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# Total Synthesis, Proof of Absolute Configuration, and Biosynthetic Origin of Stylopsal, the First Isolated Sex Pheromone of *Strepsiptera*

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*Dedicated to Professor Dr. Ekkehard Winterfeldt on the occasion of his 80th birthday*

**Abstract:** The asymmetric total synthesis of the diastereomers of stylopsal establishes the absolute configuration of the first reported sex pheromone of the twisted-wing parasite *Stylops muelleri* as (3*R*,5*R*,9*R*)-trimethyldodecanal. The key steps for the diastereo- and enantiodivergent introduction of the methyl groups are two different types of asymmetric conjugate addition reactions of organocopper reagents to α,β-unsaturated esters, whereas the dodecanal skeleton is assembled by Wittig reactions. The structure of the natural product was confirmed by chiral gas chromatography (GC) techniques, GC/MS and GC/electroantennography (EAD) as well as field tests. An investigation into the biosynthesis of the pheromone revealed that it is likely to be produced by decarboxylation of a 4,6,10-trimethyltridecanoic acid derivative, which was found in substantial amounts in the fat body of the female, but not in the host bee *Andrena vaga*. This triple-branched fatty acid precursor thus seems to be biosynthesized *de novo* through a polyketide pathway with two consecutive propionate-propionate-acetate assemblies to form the complete skeleton. The simplified, motionless and fully host-dependent female exploits a remarkable strategy to maximize its reproductive success by employing a relatively complex and potent sex pheromone.

**Keywords:** asymmetric synthesis · configuration determination · pheromones · total synthesis · Wittig reactions

## Introduction

The twisted-wing parasites (*Strepsiptera*) are a fascinating insect order, with all species being endoparasites of various insect *taxa* including silverfishes, bush-crickets, bees, wasps, and others.[1] They display an extreme sexual dimorphism:[2] the wingless larviform female is embedded in the host's abdomen with the cephalothorax protruding from it, whereas the male is a winged free-living insect with a very short lifespan of only a few hours.[3] The order *Strepsiptera* includes more than 400 species, of which almost 100 belong to the most diversified genus *Stylops* with all species being parasites of the bee genus *Andrena*.

Twisted-wing parasites belong to one of the least known groups of insects; males are very difficult to collect owing to their short lifespan, and the lack of helpful characteristics on females makes their identification very difficult. Mate-location is one of many unknowns; a very efficient signal must operate because of the short lifespan of males, which possess relatively large antennae.[4] Once hatched, males gather at the host's nesting sites to find a mate, and efficiently recognize host individuals with female parasites from a distance.[5]

We recently reported the isolation and partial configurational assignment of the sex pheromone of *Stylops muelleri*.[6,7] These investigations revealed the presence of a single-component pheromone, called stylopsal, having a constitution consistent with (9*R*)-3,5-*syn*-3,5,9-trimethyldodecanal (**1**; Figure 1). Because females of this insect produce 50–150 ng of pheromone *per individuum*, the amount of natural material available did not allow further characterization. Therefore, its relative and absolute configuration had to be derived from synthetic standards.

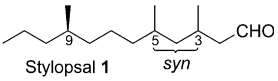


Figure 1. Constitution and configuration of stylopsal as reported in ref. [6].

The proposed constitution of stylopsal appeared surprising

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201204196. It contains experimental procedures, analytical data, copies of $^{1}H$ and $^{13}C$ NMR spectra of **1**, **3**, **6**, **7**, **10**–**14**, and **20**–**22**, comparison of the FAME content of the fat bodies of female *Stylops muelleri* and the host bee *Andrena vaga*, and chiral gas chromatograms of all diastereomers of **1**.


