Synthesis and aggregation behavior of nature-inspired amphiphiles

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Total Synthesis of Majusculoic acid, a Natural *Trans*-Cyclopropyl Fatty Acid

Emerging trends in drug discovery are stimulating interest in natural fatty acids as a source of lead compounds. In the last decade their application as potentials drug candidates was demonstrated to fight diseases such as tuberculosis, cancer and fungal infections. In this regard, the natural product majusculoic acid has been proven to be of potential as drug lead, since it owns antifungal activity against *Candida* species. However, the availability of this natural fatty acid is limited due to the fact that it has been so far only isolated from natural sources. To allow extensive biological studies and lead optimization in the drug discovery process, the synthesis of this structurally complex amphiphilic molecule is essential. Here, for the first time we demonstrate two total synthesis pathways giving access to majusculoic acid. In this study a number of key synthetic steps, i.e. asymmetric cyclopropanation, selective reduction of alkenes and double bound isomerization, have been successfully employed. Undoubtedly, the synthesis of majusculoic acid developed in the present study will accelerate the lead optimization of this class of fatty acids resulting in new potential drug candidates.
4.1 Introduction

Marine microorganisms are an important source of a variety of still undiscovered organic compounds exhibiting fascinating molecular structures.\(^1\) Especially, a growing interest for these molecules is reported, since they can be applied as lead compounds for drug development.\(^2\)-\(^5\) In this regard, during the last decades many molecules were isolated and characterized revealing often intriguing chemical and biological properties.\(^1\),\(^6\),\(^7\) Furthermore, approaches to use these substances as potential drugs against diseases like malaria,\(^8\) tuberculosis,\(^9\) cancer\(^10\),\(^11\) and fungal infection have been published.\(^12\),\(^13\)

Among the isolated molecules a broad range of unique, rare and biological active fatty acids is contained. Different studies showed that some of these fatty acids can act as inhibitors during the fatty acid biosynthesis of the bacteria leading to a reduced progeny of parasites. For example, in 1992 Kumaratilake et al. observed the antimalarial properties of polyunsaturated fatty acids.\(^14\)

In 2005, MacMillan et al. reported the isolation of majusculoic acid \(1\) (Figure 4.1.1) from a cyanobacterial mat assemblage.\(^15\) As shown in Figure 4.1.1, the molecular structure of fatty acid \(1\) offers unique structural features. One of these, is the presence of a \textit{trans}-substituted cyclopropyl ring at the C4-position of acid \(1\). Other features are the di- and the tri-substituted double bound which are located in C9- and C11-position, respectively. The latter alkene is brominated at the C12-position of the molecule. Using 1D and 2D NMR (nuclear magnetic resonance) spectroscopy the configurations of both olefins and of the cyclopropyl ring were analyzed revealing the structure of the natural product \(1\) (Figure 4.1.1).\(^15\) This study performed by MacMillan et al. proved the E- and Z-configuration of the first (C9-C10) and second double bond (C11-C12) as well as the \textit{trans}-configuration of the cyclopropyl ring (Figure 4.1.1). However, the absolute configuration at the C4 and C6 position could not be established so far.

![Majusculoic acid](image)

**Figure 4.1.1:** Molecular structure of majusculoic acid \(1\).

Furthermore, biological studies of majusculoic acid \(1\) revealed its antifungal activity against \textit{Candida albicans} ATCC 14503 and \textit{Candida glabrata} with a minimum inhibition concentration (MIC) of 8 µM and 19.3 µM, respectively.\(^15\) During the last decade a growing interest in such antymycotic agents was observed. This can be traced back to the fast increasing amount of fungal species, infection and resistance against current available drugs resulting in serious problems for debilitated humans e.g. in hospitals and during transplantations.\(^16\)

Additionally, in 2012 Fisher et al. summarized also the rising fungal threat to animals, plants and the ecosystem leading to a decreased biodiversity through extinction of wild species.\(^17\)
Hence, the investigation of potential antifungal compounds, such as majusculoic acid 1, and the understanding of the mode of action of these substances are necessary to antagonize the fast growing threat through fungal infections. However, due to the low availability of these natural compounds, which have been so far isolated from limited natural resources, an efficient synthesis is required to allow access to a sufficient amount of material for extensive biological, chemical and physiological studies as well as for the synthesis of derivatives in the drug development process.

Therefore, in this Chapter an efficient synthesis for the naturally occurring fatty acid, majusculoic acid 1, is described to give access to a sufficient amount of the antifungal compound 1 and its derivatives for future studies. Furthermore, the absolute configuration of the natural product was unequivocally established for the first time.
4.2 Results and Discussion

4.2.1 Synthesis of Majusculoic Acid

From a retrosynthetic point of view the molecular structure of majusculoic acid 1 can be divided into two building blocks (Scheme 4.2.1), which can be combined via a coupling reaction in the last steps to the final product 1. As shown in Scheme 4.2.1, the most suitable cleavage position seems to be the trans-disubstituted double bond located in the center of the majusculoic acid 1. The two resulting units 2 and 3 exhibit synthetically challenging moieties, i.e. a cis-alkene substituted with a bromide and a trans-substituted cyclopropane unit, respectively.

Scheme 4.2.1: Retrosynthetic pathway for majusculoic acid 1 resulting in two key compounds 2 and 3.

Efficient synthetic strategies considered to allow the combination of both fragments 2 and 3 are a cross metathesis or a Wittig reaction. Both pathways result in the formation of a carbon-carbon double bound that is also present in 1. For the cross metathesis it is required that both building blocks are carrying a terminal alkene. In contrast, during a Wittig olefination an aldehyde 2b and a triphenyl phosphonium bromide salt 3b are reacting with each other.

As shown in Scheme 4.2.2, the brominated building block 2 exhibiting a terminal alkene, i.e. 2a, or an aldehyde moiety, i.e. 2b, can be synthesized in three and four synthetic steps, respectively. Here, it needs to be emphasized that both compounds 2a and 2b are sharing the same synthetic pathway. Hence, alkene 2a can be synthesized from aldehyde 2b in only one additional synthetic step (Scheme 4.2.2).
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**Scheme 4.2.2**: Synthesis of the brominated aldehyde 2b and diene 2a.

As shown in Scheme 4.2.2, the synthesis of olefin 2a and aldehyde 2b starts with the commercial available *trans*-2-hexenal 4. During the first reaction, the aldehyde moiety of 4 was converted into the corresponding hydrazone 6 with a yield of 84% using 1,1-dimethylhydrazine 5. Subsequent bromination in β-position using *N*-bromosuccinimide (NBS) yielded the bromide substituted cis-alkene 7.18 Finally, hydrolysis of the dimethylhydrazone 7 under acidic conditions yielded the first building block 2b exhibiting an aldehyde moiety required for the Wittig reaction. As emphasized above, an additional step was performed to obtain 2a, exhibiting a terminal alkene, via a Wittig olefination using methyltriphenylphosphonium bromide. Therewith, the building block 2a that can be used in a cross metathesis was synthesized in only four synthetic steps.

