

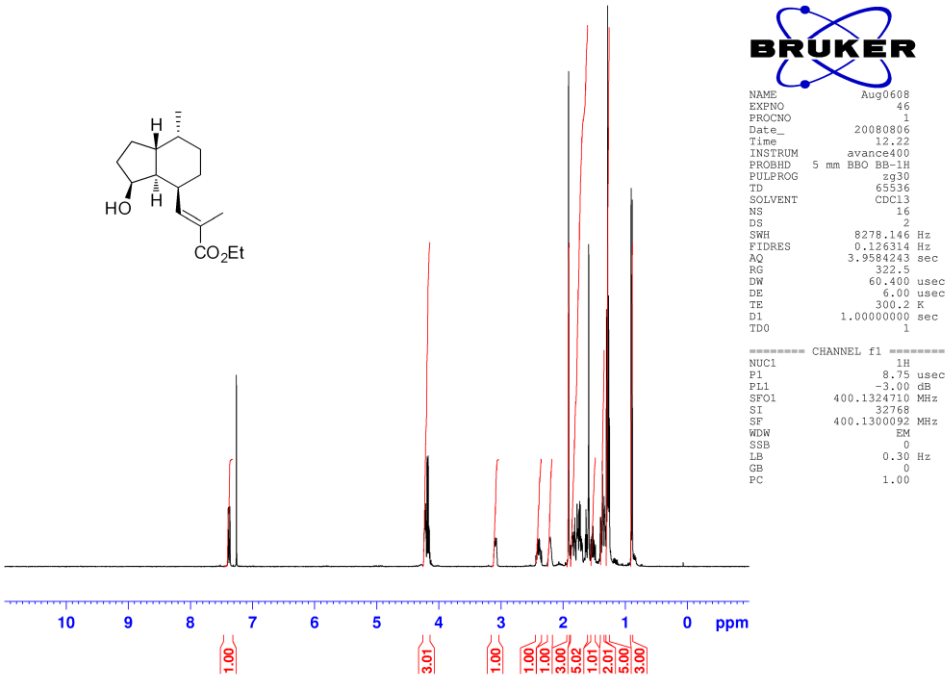


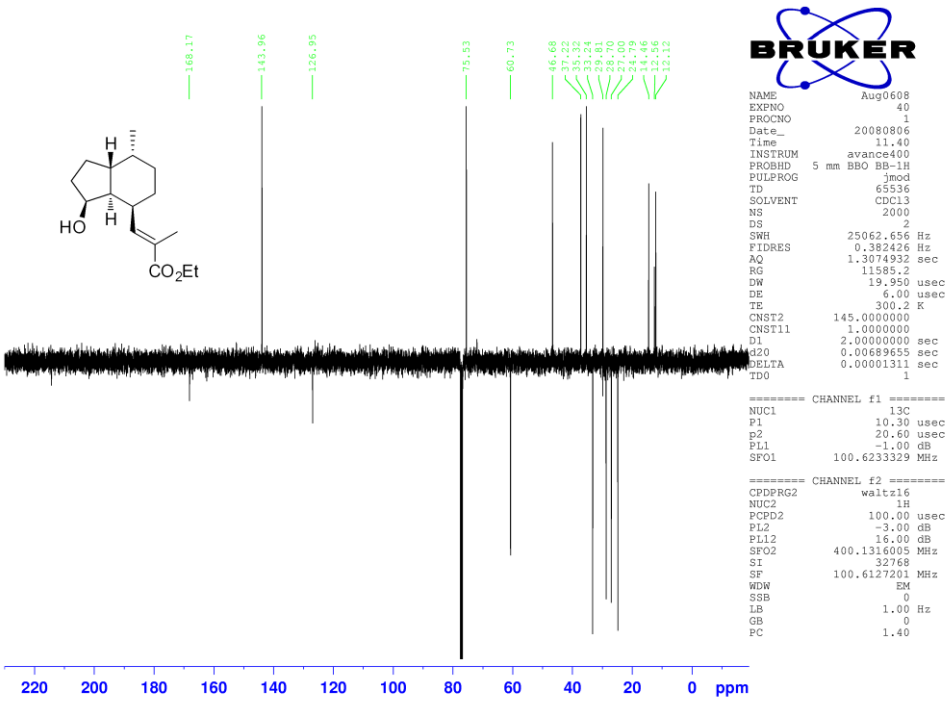

```
NAME                Oct0108
EXPNO                    60
PROCNO                    1
Date_              20081001
Time                  16.54
INSTRUM          avance400
PROBHD    5 mm BBO BB-1H
PULPROG                zg30
TD                    65536
SOLVENT             CDCl3
NS                       32
DS                        2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ                3.9584243 sec
RG                      362
DW                   60.400 usec
DE                    6.00 usec
TE                   300.2 K
D1                1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    1H
P1                    8.75 usec
PL1                  -3.00 dB
SFO1          400.1324710 MHz
SI                    32768
SF            400.1300094 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```



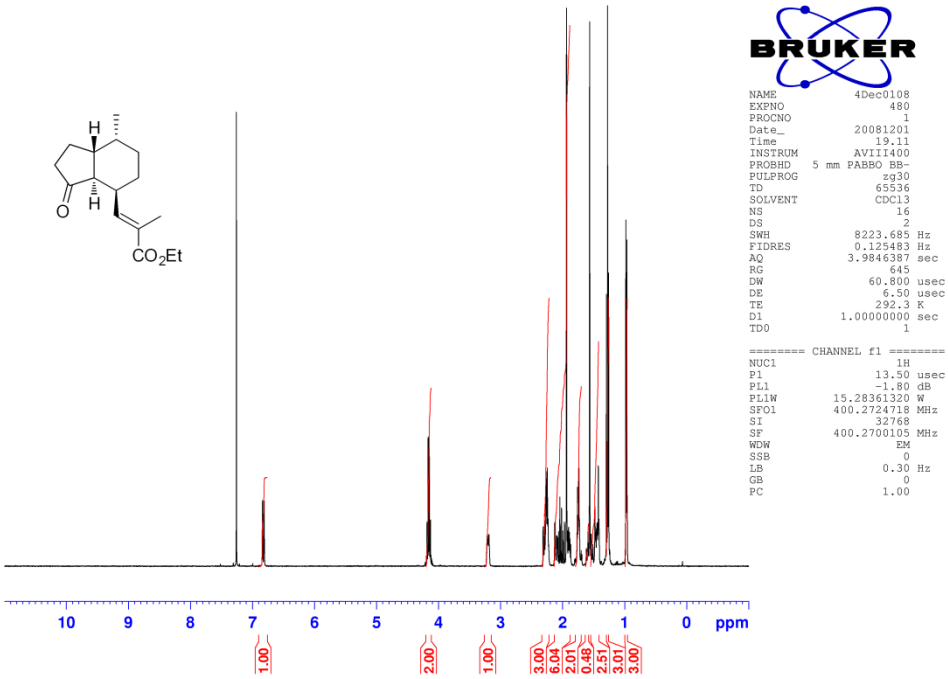

```
NAME                Oct0108
EXPNO                    61
PROCNO                    1
Date_              20081001
Time                  23.27
INSTRUM          avance400
PROBHD    5 mm BBO BB-1H
PULPROG                jmod
TD                    65536
SOLVENT             CDCl3
NS                     7000
DS                        2
SWH              25062.656 Hz
FIDRES            0.382426 Hz
AQ                1.3074932 sec
RG                     6502
DW                   19.950 usec
DE                    6.00 usec
TE                   300.2 K
CNST2           145.0000000
CNST11            1.0000000
D1                2.00000000 sec
d20               0.00689655 sec
DELTA             0.00001311 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                   10.30 usec
p2                   20.60 usec
PL1                  -1.00 dB
SFO1          100.6233329 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                    1H
PCPD2               100.00 usec
PL2                  -3.00 dB
PL12                 16.00 dB
SFO2          400.1316005 MHz
SI                    32768
SF            100.6127533 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

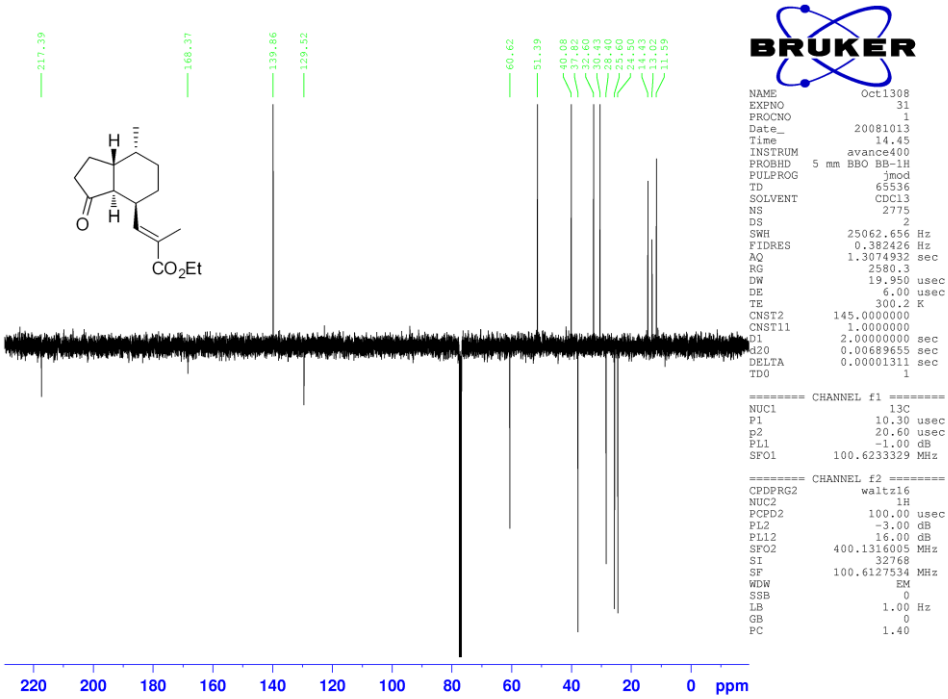
(*E*)-3-((*3S,3aS,4S,7R,7aR*)-3-Hydroxy-7-methyl-octahydro-inden-4-yl)-2-methyl-acrylic acid ethyl ester (45)



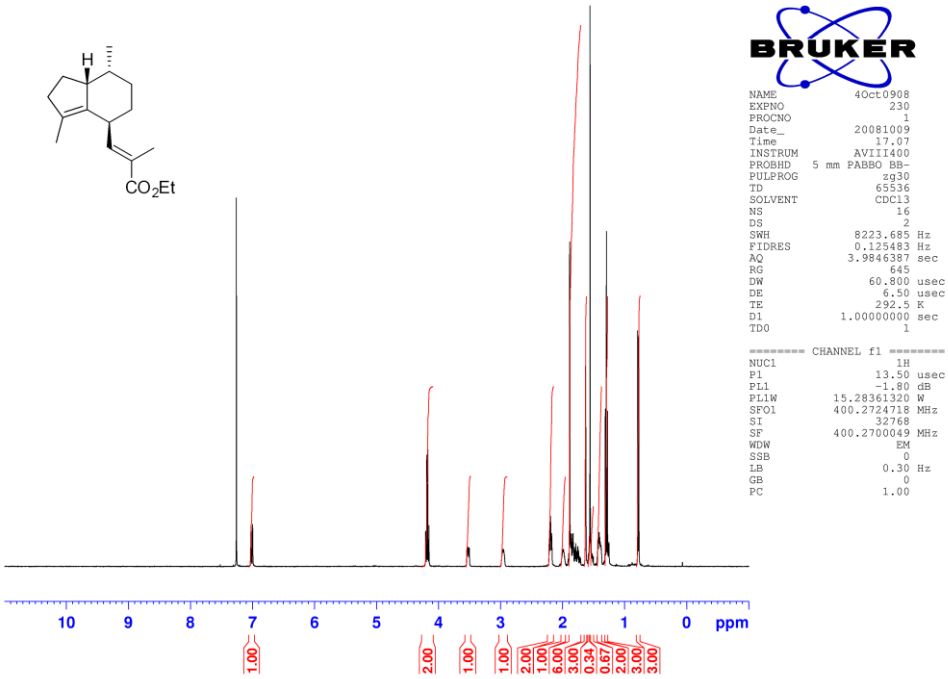


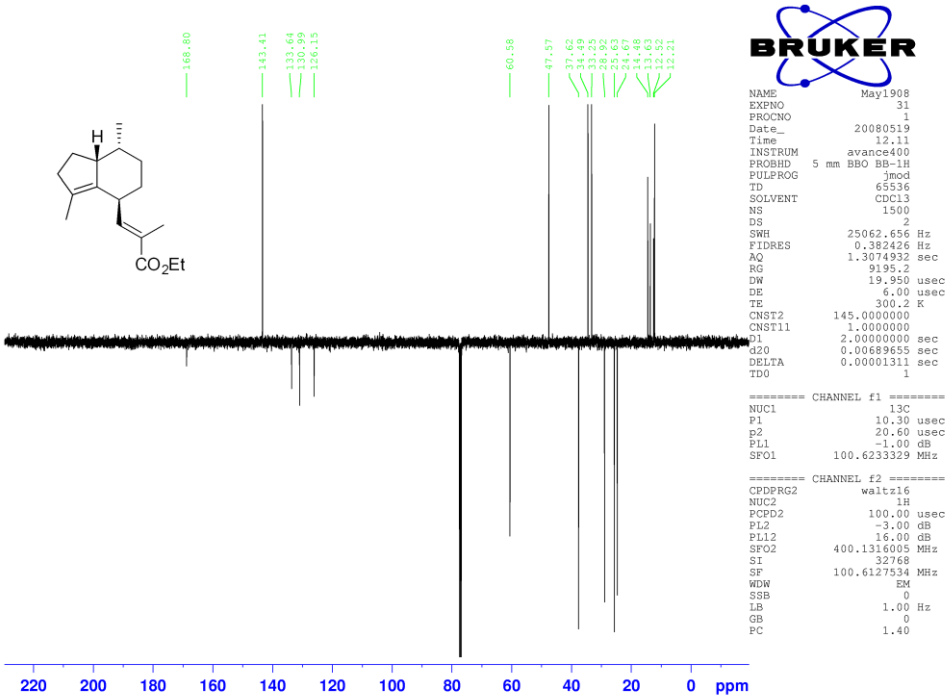
(*E*)-2-Methyl-3-((*3aS,4S,7R,7aR*)-7-methyl-3-oxo-octahydro-inden-4-yl)-acrylic acid ethyl ester (6a)



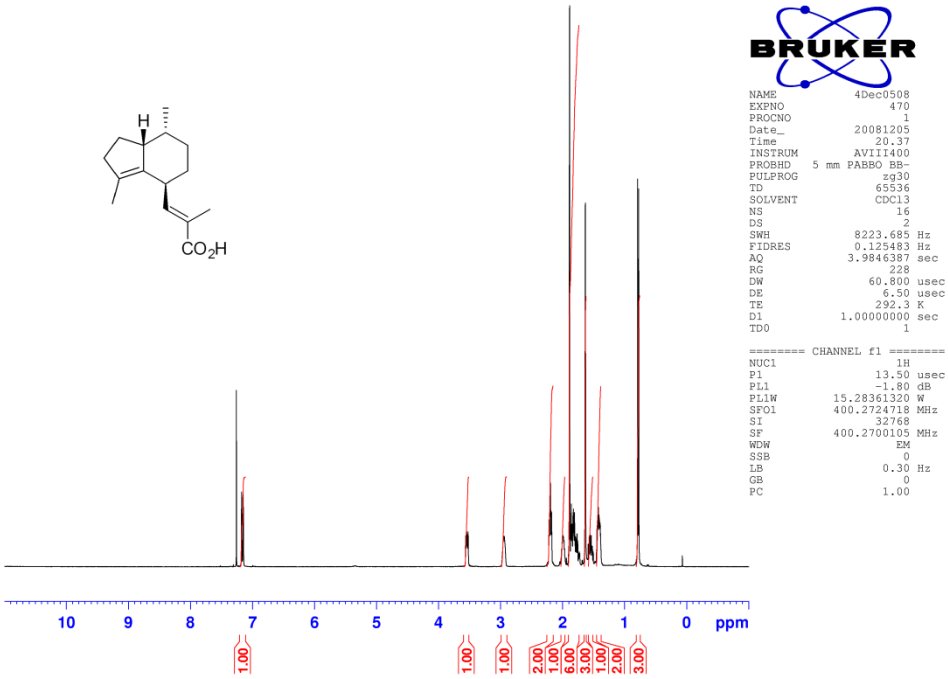


Valerenic ethyl ester (46)

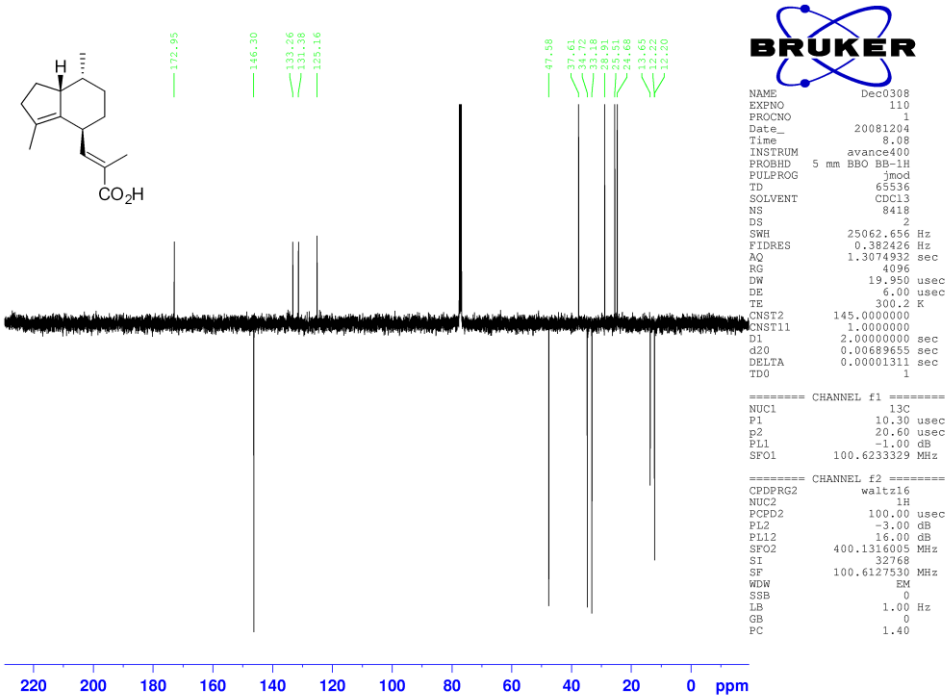




Valerenic acid (1)

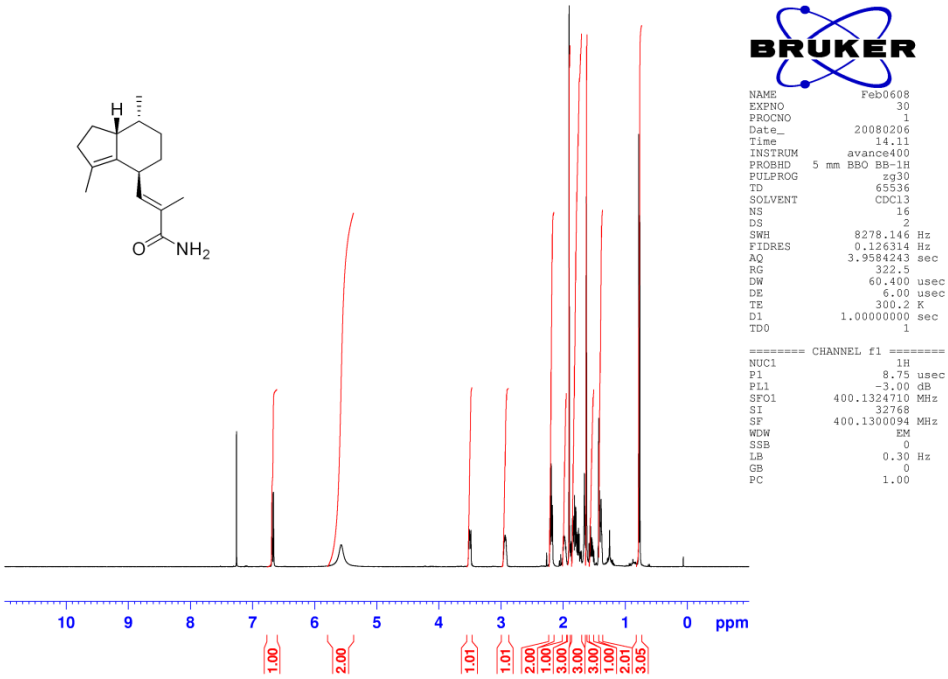



```
NAME                4Dec0508
EXPNO                    470
PROCNO                     1
Date_               20081205
Time                   20.37
INSTRUM              AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                       228
DW                    60.800 usec
DE                     6.50 usec
TE                   292.3 K
D1                  1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PL1                    -1.80 dB
PL1W            15.28361320 W
SFO1           400.2724718 MHz
SI                     32768
SF             400.27001105 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```

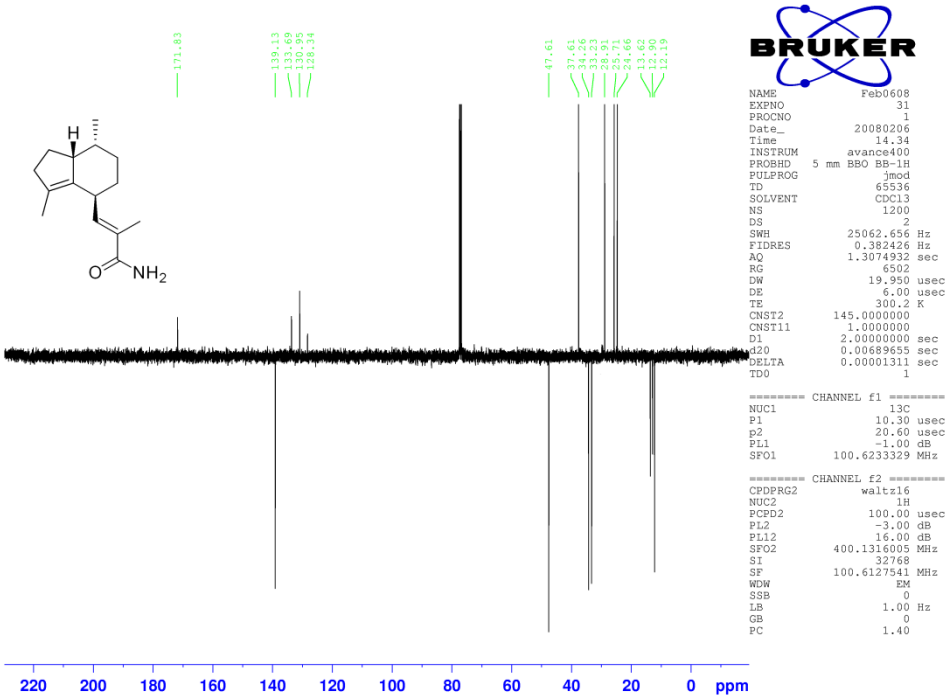



```
NAME                Dec0308
EXPNO                    110
PROCNO                     1
Date_               20081204
Time                   8.08
INSTRUM            avance400
PROBHD     5 mm BBO BB-1H
PULPROG                 jmod
TD                     65536
SOLVENT                CDCl3
NS                      8418
DS                         2
SWH                25062.656 Hz
FIDRES              0.382426 Hz
AQ                  1.3074932 sec
RG                      4096
DW                    19.950 usec
DE                     6.00 usec
TE                   300.2 K
CNST2              145.0000000
CNST11               1.0000000
D1                   2.00000000 sec
d20                  0.00689655 sec
DELTA                0.00001311 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                     10.30 usec
p2                     20.60 usec
PL1                    -1.00 dB
SFO1           100.6233329 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -3.00 dB
PL12                   16.00 dB
SFO2           400.1316005 MHz
SI                     32768
SF             100.6127530 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```

Valerenic amide (47)

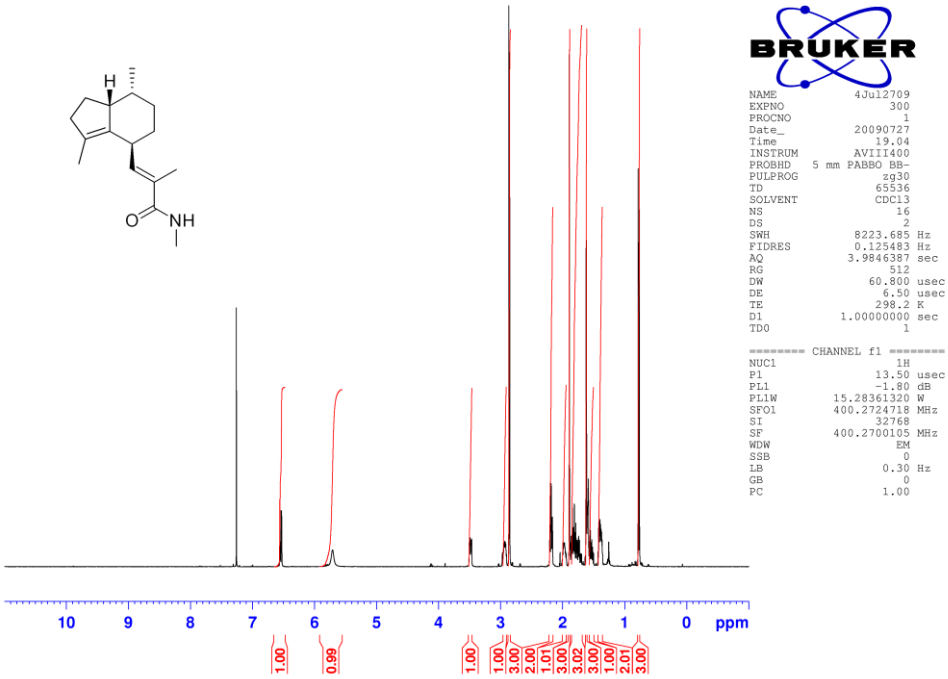



```
NAME                Feb0608
EXPNO                    30
PROCNO                    1
Date_              20080206
Time                  14.11
INSTRUM          avance400
PROBHD     5 mm BBO BB-1H
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8278.146 Hz
FIDRES             0.126314 Hz
AQ                 3.9584243 sec
RG                     322.5
DW                    60.400 usec
DE                     6.00 usec
TE                    300.2 K
D1              1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                      1H
P1                      8.75 usec
PL1                    -3.00 dB
SFO1           400.1324710 MHz
SI                    32768
SF             400.1300094 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```

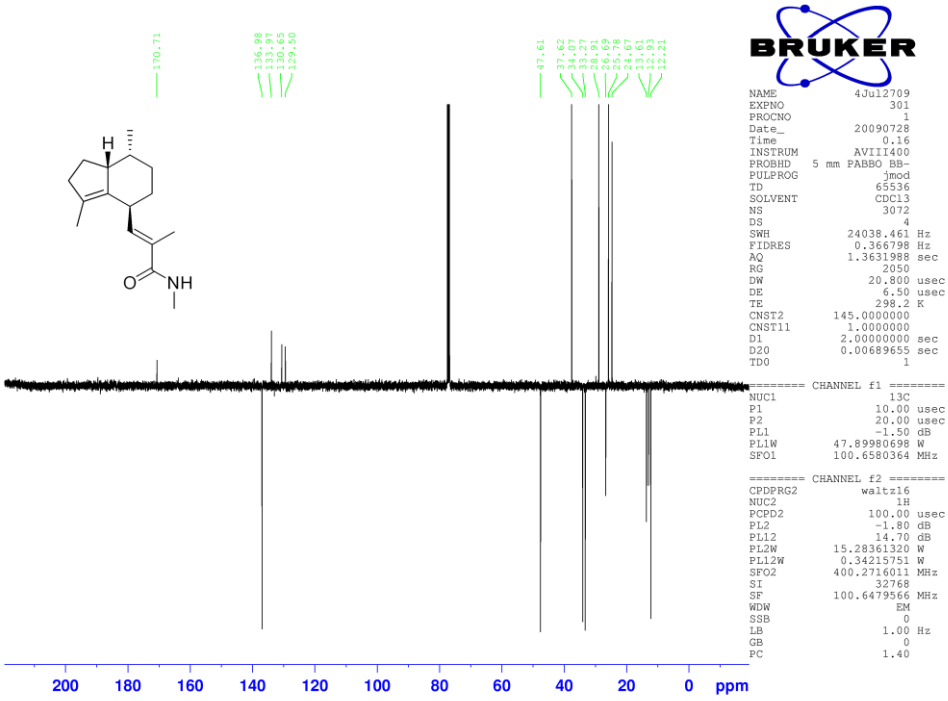



```
NAME                Feb0608
EXPNO                    31
PROCNO                    1
Date_              20080206
Time                  14.34
INSTRUM          avance400
PROBHD     5 mm BBO BB-1H
PULPROG               jmod
TD                    65536
SOLVENT               CDCl3
NS                     1200
DS                        2
SWH                25062.656 Hz
FIDRES             0.382426 Hz
AQ                 1.3074932 sec
RG                     6502
DW                   19.950 usec
DE                     6.00 usec
TE                    300.2 K
CNST2             145.0000000
CNST11              1.0000000
D1                  2.00000000 sec
d20                 0.00689655 sec
DELTA               0.00001311 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                      13C
P1                     10.30 usec
p2                     20.60 usec
PL1                    -1.00 dB
SFO1           100.6233329 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -3.00 dB
PL12                   16.00 dB
SFO2           400.1316005 MHz
SI                    32768
SF             100.6127541 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```

Valerenic N-methylamide (48)

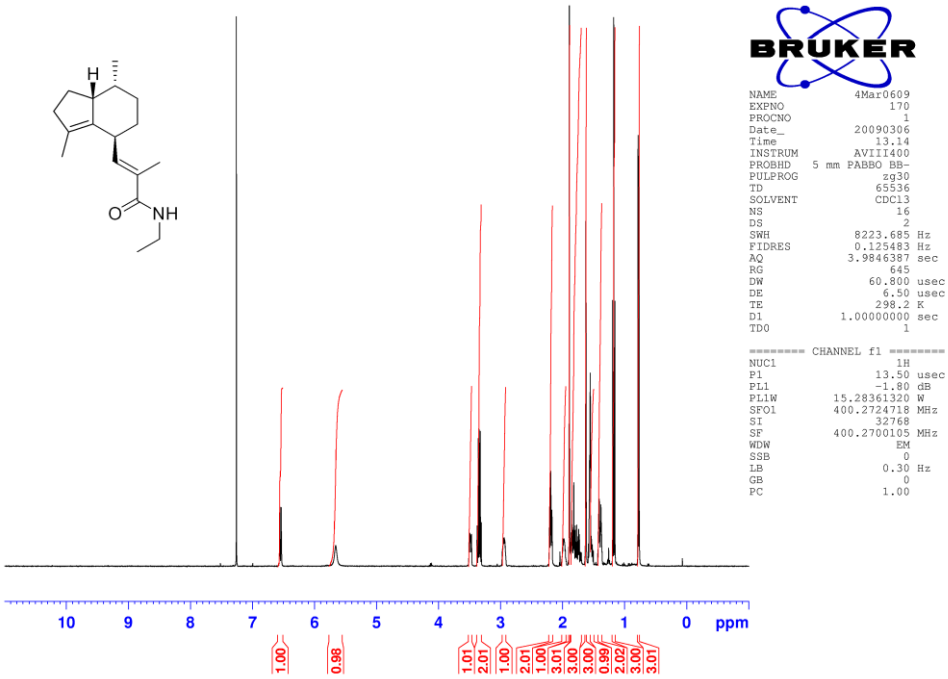



```
NAME                4Jul2709
EXPNO                    300
PROCNO                     1
Date_               20090727
Time                   19.04
INSTRUM              AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                       512
DW                    60.800 usec
DE                     6.50 usec
TE                    298.2 K
D1                  1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PL1                    -1.80 dB
PL1W            15.28361320 W
SFO1           400.2724718 MHz
SI                     32768
SF             400.2700105 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```

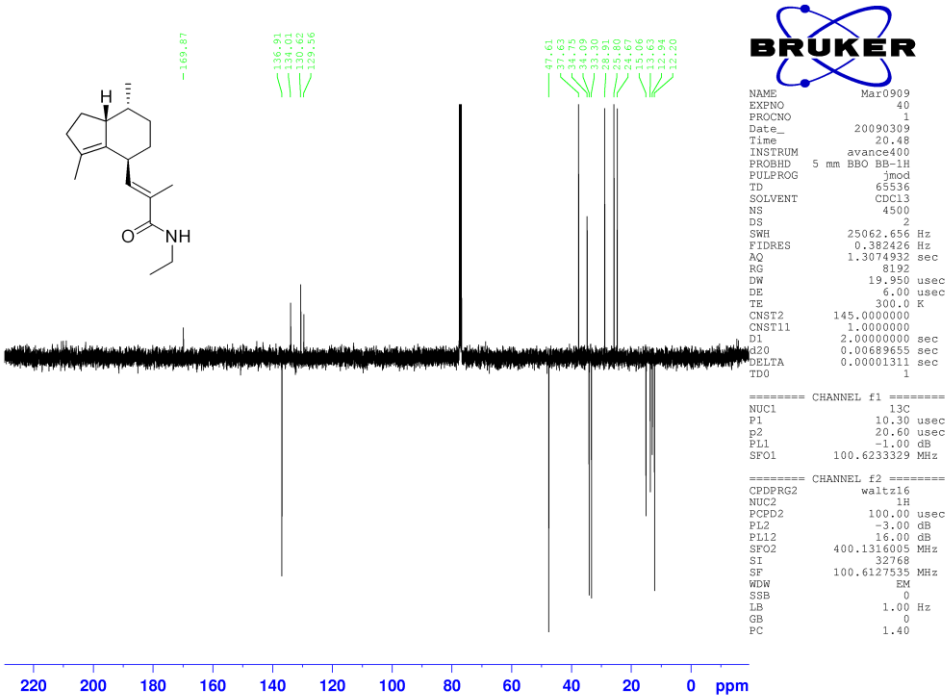



