TECHNISCHE UNIVERSITÄT WIEN
Vienna University of Technology

Dissertation

SYNTHESIS AND PHARMACOLOGICAL CHARACTERISATION OF NOVEL $GABA_A$-RECEPTOR MODULATORS

ausgeführt zum Zwecke der Erlangung des akademischen Grades eines Doktors der technischen Wissenschaften unter der Leitung von

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“It ain’t what you don’t know that gets you in trouble. It’s what you know for sure that just ain’t so.”

Mark Twain

“Someone who doesn’t take life with humor, hasn’t recognized, that it’s a joke!”

Mr. M.

“In chess, it’s called Zugzwang when the only viable move, is not to move... That’s why it’s so hard to choose, as long as you don’t choose, everything remains possible.”

Mr. N.

Acknoledgements

First and most importantly, I want to thank my parents Alois and Eveline for supporting me and my decisions my whole, entire life. Without their financial –despite being not monetary rich people- and especially moral support, conducting this thesis would have been impossible for me. In addition, I want to thank my sister Isabella and her husband Michael for all the good times we spend together, while reminding me of the really important things in life. Of course i want to thank my little nephew Kristian for showing me how interesting new experiences and impressions in life can be- discovering it with the enthusiasm and childlike curiosity of ... a scientist!

Next i want to thank my two supervisors Prof. Mihovilovic and Prof. Hering for giving me the opportunity to conduct my PhD-thesis at the interface of chemistry and pharmacology- without these two honourable men, my thesis wouldn't have been possible this way. Additionally I want to thank Michael Schnürch for his co-supervision and for the open-minded discussions, scientifically and personally. In the same breath I want to thank Florian Rudroff for his co-supervision and a little teaching in molecular biology. Of highest gratitude I want to thank Valentin for helping me with any synthetic questions, for his advice regarding my scholarship proposal and for each conversation we had in his office- thank you Valentin! I also want to thank Fru for his job offer and Prof. Adam of BOKU for the highly valuable and interesting project I am able to work while finishing my thesis. Furthermore I want to thank my dear friend Hannes for his postdoctoral offer and the chance of working with one of the most intelligent persons I have ever met. Thanks Hannes, you helped me in grim times and I will never forget you that! Special thanks to Flo Untersteiner for all the advice, the big discussions and all the fun we had the last years.

Finally I want to thank all my friends and colleagues – present and past- for walking the way of life with me-it has been a lot of fun with you all. Thank you my colleagues for the nice working atmosphere and the great discussions, thank you my dear friends for never letting me down. I am glad and honoured, having met such great people: you make me the richest man in the world, priceless!

P.S.: Navid: Germany will win the UEFA Euro 2016, you know what that means...

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Abstract

The main goal of this Thesis was the investigation of $GABA_A$-receptor modulators, based on the natural product valerenic acid. Therefore, variation of three different structural features should – through chemical modification and subsequent pharmacological investigation- determine the influence of these modifications on efficacy and selectivity. Each modification made, represents a chapter within this thesis.

The first chapter contains the derivatization of the carboxylic acid function. It was crucial to study the pharmacological effects exhibited by the chemical properties of the only polar (heteroatomic) group. Therefore, this functionality was transformed into various esters and amides, to investigate the role of hydrogen acceptor or hydrogendonor interactions. Through 17 synthesized acid-derivatives (including the carboxylic acid bioisostere tetrazole) it could be proven, that a hydrogen donor interaction is crucial for the observed pharmacological effect.

Furthermore the role of both exocyclic methyl substituents, attached on the indanyl core, was investigated in terms of efficacy and selectivity. This was accomplished through appropriate substitution of each methyl group via alkyl- respectively alkenyl residues of different size. As a result, methyl substitution in 7-position seems to be crucial for both efficacy and selectivity, as each modification led to severe loss of both pharmacological parameters. Furthermore, it could be demonstrated, that at maximum an ethyl substituent is tolerated for the vinylogous substituent in 3-position, as each larger modification significantly lowered efficacy and selectivity at the $GABA_A$-receptor.

Finally, synthetic limitaions of the published valerenic acid total synthesis in terms of modularity could be illustrated. Therefore, a slightly different synthetic approach was developed to enable structural variations – especially in 7-position- yet not accessible through published syntheses. As a result, a more economical and versatile alternative synthesis for valerenic acid derivatives was developed within this thesis.

Kurzfassung

Ziel dieser Arbeit war die systematische Untersuchung von $GABA_A$-Rezeptor Modulatoren, welche strukturell auf dem Naturstoff Valerensäure basieren. Hierzu wurden drei verschiedene strukturelle Eigenschaften – durch chemische Modifikation und anschließender pharmakologischer Untersuchung- variiert, um deren Einfluss auf Effektivität und Selektivität am $GABA_A$-Rezeptor zu determinieren. Folglich stellt jede Modifikation ein Kapitel dieser Arbeit dar.

Das erste Kapitel befasst sich mit der Derivatisierung der Carboxylat-Funktion. Hier galt es herauszufinden, durch welche chemischen Eigenschaften die einzig polare (heteroatomare) Gruppe ihre Wirkung am Rezeptor entfaltet. Diesbezüglich wurde diese Funktionalität durch Derivatisierung in verschiedene Ester und Amide vor allem auf die Notwendigkeit von Wasserstoffbrückenakzeptor- beziehungsweise Wasserstoffbrückendonor-Wechselwirkungen untersucht. Aus den 17 verschiedenen synthetisierten Säurederivaten (inklusive dem Bioisoster Tetrazol) konnte bewiesen werden, dass eine Wasserstoffbrückendonor-Eigenschaft für eine pharmakologisch relevante Wirkung unabdingbar ist.

Weiters wurden noch Untersuchungen - und damit chemische Modifikationen - an beiden exocyclischen Methylgruppen der Indanylkernstruktur durchgeführt. Auch hier galt als Zielsetzung die Notwendigkeit beider Methylsubstituenten für $GABA_A$- Subtypenselektivität und Effektivität herauszufinden. Dies konnte durch Substitution der entsprechenden Methylgruppen durch unterschiedlich große Alkyl-respektive Alkenylreste demonstriert werden. Als Ergebnis dieser Untersuchung sei hier vor allem die entscheidende Rolle des axialen Methylsubstituenten in 7-Position hervorzuheben, da jegliche Modifikation der Methylgruppe in einem drastischen Verlust an Effektivität und Subtypenselektivität resultiert. Des Weiteren konnte gezeigt werden, dass für den vinylogen Substituent in 3-Position nur eine limitierte räumliche Ausdehnung (maximal Ethyl) toleriert wird.

Schließlich wurden auch synthetische Limitierungen der verwendeten, publizierten Valerensäure-Totalsynthese bezüglich ihrer Modulation in 7-Position aufgezeigt. Infolgedessen konnte dieser Synthesezugang leicht abgewandelt werden und stellt somit einen Zugang für bisher weder bekannte, noch auf diesem Weg machbare, Valerensäuremodifikationen dar. Kurzum stellt der in dieser Arbeit entwickelte Syntheseweg sowohl eine kostengünstigere als auch bei weitem modularere Alternative dar.

Abbreviations

2,6-DtBP	2,6-ditert-butylpyridine
4 Å MS	4 angstrom molecular sieves
AcCl	acetic acid chloride
AcOH	acetic acid
AllylBO_2pin	allylboronicaid pinacol ester
APCI	Atmospheric pressure chemical ionization
C-Phos	2-(2-dicyclohexylphosphanylphenyl)-N1,N1,N3,N3-tetramethyl-benzene-1,3-diamine
CyPrZnBr	cyclopropylzinc bromide
DBU	1,8-diazabicycloundec-7-ene
DCM	dichloromethane
DIBALH	diisobutylaluminium hydride
DIPEA	N,N-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	N,N-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DMT	dimercaptotriazine
EDCI	1-ethyl-3-(3-diaminopropyl)carbodiimide
ESI	Electrospary inization
Et_2O	diethylether
EtOAc	ethyl acetate
IBX	2-iodoxybenzoic acid
i-PrOH	iso-propanol
$[Ir(cod)(PCy_3)(py)]PF_6$	Crabtree's Catalyst
$LiOH.H_2O$	litium hydroxide(monohydrate)
LP	light petrol
MeOH	methanol
MTBE	methyl tert-butylether
NEt_3	triethylamine
NHS	N-hydroxy succinimide
$Ni(dppp)Cl_2$	dichloro[1,3-bis(diphenylphosphino)propane]nickel
NMO	N-methylmorpholine N-oxide
NMR	Nuclear Magnetic Resonance
nPrZnBr	n-propylzinc bromide
$P(OPh)_3$	triphenylphosphite
$Pd(Oac)_2$	palladium(II) acetate
$Pd(PPh_3)_2Cl_2$	bis(triphenylphosphine)palladium(II) chloride
$PhB(OH)_2$	phenylboronic acid
Rochelle's salt	potassium sodium tartrate
SIBX	stabilized 2-iodoxybenzoic acid
TBAF	tetrabutylammonium fluoride

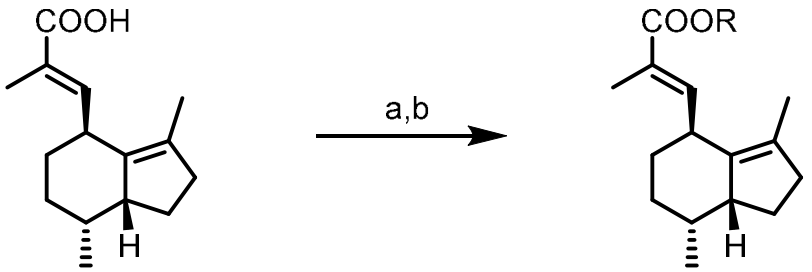
TBDMSCl	tert-butyldimethylsilyl chloride
t-BuLi	tert-butyl lithium
Tf_2O	triflic anhydride
TFA	trifluoro acetic acid
THF	tetrahydrofurane
TLC	thin-layer chromatography
TMSacetylene	trimethylsilylacetylene
TPAP	tetrapropylammonium perruthenate
X-Phos	2-dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl
$Zn(Et)_2$	diethylzinc
$Zn(iPr)_2$	diisopropylzinc
$Zn(Me)_2$	dimethyl zinc

A Synthetic schemes

All compounds prepared or used as starting materials in this thesis are numbered in bold Arabic numerals. Compounds unknown to the literature are additionally underlined. Compounds of prior published syntheses[1,2] are numbered with a bold letter indicating the origin (A= Altmann, M=Mulzer) followed by the ascending numbers. Compounds or intermediates referred to synthetic discussions are numbered in roman letters.

A I Modification of the carboxyl functionality

A I.1 Synthesis of valerenic acid esters

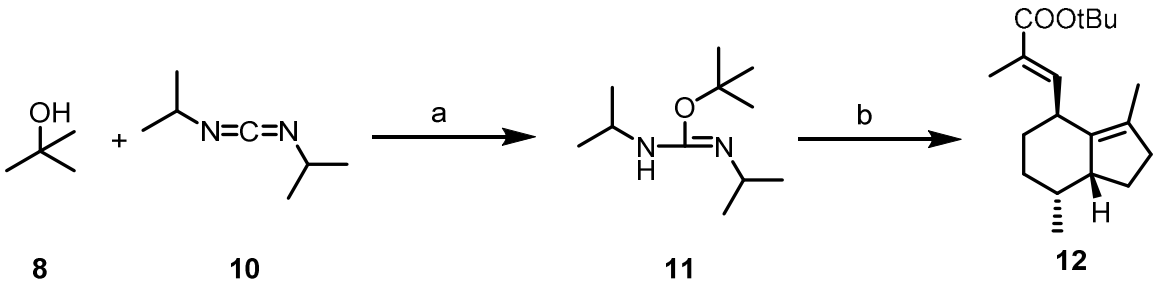


1 **2-12**

Reagents and Conditions: a) EDCI.HCl, DMAP, R-OH, DCM, r.t.; b) PivCl, DBU, DCM, r.t.

Coupled Esters with yield

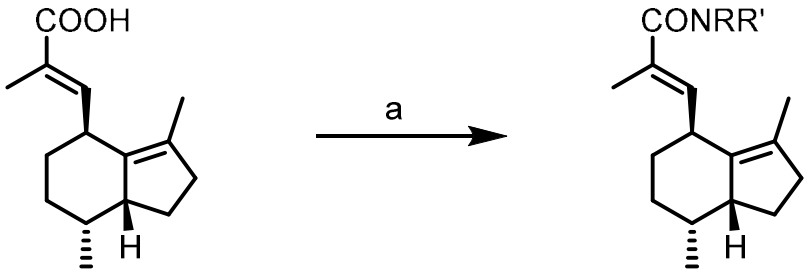
Product No.	R=	Yield [%]
2	**Methyl**	**95**
3	**Ethyl**	**95**
4	***n*-Propyl**	**99**
5	**Benzyl**	**94**
6	**Allyl**	**97**
7	**Pom**	**85**
12	***t*-Butyl**	**67**



8 10 11 12

Reagents and conditions: a) Cu(I)Cl, neat, r.t.; b) Valerenic acid, DCM, r.t., 67%;

A I.2 Synthesis of valerenic acid amides



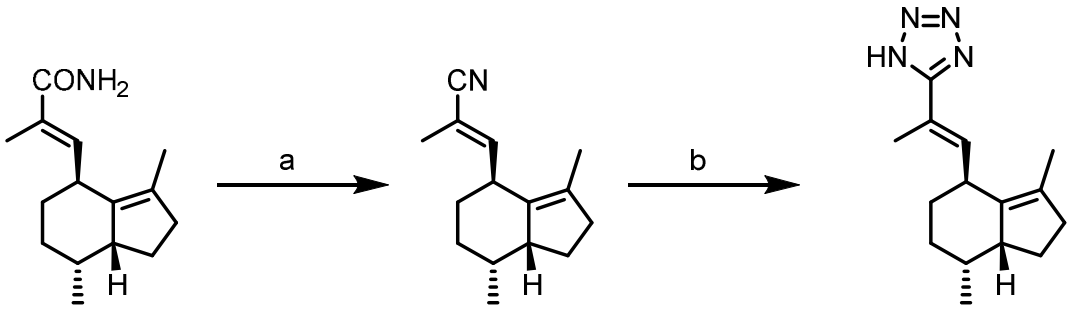
1 13-20

Reagents and conditions: a) NHS, EDCI.HCl, NRR', DCM, r.t.;

Coupled amides with yield

Product No.	R=	R'=	Yield [%]
13	H	H	99
14	H	Methyl	71
15	Methyl	Methyl	79
16	H	Ethyl	76
17	Ethyl	Ethyl	89
18	Methyl	Ethyl	99
19	H	Allyl	76
20	H	Benzyl	97

A I.3 Synthesis of valerenic acid tetrazole

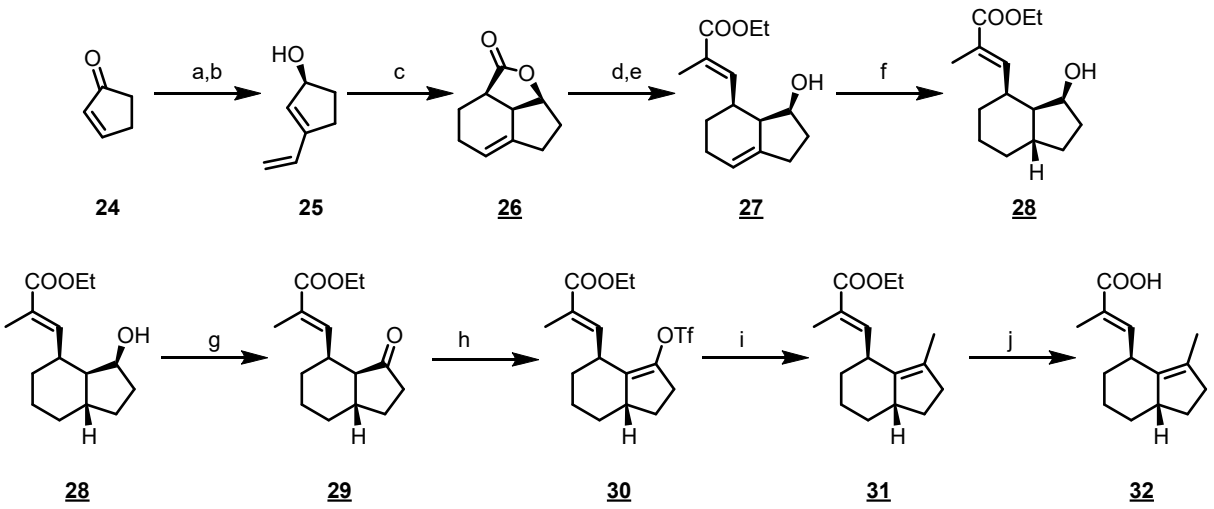


13 22 23

Reagents and conditions: a) Oxallyl chloride, DMF, Pyridine, MeCN, 0°C, 98%; b) NaN_3, $(Bu)_3SnCl$, toluene, 100°C 84%

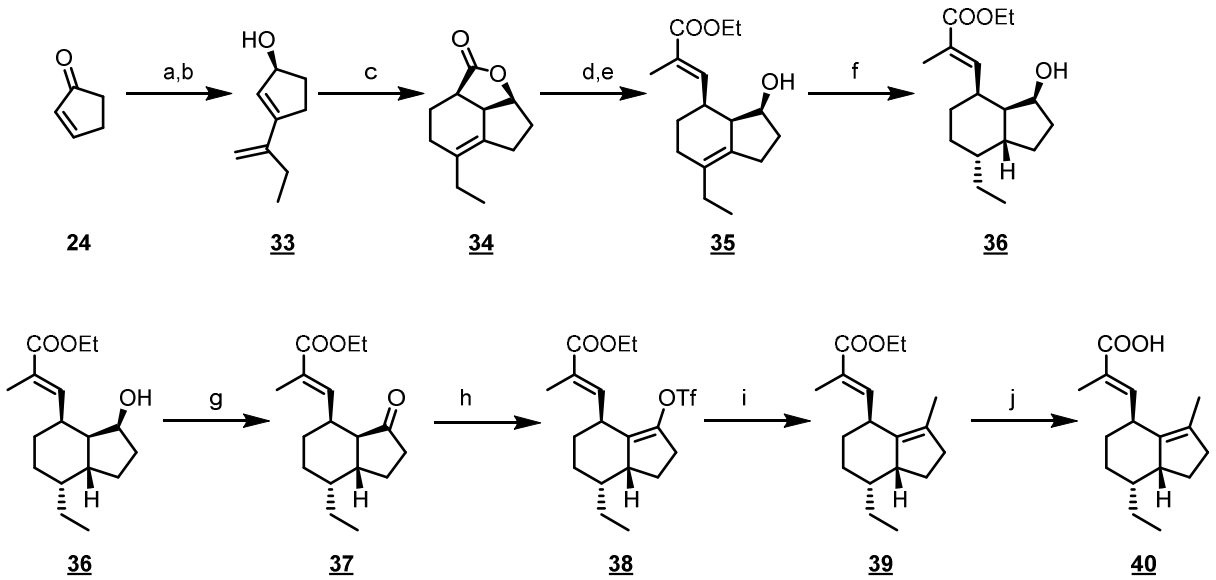
A II Modification of the axial methyl group at C7

A II.1 Synthesis of 7-Normethylvalerenic acid



Reagents and conditions: a) Vinylmagnesiumbromide, $LaCl_3.2LiCl$, TFA, THF, 0°C, 74%; b) LipasePPL, Vinylacetate, MTBE, r.t., 21% over 2 steps; c) $MgBr_2.Et_2O$, DIPEA, methacrylate, DCM, r.t., 79%; d) DIBALH, DCM, -78°C, crude; e) (1-ethoxycarbonylethyliden)-triphenylphosphorane, toluene, 100°C, 82% over 2 steps; f) cat. $Ir(cod)(py)PCy_3PF_6$, H_2, DCM, r.t., 97%; g) SIBX, DMSO, r.t., 94%; h) Tf_2O, 2,6-DTBP, DCM, r.t, crude; i) cat. $Pd(OAc)_2$, C-Phos, dimethylzinc, THF, 0°C- r.t., 40%; j) LiOH, $iPrOH:H_2O$=2:1, 40°C, quant.

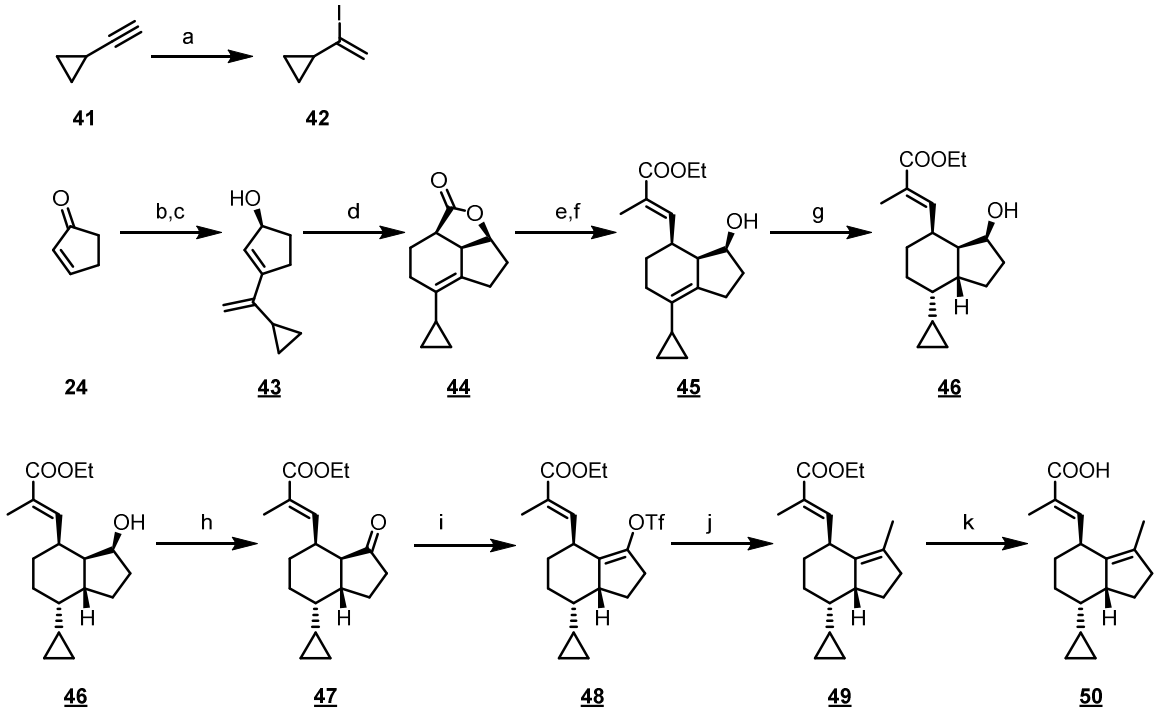
A II.2 Synthesis of 7-Ethylvalerenic acid



Reagents and conditions: a) 2-bromo-1-butene, t-BuLi, TFA, THF, -78°C, crude; b) LipasePS, Vinylacetate, MTBE, r.t., 47% over 2 steps; c) $MgBr_2.Et_2O$, DIPEA, methacrylate, DCM, r.t., 83%; d) DIBALH, DCM, -78°C, crude; e) (1-ethoxycarbonylethyliden)-triphenylphosphorane, toluene, 100°C, 77% over 2 steps; f) cat. $Ir(cod)(py)PCy_3PF_6$, H_2, DCM, r.t., 53%; g) SIBX, DMSO, r.t., 80%; h) Tf_2O, 2,6-DTBP, DCM, r.t, crude; i) cat. $Pd(OAc)_2$, C-Phos, dimethylzinc, THF, 0°C- r.t., 48%; j) LiOH, iPrOH:H_2O=2:1, 40°C, quant.

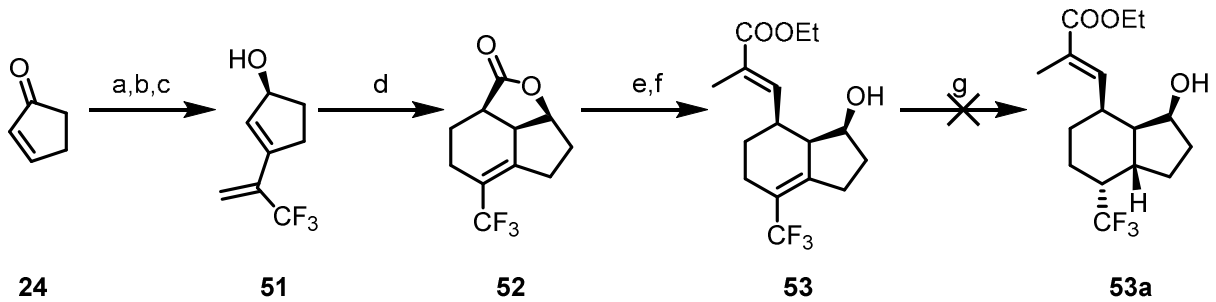
A II.3 Synthesis of 7-Cyclopropylvalerenic acid

A II.3.1 Synthesis of precursor 1-(Iodovinyl)cyclopropane



Reagents and conditions: a) cat. $Ni(dppp)Cl_2$, DIBALH reagent grade, I_2, 0°C to r.t. to -78°C, THF, 34% b) 1-(Iodovinyl)cyclopropane, $LaCl_3.2LiCl$, t-BuLi, TFA, THF,-78°C, 61%; c) LipasePS, vinylacetate, MTBE, r.t., 43%; d) $MgBr_2.Et_2O$, DIPEA, methacrylate, DCM, r.t., 75%; e) DIBALH, DCM, -78°C, crude; f) (1-ethoxycarbonylethyliden)-triphenylphosphorane, toluene, 100°C, 74% over 2 steps; g) cat. $Ir(cod)(py)PCy_3PF_6$, H_2, DCM, r.t., 49%; h) IBX, DMSO, r.t., 73%; i) Tf_2O, 2,6-DTBP, DCM, r.t, crude; j) cat. $Pd(OAc)_2$, C-Phos, dimethylzinc, THF, 0°C- r.t., 63% as a mixture of isomeres; k) LiOH, $iPrOH:H_2O$=2:1, 40°C, 97% as a mixture of isomeres

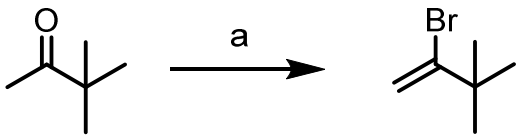
A II.4 Towards the synthesis of 7-Trifluoromethylvalerenic acid



Reagents and conditions: a) 2-bromo-3,3,3-trifluoropropene, t-BuLi, Et_2O, -110°C, crude; b) TFA, THF/H_2O, r.t., crude c) LipasePS, Vinylacetate, MTBE, r.t., 31% over 3 steps; d) $MgBr_2.Et_2O$, DIPEA, methacrylate, DCM, r.t., 77%; e) DIBALH, DCM, -78°C, crude; f) (1-ethoxycarbonylethyliden)-triphenylphosphorane, toluene, 100°C, 71% over 2 steps; g) cat. $Ir(cod)(py)PCy_3PF_6$, H_2, DCM, r.t.;

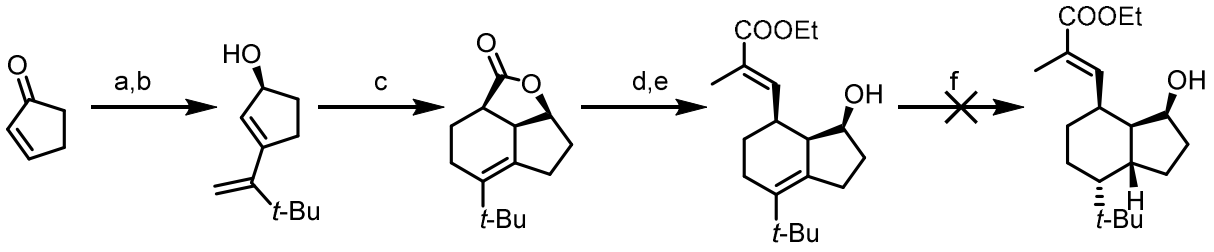
A II.5 Towards the synthesis of 7-tert-Butylvalerenic acid

A II.5.1 Synthesis of precursor 2-Bromo-3,3-dimethyl-but-1-ene



54 **55**

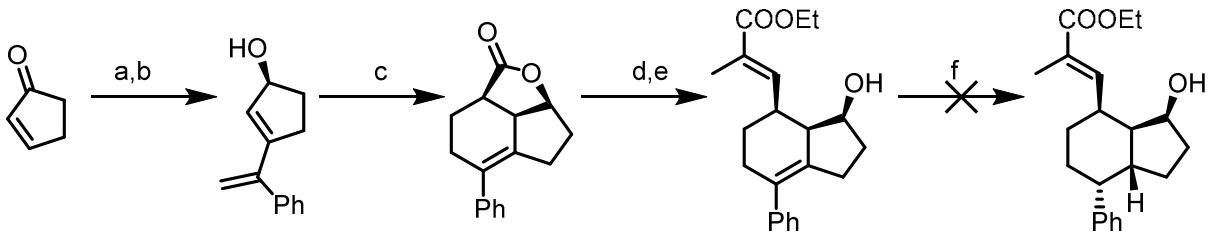
Reagents and conditions: a) Triphenylphosphite, Br_2, NEt_3, DCM, -50°C then reflux, 29%



24 **56** **57** **58** **58a**

Reagents and conditions: a) 2-bromo-3,3-dimethyl-but-1-ene, t-BuLi, TFA, THF, -78°C, 50%; b) LipasePS, vinylacetate, MTBE, r.t., 42%; c) $MgBr_2.Et_2O$, DIPEA, methacrylate, DCM, r.t., 76%; d) DIBALH, DCM, -78°C, crude; e) (1-ethoxycarbonylethyliden)-triphenylphosphorane, toluene, 100°C, 62% over 2 steps; f) cat. $Ir(cod)(py)PCy_3PF_6$, H_2, DCM, r.t.;

A II.6 Towards the synthesis of 7-Phenyl-Valerenic acid

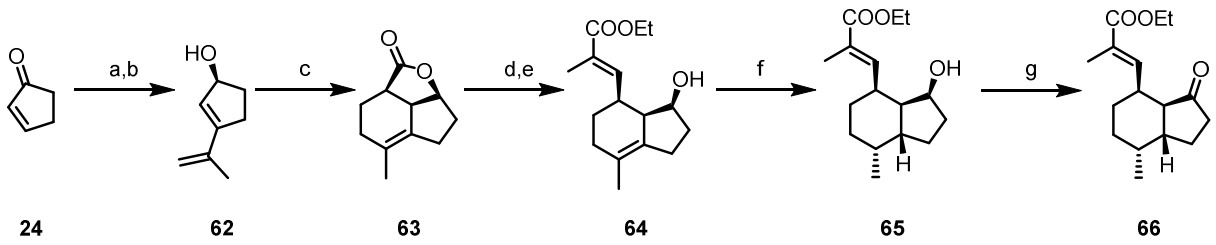


24 **59** **60** **61** **61a**

Reagents and conditions: a) α-bromostyrene, t-BuLi, TFA, THF, -78°C, 73%; b) LipasePS, Vinylacetate, MTBE, r.t., 45% ; c) $MgBr_2.Et_2O$, DIPEA, methacrylate, DCM, r.t., 88%; d) DIBALH, DCM, -78°C, crude; e) (1-ethoxycarbonylethyliden)-triphenylphosphorane, toluene, 100°C, 73% over 2 steps; f) cat. $Ir(cod)(py)PCy_3PF_6$, H_2, DCM, r.t.;

A III Modification of the vinylogous methyl group at C3

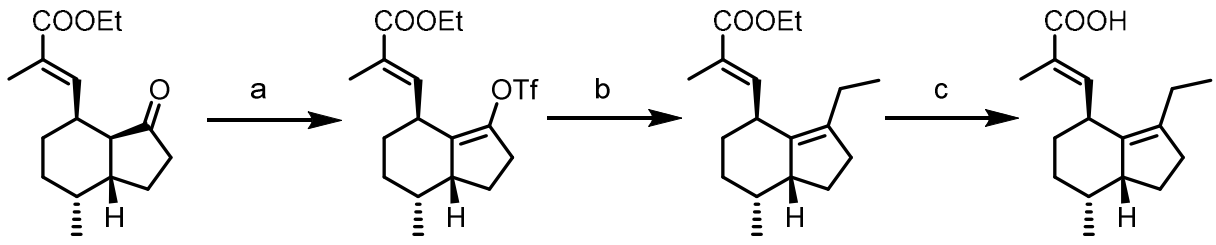
A III.1 Synthesis of common intermediate ketone 66



24 62 63 64 65 66

Reagents and conditions: a) 2-bromo-1-propene, t-BuLi, TFA, THF, -78°C, crude; b) LipasePS, vinylacetate, MTBE, r.t., 46% over 2 steps; c) $MgBr_2.Et_2O$, DIPEA, methacrylate, DCM, r.t., 86%; d) DIBAlH, DCM, -78°C, crude; e) (1-ethoxycarbonylethyliden)-triphenylphosphorane, toluene, 100°C, 84% over 2 steps; f) cat. $Ir(cod)(py)PCy_3PF_6$, H_2, DCM, r.t., 74%; g) IBX, DMSO, r.t., 85%

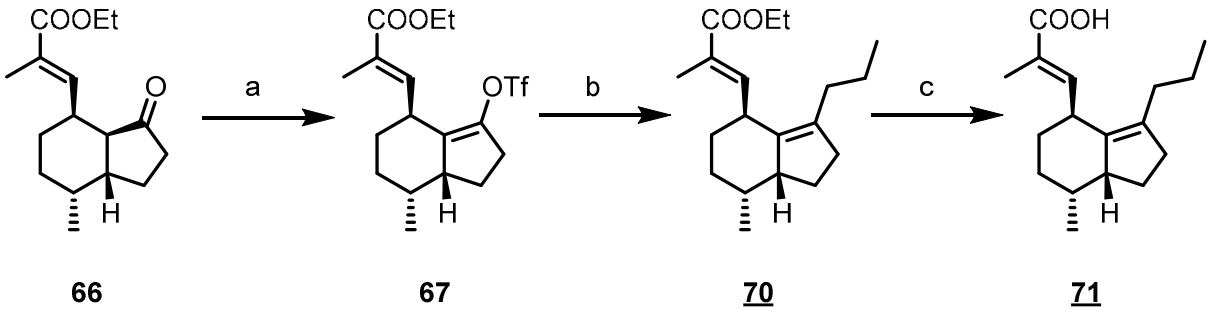
A III.2 Synthesis of 3-Ethylvalerenic acid



66 67 **68** **69**

Reagents and conditions: a) Tf_2O, 2,6-DTBP, DCM, r.t, crude; b) cat. $Pd(OAc)_2$, C-Phos, diethylzinc, THF, 0°C- r.t., 63%; c) LiOH, iPrOH:H_2O=2:1, 40°C, 96%

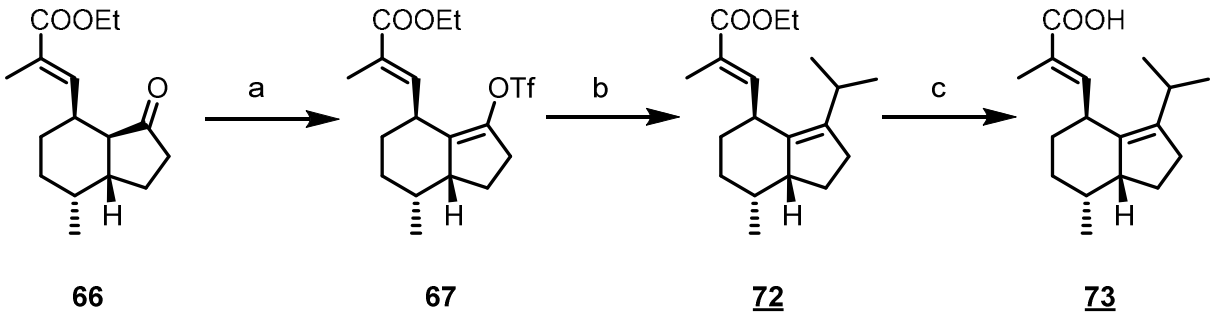
A III.3 Synthesis of 3-n-Propylvalerenic acid



66 **67** **<u>70</u>** **<u>71</u>**

Reagents and conditions: a) Tf_2O, 2,6-DTBP, DCM, r.t, crude; b) cat. $Pd(OAc)_2$, C-Phos, LiCl, *n*-propylzincbromide, THF, 0°C-r.t., 47%; c) LiOH, iPrOH:H_2O=2:1, 40°C, 96%

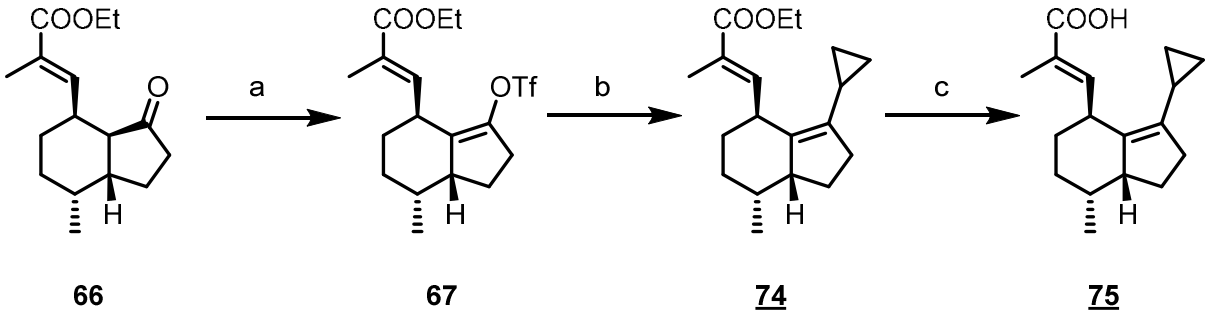
A III.4 Synthesis of 3-i-Propylvalerenic acid



66 **67** **<u>72</u>** **<u>73</u>**

Reagents and conditions: a) Tf_2O, 2,6-DTBP, DCM, r.t, crude; b) cat. $Pd(OAc)_2$, C-Phos, LiCl, *i*-propylzincbromide, THF, 0°C-r.t., 42%; c) LiOH, iPrOH:H_2O=2:1, 40°C, 97%

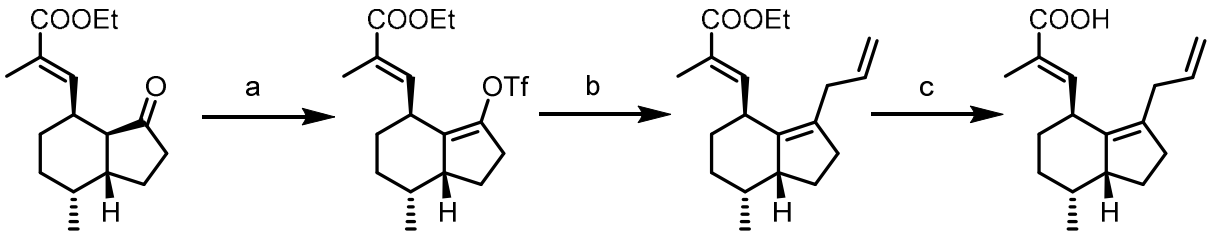
A III.5 Synthesis of 3-Cyclopropylvalerenic acid



66 **67** **<u>74</u>** **<u>75</u>**

Reagents and conditions: a) Tf_2O, 2,6-DTBP, DCM, r.t, crude; b) cat. $Pd(OAc)_2$, C-Phos, LiCl, cyclopropylzincbromide, THF, 0°C- r.t., 42%; c) LiOH, iPrOH:H_2O=2:1, 40°C, 99%

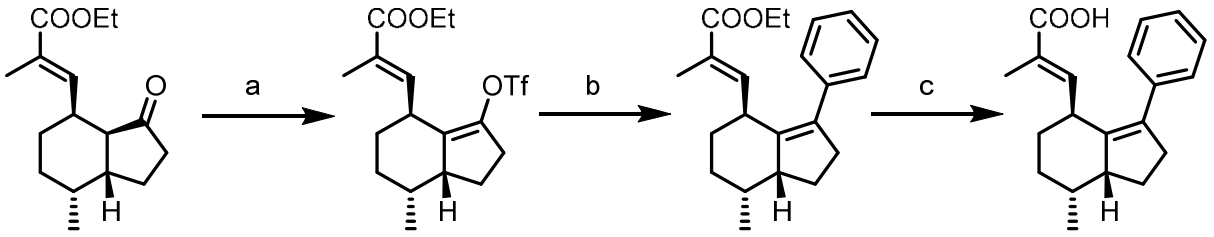
A III.6 Synthesis of 3-Allylvalerenic acid



66 **67** **76** **77**

Reagents and conditions: a) Tf_2O, 2,6-DTBP, DCM, r.t, crude; b) cat. $Pd(OAc)_2$, X-Phos, K_3PO_4, allylpinacolboronic ester, THF, 80°C- r.t., 57%; c) LiOH, iPrOH:H_2O=2:1, 40°C, 87%

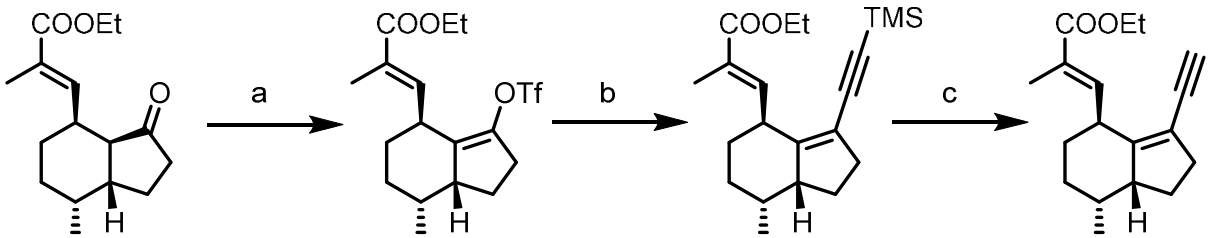
A III.7 Synthesis of 3-Phenylvalerenic acid



66 **67** **78** **79**

Reagents and conditions: a) Tf_2O, 2,6-DTBP, DCM, r.t, crude; b) cat. $Pd(OAc)_2$, X-Phos, K_3PO_4, phenylboronic acid, THF, 80°C- r.t., 50%; c) LiOH, i-PrOH:H_2O=2:1, 40°C, 98%

A III.8 Towards the synthesis of 3-Alkynylvalerenic acid

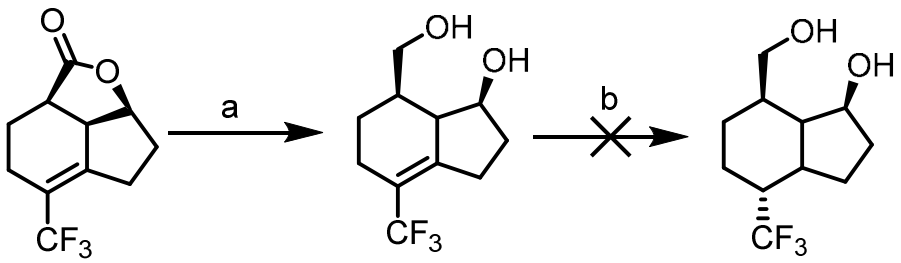


66 **67** **80** **81**

Reagents and conditions: a) Tf_2O, 2,6-DTBP, DCM, r.t, crude; b) cat. $Pd(PPh_3)_2Cl_2$,cat. CuI, TMS-acetylene,NEt_3, DMF, r.t. crude; c) TBAF, THF, 0°C,

A IV Alternative approaches to C7-derivatives

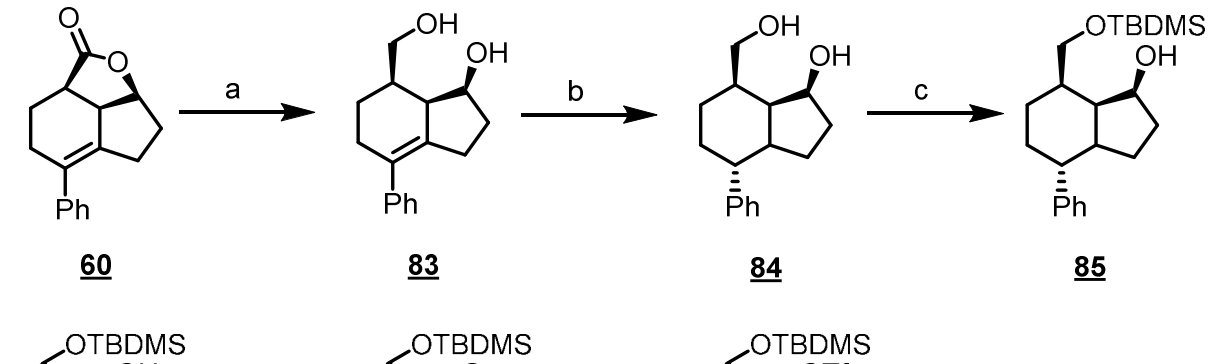
A IV.1 Synthesis-attempt of 7-trifluoromethyl-valerenic acid



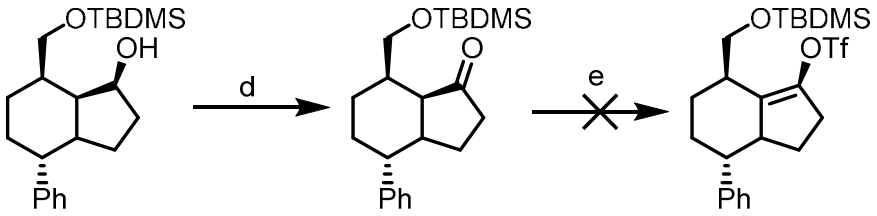
52 **82** **82a**

Reagents and conditions: a) $LiALH_4$, Et_2O, 0°C to r.t.; 92% b) cat. $Ir(cod)(py)PCy_3PF_6$, H_2, DCM, r.t.,

A IV.2 Synthesis-attempt of 7-phenyl-valerenic acid



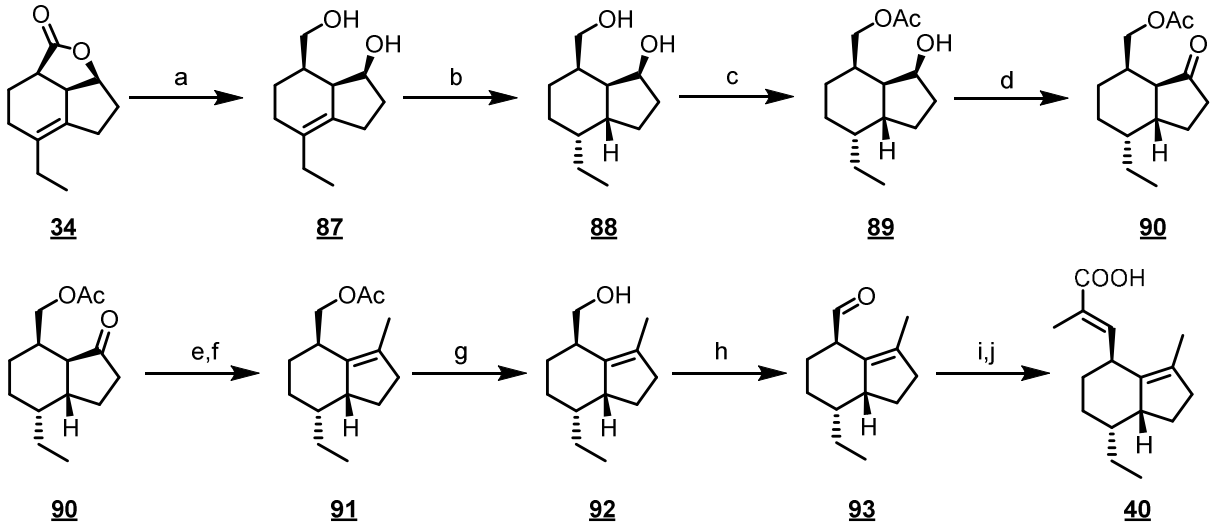
60 **83** **84** **85**



85 **86** **86a**

Reagents and conditions: a) $LiAlH_4$, Et_2O, 0°C to r.t., 96%; b) cat. $Ir(cod)(py)PCy_3PF_6$, H_2, DCM, r.t., 93%, c) TBDMSCl, imidazole, DMAP, DMF, r.t, 82% d) DMP, DCM, r.t., 96%; e) DTBP, Tf_2O, DCM, 0°C to r.t.

A IV.3 Alternative synthesis of 7-Ethyl-valerenic acid



34 **87** **88** **89** **90**

90 **91** **92** **93** **40**

Reagents and conditions: a) $LiALH_4$, Et_2O, 0°C to r.t., 99%; b) cat. $Ir(cod)(py)PCy_3PF_6$, H_2, DCM, r.t., 93%; c) 2,4,6-Collidine, acetylchloride, DCM, -78°C to r.t., 72%; d) DMP, DCM, r.t, 75%, e) DTBP, Tf_2O, DCM, r.t, crude; f) $Pd(OAc)_2$, C-Phos, dimethylzinc, THF, 0°C to r.t., 62%; g) K_2CO_3, MeOH, r.t.; 98%; h) TPAP, NMO, 4ÅMS, DCM, r.t, crude; i) (1-ethoxycarbonylethyliden)-triphenylphosphorane, toluene, 140°C, µW, 51%; j) LiOH, iPrOH:H_2O= 2:1, 40°C, 93%

B Introduction

B I Ion Channels

Ion channels are transmembrane proteins which function as an activatable transport gate for inorganic ions through the cell membrane by passive transport[3]. They determine the permeability of the plasmamembrane for specific ions like Na^+, K^+, Ca^{2+} and Cl^- . Two types of ion channels exist: voltage gated ion channels and ligand gated ion channels.

Besides ion channels, ion pumps are also transmembrane proteins regulating the influx of ions into the cell-plasma. The main difference between those two types of ion transporters is their transport mode: active or possive. Ion channels are regarded as passive transporters, whereas ion pumps actively transport ions like Na^+ or K^+ through the membrane while consuming energy in form of ATP. In the next few subchapters, the three different types of ion channels are briefly discussed, before a more detailed introduction into the function of the $GABA_A$-receptor is presented (see B II).

B I.1 Voltage gated ion channels

In nearly all eukaryotic cells transmembrane proteins are found that are activated by changes in the membrane potential- voltage gated ion channels. Such channels can be found in neuronal cells and muscle tissue and are ion-specific transporters for Na^+-, K^+- and Ca^{2+}-Ions. The sodium channels are responsible for the initiation and propagation of an action potential in neuronal cells[4], whereas voltage gated potassium channels regulate the cell membrane potential and excitability in neurons through depolarisation of a nervous cell[5]. In contrast the calcium influx, mediated by the voltage gated calcium channel, regulates intracellular processes like contraction, secretion, neurotransmission and gene-expression[6].

B I.2 Ligand-gated ion channels

In opposition to the voltage gated ion channels, which open/close upon an electric stimulus, ligand gated ion channels open or close through binding of a chemical ligand. These ligand gated ion channels are classified into three superfamilies, based on their protein sequence[7]:

1. Nicotinic acetylcholine receptors (nAChR)
2. Ionotropic glutamate receptors (GluR)
3. ATP-gated purino receptors (P2X)

These three superfamililies were classified by having distinct similarities in their genome and consequentially in their quaternary protein structure. Furthermore these receptor superfamilies are subdiversified into receptor families, which basically react through the

same mechanism, but having different ligands (neurotransmitters) for activation. The relevant receptor, investigated within this thesis, is the $GABA_A$-receptor, belonging to the nicotinic acetylcholine receptors and will be discussed in detail within the next chapter (B II).

B II The $GABA_A$ Receptor

B II.1 Structure and Location

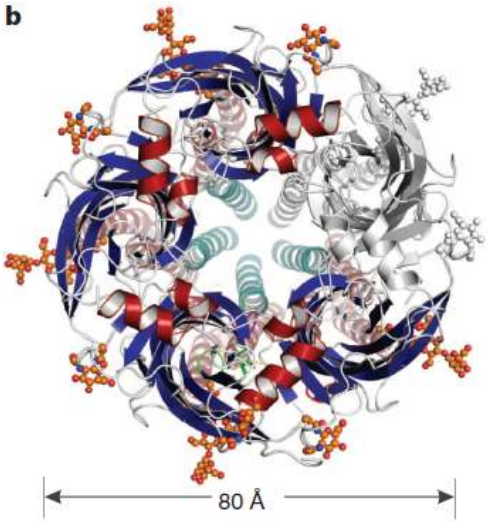


Figure 1: Crystal structure oft he $GABA_A$-receptor[8]

$GABA_A$ receptors are ligand-gated ion channels in the central nervous system (CNS) and belong to the Cys loop superfamily along with the nicotinic acetylcholine-, glycine-, serotonine- and glutamate receptors, sharing similar structural features[9]. As they share significant sequence similarity, this similarity was believed to be conserved in their quaternary structure as well, containing an extracellular Cys-Cys loop as part of the N-terminal region. In 2014 Miller et Aricescu [8] were the first ones who discovered the three-dimensional structure of the $GABA_A$-receptor at a 3 Å resolution. With this discovery, the proposed topological similarity to the other Cys-loop receptors could be proven. As shown in Figure 1, the pentamer has a toroidal profile where each extracellular domain consists of an amino-terminal α-helix. On each α-helix, ten β-strands are attached and curled into a sandwich-like structure. Combined with four additional helices, the heteropentameric structure is assembled.The only distinctions made within this family are the ligands which activate and the ions (cations or anions) which pass through a particular channel. In case of the $GABA_A$-receptors the endogenous ligand is GABA (γ –amino butyric acid) and the ion gated is chloride. GABA is the major inhibitorial neurotransmitter in the CNS followed by glycine, whereas glutamate -for example - evokes excitation and acetylcholine and serine are responsible for synaptic transmission[10].

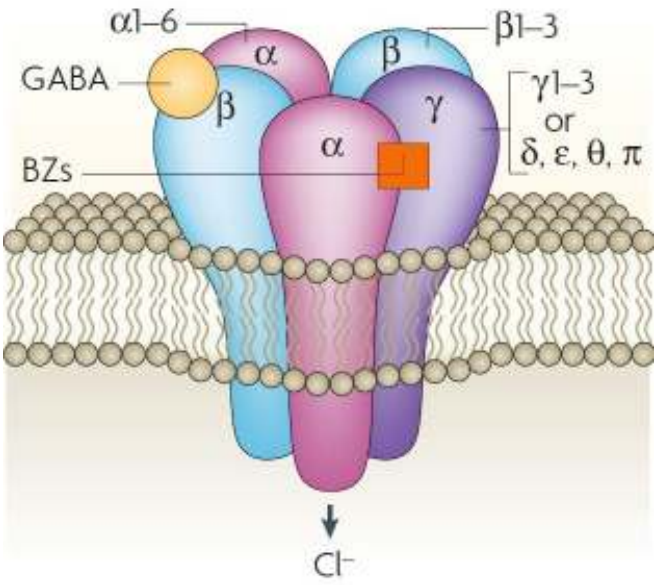


Figure 2: Schematic structure of the $GABA_A$-receptor[11]

The $GABA_A$ receptor is a transmembrane protein of neuronal synaptic cells (post and extrasynaptic). Structurally, this receptor is a heteropentamer consistent of 5 different subunits, composed out of 19 isoforms[12] (α_{1-6}, β_{1-3}, γ_{1-3},δ,ε,θ,π and ρ_{1-3}) embedding the Cl^- ion channel. Each subunit is approximately 450 amino acid residues long, and about half of the N-terminal subunit is located extra cellular containing the Cys loop, followed by four transmembrane α-helices[12]. Due to the high diversity of subunits, it has been estimated that several hundred subunit combinations and more than 150 000 different subunit arrangements[13] are possible. Although the actual number of physiologically and pharmacologically active $GABA_A$ receptors with respect to their subunit stochiometry is not elucidated and fully understood yet, the most abundant pentameric composition is an arrangement of 2α, 2β and 1γ subunits containing two GABA binding sites between the α/β interface and a benzodiazepine (BDZ) site between α and γ (Figure 2), reflected by a compositional distribution[14] of:

- 60% $\alpha_1\beta_2\gamma_2$
- 15-20% $\alpha_2\beta_3\gamma_2$
- 10-15% $\alpha_3\beta_n\gamma_2$
- ~5% $\alpha_4\beta_n\gamma$ or $\alpha_4\beta_n\delta$
- <5% $\alpha_5\beta_2\gamma_2$ or $\alpha_6\beta_{2/3}\gamma_2$

As the subunit composition of $GABA_A$ receptors differs, their allocation within the brain does as well (Figure 9). For this reason the subunit composition essentially determines the pharmacological effects, when a specific $GABA_A$ receptor is targeted by a drug/modulator (see chapter B II.5).

B II.2 The neuronal action potential

GABA is the main inhibitory neurotransmitter and its mode of action will be discussed in the following chapter (**Fehler! Verweisquelle konnte nicht gefunden werden.**). For better comprehension of inhibitory effects, this chapter will deal with excitory effects, respectively the setup of a neuronal action potential[15] (Figure 3).

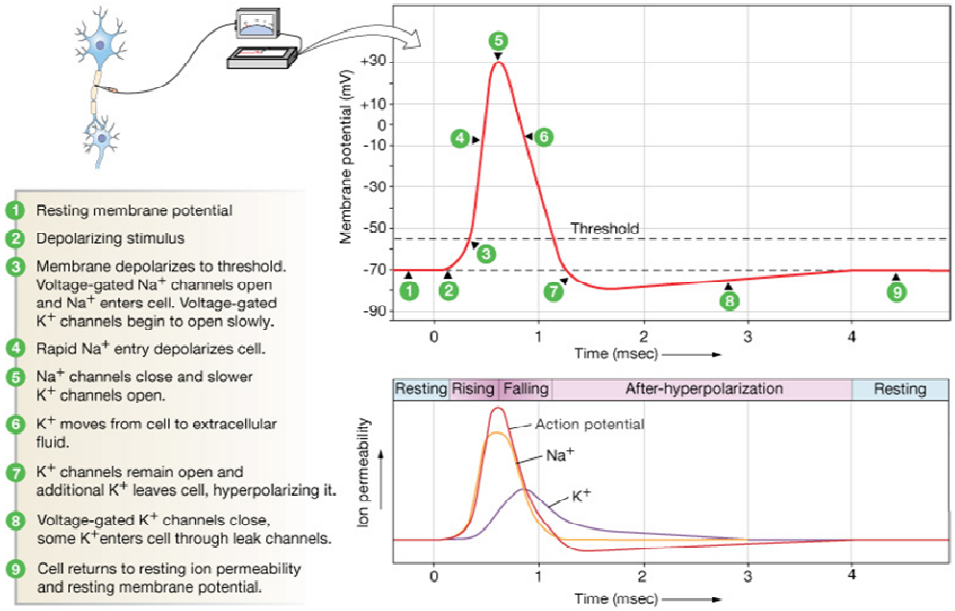


Figure 3 Buildup of an action potential[16]

In its rest state, a neuronal cell has a membranepotential of -70mV. When an endogenous stimulus, respectively an excitatory neurotransmitter (e.g. acetylcholine, glutamate…), causes the membrane sodium channels to open, Na^+-ions start influxing into the cell. This causes the membrane potential to rise from the resting state of -70mV to -55mV. At a threshold-voltage of -55mV, voltage gated sodium channels start to open, causing a rapid influx of more Na^+- the cell depolarizes. At a peak-potential of +30mV, the the sodium channels close and the potassium channels open (both voltage gated), leading to an efflux of K^+-ions. The leaving K^+-ions repolarize the membrane potential to -70mV. Still, at this voltage the potassium channels do not close, leading to an "overshoot" of -90mV. This "overshoot" is termed hyperpolarisation and prevents the neuron from receiving any other stimulus and additionally prevents any action potential from triggering backwards again, thus guiding the electric signal in just one direction. After the hyperpolarisation phase, the Na^+/K^+-pump resets the initial concentrations of sodium and potassium ions across the membrane and concomittantly the resting potential of -70mV. Now the nervous cell is ready to receive another excitory impulse.

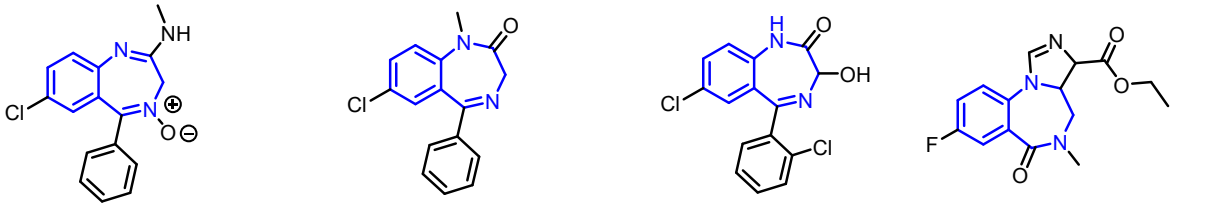
B II.3 Mode of action

As already mentioned briefly two types of neurotransmitters, excitatory and inhibitory, exist. Excitatory ion channels (e.g. nicotinic acetylcholine receptors) gate cations through the membrane and thereby increase the depolarisation level of a neuronal cell membrane being prerequisite for signal transmission (build up of the action potential of a neuronal cell!). On the contrary, inhibitory neurotransmitters like GABA block signal transmission through hyperpolarizing the nervous cell membrane caused by Cl^- ion influx. The sequence is as followed: Through Ca^{2+} induced exocytosis, a GABAergic synapse releases GABA into the postsynaptic cleft. Then GABA binds to its receptor at the α/β interface located in the membrane of the postsynaptic neuron, leading to a conformational change of the heteropentamer. This conformational change causes the central pore, respectively the ion channel itself, to open and permeates Cl^- through the membrane. As a result the membrane potential drops significantly below a certain threshold value (< -70mV = resting state). This state is called hyperpolarisation and no excitation (depolarisation) can appear in this state. The built up of an action potential cannot happen, before the resting state is re-established and depolarisation through Na^+ influx starts. As a consequence the neuronal excitability is reduced through $GABA_A$ receptor opening. This feature of the $GABA_A$ receptor makes it an important target for various diseases associated with neuronal excitability such as insomnia, anxiety, epilepsy and schizophrenia[17a].

B II.4 $GABA_A$ Receptor Modulators

Besides the natural endogenous agonist GABA, several other modulators have been identified[18]. Among these are several drugs like the very prominent benzodiazepines (BDZ), barbiturates, anesthetics, steroids, anticonvulsants, and some multivalent cations like zinc or lanthanum [13]. Although these species all modulate the same receptor, the actual type of modulation is different and will be briefly discussed within the following subsections.

B II.4.1 Benzodiazepines



Chlordiazepoxide (Librium®) Diazepam (Valium®) Lorazepam (Orfidal®) Flumazenil (BDZ-antagonist)

Figure 4 Examples of benzodiazepines with diazepinic core in blue and flumazenil a BDZ-antagonist

The most prominent marketed drugs modulating the $GABA_A$ receptor are the benzodiazepines. Since the invention of Librium© (chlordiazepoxide) in 1960 by Hoffmann-LaRoche, numerous structural variants have captured the market[19]. Structurally, benzodiazepines are defined through a benzene ring fused to a seven membered heterocyclic ring containing two nitrogen atoms (as the name already implies, Figure 4). They exhibit sedative, hypnotic, anxiolytic, muscle relaxant, and anticonvulsive effects through enhancing the effect of GABA[20]. Thus they represent drugs medicating anxiety and sleep disorder and have replaced the barbiturates (see B II.5); additionally, they are considered to possess high potential in the treatment of pain, depression, schizophrenia, stroke, and cognitive impairment. It was found, that the BDZs have a distinctly different binding site than GABA (at the α/β interface) at the α/γ interface, thus being positive allosteric modulators[21]. This binding pocket at the α/γ interface, which shows a high homology to the actual agonistic GABA binding site[22], has been termed "*benzodiazepine binding site*" and will be referred to as such in further discussions as well. BDZs derive their positive modulation through enhancing the channel opening frequency, hence increasing the net chloride ion flux. The BDZ binding site is found in most but not all $GABA_A$ receptors, thus limiting the selective modulation evoked by BDZs resulting in severe side effects like sedation and addiction (see section subunit selectivity/side effects). For treatment of sedative effects or benzodiazepine overdosage, antagonists such as flumazenil have been developed. Structurally similar to the benzodiazepines (Figure 4), the BDZ-antagonists selectively block the bezodiazepinic site, while not exhibiting any behavioural or neurological effecs associated to BDZ-treatment[23].

B II.4.2 Barbiturates

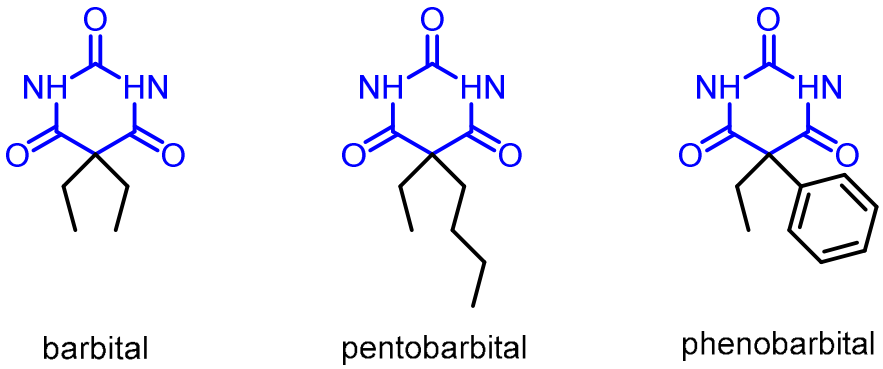


Figure 5 Examples of the first barbiturates

Barbiturates is a generic term for derivatives of barbituric acid, first synthesized by Adolph von Bayer 1864 through condensation of urea with diethylmalonate, before marketed as Veronal (barbital, see Figure 5) from 1903 until the mid 1950s. Due to their hypnotic, anxiolytic, anticonvulsive, and sedative effects they were pharmaceutically applied to treat first insomnia and later on epilepsy and anxiety.[24] Although they are positive allosteric modulators of the $GABA_A$ receptor, their mechanism of action differs from the previously discussed benzodiazepines (B II.4.1). While BDZs enhance channel open frequencies, barbiturates increase the mean duration of the open channel conformation (from 24 to 120ms) [25], rising the overall Cl^- influx this way. Besides the $GABA_A$ receptor other cerebral regions are affected by barbiturates as well, leading to a severe side effect profile of sedation, dependence, and death through respiratory depression upon over dosage. Although widely used in the first half of the 20th century, these side effects combined with the discovery of BDZs lead to a complete expulsion of barbiturates as medicinal therapeutics.

B II.4.3 Anesthetics, Steroids and Anticonvulsants

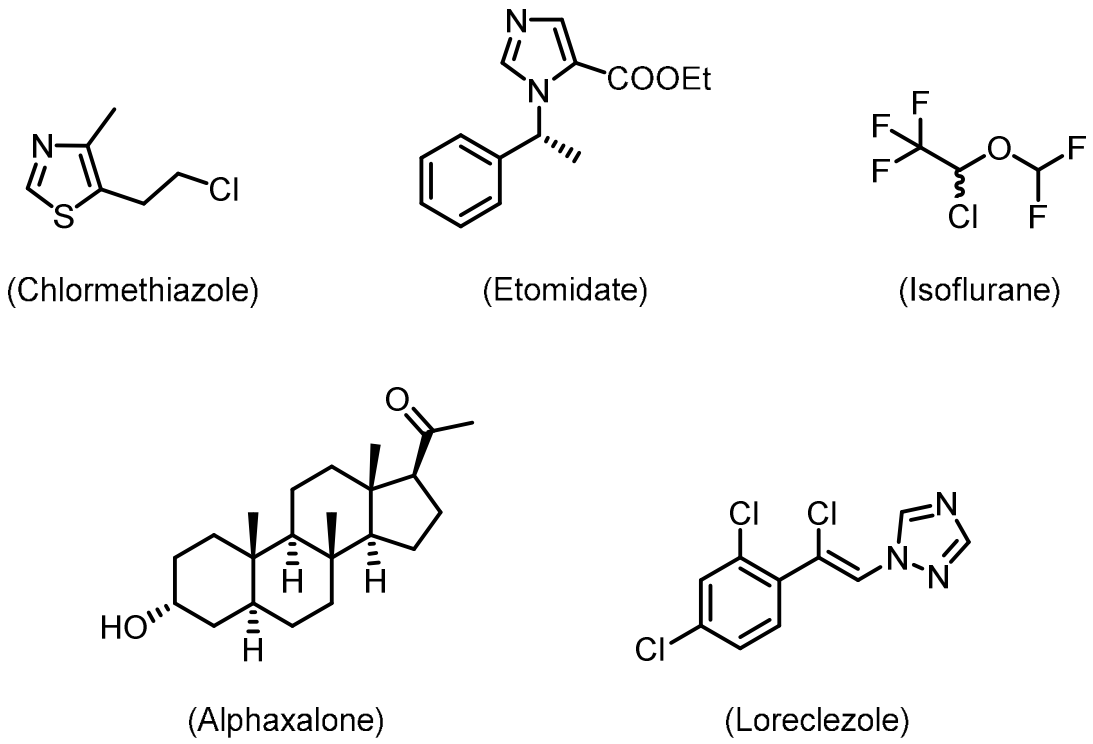


Figure 6: Examples of anesthetics, steroids and anticonvulsants modulating the $GABA_{A\ receptor}$

Some intravenous general anesthetics like chlormethiazole, etomidate, propofol as well as volatile inhalation anesthetics like isoflurane, enflurane and halothane show anxiolytic, anticonvulsant, and sedative as well as hypnotic effects associated through modulation of the $GABA_A$ receptor complex (Figure 6). They are able to potentiate Cl^- ion influx when administered in low concentrations, while at higher dosages they directly open the ion channel[13]. Their binding mode might differ from the previously discussed barbiturates and BDZs as well as GABA agonists.

Some metabolites of progesterone and deoxycorticosterone, as well as the synthetic steroid alphaxalone exert BDZ and barbiturate like behavior[26] on the $GABA_A$ receptor, increasing both the channel opening duration and frequency. They exhibit sedative, hypnotic, anxiolytic and anticonvulsant effects[18].

The anticonvulsant loreclezole, which shows anxiolytic activity as well, was shown through point mutations to bind specifically to β_2 or β_3 subunit isoforms[27], being responsible for its anxiolytic activity.

B II.4.4 GABA$_A$ Receptor Agonists and Allosteric Antagonists

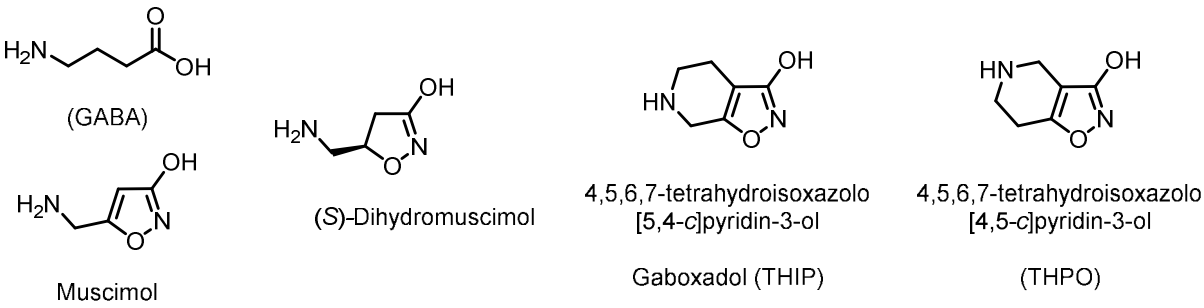
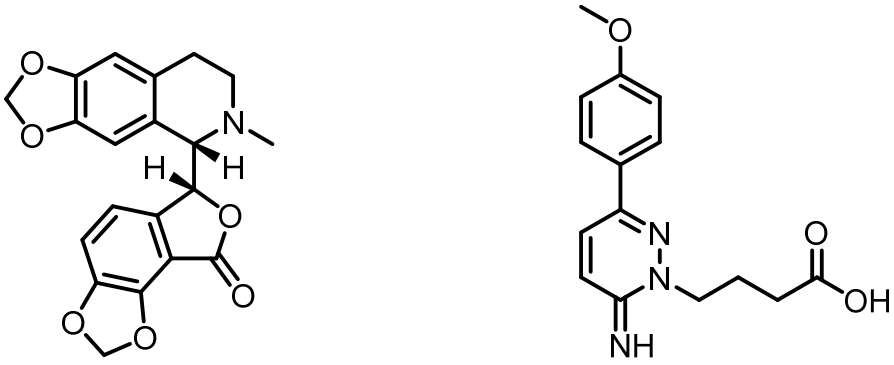


Figure 7 GABA$_A$ receptor agonists structurally related to GABA

GABA$_A$ receptor agonists specifically bind to the GABA binding site, while showing a high efficacy. Structurally they are derived from muscimol (a natural constituent of *Amanita muscaria)* and actually they represent acid-bioisosters of GABA, mainly through replacement of the carboxylic acid function via 3-hydroxy- isoxazole, -isothiazole, and –pyrozole.[28] Thus manifold synthetic variants, derived from muscimol, have been synthesized to serve as specific agonist. The most prominent besides muscimol itself are *(S)*-dihydromuscimol as the most potent agonist and gaboxadol (4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridine-3-ol, THIP) along with its isomer (4,5,6,7-tetrahydroisoxazolo [4,5-*c*]pyrdidin-3-ol, THPO), although they are already considered as partial agonists with a high level of receptor-efficacy. With the aid of THIP and THPO it was possible to separate GABA$_A$ receptor affinity to GABA uptake affinity, as THIP is a specific GABA$_A$-receptor agonist, whereas THPO specifically blocks the GABA transporters, thus leading to increased extracellular GABA concentrations resulting in an increased GABAergic neurotransmission. Furthermore the partial agonist gaboxadol exhibits anxiolytic and antinociceptive effects equipotent to morphine but lacking respiratory depressant side effects. With these two indications, gaboxadol displays a potent drug candidate, while pure agonists where just designed to investigate the GABA$_A$ receptor.



Bicuculline Gabazine

Figure 8 $GABA_A$ receptor antagonists

Like the GABA agonists, receptor antagonists provide a tool for the fundamental pharmacological and physiological role of $GABA_A$ receptors. The most prominent representatives of this class are bicuculline and gabazine[29]. Antagonists show inverse effects than GABA, thus being stimulating and convulsive. It is assumed that GABA antagonists bind to the α/β interface but stabilize an inactive conformation that does not allow the channel to open for Cl^- influx. So far, their therapeutical usage has not been exploited, but their modulation potential of GABA release through negative feed-back mechanisms, might have future potential.

B II.5 Subunit Composition and Pharmacology

Due to the heterogeneity of subunit composition and distribution of various different $GABA_A$ receptor types in the CNS, the pharmacology differs. A comparison of subunit composition and clinical effects is shown in Figure 9. Unfortunately, current marketed drugs, especially the most prominent benzodiazepines, lack subunit specific modulatory effects.

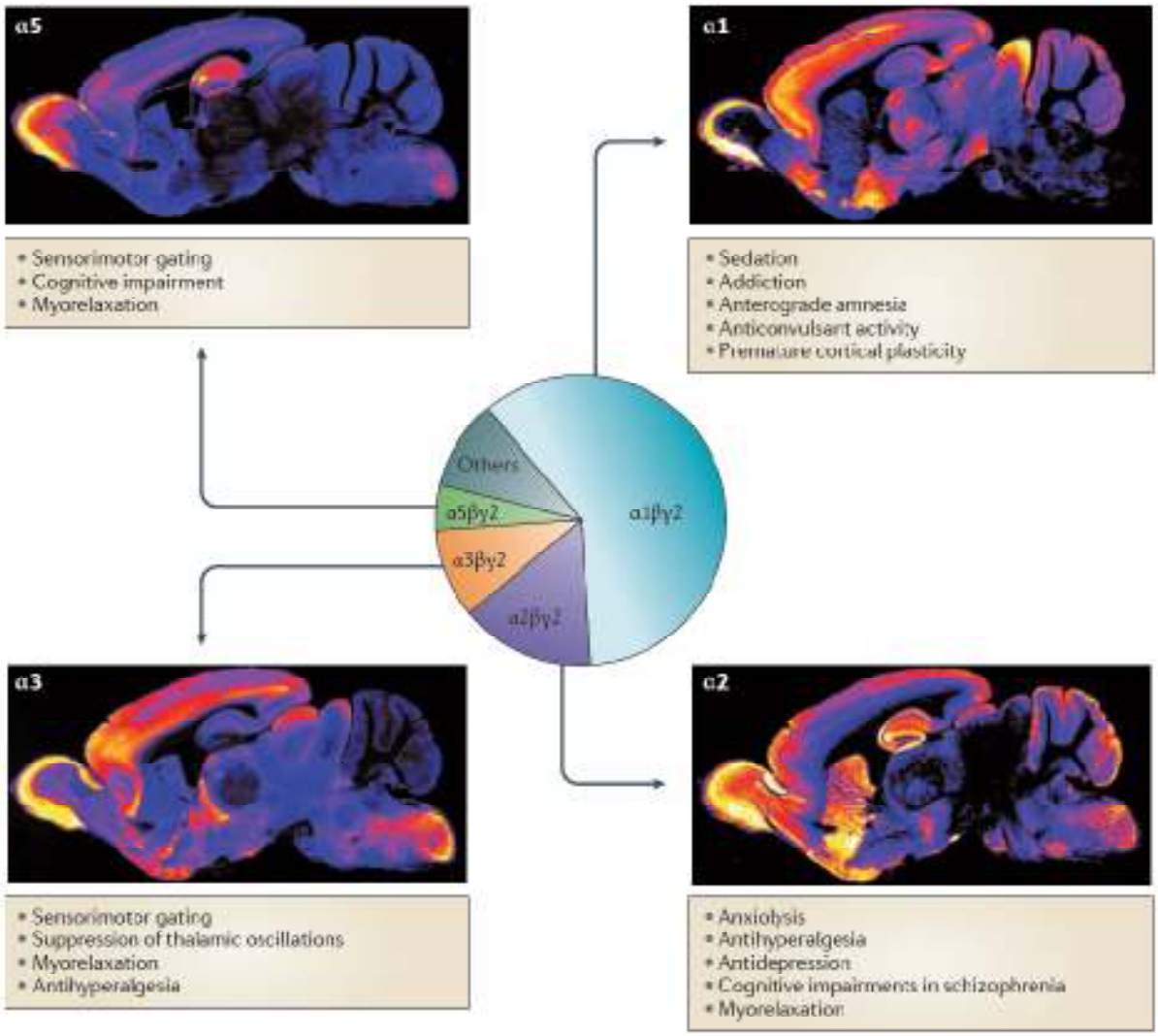


Figure 9 Pharmacological effects and distribution of $GABA_A$ receptor subunits in the mouse brain[14]

The most studied subunit isoform of the $GABA_A$ receptor is the α isoform, due to its high diversity (6 different α isoforms) and prerequisite for benzodiazepine binding. Modulatory effects associated to a discrete receptor isoform were investigated through administration of diazepam to genetically modified mice. Benzodiazepines are known to be insensitive at α_4 and α_6 subunits due to a variation of a histidine into arginine at certain positions in the polypeptide. Therefore, diazepam insensitivity at α_1, α_2, α_3 and α_5 subunits can be induced by replacement of histidine by arginine[30] at these requisite positions. Such experiments revealed that sedative, anterograde amnestic and anticonvulsant action is controlled by α_1 subunit modulation, while anxiolysis is mediated by α_2 and myorelaxant actions are mediated by α_2, α_3 and α_5 subunits. Furthermore, development of tolerance has been associated to α_5, while dependence has been linked to α_1 containing $GABA_A$ receptors[31]. Unfortunately, benzodiazepines predominantly act on the α_1 subunit. This behavior on the one hand makes them potent sleeping or sedation agents, but on the other hand reduces their potential on the treatment of anxiety, due to the sedative effect. Furthermore the biggest drawback associated to BDZs, namely dependence, limits their anxiolytic perspective.

As already mentioned, dependence is linked to the modulation of α_1 containing $GABA_A$ receptors, but just indirectly. Actually, dependence is related to a substance-induced increase of mesocorticolimbic dopamine levels[32]. Dopaminergic neurons themselves express $GABA_A$ receptors comprising of α_3 subunits, they possess no α_1 subunits. Typically, the dopamine release is controlled by GABA release of adjacent interneurons. The interneuronal released GABA binds to the α_3 containing $GABA_A$ receptor, resulting in dopamine release inhibition. If the interneuron activity is reduced through enhanced inhibition, caused by benzodiazepines binding to their α_1 expressed $GABA_A$ receptor, the interneuronal GABA release is decreased, leading to disinhibition (enhancement of neuronal excitation caused by functional activity loss of inhibitory interneurons) of the dopamine release. As a consequence the dopamine level rises, leading to a euphoric, rewarding behavior of the affected individual, resulting in the ultimate will to maintain or regain this state of mind-dependence. Conclusively, dependence is directly related to modulation of $GABA_A$ receptors bearing the α_1 subunit isoform.

Currently huge efforts are undertaken to find $GABA_A$ receptor modulators that show anxiolytic activity, lacking the BDZ side effects like sedation and dependence. As the α_1 subunit isoform was identified being responsible for these side effects, the most obvious goal is the development of subunit selective modulators apart from α_1 lacking those effects.

B II.6 Valerenic Acid as a novel $GABA_A$ Receptor Modulator

Valerenic acid (VA) is a natural constituent of valerian root from *Valeriana officinalis*. Valerian essential oils were used in traditional folkloric medicine as depressant and mild anxiolytic, whereas nowadays the range of applications covers personal care products, cosmetics and modern phytomedical products[33] making valerian to the 8th top selling herbal supplement in North America. The oil content of valerian root varies from 0.1% up to 2% and is composed of numerous different compounds. The majority is made up by monoterpenes like camphene (11.0%), bornyl acetate (10.1%), borneol (6.6%), α-fenchen (6.1%) along with sesquiterpenes like valerenal (12.9%), valeranone (5.8%) and valerianol (1.1%)[34]. Valerenic acid, on the other hand, just makes a proportion of 0.6%.

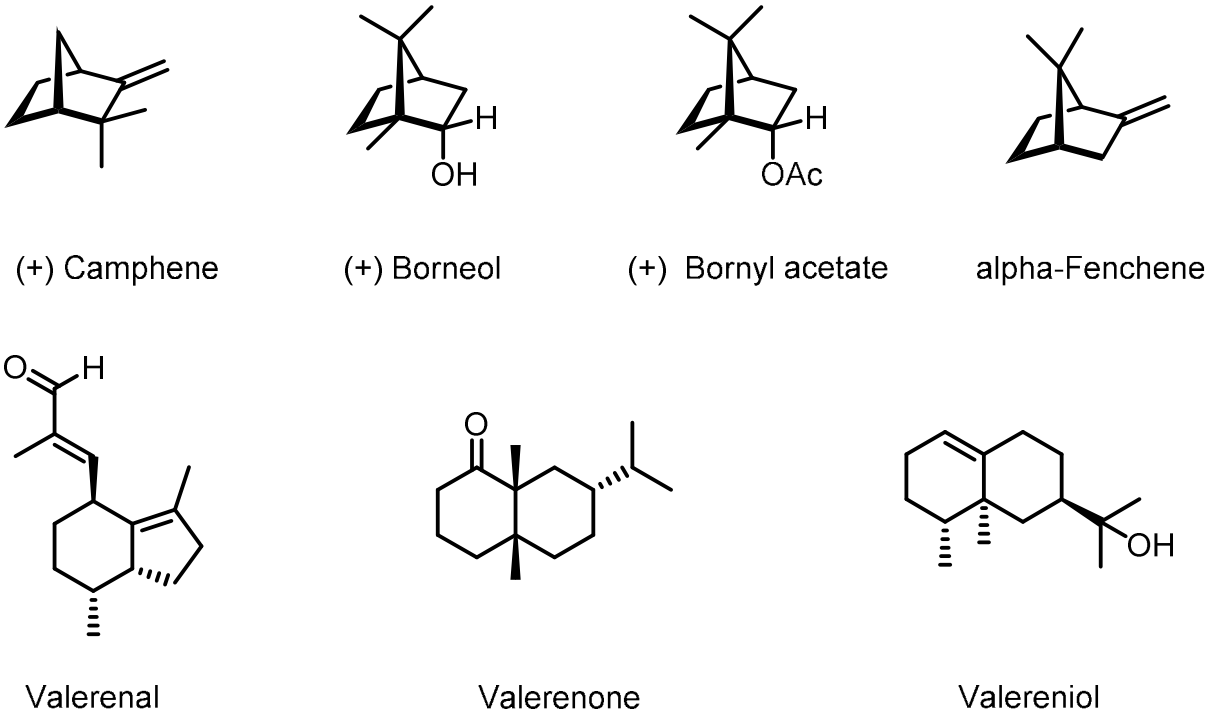
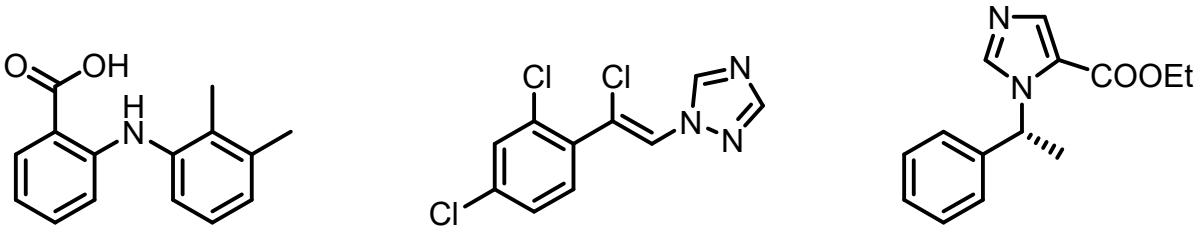


Figure 10 Major constituents of *Valeriana officinalis* along with Valerenic acid

B II.6.1 Pharmacology of Valerenic Acid

In 2007 it was found by Khom et al. that valerenic acid (VA) is an allosteric modulator of the $GABA_A$ receptor[35], blocking the receptor at concentrations higher than 100µM. Through expression of different subunit compositions of $GABA_A$ receptors in *Xenopus laevis* oocytes, it was demonstrated that the modulatory effect of VA is dependent on the β isoform. While β_2 and β_3 composed receptors showed a stimulatory effect, this effect is drastically reduced with incorporation of β_1 subunits, thus implying a β_2/β_3 selectivity for VA. Furthermore the stimulatory effect seems to be independent of the coexpressed α subunit as variation of the α isoform, except α_4, did not reduce the effect. Although most receptor systems modulated by VA where comprised of α/β subunits solely, γ containing receptors showed positive modulatory effects, as well. The strong dependence of $\alpha/\beta_{2/3}$ expression for stimulation implied a different allosteric binding site then the α/γ interface for benzodiazepines. As co-application of flumazenil (a BDZ antagonist) did not abolish the effect of VA and effects of VA and diazepam were shown to be additive, the VA binding site is independent from the BDZ one. The point mutation of β_{2N265S}, leading to nearly complete loss of activity confirms the necessity of a $\beta_{2/3}$ subunit for stimulation. Further this proves a different binding site than BDZs as well, while indicating that VA and the anticonvulsant loreclezole share the same (or

a structurally overlapping) binding site[27]. Independently the same result was found by Möhler et al. who investigated the binding site of VA through a different approach. They demonstrated via radiolabelled [^{3}H]VA binding studies and competition experiments, that VA binding is suppressed in the presence of mefenamic acid (Figure 11)



Mefenamic acid Loreclezole Etomidate

Figure 11 Structures of mefenamic acid, loreclezole and etomidate binding at $\beta_{2/3}$ subunits like valerenic acid

On the basis of the aforementioned pharmacological results *in vitro*, VA was tested for anxiolysis *in vivo*. Indeed VA, administered orally or intraperitoneally, induced anxiolytic behaviour of mice in light-dark box test[36] and elevated plus maze test[37], concomitantly displaying no sedative effect. Furthermore, it was demonstrated through point mutation studies, that β_{3N265M} mutated mice lost their anxiolytic like behaviour. This clearly establishes the necessity of β_3 subunit containing $GABA_A$ receptors interacting with VA to mediate anxiolysis and is in line with the findings of Löw et al., who demonstrated that anxiolytic activity of benzodiazepines is associated to a $\alpha_2\beta_3\gamma_2$ composition[38]. Based on these results VA is a potent candidate for an anxiolytic, lacking the pronounced benzodiazepine side-effects like sedation –as demonstrated- and potentially addiction through its $\alpha_2\beta_3\gamma_2$ selectivity (compare section B II.5).

B II.6.2 Biosynthesis of Valerenic Acid

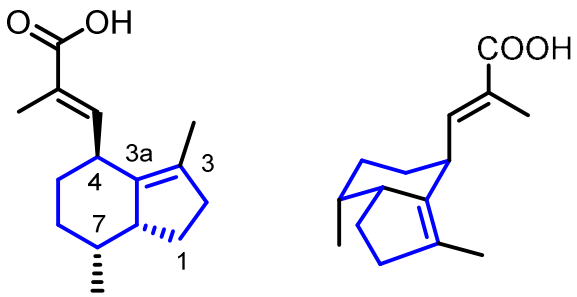


Figure 12 Structure of Valerenic acid

VA belongs to the sesquiterpene class of guaianes. Structurally, an indanyl core is decorated with two methyl groups in 3 respectively 7 position. The latter one shows an unusual 1,4-diaxial conformational relationship –with respect to the cyclohexyl ring- relative to the methacrylic acid substituent in position 4. The indanyl entity bears three stereogenic centers (C4,C7,C7a) and two double bonds, one being endocyclic between C3 and C3a. The structure has first been elucidated in 1960 by Büchi et al.[39] before the exact conformation was proven by X-ray crystallography in 1978 by Birnbaum et al.[40]. Both Büchi and Birnbaum were the first to make different suggestions for the biosynthesis of VA.

In the initial report of Büchi it was hypothesized, that the unusual structure of VA is a result of a biogenic ring contraction of guianolide . Interestingly, no correlation between any sesquiterpene synthesis and the proposed guianolide structure is mentioned in the literature. Therefore, this biosynthetical "pathway" seems highly speculative, but for the sake of completeness it shall be mentioned here.

