Chapter 6

Synthesis of a putative sex pheromone of *Trichogramma turkestanica*

*In this chapter, the asymmetric synthesis of a putative sex pheromone of the parasitoid wasp Trichogramma turkestanica is reported. Using a previously established iterative approach, three methyl ramifications were introduced stereoselectively in a 1,3-syn fashion. The availability of this putative pheromone should allow the further structure elucidation, in particular the stereochemistry, of the natural product. This, in turn, will assist entomologists to determine whether the isolated compound actually is a sex pheromone of Trichogramma turkestanica.*

The work in this chapter was carried out in collaboration with Jeffrey Buter, as part of his M.Sc. research project.
6.1 Introduction

Pheromones are essential messenger molecules in our ecosystem and used for a wide diversity of purposes. The communication, in particular within insect species, occurs by means of the secretion of (mostly) volatile compounds and the recognition thereof, which triggers a response. Some common types of pheromones are necromones, which indicate a dead individual, trail pheromones, which can track back a path to food, or territorial pheromones indicating the boundaries of a territory. In addition to these, the most important pheromones for the reproduction of insect species are sex pheromones.\[1\]

In 2005, the isolation and partial characterization of two sex pheromones, isolated from the virgin females of *Trichogramma turkestanica*, a parasitoid wasp, was reported by van Beek *et al.*\[2\] These wasps, belonging to the large Trichogrammatidae family, are minute in size (0.2 – 1.5 mm) and characterization of the family members, whose appearance is very alike, is therefore difficult.\[3\] For the reproduction, the female wasp plants her fertilized eggs inside the egg of a host insect, which functions as a food source for the hatched wasps.\[4\]

![Figure 6.1 Initial structural assignment of the putative sex pheromones](image)

Preliminary biological studies revealed that only virgin females, were able to trigger casting behavior at males. This response led to the assumption that virgin females of *Trichogramma turkestanica* produce sex pheromones. The analysis of an isolate of virgin females showed the presence of two major components, which, after derivatization studies and extensive analysis, were initially identified as a diene and a dienol (Figure 6.1).\[2\] It is hypothesized that these compounds are sex pheromones. Although the analysis revealed the presence of a conjugated diene in both strongly related compounds, the configuration of these double bonds could not be established beyond doubt. However, due to a personal communication, we are now aware of the fact that the initially proposed structures do not represent the actual, isolated compounds. Careful analysis of the mass spectra and comparison with those of previously synthesized racemic compounds, have revealed a slightly different substitution pattern of the methyl ramifications. The now anticipated structures are represented by \textbf{6.1 and 6.2} (Figure 6.2).
Besides the molecular structure, the absolute and relative stereochemistry of the chiral 1,3-methyl ramifications has not been elucidated to date. Based on the biosynthesis of polypropionates (polyketides), it can be assumed with some confidence that the configuration of the methyl groups is all-syn.

![Figure 6.2 Structures of the putative sex pheromones of Trichogramma turkestanica](image)

Elucidation of the (sex) pheromones of each species could lead to a platform, which ensures more facile identification. A drawback is that pheromones are not always species-specific. However, the ratio of the volatiles most often is species-specific. In addition to the use of sex pheromones in species identification, a more interesting application from a financial point of view, is its use in crop protection.[5]

As the isolation of sex pheromones is difficult and the isolated amounts are minute, a stereoselective chemical synthesis would afford larger quantities for thorough studies on their exact structure and function.

### 6.2 Reported syntheses of the *Trichogramma turkestanica* sex pheromones

To date, no enantioselective synthesis of either 6.1 or 6.2 has been reported. However, by personal communication we are aware of an existing synthesis of both compounds with all-syn stereochemistry as a racemic mixture. These syntheses were developed by the group of Francke in Hamburg, in order to elucidate the structure of the pheromones.[6] Both racemates will be used to identify the relative stereochemistry of the methyl array, and the configuration of the double bonds. Initial experiments have shown that the synthesized (E,E)-isomer and the natural product have identical retention times on GC, strongly indicating a (2E,4E)-configuration of 6.2 and most likely also 6.1.

### 6.3 Strategy

The desire to elucidate the absolute stereochemistry of the 1,3-methyl array in 6.1 and 6.2 calls for the preparation of these compounds using our earlier reported iterative conjugate addition strategy.[7] The asymmetric copper-catalyzed conjugate addition of methylmagnesium bromide to α,β-unsaturated thioesters has proven its versatility in the
creation of methyl arrays multiple times. For the subsequent introduction of the diene, we reasoned that the use of stabilized Wittig reactions or HWE olefinations would allow a stepwise approach to the target molecules. However, to minimize synthetic effort, alternatives were studied first.

6.4 Synthesis

6.4.1 Construction of the all-syn 1,3-methyl array

Following the same strategy as for the synthesis of phthioceranic acid (Chapter 2), compound 6.4 was prepared in excellent stereoselectivity, as judged by $^1$H-NMR spectroscopy, and high yield over four steps (Scheme 6.1). Addition of the third methyl ramification was performed on $\alpha,\beta$-unsaturated ketone 6.3 with the knowledge that the ketone moiety could be more easily cleaved afterwards, leaving an $n$-propyl chain. Using identical conditions as used for the conjugate addition to thioesters, 6.4 was obtained in 92% yield.

