The first stereoselective syntheses of (all-*Z*)-hentriaconta-3,6,9,12,15,19,22,25,28-nonaene and obscuraminol A, two polyunsaturated natural products

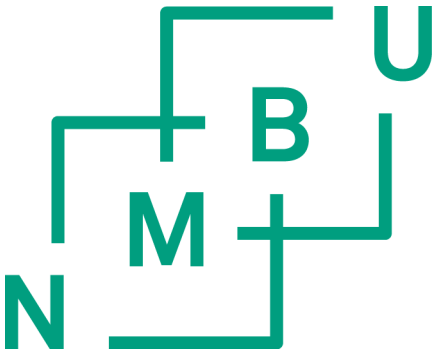
Første stereoselektive syntese av (all-*Z*)-hentriaconta-3,6,9,12,15,19,22,25,28-nonaen og obscuraminol A, to polyumettede naturprodukter

Philosophiae Doctor (PhD) Thesis

Liudmila Filippova

Department of Chemistry, Biotechnology and Food Science
Faculty of Veterinary Medicine and Bioscience
Norwegian University of Life Sciences

Ås 2015



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Liudmila Filippova

Ås, July 2015

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List of publications and manuscript

I. *An asymmetric iodolactonization reaction catalyzed by a zinc bis-proline phenol complex*
Liudmila Filippova, Yngve Stenstrøm, Trond Vidar Hansen, *Tetrahedron Lett***.** **2014**, *55*, 419-422.

II. *Stereoselective synthesis of (all-Z)-hentriaconta-3,6,9,12,15,19,22,25,28-nonaene*
Liudmila Filippova, Ida Aarum, Martine Ringdal, Martin Kirkus Dahl, Trond Vidar Hansen, Yngve Stenstrøm, *Org. Biomol. Chem*. **2015**, *13*, 4680-4685.

III. *Cu(II)-catalyzed asymmetric Henry reaction with a novel C_1-symmetric aminopinane-derived ligand*
Liudmila Filippova, Yngve Stentrøm, Trond Vidar Hansen, *Molecules* **2015**, *20*, 6224-6236.

IV. *Synthetic study towards obscuraminol A using an enantioselective Henry reaction*
Liudmila Filippova, Trond Vidar Hansen, Yngve Stentrøm, Manuscript.

Abstract

The research described herein focuses on stereoselective synthesis of some *Z*-polyenoic natural products, making them available for biological studies. The objectives of the study can be subdivided into three parts integrated by a general idea of using eicosapentaenoic acid (EPA- ethyl ester) as the starting material for syntheses. The particular attention is paid to development of enantioselective approaches.

The iodolactonization reaction, a useful synthetic tool widely employed in natural product synthesis, is especially attractive in its asymmetric version. In the first part of the thesis a new enantioselective protocol for iodolactonization of 1,1-disubstituted δ-olefinic acids was introduced. The employment of a dinuclear zinc *bis*-proline phenol complex as a catalyst provides entry to iodolactones with good yields and up to 83% ee.

In the second part of this work the total stereoselective synthesis of the bacterial very long-chain hydrocarbon metabolite, all-*Z*-hentriaconta-3,6,9,12,15,19,22,25,28-nonaene, has been described. Based on *Z*-selective Wittig reaction as the key step, the synthesis confirmed the all-*Z* configuration of the compound. This is the first reported total synthesis of all-*Z*-hentriaconta-3,6,9,12,15,19,22,25,28-nonaene.

The last part presents the first total synthesis of the polyunsaturated amino-alcohol obscuraminol A, based on the use of a diastereoselective Henry reaction. The samarium (II) iodide promoted reduction of the intermediate nitro-alcohol was utilized for the first time in total synthesis of natural product. An attempt to develop a new enantioselective Henry protocol is also described. The aminopinane-derived C_1-symmetric ligand in complex with copper (II) salts can catalyze the nitroaldol reaction between aliphatic and aromatic aldehydes with nitromethane with yields up to 97% and moderate enantioselectivities up to 67%.

Sammendrag

Forskningen som er beskrevet i denne avhandlingen fokuserer på stereoselektiv syntese av noen Z-polyalken naturprodukter for å gjøre disse tilgjengelige for biologiske studier. Målene for undersøkelsen kan deles inn tre deler som bindes sammen med ved at eikosapentaensyreetylester (EPA-etylester) benyttes som startmateriale for syntesene.

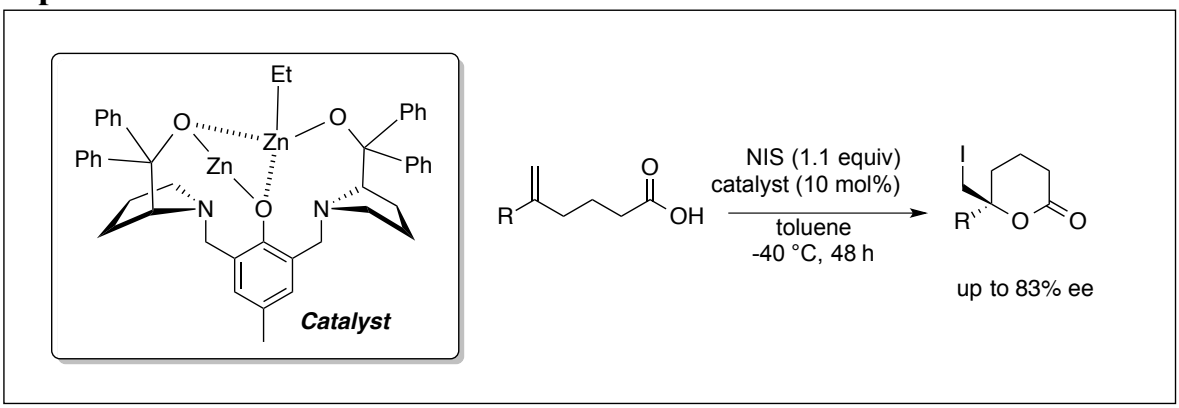
Jodlaktoniserinsreaksjonen som benyttes, er et nyttig syntetisk verktøy som anvendes i stor utstrekning i syntesen naturprodukter, og vil være spesielt interessant i en asymmetrisk versjon. I den første delen av oppgaven beskrives en ny, enantioselektiv protokoll for jodlaktonisering av 1,1-disubstituerte δ-olefiniske syrer. Anvendelse av et tokjerne sink-bis-prolin-fenol kompleks som katalysator gir jodlaktoner med gode utbytter og opptil 83% ee.

I den andre del av dette arbeidet beskrives en stereoselektiv totalsyntese av et polyumettet, langkjedet hydrokarbon, all-Z-hentriaconta-3,6,9,12,15,19,22,25,28-nonaen, som er rapportert å være en bakterie metabolitt. Syntesen ble vellykket utført ved en *Z*-selektiv Wittig-reaksjon som nøkkeltrinn. Syntesen bekreftet all-*Z* konfigurasjonen av forbindelsen. Dette er den første rapporterte totalsyntesen av all-*Z*-hentriaconta-3,6,9,12,15,19,22,25,28-nonaen.

Den siste delen av avhandlingen beskriver den første totalsyntesen av den flerumettede amino-alkoholen obscuraminol A. Syntesen benytter en diastereoselektiv Henry reaksjon som nøkkeltrinn. En samarium(II)jodid-basert reduksjon av mellomproduktet, en nitro-alkohol, ble for første gang benyttet i totalsyntesen av et naturprodukt. Et forsøk på å utvikle en ny enantioselektiv protokoll for Henry-reaksjonen er også beskrevet. Et kompleks av en aminopinan-avledet C1-symmetrisk ligand og et kobber(II)salt katalyserer nitroaldol-reaksjonen mellom alifatiske eller aromatiske aldehyder og nitrometan med utbytter opp til 97% og en moderat enantioselektivitet på opp til 67%.

Graphical abstracts

Paper I:



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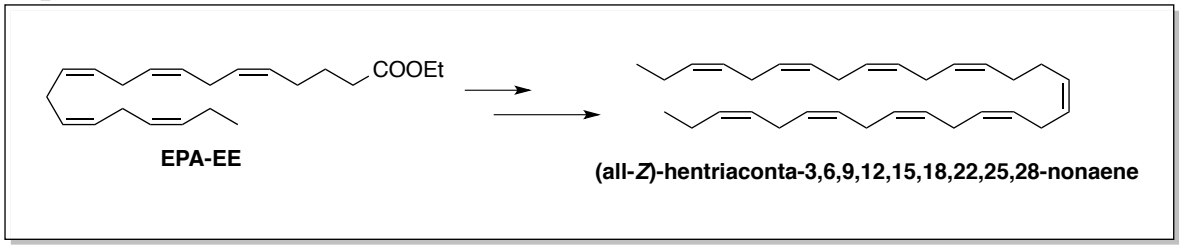

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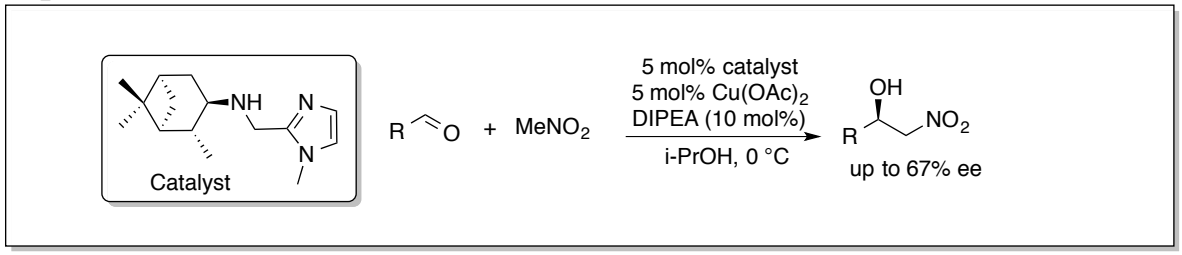

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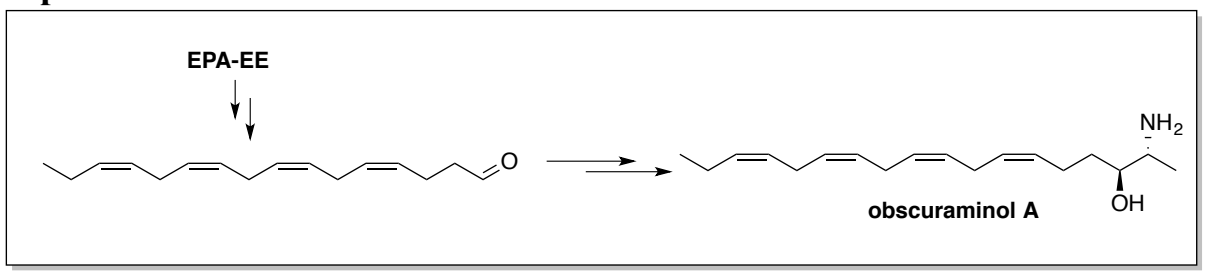


Abbreviations

AA	Arachidonic acid
ALA	*Alpha*-linolenic acid
BINOL	Bi-2-naphthol
COX	Cyclooxygenase
CYP	Cytochrome P450
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DGLA	Dihomo-*gamma*-linoleleic
DHA	Docosahexaenoic acid
DIBAL-H	Diisobutyl aluminium hydride
DIPEA	Diisopropylethylamine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DPA	Docosapentaenoic acid
dr	Diastereomeric ratio
ee	Enantiomeric excess
EPA	Eicosapentaenoic acid
EPA-EE	Ethyl ester eicosapentaenoate
EpDHE	Epoxydocosapentaenoic acid
EpEHE	Epoxyeisocatetraenoic acid
ETA	Eicosatetraenoic acid
GC	Gas chromatography
GLA	*Gamma*-linoleic acid
FTIR	Fourier transform infrared spectroscopy
HDHA	Hydroxydocosahexaenoic acid
HETE	Hydroxyeicosatetraenoic acid
HEPE	Hydroxyeicosapenaenoic acid
HMPA	Hexamethylphosphoramide
HpDHA	Hydroperoxydocosahexaenoic acid
HpEPE	Hydropepoxyeicosapentaenoic acid
HpETE	Hydroperixyeicosatetraenoic acid
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
LA	Linoleic acid

LC	Long chain
LDA	Lithium diisopropyl amine
LM	Lipid mediator
LO	Lipooxygenase
LT	Leukotriene
LX	Lipoxin
MaR	Maresin 1
NaHDMS	Sodium *bis*(trimethylsilyl)amide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosucciimide
NMR	Nuclear magnetic resonance
NOESY	Nuclear overhouser effect spectroscopy
PD	Protectin D
PG	Prostaglandin
PPAR	Peroxisome proliferator activator receptor
PUHC	Polyunsaturated hydrocarbon
PUFA	Polyunsaturated fatty acid
ROESY	Rotating overhouser effect spectroscopy
rt	Room temperature
Rv	Resolvin
SDA	Stearidonic acid
SPM	Special resolving mediator
THF	Tetrahydrofuran
TMS	Trimethylsilyl

1 Introduction

Natural products of diverse biosynthetic origin have been the most important source of useful substances for development of new drugs for instance as anti-tumor, anti-bacterial and anti-fungal agents.[1] However, the possible application of bioactive natural products is not limited to drug design, but can also be found in nutrition supplements and cosmeceuticals.[2]

Lipids are a large class of natural products originally defined by its solubility in non-polar organic solvents like hexane, but it is also defined by its general hydrophobic and amphipathic nature. Due to this loose definition, the structural diversity of this class of compounds is large, spanning from fatty acids, phospholipids, triglycerides, through terpenes, steroids and waxes. A more restricted and specific definition more commonly used today, is based on the biosynthesis of these where two fundamental building blocks is used, *i.e.* ketoacyl thioesters and/or isoprene units.[3] Using this more recent definition, lipids are commonly divided into eight subgroups: fatty acids, sphingolipids, glycerolipids, glycerophospholipids, saccharolipids, polyketides, steroids and prenol lipids.[4] Extensive studies over the past decades have revealed the broad spectrum of their biological functions in living organisms. One of the real basic role is energy storage. In addition, they are essential parts of cell and organelle membranes. Furthermore, they participate in biological signals transmission, and especially in this context, many compounds of very high biological activity can be found.[3] Polyunsaturated fatty acids (PUFAs) present a special class of lipids of crucial importance for biological systems.[4] PUFAs, their derivatives and many secondary metabolites structurally related to them, possess a wide diversity of interesting biological activities and can be potentially useful as starting materials in drug design programs.[5]

For a detailed investigation of bioactivities, the samples of any individual natural product are required in quantities sufficient for performing biological screening. However, the natural PUFA-derivatives and bioregulators structurally related to them are not always available for this, mainly due to low content, difficulties in isolation or inaccessibility of the organisms themselves. For these reasons, alone synthesis of the natural products is important. Synthesis may also be necessary to prove exact structures of natural products. In addition, based on general strategies, synthesis of analogs improving the biological activities is also an issue.

1.1 Polyunsaturated fatty acids, their sources and health benefits

The PUFAs in a broad context are fatty acids containing more than one double bond in their structures. In this thesis, the term PUFA mainly refer to essential fatty acids of the ω-6 and ω-3 families, containing multiple methylene interrupted *Z*-double bonds and derived biosynthetically from *cis*-linoleic (LA, **1**) and α-linolenic (ALA, **2**) acids respectively.[6, 7] A special attention has been paid to the long chain (LC) ω-3 eicosapentaenoic (EPA, **4**) and docosahexaenoic (DHA, **6**) acids (Figure 1.1).

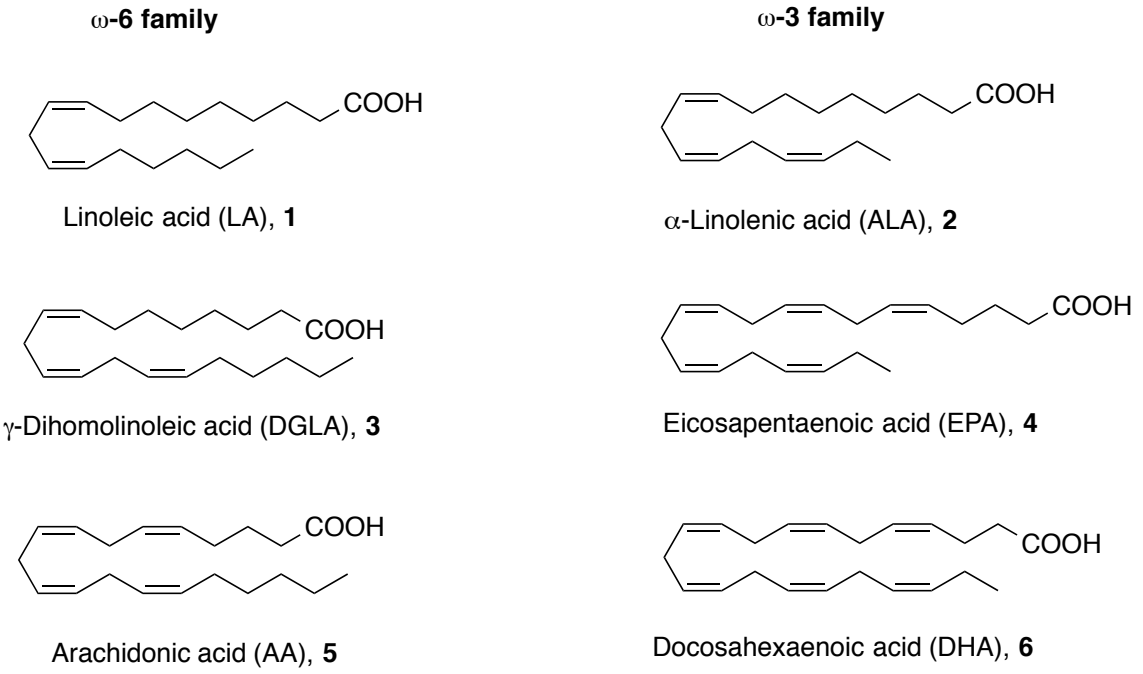


Figure 1.1 The chemical structures of ω-6 and ω-3 families PUFAs.

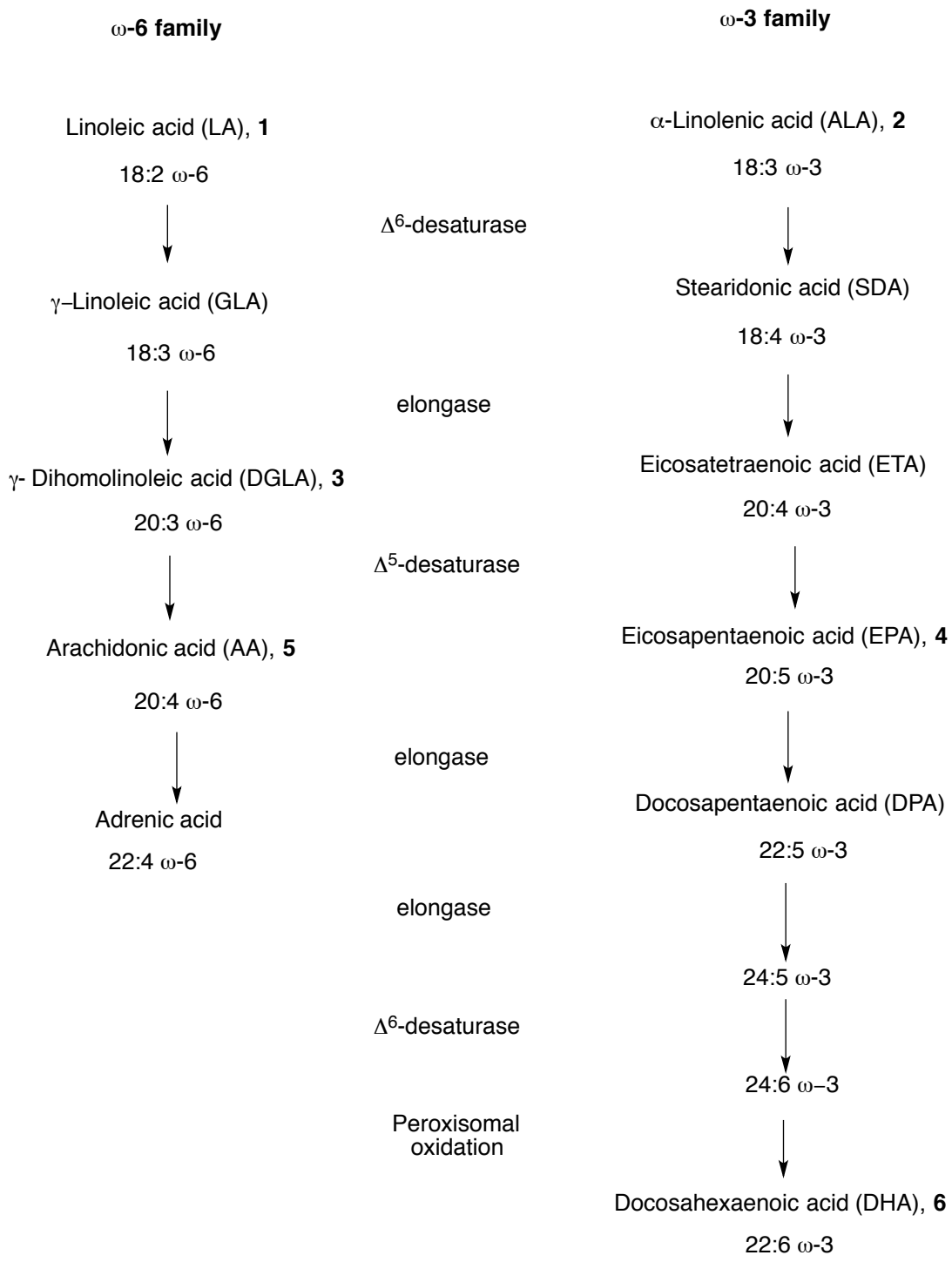
The ω-6 PUFAs and ALA are widely distributed in nature, mainly in plant oils, whereas the LC ω-3 PUFAs are obtained from marine sources, predominantly fish oils. The global market of LC ω-3 PUFAs has abruptly increased over the past decades and there seem to be a further growth that is connected to consumers increased awareness of the essential role ω-3 PUFAs has in nutrition.

The boomed interest to fatty acid profile of dietary fats has its beginning in the 1980s, succeeding the publication of the results on epidemiologic studies of Greenland Eskimos and their low level of cardiovascular diseases (atherosclerosis, coronary heart disease)[8] and some autoimmune diseases.[9] This was linked to the high consumption of fish oils among the native population in these areas. Comparing the blood serum of the indigenous Greenland population with Danes a high content EPA and DHA acids was found. These fatty acids are

recognized as biomarkers of high fish intake, especially when connected to a low concentration of arachidonic (AA, **5**) and linoleic acids.[10] Following these findings, a plethora of health-promoting effects were reported to be in close association with high ω-3 LC PUFAs intake. In particular, they are found to mediate anti-inflammatory,[11] anti-bacterial,[12] anti-cancer,[13] hypolipidemic, anti-arrhythmic and anti-aggregative activity[14] in addition to some other effects.[15] More recent findings revealed that ω-3 LC PUFAs, in particular DHA, affect behavioral patterns and are beneficial against mental disorders,[16] including depression, schizophrenia,[17] Alzheimeir´s disease and dementia.[18]

Humans have the necessary enzymes for conversion of essential dietary ALA to its higher analogs that is proven in stable-isotope-tracer studies.[19] (Scheme 1.1) However, the capability for biosynthesis of DHA in man is limited, and differs depending on gender, age[20] and, as discovered recently, genetic variability.[21] Moreover, ALA and LA compete for the same reaction rate-limiting Δ^5 and Δ^6 desaturase enzymes (Scheme 1.1). Therefore, the excess of fatty acids of one family inhibits the biosynthesis of LC PUFAs of the other family. At the same time, the Western type diet is strongly misbalanced to excess of ω-6 PUFAs. Notably, DHA is the major PUFA component of the brain and retina,[22, 23] essential for maintaining normal proper neurological and visual functions. There are crucial periods for accumulation of DHA in tissues during fetal and postnatal period, the deficiency of which can lead to visual disabilities.[24]

The numerous clinical trials have provided evidence of positive role of ω-3 LC PUFAs in prevention of cardiovascular,[25, 26] inflammation and autoimmune diseases, including allergy and bronchial asthma,[27] rheumatoid arthritis[28] and diabetes.[29, 30] These beneficial effects, easy availability and safety make EPA and DHA attractive as potential pharmaceuticals and nutrition supplements.



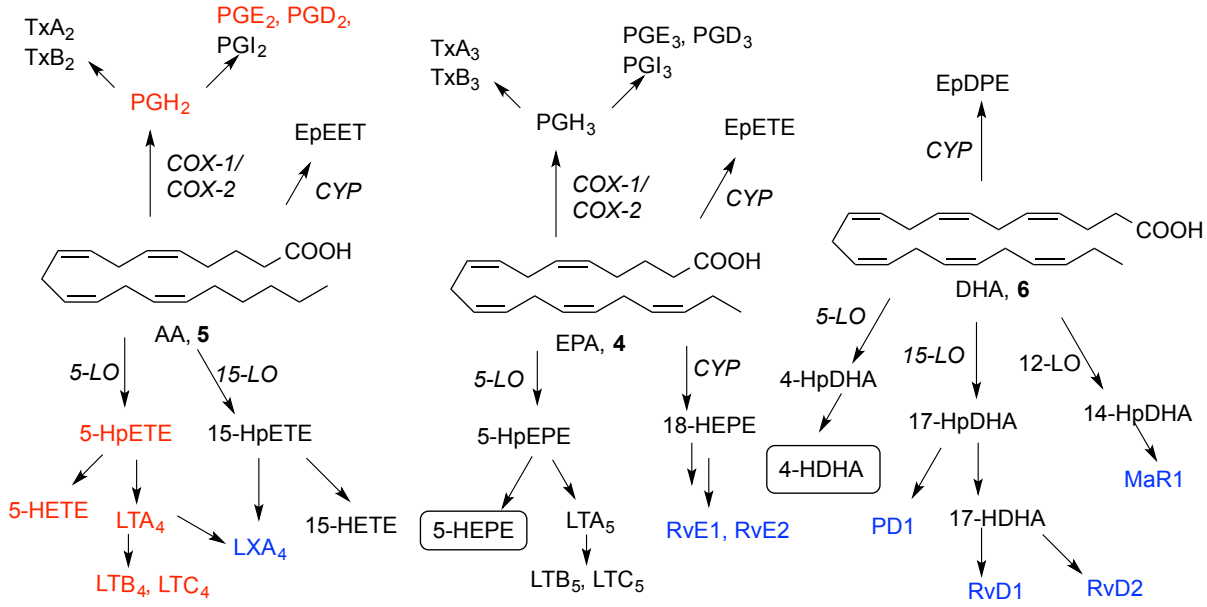
Scheme 1.1 Biosynthesis of LC PUFAs from ALA and LA.

1.2 Oxygenated PUFA metabolites

The enzymatic and non-enzymatic oxidation of intracellular free PUFAs, released enzymatically from membrane phospholipids, results in hundreds of biologically active oxygenated metabolites (lipid mediators, LM). These LMs are involved in regulation of a wide array of physiological and pathological processes including immune responses,

inflammation, cell proliferation and angiogenesis.[31, 32] There are three main enzymatic pathways for generation of oxygenated species catalyzed by cyclooxygenase (COX), lipoxygenase (LO) and cytochrome P450 (CYP) isoforms (Scheme 1.2).

The standard explanation for the beneficial effects of LC ω-3 PUFAs is linked to the alterations in the overall balance of LMs. It is widely recognized that most of chronic diseases, including cancer, originates from inflammatory disorders.[33] Dietary ω-3 LC PUFAs being incorporated in phospholipids of cellular membranes at expense of AA shift the substrate pool for enzymes from ω-6 to ω-3 PUFAs and, consequently, change the ratio of LMs that modulate the inflammatory state of the tissues. COX- and LO-derived metabolites of AA, prostaglandins and leukotrienes, are predominately proinflammative,[34, 35] whereas anti-inflammatory and pro-resolving lipid autacoids such as resolvins, protectins and maresins (specialized pro-resolving lipid mediators, SPM) originate from ω-3 PUFAs (EPA, DHA, DPA).[36,37]



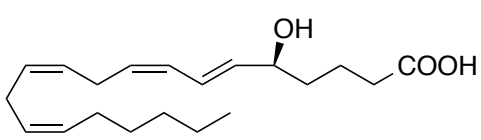
Scheme 1.2 Schematic overview of enzymatic generation of selected PUFA oxygenated lipid mediators. Abbreviations: HpEHE - hydroperoxyeicosatetraenoic acid, HETE - hydroxyeicosatetraenoic acid, HpEPE – hydroperoxyeicossapentaenoic acid, HEPE – hydroxyeicosapentaenoic acid, HpDHA – hydroperoxydocosahexaenoic acid, HDHA – hydroxydocosaphexaenoic acid, PG –prostaglandin, Tx – thromboxane, LT – leukotriene, LX – lipoxin, EpEHE – epoxyeicosatetraenoic acid; EpDHE – epoxydocosapentaenoic acid, Rv – resolvin, PD – protectin, MaR – maresin, COX – cyclooxygenase, LO - lipoxygenase, CYP cytochrome P450, red – proinflammatory, blue – pro-resolving, frame – compounds of interest.

1.2.1 Lipoxygenases

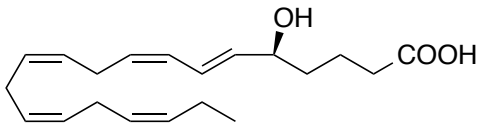
Lipoxygenase enzymes (LO) catalyze stereoselective insertion of molecular oxygen into methylene interrupted PUFAs with the formation of predominately *S*-configured hydroperoxyl acids (e.g. HpETE, HpEPE, HpDHA). Lipoxygenases are found widely in plants, fungi, and animals.[38] LO isoforms are conventionally named after the stereospecific carbon at which they oxygenate PUFAs. Human cells express six different LOs (5-LO, 12-LO, 12/15-LO, 15-LO, 12*R*-LO and epithelial LO). The primary products of LO pathways are subject to further enzymatic transformations, thereby forming a large array of bioactive lipid mediators including leukotrienes, lipoxins, resolvins, protectins, etc (Scheme 1.2).

1.2.1.1 5-LO derived hydroxyl PUFAs and their biological importance

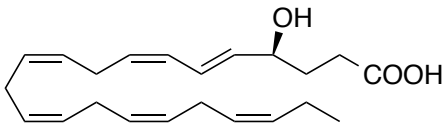
The 5-LO isoform is expressed exclusively in bone-marrow derived cells. It oxidizes AA and EPA at C-5 and DHA at C-4 or C-7. The initial *S*-hydroperoxyl PUFAs can be either reduced by peroxidase to the corresponding hydroxyl PUFAs (Figure 1.2) or, in case of C20 PUFAs, undergo further enzymatic transformations to a series of leukotrienes that are potent proinflammatory mediators.[39]



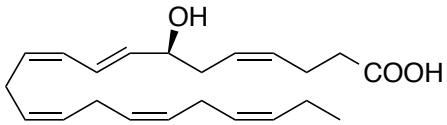
5-HETE, **7**



5-HEPE, **8**



4-HDHA, **9**



7-HDHA, **10**

Figure 1.2 Structures of 5-LO derived hydroxyl substituted PUFAs.

For 5*S*-eicosatetraenoic acid (5*S*)-HETE, **7**) and its keto-derivative the chemotactic and proinflammatory action is well known.[40, 41] In contrast, the bioactivities of 5*S*-hydroxyeicosapentaenoic acid (5*S*-HEPE, **8**) and 4*S*-hydroxydocosahexaenoic acid (4*S*-HDHA, **9**) are only poorly documented.

In the study of Yamamoto with co-workers targeted design of novel peroxisome proliferator-activated receptor γ (PPARγ) agonists and antidiabetic agents, various DHA oxygenated derivatives as ligands were explored. Both 4*S*-HDHA and 4-oxo-DHA were

identified to be strong PPARγ activators and potential leads in diabetes type 2 treatment.[42] 5-HEPE, which was reported to be potent GPR119 agonist and induce glucose-dependent insulin secretion, is also expected to have an anti-diabetic benefical effect.[43]

Recently, it was reported that a central role in the beneficial protective effects of ω-3 PUFAs against retinopathy is linked to the main 5-LO metabolite of DHA, 4*S*-HDHA.[44] This was shown to directly suppress endothelial cell proliferation, angiogenesis and neovasculization *via* PPARγ, independent of anti-inflammatory effects of 5-LO derived SPMs. These findings pointed to the therapeutic potential of 4*S*-HDHA in vasoproliferation diseases. Taking in consideration the importance of angiogenesis in tumor progression, the study of antiangiogenic effect of 4*S*-HDHA in tumor progression and metastasis might be of interest.

1.3 Polyunsaturated microbial metabolites

A number of microorganism species including some marine bacteria, algae, protists and fungi are known to be natural producers of EPA and DHA, and are considered to be alternative source for these PUFAs.[45] In addition, many microbial strains can also biosynthesize different types of hydrocarbons which present considerable interest for metabolic engineering production of biofuels and chemicals for healthcare and food industries (Figure 1.3).[46] Some microorganisms are characterized by their content of long-chain polyunsaturated hydrocarbons with methylene skipped all-*Z*-double bonds that can serve as biomarkers of PUFAs-producing organisms. In particular, green microalgae contain high amounts of C21:6 hydrocarbon **15**;[47] while some PUFAs-producing bacteria strains are characterized by the presence of small amounts of the C31:9 polyolefin **16**.[48]

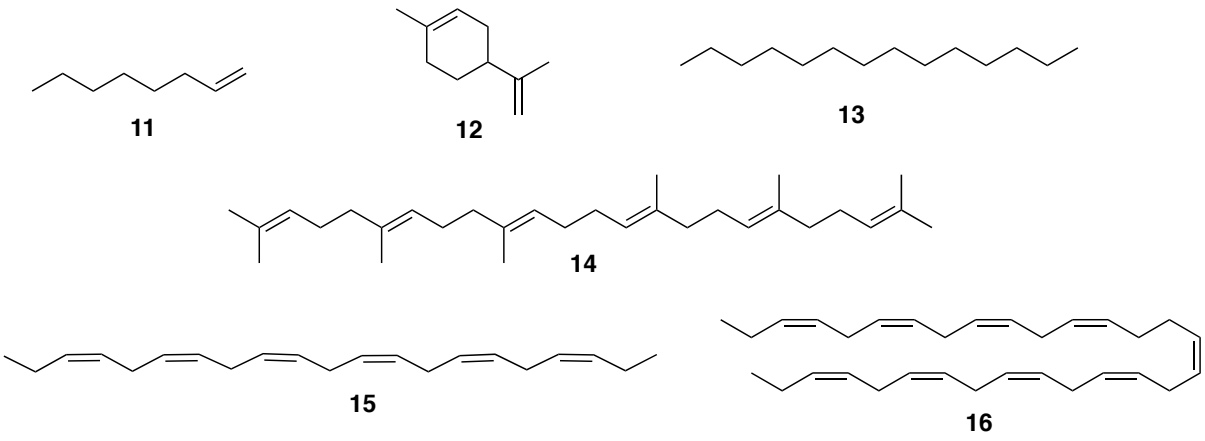
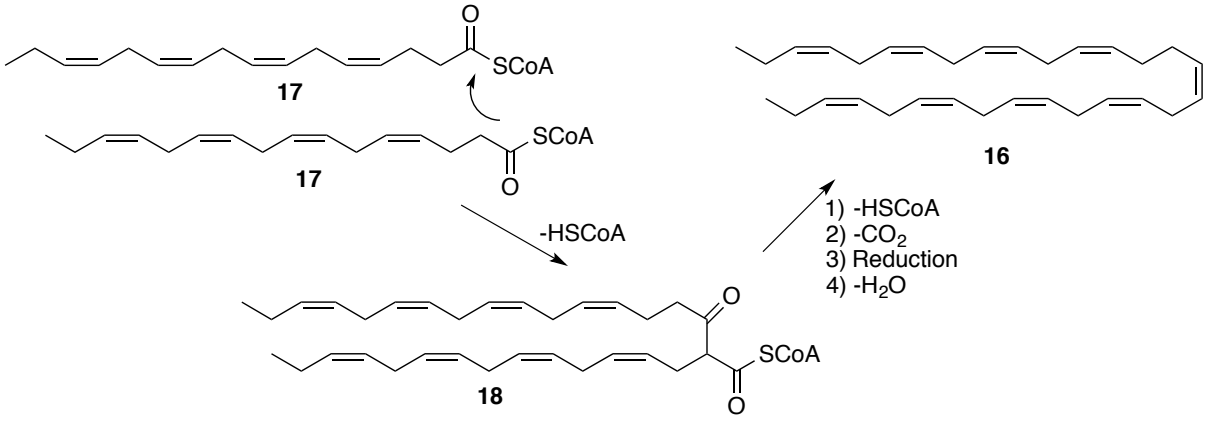


Figure 1.3 Structures of some selected microbial hydrocarbon metabolites.

The hydrocarbons, such as **16**, arouse an interest in providing a detailed investigation of the metabolic processes responsible for formation of long-chain polyunsaturated hydrocarbons (PUHC). The exact pathway for formation of **16** have not been proved yet, but most likely the hydrocarbon is biosynthesized *via* a head-to-head condensation mechanism between (all-*Z*)-4,7,10,13-hexadecatetraenoic acid derived species **17** (Scheme 1.3).[47, 49, 50]



Scheme 1.3 The proposed biosynthesis of **16**.

It is to be mentioned that configuration of the nine double bonds in **16** has been elucidated as all-*Z* on the basis of predominately FTIR data and unconfirmed biosynthetic pathway.[47,49,50] Therefore, the absolute stereochemistry of C31:9 as well as its ecological role and biological activity remain to be established.

1.4 Polyunsaturated amino-alcohol metabolites of marine invertebrates

The diverse marine ascidian species are found to be a rich source of long-chain linear and cyclic vicinal aminoalcohols. Structurally they have differences in the carbon chain length (from C12 to C30), the saturation degree and absolute configuration of the amino-alcohol functionality (Figure 1.4).[51] Several of these metabolites exhibit antimicrobial, antifungal or cytotoxic activities. Of particular interest are linear C18-aminoalcohols bearing the skipped *Z*-polyene skeleton obscuraminol A[52] (**19**) and crucigasterins 277 (**20**) and 275 (**21**).[53] These natural products are most likely biosynthesized from L- or D-alanine and the corresponding ω-PUFAs *via* a pathway related to formation of sphingosine (Scheme 1.4).

The polyunsaturated amino-alcohols are assumed to be biosynthetic precursors of diverse bioactive cyclic amino-alcohols such as amaminols (**22**) and heterocyclic marine alkaloids (structures are not shown).[54]

The saturated C18 amino-alcohol spisulosine ES 285 (**23**) isolated from clam *Spisula polynyma* was found to possess potent cytotoxic activity against prostate tumor PC-3 and LNCaP cells, and was included in the clinic trials for solid cancer treatment, which were discontinued after the phase I studies.[55, 56] The mechanism of the cytotoxicity of **23** is considered to be linked with the activation of *de novo* synthesis of intracellular ceramides.[56] The less investigated obscuraminol A (**19**) and crucigasterin 277 (**20**) are known to exhibit moderate cytotoxic activity,[57] that makes them interesting as new leads for anticancer drugs development programs.

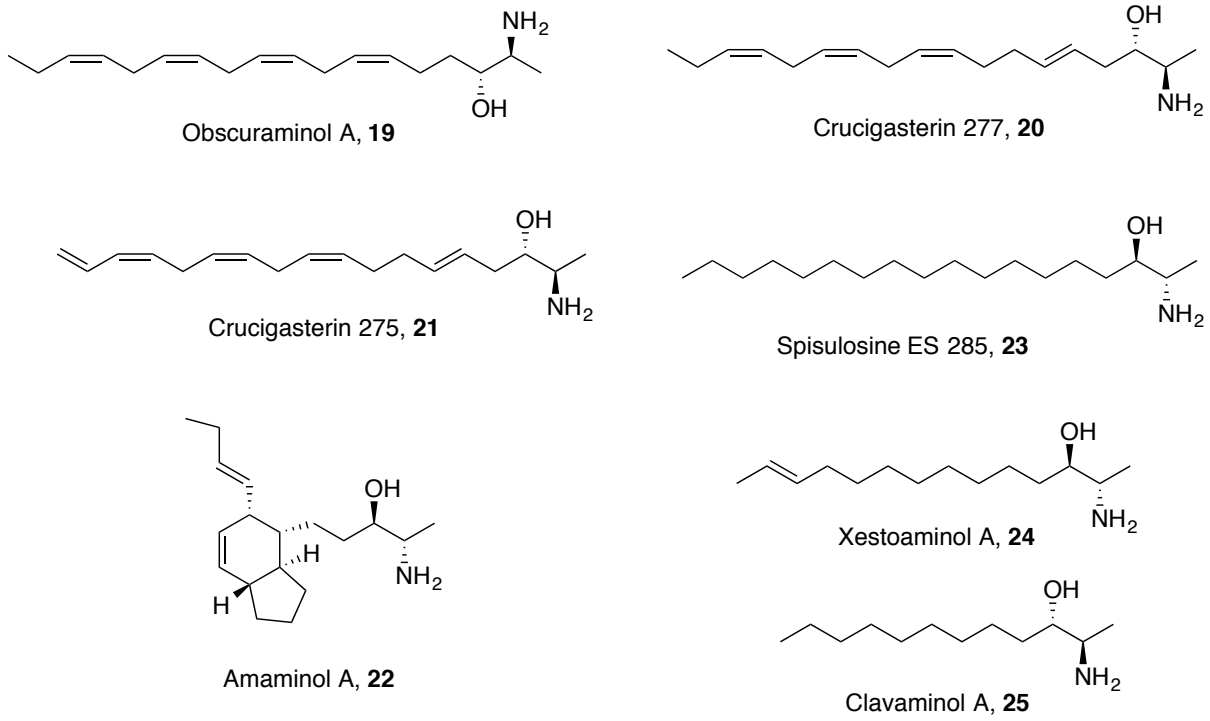
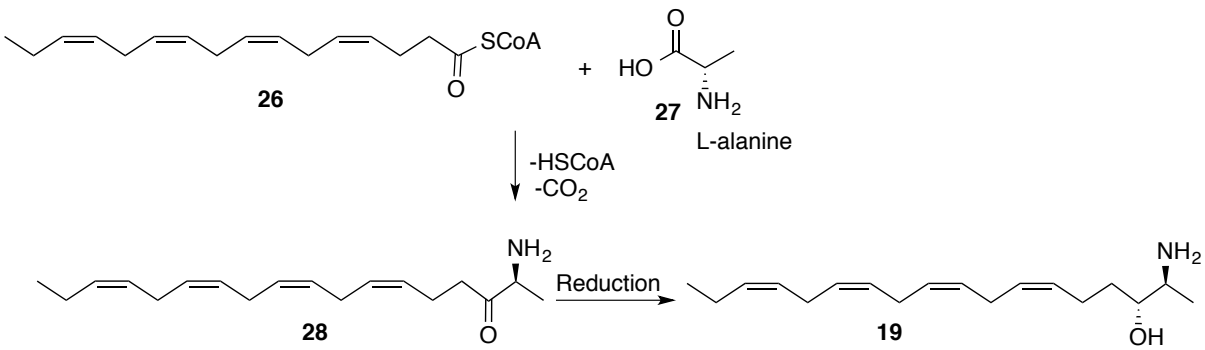


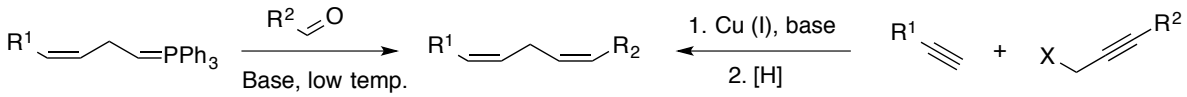
Figure 1.4 Structures of a few selected marine amino-alcohols



Scheme 1.4 An outline of the proposed biosynthesis of obscuraminol A.

1.5 General approaches towards synthesis of skipped all-*Z*-polyenes

The generation of *all-Z*-methylene interrupted polyene backbone has always been a challenge in the synthesis of natural PUFAs analogs and derivatives. There are two classic approaches for this problem: synthesis of polyyne structure with subsequent stereoselective semi-reduction or construction of double bonds by Wittig *cis*-olefination (Scheme 1.5). Both of these will only briefly be described herein.

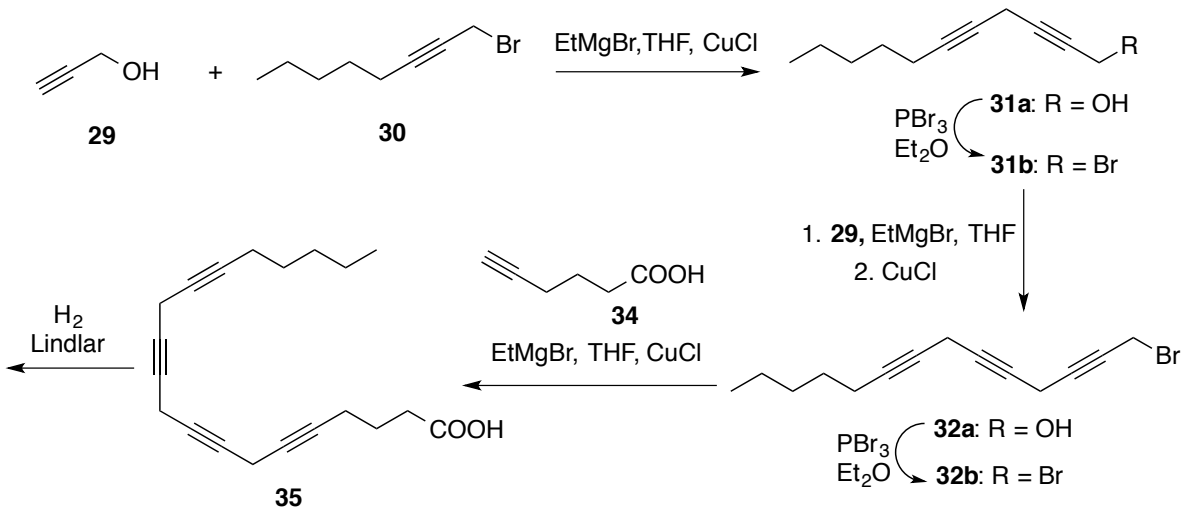


Scheme 1.5 Synthesis of skipped *Z*-dienes.

1.5.1 The acetylenic approach

There are two major methods for preparation of skipped polyyne intermediates. In the earliest version of the approach, the synthesis of polyynes was based on alkylation of terminal acetylene derivatives with a propargylic electrophile in the presence of catalytic amount of copper (I) salts via formation of Grignard acetylide intermediates.[58]

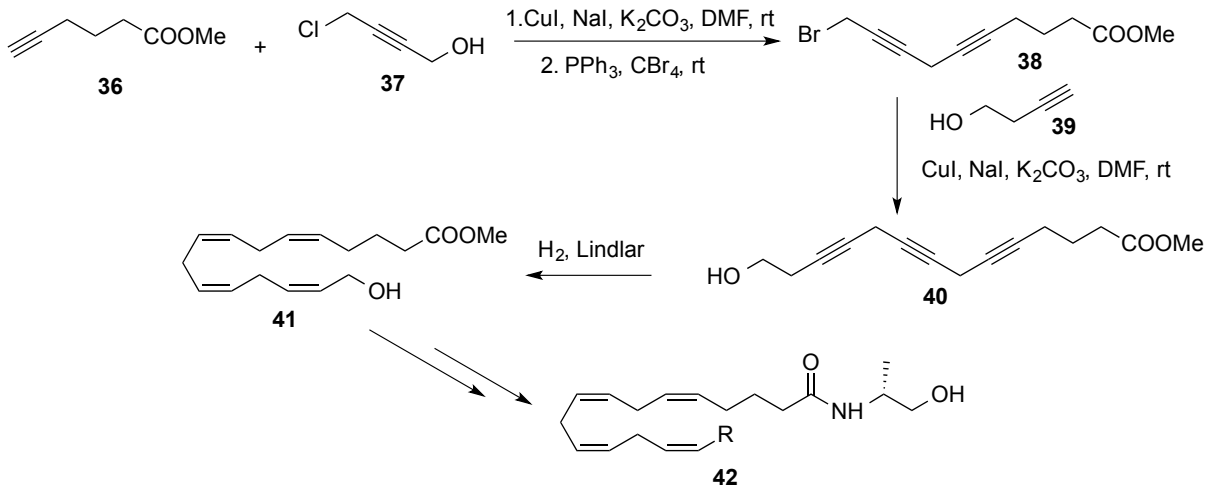
The classic illustration of the methodology is depicted in Scheme 1.6 showing the synthetic strategy towards PUFAs. This was proposed by Osbond *et al*. and is based upon a C3 elongation of polyyne halides by iterative coupling with the propargyl alcohol **29** (Scheme 1.6).[59]



Scheme 1.6 Synthesis of AA (**4**) by method of Osbond *et al.*[59]

The methodology has some drawbacks, such as the use of labile polyacetylenic bromides as intermediates. Hence, an the alternative procedure was developed.[60, 61] The modified

protocol is based on a copper (I) catalyzed cross-coupling reaction of primary propargyl halides or tosylates with terminal alkynes in the presence of a weak inorganic base (Na_2CO_3 or Cs_2CO_3) and NaI or *n*-Bu_4NCl additives. This allows the reactions to be done under milder conditions (room temperature), avoiding undesired isomerization of polyynes. Therefore, the method is widely employed in the total synthesis of polyunsaturated fatty acids and their derivatives.[62-66] One example of this strategy is the synthesis of anandamide analogs as depicted in Scheme 1.7.



Scheme 1.7 Synthesis of modified anandamide analogs.[65]

In addition to the procedures mentioned above involving copper acetylide intermediates, some novel methodologies towards the generation of skipped polyynes has appeared in recent years. Examples of such are copper free propargylation of alkylnylalanes[67] or the use of terminal TMS-alkynes.[68] However, none notable application in the total synthesis of natural products has emerged so far.

The last step in the sequence toward the desired *all-Z*-polyene products requires stereoselecive semi-reduction of triple bonds in polyacetylide backbone. Numerous procedures have appeared. The most popular method is the heterogeneous hydrogenation using Lindlar catalyst, which generally consists of metallic Pd supported on calcium carbonate and deactivated by lead acetate poisoning.[69] Further addition of deactivating agents, such as quinoline in the original version, enhances selectivity. The second most often used reducing system is P2-Ni, also known as Brown catalyst, obtainable *in situ* by reaction of sodium borohydride with nickel acetate in ethanol media and presence of ethylendiamine as modifier.[70]

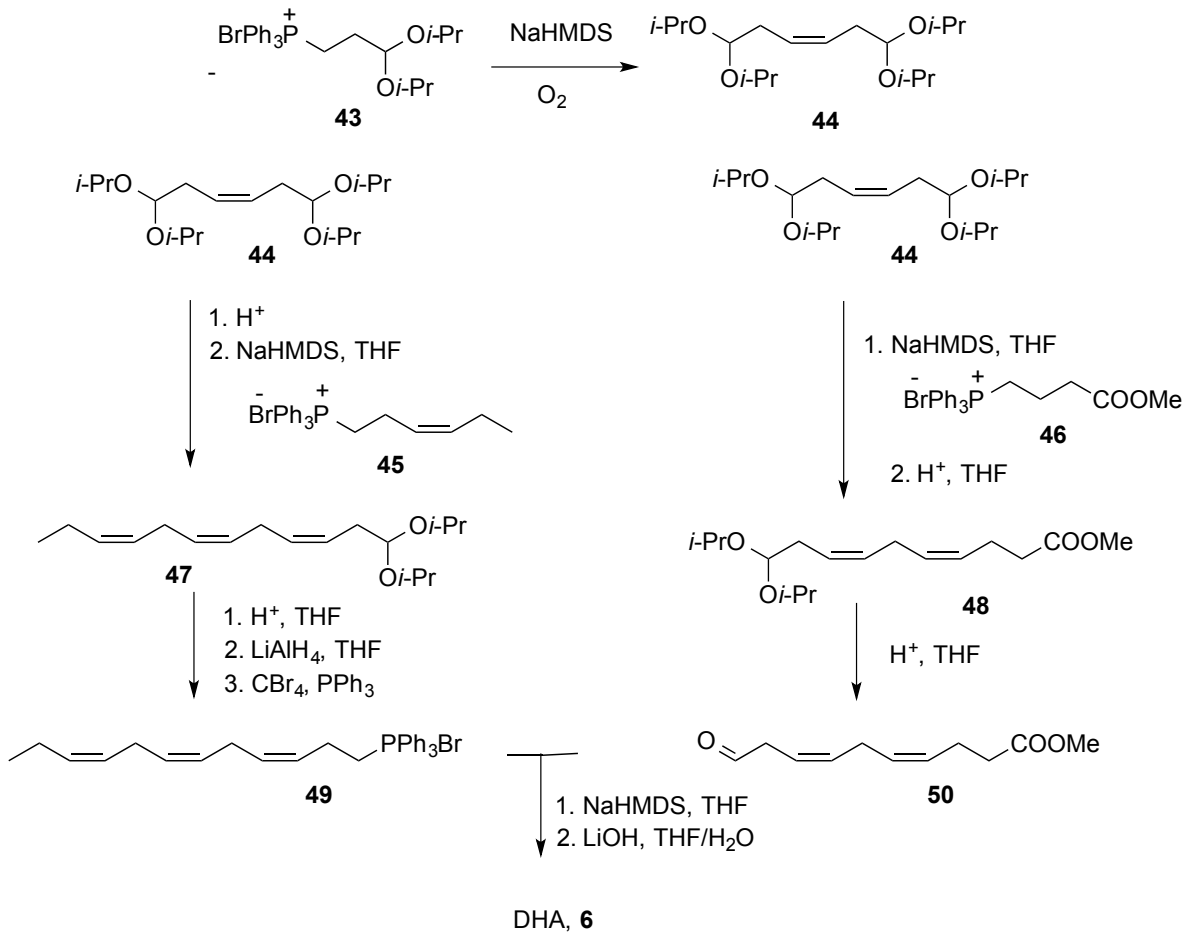
In general, the stereoselective semi-reduction of polyynes, bearing functional groups and additional double bonds, is not a trivial task. Reduction conditions providing high yields and

selectivities in a particular synthesis, quite often cannot be directly replicated in another one. Over-reduction and isomerization are serious drawbacks. In particular when multiple triple bonds are reduced at the same time.[71] Even when side products are formed as minor impurities, they can impede purification processes, leading to a significant decrease of the overall yields. Nevertheless, the procedures mentioned above are employed in the total syntheses of natural products in numerous modifications; the subtle variations of those as well as application of other reducing systems have been summarized in a recent review.[71]

1.5.2 The Wittig reaction approach

The second approach towards syntheses of skipped Z-polyenes employs *Z*-selective Wittig reaction between non-stabilized ylides and aldehydes,[72] which usually provide a high degree of stereoselectivity if reacted under salt-free conditions in dipolar solvents at low temperatures. As an example, Viala and co-workers proposed the iterative use of C3 homologating Wittig reagent **43** for generation of methylene interrupted *Z*-double bonds backbone in the synthesis of some pheromones and PUFAs.[73, 74] The treatment of **43** with NaHMDS and oxygen at -85 °C causes an oxidative dimerization to versatile C6 homologation reagent **44**, which can be converted either into a Wittig salt or the aldehyde.[75] The application of this strategy is illustrated in the synthesis of DHA as depicted in Scheme 1.8.

The iterative Wittig methodology has some drawbacks. In particular, it requires a large number of steps that usually results in low overall yield of the final product. Moreover, there are restrictions in the reaction regime to low temperatures in order to avoid *Z/E* isomerization causing prolonged reaction times. Finally, the Wittig reaction will always give some *E*-isomers albeit in low to minute amounts, but still making it a challenge to achieve the pure all-*Z* target molecule.

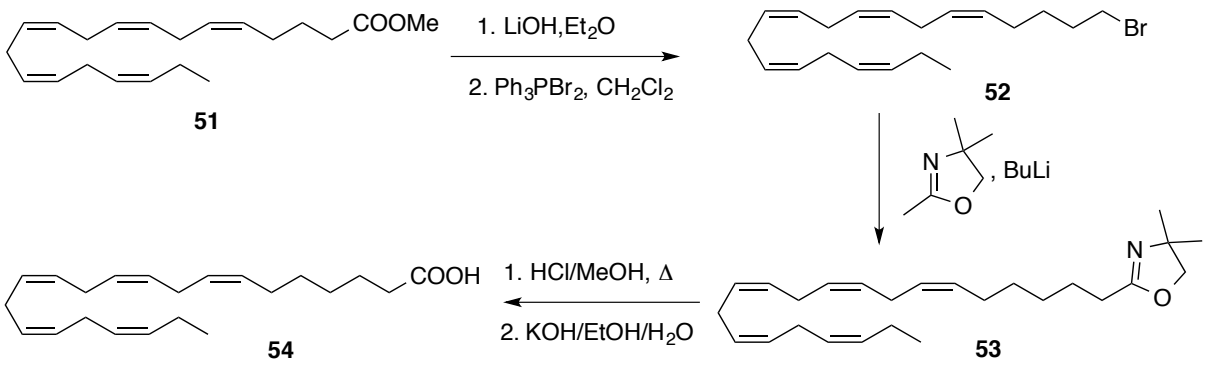


Scheme 1.8 Synthesis of DHA by the method of Sandri and Viala.[75]

1.6 Hemisynthesis of PUFAs and natural polyenes

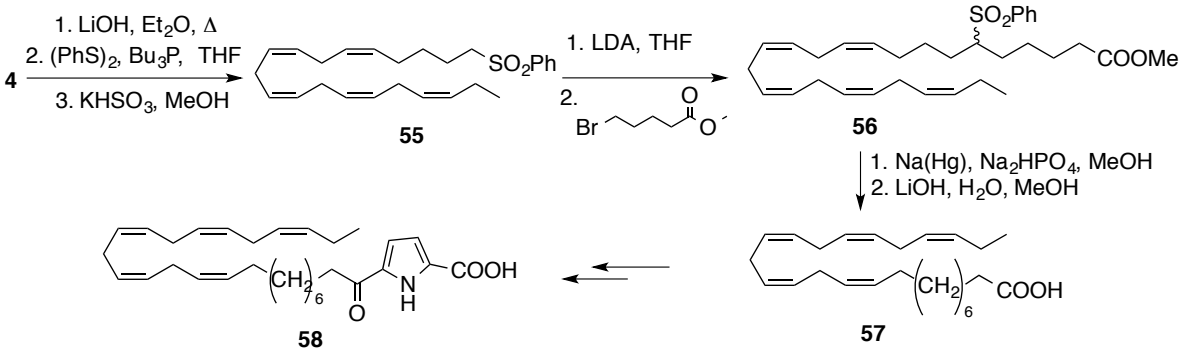
An attractive and alternative approach towards synthesis of polyunsaturated natural product is the use PUFAs such as AA, EPA, DHA and some others, as starting materials. These can be elongated or degraded leaving the configuration of all or some of the double bonds unaltered.

The long chain homologs of PUFAs, which are less available from the natural sources, can be obtained by C2 elongation of their shorter but abundant precursors such as LA, EPA, SDA using 2,4,4-trimethyl-2-oxazoline as the homologating reagents (Scheme 1.9).[76]



Scheme 1.9 Synthesis of DPA by C2 elongation of EPA-EE.

In the synthesis of a polyunsaturated pyrrole metabolite of the marine sponge **58**, Skattebøl and Hansen performed a C5 elongation of EPA (Scheme 1.10) based on coupling of lithiated α-sulfonyl carbanion and 5-bromovaleriate.[77]

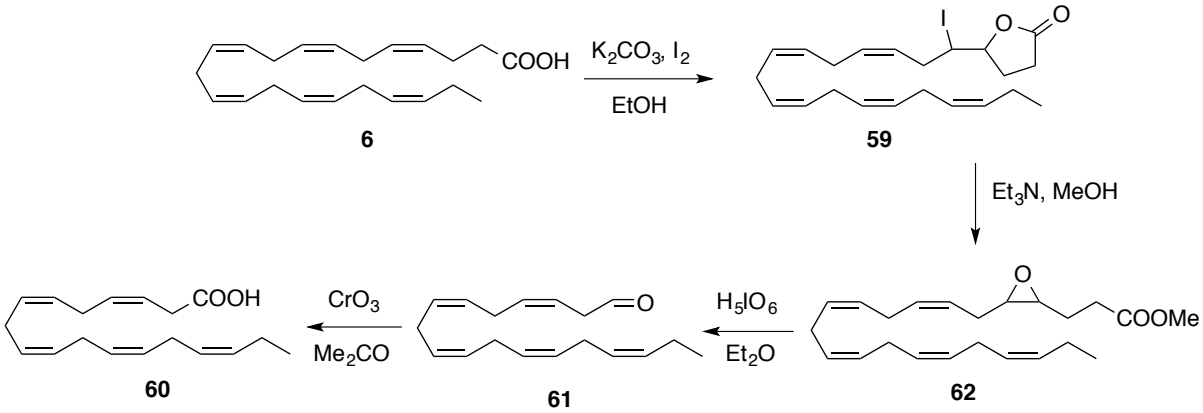


Scheme 1.10 C5-elongation of EPA in the synthesis of polyunsaturated pyrrole metabolite.

1.6.1 Iodolactonization and its synthetic utility

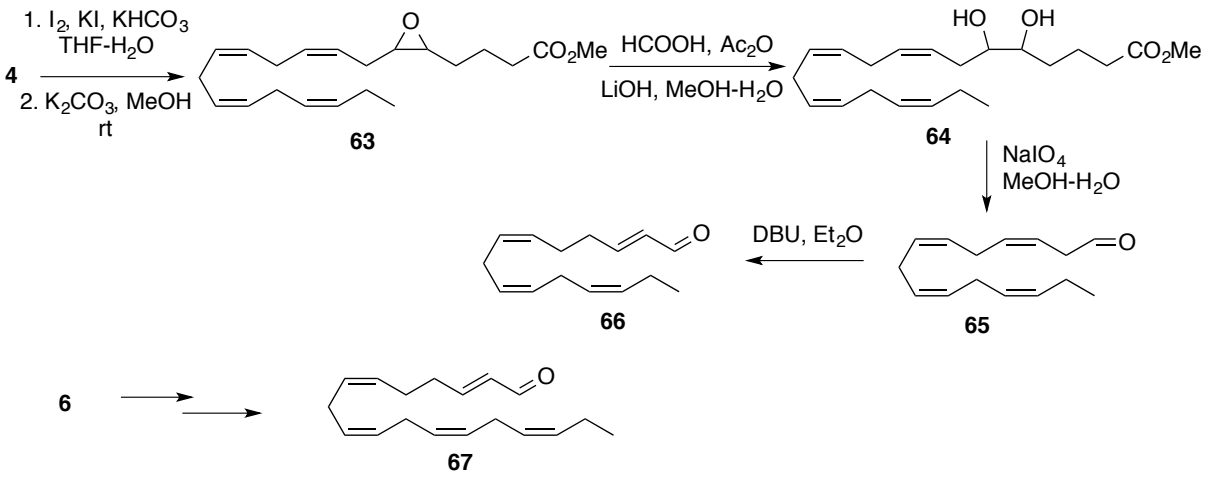
Corey and co-workers was the first to report the iodolactonization of a PUFA when they managed to do this in a high yield and with high selectivity using AA as the substrate.[78] Later other PUFAs were also used. This has now become one of the most used synthetic tools in the chemistry of this class of compounds. Although Corey and co-workers used the intermediate iodolactone to selectively isolate this, and then regained the double bond of AA to give pure samples of this fatty acid. This was done by the formation of iodolactones with subsequent selective reduction with Me_3SiI to regain the original acids and was proposed as a convenient pathway for the isolation on a preparative scale of individual AA, EPA and DHA from multicomponent PUFA mixtures of natural origin. The success of this reaction also revealed the possible selective manipulation of the one double bond closest to the carboxyl end.[79-82]

The iodolactones can be converted by treatment with base (Et_3N/MeOH, K_2CO_3/MeOH, LiOH/H_2O) into the corresponding monoepoxide esters, the oxidative degradation of which give rise to synthetically useful polyunsaturated aldehydes. These can be exploited as key intermediates in the synthesis of many PUFA derivatives and analogs. In the synthesis of all-*Z*-3,6,9,12,15-octadecapentaenoic acid **60**, performed by Kuklev *et al*., the polyunsaturated C18 aldehyde **61** was obtained by direct cleavage of DHA-derived monoepoxide **62** with periodic acid (Scheme 1.11). Oxidation with Jones reagent gave the target molecule.[83]



Scheme 1.11. Synthesis of all-*Z*-3,6,9,12,15-octadecapentaenoic acid.