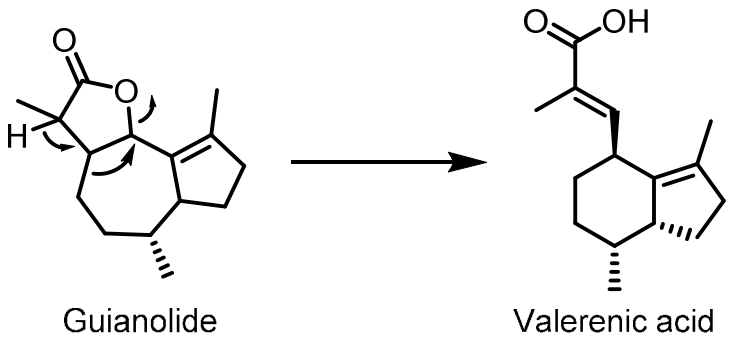


Figure 13 Biosynthetic ring contraction suggested by Büchi et al.

In the later work of Birnbaum, this pathway was revised and the biosynthesis was proposed to proceed via key intermediate α-gurjunene. Here α-gurjunene first gets epoxidized, followed by acidic epoxide opening and subsequent collapse of the cyclopropane ring. Acidic elimination of the tertiary alcohol triggers a cascade reaction in which an anionotropic 1,2 shift sets the 5,6 bicyclic core system. The resulting valerenol is then further oxidized to valerenal and finally to valerenic acid (see Figure 14).

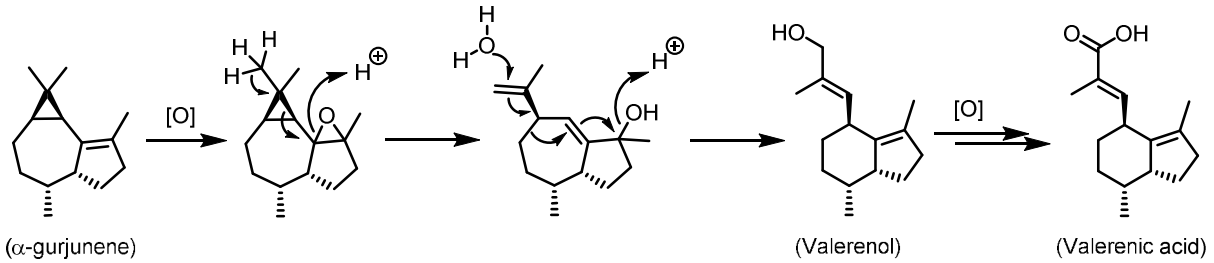


Figure 14 Biosynthetic approach according to Birnbaum et al.

The latest and most elaborate hypothesis towards the biosynthesis of VA was published by Pyle et al. 2012 [41]. First the diphosphate residue of farnesyl diphosphate is cleaved by

sesquiterpene synthase (VoTPS2) generating a reactive carbocation. This carbocation is attacked by a double bond, cyclizing towards a ten membered ring with a stabilized exocyclic tertiary carbocation. A 1,3-hydride shift migrates the carbocation into endocyclic position 6, where ring contraction through carbanionic C8 attack sets the 9-membered skeleton. Finally a deprotonation-reprotonation cascade, guided by VoTPS2, fuses the indanyl core towards valerena-4,7(11)-diene, which upon further oxidation yields valerenic acid. It has to be mentioned, that several pathways from the carbocation are possible, but VoTPS2 was identified to catalyze cyclisation towards valerena-4,7(11)-diene.

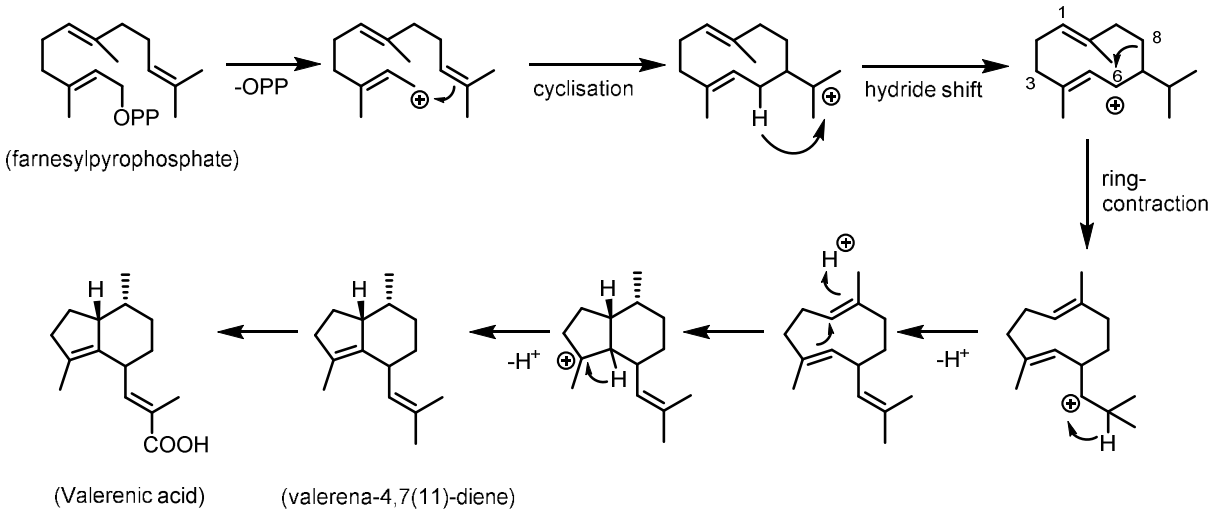


Figure 15 Biosynthesis of valerena-4,7(11)-diene and valerenic acid according to Pyle et al.

B II.6.3 Total Syntheses of Valerenic Acid

Up to date two stereoselective total syntheses of VA are known. This first, more elegant and efficient synthesis was published by Ramharter and Mulzer in 2009[2], followed shortly after by a completely different approach by Kopp and Altmann within the same year[42]. Due to the methodological impact of the Mulzer synthesis for this thesis, the aforementioned syntheses will not be discussed chronologically.

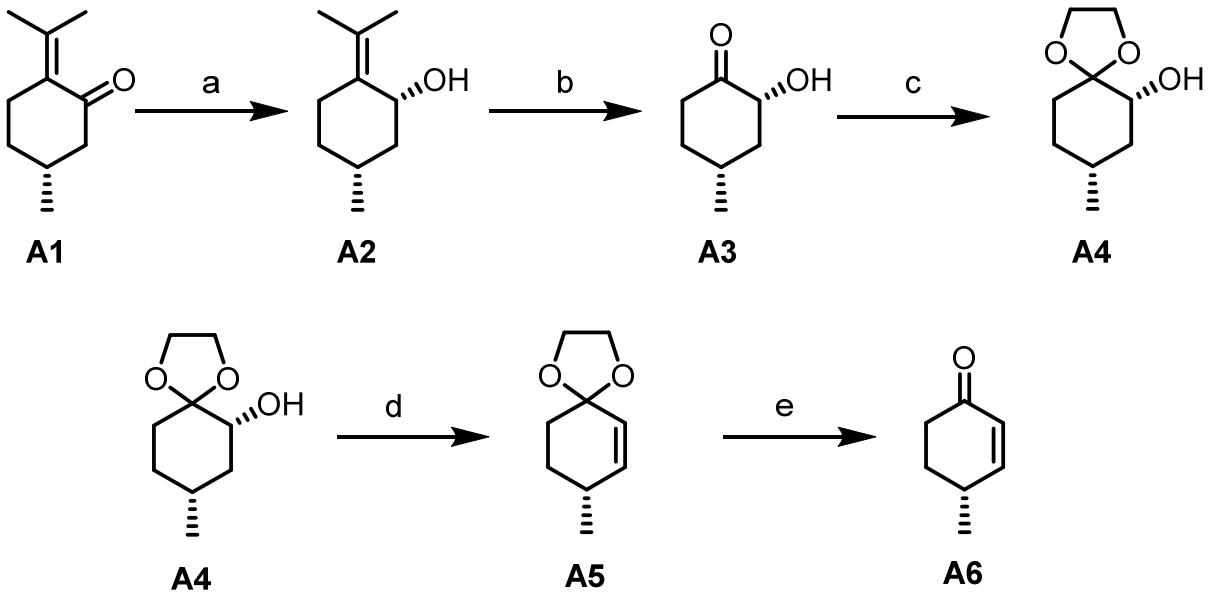


Figure 16 Reagents and Conditions: a) $LiAlH_4$, THF, 99%; b) O_3, DCM:MeOH=1:1, 95%; c) 2-ethyl-2-methyl-1,3-dioxolane, CSA, ethylene glycol, 80% d) Tf_2O, pyridine, DCM, then DBU neat; e) 15% H_2SO_4, THF, 77% over 3 steps

The synthesis of Altmann starts with commercially available (R)-(+)-pulegone **A1** and is based on a protocol published by Lee et al. (Figure 16)[43] to produce crucial intermediate (R)-(+)-4-methyl-2-cyclohexe-1-one **A6** in multigram scale . First the naturally occuring monoterpene (R)-(+)-pulegone is stereoselectively reduced by lithiumaluminiumhydride (through substrate-control) to allylic alcohol **A2**. Then the exocyclic double bond is ozonolytically cleaved in methanol-dichloromethane 1:1 mixture, as methanol seems to be crucial for preventing a sluggish reaction. The gained α-hydroxy ketone **A3** is subsequently acetal protected through transketalization with catalytic amounts of camphorsulfonic acid and commercially available 2-ethyl-2-methyl-1,3-dioxolane in ethylene glycol to yield bicyclic alcohol **A4**.

Next the alcohol is converted into a triflate, before eliminated in neat DBU and cleavage of the ketal under aqueous acidic conditions, to yield (R)-(+)-4-methyl-2-cyclohexen-1-one **A6** with an overall yield of 71% over six steps (Fehler! Verweisquelle konnte nicht gefunden werden.).

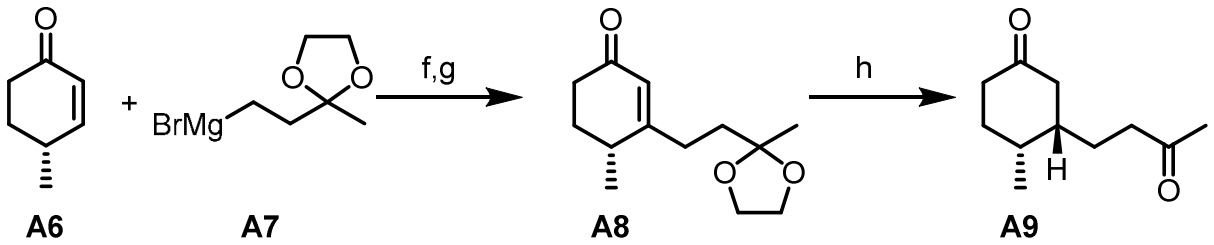


Figure 17 Reagents and Conditions: f) Mg, $CuBr_2.SMe_2$, then TMSCl, NEt_3, THF; g) O_2, $Pd(OAc)_2$, then 2N HCl, DMSO, 43% over 3 steps; h) $[PPh_3CuH]_6$, benzene, 76%;

Normant cupprate – derived from transmetallation of *in situ* generated Grignard reagent **A7** with $CuBr_2.SMe_2$ – was added to α,β unsaturated ketone **A6** in a 1,4 fashion and the

intermediate enolate was trapped with TMSCl. The crude silylether was then subjected to Saegusa oxidation[44] and ketal deprotection of the side-chain for reestablishment of the enone moiety, being crucial for setting the stereocenter in 3-position through stereoselective, conjugated hydride addition mediated via equimolar amounts of Stryker's reagent ($[PPh_3CuH]_6$) leading to diketone **A9** (Figure 17).

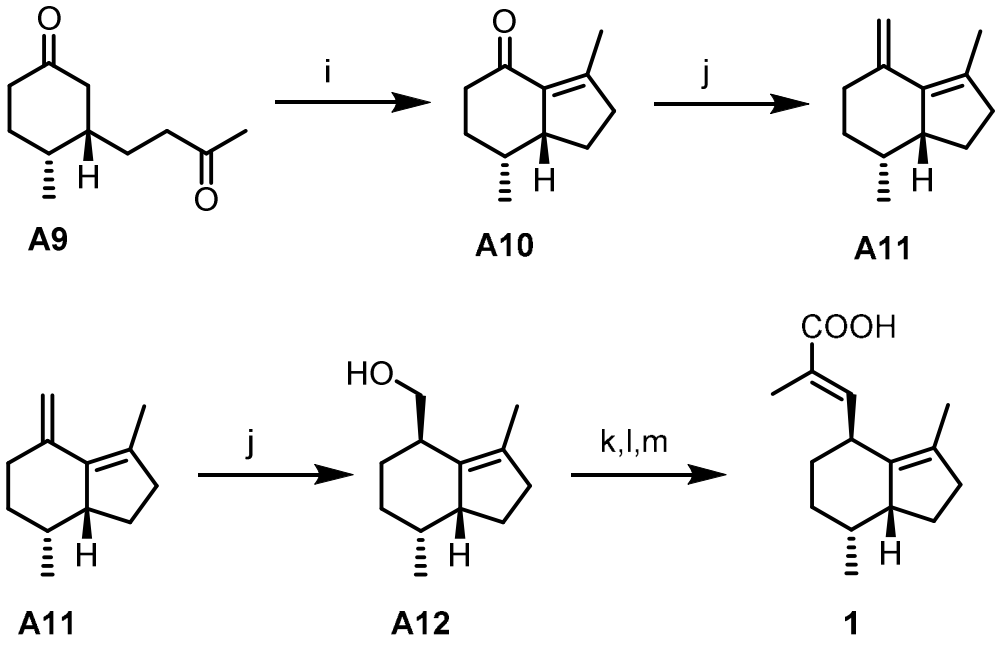


Figure 18 Reagents and Conditions: i) NaO*t*-Bu, *t*-BuOH, 71%; j) $MePPh_3Br$, $NaNH_2$, Et_2O, 75% j) 9-BBN, THF, then H_2O_2, 82%; k) DMP, THF, then $Ph_3P{=}C(Me)CO_2Et$, MeOH, µW, 62%; l) LiOH, iPrOH/H_2O, 97%

Within product **A9**, two out of three stereocenters are already set and indanyl-core **A10** is introduced through intramolecular aldol condensation under basic conditions (Figure 18). Subsequent Wittig olefination and hydroboration/oxidation sequence yields alcohol **A12** while selectively setting the residual stereocenter in C4. Finally, Dess-Martin-Oxidation and Wittig olefination of the crude, emerged aldehyde delivers valerenic acid ethyl ester.Upon saponification with lithiumhydroxide valerenic acid **1** is obtained in 6% overall yield in 16 linear steps

The first generation synthesis of valerenic acid **1** by Mulzer et al.[2] started from commercially available (R)-glycidol **M1** (Figure 19). The epoxide was regioselectively opened by propargylmagnesiumbromide to yield diol **M2** on which the primary alcohol was selectively tosylated in the presence of catalytic amounts of dibutyltin oxide. Subjection of tosylate **M3** to Corey-Chaykovsky-reaction conditions afforded - via an intermediate epoxide[45] – allylic alcohol which was *in situ* silyl protected to generate **M4**.

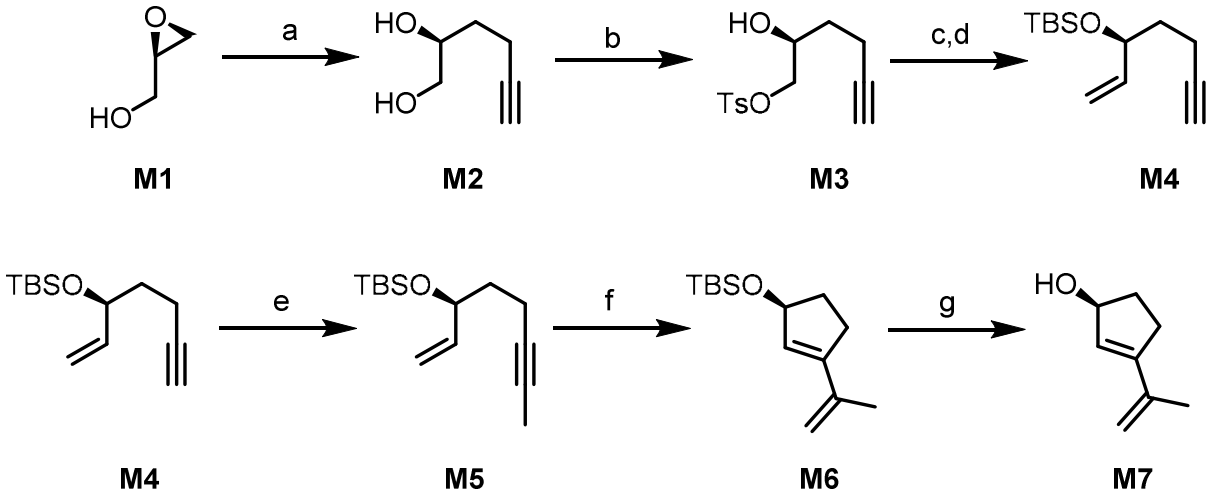


Figure 19 Reagents and conditions: a) $HC{\equiv}CH_2MgBr$, Et_2O, -78°C, 94%; b) TsCl, NEt_3cat. B_uSnO, DCM, r.t., 80%; c) Me_3SI, *n*-BuLi, THF, -20°C; d) TBSOTf, NEt_3, DCM, 0°C, 58% over two steps; e) *n*-BuLi, MeI, THF, -78°C, 89%; f) ethylene, Grubb I catalyst, r.t., 86%; g) TBAF, THF, r.t., 94%

Alkyne **M4** was then methylated followed by enyne-RCM with Grubbs I catalyst under an ethylene atmosphere to afford cyclopentenol derivative **M6**. This compound was deprotected with TBAF to allylic alcohol **M7**. This structure represents a key intermediate of the whole synthetic route, as its chirality will direct formation of all subsequent stereogenic centers; access to the compound was accomplished in 7 linear steps with a yield of 27%. Due to its importance within the whole synthesis, a shortened route towards (S)-3-(prop-1-en-2-yl)cyclopent-2-en-1-ol **M7** was published later on[1, 46, 1].

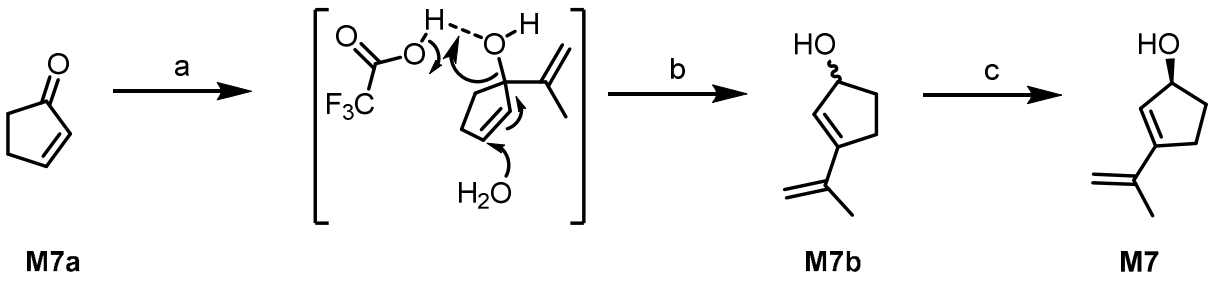


Figure 20 Reagents and conditions: a) 2-bromopropene, *t*-BuLi, Et_2O, -78°C; b) TFA,H_2O/THF,0°C, 81%; c) vinylacetate, LipasePS, MTBE, r.t., >95%ee, 45%

This shortened, second generation approach (Figure 20) commences with 1,2-addition of *in situ* generated 2-propenyllithium to cyclopent-2-en-1-one **M7a**. The highly labile tertiary alcohol generated by this addition is directly rearranged to the more stable racemic, conjugated allylic alcohol **M7b** upon TFA addition under an aqueous environment. Subsequent kinetic resoultion with lipase delivers (S)-3-(prop-1-en-2-yl)cyclopent-2-en-1-ol **M7** with greater 95%ee and 36% overall yield and reduces the sequence by 5 steps.

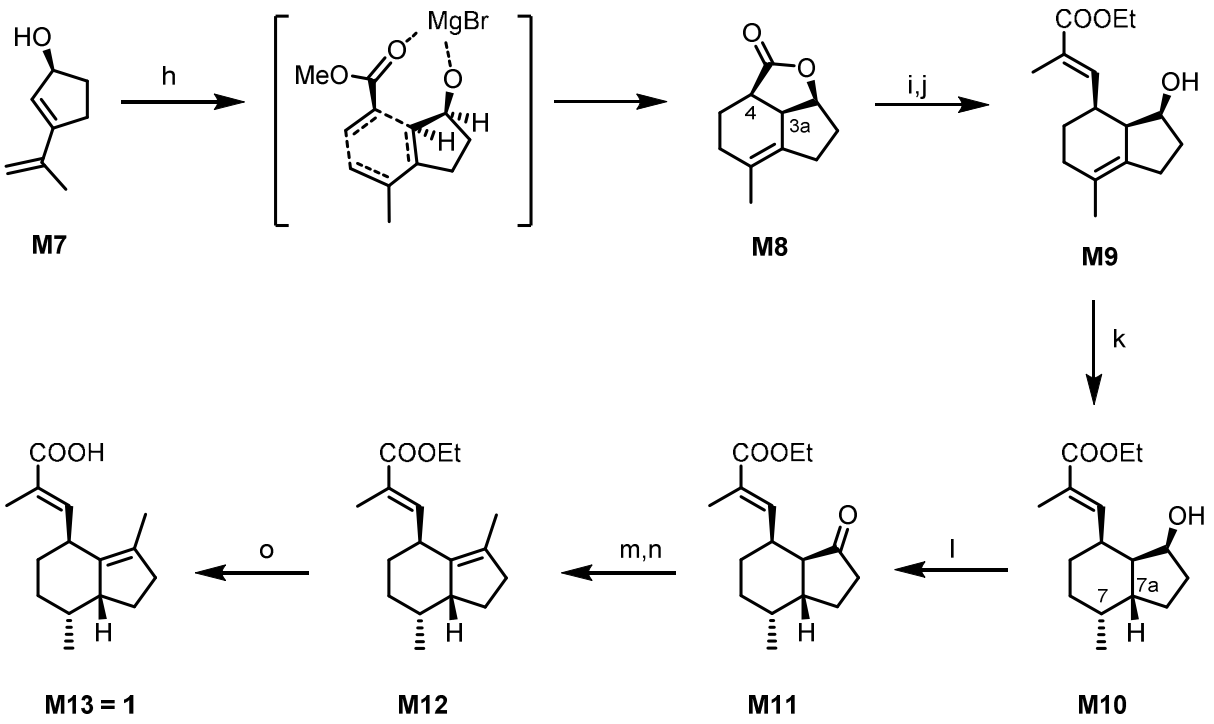


Figure 21 Reagents and conditions: h) $MgBr_2.Et_2O$, methacrylate, DIPEA, DCM, r.t., 81%; i) DIBALH, DCM, -78°C, crude; j) $Ph_3P=C(Me)CO_2Et$, benzene, reflux, 83% over 2 steps; k) cat. $[Ir(cod)(py)PCy_3]PF_6$, H_2, DCM, r.t., 72%; l) IBX, DMSO, r.t., 93%; m) Tf_2O, pyridine, DCM, r.t, crude; n) cat. $Pd(PPh_3)_4$, $Zn(Me)_2$, THF, r.t., 78% over two steps; o) LiOH, THF,H_2O, MeOH, r.t., 99%

The enantiopure alcohol is then tethered through Mg^{2+} with methacrylate to selectively set the stereocenter at C4 and C3a after Diels-Alder reaction as described by Barriault et al[47]. Lactone **M8** is then reduced to the corresponding lactol and subjected to Wittig-Olefination installing the methacrylate functionality at C4 (Figure 21). Diastereoselective hydrogenation of hydroxy ester **M9** with Crabtree's catalyst[48] ($[Ir(cod)(py)PCy_3]PF_6$ establishes the 4,7-diaxial relationship, as well as the remaining stereocenter at C7a. After all stereocenters have been set, installation of the methyl group in C3 represents the remaining task. Therefore alcohol **M10** is oxidized to ketone **M11**, which is converted into enol-triflate prior to Negishi-Coupling with dimethylzinc furnishes valerenic acid ethyl ester **M12**. Hydrolysis of the ethyl ester under basic aqueous conditions finally delivers valerenic acid **1** in 13% isolated yield over 10 steps through the more efficient cyclopentenone-route.

Comparing the two independently developed syntheses of Altmann and Mulzer for valerenic acid **1** it is clear, that the Mulzer approach is the more efficient one with respect to the number of steps as well as regarding yield (10 vs. 16 steps with 13% vs. 6% yield, respectively 13 vs 16 steps with 8% vs 6% yield for the first generation approach). Furthermore, the Mulzer synthesis provides more modularity for medicinal chemistry variation such as installation of different residues substituting the two methyl groups of the indanyl core at C3 respectively C7. The vinylogous methyl group at C3 can easily be exchanged with commercially available reagents through coupling of different functionalities starting from the ketone **M12**. The same modification applying the Altmann strategy would require the

synthesis of protected β-halo(bromo)-ketones like **A7** (see Figure 17) of different chain length or functionalities attached in β' position. Exchanging the axial methyl group at C7- through the Mulzer approach- would be possible through 1,2-addition and subsequent rearrangement of different carbon nucleophiles to cyclopent-2-en-1-one **M8a** (see Figure 20), thus making it necessary to perform the whole sequence for each individual derivative. Still, the Altmann route does not even provide this flexibility, as the stereochemical origin of methyl residue in C7 stems from the natural product (R)-pulegone **A1** (see Figure 16). Summarizing, the Mulzer synthesis proves to be more efficient and modular. These key requirements for the performance of SARs on the valerenic acid scaffold make the aforementioned synthesis the approach of choice related to the targets of this thesis.

B II.7 Scope and Aim of this Thesis

This thesis was part of the IK doctoral program on functional molecules and constitutes a cooperation between the Institute of Applied Synthetic Chemistry from Vienna University of Technology, where the synthesis of compounds was performed, and the Institute of Pharmacology and Toxicology from the University of Vienna, where the synthesized compounds were tested for biological activity. The goal was the identification of novel $GABA_A$ receptor modulators based on the structure of the natural product valerenic acid. As there was no X-ray structure of the $GABA_A$ receptor known at the start of this project (structure published in *Nature* 2014[8]) an the three-dimensional structure of the VA binding site is yet unknown, a classical medicinal chemical approach, meaning modification of a given functionality and comparison of the modification-associated change in effect, was chosen for investigation of $GABA_A$ receptor modulators.

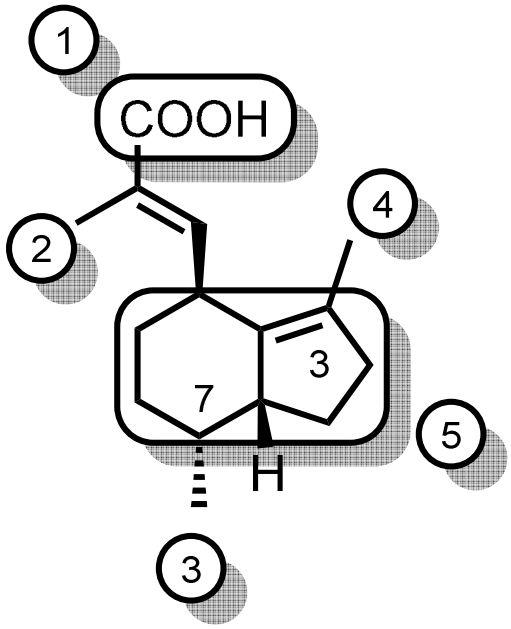


Figure 22 Valerenic acid with the different sites of modifications numbered

Looking at the structure of valerenic acid, five structural parameters for modification seem obvious:

1. modification of the carboxylate moiety
2. the configuration of the exocyclic double bond and the necessity of its methyl group
3. modification of the axial methyl group at C7 of the cyclohexyl ring
4. modification of the methyl group at C3 of the cyclopentyl ring
5. modification of the ring sizes of either 5-or 6-membered ring of the indanyl core

Within this thesis three out of five modifications, covering the carboxylate functionality (nr. 1), the axial methyl group at C7 (nr. 3) and the vinylogous methyl group at C3 (nr. 4), have been addressed. Partly, modifications of the carboxylate functionality, as well as the necessity of the exocyclic double bond have already been conducted by Altmann[49]. As a result it was found, that reduction of the exocyclic double bond leads to complete loss of activity for both generated diastereomeres and that a hydrogen donor moiety seems to be crucial for activity. Furthermore the double bond geometry as well as its methyl substituent seem to be crucial for activity as well. Therefore no further investigations, changing the exocyclic double bond geometry or its aliphatic substituent were performed within this work. Last to mention the effect of different ring sizes, besides the 5/6 fused indanyl core, was omitted for investigation within this thesis, as it is part of another project of the aforementioned cooperation.

Within the modification of the carboxylate moiety, the necessity of a hydrogen donor – as already indicated from the results obyf Altmann- was investigated further. Therefore several esters and amides were prepared from valerenic acid- bearing or lacking hydrogen donor ability. In this context potential pro-drugs of valerenic acid were investigated as well. The chemistry associated to carboxylate modification will be discussed in chapter **Fehler! Verweisquelle konnte nicht gefunden werden.** and the observations of pharmacological effects in chapter G.

Further the axial methyl group at C7 was planned to be substituted through diverse residues including hydrogen-, ethyl-, cyclopropyl-, *t*-butyl-, -phenyl and trifluoromethyl residues. Not only derivatives at the valerenic acid stage were tested for modulation of the $GABA_A$ receptor within this project, as prior results also indicated a high affinity of intermediate **M10**. The chemical challenges, as well as intrinsic limitations will be discussed in chapter D and the pharmacological consequences of modulations in chapter G.

Then modification of the vinylogous methyl group at C3 through diverse coupling reactions and the influence on pharmacological activity was investigated (chapter E and G).

Finally, a new strategy for the total synthesis of analogues - derived from valerenic acid - was demonstrated, as the template synthesis of Mulzer[2,1] has its limitations in modularity (see chapter F).

C Results and discussion

C I Modification of the carboxyl moiety

Although structural derivatisation of carboxyl moiety and its accompanied modulatory effects on the $GABA_A$-receptor was already investigated *in vitro* by Kopp *et. al*[49], we still opted to investigate carboxyl of valerenic acid derivatives, both *in vitro* and *in vivo*. First we wanted to identify a carboxyl derivative with higher potentiation on the $GABA_A$ receptor (*in vitro*-studies) to determine the structural needs at this requisite position for effective modulation. In addition we wanted to optimize the "drug-like" properties of valerenic acid by investigating several *in vitro* inactive modifications *in vivo* to test their potential as pro-drugs. One of the most common approaches for prodrug design is to use metabolic bioconversions into the active drug by hydrolases such as peptidases, phosphatases or carboxylesterases[50]. With the low *in vitro* activity of valerenic acid esters demonstrated prior to this work[49], such esters seemed a very appealing target as valerenic acid prodrugs.

C I.1 Synthesis of Valerenic Acid Esters

For the formation of various esters starting from commercially available valerenic acid, Steglich[51]-esterification was chosen, as it is known to be a very mild and functional group tolerant protocol, as well as high yielding

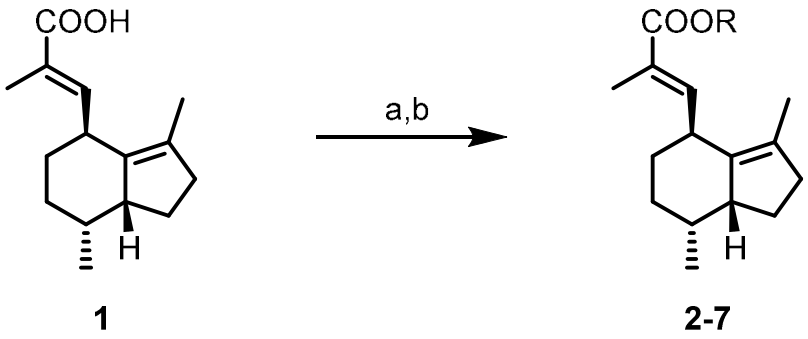


Figure 23: Reagents and Conditions: a) EDCI.HCl, DMAP, R-OH, DCM, r.t.; b) PivCl, DBU, DCM/MeCN, r.t.

Treatment of valerenic acid **1** with catalytic amounts of DMAP and excess amounts of EDCI in DCM at 0°C followed by addition of the appropriate alcohol afforded the desired esters **2-6** in very good yields. For the formation of pivaloyloxymethylester **7**, a different protocol was

chosen[52]. Here valerenic acid **1** acts as the nucleophile substituting chloride from commercially available pivaloyloxymethyl chloride. The only challenging esterification was the installation of a *t*-butyl group. Various attempts to install the *t*-butyl ester functionality via EDCI activation of valerenic acid **1** failed. Neither application of *t*-butanol as cosolvent, nor prolongation of reaction time from one day to three days, nor heating to 50°C showed any significant conversion towards *t*-butylester **12**. It was observed (TLC, GCMS), that the reaction proceeds until the EDCI-valerenic acid conjugate, but not further. Thus it was concluded, that the nucleophilicity of *t*-butanol **8** is too low for a successful transformation due to the steric demand. Instead the role of reaction partners was reversed, making valerenic acid **1** the nucleophile attacking an activated *t*-butyl-O-isourea **11** (Figure 24), a strategy known from protective group chemistry. As EDCI.HCl and *t*-butanol **8** are solids at room temperature, the activating carbodiimide was substituted to liquid diisopropylcarbodiimid (DIC) **10**. The *t*-butyl-O-isourea **11** was formed in excess and was then diluted with DCM to be treated with valerenic acid **1**; this protocol gave smooth conversion to *t*-butylester **12** overnight in 67% (non optimized)[53]. The prepared valerenic acid esters are summarized inTable 1.

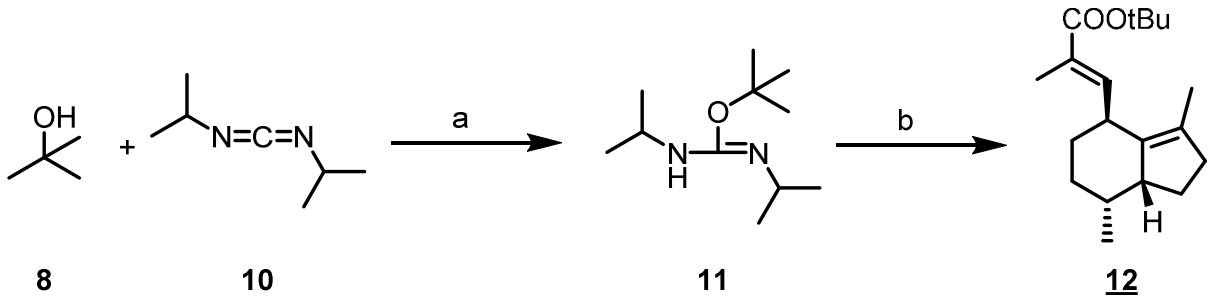


Figure 24: Reagents and conditions: a) Cu(I)Cl, neat, r.t.; b) Valerenic acid, DCM, r.t., 67%;

Table 1 Coupled Esters with yields

Product No.	R=	Yield [%]
2	**Methyl**	**95**
3	**Ethyl**	**95**
4	***n*-Propyl**	**99**
5	**Benzyl**	**94**
6	**Allyl**	**97**
7	**Pom**	**85**
12	***t*-Butyl**	**67**

C II Synthesis of Valerenic Acid Amides

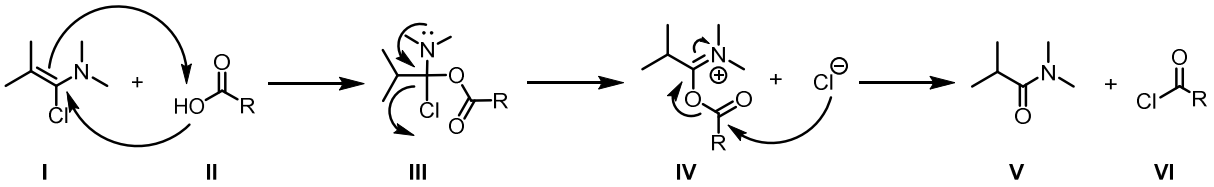


Figure 25: Reaction Mechanism of the formation of acidchlorides applying Ghosez' Reagent

Initially, valerenic acid amides were synthesized according to a protocol published by Mulzer et al.[1] employing Ghosez´s-reagent (Figure 25). This reagent, an imidoylchloride (1-chloro-N,N,2-trimethyl-1-propenylamine **I**), should transform the acid functionality mildly into the corresponding chloride **VI** . Unfortunately, when applying the published conditions for synthesis of methyl-, dimethyl-, ethyl- and diethyl valerenic acid amide, N,N-dimethyl valerenic acid amide **15** was observed as a side product, which was not reported in the literature. It was figured, that the origin of this – mostly unseperable- side product is associated to Ghosez´s reagent, bearing an N,N-dimethylamine moiety. Therefore it was opted to synthesize the amides via a different protocol[54]. Here the acid functionality is first activated via EDCI, which is further reacted with N-hydroxysuccinimide (NHS) to the corresponding NHS-conjugate **I 13**. Subsequent addition of an aqueous amine results in clean amide formation, as the NHS-conjugate is just electrophilic enough for attack by amines, but not for reaction with water. With this method, amides **13-20** could be obtained in good to excellent yield in a convenient protocol applying cheap, abundant amines in aqueous solution (summarized in Table 2).

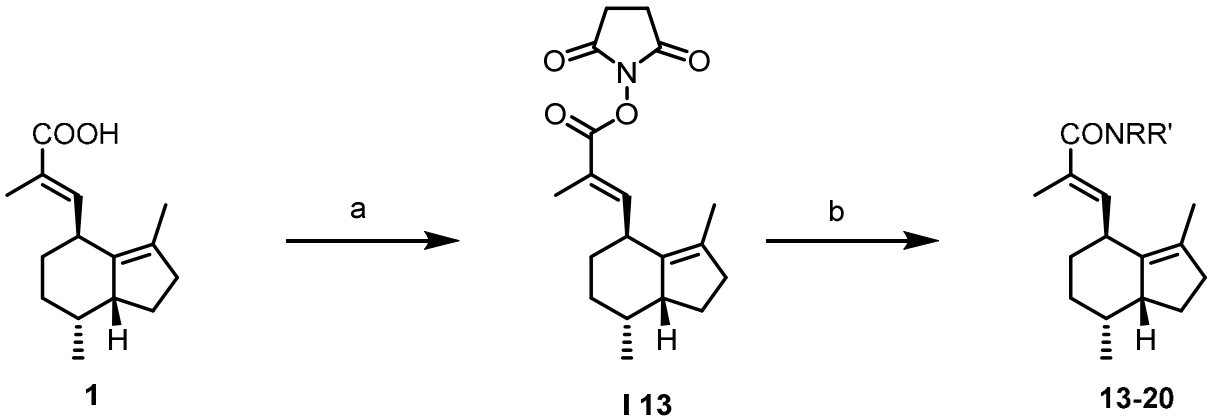


Figure 26 Reagents and conditions: a) NHS, EDCI.HCl, DCM, r.t. then b) NHRR', as a one pot operation

Table 2: Coupled amides with yields

Nr	R=	R'=	Yield [%]
13	H	H	99
14	H	Methyl	71
15	Methyl	Methyl	79
16	H	Ethyl	76
17	Ethyl	Ethyl	89
18	Methyl	Ethyl	99
19	H	Allyl	76
20	H	Benzyl	97

C II.1 Synthesis of Valerenic Acid Tetrazole (23)

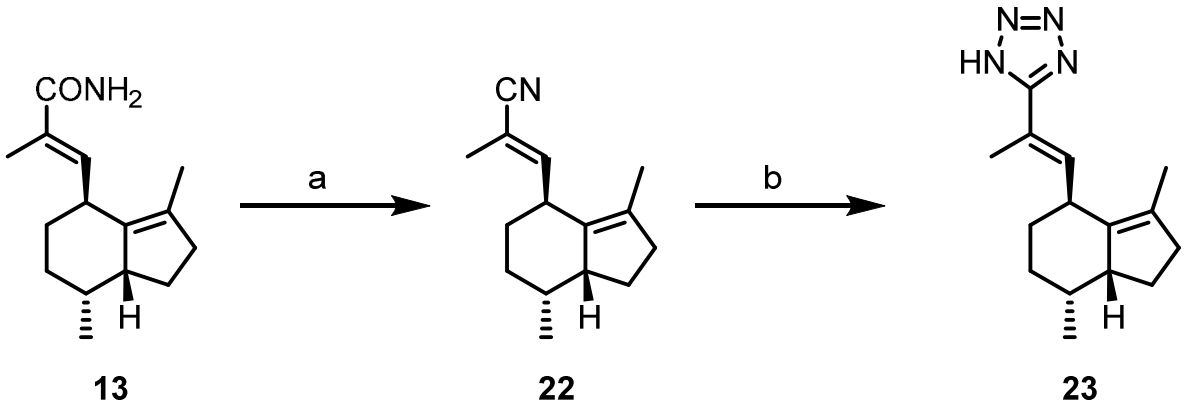


Figure 27 Reagents and conditions: a) Oxalyl chloride, DMF, pyridine, MeCN, 0°C, 98%; b) NaN_3, $(Bu)_3SnCl$, toluene, 100°C 84%

Tetrazole **23** is accessible from valerenic acid **1** in three steps, respectively two steps from amide **13**. Initial dehydration of DMF with oxalyl chloride generates *in situ* Vilsmeier´s-reagent, which in turn dehydrates amide **13** to nitrile **22**. Subsequent 1,3-dipolar cycloaddition of the crude nitrile **22** with *in situ* generated tributyltinazide furnished tetrazole **23** in 81% yield over three steps following the procedure published by Altmann[49].

D Modification of the Axial Methyl Group at C7 - Chemistry

Within this chapter the total syntheses – respectively the synthesis attempts if unsuccessful- of C7 modifications of valerenic acid **1** are discussed. The synthesis, based on the total synthesis of Mulzer[2,1], will be discussed in detail once on the example of 7-normethylvalerenic acid **32**. All further modifications at C7 were conducted following mostly the same synthetic route. Therefore, just the differences to the 7-normethylvalerenic acid **32** synthesis will be outlined and discussed, whereas the same synthetic operations will be briefly mentionedfor completion.

D I General Considerations on the Stereoconfiguration of C7-Derivatives

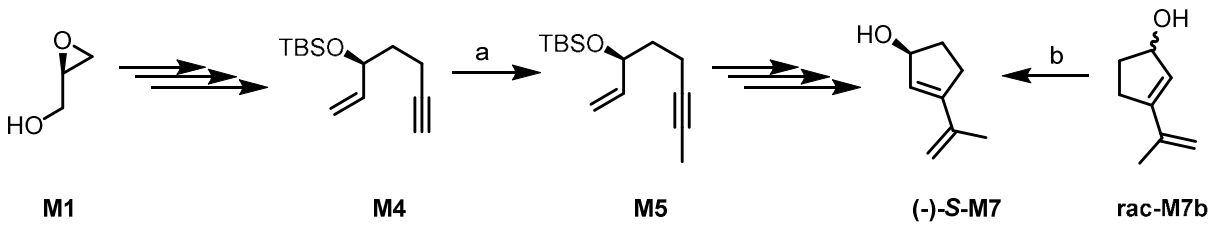


Figure 28 stereoconvergent routes to (S)-3-(prop-1-en-2-yl)cyclopentenone a) lithiation/nucleophilic-substitution; b) kinetic resolution with lipase PS

Within the following chapter the preparation of several C7-derivatives of valerenic acid **1**, synthesized via the published Mulzer-route[1] will be discussed. As all stereocenters of valerenic acid are set by the stereochemistry of crucial intermediate alcohol **(-)-S-M7** and subsequent stereoconvergent transformations, any derivative of the methyl-group at C7 can be deduced to the appropriate derivative of **(-)-S-M7**. As depicted in Figure 28, alcohol **(-)-S-M7** is accessible via two different routes according to Mulzer. The first way is the synthesis starting from commercially available (*R)*-glycidol **M1** which is transformed in several stereoconvergent steps to intermediate **M4**. As depicted, methylation of **M4** produces **M5** without loss of stereochemical information. As expected, methylation of **M4** causes neither inversion, nor erosion of the stereocenter at C3. En-yne-metathesis of **M5** followed by

deprotection then delivers crucial intermediate (-)-(*S*)-3-(prop-1-en-2-yl)cyclopent-2-en-1-ol **(-)-S-M7**. Alternatively, **(-)-*S*-M7** can be obtained through kinetic resolution via lipase PS from ***rac*-M7b**, which was published by Mulzer et. al[46] as an optimized route towards (-)-(S)-3-(prop-1-en-2-yl)cyclopent-2-en-1-ol **(-)-S-M7**. All C7-derivatives in this thesis were synthesized via this approach (Figure 29). As depicted, the stereoconfiguration of the alcohol has been established through kinetic resolution employing lipases. It has to be noted, that the stereoconfiguration of 3-(prop-1-en-2-yl)cyclopent-2-en-1-ol **(-)-S-M7** has been demonstrated to be (-)-(*S*) from kinetic resolution with lipase.

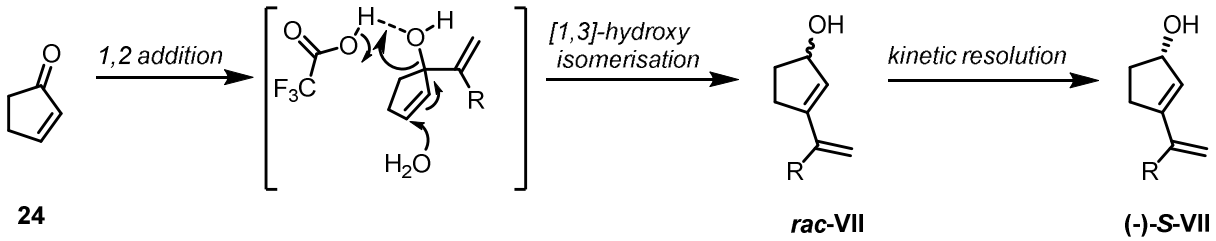


Figure 29 Synthesis of (-)-*S*-cyclopentenol-derivatives

In the case of kinetic resolution applying lipases, one enantiomer of the racemate reacts faster ($k_R >> k_S$) with an acyl donor (e.g. vinyl acetate, isopropenyl acetate...) by catalysis through lipase (triacylglycerol hydrolase). As a result, the (-)-*(S)*-enantiomer ***(S)*-VII** can be isolated, if the acetylation reaction is stopped at a conversion of about 50% (see Figure 30). This was typically achieved through reaction times of 17 to 23 hours, a lipase loading of 50 w/w% and an acyl-donor loading (vinylacetate) of 0.52 equivalents (Table 3).

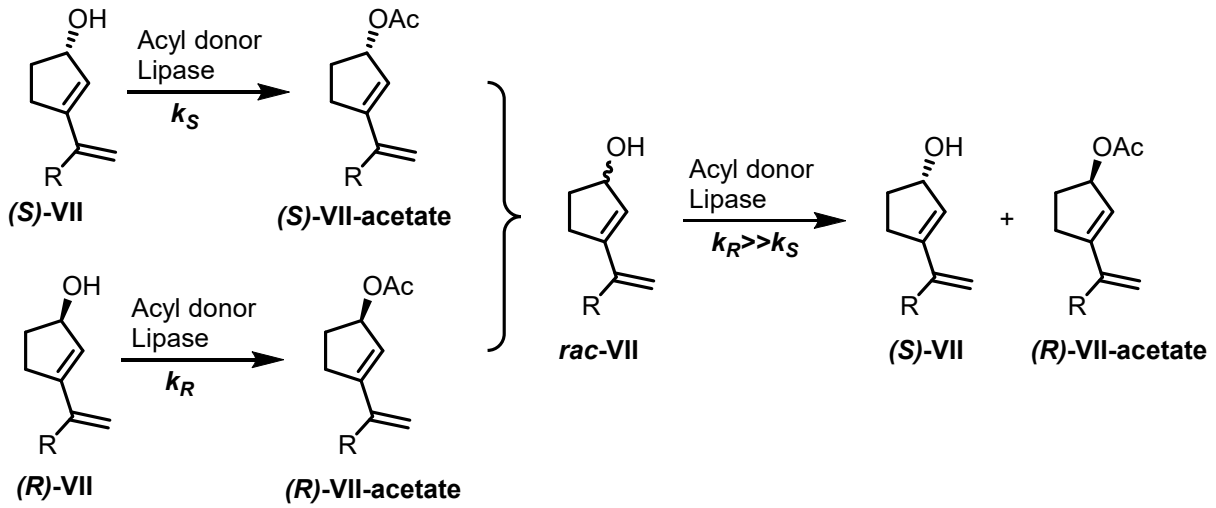


Figure 30 Kinetic resolution with lipase on the example of applied cyclopentenols

It has to be mentioned, that derivatives **33**-**62** have been resolved with Lipase PS in excellent ee, indicating a high selectivity ($k_R >> k_S$). Unfortunately, derivative **25** did not exhibit the same level of selectivity under the same conditions (Lipase PS, 0.52equiv. vinylacetate). Therefore, acylating conditions had to be changed from Lipase PS to Lipase PPL with an enhanced acyl donor loading (4 eqiv. vinylacetate), delivering (S)-3-vinylcyclopent-2-en-1-ol **25** in 90% ee. This can be associated to the sterical demand of the residue in 3-position of the cyclopentenol core, being the least with hydrogen. Increasing the sterical demand by one carbon or more, lipase selectivity and therefore ee's are increased.

Table 3 Isolated cyclopentenol-derivatives with ee

Product no.	-R	ee [%]	Yield [%]
25[a]	-H	90	21
62[b]	-Methyl	>99	46
33[b]	-Ethyl-	99	47
43[b]	-Cyclopropyl	>99	26
51[b]	-Trifluoromethyl	99	31
56[b]	-*t*-Butyl	>99	29
59[b]	-Phenyl	>99	33

Reaction conditions: a) LipasePPL, 4 eqiv. vinylacetate, 20h; b) Lipase PS, 0.52eqiv. vinylacetate, 17-23h;

This observation follows the empirical Kazlauskas rule[55], which explains the chiral recognition of lipases on secondary alcohols based on sterical interactions between homologues of secondary alcohols and the active site (pocket) of a lipase (Figure 31). In detail the Kazlauskas rule explains, depending on the difference in size of the hydroxymethane attached residues (generally annotated as small and large residue), the increase of enantioselectivity in kinetic resolution employing lipases. This is deduced from the fact, that lipases acylate both antipodes of a racemic secondary alcohol with different kinetics, based on the sterical bias of the substrate. Therefore one can control the enantioenrichment of either the substrate-alcohol or the product-acetate via conversion. Of course the theoretical yield in kinetic resolutions is lilmited by 50%, if one enantiomer reacts substantially faster ($k_R >> k_S$) than the other.

Thus it explains the (R)-enantioselectivity in acylation reactions of secondary alcohols of most lipases. As it has been demonstrated[46] that cyclopentenol **62** has (S)-configuration, all homologous cyclopentenols **25**-**59** (which just differ in the size of the large residue) must have (S)-configuration as well, following the Kazlauskas rule. This is further underlined by a (-) optical rotation of all resolved cyclopentenol derivatives. In consequence no individual

assignment of each cyclopentenol derivative in terms of absolute configuration has been conducted.

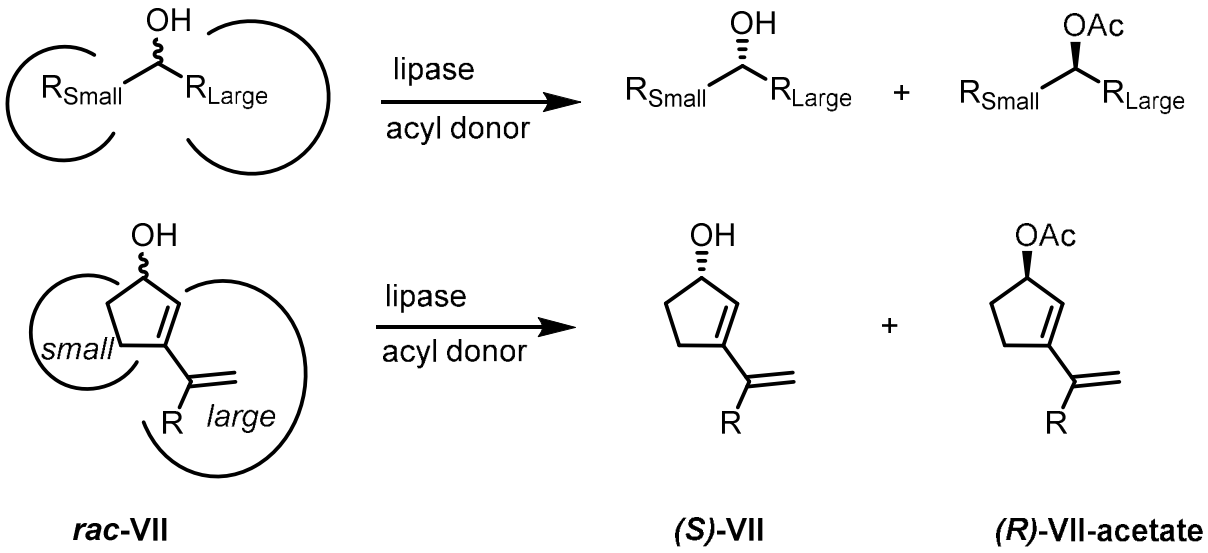


Figure 31 (R)-selectivity for acylation of secondary alcohols by Lipases according to Kazlauskas rule

Based on the above mentioned reasons it was concluded, that any optically active cyclopentenol exhibiting negative optical rotation, has the absolute configuration (S). Therefore no additional experiments were conducted to prove the assignment of the produced cyclopentenols, as they can be predicted by application of the Kazlauskas rule.

D II Synthesis of 7-Normethylvalerenic Acid (32)

D II.1 Synthesis of (S)-3-Vinylcyclopent-2-en-1-ol

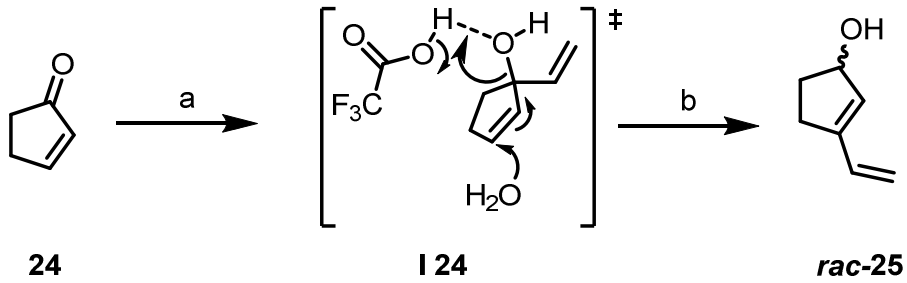


Figure 32 Reagents and conditions: a) Vinylmagnesium bromide, Et_2O, 0°C; b) H_2O, TFA, 0°C

The synthesis of *rac*-3-vinylcyclopent-2-enol, along with similar molecules, was published by Mulzer in 2011[46]. It represents an improvement (especially stepwise) for the synthesis of crucial intermediate **M8** (see B II.6.3), reducing the number of steps from seven to two. The underlying rationale is the 1,2-addition of a (vinylic) carbon nucleophile (here vinylmagnesium bromide) to α,β unsaturated ketone **24** and subsequent acidic rearrangement to the thermodynamically more stable conjugated dienol (here *rac*-3-vinylcyclopent-2-en-1-ol ***rac*-25**) as depicted in Figure 32. This 1,3-hydroxy shift is based on a Dauben-Michno rearrangement[56] where tertiary, allylic alcohols are 1,3-transpositioned and oxidized through pyridinium chlorochromate (PCC). Summing up, the labile tertiary allylic alcohol (generated through 1,2-addition) is protonated by catalytic amounts of TFA, while water attacks in a concerted way, exemplified by structure **I 24**, migrating the double bond towards the leaving oxonium ion. The result is a 2,4-dienol bearing both double bonds in conjugation, resulting in a thermodynamically more stable isomer than the isolated double bond configuration before rearrangement. It is noteworthy, that water is crucial for this rearrangement, being the origin of the transposed alcohol functionality. Without water the tertiary alcohol simply eliminates to a fully conjugated triene, respectively polymerizes!

Dienol ***rac*-25** was synthesized according to the published conditions. Unfortunately the 1,2 addition and subsequent rearrangement with TFA in an Et_2O/water mixture at 0°C proved to be very sluggish (multiple spots on TLC) resulting in isolated yields in the 30-40% range after several attempts. It was reasoned, that the water content of the biphasic ether/water mixture is too low, thus providing too little proportions of water preferring 1,3-hyroxy shift over other side reactions. Consequently it was expected, tha switching the solvent from ether to more polar and water miscible THF should resolve this problem. Unfortunately, side reactions like Grignard-reduction or 1,4-addition are predominant over 1,2-addition on enones in THF.[57] Fortunately Knochel et al.[58] addressed this problem before and found a

solution in the activation of the carbonyl functionality with oxophilic lanthanide salts, suppressing the aforementioned side reactions. These conditions were successfully adapted for the preparation of ***rac*-25** (see Figure 33).

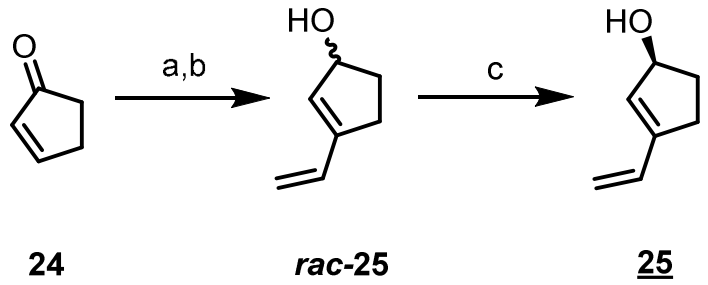


Figure 33 Reagents and conditions: a) 24+$LaCl_3$.2LiCl, vinylmagnesiumbromide, THF, 0°C; b) H_2O, then TFA, 0°C; 74%; c) lipasePPL, vinylacetate, MTBE, r.t., 21%

After pre-activation of cyclopentenone **24** with commercially available $LaCl_3$.2LiCl complex in THF, vinylmagnesiumbromide was added. Subsequent rearrangement in a THF-water mixture (2:1 v/v) worked cleanly according to TLC. Column chromatography (NEt_3 doped silica due to the acid-lability of allylic alcohols) afforded *rac*-3-vinylcyclopent-2-en-1-ol ***rac*-25** in 74% yield (comparable to 78% published yield[46]!). Finally *rac*-cyclopentenol ***rac*-25** was kinetically resolved with lipase PPL and excess vinylacetate (4 eqiv.) to deliver (S)-3-vinylcyclopentenol **25** in 90%ee and 21% overall yield from cyclopentenone **24**.

D II.2 Synthesis of (2aR,7aS,7bR)-3,4,6,7,7a,7b-hexahydroindeno[1-7-*bc*]furan-2(2a*H*)-one (26)

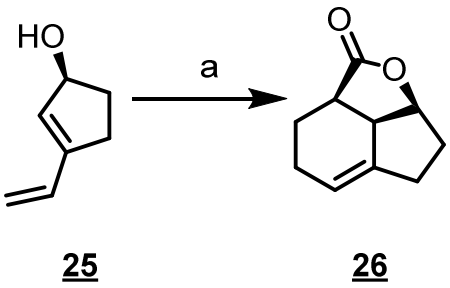
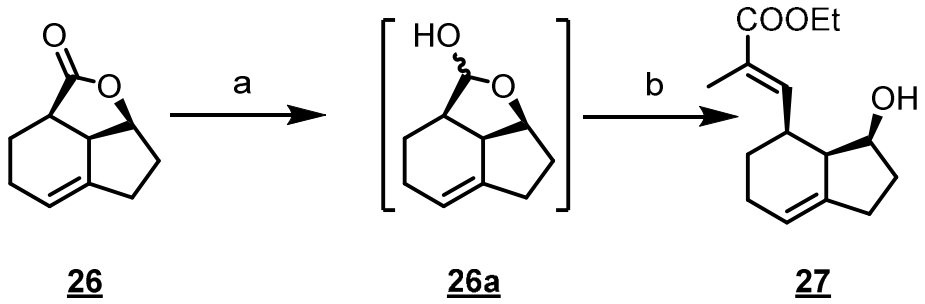


Figure 34: Reagents and conditions: a) $MgBr_2$.Et_2O, DIPEA, methacrylate, DCM, r.t., 79%

Conversion of alcohol **25** to lactone **26** (Figure 34) was performed through tethering the hydroxy group with the methacrylate carbonyl with divalent cation Mg^{2+} employing $MgBr_2$.Et_2O as magnesium source. Therefore $MgBr_2$-etherate complex was stirred with Hünig's Base (DIPEA) in DCM at room temperature, turning the solution magenta. Then

alcohol **25** was added slowly (addition velocity has an impact on the yield, meaning that slow addition is beneficial for a high yield!) and stirred for another hour before methacrylate was added. Acidic quench, extractive workup and column chromatography provided the desired lactone **26** in good yield of 79%.

D II.3 Synthesis of (E)-3-((3S,3aR,4S)-3-hydroxy-2,3,3a,4,5,6-hexahydro-1*H*-inden-4-yl)-2-methyl-acrylic-acid ethyl ester (27)

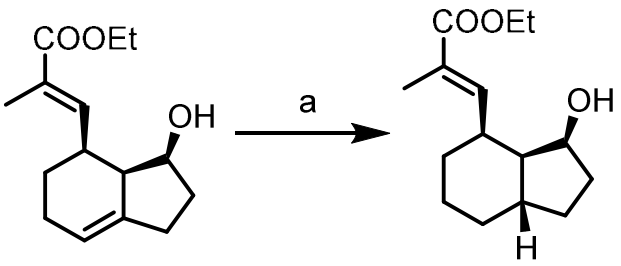


26 **26a** **27**

Figure 35 Reagents and conditions: a) DIBALH, DCM, -78°C, crude; b) (1-ethoxycarbonylethyliden)-triphenylphosphorane, toluene, 100°C, 82% over 2 steps;

Lactone **26** was first reduced with DIBALH at -78°C to the corresponding lactol **26a**. After extractive workup lactol **26a** was submitted to Wittig-olefination conditions with excess of phosphorane in toluene at 100°C. Under these conditions, only the E-isomere of hydroxy-ester **27** was formed in good yield of 82% over 2 steps (Figure 35). It is noteworthy to mention, that commercially available (1-ethoxycarbonylethyliden)-triphenylphosphorane has a limited storage stability (even under argon and in the freezer!), decreasing the yields in this type of transformation below 60%. Alternatively, (1-ethoxycarbonylethyliden)-triphenylphosphorane can be prepared by deprotonation of the corresponding phosphoniumbromide dissolved in DCM by simple extraction with 2M NaOH aqueous solution. The colorless DCM solution turns deep yellow when the ylide is formed upon deprotonation, yielding a sticky, yellow solid upon evaporation of the solvent. Using this freshly prepared reagent, the yield could be improved to 82% over two steps.

D II.4 Synthesis of (E)-3-((3S,3aR,4S,7R,7aR)-3-hydroxyoctahydro-inden-4-yl)-2-methyl-acrylic-acid ethyl ester (28)



27 **28**

Figure 36 Reagents and conditions: a) H_2, Ir(cod)(py)PCy_3, H_2, DCM, r.t. 97%

Next, the stereocenter at C7a was set via Crabtree-reduction.[48] The cationic iridium complex ([Ir(cod)(py)PCy_3]PF_6= Crabtree's catalyst)- with a strong electrophilic nature of the central iridium ion- is bound by the Lewis-basic hydroxy functionality, thus delivering dihydrogen to the olefin from the same side as the anchoring (-OH) group. Although the binding ability of Lewis basic groups for this catalyst - as suggested by Crabtree[48] based on experimental results- has the tentative order –$CONH_2$< -OH < -C=O < COOR< -OMe, the acrylate olefinic group is not reduced. This might be attributed to an electronic effect, as the α,β-unsaturated olefin is electron poor, due to the electron withdrawing ester group, compared to the endocyclic olefin bearing three slightly electron donating aliphatic residues. From a steric point of view both the exo- as well as the endocyclic double bond are trisubstitued, making steric effects negligible. So, based on the electronic nature of both trisubstituted double bonds, only diastereoselectivly hydrogenated **28** was obtained in almost quantitative yield of 97% within the hydrogenation of unsaturated hydroxy-ester **27,** which was already indicated by GC-MS (Figure 37)used for conversion control.

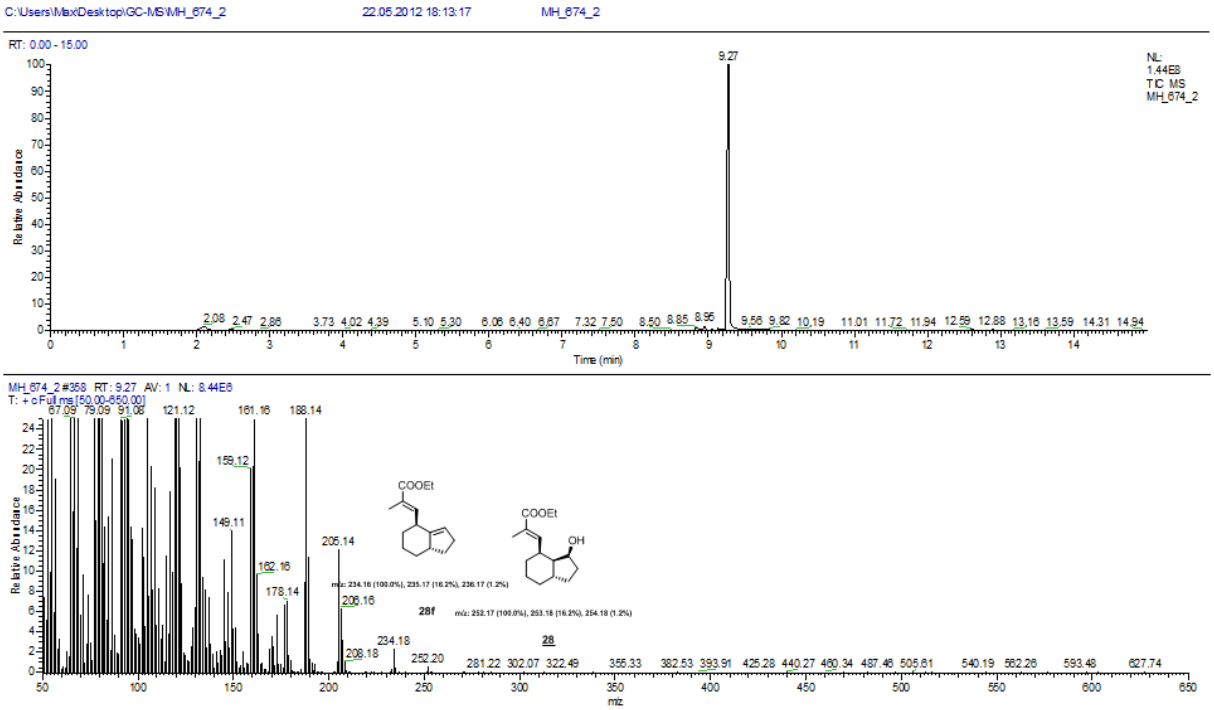
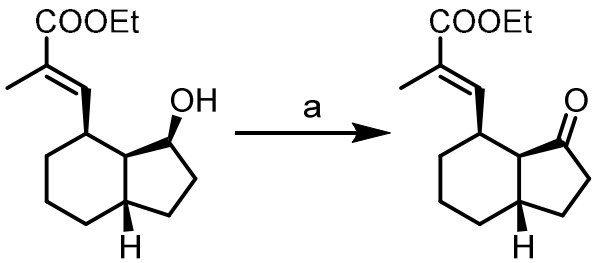


Figure 37 GC-MS spectrum oft he crabtree reduction of hydroxy ester 27

D II.5 Synthesis of (E)-2-Methyl-3-((3aR,4S,7aR)-3-oxo-octahydro-inden-4-yl)-acrylic-acid ethyl ester (29)



28 **29**

Figure 38 Reagents and conditions: a) SIBX, DMSO, r.t., 94%

After all stereocenters had been set successfully, the alcohol was oxidized to the corresponding ketone. Best results were obtained with commercially available SIBX[59] (a stabilized mixture containing benzoic acid, isophtalic acid and IBX= 2-iodobenzoic acid). Nevertheless, oxidation with DMP or IBX delivers ketone **29** in yields ranging from 80 to 90%. It is worth mentioning, that although SIBX is acidic due to its stabilizing additives, no epimerisation at C3a was observed. At first glance it might seem that the configuration of C3a is not of importance as the stereocenter in this requisite position is erased in later stages of the synthesis, anyway. Still, Mulzer et al. have reported, that the stereocenter at C3a-

respectively the conformation of the annulated 5-memberd ring- is crucial for successful regioselective installation of the vinylic methyl group at C3 (see D VII.4)[1].

D II.6 Synthesis of 7-Normethylvalerenic acid ethyl ester (31)

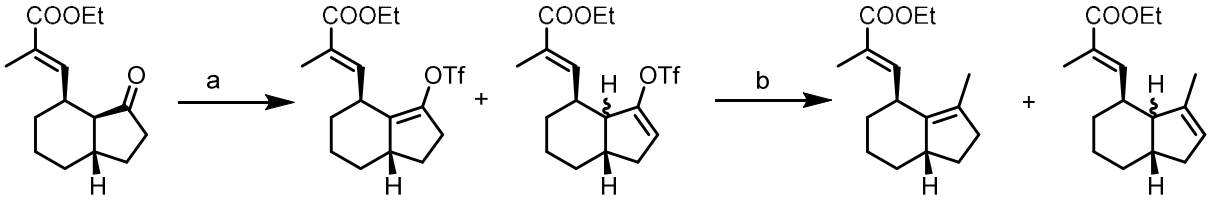


Figure 39 Reagents and conditions: a) 2,6-DTBP, Tf_2O, DCM, r.t., crude; b) $Pd(OAc)_2$, C-Phos, $Zn(Me)_2$, THF, 0°C to r.t.; 40%

For the endgame of the synthesis, the vinylic methyl group had to be installed via enoltriflatisation and subsequent Negishi-coupling. First, triflation of ketone **29** was tried according to the published conditions.[2] Interestingly, the literature conditions reported use 10 equivalents of pyridine and 10 equivalents of triflic anhydride. Such high reagent-loadings are rather counterintuitive for the conversion of a ketone to a triflate employing highly electrophilic triflic anhydride. After conducting the experiment under the stated conditions once successfully, but with no ability to reproduce enol triflate formation towards **30** ever again, the reason for these "unusual" conditions became evident. The problem associated to a reagent combination of triflic anhydride and pyridine is the fact, that both reagents in DCM form an insoluble salt (see Figure 40). Therefore all attempts to convert ketone **29** completely into enol triflate **30** failed as the reaction got stuck at around 10% conversion even after prolonged (several days!) reaction times. The reason for this is clearly the salt formation as triflic anhydride causes formation of a brown solid upon addition of pyridine even preventing magnetical stirring. Fortunately the undesired salt-formation could be impeded substituting pyridine by sterically demanding, *so called* "*proton scavengers*", such as 2,6-di-*t*-butylpyridine (2,6-DTBP) respectively its 4-methylated derivative[60].

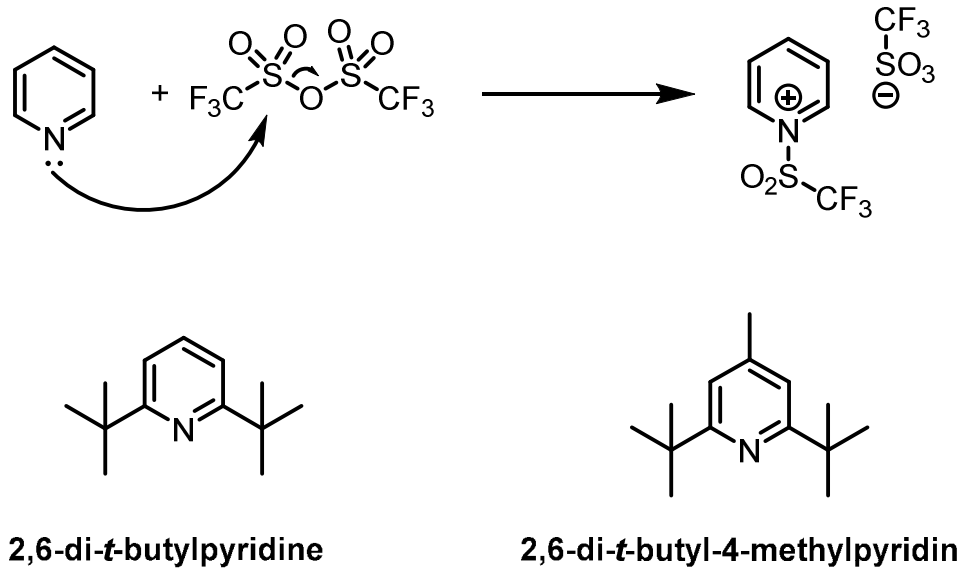
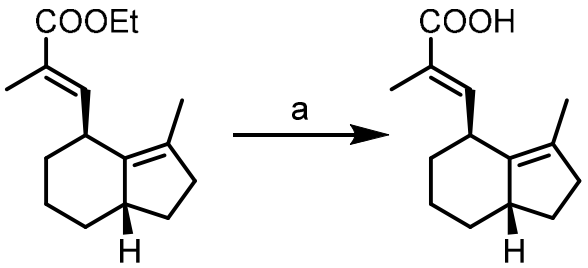


Figure 40 Pyridinium triflate-salt formation and sterically demanding pyridine bases

As a result, reaction equivalents of 2,6-di-*t*-butylpyridine and triflic anhydride could successfully be reduced from 10 to 2. Furthermore the reaction time dropped from 24 hours to three hours, delivering a mixture of enol triflates **30** and **30a** with a ratio of approximately 80:20 in favour of thermodynamically more stable triflate **30**. Neither prolonged reaction time (stirring for 24h does not change the initially formed ratio), nor lowering the equivalents of triflic anhydride to 1.2, changed the observed ratio. It has to be stated here, that the same ratio was observed applying pyridine as base. In addition, polymer bound 2,6-di-*t*-butyl-4-methylpyridine showed no improvement either. Therefore it was concluded, that this ratio seemed to reflect the equilibrium between thermodynamic **30** and kinetic **30a** enol triflate at room temperature and no further optimisation attempts were made.

The crude enol triflate is then subjected to Negishi coupling conditions. Like the initial enol triflate formation, the coupling was first conducted as reported in the literature applying $Pd(PPh_3)_4$ as catalyst along with four equivalents of dimethylzinc in THF. Unfortunately, different batches of $Pd(PPh_3)_4$ applied resulted sometimes in low conversion. Therefore the catalyst system was switched to a combination of $Pd(OAc)_2$ as palladium source and the sterically demanding Buchwald-Ligand C-Phos[61] resulting in full conversion after 15 hours and reproducible coupling yields. As expected, the isomeric ratio of 80:20 is not affected by Negishi-coupling conditions, leading to the same isomeric distribution of 80:20 after coupling. Still, 7-normethyl valerenic acid ester **31** could be isolated in 40% pure yield through column chromatography on 10% $AgNO_3$-doped silica[62].

D II.7 Synthesis of 7-Normethylvalerenic acid (32)



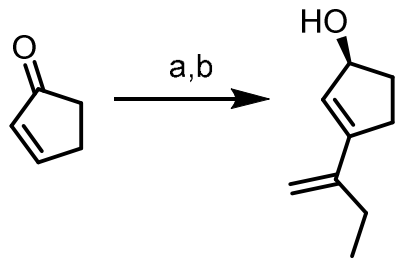
31 **32**

Figure 41 Reagents and conditions: LiOH.H_2O, iPrOH:H_2O = 2:1, 40°C

The final step in the synthesis was the hydrolysis of ethylester **31** to acid **32**. Hydrolysis conditions published by Altmann[42] (LiOH in an *i*-PrOH-H_2O mixture at 40°C) proved to be superior compared to the Mulzer conditions[2] (1M aqueous LiOH in THF-methanol at room temperature), as hydrolysis conducted in THF-methanol led exclusively to transesterification from ethyl- to methyl ester. Clearly this transesterifiaction is associated to methanol employed as a cosolvent. Therefore the hydrolysis in *i*-PrOH-water mixture offered a suitable solution for this problem. The workup procedure was slightly modified to the literature conditions to avoid column chromatography, which eroded yield upon purification presumably due to adsorption issues on silica caused by the carboxylate functionality. Instead, the basic reaction mixture was acidified by addition of Amberlite IR-120 (a polymer supported sulfonic acid), subsequently filtered and lyophyllized to yield 7-normethyl valerenic acid **32** in 99% yield (overall yield: 5% over 10 steps).

D III Synthesis of 7-Ethylvalerenic acid (40)

D III.1 Synthesis of (S)-3-(but-1-en-2-yl)cyclopent-2-en-1-ol (33)

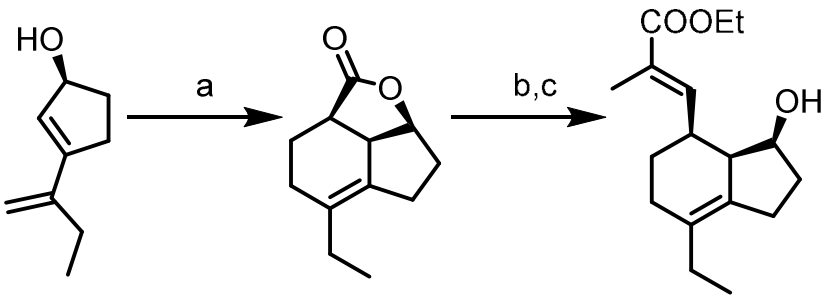


24 **33**

Figure 42 Reagents and conditions: a) 2-bromo-1-butene, *t*-BuLi, THF, -78°C, then H_2O, TFA, 0°C, crude; b) Lipase PS, MTBE, r.t., 47% over 2 steps

Compared to the synthesis of (S)-3-vinylcyclopentenol **25**, no carbonyl activation via $LaCL_3$.2LiCl was necessary, as *in situ* generated 2-lithio-1-butene added smoothly in a 1,2 fashion to cyclopentenone **24**. Subsequent 1,3-hydroxy shift was completed within 15 minutes, indicating a four-fold rearrangement rate compared to the unsubstituted vinyl analogue (1 hour). Additionally no intermediate purification before kinetic resolution was necessary, as there is no $LaCl_3$.2LiCl employed. Kinetic resolution was achieved as published[1] with Lipase PS delivering (S)-3-(but-1-en-2-yl)cyclopent2-en-1-ol **33** in 99%ee and 47% yield over two steps.

D III.2 Synthesis of (E)-3-((3S,3aR, 4S)-7-ethyl-3-hydroxy-2,3,3a,4,5,6-hexahydro-1H-inden-4-yl)-2-methyl-acrylic acid ethyl ester (35)

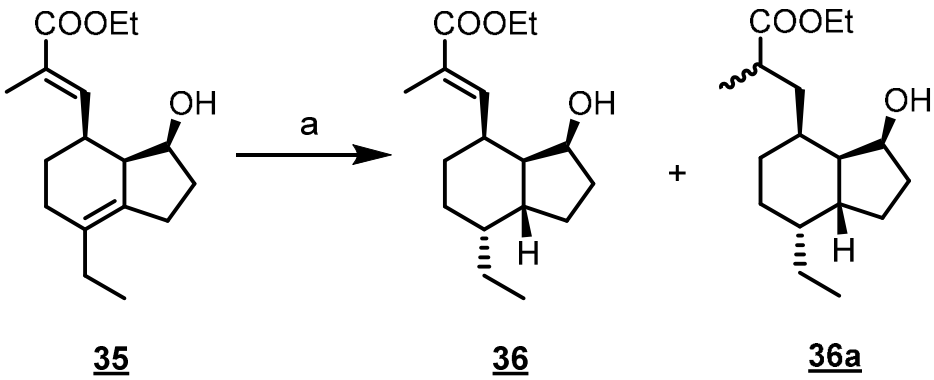


33 **34** **35**

Figure 43: Reagents and conditions: a) $MgBr_2.Et_2O$, DIPEA, methacrylate, DCM, r.t., 83%; b) DIBALH, DCM, -78°C, crude; c) (1-ethoxycarbonylethyliden)triphenylphosphorane, toluene, 100°C, 77% over 2 steps;

Hydroxy-directed Diels-Alder reaction of cyclopentenol **33** with methacrylate furnished lactone **34** with 83% yield (Figure 43), being in a comparable yield range with unsubstituted lactone **26** (79%). Reduction with DIBALH to the lactol and subsequent Wittig-olefination also worked in comparable yield (77% of **35** vs. 82% of **27**) to the initially performed reaction en route to 7-normethylvalerenic acid **32**.

D III.3 Synthesis of (E)-3-((3S,3aR, 4S, 7R, 7aR)-7-ethyl-3-hydroxyoctahydroinden-4-yl)-2-methyl-acrylic acid ethyl ester (36)



35 **36** **36a**

Figure 44 Reagents and conditions: a)cat. $Ir(cod)(py)PCy_3PF_6$, H_2, DCM, r.t., 53%;

While Crabtree-hydrogenation for C7-unsubstituted hydroxy ester **27** worked almost quantitatively (94%), ethyl substituted hydroxy-ester **35** could only be reduced in 53% yield to **36** **(**for the valerenic acid intermediate **64** 72% yield was published and *en rote* to ketone **65** 74% were isolated) . This is quite a significant difference caused by the ethyl substituent at position C7. As already indicated (see chapter D II.4), preferred chemoselective reduction of the endocyclic over the exocyclic double bond is an issue. While the selectivity for hydrogenation of unsubstituted **27** is only determined by electronic factors - as the electron poor trisubstituted acrylate olefin stays untouched and exclusively the electron-rich trisubstituted endocyclic double bond gets reduced – steric factors seem to play a dominating role when the endocyclic double bond is tetrasubstituted. In this case a tetrasubstituted, electron rich olefin competes with an electron poor trisubstituted olefin. This results in an unselective hydrogenation observed during the reaction, as overreduced (exo-and endocyclic double bond hydrogenated) product **36a** is already formed before all starting material **35** is consumed (observed by GC-MS,Figure 45). Unfortunately starting material **35** and product **36** have the same R_f-value on silica, which makes a separation via classical column chromatography impossible. As a consequence there is no possibility to stop the hydrogenation before full conversion of **35** to keep losses, due to overreduction to **36a**, low and concomitantly recycle reisolated **35**. To address this problem, the reaction temperature was lowered from 25°C to 0 C° in the aspiration to avoid overreduction to **36a**. Unfortunately, no reaction occurred at 0°C, while reaction at 10°C just slowed down the

hydrogenation but did not display any beneficial effect in selectivity. Decreasing the catalyst loading from 0.1 equivalents to 0.05 resulted in no conversion of **35** which was puzzling at the beginning. But it was observed, that with half catalyst loading the reaction mixture turned immediately deep yellow after Crabtree's catalyst was added and hydrogen was bubbled through the solution. This unusual colour change at this stage of the reaction (usually the reaction turns deep yellow when already finished) together with the observation of no reaction progress, led to the conclusion, that the catalyst got deactivated. Indeed, it was published by Crabtree himself in 1979[63] that irreversible deactivation of $Ir(cod)(py)PCy_3PF_6$ is observed due to the formation of hydride-bridged binuclear iridium clusters, which are coloured in yellow. In retrospect it seems quite logical that with increased hydrogen concentration with respect to iridium catalyst, the formation of hydride-bridged clusters is favoured. With this gathered knowledge, no further optimisation attempts were made, as the steric and electronic profile of the substrate seems to direct the selectivity of this hydrogenation.

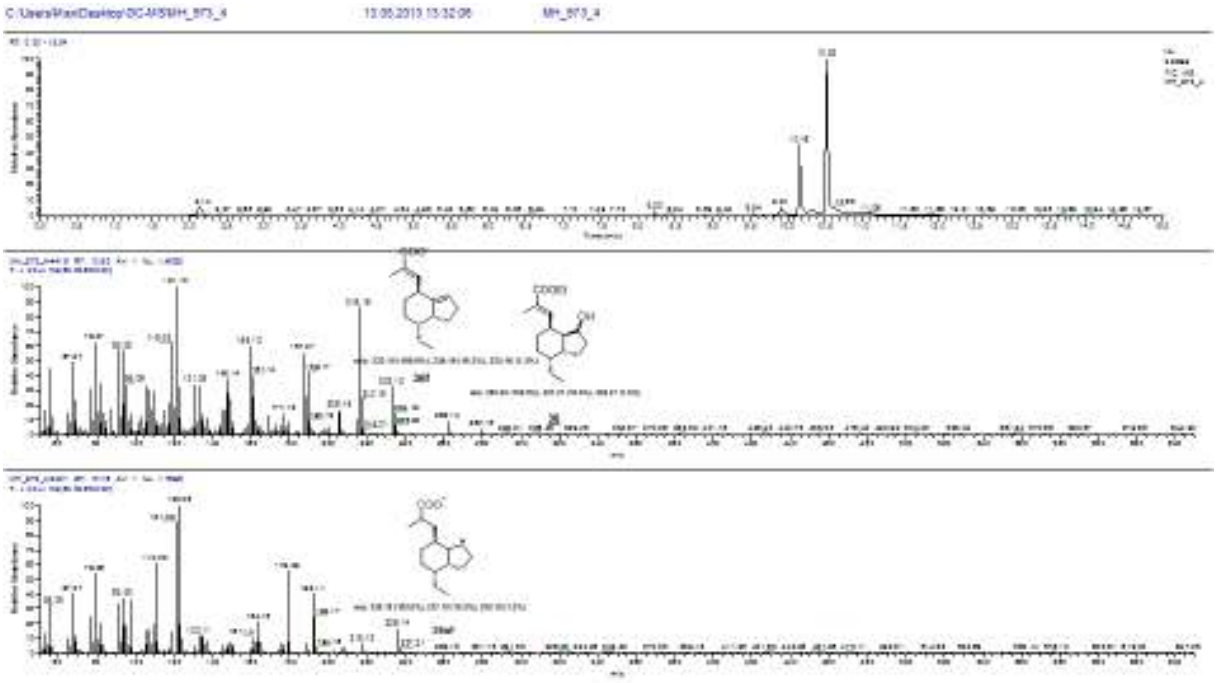


Figure 45 GC-MS spectrum of the crabtree reduction of hydroxy ester 35

D III.4 Synthesis of 7-Ethyl-valerenic acid (40)

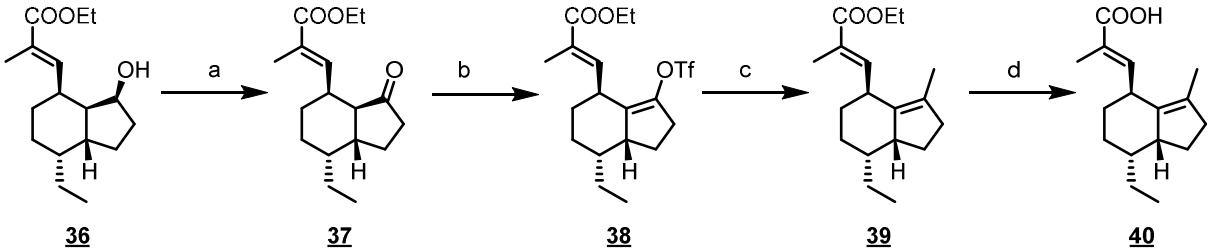


Figure 46 Reagents and conditions: a) SIBX,DMSO, r.t., 80%; b)2,6-di-*t*-butylpyridine, Tf_2O, DCM, crude; c) cat. $Pd(OAc)_2$, C-Phos, dimethylzinc, THF, 0°C to r.t., 48%; d) LiOH.H_2O, iPrOH:H_2O= 2:1, 40°C, 99%

The remaining reaction sequence towards 7-ethylvalerenic acid **40** worked as previously described (see D II.3 to D II.7). Oxidation with SIBX in DMSO furnished ketone **37** in 80% yield. Subsequent formation of enol triflate **38** under standard conditions again gave a mixture of isomeres (not depicted) in about the same ration of 80:20, leading to this exact mixture of products after Negishi-coupling (Figure 46). This eventually resulted in a pure yield of single isomer **39** of 48%, which upon hydrolysis (quantitative) provided 7-ethylvalerenic acid **40** in 6% overall yield in 10 steps from cyclopentenone **24**.

D IV Synthesis of 7-Cyclopropylvalerenic acid (50)

D IV.1 Synthesis of precursor 1-(Iodovinyl)cyclopropane (42)

Vinyl iodide **42** was prepared via a method developed by Hoveyda et al.[64] For a better understanding the mechanism for the conversin of terminal alkynes to α-vinyl halides (or α-vinyl boronates) shall be briefly discussed (see Figure 47).