Scheme 6.1 Introduction of three methyl ramifications

To remove the ketone functionality, several strategies were investigated. Initially, an attempt was made to obtain 6.6 using the Myers modification of the Wolf-Kishner reduction (Scheme 6.2). This modification was chosen since it allows the removal of the silylhydrazone at much lower temperatures than the originally reported procedure.
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Scheme 6.2 Myers modification of the Wolf-Kishner reduction

(180 – 200 °C) for the hydrazone. After the presumed construction of silylhydrazone 6.5, the basic conditions used afforded a mixture of multiple products with no apparent formation of 6.6.

Next, we turned our attention to the Caglioti modification of the Wolf-Kishner reduction (Scheme 6.3).

Although the reaction was executed multiple times, the isolated yield never exceeded 30%. As a result, also the Caglioti modification was discarded for further use.

Scheme 6.3 Caglioti modification of the Wolf-Kishner reduction

An alternative approach to remove isolated ketones is the two-step procedure developed by Mozingo. Treatment of the ketone with ethanedithiol in the presence of BF$_3$•Et$_2$O gave thio-ketal 6.8 (Scheme 6.4). Although the procedure was reported to be catalytic with respect to the amount of Lewis acid added, we found a linear correlation between the added amount and the conversion. We thus added 1.2 equivalent of Lewis acid, which afforded 6.6 in 84% isolated yield. For the cleavage of the thioacetal it proved to be important to prepare a fresh batch of (dry) Raney Nickel. An older, presumably wet batch afforded the desired 6.6, but in addition led to formation of 6.4 by hydrolysis. On the contrary, a fresh batch afforded 6.6 in 82% yield.
6.4.2 A first attempt: the use of a vinylogous HWE reaction

To introduce the diene moiety, we relied on a procedure by Markiewicz et al. who reported the use of a vinylogous HWE olefination to introduce the diene in a single step.\[^{13}\]

To this end, reagent 6.11 was prepared in a two-step procedure (Scheme 6.5). Starting from methyl trans-2-pentenoate (6.9), a Whol-Ziegler γ-bromination afforded 6.10. Direct addition of triethyl phosphite to the reaction mixture in the succeeding step led to no conversion. Because the Arbuzov-Michaelis reaction was reported at a high concentration of the reagents, 6.10 (bp = 72 °C) was concentrated using fractional distillation. Although still some benzene remained, HWE reagent 6.11 could now be obtained in 35% yield as a 1:1 mixture of regioisomers.

Although lower than the reported 50% yield, sufficient material was available to proceed. Thus, silyl ether 6.6 was cleaved using TBAF affording 6.12 in 89% yield (Scheme 6.6). A Ley oxidation gave 6.13 in quantitative yield which was subjected to the

\[ TBAF (3 \text{ eq.)}, \quad \text{THF, 5 h, 88%} \]

\[ \text{TBDPSO, THF, 1 h, quant.} \]

\[ \text{Scheme 6.5 Preparation of a HWE reagent for a vinylogous HWE olefination} \]

\[ \text{Scheme 6.6 Vinylogous HWE olefination} \]
reported conditions for the vinylogous HWE oleination.\cite{14} Dienoate 6.14 could be isolated in 75% yield, but as a 1:1 mixture of (2E,4E)- and (2Z,4E)-isomers.

In addition, an impurity was observed in the $^1$H-NMR spectrum which appeared as a multiplet between 5.00 and 5.45 ppm, indicative for the formation of a double bond regioisomer, although no direct proof could be obtained for this assumption. Although minimal amounts of pure (Z,E)-6.14 could be obtained using flash chromatography, (E,E)-6.14 could not be separated from the impurity. Therefore we decided to continue to the last step with the mixture, as in our experience with similar compounds, separation of the more polar alcohols would be more facile.

As expected, 6.14 could be reduced to dienol 6.15 using DIBALH at low temperature (Scheme 6.7). After work-up, crude 6.15 was obtained in an excellent 96% yield. TLC analysis indeed showed a much better separation of the alcohols than that of the esters in the previous step. However, upon purification with flash column chromatography on silica, $^1$H-NMR indicated the formation of a side-product around 4.0 ppm in both isomers. After a second chromatographic purification, the side-product became even more apparent. The side-product was present in both regio-isomers and proved inseparable from the desired products. We reasoned that the acidity of the silica caused degradation of 6.15, something reported earlier for similar molecules.\cite{15} However, purification over neutral aluminium oxide led to complete degradation of the product and the appearance of signals around 7.5 ppm in $^1$H-NMR. Although the pure product could not be isolated via this approach, at least we learned that purification of 6.15 should be avoided. A considerable roadblock as this purification should also include the separation of the double bond isomers.