After successful synthesis of the brominated building blocks 2a and 2b the second molecular part 3 (Scheme 4.2.1) carrying the *trans*-cyclopropyl moiety had to be approached. The retrosynthetic strategy for the corresponding phosphonium salt 3b and the olefin 3a applicable in a Wittig reaction and cross metathesis, respectively, is shown in Scheme 4.2.3. Hereby, the olefin 3a can be synthesized in six synthetic steps, whereas phosphonium salt 3b is accessible in nine steps. However, employing this synthetic pathway we face two major challenges. The first hurdle is the selective reduction of the double bond which is conjugated to the cyclopropyl- and ester moieties in 8, while the terminal olefin needs to be retained (Scheme 4.2.3, step a). The second challenge is the diastereo- and enantioselective incorporation of a *trans*-disubstituted cyclopropane ring resulting in intermediate 9 (Scheme 4.2.3, step b). As shown in Scheme 4.2.3, the precursor for the cyclopropanation, namely E-S-ethyl 4-chlorobut-2-enethionate 10, can be obtained in two synthetic steps starting from the commercially available 3-butenic acid 11.
The terminal position of 3-butenolic acid 11 was chlorinated using recrystallized
\( N \)-chlorosuccinimide (NCS) and phenylselenyl chloride (PhSeCl) (Scheme 4.2.4).\(^\text{19}\) The resulting product, i.e. E-4-chlorobut-2-enoic acid 12, was used for the subsequent esterification employing ethanethiol (EtSH) yielding the corresponding thioester 10 as main product. However, under the applied reaction condition a side reaction took place resulting also in formation of the disubstituted cyclopropane 13 (Scheme 4.2.4). This side product 13 is formed through a nucleophilic addition of a second ethanethiol in the \( \beta \)-position of thioester 10 followed by an intramolecular nucleophilic substitution at the chlorinated carbon. The resulting mixture of 10 and 13 was successfully separated using Oxone® (potassium peroxymonosulfate) as oxidizing reagent for thioether 13 followed by an extraction yielding the desired \( \alpha \)-\( \beta \) unsaturated thioester 10 with an isolated yield of 61%.

To obtain the desired \( \text{trans} \)-cyclopropyl moiety, an asymmetric conjugate addition and a subsequent intramolecular trapping reaction of the enolate 15 as described by \textit{den Hartog} et. al. in 2010 was applied.\(^\text{20}\) As shown in Scheme 4.2.5, during the first step of this reaction the freshly synthesized \textit{Grignard} reagent 14 and catalytic amounts of \( R \)-TolBINAP ((\( R \))-(+)-2,2'-Bis(di-p-tolylphosphino)-1,1'-binaphthyl) were used to convert 10 to the intermediate 15. In the second part of the asymmetric cyclopropanation the resulting reaction mixture was warmed slowly to room temperature before it was quenched with ethanol and aq. NH\(_4\)Cl resulting in thioester 9 with a cyclopropyl moiety (Scheme 4.2.5). It needs to be emphasized that the resulting compound 9 exist as pure \( \text{trans} \)-diastereomer with an enantiomeric excess of 95%.

Furthermore, the amount of \textit{Grignard} reagent (1.1 equiv.) is crucial to reduce side reactions and to enable the isolation of 70% of the compound 9.

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\textbf{Scheme 4.2.3:} Retrosynthetic pathway for building block 3 applying a nine synthetic step.

\textbf{Scheme 4.2.4:} Two-step synthesis of E-S-ethyl 4-chlorobut-2-enethionate 10.
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Scheme 4.2.5: Cyclopropanation using an asymmetric conjugate addition of Grignard reagent 14 followed by a cyclization leading to the disubstituted trans-cyclopropane 9.

After successful incorporation of the trans-cyclopropyl moiety, in the next steps an elongation of the chain was performed (Scheme 4.2.6). First, thioester 9 was selectively reduced to an aldehyde 16 using diisobutylaluminium hydride (DIBAL-H) reaching an isolated yield of 70%. Then, the freshly synthesized aldehyde 16 was immediately utilized in a Horner-Wadsworth-Emmons (HWE) olefination using the commercially available triethyl phosphonoacetate 17 resulting in α,β-unsaturated ethyl ester 8 (Scheme 4.2.6).

Finally, a selective reduction of the conjugated carbon-carbon double bond of 8 with NaBH₄ resulted in the above introduced building block 3a. However, as shown in Scheme 4.2.7, depending on the reaction condition, a simultaneous reduction of the terminal olefinic group occurred leading also to side products 18 and 19.

Scheme 4.2.7: Reduction of the carbon-carbon double bound of ethyl ester 8 using NaBH₄ and metal halides (MXₙ).
In order to optimize the selective reduction of the conjugated olefinic group, a set of reactions was carried out using different metal halides (MX_n), different quantities NaBH_4 and employing different temperatures and reaction times. The results are summarized in Table 4.2.1 showing a major influence of the metal halides on the product formation and conversion.

As shown in Table 4.2.1, using 20 mol% CuCl and employing a reaction temperature of 0 °C no conversion of 8 was detected (entry 1), while performing the reduction at room temperature a low conversion could be observed resulting in the desired building block 3a as the main product (entry 2). Comparable results were observed using 20 mol% of Cul at room temperature (Table 4.2.1, entry 3). In contrast, using CoCl_2 lead to a significant acceleration of the reaction through the *in situ* formation of highly reactive cobalt boride species. At room temperature full conversion of the starting material 8 was already observed after 30 minutes (Table 4.2.1, entry 4). However, employing the latter conditions only the fully saturated ester 19 was isolated. Further, at lower temperatures mainly compounds 18 and 19 were obtained as a mixture (Table 4.2.1 entry 5) suggesting that the terminal olefin is more reactive than the one conjugated to the ester moiety. Considering the higher reactivity of the terminal double bound using CoCl_2 as metal halide (Table 4.2.1, entries 4 and 5) we decided to utilize Cu(I) halide as catalyst, since a selective reduction was previously observed (Table 4.2.1, entries 1-3). However, in order to increase the conversion of the selective reduction an increased amount of NaBH_4 was employed. As shown in Table 4.2.1 (entry 6), the ester 8 was selectively reduced to the desired product 3a in presence of six equivalents of NaBH_4 reaching an isolated yield of 81% (Table 4.2.1, entry 6). The necessity of CuCl for this reaction was demonstrated in entry 7 of Table 4.2.1, where no reaction took place.

<table>
<thead>
<tr>
<th>Entry</th>
<th>MX_n *</th>
<th>NaBH_4 (equiv.)</th>
<th>temp. (°C)</th>
<th>Time (h)</th>
<th>conv. (%)</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl</td>
<td>1.5</td>
<td>0</td>
<td>24</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>CuCl</td>
<td>1.5</td>
<td>rt</td>
<td>24</td>
<td>5</td>
<td>3a</td>
</tr>
<tr>
<td>3</td>
<td>CuI</td>
<td>1.5</td>
<td>rt</td>
<td>24</td>
<td>2</td>
<td>3a</td>
</tr>
<tr>
<td>4</td>
<td>CoCl_2</td>
<td>1.5</td>
<td>rt</td>
<td>0.5</td>
<td>100</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>CoCl_2</td>
<td>1</td>
<td>0</td>
<td>0.5</td>
<td>100</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>CuCl</td>
<td>6**</td>
<td>rt</td>
<td>5</td>
<td>84</td>
<td>3a</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>6**</td>
<td>rt</td>
<td>5</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

*20 mol% were used of the metal halide. **Repetitive addition of one equivalent NaBH_4 every 45 minutes.