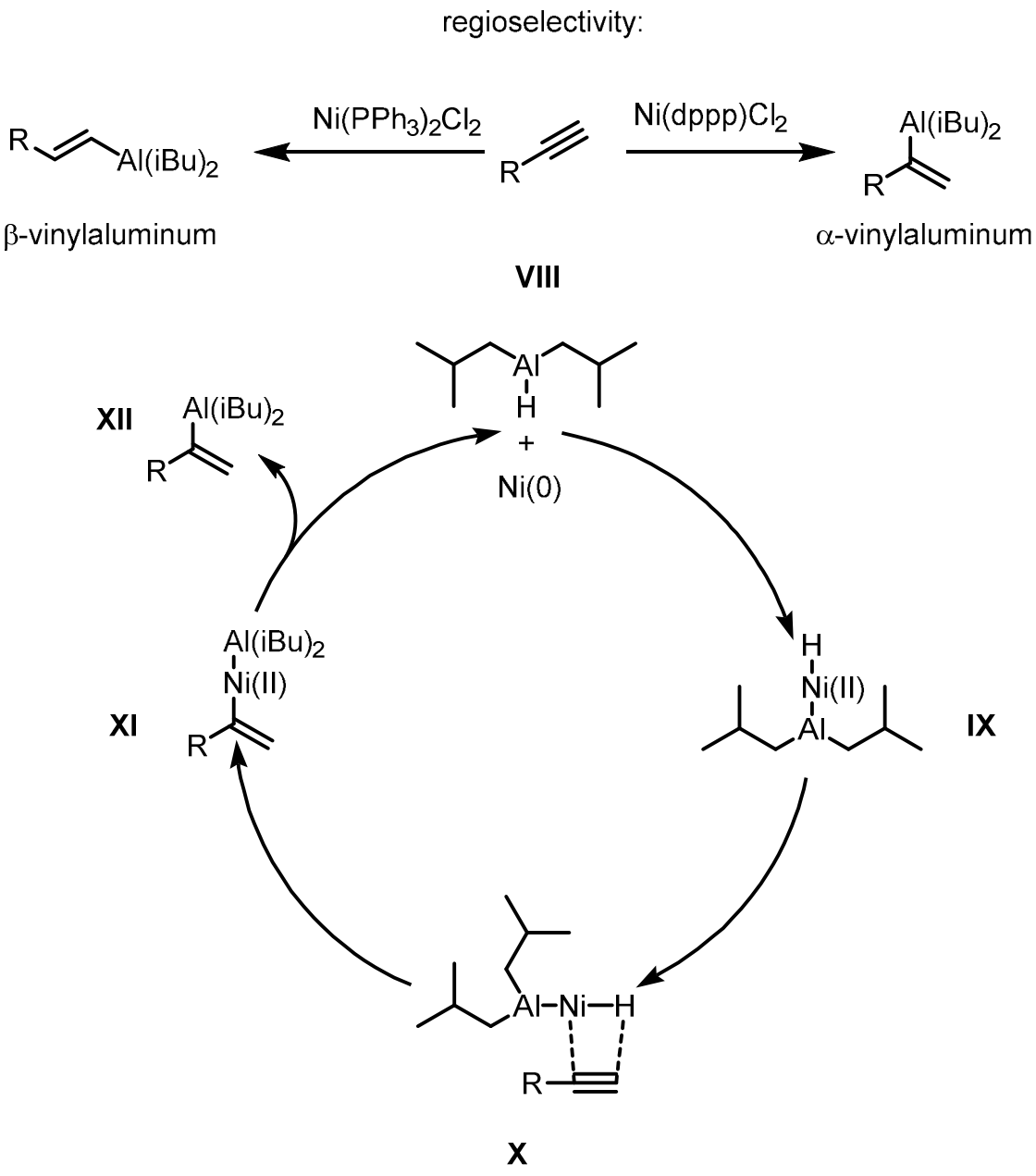


Figure 47 Mechanism of α-selective hydroalumination

Interestingly, the property of the ligand, which is bonded to nickel, determines the regioselectivity of this reaction. While monodentate phosphine ligands (like PPh_3) selectively catalyze DIBALH-addition in a terminal fashion (β-product), bidentate bis,1,3-bis(diphenylophosphine)propane (dppp) ligands reverse the selectivity to internal (α-product) addition.

The actual catalytic species is a Ni(0) complex (formed by reduction of Ni(dppp)Cl_2 with excess DIBALH) that oxidatively inserts into the Al-H bond (**VIII**) to give Al-Ni-hydride (**IX**). This bimetallic hydride adds in a *syn*-fashion to a terminal alkyne (**X**) forming an organo-nickel complex (**XI**). After alkenyl-aluminium reductive elimination, catalytically active Ni(0) is regenerated and the desired α-vinylaluminium species (**XII**) is formed. The formed vinylaluminium is a soft nucleophile that can be transformed into a halide (via halo-succinimide or elemental halogen), boronate (via boronic esters) or even cross coupled depending on the electrophile employed.

In the course of the synthesis towards a cyclopropylvinyl halide, which provides access to a cyclopropyl residue at C7 on the indanyl core of a valerenic acid analogue, first it was attempted to synthesize 1-(bromovinyl)cyclopropane. Although initial small scale experiments looked very promising in terms of accessibility of the desired product, scale-up experiments revealed its inaccessibility. It was found, that the initial hydroalumination-reaction works cleanly and with the desired α-selectivity. Unfortunately, trapping of the intermediate hydroaluminum with recrystallized NBS at a 10 mmol scale produced a complex mixture of (presumably) polymerized and overbrominated products, although the reaction working fine in a 1mmol scale. Switching to basified bromine as halide source (stirring bromine for two hours with basic alumina with subsequent filtration over basic alumina) even worsened the outcome, as elemental bromine reacted vigorously at even -78°C. As a consequence the halide source was changed into elemental iodine, expected to be less reactive upon addition then bromine. Indeed the change of the electrophile turned out to be the breakthrough for a clean reaction. Eventually 1-(iodovinyl)cyclopropane **42** could be obtained after distillation in 34% yield along with 7% isobutyliodie **42a** (presumably resulting from reductive elimination of (*i*-Bu)$_2$Al-I).

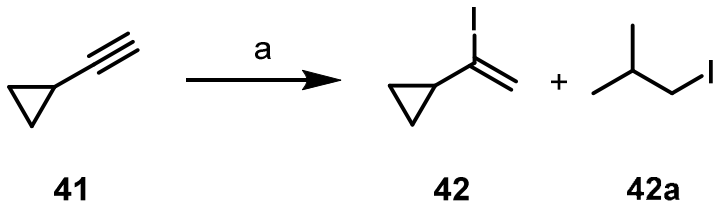
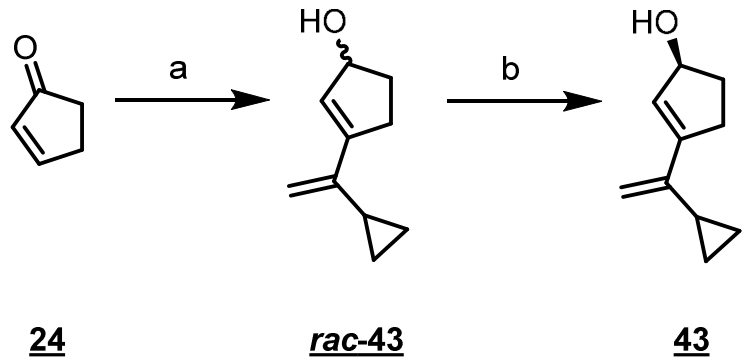


Figure 48: Reagents and conditions: a) cat. Ni(dppp)Cl_2, DIBALH, I_2, THF, 0°C to r.t. to -78°C, THF, 34% (along with 7% isobutyliodide 42a)

D IV.2 Synthesis of (S)-3-(1-cyclopropylvinyl)cyclopent-2-en-1-ol (43)

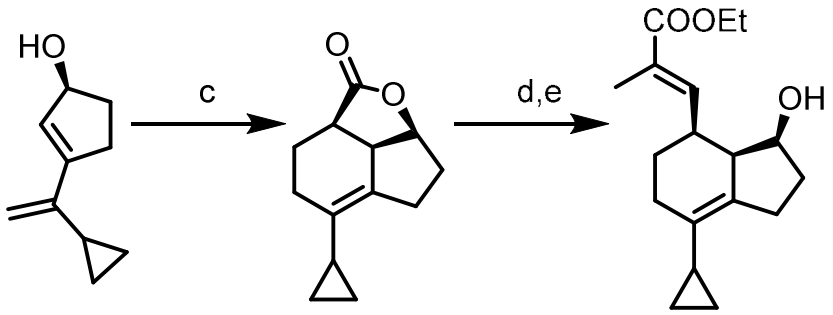


24 ***rac*-43** **43**

Figure 49: Reagents and conditions: a) 1-(Iodovinyl)cyclopropane 42, $LaCl_3$.2LiCl, t-BuLi, TFA, THF,-78°C, 61%; b) LipasePS, vinylacetate, MTBE, r.t., 43%;

Again cyclopentenone **24** was activated with $LaCl_3$.2LiCl for selective 1,2 addition of lithiated vinyliodide **42** (Figure 50). Subsequent rearrangement delivered cyclopentenol ***rac*-43** in 61% yield after column chromatography. As vinyliodide **42** was not employed in pure form (7% *iso*-butyliodide as impurity), column chromatography was necessary to obtain ***rac*-43** in pure form for subsequent kinetic resolution with lipase PS delivering (S)-3-(1-cyclopropylvinyl)cyclopent-2-en-1-ol **43** in 43% yield and >99% ee (combined yield over two steps: 26%).

D IV.3 Synthesis of (E)-3-((3S,3aR, 4S)-7-cyclopropyl-3-hydroxy-2,3,3a,4,5,6-hexahydro-1H-inden-4-yl)-2-methyl-acrylic acid ethyl ester (45)

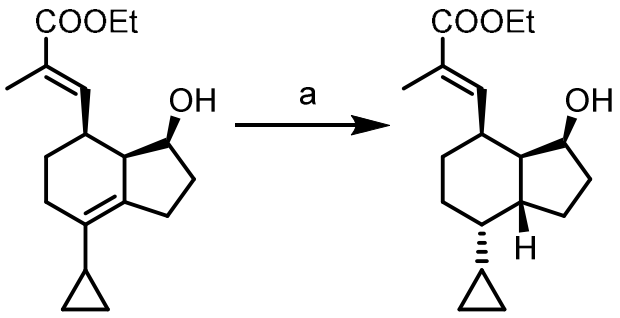


43 **44** **45**

Figure 50: Reagents and conditions: a) $MgBr_2.Et_2O$, DIPEA, methacrylate, DCM, r.t., 75%; b) DIBALH, DCM, -78°C, crude; c) (1-ethoxycarbonylethyliden)triphenylphosphorane, toluene, 100°C, 74% over 2 steps;

As expected, lactonisation towards **44** worked with 75% yield which is within the familiar range. The same applied for generation of hydroxy ester **45** which was obtained with 74% yield over two steps including reduction to the according lactol, followed by Wittig-olefination (Figure 50).

D IV.4 Synthesis of (E)-3-((3S,3aR, 4S, 7R, 7aR)-7-cyclopropyl-3-hydroxyoctahydroinden-4-yl)-2-methyl-acrylic acid ethyl ester (46)



45 **46**

Figure 51: Reagents and conditions: a) cat. $Ir(cod)(py)PCy_3PF_6$, H_2, DCM, r.t., 49%;

Crabtree reduction of **45** delivered hydroxy-ester **46** in 49% yield. Again the sterical congestion on the endocyclic double bond caused regioselectivity problems during reduction (see GC-MS . Here in principle the same arguments as for the according ethyl-derivative **36** explain the moderate yield. Both, the ethyl and the cyclopropyl derivative are obtained with about 50% yield (53% vs. 49%) which reflects their similar steric impact (see discussion D III.3).

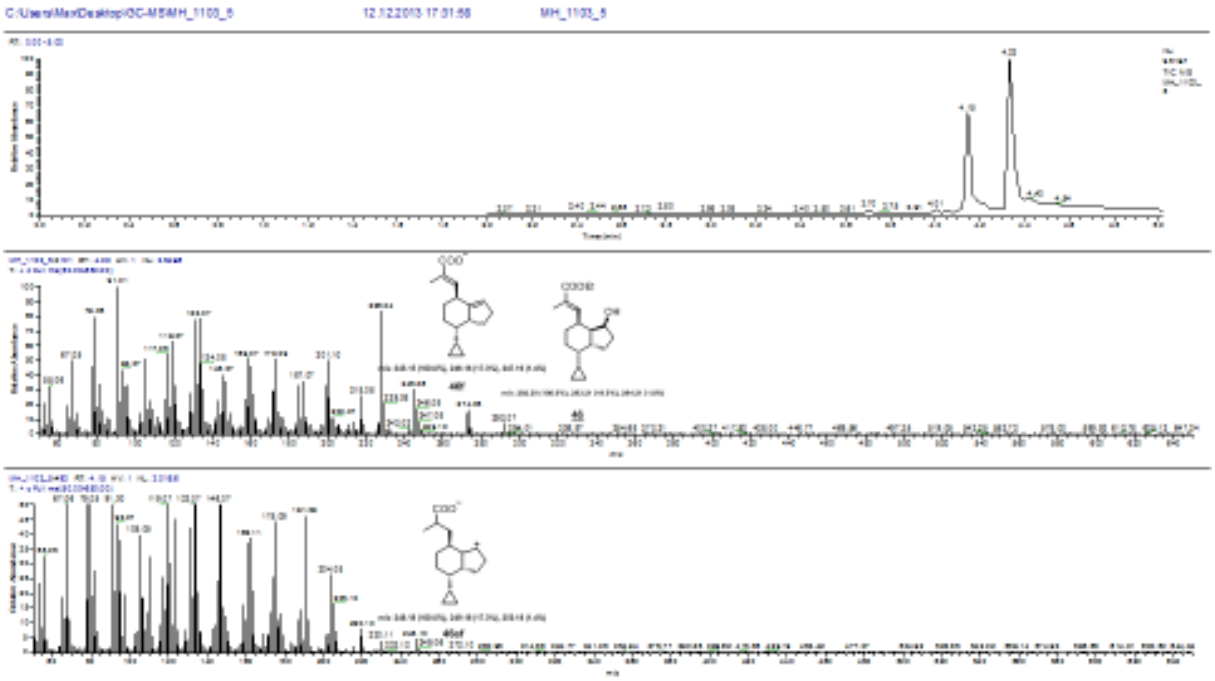
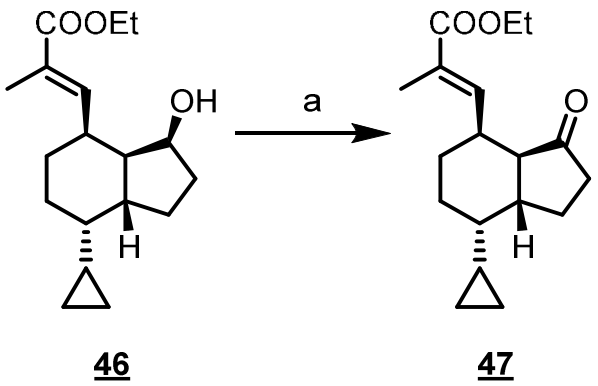


Figure 52 GC-MS spectrum oft he crabtree reduction from hydroxy ester 45

D IV.5 Synthesis of (E)-2-methyl-((3aR, 4S, 7R, 7aR)-7-cyclopropyl-3-oxo-octahydroinden-4-yl)-2-methyl-acrylic acid ethyl ester (47)



46 **47**

Figure 53: Reagents and conditions: a) IBX, DMSO, r.t., 73%

Oxidation of hydroxy-ester **46** with IBX in DMSO worked moderately with 73%. It is noteworthy that ketone **47** seems to be more prone to epimerisation than C7-ethyl (**37**) and C7-normethyl (**29**) derivatives. It was observed that the slightly acidic NMR-solvent $CDCl_3$ epimerizes **47** at C3a. This, in consequence, disfavours the distribution of isomers during the upcoming enoltriflatisation and coupling events. As it was already demonstrated (see D II.6 and D III.4), even diastereomerically pure ketone ends up to be epimerized to an extent of 20% under triflatisation conditions. Therefore it was expected, that already epimerized ketone would give an even worse ratio of enol-triflate isomeres than the usually observed 80:20 mixture. Indeed this happened to be the case, as under these conditions, starting from epimerized ketone **47**, undesired enol triflate was formed nearly exclusively (92:8 !!). Therefore ketone **47** had to be prepared once again, taking caution not to epimerize it (NMR measurements in D2-dichloromethane!). For a detailed discussion about epimeristaion at C3a see D VII.4.

D IV.6 Synthesis of 7-Cyclopropyl-valerenic acid (50)

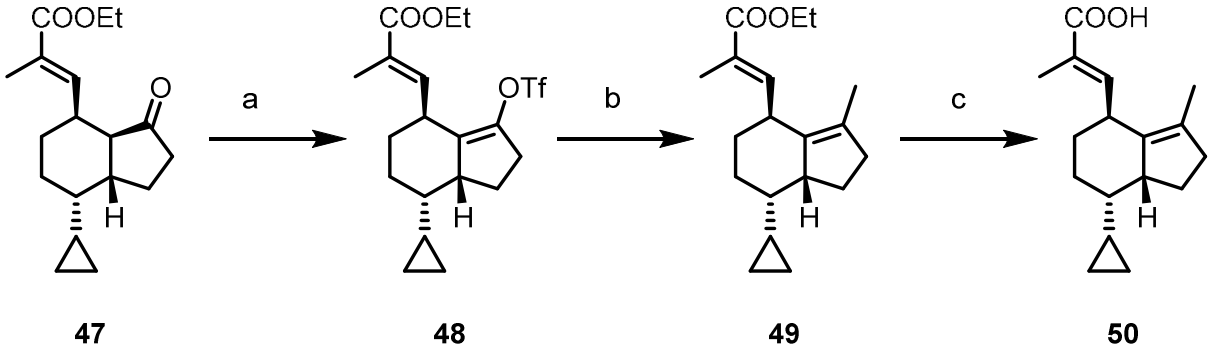


Figure 54: Reagents and conditions: a) Tf_2O, 2,6-DTBP, DCM, r.t, crude; b) cat. $Pd(OAc)_2$, C-Phos, dimethylzinc, THF, 0°C-r.t., 63% as a mixture of isomers; c) LiOH, iPrOH:H_2O=2:1, 40°C, 97% as a mixture of isomers

Due to the conformational instability of ketone **47** (as discussed in D IV.5), enol triflatisation conditions were slightly adapted to avoid acidic conditions. To achieve this, the usually conducted enol-triflatisation conditions, involving 2 equivalents of sterically hindered base (DtBP) as well as triflic anhydride, were modified towards an excess of base (1.5 eqiv. of Tf_2O and 3 eqiv. of DtBP). Without further screening this assured a ratio of triflate isomers of 79:21. Subsequent Negishi coupling of the crude mixture provided 63% as a mixture of isomers of the same ratio. Interestingly, C7-cyclopropyl substituent is not compatible with $AgNO_3$-doped silica. Submission of the crude mixture of ethyl ester **49** resulted in no isolation of any product after column chromatography, implying either complete adsorption or degradation on $AgNO_3$-doped silica. At least the adsorption phenomenon can be rationalized with cyclopropyl-rings being isolobal to olefines thus interacting with Ag^+-ions. Indeed such interactions have already been proposed in the literature[65]. As a result, the isomers were not separated from each other at this stage (possible through preparative HPLC), thus applying purification on unmodified silica. Finally hydrolysis under standard conditions leads to a mixture of isomers, steming from the Negishi-coupling, with the main constituent being 7-cyclopropylvalerenic-acid **50**. If compound **50** had any pharmacological impact, it would have been synthesized in isomerically pure form of course.

D V Towards the synthesis of 7-trifluoromethylvalerenic acid

D V.1 Synthesis of (S)-3-(3,3,3-trifluoroprop-1-en-2-yl)cyclopent-2-en-1-ol (43)

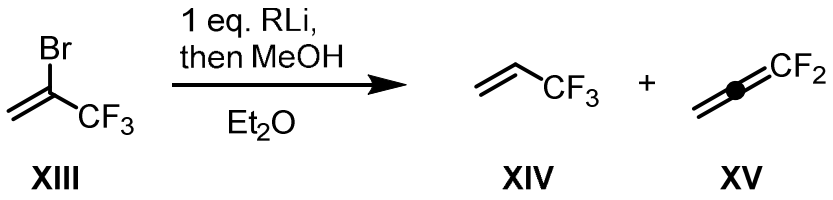


Figure 55 Lithiation of fluorinated vinylbromide

Table 4 Product distribution after lithiation at different temperatures in Et_2O

R	T [°C]	XIII	XIV	XV
***n*-Bu**	-78	17%	20%	54%
***n*-Bu**	-96	58%	31%	11%
***n*-Bu**	-105	76%	14%	1%
***s*-Bu**	-105	10%	60%	26%
***t*-Bu**	-105	5%	50%	35%

Performing 1,2-addition of *in situ* lithiated 2-bromo-3,3,3-trifluorpropene **XIII** under the prior established conditions at -78°C in THF turned out to be not feasible. Upon addition of *t*-Buli to 2-bromo-3,3,3-trifluorpropene at -78°C the reaction mixture immediately turned dark violet already indicating a different reaction pathway as expected prior. When cyclopentenone **24** was then added to this reaction mixture no evidence of successful 1,2-addition was found (neither TLC nor GC-MS). A quick literature research revealed the fact that lithiation of fluorinated vinyl bromides is not a trivial task. Due to their thermal instability, lithiated trifluoromethylvinyl-reagents tend to form difluorinated allenes **XV** via loss of LiF[66,67]. A distribution of species formed by lithiation of 2-bromo-3,3,3-trifluorpropene is depicted in Figure 55 and Table 4 as found by Nadano and Ichikawa. It seems to be rational that in a more polar solvent than diethylether (e.g. THF), elimination of LiF towards allene **XV** would be the preferred reaction. Therefore a reaction setup in Et_2O at -105°C was chosen for lithiating **XIII**. At this temperature only about 50% of vinylbromide **XIII** got lithiated, causing

the need for 3.5 equivalents of vinyl halide source for complete 1,2-addition of cyclopentenone **24**. As the stability of lithiated **XIII** is rather limited, the carbonyl-function of **24** was activated with $LaCl_3.2LiCl$ to assure highest possible conversion to 1,2-addition product **I 51** (see Figure 56). For a smooth rearrangement of **I 51** to cyclopentenol ***rac*-51** the solvent was exchanged from ether to THF/water mixture. Due to the electron withdrawing effect of the trifluoromethyl substituent –concomitantly making 1,2-addition product **I 51** quite stable - 1,3-hydroxy shift from **I 51** to ***rac*-51** was performed at room temperature over a course of 85 minutes. Intermediate purification via column chromatography on NEt_3-doped silica provided ***rac*-51** in 68% yield. Finally, kinetic resolution with Lipase PS furnished (S)-3-(3,3,3-trifluoroprop-1-en-2-yl)cyclopent-2-en-1-ol **51** in 45% yield and 99% ee.

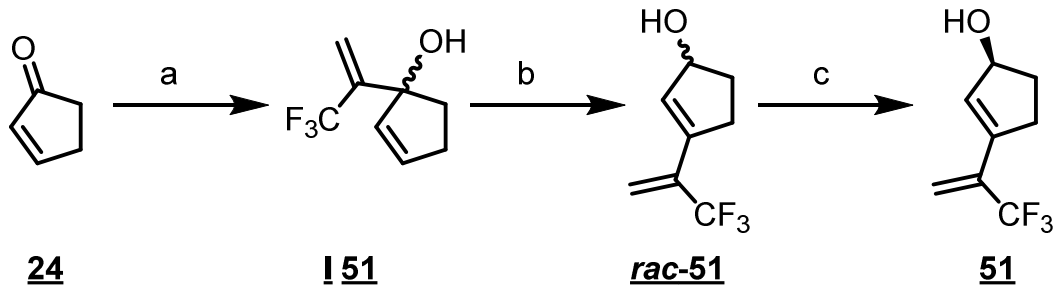


Figure 56 Reagents and conditions: a) 2-bromo-3,3,3-trifluoropropene, t-BuLi, Et_2O, -105°C, crude; b) TFA, THF/H_2O, r.t., 68% over two steps c) Lipase PS, vinylacetate, MTBE, r.t., 45%;

D V.2 Synthesis of (E)-3-((3S,3aR, 4S)-7-(trifluoromethyl)-3-hydroxy-2,3,3a,4,5,6-hexahydro-1*H*-inden-4-yl)-2-methyl-acrylic acid ethyl ester (53)

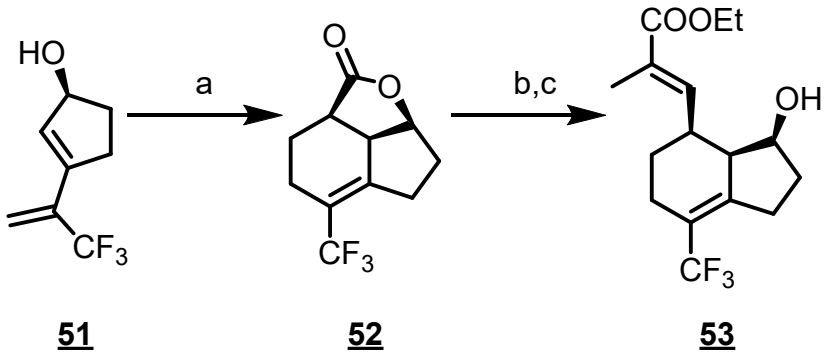
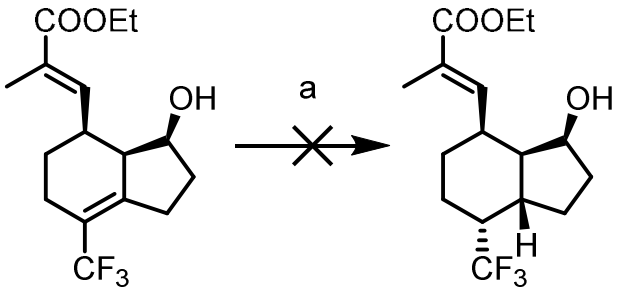


Figure 57 Reagents and conditions: a) $MgBr_2.Et_2O$, DIPEA, methacrylate, DCM, r.t., 77%; b) DIBALH, DCM, -78°C, crude; c) (1-ethoxycarbonylethyliden)-triphenylphosphorane, toluene, 100°C, 71% over 2 steps;

Cyclopentenol **51** was converted to lactone **52** under standard conditions yielding 77%. Subsequent reduction and Wittig-olefination delivered hydroxy-ester **53** in 71% over two steps (Figure 57). Both the Diels-Alder reaction and the Wittig-olefination worked in the

same yield range as demonstrated on other derivatives before and no unexpected reaction behavior was observed.

D V.3 Attempted synthesis of (E)-3-((3S,3aR, 4S, 7R, 7aR)-7-(trifluoromethyl)-3-hydroxyoctahydroinden-4-yl)-2-methyl-acrylic acid ethyl ester (53a)



53 **53a**

Figure 58 Reagents and conditions: a) cat. $Ir(cod)(py)PCy_3PF_6$, H_2, DCM, r.t.;

As already discussed in previous chapters (see chapters D II.4, D III.3, D IV.4) the substituent at C7 plays a crucial role in selective Crabtree hydrogenation. Although the sterical demand of trifluoromethyl is minor compared to ethyl or cyclopropyl, no reduction of the endocyclic double bond was achieved. Monitoring the reaction via GC-MS revealed a complex product mixture, where no mass could be directly assigned to product **53a**. The GC-MS for the starting material **53** is depicted in Figure 59. From the chromatogram (see Figure 60 and Figure 61) of a sample taken after 45minutes, a mixture of 4 different materials is visible. The peak at retention time 9.54 can be clearly assigned to hydroxyl ester **53**. For the other three peaks (r.t.: 9.19 minutes, 9.25 minutes, 9.33 minutes) assignment to a dedicated structure gets difficult, as it is not clear if those peaks are fragment peaks or mass peaks. Still a tentative assignment to fragment peaks is depicted in Figure 60 and Figure 61. If this tentative assignment is correct (which cannot be proven as no nmr was measured of this complex mixture), it would indicate a double reduced product **53a f overreduced**(Figure 60; r.t: 9.19 min; m/z= 276.15), an endocyclic reduced (desired) product **53a f** (Figure 61; r.t.: 9.25 min; m/z= 274.07) and a product having the exocyclic double bond reduced **53 f exo** (Figure 61;r.t.:9.33; m/z= 274.04). Still it has to be pointed out, that the structural assignment is based on mass-spectra and no m/z=320 – the mass of **53a** – could be found, whereas in the successful reduction of hydroxyl-esters **27** (D II.4), **35** (D III.3), **45** (D IV.4) and 64 (E I.1) the appropriate mass-peak of the product was always found!.Although these products were not isolated and characterized via nmr, it is clear from the observed GC-MS that the exocyclic double bond interfers with the reaction conditions, thus making this route not viable.As there was no clear indication of **53a** formed, this synthetic route proved to be a dead end in the synthesis towards trifluoromethylated valerenic acid C7-derivatives. An alternative approach lacking an exocyclic double bond at this stage- that failed as well- will be discussed in chapter F I.1

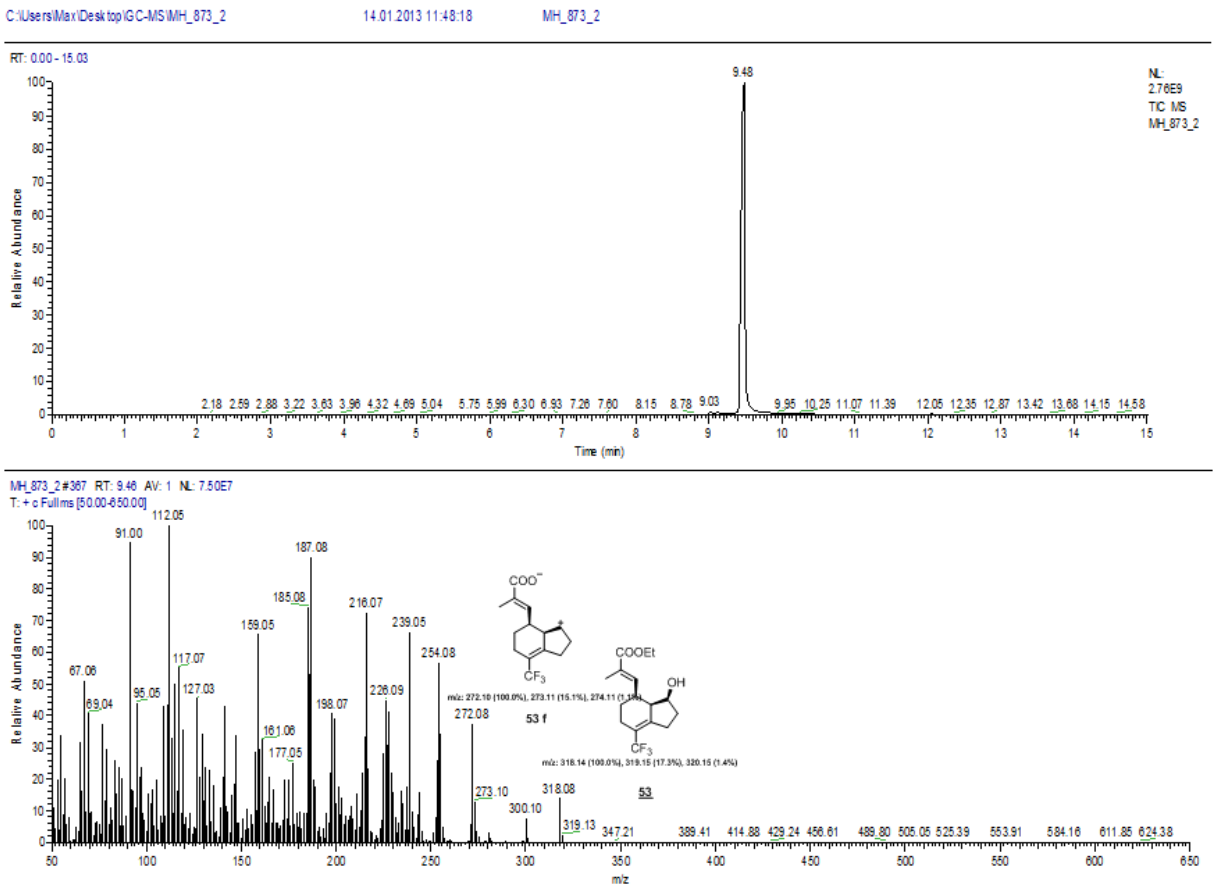


Figure 59 GC-MS spectrum of starting material 53

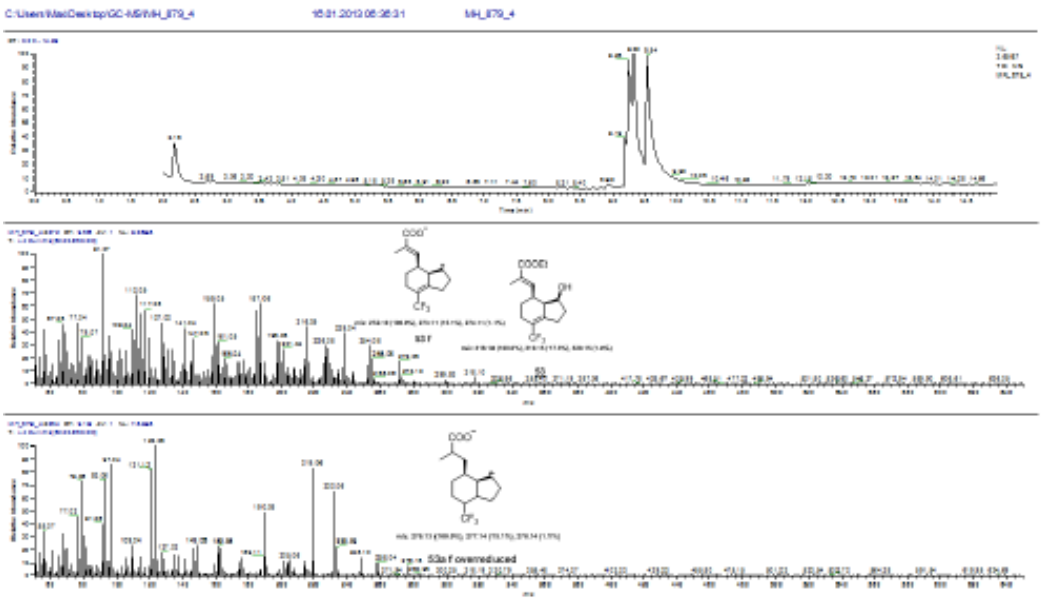


Figure 60 GC-MS of crabtree reduction of hydroxy ester 53 after 45 minutes (1)

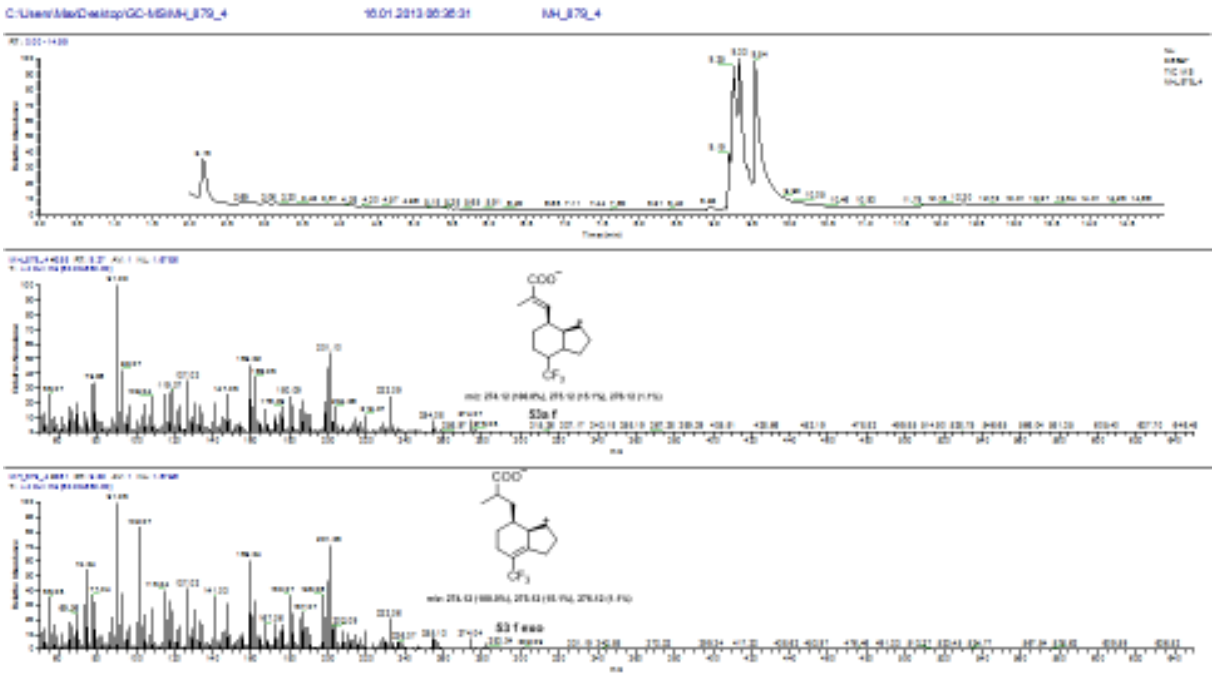
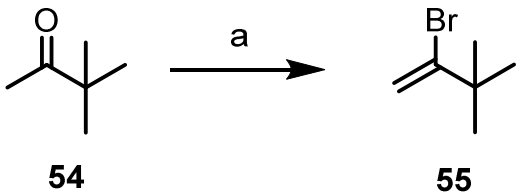


Figure 61 GC-MS of crabtree reduction of hydroxy ester 53 after 45 minutes (2)

D VI Towards the synthesis of 7-*t*-butylvalerenic acid

D VI.1 Synthesis of precursor 2-bromo-3,3-dimethylbut-1-ene (55)



54 **55**

Figure 62 : a) Triphenylphosphite, Br_2, NEt_3, DCM, -50°C then reflux, 29%

Vinylbromide **55** was prepared according to the conditions published by Prati et al., who just isolated this compound for analytical purposes.[68] A detailed mechanism- as published- is shown in Figure 63. First, triphenylphosphite reacts with elemental bromine under the

formation of bromide-salt **XVII**. This salt formation turns the phosphorous positively charged enhancing its electrophilicity. Therefore the carbonyl-oxygen of **XVI** can attack the phosphorous while bromide adds to the carbonyl function. After expulsion of bromine from phosphorous, intermediate oxyphosphonium bromide **XVIII** is formed. Due to the high oxophilicity of phosphonium, **XVIII** collapses to *gem*-dibromide **XIX**. Finally, base promoted dehydrobromination of **XIX** forms vinyl bromide **XX**. From this mechanism it is obvious that ketones bearing two residues with an α-hydrogen give regioisomeric mixtures. As a consequence vinyl halide **42** (see D IV.1) was not prepared via this route starting from the appropriate ketone. Instead the reaction turns out to be very feasible for the transformation of pinacolone **54** to vinyl bromide **55**, as the *t*-butyl group does not provide any α-hydrogen for elimination of HBr causing regioisomers. As expected, 2-bromo-3,3-dimethylbut-1-ene **55** could be isolated in 29% yield after distillation as the only isomer. Although pinacolone **54** was fully converted, isolation of **55** is accompanied with significant losses attributed to the high volatility of **55**.

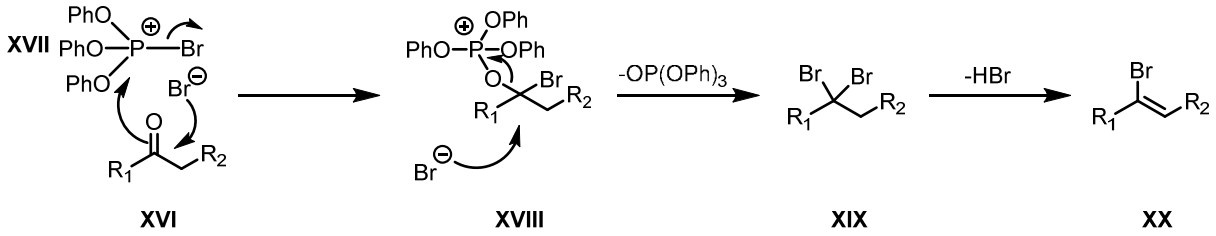
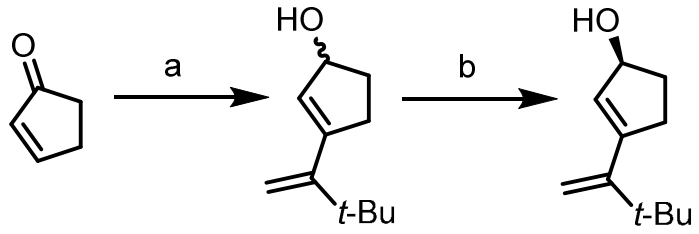


Figure 63: Formation of vinylbromides according to Prati et al.

D VI.2 Synthesis of (S)-3-(3,3-dimethylbut-1-ene-2-yl)cyclopent-2-en-1-ol (56)



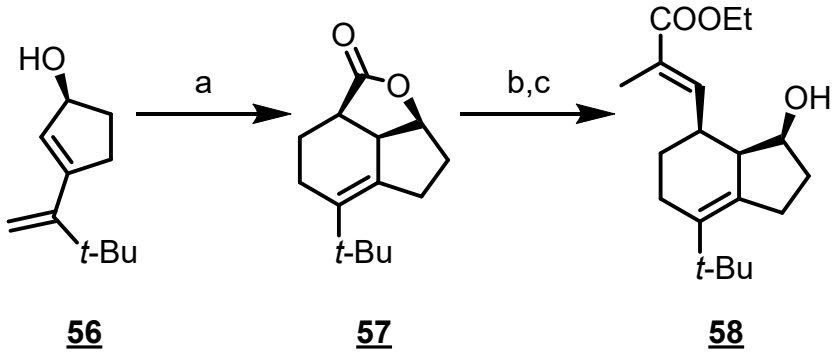
24 **rac-56** **56**

Figure 64 Reagents and conditions: a) bromo-3,3-dimethyl-but-1-ene, t-BuLi, TFA, THF, -78°C, 50%; b) Lipase PS, vinylacetate, MTBE, r.t., 42%;

Vinyl bromide **55** was lithiated with *t*-Buli in THF and cleanly added to cyclopentenol **24** in a 1,2-fashion (Figure 64). Subsequent rearrangement with TFA to ***rac*-56** caused partial elimination of the alcohol (as judged by TLC) which made an intermediate column

chromatography necessary. After kinetic resolution with Lipase PS, (S)-3-(3,3-dimethylbut-1-ene-2-yl)cyclopent-2-en-1-ol was obtained in 21% overall yield and >99% e.e. from **24**.

D VI.3 Synthesis of (E)-3-((3S,3aR, 4S)-7-(*t*-butyl)-3-hydroxy-2,3,3a,4,5,6-hexahydro-1*H*-inden-4-yl)-2-methyl-acrylic acid ethyl ester (58)

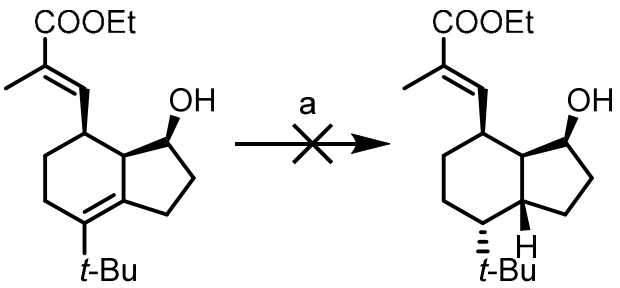


56 **57** **58**

Figure 65 Reagents and conditions: a) $MgBr_2.Et_2O$, DIPEA, methacrylate, DCM, r.t., 76%; b) DIBALH, DCM, -78°C, crude; c) (1-ethoxycarbonylethyliden)-triphenylphosphorane, toluene, 100°C, 61% over 2 steps;

Enantiopure alcohol **56** was converted to lactone **57** in good yield of 76%, fitting the rest of this series. Next, lactol formation was conducted in quantitative yield as crude intermediate, while subsequent Wittig olefination provided hydroxy-ester **58** in moderate yield of 61% (Figure 65).

D VI.4 Attempted synthesis of (E)-3-((3S,3aR, 4S, 7R, 7aR)-7-(*t*-butyl)-3-hydroxyoctahydroinden-4-yl)-2-methyl-acrylic acid ethyl ester (58a)



58 **58a**

Figure 66 Reagents and conditions: a) cat. $Ir(cod)(py)PCy_3PF_6$, H_2, DCM, r.t.

Diastereoselective Crabtree-hydrogenation proved to be unfeasible for reduction of **58** to **58a**. Although GC-MS reaction control indicated a mono- reduced product (Figure 68) formed from **58** (Figure 67), the ^{1}H-NMR of the isolated material (Figure 70) clearly demonstrates, that the exocyclic double bond got reduced, as the olefinic CH-signal at 7.08 dissapeared.The reasons for this have already been outlined before (D III.2) and the big steric demand of the *t*-butyl residue at C7 exclusively dictates hydrogenation towards the exocyclic double bond. As a result, *t*-butyl derivatives of valerenic acid are not accessible via this route, due to preferential reduction of the acrylate olefin.

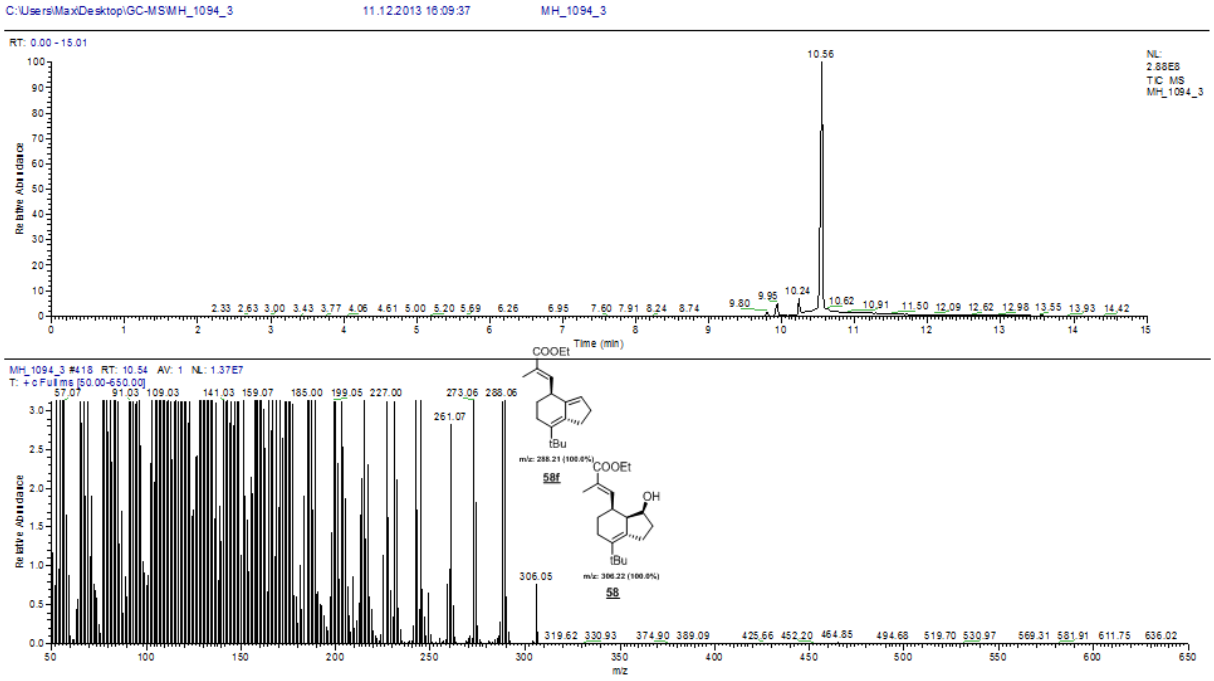


Figure 67 GC-MS of starting material 58

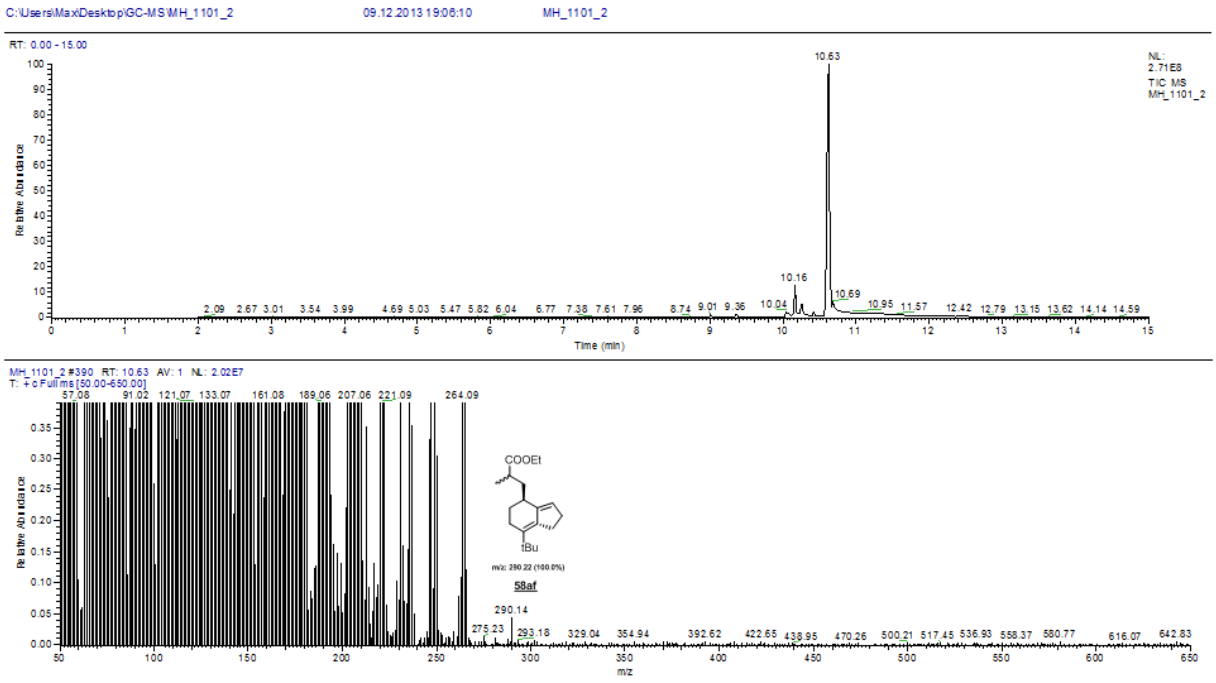


Figure 68 GC-MS of crabtree reduction of 58

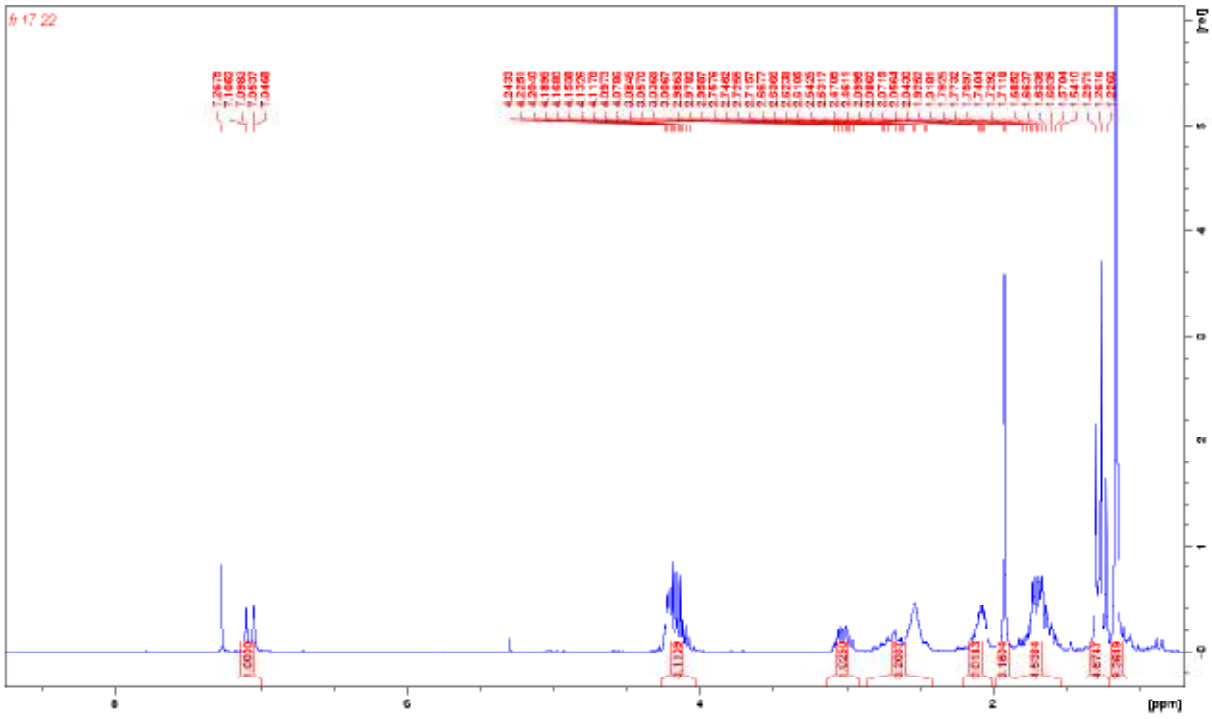


Figure 69 ^{1}H-NMR of starting material 58

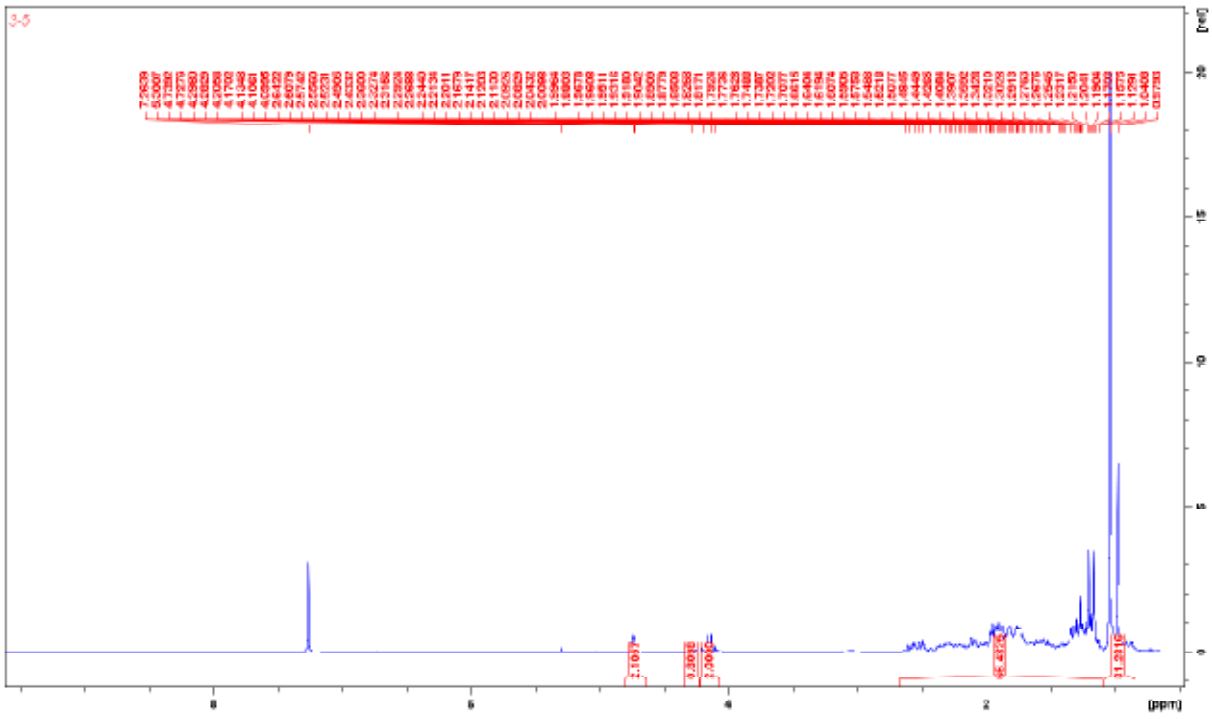
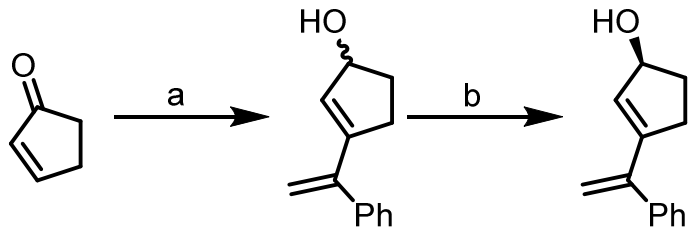


Figure 70 ^{1}H-NMR spectrum of isolated product after crabtree reduction

D VII Towards the synthesis of 7-phenylvalerenic acid

D VII.1 Synthesis of (S)-3-(1-phenylvinyl)cyclopent-2-en-1-ol (56)



24 ***rac*-59** **59**

Figure 71 Reagents and conditions: a) α-bromostyrene, t-BuLi, TFA, THF, -78°C, 73%; b) Lipase PS, vinylacetate, MTBE, r.t., 45% ;

Commercially available α-bromostyrene (90% purity) was lithiated and added to cyclopentenone **24** (Figure 71). Then standard rearrangement conditions provided racemic alcohol ***rac*-59** in 73% yield after column chromatography. Certainly, intermediate purification via column chromatography can be avoided when pure α-bromostyrene is employed. Still the losses are within an acceptable range. After kinetic resolution (S)-3-(1-phenylvinyl)cyclopent-2-en-1-ol **59** is obtained in >99% ee and 45%yield (33% over three steps).

D VII.2 Synthesis of (E)-3-((3S,3aR, 4S)-7-(phenyl)-3-hydroxy-2,3,3a,4,5,6-hexahydro-1*H*-inden-4-yl)-2-methyl-acrylic acid ethyl ester (61)

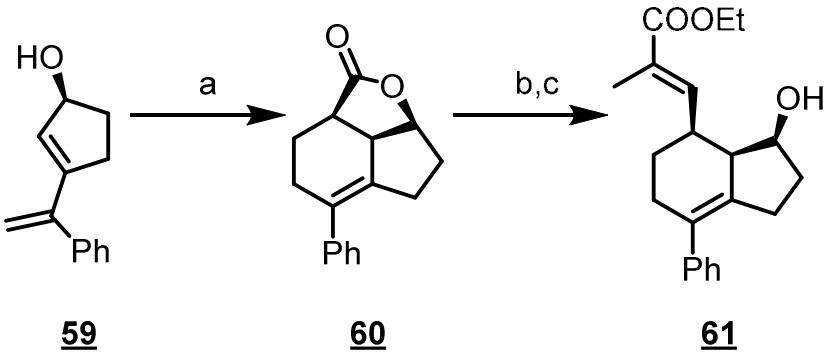


Figure 72 Reagents and conditions: a) $MgBr_2.Et_2O$, DIPEA, methacrylate, DCM, r.t., 88%; b) DIBALH, DCM, -78°C, crude; c) (1-ethoxycarbonylethyliden)-triphenylphosphorane, toluene, 100°C, 73% over 2 steps;

Synthesis of C7-phenyl substituted hydroxy-ester **61** was conducted under the same conditions previously described. The yield of lactone **60** is surprisingly excellent (Figure 72), while hydroxy-ester **61** is obtained in the same 70 to 80% range as other derivatives at this stage.

D VII.3 Attempted synthesis of (E)-3-((3S,3aR, 4S, 7R, 7aR)-7-(phenyl)-3-hydroxyoctahydroinden-4-yl)-2-methyl-acrylic acid ethyl ester (61a)

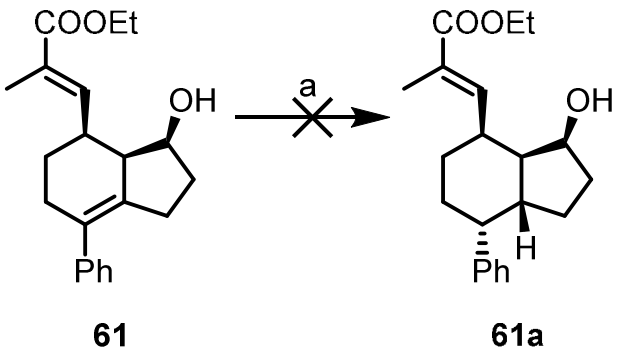


Figure 73 Reagents and conditions: a) cat. $Ir(cod)(py)PCy_3PF_6$, H_2, DCM, r.t.;

As suspected, diastereoselective hydrogenation of hydroxy ester **61** exclusively reduces the exocyclic double bond. Again, GC-MS control implicates a mono-reduced product with m/z=328.09, but the 1H-NMR of the isolated material corresponds to a product, having the exocyclic double bond reduced(compare Figure 75 with Figure 76; 5 protons instead of 6 in

the olefinic/aromatic region and the vinylic methyl group at 1.96 is shifted upfield and a triplet).The sterical demand of the phenyl substituent directs the hydrogenation with the same regioselectivity as in the *t*-butyl-case (see D VI.4).

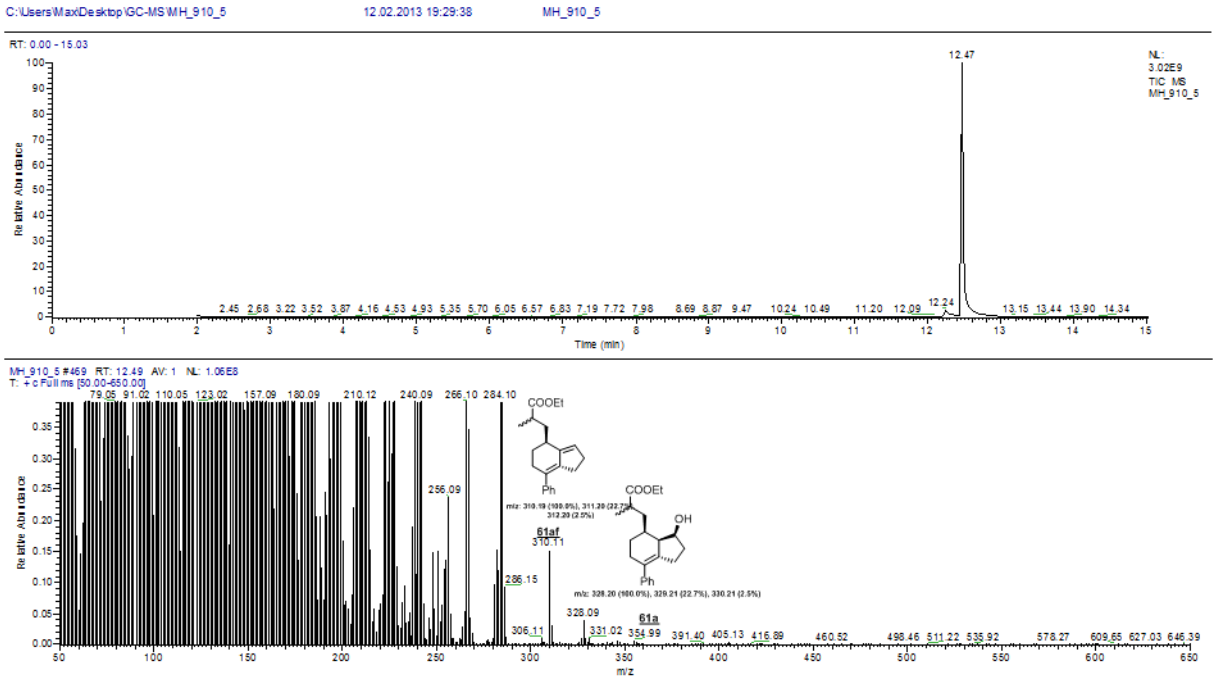


Figure 74 GC-MS of crabtree reduction of hydroxy ester 61

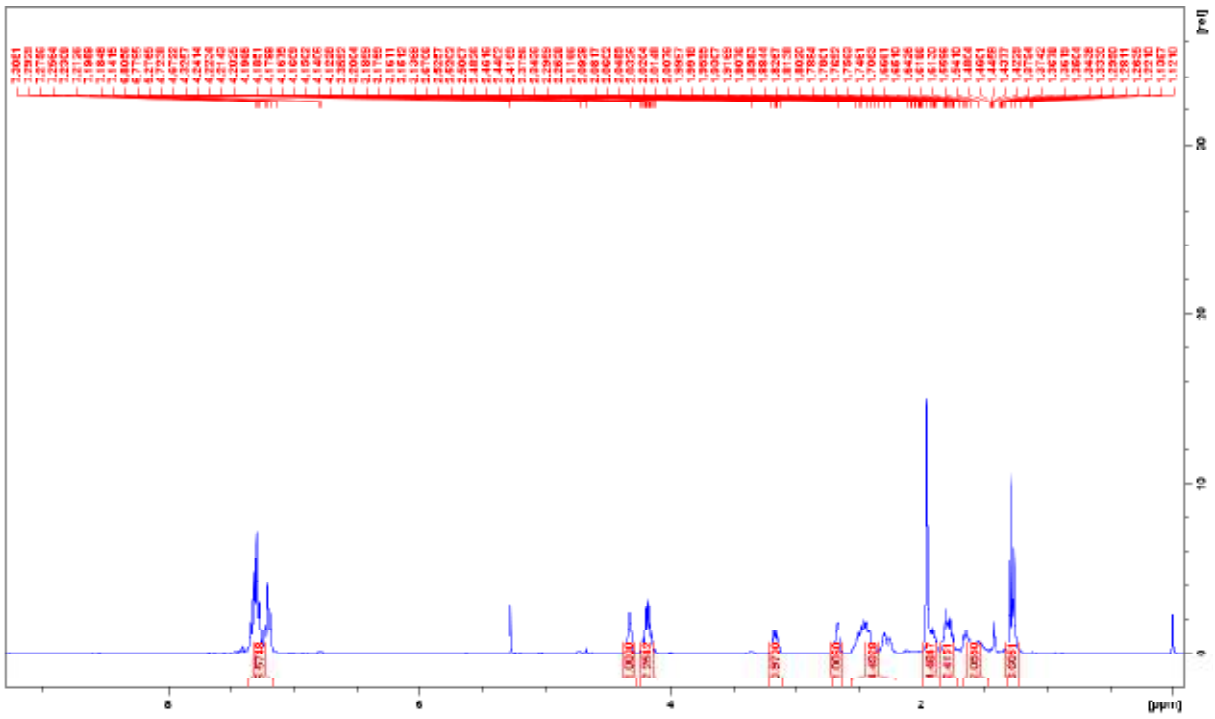


Figure 75 ^{1}H-NMR of starting material 61

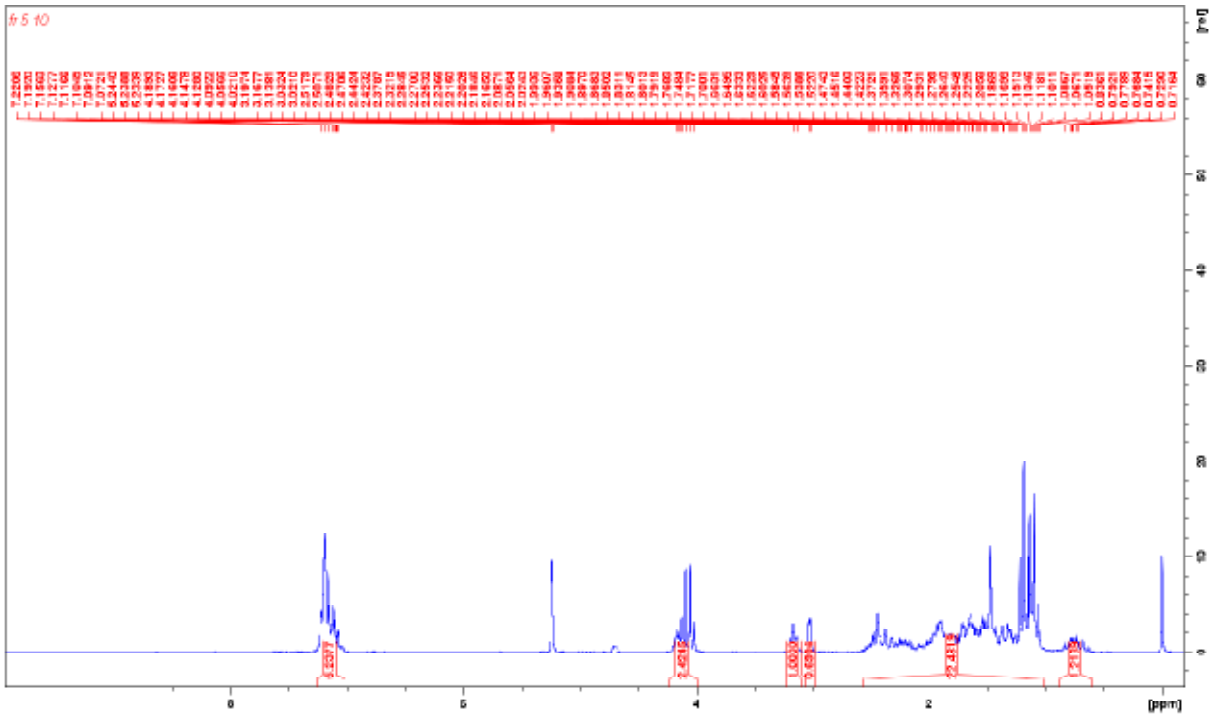
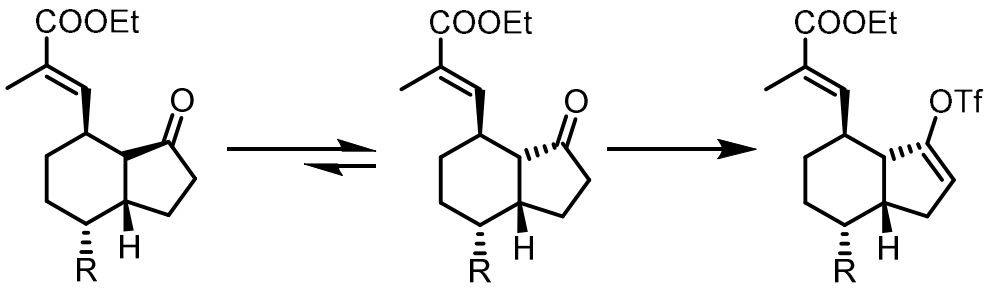


Figure 76 ^{1}H-NMR of isolated product after crabtree reduction

D VII.4 Epimerisation of 6-5-fused indanes



trans-fused *cis*-fused

XXI **epi-XXI** **XXII**

Figure 77: Epimerisation of 6-5 fused indanones

The strategical key-element for the construction of the unusual 1,4-diaxial relationship of valerenic acid **1,** according to the Mulzer synthesis[1], is the installation of the *trans*-fused cyclopentanyl ring (achieved via Diels Alder reaction and Crabtree reduction). Unfortunately, this conformation is not the thermodynamically more stable one, as 6/5 annulated ring systems prefer the *cis*-configuration as already demonstrated on steroid-related compounds by Bachmann in 1950[69].Ketone **XXI** is prone to epimersiation to ketone **epi-XXI**, which will not revert back into configurational isomer **XXI**. As a consequence, under all conducted enol-

triflatisations, the less substituted enol triflates of type **XXII** were observed to at least 20% as byproducts. This either decreases the achieved yields by a minimum of 20% or makes some derivatives (like C7-Cyclopropylderivative **50**, D IV.3 to D IV.6) not accessible in pure form, if they are not compatible with $AgNO_3$-doped silica purification.

E Modification of the vinylic methyl group at C3

Derivatisation at C3 on the indanyl core was performed through different cross-coupling strategies starting from ketone **66**. These types of modifications are more readily available since not the whole synthesis sequence had to be performed for each single derivative compared to the C7-derivatives. In comparison to the C7-derivatives, the synthesis proposed by Mulzer et. al[2,1] proved to be highly modular. Therefore the synthesis towards intermediate ketone **66** was performed as published by Mulzer et al. In the following chapters the synthesis towards common intermediate ketone **66** (Figure 78) will be discussed once, while the main focus of discussion will be put on the different residues coupled into C3-position associated with the synthetic challenges faced.

E I.1 Synthesis of (E)-2-methyl-((3aR, 4S, 7R, 7aR)-7-methyl-3-oxo-octahydroinden-4-yl)-2-methyl-acrylic acid ethyl ester (66)

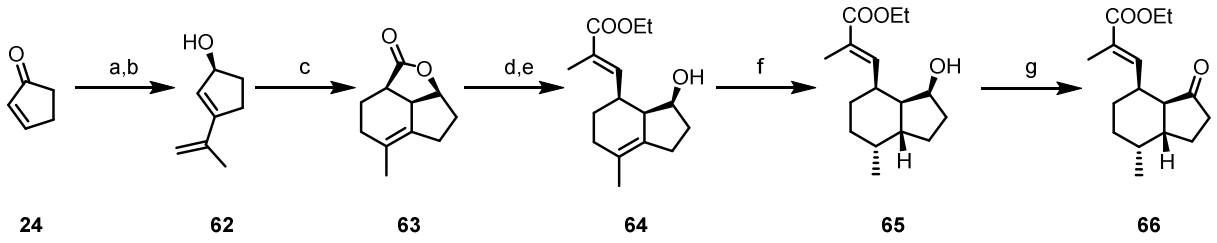
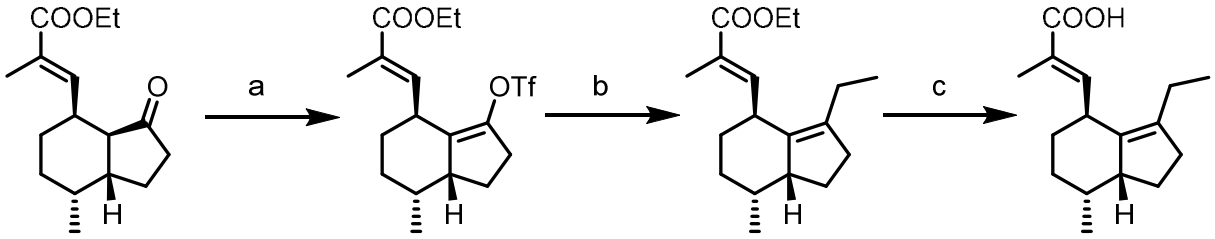


Figure 78 Reagents and conditions: a) 2-bromo-1-propene, t-BuLi, TFA, THF, -78°C, crude; b) Lipase PS, vinylacetate, MTBE, r.t., 46% over 2 steps; c) $MgBr_2.Et_2O$, DIPEA, methacrylate, DCM, r.t., 86%; d) DIBALH, DCM, -78°C, crude; e) (1-ethoxycarbonylethyliden)-triphenylphosphorane, toluene, 100°C, 84% over 2 steps; f) cat. $Ir(cod)(py)PCy_3PF_6$, H_2, DCM, r.t., 74%; g) IBX, DMSO, r.t., 85%

Addition of *in situ* generated isopropenyllithium to cyclopentenone **24** furnished the 1,2-adduct which was rearranged in a one-pot fashion with TFA and subsequently kinetically resolved with Lipase PS. Due to limited stability of cyclopentenols on silica, it was decided to perform kinetic resolution with the obtained crude material after 1,2-addition and 1,3-hydroxy isomerisation without any observed kinetic effect on the biotransformation. As a benefit cyclopentenol **62** could be obtained in 46% yield (>99%ee) in multigram scale compared to the published 32%. Hydroxy-directed Diels-Alder-reaction delivered lactone **63** in a very good yield of 86%. Although purification on unmodified silica, respectively basic alumina is reported, it was found that best results are obtained employing NEt_3-doped silica together with 1% NEt_3 in the eluent mixture. Subsequent reduction followed by Wittig-olefination delivered hydroxy-ester **64** in 84% over two steps. It has to be noted that within the olefination procedure the solvent was changed from benzene to toluene without decrease of yield. The higher reaction temperature reached with toluene shortened the reaction time by 9 hours. Crabtree-hydrogenation of **64** was achieved with 74% yield and in the range of literature. The only striking difference to the published protocol is the hydrogenation time. Hydrogenation of substrate **64** was complete in 45 minutes independent of scale or catalyst batch, while in the literature a reaction time of more than two hours is reported. Finally oxidation of alcohol **65** to ketone **66** was achieved with 85% yield. As already stated, several different oxidation methods can be applied (SIBX, IBX, DMP). Most importantly, the workup should always include a basic wash with $NaHCO_3$, as ketone **66** (like the other ketones at this synthetic stage) is more prone to epimerisation in an acidic environment.

E I.2 Synthesis of 3-Ethylvalerenic acid (69)



66 **67** **68** **69**

Figure 79 Reagents and conditions: a) Tf_2O, 2,6-DTBP, DCM, r.t, crude; b) cat. $Pd(OAc)_2$, C-Phos, diethylzinc, THF, 0°C- r.t., 63%; c) LiOH, iPrOH:H_2O=2:1, 40°C, 96%

The conditions for the coupling electrophile (enol triflate **67)** have already been successfully adapted and discussed within the 7-normethylvalerenic acid series (D II.6). Initially, it was

tried to install the ethyl-substituent via $Pd(PPh_3)_4$ catalysis. Unfortunately, coupling of **67** with the aforementioned catalyst and commercially available diethylzinc, led predominantly to the formation of ester **68a** over desired C3-ethyl derivative **68** (86:14 in favour of product **68a** according to GC-MS). It was quickly rationalized that sideproduct **68a** must result from a hydride coupling, caused by β-hydride-elimination from the ethyl group during the catalytic coupling process. With this rationalisation, the reason for the failed ethyl coupling must have its origin in the catalyst applied. It is known that β-hydride elimination in cross-coupling chemistry is alleviated by vacant coordination sites on the catalyst metal center[70]. A reaction course from enol triflate **67** to sideproduct **68a** is depicted in Figure 80.The mechanism of this reaction shall be discussed briefly for a better comprehension of the undesired hydride-coupling.

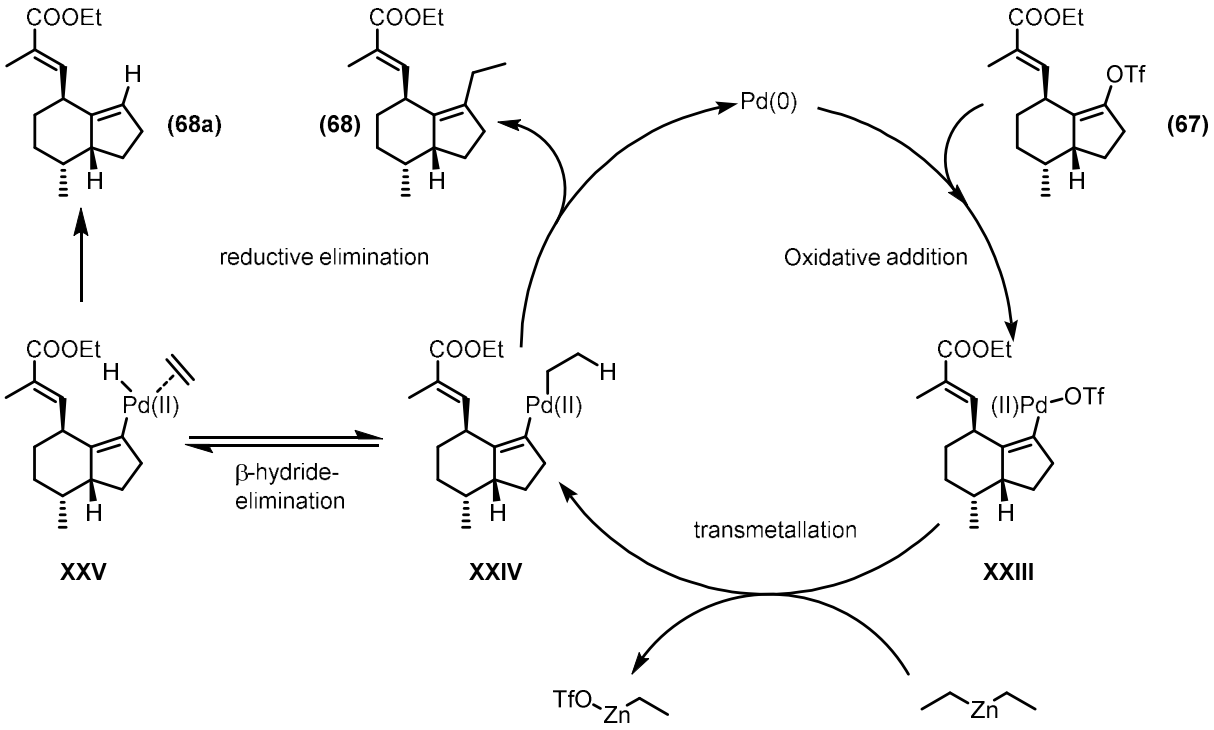


Figure 80 Reaction course of Negishi-coupling with $Pd(PPh_3)_4$ and diethylzinc

First, palladium (0) (ligands omitted for clarity) inserts into the $C(sp^2)$-OTf bond through oxidative addition. Then, an ethyl substituent from diethylzinc is transmetallated from zinc to Pd(II)-intermediate **XXIII,** resulting in the formation of Pd(II) complex **XXIV**. If the alkyl residue on intermediate **XXIV** is methyl - intrinsically lacking β-hydrogen - no β-hydride elimination but solely reductive elimination can occur at this point, regenerating the catalytically active Pd(0)-species concomitantly with the desired coupling product. This changes if the alkyl residue bears β-hydrogens, like in the depicted ethyl case. Here, reversible β-hydride elimination can occur besides reductive elimination towards **68**. This generates Pd(II)-hydride species **XXV**, leaving ethylene η-bonded, which is in equilibrium

with **XXIV**. The equilibrium driving reaction is a reductive elimination forming the C(sp^2)-H bond that generates product **68a**. The relative rates of reductive elimination from **XXIV** respectively **XXV** determines then the product distribution between **68** and **68a**. Therefore, a catalyst (ligand) enhancing the rate of reductive elimination from **XXIV** to **68** relative to the β-hydride elimination rate is prerequisite for successful ethyl-coupling. Gratifyingly, this problem has already been successfully addressed in the literature by Buchwald et al[61] in the context of Negishi-couplings.

Applying the suggested catalyst system $Pd(OAc)_2$/C-Phos to Negishi-coupling with diethylzinc completely shut down the side reaction and exclusively produced **68** (besides ~20% of regioisomers determined by enol triflate-formation). After purification of the regioisomers with $AgNO_3$-doped silica, 3-ethyl-valerenic acid ethylester **68** was obtained in 63% yield. Subsequent hydrolysis under prior modified conditions yielded 3-ethylvalerenic acid **69** in 96% (60% from ketone **66** over three steps).

E I.3 Synthesis of 3-n-Propylvalerenic acid (71)

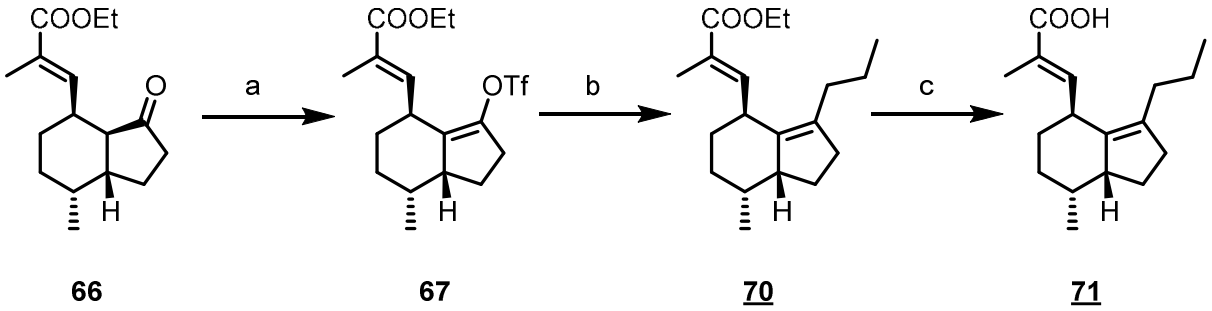


Figure 81 Reagents and conditions: a) Tf_2O, 2,6-DTBP, DCM, r.t, crude; b) cat. $Pd(OAc)_2$, C-Phos, LiCl, *n*-propylzincbromide, THF, 0°C- r.t., 47%; c) LiOH, iPrOH:H_2O=2:1, 40°C, 96%

Initial coupling of enol-triflate **67** with n-propylzincbromide under the prior established conditions ($Pd(OAc)_2$, C-Phos) surprisingly led to the formation of side-product **68a** in 21% (see Figure 80) stemming from β-hydride elimination. The result was puzzling, as the employment of sterically demanding C-Phos-ligand instead of PPh_3 successfully eliminated β-hydride elimination –and subsequent hydride coupling to **68a** - in the ethyl-case (see E I.2). It was rationalized that the only difference between both reactions is the reagent employed (diethylzinc vs. *n*-propylzinc bromide). Therefore, the side-reaction observed must originate from the zinc-reagent applied. It has already been demonstrated by Knochel et al.[71,72] that the addition of LiBr or LiCl has beneficial effects not only in the *in situ* preparation of organozinchalides, but for the subsequent Negishi-coupling as well. The main reason for this beneficial effect of Li-halide addition is believed to originate in deaggregation of organozinc-clusters in solution thus rendering the organozinchalide more reactive. Furthermore, it was demonstrated by Organ et al.[73], that the addition of LiBr is crucialfor the success of alkyl-

alkyl Negishi couplings. It was proven that the active transmetalating agent is actually a higher order zincate species formed by the addition of LiBr to *n*-butylzincbromide. In addition to this, Lu et al.[74] have demonstrated that addition of overstochiometric (two equivalents) amounts of LiBr suppresses β-hydride-elimination through blocking vacant coordination sites on the metal center with excess halide.

Therefore Negishi-coupling of **67** was conducted in the presence of 4 equivalents of LiBr (2 equivalents LiBr per equivalent *n*-propylzincbromide). Indeed the side-product formation of **68a** decreased to 11%. Substituting LiBr for LiCl even further decreased the amount of **68a** to 7%. Additionally, the coupling time could be decreased from overnight (~15h) to one hour, attributed to accelerated transmetalation caused by *in situ* formed zincate complex from *n*-propylzinc and LiCl. With this newly developed protocol, coupling of enol-triflate **67** yielded 3-*n*-propylvalerenicacid ethyl ester **70** in 47% yield. Subsequent hydrolysis with LiOH in iPrOH:H_2O mixture delivered 3-*n*-propylvalerenic acid **71** in 96% yield (45% over three steps from ketone **66**).

E I.4 Synthesis of 3-i-Propylvalerenic acid (73)

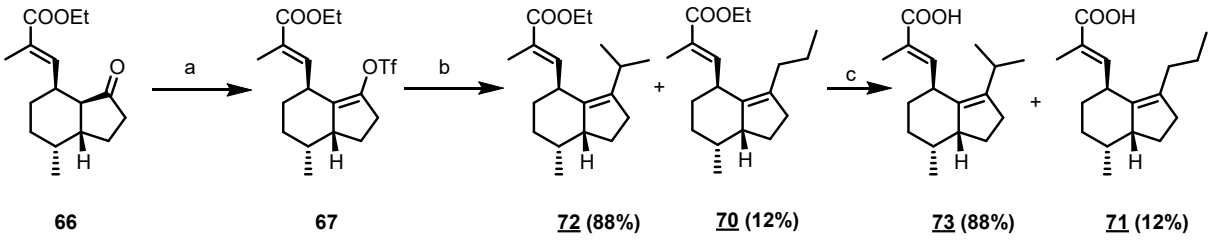


Figure 82 Reagents and conditions: a) Tf_2O, 2,6-DTBP, DCM, r.t, crude; b) cat. $Pd(OAc)_2$, C-Phos, LiCl, *i*-propylzincbromide, THF, 0°C- r.t., 42%; c) LiOH, iPrOH:H_2O=2:1, 40°C, 97%

Synthesis of *i*-propyl derivative **72** proved to be synthetically challenging. As already outlined in chapters E I.2 and E I.3 a β-hydride-elimination pathway caused significant problems for installation of the isopropyl moiety, which could not be overcome completely. While for the *n*-propyl case side product amount of hydride-coupled product **68a** could be decreased from 21% to 7%, the remaining 7% **68a** could be removed via $AgNO_3$-doped silica. Unfortunately, when coupling with isopropylzinchalide or diisopropylzinc, β-hydride-elimination opens another pathway for side-product formation than simple hydride coupling. The mechanism of β-hydride-elimination for isopropyl-coupling is depicted in Figure 83. For clarity-reasons the whole catalytic cycle of the Negishi-coupling is omitted. Instead, the decisive step of β-hydrogen-elimination is depicted. The crucial intermediate **XXVI** (formed through transmetallation of (di)alkylzinc(halide)) has again two reaction pathways: One being the desired reductive elimination towards product **72**, the other being β-hydrogen elimination towards **XXVII**. Intermediate **XXVII** actually has three possible pathways to react: it can revert to Intermediate **XXVI**, reductively eliminate to couple a hydride giving **68a** or the η-

alkenyl reinserts under hydride migration forming intermediate **XXVIII**. It is plausible, that reinsertion of η-alkenyl preferetially goes towards the linear intermediate **XXVIII** rather than back to the sterical demanding branched intermediate **XXVI** under the sterical congestion of the phosphine-ligands (not depicted) at the palladium center. As a consequence reductive elimination of **XXVIII** gives the linear *n*-alkyl (propyl) derivative **70**. This is underlined by the fact that no *i*-propyl derivative **72** was observed when coupling with *n*-propylzincbromide (see E I.3). Unfortunately *n*-propyl derivative **71** is not separable from desired *i*-propyl derivative **72**. Therefore 3-*i*-propylvalerenic acid ethyl ester **72** could be obtained only together with **70** in a molar ratio of (**72**:**70** = 88:12 according to NMR) in 42% yield. Consequentially, 3-*i*-propylvalerenic acid **73** was obtained in 97% yield after hydrolysis as a mixture of isomers being the same ratio (41% over three steps from ketone **66**).

