Synthesis of Isoprenyl Diphosphate Surrogates as Potential Inhibitors of Prenyl Converting Enzymes

Dissertation

zur Erlangung des akademischen Grades

doctor rerum naturalium (Dr. rer. nat.)

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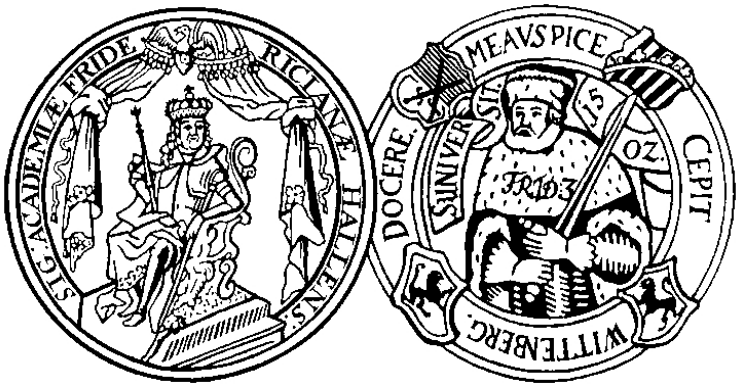
Naturwissenschaftlichen Fakultät II – Chemie und Physik

der Martin-Luther-Universität Halle-Wittenberg

von

Herrn M.Sc. Dimitar Vasilev

geboren am 14.10.1979 in Plovdiv, Bulgarien



Halle, 2015

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Gutachter:

1. Prof. Dr. Ludger A. Wessjohann
2. Prof. Dr. Christoph Schneider

Öffentliche Verteidigung der Arbeit am: 29. Mai 2015

Un scientifique dans son laboratoire est non seulement un technicien:
il est aussi un enfant placé devant des phénomènes naturels
qui l'impressionnent comme des contes de fées.‡

Marie Curie

(1903, Nobel Prize in Physics
1911, Nobel Prize in Chemistry)

‡ *Ein Gelehrter in seinem Laboratorium ist nicht nur ein Techniker; er steht auch vor den Naturgesetzen wie ein Kind vor der Märchenwelt.*

Acknowledgments / Danksagung

On ne fait jamais attention à ce qui a été fait;
on ne voit que ce qui reste à faire.

Marie Curie

Mein erster Dank gilt Herrn Prof. Dr. L. A. Wessjohann für die Überlassung des interessanten und spannenden Themas. Herr Prof. Wessjohann, ich danke Ihnen für das Vertrauen und die Verantwortung, die Sie mir entgegengebracht haben, ebenso wie für die Überlassung von kreativen Freiräumen bei der Ausarbeitung der Doktorarbeit und der fortwährenden finanziellen Unterstützung in allen wissenschaftlichen Belangen. Danke auch, dass Sie mich dem DAAD für den Forschungsaufenthalt in Brasilien empfohlen haben und dass Sie es mir ermöglicht haben, an zwei Übersee-Konferenzen teilzunehmen.

Herrn Prof. Dr. C. Schneider möchte ich für die Übernahme des Zweitgutachtens danken.

Mein herzlicher Dank gilt weiterhin:

Frau Dr. Andrea Porzel und Herrn Dr. Jürgen Schmidt für die zahlreichen Diskussionen und die Aufnahme von NMR- und Massenspektren. Frau Martina Lerbs möchte ich für die Aufnahme unzähliger ESI-MS Spektren danken. Bei Frau Gudrun Hahn möchte ich mich sowohl für die Aufnahme vieler NMR Spektren als auch für die Unterstützung bei der HPLC-Analytik bedanken. Frau Anja Ehrlich danke ich ganz besonders für Ihre stetige Unterstützung und eiserne Geduld bei hartnäckigen HPLC-Trennproblemen. Frau Christine Kuhnt danke ich für die LC-MS und GC-MS Messungen.

Herrn Prof. Dr. Bernhard Westermann, Herrn Dr. Wolfgang Brandt und Herrn Dr. Norbert Arnold möchte ich für zahlreiche Diskussionen und Anregungen bezüglich dem Fortlauf meiner Arbeit danken.

Herrn Hannes Rost, Herrn Prof. Dr. Daniel Garcia Rivera und Herrn Dr. Devender Singh möchte ich für die sehr schöne und fröhliche Zeit im Labor danken. Herrn Dr. Singh danke ich des Weiteren, dass er mir sein Heimatland Indien nähergebracht hat. (Devender, you do a good job as a tourist guide!).

Für das unermüdliche Erledigen aller, meine Person betreffenden, administrativen Angelegenheiten möchte ich mich hier ganz besonders bei diesen zwei netten Damen bedanken: Frau Ines Stein und Frau Kerstin Balkenhohl.

Herrn Dr. Frank Broda und Herrn Holger Bartz danke ich für die stets schnelle „Erste Hilfe“ bei IT-Problemen.

Für die nette Zusammenarbeit und die schöne Zeit am Leibniz-Institut für Pflanzenbiochemie möchte ich diesen Kollegen meinen Dank aussprechen (alphabetisch geordnet):
Alexander Otto, Alfredo Rodriguez Puentes, Amina Msonga, Andre Gohr, Angela Schaks, Anne-Katrin Bauer, Annika Denkert, Benjamin Weigel, Daniel da Silveira Rampon, Felix Schreckenbach, Jeanette Keim, Julia Kufka, Julia Christke, Juliane Mewes, Katharina Wolf, Kristin Brand, Micjel Chavez Morejon, Nicole Hünecke, Peter-Paul Heym, Rainer Preusentanz, Ramona Heinke, Ricardo Wanderley Neves Filho, Robert Klein, Roman Weber, Sebastian Brauch, Sebastian Stark und Steve Ludwig.

Der allergrößte Dank gilt meiner gesamten Familie, die alles mit mir durchgestanden und immer zu mir gehalten hat.

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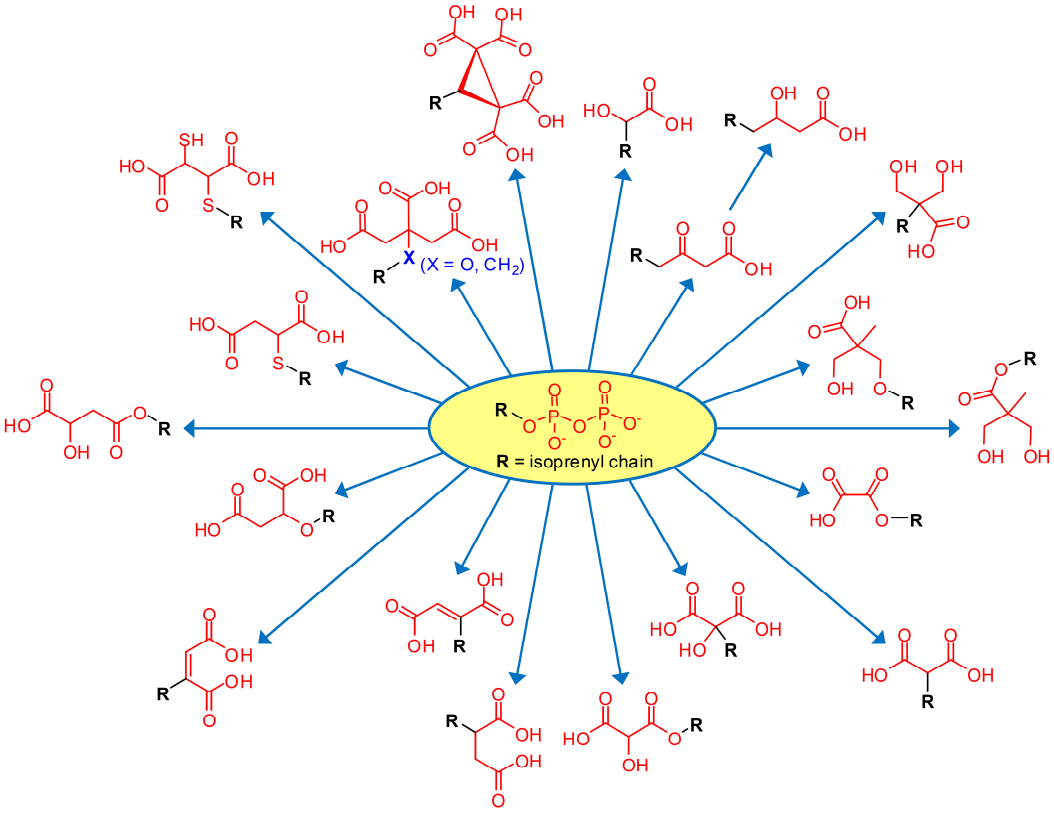
List of Abbreviations

ACN	acetonitrile
Boc	*tert*-butyloxycarbonyl
COSY	correlation spectroscopy
DCC	*N,N'*-dicyclohexylcarbodiimide
DEPT	distortionless enhancement by polarization transfer
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-(*N,N'*-dimethylamino)-pyridine
DMAPP	dimethylallyl diphosphate
DMF	dimethylformamide
DMPA	dimethylolpropionic acid = 2,2-Bis(hydroxymethyl)propionic acid
DMSO	dimethyl sulfoxide
ESI	electrospray ionization
Et	ethyl
Et_2O	diethylether
EtOAc	ethyl acetate
EtOH	ethanol
FGA	functional group addition
FPP	farnesyl diphosphate
FPPS	farnesyl diphosphate synthase
FT-ICR	fourier transform ion cyclotron resonance
GPP	geranyl diphosphate
GPPS	geranyl diphosphate synthase
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple-quantum correlation
HPLC	high performance liquid chromatography
HSBC	heteronuclear single bond correlation
HSQC	heteronuclear single-quantum correlation
K_a	acid dissociation constant
LDA	lithium diisopropylamide
Me	methyl
MeOH	methanol

MS	mass spectrometry
***n*-BuLi**	*n*-butyl lithium
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
PG	protective group
Ph	phenyl
pK_a	the negative logarithm of K_a with base ten ($pK_a = -\log_{10}K_a$)
R, R_1, R_2, …	organic residues
ROESY	rotating frame nuclear Overhauser effect spectroscopy
RP-HPLC	reverse phase high performance liquid chromatography
rt	room temperature
S_N2	bimolecular nucleophilic substitution
TEMT	triethyl methanetricarboxylate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
t_R	retention time

Abstract

The main focus of this work was to generate a small library of synthetic compounds which are supposed to function as chemical mimicries of the naturally abundant isoprenyl diphosphate substrates 3,3-dimethylallyl diphosphate (DMAPP), geranyl diphosphate (GPP) and farnesyl diphosphate (FPP) with a special emphasis on the charged diphosphate group. In contrast to the extensively studied diphosphate analogues in the literature which are primarily based on phosphorus containing acids, the present work rather attempts the synthetic exploitation of substrates based on carbon and oxygen alone, i.e. diphosphate surrogates based on carboxylic acids. Some exceptionally bioactive natural products (e.g. chaetomellic acid and zaragozic acid) feature a polycarboxylic acid core that mimics the diphosphate group of natural substrates and which is responsible for an efficient inhibition of particular prenylating enzymes. Being inspired by Nature´s creativity, a whole series of various mono-, di-, tri- and tetra-carboxylic acids bearing an isoprenyl chain of different size (C_5, C_{10}, C_{15}) have been synthesized and characterized by means of mass spectrometric, NMR spectroscopic and chromatographic techniques. More than half of the compounds presented in this thesis have not been published or registered previously. Thus, their structures can be denoted as completely new, and their impact on biological targets, especially prenylating enzymes, still remains to be evaluated.



1 Introduction

1.1 General aspects of terpenes (isoprenoids)[1]

With their usage dating as far back as ancient Egypt, terpenes hold a special place in both chemical and world history. Scientists, as well as non-scientists, appreciate these truly functional molecules, whose applications range from flavor and fragrance to hormones, medicine and even rubber.[1] Synthetic chemists were attracted to terpenes even before their polymeric properties were first postulated by Otto Wallach[2-3] in 1877 and described as the "biogenetic isoprene rule" by Leopold Ružička[4-5] in 1953. The continuous advancement of spectroscopic and chromatographic techniques brought about a drastic increase in the chemical and pharmacological aspects of terpene research that continues to this day. As a consequence, more than 55,000[6] terpenes have been already isolated and their structures characterized. Many of these secondary metabolites exhibit highly complex carbon skeletons incorporating multiple stereogenic centers and rigidly fused ring systems – a true charm and challenge for hard-core synthetic chemists (Figure 1). Also remarkable to mention is the fact that in contrast to proteins, which are made of twenty proteogenic amino acids, and in contrast to nucleic acids which are composed of four nucleotides, terpenes are built on only one five-carbon biosynthetic unit, i.e. isopentenyl diphosphate (IPP). Nonetheless, the immense chemodiversity and structural complexity of terpenoids arise from their highly rearranged and functionalized carbon frameworks (Figure 1).

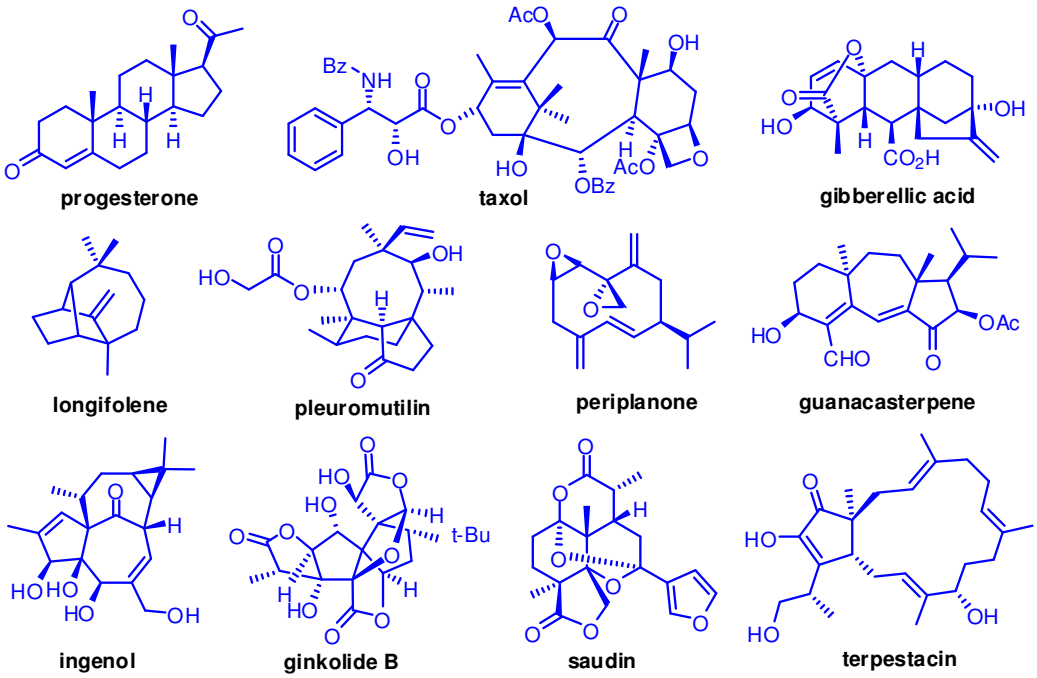


Figure 1: Examples of complex, biologically active terpenes.

1.2 Properties of isoprenoid coupling reactions[7]

Isopentenyl diphosphate (IPP) is synthesized from three molecules of acetyl coenzyme A through the classic mevalonate pathway, and in some bacteria and plants from a non-classic methylerythritol phosphate pathway.[8-9] IPP is then converted to its isomer dimethylallyl diphosphate (DMAPP) by IPP:DMAPP isomerase.[10] By condensation of DMAPP with one to three molecules of IPP, C_{10}-geranyl diphosphate (GPP), C_{15}-farnesyl diphosphate (FPP), and C_{20}-genanylgeranyl diphosphate (GGPP) are synthesized by the respective synthases, GPPS, FPPS, and GGPPS (Figure 2). These short-chain-length products serve as precursors leading to a variety of natural isoprenoid products (Figure 2) such as sterols, carotenoids, dolichols, ubiquinones, and prenylated proteins found in all organisms, functioning as hormones, visual pigments, constituents of membranes, and components of signal transduction[11].

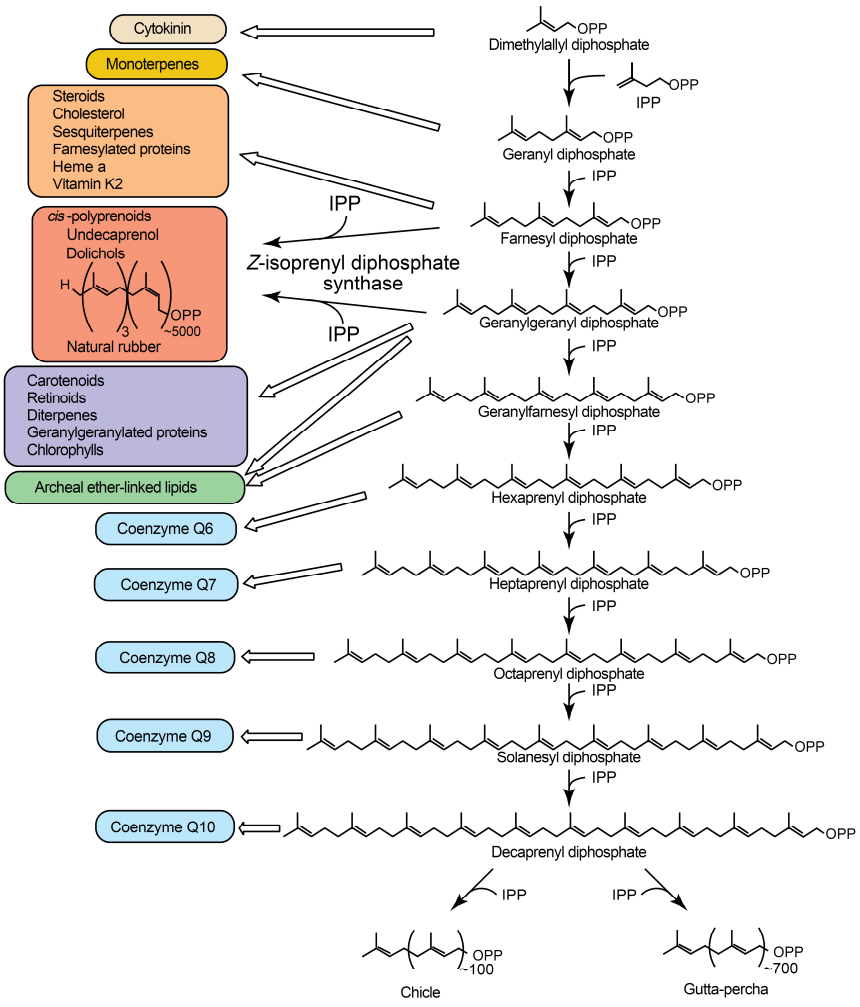
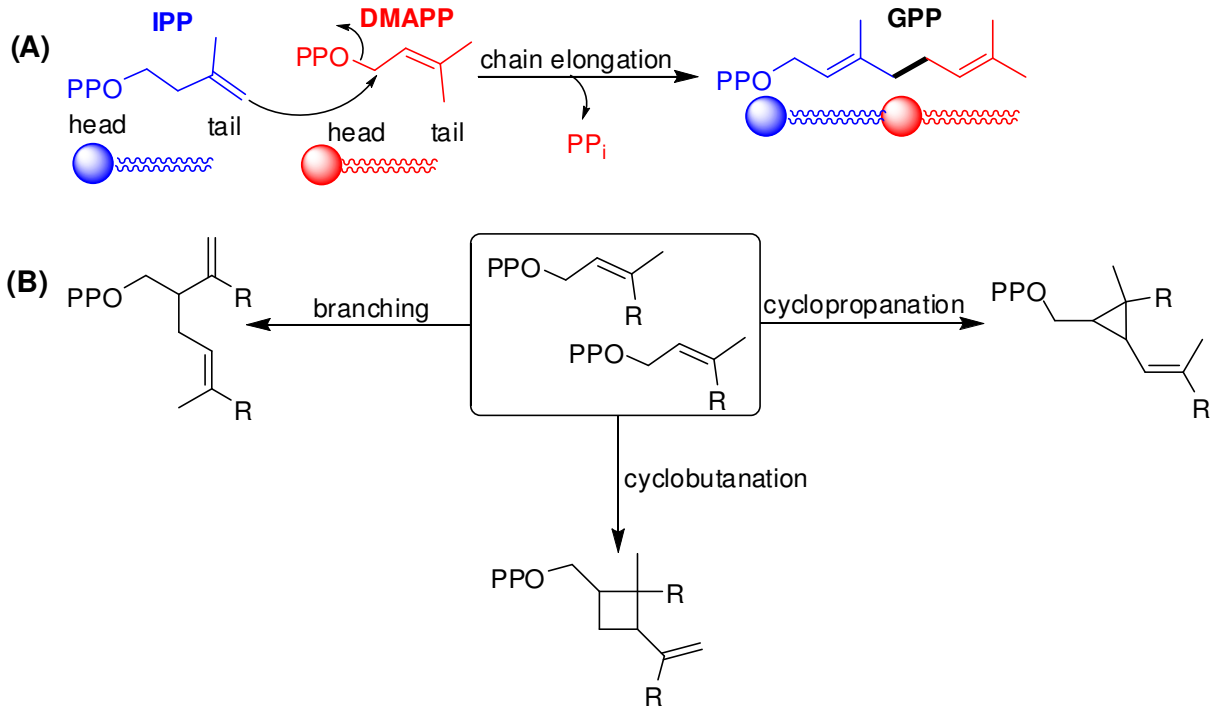


Figure 2: Chain elongation of linear *trans*-isoprenyl diphosphates by *trans*-isopentenyl diphosphate synthases. Each isopentenyl diphosphate is formed by a specific *trans*-isoprenyl diphosphate synthase. Final natural products derived from the linear polyprenyl diphosphates are shown on the left. Picture was adapted from reference [12].

In the chain elongation reaction of terpenoids, which occurs in all organisms, the growing isoprenoid chain of an isoprenoid allylic diphosphate is added to the double bond of isopentenyl diphosphate (IPP) (Scheme 1A). The 1′-4 linkage[13] is by far the most common one that is observed in isoprenoids, and compounds with this attachment between isoprene units are called head-to-tail or regular terpenes. Other connectivity patterns (Scheme 1B) are designated as irregular.[14] For example, the cyclopropanation reaction is the first pathway-specific step in the biosynthesis of sterols[15] and carotenoids[16] to provide metabolites that are widely distributed in Eukarya, Archaea, and some Bacteria. Branching is only found in a limited number of plants.[17-18] The only documented compounds from cyclobutanation are mealybug mating pheromones.[19-20]

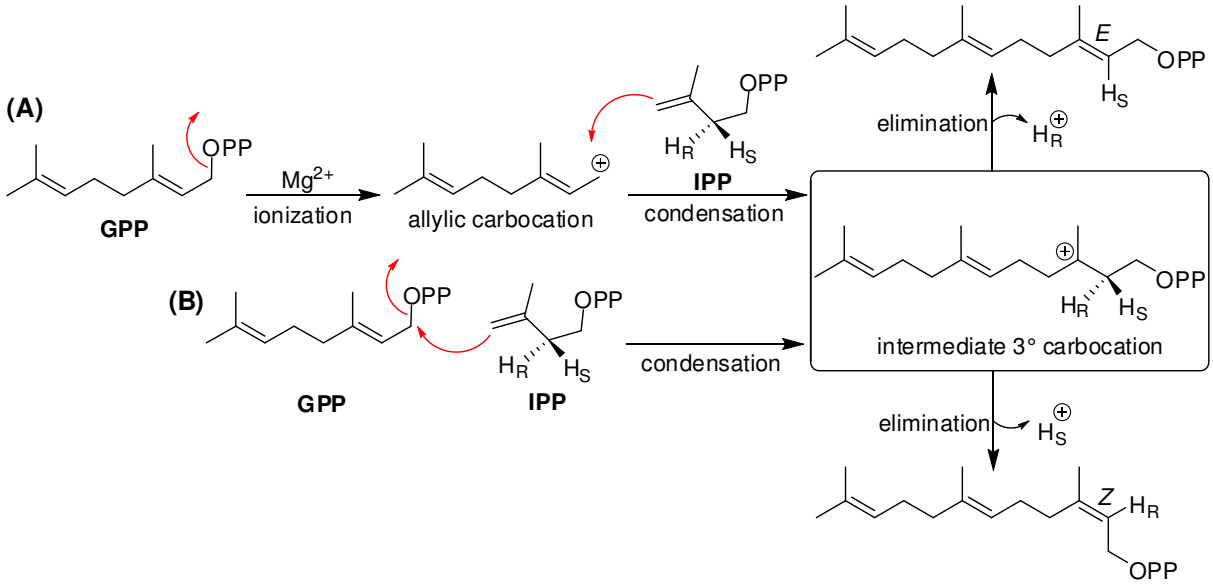


Scheme 1: Building reactions in the isoprenoid biosynthetic pathway. (A) chain elongation, (B) branching, cyclopropanation and cyclobutanation. Adapted from reference [14].

1.3 Mechanistic insights into the chain elongation reaction[7]

The chain elongation reactions catalyzed by prenyltransferases are very unique and interesting from a mechanistic point of view. For instance, geranyl diphosphate (GPP) can be elongated to a variety of linear polyprenyl diphosphates via consecutive condensation reactions with specific numbers of IPP (see Figure 2).[21-23] There are two possible mechanisms proposed in the literature for prenyltransferase reactions: (i) a sequential ionization–condensation–elimination mechanism (Scheme 2A) in which the allylic substrate (here: GPP) releases its diphosphate ion to form an allylic carbocation intermediate, which is

attacked by IPP, with stereospecific removal of a prochiral proton (H_R for the *trans* type) to form a new C-C bond and a new double bond in the product; and (ii) a concerted condensation–elimination mechanism (Scheme 2B) in which ionization of the allylic substrate and condensation of IPP occur simultaneously.[13]

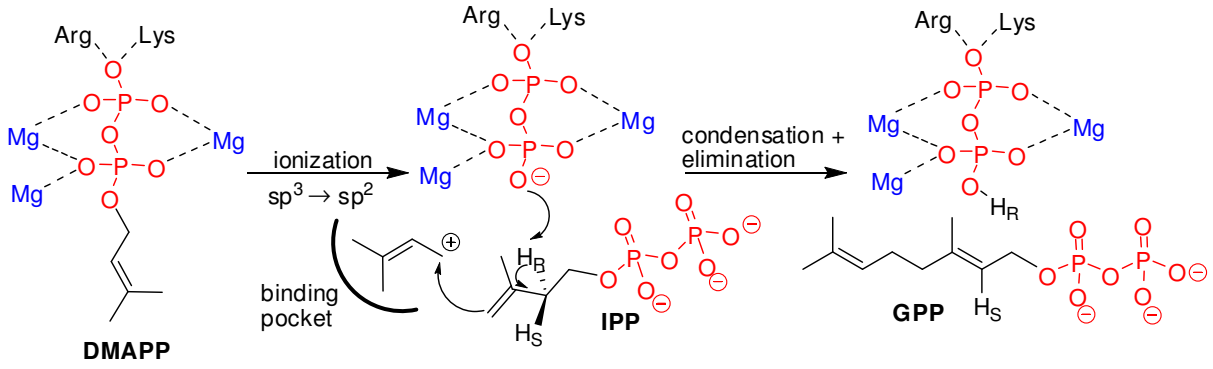


Scheme 2: (A) The reactions of *trans*-prenyltransferases proceed with the ionization, condensation, and elimination sequential mechanism. Diphosphate is dissociated from FPP to form a carbocation, which is then condensed with IPP, and the H_R proton is eliminated from IPP to form the condensation adduct. (B) In *cis*-prenyltransferase reactions, dissociation of diphosphate occurs with IPP condensation in a concerted way, and then the H_S is eliminated from IPP by a general base to form the condensation adduct. Adapted from reference [24].

Both *trans*-type FPPS and octaprenyl diphosphate synthase (OPPS) have been shown to proceed through a sequential mechanism.[24-25] In contrast, *cis*-type undecaprenyl diphosphate synthase (UPPS) utilize a concerted mechanism which is consistent with the failure to trap the carbocation intermediate as farnesol under basic conditions from the FPP substrate in the presence of Br-IPP (i.e an IPP analogue), to slow the condensation step.[24] In summary, *cis*- and *trans*-prenyltransferases utilize different strategies for catalysis, as suggested by the lack of sequence similarity.[26-27]

On the basis of the crystal structure of *E. coli* FPPS, DMAPP is bound to FPPS through a trinuclear Mg^{2+} cluster (Scheme 3) that is coordinated by three conserved aspartate residues, called DDxxD motif (not shown here).[28] Two Mg^{2+} ions each form six-membered ring chelated structures with two unesterified diphosphate oxygens, while the third Mg^{2+} ligates a single unesterified oxygen of the linking diphosphate (Scheme 3).[28] The carbocation from the allylic substrate is stabilized by electrostatic interactions with the released diphosphate and also through the main-chain carbonyl oxygen of Lys202 and the side-chain oxygens of

Thr203 and Gln241. The homoallylic substrate IPP is bound in a positively charged pocket formed by Lys, Arg, and His residues. These interactions position the nucleophilic double bond of IPP 3.2 Å from the electrophilic carbon atom of DMAPP. A non-metal coordinated diphosphate oxygen (ligated by conserved Arg116 and Lys258) is positioned such that it can stereospecifically abstract the prochiral H_R of IPP after the condensation reaction to yield GPP (Scheme 3).[28] A second chain elongation reaction with geranyl diphosphate thus formed and another molecule of IPP yields farnesyl diphosphate.



Scheme 3: Substrate ionization by the trinuclear Mg^{2+}center generates an allylic carbocation that alkylates the olefinic carbon atom of IPP. *Trans*-double bond formation in the final product is mediated by a DMAPP diphosphate oxygen that serves as the catalytic base removing the prochiral H_R-hydrogen of IPP. Adapted from reference [28].

1.4 Non-hydrolyzable mimetics of the phosphate and diphosphate group and their importance in medicinal chemistry

1.4.1 Mimetics based on phosphorus

One of the most challenging functionalities to mimic in the design of drugs for development has been the phosphate or diphosphate functionality.[29] Aside from prodrug applications, phosphate esters are normally considered impractical functional groups for drug design because they are subject to cleavage by digestive phosphatases. The potential of phosphonates as phosphate mimics has been recognized for many years.[30] Unlike a phosphate group, the phosphonate linkage is not readily hydrolyzed in a biological environment, and this unique property has made these compounds attractive as phosphate analogues in numerous applications. Stated differently, the structural correspondence of C–C–P bonds with C–O–P bonds, although significantly dissimilar in their chemical characteristics, has paved the way for systematic chemical and biomedical studies of phosphonic acids and their derivatives.[31-35]

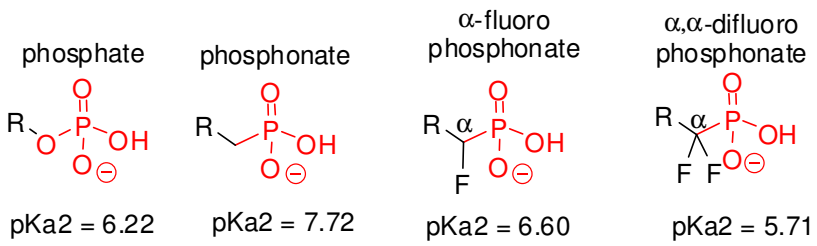


Figure 3: Comparison of the chemical structures and acidities (i.e. pKa´s of the second deprotonation) of alkylphosphate to alkylphosphonate analogues (R=alkyl, aryl). Adapted from references [36-37].

For in vitro inhibitors, a phosphonate is a useful and stable (i.e. non-hydrolyzable) phosphate mimetic that can be improved by fluorination of the α-C atom to increase the acidity to more closely match that of the phosphate moiety (Figure 3).[38] An improvement of the bioisostere strategy in phosphonate chemistry has been developed by Blackburn and co-workers[39] and McKenna and Shen.[40] They suggested that superior bioisosteres might be obtained by the introduction of halogen and, in particular, fluorine on the α-carbon of alkylphosphonates since these surrogates are supposed to more accurately mimic the steric and polar character of the phosphate function. In fact, α-monofluoro- and α,α-difluoroalkylphosphonates (Figure 3) were found to be more effective analogues of phosphonates compared with the non-fluorinated congeners because the CHF and CF_2 groups can both sterically and electronically mimic an oxygen, enabling the second dissociation constant (pK_{a2}), to more closely mirror those of the phosphates due to the electron-withdrawing effect of fluorine (Figure 3).[37-38, 41-42] A theoretical study also indicates that the electrostatic profile of a CHF–phosphonate is close in magnitude to that of a phosphate.[43]

In a direct analogy to the above mentioned phosphonates, *gem*-diphosphonates have also attracted considerable interest as a mimicry for the diphosphate group, in which the bridging phosphoanhydride oxygen is replaced by carbon, thus suppressing hydrolysis of the P–O–P linkages (Figure 4).

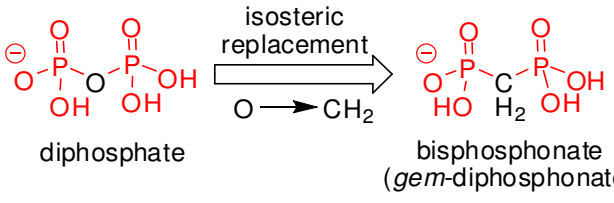
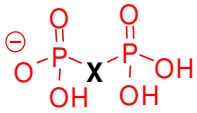


Figure 4: Comparison of the chemical structures of diphosphate and bisphosphonate. Isosteric replacement (O → CH_2) prevents hydrolytic cleavage of the high-energy phosphoanhydride bond.

However, the major concerns associated with this strategy are differences between reactivities of the bisphosphonate analogues and normal diphosphate substrates. The lower

electronegativity of the methylene group, compared to oxygen, leads to a significant decrease in the acid dissociation constants of the phosphonic analogues, which is often reflected in a reduction of biological activity.[38] A particular tuning of the diphosphate/bis-phosphonate strategy has been developed by Blackburn and co-workers.[44-45] They found that the replacement of a bridging methylene group by a difluoromethylene unit in diphosphonates restored the pK_a of analogues to values almost identical with those of the natural diphosphate substrates, thus providing compounds with an improved potential as diphosphate mimetics (Table 1). However, the highly acidic nature of fluorophosphonates has limited their application and utility in drug design largely to biochemical evaluation in vitro.



X	pKa2	pKa3	pKa4
O	2.36	5.77	8.22
CH_2	2.87	7.45	10.96
CCl_2		6.11	9.78
$C(OH)_2$		5.81	8.42
CHF	< 2.7	6.15	9.35
CF_2	< 2.6	5.80	8.00

Table 1: Comparison of the acidities of diphosphate to a series of diphosphonates. Adapted from reference [36].

Up to now, only bisphosphonates[46-47] have proved as potent and useful inhibitors of disease-related prenyltransferases like FPPS and GGPPS. Various examples of diphosphate mimetics based on phosphonophosphate, phosphonophosphinate and bisphosphonate structures have been reviewed extensively elsewhere.[48-57] The application of mono- and diphosphate bioisosteres on biological targets other than prenyltransferases is outlined in a very recent review by Conway et al.[58]

1.4.2 Mimetics based on carboxylic acids

Most of the inhibitors that have been developed for targeting oncogenic proteins are focused on bisphosphonate structures or on peptidomimetics that contain the CAAX[1] recognition motif. However, much less attention has been paid to inhibitors that resemble the diphosphate group but are completely phosphorus-free. For example, there are several natural products with polycarboxylic acid functionalities that have been isolated and which exhibit a high inhibitory activity towards several prenylating enzymes (Figure 5).

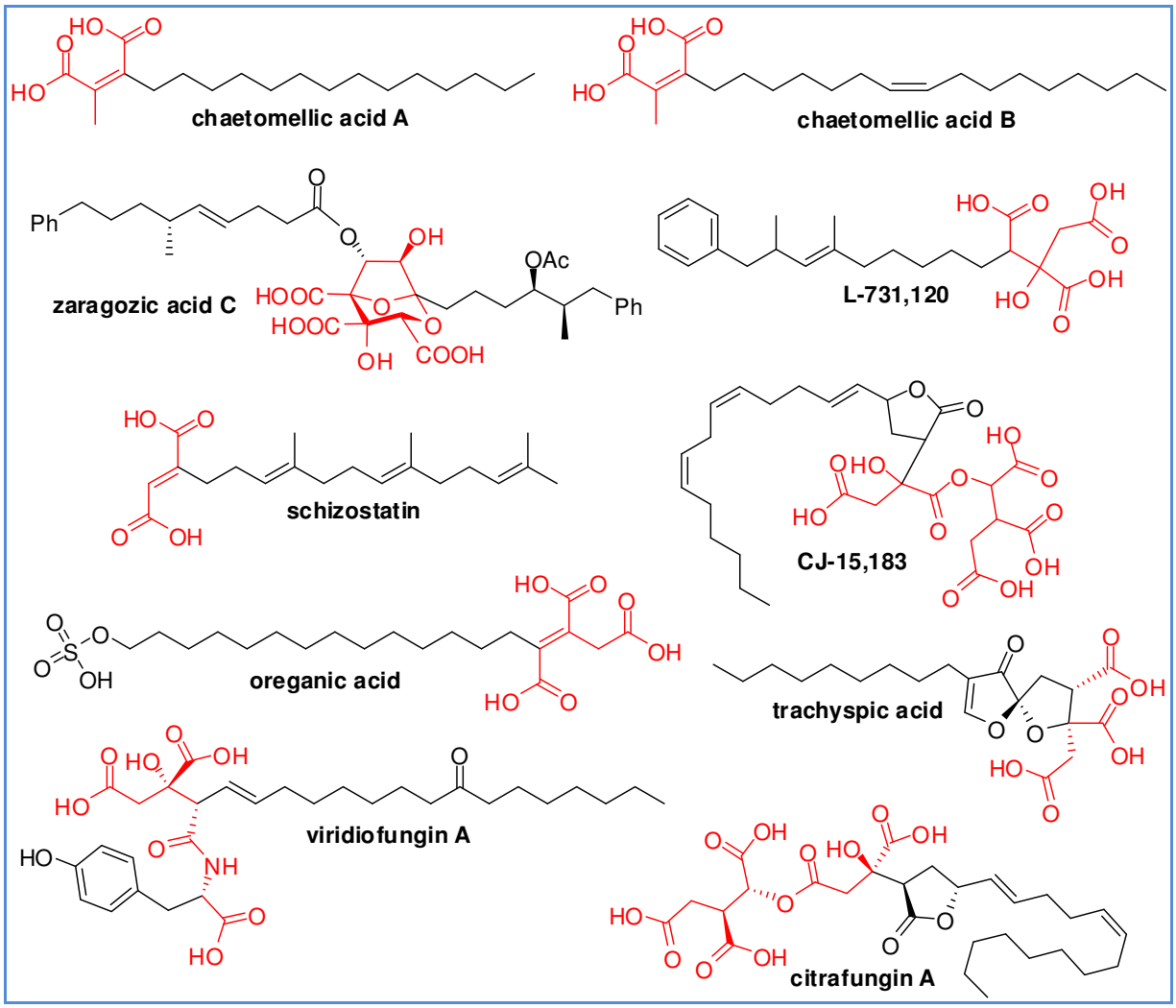


Figure 5: Representative examples of natural products which are known to be potent inhibitors of disease-related prenyl transferases. The polar non-phosphorus groups show a function as non-hydrolyzable mimetics of the naturally occurring labile diphosphate group.

[1] CAAX is a tetrapeptide sequence at the carboxyl terminus of proteins. The isoprenoid chain of the isoprenyl diphosphate substrate is transferred to the cysteine (C) residue of the tetrapeptide. A = aliphatic amino acid, X = methionine or serine.

A prominent example is given by the group of chaetomellic acids which were isolated from the coelomycete *Chaetomella acutiseta*.[59-61] Chaetomellic acids A and B inhibit farnesyl protein transferase at IC_{50}-values in the nanomolar range.[59-61] Due to their structural (topological) mimicry[61] of farnesyl diphosphate (Figure 6), they compete with the natural substrate for the binding site in the enzyme, and act therefore as reversible inhibitors. A closely related mimicry of FPP and a potent inhibitor of squalene synthase is schizostatin[62-64] (Figure 5) exhibiting a *trans*-geometry of the 1,4-dicarboxylic acid unit (fumaric acid).

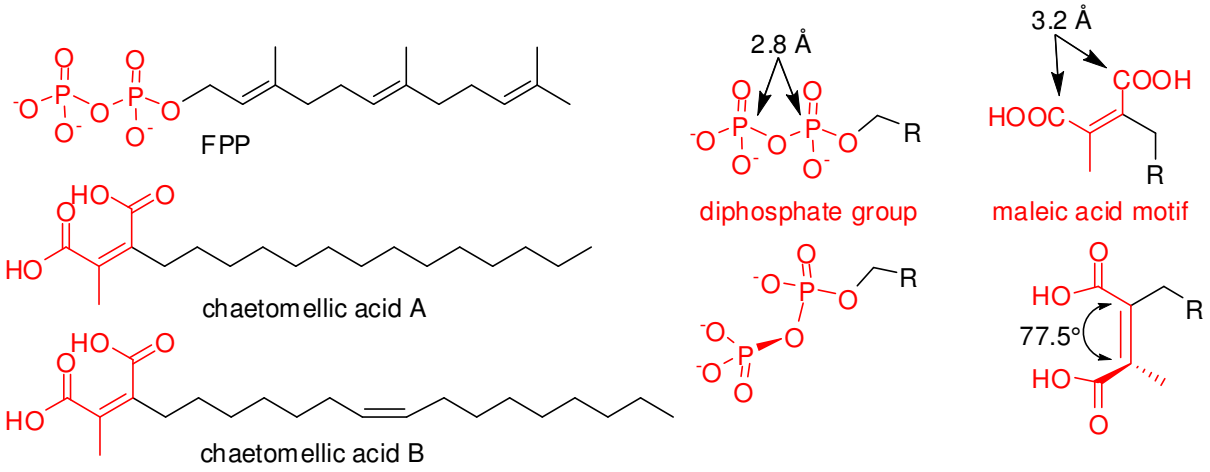


Figure 6: Topological and non-hydrolyzable mimicry of the diphosphate group of FPP realized by the maleic acid motif found in chaetomellic acids A and B.[61]

The zaragozic acids[65-70] (squalestatins) are very potent picomolar inhibitors of squalene synthase. They represent a family of fungal natural products characterized by a bicyclic tricarboxylic acid containing core with two lipophilic side chains (Figure 5). Further natural products with a polycarboxylic acid (isocitrate) core showing inhibitory activity towards prenyl converting enzymes are depicted in Figure 5: L-731,120[71], CJ-13,981[72-73], CJ-13,982[72-73], CJ-15,183[74], oreganic acid[75-76], trachyspic acid[77-78], viridiofungin A[79-80] and citrafungin A[81-82].

Inspired by the strategy employed by nature, the major objective of this thesis is to establish and expand the scope of synthetic[83-86], non-phosphorus-based isoprenyl diphosphate surrogates. Their potential to serve as effective diphosphate mimetics still remains to be evaluated in selected *in-vitro* assays.

2 Aims and scopes of the thesis

The aim of the present work was to generate a small library of synthetic compounds which are supposed to function as non-hydrolyzable mimetics of the naturally abundant isoprenyl diphosphate substrates 3,3-dimethylallyl diphosphate (DMAPP), geranyl diphosphate (GPP) and farnesyl diphosphate (FPP) with a special focus on the charged diphosphate group. In contrast to the extensively studied diphosphate mimetics in the literature which are primarily based on phosphorus containing acids (e.g. medronic acid and oxidronic acid), the present work rather attempts the synthetic exploitation of substrates based on carbon and oxygen alone, i.e. diphosphate surrogates based on carboxylic acids. Such diphosphate group mimicries which are exclusively made of carboxylic acids are known for some exceptionally bioactive natural products (e.g. chaetomellic acid and zaragozic acid, see Chapter 1.4.2) that have been isolated from fungal species. For this purpose, a whole series of various mono-, di-, tri- and tetra-carboxylic acids bearing an isoprenyl chain of different length (C_5, C_{10}, C_{15}) have been synthesized and characterized by means of mass spectrometric, NMR spectroscopic and chromatographic techniques. More than half of the compounds presented in this thesis have not been published previously and they also are not registered in chemical databases. Thus, their structures can be denoted as completely new, and their impact on biological targets still remains to be explored.

Studies on their evaluation as putative inhibitors for prenyltransferases are in progress. Especially the synthetic analogues bearing a C_{10} isoprenyl chain are attractive candidates for the use into the enzyme assay with bacterial *UbiA*, an aromatic oligoprenyl transferase which has been studied in detail by our group. The hit-structures that might result from bioassays with *UbiA* and/or other prenyl transferases could shed light on the mechanism and mode of action of prenylating enzymes belonging to the same genre. Moreover, the kinetic profile obtained with the identified hits would provide further clues on the nature of the detected inhibition, i.e. whether it is competitive, non-competitive or a mixture of both types. In this context, the future design of synthetic affinity-based chemical probes and chromatographic stationary phase materials incorporating the structural motif of the established mimicry-hits would furnish an additional powerful tool for the growing needs of the continuously expanding research in the biosciences.

3 Results and Discussion

The following chapter discusses the synthetic routes that have been established for the various diphosphate mimetics, and it also comments on the unexpected obstacles encountered on the way towards their preparation. As already mentioned in Chapter 2, the diphosphate surrogates treated in the present work are based on non-phosphorus-containing polycarboxylic acids. The reason for this decision was solely inspired by Nature since there are very potent natural products known (see Chapter 1.4.2) which exhibit a remarkable inhibitory effect on medically relevant prenyltransferases (e.g. Ras, Rab). With this in mind, the leading “carboxylic acid”-motif was explored in its variety. An overview of the diphosphate mimetics discussed in the following sections of this chapter is given in Figure 7.

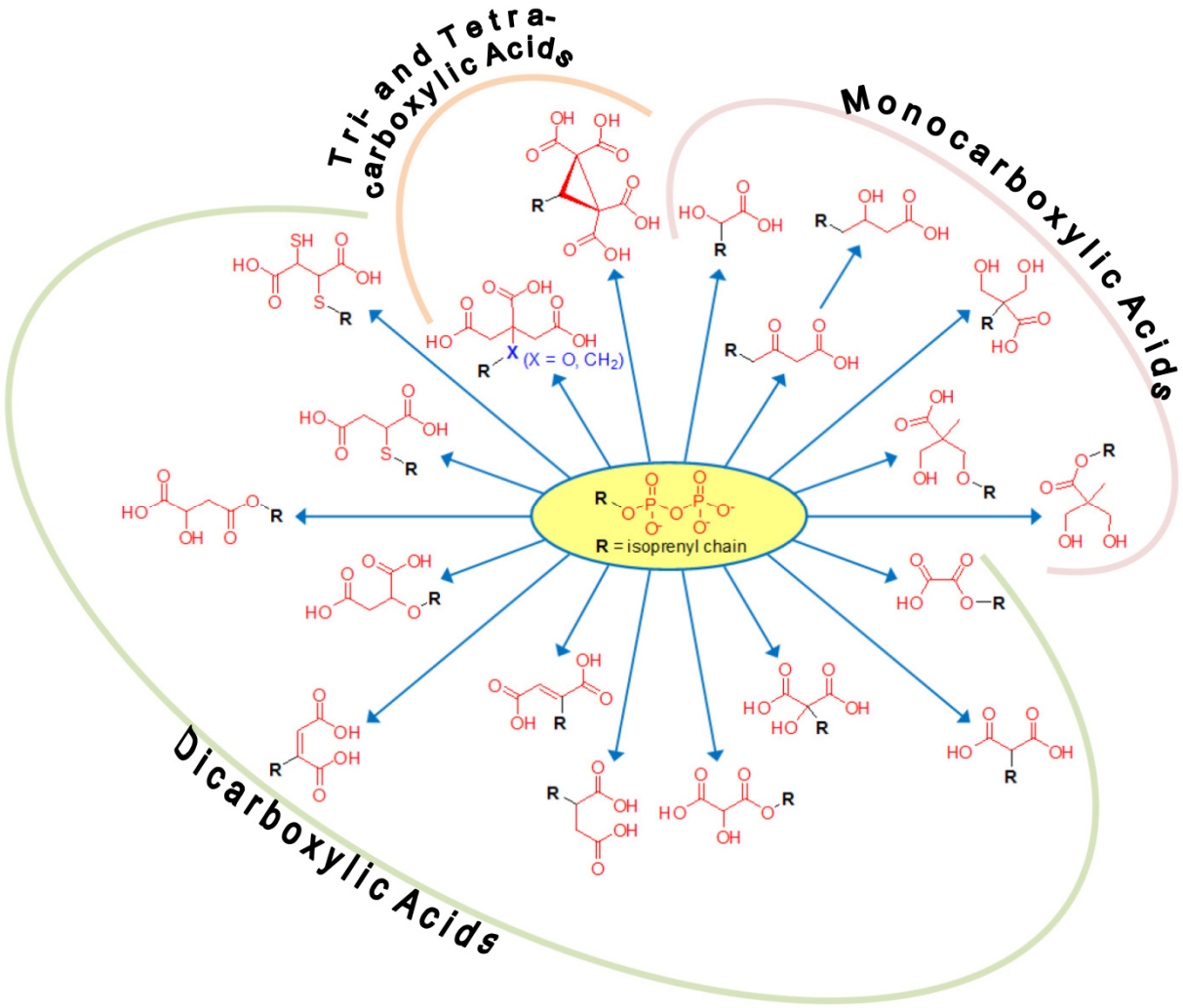


Figure 7: An overview of the diphosphate mimetics treated in the present work.

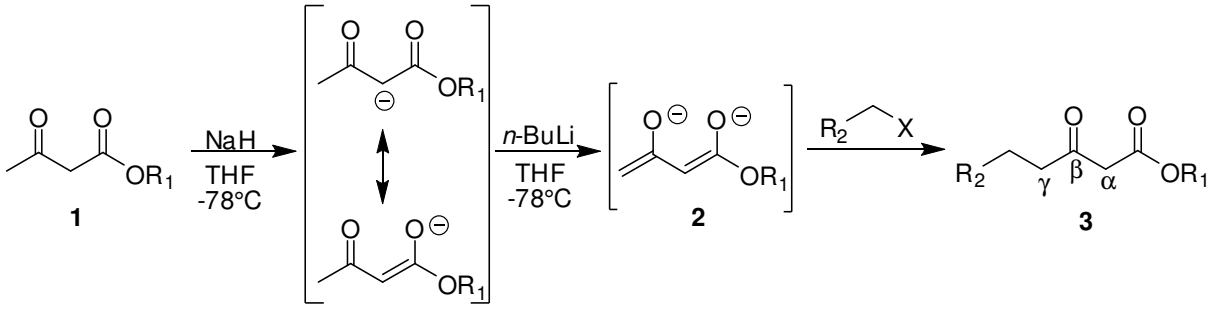
3.1 Derivatives of monocarboxylic acids

3.1.1 Mimetics derived from β-keto and β-hydroxy acids

3.1.1.1 Surrogates of 3-oxobutanoic acid and β-hydroxybutyric acid

Geranyl functionalized derivatives of 3-oxobutanoic acid and β-hydroxybutyric acid have already been synthesized and tested for their inhibitory potential in *ubiA*-prenyltransferase.[84] In terms of having a broader spectrum of derivatives, suitable for prenyl transferases with a preference for short prenyl chain substrates, C_5-allylic and C_6-homoallylic hydrocarbon chains were attached to the acetoacetic acid core structure.

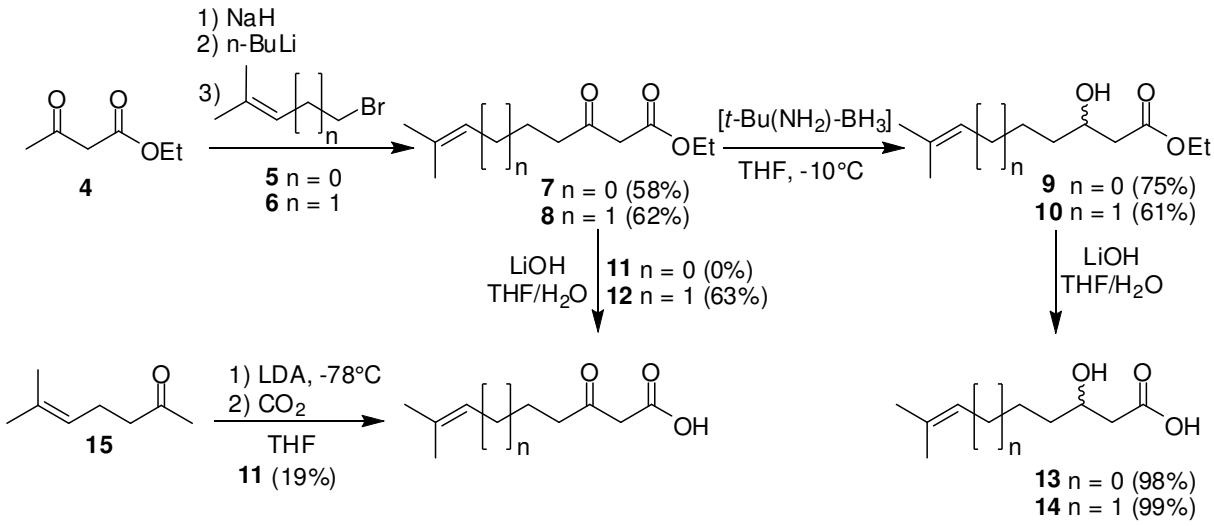
The cruical step in the synthesis comprises the formation of a dianionic species **2** by a two-fold proton abstraction from **1** and then its trapping with an alkyl halide. This procedure generates γ-alkylated products **3** and is named according to its founder as Weiler homologation[87] (Scheme 4).



Scheme 4: The Weiler homologation gives access to γ-alkylated β-ketoesters **3**.[87]

The synthesis of β-keto acids (**11**, **12**) and β-hydroxy acids (**13**, **14**) is shown in Scheme 5. Ethyl acetoacetate **4** was selectively alkylated at the γ-position with each of alkyl bromides **5** and **6**. Treatment of the resulting β-keto ester **8** with LiOH in THF/H_2O gave the desired alkylated β-carboxylic acid **12**. Unexpectedly, β-keto ester **7** resulting from homologation with allylic **5** was prone to decomposition under the applied conditions for hydrolysis and the corresponding acid **11** could not be isolated. Therefore, a more direct approach was envisioned: carbonylation of the lithium enolate of commercially available methyl ketone **15** readily afforded β-keto acid **11** as a white soft solid.[88] Reduction of β-keto esters **7** and **8** with borane *tert*-butylamine complex in THF produced racemic β-hydroxy esters **9** and **10**,

which upon saponification with LiOH afforded the corresponding racemic β-hydroxy acids **13** and **14**, respectively.

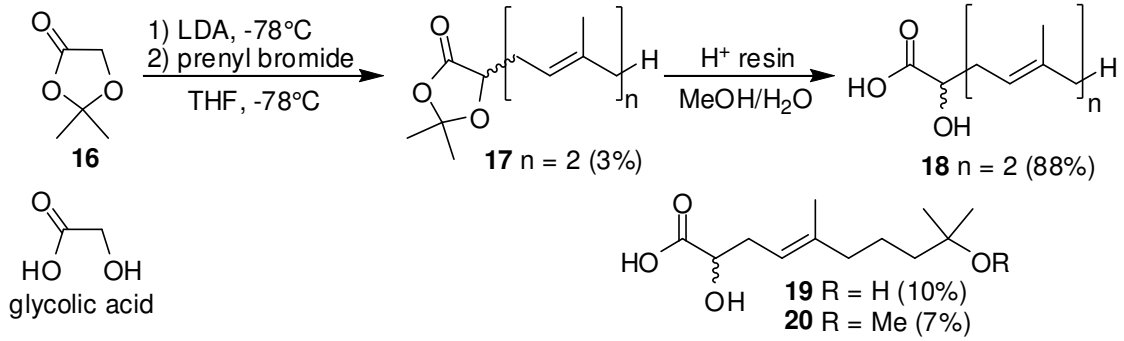


Scheme 5: Synthetic route to β-keto derivatives (**7, 8, 11** and **12**) and their β-hydroxy derivatives (**9, 10, 13** and **14**).

3.1.2 Mimetics derived from α-hydroxy acids

3.1.2.1 Surrogates of glycolic acid

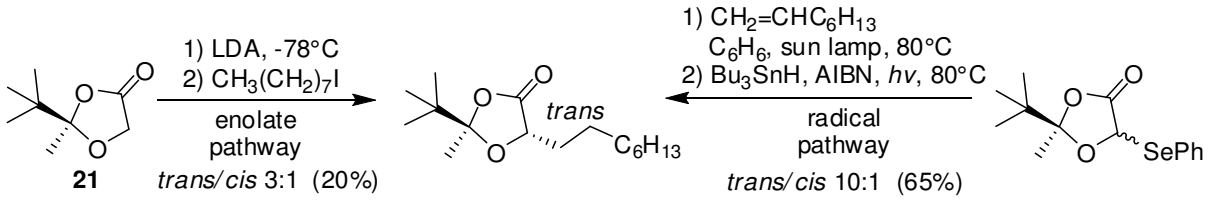
The corresponding α-prenyl-glycolic acid derivatives (**18**–**20**) were prepared from 2,2-dimethyl-1,3-dioxolane-4-one **16**, which is formally glycolic acid whose hydroxyl groups are masked within a 1,3-dioxolane ring (Scheme 6).



Scheme 6: Synthesis of α-hydroxy acid **18** by alkylation of dioxolanone **16** and subsequent acetal cleavage. Due to the reaction conditions, compounds **19** and **20** were isolated as side-products.

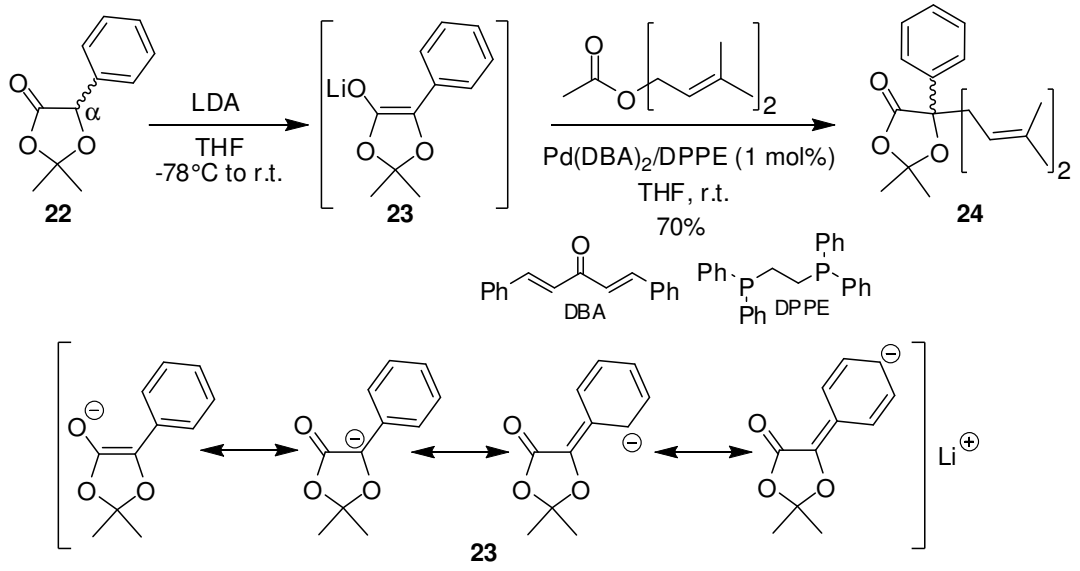
As shown above, alkylation of **16** at the α-position afforded racemic **17**. Acid-catalyzed removal of the acetonide group provided target compound **18** along with small amounts of side-products **19** and **20** that resulted from the Markovnikov addition of water and methanol, respectively, to the terminal double bond of the geranyl chain (cf. compounds **63**, **64**, **145** and **168**). Their structures were confirmed by 2D-NMR measurements.

Disappointingly, the yields obtained from the α-alkylation of the lithium enolate of 1,3-dioxolanone **16** proved miserable in all trials. Changing the base to sodium bis(trimethylsilyl)amide did not furnish better results. In accordance with these drawbacks are the findings reported by Renaud et al.[89] In their studies on the asymmetric synthesis of α-monoalkylated α-hydroxyacids from a chiral dioxolanone building block, they observed that the enolate of (*R*)-2-(*tert*-butyl)-1,3-dioxolan-4-one **21** is not sufficiently stable to be efficiently alkylated.[89] In contrast, its radical mediated alkylation showed to be diastereoselective and good-yielding (Scheme 7).[90-91]



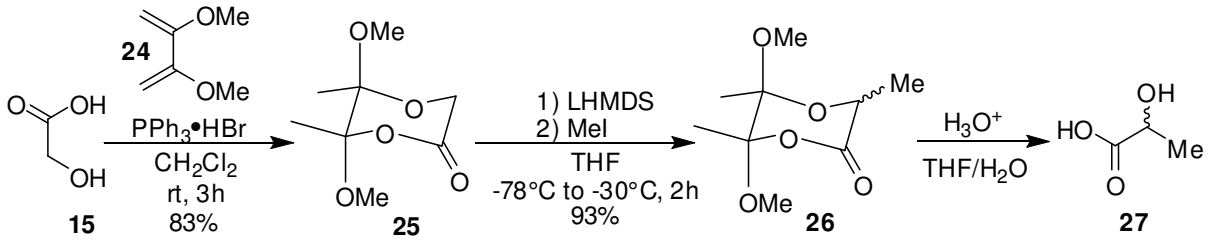
Scheme 7: Juxtaposition of radical alkylation (right) and enolate alkylation (left) of 2-(*tert*-butyl)-2-methyldioxolan-4-one **21**, a chiral equivalent of glycolic acid, with respect to diastereoselectivity and product yield.[90]

Unlike 5-unsubstituted 1,3-dioxolanones **16** and **21**, the palladium-catalyzed α-allylation of enolate **23** with geranyl acetate to 5,5-disubstituted 1,3-dioxolanone **24** proceeded with 70% yield.[92] This suggests that the phenyl group in mandelic acid acetonide **22** enhances the stability of enolate ion **23** (in contrast to the enolate of **16**) by delocalization of electron density (Scheme 8).



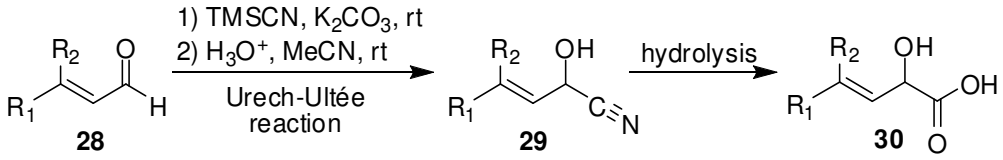
Scheme 8: Alkylation of the enolate ion **22** of mandelic acid acetonide as reported by Kellogg[92] (upper part). Resonance structures of enolate **22** (lower part).

A more contemporary and high-yielding approach for the preparation of α-glycolic acid derivatives (and related systems like thioglycolic acid, mandelic acid and lactamide) was pioneered by the work of Ley and co-workers.[93-94] Although Ley´s method was not used in the present work it should be mentioned here briefly. As shown in Scheme 9, glycolic acid **15** can be protected with *bis*-enol ether **24**[95] to give racemic butanediacetal (BDA) protected compound **25**. Deprotonation and subsequent alkylation of the resulting enolate with alkyl halides (here: methyl iodide) gives compound **26**. Diacetal deprotection by acid mediated hydrolysis delivers the racemic α-hydroxyacid **27**. An enantiospecific route to (*R,R*)-**25** and (*S,S*)-**25** and the diastereoselective alkylation of their enolates have also been reported by Ley.[93]



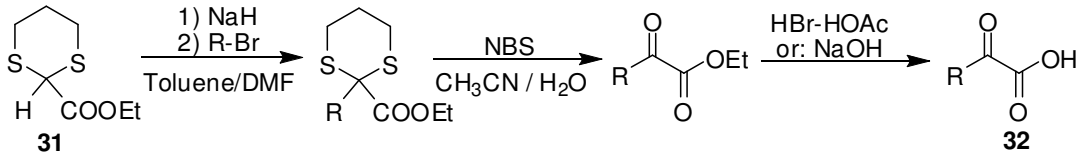
Scheme 9: Ley´s method for the preparation of racemic butane-2,3-diacetal **25** from glycolic acid **15**. Alkylation of **25** with methyl iodide and subsequent deprotection of the diacetal group in **26** afforded racemic lactic acid **27**.[93]

In addition to the aforementioned *homo*-allylic derivatives **18-20** (Scheme 6), the corresponding allylic analogues easily can be obtained by the Urech-Ultée cyanohydrin method[96-97] in which enal **28** is reacted with cyanide to give allylic cyanohydrin[98] **29**. Its hydrolysis provides the corresponding allylic α-hydroxy acid **30** (Scheme 10).



Scheme 10: Synthesis of allylic α-hydroxy acid derivatives **30** by the Urech-Ultée cyanohydrin method.[96-97]

Although it has not been carried out in this thesis, it should be noted that smooth oxidation of the α-hydroxy moiety would readily give access to prenylated derivatives of glyoxylic acid (i.e. 2-oxo-acetic acid, **32** with R=Me). Alternatively, one can make direct use of Eliel and Hartmann´s[99-101] α-keto ester synthesis by alkylation of dithiane **31**, followed by thioacetal cleavage and ester hydrolysis to provide the free α-keto acid **32** (Scheme 11).



Scheme 11: Preparation of glyoxylic acid derivatives **32** by making use of Eliel and Hartmann´s α-keto ester synthesis.[99-101]

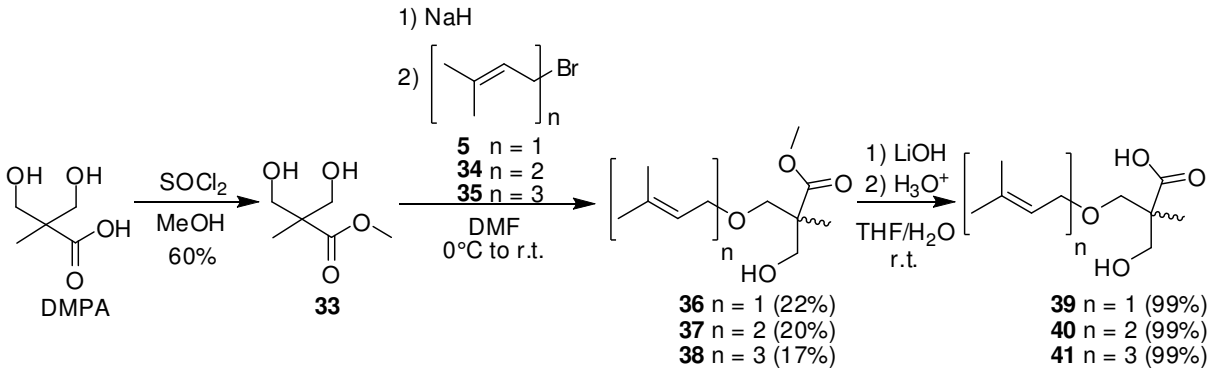
3.1.3 Mimetics derived from α,α-bis(hydroxymethyl) carboxylic acids

3.1.3.1 Surrogates of dimethylolpropionic acid (DMPA)

Dimethylolpropionic acid (DMPA, 2,2-*bis*(hydroxymethyl)propionic acid) is a versatile reagent in organic synthesis. Due to its 1,3-diol functionality and one free carboxylic acid group, DMPA offers three possible connecting points. Therefore it is often used as a branching element in the synthesis of dendrimers.[102-104] In the present work, however, DMPA was – for the very first time – derivatized with isoprenyl chains of varying size, thus allowing two out of the three polar groups to assume the function of the diphosphate group.