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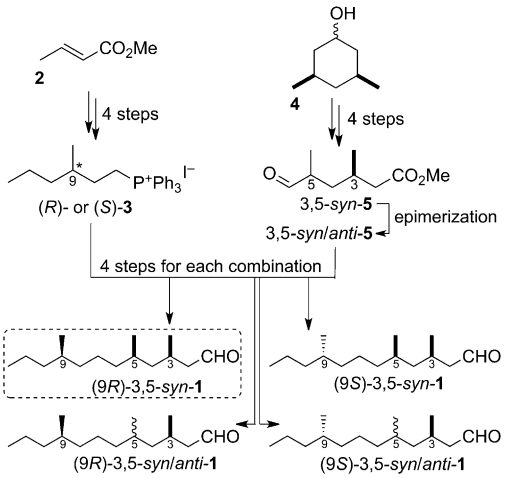
considering the three methyl branches. Although pheromones promoting sexual attraction in both sexes of various insects[8] display a relatively wide structural diversity, many of them are derived from palmitoyl-CoA formed in the fatty acid cycle and subsequently biosynthetically modified.[8,9,10] Terpenoid-derived pheromones aside, sex pheromones with methyl branching often contain one or two branches and are biosynthesized by polyketide pathways incorporating propionate, methylmalonate, or isovalerate units.[8,10] Exceptions exist, however; a few polyketide-derived insect female-released sex pheromones contain up to six methyl branches.[10,11]

To obtain as much information as possible on the constitution and configuration of stylopsal, while minimizing the synthetic effort, a partially racemic diastereodivergent synthesis was previously pursued (Scheme 1).[6] Because a late




Scheme 1. Stereodivergent partially racemic synthesis of synthetic standards **1** of stylopsal[6] (only one absolute configuration at C3 and C5 for compounds **1** and **5** is shown for clarity).

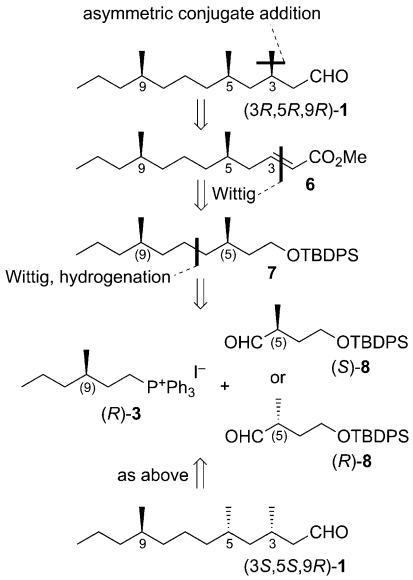
stage unequivocal determination of the configuration at the remote C9 center was felt impossible, the configuration at C9 was fixed from the beginning by an enantioselective conjugate addition to methyl crotonate (**2**).[12] Racemic aldehyde 3,5-*syn*-**5** was obtained in four steps from commercially available cyclohexanol **4**, whereas 3,5-*syn*/*anti*-**5** was obtained by partial epimerization of 3,5-*syn*-**5**. A Wittig coupling of fragments **5** and **3** followed by catalytic hydrogenation and functional group manipulations furnished four different diastereomers **1**. Chiral GC/MS, GC/EAD and bioassays revealed that stylopsal (**1**) has a configuration consistent with (9*R*)-3,5-*syn*-trimethyldodecanal. The mixture of the two potential diastereomeric candidates (3*R*,5*R*,9*R*)-**1** and (3*S*,5*S*,9*R*)-**1** was separated on very small scale after derivatization as mandelate esters, showing that only one of the candidates was the actual pheromone; the absolute configuration of the pheromone at C3 and C5 could, however, not be established.