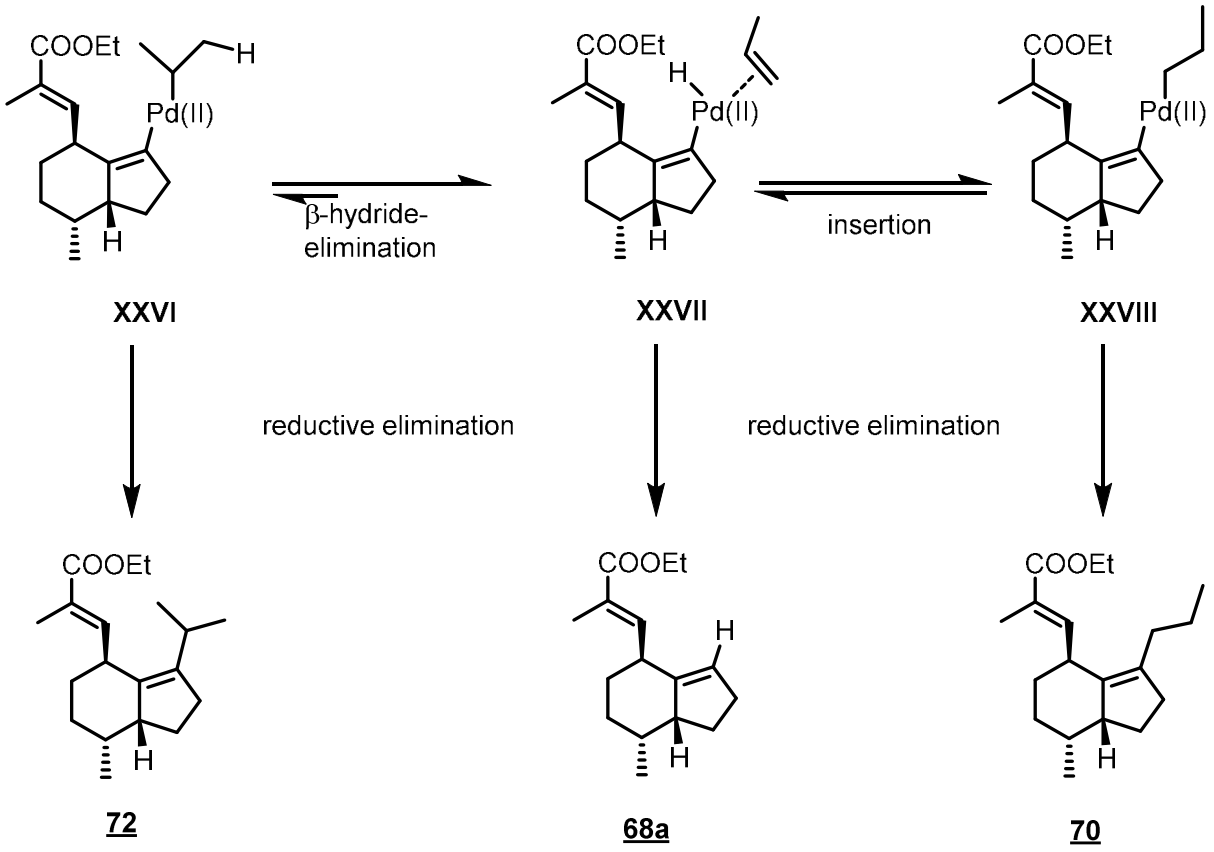
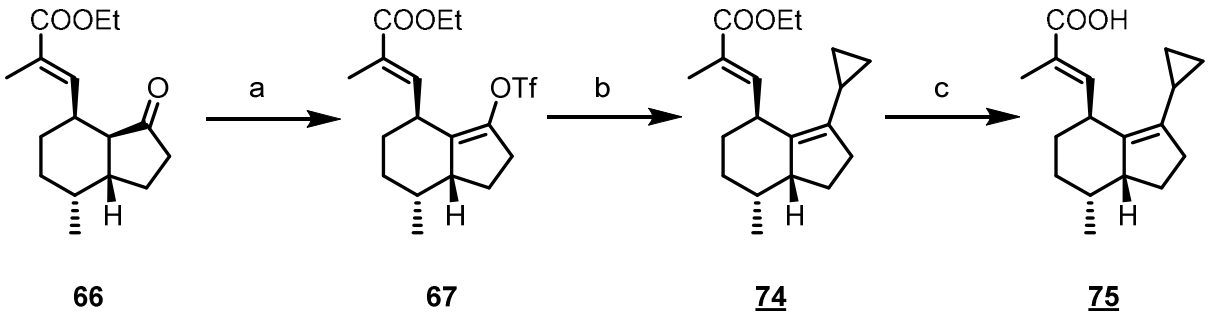


Figure 83 β-hydride-elimination/isomerisation mechanism

E I.5 Synthesis of 3-Cyclopropylvalerenic acid (75)



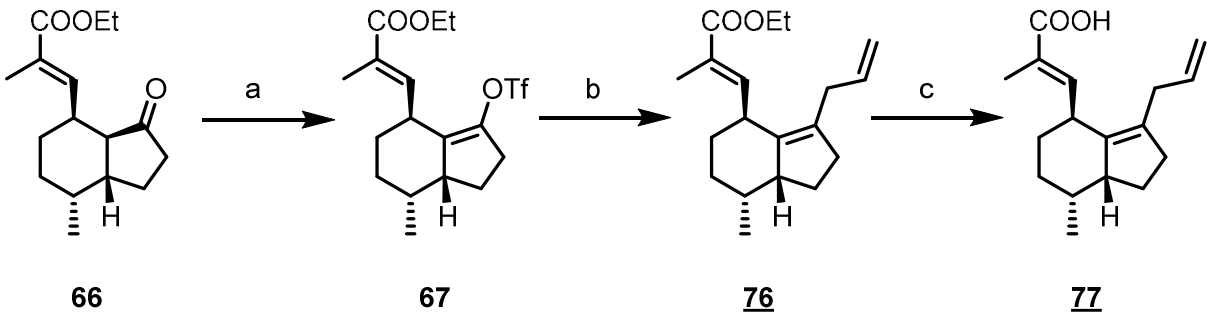
66 **67** **74** **75**

Figure 84 Reagents and conditions: a) Tf_2O, 2,6-DTBP, DCM, r.t, crude; b) cat. $Pd(OAc)_2$, C-Phos, LiCl, cyclopropylzincbromide, THF, 0°C- r.t., 42%; c) LiOH, iPrOH:H_2O=2:1, 40°C, 99%

Coupling of enol triflate **67** under the prior established conditions delivered 3-cyclopropylvalerenic acid ehtyl ester **74** in 42% yield. It is noteworthy, that no β-hydride elimination was observed when coupling cyclopropylzinbromide with enol triflat **67**, even if LiCl was omitted. This can be rationalized when the abnormal bond angles of cyclopropyl rings are taken into consideration[75]. While C-C-alkyl bond angles are 109.5°, C-C bond angles in cyclopropane are 60°. As a consequence, the β-hydrogen atoms of a cyclopropyl residue in a Pd(II) intermediate cannot arrange in a coplanar fashion to have agostic interactions with an empty d-orbital of the metal center as required for β-hydride elimination. Furthermore, the resulting olefin cyclopropene is reasonably more strained than cyclopropane (nearly double the ringstrain of cyclopropene compared to cyclopropane[76]), thus making this reaction thermodynamically unfavourable. As a result, β-hydride elimination is not an issue in the coupling of cyclopropylzincbromide.

Finally, ethylester **74** was hydrolyzed to 3-Cyclopropylvalerenic acid **75** in 99% (42% over three steps from ketone **66**).

E I.6 Synthesis of 3-Allylvalerenic acid (77)



66 **67** **76** **77**

Figure 85 Reagents and conditions: a) Tf_2O, 2,6-DTBP, DCM, r.t, crude; b) cat. $Pd(OAc)_2$, X-Phos, K_3PO_4, allylpinacolboronic ester, THF, 80°C, 57%; c) LiOH, iPrOH:H_2O=2:1, 40°C, 87%

Owing to the fact that allylzincreagents are not commercially available and usually prepared prior to use from allylbromide and activated zinc, a Suzuki-coupling with potassium allyltrifluoroborate was considered to be the more convenient option. Buchwald[77] already reported the successful Suzuki-coupling on enol-tosylates under palladium catalysis and X-Phos as a ligand. As the leaving group ability of triflates is about 10^4-times higher than that of tosylates[78], the reported protocol seemed to be adaptable for the Suzuki-coupling of enol triflate **67**. Therefore coupling of enol triflate **67** was performed with $Pd(OAc)_2$/X-Phos as the catalytic system together with potassium allyltrifluoroborate as coupling partner and K_3PO_4 as reported. Unfortunately, under these coupling-conditions double bond migration of the allyl residue towards the internal, conjugated vinyl analogues **76a** and the cis-isomer **76b** was observed (see Figure 86; trans **76a**:cis **76b**= 88:12 according to ^{1}H-NMR). Interestingly this double-bond migration could be fully suppressed by changing the allyl-donor from trifluoroborate-salt to allylpinacoloboronate. In this case, the only isomer isolated was desired 3-allylvalerenic acid ester **76** in 57% yield. Subsequent hydrolysis provided 3-allylvalerenic acid **77** in 87% yield (50% over three steps from ketone **66**).

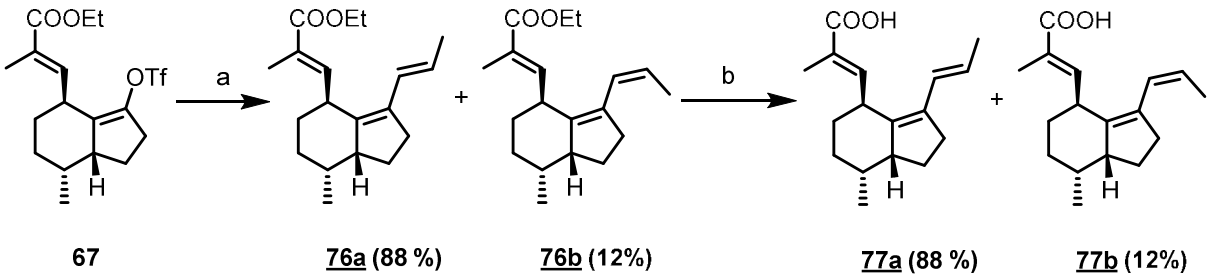


Figure 86 Reagents and conditions: a) cat. $Pd(OAc)_2$, X-Phos, K_3PO_4, potassium allyltrifluoroborate, THF, 80°C, 47% (76a:76b=88:12); b) LiOH, iPrOH:H_2O=2:1, 40°C, 90% (77a:77b=88:12)

E I.7 Synthesis of 3-Phenylvalerenic acid (79)

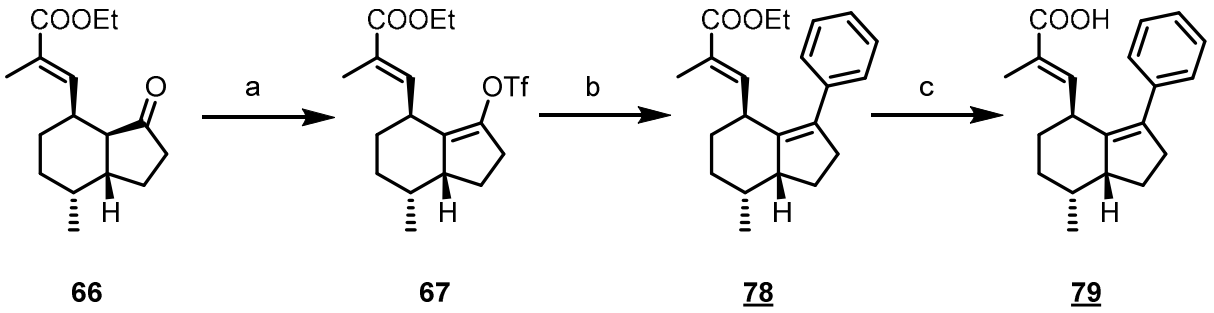


Figure 87 a) Tf_2O, 2,6-DTBP, DCM, r.t, crude; b) cat. $Pd(OAc)_2$, X-Phos, K_3PO_4, Phenylboronic acid, THF, 80°C- r.t., 50%; c) LiOH, iPrOH:H_2O=2:1, 40°C, 98%

Initially it was tried to couple enol triflate **67** with commercially available phenylzincbromide, but no conversion of **67** was observed. Although this result was puzzling at that time, the reaction conditions were switched to the before discussed (E I.6) Suzuki conditions. Later it was published, that lithium halide additives are crucial for the success of Negishi-coupling with arylzinchalides[79] which was not taken into consideration while performing this Negishi-coupling. Instead, enol triflate **67** was coupled with phenylboronic acid, yielding 3-phenylvalerenic acid ester **78** in 50%. The ester was then hydrolyzed as usual to provide 3-phenylvalerenic acid **79** in 98% yield (49% in three steps from ketone **66**).

E I.8 Synthesis of 3-Alkynylvalerenic acid ester (81)

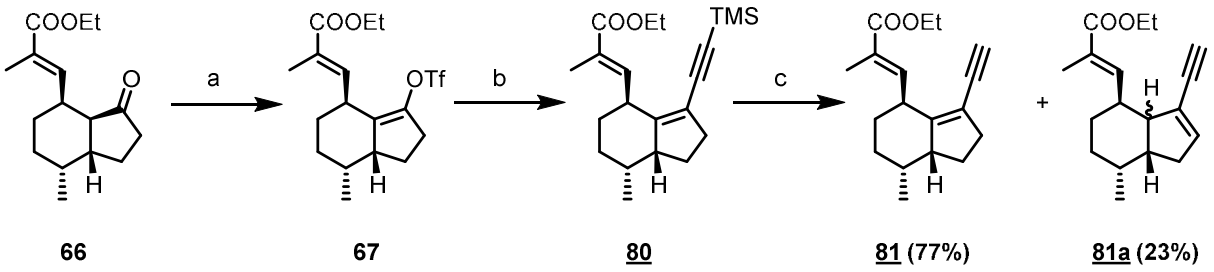


Figure 88 Reagents and conditions: a) Tf_2O, 2,6-DTBP, DCM, r.t, crude; b) cat. $Pd(PPh_3)_2Cl_2$,cat. CuI, TMS-acetylene,NEt_3, DMF, r.t. crude; c)TBAF, THF, 0°C, 23% over three steps (81:81a =77:23%)

Sonogahsira-coupling between enol-triflat **67** and TMS-acetylene was envisioned for the installation of an alkynyl-residue at C3. Several known literature conditions[80,81,81b,] with $Pd(PPh_3)_4$ as catalyst were screened (see Table 5). As those literature conditions mainly differed in the added silver(I)salts, first the counterion was screened. Unfortunately, none of the screened silver(I)salts had striking impact on the conversion of enol triflate **67** to TMS-alkyne **80**. Moreover by adding more TMS-acetylene and catalyst plus silver additive the

conversion of none of the screened $Pd(PPh_3)_4$/Ag(I)-combinations could be increased, thus prompting this catalyst combination unsuitable for this transformation.

Table 5 Screening results Sonogashira-coupling

Nr	Catalyst	Additive	Conversion after 19h [%]
1[a]	$Pd(PPh_3)_4$	$Ag_2(I)CO_3$	39
2[b]	$Pd(PPh_3)_4$	$Ag_2(I)CO_3$	28
3[a]	$Pd(PPh_3)_4$	Ag(I)Br	25
4[a]	$Pd(PPh_3)_4$	Ag(I)OTf	49
5[a]	$Pd(PPh_3)_4$	$Ag_2(I)O$	0
6[c]	$Pd(PPh_3)_2Cl_2$	Cu(I)I	100

Reagents and conditions: a) 10mol%Pd-catalyst, 50mol% additive, 2eqiv. TMS-acetylene, 2eqiv. DIPEA, DMF; b) Bu_4NCl instead of DIPEA as a base;c) 10mol% $Pd(PPh_3)_2Cl_2$, 10mol%Cu(I)I, 2eqiv. TMS-acetylene, 3eqiv. NEt_3, DMF

Upon this knowledge refined literature research brought the striking explanation for the failed Sonogashira coupling[82]. The problem upon employing $Pd(PPh_3)_4$ is associated to the generation of catalytically active species $Pd(PPh_3)_2$, which is not formed in a reasonable amount via ligand loss of PPh_3 from $Pd(PPh_3)_4$. Instead several different Pd^0-species are prevalent in solution, but not each is capable of successful coupling. Therefore the process described in Figure 89 is more suitable for pre-production of uniformly $Pd^0(PPh_3)_2$ species. Therefore, $Pd^{II}(PPh_3)Cl_2$ **XXIX** is first transmetallated with copper-acetylide generated by catalytic cycle B. $Pd^{(II)}$-aceylide complex **XXX** then undergoes reductive elimination, generating defined catalytically active $Pd^{(0)}$-complex **XXXII**, concomitantly producing Glaser-coupled bisacetylene **XXXI** (visible in GC-MS). Next oxidative addition of an alkenyl(pseudo)-halide or aryl- (pseudo)halide (R'X) leads to complex **XXXIII**. Again catalytic cycle **B** provides copper-acetylide for transmetallation to $Pd^{(II)}$-complex **XXXIV**, before reductive elimination liberates coupling-product **XXXV** and regenerates catalytically active species **XXXII**. As already stated, the employment of this protocol delivered Sonogashira-coupled product **80** with full consumption of **67** and as the only detectable enol-triflate-coupled product. Furthermore the initial screening time of 19 hours could be reduced, as the coupling process is finished within one hour. Initially cleavage of the TMS-group of **80** was attempted under the influence of K_2CO_3 in MeOH. Unfortunately, these conditions allow transesterification of the ethylester to the methylester. Therefore the TMS-group of **80** was cleaved by TBAF in THF without prior purification conserving the ethylester moiety. Finally, alkynylated product **81** is purified via column chromatography on silica gel, delivering a mixture of regioisomers **81** and **81a** as purification with $AgNO_3$-doped silica did not lead to any isolated product. Unfortunately enyne **81** is not bench stable (product-colour turns from colourless to yellow within one day; ^{1}H-NMR not interpretable) and degrades into a mixture of undefined products. Due to the instability of this intermediate ester, the final acid stage could not be reached and therefore no 3-alkynyl valerenic acid derivative was acessible for biological testing.

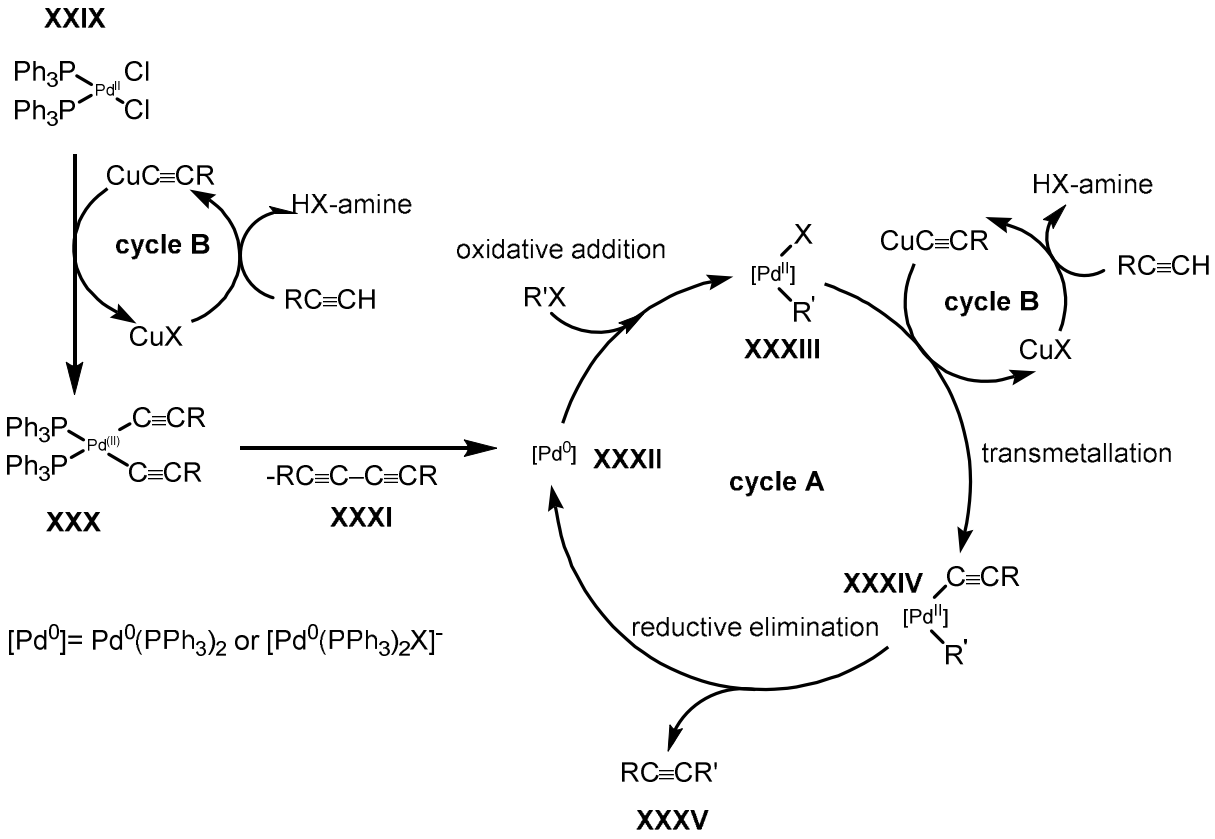


Figure 89 Mechanism of Sonogashira-coupling with Pd(II)-Catalyst precursor[82]

E I.9 Attempts for stereochemical inversion of hydroxy-ester 65

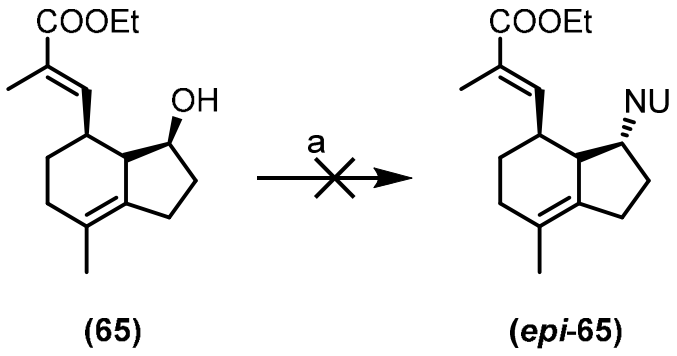


Figure 90 Reagents and conditions: a)PPh_3, DIAD, NuH, THF, 0°C

Besides the modifications of the vinylogous methyl-group at C3, it was intended to modify (invert) the hydroxy-functionality of intermediate **65**. Initial screening results indicated a high potency of intermediate **65** and of some of its C7-derivatives (see G I.4). The Mitsunobu-reaction[83,84] seemed to be a viable tool for inversion and/or modification of the

hydroxy-group with various nucleophiles (-OR,-SR, -NRR', -X). A general mechanism of the Mitsunobu-inversion is depicted in Figure 91. Prior to the problems associated with Mitsunobu-reaction on substrate **65**, the mechanism shall be discussed.

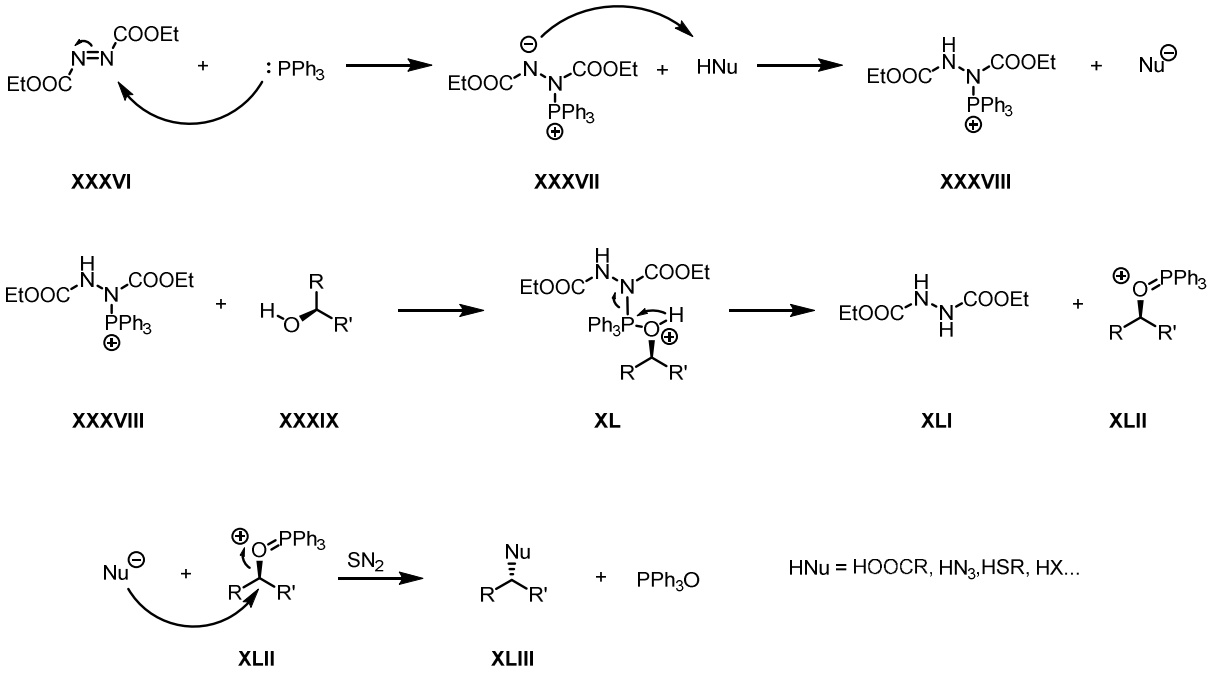


Figure 91: General mechanism of alcohol-inversion via Mitsunobu-reaction

The first step in the Mitsunobu-reaction requires the activation of triphenylphosphine (PPh_3) with an azodicarboxylate, in this case DEAD **XXXVI**, generating Morrison-Brunn-Huisgen (MBH) betaine **XXXVII**[85]. This betaine **XXXVII** then deprotonates the employed nucleophile (NuH) -usually a carboxylic acid for Mitsunobu-esterification or Mitsunobu-inversion upon hydrolysis - leaving behind cationic species **XXXVIII**. The so activated phosphorous is now electrophilic enough thus being attacked by alcohol **XXXIX**. The consequence is the formation of oxonium-ion **XL**, which readily collapses into hydrazide **XLI** and activated alkoxyphosphonium-ion **XLII**. Now the before deprotonated nucleophile attacks in an S_N2-fashion, while triphenylphosphineoxide leaves, resulting in the inverted species **XLIII**.

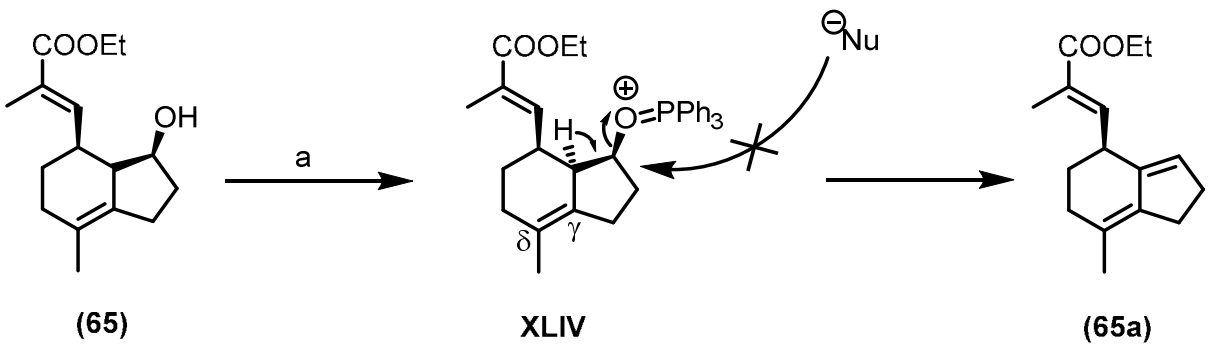


Figure 92 Reagents and conditions: a) PPh_3, DIAD, NuH, THF, 0°C

As already indicated, Mitsunobu-reaction on hydroxy-ester substrate **65** did not show any conversion to a product from nucleophilic substitution (**epi**-**65**). Instead, eliminated product **65a** is formed, caused by the strong leaving group ability of intermediately formed triphenylphosphine oxonium ion **XLIV**. While standard Mitsunobu-reaction is usually conducted at room temperature[85], alcohol **65** eliminates even at 0°C within 15 minutes, with no indication of a successful nucleophilic substitution. Instead intermediate **XLIV** may be highly susceptible to elimination, due to its γ,δ-unsaturation. This may drive the reaction from nucleophilic substitution (in addition alcohol **65** is sterically congested, thus limiting nucleophilic attack) to an elimination reaction. Each reaction conducted, indicated successful activation of alcohol **65** through Mitsunobu-conditions, as there was always production of hydrazide - stemming from DIAD - and triphenylphosphine oxide – stemming from the activated alcohol- observed. Therefore, it could be excluded that any other process (like acidic dehydration from the employed acid) except Mitsunobu-activation is responsible for dehydration of hydroxy-ester **65** to diene **65a**. Furthermore, switching the order of addition events from alcohol **65** together with DIAD and PPh_3 in solution before the nucleophile (typically acetic acid or p-nitrobenzoic acid) was added, to addition of alcohol **65** to a pre-stirred solution of PPh_3, DIAD and nucleophile, did not change the outcome of the reaction. As a result it was figured, that the elimination-pathway towards **65a** – once the alcohol is converted into a leaving group- dominates over the substitution-pathway, which would give the desired product **epi-65**. As a consequence the inversion of stereocenter C3, respectively the substitution at C3, seems impossible, as any activation of the alcohol will result in elimination to conjugated diene **65**.

F Alternative approaches to C7-derivatives

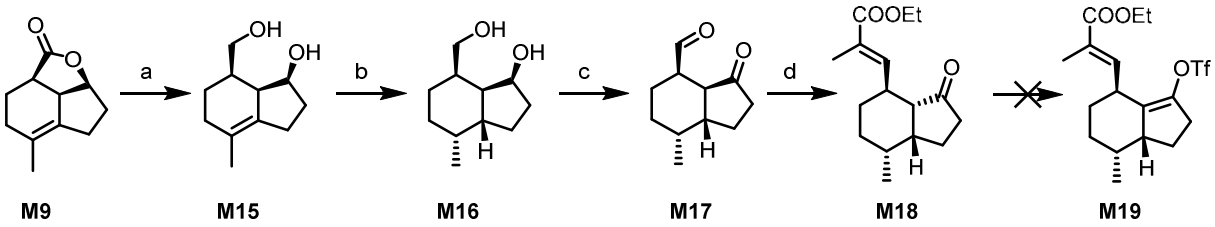


Figure 93 Reagents and conditions: a) $LiAlH_4$, Et_2O,r.t., 90%; b) cat. $Ir(cod)(py)PCy_3PF_6$, H_2, DCM, r.t., 91%; c) IBX, DMSO, r.t., 80%; e) (1-ethoxycarbonylethyliden)-triphenylphosphorane, DCM, reflux, 65%

Although several C7-derivatives were successfully synthesized via the Mulzer-approach, some modifications at C7 turned out to be inaccessible, at all. The reason for this was already outlined in the appropriated subchapters (see D VII.3, D VI.4, D V.3) and is related to lacking chemoselective reduction at the hydroxy-ester stage. It was figured, that this selectivity-issue could be circumvented, if the methyl-acrylate substituent is installed at a later stage. Actually, this was the initial plan in the Mulzer synthesis[1] as well. Unfortunately this failed as keto-aldehyde **M17** epimerizes under the Wittig-olefination conditions predominantly to the cis-fused isomer (65:14 in favour of cis), thus making a further conversion into enol-triflate **M19** impossible (D VII.4**)**. Still, Crabtree hydrogenation of diol **M15** into **M16** worked with 91% yield, being superior to the isolated yield when conducted at hydroxy-ester **64** (see E I.1, 74% yield, published: 72%). With this indication, the problems associated to regioselective Crabtree hydrogenation should be omitted, as the only olefin bond present in **M15** is the endocyclic one. The only challenge left towards C7-derivatives was the epimerisation at C3a under Wittig-conditions. Therefore, it seemed to be suitable to install the vinylic methyl-group at C3 prior to the methyl acrylate substituent, which was demonstrated by Altmann[42] as a feasible alternative.

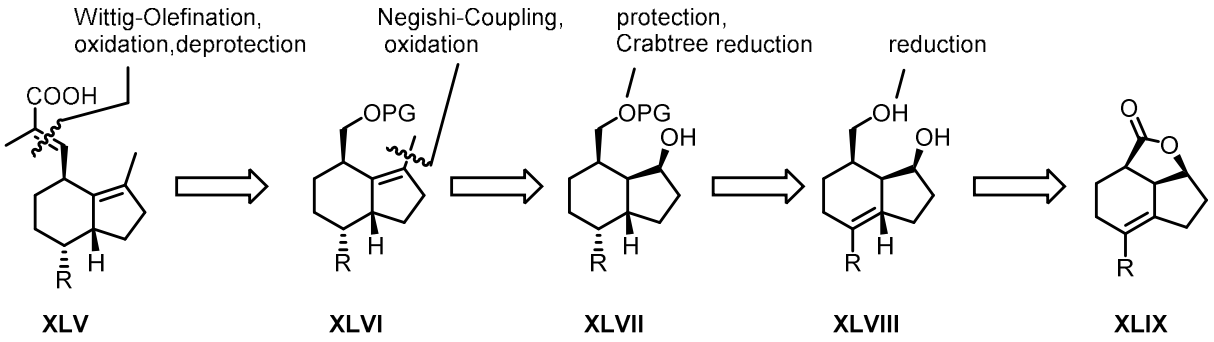
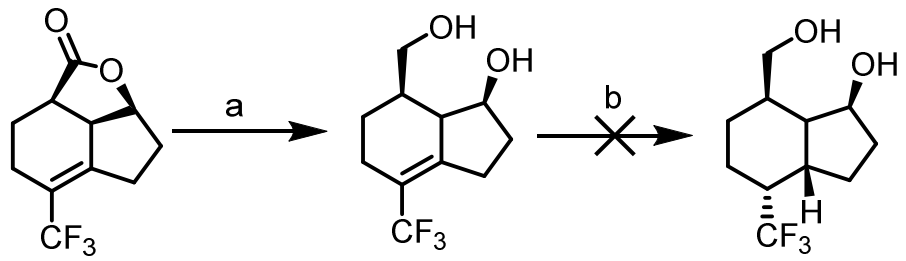


Figure 94 Alternative retrosynthetic approach towards C7-valerenic acid derivatives

With this inspiration, the synthesis of a C7-valerenic acid derivative **XLV** can be deduced to the first key intermediate, protected alcohol **XLVI**. The forward synthetic plan is the deprotection of the alcohol followed by oxidation to the appropriate aldehyde and subsequent Wittig-olefination. The vinylic methyl group at C3 should be installed via the already applied enol-triflatisation and Negishi-coupling- sequence, but from a different substrate, arising from the oxidation of mono-protected alcohol **XLVII**. The alcohol **XLVII** should be synthesized - as already successfully demonstrated by Mulzer - using a Crabtree-reduction followed by selective protection of the primary over the secondary alcohol. This leads back to diol **XLVIII** which is accessible via reduction of lactone **XLIX**, a common intermediate of the 2nd generation approach published by Mulzer[2,1]. Although the overall sequence towards valerenic acid (derivatives) is elongated via this approach by two steps (9 vs. 7 steps starting from lactone **XLIX**), this shortcoming is compensated by the accessibility of novel valerenic acid derivatives impossible to be synthesized via the published routes. Furthermore, the efficiency at the Crabtree hydrogenation step (~1.3 million euro per mole at Sigma Aldrich) can be increased due to lower catalyst loadings (6.5mol% vs. 10mol%) applicable at the reduction of diol **XLVIII**, while concomitantly delivering higher yields in the reduction step.

F I.1 Attempted synthesis of 7-trifluoromethyl-valerenic acid



52 **82** **82a**

Figure 95 a) $LiAlH_4$, Et_2O, 0°C to r.t.; 92% b) cat. $Ir(cod)(py)PCy_3PF_6$, H_2, DCM, r.t.,

As trifluoromethyl derivative **53** (see D V.3) was not reduced successfully under the employed Crabtree-hydrogenation conditions, it was emphasized to test the novel synthetic approach first with this substituent at C7. Lactone **52** could be reduced to diol **82** without any problems and in 92% yield, corresponding to the published literature[1] on a similar substrate. Next it was hoped, that without any selectivity bias, the reduction of **82** would cleanly lead to diol **82a**. Unfortunately, when performing the reduction as published, no conversion to **82a** could be observed. Instead only starting material was isolated. This prompted to a significant reactivity difference of vinylic trifluoromethyl olefins, compared to aliphatic, tetrasubstituted olefins. This seems to be a major problem associated to the delicate electronic effect of a CF_3 functionality on an adjacent olefin, as there is no literature precedence for success in directed, asymmetric reduction of tetrasubstituted, trifluoromethylated olefins. Instead, the only examples given in the literature involve trisubstituted, trifluoromethylated olefins, with the directing group being geminal to the reduced double-bond[86]. Furthermore this substance class has just been asymmetrically reduced with chiral Rh or Ru-catalysts, which are known to be not powerful enough to reduce tetrasubstituted olefines[63]. Therefore the accessibility of a trifluoromethylated valerenic acid derivative at C7 was found to be impossible with current methods of asymmetric reductions.

F I.2 Attempted synthesis of 7- phenyl-valerenic acid

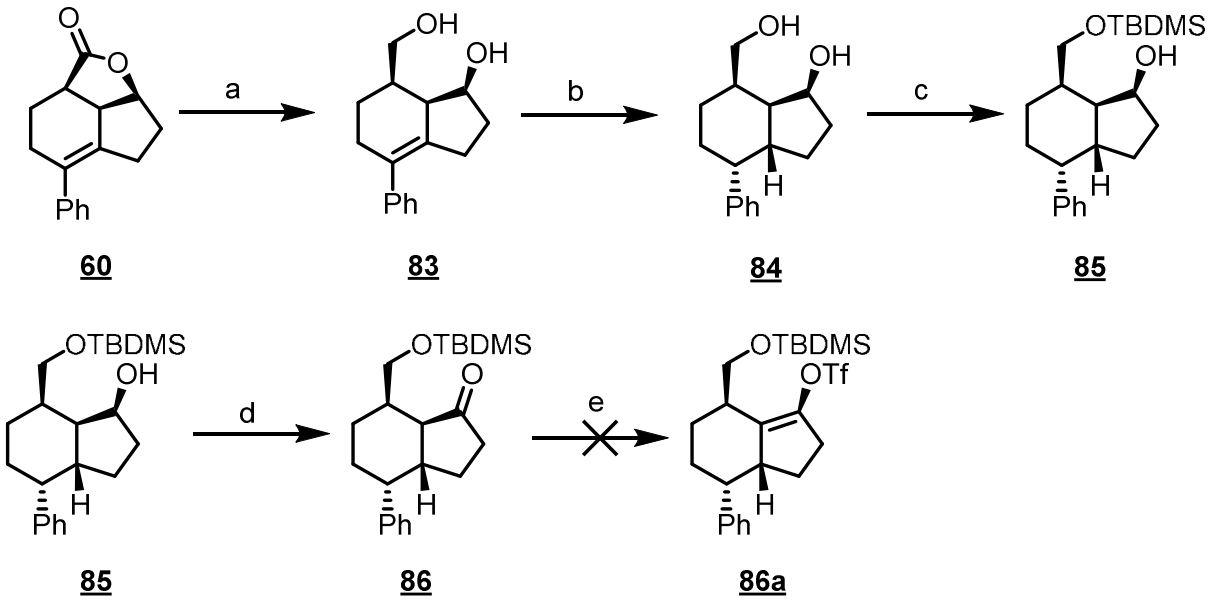


Figure 96 Reagents and conditions: a) $LiAlH_4$, Et_2O, 0°C to r.t., 96%; b) cat. $Ir(cod)(py)PCy_3PF_6$, H_2, DCM, r.t., 93%, c) TBDMSCl, imidazole, DMAP, DMF, r.t, 82% d) DMP, DCM, r.t., 96%; e) DTBP, Tf_2O, DCM, 0°C to r.t.

Due to the unique reactivity of trifluoromethylated olefins, the case study for proving the different synthetic approach was switched to C7-phenyl derivative synthesis. Reduction of lactone **60** with $LiALH_4$ to diol **83** worked in excellent yield of 96%. Alsodirected asymmetric reduction to saturated diol **84** with the described Crabtree reduction conditions worked with excellent diastereoselectivity and comparable to the literature, thus bearing the bulky, electron-withdrawing phenyl substituent. A silyl protective group (TBDMS) was chosen for selective protection of the primary alcohol, as orthogonal protection of alcohols with silyl groups is widely known in the literature. Selective protection of primary alcohol from diol **84** delivered TBDMS-protected alcohol **85** in 82% yield, which rendered the applied conditions very feasible. Next the secondary alcohol of **85** was oxidized to ketone **86** again in excellent yield of 96%. Subsequent conversion into enol-triflate **86a** – prerequisite for Negishi coupling - completely failed. Although ketone **86** was consumed under enolisation conditions employing DTBP and Tf_2O, no formation of enol-triflate **86a** could be observed (NMR, GC-MS). Instead the TBDMS-group gets cleaved under this reaction conditions (according to crude NMR) resulting in scrambling of **86** to an unidentified product. In consequence, a silyl protective group does not appear to be stable under triflating conditions. Therefore this route has to be modified in terms of the chosen protective group towards a stable one.

F I.3 Alternative synthesis of 7-Ethyl-valerenic acid

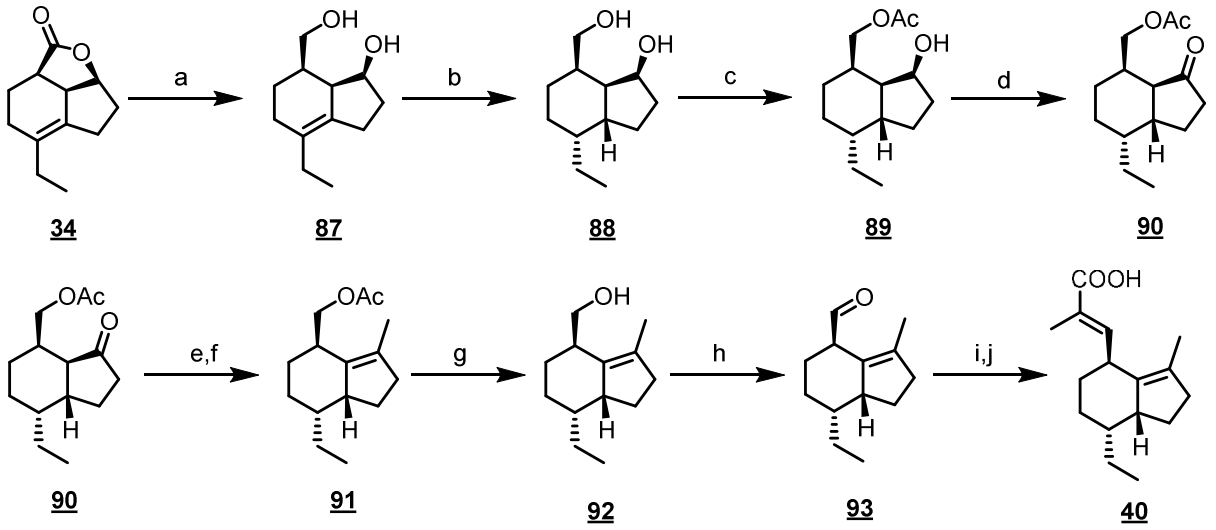


Figure 97) $LiAlH_4$, Et_2O, 0°C to r.t., 99%; b) cat. $Ir(cod)(py)PCy_3PF_6$, H_2, DCM, r.t., 93%; c) 2,4,6-Collidine, acetylchloride, DCM, -78°C to r.t., 72%; d) DMP, DCM, r.t, 75%, e) DTBP, Tf_2O, DCM, r.t, crude; f) $Pd(OAc)_2$, C-Phos, dimethylzinc, THF, 0°C to r.t., 62%; g) K_2CO_3, MeOH, r.t.; 98%; h) TPAP, NMO, 4Å MS, DCM, r.t, crude; i) (1-ethoxycarbonylethyliden)-triphenylphosphorane, toluene, 140°C, µW, 51%; j) LiOH, iPrOH:H_2O= 2:1, 40°C, 93%

With the previous failed attempts in mind, it was chosen to switch to a molecule, where reference material - at least for the endgame of the synthesis - was already available. Therefore, C7-ethyl derivative **40** was chosen to be synthesized via the envisioned alternative route. The failed C7-phenyl derivative synthesis illustrated the crucial role of the applied protective group, as silyl-protective-groups seem to be inadequate for enol triflate formation. Due to the already experienced fact, that each successful synthesis of any C3 or C7 valerenic acid derivative contained an ester functionality, an acetate protective group seemed to be self-evident.

So, diol **88** was synthesized via reduction of lactone **34** and subsequent asymmetric reduction of unsaturated diol **87**. Both reactions worked with more than 90% yield, providing diol **88** diastereoselectively. Subsequent selective protection was accomplished with acetylchloride and imidazole under DMAP catalysis at low temperature. Although over-acetylation was observed, the desired alcohol could be isolated in 72% yield. Dess-Martin oxidation provided ketone **90** in 75% yield. The acetyl-protected ketone **90** was cleanly converted to the appropriate enol-triflate (also showing an 80:20 distribution of regioisomers) without any degradation or deprotection evident. The crude enol-triflate was subsequently coupled under established Negishi-coupling conditions to give acetate **91** in 62% yield as a single isomer after purification with $AgNO_3$-doped silica. The following deprotection was accomplished by stirring in methanol with potassium carbonate as base in almost quantitative yield and without the necessity of column chromatography. For the endgame of the alternative synthesis of 7-ethylvalerenic acid **40**, alcohol **92** had to be

oxidized to aldehyde **93** prior to Wittig olefination. As it was already known from the Altmann synthesis[42], aldehyde **93** (respectively the C7-methyl derivative) is prone to epimerisation at C7 and is highly volatile. Therefore it was opted to keep the purification steps of **93** as gentle as possible, omitting column chromatography, as aldehyde **93** is very likely to epimerize on silica. In a first attempt, alcohol **92** was oxidized via neutral Ley-oxidation conditions[87], followed by filtration over celite. Excess solvent was gently evaporated and the crude brownish oil was subjected to microwave assisted Wittig-olefination conditions employing methanol as a solvent, as published by Altmann[42]. Unfortunately, two side reactions became evident on this initial trial: First, traces of TPAP or NMO *in situ* oxidize aldehyde **93** to the corresponding acid upon microwave irradiation. Secondly methanol transesterified the ethyl ester after Wittig-olefination, leading to an inseparable mixture of esters. Therefore, an extractive workup with sodium sulfite and $CuSO_4$ was included into purification of aldehyde **93** to scavenge NMO, as well as a filtration through DMT-doped silica for scavenging residual TPAP. In addition, the solvent was changed to toluene, thus making 7-ethylvalerenic acid ethyl ester **39** accessible in 51% yield from alcohol **92**. Although no side-product formation could be observed the yield of **39** is still moderate, attributed to the volatility of aldehyde **93**. Finally, ethyl ester **39** was hydrolyzed under standard conditions yielding 7-ethylvalerenic acid **40** in 93% yield.

Through development of this partly novel synthetic route, it was possible to pave the way for yet not accessible valerenic acid derivatives. Furthermore, this reaction pathway is more convenient with respect of the crabtree hydrogenation as it avoids any chemoselectivity problems. This leads to reduced catalyst loadings of expensive Crabtree's catalyst accompanied with an easier and more reproducible way of conducting this transformation for the synthetic chemist in the lab. Although being a 3 step longer sequence (Mulzer synthesis: 9 steps, this synthesis 12 steps), the overall yield for the benchmark-synthesis of 7-ethylvalerenic acid **40** is with 5.6% overall yield comparable to the shorter sequence prior performed (5.7%). It has to be noted, that at the time this thesis was written, not all novel steps were optimized, as this should be more a proof of concept, than an already optimized synthesis. Furhtermore the reactive acrylate-residue is introduced latest possible in the sequence and opens up a broader array of chemical transformations conducted on ketone **90** (or structural homologues) and consequentially more potential C-3 and C-7 valerenic acid derivatives yet not even imagined.

G Pharmacological Results

The screening of synthesized compounds for modulatory action on the $GABA_A$-receptor was conducted by the group of Prof. Hering at the Institute of Pharmacology and Toxicology at the University of Vienna.

G I.1 Biological testing

All substances were tested on oozytes from *Xenopus laevis* bearing a defined $GABA_A$ subunit composition. Therefore female frogs of genus *Xenopus laevis* are anesthetized to surgically remove parts of the ovarian[88,35]. In these oozytes, expression of determined $GABA_A$-receptor subtypes is induced via cRNA injection, resulting in a defined $GABA_A$-receptor profile. These well-defined oozytes serve as a template for testing of ion channel modulation by means of two microelectrode voltage clamp technique[89]. In this assay the transmembrane potential difference is measured through balancing variations in the electric potential through an applied current I. As the $GABA_A$-receptor is influencing this potential through chloride ion influx, modulation of the receptor can be tracked by current measurements. To achieve this, first the potential differentiation by GABA alone is measured. Then GABA and the testing substance (e.g. valerenic acid) are co-applied resulting in an elevated potential difference – presupposed the applied substance acts as a modulator. The measured effect is later on displayed as a percentage of potentiation being the quotient of $I_{GABA+modulator}$ and the initial current I_{GABA}.

To test a certain substance for subunit selectivity, one has to compare the potentiation values on different subunit expressed receptors. It has been shown, that valerenic acid selectively modulates $GABA_A$-receptors comprising β_2 or β_3 subunits. Therefore a subunit composition of $\alpha_1\beta_3\gamma_{2s}$ is chosen for demonstrating the effectivity, while $\alpha_1\beta_1\gamma_{2s}$ subunit containing receptors-staying unmodulated-serve as selectivity indicator.

G I.2 Valerenic acid esters

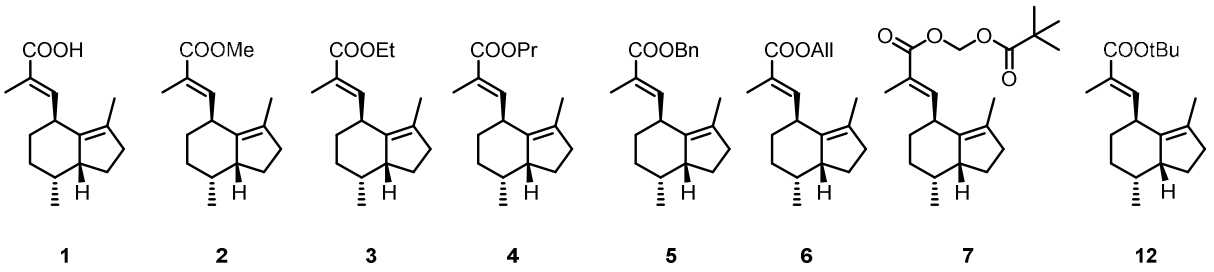


Figure 98 Valerenic acid and synthesized valerenic acid esters

Valerenic acid esters (Figure 98) were tested, together with valerenic acid as a reference compound, on $GABA_A$-receptors comprising the subunit composition $\alpha_1\beta_3$. In Figure 99 the potentiation of GABA current I_{GABA} is displayed for valerenic acid **1** and the synthesized ester-modifications **2-12**. It is clearly visible, that all ester-modifications decrease the modulation-ability on the $GABA_A$ receptor *in vitro*. Their potency drops by an average factor of 9, indicating a hydrogen-donor ability at this functional group as crucial. This eventually goes in line with the published results of Altmann[49], who came to the same conclusion. Interestingly the potentiation drops with increased chain length (bulkiness) of the alkyl residue, displayed by the potentiation order VA-Me **2** > VA-Et **3** > VA-Pr **4** >> VA-*t*-Bu. Interestingly the potentiation is increased for the benzyl- **5** and allyl-derivative **6** compared to propylester **4**. This may indicate a beneficial π-π-interaction with the receptor by these compounds. Still, the predominating role for potentiation may lie – as already stated- in the hydrogen-donor ability of valerenic acid **1**, as this structural difference displays the most significant effect.

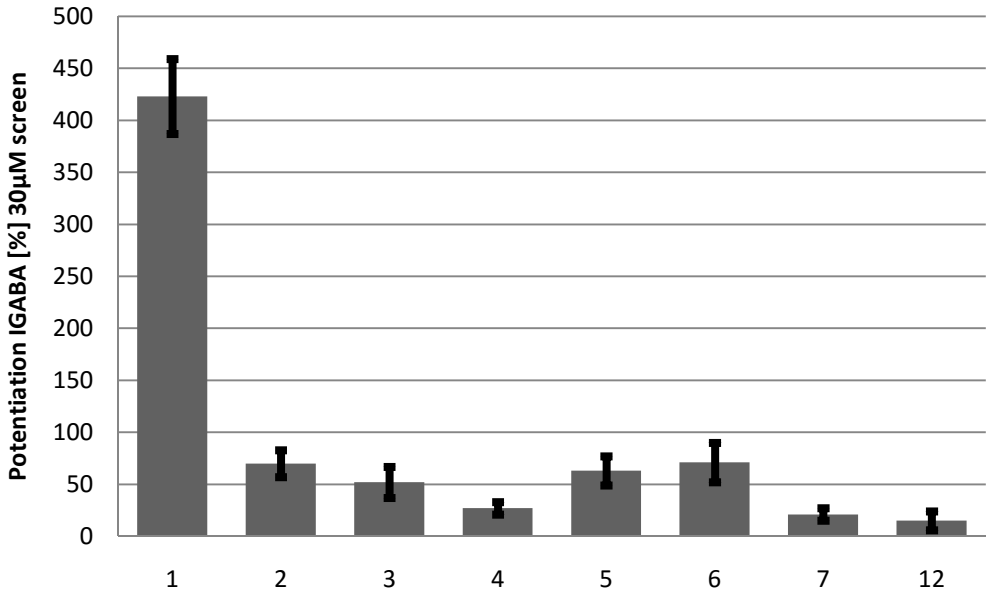


Figure 99: Potentiation IGABA of valerenic acid esters compared to Valerenic acid

Nevertheless, little is known how valerenic acid **1** crosses the blood-brain barrier[90]. Therefore ester-functionalisation of the polar carboxyl moiety might enhance the uptake of "masked" valerenic acid, being liberated through esterase cleavage *in vivo*. Based on the significantly low modulation-ability of the tested esters, they might serve as potential prodrugs, exhibiting modulatory effects on $GABA_A$-receptors after *in vivo* hydrolysis. For this study, four esters with different lipophilicity were chosen (calculated Log P: VA **1** = 5.13±0.31 < VA-Me **2** = 5.64 ±0.28 < VA-Et **3** = 6.17± 0.28 < VA-Pr **4** = 6.70±0.28 < VA-Pom **7** = 6.97±0.40) and the plasma-concentration of valerenic acid at three different time points (15, 30 and 60 minutes) was monitored via LC-MS[91] (see Table 6). Indeed the obtained data confirms *in vivo* hydrolysis of the applied esters.

Table 6: Plasma concentrations [ng/ml] of free valerenic acid 1 at 15, 30 and 60 minutes

No.	15min	30 min	60 min
1	640.7±131.8	105.2±18.6	61.3±21.8
2	164.2±42.7	76.7±19.7	24.2±21.8
3	117.4±19.3	84.1±11.3	20.2±4.1
4	274.5±51.8	174.6±52.3	43.7±6.7
7	166.5±9.1	80.4±27.1	11±1.5

Based on these results, anxiety-related behaviour of mice were tested, applying the elevated plus maze test[37] In this behavioral test, a plus-shaped metal-construct with two open and two wall-enclosed arms serves as the testing area. As mice are very shy and anxious specimen, the plus-maze construct is elevated from the ground to create an unfamiliar environment, before the test-mouse is placed in the center of all four arms. Due to its nature an uninfluenced mouse will spend the most time in the enclosed arms, whereas a mouse treated with anxiolytics spends most of its time in the open arms. To gain information about the anxiolytic effect, one just has to measure the time of the mouse spent in open amrs and compare it to the time spent in closed arms.The results are displayed in Figure 100 with % time spent in open arms (**A**-**C**) and the open arm distance covered (**D**-**E**).

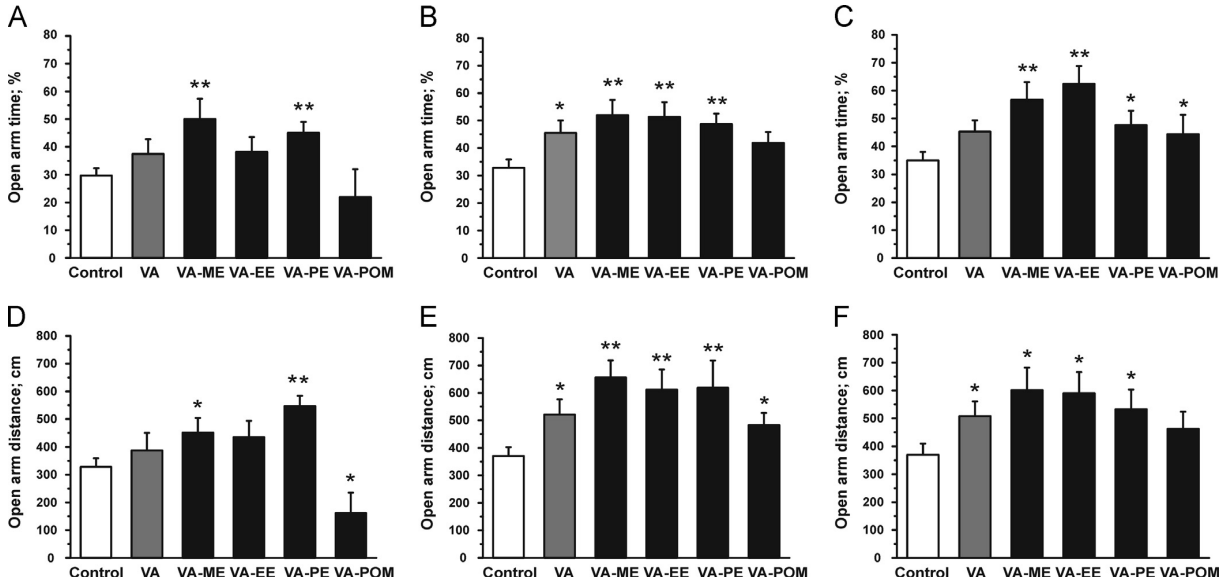


Figure 100: Effects on explorative behaviour of valerenic acid esters in the elevated plus maze test compared to saline-treated control after 15 min (left column), 30 min (middle column) and 60 min (right column)

15 minutes after injection, VA-ME **2** and VA-PE **4** show increased time spent in the open field as well as overall distance covered. This implicates a significant anxiolytic activity of those derivatives after 15 minutes, while VA-EE **3** showed the same effect than the control and VA-POM **7** even decreased effects on time spent and distance covered.

After 30 minutes, the effect of VA-EE **3** and VA-POM **7** seems to kick in as well and all ester-treated mice show an increased time spent and distance covered in open field. The same result is obtained 60 minutes after injection.

In line with the anxiolytic activity, the anticonvulsant activity was measured as well. Therefore the influence of valerenic acid **1** and esters **2**, **3**, **4** and **7** on pentylenetetrazole (PTZ)-induced seizures was investigated (see Figure 101) .

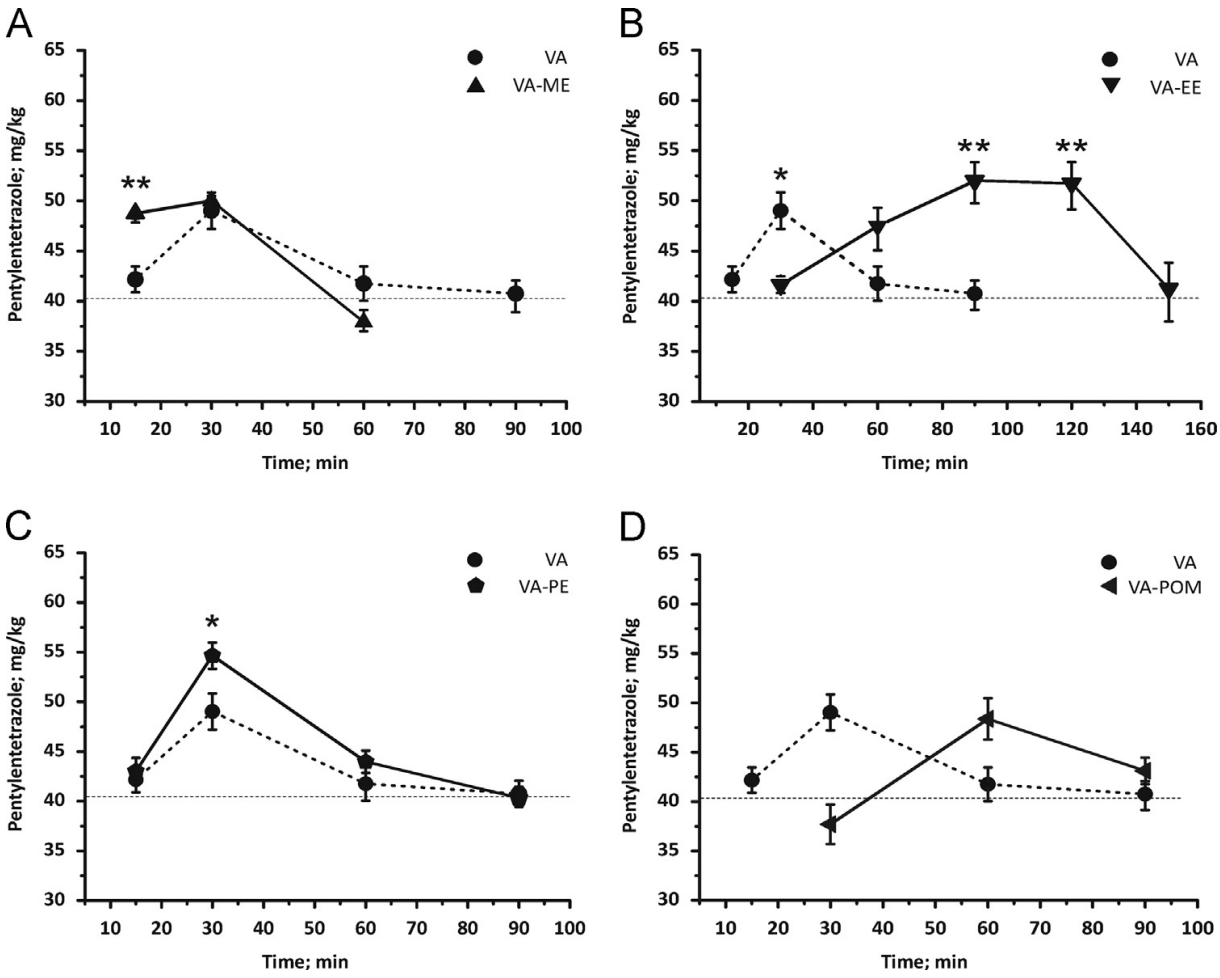


Figure 101: Changes in seizure threshold upon PTZ-infusion evoked by valerenic acid 1 compared to VA-ME 2 (A), VA-EE 3 (B), VA-PE 4 (C) and VA-POM 7 (D)

Like valerenic acid **1,** the methyl ester **2** and propyl ester **4** exhibit increased seizure-threshold 30 minutes after injection, disappearing after 60 minutes. Ethyl ester **3** behaves significantly different than the latter, as the observed effect starts 60 minutes after injection, reaching its maximum at 120 minutes. Pom-ester **7** instead, seems to have a parallel shifted effect-profile, having the maximum at 60 minutes compared to the 30 minutes of valerenic acid **1**. The identical effects of valerenic acid **1**, methyl- **2** and propyl-ester **4** indicate a fast hydrolysis of both esters *in vivo*, while ethylester **3** seems to be hydrolyzed slower, but in steady concentrations over a longer time period. This indicates kind of a reservoir set-up of ethyl-ester **3** available for hydrolysis over a long time course. The most lipophilic Pom-ester **7** however, shows the same onset time than the ethyl-ester **3**, but the effect is less pronounced and shorter lasting.

G I.3 Valerenic acid amides

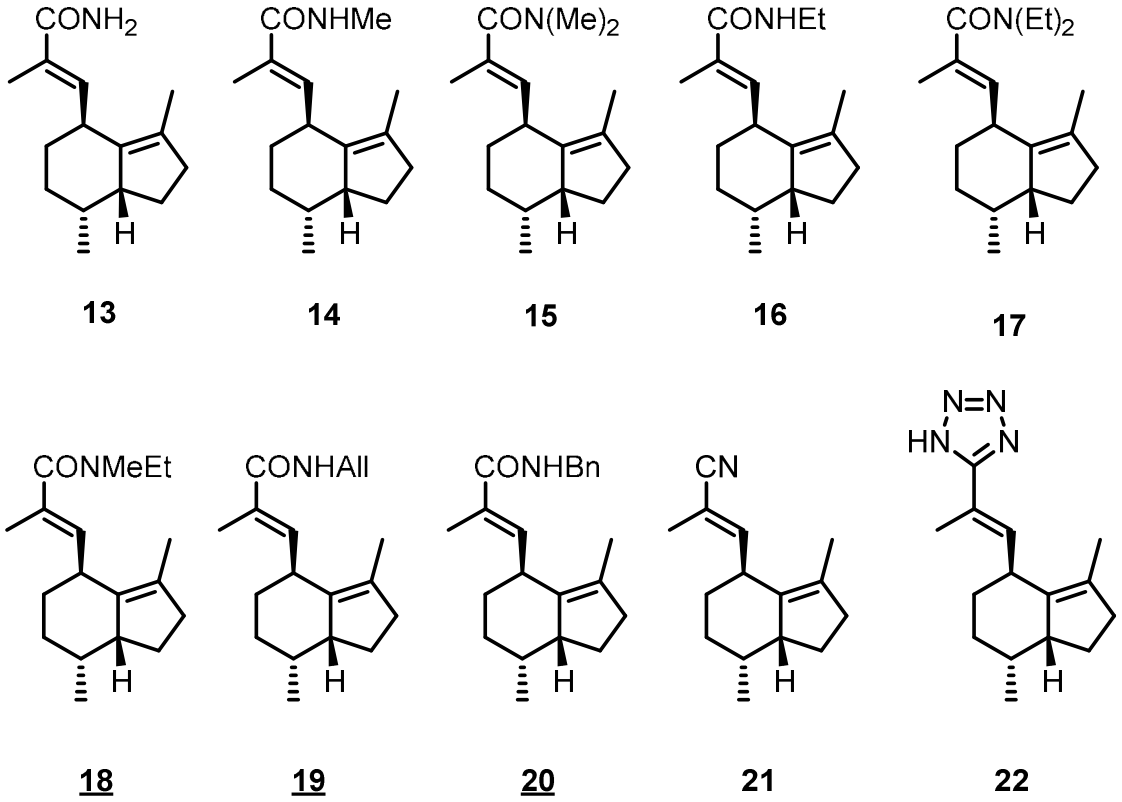


Figure 102 Synthesized valerenic acid amides, valerenic acid nitrile and tetrazole

In comparison to the ester derivatives, amide derivatives **13**-**20** as well as nitrile **21** and tetrazole **22**were first tested *in vitro*. The results of potentiation on a $GABA_A$ subtype composition of $\alpha_1\beta_3\gamma_2$ are depicted in Figure 102 on a 30µM screen.

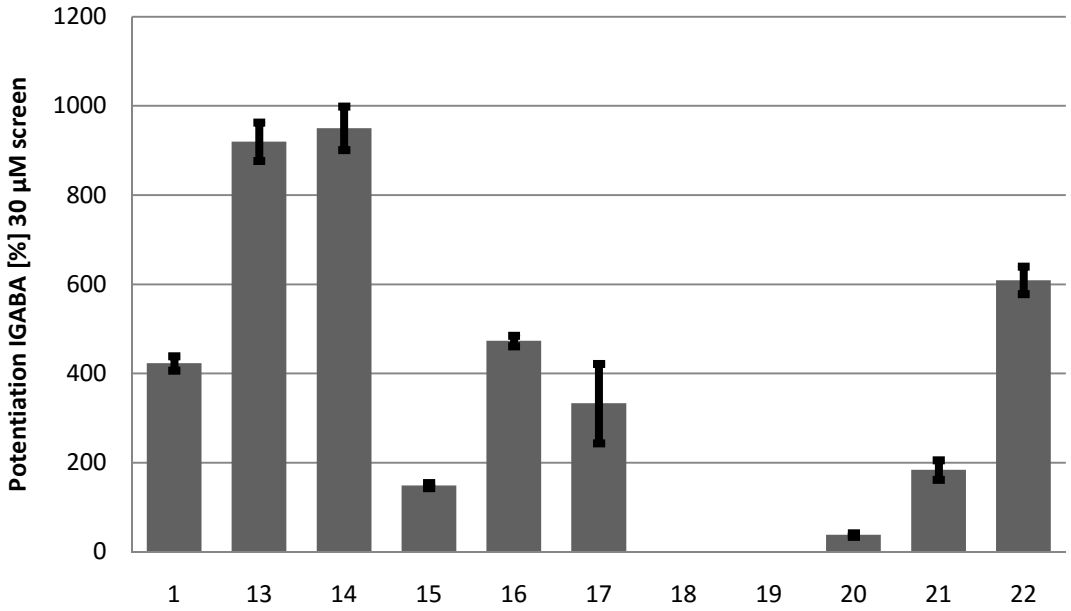


Figure 103: Potentiation I_{GABA} [%] on $\alpha_1\beta_3\gamma_2$-receptors at 30µM

It was observed that amides bearing a hydrogen donor moiety, like valerenic acid amide **13**, monomethylamide **14** and monoethylamide **16**, exhibit a higher potentiation than their dialkyl homologues (diemethylamide **15** and diethylamide **17**). Whereas amide **13** and monomethylamide **14** are in the same range of potentiation, monoethylamide **16** is already decreased to around 50% and in the range of valerenic acid **1**. Interestingly this trend is reversed from dimethylamide **15** to diethylamide **17**. Benzylamide **20** seems to be too bulky for reasonable potentiation, thus bearing a hydrogen donor, while nitrile **21** is comparable to dimethylamide **15**. The bioisostere of the acid function, the tetrazole **22**, shows a 1.5-fold increase in potency compared to acid **1**, lying in between acid **1** and amides **13** and **14**. The main conclusion of these results is the fact that a hydrogen-bonding ability is necessary for an increased modulatory effect. Furthermore a slight increase in lipophilicity seems to be beneficial as well, indicated by monomethylamide **14** and tetrazole **22**. As a result, amide **13**, monomethylamide **14** and tetrazole **22** were the most powerful modifications of the carboxylic acid function.

Of a set of valerenic acid amides, the nitrile **21** and the tetrazole **22,** the dose-dependent potentiation of I_{GABA} of different $GABA_A$-receptor subtype-compositions ($\alpha_1\beta_1\gamma_{2s}$, $\alpha_1\beta_2\gamma_2$, $\alpha_1\beta_3\gamma_2$) were measured to determine the influence of the carboxylic acid function derivatisation on subunit selective $GABA_A$-modulation[92]. The results are summarized in Figure 104 and 92. For valerenic acid **1** (Figure 104 **A**), valerenic acid amide **13** (Figure 104 **C**) and valerenic acid methylamide (Figure 104 **E**) a clear subunit selectivity for β_2 and β_3 subunit (equally pronounced effect) composed receptors was demonstrated. Interesingly, valerenic acid tetrazole **22** (Figure 104 **G**) shows an increased β_2 efficacy compared to β_3-efficacy.

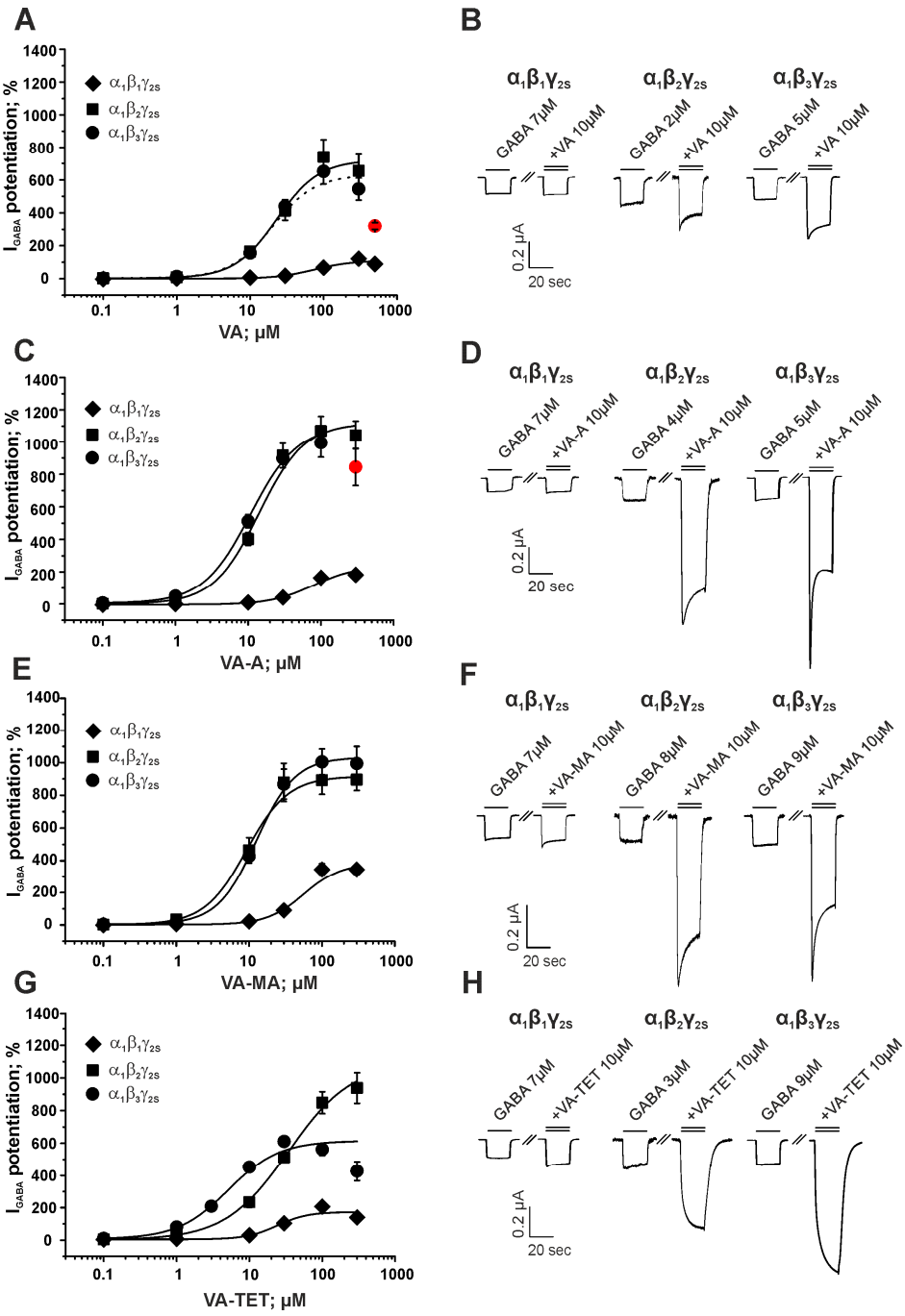


Figure 104 Determination of subunit selectivity of valertenic acid 1 (A), valerenic acid amide 13 (C), valerenic acid methylamide 14 (E), and valerenic acid tetrazole 22 (G)

From the other tested valerenic acid derivatives just valerenic acid nitrile **21** (Figure 105 **A**) shows a subunit selectivity for β_2 and β_3. No significant difference of efficacies between β_1, β_2 and β_3 subunits could be demonstrated for valerenic acid ethylamide **16** (Figure 105 **B**), dimethylamide **15** (Figure 105 **C**) and diethylamide **17** (Figure 105 **D**).

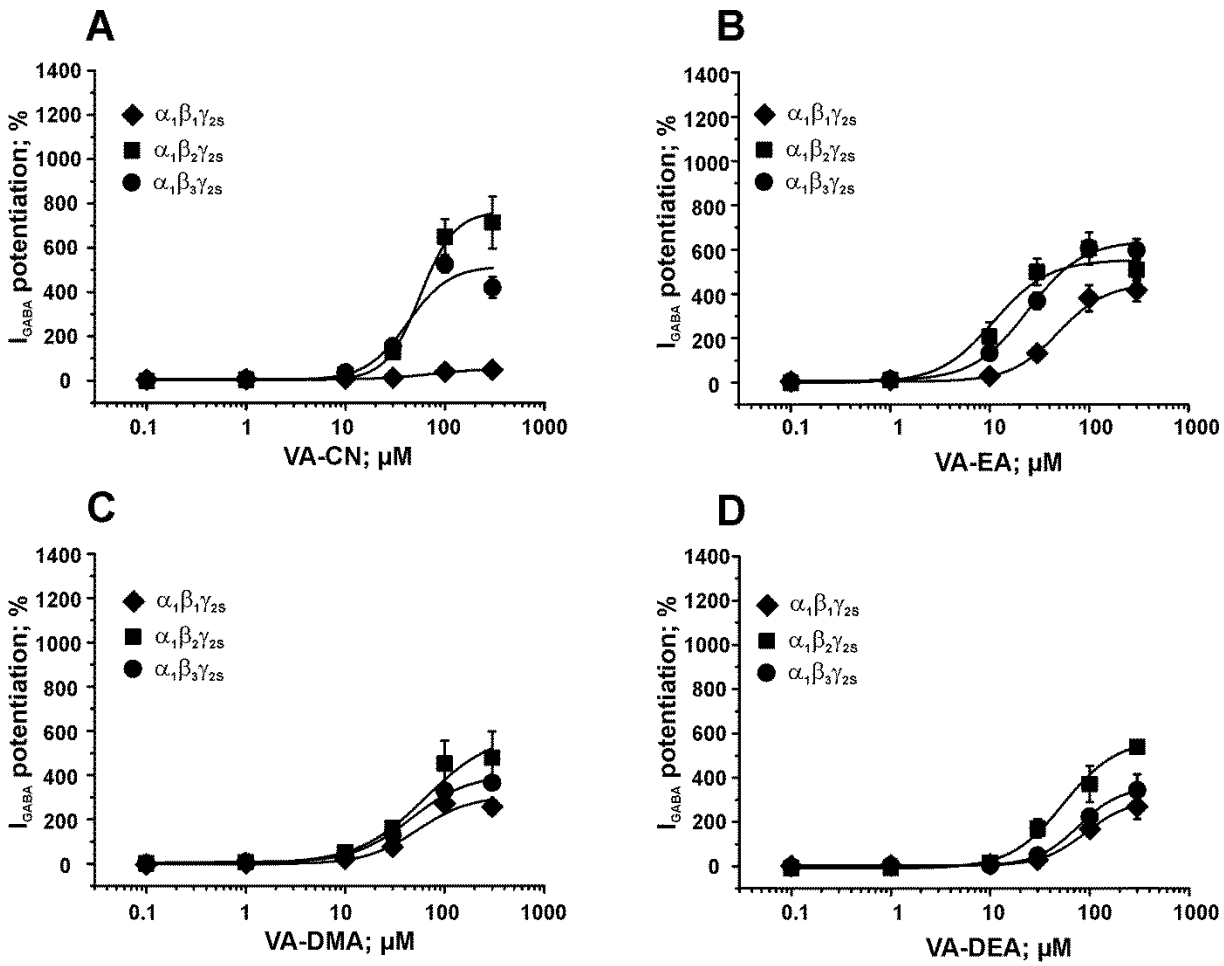


Figure 105 Determination of subunit selectivity of valerenic acid nitrile 21 (A), valerenic acid ethylamide 16 (B) and valerenic acid dimethylamide 15 (C) and valerenic acid diethylamide (D)

In addition to these results, some valerenic acid derivatives (valerenic acid amide **13** VA-A, monomethylamide **14** VA-MA, dimethylamide **15** VA-DMA, ethylamide **16** VA-EA, dimethylamide **17** VA-DEA, valerenic acid nitrile **21** and valerenic acid tetrazole **22** VA-TET) were characterized *in vivo*, to determine their anticonvulsant and anxiolytic activity and their sedative effects, based on their subunit specific modulation.

For determination of an anticonvulsant activity, male mice were trated with valerenic acid derivatives **13**, **14**, **15**, **16**, **17**, **21** and **22**, before seizures were induced by *intraperitoneal injection* of pentylenetetrazol (PTZ), a CNS stimulant. Seizure threshold was determined by pentylenetetrazole (PTZ) tail-vein infusion on freely moving animals at a rate of 100µl/min (10mg/ml PTZ in saline, pH=7.4). Infusion was stopped when animals displayed generalized clonic seizures. Animals were immediately killed by cervical displacement after onset of seizures. The seizure threshold dose was calculated from the infused dose in relation to body weight (mg/kg). The results are summarized in Figure 106.

For the reference compound valerenic acid **1**, the seizure threshold did not alter at doses lower than 3mg/kg bodyweight, while seizure threshold elevation was observed at doses of

3mg/kg respectively 10mg/kg (Figure 106 **A**; control: 40.4±1.4 mg/kg PTZ, n=6 vs. VA 3mg/kg: 47.7±1.4mg/kg PTZ, n=4, $p<0.01$ and VA 10mg/kg: 49.0±1.8mg/kg PTZ, n=4; $p<0.05$). At a dose of 30mg/kg, valerenic acid **1** traeted animals did not differ from diluents-treated control animals (30mg/kg VA: 43.4±1.8mg/kg PTZ, n=3, $p>0.05$). Valerenic acid amide **13** exerted, in comparison to valerenic acid **1**, a more pronounced anticonvulsive activity at doses higher than 3mg/kg (VA-A 3mg/kg: 57.9±1.9mg/kg PTZ, n=4; VA-A 10mg/kg: 55.4±0.7mg/kg PTZ, n=4, $p<0.001$) bodyweight with dropping anticonvulsive activity at higher doses (Figure 106 **B**; VA-A 30mg/kg: 50.6±2.2mg/kg PTZ, n=3, $p<0.01$). The most pronounced increase in seizure threshold was achieved by valerenic acid monomethylamide **14**. In contrast to VA **1** and VA-A **13**, a significant effect was observed at a dose of 10mg/kg (VA-MA 10mg/kg: 50.4±1.4mg/kg PTZ, n=4, $p<0.001$) and continued to rise even at higher doses (Figure 106 D;VA-MA 30mg/kg: 63.6±2.5mg/kg PTZ, n=3, $p<0.001$). Interestingly, the anticonvulsive effects of valerenic acid tetrazole **22** are shifted by a factor of ten to lower doses compared to valerenic acid **1**, with a PTZ-induced seizure threshold already observed at 0.3mg/kg (Figure 106 **C**; VA-TET 0.3mg/kg: 47.3±0.5mg/kg PTZ, n=5, $p<0.05$), concomitantly losing its anticonvulsive effect at doses higher than 1mg/kg. The other tested valerenic acid derivatives (valerenic acid dimethylamide **15**, valerenic acid ethylamide **16**, valerenic acid dimethylamide **17** and valerenic acid nitrile **21**) required similar doses for seizure threshold as valerenic acid **1** (Figure 106 **E-H**; compare VA 3mg/kg: 47.7±1.4mg/kg PTZ, n=4, vs. VA-EA 30mg/kg: 55.6±0.4 mg/kg PTZ, n=4, vs. VA-DEA: 48.7±1.7mg/kg PTZ, n=3, vs. VA-CN 10mg/kg: 51.1±0.6mg/kg PTZ, n=3).

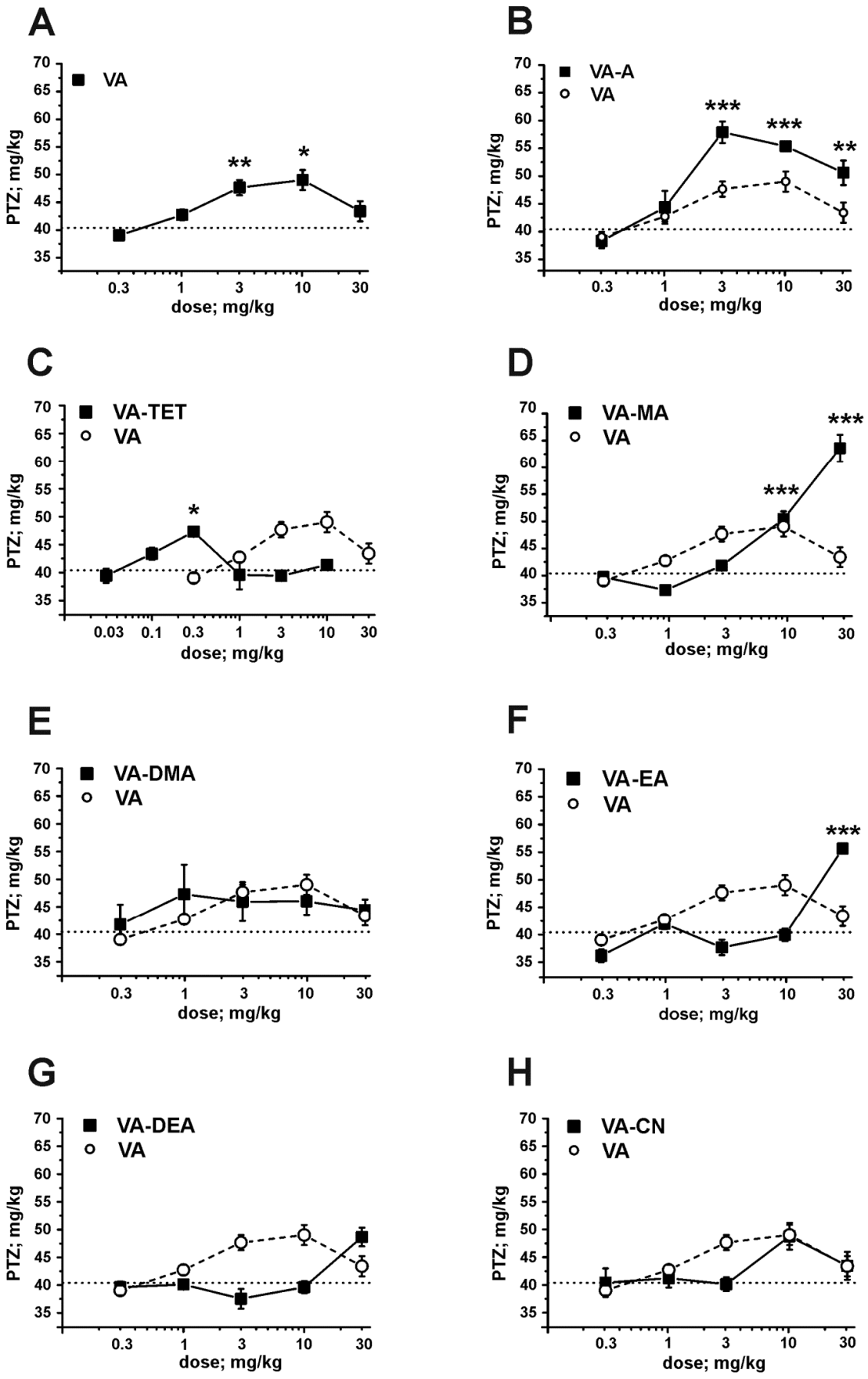


Figure 106 Effects of valerenic acid derivatives PTZ-induced seizure threshold

Besides their anticonvulsive activity, compounds **13**, **14**, **15**, **16, 17**, **21** and **22** were tested for sedative effects as well (Figure 107). No significant difference in locomotor activity could be observed for any valerenic acid derivative in the open field test, respectively no sedative effects were observed.

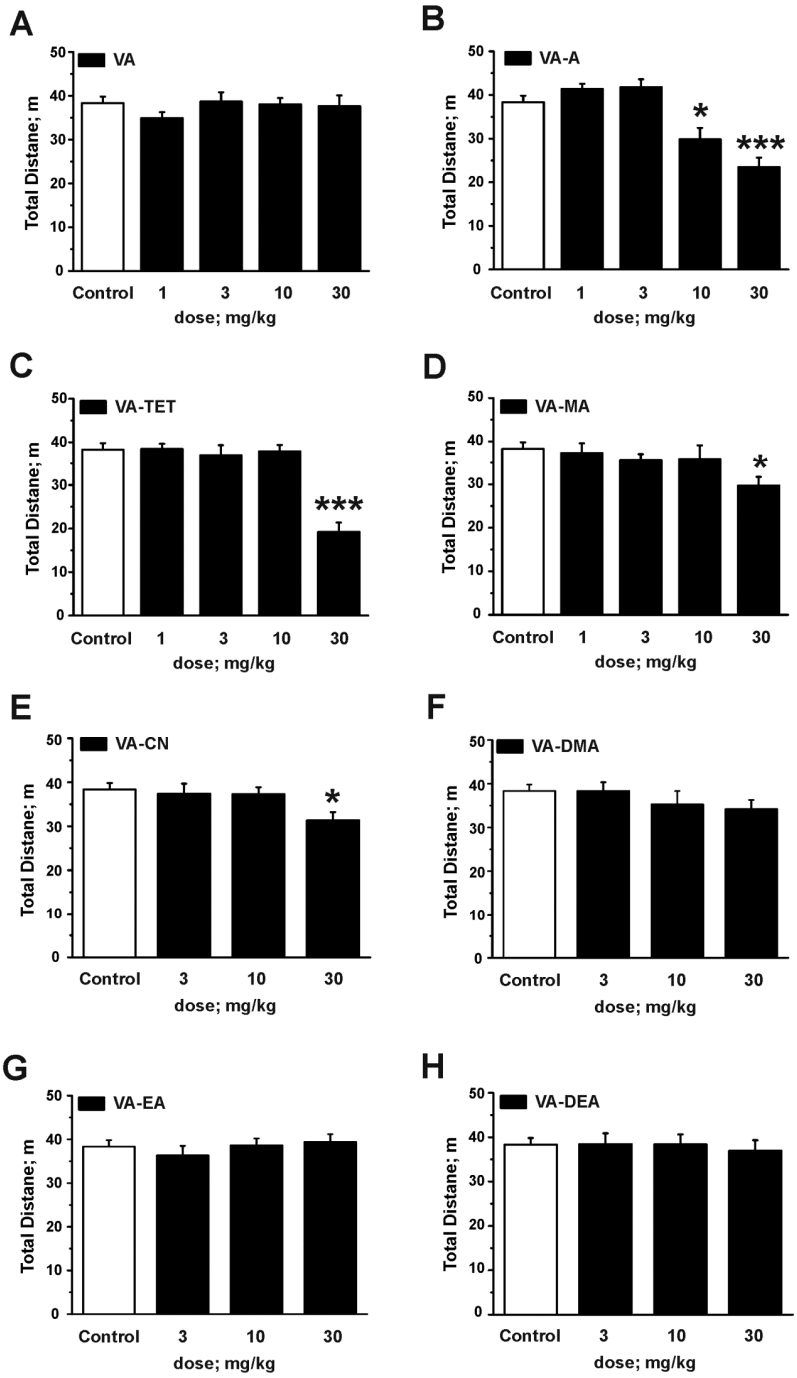


Figure 107 Effects of valerenic acid derivatives on locomotion in the open field test

G I.4 Derivatives at C7- the hydroxy-ester stage

Prior to the work of this thesis, synthetic intermediates of valerenic acid **1** had been tested for potency on the $GABA_A$-receptor, as well. Interestingly, derivatives of the C7-subtituent

showed partly surperior modulative effects than valerenic acid **1** at a certain intermediate stage.Therefore, it was initially opted to synthesize the C7-derivatives just until this intermediate stage (Figure 108), as it would shorten the synthesis of potent $GABA_A$-receptor modulatores by five steps.