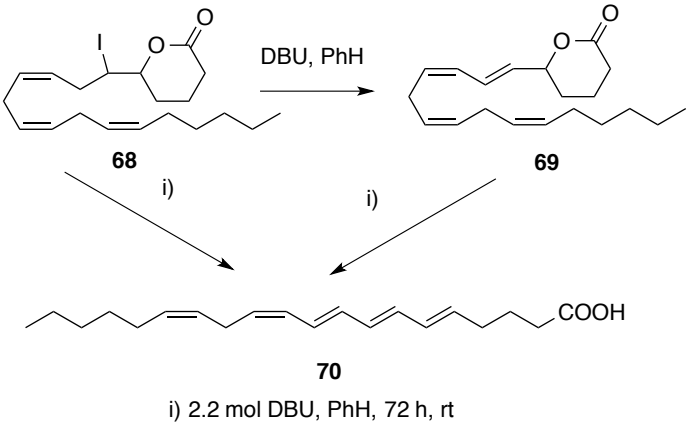
Skattebøl and co-workers improved the protocol of epoxides degradation. Starting by opening the epoxide ring into the corresponding diol acids followed by cleavage with sodium periodate both EPA-derived C15 **65** and DHA-derived C18 **61** polyunsaturated aldehydes were obtained. The reported method gave higher yields and better reproducibility.[84-85] Both of the aldehydes **61** and **65** were found to undergo rearrangement when treated with DBU resulting in formation of conjugated *E*-isomers (Scheme 1.12).[86] The obtained aldehydes were converted into sulfur and oxygen PUFAs by conversion of the corresponding alcohols into bromides and subsequent treatment of these with mercaptoacetate in the presence of lithium hydroxide in methanol or similar reagents.[86]



Scheme 1.12 Oxidative degradation of PUFAs to synthetically useful aldehydes.

The synthetic utility of C15 aldehydes **65** and **66**, prepared by similar methodology, is mirrored in the syntheses of number polyene natural products such as docosapentaenoic (DPA), eisocatetraenoic (ETA) and stearidonic (SDA) acids,[87] juniperonic acid,[88] polyunsaturated emerald moths pheromone,[89] polyunsaturated ketone[90] and amino-ketone metabolites of marine sponges[91] amongst some others.

The iodolactonization followed by dehydrohalogenation in the present of DBU is an effective two-step pathway for obtaining unsaturated lactones. Prolonged contact of either iodolactones or unsaturated lactones of AA, EPA and DHA with DBU has been reported to result in formation of polyconjugated derivatives (Scheme 1.13).[92]

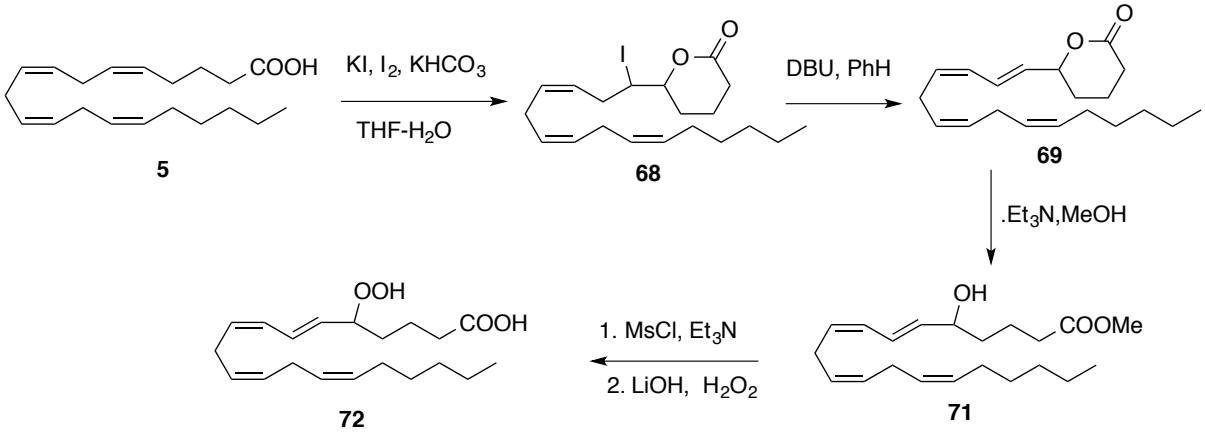


Scheme 1.13 Synthesis of the polyconjugated fatty acid **70**

1.6.2 Synthesis of 5-LO derived hydroxy-PUFAs

The straightforward four steps synthesis of racemic 5-hydroxyeicosapentaenoic (5-HETE) was reported by Corey and co-workers (Scheme 1.14).[93] This included iodolactonization of AA, dehydrohalogenation of the formed iodolactone followed by opening the lactone ring with Et_3N in MeOH. The obtained methyl ester of 5-HETE **70** was either saponified to the

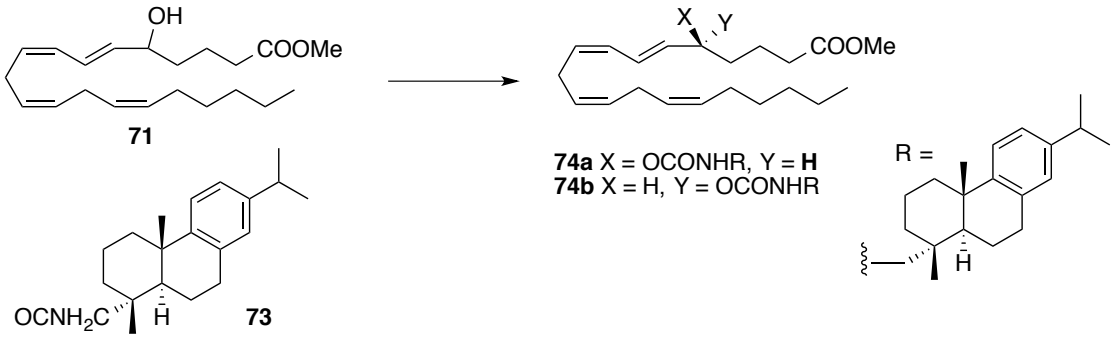
corresponding acid or oxidized with H_2O_2 to form its biosynthetic precursor, 5-hydroperoxyeicosapentaenoic acid (5-HpETE) **71**.



Scheme 1.14 Synthesis of 5-HpETE by Corey *et al*.

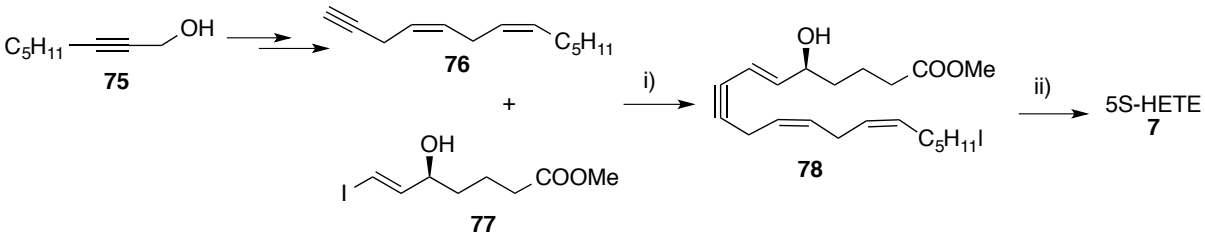
Ulven and co-workers improved the initial iodolactonization step in the synthesis of 5-oxo-eicosatetranoic acid (5-oxo-ETE), an oxidative derivative of 5-HETE.[94] The use of γ-colidine as base and dichlormethane as solvent allowed to achieve complete conversion of AA into the corresponding iodolactone. The same protocol was employed by *Itoh et al.* in the syntheses of both racemic 4-HDHA and 5-HEPE.[95-96]

Hydroxy-PUFAs can be obtained in enantiopure form by racemic resolution as proposed by Corey and co-workers.[97] They based this on derivatization of the racemic acid with isocyanate **73** to give diastereomeric urethanes **74a** and **74b** with subsequent chromatographic separation of the diastereomers, followed by hydrolysis into the separated enantiomers. This can also be performed on a preparative scale (Scheme 1.15).



Scheme 1.15 Derivatization of 5-HETE into diastereomers.

Besides racemic resolution, some stereoselective methods of 5*S*-HETE syntheses are known. These are based on the acetylenic approach, use of chiral building blocks and palladium-catalyzed cross coupling as key reactions (Scheme 1.16).[98-99]



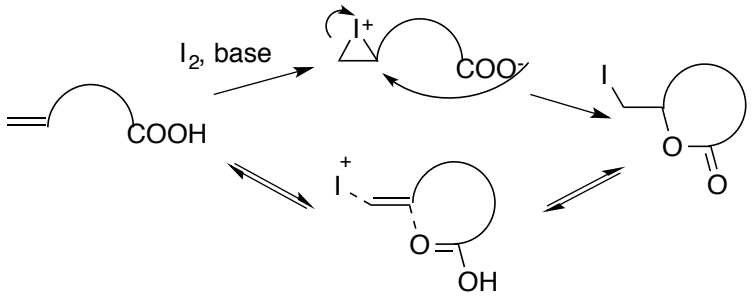
i) 10% CuI, 5 % $Pd(PPh_3)_4$, C_6H_6, 2 equiv. piperidine, 20 °C; ii) Zn (Cu/Ag), MeOH-H_2O 1:1, 30 °C, 15h

Scheme 1.16 Stereoselective synthesis of 5*S*-HETE by Guengnot *et al.*

Considering the synthesis of asymmetric hydroxyl derivatives of PUFAs from achiral precursors, two options can in theory be applied: synthesis of oxo-PUFAs followed by asymmetric reduction of the keto group or the use of asymmetric iodolactonization protocol as the first step. To date, there are no reports on any successful synthesis of 5-LO derived hydroxy-PUFAs from achiral precursors. Itoh and co-workers reported that attempted asymmetric synthesis of optically pure 4*S*- and 4*R*-DHDA employing both mentioned methodologies, yielded only poor enantiomeric excess. However, no specification of the reaction conditions was given.[95] Taking in attention the high synthetic versatility of iodolactones, the approach towards stereoselective synthesis involving asymmetric iodolactonization seems more promising.

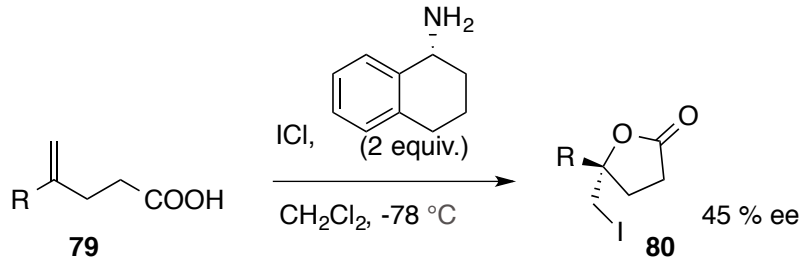
1.7 Asymmetric iodolactonization

The mechanism of iodolactonization depend on reaction conditions as it can proceeds in two possible pathways.[100-101] In aqueous media and presence of base it involves formation of iodiranium ion, followed by an intramolecular nucleophilic attack. In aprotic solvent it is more likely it proceeds via reversible formation of π-complex, the subsequent deprotonation of which yield the desired iodolactone (Scheme 1.17).



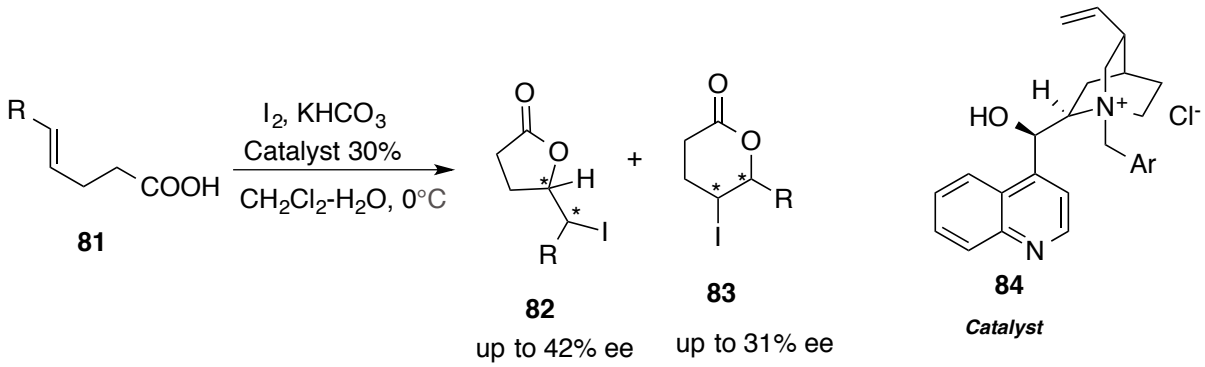
Scheme 1.17 Plausible reaction pathways of iodoactonization

In the past few years notable success has been revealed in the development of reagent controlled enantioselective iodolactonization and its catalytic version.[102] Considering the mechanism of reaction mentioned above and existing enantioselective iodolactonization protocols, several activation modes of reaction can be distinguished. The catalysis can be affected by Lewis bases, Lewis acids, Brønsted acids and phase-transfer catalysts. However, frequently the successful examples of iodolactonization involve multiple control elements.[103] In the first strategy the chiral environment is mediated by association of the iodiranium intermediate with a chiral Lewis base. The catalyst have to remain bound until the irreversible formation of a stereogenic center in order to prevent rapid racemization *via* iodine exchange of iodonium ions with unreacted alkene.[104] As an example, the strategy was employed in one of the earliest protocol of enantioselective reagent control iodolactonization performed by Wirth and co-workers.[105] The use of a combination of primary amines and ICl in the cyclization of γ-unsaturated acids yielded modest selectivities of the corresponding γ-iodolactones (Scheme 1.18).



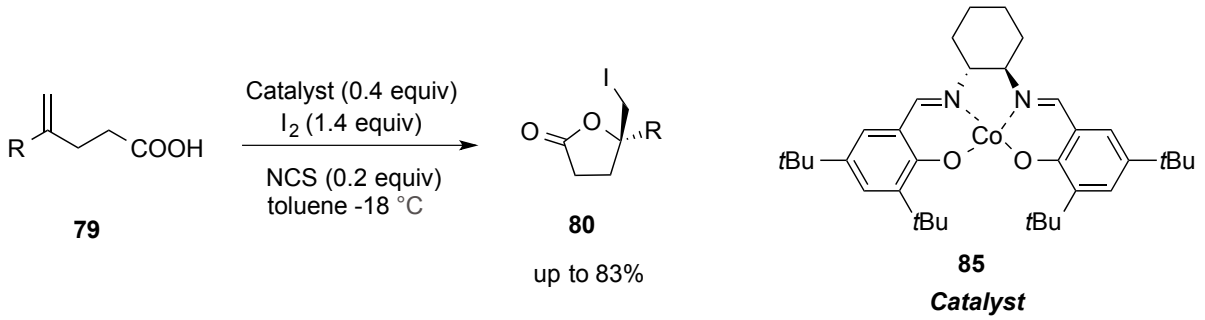
Scheme 1.18 Wirth´s enantiosleective iodolactonization protocol.

The induction of asymmetry can be achieved by ionic-pairing of substrate with chiral catalyst based on Coulombic interaction. The first catalytic asymmetric iodolactonization, reported by Gao and co-workers, was based on the use of chiral quaternary ammonium salt derived from cinchonidine as a phase transfer catalyst. Most likely, ionic pair with the deprotonated carboxylate maintains the moderate enantioselectivities of cyclic products.[106] (Scheme 1.19)



Scheme 1.19 Enantioselective iodolactonization catalyzed by a chiral cinchonidium salt.

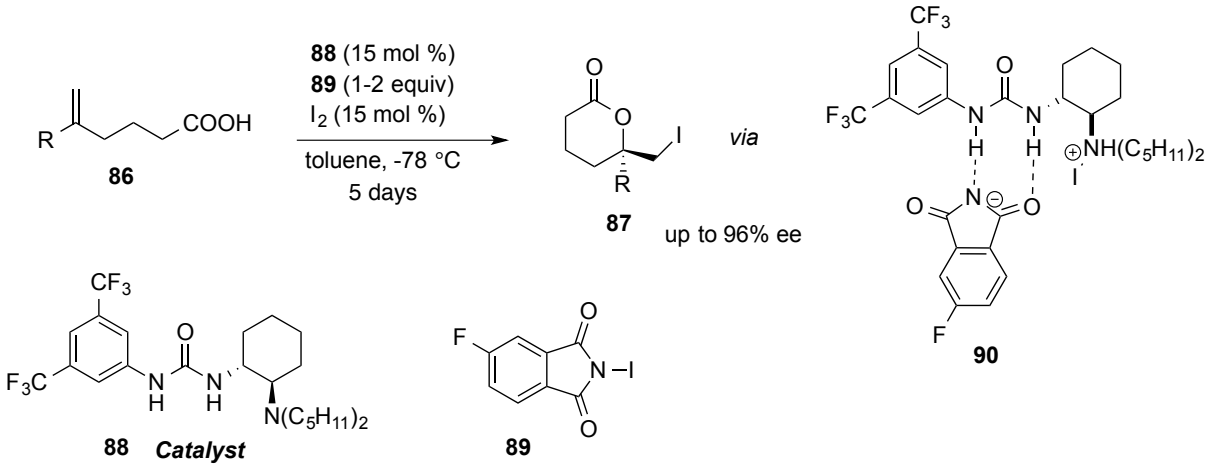
The next strategy relies on Lewis acid activation of either the iodination agent or the substrate nucleophile. As an example, Gao's iodolactonization of γ-unsaturated carboxylic acids mediated by combination of chiral salen-Co^{II} complex with catalytic NCS and iodine, afforded the corresponding γ-iodolactones in high yields and moderate to good enantioselectivities (Scheme 1.20).[107] The activation of iodine is attained by complexation of Lewis acidic catalyst with ICl generated in situ by reaction of iodine with NSC.



Scheme 1.20 Enantioselective iodolactonization catalyzed by a chiral salen-Co^{II} complex.

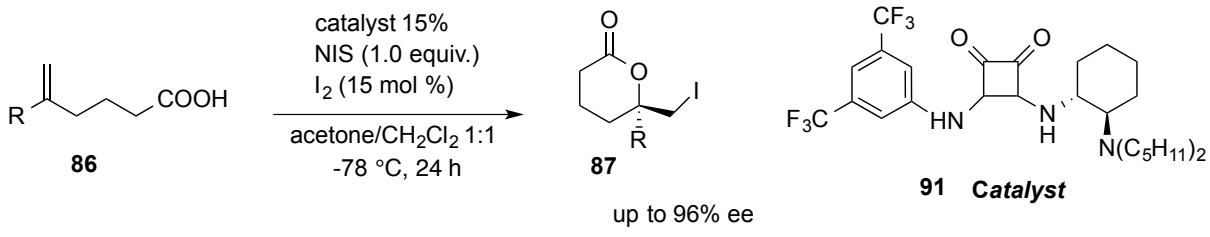
One of the most powerful tactics to attain high levels of stereoinduction in the iodolactonization reaction involves hydrogen-bond (H-bond) interactions between a chiral catalyst and the substrate as additional controlling elements for conformation constraints. Veitch and Jacobsen developed anion-binding catalyst able to for successful cyclization of δ- and γ-unsaturated carboxylic acids with the use of tertiary aminourea chiral catalyst **88** and *N*-iodofluorophthaloimide **89**. High enantioselectivity was observed in the presence of catalytic amounts of iodine, whose primary role is believed to be formation of an activated iodinating agent in a complex with *N*-iodofluorophthaloimide. (Scheme 1.21).[108] The mechanism of catalytic stereoinduction, based of NMR observation, suggests an *in situ* interaction of **88** with **89** to generate the *N*-iodo catalyst derivative **90**. This catalytic species forms an ion pair intermediate with a substrate, where the urea-bonded fluorophtalimide

assists deprotonation of the carboxylic acid and iodoammonium ion provides delivery of iodine to the alkene.



Scheme 1.21 Jacobsen´s enantioselective iodolactonization in the presence of a chiral bifunctional urea catalyst.

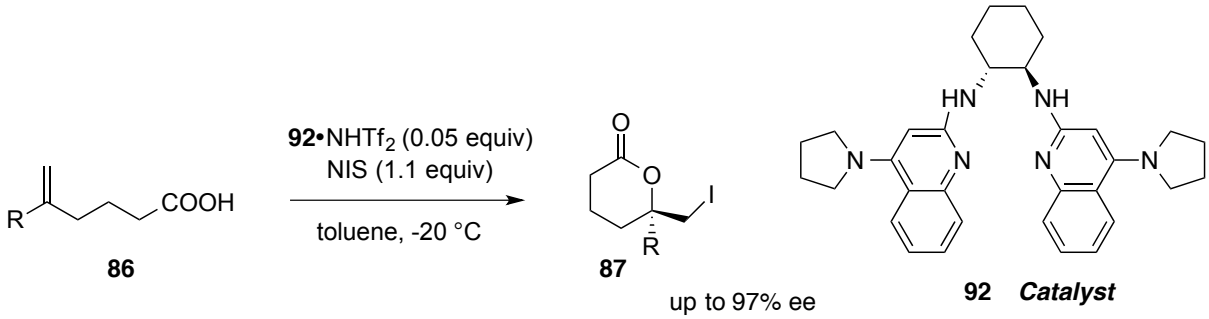
The bifunctional chiral catalyst **91** with a squaramide moiety as a H-bond donating functionality and employing NIS/I_2 as an iodine source, promotes the conversion of δ-unsaturated carboxylic acids to the corresponding iodolactones sometimes with excellent enantioselectivities (Scheme 1.22).[109] Despite an apparent similarity of **91** with tertiary aminourea catalyst **88**, the mechanism of asymmetry induction drastically differs from this, presumably due to an acid/base ion paring of the catalyst with the substrate. Stabilizing π-π interactions between (*bis*)trifluoromethylphenyl group of **88** and the aryl appendage of the substrate was proposed as the basis for the stereodifferentiation.



Scheme 1.22 Enantioselective iodolactonization in the presence of a bifunctional squaramide.

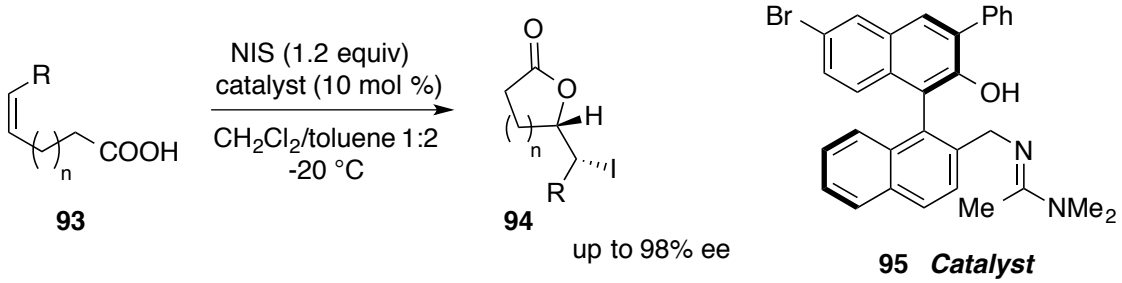
The peculiar case of H-bonding mode in the Brønsted acid activation, act *via* donation of the polar ionic hydrogen bond. The iodolactonization of 5-substituted δ-unsaturated carboxylic acids catalyzed by chiral bis(amidine) protonated acid complex – NIS reagent system affords iodolactones in moderate to high enantioselectivities at -20 °C (Scheme 1.23).[110]

The efficacy of chiral Brønsted acid catalysts is shown to be dependent upon its achiral conjugate base. The proposed mechanistic hypothesis suggests the tandem Brønsted acid activation of an iodine source and Brønsted base activation of the nucleophile.[110]



Scheme 1.23 Enantioselective iodolactonization in th presence of a chiral Brønsted acid catalyst.

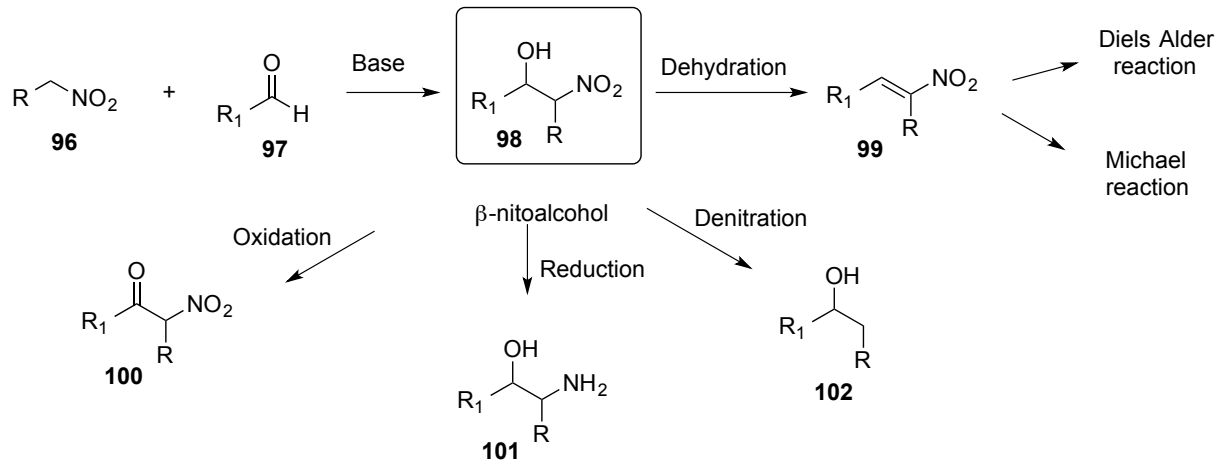
The development of an asymmetric iodolactonization protocol is a dynamic topic, and some catalytic systems have emerged recently and in the course of the progression of this project.[111-115] One of the most effective is a chiral BINOL-derived catalyst **95** developed by Martin and co-workers, containing amidine and phenolic moieties.[111] Possessing dual Lewis base and H-bonding activation mode, it facilitates, in the presence of NIS, cyclization of both δ- and γ-carboxylic acids with internal *Z*-double bond with excellent enantiomeric outcome through stereoorientation of the substrate by hydrogen bonding between phenolic hydroxyl and carboxyl group and stabilizing the iodoranium ion by amidine (Scheme 1.23). The catalytic system based on the chiral BINOL backbone was shown to be suitable for both for iodo- and bromofunctionalization[111, 114] and presents the most general methodology for asymmetric halolactonization reported to date.



Scheme 1.23 Enantioselective iodolactonization catalyzed by a chiral BINOL derivative.

1.8 Overview of the Henry reaction

The nitroaldol, oftened named the Henry reaction, is defined by a base accelerated addition of nitroalkanes to carbonyl groups of aldehydes or ketones, yielding β-nitroalcohol products. Discovered in 1895 by L. Henry,[116] it became a powerful tool in organic synthesis for the introduction of valuable functionalities as summarized in Scheme 1.24.[117]



Scheme 1.24. Synthetic utility of nitroaldol reaction.

The Henry reaction can be compared with an aldol reaction, with similar features. However, it also has some distinguishable differences. Considering the stereochemical aspects, the achievement of high stereoselectivity of nitroaldol products is challenging due to retroaldolization and epimerization of the nitro substituted carbon atom. Therefore, the earliest approaches for stereocontrolled synthesis of nitroalcohols involved formation of activated nitronate species irreversibly reacting with aldehydes (ketones).[117, 118] In particular, the use of silyl nitronates, accessible by silation of nitroalkane with trialkylsilyl chloride in the presence of Et_3N at -78 °C, led to the formation of *anti*-diastereomers whereas the lithium nitronates, formed by treatment with *n*-BuLi in THF/HMPA at low -90 °C, afforded *syn*-nitroaldol products.[117, 118]

The asymmetric Henry reaction with unmodified nitroalkanes requires preferably synergetic base-accelerated nitroalkane activation and Lewis acid carbonyl acceptor activation in one catalytic cycle. This can be promoted by both diverse metal-based and organocatalytic systems.[118] In particular, the first catalytic system for asymmetric Henry reaction designed by the Shibasaki group was a bimetallic La-Li BINOL complex **103** (Figure 1.5).[119] The essence of this is a cooperative Lewis acid and Brønsted base activation function by lanthanum and phenoxy-Li groups, respectively. This afforded the desired nitroalcohol product with high selectivities and reported *syn/anti* ratios up to 94:6 and ee's up to 97%.[120]

The similar activation approach was realized in a dinuclear zinc complex with a chiral semi-azacrown ligand **105** (Figure 1.5) developed by Trost and co-workers.[121] Another successful example of dual bimetallic catalysts is the heterobimetalic Pd/La Shiff base complex **106**[122] and Na/Nd heretogenious complex of amide ligand **107**,[123] both of them were found to be effective for achieving *anti*-diastereoselectivity of aromatic nitroalcohols (Figure 1.5).

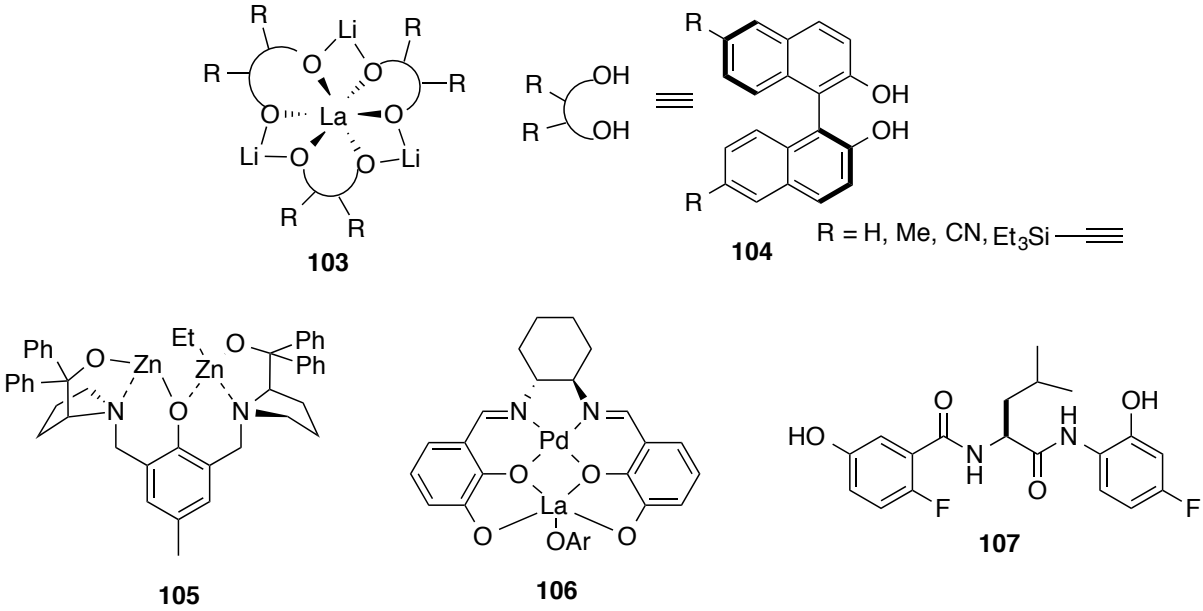
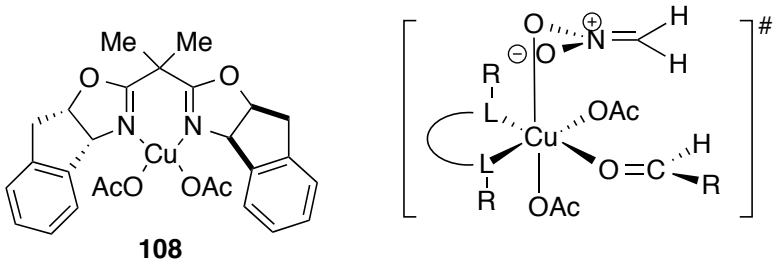


Figure 1.5 Bimetalic Henry reaction catalysts.

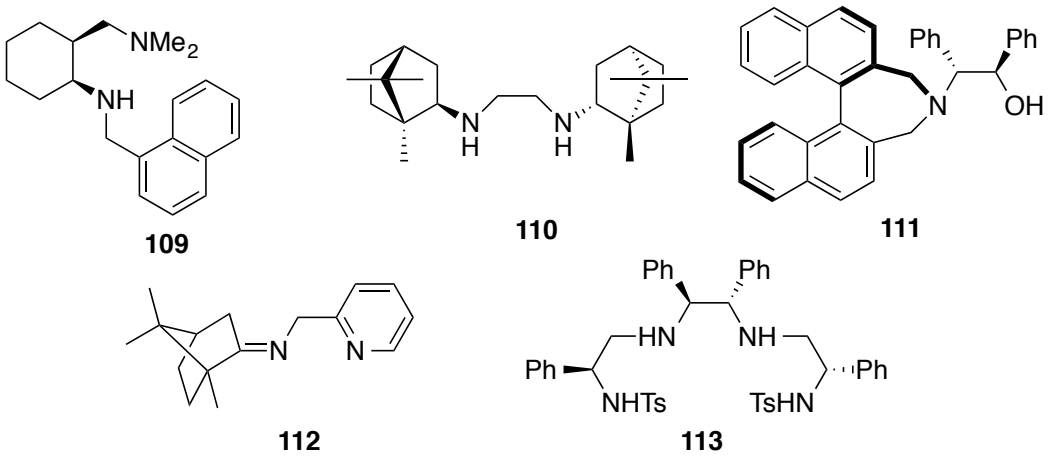
The most extensive group of metal-based catalysts utilizes copper complexes with chiral bidentate (polydentate) aza-containing ligands. In accordance with activation principles formulated by Evans stating that weakly Lewis acidic metal complex bearing moderately charged ligands can facilitate deprotonation of nitroalkanes, C_2-symmetric copper (II) bis(oxazolidine) complex **108** was designed and shown to promote nitroaldol reactions of various aldehydes and nitromethane with excellent enantioselectivities (Figure 1.6).[124] The generally accepted transition state model involves a Jahn-Teller effect on Cu (II) coordination, in compliance with which the octahedral copper (II) complex has four strong equatorial coordination sites and two weak apical. Both nitroalkane and aldehyde reactants achieve the best activation by coordination to the equatorial and apical position respectively (Figure 1.6), whereas the favorable orientations are determined according to steric and electronic considerations.



108

Figure 1.6 Evans´s copper(II)-*bis*-oxazolidine complex and transition state for nitromethane addition to aldehydes.

The catalytic concept was realized also in a wide array of copper (II) complexes with both C_2- and C_1-symmetric chiral ligands such as diamines,[125-128] amino-alcohols,[129,130] amino/iminopiridines,[131-133] sulfonamides (Figure 1.7).[134, 135]

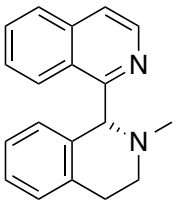


109 **110** **111**

112 **113**

Figure 1.7. Selected examples of chiral ligands.

The application of copper (I) chiral complexes in asymmetric nitroaldol condensation is less common, but a few effective enantioselective protocols are known. As one example, the copper complex of *N*-methyl-C_1-tetrahydro-1,1´-bisisoquinoline **114** was reported to promote nitroaldol condensation with both aliphatic and aromatic aldehydes and nitromethane in highly enantioselective way (Figure 1.8). However, the catalyst was efficient only when nitromethane was used; other nitroalkanes gave moderate to very poor results.[136] Another example is *bis*(sulfonamide)-diamine ligand **115**, which in the presence of CuBr is able to catalyze high *syn*-selective Henry reaction with up to excellent ee% of *syn*-nitroaldol adducts.[135]



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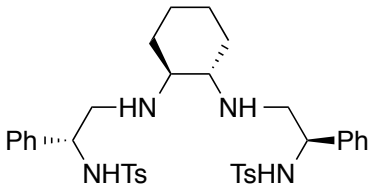

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Figure 1.8 Selected examples of chiral ligands.

Besides the transition metal complexes, the extensive collection of organocalalysts have been developed summarized in a recent review.[137]

Aims of study

The main objective of this study was to exploit the use of ω-3 PUFA as starting materials towards total synthesis of selected polyunsaturated natural products.

The work involves the following partial objectives:

- Investigating the catalytic properties of the Trost *bis*-proline-phenol ligand in asymmetric iodolactonization reactions;

- Developing a stereoselective synthesis of all-*Z*-hentriacontanonaene, a very long-chain microbial metabolite;

- Investigating the application of asymmetric nitroaldol approach towards the total synthesis of the polyunsaturated vicinal amino-alcohols obscuraminol A. Within this realm, investigating the catalytic activity of copper complex of C_1-pinane-derived ligand in the asymmetric Henry reaction.

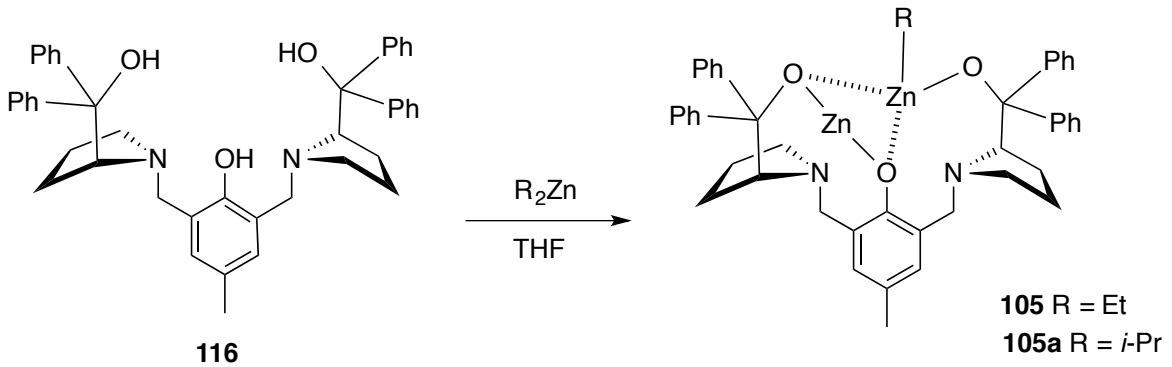
2 Results and discussion

2.1 An asymmetric iodolactonization catalyzed by a zinc *bis*-proline phenol complex (Paper I)

The following chapter describes the results towards the development of an enantioselective protocol for iodolactonization of unsaturated carboxylic acids. These efforts were a part of the objective within the fargoing aim of synthesizing hydroxyl-PUFAs **8** and **9**.

2.1.1 Preliminary considerations

The stereoselective iodolactonization protocols, known at the start of the project[107-110] had significant limitations in their substrate scope. In addition, these were unpractical in the view of their application towards iodolactonization of PUFAs[138]. Therefore, the problem of developing suitable catalytic systems using PUFAs as substrates remained open. As shown in the introductory literature section, the achievement of high stereoselective outcome in asymmetric iodolactonization reaction requires preferably dual activation and enantioselective control of both the carboxylate and the iodiranium ion.[102, 103] In search of a chiral scaffold bearing multiple active sites, the *bis*-proline phenol ligand **116** was of particular interest (Scheme 2.1). Commercially available in both enantiomeric forms and containing two tertiary amine sites (potential carboxylate activators) and H-bonding phenolic hydroxyl moiety (potential NIS activator), **116** was envisioned to catalyze the iodolactonization reaction in an enantioselective fashion. At the same time, treatment of **116** with Et_2Zn in THF gives the dinuclear zinc complex **105** (Scheme 2.1) which have been extensively employed as a bifunctional catalyst in a number of enantioselective reactions including aldol, nitroaldol condensation, nitroalkene addition, and others.[139-146] The two active metal centers are believed to act as either a Lewis acid or a Lewis base, respectively. This is expected to promote the asymmetric induction.

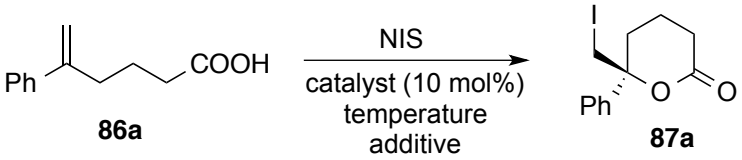


Scheme 2.1 Structure of semi-aza crown ligand **116** and the dinuclear zinc complex **105**.

2.1.2 Investigation of reaction conditions

The catalytic abilities of **116** and **105** were tested in the iodolactonization reaction of 5-phenyl-5-hexenoic acid **86a** as a model substrate using an equimolar amount of *N*-iodosuccinimide (NIS) as the iodine source keeping it in toluene at -20 °C for an extended time. Moderate yields (up to 48%) of racemic products were observed with **116**, while the use of an *in situ* prepared THF solution of complex **105** resulted in formation of enatioenriched iodolactones **118** (55% ee, 70% yield) (Table 2.1, entries 1 and 3, respectively). It has previously been reported that the catalytic amounts of iodine in combination with *N*-iodimines could accelerate the iodolactonization reaction[107-109] through generation of a more reactive iodine species. However, in the presence 0.15 equivalents of I_2 the enhancement of the reaction rate was accompanied by a drop in the enantioselectivity (entry 4).

Table 2.1 Optimization of the reaction conditions

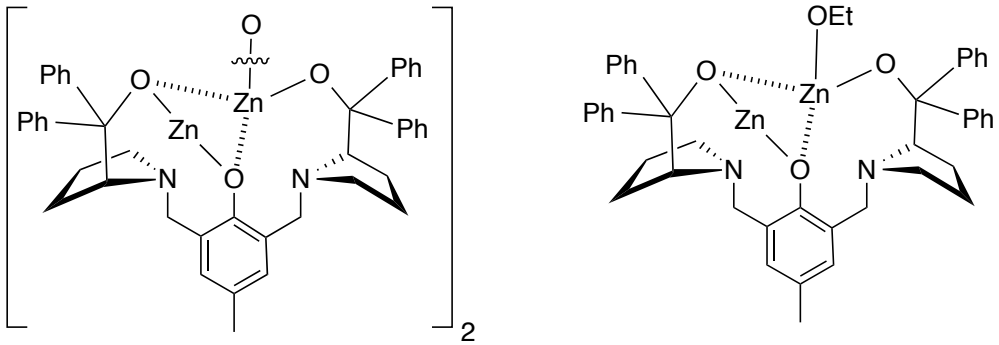


Entry	Catalyst	Solvent	Additive	°C	Time (h)	Yield (%)[a]	ee (%)[b]
1	**116**	PhMe	-	-20	72	30	racemic
2	**116**	PhMe	0.15 equiv I_2	-20	24	48	racemic
3	**105**[c]	PhMe	-	-20	70	70[d]	55-74
4	**105**[c]	PhMe	0.15 equiv I_2	-20	24	68	50
5	**105a**[c]	PhMe	-	-20	24	80[d]	57-62
6	**105**[c]	PhMe	4Å MS	-20	70	62	44
7	**105**[c]	THF	4Å MS	-20	70	71	27
8	**105**[c]	THF	-	-20	70	72	31
9	**105**[c]	Et_2O	-	-20	70	66	57
10	**105**[c]	CH_2Cl_2	-	-20	70	84	31
11	**105**[c]	Me_2CO	-	-20	70	65	30
12	**105**[e]	PhMe	-	-20	48	70	76
13[f]	**105**[e]	PhMe	EtOH	-20	48	71	74
14	**105**[e]	PhMe	-	-40	48	70	82
15	**105**[e]	PhMe	-	0	24	74	72

[a]Isolated material. [b]Determined by HPLC analysis. [c]THF in situ generated solution. [d]Average yield. [e]Solid residue after evaporation of THF. [f]The catalyst was obtained by addition of stoichiometric amount of ethanol to in situ generated solution of **105**.

In some of the reactions, when optimizing the conditions, low reproducibility in the ee was encountered (entries 3 and 5). We thought that the most likely reason for this was the insufficient elimination of adventitious moisture that could affect the labile complex **105**.

However, contrary to this hypothesis, in the presence of 4Å molecular sieves the ee-values unexpectedly decreased significantly (entries 6 and 7). Further studies on the solvent effect revealed that the non-polar toluene gave the best and most reproducible results. All further variation of the reaction system (the alterations in concentration, catalyst and NIS loadings, iodine and base additives, reaction time) had no significant effect on enantioselectivity, which did not exceed 57% ee. Surprisingly we also observed that the reaction apparently resulted in higher selectivity (up to 74% ee) when **105** was handled with less precautions against air and moisture. Moreover, the complex **105** retained high catalytic activity even after the complete evaporation of THF and shelf storage of the amorphous solid residue (entry 12). The use of this as a catalyst ensured sufficient reproducibility. The best explanation for these results are that the active catalytic species probably is formed from *in situ* generated complex **105** exposed to air. Regarding the nature of the active catalyst, two possible structures can be theorized (Figure 2.1). The oxo-bridged dimer **117** has previously been reported[144] and can likely be derived by reaction of **105** with trace amounts of water. At the same time, trace amounts of oxygen may oxidize the complex **105** to form the alkoxy-bridged dinuclear species **118**. The latter can also be generated as a result of a ligand exchange with an alcohol.[145] The modified treatment with EtOH of the *in situ* prepared solution of **105** was found to have similar efficiency as the solidified species (entry 13). Unfortunately all attempts to obtain crystals suitable for X-ray analysis of either pure complex **105** or in aggregation with the substrate were unsuccessful.



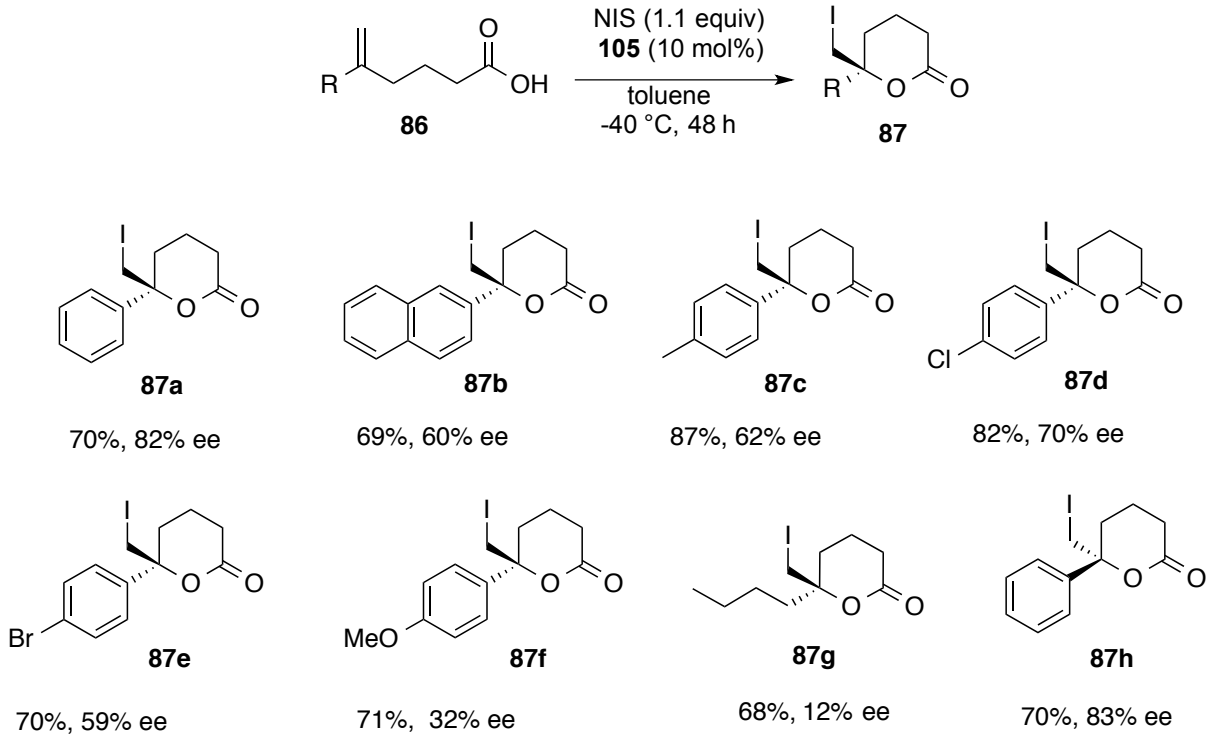
117 **118**

Figure 2.1 The oxo-bridged dimer and the alkoxy derivative of complex **105**.

Next the temperature effect on iodolactonization was investigated. Temperature reduction from -20 °C to -40 °C had a positive effect on the enantioselectivity of the iodolactones (entries 12 and 14). However, further lowering the temperature significantly decreased the reaction rate and led to impractical yields. Overall, the highest ee-values (82%) was obtained at -40 °C in toluene.

2.1.3 Substrate scope

After having established a combination of 10 mol% of amorphous **105**, -40 °C and 48 h as the most general set of reaction conditions, a range of substrates to which this protocol is applicable were examined (Scheme 2.2). The absolute configuration of the products **87a-87h** was assigned by comparison of retention times on HPLC and optical rotation of authentic samples with reported in literature data.[108-110] In most cases, the iodolactone products were obtained in good yields and ee values between 59% and 82% for the substrates bearing electron-deficient aryl groups. The presence of electron-donating aryl and alkyl substituents on the unsaturated acid, strongly decreased the enantioselective outcome.



Scheme 2.2 Scope of the asymmetric iodolactonization catalyzed by a dinuclear zinc *bis*-proline phenol complex.

To rationalize how the asymmetry is controlled by the catalyst, NMR studies of variable mixtures of **105** and **86a** (from 1:100 to 1:10) was performed. The linear effect on up-field shift of alpha methylene signal was revealed, while the same effect on **116** and **86a** mixtures was less pronounced (See Figure 2.2). This observation indicates that induction of asymmetry is realized through the interaction of carboxylate with the zinc metal center of the **105** complex. The ^{13}C NMR spectra provide additional evidence for the same type of interaction (Figure 2.3).

Finally, the iodolactonization of EPA employing a dinuclear zinc complex was attempted. Unfortunately, only racemic δ-iodolactone was observed as a single diastereomer.

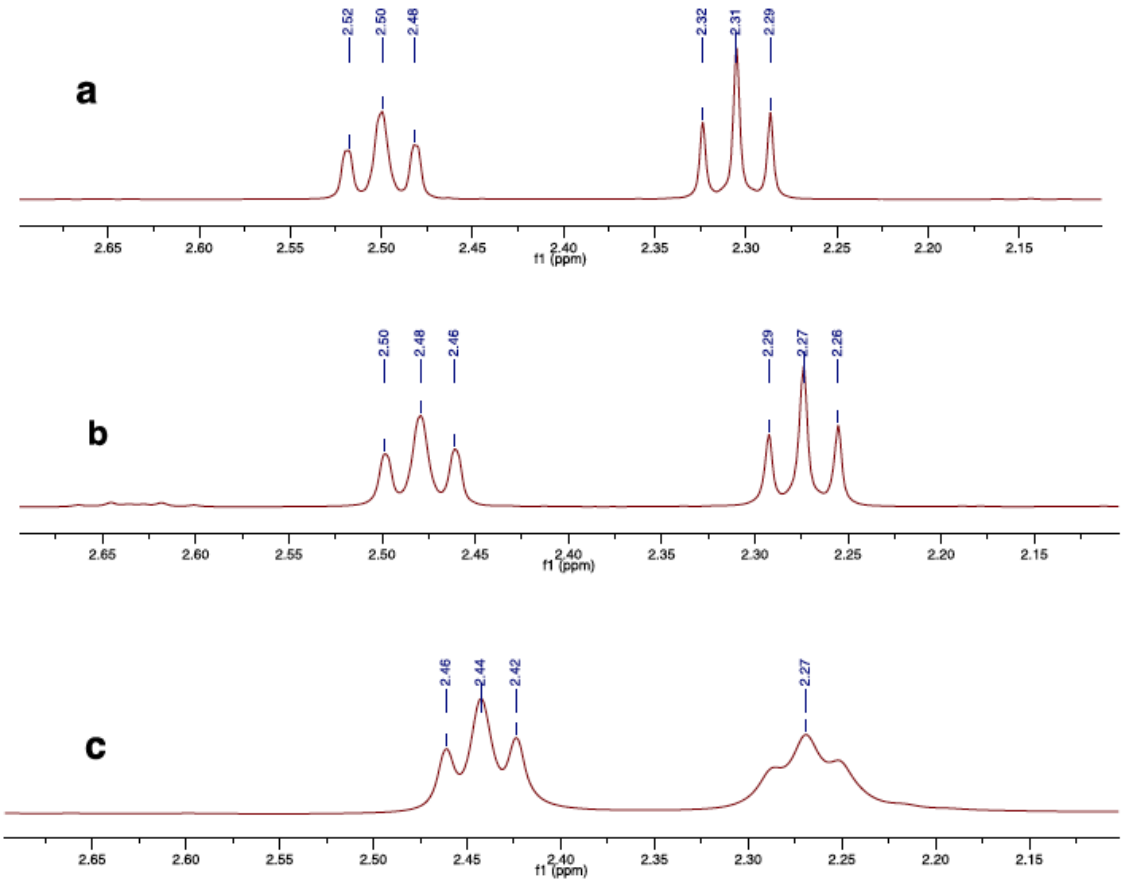


Figure 2.2 [1]H NMR spectra of: a) **86a**, b) 1:10 mixture of **116** and **86a**, c) 1:10 mixture of **105** and **86a**.

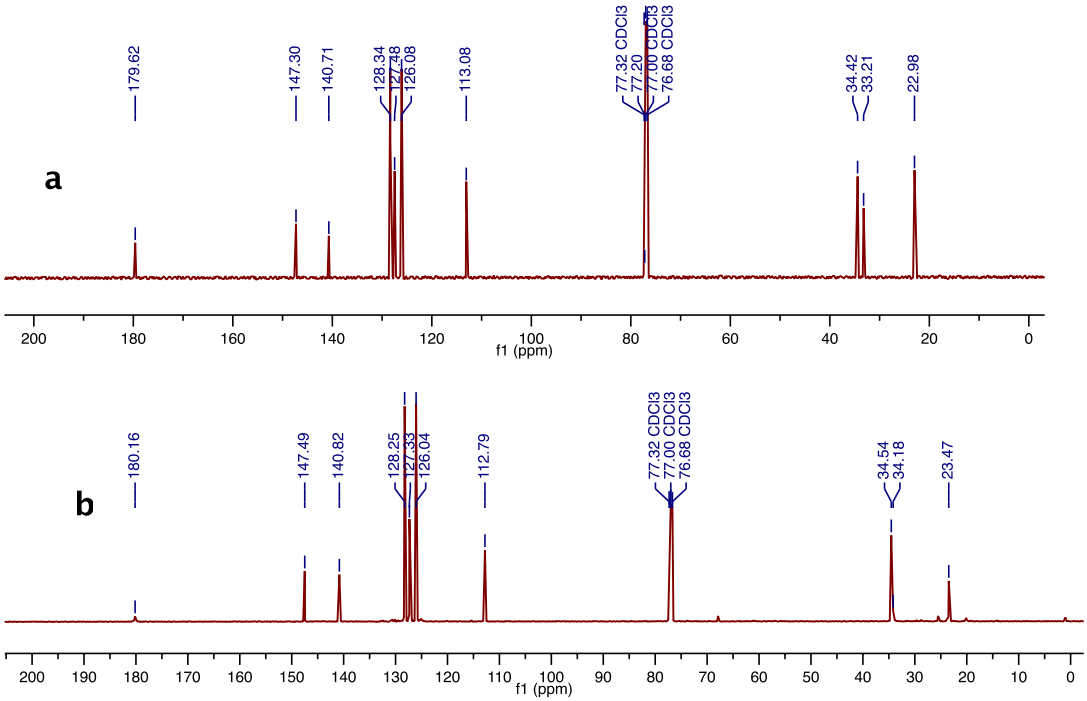


Figure 2.3 [13]C NMR spectra of: a) **86a**, b) 1:10 mixture of **105** and **86a**.

2.1.4 Conclusion and future perspectives

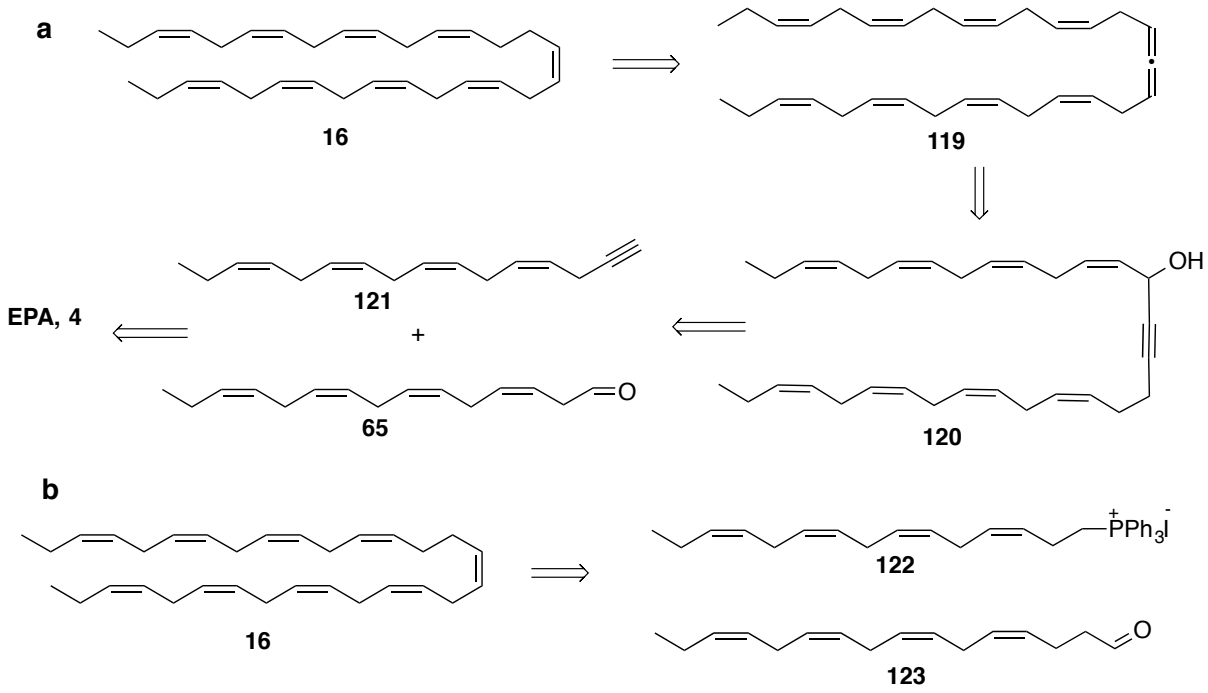
The application of Trost´s dinuclear zinc complex was expanded to enantioselective iodolactonization of 1,1-disubstituted δ-unsaturated carboxylic acids. The corresponding δ-iodolactones were obtained in up to 83% ee. The contact of the dinuclear zinc complex with moisture and air was shown to be crucial for formation of more selective catalytic species. Modularity of the *bis*-proline phenol ligand allows to modify its diarylcarbinol moiety.[146] The investigation of electronic and steric effects of aryl substituents in modified ligands on enantioselective outcome of iodolactonization might be of interest for understanding the origin of enantioselectivity as well as for further improvements.

2.2. Synthesis of an (all-*Z*)-hentriaconta-3,6,9,12,15,19,22,25,28-nonaene (Paper II)

The aim of this part of the study was to achieve a stereoselective total synthesis of the bacterial very long chain (VLC) C31-polyunsaturated hydrocarbon **16**, which previously has been isolated only in minute quantities. In particular we wanted to confirm the claimed[47, 49] all-*Z* absolute stereochemistry of this molecule.

2.2.1 Retrosynthetic analysis

Inspection of the target molecule of hydrocarbon **16** revealed the latent symmetry around the middle chain double bond. Our retrosynthetic analysis of **16** was based on a *Z*-stereoselective reduction of the symmetric allene **119** (Scheme 2.3). The latter we anticipated to access from a propargylic rearrangement of alcohol **120**, the coupling product of known C15 unsaturated aldehyde **65** and terminal C16 alkyne **121**. Alternatively, the C15-C16 middle bond can be generated *via* a *Z*-selective Wittig reaction between Wittig salt **122** and C16 aldehyde **123**.

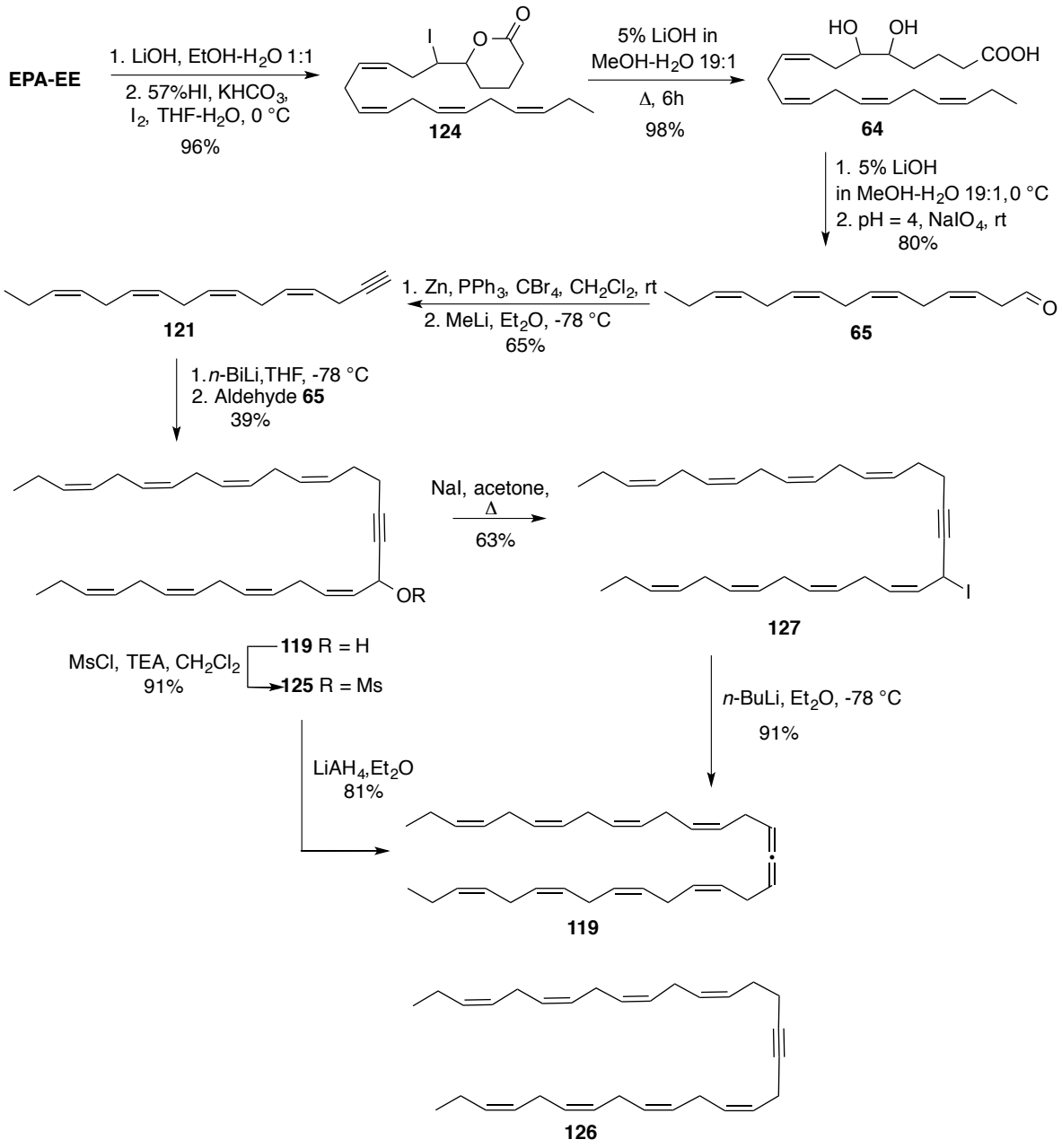


Scheme 2.3 Retrosynthetic analysis of C31 hydrocarbon **16**: a) the allene *semi*-reduction pathway; b) the Wittig reaction pathway.