![Scheme 6.7](image)

**Scheme 6.7** Formation of the putative sex pheromone

### 6.4.3 A second attempt: the stepwise approach using Wittig reactions

Although the first approach was efficient in terms of the number of steps, the separation of the double-bond isomers of dienoate 6.14 proved not viable by standard purification techniques and we reconsidered our approach. We realized that a stepwise synthesis
would allow more variation in the steps and offer more purification opportunities. In addition, if the penultimate step affording 6.14 could be a standard highly (E)-selective HWE olefination, the separation of double-bond isomers should be unnecessary. Reduction of 6.14 should then, after work-up, afford 6.15 without the need for purification.

To this end, 6.13 was prepared again and allowed to react in a Wittig reaction with commercially available 6.16 (Scheme 6.8). Although 6.17 could be obtained in moderate yield, ~39% (based on integration) of an impurity was detected by 1H-NMR spectroscopy as a set of multiplets between 4.95 and 5.45 ppm. When Wittig reagent 6.16 was recrystallized twice, the impurity could be reduced to 6.5%. Analysis of the commercial Wittig reagent (Sigma Aldrich, 94% pure) by 1H-NMR spectroscopy showed no evidence of organic impurities.

\[
\begin{align*}
\text{O} & \quad \text{Ph}_2\text{P} & \quad \text{O} \\
\text{6.13} & \quad \text{OEt} & \quad \text{6.16} \\
\text{DCM, 40 h} & \quad 63\% + \text{impurities} & \quad \text{EtO} \\
\text{O} & \quad \text{6.17}
\end{align*}
\]

\text{Scheme 6.8 Synthesis of α,β-unsaturated ester 6.17 using a Wittig reaction}

Given that a previous synthesis from our group had been carried out with freshly prepared 6.16, the Wittig reagent was prepared following this procedure, starting from ethyl 2-bromopropionate.\textsuperscript{[16]} Unfortunately, the Wittig reaction with 6.13 still gave rise to the formation of the same impurity. Although 1H-NMR and GC-MS analysis gave no conclusive evidence for the structure of the impurity, out-of-conjugation isomerization of the double bond could be a valid explanation for the observed chemical shift. As the impurity could not be removed using flash column chromatography, the subsequent reduction with DIBALH was performed with the mixture of products (Scheme 6.9). Allylic alcohol 6.18 was obtained in 97% yield, but could still not be separated from its impurity. Also aldehyde 6.19, obtained quantitatively after a Ley-Griffith oxidation contained the same impurity. These findings supported our hypothesis that the molecular structure of the side-product is very similar. To obtain dienoate 6.14, yet another subsequent Wittig reaction was performed. The reaction proved to be slow at room temperature as considerable amounts of starting aldehyde 6.19 were left after 17 h. Eventually, a large excess of ylide, combined with an
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Scheme 6.9 Stepwise preparation of dienoate 6.14 using Wittig reactions

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Elevated temperature were needed to achieve a conversion of 94% after six days. After purification, 6.14 was obtained in 47% yield, but still contained the inseparable impurity. As it was known that the final product could not be purified using column chromatography the synthesis via the second approach was discontinued.

6.4.4 A third attempt: the stepwise approach using HWE reactions

As the Wittig reaction of 6.13 did afford 6.17, although with the mutual formation of an inseparable side-product, we were curious how the HWE olefination towards 6.17 would perform. Thus, aldehyde 6.13 was prepared and subjected to deprotonated 6.20 (Scheme 6.10). The HWE olefination proved to be much faster, but afforded 6.17 as a 1:1 mixture of (E)- and (Z)-isomers as determined by 1H-NMR spectroscopy. This was attributed to a destabilizing interaction of the α-methyl moiety from the HWE reagent in the transient four-centered intermediate, leading to a mixture of kinetic (Z)- and thermodynamic (E)-olefin. The impurity previously observed as a result of the Wittig reaction fortunately was not present. In addition, the (E)- and (Z)-isomers could be separated using column chromatography affording pure (E)-6.17 in 45% yield. Reduction of 6.17 was achieved using DIBALH, affording allylic alcohol 6.18 in 90% yield, which in turn was oxidized to aldehyde 6.19 using Dess-Martin periodinane (Scheme 6.11). Given that the conversion of

Scheme 6.10 Synthesis of α,β-unsaturated ester 6.17 using a HWE olefination
6.19 into 6.14 using Wittig reaction had proven to be sluggish, we switched to a HWE olefination, expecting to prepare 6.14 with high (E)-selectivity and, with some luck, in a reduced reaction time. Indeed, 6.14 was obtained in 64% yield over two steps, as the pure (E,E)-isomer. Reduction of pure 6.14 with DIBALH finally afforded 6.1 in 96% yield after work-up. Overall, 6.1 was obtained in 4.4% yield over 16 linear steps.

Overall, 6.1 was obtained in 4.4% yield over 16 linear steps.