This approach could not subsequently be applied in a fully asymmetric total synthesis of the natural product and its diastereomers because efficient asymmetric Baeyer–Villiger oxidation protocols did not exist at the beginning of the work, and biocatalytic methods[13] were not available to us. Kinetic resolution has been described[14] but would require a cumbersome synthetic sequence. After completion of the syntheses, Feng reported a scandium-catalyzed asymmetric Baeyer–Villiger oxidation, which could potentially be used as an alternative.[15] In parallel to our synthetic effort, the Tolasch group developed a different asymmetric approach to **1**.[7]

A different, fully asymmetric approach to both pheromone candidates had therefore to be devised. Here, the enantioselective total synthesis of stylopsal is reported, establishing its absolute configuration unequivocally as (3*R*,5*R*,9*R*)-3,5,9-trimethyldodecanal. The absolute configuration (**1**) is supported by a variety of analytical techniques and field tests. The likely biosynthetic origin of the pheromone is discussed on the basis of fatty acid components found in the fat body of the parasite.

## Results and Discussion

**Asymmetric synthesis of stylopsal**: The retrosynthetic disconnection of the pheromone candidate had to account for the diastereodivergent generation of the C3 and C5 stereocenters based on a fixed 9*R* configuration in product **1** (Scheme 2). This is best achieved by sequential introduction of those chiral centers. The C3 stereocenter is therefore introduced by catalytic asymmetric conjugate addition to α,β-unsaturated ester **6** using a protocol in which the cata-




Scheme 2. Retrosynthesis for the pheromone candidates (for all intermediates, the numbering in parentheses reflects that of the full backbone of the pheromone).

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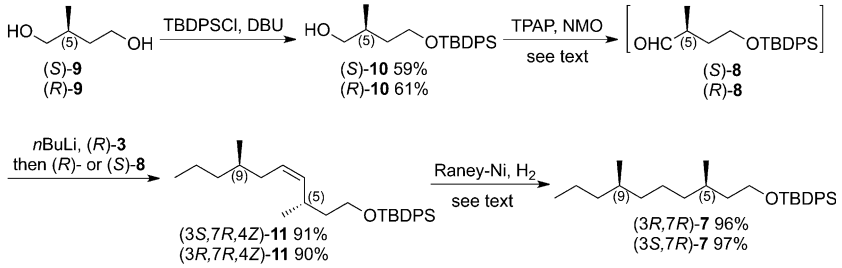
lyst was expected to determine the stereochemical outcome as completely as possible with minimal impact of the residing stereocenters at C5 and C9.[16]

Precursors **6** could be synthesized by a standard Wittig reaction with the aldehydes derived from (*R*,*R*)- or (*R*,*S*)-**7**. This compound will be approached by another Wittig coupling of enantiomerically enriched phosphonium salt (*R*)-**3** with enantiomerically pure aldehydes (*R*)-**8** or (*S*)-**8**, which are readily available from the corresponding chiral pool-derived 2-methylbutanediols.

The synthesis of the diastereomeric C3–C12 fragments (3*R*,7*R*)- and (3*S*,7*R*)-**7** started from commercially available (*R*)- and (*S*)-butanediols **9**, but proved to be slightly more challenging than expected (Scheme 3). The regioselective silylation of **9** by using *tert*-butyldiphenylsilyl chloride (TBDPSCl) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base has been reported several times,[17] with regioselectivities ranging from 16:1[17a] to 3:1.[17b] In our hands, a result at the lower end of the selectivity scale was initially observed. Unsatisfied with this outcome, a rapid rescreening of the conditions improved the regioselectivity to 6.6:1 in favor of the desired silyl ethers **10**. The key proved to be a very slow dropwise addition of TBDPSCl in reactions on 5 mmol scale, presumably to allow for better heat transfer.




Scheme 3. Preparation of the C3–C12 fragment (for all compounds, only one absolute configuration at C3 is shown; the numbering in parentheses reflects that of the full backbone of the pheromone).