3.1.3.1.1 Ether derivatives of DMPA

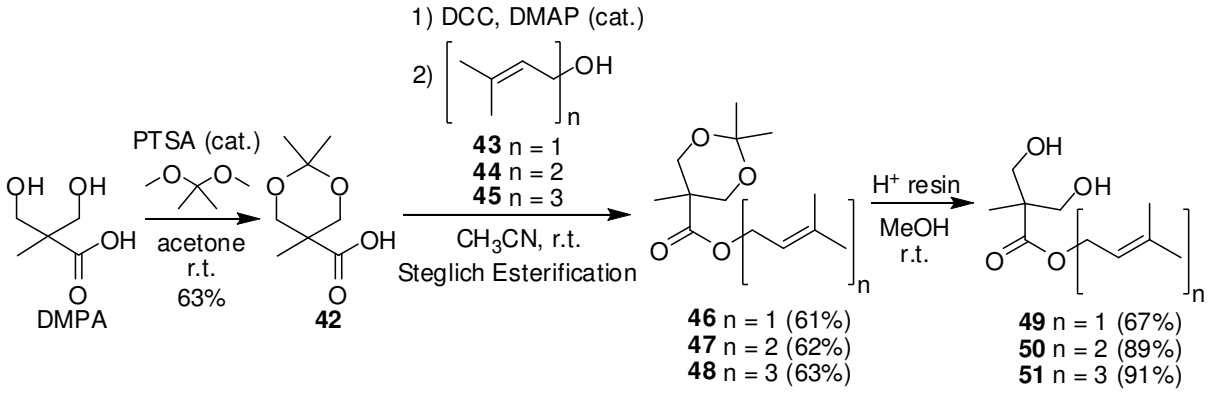
β-(Isoprenyloxy)-α-(hydroxymethyl)-α-methylpropanoic acid derivatives **39-41** were synthesized starting from commercially available DMPA. In a first step, the free acid function in DMPA was protected as methyl ester **33**[105]. Etherification with prenyl bromides (**5, 34, 35**) in DMF under standard Williamson[106-107] conditions afforded the corresponding racemic ethers **36-38** in moderate yields. After saponification under alkaline conditions and subsequent acidification, the desired carboxylic acids **39-41** were obtained from their esters in almost quantitative yield (Scheme 12).



Scheme 12: Synthetic route to isoprenyl ether derivatives of DMPA.

3.1.3.1.2 Ester derivatives of DMPA

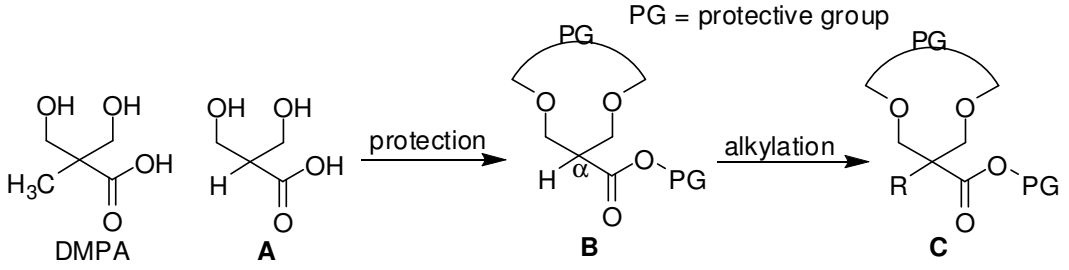
For the preparation of ester substrates **49-51** the two hydroxyl functions of DMPA were protected as acetonide **42**[102] with 2,2-dimethoxypropane in acetone under acid-catalysis. Esterification of the free acid group with terpene alcohols **43-45** was nicely accomplished under mild conditions following the Steglich[108] protocol. Finally, the acetonide protecting group of esters **46-48** was removed under acid catalysis in methanol to give 1,3-diols **49-51** in good to excellent yields (Scheme 13).



Scheme 13: Synthetic route to isoprenyl esters of DMPA.

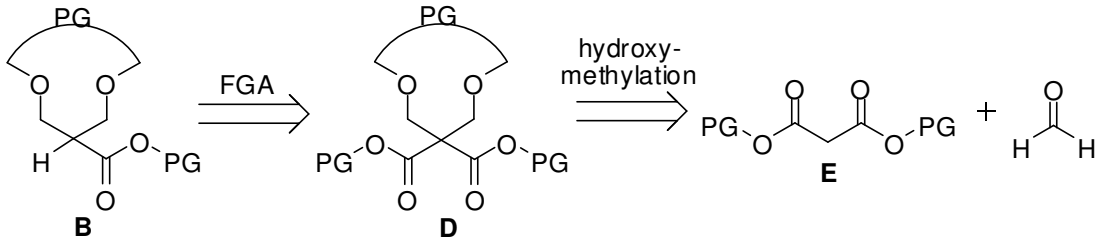
3.1.3.2 Surrogates of dimethylolethanoic acid

In analogy to the structural motif of DMPA (two hydroxymethyl groups and one carboxylic acid function) the access to prenyl-derived compounds appeared attractive. Key building block **A** (DMPA without the methyl group) is not commercially available, and the synthesis of its protected form **B** would have to be carried out prior to an alkylation at the α-position to give building block **C** (Scheme 14).



Scheme 14: Reasoning how to access *C*-alkylated derivatives of dimethylolethanoic acid (A). Protected precursor (B) needs to be addressed synthetically prior to alkylation at the α-carbon.

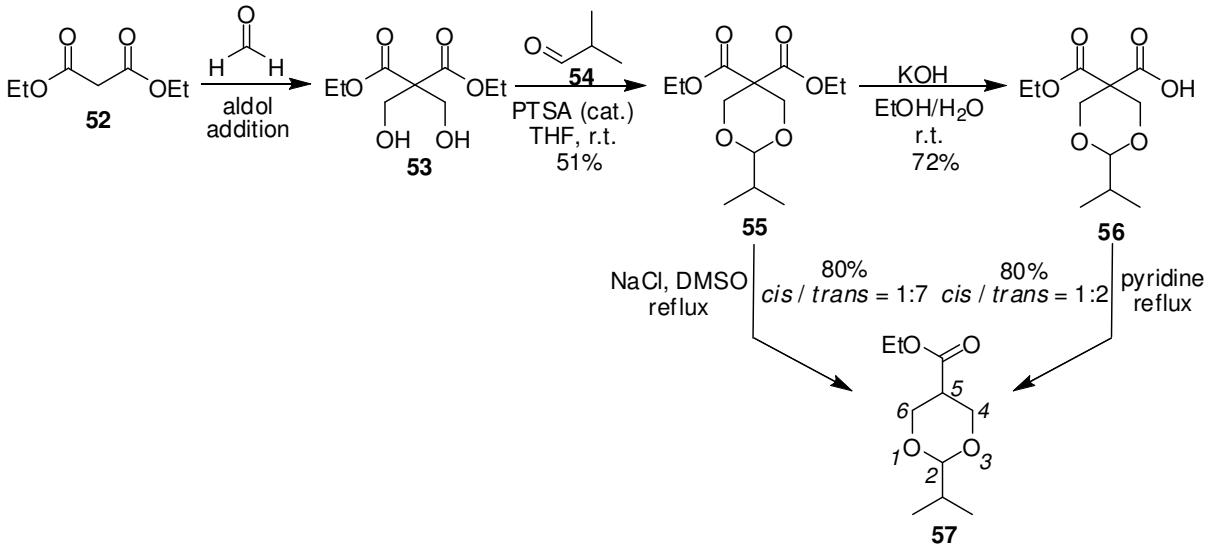
Viewed retrosynthetically, precursor **B** can be derived from **D** via decarboxylation. As **B** is symmetric, the addition of a functional group can be applied here without destroying the overall C_s-symmetry. Geminal diester **D** in turn, can be obtained by hydroxymethylation of malonate **E** followed by protection of the 1,3-dihydroxyl groups (Scheme 15).



Scheme 15: Retrosynthetic analysis of precursor **B**.

The forward synthesis started from key compound **53** that is readily and is easily prepared by a two-fold aldol addition of formaldehyde to diethyl malonate **52**.[109] Similarly to compound **42**, the free hydroxyl groups in **53** were protected with isobutyraldehyde **54** to 1,3-dioxane **55**. Selective hydrolysis of di-ester **55** to mono-ester **56** was achieved with an excess of potassium hydroxide in aqueous ethanol at room temperature. Mono-ester **56** was the major product under the employed conditions. In the next step, **56** was decarboxylated to **57** in refluxing pyridine. A more direct access to **57** from geminal diester **55** was obtained by

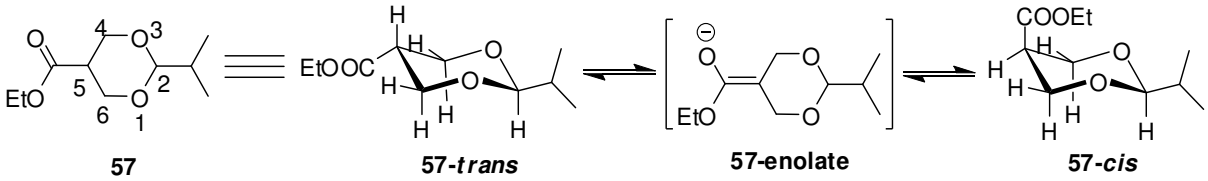
applying the decarbalkoxylation protocol of Krapcho and co-workers[110-111] with sodium chloride in refluxing DMSO (Scheme 16).



Scheme 16: Synthetic route to compound **57** (corresponds to precursor **B** in Schemes 14 and 15).

Before carrying on with the synthetic discussion (see page 22), some additional remarks should be made concerning the 2,5-disubstituted 1,3-dioxane structure of **57**. The conformational analysis of a series of 2-substituted-1,3-dioxane derivatives[112-115] has pointed out the equatorial preference of alkyl and aryl groups located in the acetal part of the 1,3-dioxacyclohexane ring. Because of the shorter C–O bonds in these molecules (1.38 Å[116]; cf. C–C bonds in cyclohexane: 1.54 Å), groups even smaller than *tert*-butyl (e.g. methyl, isopropyl) can be used as anchoring groups at carbon C2.[117] The isopropyl group at C2 in **57** prefers exclusively an equatorial orientation in the ring, whereas the carbethoxy group at C5 can adopt either an axial or an equatorial position, with predominance for the latter. Thus, compounds of type **57** exhibit an anancomeric (i.e. conformationally fixed) structure and the flipping of the heterocycle is strongly shifted towards or locked as the conformer with the hydrocarbon substituents positioned in equatorial orientation. As a result of this, the two diastereomers (specified here as **57-*trans*** and **57-*cis***, Scheme 17) exist only in the boat form with equatorial isopropyl group. The *trans*-isomer (**57-*trans***) is the thermodynamically more stable diastereomer due to the equatorial arrangement of both isopropyl and ester group in positions 2 and 5 of the 1,3-dioxane ring, respectively.[113-115]a In the case of the *cis*-diastereomer (**57-*cis***), the carbethoxy group acquires an axial position whereas the isopropyl group remains anchored to the equatorial position.

[a] The equilibrium constants were measured for 5-(carbomethoxy)-2-isopropyl-1,3-dioxane in diethyl ether and acetonitrile. It is reasonable to assume that the *trans*-isomer of the 5-carbethoxy derivative will also be the more stable. Ref. [61c]



Scheme 17: Compound **57** exists in two diastereomeric forms: *trans*-isomer (both substituents in positions 2 and 5 of the dioxane ring occupy equatorial orientation) and *cis*-isomer(*iso*-propyl group stays fixed to the equatorial position whereas the carbethoxy group is axial). Their interconversion proceeds through the enolate-form.

The configurations of **57-*trans*** and **57-*cis*** were determined by inspection of their ^{1}H NMR spectra. The chemical shifts of selected protons are listed in the table integrated in Figure 9. In the case of **57-*cis***, the equatorial hydrogen at C5 gives a signal at δ 2.273 ppm. The axial orientation of the C5 hydrogen in dioxane **57-*trans*** is characterized by its large vicinal coupling constant (11.3 Hz = $^{3}J(H_{5ax}/H_{4eq}) = {}^{3}J(H_{5ax}/H_{6eq})$) and also by its low field chemical shift (δ 2.960 ppm) which can be attributed to the deshielding effect of the two axial electron pairs on the ring oxygen atoms. In addition to these findings, the configurational assignments of each isomer were corroborated by performing a NOE experiment in the rotating frame (ROESY, mixing time 0.4 sec). As shown in Figure 8 the equatorial H5 in **57-*cis*** shows through-space correlations to both axial *and* equatorial methylene protons (H4, H6) which confirm the equatorial orientation of H5. In contrast, proton H5 in **57-*trans*** signifies spatial proximity only to equatorial protons H4 and H6, thus indicating that H5 must be axial. In **57-*cis*** as well as in **57-*trans*** proton H2 shows NOE correlations to axial H4 and H6. This confirms that H2 adopts an axial orientation in both conformers, i.e. the isopropyl group remains fixed in the equatorial position as a proof of the anancomeric property.

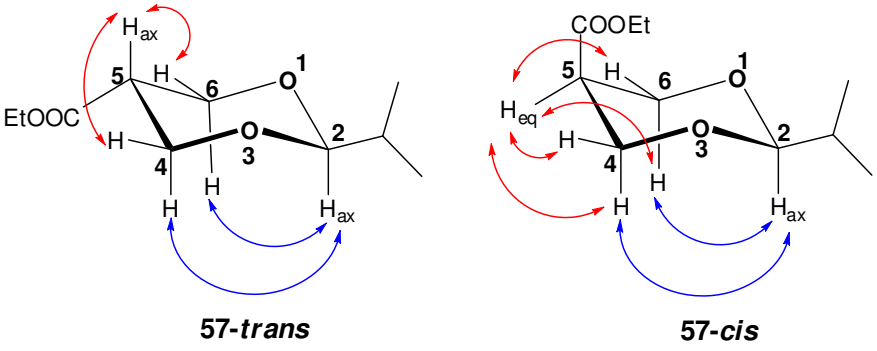
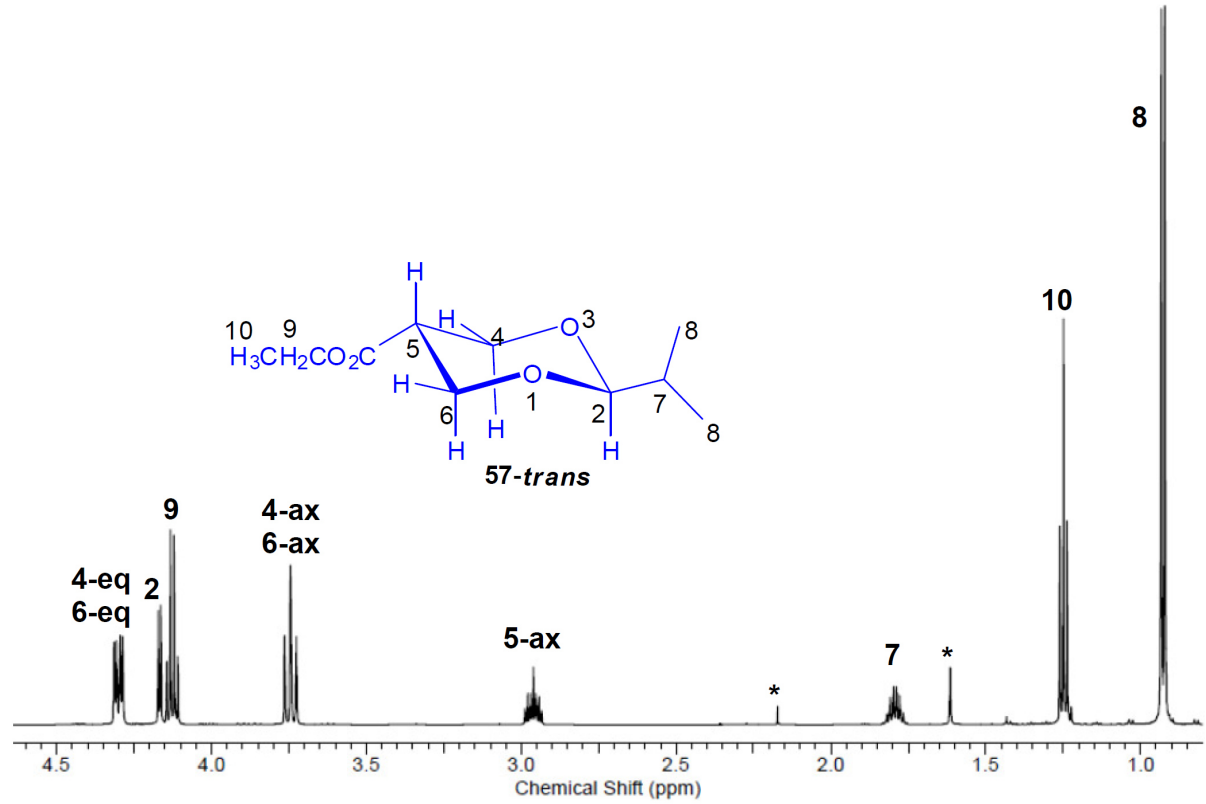
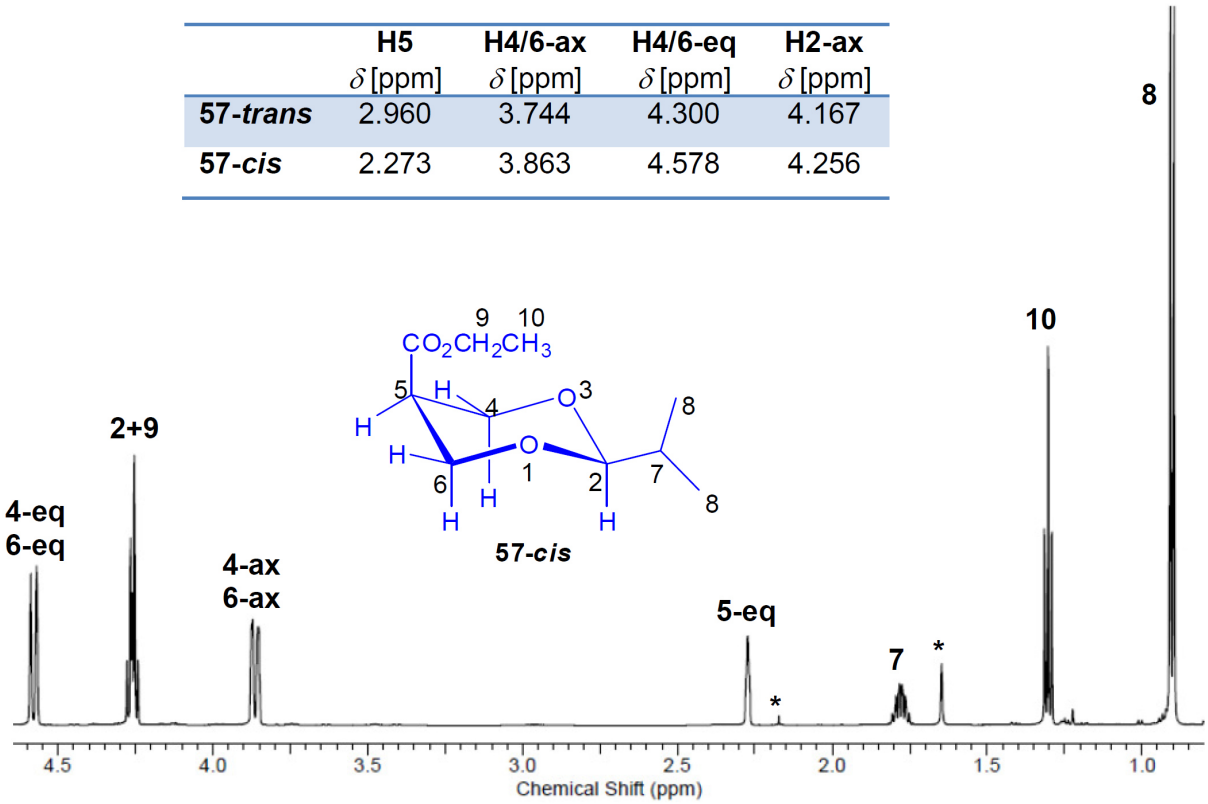


Figure 8: NOE correlations in anancomeric 1,3-dioxanes **57-*trans*** and **57-*cis***. (ROESY, mixR = 0.4 sec)



57-*trans*

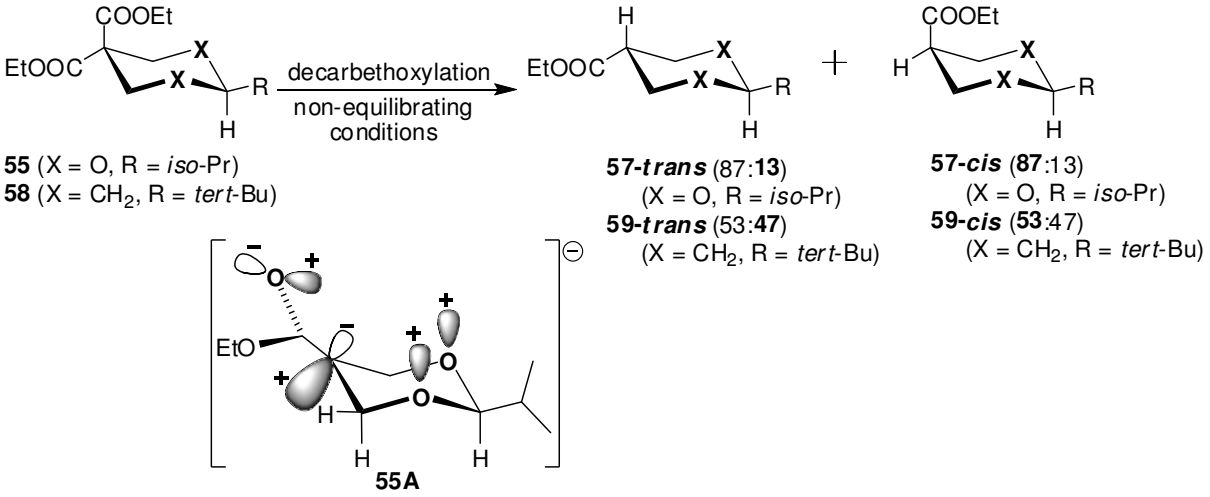
	H5 δ [ppm]	H4/6-ax δ [ppm]	H4/6-eq δ [ppm]	H2-ax δ [ppm]
57-*trans*	2.960	3.744	4.300	4.167
57-*cis*	2.273	3.863	4.578	4.256



57-*cis*

Figure 9: Comparison of the ^{1}H NMR spectra of **54-*trans*** and **54-*cis*** ($CDCl_3$, 400 MHz). (*) is residual solvent; Inserted table shows the chemical shifts of selected protons.

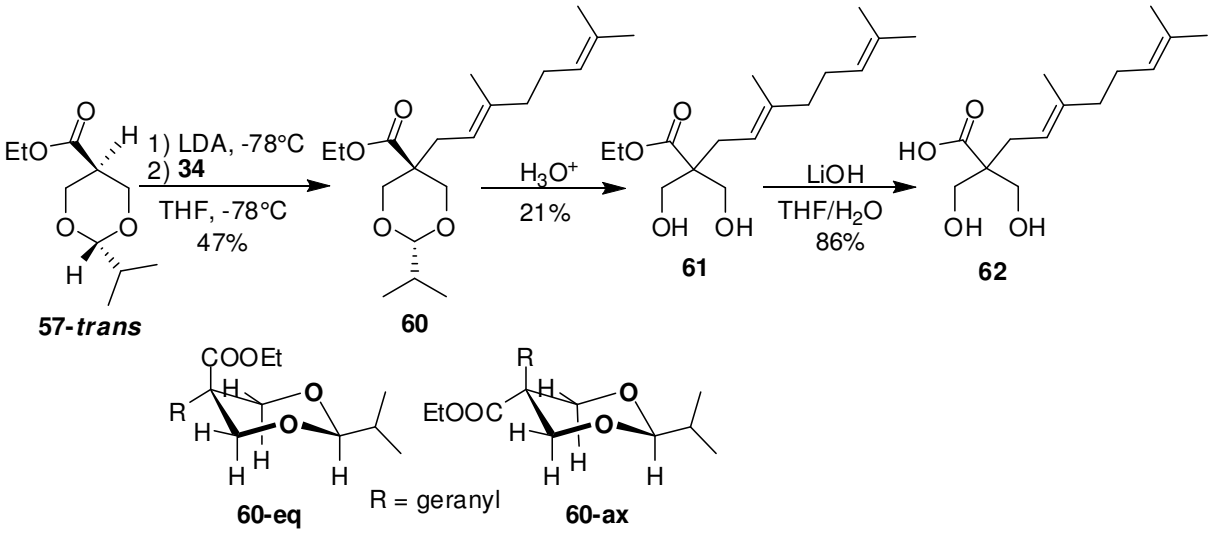
Continuing with the discussion related to Scheme 16 (page 19), decarboxylation of acid **56** in pyridine gave a ratio of **57-*trans*** / **57-*cis*** ~ 2/1 (determined by NMR). Decarbethoxylation of diester **55** using the method of Krapcho[110-111] afforded a ratio of 7/1 (isolated yield) in favour of the *trans*-isomer. These results are in complete agreement with Banks´ report on the decarbethoxylation of 1,3-dioxane diester **55**, which proceeded initially with high preference for the *cis*-isomer but was transformed into the thermodynamically more stable *trans*-isomer at long reaction times because of equilibration. The *early-stage* decarbethoxylated products were formed with high stereochemical control yielding a mixture of *cis* and *trans* monoesters **57-*cis*** and **57-*trans*** in a 87:13 ratio, respectively (Scheme 18).[118]



Scheme 18: Diastereoselectivities observed for the decarbethoxylation of 1,3-dioxane **55** and cyclohexane **58** under non-equilibrating conditions. **55A** represents the HOMO of the intermediately formed ester enolate prior to protonation. Adapted from reference [118].

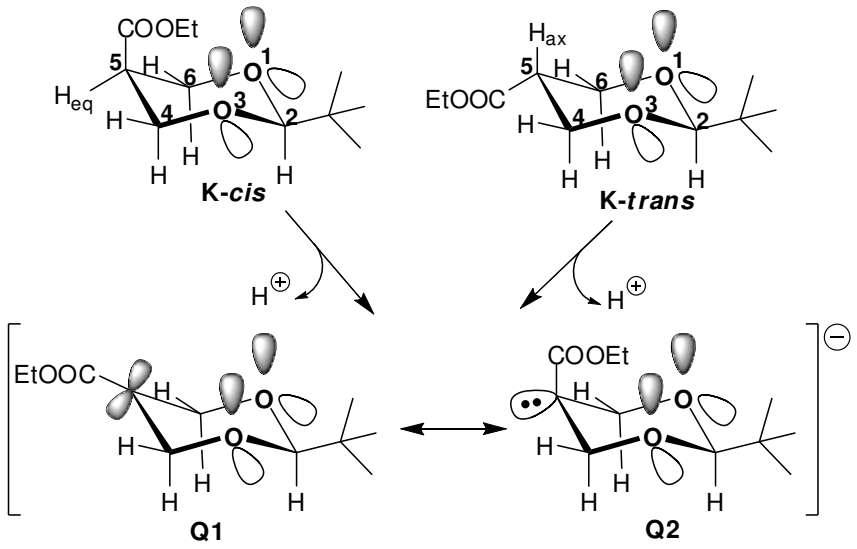
In contrast to 1,3-dioxane **55**, Banks observed that the decarboethoxylation of the corresponding cyclohexane diester **58** was not diastereoselective, giving an approximate 1:1 ratio of *cis* and *trans* ethyl esters **59-*cis*** and **59-*trans***, respectively (Scheme 18).[118] A plausible explanation for the *cis*-stereoselectivities observed for the early (non-equilibrated) decarbethoxylation products of 1,3-dioxanes is provided by Banks whose arguments are backed by the work of Klein[119-120]: "Attack on the [ester enolate] **55A** takes place preferentially from the equatorial direction. The HOMO of this carbanion has antibonding interactions on its upper face of the axial non-bonding electron pair on the ring oxygens, producing an accumulation of electron density below the plane of the intermediate."[118]

Carrying on with the discussion towards the synthesis of target compound **62**, the enolate of ethyl ester **57** was generated with LDA in THF at –78°C and alkylated at its α-carbon with geranyl bromide **34** to yield compound **60** (Scheme 19).



Scheme 19: Synthetic route to target compound **62** starting from key building block **57-*trans***. Upon alkylation of **57-*trans***, two isomers can be formed: **60-eq** (the introduced alkyl group occupies an equatorial position) and **60-ax** (alkyl group is axial). As discussed in the text below, alkylation at the equatorial position is kinetically favored due to the influence of stereoelectronic effects.

As reported by Deslongchamps and Ndibwami[121] the alkylation of the enolate of 5-ester-substituted 1,3-dioxanes proceeds with high stereochemical control in preference for the equatorial isomer (e.g. **60-eq**) which hypothesizes an equatorial approach of the alkylating agent as explained above for proton addition. Also the preceding deprotonation is different for the diastereomers. The authors provide an explanation of this assumption by taking into account stereoelectronic effects: "At the transition state level for deprotonation, the *cis*-isomer **K-*cis*** with an equatorial hydrogen at C5 ought to be more readily deprotonated than the *trans*-isomer **K-*trans*** which has an axial hydrogen at C5 (Scheme 20).

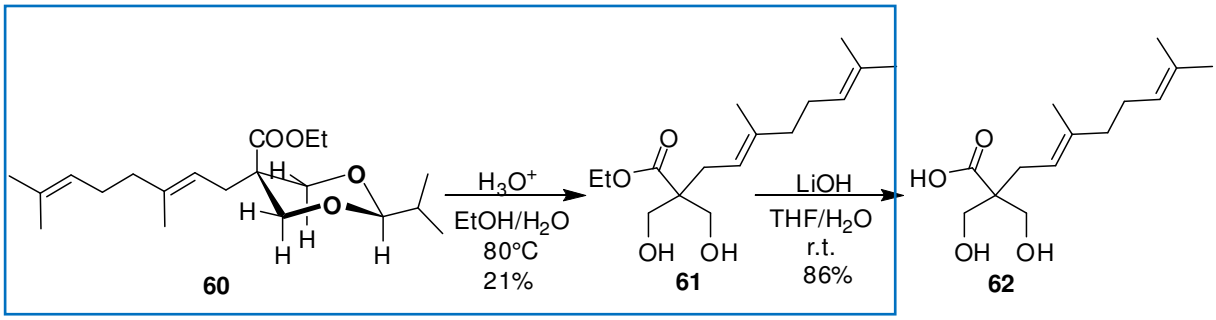


Scheme 20: Difference in deprotonation rates of ananchomers **K-*cis*** and **K-*trans***. The resulting anion is represented by its mesomeric structures **Q1** and **Q2**. Adapted from reference [121].

In the *cis*-isomer **K-*cis***, the equatorial C5–H bond to be broken is antiperiplanar to the polar C4–O3 and C6–O1 bonds, whereas in **K-*trans*** the axial C5–H bond is antiperiplanar to the nonpolar axial C4–H and C6–H bonds. Thus, in **K-*cis*** the electron pair orbital of the equatorial C5–H bond can be delocalized by an interaction with the antibonding orbital (σ*) of two polar C–O bonds. This electronic delocalization should therefore increase the acidity of the equatorial C5 hydrogen, and deprotonation of the *cis*-isomer **K-*cis*** (to give the corresponding enolate anion being a hybrid of **Q1** and **Q2**) should proceed at a faster rate than that of the *trans*-isomer **K-*trans***. Furthermore, the cyclohexane esters are much less acidic then the corresponding 1,3-dioxane esters, and this striking results indicates that the replacement of two methylene groups by two oxygen atoms in the cyclohexane ring shows an enormous influence in the ease of proton abstraction. This is attributed to the inductive effect of the oxygen atoms, which increase the acidity of both the equatorial and axial hydrogen at carbon C5."[121]

Reasoning about the moderate yields obtained from the alkylation reaction of **57-*trans***:
The major product of the decarboxylation/decarbethoxylation reaction, conducted under equilibration conditions, was the *trans*-isomer **57-*trans***. As already mentioned, its α-proton (H5) occupies an axial orientation. According to Deslongchamps[121] (see foregoing paragraph), this axial proton is less acidic than the equatorial H5 in the corresponding *cis*-isomer, thus proton abstraction takes place at a slower rate. During the experiment, **57-*trans*** was exposed to base (LDA) for only twenty minutes before the alkylating agent was added. Therefore, it is most likely that this period was not sufficient enough for complete deprotonation of **57-*trans***. This explains why mostly starting material was recovered, along with low amounts of desired product **60** (Scheme 19). For the future, longer reaction times should be allowed to guarantee complete enolate formation.

With compound **60** in hands, the next step was the removal of the acetonide group to provide 1,3-diol **61** (Scheme 21A). The deprotection step proved more complex than expected. Indeed, **60** was quite resistant towards acid-catalyzed acetal cleavage. For this reason different conditions were investigated (Table 2) and a preliminary solution was to heat up acetal **60** for prolonged times under acidic conditions in a mixture of ethanol/water (2/1). Ethanol was chosen as a co-solvent mainly for two reasons: (a) to solubilize acetal **60** since it is insoluble in pure water, and (b) to avoid transesterification reactions that may occur in the case of other alcohols.



Scheme 21A: Synthetic route to compound **62** (continued). Full deprotection (acetal cleavage + ester hydrolysis) of intermediate **60** provided desired product **62**. A detailed description of the highlighted transformation (blue box) is given in the text and in Table 2.

H^+ source	Solvent	Temperature	Reaction time	Outcome
Amberlite IR-120	$EtOH/H_2O$	room temp.	1h, 2h, 24h	**60** (no cleavage)
		80-100°C	14h	**60** + **61** + byproducts
Dowex 50WX2	$EtOH/H_2O$	room temp.	1h, 2h, 24h	**60** (no cleavage)
		80-100°C	1h, 2h, 6h, 24h	**61** + byproducts
HCl (37%)	$EtOH/H_2O$	80°C	1h, 2h, 6h, 2d	**61** + byproducts

Table 2: Screening of conditions for the acid-catalyzed cleavage of acetal **60**.

The progress of the reaction was monitored by ESI-MS. Eventually, **60** was completely consumed and desired 1,3-diol **61**, accompanied by other byproducts, was assured by mass. RP-HPLC analysis of the crude reaction mixture (after complete consumption of **60**) showed a bunch of peaks (Figure 10). Two out of these side-products were well pronounced, so they were isolated and their structure was characterized by HRMS and NMR spectroscopy (Table 3). In any of the conditions listed in Table 2, no product **62** resulting from acid-catalyzed ester hydrolysis was observed.

RP-HPLC		Cmpd.	HRMS analysis	Structural features at C7	^{13}C-NMR δ[ppm] for C7
Peak	t_R [min]				
A	10.9	**63**	$[C_{16}H_{30}O_5+Na]^+ \equiv [\mathbf{61}+H_2O]^+$	3° ; alcohol	70.87
B	14.5	**64**	$[C_{18}H_{34}O_5+Na]^+ \equiv [\mathbf{61}+EtOH]^+$	3° ; ether	74.28
C	15.5	**61**	$[C_{16}H_{28}O_4+Na]^+$	4° ; olefinic	131.66

Table 3: Analytical data related to compounds **61**, **63** and **64**. Cf. HPLC chromatogram in Figure 10.

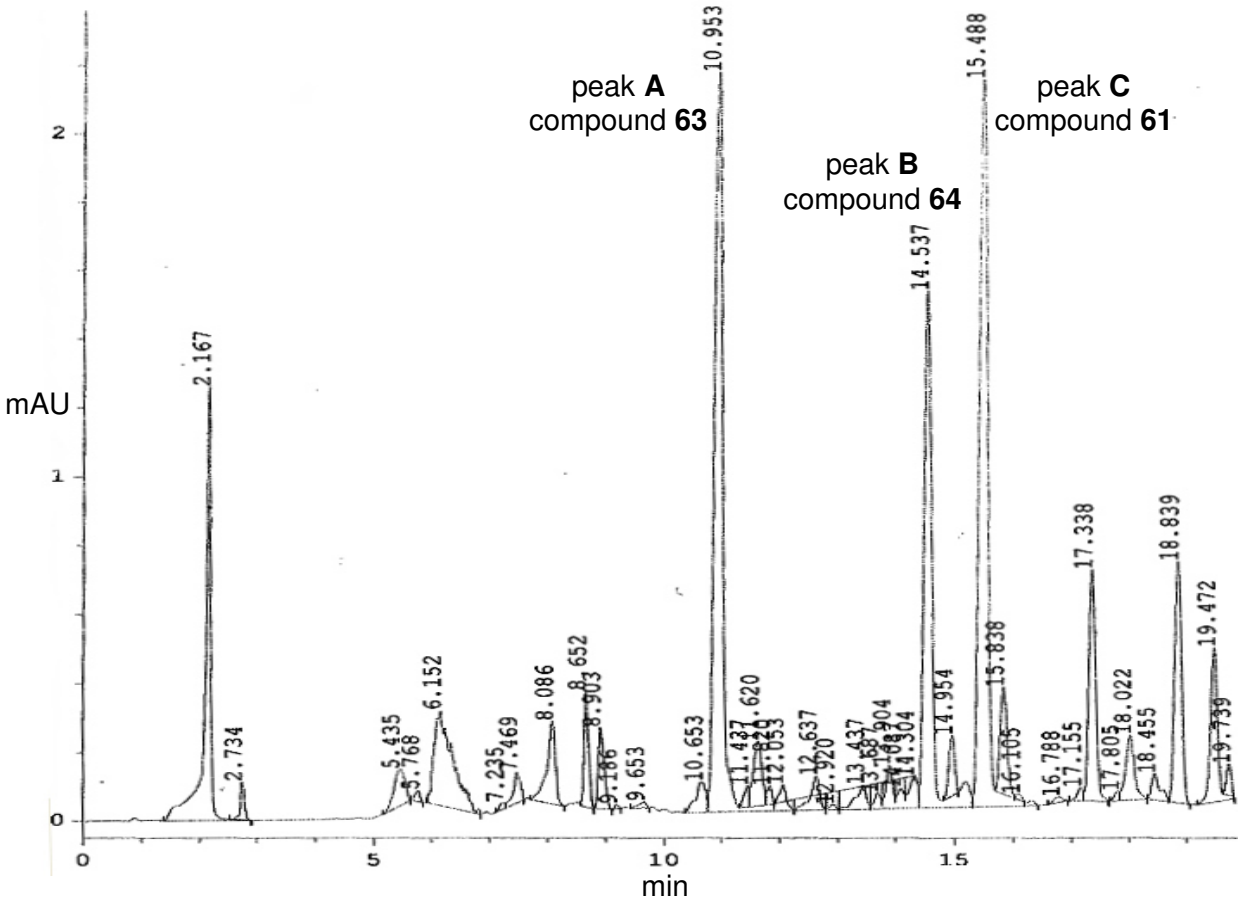
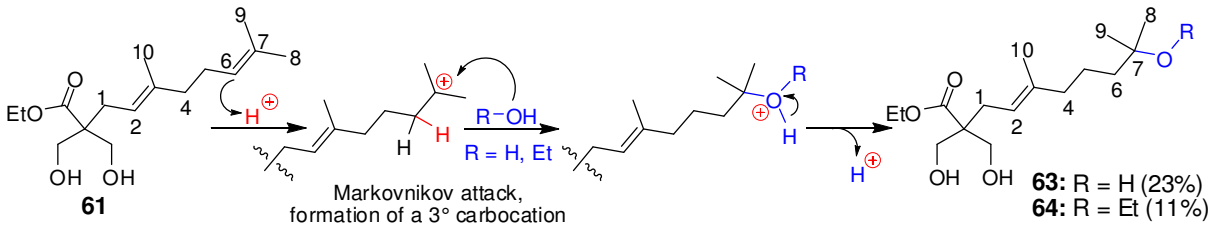


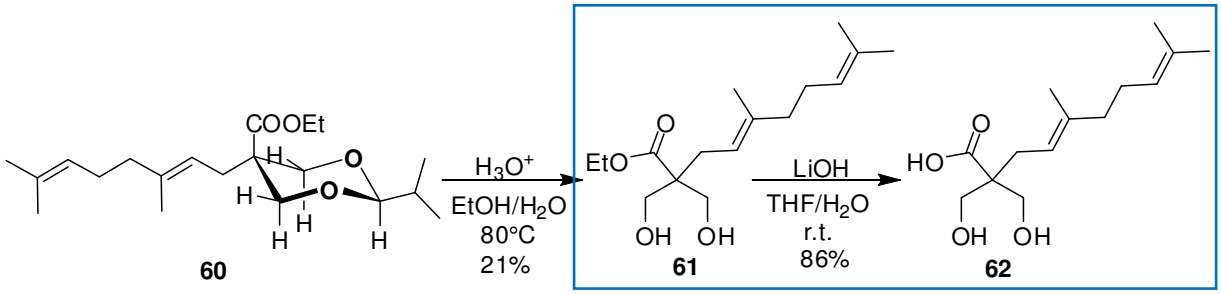
Figure 10: RP-HPLC chromatogram showing the crude product mixture resulting from the transformation shown in Scheme 21A. (Conditions: H_2O + ACN; 2% ACN –(17 min)→ 87% –(1 min)→ 100%; 4 mL/min; λ = 210 nm; column: YMC-Pack 150-10; ODS-A 120 Å, 5 µm; measured on: Knauer Wellchrom ("K2"), see chapter 5.2)

As it becomes evident, the terminal double bond of the geranyl chain presented a higher reactivity towards electrophilic attack than the acetal: the identified compounds **63** and **64** were the inevitable side-products formed from the acid-catalyzed addition of water and ethanol to the olefinic double bond (C6/C7) of the prenyl chain, respectively (see also compounds **20**, **145** and **168**). The mechanism of formation is illustrated in Scheme 22.



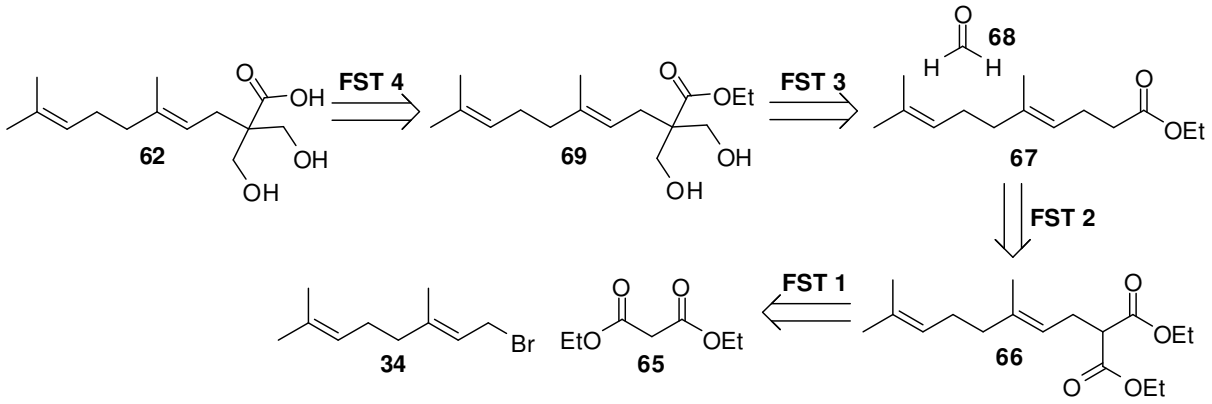
Scheme 22: Acid-catalyzed addition of water and ethanol to the C6/C7 double bond of the geranyl chain results in the formation of byproducts **63** and **64**, respectively.

The final step in the synthesis of compound **62** was the hydrolysis of the ester group (Scheme 21B). Thus, ethyl ester **61** was saponified under mild conditions to yield the target compound **62** in 86% yield.



Scheme 21B: Synthetic route to compound **62** (continued). Full deprotection (acetal cleavage + ester hydrolysis) of intermediate **60** provided desired product **62**. A detailed description of the highlighted transformation (blue box) is given in the upper paragraph.

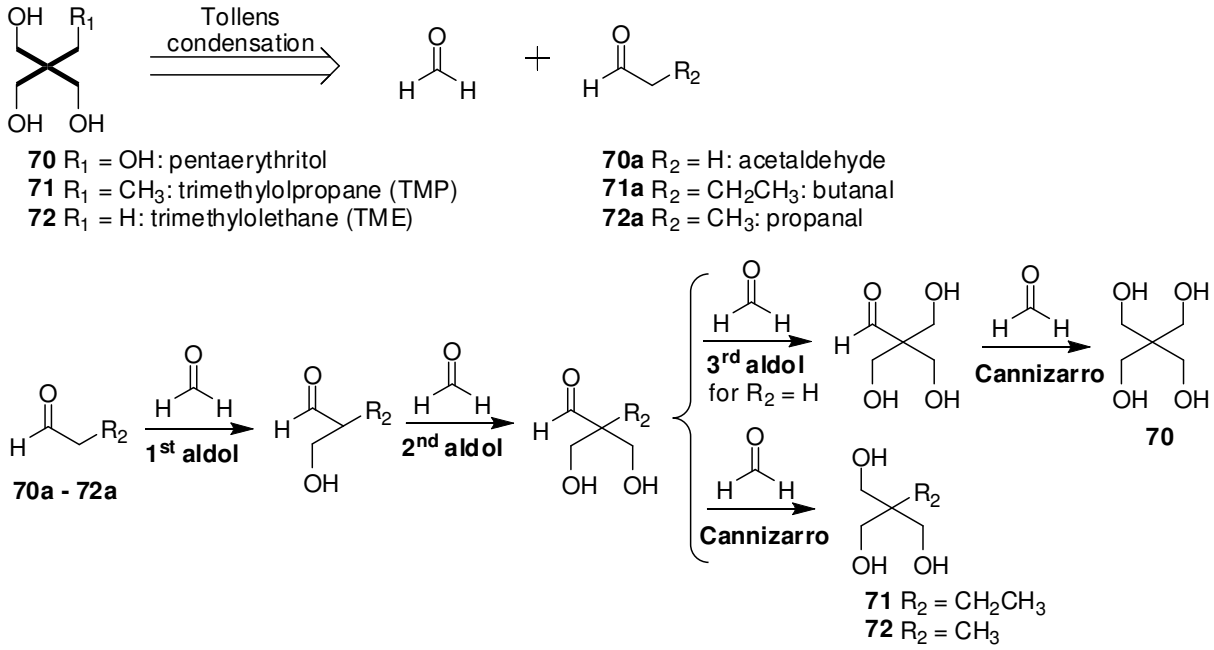
As the aforementioned synthetic route proved to be only moderately successful, in the following an alternative new route to target molecule **62** is suggested. The synthetic scheme is represented from a retrosynthetic point of view (Scheme 23). The respective forward synthetic transformations (**FST**) will be discussed briefly.



Scheme 23: Retrosynthetic analysis of compound **62**. The corresponding forward synthetic transformation steps (**FST**) are discussed within the text. The efficiency of this synthetic route remains to be explored in the lab.

Alkylation of diethylmalonate **65** with geranyl bromide **34** (**FST 1**; see Section 3.2.2.1) and successive Krapcho-decarbethoxylation (**FST 2**) readily provides ester **67** which is a two-carbon homologue of geraniol. Subsequent two-fold aldol addition of formaldehyde **68** to the α-carbon of **67** (**FST 3**) readily provides ethyl ester **69**. Its hydrolysis under mild conditions with alkli base (e.g. LiOH in THF/H_2O) completes the synthesis of target compound **62** (**FST 4**). The extent to which this logical reaction sequence is suitable for the delivery of compounds like **62** still remains to be investigated experimentally.

Closely related to the transformation **FST 3** in Scheme 23 is the technical preparation of pentaerythritol **70**, trimethylolpropane (TMP) **71** and trimethylolethane (TME) **72** (Scheme 24). The main feature of these compounds is the compact arrangement of three or four primary alcohol groups in a neopentyl backbone. These polyols find broad industrial applications as versatile building blocks for the preparation of many polyfunctionalized compounds. Their syntheses consist basically in a two-fold (for **71** and **72**) or three-fold (for **70**) mixed aldol addition of formaldehyde to the corresponding alkyl aldehyde (**70a**–**72a**) followed by a crossed Cannizarro reaction in which the aldehyde function is reduced to a primary alcohol by formaldehyde in a disproportionation reaction. The complete sequence comprising both aldol addition and Cannizarro reaction is also known as the Tollens condensation[122].



Scheme 24: Industrial synthesis of pentaerythritol **70**, trimethylolpropane **71** and trimethylolethane **72** by the Tollens condensation. The neopentyl carbon scaffold that all of these compounds have in common is highlighted in bold lines.

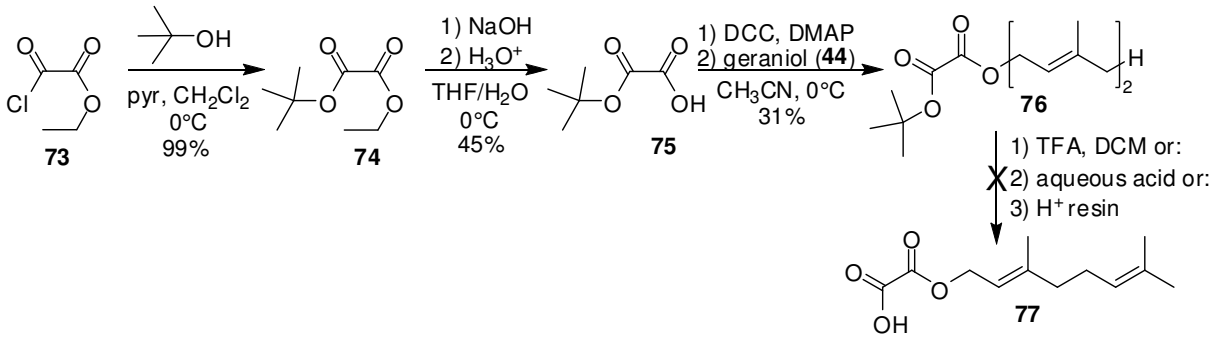
3.2 Derivatives of dicarboxylic acids

3.2.1 Mimetics derived from 1,2-dicarboxylic acids

3.2.1.1 Surrogates of oxalic acid

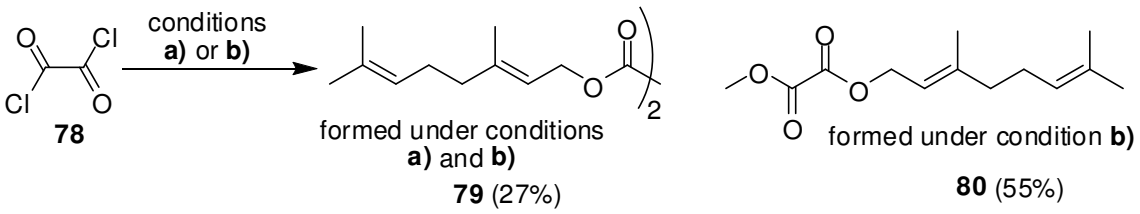
In the following, two approaches towards the synthesis of ethanedioic acid monogeranyl ester **77** were examined. The first one considers the application of orthogonal protection groups (Scheme 25), whereas the second one makes use of a direct approach (Scheme 26).

As shown in Scheme 25, commercially available acyl chloride of oxalic acid monoethyl ester **73** was reacted with *tert*-butanol to provide mixed di-ester **74**.[123-125] The base-sensitive and sterically less demanding ethyl ester was hydrolyzed regioselectively to free carboxylic acid **75**[126-127] which in turn was esterified under standard Steglich conditions with geraniol **44** to give di-ester **76**. Unfortunately, several attempts at various conditions to selectively cleave off the *tert*-butyl ester in **76** by means of acid-catalyzed E_1-elimination of isobutene turned out to be problematic and resulted in a complex mixture of decomposition products.



Scheme 25: Approach to the preparation of geraniol derived oxalic acid **77** by using an orthogonal protection group strategy. However the final deprotection step **76** → **77** failed.

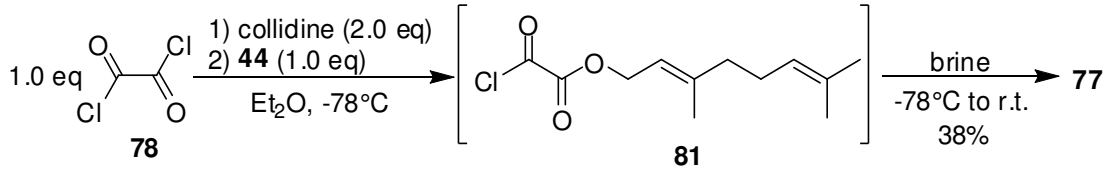
The direct approach aimed at the one-side esterification of oxalyl chloride **78** with geraniol **44** followed by hydrolysis of the free acyl chloride. However, no free acid **77** could be isolated. As shown in Scheme 26, the major products obtained from the conditions employed were symmetrical diester **79**, and unexpectedly, methyl ester **80** (δ 3.902 ppm for CO_2CH_3). The formation of **80** remains a mystery, since no methanol was used at all (Note: the reaction using condition **b** was performed only once. To check if methyl ester **80** was really formed without the presence of methanol, the reaction should be repeated in order to exclude any doubts of a possible contamination of reaction solvents by methanol).



a) (i) **78** (2.0 eq), **44** (0.9 eq), CH_2Cl_2, pyridine (5.0 eq), -78°C; (ii) brine/H_2O
b) (i) **78** (4.0 eq), **44** (1.0 eq), CH_2Cl_2, collidine (1.5 eq), -30°C; (ii) brine/H_2O

Scheme 26: Products obtained upon reacting oxalyl chloride **78** with geraniol **44** under reaction conditions a) and b).

Slight modifications to the upper conditions afforded finally the desired mono-acid **77** as a viscous oil. Thus, oxalyl chloride **78** and geraniol **44** were reacted in diethyl ether at low temperatures with collidine as proton scavenger. Subsequent hydrolysis of the intermediate acyl chloride species **81** yielded **77** in 38% yield (Scheme 27).



Scheme 27: Synthetic route to geraniol derived oxalic acid **77**.

Despite repeated purification cycles by HPLC, compound **77** suffers from instability problems and decomposes upon time, especially in solution. Hence, any further re-purification efforts would not result in a product of a higher purity.

Closely related to oxalic acid **82** are pyruvic acid **83** and glyoxylic acid **32** (see section 1.2.1). They all feature an α-oxo structure (Figure 11). Whereas oxalic acid **82** is a symmetric 1,2-dicarboxylic acid, pyruvic acid **83** is formally acetyl formic acid. The somewhat elaborate synthesis of geranyl-derived pyruvic acid **84** has been reported by Toste et al.[128]

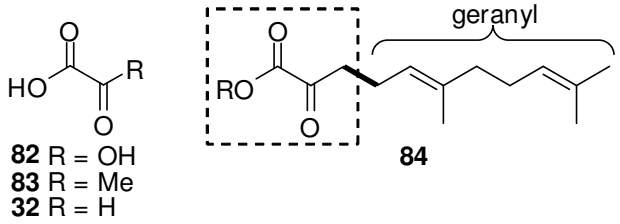
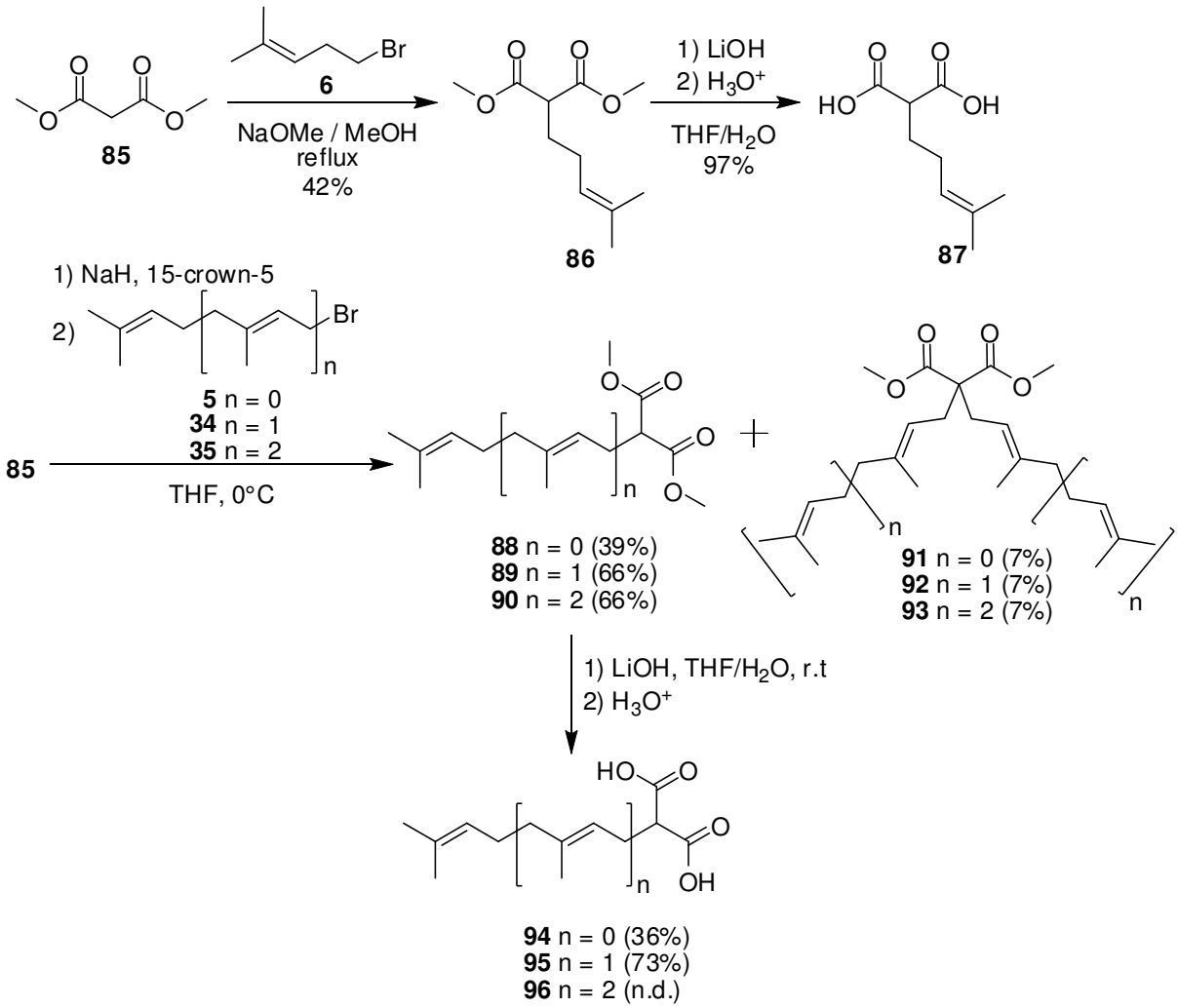


Figure 11: Comparison of three different α-oxo carboxylic acids: oxalic acid **82**, pyruvic acid **83** and glyoxylic acid **32**. Compound **84**[128] exemplifies a geranylated derivative of **83**.

3.2.2 Mimetics derived from 1,3-dicarboxylic acids

3.2.2.1 Surrogates of malonic acid

Since isoprenyl halides are readily available and good electrophiles, the most attractive and used approach for the synthesis of alkyl derived malonates involves alkylation of the anion of commercially available malonate esters.



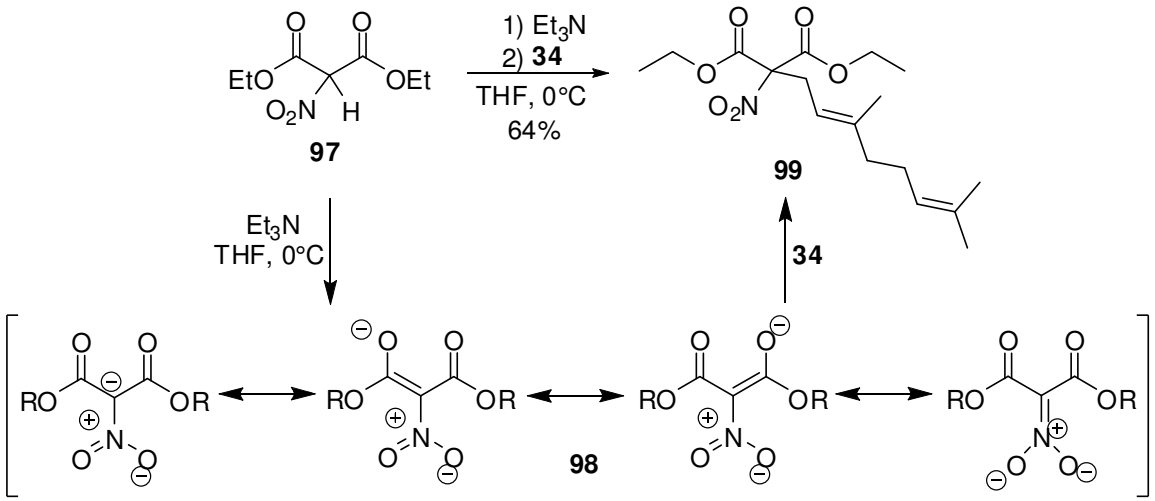
Scheme 28: Synthetic route to mono- and bis-alkylated malonic acid derivatives.

For the synthesis of the short chain diphosphate mimetics **87** and **94**, dimethyl malonate **85** was deprotonated and alkylated in the usual manner with homoallylic bromide **6** and allylic bromide **5**, respectively. Saponification of the corresponding diesters **86** and **88** followed by a careful acidification afforded the desired β-dicarboxylic acids **87** and **94** (Scheme 28).

The longer chain substrates **95** and **96** were designed with a geranyl (C_{10}) and a farnesyl (C_{15}) chain, respectively. Their synthesis also started from **85**, however the alkylation protocol was modified, due to avoid the use of sodium metal and the necessity of preparing fresh sodium methoxide solution for each reaction. This was circumvented by treating compound **85** with sodium hydride, 15-crown-5, and geranyl bromide **34** in an aprotic solvent (THF) at 0°C. The reaction outcome provided a mixture of mono- and disubstituted malonic esters **89** and **92**. When the ratio of base and prenyl halide relative to **85** was kept low, the major product was the monoalkylated compound **89** while a high ratio favoured the formation of dialkylated product **92**. Farnesylated compounds **90** and **93** were prepared in an analogous way. Once the desired set of monoalkyl malonic esters (**88**–**90**) had been generated, ester hydrolysis under mild conditions was accomplished with lithium hydroxide in a solvent system of THF/H_2O, followed by an acidic workup to afford the corresponding malonic acids.

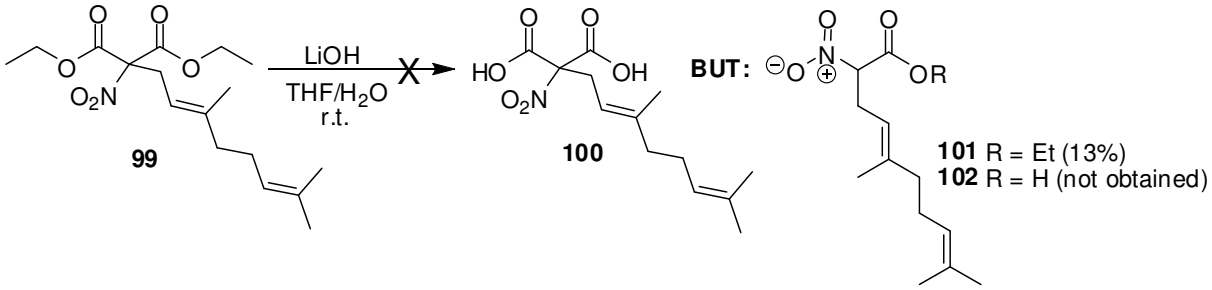
3.2.2.2 Surrogates of nitromalonic acid

In analogy to the previously discussed examples in section 3.2.2.1, nitromalonic acid diethyl ester **97** was alkylated with geranyl bromide **34** (Scheme 29). Since the α-proton in **97** is surrounded by three strong electron withdrawing groups (2x ester + 1x nitro group) it is exceptionally acidic (pKa ~6.5; cf. pKa ~13 of diethyl malonate) and can easily be removed by much weaker bases than alkali metal alkoxides or hydrides. For this reason, triethylamine was chosen as a base in the following synthesis. The resulting enolate anion **98** is well resonance-stabilized (Scheme 29) and features, due to the –M-effect of the nitro group, one additional mesomeric structure compared to the enolate of malonic ester **85**.



Scheme 29: Synthetic route to geraniol derived nitromalonic acid diethyl ester **99**. The nitromalonate anion **98** is well resonance stabilized.

Several attempts to saponify the two ester groups in **99** failed. HPLC and NMR analysis showed the major product to be **101** and not **100** (Scheme 30). Apparently, as soon as one of the ester groups in **99** becomes hydrolyzed, it decarboxylates either spontaneously, or nitro-group-assisted to nitroester **101**.



Scheme 30: Saponification of geranylated nitromalonic acid diethyl ester **99** provided monoester **101** as the only product. Products **100** and **102** were not observed.

Since **100** could not be isolated because of instability problems, the attention was focused on the preparation of nitroacid **102**. For this purpose, compound **101** was selectively synthesized by alkylation of ethyl nitroacetate with halide **34**. Disappointingly, the yields of the alkylation were rather poor. Various attempts to hydrolyze the ester function in **101** with alkali base were without success. HPLC monitoring of the reaction revealed complete disappearance of the starting material **101** (t_R = 18.3 min) and the occurrence of a new peak at t_R = 17.4 min (Figure 12).

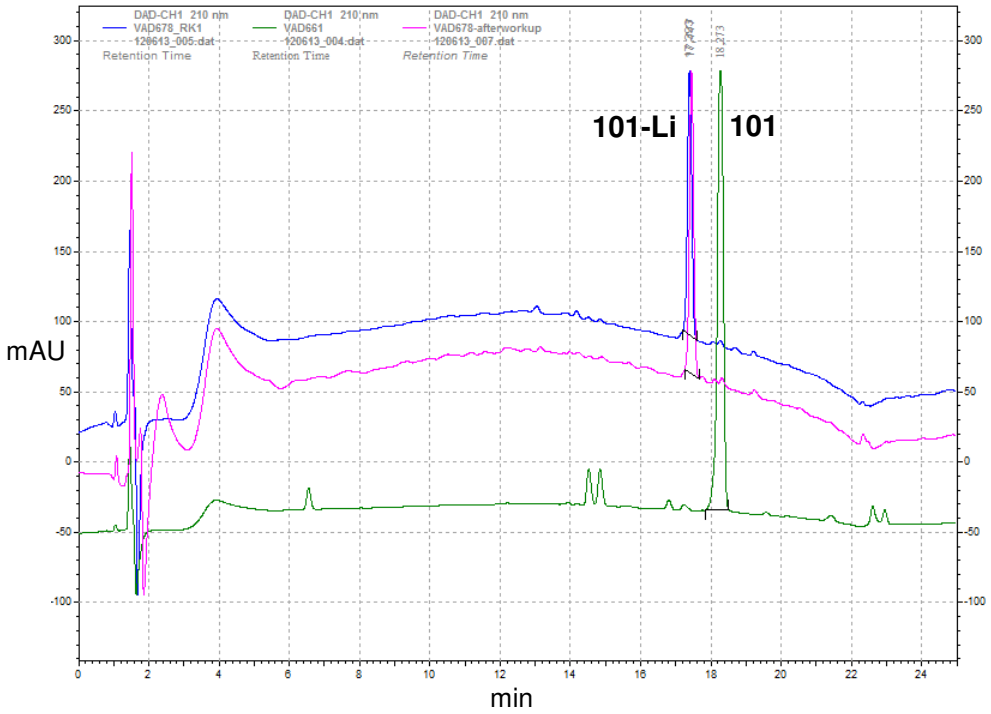
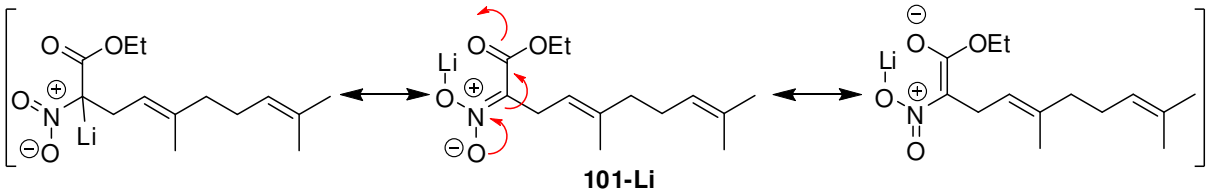


Figure 12: RP-HPLC chromatogram of starting material **101** (t_R = 18.3 min) before hydrolysis (green line). Exposing **101** under conditions for alkaline hydrolysis (LiOH/THF/H_2O) furnishes lithium salt **101-Li** (t_R = 17.4 min). Control sample taken from the reaction mixture (blue line) and after acidic work-up (pink line). (Conditions: (CH_3CN/H_2O) + 0.1% HCO_2H; 2% CH_3CN –(20 min)→ 100%; 1.0 mL/min; λ = 210 nm; column: LiChroCART® 125-4 ; LiChrospher® 100 RP-18 (5µm); measured on: VWR LaChrom Elite (“Mary”), see chapter 5.2).