2.2.2 The first total synthesis of (all-*Z*)-hentriaconta-3,6,9,12,15,19,22,25,28-nonaene

Following the first strategy (Scheme 2.3, a), the synthesis of **16** started with the preparation of the key intermediate aldehyde **65** from EPA ethyl ester by a known three step sequence[90] in 75% overall yield. The terminal alkyne **121** was readily available from **65** in 65% yield

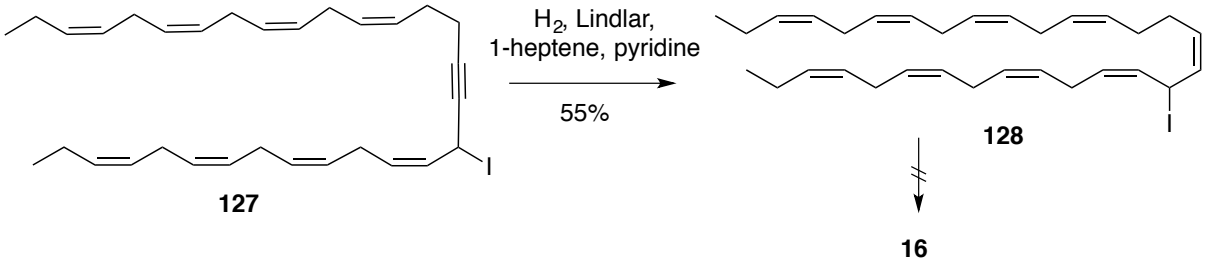
by a Corey-Fuchs reaction (Scheme 2.4).[87] The anion derived from **121** by treatment with *n*-BuLi at -78 °C was reacted with aldehyde **65** to afford the propargylic alcohol **120** in moderate 39% yield.[148] The alcohol **120** was smoothly transformed into the corresponding mesylate **125** followed by reduction with $LiAlH_4$. This resulted in an inseparable mixture of the allene **119** and the isomeric C31 alkyne **126** in 81% total yield and 92:8 ratio (GC). Alternatively, by a Finkelstein reaction, the mesylate **125** was converted to the propargylic iodide **127**. This was treated with *n*-BuLi at -78 °C to afford a hydrocarbon, which was identified as the target allene **119** based on ^{13}C NMR (203.2 and 89.5 ppm), Raman (1955 cm^{-1}) and HRMS (m/z = 416.3434) data.[149]



Scheme 2.4 Synthesis of allene **119**.

The *Z*-selective partial reduction of allene functionality in **119** was originally planned to be perform by the Lindlar hydrohenolysis procedure,[150] with the use of 1-heptene and pyridine as modifiers. However, only starting material has been isolated from this reaction. Hydrogenation with the use of more powerful reduction catalysts such as 10% Pd/C[151] led to mixture of target alkene with products of over-reduction proven to be difficult separate by chromatography.

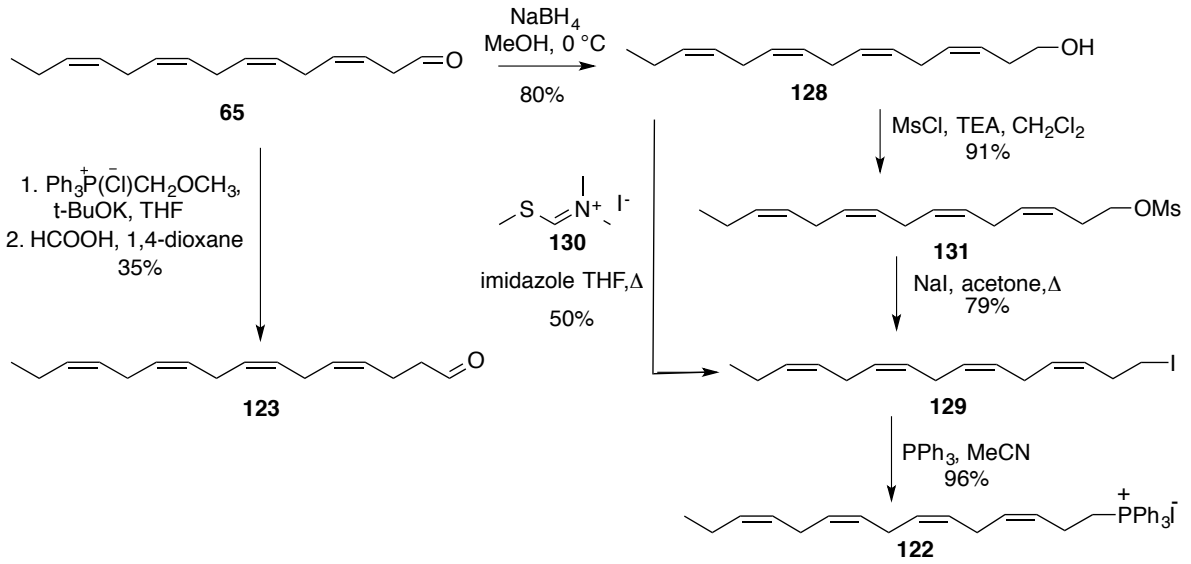
The propargylic iodide **127** was partially reduced using the same Lindlar modified protocol to the corresponding vinylic iodide **128,** isolated in 55% yield by column chromatography (Scheme 2.5). We anticipated that by conversion of **128** into the organometallic compound with subsequent aqueous work-up, the target hydrocarbon **16** should be accessed. But disappointingly, the treatment with either Mg or *n*-BuLi did not result in **16**.



Scheme 2.5 Semi-reduction of propargylic iodide **127**.

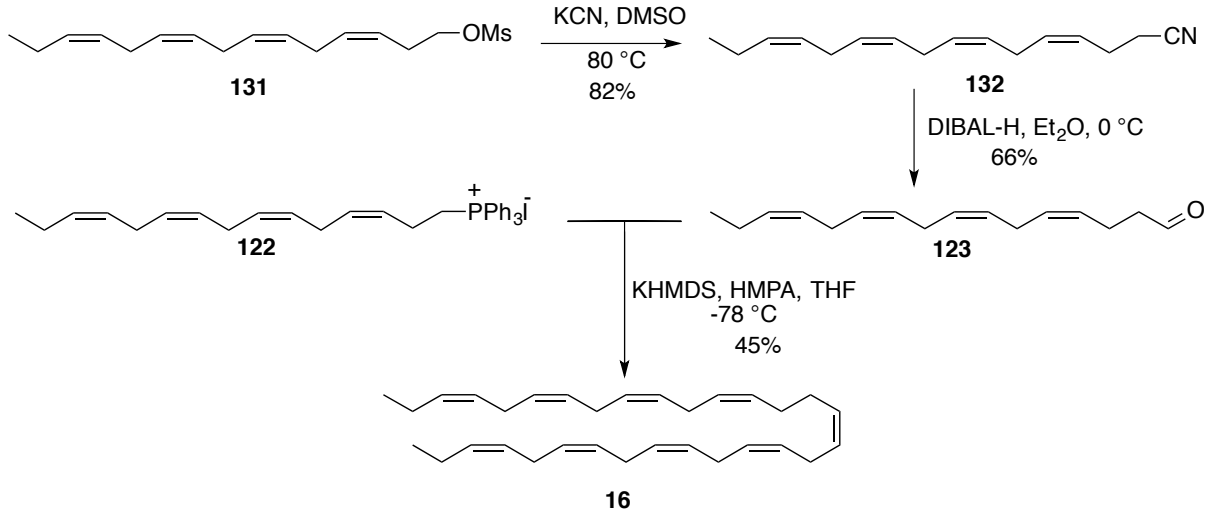
After these discouraging results, the attention was turned to an alternative route where the *Z*-selective Wittig reaction is a key step (Scheme 2.3, b). The Wittig salt **122** was prepared a by four step procedure in 55% overall yield from **65** as depicted in Scheme 2.6. Initially, the direct conversion of alcohol **128**[86] to iodide **129** was planned to be achieved by treatment with *N,N*-dimethyl-*v* -(methylsulfanylmethylene)ammonium iodide **130**.[152] However, the unsatisfactory yield of this reaction (50%) forced us to use a the step procedure of making iodide **129** *via* formation of the intermediate mesylate **131** (72% over 2 steps).

The C16 aldehyde **123** has been prepared in 35% yield by a one-pot elongation of the aldehyde **65** employing the Wittig type reaction with phosphonium ylide derived from the commercially available (methoxymethyl)triphenylphosphonium chloride as previously reported (Scheme 2.6).[90] In addition to the poor yield, the reaction had a drawback in formation of isomeric to **65** and **123** by-products hardly separable by chromatography.



Scheme 2.6 Synthesis of the Wittig salt **122** and aldehyde **123**.

With this in mind, alternatives were sought, and the aldehyde **123** was synthesized *via* the selective DIBAL-H reduction of nitrile **132**,[153] obtained from the mesylate **131** by a simple S_N2 transformation (KCN, DMSO) (Scheme 2.7). This pathway has proven to be superior to the C1 elongation in the terms both of yield (39% overall yield from **65**) and purity of the obtained product.



Scheme 2.7 The final steps in the total synthesis of **16**.

In the final step of the total synthesis the target natural product, the ylide derived from phosphonium iodide **122** by treatment with KHMDS in THF at -78 °C, was reacted with the aldehyde **123** to afford **16** in 45% yield and >95% chemical purity. The *Z/E* ratio has been determined by GC as >98:2. Within the detection limit, ^{13}C NMR spectra revealed no carbon peaks at the region 30-31 ppm (Figure 2.4), characteristic for the methylene carbon

in allylic position to an *E*-double bond[154] and, by this, confirmed the all-*Z* configuration of double bonds. Other spectral data (^{1}H NMR and IR) of synthetic **16** were in agreement with those reported for the authentic product.[47- 49]

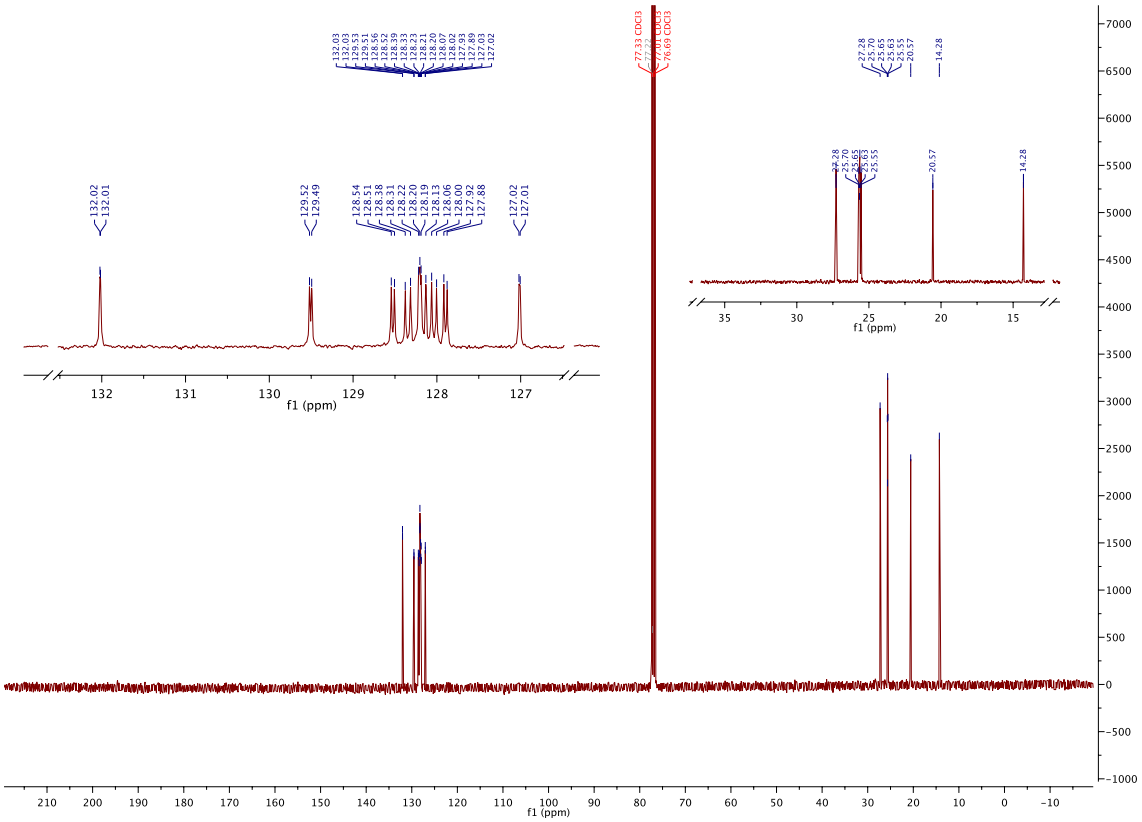


Figure 2.4 ^{13}C NMR spectrum of **16**.

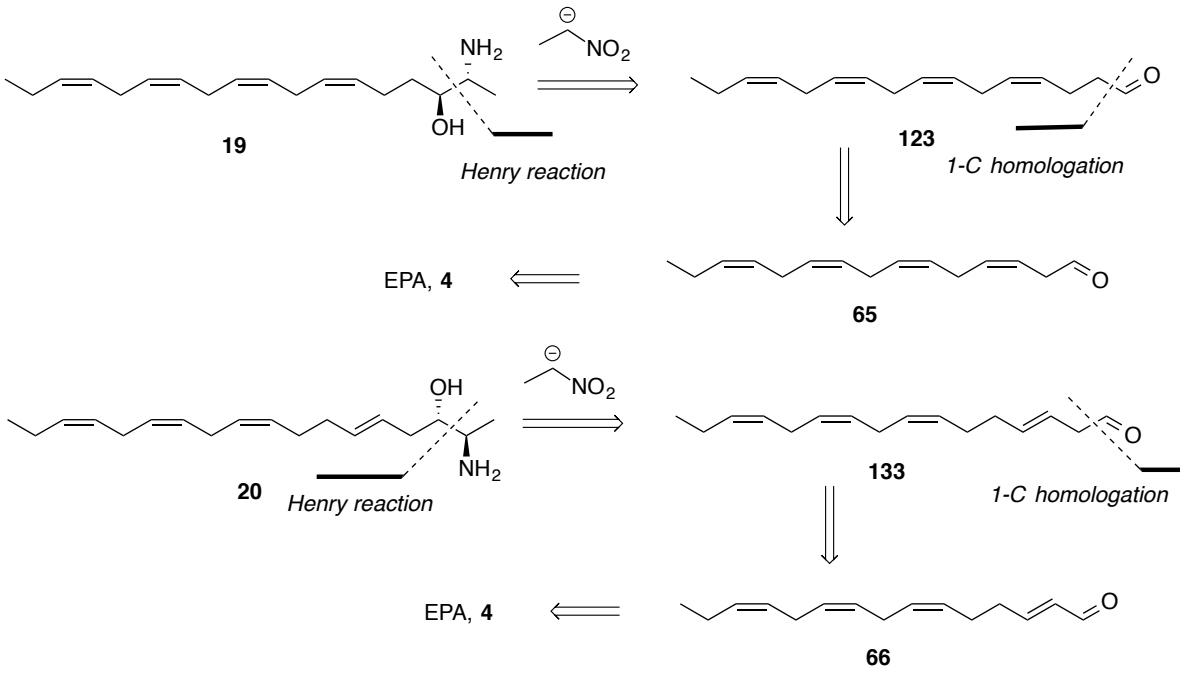
2.2.3 Conclusions

The first total synthesis of the VLC bacterial metabolite, all-*Z*-hentriconta-3,6,9,12,15,19,22,25,28-nonaene (**16**) have been successfully acomplished in eight step and 15% overall yield starting from EPA ethyl ester. The synthesis confirmed the absolute configuration of the double bonds as all-*Z*. The synthesis provides the access of the natural product **16** on multi-gram scale, sufficient for performing biological test. The synthetic strategy can also be used for preparation of labeled analogs of **16**.

2.3 Synthetic study towards polyunsaturated amino-alcohol lipids (Papers III and IV)

As it was briefly mentioned in the introductory section, the tunicate-derived amino-alcohol metabolites possess various interesting biological activities including anti-cancer. Due to this, these metabolites have been targeted for total synthesis by several research groups. To date, the amino-alcohols spisulosine ES 285 (**23**) and several cyclic amaminols have been synthesized in enantiopure forms by several different methodologies.[155-160] In contrast, no total syntheses of their polyunsaturated analogs obscuraminol A (**19**) and crucigasterin 277 (**20**) have yet been reported. However, two unsuccessful chiral pool strategies of synthesis of crucigasterin 277 and one on synthesis of obscuraminol A have been described.[161-163]

The rapidly evolving asymmetric catalytic methodologies prompted us to investigate the enantioselective synthetic approaches towards C18 polyunsaturated amino-alcohols **19** and **20**. As outlined in retrosynthetic Scheme 2.8, the amino-alcohol functionalities can be derived *via* an asymmetric catalytic nitroaldol (Henry) reaction between nitroethane and the corresponding C16 aldehydes followed by a reduction of the nitro group. Obviously, this is the most straightforward synthetic pathway. The C16 aldehyde precursors can be obtained by C1 homologation of the corresponding C15 aldehydes **65** and **66**. The latter two are easily available by oxidative degradation of EPA.



Scheme 2.8 Retrosynthetic analysis of obscuraminol A (**19**) and crucigasterin 277 (**20**).

With the already established synthetic protocol for the C16 aldehyde **123**, initially, the general applicability of the asymmetric Henry strategy was explored towards the synthesis of obscuraminol A (**19**).

2.3.1 Copper(II)-catalyzed asymmetric Henry reaction with a novel C_1-symmetric aminopinane-derive ligand (Paper III)

The study commenced with the selection of an appropriate catalyst for the key step, the diastereoselective Henry reaction. The ideal catalyst should in our mind satisfy the following criteria: 1) it should provide high level of both *anti*-diastereo- and enantioselectivity in a reaction with challenging aliphatic substrates; 2) be accessible from commercial chiral sources preferably *via* a short synthetic sequence and, 3) bearing in mind the synthesis of **20** as well, be available in both enantiomeric forms. Despite all advances made in enantio- and diastereoselective catalysis development, the most of the catalysts are substrate dependent and there is a lack of a general method for the nitroaldol reaction meeting all criteria 1)-3) at the same time. In addition, the most of catalytic systems are either not applicable or have not been tested in reaction with nitroalkanes other than nitromethane. These factors prompted us to attempt developing a new catalyst. The results are summarized in the sections given below.

2.3.1.1 Preliminary considerations

Among many useful chiral promoters, bicyclic monoterpenes are convenient natural source of chirality, and usually readily available in both enantiomeric forms. As a starting point for the catalyst design, a set of C_1- and C_2-symmetric bidental *N,N*-ligands **112**[131], **134**[132], **135**[128], **136**[164] and **137**[126] bearing a camphor auxiliary was considered (Figure 2.5). In general the copper (II) complexes of these ligands have been reported to promote the asymmetric Henry reaction between nitromethane and various aldehydes, including aliphatic ones, with high enantioselective outcome up to 98% ee. The C_1-symmetric ligands in coordination with a copper (II) ion, according to the generally accepted Evans' model, cause the larger electronic and steric differentiation of equatorial coordination positions in formed complexes.[131] Hence, in most cases the efficiency of non-symmetric ligands are superior to relative C_2-symmetric.[165] This has also been observed also for the C_2-symmetric ligand **110** which was shown to be less selective compared to the relative non-symmetric ligands.[126]

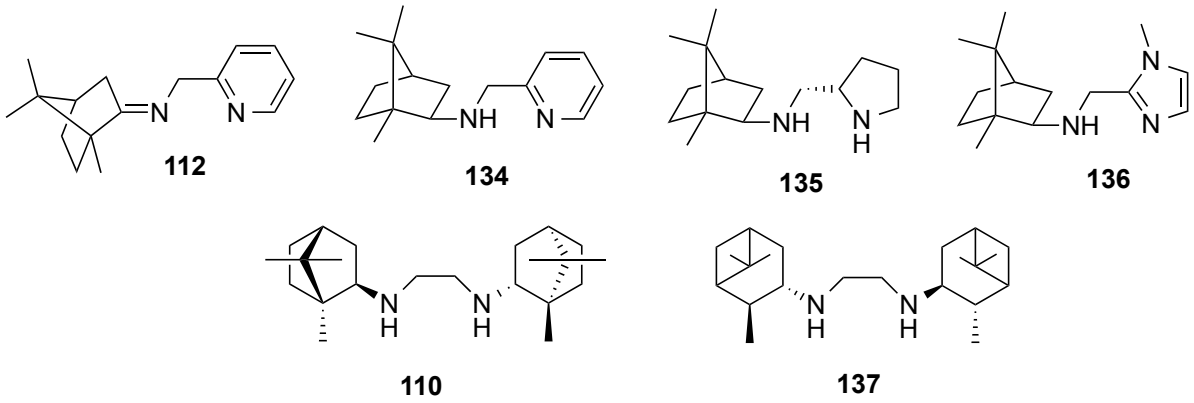
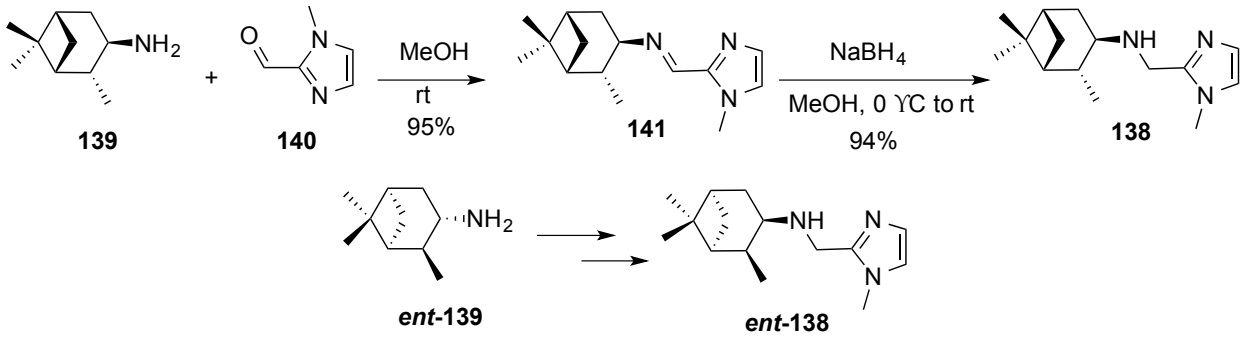


Figure 2.5 Some camphor and pinnae-derived *N,N*-ligands.

The pinane-type chiral derivatives can be considered as alternative terpene asymmetry inducers. The pinane core has gained wide application in chiral reducing boron reagents[166, 167] and as chiral auxiliaries in some asymmetric transformations such as aldol type reactions[168] and diethylzinc addition to aldehydes.[169, 170] The application of ligands based on pinane in asymmetric catalysis has been only rarely explored. However, recently it was reported on application of the C_2-symmetric pinane-diamine ligand **137** in an enantioselective Henry reaction.[127]

Based on structure **136**, the C_1-symmetric ligand **138** has been synthesized in a one pot-reaction from commercial available (1*R*,2*R*,3*R*,5*S*)-isopinocampheylamine **139** and 1-methyl-2-imidazolecarboxaldehyde **140** (Scheme 2.9). The non-symmetric **138** was expected to have a comparable or even higher catalytic potential than the analogous **137**.



Scheme 2.9 Synthesis of aminopinane-derived ligand **138** and its enantiomer.

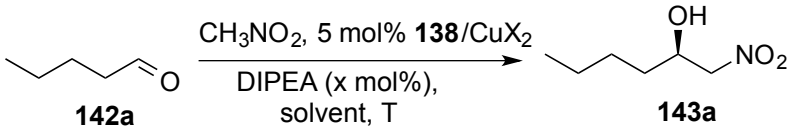
2.3.1.2 Results and discussion

Initially the reactivity and selectivity of **138** was tested in the nitroaldol reaction between valeraldehyde **142a** as a model substrate and nitromethane in the presence of $CuCl_2 \cdot 2H_2O$ or $Cu(OAc)_2 \cdot H_2O$ as copper (II) ion sources (5 mol%) and DIPEA (1.0 equiv.) as external base at 0-4 ºC. Some representative results of the reaction condition screening are presented in Table 2.2. The **138**/$CuCl_2 \cdot 2H_2O$ complex promoted the reaction with high yield and

moderate enantioselective outcome (entry 1). It was also observed that the reactivity of the complexes derived from **138** and both coppers salts was influenced by the both counter-ion and the used solvent. Most likely, this was due to the differences of solubility. With respect to selectivity both complexes gave approximately similar results, though **138**/$Cu(OAc)_2 \cdot H_2O$ is slightly preferred. We then subjected this complex to solvent screening (entries 4-7), and this revealed *i*-PrOH to be the best in terms of both yield and enantioselectivity (entry 6). Lowering the temperature of the reaction to -20 ºC significantly decreased the reaction rate with no effect on enantioselectivity.

The enantioselectivity of the Henry reaction was still quite low. Assuming that ee-values of nitro-alcohol adducts can gradually erode due to retroaldolization,[117] the time-course study of the reaction was undertaken to investigate the effect of a possible retro-Henry reaction. The reaction was almost complete in four hours (entries 10-13). Leaving the reaction mixture for an additional extended time, no decrease in ee-values of formed nitro-aldol product could be observed. The results then indicated that there was no retro-nitroaldol reaction taking place under these conditions.

Table 2.2 Screening of the reaction conditions.



142a **143a**

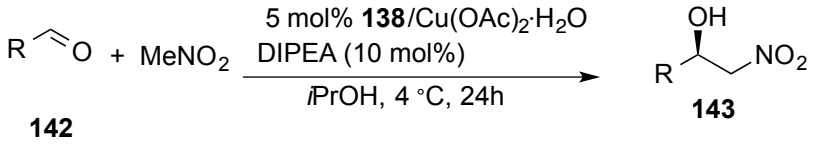
Entry[a]	Copper salt	Solvent	T (°C)	Time (h)	DIPEA (mol %)	Yield (%)[b]	ee (%)[c]
1	$CuCl_2 \cdot 2H_2O$	THF	4	20	100	90	53
2	$Cu(OAc)_2 \cdot H_2O$	THF	4	20	100	52	52
3	$CuCl_2 \cdot 2H_2O$	EtOH	4	20	100	88	33
4	$Cu(OAc)_2 \cdot H_2O$	EtOH	4	20	100	92	37
5	$Cu(OAc)_2 \cdot H_2O$	CH_2Cl_2	4	20	100	68	47
6	$Cu(OAc)_2 \cdot H_2O$	*i*-PrOH	4	20	100	97	55
7	$Cu(OAc)_2 \cdot H_2O$	Et_2O	4	20	100	63	46
8	$Cu(OAc)_2 \cdot H_2O$	THF	-25	20	100	<5	n.d.[d]
9	$Cu(OAc)_2 \cdot H_2O$	*i*-PrOH	-25	72	100	88	57
10	$Cu(OAc)_2 \cdot H_2O$	*i*-PrOH	4	2	100	68	57
11	$Cu(OAc)_2 \cdot H_2O$	*i*-PrOH	4	4	100	88	56
12	$Cu(OAc)_2 \cdot H_2O$	*i*-PrOH	4	6	100	85	55
13	$Cu(OAc)_2 \cdot H_2O$	*i*-PrOH	4	8	100	89	57
15	$Cu(OAc)_2 \cdot H_2O$	*i*-PrOH	4	20	0	36	56
16	$Cu(OAc)_2 \cdot H_2O$	*i*-PrOH	4	20	5	88	57
17	$Cu(OAc)_2 \cdot H_2O$	*i*-PrOH	4	20	10	98	56

[a]The reactions were carried out on 0.5 mmol scale of valeraldehyde with 10 equiv. of nitromethane in 2 mL of solvent. [b]Isolated product. [c]Enantiomeric excesses by HPLC analyis using a column with a chiral stationary phase. [d]Not determined.

The excess of external base can also influence the enantioselective outcome of the Henry reaction due to enhancement of the non-enantioselective pathway, and examples of these have been reported in the literature.[125, 171] Therefore, the effect of the external base loading was tested. The addition of increased amounts of DIPEA significantly improved the reaction yields without any loss in enantioselectivity (entries 15-17). The addition of 10 mol% of DIPEA was found to be the optimal loading to promote complete reactions.

Having established the reaction conditions, the scope of the transformation was examined using a set of different aliphatic and aromatic aldehydes (Tables 2.3 and 2.4). In the most cases the aliphatic aldehydes were converted to the corresponding products with good yield and moderate enantioselectivity in the range of 47 to 67% ee (Table 2.3). The higher ee-values were observed for bulky α-branched pivaldehyde **142c** (entry 3). For the long-chain aldehydes somewhat prolonged reaction times were needed in order to achieve a full conversion (monitored by TLC). The absolute configuration of the resulting nitro-alcohols was assigned based on comparison of the specific optical rotation values with the literature data.

Table 2.3 Enantioselective Henry reaction of aliphatic aldehydes with nitromethane.



142 **143**

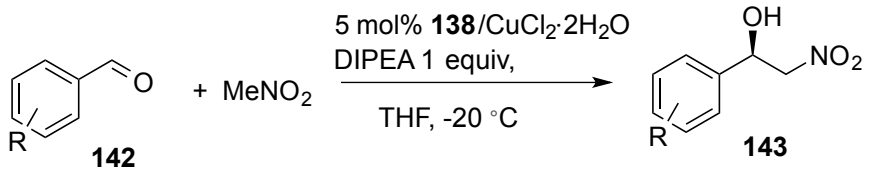
Entry[a]	R	Aldehyde	Product	Yield (%)[b]	ee (%)[c]
1	*n*-Bu	**142a**	**143a**	91	57
2	*i*-Bu	**142b**	**143b**	89	49
3	*t*-Bu	**142c**	**143c**	88	67
4	*i*-Pr	**142d**	**143d**	83	60
5	*n*-nonyl	**142e**	**143e**	75	55
6[d]	*n*-undecyl	**142f**	**143f**	82	53
7	*trans*-2-decenyl	**142g**	**143g**	65	47

[a] The reactions were performed on 0.5 mmol scale. [b] Isolated yield. [c] Determined by HPLC using a column with a chiral stationary phase. [d]Prolonged reaction time is required.

Then attention was turned to the aromatic aldehydes. Surprisingly, the usually more reactive aromatic substrates turned out less tolerant under these conditions. First, the resulting nitro-alcohols had tendency to rapidly decompose before a reasonable conversion of the starting material had been achieved. The decomposition was minimized by employing **138**/$CuCl_2$·$2H_2O$ complex as a catalyst and with the use of THF instead of *i*-PrOH. Second, the conversion of benzaldehyde **142h** did not reach completion after reacting for 24h at 0-4 ºC while the ee-valued of the resulting adduct was lower compared with aliphatic aldehydes

(Table 2.4, entry 1). Lowering the temperature of the reaction, the nitroaldol products were formed in diminished yields, but with improved ee-values (entry 2, 3), indicating a great effect of the retroaldolization and a competing kinetic *versus* thermodynamic control. Further, the scope of aromatic aldehydes were converted into corresponding nitroalcohols at -20 °C. As expected, the ee-values of the products were greatly affected by the prolonged reaction time due to racemization most likely *via* a reversible reaction (entries 5-7). In most cases 120 hours of reaction time were necessary to achieve the reasonable conversion. In general, the electron-rich substrates turned out to be less reactive (entries 5, 6) while the *p*-hydroxybenzaldehyde was recovered unchanged after 48 hours (entry 4). In all cases the ee-values of the resulting thermodynamic products did not exceed 55%.

Table 2.4 Enantioselective Henry reaction of various aromatic aldehydes with nitromethane.



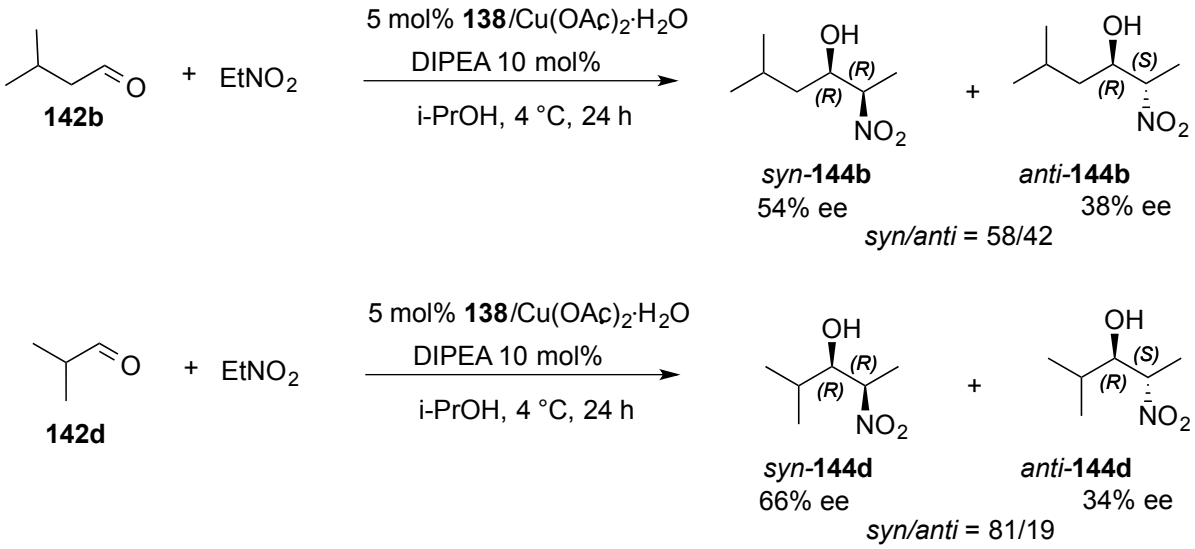
142 143

Entry[a]	Substrate	Product	Time (h)	Yield (%)[b]	ee (%)[c]
1[d]	Ph	**143h**	24	80	38
2	Ph	**143h**	48	63	45
3[e]	Ph	**143h**	48	10	76
4	*p*-OHC_6H_4	**143i**	48	No reaction	-
5	3,4-$(MeO)_2C_6H_3$	**143j**	48	37	54
			120	85	46
6	3,4,5-$(MeO)_3C_6H_2$	**143k**	48	31	52
			120	86	40
7	*p*-BrC_6H_4	**143l**	48	91	59
			120	98	45
8	*p*-*t*BuC_6H_4	**143m**	120	93	48
9	*p*-O_2NC6H4	**143n**	120	86	55
10	*p*-ClC_6H_4	**143o**	120	57	63

[a]The reactions were performed on 0.5 mmol scale. [b]Yield of the isolated product. [c]Determined by HPLC analysis using a column with a chiral stationary phase. [d]The reaction was carried out at 4 °C. [e]The reaction was carried out at -40 °C.

To get an extended picture of the catalytic activity of **138**/$Cu(OAc)_2 \cdot H_2O$, the diastereoselective Henry was carried out reacting nitroethane with aliphatic aldehydes (Scheme 2.10). The reaction proceeded cleanly to afford the nitroaldol adducts bearing two stereogenic centers in high yields (up to 93%) with slight prevalence of *syn*-diastereomers. The *syn/anti* ratios and absolute configuration of the products were assigned by comparison of the ^1H NMR spectra, retention times in HPLC and optical rotations with the reported data.[172] The optical purity of the minor *anti*-adducts were lower than those of *syn*-adducts,

indicating that the minor products were not a result of epimerization of the nitro group.[128] The reaction of the α-branched aldehyde **142d** resulted in an improved *syn/anti* ratio.



Scheme 2.10 Diatereoselective Henry reaction using nitroethane.

As no improvements in stereoselectivity were achieved, the exploration of the catalyst was halted at this stage. The observed enantioselectivities were much lower compare with those reported for the analogous C_2-symmetric ligand **137.** Such moderate results probably can be explained by a loose character of the chiral motif that is relatively remote from the coordinating unit, and by higher conformational flexibility of **138** increasing the number of competing diapathways. Just recently a small library of both C_1- and C_2-symmetric pinene-derived diamine ligands were reported to be screened in a copper(II) catalyzed Henry reaction between *p*-nitrobenzaldehyde and nitromethane;[173] the reported ee-values did not exceed moderate 57% in close agreement with our findings.

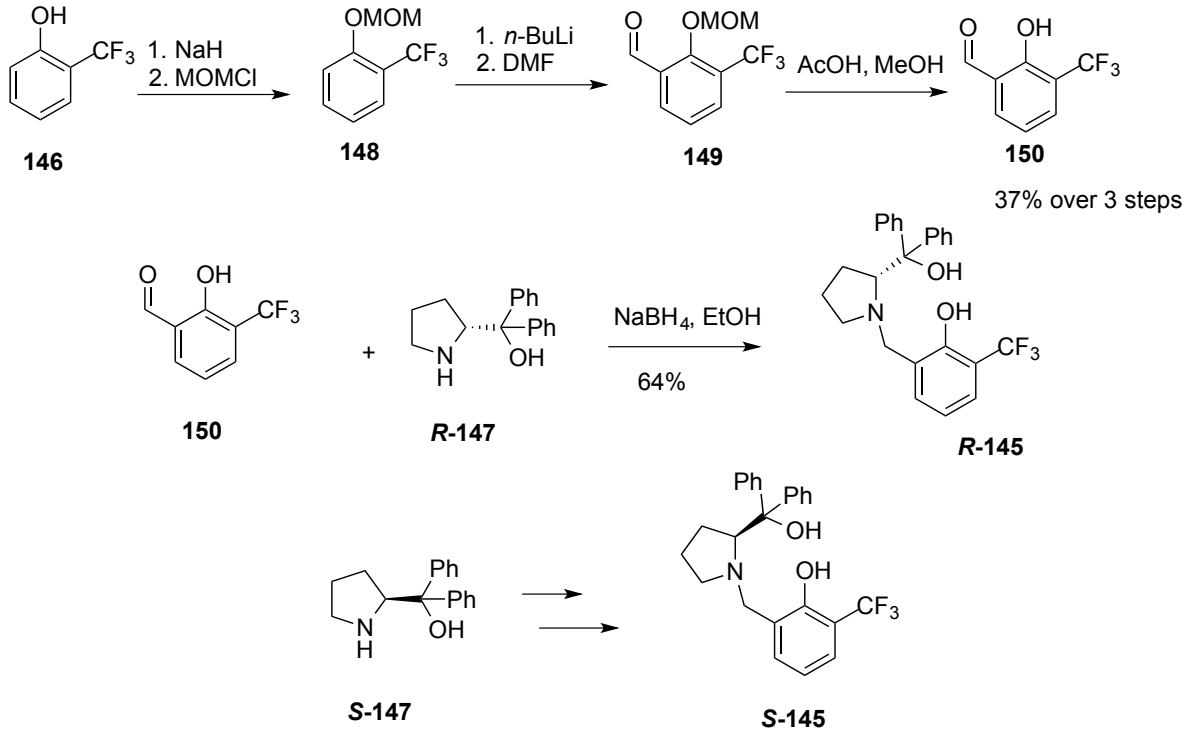
2.3.1.3 Conclusion

The copper (II) complex of novel C_1-symmetric aminopinane-derived ligand was found to exhibit reasonable catalytic asymmetric activity in the Henry reaction. High yield (up to 91%) and moderate enantioselectivities (up to 67%) were observed for aliphatic aldehyde under the mild reaction conditions.

2.3.2 Synthetic studies towards obscuraminol A (Paper IV)

2.3.2.1. Diastereoslecitve Henry reaction

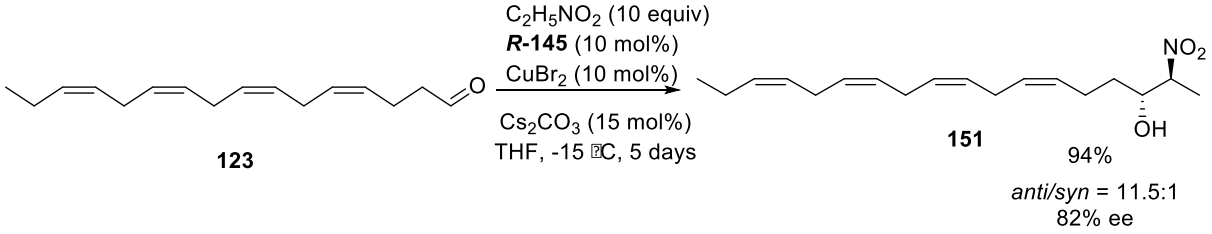
The unpractical levels of enantio-induction obtained in the Henry reaction catalyzed by copper(II) complex of aminopinane-derived ligand, forced us to focus the attention on *anti*-diastereoslective catalysts that have been reported in the literature. The collection of effective catalytic systems of such kind is quite limited.[122, 123, 174-178] In addition, most of them have limitation in the substrate scope using only aromatic aldehydes. Within this point of view the proline-phenol ligand **145,** reported in 2012 by Wang and co-workers[177] was of particular interest (Scheme 2.11). Available in both enantiomeric forms, it was demonstrated to possess high diastereoselective catalytic activity (above 15:1 in most cases) towards a broad range of aldehydes, including long-chain aliphatic ones, while maintaining the excellent ee-values. Therefore, the ligand **145** was synthesized in four steps from commercial available 2-trifluoromethylphenol **146** and *R*- or *S*-α,α-diphenyl-2-pyrrolidinemethanol (**147**) according to the previously reported procedure.[179] The results are compiled in Scheme 2.11.



Scheme 2.11 Outline of the catalyst synthesis.

The *R*- and *S*-epimers of **145** should provide the (2*S*,3*R*) and (2*R*,3*S*) absolute configurations of the nitro-alcohol core as major diastereomers, respectively, in analogy with related

nitroaldols reported in the literature.[177] Thus, ***R*-145** was first examined in the target nitroaldol reaction between **123** and nitroethane (Scheme 2.12). In the initial experiment under original conditions (5 mol% ***R*-145**, 5 mol% $CuBr_2$, 7.5 mol% Cs_2CO_3, 10 equiv. of nitroethane, THF 0.5M, -15 °C) the reaction was sluggish and yielded the desired nitroaldol adduct **151** only in 23% yield and 15.6:1 *anti/syn* ratio after 24 hours. Prolonging the reaction time for another 24 hours gave a drop in dr to 9.6:1 but, interestingly, was accompanied by the improvement of optical purity of the major diastereomer (62% ee against 56% ee). Therefore, a set of experiments was carried out to settle the optimal reaction conditions in terms of both yield and stereochemical outcome. In general, raising the reaction temperature improved the yield and reduced both dr (7.3:1 at -10 °C and 3.4:1 at -5°C) and ee-values (approximately 40%). On the basis of these observations we assumed that the decrease of dr during the course of the reaction most likely is caused by epimerization of the nitro group of the kinetic (2*R*,3*S*)-nitroaldol product. According to Wang's mechanistic proposal for **145**, the (2*R*,3*S*)-diastereomer is formed *via* the least favored transition state in the catalytic reaction pathway,[177] and hence, most likely it was rapidly formed through a non-catalytic pathway in the initial stage of the reaction. In order to maximally suppress the non-catalytic side reaction, the catalyst loading was increased to 10 mol%, and, what was important, the generated *in situ* in THF/***R*-145** mixture with nitroethane was pre-cooled to -15 °C prior to the aldehyde addition. Although at -15 °C the reaction rate was still slow, the thermodynamic nitro-alcohol (2*S*, 3*R*) **151** was formed after 120 hours in 94% yield, 11.5:1 dr and 82% ee of the major diastereomer (Scheme 2.12).

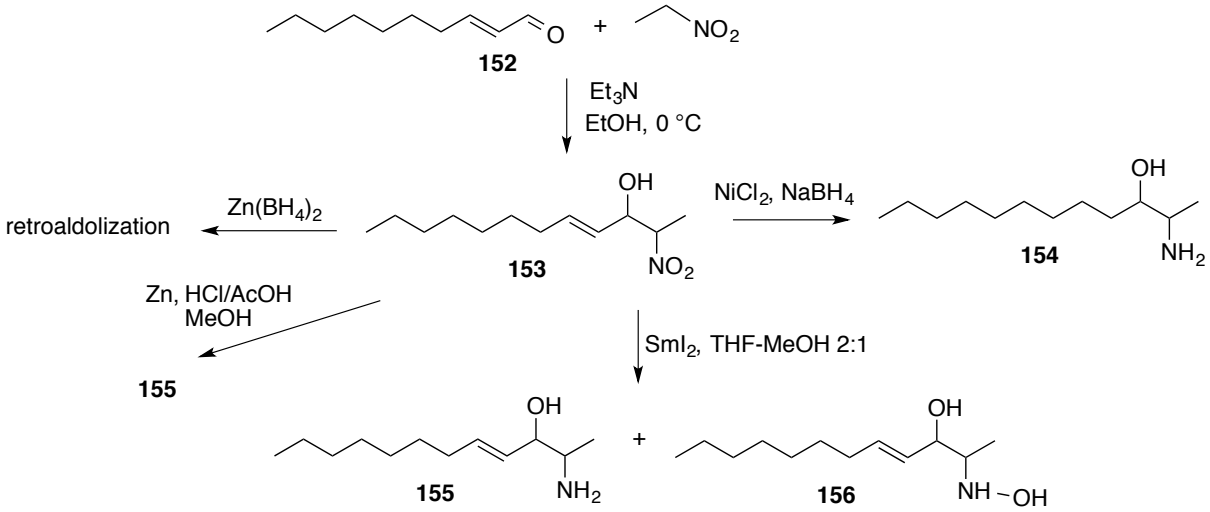


Scheme 2.12 The diastereoselecitve Henry reaction under optimized conditions.

2.3.2.2. Reduction of the nitro group

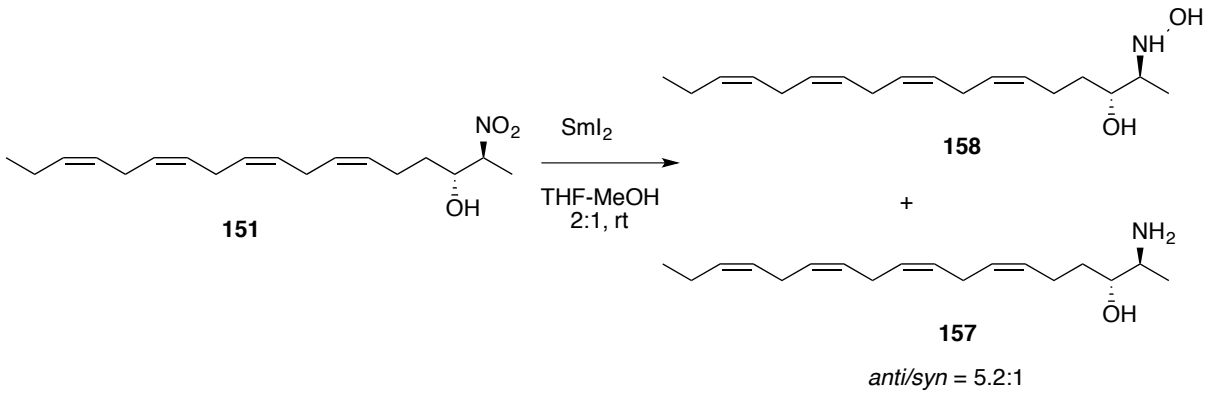
Reduction of the nitro-alcohol functionality with retention of the absolute stereochemistry, was now the major challenge. Two problems had to be encountered: competing reduction of the double bonds and β-elimination. Due to these reasons, the most reliable method, catalytic transfer hydrogenation over Pd/C or Raney-Ni, was abandoned.[122, 175-177, 180]

Different reducing agents and reaction conditions were then screened in the reaction employing inexpensive racemic (*E*)-2-nitrododec-4-en-3-ol **153** as a model substrate. The latter was obtained by racemic Henry reaction from commercial 2*E*-decenal **152** (Scheme 2.13). The first experiments were conducted with activated sodium borohydride. Reduction with $NaBH_4/NiCl_2$ resulted in formation of the saturated amino-alcohol **154** as the main product.[181] By running the reaction with $NaBH_4/ZnCl_2$ reducing agent, a complex, inseparable mixture consisting of the starting material, products of retro-nitroaldol reaction and intermediates of the nitro group reduction, was obtained.[182] Reduction with zinc powder in acidic media gave amino-alcohol **155** but in insignificant yield.[183] Finally, by treatment with THF solution of SmI_2 the nitroaldol **153** was converted to mixture of the corresponding amino-alcohol **155** and hydroxylamine **156**, easily separable by means of column chromatography.[184-185]



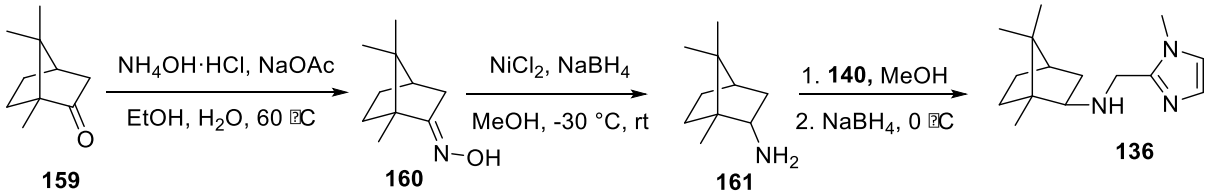
Scheme 2.13 Screening of reduction methods.

Having established in the preliminary screening SmI_2 as the most promising reducing agent, this procedure was applied to **151.** The reaction resulted in the amino-alcohol **157** and a mixture of products due to incomplete reduction, with hydroxylamine **158** as the major compound. Fortunately, isolation of the target amino-alcohol **157** by means of column chromatography was easily achieved in 59% yield (Scheme 2.14). Disappointingly, the SmI_2-mediated reduction had a significant impact on the stereochemical purity of the amino-alcohol product **157,** which turned out to be significantly lower than expected (dr *anti/syn* 5.2:1 against 11.5:1 for starting material), as demonstrated by NMR analysis. The drop in the diastereomeric ratio can be better explained by a *syn*-favorable transition state controlled by chelation of Sm(III) with Lewis basic functionalities, rather than by epimerization of the nitro group on intermediate stages of reduction.[186]



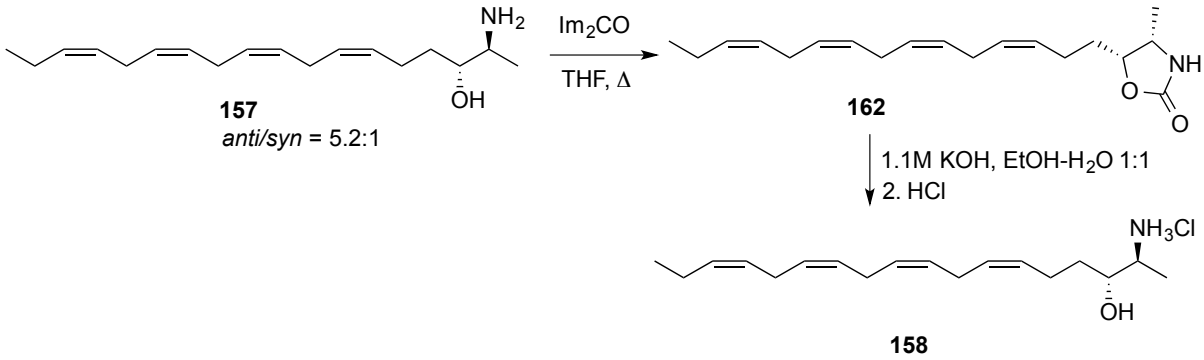
Scheme 2.14 Reduction of **151**.

To verify this assumption, the *syn*-enriched nitro-alcohol was prepared by a Henry reaction employing a *syn*-selective catalyst. The first choice of catalyst of such kind was, of course, the copper complex of aminopinane-derived ligand **138**. However, the obtained nitroaldol product had insignificant dominance of the *syn*-diastereomer. The ligand **136** was then prepared in three steps from available materials (Scheme 2.15).[128] and applied to the asymmetric Henry reaction with **123**. This afforded the nitroaldol product with a 1:2.8 *anti/syn* ratio. Reduction by SmI_2 gave the corresponding amino-alcohol with slightly improved *anti/syn* ratio of 1:4, according to ^1H NMR analysis, providing indirect evidence of a *syn*-favoring manner of the SmI_2-mediated reduction of nitro-alcohols.



Scheme 2.15 Synthesis of the ligand **136.**

At this stage it seemed impossible to isolate the pure *anti*-diastereomer of **157**. To achieve a more easy separation of the diastereomers we anticipated that a cyclic intermediate would be more rigid and thus make a separation possible. Then compound **157** was treated with carbonyl diimidazole to afford the corresponding oxazolidinones (Scheme 2.16). The major epimer could then be isolated in 61% yield. Based on data from NOESY and ROESY experiments, which clearly showed a correlation for the C1-C4 protons. Hence the configuration was assigned as *cis*, confirming the *anti*-configuration of the parent amino-alcohol. Alkaline hydrolysis of **162** afforded the target amino-alcohol in 63% yield.



Scheme 2.16 Isolation of the target diastereomer.

Comparing the NMR data for the obtained amino-alcohol with those for the authentic natural product,[52] some discrepancies was observed. A careful look at the literature data revealed obscuraminol A was isolated in the form its hydrochloride salt. Therefore, the amino-alcohol product obtained after alkaline hydrolysis of oxazolidinone **162** was transformed into the corresponding hydrochloride **158** by treatment with gaseous HCl. The NMR spectra of crude obscuraminol A as its free base are presented in Figure 2.6. In the ^{1}H NMR spectrum the multiplet signals at δ 3.60 and 3.08 ppm, corresponding to the protons at C3 and C2 are observed. After treatment with HCl gas, these signals shifted to δ 4.01 and 3.46 ppm respectively. In the isolation paper Garrido *et al*. reported those signal at 3.97 and 3.41 ppm respectively. The same pattern is also observed in the ^{13}C NMR spectrum: the signals at δ 73.1 (C3), 50.8 (C2) and 15.7 (C1) all shifted to new positions at δ 70.1, 52.1 and 12.0 with corresponding literature values reported at 70.0, 51.9, and 12.0. The similar minor discrepancies in positions of the mentions signal were observed for **157**. These observations are probably connected with the degree of protonation and rapid exchange processes on the NMR time scale between the free amine and its HCl-salt observable only in the ^{1}H NMR spectrum. The minor impurities observed in the NMR spectra shown in Figure 2.6 were identified as traces of unconverted **162**.

Due to the degradation of *anti/syn* ratio in the reduction step, the overall yield of obscuraminol A was low. This prompted us to revise the reduction methods of nitro-alcohol functionality using zinc powder in acidic conditions, which, according to the literature, should maintain the diastereo- and enantioselectivity.[183] The essential factor of concern was a hydroxyl elimination. When **151** was treated by zinc powder in HCl/AcOH the expected product was isolated in insignificant yield (≤ 20%). NMR analysis of the crude mixture revealed partial β-elimination. As an option, the elimination could be avoided by reduction with zinc in neutral media (NH_4Cl/MeOH).[187] However, no successful results were obtained so far and further experiments are required.

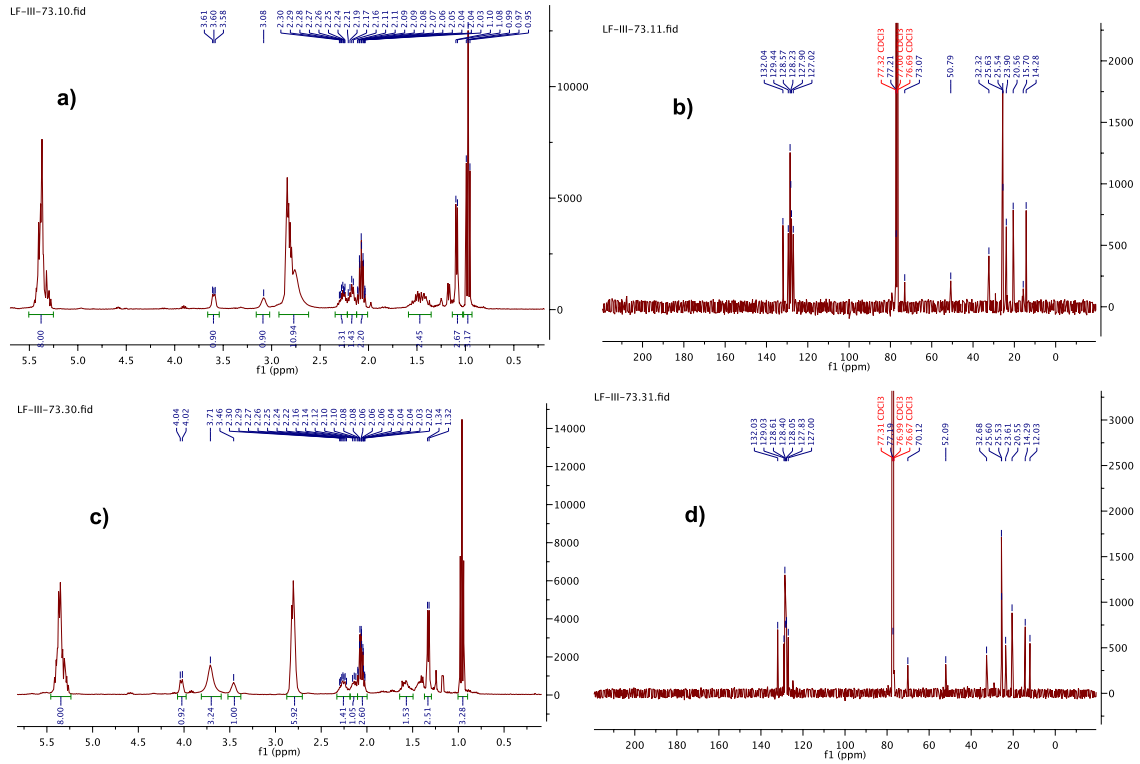
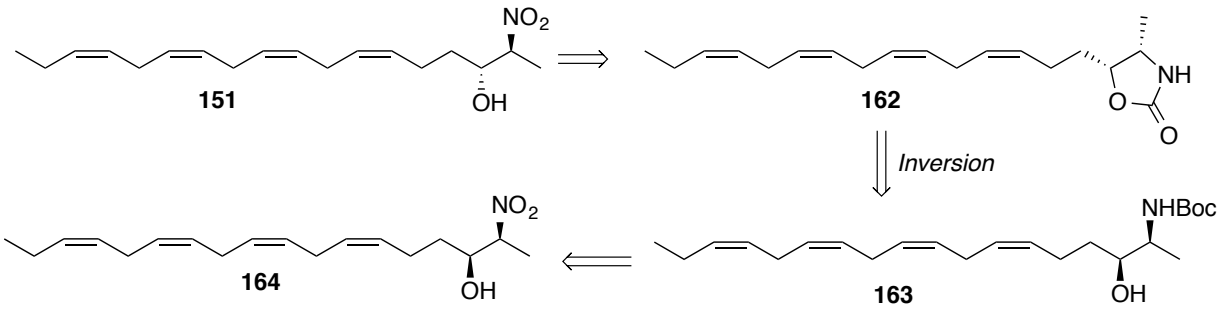


Figure 2.6 NMR spectra of crude obscuraminol A: a) and b) NMR spectra of obscuraminol A in free amine form, c) and d) NMR spectra of obscuraminol A as the hydrochloride salt.

2.3.2.3 Conclusion and further work

The synthesis of obscuraminol A (**19**) was completed *via* the catalytic asymmetric Henry reaction, yielding **19** in 5% overall yield starting from the ethyl ester of EPA (**4**). The *syn*-favorable reduction with SmI_2 was the crucial point of the synthesis. Taking this moment in consideration, one of the possible options for further improvements can be redesigning of the synthetic plan in favor of a new sequence: *syn*-diastereoselective Henry reaction,[188-189] SmI_2-mediated reduction, Boc-protection of amino-group and inverse cyclization[190, 191] to oxazolidinone with subsequent hydrolysis (Scheme 2.17).

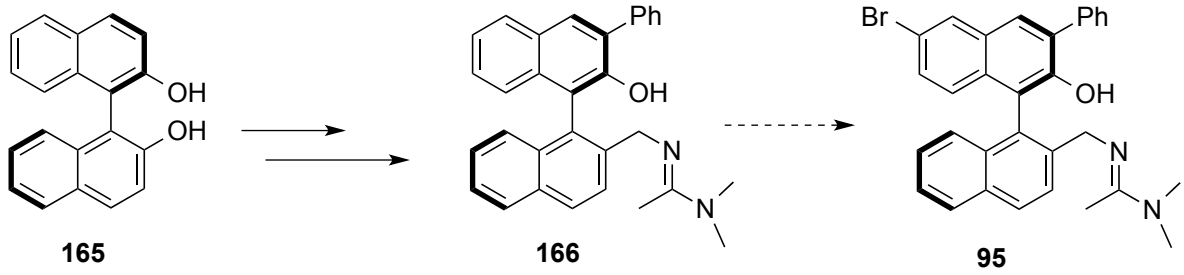


Scheme 2.17 Alternative route for obscuraminol A.

3. Summary and future work

This thesis deals with the stereoselective synthesis of biologically interesting polyunsaturated natural products of diverse biosynthetic origin starting from EPA ethyl ester In addition, the development of new asymmetric catalytic procedures for some useful transformation have also been achieved.

Specifically, the enantioselective iodolactonization reaction of DHA and EPA provides the shortest route to the corresponding enantiopure hydroxyl polyunsaturated fatty acids 5-HEPE, **8** and 4-HDHA, **9**. In this work the application of one of the "privileged" catalysts, a dinuclear zinc *bis*-proline phenol complex **105**, was expanded to asymmetric iodolactonization of δ-alkenoic acids. The corresponding iodolactones were obtained in good yields and with up to 83% ee. Unfortunately, the enantioselectivities achieved in reaction with 1,1-disubstituted olefinic acids could not been reproduced with EPA.
All efforts on enantioselective iodolactonization of EPA and DHA resulted only in racemic iodolactones or with very low ee values.[138] The BINOL-derived organocatalyst **95** seems the most promising for application on PUFA substrates.[111] The nine-step synthesis of the catalysts was initiated starting from *R*-1,1-binaphthol for further investigations and, so far, failed at the last transformation (Scheme 3.1).