After a successful synthesis of building block 3a for the cross metathesis, the same compound was also employed as starting material to obtain the corresponding triphenylphosphonium bromide salt 3b, which represents a reactant for the Wittig reaction (*vide supra*). As shown in Scheme 4.2.8, employing an ozonolysis and reductive workup with NaBH_4 alkene 3a was converted to a primary alcohol 20 reaching a yield of 86%. The alcohol 20 was further reacted in an *Appel* reaction using tetrabromomethane (CBr_4) and triphenylphosphine (PPh_3) resulting in the corresponding bromide 21, which was directly used for the synthesis of the
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above mentioned phosphonium building block 3b (Scheme 4.2.8). As shown in Scheme 4.2.8, the final step was performed in melted triphenylphosphine resulting in Wittig salt 3b with an isolated yield of 67%.

Scheme 4.2.8: Three-step synthesis of Wittig salt 3b from building block 3a.

With all four building blocks 2a, 3a, 2b and 3b in hand, the final part of the synthesis of the majusculoic acid ethyl ester 22 was performed. As shown in Scheme 4.2.9, a cross metathesis reaction using compounds 2a and 3a can result in the desired ester 22. Alternatively, employing a Wittig reaction of compounds 2b and 3b the majusculoic acid derivative 22 can be obtained as well (Scheme 4.2.9).

Scheme 4.2.9: Two possible synthetic pathways using 2a, 3a, 2b and 3b to form the majusculoic acid ethyl ester 22: (a) cross metathesis and (b) Wittig reaction.

To obtain the final product 22 we evaluated first the cross metathesis. As shown in Scheme 4.2.10, employing this reaction not only the desired products 22, but also side products 23 and 24 can be expected due to homodimerization of the corresponding building blocks. Also attention deserves the choice of the catalyst, which can influence the ratio of the corresponding E- to Z-isomer ratio of 22. In this regard, different generations of the Grubbs- (G), Hoveyda Grubbs- (HG) as well as the Metathesis- (M) catalysts (Figure 4.1.1) were tested in order to obtain the required E-isomer of 22. The obtained results utilizing the same reaction conditions for all catalysts are summarized in Table 4.2.2. In presence of G-I exclusively the homodimers 23 and 24 were formed (Table 4.2.2, entry 1). The formation of the same product was observed using the second generation of catalysts G-II, HG-II and MII, as shown in Table 4.2.2 entries 2, 4 and 6, respectively. However, traces of the desired heterodimer 22 could be detected via
NMR-spectroscopy. In contrast, in presence of catalysts HG-I and M-I exclusively heterodimer 22 was obtained. Employing NMR to examine the latter reaction mixtures revealed a slow reaction resulting in low conversions (< 10%) of the building block 2a and 3a. Also, change of reaction conditions, such as solvent, reaction time and temperature (RT – 110 °C), or using different concentrations and stoichiometry of reactants/catalyst did not result in increased conversion. Another drawback of the performed cross metathesis is the fact that only a mixture of E- and Z-isomers of 22 was obtained using HG-I and M-I as catalyst, as shown in Table 4.2.2, entries 3 and 5, respectively.

Figure 4.1.1: Chemical structure of all used ruthenium-based metathesis catalysts (Grubbs- (G), Hoveyda Grubbs- (HG), Metathesis- (M) catalysts).

Scheme 4.2.10: Possible product formation during cross metathesis using building block 2a and 3a.
Total Synthesis of Majusculoic acid, a Natural Trans-Cyclopropyl Fatty Acid

Table 4.2.2: Catalyst screening for cross metathesis.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>homodimer</th>
<th>heterodimer</th>
<th>E:Z ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GI</td>
<td>√</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>GII</td>
<td>√</td>
<td>traces</td>
<td>E</td>
</tr>
<tr>
<td>3</td>
<td>HGI</td>
<td>-</td>
<td>√**</td>
<td>2:1</td>
</tr>
<tr>
<td>4</td>
<td>HGII</td>
<td>√</td>
<td>traces</td>
<td>E</td>
</tr>
<tr>
<td>5</td>
<td>MI</td>
<td>-</td>
<td>√**</td>
<td>2:1</td>
</tr>
<tr>
<td>6</td>
<td>MII</td>
<td>√</td>
<td>traces</td>
<td>E</td>
</tr>
</tbody>
</table>

*Ratio given for heterodimer 22. **Yield lower than 10%.

Considering the formation of isomer mixtures of 22 and the low yield performing the cross metathesis reaction, a second synthetic strategy was carried out. As shown in Scheme 4.2.11, aldehyde 2b and triphenylphosphonium bromide salt 3b were used in a Wittig reaction to obtain the desired product 22. In order to minimize the formation of the undesired Z-isomer and in the same time obtain the E-isomer of 22 in a good yield the Wittig reaction was performed in presence of different bases (B). Table 4.2.3 summarizes the outcome of this study using n-butyl lithium (n-BuLi), lithium diisopropylamide (LDA), Lithium hexamethyldisilazide (LiHMDS) and sodium (Na) hexamethyldisilazide (NaHMDS) as a base. Comparing the Wittig reaction (Scheme 4.2.11, Table 4.2.3) with the cross metathesis (vide supra) the Majusculoic acid ethyl ester 22 could be obtained with higher yields of up to 43%. However, at the same time also this reaction resulted mainly in Z-isomer of 22 independent of the base utilized (Table 4.2.3).

Scheme 4.2.11: Wittig reaction using building block 2b and 3b. (B = base)

Table 4.2.3: Base screening for Wittig reaction.

<table>
<thead>
<tr>
<th>Base</th>
<th>Yield (%)</th>
<th>E:Z ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-BuLi</td>
<td>43</td>
<td>1:3</td>
</tr>
<tr>
<td>LDA</td>
<td>19</td>
<td>1:9</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>39</td>
<td>1:10</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>40</td>
<td>0:1</td>
</tr>
</tbody>
</table>

Due to the unfavorable diastereomeric ratio of E- and Z-isomer (Table 4.2.3) we considered to perform an isomerisation reaction of the disubstituted double bound of 22 employing iodine. Therefore, the isomer mixture obtained from the reaction performed in the presence of n-BuLi (Table 4.2.3) was incubated with a small amount of iodine in D-chloroform at 40 °C. The progress of the reaction was followed by NMR-spectroscopy (Figure 4.2.2). The NMR-study
demonstrates a successful isomerization of the Z-isomer to the desired E-isomer of 22. An equilibrium of the isomerization was reached after a reaction time of 30 minutes and the excess of iodine was eliminated through extraction with aqueous Na$_2$S$_2$O$_3$ solution. The isomerization resulted in the E-22 isomer containing less than 10% of the corresponding Z-22 isomer (Figure 4.2.2).