Aldehydes (*R*)- and (*S*)-**8** have also been prepared numerous times and under various oxidation conditions,[17a,b,d,e,18] but have been described as unstable.[17d] The Dess–Martin oxidation was initially chosen because of its mild conditions, and it was decided to proceed with the Wittig olefination immediately after work-up of the reaction mixture. The oxidation of (*R*)-**10** provided aldehyde (*R*)-**8** as confirmed by $^1$H NMR spectroscopic analysis of the crude product. Wittig olefination with the ylide derived from (*R*)-**3**, which was prepared in four high-yielding steps by slight modifications of the approach described before (see the Supporting Information),[6] proceeded smoothly, resulting in 80% yield and good *Z* selectivity (*E*/*Z* = 10:90) of **11**. However, $^1$H NMR spectroscopic analysis revealed epimerization at C3 (3*R*,7*R*/3*S*,7*R* = 83:17). The Wittig reaction conditions did not seem to be responsible for the epimerization because this was not observed during the previous semiracemic synthesis.[6] Because the only difference was the oxidation conditions, these were reinvestigated. Indeed, it is known that the acetic acid by-product in the Dess–Martin oxidation may promote enolization of the aldehyde, and thereby epimerization.[19] Attempted buffering of the Dess–Martin oxidation with an organic base, such as pyridine,[20] did not suppress epimerization (63% **11**, 3*R*,7*R*/3*S*,7*R* = 86:14). However, much less epimerization occurred on addition of solid $NaHCO_3$ (71% **11**, 3*R*,7*R*/3*S*,7*R* = 92:8).

Looking out for alternatives, tetrapropylammonium perruthenate (TPAP)-mediated oxidation with its essentially neutral conditions and very short reaction times seemed to be a good choice. Moreover, Ley et al. reported a tandem TPAP oxidation/Takai olefination with **8** as a nonisolated intermediate,[17d] and a tandem TPAP oxidation/Wittig olefination protocol with different substrates, including intermediate α-chiral aldehydes for which no epimerization was observed.[21] This protocol led to higher yields (90%), little epimerization (3*R*,7*R*/3*S*,7*R* = 90:10) and essentially unchanged *Z* selectivity (*E*/*Z* = 10:90). Because of the favorable diastereomeric outcome, the better isolated yields obtained, as well as the practical convenience, the tandem TPAP oxidation/Wittig olefination protocol was applied on larger scale toward the target products.

The catalytic hydrogenation of **11** also required an optimization effort. With palladium on charcoal, further epimerization at C3 took place, as observed by an increase of a second set of signals in the $^{13}$C NMR spectra, but the diastereomeric ratio could not be quantified at this stage. Interestingly, no epimerization had been observed during the semiracemic synthesis.[6] Epimerization during catalytic hydrogenation of substrates with allylic chiral centers has been studied and was proposed to occur through partial double bond migration and subsequent hydrogenation of the resulting trisubstituted double bond, leading to overall epimerization.[22] Based on Cram's early report that Raney nickel does not mediate this epimerization,[22a] the hydrogenation of **11** proceeded very smoothly using these conditions, affording silyl ethers **7** in high yields and with virtually no epimerization, as revealed by $^{13}$C NMR spectroscopic analysis.

Tetrabutylammonium fluoride (TBAF)-mediated desilylation afforded alcohols **12** in high yields (Scheme 4). These were submitted to another tandem TPAP oxidation/Wittig olefination reaction according to Ley's procedure[19] to afford α,β-unsaturated esters **6** in high yield and high *E* selectivity (*E*/*Z* ≥ 99:1). For the completion of the full C15 skeleton, the introduction of the methyl group at C3 remained. Because this also had to be accomplished in a diastereodivergent manner, a reagent-controlled approach was mandatory, and an adaptation of the catalytic conjugate ad-