165 **166** **95**

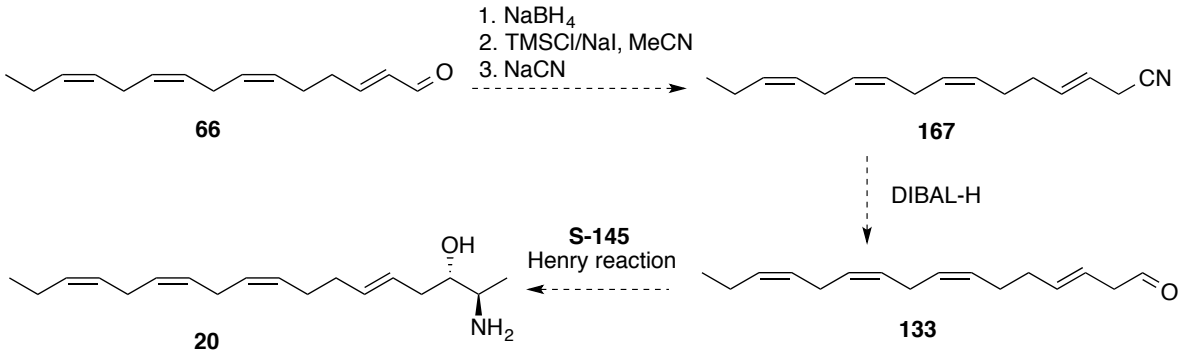
Scheme 3.1 Synthesis of BINOL-derived organocatalyst **95**.

Stereoselective synthesis of the microbial very long-chain polyunsaturated hydrocarbon **16** has been successfully accomplished starting from EPA ethyl ester and utilizing a *Z*-selective Wittig reaction as a key step. The use of the same intermediates for construction of both fragments of the molecule shortened the synthetic sequence and improved the overall yield of the product, making it available in quantities sufficient for biological evaluation. The

advantage of the reported protocol is that all *Z*-double bonds retained their configuration throughout the synthesis of **16**.

The attempts to design a new ligand for copper (II) catalytic asymmetric Henry reaction based on the use of a pinane core as a source of chirality, unfortunately, was not very successful. Nonetheless, in the presence of the copper complex of aminopinane-imidazole ligand **138** the aliphatic aldehydes can be smoothly converted to corresponding nitroaldol adducts in high yields with moderate ee values and diastereoselectivity.

The applicability of the diastereoselective Henry reaction in the total synthesis of polyunsaturated amino-alcohols was demonstrated for a total synthesis of obscuraminol A, **19** which was obtained in 6% yield over 11 steps starting from EPA ethyl ester. The challenging reduction of the nitro-alcohol functionality has been achieved by the use of samarium (II) iodide reagent. There is, of course, a lot what can be done for further improvements and a new possible strategy was mentioned in section 2.3.2.3. It also should be possible to apply this chemistry towards synthesis of a related amino-alcohol, namely crucigasterin 277, **20**. The suggested synthetic route is outlined in Scheme 3.2.



Scheme 3.2 Suggested synthesis of crucigasterin 277.

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Appendix

Paper I

An asymmetric iodolactonization reaction catalyzed by a zinc bis-proline phenol complex
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An asymmetric iodolactonization reaction catalyzed by a zinc bis-proline–phenol complex

Liudmila Filippova [a], Yngve Stenstrøm [a,*], Trond Vidar Hansen [a,b]

[a] Department of Chemistry, Biology and Food Science, Norwegian University of Life Sciences, PO Box 5003, N-1432 Ås, Norway
[b] School of Pharmacy, Department of Pharmaceutical Chemistry, University of Oslo, Blindern, PO Box 1068, N-0316 Oslo, Norway

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ABSTRACT

The intramolecular zinc bis-proline-phenol complex **2a** was found to promote enantioselective iodolactonization reactions of both electron-rich and electron-poor 5-aryl-5-hexenoic acids affording δ-iodolactones in good chemical yields with up to 82% enantiomeric excess. The reactions were found to be insensitive to air and moisture, providing an experimentally simple protocol for synthetically useful compounds.

The halolactonization of alkenoic acids has been known for more than a century.[1] This reaction presents an attractive route to halolactones which can be key intermediates in the synthesis of natural products and are used as starting materials for further synthetic transformations.[2] Catalytic enantioselective versions of halolactonizations have been developed, but mostly for chloro- and bromo-lactonization reactions.[3] Some reagent-controlled and selective iodolactonization protocols have been reported.[4–6] For example, Taguchi and co-workers reported the use of one equivalent of a chiral titanium complex in the synthesis of γ-lactones with 65% ee.[4] Grossman and Trupp[5] reported, in 1998, the first successful reagent-controlled enantioselective iodolactonization. However, the stereoselectivity was disappointingly low with ee values in the range of 3–7%, and as such demonstrated the principle without any practical impact. Rousseau and co-workers[6] reported the preparation of 5-*endo*-γ-lactones with ee values between 10% and 20% in the presence of stoichiometric amounts of a chiral silver-ephedrine complex. Although some improvements were made in the enantioselectivity, it was still very low. The first catalytic, enantioselective iodolactonization was reported in 2004 by Gao and co-workers.[7a] using quaternary ammonium salts derived from cinchonidine, but with only moderate enantioselectivity. Moreover, the formation of mixtures of both γ- and δ-lactones was observed. The same group later reported that a salen-Co(II) complex catalyzed the enantioselective iodolactonization reaction of several 4-aryl-4-pentenoic acids to give γ-lactones with up to 85% ee.[7b] Veitch and Jacobsen[7c] reported that 5-aryl-5-hexenoic acids underwent iodolactonizations in the presence of a tertiary aminourea catalyst yielding the desired δ-iodolactones in high chemical yields with ee values between 48% and 96%. Dobish and Johnston[7d] employed a chiral Brønsted acid catalyst in their studies of the same type of acids; the obtained aryl substituted δ-iodolactones had ee values between 57% and 96%. In addition Hansen and co-workers[7e] recently published their work on using squaramides as organocatalysts for obtaining δ-iodolactones with enantiomeric excesses between 12% and 96% with 5-aryl-5-hexenoic acids as substrates. The research group of Martin[7f] reported a BINOL-derived, bifunctional catalyst that was employed for the preparation of a few δ-iodolactones in high yields and with ee values ⩾98%; several γ-iodolactones were obtained in a highly enantioselective manner with the same catalyst.

In connection with our ongoing projects on the synthesis of polyunsaturated fatty acid derived natural products employing iodolactonizations,[8] we became interested in developing a new enantioselective protocol. The commercially available semi-azacrown ether ligand **1**[9] and the corresponding di-nuclear zinc complexes **2a** and **2b** (Fig. 1) attracted our attention.[10] The dinuclear zinc complex **2a** has successfully been applied in a large variety of asymmetric transformations.[11] Similarly the bis-proline derived ligand **1**, containing two tertiary amines and a phenol, could exhibit catalytic activity in an enantioselective iodolactonization. The tertiary amines should provide H-bonding motifs[12] which have been reported to be of great importance in some organocatalytic

* Corresponding author. Tel.: +47 64965893; fax: +47 64965901.
E-mail address: yngve.stenstrom@umb.no (Y. Stenstrøm).

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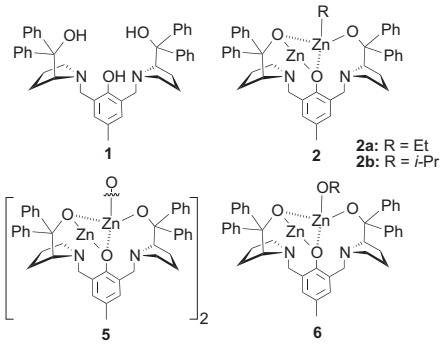


Figure 1. Structures of the semi-azacrown ether ligand **1**, the dinuclear zinc complex **2**, the *oxo*-bridged dimer **5**, and the alkoxy derivative **6**.

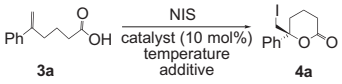
iodolactonizations.[7c,e] Herein, we report the results of our study on asymmetric iodolactonization mediated by the zinc complex **2a**.

Initially, the ability of the Trost-ligand **1** to catalyze the iodolactonization of 5-phenylhex-5-enoic acid (**3a**) in the presence of *N*-iodosuccinimide (NIS) in toluene at −20 °C was investigated. The ligand **1** yielded the racemic product **4a** in 30–48% yield (Table 1, entries 1 and 2). The ^{1}H NMR spectrum of a 1:10 mixture of **1** and **3a**, respectively, revealed that the chemical shift values of the alpha protons in **3a** were only slightly affected (see Fig. 2b). On the other hand, ^{1}H NMR-analyses of various mixtures of **2a** and **3a** showed a linear effect on the Δδ-values for the protons at C2 in **3a** indicating weak interactions between the acid and the zinc-complex (Fig. 2c and Supplementary data).

Moreover, the ^{13}C NMR spectra of mixtures of **2a** and **3a** also revealed the same type of interactions (see Supplementary data). These NMR observations encouraged us to use the adduct **2a**, previously reported by Trost et al.,[9,10a] as a catalyst in an enantioselective iodolactonization protocol. Adding a THF solution of **2a** to a solution of **3a** and NIS in toluene yielded the desired iodolactone **4a** in 70% chemical yield with variable enantioselectivity (Table 1, entry 3).

However, the observed enantiomeric excess of 55–74% in the reaction catalyzed by **2a** varied in the individual experiments. The addition of 0.15 equiv of iodine did not enhance the selectivity (entry 4). Employing the adduct **2b**, with the more bulky *iso*-propyl group, afforded iodolactone **4a** with improved yield, but with lower ee values. Again, low reproducibility was observed (entry 5). Our first concern was the lack of a strict control of moisture content. Surprisingly, the addition of 4 Å molecular sieves to the reaction mixture caused a drop in enantioselectivity (entries 6 and 7). The reaction conditions were then investigated. A solvent screen revealed that toluene was the best solvent (entries 2, 8–11). Further changes in the reaction conditions in terms of catalyst loadings, variations in concentration, amount of iodine added, the use of sodium bicarbonate as base, or altering the reaction times, did not enhance the enantioselectivity. To our surprise, the complex **2a** showed catalytic activity even after slow evaporation of the solvent and storage of the residue without any precautions against moisture and air. However, significant improvement in the reproducibility of the results was observed (Table 1, entry 12). This reaction was performed three times with the same results with respect to the yield and enantiomeric excess. These data suggest that in situ generated complex **2a** might act as a precatalyst with the formation of an even more active catalyst by contact with air and/or moisture. This was also supported by the above-mentioned observation that the addition of 4 Å molecular sieves gave a drop in the enantioselectivity. Unfortunately, our attempts to isolate crystals suitable for X-ray analysis were not successful. The nature of the active catalytic species therefore remains unknown. However, it has been reported that **2a** might form *oxo*-bridged dimers, such as **5** (Fig. 1), in the presence of adventitious amounts of water.[11] The addition of ethanol to the in situ generated complexes **2a** has been reported to alter the formation of the alkoxy-bridged dinuclear zinc species **6** as a result of exchange of the labile alkyl group.[11] We then performed the enantioselective iodolactonization reaction with the addition of ethanol to complex **2a**. These experiments yielded similar and results reproducible with those obtained in the absence of ethanol using the obtained solid (entry 13).

Table 1
Investigation of the reaction conditions



Entry[a]	Catalyst	Solvent	Additive	°C	Time (h)	Yield[b] (%)	ee[c] (%)
1	1	PhMe	—	−20	72	30	Racemic
2	1	PhMe	0.15 equiv I_2	−20	24	48	Racemic
3	**2a**[d]	PhMe	—	−20	70	70	55–74
4	**2a**[d]	PhMe	0.15 equiv I_2	−20	24	68	50
5	**2b**[d]	PhMe	—	−20	24	80	57–62
6	**2a**[d]	PhMe	4 Å MS	−20	70	62	44
7	**2a**[d]	THF	4 Å MS	−20	70	71	27
8	**2a**[d]	THF	—	−20	70	72	31
9	**2a**[d]	Et_2O	—	−20	70	66	57
10	**2a**[d]	CH_2Cl_2	—	−20	70	84	31
11	**2a**[d]	Me_2CO	—	−20	70	65	30
12	**2a**[e]	PhMe	—	−20	48	70	76
13[f]	**2a**[e]	PhMe	EtOH	−20	48	71	74
14	**2a**[e]	PhMe	—	−40	48	70	82
15	**2a**[e]	PhMe	—	0	24	74	72

[a] The reactions were carried out with acid **3a** (0.2 mmol), catalyst (0.02 mmol), and NIS (0.22 mmol) in solvent (4 mL) in the absence of light.
[b] Isolated yield as an average of at least two experiments.
[c] Determined by using HPLC with a chiral stationary phase (see supporting data for details).
[d] In situ generated solution. The reactions were run under protection from air and moisture.
[e] Solid residue after evaporation of THF from the catalyst solution.
[f] The catalyst was obtained by addition of a stoichiometric amount of ethanol to an in situ generated solution of **2a.**

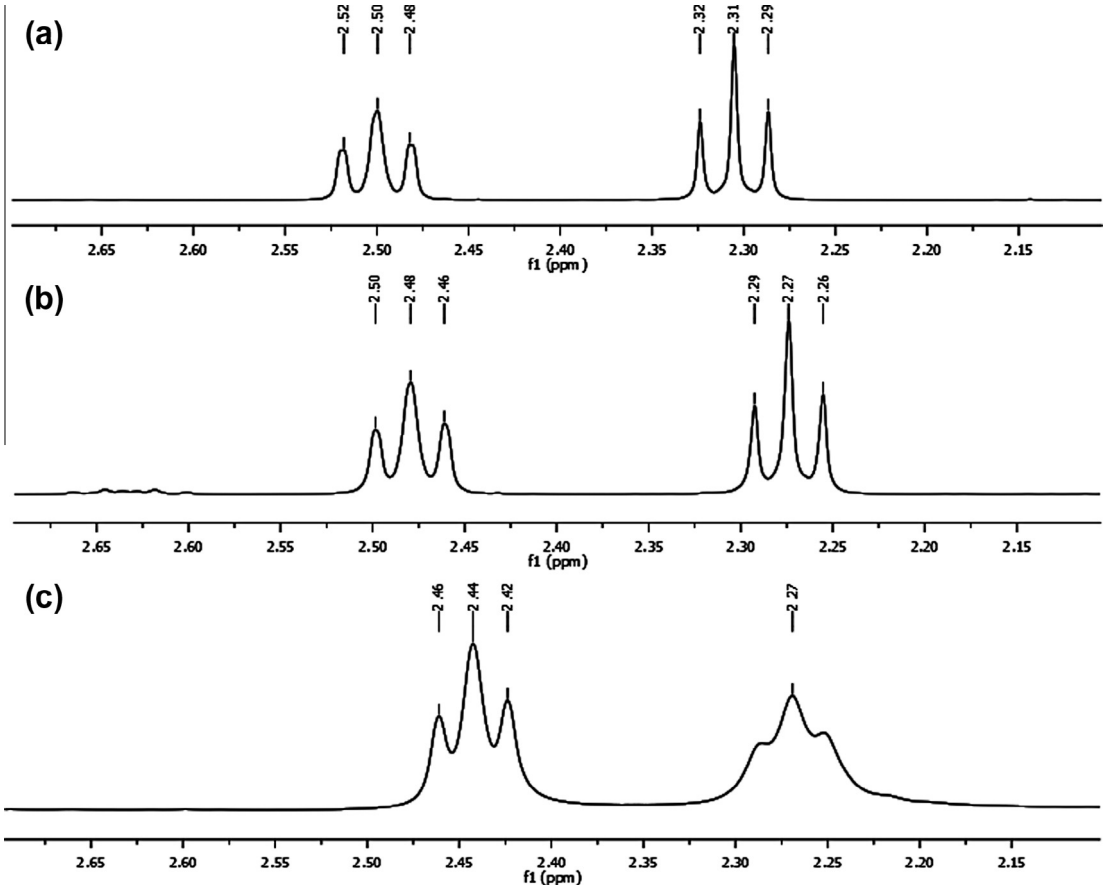


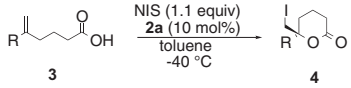
Figure 2. ^{1}H NMR spectroscopic study (400 MHz in $CDCl_3$): (a) **3a**; (b) 1:10 mixture of **1** and **3a**; (c) 1:10 mixture of **2a** and **3a**.

The next step in our efforts to improve the enantioselective iodolactonization reaction using complex **2a** was to lower the temperature to −40 °C. This led to a slight increase in the selectivity with the iodolactone **4a** formed with 82% ee and in 70% yield (Table 1, entry 14). However, at −78 °C the reaction was sluggish and did not go to completion. Raising the temperature to 0 °C increased notably the reaction rate, but lowered the ee value to 72% (entry 15). In summary, the best result was achieved at −40 °C in toluene yielding iodolactone **4a** in 70% yield and 82% ee.

Having established the conditions for the enantioselective iodolactonization of **3a**, we next applied them to a panel of 5-aryl-substituted 5-hexenoic acids. As shown in Table 2, good yields with ee values between 59% and 82% were observed for these substrates with either electron-rich or electron-deficient aryl substituents (Table 2). The electron-deficient substrates were less reactive and prolonged reaction times were necessary to achieve good conversions. The level of asymmetric induction was strongly diminished for the reaction of reactive electron-rich substrate **3f**; the lactone **4f** was obtained with 32% ee. The absolute configuration of the products **4a**–**4f** was determined to be *S* by comparison with authentic samples[7f] and literature optical rotations.[7c–f] When replacing the phenyl group with an *n*-butyl group, the corresponding product **4g** was returned with a poor ee value of 12%. Also, the opposite absolute configuration was observed for this product.[7e] When the antipode of the ligand **1** was applied, the *R*-configured product **4** was formed with the same enantiomeric excess (compare Table 2, entries 1 and 8).

In summary, we have demonstrated the application of Trosťs dinuclear zinc complex **2a** in a catalytic, enantioselective iodolactonization reaction with 5-aryl-5-hexenoic acids in the presence of commercially available NIS. No additives were necessary to afford the iodolactones in good yields and with enantioselectivities up to 82% under mild conditions. The protocol reported herein was not shown to be air and/or moisture sensitive. Further studies will concentrate on gaining a better understanding of the nature of the active catalytic species, as well as the origin of the enantioselectivity for further improvements and to expand the substrate scope.

Table 2
Iodolactonization of substituted 5-hexenoic acids mediated by **2a**[a]



3 4

Entry	Substrate	Product	Yield[b] (%)	ee[c] (%)
1	**3a:** R = Ph	**4a**	70	82
2	**3b:** R = 2-Np	**4b**	69	60
3	**3c:** R = *p*-MeC_6H_4	**4c**	87	62
4[d]	**3d:** R = *p*-ClC_6H_4	**4d**	82	70
5	**3e:** R = *p*-BrC_6H_4	**4e**	70	59
6	**3f:** R = *p*-MeOC_6H_4	**4f**	71	32
7	**3g:** R = *n*-Bu	**4g**	68	12
8[e]	**3a**: R = Ph	**4h**	70	83

[a] Reactions were run on 0.1 mmol scale employing complex **2a** in solid form.
[b] Isolated yield after purification by column chromatography.
[c] Determined by HPLC using chiral columns.
[d] The reaction was run for 72 h.
[e] Catalyzed by the zinc complex generated from the antipode of ligand **1.**

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.11.028.

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An asymmetric iodolactonization reaction catalyzed by a zinc *bis*-proline-phenol complex

Liudmila Filippova[a], Yngve Stenstrøm[a], Trond Vidar Hansen[a,b]

a: Department of Chemistry, Biology and Food Science, Norwegian University of Life Sciences, PO Box 5003, NO-1432, Ås, Norway
b: School of Pharmacy, Department of Pharmaceutical Chemistry, University of Oslo, PO 1068, Blindern, 0315 Oslo, Norway
e-mail:yngve.stenstrom@umb.no

Supporting information

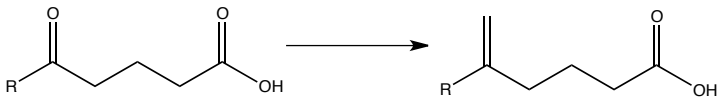
General information

All commercially available reagent and solvents were supplied by Sigma Aldrich or Rieke Metals, Inc. and used without additional purification. The stated yields are reported based on isolated material. Analytical TLC was performed on silica gel 60 F_{254} plates (Merck), developed with UV light and potassium permanganate solution. Flash column chromatography utilized silica gel 60 (40-63 nm) from Merck. NMR spectra were acquired on Bruker Ascend™ 400 spectrometer at 400 MHz for ^{1}H MNR and 100 MHz for ^{13}C NMR respectively. Chemical shifts are reported in parts per million (δ) relative to residual solvent peak as an internal standard set to $CDCl_3$ (δ 7.24 ^{1}H MNR and δ 77.00 ^{13}C MNR) and coupling constants (J) are reported in hertz. IR spectra (4000 – 600 cm^{-1}) were obtained on a Perkin-Elmer FT-IR spectrophotometer. Optical rotations were measured using a 1mL cell with 1.0 dm path length on Perkin Elmer 341 polarimeter. Enantiomeric excess were determined by HPLC on Agilent Technologies 1200 Series instrument with diode array detector set at 254 nm.

Preparation of 2a

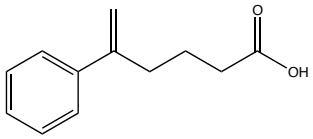
The catalyst solution was prepared according to the procedure reported by Trost *et al.*[1] To the cooled (0°C) and stirred solution of (*S*,*S*)-(+)-2,6-*bis*-[2-(hydroxydiphenylmethyl)-1-pyrrolidinylmethyl]-4-methylphenol (64 mg, 0,1 mmol) in dry THF was added a solution of Et_2Zn (0.2 mL, 0.2 mmol, 1M in hexane) under nitrogen atmosphere. After the addition the cooling bath was removed and resulting solution was further stirred for 30 minutes to form a c.a. 1M solution of catalyst. The solution was allowed to vaporize slowly on the air by introducing the needle to the rubber septum covering the flask to obtain the residue as an amorphous yellowish solid, which was used further without additional purification.

General procedure for the preparation of alkenoic acids 3a-3g



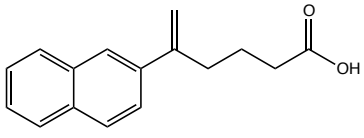
Alkenoic acids were prepared via a Wittig reaction from the commercially available keto-acids according to the procedure reported by Hartwig *et al*.[2] To a suspension of methyltriphenylphosphnium bromide (1.3 eq.) in THF (c.a. 0.25M) was added sodium *tert*-butoxide (2.6 eq.) at 0 °C. The mixture was stirred for 30 min. Keto-acid (1.0 eq.) was then added to the reaction mixture at 0 °C. The mixture was allowed to warm up to room temperature and stirred for 16 h. After the mentioned time, the reaction mixture was concentrated under reduced pressure, diluted with CH_2Cl_2 (10 mL) and NaOH (1N, 10 mL). The aqueous layer was washed with CH_2Cl_2 twice. The pH was adjusted to approx. 2 and the aqueous layer was extracted with CH_2Cl_2 twice. The combined organic extracts were dried over $MgSO_4$, filtered and evaporated *in vacuo* to afford the crude product that was purified by flash column chromatography (hexane/EtOAc 1:1) to afford the corresponding alkenoic acids **3a**-**3g**.

5-Phenylhex-5-enoic acid (3a)[3]



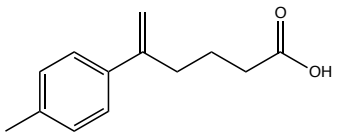
Prepared using 5-phenyl-5-oxopentanoic acid. All physical data were in agreement with those reported in literature.[3] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.38 (m, 5H), 5.29 (d, J = 1.2 Hz, 1H), 5.06 (d, J = 1.3 Hz, 1H), 2.55 (t, J = 7.3 Hz, 2H), 2.35 (t, J = 7.5 Hz, 2H), 1.77 (quint, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.6, 147.3, 140.7, 128.3 (2C), 127.5, 126.1 (2C), 113.1, 34.4, 33.2, 23.0.

5-(Naphthalen-2yl)hex-5-enoic acid (3b)[3]



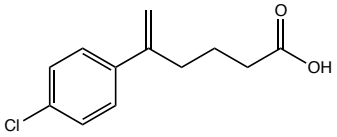
Prepared using 5-(naphthalen-2-yl)-5-oxopentanoic acid. All physical data were in agreement with those reported in literature.[3] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77-7.81 (m, 4H), 7.56 (dd, J_1 = 8.6 Hz, J_2 = 1.8 Hz, 1H), 7.41-7.47 (m, 2H), 5.45 (d, J = 0.9 Hz, 1H), 5.17 (d, J = 1.2 Hz), 2.68 (t, J = 7.5 Hz, 2H), 2.40 (t, J = 7.4 Hz, 2H), 1.84 (quin., J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.1, 147.1, 137.9, 133.4, 132.9, 128.2, 127.9, 127.5, 126.2, 125.9, 124.8, 124.6, 113.7, 34.5, 33.1, 23.1.

5-(*p*-Tolyl)hex-5-enoic acid (3c)[3]



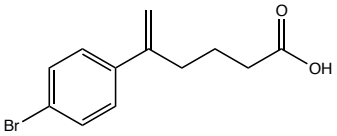
Prepared using 5-(*p*-tolyl)-5-oxopentanoic acid. All physical data were in agreement with those reported in literature.[3] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.97 (br s, 1H), 7.28 (d, J = 8.2 Hz, 2H), 7.12 (d, J = 7.9 Hz, 2H), 5.26 (d, J = 1.3 Hz, 1H), 5.01 (d, J = 1.2 Hz, 1H), 2.54 (t, J = 7.1 Hz, 2H), 2.35 (t, J = 7.4 Hz, 2H), 2.32 (s, 3H), 1.77 (quint., J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.2, 147.1, 137.7, 137.2, 129.0(2C), 126.0 (2C), 112.3, 34.4, 33.1, 23.0, 21.1.

5-(*p*-Chlorophenyl)hex-5-enoic acid (3d)[3]



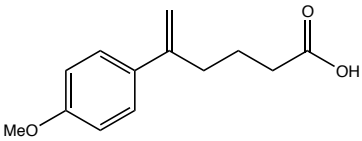
Prepared using 5-(*p*-chlorophenyl)-5-oxopentanoic acid. All physical data were in agreement with those reported in literature.[3] ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.67 (br s, 1H), 7.26-7.32 (m, 4H), 5.28 (d, J = 0.9 Hz, 1H), 5.08 (d, J = 1.2 Hz, 1H), 2.52 (t, J = 7.2 Hz, 2H), 2.36 (t, J = 7.4 Hz, 2H), 1.76 (quint, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.4, 146.2, 139.1, 133.3, 128.5 (2C), 127.4 (2C), 113.6, 34.3, 33.1, 22.9.

5-(*p*-Bromophenyl)hex-5-enoic acid (3e)[3]



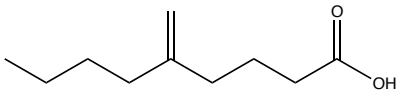
Prepared using 5-(*p*-bromophenyl)-5-oxopentanoic acid. All physical data were in agreement with those reported in literature.[3] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.44 (m, 2H), 7.23-7.26 (m, 2H), 5.28 (d, J = 0.9 Hz, 1H), 5.08 (d, J = 1.2 Hz, 1H), 2.52 (t, J = 7.4 Hz, 2H), 2.35 (t, J = 7.4 Hz, 2H), 1.76 (quin., J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.1, 146.3, 139.6, 131.5 (2C), 127.8 (2C), 121.4, 113.7, 34.3, 33.1, 22.9.

5-(*p*-Methoxyphenyl)hex-5-enoic acid (3f)[3]



Prepared using 5-(*p*-methoxyphenyl)-5-oxopentanoic acid. All physical data were in agreement with those reported in literature. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.31 (m, 2H), 6.85-6.83 (m, 2H), 5.22 (d, J = 1.3 Hz, 1H), 4.98 (d, J = 1.2 Hz, 1H), 3.79 (s, 3H), 2.53 (t, J = 7.5 Hz, 2H), 2.36 (t, J = 7.4 Hz, 2H), 1.78 (quin., J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.3, 159.1, 146.6 (2C), 133.1, 127.2, 113.7 (2C), 113.6, 114.6, 55.29, 34.5, 33.2, 23.1.

5-Methylenenonanoic acid (3g)[4]



Prepared using 5-oxononanoic acid. All physical data were in agreement with those reported in literature. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.73 (s, 1H), 4.70 (s, 1H), 2.34 (t, J = 7.5 Hz, 2H), 2.04 (t, J = 7.5 Hz, 2H), 1.98 (t, J = 7.5 Hz, 2H), 1.76 (quin., J = 7.5 Hz, 2H), 1.34-1.42 (m, 2H), 1.28 (hept, J = 7.2 Hz, 2H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7, 148.7, 109.5, 35.5, 35.2, 33.4, 29.9, 22.6, 22.4, 14.0.

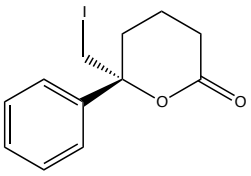
Enantioselective iodolactonization reactions

General procedure

An alkenoic acid (1 equiv.) and zinc catalyst (0.1 equiv.) were dissolved in toluene (0.05M) and cooled to -40°C. N-iodosuccinimide (1.1 equiv.) was added and the resulting reaction mixture was kept stirring indicated time controlled by TLC. The reaction mixture was quenched with 25% aq. $Na_2S_2O_3$ (4 ml), allowed to warm to room temperature, partioned between 1.0 M NaOH (15 mL) and CH_2Cl_2 (15 ml). The organic aqueous layer was extracted twice and combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica (10-25% ethyl acetate in hexane) to afford the corresponding iodolactone.

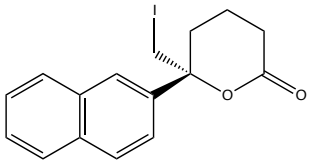
The iodolactones decomposed in the condensed state under vacuum. No melting points are reported since all solids isolated decomposed at non-specific temperatures when heated. All iodolactones were treated as light sensitive and stored under nitrogen at -20°C.

(*S*)-6-(Iodomethyl)-6-phenyltetrahydro-2H-pyran-2-one (4a)[3a,c]



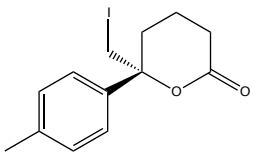
The reaction was performed on 0.2 mmol scale according the general procedure. Purified by silica gel column chromatography (10-25% hexane in EtOAc) to give (*S*)-**4a** as a colourless oil (44 mg, 70%). The enantiomeric excess was determined to be 82% by chiral HPLC analysis (Chiralpack AD-H column, 1 ml/min, hexane/iPrOH 90/10 v/v, 254mn): t_R (major) = 10.18 min and t_R (minor) = 11.29 min; $[\alpha]^{25}_D$ = +25.1° (c = 0.9 $CHCl_3$), [lit. $[\alpha]^{24}_D$ = +29.1° (c = 1.2 $CHCl_3$, 94% ee(S))][3a]; IR (film) 2966, 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40-7.30 (m, 5H), 3.55 (s, 2H), 2.30-2.51 (m, 4H), 1.76-1.84 (m, 1H), 1.50-1.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 140.2, 129.0(2C), 128.4, 125.2 (2C), 84.4, 32.0, 28.9, 17.6, 16.5.

(*S*)-6-Iodomethyl-6-(naphthalene-2-yl)tetraydro-2H-pyran-2-one (4b)[3a,c]



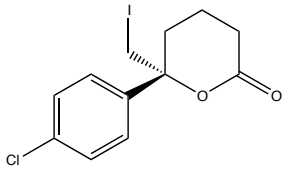
The reaction was performed on 0.15 mmol scale according general procedure. Purified by silica gel column chromatography (10-25% hexane in EtOAc) to give (*S*)-**4b** as a colourless oil (36 mg, 69%). The enantiomeric excess was determined to be 59% by chiral HPLC analysis (Chiralpack AD-H column, 1 ml/min, hexane/iPrOH 98/2 v/v, 254mn): t_R (major) = 54.65 min and t_R (minor) = 60.18 min; $[\alpha]^{25}_D$ = +16° (c = 1.18 $CHCl_3$), [lit. $[\alpha]^{24}_D$ = +25.8° (c = 2.0 $CHCl_3$, 94% ee(S))][3a]; IR (film) 2973, 2883, 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.81-7.87 (m, 4H), 7.49-7.54 (m, 2H), 7.38 (dd, J_1 = 8.7 Hz, J_2 = 1.9 Hz, 1H), 3.64 (dd, J_1 = 13.8 Hz, J_2 = 11.1 Hz, 2H), 2.35-2.55 (m, 4H), 1.78-1.87 (m, 1H), 1.52-1.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 137.4, 133.0, 132.8, 129.0, 128.3, 127.5, 126.8 (2C), 125.0, 122.3, 84.5, 32.1, 29.0, 17.4, 16.6.

(*S*)-6-(Iodomethyl)-6-(*p*-tolyl)tetrahydro-2H-pyran-2-one (4c)[3a,c]



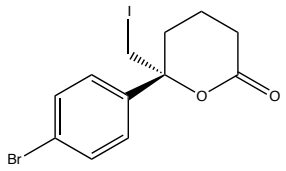
The reaction was performed on 0.2 mmol scale according the general procedure. Purified by silica gel column chromatography (10-25% hexane in EtOAc) to give (*S*)-**4c** as a colourless solid (54 mg, 87%). The enantiomeric excess was determined to be 62% by chiral HPLC analysis (Chiralpack AD-H column, 1 ml/min, hexane/iPrOH 90/10 v/v, 254mn): t_R (major) = 9.85 min and t_R (minor) = 12.18 min; $[\alpha]^{25}_D$ = +26.5° (c = 0.17 $CHCl_3$), [lit. $[\alpha]^{24}_D$ = +34.1° (c = 1.1 $CHCl_3$, 88% ee(S))][3a]; IR (film) 2973, 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.2 Hz, 2H), 3.53 (s, 2H), 2.39-2.50 (m, 2H), 2.33 (s, 3H), 2.26-2.37 (m, 2H), 1.75-1.83 (m, 1H), 1.50-1.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.5, 138.3, 137.1, 129.6 (2C), 125.1 (2C), 84.4, 31.9, 28.9, 21.0, 17.9, 16.5.

(*S*)-6-(Iodomethyl)-6-(*p*-chlorophenyl)tetrahydro-2H-pyran-2-one (4d)[3a]



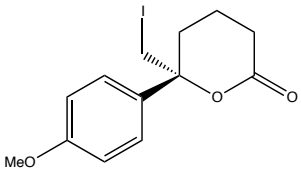
The reaction was performed on 0.2 mmol scale according the general procedure. Purified by silica gel column chromatography (10-25% hexane in EtOAc) to give (*S*)-**4d** as a white solid (58 mg, 82%). The enantiomeric excess was determined to be 70% by chiral HPLC analysis (Chiralpack AD-H column, 1 ml/min, hexane/*i*PrOH 90/10 v/v, 254mn): t_R (major) = 11.17 min and t_R (minor) = 14.23 min; $[\alpha]^{25}_D$ = +21.8° (c = 0.54 $CHCl_3$), [lit. $[\alpha]^{24}_D$ = +27.8° (c = 1.0 $CHCl_3$, 96% ee(S))][3a]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.7 Hz, 2H), 3.51 (s, 3H), 2.41-2.51 (m, 2H), 2.26-2.39 (m, 2H), 1.78-1.86 (m, 2H), 1.48-1.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 138.8, 134.4, 129.1 (2C), 126.7 (2C), 84.0, 31.9, 28.9, 17.1, 16.5.

(*S*)-6-(Iodomethyl)-6-(*p*-bromophenyl)tetrahydro-2H-pyran-2-one (4e)[3a,c]



The reaction was performed on 0.1 mmol scale according the general procedure. Purified by silica gel column chromatography (10-25% hexane in EtOAc) to give (*S*)-**4e** as a white solid (30 mg, 70%). The enantiomeric excess was determined to be 59% by chiral HPLC analysis (Chiralpack AD-H column, 1 ml/min, hexane/*i*PrOH 90/10 v/v, 254mn): t_R (major) = 11.70 min and t_R (minor) = 15.44 min; $[\alpha]^{25}_D$ = +16.2° (c = 0.31 $CHCl_3$), [lit. $[\alpha]^{24}_D$ = +28.7° (c = 1.0 $CHCl_3$, 96% ee(S))][3a]; IR (film) 2962, 1737 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 8.6 Hz, 2H), 3.51 (s, 3H), 2.39-2.52 (m, 2H), 2.27-2.37 (m, 2H), 1.78-1.87 (m, 1H), 1.49-1.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 139.4, 132.1 (2C), 127.0 (2C), 122.6, 84.1, 31.9, 29.0, 16.9, 16.5.

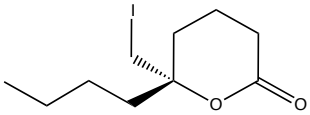
(*S*)-6-(Iodomethyl)-6-(*p*-methoxyphenyl)tetrahydro-2H-pyran-2-one (4f)[3a,c]



The reaction was performed on 0.11 mmol scale according the general procedure. Purified by silica gel column chromatography (hexane – EtOAc 5:1 to 3:1) to give (*S*)-**4f** as a colourless oil (32 mg, 65%). The enantiomeric excess was determined to be 32% by chiral HPLC analysis (Chiralpack AD-H column, 1

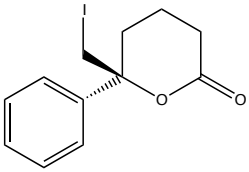
ml/min, hexane/iPrOH 90/10 v/v, 254mn): t_R (major) = 15.22 min and t_R (minor) = 18.72 min; $[\alpha]^{25}_D$ = + 13.1° (c = 0.55 $CHCl_3$), [lit. $[\alpha]^{24}_D$ = +11.8° (c = 1.0 $CHCl_3$, 48% ee(S))][3a]; IR (film) 2958, 2836, 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, J = 8.9 Hz, 2H), 6.88 (d, J = 8.9 Hz, 2H), 3.79 (s, 3H), 3.51-3.55 (dd, J_1 = 14.9 Hz , J_2 = 10.9 Hz, 2H), 2.39-2.49 (m, 2H), 2.26-2.37 (m, 2H), 1.75-1.84 (m, 1H), 1.52-1.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 159.5, 132.0, 126.5 (2C), 114.2 (2C), 84.2, 55.3, 31.8, 28.9, 18.1, 16.5.

(*R*)-6-(Iodomethyl)-6-butyltetrahydro-2H-pyran-2-one (4g)[3b]



Reaction was performed on 0.2 mmol scale according the general procedure. Purified by silica gel column chromatography (20% EtOAc in hexane) to give (*R*)-**4g** as a colourless oil (40 mg, 68%). The enantiomeric excess was determined to be 12% by chiral HPLC analysis (Chiralpack AD-H column, 1 ml/min, hexane/iPrOH 98/2 v/v, 254mn): t_R (major) = 13.87 min and t_R (minor) = 14.55 min; $[\alpha]^{25}_D$ = + 5.1° (c = 0.37 $CHCl_3$), [lit. $[\alpha]^{20}_D$ = -24° (c = 1.0 $CHCl_3$, 89% ee(S))][3]; IR (film) 2955, 2870, 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.35 (dd, J_1 = 12.4 Hz , J_2 = 10.7 Hz, 2H), 2.47 (t, J = 6.7 Hz, 2H), 2.00-2.12 (m, 1H), 1.75-1.87 (m, 5H), 1.23-1.42 (m, 4H), 0.90 (t, J = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 83.4, 38.7, 29.9, 25.0, 22.7, 16.5, 13.9, 12.8.

(*R*)-6-(Iodomethyl)-6-phenyltetrahydro-2H-pyran-2-one (4a)[3b]



Reaction was performed on 0.2 mmol scale according the general procedure. Purified by silica gel column chromatography (10-25% hexane in EtOAc) to give (*R*)-**4a** as a colourless oil (44 mg, 70%). The enantiomeric excess was determined to be 82% by chiral HPLC analysis (Chiralpack AD-H column, 1 ml/min, hexane/iPrOH 90/10 v/v, 254mn): t_R (major) = 10.18 min and t_R (minor) = 11.29 min; $[\alpha]^{25}_D$ = -26.2°(c = 1.33 $CHCl_3$), [lit. $[\alpha]^{20}_D$ = -27° (c = 1.2 $CHCl_3$, 98% ee(R))][3b]. ^1H NMR (400 MHz, $CDCl_3$): δ 7.40-7.30 (m, 5H), 3.55 (s, 2H), 2.30-2.51 (m, 4H), 1.76-1.84 (m, 1H), 1.50-1.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 140.2, 129.0(2C), 128.4, 125.2 (2C), 84.4, 32.0, 28.9, 17.6, 16.5.

The absolute configurations of iodolactones were assigned on the basis of the measurement and comparison of their specific rotations with the literature data.

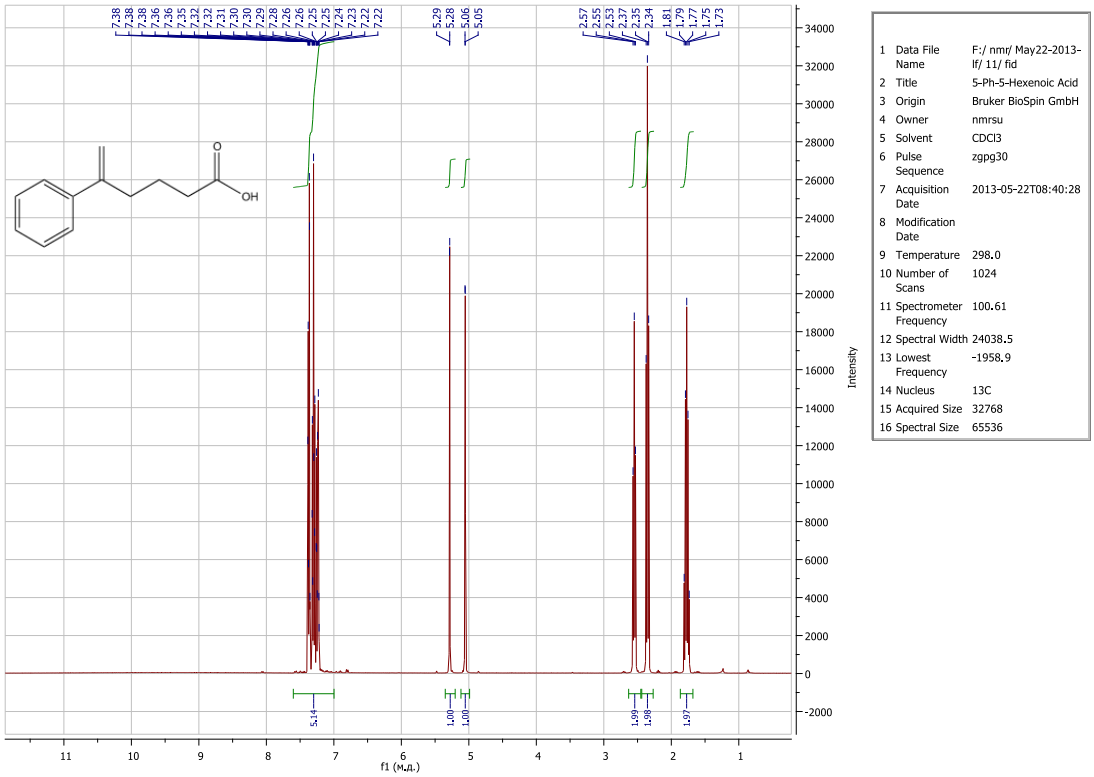


Figure S-1. ^{1}H NMR spectrum of **3a**.

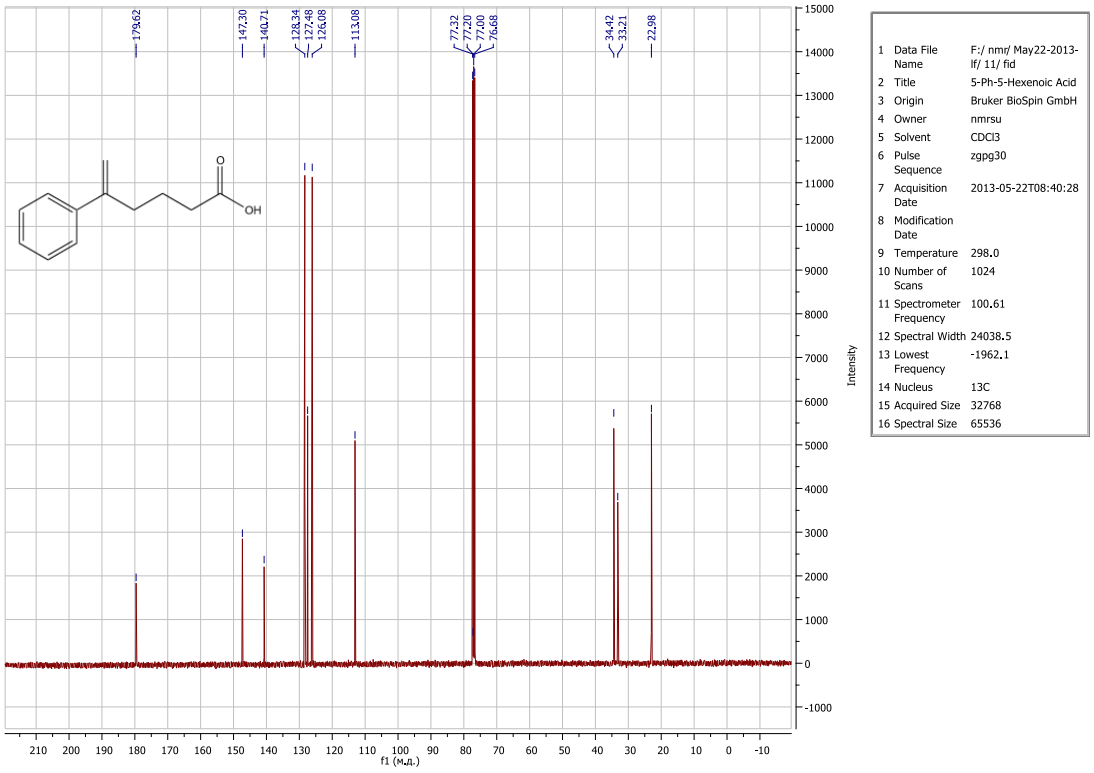


Figure S-2. ^{13}C NMR spectrum of **3a**.

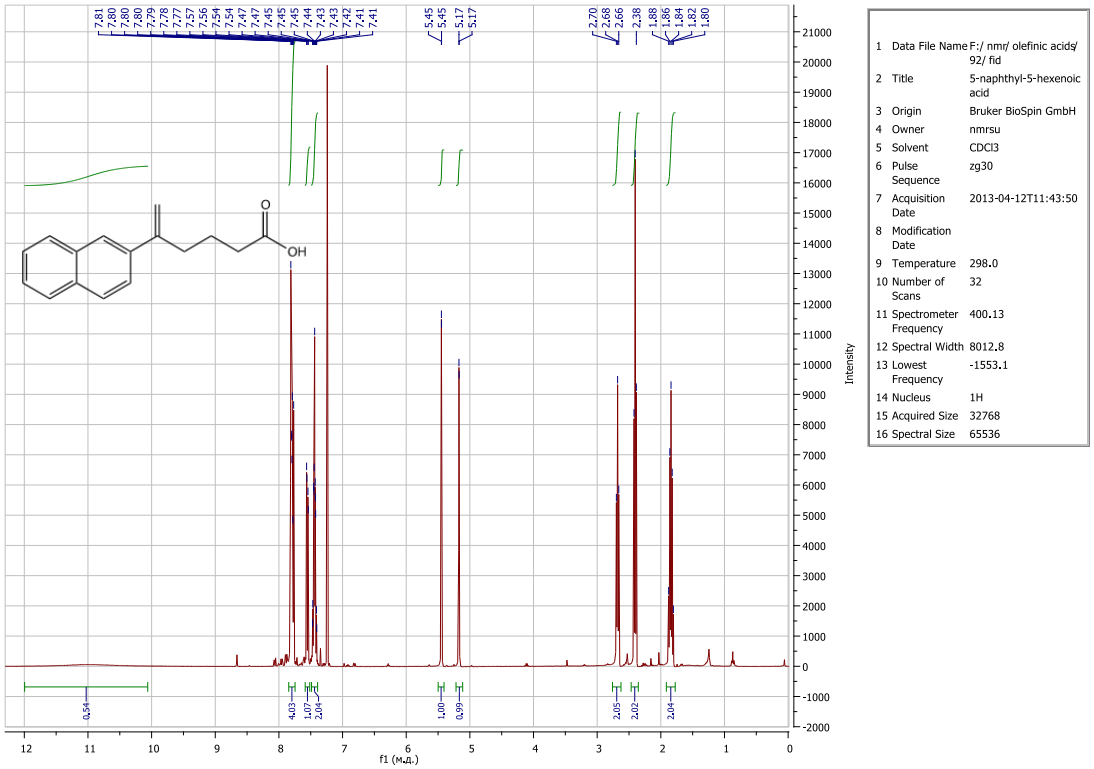


Figure S-3. ^{1}H NMR spectrum of **3b**.

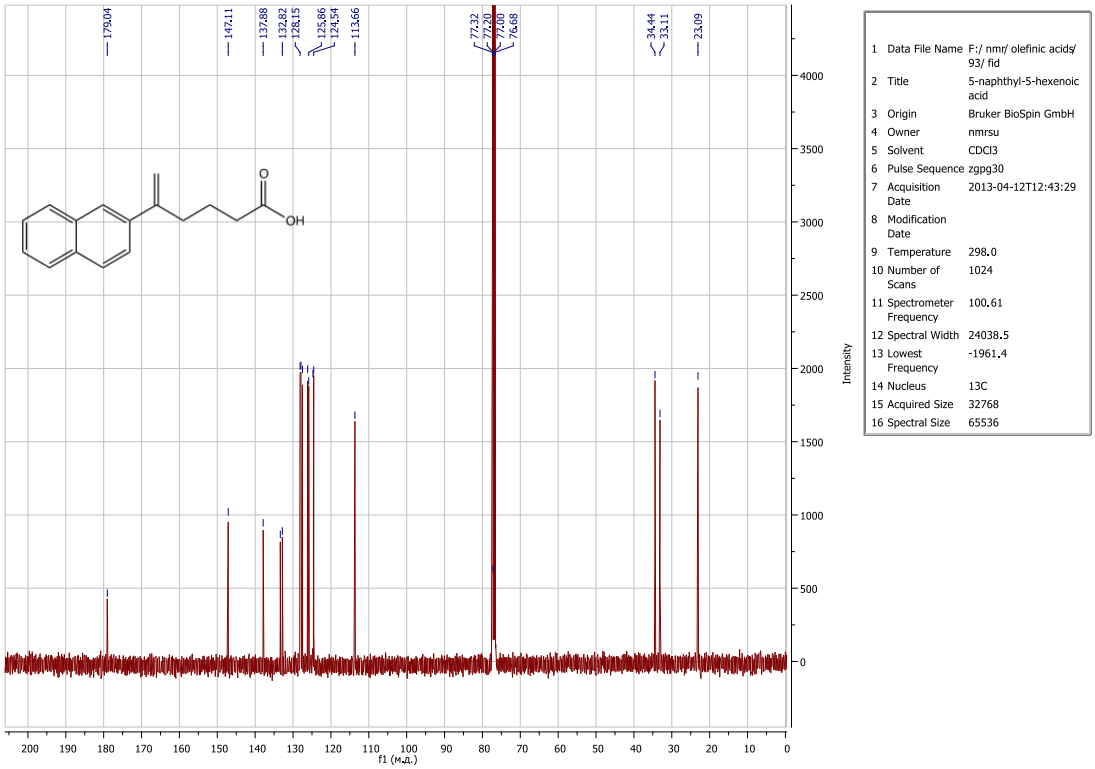


Figure S-4. ^{13}C NMR spectrum of **3b**.

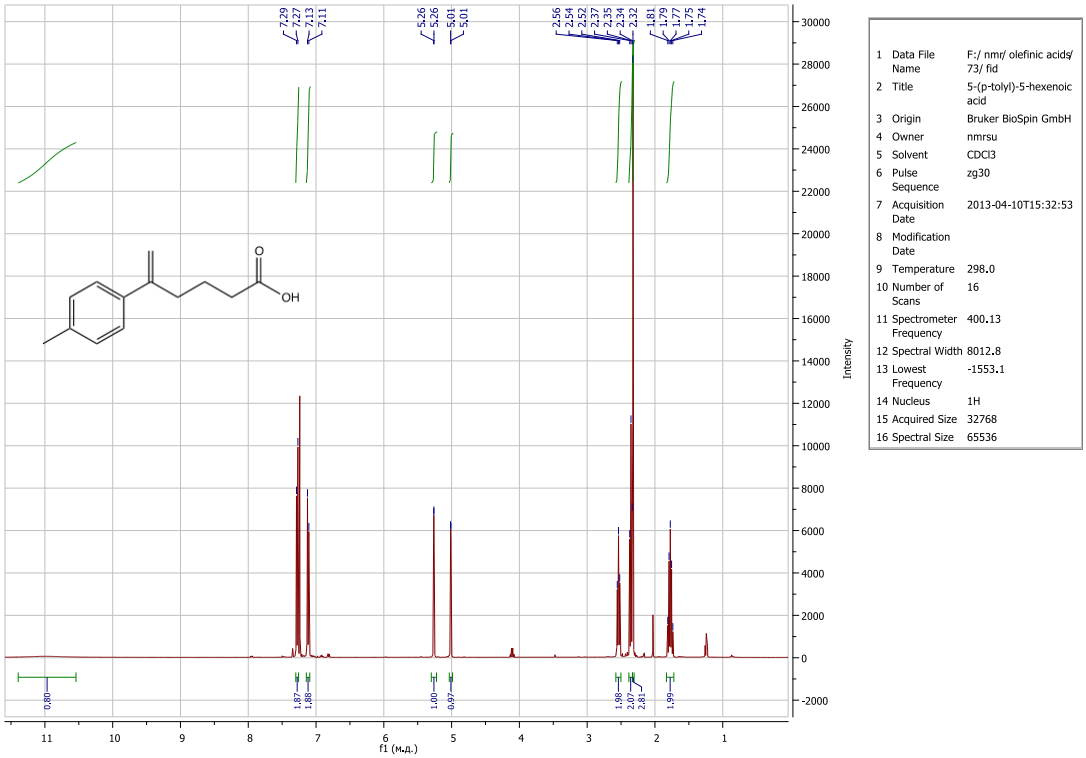


Figure S-5. ^{1}H NMR spectrum of **3c**.

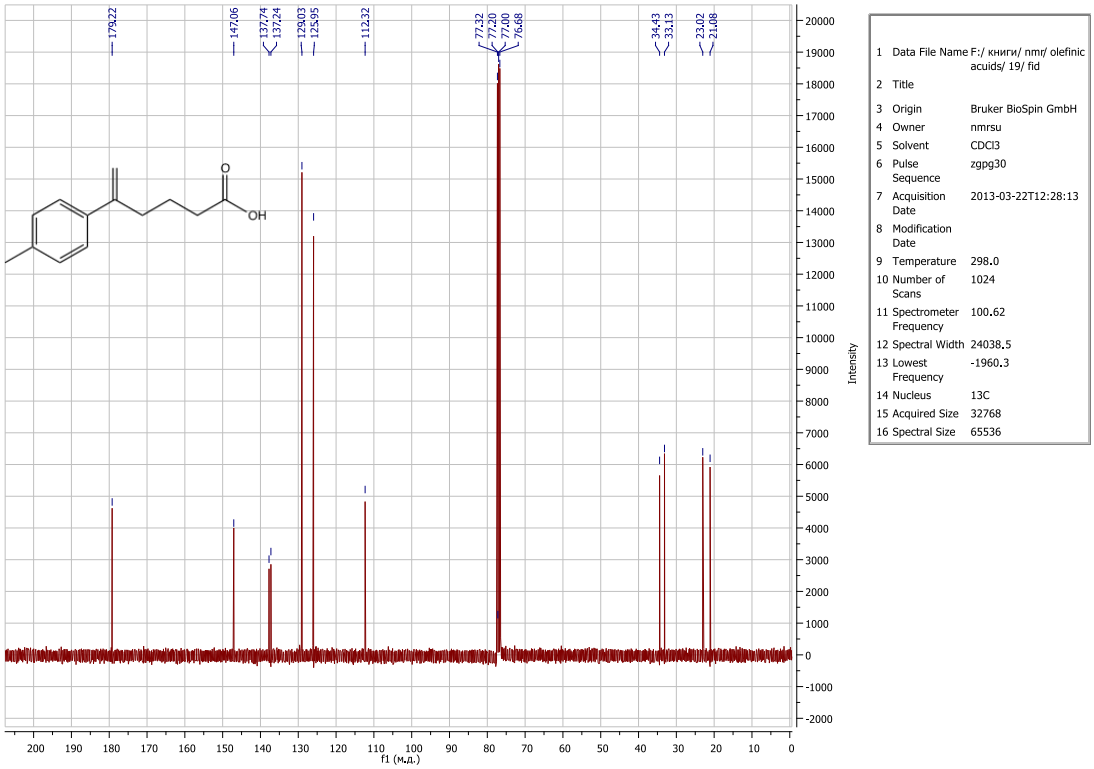


Figure S-6. ^{13}C NMR spectrum of **3c**.

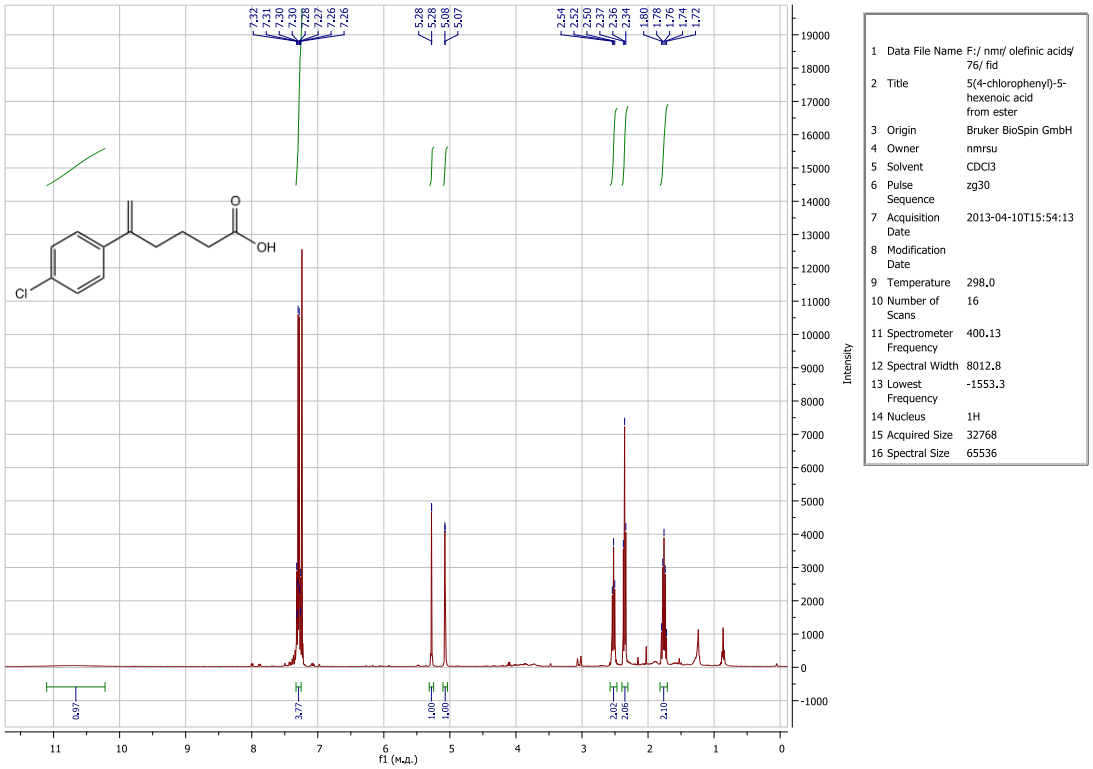


Figure S-7. ^{1}H NMR spectrum of **3d**.

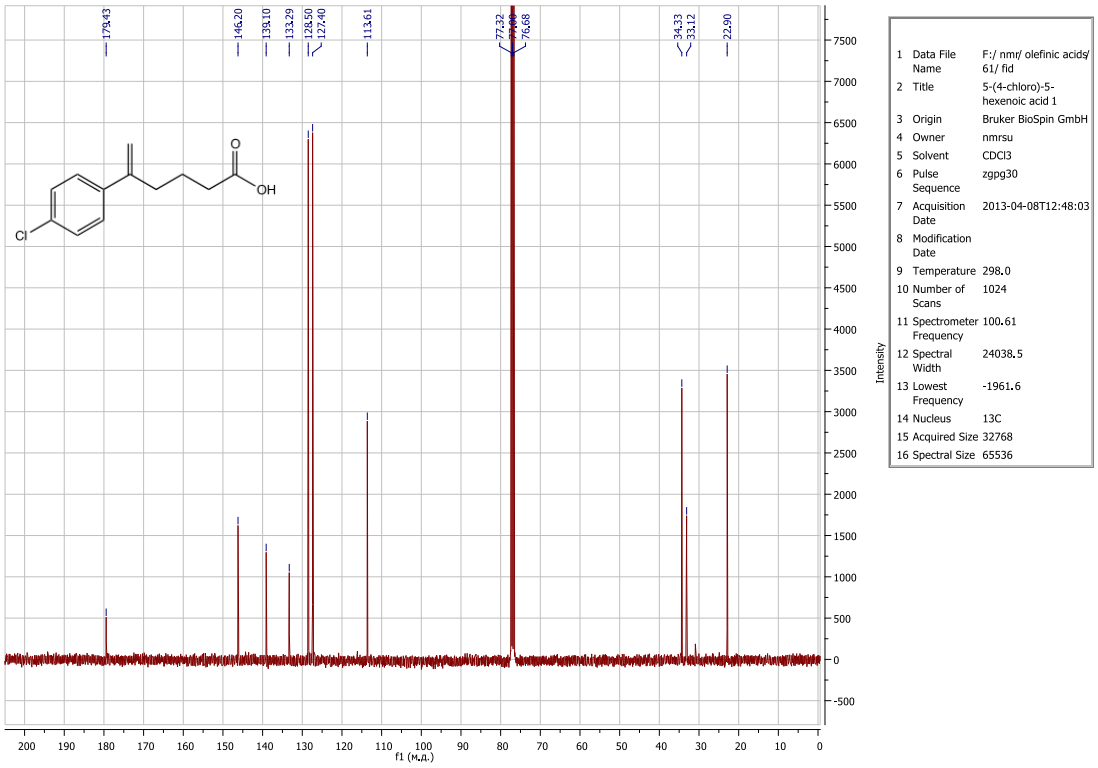


Figure S-8. ^{13}C NMR spectrum of **3d**.