LC-MS analysis of this peak revealed the new peak to be the more polar Li-salt ester **101-Li**. It showed an unexpected robustness towards alkaline hydrolysis, presumably because of its resonance-stabilized nature (Scheme 31).



101-Li

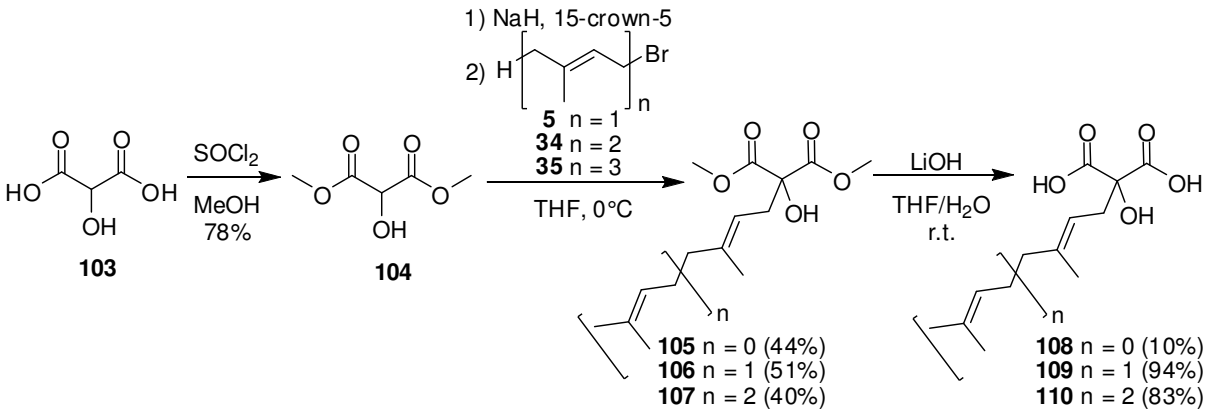
Scheme 31: Representation of the resonance structures of **101-Li**.

In the case some hydrolysis of the ester group in compound **101** occurs, the resulting α-nitro carboxylate probably is prone to decomposition. In agreement with this assumption is the fact that free nitroacetic acid (CAS 625-75-2) *cannot* be obtained commercially from any common chemical suppliers (e.g. Aldrich, AlfaAesar, TCI, ABCR, Acros Organics). A solution would be to use esterase to evoke hydrolysis.

3.2.2.3 Surrogates of tartronic acid

3.2.2.3.1 *C*-alkylated derivatives of tartronic acid

Closely related to the prenylated analogues of malonic acid (Section 3.2.2.1) are the derivatives of tartronic acid **103**, formally known as 2-hydroxymalonic acid (Scheme 32). Alkylation at carbon C2 with prenyl halides of different chain lengths (**5, 34, 35**), was carried out under the same conditions as previously described for the alkylation of malonic acids. The reaction sequence started from commercially available **103** which was protected as its dimethyl ester **104** prior to alkylation. Subsequent base induced hydrolysis of prenyl tartronic diesters **105-107** afforded the desired 2-isoprenyl-2-hydroxymalonic acids **108-110** in good yields.



Scheme 32: Synthetic route to *C*-alkylated isoprenyl derivatives of tartronic acid.

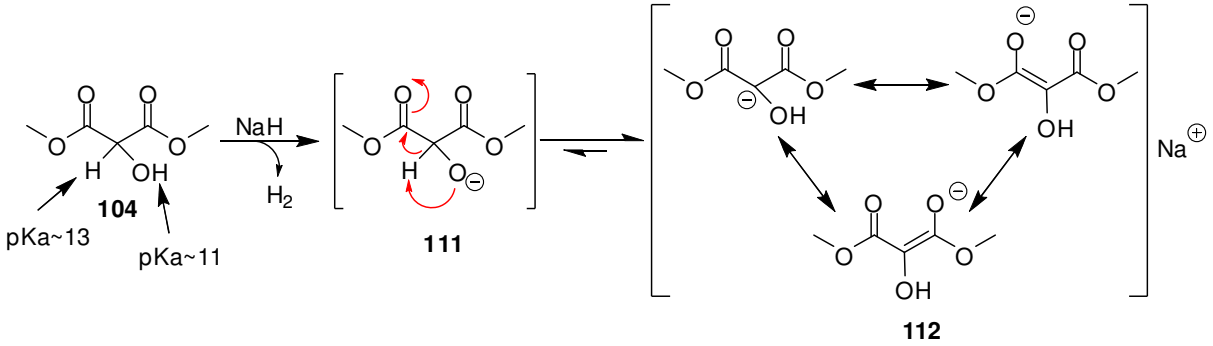
An interesting aspect was also to see if any *O*-alkylated product had also been formed under the applied reaction conditions. Since sodium hydride is a strong base, it is thinkable that the hydride ion is not only capable of abstracting the tartronic α-CH proton (pKa ~13[2]) but also the slightly more acidic proton of the hydroxyl group (pKa ~11[2]). Thus, deprotonation of the alcoholic function would generate an alkoxide ion whose trapping with a reactive alkyl halide would result in an alkyl ether. Surprisingly, no *O*-alkylated products were observed. NMR analysis of the isolated compounds **105-110** indicated clearly *C*-alkylation: In the ^{1}H NMR spectrum, tartronic acid dimethyl ester **104** shows one doublet (4.76 ppm, J = 8.4 Hz) for the acidic α-proton and another doublet (3.53 ppm, J = 8.4 Hz) for the hydroxyl proton. In contrast, alkylated compounds **105-107** exhibit only a singulet at 3.70 ppm for the hydroxyl proton. In addition, alkylation in favor of the *C*-alkylated product was further substantiated by inspection of the corresponding ^{13}C DEPT NMR spectra: whereas the α-carbon in **104** is tertiary, in compounds **105-107** it is quaternary (Table 4).

	^{1}H NMR ($CDCl_3$, 400 MHz)		^{13}C NMR ($CDCl_3$, 100 MHz)	
compound	**α-CH proton** δ [ppm]	**Hydroxyl proton** δ [ppm]	**α-C carbon** δ [ppm]	**DEPT-135**
104	4.76	3.53	71.26	CH
105	---	3.70	78.97	C_q
106	---	3.70	78.98	C_q
107	---	3.70	78.99	C_q

Table 4: Comparison of the ^{1}H and ^{13}C NMR chemical shifts of compounds **104-107** visualizing the chemo- and regioselectivity (*C*- vs. *O*- alkylation) of the substitution reaction shown in Scheme 32. DEPT analysis provides information about the number of carbon neighbors attached to the α-carbon.

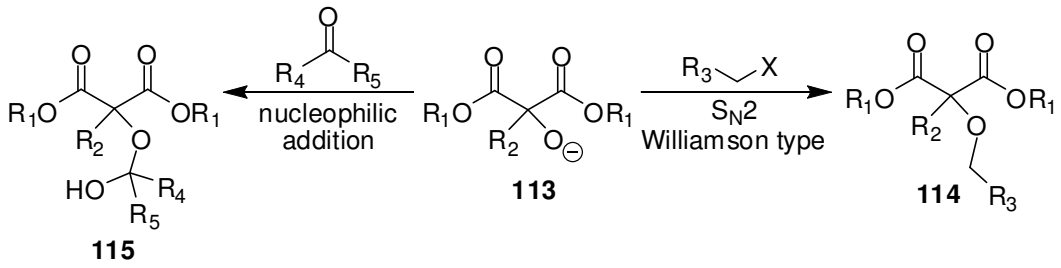
[2] Calculated with the pKa prediction tool of ACD/Labs (10.0).

The main reason for these findings can be explained as follows: the hard hydride ion (pKa of its conjugate acid is ~35[129]) abstracts the more acidic alcoholic hydrogen first, thus leading directly to alkoxide **111** (Scheme 33). However, species **111** is energetically less favorable since the negative charge resides on oxygen alone (hard nucleophile) without any stabilization by resonance. Consequently, it is very likely that strongly nucleophilic **111** abstracts the geminal α-proton of this or another tartronate and interconverts into the energetically more stable enolate **112** which is well stabilized by charge delocalization (Scheme 33).



Scheme 33: Proton abstraction from tartronate **104** with one equivalent of base generates resonance-stabilized enolate **112** which provides C-alkylated products upon alkylation.

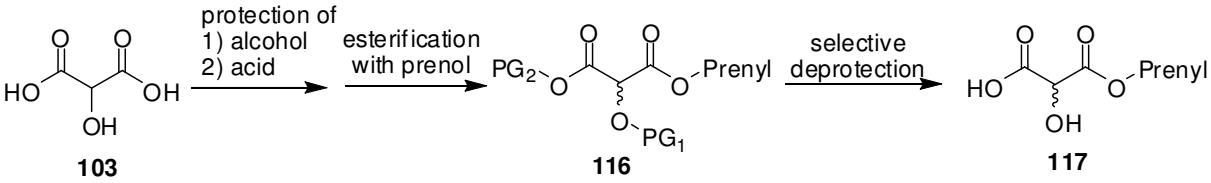
In the case of 2-alkyl/aryl-1,3-alkoxy-1,3-dioxopropanolates **113**, there is no α-acidic hydrogen available any more that can be abstracted to generate an anionic species of stabilizing resonance energy. Thus, the "naked" alkoxide ion can either attack primary alkyl halides in polar aprotic solvents to yield the corresponding ether derivatives **114**, or it can undergo nucleophilic addition to the carbonyl function of other molecules to give acetals (or esters) of type **115** (Scheme 34). Intermolecular self-condensation of **113** may lead to transesterification products.



Scheme 34: Alkoxides **113** can either react with primary halides to produce ethers **114**, or they can undergo a nucleophilic addition to the carbonyl group of other molecules to give products of type **115**.

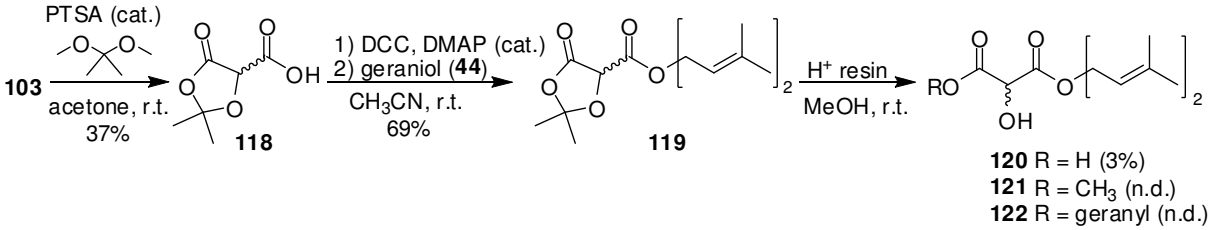
3.2.2.3.2 Ester derivatives of tartronic acid

For a concise and selective synthesis of isoprenyl-derived monoester derivatives of tartronic acid **117**, a strategy was needed, that avoids long protection-deprotection sequences. As shown in Scheme 35, the final deprotection step(s) of **116** could prove tricky because of selectivity problems. Depending on the careful choice of protection groups and reaction conditions, target compound **117** might be obtained from mixed di-ester **116** by a regio- and chemoselective deprotection in reasonable yields.



Scheme 35: Suggested route to isoprenyl derived monoesters of tartronic acid **117** employing a protection-deprotection strategy.

In order to minimize protection-deprotection issues, a more elegant way was considered: “to kill two birds with one stone”. In other words, the hydroxyl group and one of the carboxylic acid functions in tartronic acid **103** were masked simultaneously in a 1,3-dioxolanone ring **118**, that incorporates an acetal (acetonide) and a lactone functionality at the same time. Thus, racemic 2,2-dimethyl-1,3-dioxolane-4-carboxylic acid **118** was prepared from non-chiral **103** by acid-catalyzed protection with 2,2-dimethoxypropane in acetone (Scheme 36). It is interesting to note that ketoacid **118** has been previously prepared *only once*, i.e. by photolysis of diazo Meldrum’s acid.[130-132]



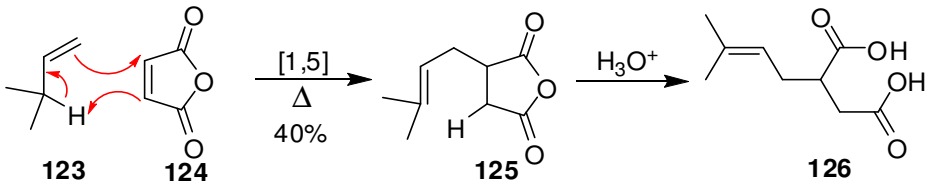
Scheme 36: Synthetic route to isoprenyl derived monoesters of tartronic acid.

Applying the Steglich[108] method, the free acid function in **118** was esterified with geraniol **44** to give isoprenyl ester **119**. Acetonide group removal under acid-catalyzed conditions finally afforded target compound **120** as a racemic mixture, unfortunately in very low yield, along with methyl ester **121** and a small amount of symmetric *bis*-prenylated di-ester **122**.

3.2.3 Mimetics derived from 1,4-dicarboxylic acids

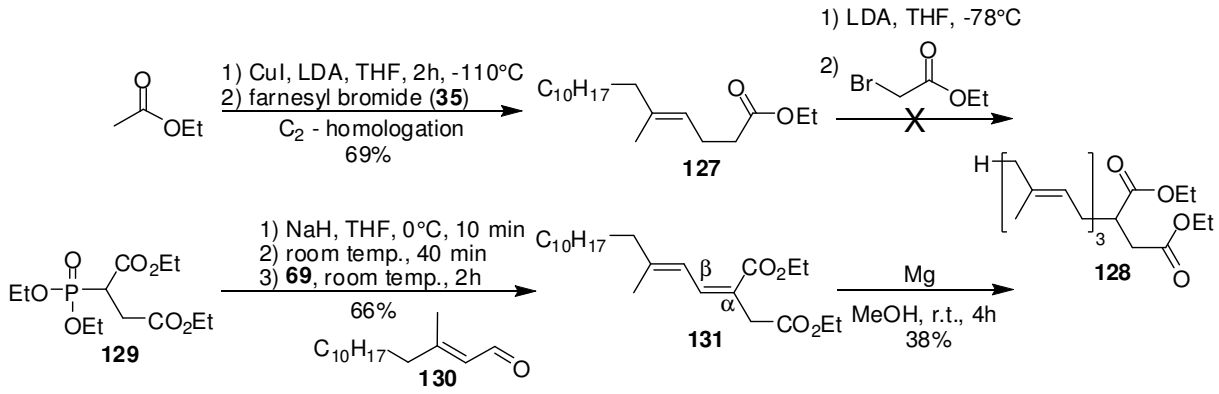
3.2.3.1 Surrogates of succinic acid

Preparation of isoprenyl derivatives of succinic acid already have been reported by different groups. For example, Agami et al.[133] reported the synthesis of α-(3,3-dimethylallyl)succinic acid **126** by reacting allylic ene-component **123** with maleic anhydride **124** in a thermally induced 1,5-sigmatropic rearrangement (Alder-ene-reaction[134]) to give anhydride **125**. Subsequent hydrolysis of the latter readily afforded γ-dicarboxylic acid **126** (Scheme 37).



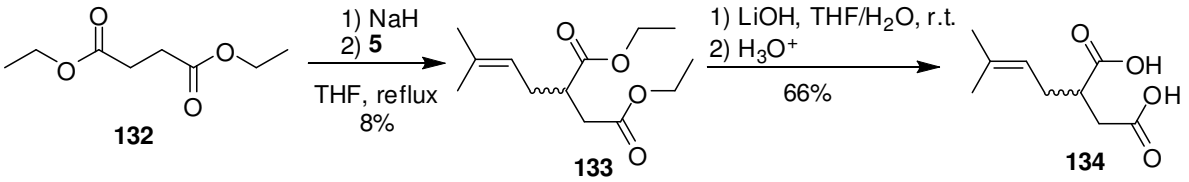
Scheme 37: Agami´s synthesis of 2-(3,3-dimethylallyl)succinic acid **126** via an Alder-ene-reaction.[133]

Other approaches to synthesize terpene-type derivatives of succinic acid have been made based on the successive construction of the 1,4-dicarboxylic acid motif. Thus, in their study of imidazole-containing analogues of farnesyl pyrophosphate, the group of Dubois[135] tried the stepwise build-up of the succinic acid skeleton starting from readily available farnesol (Scheme 38). Two-carbon homologation of the farnesyl chain with ethyl acetate provided ester **127**. Attempts to alkylate **127** at the α-position with ethyl bromoacetate to 1,4-diester **128** failed. With this unexpected drawback, Dubois at al.[135] finally succeeded in synthesizing 2-farnesyl succinate **128** by applying a Horner-Wadsworth-Emmons (HWE) reaction[136] on farnesal **130** with tetraethylphosphono-succinate **129**[137] followed by a regioselective reduction of the conjugated α,β-double bond in **131** by magnesium[138-139] in dry methanol.



Scheme 38: Dubois´ synthesis of 2-farnesyl-succinic acid ester **128**.[135]

In the present work, DMAPP-mimetic **134** was prepared by a direct method: succinic acid diethyl ester **132** was reacted with sodium hydride and 3,3-dimethylallylbromide **5** in boiling THF. Yields were low, but the reaction was the simplest one from available starting materials. The resulting racemic α-prenyl succinic diester **133** was subjected to base-mediated hydrolysis with lithium hydroxide. After acidic work-up, the desired 1,4-dicarboxylic acid **134** was isolated in good yields (Scheme 39).



Scheme 39: Synthetic route to 2-(3,3-dimethylallyl)succinic acid **134** by direct alkylation.

3.2.3.2 Surrogates of fumaric acid

Replacement of the C2-C3 σ-bond in succinic acid by a conjugated π-bond generates two geometric isomers of 2-butenedioic acid: fumaric acid (*trans*-isomer) and maleic acid (*cis*-isomer) (Figure 13).

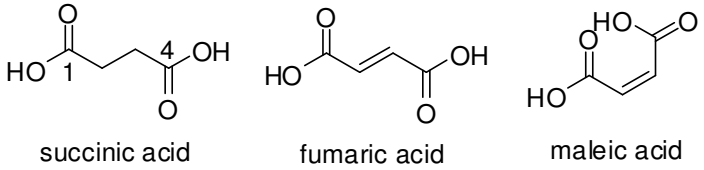
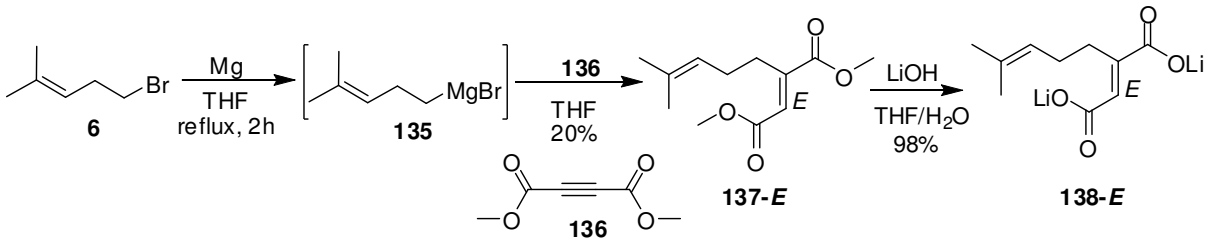


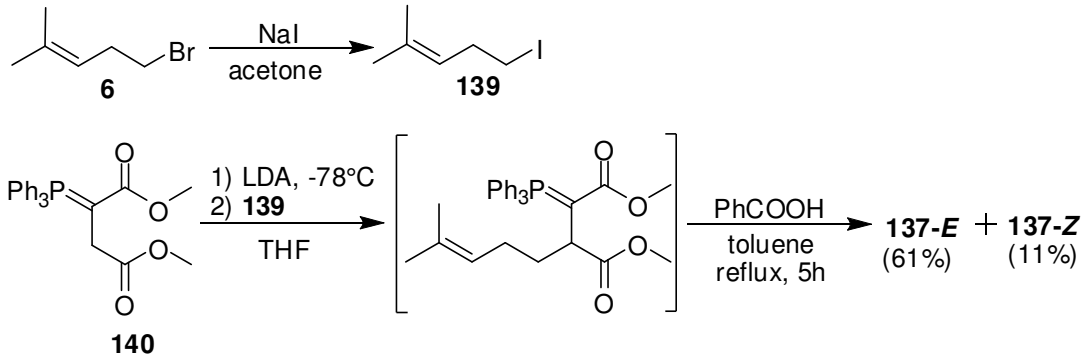
Figure 13: Comparison of succinic acid and its two 2,3-dehydrogenated isoforms: fumaric acid and maleic acid.

Short isoprenyl chain substituted fumaric acid **137-*E*** was prepared by a conjugate addition of *homo*-allylic Grignard reagent **135** to dimethyl acetylenedicarboxylate (DMAD, **136**). Subsequent saponification of the ester groups provided the desired *trans*-dicarboxylate **138-*E*** (Scheme 40). The stereochemistry of **137-*E*** was confirmed by a NOE experiment (see Section 3.2.3.3).



Scheme 40: Synthetic route to *E*-2-alkyl-2-butenedioic acid derivatives.

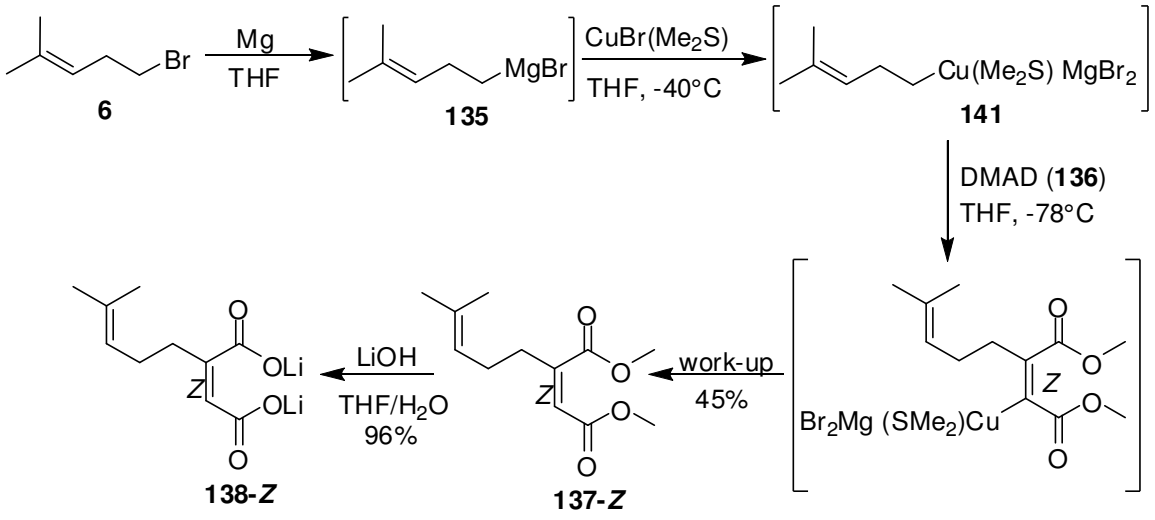
A different approach to **137-*E*** was reported in a paper discussing the synthesis of 5-methyl coumarins.[140] The authors applied the following strategy (Scheme 41): alkylation of the anion of phosphorane **140**[141] with *homo*-allylic iodide **139** (readily obtained from the corresponding bromide **6** via the Finkelstein reaction) afforded, after benzoic acid induced elimination of triphenylphosphine, the *trans*-configured diester **137-*E*** as the predominant diastereoisomer along with 11% of the *cis*-isomer **137-*Z***.[140]



Scheme 41: Bohlmann´s synthesis of *trans*- and *cis*- 2-(4-methylpent-3-enyl)butenedioic acid dimethyl ester **137-*E*** and **137-*Z***, respectively.[140]

3.2.3.3 Surrogates of maleic acid

Closely related to the analogues of fumaric acid (**137-*E*** and **138-*E***) are the corresponding diastereoisomers (**137-*Z*** and **138-*Z***) with a *cis*-configuration of the double bond. Since the *Z*-geometric isomers are in general thermodynamically less favorable than their *E*-counterparts, their stereoselective preparation requires a slightly modified approach from the one already discussed in section 3.2.3.2. Thus, the crucial step in the synthesis was the use of organocopper reagents.[142-144] Organocuprate **141** was prepared by transmetallation of Grignard reagent **135** with cuprous bromide-dimethyl sulfide complex[145]. The *syn*-addition of **141** to the triple bond of DMAD **136** afforded after work-up 2-substituted maleate **137-*Z*** in moderate yields. Finally, saponification of the two ester groups under mild conditions provided the desired di-lithium carboxylate **138-*Z*** (Scheme 42).



Scheme 42: Synthetic route to *Z*-2-alkyl-2-butenedioic acid derivatives.

The *cis*- and *trans*-geometry of the double bond in **137-*Z*** and **137-*E***, respectively, was confirmed by performing a NOE experiment in the rotating frame (ROESY, mixR = 0.5 sec). As seen in Figure 15, olefinic hydrogen H6 in **137-*Z*** shows strong through-space correlation signals to methylene protons H4 and H5 (signals marked within an orange ellipse). Conversely, proton H6 in **137-*E*** shows a very weak correlation to H5 and no correlation to H4. By this comparison of the ROESY spectra of the geometrical isomers **137-*Z*** and **137-*E***, the assignment of each isomer to its corresponding ^{1}H NMR spectrum (Figure 14) becomes unambiguous.

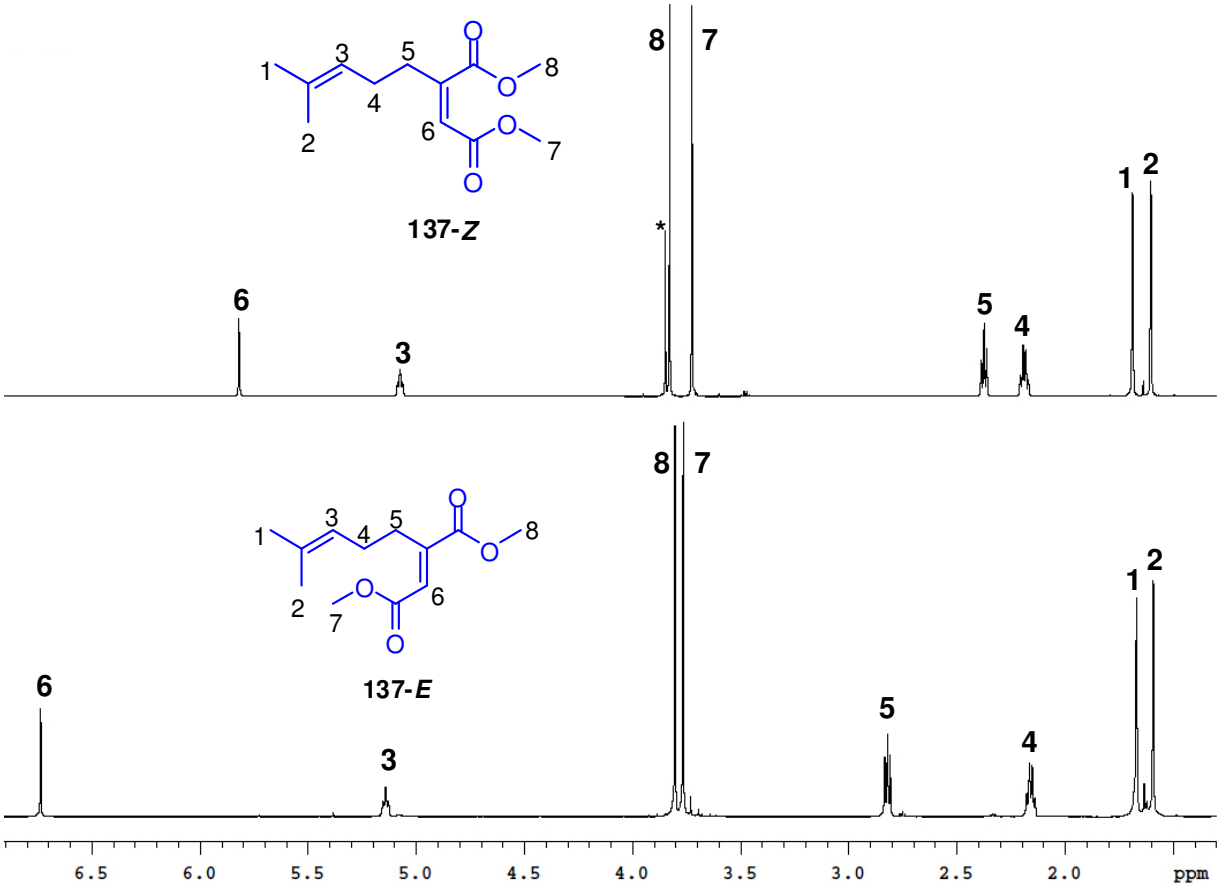


Figure 14: Comparison of the ^{1}H NMR spectra of diastereoisomers **137-*Z*** and **137-*E***. (*) signifies some impurity. Conditions: $CDCl_3$, 600 MHz

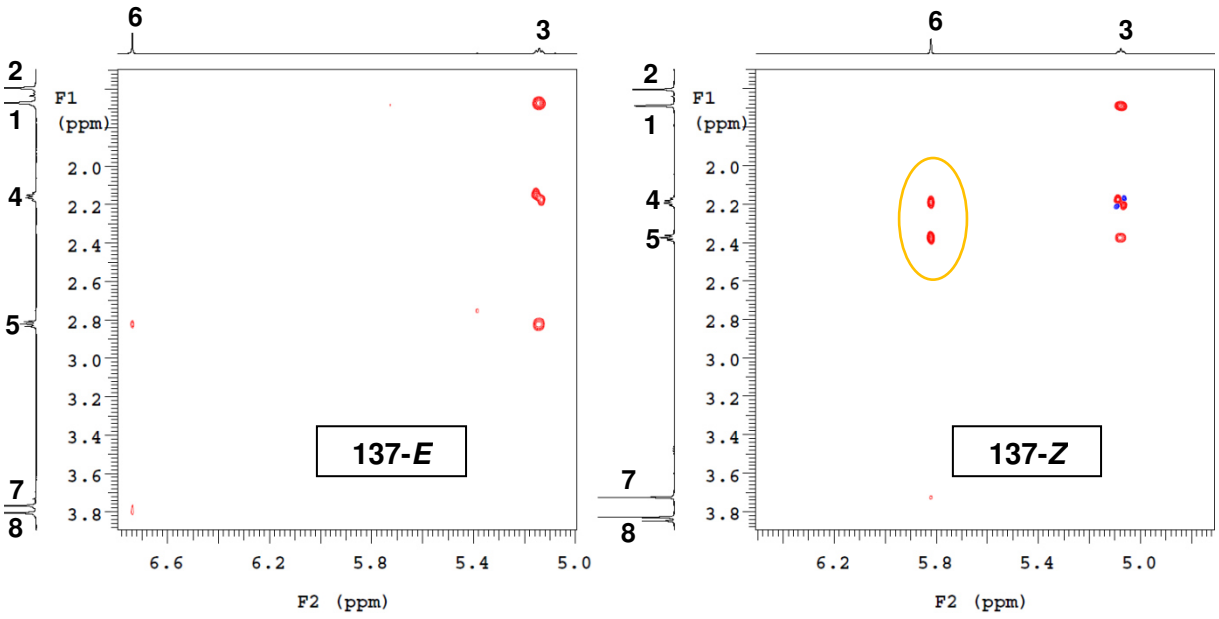
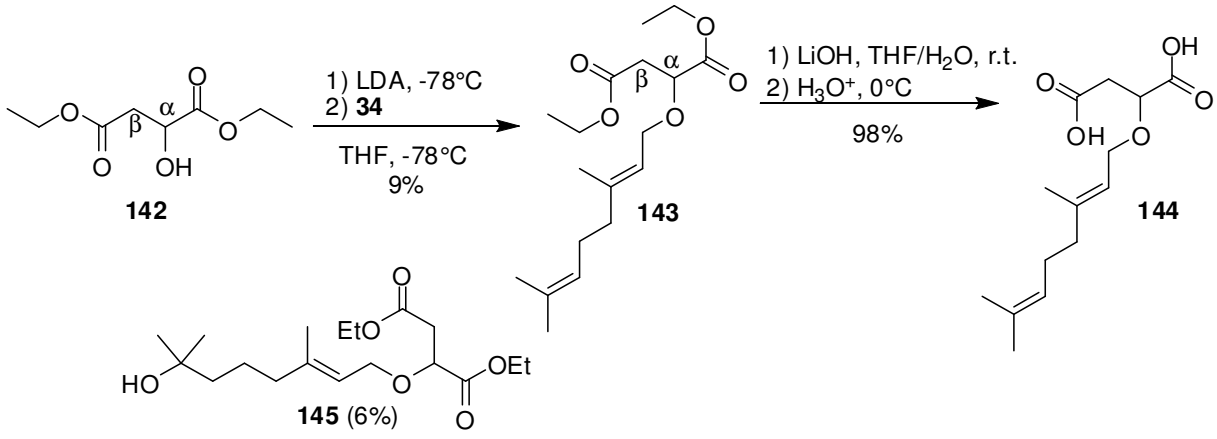


Figure 15: Comparison of the ROESY (rotating frame nuclear Overhauser effect spectroscopy) spectra of diastereoisomers **137-*E*** and **137-*Z***. ($CDCl_3$, 600 MHz, mixing time = 0.5 sec)

3.2.3.4 Surrogates of malic acid

3.2.3.4.1 Ether derivatives of malic acid

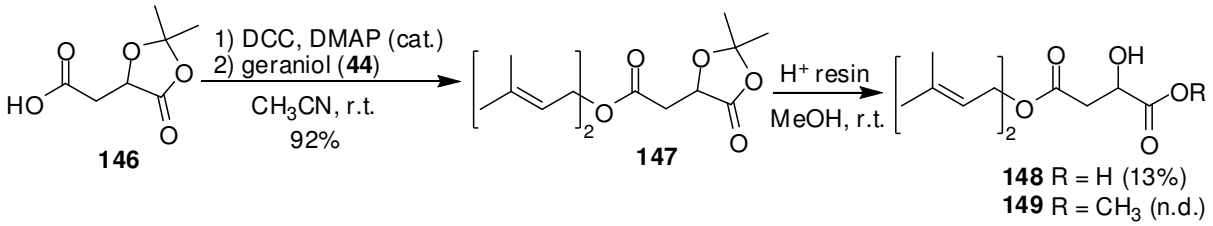
The diethyl ester of hydroxybutanedioic acid (malic acid) **142** was alkylated with geranyl bromide **34** at the α-hydroxy function under kinetic reaction conditions (Scheme 43). The isolated product showed to be ether **143**. ^{13}C NMR and DEPT analysis reveals that the β-carbon in both **142** (δ 38.64 ppm) and **143** (δ 38.07 ppm) is methylenic (secondary), and not tertiary as it would be in the case of *C*-alkylation. Surprisingly, diastereoselective *C*-alkylation of malic acid has also been reported under comparable reaction conditions.[146-147] In addition to product **143**, a second compound was detected in the TLC. Its isolation and analysis by NMR revealed hydrated compound **145**, presumably formed during work-up (cf. also compounds **20**, **63**, **64** and **168**). With ester **143** in hands, saponification under mild conditions and subsequent acidification provided *O*-prenylated malic acid **144** in excellent yields.



Scheme 43: Synthetic route to geraniol derived ether **144** of malic acid. Hydrated product **145** was obtained as a byproduct.

3.2.3.4.2 Ester derivatives of malic acid

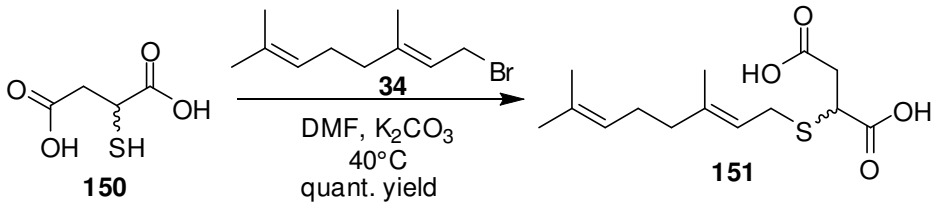
In analogy to the strategy used for the preparation of terpene derived mono-esters of tartronic acid **103** (section 3.2.3.2), mono-ester of malic acid **147** was prepared accordingly. In a first step, commercially available 2,2-dimethyl-5-oxo-1,3-dioxolane-4-acetic acid **146**[148-149] was esterified with geraniol **44** under Steglich[108] conditions to give ester **147**. Acid-catalyzed removal of the acetonide protecting group afforded target compound **148** along with small amounts of methyl ester **149** as a side-product (Scheme 44).



Scheme 44: Synthetic route to isoprenyl derived esters of malic acid.

3.2.3.5 Surrogates of thiomalic acid

Alkylation at the thiol function of thiomalic acid **150** proceeded under milder conditions than the *O*-alkylation of malic acid **142** (cf. Section 3.2.3.4.1). That is attributed to the higher polarizability ("softness") of the sulfur atom compared to oxygen. Because of this property, thiols in general exhibit a lower pKa value than the corresponding alcohols and are, therefore, readily deprotonated by weak bases such as carbonates. Accordingly, racemic thiomalic acid **150** was treated with an excess of geranyl bromide **34** in a mixture of potassium carbonate in warm DMF. After acidic work-up, the racemic thioether **151** was obtained in a quantitative yield (Scheme 45).



Scheme 45: Thioalkyalation of *rac*-mercaptosuccinic acid **150**.

3.2.3.6 Surrogates of succimer

Succimer **152**, formally known as *meso*-2,3-dimercaptosuccinic acid, is a well known chelating agent used in medicine for the treatment of lead poisoning in children (Figure 16).[150-152] Because of its two sulfur atoms (soft nucleophiles) succimer is able to "capture" heavy metals (soft electrophiles) by formation of a strong coordination complex.

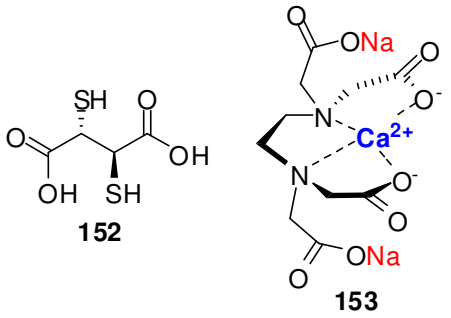
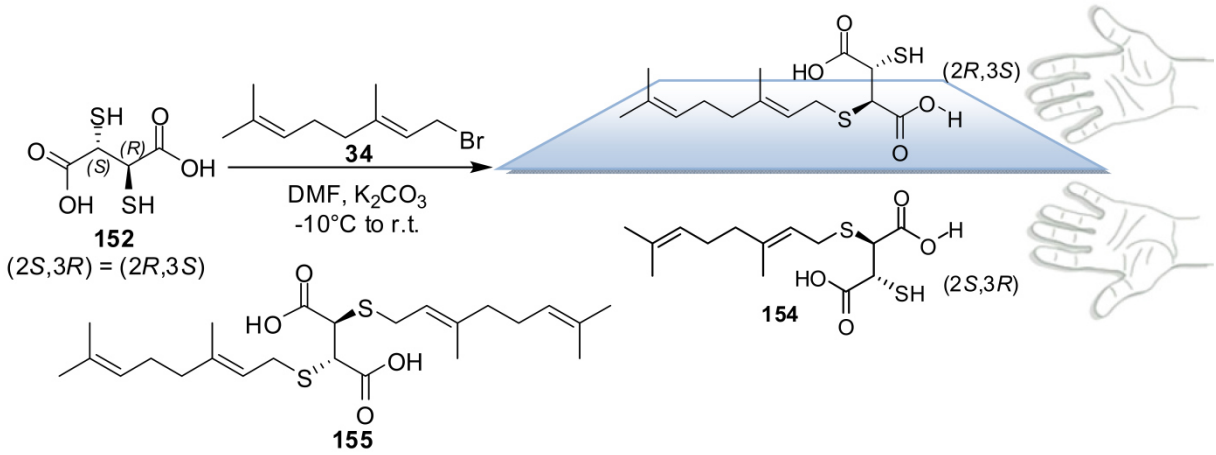


Figure 16: Representation of two pharmaceutically relevant metal ion chelating agents: succimer **152** and Ca·EDTA·2Na **153**.

The main medical advantage of succimer is its efficacy in oral administration due to its excellent water solubility. Furthermore, succimer is well-tolerated, exhibits relatively low toxicity and can be applied at the same time as iron supplements to treat iron deficiency anaemia. Unlike other widely used lead chelating agents, e.g. ethylenediaminetetraacetic acid calcium disodium salt (Ca·EDTA·2Na, **153**), succimer does not cause significant increase in urinary excretion of essential minerals.[150-152]

For the synthesis of compound **154**, commercially available succimer **152** was alkylated with geranyl bromide **34** at one of its sulfur atoms (Scheme 46). The resulting *mono*-isoprenyl thioether **154** was obtained as a racemic mixture of the (2*S*,3*R*) and (2*R*,3*S*) enantiomers. In addition, *bis*-alkylated *meso*-compound **155** was recovered as an accompanying side-product from the reaction.

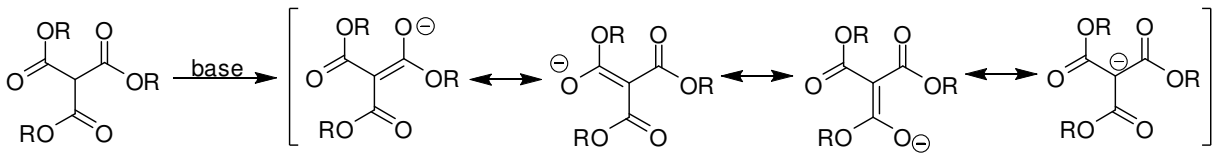


Scheme 46: Thioalkylation of succimer **152** produces enantiomeric pair **154**. Disubstituted symmetric *meso*-compound **155** was isolated as a byproduct.

3.3 Derivatives of tricarboxylic acids

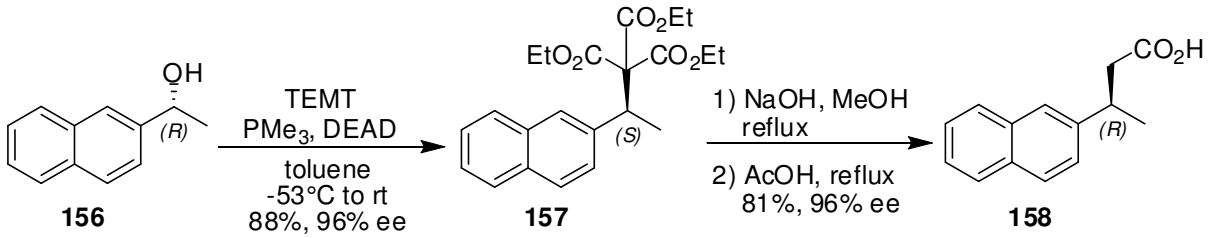
3.3.1 Mimetics derived from triethyl methanetricarboxylate (TEMT)

Alkyl-1,1,1-tricarboxylic esters were first reported by Conrad et al.[153] over a century ago, but did not find broad synthetic applications until 1911.[154] For example, triethyl methanetricarboxylate (TEMT)[155] is a commercially available compound and acts as an expedient protonated *C*-nucleophile due to its high acidity of pKa ~ 7.8[156] (cf. pKa of diethyl malonate ~ 13.3[156]). Flanked by three electron-withdrawing groups, the tertiary carbon in TEMT experiences a very high positive polarization. As a result of this, the proton at the branching carbon can easily be abstracted by weak bases to generate a highly resonance stabilized enolate anion in which the negative charge is delocalized over seven atoms (Scheme 47).



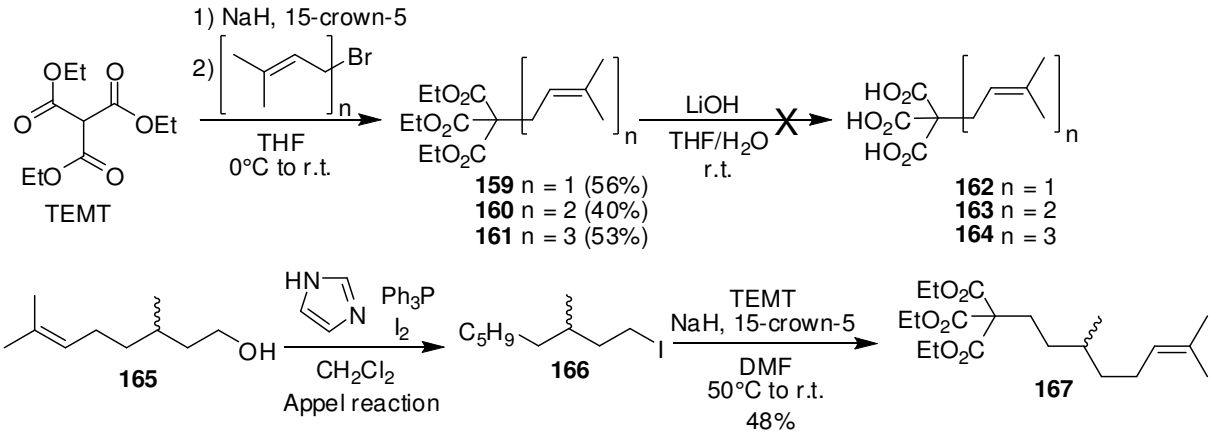
Scheme 47: Representation of the resonance structures of TEMT enolate anion.

The TEMT enolate was shown to exhibit good behavior in S_N2-type reactions, e.g. Mitsunobu reactions[157-158] (Scheme 48). Furthermore, the incorporated $-C(CO_2Et)_3$ group provides scope for further synthetic manipulations, including the preparation of dendrimers[159], malonates[160], two-carbon elongated acids, α-alkylated allylic alcohols[161] and nitrogen containing heterocycles[162-163].



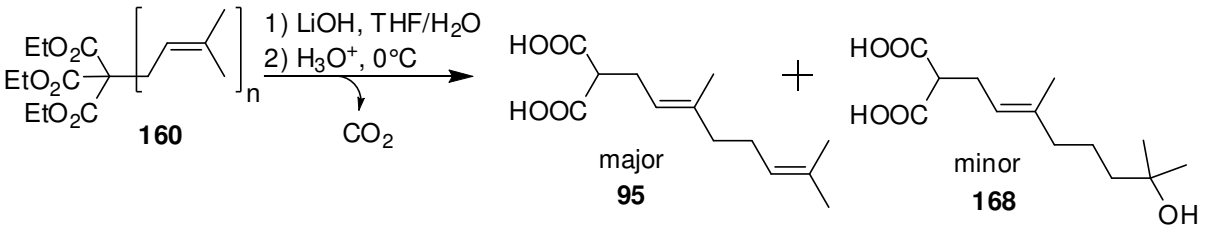
Scheme 48: Stereoselective C–C bond formation via the Mitsunobu displacement of (*R*)-α-methyl-2-naphtalenemethanol **156** with TEMT. Subsequent saponification and decarboxylation of the resulting triester adduct **157** provided two-carbon homologated acid **158**.[157]

The synthetic route, applied in the present work for the preparation of isoprenyl chain derived TEMT derivatives is shown in Scheme 49.



Scheme 49: Functionalization of TEMT with different isoprenyl chains.

After treatment of TEMT with sodium hydride, the resulting sodium enolate was trapped with prenyl bromides of various chain lengths to give triesters **159-161**. In an analogous way, citronellyl derivative **167** was prepared by first converting citronellol **165** to its primary halide **166** by an Appel reaction and then reacting it with TEMT enolate in DMF at 50°C. Attempts to obtain the attractive triacid derivatives **162-164** and the acid corresponding to **167** failed. For example, when **160** was hydrolysed under mild conditions, only two products could be detected in the HPLC. Their isolation and characterization by NMR showed them to be compounds **95** (t_R = 13.41 min) and **168** (t_R = 9.97 min) (Scheme 50 and Figure 17). Compound **95** is identical to the one obtained by the alkylation of malonic ester (cf. section 3.2.2.1). The minor component **168** is the result of acid-catalyzed addition of water to the terminal double bond of **95** due to acidification during work-up and HPLC eluent conditions (cf. compounds **20**, **63**, **64** and **145**).



Scheme 50: Products obtained upon saponification and subsequent acidification of triester **160**.

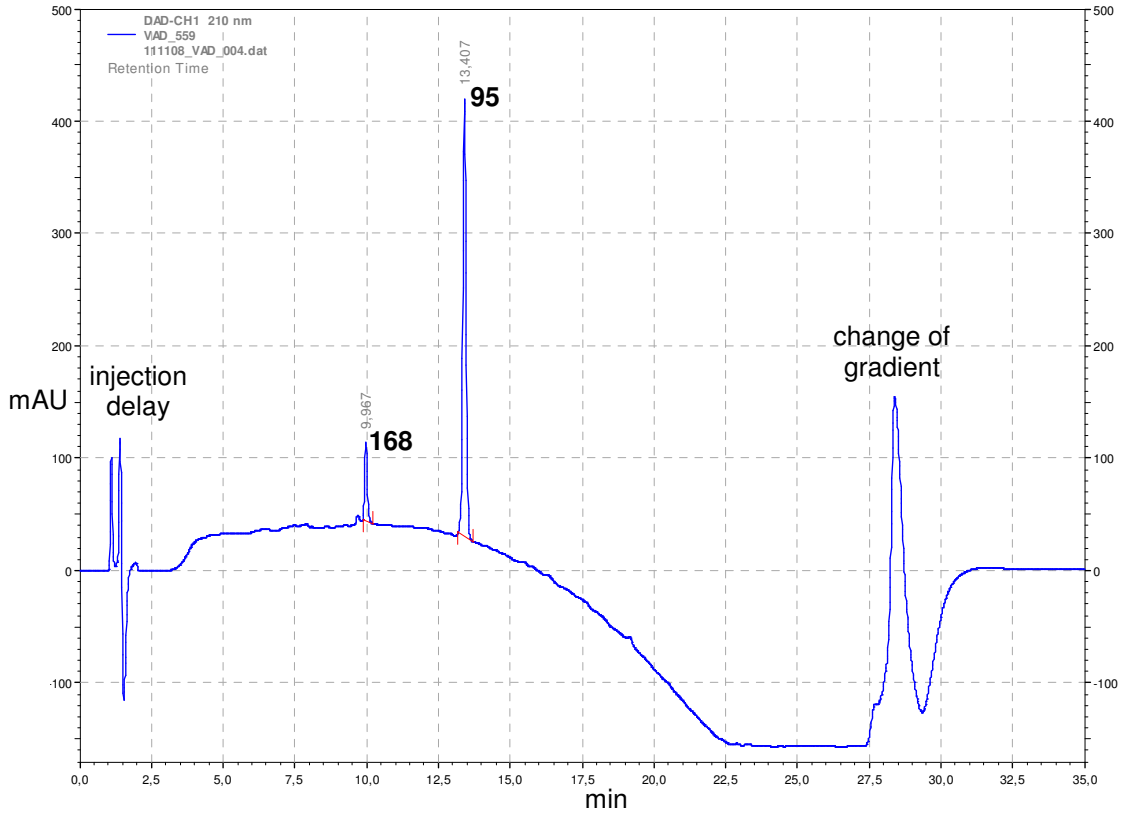
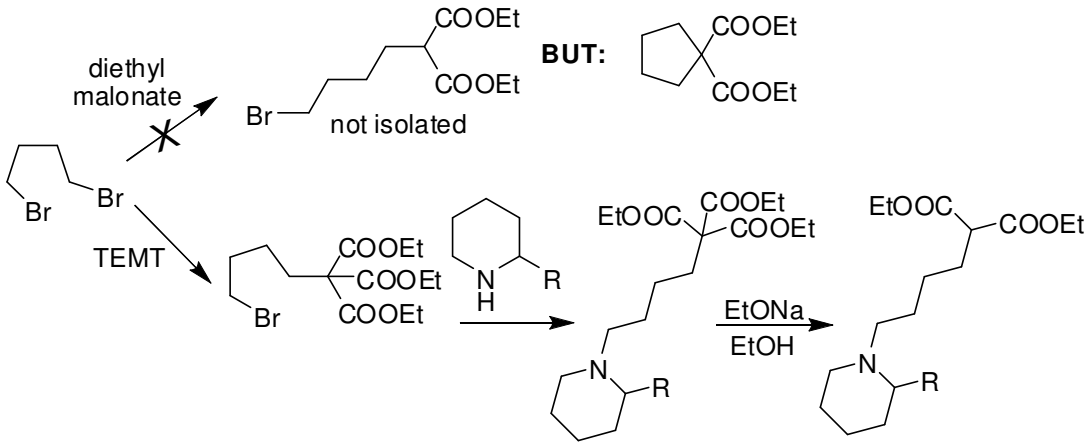


Figure 17: RP-HPLC chromatogram showing the outcome of the reaction shown in Scheme 50. Saponification of **160** provided two products: 2-geranylmalonic acid **95** (t_R = 13.41 min) as the predominant product and its hydrated form **168** (t_R = 9.97 min) as a side-product. Tricarboxylic acid **163** was not obtained. (Conditions: (CH_3CN/H_2O) + 0.1%TFA; 2% CH_3CN –(20 min)→ 100%; 1 mL/min; λ = 210 nm; column: LiChroCART® 125-4 ; LiChrospher® 100 RP-18 (5µm); chromatogram: 111108_VAD_004; measured on: VWR LaChrom Elite ("Mary"), see chapter 5.2).

From the literature[160] it is known that TEMT shows to be a suitable reagent for the selective preparation of mono-substituted malonates. The trick is that one of the three carbethoxy moieties serves as a blocking group, thus preventing a second alkylation.[160] Decarbethoxylation finally yields the desired mono-malonates. In this regard, TEMT provides an excellent alternative to haloalkyl malonic esters derived from dihalo alkanes the synthesis of which is practically impossible due to the perturbation by inter- or intramolecular[164] dialkylation or alkenylation (Scheme 51).



Scheme 51: TEMT used as a reagent for the synthesis of mono-alkylated malonate analogues derived from dihalo alkanes.[160]

3.3.2 Mimetics derived from tricarballylic acid (1,2,3-propanetricarboxylic acid)

Tricarballylic acid **169** is a symmetric tricarboxylic acid. It features one tertiary (3°) and two secondary (2°) carbon centers each of which bears a carboxyl group. To the best of my knowledge, no alkylated derivatives of either **169** or **170** have been reported previously. In this work they have been prepared by alkylation of the enolate generated from **170** with isoprenyl halides of varying chain length (Figure 18).

In the first step of the synthesis, commercially available tricarballylic acid **169** was protected as its trimethyl ester **170** by a standard esterification protocol with thionyl chloride in methanol. Proton abstraction from **170** with a strong base generates a resonance-stabilized enolate **171a**/**b**. For symmetric reasons, resonance structure **171b** is twice as abundant as **171a**. Trapping the enolate species with various isoprenyl bromides (**5**, **34** and **35**) resulted in the formation of five products for *each* prenyl chain: one non-chiral (**172** to **174**) with substitution at the tertiary carbon, and four stereoisomers (**175a-d** to **177a-d**) with substitution at one of the prochiral methylene carbon centers. All chiral and non-chiral compounds were analyzed by HR-MS, chiral HPLC and NMR (Figure 18 and Table 5).

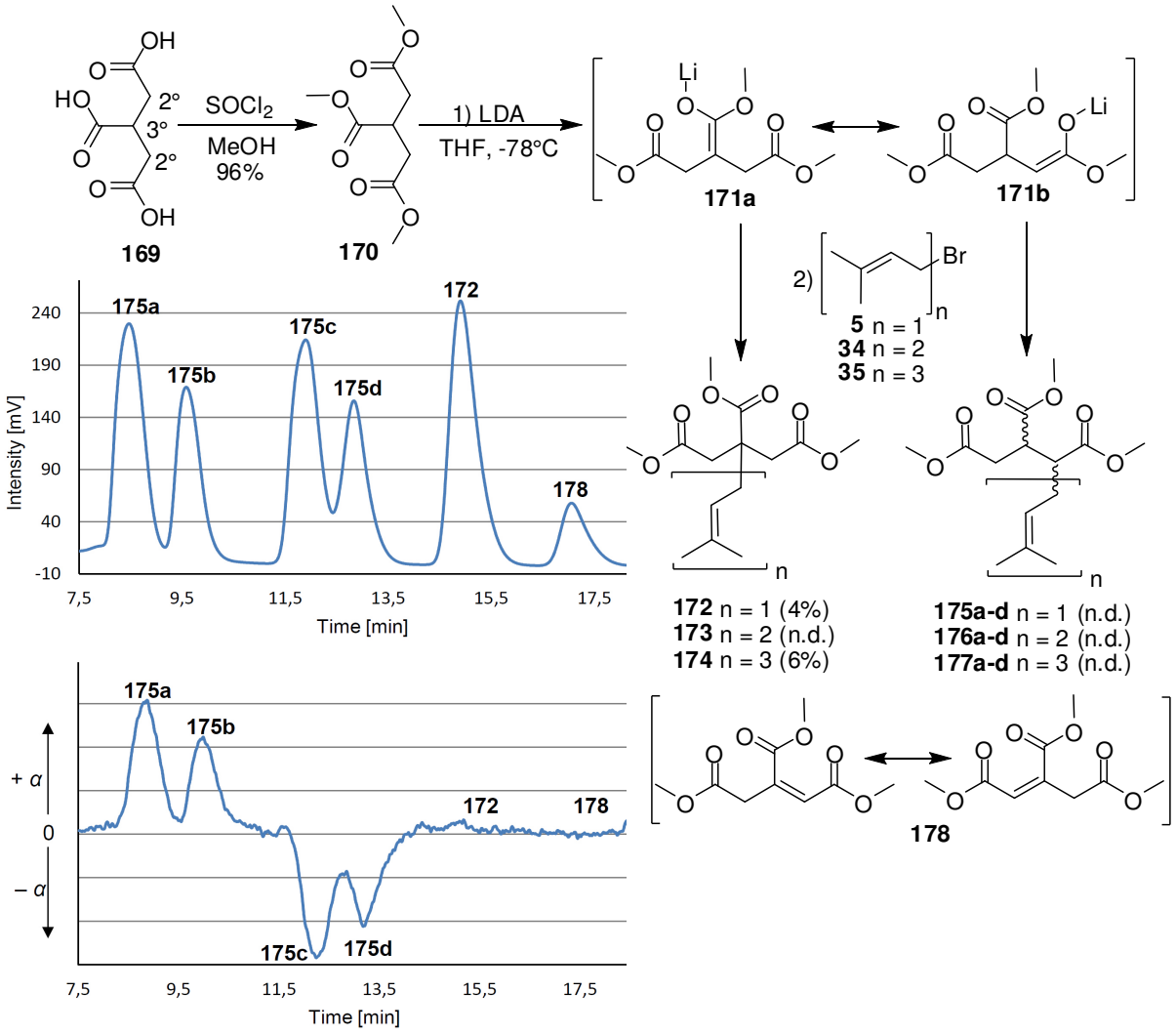


Figure 18: Synthetic route leading to isoprenylated derivatives of tricarballylic acid. Inlet: Normal-phase chiral HPLC chromatogram showing the crude product mixture obtained from the alkylation of **170** with prenyl halide **5** (upper diagram). Chiral analysis reveals four (**175a-d**) out of the six detected products to be optically active. The remaining two compounds (**172** and **178**) are non-chiral (lower diagram). Compound **178** was formed as a byproduct and corresponds formally to dehydrogenated **170**. (Conditions: isocratic flow: *n*-hexane / *iso*-propanol = 80/20; 0.5 mL/min; λ = 210 nm; column: Chiralcel® OD 250×4.6 mm; Data path: C:\Win32App\HSM\Chiral\DATA\1727\; measured on: Merck Hitachi ("Pater Borni"), see chapter 5.2).

	175a	**175b**	**175c**	**175d**	**172**	**178**
t_R [min]	8.47	9.58	11.90	12.83	14.90	17.06
Area	9,406,999	5,828,263	8,249,049	5,584,372	9,599,418	2,273,813
Area [%]	22.98	14.23	20.15	13.64	23.45	5.55

Table 5: Analysis of the detected peaks from the UV-absorption chromatogram shown in Figure 18.

Since symmetric compounds **172-174** constituted the main focus of interest, most of the effort was invested into their isolation and characterization. Due to their potential biological

activity, the quadruple set of diastereoisomers (**a-d**) belonging to each of asymmetric compounds **175-177** was also isolated and characterized. However, the determination of the relative stereochemistry of each diastereoisomer was not pursued any further before having any results from biological assay testing. Evidence for which two of the four stereoisomers **175a-d** belong to an enantiomeric pair can be derived from both the chiral HPLC analysis and NMR spectroscopic data.

By taking a closer look into the HPLC chromatogram it becomes obvious that peaks **175a** and **175c** show nearly the same area integral, as do peaks **175b** and **175d** (Figure 18, and Table 5). In addition, detection of the optical rotation with a Chiralyzer® detector reveals that each pair of compounds **175a** and **175c**, as well as **175b** and **175d** exhibits an opposing optical activity with respect to each other. These findings indicate clearly that **175a**/**175c** and **175b**/**175d** form enantiomeric pairs.

NMR analysis of all four isolated chiral fractions **175a-d** confirms the aforementioned assumption: the ^{1}H and ^{13}C chemical shifts within each enantiomeric couple (**175a** ↔ **175c**, as well as **175b** ↔ **175d**) are identical, but differ considerably with respect to the shifts of the other enantiomeric pair (Figure 20). As a comparison, the ^{1}H NMR spectrum of C_s-symmetric compound **172** is shown in Figure 19.

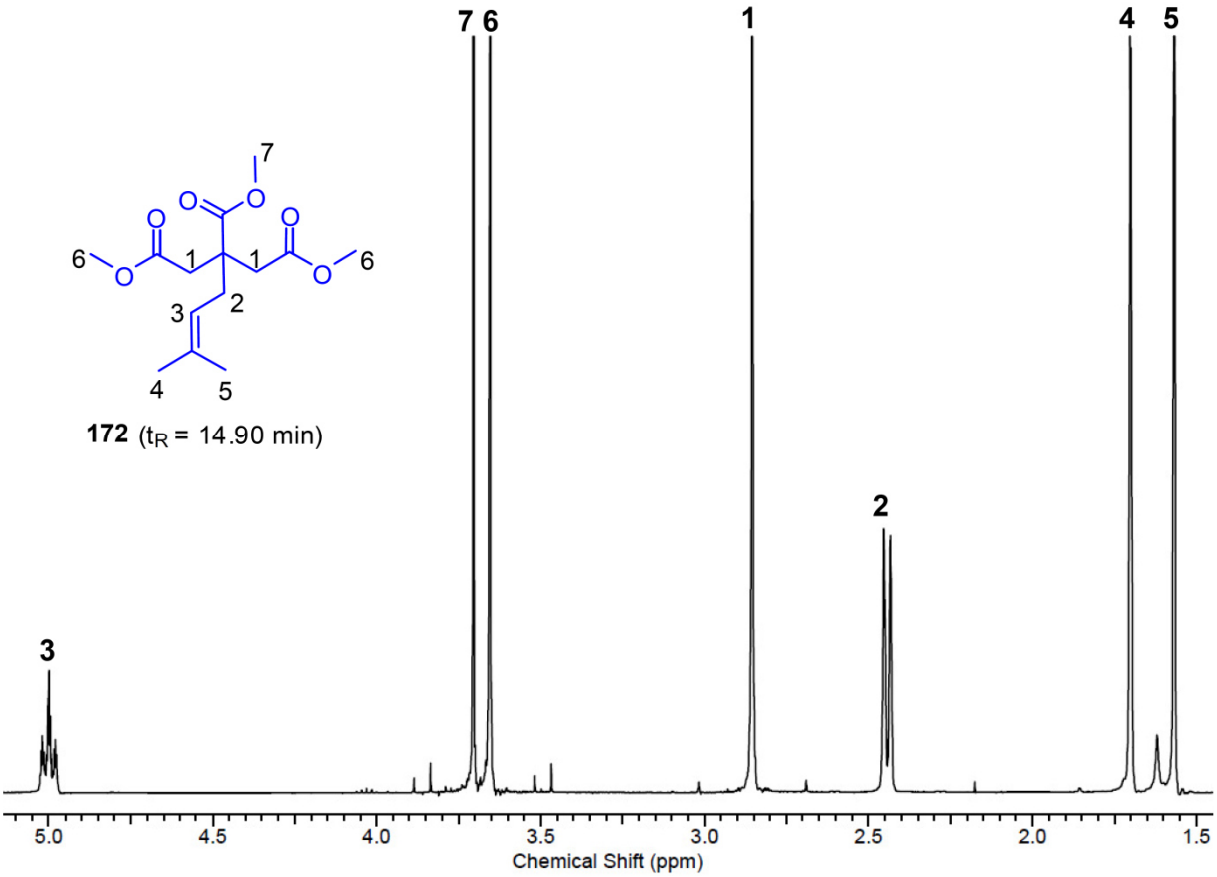


Figure 19: ^{1}H NMR spectrum with signal assignments of non-chiral compound **172**. ($CDCl_3$, 400 MHz)

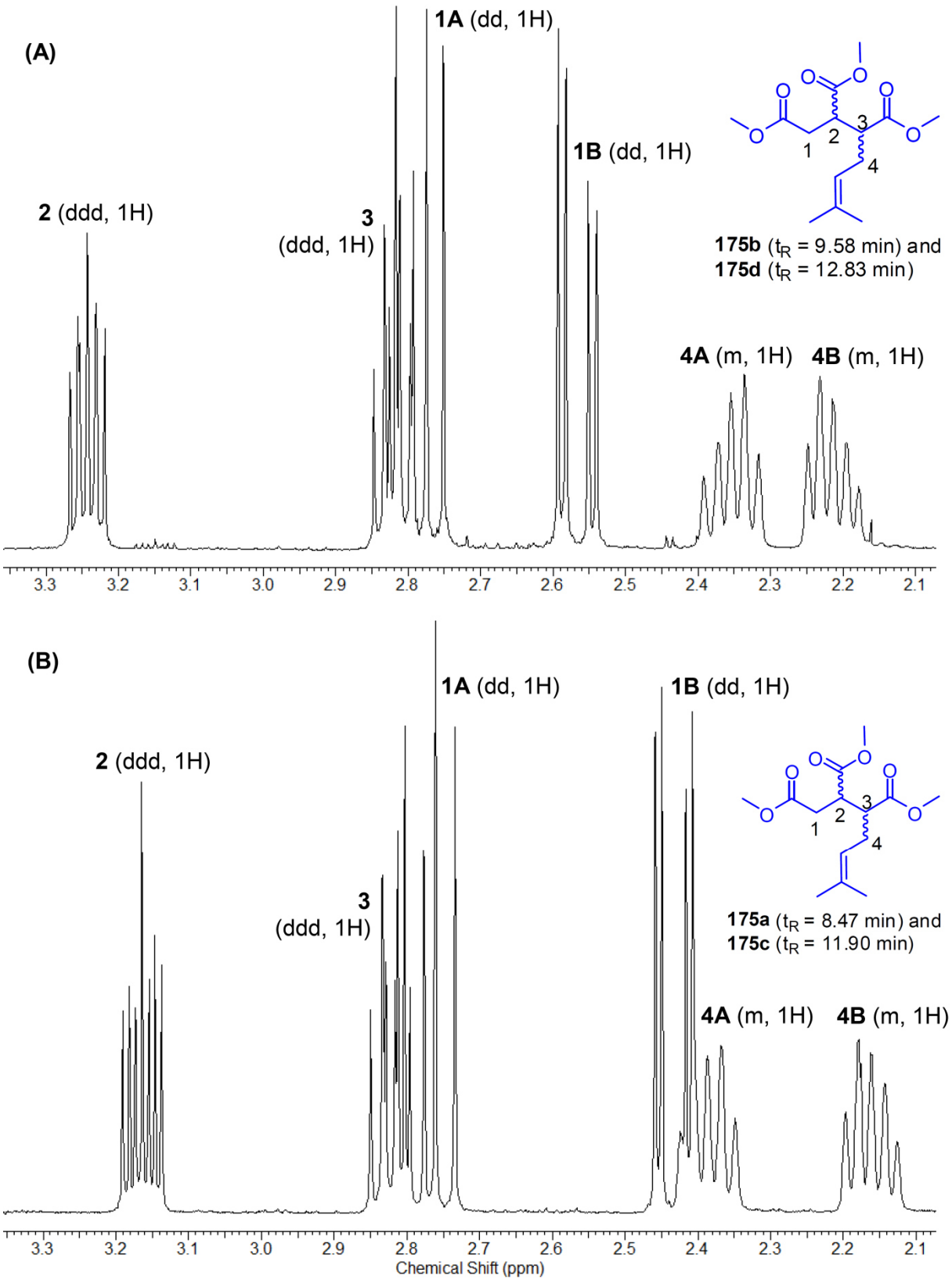
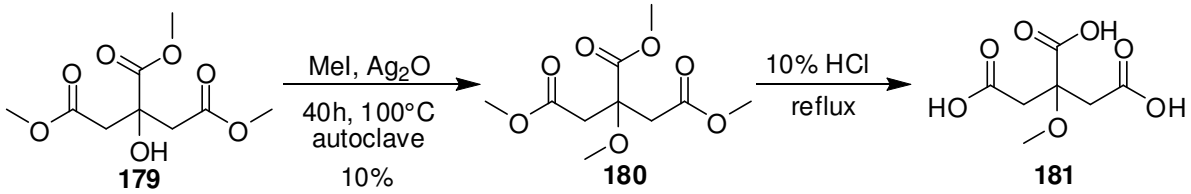


Figure 20: Comparison of selected ^{1}H NMR ($CDCl_3$, 400 MHz) signals of chiral compounds (A) **175b** and (B) **175a**. Each pair of enantiomers **175a↔175c** and **175b↔175d** shows identical chemical shifts. Since these pairs are diastereoisomers to each other, the NMR spectrum of each enantiomeric pair differs from the other with respect to chemical shift.