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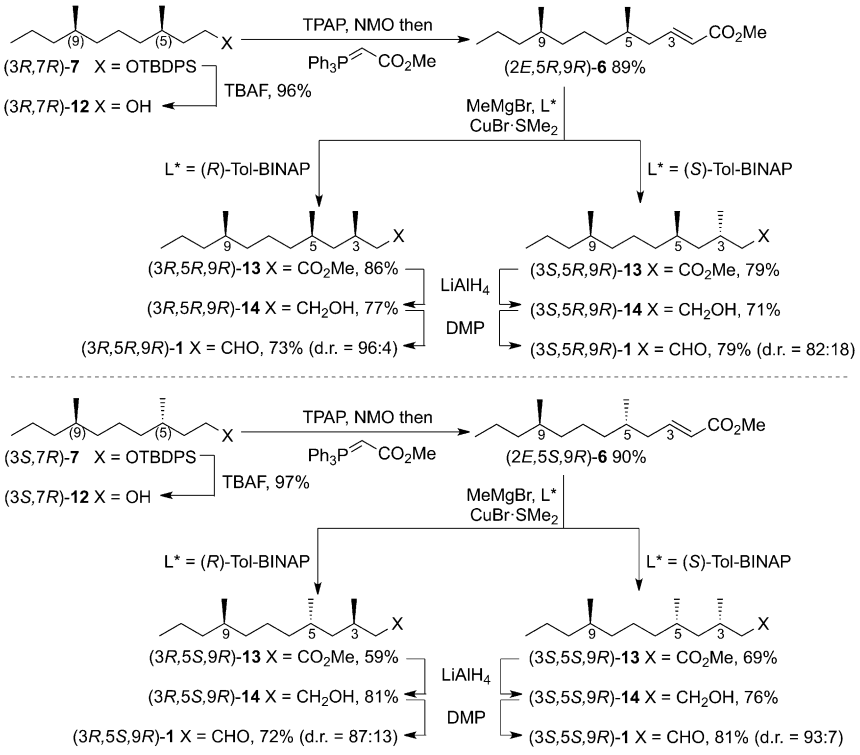


Scheme 4. Formation of the full C1–C12 backbone, and completion of the syntheses (for intermediates **7** and **12**, the numbering in parentheses reflects that of the full backbone of the pheromone).

dition protocol developed by Lum et al.[16] proved to be optimal to accomplish this task. Premixing $CuBr{\cdot}SMe_2$ with (*R*)- or (*S*)-Tol-BINAP in dichloromethane generated the active catalyst, which promoted the conjugate addition of methylmagnesium bromide to the individual diastereomers of **6** in anhydrous methyl *tert*-butyl ether (MTBE) in good yields. It must be mentioned, however, that for reasons we do not understand, no reaction occurred at scales lower than 0.2 mmol of starting α,β-unsaturated ester **6**. The enantio- and diastereoselectivity of the process was nonetheless to some extent dependent on the configuration of the substrate and ligand (catalyst). Best diastereomeric ratios of more than 93:7 were obtained when the absolute configurations at C5 and the ligand were matched, leading to the *syn* products. Substrates with mismatched absolute configurations at C5 and the ligand gave markedly lower diastereoselectivities, indicating less favorable interactions in the transition state of the conjugate additions.

The diastereomers of **13** were not separable and were subjected to reduction by $LiAlH_4$. Dess–Martin oxidation of the resulting diastereomerically enriched alcohols **14** afforded the four desired aldehydes **1**, in good yields over two steps. Because the aldehydes were well-resolved on chiral GC, the diastereomeric ratios were determined and found to be acceptable for further study. These aldehydes are relatively stable on storage in a freezer in the dark. However, over extended periods they slowly underwent spontaneous oxidation to the corresponding carboxylic acids as revealed by GC/MS.