6.5 Conclusions

After two unsuccessful attempts to obtain a pure sample of 6.1, the third approach, using two HWE olefinations to install the diene moiety, proved to be effective. Although the route via a vinylogous HWE olefination allows a drastic shortcut to 6.1, the simultaneous formation of an inseparable side-product proved to be the bottleneck for this approach. In the second approach a similar looking side-product was formed in the formation of the first unsaturation using a Wittig reaction, as judged by 1H-NMR spectroscopy. Whether the prolonged reaction times, compared to the stepwise third approach using a HWE olefination, is causing the formation of the impurity is not clear. The precise structure of this impurity could not be elucidated, however. As we were unable to separate it from the products in multiple stages of the reaction pathway, we believe that their structures must be very alike. An isomerization of a double bond could account for this behavior.

6.6 Outlook

With the preparation of (E,E-S,S,S)-6.1, one of the isolated sex pheromones has been prepared. However, as mentioned above, the absolute and relative stereochemistry of
natural 6.1 are unknown. Comparison of the now available enantiopure 6.1 using chiral GC analysis with an earlier synthesized racemic mixture of 6.1 by Francke et al., and the natural material, will hopefully provide an answer to these questions.

After these problems have been addressed, we also aim to prepare the deoxygenated analogue 6.2. A possibility to do so could be the reductive deoxygenation of 6.1, to directly afford 6.2 (Scheme 6.12). This approach has been studied by Mori et al. in the synthesis of a sex pheromone of the Israeli pine bast scale, Matsucoccus josephi (Scheme 6.12).[17] Transforming the depicted diol into its dimesylate, followed by treatment with LiHBEt3 afforded the desired deoxygenated product. However, this approach presumably led to partial isomerization of the double bond.

As an alternative, the stepwise introduction of the diene using a Wittig reaction could afford 6.2. As the required ylide is not stabilized, this should lead to the unwanted (Z)-isomer. A Schlosser modification, favoring the thermodynamic (E)-isomer, could address this problem (Scheme 6.13).[18]

Another approach to 6.2 would be to use an olefination strategy developed by Buss and Warren,[19] and applied to the total synthesis of the sex pheromone of the red pine scale Matsucoccus resinosae and the Japanese pine scale Matsucoccus matsumurae by Mori (Scheme 6.14).[20] In this case, a β-ketophosphine oxide is prepared by α-deprotonation of diphenylethylphosphine oxide, followed by addition to an α,β-unsaturated ester. A Luche reduction of the ketone afforded a 4:1 mixture of threo and erythro β-hydroxyphosphine oxides,[21] which could be separated using column chromatography. The reason for the observed selectivity is most likely the simultaneous chelation of cerium by the ketone and the phosphine oxide. Treatment of the threo intermediate with NaH allowed
the selective formation of the (E)-alkene in high yield. As the compounds in this study are structurally very similar to intermediates in our current synthesis towards the pheromone of *Trichogramma turkestanica*, this approach would be worthwhile to look into in future research.

6.7 Experimental section

For general experimental information: see Chapter 2.

**General procedure for the preparation of Raney nickel (procedure A)**

An aqueous solution of NaOH (6.4 M, 500 mL) was cooled with an ice/salt bath. To the cooled solution a nickel/aluminum alloy (Ni:Al = 50:50, 100 g) was added in small portions over 2 h. The temperature was never allowed to rise above 15 °C. After addition, the ice/salt bath was removed and the suspension was allowed to warm to rt. The water was decanted and an aqueous solution of NaOH (2.5 M, 200 mL) was added to the residue. Stirring was applied for 15 min, whereafter the suspension was allowed to settle. Decantation of the alkali solution was performed and the residue was washed with water. Washing and decantation was repeated until the washings were pH-neutral. The Raney nickel residue was washed with three portions of EtOH (95%, 600 mL) and three times with absolute EtOH (600 mL). The Raney Nickel was stored under absolute ethanol.

**General procedure for the Ley oxidation of primary alcohols (procedure B)**

To a stirred solution of alcohol in dry DCM were added freshly activated 4 Å molecular sieves (200 mg), *N*-methylmorpholine *N*-oxide (NMO, 2.1 eq.) and tetrapropylammonium perruthenate (TPAP, 5 mol%). The solution was stirred for 1 h whereafter it was flushed over a pad of silica with pentane/Et₂O (1:1). The filtrate was concentrated under reduced pressure affording the corresponding aldehyde.

*(4R,6S,8S)-9-((tert-butyldiphenylsilyl)oxy)-4,6,8-trimethylnonan-2-one (6.4):* *(R,S⁶)-Josiphos•CuBr complex L2.2* (29.7 mg, 0.04 mmol, 1 mol%)
was dissolved in t-BuOMe (25 mL) under a nitrogen atmosphere. The mixture was cooled to –80 °C and methylmagnesium bromide (1.60 mL, 4.80 mmol, 3 M in Et2O, 1.2 equiv.) was added dropwise over 15 min. After stirring for an additional 20 min, a solution of ketone 6.3[8] (1.69 g, 4.00 mmol) in t-BuOMe (6.8 mL) was added over 1.5 h using a syringe pump. The reaction mixture was stirred at –80 °C for 18 h, then quenched by addition of MeOH (25 mL) and allowed to warm to rt. Saturated aq. NH4Cl solution (35 mL) was then added. After phase separation and three extractions of the aqueous phase with Et2O (120 mL), the combined organic phases were dried over Na2SO4, filtered, concentrated under reduced pressure and purified by flash chromatography (pentane/Et2O 7:1) to afford 6.4 a colorless oil (1.21 g, 91% yield, syn/anti ratio by 1H-NMR = 98:2).[8]