3.3.3 Mimetics derived from citric acid

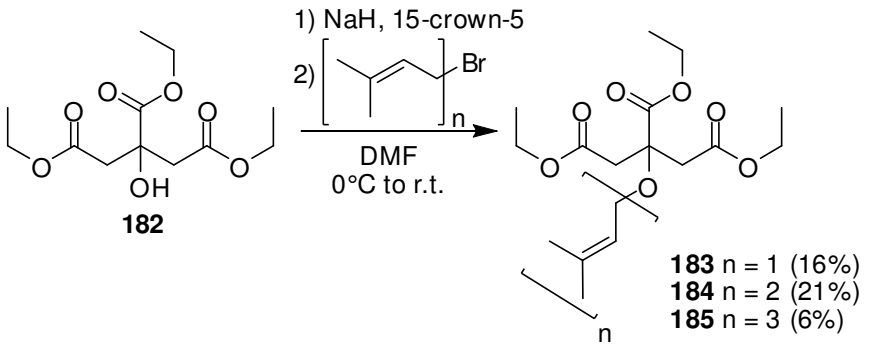
Prenyl chain derived ethers of 2-hydroxypropane-1,2,3-tricarboxylic acid were prepared by *O*-alkylation of the free hydroxyl group. The first etherification protocol of trimethyl-2-hydroxypropane-1,2,3-tricarboxylate (**179**) was established by Anschütz in 1903 (Scheme 52).[165]



Scheme 52: Anschütz´original synthesis of trimethyl 2-methoxypropane-1,2,3-tricarboxylate (**180**) and its tricarboxylic acid (**181**).[165]

The reaction of **179** with iodomethane and silver oxide in an autoclave for 40 h at 100°C yielded up to 10% of trimethyl 2-methoxypropane-1,2,3-tricarboxylate **180** which was still contaminated with **179**. Acidic cleavage of the methyl esters led to 2-ethoxypropane-1,2,3-tricarboxylic acid **181**. Since that time this apparently simple reaction did not find broad application probably due to the poor yields and harsh conditions of the process described in the original paper.[165]

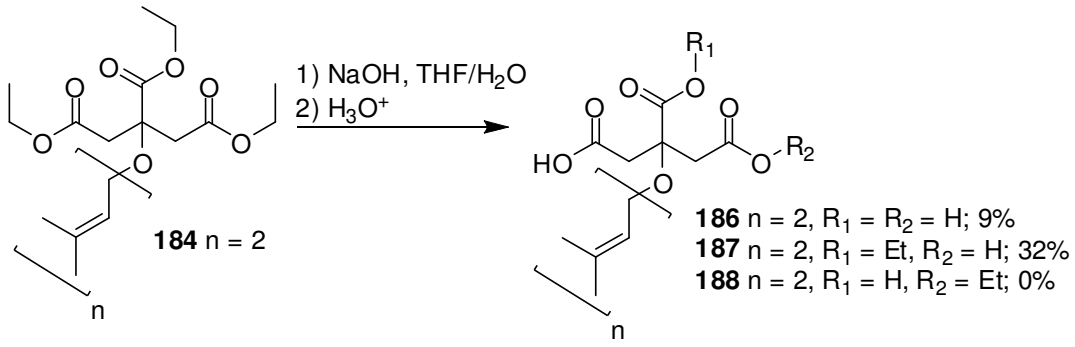
The procedure described in the present work for the preparation of isoprenylated ethers of citric acid employs a Williamson[166]–type method for ether synthesis (Scheme 53). Thus, commercially available triethyl citrate **182** was deprotonated with sodium hydride in DMF with the addition of a catalytic amount of 15-crown-5, a sodium-ion chelating agent. The resulting sodium alkoxide was reacted with electrophilic isoprenyl bromides to provide ethers **183-185**. Unfortunately, the yields obtained with this method were rather poor, varying between 6% and 21%.



Scheme 53: Williamson-type *O*-alkylation of triethyl citrate **182** with isoprenyl halides of varying chain size.

One possible explanation for the low yields can be attributed to the very weak nucleophilc character of the alkali metal alcoholate derived from citric acid as it does not react satisfactorily with common alkylating agents such as alkyl halides or tosylates.[167] As a consequence, alkylating agents possessing a stronger carbocationic character are necessary for the reaction with the quite unreactive alkoxide ion of citric acid. For this purpose *O*-alkylation reactions with alkyl chain electrophiles based on oxonium salts[168] (e.g. alkoxonium tetrafluoroborates) or alkyl triflates[167, 169] have already been reported in the literature.

The corresponding *O*-alkylated tricarboxylic acids were obtained from their esters **183-185** by base hydrolysis and subsequent careful acidification. As exemplified in Scheme 54, after subjecting tri-ester **184** to saponification conditions, triacid **186** and symmetric mono-ester **187** were isolated. The elemental composition [$C_{18}H_{28}O_7$] of product **187** was confirmed by HRMS.



Scheme 54: Ester hydrolysis of **184** afforded two non-chiral products: **186** and **187**. Hypothetical regioisomer **188** was not formed.

The position of the ester group in compound **187** was deduced from examining the ^{13}C NMR and DEPT-135 spectra. Since there is a mirror plane through the middle axis of molecule **187** it is non-chiral (C_s symmetry). ^{13}C NMR analysis shows two signals for three carbonyl groups (1 ester group at δ 172.50 ppm and 2 symmetric carboxylic acid groups at δ 173.33 ppm, with an intensity of the ^{13}C signals 1.00/2.29, respectively) and only one signal for two methylene ($\underline{C}H_2CO_2H$) carbons. In contrast, for the chiral regioisomer **188** (not observed) one would expect 3 different chemical shifts for each carbonyl carbon and 2 signals for each methylene group ($\underline{C}H_2CO_2H$ and $\underline{C}H_2CO_2Et$). In addition, if it is anticipated that carbon C4 (δ 172.50 ppm) in compound **187** is part of the carbonyl group directly attached to the branching carbon C3, it can easily be derived from HMBC analysis that the ethyl ester belongs to the carbonyl group at C4 (Figure 21).

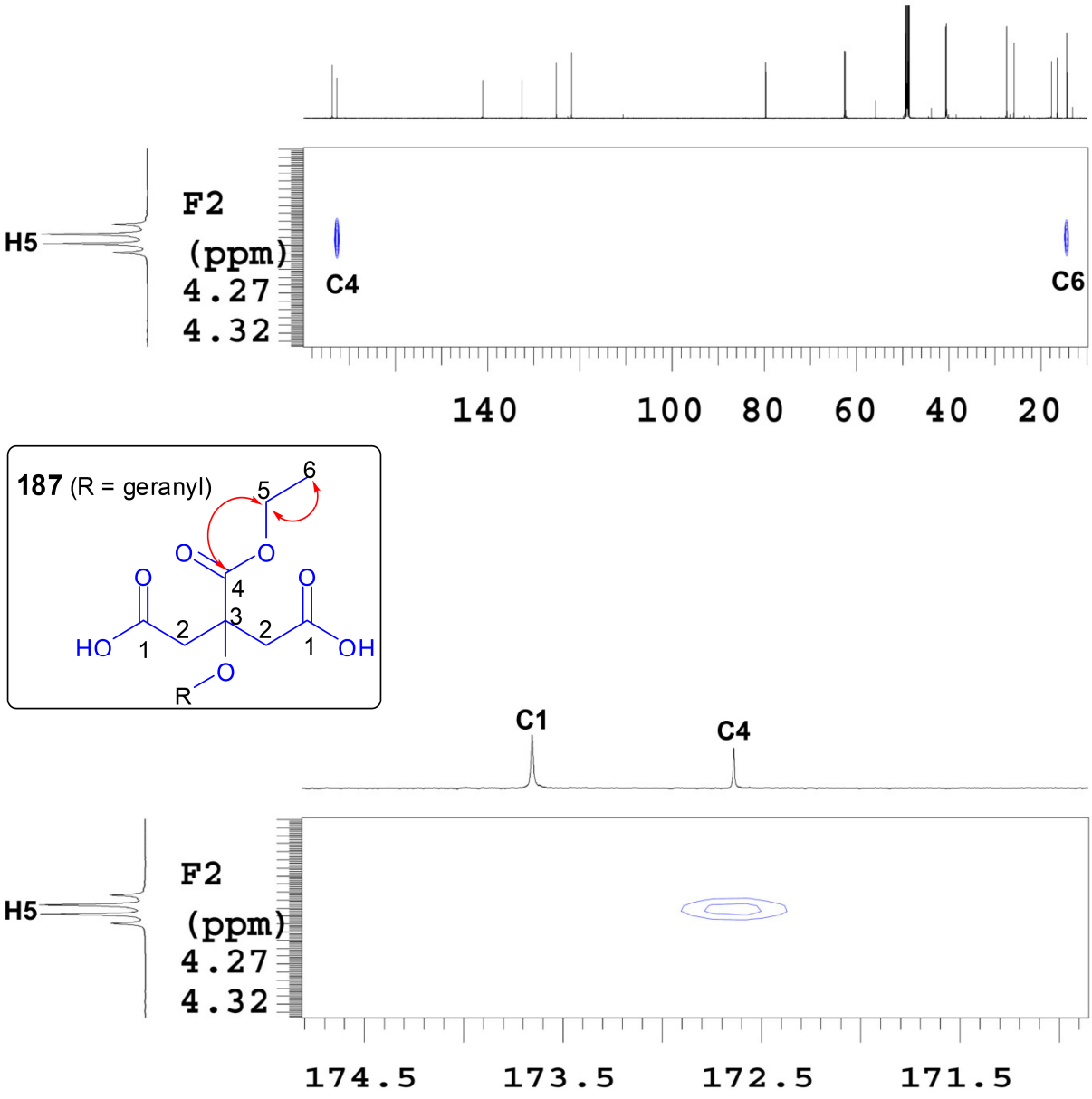


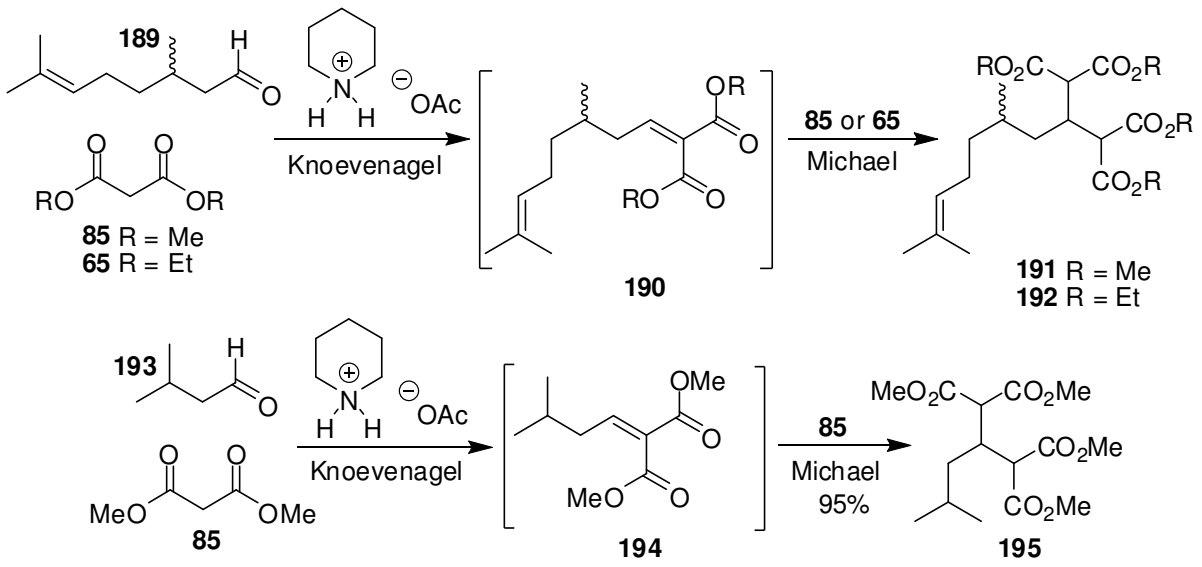
Figure 21: HMBC spectrum of compound **187** showing the position of the ethyl ester group. H5 methylene protons show correlations to C4 and C6 (upper spectrum). Magnification of the upper spectrum shows that the ethyl group belongs to the carbonyl group at C4 and not at C1 (lower spectrum).

3.4 Derivatives of tetracarboxylic acids

As it has been demonstrated in Chapter 1.4.2, nature´s strategy for the design of highly potent prenyl transferase inhibitors based on a polycarboxylic acid core is unprecedented. In the attempt to emulate nature, here follow some synthetic expeditions into the preparation of tetracarboxylic acids as putative mimicries of the naturally occurring prenyl diphopshate substrates.

3.4.1 Towards the synthesis of 2-alkyl-propane-1,1,3,3-tetracarboxylic acids

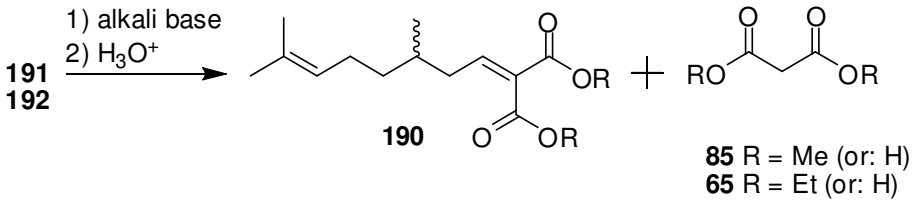
Citronellal **189** was reacted with malonic esters **85** and **65** to propane-1,1,3,3-tetra-carboxylic esters **191** and **192**, respectively, in a Knoevenagel condensation followed by a Michael addition of one unit malonic ester to the α,β-unsaturated Knoevenagel intermediate **190**. The same procedure was also performed with isovaleraldehyde **193** and malonic ester **85** to give short-chain tetracarboxylic ester **195** in excellent yields (Scheme 55).



Scheme 55: Synthetic route to 2-alkyl-propane-1,1,3,3-tetracarboxylic esters **191**, **192** and **195** *via* a sequence of Knoevenagel condensation followed by a Michael addition.

Attempts to isolate **191**, **192** and **195** by vacuum-distillation failed. In all of the cases malonic ester (**85** or **65**) and the corresponding α,β-unsaturated ester (**190** or **194**) were found in the distillate, thus indicating the instability of these compounds. In contrast, silica gel column chromatography proved as a compatible and neat purification method for this class of compounds.

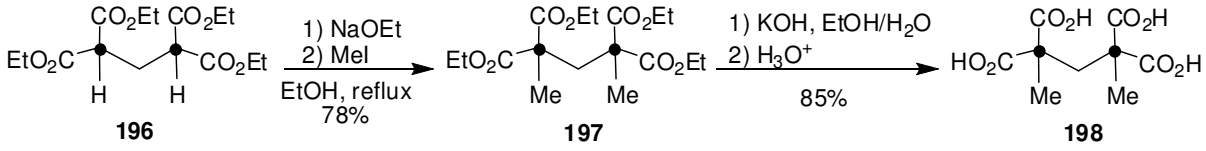
The next obvious step to conduct was the complete hydrolysis of all four ester groups. Several attempts to cleave off all esters failed. Under the conditions of aqueous alkaline hydrolysis the tetraesters decomposed to Knoevenagel product **190** and malonic ester (**85**, **65**) or the carboxylic acids thereof (Scheme 56).



Scheme 56: Tetraesters **191** and **192** are prone to *retro*-Michael addition under alkaline conditions.

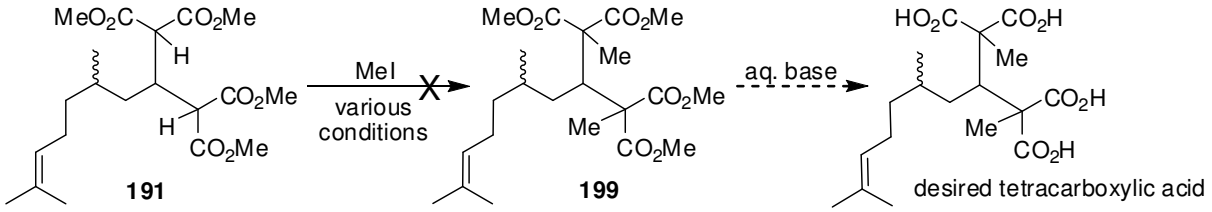
Apparently, this observation is the result of a *retro*-Michael addition. These findings are in agreement with Wittig´s report about the breakdown of tetraesters in alcoholic sodium ethoxide solution with formation of benzylidenemalonic ester and sodium malonic ester.[170] On the other hand, acid-catalyzed ester hydrolysis under *retro*-Fischer esterification conditions appears critical in the present case due to the required elevated temperatures (reflux) and the danger of decarboxylation connected therewith.

In order to suppress the reversibility of the Michael addition observed under basic conditions, it was envisioned to replace the acidic hydrogens in the malonate units by a methyl group. By doing so, no *retro*-Michael should be possible any longer. In an encouraging report, Crouse and Terando demonstrated the synthesis of the highly water-soluble pentane-2,2,4,4-tetracarboxylic acid **198** in 85% yield from tetraethyl pentane-2,2,4,4-tetracarboxylate **197** which was obtained by methylation of tetra-ester **196** (Scheme 57).[171]



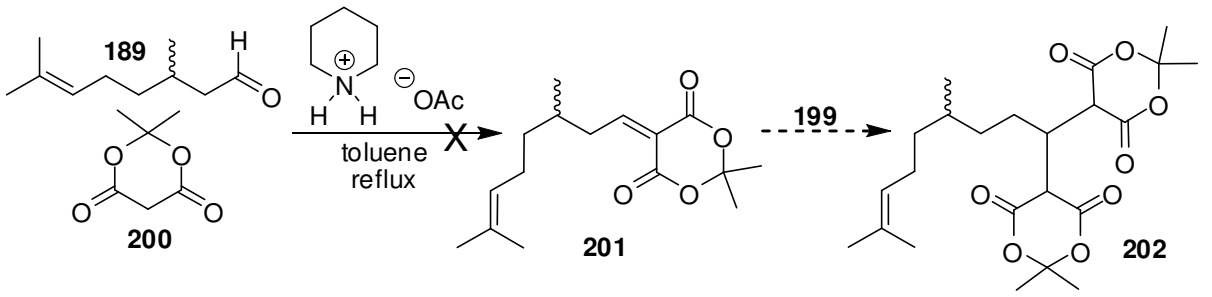
Scheme 57: Detailed view of Crouse´s synthesis of ^{14}C radiolabelled tilmicosin.[171]

In an analogous manner, the alkylation of **191** to **199** appeared promising. However, several attempts to replace the acidic hydrogens by a methyl group with an excess of methyl iodide under various conditions were not successful (Scheme 58).



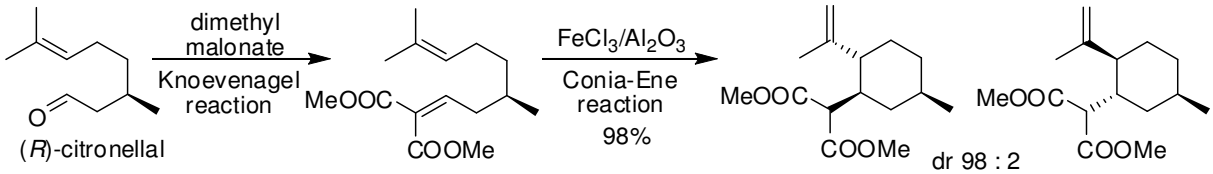
Scheme 58: Attempts to mask the active hydrogens in **191** by a C-C bond via alkylation with methyl iodide.

Another idea that came up was to use Meldrum´s acid **200**[172-173] as a substitute for the malonic esters (**65**, **85**). Isopropylidene malonate **200** contains a methylene group of unusual acidity[174-175] and an ester group that undergoes hydrolysis under mild conditions. These features make Meldrum´s acid an attractive reagent for the synthesis of tetra-ester **202** whose acetonide protecting group can be easily cleaved off in the final step to provide the corresponding tetra-carboxylic acid (Scheme 59).



Scheme 59: Assumed route to 5,5'-(3,7-dimethyloct-6-ene-1,1-diyl)*bis*(2,2-dimethyl-1,3-dioxane-4,6-dione) **202** via condensation of citronellal **189** with Meldrum´s acid **200**.

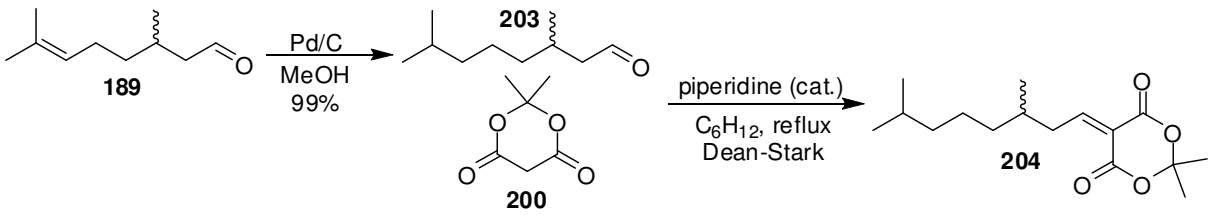
Unexpectedly, all attempts to prepare Knoevenagel product **201** by azeotropic removal of water were fruitless (Scheme 59). All of the byproducts prevailing in the crude reaction mixture were tediously isolated one-by-one and analyzed by HRMS and NMR. None of them was the desired product. One major finding that became obvious upon inspection of the ^{13}C NMR spectra was that the double bond at C6/C7 of the citronellyl chain was no longer existent. The corresponding signals at about δ 124.00 and 131.75 ppm were missing. This led to the conclusion that the double bond must have been involved into some reaction. This is in fact very uncommon for a standard Knoevenagel condensation protocol. Furthermore, citronellal is not a notably reactive aldehyde and its double bond is in general also relatively unreactive. However, there is one case reported, where (*R*)-citronellal reacts with dimethyl malonate in a Lewis-acid promoted domino-Knoevenagel-Conia-Ene reaction to produce *trans*-1,2-disubstituted cyclohexanes diastereoselectively (Scheme 60).[176]



Scheme 60: Tietze´s diastereoselective synthesis of *trans*-1,2-disubstituted cyclohexanes.[176]

Accounting for the expected problems, it was decided to perform the Knoevenagel reaction at room temperature having in mind that the elevated temperatures needed for azeotropic removal of water could be a problem. Thus, citronellal **189** was reacted with Meldrum´s acid **200** at room temperature and molecular sieves (3Å) were added to trap the eliminated water. The new product detected as a single spot on TLC showed the desired mass of *m/z* 281 $[M+H]^+$ and 303 $[M+Na]^+$. However, NMR analysis did *not* confirm the expected structure for **201**. Again, the ^{13}C signals corresponding to the double bond of the citronellyl chain were not present. HRMS analysis confirmed that the atomic composition of the isolated compound is identical with that of the expected one: $C_{16}H_{24}O_4$. A closer look into the 2D NMR spectra revealed that the isolated "single" spot was in fact a complex mixture of several compounds. Eventually, structure elucidation of the formed products proved laborious and was not pursued any further.

In order to circumvent the issue with the troubling alkene bond during Knoevenagel condensation, it was decided to "erase" it straight beforehand. Thus, citronellal **189** was hydrogenated catalytically over Pd/C to produce 6,7-dihydrocitronellal (3,7-dimethyloctanal, **203**). The latter was successfully subjected to Knoevenagel condensation with Meldrum´s acid **200** to provide alkylidene compound **204** (Scheme 61). 2D NMR experiments confirmed the expected structure. The ^1H NMR spectrum of **204** is displayed in Figure 22.



Scheme 61: Catalytic hydrogenation of citronellal **189** gave dihydrocitronellal **203**. Its condensation with Meldrum´s acid **200** under Knoevenagel conditions provided alkylidene product **204**.

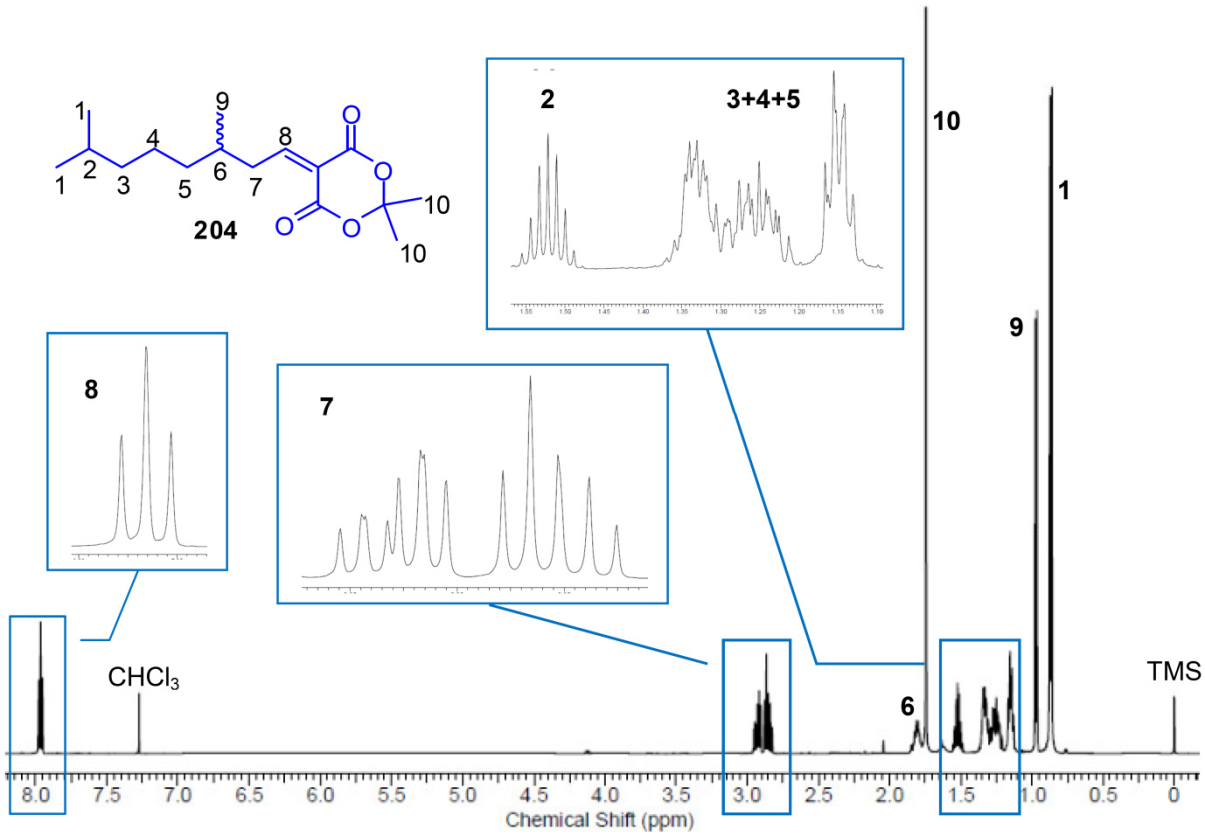
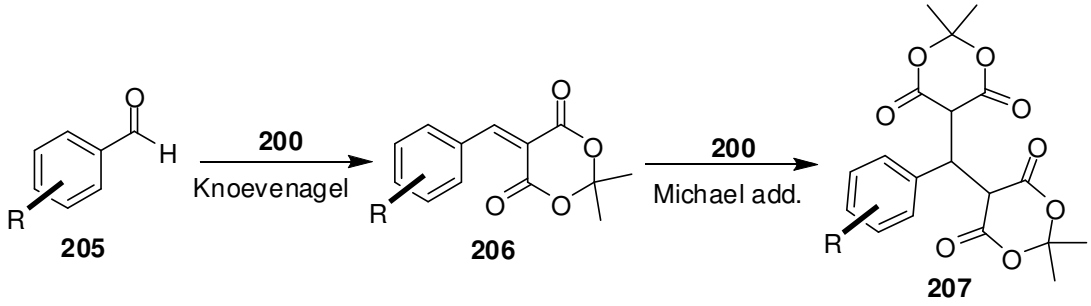


Figure 22: ^{1}H NMR spectrum of compound **204** with assigned signals. Conditions: $CDCl_3$, 400 MHz.

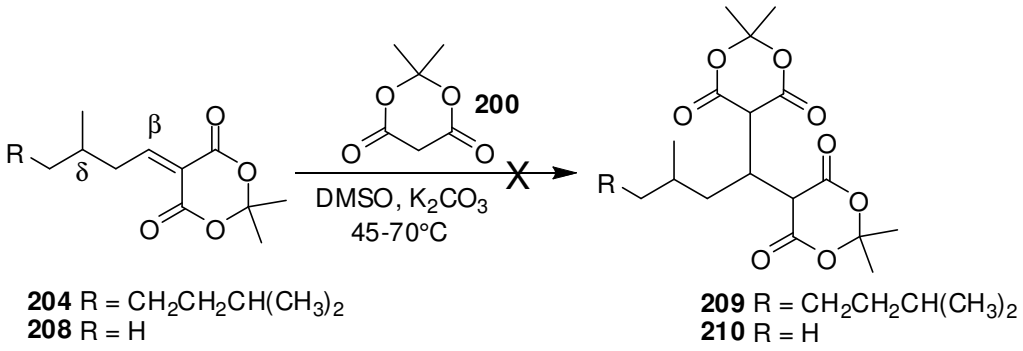
Although Michael adducts of type **207** derived from arylidene analogues **206** with Meldrum´s acid **200** are reported [177-180] to proceed with ease (Scheme 62), the same turned out not to be true for compounds derived from long-chain aliphatic aldehydes.



Scheme 62: Knoevenagel condensation of aromatic aldehydes **205** with Meldrum´s acid **200** readily provides the corresponding 5-(1-arylmethylidene) Meldrum's acids **206**. Subsequent conjugate addition of a second molecule of **200** to **206** gives *bis*-adducts of type **207**.[177-180]

Despite several attempts, formation of *bis*-adduct **209** by a conjugate 1,4-addition failed (Scheme 63). Although compound **210** has been mentioned in a patent (US 2007/0259917) as an intermediate towards the synthesis of 3-isobutylglutaric acid, its isolation and

characterization had not been reported previously. The preparation of **210** could also not be accomplished in the present work.

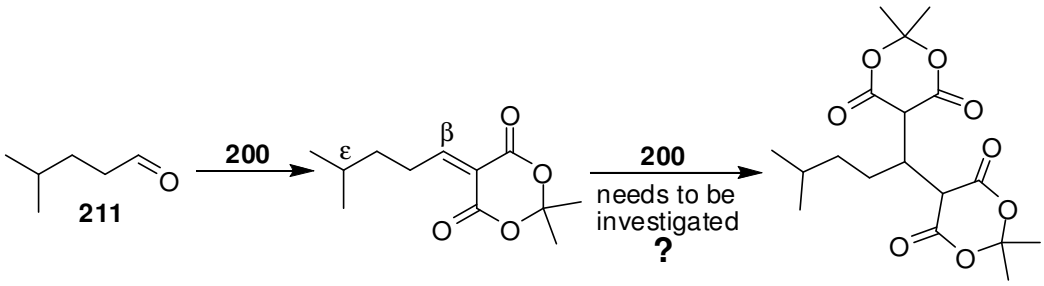


204 R = $CH_2CH_2CH(CH_3)_2$
208 R = H

209 R = $CH_2CH_2CH(CH_3)_2$
210 R = H

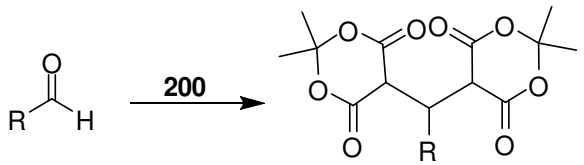
Scheme 63: 1,4-addition of Meldrum´s acid **200** to Michael acceptors **204** and **208** did not work.

From all the unsuccessful attempts to effect a 1,4-conjugate addition the assumption arose that the methyl group at δ-position in alkylidene compounds **204** and **208** might be a hindering factor. Probably because of steric and/or electronic reasons the bulky enolate ion of Meldrum´s acid cannot approach efficiently the β-carbon of the Michael acceptor. Before this can be considered as a main reason, an experiment remains to be done with an aldehyde (e.g. 4-methylpentanal (**211**), Scheme 64) in which the isopropyl group is positioned one methylene group further apart from the carbonyl group when compared to isovaleraldehyde **193**.



Scheme 64: An experiment that still remains to be tried. It should help answer the question if Michael addition is possible when the methyl group is in ε-position instead of δ-position (cf. compound **208**).

In accordance with the upper hypothesis of steric hindrance is the fact that *bis*-adducts (**215**-**217**) of Meldrum´s acid derived from sterically unhindered aldehydes (**212**-**214**) have already been reported (Scheme 65).[181-182] Unfortunately, no spectroscopic data exist for these compounds.



212 R = H
213 R = Me
214 R = *n*-propyl

215 R = H
216 R = Me
217 R = *n*-propyl

Scheme 65: Reported synthesis of 5,5'-methylene*bis*(2,2-dimethyl-1,3-dioxane-4,6-dione) **215**[181], 5,5'-ethane-1,1-diyl*bis*(2,2-dimethyl-1,3-dioxane-4,6-dione) **216**[181] and 5,5'-propane-1,1-diyl*bis*(2,2-dimethyl-1,3-dioxane-4,6-dione) **217**[182].

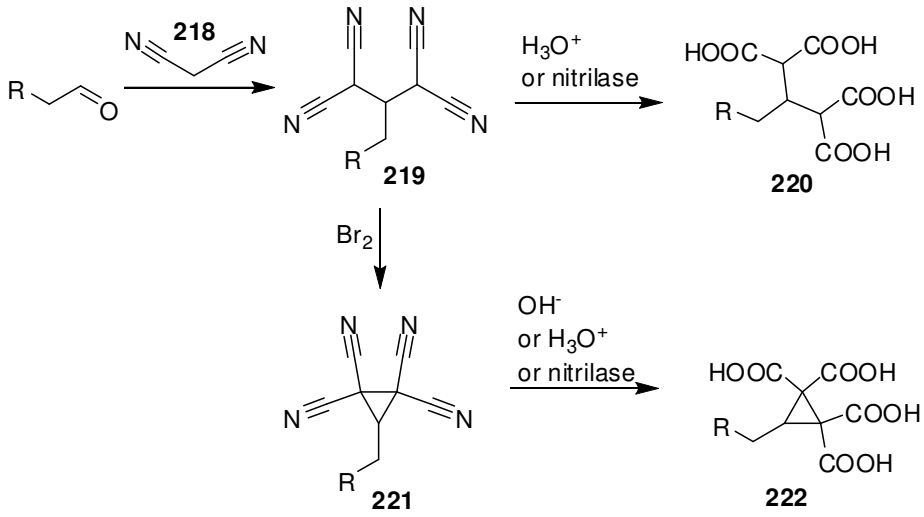
Because of time constraints, further experimental work on this subject was discontinued. However, here are some suggestions for further investigations:

(i) It needs to be clarified if the δ-methyl group in **204** and **208** is really responsible for the encumbered conjugate addition of a second molecule of Meldrum´s acid to the Michael acceptor.

(ii) In respect to point (i) several reported conditions to initiate a Michael addition should be evaluated on the model system: isovaleraldehyde + Meldrum´s acid. The use of Lewis-acid catalysts and transition metals should be taken into consideration, e.g. Lehnert-reagent: $TiCl_4$/pyridine/THF.[183-185]

(iii) Since acyclic tetra-esters (**191, 192** and **195**) were obtained easily and in good yields, their hydrolysis should be tried in an enzymatic way to deliver the corresponding tetra-acids, e.g. with pig liver esterase.

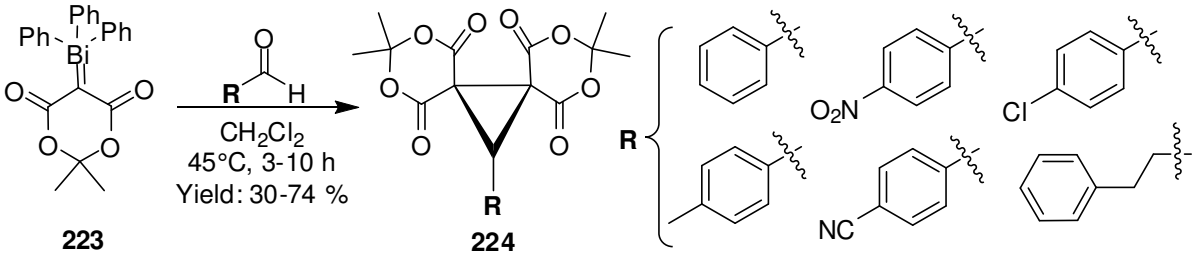
(iv) In analogy to malonic esters **65** and **85**, commercially available propanedinitrile (malononitrile, **218**) can be used as the active-hydrogen component for the domino-Knoevenagel-Michael reaction sequence (Scheme 66). Subsequent hydrolysis of the four nitrile groups to give compound **220** can be achieved either by aqueous acid or by microbial nitrilases[186]. Base promoted nitrile hydrolysis should be avoided at this point due to competing *retro*-Michael addition discussed earlier in this section. However, base-promoted hydrolysis can be tried if the active hydrogens in **219** are masked by a C-C bond as it is the case for cyclopropane-1,1,2,2-tetracarbonitrile **221**. Bromine initiated cyclopropanation of 1,1-methane-*bis*-malononitrile **219** gives **221**. Its hydrolysis to the corresponding cyclopropane-1,1,2,2-tetracarboxylic acid **222** has already been reported.[187-188]



Scheme 66: Proposed route for the synthesis of 2-alkyl-propane-1,1,3,3-tetracarboxylic acids **220** and 3-alkyl-cyclopropane-1,1,2,2-tetracarboxylic acids **222** from 2-alkyl-propane-1,1,3,3-tetracarbonitriles **219**.

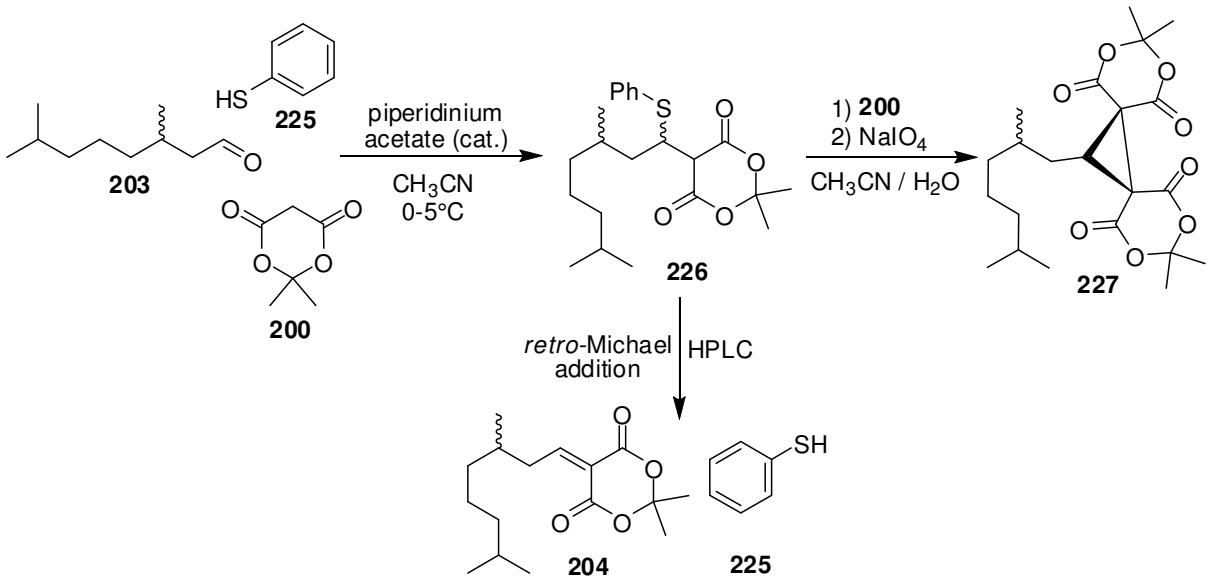
3.4.2 Synthesis of 3-alkyl-cyclopropane-1,1,2,2-tetracarboxylic acids

One possible way to access 3-alkyl-cyclopropane-1,1,2,2-tetracarboxylic acids **222** is the hydrolysis of polynitriles as discussed in Section 3.4.1 (Scheme 66). A second and more direct approach to such exciting cyclopropane derivatives was reported by the group of Ogawa et al.[189] With his new methodology, Ogawa demonstrated the synthesis of several examples of type **224** by a condensation reaction of an aldehyde with a bismuthonium ylide **223**[190] (Scheme 67). The resulting cyclopropanes, each of which is flanked by two units of Meldrum´s acid, can be smoothly hydrolyzed to afford the corresponding cyclopropane-1,1,2,2-tetracarboxylic acids. Prospectively, Ogawa´s method remains to be explored in respect to its applicability for the synthesis of isoprenylated cyclopropane-1,1,2,2-tetracarboxylic acids. Also, bismuth is not the most comfortable metal to have for bioapplications.



Scheme 67: Ogawa´s method for the preparation of 13-substituted-3,3,10,10-tetramethyl-2,4,9,11-tetraoxadispiro[5.0.5.1]tridecane-1,5,8,12-tetrones **224**.[189]

A third method that was successfully applied in the present work makes use of thioalkylated Meldrum´s acid.[191] Thus, dihydrocitronellal **203**, Meldrum´s acid **200** and thiophenol **225** were reacted in acetonitrile in the presence of a catalytic amount of piperidinium acetate to provide the corresponding diastereoisomeric adduct **226** as a white crystalline solid (Scheme 68).



Scheme 68: Synthetic route to thiophenol derived intermediate **226** and cyclopropane **227**. Unfortunately, compound **226** was not especially stable and eliminated thiophenol **225** upon HPLC purification.

According to NMR, the crude product **226** was contaminated with some residual thiophenol. Several attempts to obtain a pure analytical sample of **226** by RP-HPLC purification were not successful. As shown in Figure 23, every time after injection of **226**, there were two peaks detectable at t_R = 5.03 min and t_R = 11.67 min. Their isolation and analysis by NMR revealed two main products: volatile thiophenol[3] **225** and racemic alkylidene derivative **204**.

[3] After evaporation of the mobile phase out of the thiophenol fraction, the flask was always empty.

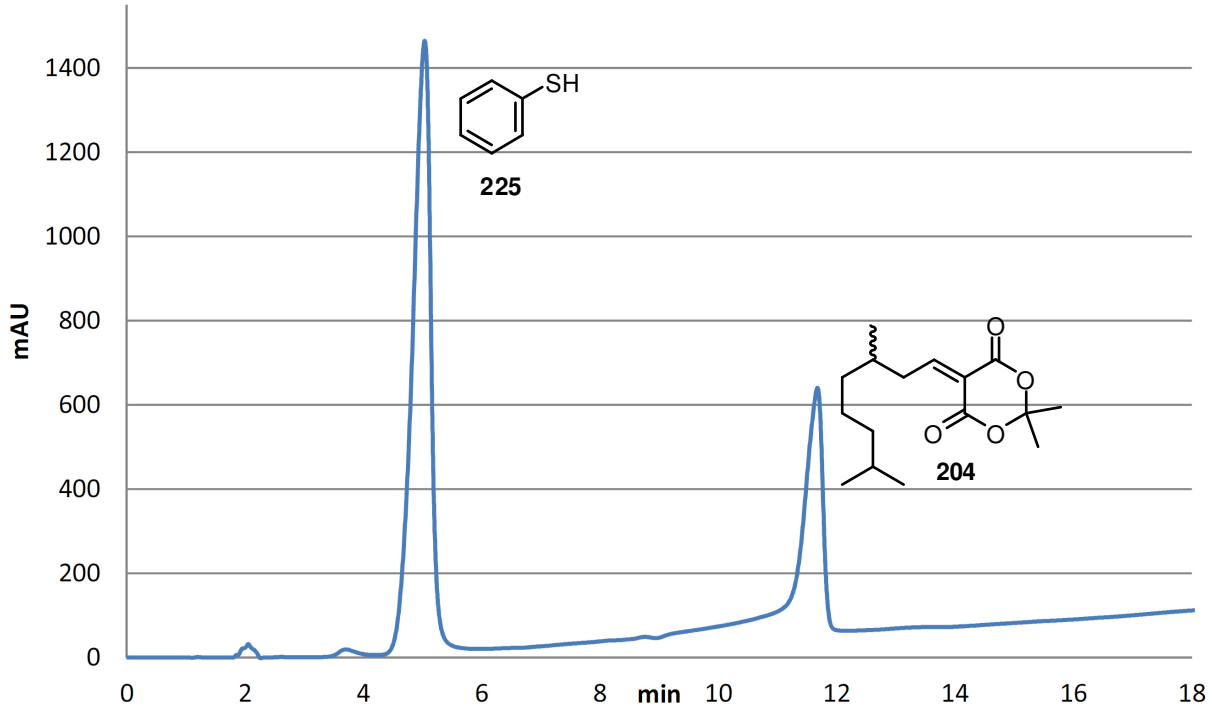
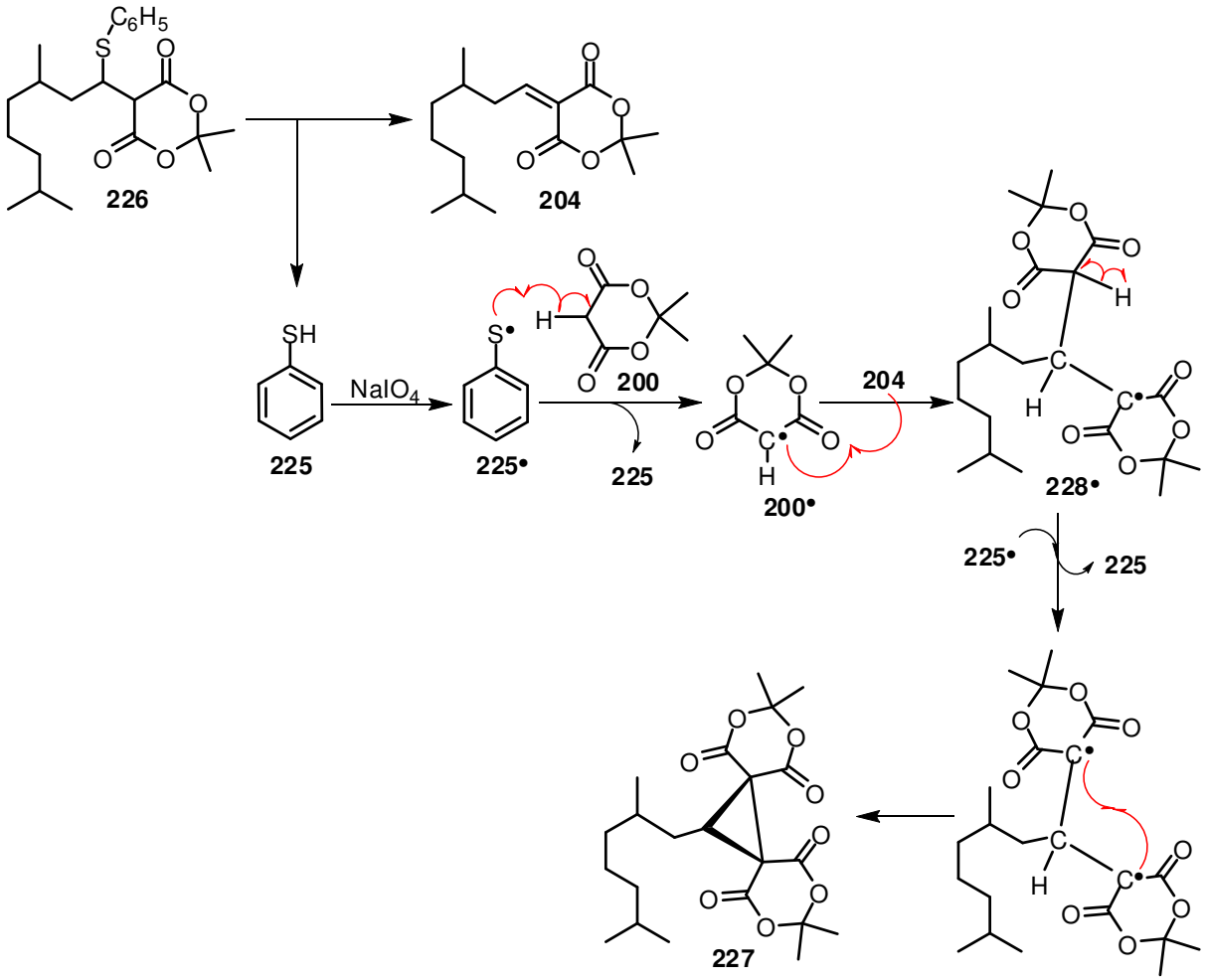


Figure 23: RP-HPLC chromatogram showing the decomposition of **226** into thiophenol **225** (t_R = 5.03 min) and alkylidene product **204** (t_R = 11.67 min) upon chromatography, obviously a result due to a *retro*-Michael addition. (Conditions: MeOH/H_2O; 70% MeOH –(20 min)→ 100%; 0.5 mL/min; λ=210 nm; column: LiChroCART® 125-4 ; LiChrospher® 100 RP-18 (5µm); chromatogram: 2012\XEA\121009\000003.D; measured on: Agilent ("Ava"), see chapter 5.2).

With these results it was concluded that Michael-adduct **226** is not fairly stable in solution and decomposes during HPLC. As a consequence of this, **226** was taken directly into the next step which involved its oxidative cyclization with Meldrum´s acid **200** to give cyclopropane **227** (Scheme 68). As suggested by Lawton[191], the mechanism of cyclization could be of radical nature. For the present case it may be described as follows (Scheme 69):

a) In solution, Michael-adduct **226** dissociates into alkylidene compound **204** and thiophenol **225**. (Note: the reaction is carried out in a mixture of CH_3CN/H_2O = 1/1).
b) Sodium periodate promoted oxidative cleavage of the S–H bond in thiophenol **225** generates a thiyl radical **225•** which abstracts a hydrogen atom from Meldrum´s acid to give the corresponding radical **200•**.
c) **200•** may add to the double bond of **204** in an *anti*-Markovnikov fashion to produce intermediate tertiary radical **228•**.
d) A further hydrogen atom abstraction from **228•** followed by a homolytic ring closure finally affords cyclopropane **227**.



Scheme 69: Suggested mechanism for the formation of 13-(2,6-dimethylheptyl)-3,3,10,10-tetramethyl-2,4,9,11-tetraoxadispiro[5.0.5.1]tridecane-1,5,8,12-tetrone **227** by reacting **226** with 1.0 eq of Meldrum´s acid **200** in the presence of a catalytic amount of sodium periodate.

The structure of **227** is in agreement with the HRMS as well as NMR data. What becomes conspicuous when inspecting the ^{1}H NMR spectrum is the unusually high chemical shift (δ 3.439 ppm) of the tertiary proton H8 attached to the cyclopropane ring (Figure 24). In general, protons in cyclopropanes resonate in the range of δ 0.2–2.0 ppm, depending on their substitution.[192] The reason for the pronounced deshielding observed in the case of **227** may be due to the conformationally fixed position of the carbonyl groups into a six-membered ring. Making a model of **227** with a molecular model kit reveals that the carbonyl oxygens are aligned almost parallel to hydrogen H8, and show a close spatial proximity to the latter. In contrast, no such restriction exists for the carbonyl groups in **229** because of conformational freedom.

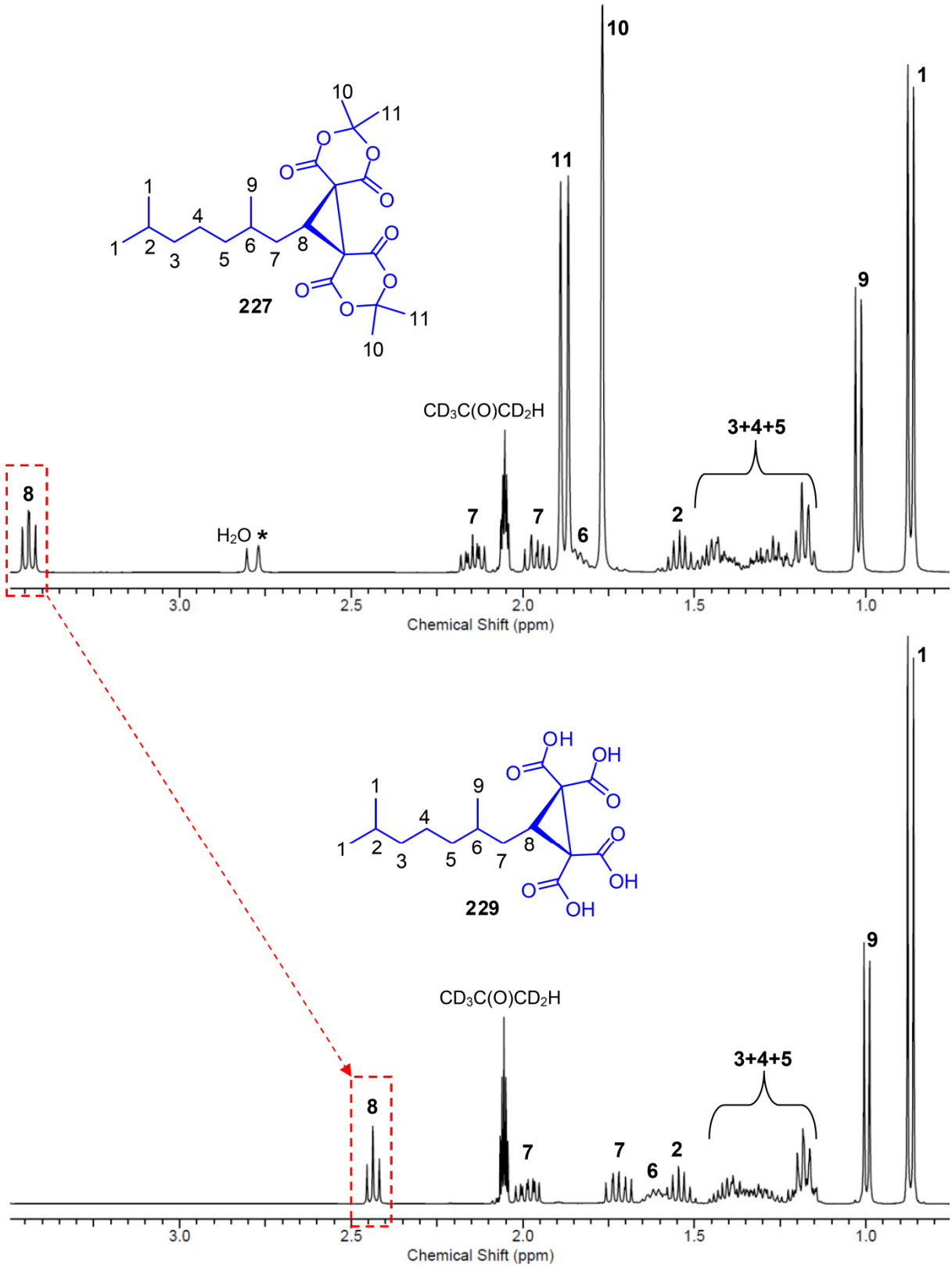
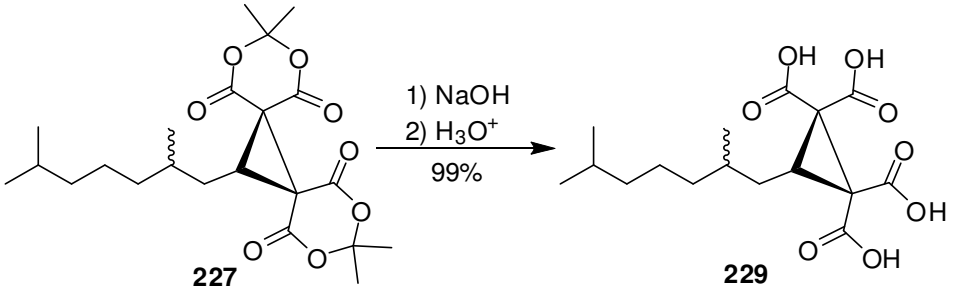


Figure 24: Comparison of the ^{1}H NMR spectra of compounds **227** (upper) and **229** (lower). The cyclopropane proton at δ 3.439 ppm in **227** experiences a strong upfield shift of Δδ 1.00 ppm upon removal of the acetonide protective groups. Measurement conditions: acetone-d_6, 400 MHz. (*) signifies some solvent impurity.

Finally, the last step in the synthesis of tetracarboxylic acid **229** comprised the removal of the acetonide protective groups under alkaline conditions (Scheme 70).



Scheme 70: Deprotection of **227** readily affords 3-(2,6-dimethylheptyl)cyclopropane-1,1,2,2-tetracarboxylic acid **229** in quantitative yields.

When the ^{1}H NMR spectra of compounds **229** and **227** are compared to each other (Figure 24), the following peculiarities become noticeable at first sight: (i) the methyl protons of the acetonide protecting group are not more present, (ii) both methylene protons at carbon 7 are upfield shifted, and (iii) cyclopropane proton at carbon 8 experiences a drastic upfield shift of $\Delta\delta$ 1.00 ppm. The RP-HPLC chromatogram visualizing the retention times of both **227** and **229** is shown in Figure 25.

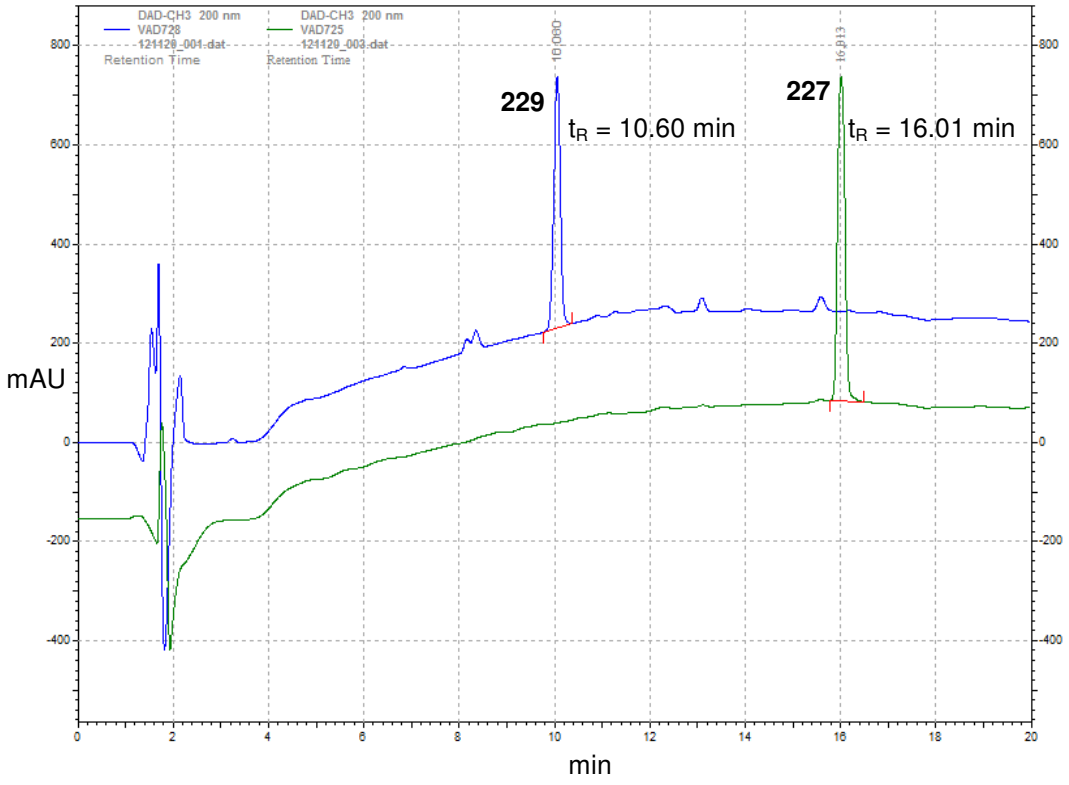


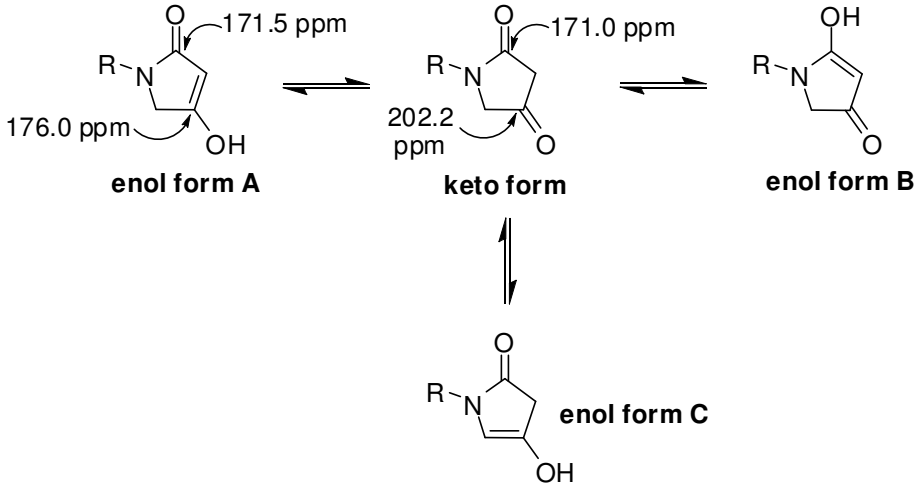
Figure 25: Comparison of the RP-HPLC chromatograms of compounds **227** and **229**. (Conditions: (CH_3CN/H_2O) + 0.1% HCO_2H; 5% CH_3CN –(15 min)→ 100%; 0.8 mL/min; λ = 210 nm; column:125x4 mm; LiChrospher 100-5, RP-18; chromatogram: 2012\XEA\121009\000003.D; measured on: VWR LaChrom Elite (“Mary”), see chapter 5.2).

4 Diphosphate Mimetics: The Search Goes On …

The following short chapter was included in place of an "outlook" chapter since the scope and long-term continuation of the project treated in the present thesis was already introduced in Chapter 2 and specific points are discussed at the end of Chapter 3.4.1. Rather, Chapter 4 provides a brief overview on three selected compound classes relevant to the topic of this thesis, giving stimuli for further research at the same time.

4.1 Derivatives of tetramic acid

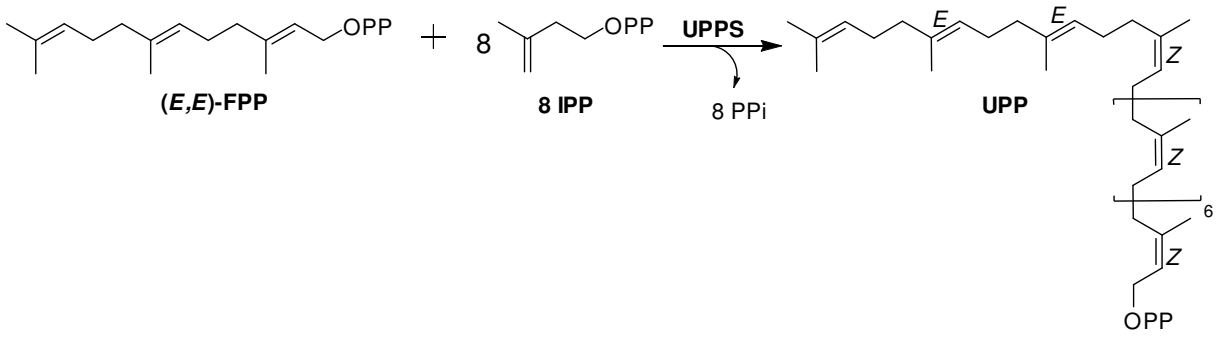
The tetramic acid family was recognized in the sixties to be a reoccurring structural motif in a variety of isolated natural products. It is based on the 2,4-pyrrolidinedione core (keto form in Scheme 71) and is documented to affect a wide variety of biological targets.[193] Theoretically, tetramic acids may exist as a keto form and three enol forms in solution (Scheme 71). However, only the keto form and/or enol form A are actually observed by NMR spectroscopy on the basis of chemical shift evidence, and their ratio is strongly dependent on the applied solvent.[194]



Scheme 71: Tautomeric forms of tetramic acids.[194] ^{13}C NMR shifts for enol A and keto form are given.

Undecaprenyl diphosphate synthase (UPPS) is an enzyme essential for bacterial viability. As shown in Scheme 72, it catalyzes the *cis*-double bond formation during sequential condensation of eight isopenetenyl disphosphate (IPP) molecules with farnesyl diphosphate (FPP) to form C_{55}–undecaprenyl disphosphate (UPP) which is the lipid carrier for the precursors of various cell wall structures, such as peptidoglycan, teichoic acids and *O*-antigens.[23] UPPS is highly conserved among Gram-positive and Gram-negative bacteria.

The critical biological function of UPPS, as well as the existence of an active site which is susceptible to inhibition by small molecules, make UPPS an attractive target for the discovery of novel antibacterial agents.[195-198]



Scheme 72: Chain elongation catalyzed by undecaprenyl diphosphate synthase (UPPS).

UPPS inhibitors based on tetramic acids have been identified by high-throughput screening (HTS) and a subsequent medicinal chemsistry program.[199] The complexity of the *Streptococcus pneumoniae* UPPS reaction mechanism, which was established as a random-sequential substrate binding mechanism[200], makes the characterization of the UPPS inhibitors using traditional enzyme kinetics rather challenging. For this reason, the group of Deng et al.[200] used biophysical approaches to investigate the mode of inhibition related to tetramic acids. In their studies, Deng et al. applied a fluorescent FPP analogue (Figure 26) to evaluate the possibility of tetramic acid binding to the FPP binding side of UPPS. Likewise, a tetramic acid analogue containing a photosensitive moiety (Figure 26) was used to probe the site of binding. The inhibition mechanism of tetramic acids was investigated by determining the interaction of a representative tetramic acid inhibitor with UPPS in the presence and absence of substrate analogues farnesyl thiodiphosphate (FSPP) and isopentyl *S*-thiolodiphosphate (ISPP) (Figure 26) using photo-cross-linking and protein fluorescence spectroscopy.[200]

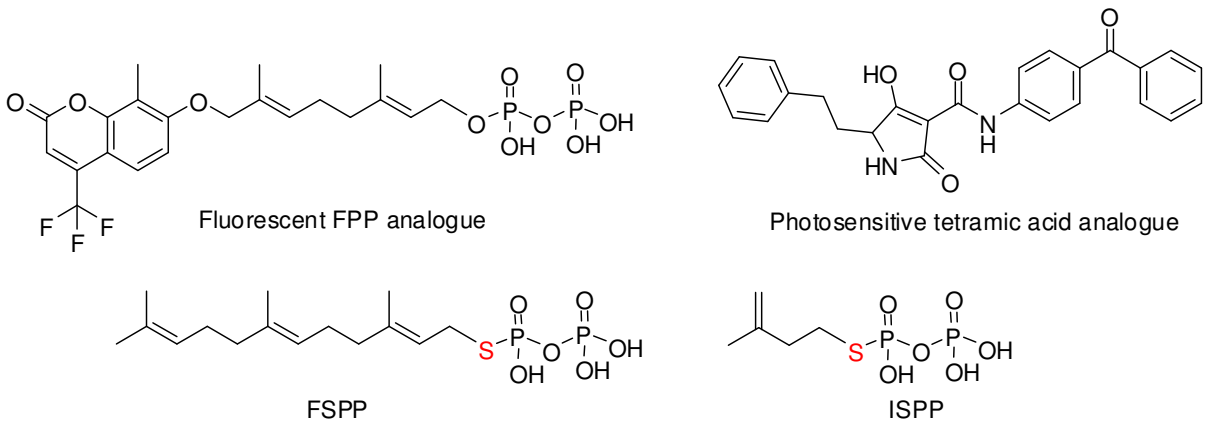


Figure 26: Chemical structures of compounds mentioned in the text.