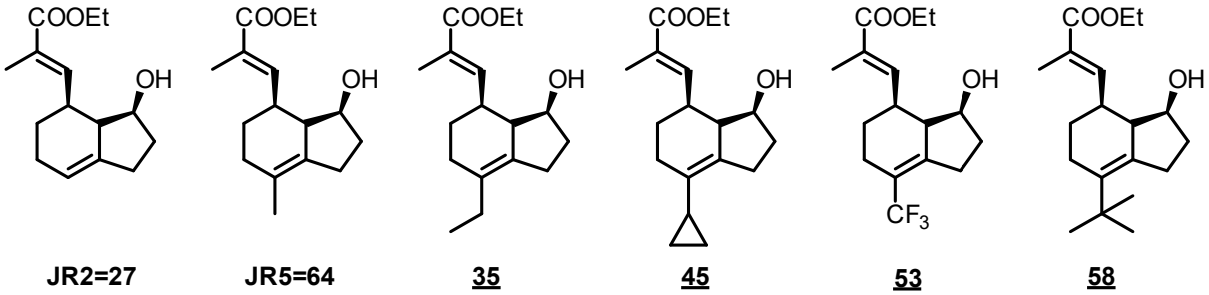


Figure 108: Hydroxy-Ester intermediates of valerenic acid and C7-derivatives

The prior synthesized intermediates were titled **JR2** (an intermediate of C7-normethyl valerenic acid **32**, synthesized within this thesis as **27**) and **JR5** (a valerenic acid **1** intermediate, synthesized within this thesis as **64**). The results of the tested intermediates are summarized in Figure 109.

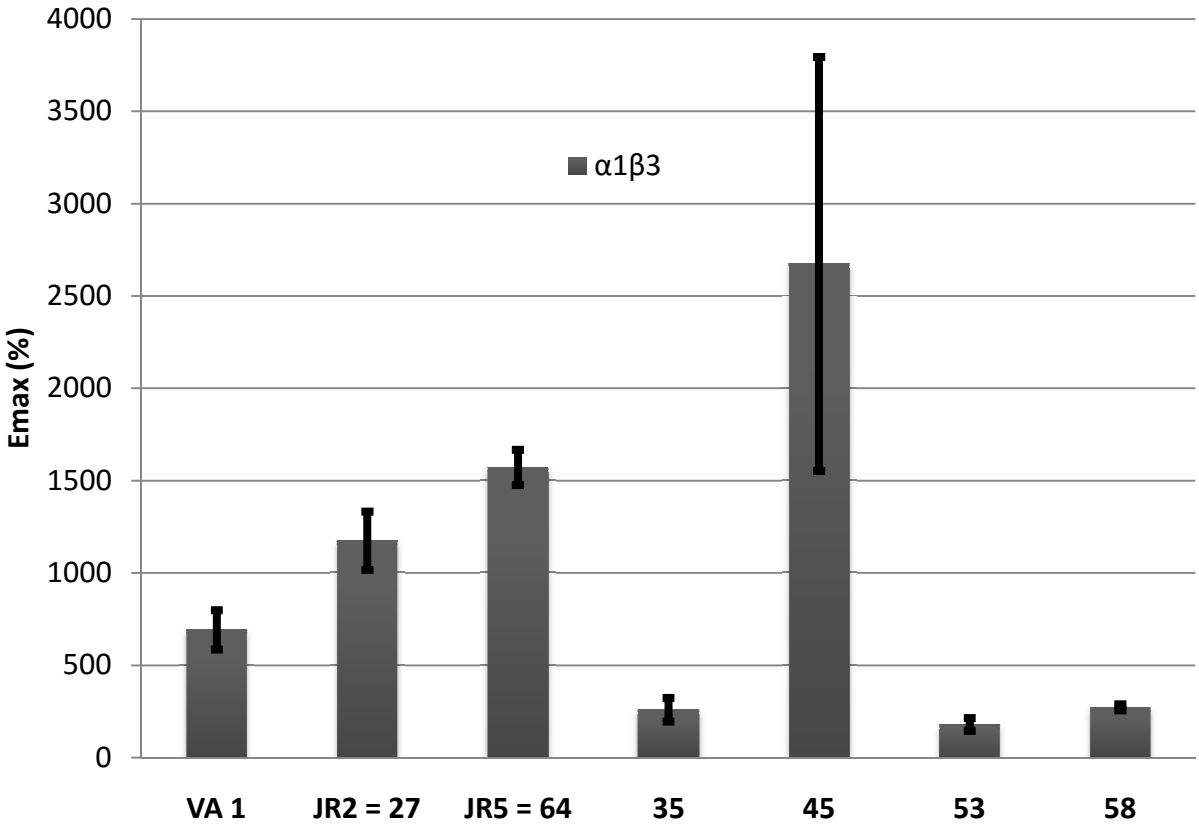
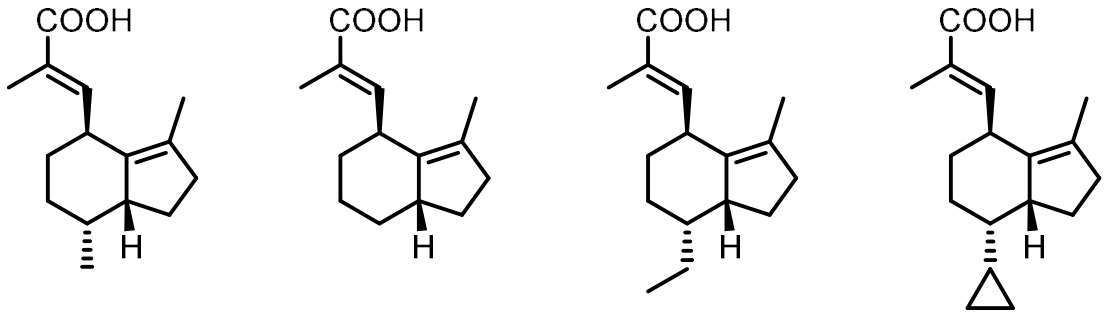


Figure 109: Maximum potentiation of synthetic intermediates compared to valerenic acid

Interestingly at this intermediate stage the esters, bearing a hydroxyl substituent in 3-position, are responsible for higher potentiation than valerenic acid **1** (Emax VA= 692±107 compared to intermediate hydroxyl-ester **64** = 1572±95), whereas valerenic acid ethyl ester shows a 9-fold decrease of potentiation (G I.2). This leads to the conclusion, that the hydrogen donor ability, needed for potentiation of $GABA_A$-receptors, stems from hydroxyl substituent in the 3-position. This is actually a very puzzling result and leads to the conclusion that a different binding mode of valerenic acid **1** and its hydroxyl-ester analogues is very likely.

Unfortunately, these derivatives seem to have limited storage stability as stock solutions in DMSO at -80°C. When, for example, the exact same batch of **JR2** was tested a few months later, the initially measured maximum efficacy of **JR2** (E_{max}= 1174.8±158.3µM) dropped to E_{max}= 632.7±22.4µM. Instead, a newly synthesized batch - simultaneously measured - displayed an even increased maximum efficacy of E_{max}= 1714.3±45.3µM. Therefore it was concluded, that the gathered data set (Figure 109) is invalid. It has to be stated, that no investigations on the degradation of these intermediates were conducted. Instead, it was attempted to synthesize the according C7-methyl derivatives of valerenic acid **1**, without any further consideration of the observed effects at the intermediate-stage for a given modification.

G I.5 Derivatives of the axial methyl group at C7



1 **32** **40** **50**

Figure 110 Valerenic acid and its C7-methyl derivatives

All successfully synthesized derivatives of the axial methyl group in C7 are depicted - along with valerenic acid **1** - in Figure 110. The purpose of these modifications was to determine the functional role of the axial C7-methyl group for potency and/or selectivity on $GABA_A$ receptors with a subunit composition bearing an α/β subunit interface. Therefore, the C7-methyl group was omitted decreasing sterical demand while erasing the C7 stereocenter through the 7-normethylvalerenic acid **32** modification. On the other hand, sterical bulk was increased stepwise, given by the 7-ethyl **40** and 7-cyclopropyl **50** modifications. Although the set of molecules is very low (just three), it still should provide enough information about the

role of the axial C7-methyl group when potency and selectivity of these derivatives are compared to the according values of valerenic acid **1**.

For determination of the efficacy of the aforementioned derivatives valerenic acid **1**, along with the 7-normethyl **32**, 7-ehtyl **40** and the 7-cyclopropyl **50** modification were tested on $GABA_A$ receptors composed of $\alpha_1\beta_3\gamma_{2s}$ subunits for their maximal potentiation (Figure 111). Unfortunately, none of the aforementioned derivatives shows even half the effect of valerenic acid **1**. While 7-normethylvalerenic acid **32** barely displayes half of the potentiation of valerenic acid, the 7-ethyl-derivative **40** is even further down with about a third of the effect from valerenic acid **1**, followed by the 7-cyclopropyl-derivative **50**, exhibiting a nearly five-fold decreased effect.

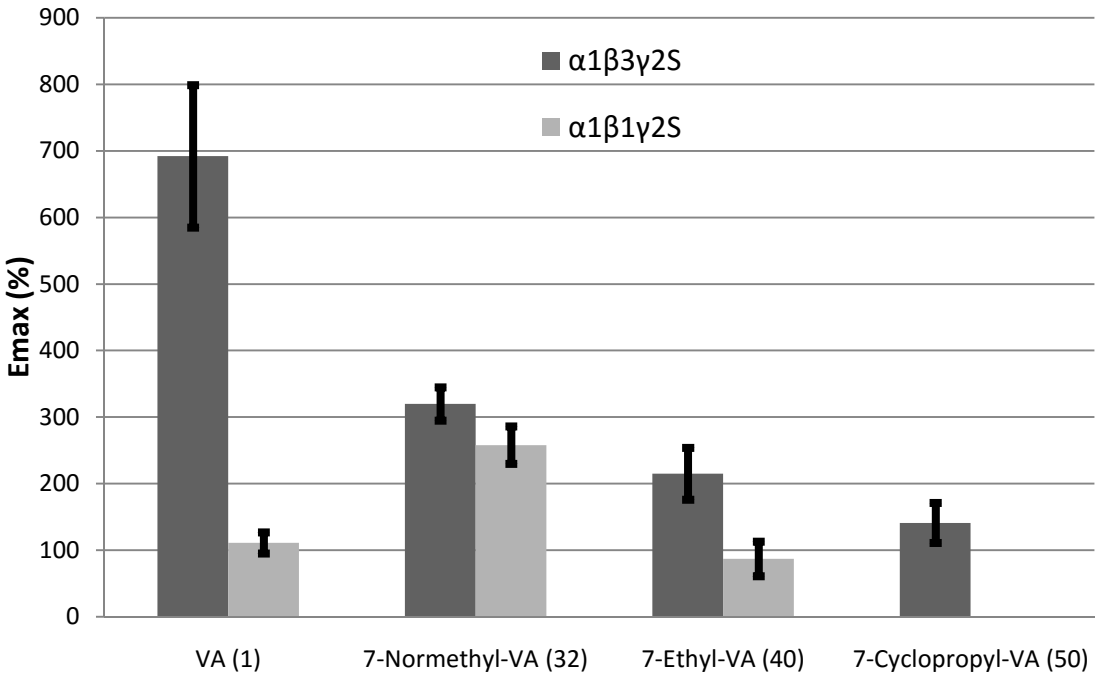


Figure 111 Maximum potentiation of valerenic acid and its C7-derivatives

Additionally, EC_{50}-values of the C7-derivatives were measured as well to determine their receptor affinity (Figure 112). Again, valerenic acid **1** (EC_{50}= 14.3±1.9 µM) shows a superior receptor affinity compared to the other C7-modifications. While 7-normethyl derivative **32** has a five times decreased receptor affinity (EC_{50}=75.6±13.7 µM) , 7-ethyl derivative **40** displays a little higher affinity, still being decreased to about 30% (EC_{50}= 51.7±22.0 µM). Unsurprisingly the affinity of 7-cyclopropyl derivative **50** is seven-fold less (104.8 µM±27.5 µM) than valerenic acid **1** and by far the lowest.

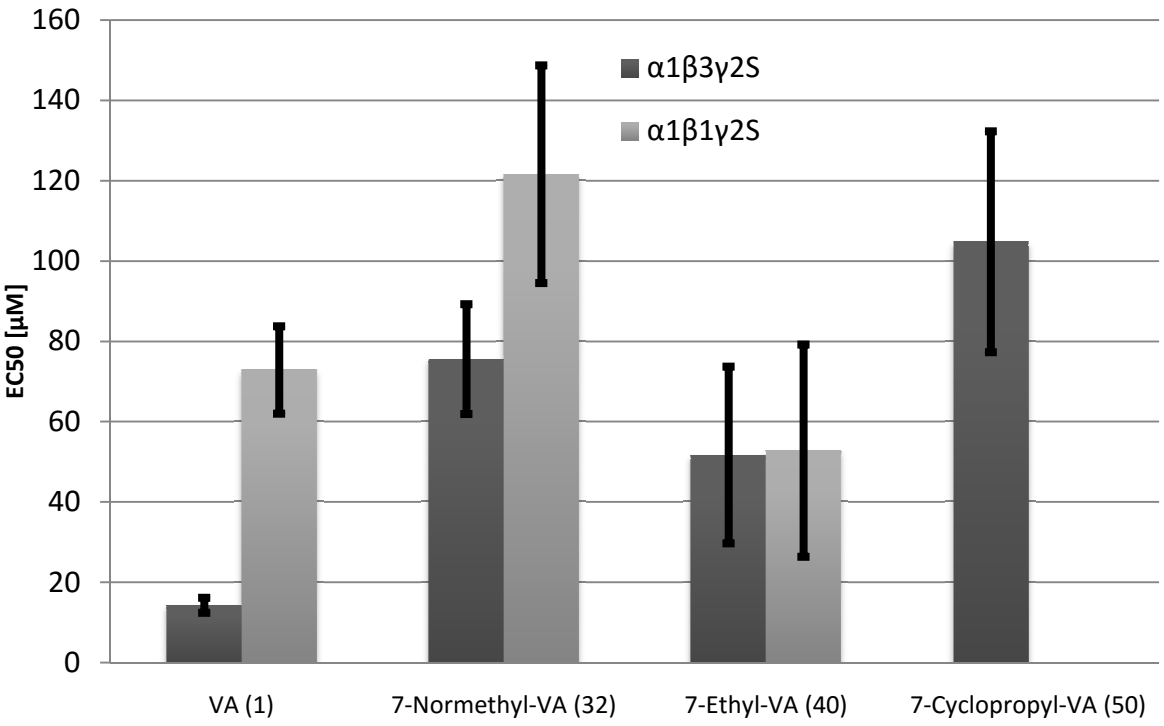


Figure 112 EC50 Values of C7-Methyl Derivatives

In comparison to the efficacy or affinity, selectivity was determined through measurement on $\alpha_1\beta_1\gamma_{2s}$ subunit composed $GABA_A$-receptors. Here, the ratios between the mean EC_{50}-values of $\alpha_1\beta_1\gamma_{2s}$ to $\alpha_1\beta_3\gamma_{2s}$ serves as aselectivity indicator and are summarized in Table 7 While valerenic acid **1** is highly selective for $\alpha_1\beta_3\gamma_{2s}$ receptors (about five times higher affinity!), the C7-normethyl derivative **32** is drastically decreased in terms of subunit selectivity displayed by a value of 1.6, while 7-ethyl derivative **40** is completely unselective. As a conclusion, this finding indicates a substantial role of the C7-substituent for selective modulation on $GABA_A$-receptors bearing an $\alpha_1\beta_3$-subunit interface.Unfortunately, the modification with the poorest efficacy (7-cyclopropyl derivative **50**) was not even investigated in terms of subunit selectivity by the pharmacologists, although it would underline the stated hypothesis.

Table 7 Selectivity values of C7-derivatives

Compound	$\alpha_1\beta_1\gamma_{2s}$/ $\alpha_1\beta_3\gamma_{2s}$
Valerenic acid **1**	5.1
7-Normethylvalerenic acid 32	1.6
7-Ethylvalerenic acid 40	1.0
7-Cyclopropylvalerenic acid 50	n.d.

As a result, it was found that the C7-methyl substituent is crucial for selective and effective potentiation of the investigated $GABA_A$-receptor subtypes. On the one hand, potentiation on $GABA_A$ receptors with an $\alpha_1\beta_3$ subunit interface decreases with and without steric bulk at the requisite C7-position, thus leading to the very speculative – as only three modifications were investigated- conclusion, that only a methyl substituent at C7 is tolerated for potent, high affine modulation. Furthermore, it had been demonstrated, that this methyl substituent is essential for subunit selectivity as well, given by the fact, that any modification in substituent size erases subunit selectivity between $\alpha_1\beta_3$ and $\alpha_1\beta_1$ subunit composed receptors. With the data gathered so far it has to be concluded, that the axial C7 methyl substituent is responsible for selective and effective modulation, as not any C7-position derivative exhibited higher efficacy, affinity or selectivity. Still, for a more comprehensive understanding of the substituent-role at C7, different modifications in this position have to be synthesized and tested. Unfortunately, such derivatives were beyond the scope of this thesis, as most of them- especially when di-substituting the C7-position or introducing heteroatomic substituents (trifluoromethyl-derivative failed, see F I.1) - would need a completely different synthetic approach yet to be established.

G I.6 Derivatives of the vinylic methyl group at C3

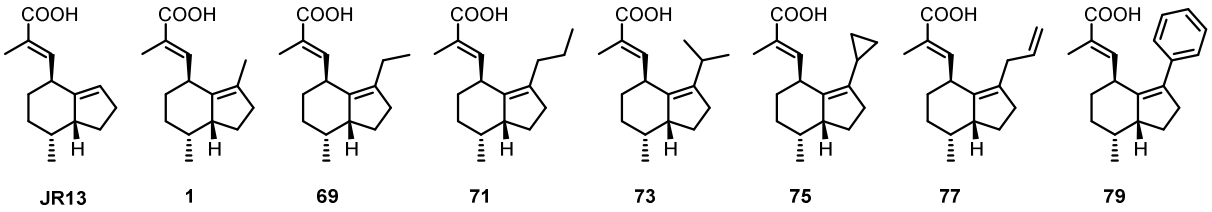


Figure 113 JR13, valerenic acid and C3-metyl derivatives

The sucessfully synthesized derivatives of the vinylic C3-methyl group are depicted- along with valerenic acid **1** and nor-methyl analog **JR13** – in Figure 113. To clarify the role of the methyl substituent in C3, derivatives, like C3-ethyl **69** and C3-propyl **71**, were chosen in order to investigate any efficacy and/or selectivity change associated to linear chain length. It has to be stated here, that a derivative, lacking the methyl (**JR13**) group at C3, has already been synthesized prior to this work and will not be discussed here. Furthermore branched substituents (C3-isopropyl **73** and C3-cyclopropyl **75** derivatives) as well as unsaturated substituents (C3-allyl **77**, C3-phenyl **79** and again C3-cyclopropyl **75** derivatives) have been introduced into the C3-position, to determine any influence associated to their chemical functionality. At this stage of the project, no heteroatomic substituents and no vinylic substituents were introduced in the C3-position, as they would require a different kind of chemistry applied than simple Negishi coupling chemistry. Arguably, vinylic substituents could have been introduced via cross-coupling chemistry as well (e.g. Stille coupling, Suzuki coupling), but this chemistry has not been investigated on this exact chemical entity yet.

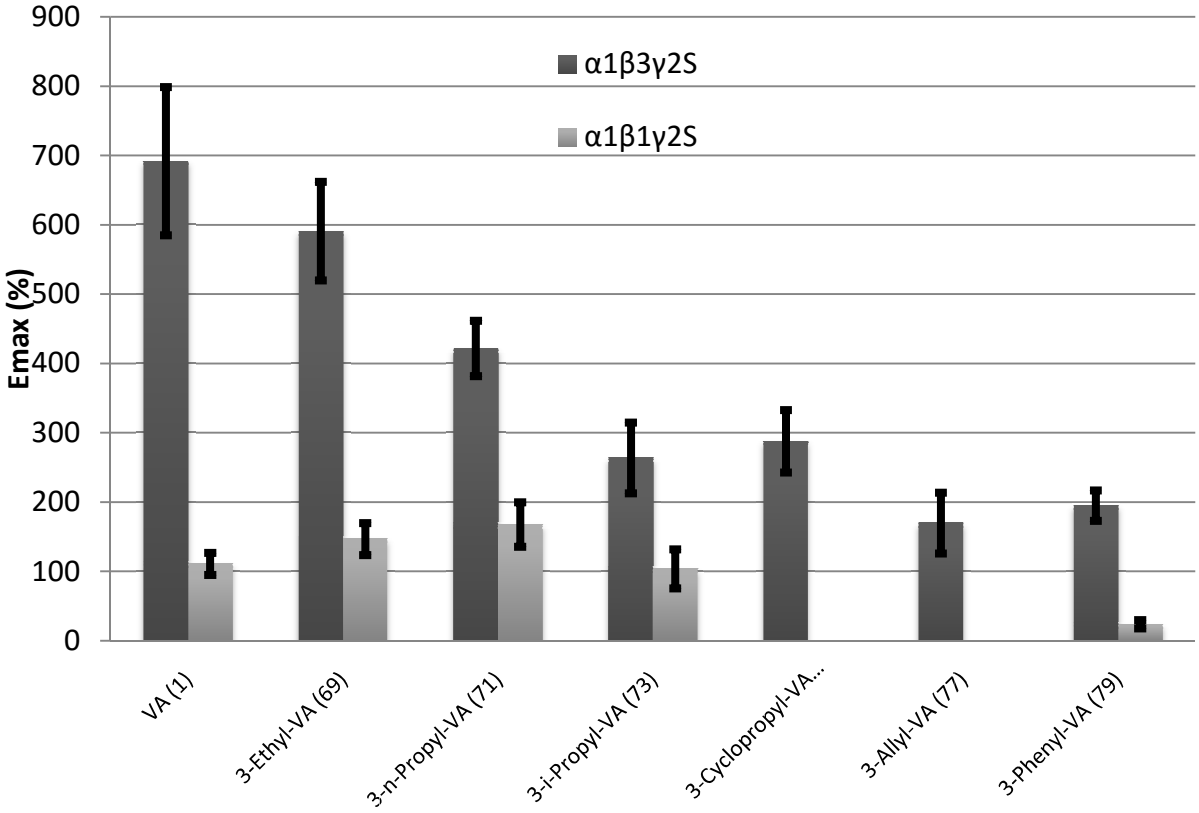


Figure 114 Maximum potentiation of valerenic acid compared to 3-methyl derivatives

Like the C7-derivatives, the C3-derivatives were pharmacologically investigated on $GABA_A$-receptors composed of $\alpha_1\beta_3\gamma_{2s}$ subunits (for potency and affinity) or $\alpha_1\beta_1\gamma_{2s}$ subunits (for selectivity) and compared to valerenic acid **1**. The maximum potentiation values measured for all C3-methyl derivatives are summarized in Figure 114. The only modification exhibiting a maximum potentiation close to valerenic acid **1** (E_{max}= 692±107%) is the C3-ethyl modification **69** (E_{max}= 591±71%). With increased C3-substituent size, the maximum effect drops in a nearly linear fashion, following the order 3-*n*-propyl-VA **71** (E_{max}= 422±40%) > 3-cyclopropyl-VA **75** (E_{max}= 288±45%) > 3-*i*-propyl-VA **73** (E_{max}= 264±51%) > 3-phenyl-VA **79** (E_{max}= 195±22%) > 3-allyl-VA **77** (E_{max}= 170±44%). This clearly indicates a relationship between steric bulk and observed effect, thus limiting the residue in C3 to a maximum size of ethyl. Again, like in the C7-modification set, a methyl substituent displays the highest potency (compare Figure 111), although an ethyl substituent is still tolerated by limiting the maximum effect by 86% compared to the C7-series, where the maximum effect is decreased to 31%.

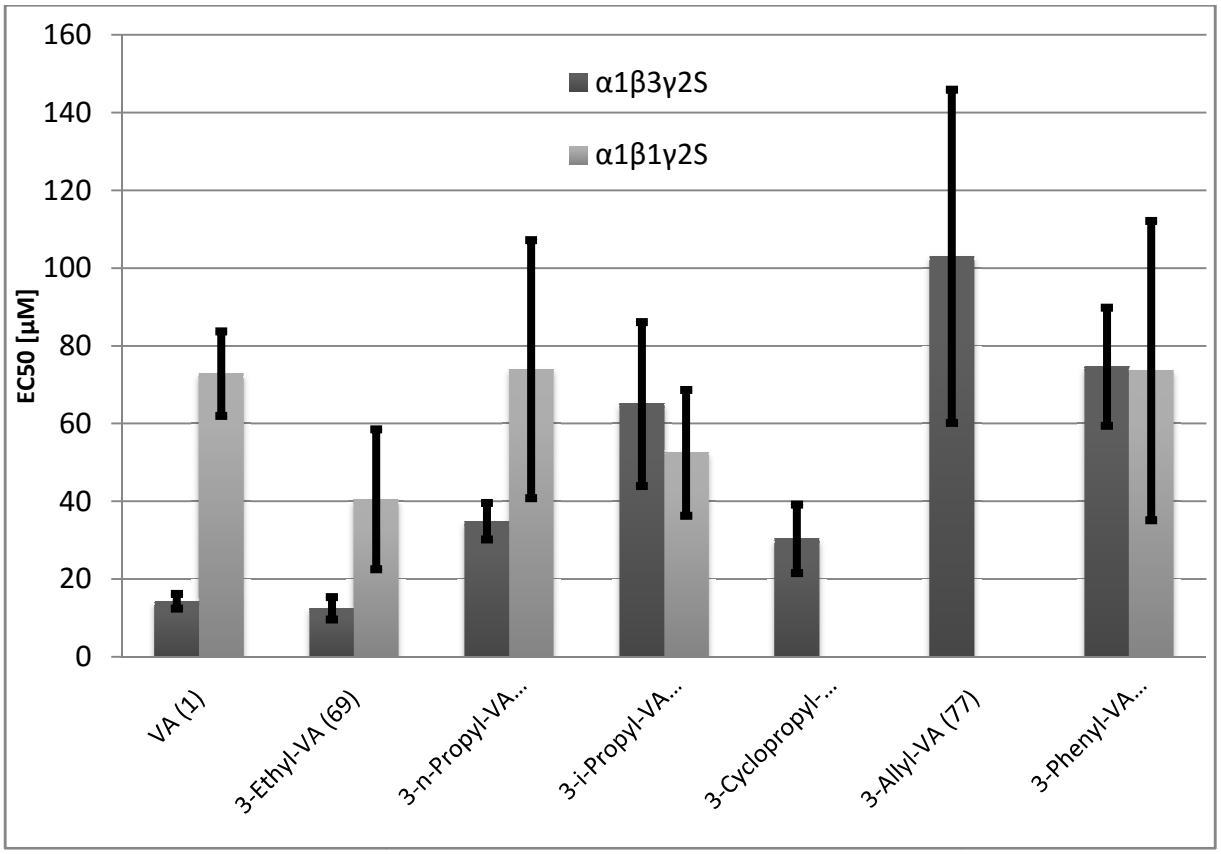


Figure 115 EC_{50}-values of C3-methyl derivatives compared to valerenic acid

Furthermore, receptor affinity studies – visualized by EC_{50}-values (Figure 115)- were conducted. Surprisingly C3-ethyl derivative **69** (EC_{50}=12.5±2.9 µM) shows a higher – although insignificantly - receptor affinity compared to valerenic acid **1** (EC_{50}=14.3±1.9 µM). With additional linear and especially with branched steric demand of substituents, the affinity significantly drops following the order C3-cyclopropyl **75** (EC_{50}=30.4±8.8 µM) ≈ 3-*n*-propyl **71** (EC_{50}=34.9±4.7 µM) > 3-*i*-propyl **73** (EC_{50}=65.1±21.1 µM). Both unsaturated substituents already show very high affinity loss being five times (C3-phenyl **79**; EC_{50}=74.7±15.2 µM) respectively seven times (C3-allyl **77**; EC_{50}=103.1±42.9 µM) less efficient than valerenic acid **1**.

In terms of subunit selectivity a similar trend associated to the sterical bulk of C3-substituents can be observed. Like the efficacy, the selectivity decreases with increased carbon chain length, dropping from 5.1 for valerenic acid **1**, to 3.2 for 3-ethylvalerenic acid **69** and 2.1 for 3-*n*-propylvalerenic acid **71**. Interestingly, the selectivity seems to be slightly inverted with a value of 0.8 for the 3-*i*-propyl **73** modification and the 3-phenyl **79** modification- Although the selectivity-ratio is 1.0, the error margin for the EC_{50} ($\alpha_1\beta_1\gamma_{2s}$= 73.7±38.5 µM; see Figure 114) is significantly high to at least assume an even, respectively an inverted selectivity, and therefore associate this phenomenon to branched substituents. Nevertheless, for imaging a clear trend of the influencing factors on selectivity, at least the EC_{50}-values on $\alpha_1\beta_1\gamma_{2s}$-composed receptors of the 3-allyl **77** and 3-cyclopropyl **75** derivatives

would be beneficial, but unfortunately these measurements were not conducted by the pharmacological partner. As a result, this hypothesis stays highly speculative.

Concluding, only the 3-ethyl modification **69** showed similar efficacy – while being less subunit selective. No modification at C3 had any striking effect on either efficacy or selectivity. Although increased steric bulk decreases the efficacy on $\alpha_1\beta_3\gamma_{2s}$ composed receptors, the same trend cannot be observed for $\alpha_1\beta_1\gamma_{2s}$ composed receptors. Here the affinities for the 3-ethyl **69** and the 3-*i*-propyl **73** are higher compared to valerenic acid **1**, leading to decreased or even inversed selectivity values. As a consequence, the only valuable information gathered from the investigated C3 modifications is that just very narrow changes, from a sterical point of view, are allowed at this position. Therefore a C3-vinyl modification as well as short chain heteroatomic subsituents (eg.: $-CF_3$, $-CF_2H$, $-CH_2CF_3$,-CN, CH_2OH...) could still exhibit superior efficacy than valerenic acid itself, presupposed they are chemically stable and readily synthetically accessible.

Table 8 Selectivity values for C3-derivatives

Compound	$\alpha_1\beta_1\gamma_{2s}$/ $\alpha_1\beta_3\gamma_{2s}$
Valerenic acid **1**	5.1
3-Ethylvalerenic acid **69**	3.2
3-n-Propylvalerenic acid **71**	2.1
3-i-Propylvalerenic acid **73**	0.8
3-Cyclopropylvalerenic acid **75**	n.d
3-Allylvalerenic acid **77**	n.d
3-Phenylvalerenic acid **79**	1.0

H Conclusion and perspective

The results generated within this thesis certainly give a deeper insight in the structural motives needed for potent and subunit-selective modulation of the $GABA_A$-receptor based on the valerenic acid scaffold.

Through modification of the acid functionality it has been demonstrated that a hydrogen donating group bearing a small alkyl substituent (methyl or ethyl) is necessary for increased potency when comparing the results of the various tested esters and amides. This was demonstrated by a two-fold increased modulation of valerenic acid amide **13**, valerenic acid monomethylamide **14** and the significant drop of modulation with their bis-alkyl homologues (dimethylamide **15** and diethylamide **17**). Furthermore it had been demonstrated, that modification of the carboxyl-moiety has an effect on the subunit selectivity. The only subunit selective dervivatives are valerenic acid amide **13**, methylamide **14** and alerenic acid tetrazole **22**. Graftifyingly none of the tested acid derivatives showed any sedative effect while exhibiting anticonvulsive activity.So a potential lead structure, based on these results, should feature either an amid or monomethylamide moiety at this position.

Modification of the C-7 position on the indanyl core revealed the crucial role of the axial-methyl group for both selective and effective modulation. In this regard C-7 geminal dimethyl, geminal cycloproyl, a methylene substituent and the aimed, but failed, trifluoromethyl modifications seem to be the most interesting and promising structural targets for a deeper investigation of the axial methyl group. Unfortunately, such derivatives are not available through the current synthetic route and a different synthesis enabling these aforementioned derivatives – preferably from the same intermediate – should be the future go-to strategy.

In comparison to the C-7 methyl group, the C-3 methyl group seems to have no effect on the subunit selective modulation. To assure this observation, more accurate pharmacological investigation of the C-3- normethylderivative **JR13** and synthesis and pharmacological investigation of a C-3-vinyl derivative need to be conducted. Still the yet investigated derivatives imply a maximum sterical bulk of an ethyl group and the optimal substituent at this position so far is the methyl like in valerenic acid **1**.

In addition to the investigated modifications a partly novel synthetic route has been developed. This route overcomes chemoselectivity-problems faced when applying the Mulzer synthesis for some of the aimed derivatives with regard of the crabtree reduction. Concomittantly the whole synthesis is more cost-effective due to the lower iridium-catalyst loadings needed (10mol% $Ir(cod)(py)PCy_3PF_6$ loading decreased to 3%). Shifting the introduction of the metacrylate functionality towards the end of the synthesis has also benifical effects for future modifications at the indanyl core, as the reactive Michael-acceptor is not present at this stage. This allows the application of reaction

conditions/reagents incompatible with an acrylate group and enables a higher versatility from a synthetic and therefore from a structural point of view.

I Experimental part

I I Materials and methods – chemical synthesis

Unless noted otherwise, all reagents were purchased from commercial suppliers and used without further purification. DCM, Et_2O, dioxane, MeOH, THF and toluene intended for water-free reactions were pre-distilled and then desiccated on Al_2O_3 columns (PURESOLV, Innovative Technology). Chromatography solvents were distilled prior to use. For all other solvents, quality grade is given in the reaction procedures. Solvents were degassed by means of freeze-thaw degassing method (three cycles): The appropriate solvent was placed in a one-necked roundbottom flask, being at least double the volume of the solvent amount (e.g. for 50ml of solvent use a 100ml flask) equipped with a rubber septum. Then the flask is frozen with liquid nitrogen. When all of the liquid is frozen, the flask is evacuated at the schlenkline. Then the vacuum is shut off and the frozen liquid is thawed. During this process gasbubbles evolve. Then argon is passed into the flask, before it is frozen and evacuated again. The whole procedure is repeated at least three times.

Column chromatography was performed on a Büchi Sepacore Flash System (2 x Büchi Pump Module C-605, Büchi Pump Manager C-615, Büchi UV Photometer C-635, Büchi Fraction Collector C-660) or standard manual glass columns using silica gel from Merck (40-63 µm) using LP and Et_2O or EtOAc mixtures.

Argentated silica gel ($AgNO_3$-doped SiO_2) was used to separate olefin-isomeres from each other based on the ability of silver compounds, to reversibly form polar complexes with double bonds based on their geometry. For preparation of $AgNO_3$-silica the procedure of Cert and Moreda[62] was applied: To 150 g of activated silica (heating in the drying oven at 120°C overnight) in an 1000ml roundbottom flask coverd with aluminum foil, 15 g of $AgNO_3$ dissolved in 35ml was dispensed evely with a Pasteur pipette dropwise while shaking the flask. Then the flask was placed on a rotary evaporator and rotated for 30 minutes under atmospheric pressure and room temperature. For storage, the doped silica was transferred into a brown glass bottle. Note: $AgNO_3$-doped silica should be stored in darkness!

Desiccation of organic solvents after extraction in reaction workup was performed using sodium sulfate and subsequent filtration.

GC-MS analyses were conducted on a Thermo-Fisher BGB5 column (30m*0.32mm, 1.0µm film, achiral) GC Focus/MS DSQ II (quadrupole, EI+).

NMR spectra were recorded from $CDCl_3$ or CD_2Cl_2 solutions on a Bruker AC 200 (200 MHz) or Bruker Advance UltraShield 400 (400 MHz) spectrometer and chemical shifts are reported in ppm using tetramethylsilane as an internal standard. Whenever possible, calibration *via* residual solvent peaks was performed. Peak assignment is based on software prediction. For peak-numbering (annotation) see Figure 116. For simplification reasons, the indanyl-core numbering is in every intermediate structure the same, although IUPAC nomenclature changes the numbering of the indanyl core several times!

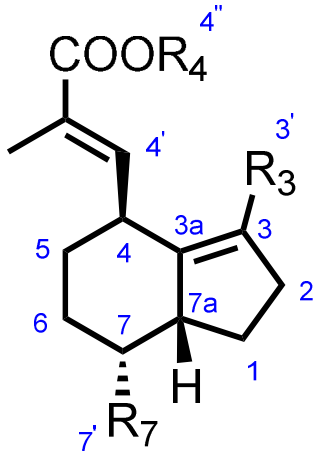


Figure 116 Structural numbering for NMR-interpretation

Specific rotation was measured on an Anton Paar MCP500 polarimeter at the specified conditions.

High resolution mass spectrometry was recorded on a Shimadzu IT-TOF-MS with ESI and APCI interface.

Measurement and quantification of enantiomeric excess was performed on chiral HPLC with a Diacel CHIRALPAK AS-H column and heptane/*i*-PrOH as eluent with the following methods:

- Isocratic 16: heptane:iPrOH= 97.0:3.0; 1ml/min, 45min, UV_1=220 nm, UV_2=235 nm, UV_3= 280 nm
- Isocratic 17: heptane:iPrOH= 98.0:2.0; 1ml/min, 20min, UV_1=220 nm, UV_2=235 nm, UV_3= 280 nm
- Isocratic 18: heptane:iPrOH= 98.5:1.5; 1ml/min, 30min, UV_1=210 nm, UV_2=254 nm, UV_3= 280 nm
- Isocratic 19: heptane:iPrOH= 98.5:1.5; 1ml/min, 20min, UV_1=210 nm, UV_2=254 nm, UV_3= 280 nm

- Isocratic 20: heptane:iPrOH= 98.5:1.5; 1ml/min, 40min, UV_1=210 nm, UV_2=254 nm, UV_3= 280 nm
- Isocratic 21: heptane:iPrOH= 98.8:1.2; 1ml/min, 30min, UV_1=210 nm, UV_2=254 nm, UV_3= 280 nm

Microwave experiments were conducted at a Biotage Initiator microwave:

Temperature 40-250 °C (104-482 °F)

Temperature increase 2-5 °C/sec (3.6-9 °F/sec)

Pressure range 0-20 bar (2 MPa, 290 PSI)

Power range 0-400 W at 2.45 GHz

Reaction vials 4 sizes: 0.2-0.5, 0.5-2, 2-5, 10-20 mL

Vial volume range 0.2-20 mL (EXP) 0.5-5 mL

Agitation Variable magnetic stirrer (300-900 RPM)

Sample Processor upgradeable with Robot Eight/ Robot Sixty

Processing capacity 8 vials / 60 vials

Rack capacity (large) 2x2 vials / 2x12 vials

Rack capacity (small) 2x4 vials / 2x30 vials

Temperature 18-32 °C (65-90°F)

Humidity 20-95% RH

Electrical supply EU: 220-240 V, 50 Hz (5 A) US: 120 V, 60 Hz (10 A) JP: 100V, 5

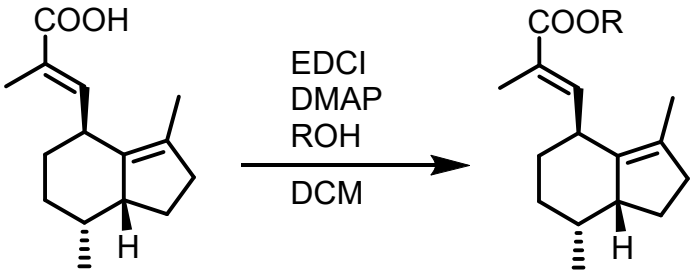
Maximum power consumed 1000 VA

Standby/Off 45/0W

Pressurized air supply (reaction cooling) Cooling Pressurized air supply >60 L/min (2.1 cubic feet/min), 2.5 – 4 b

I II Synthesis of valerenic acid derivatives

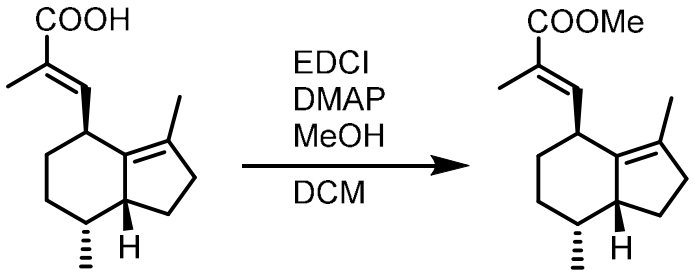
I II.1 Synthesis of valerenic acid esters-general procedure



1 **2-7**

Valerenic acid **1** (1.00 equiv.) and DMAP (0.1eq) were dissolved in dry DCM (10 mol% solution) under an argon atmosphere and cooled to 0°C before EDCI (1.50eqiv.) was added in one portion. After stirring the mixture for five minutes, 4.5 eqiv. of the appropriate alcohol was added dropwise and the mixture was allowed to warm to room temperature overnight. The solution was taken up in 50ml EtOAc and subsequently washed with saturated NH_4Cl solution (three times), saturated $NaHCO_3$ solution (three times), and once with brine before it was dried and concentrated under reduced pressure. Purification of the crude material via column chromatography (LP and EtOAc) yielded pure esters **2-7**.

I II.1.1 Valerenic acid methyl ester 2



1 **2**

Applied Reagents: Valerenic acid **1** (30.00mg, 1.00eqiv., 0.13mmol), DMAP (1.56mg, 0.1eqiv., 0.01mmol), EDCI.HCl (36.80mg, 1.50eqiv.,0.19mmol), methanol (24µl=19mg, 4.50eqiv., 0.59mmol)

Column Chromatography: 10g SiO_2 (LP:EE=10:1)

Yield: 30.7mg (95%) colorless oil[49]

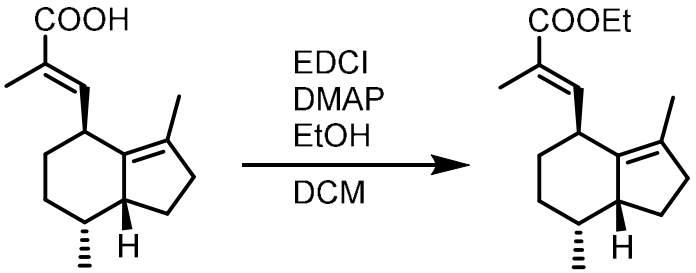
Molecular Formula: $C_{16}H_{24}O_2$

Molecular weight [g/mol]: 248.36

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.77 (d, J = 7.0 Hz, 3H, 7'-CH_3), 1.37-1.98 (bm, 14H), 2.14-2.22 (m, 2H,2-CH_2), 2.90-2.99 (m, 1H, 7a-CH), 3.52 (dd, J_1 = 9.6Hz, J_2=4.4 Hz, 1H, 4-CH), 3.72 (s, 3H, 4''-OCH_3), 7.01 (dd, J_1 = 9.8 Hz, J_2 = 1.4Hz , 1H, 4'-CH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 12.0 (q, 7-CH_3), 12.4 (q, 3-CH_3), 13.5 (q, 4'-CH_3), 24.5 (t,1-CH_2), 25.4 (t,5-CH_2), 28.7 (t,6-CH_2), 33.0 (d, 4-CH), 34.3 (d, 7-CH), 37.4 (t,2-CH_2), 47.4 (d, 7a-CH), 51.7 (q, 4''-OCH_3), 125.7 (s,4'-C), 130.9 (s, 3-C), 133.4 (s, 3a-C),143.6 (d, 4'-CH) 169.0 (s, 4'-CO)

I II.1.2 **Valerenic acid ethyl ester 3**



1 **3**

Applied Reagents: Valerenic acid **1** (20.00mg, 1.00eqiv., 0.09mmol), DMAP (0.96mg, 0.1eqiv., 0.01mmol), EDCI.HCl (25.88mg, 1.50eqiv.,0.14mmol), ethanol (24µl=19mg, 4.50eqiv., 0.41mmol)

Column Chromatography: 10g SiO_2 (LP:EE=10:1)

Yield: 20.2mg (95%) colorless oil[93]

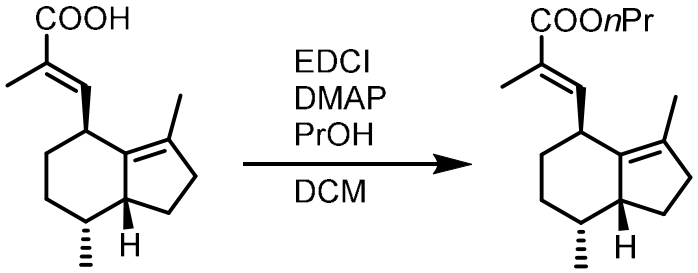
Molecular Formula: $C_{17}H_{26}O_2$

Molecular weight [g/mol]: 262.39

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.78 (d, J=7.0 Hz, 3H, 7-CH_3), 1.29 (t, J=7.12 Hz, 3H, 4''-CH_3), 1.37-2.02 (bm, 14H), 2.19 (t, J=7.6 Hz, 2H, 2-CH_2), 2.92-2.98 (m, 1H, 4-CH), 3.46-3.56 (m, 1H, 7a-CH), 4.17 (q, J= 7.1 Hz, 2H, 4''-OCH_2), 7.01 (dd, J_1 =9.8 Hz, J_2 = 1.4Hz, 1H, 4'-CH_2)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 12.0 (q, 7-CH_3), 12.4 (q, 3-CH_3), 13.5 (q, 4'_CH_3), 14.3 (q, 4''-CH_3), 24.5 (t, 1-CH_2), 25.5 (t, 5-CH_2), 28.7(t, 6-CH_2), 33.1 (d, 4-CH), 34.3 (d, 7-CH), 37.4 (t, t-CH_2), 47.4 (d,7a-CH), 60.4 (t, 4''-OCH_2), 126.0 (s, 4'-C), 130.8 (s, 3-C), 133.5 (s, 3a-C), 143.2 (d, 4'-CH), 168.6 (s, 4'-CO)

I II.1.3 **Valerenic acid propyl ester 4**



1 **4**

Applied Reagents: Valerenic acid **1** (30.00mg, 1.00eqiv., 0.13mmol), DMAP (1.56mg, 0.1eqiv., 0.01mmol), EDCI.HCl (36.80mg, 1.50eqiv.,0.19mmol), *n*-propanol (44µl= 35mg, 4.50eqiv., 0.59mmol)

Column Chromatography: 10g SiO_2 (LP:EE=10:1)

Yield: 35.1mg (99%) colorless oil

Molecular Formula: $C_{18}H_{28}O_2$

Molecular weight [g/mol]: 276.41

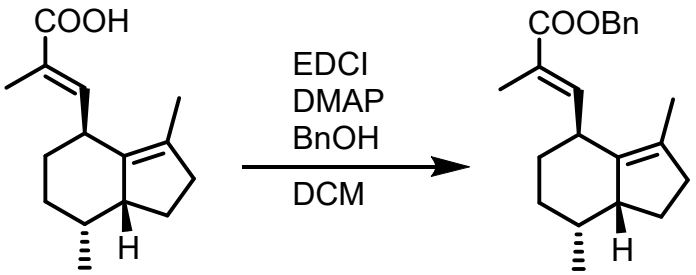
$[\alpha]_D^{20}$: -77.0° (0.20g/100ml DCM)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.77 (d, J=7.0, 3H, 7'-CH_3), 0.95 (t, J=7.41 Hz, 3H, 4''-CH_3), 1.37-2.01 (bm, 16H), 2.19 (t, J=7.7 Hz, 2H, 2-CH_2), 2.91-2.97 (m, 1H, 7a-CH), 3.48-3.55 (m, 1H, 4-CH), 4.07 (t, J= 6.7 Hz, 2H, 4''-O-CH_2), 7.02 (dd, J_1 =9.8 Hz, J_2 = 1.3Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ =10.5 (q, 4''-CH_3), 12.0 (q, 7-CH_3), 12.4 (q, 3-CH_3), 13.5 (q, 4'-CH_3), 24.5 (t, 1-CH_2), 25.5 (t, 5-CH_2), 28.7 (t, 6-CH_2), 33.1 (d, 4''-CH_2-$\underline{C}H_2$), 34.3 (d, 7-CH), 37.4 (t, 2-CH_2), 47.4 (d, 7a-CH), 66.0

(t,4‘‘-OCH_2), 126.0 (s,4‘-C), 130.7 (s, 3-C), 133.5 (s, 3a-C), 143.3 (d, 4‘-CH) 168.7 (s,4‘-CO)

I II.1.4 **Valerenic acid benzyl ester 5**



1 **5**

Applied Reagents: Valerenic acid **1** (30.00mg, 1.00eqiv., 0.13mmol), DMAP (1.56mg, 0.1eqiv., 0.01mmol), EDCI.HCl (36.80mg, 1.50eqiv.,0.19mmol), benzylalcohol (61µl=63mg, 4.50eqiv., 0.59mmol)

Column Chromatography: 10g SiO_2 (LP:EE=4:1)

Yield: 39.0mg (94%) yellow oil

Molecular Formula: $C_{22}H_{28}O_2$

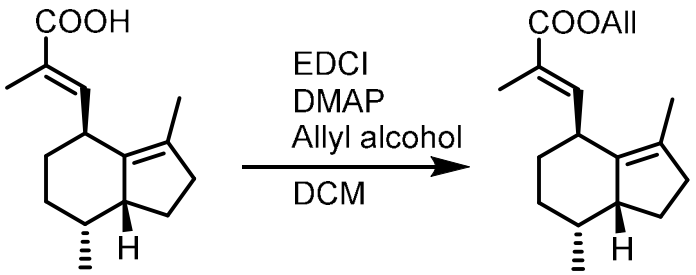
Molecular weight [g/mol]: 324.46

$[\alpha]_D^{20}$: -60.9° (c=0.30g/100ml DCM)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.78 (d, J=6.9 Hz, 3H, 7'-CH_3), 1.37-2.01 (bm, 14H), 2.20 (t, J=7.6 Hz, 2H, 2-CH_2), 2.91-2.96 (m, 1H, 7a-CH), 3.50-3.57 (m, 1H, 4-CH), 5.19 (s, 2H, 4''-CH_2Ph), 7.09 (dd, J_1=9.8 Hz, J_2= 1.3Hz, 1H, 4'_CH), 7.33-7.39 (m, 5H, 4''-Ph)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 12.0 (q, 7-CH_3), 12.4 (q, 3-CH_3), 13.5 (q,4'-CH_3), 24.5 (t, 1-CH_2), 25.4 (t, 5-CH_2), 28.7(t, 6-CH_2), 33.1 (d, 4-CH), 34.4 (d, 7-CH), 37.4 (t, 2-CH_2), 47.4 (d, 7a-CH), 66.2 (t, 4''-CH_2Ph), 125.7 (s, 4'-C),127.97 (d,4''-ArCH), 128.01 (d,4''-ArCH), 128.5 (d,4''-ArCH) 130.9 (s, 3-C), 133.3 (s,3a-C),136.5 (q, 4''-ArC) 144.1 (d,4'-CH) 168.7 (s, 4'-CO)

I II.1.5 **Valerenic acid allyl ester 6**



1 **6**

Applied Reagents: Valerenic acid **1** (50.00mg, 1.00eqiv., 0.21mmol), DMAP (2.36mg, 0.1eqiv., 0.02mmol), EDCI.HCl (60.39mg, 1.50eqiv.,0.32mmol), allylalcohol (65µl=55mg, 4.50eqiv., 0.95mmol)

Column Chromatography: 10g SiO_2 (LP:EE=5:1)

Yield: 56.2mg (97%) yellow oil

Molecular Formula: $C_{18}H_{26}O_2$

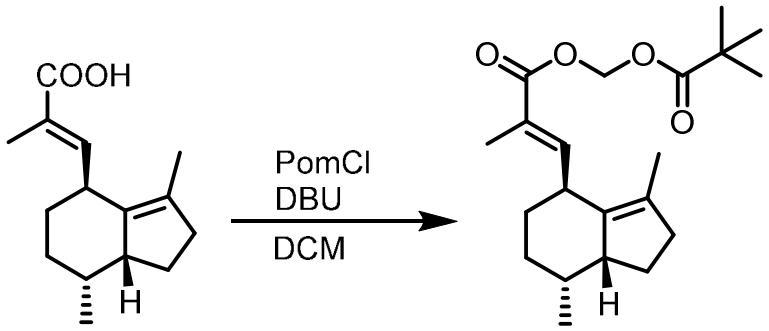
Molecular weight [g/mol]: 274.40

$[\alpha]_D^{20}$: -50.1° (c=0.61g/100ml DCM)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.77 (d, J=7.0, 3H, 7-CH_3), 1.37-2.01 (bm, 14H), 2.19 (t, J=7.7 Hz, 2H, 2-CH_2), 2.91-2.98 (m, 1H, 7a-CH), 3.50-3.56 (m, 1H, 4-CH), 4.63 (dd, J_1=5.5 Hz, J_2 = 1.3 Hz, 2H, 4'-OCH_2), 5.22 (dd, J_1 = 10.39 Hz, J_2 = 1.34 Hz, 1H, 4''-CH_2), 5.32 (dd, J_1 = 17.2 Hz, J_2 = 1.5 Hz, 1H, 4''-CH_2), 5.87-6.06 (m, 1H, 4''-CH), 7.05 (dd, J=9.8 Hz, J= 1.4Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 12.0 (q, 7-CH_3), 12.4 (q, 3-CH_3), 13.5 (q, 4'-CH_3), 24.5 (t, 1-CH_2), 25.4 (t, 5-CH_2), 28.7(t, 6-CH_2), 33.0 (d, 4-CH), 34.3 (d, 7-CH), 37.4 (t, 2-CH_2), 47.4 (d, 7a-CH), 65.1 (t, 4''-OCH_2), 117.7 (t,4''-olefinicCH_2), 125.7 (s, 4'-C), 130.9 (s, 3-C), 132.6 (q, 4''-olefinicCH) 133.3 (s, 3a-C), 143.8 (d, 4'-CH) 168.2 (s, 4'-CO)

I II.1.6 **Valerenic acid pivaloyloxymethylester 7**



1 **7**

Valerenic acid **1** (20mg, 1eqiv., 0.13mmol) and DBU (21.4µl=21.8mg, 1.1eqiv., 0.14mmol) were dissolved in 1.3ml dry DCM under an argon atmosphere and pivaloyloxymethyl chloride (20µl=19.1mg, 1.1eqiv., 0.14mmol) was added dropwise at room temperature. The mixture was stirred overnight until full conversion before it was taken up in 50 ml EtOAc and subsequently washed three times with saturated NH_4Cl and $NaHCO_3$ solution and one time with brine. The organic phase was dried and concentrated in vacuo. Purification with column chromatography (5g SiO_2, LP: EtOAc= 4:1) furnished the product in 85% yield.

Yield: 19.1mg (85%) colorless oil

Molecular Formula: $C_{21}H_{32}O_4$

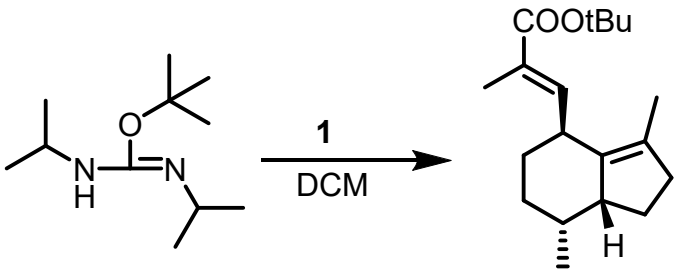
Molecular weight [g/mol]: 348.48

$[\alpha]_D^{20}$: -70.4° (c=0.64g/100ml DCM)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.78 (d, J=6.9, 3H, 7'-CH_3), 1.21 (s, 9H, 3x4''-pivCH_3), 1.38-1.98 (bm, 15H), 2.20 (t, J=7.44 Hz, 2H, 2-CH_2), 2.91-2.95 (m, 1H, 7a-CH), 3.50-3.55 (m, 1H, 4-CH), 5.81 (s, 2H, 4''-OCH_2), 7.09 (dd, J_1 =9.8 Hz, J_2 = 1.14Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 12.0 (q, 7-CH_3), 12.2 (q, 3-CH_3), 13.5 (q, 4'-CH_3), 24.5 (t, 1-CH_2), 25.3 (t, 5-CH_2), 26.8 (q, 4''-CH_3), 28.7(t, 6-CH_2), 33.0 (d, 4-CH), 34.3 (d, 7-CH), 37.4 (t, 2-CH_2), 38.8 (s, 4''-$C(CH_3)_3$), 47.4 (d, 7a-CH), 79.9 (t, 4''-OCH_2), 125.0 (s, 4'-C), 131.2 (s, 3-C), 133.1 (s, 3a-C), 145.6 (t, 4'-CH) 167.0 (s, 4'CO), 177.2 (s, 4''-CO)

I II.1.7 **Valerenic acid *tert*-butyl ester 12**



11 **12**

Diisopropylcarbodiimid (67 µl=82mg, 10eqiv., 0.43mmol) was added to Cu(I)Cl (2mg, 1eqiv., 0.043mmol) in a 3 ml vial under argon atmosphere followed by the addition of *t*-butanol **9** (44µl =56mg, 10.6 eqiv., 0.46mmol). The mixture was stirred neat at room tempertature for 24h and diluted with 430 µl dry DCM and valerenic acid **1** (10mg, 1eqiv., 0.043mmol) was added. After stirring for another 19h at ambient temperature, the mixture was taken up in 20ml of Et_2O and washed three times consecutively with saturated NH_4Cl and $NaHCO_3$ and once with brine. The ethereal phase was dried with Na_2SO_4, filtered and concentrated in vacuo. Column chromatography (5g SiO_2 ;LP:EtOAc= 98:2) yielded **12** 8.2 mg colorless Oil.

Yield: 8.2mg (67%) colorless oil

Molecular Formula: $C_{19}H_{30}O_2$

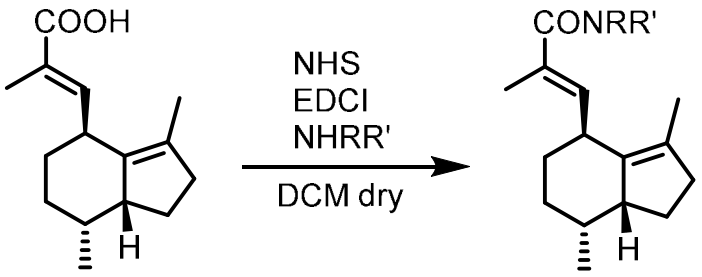
Molecular weight [g/mol]: 290.44

HRMS: calculated $(M-57)^+$= 233.1530, found $(M-57)^+$ = 233.1536

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.77 (d, J=7.0, 3H, 7'-CH_3), 1.36-2.01 (bm, 22H), 2.19 (t, J=7.4 Hz, 2H, 2-CH_2), 2.91-2.97 (m, 1H, 7a-CH), 3.46-3.52 (m, 1H, 4-CH), 7.09 (dd, J_1 =9.8 Hz, J_2= 1.4Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 12.0 (q, 7-CH_3), 12.4 (q, 3-CH_3), 13.5 (q, 4'CH_3), 24.5 (t, 1-CH_2), 25.2 (t, 5-CH_2), 28.1 (q, 3x4''-CH_3), 28.7(t, 6-CH_2), 33.2 (d4-CH), 34.3 (d, 7-CH), 37.5 (t, 2-CH_2), 47.4 (d, 7a-CH), 79.9 (s, 4''-$C(CH_3)_3$), 127.3 (s, 4'-C), 130.6 (s, 3-C), 133.7 (s, 3a-C), 142.2 (d,4'-CH) 168.0 (s, 4'-CO)

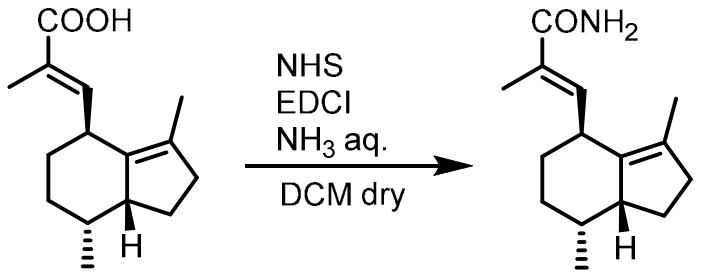
I II.2 Synthesis of Valerenic acid amides-general procedure



1 **13-20**

Valerenic acid **1** (1.00eq) and NHS (2.00eq) were dissolved in dry DCM (resulting in a 10 molar % solution) under an argon atmosphere and cooled to 0°C before EDCI (2.00eqiv.) was added in one portion. The mixture was allowed to warm to room temperature and stirred for three hours before it was cooled again to 0°C and 4.5eqiv. of the appropriate amine was added. After the solution had stirred at room temperature overnight it was taken up in 50ml EtOAc and subsequently washed with saturated NH_4Cl solution (three times), saturated $NaHCO_3$ solution (three times) and once with brine before it was dried and concentrated under reduced pressure. Purification of the crude material via column chromatography (LP and EtOAc) yielded pure amides **13-20**.

I II.2.1 Valerenic acid amide 13



1 **13**

Applied Reagents: Valerenic acid **1** (100.00mg, 1.00eqiv., 0.43mmol), NHS (98.20mg, 2.00eqiv., 0.85mmol), EDCI.HCl (162.95mg, 2.00eqiv.,0.85mmol), 25% aqueous NH_3 solution (132µl=102mg ,4.50eqiv., 1.94mmol)

Yield: 99.1mg (99%) white solid[93,1]

Molecular Formula: $C_{15}H_{23}NO$

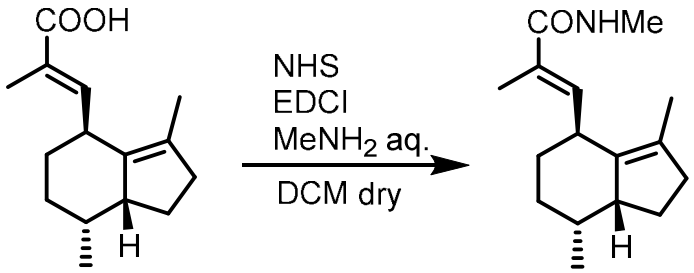
Molecular weight [g/mol]: 233.35

$[\alpha]_D^{20}$: - 101.3° (c=0.98g/100ml DCM), Lit[1].: -119.2° (c= 0.78g/100ml, DCM)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.77 (d, J=7.0, 3H, 7'-CH_3), 1.37-2.04 (bm, 14H), 2.19 (t, J=7.6 Hz, 2H, 2-CH_2), 2.89-2.96 (m, 1H, 7a-CH), 3.47-3.54 (m, 1H, 4-CH), 5.67 (bs, 2H, 4''-NH_2), 6.68 (dd, J=9.5 Hz, J_2= 1.4Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 12.0 (q, 7-CH_3), 12.7 (q, 3-CH_3), 13.5 (q, 4'-CH_3), 24.5 (t, 1-CH_2), 25.5 (t, 5-CH_2), 28.7(t, 6-CH_2), 33.1 (d, 4-CH), 34.1 (d, 7-CH), 37.4 (t, 2-CH_2), 47.4 (d, 7a-CH), 128.1 (s, 4'-C), 130.7 (s, 3-C), 133.5 (s-3a-C), 139.0 (d, 4'-CH), 172.0 (s, 4''-$CONH_2$)

I II.2.2 **Valerenic acid methyl amide 14**



1 **14**

Applied Reagents: Valerenic acid **1** (60.00mg, 1.00eqiv., 0.26mmol), NHS (58.93mg, 2.00eqiv., 0.51mmol), EDCI.HCl (97.8mg, 2.00eqiv.,0.51mmol), 41% aqueous methylamine solution (99µl=68mg ,4.50eqiv., 1.17mmol)

Yield: 48.0mg (71%) yellow oil[1]

Molecular Formula: $C_{16}H_{25}NO$

Molecular weight [g/mol]: 247.38

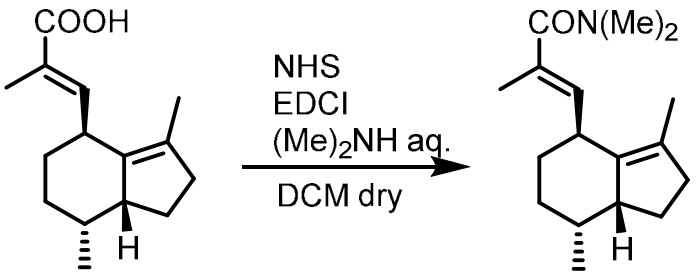
$[\alpha]_D^{20}$: - 196.1 (c=0.372g/100ml DCM)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.74 (d, J=7.0 Hz 3H, 7'-CH_3), 1.23-2.18 (bm, 14H), 2.16 (t, J=7.5 Hz, 2H, 2-CH_2), 2.82-2.93 (m, 4H, 7a-CH+NHMe), 3.42-3.47

(m, 1H, 4-CH), 5.89 (bs, 1H, 4''-NHMe), 6.54 (dd, J_1 =9.5 Hz, J_2 = 1.4Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 12.0 (q, 7-CH_3), 12.7 (q, 3-CH_3), 13.5 (q, 4'-CH_3), 24.5 (t, 1-CH_2), 25.6 (t, 5-CH_2), 26.5 (q,4''-$NHCH_3$), 28.7(t, 6-CH_2), 33.1 (d, 4-CH), 33.9 (d, 7-CH), 37.5 (t, 2-CH_2), 47.4 (d, 7a-CH), 129.4 (s, 4'-C), 130.5 (s, 3-C), 133.9 (s, 3a-C), 136.9 (d, 4'CH), 170.5 (s, 4'-CONHMe)

I II.2.3 **Valerenic acid dimethylamide 15**



1 **15**

Applied Reagents: Valerenic acid **1** (80.00mg, 1.00eqiv., 0.34mmol), NHS (78.26mg, 2.00eqiv., 0.68mmol), EDCI.HCl (130.36mg, 2.00eqiv.,0.68mmol), 60% aqueous dimethylamine solution (102µl = 68 mg ,4.50eqiv., 1.36mmol)

Yield: 70.2mg (79%) yellow oil[1]

Molecular Formula: $C_{17}H_{27}NO$

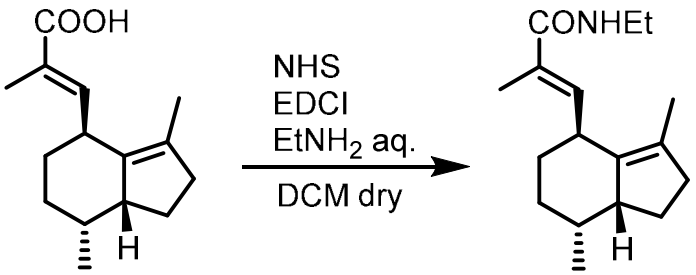
Molecular weight [g/mol]: 261.41

$[\alpha]_D^{20}$: -114.8 (c=0.59g/100ml DCM)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.74 (d, J=7.0, 3H, 7'-CH_3), 1.36-1.93 (bm, 14H), 2.16 (t, J=7.5 Hz, 2H, 2-CH_2), 2.79-2.89 (m, 1H, 7a-CH), 2.95 (bs, 6H, 4''$N(CH_3)_2$) 3.41-3.47 (m, 1H, 4-CH), 6.79 (dd, J_1=9.1 Hz, J_2 = 1.5Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 12.2 (q, 7-CH_3), 13.6 (q, 3-CH_3), 14.3 (q, 4'-CH_3), 24.7 (t, 1-CH_2), 25.8 (t, 5-CH_2), 28.9 (t, 6-CH_2), 33.3 (d, 4-CH), 33.4 (d, 7-CH), 37.8 (t, 2-CH_2), 46.7 (d, 7a-CH), 129.6 (s, 4'-C),130.1 (s, 3-C), 133.0 (d, 4'-CH), 134.1 (s, 3a-C), 174.2 (s, 4''-$CONMe_2$)

I II.2.4 **Valerenic acid ethylamide 16**



1 **16**

Applied Reagents: Valerenic acid **1** (50.00mg, 1.00eqiv., 0.21mmol), NHS (48.34mg, 2.00eqiv., 0.42mmol), EDCI.HCl (80.51mg, 2.00eqiv.,0.42mmol), 70% aqueous ethylamine solution (61µl=42mg ,4.50eqiv., 0.95mmol)

Yield: 43.2mg (76%) yellow oil[1]

Molecular Formula: $C_{17}H_{27}NO$

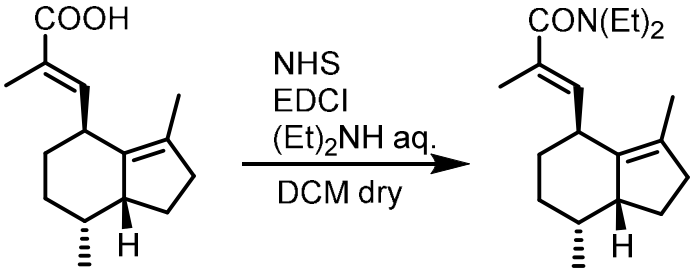
Molecular weight [g/mol]: 273.42

$[\alpha]_D^{20}$: - 121.6° (c=0.46g/100ml DCM),

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.77 (d, J=7.0, 3H, 7'-CH_3), 1.13 (t, J=7.2Hz, 3H, 4''-$NHCH_2CH_3$) 1.36-1.99 (bm, 13H), 2.16 (t, J=7.5 Hz, 2H, 2-CH_2), 2.91-2.96 (m, 1H, 7a-CH),3.31 (t, J=7.2Hz, 2H, 4''-$NHCH_2$) 3.42-3.49 (m, 1H, 4-CH), 5.81 (bs, 1H, 4''-NH) 6.54 (dd, J=9.4 Hz, J= 1.3Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 12.0 (q, 7-CH_3), 12.7 (q, 3-CH_3), 13.5 (q, 4'-CH_3), 14.9 (q, 4''-$NHMeCH_3$), 24.5 (t, 1-CH_2), 25.6 (t, 5-CH_2), 28.7(t, 6-CH_2), 33.1 (d, 4-CH), 33.9 (d, 7-CH), 34.6 (t, 4''-$NHCH_2$Me), 37.4 (t, 2-CH_2), 47.4 (d, 7a-CH), 129.3 (s, 4'C), 130.4 (s, 3-C), 133.8 (s, 3a-C), 136.8 (d, 4'-CH), 169.7 (s, 4'CONHEt)

I II.2.5 Valerenic acid diethylamide 17



1 **17**

Applied Reagents: Valerenic acid **1** (80.00mg, 1.00eqiv., 0.34mmol), NHS (78.26mg, 2.00eqiv., 0.68mmol), EDCI.HCl (130.36mg, 2.00eqiv.,0.68mmol), diethylamine (142.10µl, 4.50eqiv., 1.36mmol)

Yield: 88.0mg (89%) yellow oil[1]

Molecular Formula: $C_{19}H_{31}NO$

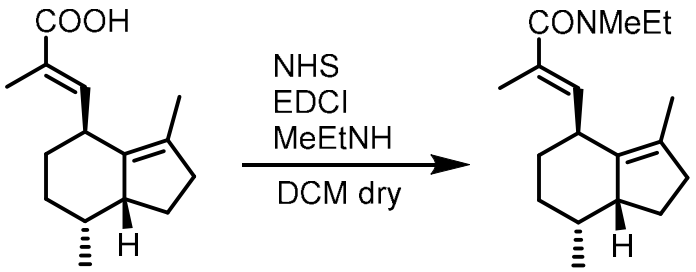
Molecular weight [g/mol]: 289.46

$[\alpha]_D^{20}$: -123.4 (c=0.46g/100ml DCM)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.76 (d, J=7.0, 3H, 7'-CH_3), 1.13 (t, J= 7.1Hz, 6H, 4''-$N(CH_2CH_3)_2$), 1.37-1.94 (bm, 14H), 2.17 (t, J=7.4 Hz, 2H, 2-CH_2), 2.82-2.88 (m, 1H, 7a-CH), 3.29-3.42 (m, 5H, 4-CH+2xNCH_2), 5.75 (dd, J_1 =9.1 Hz, J_2= 1.5Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 12.1 (q, 7-CH_3+4''-$N(CH_2CH_3)_2$), 13.5 (q, 3-CH_3), 14.3 (q, 4'-CH_3), 24.6 (t, 1-CH_2), 25.6 (t,5-CH_2), 28.8 (t, 6-CH_2), 29.7 (t, 4''-NCH_2), 33.0 (d, 4-CH), 33.2 (d, 7-CH), 37.4 (t, 2-CH_2), 47.5 (d, 7a-CH), 129.9 (s, 4'-C), 130.0 (s, 3-C), 130.9 (d, 4'-CH), 134.1 (s, 3a-C), 173.7 (s, 4''-$CONEt_2$)

I II.2.6 **Valerenic acid *N*-ethyl-*N*-methylamide 14**



1 **18**

Applied Reagents: Valerenic acid **1** (60.00mg, 1.00eqiv., 0.26mmol), NHS (59.85mg, 2.00eqiv., 0.52mmol), EDCI.HCl (99.68mg, 2.00eqiv.,0.52mmol), N-ethylmethylamine (100.52µl, 4.50eqiv., 1.36mmol)

Yield: 70.8mg (99%) yellow oil

Molecular Formula: $C_{18}H_{29}NO$

Molecular weight [g/mol]: 275.44

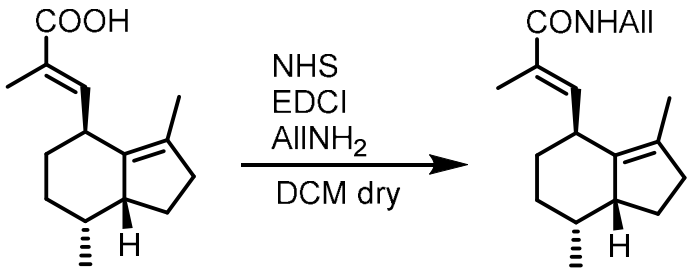
HRMS: calculated $(M+1)^+$= 276.2322, found $(M+1)^+$ = 276.2312

$[\alpha]_D^{20}$: -71.1 (c=0.68g/100ml DCM)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.73 (d, J=7.0, 3H, 7'-CH_3), 1.09 (t, J= 7.1, 3H, 4''-$NHCH_2CH_3$) 1.29-1.94 (bm, 14H), 2.14 (t, J=7.4 Hz, 2H, 2-CH_2), 2.80-2.88 (m, 4H, 7a-CH+4''NCH_3), 3.31-3.43 (m,3H, 4-CH+4''-$NNCH_2$), 5.78 (dd, J_1 =9.1 Hz, J_2= 1.5Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 12.0 (q, 7-CH_3), 13.4 (q, 3-CH_3), 14.9 (q, 4'-CH_3) 24.5 (t, 1-CH_2), 25.6 (t, 5-CH_2), 28.7(t, 6-CH_2), 33.1 (d, 4-CH), 33.3 (d, 7-CH), 37.4 (t, 2-CH_2), 47.6 (d, 7a-CH), 129.7 (s, 4'-C), 129.9 (s, 3-C),134.1 (3a-C)

I II.2.7 **Valerenic acid allylamide 19**



1 **19**

Applied Reagents: Valerenic acid **1** (50.00mg, 1.00eqiv., 0.21mmol), NHS (48.34mg, 2.00eqiv., 0.42mmol), EDCI.HCl (80.51mg, 2.00eqiv., 0.42mmol), allylamine (71.36µl, 4.50eqiv., 0.95mmol)

Yield: 43.2mg (76%) yellow oil

Molecular Formula: $C_{18}H_{27}NO$

Molecular weight [g/mol]: 273.42

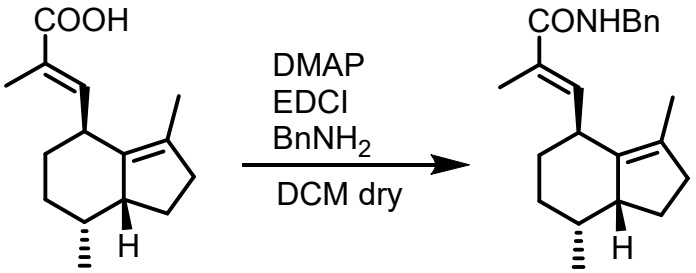
HRMS: calculated $(M+1)^+$= 274.2165, found $(M+1)^+$ = 274.2165

$[\alpha]_D^{20}$: - 62.9° (c=0.49g/100ml DCM)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.77 (d, J=7.0, 3H, 7'-CH_3), 1.36-1.99 (bm, 13H), 2.16 (t, J=7.5 Hz, 2H, 2-CH_2), 2.91-2.96 (m, 1H, 7a-CH), 3.47-3.53 (m, 1H, 4-CH), 3.94 (dt, J_1 =5.7 Hz, J_2= 2.8Hz, 2H, 4''-NH-CH_2), 5.11-5.24 (m, 2H, 4''-NHCH2CH-$\underline{CH_2}$), 5.79-5.95 (m, 2H, 4''-NH+4''-$NHCH_2\underline{CH}$), 6.60 (dd, J_1 =9.1 Hz, J_2= 1.5Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 12.0 (q, 7-CH_3), 12.7 (q, 3-CH_3), 13.5 (q, 4'-CH_3), 24.5 (t, 1-CH_2), 25.6 (t, 5-CH_2), 28.7 (t, 6-CH_2), 33.1 (d, 4-CH), 33.9 (d, 7-CH), 37.4 (t, 2-CH_2), 42.2 (t, 4''NH-CH_2), 47.4 (d, 7a-CH), 116,4 (t, 4''-$NHCH_2CH\underline{CH_2}$), 129.1 (s, 4'-C), 130.5 (s, 3-C), 133.7 (s, 3a-C), 134.5 (d, 4'-CH), 137.3 (d, 4''-$NHCH_2\underline{CH}$), 169.6 (s, 4'-CONHAll)

I II.2.8 **Valerenic acid benzylamide 20**



1 **20**

Valerenic acid **1** (50 mg, 1eqiv., 0.21mmol) and DMAP (2.57mg, 0.1eqiv., 0.02mmol) were dissolved in 2.1ml dry DCM under an argon atmosphere and cooled to 0°C before benzylamine (35µl=34mg, 1.5eqiv., 0.32mmol) was added. The mixture was allowed to warm to room temperature and stirred overnight. Then this mixture was taken up in 50ml EtOAc and subsequently washed with saturated NH_4Cl solution (three times), saturated $NaHCO_3$ solution (three times) and once with brine before it was dried and concentrated under reduced pressure to yield pure **20** as a slightly yellow oil.

Yield: 65.7mg (97%) slightly yellow oil

Molecular Formula: $C_{22}H_{29}NO$

Molecular weight [g/mol]: 323.48

HRMS: calculated $(M+1)^+$= 324.2322, found $(M+1)^+$ = 324.2306

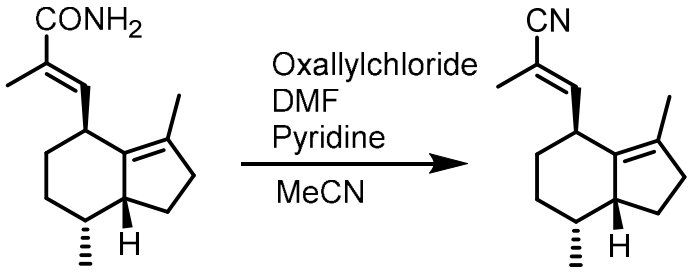
$[\alpha]_D^{20}$: - 76.2° (c=0.66g/100ml DCM)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.69 (d, J=6.9, 3H, 7'-CH_3), 1.29-1.96 (bm, 14H), 2.16 (t, J=7.5 Hz, 2H, 2-CH_2), 2.83-2.87 (m, 1H, 7a-CH), 3.39-3.46 (m, 1H, 4-CH), 4.42 (d, J= 5.7Hz, 2H, 4''-CH_2Ph), 5.98 (bs, 1H, 4''-NH), 6.55 (dd, J_1 =9.4 Hz, J_2= 1.0Hz, 1H, 4'-CH), 7-16-7.31 (m, 5H, 4''-CH_2Ph)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 12.0 (q, 7-CH_3), 12.8 (q, 3-CH_3), 13.5 (q, 4'-CH_3), 24.5 (t, 1-CH_2), 25.6 (t, 5-CH_2), 28.7(t, 6-CH_2), 33.1 (d, 4-CH), 33.9 (d, 7-CH), 37.4 (t, 2-CH_2), 43.9 (t, 4''-CH_2Ph), 47.4 (d, 7a-CH), 127.4 (d, 4''-ArCH), 127.9 (d, 4''-ArCH), 128.7 (d, 4''-ArCH), 129.0 (s, ArC), 130.5 (s, 3-C), 133.7 (s, 3a-C), 137.5 (d, 4'-CH), 138.6 (s), 169.6 (s, 4'-CONHBn)

I II.3 Synthesis of 5-((E)-((4*S*,7*R*,7aR)-3,7-Dimethyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)prop-1-en-2-yl)-1*H*-tetrazole (Valerenic acid tetrazole)

I II.3.1 (E)-3-((4*S*,7*R*,7a*R*)-3,7-Dimethyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methycrylonitrile (Valerenic acid nitrile) 21



13 **21**

Oxalylchloride (228µl=337mg, 7.0eqiv., 2.66mmol) was slowly added at 0°C to a mixture of dry DMF (221µl=210mg, 7.6eqiv., 2.87mmol) in 4ml dry MeCN (caution: vigorous CO evolution!). The mixture was stirred for 5 minutes at this temperature until it solidified. Upon addition of valerenic acid amide **13** (88.7mg, 1.0eqiv. , 0.38mmol) in 1.4ml dry DMF the white solid slowly turned into a yellow liquid, which was stirred for 30 minutes and was allowed to reach room temperature before it was eventually quenched with pyridine (420.8µl=412.6mg, 14.0eqiv., 5.32mmol) turning the solution deep red. This deep red solution was taken up in 50ml EtOAc and subsequently washed with sat. NH_4Cl (3x), 10% $Na_2S_2O_3$, water, and finally with brine (3x). The organic layer was dried over Na_2SO_4 , filtered and concentrated in vacuo to afford 80.0mg of valerenic acid nitrile **21** as a yellow oil matching the literature appearence(Note: valerenic acid nitrile is volatile!).

Yield: 80.0mg (98%) yellow oil[49]

Molecular Formula: $C_{15}H_{21}N$

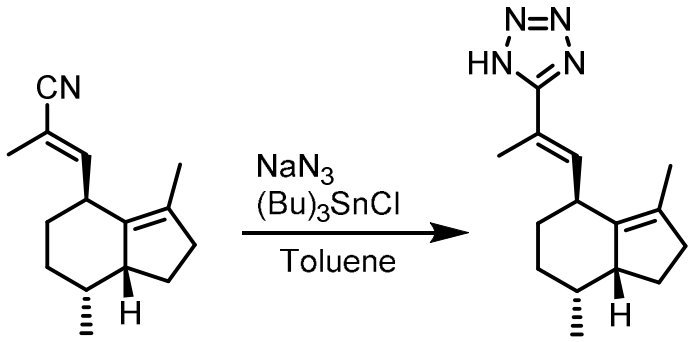
Molecular weight [g/mol]: 215.34

$[\alpha]_D^{20}$: - 128.1° (c=0.39g/100ml DCM); Lit[49].: -118.9 (c=2.02 g/100ml $CHCl_3$)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.75 (d, J=7.0, 3H, 7'-CH_3), 1.24-2.02 (bm, 14H), 2.19 (t, J=7.6 Hz, 2H, 2-CH_2), 2.90-2.89 (m, 1H, 7a-CH), 3.46-3.52 (m, 1H, 4-CH), 6.59 (dd, J_1 =9.7 Hz, J_2= 1.5Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 11.9 (q, 7-CH_3), 13.5 (q, 3-CH_3), 14.8 (q4'-CH_3), 24.5 (t, 1-CH_2), 25.2 (t, 5-CH_2), 28.6 (t, 6-CH_2), 32.9 (d, 4-CH), 34.3 (d, 7-CH), 37.4 (t, 2-CH_2), 47.4 (d, 7a-CH), 107.4 (s, 4'-C), 121.0 (s, 4'-CN), 131.9 (s, 3-C), 132.1 (s, 3a-C), 149.7 (d, 4'-CH)

I II.3.2 **5-((E)-((4*S*,7*R*,7aR)-3,7-Dimethyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)prop-1-en-2-yl)-1*H*-tetrazole (Valerenic acid tetrazole) 22**



20 **22**

Valerenic acid nitrile **20** (80.0mg, 1.0eqiv. , 0.37mmol) and NaN_3 (72.5mg, 3eqiv., 1.11mmol) were dissolved in 4ml dry toluene under argon, then tributyltinchloride (301 µl, 3eqiv., 1.11mmol) was added slowly at 0°C. The mixture was heated to 100°C for 6 days. The mixture was washed with 2N HCl (2x). The aqueous extract was reextracted with EtOAc (50ml, 3x). Subsequently the combined organic layers were dried, concentrated in vacuo and columned (10g SiO_2;1.2l LP:EtOAc = 95:5 + 1% AcOH, then elution with LP:EtOAc= 3:1+1%AcOH). Residual acetic acid was removed under high vacuum to afford 80.4mg (84%) valerenic acid tetrazole **22** as yellow oil.

Yield: 80.4mg (84%) yellow oil

Molecular Formula: $C_{15}H_{22}N_4$

Molecular weight [g/mol]: 258.37

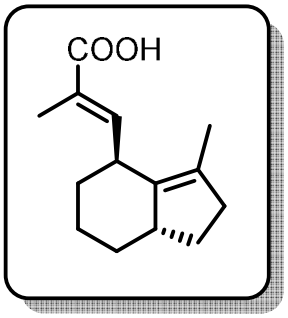
$[\alpha]_D^{20}$: - 111.1° (c=0.39g/100ml $CHCl_3$); Lit[49].: -116.5 (c=1.72 g/100ml $CHCl_3$)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.69 (d, J=6.90, 3H, 7'-CH_3), 1.29-2.02 (bm, 12H), 2.07-2.12 (m, 5H, 2-CH_2+3'-CH_3), 2.82-2.85 (m, 1H, 7a-CH), 3.52-3.57 (m, 1H, 4-CH), 6.85 (dd, J_1 =9.5 Hz, J_2= 1.3Hz, 1H, 4'-CH), 10.6-11.8 (bs, 1H, 4'tetrazolylH)

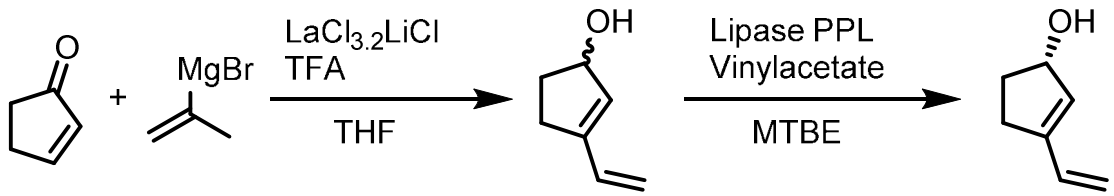
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 12.0 (q, 7-CH_3), 13.5 (q, 3-CH_3), 13.9 (q, 4'-CH_3), 24.8 (t, 1-CH_2), 25.9 (t, 5-CH_2), 28.6 (t, 6-CH_2), 33.1 (d, 4-CH), 33.9 (d, 7-CH), 37.6 (t, 2-CH_2), 47.3 (d, 7a-CH), 118.6 (s, 4'-C), 130.8 (s, 3-C), 133.7 (s, 3a-C), 138.4 (d,4'-CH), 157.5 (s, 4'-C-tetrazole)

I III Synthesis of axial methyl group derivatives on the cyclohexyl ring

I III.1 Synthesis of (E)-2-Methyl-3-((4*S*,7a*S*)-3-methyl-2,4,5,6,7a-hexahydro-1*H*-inden-4-yl)acrylic acid (normethyl valerenic acid)



I III.1.1 (S)-3-Vinylcyclopent-2-en-1-ol **25**



24 **rac-25** **25**

Cyclopent-2-en-1-one **24** (2.00ml=1.96g, 1.00eqiv., 23.90mmol) was added to a 0.6M solution of $LaCl_3$.2LiCl in THF (39.80ml, 1.00eqiv., 23.90mmol) under argon atmosphere and stirred for 1h (the solution turns from yellow to orange) at room temperature. Then the reaction solution was cooled to 0°C and 1M vinylmagnesiumbromide solution in THF (35.80ml, 1.50eqiv., 35.80mmol) was added dropwise. After complete addition, the mixture

was allowed to reach room temperature again and stirred until TLC showed full conversion (1h). Subsequently, it was cooled to 0°C again and quenched with 20 ml water forming a colorless precipitate. After 5 minutes of stirring at 0°C, TFA (2.93ml, 1.60 eqiv., 38.24mmol) was added dropwise and the colorless precipitate got completely dissolved upon complete addition (mixture is now acidic). Further 60 minutes of stirring at 0°C provided complete conversion towards racemic 3-cyclopent-2-en-1-ol, which was quenched by addition of 20ml saturated $NaHCO_3$ solution (again a colorless precipitate is formed as the mixture is basic). The heterogeneous mixture is extracted with Et_2O (3x) – sat. NH_4Cl solution can be added to avoid extraction problems caused by residual solids in the basic aqueous solution – washed with $NaHCO_3$ (1x) and brine (1x), then it was dried and concentrated in vacuo to afford 1.96g of racemic 3-cyclopent-2-en-1-ol (74%) as an orange oil.

The crude racemic alcohol (1.96g, 1.00eqiv., 17.80mmol) was dissolved in 178ml MTBE. Lipase PPL (0.98g, 50w/w%) and vinylacetate (6.67ml, 4eqiv., 71.2mmol) were added and stirred until an enantiomeric excess of 90% was reached (~20h). After filtration through a short pad of celite and evaporation of the solvent, column chromatography (90g NEt_3-doped-SiO_2; LP:EtOAc=10:1+1% NEt_3 to 5:1+1% NEt_3) delivered 554.3mg (S)-3-cyclopent-2-en-1-ol **25** (21% overall yield, 90%ee) as yellow oil (21%).

Note: Compound **25** is labile and should be stored in the freezer!