```
NAME                4Jul2709
EXPNO                    301
PROCNO                     1
Date_               20090728
Time                   0.16
INSTRUM              AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                jmod
TD                     65536
SOLVENT                CDCl3
NS                      3072
DS                         4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                      2050
DW                    20.800 usec
DE                     6.50 usec
TE                    298.2 K
CNST2              145.0000000
CNST11               1.0000000
D1                   2.00000000 sec
D20                  0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                     10.00 usec
P2                     20.00 usec
PL1                    -1.50 dB
PL1W            47.89980698 W
SFO1           100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -1.80 dB
PL12                   14.70 dB
PL2W            15.28361320 W
PL12W            0.34215751 W
SFO2           400.2716011 MHz
SI                     32768
SF             100.6479566 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```

Valerenic N-ethylamide (49)

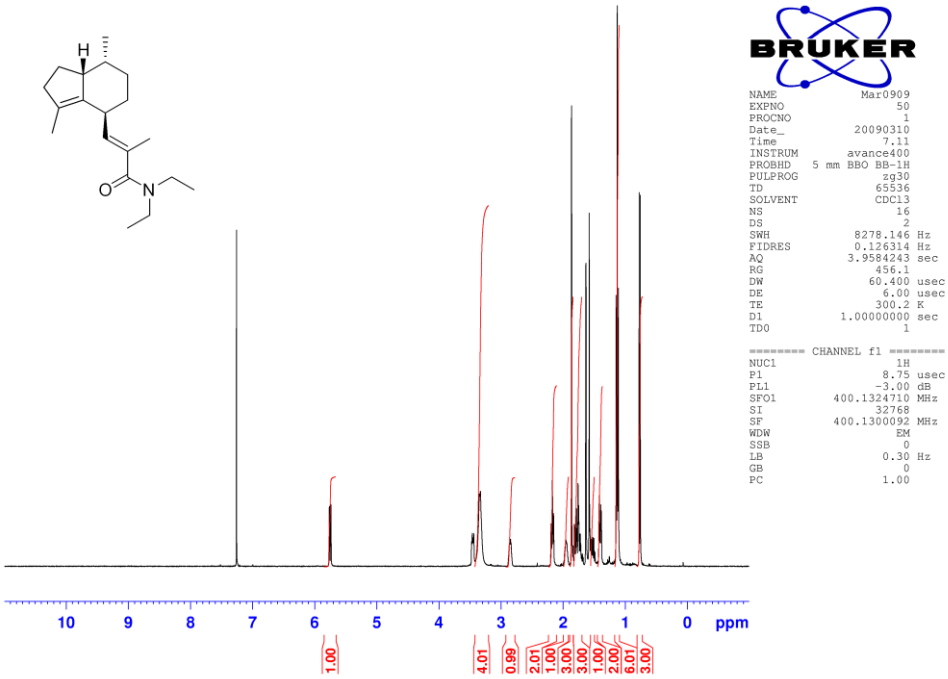



```
NAME                4Mar0609
EXPNO                    170
PROCNO                     1
Date_               20090306
Time                   13.14
INSTRUM              AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                       645
DW                    60.800 usec
DE                     6.50 usec
TE                   298.2 K
D1                  1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PL1                    -1.80 dB
PL1W            15.28361320 W
SFO1            400.2724718 MHz
SI                     32768
SF              400.2700105 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```

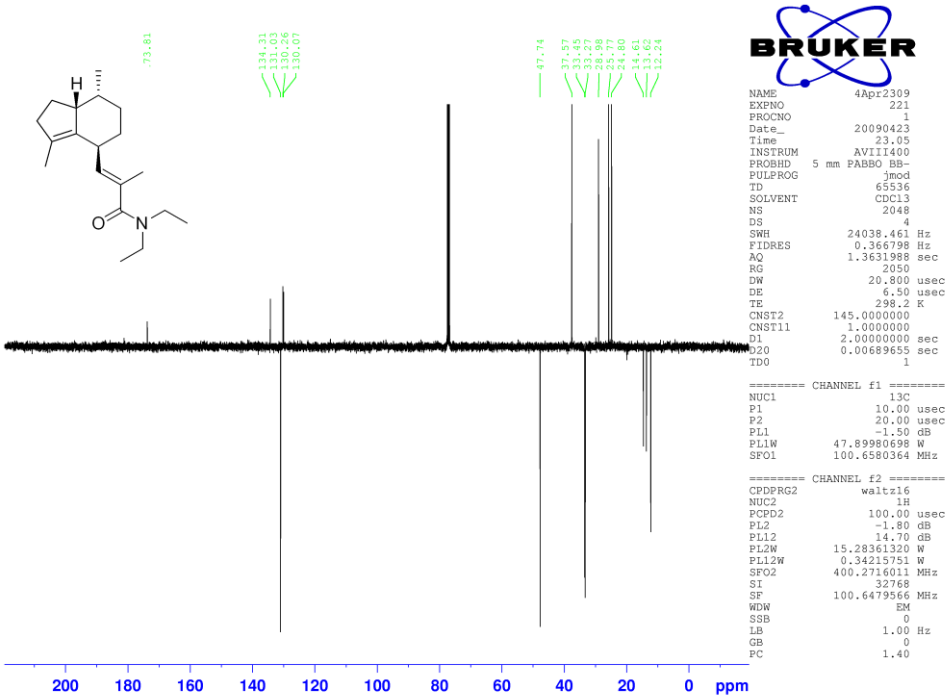



```
NAME                Mar0909
EXPNO                    40
PROCNO                     1
Date_               20090309
Time                   20.48
INSTRUM             avance400
PROBHD     5 mm BBO BB-1H
PULPROG                 jmod
TD                     65536
SOLVENT                CDCl3
NS                       4500
DS                         2
SWH                25062.656 Hz
FIDRES              0.382426 Hz
AQ                  1.3074932 sec
RG                      8192
DW                    19.950 usec
DE                     6.00 usec
TE                   300.0 K
CNST2           145.0000000
CNST11            1.0000000
D1                2.00000000 sec
D20               0.00689655 sec
DELTA             0.00001311 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                     10.30 usec
p2                     20.60 usec
PL1                    -1.00 dB
SFO1            100.6233329 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -3.00 dB
PL12                   16.00 dB
SFO2            400.1316005 MHz
SI                     32768
SF              100.6127535 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```

Valerenic N,N-diethylamide (50)

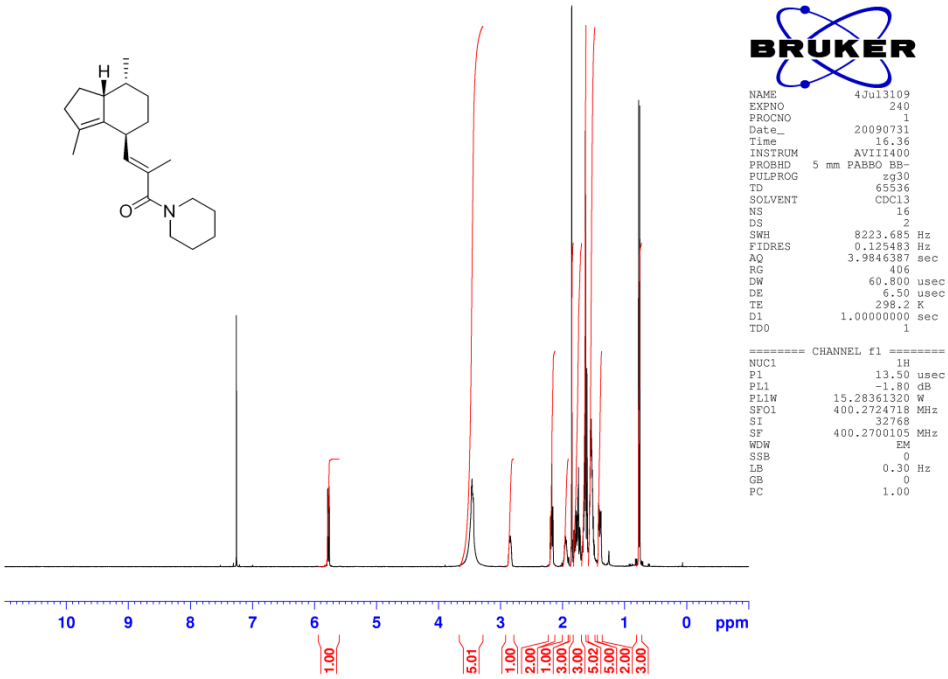



```
NAME                Mar0909
EXPNO                    50
PROCNO                    1
Date_              20090310
Time                   7.11
INSTRUM          avance400
PROBHD     5 mm BBO BB-1H
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8278.146 Hz
FIDRES            0.126314 Hz
AQ                3.9584243 sec
RG                    456.1
DW                   60.400 usec
DE                    6.00 usec
TE                   300.2 K
D1              1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    1H
P1                    8.75 usec
PL1                  -3.00 dB
SFO1          400.1324710 MHz
SI                    32768
SF            400.1300092 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```




```
NAME                4Apr2309
EXPNO                    221
PROCNO                    1
Date_              20090423
Time                   23.05
INSTRUM          AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                jmod
TD                    65536
SOLVENT               CDCl3
NS                     2048
DS                        4
SWH                24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631988 sec
RG                     2050
DW                   20.800 usec
DE                    6.50 usec
TE                   298.2 K
CNST2           145.0000000
CNST11            1.0000000
D1                2.00000000 sec
D20               0.00689655 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                   10.00 usec
P2                   20.00 usec
PL1                  -1.50 dB
PL1W           47.89980698 W
SFO1          100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2               100.00 usec
PL2                  -1.80 dB
PL12                 14.70 dB
PL2W           15.28361320 W
PL12W           0.34215751 W
SFO2          400.2716011 MHz
SI                    32768
SF            100.6479566 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```

Valerenic piperidine amide (51)

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PROCNO                     1
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PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
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FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                       406
DW                    60.800 usec
DE                     6.50 usec
TE                    298.2 K
D1                  1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
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P1                     13.50 usec
PL1                    -1.80 dB
PL1W            15.28361320 W
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SI                     32768
SF             400.2700105 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
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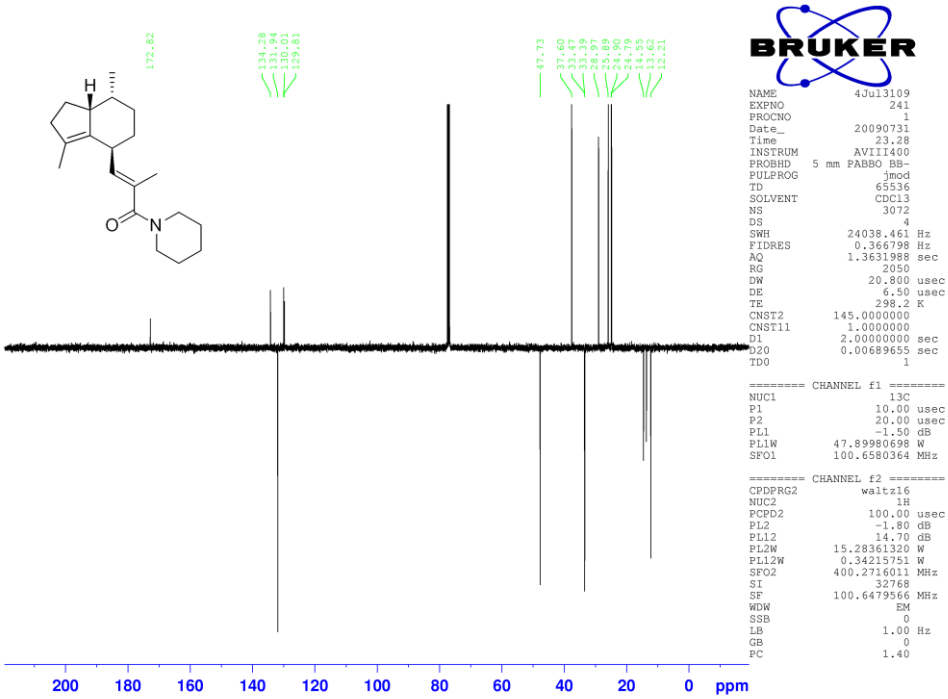


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PROCNO                     1
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TD                     65536
SOLVENT                CDCl3
NS                      3072
DS                         4
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FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                      2050
DW                    20.800 usec
DE                     6.50 usec
TE                    298.2 K
CNST2           145.0000000
CNST11            1.0000000
D1                2.00000000 sec
D20               0.00689655 sec
TD0                        1

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SFO1           100.6580364 MHz

======== CHANNEL f2 ========
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NUC2                      1H
PCPD2                 100.00 usec
PL2                    -1.80 dB
PL12                   14.70 dB
PL2W            15.28361320 W
PL12W            0.34215751 W
SFO2           400.2716011 MHz
SI                     32768
SF             100.6479566 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
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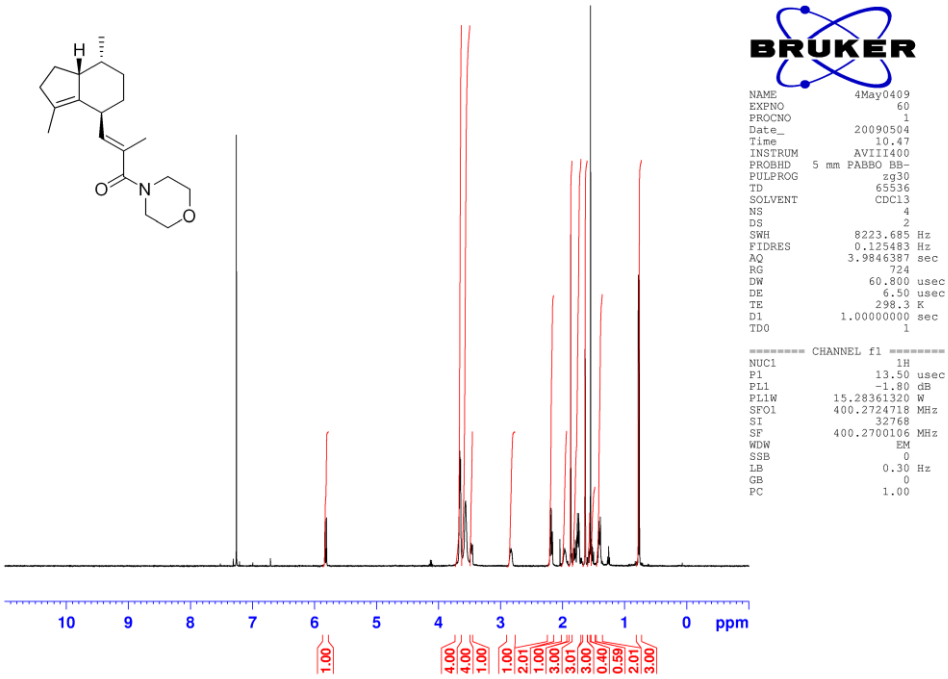
Valerenic morpholine amide (52)



BRUKER

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PROCNO                     1
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PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                         4
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                       724
DW                    60.800 usec
DE                     6.50 usec
TE                    298.3 K
D1                  1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
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PL1                    -1.80 dB
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LB                      0.30 Hz
GB                         0
PC                      1.00
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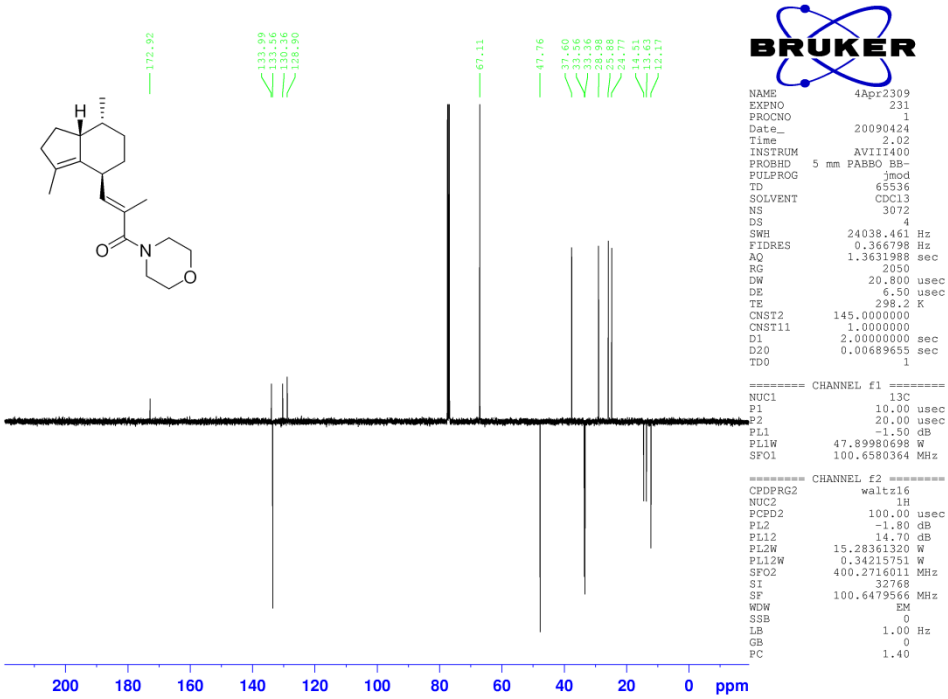

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PROCNO                     1
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Time                   2.02
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TD                     65536
SOLVENT                CDCl3
NS                      3072
DS                         4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                      2050
DW                    20.800 usec
DE                     6.50 usec
TE                    298.2 K
CNST2             145.0000000
CNST11              1.0000000
D1                  2.00000000 sec
D20                 0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                     10.00 usec
P2                     20.00 usec
PL1                    -1.50 dB
PL1W            47.89980698 W
SFO1           100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -1.80 dB
PL12                   14.70 dB
PL2W            15.28361320 W
PL12W            0.34215751 W
SFO2           400.2716011 MHz
SI                     32768
SF             100.6479566 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```

5.2 [1,3]-Isomerization of Allylic Alcohols, SI

Experimental procedures and analytical data of all compounds discussed in chapter 3.2.2 (*Efficient and Scalable One-Pot Synthesis of 2,4-Dienols from Cycloalkenones; Optimized Total Synthesis of Valerenic Acid*) can be found in the following supporting information.

Efficient and Scalable One-Pot Synthesis of 2,4-Dienols from Cycloalkenones; Optimized Total Synthesis of Valerenic Acid

Supporting Information

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Table of Contents:

1. Procedures

1.1 General Information:

All reactions were carried out in oven-dried glassware under an argon atmosphere unless stated otherwise. Diisopropylethylamine was distilled under Argon from CaH_2, anhydrous diethyl ether (99.9%) and anhydrous Methyl-*tert*-butyl ether (MTBE, 99.8%) were purchased from Aldrich. All other solvents were HPLC grade. Commercially available reagents were used without further purification. Racemic 6-methylcyclohex-2-enone and racemic 5-methylcyclohex-2-enone were prepared according to literature known procedures.[1,2] Reactions were magnetically stirred and monitored by thin layer chromatography with E. Merck silica gel 60 F_{254} plates. Flash column chromatography was performed with Merck silica gel (0.04-0.063 mm, 240-400 mesh) under pressure besides stated otherwise. Yields refer to chromatographically and spectroscopically pure compounds unless stated otherwise. ^{1}H NMR (400 MHz or 600 MHz) and ^{13}C NMR (100 MHz or 150 MHz) spectra were either recorded on Bruker Avance 400, DRX 400, or DRX 600 spectrometers at 400.13 MHz (100.61 MHz) or 600.13 MHz (150.90 MHz). All NMR spectra were measured in $CDCl_3$ solutions. The chemical shifts δ are reported relative to the residual solvent peaks (^{1}H, δ_{CDCl3} = 7.26 ppm; ^{13}C, δ_{CDCl3} = 77.16 ppm). All ^{1}H and ^{13}C shifts are given in ppm (s = singulet; d = doublet; t = triplet; q = quadruplet; m = multiplet; bs = broad signal). If possible, assignments of proton resonances were confirmed by correlated spectroscopy. Optical rotations were measured at 20°C on a P 341 Perkin-Elmer polarimeter at 589 nm. IR spectra were recorded of samples prepared as films on silicium plates on a Perkin-Elmer Spectrum 2000 Series FTIR spectrometer. High resolution mass spectra (HRMS) were measured on a Finnigan MAT 8230 apparatus with a resolution of 10000.

[1] For preparation of racemic 6-methylcyclohex-2-enone, see: F. A. Marques; Lenz, C. A.; Simonelli, F.; Noronha Sales Maia, B. H. L.; Vellasco, A. P.; Eberlin, M. N. *J. Nat. Prod.* **2004**, *67*, 1939

[2] For preparation of racemic 5-methylcyclohex-2-enone see: Chong, B.-D.; Ji, Y.-I.; Oh, S.-S.; Yang, J.-D.; Baik, W.; Koo, S. *J. Org. Chem.* **1997**, *62*, 9323

1.2 Experimental Procedures

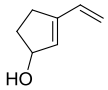
General Procedure (method A)

A solution of cycloalkenone (1.0 eq) and anhydrous diethyl ether (0.1 M) was cooled to 0 °C and treated with 1.0 M vinylmagnesium bromide (2.0 eq). After TLC indicated full conversion (usually 1 hour) water (0.1 M) and trifluoroacetic or acetic acid (2.5 eq) were added. The biphasic solution was vigorously stirred at 0 °C or ambient temperature until full conversion was observed by TLC. Then saturated aqueous $NaHCO_3$ was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (3x) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by chromatography provided the corresponding 2,4-dienol.

General Procedure (method B)

tert-Butyllithium (3.9 eq) was slowly added to solution of 2-bromopropene (2.0 eq) and anhydrous diethyl ether (1.0 M) precooled to -78 °C. The resulting slightly turbid solution was stirred for 2 hours at the same temperature before it was warmed to ambient temperature. After 15 minutes the clear yellow solution was transferred via canula to a solution of cycloalkenone (1.0 eq) and anhydrous diethyl ether (0.1 M) precooled to -78 °C. After TLC indicated full conversion (usually 1 hour) the resulting turbid mixture was warmed to 0°C before water (0.1 M) and trifluoroacetic or acetic acid (2.5 eq) were added. The vigorously stirred biphasic solution was stirred at the same temperature until full conversion was observed by TLC. Saturated aqueous $NaHCO_3$ was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (3x) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by chromatography provided the corresponding 2,4-dienol.

3-Vinylcyclopent-2-enol (3a)[3]

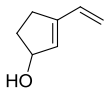


According to "method A" reaction of 2-cyclopentenone (98%, 50 µL, 0.5849 mmol, 1.0 eq) with 1.0 M vinylmagnesium bromide (1.16 mL, 1.16 mmol, 2.0 eq) in anhydrous diethyl ether (5.9 mL) and subsequent treatment with water (5.9 mL) and trifluoroacetic acid (113 µL, 1.4668 mmol, 2.5 eq) for 1.0 hours at 0 °C provides 50.6 mg of 3-vinylcyclopent-2-enol as slightly yellow oil with 78% yield (column chromatography H/EE = 5/1). (Attention: Dienol **3a** should be stored below 0°C.)

[3] In agreement with: Fisher, M. J.; Hehre, W. J.; Kahn, S. D.; Overmann, L. E. *J. Am. Chem. Soc.* **1988**, *110,* 4625.

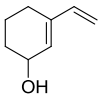
^{1}H-NMR (400MHz, $CDCl_3$): 6.58 (dd, J=17.5 Hz, 10.6 Hz, 1H), 5.79-5.75 (m, 1H), 5.27-5.15 (m, 2H), 4.94-4.85 (bs, 1H), 2.70-2.57 (m, 1H), 2.42-2.30 (m, 2H), 1.83-1.72 (m, 1H), 1.43 (d, J=5.6 Hz, 1H).
^{13}C-NMR (100MHz, $CDCl_3$, ppm): 146.1, 133.3, 132.1, 117.0, 77.6, 33.7, 29.2.
IR (film, cm^{-1}): 3297, 2922, 2853, 2359, 1591, 1455, 1416, 1319, 1275, 1264, 1158, 1042, 986, 968, 905, 750.
HRMS (EI, m/z): $[M]^+$ calc.: 110.0732; found: 110.0728.

3-Vinylcyclopent-2-enol (3a) (large scale)



According to "method A" reaction of 2-cyclopentenone (98%, 0.6 mL, 7.019 mmol, 1.0 eq) with 1.0 M vinylmagnesium bromide (14.0 mL, 14.0 mmol, 2.0 eq) in anhydrous diethyl ether (70 mL) and subsequent treatment with water (70 mL) and trifluoroacetic acid (1.35 mL, 17.52 mmol, 2.5 eq) for 1.5 hours at 0 °C provides 562 mg of 3-vinylcyclopent-2-enol as slightly yellow oil with 73% yield (column chromatography H/EE = 5/1). (Attention: Dienol **3a** should be stored below 0°C.)
For analytical data, see above.

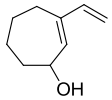
3-Vinylcyclohex-2-enol (5)[4]



According to "method A" reaction of 2-cyclohexenone (95%, 20 µL, 0.1957 mmol, 1.0 eq) with 1.0 M vinylmagnesium bromide (0.40 mL, 0.40 mmol, 2.0 eq) in anhydrous diethyl ether (2.0 mL) and subsequent treatment with water (2.0 mL) and trifluoroacetic acid (38 µL, 0.4932 mmol, 2.5 eq) for 1.5 hours at 0 °C provides 19.2 mg of 3-vinylcyclohex-2-enol as colorless oil with 79% yield (column chromatography H/EE = 5/1).
^{1}H-NMR (400MHz, $CDCl_3$): 6.35 (dd, J=17.5 Hz, J=10.8 Hz, 1H), 5.80-5.74 (m, 1H), 5.21 (d, J=17.5 Hz, 1H), 5.05 (d, J=10.8 Hz, 1H), 4.35-4.26 (m, 1H), 2.24-2.04 (m, 2H), 1.97-1.76 (m, 2H), 1.69-1.54 (m, 2H), 1.53-1.42 (bs, 1H).
^{13}C-NMR (100MHz, $CDCl_3$, ppm): 139.4, 138.9, 130.9, 113.1, 66.4, 32.3, 23.9, 19.0.
IR (film, cm^{-1}): 3389, 2934, 2869, 1714, 1666, 1453, 1427, 1258, 1189, 1056, 995, 966, 912, 749.
HRMS (EI, m/z): $[M]^+$ calc.: 124.0888; found: 124.0884.

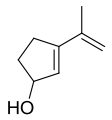
[4] In agreement with: Datta, S. C.; Franck, R. W.; Tripathy, R.; Quigley, G. J.; Huang, L.; Chen, S.; Sihaed, A. *J. Am. Chem. Soc.* **1990**, *112,* 8472.

3-Vinylcyclohept-2-enol (7)



According to "method A" reaction of 2-cycloheptenone (50 µL, 0.4484 mmol, 1.0 eq) with 1.0 M vinylmagnesium bromide (0.90 mL, 0.90 mmol, 2.0 eq) in anhydrous diethyl ether (4.5 mL) and subsequent treatment with water (4.5 mL) and trifluoroacetic acid (87 µL, 1.1293 mmol, 2.5 eq) for 1.5 hours at ambient temperature provides 49.7 mg of 3-vinylcyclohept-2-enol as colorless oil with 80% yield (column chromatography H/EE = 5/1).
^{1}H-NMR (400MHz, $CDCl_3$): 6.30 (dd, J=17.4 Hz, J=10.7 Hz, 1H), 5.81-5.75 (m, 1H), 5.15 (d, J=5.15 Hz, 1H), 4.98 (dd, J=10.7 Hz, J=0.58 Hz, 1H), 4.56-4.47 (m, 1H), 2.54-2.43 (m, 1H), 2.10-2.00 (m, 1H), 2.00-1.89 (m, 1H), 1.89-1.79 (m, 1H), 1.77-1.59 (m, 4H), 1.32-1.22 (m, 1H).
^{13}C-NMR (100MHz, $CDCl_3$, ppm): 140.2, 140.0, 139.3, 111.3, 71.8, 36.6, 27.8, 26.5, 25.7.
IR (film, cm^{-1}): 3343, 2928, 2853, 1605, 1450, 1351, 1276, 1028, 989, 891, 839.
HRMS (EI, m/z): $[M]^+$ calc.: 138.1045; found: 138.1047.

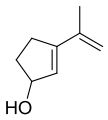
3-Isopropenylcyclopent-2-enol (8)[5]



According to "method B" reaction of 2-cyclopentenone (98%, 25 µL, 0.2924 mmol, 1.0 eq) with 2-propenyllithium, prepared from 2-bromopropene (52 µL, 0.5846 mmol, 2.0 eq) and *tert*-butyllithium (1.6 M, 0.71 mL, 1.136 mmol, 3.9 eq), in anhydrous diethyl ether (3.0 mL) and subsequent treatment with water (3.0 mL) and trifluoroacetic acid (58 µL, 0.7529 mmol, 2.5 eq) for 1 hour at 0 °C provides 29.5 mg of 3-isopropenylcyclopent-2-enol as colorless oil with 81% yield (column chromatography H/EE = 5/1 to 3/1). (Attention: Dienol **8** should be stored below 0°C.)
^{1}H-NMR (400MHz, $CDCl_3$): 5.83-5.78 (m, 1H), 5.02 (s, 2H), 4.97-4.88 (m, 1H), 2.74-2.64 (m, 1H), 2.46-2.32 (m, 2H), 1.94 (s, 3H), 1.80-1.73 (m, 1H), 1.48-1.41 (bs, 1H).
^{13}C-NMR (100MHz, $CDCl_3$, ppm): 147.7, 139.8, 129.0, 114.9, 78.1, 34.1, 30.6, 20.7.
IR (film, cm^{-1}): 3324, 2924, 2854, 1599, 1458, 1032, 970, 888.
HRMS (EI, m/z): $[M]^+$ calc.: 124.0888; found: 124.0884.

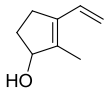
[5] In agreement with: Ramharter, J.; Mulzer, J. *Org. Lett.* **2009**, *11,* 1151.

3-Isopropenylcyclopent-2-enol (8) (large scale)



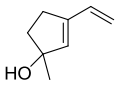
According to "method B" reaction of 2-cyclopentenone (98%, 1.5 mL, 17.55 mmol, 1.0 eq) with 2-propenyllithium, prepared from 2-bromopropene (3.1 mL, 34.85 mmol, 2.0 eq) and *tert*-butyllithium (1.9 M, 36.0 mL, 68.4 mmol, 3.9 eq), in anhydrous diethyl ether (175 mL) and subsequent treatment with water (175 mL) and trifluoroacetic acid (3.4 mL, 44.13 mmol, 2.5 eq) for 1 hour at 0 °C provides 1.57 g of 3-isoprpenylcyclopent-2-enol as colorless oil with 72% yield (column chromatography H/EE = 5/1 to 3/1). (Attention: Dienol **8** should be stored below 0°C.)
For analytical data, see above.