1H NMR (400 MHz, CDCl3) δ 7.73 – 7.54 (m, 4H), 7.54 – 7.31 (m, 6H), 3.51 (dd, J = 9.8, 5.1, 1H), 3.41 (dd, J = 9.8, 6.5, 1H), 2.47 – 2.28 (m, 1H), 2.18 – 1.98 (m, 5H), 1.81 – 1.64 (m, 1H), 1.51 – 1.41 (m, 1H), 1.41 – 1.33 (m, 1H), 1.19 – 1.11 (m, 1H), 1.10 – 1.05 (m, 1H), 1.06 (s, 9H), 0.98-0.88 (m, 1H), 0.93 (d, J = 6.6, 3H), 0.85 (d, J = 6.2, 3H), 0.82 (d, J = 6.4, 3H); 13C NMR (101 MHz, CDCl3) δ 209.15, 135.64, 135.61, 134.05, 134.02, 129.51, 127.57, 68.74, 50.85, 45.01, 41.20, 33.10, 30.43, 27.64, 26.90, 26.78, 20.75, 20.60, 19.32, 18.06; HRMS-(ESI+) for C28H42O2Si [M + H]+ calculated 439.3032, found 439.3027.

tert-butyldiphenyl(((2S,4S,6R)-2,4,6-trimethyl-7-(2-methyl-1,3-dithiolan-2-yl)heptyloxy)silane (6.8): Ketone 6.4 (0.50 g, 1.3 mmol) and ethanedithiol (0.27 g, 2.9 mmol, 2.3 eq.) were dissolved in dry DCM (25 mL) and cooled with an ice/salt bath. To the cooled solution were added 4 Å molecular sieves and BF3·OEt2 (0.204 g, 1.44 mmol, 1.2 equiv). The resulting solution was allowed to warm to rt and was stirred 15 h under a nitrogen atmosphere. The reaction mixture was quenched with an aqueous solution of 5% NaOH (10 mL). After phase separation, the aqueous phase was extracted three times with DCM (75 mL). The organic phase was dried using Na2SO4, filtered and concentrated under reduced pressure. Flash chromatography was performed (pentane/Et2O 25:1) to isolate 6.8 as a colorless oil (0.49 g, 84% yield).

1H NMR (400 MHz, CDCl3) δ 7.74 – 7.67 (m, 4H), 7.49 – 7.36 (m, 6H), 3.56 (dd, J = 9.8, 5.0, 1H), 3.46 (dd, J = 9.8, 6.5, 1H), 3.39 – 3.26 (m, 4H), 2.06 – 2.02 (m, 1H), 1.83 – 1.71 (m, 6H), 1.60 – 1.51 (m, 1H), 1.47 – 1.38 (m, 1H), 1.32 (m, 1H), 1.10 (s, 9H), 1.02 (d, J = 6.3, 3H), 0.98 (d, J = 6.7, 3H), 0.96 – 0.90 (m, 2H), 0.88 (d, J = 6.5, 3H); 13C NMR (101 MHz, CDCl3) δ 135.57, 135.56, 134.37, 134.33, 134.02, 130.17, 129.42, 127.83, 127.52, 68.70, 66.79, 51.78, 46.91, 41.09, 39.74, 39.03, 33.14, 33.02, 29.25, 27.66, 26.90, 25.97,
tert-butyldiphenyl(((2S,4S,6S)-2,4,6-trimethylnonyl)oxy)silane (6.6): To a solution of 6.8 (447 mg, 0.87 mmol) in dry EtOH (25 mL) was added an excess of freshly prepared Raney nickel. The reaction was refluxed for 8 h, cooled down to rt, and filtered over a SiO₂ column (pentane/Et₂O 5:1). The filtrate was dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography (pentane) afforded 6.6 as a colorless oil (300 mg, 82% yield).

1H NMR (400 MHz, CDCl₃) δ 7.93 – 7.65 (m, 4H), 7.65 – 7.38 (m, 6H), 3.61 (dd, J = 9.8, 5.0, 1H), 3.52 (dd, J = 9.7, 6.4, 1H), 1.83 (dt, J = 13.0, 6.6, 1H), 1.73 – 1.53 (m, 2H), 1.53 – 1.22 (m, 6H), 1.16 (s, 9H), 1.03 (d, J = 6.7, 3H), 0.98 – 0.93 (m, 5H), 0.92 (d, J = 3.6, 3H), 0.90 (d, J = 3.5, 3H); 13C NMR (101 MHz, CDCl₃) δ 135.95, 135.93, 134.74, 134.71, 134.42, 134.39, 130.54, 129.76, 128.19, 127.85, 69.10, 45.78, 41.76, 39.18, 33.51, 30.05, 27.93, 27.21, 26.30, 21.18, 20.84, 20.30, 19.63, 18.40, 14.77; HRMS-(ESI+) for C₂₈H₄₅O₅Si [M + H]⁺ calculated 425.3240 Da, found 425.3234 Da.