Yield: 554.3mg (21%) yellow oil

Rf: 0.23 (LP:EtOAc=3:1)

Molecular Formula: $C_7H_{10}O$

Molecular weight [g/mol]: 110.16

$[\alpha]_D^{20}$: -125.3° (0.66g/100ml DCM)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.69-1.85 (m, 2H, 5-CH_2), 2.25-2.42 (m, 2H, 4-CH_2), 2.52-2.72 (m, 1H, 1-CH), 4.86-4.89 (bm, 1H, 2-CH), 5.14-5.25 (m, 2H, 3'-CH_2), 5.75 (bs, 1H, OH), 6.56 (dd, J= 17.5Hz, J_2 = 10.6 Hz, 1H, 3'-CH)

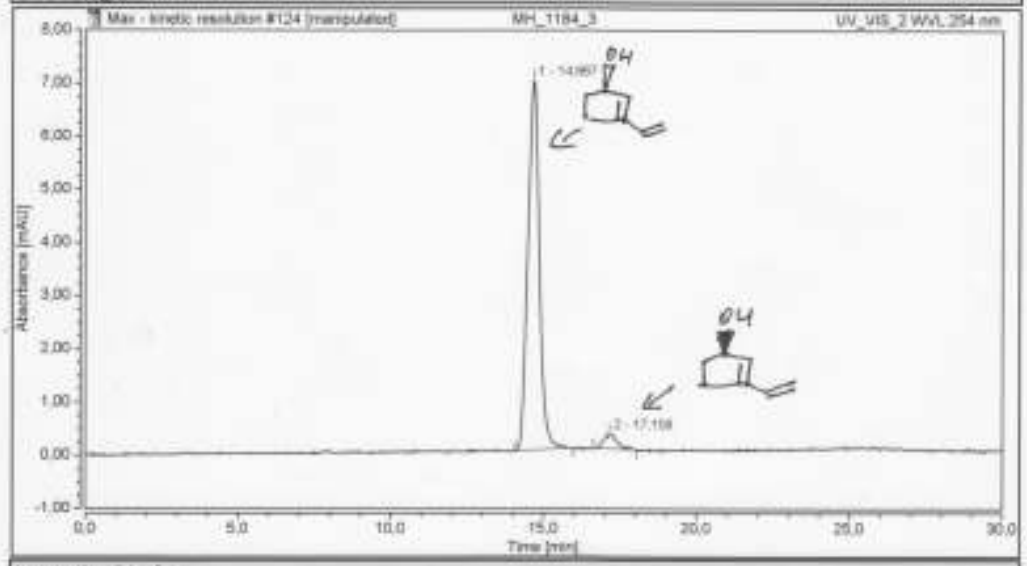
^{13}C-NMR (50 MHz, $CDCl_3$): n.d.[46]

Chromatogram and Results

Injection Details

Injection Name:	MH_1184_3	*Run Time (min):*	30,00
Vial Number:	RC1	*Injection Volume:*	1,00
Injection Type:	Unknown	*Channel:*	UV_VIS_2
Calibration Level:		*Wavelength:*	280,0
Instrument Method:	Isocratic 18	*Bandwidth:*	2
Processing Method:	2D Quant. Std.	*Dilution Factor:*	1,0000
Injection Date/Time:	14.Aug.14 13:36	*Sample Weight:*	1,0000

Chromatogram

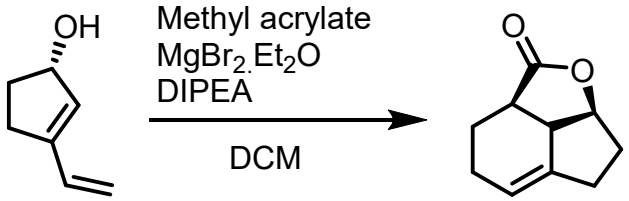


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		14,667	3,029	6,956	95,39	95,98	n.a.
2		17,158	0,146	0,292	4,61	4,02	n.a.
Total:			**3,175**	**7,259**	**100,00**	**100,00**	

Figure 117 Kinetic resolution of 3-vinylcyclopentenol 25

I III.1.2 (2aR,7aS,7bR)-3,4,6,7,7a,7b-Hexahydroindeno[1,7-*bc*]furan-2(2a*H*)-one **26**



25 **26**

Anhydrous $MgBr_2.Et_2O$ (4.65g, 2.00eqiv., 18.16mmol) was suspended in 30ml dry DCM under argon at room temperature, then anhydrous diisopropylethylamine (6.33ml, 4.00eqiv., 36.32mmol) was added and the mixture was stirred until it turned magenta (~15 minutes). Subsequently, (S)-3-vinylcyclopent-2-en-1-ol **25** (1.00g, 1.00eqiv., 9.08mmol) dissolved in 90 ml dry DCM was added slowly at ambient temperature and stirred for 1 hour followed by dropwise addition of methyl acrylate (1.65ml, 2.00eqiv., 18.16mmol). The mixture was stirred overnight at room temperature, quenched with sat. NH_4Cl, extracted with DCM (4x), dried and the solvent evaporated. Purification by column chromatography (90g SiO_2; LP:EtOAc = 6:1) provided 1.17g lactone **26** as a slightly yellow oil.

Yield: 1.17g (79%)

Rf: 0.32 (LP:EtOAc=3:1)

Molecular Formula: $C_{10}H_{12}O_2$

Molecular weight [g/mol]: 164.20

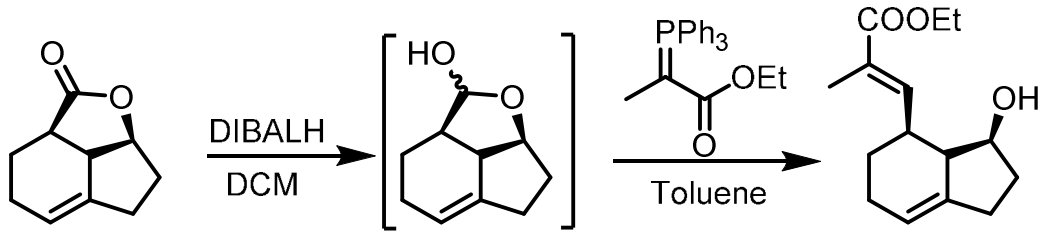
HRMS: calculated $(M+1)^+$= 165.0910, found $(M+1)^+$ = 165.0925

$[\alpha]_D^{20}$: -80.2° (c= 0.44g/100ml DCM)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.74-1.98 (m, 2H, 2-CH_2), 2.02-2.22 (m, 4H, 1-CH_2+5-CH_2), 2.36-2.43 (m, 2H, 6-CH_2), 2.89 (bs, 1H, 3a-CH), 3.02-3.09 (m, 1H, 4-CH), 4.87 (t, J= 5.5Hz, 1H, 3-CH), 6.66 (bs, 1H, 7-CH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 18.8 (t, 5-CH_2), 21.1 (t, 6-CH_2), 28.8 (t, 1-CH_2), 31.0 (t, 2-CH_2), 39.0 (d, 3a-CH), 42.6 (q, 4-CH), 82.7 (q, 3-CH), 122.3 (q, 7-CH), 137.1 (s, 7a-CH), 178.0 (s, 4'-CO)

I III.1.3 (***E***)-3-((3S,3aR,4S)-3-Hydroxy-2,3,3a,4,5,6-hexahydro-1*H*-inden-4-yl)-2-methyl-acrylic acid ethyl ester **27**



26 **26a** **27**

Lactone **26** (340.0mg,1.00eqiv., 2.07mmol) was dissolved in 21ml dry DCM and cooled to -78°C, then 1M DIBALH solution in heptane (3.11ml, 1.50eqiv., 3.11mmol) was added. After stirring for 70 minutes at the aforementioned temperature, the solution was quenched with 1ml EtOAc followed by addition of 5ml saturated Rochelle´s salt solution. The mixture was allowed to reach room temperature and stirred for at least 30 minutes until the phases were clearly separated. Extraction with DCM (4x), drying with Na_2SO_4 and evaporation of the solvent provided crude lactol **26a** as a slightly yellow oil. Lactol **26a** combined with (1-ethoxycarbonylethyliden)-triphenylphosphorane (2.25g ,3.00eqiv., 6.21mmol) were dissolved in 21 ml dry toluene and heated to 100°C under an argon atmosphere for 19h. Toluene was evaporated and purification by column chromatography (40g SiO_2; LP:EtOAc=10:1 to 5:1) yielded 424.6 mg of **27** as colorless oil.

Yield: 424.6mg (82%)

Rf: 0.22 (LP:EtOAc=4:1)

Molecular Formula: $C_{15}H_{22}O_3$

Molecular weight [g/mol]: 250.34

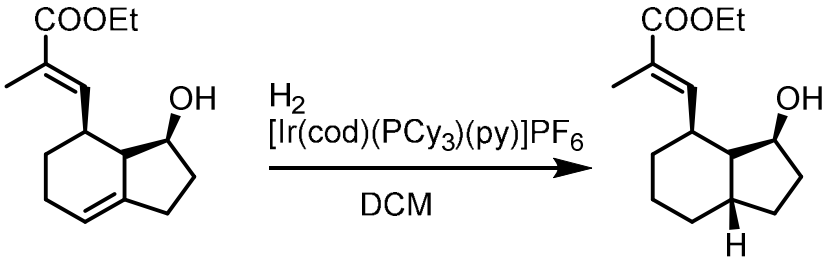
HRMS: calculated $(M-17)^+$= 233.1536, found $(M-17)^+$ = 233.1541

$[\alpha]_D^{20}$: +11.9° (c= 0.44g/100ml DCM)

^{1}H-NMR (400 MHz, CD_2Cl_2): δ = 1.26 (t, J=7.1 Hz, 3H, 4''-CH_3), 1.32 (bs, 1H, 3a-CH_2), 1.56-1.66 (m, 2H, 2-CH_2), 1.71-1.80 (m, 2H, 5-CH_2), 1.90 (d, J=1.4Hz, 3H, 4'-CH_3), 1.99-2.11 (m, 2H, 1-CH_2), 2.29- 2.47 (m, 2H, 6-CH_2), 2.51 (bs, 1H, 4-CH), 3.09-3.16 (m, 1H, 3-CH), 4.15 (q, J=7.1Hz, 2H, 4''-OCH_2), 4.25 (bs, 1H, 3-CH), 5.64 (bs, 1H, 7-CH), 7.04 (d, J=10.4Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, CD_2Cl_2): δ = 12.3 (q, 4‘‘-CH_3), 14.1 (q, 4‘-CH_3), 22.4 (t, 6-CH_2), 27.5 (t, 5-CH_2), 28.4 (t, 1-CH_2), 33.1 (t, 2-CH_2), 33.8 (d, 3a-CH), 49.0 (d, 4-CH), 60.4 (t, 4‘‘-CH_2), 74.6 (d, 3-CH), 118.9 (d, 7-CH), 127.2 (s, 7a-CH), 139.9 (s, 4‘-C), 143.5 (d, 4‘-CH), 167.9 (s, 4‘-COOEt)

I III.1.4 (***E***)-3-((3S,3aR,4S,7R,7aR)-3-Hydroxyoctahydroinden-4-yl)-2-methyl-acrylic acid ethyl ester **28**



27 **28**

Hydroxy ester **27** (50.00mg, 1.00eqiv., 19.97mmol) was dissolved in 50ml dry DCM and degassed by means of freeze-thaw degassing method (3 times). The freshly degassed solution was backfilled with H_2 and cooled to 0°C. H_2 was bubbled through the solution for one minute, then Crabtree's catalyst (16.10mg, 0.10eqiv., 0.02mmol) was added. Immediately H_2 was bubbled through the deep orange solution turning it into faint yellow transparent. The cooling bath was removed and the mixture was stirred for 1 hour and 20 minutes (GC-MS control) and the H_2 atmosphere was substituted by argon which was bubbled through the solution for 5 minutes. The deep yellow mixture was concentrated in vacuo and purification via column chromatography (5g SiO_2;LP:EtOAc= 7:1) provided 49.0mg of **28** as colorless solid.

Yield: 49.0mg (97%)

Rf: 0.22 (LP:EtOAc=4:1)

Melting point: 98-100°C

Molecular Formula: $C_{15}H_{24}O_3$

Molecular weight [g/mol]: 252.35

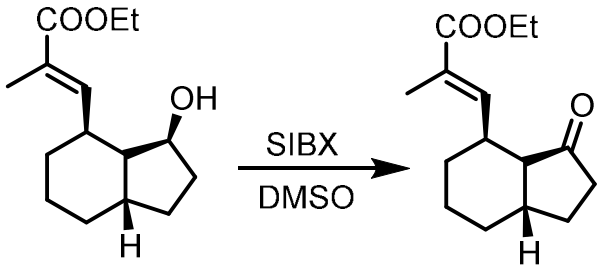
HRMS: calculated $(M+1)^+$= 253.1798, found $(M+1)^+$ = 253.1796

$[\alpha]_D^{20}$: -87.6° (c=0.31g/100ml DCM)

^{1}H-NMR (400 MHz, CD_2Cl_2): δ = 1.00-1.14 (m, 2H, 7-CH_2), 1.29-1.32 (m, 4H, 4''-CH_3+3a-CH), 1.36 (bs, 1H, 7a-CH), 1.41-1.53 (m, 2H, 1-CH_2), 1.56-1.65 (m, 3H, 4-CH+2-CH_2), 1.91-2.00 (bm, 5H, 4'CH_3+5-CH_2), 2.08-2.11 (bm, 2H, 6-CH_2) 3.14-3.17 (m, 1H, 3-CH), 4.14-4.23 (m, 3H, 4''-CH_2+OH), 7.31 (d, J=11.7 Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, CD_2Cl_2): δ = 12.2 (q, 4‘‘-CH_3), 14.1 (q, 4‘-CH_3), 21.7 (t, 6-CH_2), 29.6 (t, 1-CH_2), 32.9 (t, 5-CH_2), 33.1 (t, 7-CH_2), 33.2 (t, 2-CH_2), 34.5 (d,7a-CH), 35.4 (d, 4-CH), 54.6 (d, 3a-CH), 60.4 (t, 4‘‘-CH_2), 75.0 (d, 3-CH), 126.4 (s, 4‘-C), 144.3 (d, 4‘-CH), 167.9 (s, 4‘-COOEt)

I III.1.5 (***E***)-2-Methyl-3-((3aR,4S,7aR)-3-oxo-octahydro-inden-4-yl)-acrylic acid ethyl ester **29**



28 **29**

SIBX 45w/w% (241.66mg, 2eqiv., 0.40mmol) in 1.6ml DMSO was added to compound **28** (49.00mg, 1.00eqiv., 0.19mmol) dissolved in 0.8ml DMSO at room temperature. The mixture was stirred for 2 hours then it was quenched through the addition of water. The white precipitate was removed by filtration through a short pad of celite. The residual solid was redissolved in DMSO, water and EtOAc were added and the mixture was filtrated again. Finally the product was extracted with Et_2O (4x), washed with $NaHCO_3$ and brine (3x), dried and concentrated before purification via column chromatography (10g SiO_2; LP:EtOAc 7:1) provided **29** 46.8mg slightly yellow oil.

Yield: 46.8mg (94%)

Rf: 0.30 (LP:EtOAc=4:1)

Molecular Formula: $C_{15}H_{22}O_3$

Molecular weight [g/mol]: 250.34

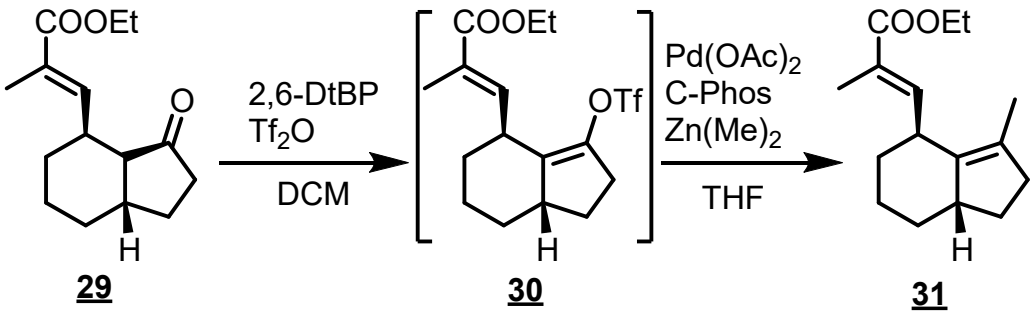
HRMS: calculated $(M+1)^+$= 251.1642, found $(M+1)^+$ = 251.1645

$[\alpha]_D^{20}$: -126.15° (c=0.90g/100ml DCM)

^{1}H-NMR (200 MHz, CD_3Cl): δ = 1.20-2.30 (m, 18H), 3.18-3.23 (m, 1H, 4-CH), 4.11 (t, J=7.1Hz, 2H, 4''-CH_2), 6.74 (dd, J_1 = 10.2 Hz, J_2= 1.3Hz, 4'-CH)

^{13}C-NMR (50 MHz, CD_3Cl): δ = 12.9 (q, 4''-CH_3), 14.3 (q, 4'-CH_3), 21.6 (t, 6-CH_2), 28.0 (t, 1-CH_2), 31.1 (t, 5-CH_2), 32.2 (d, 7a-CH), 32.9 (t, 7-CH_2), 37.3 (d, 4-CH), 37.5 (t, 2-CH_2), 59.1 (d, 3a-CH), 60.5 (t, 4''-CH_2), 129.3 (s, 4'_C), 139.9 (d, 4'-CH), 168.2 (s, 4''-COOEt), 216.6 (s, 3-CO)

I III.1.6 7-Normethyl-valerenic acid ethyl ester **31**



Ketone **29** (126.50mg, 1.00eqiv., 0.51mmol) was dissolved in 3.2ml dry DCM under argon and cooled to 0°C. Subsequently 2,6-ditert.-butylpyridine (234.00µl, 2.00eqiv., 1.01mmol) and freshly distilled triflic anhydride (170.00µl, 2.00eqiv., 1.01mmol) were added under vigorous stirring. The mixture was stirred for 5 minutes at that temperature before it was allowed to warm to room temperature. After 3 hours the slightly yellow mixture was taken up in 100ml pentane and stirred for 5 minutes before the precipitated solids were removed via filtration through a short pad of celite. After the solvents had been removed on the rotary evaporator, 50 ml of pentane were added and the organic phase was washed with 2N HCl and $NaHCO_3$, dried and again concentrated. The residual crude enol triflate **30** was dissolved in 2.2ml dry THF under argon and cooled to 0°C, then $Pd(OAc)_2$ (11.40mg, 0.1eqiv., 0.05mmol) and C-Phos (44.10mg, 0.20eqiv., 0.10mmol) dissolved in 1ml dry THF were added. The orange solution was stirred for 5 minutes at 0°C and then 1M dimethylzinc solution in heptane (2.04ml, 4.00eqiv., 2.04mmol) was added, the ice bath was removed and the mixture was stirred overnight and allowed to reach room temperature. Again the mixture was cooled to 0°C and quenched with saturated NH_4Cl solution, extracted with Et_2O (4x), once washed with brine, dried and concentrated in vacuo. Purification by column chromatography (10g 10w/w% $AgNO_3$-doped SiO_2; heptane:EtOAc = 100:0 to heptane:EtOAc = 97:3) yielded 50.1mg 7-normethyl-valerenic acid ethyl ester **31** as colorless oil.

Yield: 50.1mg (40%)

Rf: 0.71 (LP:EtOAc=20:1)

Molecular Formula: $C_{16}H_{24}O_2$

Molecular weight [g/mol]: 248.37

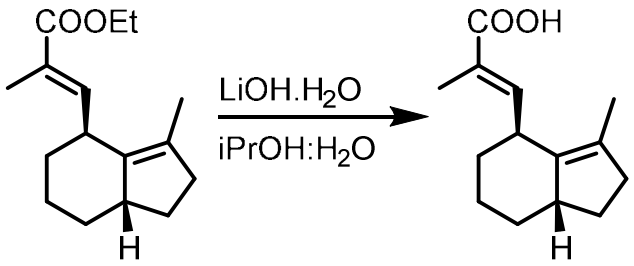
HRMS: calculated $(M-1)^+$= 247.1693, found $(M-1)^+$ = 247.1683

$[\alpha]_D^{20}$: -30.8° (c=0.75g/100ml DCM)

^{1}H-NMR (200 MHz, CD_3Cl): δ = 0.89-1.08 (m, 1H), 1.21-1.36 (m, 4H, 6-CH_2+7-CH_2), 1.44-1.70 (m, 7H), 1.90-2.23 (m, 7H), 2.66-2.69 (m, 1H, 7a-CH), 3.54-3.59 (m, 1H, 4-CH), 4.18 (q, J= 7.1Hz, 2H, 4''-OCH_2), 6.93 (dd, J_1 = 10.0Hz, J_2= 1.4Hz, 4'-CH)

^{13}C-NMR (50 MHz, CD_3Cl): δ = 12.4 (q, 4''-CH_3), 13.6 (q, 3-CH_3), 14.3 (q, 4'-CH_3), 21.6 (t, 6-CH_2), 29.3 (t, 1-CH_2), 31.7 (t, 5-CH_2), 34.5 (d, 4-CH), 35.7 (t, 7-CH_2), 36.9 (t, 2-CH_2), 43.5 (d, 7a-CH), 60.4 (t, 4''-OCH_2), 125.8 (s, 4'-C), 130.1 (s, 3-C), 136.9 (s, 3a-C), 143.1 (d, 4'-CH), 168.6 (s, 4'COOEt)

I III.1.7 7-Normethyl-valerenic acid **32**



31 **32**

Ethylester **31** (9.80mg, 1.00eqiv., 0.04mmol) together with LiOH.H_2O (9.93mg, 6.00eqiv., 0.24mmol) were dissolved in 200µl *i*-PrOH:H_2O mixture (2:1) and heated to 40°C for 21h. After cooling to room temperature, the mixture was diluted with 4ml *i*-PrOH:H_2O (3:1) and 1ml volume of Amberlite IR 120 was added. The suspension was stirred for 30 minutes and the Amberlite was filtered off, then the residual solvents were lyophyllized to furnish 7.7 mg 7-normethylvalerenic acid **32** as colorless solid.

Yield: 7.7mg (90%)

Rf: 0.44 (LP:EtOAc=3:1)

Melting Point: 120-121°C

Molecular Formula: $C_{14}H_{20}O_2$

Molecular weight [g/mol]: 220.31

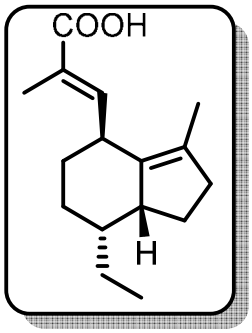
HRMS: calculated $(M+1)^+$= 221,1536 found $(M+1)^+$ = 221.1546

$[\alpha]_D^{20}$: -26.0° (c=0.15g/100ml DCM)

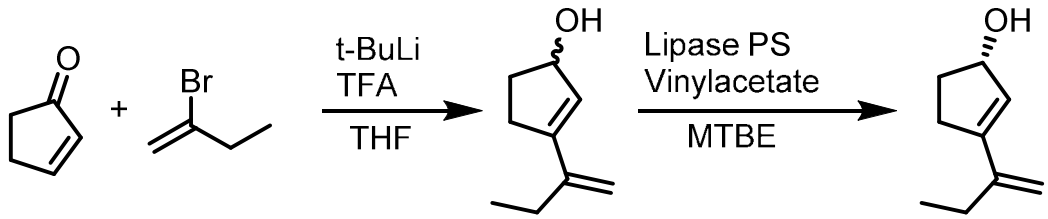
^{1}H-NMR (200 MHz, CD_2Cl_2): δ = 0.81-1.01 (m, 1H), 1.13-1.64 (m, 9H), 1.81-2.16(m, 7H), 2.58-2.60 (m, 1H, 7a-CH), 3.51-3.56 (m, 1H, 4-CH), 7.00 (dd, J_1 = 10.0Hz, J_2= 1.4Hz)

^{13}C-NMR (50 MHz, CD_2Cl_2): δ = 12.0 (q, 3-CH_3), 13.6 (q, 4'-CH_3), 21.6 (t, 6-CH_2), 29.3 (t, 1-CH_2), 31.6 (t, 5-CH_2), 34.8 (d, 4-CH), 35.6 (t, 2-CH_2), 36.9 (t, 7a-CH_2), 43.6 (d, 7-CH), 124.9 (s, 4'-C), 130.6 (s, 3-C), 136.5 (s, 3a-C), 146.1 (d, 4'-CH), 173.6 (s, 4'-COOH)

I III.2 Synthesis of (*E*)-3-((4*S*,7*R*,7a*R*)-7-Ethyl-3-methyl-2,4,5,6,7,7a-heahydro-1*H*-inden-4-yl)-2methacrylic acid (7-Ethyl-Valerenic acid) **40**



I III.2.1 (S)-3-(But-1-en-2-yl)cyclopent-2-en-1-ol **33**



24 **rac-33** **33**

2-Bromo-1-buten 98% (0.74ml=0.97g, 1.20eqiv., 7.16mmol) in 60 ml dry THF under argon was cooled to -78°C and 1.7M t-BuLi solution in pentane (8.40ml, 2.40eqiv., 14.32mmol) was added. The yellow solution was left to warm to -60°C for 40 minutes until the yellow color vanished. The colorless solution was again cooled to -78°C and cyclopent-2-en-1-one (0.50ml=0.49g, 1.00eqiv., 5.97mmol) dissolved in 6ml dry THF was added dropwise while the color changed to slight orange. The mixture was stirred for 1.5 h at -78°C and warmed to 0°C. Then it was quenched with 30ml water and stirred for 5 minutes. TFA (1.14ml, 2.50eqiv., 14.93mmol) was added slowly at 0°C (color changes from orange to colorless when acidic) and stirred for 20 minutes before it was quenched with saturated $NaHCO_3$ solution. The phases were separated and the aqueous layer was extracted with Et_2O (3x), once washed with saturated $NaHCO_3$ solution, dried and concentrated to deliver 810.3mg racemic alcohol ***rac*-33** .

The crude racemic alcohol (0.81g, 1.00eqiv., 5.86mmol) was dissolved in 32ml MTBE and Lipase PS (0.16g, 20w/w%) together with vinylacetate (0.28ml, 0.52eqiv., 3.05mmol) were added and stirred until an enantiomeric excess of 99% was reached (17h). After filtration

through a short pad of celite and evaporation of the solvent, column chromatography (90g NEt_3-doped SiO_2;LP:EtOAc=8:1+1%NEt_3 to 4:1+1% NeE_3) delivered 387.4mg (S)-3-(but-1-en-2-yl)cyclopent-2-en-1-ol **33**.

Note: Compound **33** is labile and should be stored in the freezer!

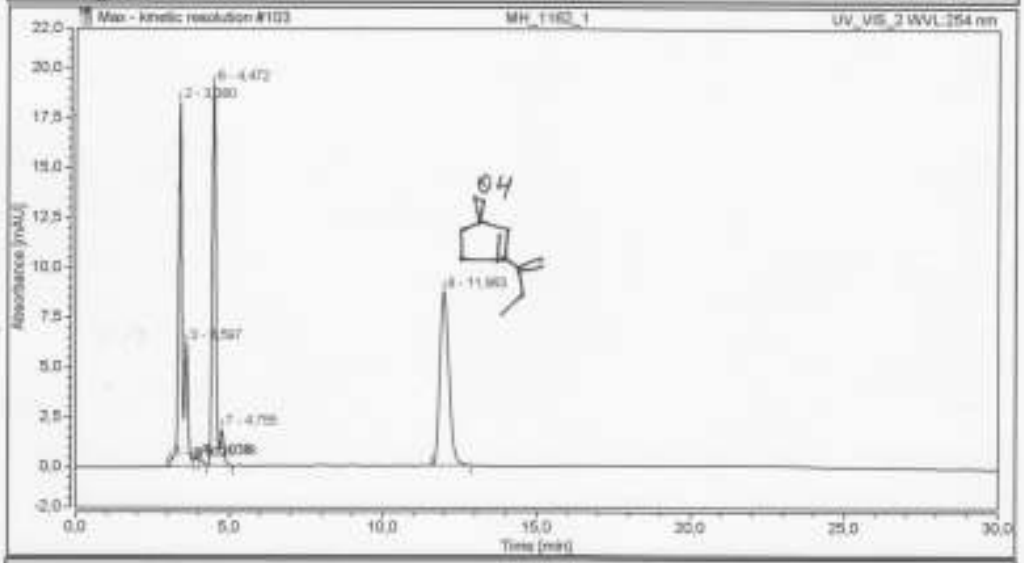
Yield:	387.4mg (47%) yellow oil
Rf:	0.19 (LP:EtOAc=4:1)
Molecular Formula:	$C_9H_{14}O$
Molecular weight [g/mol]:	138.21
HRMS:	calculated $(M-17)^+$= 121.1012, found $(M-17)^+$ = 121.1014
$[\alpha]_D^{20}$:	-96.6° (0.47g/100ml DCM)
^{1}H-NMR (200 MHz, $CDCl_3$):	δ = 1.11 (t, J=7.4 Hz, 3H, 3'-CH_3), 1.68-1.85 (m, 2H, 5-CH_2), 2.25-2.48 (m, 4H, 4-CH_2+3'-CH_2), 2.60-2.75 (m, 1H, 1-CH), 4.92 (bs, 1H, 1-OH), 5.03-5.05 (m, 2H, 3'-olefinicCH_2), 5.83-5.84 (m, 1H, 2-CH)
^{13}C-NMR (50 MHz, $CDCl_3$):	δ = 13.0 (q, 3'-CH_3), 26.5 (t, 3'-CH_2), 30.8 (t, 5-CH_2), 33.5 (t, 5-CH_2), 77.8 (d, 1-CH), 112.6 (t, 3'-olefinic-CH_2), 128.0(d, 2-CH),145.5 (s, 3'-C), 146.6 (s, 3-C)

Chromatogram and Results

Injection Details

Injection Name:	**MH_1162_1**	*Run Time (min):*	**30,00**
Vial Number:	**RD3**	*Injection Volume:*	**0,50**
Injection Type:	**Unknown**	*Channel:*	**UV_VIS_2**
Calibration Level:		*Wavelength:*	**280,0**
Instrument Method:	**Isocratic 18**	*Bandwidth:*	**2**
Processing Method:	**2D Quant. Std.**	*Dilution Factor:*	**1,0000**
Injection Date/Time:	**23.Mai.14 12:37**	*Sample Weight:*	**1,0000**

Chromatogram

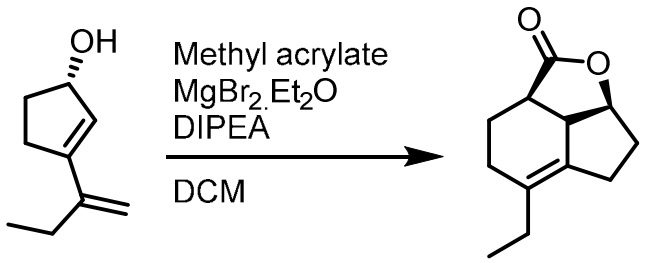


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		3,100	0,086	0,298	0,97	0,54	n.a.
2		3,380	2,125	18,275	23,82	33,17	n.a.
3		3,597	0,773	6,146	8,66	11,16	n.a.
4		3,918	0,058	0,398	0,65	0,72	n.a.
5		4,085	0,040	0,282	0,45	0,51	n.a.
6		4,472	2,610	19,126	29,25	34,71	n.a.
7		4,755	0,269	1,660	3,01	3,36	n.a.
8		11,993	2,962	8,725	33,19	15,84	n.a.
Total:			**8,923**	**55,101**	**100,00**	**100,00**	

Figure 118 Kinetic resolution of 3-(But-1-en-2-yl)cyclopent-2-en-1-ol 33

I III.2.2 (2aR,7aS,7bR)-5-Ethyl-3,4,6,7,7a,7b-hexahydroindeno[1,7-*bc*]furan-2(2a*H*)-one **34**



33 **34**

Anhydrous $MgBr_2.Et_2O$ (2.04g, 2.00eqiv., 7.90mmol) was suspended in 9.1ml dry DCM under argon at room temperature before anhydrous diisopropylethylamine (2.92ml, 4.00eqiv., 15.80mol) was added and the mixture was stirred until it turned magenta (~15 minutes). Then (S)-3-(but-1-en-2-yl)cyclopent-2-en-1-ol **33** (0.55g, 1.00eqiv., 3.95mmol) dissolved in 31 ml dry DCM was added slowly and stirred for 1 hour before methyl acrylate (0.72ml, 2.00eqiv., 7.90mmol) was added dropwise. The mixture was stirred overnight at room temperature, quenched with sat. NH_4Cl, extracted with DCM (4x), dried and the solvent evaporated. Purification by column chromatography (LP:EtOAc = 6:1) provided 627.1g lactone **34** as a slightly yellow oil.

Yield: 627.1g (83%)

Rf: 0.24 (LP:EtOAc=4:1)

Molecular Formula: $C_{12}H_{16}O_2$

Molecular weight [g/mol]: 192.26

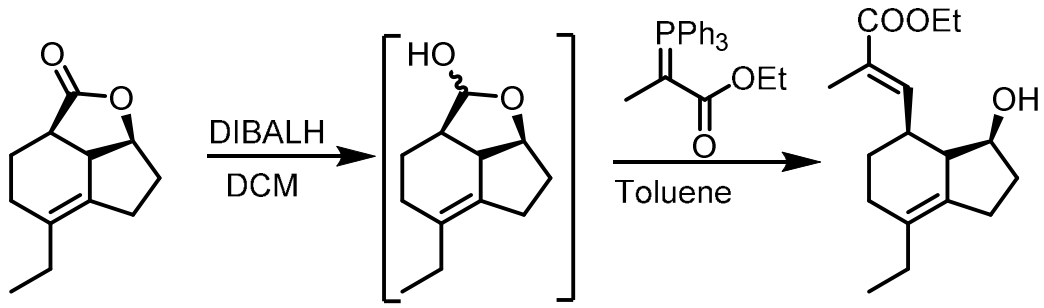
HRMS: calculated $(M+1)^+$= 193.1223, found $(M+1)^+$ = 193.1228

$[\alpha]_D^{20}$: -76.6° (c= 0.58g/100ml DCM)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.85 (t, J=7.5 Hz, 3H, 7'-CH_3), 1.77-2.26 (m, 9H), 2.41- 2.55 (m, 1H), 2.77-2.80 (m, 1H, 4-CH), 2.90-2.98 (m, 1H, 3a-CH), 4.76 (t, J=5.1 Hz, 1H, 3-CH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 12.6 (q, 7'-CH_3), 20.4 (t, 5-CH_2), 24.5 (t, 1-CH_2), 26.4 (t, 6-CH_2), 26.9 (t, 2-CH_2) 29.2 (t, 7'-CH_2), 38.4 (d, 7a-CH), 43.6 (d, 3a-CH) 83.2 (d, 3-CH), 130.1 (s, 7-C), 135.2 (s, 7a-C), 178.8 (s, 4'-COO)

I III.2.3 (***E***)-3-((3S,3aR,4S)-7-Ethyl-3-hydroxy-2,3,3a,4,5,6-hexahydro-1*H*-inden-4-yl)-2-methyl-acrylic acid ethyl ester **35**



34 **34a** **35**

Lactone **34** (300.0mg,1.00eqiv., 1.56mmol) was dissolved in 16ml dry DCM and cooled to -78°C before 1M DIBALH solution in heptane (2.34ml, 1.50eqiv., 2.34mmol) was added. After stirring for 1hour 30 minutes at the aforementioned temperature, the solution was quenched with 1ml EtOAc followed by addition of 5ml saturated Rochelles salt solution. The mixture was allowed to reach room temperature and stirred for at least 30 minutes until the phases were clearly separated. After extraction with DCM (4x), drying with Na_2SO_4 and evaporation of the solvent crude lactol **34a** was obtained as a slightly yellow oil. Lactol **34a** combined with (1-ethoxycarbonylethyliden)-triphenylphosphorane (1.70g, 3.00eqiv., 4.68mmol) were dissolved in 16 ml dry toluene and heated to 100°C under an argon atmosphere for 19h. Toluene was evaporated and purification by column chromatography (LP:EtOAc=10:1 to 5:1) yielded 332.4 mg of **35** as colorless oil.

Yield: 332.4mg (77%)

Rf: 0.17 (LP:EtOAc=4:1)

Molecular Formula: $C_{17}H_{26}O_3$

Molecular weight [g/mol]: 278.39

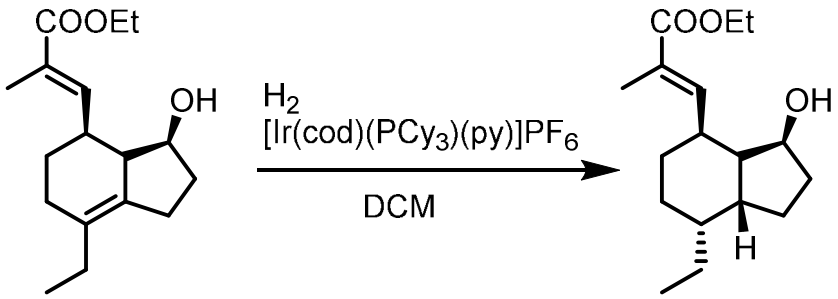
HRMS: calculated $(M+1)^+$= 279.1955, found $(M+1)^+$ = 279.1956

$[\alpha]_D^{20}$: +43.05 (0.98g/100ml DCM)

^{1}H-NMR (200 MHz, CD_2Cl_2): δ = 0.98 (t, J= 7.5Hz, 3H, 7'-CH_3), 1.25 (t, J=7.1Hz, 3H, 4''-CH_3), 1.33-1.35 (m, 1H), 1.57-2.10 (m, 12H), 2.23-2.52 (m, 3H, 4-CH), 3.04-3.16 (m, 1H, 3-CH), 4.07-4.28 (m, 3H, 4''-CH_2+OH), 7.07 (dd, J_1 = 10.5 Hz, J_2= 1.3 Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, CD_2Cl_2): δ = 12.1 (q, 7‘-CH_3), 12.5 (q, 4‘‘-CH_3), 14.2 (q, 4‘-CH), 24.6 (t, 1-CH_2), 25.3 (t, 5-CH_2), 26.7 (t, 7‘-CH_2), 29.2 (t, 6-CH_2), 32.9 (t, 2-CH_2), 33.8 (d, 4-CH), 50.0 (d, 3a-CH), 60.5 (t, 4‘‘-OCH_2), 75.1 (d, 3-CH), 127.3 (s, 4‘C), 131.3 (s, 7-C), 143.4 (s,7a-C) 143.5 (d, 4‘-CH),168.1 (s, 4‘-COOEt)

I III.2.4 (***E***)-3-((3S,3aR,4S,7R,7aR)-7-Ethyl-3-hydroxyoctahydro-inden-4-yl)-2-methyl-acrylic acid ethyl ester **36**



35 **36**

Hydroxy ester **35** (236.1mg, 1.00eqiv., 0.85mmol) was dissolved in 35ml dry DCM and degassed by means of freeze-thaw degassing method (3 times). The freshly degassed solution was backfilled with H_2 and cooled to 0°C and H_2 was bubbled through the solution for one minute before Crabtree's catalyst (68.23mg, 0.10eqiv., 0.09mmol) was added. Immediately H_2 was bubbled through the deep orange solution turning it into faint yellow transparent. The cooling bath was removed and the mixture was stirred for 45minutes (GC-MS control) and the H_2 atmosphere was substituted by argon which was bubbled through the solution for 5 minutes. The deep yellow mixture was concentrated in vacuo and purification via column chromatography (LP:EtOAc= 7:1) provided 126.9mg of **36** as colorless solid.

Yield: 126.9mg (53%) colorless solid

Rf: 0.17 (LP:EtOAc=4:1)

Melting point: 52-53°C

Molecular Formula: $C_{17}H_{28}O_3$

Molecular weight [g/mol]: 280.41

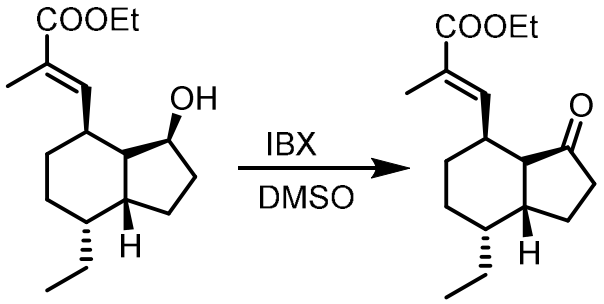
HRMS: calculated $(M+1)^+$= 281.2111, found $(M+1)^+$ = 281.2113

$[\alpha]_D^{20}$: -81.6° (c=0.45g/100ml DCM)

^{1}H-NMR (400 MHz, CD_2Cl_2): δ = 0.90 (t, J=7.3 Hz, 3H), 1.18-1.91 (m, 19H), 2.32-2.30 (m, 1H), 3.05-3.10 (m, 1H), 4.12-4.23 (m, 3H), 7.39 (dd, J_1 = 10.7 Hz, J_2= 1.4Hz, 1H)

^{13}C-NMR (50 MHz, CD_2Cl_2): δ = 12.4 (q), 12.9 (q), 14.3 (q), 17.4 (t), 23.9 (t), 24.1 (t), 26.8 (t), 33.2 (t), 35.0 (d), 37.3 (d), 37.7 (d), 47.4 (d), 60.6 (t), 75.4 (d), 126.8 (s), 143.9 (d), 168.0 (s)

I III.2.5 (***E***)-2-Methyl-3-((3aR,4S,7R,7aR)-7-ethyl-3-oxo-octahydro-inden-4-yl)-acrylic acid ethyl ester **37**



36 **37**

IBX (241.66mg, 2eqiv., 0.86mmol) in 3.6ml DMSO was added to compound **36** (120.9mg, 1.00eqiv., 0.43mmol) dissolved in 1.8ml DMSO, and the mixture was stirred for 2 hours before it was quenched through the addition of water. The white precipitate was removed by filtration through a short pad of celite. The residual solid was re-dissolved in DMSO, water and EtOAc were added and the suspension was filtrated again. Finally the product was extracted with Et_2O (4x), washed with $NaHCO_3$ and brine (3x), dried and concentrated before purification via column chromatography (LP:EtOAc= 7:1) provided 95.5mg of **37** slightly yellow oil.

Yield: 95.5mg (80%) yellow oil

Rf: 0.40 (LP:EtOAc=4:1)

Molecular Formula: $C_{17}H_{26}O_3$

Molecular weight [g/mol]: 278.39

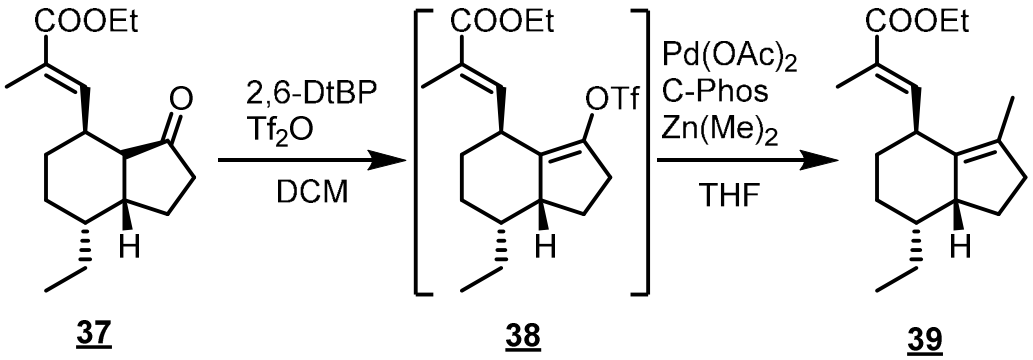
HRMS: calculated $(M+1)^+$= 279.1955, found $(M+1)^+$ = 279.1946

$[\alpha]_D^{20}$: -126.33° (c=0.30g/100ml DCM)

^{1}H-NMR (200 MHz, CD_2Cl_2): δ = 0.86 (t, J=7.4 Hz, 3H, 7'-CH_3), 1.18 (t, J= 7.1 Hz, 3H, 4''-CH_3), 1.25-2.22 (m, 16H), 3.02-3.10 (m, 1H, 3-CH), 4.05 (q, J=7.2 Hz, 2H, 4''-OCH_2), 6.73 (dd, J_1 = 10.1Hz, J_2= 1.5Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, CD_2Cl_2): δ = 12.7 (q, 7'-CH_3), 12.9 (q, 4''-CH_3), 14.4 (q, 4'-CH_3), 17.6 (t, 7'-CH_2), 24.3 (t, 1-CH_2), 24.4 (t, 6-CH_2), 25.8 (t, 2-CH_2), 32.7 (d, 4-CH), 38.1 (t, 5-CH_2), 38.3 (d, 7a-CH), 40.9 (d, 3a-CH), 52.2 (d, 3-CH), 60.7 (t, 4''-OCH_2), 129.5 (s, 4'-C), 140.3 (d, 4'-CH), 168.3 (s, 4'-COOEt)

I III.2.6 Ethyl (*E*)-3-((4*S*,7*R*,7a*R*)-7-ethyl-3-methyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methacrylate (7-Ethylvalerenic acid ethyl ester) **39**



37 **38** **39**

Ketone **37** (95.50mg, 1.00eqiv., 0.43mmol) was dissolved in 8.6ml dry DCM under dry argon and cooled to 0°C. Subsequently, 2,6-ditert.-butylpyridine 97% (152.90µl, 2.00eqiv., 0.86mmol) and freshly distilled triflic anhydride (115.40µl, 2.00eqiv., 0.86mmol) were added under vigorous stirring. The mixture was stirred for 5 minutes at that temperature before it was allowed to warm to room temperature. After 3 hours the slightly yellow mixture was taken up in 100ml pentane and stirred for 5 minutes before the precipitated solids were removed via filtration through a short pad of celite. After the solvents have been removed on the rotary evaporator, 50 ml of pentane were added and the organic phase was washed with 2N HCl and $NaHCO_3$, dried and again concentrated. The residual crude enol triflate **38** was dissolved in 7.6ml dry THF under argon and cooled to 0°C then $Pd(OAc)_2$ (7.70mg, 0.1eqiv., 0.03mmol) and C-Phos (29.90mg, 0.20eqiv., 0.07mmol) dissolved in 1ml dry THF were added. The orange solution was stirred for 5 minutes and then 1M dimethylzinc solution in heptane (0.68ml, 2.00eqiv., 0.68mmol) was added, the ice bath removed and stirred overnight. Again the mixture was cooled to 0°C and quenched with saturated NH_4Cl solution, extracted with Et_2O (4x), once washed with brine, dried wit Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (10w/w% $AgNO_3$-doped SiO_2; heptane:EtOAc=100:0 to heptane:EtOAc=97:3) yielded 45.9mg 7-ethyl-valerenic acid ethyl ester **39** as colorless oil.

Yield: 45.9mg (48%) colorless oil

Rf: 0.38 (LP:EtOAc=30:1)

Molecular Formula: $C_{18}H_{28}O_2$

Molecular weight [g/mol]: 276.42

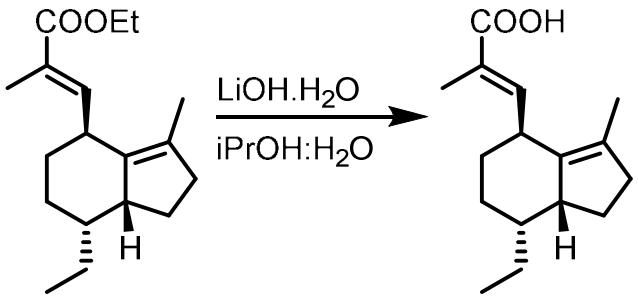
HRMS: calculated $(M+1)^+$= 277.2162, found $(M+1)^+$ =277.2164

$[\alpha]_D^{20}$: -91.5° (c=0.56g/100ml DCM)

^{1}H-NMR (400 MHz, CD_3Cl): δ =0.83 (t, J= 7.4Hz, 3H, 7'-CH_3), 1.08-1.16 (m, 1H), 1.24-1.37 (m, 5H), 1.58-1.68 (m, 8H), 1.78-1.86 (m, 4H), 2.16-2.20 (m, 2H, 2C-CH_2), 2.97-2.98 (m, 1H, 7a-CH), 3.49-3.52 (m, 1H, 4-CH), 4.18 (q, J=7.1Hz, 2H, 4''-O-CH_2), 7.02 (dd, J_1 = 9.8Hz, J_2= 1.3 Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, CD_3Cl): δ = 11.0 (q, 7'-CH_3), 11.4 (q, 4''-CH_3), 12.4 (q, 4'-CH_3), 13.3 (q, 3'-CH_3), 16.1 (t, 1-CH_2), 22.7 (t, 6-CH_2), 23.2 (t, 7'-CH_2), 24.4 (t, 5-CH_2), 33.3 (d, 7-CH), 36.6 (t, 2-CH_2), 39.5 (d, 4-CH), 47.1 (d, 7a-CH), 59.4 (t, 4''-OCH_2), 124.9 (s, 4'-C), 129.3 (s, 3-C), 133.1 (s, 3a-C), 142.4 (d, 4'-CH), 167.6 (s, 4'-COOEt)

I III.2.7 (*E*)-3-((4*S*,7*R*,7a*R*)-7-Ethyl-3-methyl-2,4,5,6,7,7a-heahydro-1*H*-inden-4-yl)-2methacrylic acid (7-Ethylvalerenic acid) **40**



39 **40**

Ethylester **39** (15.10mg, 1.00eqiv., 0.05mmol) together with LiOH.H_2O (13.75mg, 6.00eqiv., 0.33mmol) were dissolved in 270µl *i*-PrOH:H_2O mixture (2:1) and heated to 40°C for 21h.

eqiv.eqiv.After cooling to room temperature, the mixture was diluted with 4ml *i*-PrOH:H_2O (3:1) and 1ml volume of Amberlite IR 120 was added. The suspension was stirred for 30 minutes and the Amberlite was filtered off, before the residual solvents were lyophyllized to furnish 12.6mg 7-ethylvalerenic acid **40** as colorless solid.

Yield: 12.6mg (93%)

Rf: 0.45 (LP:EtOAc=3:1)

Melting Point: 75-76°C

Molecular Formula: $C_{16}H_{24}O_2$

Molecular weight [g/mol]: 248.37

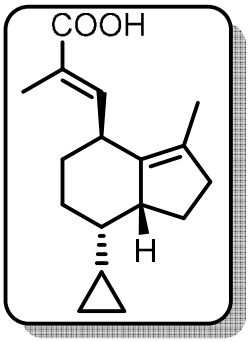
HRMS: calculated $(M-1)^+$= 247.1693, found $(M-1)^+$ = 247.1666

$[\alpha]_D^{20}$: -26.0° (c=0.15g/100ml DCM)

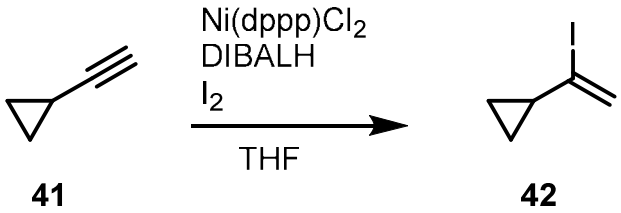
^{1}H-NMR (200 MHz,CD_2Cl_2): δ = 0.75 (t, J=7.4Hz, 3H, 7'-CH_3), 0.99-1.11 (m, 1H), 1.14-1.29 (m, 2H), 1.53-1.61 (m, 8H), 1.69-1.81 (m, 4H), 2.09-2.13 (m, 2H), 2.88 (bs, 1H, 7a-CH), 3.43-3.54 (m, 1H, 4-CH), 6.98 (d, J=9.5Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, CD_2Cl_2): δ = 11.8 (q, 7'-CH_3), 12.1 (q, 4'-CH_3), 13.1 (q, 3'-CH_3), 17.1(t, 1-CH_2), 23.7 (t, 6-CH_2), 24.2 (t, 7'-CH_2), 25.3(t, 5-CH_2), 34.5 (d, 7-CH), 37.5 (t, 2-CH_2), 40.7(d, 4-CH), 48.1 (d, 7a-CH), 126.6 (s, 4'-C), 130.2 (s, 3-C), 134.1 (s, 3a-C), 144.6 (d, 4'-CH), 174.7 (s, 4'-COOH)

I III.3 Synthesis of (*E*)-3-((4*S*,7*S*,7a*R*)-7-Cyclopropyl-3-methyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methylacrylic acid (7-Cyclopropylvalerenic acid)



I III.3.1 1-(Iodovinyl)cyclopropane **42**



41 **42**

$Ni(dppp)Cl_2$ (319.80mg, 0.01eqiv., 0.59mmol) was dissolved in 59ml dry THF and reagent grade DIBALH (11.71ml, 1.10eqiv., 64.90mmol) was added slowly turning the solution immediately from deep red to dark brown. After complete addition the reaction mixture was cooled to 0°C and cyclopropylacetylene **41** (5.00ml, 1.00eqiv., 59.00mmol) was added slowly over a period of 20 minutes. The ice bath was removed and the mixture was stirred for two hours before it was cooled to -90°C and freshly sublimated iodine (16.47g, 1.10eqiv., 64.90mmol) dissolved in 33ml dry THF was added slowly. After complete iodine addition the reaction mixture was warmed again to room temperature and stirred for another hour before it was carefully quenched at 0°C with 20ml saturated Rochelles salt solution (quenching is very exothermic!). 100ml Pentane were added to the quenched solution and stirred for 30 minutes. Solids were filtered and the biphasic mixture was extracted with pentane (4x), washed with 10% $Na_2S_2O_3$ solution (2x) and brine (1x), dried over sodium sulfate and concentrated on the rotary evaporator. Vacuum-distillation (60-62°C, 20mbar) afforded 3.91g of 1-(iodovinyl)cyclopropane **42** in 94.5% purity (5.5% 1-iodo-2-methylpropane).

Yield: 3.91g (34%) colourless oil (94.5% purity)

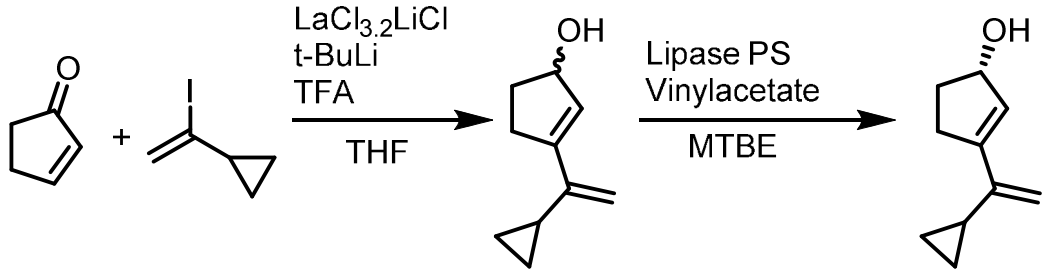
Molecular Formula: C_5H_7I

Molecular weight [g/mol]: 194.02

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.59- 0.79 (m, 4H, 2x-cyclopropyl CH_2), 1.44-1.57 (m, 1H, cyclopropyl CH), 5.67 (s, 1H, olefinic CH), 6.07 (s, 1H olefinic CH)

^{13}C-NMR (50 MHz, $CDCl_3$): n.d.[94]

I III.3.2 (S)-3-(1-Cyclopropylvinyl)cyclopent-2-en-1-ol **43**



24 **42** **rac-43** **43**

Cyclopent-2-en-1-one **24** (1.20ml, 1.00eqiv., 14.40mmol) was added to 0.6 M $LaCl_3$.2LiCl solution (24.00ml, 1.00eqiv., 14.40mmol) and stirred for 30 minutes. Meanwhile 1-(iodovinyl)cyclopropane (3.90g, 1.30eqiv., 18.7mmol, 94.50% purity) was dissolved in 190ml dry THF and cooled to -78°C before 1.7M t-BuLi solution in pentane (22.02ml, 2.60eqiv., 37.44mmol) was added dropwise. Upon t-BuLi addition, the solution turned slightly yellow and LiI precipitated. After stirring for 35 minutes at -78°C the cyclopentenone/ $LaCl_3$.2LiCl solution was added dropwise and stirred for 2 hours at this temperature before it was warmed to 0°C and quenched with 50ml water. The mixture was stirred for 5 minutes and TFA (2.98ml, 2.70eqiv., 38.90mol) was added. After stirring for another 35 minutes at 0°C the mixture was quenched with $NaHCO_3$ solution and extracted with Et_2O (4x), washed with saturated $NaHCO_3$ solution (2x), dried and concentrated, before purification by column chromatography (LP:EtOAc = 10:1 to 5:1 +1% NEt_3) provided 1.31g of ***rac*-43** (61%) as yellow oil.

The racemic alcohol ***rac*-43** (1.31g, 1.00eqiv., 8.40mmol) was dissolved in 39ml MTBE and Lipase PS (0.25g, 20w/w%) together with vinylacetate (0.43ml, 0.55eqiv., 4.62mmol) were added and stirred for 21h. After filtration through a short pad of celite and evaporation of the solvent, column chromatography (90g NEt_3-doped SiO_2;LP:EtOAc=8:1+1%NEt_3 to

4:1+1%NEt_3) delivered 569.5mg (S)-3-(1-Cyclopropylvinyl)cyclopent-2-en-1-ol **43** as colorless oil with an enantiomeric excess of >99%.

Note: Compound **43** is labile and should be stored in the freezer!

Yield: 569.5mg (26%) colorless oil

Rf: 0.43 (LP:EtOAc=3:1)

Molecular Formula: $C_{10}H_{14}O$

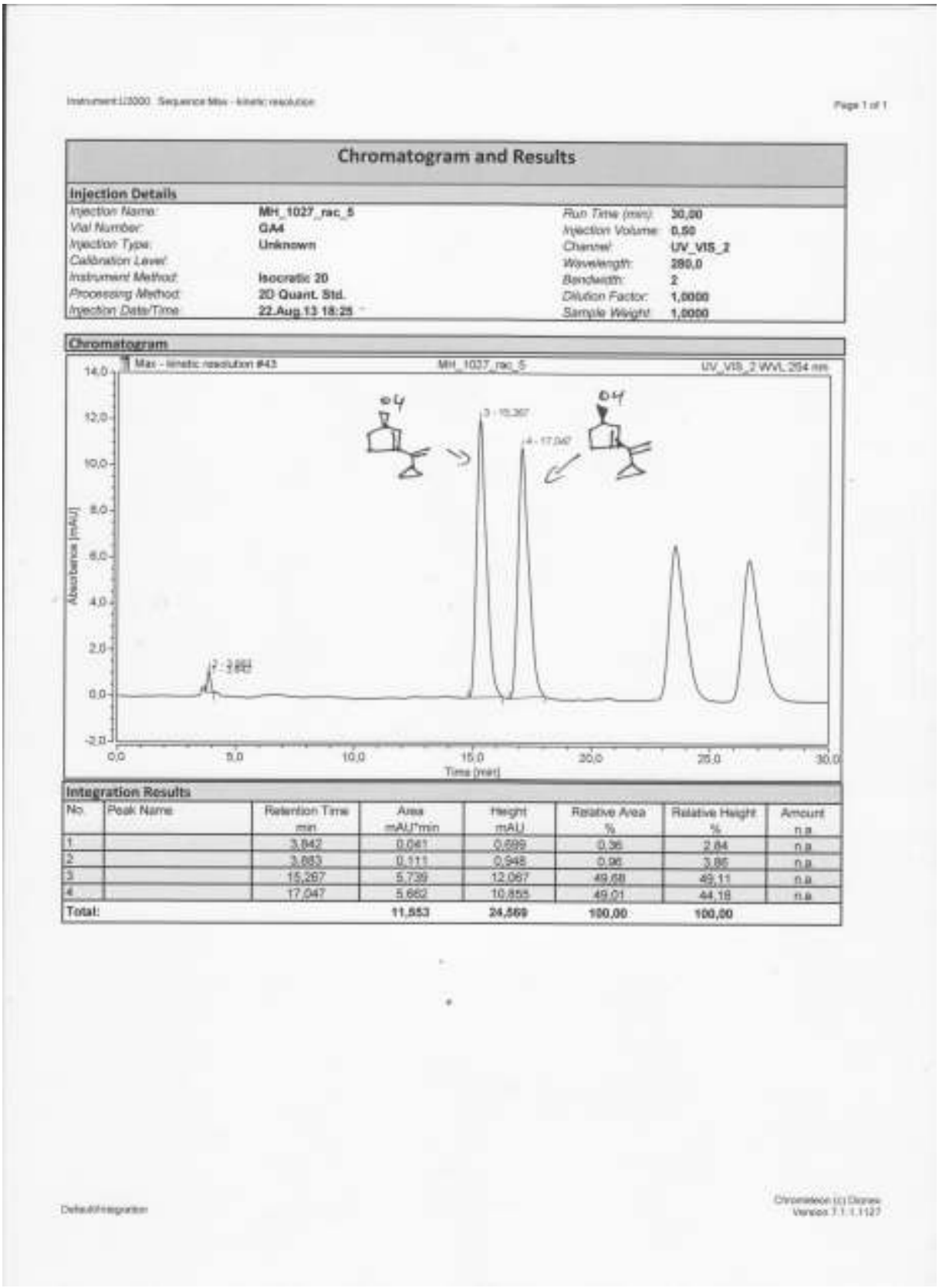
Molecular weight [g/mol]: 150.22

HRMS: calculated $(M-17)^+$= 133.1012, found $(M-17)^+$ = 133.1019

$[\alpha]_D^{20}$: -58.99 (c=0.54g /100ml DCM)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.43-0.49 (m, 2H, 3'-cyclopropylCH_2), 0.69-0.74 (m, 2H, 3-cyclopropyl CH_2), 1.49-1.62 (m, 2H, 5-CH_2), 1.70-1.85 (m, 1H, 3'-cyclopropyl CH), 2.28-2.47 (m, 2H, 4-CH_2), 2.59-2.75 (m, 1H, 1-CH), 4.90-4.96 (m, 3H, 3'-olefinicCH_2+ 1-OH), 6.10-6.11 (m, 1H, 2-CH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 5.7 (t, 3'-cyclopropyl CH_2), 5.9 (t, 3'-cyclopropyl CH_2), 14.1 (d, 3'-cyclopropyl CH), 30.9 (t, 5-CH_2), 33.7 (t, 4-CH_2), 77.8 (d, 1-CH), 111.2 (t, 3'-olefinic CH_2), 128.7 (d, 2-CH), 145.2 (s, 3-C), 147.4 (s, 3'-C)



Chromatogram and Results

Injection Details

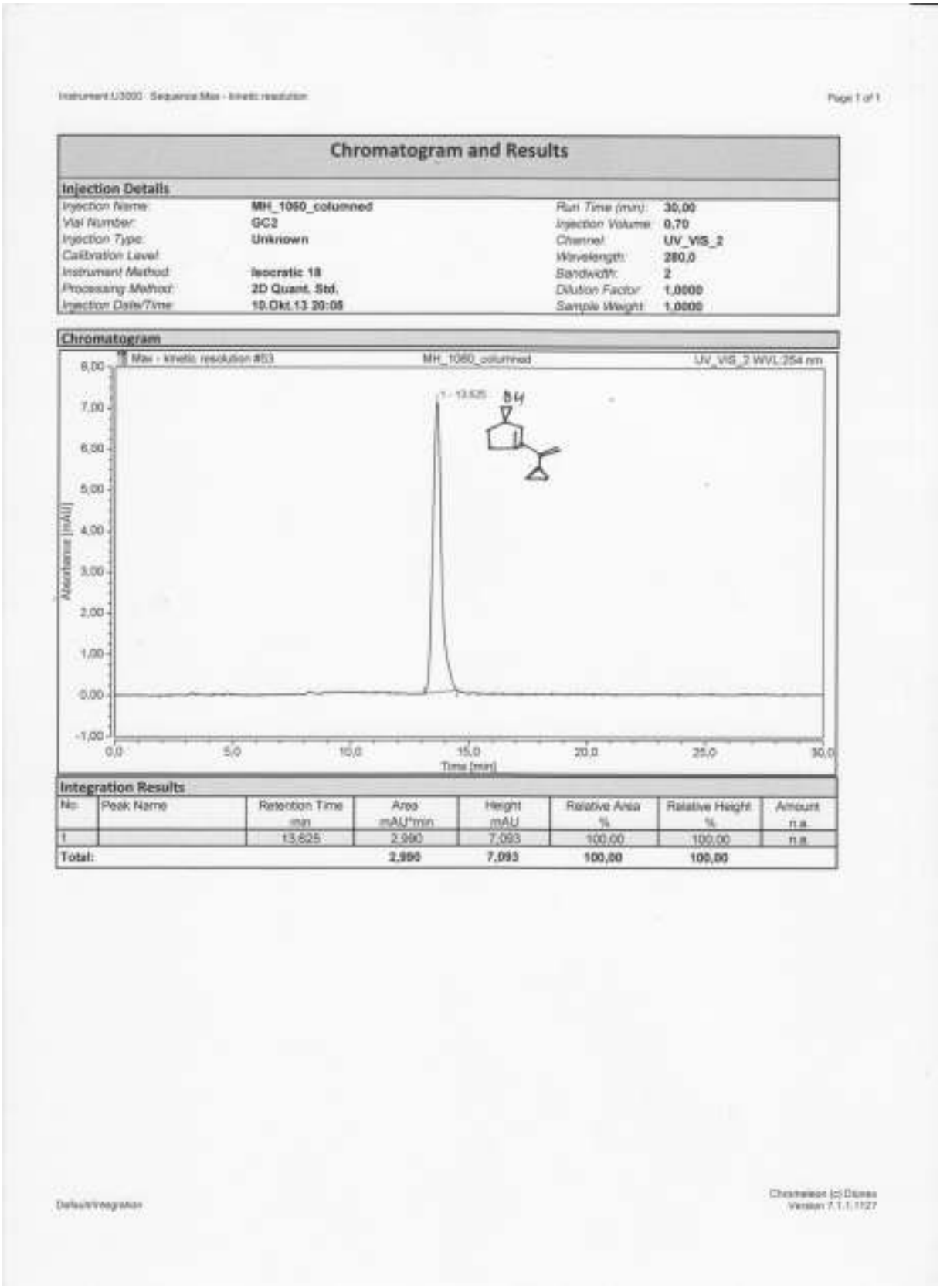
Injection Name:	MH_1027_rac_5	*Run Time (min):*	30,00
Vial Number:	GA4	*Injection Volume:*	0,50
Injection Type:	Unknown	*Channel:*	UV_VIS_2
Calibration Level:		*Wavelength:*	280,0
Instrument Method:	Isocratic 20	*Bandwidth:*	2
Processing Method:	2D Quant. Std.	*Dilution Factor:*	1,0000
Injection Date/Time:	22.Aug.13 18:25	*Sample Weight:*	1,0000

Chromatogram

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		3,842	0,041	0,599	0,36	2,64	n.a.
2		3,883	0,111	0,948	0,96	3,86	n.a.
3		15,267	5,739	12,067	49,68	49,11	n.a.
4		17,047	5,662	10,855	49,01	44,18	n.a.
Total:			**11,553**	**24,569**	**100,00**	**100,00**	

Figure 119 Racemic sample of 3-(1-Cyclopropylvinyl)cyclopent-2-en-1-ol 43



Chromatogram and Results

Injection Details

Injection Name:	**MH_1060_columned**	*Run Time (min):*	**30,00**
Vial Number:	**GC2**	*Injection Volume:*	**0,70**
Injection Type:	**Unknown**	*Channel*	**UV_VIS_2**
Calibration Level		*Wavelength:*	**280,0**
Instrument Method:	**Isocratic 18**	*Bandwidth:*	**2**
Processing Method:	**2D Quant. Std.**	*Dilution Factor:*	**1,0000**
Injection Date/Time:	**10.Okt.13 20:08**	*Sample Weight:*	**1,0000**

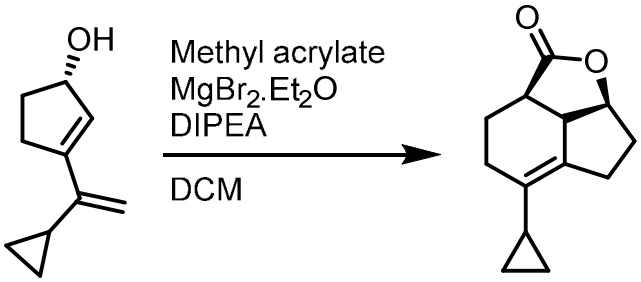
Chromatogram

Integration Results

No:	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		13,625	2,990	7,093	100,00	100,00	n.a.
Total:			**2,990**	**7,093**	**100,00**	**100,00**	

Figure 120 Kinetic resolution of 3-(1-Cyclopropylvinyl)cyclopent-2-en-1-ol 43

I III.3.3 (2aR,7aS,7bR)-5-cyclopropyl-3,4,6,7,7a,7b-hexahydroindeno[1,7-*bc*]furan-2(2a*H*)-one **44**



43 **44**

Anhydrous $MgBr_2.Et_2O$ (1.77g, 2.00eqiv., 6.84mmol) was suspended in 8ml dry DCM under argon at room temperature before anhydrous diisopropylethylamine (2.38ml, 4.00eqiv., 13.68mol) was added and the mixture was stirred until it turned magenta (~15 minutes). Then (S)-3-(1-cyclopropylvinyl)cyclopent-2-en-1-ol **44** (514.50mg, 1.00eqiv., 3.42mmol) dissolved in 34ml dry DCM was added slowly and stirred for 1 hour, before methyl acrylate (619.80µl = 652.42mg, 2.00eqiv., 6.84mmol) was added dropwise. The mixture was stirred overnight at room temperature, quenched with sat. NH_4Cl, extracted with DCM (4x), dried with sodium sulfate and the solvent evaporated. Purification by column chromatography (LP:EtOAc = 6:1) provided 533.0 mg lactone **44** as yellow solid.

Yield: 533.0mg (75%) yellow solid

Rf: 0.35 (LP:EtOAc=3:1)

Melting Point: 55-57°C

Molecular Formula: $C_{13}H_{16}O_2$

Molecular weight [g/mol]: 204.27

HRMS: calculated $(M+1)^+$= 205.1223 , found $(M+1)^+$ = 205.1228

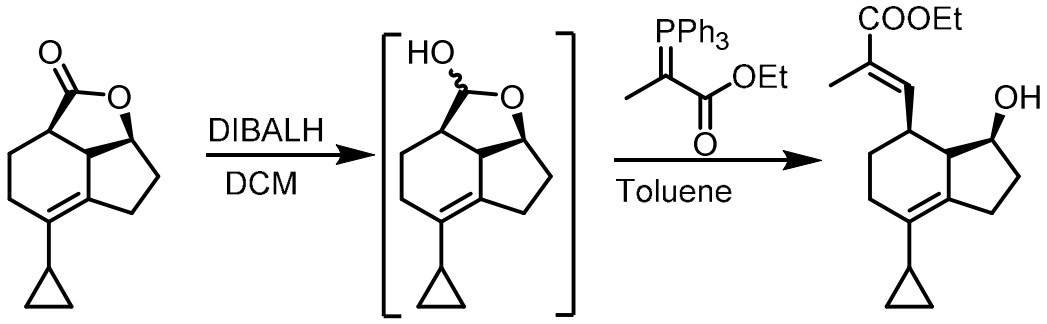
$[\alpha]_D^{20}$: -28.5° (c=0.33g/100ml DCM)

^{1}H-NMR (200 MHz, CD_2Cl_2): δ = 0.34 -0.57 (m, 4H, 2x7'-cyclopropyl CH_2), 1.41- 1.59 (m, 3H, 7'-CH+2-CH_2), 1.63-2.13 (m, 4H, 1-CH_2+6-CH_2), 2.23-2.36 (m, 1H, 4-CH), 2.57-2.82 (m, 2H, 5-CH_2), 2.89-2.98 (m, 1H, 3a-CH), 4.76 (dt, J_1 = 5.0 Hz, J_2= 1.3 Hz, 1H, 3-CH)

^{13}C-NMR (50 MHz, CD_2Cl_2): δ = 3.6 (t, 7'-cyclopropyl CH_2), 4.4 (t, 7'-cyclopropyl CH_2), 14.0 (d, 7'-cyclopropyl CH), 21.0 (t, 5-CH_2), 21.2 (t, 6-CH_2), 27.4 (t, 1-

CH_2), 29.9 (t, 2-CH_2), 39.9 (d, 3a-CH), 44.6 (d, 4-CH), 83.8 (d, 3-CH), 132.3 (s, 7-C), 133.6 (s, 7a-C), 179.1 (s, 4'-COO)

I III.3.4 (***E***)-3-((3S,3aR,4S)-7-Cyclopropyl-3-hydroxy-2,3,3a,4,5,6-hexahydro-1*H*-inden-4-yl)-2-methyl-acrylic acid ethyl ester **45**



44 **44a** **45**

Lactone **44** (244.4mg,1.00eqiv., 1.20mmol) was dissolved in 12ml dry DCM and cooled to -78°C before 1M DIBALH solution in heptane (1.44ml, 1.50eqiv., 1.44mmol) was added. After stirring for 1hour 30 minutes at the aforementioned temperature, the solution was quenched with 1ml EtOAc followed by addition of 5ml saturated Rochelles salt solution. The mixture was allowed to reach room temperature and stirred for at least 30 minutes until the phases were clearly separated. Then, extraction with DCM (4x), drying with Na_2SO_4 and evaporation of the solvent, provided crude lactol **44a** as a slightly yellow oil. Lactol **44a** combined with (1-ethoxycarbonylethyliden)-triphenylphosphorane (1.30g ,3.00eqiv., 3.60mmol) were dissolved in 12 ml dry toluene and heated to 100°C under an argon atmosphere for 19h. Toluene was evaporated and purification by column chromatography (LP:EtOAc=10:1 to 5:1) yielded 258.0 mg of (***E***)-3-((3S,3aR,4S)-7-cyclopropyl-3-Hydroxy-2,3,3a,4,5,6-hexahydro-1*H*-inden-4-yl)-2-methyl-acrylic acid ethyl ester **45** as colorless oil.

Yield: 258.0mg (74%) colorless oil

Rf: 0.19 (LP:EtOAc=4:1)

Molecular Formula: $C_{18}H_{26}O_3$

Molecular weight [g/mol]: 290.40

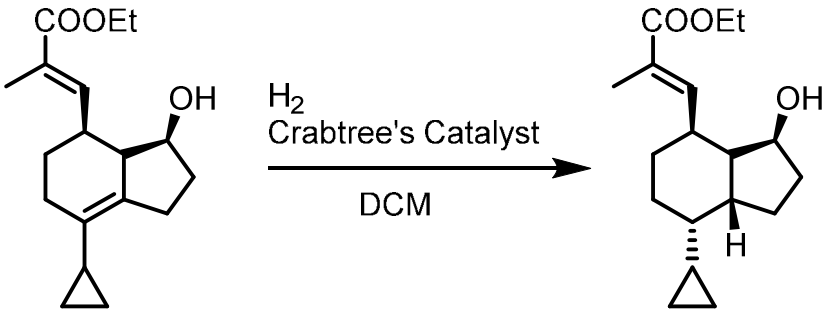
HRMS: calculated $(M-17)^+$= 273.1849, found $(M-17)^+$ = 273.1841

$[\alpha]_D^{20}$: +30.5 (0.83g/100ml DCM)

^{1}H-NMR (200 MHz, CD_2Cl_2): δ = 0.41-0.62 (m, 4H, 2x7'-cyclorpoyl CH_2), 2.14 (t, J= 7.1Hz, 3H, 4''-CH_3), 1.36-1.38 (m, 1H, 7'-CH), 1.51-1.77 (m, 7H), 1.90 (d, J= 1.3 Hz, 3H, 4'-CH_3), 2.33-2.66 (3H, 4-CH+1-CH_2), 3.02-3.12 (m, 1H, 3-CH), 4.09-4.26 (3H, 4''-OCH_2+3-OH), 7.02 (dd, J_1 = 10.4 Hz, J_2= 1.3 Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, CD_2Cl_2): δ = 3.0 (t, 7'-cyclopropyl CH_2), 3.6 (t, 7'-cyclopropyl CH_2), 12.5 (q, 4''-CH_3), 13.8 (d, 7'-CH), 14.2 (q-4'-CH_3), 20.5 (t, 6-CH_2), 26.8 (t, 1-CH_2), 28.8 (t, 5-CH_2), 30.1 (t, 2-CH_2), 33.8 (d, 4-CH), 50.3 (d, 3a-CH), 60.5 (t, 4''-OCH_2), 74.9 (d, 3-CH), 127.4 (s, 4'-C), 128.6 (s, 7-C), 132.9 (s, 7a-C), 143.3 (d, 4'-CH), 168.2 (s, 4'-COOEt)

I III.3.5 (***E***)-3-((3S,3aR,4S,7R,7aR)-7-cyclopropyl-3-Hydroxyoctahydro-inden-4-yl)-2-methyl-acrylic acid ethyl ester **46**



45 **46**

Hydroxy ester **45** (83.7mg, 1.00eqiv., 0.29mmol) was dissolved in 11.5ml dry DCM and degassed by means of freeze-thaw degassing method (3 times). The freshly degassed solution was backfilled with H_2 and cooled to 0°C and H_2 was bubbled through the solution for one minute before Crabtree's catalyst (23.20mg, 0.10eqiv., 0.03mmol) was added. Immediately H_2 was bubbled through the deep orange solution turning it into faint-yellow transparent. The cooling bath was removed and the mixture was stirred for 55 minutes (GC-MS control) after which the H_2 atmosphere was substituted by argon bubbling it through the solution for 5 minutes. The deep yellow mixture was concentrated in vacuo and purification via column chromatography (LP:EtOAc= 7:1) provided 41.2mg of (***E***)-3-((3S,3aR,4S,7R,7aR)-7-cyclopropyl-3-hydroxyoctahydro-inden-4-yl)-2-methyl-acrylic acid ethyl ester **46** as colorless solid.

Yield: 41.2mg (49%) colorless solid

Rf: 0.19 (LP:EtOAc=4:1)

Melting point: 78-81°C

Molecular Formula: $C_{18}H_{28}O_3$

Molecular weight [g/mol]: 292.42

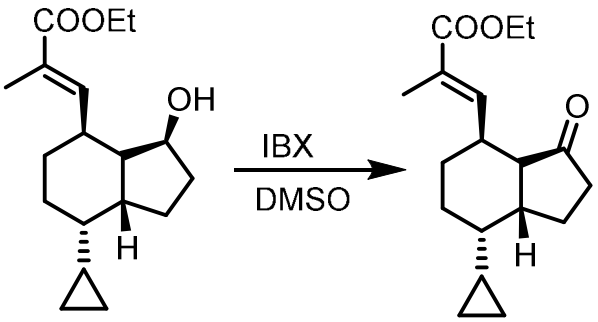
HRMS: calculated $(M-17)^+$= 275.2006, found $(M-17)^+$ = 275.2002

$[\alpha]_D^{20}$: -85.5° (c=0.59g/100ml DCM)

^{1}H-NMR (400 MHz, CD_2Cl_2): δ = -0.08-0.03 (m, 3H (1H+TMS, 7'-cyclopropyl CH_2), 0.08-0.19 (m, 1H, 1 H of 7'-cyclopropyl CH_2), 0.33-0.46 (m, 1H, 1H of 7'-cyclopropyl CH_2), 0.52-0.65 (m, 1H, 7'-cyclopropyl CH), 0.70-0.83 (m, 1H, 7a-CH), 1.09-2.00 (m, 17H), 2.33-2.47 (m, 1H, 4-CH), 3.12-3.16 (m, 1H, 3-CH), 4.13-4.28 (m, 3H, 4''-OCH_2+3-OH), 7.37 (dd, J_1 = 10.6Hz, J_2 1.3Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, CD_2Cl_2): δ = 0.0 (t, 7'-caclopropyl CH_2), 5.2 (t, -7'-cyclopropyl CH_2), 6.6 (d, 7'-CH), 10.2 (q, 4''-CH_3), 12.1 (q, 4'-CH_3), 22.7 (t, 1-CH_2), 25.0 (t, 6-CH_2), 26.0 (t, 2-CH_2), 31.0 (t, 5-CH_2), 32.9 (d, 4-CH), 40.4 (q, 3a-CH), 46.1 (q,7a-CH), 58.4 (t, 4''-OCH_2), 73.0 (q, 3-CH), 124.5 (s, 4'-C), 141.8 (q, 4'-CH), 165.9 (s, 4'-COOEt)

I III.3.6 (**E**)-2-Methyl-3-((3aR,4S,7R,7aR)-7-cyclopropyl-3-oxo-octahydroinden-4-yl)-acrylic acid ethyl ester **47**



46 **47**

To compound **46** (55.2mg, 1.00eqiv., 0.19mmol) dissolved in 0.8ml DMSO, IBX (105.85mg, 2.00eqiv., 0.38mmol) dissolved in 1.6ml DMSO was added and the mixture was stirred for 1 hour 40 minutes before it was quenched through the addition of water. The white precipitate was removed by filtration through a short pad of celite. The residual solid was re-dissolved in DMSO, water and EtOAc were added and the suspension filtrated again. Finally the product was extracted with Et_2O (4x), washed with $NaHCO_3$ and brine (3x), dried and concentrated, before purification via column chromatography (LP:EtOAc= 7:1) provided 40.2mg of (***E***)-2-Methyl-3-((3aR,4S,7R,7aR)-7-cyclopropyl-3-oxo-octahydroinden-4-yl)-acrylic acid ethyl ester **47** as slightly yellow oil. (Ketone **47** epimerizes easily under acidic conditions-even in $CDCl_3$!)

Yield: 40.2mg (73%) yellow oil

Rf: 0.35 (LP:EtOAc=4:1)

Molecular Formula: $C_{18}H_{26}O_3$

Molecular weight [g/mol]: 290.40

HRMS: calculated $(M+1)^+$= 291.1955, found $(M+1)^+$ = 291.1952

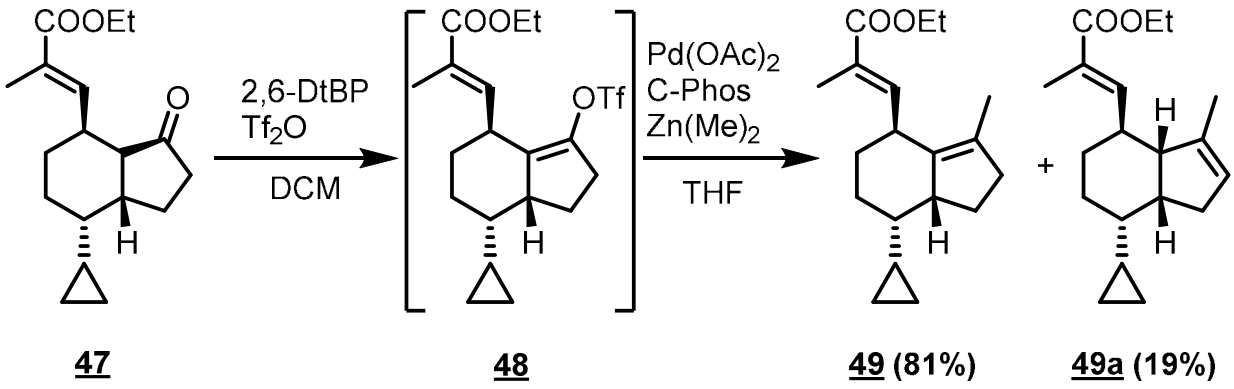
$[\alpha]_D^{20}$: -138.33° (c=0.77g/100ml DCM)

^{1}H-NMR (200 MHz, CD_2Cl_2): δ = -0.19-0.07 (m, 2H, 7'-cyclopropyl CH_2), 0.22-0.50 (m, 2H, 7'-cyclopropyl CH_2), 0.61-0.79 (m, 1H, 7'-CH), 0.92-1.14 (m, 4H, 4''-CH_3+7CH), 1.32-2.16 (m, 13H), 3.01-3.07 (m, 1H, 4-CH), 3.95 (q, 7.1Hz, 2H, 4''-OCH_2), 6.63 (dd, J_1 = 10.1 Hz, J_2= 1.5Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, CD_2Cl_2): δ = 2.5 (t, 7'-cyclopropyl CH_2), 6.6 (t, 7'-cyclopropyl CH_2), 8.4 (q, 7'-CH), 13.0 (q, 4''-CH_3), 14.4 (q, 4'-CH_3), 25.1 (t, 1-CH_2), 27.0 (t,

6-CH_2), 27.3 (t, 5-CH_2), 32.8 (d, 4-CH), 38.0 (t, 2-CH_2), 40.9 (d, 7a-CH), 43.6 (d, 3a-CH), 60.7 (t, 4‘‘-OCH_2), 129.6 (s, 4‘-C), 140.2 (d, 4‘-CH), 168.3 (s, 4‘-COOEt), 217.2 (s, 3-CO)

I III.3.7 Ethyl (*E*)-3-((4*S*,7*S*,7a*R*)-7-cyclopropyl-3-methyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methylacrylate (7-Cyclopropylvalerenic acid ethyl ester) **49**



47 **48** **49** (81%) **49a** (19%)

Ketone **47** (79.30mg, 1.00eqiv., 0.27mmol) was dissolved in 5.4ml dry DCM under argon and cooled to 0°C. Subsequently 2,6-ditert.-butylpyridine (183.00µl, 3.00eqiv., 0.85mmol) and freshly distilled triflic anhydride (68.90µl, 1.50eqiv., 0.41mmol) were added under vigorous stirring. The mixture was stirred for 5 minutes at that temperature before it was allowed to warm to room temperature. After 4 hours the slightly yellow mixture was taken up in 100ml pentane and stirred for 5 minutes before the precipitated solids were removed via filtration through a short pad of celite. After the solvents had been removed on the rotary evaporator, 50 ml of pentane were added and the organic phase was washed with 2N HCl and $NaHCO_3$, dried and again concentrated. The residual crude enol triflate **48** was dissolved in 4.4ml dry THF under argon and cooled to 0°C before $Pd(OAc)_2$ (6.10mg, 0.1eqiv., 0.03mmol) and C-Phos (23.81mg, 0.20eqiv., 0.05mmol) dissolved in 1ml dry THF were added. The orange solution was stirred for 5 minutes and then 1M dimethylzinc solution in heptane (0.55ml, 2.00eqiv., 0.55mmol) was added, the ice bath removed and stirred overnight. Again the mixture was cooled to 0°C and quenched with saturated NH_4Cl solution, extracted with Et_2O (4x), once washed with brine, dried and concentrated in vacuo. Purification by column chromatography (Heptane:EtOAc=100:0 to Heptane:EtOAc=97:3) yielded a mixture of isomers (49:49a = 81:19%) in 45.1mg of 7-cyclopropylvalerenic acid ethyl ester **49** as slightly yellow oil.

Yield: 45.1mg (63%) yellow oil (49:49a = 81:19%)

Rf: 0.29 (LP:EtOAc=30:1)

Molecular Formula: $C_{19}H_{28}O_2$

Molecular weight [g/mol]: 288.43

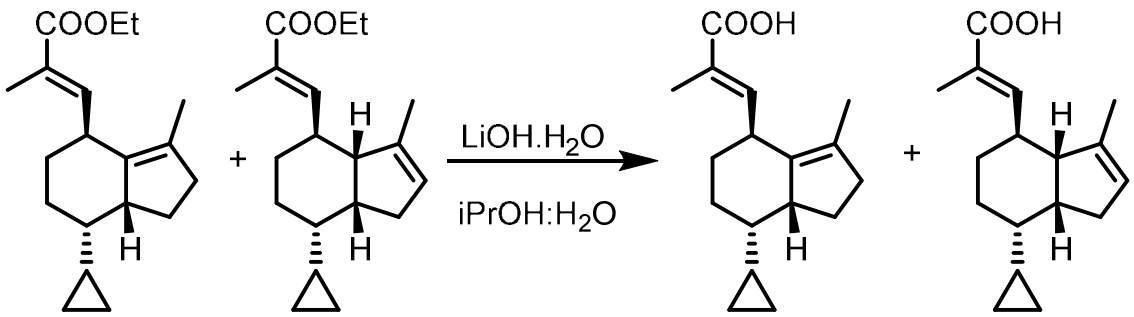
HRMS: calculated $(M-1)^+$= 287.2006, found $(M-1)^+$ = 287.2001

$[\alpha]_D^{20}$: -91.5° (c=0.56g/100ml DCM)

^{1}H-NMR (400 MHz, CD_3Cl): δ = -0.10-0.00 (m, 1H, 1H of 7'-cyclopropyl CH_2), 0.12-0.22 (m, 1H, 1H of 7'-cyclopropyl CH_2), 0.28-0.39 (m, 1H, 1H of 7'-cyclopropyl CH_2), 0.55-0.68 (m, 1H, 1H of 7'-cyclopropyl CH_2), 0.84-0.98 (m, 2H, 7'-CH+7-CH), 1.26-1.33 (m, 4H), 1.43-2.14 (m, 12H), 2.21-2.34 (m, 2H, 2-CH_2), 2.60 (m, 0.24H, 4-CH-isomer), 2.99-3.03 (m, 1H, 7a-CH), 3.55-3.61 (m, 1H, 4-CH), 4.18 (t, J= 7.1Hz, 2H, 4''-OCH_2), 5.38-5.39 (m, 0.24H, 2-olefinic CH-isomer), 7.00 (dd, J_1 = 9.9Hz, J_2= 1.4Hz, 1H, 4'-CH), 7.10 (dd, J_1 = 10.0Hz, J_2=1.4Hz, 0.24H, 4'-CH-isomer)

^{13}C-NMR (50 MHz, CD_3Cl): δ = 1.2 (t, 7'-cyclopropyl CH_2), 7.9 (t, 7'-cyclopropyl CH), 9.5 (d, 7' CH), 12.4 (q, 4''-CH_3), 13.6 (q, 4'-CH_3), 14.3 (q, 3'-CH_3), 24.0 (t, 6-CH_2), 26.5 (t, 1-CH_2), 27.5 (t, 5-CH_2), 34.4 (d, 4-CH), 37.5 (t, 2-CH_2), 44.6 (d, 7a-CH), 47.7 (d, 7-CH), 60.4 (t, 4''-OCH_2), 125.9 (s, 4'-C), 131.3 (s, 3-C), 134.4 (s, 3a-C), 143.3 (d, 4'-CH), 168.6 (s, 4'-COOEt)

I III.3.8 (*E*)-3-((4*S*,7*S*,7a*R*)-7-cyclopropyl-3-methyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methylacrylic acid (7-Cyclopropylvalerenic acid) **<u>50</u>**



<u>49</u> (81%) **<u>49a</u> (19%)** **<u>50</u> (81%)** **<u>50a</u> (19%)**

Ethyl-ester **<u>49</u>** (21.10mg, 1.00eqiv., 0.07mmol) and LiOH.H_2O (18.42mg, 6.00eqiv., 0.44mmol) were dissolved in 366µl HPLC-grade iPrOH:H_2O =2:1 and heated to 40°C for two days. After complete hydrolysis 4ml iPrOH:H_2O= 3:1 and 1ml volume of Amberlite IR-120

were added and the mixture was stirred for 30 minutes. The Amberlite was filtered off, water was added to the filtrate and lyophyllized to yield 18.40mg white solid as a mixture of isomeric acids **<u>50</u> : <u>50a</u>** (81:19 %).