2-Methyl-3-vinylcyclopent-2-enol (10)[6]



According to "method A" reaction of 2-methyl-2-cyclopentenone (98%, 50 µL, 0.4990 mmol, 1.0 eq) with 1.0 M vinylmagnesium bromide (1.02 mL, 1.02 mmol, 2.0 eq) in anhydrous diethyl ether (5.0 mL) and subsequent treatment with water (5.0 mL) and trifluoroacetic acid (98 µL, 1.2721 mmol, 2.5 eq) for 0.75 hours at 0 °C provides 49.8 mg of 2-methyl-3-vinylcyclopent-2-enol as colorless oil with 79% yield (column chromatography H/EE = 5/1). (Attention: Dienol **10** should be stored below 0°C.)
^{1}H-NMR (400MHz, $CDCl_3$): 6.65 (dd, J=17.2 Hz, J=10.8 Hz, 1H), 5.21-5.13 (m, 2H), 4.71-4.60 (m, 1H), 2.65-2.53 (m, 1H), 2.38-2.26 (m, 2H), 1.83 (s, 3H), 1.71-1.62 (m, 1H), 1.45 (d, J=4.7 Hz, 1H).
^{13}C-NMR (100MHz, $CDCl_3$, ppm): 138.9, 136.7, 131.3, 115.4, 81.6, 32.5, 29.4, 11.3.
IR (film, cm^{-1}): 3345, 2960, 2936, 2912, 2854, 1443, 1421, 1276, 1261, 1198, 1049, 1005, 986, 900, 750.
HRMS (APCI, m/z): $[M-H_2O+H]^+$ calc.: 107.0855; found: 107.0850.

1-Methyl-3-vinylcyclopent-2-enol (12)



According to "method A" reaction of 3-methyl-2-cyclopentenone (97%, 60 µL, 0.5879 mmol, 1.0 eq) with 1.0 M vinylmagnesium bromide (1.10 mL, 1.10 mmol, 2.0 eq) in anhydrous

[6] In agreement with: Kita, Y.; Furukawa, A.; Futamura, J.; Ueda, K.; Sawama, Y.; Hamamoto, H.; Fujioka, H. *J. Org. Chem.* **2001**, *66,* 8779.

diethyl ether (6.0 mL) and subsequent treatment with water (6.0 mL) and acetic acid (85 µL, 1.4863 mmol, 2.5 eq) for 0.75 hours at 0 °C provides 72.3 mg of 1-methyl-3-vinylcyclopent-2-enol as slightly colorless oil with 99% yield (purification by column chromatography was not necessary, see spectra). (Attention: Dienol **12** should be stored below 0°C.)

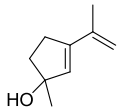
^{1}H-NMR (400MHz, $CDCl_3$): 6.53 (dd, J=17.5 Hz, J=10.6 Hz, 1H), 5.67-5.64 (m, 1H), 5.21 (dd, J=17.5 Hz, J=0.9 Hz, 1H), 5.16 (dd, J=10.6 Hz, J=1.3 Hz, 1H), 2.66-2.57 (m, 1H), 2.47-2.37 (m, 1H), 2.13-1.95 (m, 2H), 1.55-1.48 (bs, 1H), 1.40 (s, 3H).

^{13}C-NMR (100MHz, $CDCl_3$, ppm): 143.8, 136.5, 133.4, 116.5, 83.3, 40.0, 29.3, 27.6.

IR (film, cm^{-1}): 3338, 2965, 2929, 2852, 1593, 1450, 1367, 1287, 1236, 1178, 1107, 1081, 986, 904, 852.

HRMS (EI, m/z): $[M-CH_3]^+$ calc.: 109.0653; found: 109.0651.

3-Isopropenyl-1-methylcyclopent-2-enol (13)



According to "method B" reaction of 3-methyl-2-cyclopentenone (0.57 mL, 5.585 mmol, 1.0 eq) with 2-propenyl lithium, prepared from 2-bromopropene (1.0 mL, 11.24 mmol, 2.0 eq) and *tert*-butyllithium (1.9 M, 11.5 mL, 21.85 mmol, 3.9 eq), in anhydrous diethyl ether (56 mL) and subsequent treatment with water (56 mL) and acetic acid (0.8 mL, 13.99 mmol, 2.5 eq) for 1 hour at 0 °C provides 599.5 mg of 3-isopropenyl-1-methylcyclopent-2-enol as slightly yellow oil with 78% yield (column chromatography H/EE = 5/1). (Attention: Dienol **8** should be stored below 0°C.)

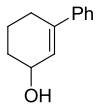
^{1}H-NMR (400MHz, $CDCl_3$): 5.68 (s, 1H), 5.02-4.97 (m, 2H), 2.71-2.61 (m, 1H), 2.51-2.41 (m, 1H), 2.12-1.95 (m, 2H), 1.92 (s, 3H), 1.56-1.52 (bs, 1H), 1.41 (s, 3H).

^{13}C-NMR (100MHz, $CDCl_3$, ppm): 145.4, 139.9, 133.4, 114.5, 83.7, 40.2, 30.8, 27.7, 20.6.

IR (film, cm^{-1}): 3354, 2967, 2928, 2855, 2346, 1600, 1452, 1368, 1304, 1180, 1133, 1084, 889, 851.

HRMS (EI, m/z): $[M]^+$ calc.: 138.1045; found: 138.1045.

3-Phenylcyclohex-2-enol (15)[7]



According to "method A" reaction of 2-cyclohexenone (95%, 50 µL, 0.4892 mmol, 1.0 eq) with 1.0 M phenylmagnesium bromide (0.98 mL, 0.98 mmol, 2.0 eq) in anhydrous diethyl ether (4.9 mL) and subsequent treatment with water (4.9 mL) and trifluoroacetic acid (95 µL,

[7] In agreement with: Reich, H. J.; Wollowitz, S. *J. Am. Chem. Soc.* **1982**, *104,* 7051.

1.2331 mmol, 2.5 eq) for 48 hours at ambient temperature provides 80.5 mg of 3-phenylcyclohex-2-enol as colorless oil with 94% yield (column chromatography H/EE = 3/1).

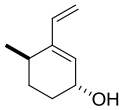
^{1}H-NMR (400MHz, $CDCl_3$): 7.44-7.39 (m, 2H), 7.36-7.30 (m, 2 H), 7.29-7.23 (m, 1H), 6.17-6.09 (m, 1H), 4.45-4.34 (bs, 1H), 2.53-2.43 (m, 1H), 2.43-2.32 (m, 1H), 2.01-1.86 (m, 2H), 1.82-1.63 (m, 2H), 1.55 (d, J=5.2 Hz, 1H).

^{13}C-NMR (100MHz, $CDCl_3$, ppm): 141.5, 140.4, 128.5, 127.6, 126.7, 125.5, 66.5, 31.9, 27.7, 19.6.

IR (film, cm^{-1}): 3336, 2934, 2862, 2358, 1494, 1446, 1344, 1276, 1053, 973, 907, 757, 695.

HRMS (ESI, m/z): $[M+Na]^+$ calc.: 197.0937; found: 197.0938.

***trans* 4-Methyl-3-vinylcyclohex-2-enol (18)**



According to "method A" reaction of 6-methylcyclohex-2-enone (48.0 mg, 0.4358 mmol, 1.0 eq) with 1.0 M vinylmagnesium bromide (0.87 mL, 0.87 mmol, 2.0 eq) in anhydrous diethyl ether (4.4 mL) and subsequent treatment with water (4.4 mL) and trifluoroacetic acid (84 µL, 1.0903 mmol, 2.5 eq) for 2 hours at 0 °C and additional 2 hours at ambient temperature provides 50.1 mg of 4-methyl-3-vinylcyclohex-2-enol as colorless oil with a *trans*/*cis* ratio of 2.3 to 1 and an combined yield of 83% yield (column chromatography H/EE = 5/1). Diastereomers were separated by means of HPLC.

Analytical data for the *trans*-isomer **18a**:

^{1}H-NMR (400MHz, $CDCl_3$): 6.23 (dd, J=17.7 Hz, J=10.9 Hz, 1H), 5.74 (d, J=4.3 Hz, 1H), 5.27 (dd, J=17.7 Hz, J=0.3 Hz, 1H), 5.10 (dd, J=10.8 Hz, J=0.4 Hz, 1H), 4.24-4.16 (bs, 1H), 2.61-2.51 (m, 1H), 1.96-1.86 (m, 2H), 1.72-1.64 (m, 1H), 1.47-1.39 (m, 2H), 1.06 (d, J=7.1 Hz, 3H).

^{13}C-NMR (100MHz, $CDCl_3$, ppm): 144.4, 138.5, 128.6, 113.9, 64.7, 27.9, 27.4, 25.2, 18.9.

IR (film, cm^{-1}): 3337, 2933, 2872, 1602, 1451, 1276, 1188, 1085, 1042, 1017, 998, 902, 876.

HRMS (APCI, m/z): $[M-H_2O+H]^+$ calc.: 121.1012; found: 121.1007.

Analytical data for the *cis*-isomer **18b**:

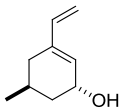
^{1}H-NMR (400MHz, $CDCl_3$): 6.22 (dd, J=17.7 Hz, J=10.9 Hz, 1H), 5.66-5.60 (m, 1H), 5.23 (d, J=17.6 Hz, 1H), 5.07 (d, J=10.9 Hz, 1H), 4.38-4.26 (m, 1H), 2.60-2.48 (m, 1H), 1.99-1.89 (m, 1H), 1.84-1.73 (m, 1H), 1.68-1.59 (m, 2H), 1.50-1.41 (bs, 1H), 1.15 (d, J=7.0 Hz, 3H).

^{13}C-NMR (100MHz, $CDCl_3$, ppm): 143.4, 138.3, 130.9, 113.4, 68.3, 28.6, 28.3, 27.6, 19.7.

IR (film, cm^{-1}): 3383, 2926, 2855, 1666, 1461, 1276, 1262, 1070, 1052, 1020, 994, 765, 757.

HRMS (ESI, m/z): $[M+Na]^+$ calc.: 161.0937; found: 161.0937.

***trans* 5-Methyl-3-vinylcyclohex-2-enol (21)**



According to "method A" reaction of 5-methylcyclohex-2-enone (49.7 mg, 0.4512 mmol, 1.0 eq) with 1.0 M vinylmagnesium bromide (0.90 mL, 0.90 mmol, 2.0 eq) in anhydrous diethyl ether (4.5 mL) and subsequent treatment with water (4.5 mL) and trifluoroacetic acid (87 µL, 1.1293 mmol, 2.5 eq) for 5 hours at ambient temperature provides 51.0 mg of 5-methyl-3-vinylcyclohex-2-enol as colorless oil with a *trans*/*cis* ratio of 7 to 1 and a combined yield of 82% yield (column chromatography H/EE = 5/1). Diastereomers were separated by means of HPLC.

Analytical data for the *trans*-isomer **21a**:

^{1}H-NMR (400MHz, $CDCl_3$): 6.36 (dd, J=17.5 Hz, J=10.8 Hz, 1H), 5.81 (d, J=4.1 Hz, 1H), 5.26 (d, J=17.5 Hz, 1H), 5.06 (d, J=10.8 Hz, 1H), 4.35-4.26 (m, 1H), 2.35 (dd, J=17.1 Hz, J=4.8 Hz, 1H), 2.02-1.86 (m, 1H), 1.82 (d, J=13.7 Hz, 1H), 1.64 (dd, J=17.2 Hz, J=10.5 Hz, 1H), 1.53-1.35 (m, 2H), 1.04 (d, J=6.6 Hz, 3H).

^{13}C-NMR (100MHz, $CDCl_3$, ppm): 139.5, 139.3, 128.8, 113.5, 65.3, 39.8, 32.7, 23.6, 21.7.

IR (film, cm^{-1}): 3344, 2951, 2924, 2870, 1607, 1456, 1439, 1418, 1377, 1181, 1061, 999, 952, 900, 872.

HRMS (ESI, m/z): $[M+Na]^+$ calc.: 161.0937; found: 161.0935.

Analytical data for the *cis*-isomer **21b**:[8]

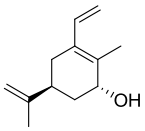
^{1}H-NMR (400MHz, $CDCl_3$): 6.36 (dd, J=17.5 Hz, J=10.7 Hz, 1H), 5.70-5.66 (s, 1H), 5.19 (d, J=17.5 Hz, 1H), 5.04 (d, J=10.8 Hz, 1H), 4.44-4.33 (bs, 1H), 2.31-2.22 (m, 1H), 2.12-2.05 (m, 1H), 1.81-1.63 (m, 2H), 1.46-1.38 (bs, 1H), 1.17-1.07 (m, 1H), 1.06 (d, J=6.4 Hz, 3H).

^{13}C-NMR (100MHz, $CDCl_3$, ppm): 139.0, 137.7, 132.1, 113.0, 68.7, 41.7, 32.6, 28.0, 22.2.

IR (film, cm^{-1}): 3321, 2951, 2926, 2871, 2360, 2341, 1606, 1456, 1375, 1358, 1302, 1190, 1158, 1074, 1031, 1009, 989, 971, 898.

HRMS (EI, m/z): $[M]^+$ calc.: 138.1045; found: 138.1043.

***(1R,5S)*-5-Isopropenyl-2-methyl-3-vinylcyclohex-2-enol (24)**



According to "method A" reaction of *(R)*-carvone (98%, 65 µL, 0.4067 mmol, 1.0 eq) with 1.0 M vinylmagnesium bromide (0.81 mL, 0.81 mmol, 2.0 eq) in anhydrous diethyl ether (4.0 mL) and subsequent treatment with water (4.0 mL) and trifluoroacetic acid (157 µL, 2.0379 mmol, 5.0 eq) for 7 days at ambient temperature provides 57.2 mg of *(1R,5S)*-5-Isopropenyl-2-methyl-3-vinylcyclohex-2-enol as colorless oil with a *trans*/*cis* ratio

[8] In agreement with: Shimizu, N.; Akita, H.; Kawamata, T. *Chem. Pharm. Bull.* **1996**, *44,* 665.

of 6 to 1 and an combined yield of 79% yield (column chromatography H/EE = 10/1). Diastereomers were separated by means of HPLC.

Analytical data for the *trans*-isomer **24a**:

^{1}H-NMR (400MHz, $CDCl_3$): 6.78 (dd, J=17.5 Hz, J=11.0 Hz, 1H), 5.27 (dd, J=17.4 Hz, J=1.1 Hz, 1H), 5.11 (dd, J=11.1 Hz, J=0.9 Hz, 1H), 4.81-4.75 (m, 2H), 4.15-4.08 (m, 1H), 2.47-2.36 (m, 2H), 1.99-1.87 (m, 5H), 1.79 (s, 3H), 1.66-1.55 (m, 2H).

^{13}C-NMR (100MHz, $CDCl_3$, ppm): 149.3, 134.9, 132.5, 131.4, 113.7, 109.5, 70.7, 36.6, 35.6, 30.8, 21.0, 16.9.

IR (film, cm^{-1}): 3332, 3087, 2967, 2917, 1644, 1441, 1421, 1375, 1169, 1051, 1010, 987, 949, 890.

HRMS (APCI, m/z): $[M-H_2O+H]^+$ calc.: 161.1325; found: 161.1321.

Analytical data for the *cis*-isomer **24b**:

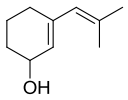
^{1}H-NMR (400MHz, $CDCl_3$): 6.79 (dd, J=17.5 Hz, J= 11.0 Hz, 1H), 5.22 (d, J=17.4 Hz, 1H), 5.10 (d, J=11.2 Hz, 1H), 4.81-4.74 (m, 2H), 4.28-4.19 (m, 1H), 2.40-2.14 (m, 3H), 2.12-2.01 (m, 1H), 1.89 (s, 3H), 1.79 (s, 3H), 1.54-1.46 (m, 2H).

^{13}C-NMR (100MHz, $CDCl_3$, ppm): 149.2, 135.0, 134.6, 130.3, 113.4, 109.6, 72.5, 39.4, 37.9, 30.9, 20.8, 14.3.

IR (film, cm^{-1}): 3361, 2925, 2857, 1645, 1449, 1376, 1277, 1260, 1073, 1049, 1025, 1008, 990, 891.

HRMS (APCI, m/z): $[M-H_2O+H]^+$ calc.: 161.1325; found: 161.1318.

3-(2'-Methyl-1'-propenyl)cyclohex-2-enol (25)



According to "method A" reaction of 2-cyclohexenone (95%, 50 µL, 0.4892 mmol, 1.0 eq) with 0.5 M 2-methyl-1-propenylmagnesium bromide (1.95 mL, 0.975 mmol, 2.0 eq) in anhydrous diethyl ether (4.9 mL) and subsequent treatment with water (4.9 mL) and trifluoroacetic acid (95 µL, 1.2331 mmol, 2.5 eq) for 1 hour at 0 °C provides 36.5 mg of 3-(2'-Methyl-1'-propenyl)cyclohex-2-enol as colorless oil with 49% yield and 35.0 mg of an inseparable cis/trans mixture of 1-(cyclohex-2-enylidene)-2-methyl-2-propanol with 47% yield (column chromatography H/EE = 10/1 to 5/1).

Analytical data for **25**:

^{1}H-NMR (400MHz, $CDCl_3$): 5.59-5.34 (m, 2H), 4.34-4.23 (m, 1H), 2.15-1.93 (m, 2H), 1.89-1.67 (m, 8H), 1.66-1.58 (m, 2H), 1.45-1.35 (bs, 1H).

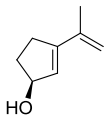
^{13}C-NMR (100MHz, $CDCl_3$, ppm): 139.2, 134.6, 127.3, 126.8, 66.2, 31.9, 29.6, 27.1, 19.8, 19.4.

IR (film, cm^{-1}): 3369, 2933, 2863, 2359, 1447, 1377, 1276, 1261, 1190, 1158, 1056, 1018, 975, 914, 891, 764, 750.

HRMS (ESI, m/z): $[M+Na]^+$ calc.: 175.1093; found: 175.1086.

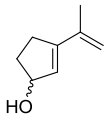
Analytical data for **26** (E/Z = 3/1):
^{1}H-NMR (400MHz, $CDCl_3$): 6.97-6.91 (m, 0.25H), 6.00-5.92 (m, 0.75H), 5.90-5.73 (m, 1H), 5.41-5.22 (2 s, 1H), 2.69-2.59 (m, 1.5H), 2.27-2.20 (m, 0.5H), 2.16-2.04 (m, 2H), 1.76-1.65 (m, 2H), 1.54-1.42 (2 bs, 1H), 1.39 (s, 6H).
^{13}C-NMR (100MHz, $CDCl_3$, ppm): 136.7 (E), 134.8 (Z), 134.1 (E), 131.9 (Z), 131.7 (E), 131.0 (Z), 129.4 (E), 125.3 (Z), 71.4 (Z), 71.3 (E), 33.1 (Z), 31.9 (Z), 31.3 (E), 26.1 (Z), 26.1 (E), 25.4 (E), 23.4 (Z), 22.6 (E).
IR (film, cm^{-1}): 3387, 2974, 2936, 2867, 1685, 1451, 1377, 1276, 1260, 1159, 1059, 956, 917, 764, 750.
HRMS (ESI, m/z): $[M+Na]^+$ calc.: 175.1093; found: 175.1089.

***(1S)*-3-Isopropenylcyclopent-2-enol (28)**[5]



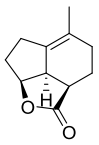
To a solution of racemic dienol **8** (520.5 mg, 4.191 mmol, 1.0 eq) and anhydrous MTBE (14.5 mL) were added Amano lipase PS (111.0 mg) and vinyl acetate (0.4 mL, 4.340 mmol, 1.0 eq). The resulting mixture was stirred at ambient temperature for 24 hours. After a small NMR-sample indicated conversion > 50% solids were removed by filtration and the resulting filtrate concentrated in vacuo. Purification of the residue by chromatography (H/EE = 10/1 to 1/1) using Merck aluminium oxide 90 (0.063-0.200 mm70-230 mesh) provided 321.0 mg of ester **27** with 46% yield and 234.8 mg of optically enriched alcohol **28** with 45% yield and an enantiomeric excess > 95% (Attention: Ester **27** is acid labile and should be stored below 0°C.). Analytical data for compound **28** is consistent with racemic alcohol **8**, see above. $[\alpha]_D^{20}$ = - 124.9 (c = 1.175 g/100 ml, DCM).
Analytical data for ester **27**:
^{1}H-NMR (400MHz, $CDCl_3$): 5.81-5.71 (m, 2H), 5.05 (s, 2H), 2.74-2.65 (m, 1H), 2.52-2.33 (m, 2H), 2.04 (s, 3H), 1.95 (s, 3H), 1.93-1.85 (m, 1H).
^{13}C-NMR (100MHz, $CDCl_3$, ppm): 171.2, 150.0, 139.5, 124.9, 115.6, 81.0, 30.7, 30.3, 21.5, 20.6.
IR (film, cm^{-1}): 2947, 2857, 1732, 1600, 1454, 1372, 1238, 1165, 1100, 1027, 962, 888.
HRMS (ESI, m/z): $[M]^+$ calc.: 166.0994; found: 166.0995.
$[\alpha]_D^{20}$ = + 213.7 (c = 1.110 g/100 ml, DCM).

Racemization of ester 27:



To solution of acetate **27** (251.4 mg, 1.512 mmol, 1.0 eq) and THF (8 mL) cooled to 0°C was added water (8 mL) and Merck silica gel (0.04-0.063 mm, 240-400 mesh) (256.5 mg). The resulting mixture was vigorously stirred for 36 hours at ambient temperature before solids were removed by filtration. The filtrate was treated with saturated aqueous $NaHCO_3$ and extracted with dichloromethane (4x). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by chromatography (H/EE = 4/1) provided 178.1 mg of 3-isopropenylcyclopent-2-enol (**8**) with 95% yield. For analytical data, see above. $[\alpha]_D^{20} = 0.000$ (c =1.05 g/100 ml, DCM).

Lactone 29[5]



Anhydrous $MgBr_2 \bullet Et_2O$ (977 mg, 3.783 mmol, 2.0 eq) was suspended in anhydrous dichloromethane (4.5 mL), treated with diisopropylethylamine (1.3 mL, 7.644 mmol, 4.0 eq) and stirred for 15 minutes until the suspension turns magenta. Then compound **28** (234.8 mg, 1.891 mmol, 1.0 eq) dissolved in dichloromethane (14.5 mL) was added slowly via canula. After stirring for 1 hour methyl acrylate (0.34 mL, 3.776 mmol, 2.0 eq) was added dropwise. The resulting mixture was stirred for 6 hours before it was quenched with saturated aqueous NH_4Cl. For a better phase separation potassium sodium tartrate was added and the solution extracted with diethyl ether (2x) and dichloromethane (3x). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by chromatography (H/EE = 6/1) furnished 273.7 mg of compound **29** as white solid with 81% yield.

^{1}H-NMR (400 MHz $CDCl_3$, ppm): 4.84 (dt, J=5.5Hz, J=1.0Hz, 1H), 3.02 (ddd, J=6.5Hz, J=6.0Hz, J=3.2Hz, 1H), 2.88-2.80 (m, 1H), 2.63-2.51 (m, 1H), 2.32-2.18 (m, 1H), 2.15-1.87 (m, 6H), 1.65 (s, 3H).

^{13}C-NMR (100MHz, $CDCl_3$, ppm): 178.7, 130.4, 129.3, 83.4, 43.8, 39.7, 29.1, 27.5, 27.2, 20.2, 19.9.

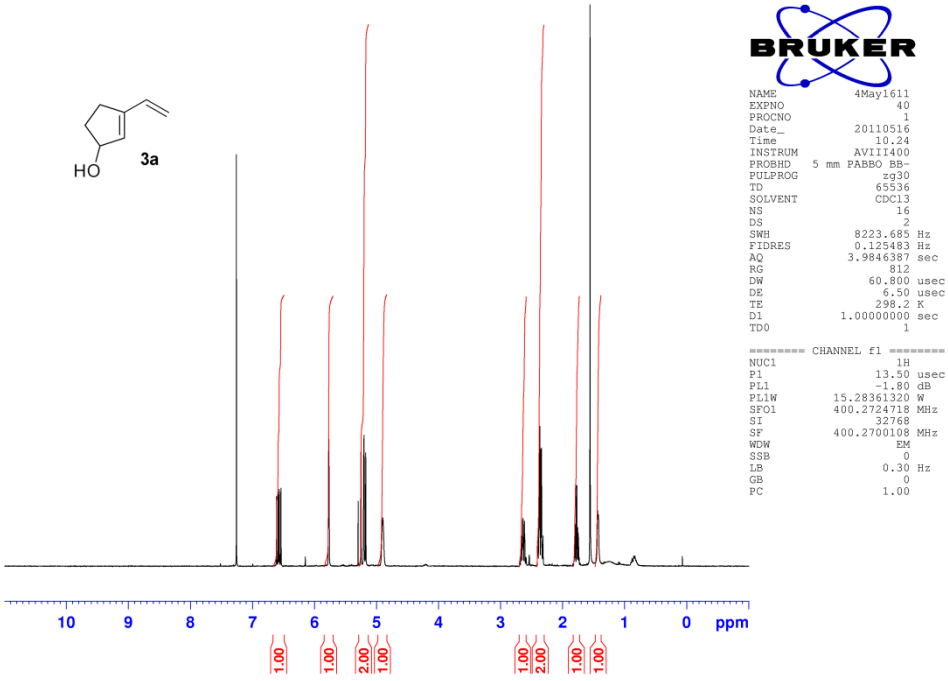
IR (film, cm^{-1}): 2925, 1763, 1449, 1335, 1142, 1020, 985, 932, 877.

HRMS (EI, m/z): $[M]^+$ calc.: 178.0994; found: 178.0997.

$[\alpha]_D^{20} = -94.4$ (c = 0.710 g/100mL, DCM).

2. NMR Spectra

3-Vinylcyclopent-2-enol (3a)

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PROCNO                     1
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TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                       812
DW                    60.800 usec
DE                     6.50 usec
TE                    298.2 K
D1                  1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
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P1                     13.50 usec
PL1                    -1.80 dB
PL1W            15.28361320 W
SFO1            400.2724718 MHz
SI                     32768
SF              400.2700108 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
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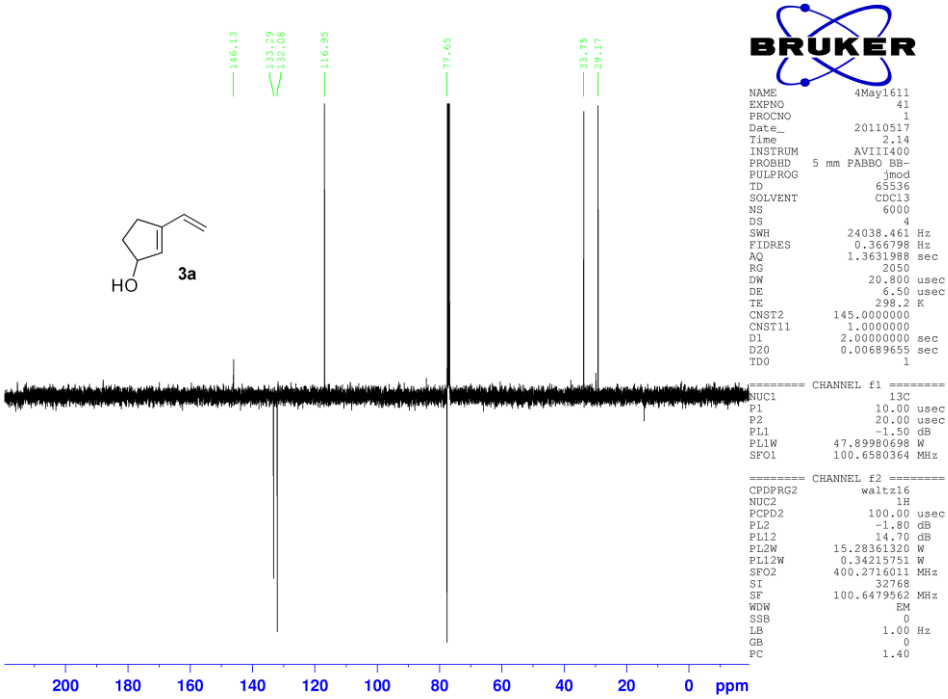


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TD                     65536
SOLVENT                CDCl3
NS                       6000
DS                         4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                      2050
DW                    20.800 usec
DE                     6.50 usec
TE                    298.2 K
CNST2              145.0000000
CNST11               1.0000000
D1                  2.00000000 sec
D20                 0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                     10.00 usec
P2                     20.00 usec
PL1                    -1.50 dB
PL1W            47.89980698 W
SFO1            100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -1.80 dB
PL12                   14.70 dB
PL2W            15.28361320 W
PL12W            0.34215751 W
SFO2            400.2716011 MHz
SI                     32768
SF              100.6479562 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```
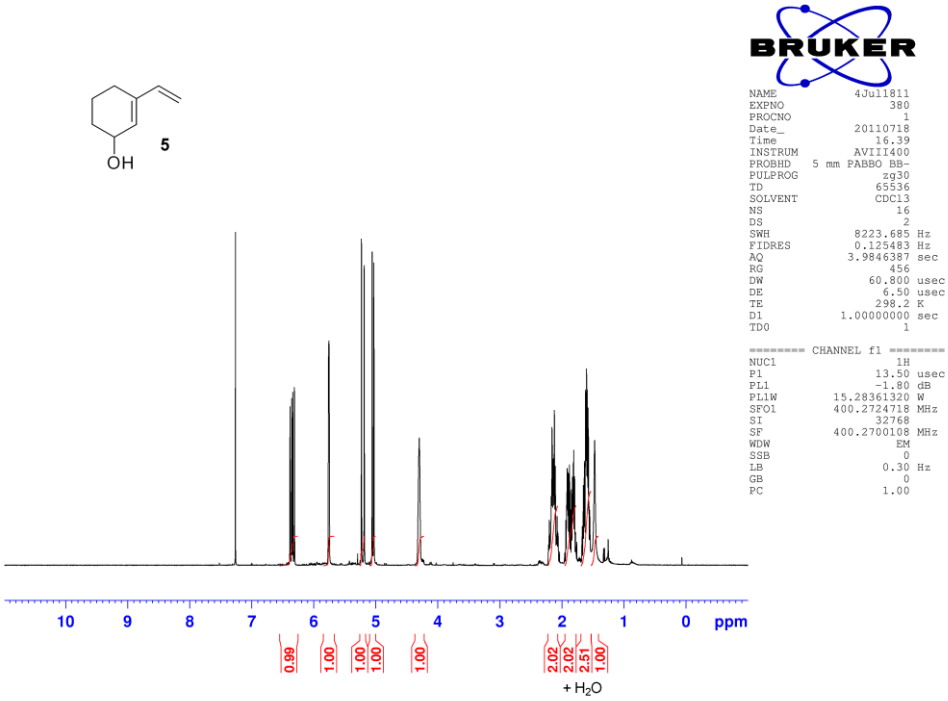
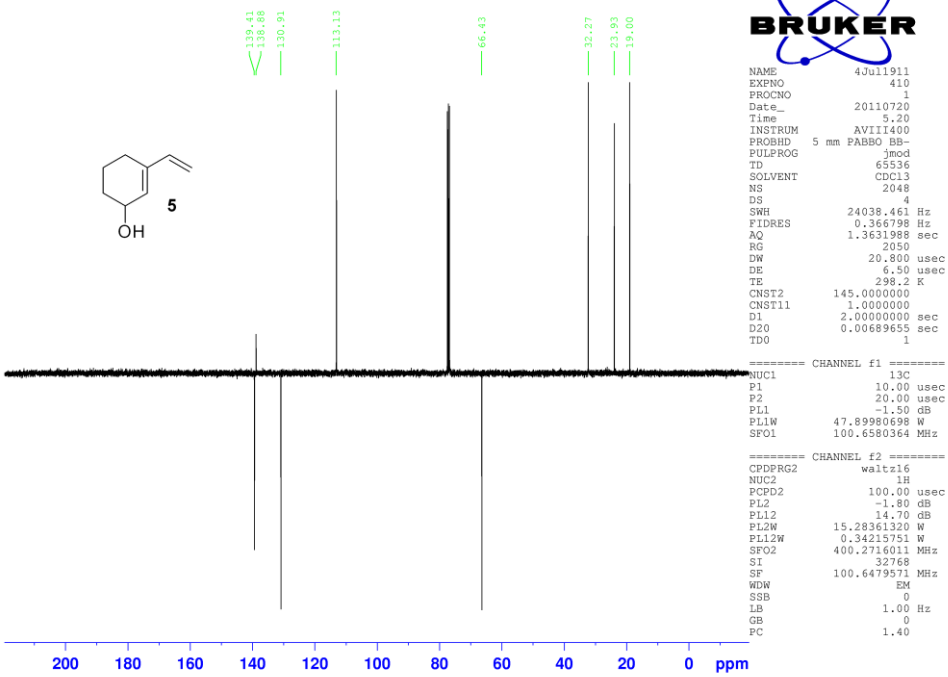

3-Vinylcyclohex-2-enol (5)