The possibility of binding of tetramic acids inhibitors to the FPP binding site was examined via titration of UPPS into a fixed concentration of a fluorescent FPP probe and tetramic acid. The obtained results suggested that tetramic acids did *not* compete with the FPP probe, thus indicating that they bind to UPPS at an allosteric site adjacent to the FPP binding site (i.e. tetramic acids are *not* competitive inhibitors with respect to FPP).[200] Moreover, tetramic acids (TA) bind to free UPPS enzyme but not to substrate-bound UPPS. In the case of *S. pneumoniae* UPPS, only one substrate (FPP or IPP) is able to bind to the UPPS·TA complex, but the quaternary complex UPPS·TA·FPP·IPP cannot be formed.[200]

4.2 Derivatives of α,γ-diketo acid

The screening of a library of 200,000 compounds by a team of Italian researchers has shown that 2,4-dioxo-4-phenylbutyric acid (α,γ-diketo acid, DKA) (Figure 27A) functions as a selective and reversible inhibitor of RNA-dependent RNA polymerase of the hepatitis C virus (RdRP HCV, viral nonstructural protein NS5b).[201]

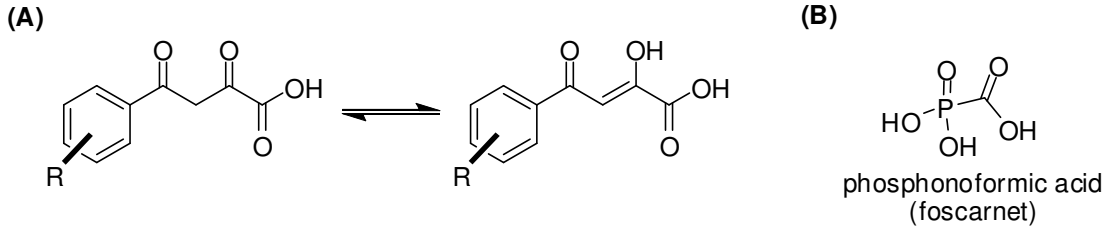
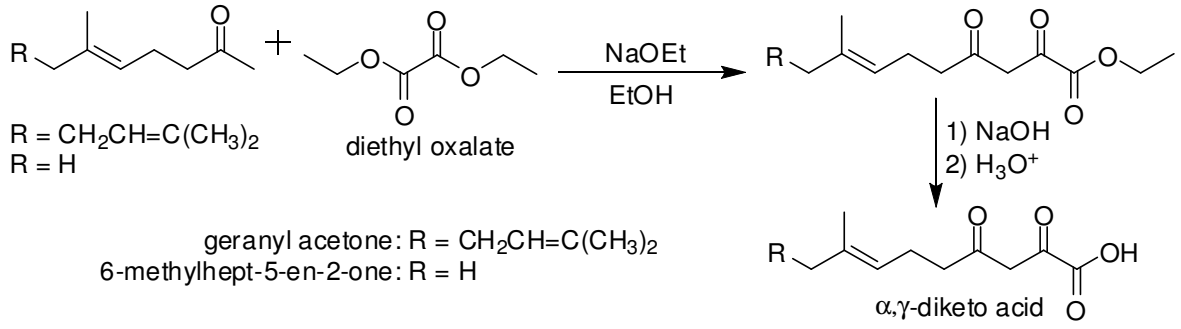


Figure 27: (A) Tautomeric forms of DKA (left: keto form; right: enol form); (B) Structure of foscarnet.

According to data of the same authors, inhibition was non-competitive with respect to the nucleoside triphosphate (NTP) substrate and RNA template. Comparison of the effects of DKAs and a pyrophosphate analog, foscarnet (Figure 27B), also showed that both compounds competed for the common binding center in the active center of RdRP.[202] Based on this fact the authors suggested that diketo acids can be considered as diphosphate analogues. According to their hypothesis, the enol-form dianion of DKAs (Figure 27A, right structure) forms a metal complex with Mg^{2+} or Mn^{2+} present in the enzyme active center, which, in turn, prevents the binding of NTP substrate and formation of phosphodiester bond. In accordance with this mechanism, the aromatic component of the inhibitor is responsible for specificity and strength of additional interactions with the binding center.[203]

Based on these findings, it can be reasoned that the α,γ-diketo acid structural motif could also prove effective on prenyl transferases (instead of RNA polymerases). For this reason the synthesis of a series of prenyl chain derived α,γ-diketo acids appears attractive. Scheme

73 gives a first idea how such type of diphosphate mimetics can be accessed easily from commercially available starting materials via the Claisen ester condensation. Since this class of compounds – to the best of my knowledge – has not been reported previously, neither in a synthetic nor in a use-applied sense, there is still a gap that remains to be filled.



Scheme 73: Suggested synthesis of prenylated α,γ-diketo acids via the Claisen condensation.

4.3 Derivatives of quadratic acid (squaric acid, cyclobutenedione)

Squaric acid is a diacid that exhibits two acidic hydroxyl groups with pK_a values of 0.54 and 3.48, respectively, as well as two highly polarized carbonyl groups.[204-205] This structure provides not only unique versatile proton acceptor carbonyl groups[206] but also nucleophilic binding sites to divalent metal ions.[207-208] Since the work of Cohen[209-211] in 1959, many examples of the use of squaric template (Figure 28) have been described particularly in the fields of bioorganic and medicinal chemistry.[212-216] Medicinal chemists use squaric template as either a linker, or a precursor of acidic or metal binding functions.[217]

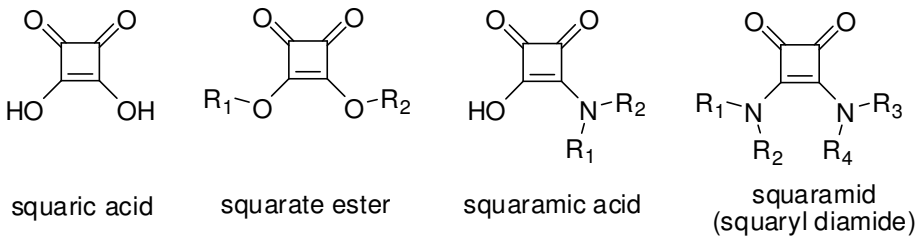


Figure 28: The squarate template – derivatives of squaric acid.

Because of their low pK_a values, derivatives of squaric acid are easily deprotonated at one of their hydroxyl functions thus giving an aromatic cyclobutenyl anion ring system that contains

two π electrons. This resonance structure is known to function as a good electrostatic mimic for both the carboxylic acid and phosphate group (Figure 30).[36] A typical example of a squaric acid derivative which serves as a useful isostere of carboxylic acids and tetrazoles in the context of angiotensin II antagonists is compound **M** (Figure 29).[36, 218]

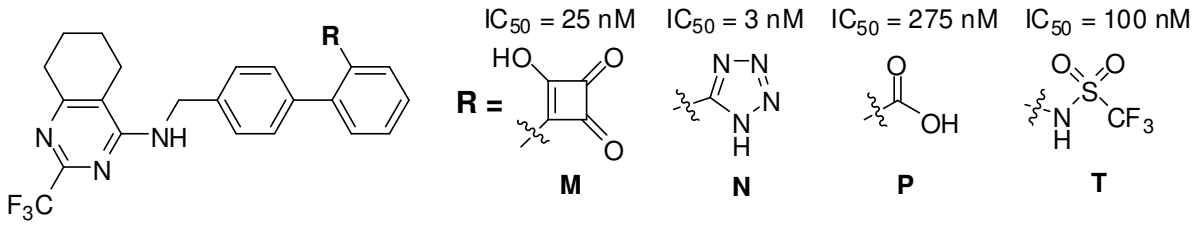


Figure 29: Structure-activity relationships associated with isosteres of carboxylic acid (**P**) in a series of angiotensin II receptor antagonists.

The affinity of the squaric acid derivative **M** for the angiotensin II receptor was within 10-fold of that measured for the tetrazole **N** and superior to both the carboxylic acid **P** and sulfonamide **T**.[218-219] This was attributed to the increased size of the cyclobutenedione moiety and its ability to project acidic functionality an optimal distance from the biphenyl core.[218-219] Squarate **M** reduced blood pressure in Goldblatt hypertensive rats following oral administration with a long lasting effect, although efficacy (IC_{50} = 25 nM) was lower than the analogous tetrazole (IC_{50} = 3 nM).[218]

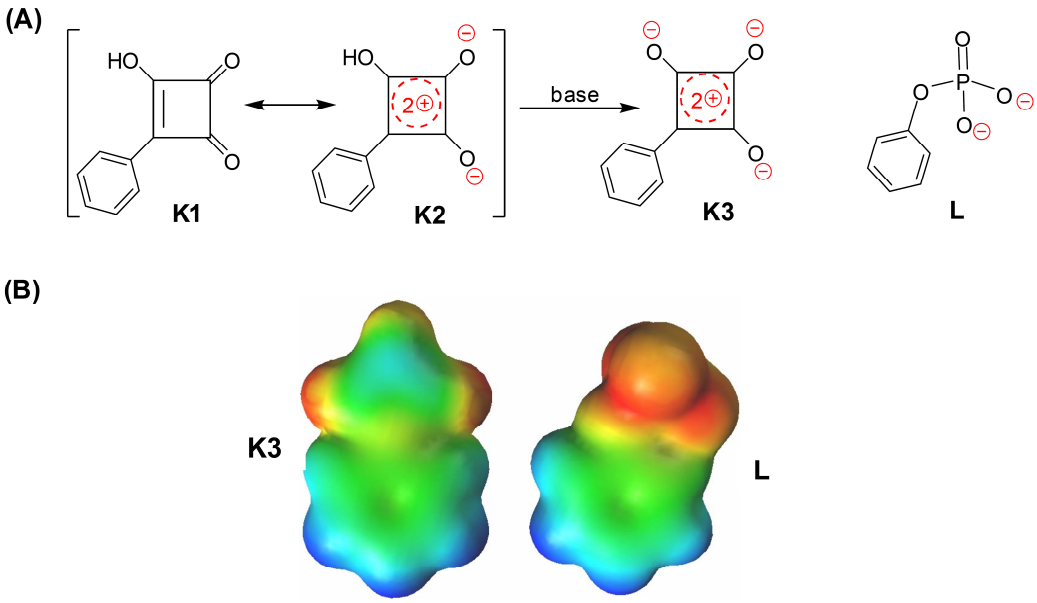


Figure 30: (A) Representation of the structures of squaric acid derivative **K1**/**K2** and its monoanionic form **K3**. (B) Comparison of the electron density calculations for phenyl phosphate dianion **L** (right) and 2-phenyl-1-hydroxycyclobut-1-ene-3,4-dione monoanion **K3** (left). Adapted from ref. [214].

Last but not least, a recent attempt for diphosphate isosterism was probed in the introduction of an additional metal coordinating element to a squaryldiamide, examined in a molecule designed to mimic the sugar-nucleotide GDP-mannose (Figure 31).[220]

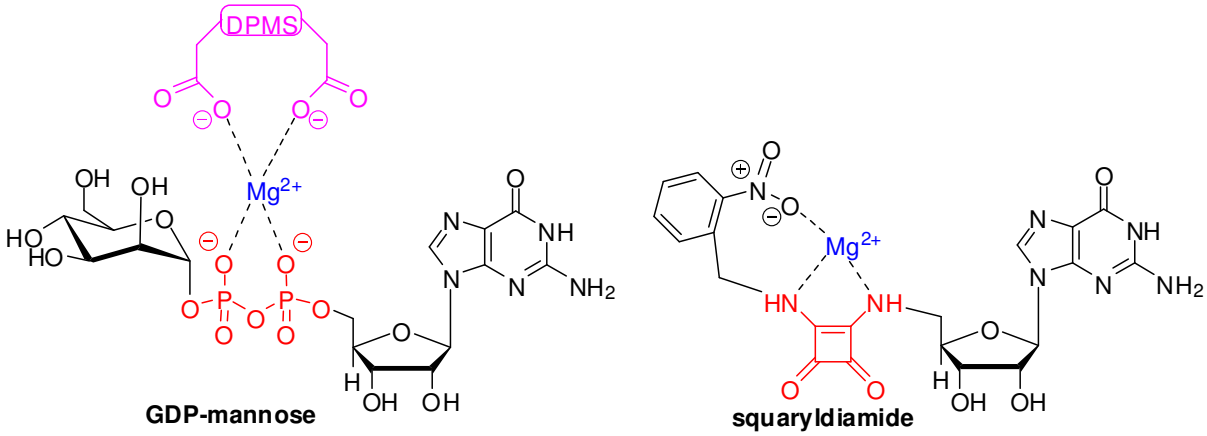


Figure 31: Molecular structures of GDP-mannose coordinated to DPMS enzyme (left) and of a representative squaryldiamide (GDP-sugar mimic) targeted in the study of Wagner.[220] Both the diphosphate group in GDP-mannose and the squaric acid moiety in the squaryldiamide (red colour) can coordinate to a divalent metal like magnesium (blue colour).

Sugar-nucleotides such as GDP-mannose, GDP-fucose and UDP-glucose are important biomolecules with a central role in carbohydrate and glycoconjugate biosynthesis, metabolism and cell signalling.[220] Analogues and mimics of naturally occurring sugar-nucleotides are sought after as chemical tools and inhibitor candidates for sugar-nucleotide-dependent enzymes including glycosyltransferases.[220] Many sugar-nucleotides bind to their target glycosyltransferases *via* coordination of the diphosphate group to a divalent metal cofactor in the active site.[220] The identification of uncharged, chemically stable surrogates for the diphosphate group, with the ability to coordinate to a divalent metal (Mg^{2+}), is therefore an important design criteria for the development of sugar-nucleotide mimics.[220] The group of Wagner et al. described the rational design and synthesis of a novel class of sugar-nucleotide mimics based on a squaryldiamide scaffold (Figure 31), an uncharged phosphate isostere which was designed as a potential inhibitor of the GDP-mannose-dependent mannosyl transferase dolichol-phosphate mannose synthase (DPMS) from *Trypanosoma brucei*, a validated antitrypanosomal target.[220]

In view of these remarkable findings, the design and synthesis of isoprenoid-derived squaric acids as diphosphate mimetics and potential inhibitors for prenyldiphosphate converting enzymes appears very promising and challenging at the same time.

5 Experimental Section

5.1 Materials and Methods

All commercially available reagents were used without further purification and solvents were purified via literature procedures. Analytical thin layer chromatography was performed on Merck silica gel 60 F_{254} precoated aluminum sheets and spots visualized using a combination of UV (254 nm), anisaldehyde, or ceric ammonium molybdate, or potassium permanganate staining. Flash column chromatography was carried out on silica [Merck: Kieselgel 60, particle size 0.040-0.063 mm].

^{1}H and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ (unless otherwise noted) on either a 300 MHz Varian MERCURY-VX 300 apparatus (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR, respectively), on a 400 MHz Varian MERCURY-VX 400 apparatus (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR, respectively) or on a 600 MHz Varian MERCURY-VX 600 apparatus (600 MHz for ^{1}H-NMR and 150 MHz for ^{13}C NMR, respectively). Chemical shifts are reported in ppm relative to Me_4Si (δ 0.00) for ^{1}H NMR spectra; and relative to the solvent signal for ^{13}C NMR spectra. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. On the assignment the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, br m = broad multiplet, br s = broad singlet).

The *low resolution positive and negative ion ESI mass spectra* of the compounds were obtained either from a API-150EX single quadrupole system or an API 3200 triple quadrupole system (AB Sciex, Toronto, Canada) equipped with a Turbo ion spray probe by direct infusion via a CTC PAL autosampler.

The positive and negative *high resolution ESI mass spectra* were obtained from a Bruker Apex III Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer (Bruker Daltonics, Billerica, USA) equipped with an Infinity™ cell, a 7.0 Tesla superconducting magnet (Bruker, Karlsruhe, Germany), a RF-only hexapole ion guide and an external electrospray ion source (Agilent, off axis spray). Nitrogen was used as drying gas at 150°C. The sample solutions were introduced continuously via a syringe pump with a flow rate of 120µl h^{-1}. The data were acquired with 512k data points, zero filled to 2048k by averaging 16 scans and evaluated using the Bruker XMASS software (Versions 6.1.2 or 7.0.8).

Melting points were recorded on a Gallenkamp melting apparatus (uncorrected).

5.2 HPLC: Instruments & Conditions

5.2.1 Instruments

5.2.1.1 Analytical HPLC Systems

- *VWR LaChrom Elite (internal name: "Mary")*
  Components: solvent organizer, pump L-2130, column oven L-2300, autosampler L-2200, DAD L-2455

- *Agilent (internal name: "Ava")*
  Components: solvent organizer, quaternary pump, column oven, well plate autosampler, degasser, DAD

- *Merck Hitachi (internal name: "Pater Borni")*
  Components: interface D-7000, pump L-7100, autosampler L-7200, degasser, UV-VIS detector L-7420

5.2.1.2 Semi-preparative HPLC Systems

- *Knauer Wellchrom (internal name: "K2")*
  Components: two pumps K-1001, manual injector, degasser, UV-detector K-2501

- *Merck Hitachi (internal name: "Witwe Bolte")*
  Components: pump L-7150, manual injector, degasser, UV-detector L-7400

5.2.2 Conditions

A) System: VWR LaChrom Elite ("Mary")
Column: LiChroCART® 125-4 ; LiChrospher® 100 RP-18 (5µm)
Solvents: (H_2O : ACN) + 0.1% TFA ; 25°C ; λ = 210 nm
Gradient: 2% ACN –(20 min)→ 100% (5min) ; Flow rate: 0.8 mL/min

B) System: VWR LaChrom Elite ("Mary")
Column: LiChroCART® 125-4 ; LiChrospher® 100 RP-18 (5µm)
Solvents: (H_2O : ACN) + 0.1% TFA ; 25°C ; λ = 210 nm
Gradient: 2% ACN –(20 min)→ 100% (5min) ; Flow rate: 1 mL/min

C) System: Knauer Wellchrom (“K2”)
Column: Bischoff® 125-8 ; LiChrospher® 100 RP-18 (5µm)
Solvents: H_2O + ACN; 25°C ; λ = 210 nm
Gradient: 50% MeCN –(10 min)→ 100% (1 min); Flow rate: 4 mL/min

D) System: Knauer Wellchrom (“K2”)
Column: Bischoff® 125-8 ; LiChrospher® 100 RP-18 (5µm)
Solvents: (H_2O : ACN) + 0.1% TFA; 25°C ; λ = 210 nm
Gradient: 2% ACN (1 min) –(4 min)→ 70% –(1 min)→ 100%; Flow rate: 4 mL/min

E) System: Knauer Wellchrom (“K2”)
Column: Bischoff® 125-8 ; LiChrospher® 100 RP-18 (5µm)
Solvents: (H_2O : ACN) + 0.1% TFA; 25°C ; λ = 210 nm
Gradient: 2% ACN –(20 min)→ 100% (5 min) –(1 min)→ 2%; Flow rate: 4 mL/min

F) System: Knauer Wellchrom (“K2”)
Column: Bischoff® 125-8 ; LiChrospher® 100 RP-18 (5µm)
Solvents: (H_2O : ACN) + 0.1% TFA; 25°C ; λ = 210 nm
Gradient: 2% ACN –(14 min)→ 70% –(1 min)→ 100%; Flow rate: 4 mL/min

G) System: Knauer Wellchrom (“K2”)
Column: Bischoff® 125-8 ; LiChrospher® 100 RP-18 (5µm)
Solvents: H_2O + ACN; 25°C ; λ = 210 nm
Gradient: 50% ACN –(10 min)→ 100% (1 min) –(1 min)→ 50%; Flow rate: 4 mL/min

H) System: Knauer Wellchrom (“K2”)
Column: YMC-Pack 150-10; ODS-A 120 Å, 5 µm
Solvents: H_2O + ACN; 25°C ; λ = 210 nm
Gradient: 2% ACN –(17 min)→ 87% –(1 min)→ 100%; Flow rate: 4 mL/min

J) System: Knauer Wellchrom (“K2”)
Column: YMC-Pack 150-10; ODS-A 120 Å, 5 µm
Solvents: (H_2O : ACN) + 0.2% formic acid; 25°C ; λ = 210 nm
Gradient: 2% ACN –(17 min)→ 87% –(1 min)→ 100%; Flow rate: 4 mL/min

K) System: Merck Hitachi (“Witwe Bolte”)

Column: YMC-Pack 150-20; ODS-A 120 Å, 5 µm

Solvents: (H_2O : ACN) + 0.2% formic acid; 25°C ; λ = 210 nm

Gradient: 20% ACN –(15 min)→ 80% –(1 min)→ 100%; Flow rate: 16 mL/min

L) System: Agilent (“Ava”)

Column: LiChroCART® 125-4 ; LiChrospher® 100 RP-18 (5µm)

Solvents: H_2O + MeOH; 25°C ; λ = 210, 254, 200-400 nm

Gradient: 70% MeOH –(20 min)→ 100% ; Flow rate: 0.5 mL/min

M) System: VWR LaChrom Elite (“Mary”)

Column: LiChroCART® 125-4 ; LiChrospher® 100 RP-18 (5µm)

Solvents: (H_2O : ACN) + 0.1% formic acid; λ = 210 nm

Gradient: 5% ACN –(15 min)→ 100% ; Flow rate: 0.8 mL/min

N) System: Merck Hitachi (“Pater Borni”)

Column: Chiralcel® OD 250×4.6 mm

Gradient: isocratic flow: *n*-hexane / *iso*-propanol = 80/20; λ = 210 nm; 0.5 mL/min

5.3 General Synthetic Procedures (GSP)

GSP 1: Alkylation (I)

To a stirred suspension of NaH (1.1 eq, 60% dispersion in mineral oil, washed with hexanes (2x10 mL)) in anhydrous THF (or DMF, 20 mL) at 0°C were added 15-crown-5 (0.05 eq) and malonic ester (1.0 eq). Once hydrogen gas evolution had ceased, prenyl bromide (1.1 eq, diluted in 1 mL of THF) was added dropwise via syringe at 0°C. The reaction mixture was allowed to stir for 1-2 h slowly allowing to warm to room temperature. Finally, the reaction mixture was quenched by addition of saturated NH_4Cl solution, diluted with water and extracted 3x into EtOAc or CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Purification of the crude oily material was done by silica gel flash chromatography with Hex/EtOAc.

GSP 2: Saponification of carboxylic esters

The starting material (1.0 eq) was dissolved in a THF/H_2O (3/1 or 5/1) mixture and cooled to 0°C. Excess LiOH*H_2O was added and the reaction mixture was stirred for 2-10 h, slowly allowing to reach room temperature. After complete consumption of starting material, the reaction mixture was cooled again to 0°C and acidified carefully to pH 2-3 with diluted HCl solution. All solvents were evaporated in vacuo and the residue was purified by reverse phase HPLC.

GSP 3: Esterification of carboxylic acids with thionyl chloride

The carboxylic acid (1.0 eq) to be esterified was dissolved in the corresponding anhydrous alcohol (MeOH or EtOH) and cooled to -10°C. Thionyl chloride was added dropwise to the cooled and well stirred solution. The reaction mixture was stirred for 1h at -10°C and then was allowed to reach room temp. over night. On the next day, the reaction mixture was neutralized carefully at 0°C with diluted NaOH solution. After extraction into EtOAc (3x) the organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The isolated product was usually pure enough (NMR!) and could be used directly for the next step without further purification.

GSP 4: Steglich esterification[108]

The carboxylic acid (1.0 eq) to be esterified, the corresponding alcohol (1.0 eq) and DMAP (0.05 eq) were dissolved in anhydrous acetonitrile and cooled to 0°C. Then, DCC (1.0-2.0 eq, dissolved in a small amount of CH_3CN) was added at once. The reaction mixture was stirred at room temperature for 10-14 h. Work-up: the insoluble white precipitate (1,3-dicyclohexylurea) was removed by filtration (or centrifugation). The clear filtrate (or

supernatant) was separated and concentrated in vacuo. The residue was treated one more time with CH_3CN and stored in the fridge for 1 h. The formed precipitate was removed and the clear supernatant was purified by silica gel column chromatography.

GSP 5: Acid-catalyzed acetal cleavage (deprotection)

The corresponding acetal (1.0 eq), was dissolved in an excess of (m)ethanol. An excess of a H^+–resin (Amberlite or Dowex) was added, and the reaction mixture was stirred for 3-10 h at room temperature. When the reaction was complete by TLC, the H^+–resin was filtered off and carefully washed with (m)ethanol. The solvent was evaporated to give the deprotected 1,2-diol.

GSP 6: **Alkylation (II)**

Tricarballylic acid trimethyl ester **169** (1.0 eq) was dissolved in anhydrous THF and cooled to –78°C. LDA (2.0 M in THF, 1.1 eq) was added dropwise via syringe and the reaction mixture was stirred for 40 min at -78°C. Then, the corresponding prenyl bromide (dissolved into 1-2 mL of THF) was added slowly to the cold solution. After addition was complete, the reaction mixture was stirred for 30 min at –78°C and then for 1 h at –50°C. Finally, the reaction mixture was quenched with saturated NH_4Cl solution and was allowed to warm to room temperature. Work-up: THF was removed in vacuo, the reaction diluted with water and extracted 3x into EtOAc. The organic layers were combined, washed with brine and dried over Na_2SO_4. The solvents were evaporated and the crude residue was purified by preparative HPLC.

GSP 7: Alkylation of mercaptans

The corresponding thiol compound (1.0 eq) was dissolved in dry DMF and an excess of K_2CO_3 was added. Prenyl bromide (1.1 eq) was added drowise via syringe and the reaction mixture was stirred at 40°C under inert atmosphere for 14 h. Work-up: DMF was removed in vacuo and the residue was diluted with water and acidified carefully with diluted HCl to pH 3 at 0°C. The aqueous phase was extracted into EtOAc (3x), the organic layers were combined, washed with brine and dried over Na_2SO_4. After evaporation of all solvents the crude residue was purified by preparative HPLC.

GSP 8: Preparation of α-substituted maleates[85],[142]

In a flame dried, nitrogen flushed round-bottom flask was added dropwise freshly ground magnesium turnings (1.2 eq) and THF (3 mL). To this was then added a solution of alkyl bromide (1.0 eq) in THF (5 mL), and a crystal of iodine. The reaction mixture was refluxed for 2 h and cooled to room temperature. The prepared Grignard was then added dropwise to a

suspension of cuprous bromide-dimethyl sulfide complex (1.2 eq) in THF (10 mL) at –40 °C. The resulting solution was stirred at –40 °C for 2 h and then cooled to –78 °C, and freshly distilled DMAD (1.0 eq) in THF (5 mL) was added dropwise to give a dark red-brown mixture. After 1 h, the reaction mixture was quenched with a saturated solution of ammonium chloride (5 mL, adjusted to pH 8 with 10% ammonia) and allowed to warm to room temperature. After 30 min, the mixture was partitioned between water and ether. The aqueous layer was extracted with ether (3x) and the combined organic extracts were washed with an additional portion of saturated aqueous NH_4Cl solution and brine. Drying over Na_2SO_4 and concentration in vacuo afforded a yellow oil. Finally, the crude material was purified by flash column chromatography.

GSP 9: Preparation of α-substituted fumarates[85]

In a flame dried, nitrogen flushed round-bottom flask was added dropwise freshly ground magnesium turnings (1.2 eq) and THF (3 mL). To this was then added a solution of bromide (1.0 eq) in THF (5 mL), and a crystal of iodine. The reaction mixture was refluxed for 2 h and cooled to room temperature. The prepared Grignard was then added dropwise to a stirring solution of freshly distilled DMAD (1.0 eq) at –78 °C to give a dark red-brown mixture. After 1 h, the reaction mixture was quenched with a saturated solution of ammonium chloride (5 mL, adjusted to pH 8 with 10% ammonia) and allowed to warm to room temperature. After 30 min, the mixture was partitioned between water and ether. The aqueous layer was extracted with ether (3x) and the combined organic extracts were washed with an additional portion of saturated aqueous NH_4Cl solution and brine. Drying over Na_2SO_4 and concentration in vacuo afforded a yellow oil. Finally, the crude material was purified by flash column chromatography.

GSP 10: γ-alkylation of β-keto esters[87]

(A) Generation of Dianion: Approximately 25 mL of anhydrous THF was added into a 50 mL flask containing sodium hydride (60% in mineral oil, 1.1 eq). The flask was stoppered with a septum cap, flushed with nitrogen, and cooled in ice. Then methyl acetoacetate (1.1 eq) was added dropwise and the colorless solution was stirred at 0°C for 10 min. To this solution was added dropwise 2.0 M *n*-butyllithium in hexane (1.05 eq) and the yellow to orange solution of the dianion was stirred at 0°C for an additional 10 min before using into the next step.

(B) Alkylation of Dianion: A solution of dianion (1.0 eq) in ca. 25 mL of THF was prepared as above and 1.1 eq of alkylating agent in 2 ml of THF was added. This reaction mixture was allowed to slowly warm to room temperature with stirring. The color of the dianion faded immediately on addition of the alkylating agent. Approximately 1h after the addition of the alkylating agent, the reaction was quenched with saturated NH_4Cl solution and 15 ml of

diethyl ether. The aqueous layer was further extracted with 2x20 ml of diethyl ether. The extracts were combined, washed with water until neutral, dried over anhydrous sodium sulfate, and filtered. The solvents were removed under reduced pressure and the crude product was purified by flash column chromatography.

GSP 11: Alkylation (III)[146]

To LDA at –78°C [2.0 M solution in THF/heptane/ethylbenzene, 2.2 eq.] was added dropwise diethyl malate (1.0 eq.) dissolved in THF. The reaction was stirred for 20 min before addition of the alkyl halide (1.5 equiv). The mixture was stirred for 2 h at –78°C and then allowed to warm slowly to room temperature. Afterwards, the reaction was cooled down to –50°C and quenched with saturated ammonium chloride solution. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated to give an oil that was purified by flash chromatography on silica gel.

GSP 12: Reduction of β-keto esters to β-hydroxy esters

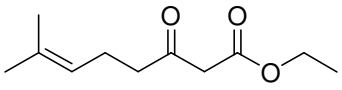
The corresponding β-keto ester (1.0 eq) was dissolved in anhydrous THF and cooled to –10°C. Borane-*tert*-butylamine complex (total amount: 1.5–2.0 eq) was added portionwise. The reaction mixture was stirred at –10°C for 1 h and then was slowly allowed to reach room temperature over one more hour. After TLC analysis indicated that all of the starting material had been consumed, the reaction was quenched by the addition of 10% HCl solution. THF was removed in vacuo and the product was extracted 3x into chloroform. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give the crude material. Purification by flash column chromatography (Hex/EtOAc) afforded the desired β-hydroxy ester.

5.4 Characterization of synthesized compounds

Each of the compounds (structures) listed in this section is assigned to two numbers. The numbers mentioned in the first column are used throughout the text and specify the corresponding compound. The numbers in the third column (Mol-ID) are internal identification codes associated to the institution´s internal compound database. The corresponding experiments are denoted as their "three-letter-codes": *VAD 009, VAD 023* etc.

7	**Ethyl 7-methyl-3-oxooct-6-enoate**[83],[221],[222],[223]	Mol-ID: 10259

VAD 009



$C_{11}H_{18}O_3$
Mol. Wt.: 198,26

GSP 10 was followed. To a suspension of NaH (60% dispersion in oil washed with hexanes, 1.05 g, 43.93 mmol) in THF (100 mL) was added ethyl acetoacetate (5.0 g, 38.42 mmol), and the mixture was stirred at 0°C for 10 min. Then *n*-BuLi (2.7 M heptane solution, 15.65 mL, 42.26 mmol) was added to the suspension, followed by stirring at 0°C for additional 10 min. After addition of 1-bromo-3-methyl-2-butene (6.30 g, 42.26 mmol), the solution was stirred at room temperature for 1 h, quenched with saturated NH_4Cl aqueous solution. The mixture was extracted with EtOAc (3x50 mL), followed by standard workup. The residue was purified by flash column chromatography on silica gel (Hex/EtOAc = 1:1) to give **7** (4.42 g, 22.28 mmol, 58%) as a pale yellow oil.

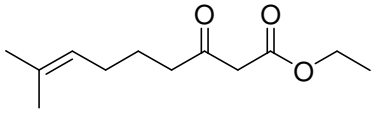
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.282 (t, *J*=7.3 Hz, 3 H), 1.615 (br. s, 3 H), 1.680 (br. s, 3 H), 2.278 (m, *J*=7.3 Hz, 2 H), 2.567 (t, *J*=7.3 Hz, 2 H), 3.431 (s, 2 H), 4.197 (q, *J*=7.3 Hz, 2 H), 5.062 (m, 1 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 14.04 ($CH_2\mathit{C}H_3$), 17.59 (CH_3), 22.15 (CH_2), 25.60 (CH_3), 42.98 (CH_2), 49.33 (CH_2), 61.28 ($\mathit{C}H_2CH_3$), 122.18 (3°C), 133.05 (4°C), 167.17 (C=O, ester), 202.59 (C=O, keto)

(+)-ESI-FTICR-MS: $[C_{11}H_{18}O_3 + Na]^+$ found: *m/z* 221.11454, calc. *m/z* 221.11482

8	**Ethyl 8-methyl-3-oxonon-7-enoate**[224]	Mol-ID: 5580

VAD 023



$C_{12}H_{20}O_3$
Mol. Wt.: 212,29

GSP 10 was followed. To a suspension of NaH (60% dispersion in oil washed with hexanes, 2.10 g, 87.86 mmol) in THF (100 mL) was added ethyl acetoacetate (10.0 g, 76.84 mmol), and the mixture was stirred at 0°C for 10 min. Then *n*-BuLi (2.7 M heptane solution, 31.3 mL, 84.52 mmol) was added to the suspension, followed by stirring at 0°C for additional 10 min. After addition of 5-bromo-2-methyl-2-pentene (12.52 g, 76.84 mmol), the solution was stirred at room temperature for 1 h, quenched with saturated NH_4Cl aqueous solution. The mixture was extracted with EtOAc (3x50 mL), followed by standard workup. The residue was purified by flash column chromatography on silica gel (Hex/EtOAc = 3:1) to give **8** (10.11 g, 47.64 mmol, 62%) as a pale yellow oil.

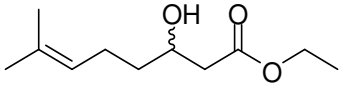
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.279 (t, *J*=7.3 Hz, 3 H, $CO_2CH_2CH_3$), 1.591 (br. s, 3 H), 1.639 (t, *J*=7.1 Hz, 2 H), 1.688 (br. s, 3 H), 1.996 (br. q, *J*=7.2 Hz, 2 H), 2.526 (t, *J*=7.3 Hz, 2 H), 3.426 (s, 2 H, CH_2COOEt), 4.195 (q, *J*=7.3 Hz, 2 H, $CO_2CH_2CH_3$), 5.069 (m, 1 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 14.03 (CH_2CH_3), 17.63 (CH_3), 23.51 (CH_2), 25.64 (CH_3), 27.08 (CH_2), 42.33 (CH_2), 49.28 (CH_2), 61.25 (CH_2CH_3), 123.43 (3°C), 132.54 (4°C), 167.21 (C=O, ester), 202.91 (C=O, keto)

(+)-ESI-FTICR-MS: $[C_{12}H_{20}O_3 + Na]^+$ found: *m/z* 235.13069, calc. *m/z* 235.13046

9	**Ethyl 3-hydroxy-7-methyloct-6-enoate**[223]	Mol-ID: 5581

VAD 050, 051



$C_{11}H_{20}O_3$
Mol. Wt.: 200.27

The title β-hydroxy ester was obtained according to **GSP 12**: Ethyl 7-methyl-3-oxo-6-octenoate (**7**, 700 mg, 3.53 mmol) and borane *tert*-butylamine complex (627 mg, 7.21 mmol) were reacted in dry THF (10 mL) at –10°C for 2-4 h. After TLC analysis indicated that all of the starting material had been consumed, the reaction was quenched with 10% HCl solution, worked-up and the crude material was purified by flash silica column chromatography (Hex/EtOAc = 10/1) to yield the title compound (528 mg, 2.64 mmol, 75%) as a colourless oil. The compound is known but there are no spectral data reported.[223]

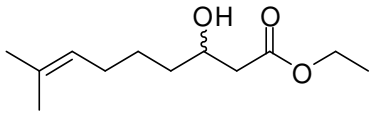
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.277 (t, *J*=7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.380 - 1.599 (m, 2 H), 1.614 (br. s, 3 H), 1.689 (br. s, 3 H), 2.107 (m, 2 H), 2.351 - 2.546 (m, 2 H, CH_2COOEt), 2.995 (br. d, *J*=3.7 Hz, 1 H, OH), 4.009 (m, 1 H, CHOH), 4.173 (q, *J*=7.3 Hz, 2 H, $CO_2CH_2CH_3$), 5.116 (m, 1 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 14.12 (CH_2CH_3), 17.62 (CH_3), 24.02 (CH_2), 25.66 (CH_3), 36.44 (CH_2), 41.29 (CH_2), 60.61 (CH_2CH_3), 67.57 (CHOH), 123.62 (3°C), 132.26 (4°C), 173.01 (C=O)

(+)-ESI-FTICR-MS: $[C_{11}H_{20}O_3 + Na]^+$ found: *m/z* 223.13016, calc. *m/z* 223.13047

10	**Ethyl 3-hydroxy-8-methylnon-7-enoate**	Mol-ID: 10255

VAD 039, 040



$C_{12}H_{22}O_3$
Mol. Wt.: 214.30

The title β-hydroxy ester was obtained according to **GSP 12**: Ethyl 8-methyl-3-keto-7-nonenoate (**8**, 600 mg, 2.83 mmol) and borane *tert*-butylamine complex (320 mg, 3.68 mmol) were reacted in dry THF (10 mL) at –10°C for 1.5 h. After TLC analysis indicated that all of the starting material had been reduced, the reaction was quenched with 10% HCl solution, worked-up and the crude material was purified by flash silica column chromatography (Hex/EtOAc = 5/1) to yield the title compound (369 mg, 1.72 mmol, 61%) as a colourless oil.

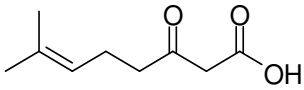
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.277 (t, *J*=7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.316 - 1.571 (m, 4 H), 1.597 (br. s, 3 H), 1.684 (br. s, 3 H), 2.001 (m, 2 H), 2.343 - 2.546 (m, 2 H), 2.961 (d, *J*=3.9 Hz, 1 H, OH), 3.943 - 4.054 (m, 1 H, CHOH), 4.174 (q, *J*=7.1 Hz, 2 H, $CO_2CH_2CH_3$), 5.105 (m, 1 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 14.14 (CH_2CH_3), 17.67 (CH_3), 25.67 (CH_2), 25.68 (CH_3), 27.76 (CH_2), 36.02 (CH_2), 41.26 (CH_2), 60.63 (CH_2CH_3), 67.96 (CHOH), 124.23 (3°C), 131.74 (4°C), 173.10 (C=O, ester)

(+)-ESI-FTICR-MS: $[C_{12}H_{22}O_3 + Na]^+$ found: *m/z* 237.14587, calc. *m/z* 237.14612

11	**7-Methyl-3-oxooct-6-enoic acid**[88],[225],[226]	Mol-ID: 10693

VAD 669



$C_9H_{14}O_3$
Mol. Wt.: 170.21

The title β-ketoacid was prepared by carbonation of an α-lithiated methyl ketone. Thus, 6-methyl-5-heptene-2-one (2.0 g, 15.85 mmol) was dissolved in 20 mL of anhydrous THF and cooled to –78°C. To the cold mixture was added slowly LDA (2.0 M, 9.51 mL, 19.02 mmol) and stirring was continued for more 20 min. After the addition of excess amount of crushed solid CO_2 (dry ice) the reaction mixture was stirred at –78°C for further 2h and then gradually allowed to warm to room temperature. After acidification with HCl and extraction into EtOAc, the crude material was subjected to purification by column chromatography ($CHCl_3$/MeOH = 5/1). The desired compound was isolated as white soft solid (508 mg, 2.98 mmol, 19%). Unfortunately, the target compound showed to be unstable at ambient temperatures, and gradually decarboxylated to the starting methyl ketone (bloomy odor).

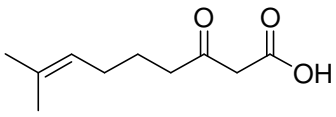
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.616 (s, 3 H), 1.678 (s, 3 H), 2.289 (m, 2 H), 2.597 (t, *J*=7.3 Hz, 2 H), 3.506 (s, 2 H), 5.058 (m, 1 H), 10.767 (br. s., 1 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 17.55 (CH_3), 22.10 (CH_2), 25.55 (CH_3), 43.15 (*C*H_2CO), 48.32 (CO*C*H_2CO)), 121.90 (CH), 133.29 (4°C), 172.16 (COOH), 203.58 (C=O, ketone)

(+)-ESI-FTICR-MS: $[C_9H_{14}O_3 + Na]^+$ found: *m/z* 193.08343, calc. *m/z* 193.08351
(–)-ESI-FTICR-MS: $[C_9H_{14}O_3 - H]^-$ found: *m/z* 169.08702, calc. *m/z* 169.08702

12	**8-Methyl-3-oxonon-7-enoic acid**	Mol-ID: 10256

VAD 042



$C_{10}H_{16}O_3$
Mol. Wt.: 184,23

GSP 2 was followed. Hydrolysis of β-keto ester **8** (50 mg, 0.4 mmol) gave the title compound (28 mg, 0.15 mmol, 63%) as a yellow oil.

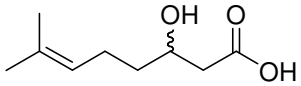
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.592 (br. s, 3 H), 1.611 - 1.673 (m, 2 H), 1.690 (br. s, 3 H), 2.011 (m, 2 H), 2.554 (t, *J*=7.3 Hz, 2 H), 3.506 (s, 2 H), 5.063 (m, 1 H), 9.300 (br. s, 1 H, COOH)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 17.65 (CH_3), 23.45 (CH_2), 25.65 (CH_3), 27.03 (CH_2), 42.55 (CH_2), 47.89 (CH_2), 123.24 (3°C), 132.80 (4°C), 171.28 (C=O, acid), 204.24 (C=O, keto)

(+)-ESI-FTICR-MS: $[C_{10}H_{16}O_3 + Na]^+$ found: *m/z* 207.09876, calc. *m/z* 207.09917

13	**3-Hydroxy-7-methyloct-6-enoic acid**[222],[226],[227] ,[228]	Mol-ID: 5579

VAD 053



$C_9H_{16}O_3$
Mol. Wt.: 172,22

This β-hydroxy acid was obtained according to **GSP 2**. Thus, hydrolysis of β-hydroxy ester **9** (150 mg, 0.75 mmol) gave the title compound (126 mg, 0.73 mmol, 98%) as a yellow oil.

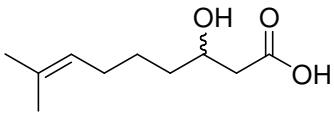
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.277 (t, *J*=7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.380 - 1.599 (m, 2 H), 1.614 (br. s, 3 H), 1.689 (br. s, 3 H), 2.107 (m, 2 H), 2.351 - 2.546 (m, 2 H, CH_2COOEt), 2.995 (br. d, *J*=3.7 Hz, 1 H, OH), 4.009 (m, 1 H, CHOH), 4.173 (q, *J*=7.3 Hz, 2 H, $CO_2CH_2CH_3$), 5.116 (m, 1 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 17.56 (CH_3), 23.93 (CH_2), 25.61 (CH_3), 36.26 (CH_2), 41.06 (CH_2), 67.70 (CHOH), 123.35 (3°C), 132.35 (4°C), 177.42 (C=O)

(–)-ESI-CID-MS: *m/z* 171.4 $[M - H]^-$

14	**3-Hydroxy-8-methylnon-7-enoic acid**	Mol-ID: 5577

VAD 044



$C_{10}H_{18}O_3$
Mol. Wt.: 186,25

This β-hydroxy acid was obtained according to **GSP 2**. Thus, hydrolysis of β-hydroxy ester **10** (163 mg, 0.76 mmol) gave the title compound (143 mg, 0.76 mmol, 100%) as a reddish oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.277 (t, *J*=7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.316 - 1.571 (m, 4 H), 1.597 (br. s, 3 H), 1.684 (br. s, 3 H), 2.001 (m, 2 H), 2.343 - 2.546 (m, 2 H), 2.961 (d, *J*=3.9 Hz, 1 H, OH), 3.943 - 4.054 (m, 1 H, CHOH), 4.174 (q, *J*=7.1 Hz, 2 H, $CO_2CH_2CH_3$), 5.105 (m, 1 H)

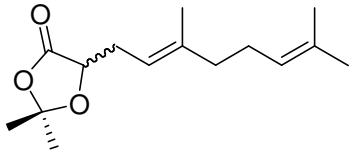
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 17.65 (CH_3), 25.61 (CH_2), 25.65 (CH_3), 27.67 (CH_2), 35.91 (CH_2), 41.09 (CH_2), 68.06 (CHOH), 124.09 (3°C), 131.83 (4°C), 177.77 (C=O)

(+)-ESI-FTICR-MS: $[C_{10}H_{18}O_3 + Na]^+$ found: *m/z* 209.11453, calc. *m/z* 209.11481

(–)-ESI-FTICR-MS: $[C_{10}H_{18}O_3 - H]^-$ found: *m/z* 185.11822, calc. *m/z* 185.11832

17	**2,2-Dimethyl-5-((*E*)-3,7-dimethylocta-2,6-dienyl)-1,3-dioxolan-4-one**	Mol-ID: 9856

VAD 608, 610



$C_{15}H_{24}O_3$
Mol. Wt.: 252,35

The synthesis was carried out following **GSP 11**: 2,2-dimethyl-1,3-dioxolan-4-one[229-231] (96%, 215 mg, 1.77 mmol), LDA (2.0 M, 1.15 mL, 2.31 mmol), and geranyl bromide (97%, 463 mg, 2.07 mmol) were reacted in dry THF (10 mL) at –78°C for 2 h. After work-up the crude material was purified by flash silica column chromatography (Hex/EtOAc = 5/1) to yield the title compound (13 mg, 51.5 µmol, 3%) as a yellow oil.

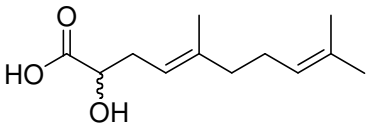
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.537 (s, 3 H), 1.597 (s, 6H), 1.647 (s, 3 H), 1.678 (s, 3 H), 2.059 (m, 4 H), 2.480 (m, 1 H), 2.593 (m, 1 H), 4.452 (dd, *J*=6.2, 4.3 Hz, 1 H), 5.083 (tsept, *J*=6.8, 1.4 Hz, 1 H), 5.194 (tq, *J*=7.3, 1.3 Hz, 1 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.39 (CH_3), 17.65 (CH_3), 25.67 (CH_3), 26.01 (CH_3, acetonide), 26.47 (CH_2), 27.01 (CH_3, acetonide), 30.00 (CH_2), 39.74 (CH_2), 74.41 (CH), 110.47 (4°C, acetonide), 117.04 (CH), 123.97 (CH), 131.56 (4°C), 139.81 (4°C), 172.95 (C=O)

(+)-ESI-FTICR-MS: $[C_{15}H_{24}O_3 + MeOH + Na]^+$ found: *m/z* 307.18754, calc. *m/z* 307.18798

18	**(*E*)-2-Hydroxy-5,9-dimethyldeca-4,8-dienoic acid**	Mol-ID: 10328

VAD 631, 644A, 645



$C_{12}H_{20}O_3$
Mol. Wt.: 212,29

Acetonide group removal of **17** was carried out according to **GSP 5**. The title compound was obtained as a white fluffy solid (59 mg, 0.28 mmol, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.601 (s, 3 H), 1.648 (s, 3 H), 1.686 (s, 3 H), 2.071 (m, 4 H), 2.511 (m, 1 H), 2.612 (m, 1 H), 4.310 (dd, *J*=6.4, 4.7 Hz, 1 H), 5.064 (m, 1 H), 5.163 (m, 1 H)

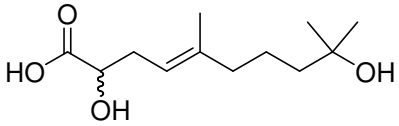
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.27 (CH_3), 17.68 (CH_3), 25.67 (CH_3), 26.41 (CH_2), 32.73 (CH_2), 39.80 (CH_2), 70.06 (CHOH), 117.06 (CH), 123.94 (CH), 131.87 (4°C), 140.87 (4°C), 178.25 (C=O)

(–)-ESI-FTICR-MS: $[C_{12}H_{20}O_3 - H]^-$ found: *m/z* 211.13380, calc. *m/z* 211.13397

HPLC: t_R = 11.10 min (condition **F**)

19	**(*E*)-2,9-Dihydroxy-5,9-dimethyldec-4-enoic acid**	Mol-ID: 10330

VAD 644



$C_{12}H_{22}O_4$
Mol. Wt.: 230,3

The title compound (7.4 mg, 0.03 mmol, 10%, colourless oil) was isolated as a byproduct under the conditions for the synthesis of **18**.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.196 (s, 3 H), 1.232 (s, 3 H), 1.304 - 1.522 (m, 4 H), 1.621 (s, 3 H), 2.007 (m, 2 H), 2.551 (m, 2 H), 4.333 (t, *J*=5.0 Hz, 1 H), 5.191 (t, *J*=7.3 Hz, 1 H), 5.617 (br. s., OH)

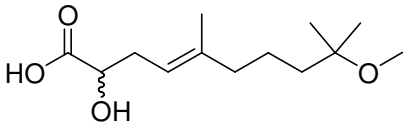
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.18 (CH_3), 21.79 (CH_2), 28.15 (CH_3), 29.23 (CH_3), 32.72 (CH_2), 39.54 (CH_2), 42.31 (CH_2), 70.22 (CHOH), 72.16 (Me_2COH), 117.94 (CH), 139.17 (4°C), 177.38 (C=O)

(–)-ESI-FTICR-MS: $[C_{12}H_{22}O_4 - H]^-$ found: *m/z* 229.14422, calc. *m/z* 229.14453

HPLC: t_R = 7.42 min (condition **F**)

20	**(*E*)-2-Hydroxy-9-methoxy-5,9-dimethyldec-4-enoic acid**	Mol-ID: 10331

VAD 644



$C_{13}H_{24}O_4$
Mol. Wt.: 244,33

The title compound (5.5 mg, 0.02 mmol, 7%, colourless oil) was obtained as a byproduct under the conditions for the preparation of **18**.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.211 (s, 6 H), 1.371 - 1.518 (m, 4 H), 1.621 (s, 3 H), 2.015 (t, *J*=6.9 Hz, 2 H), 2.487 (m, 2 H), 3.779 (s, 3 H), 4.261 (dd, *J*=6.0, 4.8 Hz, 1 H), 5.165 (m, 1 H)

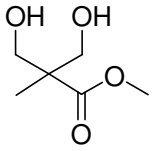
^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 16.15 (CH_3), 22.36 (CH_2), 29.19 (CH_3), 29.31 (CH_3), 32.96 (CH_2), 39.98 (CH_2), 43.19 (CH_2), 52.43 ($Me_2CO\mathit{C}H_3$), 70.49 (CHOH), 70.93 ($Me_2\mathit{C}OCH_3$), 117.75 (CH), 139.38 (4°C), 175.19 (C=O)

(+)-ESI-FTICR-MS: $[C_{13}H_{24}O_4 + Na]^+$ found: *m/z* 267.15643, calc. *m/z* 267.15668

HPLC: t_R = 9.28 min (condition **F**)

33	**Methyl 2,2-bis(hydroxymethyl)propanoate**[105]	Mol-ID: 9281

VAD 453, 465



$C_6H_{12}O_4$
Mol. Wt.: 148,16

The synthesis was carried out according to **GSP 3:** 2,2-bis(hydroxymethyl)propionic acid (5.0 g, 37.28 mmol) was dissolved in 60 mL of anhydrous MeOH and cooled to –10°C. Thionyl chloride (4.66 g, 39.14 mmol) was added dropwise. The title compound (3.3 g, 22.27 mmol, 60%) was isolated as a white crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.08 (s, 3 H), 3.18 (br. s., 2 H), 3.71 (d, *J*=11.1 Hz, 2 H), 3.76 (s, 3 H), 3.89 (d, *J*=11.1 Hz, 2 H)

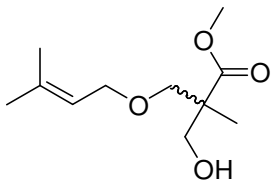
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 17.09 (CH_3), 49.13 (4°C), 52.15 ($CO_2\mathit{C}H_3$), 67.75 (2x CH_2), 176.32 (C=O)

(+)-ESI-FTICR-MS: $[C_6H_{12}O_4 + Na]^+$ found: *m/z* 171.06277, calc. *m/z* 171.06278

Melting point: 28–29 °C

36	**Methyl 3-(3-methylbut-2-enyloxy)-2-(hydroxymethyl)-2-methylpropanoate**	Mol-ID: 9209

VAD 458, 459



$C_{11}H_{20}O_4$
Mol. Wt.: 216,27

The synthesis was carried out according to **GSP 1**: NaH (60% dispersion in oil washed with hexanes, 148 mg, 3.71 mmol), methyl 2,2-bis(hydroxymethyl)propanoate **33** (500 mg, 3.37 mmol), 15-crown-5 (38 mg, 0.17 mmol) and 3,3-dimethylallyl bromide (614 mg, 3.71 mmol) in anhydrous DMF (15 mL) were reacted at 0°C. After work-up the crude material was purified by flash silica column chromatography (Hex/EtOAc = 1/1). The title compound (160 mg, 0.74 mmol, 22%) was obtained as a pale yellow oil.

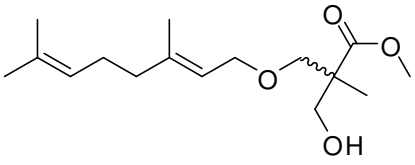
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.17 (s, 3 H), 1.66 (s, 3 H), 1.74 (s, 3 H), 2.70 (br. t, *J*=6.1 Hz, 1 H), 3.44 (d, *J*=9.0 Hz, 1 H), 3.71 (d, *J*=9.0 Hz, 1 H), 3.73 (s, 3 H), 3.79 - 3.86 (m, 2 H), 3.95 - 3.99 (m, 2 H), 5.31 (m, 1 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 17.84 (CH_3), 18.03 (CH_3), 25.75 (CH_3), 48.68 (4°C), 52.01 (CH_3), 66.93 (CH_2), 67.97 (CH_2), 73.59 (CH_2), 120.74 (3°C), 137.22 (4°C), 175.77 (C=O)

(+)-ESI-FTICR-MS: $[C_{11}H_{20}O_4 + Na]^+$ found: *m/z* 239.12517, calc. *m/z* 239.12538

37	**Methyl 3-((*E*)-3,7-dimethylocta-2,6-dienyloxy)-2-(hydroxymethyl)-2-methylpropanoate**	Mol-ID: 9212

VAD 464



$C_{16}H_{28}O_4$
Mol. Wt.: 284,39

The synthesis was carried out according to **GSP 1**: NaH (60% dispersion in oil washed with hexanes, 267 mg, 6.68 mmol), methyl 2,2-bis(hydroxymethyl)propanoate **33** (900 mg, 6.07 mmol), 15-crown-5 (68 mg, 0.30 mmol) and geranyl bromide (1.58 g, 6.98 mmol) in anhydrous DMF (20 mL) were reacted at 0°C. After work-up the crude material was purified by flash silica column chromatography (Hex/EtOAc = 1/1). The title compound (344 mg, 0.74 mmol, 20%) was obtained as a yellow oil.

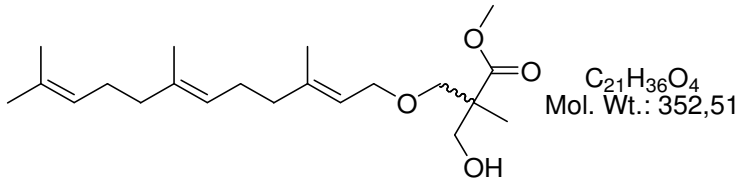
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.17 (s, 3 H), 1.61 (s, 3 H), 1.65 (s, 3 H), 1.68 (s, 3 H), 1.95 - 2.16 (m, 5 H), 2.70 (dd, *J*=7.4, 5.5 Hz, 1 H), 3.44 (d, *J*=9.0 Hz, 1 H), 3.71 (d, *J*=9.0 Hz, 1 H), 3.73 (s, 3 H), 3.83 (dd, *J*=11.3, 5.5 Hz, 1 H), 3.94 - 4.05 (m, 2 H), 5.09 (m, 1 H), 5.29 (m, 1 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.42 (CH_3), 17.68 (CH_3), 17.85 (CH_3), 25.67 (CH_3), 26.29 (CH_2), 39.52 (CH_2), 48.67 (4°C), 52.02 (CH_3), 66.98 (CH_2), 67.94 (CH_2), 73.57 (CH_2), 120.51 (3°C), 123.83 (3°C), 131.68 (4°C), 140.47 (4°C), 175.76 (C=O)

(+)-ESI-FTICR-MS: $[C_{16}H_{28}O_4 + Na]^+$ found: *m/z* 307.18779, calc. *m/z* 307.18798

38	**Methyl 3-((*2E,6E*)-3,7,11-trimethyldodeca-2,6,10-trienyloxy)-2-(hydroxymethyl)-2-methylpropanoate**	Mol-ID: 9214

VAD 467



$C_{21}H_{36}O_4$
Mol. Wt.: 352,51

The synthesis was carried out according to **GSP 1**: NaH (60% dispersion in oil washed with hexanes, 297 mg, 7.42 mmol), methyl 2,2-bis(hydroxymethyl)propanoate **33** (1.00 g, 6.75 mmol), 15-crown-5 (76 mg, 0.34 mmol) and farnesyl bromide (2.31 g, 7.76 mmol) in anhydrous DMF (20 mL) were reacted at 0°C. After work-up the crude material was purified by flash silica column chromatography (Hex/EtOAc = 3/1). The title compound (394 mg, 0.74 mmol, 17%) was obtained as a colourless oil.

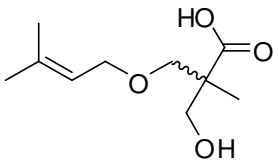
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.166 (s, 3 H), 1.601 (br. s, 6 H), 1.653 (br. s, 3 H), 1.680 (br. s, 3 H), 2.045 (m, 8 H), 2.683 (br. t, *J*=6.0 Hz, 1 H), 3.437 (d, *J*=9.1 Hz, 1 H), 3.709 (d, *J*=9.1 Hz, 2 H), 3.729 (s, 3 H), 3.826 (m, 1 H), 3.993 (m, 2 H), 5.096 (m, 2 H), 5.294 (m, 1 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 15.98 (CH_3), 16.47 (CH_3), 17.67 (CH_3), 17.85 (CH_3), 25.68 (CH_3), 26.27 (CH_2), 26.69 (CH_2), 39.54 (CH_2), 39.68 (CH_2), 48.67 (4°C, chiral), 52.01 (CH_3, ester), 66.98 (CH_2), 67.97 (CH_2OH), 73.60 (CH_2), 120.50 (3°C), 123.74 (3°C), 124.28 (3°C), 131.31 (4°C), 135.31 (4°C), 140.53 (4°C), 175.77 (C=O)

(+)-ESI-FTICR-MS: $[C_{21}H_{36}O_4 + Na]^+$ found: *m/z* 579.43773, calc. *m/z* 579.43838

39	**3-Hydroxy-2-methyl-2-((3-methylbut-2-enyloxy)methyl) propanoic acid**	Mol-ID: 10850

VAD 682



$C_{10}H_{18}O_4$
Mol. Wt.: 202,25

Compound **36** (64 mg, 0.30 mmol) was hydrolyzed according to **GSP 2**. The title compound (60 mg, 0.30 mmol, 99%) was obtained as yellow viscous oil.

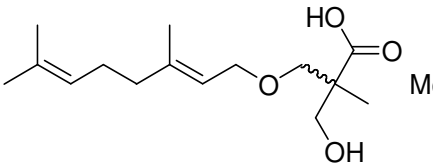
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.202 (s, 3 H), 1.667 (s, 3 H), 1.749 (s, 3 H), 3.520 (d, *J*=9.2 Hz, 1 H), 3.673 (d, *J*=9.2 Hz, 1 H), 3.769 (m, 2 H), 4.012 (br. d, *J*=7.0 Hz, 2 H), 5.309 (m, 1 H) (O*H* and COO*H* do not show up)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 17.83 (CH_3), 18.02 (CH_3), 25.72 (CH_3), 48.38 (4°C), 66.53 (CH_2O), 68.08 (CH_2O), 73.20 (CH_2O), 120.29 (CH), 137.79 (4°C), 179.80 (C=O)

(–)-ESI-FTICR-MS: $[C_{10}H_{18}O_4 - H]^-$ found: *m/z* 201.11303, calc. *m/z* 201.11323

40	**3-((*E*)-3,7-Dimethylocta-2,6-dienyloxy)-2-(hydroxymethyl)-2-methylpropanoic acid**	Mol-ID: 9213

VAD 552



$C_{15}H_{26}O_4$
Mol. Wt.: 270,36

Compound **37** (102 mg, 0.36 mmol) was hydrolyzed according to **GSP 2**. The title compound (96 mg, 0.74 mmol, 99%) was obtained as yellow viscous oil.

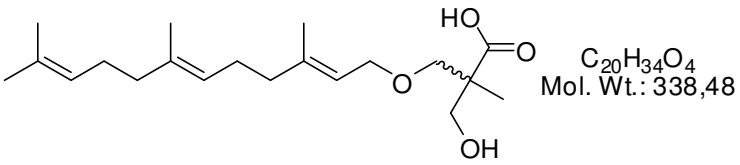
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.205 (s, 3 H), 1.605 (br. s, 3 H), 1.665 (br. s, 3 H), 1.683 (br. s, 3 H), 1.959 - 2.150 (m, 4 H), 3.566 (d, *J*=9.1 Hz, 1 H), 3.648 (d, *J*=9.1 Hz, 1 H), 3.754 (m, 2 H), 4.057 (m, 2 H), 5.080 (m, 1 H), 5.311 (m, 1 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.45 (CH_3), 17.69 (CH_3), 17.99 (CH_3), 25.68 (CH_3), 26.24 (CH_2), 39.51 (CH_2), 48.25 (4°C), 66.77 (CH_2), 68.10 (CH_2OH), 73.35 (CH_2O), 119.73 (3°C), 123.72 (3°C), 131.82 (4°C), 141.57 (4°C), 178.89 (C=O)

(–)-ESI-FTICR-MS: $[C_{15}H_{26}O_4 - H]^-$ found: *m/z* 269.17558, calc. *m/z* 269.17583

41	**3-Hydroxy-2-methyl-2-(((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienyloxy)methyl)propanoic acid**	Mol-ID: 9215

VAD 681



$C_{20}H_{34}O_4$
Mol. Wt.: 338,48

Compound **38** (90 mg, 0.25 mmol) was hydrolyzed according to **GSP 2**. The title compound (84 mg, 0.25 mmol, 99%) was obtained as yellow viscous oil.

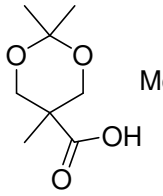
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.200 (s, 3 H), 1.598 (s, 6 H), 1.661 (br. s, 3 H), 1.678 (br. s, 3 H), 1.932 - 2.009 (m, 2 H), 2.011 - 2.157 (m, 6 H), 3.519 (d, *J*=9.2 Hz, 1 H), 3.676 (d, *J*=9.2 Hz, 1 H), 3.767 (m, 2H), 4.036 (m, 2 H), 5.094 (m, 2 H), 5.314 (m, 1 H), 6.479 (br.s, 1H, COOH) (O*H* is not seen)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 15.96 (CH_3), 16.46 (CH_3), 17.63 (CH_3), 17.84 (CH_3), 25.65 (CH_3), 26.25 (CH_3), 26.67 (CH_2), 39.53 (CH_2), 39.65 (CH_2), 48.37 (4°C), 66.56 (CH_2O), 68.08 (CH_2O), 73.20 (CH_2O), 120.02 (CH), 123.68 (CH), 124.27 (CH), 131.26 (4°C), 135.33 (4°C), 141.15 (4°C), 179.72 (C=O)

(–)-ESI-FTICR-MS: $[C_{20}H_{34}O_4 - H]^-$ found: *m/z* 337.23816, calc. *m/z* 337.23843

42	**2,2,5-Trimethyl-1,3-dioxane-5-carboxylic acid**[102]	Mol-ID: 9253

VAD 477



$C_8H_{14}O_4$
Mol. Wt.: 174,19

2,2-*Bis*(hydroxymethyl)propionic acid (10.0 g, 74.55 mmol), 2,2-dimethoxypropane (13.8 mL, 111.83 mmol) and *p*-toluenesulfonic acid monohydrate (0.71 g, 3.73 mmol) were dissolved in 50 mL of acetone. The reaction mixture was stirred for 14 h at room temperature. After the catalyst was neutralized by adding approximately 1 mL of a 25% NH_4OH/EtOH (1/1) solution, the solvent was evaporated at room temperature. The residue was then dissolved in (250 mL) CH_2Cl_2 and washed with two portions (20 mL) of water. The organic phase was dried with Na_2SO_4 and evaporated to give **42** (8.2 g, 47.13 mmol, 63%) as white crystals.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.22 (s, 3 H), 1.42 (s, 3 H), 1.45 (s, 3 H), 3.68 (d, *J*=11.73 Hz, 2 H), 4.20 (d, *J*=11.73 Hz, 2 H), 10.70 (br. s., 1 H)

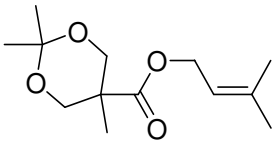
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 18.39 (CH_3), 21.88 (CH_3), 25.20 (CH_3), 41.71 (4°C), 65.80 (2xCH_2), 98.28 (*C*$(Me)_2$), 180.31 (C=O)

(–)-ESI-FTICR-MS: $[C_8H_{14}O_4 - H]^-$ found: *m/z* 173.08158, calc. *m/z* 173.08193

Melting point: 107–108 °C

46	**3-Methylbut-2-enyl-2,2,5-trimethyl-1,3-dioxane-5-carboxylate**	Mol-ID: 9274

VAD 482



$C_{13}H_{22}O_4$
Mol. Wt.: 242,31

The synthesis was performed following **GSP 4**: Compound **42** (1.3 g, 7.46 mmol), 3-methyl-2-buten-1-ol (643 mg, 7.46 mmol), DCC (1.54 g, 7.46 mmol) and DMAP (46 mg, 0.37 mmol) were reacted in anhydrous CH_3CN (20 mL) at 0°C. After work-up the crude material was purified by flash silica column chromatography (Hex/EtOAc = 3/1). The title compound (1.07 g, 0.74 mmol, 59%) was obtained as a colourless oil.

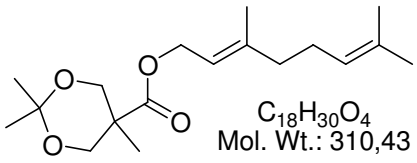
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.209 (s, 3 H), 1.394 (s, 3 H), 1.428 (s, 3 H), 1.713 (br. s, 3 H), 1.756 (br. s, 3 H), 3.636 (d, *J*=11.8 Hz, 2 H), 4.187 (d, *J*=11.8 Hz, 2 H), 4.630 (dt, *J*=7.1, 0.8 Hz, 2 H), 5.331 (tsept, *J*=7.1, 1.4 Hz, 1 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 18.06 (CH_3), 18.69 (CH_3), 23.26 (CH_3), 23.98 (CH_3), 25.71 (CH_3), 41.71 (4°C), 61.81 (*CH_2*OCO), 65.97 (2xCH_2), 97.98 (*C*$(CH_3)_2$), 118.43 (3°C), 139.03 (4°C), 174.23 (C=O)

(+)-ESI-FTICR-MS: $[C_{13}H_{22}O_4 + Na]^+$ found: *m/z* 265.14113, calc. *m/z* 265.14103

47	**(*E*)-3,7-Dimethylocta-2,6-dienyl-2,2,5-trimethyl-1,3-dioxane-5-carboxylate**	Mol-ID: 9276

VAD 478



$C_{18}H_{30}O_4$
Mol. Wt.: 310,43

The synthesis was performed following **GSP 4**: Compound **42** (1.3 g, 7.46 mmol), geraniol (1.12 g, 7.23 mmol), DCC (1.54 g, 7.46 mmol) and DMAP (46 mg, 0.37 mmol) were reacted in anhydrous CH_3CN (20 mL) at 0°C. After work-up the crude material was purified by flash

silica column chromatography (Hex/EtOAc = 5/1). The title compound (1.44 g, 4.64 mmol, 62%) was obtained as a colourless oil.