Finally, in order to obtain the natural product, namely majusculoic acid 1, the ethyl ester E-22 was subsequently hydrolyzed under basic conditions resulting in the corresponding acid 1 with an isolated yield of 75% (Scheme 4.2.12). Majusculoic acid 1 was obtained as colorless solid which was analyzed by NMR-spectroscopy, exact mass (see Chapter 4.5) and determination of the optical rotation ([α]D). The NMR-spectra obtained from the in this work synthesized majusculoic acid 1 carrying a trans-(4R,5R)-cyclopropane moiety are in accordance with the in ref. 15 reported data. Furthermore, a value of [α]D = -16.2 for the optical rotation was determined which is also comparable with the in 2005 by MacMillan et al. determined rotation for majusculoic acid isolated from cyanobacteria ([α]D = -15.8). Based on this data we can conclude that the natural occurring majusculoic acid 1 should have the same absolute configuration (4R, 5R) as the in our laboratories synthesized acid 1 (Scheme 4.2.12).

Figure 4.2.2: Isomerisation of the disubstituted double bound of compound 22. (a) $^1$H-NMR of the isomer mixture of 22 before isomerisation. (b) $^1$H-NMR of the isomer mixture of 22 after isomerisation.

Scheme 4.2.12: Basic hydrolysis of 22 resulting in majusculoic acid 1.
4.3. Conclusion

In conclusion, the natural product majusculoic acid that is produced in cyanobacteria was successfully synthesized for the first time. In this regard, two total synthetic pathways were identified reaching overall yields of 1.4% over 12 steps (cross metathesis) and 3.7% over 14 steps (Wittig reaction) for the natural product. It needs to be emphasized that majusculoic acid bears synthetically challenging molecular units, which require advanced diastereo- and enantioselective chemistry. Examples are the incorporation of a trans-cyclopropyl moiety and selective introduction of E- and Z- olefinic groups. Those exceptional structural features were successfully incorporated employing first the by den Hartog et. al. in our laboratories established asymmetric conjugate addition of Grignard reagent followed by a subsequent intramolecular trapping reaction of the enolate leading to the desired disubstituted trans-cyclopropyl moiety with high ee and known absolute configuration. Furthermore, cross metathesis, Wittig reaction and thermodynamic double bond isomerization were applied resulting in the first synthesizes of majusculoic acid allowing for the first time the determination of the absolute configuration (4R,5R) of the trans-cyclopropyl unit incorporated in the natural compound.

This natural product is of interest to be investigated more in detail, since it shows antifungal activity against Candida species. However, biological test were so far restricted due to the limited availability of the majusculoic acid. Now, having this compound in hand and having evaluated its scalable total synthesis this natural product is accessible for further biological studies to allow understanding of its action and role. Furthermore, the gained knowledge might result in new drug candidates inspired by natural fatty acids in the near future.
4.4 Experimental Section

4.4.1 Materials and Methods

All chemicals and reagents were purchased from commercial suppliers (Acros and Sigma-Aldrich) and used without further purification. Dry solvents were taken from an MBrAn solvent purification system (SPS-800). Thin layer chromatographic (TLC) analysis was performed on Merck silica gel 60/Kieselguhr F254, 0.25 mm and visualized by UV and staining with Seebach’s reagent. Column chromatography was performed using silica gel (P60, 230 – 400 mesh).

$^1$H-NMR-, $^{13}$C-NMR-, $^{31}$P-NMR-, heteronuclear single-quantum correlation- (HSQC) spectra, Nuclear Overhauser effect spectroscopy (NOESY) and correlation spectroscopy (COSY) were recorded on a Agilent 400 (400 MHz for $^1$H-NMR, 100.59 MHz for $^{13}$C-NMR) using CDCl$_3$ (CDCl$_3$: δ 7.26 for $^1$H-NMR, δ 77.16 for $^{13}$C-NMR). Data are reported as follows: chemical shifts, multiplicity (s= singlet, d= doublet, t= triplet, q= quartet, br= broad, m= multiplet), coupling constants ($J$ Hz) and integration.

High resolution mass spectrometry (HRMS) was carried out on a LTQ ORBITRAP XL spectrometer (Thermo Scientific) employing electrospray ionization (ESI) in positive ion mode (EI+) and negative ion mode (EI-). Optical rotations were measured on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (concentration $c$ given in g/100 mL).

Melting points were measured on a Büchi B-545 and recorded in °C. The enantiomeric excess ($ee$) was determined by chiral GC (HP6890, Chiraldex G-TA 30 m x 0.25 mm x 0.25 μm) using flame ionization detection.

Optical rotations were measured on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (concentration $c$ given in g/100 mL).

4.4.2 General Procedures

**Copper catalyst**

Cu(I) (1 equiv) and R-TolBINAP (1.5 equiv) were dissolved in anhydrous tBME (800 mL/mmol of Cu(I)) and stirred for 2 h at rt. The obtained mixture was used without further purification.

**Grignard reagent 14**

Grinded Mg (1.1 equiv) was added to anhydrous ether (4 mL/30 mmol). 1/20 of the amount of bromide (0.05 equiv) was added at once to the solution to start the reaction. The rest of the bromide (0.95 equiv) was dissolved in anhydrous ether (1 mL/3 mmol of substrate) and added slowly to the reaction mixture. The molarity of the resulting Grignard solution was determined by titration before it was used in the next synthetic step.
Titration of Grignard reagent 14

1 mL of the Grignard solution 14 is added to a solution of one crystal of 1.10 phenanthroline in 5 mL ether. 2-Butanol is added slowly to the resulting red mixture till the color disappears.

4.4.3 Synthesis and Characterization

(E)-2-((E)-Hex-2-en-1-ylidene)-1,1-dimethylhydrazine (6). Aldehyde 4 (1 equiv) was dissolved in anhydrous CH₂Cl₂ (10 mL/ mmol). Dimethylhydrazine (1.05 equiv) was added at rt to the solution and the mixture stirred for 40 h. Subsequently, water (10 mL/ mmol) was added and the resulting mixture was extracted with ether (10 mL/ mmol). All organic layers were combined, dried over MgSO₄ and the solvent was removed by rotary evaporation. The hydrazone 6 was obtained as a yellowish oil with a yield of 87% and was used without further purification in the next step of the synthesis. ¹H NMR (400 MHz, CDCl₃); δ (ppm): 7.0 (d, J= 8.8 Hz, 1H); 6.17 (dd, J= 15.2 Hz, J= 8.8 Hz, 1H); 5.79 (dt, J= 16.6 Hz, J= 6.8 Hz, 1H); 2.81 (s, 6H); 2.12 (q, J= 7.2 Hz, 2H); 1.42 (q, J= 7.2 Hz, 2H); 0.91 (t, J= 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃); δ (ppm): 137.22 (1C; CH); 135.79 (1C, CH); 129.2 (1C, CH); 43.07 (2C, CH₃); 34.85 (1C, CH₂); 22.39 (1C, CH₂); 13.80 (1C, CH₃). HR-MS (EI+) (m/z): found 141.139 [M+H]⁺, calculated 141.139 [M+H]⁺.