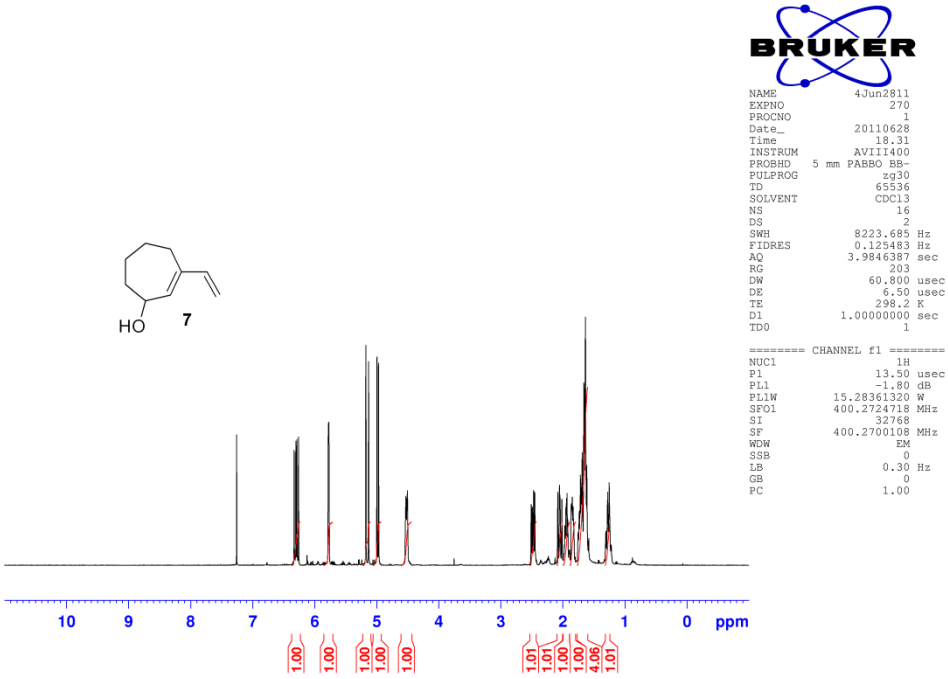



```
NAME                4Jul1811
EXPNO                    380
PROCNO                     1
Date_               20110718
Time                   16.39
INSTRUM              AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                       456
DW                  60.800 usec
DE                   6.50 usec
TE                   298.2 K
D1                 1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PL1                    -1.80 dB
PL1W            15.28361320 W
SFO1           400.2724718 MHz
SI                       32768
SF             400.2700108 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```

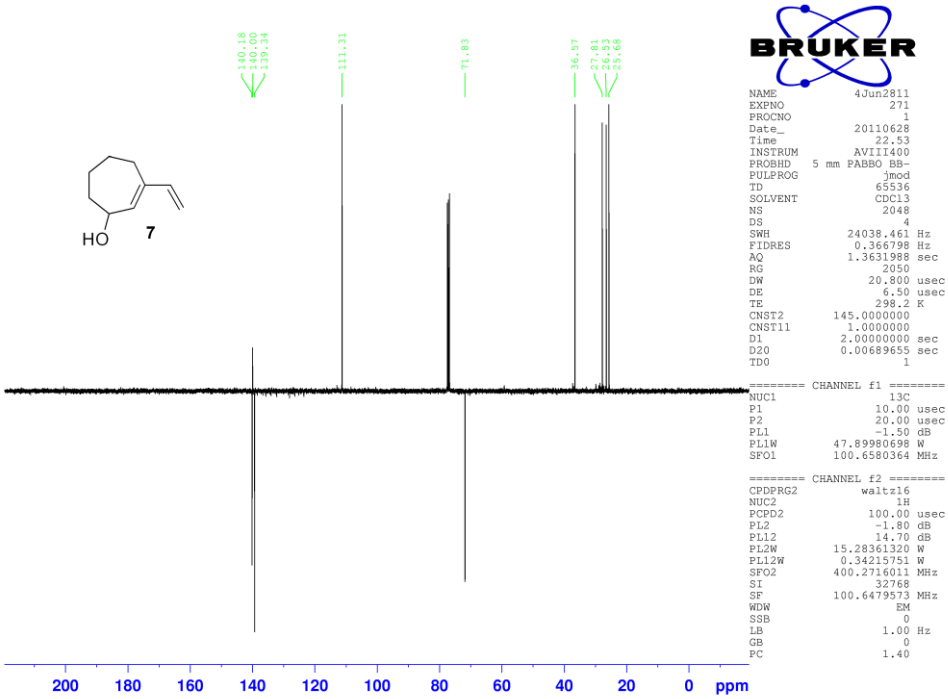



```
NAME                4Jul1911
EXPNO                    410
PROCNO                     1
Date_               20110720
Time                    5.20
INSTRUM              AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                jmod
TD                    65536
SOLVENT               CDCl3
NS                     2048
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631988 sec
RG                     2050
DW                  20.800 usec
DE                   6.50 usec
TE                   298.2 K
CNST2             145.0000000
CNST11              1.0000000
D1                 2.00000000 sec
D20                0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                     13C
P1                     10.00 usec
P2                     20.00 usec
PL1                    -1.50 dB
PL1W            47.89980698 W
SFO1           100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -1.80 dB
PL12                   14.70 dB
PL2W            15.28361320 W
PL12W            0.34215751 W
SFO2           400.2716011 MHz
SI                       32768
SF             100.6479571 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```

3-Vinylcyclohept-2-enol (7)

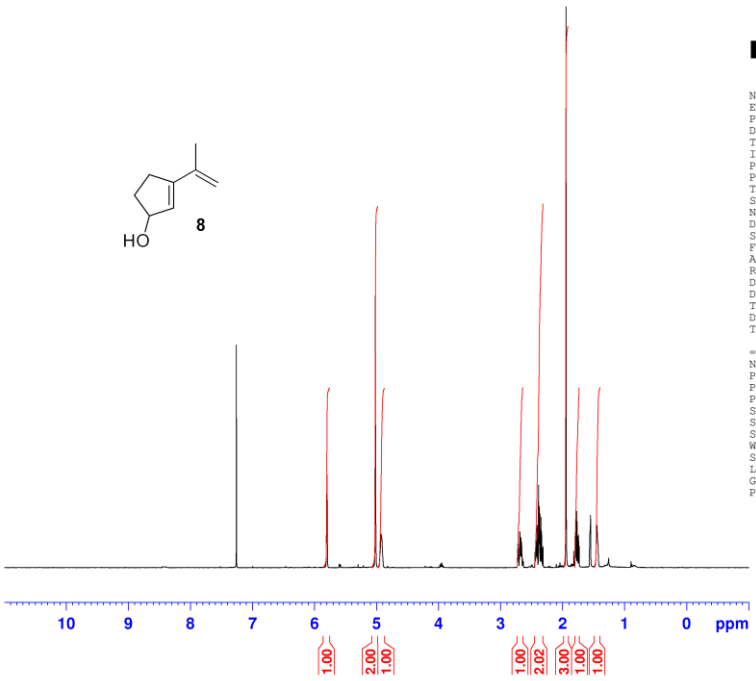



```
NAME                4Jun2811
EXPNO                    270
PROCNO                     1
Date_               20110628
Time                   18.31
INSTRUM              AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                       203
DW                    60.800 usec
DE                     6.50 usec
TE                    298.2 K
D1                 1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PL1                    -1.80 dB
PL1W            15.28361320 W
SFO1           400.2724718 MHz
SI                      32768
SF             400.2700108 MHz
WDW                        EM
SSB                         0
LB                      0.30 Hz
GB                          0
PC                      1.00
```



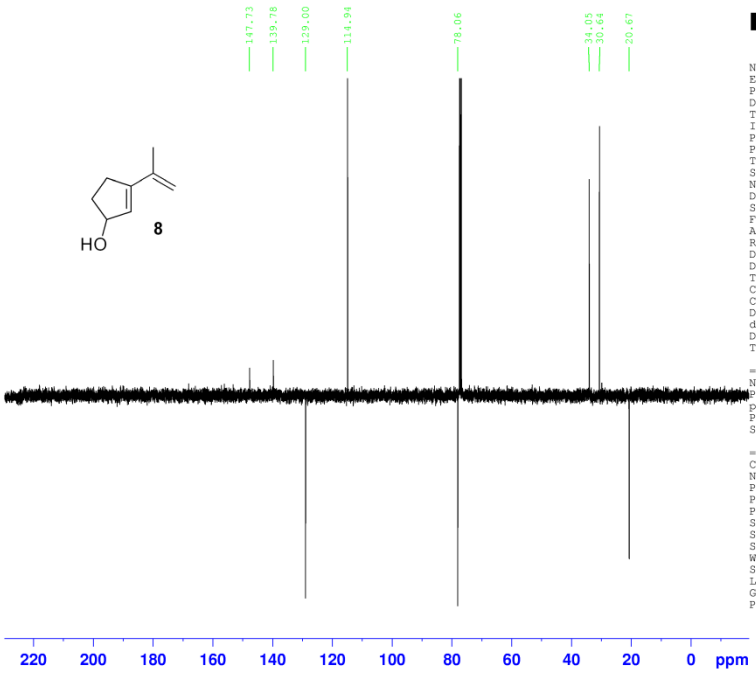

```
NAME                4Jun2811
EXPNO                    271
PROCNO                     1
Date_               20110628
Time                   22.53
INSTRUM              AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                jmod
TD                    65536
SOLVENT               CDCl3
NS                       2048
DS                          4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631988 sec
RG                       2050
DW                    20.800 usec
DE                     6.50 usec
TE                    298.2 K
CNST2             145.0000000
CNST11              1.0000000
D1                 2.00000000 sec
D20                0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                     10.00 usec
P2                     20.00 usec
PL1                    -1.50 dB
PL1W            47.89980698 W
SFO1           100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -1.80 dB
PL12                   14.70 dB
PL2W            15.28361320 W
PL12W            0.34215751 W
SFO2           400.2716011 MHz
SI                      32768
SF             100.6479573 MHz
WDW                        EM
SSB                         0
LB                      1.00 Hz
GB                          0
PC                      1.40
```

3-Isopropenylcyclopent-2-enol (8)



BRUKER

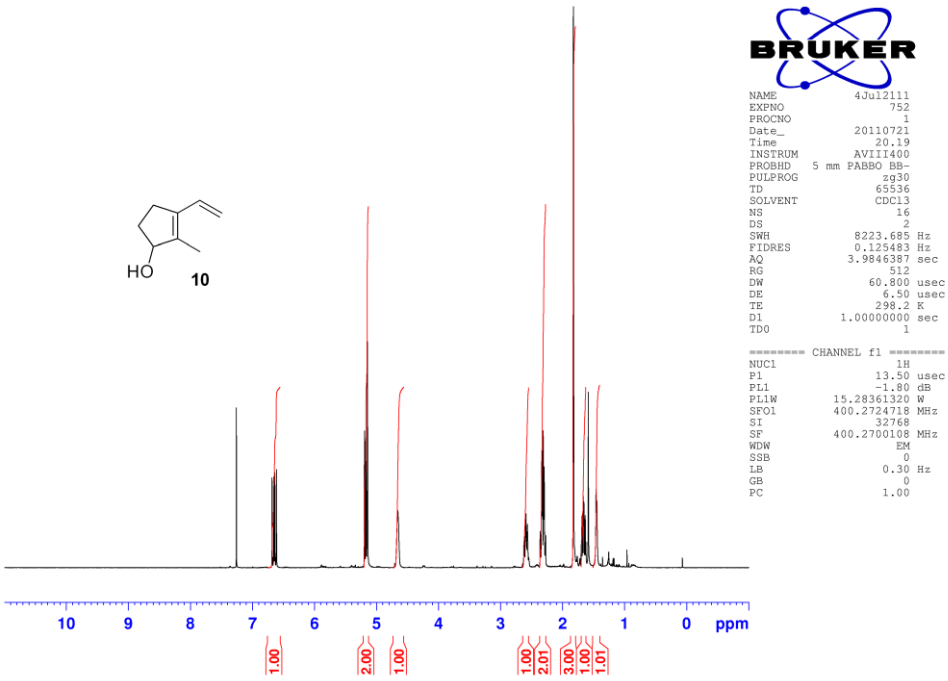
```
NAME                 4Feb1811
EXPNO                     170
PROCNO                      1
Date_                20110218
Time                    12.12
INSTRUM                AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                  zg30
TD                      65536
SOLVENT                 CDCl3
NS                         16
DS                          2
SWH                  8223.685 Hz
FIDRES               0.125483 Hz
AQ                   3.9846387 sec
RG                        724
DW                     60.800 usec
DE                      6.50 usec
TE                     298.2 K
D1                  1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      13.50 usec
PL1                     -1.80 dB
PL1W            15.28361320 W
SFO1            400.2724718 MHz
SI                      32768
SF              400.2700109 MHz
WDW                        EM
SSB                         0
LB                      0.30 Hz
GB                          0
PC                      1.00
```



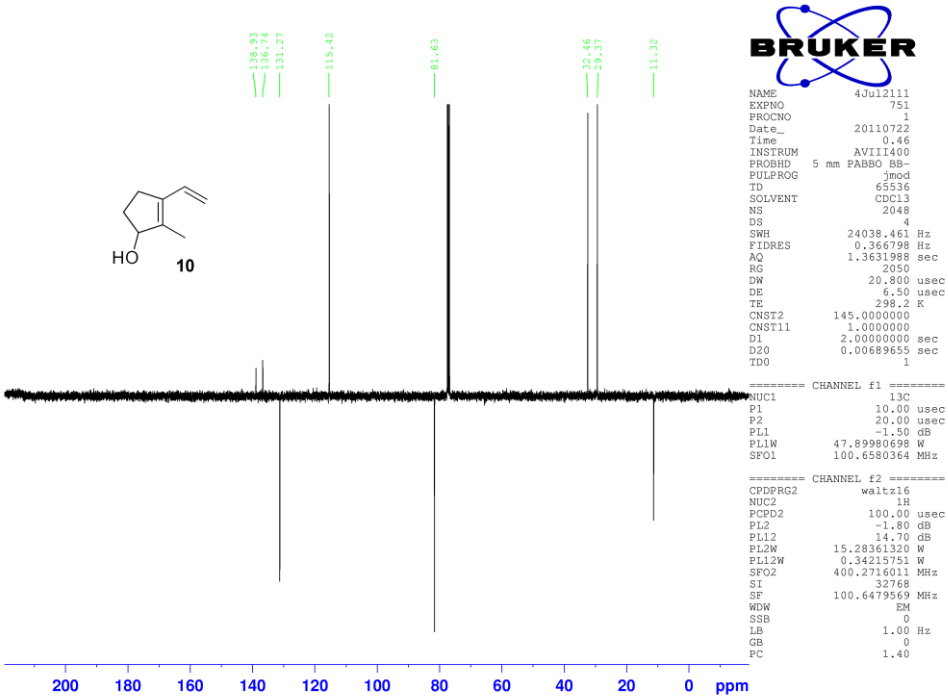
BRUKER

```
NAME                    Sep2608
EXPNO                        30
PROCNO                        1
Date_                  20080926
Time                      11.41
INSTRUM                avance400
PROBHD    5 mm BBO BB-1H
PULPROG                    jmod
TD                        65536
SOLVENT                   CDCl3
NS                         1500
DS                            2
SWH                  25062.656 Hz
FIDRES               0.382426 Hz
AQ                   1.3074932 sec
RG                      4597.6
DW                     19.950 usec
DE                      6.00 usec
TE                     300.2 K
CNST2               145.0000000
CNST11                1.0000000
D1                   2.00000000 sec
d20                  0.00689655 sec
DELTA                0.00001311 sec
TD0                           1

======== CHANNEL f1 ========
NUC1                      13C
P1                      10.30 usec
p2                      20.60 usec
PL1                     -1.00 dB
SFO1            100.6233329 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                  100.00 usec
PL2                     -3.00 dB
PL12                    16.00 dB
SFO2            400.1316005 MHz
SI                      32768
SF              100.6127538 MHz
WDW                        EM
SSB                         0
LB                      1.00 Hz
GB                          0
PC                      1.40
```

2-Methyl-3-vinylcyclopent-2-enol (10)

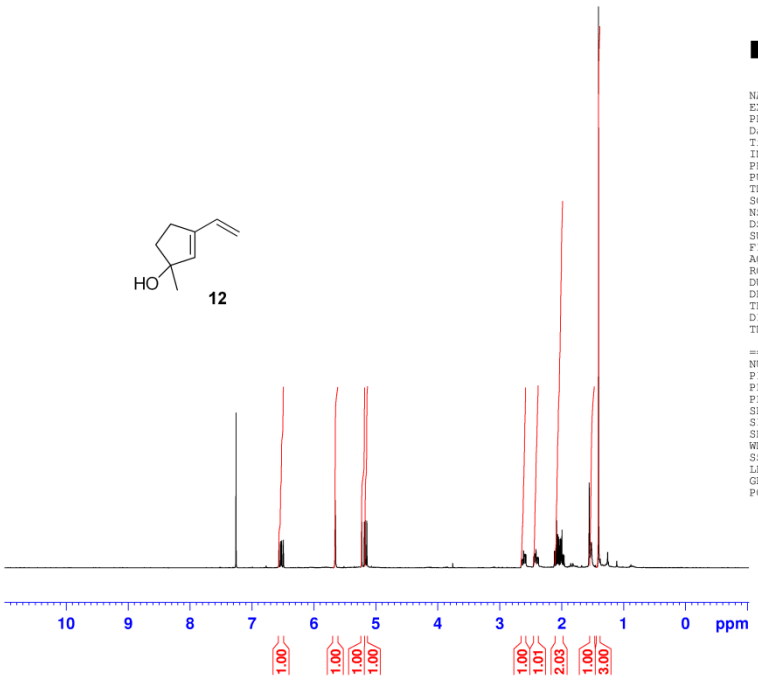



```
NAME                4Jul2111
EXPNO                    752
PROCNO                     1
Date_               20110721
Time                   20.19
INSTRUM             AVIII400
PROBHD   5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                       512
DW                    60.800 usec
DE                     6.50 usec
TE                   298.2 K
D1                 1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PL1                    -1.80 dB
PL1W            15.28361320 W
SFO1           400.2724718 MHz
SI                       32768
SF              400.2700108 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```



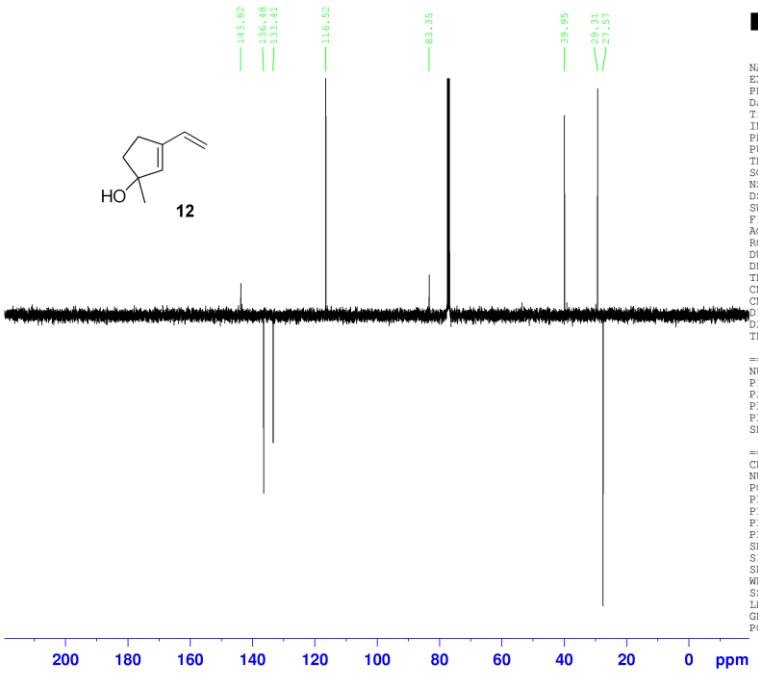

```
NAME                4Jul2111
EXPNO                    751
PROCNO                     1
Date_               20110722
Time                   0.46
INSTRUM             AVIII400
PROBHD   5 mm PABBO BB-
PULPROG                jmod
TD                    65536
SOLVENT               CDCl3
NS                     2048
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631988 sec
RG                     2050
DW                    20.800 usec
DE                     6.50 usec
TE                   298.2 K
CNST2             145.0000000
CNST11              1.0000000
D1                 2.00000000 sec
D20                0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                     13C
P1                     10.00 usec
P2                     20.00 usec
PL1                    -1.50 dB
PL1W            47.89980698 W
SFO1           100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -1.80 dB
PL12                   14.70 dB
PL2W            15.28361320 W
PL12W            0.34215751 W
SFO2           400.2716011 MHz
SI                       32768
SF              100.6479569 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```

1-Methyl-3-vinylcyclopent-2-enol (12)



BRUKER

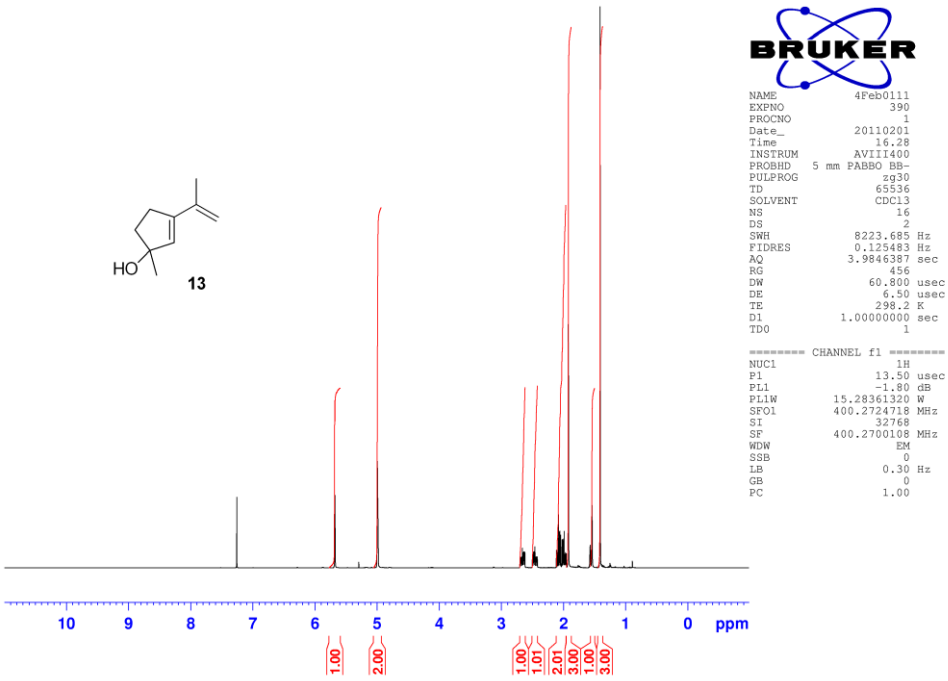
```
NAME                 4Jan2811
EXPNO                     190
PROCNO                      1
Date_             20110128
Time                    11.00
INSTRUM              AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                        724
DW                     60.800 usec
DE                      6.50 usec
TE                     298.2 K
D1                  1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      13.50 usec
PL1                     -1.80 dB
PL1W             15.28361320 W
SFO1            400.2724718 MHz
SI                      32768
SF               400.2700108 MHz
WDW                        EM
SSB                         0
LB                      0.30 Hz
GB                          0
PC                      1.00
```



BRUKER

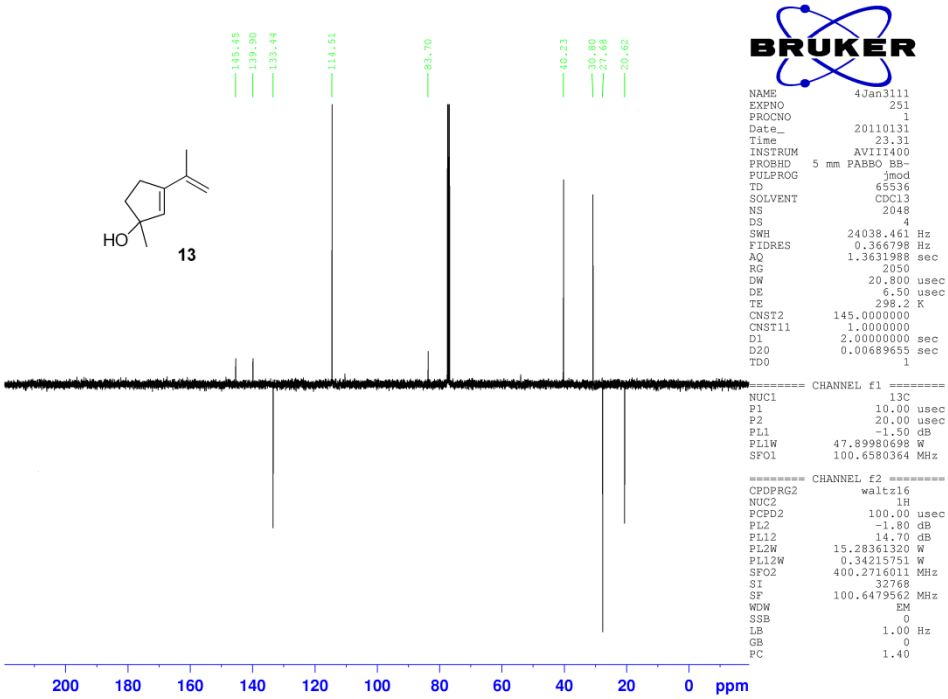
```
NAME                 4Jan2811
EXPNO                     191
PROCNO                      1
Date_             20110129
Time                     0.59
INSTRUM              AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                 jmod
TD                     65536
SOLVENT                CDCl3
NS                        4096
DS                           4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                        2050
DW                     20.800 usec
DE                      6.50 usec
TE                     298.2 K
CNST2              145.0000000
CNST11               1.0000000
D1                  2.00000000 sec
D20                 0.00689655 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                      13C
P1                      10.00 usec
P2                      20.00 usec
PL1                     -1.50 dB
PL1W             47.89980698 W
SFO1            100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                  100.00 usec
PL2                     -1.80 dB
PL12                    14.70 dB
PL2W             15.28361320 W
PL12W             0.34215751 W
SFO2            400.2716011 MHz
SI                      32768
SF               100.6479562 MHz
WDW                        EM
SSB                         0
LB                      1.00 Hz
GB                          0
PC                      1.40
```

3-Isopropenyl-1-methylcyclopent-2-enol (13)



BRUKER

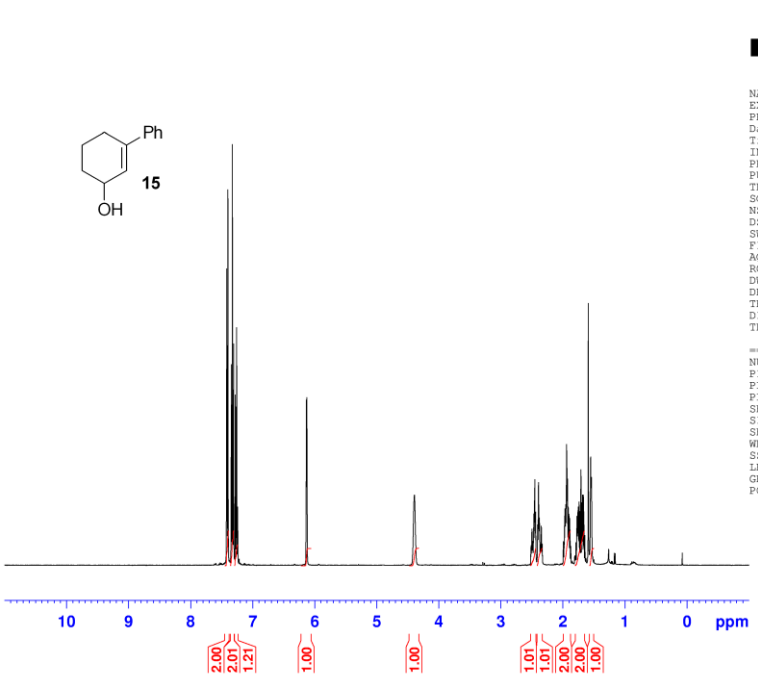
NAME	4Feb0111
EXPNO	390
PROCNO	1
Date_	20110201
Time	16.28
INSTRUM	AVIII400
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	456
DW	60.800 usec
DE	6.50 usec
TE	298.2 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	13.50 usec
PL1	-1.80 dB
PL1W	15.28361320 W
SFO1	400.2724718 MHz
SI	32768
SF	400.2700108 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



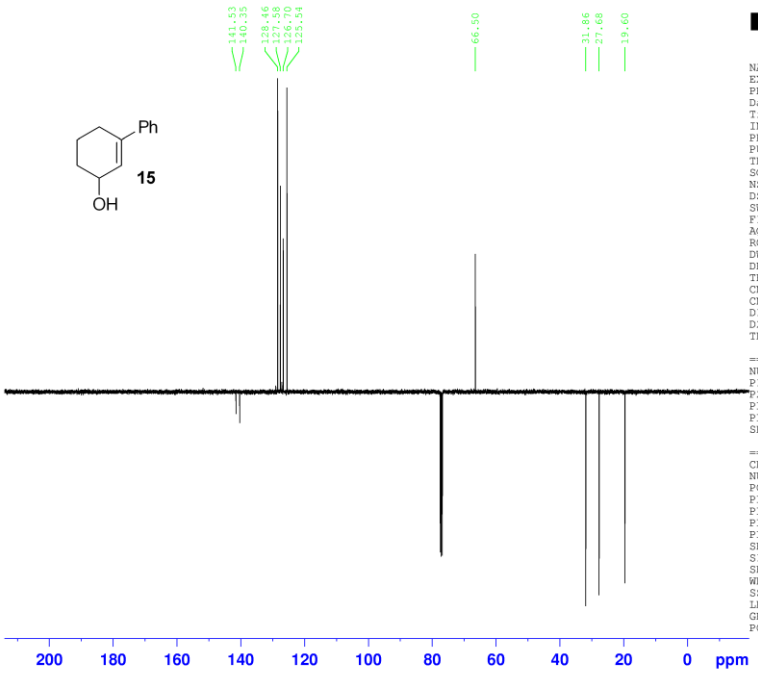
BRUKER

NAME	4Jan3111
EXPNO	251
PROCNO	1
Date_	20110131
Time	23.31
INSTRUM	AVIII400
PROBHD	5 mm PABBO BB-
PULPROG	jmod
TD	65536
SOLVENT	CDCl3
NS	2048
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	2050
DW	20.800 usec
DE	6.50 usec
TE	298.2 K
CNST2	145.0000000
CNST11	1.0000000
D1	2.00000000 sec
D20	0.00689655 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
P2	20.00 usec
PL1	-1.50 dB
PL1W	47.89980698 W
SFO1	100.6580364 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	-1.80 dB
PL12	14.70 dB
PL2W	15.28361320 W
PL12W	0.34215751 W
SFO2	400.2716011 MHz
SI	32768
SF	100.6479562 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

3-Phenylcyclohex-2-enol (15)

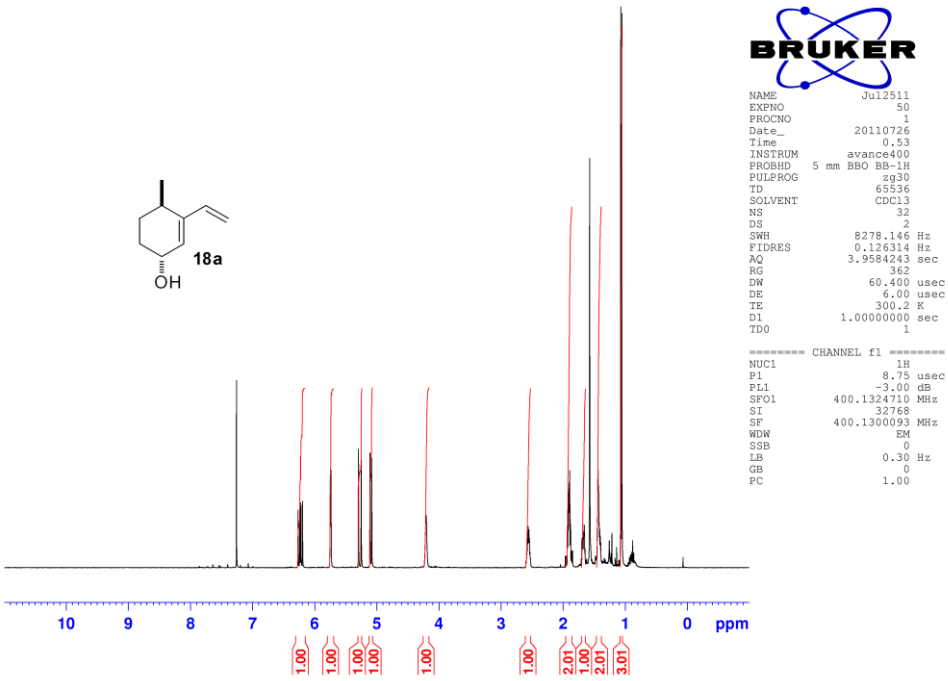



```
NAME                4Jul2111
EXPNO                    741
PROCNO                     1
Date_               20110721
Time                   20.14
INSTRUM              AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                       287
DW                  60.800 usec
DE                   6.50 usec
TE                   298.2 K
D1                1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                   13.50 usec
PL1                  -1.80 dB
PL1W            15.28361320 W
SFO1            400.2724718 MHz
SI                     32768
SF              400.2700109 MHz
WDW                       EM
SSB                        0
LB                   0.30 Hz
GB                         0
PC                    1.00
```