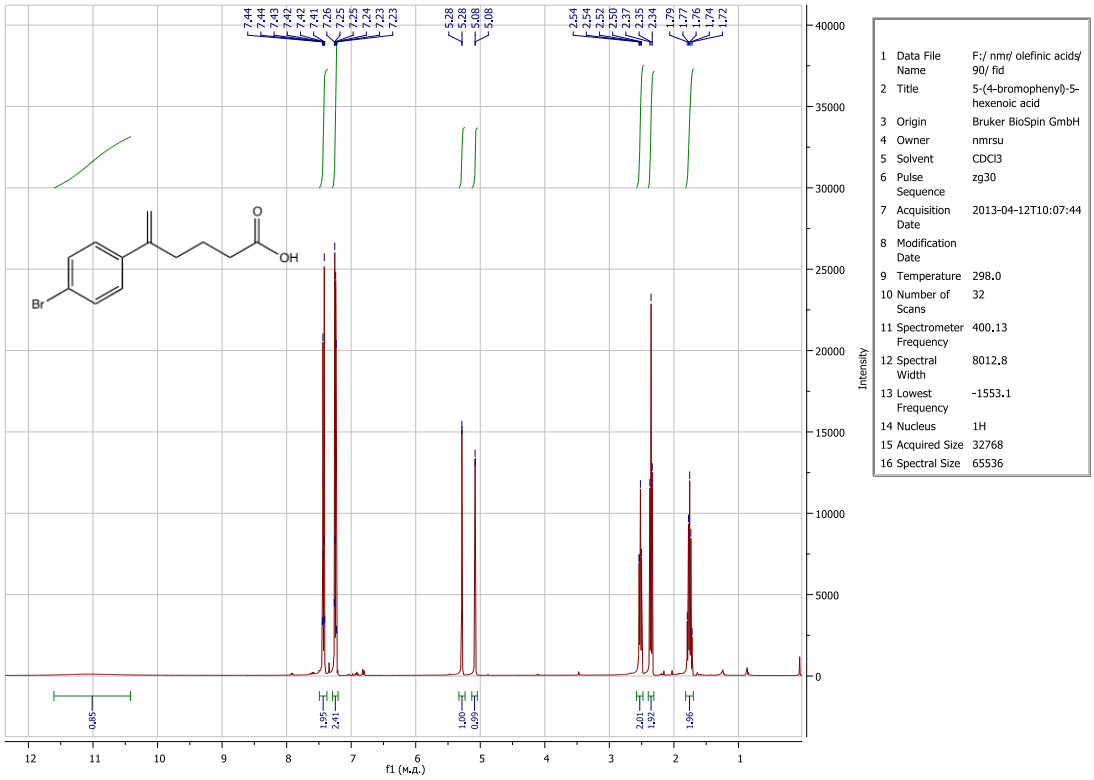


Figure S-9. ^{1}H NMR spectrum of **3e**.

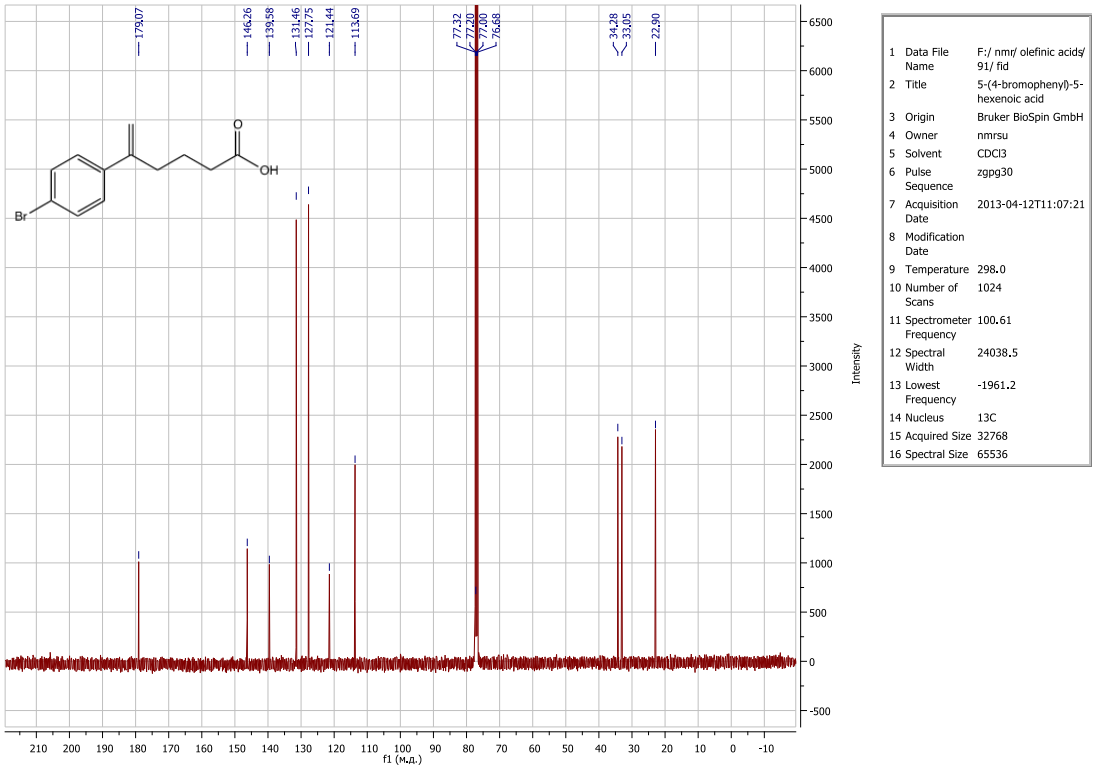


Figure S-10. ^{13}C NMR spectrum of **3e**.

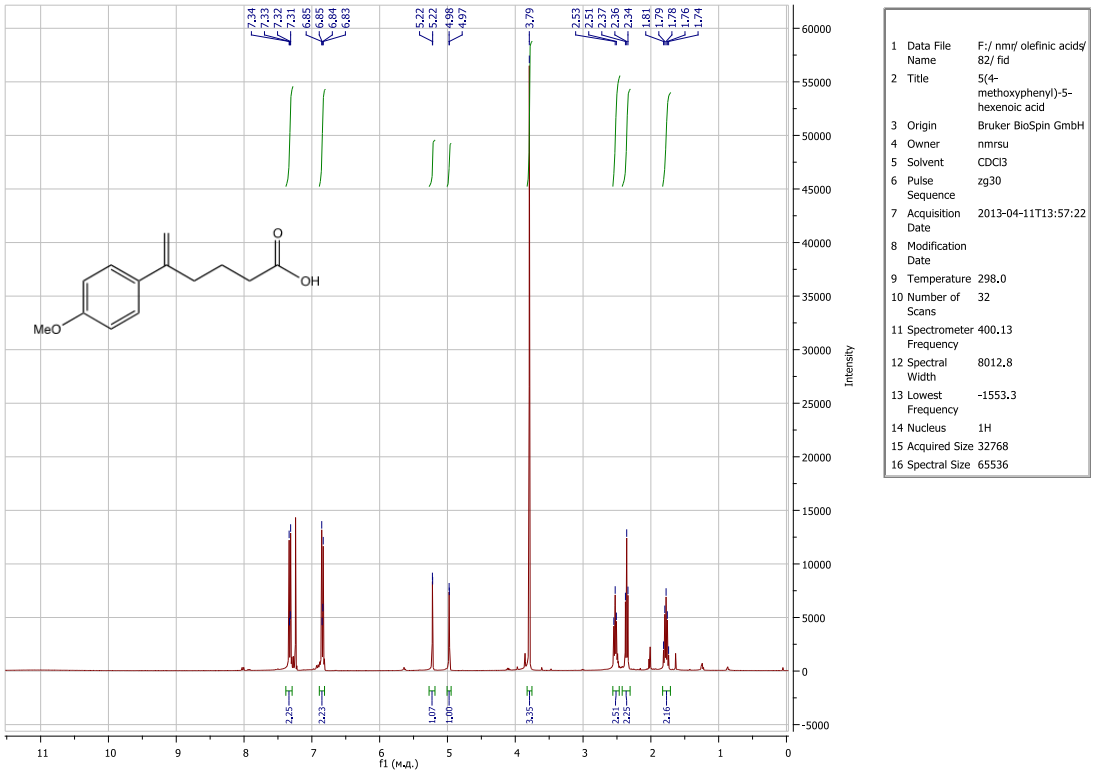


Figure S-11. ^{1}H NMR spectrum of **3f**.

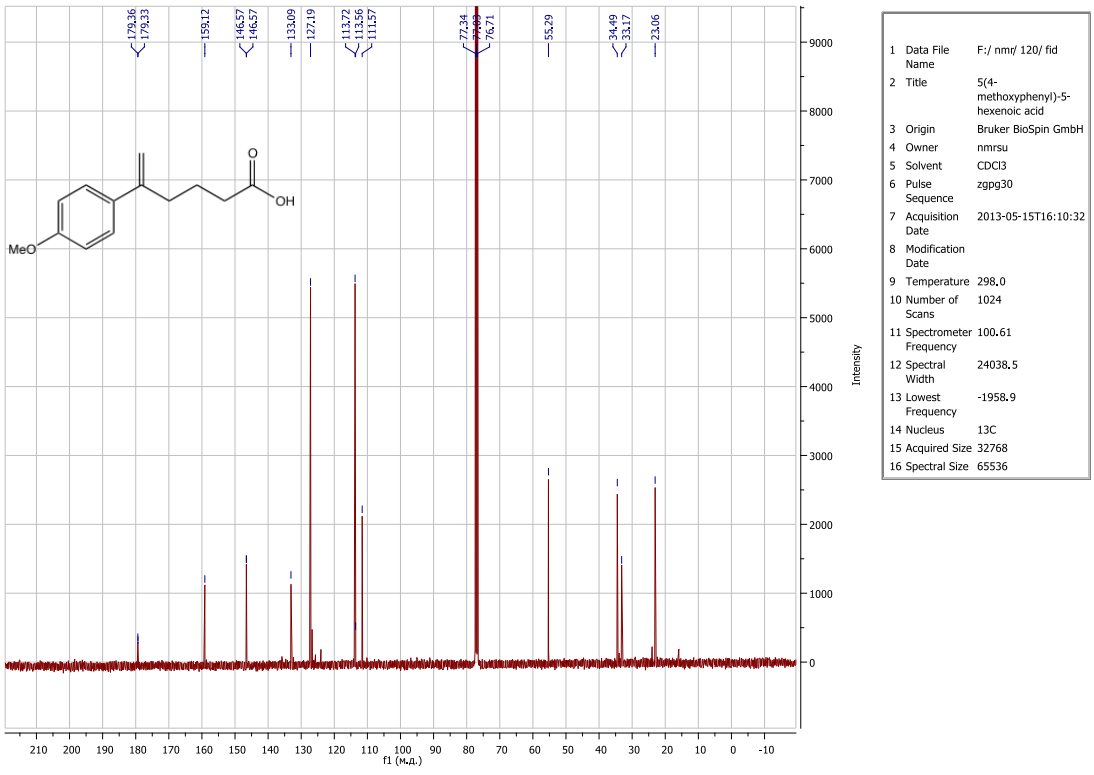


Figure S-12. ^{13}C NMR spectrum of **3f**.

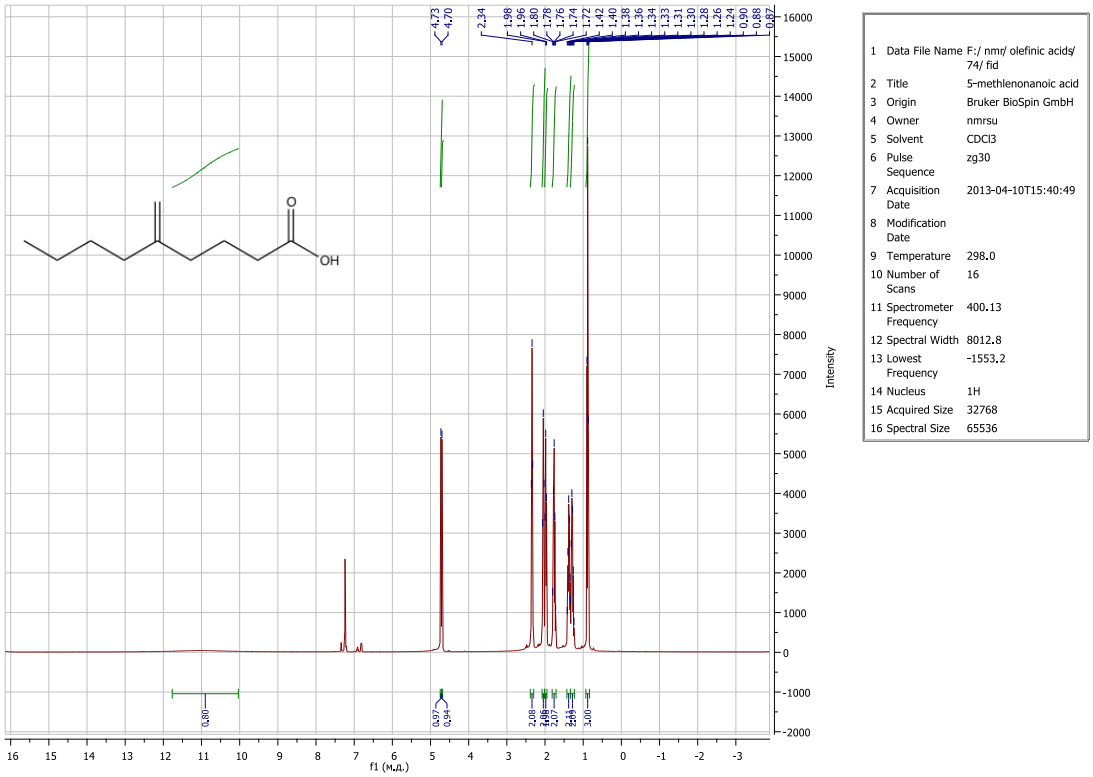


Figure S-13. ^{1}H NMR spectrum of **3g**.

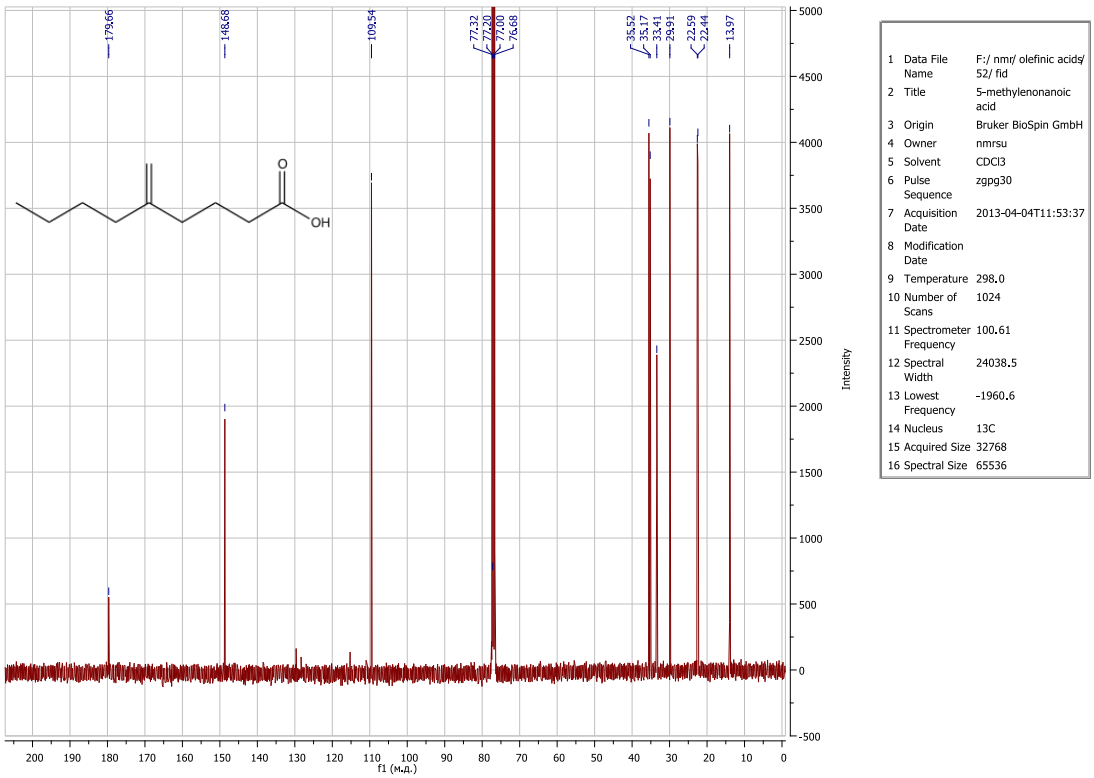


Figure S-14. ^{13}C NMR spectrum of **3g**.

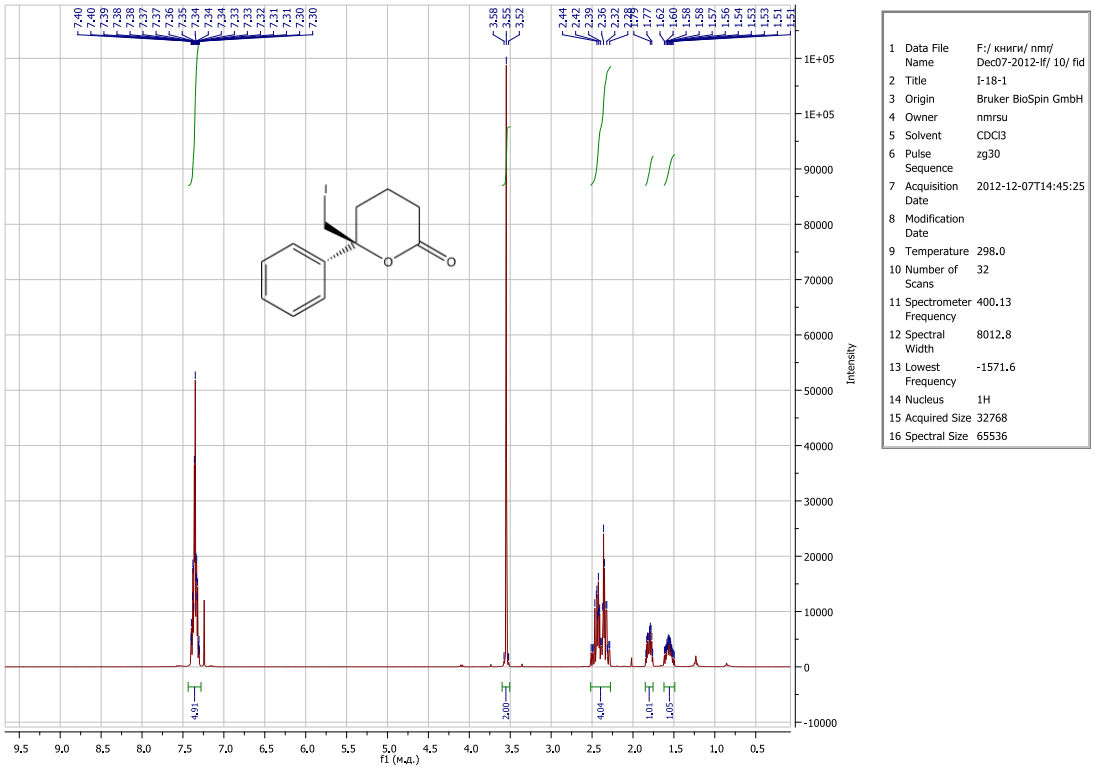


Figure S-15. ^{1}H NMR spectrum of **4a**.

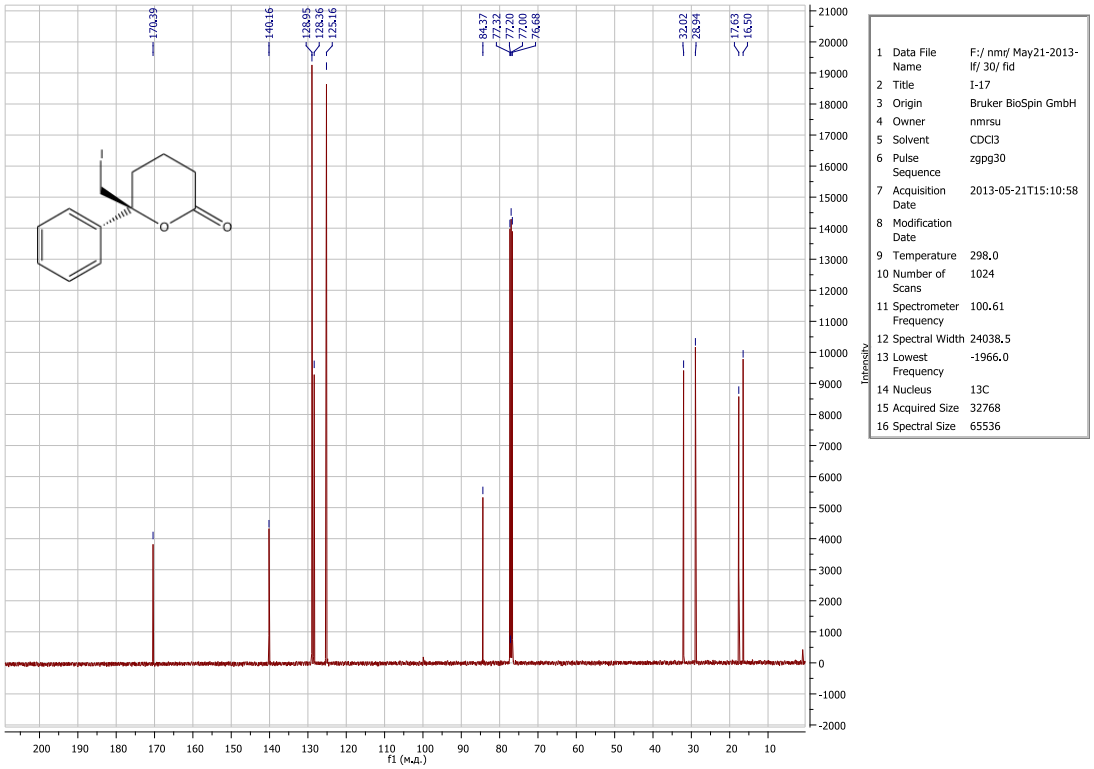
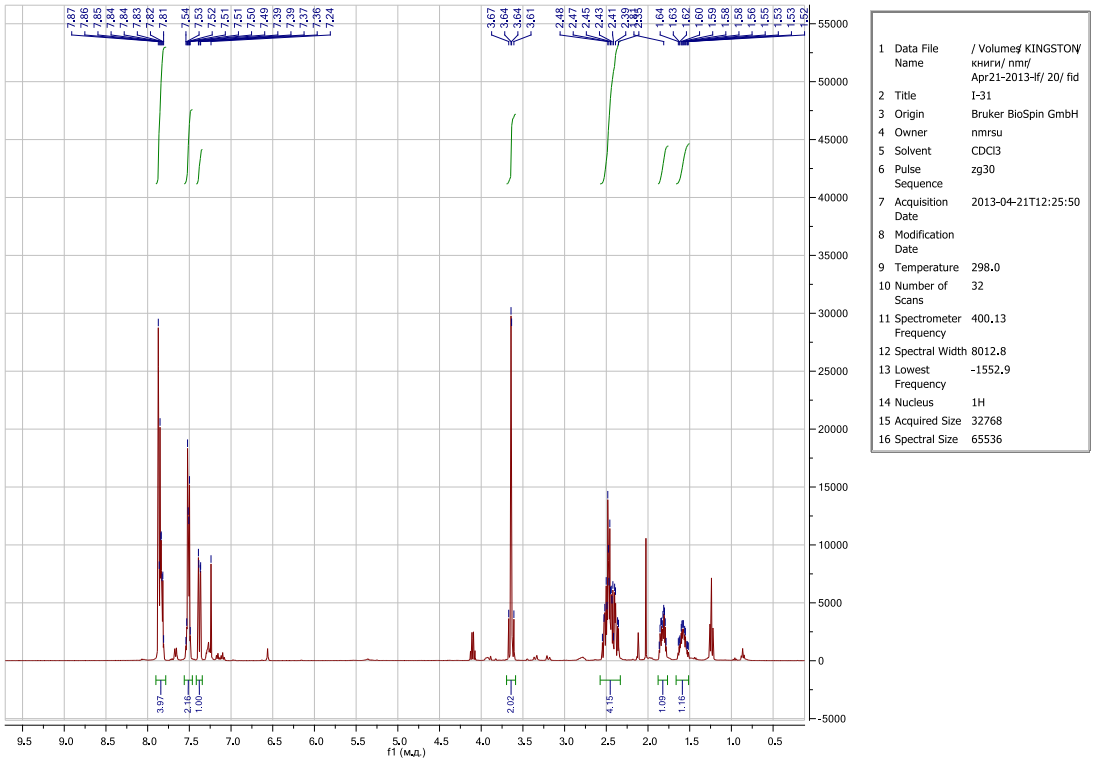


Figure S-16. ^{13}C NMR spectrum of **4a**.



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4	Owner	nmrsu
5	Solvent	CDCl3
6	Pulse Sequence	zg30
7	Acquisition Date	2013-04-21T12:25:50
8	Modification Date	
9	Temperature	298.0
10	Number of Scans	32
11	Spectrometer Frequency	400.13
12	Spectral Width	8012.8
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14	Nucleus	1H
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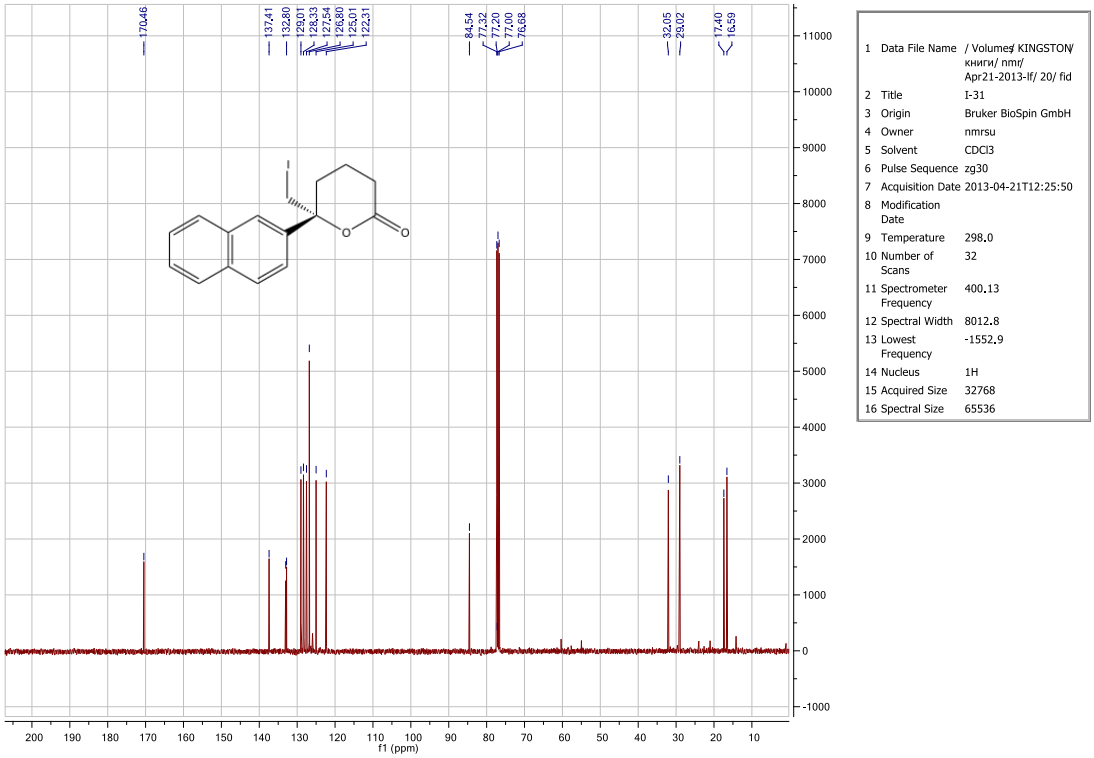
16	Spectral Size	65536

Figure S-17. ^{1}H NMR spectrum of **4b**.



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4	Owner	nmrsu
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6	Pulse Sequence	zg30
7	Acquisition Date	2013-04-21T12:25:50
8	Modification Date	
9	Temperature	298.0
10	Number of Scans	32
11	Spectrometer Frequency	400.13
12	Spectral Width	8012.8
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16	Spectral Size	65536

Figure S-18. ^{13}C NMR spectrum of **4b**.

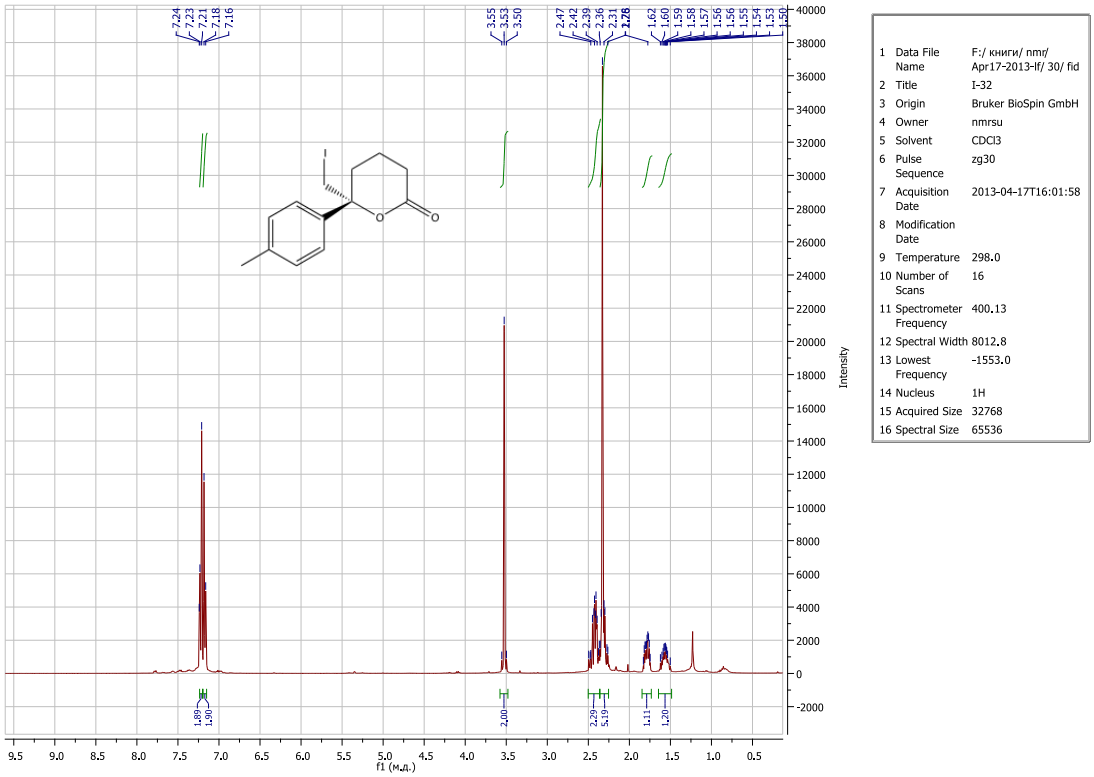


Figure S-19. ^{1}H NMR spectrum of **4c**.

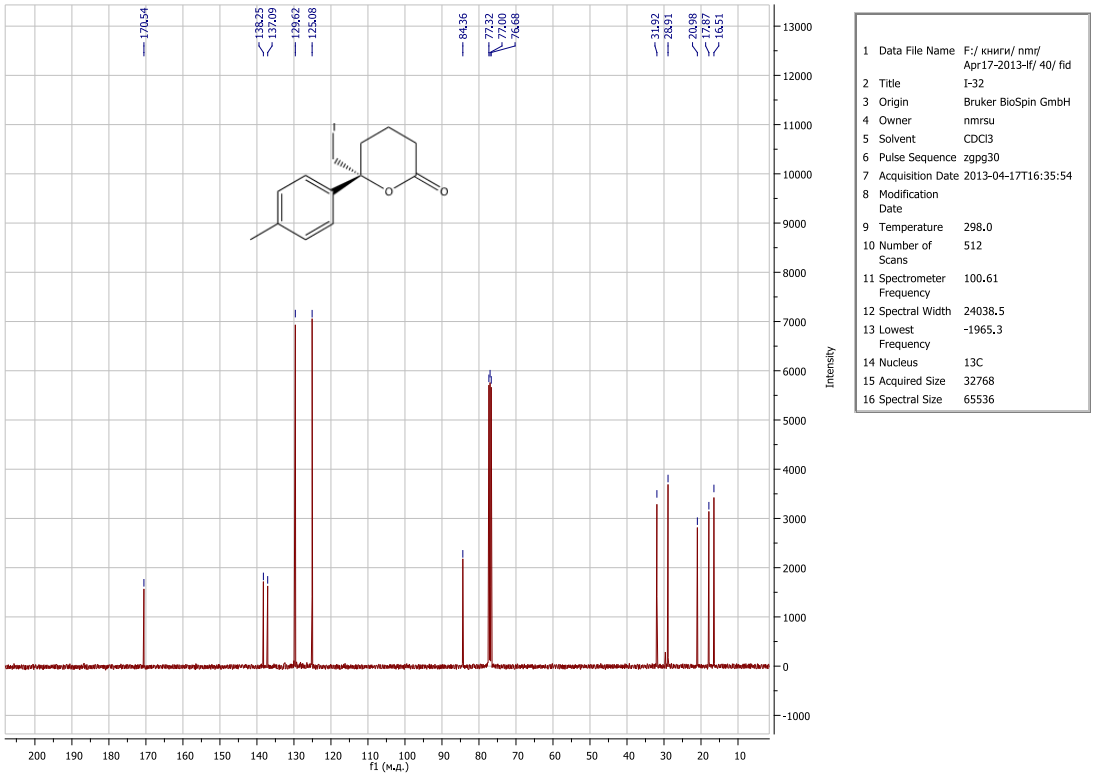


Figure S-20. ^{13}C NMR spectrum of **4c**.

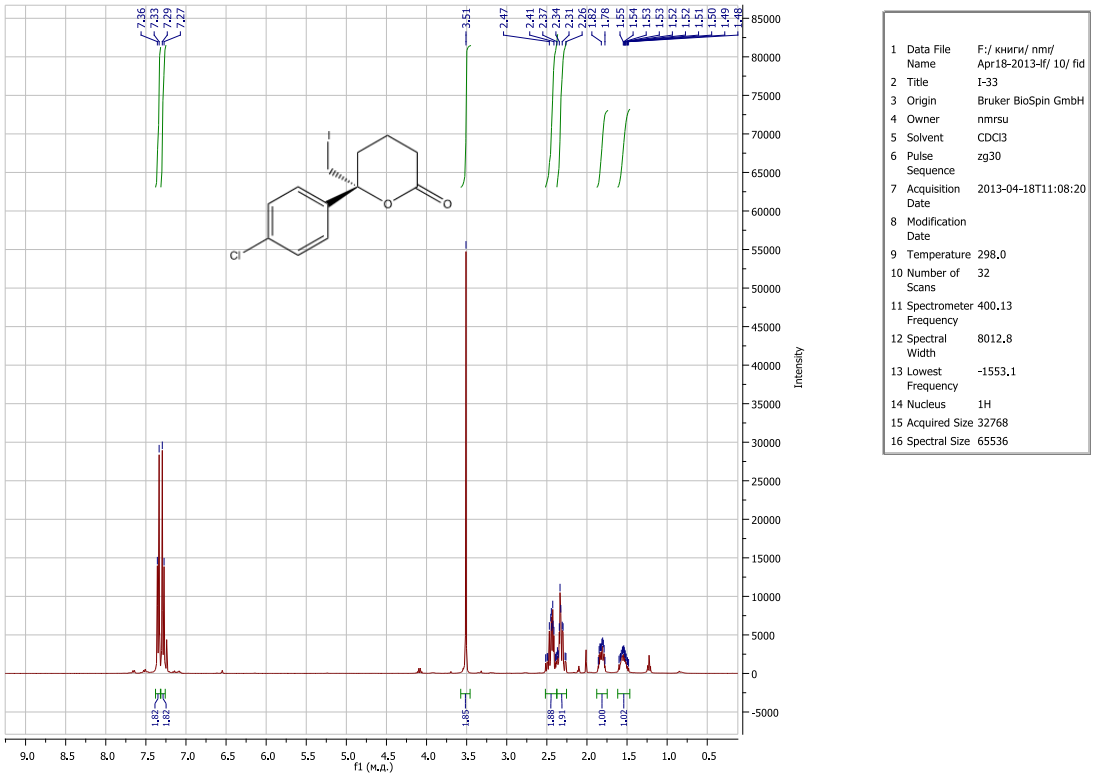


Figure S-21. ^{1}H NMR spectrum of **4d**.

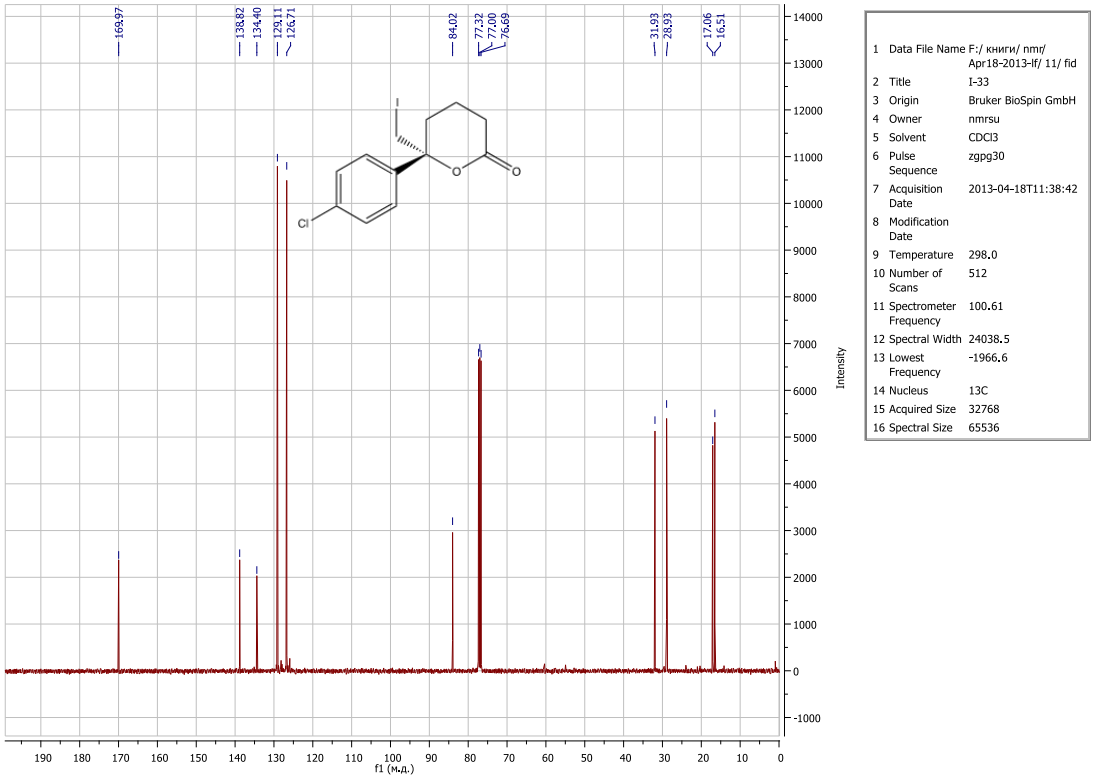


Figure S-22. ^{13}C NMR spectrum of **4d**.

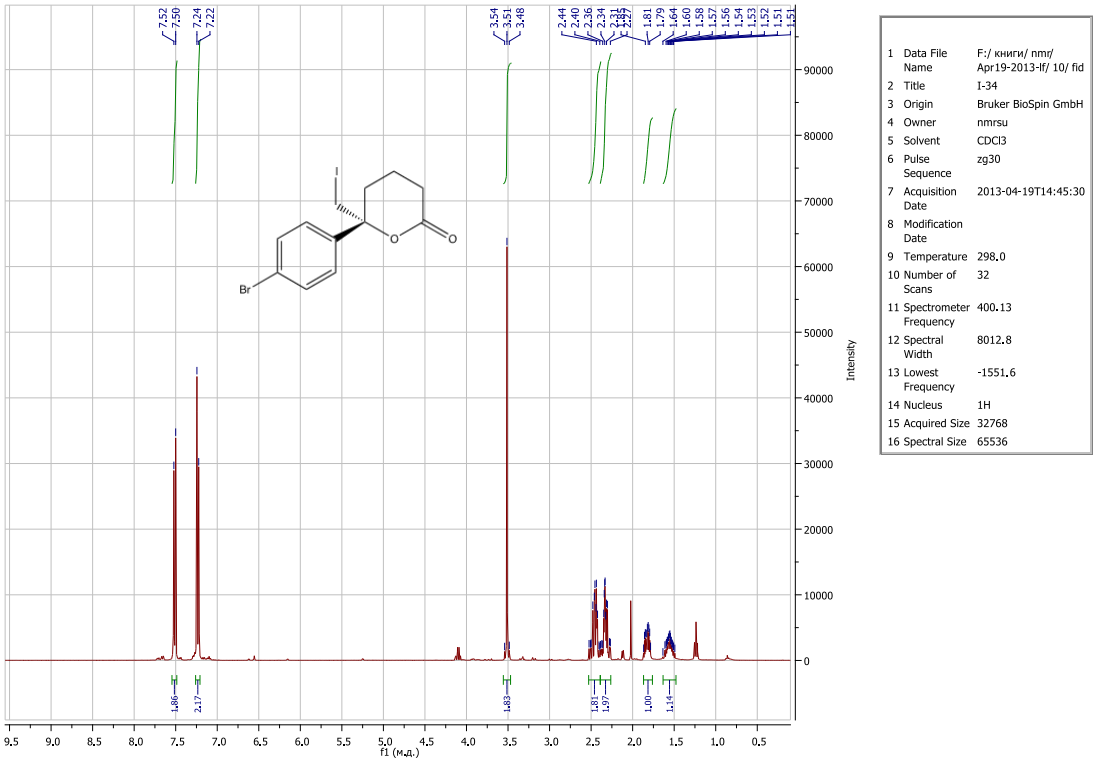


Figure S-23. ^{1}H NMR spectrum of **4e**.

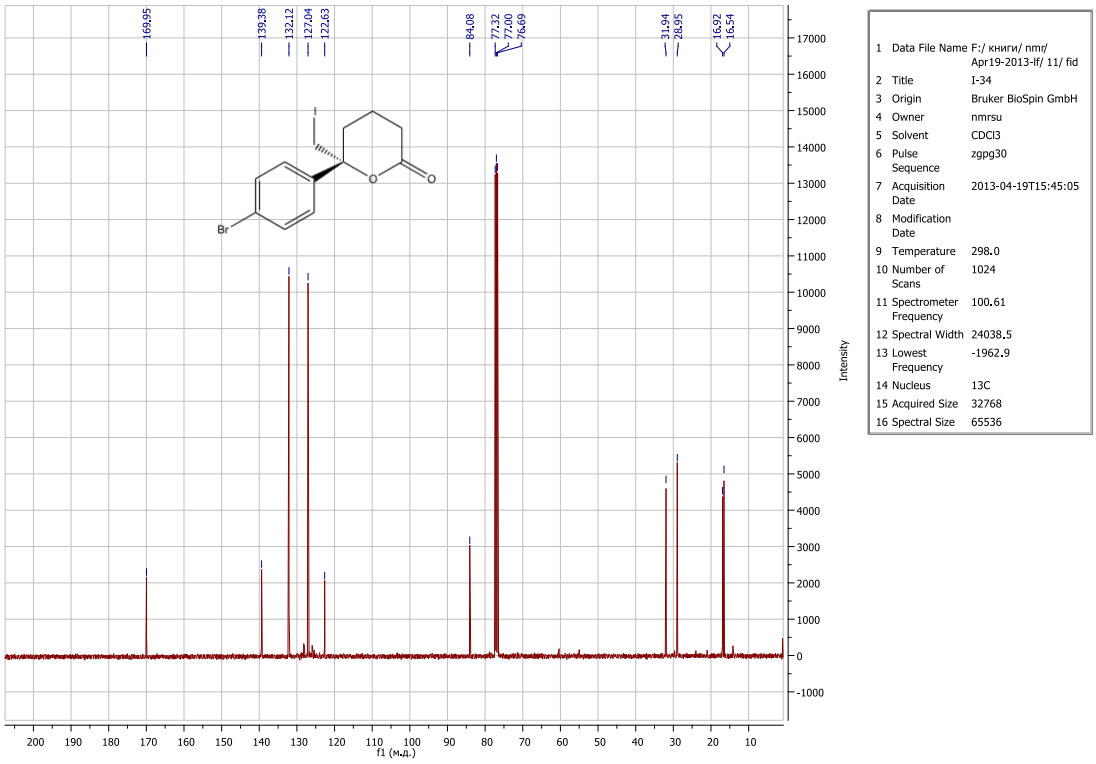


Figure S-24. ^{13}C NMR spectrum of **4e**.

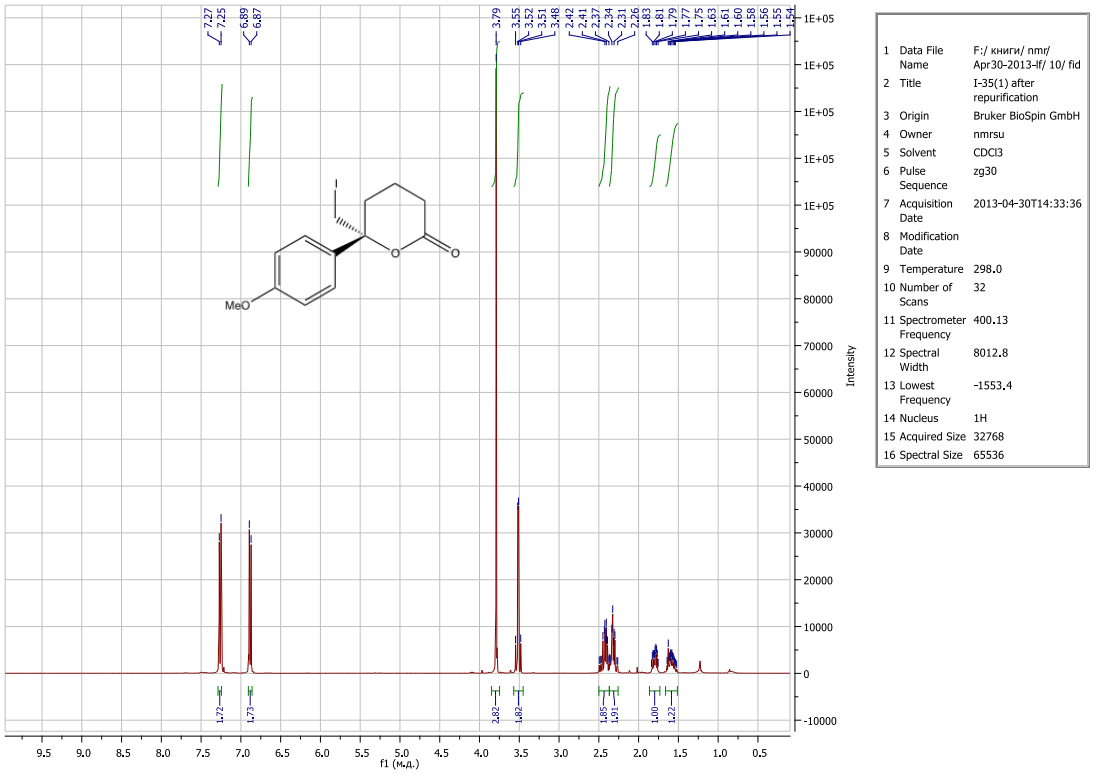


Figure S-25. ^{1}H NMR spectrum of **4f**.

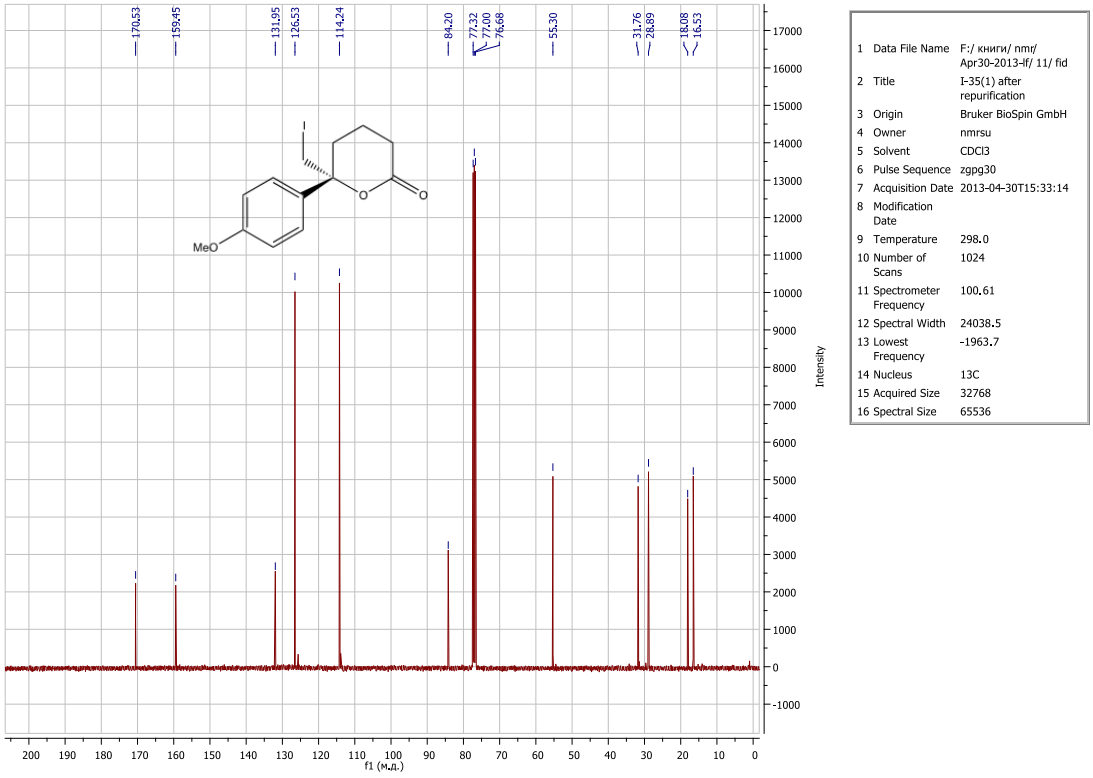


Figure S-26. ^{13}C NMR spectrum of **4f**.

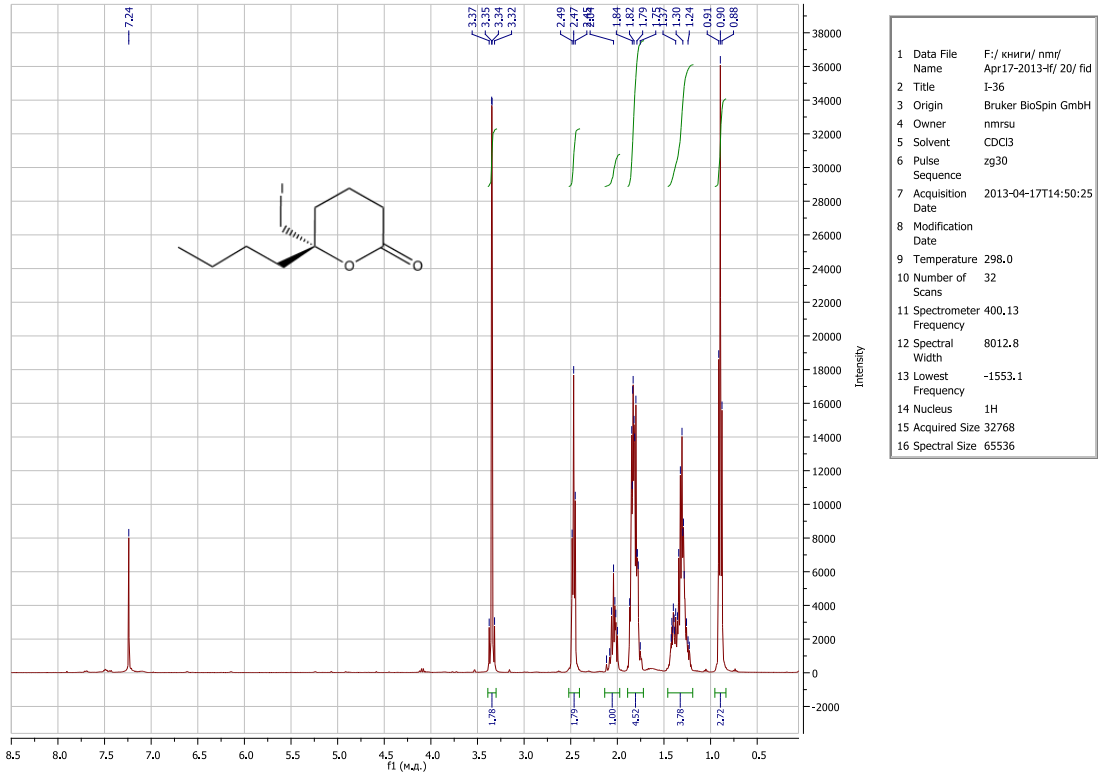


Figure S-27. ^{1}H NMR spectrum of **4g**.

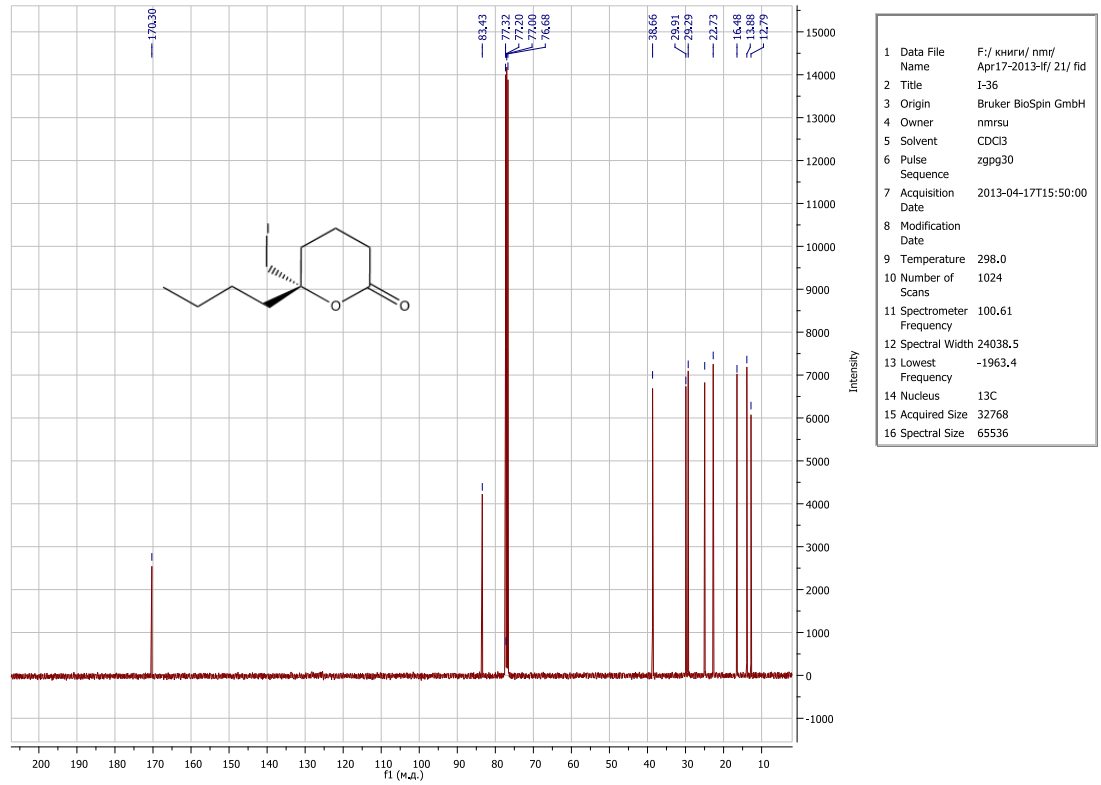
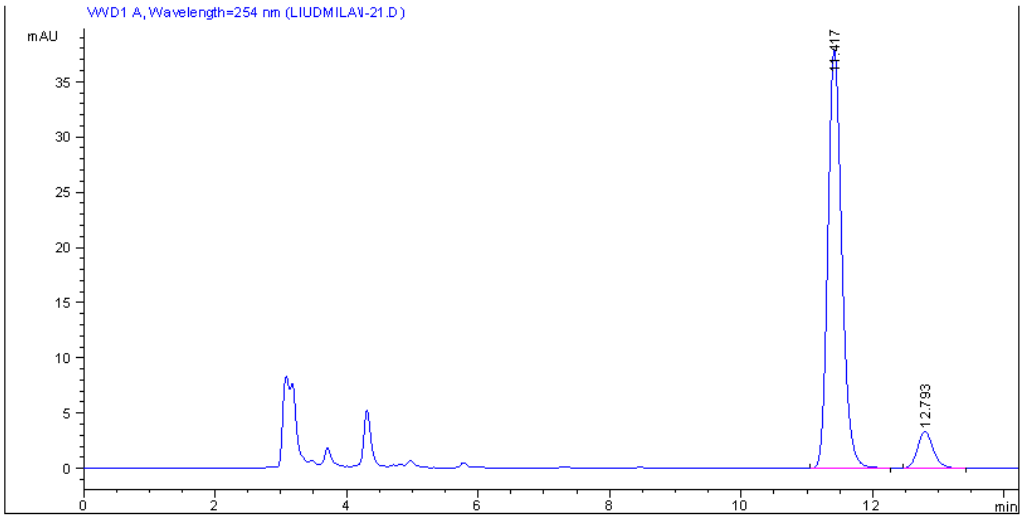


Figure S-28. ^{13}C NMR spectrum of **4g**.

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Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount         :      1.00000  [ng/ul]   (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
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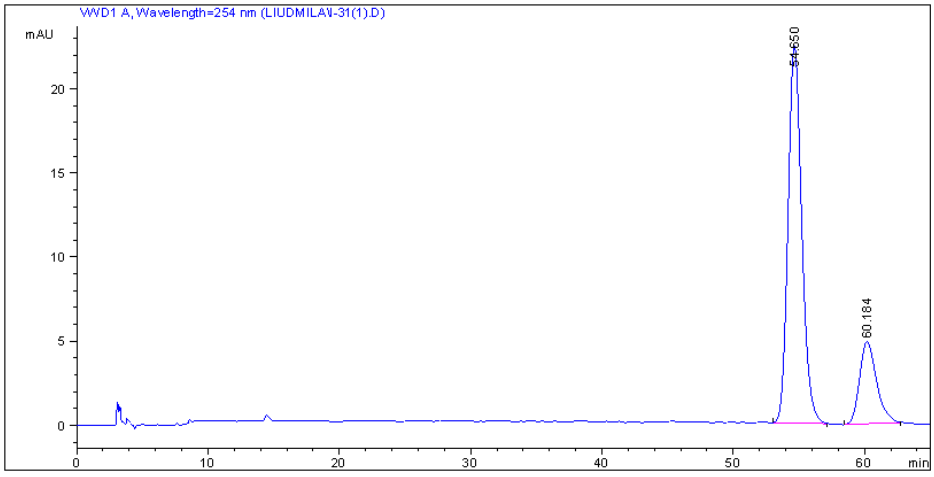
Figure S-29. HPLC chromatogram of the chiral compound **4a**.

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Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
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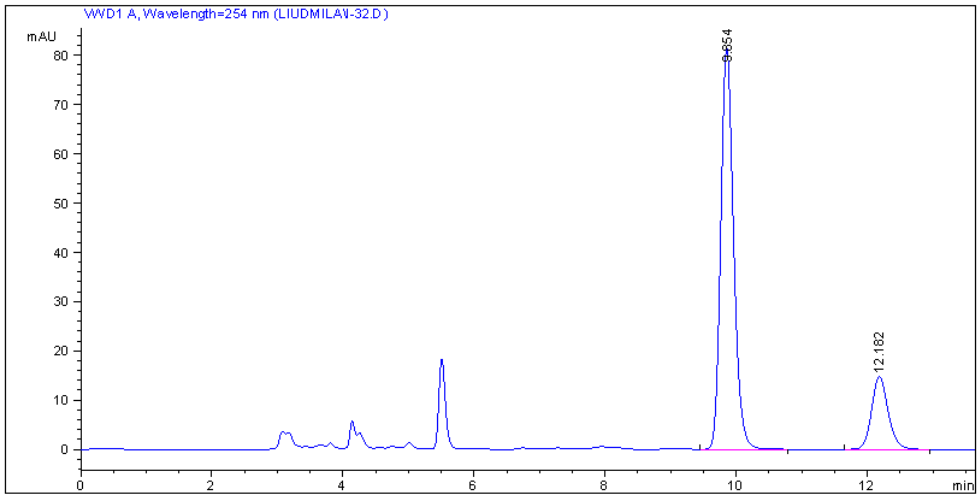
Figure S-30. HPLC chromatogram of the chiral compound **4b**.

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Dilution              :      1.0000
Sample Amount         :      1.00000  [ng/ul]   (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
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   2  12.182 BB     0.2718  260.49335   14.73068  19.0245

Totals :                   1369.25226   96.11069
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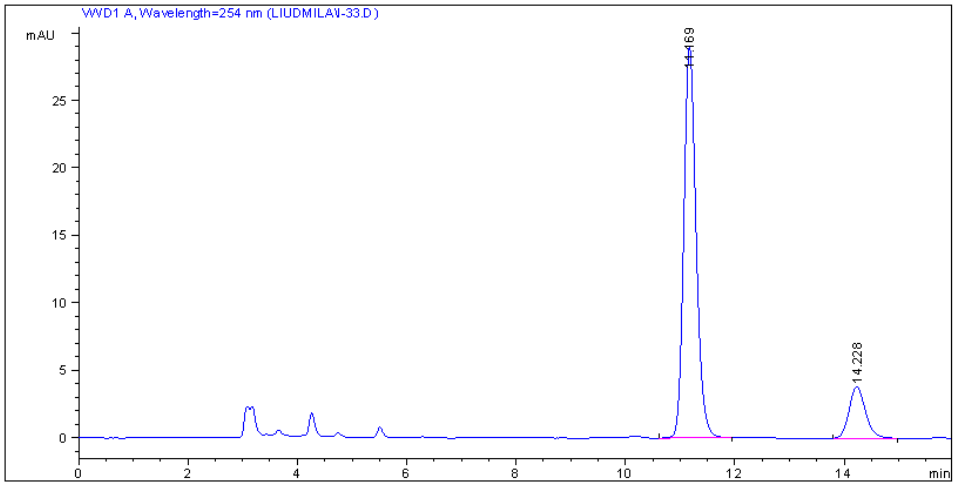
Figure S-31. HPLC chromatogram of the chiral compound **4c**.