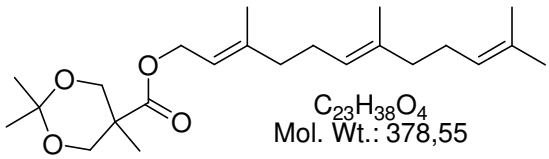
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.210 (s, 3 H), 1.395 (s, 3 H), 1.429 (s, 3 H), 1.601 (br. s, 3 H), 1.680 (br. s, 3 H), 1.706 (br. s, 3 H), 1.977 - 2.159 (m, 4 H), 3.638 (d, *J*=11.8 Hz, 2 H), 4.190 (d, *J*=11.8 Hz, 2 H), 4.651 (d, *J*=7.0 Hz, 2 H), 5.075 (m, 1 H), 5.333 (m, 1 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 16.48 (CH_3), 17.67 (CH_3), 18.70 (CH_3), 23.29 (CH_3), 23.97 (CH_3), 25.67 (CH_3), 26.23 (CH_2), 39.45 (CH_2), 41.71 (4°C), 61.77 (*CH_2*OCO), 65.97 (2xCH_2), 97.99 (*C*(CH_3)$_2$), 118.18 (3°C), 123.67 (3°C), 131.79 (4°C), 142.32 (4°C), 174.20 (C=O)

(+)-ESI-FTICR-MS: $[C_{18}H_{30}O_4 + Na]^+$ found: *m/z* 333.20378, calc. *m/z* 333.20363

48	**(*2E,6E*)-3,7,11-Trimethyldodeca-2,6,10-trienyl-2,2,5-trimethyl-1,3-dioxane-5-carboxylate**	Mol-ID: 9277

VAD 479



$C_{23}H_{38}O_4$
Mol. Wt.: 378,55

The synthesis was performed following **GSP 4**: Compound **42** (1.3 g, 7.46 mmol), farnesol (1.66 g, 7.23 mmol), DCC (1.54 g, 7.46 mmol) and DMAP (46 mg, 0.37 mmol) were reacted in anhydrous CH_3CN (20 mL) at 0°C. After work-up the crude material was purified by flash silica column chromatography (Hex/EtOAc = 5/1). The title compound (1.77 g, 4.68 mmol, 63%) was obtained as a colourless oil.

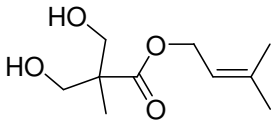
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.208 (s, 3 H), 1.393 (s, 3 H), 1.428 (s, 3 H), 1.598 (br. s, 6 H), 1.679 (br. s, 3 H), 1.710 (br. s, 3 H), 1.905 - 2.176 (m, 8 H), 3.635 (d, *J*=11.7 Hz, 2 H), 4.187 (d, *J*=11.7 Hz, 2 H), 4.650 (d, *J*=7.0 Hz, 2 H), 5.091 (m, 2 H), 5.337 (m, 1 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 15.98 (CH_3), 16.51 (CH_3), 17.66 (CH_3), 18.70 (CH_3), 23.29 (CH_3), 23.96 (CH_3), 25.68 (CH_3), 26.19 (CH_2), 26.67 (CH_2), 39.47 (CH_2), 39.66 (CH_2), 41.71 (4°C), 61.79 (*CH_2*OCO), 65.97 (2xCH_2), 97.99 (*C*(CH_3)$_2$), 118.16 (3°C), 123.57 (3°C), 124.25 (3°C), 131.31 (4°C), 135.42 (4°C), 142.37 (4°C), 174.21 (C=O)

(+)-ESI-FTICR-MS: $[C_{23}H_{38}O_4 + Na]^+$ found: *m/z* 401.26616, calc. *m/z* 401.26623

49	**3-Methylbut-2-enyl-2,2-*bis*(hydroxymethyl)propanoate**	Mol-ID: 9278

VAD 524



$C_{10}H_{18}O_4$
Mol. Wt.: 202,25

The removal of the acetonide protective group was carried out according to **GSP 4:** Compound **46** (500 mg, 2.06 mmol) was dissolved in 10 mL of MeOH. Approx. 3.0 g of Amberlite IR-120 resin was added and the reaction mixture was stirred for 3 h. After all starting material had been consumed, the resin was removed and the solvent evaporated to give the title compound (279 mg, 1.38 mmol, 67%) as a colourless oil.

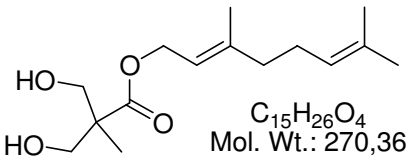
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.07 (s, 3 H), 1.72 (s, 3 H), 1.77 (s, 3 H), 2.75 (br. s., 2 H), 3.71 (d, *J*=11.2 Hz, 2 H), 3.90 (d, *J*=11.2 Hz, 2 H), 4.66 (dt, *J*=7.1, 0.6 Hz, 2 H), 5.34 (tsept, *J*=7.2, 1.4 Hz, 1 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 17.12 (CH_3), 18.06 (CH_3), 25.72 (CH_3), 49.09 (4°C), 62.00 (CH_2O), 68.33 (2x CH_2OH), 118.14 (CH), 139.51 (4°C), 175.97 (C=O)

(+)-ESI-FTICR-MS: $[C_{10}H_{18}O_4 + Na]^+$ found: *m/z* 225.10983, calc. *m/z* 225.10973

50	**(*E*)-3,7-Dimethylocta-2,6-dienyl-2,2-bis(hydroxymethyl) propanoate**	Mol-ID: 9279

VAD 526



$C_{15}H_{26}O_4$
Mol. Wt.: 270,36

The removal of the acetonide protective group was carried out according to **GSP 4:** Compound **47** (600 mg, 1.93 mmol) was dissolved in 10 mL of MeOH. Approx. 3.0 g of Amberlite IR-120 resin was added and the reaction mixture was stirred for 3 h. After all starting material had been consumed, the resin was removed and the solvent evaporated. The residue was purified by flash silica column chromatography (Hex/EtOAc = 1/1) to give the title compound (464 mg, 1.72 mmol, 89%) as a colourless oil.

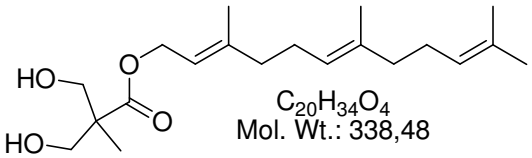
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.07 (s, 3 H), 1.61 (s, 3 H), 1.68 (s, 3 H), 1.71 (s, 3 H), 2.07 (m, 4 H), 2.86 (br. s, 2 H), 3.71 (d, *J*=11.1 Hz, 2 H), 3.90 (d, *J*=11.1 Hz, 2 H), 4.68 (d, *J*=7.3 Hz, 2 H), 5.07 (m, 1 H), 5.35 (m, 1 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 16.47 (CH_3), 17.11 (CH_3), 17.68 (CH_3), 25.66 (CH_3), 26.19 (CH_2), 39.44 (CH_2), 49.08 (4°C), 61.97 (*C*H_2OCO), 68.44 (2x *C*H_2OH), 117.88 (CH), 123.58 (CH), 131.88 (4°C), 142.84 (4°C), 175.96 (C=O)

(+)-ESI-FTICR-MS: $[C_{15}H_{26}O_4 + Na]^+$ found: *m/z* 293.17194, calc. *m/z* 293.17233

51	**(*2E*,*6E*)-3,7,11-Trimethyldodeca-2,6,10-trienyl-2,2-*bis*(hydroxymethyl)propanoate**	Mol-ID: 9280

VAD 622



$C_{20}H_{34}O_4$
Mol. Wt.: 338,48

The removal of the acetonide protective group was carried out according to **GSP 4:** Compound **48** (553 mg, 1.46 mmol) was dissolved in 10 mL of MeOH. Approx. 3.0 g of Amberlite IR-120 resin was added and the reaction mixture was stirred for 10 h at room temp. Since there was still starting material left, the reaction mixture was heated to 40°C for 1h. After all starting material had been consumed, the resin was removed and the solvent evaporated. The residue was purified by flash silica column chromatography (Hex/EtOAc = 1/1) to give the title compound (449 mg, 1.33 mmol, 91%) as a colourless oil.

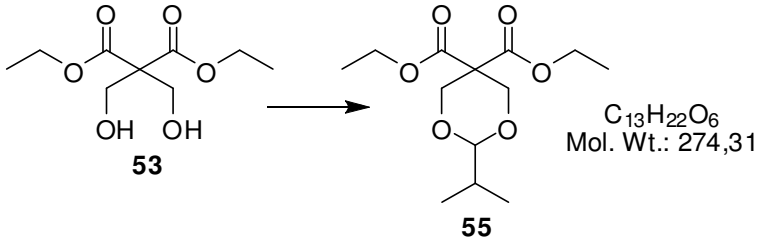
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.063 (s, 3 H), 1.602 (br. s, 6 H), 1.681 (br. s, 3 H), 1.717 (br. s, 3 H), 2.052 (m, 8 H, CH_2), 2.866 (br. s., 2 H, OH), 3.709 (d, *J*=11.3 Hz, 2 H, C*H*$_2$OH), 3.896 (d, *J*=11.3 Hz, 2 H, C*H*$_2$OH), 4.681 (d, *J*=6.6 Hz, 2 H, C*H*$_2$OCO), 5.092 (m, 2 H), 5.349 (m, 1 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.03 (CH_3), 16.53 (CH_3), 17.14 (CH_3), 17.70 (CH_3), 25.71 (CH_3), 26.19 (CH_2), 26.70 (CH_2), 39.49 (CH_2), 39.68 (CH_2), 49.12 (4°C), 61.99 (CH_2), 68.38 (2xCH_2OH), 117.90 (3°C), 123.51 (3°C), 124.27 (3°C), 131.36 (4°C), 135.52 (4°C), 142.89 (4°C), 175.98 (C=O)

(+)-ESI-FTICR-MS: $[C_{20}H_{34}O_4 + Na]^+$ found: *m/z* 361.23482, calc. *m/z* 361.23493

55	**5,5-Dicarbethoxy-2-isopropyl-1,3-dioxane**[232],[233]	Mol-ID: 9318

VAD 490



Diethyl *bis*(hydroxymethyl)malonate **53**[109] was prepared by hydroxymethylation of diethylmalonate. Dihydroxy-protection of **53** (5.15 g, 22.70 mmol) was carried out with isobutyraldehyde (2.46 g, 34.05 mmol) under acid catalysis with *p*TsOH·H_2O (216 mg, 1.14 mmol) in THF at r.t. The desired 5,5-dicarbethoxy-2-isopropyl-1,3-dioxane **55** (3.2 g, 11.67 mmol, 51%) was obtained as a colourless liquid.

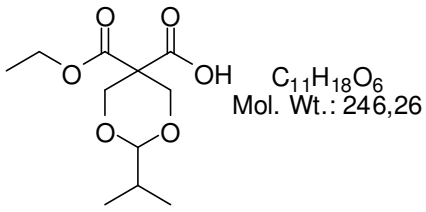
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.90 (d, *J*=6.74 Hz, 6 H), 1.24 (t, *J*=7.18 Hz, 3 H), 1.31 (t, *J*=7.18 Hz, 3 H), 1.73 - 1.86 (m, 1 H), 3.91 (dt, *J*=11.43, 1.32 Hz, 2 H), 4.16 (q, *J*=7.04 Hz, 2 H), 4.24 (d, *J*=4.98 Hz, 1 H), 4.31 (q, *J*=7.13 Hz, 2 H), 4.70 (dt, *J*=11.43, 1.32 Hz, 2 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 13.92 (CH_3, ester), 14.07 (CH_3, ester), 16.70 (2xCH_3, *i*-Pr), 32.32 (3°C, *i*-Pr), 53.41 (4°C), 61.86 (2xCH_2, ester), 69.25 (2xCH_2), 105.87 (3°C), 167.04 (C=O), 168.02 (C=O)

(+)-ESI-FTICR-MS: $[C_{13}H_{22}O_6 + Na]^+$ found: *m/z* 297.13125, calc. *m/z* 297.13086

56	**5-(Ethoxycarbonyl)-2-isopropyl-1,3-dioxane-5-carboxylic acid**	Mol-ID: 9319

VAD 511, 515, 523, 539



Diester **55** (2.0 g, 7.29 mmol) was hydrolysed with KOH (1.64 g, 29.16 mmol) in 40 mL mixture of ethanol/water (1/1). The reaction mixture was stirred at r.t. for 14h. Then, ethanol was removed in vacuo and the aqueous layer was acidified carefully at 0°C with 1M HCl solution. The acidified aqueous phase was extracted 5x with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The title compound was isolated as a yellow viscous oil (1.29 g, 5.24 mmol, 72%) which crystallized to a white solid upon time.

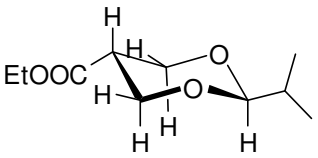
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.90 (d, *J*=7.04 Hz, 6 H), 1.32 (t, *J*=7.00 Hz, 3 H), 1.73 - 1.87 (m, 1 H), 3.92 (dt, *J*=11.43, 1.32 Hz, 2 H), 4.26 (d, *J*=4.69 Hz, 1 H), 4.33 (q, *J*=7.23 Hz, 2 H), 4.72 (dt, *J*=11.43, 1.32 Hz, 2 H), 8.96 (br s, 1H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 14.00 (CH_3, ester), 16.61 (2xCH_3, *i*-Pr), 32.27 (3°C, *i*-Pr), 53.38 (4°C), 62.32 (CH_2, ester), 69.03 (2xCH_2), 105.88 (3°C), 167.68 (C=O, ester), 172.28 (C=O, acid)

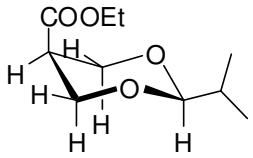
(+)-ESI-FTICR-MS: $[C_{11}H_{18}O_6 + Na]^+$ found: *m/z* 269.09969, calc. *m/z* 269.09956

57	**5-Carbethoxy-2-isopropyl-1,3-dioxane**[118]	Mol-ID: 9320

VAD 513, 525, 540



57-*trans*



57-*cis*

$C_{10}H_{18}O_4$
Mol. Wt.: 202,25

A stirred mixture of **56** (3.0 g, 12.18 mmol) and 5 mL of anhydrous pyridine was refluxed for 1.5h. After completion, pyridine was removed in vacuo and the residue was diluted with water and cooled to 0°C. Careful acidification with 1M HCl and extraction into Et_2O afforded a yellow crystalline solid as a crude material. Purification of it by flash silica column chromatography (Hex/EtOAc = 1/1) yielded the desired compound (1.98 g, 9.79 mmol, 80%, colourless oil) as a mixture of *cis*- and *trans*-isomers (*cis* / *trans* ≈ 1/2 by NMR analysis).

• ***trans*-isomer: 57-*trans***

^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 0.927 (d, *J*=6.9 Hz, 6 H), 1.249 (t, *J*=7.2 Hz, 3 H), 1.792 (sept d, *J*=6.8, 5.1 Hz, 1 H), 2.960 (tt, *J*=11.3, 4.8 Hz, 1 H, H-ax), 3.744 (m, 2 H, CH_2O-ax), 4.126 (q, *J*=7.2 Hz, 2 H), 4.167 (d, *J*=5.1 Hz, 1 H), 4.300 (m, 2 H, CH_2O-eq)

^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 14.10 (CH_3, ester), 16.95 (2xCH_3, i-Pr), 32.52 (3°C, i-Pr), 40.21 (3°C), 60.68 (CH_2, ester), 67.66 (2x CH_2O), 105.74 (3°C, acetal), 170.12 (C=O)

(+)-ESI-FTICR-MS: $[C_{10}H_{18}O_4 + Na]^+$ found: *m/z* 225.10927, calc. *m/z* 225.10973

HPLC: t_R = 15.27 min (condition **A** but *without* mobile-phase additive)

• ***cis*-isomer: 57-*cis***

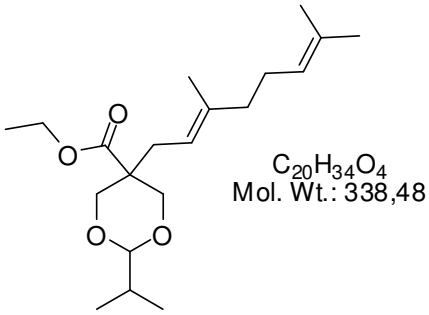
^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 0.902 (d, *J*=6.9 Hz, 6 H), 1.302 (t, *J*=7.1 Hz, 3 H), 1.778 (sept d, *J*=6.9, 5.1 Hz, 1 H), 2.273 (s-like, 1 H, H-eq), 3.863 (m, 2 H, CH_2O-ax), 4.256 (d, *J*=5.1 Hz, 1 H), 4.259 (q, *J*=7.1 Hz, 2 H), 4.578 (m, 2 H, CH_2O-eq)

^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 14.21 (CH_3, ester), 16.78 (2xCH_3, i-Pr), 32.58 (3°C, i-Pr), 40.17 (3°C), 61.01 (CH_2, ester), 66.84 (2x CH_2O), 106.14 (3°C, acetal), 171.47 (C=O)
(+)-ESI-FTICR-MS: $[C_{10}H_{18}O_4 + Na]^+$ found: *m/z* 225.10934, calc. *m/z* 225.10973

HPLC: t_R = 13.45 min (condition **A** but *without* mobile-phase additive)

60	**Ethyl 5-[(2*E*)-3,7-dimethylocta-2,6-dien-1-yl]-2-isopropyl-1,3-dioxane-5-carboxylate**	Mol-ID: 9321

VAD 528, 537, 543, 674



$C_{20}H_{34}O_4$
Mol. Wt.: 338,48

The synthesis was performed following **GSP 11**: 5-carbethoxy-2-isopropyl-1,3-dioxane **57** (779 mg, 3.85 mmol), LDA (2.0 M, 2.50 mL, 5.00 mmol), and geranyl bromide (1.68 g, 7.74 mmol) were reacted in anhydrous THF (10 mL) at –78°C for 2 h. After work-up the crude material was purified by flash silica column chromatography (Hex/EtOAc = 5/1) to yield the title compound (617 mg, 1.82 mmol, 47%) as a yellow oil.

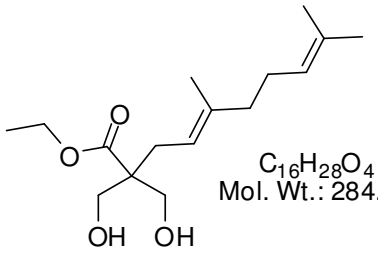
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.89 (d, *J*=7.0 Hz, 6 H), 1.28 (t, *J*=7.2 Hz, 3 H), 1.56 (s, 3 H), 1.60 (s, 3 H), 1.68 (s, 3 H), 1.73 - 1.84 (m, 1 H), 1.92 - 2.12 (m, 6 H), 3.46 (m, 2 H), 4.18 (d, *J*=4.7 Hz, 1 H), 4.23 (q, *J*=7.0 Hz, 2 H), 4.51 (m, 2 H), 4.98 (m, 1 H), 5.06 (m, 1 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 14.30 (CH_3, ester), 16.02 (CH_3), 16.85 (2xCH_3, *i*-Pr), 17.67 (CH_3), 25.69 (CH_3), 26.46 (CH_2), 31.14 (CH_2), 32.38 (3°C, i-Pr), 39.81 (CH_2), 46.45 (4°C), 60.81 (CH_2, ester), 72.15 (2x CH_2O), 105.99 (3°C, *C*H(OCH_2)$_2$), 116.53 (3°C), 123.92 (3°C), 131.63 (4°C), 139.07 (4°C), 173.38 (C=O)

(+)-ESI-FTICR-MS: $[C_{20}H_{34}O_4 + Na]^+$ found: *m/z* 361.23455, calc. *m/z* 361.23493

61	**(*E*)-Ethyl 2,2-*bis*(hydroxymethyl)-5,9-dimethyldeca-4,8-dienoate**	Mol-ID: 10819

VAD 676, 677



$C_{16}H_{28}O_4$
Mol. Wt.: 284.39

The masked 1,3-diol function of **60** (118 mg, 0.35 mmol) was deprotected according to **GSP 5**: Dioxane **60** was dissolved in wet ethanol (5 mL) and treated with Dowex (H^+) at 50°C for 1h. The title compound was isolated by HPLC as a colourless oil (21 mg, 73.8 µmol, 21%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.300 (t, *J*=7.1 Hz, 3 H), 1.593 (br. s, 6 H), 1.684 (br. s, 3 H), 1.931 - 2.116 (m, 4 H), 2.201 (d, *J*=7.5 Hz, 2 H), 2.568 (br. s, 2 H, OH), 3.741 (d, *J*=11.2 Hz, 2 H), 3.994 (d, *J*=11.2 Hz, 2 H), 4.230 (q, *J*=7.1 Hz, 2 H), 4.953 - 5.098 (m, 2 H)

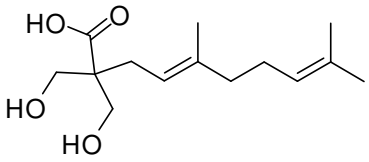
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 14.17 (CH_3, ester), 16.06 (CH_3), 17.66 (CH_3), 25.66 (CH_3), 26.41 (CH_2), 30.18 (CH_2), 39.85 (CH_2), 52.94 (4°C), 60.99 (CH_2, ester), 67.41 (2xCH_2OH), 117.59 (CH), 123.93 (CH), 131.66 (4°C), 138.98 (4°C), 175.16 (C=O)

(+)-ESI-FTICR-MS: $[C_{16}H_{28}O_4 + H]^+$ found: 285.20601, calc. 285.20603

HPLC: t_R = 15.48 min (condition **H**)

62	**(*E*)-2,2-*Bis*(hydroxymethyl)-5,9-dimethyldeca-4,8-dienoic acid**	Mol-ID: 10262

VAD 680



$C_{14}H_{24}O_4$
Mol. Wt.: 256,34

The title free acid was prepared according to **GSP 2**: Ethyl ester **61** (9 mg, 31.6 µmol) was dissolved in 1.5 mL of THF/H_2O (2/1). LiOH*H_2O (5 mg, 0.12 mmol) was added and the reaction mixture was stirred at room temperature for 6-7 h. After careful acidification to pH 2-3 at 0°C, the crude mixture was lyophilized. Purification of the residue by preparative HPLC afforded the desired compound (6.6 mg, 25.7 µmol, 81%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.593 (s, 6 H), 1.679 (s, 3 H), 1.921 - 2.120 (m, 4 H), 2.227 (d, *J*=7.5 Hz, 2 H), 3.770 (d, *J*=11.0 Hz, 2 H), 4.017 (d, *J*=11.0 Hz, 2 H), 4.586 (br. s., 2 H, OH), 5.045 (t, *J*=6.8 Hz, 2 H)

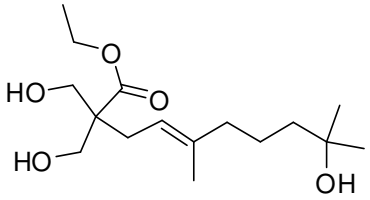
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.08 (CH_3), 17.68 (CH_3), 25.67 (CH_3), 26.43 (CH_2), 30.13 (CH_2), 39.87 (CH_2), 52.76 (4°C), 66.90 (2x CH_2O), 117.30 (CH), 123.95 (CH), 131.69 (4°C), 139.44 (4°C), 178.49 (C=O)

(+)-ESI-FTICR-MS: $[C_{14}H_{24}O_4 + Na]^+$ found: 279.15645, calc. 279.15668

HPLC: t_R = 12.60 min (condition **J**)

63	**Ethyl (4*E*)-9-hydroxy-2,2-*bis*(hydroxymethyl)-5,9-dimethyldec-4-enoate**	Mol-ID: 10845

VAD 679



$C_{16}H_{30}O_5$
Mol. Wt.: 302,41

The title compound (colourless oil) was isolated as a byproduct under the conditions for the synthesis of **61**.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.206 (s, 6 H), 1.300 (t, *J*=7.0 Hz, 3 H), 1.348 - 1.497 (m, 4 H), 1.589 (s, 3 H), 1.978 (t, *J*=6.6 Hz, 2 H), 2.209 (d, *J*=7.5 Hz, 2 H), 2.236 (br. s., 3 H), 3.747 (d, *J*=11.0 Hz, 2 H), 4.003 (d, *J*=11.0 Hz, 2 H), 4.224 (q, *J*=7.0 Hz, 2 H), 5.015 (td, *J*=7.7, 0.9 Hz, 1 H)

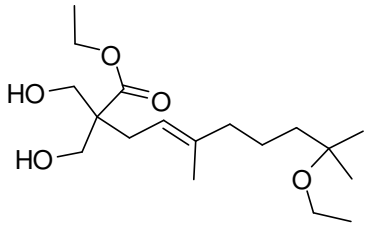
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 14.17 ($CO_2CH_2\underline{C}H_3$), 16.02 (CH_3), 22.35 (CH_2), 29.21 ($C(\underline{C}H_3)_2$), 30.17 (CH_2), 40.06 (CH_2), 43.19 (CH_2), 53.02 (4°C, $\underline{C}(CH_2OH)_2$), 61.03 ($CO_2\underline{C}H_2CH_3$), 67.18 (2x$\underline{C}H_2OH$), 70.87 (4°C, $\underline{C}(CH_3)_2$), 117.73 (CH), 138.93 (4°C), 175.14 (C=O)

(+)-ESI-FTICR-MS: $[C_{16}H_{30}O_5 + Na]^+$ found: 325.19868, calc. 325.19854

HPLC: t_R = 10.95 min (condition **H**)

64	**Ethyl (4*E*)-9-ethoxy-2,2-*bis*(hydroxymethyl)-5,9-dimethyldec-4-enoate**	Mol-ID: 10844

VAD 679



$C_{18}H_{34}O_5$
Mol. Wt.: 330,46

The title compound (colourless oil) was isolated as a byproduct under the conditions for the synthesis of **61**.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.137 (ovlp s, 6H), 1.149 (ovlp t, *J*=7.0 Hz, 3 H), 1.300 (t, *J*=7.2 Hz, 3 H), 1.339 - 1.491 (m, 4 H), 1.584 (s, 3 H), 1.904 - 2.013 (m, 2 H), 2.204 (d, *J*=7.5 Hz, 2 H), 2.453 (br. s., 2 H), 3.351 (q, *J*=7.0 Hz, 2 H), 3.748 (d, *J*=11.4 Hz, 2 H), 4.004 (d, *J*=11.4 Hz, 2 H), 4.228 (q, *J*=7.2 Hz, 2 H), 4.962 - 5.052 (m, 1 H)

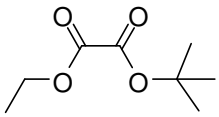
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 14.17 ($CO_2CH_2\underline{C}H_3$), 15.97 (CH_3, ether), 16.17 (CH_3), 22.03 (CH_2), 25.66 ($C(\underline{C}H_3)_2$), 30.18 (CH_2), 39.68 (CH_2), 40.28 (CH_2), 52.92 (4°C, $\underline{C}(CH_2OH)_2$), 56.29 (CH_2, ether), 61.01 ($CO_2\underline{C}H_2CH_3$), 67.35 (2x$\underline{C}H_2OH$), 74.28 (4°C, $\underline{C}(CH_3)_2$), 117.49 (CH), 139.21 (4°C), 175.14 (C=O)

(+)-ESI-FTICR-MS: $[C_{18}H_{34}O_5 + Na]^+$ found: 353.22998, calc. 353.22984

HPLC: t_R = 14.54 min (condition **H**)

74	***Tert*-butyl ethyl oxalate**[123-125]	Mol-ID: 10885

VAD 684, 686



$C_8H_{14}O_4$
Mol. Wt.: 174,19

To a solution of 2-methyl-2-propanol (597 mg, 8.06 mmol) and pyridine (638 mg, 8.06 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C was added dropwise ethyl oxalyl chloride (1.0 g, 7.32 mmol). The reaction mixture was stirred at 0°C and was slowly allowed to reach to r.t. over 5 h. The reaction was quenched with water. The organic layer was separated and washed with cold 1N HCl solution. Methylene chloride extraction, drying over sodium sulfate and evaporation of the solvent gave the desired product **74** (1.27 g, 99%) as a slightly yellow oil.

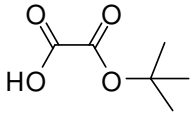
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.360 (t, *J*=7.2 Hz, 3 H), 1.550 (s, 9 H), 4.310 (q, *J*=7.2 Hz, 2 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 13.90 ($CH_2\underline{C}H_3$), 27.71 ($C(\underline{C}H_3)_3$), 62.76 ($\underline{C}H_2CH_3$), 84.79 (4°C, $\underline{C}(CH_3)_3$), 157.12 (C=O), 158.63 (C=O)

(+)-ESI-FTICR-MS: $[C_8H_{14}O_4 + Na]^+$ found: 197.07829, calc. 197.07843

75	**2-*Tert*-butoxy-2-oxoacetic acid**[126-127]	Mol-ID: 10886

VAD 685, 687, 688



$C_6H_{10}O_4$
Mol. Wt.: 146,14

Ethyl ester **74** (1.01g, 5.80 mmol) was dissolved into 20 mL of a solvent mixture AcN/H_2O (3/1) and cooled to –5°C. LiOH*H_2O (268 mg, 6.38 mmol) was added and the reaction mixture was stirred for 1h at –5°C. Then, the reaction solution was acidified carefully with diluted HCl solution and extracted 3x into EtOAc. Drying over sodium sulfate, and evaporation of the solvent gave the desired compound (383 mg, 2.62 mmol, 45%) as a yellow oil. The product was pure enough and was applied directly into the next step.

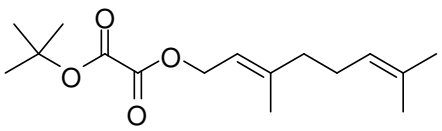
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.571 (s, 9H, boc), 9.522 (br.s., 1H, COOH)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 27.54 (CH_3, boc), 85.98 (4°C, boc), 157.08 (C=O), 159.45 (C=O)

(–)-ESI-FTICR-MS: $[C_6H_{10}O_4 - H]^-$ found: 145.05044, calc. 145.05063

76	**(*E*)-*Tert*-butyl-3,7-dimethylocta-2,6-dienyl oxalate**	Mol-ID: 10896

VAD 689



$C_{16}H_{26}O_4$
Mol. Wt.: 282,38

The title compound was prepared according to **GSP 4**. Compound **75** (380 mg, 2.60 mmol), geraniol (450 mg, 2.86 mmol), DCC (644 mg, 3.12 mmol) and DMAP (16 mg, 0.13 mmol) were reacted in anhydrous CH_3CN (15 mL) at –5°C and slowly allowed to reach room temperature. After work-up the crude material was purified by flash silica column

chromatography (Hex/EtOAc = 5/1 → 1/1). The title compound (225 mg, 0.80 mmol, 31%) was obtained as a colourless oil.

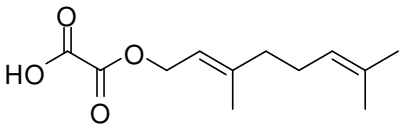
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.553 (s, 9 H), 1.599 (br. s, 3 H), 1.681 (br. s, 3 H), 1.734 (br. s, 3 H), 2.017 – 2.155 (m, 4 H), 4.766 (d, *J*=7.0 Hz, 2 H), 5.073 (m, 1 H), 5.398 (m, 1 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.55 (CH_3), 17.66 (CH_3), 25.65 (CH_3), 26.16 (CH_2), 27.73 (3xCH_3, boc), 39.51 (CH_2), 63.51 (CH_2), 84.77 (4°C, boc), 116.98 (CH), 123.58 (CH), 131.94 (4°C), 143.91 (4°C), 157.16 (C=O), 158.67 (C=O)

(+)-ESI-FTICR-MS: $[C_{16}H_{26}O_4 + Na]^+$ found: 305.17218, calc. 305.17233

77	**(*E*)-2-(3,7-Dimethylocta-2,6-dienyloxy)-2-oxoacetic acid**	Mol-ID: 11047

VAD 700



$C_{12}H_{18}O_4$
Mol. Wt.: 226,27

The title ethanedioic acid monogeranyl ester was prepared as follows: To a pre-cooled (–70°C) solution of oxalyl chloride (4.80 g, 37.8 mmol) in 60 mL of anhydrous Et_2O was added slowly collidine (10.0 mL, 75.60 mmol). Then, geraniol (2.92 g, 18.90 mmol) dissolved into 5 mL of Et_2O was added dropwise via syringe to the cold and vigorously stirred reaction mixture. Upon addition of geraniol a white precipitate (presumably pyridinium chloride) was formed. After stirring for approx. 1h at –70°C the reaction was quenched with 5 mL of saturated NaCl solution. After warming-up to room temperature, the etheral layer was separated. The acidic(!) aqueous phase was extracted 3x with Et_2O. All organic layers were combined, washed 1x with water, 1x with brine, dried over Na_2SO_4 and concentrated in vacuo to give a yellow oil. The crude material was purified by preparative HPLC (condition **K**) and the corresponding fractions were lyophilized. The oily viscous residue was contaminated with some finely dispersed white solid (oxalic acid). The residue was titurated with a small amount of cold CH_2Cl_2 and the resulting milky suspension was centrifuged. The clear supernatant was separated and concentrated to afford the target compound (1.62 g, 7.16 mmol, 38%) as viscous pale yellow oil. Unfortunately, the target compound suffers from instability and decomposes upon time. Consequently, repeated re-purification runs do not result in a more pure product.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.599 (br. s, 3 H), 1.680 (br. s, 3 H), 1.734 (br. s, 3 H), 2.004 - 2.178 (m, 4 H), 4.804 (d, *J*=7.4 Hz, 2 H, CH_2O), 5.067 (m, 1 H), 5.408 (m, 1 H)

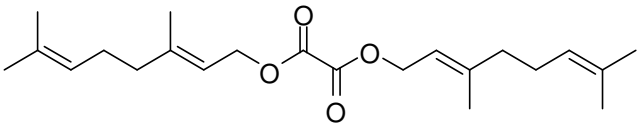
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.56 (CH_3), 17.67 (CH_3), 25.65 (CH_3), 26.09 (CH_2), 39.50 (CH_2), 64.83 (CH_2O), 116.18 (CH), 123.41 (CH), 132.09 (4°C), 145.22 (4°C), 157.24 (C=O), 158.14 (C=O)

(–)-ESI-FTICR-MS: $[C_{12}H_{18}O_4 - H]^-$ found: 225.11287 , calc. 225.11323

HPLC: intense broad peak at t_R = 13.0 min (condition **K**)

79	***Bis*((*E*)-3,7-dimethylocta-2,6-dienyl) oxalate**	Mol-ID: 11034

VAD 695, 696



$C_{22}H_{34}O_4$
Mol. Wt.: 362,5

The title symmetrically disubstituted compound **79** was obtained as a major side-product in the attempt to prepare monoester **77** with the following protocol: To a pre-cooled (–78°C) solution of oxalyl chloride (1.2 g, 9.45 mmol) in 50 mL of anhydrous CH_2Cl_2 was added slowly pyridine (2.28 mL, 28.35 mmol). Then, geraniol (1.50 mL, 8.51 mmol) dissolved into 8 mL of CH_2Cl_2 was added dropwise via syringe to the cold and vigorously stirred reaction mixture. After stirring for approx. 1.5 h at –78°C the reaction was quenched with saturated NH_4Cl solution. After warming-up to room temperature, the organic layer was separated. The aqueous phase was extracted 3x with EtOAc. All organic layers were combined, washed 1x with brine, dried over Na_2SO_4 and concentrated in vacuo to give a pale yellow oil. The crude material was purified by flash column chromatography (Hex/EtOAc = 4/1) to afford the symmetric diester (940 mg, 2.59 mmol, 27%) as a pale yellow oil.

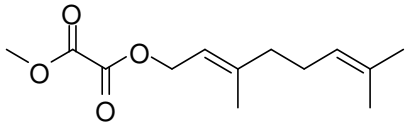
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.597 (s, 6 H), 1.678 (s, 6 H), 1.736 (s, 6 H), 2.004 - 2.158 (m, 8 H), 4.802 (d, *J*=7.5 Hz, 4 H), 5.069 (m, 2 H), 5.405 (m, 2 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.55 (CH_3), 17.65 (CH_3), 25.63 (CH_3), 26.14 (CH_2), 39.51 (CH_2), 63.80 (CH_2O), 116.77 (CH), 123.53 (CH), 131.97 (4°C), 144.27 (4°C), 157.95 (C=O)

(+)-ESI-FTICR-MS: $[C_{22}H_{34}O_4 + Na]^+$ found: 385.23501, calc. 385.2349307

80	**(*E*)-3,7-Dimethylocta-2,6-dienyl methyl oxalate**	Mol-ID: 11035

VAD 698



$C_{13}H_{20}O_4$
Mol. Wt.: 240,3

The title methyl ester was obtained unexpectedly as the major product from the following reaction: To a pre-cooled (–30°C) solution of oxalyl chloride (3.2 mL, 37.8 mmol) in 50 mL of anhydrous CH_2Cl_2 was added slowly collidine (1.87 mL, 14.18 mmol). Then, geraniol (1.64 mL, 9.45 mmol) dissolved into 4 mL of CH_2Cl_2 was added dropwise via syringe to the cold and vigorously stirred reaction mixture. After stirring for approx. 1h at –30°C the reaction was quenched with 10 mL of brine. After warming-up to room temperature, the organic layer was separated. The aqueous phase was extracted 3x with CH_2Cl_2. All organic layers were combined, washed 1x with water, 1x with brine, dried over Na_2SO_4 and concentrated in vacuo to give a red-brown oil. The crude material was purified by flash column chromatography (Hex/EtOAc = 2/1) to afford the unexpected methyl ester (1.24 g, 5.16 mmol, 55%) as a pale yellow oil.

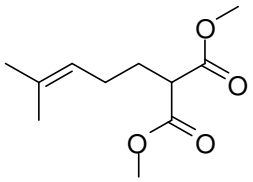
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.599 (s, 3 H), 1.680 (s, 3 H), 1.742 (s, 3 H), 2.017 - 2.162 (m, 4 H), 3.902 (s, 3 H, CO_2CH_3), 4.815 (d, *J*=7.5 Hz, 2 H, CH_2O), 5.070 (m, 1 H), 5.408 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.54 (CH_3), 17.63 (CH_3), 25.60 (CH_3), 26.13 (CH_2), 39.50 (CH_2), 53.48 (CH_3, ester), 63.88 (CH_2O), 116.59 (CH), 123.49 (CH), 131.97 (4°C), 144.55 (4°C), 157.54 (C=O), 158.27 (C=O)

(+)-ESI-FTICR-MS: $[C_{13}H_{20}O_4 + Na]^+$ found: 263.12544 , calc. 263.12538

86	**Dimethyl 2-(4-methylpent-3-enyl)malonate**[234]	Mol-ID: 5583

VAD 076



$C_{11}H_{18}O_4$
Mol. Wt.: 214,26

The title alkylated malonate was prepared as follows: malonic acid dimethyl ester (1.0 g, 7.57 mmol) was treated with sodium metal (180 mg, 7.83 mmol) in methanol (20 mL) to generate the enolate anion. 5-bromo-2-methyl-2-pentene (1.30 g, 7.95 mmol) was subsequently added and the reaction mixture was refluxed gently for 3h. After standard aqueous work-up, the

crude material was purified by flash column chromatography using Hex/EtOAc (5/1). The desired compound (677 mg, 3.16 mmol, 42%) was obtained as a colourless oil.

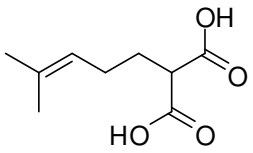
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.579 (br. s, 3 H), 1.688 (br. s, 3 H), 1.889 - 2.088 (m, 4 H), 3.381 (t, *J*=7.2 Hz, 1 H), 3.736 (s, 6 H), 5.069 (m, 1 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 17.84 (CH_3), 25.88 (CH_2), 25.93 (CH_3), 29.12 (CH_2), 51.19 (CH, malonate), 52.66 (2x CO_2CH_3), 122.74 (CH), 133.64 (4°C), 170.19 (2x C=O)

(+)-ESI-FTICR-MS: $[C_{11}H_{18}O_4 + Na]^+$ found: *m/z* 237.10940, calc. *m/z* 237.10973

87	**2-(4-Methylpent-3-enyl)malonic acid**[235]	Mol-ID: 5586

VAD 078



$C_9H_{14}O_4$
Mol. Wt.: 186,21

The synthesis was performed following **GSP 2**: Diester **86** (595 mg, 2.81 mmol) was dissolved in 5 mL of THF/H_2O (3/2). LiOH*H_2O (318 mg, 7.58 mmol) was added and the reaction mixture was stirred at room temp. for 6h. After careful acidification to pH 2-3 at 0°C, the crude material was purified to afford 508 mg (2.73 mmol, 97%) of **87** as a white powder.

^{1}H NMR (300 MHz, D_2O) δ ppm 1.567 (br. s, 3 H), 1.659 (br. s, 3 H), 1.705 (m, 2 H), 1.941 (q, *J*=7.5 Hz, 2 H), 3.027 (t, *J*=7.6 Hz, 1 H), 5.186 (m, 1 H) *COO*H *protons exchange with solvent.*

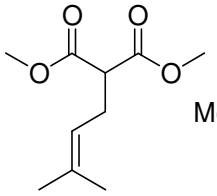
^{13}C NMR (75 MHz, D_2O) δ ppm 17.96 (CH_3), 25.85 (CH_3), 27.08 (CH_2), 31.61 (CH_2), 59.06 (CH, malonate), 125.00 (CH), 134.91 (4°C), 180.98 (2x C=O)

(–)-ESI-FTICR-MS: $[C_9H_{14}O_4 - H]^-$ found: *m/z* 185.08183 calc. *m/z* 185.08193

Melting point[235]**:** 88–89 °C

88	**Dimethyl 2-(3-methylbut-2-enyl)malonate**[236-239]	Mol-ID: 5584

VAD 395A



$C_{10}H_{16}O_4$
Mol. Wt.: 200,23

The synthesis was conducted according to **GSP 1**: NaH (60% dispersion in mineral oil, washed with hexanes, 500 mg, 12.49 mmol), malonic acid dimethyl ester (96%, 1.56 g, 11.35 mmol), 15-crown-5 (125 mg, 0.57 mmol) and 3,3-dimethylallyl bromide (90%, 2.07 g, 12.49 mmol) in THF (20 mL) were reacted at 0°C. After work-up the crude material was purified by flash silica column chromatography (Hex/EtOAc = 4/1). The title mono-alkylated compound (886 mg, 4.43 mmol, 39%) was obtained as a colourless oil. Physical and spectral data were in accordance with literature data.[236-239]

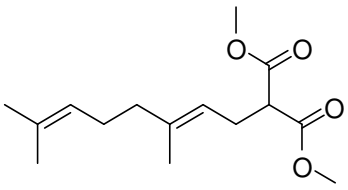
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.632 (br. s, 3 H), 1.684 (br. s, 3 H), 2.597 (m, 2 H), 3.370 (t, *J*=7.7 Hz, 1 H), 3.733 (s, 6 H), 5.051 (m, 1 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 17.68 (CH_3), 25.73 (CH_3), 27.58 (CH_2), 51.86 (3°C), 52.42 (2xCH_3), 119.39 (3°C), 135.10 (4°C), 169.58 (2xC=O)

(+)-ESI-FTICR-MS: $[C_{10}H_{16}O_4 + Na]^+$ found: *m/z* 223.09412, calc. *m/z* 223.09408

89	**Dimethyl 2-((*E*)-3,7-dimethylocta-2,6-dienyl)malonate**[240]	Mol-ID: 1806

VAD 411A



$C_{15}H_{24}O_4$
Mol. Wt.: 268,35

The synthesis was performed following **GSP 1**: NaH (60% dispersion in mineral oil, washed with hexanes, 500 mg, 12.49 mmol), malonic acid dimethyl ester (96%, 1.56 g, 11.35 mmol), 15-crown-5 (125 mg, 0.57 mmol) and geranyl bromide (96%, 2.82 g, 12.49 mmol) in THF (20 mL) were reacted at 0°C. After work-up the crude material was purified by flash silica column chromatography (Hex/EtOAc = 3/1). The title mono-alkylated compound (2.0 g, 7.45 mmol, 66%) was obtained as a colourless oil. Physical and spectral data were in accordance with literature data.[240]

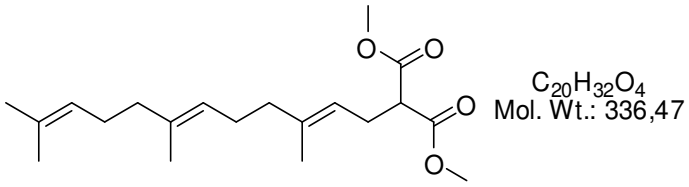
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.591 (br. s, 3 H), 1.630 (br. s, 3 H), 1.675 (br. s, 3 H), 1.923 - 2.099 (m, 4 H), 2.610 (td, *J*=7.5, 0.7 Hz, 2 H), 3.380 (t, *J*=7.7 Hz, 1 H), 3.731 (s, 6 H), 5.062 (m, 2 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 15.98 (CH_3), 17.65 (CH_3), 25.63 (CH_3), 26.49 (CH_2), 27.51 (CH_2), 39.63 (CH_2), 51.87 (CH, malonate), 52.40 (2x CO_2CH_3), 119.36 (CH), 123.93 (CH), 131.48 (4°C), 138.70 (4°C), 169.59 (2x C=O)

(+)-ESI-FTICR-MS: $[C_{15}H_{24}O_4 + Na]^+$ found: *m/z* 291.15684, calc. *m/z* 291.15668

90	**Dimethyl 2-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienyl) malonate**[241]	Mol-ID: 10107

VAD 412A



The synthesis was performed following **GSP 1**: NaH (60% dispersion in mineral oil, washed with hexanes, 500 mg, 12.49 mmol), malonic acid dimethyl ester (96%, 1.56 g, 11.35 mmol), 15-crown-5 (125 mg, 0.57 mmol) and farnesyl bromide (2.40 g, 7.99 mmol) in THF (20 mL) were reacted at 0°C. After work-up the crude material was purified by flash silica column chromatography (Hex/EtOAc = 3/1). The title mono-alkylated compound (2.0 g, 7.45 mmol, 66%) was obtained as a pale yellow oil. Physical and spectral data were in accordance with literature data.[241]

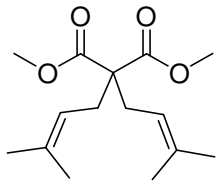
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.587 (br. s, 3 H), 1.601 (br. s, 3 H), 1.633 (br. s, 3 H), 1.679 (br. s, 3 H), 1.914 - 2.116 (m, 8 H), 2.610 (t, *J*=7.6 Hz, 2 H), 3.378 (t, *J*=7.7 Hz, 1 H), 3.728 (s, 6 H), 5.021 - 5.132 (m, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 15.95 (CH_3), 16.03 (CH_3), 17.65 (CH_3), 25.67 (CH_3), 26.49 (CH_2), 26.70 (CH_2), 27.52 (CH_2), 39.66 (2x CH_2), 51.87 (CH, malonate), 52.40 (2x CO_2CH_3), 119.32 (CH), 123.83 (CH), 124.30 (CH), 131.28 (4°C), 135.13 (4°C), 138.78 (4°C), 169.59 (2x C=O)

(+)-ESI-FTICR-MS: $[C_{20}H_{32}O_4 + Na]^+$ found: *m/z* 359.21929, calc. *m/z* 359.21928

91	**Dimethyl 2,2-*bis*(3-methylbut-2-enyl)malonate**[242]	Mol-ID: 10106

VAD 395B



$C_{15}H_{24}O_4$
Mol. Wt.: 268,35

The dialkylated product **91** (220 mg, 0.82 mmol, 7.2%, colourless oil) was obtained as a byproduct in the synthesis of **88.**

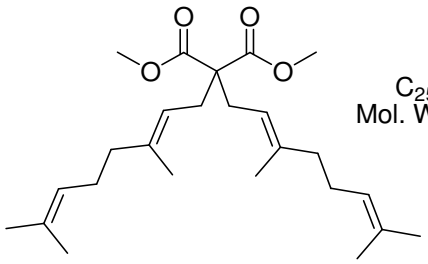
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.587 (br. s, 6 H), 1.684 (br. s, 6 H), 2.584 (m, 4 H), 3.696 (s, 6 H), 4.939 (m, 2 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 17.77 (2xCH_3), 26.02 (2xCH_3), 30.89 (2xCH_2), 52.26 (2xCH_3), 57.79 (4°C), 117.75 (2x3°C), 135.49 (2x4°C), 171.92 (2xC=O)

(+)-ESI-FTICR-MS: $[C_{15}H_{24}O_4 + Na]^+$ found: *m/z* 291.15638, calc. *m/z* 291.15668

92	**Dimethyl 2,2-*bis*((*E*)-3,7-dimethylocta-2,6-dienyl)malonate**	Mol-ID: 9323

VAD 411B



$C_{25}H_{40}O_4$
Mol. Wt.: 404,58

The dialkylated product **92** (324 mg, 0.80 mmol, 7.0%, pale yellow oil) was obtained as a byproduct in the synthesis of **89.**

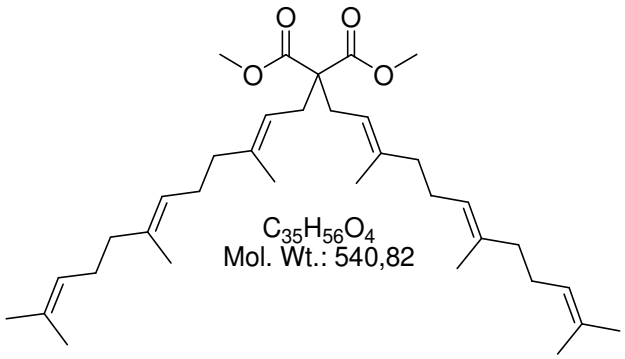
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.590 (br. s, 12 H), 1.677 (br. s, 6 H), 1.916 - 2.103 (m, 8 H), 2.603 (d, *J*=7.4 Hz, 4 H), 3.691 (s, 6 H), 4.959 (m, 2 H), 5.058 (m, 2 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 16.05 (2x CH_3), 17.67 (2x CH_3), 25.64 (2x CH_3), 26.54 (2x CH_2), 30.75 (2x CH_2), 39.93 (2x CH_2), 52.22 (2x CO_2CH_3), 57.82 (4°C, malonate), 117.82 (2x CH), 124.04 (2x CH), 131.47 (2x 4°C), 139.03 (2x 4°C), 171.88 (2x C=O)

(+)-ESI-FTICR-MS: $[C_{25}H_{40}O_4 + Na]^+$ found: *m/z* 427.28195, calc. *m/z* 427.28188

93	**Dimethyl 2,2-*bis*((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienyl)malonate**[243]	Mol-ID: 10108

VAD 412B

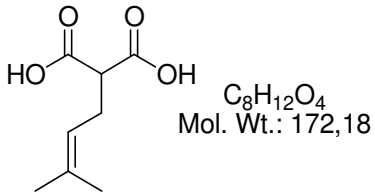


The dialkylated product **93** (324 mg, 0.80 mmol, 7.0%) was obtained as a byproduct in the synthesis of **90.** Physical and spectral data were in accordance with literature data.[243]

(+)-ESI-FTICR-MS: $[C_{35}H_{56}O_4 + Na]^+$ found: *m/z* 563.40673, calc. *m/z* 563.40708

94	**2-(3-Methylbut-2-enyl)malonic acid**[244]	Mol-ID: 11226

VAD 550



The synthesis was performed following **GSP 2**: Diester **88** (100 mg, 0.50 mmol) was dissolved in 5 mL of THF/H_2O (1/1). LiOH*H_2O (63 mg, 1.50 mmol) was added and the reaction mixture was stirred at room temp. for 6h. After careful acidification with diluted HCl to pH 2-3 at 0°C, the crude material was purified by HPLC to afford 31 mg (0.18 mmol, 36%) of **94** as a colorless crystalline solid.

^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.645 (br. s, 3 H), 1.686 (br. s, 3 H), 2.533 (tt, *J*=7.5, 0.9 Hz, 2 H), 3.265 (t, *J*=7.6 Hz, 1 H), 5.112 (m, 1 H) *COO*H *protons exchange with solvent.*

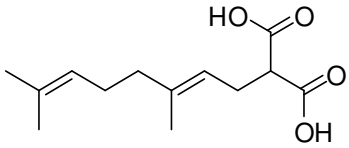
^{13}C NMR (100 MHz, CD_3OD) δ ppm 17.81 (CH_3), 25.95 (CH_3), 28.80 (CH_2), 53.25 (CH), 121.43 (CH), 135.45 (4°C), 173.00 (2x C=O)

(+)-ESI-FTICR-MS: $[C_8H_{12}O_4 + Na]^+$ found: *m/z* 195.06276, calc. *m/z* 195.06278

HPLC: t_R = 5.45 min (condition **A**) **Melting point**[244]**:** 95–97 °C

95	**2-((*E*)-3,7-Dimethylocta-2,6-dienyl)malonic acid**[245]	Mol-ID: 9322

VAD 559 (peak 2), 549



$C_{13}H_{20}O_4$
Mol. Wt.: 240,3

The synthesis was performed following **GSP 2**: Diester **89** (100 mg, 0.37 mmol) was dissolved in 5 mL of THF/H_2O (1/1). LiOH*H_2O (47 mg, 1.12 mmol) was added and the reaction mixture was stirred at room temp. for 6h. After careful acidification to pH 2-3 at 0°C, the crude material was purified by HPLC to afford 65 mg (0.27 mmol, 73%) of **95** as viscous yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.59 (s, 3 H), 1.64 (s, 3 H), 1.67 (s, 3 H), 2.02 (m, 4 H), 2.66 (t, *J*=7.04 Hz, 2 H), 3.44 (t, *J*=7.18 Hz, 1 H), 5.07 (m, 2 H), 5.88 (br s, 2 H)

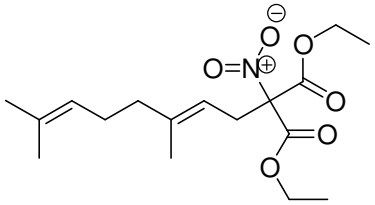
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.05 (CH_3), 17.65 (CH_3), 25.63 (CH_3), 26.43 (CH_2), 27.50 (CH_2), 39.64 (CH_2), 51.58 (CH, malonate), 118.72 (CH), 123.87 (CH), 131.61 (4°C), 139.46 (4°C), 174.18 (2x C=O)

(+)-ESI-FTICR-MS: $[C_{13}H_{20}O_4 + Na]^+$ found: *m/z* 263.12500, calc. *m/z* 263.12538

HPLC: t_R = 13.41 min (condition **B**)

99	**Diethyl 2-((*E*)-3,7-dimethylocta-2,6-dienyl)-2-nitromalonate**	Mol-ID: 10264

VAD 570



$C_{17}H_{27}NO_6$
Mol. Wt.: 341,4

The synthesis was conducted in analogy to **GSP 1**: Diethyl nitromalonate (97%, 1.03 g, 4.87 mmol) was dissolved in 10 mL of dry THF and cooled to 0°C. Triethylamine was added and stirring at 0°C was continued for further 10 min. Then, geranyl bromide (96%, 1.22 g, 5.60 mmol) were added dropwise via syringe. The reaction mixture was heated to 70°C for 10h. After work-up the crude material was purified by flash silica column chromatography (Hex/EtOAc = 1/2). The title compound (1.06 g, 3.10 mmol, 64%) was obtained as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.32 (t, *J*=7.0 Hz, 6 H), 1.59 (s, 3 H), 1.64 (s, 3 H), 1.68 (s, 3 H), 1.94 - 2.12 (m, 4 H), 3.13 (d, *J*=7.3 Hz, 2 H), 4.33 (q, *J*=7.0 Hz, 4 H), 5.05 (m, 1 H), 5.29 (tq, *J*=7.2, 1.3 Hz, 1 H)

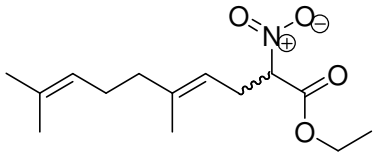
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 13.75 (2x CH_3, $CH_2\mathit{CH_3}$), 16.26 (CH_3), 17.66 (CH_3), 25.63 (CH_3), 26.36 (CH_2), 33.24 (CH_2), 39.83 (CH_2), 63.46 (2x CH_2, $\mathit{CH_2}CH_3$), 96.80 (4°C, CNO_2), 114.88 (3°C), 123.67 (3°C), 131.73 (4°C), 141.71 (4°C), 162.56 (2x C=O)

(+)-ESI-FTICR-MS: $[C_{17}H_{27}NO_6 + Na]^+$ found: *m/z* 364.17254, calc. *m/z* 364.17306

HPLC: t_R = 19.99 min (condition **A**)

101	**(*E*)-Ethyl 5,9-dimethyl-2-nitrodeca-4,8-dienoate**	Mol-ID: 10265

VAD 574, 653, 661



$C_{14}H_{23}NO_4$
Mol. Wt.: 269,34

The title compound was obtained as a yellow oil (51 mg, 0.19 mmol, 13%) during saponification (**GSP 1**) of compound **99**.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.31 (t, *J*=7.2 Hz, 3 H), 1.59 (br. s, 3 H), 1.66 (br. s, 1 H), 1.68 (br. s, 3 H), 2.02 (m, 4 H), 2.82 (m, 1 H), 3.02 (m, 1 H), 4.29 (q, *J*=7.0 Hz, 2 H), 5.05 (m, 3 H)

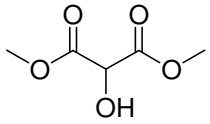
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 13.90 ($CH_2\mathit{CH_3}$), 16.16 (CH_3), 17.67 (CH_3), 25.63 (CH_3), 26.27 (CH_2), 29.23 (CH_2), 39.59 (CH_2), 62.94 ($\mathit{CH_2}CH_3$), 87.82 ($\mathit{C}HNO_2$), 115.70 (3°C), 123.56 (3°C), 131.85 (4°C), 141.59 (4°C), 164.33 (C=O)

(+)-ESI-FTICR-MS: $[C_{14}H_{23}NO_4 + Na]^+$ found: *m/z* 292.15175, calc. *m/z* 292.15193

HPLC: t_R = 19.05 min (condition **A**)

104	**Dimethyl 2-hydroxymalonate**[246-248]	Mol-ID: 10118

VAD 431



$C_5H_8O_5$
Mol. Wt.: 148,11

The synthesis was carried out according to **GSP 3:** Tartronic acid (5.15 g, 41.65 mmol) was dissolved in 50 mL of anhydrous MeOH and cooled to -10°C. Thionyl chloride (11.15 g, 93.70 mmol) was added dropwise. The desired compound (4.8 g, 32.44 mmol, 78%) was isolated as a white crystalline solid. Physical and spectral data were in accordance with literature data.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.533 (d, *J*=8.4 Hz, 1 H, OH), 3.849 (s, 6 H), 4.759 (d, *J*=8.4 Hz, 1 H, C*H*OH)

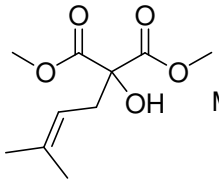
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 53.35 (2x CH_3), 71.26 (CH), 168.82 (2x C=O)

(+)-ESI-CID-MS: *m/z* 171.3 $[M + Na]^+$

Melting point: 36–37 °C

105	**Dimethyl 2-hydroxy-2-(3-methylbut-2-enyl)malonate**	Mol-ID: 9216

VAD 436



$C_{10}H_{16}O_5$
Mol. Wt.: 216,23

The synthesis was carried out according to **GSP 1**: NaH (60% in oil, washed with hexanes, 297 mg, 7.43 mmol), tartronic acid dimethyl ester **104** (1.0 g, 6.75 mmol), 15-crown-5 (76 mg, 0.34 mmol) and 3,3-dimethylallyl bromide (90%, 1.29 g, 7.76 mmol) in THF (20 mL) were reacted at 0°C. After work-up and extraction into EtOAc the crude material was purified by flash silica column chromatography (Hex/EtOAc = 1/1). The title compound (637 mg, 2.95 mmol, 44%) was obtained as a pale yellow oil.

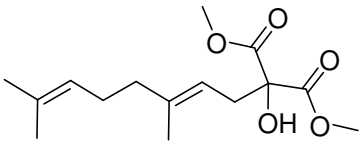
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.640 (br. s, 3 H), 1.708 (br. s, 3 H), 2.762 (d, *J*=7.4 Hz, 2 H), 3.700 (s, 1 H, OH), 3.801 (s, 6 H), 5.077 (tsept, *J*=7.4, 1.4 Hz, 1 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 17.95 (CH_3), 25.96 (CH_3), 33.87 (CH_2), 53.29 (2x CO_2CH_3), 78.97 (4°C, COH), 115.97 (CH), 136.93 (4°C), 170.71 (2x C=O)

(+)-ESI-FTICR-MS: $[C_{10}H_{16}O_5 + Na]^+$ found: *m/z* 239.08891, calc. *m/z* 239.08899

106	**Dimethyl 2-hydroxy-2-((*E*)-3,7-dimethylocta-2,6-dienyl) malonate**	Mol-ID: 9219

VAD 438



$C_{15}H_{24}O_5$
Mol. Wt.: 284,35

The synthesis was performed following **GSP 1**: NaH (60% in oil, washed with hexanes, 297 mg, 7.43 mmol), tartronic acid dimethyl ester **104** (1.0 g, 6.75 mmol), 15-crown-5 (76 mg, 0.34 mmol) and geranyl bromide (1.76 g, 7.76 mmol) in THF (20 mL) were reacted at 0°C. After work-up the crude material was purified by flash silica column chromatography (Hex/EtOAc = 4/1). The title compound (976 mg, 2.95 mmol, 51%) was obtained as a pale yellow oil.

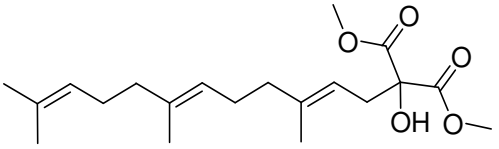
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.593 (br. s, 3 H), 1.633 (br. s, 3 H), 1.683 (br. s, 3 H), 2.027 (m, 4 H), 2.773 (d, *J*=7.4 Hz, 2 H), 3.702 (s, 1 H, OH), 3.795 (s, 6 H), 5.075 (m, 2 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.20 (CH_3), 17.68 (CH_3), 25.64 (CH_3), 26.44 (CH_2), 33.82 (CH_2), 39.81 (CH_2), 53.24 (2x CO_2CH_3), 78.98 (4°C, COH), 115.98 (CH), 123.89 (CH), 131.60 (4°C), 140.53 (4°C), 170.67 (2x C=O)

(+)-ESI-FTICR-MS: $[C_{15}H_{24}O_5 + Na]^+$ found: *m/z* 307.15114, calc. *m/z* 307.15159

107	**Dimethyl 2-hydroxy-2-((*2E,6E*)-3,7,11-trimethyldodeca-2,6,10-trienyl)malonate**	Mol-ID: 9222

VAD 439



$C_{20}H_{32}O_5$
Mol. Wt.: 352,47

The synthesis was carried out according to **GSP 1**: NaH (60% in oil, washed with hexanes, 297 mg, 7.43 mmol), tartronic acid dimethyl ester **104** (1.0 g, 6.75 mmol), 15-crown-5 (76 mg, 0.34 mmol) and farnesyl bromide (2.33 g, 7.76 mmol) in THF (20 mL) were reacted at 0°C. After work-up the crude material was purified by flash silica column chromatography

(Hex/EtOAc = 4/1). The title compound (948 mg, 2.69 mmol, 40%) was obtained as a pale yellow oil.

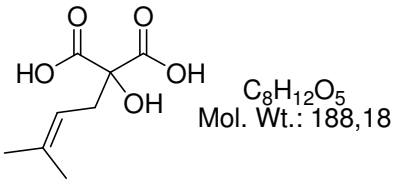
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.588 (br. s, 3 H), 1.602 (br. s, 3 H), 1.639 (br. s, 3 H), 1.680 (br. s, 3 H), 1.926 - 2.108 (m, 8 H), 2.773 (d, *J*=7.4 Hz, 2 H), 3.702 (s, 1 H), 3.794 (s, 6 H), 5.085 (m, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.26 (CH_3), 17.65 (CH_3), 25.67 (CH_3), 26.49 (CH_2), 26.70 (CH_2), 33.79 (CH_2), 39.66 (CH_2), 39.84 (CH_2), 53.25 (2x CO_2CH_3), 78.99 (4°C, COH), 115.92 (CH), 123.78 (CH), 124.30 (CH), 131.27 (4°C), 135.22 (4°C), 140.58 (4°C), 170.68 (2x C=O)

(+)-ESI-FTICR-MS: $[C_{20}H_{32}O_5 + Na]^+$ found: *m/z* 375.21395, calc. *m/z* 375.21419

108	**2-Hydroxy-2-(3-methylbut-2-enyl)malonic acid**[244]	Mol-ID: 9217

VAD 647



$C_8H_{12}O_5$
Mol. Wt.: 188,18

The synthesis was performed following **GSP 2**: Diester **105** (81 mg, 0.37 mmol) was dissolved in 5 mL of THF/H_2O (3/2). LiOH*H_2O (47 mg, 1.12 mmol) was added and the reaction mixture was stirred at room temp. for 6h. After careful acidification to pH 2-3 at 0°C, the crude material was purified by HPLC to afford 7 mg (37 µmol, 10%) of **108** as a white solid.

^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.642 (s, 3 H), 1.696 (s, 3 H), 2.687 (d, *J*=7.5 Hz, 2 H), 5.173 (m, 1 H)

^{13}C NMR (100 MHz, CD_3OD) δ ppm 18.13 (CH_3), 26.13 (CH_3), 35.60 (CH_2), 80.07 (4°C, COH), 118.53 (CH), 136.39 (4°C), 173.67 (2x C=O)

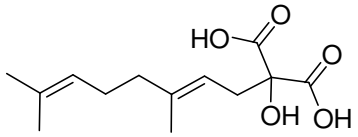
(–)-ESI-FTICR-MS: $[C_8H_{12}O_5 - H]^-$ found: *m/z* 187.06078, calc. *m/z* 187.06120

HPLC: t_R = 8.05 min (condition **A**)

Melting point:[244] 135-137 °C

109	**2-Hydroxy-2-((E)-3,7-dimethylocta-2,6-dienyl)malonic acid**	Mol-ID: 9220

VAD 551



$C_{13}H_{20}O_5$
Mol. Wt.: 256,29

The synthesis was performed following **GSP 2**: Diester **106** (100 mg, 0.35 mmol) was dissolved in 5 mL of THF/H_2O (1/1). LiOH*H_2O (44 mg, 1.06 mmol) was added and the reaction mixture was stirred at room temp. for 6h. After careful acidification to pH 2-3 at 0°C, the crude material was purified by HPLC to afford 85 mg (0.33 mmol, 94%) of **109** as a white solid.