**Confirmation of the structure of stylopsal**: In the preliminary report, the relative configuration of stylopsal was established as that of (9*R*)-3,5-*syn*-**1** by comparison of the retention times and coinjection of the natural extract of a mixture of both (9*R*)-3,5-*syn*-**1** isomers (Figure 2a).[6] When (3*R*,5*R*,9*R*)-**1** and (3*S*,5*S*,9*R*)-**1** were coinjected, they cleanly separated (Figure 2b). Each peak of the 92:8 (9*R*)-3,5-*syn*-**1**/(9*R*)-3,5-*anti*-**1** mixture was identified by coinjection with synthetic (3*S*,5*S*,9*R*)-**1**, (3*R*,5*R*,9*R*)-**1**, (3*R*,5*S*,9*R*)-**1**, and (3*S*,5*R*,9*R*)-**1** (Figure 2c–f). The final proof for the identity of stylopsal (Figure 2g) was furnished by coinjection of the natural extract and (3*R*,5*R*,9*R*)-**1** (Figure 2h). The retention times matched perfectly and the mass spectra were essentially identical. The chromatograms of the individual isomers also revealed that (3*R*,5*R*,9*R*)-**1** or (3*S*,5*S*,9*R*)-**1** were not contaminated with each other.

Based on this result, both synthetic (9*R*)-3,5-*syn*-isomers **1**, namely (3*R*,5*R*,9*R*)-**1** and (3*S*,5*S*,9*R*)-**1**, were subjected to gas chromatography/electroantennography (GC/EAD) measurements with male antennae (Figure 3). On an achiral column, both (3*R*,5*R*,9*R*)-**1** and (3*S*,5*S*,9*R*)-**1** were found to elute at the same time ($t_R = 9.09$ min; Figure 3). (3*R*,5*R*,9*R*)-**1** elicited a strong EAD response, whereas the response for (3*S*,5*S*,9*R*)-**1** was about 10 times weaker. Because (3*R*,5*R*,9*R*)-**1** or (3*S*,5*S*,9*R*)-**1** were not contaminated with each other (see above), the active pheromone is undoubtedly (3*R*,5*R*,9*R*)-**1**. This underlines the importance of the absolute and relative configuration of the chiral centers in stylopsal.[23] Coinjection of the two synthetic standards also led to a clear response, suggesting that (3*S*,5*S*,9*R*)-**1** has no inhibitory activity.[23b]

With the identity of stylopsal established, field tests were carried out with synthetic stylopsal (3*R*,5*R*,9*R*)-**1** in the Czech Republic. Ten sets of traps, each set consisting of three traps with different pheromone loadings (14 μg, 140 μg or none (control)), were prepared and exposed during the only day of *Stylops muelleri* occurrence in 2012 on five different localities (Figure 4). Within three hours of exposition, the combined catch was 50 (s.d. = 6.148), 552 (s.d. = 62.150), and no males, respectively.

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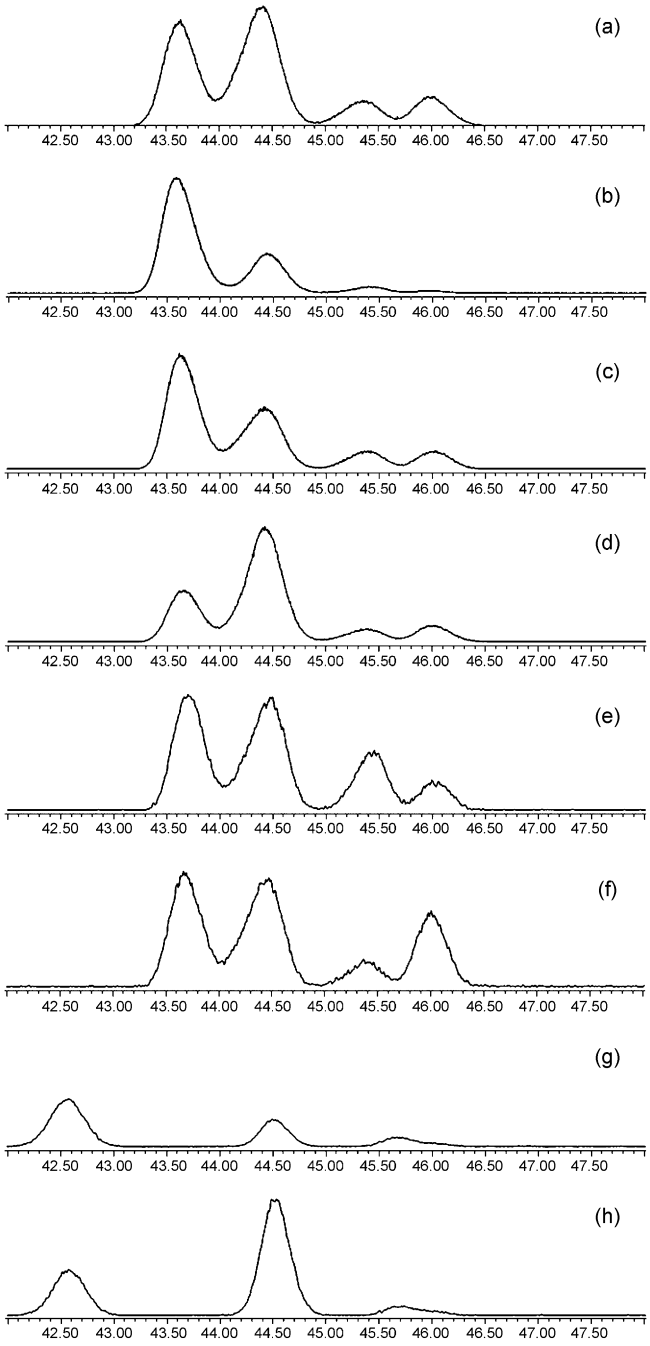