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Dilution              :      1.0000
Sample Amount         :      1.00000  [ng/ul]   (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
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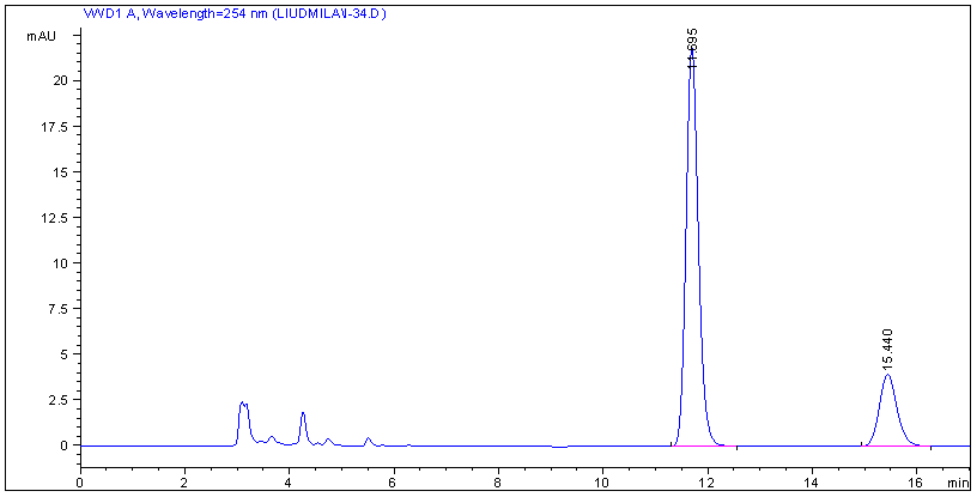
   1  11.169 VB     0.2406  453.17087   28.99534  85.1207
   2  14.228 BB     0.3192   79.21561    3.81886  14.8793

Totals :                   532.38648   32.81420
```

Figure S-32. HPLC chromatogram of the chiral compound **4d**.




```
=====================================================================
                        Area Percent Report
=====================================================================

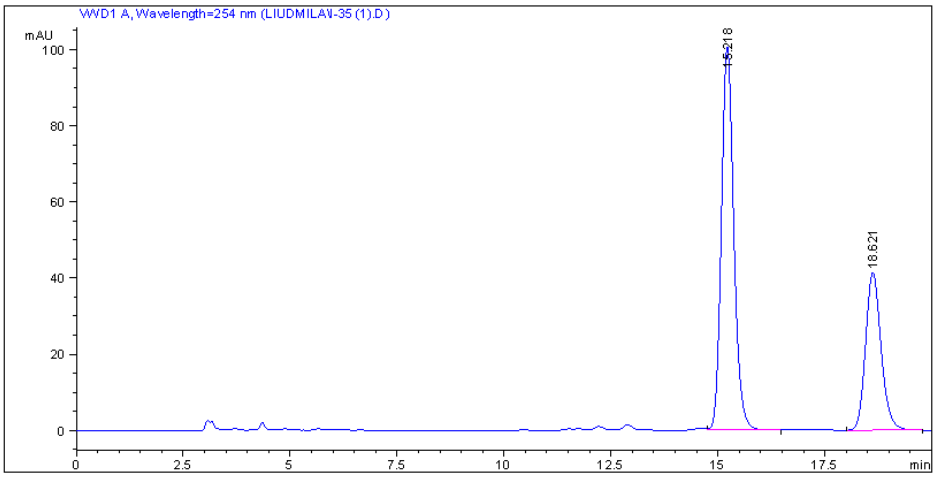
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount         :      1.00000  [ng/ul]    (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  11.695 BB    0.2534  359.90561   21.84019  79.3961
   2  15.440 BB    0.3650   93.39799    3.94505  20.6039

Totals :                   453.30360   25.78524
```

Figure S-33. HPLC chromatogram of the chiral compound **4e**.

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=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount         :      1.00000  [ng/ul]    (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  15.218 VB    0.3115 2033.80823  100.65263  66.0365
   2  18.621 BB    0.3876 1046.01831   41.44878  33.9635

Totals :                  3079.82654  142.10141
```
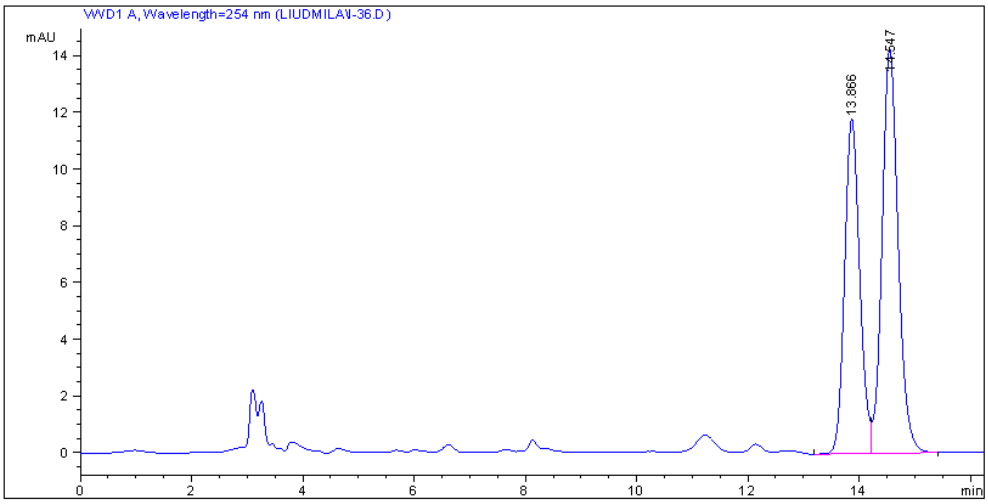
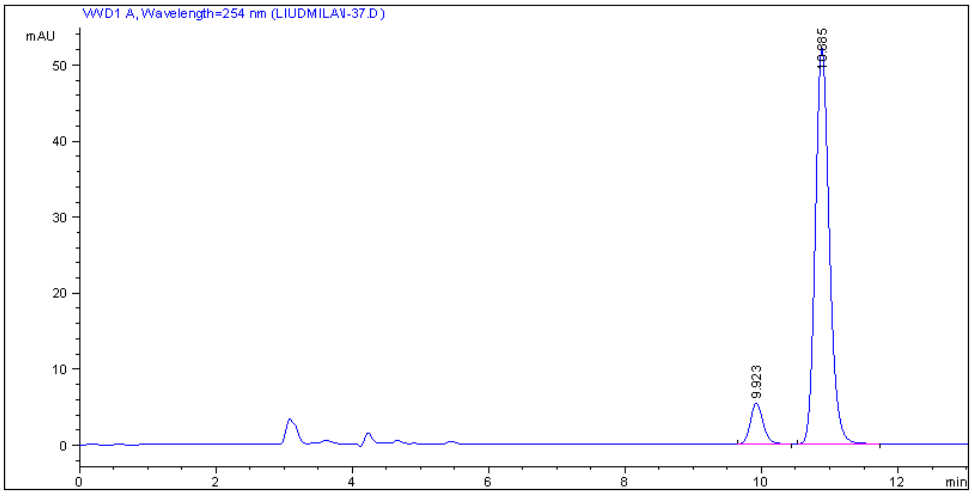

Figure S-34. HPLC chromatogram of the chiral compound **4f**.




```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount         :      1.00000  [ng/ul]   (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  13.866 VV    0.2907  223.00287   11.78496  43.7710
   2  14.547 VB    0.3075  286.47342   14.23904  56.2290

Totals :                   509.47629   26.02399
```

Figure S-35. HPLC chromatogram of the chiral compound **4g**.




```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount         :      1.00000  [ng/ul]   (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1   9.923 BB    0.1981   70.17276    5.40274   8.6431
   2  10.885 BB    0.2186  741.72058   52.08399  91.3569

Totals :                   811.89334   57.48673
```

Figure S-36. HPLC chromatogram of the chiral compound **4h**.

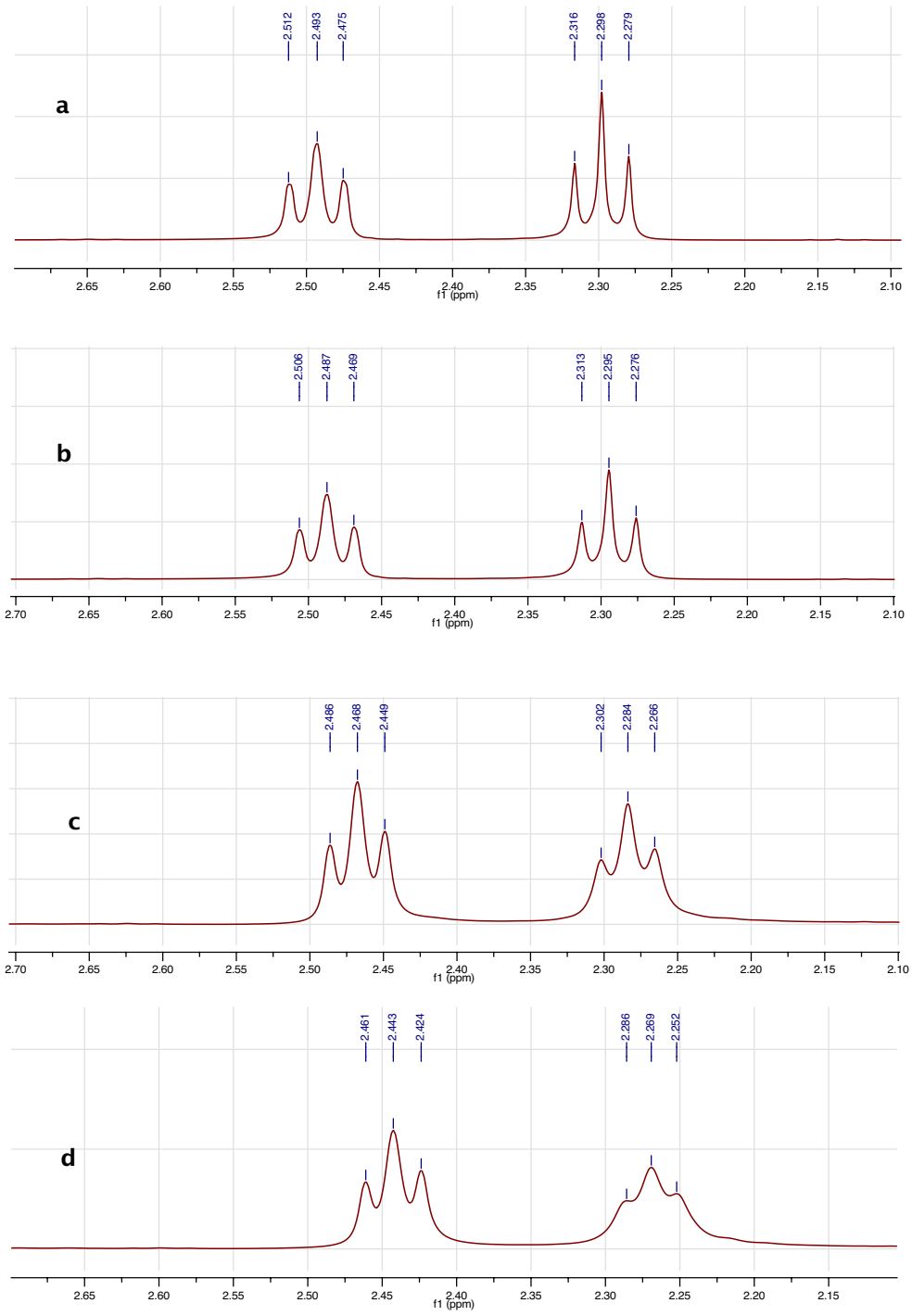


Figure S-37. ^{1}H NMR spectroscopic study of mixtures **2a** and **3a**: a) **3a**, b) 1:100 mixture of **2a** and **3a,** c) 1: 50 mixture of **2a** and **3a**; d) 1:10 mixture of **2a** and **3a.**

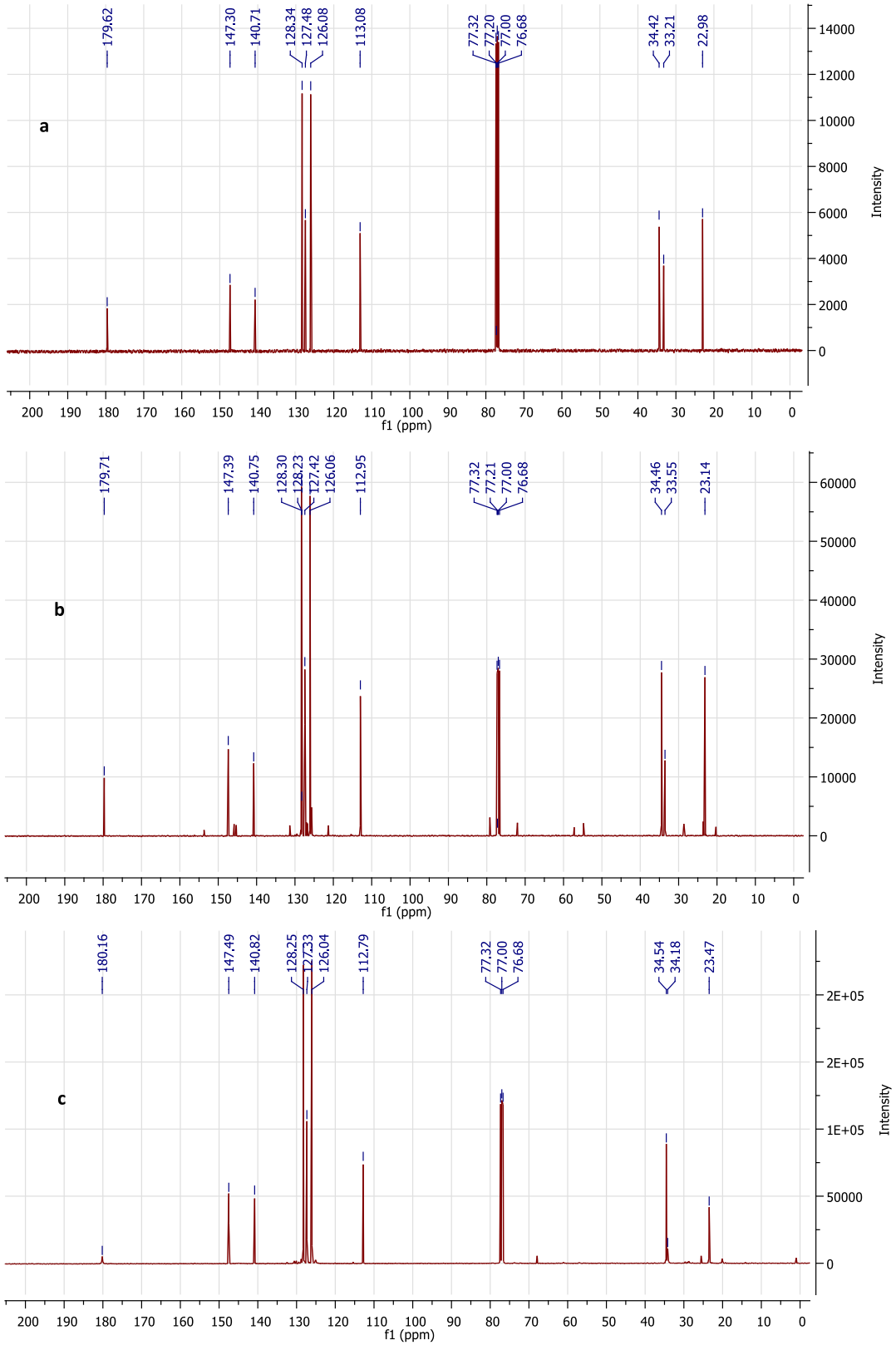


Figure S-3. ^{13}C NMR spectroscopic study: a) **3a**, b) 1:10 mixture of **1** and **3a,** c) 1: 10 mixture of **2a** and **3a**

References:

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Paper II

Stereoselective synthesis of (all-Z)-hentriaconta-3,6,9,12,15,19,22,25,28-nonaene
Liudmila Filippova, Ida Aarum, Martine Ringdal, Martin Kirkus Dahl, Trond Vidar Hansen, Yngve Stenstrøm, *Org. Biomol. Chem*. **2015**, *13*, 4680-4685.

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Stereoselective synthesis of (all-*Z*)-hentriaconta-3,6,9,12,15,19,22,25,28-nonaene†

Liudmila Filippova,[a] Ida Aarum,[a] Martine Ringdal,[a] Martin Kirkhus Dahl,[a] Trond Vidar Hansen[a,b] and Yngve Stenstrøm*[a]

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Several microorganisms produce small quantities of polyunsaturated hydrocarbons and such natural products are of interest. Starting from the ethyl ester of eicosapentaenoic acid, the total synthesis of the natural product (all-*Z*)-hentriaconta-3,6,9,12,15,19,22,25,28-nonaene has been achieved in eight steps and 15% overall yield. The synthesis is based on a stereoselective Wittig reaction and confirms the all-*Z*-configuration of the nine double bonds in this highly unsaturated natural product.

Introduction

Microbial fatty acid and lipid metabolisms are currently explored for potential applications in bio-based production of hydrocarbons and other useful metabolites, such as polyunsaturated fatty acids (PUFAs).[1,2] Hydrocarbons are present in most microorganisms,[3] but the capability to produce long chain PUFAs, such as the ω-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), has mostly been reported for psychrophilic, piezophilic and some mesophilic (*Shewanella* sp.) bacteria phyla.[4,5] Recently, it has been reported that the bacterial strains producing long-chain PUFAs are also characterized by the presence of a small amount of an uncommon polyolefin natural product, namely (all-*Z*)-hentriaconta-3,6,9,12,15,19,22,25,28-nonaene (C31:9, **1**), see Scheme 1.[5–7] The positions and the *Z*-configuration of the nine double bonds as well as the structure of this un-branched very long-chain hydrocarbon (VLCH) **1** were assigned mainly on data obtained from FTIR and MS experiments.[5,7] Sukovich *et al.* discussed that the C31:9 lipid **1** may be biosynthesized *via* a head-to-head condensation pathway between two entities derived from (all-*Z*)-4,7,10,13-hexadecatetraenoic acid (**2**) (Scheme 1).[7,8]

As of now, no biochemical proof of this type of biosynthesis has been presented. Therefore, the geometry of the middle-chain double bond as well as the stereochemistry of the eight methylene interrupted *Z*-double bonds remains to be established by evidence other than the FTIR spectra. In addition, no biological data of the natural product **1** have been reported. Most likely, the C31:9 natural product **1** is involved in cold adaptation mechanisms beneficial for the bacteria.[9] Hence, a stereoselective total synthesis of the natural occurring VLCH **1** is required both for the exact structure elucidation and for providing enough material for conducting biological studies. These reasons, together with our interest in the synthesis of PUFA-derived natural products,[10] motivated us to achieve the first total synthesis of **1**. These efforts are reported herein.

Results and discussion

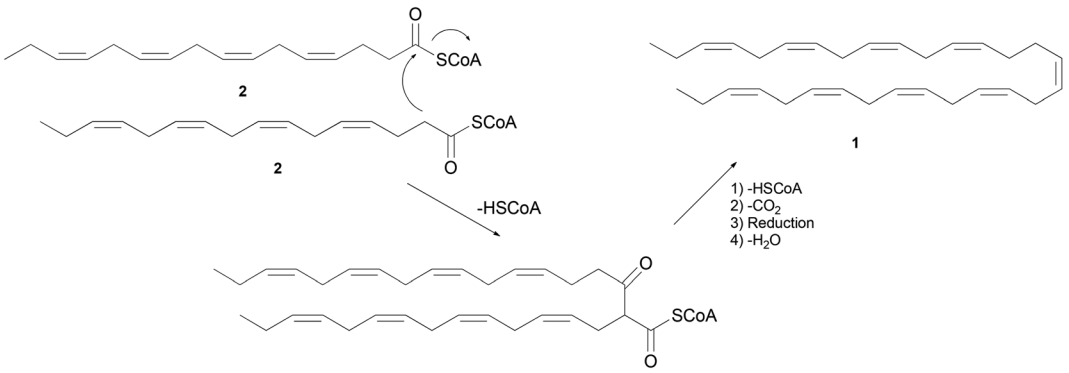
Considering the latent symmetry present in the hydrocarbon **1** around the C15–C16 bond, we assumed that the target molecule **1** could be obtained by a stereoselective semi-reduction of the symmetric allene **3**. It is to be noted that the regiochemistry is of no concern since any partial *Z*-selective reduction of **3** should lead to the formation of **1**. Our retrosynthetic analysis of **1** is outlined in Scheme 2.

The C15-aldehyde **4** and the terminal alkyne **5** should be easily available from the EPA ethyl ester **6**. This and similar esters have been employed as a convenient starting material for the synthesis of some methylene interrupted *Z*-double bond containing PUFAs[10c–e] and such derived natural products.[11] This type of approach renders the use of consecutive *Z*-selective Wittig reactions[12] or stereoselective semi-reduction of internal alkynes[13] unnecessary. Such reactions give most often low *Z*-selectivity.

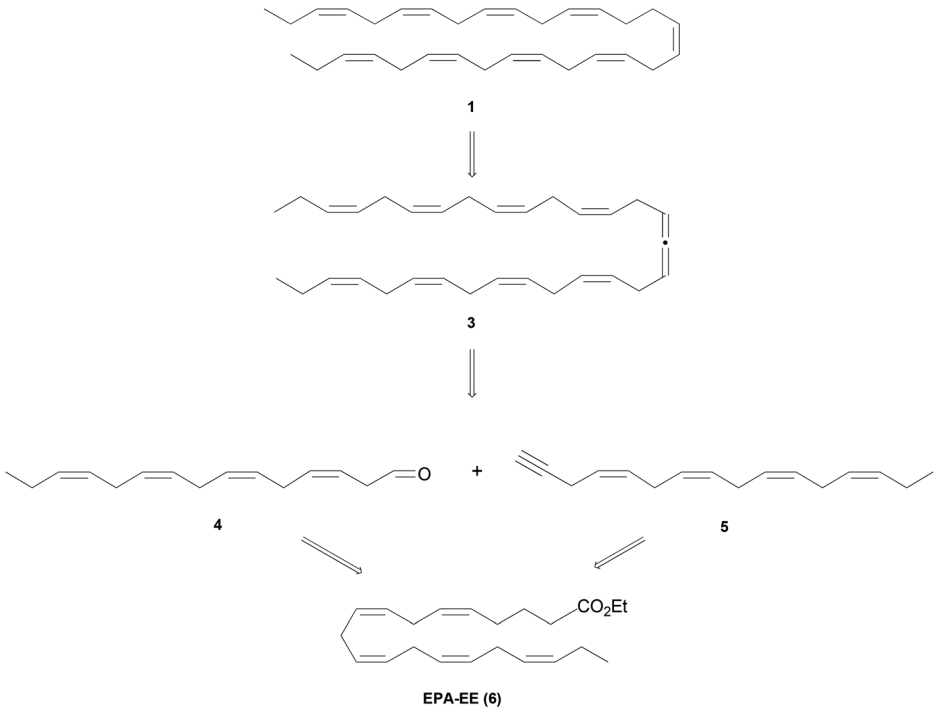
The total synthesis of **1** commenced with the preparation of aldehyde **4** from ethyl ester **6** by an established three step procedure (Scheme 3).[10c] The aldehyde **4** was subsequently converted into the terminal C-16 alkyne **5** in 65% yield using the Corey–Fuchs reaction.[14] The treatment of alkyne **5** with *n*-BuLi at −78 °C in THF, followed by the addition of aldehyde **4**, afforded the secondary propargylic alcohol **7a** in 39% yield.

[a]*Department of Chemistry, Biology and Food Science, Norwegian University of Life Sciences, PO Box 5003, N-1432 Ås, Norway. E-mail: yngve.stenstrom@nmbu.no*
[b]*School of Pharmacy, Department of Pharmaceutical Chemistry, University of Oslo, PO Box 1068, Blindern, N-0316 Oslo, Norway*

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c5ob00313j

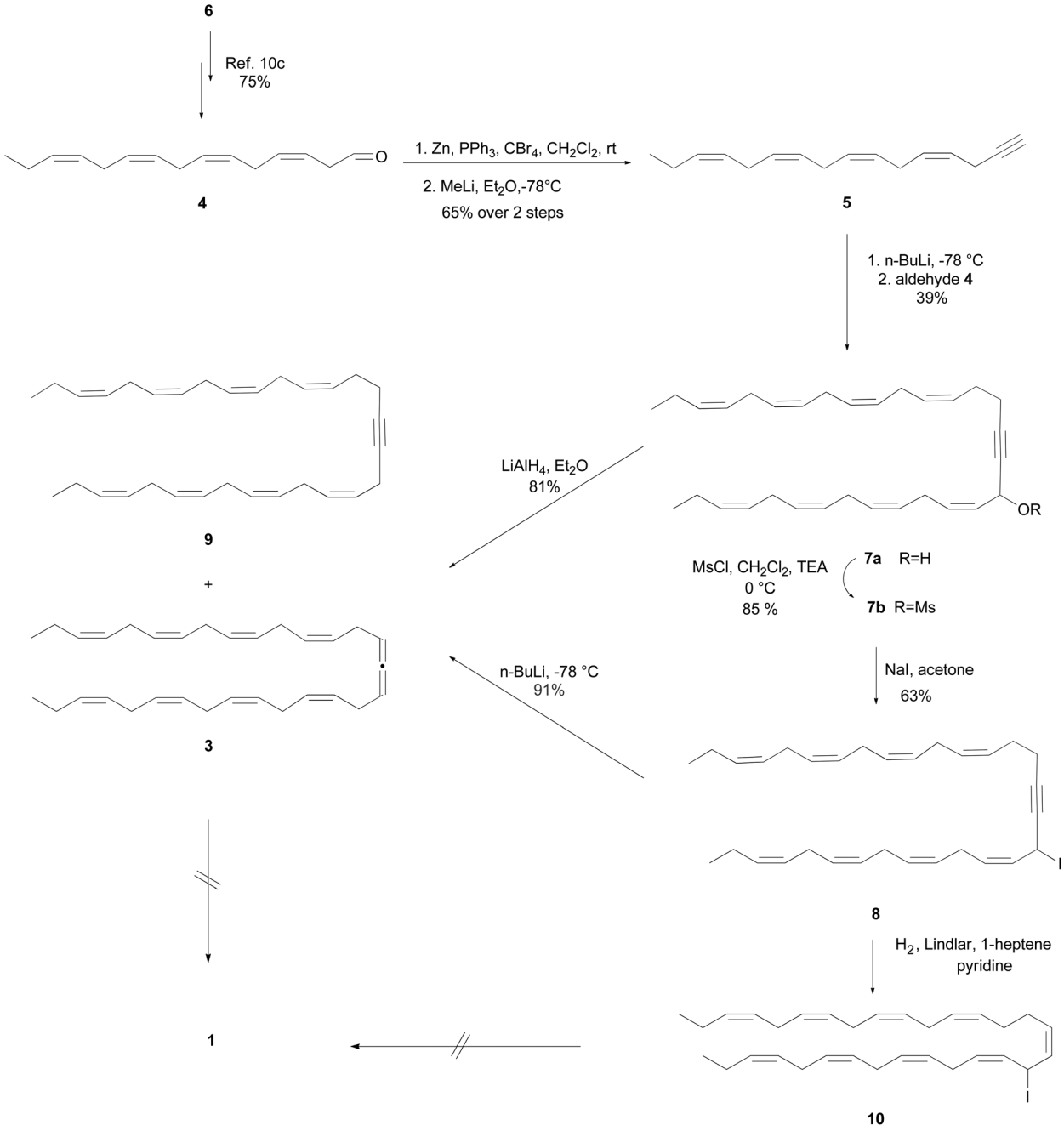


Scheme 1 The proposed biosynthesis of the VLCH **1**.



Scheme 2 Retrosynthetic analysis of the natural occurring VLCH compound **1**.

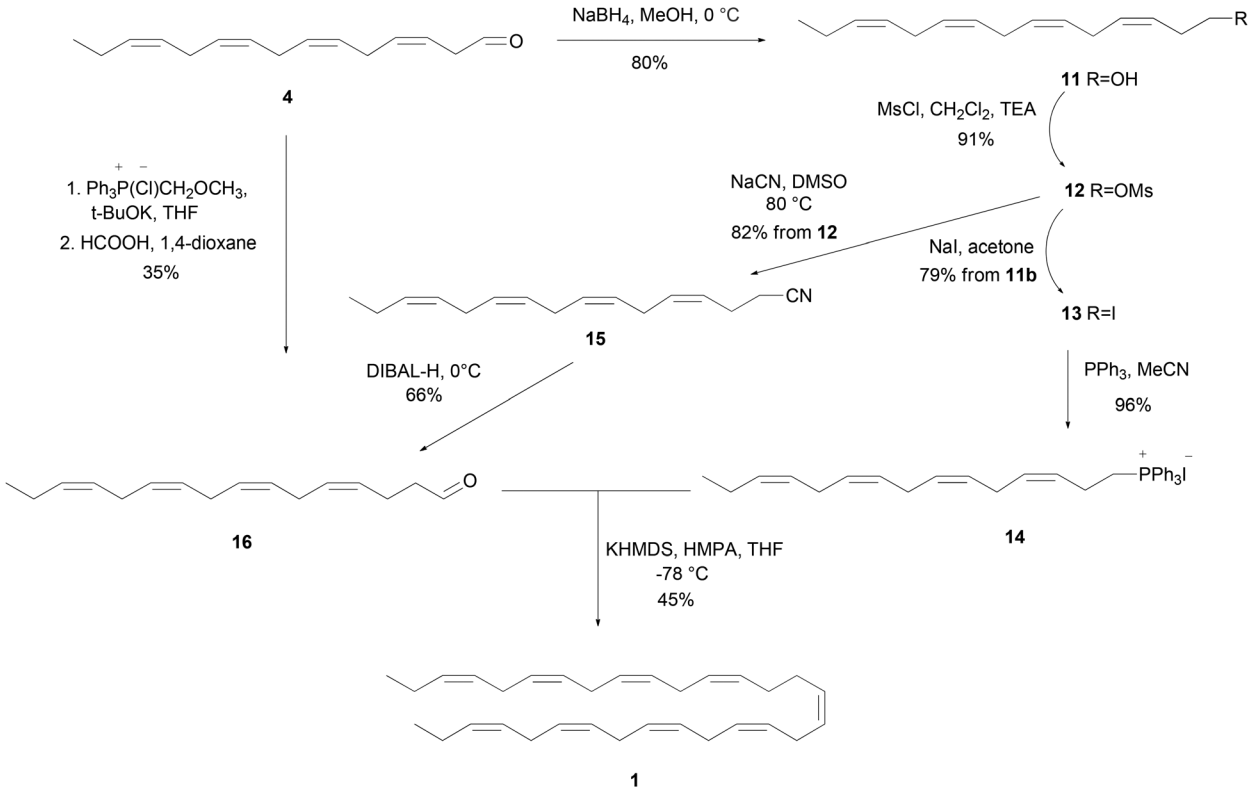
Alcohol **7a** was converted into its corresponding mesylate **7b**. The subsequent reduction of the mesylate **7b** with $LiAlH_4$ led to the formation of a mixture of the desired allene **3** and the isomeric C-31 alkyne **9** in 85% yield with the allene **3** as the main product. The ratio of **3** to the other products present was 92 : 8 as determined by GC analysis. Unfortunately, all efforts to obtain sufficient pure materials by column chromatography, or improving the yield of **3**, failed. Then we investigated the radical deoxygenation reaction of mesylate **7b** by employing a Barton–McCombie reaction[15] (Bu_3SnH, AIBN, dry benzene and reflux). However, only unreacted starting material **7b** was isolated. Therefore, the mesylate **7b** was converted into propargylic iodide **8** in 63% yield by a Finkelstein reaction. The reduction of iodide **8** using a modified Lindlar hydrogenolysis protocol, using 1-heptene and pyridine as additives, was then attempted.[16] The reaction afforded vinylic C-31 iodide **10** as the main product in 55% yield after purification by column chromatography. Then compound **10** was treated with either magnesium metal or *n*-BuLi. An aqueous work-up should in either case give the target hydrocarbon **1**. However, only starting material was observed by NMR analyses. On the other hand, the treatment of the propargylic iodide **8** with *n*-BuLi at −78 °C afforded allene **3** that was gratifyingly isolated in an excellent 91% yield.[17] The presence of the allene functionality was confirmed by ^{13}C-NMR (203.2 and 89.5 ppm), Raman (1955 cm^{-1}) and HRMS (m/z = 416.3434) experiments. Then the *Z*-selective reduction of the allenic double bond in **3** was attempted. Disappointingly, all of our attempts were unsuc-



Scheme 3 Attempted synthesis of **1**.

cessful. For example, the use of the modified Lindlar procedure, previously reported to be effective for the partial reduction of other allenes,[16] returned only the starting material **3**. When 10% Pd/C was used as the catalyst for the hydrogenation reaction,[18] significant amounts of several over-reduced products were detected by NMR analyses.

Since the semi-reduction of the allene functionality in **3** was difficult to achieve, we turned our attention to the development of an alternative synthesis of **1**. The middle chain double bond can be constructed *via* a *Z*-selective Wittig reaction between the C-15 Wittig salt **14** and the C-16 aldehyde **16**. It is noteworthy that both fragments can be obtained from aldehyde **4**. First the phosphonium iodide **14** was obtained from C-15 aldehyde **4** in 55% yield in a four-step protocol (Scheme 4). The C-16 aldehyde **16** can be synthesized by a one-carbon elongation reaction from the same aldehyde **4**. The Wittig reaction between **4** and the ylide obtained from (methoxymethyl)triphenylphosphonium chloride and potassium *tert*-butoxide, was followed by the consequent acid hydrolysis of the enol ether functionality in the Wittig product.[10c] This process afforded aldehyde **16** in a disappointing 35% yield. Alternatively, a selective reduction of the cyanide **15**[19] should



Scheme 4 The synthesis of the VLCH **1**.

also produce aldehyde **16**. Towards this end, alcohol **11** was first obtained from **4** ($NaBH_4$ in MeOH) and then converted into mesylate **12** under standard conditions. A successful conversion of **12**, by an S_N2-reaction (KCN, DMSO), to **15** was achieved. The DIBAL-H reduction of nitrile **15** afforded aldehyde **16** in 39% yield from aldehyde **4**. This protocol afforded the best overall yield of **16** since the Wittig reaction of the labile aldehyde **4** afforded variable amounts of isomerized products that proved difficult to be separated from the desired aldehyde **16**.

Finally, the reaction between aldehyde **16** and the ylide of phosphonium iodide **14**, the latter obtained after reaction with NaHMDS in dry THF at −78 °C in the presence of HMPA, completed the total synthesis of the natural product **1**. The chemical purity and the *Z* : *E*-ratio of synthetic **1** were determined to be >95% and >98 : 2, respectively, by GC and NMR analyses. The spectral data (NMR and IR) were in agreement with the literature.[5–7] Within the detection limits of ^{13}C NMR, no characteristic signals for allylic carbons of *E*,*Z*-conjugated polyolefins were observed.[20] This renders support to the fact that no isomerization of the polyene system has occurred.

Conclusions

In summary, the first total synthesis of the natural occurring VLCH compound (all-*Z*)-hentriaconta-3,6,9,12,15,19,22,25,28-nonaene (**1**), has been achieved in eight steps and in 15% overall yield from the ethyl ester **6**. Our synthesis confirmed the structure of **1**. An advantage in the reported approach is the utilization of the same starting material for the construction of two rather similar intermediates. The developed strategy is scalable and can be used for the preparation of labeled analogs of **1** for biological studies. Note that the all-*Z* methylene interrupted double bonds remained intact throughout the synthesis of **1**. This is an advantage when employing PUFAs, such as **6**, as starting materials in the total synthesis of polyunsaturated natural products.

Experimental section

General

All reactions were performed under a nitrogen atmosphere protected from light exposure. All reagents and solvents were of commercial grade and used without further purification unless where necessary. EPA ethyl ester (**6**) was a gift from Pronova Biopharma, AS, Sandefjord, Norway. Acetone was dried under anhydrous $CaSO_4$ and distilled. Thin layer chromatography (TLC) was performed using aluminum-backed silica gel 60 F_{254} plates and flash chromatography utilized silica gel 60 (40–63 μm) from Merck. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a Bruker Ascend™ 400 instrument with $CDCl_3$ as a solvent. Chemical shifts are expressed in

ppm relative to the residual solvent peak as an internal standard set to δ 7.26 and 77.0. Mass spectra were recorded at 70 eV on a Waters Prospec Q spectrometer using CI as the ionization method. The GC analyses were performed on a Agilent GC system using an Agilent J1W HP-5 GC column (20 m, i.d. = 0.18 mm) with an FID detector. IR spectra (4000–600 cm^{-1}) were recorded on a Perkin-Elmer Spectrum BX series FT-IR spectrophotometer by using a reflectance cell (HATR).

(3*Z*,6*Z*,9*Z*,12*Z*)-Pentadeca-3,6,9,12-tetraenyl methanesulfonate 12. Mesyl chloride (1.55 mL, 20 mmol) was added to an ice-cooled solution of alcohol **11** (2.20 g, 10 mmol) and triethylamine (2.78 mL, 20 mmol) in dry dichloromethane (30 mL). The reaction mixture was allowed to reach the room temperature and was stirred for 2 h. Brine (20 mL) was added and volatiles were removed under reduced pressure. The solution was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with saturated $NaHCO_3$ (2 × 15 mL), brine (2 × 10 mL) and dried (Na_2SO_4). The extract was concentrated by evaporation and the residue was purified by column chromatography eluting with hexane–EtOAc 10 : 1 to obtain mesylate **12** (2.72 g, 91%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61–5.23 (m, 8H), 4.20 (t, J = 6.8 Hz, 2H), 2.98 (s, 3H), 2.86–2.75 (m, 6H), 2.52 (qd, J = 6.9, 1.5 Hz, 2H), 2.11–2.01 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.1, 131.9, 128.7, 127.6, 127.4, 126.9, 123.3, 69.0, 37.5, 27.3, 25.7, 25.6, 25.5, 20.5, 14.3. IR: 3012, 2963, 2935, 2875, 1653, 1351, 1171, 717 cm^{-1}.

(3*Z*,6*Z*,9*Z*,12*Z*)-1-Iodopentadeca-3,6,9,12-tetraene 13. A solution of mesylate **12** (1.0 g, 3.35 mmol) and NaI (1.50 g, 10.0 mmol) in dry acetone (12 mL) was heated under reflux for 2 h. Water (50 mL) was added to the reaction mixture followed by cooling to room temperature when ethyl ether (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with ether (2 × 20 mL). The combined organic extracts were washed with water, brine and dried ($MgSO_4$). Evaporation followed by silica gel column chromatography eluting with hexane gave iodide **13** (880 mg, 79%) as a pale yellow oil. TLC (hexane, $KMnO_4$ stain): R_f = 0.25. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61–5.24 (m, 8H), 3.13 (t, J = 7.2 Hz, 2H), 2.89–2.75 (m, 6H), 2.65 (qd, J = 7.3, 1.4 Hz, 2H), 2.06 (pd, J = 7.5, 1.4 Hz, 2H), 0.96 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.1, 130.4, 128.6, 128.5, 128.3, 127.7, 127.6, 127.0, 31.5, 25.8, 25.7, 25.6, 20.6, 14.3, 5.2. IR: 3011, 2962, 2931, 2783, 1650, 1427, 1392, 1240, 1168, 713 cm^{-1}.

((3*Z*,6*Z*,9*Z*,12*Z*)-Pentadeca-3,6,9,12-tetraenyl) triphenylphosphonium iodide 14. Iodide **13** (860 mg, 2.6 mmol) was dissolved in dry acetonitrile (25 mL). Triphenylphosphine (1.73 g, 6.6 mmol) was added and then the solution was stirred under reflux for 20 hours. The reaction mixture was concentrated *in vacuo*. The crude product was purified by column chromatography eluting with CH_2Cl_2 (until all of the triphenylphosphine was washed out of the column) followed by CH_2Cl_2–MeOH 95 : 5 to produce **14** (1.48 g, 96%) as a deep yellow syrup. The compound decomposes during storage under an inert atmosphere at a low temperature. TLC (CH_2Cl_2 : MeOH 95 : 5, UV): R_f = 0.25. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88–7.74 (m, 9H), 7.71–7.66 (m, 6H), 5.65–5.58 (m, 1H), 5.44–5.12 (m, 5H), 3.87–3.75 (m, 2H), 2.72 (t, J = 7.2 Hz, 2H), 2.65 (t, J = 7.2 Hz, 2H), 2.57 (t, J = 7.3 Hz, 2H), 2.46 (dq, J = 16.7, 7.2 Hz, 2H), 2.02 (pd, J = 7.4, 1.5 Hz, 2H), 0.93 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.2 (d, $^4J_{CP}$ = 3.2 Hz, 3C), 133.8 (d, $^3J_{CP}$ = 10.1 Hz, 6C), 132.2, 130.6 (d, $^2J_{CP}$ = 12.1 Hz, 6C), 130.4, 128.8 (d, $^2J_{CP}$ = 7.1 Hz), 127.5, 127.2, 126.8, 126.5, 118.1 (d, $^1J_{CP}$ = 85.9 Hz, 3C), 25.6, 25.6, 25.5, 23.3 (d, $^1J_{CP}$ = 48.5 Hz), 20.6, 20.4 (d, $^3J_{CP}$ = 3 Hz), 14.3.

(4*Z*,7*Z*,10*Z*,13*Z*)-Hexadeca-4,7,10,13-tetraenenitrile 15. A mixture of mesylate **12** (894 mg, 3.0 mmol) and KCN (293 mg, 4.5 mmol) in DMSO (8 mL) was stirred at 70 °C for 2.5 hours. Water (30 mL) was added and the mixture was extracted with ethyl acetate (3 × 15 mL). The organic phases were combined; washed with brine, dried (Na_2SO_4) and evaporated. The crude residue was purified by column chromatography eluting with hexane–EtOAc 15 : 1 to obtain nitrile **14** (563 mg, 82%) as a pale yellow oil. TLC (hexane–EtOAc 15 : 1, $KMnO_4$ stain): R_f = 0.19. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61–5.23 (m, 8H), 2.81 (dq, J = 13.0, 6.5 Hz, 6H), 2.48–2.30 (m, 4H), 2.06 (p, J = 7.4 Hz, 2H), 0.96 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.1, 131.5, 128.8, 128.7, 127.6, 127.3, 126.9, 125.5, 119.3, 25.6, 25.6, 25.5, 23.3, 20.6, 17.5, 14.3. IR: 3012, 2963, 2932, 2874, 2245, 1653, 1427, 1394, 1068, 711 cm^{-1}.

(4*Z*,7*Z*,10*Z*,13*Z*)-Hexadecatetraenal 16. *Method 1*. At 0 °C, 1.0 M DIBAL-H in hexane (1.9 mL, 1.9 mmol) was added slowly to a solution of nitrile **15** (387 mg, 1.69 mmol) in 2 mL of dry ethyl ether. After 30 min the reaction was quenched with 1.0 M H_2SO_4 (5 mL). The salts were filtered off, brine was added and the reaction mixture was extracted with hexane. The extract was washed with brine twice, dried ($MgSO_4$) and concentrated. The residue was purified on a silica gel column eluting with hexane–EtOAc 95 : 5 to obtain aldehyde **16** (259 mg, 66% yield) as a colourless oil.

Method 2. The aldehyde **16** was obtained by a Wittig reaction according to the procedure reported by Langseter.[10c] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, J = 1.5 Hz, 1H), 5.46–5.23 (m, 8H), 2.89–2.72 (m, 6H), 2.49 (tt, J = 7.2, 1.3 Hz, 2H), 2.46–2.32 (m, 2H), 2.06 (pd, J = 7.5, 1.3 Hz, 2H), 0.95 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 132.1, 129.4, 128.6, 128.4, 127.8, 127.8, 127.7, 127.0, 43.7, 25.6, 25.6, 25.6, 20.6, 20.1, 14.3.

(3*Z*,6*Z*,9*Z*,12*Z*,15*Z*,19*Z*,22*Z*,25*Z*,28*Z*)-Hentriaconta-3,6,9,12,15,19,22,25,28-nonaene 1. To the Wittig salt **14** (284 mg, 0.48 mmol) dissolved in THF (4 mL), molecular sieves and HMPA (0.65 mL) were added and the solution was cooled to −78 °C. NaHMDS (1.0 M in THF, 0.48 mL, 1.0 equiv.) was added slowly and the mixture was stirred for 1 hour at the same temperature. Then the aldehyde **16** (93 mg, 0.4 mmol) was added at −78 °C. After the complete addition, the reaction mixture was allowed to reach ambient temperature slowly and was stirred for the next 24 hours. The reaction mixture was quenched by adding phosphate buffer (pH = 7.2, 5 mL) and additional hexane (8 mL). The phases were separated and the aqueous phase was extracted with hexane (8 mL) twice. The combined organic layers were washed with brine, dried (Na_2SO_4) and

evaporated to obtain the crude product. Purification by column chromatography eluting with hexane afforded the title compound **1** (75 mg, 45% yield) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.44–5.24 (m, 18H), 2.88–2.73 (m, 14H), 2.16–2.00 (m, 8H), 0.95 (t, J = 7.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.02, 132.01, 129.52, 129.49, 128.54, 128.51, 128.38, 128.31, 128.22, 128.20, 128.19, 128.13, 128.06, 128.00, 127.92, 127.88, 127.02, 127.01, 27.28 (×2), 25.70 (×2), 25.65, 25.63 (×2), 25.55 (×2), 20.57 (×2), 14.28 (×2). IR: 3012, 2963, 2932, 2874, 1652, 1454, 1392, 1266, 707 cm^{-1}. TOF-HRMS: Exact mass calculated for $C_{31}H_{46}Na$ $[M + Na]^+$: 441.3497, found 441.3485.

Acknowledgements

Pronova Biopharma, AS, Sandefjord, Norway is gratefully acknowledged for the generous gift of EPA ethyl ester. Financial support from the University of Life Sciences to L.F. (Quota Scheme) and a grant from the Norwegian Research Council, NFR 209335, are highly appreciated.

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Electronic supplementary information for

Stereoselective synthesis of (all-Z)-hentriaconta-3,6,9,12,15,19,22,25,28-nonaene

Liudmila Filippova,[a] Ida Aarum,[a] Martine Ringdal,[a] Martin Kirkhus Dahl,[a] Trond Vidar Hansen,[a,b] Yngve Stenstrøm[a]

[a]*Department of Chemistry, Biology and Food Science, Norwegian University of Life Sciences, PO Box 5003, N-1432, Ås, Norway*
[b]*School of Pharmacy, Department of Pharmaceutical Chemistry, University of Oslo, PO Box 1068, Blindern, N-0316 Oslo, Norway*

General information

All reactions were performed under a nitrogen atmosphere protected from light exposure. All reagents and solvents were commercial grade and used without further purification unless when necessary. EPA ethyl ester was obtained as a gift from Pronova Biofarma, BASF, Sandefjord, Norway. Acetone was dried under anhydrous $CaSO_4$ and distilled. Thin layer chromatography (TLC) was performed using aluminum-backed silica gel 60 F_{254} plates and flash chromatography with silica gel 60 (40-63 μm) from Merck. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a Bruker Ascend™ 400 instrument using $CDCl_3$ as a solvent. Chemical shifts are measured in ppm relative to residual solvent peak as internal standart set to δ 7.26 and 77.0. Mass spectra were recorded at 70 eV on a Waters Prospec Q spectrometer using EI and CI as the ionization method. The GC analyses were performed on an Agilent GC system using an Agilent J1W HP-5 GC column (20 m, i.d. = 0.18 mm) with FID detector. IR spectra (4000 – 600 cm^{-1}) were recorded on a Perkin-Elmer Spectrum BX series FT-IR spectrophotometer using a reflectance cell (HATR).

(3Z,6Z,9Z,12Z,19Z,22Z,25Z,28Z)-hentriaconta-3,6,9,12,19,22,25,28-octaen-15-yn-14-ol (7a)

n-BuLi (6.5 mL, 10.4 mmol, 1.6 M in hexane) was added to a solution of **5** (2.14 g, 10.4 mmol) in THF (100 mL) under nitrogen at -78 °C and stirred at this temperature for 10 min. A solution of aldehyde **4** (2.27 g, 10.4 mmol) in THF (60 mL) was added dropwise over 15 min. The mixture was stirred at -78 °C for 1 h before the solution was left to reach ambient temperature over 2 h. The reaction was quenched by the addition of aqueous NH_4Cl (pH = 8), and the mixture extracted with diethyl ether (3×25 mL). The combined organic layers were washed with brine (2×25 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash chromatography (SiO_2, hexane/EtOAc 95:5) to yield 1.75 g (39%) alcohol **7a** as pale yellow oil. TLC (hexane: EtOAc 95:5, $KMnO_4$ stain): R_f = 0.28. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J=8Hz, 6H), 1.73 (m, 1H), 2.01 (t, J=8 Hz, 4H), 2.41-2.43 (m, 2H), 2.74-2.77 (m, 12H), 2.93 (m, 2H), 4.32 (m, 1H), 5.30-5.50 (m, 16H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.3, 17.2, 20.6, 25.6, 25.7, 25.9, 26.4, 35.9, 62.1, 80.6, 83.7,

124.2, 124.4, 127.0, 127.4, 127.7, 127.8, 127.9,128.5, 128.6, 128.7, 129.8, 131.7, 132.0, 132.1. HMRS: Exact mass calculated for $C_{31}H_{46}O$ [M^+]: 432.3392, found 432.3376.

(3Z,6Z,9Z,12Z,19Z,22Z,25Z,28Z)-hentriaconta-3,6,9,12,19,22,25,28-octaen-15-yn-14-yl methanesulfonate (7b)

Mesyl chloride (36 µl, 0.462 mmol) was added to an ice cooled solution of the propargylic alcohol **7a** (100 mg, 0.231 mmol) and Et_3N (65 µL, 0.462 mmol) in dry dichloromethane (2.5 mL). The reaction mixture was left stirring at room temperature for 2 h. Brine was added and the volatiles were removed under reduced pressure. The residue was extracted with ether (3×5mL), washed with saturated $NaHCO_3$ (2×5mL) and brine (3×5mL) and evaporated to obtain yellow oil. The crude oil was purified on silica gel column eluting with hexane: EtOAc 9:1 to afford 107 mg of mesylate **7b** (85% yield). TLC (hexane: EtOAc 95:5, $KMnO_4$ stain): R_f = 0.26. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J=8 Hz, 6H), 2.01 (m, 4H), 2.58-2.59 (m, 2H), 2.75-2.76 (m, 12H), 2.96-3.02 (m, 5H), 5.09 (s, 1H), 5.30-5.54 (m, 16H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 17.2, 20.6, 25.6, 25.9, 34.0, 39.2, 71.7, 75.6, 88.0, 122.3, 123.2, 126.9, 127.1, 127.5, 127.6, 127.7, 128.7, 28.8, 128.9, 130.6, 132.1, 132.4.

(3Z,6Z,9Z,12Z,19Z,22Z,25Z,28Z)-14-iodohentriaconta-3,6,9,12,19,22,25,28-octaen-15-yne (8)

A solution of mesylate **7b** (85 mg, 0.166 mmol) and NaI (75 mg, 0.5 mmol) in dry acetone was heated under reflux for 3 h. Water was added to the reaction mixture and haxane after cooling down to room temperature. The organic layer was separated; the aqueous layer was extracted with hexane (3×5 mL). The combined organic extracts were washed with water, brine and dried ($MgSO_4$). Evaporation followed by silica gel column chromatography eluting with hexane: EtOAc 9:1 gave 57 mg of iodide **8** (63% yield) as pale yellow oil. TLC (hexane: EtOAc 9:1, $KMnO_4$ stain): R_f = 0.70. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J=8 Hz, 6H), 1.99-2.03 (m, 4H), 2.76-2.94 (m, 16H), 4.46 (m, 1H), 5.16-5.55 (m, 16H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9, 14.1, 14.3, 17.6, 20.6, 25.6, 25.7, 26.1, 38.0, 81.3, 85.6, 123.8, 126.8, 127.0, 127.4, 127.6, 127.7, 127.8, 128.6, 128.7, 130.0, 131.1, 132.1.

(3Z,6Z,9Z,12Z,19Z,22Z,25Z,28Z)-hentriaconta-3,6,9,12,15,16,19,22,25,28-decaene (3)

Prorargylic iodide **8** (20 mg, 0.037 mmol) was dissolved in dry ether and cooled down to -78 °C under nitrogen and added *n*-BuLi (7.1 µL, 0.074 mmol, 1.6 M in hexane). After stirring at -78 °C for 1 h the reaction mixture was allowed to warm up to room temperature. Water was added and the reaction mixture was extracted with diethyl ether (3×10 mL), washed with brine (2×10 mL), dried ($MgSO_4$) and evaporated to obtain 14 mg of allene **3** (91% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J=8 Hz ,6H), 2.01 (m, 6H), 2.74-2.76 (m, 14H), 5.06-5.31 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 19.5, 24.5, 24.6, 24.7, 24.9, 25.9, 28.7, 89.5, 126.0, 126.6,

126.7, 127.1, 127.2, 127.5, 127.6, 131.0, 203.2. HMRS: Exact mass calculated for $C_{31}H_{46}$ [M^+]: 416.3443, found 416.3434.