^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.593 (br. s, 3 H), 1.642 (br. s, 3 H), 1.666 (br. s, 3 H), 1.945 - 2.115 (m, 4 H), 2.696 (dd, *J*=7.2, 0.7 Hz, 2 H), 5.093 (m, 1 H), 5.195 (m, 1 H) *COO*H *and O*H *protons exchange with solvent.*

^{13}C NMR (100 MHz, CD_3OD) δ ppm 16.52 (CH_3), 17.72 (CH_3), 25.87 (CH_3), 27.68 (CH_2), 35.48 (CH_2), 41.11 (CH_2), 80.07 (4°C, COH), 118.51 (CH), 125.27 (CH), 132.23 (4°C), 140.05 (4°C), 173.68 (2x C=O)

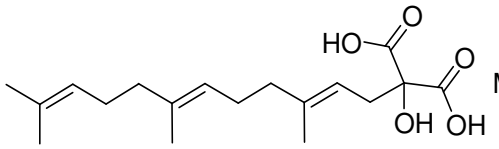
(–)-ESI-FTICR-MS: $[C_{13}H_{20}O_5 - H]^-$ found: *m/z* 255.12353, calc. *m/z* 255.12380

HPLC: t_R = 12.95 min (condition **A**)

Melting point: 84 °C

110	**2-Hydroxy-2-((*2E,6E*)-3,7,11-trimethyldodeca-2,6,10-trienyl)malonic acid**	Mol-ID: 9221

VAD 648



$C_{18}H_{28}O_5$
Mol. Wt.: 324,41

The synthesis was performed following **GSP 2**: Diester **107** (100 mg, 0.28 mmol) was dissolved in 5 mL of THF/H_2O (3/2). LiOH*H_2O (36 mg, 0.85 mmol) was added and the reaction mixture was stirred at room temp. for 6h. After careful acidification to pH 2-3 at 0°C, the crude material was purified by HPLC to afford 75 mg (0.23 mmol, 83%) of **110** as an amorphous solid.

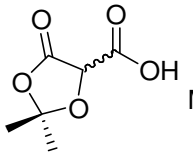
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.587 (br. s, 3 H), 1.598 (br. s, 3 H), 1.652 (br. s, 3 H), 1.677 (br. s, 3 H), 1.854 - 2.151 (m, 8 H), 2.810 (d, *J*=7.4 Hz, 2 H), 5.035 - 5.186 (m, 3 H), 7.258 (br. s, 2H, COOH)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 15.97 (CH_3), 16.44 (CH_3), 17.66 (CH_3), 25.67 (CH_3), 26.45 (CH_2), 26.70 (CH_2), 37.34 (CH_2), 39.66 (CH_2), 39.88 (CH_2), 78.77 (4°C, COH), 114.99 (CH), 123.75 (CH), 124.33 (CH), 131.34 (4°C), 135.35 (4°C), 141.98 (4°C), 172.32 (2x C=O)
(–)-ESI-FTICR-MS: $[C_{18}H_{28}O_5 - H]^-$ found: *m/z* 323.18566, calc. *m/z* 323.18640

HPLC: t_R = 13.44 min (condition **A**)

118	**2,2-Dimethyl-5-oxo-1,3-dioxolane-4-carboxylic acid**[130]	Mol-ID: 10072

VAD 615



$C_6H_8O_5$
Mol. Wt.: 160,12

To a solution of tartronic acid (97%, 2.02 g, 16.32 mmol) in dry acetone (100 mL) was added pyridine *p*-toluenesulfonate (410 mg, 1.63 mmol) and the reaction mixture was heated to 50°C. Subsequently, a solution of 2,2-dimethoxypropane (98%, 2.2 mL, 17.95 mmol) in 10 mL of acetone was added via syringe and the reaction solution was refluxed gently for 14 h. The crude material was purified by flash column chromatography (CH_2Cl_2/MeOH = 7/3) to yield the title compound (955 mg, 5.96 mmol, 37%) as a yellow oil which slowly crystallized to a white solid upon standing.

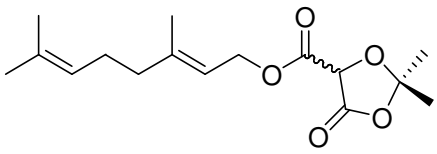
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.649 (s, 3H), 1.719 (s, 3H), 5.007 (s, 1H, CH), 9.892 (br. s., 1 H, COOH)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 26.84 (CH_3), 26.98 (CH_3), 73.50 (CH), 113.70 (4°C), 165.81 (C=O), 169.36 (COOH)

(+)-ESI-FTICR-MS: $[C_6H_8O_5 + Na]^+$ found: *m/z* 183.02615, calc. *m/z* 183.02639
(–)-ESI-FTICR-MS: $[C_6H_8O_5 - H]^-$ found: *m/z* 159.03029, calc. *m/z* 159.02990

119	**(*E*)-3,7-Dimethylocta-2,6-dienyl 2,2-dimethyl-5-oxo-1,3-dioxolane-4-carboxylate**	Mol-ID: 9854

VAD 616



$C_{16}H_{24}O_5$
Mol. Wt.: 296,36

The synthesis was performed following **GSP 4**: Compound **118** (526 mg, 3.28 mmol), geraniol (507 mg, 3.28 mmol), DCC (812 mg, 3.94 mmol) and DMAP (20 mg, 0.16 mmol) were reacted in anhydrous CH_3CN (15 mL) at 0°C. After work-up the crude material was purified by flash silica column chromatography (Hex/EtOAc = 3/1). The title compound (672 mg, 2.27 mmol, 69%) was obtained as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.601 (br s, 3 H), 1.626 (s, 3 H), 1.682 (br s, 3 H), 1.716 (s, 3 H), 1.726 (br s, 3 H), 2.079 (m, 4 H), 4.734 (dd, $^2J(H_AH_B)$=12.1 Hz, $^3J(H_AH_X)$= 7.2 Hz, 1 H, CH_2O), 4.805 (dd, $^2J(H_BH_A)$=12.1 Hz, $^3J(H_BH_X)$= 7.2 Hz, 1 H, CH_2O), 4.924 (s, 1 H), 5.070 (m, 1 H), 5.376 (m, 1 H)

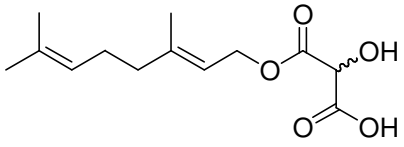
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.52 (CH_3), 17.67 (CH_3), 25.64 (CH_3), 26.17 (CH_2), 26.96 (CH_3, acetonide), 27.08 (CH_3, acetonide), 39.48 (CH_2), 63.52 (CH_2O), 74.02 (CH), 113.26 (4°C, acetonide), 117.00 (CH), 123.53 (CH), 131.93 (4°C), 144.04 (4°C), 165.15 (C=O), 166.30 (C=O)

(+)-ESI-FTICR-MS: $[C_{16}H_{24}O_5 + Na]^+$ found: *m/z* 319.15134, calc. *m/z* 319.15160

TLC: R_f = 0.49 (Hex / EtOAc = 3/1)
HPLC: t_R = 15.93 min (condition **E**)

120	**2-(((*E*)-3,7-Dimethylocta-2,6-dienyloxy)carbonyl)-2-hydroxyacetic acid**	Mol-ID: 9855

VAD 631



$C_{13}H_{20}O_5$
Mol. Wt.: 256,29

Acetonide group removal of **119** was carried out according to **GSP 5**. The title compound was obtained as a colourless solid (6 mg, 23.4 µmol, 3%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.601 (br. s, 3 H), 1.682 (br. s, 3 H), 1.728 (br. s, 3 H), 2.078 (m, 4 H), 4.766 (ddd, *J*=12.1, 7.1, 0.4 Hz, 1 H, CH_2O), 4.778 (s, 1 H, C*H*OH), 4.833 (ddd, *J*=12.1, 7.1, 0.4 Hz, 1 H, CH_2O), 5.067 (m, 1 H), 5.371 (tq, *J*=7.3, 1.3 Hz, 1H)

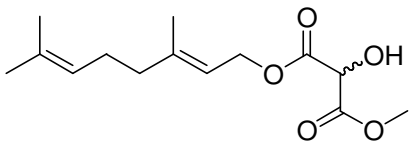
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.55 (CH_3), 17.69 (CH_3), 25.66 (CH_3), 26.16 (CH_2), 39.49 (CH_2), 64.22 (CH_2), 70.85 (CHOH), 116.70 (CH), 123.48 (CH), 132.03 (4°C), 144.52 (4°C), 168.29 (C=O), 170.19 (C=O)

(+)-ESI-FTICR-MS: $[C_{13}H_{20}O_5 + Na]^+$ found: *m/z* 279.12010, calc. *m/z* 279.12029
(–)-ESI-FTICR-MS: $[C_{13}H_{20}O_5 - H]^-$ found: *m/z* 255.12349, calc. *m/z* 255.12380

HPLC: t_R = 11.10 min (condition **E**)

121	**1-Methyl-3-(*E*)-3,7-dimethylocta-2,6-dienyl 2-hydroxy-malonate**	Mol-ID: 10071

VAD 631



$C_{14}H_{22}O_5$
Mol. Wt.: 270,32

The title methyl ester (3.1 mg, 11.5 µmol, 1.2%, colourless oil) was obtained as a byproduct under the conditions employed for the preparation of **120**.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.602 (br. s, 3 H), 1.685 (br. s, 3 H), 1.715 (br. s, 3 H), 2.078 (m, 4 H), 3.409 (br. s., 1 H, O*H*), 3.832 (s, 3 H, COCH_3), 4.746 (m, 3 H, CH_2O and C*H*OH), 5.071 (tsept, *J*=6.8, 1.4 Hz, 1 H), 5.351 (tq, *J*=7.2, 1.3 Hz, 1 H)

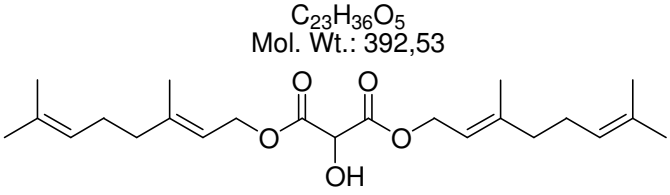
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.51 (CH_3), 17.67 (CH_3), 25.65 (CH_3), 26.21 (CH_2), 39.49 (CH_2), 53.23 (CH_3 ester), 63.47 (*C*H_2O), 71.44 (*C*HOH), 117.04 (CH), 123.52 (CH), 131.99 (4°C), 143.98 (4°C), 168.40 (C=O), 168.91 (C=O)

(+)-ESI-FTICR-MS: $[C_{14}H_{22}O_5 + Na]^+$ found: *m/z* 293.13542, calc. *m/z* 293.13594

HPLC: t_R = 13.22 min (condition **E**)

122	***Bis*((*E*)-3,7-dimethylocta-2,6-dienyl)-2-hydroxymalonate**	Mol-ID: 10061

VAD 629



The title prenyl diester (105 mg, 0.27 mmol, 5%, colourless oil) was obtained as a byproduct under the reaction conditions employed for the preparation of **119**.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.601 (br. s, 6 H), 1.683 (br. s, 6 H), 1.710 (br. s, 6 H), 2.067 (m, 8 H), 3.426 (br. d, *J*=8.2 Hz, 1 H), 4.663 - 4.840 (m, 5 H), 5.072 (tsept, *J*=6.8, 1.4 Hz, 2 H), 5.342 (tq, *J*=7.2, 1.3 Hz, 2 H)

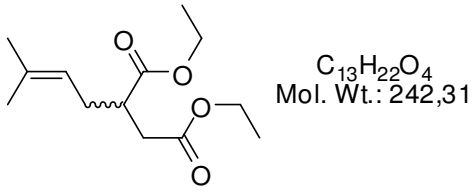
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.49 (2x CH_3), 17.66 (2x CH_3), 25.65 (2x CH_3), 26.21 (2x CH_2), 39.50 (2x CH_2), 63.32 (2x CH_2O), 71.54 (CHOH), 117.10 (2x CH), 123.51 (2x CH), 131.95 (2x 4°C), 143.76 (2x 4°C), 168.47 (2x C=O)

(+)-ESI-FTICR-MS: $[C_{23}H_{36}O_5 + Na]^+$ found: *m/z* 415.24547, calc. *m/z* 415.24550

HPLC: t_R = 8.29 min (condition **G**)

133	**Diethyl 2-(3-methylbut-2-enyl)succinate**[249]	Mol-ID: 10254

VAD 637



The synthesis was conducted according to **GSP 1**: NaH (60% in oil, washed with hexanes, 826 mg, 20.67 mmol), succinic acid diethyl ester (3.0 g, 17.22 mmol), and 3,3-dimethylallyl bromide (90%, 2.28 g, 13.78 mmol) were refluxed at 80°C in dry THF (20 mL) for 4h. After work-up the crude material was purified by flash silica column chromatography (Hex/EtOAc = 5/1). The title compound (334 mg, 1.38 mmol, 8%) was obtained as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.247 (t, *J*= 7.1 Hz, 3 H, CH_2CH_3), 1.253 (t, *J*= 7.1 Hz, 3 H, CH_2CH_3), 1.600 (s, 3 H), 1.695 (s, 3 H), 2.198 - 2.294 (m, 1 H), 2.302 - 2.389 (m, 1 H), 2.420 (dd, *J*=16.8, 5.1 Hz, 1 H), 2.620 - 2.726 (dd, *J*=16.8, 9.4 Hz, 1 H), 2.851 (m, 1 H, $CHCO_2Et$), 4.141 (m, 4 H, CH_2CH_3), 5.063 (m, 1 H)

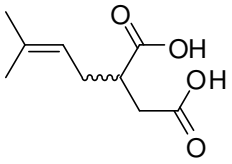
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 14.14 (*CH_3*CH_2), 14.16 (*CH_3*CH_2), 17.74 (CH_3), 25.77 (CH_3), 30.20 (CH_2), 35.19 (CH_2), 41.50 (CH), 60.49 (CH_3*CH_2*), 60.51 (CH_3*CH_2*), 120.18 (CH), 134.65 (4°C), 172.15 (C=O), 174.60 (C=O)

(+)-ESI-FTICR-MS: $[C_{13}H_{22}O_4 + Na]^+$ found: *m/z* 265.14075, calc. *m/z* 265.14103

HPLC: t_R = 16.71 min (condition **A**), t_R = 4.84 min (condition **C**)

134	**2-(3-methylbut-2-enyl)succinic acid**[133]	Mol-ID: 5587

VAD 639



$C_9H_{14}O_4$
Mol. Wt.: 186,21

The synthesis was performed following **GSP 2**: Diester **133** (185 mg, 0.76 mmol) was dissolved in 5 mL of THF/H_2O (3/2). NaOH (92 mg, 2.29 mmol) was added and the reaction mixture was stirred at room temp. for 14h. After careful acidification to pH 2-3 at 0°C, the crude material was purified by HPLC to afford 94 mg (0.50 mmol, 66%) of **134** as a white powder.

^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.629 (br. s, 3 H), 1.710 (br. s, 3 H), 2.232 - 2.366 (m, 2 H), 2.400 (dd, *J*=16.8, 5.3 Hz, 1 H), 2.603 (dd, *J*=16.8, 9.1 Hz, 1 H), 2.745 - 2.830 (m, 1 H), 5.118 (m, 1 H) *COO*H *protons exchange with solvent.*

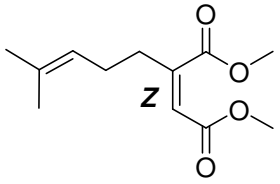
^{13}C NMR (100 MHz, CD_3OD) δ ppm 17.85 (CH_3), 25.95 (CH_3), 31.20 (CH_2), 35.99 (CH_2), 42.83 (CH), 121.64 (CH), 135.54 (4°C), 175.80 (C=O), 178.39 (C=O)

(+)-ESI-FTICR-MS: $[C_9H_{14}O_4 + Na]^+$ found: *m/z* 209.07803, calc. *m/z* 209.07843
$[2(C_9H_{14}O_4) + Na]^+$ found: *m/z* 395.16744, calc. *m/z* 395.16764

HPLC: t_R = 10.40 min (condition **A**), t_R = 4.99 min (condition **D**)

137-*Z*	**Dimethyl 2-(4-methylpent-3-enyl)maleate**[142],[250]	Mol-ID: 5595

VAD 055, 683



$C_{12}H_{18}O_4$
Mol. Wt.: 226,27

The preparation was done following **GSP 8**. Thus, 5-bromo-2-methyl-2-pentene (1.0 g, 6.13 mmol), magnesium turnings (298 mg, 12.26 mmol), $CuBr \cdot Me_2S$ (1.51 g, 7.36 mmol) and DMAD (958 mg, 6.74 mmol) were reacted as described. Purification of the crude product by flash column chromatography (Hex/EtOAc = 10/3) gave **137-*Z*** as a pale yellow oil (1.13 g, 4.99 mmol, 81%).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.605 (br. s, 3 H), 1.689 (br. s, 3 H), 2.133 - 2.241 (m, 2 H), 2.335 - 2.414 (m, 2 H), 3.725 (s, 3 H, CO_2CH_3), 3.828 (s, 3 H, CO_2CH_3), 5.077 (tsept, *J*=7.0, 1.4 Hz, 1 H), 5.822 (t, *J*=1.5 Hz, 1 H, $CHCO_2Me$)

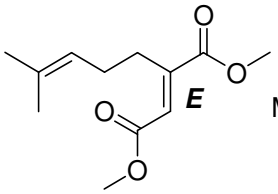
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 17.62 (CH_3), 25.52 (CH_2), 25.55 (CH_3), 34.35 (CH_2), 51.71 (CO_2CH_3), 52.20 (CO_2CH_3), 119.28 (3°C), 121.92 (3°C), 133.27 (4°C, prenyl), 150.18 (4°C), 165.35 (C=O), 169.23 (C=O)

(+)-ESI-FTICR-MS: $[C_{12}H_{18}O_4 + Na]^+$ found: *m/z* 249.10936, calc. *m/z* 249.10973

HPLC: t_R = 16.12 min (condition **A** but *without* mobile-phase additive)

137-*E*	**Dimethyl 2-(4-methylpent-3-enyl)fumarate**[250]	Mol-ID: 5582

VAD 060, 670



$C_{12}H_{18}O_4$
Mol. Wt.: 226,27

The preparation was done following **GSP 9**. Thus, 5-bromo-2-methyl-2-pentene (1.0 g, 6.13 mmol), magnesium turnings (298 mg, 12.26 mmol) and DMAD (958 mg, 6.74 mmol) were reacted as described. Purification of the crude product by flash column chromatography (Hex/EtOAc = 10/2) gave **137-*E*** as a yellow oil (272 mg, 1.20 mmol, 20%).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.593 (br. s, 3 H), 1.671 (br. s, 3 H), 2.158 (br. q, *J*=7.6 Hz, 2 H), 2.823 (m, 2 H), 3.767 (s, 3 H, CO_2CH_3), 3.805 (s, 3 H, CO_2CH_3), 5.143 (tsept, *J*=7.4, 1.4 Hz, 1 H), 6.739 (s, 1 H, $CHCO_2Me$)

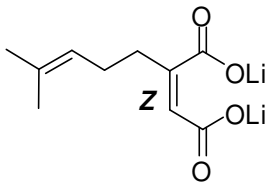
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 17.50 (CH_3), 25.61 (CH_3), 27.64 (CH_2), 27.93 (CH_2), 51.65 (CO_2CH_3), 52.44 (CO_2CH_3), 123.01 (3°C), 126.42 (3°C), 132.81 (4°C, prenyl), 147.61 (4°C), 166.03 (C=O), 167.39 (C=O)

(+)-ESI-FTICR-MS: $[C_{12}H_{18}O_4 + Na]^+$ found: *m/z* 249.10970, calc. *m/z* 249.10973

HPLC: t_R = 17.15 min (condition **A** but *without* mobile-phase additive)

138-*Z*	**2-(4-Methylpent-3-enyl)maleic acid di-lithium salt**	Mol-ID: 5589

VAD 057



$C_{10}H_{12}Li_2O_4$
Mol. Wt.: 210,08

GSP 1 was followed. The hydrolysis of diester **137-*Z*** (64 mg, 0.28 mmol) gave the title compound (56 mg, 0.27 mmol, 96%) as a white powder.

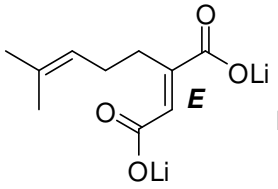
^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.614 (br. s, 3 H), 1.676 (br. s, 3 H), 2.081 - 2.311 (m, 4 H), 5.505 (m, 1 H), 6.019 (t, *J*=1.2 Hz, 1 H, $CHCO_2H$)

^{13}C NMR (75 MHz, CD_3OD) δ 17.84 (CH_3), 25.92 (CH_3), 27.49 (CH_2), 36.67 (CH_2), 121.37 (3°C), 124.97 (3°C), 132.79 (4°C), 152.25 (4°C), 175.52 (C=O), 179.80 (C=O)

(–)-ESI-FTICR-MS: $[C_{10}H_{14}O_4 - H]^-$ found: *m/z* 197.08172, calc. *m/z* 197.08193

138-*E*	**2-(4-Methylpent-3-enyl)fumaric acid di-lithium salt**	Mol-ID: 5590

VAD 061



$C_{10}H_{12}Li_2O_4$
Mol. Wt.: 210,08

GSP 1 was followed. The hydrolysis of diester **137-*E*** (102 mg, 0.45 mmol) gave the title compound (93 mg, 0.44 mmol, 98%) as a white powder.

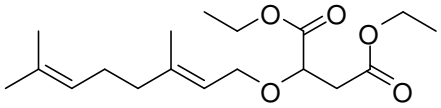
^{1}H NMR (300 MHz, D_2O) δ ppm 1.540 (br. s, 3 H), 1.624 (br. s, 3 H), 1.978 - 2.096 (m, 2 H), 2.448 (m, 2 H), 5.132 (m, 1 H), 6.333 (s, 1 H, C*H*CO_2H) *COO*H *protons exchange with solvent.*

^{13}C NMR (75 MHz, D_2O; ref. to CD_3OD) δ ppm 17.93 (CH_3), 25.86 (CH_3), 27.88 (CH_2), 29.74 (CH_2), 124.61 (3°C), 129.77 (3°C), 135.10 (4°C), 144.38 (4°C), 177.43 (C=O), 178.33 (C=O)

(–)-ESI-FTICR-MS: $[C_{10}H_{14}O_4 - H]^-$ found: *m/z* 197.08166, calc. *m/z* 197.08193

143	**Diethyl 2-((*E*)-3,7-dimethylocta-2,6-dienyloxy)succinate**	Mol-ID: 9857

VAD 582, 584



$C_{18}H_{30}O_5$
Mol. Wt.: 326,43

The synthesis was performed following **GSP 11**: Diethyl malate (97%, 1.03 g, 2.63 mmol), LDA (2.0 M, 2.89 mL, 5.79 mmol), and geranyl bromide (856 mg, 3.94 mmol) were reacted in dry THF (20 mL) at –78°C for 2 h. After work-up the crude material was purified by flash silica column chromatography (Hex/EtOAc = 3/1) to yield the title compound (74 mg, 0.17 mmol, 9%) as a yellow oil.

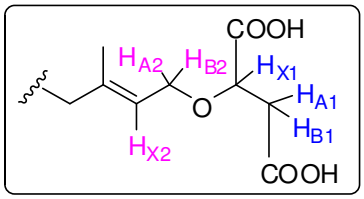
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.26 (t, *J*=7.0 Hz, 3 H), 1.30 (t, *J*=7.0 Hz, 3 H), 1.60 (s, 3 H), 1.66 (s, 3 H), 1.68 (s, 3 H), 2.05 (m, 4 H), 2.74 (dd, $^2J(H_AH_B)$=16.0 Hz, $^3J(H_AH_X)$= 8.0 Hz, 1 H), 2.76 (dd, $^2J(H_BH_A)$=16.0 Hz, $^3J(H_BH_X)$= 5.2 Hz, 1 H), 4.07 (dd, *J*=11.3, 7.4 Hz, 1 H), 4.11 - 4.29 (m, 5 H), 4.32 (dd, *J*=7.8, 5.1 Hz, 1 H), 5.09 (tsept, *J*=6.7, 1.4 Hz, 1 H), 5.35 (tq, *J*=7.0, 1.3 Hz, 1 H)

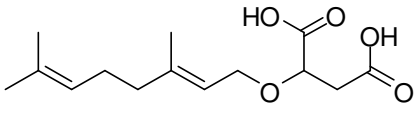
^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 14.13 (CH_2CH_3, ester), 14.17 (CH_2CH_3, ester), 16.39 (CH_3), 17.65 (CH_3), 25.65 (CH_3), 26.27 (CH_2), 38.07 (CH_2), 39.58 (CH_2), 60.79 (CH_2CH_3, ester), 61.12 (CH_2CH_3, ester), 67.29 (CH_2O), 73.95 (CH, chiral), 119.76 (3°C), 123.87 (3°C), 131.69 (4°C), 141.65 (4°C), 170.14 (C=O), 171.72 (C=O)

(+)-ESI-FTICR-MS: $[C_{18}H_{30}O_5 + Na]^+$ found: *m/z* 349.19836, calc. *m/z* 349.19854

144	**2-((*E*)-3,7-Dimethylocta-2,6-dienyloxy)succinic acid**	Mol-ID: 9859

VAD 592





$C_{14}H_{22}O_5$
Mol. Wt.: 270,32

GSP 2 was followed. The hydrolysis of diester **143** (54 mg, 0.17 mmol) gave the title compound (20 mg, 74.0 µmol, 45%) as a colourless solid.

^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.605 (s, 3 H), 1.671 (s, 6 H), 2.078 (m, 4 H), 2.611 (dd, $^2J(H_{A1}H_{B1})$=16.1 Hz, $^3J(H_{A1}H_{X1})$= 8.7 Hz, 1 H, CH_2COOH), 2.751 (dd, $^2J(H_{B1}H_{A1})$=16.1 Hz, $^3J(H_{B1}H_{X1})$= 4.2 Hz, 1 H, CH_2COOH), 4.069 (dd, $^2J(H_{A2}H_{B2})$=11.6 Hz, $^3J(H_{A2}H_{X2})$= 7.4 Hz, 1 H, CH_2O), 4.184 (dd, $^2J(H_{B2}H_{A2})$=11.6 Hz, $^3J(H_{B2}H_{X2})$= 6.8 Hz, 1 H, CH_2O), 4.280 (dd, ^3J=8.7, 4.2 Hz, 1 H, C*H*O), 5.106 (tsept, *J*=7.0, 1.5 Hz, 1 H), 5.327 (ddq, *J*=7.4, 6.8, 1.3 Hz, 1 H) *COO*H *protons exchange with solvent.*

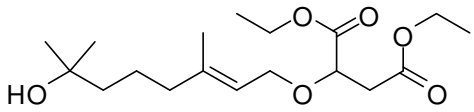
^{13}C NMR (100 MHz, CD_3OD) δ ppm 16.44 (CH_3), 17.74 (CH_3), 25.87 (CH_3), 27.36 (CH_2), 38.90 (CH_2), 40.69 (CH_2), 67.96 (CH_2O), 74.93 (CH, chiral), 121.34 (3°C), 125.04 (3°C), 132.56 (4°C), 142.56 (4°C), 173.71 (C=O), 175.35 (C=O)

(+)-ESI-FTICR-MS: $[C_{14}H_{22}O_5 + Na]^+$ found: *m/z* 293.13583, calc. *m/z* 293.13594
(–)-ESI-FTICR-MS: $[C_{14}H_{22}O_5 - H]^-$ found: *m/z* 269.13956, calc. *m/z* 269.13945

HPLC: t_R = 11.08 min (condition **E**)

145	**Diethyl 2-((*E*)-7-hydroxy-3,7-dimethyloct-2-enyloxy)succinate**	Mol-ID: 9858

VAD 582, 584



$C_{18}H_{32}O_6$
Mol. Wt.: 344,44

The hydrated product (58 mg, 0.17 mmol, 6%) was obtained as a byproduct of the synthesis of **143.**

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.265 (t, *J*=6.9 Hz, 3 H), 1.301 (t, *J*=6.9 Hz, 3 H), 1.551 - 1.781 (m, 4 H), 1.675 (br. s, 3 H), 1.752 (s, 6 H), 2.060 (t, *J*=7.2 Hz, 2 H), 2.724 (dd, $^2J(H_AH_B)$ =16.0 Hz, $^3J(H_AH_X)$= 8.0 Hz, 1 H), 2.785 (dd, $^2J(H_BH_A)$=16.0 Hz, $^3J(H_BH_X)$=5.1 Hz, 1 H), 4.068

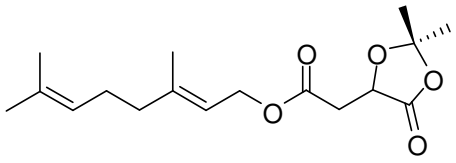
(ddd, *J*=11.4, 7.1, 0.5 Hz, 1 H), 4.167 (q, *J*=7.1 Hz, 2 H), 4.197 - 4.276 (m, 3 H), 4.324 (dd, *J*=8.0, 5.1 Hz, 2 H), 5.367 (tq, *J*=7.0, 1.3 Hz, 1 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 14.13 (CH_2CH_3, ester), 14.17 (CH_2CH_3, ester), 16.22 (CH_3), 24.09 (CH_2), 34.19 (CH_3), 34.23 (CH_3), 38.03 (CH_2), 39.20 (CH_2), 46.88 (CH_2), 60.80 (CH_2CH_3, ester), 61.14 (CH_2CH_3, ester), 67.25 (CH_2O), 68.26 (4°C, Me_2COH), 74.07 (3°C, $CHCO_2Et$), 120.25 (CH), 141.04 (4°C), 170.10 (C=O), 171.65 (C=O)

(+)-ESI-FTICR-MS: Product **145** eliminates water upon ionization. Thus, only **143** is detected in the mass spectrum.

147	**(*E*)-3,7-Dimethylocta-2,6-dienyl 2-(2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl)acetate**	Mol-ID: 9851

VAD 611, 619



$C_{17}H_{26}O_5$
Mol. Wt.: 310,39

The synthesis was performed following **GSP 4**: 2,2-Dimethyl-5-oxo-1,3-dioxolane-4-acetic acid[148-149] (95%, 526 mg, 2.87 mmol), geraniol (98%, 376 mg, 2.39 mmol), DCC (592 mg, 2.87 mmol) and DMAP (18 mg, 0.14 mmol) were reacted in anhydrous CH_3CN (15 mL) at 0°C. After work-up the crude material was purified by flash silica column chromatography (Hex/EtOAc = 3/1). The title compound (684 mg, 2.20 mmol, 92% ref. to geraniol) was obtained as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.568 (s, 3 H), 1.603 (s, 3 H), 1.622 (s, 3 H), 1.684 (s, 3 H), 1.704 (s, 3 H), 2.084 (m, 4 H), 2.797 (dd, ^2J=16.8, ^3J=6.6 Hz, 1 H), 2.938 (dd, ^2J=16.8, ^3J=3.7 Hz, 1 H), 4.660 (d, ^3J =7.0 Hz, 2 H, CH_2O), 4.729 (dd, ^3J=6.4, 3.7 Hz, 1 H, C*H*COO), 5.079 (m, 1H), 5.344 (m, 1H)

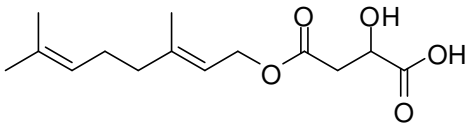
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.45 (CH_3), 17.66 (CH_3), 25.65 (CH_3), 25.84 (CH_3, acetonide), 26.20 (CH_2), 26.72 (CH_3, acetonide), 36.27 (CH_2COO), 39.48 (CH_2), 62.09 (CH_2O), 70.68 (CH), 111.11 (4°C, acetonide), 117.69 (CH), 123.62 (CH), 131.86 (4°C), 142.88 (4°C), 169.19 (C=O, ester), 172.09 (C=O, dioxolane)

(+)-ESI-FTICR-MS: $[C_{17}H_{26}O_5 + Na]^+$ found: *m/z* 333.16675, calc. *m/z* 333.16725

TLC: R_f = 0.37 (Hex / EtOAc = 3/1)

148	**3-(((*E*)-3,7-Dimethylocta-2,6-dienyloxy)carbonyl)-2-hydroxypropanoic acid**	Mol-ID: 9853

VAD 613



$C_{14}H_{22}O_5$
Mol. Wt.: 270,32

Acetal deprotection of **147** was carried out according to **GSP 5**. The title compound was obtained as a pale yellow oil (10 mg, 0.04 mmol, 13%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.604 (s, 3 H), 1.685 (s, 3 H), 1.707 (s, 3 H), 2.070 (m, 4 H), 2.860 (dd, $^2J(H_AH_B)$=17.1 Hz, $^3J(H_AH_X)$= 6.3 Hz, 1 H, CH_2), 2.945 (dd, $^2J(H_BH_A)$=17.1 Hz, $^3J(H_BH_X)$= 4.6 Hz, 1 H, CH_2), 4.557 (dd, *J*=6.3, 4.6 Hz, 1 H, C*H*OH), 4.668 (pseudo d, 2 H, CH_2O), 5.076 (tsept, *J*= 6.8, 1.4 Hz, 1 H), 5.338 (tq, *J*= 7.2, 1.3 Hz, 1 H)

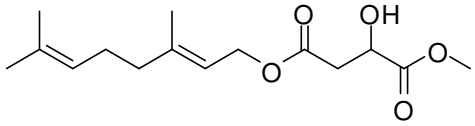
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.48 (CH_3), 17.68 (CH_3), 25.67 (CH_3), 26.21 (CH_2), 38.06 (*C*H_2COOH), 39.48 (CH_2), 62.35 (CH_2O), 66.91 (CHOH), 117.43 (CH), 123.59 (CH), 131.96 (4°C), 143.31 (4°C), 171.47 (C=O, ester), 175.98 (COOH)

(+)-ESI-FTICR-MS: $[C_{14}H_{22}O_5 + Na]^+$ found: *m/z* 293.13572, calc. *m/z* 293.13594
(–)-ESI-FTICR-MS: $[C_{14}H_{22}O_5 - H]^-$ found: *m/z* 269.13929, calc. *m/z* 269.13945

HPLC: t_R = 11.9 min (condition **E**)

149	**1-Methyl 4-(*E*)-3,7-dimethylocta-2,6-dienyl 2-hydroxysuccinate**	Mol-ID: 9852

VAD 612



$C_{15}H_{24}O_5$
Mol. Wt.: 284,35

The title methyl ester (75mg, 0.26 mmol, 60%, colourless oil) was obtained as a byproduct during the synthesis of **148**.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.603 (s, 3 H), 1.685 (s, 3 H), 1.700 (s, 3 H), 2.077 (m, 4 H), 2.802 (dd, $^2J(H_AH_B)$=16.5 Hz, $^3J(H_AH_X)$= 6.0 Hz, 1 H, CH_2CHOH), 2.872 (dd, $^2J(H_BH_A)$= 16.5 Hz, $^3J(H_BH_X)$= 4.4 Hz, 1 H, CH_2CHOH), 3.238 (br s, 1 H, O*H*), 3.812 (s, 3 H), 4.508 (dd, *J*=6.1, 4.5 Hz, 1 H, C*H*OH), 4.639 (m, 2 H, CH_2O), 5.080 (m, 1 H), 5.332 (m, 1 H)

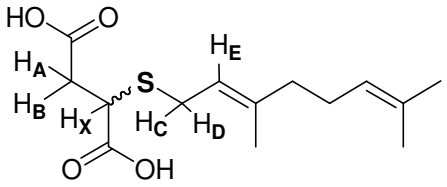
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.46 (CH_3), 17.67 (CH_3), 25.66 (CH_3), 26.23 (CH_2), 38.62 (CH_2), 39.49 (CH_2), 52.80 (CH_3, ester), 61.92 (CH_2O), 67.28 (*C*HOH), 117.74 (CH), 123.63 (CH), 131.89 (4°C), 142.83 (4°C), 170.58 (C=O), 173.75 (*C*OOMe)

(+)-ESI-FTICR-MS: $[C_{15}H_{24}O_5 + Na]^+$ found: *m/z* 307.15138, calc. *m/z* 307.15160

TLC: R_f = 0.14 (Hex / EtOAc = 3/1)

151	**2-((*E*)-3,7-Dimethylocta-2,6-dienylthio)succinic acid**	Mol-ID: 10132

VAD 572



$C_{14}H_{22}O_4S$
Mol. Wt.: 286,39

The synthesis was performed following **GSP 7**: Mercaptosuccinic acid (500 mg, 3.33 mmol), K_2CO_3 (1.47 g, 10.6 mmol), and geranyl bromide (96%, 795 mg, 3.66 mmol) were reacted in dry DMF (10 mL) at 40°C. After work-up the crude material was purified by prep. HPLC to give the title sulfide (934 mg, 3.26 mmol, 98%) as a white amorphous soild.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.600 (s, 3 H), 1.675 (s, 3 H), 1.703 (s, 3 H), 2.072 (m, 4 H), 2.724 (dd, $^2J(H_AH_B)$=17.6 Hz, $^3J(H_AH_X)$= 4.0 Hz, 1 H), 2.985 (dd, $^2J(H_BH_A)$=17.6 Hz, $^3J(H_BH_X)$= 12.2 Hz, 1 H), 3.245 (dd, $^2J(H_CH_D)$=13.2 Hz, $^3J(H_CH_E)$= 6.8 Hz, 1 H), 3.505 (dd, $^2J(H_DH_C)$=13.2 Hz, $^3J(H_DH_E)$= 8.7 Hz, 1 H), 3.595 (dd, $^3J(H_XH_B)$=12.2 Hz, $^3J(H_XH_A)$= 4.0 Hz, 1 H), 5.074 (m, 1 H), 5.229 (m, 1 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 16.11 (CH_3), 17.70 (CH_3), 25.65 (CH_3), 26.39 (CH_2), 29.89 (CH_2S), 36.37 (CH_2), 39.60 (CH_2), 40.08 (CHS), 118.59 (3°C), 123.71 (3°C), 131.85 (4°C), 141.32 (4°C), 177.40 (C=O), 178.68 (C=O)

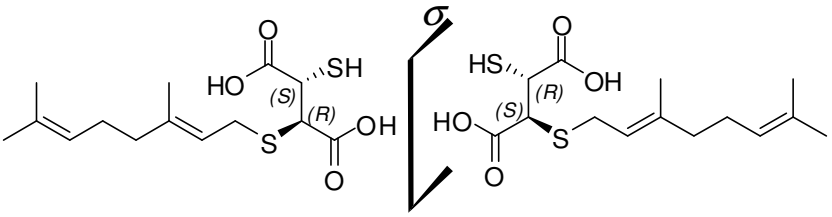
(+)-ESI-FTICR-MS: $[C_{14}H_{22}O_4S + Na]^+$ found: *m/z* 309.11331, calc. *m/z* 309.11310

HPLC: t_R = 14.89 min (condition **A**)

Melting point: 71-73 °C

154	**(*2R,3S*)-** and **(*2S,2R*)-2-((*E*)-3,7-Dimethylocta-2,6-dienylthio)-3-mercaptosuccinic acid**	Mol-ID: 10361

VAD 650



$C_{14}H_{22}O_4S_2$
Mol. Wt.: 318,45

racemate

The synthesis was performed following **GSP 7**: 2,3-dithio-*meso*-tartaric acid (500 mg, 2.73 mmol), K_2CO_3 (1.21 g, 8.78 mmol), and geranyl bromide (96%, 534 mg, 2.46 mmol) were reacted in dry DMF (10 mL) at 0°C for 14 h. After work-up the crude material was purified by prep. HPLC to give the title monosulfide (yield not determined) as a white solid.

^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.602 (br. s, 3 H), 1.668 (br. s, 3 H), 1.686 (br. s, 3 H), 1.988 - 2.061 (m, 2 H), 2.066 - 2.153 (m, 2 H), 3.331 (dd, $^2J(H_AH_B)$=12.5 Hz, $^3J(H_AH_X)$= 7.9 Hz, 1 H), 3.394 (dd, $^2J(H_BH_A)$=12.5 Hz, $^3J(H_BH_X)$= 7.9 Hz, 1 H), 3.427 (d, *J*=11.4 Hz, 1 H), 3.563 (d, *J*=11.4 Hz, 1 H), 5.096 (tsept, *J*=7.0, 1.4 Hz, 1 H), 5.210 (tq, *J*=7.8, 1.3 Hz, 1 H)

^{13}C NMR (100 MHz, CD_3OD) δ ppm 16.17 (CH_3), 17.77 (CH_3), 25.87 (CH_3), 27.51 (CH_2), 30.93 (CH_2), 40.70 (CH_2), 43.03 (CHS), 51.49 (CHS), 120.09 (CH), 125.07 (CH), 132.51 (4°C), 142.03 (4°C), 173.61 (C=O), 174.24 (C=O)

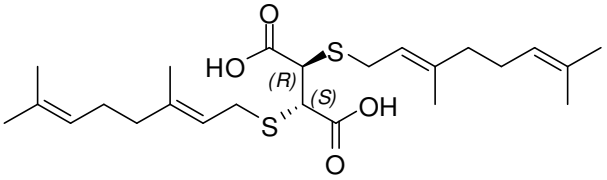
(–)-ESI-FTICR-MS: $[C_{14}H_{22}O_4S_2 - H]^-$ found: *m/z* 317.08861, calc. *m/z* 317.08867

HPLC: t_R = 14.77 min (condition **A**)

Melting point: 132 °C

155	***Meso*-2,3-*bis*((*E*)-3,7-dimethylocta-2,6-dienylthio)succinic acid**	Mol-ID: 10362

VAD 650



$C_{24}H_{38}O_4S_2$
Mol. Wt.: 454,69

The title disubstituted *meso*-compound was obtained as a by-product (white powder, yield n.d.) during the synthesis of **154**.

^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.601 (br. s, 6 H), 1.667 (br. s, 6 H), 1.687 (br. s, 6 H), 1.989 - 2.063 (m, 4 H), 2.067 - 2.154 (m, 4 H), 3.324 (dd, $^2J(H_AH_B)$=12.5 Hz, $^3J(H_AH_X)$= 8.0 Hz, 2 H), 3.401 (dd, $^2J(H_BH_A)$=12.5 Hz, $^3J(H_BH_X)$= 8.0 Hz, 2 H), 3.472 (s, 2 H), 5.097 (tsept, *J*=7.0, 1.4 Hz, 2 H), 5.214 (tq, *J*=7.8, 1.3 Hz, 2 H) *COO*H *protons exchange with solvent.*

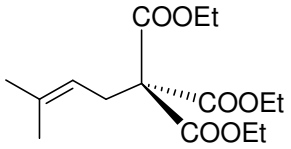
^{13}C NMR (100 MHz, CD_3OD) δ ppm 16.22 (2x CH_3), 17.79 (2x CH_3), 25.88 (2x CH_3), 27.58 (2x CH_2), 31.01 (2x CH_2), 40.76 (2x CH_2), 48.46 (2x CHS), 120.34 (2x CH), 125.11 (2x CH), 132.50 (2x 4°C), 141.81 (2x 4°C), 173.82 (2x C=O)

(–)-ESI-FTICR-MS: $[C_{24}H_{38}O_4S_2 - H]^-$ found: *m/z* 453.21329, calc. *m/z* 453.21387

HPLC: t_R = 19.04 min (condition **A**)

159	**Triethyl 4-methylpent-3-ene-1,1,1-tricarboxylate**[251]	Mol-ID: 9229

VAD 426



$C_{15}H_{24}O_6$
Mol. Wt.: 300,35

The synthesis was carried out according to **GSP 1**: NaH (60% in oil, washed with hexanes, 190 mg, 4.74 mmol), triethyl methanetricarboxylate (TEMT) (1.02 g, 4.31 mmol), 15-crown-5 (48 mg, 0.22 mmol) and 3,3-dimethylallyl bromide (856 mg, 5.17 mmol) in THF (20 mL) were reacted at 0°C. After work-up the crude material was purified by flash silica column chromatography (Hex/EtOAc = 3/1). The title compound (721 mg, 2.40 mmol, 56%) was obtained as a pale yellow oil.

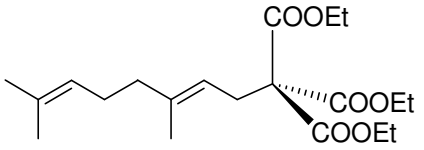
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.270 (t, *J*=7.1 Hz, 9 H), 1.625 (br. s, 3 H), 1.691 (br. s, 3 H), 2.843 (m, 2 H), 4.240 (q, *J*=7.1 Hz, 6 H), 5.302 (tsept, *J*=7.2, 1.4 Hz, 1 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 13.87 (3x $CO_2CH_2CH_3$), 17.81 (CH_3), 25.93 (CH_3), 32.02 (CH_2), 61.92 (3x $CO_2CH_2CH_3$), 65.41 (4°C), 117.93 (CH), 135.37 (4°C), 166.88 (3x C=O)

(+)-ESI-FTICR-MS: $[C_{15}H_{24}O_6 + Na]^+$ found: *m/z* 323.14624, calc. *m/z* 323.14651

160	**(*E*)-Triethyl-4,8-dimethylnona-3,7-diene-1,1,1-tricarboxylate**[158]	Mol-ID: 9230

VAD 427, 456



$C_{20}H_{32}O_6$
Mol. Wt.: 368,46

The synthesis was carried out according to **GSP 1**: NaH (60% in oil, washed with hexanes, 190 mg, 4.74 mmol), triethyl methanetricarboxylate (TEMT) (1.02 g, 4.31 mmol), 15-crown-5 (48 mg, 0.22 mmol) and geranyl bromide (1.17 g, 5.17 mmol) in THF (20 mL) were reacted at 0°C. After work-up the crude material was purified by flash silica column chromatography (Hex/EtOAc = 3/1). The title compound (629 mg, 2.40 mmol, 40%) was obtained as a pale yellow oil.

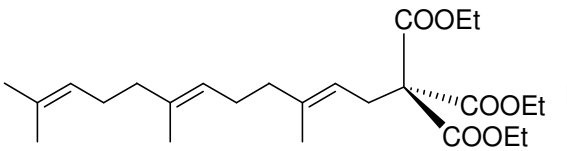
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.270 (t, *J*=7.1 Hz, 9 H), 1.587 (br. s, 3 H), 1.629 (br. s, 3 H), 1.671 (br. s, 3 H), 1.915 - 2.110 (m, 4 H), 2.853 (m, 2 H), 4.237 (q, *J*=7.1 Hz, 6 H), 5.072 (m, 1 H), 5.335 (m, 1 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 13.90 (3x $CO_2CH_2\mathit{C}H_3$), 16.15 (CH_3), 17.64 (CH_3), 25.63 (CH_3), 26.60 (CH_2), 39.50 (CH_2), 39.89 (CH_2), 61.92 (3x $CO_2\mathit{C}H_2CH_3$), 65.49 (4°C), 117.92 (CH), 124.05 (CH), 131.41 (4°C), 138.96 (4°C), 166.91 (3x C=O)

(+)-ESI-FTICR-MS: $[C_{20}H_{32}O_6 + Na]^+$ found: *m/z* 391.20865, calc. *m/z* 391.20911

161	**(*3E,7E*)-Triethyl-4,8,12-trimethyltrideca-3,7,11-triene-1,1,1-tricarboxylate**[158]	Mol-ID: 9231

VAD 428



$C_{25}H_{40}O_6$
Mol. Wt.: 436,58

The synthesis was carried out according to **GSP 1**: NaH (60% in oil, washed with hexanes, 190 mg, 4.74 mmol), triethyl methanetricarboxylate (TEMT) (1.02 g, 4.31 mmol), 15-crown-5 (48 mg, 0.22 mmol) and farnesyl bromide (1.55 g, 5.17 mmol) in THF (20 mL) were reacted at 0°C. After work-up the crude material was purified by flash silica column chromatography (Hex/EtOAc = 3/1). The title compound (998 mg, 2.29 mmol, 53%) was obtained as a pale yellow oil.

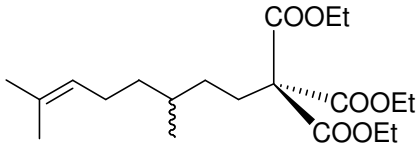
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.269 (t, *J*=7.2 Hz, 9 H), 1.582 (br. s, 3 H), 1.599 (br. s, 3 H), 1.629 (br. s, 3 H), 1.678 (br. s, 3 H), 1.922 - 2.099 (m, 8 H), 2.853 (d, *J*=7.2 Hz, 2 H), 4.236 (q, *J*=7.2 Hz, 6 H), 5.090 (m, 2 H), 5.338 (m, 1 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 13.90 (3x $CO_2CH_2\mathit{C}H_3$), 15.94 (CH_3), 16.20 (CH_3), 17.65 (CH_3), 25.67 (CH_3), 26.65 (CH_2), 26.73 (CH_2), 39.68 (CH_2), 39.94 (CH_2), 61.91 (3x $CO_2\mathit{C}H_2CH_3$), 65.52 (4°C), 117.91 (CH), 123.97 (CH), 124.35 (CH), 131.24 (4°C), 135.07 (4°C), 139.07 (4°C), 166.90 (3x C=O)

(+)-ESI-FTICR-MS: $[C_{25}H_{40}O_6 + Na]^+$ found: *m/z* 459.27176, calc. *m/z* 459.27171

166	**Triethyl-4,8-dimethylnon-7-ene-1,1,1-tricarboxylate**	Mol-ID: 9300

VAD 518



$C_{20}H_{34}O_6$
Mol. Wt.: 370,48

The synthesis was carried out according to **GSP 1**: NaH (60% in oil, washed with hexanes, 43 mg, 1.07 mmol), triethyl methanetricarboxylate (TEMT) (238 mg, 1.07 mmol) and 15-crown-5 (12 mg, 0.05 mmol) were reacted in anhydrous DMF (8 mL) at 0°C. After evolution of H_2 had ceased, the reaction mixture was heated to 50°C. Citronellyl iodide (300 mg, 1.13 mmol) diluted in 2 mL of DMF was added slowly via syringe. Heating and stirring was continued for 2 h. After work-up the crude material was purified by flash silica column chromatography (Hex/EtOAc = 3/1). The title compound (189 mg, 0.51 mmol, 48%) was obtained as a colourless oil.

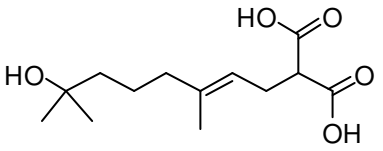
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.90 (d, *J*=6.4 Hz, 3 H), 1.03 - 1.24 (m, 1 H), 1.28 (t, *J*=7.1 Hz, 9 H), 1.31 - 1.56 (m, 4 H), 1.59 (s, 3 H), 1.68 (s, 3 H), 1.82 - 2.23 (m, 4 H), 4.25 (q, *J*=7.1 Hz, 6 H), 5.08 (m, 1 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 13.92 (3x $CO_2CH_2\mathit{C}H_3$), 17.61 (CH_3), 19.31 (CH_3), 25.42 (CH_2), 25.70 (CH_3), 30.96 (CH_2), 31.52 (CH_2), 32.77 (3°C), 36.65 (CH_2), 61.91 (3x $CO_2\mathit{C}H_2CH_3$), 65.54 (4°C), 124.74 (3°C), 131.14 (4°C), 167.11 (3x C=O)

(+)-ESI-FTICR-MS: $[C_{20}H_{34}O_6 + Na]^+$ found: *m/z* 393.22428, calc. *m/z* 393.22476

168 | **2-((*E*)-7-Hydroxy-3,7-dimethyloct-2-enyl)malonic acid** | Mol-ID: 10267

VAD 559 (peak 1)



$C_{13}H_{22}O_5$
Mol. Wt.: 258,31

This hydrated compound was isolated as a by-product during the base hydrolysis of **160**.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.22 (s, 6 H), 1.41 (m, 4 H), 1.62 (s, 3 H), 1.98 (m, 2 H), 2.70 (t, *J*=7.2 Hz, 2 H), 3.47 (t, *J*=7.2 Hz, 1 H), 3.95 (br. s, 1 H), 5.12 (m, 1 H)

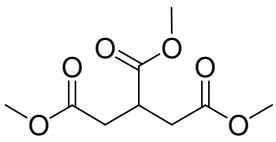
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 15.93 (CH_3), 21.78 (CH_2), 28.21 (CH_2), 28.75 (2xCH_3), 39.47 (CH_2), 42.04 (CH_2), 50.64 (CH, malonate), 72.59 (4°C, Me_2*C*OH), 119.29 (3°C), 139.23 (4°C), 172.78 (2x C=O)

(+)-ESI-FTICR-MS: $[C_{13}H_{22}O_5 + Na]^+$ found: *m/z* 281.13580, calc. *m/z* 281.13594

HPLC: t_R = 9.97 min (condition **B**)

170 | **Trimethylpropane-1,2,3-tricarboxylate** | Mol-ID: 10117

VAD 396, 450



$C_9H_{14}O_6$
Mol. Wt.: 218,2

The synthesis was performed following **GSP 3**: Tricarballylic acid (5.0 g, 28.39 mmol) was dissolved in 50 mL of anhydrous MeOH and cooled to –10°C. Thionyl chloride (11.15 g, 93.69 mmol) was added dropwise. The title compound (5.96 g, 22.27 mmol, 96%) was isolated as a colourless oil.

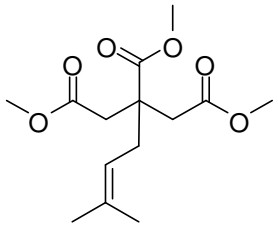
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.615 (dd, $^2J(H_AH_B)$=16.7 Hz, $^3J(H_AH_X)$= 6.5 Hz, 2 H), 2.787 (dd, $^2J(H_BH_A)$=16.7 Hz, $^3J(H_BH_X)$= 6.8 Hz, 2 H), 3.278 (quin, $^3J(H_XH_{AB})$=6.7 Hz, 1 H), 3.694 (s, 6 H), 3.718 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 34.97 (3xCH_2), 37.23 (CH), 51.86 (2x CH_3), 52.25 (CH_3), 171.73 (2x C=O), 173.55 (C=O)

(+)-ESI-FTICR-MS: $[C_9H_{14}O_6 + Na]^+$ found: *m/z* 241.06801, calc. *m/z* 241.06826

172	**Trimethyl-2-(3-methylbut-2-enyl)propane-1,2,3-tri-carboxylate**	Mol-ID: 9238

VAD 403



$C_{14}H_{22}O_6$
Mol. Wt.: 286,32

The synthesis was conducted according to **GSP 6**: Tricarballylic acid trimethyl ester **170** (1.0 g, 4.58 mmol) was dissolved in 20 mL of THF and cooled to –78°C. LDA (2.0 M in THF, 2.52 mL, 5.04 mmol) was added dropwise and the reaction mixture was stirred for 40 min at –78°C. Then, 3,3-dimethylallyl bromide (90%, 911 mg, 5.50 mmol) was added to the cold solution. After work-up the crude material was pre-purified by flash silica column chromatography (Hex/EtOAc = 3/1). The title non-chiral product (55 mg, 4.2%) was separated from its constitutional isomer by preparative HPLC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.568 (br. s, 3 H), 1.701 (br. s, 3 H), 2.442 (dt, *J*=7.7, 0.8 Hz, 2 H), 2.854 (s, 4 H), 3.654 (s, 6 H), 3.704 (s, 3 H), 5.000 (tsept, *J*=7.8, 0.8 Hz, 1.4 H)

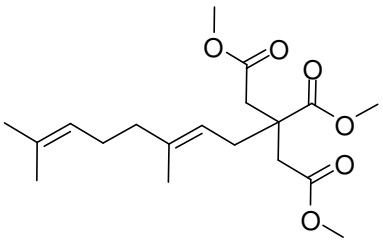
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 17.77 (CH_3), 26.04 (CH_3), 34.67 (CH_2), 37.87 (2x *C*H_2CO_2Me), 46.40 (4°C), 51.53 (2x CO_2CH_3), 52.19 (CO_2CH_3), 117.72 (CH), 136.23 (4°C, prenyl), 171.76 (2x *C*O_2CH_3), 174.81 (*C*O_2CH_3)

(+)-ESI-FTICR-MS: $[C_{14}H_{22}O_6 + Na]^+$ found: *m/z* 309.13045, calc. *m/z* 309.13086

HPLC: t_R = 14.90 min (condition **A**)

173	**Trimethyl-2-((*E*)-3,7-dimethylocta-2,6-dienyl)propane-1,2,3-tricarboxylate**	Mol-ID: 9239

VAD 406, 451



$C_{19}H_{30}O_6$
Mol. Wt.: 354,44

The synthesis was conducted according to **GSP 6**: Tricarballylic acid trimethyl ester **170** (1.5 g, 6.87 mmol) was dissolved in 20 mL of THF and cooled to –78°C. LDA (2.0 M in THF, 3.78 mL, 7.56 mmol) was added dropwise and the reaction mixture was stirred for 40 min at –78°C. Then, geranyl bromide (96%, 1.64 g, 7.56 mmol) was added to the cold solution.

After work-up the crude material was pre-purified by flash silica column chromatography (Hex/EtOAc = 3/1). The title non-chiral product was separated from its constitutional isomer by preparative HPLC as a yellow oil.

TLC: R_f = 0.33 (Hex/EtOAc = 3/1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.56 (br. s, 3 H), 1.60 (br. s, 3 H), 1.68 (br. s, 3 H), 1.93 - 2.11 (m, 4 H), 2.46 (d, J=7.42 Hz, 2 H), 2.85 (s, 4 H), 3.65 (s, 6 H), 3.70 (s, 3 H), 5.005 (tq, *J*=7.8, 1.2 Hz, 1 H), 5.056 (tsept, *J*=6.9, 1.4 Hz, 1 H)

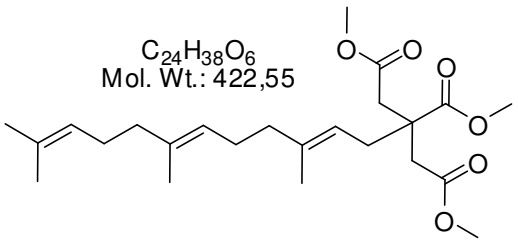
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 15.98 (CH_3), 17.67 (CH_3), 25.65 (CH_3), 26.41 (CH_2), 34.49 (CH_2), 37.83 (2x *CH_2*COOMe), 39.93 (CH_2), 46.39 (4°C), 51.52 (2x CH_3, ester), 52.16 (CH_3,ester), 117.82 (3°C), 123.99 (3°C), 131.57 (4°C), 139.72 (4°C), 171.76 (2xC=O), 174.84 (C=O)

(+)-ESI-FTICR-MS: $[C_{19}H_{30}O_6 + Na]^+$ found: *m/z* 377.19305, calc. *m/z* 377.19346

HPLC: t_R = 18.68 min (condition **A**)

174	**Trimethyl-2-((*2E,6E*)-3,7,11-trimethyldodeca-2,6,10-trienyl)propane-1,2,3-tricarboxylate**	Mol-ID: 9240

VAD 420



The synthesis was conducted according to **GSP 6**: Tricarballylic acid trimethyl ester **170** (1.0 g, 4.58 mmol) was dissolved in 20 mL of THF and cooled to –78°C. LDA (2.0 M in THF, 2.56 mL, 5.13 mmol) was added dropwise and the reaction mixture was stirred for 40 min at –78°C. Then, farnesyl bromide (1.57 g, 5.50 mmol) was added to the cold solution. After work-up the crude material was pre-purified by flash silica column chromatography (Hex/EtOAc = 3/1). The title non-chiral product (128 mg, 6.6%) was separated from its constitutional isomer by preparative HPLC as a yellow oil.

TLC: R_f = 0.40 (Hex/EtOAc = 3/1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.57 (br. s, 3 H), 1.60 (br. s, 6 H), 1.68 (br. s, 3 H), 1.93 - 2.13 (m, 8 H), 2.46 (d, *J*=7.42 Hz, 2 H), 2.85 (s, 4 H), 3.65 (s, 6 H), 3.70 (s, 3 H), 5.01 (m, 1H), 5.09 (m, 2H)

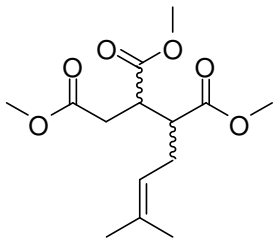
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 15.98 (CH_3), 16.04 (CH_3), 17.64 (CH_3), 25.67 (CH_3), 26.44 (CH_2), 26.69 (CH_2), 34.47 (CH_2), 37.85 (2xCH_2), 39.67 (CH_2), 39.95 (CH_2), 46.38 (4°C), 51.51 (2xCH_3, ester), 52.15 (CH_3, ester), 117.72 (3°C), 123.81 (3°C), 124.31 (3°C), 131.28 (4°C), 135.21 (4°C), 139.83 (4°C), 171.76 (2x C=O), 174.81 (C=O)

(+)-ESI-FTICR-MS: $[C_{24}H_{38}O_6 + Na]^+$ found: *m/z* 445.25604, calc. *m/z* 445.25606

HPLC: t_R = 21.67 min (condition **A**); **:** t_R = 14.90 min (condition **N**)

175 a-d	**Trimethyl-6-methylhept-5-ene-1,2,3-tricarboxylate (mixture of four stereoisomers)**	

VAD 403



$C_{14}H_{22}O_6$
Mol. Wt.: 286,32

In addition to non-chiral, symmetric **172**, the alkylation reaction (**GSP 6**) produced regioisomer **175** which exists in two pairs of enantiomers (i.e. four stereoisomers **a–d**). The absolute configuration of each stereoisomer was not clarified.

• Enantiomeric pair: peak 1 (t_R = 8.47 min) and peak 3 (t_R = 11.90 min)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.591 (br. s, 3 H), 1.686 (br. s, 3 H), 2.161 (m, 1 H), 2.386 (m, 1 H), 2.433 (dd, *J*=16.8, 3.6 Hz, 1 H), 2.768 (dd, *J*=16.8, 10.8 Hz, 1 H), 2.822 (ddd, *J*=8.4, 6.8, 6.2 Hz, 1 H), 3.163 (ddd, *J*=10.8, 6.8, 3.6 Hz, 1 H), 3.663 (s, 3H), 3.677 (s, 3H), 3.716 (s, 3H), 5.038 (ddsept, *J*=7.3, 7.3, 1.5 Hz,1 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 17.71 (CH_3), 25.78 (CH_3), 28.26 (CH_2), 33.09 (CH_2), 42.54 (CH), 46.91 (CH), 51.82 (CH_3), 51.88 (CH_3), 52.13 (CH_3), 119.90 (CH), 134.87 (4°C), 172.14 (C=O), 173.42 (C=O), 173.63 (C=O)

HPLC: peak 1 (t_R = 8.47 min); peak 3 (t_R = 11.90 min) (condition **N**)

• Enantiomeric pair: peak 2 (t_R = 9.58 min) and peak 4 (t_R = 12.83 min)

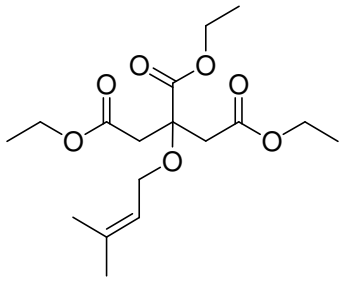
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.600 (br. s, 3 H), 1.678 (br. s, 3 H), 2.228 (m, 1 H), 2.369 (m, 1 H), 2.581 (dd, *J*=16.9, 4.5 Hz, 1 H), 2.798 (dd, *J*=16.9, 9.5 Hz, 1 H), 2.836 (ddd, *J*=8.3, 6.1, 5.5 Hz, 1 H), 3.257 (ddd, *J*=9.5, 5.5, 4.5 Hz, 1 H), 3.683 (s, 6 H), 3.699 (s, 3 H), 5.020 (ddsept, *J*=7.3, 7.3, 1.5 Hz,1 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 17.68 (CH_3), 25.76 (CH_3), 27.35 (CH_2), 32.86 (CH_2), 41.99 (CH), 46.23 (CH), 51.86 (CH_3), 51.88 (CH_3), 52.11 (CH_3), 120.05 (CH), 134.72 (4°C), 172.15 (C=O), 173.24 (C=O), 173.88 (C=O)

HPLC: peak 2 (t_R = 9.58 min); peak 4 (t_R = 12.83 min) (condition **N**)

183	**Triethyl-2-(3-methylbut-2-enyloxy)propane-1,2,3-tricarboxylate**	Mol-ID: 9232

VAD 440



$C_{17}H_{28}O_7$
Mol. Wt.: 344,4

The synthesis was conducted according to **GSP 1**: NaH (60% in oil, washed with hexanes, 159 mg, 3.98 mmol), triethyl citrate (98%, 1.02 g, 3.62 mmol), 15-crown-5 (41 mg, 0.18 mmol) and 3,3-dimethylallyl bromide (90%, 689 mg, 4.16 mmol) were reacted in dry DMF (20 mL) at 0°C. After work-up the crude material was purified by flash silica column chromatography (Hex/EtOAc = 5/2). The title *O*-alkylated compound (193 mg, 0.56 mmol, 15.5%) was obtained as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.25 (t, *J*=7.2 Hz, 6 H), 1.30 (t, *J*=7.0 Hz, 3 H), 1.64 (s, 3 H), 1.72 (s, 3 H), 3.02 (d, *J*=15.6 Hz, 2 H), 3.19 (d, *J*=15.6 Hz, 2 H), 3.99 (d, *J*=6.6 Hz, 2 H), 4.14 (q, *J*=7.3 Hz, 4 H), 4.25 (q, *J*=7.2 Hz, 2 H), 5.27 (tdt, *J*=6.9, 2.8, 1.5 Hz, 1 H)

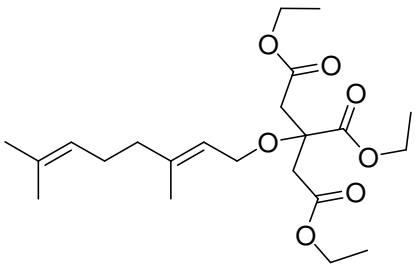
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 14.05 (CH_3), 14.09 (2xCH_3), 17.94 (CH_3), 25.78 (CH_3), 38.98 (2xCH_2), 60.62 (CH_2), 61.40 (2xCH_2), 61.56 (CH_2), 78.27 (4°C), 120.25 (3°C), 137.34 (4°C), 169.91 (2xC=O), 170.68 (C=O)

(+)-ESI-FTICR-MS: $[C_{17}H_{28}O_7 + Na]^+$ found: *m/z* 367.17231, calc. *m/z* 367.17272

HPLC: t_R = 16.78 min (condition **A**)

184	**Triethyl-2-((*E*)-3,7-dimethylocta-2,6-dienyloxy)propane-1,2,3-tricarboxylate**	Mol-ID: 9233

VAD 442, 665



$C_{22}H_{36}O_7$
Mol. Wt.: 412,52

The synthesis was conducted according to **GSP 1**: NaH (60% in oil, washed with hexanes, 159 mg, 3.98 mmol), triethyl citrate (98%, 1.02 g, 3.62 mmol), 15-crown-5 (41 mg, 0.18 mmol) and geranyl bromide (96%, 941 mg, 4.16 mmol) were reacted in dry DMF (20 mL) at 0°C. After work-up the crude material was purified by flash silica column chromatography (Hex/EtOAc = 2/1). The title *O*-alkylated compound (309 mg, 0.75 mmol, 21%) was obtained as a yellow oil.