(2S,4S,6S)-2,4,6-trimethylnonan-1-ol (6.12): To a solution of 6.6 (300 mg, 0.71 mmol) in dry THF (10 mL), was added TBAF (2.1 mL, 2.1 mmol, 3.0 eq., 1 M solution in THF) under a nitrogen atmosphere. The resulting reaction mixture was stirred for 5 h whereafter it was concentrated under reduced pressure. Flash chromatography (eluent pentane/Et₂O 5:1) was performed to obtain 6.12 as a colorless oil (117 mg, 89% yield). The product contained trace amounts of siloxane.

1H NMR (400 MHz, CDCl₃) δ 3.51 (dd, J = 10.4, 4.9, 1H), 3.33 (dd, J = 10.3, 7.0, 1H), 1.80 – 1.64 (m, 2H), 1.60 – 1.43 (m, 2H), 1.39 – 1.11 (m, 6H), 0.91 (d, J = 6.6, 3H), 0.88 – 0.82 (m, 11H); 13C NMR (101 MHz, CDCl₃) δ 68.41, 45.36, 41.51, 39.03, 33.29, 29.94, 27.73, 21.11, 20.63, 20.14, 17.74, 14.61; HRMS-(ESI−) for C₁₂H₂₅O [M − H]⁻ calculated 185.1905 Da, found 185.1910 Da.

(2E,6S,8S,10S)-methyl 4,6,8,10-tetramethyltrideca-2,4-dienoate (6.14): Procedure 1. The Ley-oxidation of alcohol 6.12 (120 mg, 0.64 mmol) to the corresponding aldehyde with TPAP (12 mg, 32 μmol, 5 mol%) and NMO (156 mg, 1.33 mmol, 2.0 equiv) was performed according to procedure B. The aldehyde was obtained as a colorless oil (119 mg, quantitative yield) and used without further purification. To a cooled solution of phosphonate 6.11 (234 mg, 0.94 mmol, 1.5 equiv) in dry THF (6 mL) at −78 °C, lithium bis(trimethylsilyl)amide (LHMDS, 146 mg, 0.87 mmol, 1 m in THF, 1.4 eq.) was slowly
added under a nitrogen atmosphere. The resulting solution was allowed to warm to rt for 30 min whereafter the solution was cooled to –78 °C. To the cooled solution, aldehyde 6.13 (115 mg, 0.62 mmol) in dry THF (5 mL) was added dropwise. The reaction mixture was allowed to warm to rt and was stirred for 20 h. The reaction was quenched with a saturated aq. solution of NH₄Cl (1.5 mL) and Et₂O (10 mL) was added. After phase separation, the aqueous phase was extracted with Et₂O (3 x 30 mL) and the combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. Flash chromatography was performed (pentane/ether 50:1) but the E,E- and E,Z-isomers could not be completely separated. A colorless oil was isolated (131 mg, 75% yield) with a 1:1 ratio of dienoate isomers (E,E / E,Z) as observed by ¹H-NMR spectroscopy.

**Procedure 2:**
The Ley-oxidation of allyl alcohol 6.18 (30 mg, 0.12 mmol) to the corresponding aldehyde with TPAP (2.3 mg, 6.0 μmol, 5 mol%) and NMO (28 mg, 0.24 mmol, 2.0 eq.) was performed according to procedure B. The α,β-unsaturated aldehyde 6.19 was obtained as a colorless oil (119 mg, quantitative yield) and used without further purification. 6.19 (29 mg, 0.113 mmol) was then dissolved in dry DCM (5 mL) and methyl (triphenylphosphoranylidene)acetate (47 mg, 0.14 mmol, 1.2 equiv) was added. The resulting solution was stirred for 17 h under a nitrogen atmosphere. The reaction did not result in full conversion, even not after stirring for 3 h with 0.2 eq of additional phosphorane. The reaction mixture was concentrated under reduced pressure and flash chromatography (eluent pentane/ether 25:1) was performed. The obtained colorless oil proved to contain substantial amounts of α,β-unsaturated aldehyde 6.19. The crude oil was redissolved in dry benzene (6 mL) and methyl (triphenylphosphoranylidene)acetate (47 mg, 0.14 mmol, 1.2 eq) was added. The resulting solution was heated to 70 °C for 24 h under a nitrogen atmosphere. Incomplete conversion was observed and additional phosphorane (0.5 eq) was added. Heating was continued for another 48 h. Again significant amounts of starting material were present in the reaction mixture. Heating was continued with addition of in total 1.5 eq of phosphorane over 3 d. The reaction mixture was concentrated under reduced pressure and flash chromatography (pentane/Et₂O 50:1) was performed to obtain 6.14 (18 mg, 47%), containing approximately 6% of α,β-unsaturated aldehyde 6.19 as observed by ¹H-NMR.