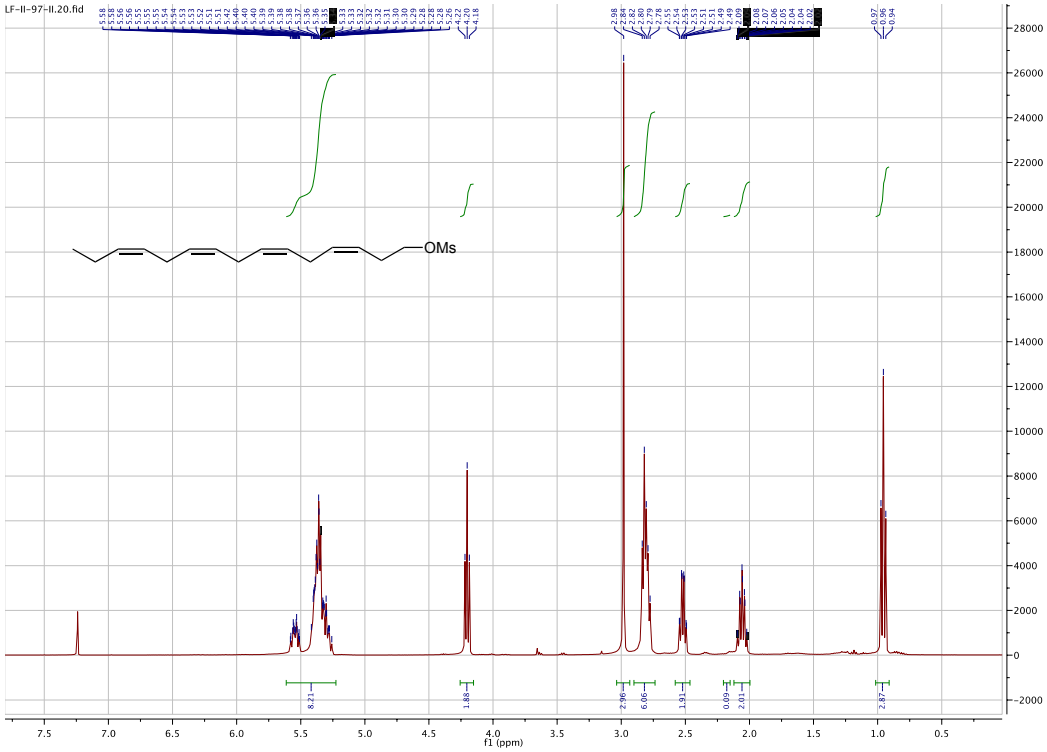


Figure S-1 ^{1}H MNR spectrum of **11b**

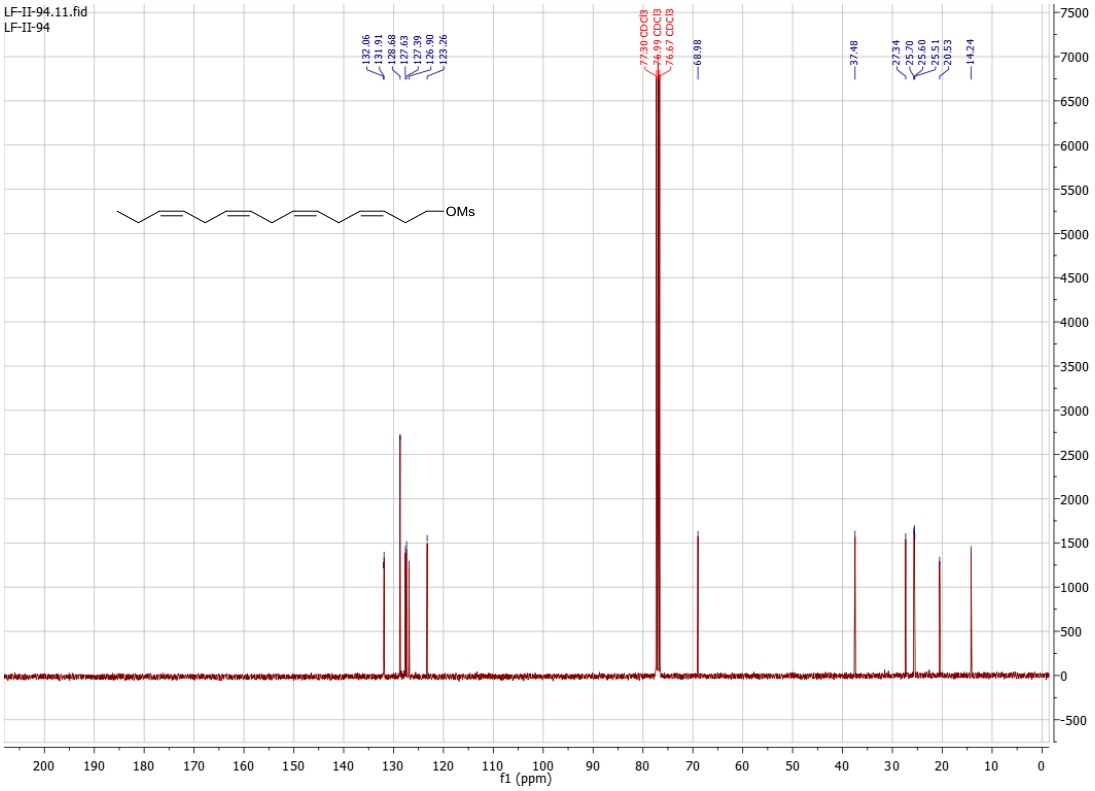


Figure S-2 ^{13}C NMR spectrum of **11b**

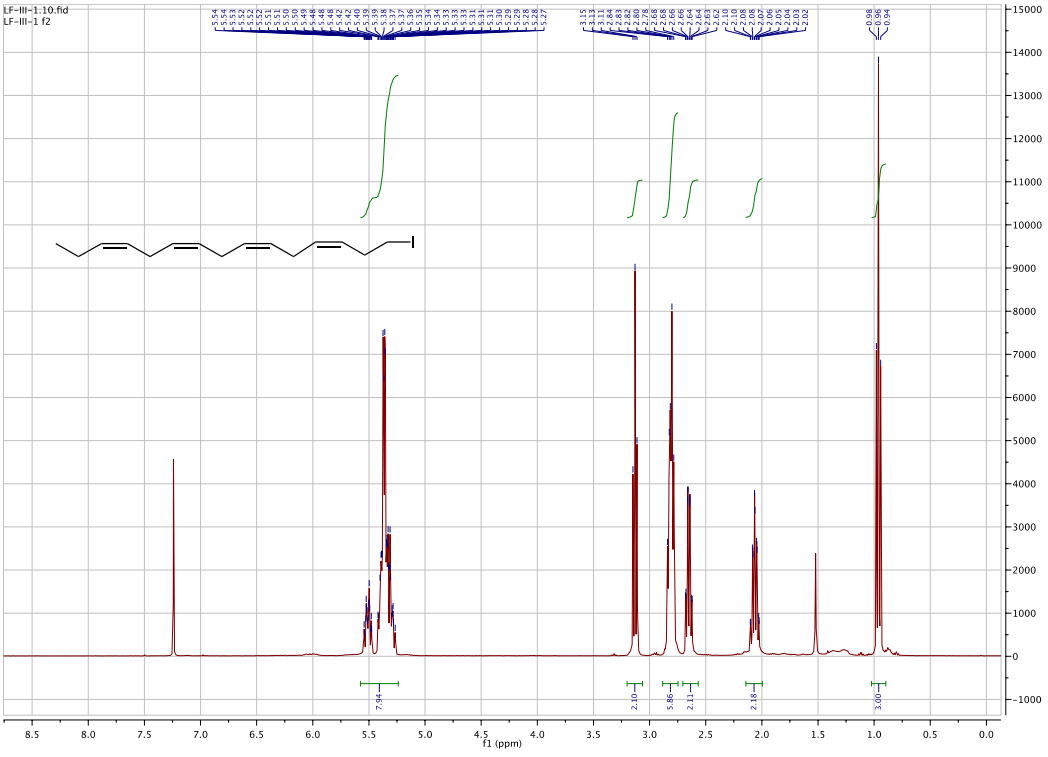


Figure S-3 ^{1}H MNR spectrum of **12**

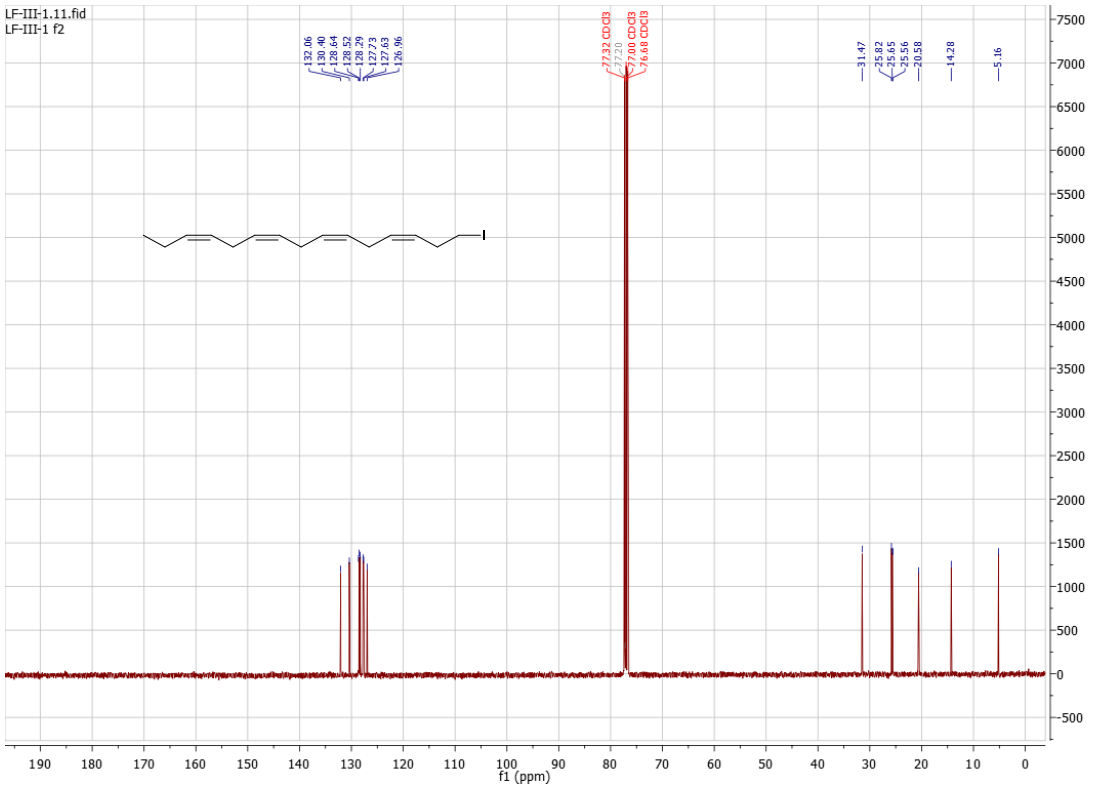


Figure S-4 ^{13}C NMR spectrum of **12**

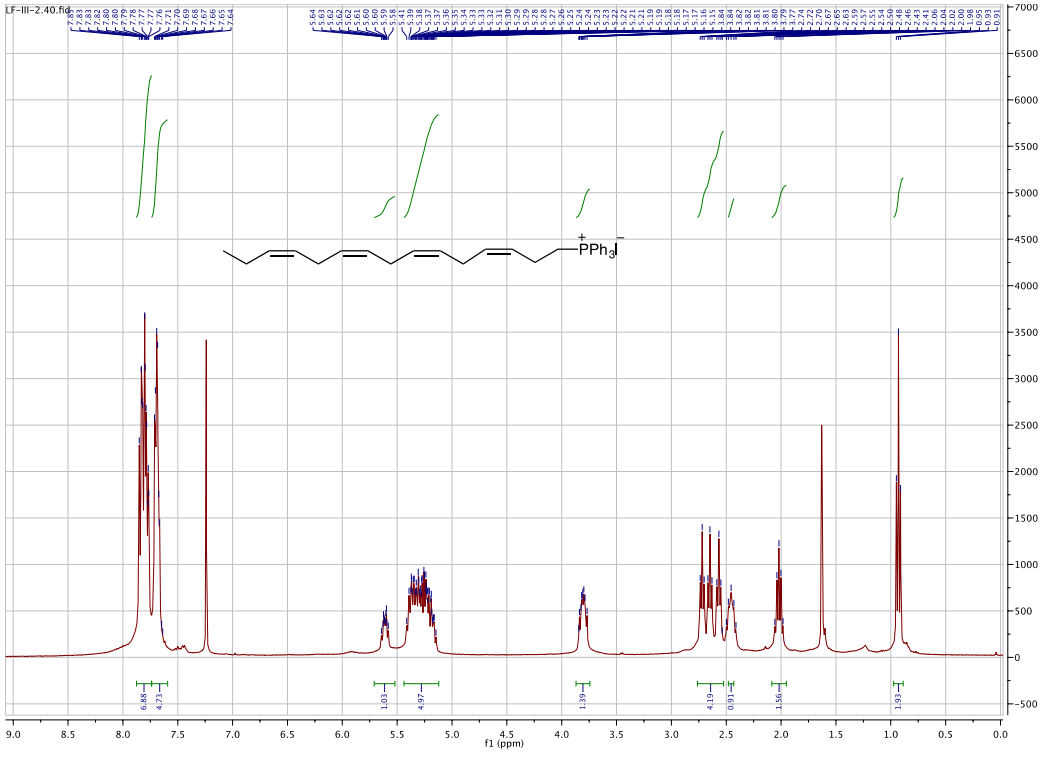


Figure S-5 ^{1}H MNR spectrum of **13**

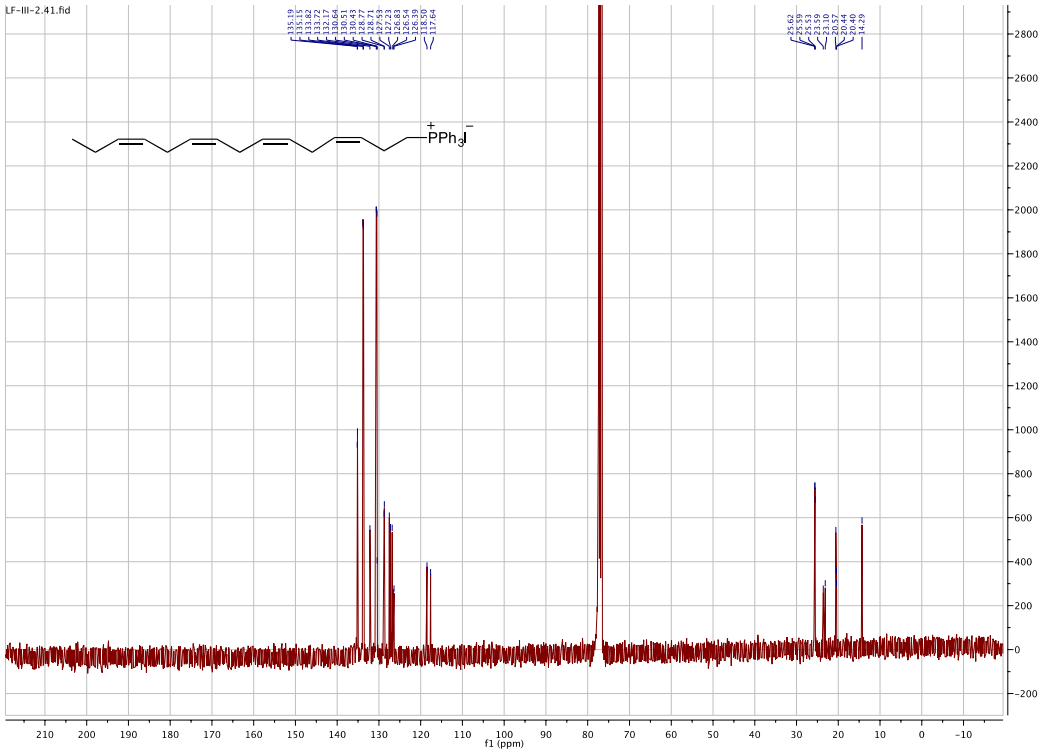


Figure S-6 ^{13}C NMR spectrum of **13**

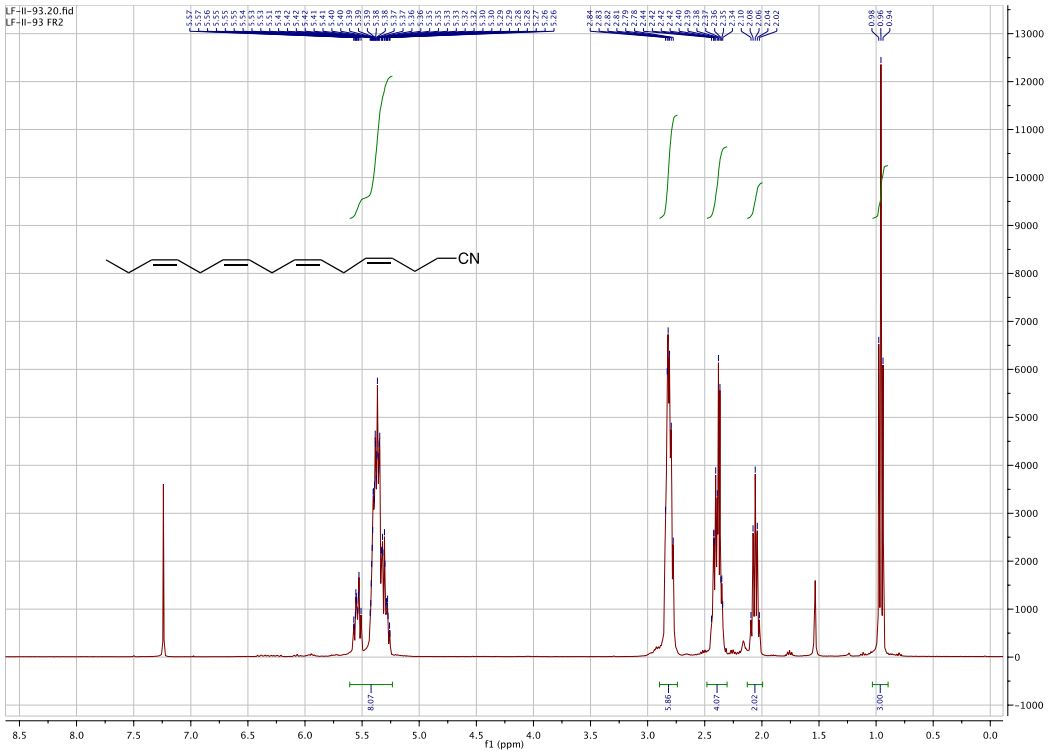


Figure S-7 ^{1}H NMR spectrum of **14**

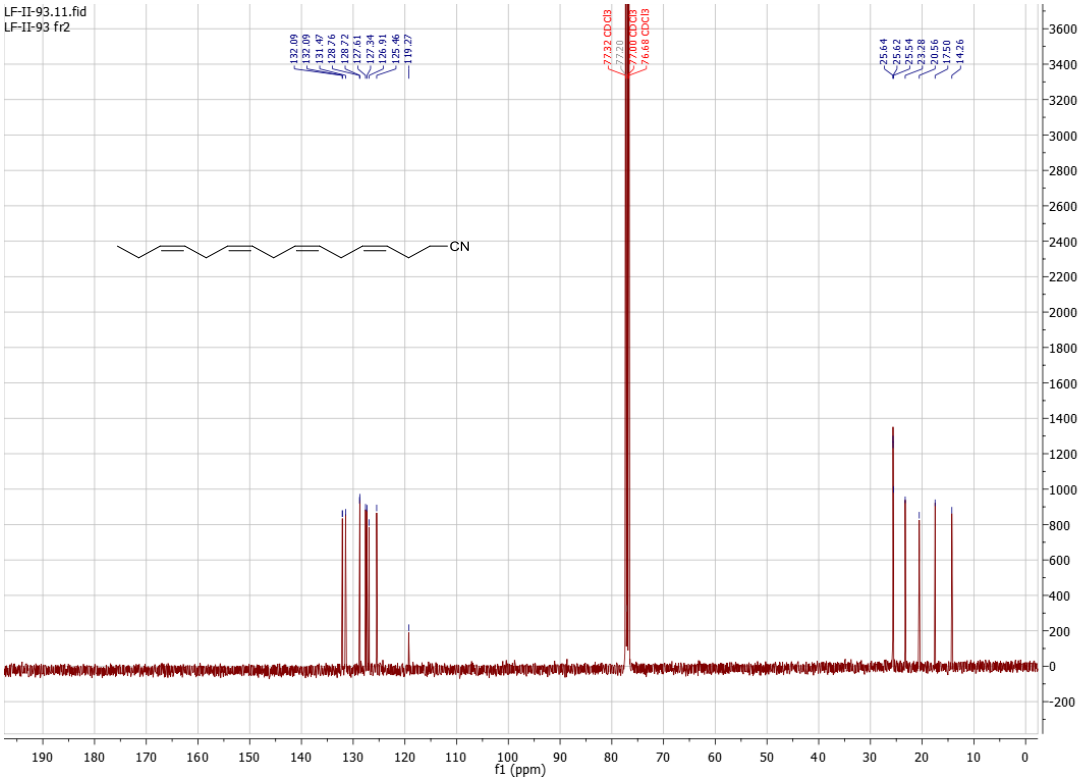


Figure S-6 ^{13}C NMR spectrum of **14**

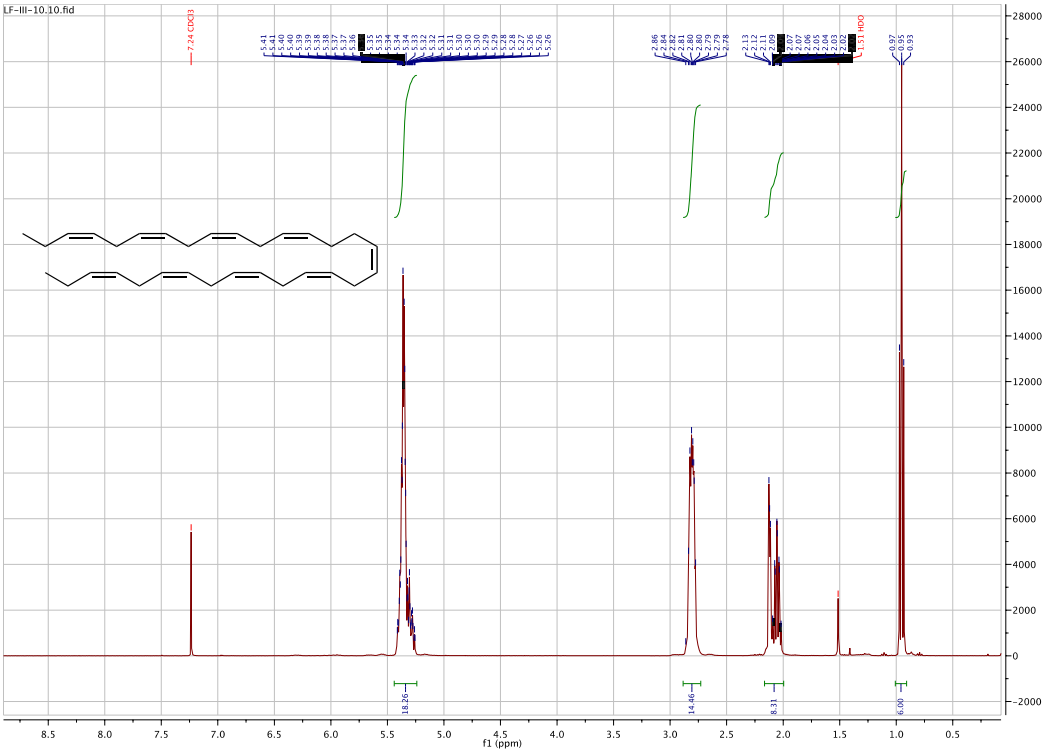


Figure S-9 ^{1}H MNR spectrum of **1**

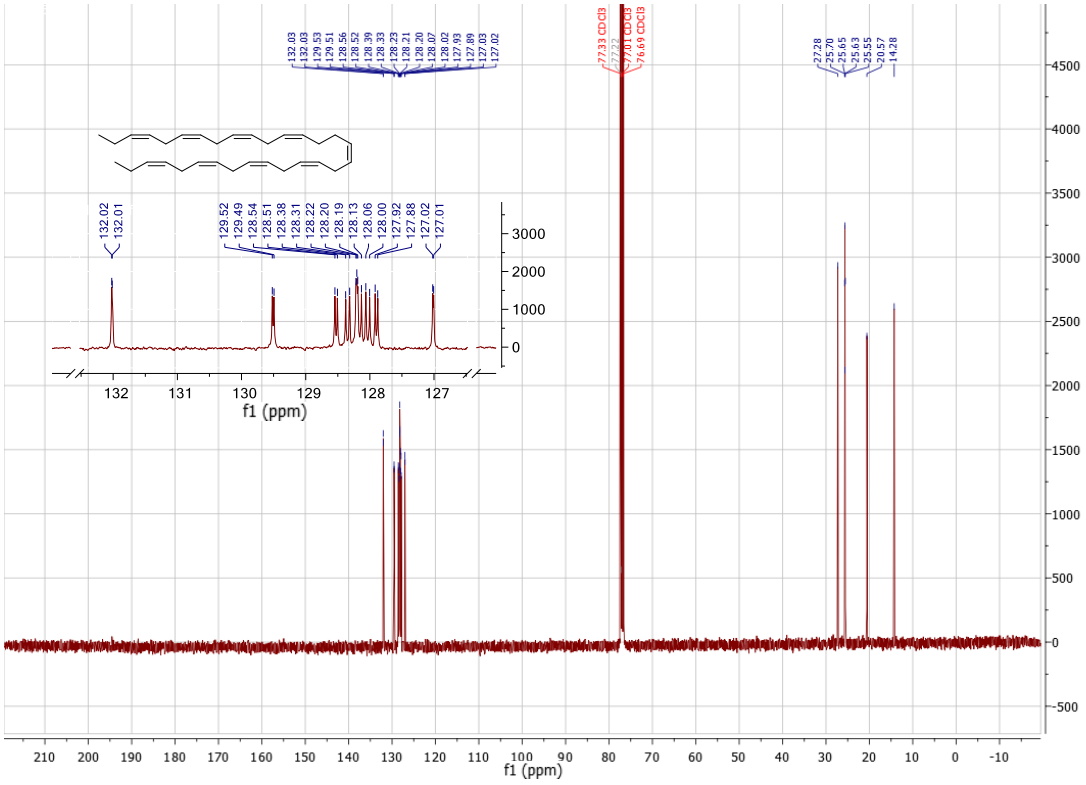


Figure S-10 ^{13}C NMR spectrum of **1**

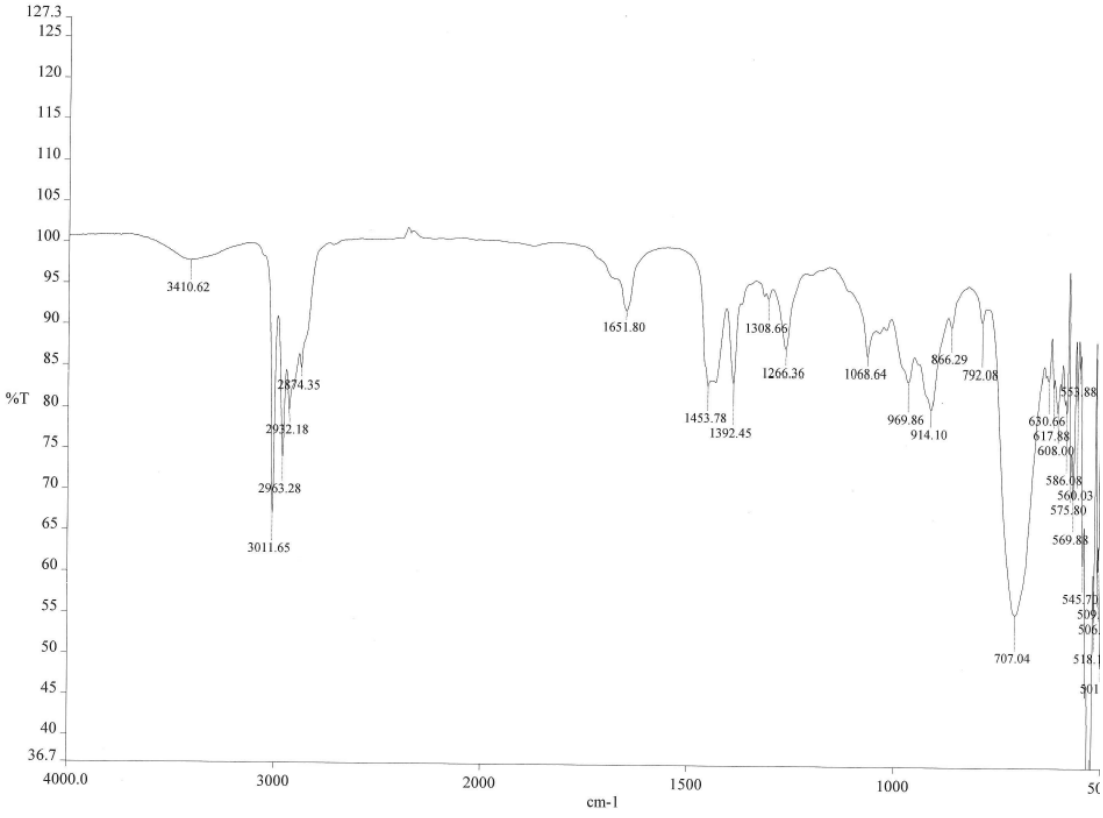
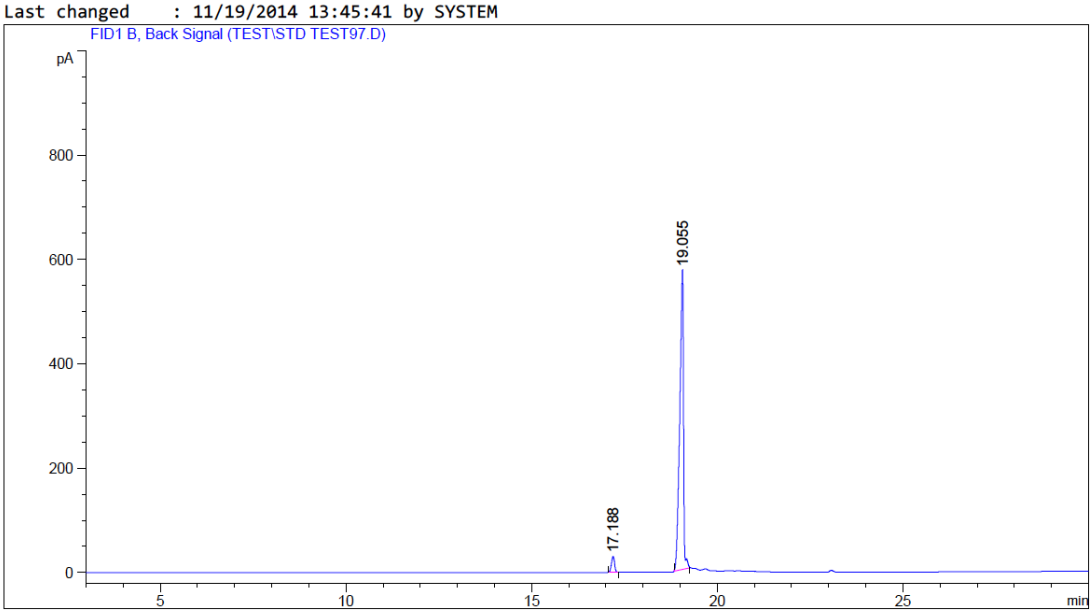


Figure S-11 IR spectrum of **1**

```
Acq. Operator   : SYSTEM
Sample Operator : SYSTEM
Acq. Instrument : 7820 GC                        Location : Vial 1
Injection Date  : 11/24/2014 15:11:35
                                                 Inj Volume : Manually
Method          : C:\CHEM32\1\METHODS\ANDERS METODER\C31 POLYENE UMBU.M
Last changed    : 11/19/2014 13:45:41 by SYSTEM
```



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	17.188	BB	0.0826	175.65181	30.31780	4.09220
2	19.055	BB	0.0997	4116.70557	573.95050	95.90780
Totals :				4292.35738	604.26830	

Figure S-12 GC chromatogram of **1**

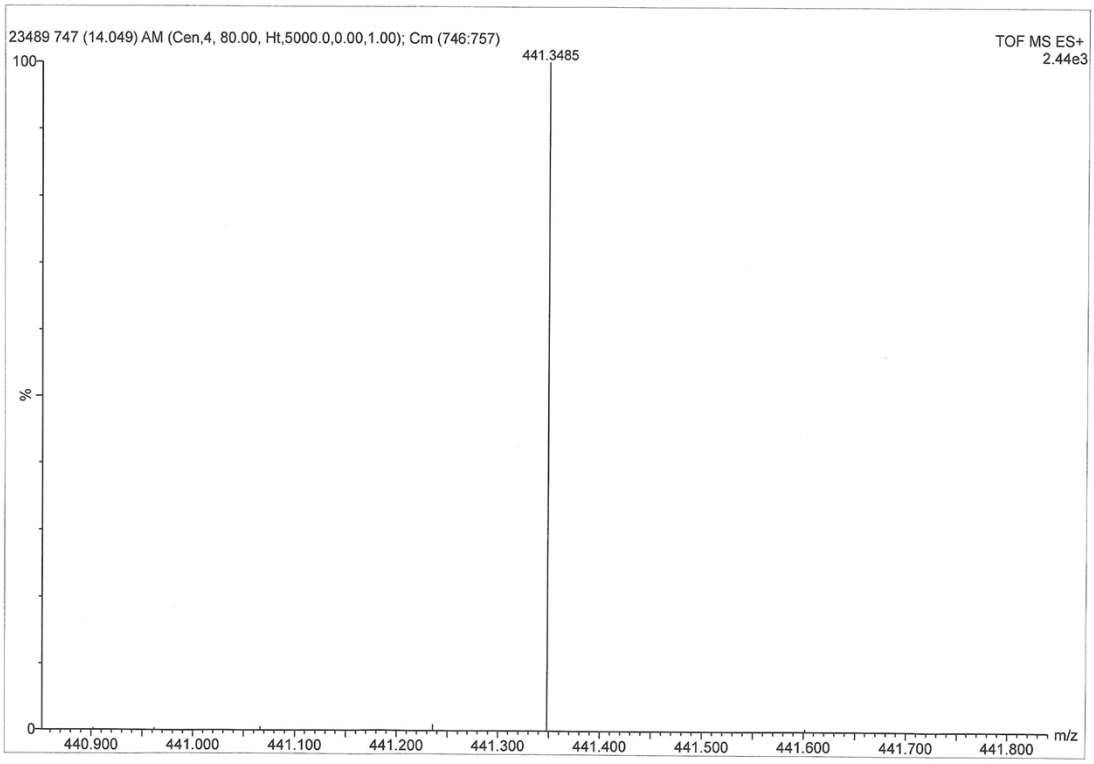


Figure S-13 CI-HRMS spectrum of **1**

Elemental Composition Analysis from Mass Spectrometric Data
Date: 2.2.2015

Input

Measured mass: 441.3485, Tolerance: 100 ppm

Element	Mass	min	max
C	12.0000	20	40
H	1.0078	25	65
Na	22.9897	0	1

RESULTS

	C	H	Na	Mass	diff(amu)	diff(ppm)
1:	31	46	1	441.3497	-0.0012	-2.76
2:	33	45	0	441.3521	-0.0036	-8.21

Number of hits: 2

Paper III

Cu(II)-catalyzed asymmetric Henry reaction with a novel C_1-symmetric aminopinane-derived ligand
Liudmila Filippova, Yngve Stentrøm, Trond Vidar Hansen, *Molecules* **2015**, *20*, 6224-6236.

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Article

Cu (II)-Catalyzed Asymmetric Henry Reaction with a Novel C_1-Symmetric Aminopinane-Derived Ligand

Liudmila Filippova [1], Yngve Stenstrøm [1,*] and Trond Vidar Hansen [1,2]

[1] Department of Chemistry, Biology and Food Science, Norwegian University of Life Sciences, P.O. Box 5003, N-1432 Ås, Norway; E-Mail: liudmila.filippova@nmbu.no

[2] Department of Pharmaceutical Chemistry, School of Pharmacy, University of Oslo, P.O. Box 1068, Blindern, N-0316 Oslo, Norway; E-Mail: t.v.hansen@farmasi.uio.no

* Author to whom correspondence should be addressed; E-Mail: yngve.stenstrom@nmbu.no; Tel.: +47-6496-5893; Fax: +47-6496-5901.

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Abstract: A novel C_1-symmetric dinitrogen ligand was synthesized in high yield from commercially available (1*R*,2*R*,3*R*,5*S*)-(−)-isopinocampheylamine and 1-methyl-2-imidazolecarboxaldehyde. In combination with $Cu(OAc)_2 \cdot H_2O$, this new ligand promote the reaction between nitromethane and aliphatic aldehydes with high yields (up to 97%) and moderate enantioselectivities (up to 67% ee). The reactions with benzaldehyde required prolonged reaction time that resulted in diminished yields, but accompanied with ee-values in the 55%–76% range.

Keywords: asymmetric catalysis; Henry reaction; nitrooaldol; chiral ligand; copper

1. Introduction

The asymmetric Henry (nitroaldol) reaction provides a straightforward entry to enantiomerically enriched β-nitro alcohols, which are valuable intermediates in the synthesis of natural compounds and biologically interesting molecules [1,2]. In particular, the nitroaldol products can be reduced into vicinal amino-alcohols which is a common structural motif found in many pharmaceuticals, such as (−)-pindolol [3], (−)-arbutamine [4], ritonavir [5], (*R*)-salmeterol [6], and epinephrine [7]. In addition,

the β-amino alcohol functionality is present in long-chain lipids such as sphingosines [8,9]. Thus, the development of an efficient asymmetric protocol for this type of reaction is of current interest [10,11].

The first asymmetric procedure for nitroaldol reaction employing a bimetallic Li-La BINOL complex was reported in 1992 by the Shibasaki group [3]. Since then, extensive collection of organocatalysts [12–15] and transition metal based catalytic systems, *i.e.*, Zn [4,16], Co [17,18] Cr [19,20], Cu [21–50], have been developed with variable success. The majority of these metal-based catalysts reported involved the use of copper complexes with either a bi- or polydentate aza-containing chiral ligand (such as BOX-type [21–23], diamines [7,24–32], Schiff bases [17,33–35] amino-alcohols [9,36–39], amino/iminopyridines [40–44], sulfonamides [45,46]). These systems have gained some applications, but some limitations still exist. For example, multistep synthetic procedures are often necessary for the preparation of some of the ligands, and obtaining the catalyst in both enantiomeric forms is sometimes a challenge. Moreover, many of the catalytic systems display poor enantioselectivity together with low yields of the products when employing aliphatic aldehydes as substrates. Therefore, the development of easily obtainable, novel ligands, in both enantiomeric forms, is still desired for this class of aldehydes. In this view, the chiral camphor and pinane based terpenes are examples of convenient building blocks for the development of effective chiral auxiliaries. For instance, the copper complexes with camphor-based dinitrogen ligands **1a** [40], **1b** [7], **1c** [47] and **1d** [48] have been reported to give high level (up to 98%) of asymmetric induction when reacting nitromethane with a broad range of aldehydes, including aliphatic ones (Figure 1).

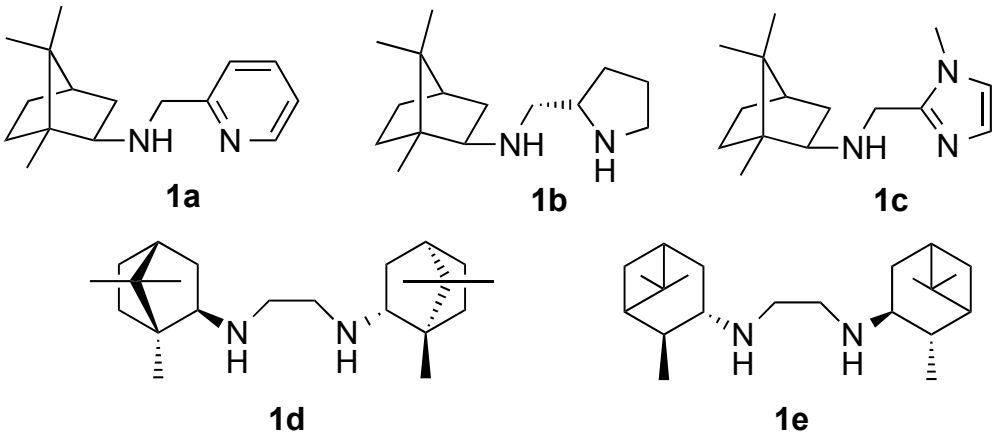
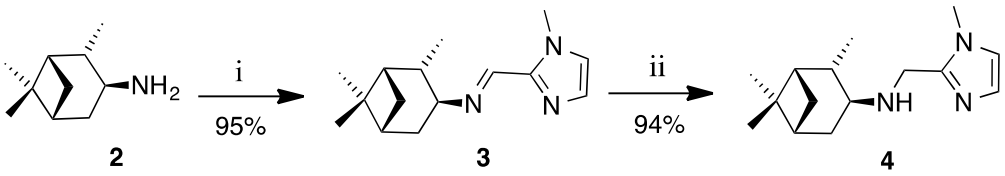


Figure 1. Some camphor and pinane-derived *N*,*N*-ligands.

Compounds bearing a pinane core have been utilized in some asymmetric transformations such as the enantioselective addition of diethylzinc to aldehydes [51–53], aldol condensation [54] and reduction of ketones [55]. Recently, the copper complex of C_2-symmetric ligand **1e** was reported to promote the asymmetric Henry reaction between nitromethane and aliphatic aldehydes affording nitroaldol products with enantiomeric excess from 57% to 93% ee [56]. Based on the synthesis of **1c** [47], we designed the novel pinane-derived C_1-symmetric ligand **4** (Scheme 1). Herein, we describe its application in a copper-catalyzed asymmetric nitroaldol reaction.

2. Results and Discussion

The C_1-symmetric ligand **4** was easily prepared from commercially available (1*R*,2*R*,3*R*,5*S*)-(−)-isopinocampheylamine (**2**) and 1-methyl-2-imidazolecarboxalehyde in a one-pot reaction as outlined in Scheme 1.

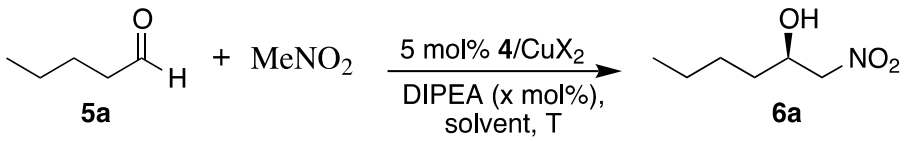


Reagents and conditions: (i) 1-methyl-2-imidazolecarboxaldehyde (1 equiv.), MeOH, rt; (ii) $NaBH_4$ (3 equiv), MeOH, 0 °C to rt.

Scheme 1. Synthesis of the ligand **4**.

Initially, in connection with our interest in the synthesis of aliphatic nitroalcohols, we examined the ability of **4** to promote the nitroaldol reaction between valeraldehyde (**5a**) and nitromethane in the presence of $CuCl_2{\cdot}2H_2O$ (5 mol %) at 0 °C with DIPEA (1 equiv.) as base additive. The results are summarized in Table 1. When THF was used as solvent, the reaction proceeded smoothly resulting in high yield (92%), but moderate enantioselectivity was observed (Table 1, entry 1). Then $Cu(OAc)_2{\cdot}H_2O$ was tested to see if there were any influence of the counterions on the reaction. Both copper salts gave similar results in terms of enantioselectivity, but the yields varied significantly depending on the solvent (Table 1, entries 1–4). Most likely, this is due to differences in the solubility of the formed complexes. Hence, the use of other solvents was investigated. Of the solvents tested, *i*-PrOH was the best choice (Table 1, entry 6, 97% yield, 55% ee). Lowering the temperature of the reaction to −20 °C resulted in a significant decrease of the reaction rate with no improvements in enantioselectivity (Table 1, entries 8 and 9). The absolute configuration in the product **6a** was determined based on comparison of the specific optical rotation value with literature [24–32].

Table 1. Selected experimental conditions for asymmetric Henry reaction between pentanal and nitromethane.



Entry [a]	Copper Salt	Solvent	T (°C)	Time (h)	DIPEA (mol %)	Yield (%) [b]	e.e. (%) [c]
1	$CuCl_2{\cdot}2H_2O$	THF	4	20	100	90	53
2	$Cu(OAc)_2{\cdot}H_2O$	THF	4	20	100	52	52
3	$CuCl_2{\cdot}2H_2O$	EtOH	4	20	100	88	33
4	$Cu(OAc)_2{\cdot}H_2O$	EtOH	4	20	100	92	37
5	$Cu(OAc)_2{\cdot}H_2O$	CH_2Cl_2	4	20	100	68	47
6	$Cu(OAc)_2{\cdot}H_2O$	*i*-PrOH	4	20	100	97	55
7	$Cu(OAc)_2{\cdot}H_2O$	Et_2O	4	20	100	63	46
8	$Cu(OAc)_2{\cdot}H_2O$	THF	−25	20	100	<5	n.d. [d]

Table 1. *Cont.*

Entry [a]	Copper Salt	Solvent	T (°C)	Time (h)	DIPEA (mol %)	Yield (%) [b]	e.e. (%) [c]
9	$Cu(OAc)_2 \cdot H_2O$	*i*-PrOH	−25	72	100	88	57
10	$Cu(OAc)_2 \cdot H_2O$	*i*-PrOH	4	2	100	68	57
11	$Cu(OAc)_2 \cdot H_2O$	*i*-PrOH	4	4	100	88	56
12	$Cu(OAc)_2 \cdot H_2O$	*i*-PrOH	4	6	100	85	55
13	$Cu(OAc)_2 \cdot H_2O$	*i*-PrOH	4	8	100	89	57
15	$Cu(OAc)_2 \cdot H_2O$	*i*-PrOH	4	20	0	36	56
16	$Cu(OAc)_2 \cdot H_2O$	*i*-PrOH	4	20	5	88	57
17	$Cu(OAc)_2 \cdot H_2O$	*i*-PrOH	4	20	10	98	56

[a] The reactions were carried out on 0.5 mmol scale of valeraldehyde with 10 equiv. of nitromethane in 2 mL of solvent. [b] Isolated product. [c] Enantiomeric excesses by HPLC analyis using a column with a chiral stationary phase. [d] Not determined.

The Henry reaction is reversible [1]. The enantiomeric excess of the nitroaldol adducts can decrease as a result of the retro-nitroaldol reaction. Hence, a time-course study was performed to investigate the possibility of reversibility. The reaction was almost complete within four hours, while the ee-values of the product **6a** remained constant in the conditions explored (Table 1, entry 10–13), indicating the absence of reversibility.

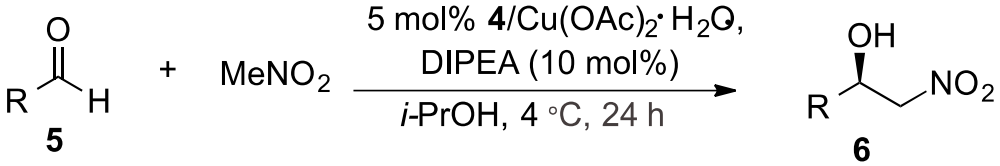
An external base is usually added to promote the reaction. Considering the still low ee of the product observed, and the fact that the excess of additional base can enhance the non-enantioselective reaction pathway [26], the effect of base loading was examined. The addition of even small amounts of external base noticeably improved the reaction rate, while the ee-values of the products were unchanged with increasing amounts of base added. These experiments verified that inhibition of an unselective pathway occurred (Table 1, entries 15–17). The loading of 10 mol % of external base was sufficient to promote the reaction until completion.

Based on the conditions investigated, different aliphatic aldehydes were tested. As shown in Table 2, all of the aldehydes smoothly converted into the nitroaldol products with good to excellent yields. Moderate ee-values ranging from 49% to 67% were observed; the highest ee-value was observed with 2,2-dimethylpropanal (**5c**) (Table 2, entry 3, 67% ee). Again, the absolute configuration in the products **6a**–**6h** was assigned based on specific optical rotation values.

Then we tested the catalyst system with benzaldehyde (**5h**) (Table 2, entries 8–10). The reaction between **5h** and nitromethane in the presence of ligand **4** and $CuCl_2 \cdot 2H_2O$ did not reach completion even after 20 hours at 4 °C (Table 2, entry 8). Lowering the temperature of the reaction improved the level of enantioinduction to 76% ee, but drastically diminished the yields to impractical values (Table 2, entries 9–10). Hence, other aromatic aldehydes were not investigated.

Finally, in view to explore the nitroalkane substrate scope, nitroethane was reacted with aliphatic aldehydes employing optimized catalytic procedure (Table 3). The corresponding nitroaldol adducts bearing two stereogenic centers were obtained in high yields (up to 94%) albeit moderate diastereoselectivities favoring *syn*-product and enantioselectivities were observed. Diastereoselectivity was improved when α-branched aldehyde was used (Table 3, entry 2).

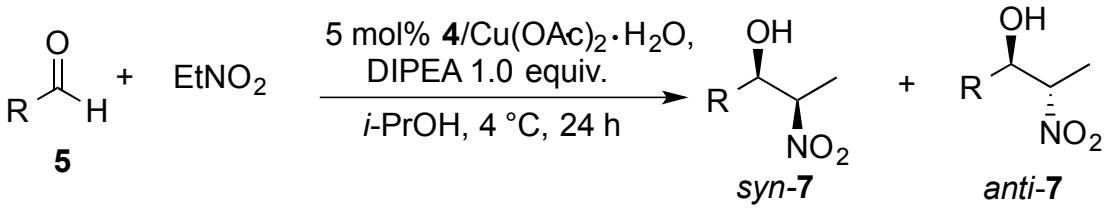
Table 2. Enantioselective Henry reaction of various aldehydes with nitromethane.



Entry [a]	R	Aldehyde	Product	Yield (%) [b]	e.e. (%) [c]
1	*n*-Bu	5a	6a	91	57
2	*i*-Bu	5b	6b	89	49
3	*t*-Bu	5c	6c	88	67
4	*i*-Pr	5d	6d	83	60
5	*n*-nonyl	5e	6e	75	55
6	*n*-undecyl	5f	6f	82	53
7	*trans*-2-decenyl	5g	6g	65	47
8 [d]	phenyl	5h	6h	80	38
9 [e]	phenyl	5h	6h	63	45
10 [f]	phenyl	5h	6h	10	76

[a] The reactions were performed on 0.5 mmol scale. [b] Isolated yield. [c] Determined by HPLC using a column with a chiral stationary phase. [d] $CuCl_2 \cdot 2H_2O$ was used as a copper source. [e] The reaction was carried out at −20 °C for 48 h in the presence of 1 equiv. of DIPEA. [f] The reaction was carried out at −40 °C for 48 h in the presence of 1 equiv. of DIPEA.

Table 3. Diastereoselective Henry reaction using nitroethane.



Entry [a]	R	Product	Yield (%) [b]	*syn*/*anti* (%) [c]	ee (%) [d]
1	*i*-Bu	7a	93	58/42	54/38
2	*i*-Pr	7b	94	81:19	66/34

[a] The reactions were performed on 0.5 mmol scale. [b] Isolated yield. [c] Determined by ^{1}H-NMR spectroscopy analysis of isolated compound. [d] Determined by HPLC analysis using a column with a chiral stationary phase.

3. Experimental Section

All starting reagents and solvents were obtained from Sigma Aldrich and used as purchased without further purification. Analytical TLC was performed using silica gel 60 F_{254} plates (Merck). Flash column chromatography was performed on silica gel 60 (40–63 nm). NMR spectra were recorded on Varian Gemini and Bruker Ascend^{TM} 400 spectrometers 300 MHz and 400 MHz for ^{1}H-NMR and 75 MHz and 100 MHz for ^{13}C-NMR, respectively. Chemical shifts are reported in ppm downfield from tetramethylsilane relative to $CDCl_3$ as internal standard (7.24 ppm for ^{1}H and 77.00 for ^{13}C). IR spectra (4000–600 cm^{-1}) were recorded on a Perkin-Elmer Spectrum BX series FT-IR spectrophotometer using a reflectance cell (HATR). Optical rotations were measured using a 1 mL cell with 1.0 dm path length

on Perkin Elmer 341 polarimeter in dedicated solvent. HPLC analyzes were performed on Agilent 1200 Series instrument using chiral OD-H or AD-H columns.

3.1. Preparation of Ligands

3.1.1. Synthesis of (*E*)-1-(1-Methyl-1*H*-imidazol-2-yl)-*N*-((1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)methanimine (**3**)

To (1*R*,2*R*,3*R*,5*S*)-(−)-isopinocampheylamine (**2**) (612 mg, 4.0 mmol) was added of 1-methyl-2-imidazolecarboxaldehyde (440 mg, 4.0 mmol) in 20 ml of dry methanol. The reaction mixture was left stirring at room temperature until no more starting material was detected (controlled by TLC, visualized by ninhydrine stain). Then mixture was directly concentrated under reduced pressure and purified by column chromatography eluting with hexane and ethyl acetate to obtain 930 mg of compound **3** as colourless oil (95% yield). $[\alpha]_D^{20} = -45.1$ (c = 2.0, EtOH). ^{1}H-NMR ($CDCl_3$, 400MHz, TMS): δ = 8.16 (s, 1H), 7.07 (s, 1H), 6.88 (s, 1H), 3.99 (s, 3H), 3.36–3.33 (m, 1H), 2.38–2.25 (m, 2H), 2.10–2.01 (m, 1H), 1.98–1.91 (m, 1H), 1.89–1.81 (m, 2H), 1.22 (s, 3H), 1.47 (d, *J* = 9.3 Hz, 1H), 1.03 (s, 3H), 0.98 (d, *J* = 8.7 Hz, 3H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$, TMS): δ = 149.7, 143.2, 128.9, 124.4, 70.5, 47.5, 44.1, 41.6, 38.7, 36.2, 35.4, 33.6, 27.9, 23.5, 19.8 ppm.

3.1.2. Synthesis of (1*S*,2*S*,3*S*,5*R*)-2,6,6-Trimethyl-*N*-((1-methyl-1*H*-imidazol-2-yl)methyl)-bicyclo[3.1.1]heptan-3-amine (**4**)

Sodium borohydride (456 mg, 12.1 mmol, 3.2 equiv.) was added in portions to a chilled 0 °C solution of **2** (930 mg, 3.8 mmol) in methanol. The mixture then was allowed to warm to room temperature and left stirred until no more starting material was detected (controlled by TLC, UV detection). The reaction was quenched with aqueous HCl, and MeOH solvent was removed under reduced pressure. The aqueous part was basified until pH = 9–10 and extracted by ethyl acetate, dried over anhydrous Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (hexane: EtOAc 7:3) to obtain 884 mg (94% yield) of **4** as a solid compound. $[\alpha]_D^{20} = -66.9$ (c = 1.85, EtOH). ^{1}H-NMR ($CDCl_3$, 400 MHz, TMS): δ = 6.88 (s, 1H), 6.78 (s, 1H), 3.80 (dd, J_1 = 13.2 Hz, J_2 = 24.5 Hz, 2H), 3.69 (s, 3H), 2.88–2.81 (m, 1H), 2.41–2.24 (m, 2H), 1.93–1.90 (m, H), 1.78–1.74 (m, H), 1.64–1.57 (m, H), 1.18 (s, 3H), 1.06 (d, *J* = 7.5 Hz, 3H), 0.93 (s, 3H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$, TMS): δ = 147.5, 127.7, 121.7, 57.6, 48.4, 45.7, 44.9, 42.3, 39.1, 37.1, 34.3, 33.3, 28.4, 24.0, 22.1 ppm. HRMS (TOF ES$^+$): exact mass calculated for $C_{15}H_{26}N_3$ $[M + H]^+$ 248.2126; found 248.2124.

3.2. General Procedure for the Enantioselective Henry Reaction

Ligand **4** (6.2 mg, 5 mol %) and $Cu(OAc)_2 \cdot H_2O$ (5 mg, 5 mol %) were added to the test tube containing 2 mL of *i*-PrOH and stirred for an hour to obtain a blue solution. Then the test tubes were transferred to a bath at the given reaction temperature and 0.5 mmol of aldehyde, 10 equivalents of nitroalkane and 0.1 equivalent of DIPEA (9 μL) were added. The reaction mixture was left stirring for the 24 h, after that the volatile compounds were removed under reduced pressure and the residue was directly purified on silica gel column eluting with hexane:EtOAc to afford the corresponding product.

3.2.1. *R*-(−)-1-Nitro-2-hexanol (**6a**)

Purified by column chromatography on silica (hexane:EtOAc 9:1), colorless oil, 90% yield, 57% ee. Enantiomeric excess was determined by HPLC (Chiralcel OD-H column, hexane/isopropanol, 90/10 *v*/*v*, 0.5 mL/min, 210 nm): $t_{R\ (major)}$ = 8.34 min, $t_{R\ (minor)}$ = 9.95 min; $[\alpha]_D^{20}$ = −6.5° (c = 1.2, CH_2Cl_2), (lit. [21] $[\alpha]_D^{20}$ = −9.3° (c = 2.73, CH_2Cl_2, 93% ee (*R*))).^{1}H-NMR ($CDCl_3$, 300 MHz, TMS): δ = 4.44–4.25 (m, 3H), 2.51 (d, *J* = 4.7 Hz, 1H), 1.49–1.31 (m, 6H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$, TMS): δ = 80.6, 68.7, 33.4, 27.3, 22.4, 13.9 ppm.

3.2.2. *R*-(+)-4-Methyl-1-nitropentan-2-ol (**6b**)

Purified by column chromatography (hexane:EtOAc 10:1), colourless oil, 89% yield, 49% ee. Enantiomeric excess was determined by HPLC (Chiralcel AD-H column, hexane/isopropanol, 90/10 *v*/*v*, 0.5 mL/min, 23 °C, 210 nm): $t_{R\ (major)}$ = 13.53 min, $t_{R\ (minor)}$ = 17.72 min; $[\alpha]_D^{20}$ = +1.0° (c = 1.0, CH_2Cl_2), (lit. [4] $[\alpha]_D^{20}$ = +2.3° (c = 2.5, CH_2Cl_2, 82% ee (*R*))). ^{1}H-NMR ($CDCl_3$, 400 MHz, TMS): δ = 4.40–4.32 (m, 3H), 2.53 (d, *J* = 4.0 Hz, 1H), 1.84–1.78 (m, 1H), 1.51–1.44 (m, 1H), 1.23–1.17 (m, 1H), 0.94 (app t, *J* = 6.2 Hz, 6H). ^{13}C-NMR 100 MHz, $CDCl_3$, TMS): δ = 81.0, 67.0, 42.4, 24.3, 23.2, 21.7.

3.2.3. *R*-(−)-3,3-Dimethyl-1-nitrobutan-2-ol (**6c**)

Purified by column chromatography (hexane:EtOAc 10:1), colourless oil, 88% yield, 67% ee. Enantiomeric excess was determined by HPLC (Chiralcel OD-H column, hexane/isopropanol, 98/2 *v*/*v*, 1.0 mL/min, 23 °C, 210 nm): $t_{R\ (major)}$ = 16.39 min, $t_{R\ (minor)}$ = 19.31 min; $[\alpha]_D^{20}$ = −29.3° (c = 0.15, CH_2Cl_2), (lit. [57] $[\alpha]_D^{20}$ = −28.1° (c = 1.78, CH_2Cl_2, 69% ee (*R*))). ^{1}H-NMR ($CDCl_3$, 400 MHz, TMS): δ = 4.5 (dd, J_1 = 13.0 Hz, J_2 = 2.0 Hz, 1H), 4.35 (dd, J_1 = 13 Hz, J_2 = 10.1 Hz, 1H), 4.01 (ddd, J_1 = 10.1 Hz, J_2 = 4.7 Hz, J_3 = 2 Hz), 2.39 (d, *J* = 4.7 1H), 0.96 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$, TMS): δ = 78.2, 76.2, 34.3, 25.6.

3.2.4. *R*-(−)-3-Methyl-1-nitrobutan-2-ol (**6d**)

Purified by column chromatography (hexane:EtOAc 10:1), colourless oil, 83% yield, 60% ee. Enantiomeric excess was determined by HPLC (Chiralcel OD-H column, hexane/isopropanol, 98/2 *v*/*v*, 1.0 mL/min, 23 °C, 210 nm): $t_{R\ (major)}$ = 20.46 min, $t_{R\ (minor)}$ = 22.90 min; $[\alpha]_D^{20}$ = −17.9° (c = 0.2, CH_2Cl_2), (lit. [45] $[\alpha]_D^{20}$ = −30.6° (c = 0.69, CH_2Cl_2, 99% ee (*R*))). ^{1}H-NMR ($CDCl_3$, 400 MHz, TMS): δ = 4.53–4.36 (m, 2H), 4.10–4.07 (m, 1H), 2.51 (br s, 1H), 1.82–1.74 (m, 1H), 0.97 (app t, *J* = 6.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$, TMS): δ = 79.3, 73.4, 31.7, 18.4, 17.5.

3.2.5. *R*-(−)-1-Nitroundecan-2-ol (**6e**)

Purified by column chromatography (hexane:EtOAc 10:1), yellowish oil, 82% yield; 55% ee. Enantiomeric excess was determined by HPLC (Chiralcel AD-H column, hexane/isopropanol, 90/10 *v*/*v*, 0.5 mL/min, 23 °C, 210 nm): $t_{R\ (major)}$ = 13.19 min, $t_{R\ (minor)}$ = 17.99 min; $[\alpha]_D^{20}$ = −2.8° (c = 1.9, CH_2Cl_2), (lit. [45] $[\alpha]_D^{20}$ = −4.9° (c = 1.04, CH_2Cl_2, 97% ee (*R*))). ^{1}H-NMR ($CDCl_3$, 400 MHz, TMS): δ = 4.43–4.28

(m, 3H), 2.47 (d, *J* = 4.5 Hz, 1H), 1.57–1.44 (m, 3H), 1.37–1.24 (m, 13H), 0.86 (t, *J* = 6.7 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$, TMS): δ = 80.6, 68.7, 33.7, 31.9, 29.5, 29.4, 29.3, 29.3, 25.2, 22.7, 14.1.

3.2.6. *R*-(−)-1-Nitrotridecan-2-ol (**6f**)

Purified by column chromarography (hexane:EtOAc 10:1), pale yellow oil, 75% yield, 57% ee. Enantiomeric excess was determined by HPLC (Chiralcel AD-H column, hexane/isopropanol, 90/10 *v*/*v*, 0.5 mL/min, 23 °C, 210 nm): $t_{R\ (major)}$ = 11.51 min, $t_{R\ (minor)}$ = 14.79 min; $[\alpha]_D^{20}$ = −2.5° (c = 0.4, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$, 400 MHz, TMS): δ = 4.35–4.32 (m, 2H), 4.31–4.27 (m, 1H), 2.47 (d, *J* = 4.6 Hz, 1H), 1.56–1.44 (m, 2H), 1.34–1.24 (m, 18H), 0.86 (t, *J* = 6.7 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$, TMS): δ = 80.6, 68.7, 33.7, 31.9, 29.6, 29.5, 29.4, 29.3 (2H), 25.2, 22.7, 14.1.

3.2.7. *R*-(−)-(*E*)-1-Nitroundec-3-en-2-ol (**6g**)

Purified by column chromatography (hexane:EtOAc 95:5), yellow oil, 65% yield, 47% ee. Enantiomeric excess was determined by HPLC (Chiralcel AD-H column, hexane/isopropanol, 98/2 *v*/*v*, 0.8 mL/min, 23 °C, 210 nm): $t_{R\ (major)}$ = 28.80 min, $t_{R\ (minor)}$ = 30.60 min; $[\alpha]_D^{20}$ = −0.4° (c = 0.7, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$, 400 MHz, TMS): δ = 5.86 (dtd, J_1 = 15.4 Hz, J_2 = 6.8 Hz, J_3 = 1.1 Hz, 1H), 5.42 (ddt, J_1 = 15.4 Hz, J_2 = 6.6 Hz, J_3 = 1.5 Hz, 1H), 4.79 (pentet, *J* = 5.6 Hz, 1H), 4.40 (d, *J* = 5.7 Hz, 2H), 2.40 (d, *J* = 4.4 Hz, 1H), 2.03 (dd, J_1 = 14.2 Hz, J_2 = 7.2 Hz, 2H), 1.37–1.25 (m, 10H), 0.86 (t, *J* = 6.7 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$, TMS): δ = 136.3, 126.0, 8.1, 70.0, 32.2, 31.8, 29.1, 29.1, 28.8, 22.6, 14.1.

3.2.8. (*R*)-(−)-1-Phenyl-2-nitroethanol (**6h**)

Prepared according general procedure and purified by column chromatography (hexane:EtOAc, 8:1), colorless oil, 63% yield, 45% ee. Enantiomeric excess was determined by HPLC (Chiralcel OD-H column, hexane/isopropanol, 90/10 *v*/*v*, 0.5 mL/min, 254 nm): $t_{R\ (major)}$ = 19.88 min, $t_{R\ (minor)}$ = 24.00 min. $[\alpha]_D^{20}$ = −23.1° (c = 1.2 CH_2Cl_2), (lit. [45] $[\alpha]_D^{20}$ = −53.1° (c = 1.06 CH_2Cl_2, 96% ee (*R*))). ^{1}H-NMR ($CDCl_3$, 300MHz, TMS): δ = 7.40–7.34 (m, 5H), 5.46 (dt, J_1 = 9.4 Hz, J_2 = 3.5 Hz, 1H), 4.60 (dd, J_1 = 13.3 Hz, J_2 = 9.3 Hz, 1H), 4.50 (dd, J_1 = 13.4 Hz, J_2 = 3.2 Hz, 1H), 2.78 (br s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$, TMS): δ = 138.2, 129.0, 128.9, 126.0, 81.2, 71.0.

3.2.9. (2*R*,3*R*)-5-Methyl-2-nitrohexane-3-ol (**7a**)

Prepared according general procedure and purified by column chromatography (hexane:EtOAc 10:1), colourless oil, 93% yield. Enantiomeric excess was determined by HPLC (Chiralcel AD-H column, hexane/isopropanol, 98/2 *v*/*v*, 1.0 mL/min, 23 °C, 220 nm): t_R (*anti* minor) = 16.40 min, t_R (*anti* major) = 17.62 min, t_R (*syn* major) = 21.28 min, t_R (*syn* minor) = 22.85 min. $[\alpha]_D^{20}$ = +15.2° (c = 0.91 EtOH), (lit. [58] $[\alpha]_D^{20}$ = +12.5° (c = 0.96 EtOH, *syn*/*anti* 93/7, 99% ee)). Diastereomeric ratio (*syn*/*anti*) was determined by ^{1}H-NMR ($CDCl_3$, 400 MHz, TMS): δ = 4.52–4.43 (m, 1H), 4.25–4.22 (m, 0.42H, *anti*), 3.96–3.91 (m, 0.58H, *syn*), 2.18 (br s, 1H), 1.88–1.76 (m, 1H), 1.53 (dd, J_1 = 6.7 Hz, J_2 = 3.8 Hz, 3H), 1.42–1.35 (m, 1H), 1.24–1.16 (m, 1H), 0.95–0.90 (m, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$, TMS): δ = 88.1 (*syn*), 86.7 (*anti*), 71.2 (*syn*), 70.2 (*anti*), 42.0 (*syn*), 41.8 (*anti*), 24.6 (*anti*), 24.3 (*syn*), 23.6 (*syn*), 23.3 (*anti*), 21.7 (*anti*), 21.4 (*syn*), 16.2 (*syn*), 12.4 (*anti*).

3.2.10. (3*R*, 4*R*)-2-methyl-4-nitropentan-3-ol (**7b**)

Prepared according general procedure and purified by column chromatography (hexane:EtOAc 10:1), colourless oil, 94% yield. Enantiomeric excess was determined by HPLC (Chiralcel OD-H column, hexane/isopropanol, 99/1 *v*/*v*, 1.0 mL/min, 23 °C, 220 nm): t_R (*anti* major) = 18.56 min, t_R (*syn* major) = 19.26 min, t_R (*anti* minor) = 21.66 min, t_R (*anti* minor) = 22.36 min. $[\alpha]_D^{20} = -3.4°$ (c = 1.12 $CHCl_3$), (lit. [58] $[\alpha]_D^{20} = -2.0°$ (c = 0.85 $CHCl_3$, *syn*/*anti* 97/3, 90% ee)). Diastereomeric ratio (*syn*/*anti*) was determined by ^{1}H-NMR ($CDCl_3$, 400 MHz, TMS): δ = 4.68–4.61 (m, 1H), 3.86 (dd, J_1 = 8.0 Hz, J_2 = 3.2 Hz, 0.19H, *anti*), 3.67 (dd, J_1 = 7.2 Hz, J_2 = 4.5 Hz, 0.81H, *syn*), 2.18 (br s 1H), 1.82–1.74 (m, 0.81H, *syn*), 1.72–1.64 (m, 0.19H, *anti*), 1.53 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$, TMS): δ = 86.2 (*syn*), 84.6 (*anti*), 77.3 (*syn*), 77.2 (*anti*), 30.8 (*anti*), 29.9 (*syn*), 19.8 (*anti*), 18.8 (*syn*), 18.6 (*anti*), 16.4 (*syn*), 15.5 (*syn*), 12.1 (*anti*).

4. Conclusions

In conclusion, a new pinane-based dinitrogen C_1-symmetric ligand has been synthesized *via* an experimental simple one pot procedure. This ligand was found to be reasonably selective for the copper catalyzed asymmetric Henry reaction between nitromethane and aliphatic aldehydes. Of merit, high yields were observed for this class of aldehydes. The ease of availability of ligand **4** in both enantiomeric forms, together with the simple and scalable procedure for its preparation, is of advantage for the present catalytic system. Currently, this catalyst system is investigated towards the synthesis of vicinal amino-alcohol derived lipids.

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Author Contributions

LF performed all the experiments. TVH designed the concept of the study. LF, YS, and TVH wrote the paper.

Conflicts of Interest

The authors declare no conflict of interest.

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Sample Availability: Sample of the ligand **4** is available from the authors.

Paper IV

Synthetic study towards obscuraminol A using an enantioselective Henry reaction
Liudmila Filippova, Trond Vidar Hansen, Yngve Stentrøm, Manuscript.

Synthetic studies towards obscuraminol A using an enantioselective Henry reaction

Liudmila Filippova,[a] Trond Vidar Hansen,[a,b] Yngve Stenstrøm[a,*]

[a]Department of Chemistry, Biology and Food Science, Norwegian University of Life Sciences, PO Box 5003, N-1432, Ås, Norway
[b]School of Pharmacy, Department of Pharmaceutical Chemistry, University of Oslo, PO Box 1068, Blindern, N-0316 Oslo, Norway

Abstract: Starting from the ethyl ester of eicosapentaenoic acid, the first total synthesis of the polyunsaturated amino-alcohol natural product obscuraminol A is reported. The stereoselective synthesis was based on the use of anti-diastereoselective Henry reaction. In addition, using a mild and chemoselective SmI_2-mediated reduction of the nitro-group in the Henry product provided the amino-alcohol natural product with the conservation of the four all *Z*-skipped double bonds.

Introduction

1-Deoxygenated sphingoid bases are a vast class of natural long-chain vicinal amino-alcohols widely distributed among marine invertebrates, especially in marine ascidian.[1] The wide spectrum of bioactivities reported, such as cytotoxicity, antimicrobial and antifungal effects, makes them interesting targets for developing novel pharmaceuticals.[2-7] In particular, the (2*S*,3*R*)-2-amino-3-octadecanol, isolated from the mollusk *Spisula polinima* and known as spisulosine E285 (**1**),[8] showed activity against several tumor lines. The natural product 1 has entered clinical trial development programs against solid tumors which were stopped after phase I.[9] Nevertheless, the related sphingoid bases differentiated by chain-length, unsaturation degree and stereochemistry at the sphingoid backbone did possess remarkable activity and have been explored though to a lesser degree.