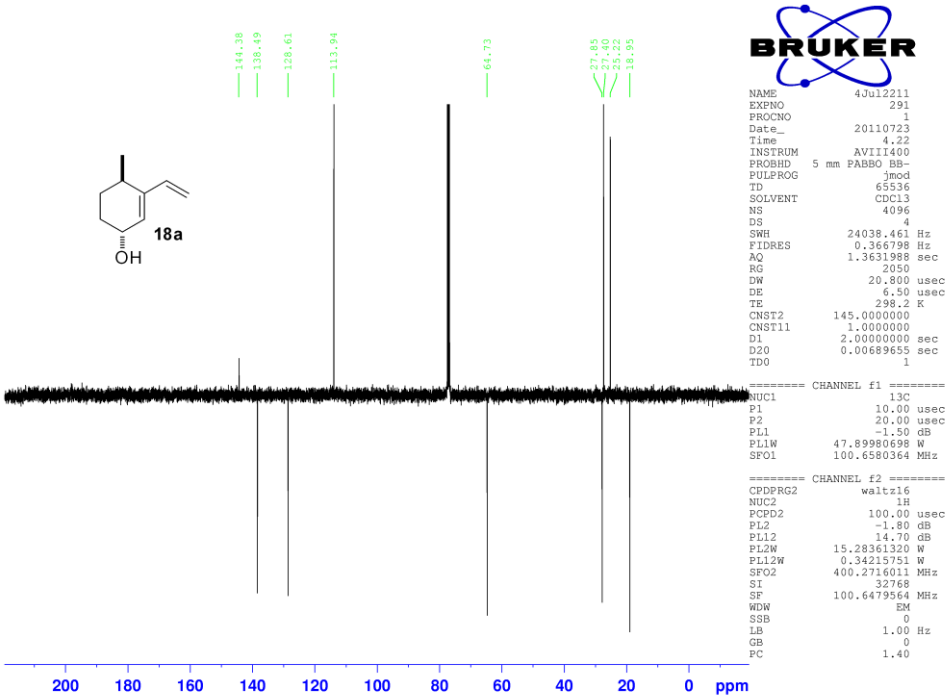



```
NAME                4Jul2111
EXPNO                    742
PROCNO                     1
Date_               20110722
Time                   2.45
INSTRUM              AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                jmod
TD                     65536
SOLVENT                CDCl3
NS                      2048
DS                         4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                      2050
DW                  20.800 usec
DE                   6.50 usec
TE                   298.2 K
CNST2             145.0000000
CNST11              1.0000000
D1                  2.00000000 sec
D20                 0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                     13C
P1                   10.00 usec
P2                   20.00 usec
PL1                  -1.50 dB
PL1W            47.89980698 W
SFO1            100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                      1H
PCPD2                100.00 usec
PL2                  -1.80 dB
PL12                 14.70 dB
PL2W            15.28361320 W
PL12W            0.34215751 W
SFO2            400.2716011 MHz
SI                     32768
SF              100.6479579 MHz
WDW                       EM
SSB                        0
LB                   1.00 Hz
GB                         0
PC                    1.40
```

trans 4-Methyl-3-vinylcyclohex-2-enol (18a)

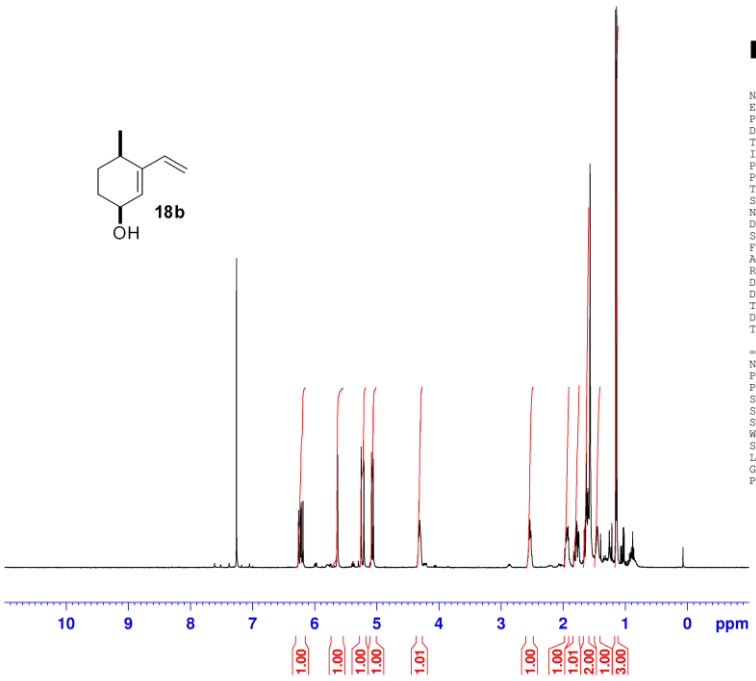



```
NAME                Jul2511
EXPNO                    50
PROCNO                    1
Date_              20110726
Time                   0.53
INSTRUM          avance400
PROBHD    5 mm BBO BB-1H
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       32
DS                        2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ                3.9584243 sec
RG                      362
DW                 60.400 usec
DE                  6.00 usec
TE                 300.2 K
D1                1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    1H
P1                   8.75 usec
PL1                 -3.00 dB
SFO1          400.1324710 MHz
SI                    32768
SF            400.1300093 MHz
WDW                     EM
SSB                      0
LB                  0.30 Hz
GB                       0
PC                    1.00
```

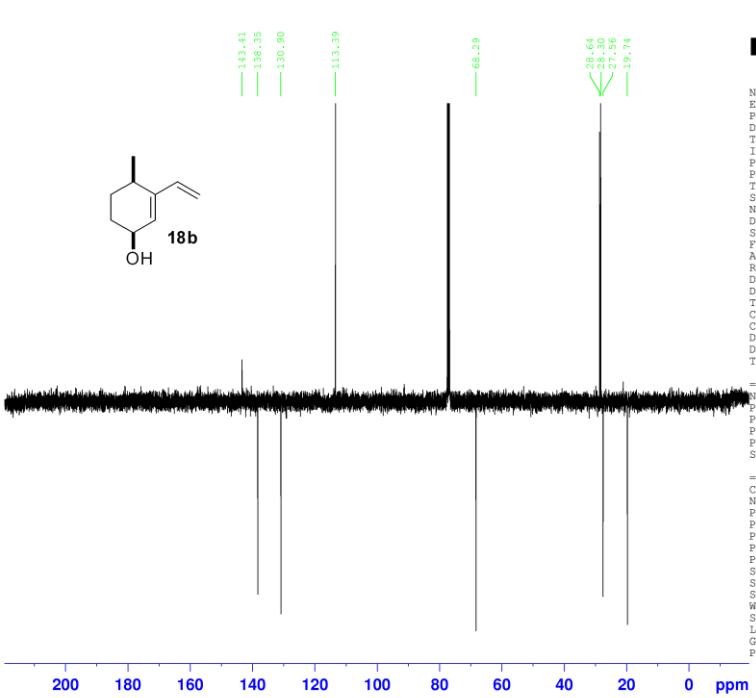



```
NAME               4Jul2211
EXPNO                   291
PROCNO                    1
Date_              20110723
Time                   4.22
INSTRUM           AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                jmod
TD                    65536
SOLVENT               CDCl3
NS                     4096
DS                        4
SWH              24038.461 Hz
FIDRES            0.366798 Hz
AQ                1.3631988 sec
RG                     2050
DW                 20.800 usec
DE                  6.50 usec
TE                 298.2 K
CNST2           145.0000000
CNST11            1.0000000
D1                2.00000000 sec
D20               0.00689655 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                   13C
P1                  10.00 usec
P2                  20.00 usec
PL1                 -1.50 dB
PL1W           47.89980698 W
SFO1          100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2              100.00 usec
PL2                 -1.80 dB
PL12                14.70 dB
PL2W           15.28361320 W
PL12W           0.34215751 W
SFO2          400.2716011 MHz
SI                    32768
SF            100.6479564 MHz
WDW                     EM
SSB                      0
LB                  1.00 Hz
GB                       0
PC                    1.40
```

cis 4-Methyl-3-vinylcyclohex-2-enol (18b)

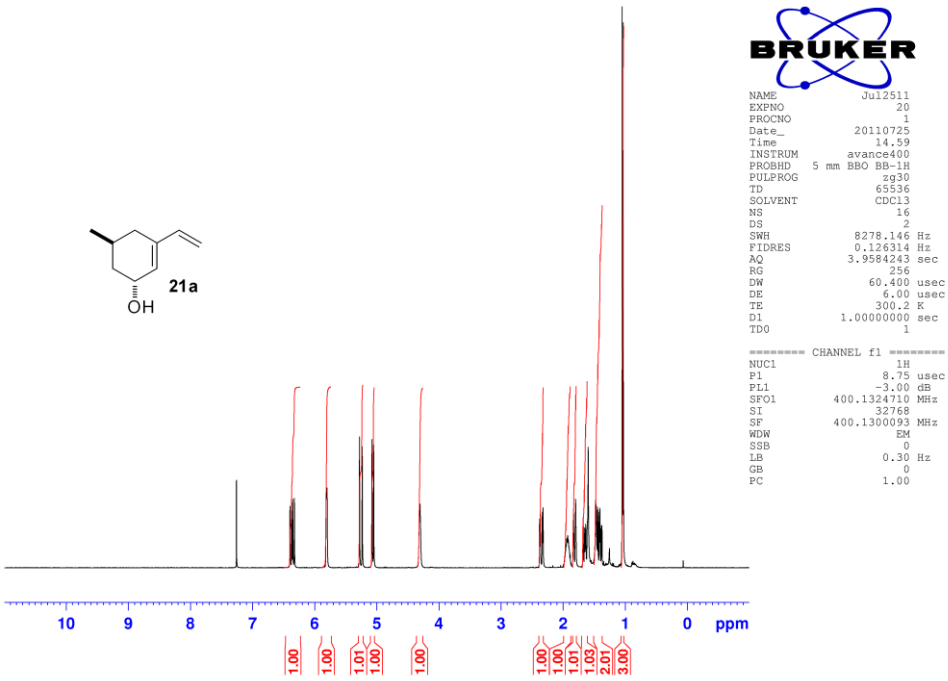



```
NAME                 Jul2511
EXPNO                     60
PROCNO                     1
Date_               20110726
Time                    4.44
INSTRUM              avance400
PROBHD    5 mm BBO BB-1H
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        32
DS                         2
SWH                 8278.146 Hz
FIDRES              0.126314 Hz
AQ                  3.9584243 sec
RG                      456.1
DW                     60.400 usec
DE                      6.00 usec
TE                     300.2 K
D1                  1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                      8.75 usec
PL1                    -3.00 dB
SFO1            400.1324710 MHz
SI                     32768
SF              400.1300093 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```

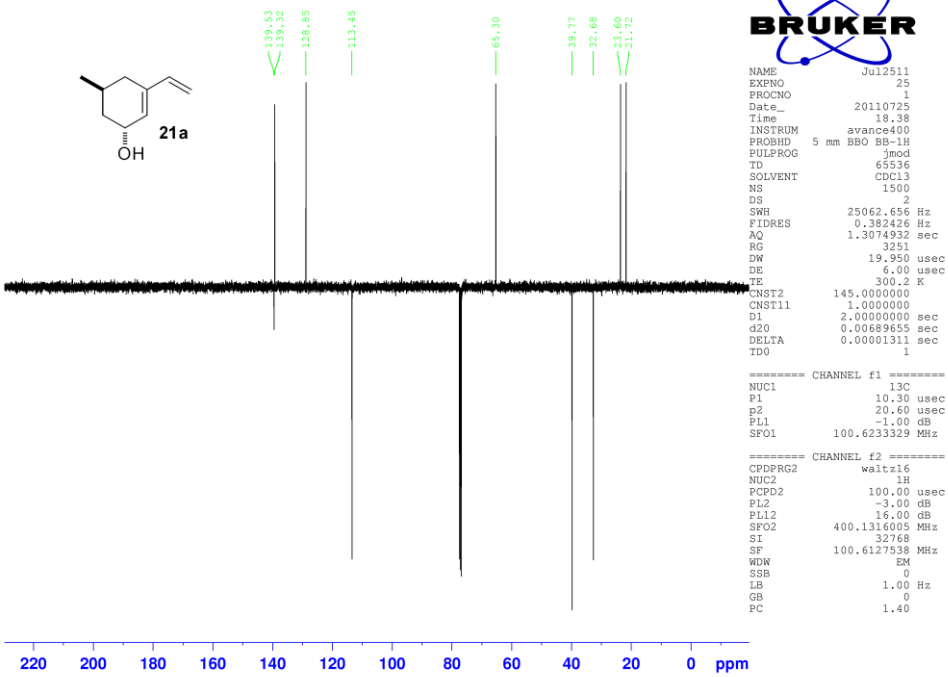



```
NAME                4Jul2211
EXPNO                    241
PROCNO                     1
Date_               20110723
Time                    0.26
INSTRUM             AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                 jmod
TD                     65536
SOLVENT                CDCl3
NS                       4096
DS                          4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                       2050
DW                     20.800 usec
DE                      6.50 usec
TE                     298.2 K
CNST2              145.0000000
CNST11               1.0000000
D1                  2.00000000 sec
D20                 0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                     10.00 usec
P2                     20.00 usec
PL1                    -1.50 dB
PL1W               47.89980698 W
SFO1            100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -1.80 dB
PL12                   14.70 dB
PL2W               15.28361320 W
PL12W               0.34215751 W
SFO2            400.2716011 MHz
SI                     32768
SF              100.6479565 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```

trans 5-Methyl-3-vinylcyclohex-2-enol (21a)

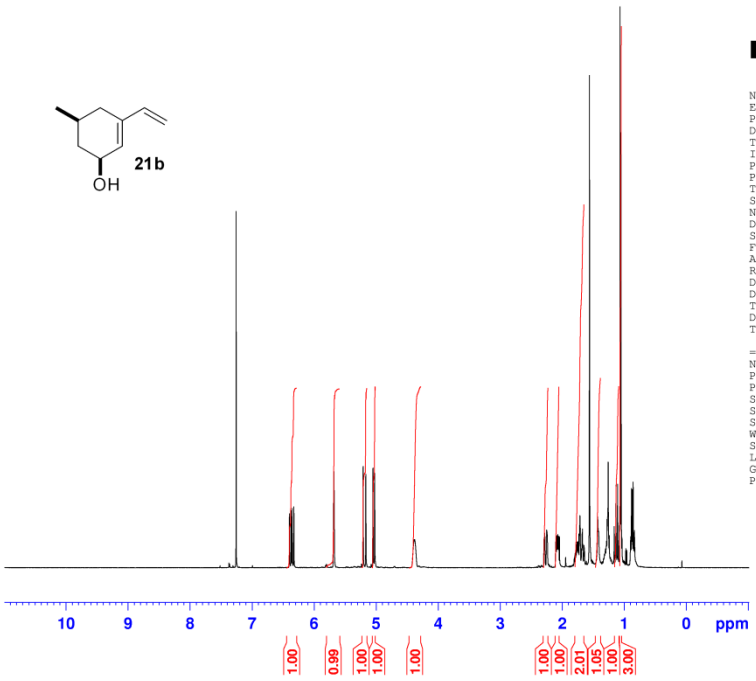



```
NAME                 Jul2511
EXPNO                     20
PROCNO                     1
Date_             20110725
Time                   14.59
INSTRUM            avance400
PROBHD     5 mm BBO BB-1H
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                        16
DS                         2
SWH                8278.146 Hz
FIDRES            0.126314 Hz
AQ                3.9584243 sec
RG                      256
DW                   60.400 usec
DE                    6.00 usec
TE                   300.2 K
D1                1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     8.75 usec
PL1                   -3.00 dB
SFO1           400.1324710 MHz
SI                     32768
SF             400.1300093 MHz
WDW                       EM
SSB                        0
LB                    0.30 Hz
GB                         0
PC                     1.00
```

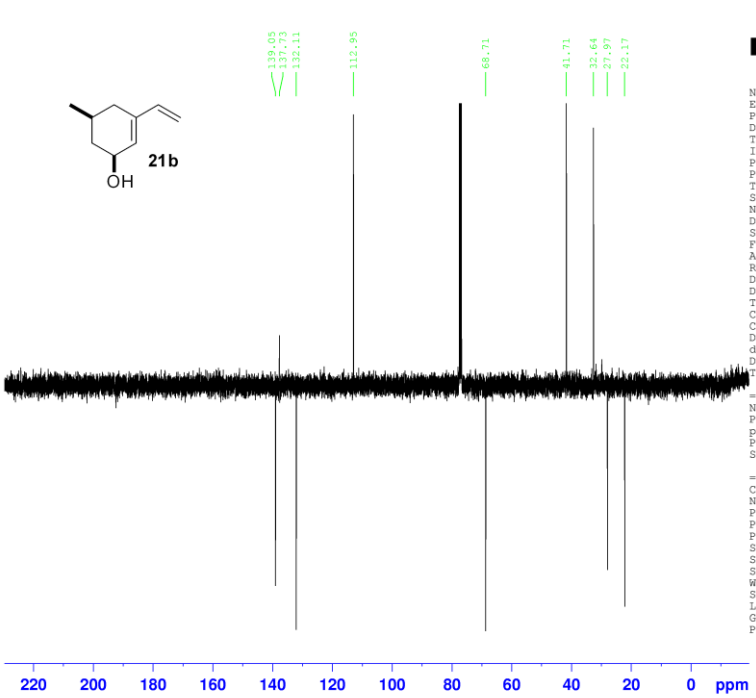



```
NAME                 Jul2511
EXPNO                     25
PROCNO                     1
Date_             20110725
Time                   18.38
INSTRUM            avance400
PROBHD     5 mm BBO BB-1H
PULPROG                jmod
TD                    65536
SOLVENT               CDCl3
NS                      1500
DS                         2
SWH               25062.656 Hz
FIDRES            0.382426 Hz
AQ                1.3074932 sec
RG                      3251
DW                   19.950 usec
DE                    6.00 usec
TE                   300.2 K
CNST2             145.0000000
CNST11              1.0000000
D1                2.00000000 sec
d20               0.00689655 sec
DELTA             0.00001311 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                     13C
P1                    10.30 usec
p2                    20.60 usec
PL1                   -1.00 dB
SFO1           100.6233329 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                      1H
PCPD2                100.00 usec
PL2                   -3.00 dB
PL12                  16.00 dB
SFO2           400.1316005 MHz
SI                     32768
SF             100.6127538 MHz
WDW                       EM
SSB                        0
LB                    1.00 Hz
GB                         0
PC                     1.40
```

cis 5-Methyl-3-vinylcyclohex-2-enol (21b)

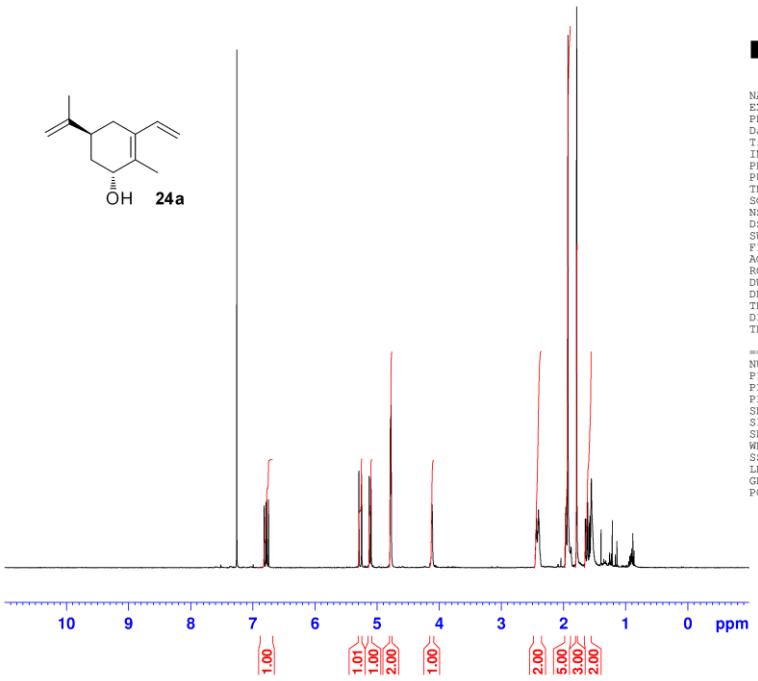



```
NAME                 Jul1411
EXPNO                     10
PROCNO                     1
Date_             20110714
Time                   8.35
INSTRUM            avance400
PROBHD     5 mm BBO BB-1H
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       64
DS                        2
SWH                8278.146 Hz
FIDRES                0.126314 Hz
AQ                 3.9584243 sec
RG                      512
DW                   60.400 usec
DE                    6.00 usec
TE                   300.2 K
D1                 1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                      1H
P1                     8.75 usec
PL1                   -3.00 dB
SFO1              400.1324710 MHz
SI                      32768
SF                400.1300092 MHz
WDW                       EM
SSB                        0
LB                     0.30 Hz
GB                         0
PC                      1.00
```

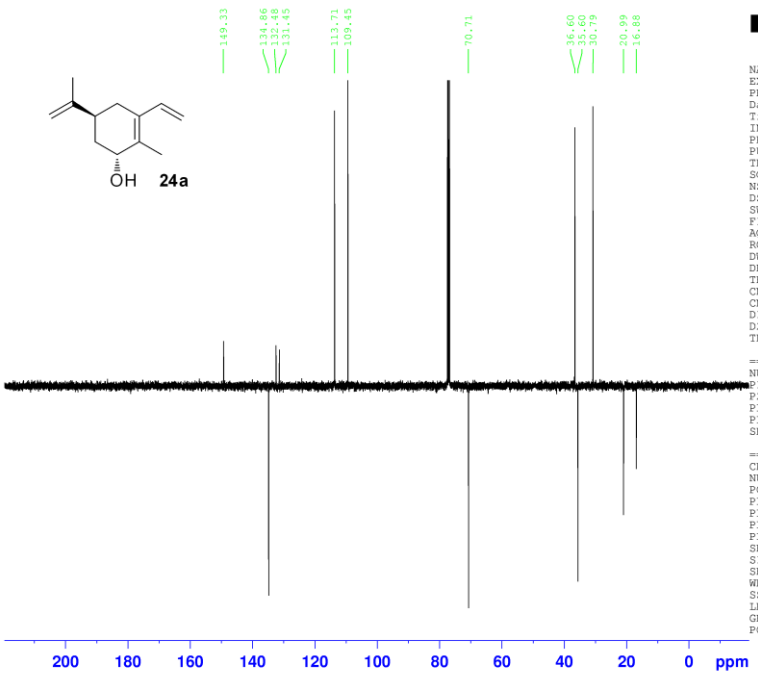



```
NAME                 Jul1411
EXPNO                     16
PROCNO                     1
Date_             20110714
Time                  13.31
INSTRUM            avance400
PROBHD     5 mm BBO BB-1H
PULPROG                jmod
TD                    65536
SOLVENT               CDCl3
NS                     2500
DS                        2
SWH               25062.656 Hz
FIDRES                0.382426 Hz
AQ                 1.3074932 sec
RG                     2298.8
DW                   19.950 usec
DE                    6.00 usec
TE                   300.2 K
CNST2             145.0000000
CNST11              1.0000000
D1                 2.00000000 sec
d20                0.00689655 sec
DELTA              0.00001311 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                     13C
P1                    10.30 usec
p2                    20.60 usec
PL1                   -1.00 dB
SFO1              100.6233329 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                      1H
PCPD2                100.00 usec
PL2                   -3.00 dB
PL12                  16.00 dB
SFO2              400.1316005 MHz
SI                      32768
SF                100.6127532 MHz
WDW                       EM
SSB                        0
LB                     1.00 Hz
GB                         0
PC                      1.40
```

(1R,5S)-5-Isopropenyl-2-methyl-3-vinylcyclohex-2-enol (24a)

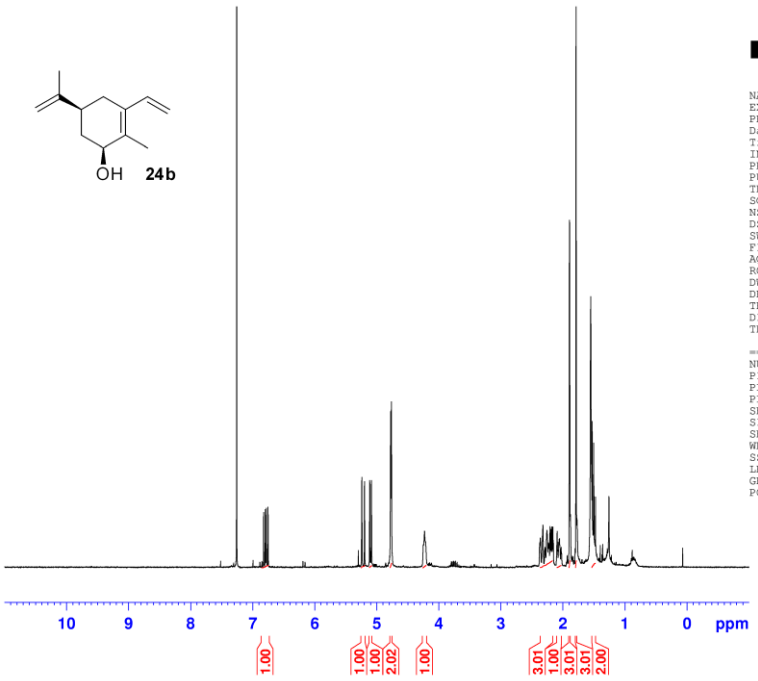



```
NAME                4Aug0311
EXPNO                    130
PROCNO                     1
Date_               20110803
Time                   15.43
INSTRUM              AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                       575
DW                  60.800 usec
DE                   6.50 usec
TE                   298.2 K
D1                 1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                     1H
P1                   13.50 usec
PL1                  -1.80 dB
PL1W           15.28361320 W
SFO1           400.2724718 MHz
SI                    32768
SF             400.2700109 MHz
WDW                      EM
SSB                       0
LB                   0.30 Hz
GB                        0
PC                     1.00
```

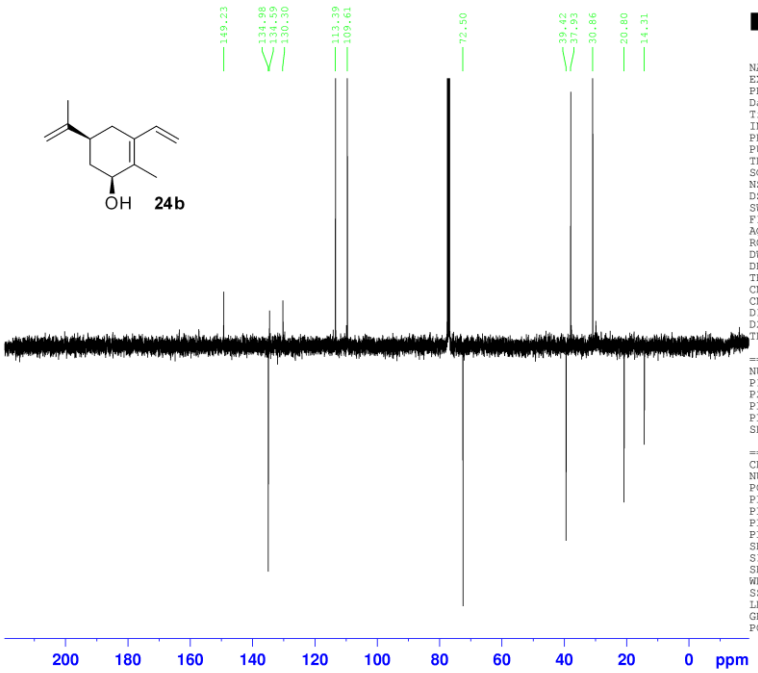



```
NAME                4Aug0311
EXPNO                    131
PROCNO                     1
Date_               20110804
Time                    7.43
INSTRUM              AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                jmod
TD                    65536
SOLVENT               CDCl3
NS                     3000
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631988 sec
RG                     2050
DW                  20.800 usec
DE                   6.50 usec
TE                   298.2 K
CNST2          145.0000000
CNST11           1.0000000
D1                 2.00000000 sec
D20                0.00689655 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                   10.00 usec
P2                   20.00 usec
PL1                  -1.50 dB
PL1W           47.89980698 W
SFO1           100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2               100.00 usec
PL2                  -1.80 dB
PL12                 14.70 dB
PL2W           15.28361320 W
PL12W           0.34215751 W
SFO2           400.2716011 MHz
SI                    32768
SF             100.6479560 MHz
WDW                      EM
SSB                       0
LB                   1.00 Hz
GB                        0
PC                     1.40
```

(1S,5S)-5-Isopropenyl-2-methyl-3-vinylcyclohex-2-enol (24b)

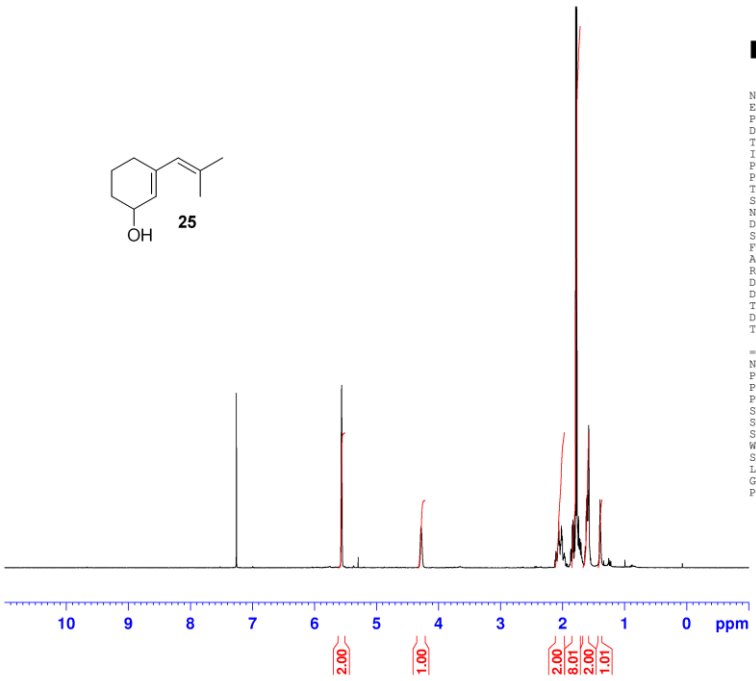



```
NAME                 4Aug0411
EXPNO                     520
PROCNO                      1
Date_                20110805
Time                     3.15
INSTRUM              AVIII400
PROBHD   5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                        812
DW                   60.800 usec
DE                    6.50 usec
TE                    298.2 K
D1                 1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                    13.50 usec
PL1                   -1.80 dB
PL1W             15.28361320 W
SFO1             400.2724718 MHz
SI                      32768
SF               400.2700110 MHz
WDW                        EM
SSB                         0
LB                     0.30 Hz
GB                          0
PC                       1.00
```

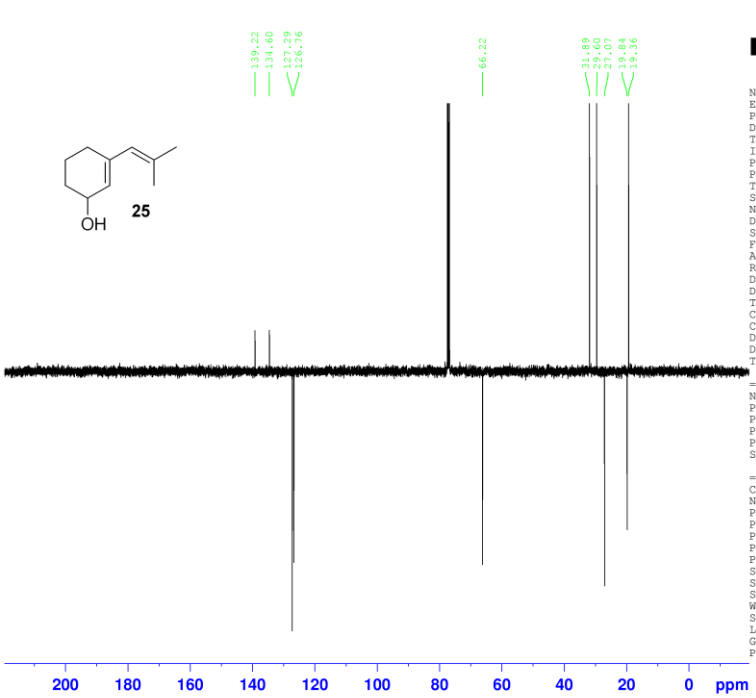



```
NAME                 4Aug0411
EXPNO                     521
PROCNO                      1
Date_                20110805
Time                     7.59
INSTRUM              AVIII400
PROBHD   5 mm PABBO BB-
PULPROG                 jmod
TD                     65536
SOLVENT                CDCl3
NS                       5000
DS                          4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                       2050
DW                   20.800 usec
DE                    6.50 usec
TE                    298.2 K
CNST2              145.0000000
CNST11               1.0000000
D1                 2.00000000 sec
D20                0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                     13C
P1                    10.00 usec
P2                    20.00 usec
PL1                   -1.50 dB
PL1W             47.89980698 W
SFO1             100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2               waltz16
NUC2                      1H
PCPD2                100.00 usec
PL2                   -1.80 dB
PL12                  14.70 dB
PL2W             15.28361320 W
PL12W             0.34215751 W
SFO2             400.2716011 MHz
SI                      32768
SF               100.6479561 MHz
WDW                        EM
SSB                         0
LB                     1.00 Hz
GB                          0
PC                       1.40
```