(E)-2-((Z)-3-Bromohex-2-en-1-ylidene)-1,1-dimethylhydrazine (7). An solution of NBS (1 equiv) in anhydrous CH₂Cl₂ (15 mL/ mmol) was added dropwise to a solution of the α,β-unsaturated hydrazone 6 (1 equiv) in CH₂Cl₂ (10 mL/ mmol). The resulting mixture was stirred for additional 20 h at rt. Subsequently, water (10 mL/ mmol) was added and the resulting mixture was extracted with CH₂Cl₂ (10 mL/ mmol). All organic layers were combined, dried over MgSO₄ and concentrated under reduced pressure. Flash column chromatography (1:6, ether: pentane) gave the pure product 7 as yellow oil with a yield of 45%. The isolated product contains a isomeric mixture of 1:11 (E:Z).

¹H NMR (400 MHz, CDCl₃); δ (ppm): Z-7: 7.06 (d, J= 8.4 Hz, 1H); 6.42 (d, J= 8.4 Hz, 1H); 2.89 (s, 6H); 2.48 (t, J= 7.2 Hz, 2H); 1.61 (q, J= 7.2 Hz, 2H); 0.88 (t, J= 7.2 Hz, 3H); E-7: 6.96 (d, J= 8.4 Hz, 1H); 6.62 (d, J= 8.4 Hz, 1H); 2.86 (s, 6H); 2.55 (t, J= 7.2 Hz, 2H); 1.63 (q, J= 7.2 Hz, 2H); 0.91 (t, J= 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃); δ (ppm): 133.54 (1C; CH); 128.53 (1C, CBr); 126.62 (1C, CH); 43.71 (1C, CH₂); 43.54 (2C, CH₃); 21.16 (1C, CH₂); 12.69 (1C, CH₃). HR-MS (EI+) (m/z): found 219.1049 [M(79Br)+H]⁺, 221.047 [M(81Br)+H]⁺, calculated 219.049 [M(79Br)+H]⁺, 221.047 [M(81Br)+H]⁺.
(Z)-3-Bromohex-2-enal (2b). The hydrazone (1 equiv) was added at rt to an aq solution of HCl (1 M, 10 mL/ mmol). After 5 min stirring pentane was added (10 mL/ mmol) and the reaction mixture was stirred for additional 16 h. The layers were separated and the aq. layer was extracted with pentane (2*10 mL/ mmol). The combined organic layers were dried over MgSO₄ and carefully concentrated under reduced pressure. Flash column chromatography (1:99, ether: pentane) yielded the pure colorless oil 2b with a yield of 73%. The isolated product contains less than 3% of the E-isomer. ¹H NMR (400 MHz, CDCl₃); δ (ppm): Z-2b: 9.89 (d, J= 6.8 Hz, 1H); 6.28 (d, J= 6.8 Hz, 1H); 2.63 (t, J= 7.2 Hz, 2H); 1.69 (q, J= 7.2 Hz, 2H); 0.93 (t, J= 7.2 Hz, 3H); E-2b: 9.81 (d, J= 7.2 Hz, 1H); 6.54 (d, J= 7.2 Hz, 1H); 2.97 (t, J= 7.2 Hz, 2H); 1.73 (q, J= 7.2 Hz, 2H); 0.87 (t, J= 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃); δ (ppm): 94.44 (1C, CHO); 128.6 (1C, CH); 45.01 (1C, CH₂); 20.91 (1C, CH₂); 12.73 (1C, CH₃). HR-MS (EI⁺) (m/z): found 176.990 [M(79Br)+H]+, 178.888 [M(81Br)+H]+, calculated 176.991 [M(79Br)+H]+, 178.889 [M(81Br)+H]+.

(Z)-4-Bromohepta-1,3-diene (2a). Methyltriphenylphosphonium bromide (1.5 equiv) was dissolved in anhydrous THF (10 mL /mmol) and cooled to 0 °C. nBuLi (1.6M, 1.4 equiv) was added drop wise and the resulting reaction mixture was stirred for 1 h at this temperature. Subsequently, the aldehyde 2b was added and the solution was stirred for additional 30 min before it was quenched by adding water (10 mL /mmol), followed, by an extraction with ether (3*10 mL / mmol). The combined organic layers were dried over MgSO₄ and carefully concentrated under reduced pressure. Flash column chromatography (1:99, ether: pentane) provided the pure colorless oil 2a with a yield of 72%. ¹H NMR (400 MHz, CDCl₃); δ (ppm): 6.59 (dt, J= 16.8 Hz, J= 10.4 Hz, 1H); 6.28 (d, J= 9.6 Hz, 1H); 5.31 (d, J= 16 Hz, 1H); 5.26 (d, J= 10.4 Hz, 1H); 2.45 (t, J= 7.2 Hz, 2H); 1.61 (q, J= 7.2 Hz, 2H); 0.87 (t, J= 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃); δ (ppm): 134.79 (1C, CH); 130.07 (1C, CBr); 128.39 (1C, CH); 118.99 (1C, CH₂); 43.84 (1C, CH₂); 21.52 (1C, CH₂); 13.08 (1C, CH₃). HR-MS (EI⁺) (m/z): found 175.010 [M(79Br)+H]+, 177.001 [M(81Br)+H]+, calculated 175.012 [M(79Br)+H]+, 177.010 [M(81Br)+H]+.

(E)-4-chlorobut-2-enoic acid (12). NCS was recrystallized in acetic acid and dried overnight under vacuum before use. The commercial available acid 11 (1 equiv) and PhSeCl (10 mol%) were dissolved in acetonitrile (5 mL/ mmol). Subsequently, a solution of NCS (1.1 equiv) in acetonitrile (2 mL / mmol) was added slowly at rt over a time period of 24 h. After stirring for an additional 40 h at this temperature the reaction mixture was concentrated. Ether was added until the precipitation of a white solid was completed and the resulting suspension was filtered. The precipitate was washed with ether, before the organic layer was washed with water (2*0.5 mL/ mmol), dried over MgSO₄ and concentrated under reduced pressure. Recrystallization in pentane:ether (4:1) leads to the pure white product 12 with an isolated yield of 68%. ¹H NMR (400 MHz, CDCl₃); δ (ppm): 7.09 (dt, J= 15.6 Hz, J= 6.0 Hz, 1H); 6.12 (dt, J= 15.6 Hz, J= 1.6 Hz, 1H); 4.19 (dd, J= 6 Hz, J= 1.6 Hz, 2H). HR-MS (EI⁺) (m/z): found 121.006 [M+H]+, calculated 121.005 [M+H]+. Mp= 74-75 °C. Data in accordance with those described in literature, ref 19.
(E)-S-Ethyl 4-chlorobut-2-enethioate (10). A solution of DMAP (0.1 equiv) and the acid 12 (1 equiv) in anhydrous CH₂Cl₂ (1.5 mL/mmol) was stirred at rt for 5 min. After cooling the reaction mixture to 0 °C, a solution of ethanethiol (1 equiv) and DCC (1.05 equiv) in anhydrous CH₂Cl₂ (0.5 mL/mmol of substrate) was added. The resulting reaction mixture was stirred for an additional 4 h in which period the temperature was allowed to rise to rt. Subsequently, the precipitate was filtered over celite and washed with pentane. The organic layer was dried over MgSO₄ and concentrated under reduced pressure. Flash column chromatography (1:99, ether:pentane) yielded the product 10 with 5-10% of byproduct 13 (trans-S-ethyl 2-(ethylthio) cyclopropanecarbothioate).