Obscuraminol A (**2**) is an amino-alcohol isolated from the chloroform extracts of the marine ascidian *Pseudodistoma obscurum*.[4] It is moderately cytotoxic with an IC_{50} value of 2.5 μm/mL against the P-338, A-549 and MEL-28 cell lines.[10] Structurally it is related to **1** and the cytotoxic and antimicrobial polyunsaturated amino-alcohol crucigasterin 277 (**3**) isolated from the Mediterranean tunicate *Preudodistoma crucigaster.*[5]

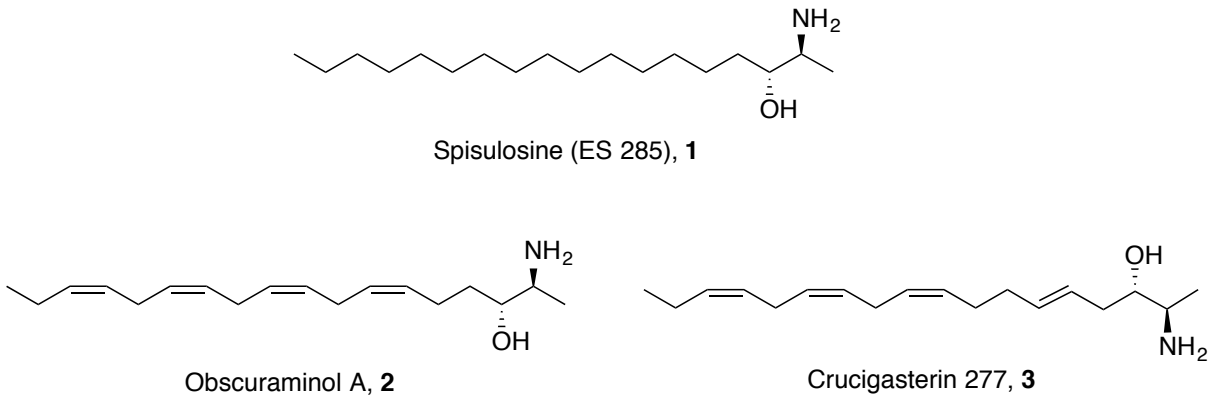
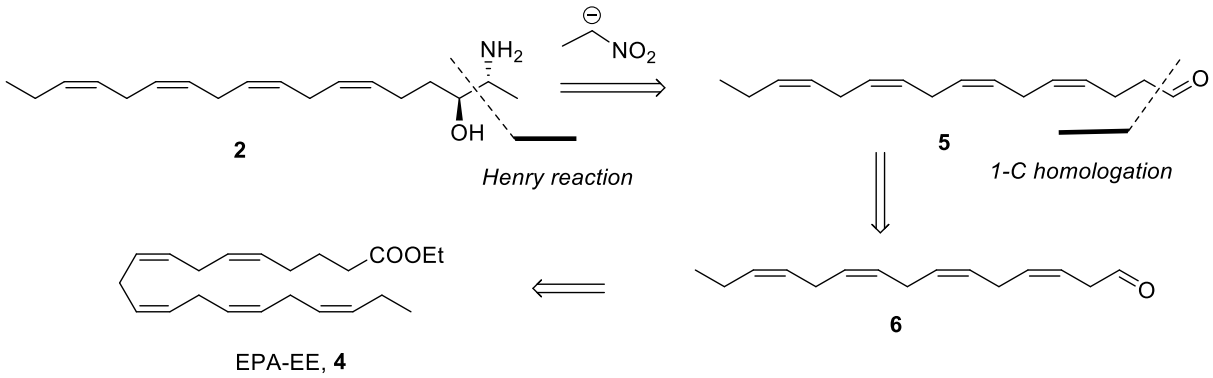


Fig. 1. Structures of spisulosine E285, obscuraminol A and crucigasterin.

To date, there are no reports on the total synthesis of obscuraminol A and crucigasterin 277.[11] In connection with our ongoing projects on utilizing natural polyunsaturated fatty acids in the synthesis of biologically active compounds,[12-16] we report our efforts towards a stereoselective synthesis of obscuraminol A, employing the ethyl ester eicosapentaenoic acid (EPA-EE)(**4**) as the starting material.

Results and discussion

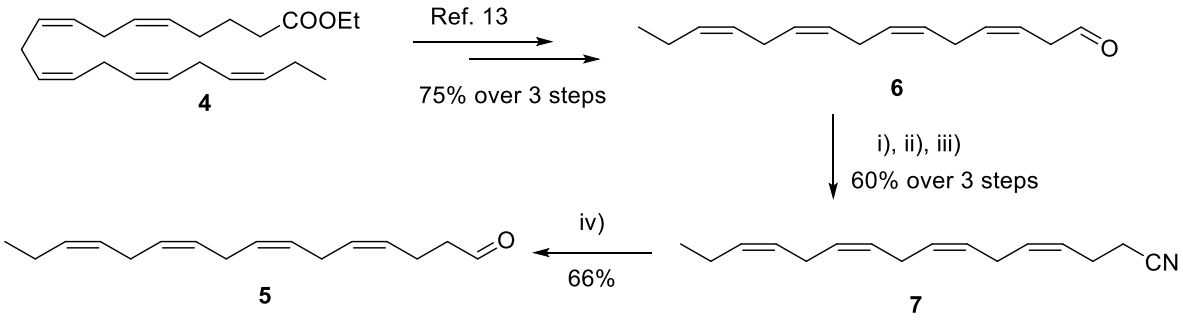
As outlined in Scheme 1, the retrosynthetic analysis suggests cleavage of the C2-C3 bond in the target molecule. In the synthesis it was contemplated that two stereogenic centers at C2 and C3 are to be formed in an *anti*-diastereoselecive Henry reaction between nitroethane and the C16 polyenoic aldehyde **5** followed by a selective reduction of the nitro group. The EPA-EE (**4)** can be readily converted into aldehyde **6**,[13] and a one-carbon homologation of which should give the C16 aldehyde **5**. We then anticipate the stereoselective Henry reaction to be the crucial point of the synthesis.



Scheme 1. Retrosynthetic analysis of obscuraminol A.

The synthesis started from the aldehyde **6**, available in 75% overall yield by oxidative degradation of the ethyl ester **4** as previously reported.[13] The aldehyde **6** was

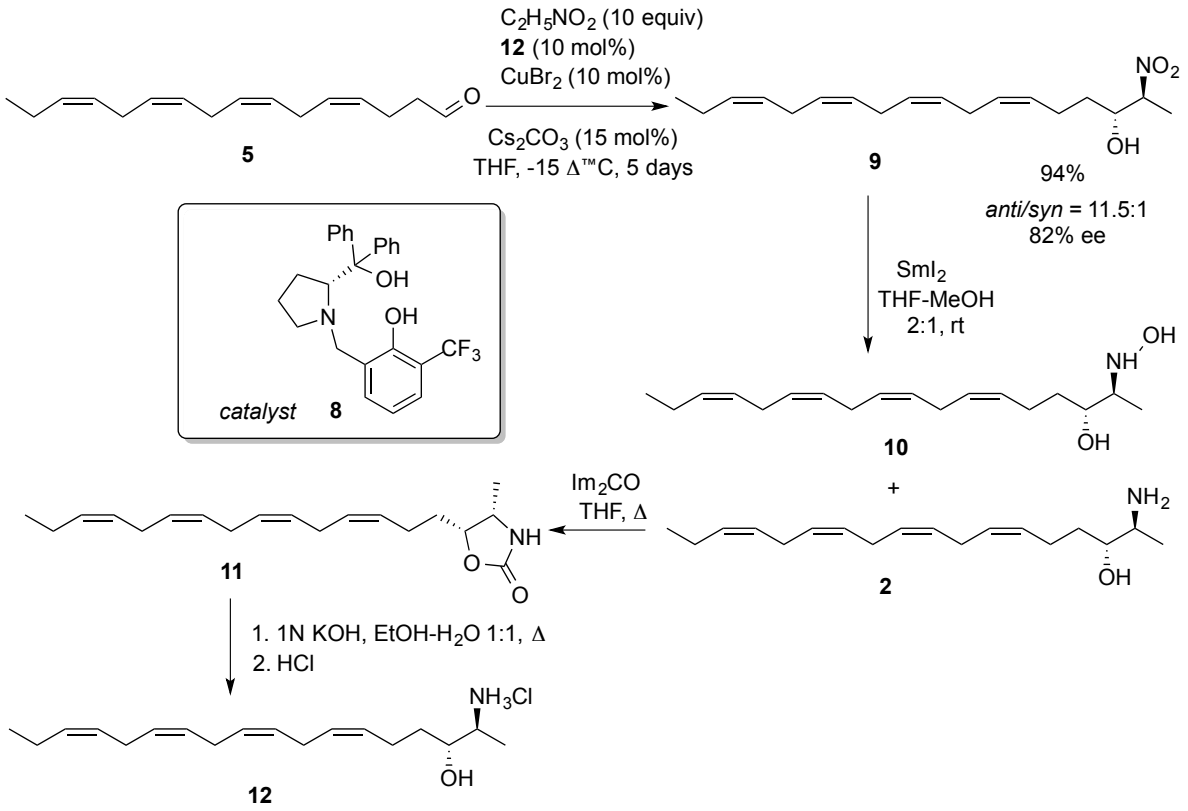
homologated to the aldehyde **5** *via* the cyanide intermediate **7** by using an established four step procedure (Scheme 2).[12]



Scheme 2. Synthesis of aldehyde **5.** i) $NaBH_4$, MeOH, 0 ˚C, 30 min; ii) MsCl, TEA, CH_2Cl_2, 0 °C to rt, 2h; iii) KCN, DMSO, 70 ˚C**;** iv) DIBAL-H, Et_2O, 0 ˚C

Then the catalytic *anti*-diastereo- and enantioselective Henry reaction followed by reduction of nitro group should give the target vicinal amino-alcohol moiety. Recently, several examples of enantio-selective Henry reaction appeared using metal-based catalysts,[17] enzymatic protocols[18] or organocatalysts.[19] The collection of catalysts for both *syn*- and *anti*-diastereoselective variations of Henry reaction has been developed as well.[20] However, it should also be mentioned that most of the *anti*-diastereoselective catalysts have been limited to substrate scope using only aromatic aldehydes.[20] Recently, we reported the asymmetric Henry reaction using a pinane-derived ligand copper (II) complex.[21] Unfortunately, when this system was applied for the reaction between **5** and nitroethane, the expected nitroaldol product was obtained in unpractical low yield and with insignificant prevalence of the undesired *syn*-diastereomer. So we turned our attention to literature protocols where precedents exist for the generation of aliphatic *anti*-nitroalcohols. The phenol-proline derived ligand **8** designed by Wang and co-workers[20e] seemed the most promising one for such kind of transformations (Scheme 3). The copper (II) complex of **8** was prepared as previously described[20e] was subjected to the nitroaldol reaction using the original conditions (THF as a solvent, -15 °C). The reaction was sluggish; nonetheless, the (2*S*,3*R*)-nitroaldol adduct* **9** was isolated after 5 days in 94% yield and good in diastereoselectivity (*anti/syn* 11.5:1) and with an enantiomeric excess of 82% ee. Rising the reaction temperature to -8 °C significantly reduced the reaction time, but resulted in diminished diastereoselectivity (*anti/syn* 5.7:1).

* The absolute stereochemistry of the nitro-alcohol was assigned based on NMR, HLPC and optical rotation data in comparison with analogs reported by Wang and co-workers.[20e] The relative configuration was, indirectly, also determined *via* the corresponding oxazolidinone derivative of **10**.



Scheme 3. The synthesis of obscuraminol A using a diastereoselective Henry reaction and SmI_2-mediated reduction,

Catalytic Pd/C hydrogenation is the most common way of reductive transformation of vicinal nitroaldols into their corresponding amino-alcohols with retention of configurational purity.[20b,c,e,h,22] Unfortunately, this method is not applicable towards substrates with high degree of unsaturation such as **9**. The conventional reduction of nitro-alcohol using zinc powder in acidic media (HCl/AcOH)[20a, 23] readily reduced the nitro group, but, in addition to low yield of the reaction, was accompanied by partial elimination of the hydroxyl group. Attempted TPDPS protection of hydroxyl functionality[24] was unsuccessful. Reduction employing nickel boride, which has previously been utilized in nitroaldol reduction,[25] affected the double bonds. Using the $NaBH_4$-$ZnCl_2$ reductive system the retro-nitroaldol reaction was observed to take place.[26] Finally we tried SmI_2 mediated reduction[27] of **9**, which resulted in amino-alcohol **2** (59% yield of isolated compound) and products of incomplete reduction with hydroxylamine **10** as a major by-product (determined by NMR-analysis of mixed fractions) (Scheme 3). Full conversion of intermediates to the target molecule was not achieved even when increased molar equivalents of SmI_2 were reacted for prolonged reaction times[27a]. Moreover, stereochemical discrimination took place during the reduction as the target amino-alcohol **2** was obtained in a lower stereochemical purity than expected from the starting material. The dr was determined as *anti/syn* = 5.2:1. In contrast, reduction of a diasteremeric mixture enriched with *syn*-nitro-alcohol (dr *anti/syn* = 1:2.8) resulted in improved diastereoselective ratio of amino-alcohol product (dr *anti/syn* = 1: 4, see appendix).

The resulting amino-alcohol diastereomeric mixture **2** was inseparable on this stage. In order to enhance the separation of the diastereomers, **2** was treated with carbonyl diimidazole to afford the cyclic carbamate derivatives which can be separated by means of column chromatography. The major epimer *cis*-oxazolidinone **11** was isolated in 61% yield. The configuration of **11** was confirmed by NOESY and ROESY experiments, which showed a clear correlation for the protons of C1 and C4. The deprotection of the obtained oxazolidinone by alkaline hydrolysis provided the access to target amino-alcohol.[28] Disappointedly, there was obvious mismatch in NMR data of the synthetic product and data reported as for the original natural product.[4] Examination of the literature data revealed that obscuraminol A was isolated as hydrochloride salt. So, the amino-alcohol was converted to the hydrochloride **12** after treatment with hydrogen chloride. The spectral data for **12** were in agreement with those reported for obscuraminol A.

Experimental:

All reactions were performed under a nitrogen atmosphere protected from light exposure. All reagents and solvents were commercial grade and used without further purification unless when necessary. EPA ethyl ester was obtained as a gift from Pronova Biofarma, AS Sandefjord, Norway. Thin layer chromatography (TLC) was performed using aluminium backed silica gel 60 F_{254} plates and flash chromatography utilized silica gel 60 (40-63 μm) from Merck. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded in $CDCl_3$ on a Bruker Ascend™ 400 spectrometer. Chemical shifts are measured in ppm relative to residual solvent peak as internal standard set to δ 7.26 and 77.0. HRMS was performed using EI method of ionization. IR spectra (4000-600 cm^{-1}) were recorded on Perkin-Elmer Specrtum BX series FT-IR spectrophotometer using a reflectance cell (HATR). Optical rotations were measured using a 1 mL cell with 1.0 dm path length on Perkin Elmer 341 polarimeter in dedicated solvent. HPLC analyzes were performed on Agilent 1200 Series instrument using chiral AD-H column.

(2*S*,3*R*,6*Z*,9*Z*,12*Z*,15*Z*)-2-Nitrooctadeca-6,9,12,15-tetraen-3-ol (9)

The catalyst was prepared according to the procesure reported by Wang *et al.* [20e] To a solution of ligand **8** (25 mg, 0.058 mmol), $CuBr_2$ (13 mg, 0.058 mmol) and Cs_2CO_3 (28 mg, 0.087mmol) in 1.2 mL of THF nitroethane (5.9 mmol, 440 μL) was added. The mixture was left stirring for next 4 hours at room temperature until the white precipitate appeared. The tube was centrifuged for 5 min (6000 rpm), and the supernatant was transferred to the test tube containing pre-cooled to -15 °C aldehyde **5** (137 mg, 0.59 mmol). The mixture was reacted at -15 °C for until completion while monitored by TLC (ca. 120 h). Then the volatiles were removed under reduced pressure and the residue was directly subjected to silica gel column eluting with hexane:EtOAc 10:1 to afford 170 mg of nitroaldol as a colourless oil. Yield: 94%. Enantiomeric excess was determined by HPLC (Chiracel AD-H column,

hexane/isopropanol 98/2, 1.0 mL/min, 25 °C, 215 nm): t_R (*anti* minor) = 10.98 min, t_R (*anti* major) = 12.05 min, t_R (*syn* major) = 13,93 min, t_R (*syn* minor) = 14.47 min. $[\alpha]_D^{20}$ = -11.5° (c = 0.3, $CHCl_3$, *anti/syn* 92:8). Diastereomeric ratio (*syn/anti*) was determined by ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.49 - 5.23 (m, 8H), 4.47 (qd, *J* = 6.9, 3.0 Hz, 1H), 4.16 (dq, *J* = 7.5, 3.6 Hz, 0.92H anti), 3.90 (m, 0.08 H, *syn*), 2.86 -2.75 (m, 6H), 2.32 - 2.12 (m, 3H), 2.05 (td, *J* = 7.4, 1.3 Hz, 2H), 1.61-1.37 (m, 3H), 1.53 (d, *J* = 7.5 Hz 3H), 0.95 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.1, 129.6, 128.7, 128.4, 128.3, 127.9, 127.8, 127.0, 87.7 (*syn*), 86.4 (*anti*), 72.3 (*syn*), 71.36 (*anti*), 32.67, 25.63, 25.56, 23.41, 20.57, 14.28, 12.55.

(2*R*,3*S*,6*Z*,9*Z*,12*Z*,15*Z*)-2-aminooctadeca-6,9,12,15-tetraene-3-ol (2, major diastereomer)

To a stirred 0.1 M solution of SmI_2 in THF (1.5 mmol, 15 mL) a solution of nitro-alcohol **9** (62 mg, 0.2 mmol) in THF:MeOH 2:1 was added. The mixture was left stirring at rt until full conversion of starting material (TLC). After 6 h the reaction was quenched with 10% aqueous solution of $Na_2S_2O_3$ and extracted with EtOAc (3×10 mL). The combined organic phase was dried (Na_2SO_4) and evaporated. The residue was subjected to silica gel column eluting with the $CHCl_3$: MeOH 9:1 to afford 33 mg of amino-alcohol as a colourless oil. Yield: 60%. Rf = 0.13 Diastereomeric ratio (*syn/anti*) was determined by ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (br s, 3H), 5.50 - 5.20 (m, 8H), 4.14 (d, *J* = 8.6 Hz, 1H), 3.63 (d, *J* = 10.1 Hz, 1H), 2.80 (m, 6H), 2.36 - 2.09 (m, 4H), 2.05 (td, *J* = 7.4, 1.3 Hz, 2H), 1.70 - 1.54 (m, 1H), 1.40 (d, *J* = 6.8 Hz, 2H), 0.95 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.1, 129.3, 128.7, 128.5, 128.4, 128.0, 127.8, 127.0, 70.0, 52.4, 32.6, 25.7, 25.7, 25.6, 25.6, 23.6, 20.6, 14.3, 12.4. HRMS (EI^+): Exact mass calculated for $C_{18}H_{31}NO$: 277.2406, found 277.2406.

(4*S*,5*S*)-4-methyl-5-((3*Z*,6*Z*,9*Z*,12*Z*)-pentadeca-3,6,9,12-tetraene-1-yl)oxazolidin-2-one (11)

To a solution of amino-alcohol **2** (16.0 mg, 0.058 mmol) in dry THF (2 mL) was added 1,1´-carbonyldiimidazole (14.0 mg, 0.087 mmol). The solution was refluxed for 12 h. The solvent was evaporated and the crude product was purified by silica gel chromatography eluting with Hexane: EtOAc 7:3 to 1: 1 to obtain 10.3 mg of yy as a colourless oil. Yield: 61%. Rf = 0.48 (hexane: EtOAc 1: 1, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 - 5.24 (m, 8H), 4.56 (ddd, *J* = 10.1, 7.4, 3.8 Hz, 1H), 3.89 (p, *J* = 6.6 Hz, 1H), 2.89 - 2.73 (m, 6H), 2.34 - 2.14 (m, 2H), 2.10 -2.01 (m, 2H), 1.82 (dddd, *J* = 14.0, 10.2, 8.4, 5.5 Hz, 1H), 1.53 (dddd, *J* = 14.0, 8.8, 7.3, 3.8 Hz, 1H), 1.15 (d, *J* = 6.5 Hz, 3H), 0.95 (t, *J* = 7.5 Hz, 3H). ^{13}C (100 MHz, $CDCl_3$): δ 159.1, 132.1, 129.6, 128.6, 128.5, 128.1, 127.9, 127.8, 127.0, 79.3, 51.0, 29.2, 25.6, 25.6, 25.6, 23.5, 20.6, 16.1, 14.3.

(2*R*,3*S*,6*Z*,9*Z*,12*Z*,15*Z*)-2-aminooctadeca-6,9,12,15-tetraene-3-ol (2a)

A solution of the carbamate **11** (6.9 mg, 0.023 mmol) in a 1N KOH in EtOH-H_2O 1:1 (1 mL) was refluxed for 4 hours. After cooling to rt, the mixture was deluted with water (1mL) and was extracted with EtOAc (3*2.5 mL). The combined organic phase was dried ($MgSO_4$) and evaporated to afford 4 mg of yellow oil. Yield: 63%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.44-5.28 (m, 8H), 3.61-3.58 (m, 1H), 3.08 (m, 1H), 2.85-2.76 (m, 6H),

2.75 (br s, 4H), 2.28-2.24 (m, 1H), 2.19-2.16 (m, 1H), 2.07(m, 2H), 1.51-1.40 (m, 2H), 1.09 (d, *J* = 6.6 Hz, 3H), 0.97 (t, *J* = 7.5 Hz, 3H). ^{13}C (100 MHz, $CDCl_3$): δ 132.0, 129.5, 128.6, 128.2, 127.9, 127.0, 73.1, 50.8, 32.3, 25.6, 25.5, 23.9, 20.6, 15.7, 14.3.

(2*R*,3*S*,6*Z*,9*Z*,12*Z*,15*Z*)-2-aminooctadeca-6,9,12,15-tetraene-3-ol hydrochloride (12)

The amino-alcohol **2a** was treated by gaseous HCl to afford its hydrochloride salt. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (br s, 2H), 5.40-5.26 (m, 8H), 4.0 (m, 1H), 3.7 (br s, 3H), 3.43 (m, 1H), 2.81-2.76 (m, 6H), 2.27-2.20 (m, 1H), 2.15-2.11 (m, 1H), 2.05-2.00 (m, 2H), 1.59-1.53 (m, 1H), 1.42-1.40(m, 1H), 1.30 (d, *J* = 6.7 Hz, 3H), 0.95 (t, *J* = 7.5 Hz). ^{13}C (100 MHz, $CDCl_3$): δ 132.0, 129.0, 128.6, 128.4, 128.1, 127.8, 127.0, 70.1, 52.1, 32.7, 25.6, 25.5, 23.6, 20.6, 14.3, 12.0.

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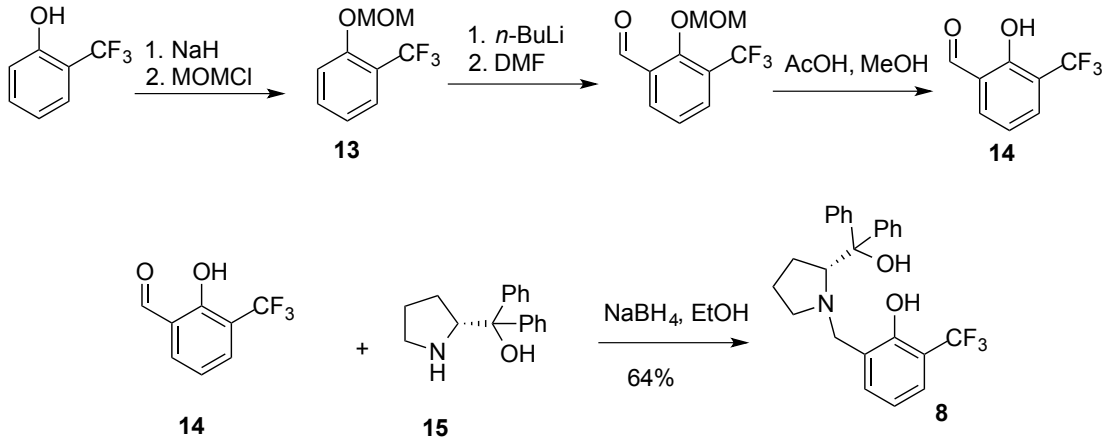
Appendix

Synthetic studies towards obscuraminol A using enantioselective Henry reaction

Liudmila Filippova,[a] Trond Vidar Hansen,[a,b] Yngve Stenstrøm[a,*]

[a]Department of Chemistry, Biology and Food Science, Norwegian University of Life Sciences, PO Box 5003, N-1432, Ås, Norway
[b]School of Pharmacy, Department of Pharmaceutical Chemistry, University of Oslo, PO Box 1068, Blindern, N-0316 Oslo, Norway

Synthesis of 8

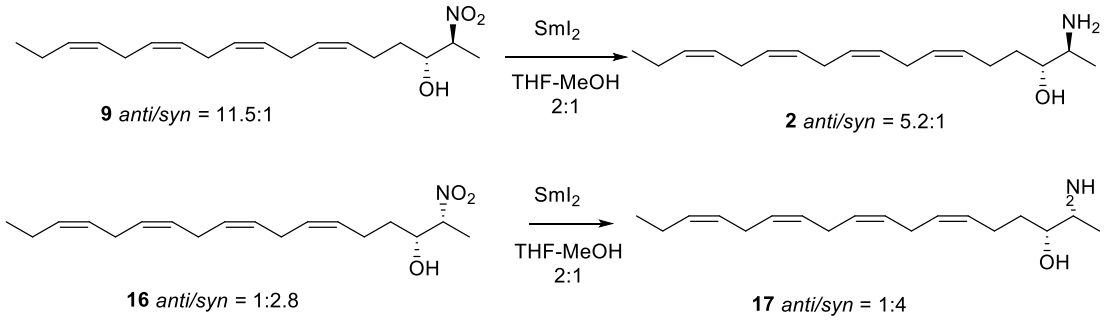


Scheme S1. Synthesis of the ligand **12**.

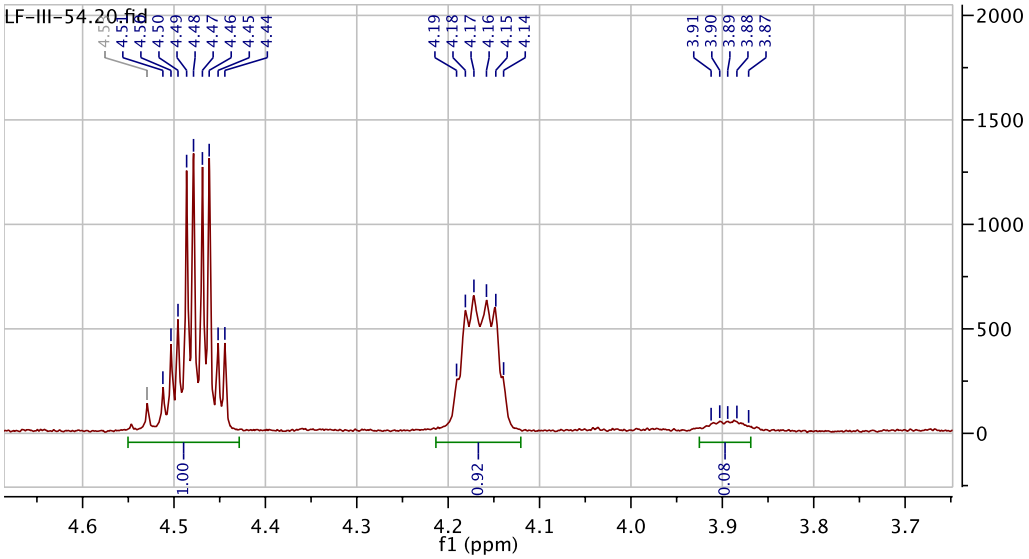
1-Methoxymethoxy-2-trifluorobenzene (13) was prepared from commercial available 2-trifluoromethylphenol according to a procedure of Xia *et al.*[1] All spectroscopic and physical data were in agreement with those reported. Yield: 86%. ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.57 (d, J = 7.8 Hz, 1H), 7.45 (dd, J_1 = 8.3 Hz, J_2 = 7.5 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.04 (dd, J_1 = J_2 = 7.6 Hz, 1H), 5.25 (s, 2H), 3.48 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.0, 133.2, 127.0 (q, J_{CF} = 5.3 Hz), 123.7 (q, J_{CF} = 272 Hz), 121.1, 119.6 (q, J_{CF} = 30.7 Hz), 115.2, 94.2, 56.3.

2-hydroxy-3-(trifluoromethyl)benzaldehyde (14) was prepared according to the two step procedure of Daly *et al.*[2] All spectroscopic and physical data were in agreement with those reported. Total yield after 2 steps: 43%. ^{1}H NMR (400 MHz, $CHCl_3$) δ 11.71 (s, 1H), 9.93 (s, 1H), 7.81 (d, J = 7.5 Hz, 1H), 7.75 (dd, J_1 = 7.8 Hz, J_2 = 1.7 Hz, 1H), 7.10 (ddd, J_1 = J_2 = 7.8 Hz, J_3 = 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.2, 159.7, 137.3, 134.0 (q, J_{CF} = 4.9 Hz), 122.9 (q, J_{CF} = 272 Hz), 121.1, 119.2, 118.9 (q, J_{CF} = 31.8 Hz)

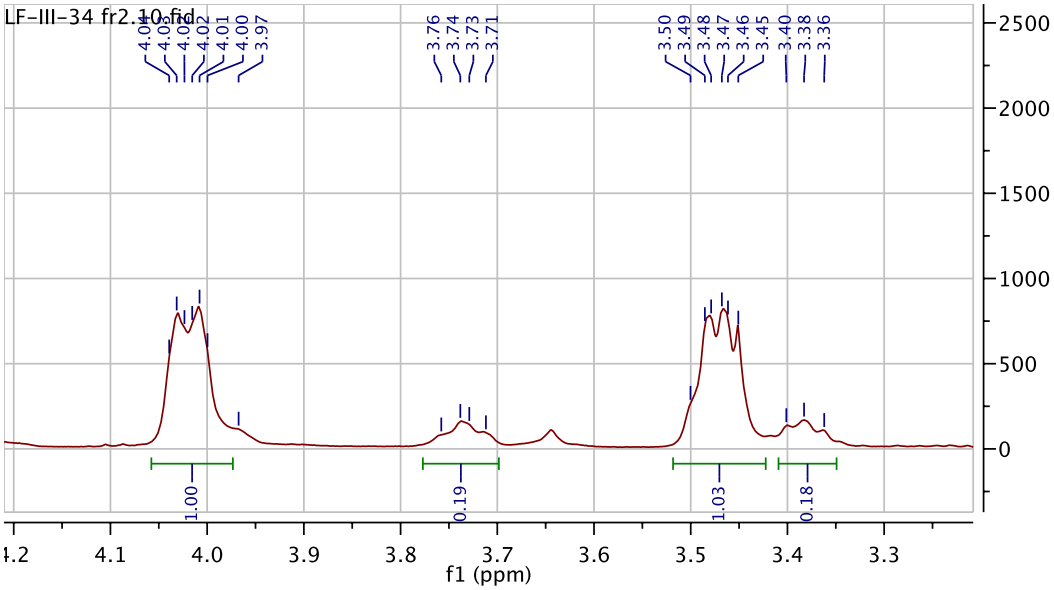
Ligand 8 was prepared from **14** and commercial available **15** according to the procedure by Wang *et al.*[3] A white foamish solid resulted. Yield – 64%. Mp: 125-127 °C. ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.59 - 7.46 (m, 4H), 7.34 - 7.18 (m, 6H), 7.12 - 7.08 (m, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 6.68 (t, *J* = 7.7 Hz, 1H), 5.20 (s, 1H), 3.91 (dd, *J* = 9.5, 4.7 Hz, 1H), 3.47 (d, *J* = 13.6 Hz, 1H), 3.30 (d, *J* = 13.7 Hz, 1H), 2.96 (ddd, *J* = 10.0, 6.3, 3.4 Hz, 1H), 2.34 (td, *J* = 9.8, 6.5 Hz, 1H), 2.17 -2.00 (m, 1H), 1.88 (ddt, *J* = 12.6, 8.2, 4.3 Hz, 1H), 1.74-1.64 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.7, 144.9, 144.3, 130.6, 127.4, 127.3, 126.0, 125.9, 125.0, 124.8, 123.1, 116.8, 78.8, 71.2, 59.4, 54.5, 28.3, 23.1.



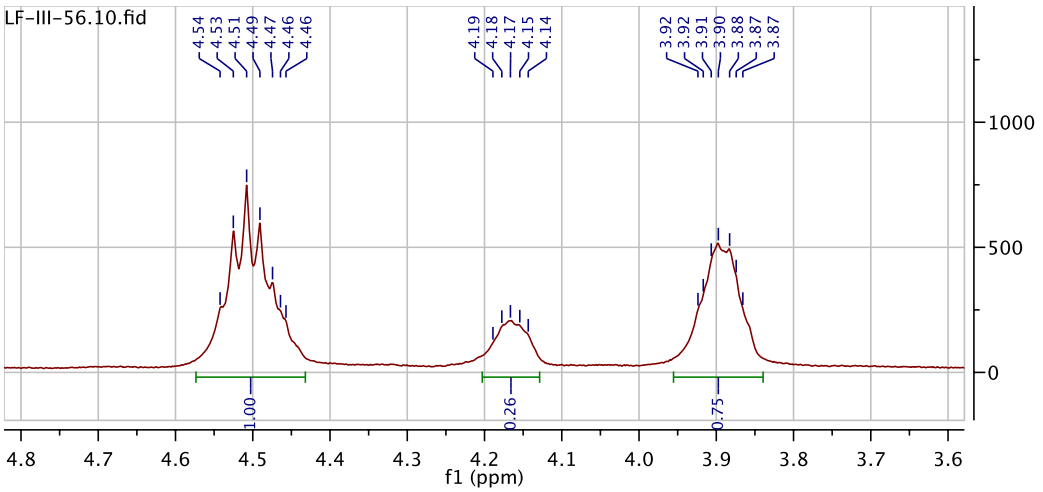
Scheme 2. Reduction of nitroaldol diastereomers mixtures.



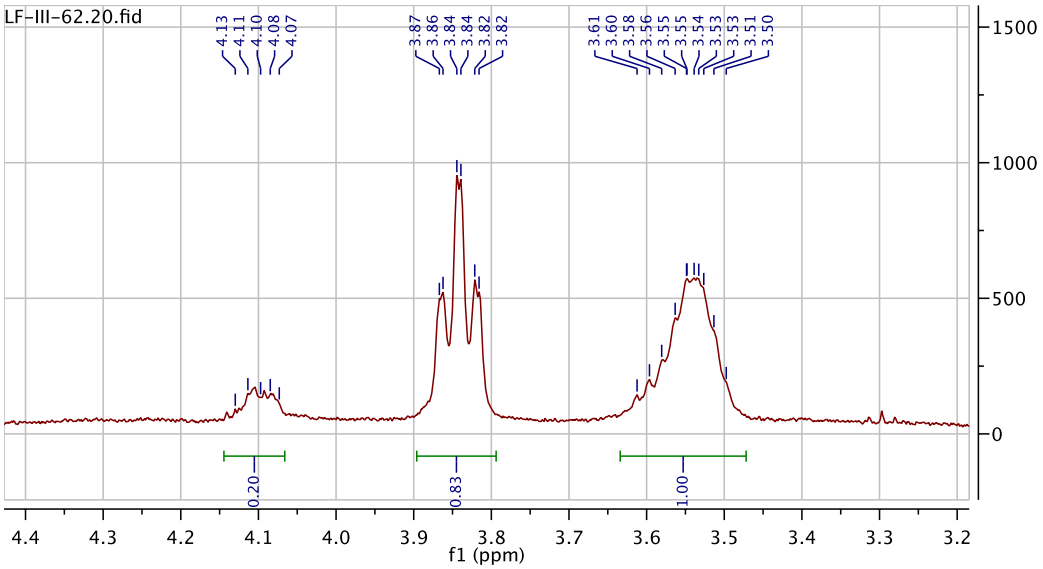
9. *Anti/syn* = 11.5:1



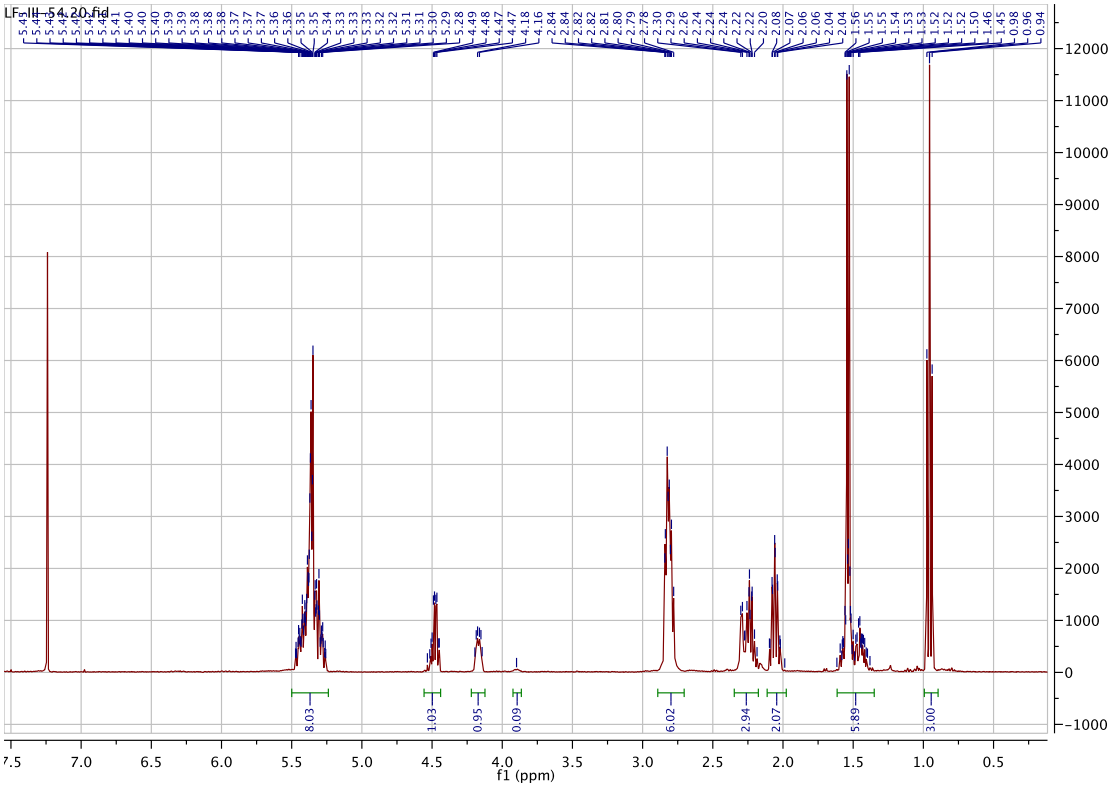
2. *Anti/syn* = 5.2:1



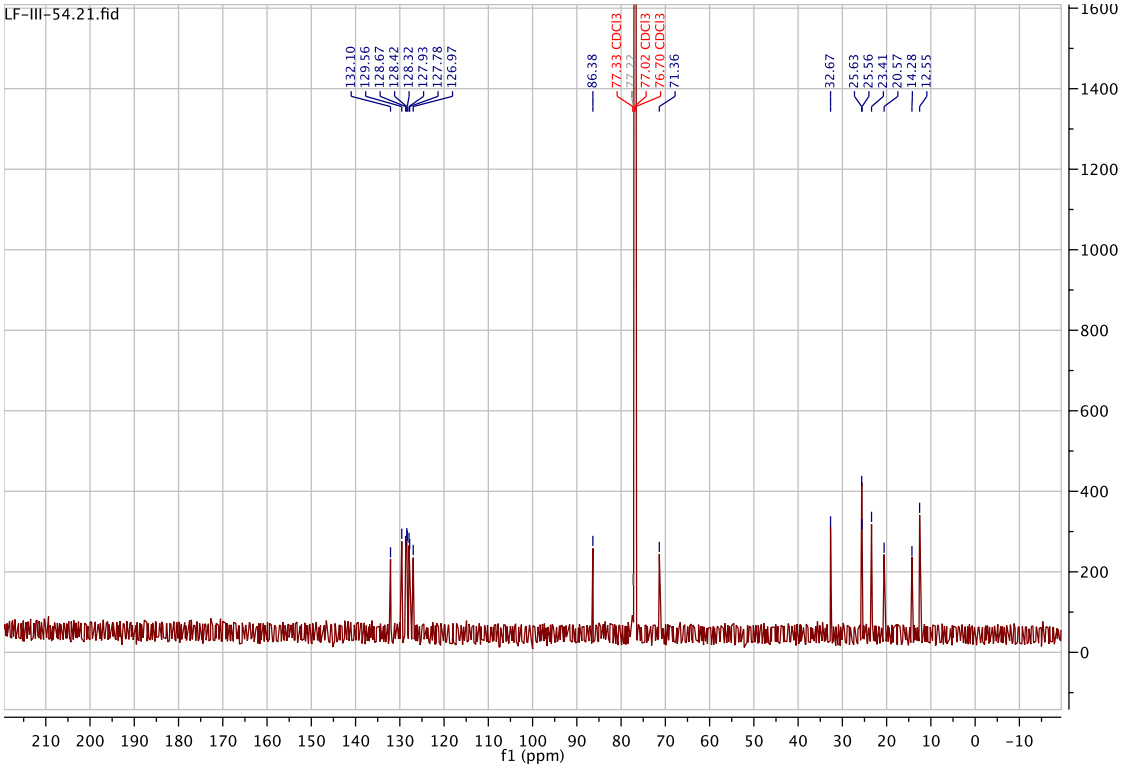
16 *Anti/syn* = 1:2.8



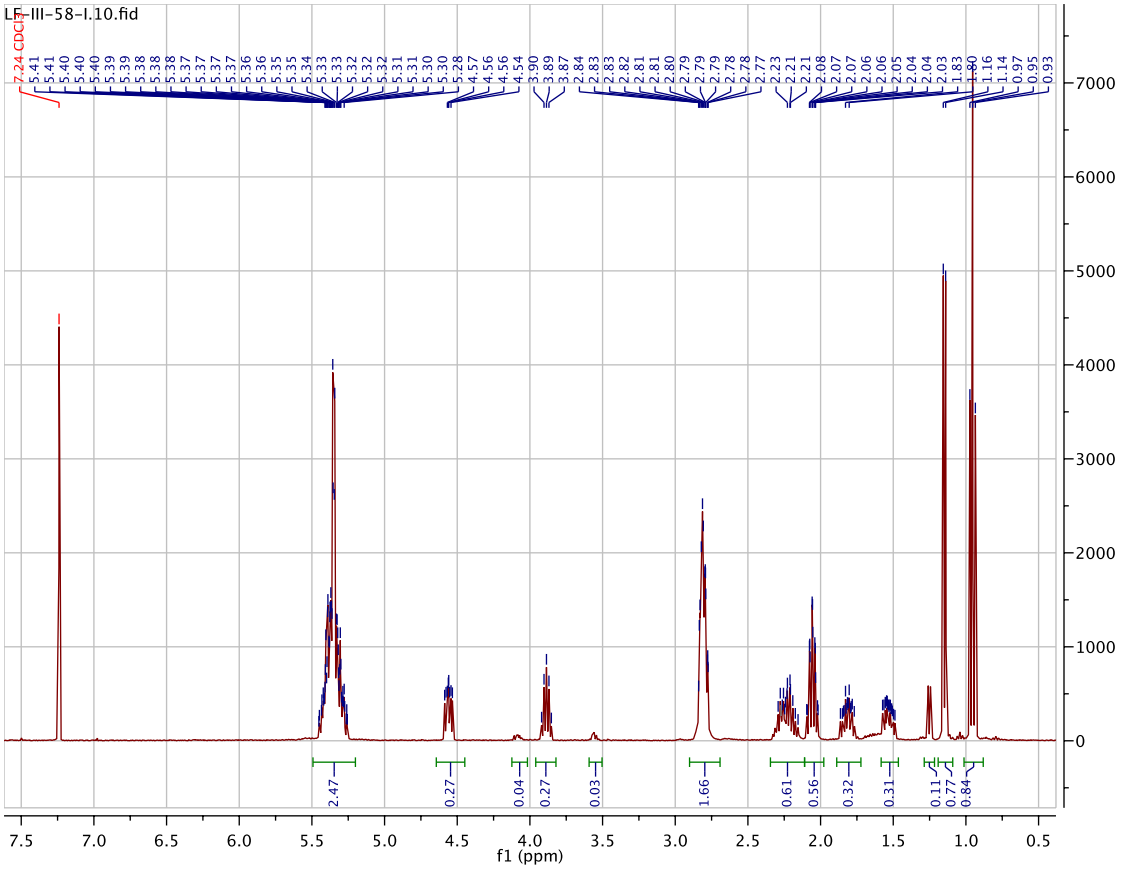
17 *Anti/syn* = 1:4



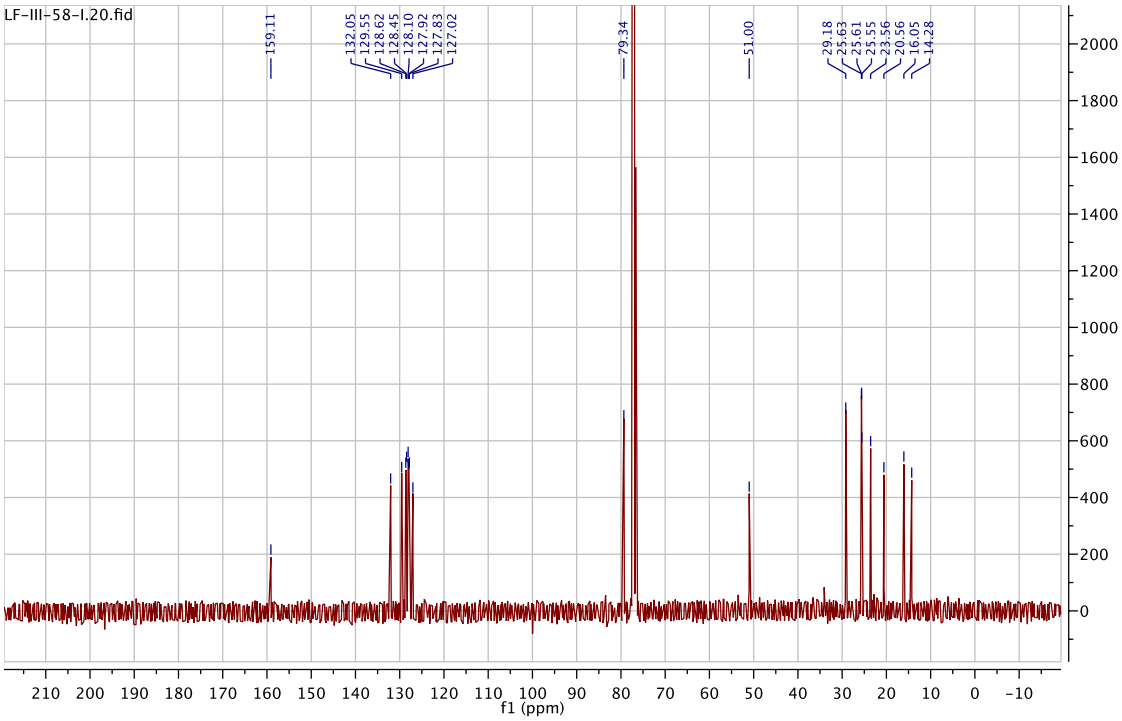
^{1}H NMR spectrum of **9**



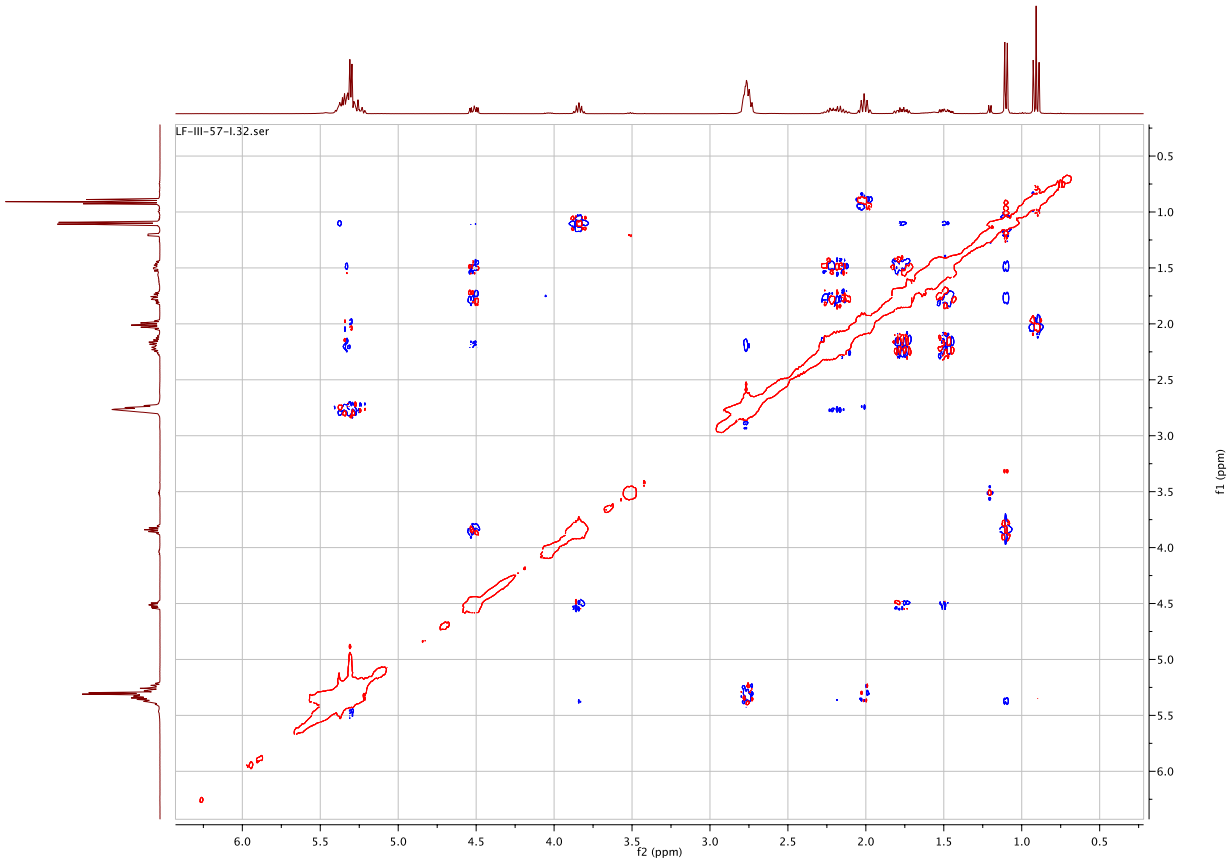
^{13}C NMR spectrum of **9**



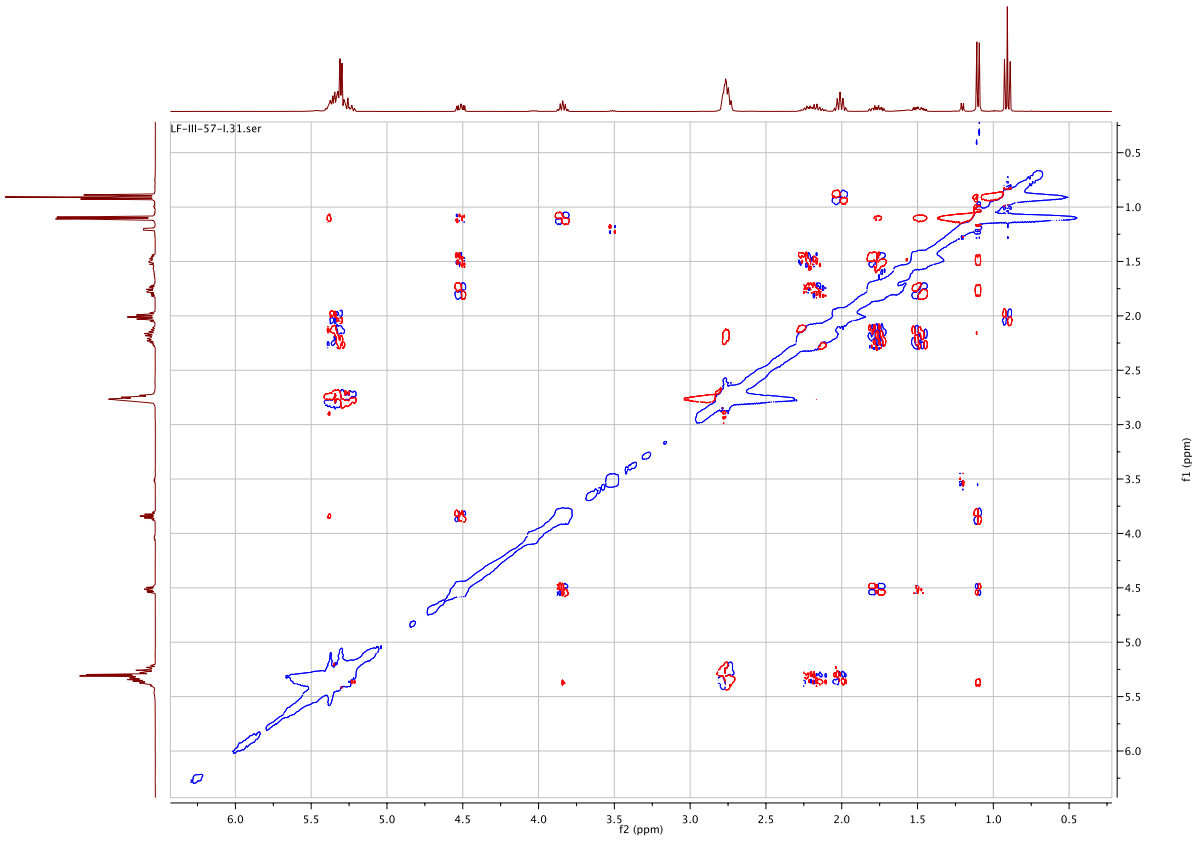
^{1}H NMR spectrum of **11**



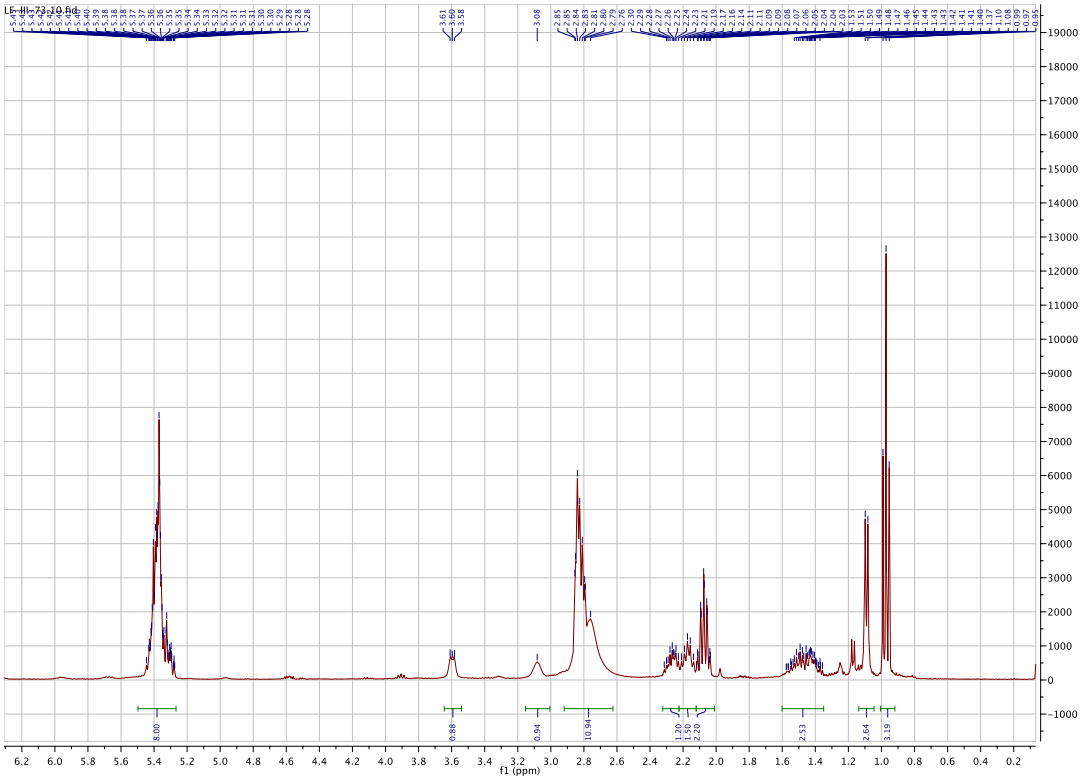
^{13}C NMR spectrum of **11**



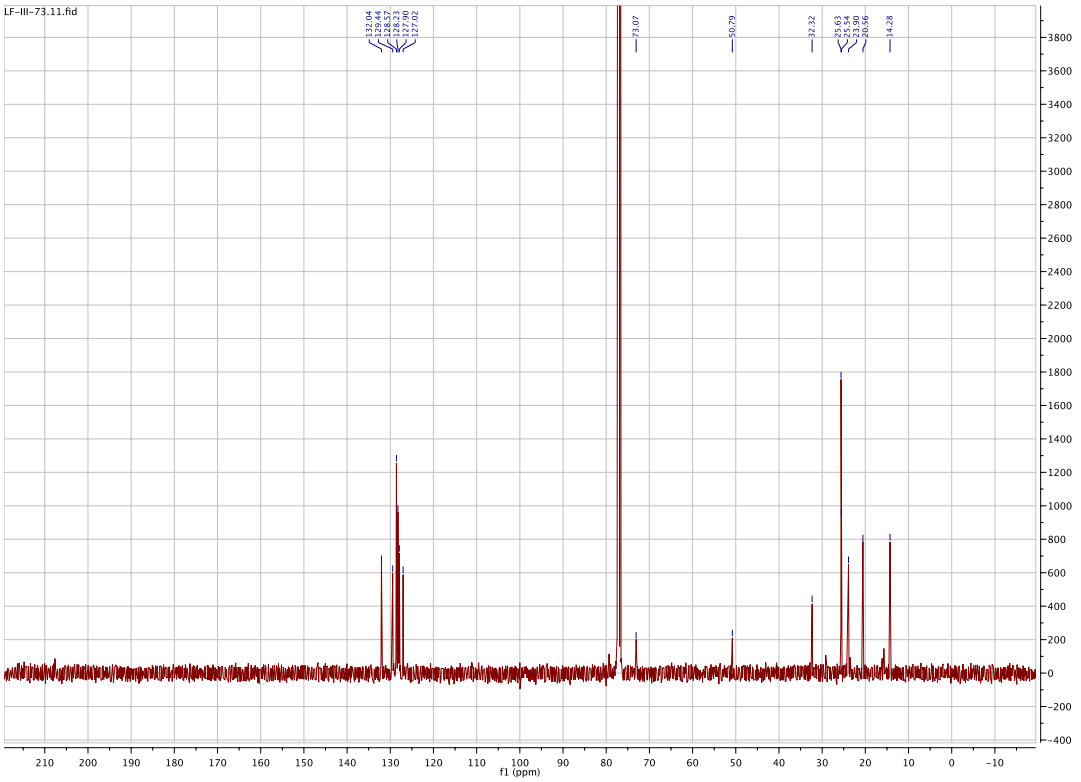
NOESY spectrum of **11**



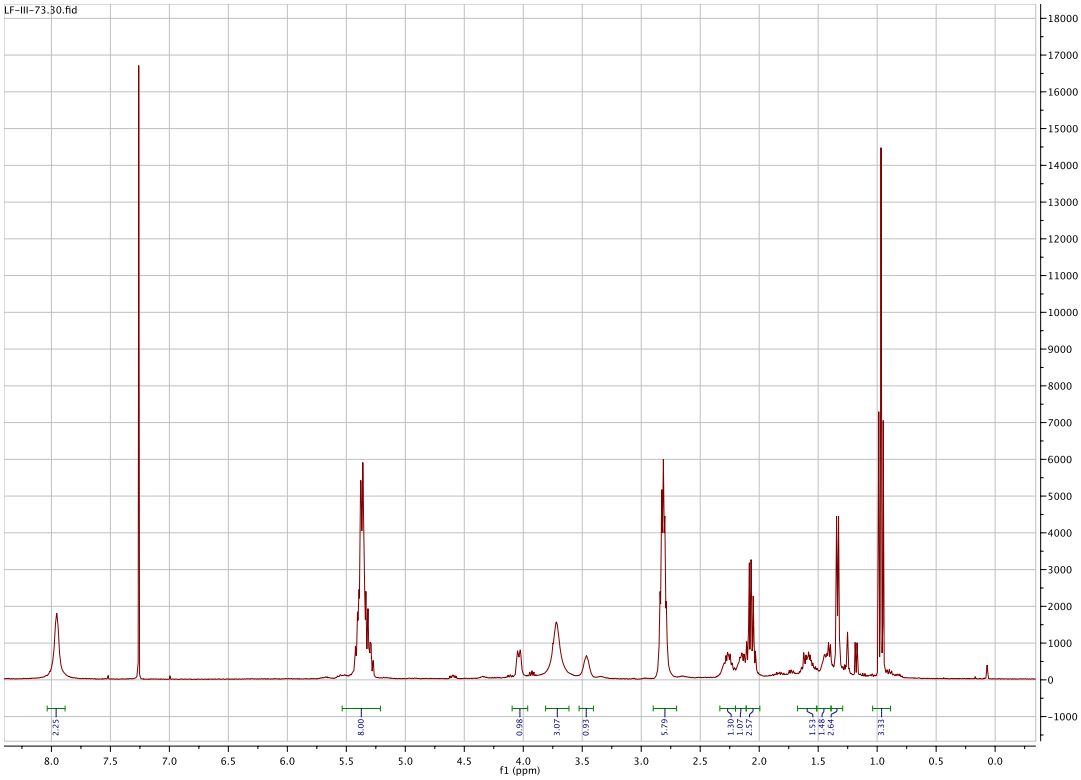
ROESY spectrum of **11**



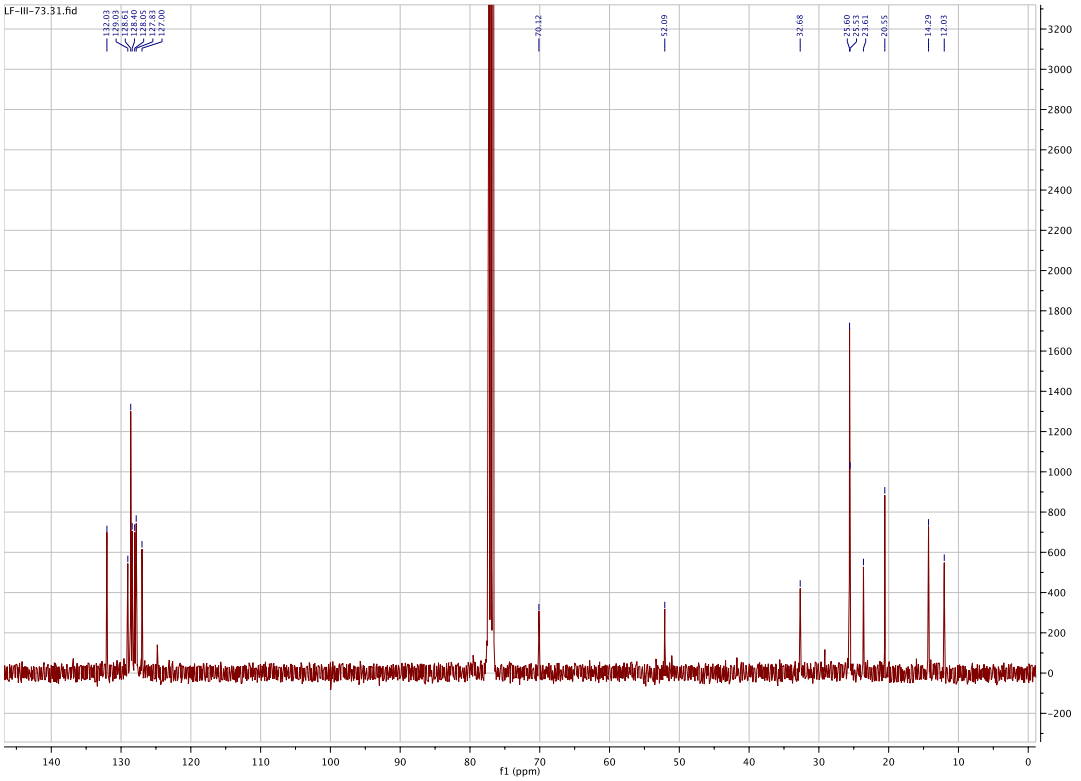
^{1}H NMR spectrum of crude **2a**



^{13}C NMR spectrum of crude **2a**



^{1}H NMR spectrum of crude **12**



^{13}C NMR spectrum of crude **12**

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