3-(2'-Methyl-1'-propenyl)cyclohex-2-enol (25)

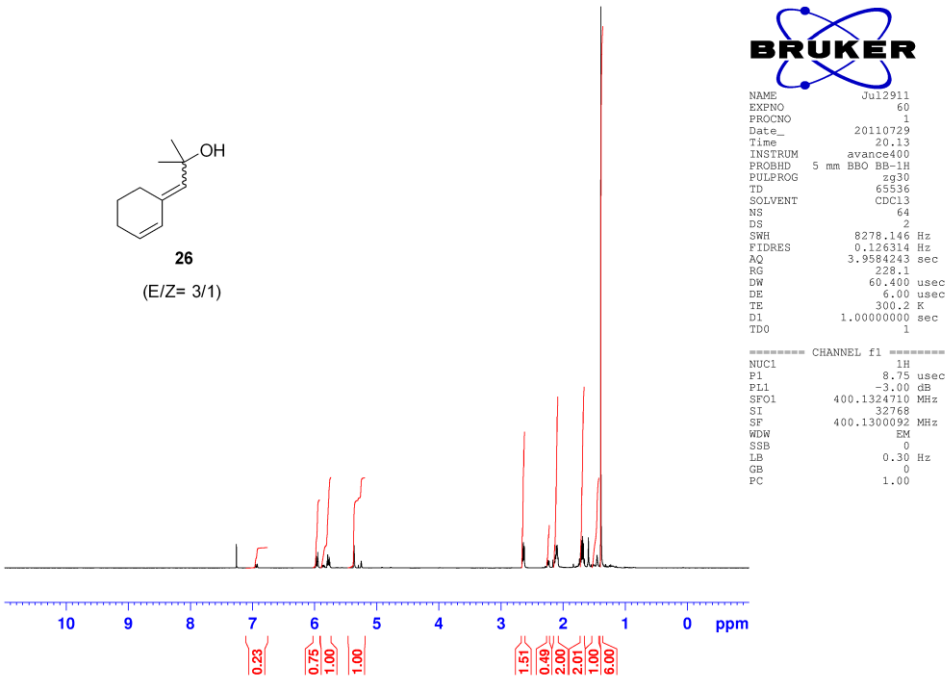



```
NAME                4Jul2811
EXPNO                    620
PROCNO                     1
Date_               20110728
Time                   18.10
INSTRUM              AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                       512
DW                  60.800 usec
DE                   6.50 usec
TE                   298.2 K
D1                 1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PL1                    -1.80 dB
PL1W            15.28361320 W
SFO1           400.2724718 MHz
SI                       32768
SF             400.2700108 MHz
WDW                       EM
SSB                        0
LB                    0.30 Hz
GB                         0
PC                      1.00
```

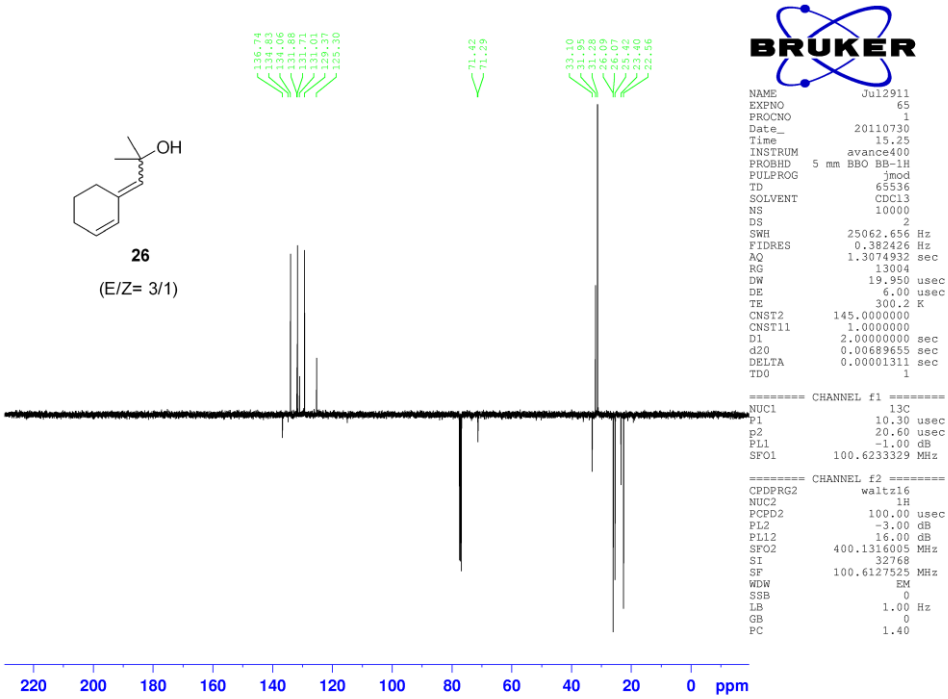



```
NAME                4Jul2811
EXPNO                    621
PROCNO                     1
Date_               20110729
Time                   7.54
INSTRUM              AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                jmod
TD                    65536
SOLVENT               CDCl3
NS                       2048
DS                          4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631988 sec
RG                       2050
DW                  20.800 usec
DE                   6.50 usec
TE                   298.2 K
CNST2             145.0000000
CNST11              1.0000000
D1                 2.00000000 sec
D20                0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                     13C
P1                     10.00 usec
P2                     20.00 usec
PL1                    -1.50 dB
PL1W            47.89980698 W
SFO1           100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -1.80 dB
PL12                   14.70 dB
PL2W            15.28361320 W
PL12W            0.34215751 W
SFO2           400.2716011 MHz
SI                       32768
SF             100.6479566 MHz
WDW                       EM
SSB                        0
LB                    1.00 Hz
GB                         0
PC                      1.40
```

1-(Cyclohex-2-enylidene)-2-methyl-2-propanol (26)

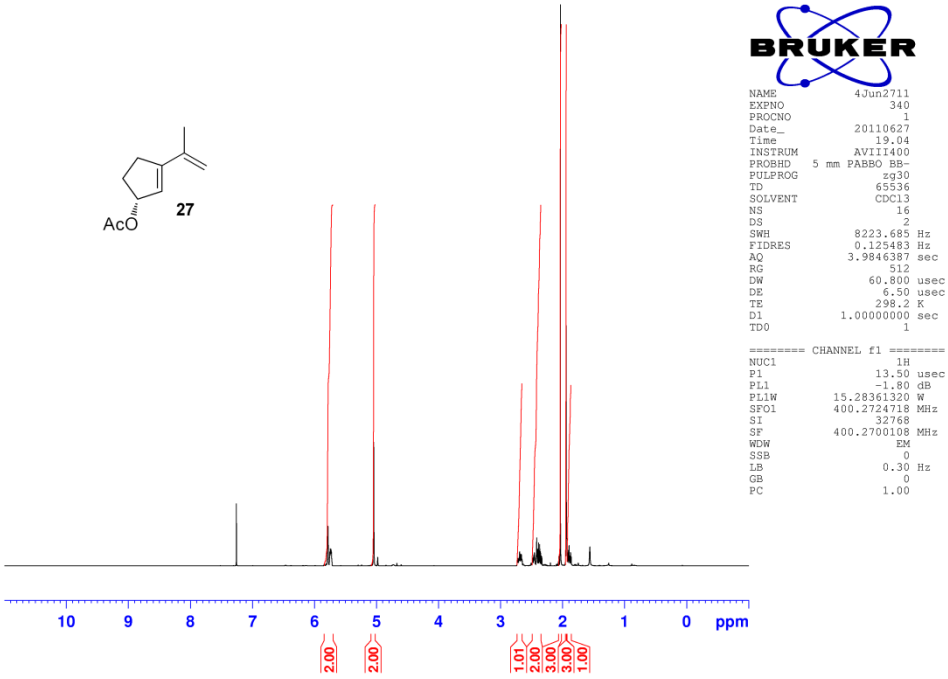



```
NAME                Jul2911
EXPNO                    60
PROCNO                    1
Date_              20110729
Time                  20.13
INSTRUM           avance400
PROBHD    5 mm BBO BB-1H
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      64
DS                       2
SWH               8278.146 Hz
FIDRES           0.126314 Hz
AQ                3.9584243 sec
RG                    228.1
DW                 60.400 usec
DE                  6.00 usec
TE                  300.2 K
D1             1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                   8.75 usec
PL1                 -3.00 dB
SFO1          400.1324710 MHz
SI                   32768
SF            400.1300092 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```

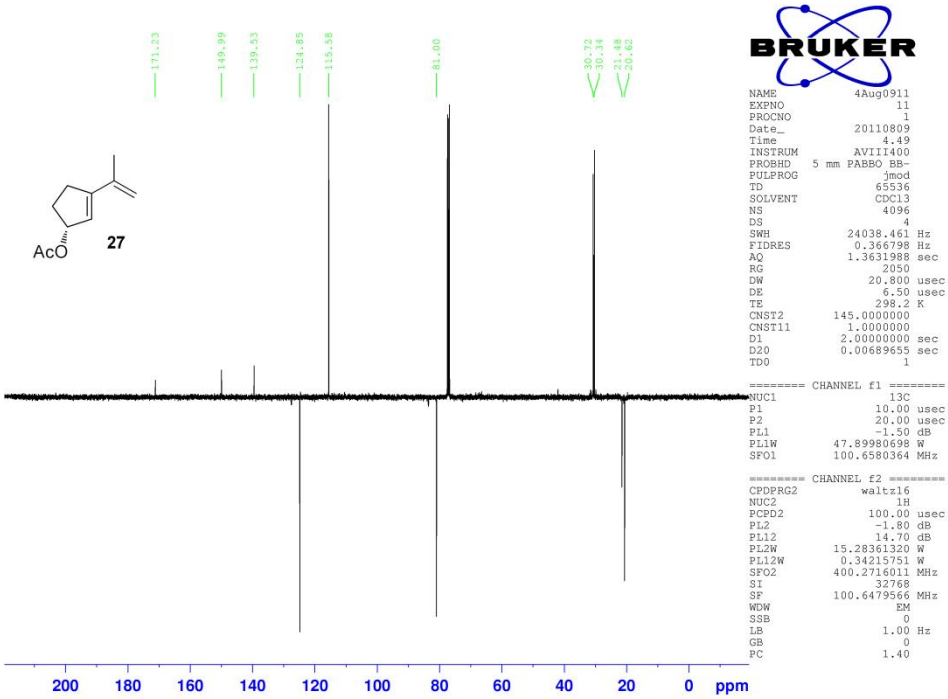



```
NAME                Jul2911
EXPNO                    65
PROCNO                    1
Date_              20110730
Time                  15.25
INSTRUM           avance400
PROBHD    5 mm BBO BB-1H
PULPROG               jmod
TD                   65536
SOLVENT              CDCl3
NS                   10000
DS                       2
SWH              25062.656 Hz
FIDRES           0.382426 Hz
AQ                1.3074932 sec
RG                    13004
DW                 19.950 usec
DE                  6.00 usec
TE                  300.2 K
CNST2          145.0000000
CNST11           1.0000000
D1             2.00000000 sec
d20            0.00689655 sec
DELTA          0.00001311 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                  10.30 usec
p2                  20.60 usec
PL1                 -1.00 dB
SFO1          100.6233329 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2              100.00 usec
PL2                 -3.00 dB
PL12                16.00 dB
SFO2          400.1316005 MHz
SI                   32768
SF            100.6127525 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

Ester 27

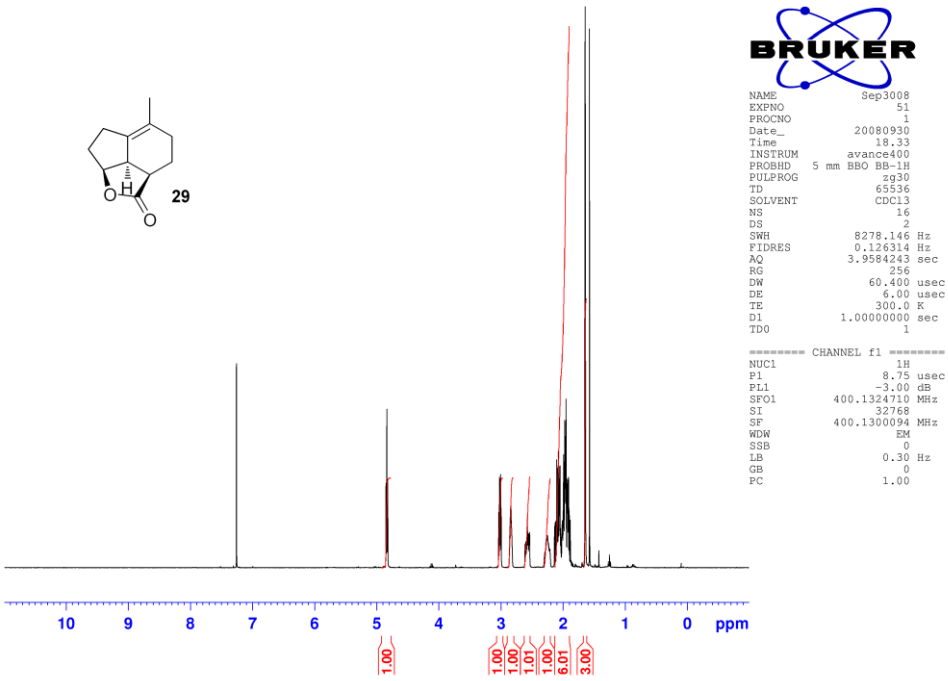



```
NAME                4Jun2711
EXPNO                    340
PROCNO                     1
Date_               20110627
Time                   19.04
INSTRUM              AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                       512
DW                    60.800 usec
DE                     6.50 usec
TE                    298.2 K
D1                  1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PL1                    -1.80 dB
PL1W            15.28361320 W
SFO1           400.2724718 MHz
SI                     32768
SF              400.2700108 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```




```
NAME                4Aug0911
EXPNO                     11
PROCNO                     1
Date_               20110809
Time                    4.49
INSTRUM              AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                 jmod
TD                     65536
SOLVENT                CDCl3
NS                       4096
DS                         4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                       2050
DW                    20.800 usec
DE                     6.50 usec
TE                    298.2 K
CNST2              145.0000000
CNST11               1.0000000
D1                  2.00000000 sec
D20                 0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                     13C
P1                     10.00 usec
P2                     20.00 usec
PL1                    -1.50 dB
PL1W            47.89980698 W
SFO1           100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -1.80 dB
PL12                   14.70 dB
PL2W            15.28361320 W
PL12W            0.34215751 W
SFO2           400.2716011 MHz
SI                     32768
SF              100.6479566 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```

Lactone 29


29
BRUKER
NAME Sep3008
EXPNO 51
PROCNO 1
Date_ 20080930
Time 18.33
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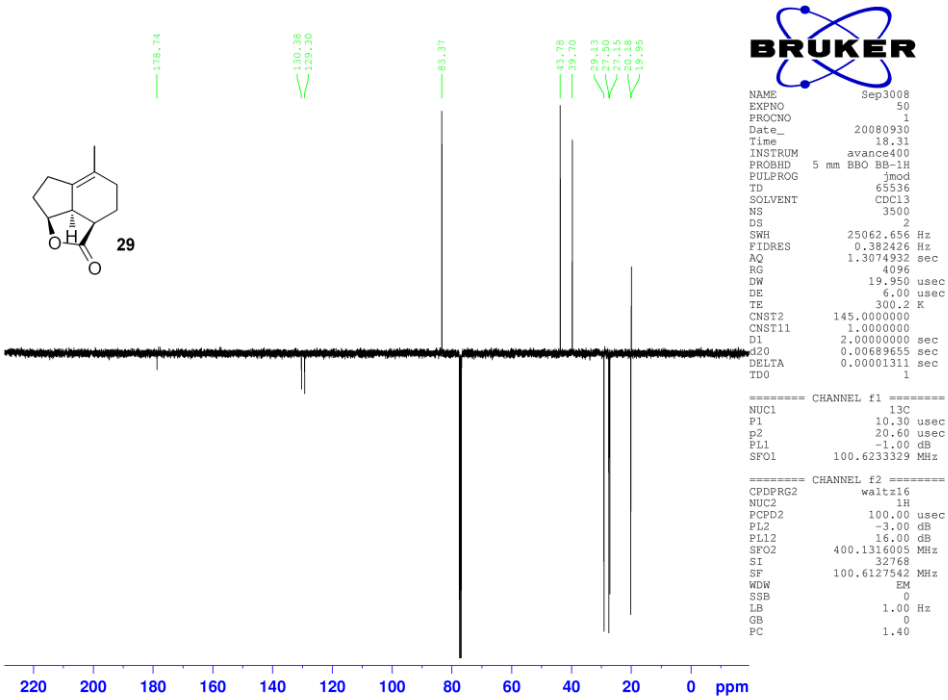
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GB 0
PC 1.40
220 200 180 160 140 120 100 80 60 40 20 0 ppm

5.3 Total Synthesis of Lycoflexine, SI

Experimental procedures and analytical data of all compounds discussed in chapter 4.4.2 (*Synthesis of the Lycopodium Alkaloid (+)-Lycoflexine*) are summarized in the following supporting information.

Synthesis of the Lycopodium Alkaloid

(+)-Lycoflexine

Supporting Information

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1. Procedures

1.1 General:

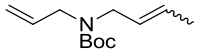
All reactions were carried out in oven-dried glassware under an argon atmosphere unless stated otherwise. Anhydrous dichloromethane and 1,2-dichloroethane were destilled under Argon from P_2O_5, pyridine from CaH_2, anhydrous tetrahydrofuran (99.9%), dimethylformamide (99.8%) and ethyl acetate (99.5%) were purchased from Aldrich, ethanol (99.9%) from Merck. All other solvents were HPLC grade. Commercially available reagents were used without further purification besides stated otherwise. *tert*-Butyloxycarbonyl protected allylamine and (*R*)-5-Methylcyclohex-2-enone were prepared according to literature known procedures.[9,10] Reactions were magnetically stirred and monitored by thin layer chromatography with E. Merck silica gel 60 F_{254} plates. Flash column chromatography was performed with Merck silica gel (0.04-0.063 mm, 240-400 mesh) under pressure besides stated otherwise. Yields refer to chromatographically and spectroscopically pure compounds unless stated otherwise. ^{1}H NMR (400 MHz or 600 MHz) and ^{13}C NMR (100 MHz or 150 MHz) spectra were either recorded on Bruker Avance 400, DRX 400, or DRX 600 spectrometers at 400.13 MHz (100.61 MHz) or 600.13 MHz (150.90 MHz). All NMR spectra were measured in $CDCl_3$ or CD_2Cl_2 solutions. The chemical shifts δ are reported relative to the residual solvent peaks (^{1}H, δ_{CDCl3} = 7.26 ppm, δ_{CD2Cl2} = 5.32 ppm; ^{13}C, δ_{CDCl3} = 77.16 ppm, δ_{CD2Cl2} = 53.80 ppm). All ^{1}H and ^{13}C shifts are given in ppm (s = singulet; d = doublet; t = triplet; q = quadruplet; m = multiplet; b = broad signal). If possible, assignments of proton resonances were confirmed by correlated spectroscopy. Optical rotations were measured at 20°C on a P 341 Perkin-Elmer polarimeter at 589 nm. IR spectra were recorded of samples prepared as films on silicium plates on a Perkin-Elmer Spectrum 2000 Series FTIR spectrometer. High resolution mass spectra (HRMS) were measured on a Finnigan MAT 8230 apparatus with a resolution of 10000. The CD spectrum of (+)-lycoflexine was measured on a Applied Photophysics π*-180 spectrometer.

[9] For preparation of Boc-protected allylamine see: Dhami, A.; Mahon, M. F.; Llyod, M. D., Threadgill, M. D. *Tetrahedron* **2009**, *65*, 4751

[10] For preparation of (*R*)-5-Methylcyclohex-2-enone see: Caine, D.; Procter, K.; Cassell, R. A. *J. Org. Chem.* **1984**, *49*, 2647

1.2 Experimetal procedures:

Allylcrotylcarbamate



A solution of allylcarbamate (3.40 g, 21.63 mmol, 1.0 eq) dissolved in DMF (43 mL) was slowly added to a suspension of sodium hydride (60%, 1.47 g, 36.75 mmol, 1.7 eq) and DMF (43 mL) while cooling to 0°C. After stirring for 30 minutes the resulting mixture was treated with crotyl bromide (85%, predominantly trans, 4.75 mL, 39.24 mmol, 1.8 eq). After 5 minutes the icebath was removed and the reaction mixture stirred for 16 hours. Saturated aqueous NH_4Cl was added after recooling to 0°C, followed by water and diethyl ether. The aqueous layer was extracted with diethyl ether (4x), the combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by chromatography (hexane/EtOAc 50/1) provided 4.43 g allylcrotylcarbamate as clear colourless oil with a cis:trans-ratio of 1:3.3 and 97% yield.

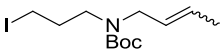
^{1}H-NMR (400MHz, $CDCl_3$): 5.84-5.69 (m, 1H), 5.66-5.49 (m, 1H), 5.45-5.34 (m, 1H), 5.16-5.03 (m, 2H), 3.93-3.63 (m, 4H), 1.69 (dd, J=6.34 Hz, J=1.30 Hz, 2.3H), 1.64 (dd, J=6.94Hz, J=1.34Hz, 0.70H), 1.47 (s, 2.09H), 1.44 (s, 6.91H)

^{13}C-NMR (100MHz, $CDCl_3$, ppm): 155.6, 134.41, 134.35, 128.2, 126.9, 126.8, 116.4, 79.64, 79.56, 48.8, 48.5, 48.1, 28.6, 17.8, 13.0

IR (film, cm^{-1}): 2977, 2923, 1692, 1456, 1406, 1365, 1243, 1172, 1146, 968, 918, 875

HRMS (ESI, m/z): $[M]^+$ calc.: 212.1651; found: 212.1654

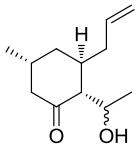
Iodocarbamate 8



Cyclohexene (4.25 mL, 41.91 mmol, 2.0 eq) was added dropwise to a cooled (0°C) 1.0 M borane solution in THF (25.0 mL, 25 mmol, 1.2 eq). After 2.5 hours the resulting white suspension was treated with allylcrotylcarbamate (4.39 g, 20.78 mmol, 1.0 eq) dissolved in THF (35 mL). The icebath was removed and the solution stirred for 1 hour at room temperature and 3 hours at 50°C. After recooling to room temperature a 1.0 M sodium acetate solution in methanol (50 mL, 50 mmol, 2.4 eq) and iodine monochloride (1.25 mL, 24.94 mmol, 1.2 eq) dissolved in methanol (24 mL) were added sequentially and stirred for another 30 minutes. The reaction was quenched with diluted aqueous $NaHCO_3$, diethyl ether was added and the excess iodine monochloride destroyed by careful addition of saturated aqueous $Na_2S_2O_3$ until the solution decolorates. The aqueous layer was extracted with ether (3x), the combined extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by chromatography (hexane/EtOAc 50/1) furnished 3.84 g of compound **8** as clear yellow oil with 54% yield. (Caution: Iodocarbamate **8** is of moderate stability and should be stored at -25°C.)

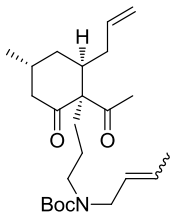
^{1}H-NMR (400 MHz CD_2Cl_2): 5.66-5.53 (m, 1H), 5.47-5.36 (m, 1H), 3.91-3.66 (m, 2H), 3.26-3.12 (m, 4H), 2.10-1.98 (m, 2H), 1.74-1.66 (m, 3H), 1.50-1.40 (s, 9H)
^{13}C-NMR (100MHz, CD_2Cl_2): 155.6, 134.8, 128.5, 127.3, 127.2, 79.6, 79.0, 48.3, 47.7, 47.3, 32.9, 28.6, 17.8, 13.1, 3.7
IR (film, cm^{-1}): 2974, 2930, 1691, 1463, 1412, 1366, 1237, 1154, 953
HRMS (ESI, m/z): $[M]^+$ calc.: 339.0695; found: 339.0688

Alcohol 10



(*R*)-5-Methylcyclohex-2-enone (803 mg, 7.290 mmol, 1.0 eq) was dissolved in dichloromethane (15 mL), cooled to -78°C and $TiCl_4$ (0.82 mL, 7.514 mmol, 1.03 eq) was added dropwise. The resulting dark red solution was stirred for 5 minutes before allyltrimethylsilane (0.87 mL, 5.451 mmol, 1.25 eq) was added within 5 minutes. After 1.5 hours TLC indicated the complete consumption of the enone the in situ formed enolate was treated with acetaldehyde (0.37 mL, 6.544 mmol, 1.5 eq) and stirred for additional 1.5 hours. Then water and diethyl ether were added and the solution was warmed to room temperature. The aqueous layer was extracted with ether (4x), the combined organic phases were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by chromatography (hexane/EtOAc 4/1 to 3/1) provided 610.4 mg of an inseparable mixture of two diastereomeric alcohols as clear colourless oil with 70% yield.
^{1}H-NMR (400 MHz $CDCl_3$): 5.80-5.66 (m, 1H), 5.11-5.00 (m, 2H), 4.10-4.00 (m, 1H), 2.48-1.96 (m, 8H), 1.72-1.60 (m, 2H), 1.30 (d, J=6.28Hz, 1.3H), 1.21 (d, J=6.28Hz, 1.7H), 0.99 (d, J=6.76Hz, 3H)
^{13}C-NMR (100MHz, $CDCl_3$): 214.4, 214.1, 135.83, 135.82, 117.42, 117.37, 67.4, 66.7, 61.44, 61.39, 48.9, 48.7, 38.1, 37.8, 37.3, 35.6, 34.9, 34.5, 29.8, 29.3, 22.9, 21.5, 21.3, 20.9
IR (film, cm^{-1}): 3425, 2957, 2925, 1702, 1642, 1457, 1378, 1277, 1092, 914
HRMS (ESI, m/z): $[M\text{-}CH_3]^+$ calc.: 181.1229; found: 181.1233

Diketone 11



Alcohol **10** (1.27 g, 6.470 mmol, 1.0 eq) was dissolved in anhydrous ethyl acetate (65 mL) and IBX (5.46 g, 19.50 mmol, 3.0 eq) was added. After refluxing for 3 hours the suspension was cooled to 0°C and hexane (65 mL) was added. The white precipitate was removed by filtration and washed with hexane/ethyl acetate (1/1) twice. The filtrate was concentrated in

vacuo to yield a clear, colourless oil, which was used in the next step without further purification. A solution of the crude diketo compound in DMF (21 mL) was treated with Cesium carbonate (4.09 g, 12.55, 2.0 eq). After 10 minutes the mixture was cooled to -15°C and iodocarbamate **8** (3.17 g, 9.345 mmol, 1.5 eq) dissolved in DMF (10 mL) was added. After stirring 15 hours the solution was slowly warmed to 0°C during additional 6 hours. The reaction was quenched with diluted aqueous ammonium chloride and diethyl ether was added. The aqueous layer was extracted with ether (4x), the combined extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by chromatography (hexane/EtOAc 20/1 to 10/1) furnished 1.79 g of compound **11** as clear slightly yellow oil with 68% yield over 2 steps.

^{1}H-NMR (400 MHz $CDCl_3$): 5.73-5.61 (m, 1H), 5.61-5.47 (m, 1H), 5.45-5.31 (m, 1H), 5.08-4.95 (m, 2H), 3.93-3.63 (m, 2H), 3.14 (b, 2H), 2.50-2.39 (m, 1H), 2.31-1.85 (m, 10H), 1.74-1.55 (m, 5H), 1.44 (s, 9H), 1.40-1.23 (m, 2H), 0.96 (d, J=6.53Hz, 3H)

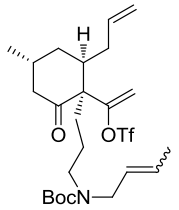
^{13}C-NMR (100MHz, $CDCl_3$): 210.0, 208.0, 155.7, 155.6, 137.0, 128.2, 127.1, 126.95, 126.90, 116.6, 79.6, 79.5, 69.5, 48.9, 47.3, 46.4, 43.4, 39.3, 34.5, 31.9, 30.3, 29.9, 28.6, 28.5, 23.4, 21.1, 17.8, 13.0

IR (film, cm^{-1}): 2957, 2929, 1691, 1456, 1414, 1365, 1236, 1171, 1140

HRMS (ESI, m/z): $[M]^+$ calc.: 406.2957; found: 406.2955

$[\alpha]_D^{20}$ = -46.7 (c = 1.62 g/100mL, DCM)

Triflate 12

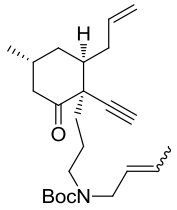


Diketone **11** (470 mg, 1.159 mmol, 1.0 eq) was dissolved in THF (18 mL) and treated with Comins reagent[11] (937 mg, 2.386 mmol, 2.0 eq). The resulting solution was cooled to -78°C and a solution of 0.7 M KHMDS in toluene (1.8 mL, 1.26 mmol, 1.1 eq) and THF (6 mL) was added slowly within 1½ hours. After stirring for 30 minutes again 0.7 M KHMDS in toluene (0.9 mL, 0.63 mmol, 0.55 eq) was added within 45 minutes. 30 minutes later additional 0.7 M KHMDS in toluene (0.45, 0.315 mmol, 0.25 eq) was added within 20 minutes and the resulting solution stirred until complete conversion of the starting material was observed (30 minutes). Diluted aqueous $NaHCO_3$ and diethyl ether were added. The aqueous layer was extracted with ether (3x), the combined extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by chromatography (hexane/EtOAc 30/1 to 10/1) provided 531 mg of compound **12** as clear colourless oil with 85% yield.

[11] Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299

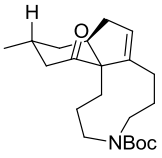
^{1}H-NMR (400 MHz $CDCl_3$): 6.14 (d, J=4.27Hz, 1H), 5.70-5.46 (m, 3H), 5.44-5.30 (m,1H), 5.07-4.94 (m, 2H), 3.88-3.56 (m, 2H), 3.37-2.95 (m, 2H), 2.39-2.03 (m, 6H), 1.86-1.74 (m, 2H), 1.74-1.61 (m, 5H), 1.57-1.40 (m, 10H), 1.21-1.08 (m, 1H), 1.00 (d, J=6.27Hz, 3H)
^{13}C-NMR (100MHz, $CDCl_3$): 208.2,.155.6, 153.2, 136.0, 128.4, 126.9, 126.7, 123.1, 120.0, 117.1, 116.8, 113.6, 109.5, 79.6, 79.5, 59.7, 49.0, 47.3, 45.9, 45.6, 43.3, 42.4, 33.9, 31.9, 30.5, 28.6, 23.2, 22.2, 17.7, 12.9
IR (film, cm^{-1}): 2959, 2932, 1694, 1409, 1366, 1209, 1174, 1141, 910, 770, 731, 609
HRMS (ESI, m/z): $[M]^+$ calc.: 537.2372; found: 537.2370
$[\alpha]_D^{20}$ = +31.6 (c = 1.46 g/100mL, DCM)

Dienyne 6



A solution of triflate **12** (527 mg, 0.980 mmol, 1.0 eq) and anhydrous pyridine (10 mL) was heated to 60°C. After 15 hours the resulting solution was cooled to room temperature and treated with 5% aqueous citric acid and diethylether. The aqueous layer was extracted with diethylether (3x), washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by chromatography (hexane/EtOAc 10/1) furnished 374.4 mg of compound **6** as clear colourless oil with 99% yield.
^{1}H-NMR (400 MHz $CDCl_3$): 5.75-5.61 (m, 1H), 5.61-5.48 (m, 1H), 5.44-5.32 (m, 1H), 5.06-4.96 (m, 2H), 3.90-3.62 (m, 2H), 3.16 (b, 2H), 2.85 (b, 1H), 2.61-2.46 (m,1H), 2.38 (s, 1H), 2.23 (b, 1H), 2.12-1.60 (m, 11H), 1.54-1.38 (m, 10H), 0.91 (d, J=7.03, 3H)
^{13}C-NMR (100MHz, $CDCl_3$): 207.9, 155.74, 155.67, 136.7, 128.0, 127.1, 127.0, 116.6, 83.3, 79.4, 79.3, 75.3, 54.9, 48.7, 46.3, 45.1, 43.1, 42.5, 35.0, 32.2, 29.5, 28.6, 23.9, 20.4, 17.7, 13.0
IR (film, cm^{-1}): 3308, 2962, 2929, 1719, 1688, 1456, 1414, 1365, 1234, 1172
HRMS (ESI, m/z): $[M]^+$ calc.: 388.2852; found: 388.2865
$[\alpha]_D^{20}$ = -29.6 (c = 1.32 g/100mL, DCM)

Tricyclic carbamate 5



Dienyne **6** (56.4 mg, 0.1455 mmol, 1.0 eq) was dissolved in freshly distilled and degassed 1,2-dichloroethane (40 mL). Grubbs II catalyst (24.1 mg, 0.0284 mmol, 0.2 eq) dissolved in 1,2-dichloroethane (8 mL) was added and the resulting solution stirred for 30 minutes at room temperature. After refluxing for 24 hours the solution was cooled to room temperature and then transferred into an autoclave via cannula. The autoclave is pressurized with dihydrogen (10 atm) and heated to 70°C for 16 hours. The solvent is evaporated and the residue purified

by chromatography (hexane/EtOAc 10/1 to 5/1) to furnish 26.1 mg of compound **5** as clear colorless oil with 52% yield.