Further purification: The crude mixture of E-S-ethyl 4-chlorobut-2-enethioate 10 was dissolved in a mixture of water and acetonitrile (1:4, 3 mL/mmol). OXONE® (0.1 equiv) was added at 0 °C to the mixture. After stirring at this temperature for 20 min the solution was warmed to rt and stirred for an additional 40 min. The reaction mixture was quenched with brine (10 mL/mmol) at 0 °C and extracted with ether (3*10 mL/mmol). All organic layers were combined, dried over MgSO₄ and concentrated under reduced pressure. Flash column chromatography (1:99, ether:pentane, Rf= 0.2) yielded the pure product 10 as colorless oil with a yield of 63% over both steps. ¹H NMR (400 MHz, CDCl₃); δ (ppm): 6.87 (dt, J= 15.2 Hz, J= 6.0 Hz, 1H), 6.34 (d, J= 15.6 Hz, 1H), 4.15 (d, J= 6 Hz, 2H); 2.95 (q, J= 7.6 Hz, 2H); 1.27 (t, J= 7.6 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃); δ (ppm): 190.12 (1C, CO); 137.66 (1C, CH); 130.95 (1C, CH); 42.46 (1C, CH₂); 23.22 (1C, CH₂); 14.40 (1C, CH₃). HR-MS (EI⁺) (m/z): found 165.014 [M(35Cl)+H⁺], 167.010 [M(37Cl)+H⁺], calculated 165.014 [M(35Cl)+H⁺], 167.011 [M(37Cl)+H⁺].

(1R,2R)-S-Ethyl 2-(but-3-en-1-yl)cyclopropanecarbothioate (9). The Grignard reagent (1-2 M solution in ether, 1.1 equiv) was added at -78 °C to a solution of the premade copper catalyst (CuI (1 mol%), R-TolBINAP (1.5 mol%) in anhydrous tBuOMe (8 mL/mmol)) and the mixture stirred for 10 min. This was followed by a slow addition over 2 h with a syringe pump of a solution of the substrate 10 (1 equiv) in anhydrous CH₂Cl₂ (0.5 mL/mmol). After additional stirring for 2 h at this temperature the reaction mixture was allowed to warm up slowly to rt overnight. Subsequently, the reaction mixture was quenched with EtOH (0.4 mL/mmol) and an aq. solution of NH₄Cl (1 M, 2 mL/mmol). Ether (10 mL/mmol) and an aq. solution of NH₄Cl (1 M, 10 mL/mmol) were added. The resulting layers were separated and the aq. layer was extracted with ether (2*10 mL/mmol of substrate). All organic layers were combined, dried over MgSO₄ and carefully concentrated under reduced pressure. Flash column chromatography (1:99, ether:pentane) yielded the pure product 9 as colorless oil with a yield of 75%. ¹H NMR (400 MHz, CDCl₃); δ (ppm): 5.8 (ddt, J= 17.2 Hz, J= 10.4 Hz, J= 6.8 Hz, 1H), 5.97 (m, 2H), 2.86 (q, J= 7.6 Hz, 2H); 2.13 (dtt, J= 7.2 Hz, J= 6.8 Hz, J= 1.2 Hz, 2H); 1.75 (dt, J= 8 Hz, J= 4 Hz, 1H), 1.51 (m, 1H), 1.4 (dtt, J= 7.6 Hz, J= 3.6 Hz, J= 7.6 Hz, 2H), 1.33 (dt, J= 8.8 Hz, J= 4.4 Hz, 1H); 1.22 (t, J= 7.6 Hz, 3H); 0.78 (dd, J= 8 Hz, J= 6.4 Hz, J= 4 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃); δ (ppm): 199.39 (1C, CO); 138.34 (1C, CH); 115.36 (1C, CH₂); 33.11 (1C, CH₂); 32.47 (1C, CH₂); 30.07 (1C, CH); 24.78 (1C, CH); 23.08 (1C, CH₂); 17.52 (1C, CH₂); 14.64 (1C, CH₃).
HR-MS (EI+) (m/z): found 185.100 [M+H]+, calculated 185.100 [M+H]+. Ee: 95%, column: Chiraldex-G-TA, 70 °C for 50 min, retention times (min): 17.269 (R,R), 19.419 (S,S). [α]D = -106.2 (10 mg/mL in MeOH).

The enantiomeric excess (ee) of 9 was determined using the methyl ester of 9: 10 mg of the acid 9 and 20 mg of K2CO3 were dissolved in 0.5 mL MeOH and stirred for 3 h. Subsequently, 0.5 mL of an aq. NH4Cl solution (1 M) was added and the resulting mixture was extracted with ether (3*0.5 mL). All organic layers were combined, dried over MgSO4 and carefully concentrated under reduced pressure. The methyl ester was filtered over SiO2 using ether as eluent. After evaporation of the ether the ee of the ester was determined in MeOH using a chiral GC.

(1R,2R)-2-(But-3-en-1-yl)cyclopropanecarbaldehyde (16). DIBAL-H (1.2 equiv, 1 M) was added dropwise to a stirred solution of the thioester 9 (1 equiv) in anhydrous CH2Cl2 (0.5 mL/mmoll) at -78°C. After stirring for 3 h at this temperature the reaction mixture was poured into a aq. Rochelle’s salt-solution (saturated, 5 mL/mmoll) and stirred for 1h at rt. The layers were separated and the aq. layer was extracted with CH2Cl2 (2x 5 mL/mmoll). All organic layers were combined, washed with the aq. Rochelle’s salt-solution (saturated, 2*5 mL/mmoll), dried over MgSO4 and carefully concentrated under reduced pressure. Flash column chromatography (5:95, ether:pentane) yielded the pure product 16 as colorless oil with an isolated yield of 74%. The obtained aldehyde 16 was used immediately in the next synthetic step to avoid decomposition. 1H NMR (400 MHz, CDCl3); δ (ppm): 9 (d, J= 5.6 Hz, 1H); 5.79 (ddt, J= 16.8 Hz, J= 10 Hz, J= 6.8 Hz, 1H), 4.98 (m, 2H), 2.16 (dt, J= 6.8 Hz, J= 6 Hz, 2H); 1.61 (m, 1H); 1.46 (m, 3H, 1H), 0.92 (m, 1H). 13C NMR (100 MHz, CDCl3); δ (ppm): 201.68 (1C, CO); 138.12 (1C, CH); 115.57 (1C, CH2); 33.17 (1C, CH2); 31.9 (1C, CH2); 30.35 (1C, CH); 22.02 (1C, CH); 14.64 (1C, CH2). HR-MS (EI+) (m/z): found 125.096 [M+H]+, calculated 125.096 [M+H]+.