TLC: R_f = 0.55 (Hex/EtOAc = 2/1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.25 (t, *J*=7.1 Hz, 6 H), 1.30 (t, *J*=7.2 Hz, 3 H), 1.59 (s, 3 H), 1.63 (s, 3 H), 1.67 (s, 3 H), 1.95 - 2.13 (m, 4 H), 3.03 (d, *J*=15.6 Hz, 2 H), 3.20 (d, *J*=15.6 Hz, 2 H), 4.02 (d, *J*=6.6 Hz, 2 H), 4.14 (q, *J*=7.2 Hz, 4 H), 4.25 (q, *J*=7.0 Hz, 2 H), 5.03 - 5.12 (m, 1 H), 5.24 - 5.33 (m, 1 H)

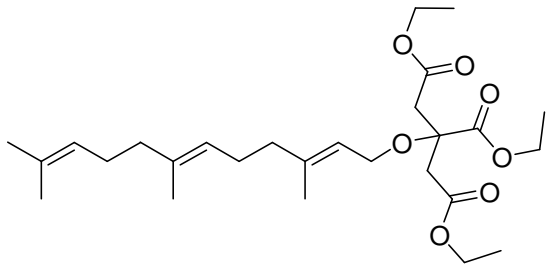
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 14.06 (CH_3), 14.10 (2 x CH_3), 16.42 (CH_3), 17.64 (CH_3), 25.65 (CH_3), 26.27 (CH_2), 39.02 (2 x CH_2), 39.56 (CH_2), 60.62 (2 x CH_2), 61.49 (CH_2), 61.56 (CH_2), 78.31 (4°C), 119.99 (3°C), 123.89 (3°C), 131.64 (4°C), 140.33 (4°C), 169.92 (2 x C=O), 170.68 (C=O)

(+)-ESI-FTICR-MS: $[C_{22}H_{36}O_7 + Na]^+$ found: 435.23483, calc. 435.23532

HPLC: t_R = 19.99 min (condition **A**)

185	**Triethyl-2-((*2E,6E*)-3,7,11-trimethyldodeca-2,6,10-trienyloxy)propane-1,2,3-tricarboxylate**	Mol-ID: 9234

VAD 445, 446



$C_{27}H_{44}O_7$
Mol. Wt.: 480,63

The synthesis was conducted according to **GSP 1**: NaH (60% in oil, washed with hexanes, 159 mg, 3.98 mmol), triethyl citrate (98%, 1.02 g, 3.62 mmol), 15-crown-5 (41 mg, 0.18 mmol) and farnesyl bromide (1.25 g, 4.16 mmol) were reacted in dry DMF (20 mL) at 0°C. After work-up the crude material was purified by flash silica column chromatography (Hex/EtOAc = 2/1). The title *O*-alkylated compound (193 mg, 0.40 mmol, 5.5%) was obtained as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.25 (t, *J*=7.2 Hz, 6 H), 1.30 (t, *J*=7.2 Hz, 3 H), 1.59 (s, 3 H), 1.60 (s, 3 H), 1.64 (s, 3 H), 1.68 (s, 3 H), 1.92 - 2.15 (m, 8 H), 3.03 (d, *J*=15.6 Hz, 2 H), 3.20 (d, *J*=15.6 Hz, 2 H), 4.02 (d, *J*=6.6 Hz, 2 H), 4.14 (q, *J*=7.3 Hz, 4 H), 4.25 (q, *J*=7.2 Hz, 2 H), 5.04 - 5.16 (m, 2 H), 5.24 - 5.32 (m, 1 H)

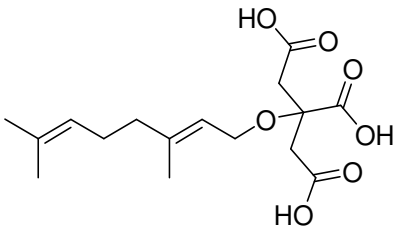
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 14.06 (2xCH_3), 14.10 (CH_3), 15.95 (CH_3), 16.43 (CH_3), 17.66 (CH_3), 25.67 (CH_3), 26.21 (CH_2), 26.67 (CH_2), 39.00 (2xCH_2), 39.57 (CH_2), 39.66 (CH_2), 60.61 (2x CH_2), 61.47 (CH_2), 61.55 (CH_2), 78.31 (4°C), 119.95 (3°C), 123.77 (3°C), 124.28 (3°C), 131.27 (4°C), 135.24 (4°C), 140.42 (4°C), 169.92 (2x C=O), 170.67 (C=O)

(+)-ESI-FTICR-MS: $[C_{27}H_{44}O_7 + Na]^+$ found: *m/z* 503.29743, calc. *m/z* 503.29792

HPLC: t_R = 22.56 min (condition **A**)

186	**2-((*E*)-3,7-Dimethylocta-2,6-dienyloxy)propane-1,2,3-tricarboxylic acid**	Mol-ID: 9236

VAD 623, 666 (peak 1)



$C_{16}H_{24}O_7$
Mol. Wt.: 328,36

The synthesis was performed following **GSP 2**: Triester **184** (102 mg, 0.25 mmol) was dissolved in 6 mL of THF/H_2O (1/1). NaOH (76 mg, 1.90 mmol) was added and the reaction mixture was stirred at room temp. for 14h. After careful acidification to pH 2-3 at 0°C, the crude material was purified by HPLC to afford **186** (6.8 mg, 20.7 µmol, 9 %) as a colourless oil.

^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.600 (s, 3 H), 1.648 (s, 3 H), 1.667 (s, 3 H), 2.059 (m, 4 H), 3.001 (d, *J*=15.8 Hz, 2 H), 3.137 (d, *J*=15.8 Hz, 2 H), 4.067 (d, *J*=6.6 Hz, 2 H), 5.100 (tt, *J*=7.0, 1.3 Hz, 1 H), 5.280 (td, *J*=6.8, 1.3 Hz, 1 H) *COO*H *protons exchange with solvent.*

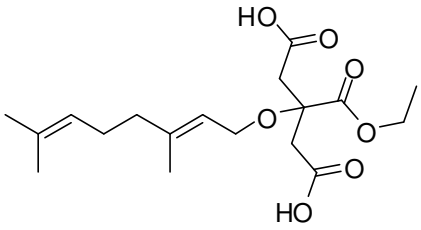
^{13}C NMR (100 MHz, CD_3OD) δ ppm 16.48 (CH_3), 17.73 (CH_3), 25.85 (CH_3), 27.43 (CH_2), 40.01 (2x $\underline{C}H_2CO_2H$), 40.68 (CH_2), 62.30 (CH_2O), 79.49 (4°C, $\underline{C}CO_2H$), 121.75 (CH), 125.09 (CH), 132.50 (4°C), 141.08 (4°C), 173.56 (2x $CH_2\underline{C}O_2H$), 174.38 ($C\underline{C}O_2H$)

(–)-ESI-FTICR-MS: $[C_{16}H_{24}O_7 - H]^-$ found: 327.14465, calc. 327.14493

HPLC: t_R = 10.47 min (condition **F**)

187	**(*E*)-3-(3,7-Dimethylocta-2,6-dienyloxy)-3-(ethoxycarbonyl) pentanedioic acid**	Mol-ID: 10611

VAD 623, 666 (peak 2)



$C_{18}H_{28}O_7$
Mol. Wt.: 356.41

The symmetric monoester (27 mg, 75.8 µmol, 32%) was isolated as a byproduct of the hydrolysis of **184.** The structure was confirmed by performing a HMBC experiment (see Chapter 3.3.3).

^{1}H NMR (400 MHz, CD_3OD) δ ppm1.280 (t, *J*=7.1 Hz, 3 H), 1.599 (br. s, 3 H), 1.640 (br. s, 3 H), 1.667 (br. s, 3 H), 1.963 - 2.139 (m, 4 H), 2.963 (d, *J*=15.8 Hz, 2 H), 3.151 (d, *J*=15.8 Hz, 2 H), 4.050 (dd, *J*=6.7, 0.5 Hz, 2 H), 4.212 (q, *J*=7.1 Hz, 2 H), 5.095 (tdt, *J*=7.0, 2.9, 1.4 Hz, 1 H), 5.254 (dddt, *J*=6.7, 5.4, 2.6, 1.3, Hz, 1 H) *COO*H *protons exchange with solvent.*

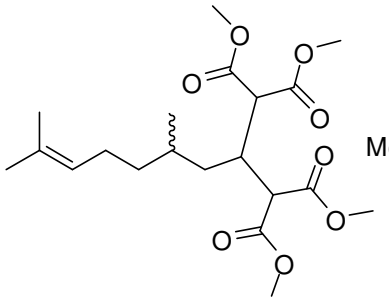
^{13}C NMR (100 MHz, CD_3OD) δ ppm 14.34 ($CO_2CH_2\underline{C}H_3$), 16.48 (CH_3), 17.74 (CH_3), 25.87 (CH_3), 27.41 (CH_2), 40.07 (2x $\underline{C}H_2CO_2H$), 40.67 (CH_2), 62.34 (CH_2O), 62.61 ($CO_2\underline{C}H_2CH_3$), 79.47 (4°C, $\underline{C}CO_2H$), 121.71 (CH), 125.05 (CH), 132.51 (4°C), 141.10 (4°C), 172.50 ($\underline{C}O_2Et$), 173.33 (2x $\underline{C}O_2H$)

(+)-ESI-FTICR-MS: $[C_{18}H_{28}O_7 + Na]^+$ found: 379.17291, calc. 379.17272

HPLC: t_R = 12.52 min (condition **F**)

191	**Tetramethyl-2-(2,6-dimethylhept-5-enyl)propane-1,1,3,3-tetracarboxylate**[252]	Mol-ID: 9293

VAD 491



$C_{20}H_{32}O_8$
Mol. Wt.: 400,46

Citronellal (2.32 mL, 12.96 mmol), dimethyl malonate (96%, 3.87 mL, 32.4 mmol), piperidine (1.28 mL, 12.96 mmol) and acetic acid (741 µL, 12.96 mmol) were diluted into a small amount of ethanol and stirred at r.t. for 20h. On the next day, the ethanol was removed and the residue was titurated with ice-water. After acidification to pH 5 with diluted HCl, the crude mixture was extracted (3x) into EtOAc. The organic layers were combined, washed with brine and dried over Na_2SO_4. All organic solvents were removed in vacuo and the crude material was purified by flash column chromatography (Hex/EtOAc = 1/1) to provide the desired product (1.55 g, 3.87 mmol, 30%) as a colourless oil.

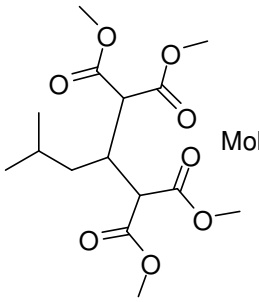
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.89 (d, *J*=6.16 Hz, 3 H), 1.00 - 1.42 (m, 4 H), 1.50 - 1.73 (m, 2 H), 1.60 (s, 3 H), 1.67 (s, 3 H), 1.82 - 2.04 (m, 2 H), 2.95 - 3.06 (m, 1 H), 3.73 (m, 12 H), 3.83 (d, *J*=5.86 Hz, 1 H), 5.03 - 5.12 (m, 1 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 17.65 (CH_3), 19.18 (CH_3), 25.34 (CH_2), 25.69 (CH_3), 30.19 (3°C, chiral), 35.70 (3°C, R<u>C</u>H[CH($CO_2Me)_2]_2$), 36.94 (CH_2), 37.26 (CH_2), 52.40 (CH_3, ester), 52.46 (CH_3, ester), 52.49 (CH_3, ester), 52.53 (CH_3, ester), 52.73 (3°C, R<u>C</u>H($CO_2Me)_2$), 53.17 (3°C, R<u>C</u>H($CO_2Me)_2$), 124.55 (3°C, Me_2C=<u>C</u>HR), 131.32 (4°C, Me_2<u>C</u>=CHR), 168.85 (C=O), 168.89 (C=O), 168.98 (2x C=O)

(+)-ESI-FTICR-MS: $[C_{20}H_{32}O_8 + Na]^+$ <u>found:</u> 423.19917, <u>calc.</u> 423.19894

195	**Tetramethyl-2-isobutylpropane-1,1,3,3-tetracarboxylate**[253]	Mol-ID: 9290

VAD 494



$C_{15}H_{24}O_8$
Mol. Wt.: 332,35

Isovaleraldehyde (97%, 2.57 mL, 23.22 mmol), dimethyl malonate (96%, 6.90 mL, 58.0 mmol), piperidine (2.29 mL, 23.22 mmol) and acetic acid (1.33 mL, 23.22 mmol) were mixed together and stirred at r.t. for 20h. On the next day, the reaction mixture was poured into ice-water. After acidification to pH 5 with diluted HCl, the crude mixture was extracted (3x) into EtOAc. The organic layers were combined, washed with brine and dried over Na_2SO_4. All organic solvents were removed in vacuo and the crude material was purified by flash column chromatography (Hex/EtOAc = 2/1) to provide the desired product (7.55 g, 22.72 mmol, 95%) as a colourless oil.

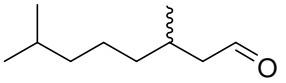
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.890 (d, *J*=6.2 Hz, 6 H), 1.374 - 1.539 (m, 3 H), 2.987 (quin, *J*=6.1 Hz, 1 H), 3.732 (s, 12 H), 3.770 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 22.38 (2x CH_3), 25.77 (CH), 35.87 (CH), 38.86 (CH_2), 52.41 (2xCH_3), 52.50 (2xCH_3), 53.00 (2xCH), 168.91 (4xC=O)

(+)-ESI-FTICR-MS: $[C_{15}H_{24}O_8 + Na]^+$ <u>found:</u> 355.13574, <u>calc.</u> 355.13634

203	**3,7-Dimethyloctanal**[254-255]	Mol-ID: 11096

VAD 707, 723



$C_{10}H_{20}O$
Mol. Wt.: 156,27

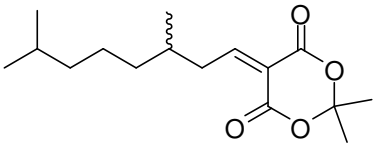
A solution of *rac*-citronellal (5.0 g, 32.41 mmol) in 80 mL of MeOH was stirred with palladium carbon (500 mg, 10%) under H_2 atmosphere. After stirring at room temperature over night, the palladium carbon was removed by filtration through a celite pad, and the clear filtrate was concentrated in vacuo to provide 6,7-dihydrocitronellal (5.0 g, 32.01 mmol, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.869 (d, *J*=6.6 Hz, 6 H), 0.962 (d, *J*=6.6 Hz, 3 H), 1.099 - 1.369 (m, 6 H), 1.527 (nonet, *J*=6.6 Hz, 1 H), 2.053 (m, 1 H), 2.225 (ddd, *J*=16.0, 7.9, 2.6 Hz, 1 H), 2.396 (ddd, *J*=16.0, 5.7, 1.5 Hz, 1 H), 9.761 (m, 1 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 19.94 (CH_3), 22.52 (CH_3), 22.59 (CH_3), 24.63 (CH_2), 27.87 (CH), 28.15 (CH), 37.10 (CH_2), 38.96 (CH_2), 51.07 (CH_2), 203.10 (CHO)

204	**5-(3,7-Dimethyloctylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione**	Mol-ID: 11099

VAD 709, 713, 724



$C_{16}H_{26}O_4$
Mol. Wt.: 282,38

3,7-dimethyloctanal **203** (1.00 g, 6.40 mmol) and Meldrum´s acid (1.20 g, 8.32 mmol) were condensed in refluxing cyclohexane in the presence of a catalytic amount of piperidine (63 µL, 0.64 mmol). Water was removed azeotropically from the reaction system (Dean-Stark!). After all water has been removed, the reaction mixture was allowed to cool to room temperature before cyclohexane was evaporated under reduced pressure. The red oily residue was dissoled into Et_2O and washed once with cold water. The organic layer was separated, dried over Na_2SO_4 and concentrated in vacuo. Finally, the crude material was purified by flash column chromatography (Hex/EtOAc = 3/1) to provide the desired Knoevenagel product **204** (773 mg, 2.74 mmol, 43%) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 0.866 (d, *J*=6.6 Hz, 6 H), 0.970 (d, *J*=6.6 Hz, 3 H), 1.108 - 1.187 (m, 2 H), 1.193 - 1.387 (m, 4 H), 1.522 (nonet, *J*=6.6 Hz, 1 H), 1.743 (s, 6 H), 1.770 - 1.860 (m, 1 H), 2.811 - 2.967 (m, 2 H), 7.966 (t, *J*=7.5 Hz, 1 H)

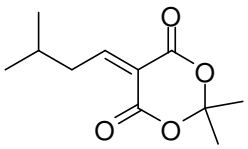
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 19.88 (CH_3), 22.52 (CH_3), 22.62 (CH_3), 24.73 (CH_2), 27.625 (CH_3, acetonide), 27.630 (CH_3, acetonide), 27.89 (CH), 33.43 (CH), 37.12 (CH_2), 38.21 (CH_2), 39.01 (CH_2), 104.75 (4°C, acetonide), 118.67 (4°C, alkylidene), 159.86 (C=O), 161.86 (C=O), 168.36 (CH, alkylidene)

(+)-ESI-FTICR-MS: $[C_{16}H_{26}O_4 + Na]^+$ found: 305.17208, calc. 305.17233

HPLC: t_R = 11.67 min (condition **L**)

208	**2,2-Dimethyl-5-(3-methylbutylidene)-1,3-dioxane-4,6-dione** [256-257]	Mol-ID: 11101

VAD 717



$C_{11}H_{16}O_4$
Mol. Wt.: 212,24

Isovaleraldehyde (1.00 g, 11.61 mmol) and Meldrum´s acid (1.84 g, 12.77 mmol) were condensed in refluxing cyclohexane in the presence of a catalytic amount of pyrrolidine (96 µL, 1.16 mmol). Water was removed azeotropically from the reaction system by a Dean-Stark trap. After all water has been removed, the reaction mixture was allowed to cool to room temperature before cyclohexane was evaporated under reduced pressure. The yellow viscous residue was directly applied on a chromatographic silica-gel column which was eluted with a solvent mixture (Hex/EtOAc = 3/1). The desired Knoevenagel product (1.82 g, 8.59 mmol, 74%) was obtained as a yellow oil.

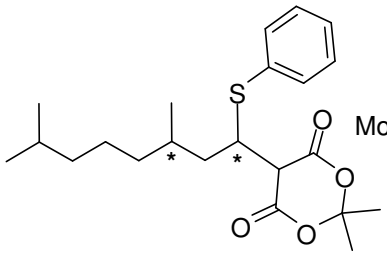
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.009 (d, *J*=7.0 Hz, 6 H), 1.745 (s, 6 H), 1.958 (dquin, *J*=13.4, 6.7, 1 H), 2.864 (m, 2 H), 7.956 (t, *J*=7.7 Hz, 1 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 22.49 (2xCH_3), 27.63 (2xCH_3), 28.60 (CH), 39.72 (CH_2), 104.77 (4°C), 118.68 (4°C), 159.83 (C=O), 161.85 (C=O), 167.93 (CH)

(–)-ESI-FTICR-MS: $[C_{11}H_{16}O_4 - H]^-$ found: 211.09726, calc. 211.09758

226	**5-(3,7-Dimethyl-1-(phenylthio)octyl)-2,2-dimethyl-1,3-dioxane-4,6-dione**	Mol-ID: 11223

VAD 724



$C_{22}H_{32}O_4S$
Mol. Wt.: 392.55

Piperidine (137 µL, 1.39 mmol) and glacial acetic acid (79 µL, 1.39 mmol) were added to a cooled solution (0-5°C) of Meldrum´s acid (2.0 g, 13.88 mmol), 3,7-dimethyloctanal **203** (2.28 g, 14.57 mmol) and thiophenol (1.60 g, 14.57 mmol) in acetonitrile. After 1h, the cooling bath was removed and stirring was continued for 2h. The resulting suspension was quenched with 10 mL of 0.5 M HCl and the product was filtered. The filtercake was washed sequentially with 100 mL of cold water and then with 100 mL of Et_2O/pentane (1/5). Drying under vacuum afforded the product as a white fluffy powder (4.69 g, 11.94 mmol, 86%). The product was formed as a mixture of diastereoisomers because of racemic starting material. Attempts to separate the diastereoisomers by RP-HPLC ($MeOH/H_2O$) failed because the product decomposes on the column in a *retro*-Michael reaction into thiophenol and alkylidene compound **204**. Consequently, the diastereomeric mixture of **226** was applied directly into the synthesis of cyclopropane **227**.

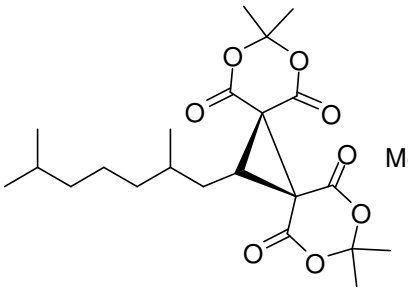
NMR: fuzzy mixture of diastereoisomers

(+)-ESI-FTICR-MS: $[C_{22}H_{32}O_4S + K]^+$ found: 431.16470, calc. 431.16529

HPLC: injected compound **226** decomposes to thiopenol (t_R = 5.03 min) and compound **204** (t_R = 11.67 min) ; Condition **L**

227	**13-(2,6-Dimethylheptyl)-3,3,10,10-tetramethyl-2,4,9,11-tetra-oxadispiro[5.0.5.1]tridecane-1,5,8,12-tetrone**	Mol-ID: 11224

VAD 725, 726



$C_{22}H_{32}O_8$
Mol. Wt.: 424,48

A solution of sodium periodate (1.18 g, 5.50 mmol) in 20 mL of water was added dropwise at 0°C to a stirred solution of compound **226** (2.0 g, 5.09 mmol) and Meldrum´s acid (741 mg, 5.14 mmol) in acetonitrile (20 mL). After stirring for approx. 1h at r.t. the reaction mixture turned red and a precipitate was formed. The reaction was quenched with water and the precipitate was filtered and washed carefully with water (100 mL) and Et_2O (100 mL). After drying under high vacuum the desired product was obtained as a white crystalline powder (288 mg, 0.68 mmol, 13%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.860 (d, J=6.7 Hz, 6 H), 1.017 (d, J=6.7 Hz, 3 H), 1.094 - 1.589 (m, 8 H), 1.794 (s, 3 H), 1.789 (s, 3 H), 1.842 (s, 3 H), 1.851 (s, 3 H), 1.898 (ddd, J=13.4, 8.2, 7.1 Hz, 1 H), 2.117 (ddd, J=13.4, 8.2, 5.8 Hz, 1 H), 3.304 (dd, J=8.2, 7.1 Hz, 1 H)

^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ ppm 0.869 (d, *J*=6.7 Hz, 6 H), 1.022 (d, *J*=6.7 Hz, 3 H), 1.12 - 1.50 (m, 6 H), 1.543 (nonet, *J*=6.6 Hz, 1 H), 1.768 (s, 3 H), 1.770 (s, 3 H), 1.86 (m, 1H), 1.867 (s, 3 H), 1.890 (s, 3 H), 1.950 (ddd, *J*=13.3, 8.0, 7.1 Hz, 1 H), 2.146 (ddd, *J*=13.3, 8.1, 5.8 Hz, 1 H), 3.439 (dd, *J*=8.2, 7.1 Hz, 1 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 19.04 (CH_3), 22.52 (CH_3), 22.66 (CH_3), 24.45 (CH_2), 26.86 (CH_3, acetonide), 27.07 (CH_3, acetonide), 27.88 (CH), 28.05 (CH_3, acetonide), 28.25 (CH_3, acetonide), 29.86 (CH_2), 32.33 (CH), 36.87 (CH_2), 39.00 (CH_2), 39.94 (CH, cyclopropane), 42.04 (4°C, cyclopropane), 42.66 (4°C, cyclopropane), 105.96 (2x 4°C, acetonide), 159.12 (C=O), 159.30 (C=O), 161.75 (C=O), 161.86 (C=O)

^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ ppm 19.31 (CH_3), 22.82 (CH_3), 22.94 (CH_3), 25.21 (CH_2), 26.86 (CH_3, acetonide), 27.08 (CH_3, acetonide), 28.15 (CH_3, acetonide), 28.35 (CH_3, acetonide), 28.58 (CH), 30.36 (CH_2), 32.97 (CH), 37.64 (CH_2), 39.81 (CH_2), 40.28 (CH, cyclopropane), 42.98 (4°C, cyclopropane), 43.64 (4°C, cyclopropane), 106.86 (4°C,

acetonide), 106.94 (4°C, acetonide), 160.12 (C=O), 160.34 (C=O), 162.37 (C=O), 162.53 (C=O)

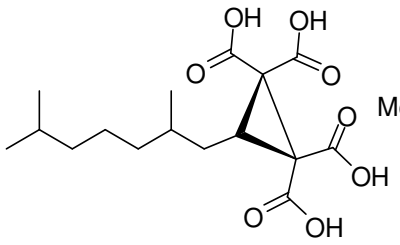
(+)-ESI-FTICR-MS: $[C_{22}H_{32}O_8 + K]^+$ found: 463.17251, calc. 463.17288

HPLC: t_R = 16.01 min (condition **M**)

Melting point: 180-181°C

229	**3-(2,6-Dimethylheptyl)cyclopropane-1,1,2,2-tetracarboxylic acid**	Mol-ID: 11403

VAD 728, 729



$C_{16}H_{24}O_8$
Mol. Wt.: 344,36

GSP 2 was followed. Hydrolysis of tetrone **227** (49 mg, 115 µmol) in a solvent mixture of 1.0 M solution of NaOH (577 µL, 577 mmol) and 1 mL of THF provided the title tetra-acid in quantitative yields.

^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ ppm 0.870 (d, *J*=6.6 Hz, 6 H), 0.997 (d, *J*=6.6 Hz, 3 H), 1.13 - 1.46 (m, 6 H), 1.546 (nonet, *J*=6.7 Hz, 1 H), 1.611 (m, 1 H), 1.720 (ddd, *J*=14.4, 8.2, 7.0 Hz, 1 H), 1.986 (ddd, *J*=14.4, 7.5, 5.5 Hz, 1 H), 2.436 (t, *J*=7.2, 1 H), 11.4 (br. s, 4 H, CO_2H)

^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ ppm 19.52 (CH_3), 22.86 (CH_3), 22.95 (CH_3), 25.42 (CH_2), 28.58 (CH), 30.81 (CH_2), 33.78 (CH), 36.03 (CH), 37.76 (CH_2), 39.92 (CH_2), 44.60 (4°C), 44.87 (4°C), 166.59 (C=O), 166.61 (C=O), 168.39 (C=O), 168.43 (C=O)

(+)-ESI-FTICR-MS: $[C_{16}H_{24}O_8+Na]^+$ found: 367.13649, calc. 367.13634

HPLC: t_R = 10.60 min (condition **M**)

6 References

[1] T. J. Maimone, P. S. Baran, *Nature Chemical Biology* **2007**, *3*, 396-407.

[2] M. Christmann, *Angewandte Chemie International Edition* **2010**, *49*, 9580-9586.

[3] O. Wallach, *Justus Liebigs Annalen der Chemie* **1887**, *239*, 1-54.

[4] A. Eschenmoser, D. Arigoni, *Helvetica Chimica Acta* **2005**, *88*, 3011-3050.

[5] L. Ruzicka, *Experientia* **1953**, *9*, 357-367.

[6] D. W. Christianson, *Current Opinion in Chemical Biology* **2008**, *12*, 141-150.

[7] P.-H. Liang, *Biochemistry* **2009**, *48*, 6562-6570.

[8] M. Rohmer, M. Knani, P. Simonin, B. Sutter, H. Sahm, *Biochemical Journal* **1993**, *295*, 517-510.

[9] D. Arigoni, S. Sagner, C. Latzel, W. Eisenreich, A. Bacher, M. H. Zenk, *Proceedings of the National Academy of Sciences* **1997**, *94*, 10600-10605.

[10] V. Durbecq, G. Sainz, Y. Oudjama, B. Clantin, C. Bompard-Gilles, C. Tricot, J. Caillet, V. Stalon, L. Droogmans, V. Villeret, *The EMBO Journal* **2001**, *20*, 1530-1537.

[11] J. C. Sacchettini, C. D. Poulter, *Science* **1997**, *277*, 1788-1789.

[12] K. Wang, S.-i. Ohnuma, *Trends in Biochemical Sciences* **1999**, *24*, 445-451.

[13] C. D. Poulter, H. C. Rilling, *Accounts of Chemical Research* **1978**, *11*, 307-313.

[14] H. V. Thulasiram, H. K. Erickson, C. D. Poulter, *Science* **2007**, *316*, 73-76.

[15] H. C. Rilling, W. W. Epstein, *Journal of the American Chemical Society* **1969**, *91*, 1041-1042.

[16] L. J. Altman, L. Ash, R. C. Kowerski, W. W. Epstein, B. R. Larsen, H. C. Rilling, F. Muscio, D. E. Gregonis, *Journal of the American Chemical Society* **1972**, *94*, 3257-3259.

[17] J.-L. Giner, J. D. Berkowitz, T. Andersson, *Journal of Natural Products* **2000**, *63*, 267-269.

[18] K. Gunawardena, S. B. Rivera, W. W. Epstein, *Phytochemistry* **2002**, *59*, 197-203.

[19] A. Zhang, D. Amalin, S. Shirali, M. S. Serrano, R. A. Franqui, J. E. Oliver, J. A. Klun, J. R. Aldrich, D. E. Meyerdirk, S. L. Lapointe, *Proceedings of the National Academy of Sciences of the United States of America* **2004**, *101*, 9601-9606.

[20] B. A. Bierl-Leonhardt, D. S. Moreno, M. Schwarz, J. Fargerlund, J. R. Plimmer, *Tetrahedron Letters* **1981**, *22*, 389-392.

[21] P.-H. Liang, T.-P. Ko, A. H. J. Wang, *European Journal of Biochemistry* **2002**, *269*, 3339-3354.

[22] B. A. Kellogg, C. D. Poulter, *Current Opinion in Chemical Biology* **1997**, *1*, 570-578.

[23] K. Ogura, T. Koyama, *Chemical Reviews* **1998**, *98*, 1263-1276.

[24] Y.-P. Lu, H.-G. Liu, P.-H. Liang, *Biochemical and Biophysical Research Communications* **2009**, *379*, 351-355.

[25] C. D. Poulter, J. C. Argyle, E. A. Mash, *Journal of the American Chemical Society* **1977**, *99*, 957-959.

[26] N. Shimizu, T. Koyama, K. Ogura, *Journal of Biological Chemistry* **1998**, *273*, 19476-19481.

[27] C. M. Apfel, B. Takács, M. Fountoulakis, M. Stieger, W. Keck, *Journal of Bacteriology* **1999**, *181*, 483-492.

[28] D. J. Hosfield, Y. Zhang, D. R. Dougan, A. Broun, L. W. Tari, R. V. Swanson, J. Finn, *Journal of Biological Chemistry* **2004**, *279*, 8526-8529.

[29] C. S. Rye, J. B. Baell, *Current Medicinal Chemistry* **2005**, *12*, 3127-3141.

[30] R. Engel, *Chemical Reviews* **1977**, *77*, 349-367.

[31] G. A. Patani, E. J. LaVoie, *Chemical Reviews* **1996**, *96*, 3147-3176.

[32] D. F. Wiemer, *Tetrahedron* **1997**, *53*, 16609-16644.

[33] R. Waschbüsch, J. Carran, A. Marinetti, P. Savignac, *Chemical Reviews* **1997**, *97*, 3401-3424.

[34] K. Moonen, I. Laureyn, C. V. Stevens, *Chemical Reviews* **2004**, *104*, 6177-6216.

[35] F. Palacios, C. Alonso, J. M. de los Santos, *Chemical Reviews* **2005**, *105*, 899-932.

[36] N. A. Meanwell, *Journal of Medicinal Chemistry* **2011**, *54*, 2529-2591.

[37] J. Nieschalk, D. O'Hagan, *Journal of the Chemical Society, Chemical Communications* **1995**, *7*, 719-720.

[38] V. D. Romanenko, V. P. Kukhar, *Chemical Reviews* **2006**, *106*, 3868-3935.

[39] G. M. Blackburn, *Chem. Ind. (London)* **1981**, *5*, 134-138.

[40] C. E. McKenna, P.-D. Shen, *The Journal of Organic Chemistry* **1981**, *46*, 4573-4576.

[41] G. M. Blackburn, D. E. Kent, F. Kolkmann, *Journal of the Chemical Society, Perkin Transactions 1* **1984**, *0*, 1119-1125.

[42] R. D. Chambers, D. O'Hagan, R. B. Lamont, S. C. Jaina, *Journal of the Chemical Society, Chemical Communications* **1990**, *15*, 1053-1054.

[43] G. R. J. Thatcher, A. S. Campbell, *The Journal of Organic Chemistry* **1993**, *58*, 2272-2281.

[44] G. M. Blackburn, D. A. England, F. Kolkmann, *Journal of the Chemical Society, Chemical Communications* **1981**, *17*, 930-932.

[45] G. M. Blackburn, D. E. Kent, F. Kolkmann, *Journal of the Chemical Society, Chemical Communications* **1981**, *22*, 1188-1190.

[46] J. M. Sanders, Y. Song, J. M. W. Chan, Y. Zhang, S. Jennings, T. Kosztowski, S. Odeh, R. Flessner, C. Schwerdtfeger, E. Kotsikorou, G. A. Meints, A. O. Gómez, D. González-Pacanowska, A. M. Raker, H. Wang, E. R. van Beek, S. E. Papapoulos, C. T. Morita, E. Oldfield, *Journal of Medicinal Chemistry* **2005**, *48*, 2957-2963.

[47] S. Sun, C. E. McKenna, *Expert Opinion on Therapeutic Patents* **2011**, *21*, 1433-1451.

[48] S. A. Holstein, C. L. Wohlford-Lenane, D. F. Wiemer, R. J. Hohl, *Biochemistry* **2003**, *42*, 4384-4391.

[49] S. A. Biller, K. Neuenschwander, M. M. Ponpipom, C. D. Poulter, *Curr. Pharm. Des.* **1996**, *2*, 1-40.

[50] S. H. Rosenberg, *Expert Opinion on Therapeutic Patents* **1998**, *8*, 521-530.

[51] F. El Oualid, L. H. Cohen, G. A. van der Marel, M. Overhand, *Current Medicinal Chemistry* **2006**, *13*, 2385–2427.

[52] R. A. Gibbs, T. J. Zahn, J. S. Sebolt-Leopold, *Current Medicinal Chemistry* **2001**, *8*, 1437-1465.

[53] M. Overhand, E. Pieterman, L. H. Cohen, A. R. P. M. Valentijn, G. A. van der Marel, J. H. van Boom, *Bioorganic & Medicinal Chemistry Letters* **1997**, *7*, 2435-2440.

[54] L. H. Cohen, A. R. P. M. Valentijn, L. Roodenburg, R. E. W. Van Leeuwen, R. H. Huisman, R. J. Lutz, G. A. Van Der Marel, J. H. Van Boom, *Biochemical Pharmacology* **1995**, *49*, 839-845.

[55] M. S. Kang, D. M. Stemerick, J. H. Zwolshen, B. S. Harry, P. S. Sunkara, B. L. Harrison, *Biochemical and Biophysical Research Communications* **1995**, *217*, 245-249.

[56] S. A. Biller, C. Forster, *Tetrahedron* **1990**, *46*, 6645-6658.

[57] A. R. P. M. Valentijn, O. van den Berg, G. A. van der Marel, L. H. Cohen, J. H. van Boom, *Tetrahedron* **1995**, *51*, 2099-2108.

[58] T. S. Elliott, A. Slowey, Y. Ye, S. J. Conway, *MedChemComm* **2012**, *3*, 735.

[59] R. Lingham, K. Silverman, G. Bills, C. Cascales, M. Sanchez, R. Jenkins, S. Gartner, I. Martin, M. Diez, F. Peláez, S. Mochales, Y.-L. Kong, R. Burg, M. Meinz, L. Huang, M. Nallin-Omstead, S. Mosser, M. Schaber, C. Omer, D. Pompliano, J. Gibbs, S. Singh, *Applied Microbiology and Biotechnology* **1993**, *40*, 370-374.

[60] S. B. Singh, *Tetrahedron Letters* **1993**, *34*, 6521-6524.

[61] S. B. Singh, D. L. Zink, J. M. Liesch, M. A. Goetz, R. G. Jenkins, M. Nallin-Omstead, K. C. Silverman, G. F. Bills, R. T. Mosley, J. B. Gibbs, G. Albers-Schonberg, R. B. Lingham, *Tetrahedron* **1993**, *49*, 5917-5926.

[62] T. Tanimoto, Y. Tsujita, K. Hamano, H. Haruyama, T. Kinoshita, T. Hosoya, S. Kaneko, K. Tago, H. Kogen, *Tetrahedron Letters* **1995**, *36*, 6301-6304.

[63] T. Tanimoto, K. Onodera, T. Hosoya, Y. Takamatsu, T. Kinoshita, K. Tago, H. Kogen, T. Fujioka, K. Hamano, Y. Tsujita, *Journal of Antibiotics* **1996**, *49*, 617-623.

[64] H. Kogen, K. Tago, S. Kaneko, K. Hamano, K. Onodera, H. Haruyama, K. Minagawa, T. Kinoshita, T. Ishikawa, T. Tanimoto, Y. Tsujita, *Journal of Antibiotics* **1996**, *49*, 624-630.

[65] O. D. Hensens, C. Dufresne, J. M. Liesch, D. L. Zink, R. A. Reamer, F. VanMiddlesworth, *Tetrahedron Letters* **1993**, *34*, 399-402.

[66] C. Dufresne, K. E. Wilson, D. Zink, J. Smith, J. D. Bergstrom, M. Kurtz, D. Rew, M. Nallin, R. Jenkins, K. Bartizal, C. Trainor, G. Bills, M. Meinz, L. Huang, J. Onishi, J. Milligan, M. Mojena, F. Pelaez, *Tetrahedron* **1992**, *48*, 10221-10226.

[67] J. D. Bergstrom, M. M. Kurtz, D. J. Rew, A. M. Amend, J. D. Karkas, R. G. Bostedor, V. S. Bansal, C. Dufresne, F. L. Vanmiddlesworth, O. D. Hensens, J. M. Liesch, D. L. Zink, K. E. Wilson, J. Onishi, J. A. Milligan, G. Bills, L. Kaplan, M. N. Omstead, R. G. Jenkins, L. Huang, M. S. Meinz, L. Quinn, R. W. Burg, Y. L. Kong, S. Mochales, M. Mojena, I. Martin, F. Pelaez, M. T. Diez, A. W. Alberts, *Proceedings of the National Academy of Sciences of the United States of America* **1993**, *90*, 80-84.

[68] C. I. Liu, W. Y. Jeng, W. J. Chang, T. P. Ko, A. H. J. Wang, *Journal of Biological Chemistry* **2012**, *287*, 18750-18757.

[69] N. Jotterand, P. Vogel, *Current Organic Chemistry* **2001**, *5*, 637-661.

[70] M. J. Dawson, J. E. Farthing, P. S. Marshall, R. F. Middleton, M. J. Oneill, A. Shuttleworth, C. Stylli, R. M. Tait, P. M. Taylor, H. G. Wildman, A. D. Buss, D. Langley, M. V. Hayes, *Journal of Antibiotics* **1992**, *45*, 639-647.

[71] G. H. Harris, C. Dufresne, H. Joshua, L. A. Koch, D. L. Zink, P. M. Salmon, K. E. Goklen, M. M. Kurtz, D. J. Rew, J. D. Bergstrom, K. E. Wilson, *Bioorganic & Medicinal Chemistry Letters* **1995**, *5*, 2403-2408.

[72] F. Calo, A. Bondke, J. Richardson, A. J. P. White, A. G. M. Barrett, *Tetrahedron Letters* **2009**, *50*, 3388-3390.

[73] S. Watanabe, H. Hirai, T. Kambara, Y. Kojima, H. Nishida, A. Sugiura, Y. Yamauchi, N. Yoshikawa, H. J. Harwood, L. H. Huang, N. Kojima, *Journal of Antibiotics* **2001**, *54*, 1025-1030.

[74] S. Watanabe, H. Hirai, M. Ishiguro, T. Kambara, Y. Kojima, T. Matsunaga, H. Nishida, Y. Suzuki, A. Sugiura, H. J. Harwood, L. H. Huang, N. Kojima, *Journal of Antibiotics* **2001**, *54*, 904-910.

[75] K. C. Silverman, H. Jayasuriya, C. Cascales, D. Vilella, G. F. Bills, R. G. Jenkins, S. B. Singh, R. B. Lingham, *Biochemical and Biophysical Research Communications* **1997**, *232*, 478-481.

[76] H. Jayasuriya, G. F. Bills, C. Cascales, D. L. Zink, M. A. Goetz, R. G. Jenkins, K. C. Silverman, R. B. Lingham, S. B. Singh, *Bioorganic & Medicinal Chemistry Letters* **1996**, *6*, 2081-2084.

[77] H. Shiozawa, M. Takahashi, T. Takatsu, T. Kinoshita, K. Tanzawa, T. Hosoya, K. Furuya, S. Takahashi, K. Furihata, H. Seto, *Journal of Antibiotics* **1995**, *48*, 357-362.

[78] K. Hirai, H. Ooi, T. Esumi, Y. Iwabuchi, S. Hatakeyama, *Organic Letters* **2003**, *5*, 857-859.

[79] G. H. Harris, E. T. T. Jones, M. S. Meinz, M. Nallinomstead, G. L. Helms, G. F. Bills, D. Zink, K. E. Wilson, *Tetrahedron Letters* **1993**, *34*, 5235-5238.

[80] S. M. Mandala, R. A. Thornton, B. R. Frommer, S. Dreikorn, M. B. Kurtz, *Journal of Antibiotics* **1997**, *50*, 339-343.

[81] S. B. Singh, D. L. Zink, G. A. Doss, J. D. Polishook, C. Ruby, E. Register, T. M. Kelly, C. Bonfiglio, J. M. Williamson, R. Kelly, *Organic Letters* **2004**, *6*, 337-340.

[82] F. Calo, J. Richardson, A. G. M. Barrett, *The Journal of Organic Chemistry* **2008**, *73*, 9692-9697.

[83] L. Wessjohann, M. Fulhorst, S. Zakharova, *Polish Journal of Chemistry* **2006**, *80*, 673-678.

[84] S. Zakharova, M. Fulhorst, L. Luczak, L. Wessjohann, *ARKIVOC* **2004**, *xiii*, 79-96.

[85] A. A. Scholte, L. M. Eubanks, C. D. Poulter, J. C. Vederas, *Bioorganic & Medicinal Chemistry* **2004**, *12*, 763-770.

[86] R. Wang, D. H. Steensma, Y. Takaoka, J. W. Yun, T. Kajimoto, C. H. Wong, *Bioorganic & Medicinal Chemistry* **1997**, *5*, 661-672.

[87] S. N. Huckin, L. Weiler, *Journal of the American Chemical Society* **1974**, *96*, 1082-1087.

[88] E. J. Corey, M. C. Kang, *Journal of the American Chemical Society* **1984**, *106*, 5384-5385.

[89] P. Renaud, S. Abazi, *Helvetica Chimica Acta* **1996**, *79*, 1696-1700.

[90] S. Abazi, L. P. Rapado, P. Renaud, *Organic & Biomolecular Chemistry* **2011**, *9*, 5773-5777.

[91] A. L. J. Beckwith, C. L. L. Chai, *Tetrahedron* **1993**, *49*, 7871-7882.

[92] H. Moorlag, J. G. de Vries, B. Kaptein, H. E. Schoemaker, J. Kamphuis, R. M. Kellogg, *Recueil des Travaux Chimiques des Pays-Bas* **1992**, *111*, 129-137.

[93] S. V. Ley, E. Diez, D. J. Dixon, R. T. Guy, P. Michel, G. L. Nattrass, T. D. Sheppard, *Organic & Biomolecular Chemistry* **2004**, *2*, 3608-3617.

[94] S. V. Ley, P. Michel, *Synlett* **2001**, *2001*, 1793-1795.

[95] E. McDonald, A. Suksamrarn, R. D. Wylie, *Journal of the Chemical Society, Perkin Transactions 1* **1979**, 1893-1900.

[96] F. Urech, *Justus Liebigs Annalen der Chemie* **1872**, *164*, 255-279.

[97] A. J. Ultée, *Berichte der deutschen chemischen Gesellschaft* **1906**, *39*, 1856-1858.

[98] K. L. Cosgrove, R. P. McGeary, *Tetrahedron* **2010**, *66*, 3050-3057.

[99] E. L. Eliel, A. A. Hartmann, *The Journal of Organic Chemistry* **1972**, *37*, 505-506.

[100] E. J. Corey, B. W. Erickson, *The Journal of Organic Chemistry* **1971**, *36*, 3553-3560.

[101] D. W. Graham, W. T. Ashton, L. Barash, J. E. Brown, R. D. Brown, L. F. Canning, A. Chen, J. P. Springer, E. F. Rogers, *Journal of Medicinal Chemistry* **1987**, *30*, 1074-1090.

[102] H. Ihre, A. Hult, J. M. J. Fréchet, I. Gitsov, *Macromolecules* **1998**, *31*, 4061-4068.

[103] H. Ihre, A. Hult, E. Söderlind, *Journal of the American Chemical Society* **1996**, *118*, 6388-6395.

[104] M. Malkoch, H. Claesson, P. Löwenhielm, E. Malmström, A. Hult, *Journal of Polymer Science Part A: Polymer Chemistry* **2004**, *42*, 1758-1767.

[105] Y. Zhou, R. Zhuo, Z. Liu, *Polymer* **2004**, *45*, 5459-5463.

[106] A. W. Williamson, *Justus Liebigs Annalen der Chemie* **1851**, *77*, 37-49.

[107] A. W. Williamson, *Journal of the Chemical Society* **1852**, *106*, 229.

[108] B. Neises, W. Steglich, *Angewandte Chemie International Edition in English* **1978**, *17*, 522-524.

[109] P. Block, *Organic Syntheses* **1960**, *40*, 27.

[110] A. P. Krapcho, E. G. E. Jahngen Jr, A. J. Lovey, F. W. Short, *Tetrahedron Letters* **1974**, *15*, 1091-1094.

[111] A. P. Krapcho, J. F. Weimaster, J. M. Eldridge, E. G. E. Jahngen, A. J. Lovey, W. P. Stephens, *The Journal of Organic Chemistry* **1978**, *43*, 138-147.

[112] E. L. Eliel, *Accounts of Chemical Research* **1970**, *3*, 1-8.

[113] E. L. Eliel, M. C. K. Sister, *Journal of the American Chemical Society* **1968**, *90*, 3444-3458.

[114] M. K. Kaloustian, N. Dennis, S. Mager, S. A. Evans, F. Alcudia, E. L. Eliel, *Journal of the American Chemical Society* **1976**, *98*, 956-965.

[115] F. W. Nader, E. L. Eliel, *Journal of the American Chemical Society* **1970**, *92*, 3050-3055.

[116] F. Freeman, K. U. Do, *Journal of Molecular Structure: THEOCHEM* **2002**, *577*, 43-54.

[117] E. Juaristi, G. A. Rosquete-Pina, M. Vázquez-Hernández, A. J. Mota, *Pure and Applied Chemistry* **2003**, *75*, 589-599.

[118] H. D. Banks, *The Journal of Organic Chemistry* **1981**, *46*, 1743-1745.

[119] J. Klein, *Tetrahedron Letters* **1973**, *14*, 4307-4310.

[120] J. Klein, *Tetrahedron* **1974**, *30*, 3349-3353.

[121] A. Ndibwami, P. Deslongchamps, *Canadian Journal of Chemistry* **1986**, *64*, 1788-1794.

[122] B. Tollens, P. Wigand, *Justus Liebigs Annalen der Chemie* **1891**, *265*, 316-340.

[123] M. C. Pirrung, H. Han, J. Chen, *The Journal of Organic Chemistry* **1996**, *61*, 4527-4531.

[124] Y. Xu, M. McLaughlin, E. N. Bolton, R. A. Reamer, *The Journal of Organic Chemistry* **2010**, *75*, 8666-8669.

[125] L. A. Carpino, *Journal of the American Chemical Society* **1960**, *82*, 2725-2727.

[126] M. Arimoto, A. Ejima, T. Watanabe, H. Tagawa, M. Furukawa, *The Journal of Antibiotics* **1986**, *39*, 1236-1242.

[127] H. Ueno, M. Kawai, H. Shimokawa, M. Hirota, M. Ohmi, R. Sudo, A. Ohta, Y. Arano, K. Hattori, T. Ohmi, N. Kato, M. Kojima, Y. Ueno, M. Yamamoto, Y. Moriguchi, H. Eda, K. Masubuchi, *Bioorganic & Medicinal Chemistry Letters* **2009**, *19*, 199-202.

[128] A. Blanc, F. D. Toste, *Angewandte Chemie International Edition* **2006**, *45*, 2096-2099.

[129] E. Buncel, B. Menon, *Journal of the American Chemical Society* **1977**, *99*, 4457-4461.

[130] A. Bogdanova, V. V. Popik, *Journal of the American Chemical Society* **2003**, *125*, 14153-14162.

[131] A. V. Selivanova, V. V. Nikolaev, R. R. Kostikov, V. A. Nikolaev, J. Siler, B. Schulze, *Russian Journal of Organic Chemistry* **2006**, *42*, 1792-1799.

[132] V. V. Shevchenko, N. N. Khimich, M. S. Platz, V. A. Nikolaev, *Tetrahedron Letters* **2005**, *46*, 435-438.

[133] C. Agami, M. Andrac-Taussig, C. Justin, C. Prévost, *Bulletin de la Societe Chimique de France* **1966**, 1195-1201.

[134] R. Huisgen, R. Grashey and J. Sauer, Cycloaddition reactions of alkenes. In: *The Chemistry of Alkenes;* S. Patai, Ed.; John Wiley & Sons: new York-London, **1964**, Vol. 1, p. 897.

[135] L. Coudray, R. M. de Figueiredo, S. Duez, S. Cortial, J. Dubois, *Journal of Enzyme Inhibition and Medicinal Chemistry* **2009**, *24*, 972-985.

[136] W. S. Wadsworth, W. D. Emmons, *Journal of the American Chemical Society* **1961**, *83*, 1733-1738.

[137] R. M. de Figueiredo, L. Coudray, J. Dubois, *Organic & Biomolecular Chemistry* **2007**, *5*, 3299-3309.

[138] I. Kwon Youn, G. Hwan Yon, C. Siek Pak, *Tetrahedron Letters* **1986**, *27*, 2409-2410.

[139] G. H. Lee, I. K. Youn, E. B. Choi, H. K. Lee, G. H. Yon, H. C. Yang, C. S. Pak, *Current Organic Chemistry* **2004**, *8*, 1263-1287.

[140] C. Wolfrum, F. Bohlmann, *Liebigs Annalen der Chemie* **1989**, *1989*, 295-298.

[141] M. P. Cooke Jr, *Tetrahedron Letters* **1981**, *22*, 381-384.

[142] H. Nishiyama, M. Sasaki, K. Itoh, *Chemistry Letters* **1981**, *10*, 905-908.

[143] E. J. Corey, J. A. Katzenellenbogen, *Journal of the American Chemical Society* **1969**, *91*, 1851-1852.

[144] A. Marfat, P. R. McGuirk, P. Helquist, *The Journal of Organic Chemistry* **1979**, *44*, 3888-3901.

[145] H. O. House, C.-Y. Chu, J. M. Wilkins, M. J. Umen, *The Journal of Organic Chemistry* **1975**, *40*, 1460-1469.

[146] D. Seebach, J. Aebi, D. Wasmuth, *Organic Syntheses* **1985**, *63*, 109 ff.

[147] D. Seebach, D. Wasmuth, *Helvetica Chimica Acta* **1980**, *63*, 197-200.

[148] D. L. C. Green, J. J. Kiddle, C. M. Thompson, *Tetrahedron* **1995**, *51*, 2865-2874.

[149] J. D. White, P. Hrnciar, *The Journal of Organic Chemistry* **2000**, *65*, 9129-9142.

[150] S. Bradberry, A. Vale, *Clinical Toxicology* **2009**, *47*, 841-858.

[151] S. Bradberry, A. Vale, *Clinical Toxicology* **2009**, *47*, 617-631.

[152] S. J. S. Flora, V. Pachauri, *International Journal of Environmental Research and Public Health* **2010**, *7*, 2745-2788.

[153] M. Conrad, M. Guthzeit, *Justus Liebigs Annalen der Chemie* **1882**, *214*, 31-38.

[154] R. Scholl, *Chemiker Zeitung* **1911**, *35*.

[155] G. R. Newkome, G. R. Baker, *Organic Preparations and Procedures International* **1986**, *18*, 119-144.

[156] J. P. Guthrie, *Canadian Journal of Chemistry* **1979**, *57*, 1177-1185.

[157] M. C. Hillier, J.-N. Desrosiers, J.-F. Marcoux, E. J. J. Grabowski, *Organic Letters* **2004**, *6*, 573-576.

[158] G. Cravotto, G. B. Giovenzana, M. Sisti, G. Palmisano, *Tetrahedron* **1996**, *52*, 13007-13016.

[159] G. R. Newkome, Z. Yao, G. R. Baker, V. K. Gupta, *The Journal of Organic Chemistry* **1985**, *50*, 2003-2004.

[160] H. C. Padgett, I. G. Csendes, H. Rapoport, *The Journal of Organic Chemistry* **1979**, *44*, 3492-3496.

[161] H. Böhme, L. Häfner, *Chemische Berichte* **1966**, *99*, 281-290.

[162] B. Arct, D. Prelicz, H. Witek, *Roczniki Chemii* **1967**, *41*.

[163] B. Arct, D. Prelicz, H. Witek, *Chemical Abstracts* **1967**, *67*.

[164] A. C. Knipe, C. J. M. Stirling, *Journal of the Chemical Society B: Physical Organic* **1968**, 67-71.

[165] R. Anschütz, *Justus Liebigs Annalen der Chemie* **1903**, *327*, 228-240.

[166] A. Williamson *Philosophical Magazine* **1850**, *37*, 350-356.

[167] D. Meißner, P. Jutzi, *Zeitschrift für Naturforschung B* **2009**, *64b*.

[168] F. Klages, H. Meuresch, *Chemische Berichte* **1953**, *86*, 1322-1326.

[169] R. R. Schmidt, U. Moering, M. Reichrath, *Tetrahedron Letters* **1980**, *21*, 3565-3568.

[170] G. Wittig, U. Todt, K. Nagel, *Chemische Berichte* **1950**, *83*, 110-119.

[171] G. D. Crouse, N. H. Terando, *Journal of Labelled Compounds and Radiopharmaceuticals* **1989**, *27*, 465-471.

[172] A. N. Meldrum, *Journal of the Chemical Society, Transactions* **1908**, *93*, 598-601.

[173] D. Davidson, S. A. Bernhard, *Journal of the American Chemical Society* **1948**, *70*, 3426-3428.

[174] J. Leitich, P. Schuster, A. Eitel, *Tetrahedron* **1967**, *23*, 2221-2227.

[175] P. Schuster, A. Stephen, O. E. Polansky, F. Wessely, *Monatshefte für Chemie / Chemical Monthly* **1968**, *99*, 1246-1276.

[176] L. F. Tietze, U. Beifuss, *Organic Syntheses* **1993**, *71*, 167.

[177] A. M. Dumas, A. Seed, A. K. Zorzitto, E. Fillion, *Tetrahedron Letters* **2007**, *48*, 7072-7074.

[178] G. Cravotto, A. Demetri, Gian M. Nano, G. Palmisano, A. Penoni, S. Tagliapietra, *European Journal of Organic Chemistry* **2003**, *2003*, 4438-4444.

[179] D. Tahmassebi, L. J. A. Wilson, J. M. Kieser, *Synthetic Communications* **2009**, *39*, 2605-2613.

[180] P. Schuster, O. E. Polansky, F. Wessely, *Monatshefte für Chemie* **1964**, *95*, 53-58.

[181] J. A. Hedge, C. W. Kruse, H. R. Snyder, *The Journal of Organic Chemistry* **1961**, *26*, 3166-3170.

[182] P. Margaretha, O. E. Polansky, *Tetrahedron Letters* **1969**, *10*, 4983-4986.

[183] G. Baxter, R. Brown, *Australian Journal of Chemistry* **1975**, *28*, 1551-1557.

[184] W. Lehnert, *Tetrahedron Letters* **1970**, *11*, 4723-4724.

[185] W. Lehnert, *Tetrahedron* **1973**, *29*, 635-638.

[186] R. N. Thuku, D. Brady, M. J. Benedik, B. T. Sewell, *Journal of Applied Microbiology* **2009**, *106*, 703-727.

[187] R. Mariella, A. Roth, *The Journal of Organic Chemistry* **1957**, *22*, 1130-1133.

[188] F. Gaudemar-Bardone, M. Gaudemar, *Bulletin de la Société Chimique de France* **1973**, *12*, 3467-3472.

[189] T. Ogawa, T. Murafuji, H. Suzuki, *Chemistry Letters* **1988**, *17*, 849-852.

[190] H. Suzuki, T. Murafuji, T. Ogawa, *Chemistry Letters* **1988**, *17*, 847-848.

[191] M. Eberle, R. G. Lawton, *Helvetica Chimica Acta* **1988**, *71*, 1974-1982.

[192] C. D. Poulter, R. S. Boikess, J. I. Brauman, S. Winstein, *Journal of the American Chemical Society* **1972**, *94*, 2291-2296.

[193] B. J. L. Royles, *Chemical Reviews* **1995**, *95*, 1981-2001.

[194] Y.-C. Jeong, M. G. Moloney, *Synlett* **2009**, *2009(15)*, 2487-2491.

[195] R.-T. Guo, T.-P. Ko, A. P.-C. Chen, C.-J. Kuo, A. H.-J. Wang, P.-H. Liang, *Journal of Biological Chemistry* **2005**, *280*, 20762-20774.

[196] S.-Y. Chang, T.-P. Ko, P.-H. Liang, A. H.-J. Wang, *Journal of Biological Chemistry* **2003**, *278*, 29298-29307.

[197] S.-Y. Chang, T.-P. Ko, A. P. C. Chen, A. H. J. Wang, P.-H. Liang, *Protein Science* **2004**, *13*, 971-978.

[198] N. O. Concha, C. A. Janson, *WO 03/048733 A2.* **2003**.

[199] S. Peukert, Y. Sun, R. Zhang, B. Hurley, M. Sabio, X. Shen, C. Gray, J. Dzink-Fox, J. Tao, R. Cebula, S. Wattanasin, *Bioorganic & Medicinal Chemistry Letters* **2008**, *18*, 1840-1844.

[200] L. V. Lee, B. Granda, K. Dean, J. Tao, E. Liu, R. Zhang, S. Peukert, S. Wattanasin, X. Xie, N. S. Ryder, R. Tommasi, G. Deng, *Biochemistry* **2010**, *49*, 5366-5376.

[201] V. Summa, A. Petrocchi, P. Pace, V. G. Matassa, R. De Francesco, S. Altamura, L. Tomei, U. Koch, P. Neuner, *Journal of Medicinal Chemistry* **2003**, *47*, 14-17.

[202] R. De Francesco, L. Tomei, S. Altamura, V. Summa, G. Migliaccio, *Antiviral Research* **2003**, *58*, 1-16.

[203] V. Summa, A. Petrocchi, V. G. Matassa, M. Taliani, R. Laufer, R. De Francesco, S. Altamura, P. Pace, *Journal of Medicinal Chemistry* **2004**, *47*, 5336-5339.

[204] L. M. Schwartz, L. O. Howard, *The Journal of Physical Chemistry* **1971**, *75*, 1798-1803.

[205] L. M. Schwartz, L. O. Howard, *The Journal of Physical Chemistry* **1970**, *74*, 4374-4377.

[206] H. Terao, T. Sugawara, Y. Kita, N. Sato, E. Kaho, S. Takeda, *Journal of the American Chemical Society* **2001**, *123*, 10468-10474.

[207] A. H. Schmidt, *Synthesis* **1980**, *1980(12)*, 961-994.

[208] R. West, H. Y. Niu, *Journal of the American Chemical Society* **1963**, *85*, 2589-2590.

[209] S. Cohen, J. R. Lacher, J. D. Park, *Journal of the American Chemical Society* **1959**, *81*, 3480-3480.

[210] J. D. Park, S. Cohen, J. R. Lacher, *Journal of the American Chemical Society* **1962**, *84*, 2919-2922.

[211] S. Cohen, S. G. Cohen, *Journal of the American Chemical Society* **1966**, *88*, 1533-1536.

[212] M. B. Onaran, A. B. Comeau, C. T. Seto, *The Journal of Organic Chemistry* **2005**, *70*, 10792-10802.

[213] Y. Xu, N. Yamamoto, D. I. Ruiz, D. S. Kubitz, K. D. Janda, *Bioorganic & Medicinal Chemistry Letters* **2005**, *15*, 4304-4307.

[214] J. Xie, A. B. Comeau, C. T. Seto, *Organic Letters* **2003**, *6*, 83-86.

[215] J. R. Porter, S. C. Archibald, K. Childs, D. Critchley, J. C. Head, J. M. Linsley, T. A. H. Parton, M. K. Robinson, A. Shock, R. J. Taylor, G. J. Warrellow, R. P. Alexander, B. Langham, *Bioorganic & Medicinal Chemistry Letters* **2002**, *12*, 1051-1054.

[216] W. A. Kinney, N. E. Lee, D. T. Garrison, E. J. Podlesny, J. T. Simmonds, D. Bramlett, R. R. Notvest, D. M. Kowal, R. P. Tasse, *Journal of Medicinal Chemistry* **1992**, *35*, 4720-4726.

[217] R. Ian Storer, C. Aciro, L. H. Jones, *Chemical Society Reviews* **2011**, *40*, 2330-2346.

[218] R. M. Soll, W. A. Kinney, J. Primeau, L. Garrick, R. J. McCaully, T. Colatsky, G. Oshiro, C. H. Park, D. Hartupee, V. White, J. McCallum, A. Russo, J. Dinish, A. Wojdan, *Bioorganic & Medicinal Chemistry Letters* **1993**, *3*, 757-760.

[219] D. Carini, D. Christ, J. Duncia, M. Pierce, in *Integration of Pharmaceutical Discovery and Development, Vol. 11* (Eds.: R. Borchardt, R. Freidinger, T. Sawyer, P. Smith), Springer US, **2002**, pp. 29-56.

[220] S. Niewiadomski, Z. Beebeejaun, H. Denton, T. K. Smith, R. J. Morris, G. K. Wagner, *Organic & Biomolecular Chemistry* **2010**, *8*, 3488-3499.

[221] A. Wada, F. Wang, Y. Suhara, Y. Yamano, T. Okitsu, K. Nakagawa, T. Okano, *Bioorganic & Medicinal Chemistry* **2010**, *18*, 5795-5806.

[222] M. Hirama, M. Shimizu, M. Iwashita, *Journal of the Chemical Society, Chemical Communications* **1983**, 599-600.

[223] E. Stephan, G. Pourcelot, P. Cresson, *Chemistry and Industry* **1988**, 562.

[224] P. Ceccherelli, M. Curini, M. C. Marcotullio, O. Rosati, *Tetrahedron* **1992**, *48*, 9767-9774.

[225] J. R. Devi, P. K. Bhattacharyya, *Indian Journal of Biochemistry & Biophysics* **1977**, *14*, 288-291.

[226] C. M. Afonso, M. T. Barros, L. Godinho, C. D. Maycock, *Tetrahedron Letters* **1989**, *30*, 2707-2708.

[227] P. J. Crocker, U. Karlsson-Andreasson, B. T. Lotz, M. J. Miller, *Heterocycles* **1995**, *40*, 691-716.

[228] M. Hirama, T. Noda, S. Ito, *The Journal of Organic Chemistry* **1985**, *50*, 127-129.

[229] V. I. Boyko, R. V. Rodik, I. N. Severenchuk, Z. V. Voitenko, V. I. Kalchenko, *Synthesis* **2007**, *14*, 2095-2206.

[230] F. Daryaee, F. Kobarfard, A. Khalaj, P. Farnia, *European Journal of Medicinal Chemistry* **2009**, *44*, 289-295.

[231] R. Willstätter, F. Königsberger, *Berichte der Deutschen Chemischen Gesellschaft* **1923**, 2107-2109.

[232] A. H. Dekmezian, M. K. Kaloustian, *Synthetic Communications* **1979**, *9*, 431-435.

[233] E. L. Eliel, H. D. Banks, *Journal of the American Chemical Society* **1972**, *94*, 171-176.

[234] V. Mouriès, B. Delouvrié, E. Lacôte, L. Fensterbank, M. Malacria, *European Journal of Organic Chemistry* **2002**, *2002*, 1776-1787.

[235] K. S. Shrestha, K. Honda, M. Asami, S. Inoue, *Bulletin of the Chemical Society of Japan* **1999**, *72*, 73-83.

[236] R. Mook, P. M. Sher, *Organic Syntheses* **1988**, 75-86.

[237] Y. I. M. Nilsson, P. G. Andersson, J. E. Baeckvall, *Journal of the American Chemical Society* **1993**, *115*, 6609-6613.

[238] E. Nyfeler, P. Renaud, *Organic Letters* **2008**, *10*, 985-988.

[239] S. Torii, K. Uneyama, N. Yamasaki, *Bulletin of the Chemical Society of Japan* **1980**, *53*, 819-820.

[240] J. C. Tripp, C. H. Schiesser, D. P. Curran, *Journal of the American Chemical Society* **2005**, *127*, 5518-5527.

[241] S. Duez, L. Coudray, E. Mouray, P. Grellier, J. Dubois, *Bioorganic & Medicinal Chemistry* **2010**, *18*, 543-556.

[242] H. Bricout, J.-F. Carpentier, A. Mortreux, *Tetrahedron Letters* **1997**, *38*, 1053-1056.

[243] R. Takagi, A. Sasaoka, H. Nishitani, S. Kojima, Y. Hiraga, K. Ohkata, *Journal of the Chemical Society, Perkin Transactions 1* **1998**, 925-934.

[244] R. Wachowiak, *Arzneimittelforschung* **1979**, *29*, 599-602.

[245] D. W. Dicker, M. C. Whiting, *Journal of the Chemical Society (Resumed)* **1958**, 1994-2000.

[246] V. V. Nikolaev, H. Heimgartner, A. Linden, I. S. Krylov, V. A. Nikolaev, *European Journal of Organic Chemistry* **2006**, *2006*, 4737-4746.

[247] H. Fisher, H. Simons, *Journal of the American Chemical Society* **1921**, *43*, 628-629.

[248] B. Bak, *Justus Liebigs Annalen der Chemie* **1939**, *537*, 286-292.

[249] S. Satoh, H. Suginome, M. Tokuda, *Tetrahedron Letters* **1981**, *22*, 1895-1898.

[250] R. C. Cookson, N. J. Liverton, *Journal of the Chemical Society, Perkin Transactions 1* **1985**, 1589-1595.

[251] G. Cravotto, G. B. Giovenzana, M. Sisti, G. Palmisano, *Tetrahedron* **1998**, *54*, 1639-1646.

[252] L. F. Tietze, U. Beifuss, M. Ruther, *The Journal of Organic Chemistry* **1989**, *54*, 3120-3129.

[253] M. N. Elinson, S. K. Fedukovich, G. I. Nikishin, *Russian Chemical Bulletin* **1990**, *39*, 2523-2529.

[254] K. Yasumoto, A. Nishigami, F. Kasai, T. Kusumi, T. Ooi, *Chemical and Pharmaceutical Bulletin* **2006**, *54*, 271-274.

[255] T. Amaya, J. Rebek, *Journal of the American Chemical Society* **2004**, *126*, 6216-6217.

[256] T. Tsuno, S. Sugiyama, H. Ago, *Heterocycles* **1994**, *38*, 2631-2654.

[257] O. Bassas, J. Huuskonen, K. Rissanen, A. M. P. Koskinen, *European Journal of Organic Chemistry* **2009**, *2009*, 1340-1351.

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Publication List

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Poster presentation at the *14th Brazilian Meeting on Organic Synthesis (BMOS)*
DOI: 10.5151/chempro-14bmos-R0387-1

2012

van Berkel, S.; Brauch, S.; Gabriel, L.; Henze, M.; Stark, S.; Vasilev, D.; Wessjohann, L.A.; Abbas, M.; Westermann, B. **Traceless Tosylhydrazone-based Triazole Formation: A Metal-Free Alternative to the Strain-Promoted Azide Alkyne Cycloaddition**
Angew. Chem. Int. Ed. **2012**, 51(22), 5343–5346

van Berkel, S.; Brauch, S.; Gabriel, L.; Henze, M.; Stark, S.; Vasilev, D.; Wessjohann, L.A.; Abbas, M.; Westermann, B. **"Spurlose" Tosylhydrazon-basierte Triazolsynthese: eine metallfreie Alternative zur ringspannungskatalysierten Azid-Alkin- Cycloaddition**
Angew. Chem. **2012**, 124(22), 5437–5441

2013

Lira, L.M.; Vasilev, D.; Pilli, R.A.; Wessjohann, L. **One-Pot Synthesis of Organophosphate Monoesters from Alcohols**
Tetrahedron Lett. **2013**, 54(13), 1690-1692

2015

Ricardo, M.G.; Morales, F.E.; Garay, H.; Reyes, O.; Vasilev, D.; Wessjohann, L.A.; Rivera, D.G. **Bidirectional macrocyclization of peptides by double multicomponent reactions**
Org. Biomol. Chem. **2015**, *13*, 438-446

Vasco, A.V.; Pérez, C.S.; Morales, F.E.; Garay, H.E.; Vasilev, D.; Gavín,J.A.; Wessjohann, L.A.; Rivera, D.G. **Macrocyclization of Peptide Side Chains by the Ugi Reaction: Achieving Peptide Folding and Exocyclic *N*-Functionalization in One Shot**
J. Org. Chem., **2015**, 80(13), 6697–6707

Declaration

Hereby I declare that this Ph.D. thesis is my original work. The literature used in this work is listed in the *References* section.

Erklärung

Hiermit erkläre ich an Eides statt, dass ich die vorliegende Arbeit selbständig und nur unter Verwendung der angegebenen Literatur und Hilfsmittel angefertigt habe. Diese Arbeit wurde bisher an keiner anderen Institution zur Erlangung eines akademischen Grades vorgelegt.

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Halle (Saale), September 2015