^{1}H-NMR (400 MHz $CDCl_3$, some peaks are doubled and/or broadened due to conformational isomers)[12]: 5.72-5.63 (m, 1H), 3.52-3.30 (m, 1H), 3.26-2.87 (m, 3H), 2.73-2.51 (m, 1H), 2.50-2.28 (m, 2H), 2.25-1.80 (m, 7H), 1.74-1.50 (m, 5H), 1.44 and 1.43 (s, 9H), 1.40-1.28 (m, 1H), 0.93 and 0.91 (d, J=6.78Hz, 3H)

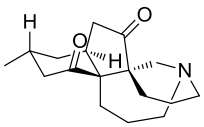
^{13}C-NMR (100MHz, $CDCl_3$, some peaks are doubled and/or broadened due to conformational isomers)[4]: 215.9, 215.6, 156.5, 156.0, 144.4, 143.9, 129.7, 129.2, 79.2, 79.1, 66.0, 65.8, 50.6, 49.9, 47.8, 47.0, 46.9, 43.7, 42.8, 39.2, 38.1, 37.7, 36.6, 32.1, 30.0, 28.7, 27.4, 26.6, 26.3, 26.0, 25.8, 24.6, 22.53, 22.48, 22.1, 21.3

IR (film, cm^{-1}): 2954, 2924, 1694, 1480, 1456, 1413, 1365, 1247, 1167

HRMS (ESI, m/z): $[M]^+$ calc.: 347.2460; found: 347.2458

$[\alpha]_D^{20}$ = -137.4 (c = 1.02 g/100mL, DCM)

(+)-Lycoflexine (1)



A solution of tricyclic carbamate **5** (18.3 mg, 0.05266 mmol, 1.0 eq) dissolved in THF (0.53 mL) was cooled to 0°C and treated with 1.0 M borane THF complex (0.53 mL, 0.53 mmol, 10 eq) before it was heated to 50°. After 8 hours the resulting solution was cooled to 0°C and methanol (0.22 mL, 5.424 mmol, ~100 eq) was added. The icebath was removed and the colourless solution stirred for an additional hour. Then the solvent is evaporated and the residue redissolved in ethyl acetate (2.1 mL). IBX (148.8 mg, 0.5314, 10 eq) is added and refluxed for 24 hours. The suspension was cooled to 0°C and ethyl acetate (2.1 mL) and hexane (2.1 mL) were added. The white precipitate was removed by filtration through a short pad of silica gel and washed with hexane/ethyl acetate (1/2). The filtrate was concentrated in vacuo to yield a clear, slightly yellow oil, which was used in the next step without further purification. The crude diketo compound was dissolved in Ethanol (3.2 mL) cooled to 0°C and treated with 0.5 M HCl (0.32 mL, 0.16 mmol, 3.0 eq). Then aqueous formaldehyde (37%, 86 µL, 1.060 mmol, 20.0 eq) was added and the resulting clear and colourless solution refluxed for 48 hours. The reaction was quenched with diluted aqueous $NaHCO_3$ and dichloromethane was added. The aqueous layer was extracted with dichloromethane (4x), dried (Na_2SO_4) and concentrated in vacuo. Purification by chromatography (DCM/ethyl acetate 200/1 to 50/1) affords 9.3 mg of compound **1** as white solid with 64% yield over 2 steps.

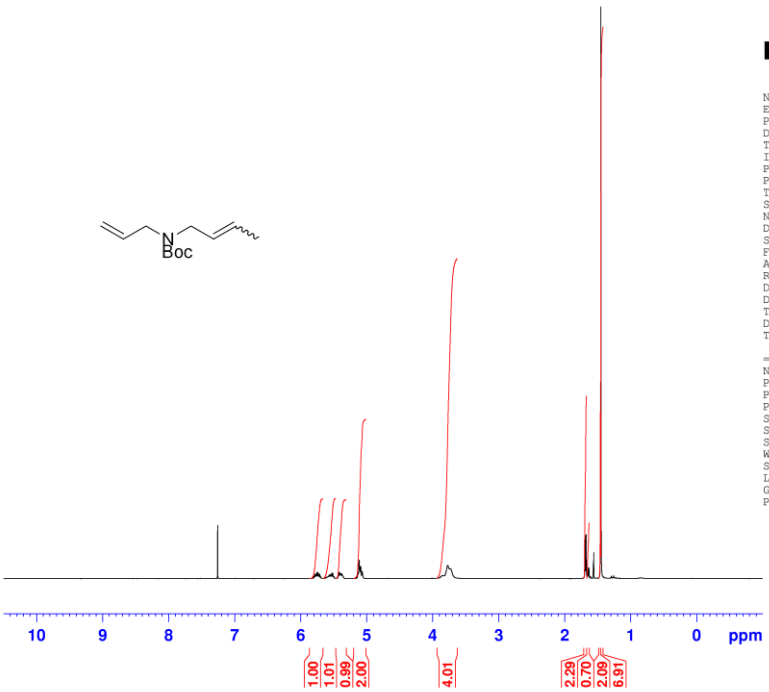
[12] consistent with: Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem. Int. Ed.* **2007**, *46*, 7671.

^{1}H-NMR (400 MHz $CDCl_3$)[13]: 3.22-3.07 (m, 2H), 3.02-2.91 (m, 1H), 2.90-2.75 (m, 2H), 2.70-2.59 (m, 2H), 2.42-1.72 (m, 13H), 1.63-1.53 (m, 1H), 1.36-1.28 (m, 1H), 1.03 (d, J=6.02, 3H)
^{13}C-NMR (100MHz, $CDCl_3$)[5]: 218.5, 214.0, 60.8, 58.6, 56.8, 53.7, 53.4, 46.8, 40.4, 40.2, 36.4, 31.4, 29.4, 28.1, 26.2, 22.5, 19.5
IR (film, cm^{-1}): 2924, 2854, 1727, 1699, 1456, 1414, 1377, 1353, 1208, 1175, 1130, 1063, 1000
HRMS (ESI, m/z): $[M-H_2O]^+$ calc.: 275.1885; found: 275.1882
$[\alpha]_D^{20}$ = +9.0 (c = 1.04 g/100mL, DCM)
m.p.: 129-130 °C

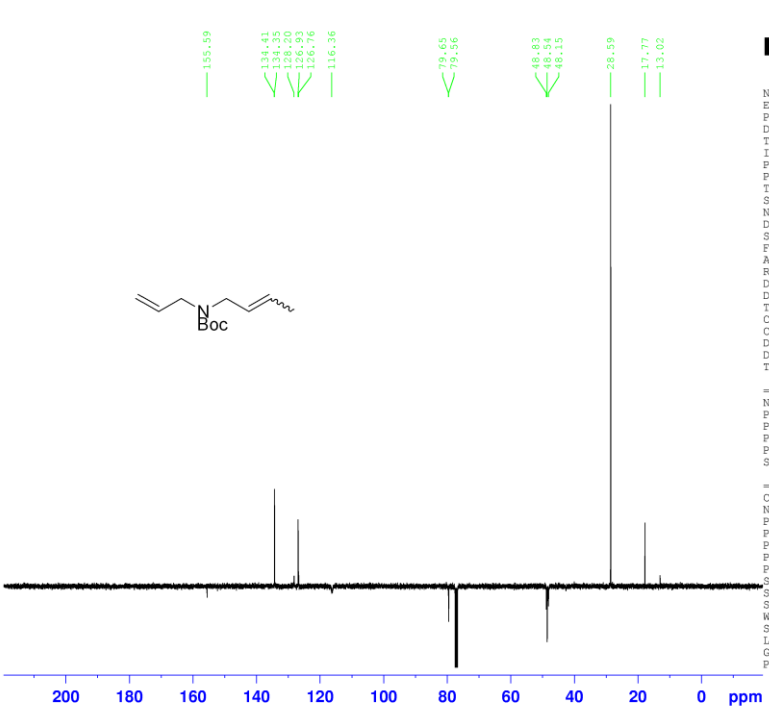
[13] In exact agreement with: Takayama, H.; Katakawa, K.; Kitajima, M.; Yamaguchi, K.; Aimi, N. *Tetrahedron Lett.* **2002**, *43*, 8307. A comparison of the NMR spectra provided by Professor Takayama can be found in section 2 of the supporting information.

2. NMR Spectra

Allylcrotylcarbamate

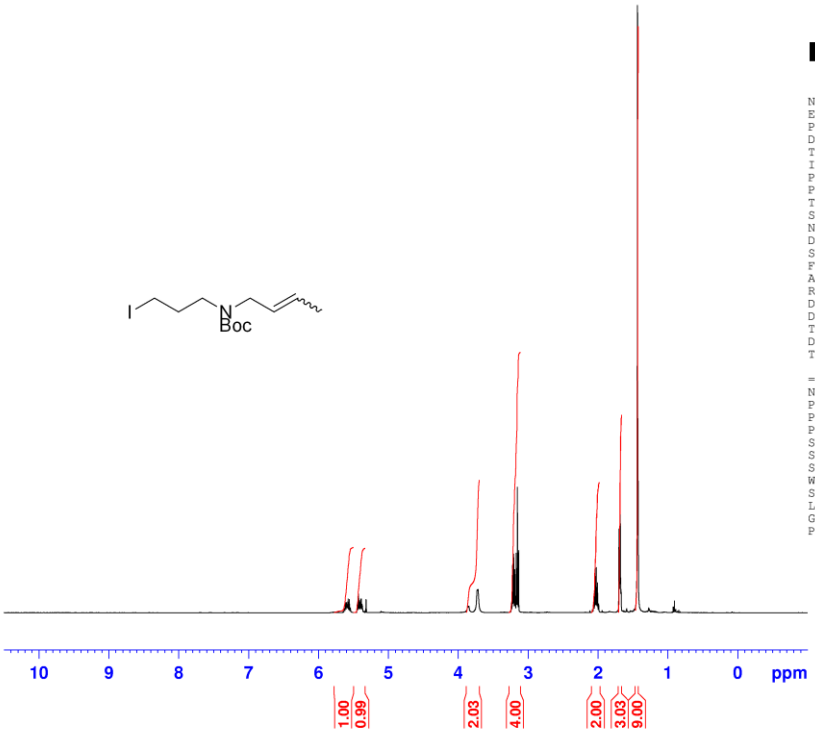



```
NAME                4May0210
EXPNO                     10
PROCNO                     1
Date_               20100502
Time                   15.16
INSTRUM              AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                       512
DW                    60.800 usec
DE                     6.50 usec
TE                    298.2 K
D1                  1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PL1                    -1.80 dB
PL1W               15.28361320 W
SFO1              400.2724718 MHz
SI                       32768
SF                400.2700108 MHz
WDW                        EM
SSB                         0
LB                     0.30 Hz
GB                          0
PC                      1.00
```

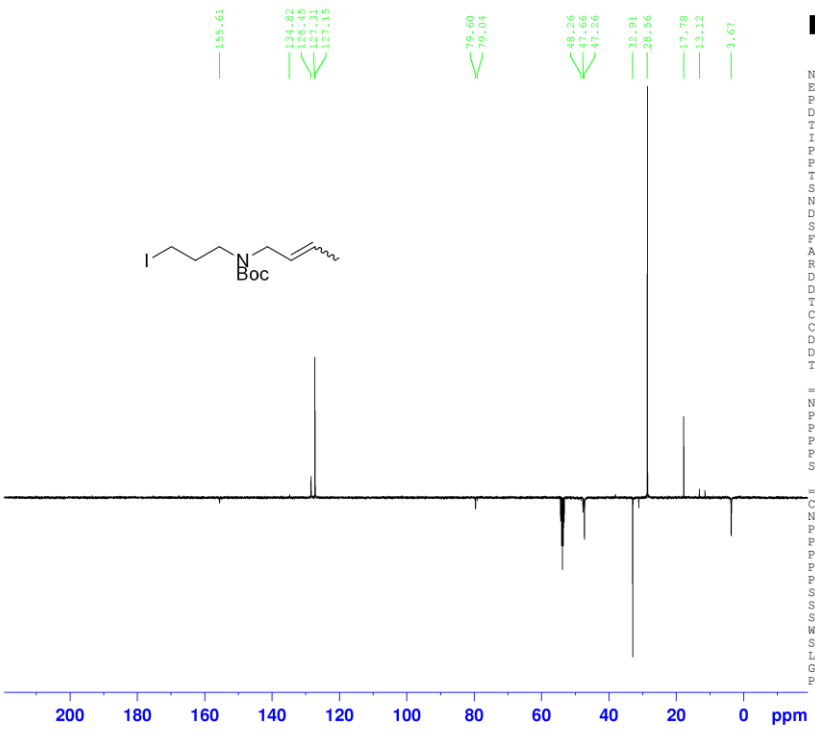



```
NAME                4May0210
EXPNO                     11
PROCNO                     1
Date_               20100503
Time                   0.25
INSTRUM              AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                 jmod
TD                     65536
SOLVENT                CDCl3
NS                       4096
DS                         4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                       2050
DW                    20.800 usec
DE                     6.50 usec
TE                    298.2 K
CNST2              145.0000000
CNST11               1.0000000
D1                   2.00000000 sec
D20                  0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                     10.00 usec
P2                     20.00 usec
PL1                    -1.50 dB
PL1W               47.89980698 W
SFO1              100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -1.80 dB
PL12                   14.70 dB
PL2W               15.28361320 W
PL12W               0.34215751 W
SFO2              400.2716011 MHz
SI                       32768
SF                100.6479562 MHz
WDW                        EM
SSB                         0
LB                     1.00 Hz
GB                          0
PC                      1.40
```

Iodocarbamate 8

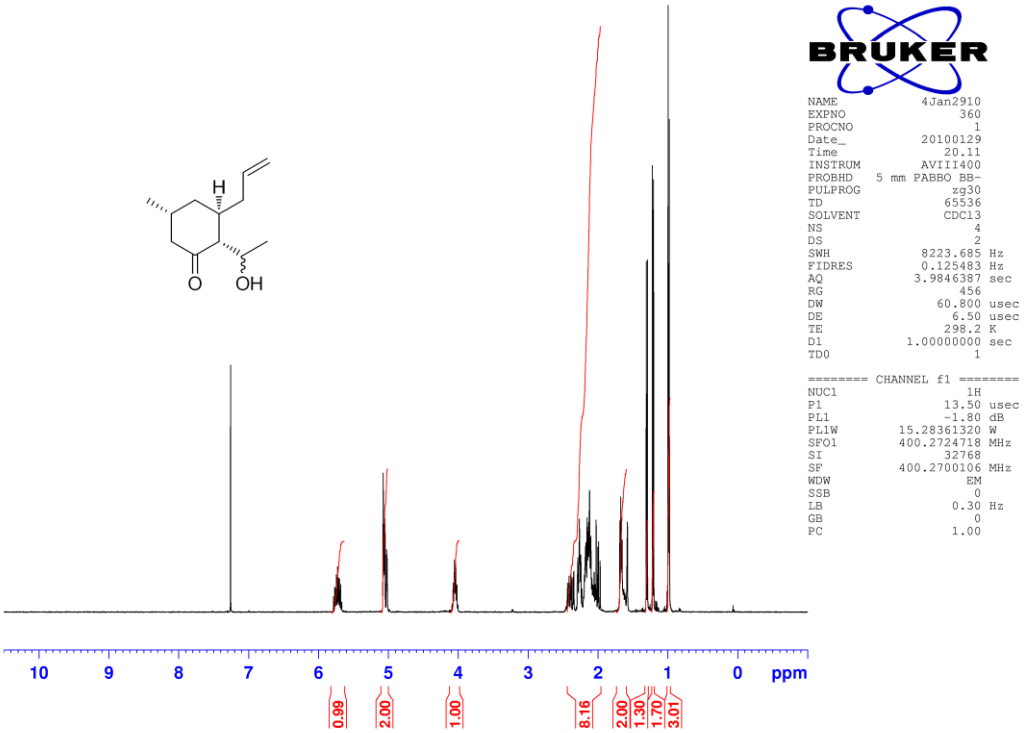



```
NAME                4Aug1610
EXPNO                    351
PROCNO                     1
Date_               20100816
Time                   20.25
INSTRUM             AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT             CD2Cl2
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                      90.5
DW                    60.800 usec
DE                     6.50 usec
TE                   298.2 K
D1                1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                    13.50 usec
PL1                   -1.80 dB
PL1W             15.28361320 W
SFO1             400.2724718 MHz
SI                      32768
SF               400.2700163 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```

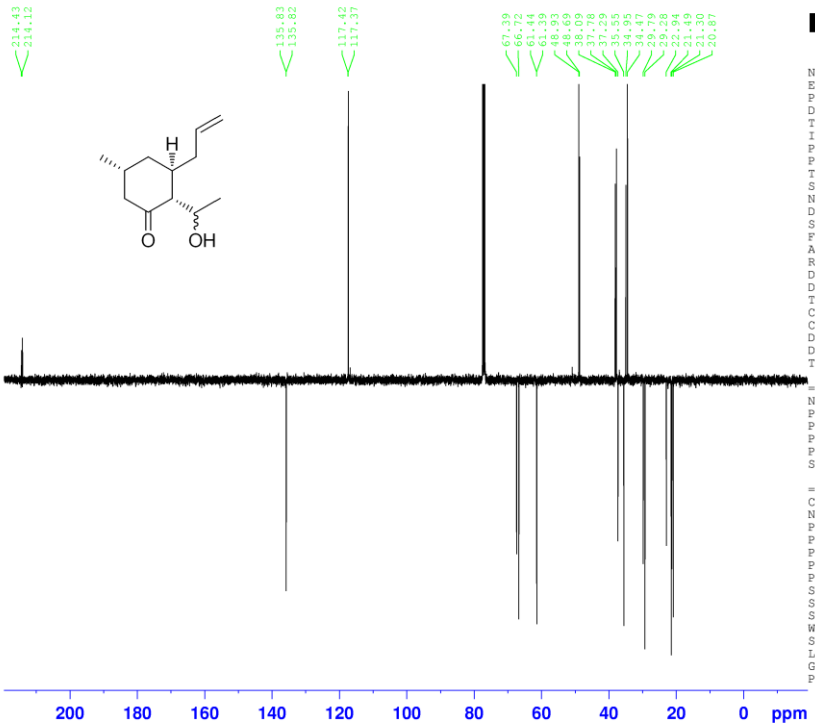



```
NAME                4Aug1610
EXPNO                    352
PROCNO                     1
Date_               20100816
Time                   21.30
INSTRUM             AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                jmod
TD                    65536
SOLVENT             CD2Cl2
NS                      1024
DS                         4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                      2050
DW                    20.800 usec
DE                     6.50 usec
TE                   298.2 K
CNST2              145.0000000
CNST11               1.0000000
D1                 2.00000000 sec
D20                0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                    10.00 usec
P2                    20.00 usec
PL1                   -1.50 dB
PL1W             47.89980698 W
SFO1             100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                      1H
PCPD2                100.00 usec
PL2                   -1.80 dB
PL12                  14.70 dB
PL2W             15.28361320 W
PL12W             0.34215751 W
SFO2             400.2716011 MHz
SI                      32768
SF               100.6479310 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```

Alcohol 10

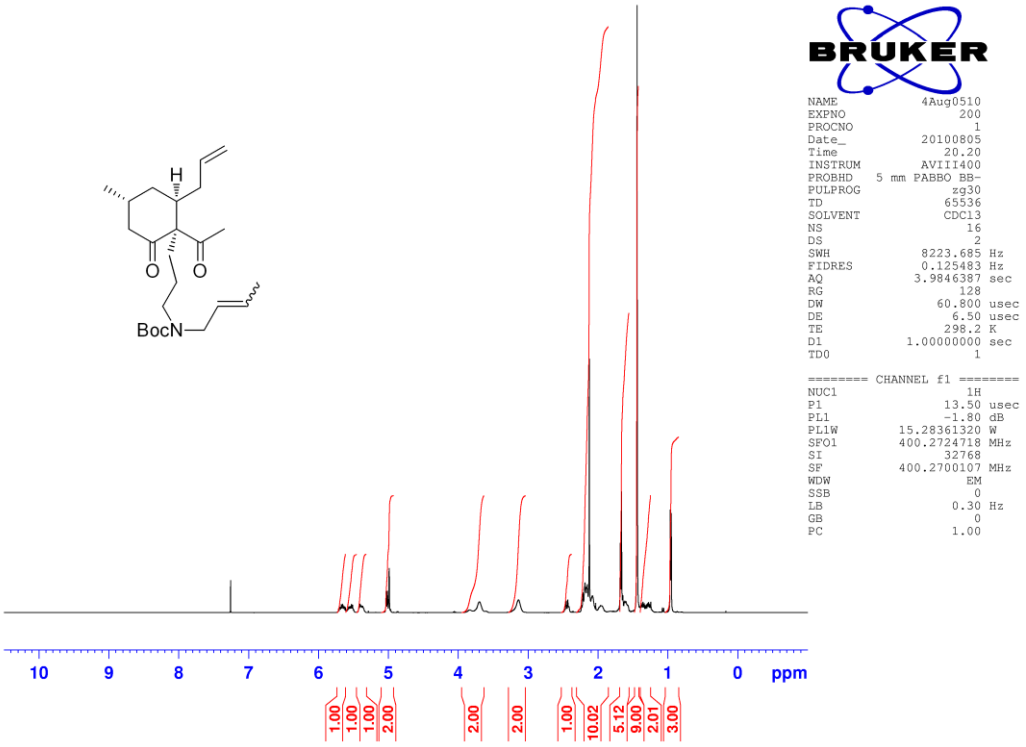



```
NAME                4Jan2910
EXPNO                    360
PROCNO                     1
Date_               20100129
Time                   20.11
INSTRUM             AVIII400
PROBHD  5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                        4
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                      456
DW                   60.800 usec
DE                    6.50 usec
TE                   298.2 K
D1                1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PL1                    -1.80 dB
PL1W              15.28361320 W
SFO1              400.2724718 MHz
SI                      32768
SF                400.2700106 MHz
WDW                        EM
SSB                         0
LB                     0.30 Hz
GB                          0
PC                      1.00
```

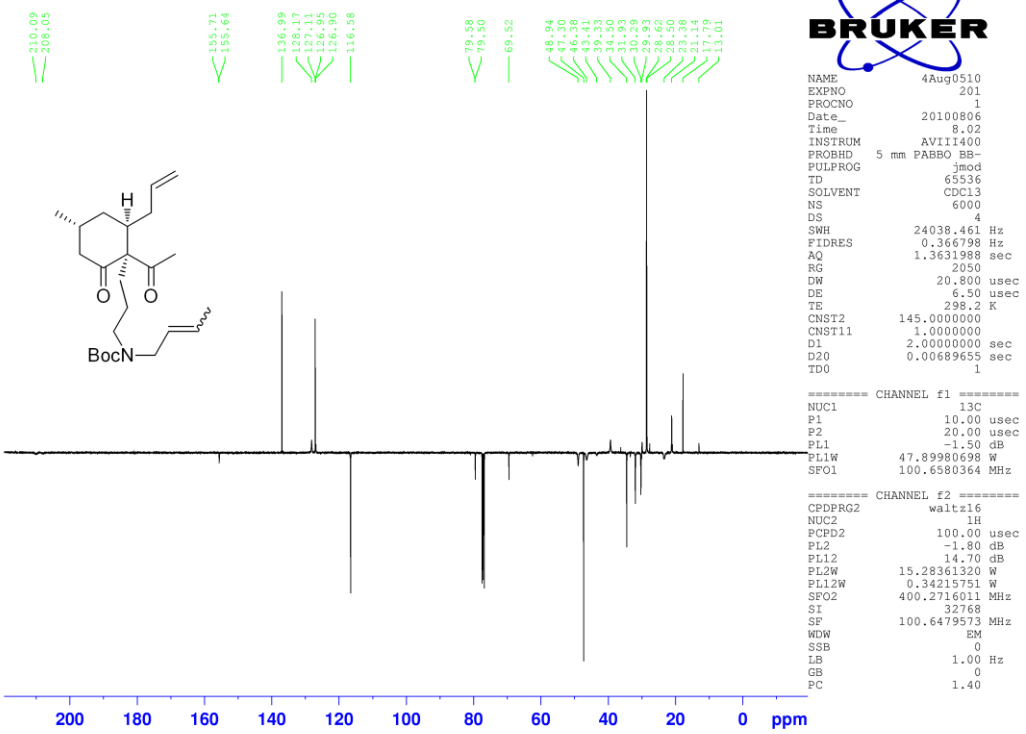



```
NAME                4Jan2910
EXPNO                    361
PROCNO                     1
Date_               20100130
Time                   0.25
INSTRUM             AVIII400
PROBHD  5 mm PABBO BB-
PULPROG                jmod
TD                    65536
SOLVENT               CDCl3
NS                     4096
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631988 sec
RG                     2050
DW                   20.800 usec
DE                    6.50 usec
TE                   298.2 K
CNST2            145.00000000
CNST11             1.00000000
D1                 2.00000000 sec
D20                0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                     13C
P1                     10.00 usec
P2                     20.00 usec
PL1                    -1.50 dB
PL1W              47.89980698 W
SFO1              100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2               waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -1.80 dB
PL12                   14.70 dB
PL2W              15.28361320 W
PL12W              0.34215751 W
SFO2              400.2716011 MHz
SI                      32768
SF                100.6479566 MHz
WDW                        EM
SSB                         0
LB                     1.00 Hz
GB                          0
PC                      1.40
```

Diketone 11

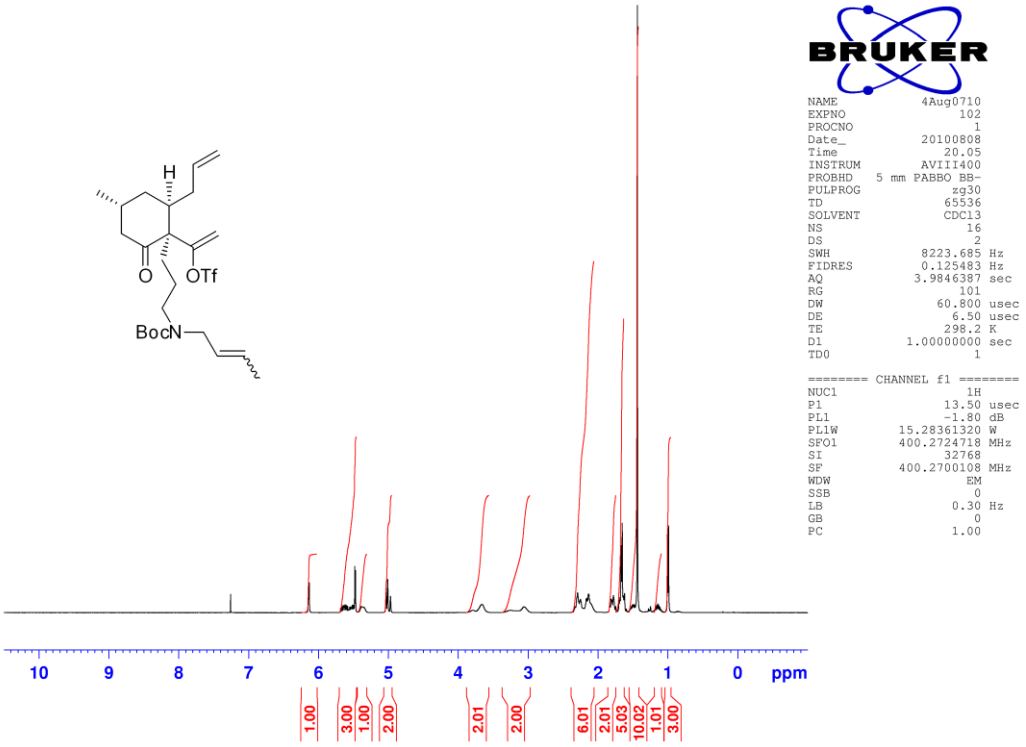



```
NAME                4Aug0510
EXPNO                    200
PROCNO                     1
Date_               20100805
Time                   20.20
INSTRUM             AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                       128
DW                  60.800 usec
DE                   6.50 usec
TE                   298.2 K
D1                1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                    13.50 usec
PL1                   -1.80 dB
PL1W             15.28361320 W
SFO1             400.2724718 MHz
SI                       32768
SF               400.2700107 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```

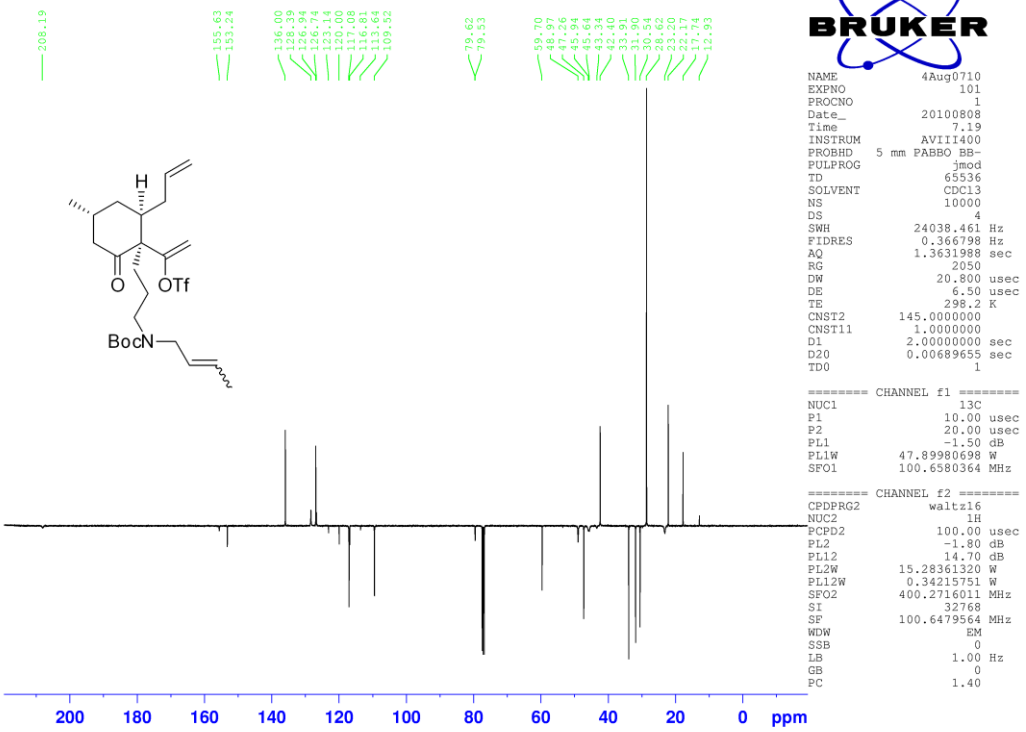



```
NAME                4Aug0510
EXPNO                    201
PROCNO                     1
Date_               20100806
Time                    8.02
INSTRUM             AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                jmod
TD                    65536
SOLVENT               CDCl3
NS                     6000
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631988 sec
RG                      2050
DW                  20.800 usec
DE                   6.50 usec
TE                   298.2 K
CNST2            145.0000000
CNST11             1.0000000
D1                 2.00000000 sec
D20                0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                     13C
P1                    10.00 usec
P2                    20.00 usec
PL1                   -1.50 dB
PL1W             47.89980698 W
SFO1             100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                      1H
PCPD2                100.00 usec
PL2                   -1.80 dB
PL12                  14.70 dB
PL2W             15.28361320 W
PL12W             0.34215751 W
SFO2             400.2716011 MHz
SI                       32768
SF               100.6479573 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```