(E,Z)-6.14: ¹H NMR (400 MHz, CDCl₃) δ 7.76 (d, J = 15.6 Hz, 1H), 5.88 (d, J = 15.7 Hz, 1H), 5.46 (d, J = 9.7 Hz, 1H), 3.76 (s, 3H), 2.86 (dt, J = 10.1 Hz, 5.7 Hz, 1H), 1.84 (s, 3H), 1.62 – 0.65 (m, 22H); ¹³C NMR (101 MHz, CDCl₃) δ 167.98, 146.38, 141.65, 129.36,
117.60, 51.47, 45.60, 44.72, 39.34, 29.98, 29.59, 27.93, 22.04, 20.36, 20.03, 19.97 - 19.94, 14.38; HRMS-(ESI+ ) for C_{18}H_{33}O_2 [M + H]^+ calculated 281.2481 Da, found 281.2436 Da.

(E,E)-6.14: ^1H NMR (400 MHz, CDCl₃) δ 7.31 (d, J = 15.7, 1H), 5.78 (d, J = 15.7, 1H), 5.63 (d, J = 9.6, 1H), 3.75 (s, 3H), 2.70 - 2.59 (m, 1H), 1.78 (s, 3H), 1.50 - 1.43 (m, 1H), 1.43 - 1.17 (m, 6H), 1.16 - 1.10 (m, 1H), 1.09 - 0.99 (m, 2H), 0.96 (d, J = 6.6, 3H), 0.87 (t, J = 7.2, 3H), 0.81 (d, J = 5.4, 3H), 0.79 (d, J = 5.6, 3H); ^13C NMR (101 MHz, CDCl₃) δ 167.64, 149.91, 148.63, 131.27, 115.48, 60.13, 45.69, 44.62, 39.33, 30.85, 29.62, 28.10, 21.22, 20.36, 20.04, 20.01, 14.39, 14.35, 12.34;

(4S,6S,8S,E)-ethyl 2,4,6,8-tetramethylundec-2-enoate (6.17): Procedure 1. To a stirred solution of aldehyde 6.13 (69 mg, 0.37 mmol) in DCM (15 mL) was added (carbethoxyethylidene) triphenylphosphorane 6.16 (244 mg, 0.67 mmol, 1.8 equiv). The resulting solution was stirred for 16 h under a nitrogen atmosphere, but the reaction did not proceed to full conversion. Additional 6.16 (0.5 eq) was added, and the reaction was extended for 24 h but full conversion was again not obtained. The resulting reaction mixture was concentrated under reduced pressure and flash chromatography (pentane/ether 25:1) was performed to afford the product as a colorless oil (64 mg, 63% yield). ^1H-NMR analysis showed a multiplet ranging from 4.9 to 5.4 ppm which corresponds to approximately 6.5% of an unidentified side-product.

Note: Washing the (carbethoxyethylidene)triphenylphosphorane 6.16 with an aqueous solution of 10% Na₂CO₃ followed by re-crystallization from EtOAc proved to reduce the formation of the unidentified product (39% vs. 6.5%).

Procedure 2. To a solution of 6.20 (1.8 eq, 42 μL, 0.20 mmol) in THF (1 mL) at 0 °C was added n-BuLi (1.4 eq, 95 μL, 0.15 mmol, 1.6 M solution in hexanes). After 15 min, aldehyde 6.13 (20 mg, 0.11 mmol, dissolved in 0.2 mL THF) was added. The reaction was allowed to stir for 8 h, after which ^1H-NMR indicated complete consumption of the starting material and showed the formation of a 1:1 E/Z-isomeric mixture. (E)-6.17 (13 mg, 45%) was obtained after careful column chromatography (pentane/Et₂O 150:1). ^1H NMR (400 MHz, CDCl₃) δ 6.53 – 6.47 (m, 1H), 4.25 – 4.09 (m, 2H), 2.69 – 2.54 (m, 1H), 1.85 (s, 3H), 1.52 – 1.43 (m, 1H), 1.38 – 1.15 (m, 9H), 1.21 (t, J = 7.0 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H), 0.91 – 0.86 (m, 6H), 0.84 – 0.80 (m, 3H); ^13C NMR (101 MHz, CDCl₃) δ 168.38, 148.16, 126.18, 60.29, 45.55, 44.30, 39.28, 38.87, 30.84, 29.58, 28.07, 20.59, 20.41, 19.95, 14.35, 14.25,
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12.44; HRMS- no successful mass analysis could be obtained.

(4S,6S,8S,E)-2,4,6,8-tetramethylundec-2-en-1-ol (6.18): To a solution of 6.17 (15 mg, 0.056 mmol) in DCM (2 mL) at -75 ºC was added DIBALH (3 eq, 0.17 mL, 1 M solution in DCM). After 1 h, TLC indicated complete conversion and the reaction was quenched with an aq. saturated Rochelle salt solution (2 mL). The product was extracted with Et2O (3 x 5 mL) and the combined organic layers were dried (MgSO4), filtered and all volatiles were evaporated. 6.18 (11.4 mg, 90%) was obtained as a colorless oil after filtration over a short silica plug (pentane/Et2O 20:1).