Figure 2. Chiral GC chromatograms of a) a synthetic mixture of (9*R*)-3,5-*syn*-**1** and (9*R*)-3,5-*anti*-**1** in a ratio of 92:8,[6] b) coinjected synthetic (3*R*,5*R*,9*R*)-**1** and (3*S*,5*S*,9*R*)-**1**, c) coinjection of (3*S*,5*S*,9*R*)-**1** and (9*R*)-3,5-*syn*-**1**, d) coinjection of (3*R*,5*R*,9*R*)-**1** and (9*R*)-3,5-*syn*-**1**, e) coinjection of (3*R*,5*S*,9*R*)-**1** and (9*R*)-3,5-*syn*-**1**, f) coinjection of (3*S*,5*R*,9*R*)-**1** and (9*R*)-3,5-*syn*-**1**, g) natural stylopsal ($t_R$ = 44.50 min), and h) coinjection of (3*R*,5*R*,9*R*)-**1** and natural stylopsal. g,h) Additional peaks ($t_R$=42.60 and 45.70 min) are decomposition products formed on storage of the natural extract.

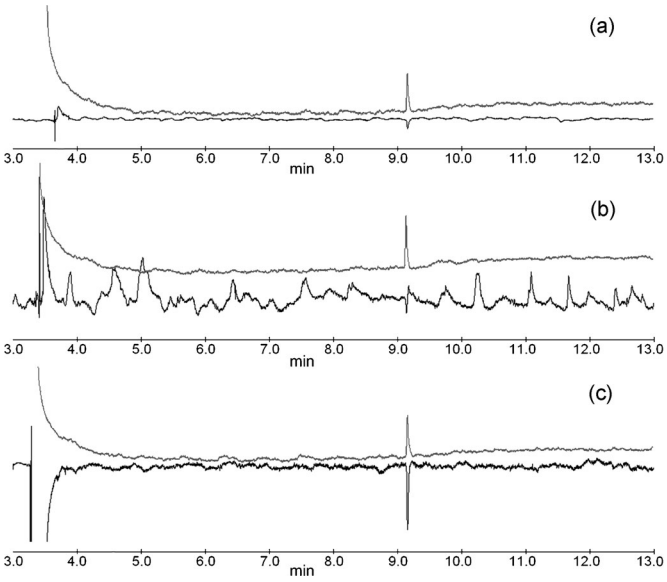


Figure 3. GC/EAD responses of male antennae to diastereomeric synthetic **1**. The upper traces correspond to the GC/FID, whereas the lower traces show the GC/EAD response. a) GC/EAD of (3*R*,5*R*,9*R*)-**1**, b) GC/EAD of (3*S*,5*S*,9*R*)-**1**, and c) GC/EAD of coinjected (3*R*,5*R*,9*R*)-**1** and (3*S*,5*S*,9*R*)-**1**.