(E)-Ethyl 3-((1R,2R)-2-(but-3-en-1-yl)cyclopropyl)acrylate (8). Triethyl phosphonoacetate (1.75 equiv) was added dropwise at 0 °C to a stirred solution of NaH (60% dispersion in mineral oil, 1.75 equiv) in anhydrous THF (1 mL/mmoll). The mixture was stirred additionally for 30 min before it was cooled to -20 °C. A solution of the aldehyde (1 equiv) in anhydrous THF (0.1 mL/mmoll) was added dropwise. The resulting mixture was stirred for 20 min at -20 °C, for 30 min at rt and diluted with ether (2 mL/mmoll). Subsequently the solution was washed with NH4Cl (saturated aq. solution, 2 mL/mmoll), Na2CO3 (saturated aq. solution, 2 mL/mmoll) and brine (2 mL/mmoll). The organic layer was dried over MgSO4 and carefully concentrated under reduced pressure. Flash column chromatography (5:95, ether: pentane) yielded the pure product E-8 as colorless oil with an isolated yield of 61%. 1H NMR (400 MHz, CDCl3); δ (ppm): 6.46 (dd, J= 15.6 Hz, J= 10 Hz, 1H); 5.82 (d, J= 15.6 Hz, 1H), 5.79 (ddt, J= 17.2 Hz, J= 10 Hz, J= 6.4 Hz, 1H); 4.97 (m, 2H); 4.15 (q, J= 7.2 Hz, 2H); 2.13 (dt, J= 7.2 Hz, J= 7.2 Hz, 2H); 1.39 (m, 2H); 1.3 (m, 1H); 1.26 (t, J= 7.2 Hz, 3H); 1.01 (m, 1H); 0.8 (ddd, J= 9.2 Hz, J= 4.8 Hz, J= 4.4 Hz, 1H); 0.76 (m, 1H). 13C NMR (100 MHz, CDCl3); δ (ppm): 167.34 (1C, CO); 153.90 (1C, CH); 138.53 (1C, CH): 117.92 (1C, CH); 115.09 (1C, CH); 59.92 (1C, CH); 33.23
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(1C, CH); 32.87 (1C, CH); 22.56 (1C, CH2); 21.86 (1C, CH2); 15.7 (1C, CH3); 14.05 (1C, CH2). HR-MS (EI+) (m/z): found 195.138 [M+H]⁺, calculated 195.138 [M+H]⁺. [α]D = -84.6 (10 mg/mL in MeOH).

Ethyl 3-((1R,2R)-2-(but-3-en-1-yl)cyclopropyl)propanoate (3a). Cu(I)Cl (20 mol%) was added to a stirred solution of the unsaturated ester 8 (1 equiv) in MeOH (5 mL/ mmol). NaBH4 (6x 1 equiv) was carefully added in portions of 1 equiv (every 45 min) to the reaction mixture. Subsequently, the reaction was quenched with HCl (2 M aq. solution) until a pH of 4 was reached. The resulting mixture was filtered and diluted with ether (0.5 mL/ mmol). After separation of the layers the organic layer was washed with water, dried over MgSO₄ and carefully concentrated under reduced pressure. Flash column chromatography (5:95, ether:pentane) yielded the pure product 3a as a colorless oil with an isolated yield of 84%. ¹H NMR (400 MHz, CDCl₃); δ (ppm): 5.81 (ddt, J= 17.2 Hz, J= 10.4 Hz, J= 6.8 Hz, 1H); 4.95 (m, 2H); 4.1 (q, J= 7.2 Hz, 2H); 2.34 (t, J= 7.2 Hz, 2H); 2.08 (q, J= 7.2 Hz, 2H); 1.48 (m, 2H); 1.29 (m, 2H); 1.22 (t, J= 7.2 Hz, 3H); 0.41 (m, 2H); 0.18 (t, J= 6.4 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃); δ (ppm): 174.33 (1C, CO); 139.31 (1C, CH); 114.59 (1C, CH2); 60.15 (1C, CH2); 34.34 (1C, CH2); 33.42 (1C, CH2); 29.46 (1C, CH2); 18.17 (1C, CH); 18.01 (1C, CH); 13.99 (1C, CH3); 11.58 (1C, CH2). HR-MS (EI+) (m/z): found 197.154 [M+H]+, calculated 197.154 [M+H]+. [α]D = -50.8 (10 mg/ mL in MeOH).

Ethyl 3-((1R,2R)-2-(3-hydroxypropyl)cyclopropyl)propanoate (20). A dried tree neck flask equipped with a stirring bar and an inlet tube was connected to a gas-washing bottle filled with an aq. KI solution. The ozone generator was connected to the inlet tube.

The olefin 3a (1 equiv) was dissolved under inert atmosphere in a mixture of EtOH and CH₂Cl₂ (1:1, 20 mL/ mmol). After cooling to -78°C a slow stream of O₃ was passing through the solution until a blue color remains. Before quenching the reaction with NaBH₄ (1.5 equiv) at -78 °C the solution was flushed with N₂ to remove the excess of O₃. The reaction mixture was stirred for 30 min at rt, an aq. HCl solution (2 M, pH 5) was added and diluted with CH₂Cl₂ (0.5 mL/ mmol). After separation of the phases the aq. layer was extracted with CH₂Cl₂ (1 mL/ mmol). Subsequently, the combined organic layers were washed with water, dried over MgSO₄ and carefully concentrated under reduced pressure. Flash column chromatography (1:1, ether:pentane) yielded the pure product 20 as a colorless oil with a yield of 86%. ¹H NMR (400 MHz, CDCl₃); δ (ppm): 4.13 (q, J= 7.2 Hz, 2H); 3.67 (t, J= 6.8 Hz, 2H); 2.38 (t, J= 7.6 Hz, 2H); 1.66 (qi, J= 7.2 Hz, 2H); 1.54 (qi, J= 7.6 Hz, 2H); 1.31 (m, 2H); 1.39 (m, 2H); 1.26 (t, J= 7.2 Hz, 3H); 0.47 (m, 2H); 0.24 (m, 2H). ¹³C NMR (100 MHz, CDCl₃); δ (ppm): 174.47 (1C, CO); 62.59 (1C, CH2); 60.25 (1C, CH2); 34.32 (1C, CH2); 32.48 (1C, CH2); 30.08 (1C, CH2); 29.40 (1C, CH2); 18.10 (1C, CH); 17.99 (1C, CH); 13.96 (1C, CH3); 11.56 (1C, CH2). HR-MS (EI+) (m/z): found 201.149 [M+H]+, calculated 201.149 [M+H]+. [α]D = -7.2 (10 mg/ mL in MeOH).
Ethyl 3-\((1R,2R)-2\)-(3-bromopropyl)cyclopropyl)propanoate (21). CBr₄ (2 equiv) was added to a solution of the alcohol 20 (1 equiv) in ether (10 mL/mmol). The reaction mixture was cooled to 0 °C and PPh₃ (2 equiv) was added in portions. After stirring for 6 h the solution was filtered and washed with ether. The combined organic layers were washed with water, dried over MgSO₄ and carefully concentrated under reduced pressure. Flash column chromatography (1:1, ether:pentane) yielded the pure product 20 as a colorless oil with a yield of 76%. ¹H NMR (400 MHz, CDCl₃); δ (ppm): 4.12 (q, J= 7.2 Hz, 2H); 3.41 (t, J= 6.8 Hz, 2H), 2.35 (t, J= 8 Hz, 2H), 1.91 (qi, J= 7.2 Hz, 2H); 1.52 (q, J= 8 Hz, 2H); 1.32 (qi, J= 6.8 Hz, 2H); 1.24 (t, J= 7.2 Hz, 3H); 0.44 (m, 2H); 0.23 (t, J= 7.2 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃); δ (ppm): 174.25 (1C, CO); 60.28 (1C, CH₂); 34.33 (1C, CH₂); 33.63 (1C, CH₂); 32.73 (1C, CH₂); 32.32 (1C, CH₂); 29.39 (1C, CH₂); 17.97 (1C, CH); 17.63 (1C, CH); 14.06 (1C, CH₃); 11.52 (1C, CH₂). HR-MS (EI⁺) (m/z): found 263.064 [M(79Br)+H]+, 265.062 [M(81Br)+H]+, calculated 263.064 [M(79Br)+H]+, 265.062 [M(81Br)+H]+. [α]D = -13.5 (10 mg/ mL in MeOH).