^1H NMR (400 MHz, CDCl3) δ 5.12 (d, J = 9.4 Hz, 1H), 3.98 (s, 2H), 3.45 (dd, J = 40.5 Hz, 5.9 Hz, 1H), 2.48 (m, 1H), 1.75 – 1.64 (m, 1H), 1.68 (s, 3H), 1.55 – 1.09 (m, 9H), 1.04 – 0.78 (m, 12H); ^13C NMR (101 MHz, CDCl3) δ 132.16, 132.11, 68.16, 44.65, 43.92, 38.36, 32.07, 28.61, 26.86, 20.69, 19.54, 19.05, 18.99, 13.40, 12.83; HRMS-(ESI+) for C15H31O [M + H]^+ calculated 227.2375 Da, found 227.2369 Da.

(2E,4E,6S,8S,10 )-ethyl 4,6,8,10-tetramethyltrideca-2,4-dienoate (6.14): To a stirred solution of 6.18 (11 mg, 0.049 mmol) in DCM (1 mL) was added DMP (1.5 eq, 0.16 mL, 0.073 mmol, 15 weight% solution in DCM). After 2 h, an aq. saturated solution of Na2S2O3 (5 mL) was added. Stirring was continued until both layers were clear and then the layers were separated. The aqueous layer was extracted with Et2O (2 x 5 mL) and the combined organic fractions were dried (MgSO4), filtered and concentrated. The crude aldehyde 6.19 was filtered over a short silica plug (pentane/Et2O 10:1) and used in the next step without further purification.

To a stirred solution of HWE reagent 6.21 (3 eq, 24 μL, 0.12 mmol) in THF (0.8 mL) at 0 ºC was added n-BuLi (2.2 eq, 55 μL, 0.088 mmol, 1.6 M solution in hexanes). After 15 min, aldehyde 6.19 (9 mg, 0.040 mmol) was added and after completion (3 – 4 h), the reaction was quenched with aq. saturated NH4Cl (1 mL). The mixture was extracted with Et2O (3 x 5 mL), dried (MgSO4), filtered and concentrated. The crude product was purified using column chromatography (pentane/Et2O 100:1) to afford pure 6.14 (7.5 mg, 64%) as a colorless oil.

^1H NMR (400 MHz, CDCl3) δ 7.31 (d, J = 15.7, 1H), 5.78 (d, J = 15.7, 1H), 5.63 (d, J = 9.6, 1H), 4.21 (q, J = 7.0, 2H), 2.70 -2.59 (m, 1H), 1.79 (s, 3H), 1.50 – 1.43 (m, 1H), 1.43 – 1.17 (m, 9H), 1.18 – 1.10 (m, 1H), 1.09 – 0.99 (m, 2H), 0.96 (d, J = 6.6, 3H), 0.87 (t, J = 7.2,
3H), 0.81 (d, J = 5.4, 3H), 0.79 (d, J = 5.6, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.64, 149.91, 148.63, 131.27, 115.48, 60.13, 45.69, 44.62, 39.33, 30.85, 29.62, 28.10, 21.22, 20.36, 20.01, 14.39, 14.35, 12.34; HRMS-(ESI–) for C$_{18}$H$_{33}$O$_2$ [M + H]$^+$ calculated 281.2481 Da, found 281.2473 Da.

$(2E,4E,6S,8S,10S)$-$4,6,8,10$-tetramethyltrideca-$2,4$-dien-$1$-ol (6.1): To a stirred solution of $^{6.14}$ (5 mg, 0.017 mmol) in DCM (1 mL) at –70 ºC was added DIBALH (3 eq, 0.051 mmol, 1 M solution in DCM). After 1 h, TLC indicated complete consumption of the starting material, and the reaction was quenched with an aq. saturated Rochelle salt solution (2 mL). The mixture was stirred until both layers were clear, and the product was extracted with Et$_2$O (3 x 5 mL). The combined organic layers were dried (MgSO$_4$), filtered and concentrated to afford $^{6.1}$ (4.1 mg, 96%) as a light-yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 6.26 (d, J = 15.6, 1H), 5.72 (dt, J = 15.6, 6.2, 1H), 5.22 (d, J = 9.6, 1H), 4.20 (dd, J = 6.2, 1.0, 2H), 2.64 – 2.55 (m, 1H), 2.10 – 1.94 (m, 1H), 1.77 (s, 3H), 1.71 – 1.52 (m, 2H), 1.52 – 1.10 (m, 6H), 1.04 – 0.96 (m, 1H), 0.93 (d, J = 6.6, 3H), 0.91 – 0.84 (m, 3H), 0.81 (d, J = 6.5, 3H), 0.80 (d, J = 6.6, 3H); HRMS-(ESI+) for C$_{17}$H$_{33}$O [M + H]$^+$ calculated 253.2531 Da, found 253.2526 Da.

6.8 References
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