Triflate 12

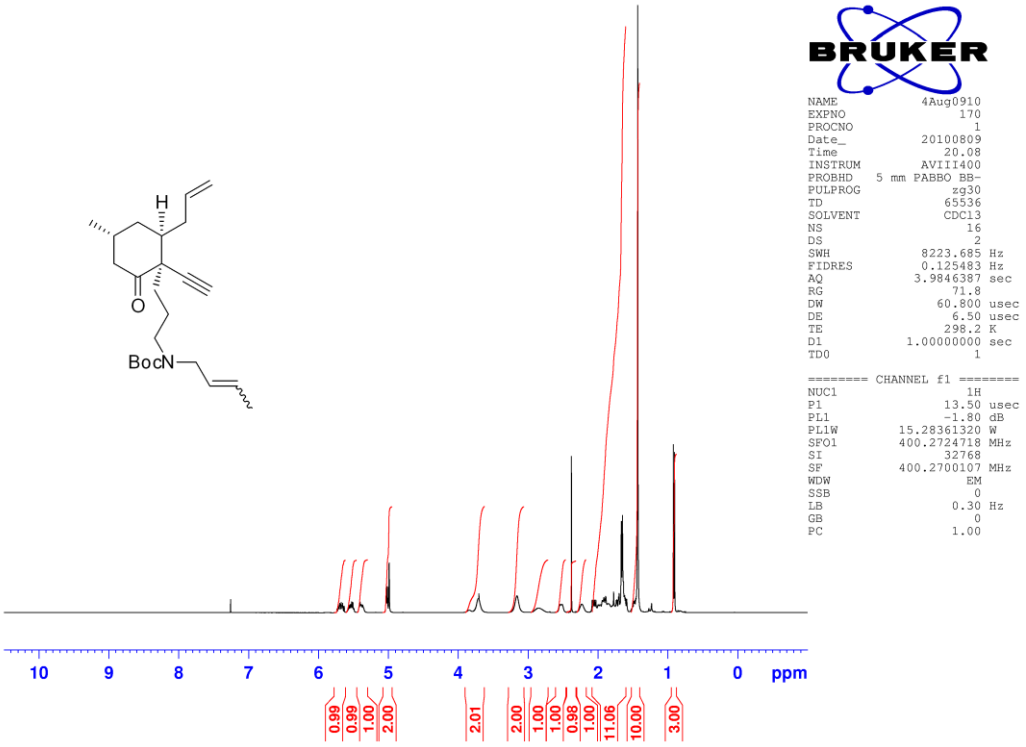



```
NAME                4Aug0710
EXPNO                    102
PROCNO                     1
Date_               20100808
Time                   20.05
INSTRUM             AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDC13
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                       101
DW                  60.800 usec
DE                   6.50 usec
TE                   298.2 K
D1                1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                    13.50 usec
PL1                   -1.80 dB
PL1W             15.28361320 W
SFO1             400.2724718 MHz
SI                       32768
SF               400.2700108 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```

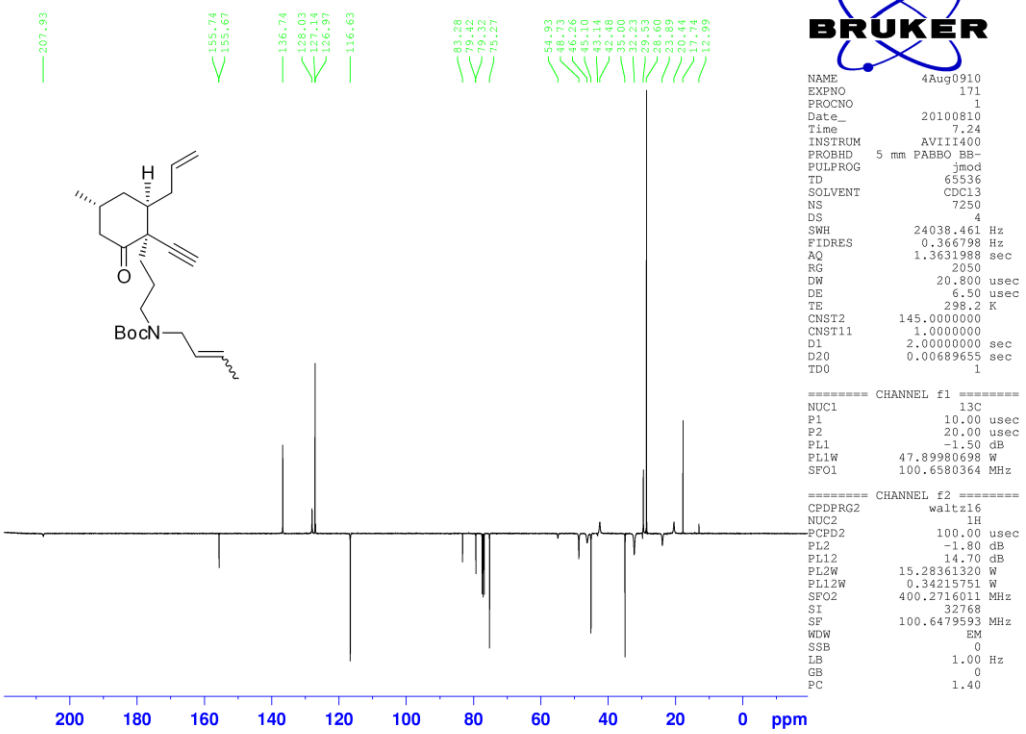



```
NAME                4Aug0710
EXPNO                    101
PROCNO                     1
Date_               20100808
Time                    7.19
INSTRUM             AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                jmod
TD                    65536
SOLVENT               CDC13
NS                    10000
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631988 sec
RG                      2050
DW                  20.800 usec
DE                   6.50 usec
TE                   298.2 K
CNST2            145.0000000
CNST11             1.0000000
D1                 2.00000000 sec
D20                0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                    10.00 usec
P2                    20.00 usec
PL1                   -1.50 dB
PL1W             47.89980698 W
SFO1             100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                      1H
PCPD2                100.00 usec
PL2                   -1.80 dB
PL12                  14.70 dB
PL2W             15.28361320 W
PL12W             0.34215751 W
SFO2             400.2716011 MHz
SI                       32768
SF               100.6479564 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```

Dienyne 6

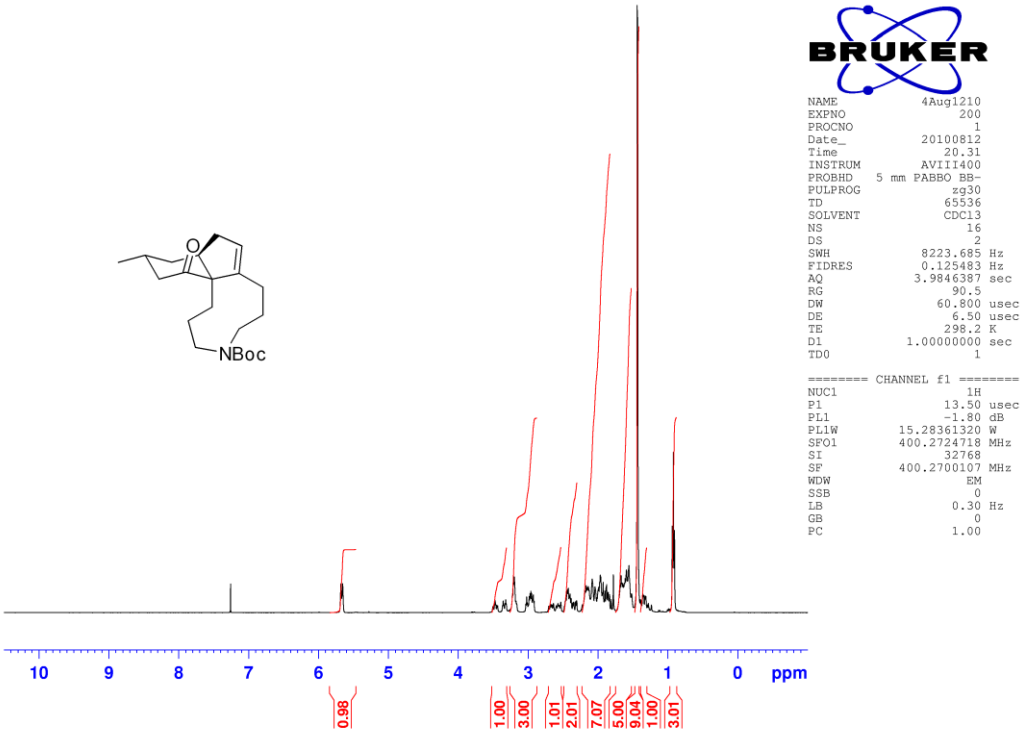



```
NAME                4Aug0910
EXPNO                    170
PROCNO                     1
Date_               20100809
Time                   20.08
INSTRUM             AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDC13
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                      71.8
DW                    60.800 usec
DE                     6.50 usec
TE                   298.2 K
D1                1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PL1                    -1.80 dB
PL1W              15.28361320 W
SFO1              400.2724718 MHz
SI                       32768
SF                400.2700107 MHz
WDW                        EM
SSB                         0
LB                     0.30 Hz
GB                          0
PC                      1.00
```

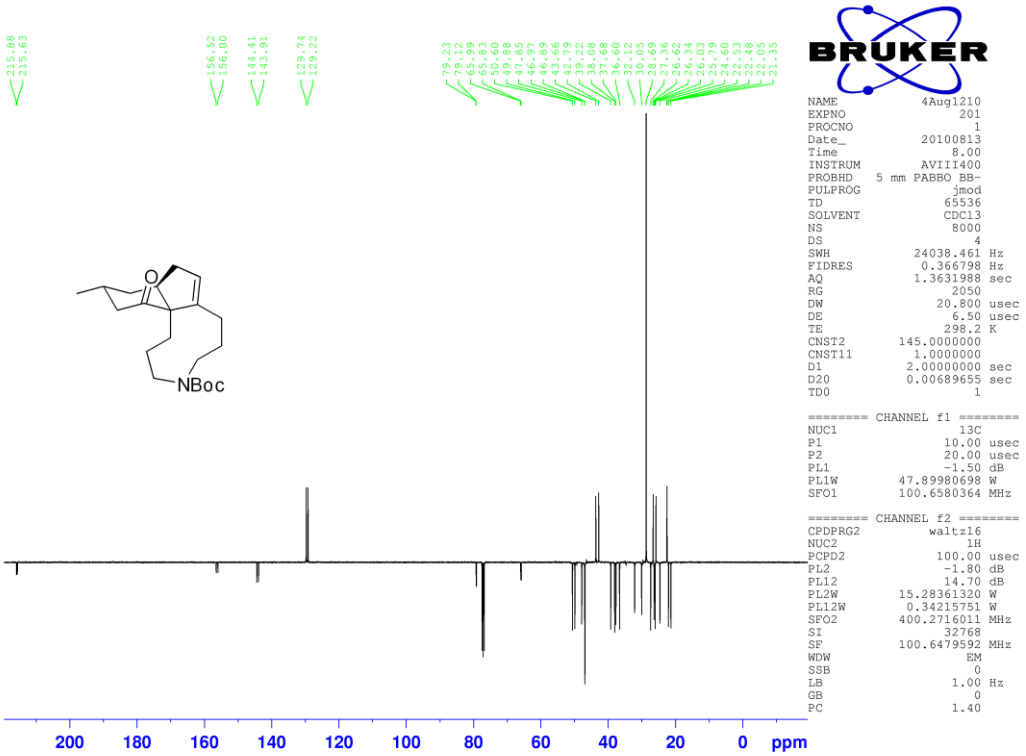



```
NAME                4Aug0910
EXPNO                    171
PROCNO                     1
Date_               20100810
Time                    7.24
INSTRUM             AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                jmod
TD                    65536
SOLVENT               CDC13
NS                     7250
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631988 sec
RG                      2050
DW                    20.800 usec
DE                     6.50 usec
TE                   298.2 K
CNST2             145.0000000
CNST11              1.0000000
D1                 2.00000000 sec
D20                0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                     10.00 usec
P2                     20.00 usec
PL1                    -1.50 dB
PL1W              47.89980698 W
SFO1              100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                 100.00 usec
PL2                    -1.80 dB
PL12                   14.70 dB
PL2W              15.28361320 W
PL12W              0.34215751 W
SFO2              400.2716011 MHz
SI                       32768
SF                100.6479593 MHz
WDW                        EM
SSB                         0
LB                     1.00 Hz
GB                          0
PC                      1.40
```

Tricyclic carbamate 5

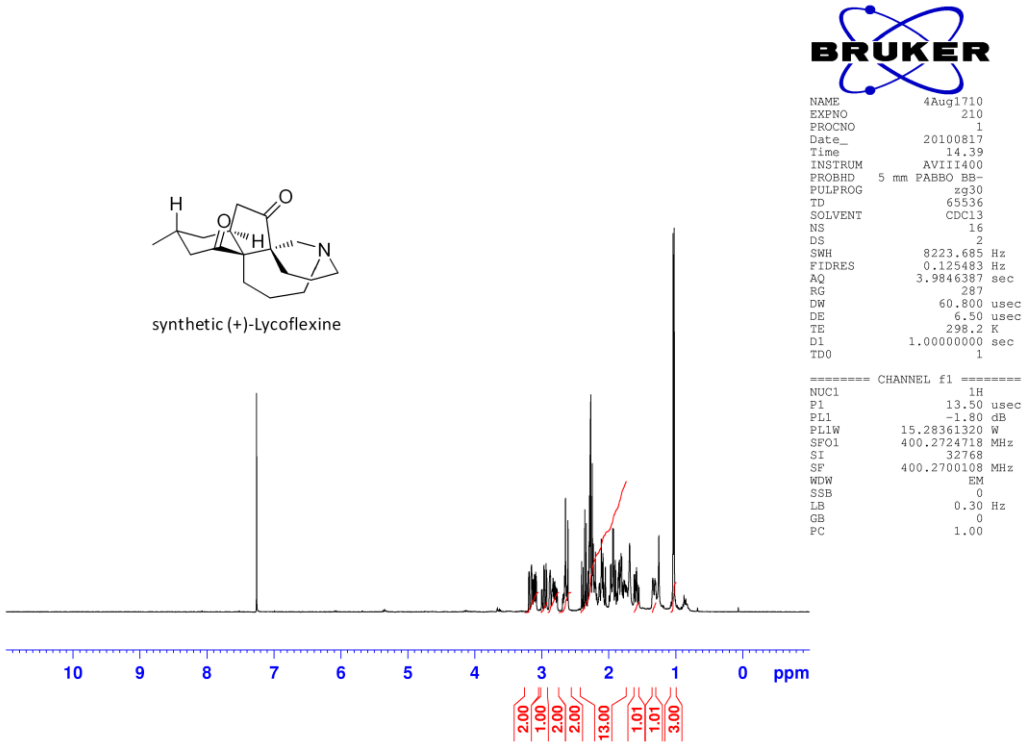


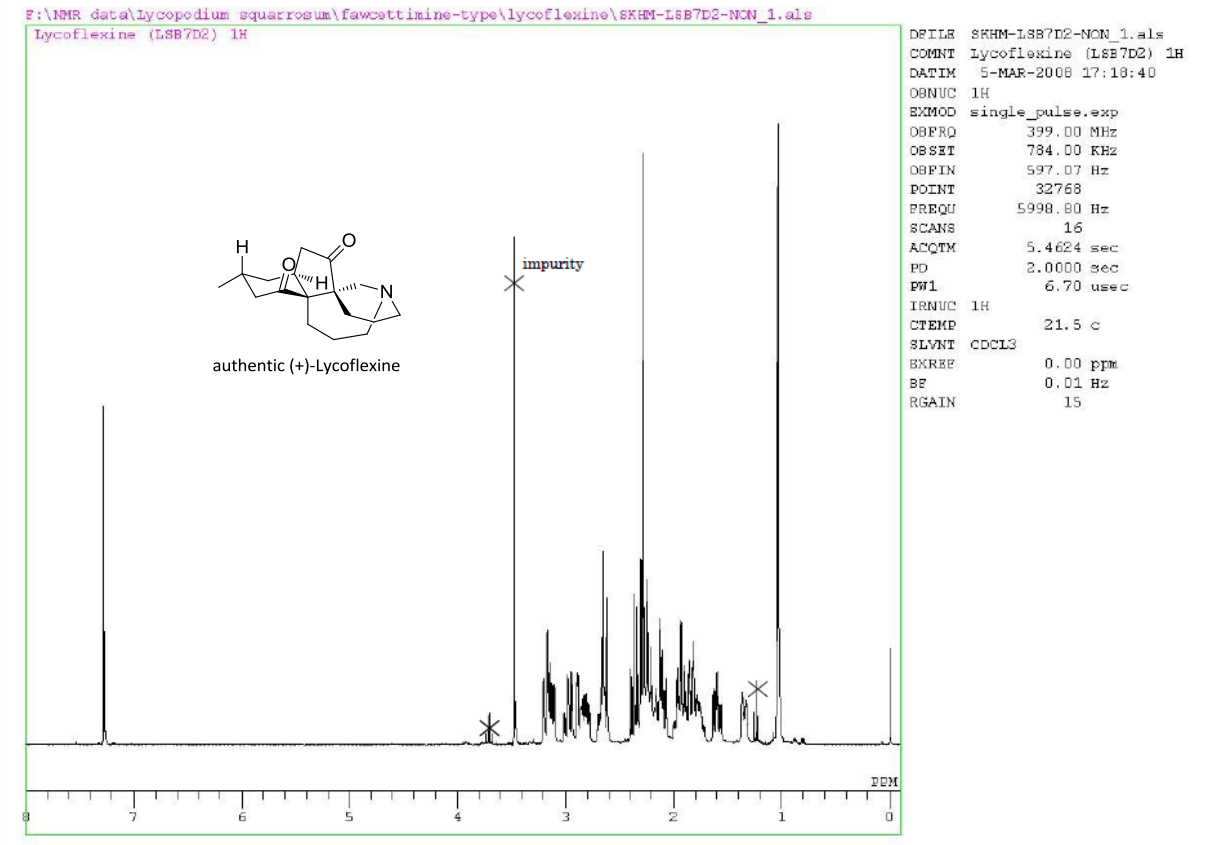

```
NAME                4Aug1210
EXPNO                    200
PROCNO                     1
Date_               20100812
Time                   20.31
INSTRUM              AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                      90.5
DW                    60.800 usec
DE                     6.50 usec
TE                   298.2 K
D1                1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                    13.50 usec
PL1                   -1.80 dB
PL1W             15.28361320 W
SFO1             400.2724718 MHz
SI                       32768
SF               400.2700107 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```




```
NAME                4Aug1210
EXPNO                    201
PROCNO                     1
Date_               20100813
Time                   8.00
INSTRUM              AVIII400
PROBHD     5 mm PABBO BB-
PULPROG                jmod
TD                    65536
SOLVENT               CDCl3
NS                     8000
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631988 sec
RG                     2050
DW                    20.800 usec
DE                     6.50 usec
TE                   298.2 K
CNST2            145.00000000
CNST11             1.00000000
D1                 2.00000000 sec
D20                0.00689655 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                     13C
P1                    10.00 usec
P2                    20.00 usec
PL1                   -1.50 dB
PL1W             47.89980698 W
SFO1             100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                      1H
PCPD2                100.00 usec
PL2                   -1.80 dB
PL12                  14.70 dB
PL2W             15.28361320 W
PL12W             0.34215751 W
SFO2             400.2716011 MHz
SI                       32768
SF               100.6479592 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```

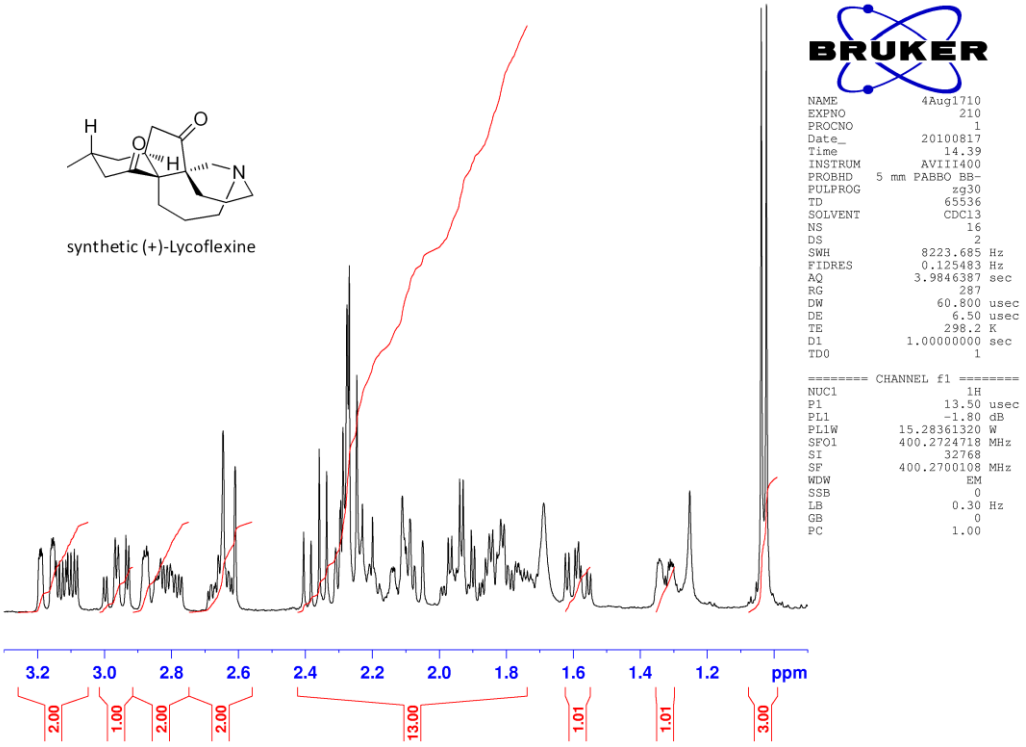
(+)-Lycoflexine (1) (comparison of synthetic (+)-lycoflexine with an authentic sample)

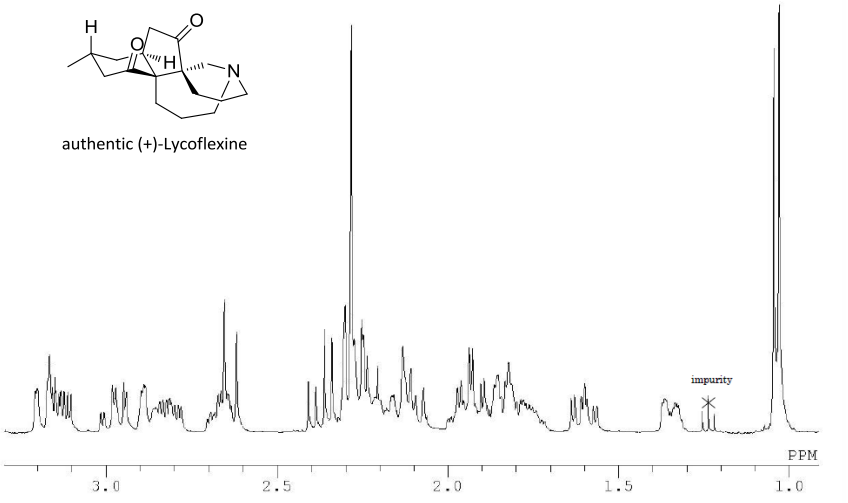




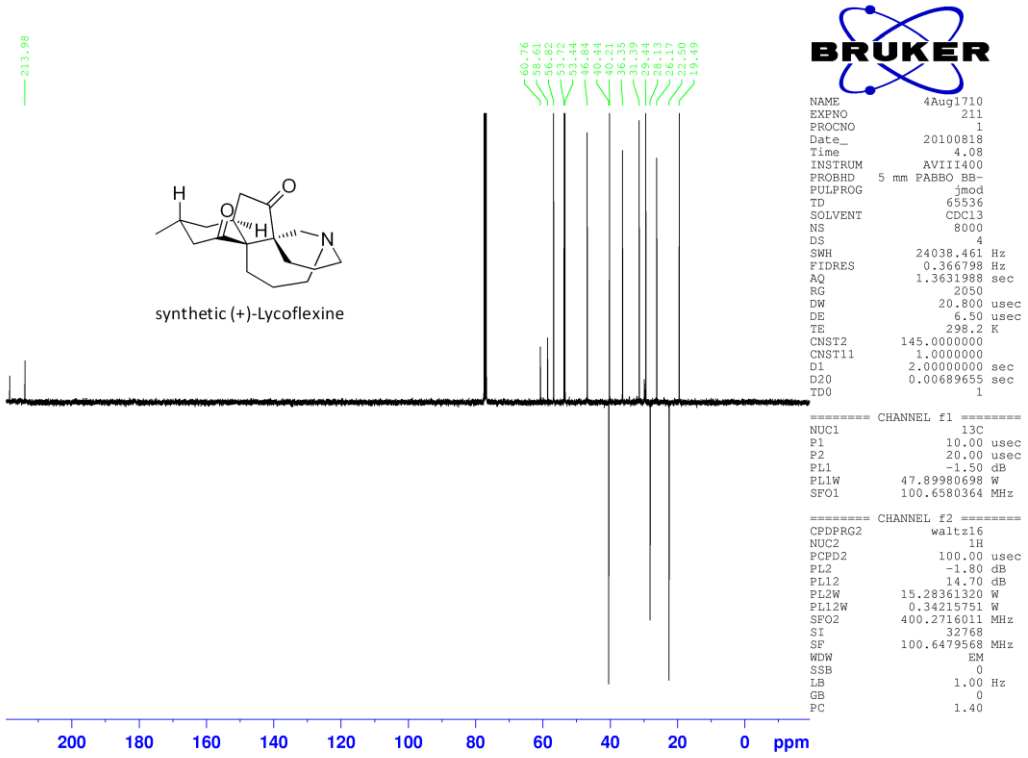
(+)-Lycoflexine (1) (comparison of synthetic (+)-lycoflexine with an authentic sample)

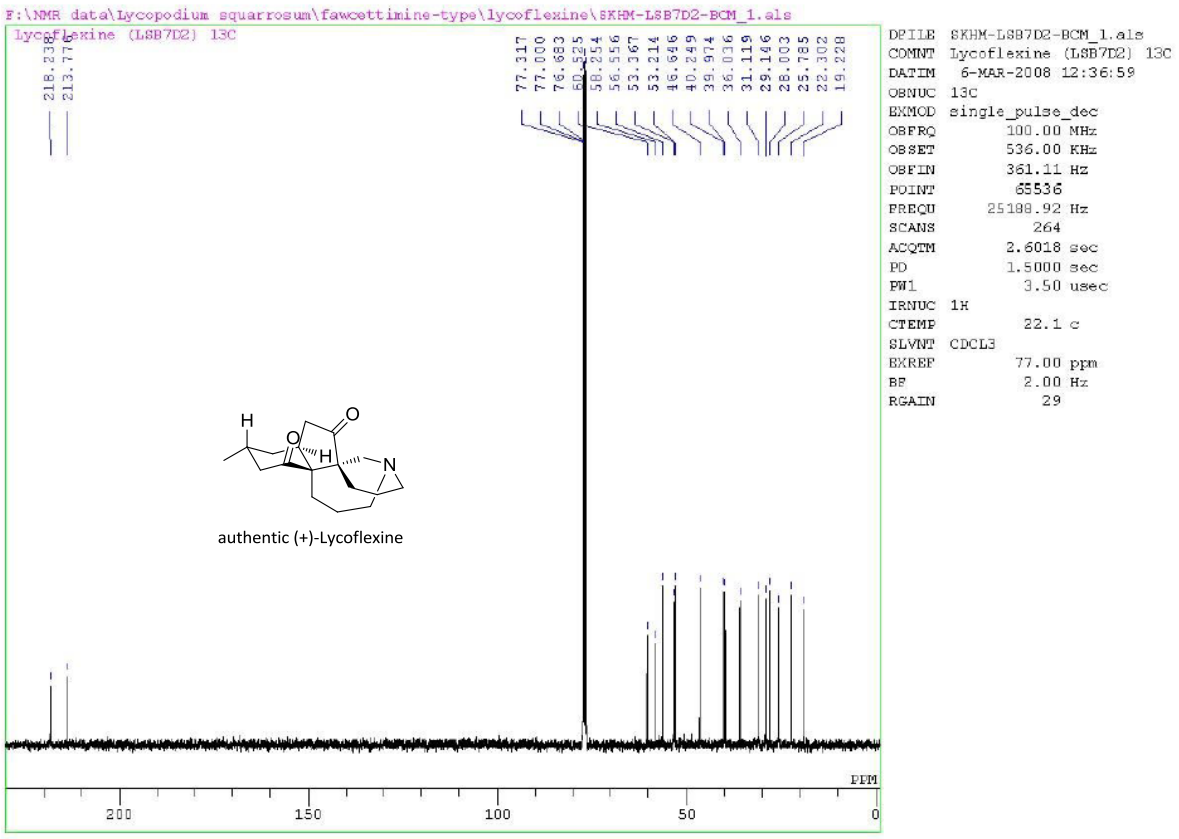
range: 3.3-0.9 ppm





(+)-Lycoflexine (1) (comparison of synthetic (+)-lycoflexine with an authentic sample)

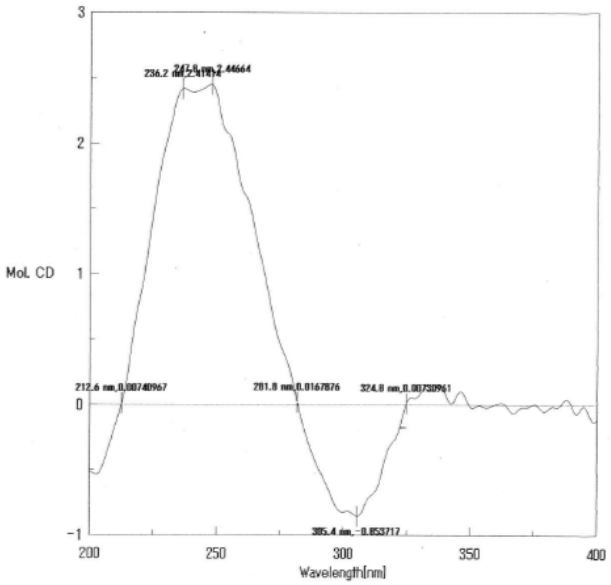




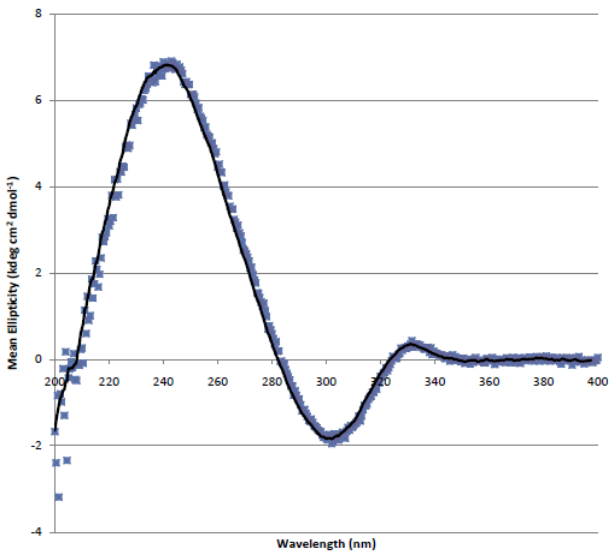
3. CD Spectra

(+)-Lycoflexine (1) (comparison of synthetic (+)-lycoflexine with an authentic sample)

authentic sample measured by Takayama



synthetic (+)-Lycoflexine



6 Abbreviations

Ac	acetyl
aq	aqueous
BBN	borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butoxycarbonyl
n-Bu	*n*-butyl
tert-Bu (*t*Bu)	*tert*-butyl
cat.	catalyst (or catalytic)
CoASH	coenzyme A
*m*CPBA	*meta*-chloroperoxybenzoic acid
DBU	diazabicyclo[5.4.0]undec-7-en
DCC	*N*,*N'*-dicyclohexylcarbodiimide
DCM	dichloromethane
DIBAH	diisobutylaluminium hydride
DMAPP	γ,γ-dimethylallylpyrophosphate
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
Et	ethyl
GABA	γ-aminobutyric acid
HDDA	hydroxy-directed Diels-Alder
IMDA	intramolecular Diels-Alder
IPP	isopentenylpyrophosphate
Me	methyl
MW	microwave
NMO	*N*-methylmorpholine *N*-oxide
Np	naphthyl
Nu	nucleophile
OP	phosphate
OPP	pyrophosphate
[Ox]	oxidation
PDC	pyridinium dichromate
Ph	phenyl
PPTS	pyridinium *p*-toluenesulfonate

*i*Pr	isopropenyl
py	pyridine
[Red]	reduction
SAR	structure-activity relationship
SI	supporting information
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	tosyl

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