(3-\((1R,2R)-2\)-(3-Ethoxy-3-oxopropyl)cyclopropyl)propyl)triphenylphosphonium bromide (3b). PPh₃ (1 equiv) and the bromide 21 (1 equiv) were heated for 16 h at 100 °C. The obtained mixture was washed with anhydrous pentane and used after drying without further purification. ¹H NMR (400 MHz, CDCl₃); δ (ppm): 7.77 (dd, J= 12.8 Hz, J= 8 Hz, 6H); 7.73 (t, J= 7.2 Hz, 3H); 7.64 (m, 6H); 7.64 (m, 6H); 7.64 (m, 6H); 7.64 (m, 6H); 3.72 (m, 2H), 2.21 (q, J= 6.4 Hz, 2H), 1.65 (m, 2H); 1.53 (m, 2H); 1.42 (m, 2H); 1.16 (q, J= 7.2 Hz, 3H); 0.41 (m, 2H); 0.16 (m, 2H). ³¹P-NMR (CDCl₃, 162 MHZ); δ (ppm): 24.61. HR-MS (EI⁺) (m/z): found 445.229 [M-Br⁻]+, calculated 445.229 [M-Br⁻]+.

Ethyl 3-\((1R,2R)-2\)-(3-Ethoxy-3-oxopropyl)cyclopropyl)propyl)cyclopropyl)propanoate (22).

Strategy 1: Cross metathesis
A solution of the alkene 2a (1.5 equiv) and the alkene 3a (1 equiv) in toluene (2 mL/ mmol) was added to a solution of the ruthenium catalyst (5 mol%) and dichlorobenzonitrile (10 mol%) in toluene (16 mL/ mmol). The resulting reaction mixture was heated at reflux for 16 h after it was stirred for 20 min at rt. Subsequently, the reaction was quenched at rt with ethylvinylether and the mixture stirred for an additional 20 min at this temperature. The resulting solution was dried over MgSO₄ and carefully concentrated under reduced pressure. Flash column chromatography (1:99, ether:pentane) yielded the pure product 22 as a colorless oil with a yield lower that 10% as a diastereomer mixture (E:Z, 2:1). Note: Changes of the substrate ratio, solvent, temperature, catalyst loading and of the ruthenium catalyst were not leading to improved yields. Instead the amount of both homodimers 23 and 24 increased resulting in a product mixture of 22, 23 and 24, which was challenging to purify.
Strategy 2: Wittig reaction

Triphenylphosphonium bromide 3b (1 equiv) was dissolved in anhydrous THF (10 mL/ mmol) and the solution cooled to -78 °C. nBuLi (1.6M, 1.2 equiv) was added dropwise and the resulting reaction mixture was stirred for 1 h at this temperature. Subsequently, the mixture was warmed up slowly to 0 °C, stirred for additionally 30 min and was cooled again to -78 °C. The aldehyde 2b (1 equiv) was dropwise added and the solution was stirred for additional 1 h at this temperature before it was quenched by adding HCl (1M, 10 mL/ mmol). This was followed, by an extraction with CH₂Cl₂ (3*10 mL/ mmol). The combined organic layers were dried over MgSO₄ and carefully concentrated under reduced pressure. Flash column chromatography (1:99, ether: pentane) yielded the pure colorless oil 22 with a yield of 43% as a diastereomer mixture (E:Z, 1:3). Further isomerization of the diastereoisomers was performed. Therefore, a solution of 22 and iodine (1 crystal for 20 mg of 22) in CHCl₃ (2 mL/ mmol) was heated for 30 min at 40 °C. The excess of iodine was destroyed by adding Na₂S₂O₃ (sat. solution, 1 mL/ mmol). The resulting solution was extracted with CHCl₃ (2 mL/ mmol), dried over MgSO₄ and carefully concentrated under reduced pressure yielding in the E-isomer of 22 (less than 10% of the Z-isomer remains). ¹H NMR (400 MHz, CDCl₃); δ (ppm): 6.29 (q, J= 14.8 Hz, J= 10, 1H); 6.19 (d, J= 14.8 Hz, J= 7.2 Hz, 1H), 4.11 (q, J= 7.2 Hz, 2H); 2.44 (t, J= 7.2 Hz, 2H); 2.36 (t, J= 7.2 Hz, 2H); 2.19 (q, J= 7.2 Hz, 2H); 1.59 (m, 3H); 1.53 (m, 2H); 1.37 (qi, J= 6.8 Hz, 1H); 1.25 (t, J= 7.2 Hz, 3H); 0.91 (t, J= 7.6 Hz, 3H); 0.46 (m, 2H); 0.23 (t, J= 6.4 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃); δ (ppm): 173.85 (1C, CO); 136.89 (1C, CH); 128.17 (1C, CH); 127.90 (1C, CH); 127.04 (1C, CBr); 60.32 (1C, CH₂); 43.75 (1C, CH₂); 34.63 (1C, CH₂); 33.87 (1C, CH₂); 33.12 (1C, CH₂); 29.73 (1C, CH₂); 21.60 (1C, CH₂); 18.56 (1C, CH); 18.44 (1C, CH); 14.40 (1C, CH₃); 13.1 (1C, CH₃); 12.03 (1C, CH₂). HR-MS (EI+) (m/z): found 343.127 [M(⁷⁹Br)+H]⁺, 345.125 [M(⁸¹Br)+H]⁺, calculated 343.127 [M(⁷⁹Br)+H]⁺, 345.125 [M(⁸¹Br)+H]⁺. [α]D = -6 (10 mg/ mL in MeOH).
3-((1R,2R)-2-((3E,5Z)-6-Bromona-3,5-dien-1-yl)cyclopropyl)propanoic acid (majusculoic acid) (1). The ethyl ester 22 was dissolved in MeOH and NaOH (1M, 1mL/mmol) was added. The solution was stirred for 2 h at rt before extraction with ether (3*2 mL/mmol) took place. The combined organic layer were dried over MgSO4 and carefully concentrated under reduced pressure. The majusculoic acid 1 was isolated as a colorless solid with a yield of 82%. HR-MS (EI+) (m/z): found 315.095 [M(79Br)+H]+, 317.093 [M(81Br)+H]+, calculated 315.095 [M(79Br)+H]+, 317.093 [M(81Br)+H]+. $[\alpha]_D = -16.2$ (10 mg/mL in MeOH).

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*Weak signals. **Number of the corresponding carbon atom is given.
4.5 References