Yield: 18.40mg (97%)

Rf: 0.39 (LP:EtOAc=3:1)

Melting Point: 61-64°C

Molecular Formula: $C_{17}H_{24}O_2$

Molecular weight [g/mol]: 260.38

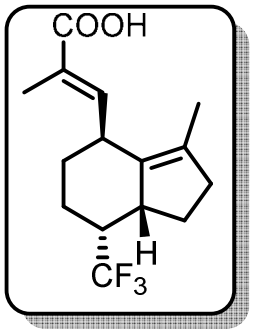
HRMS: calculated (M+1)= 261.1855, found (M+1) = 261.1840

$[\alpha]_D^{20}$: -27.1° (c=0.37g/100ml DCM)

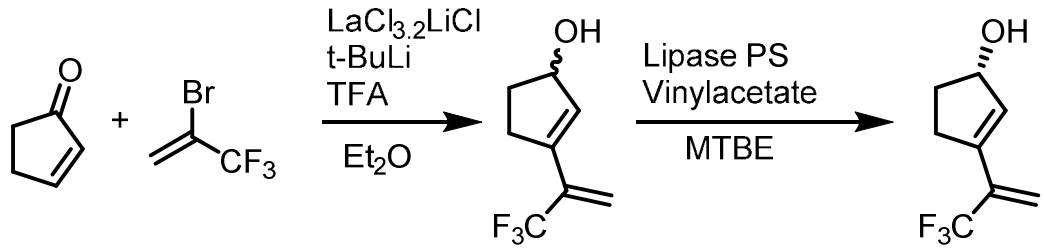
^{1}H-NMR (400 MHz, CD_3Cl): δ = -0.09-0.03 (m, 1H, 1H of 7'-cyclopropyl CH_2), 0.16-0.22 (m, 1H, 1H of 7'-cyclopropyl CH_2), 0.29-0.37 (m, 1H, 1H of 7'-cyclopropyl CH_2), 0.54-0.66 (m, 2H, 1H of 7'-cyclopropyl CH_2+7'-CH), 0.93-0.99 (m, 1H, 7-CH), 1.49-1.97 (m, 14H), 1.99-2.18 (m, 1H), 2.22-2.27 (m, 2H, 2-CH_2), 2.30-2.37 (m, 0.48H, 1-CH_2 of isomer), 2.62-2.65 (m, 0.24H, 3a-CH of isomer), 2.99-3.00 (m, 1H, 7a-CH), 3.06-3.12 (m, 0.24H, 4-CH of isomer), 3.58-3.62 (m, 1H, 4-CH), 5.39 (m, 0.24H, 2-olefinic CH of isomer), 7.15 (dd, J_1 =9.9HZ, J_2= 1.4Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, CD_3Cl): δ = -1.2 (t, 7'-cyclopropyl CH_2), 5.0 (t, 7'-cyclopropyl CH_2), 8.1 (d, 7'-CH), 10.9 (q, 4'-CH_3), 12.4 (q, 3'-CH_3), 22.9 (t, 6-CH_2), 25.3 (t, 1-CH_2), 26.3 (t, 5-CH_2), 33.5 (d, 4-CH), 36.3 (t, 2-CH_2), 43.4 (d, 7a-CH), 46.6 (d, 7-CH), 123.1 (s, 4'-C), 130.5 (s, 3-C), 132.8 (s, 3a-C), 144.4 (d, 4'-CH), 172.3 (s, 4'-COOH)

I III.4 Towards Synthesis of (*E*)-2-Methyl-3-((4*S*,7*S*,7a*R*)-3-methyl-7-(trifluoromethyl)-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methylacrylic acid (7-Trifluoromethylvalerenic acid)



I III.4.1 (S)-3-(3,3,3-trifluoroprop-1-en-2-yl)cyclopent-2-en-1-ol **51**



24 **rac-51** **51**

Cyclopent-2-en-1-one **24** (1.00ml=0.98g, 1.00eqiv., 11.90mmol) was added to a 0.6M solution of $LaCl_3.2LiCl$ in THF (16.80ml, 1.00eqiv., 11.90mmol) under argon atmosphere and stirred for one hour. Meanwhile 2-bromo-3,3,3-trifluoropropene (4.32ml, 3.50eqiv., 41.70mmol) was dissolved in 120ml dry Et_2O and cooled to -110°C before t-BuLi (24.50ml, 3.50eqiv., 41.70mmol) was added over 10 minutes relatively fast. After stirring for another 5 minutes, the before prepared cyclopent-2-en-1-one solution was added and stirred for 1 hour at -110°C. Then the orange solution was warmed to 0°C and quenched with saturated NH_4Cl, extracted with Et_2O (4x), once washed with sat. NH_4Cl and once with brine, dried over sodium sulfate and the Et_2O was evaporated. Next the mixture was taken up in 120ml THF + 60 ml H_2O and TFA (1.40ml, 1.50eqiv., 17.90mmol) was added at room temperature and stirred for 1h and 25 minutes before it was neutralized with saturated $NaHCO_3$ solution. After extraction with Et_2O (4x), washing with sat. $NaHCO_3$, drying over sodium sulfate and concentration in vacuo, column chromatography (LP:EtOAc=5:1 +1%NEt_3) yielded 1.45 g (68%) racemic alcohol ***rac*-51** as yellow oil.

The racemic alcohol ***rac*-51** (1.45g, 1.00eqiv., 8.14mmol) was dissolved in 40ml MTBE and Lipase PS (0.29g, 20w/w%) together with vinylacetate (0.46ml, 0.6eqiv., 4.88mmol) were added and stirred for 23 hours (control via chiral HPLC) . After filtration through a short pad of celite and evaporation of the solvent, column chromatography (LP:EtOAc=10:1+1%NEt_3 to 5:1+1%NEt_3) delivered 654.6mg (S)-3-(3,3,3-trifluoroprop-1-en-2yl)cyclopent-2-en-1-ol **51** as slightly yellow oil with an enantiomeric excess off 99%.

Note: Compound **51** is labile and should be stored in the freezer!

Yield: 654.6mg (31%) yellow oil

Rf: 0.25 (LP:EtOAc=4:1)

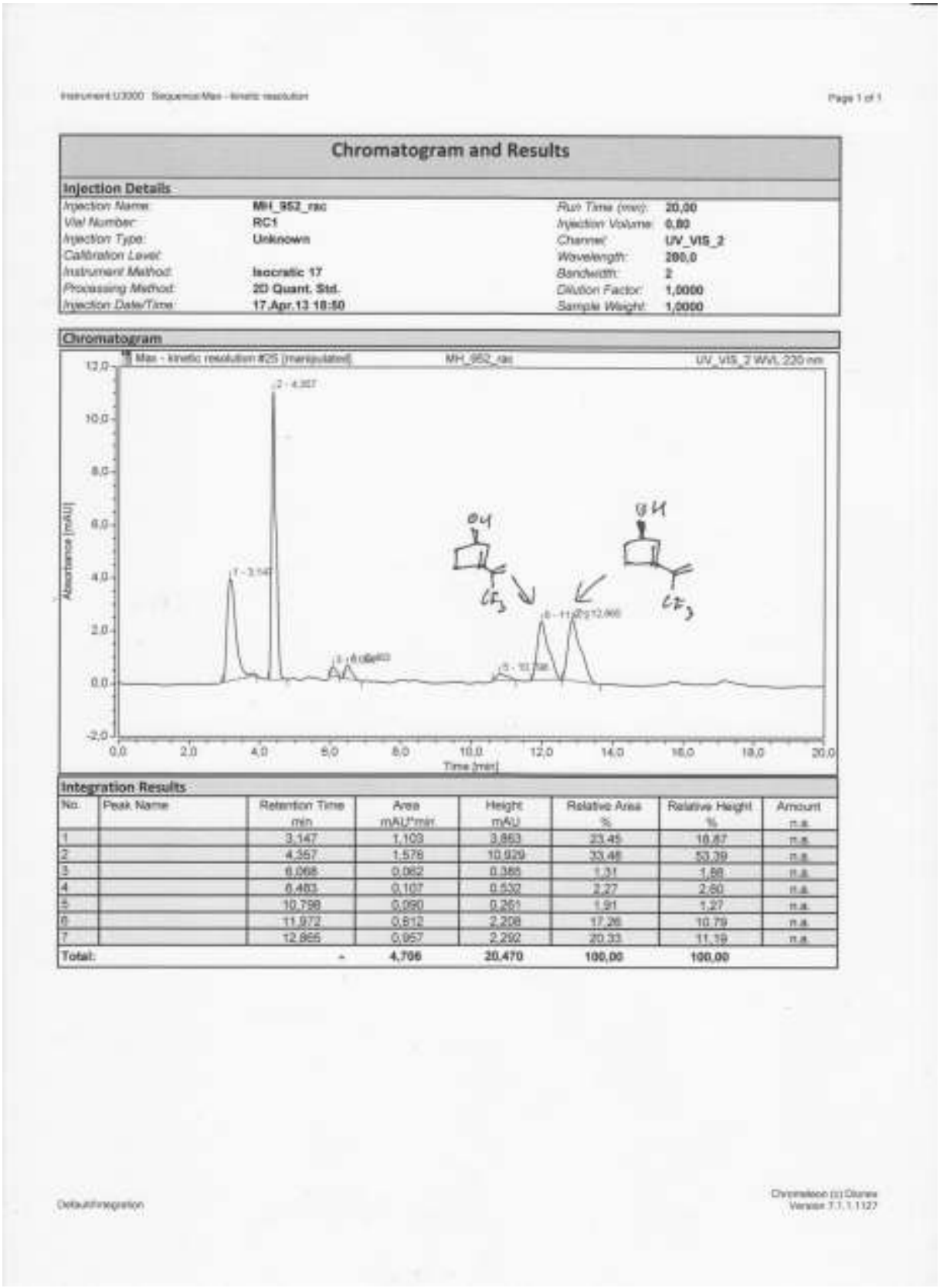
Molecular Formula: $C_8H_9F_3O$

Molecular weight [g/mol]: 178.15

$[\alpha]_D^{20}$: -103.0° (0.32g/100ml DCM)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.69-1.89 (m, 2H, 5-CH_2), 2.29-2.52 (m, 2H, 4-CH_2), 2.63-3.77 (m, 1H, 1-CH), 4.98 (bs, 1H, 1-OH), 5.52 (d, J= 1.9 Hz, 1H, 2-CH), 5.83 (s, 1H, 1H of 3'-olefinic CH_2), 6.07-6.08 (m, 1H, 1H of 3'-olefinic CH_2)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 31.3 (t, 5-CH_2), 32.5 (t, 4-CH_2), 77.8 (d, 1-CH), 119.6 (dt, J=5.7 Hz, 3'-CH_2), 122.9 (st, J=274.4 Hz, 3'CF_3), 132.9 (st, J=1.3 Hz,3-C), 134.8 (st, J=30.2 Hz, 3'-C), 137.7 (d, 2-CH)



Chromatogram and Results

Injection Details

Injection Name:	MH_952_rac	*Run Time (min):*	20,00
Vial Number:	RC1	*Injection Volume:*	0,80
Injection Type:	Unknown	*Channel:*	UV_VIS_2
Calibration Level:		*Wavelength:*	280,0
Instrument Method:	Isocratic 17	*Bandwidth:*	2
Processing Method:	2D Quant. Std.	*Dilution Factor:*	1,0000
Injection Date/Time:	17.Apr.13 18:50	*Sample Weight:*	1,0000

Chromatogram

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		3,147	1,103	3,853	23,45	18,87	n.a.
2		4,357	1,576	10,929	33,48	53,39	n.a.
3		6,068	0,062	0,385	1,31	1,88	n.a.
4		6,483	0,107	0,532	2,27	2,60	n.a.
5		10,798	0,090	0,261	1,91	1,27	n.a.
6		11,972	0,812	2,208	17,26	10,79	n.a.
7		12,865	0,957	2,292	20,33	11,19	n.a.
Total:		-	**4,706**	**20,470**	**100,00**	**100,00**	

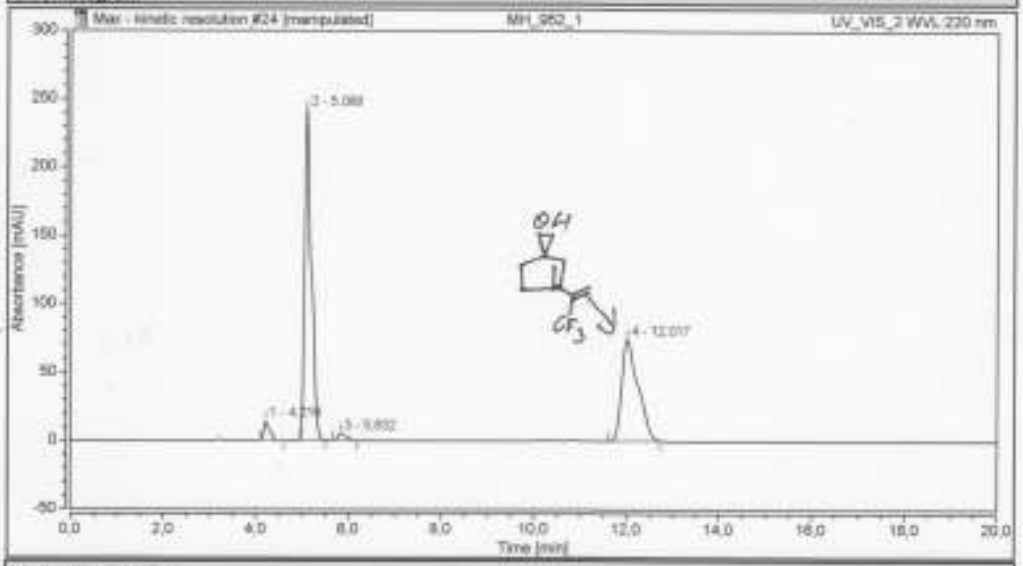
Figure 121 Crude racemic sample of 3-(3,3,3-trifluoroprop-1-en-2-yl)cyclopent-2-en-1-ol 51

Chromatogram and Results

Injection Details

Injection Name:	MH_962_1	Run Time (min):	20,00
Vial Number:	RC2	Injection Volume:	0,80
Injection Type:	Unknown	Channel:	UV_VIS_2
Calibration Level:		Wavelength:	280,0
Instrument Method:	Isocratic 17	Bandwidth:	2
Processing Method:	2D Quant. Std.	Dilution Factor:	1,0000
Injection Date/Time:	17.Apr.13 18:19	Sample Weight:	1,0000

Chromatogram

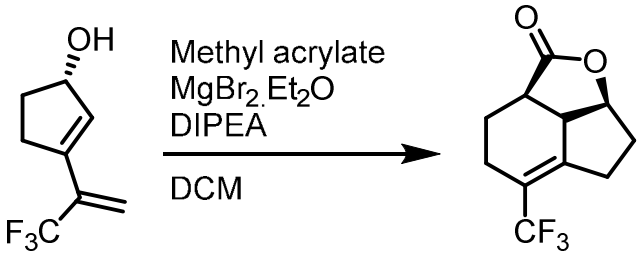


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		4,218	2,070	14,087	2,82	4,20	n.a.
2		5,068	40,234	241,732	54,84	72,11	n.a.
3		5,832	1,143	5,118	1,56	1,53	n.a.
4		12,017	29,926	74,281	40,79	22,16	n.a.
Total:			**73,373**	**335,219**	**100,00**	**100,00**	

Figure 122 Kinetic resolution of 3-(3,3,3-trifluoroprop-1-en-2-yl)cyclopent-2-en-1-ol 51

I III.4.2 (2aR,7aS,7bR)-5-(trifluoromethyl)-3,4,6,7,7a,7b-hexahydroindeno[1,7-*bc*]furan-2(2a*H*)-one **52**



51 **52**

Anhydrous $MgBr_2.Et_2O$ (870.20mg, 2.00eqiv., 3.37mmol) was suspended in 3.9ml dry DCM under argon before anhydrous diisopropylethylamine (1.24ml, 4.00eqiv., 6.72mol) was added and the mixture was stirred until it turned magenta (~15 minutes). Then (S)-3-(3,3,3-trifluoroprop-1-en-2yl)cyclopent-2-en-1-ol **51** (300.00mg, 1.00eqiv., 1.68mmol) dissolved in 13 ml dry DCM was added slowly and stirred for 1 hour before methyl acrylate (0.30ml, 2.00eqiv., 3.37mmol) was added dropwise. The mixture was stirred overnight, quenched with sat. NH_4Cl, extracted with DCM (4x), dried over sodium sulfate and the solvent evaporated. Purification by column chromatography (LP:EtOAc = 4:1) provided 299.3mg lactone **52** as yellow oil.

Yield: 299.3mg (77%) yellow oil

Rf: 0.13 (LP:EtOAc=4:1)

Molecular Formula: $C_{11}H_{11}F_3O_2$

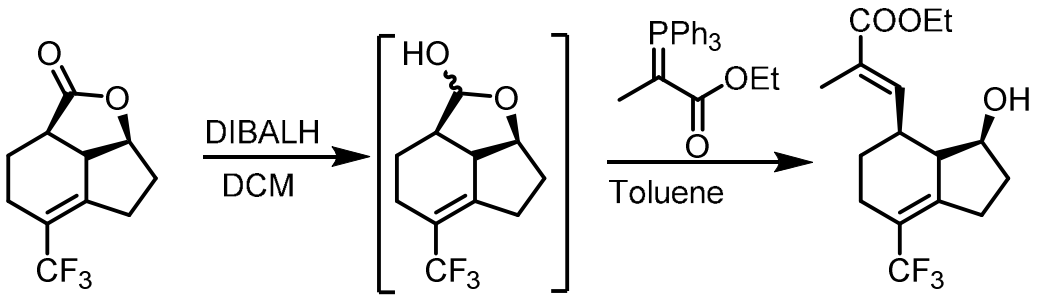
Molecular weight [g/mol]: 192.26

$[\alpha]_D^{20}$: -6.2° (c= 1.04g/100ml DCM)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.76-2.15 (m, 5H,1-CH_2+6-CH_2+4-CH), 2.22-2.31 (m, 1H, 3a-CH), 2.49-2.72 (m, 2H, 2-CH_2), 2.97-2.99 (m, 1H, 1H of 5-CH_2), 3.07-3.18 (m, 1H, 1H of 5-CH_2), 4.86-4.91 (m, 1H, 3-CH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 20.9 (t, 6-CH_2), 21.2 (tq, J=2.0 Hz, 1-CH_2), 27.9 (td, J=1.5 Hz, 5-CH_2), 29.9 (td, J=0.8Hz, 2-CH_2), 38.9 (d, 3a-CH), 45.6 (d, 4-CH), 82.3 (d, 3-CH), 123.7 (sq, J= 273.1Hz, 7'-CF_3), 124.4 (sq, J=31.1 Hz, 7-C), 145.1 (sq, H=4.0 Hz, 7a-C), 178.0 (s, 4'-COO)

I III.4.3 (***E***)-3-((3S,3aR,4S)-7-(trifluoromethyl)-3-Hydroxy-2,3,3a,4,5,6-hexahydro-1*H*-inden-4-yl)-2-methyl-acrylic acid ethyl ester **52**



52 **52a** **53**

Lactone **52** (273.0mg,1.00eqiv., 1.18mmol) was dissolved in 12ml dry DCM and cooled to -78°C before 1M DIBALH solution in heptane (1.76ml, 1.50eqiv., 1.76mmol) was added. After stirring for 1hour 30 minutes at the aforementioned temperature, the solution was quenched with 1ml EtOAc followed by addition of 5ml saturated Rochelles salt solution. The mixture was allowed to reach room temperature and stirred for at least 30 minutes until the phases were clearly separated. Extraction with DCM (4x), drying with Na_2SO_4 and evaporation of the solvent provided crude lactol **52a** as a slightly yellow oil. Lactol **52a** combined with (1-ethoxycarbonylethyliden)-triphenylphosphorane (1.28g ,3.00eqiv., 3.54mmol) was dissolved in 12 ml dry toluene and heated to 100°C under an argon atmosphere for 19h. Toluene was evaporated and purification by column chromatography (LP:EtOAc=10:1 to 5:1) yielded 266.0 mg of (***E***)-3-((3S,3aR,4S)-7-(trifluoromethyl)-3-hydroxy-2,3,3a,4,5,6-hexahydro-1*H*-inden-4-yl)-2-methyl-acrylic acid ethyl ester **53** as colorless oil.

Yield: 266.0mg (71%) colorless oil

Rf: 0.40 (LP:EtOAc=4:1)

Molecular Formula: $C_{16}H_{21}F_3O_3$

Molecular weight [g/mol]: 318.34

HRMS: calculated $(M+1)^+$= 319.1516, found $(M+1)^+$ = 319.1507

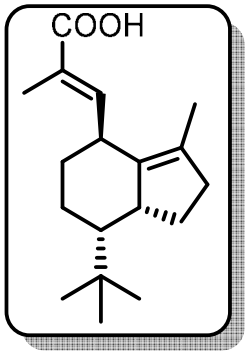
$[\alpha]_D^{20}$: n.d.

^{1}H-NMR (200 MHz, CD_2Cl_2): δ = 1.28 (t, J=7.1 Hz, 3H, 4''-CH_3), 1.43 (bs, 1H, 3a-CH), 1.68-1.86 (m, 4H, 2-CH_2+5-CH_2), 1.95 (d, J=1.4 Hz, 3H,1-CH_2+4CH), 2.20 (bs, 2H, 6-CH_2), 2.61-2.85 (m, 3H, 4'-CH_3), 3.12-3.25 (m, 1H, 3-

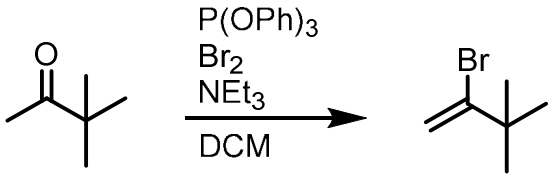
CH), 4.19 (q, J=7.2 Hz, 2H, 4''-OCH_2), 4.36-4.39 (m, 1H, 3-OH), 6.99 (dd, J_1 =10.4 Hz, J_2= 1.4Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, $CDCl_3$): n.d.

I III.5 Towards Synthesis of (E)-3-((4*S*,7*S*,7a*R*)-7-(*tert*-Butyl)-3-methyl-2,4,5,6,7a-hexahydro-1*H*-inden-4-yl)-2-methacrylic acid (7-*tert*-Butylvalerenic acid)



I III.5.1 2-Bromo-3,3-dimethyl-but-1-ene **55**



54 **55**

Triphenylphosphite (41.92ml=49.63g, 2.50eqiv., 159.94mmol) was dissolved in 440ml dry DCM and cooled to -60°C. Subsequently, Br_2 (8.42ml=26.27g, 2.6eqiv., 166.35mmol) followed by anhydrous NEt_3 (24.10ml, 2.70eqiv., 172.75mmol) were added and stirred for 5 minutes, then pinacolone **54** (8.00ml=10.00g, 1.00eqiv., 63.98mmol) was added. The orange solution was left to warm to room temperature overnight and then refluxed for 4h. Liquids were decanted and the remaining dark brown solid was digested with 500ml of pentane. The liquid fractions were combined and concentrated on the rotary evaporator before vacuum distillation (90°C, 30mbar) delivered 2.98g 2-bromo-3,3-dimethylbut-1-ene **55** as colorless liquid.

Yield: 2.98g (29%) colorless liquid

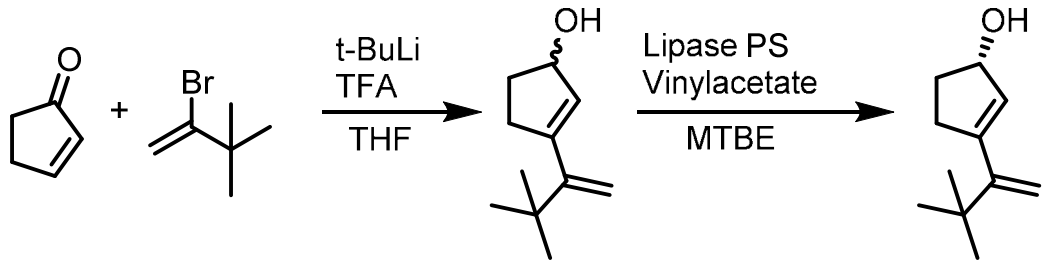
Molecular Formula: $C_6H_{11}Br$

Molecular weight [g/mol]: 163.06

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.20 (s, 9H, t-butylCH_3), 5.38 (d, J=2.1Hz, 1H, 1H of olefinic CH_2), 5.59 (d, J=2.1 Hz, 1H, 1 H of olefinic CH_2)

^{13}C-NMR (50 MHz, $CDCl_3$): n.d.[68]

I III.5.2 (S)-3-(3,3-dimethylbut-1-ene-2-yl)cyclopent-2-en-1-ol **56**



24 **55** **rac-56** **56**

2-Bromo-3,3-dimethylbut-1-ene **55** (2.98g, 1.30eqiv., 18.30mmol) in 180 ml dry THF under argon was cooled to -78°C and 1.7M t-BuLi solution in pentane (21.56ml, 2.60eqiv., 36.67mmol) was added. The orange solution was left to warm to -60°C for 40 minutes, before recooled to -78°C and cyclopent-2-en-1-one, (1.18ml, 1.00eqiv., 14.10mmol) dissolved in 14.1 ml dry THF, was added dropwise. The mixture was stirred for 1.5 h at -78°C and warmed to 0°C before it was quenched with 90ml water. After 5 minutes of stirring TFA (2.92ml, 2.70eqiv., 38.07mmol) was added slowly at 0°C (color changes from orange to colorless when acidic!) and stirred for 40 minutes before it was quenched with saturated $NaHCO_3$ solution. The phases were separated and the aqueous layer was extracted with Et_2O (3x), once washed with saturated $NaHCO_3$ solution, dried over sodium sulfate and concentrated. Purification via column chromatography delivered 1.17 g (50%) of racemic alcohol ***rac*-56** as yellow oil.

The racemic alcohol ***rac*-56** (1.17g, 1.00eqiv., 7.04mmol) was dissolved in 20ml MTBE and Lipase PS (0.23g, 20w/w%) together with vinylacetate (0.35ml, 0.55eqiv., 3.87mmol) were added and stirred for 21h (controlled via chiral HPLC). After filtration through a short pad of celite and evaporation of the solvent, column chromatography (90g NEt_3-doped SiO_2; LP:EtOAc=8:1+1% NEt_3 to 4:1+1% NEt_3) delivered 479.50mg of (S)-3-(3,3-dimethylbut-1-ene-2-yl)cyclopent-2-ene-1-ol **56** as slightly yellow oil with an enantiomeric excess of >99%.

Note: Compound **56** is labile and should be stored in the freezer!

Yield: 479.5mg (21%) yellow oil

Rf: 0.31 (LP:EtOAc=4:1)

Molecular Formula: $C_{11}H_{18}O$

Molecular weight [g/mol]: 166.26

HRMS: calculated $(M-17)^+$= 149.1325 found $(M-17)^+$ = 149.1325

$[\alpha]_D^{20}$: -34.5° (1.88g/100ml DCM)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.16 (s, 9H, 3'-t-butylCH_3), 1.63-1.81 (m, 2H, 5-CH_2), 2.21-2.49 (m, 2H, 4-CH_2), 2.58-2.76 (m, 1H, 1-CH), 4.87-4.90 (m, 2H, 1-CH+1-OH), 5.02 (d, J=1.3 Hz, 1H, 1H of 3'-olefinic CH_2), 5.75-5.77 (m, 1H, 1H of 3'-olefinic CH_2)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 30.0 (q, 3'-t-butyl CH_3), 33.5 (t, 5-CH_2), 35.4 (t, 4-CH_2), 35.7 (s, 3'-C(CH_3)$_3$), 78.1 (d, 1-CH), 111.3 (t,3'-CH_2), 129.9 (d, 2-CH), 147.3 (s, 3-C), 154.7 (s, 3'-C)

Instrument LC3000 Sequence Mas - kinetic resolution

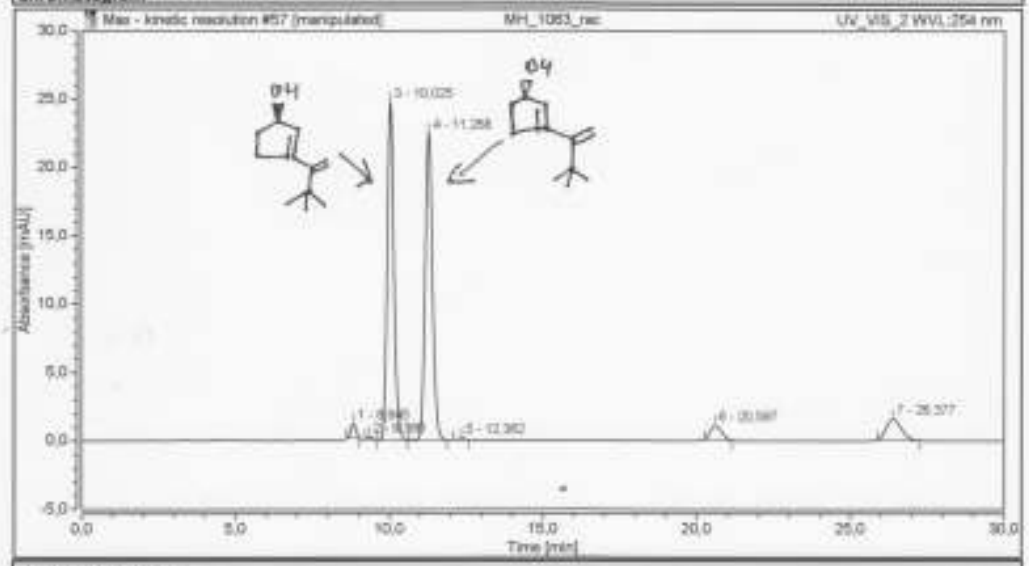
Page 1 of 1

Chromatogram and Results

Injection Details

Injection Name:	MH_1063_rac	Run Time (min):	30,00
Vial Number:	RD2	Injection Volume:	1,00
Injection Type:	Unknown	Channel:	UV_VIS_2
Calibration Level:		Wavelength:	280,0
Instrument Method:	Isocratic 21	Bandwidth:	2
Processing Method:	2D Quant. Std.	Dilution Factor:	1,0000
Injection Date/Time:	17.Okt.13 20:24	Sample Weight:	1,0000

Chromatogram



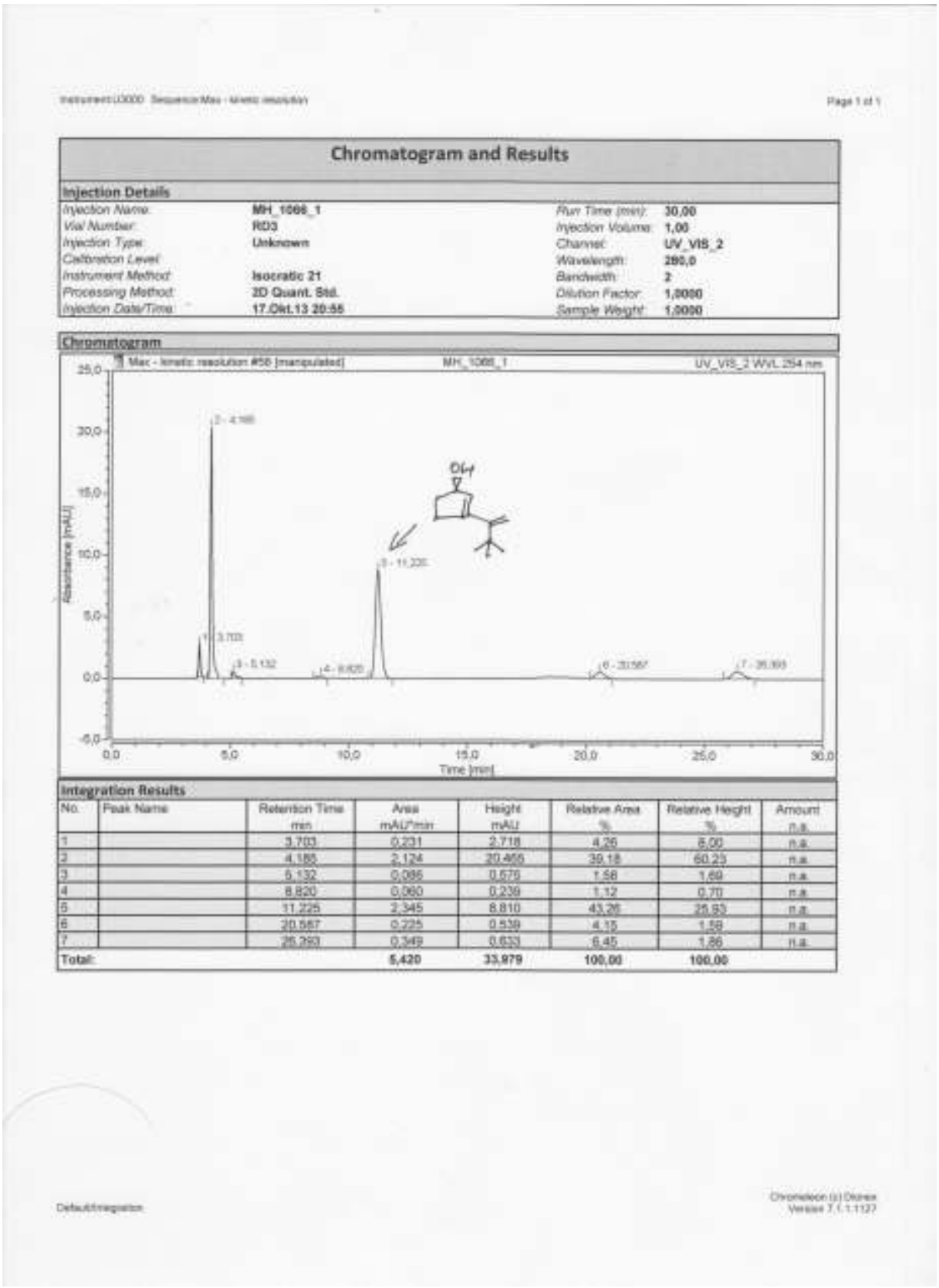
Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		8,845	0,206	1,066	1,47	2,08	n.a.
2		9,360	0,043	0,217	0,30	0,42	n.a.
3		10,025	6,198	24,774	44,26	48,28	n.a.
4		11,258	6,199	22,479	44,26	43,81	n.a.
5		12,362	0,036	0,155	0,26	0,30	n.a.
6		20,597	0,442	1,053	3,16	2,05	n.a.
7		26,377	0,880	1,554	6,28	3,06	n.a.
Total:			14,004	51,308	100,00	100,00	

Default.lrtegration

Chromeleon (c) Dionex
Version 7.1.1.1127

Figure 123 Racemic sample of 3-(3,3-dimethylbut-1-ene-2-yl)cyclopent-2-en-1-ol 56



Chromatogram and Results

Injection Details

Injection Name:	MH_1068_1	*Run Time (min):*	30,00
Vial Number:	RD3	*Injection Volume:*	1,00
Injection Type:	Unknown	*Channel:*	UV_VIS_2
Calibration Level:		*Wavelength:*	280,0
Instrument Method:	Isocratic 21	*Bandwidth:*	2
Processing Method:	2D Quant. Std.	*Dilution Factor:*	1,0000
Injection Date/Time:	17.Okt.13 20:55	*Sample Weight:*	1,0000

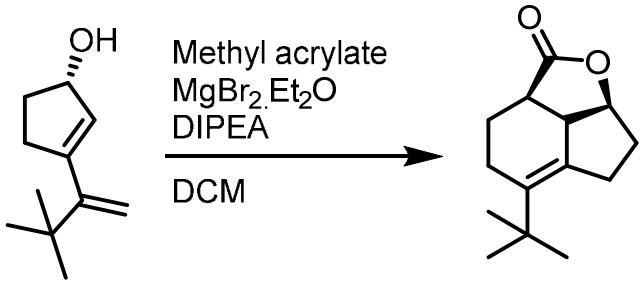
Chromatogram

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		3,703	0,231	2,718	4,26	8,00	n.a.
2		4,166	2,124	20,466	39,18	60,23	n.a.
3		5,132	0,086	0,575	1,58	1,69	n.a.
4		6,820	0,060	0,239	1,12	0,70	n.a.
5		11,225	2,345	8,810	43,26	25,93	n.a.
6		20,567	0,225	0,539	4,15	1,58	n.a.
7		26,293	0,349	0,633	6,45	1,86	n.a.
Total:			**5,420**	**33,979**	**100,00**	**100,00**	

Figure 124 Kinetic resolution of 3-(3,3-dimethylbut-1-ene-2-yl)cyclopent-2-en-1-ol 56

I III.5.3 (2aR,7aS,7bR)-5-(*tert*-butyl)-3,4,6,7,7a,7b-hexahydroindeno[1,7-*bc*]furan-2(2a*H*)-one **57**



56 **57**

Anhydrous $MgBr_2.Et_2O$ (1.25g, 2.00eqiv., 4.85mmol) was suspended in 5.8ml dry DCM under argon at room temperature before anhydrous diisopropylethylamine (1.69ml, 4.00eqiv., 9.68mol) was added and the mixture was stirred until it turned magenta (~15 minutes). Then (S)-3-(3,3-dimethylbut-1-ene-2-yl)cyclopent-2-ene-1-ol **56** (403.00mg, 1.00eqiv., 2.42mmol) dissolved in 24 ml dry DCM was added slowly and stirred for 1 hour before methyl acrylate (0.44ml, 2.00eqiv., 4.85mmol) was added dropwise. The mixture was stirred overnight at room temperature, quenched with sat. NH_4Cl, extracted with DCM (4x), dried and the solvent evaporated. Purification by column chromatography (40g SiO_2;LP:EtOAc = 6:1 to 3:1) provided 404.20mg of lactone **57** as yellow oil.

Yield: 404.20mg (76%) yellow oil

Rf: 0.27 (LP:EtOAc=4:1)

Molecular Formula: $C_{14}H_{20}O_2$

Molecular weight [g/mol]: 220.31

HRMS: calculated $(M+1)^+$= 221.1536, found $(M+1)^+$ = 221.1548

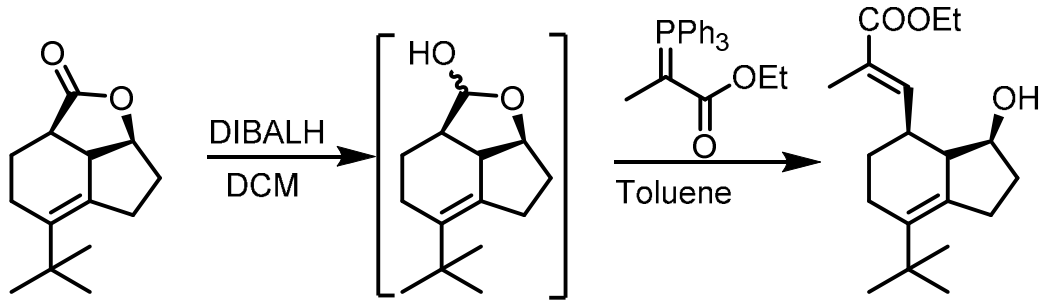
$[\alpha]_D^{20}$: -1.01 (c= 0.84g/100ml DCM)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.09 (s, 9H, 7'-tbutyl-CH_3), 1.40-1.49 (m, 1H, 1H of 2-CH_2), 1.56-1.65 (m, 1H, 1H of 2-CH_2), 1.90-2.00 (m, 1H, 1H of 5-CH_2), 2.07-2.20 (m, 2H,1-CH_2), 2.28-2.33 (m, 1H, 1H of 5-CH_2), 2.30-2.36 (m, 1H, 4-CH), 2.64-2.69 (m, 1H, 3a-CH), 3.07-3.13 (m, 1H, 3-OH), 4.85 (t, J=4.5 Hz, 1H, 3-CH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 23.6 (t, 5-CH_2), 26.4 (t, 6-CH_2), 28.4 (t, 1-CH_2), 29.6 (q, 7'-t-butyl CH_3), 31.1 (t, 2-CH_2), 37.4 (s, 7'-$C(CH_3)_3$), 40.5 (d, 3a-CH),

46.6 (d, 4-CH), 83.1 (d, 3-CH), 130.3 (s, 7a-C), 144.0 (s, 7-C), 180.2 (s, 4’-COO)

I III.5.4 (***E***)-3-((3S,3aR,4S)-7-(*tert*-butyl)-3-Hydroxy-2,3,3a,4,5,6-hexahydro-1*H*-inden-4-yl)-2-methyl-acrylic acid ethyl ester **58**



57 **57a** **58**

Lactone **57** (300.00mg,1.00eqiv., 1.36mmol) was dissolved in 13.6 ml dry DCM and cooled to -78°C before 1M DIBALH solution in heptane (2.04ml, 1.50eqiv., 2.04mmol) was added. After stirring for 1 hour 30 minutes at the aforementioned temperature, the solution was quenched with 1ml EtOAc followed by addition of 5ml saturated Rochelles salt solution. The mixture was allowed to reach room temperature and stirred for at least 30 minutes until the phases were clearly separated. Extraction with DCM (4x), drying with Na_2SO_4 and evaporation of the solvent provided crude lactol **57a** as a slightly yellow oil. Lactol **57a** combined with (1-ethoxycarbonylethyliden)-triphenylphosphorane (1.48g,3.00eqiv., 4.08mmol) were dissolved in 13.6 ml dry toluene and heated to 100°C under an argon atmosphere for 19h. Toluene was evaporated and purification by column chromatography (40g SiO_2;LP:EtOAc=10:1 to 5:1) yielded 257.3 mg of (***E***)-3-((3S,3aR,4S)-7-(*tert*-butyl)-3-Hydroxy-2,3,3a,4,5,6-hexahydro-1*H*-inden-4-yl)-2-methyl-acrylic acid ethyl ester **58** as colorless oil.

Yield: 257.3g (62%) colorless oil

Rf: 0.28 (LP:EtOAc=4:1)

Molecular Formula: $C_{19}H_{30}O_3$

Molecular weight [g/mol]: 306.45

HRMS: calculated $(M+1)^+$= 307.2268 found $(M+1)^+$ = 307.2264

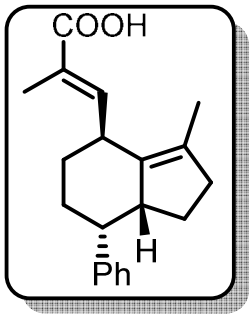
$[\alpha]_D^{20}$: +21.2° (c=0.50g/100ml DCM)

^{1}H-NMR (200 MHz, CD_2Cl_2): δ = 1.07 (s, 9H, 7'-t-butyl CH_3), 1.13-1.20 (m, 4H, 4''-CH_3+3a-CH), 1.47-1.67 (m, 4H, 1-CH_2+2-CH_2), 1.81 (d, J=1.4Hz, 3H, 4'-CH_3), 1.97-2.05 (m, 2H, 6-CH_2), 2.35-2.65 (m, 3H, 4-CH+5-CH_2),

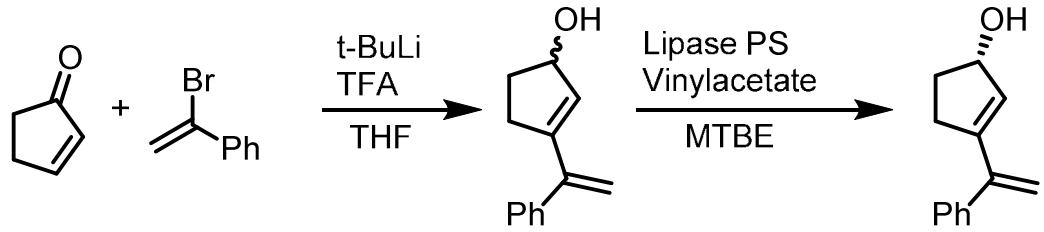
2.85-2.98 (m, 1H, 3-CH), 3.93-4.13 (m, 3H, 4''-OCH_2+ 3-OH), 6.95 (dd, J_1 =10.2 Hz, J_2=1.4Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, CD_2Cl_2): δ = 12.6 (q, 4'-CH_3), 14.4 (q, 4''-CH_3), 25.0 (t, 6-CH_2), 28.6 (t, 1-CH_2), 29.9 (q, 7'-t-butyl-CH_3), 30.0 (t, 5-CH_3), 33.7 (t, 2-CH_3), 34.3 (d, 4-CH), 36.8 (s, 7'-$C(CH_3)_3$), 51.9 (d, 3a-CH_3), 60.7 (t, 4''-oCH_2), 74.3 (d, 3-CH), 127.3 (s, 4'-C), 131.4 (s, 7a-C), 137.5 (s, 7-C), 144.2 (d, 4'-CH), 168.3 (s, 4'-COOEt)

I III.6 Towards the synthesis of (*E*)-3-((4*S*,7*S*,7a*R*)-3-methyl-7-phenyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methylacrylic acid (7-Phenyl-Valerenic acid)



I III.6.1 (S)-3-(1-Phenylvinyl)cyclopent-2-en-1-ol **59**



24 **rac-59** **59**

α-Bromostyrene 90% (2.10ml=2.96g, 1.20eqiv., 14.30mmol) in 120 ml dry THF under argon was cooled to -78°C and 1.7M t-BuLi solution (16.80ml, 2.40eqiv., 28.60mmol) was added. The brown solution was left to warm to -60°C for 40 minutes. Then the solution was recooled to -78°C and cyclopent-2-en-1-one (1.00ml=0.98g, 1.00eqiv., 11.90mmol) dissolved in 12ml dry THF was added dropwise while the color changed to slight brown. The mixture was stirred for 30 minutes at -78°C and warmed to 0°C before it was quenched with 30ml water. After 5 minutes of stirring TFA (2.30ml=3.43g, 2.50eqiv., 29.80mmol) was added slowly at 0°C and stirred for 1h 30 minutes before it was quenched with saturated $NaHCO_3$ solution. The phases were separated and the aqueous layer was extracted with Et_2O (3x), once washed with saturated $NaHCO_3$ solution, dried and concentrated. Purification via column chromatography (90g NEt_3 doped SiO_2;LP:EtOAc=8:1 +1% NEt_3 to 4:1+1% NEt_3) delivered 1.61g (73%) of racemic alcohol.

The racemic alcohol (1.61g, 1.00eqiv., 8.64mmol) was dissolved in 50ml MTBE and Lipase PS (0.32g, 20w/w%) together with vinylacetate (0.44ml, 0.55eqiv., 4.75mmol) were added and

stirred for 17h. After filtration through a short pad of celite and evaporation of the solvent, column chromatography (90g NEt_3-doped SiO_2;LP:EtOAc=8:1+1% NEt_3 to 4:1+1% NEt_3) delivered 721.0mg (S)-3-(1-phenylvinyl)cyclopent-2-en-1-ol **59** as colourless oil with an enantiomeric excess of >99%.

Note: Compound **59** is labile and should be stored in the freezer!

Yield: 721.0mg (33%)

Rf: 0.25 (LP:EtOAc=4:1)

Molecular Formula: $C_{13}H_{14}O$

Molecular weight [g/mol]: 186.25

HRMS: calculated $(M+1)^+$= 187.1117, found $(M+1)^+$ = 187.1108

$[\alpha]_D^{20}$: -22.55° (0.47g/100ml DCM)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.73-1.91 (m, 2H, 5-CH_2), 2.31-2.57 (m, 2H, 4-CH_2), 2.69-2.86 (m, 1H, 1-CH), 4.88-4.90 (m, 1H, 1-OH), 5.19-5.20 (m, 1H, 2-CH), 5.28 (bs, 1H, 1H of 3'-olefinic CH), 5.62-5.63 (m, 1H, 1H of 3'-olefinic CH), 7.23-7.35 (m, 5H, 3'-ArH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 31.1 (t, 5-CH_2), 33.8 (t, 4-CH_2), 77.7 (d, 1-CH), 116.2 (t, 3'-CH_2), 127.4 (d, 2-CH), 128.0 (d, 3'-ArCH), 128.4 (d, 3'-ArCH), 132.4 (d, 3'-ArCH), 141.4 (s, 3'-Ar-C), 146.1 (s, 3-C), 146.4 (s, 3'-C)

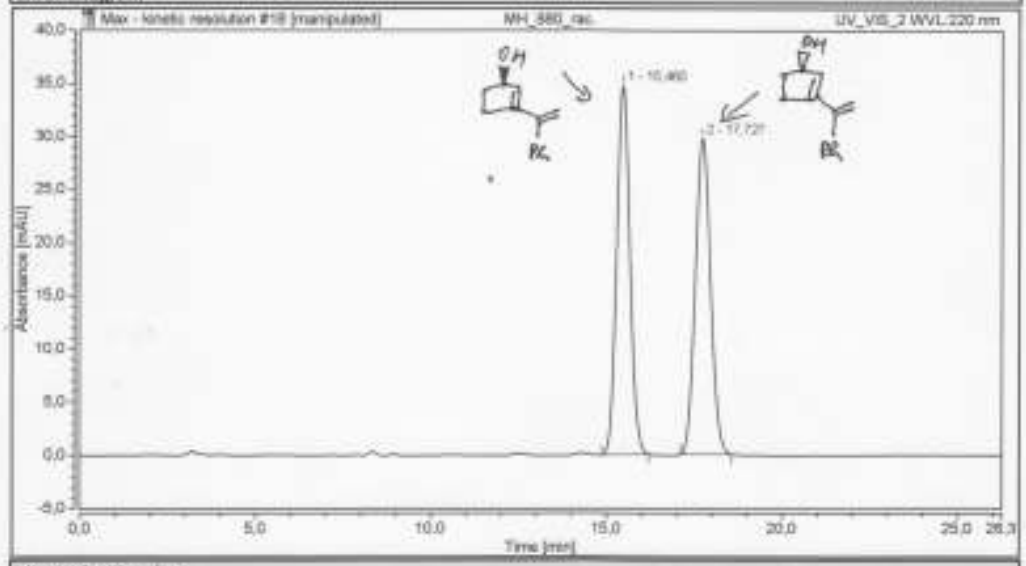
Instrument:LC3000 Sequence:Max - kinetic resolution

Chromatogram and Results

Injection Details

Injection Name:	MH_880_rac.	*Run Time (min):*	26,25
Vial Number:	RC4	*Injection Volume:*	0,50
Injection Type:	Unknown	*Channel:*	UV_VIS_2
Calibration Level:		*Wavelength:*	280,0
Instrument Method:	Isocratic 16	*Bandwidth:*	2
Processing Method:	3D Quant. Std.	*Dilution Factor:*	1,0000
Injection Date/Time:	01.Feb.13 12:19	*Sample Weight:*	1,0000

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		15,490	15,130	34,791	50,09	53,86	n.a.
2		17,727	15,073	29,804	49,91	46,14	n.a.
Total:			**30,203**	**64,596**	**100,00**	**100,00**	

DefaultIntegration

Chromeleon (c) Dionex Version 7.1.1.1127

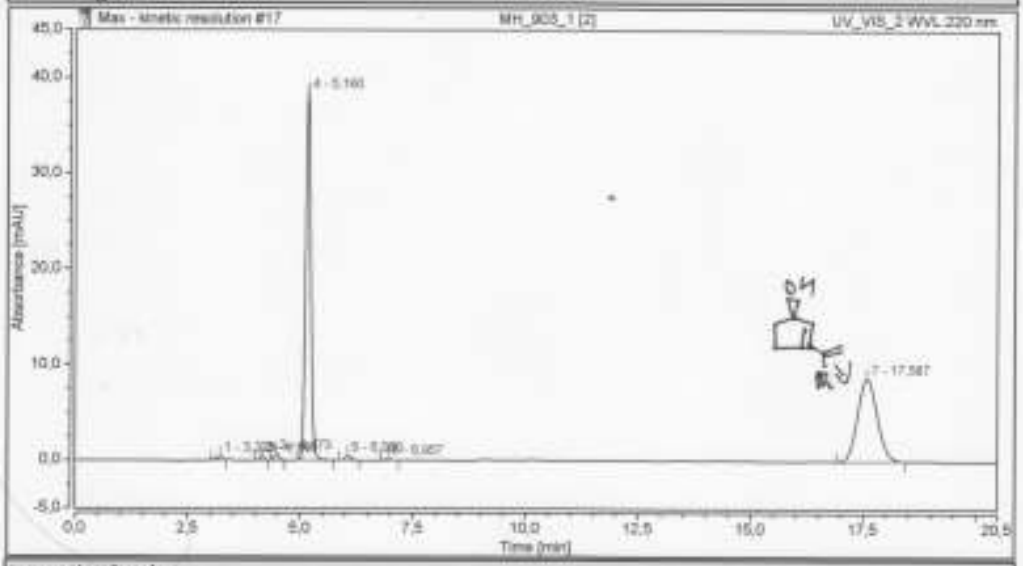
Figure 125 Racemic sample of 3-(1-Phenylvinyl)cyclopent-2-en-1-ol 59

Chromatogram and Results

Injection Details

Injection Name	MH_903_1 [2]	*Run Time (min)*	20,47
Vial Number	RC3	*Injection Volume*	0,50
Injection Type	Unknown	*Channel*	UV_VIS_2
Calibration Level		*Wavelength*	280,0
Instrument Method	Isocratic 15	*Bandwidth*	2
Processing Method	2D Quant. Std.	*Dilution Factor*	1,0000
Injection Date/Time	01.Feb.13 11:57	*Sample Weight*	1,0000

Chromatogram

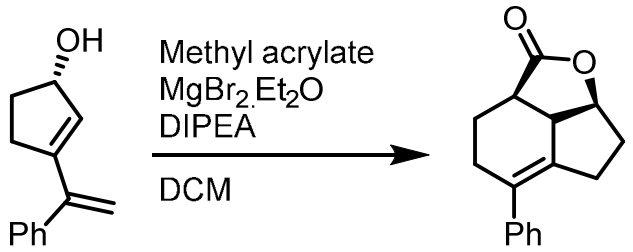


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		3,228	0,056	0,412	0,57	0,84	n.a.
2		4,148	0,049	0,448	0,49	0,91	n.a.
3		4,473	0,081	0,667	0,82	1,35	n.a.
4		5,160	5,177	38,450	52,66	78,02	n.a.
5		6,060	0,073	0,456	0,74	0,92	n.a.
6		6,957	0,029	0,158	0,29	0,32	n.a.
7		17,587	4,367	8,691	44,42	17,64	n.a.
Total:			**9,831**	**49,282**	**100,00**	**100,00**	

Figure 126 Kinetic resolution of 3-(1-Phenylvinyl)cyclopent-2-en-1-ol 59

I III.6.2 (2aR,7aS,7bR)-5-phenyl-3,4,6,7,7a,7b-hexahydroindeno[1,7-*bc*]furan-2(2a*H*)-one **60**



59 **60**

Anhydrous $MgBr_2.Et_2O$ (1.55g, 2.00eqiv., 6.00mmol) was suspended in 7.1ml dry DCM under argon at room temperature before anhydrous diisopropylethylamine (2.22ml, 4.00eqiv., 12.00mol) was added and the mixture was stirred until it turned magenta (~15 minutes). Then (S)-3-(1-phenylvinyl)cyclopent-2-en-1-ol (0.55g, 1.00eqiv., 3.00mmol) dissolved in 30 ml dry DCM was added slowly and stirred for 1 hour before methyl acrylate (0.55ml, 2.00eqiv., 6.00mmol) was added dropwise. The mixture was stirred overnight at room temperature, quenched with sat. NH_4Cl, extracted with DCM (4x), dried and the solvent evaporated. Purification by column chromatography (90g SiO_2;LP:EtOAc = 6:1) provided 631.2g lactone **57** as a colorless solid.

Yield: 631.2mg (88%)

Rf: 0.10 (LP:EtOAc=6:1)

Melting Point: 109°C

Molecular Formula: $C_{16}H_{16}O_2$

Molecular weight [g/mol]: 240.30

HRMS: calculated $(M+1)^+$= 241.1223, found $(M+1)^+$ = 241.1225

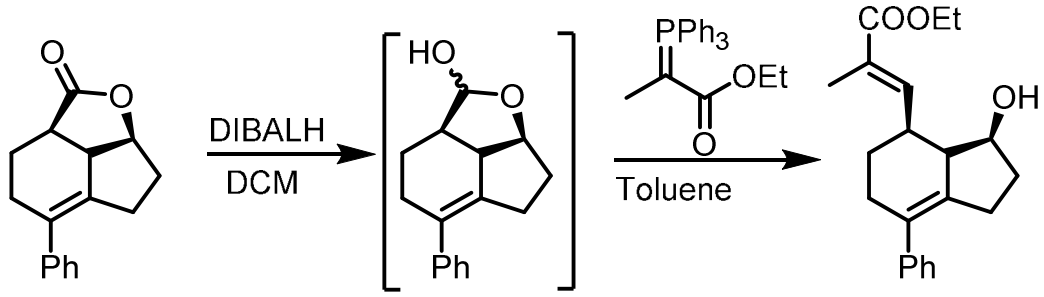
$[\alpha]_D^{20}$: -59.77° (c= 0.98g/100ml DCM)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.80-1.96 (m, 1H, 1H of 2-CH_2), 2.00-2.28 (m, 4H,1-CH_2+6-CH_2), 2.46-2.74 (m, 3H, 1H of 2-CH_2+5-CH_2), 3.12-3.20 (m, 2H, 3-OH+ 3a-CH), 4.92 (t, J=6.0Hz, 1H, 3-CH), 7.17-7.36 (m, 5H, 3'-ArH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 20.6 (t, 5-CH_2), 26.4 (t, 1-CH_2), 29.4 (t, 6-CH_2), 29.5 (t, 2-CH_2), 39.4 (d, 3a-CH), 44.4 (d, 4a-CH), 82.7 (d, 3-CH), 126.9 (d,

7'-ArCH), 127.6 (d, 7'-ArCH), 128.0 (d, 7'-ArCH), 133.9 (s, 7-CH), 134.2 (s, 7a-CH), 141.6 (s, 7'-ArC), 178.3 (s, 4'-COO)

I III.6.3 (***E***)-3-((3S,3aR,4S)-7-phenyl-3-Hydroxy-2,3,3a,4,5,6-hexahydro-1*H*-inden-4-yl)-2-methyl-acrylic acid ethyl ester **61**



60 **60a** **61**

Lactone **61** (500.0mg,1.00eqiv., 2.08mmol) was dissolved in 21ml dry DCM and cooled to -78°C before 1M DIBALH solution in heptane (3.12ml, 1.50eqiv., 3.12mmol) was added. After stirring for 1hour 20 minutes at the aforementioned temperature, the solution was quenched with 1ml EtOAc followed by addition of 5ml saturated Rochelles salt solution. The mixture was allowed to reach room temperature and stirred for at least 30 minutes until the phases were clearly separated. Extraction with DCM (4x), drying with Na_2SO_4 and evaporation of the solvent provided crude lactol **60a** as a slightly yellow oil. Lactol **60a** combined with (1-ethoxycarbonylethyliden)-triphenylphosphorane (2.26g ,3.00eqiv., 6.24mmol) were dissolved in 21 ml dry toluene and heated to 100°C under an argon atmosphere for 17h. Toluene was evaporated and purification by column chromatography (40g SiO_2; LP:EtOAc=10:1 to 5:1) yielded 498.3 mg of hydroxy ester **61** colorless oil.

Yield: 498.3mg (73%) colorless oil

Rf: 0.25 (LP:EtOAc=4:1)

Molecular Formula: $C_{21}H_{26}O_3$

Molecular weight [g/mol]: 326.44

HRMS: calculated $(M+1)^+$= 327.1995, found $(M+1)^+$ = 327.1956

$[\alpha]_D^{20}$: +41.22° (c=0.47g/100ml DCM)

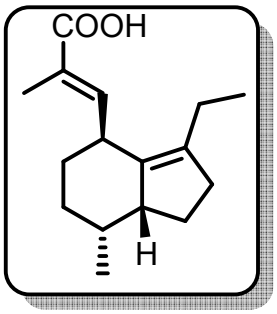
^{1}H-NMR (400 MHz,$CDCl_3$): δ = 1.28 (t, J=7.1 Hz, 3H, 4''-CH_3), 1.48-1.66 (m, 2H, 2-CH_2), 1.75-1.83 (m, 2H, 5-CH_2), 1.88-1.96 (m, 4H, 4'-CH_3+3a-CH), 2.25-2.52 (m, 4H, 1-CH_2+6-CH_2), 2.64-2.68 (m, 1H, 4-CH), 3.13-3.20 (m, 1H, 3-CH), 4.12-4.22 (m, 2H, 4''-OCH_2), 4.33 (bs, 1H, OH), 7.18-7.38 (m, 6H)

^{13}C-NMR (50 MHz,$CDCl_3$): δ = 12.6 (q, 4'-CH_3), 14.3 (q, 4''-CH_3), 27.1 (t, 1-CH_2), 27.7(t, 6-CH_2), 29.2 (t, 5-CH_2), 33.3 (t, 2-CH_2),34.0 (d, 4-CH), 50.0 (d, 3a-CH), 60.6 (t, 4''-OCH_2), 74.3 (d, 3-CH), 126.3 (d, 7'-ArCH), 127.6 (s, 7-C), 127.7 (d, 7'-ArCH), 128.1 (d, 7'-ArCH), 131.0 (s, 4'-C), 136.2 (s, 7a-C), 142.7 (s, 7'-ArC), 143.5 (d, 4'-CH), 168.2 (s, 4'-COOEt)

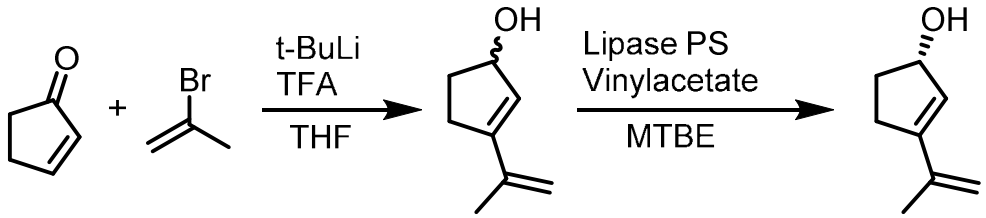
I IV Synthesis of methyl group derivatives on the cyclopentyl ring

All derivatives of the methyl group in 3-position of the indanyl core have been synthesized starting from ketone **66**. The synthesis towards this intermediate building block will be described once in chapter I IV.1 and was conducted as published prior.[2] As the ^{1}H-NMR data matched the according literature[2], ^{13}C-NMR and optical rotation values- except for **62**- are omitted.

I IV.1 Synthesis of (*E*)-3-((4*S*,7*S*,7a*R*)-3-ethyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methylacrylic acid (3-Ethyl-Valerenic acid)



I IV.1.1 (S)-3-(Prop-1-en-2-yl)cyclopent-2-en-1-ol **62**



24 **rac-62** **62**

2-Bromo-1-propene (3.90ml=5.11g, 1.30eqiv., 30.94mmol) in 240 ml dry THF under argon was cooled to -78°C and 1.7M t-BuLi solution (36.40ml, 2.60eqiv., 61.90mmol) was added. The yellow solution was allowed to warm to -60°C within 30 minutes until the yellow color vanished. The colorless solution was again cooled to -78°C and cyclopent-2-en-1-one **24** (2.00ml=1.96, 1.00eqiv., 23.80mmol) dissolved in 24ml dry THF was added dropwise while the color changed to slight orange. The mixture was stirred for 1.5 h at -78°C and warmed to 0°C before it was quenched with 130ml water. After 5 minutes of stirring, TFA

(4.94ml=7.36g, 2.70eqiv., 64.30mmol) was added slowly at 0°C (color changes from yellow to colorless when acidic!) and stirred for 1h 20 minutes before it was quenched with saturated $NaHCO_3$ solution. The phases were separated and the aqueous layer was extracted with Et_2O (3x), once washed with saturated $NaHCO_3$ solution, dried and concentrated to deliver 2.91g of racemic alcohol ***rac*-62** .

The crude racemic alcohol ***rac*-62** (2.91g, 1.00eqiv., 23.60mmol) was dissolved in 72ml MTBE and Lipase PS (0.59g, 20w/w%) together with vinylacetate (1.22ml, 0.55eqiv., 13.09mmol) were added and stirred for 20h. After filtration through a short pad of celite and evaporation of the solvent, column chromatography (90g NEt_3-doped SiO_2;LP:EtOAc=8:1+1% NEt_3 to 4:1+1% NEt_3) delivered 1.35g (S)-3-(prop-1-en-2-yl)cyclopent-2-en-1-ol **62** as colourless oil with an enantiomeric excess of >99%.

Note: Compound **62** is labile and should be stored in the freezer!!

Yield: 1.35g (46%)

Rf: 0.36 (LP:EtOAc=3:1)

Molecular Formula: $C_8H_{12}O$

Molecular weight [g/mol]: 124.18

$[\alpha]_D^{20}$: -111.7° (0.27g/100ml DCM)

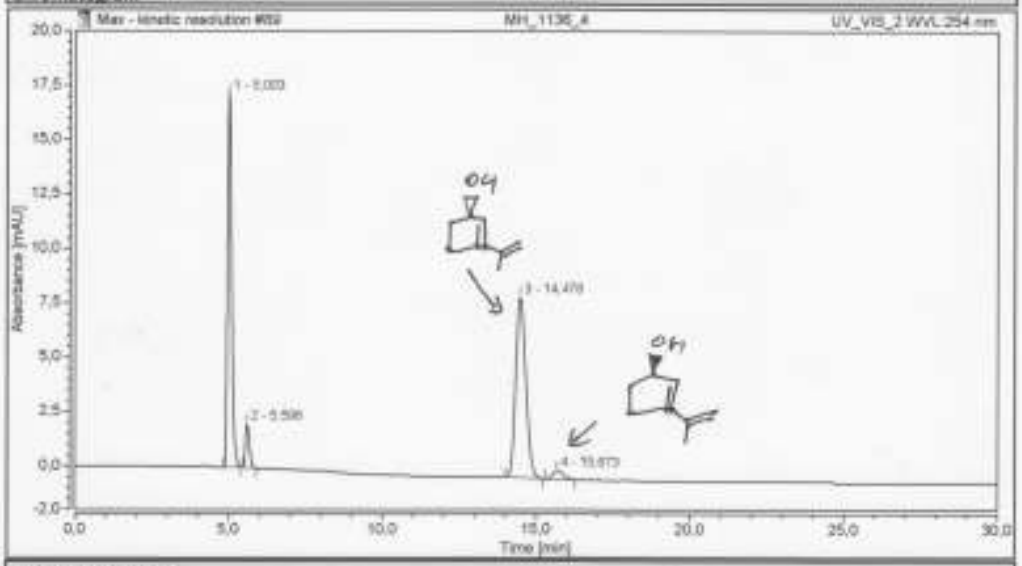
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.46 (d, J=7.2Hz, 1H, 1H of 5-CH_2), 1.69-1.86 (m, 1H, 1H of 5-CH_2), 1.94 (s, 3H, 3'-CH_3), 2.27-2.48 (m, 2H, 4-CH_2), 2.60-2.75 (m, 1H, 1-CH), 4.92-4.95 (m, 2H, 3'-CH_2), 5.02 (bs, 1H, 1-OH), 5.80 (d, J=1.7Hz, 1H, 2-CH)

Chromatogram and Results

Injection Details

Injection Name:	MH_1136_4	*Run Time (min):*	30,00
Vial Number:	RE3	*Injection Volume:*	0,50
Injection Type:	Unknown	*Channel:*	UV_VIS_2
Calibration Level:		*Wavelength:*	280,0
Instrument Method:	Isocratic 21	*Bandwidth:*	2
Processing Method:	2D Quant. Std.	*Dilution Factor:*	1,0000
Injection Date/Time:	01.Apr.14 14:31	*Sample Weight:*	1,0000

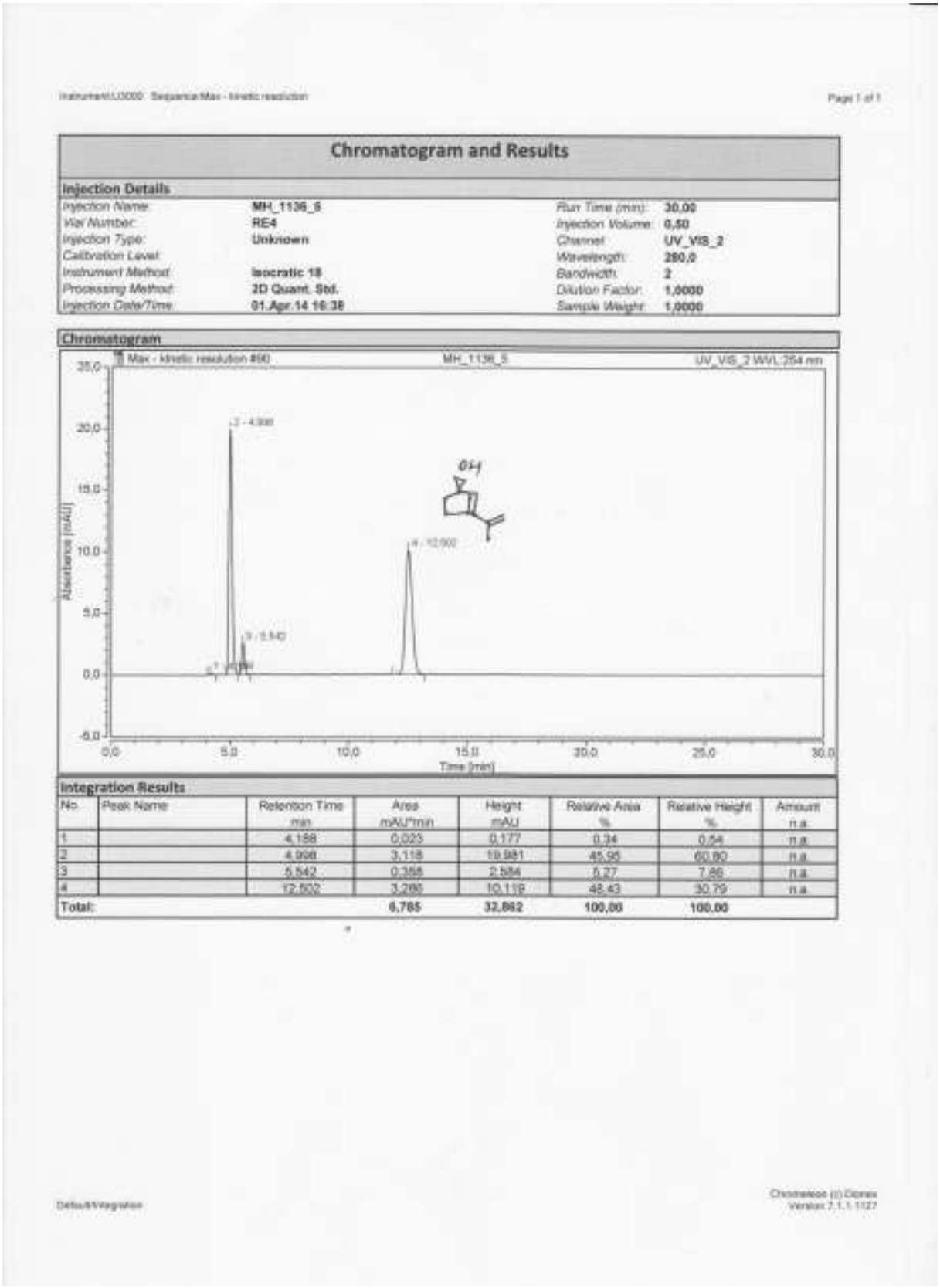
Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		5,003	2,712	17,174	42,81	61,56	n.a.
2		5,506	0,312	2,022	4,92	7,25	n.a.
3		14,478	3,155	8,310	49,80	29,78	n.a.
4		15,673	0,157	0,399	2,48	1,43	n.a.
Total:			**6,335**	**27,904**	**100,00**	**100,00**	

Figure 127 Kinetic resolution of 3-(prop-1-en-2-yl)cyclopent-2-en-1-ol 62 not finished



Chromatogram and Results

Injection Details

Injection Name:	MH_1136_5	*Run Time (min):*	30,00
Vial Number:	RE4	*Injection Volume:*	0,50
Injection Type:	Unknown	*Channel:*	UV_VIS_2
Calibration Level:		*Wavelength:*	280,0
Instrument Method:	Isocratic 18	*Bandwidth:*	2
Processing Method:	2D Quant. Std.	*Dilution Factor:*	1,0000
Injection Date/Time:	01.Apr.14 16:38	*Sample Weight:*	1,0000

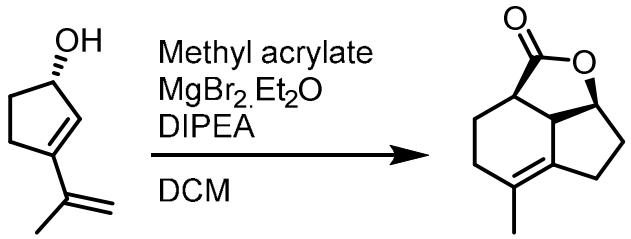
Chromatogram

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		4,188	0,023	0,177	0,34	0,54	n.a.
2		4,998	3,118	19,981	45,95	60,80	n.a.
3		5,542	0,358	2,584	5,27	7,86	n.a.
4		12,502	3,286	10,119	48,43	30,79	n.a.
Total:			**6,785**	**32,862**	**100,00**	**100,00**	

Figure 128 Kinetic resolution of 3-(prop-1-en-2-yl)cyclopent-2-en-1-ol 62

I IV.1.2 (2aR,7aS,7bR)-5-methyl-3,4,6,7,7a,7b-hexahydroindeno[1,7-*bc*]furan-2(2a*H*)-one **63**



62 **63**

Anhydrous $MgBr_2.Et_2O$ (5.16g, 2.00eqiv., 20.00mmol) was suspended in 24ml dry DCM under argon at room temperature before anhydrous diisopropylethylamine (6.97ml, 4.00eqiv., 40.00mol) was added and the mixture was stirred until it turned magenta (~15 minutes). Then (S)-3-(prop-1-en-2-yl)cyclopent-2-en-1-ol **62** (1.24g, 1.00eqiv., 10.00mmol) dissolved in 100 ml dry DCM was added slowly and stirred for 1 hour before methyl acrylate (1.81ml, 2.00eqiv., 20.00mmol) was added dropwise. The mixture was stirred overnight at room temperature, quenched with sat. NH_4Cl, extracted with DCM (4x), dried and the solvent evaporated. Purification by column chromatography (90g SiO_2; LP:EtOAc = 6:1) provided 1.53g lactone **63** as a colorless solid.

Yield: 1.53g (86%)

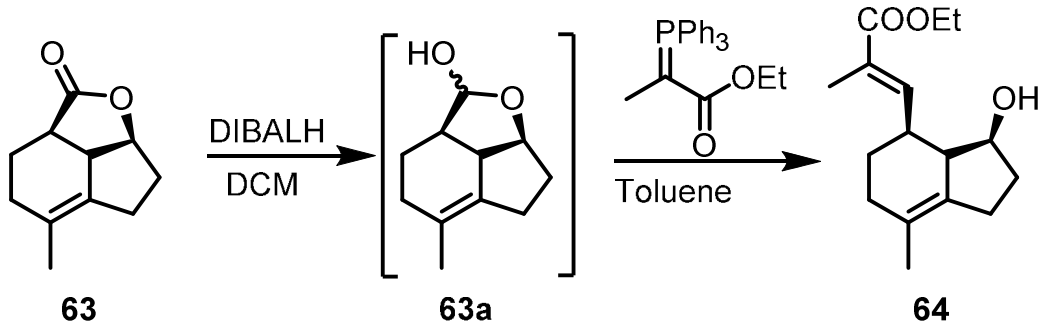
Rf-Value: 0.39 (LP:EtOAc= 3:1)

Molecular Formula: $C_{11}H_{14}O_2$

Molecular weight [g/mol]: 178.23

^{1}H-NMR (200 MHz, $CDCl_3$): δ =1.64 (s, 3H, 7'-CH_3), 1.85-2.29 (m, 7H), 2.51-2.65 (m, 1H), 2.84 (bs, 1H, 4-CH), 2.98-3.06 (m, 1H, 3a-CH), 4.84 (t, J=5.2 Hz, 1H, 3-CH)

I IV.1.3 (***E***)-3-((3S,3aR,4S)-7-methyl-3-Hydroxy-2,3,3a,4,5,6-hexahydro-1*H*-inden-4-yl)-2-methyl-acrylic acid ethyl ester **64**



63 **63a** **64**

Lactone **63** (700.0mg,1.00eqiv., 3.90mmol) was dissolved in 39ml dry DCM and cooled to -78°C before 1M DIBALH solution in heptane (5.89ml, 1.50eqiv., 5.89mmol) was added. After stirring for 1hour 30 minutes at the aforementioned temperature, the solution was quenched with 1ml EtOAc followed by addition of 5ml saturated Rochelles salt solution. The mixture was allowed to reach room temperature and stirred for at least 30 minutes until the phases were clearly separated. Extraction with DCM (4x), drying with Na_2SO_4 and evaporation of the solvent provided crude lactol **63a** as a slightly yellow oil. Lactol **63a** combined with (1-ethoxycarbonylethyliden)-triphenylphosphorane (4.24g ,3.00eqiv., 11.70mmol) was dissolved in 39 ml dry toluene and heated to 100°C under an argon atmosphere for 19h. Toluene was evaporated and purification by column chromatography (90g SiO_2;LP:EtOAc=10:1 to 5:1) yielded 865.6 mg of hydroxy ester **64** as colorless oil.

Yield: 865.6mg (84%)

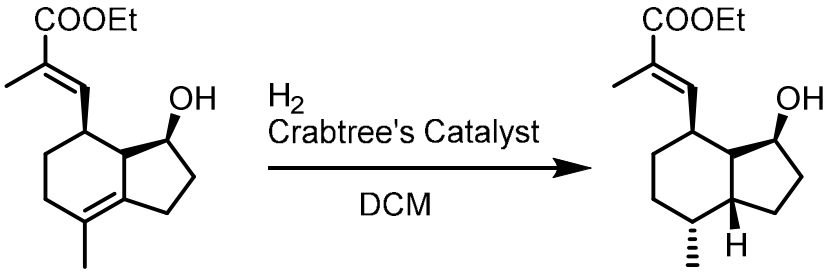
Rf: 0.20 (LP:EtOAc=4:1)

Molecular Formula: $C_{16}H_{24}O_3$

Molecular weight [g/mol]: 264.37

^{1}H-NMR (200 MHz, CD_2Cl_2): δ = 1.27 (t, J = 7.1Hz, 3H, 4''-CH_3), 1.36 (d, J=3.4 Hz, 1H), 1.59-1.94 (m, 12H), 2.22-2.53 (m, 3H, 4-CH+6-CH_2), 3.06-3.18 (m, 1H, 3-CH), 4.17 (q, J= 7.0Hz, 2H, 4''-OCH_2), 4.26-4.29 (m, 1H, 3-OH), 7.06 (dd, J_1 = 10.5Hz, J= 1.3 Hz, 1H, 4'-CH)

I IV.1.4 (***E***)-3-((3S,3aR,4S,7R,7aR)-7-methyl-3-Hydroxyoctahydro-inden-4-yl)-2-methyl-acrylic acid ethyl ester **65**



64 **65**

Hydroxy ester **64** (501.4mg, 1.00eqiv., 1.90mmol) was dissolved in 76ml dry DCM and degassed by means of freeze-thaw degassing method (3 times). The freshly degassed solution was backfilled with H_2 and cooled to 0°C and H_2 was bubbled through the solution for one minute before Crabtree's catalyst (137.4mg, 0.10eqiv., 0.19mmol) was added. Immediately H_2 was bubbled through the deep orange solution turning it into faint yellow transparent. The cooling bath was removed and the mixture was stirred for 1hour 10 minutes (GC-MS control) and the H_2 atmosphere was substituted by argon which was bubbled through the solution for 5 minutes. The deep yellow mixture was concentrated in vacuo and purification via column chromatography (20g SiO_2;LP:EtOAc= 7:1) provided 375.3mg of **65** as white solid.

Yield: 375.3mg (74%)

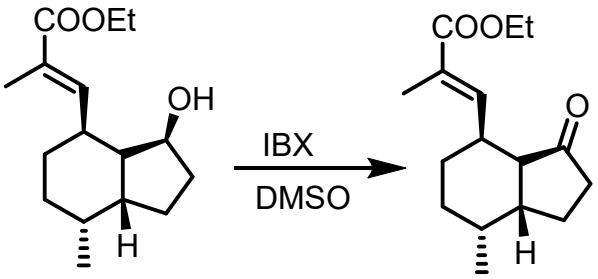
Rf: 0.20 (LP:EtOAc=4:1)

Molecular Formula: $C_{16}H_{26}O_3$

Molecular weight [g/mol]: 266.38

^{1}H-NMR (400 MHz, CD_2Cl_2): δ = 0.90 (d, J=7.1Hz, 3H, 7'-CH_3), 1.25-1.41 (m, 7H), 1.52-1.92 (m, 9H), 2.21 (bs, 1H, 4-CH), 2.31-2.49 (m, 1H3-CH), 4.13-4.25 (m, 3H, 3-OH+4''-OCH_2), 7.38 (dd, J_1 = 10.7Hz, J_2 = 1.4Hz, 1H, 4'-CH)

I IV.1.5 (***E***)-2-Methyl-3-((3aR,4S,7R,7aR)-7-methyl-3-oxo-octahydro-inden-4-yl)-acrylic acid ethyl ester **66**



65 **66**

To compound **65** (375.30mg, 1.00eqiv., 1.41mmol) dissolved in 5.7ml DMSO, IBX (789.07mg, 2eqiv., 2.82mmol) in 11.4ml was added and the mixture was stirred for 2 hours before it was quenched through the addition of water. The colorless precipitate was removed by filtration through a short pad of celite. The residual solid was redissolved in DMSO, water and EtOAc were added and filtrated again. Finally the product was extracted with Et_2O (4x), washed with $NaHCO_3$ and brine (3x), dried and concentrated before purification via column chromatography (40g SiO_2;LP:EtOAc= 7:1) provided 316.3mg of ketone **66** as slightly yellow oil.

Yield: 316.3mg (85%) yellow oil

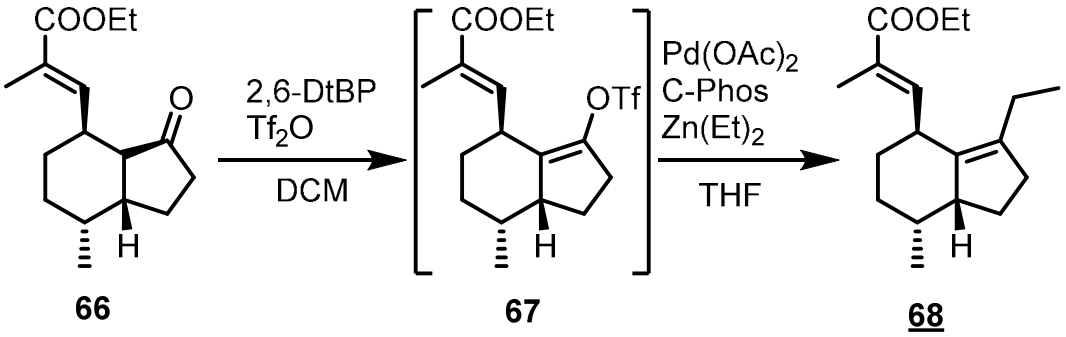
Rf: 0.38 (LP:EtOAc=4:1)

Molecular Formula: $C_{16}H_{24}O_3$

Molecular weight [g/mol]: 264.37

^{1}H-NMR (200 MHz, CD_2Cl_2): δ = 0.97 (d, J=6.9HZ, 3H, 7'-CH_3), 1.27 (t, J=7.1Hz, 3H, 4''-CH_3), 1.38-2.34 (m, 14H), 3.17-3.22 (m, 1H, 3a-CH), 4.16 (q, J= 7.1Hz, 2H, 4''-OCH_2), 6.82 (dd, J_1 = 10.1Hz, J_2 = 1.4Hz, 1H, 4'-CH)

I IV.1.6 Ethyl (*E*)-3-((4*S*,7*S*,7a*R*)-3-ethyl-7-methyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methylacrylic acid (3-Ethyl-Valerenic acid ethyl ester) **68**



66 **67** **68**

Ketone **66** (60.00mg, 1.00eqiv., 0.23mmol) was dissolved in 4.6ml dry DCM under dry argon and cooled to 0°C. Subsequently 2,6-di-*tert*-butylpyridine 97% (105.00µl, 2.00eqiv., 0.45mmol) and freshly distilled triflic anhydride (76.40µl, 2.00eqiv., 0.45mmol) were added under vigorous stirring. The mixture was stirred for 5 minutes at that temperature before it was allowed to warm to room temperature. After 3 hours the slightly yellow mixture was taken up in 100ml pentane and stirred for 5 minutes before the precipitated solids were removed via filtration through a short pad of celite. After the solvents had been removed on the rotary evaporator, 50 ml of pentane were added and the organic phase was washed with 2N HCl and $NaHCO_3$, dried and again concentrated. The residual crude enol triflate **67** was dissolved in 3.6ml dry THF under argon and cooled to 0°C before $Pd(OAc)_2$ (5.10mg, 0.10eqiv., 0.02mmol) and C-Phos (19.80mg, 0.20eqiv., 0.05mmol) dissolved in 1ml dry THF were added. The orange solution was stirred for 5 minutes and then 1M diethylzinc solution in heptane (0.45ml, 2.00eqiv., 0.45mmol) was added at 0°C, the ice bath removed and stirred overnight allowing the reaction mixture to reach room temperature. Again the mixture was cooled to 0°C and quenched with saturated NH_4Cl solution, extracted with Et_2O (4x), once washed with brine, dried and concentrated in vacuo. Purification by column chromatography (10g 10w/w% $AgNO_3$-doped SiO_2; Heptane:EtOAc=100:0 to Heptane:EtOAc=97:3) yielded 40.1mg 3-ethyl-valerenic acid ethyl ester **68** as colorless oil.

Yield: 40.1mg (63%) colourless oil

Rf: 0.58 (LP:EtOAc=30:1)

Molecular Formula: $C_{18}H_{28}O_2$

Molecular weight [g/mol]: 276.42

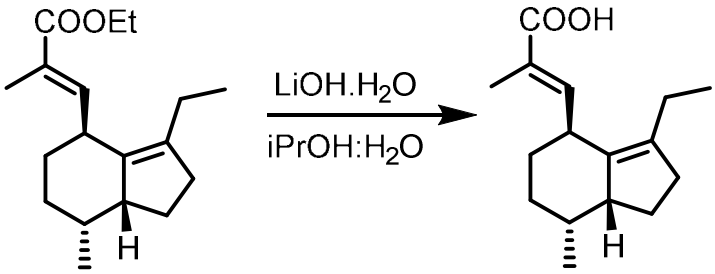
HRMS: calculated $(M+1)^+$= 277.2168 , found $(M+1)^+$ = 277.2162

$[\alpha]_D^{20}$: -78.5° (c=0.50g/100ml)

^{1}H-NMR (200 MHz, CD_3Cl): δ = 0.79 (d, J= 6.9Hz, 3H, 7'-CH_3), 0.95 (t, J= 7.6 Hz, 3H, 3'-CH_3), 1.25-2.27 (m, 17H), 2.97 (bs, 1H, 7a-CH), 3.50-3.57 (m, 1H, 4-CH), 4.17 (q, J=7.1Hz, 2H, 4''-OCH_2), 7.02 (dd, J_1 = 9.9 Hz, J_2 = 1.4Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, CD_3Cl): δ = 12.0 (q, 7'-CH_3), 12.4 (q, 3'-CH_3), 13.3 (q, 4'-CH_3), 14.3 (q, 4''-CH_3), 21.3 (t, 1-CH_2), 24.5 (t, 3'-CH_2), 25.9 (t, 5-CH_2), 28.9 (t, 6-CH_2), 33.3 (d, 4-CH), 34.27 (d, 7-CH), 34.29 (t, 2-CH_2), 47.3 (d, 7a-CH), 60.6 (t, 4''-OCH_2), 125.9 (s, 4'-C), 132.8 (s, 3-C), 136.8 (s, 3a-C), 143.2 (d, 4'-CH), 168.5 (s, 4'-COOEt)

I IV.1.7 (*E*)-3-((4*S*,7*S*,7a*R*)-3-ethyl-7-methyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methylacrylic acid (3-Ethyl-Valerenic acid) **69**



68 **69**

Ethyl-ester **68** (8.80mg, 1.00eqiv., 0.04mmol) and $LiOH.H_2O$ (8.92mg, 6.00eqiv., 0.21mmol) were dissolved in 210µl HPLC-grade iPrOH:H_2O =2:1 and heated to 40°C for two days. After complete hydrolysis 4ml iPrOH:H_2O= 3:1 and 1ml volume of Amberlite IR-120 were added and the mixture was stirred for 30 minutes. The Amberlite was separated by filtration, water was added to the filtrate and lyophyllized to yield 7.60mg colorless solid of 3-ethyl-valerenic acid **69**.

Yield: 7.60mg (96%)

Rf: 0.31 (LP:EtOAc=3:1)

Melting Point: 71-73°C

Molecular Formula: $C_{16}H_{24}O_2$

Molecular weight [g/mol]: 248.37

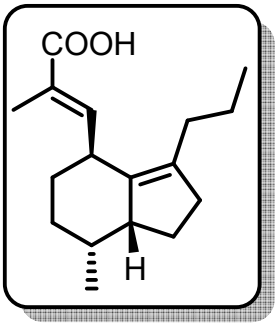
HRMS: calculated $(M+1)^+$= 249.1849 , found $(M+1)^+$ = 249.1850

$[\alpha]_D^{20}$: -143.4° (c=0.15g/100ml DCM)

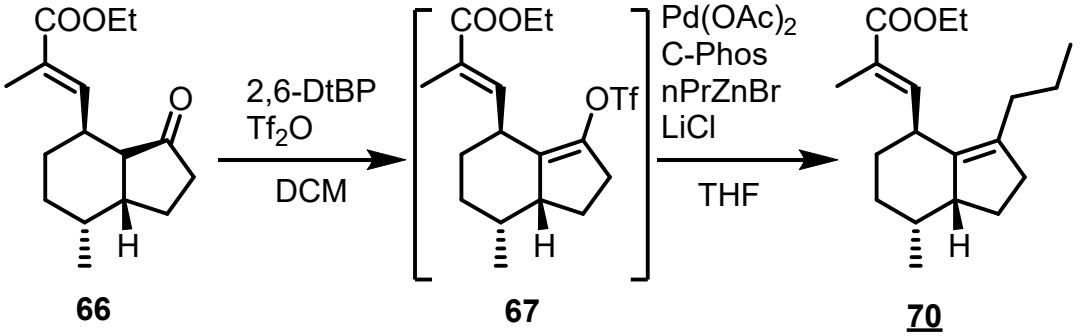
^{1}H-NMR (200 MHz, CD_3Cl): δ = 0.79 (d, J= 6.9Hz, 3H, 7'-CH_3), 0.95 (t, J=7.6Hz, 3H, 3'-CH_3), 1.39-1.67 (m, 3H), 1.68-2.15 (m, 10H), 2.20-2.27 (m, 2H, 2-CH_2), 2.95-2.97 (m, 1H, 7a-CH), 3.53-3.59 (m, 1H, 4-CH), 7.19 (dd, J_1 =9.9 Hz, J_2 = 1.3 Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, CD_3Cl): δ = 11.8 (q, 7'-CH_3), 11.9 (q, 3'-CH_3), 13.2 (q, 4'-CH_3), 21.3 (t, 3'-CH_2), 24.5 (t, 1-CH_2), 25.6 (t, 5-CH_2), 28.8 (t, 6-CH_2), 33.2 (d, 7-CH), 34.3 (t, 2-CH_2), 34.5 (d, 7a-CH), 47.4 (d, 7a-CH), 125.0 (s, 4'-C), 132.3 (s, 3-C), 137.3 (s, 3a-C), 146.3 (d, 4'-CH), 174.2 (s, 4'-COOH)

I IV.2 Synthesis of 3-Propyl-Valerenic acid



I IV.2.1 3-*n*-Propyl-Valerenic acid ethyl ester **70**



66 **67** **70**

Ketone **66** (40.00mg, 1.00eqiv., 0.15mmol) was dissolved in 3ml dry DCM under argon and cooled to 0°C. Subsequently 2,6-di-*tert*-butylpyridine 97% (70.00µl, 2.00eqiv., 0.30mmol) and freshly distilled triflic anhydride (51.00µl, 2.00eqiv., 0.30mmol) were added under vigorous stirring. The mixture was stirred for 5 minutes at that temperature before it was allowed to warm to room temperature. After 3 hours the slightly yellow mixture was taken up in 100ml pentane and stirred for 5 minutes before the precipitated solids were removed via filtration through a short pad of celite. After the solvents had been removed on the rotary evaporator, 50 ml of pentane were added and the organic phase was washed with 2N HCl and $NaHCO_3$, dried and again concentrated. To residual crude enol triflate **67** dry LiCl (25.60mg, 4.00eqiv., 0.60mmol) and 2ml dry THF were added under argon and cooled to 0°C before $Pd(OAc)_2$ (3.40mg, 0.10eqiv., 0.02mmol) and C-Phos (13.22mg, 0.20eqiv., 0.03mmol) dissolved in 1ml dry THF were added. The orange solution was stirred for 5 minutes and then 0.5M n-PrZnBr solution THF (0.61ml, 2.00eqiv., 0.30mmol) was added, the ice bath removed and stirred for 1h. Again the mixture was cooled to 0°C and quenched with saturated NH_4Cl solution, extracted with Et_2O (4x), once washed with brine, dried and concentrated in vacuo. Purification by column chromatography (10g 10w/w% $AgNO_3$-doped SiO_2;

Heptane:EtOAc=100:0 to Heptane:EtOAc=97:3) yielded 20.7mg 3-*n*-Propyl-Valerenic acid ethyl ester **70** as colorless oil.

Yield: 20.7mg (47%) colourless oil

Rf: 0.60 (LP:EtOAc=30:1)

Molecular Formula: $C_{19}H_{30}O_2$

Molecular weight [g/mol]: 290.45

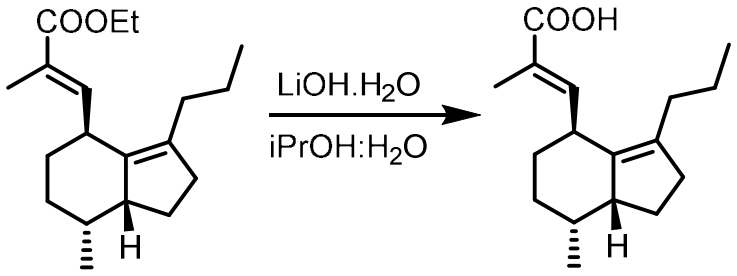
HRMS: calculated $(M+1)^+$= 291.2319, found $(M+1)^+$ = 291.2315

$[\alpha]_D^{20}$: -106.9° (c=0.22g/100ml DCM)

^{1}H-NMR (400 MHz, CD_3Cl): δ = 0.80 (d, J= 7.0Hz, 3H, 7'-CH_3), 0.87 (t, J=7.34Hz, 3H, 3'-CH_3), 1.29 (t, J=7.1 Hz, 3H, 4''-CH_3), 1.33-1.44 (m, 4H, 3'-CH_2+6-CH_2), 1.51-1.59 (m, 1H, 7-CH), 1.71-1.93 (m, 6H, 4'-CH_3+3'-CH_2+5-CH_2), 1.97-2.11 (m, 3H, 1-CH_2+7a-CH), 2.14-2.31 (m, 2H, 2-CH_2), 2.93-3.00 (m, 1H, 7a-CH), 3.52-3.56 (m, 1H, 4-CH), 4.18 (q, J= 7.1 Hz, 2H, 4''-OCH_2), 7.03 (dd, J_1 =9.9 Hz, J_2 = 1.3 Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, CD_3Cl): δ = 12.1 (q, 7'-CH_3), 12.4 (q, 3'-CH_3), 14.1 (q, 4'-CH_3), 14.3 (q, 4''-CH_3), 21.3 (t, 3'-CH_2), 24.5 (t, 1-CH_2), 25.8 (t, 5-CH_2), 28.9 (t, 6-CH_2), 30.3 (t, 3'-CH_2), 33.2 (d, 4-CH), 34.4 (d,7-CH), 34.8 (t, 2-CH_2), 47.4 (d, 7a-CH), 60.4 (t, 4''-OCH_2), 125.8 (s, 4'-C), 133.8 (s, 3_C), 135.3 (s, 3a-C), 143.4 (d, 4'-CH), 168.7 (s, 4'-COOEt)

I IV.2.2 3-*n*-Propyl-Valerenic acid **71**



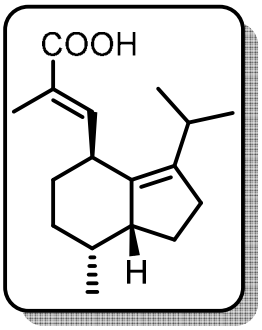
70 **71**

Ethyl-ester **70** (21.50mg, 1.00eqiv., 0.08mmol) and LiOH.H_2O (18.64mg, 6.00eqiv., 0.44mmol) were dissolved in 550µl HPLC-grade iPrOH:H_2O =2:1 and heated to 40°C for two

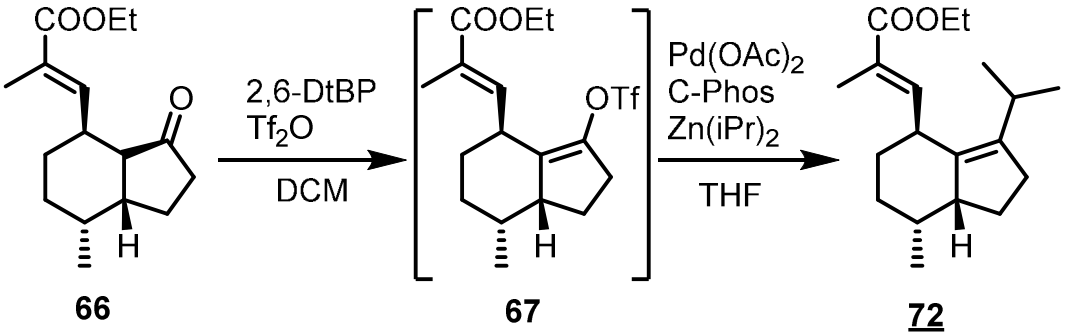
days. After complete hydrolysis 4ml iPrOH:H_2O= 3:1 and 1ml volume of Amberlite IR-120 were added and the mixture was stirred for 30 minutes. The Amberlite was filtered, water was added to the filtrate and lyophyllized to yield 17.60mg white solid of 3-*n*-Propyl-Valerenic acid **71** .

Yield:	7.60mg (96%) white solid
Rf:	0.45 (LP:EtOAc=3:1)
Melting Point:	76-78°C
Molecular Formula:	$C_{17}H_{26}O_2$
Molecular weight [g/mol]:	262.39
HRMS	calculated $(M+1)^+$= 263.2011, found $(M+1)^+$ = 263.1997
$[\alpha]_D^{20}$:	- 82.50° (c=0.30g/100ml DCM)
^{1}H-NMR (200 MHz, CD_3Cl):	δ = 0.78-0.90 (m, 6H, 7'-CH_3+3'-CH_3), 1.25-1.60 (m, 5H), 1.75-1.88 (m, 6H), 1.93-2.09 (m, 3H), 2.17-2.21 (m, 2H,2-CH_2), 2.98 (bs, 1H, 7a-CH), 3.52-3.58 (m, 1H, 4-CH), 7.16 (dd, J_1 =9.9 Hz, J_2 = 1.2Hz, 1H on acidic COOH, 4'-CH)
^{13}C-NMR (50 MHz, CD_3Cl):	δ = 12.1 (q,2xC 7'-CH_3+3'-CH_3), 14.1 (q, 4'-CH_3), 21.3 (t, 3'-CH_2), 24.6 (t, 1-CH_2), 25.7 (t, 5-CH_2), 28.9 (t, 6-CH_2), 30.4 (t, 3'-CH_2), 33.1 (d, 4-CH), 34.6 (d, 7-CH), 34.7 (t, 2-CH_2), 47.4 (d, 7a-CH), 125.2 (s, 4'-C), 133.4 (s, 3-C), 135.8 (s, 3a-C), 145.9 (d, 4'-CH), 173.8 (s, 4'-COOH)

I IV.3 Synthesis of (*E*)-3-((4*S*,7*S*,7a*R*)-3-isopropyl-7-methyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methylacrylic acid (3-*i*-Propyl-Valerenic acid) 73



I IV.3.1 Ethyl (*E*)-3-((4*S*,7*S*,7a*R*)-3-isopropyl-7-methyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methylacrylic acid (3-*i*-Propyl-valerenic acid ethyl ester) 72



66 67 72

Ketone **66** (71.00mg, 1.00eqiv., 0.27mmol) was dissolved in 5.4ml dry DCM under argon and cooled to 0°C. Subsequently 2,6-di-*tert*-butylpyridine 97% (105.90µl, 2.00eqiv., 0.54mmol) and freshly distilled triflic anhydride (90.35µl, 2.00eqiv., 0.54mmol) were added under vigorous stirring. The mixture was stirred for 5 minutes at that temperature before it was allowed to warm to room temperature. After 3 hours the slightly yellow mixture was taken up in 100ml pentane and stirred for 5 minutes before the precipitated solids were removed via filtration through a short pad of celite. After the solvents have been removed on the rotary evaporator, 50 ml of pentane were added and the organic phase was washed with 2N HCl and $NaHCO_3$, dried and again concentrated. The residual crude enol triflate **67** was dissolved in 4.4ml dry THF under argon and cooled to 0°C before $Pd(OAc)_2$ (5.20mg, 0.10eqiv., 0.02mmol) and C-Phos (20.10mg, 0.20eqiv., 0.05mmol) dissolved in 1ml dry THF were added. The orange solution was stirred for 5 minutes and then 1.0 M $Zn(i\text{-}Pr)_2$ solution in toluene (0.25ml, 1.10eqiv., 0.25mmol) was added, the ice bath removed and stirred overnight. Again the mixture was cooled to 0°C and quenched with saturated NH_4Cl solution,

extracted with Et_2O (4x), once washed with brine, dried and concentrated in vacuo. Purification by column chromatography (10g 10w/w% $AgNO_3$-doped SiO_2; Heptane:EtOAc=100:0 to Heptane:EtOAc=97:3) yielded an inseparable mixture of 32.3 mg 3-i-propyl-valerenic acid ethyl ester **72** and 3-n-propyl-valerenic acid ethyl ester **70** (91:9) as slightly yellow oil.

Yield: 32.3mg (42%) slightly yellow oil

Rf: 0.62 (LP:EtOAc=30:1)

Molecular Formula: $C_{19}H_{30}O_2$

Molecular weight [g/mol]: 290.45

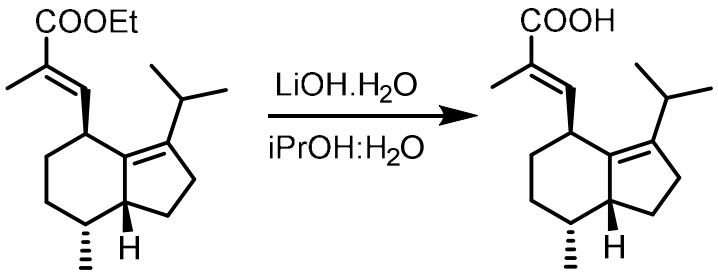
HRMS: calculated $(M+1)^+$= 291.2319, found $(M+1)^+$ = 291.2320

$[\alpha]_D^{20}$: -97.0° (c=0.29g/100ml DCM)

^{1}H-NMR (200 MHz, CD_3Cl): δ = 0.79 (d, J=7.0Hz, 3H, 7'-CH_3), 0.93 (d, J=6.8Hz, 3H, 3'-CH_3), 1.01 (d, J=6.8Hz, 3H, 3'-CH_3), 1.30 (t, J=7.1 Hz, 3H, 4''-CH_3), 1.43-2.06 (m, 12H), 2.18-2.25 (m, 2H, 2-CH_2), 2.68-2.82 (m, 0.91H, 3'-CH), 2.93-3.00 (m, 1H, 7a-CH), 3.54-3.61 (m, 1H, 4-CH), 4.18 (q, J=7.1Hz, 2H, 4''-OCH_2), 7.04 (dd, J_1 = 9.9 Hz, J_2 =1.5 Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, CD_2Cl_2): δ = 10.9 (q, 7'-CH_3), 11.2 (q, 4'-CH_3), 13.3 (q, 4''-CH_3), 20.2 (q, 3'-CH_3), 20.8 (q, 3'-CH_3), 23.5 (t, 1-CH_2), 25.1 (t, 5-CH_2), 26.1 (d, 3'-CH), 28.2 (t, 6-CH_2), 29.0 (t, 2-CH_2), 32.8 (d, 4-CH), 33.5 (d, 7-CH), 46.7 (d, 7a-CH), 59.5 (t, 4''-OCH_2), 125.2 (s, 4'-C), 131.1 (s, 3-C), 140.2 (s, 3a-C), 142.2 (d, 4'-CH), 167.5 (s, 4'-COOEt)

I IV.3.2 *E*)-3-((4*S*,7*S*,7a*R*)-3-isopropyl-7-methyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methylacrylic acid (3-*i*-Propyl-Valerenic acid) **73**



72 **73**

The inseparable mixture of ethyl-ester **72** combined with **70** (24.30mg, 1.00eqiv., 0.08mmol) and LiOH.H_2O (21.06mg, 6.00eqiv., 0.50mmol) were dissolved in 420µl HPLC-grade iPrOH:H_2O =2:1 and heated to 40°C for two days. After complete hydrolysis 4ml iPrOH:H_2O= 3:1 and 1ml volume of Amberlite IR-120 were added and the mixture was stirred for 30 minutes. The Amberlite was filtered, water was added to the filtrate and lyophyllized to yield 21.4 mg yellow oil of 3-*i*-propyl-valerenic acid **73** and 3-*n*-propyl-valerenic acid **71**

Yield: 21.4mg (97%) yellow oil

Rf: 0.46 (LP:EtOAc=3:1)

Molecular Formula: $C_{17}H_{26}O_2$

Molecular weight [g/mol]: 262.39

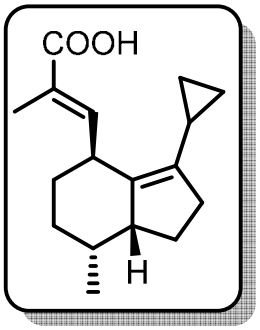
HRMS: calculated (M+1)= 263.2011, found (M+1) = 263.1996

$[\alpha]_D^{20}$: -86.91° (c=0.43g/100ml DCM)

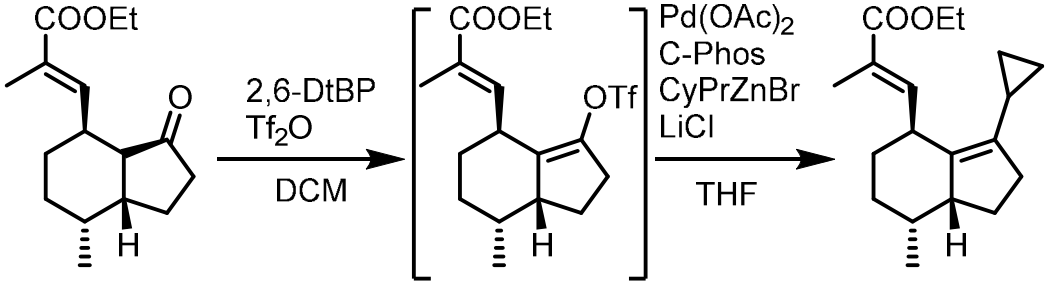
^{1}H-NMR (200 MHz, CD_3Cl): δ = 0.79 (d, J=7.0 Hz, 3H, 7'-CH_3), 0.92 (d, J= 6.8 Hz, 3H, 3'-CH_3), 1.01 (d, J=6.8 Hz, 3H, 3'-CH_3), 1.39-1.44 (m, 2H, 6-CH_2), 1.52-1.60 (m, 1H, 7-CH), 1.72-2.04 (m, 7H, 4'-CH_3+ 1-CH_2+5-CH_2), 2.19-2.23 (m, 2H, 2-CH_2), 2.69-2.77 (m, 0.86H, 3'-CH), 2.93-2.98 (m, 1H, 7a-CH), 3.57-3.60 (m, 1H, 4-CH), 7.19 (dd, J_1 = 9.9Hz, J_2 = 1.4 Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, CD_3Cl): δ = 11.91 (q, 7'-CH_3), 11.94 (q, 4'-CH_3), 21.2 (q, 3'-CH_3), 21.9 (q, 3'-CH_3), 24.3 (t, 1-CH_2), 25.7 (t, 5-CH_2), 26.9 (d, 3'-CH), 29.0 (t, 6-CH_2), 29.9 (t, 2-CH_2), 33.3 (d, 4-CH), 34.5 (d, 7-CH), 47.4 (d, 7a-CH), 125.0 (s, 4'-C), 131.4 (s, 3-C), 141.3 (s, 3a-C), 146.4 (d, 4'-CH), 173.9 (s, 4'-COOH)

I IV.4 Synthesis of (*E*)-3-((4*S*,7*S*,7a*R*)-3-cyclopropyl-7-methyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methylacrylic acid (3-Cyclopropyl-Valerenic acid) 75



I IV.4.1 Ethyl-(*E*)-3-((4*S*,7*S*,7a*R*)-3-cyclopropyl-7-methyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methylacrylic acid 3-Cyclopropyl-Valerenic acid ethyl ester **74**



66 **67** **74**

Ketone **66** (43.55mg, 1.00eqiv., 0.15mmol) was dissolved in 3ml dry DCM under argon and cooled to 0°C. Subsequently 2,6-di-*tert*-butylpyridine 97% (70.00µl, 2.00eqiv., 0.30mmol) and freshly distilled triflic anhydride (51.00µl, 2.00eqiv., 0.30mmol) were added under vigorous stirring. The mixture was stirred for 5 minutes at that temperature before it was allowed to warm to room temperature. After 3 hours the slightly yellow mixture was taken up in 100ml pentane and stirred for 5 minutes before the precipitated solids were removed via filtration through a short pad of celite. After the solvents have been removed on the rotary evaporator, 50 ml of pentane were added and the organic phase was washed with 2N HCl and $NaHCO_3$, dried and again concentrated. To residual crude enol triflate **67**, dry LiCl (25.60mg, 4.00eqiv., 0.60mmol) and 2ml dry THF were added under argon and cooled to 0°C before $Pd(OAc)_2$ (3.40mg, 0.10eqiv., 0.02mmol) and C-Phos (13.22mg, 0.20eqiv., 0.03mmol) dissolved in 1ml dry THF were added. The orange solution was stirred for 5 minutes and then 0.5M cy-PrZnBr solution THF (0.60ml, 2.00eqiv., 0.30mmol) was added, the ice bath removed

and stirred for one hour. Again the mixture was cooled to 0°C and quenched with saturated NH_4Cl solution, extracted with Et_2O (4x), once washed with brine, dried and concentrated in vacuo. Purification by column chromatography (10g 10w/w% $AgNO_3$-doped SiO_2; heptane:EtOAc=100:0 to heptane:EtOAc=97:3) yielded 18.3mg 3-cyclopropyl-valerenic acid ethyl ester **74** as colorless oil.

Yield: 18.3mg (42%)

Rf: 0.39 (LP:EtOAc=30:1)

Molecular Formula: $C_{19}H_{28}O_2$

Molecular weight [g/mol]: 288.43

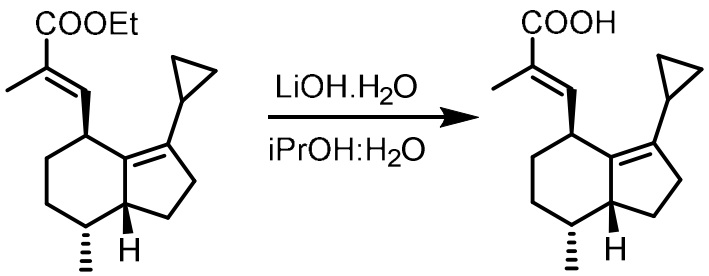
HRMS: calculated $(M+1)^+$= 289.2162, found $(M+1)^+$ = 289.2168

$[\alpha]_D^{20}$: -132.2° (c=0.48g/100ml DCM)

^{1}H-NMR (200 MHz, CD_3Cl): δ = 0.43-0.66 (m, 4H, 2x 3'-CH_2), 0.80 (d, J=7.0Hz, 3H, 7'-CH_3), 1.30 (t, J= 7.1Hz, 3H, 4''-CH_3), 1.43-2.01 (m, 13H), 2.95-3.02 (m, 1H, 7a-CH), 3.69-3.74 (m, 1H, 4-CH), 4.19 (q, J= 7.1 Hz, 2H, 4''-OCH_2), 7.05 (dd, J_1 = 9.7Hz, J_2= 1.4Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, CD_3Cl): δ = 4.26 (t, 3'-CH_2), 4.30 (t, 3'-CH_2), 10.0 (d, 3'-CH), 12.1 (q, 7'-CH_3), 12.4 (q, 4'-CH_3), 14.3 (q, 4''-CH_3), 24.0 (t, 1-CH_2), 25.5 (t, 5-CH_2), 28.9 (t, 6-CH_2), 31.0 (t, 2-CH_2), 33.2 (d, 4-CH), 34.4 (d, 7-CH), 47.9 (d, 7a-CH), 60.4 (t, 4''-OCH_2), 126.1 (s, 4'-C), 134.1 (s, 3-C), 135.3 (s, 3a-C), 143.4 (d, 4'-CH), 168.6 (s, 4'-COOEt)

I IV.4.2 (*E*)-3-((4*S*,7*S*,7a*R*)-3-cyclopropyl-7-methyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methylacrylic acid (3-Cyclopropyl-Valerenic acid) **75**

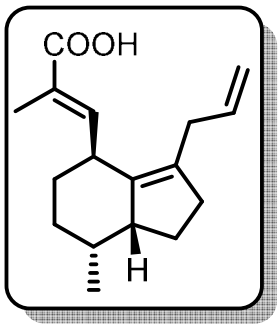


74 **75**

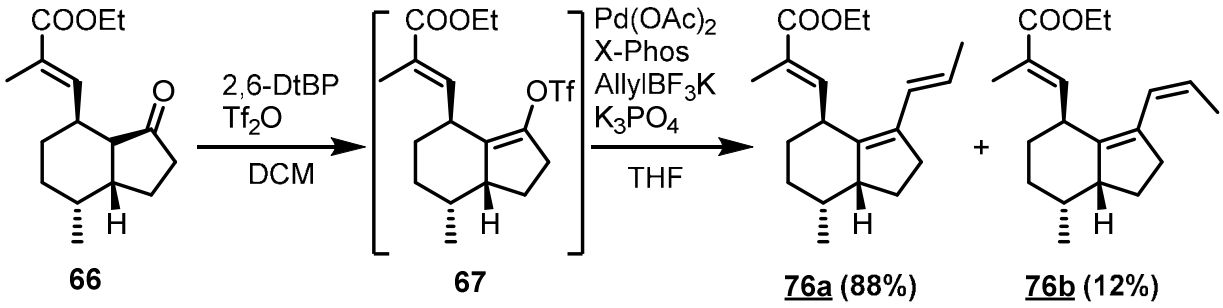
Ethyl-ester **74** (18.30mg, 1.00eqiv., 0.06mmol) and $LiOH.H_2O$ (15.99mg, 6.00eqiv., 0.38mmol) were dissolved in 320µl HPLC-grade iPrOH:H_2O =2:1 and heated to 40°C for two days. After complete hydrolysis 4ml iPrOH:H_2O= 3:1 and 1ml volume of Amberlite IR-120 were added and the mixture was stirred for 30 minutes. The Amberlite was filtered, water was added to the filtrate and lyophyllized to yield 16.40mg colorless solid of 3-Cyclopropyl-Valerenic acid **75**.

Yield:	16.4mg (99%) colorless solid
Rf:	0.46 (LP:EtOAc=3:1)
Melting Point:	135-137°C
Molecular Formula:	$C_{17}H_{26}O_2$
Molecular weight [g/mol]:	260.38
HRMS:	calculated $(M-1)^+$= 259.1693, found $(M-1)^+$ = 259.1692
$[\alpha]_D^{20}$:	-103.2° (c=0.34g/100ml DCM)
^{1}H-NMR (400 MHz, CD_3Cl):	δ = 0.45-0.62 (m, 4H, 3'-CH_2), 0.80 (d, J= 7.0Hz, 3H, 3'-CH_2), 1.42-1.61 (m, 4H, 3'-CH+7'-CH_3), 1.76-1.98 (m, 9H), 2.98 (bs, 1H, 7a-CH), 3.73-3.75 (m, 1H, 4-CH), 7.19 (d, J= 9.7Hz, 1H, 4'-CH)
^{13}C-NMR (50 MHz, CD_3Cl):	δ = 4.3 (t, 3'-CH_3), 4.4 (t, 3'-CH_3), 10.0 (d, 3'-CH), 12.09 (q, 7'-CH_3), 12.12 (q, 4'-CH_3), 24.1 (t, 1-CH_2), 25.5 (t, 5-CH_2), 28.8 (t, 6-CH_2),31.1 (t, 2-CH_2), 33.2 (d, 4-CH), 34.7 (d, 7-CH), 48.0 (d, 7a-CH), 125.3 (s, 4'-C), 133.6 (s, 3-C), 135.8 (s, 3a-C), 146.7 (d, 4'-CH), 173.7 (s, 4'-COOH)

I IV.5 Synthesis of (*E*)-3-((4*S*,7*S*,7a*R*)-3-allyl-7-methyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methylacrylic acid (3-Allyl-Valerenic acid) 77



I IV.5.1 Ethyl (*E*)-3-((4*S*,7*S*,7a*R*)-3-(7-methyl-3-((*E*/*Z*)-prop-1-yl)-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methylacrylic acid **76a/b**



Ketone **66** (35.00mg, 1.00eqiv., 0.14mmol) was dissolved in 3ml dry DCM under argon and cooled to 0°C. Subsequently 2,6-di-*tert*-butylpyridine 97% (61.00µl, 2.00eqiv., 0.28mmol) and freshly distilled triflic anhydride (44.60µl, 2.00eqiv., 0.28mmol) were added under vigorous stirring. The mixture was stirred for 5 minutes at that temperature before it was allowed to warm to room temperature. After 3 hours the slightly yellow mixture was taken up in 100ml pentane and stirred for 5 minutes before the precipitated solids were removed via filtration through a short pad of celite. After the solvents have been removed on the rotary evaporator, 50 ml of pentane were added and the organic phase was washed with 2N HCl and $NaHCO_3$, dried and again concentrated. To $Pd(OAc)_2$ (3.82mg,0.10eqiv., 0.02mmol), X-Phos (16.21mg, 0.20eqiv., 0.03mmol) and K_3PO_4 (118.88mg, 4.00eqiv., 0.56mmol) under argon enol triflate **67** dissolved in 3.4ml dry THF was added. The mixture was stirred at room temperature for 5 minutes before potassium allyltrifluoroborate (82.87mg, 4.00eqiv.,0.56mmol) was added and the mixture was heated to 80°C for two days. After cooling the mixture to room temperature, it was quenched with saturated NH_4Cl and

extracted with Et_2O (4x), washed with brine (1x), dried over Na_2SO_4 and concentrated. Purification via column chromatography (10g 10w/w% $AgNO_3$-doped SiO_2; Heptane:EtOAc=100:0 to Heptane:EtOAc=97:3) yielded 18.0mg Ethyl (*E*)-3-((4*S*,7*S*,7a*R*)-3-(7-methyl-3-((*E*/*Z*)-prop-1-yl)-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methylacrylic acid **76a/b** as an *E*/*Z* (88:12) isomeric mixture as colorless oil.

Yield: 18.0mg (47%) colorless oil as a mixture of *E*/Z-*isomeres* (88:12)

Rf: 0.37 (LP:EtOAc=30:1)

Molecular Formula: $C_{19}H_{28}O_2$

Molecular weight [g/mol]: 288.43

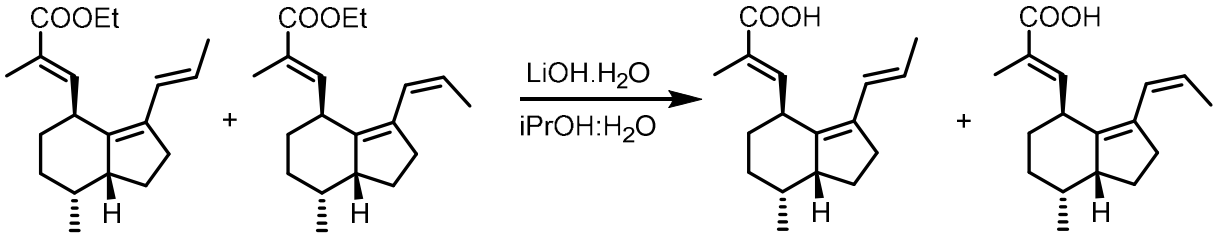
HRMS: **n.d.**

$[\alpha]_D^{20}$: **n.d.**

^{1}H-NMR (400 MHz, CD_3Cl): δ = 0.78 (d, J=7.0Hz, 3H, 7'-CH_3), 1.29 (t, J=7.1Hz, 3H, 4''-CH_3), 1.40-1.46 (m, 2H, 1-CH_2), 1.53-1.86 (m, 7H), 1.73-1.91 (m, 10H), 1.96-2.08 (bm, 1H, 7-CH), 2.34-2.41 (m, 1.74H, 2-CH_2), 2.53-2.61 (m, 0.26H, 2-CH_2 cis-isomere), 3.04 (bs, 1H, 7a-CH), 3.40-3.7 (m, 1H, 4-CH), 4.18 (q, J= 7.1Hz, 2H, 4''-OCH_2), 5.42-5.65 (m,1H, 3'-CH), 6.06 (d,J=11.9 Hz,0.12H, 3'-CH-cis-isomere), 6.33 (d, J=15.4 Hz, 0.88H, 3'-CH-trans-isomere), 7.02 (dd, J_1 = 9.7Hz, J_2= 1.4Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, CD_3Cl): n.d.

I IV.5.2 (*E*)-3-((4*S*,7*S*,7a*R*)-3-allyl-7-methyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methylacrylic acid (3-Allyl-Valerenic acid) **77**



76a **76b** **77a** **77b**

Ethyl-ester **76** (15.00mg, 1.00eqiv., 0.05mmol) and LiOH.H_2O (11.30mg, 6.00eqiv., 0.27mmol) were dissolved in 600µl HPLC-grade iPrOH:H_2O =2:1 and heated to 40°C for 19h. After complete hydrolysis, 4ml *i*-PrOH:H_2O= 3:1 and 1ml volume of Amberlite IR-120 were added and the mixture was stirred for 30 minutes. The Amberlite was filtered, water was added to the filtrate and lyophyllized to yield 12.1mg (*E*)-3-((4*S*,7*S*,7a*R*)-3-(7-methyl-3-((*E*/*Z*)-prop-1-yl)-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methylacrylic acid **77a/b** as an *E*/*Z* (88:12) isomeric mixture as colorless solid of **77a/b**.

Yield: 12.10mg (90%) as a mixture of *E*/*Z*-isomeres (88:12)

Rf: 0.30 (LP:EtOAc=3:1)

Melting Point: 45-46°C

Molecular Formula: $C_{17}H_{26}O_2$

Molecular weight [g/mol]: 260.38

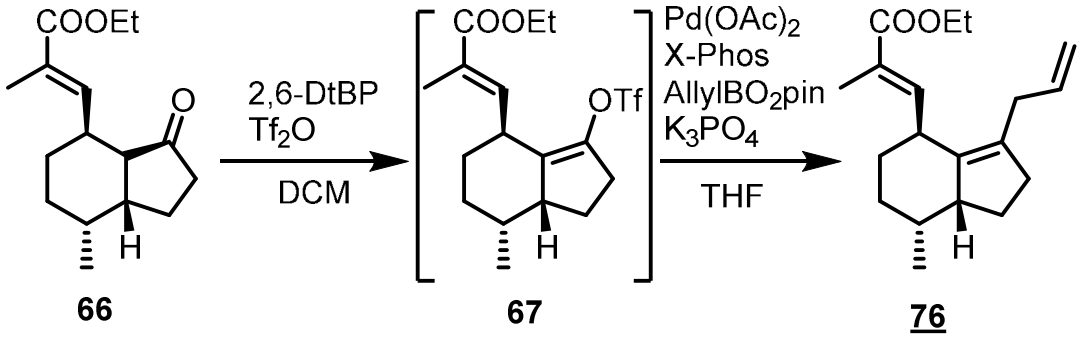
HRMS: n.d.

$[\alpha]_D^{20}$: n.d.

^{1}H-NMR (200 MHz, CD_3Cl): δ =0.79 (d, J=7.0Hz,3H, 7'-CH_3) 1.26-2.10 (m, 16H), 2.35-2.42 (m, 1.8H, 2-CH_2 trans isomere), 2.54-2.61 (m, 0.2H, 2-CH_2 cis isomere), 3.05 (bs, 1H, 7a-CH), 3.72-3.77(m, 1H, 4-CH), 5.47-5.67 (m, 1H, 3'-CH), 6.05 (d,J=11.7Hz, 0.12H, 3'-CH cis isomere), 6.33 (d, J=15.3Hz, 0.88H, 3'-CH trans isomere), 7.17(dd, J_1=9.7Hz, J_2=1.2Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, CD_3Cl): n.d

I IV.5.3 Ethyl (*E*)-3-((4*S*,7*S*,7a*R*)-3-cyclopropyl-7-methyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methylacrylic acid (3-Allyl-Valerenic acid ethyl ester) **76**



66 **67** **76**

Ketone **66** (35.00mg, 1.00eqiv., 0.14mmol) was dissolved in 3ml dry DCM under argon and cooled to 0°C. Subsequently 2,6-di-*tert*-butylpyridine 97% (61.00µl, 2.00eqiv., 0.28mmol) and freshly distilled triflic anhydride (44.60µl, 2.00eqiv., 0.28mmol) were added under vigorous stirring. The mixture was stirred for 5 minutes at that temperature before it was allowed to warm to room temperature. After 3 hours the slightly yellow mixture was taken up in 100ml pentane and stirred for 5 minutes before the precipitated solids were removed via filtration through a short pad of celite. After the solvents have been removed on the rotary evaporator, 50 ml of pentane were added and the organic phase was washed with 2N HCl and $NaHCO_3$, dried and again concentrated. To $Pd(OAc)_2$ (3.82mg,0.10eqiv., 0.02mmol), X-Phos (16.21mg, 0.20eqiv., 0.03mmol) and K_3PO_4 (89.16mg, 3.00eqiv., 0.42mmol) under argon enol triflate **67** dissolved in 3.4ml dry THF was added. The mixture was stirred at room temperature for 5 minutes before allylboronic acid pinacol ester 97% (48.51µl, 2.00eqiv., 0.28mmol) was added and the mixture was heated to 80°C for 15h. After cooling the mixture to room temperature, it was quenched with saturated NH_4Cl and extracted with Et_2O (4x), washed with brine (1x), dried over Na_2SO_4 and concentrated. Purification via column chromatography (10g 10w/w% $AgNO_3$-doped SiO_2; Heptane:EtOAc=100:0 to Heptane:EtOAc=97:3) yielded 23.5mg 3-allyl-valerenic acid ethyl ester **76** as colorless oil.

Yield: 23.5mg (57%) colorless oil

Rf: 0.37 (LP:EtOAc=30:1)

Molecular Formula: $C_{19}H_{28}O_2$

Molecular weight [g/mol]: 288.43

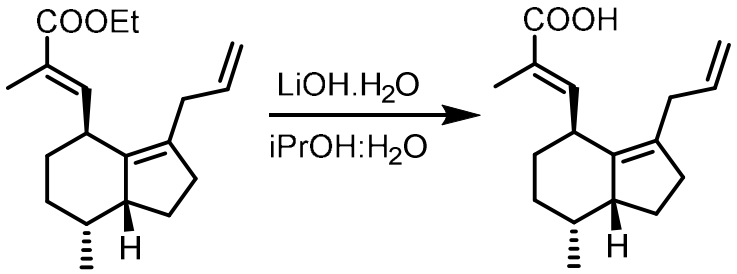
HRMS: calculated $(M+1)^+$= 289.2162, found $(M+1)^+$ = 289.2150

$[\alpha]_D^{20}$: -74.3° (c=0.29g/100ml DCM)

^{1}H-NMR (400 MHz, CD_3Cl): δ = 0.80 (d, J=7.0Hz, 3H, 7'-CH_3), 1.29 (t, J=7.2Hz, 3H, 4''-CH_3), 1.40-1.44 (m, 2H, 5-CH_2), 1.52-1.60 (m, 1H, 7-CH), 1.73-1.92 (m, 6H,), 2.01 (bs, 1H, 7a-CH), 2.20-2.22 (m, 2H, 2-CH_2), 2.81 (dt, J_1 = 14.6Hz, J_2= 6.7Hz, 2H, 3'-CH_2), 3.01 (bs, 1H, 7a-CH), 3.54-3.57 (m, 1H, 4-CH), 4.18 (q, J= 7.1Hz, 2H, 4''-OCH_2), 4.96 (dd, J_1 = 10.0 Hz, J_2= 1.5Hz, 1H, 1H of 3'-olefinic CH_2), 5.01 (dd, J_1 = 17.0Hz, J_2= 1.7Hz, 1H, 1H of 3'-olefinic CH_2), 5.66-5.76 (m, 1H, 3'-CH), 7.02 (dd, J_1 = 9.9Hz, J_2= 1.4Hz, 1H, 4'-CH)

^{13}C-NMR (50 MHz, CD_3Cl): δ = 12.1 (q, 7'-CH_3), 12.4 (q, 4'-CH_3), 14.3 (q, 4''-CH_3), 24.4 (t, 1-CH_2), 25.8 (t, 5-CH_2), 28.8 (t, 6-CH_2), 32.9 (t, 2-CH_2), 33.2 (d, 4-CH), 34.4 (d, 7-CH), 35.0 (t, 3'-CH_2), 47.6 (d, 7a-CH), 60.5 (t, 4''-OCH_2), 115.2 (t, 3'-olefinic CH_2), 126.0 (s, 4'-C), 132.8 (s, 3-C), 134.8 (s, 3a-C), 136.2 (d, 3'-CH), 143.0 (d, 4'-CH), 168.6 (s, 4'-COOEt)

I IV.5.4 (*E*)-3-((4*S*,7*S*,7a*R*)-3-allyl-7-methyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methylacrylic acid (3-Allyl-Valerenic acid) **77**



76 **77**

Ethyl-ester **76** (12.90mg, 1.00eqiv., 0.05mmol) and LiOH.H_2O (11.30mg, 6.00eqiv., 0.27mmol) were dissolved in 225µl HPLC-grade iPrOH:H_2O =2:1 and heated to 40°C for three days. After complete hydrolysis, 4ml *i*-PrOH:H_2O= 3:1 and 1ml volume of Amberlite IR-120 were added and the mixture was stirred for 30 minutes. The Amberlite was filtered, water was added to the filtrate and lyophyllized to yield 10.2mg colorless solid of 3-allyl-valerenic acid **77**.

Yield: 10.20mg (87%)

Rf: 0.30 (LP:EtOAc=3:1)

Melting Point: 45-46°C

Molecular Formula: $C_{17}H_{26}O_2$

Molecular weight [g/mol]: 260.38

HRMS: calculated (M+1)= 261.1855, found (M+1) = 261.1840

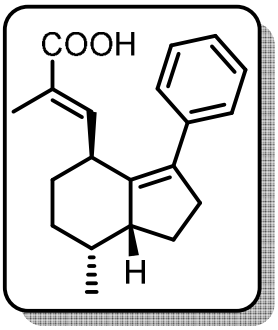
$[\alpha]_D^{20}$: -59.0° (c=0.20g/100ml DCM)

^{1}H-NMR (200 MHz, CD_3Cl): δ =0.80 (d, J=7.00Hz,3H, 7'-CH_3), 1.17-1.25 (m, 1H), 1.40-1.88 (m, 10H), 1.94-2.04(m, 1H, 7-CH), 2.20-2.24 (m, 2H, 2-CH_2), 2.80-2.83 (m, 2H, 3'-CH_2), 3.00 (bs, 1H, 7a-CH), 3.55-3.59 (m, 1H, 4-CH), 4.94-5.03 (m, 2H, 3'-olefinic CH_2), 5.66-5.76 (m, 1H, 3'-CH), 7.17(dd, J_1=9.94Hz, J_2=1.34Hz, 1H, 4'-CH)

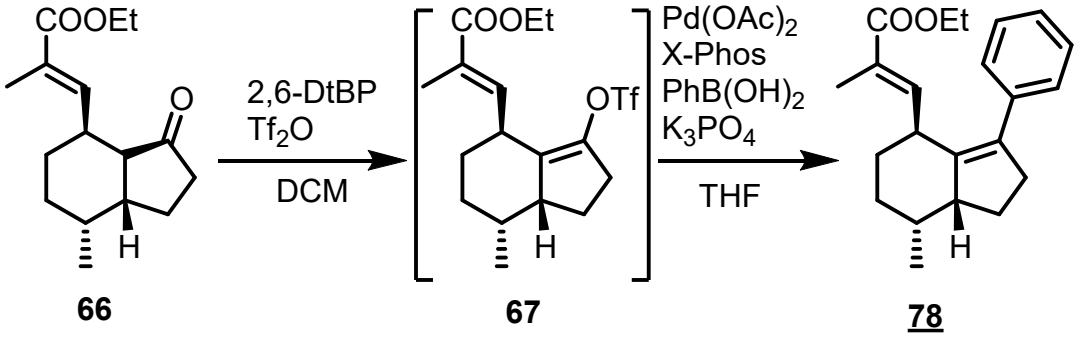
^{13}C-NMR (50 MHz, CD_3Cl): δ = 12.1 (q, 7'-CH_3+4'-CH_3), 24.4 (t, 1-CH_2), 25.6 (t, 5-CH_2), 28.8 (t, 6-CH_2), 32.8 (t, 2-CH_2), 33.1 (d, 4-CH), 34.6 (d, 7-CH), 35.0 (t,

3‘-CH_2), 47.5 (d, 7a-CH), 115.2 (t, 3‘-olefinic CH_2), 125.1 (s, 4‘-C), 133.2 (s, 3-C), 134.5 (s, 3a-C), 136.1 (d, 3‘-CH), 145.9 (d, 4‘-CH), 173.3(s, 4‘-COOH)

I IV.6 Synthesis of (*E*)-3-((4*S*,7*S*,7a*R*)-7-methyl-3-phenyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methylacrylic acid (3-Phenyl-Valerenic acid) 79



I IV.6.1 Ethyl (*E*)-3-((4*S*,7*S*,7a*R*)-7-methyl-3-phenyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methylacrylic acid (3-Phenyl-Valerenic acid ethyl ester) 78



66 **67** **78**

Ketone **66** (35.00mg, 1.00eqiv., 0.14mmol) was dissolved in 3ml dry DCM under argon and cooled to 0°C. Subsequently 2,6-di-*tert*-butylpyridine 97% (61.00µl, 2.00eqiv., 0.28mmol) and freshly distilled triflic anhydride (44.60µl, 2.00eqiv., 0.28mmol) were added under vigorous stirring. The mixture was stirred for 5 minutes at that temperature before it was allowed to warm to room temperature. After 3 hours the slightly yellow mixture was taken up in 100ml pentane and stirred for 5 minutes before the precipitated solids were removed via filtration through a short pad of celite. After the solvents had been removed on the rotary evaporator, 50 ml of pentane were added and the organic phase was washed with 2N HCl and $NaHCO_3$, dried and again concentrated. To $Pd(OAc)_2$ (3.82mg,0.10eqiv., 0.02mmol), X-Phos (16.21mg, 0.20eqiv., 0.03mmol), K_3PO_4 (89.16mg, 3.00eqiv., 0.42mmol) and phenylboronic acid (34.14mg, 2.00eqiv., 0.28mmol) under argon, enol triflate **67** dissolved in 3.4ml dry THF was added and heated to 80°C for 15h. After cooling the mixture to room temperature, the reaction mixture was quenched with saturated NH_4Cl and extracted with Et_2O (4x), washed with brine (1x), dried over Na_2SO_4 and concentrated. Purification via

column chromatography (10g 10w/w% $AgNO_3$-doped SiO_2; heptane:EtOAc=100:0 to heptane:EtOAc=97:3) yielded 22.4mg 3-phenyl-valerenic acid ethyl ester **78** as colorless oil.

Yield: 22.4mg (50%) colorless oil

Rf: 0.24 (LP:EtOAc=30:1)

Molecular Formula: $C_{22}H_{28}O_2$

Molecular weight [g/mol]: 324.26

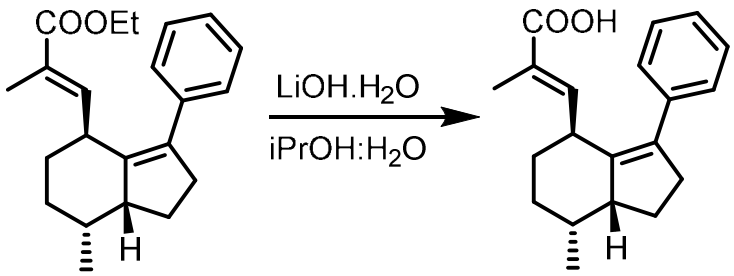
HRMS: calculated $(M+1)^+$= 325.2162, found $(M+1)^+$ = 325.2157

$[\alpha]_D^{20}$: -187.3° (c=0.32g/100ml DCM)

^{1}H-NMR (400 MHz, CD_3Cl): δ = 0.93 (d, J= 7.0 Hz, 3H, 7'-CH_3), 1.22-1.52 (m, 6H), 1.74-1.79 (m, 3H), 1.84-1.92 (m, 2H), 2.00-2.10 (m, 1H), 2.16-2.19 (m, 1H, 1H of 2-CH_2), 2.56-2.62 (m, 1H, 1H of 2-CH_2), 2.76-2.83 (m, 1H, 7-CH), 3.27-3.28 (m, 1H, 7a-CH), 3.73-3.76 (m, 1H, 4-CH), 4.23 (q, J= 7.1Hz, 2H, 4''-OCH_2), 7.16-7.36 (m, 6H, 4'-CH+3'-ArCH)

^{13}C-NMR (50 MHz, CD_3Cl): δ = 12.1 (q, 7'-CH_3), 12.2 (q, 4'-CH_3), 14.3 (q, 4''-CH_3), 24.6 (t, 1-CH_2), 26.3 (t, 5-CH_2), 28.8 (t, 6-CH_2), 33.9 (d, 4-CH), 35.3 (t, 2-CH_2), 36.5 (d, 7-CH), 48.3 (d, 7a-CH), 60.5 (t, 4''-OCH_2), 126.5 (d, 3'-ArCH), 126.7 (s, 3'-ArC), 127.7 (d, 3'-ArCH), 128.1 (d, 3'-ArCH), 135.7 (s, 4'-C), 137.6 (s, 3-C), 138.1 (s, 3a-C), 143.0 (d, 4'-CH), 168.6 (s, 4'-COOEt)

I IV.6.2 (*E*)-3-((4*S*,7*S*,7a*R*)-7-methyl-3-phenyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)-2-methylacrylic acid (3-Phenyl-Valerenic acid) **79**



78 **79**

Ethyl-ester **78** (13.20mg, 1.00eqiv., 0.04mmol) and $LiOH.H_2O$ (10.20mg, 6.00eqiv., 0.24mmol) were dissolved in 210µl HPLC-grade iPrOH:H_2O =2:1 and heated to 40°C for two days. After complete hydrolysis, 4ml iPrOH:H_2O= 3:1 and 1ml volume of Amberlite IR-120 were added and the mixture was stirred for 30 minutes. The Amberlite was filtered, water was added to the filtrate and lyophyllized to yield 12.0mg colorless solid of 3-phenyl-valerenic acid **79**.

Yield: 12.0mg (98%) colorless solid

Rf: 0.25 (LP:EtOAc=3:1)

Melting Point: 62-64°C

Molecular Formula: $C_{20}H_{24}O_2$

Molecular weight [g/mol]: 298.43

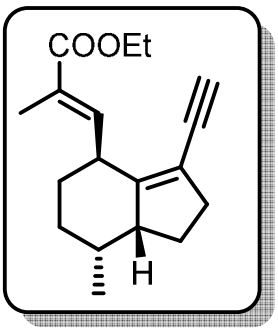
HRMS: calculated $(M+23)^+$= 321.1825, found $(M+23)^+$ = 321.1831

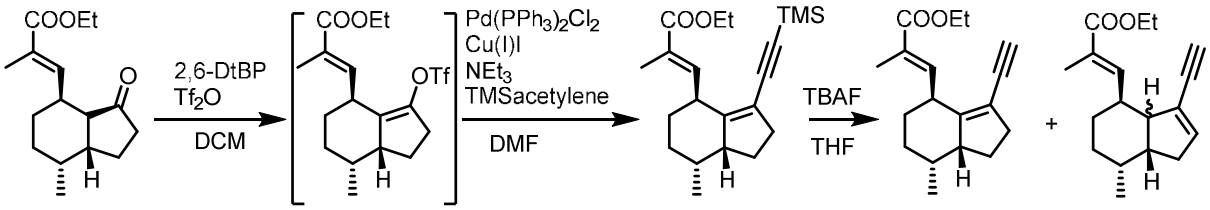
$[\alpha]_D^{20}$: -59.0° (c=0.20g/100ml DCM)

^{1}H-NMR (200 MHz, CD_3Cl): δ = 0.91 (d, J= 6.9Hz, 3H, 7'-CH_3), 1.24-1.48 (m, 4H, 6-CH_2+5-CH_2), 1.73-2.20 (m, 10H), 2.55-2.64 (m, 1H, 1H of 2-CH_2), 2.76-2.80 (m, 1H, 1H of 2-CH_2), 3.23 (bs, 1H, 4-CH), 3.71-3.73 (m, 1H, 7a-CH), 7.14-7-34 (m, 6H, 4'-CH+3'-ArCH)

^{13}C-NMR (50 MHz, CD_3Cl): δ = 10.0 (q, 7'-CH_3), 12.0 (q, 4'-CH_3), 24.7 (t, 1-CH_2), 26.2 (t, 5-CH_2), 28.9 (t, 6-CH_2), 33.8 (d, 4-CH), 35.5 (d, 7-CH), 36.5 (t, 2-CH_2), 48.2 (d, 7a-CH), 126.6 (d, 3'-ArCH+3'ArC), 127.7 (d, 3'-ArCH), 128.2 (d, 3'-ArCH), 136.0 (s, 4'-C), 137.3 (s, 3-C), 138.1 (s, 3a-C), 145.5 (d, 4'-CH) 4'-COOH not relaxated 2 fehlen!!

I IV.7 Synthesis of 3-Alkynyl-Valerenic acid ethyl ester 81





Ketone **66** (98.00mg, 1.00eqiv., 0.37mmol) was dissolved in 7,4ml dry DCM under argon and cooled to 0°C. Subsequently 2,6-di-*tert*-butylpyridine 97% (171.6µl, 2.00eqiv., 0.74mmol) and freshly distilled triflic anhydride (124.70µl, 2.00eqiv., 0.74mmol) were added under vigorous stirring. The mixture was stirred for 5 minutes at that temperature before it was allowed to warm to room temperature. After 3 hours the slightly yellow mixture was taken up in 100ml pentane and stirred for 5 minutes before the precipitated solids were removed via filtration through a short pad of celite. After the solvents had been removed on the rotary evaporator, 50 ml of pentane were added and the organic phase was washed with 2N HCl and $NaHCO_3$, dried and again concentrated. To $Pd(PPh_3)_2Cl_2$ (26.0mg, 0.10eqiv., 0.04mmol),CuI (7.10mg, 0.10eqiv., 0.4mmol), enol-triflate **67** in 2.6ml dry DMF was added under argon. Subsequently dry NEt_3 (155.10 µl, 3.00eqiv., 1.11mmol) and TMS-acetylene (105.6 µl=70.2mg, 2.00eqiv., 0.74mmol) were added. The mixture was stirred at room temperature for 45 minutes turning from transparent brown to black, before it was quenched with NH_4Cl and extracted with Et_2O (three times). After washing with brine and drying with Na_2SO_4 the mixture was concentrated on the rotary evaporator. The concentrated residue was taken up in 3.7ml dry THF and cooled to 0°C before 1 M TBAF solution in THF (853.0 µl, 2.30eqiv., 0.85mmol) was added. After TLC indicated full conversion (10 minutes), the mixture was again quenched with NH_4Cl-solution and extracted with Et_2O (3x), washed with brine and dried with Na_2SO_4. After concentration in vacuo the mixture was purified via column chromatography on SiO_2 (LP:EtOAc=100:0 to 97:3) yielding

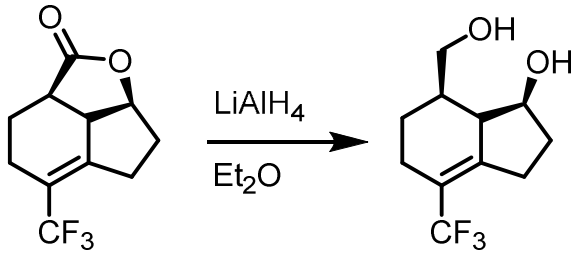
23.4mg colorless oil as a mixture of regioisomeres (81:81a= 77%:23%) of 3-alkynyl-valerenic acid ethyl ester **81**. Product **81** is highly labile and degrades into an unidentified mixture within two days getting a deep yellow oil. Therefore any further characterisations than ^{1}H-NMR were not conducted.

Yield:	23.4mg (23%) yellow oil as an isomeric mixture (81:81a=77%:23%)
Rf:	0.34 (LP:EtOAc=30:1)
Molecular Formula:	$C_{18}H_{24}O_2$
Molecular weight [g/mol]:	272.39
$[\alpha]_D^{20}$:	n.d.
^{1}H-NMR (400 MHz, CD_3Cl):	δ = 0.82 (d, J= 7.0 Hz, 3H), 0.93-0.98 (m, 1H, Methyl groups kinetic products) 1.26-1.31 (m, 4.7H), 1.41-1.97 (m, 12.5H), 2.07-2.31 (m, 2.6H), 2.40-2.44 (m, 2H), 2.89 (s, 0.22H, Alkyne-CH, kinetic product), 3.84-3.86 (m, 1H), 4.19 (q, J=7.1 Hz, 2.7H), 6.14 (bm, 0.09H, olefin CH-kinetic isomer), 6.17 (bm, 0.21H, olefin C-H other kinetic isomer), 6.68 (d, J=9.8Hz, 0.22H, acrylate C-H kinetic isomer), 6.95 (d, J=9.7Hz, 1H), 7.08 (d, 10.1Hz, 0.09H, other acrylate C-H kinetic isomer)

I V Alternative synthesis of Valerenic acid derivatives - diol route

I V.1 Towards the synthesis of trifluoromethyl-derivative

I V.1.1 (1S,7R,7aS)-7-(Hydroxymethyl)-4-(trifluoromethyl)-2,3,5,6,7,7a-hexahydro-1*H*-inden-1-ol **82**



52 **82**

$LiAlH_4$ (88.26mg, 3.00eqiv., 2.33mmol) was suspended in 5ml dry Et_2O and cooled to 0°C. Then lactone **52** (180.00mg, 1.00eqiv., 0.78mmol) dissolved in 5.7ml dry Et_2O was added slowly. After complete addition the mixture was allowed to warm to room temperature and stirred for 50 minutes. Then the mixture was again cooled to 0°C, 24ml dry Et_2O were added and the mixture was quenched upon addition of 300µl of water and 300µl of 0.5M NaOH solution. After stirring for ten minutes percipitates were filtered off through a short pad of celite and washed with EtOAc. The filtrate was dried with Na_2SO_4 before concentrated under vacuo. Purification via column chromatography (40g SiO_2, LP:EtOAc=2:1 to 1:1) delivered 169.0mg of diol **82** as a colorless solid.

Yield: 169.0mg (92%) colorless solid

Rf: 0.19 (LP:EtOAc=1:1)

Molecular Formula: $C_{11}H_{15}F_3O_2$

Molecular weight [g/mol]: 236.32

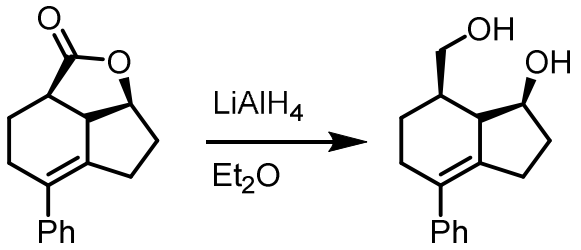
$[\alpha]_D^{20}$: n.d.

^{1}H-NMR (200 MHz, CD_3Cl): δ = 1.60- 1.93 (m, 4H, 5-CH_2+2-CH_2), 2.04-2.19 (m, 2H, 1-CH_2), 2.25-2.38 (m, 1H, 4-CH), 2.55-2.86 (m, 3H, 6-CH_2+3a-CH), 3.57-3.81 (m, 4H, 4'-CH_2+2xOH), 4.45 (t, J=3.2Hz, 1H, 3-CH)

^{13}C-NMR (50 MHz, CD_3Cl): n.d.

I V.2 Towards the synthesis of phenyl derivative

I V.2.1 (1S,7R,7aS)-7-(Hydroxymethyl)-4-phenyl-2,3,5,6,7,7a-hexahydro-1*H*-inden-1-ol **83**



60 **83**

$LiAlH_4$ (153.99mg, 3.00eqiv., 4.06mmol) was suspended in 6.9ml dry Et_2O and cooled to 0°C. Then lactone **60** (325.00mg, 1.00eqiv., 1.35mmol) dissolved in 17.2ml dry Et_2O was added slowly. After complete addition the mixture was left to warm to room temperature and stirred for 50 minutes. Then the mixture was recooled to 0°C, 24ml dry Et_2O were added and quenched upon addition of 300µl of water and 300µl of 0.5M NaOH solution. After stirring for ten minutes precipitates were filtered off through a short pad of celite and washed with EtOAc. The filtrate was dried with Na_2SO_4 before concentrated under vacuum. Purification via column chromatography (40g SiO_2, LP:EtOAc=2:1 to 1:1) delivered 327.0mg of diol **83** as a colorless solid.

Yield: 327.0mg (96%)

Rf: 0.15 (LP:EtOAc=1:1)

Melting Point: 85°C

Molecular Formula: $C_{16}H_{20}O_2$

Molecular weight [g/mol]: 244.33

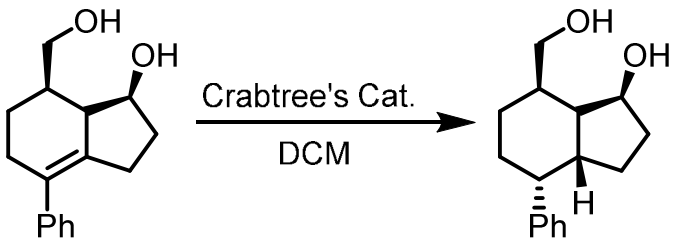
HRMS: calculated $(M+1)^+$= 245.1536, found $(M+1)^+$ = 245.1532

$[\alpha]_D^{20}$: +51.1° (c=0.57/100ml $CHCl_3$)

^{1}H-NMR (200 MHz, CD_3Cl): δ = 1.73-1.88 (m, 4H, 2-CH_2+5-CH_2), 2.25-2.63 (m, 6H), 3.32 (bs, 2H, 2xOH), 3.68 (dd, J_1 =10.8Hz, J_2=2.4Hz, 1H, 1H of 4'-CH_2), 3.91-4.01 (m, 1H, 1H of 4'-CH_2), 4.43-4.46 (m, 1H, 3-CH), 7.16-7.36 (m, 6H, 5x7'-ArCH+$CHCl_3$)

^{13}C-NMR (50 MHz, CD_3Cl): δ = 27.1 (t, 5-CH_2), 27.6 (t, 1-CH_2), 28.2 (t, 6-CH_2), 33.2(t, 2-CH_2), 36.8 (d, 4-CH), 50.2 (d, 3a-CH), 63.0 (t, 4'-CH_2), 73.7(d, 3-CH), 126.1 (d, 7'-ArCH), 127.5 (d, 7'-ArCH), 128.0 (d, 7'-ArCH), 129.8 (s, 7-C), 136.1 (s, 7a-C), 143.0 (s, 7'-C)

I V.2.2 (1S,3aR,4R,7R,7aR)-7-(Hydroxymethyl)-4-phenyloctahydro-1*H*-inden-1-ol **84**



83 **84**

En-diol **83** (30.00mg, 1.00eqiv., 0.12mmol) was dissolved in 5.3ml dry, degassed DCM. Hydrogen was bubbled through the solution for 5 minutes and subsequently cooled to 0°C. After addition of Crabtree's catalyst (6.40mg, 0.07eqiv., 0.01mmol) hydrogen was bubbled through the solution until the orange color disappeared (one minute). The mixture was warmed to room temperature and stirred for 20 hours. Then the solvent was evaporated and purification via column chromatography (10g SiO_2;LP:EtOAc=2:1 to 1:1) furnished 28.2mg of diol **84** as colorless solid

Yield: 28.2mg (93%)

Rf: 0.15 (LP:EtOAc=1:1)

Melting Point: 91°C

Molecular Formula: $C_{16}H_{22}O_2$

Molecular weight [g/mol]: 246.34

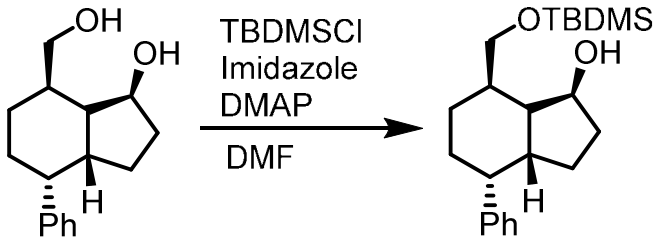
HRMS: calculated $(M-35)^+$= 211.1481, found $(M-35)^+$ = 211.1488

$[\alpha]_D^{20}$: +2.59° (c=1.10g/100ml $CHCl_3$)

^{1}H-NMR (400 MHz, CD_3Cl): δ = 1.08-1.18 (m, 1H, 3a-CH), 1.51-1.62 (m, 2H, 5-CH_2), 1.68-1.84 (m, 4H, 1-CH_2+2-CH_2), 1.93-2.04 (m, 2H, 6-CH_2), 2.35-2.37 (m, 1H, 4-CH), 2.56-2.66 (m, 1H, 7a-CH), 3.26-3.30 (m, 1H, 7-CH), 3.55 (dd, J_1 =11.0 Hz, J_2=2.4 Hz, 1H, 1H of 4'-CH_2), 4.14-4.29 (m, 4H, 2xOH+ 1H of 4'-CH_2+3-CH), 7.17-7.21 (m, 1H, 7'-ArH), 7-25-7.31 (m, 4H, 4x-7'ArH)

^{13}C-NMR (50 MHz, CD_3Cl): δ = 23.4 (t, 1-CH_2), 26.9 (t, 5-CH_2), 27.7 (t, 6-CH_2), 32.5 (t, 2-CH_2), 35.2 (d, 4-CH), 38.2 (d, 7a-CH), 41.8 (d, 3a-CH), 46.2 (d, 7-CH), 62.1 (t, 4'-CH_2), 73.4 (d, 3-CH), 125.2 (d, 7'-ArCH), 127.4 (d, 7'-ArCH), 128.9 (d, 7'-ArCH), 143.7 (s, 7-ArC)

I V.2.3 (1S,3aR,4R,7R,7aR)-7-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-phenyloctahydro-1*H*-inden-1-ol **85**



84 **85**

Imidazole (8.24mg, 1.10eqiv., 0.12mmol), DMAP (1.34mg, 010eqiv., 0.01mmol) and diol **84** (27.0mg, 1.00eqiv., 0.11mmol) were dissolved in 1.1ml dry DMF at room temperature under argon before 3M TBDMSCl solution in THF (40.30µl, 1.10eqiv., 0.12mmol) was slowly added. After stirring for 22 hours the reaction was quenched by addition of aqueous NH_4Cl and extracted with DCM (3x), washed with brine, dried with Na_2SO_4 and concentrated. Purification via column chromatography (10g SiO_2; LP:EtOAc= 10:1 to 5:1) delivered 32.5mg mono-protected **85** as a slightly yellow oil.

Yield: 32.5mg (82%)

Rf: 0.24 (LP:EtOAc=30:1)

Molecular Formula: $C_{22}H_{36}O_2Si$

Molecular weight [g/mol]: 360.61

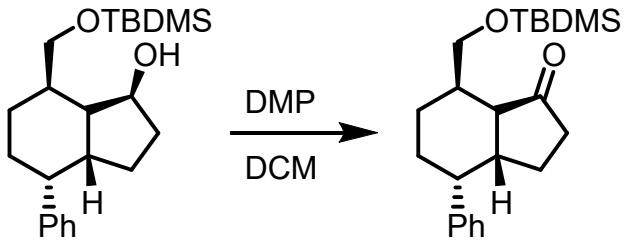
HRMS: calculated $(M-63)^+$= 297.2244, found $(M-63)^+$ = 297.2240

$[\alpha]_D^{20}$: n.d.

^{1}H-NMR (200 MHz, CD_3Cl): δ = 0.01 (m, 6H, 2xCH_3 of TBDMS), 0.79 (s, 9H, t-butyl of TBDMS), 0.89-1.20 (m, 3H, 3a-CH+5-CH_2), 1.35-1.94 (m, 9H), 2.13-2.17 (m, 1H, 4-CH), 2.39-2.58 (m, 1H, 7a-CH), 3.10-3.17 (m, 1H, 7-CH), 3.43 (dd, J_1 =10.8 Hz, J_2= 2.4Hz, 1H, 3-CH), 4.06-4.17 (m, 2H, 4'-CH_2), 4.81 (bs, 1H, 3'-OH), 7.05-7.19 (5H, 7'-ArH)

^{13}C-NMR (50 MHz, CD_3Cl): n.d.

I V.2.4 (3aR,4R,7R,7aR)-7-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-phenyloctahydro-1*H*-inden-1-one **<u>86</u>**



<u>85</u> **<u>86</u>**

TBDMS-protected **<u>85</u>** (18.0mg, 1.00eqiv., 0.05mmol) was dissolved in 0.5ml DCM before DMP 97% (26.20mg, 1.20eqiv., 0.06mmol) was added. After stirring for 50 minutes, the reaction was quenched with sat. $NaHCO_3$-solution and washed once with 10% sodiumsulfite solution. The aqueous phase was extracted with Et_2O (3x), washed once with 10% sodiumsulfite solution, once with brine and dried with Na_2SO_4 before concentrated in vacuo. Purification via chromatography on silica (10g SiO_2; LP:EtOAc=100:0 to 97:3) furnished 17.1 mg of ketone **<u>86</u>** as colorless oil.

Yield: 17.1mg (96%)

Rf: 0.38 (LP:EtOAc=30:1)

Molecular Formula: $C_{22}H_{34}O_2Si$

Molecular weight [g/mol]: 358.60

$[\alpha]_D^{20}$: n.d.

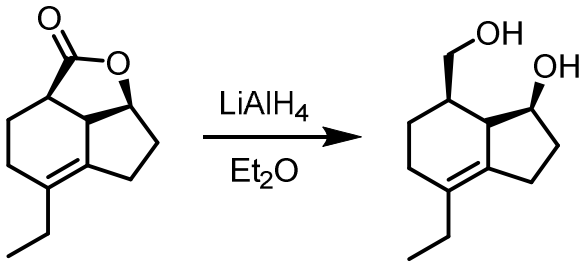
^{1}H-NMR (200 MHz, CD_3Cl): δ = 0.01 (m, 6H, 2xCH_3 of TBDMS), 0.85 (s, 9H, t-butyl of TBDMS), 0.89-1.17 (m, 1H), 1.74-2.18 (m, 10H), 3.25-3.29 (m, 1H,7-CH), 3.55-3.74(m, 2H, 4'-CH_2), 7.17-7.27 (m, 5H, 7'-ArH)

^{13}C-NMR (50 MHz, CD_3Cl): n.d.

I V.3 Alternative synthesis of 7-Ethyl-valerenic acid 69

Lactone **34** was prepared as prior described described (see I III.2.2)

I V.3.1 (1S,7R,7aS)-4-Ethyl-7-(hydroxymethyl)-2,3,5,6,7,7a-hexahydro-1*H*-inden-1-ol **87**



34 **87**

$LiALH_4$ (473.80mg, 3.00eqiv., 12.48mmol) was suspended in 21.6ml dry Et_2O then lactone **34** (800.00mg, 1.00eqiv., 4.16mmol) was added in 20ml dry Et_2O at 0°C. After the mixture was warmed to room temperature stirring was continued for 1 hour. After cooling again to 0°C the reaction was quenched with 1ml water and 100µl of 2N NaOH. The mixture was filtered through a short pad of celite and washed with EtOAc. The organic filtrate was dried with Na_2SO_4, filtered and concentrated. Purification via column chromatography (90g SiO_2; LP:EtOAc= 2:1 to 1:1) furnished 804.3mg diol **87** as a colorless solid.

Yield: 804.30mg (99%) colorless solid

Rf: 0.29 (LP:EtOAc=3:1)

Melting point: 78-79°C

Molecular Formula: $C_{12}H_{20}O_2$

Molecular weight [g/mol]: 196.29

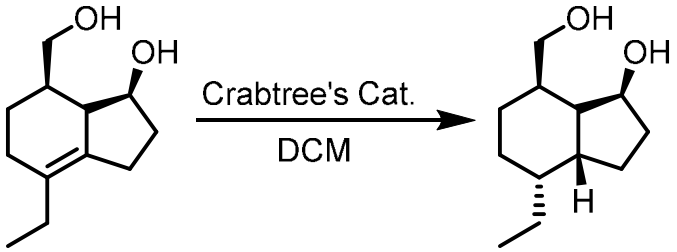
HRMS: calculated $(M+1)^+$= 197.1542, found $(M+1)^+$ = 197.1546

$[\alpha]_D^{20}$: +36.5° (c=0.32g/100ml DCM)

^{1}H-NMR (400 MHz, CD_3Cl): δ = 0.88 (t, J=7.6Hz, 3H, 7'-CH_3), 1.46-1.95 (m, 9H), 2.14-2.46 (m, 3H, 7a-CH+1 CH_2), 3.37-3.43 (m, 1H, 3-CH), 3.58-3.69 (m, 1H, 1H of 4'-CH_2), 4.24-4.28 (m, 1H, 1H of 4'-CH_2), 4.74 (bs, 2H, 2xOH)

^{13}C-NMR (50 MHz, CD_3Cl): δ = 12.1 (q, 7'-CH_3), 24.5 (t, 5-CH_2), 25.5 (t, 1-CH_2), 26.6 (t, 7'-CH_2), 28.2 (t, 6-CH_2), 33.0 (t, 2-CH_2), 36.8 (d, 4-CH), 49.6 (d, 3a-CH), 62.5 (t, 4'-CH_2), 73.9 (d, 3-CH), 130.0 (s, 7-C), 131.4 (s, 7a-C)

I V.3.2 (1S,3aR,4R,7R,7aR)-4-ethyl-7-(hydroxymethyl)-octahydro-1*H*-inden-1-ol **88**



87 **88**

En-diol **87** (500mg, 1.00eqiv., 2.55mmol) was dissolved in 103 ml dry, degassed DCM. Hydrogen was bubbled through the solution (5 minutes) before it was cooled to 0°C and Crabtree's Catalyst (133.30mg, 0.07eqiv., 0.17mmol) was added. Again hydrogen was bubbled through the solution until the orange color disappeared (one minute). The mixture was allowed to warm to room temperature and stirred for 19h. Argon was bubbled through the solution and the solvent was evaporated. Finally purification via column chromatography (40g SiO_2; LP:EE=2:1 to 1:1) yielded 466.4 mg of diol **88** as a colorless solid.

Yield: 466.40mg (93%)

Rf: 0.29 (LP:EtOAc=3:1)

Melting point: 90-91°C

Molecular Formula: $C_{12}H_{22}O_2$

Molecular weight [g/mol]: 198.32

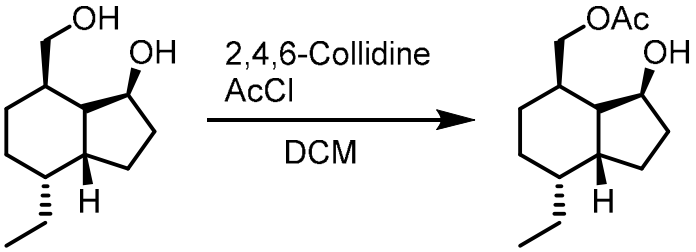
HRMS: calculated $(M+1)^+$= 199.1698 found $(M-63)^+$ = 199.1704

$[\alpha]_D^{20}$: +5.61° (0.11g/100ml DCM)

^{1}H-NMR (200 MHz, CD_3Cl): δ = 0.88 (t, J=7.3Hz, 3H, 7'-CH_3), 1.15-1.86 (m, 12H), 2.13-2.18 (m, 1H, 7-CH), 2.27-2.45 (m, 1H, 4-CH), 3.44-3.49 (m, 1H, 3-CH), 4.09 (t, J=10.6 Hz, 1H, 1H of 4'-CH_2), 4.24 (t, J=3.5 Hz, 1H, 1H of 4'-CH_2), 4.85 (bs, 2H, 2xOH)

^{13}C-NMR (50 MHz, CD_3Cl): δ = 12.9 (q, 7'-CH_3), 17.1 (t, 7'-CH_2), 22.9 (t, 1-CH_2), 24.7 (t, 5-CH_2), 25.6 (t, 6-CH_2), 33.2 (t, 2-CH_2), 36.8 (d, 4-CH), 37.6 (d, 7-CH), 39.0 (d, 7a-CH), 46.2 (d, 3a-CH), 62.7 (t, 4'-CH_2), 74.3 (d, 3-CH)

I V.3.3 ((3S,3aR,4R,7R,7aR)-7-ethyl-3-hydroxyoctahydro-1*H*-inden-4-yl)methyl acetate **89**



88 **89**

Diol **88** (200.00mg, 1.00eqiv., 1.01mmol) was dissolved in 10.1ml dry DCM. 2,4,6-Collidine (159.90µl, 1.20eqiv., 1.21mmol) was added and the mixture was cooled to -78°C. Then acetyl chloride (79.30µl, 1.10eqiv., 1.11mmol) was added dropwise and the mixture was stirred at this temperature for 6 hours before left to warm to room temperature overnight. The mixture was quenched by the addition of 2N aqueous HCl and extracted with Et_2O three times before washed with brine, dried with Na_2SO_4, filtered and concentrated in vacuo. Purification via column chromatography (20g SiO_2, LP:EtOAc=6:1 to 3:1) delivered 173.9mg of mono-acetylated diol **89** as colorless solid.

Yield: 173.90 (72%)

Rf: 0.34 (LP:EtOAc=4:1)

Melting point: 61-62°C

Molecular Formula: $C_{14}H_{24}O_3$

Molecular weight [g/mol]: 240.34

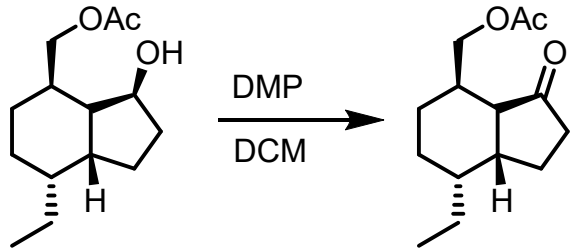
HRMS: calculated $(M+1)^+$= 241.1804 found $(M+1)^+$ = 241.1816

$[\alpha]_D^{20}$: -8.25° (c=0.31g/100ml DCM)

^{1}H-NMR (400 MHz, CD_2Cl_2): δ = 0.81 (t, J=7.4Hz, 3H, 7'-CH_3), 1.03-1.20 (m, 1H, 7a-CH), 1.23-1.78 (m, 11H), 1.94 (s, 3H, Acetyl CH_3), 2.08-2.19 (m, 2H), 4.15-4.19 (m, 2H, 4'-CH_2), 4.44 (dd, J_1 =11.3 Hz, J_2=6.6 Hz, 1H, 3-CH)

^{13}C-NMR (50 MHz, CD_2Cl_2): δ = 12.7 (q, 7'-CH_3), 17.2 (t, 7'-CH_2), 20.9 (q, Acetyl-CH_3), 23.4 (t, 1-CH_2), 23.6 (t, 5-CH_2), 23.7 (t, 2-CH_2), 34.0 (t, 6-CH_2), 35.6 (d, 4-CH), 37.4 (d, 7-CH), 37.6 (d, 7a-CH), 45.7 (d, 3a-CH), 64.3 (t, 4'-CH_2), 75.0 (d, 3-CH), 170.6 (s, Acetyl-CO)

I V.3.4 ((3S,3aR,4R,7R,7aR)-7-ethyl-3-oxooctahydro-1*H*-inden-4-yl)methyl acetate **90**



89 **90**

Acetate protected alcohol **89** (135.90mg, 1.00eqiv., 0.57mmol) was dissolved in 1.8ml DCM at room temperature before DMP (273.40mg, 1.14eqiv., 0.65mmol) was added at once. After one hour the mixture was quenched with $NaHCO_3/Na_2SO_3$ mixture and extracted with ether (3x). The combined organic extracts were washed with brine, dried with Na_2SO_4, filtered and concentrated in vacuo. Purification via column chromatography (20g SiO_2; LP:EtOAc=4:1) delivered 100.7mg ketone **90** as a colorless oil.

Yield: 100.70 (75%) colorless oil

Rf: 0.41 (LP:EtOAc=4:1)

Molecular Formula: $C_{14}H_{22}O_3$

Molecular weight [g/mol]: 238.33

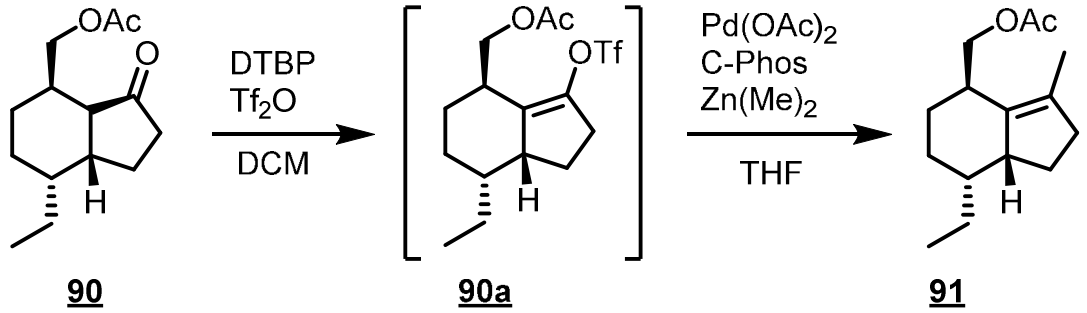
HRMS: calculated $(M+1)^+$= 239.1647 found $(M+1)^+$ = 239.1667

$[\alpha]_D^{20}$: -175.12° (c=0.42g/100ml DCM)

^{1}H-NMR (400 MHz, CD_2Cl_2): δ = 0.97 (t, J=7.4 Hz, 3H, 7'-CH_3), 1.28-1.68 (m, 7H), 1.84-1.90 (m, 2H), 1.98-2.10 (m, 6H), 2.26-2.32 (m, 1H, 1H of 2-CH_2), 2.52-2.53 (m, 1H, 1 H of2-CH), 3.99-4.03 (m, 1H, 1H of 4'-CH_2), 4.11-4.16 (m, 1H, 1-H of 4'-CH_2)

^{13}C-NMR (50 MHz, CD_2Cl_2): δ = 12.3 (q, 7'-CH_3), 17.2 (t, 7'-CH_2), 20.7 (q, acetyl CH_3), 21.2 (t, 5-CH_2), 23.0 (t, 1-CH_2), 23.8 (t, 6-CH_2), 32.1 (t, 2-CH_2), 37.8 (d, 4-CH), 38.0 (t, 7a-CH), 40.8 (d, 7-CH), 50.0 (d, 3a-CH), 61.2 (t, 4'-CH_2), 170.9 (s, acetyl-CO), 217.3 (s, 3-CO)

I V.3.5 ((4R,7R,7aR)-7-ethyl-3-methyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)methyl acetate **91**



90 **90a** **91**

Acetate protected ketone **90** (250.00mg, 1.00eqiv., 1.05mmol) was dissolved in 20ml dry DCM and cooled to 0°C before DTBP (316.00µl, 1.30eqiv., 1.36mmol) was added. The mixture was stirred for 5 minutes before triflic anhydride (203.20µl, 1.15eqiv., 1.21mmol) was added and the mixture was left to warm to room temperature before stirred for 23 hours. Then 250ml pentane was added, the precipitate removed via celite-filtration and the solvent was evaporated. The crude enol-triflate **90a** was dissolved in 18ml dry THF and added to a solution of $Pd(OAc)_2$ (23.60mg, 0.10 eqiv., 0.11mmol) and C-Phos (91.7mg, 0.20eqiv., 0.21mmol) dissolved in 2ml dry THF at 0°C. After 5 minutes of stirring 1M dimethylzinc solution in heptane (2.10ml, 2.00eqiv., 2.10mmol) was added dropwise. Then the mixture was warmed to room temperature and stirred for two hours, before being recooled to 0°C and quenched with aqueous NH_4Cl solution. The aqueous layer was extracted with Et_2O (3x), washed with brine, dried with Na_2SO_4, filtered and the solvent evaporated. The crude mixture of isomers was purified via column chromatography (20g 10% $AgNO_3$-doped SiO_2; Heptane:EtOAc=100:0 to 99:1) and yielded 161.6 mg of acetate **91** as a single isomer appearing as a colorless oil.

Yield: 161.6mg (62%) colorless oil

Rf: 0.24 (LP:EtOAc=50:1)

Molecular Formula: $C_{15}H_{24}O_2$

Molecular weight [g/mol]: 236.36

HRMS: calculated $(M+1)^+$= 237.1855 found $(M+1)^+$ = 237.1869

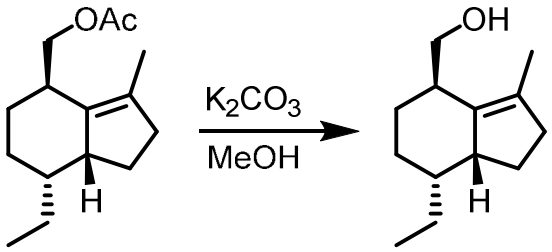
$[\alpha]_D^{20}$: -90.3° (c=0.88g/100ml DCM)

^{1}H-NMR (400 MHz, CD_2Cl_2): δ = 0.87 (t, J=7.4 Hz, 3H, 7'-CH_3), 1.08-1.17 (m, 1H, 1H of 5-CH_2), 1.31-1.39 (m, 1H, 1H of 5-CH_2), 1.50-1.58 (m, 9H), 1.79-1.89 (m,

1H), 2.02 (s, 3H, acetyl-CH_3), 2.22-2.26 (m, 2H, 4-CH+7a-CH), 2.89-2.90 (m, 2H, 2-CH_2), 4.03-4.12 (m, 2H, 4'-CH_2)

^{13}C-NMR (50 MHz, CD_2Cl_2): δ = 11.8 (q, 7'-CH_3), 13.0 (q, 3'-CH_3), 17.1 (t, 7'-CH_3), 20.7 (t, 1-CH_2), 20.7 (q, acetyl-CH_3), 23.5 (t, 5-CH_2), 24.0 (t, 6-CH_2), 33.8 (d, 7-CH), 37.5 (t, 2-CH_2), 40.0 (d, 4-CH), 48.1 (d, 7a-CH), 64.6 (t, 4'-CH_2), 132.2 (s, 3-C), 132.9 (s, 3a-C), 170.6 (s, acetyl-CO)

I V.3.6 ((4R,7R,7aR)-7-ethyl-3-methyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)methanol **92**



91 **92**

Acetate **91** (139.00mg, 1.00eqiv., 0.59mmol) was dissolved in 5.9ml dry methanol before K_2CO_3 (91.20mg, 1.10eqiv. 0.66mmol) was added. The suspension was then stirred overnight at room temperature. The resulting solution was quenched with NH_4Cl and extracted with DCM, washed with brine, dried with Na_2SO_4 and filtered. Evaporation of the solvent furnished 112.2mg of alcohol **92** as a colorless solid.

Yield: 161.6mg (98%) colorless solid

Rf: 0.45 (LP:EtOAc=4:1)

Melting point: 77-78°C

Molecular Formula: $C_{13}H_{22}O$

Molecular weight [g/mol]: 194.32

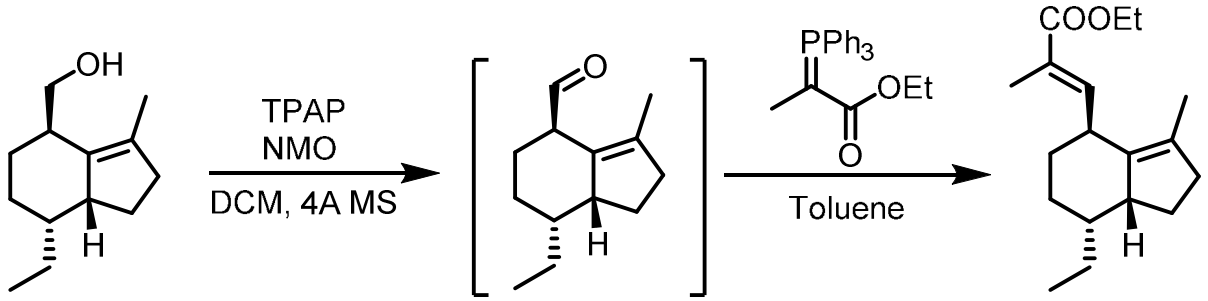
HRMS: calculated $(M+1)^+$= 195.1749 found $(M+1)^+$ = 195.1751

$[\alpha]_D^{20}$: -77.9° (c=0.49g/100ml DCM)

^{1}H-NMR (200 MHz, CD_2Cl_2): δ = 0.85 (t, J=7.4Hz, 3H, 7'-CH_3), 1.07-1.93 (m, 13H), 2.21-2.29 (m, 2H, 4-CH+7a-CH), 2.67-2.77 (m, 1H, 1H of 2-CH_2), 2.85-3.00 (m, 1H, 1H of 2-CH_2), 3.43-3.64 (m, 2H, 4'-CH_2)

^{13}C-NMR (50 MHz, CD_2Cl_2): δ = 12.1 (q, 7'-CH_3), 13.5 (q, 3'-CH_3), 17.4 (t, 7'-CH_2), 21.4 (t, 1-CH_2), 24.1 (t, 5-CH_2), 24.4 (t, 6-CH_2), 37.7 (d, 7-CH), 38.1 (t, 2-CH_2), 40.9 (d, 4-CH), 48.2 (d, 7a-CH), 63.6 (t, 4'-CH_2), 133.7 (s, 3-C), 133.9 (s, 3a-C)

I V.3.7 7-Ethyl-Valerenic acid ester **40**



92 **93** **40**

Alcohol **92** (66.30mg, 1.00eqiv., 0.34mmol), TPAP (6.00mg, 0.05eqiv., 0.02mmol) and 68.2mg powdered, activated 4Å molecular sieves were suspended in 3.4ml dry DCM. The mixture was stirred for 10 minutes before NMO (59.90mg, 1.50eqiv., 0.51mmol) was added and then stirred for 30 minutes. After the oxidation was complete the mixture was diluted with 50 ml Et_2O and subsequently washed with sodiumsulfite solution (2x), followed by aqueous $Cu(II)SO_4$- solution (2x). Finally the organic layer was washed with brine, dried with Na_2SO_4, filtered and the solvent evaporated (30°C/700mbar; aldehyde **93** is volatile!). The crude brownish oil was then filtered through a short plug of DMT-doped silica, furnishing a slightly yellow oil upon evaporation of the solvent. The crude concentrate was dissolved in 2.1ml dry toluene and (1-ethoxycarbonylethyliden)-triphenylphosphorane (494.30mg, 4.00eqiv., 1.36mmol) was added. Then the mixture was heated to 140°C for 10 minutes in the microwave. After complete conversion, the mixture was evaporated on silica before subjected to column chromatography (5g SiO_2; Heptane:EtOAc=99:1 to 98:2). Finally 48.4mg of 7-ethyl-valerenic acid ester **40** was obtained as a colorless oil.

Yield: 48.4 (51%) colorless oil

Molecular Formula: $C_{18}H_{28}O$

Molecular weight [g/mol]: 276.42

^{1}H-NMR (200 MHz, CD_2Cl_2): matched the reported shifts in chapter I III.2.6

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