Figure 4. Photograph of a trap loaded with 140 μg of synthetic (3*R*,5*R*,9*R*)-**1** during the field test.

**Biosynthesis of stylopsal**: Considering the evolutionary simplification of female *Strepsiptera* to a fully dependent organism with nutrient supply only from the host's hemolymph, it is remarkable that it takes the effort to biosynthesize stylopsal with its three chiral centers as a single-component pheromone. This may reflect the need for an extraordinarily efficient mate-location system to efficiently attract the short-living males. However, even the biosynthesis appeared initially somewhat puzzling; the location of the methyl groups in 3,5,9-positions strongly suggests that it is derived from a polyketide pathway, but this is contradicted by their positions at odd carbon linkages with respect to the carbonyl function.[24] Indeed, the methyl groups would be expected at C4, C6 and C10 or C2, C4 and C8, respectively, in a compound resulting from a regular polyketide pathway. Thus, a loss of a one-carbon linkage must occur during the biosynthesis, a process that usually takes place by decarboxylation.

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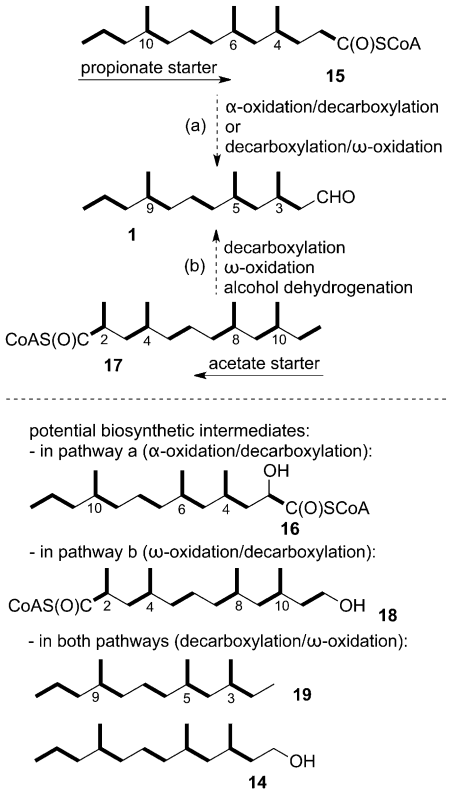



Scheme 5. Possible pathways in the biosynthesis of stylopsal.

Two possible pathways can therefore be hypothesized for this process (Scheme 5).

In pathway (a), the biosynthesis commences with a propionyl-CoA starter unit. Elongation by methylmalonyl-CoA and malonyl-CoA, followed by a repetition of the sequence provides **15**, which subsequently undergoes an α-oxidation to **16**, which decarboxylates to stylopsal (**1**). In pathway (b), acetyl-CoA serves as the starter unit and the chain would be elongated by two methylmalonyl-CoA units, before repetition of the sequence produces **17**. Subsequent ω-oxidation and decarboxylation would lead to alcohol **14** via **18**, which is oxidized to pheromone **1**. Remarkably, both pathways exhibit a similar triad repeated twice. Although ω-oxidation of fatty acids is not uncommon,[25] three distinct steps to the pheromone must take place in pathway (b) whereas the α-oxidation with concomitant decarboxylation in pathway (a) is an efficient one-step process.[26] It should be noted that the decarboxylation/ω-oxidation sequence described for pathway (b) can in principle, also take place in pathway (a). Moreover, the oxidation and decarboxylation events starting from **15** or **17** may occur in reverse order. This would lead to the formation of intermediate hydrocarbon **19** common to both pathways. Its further transformation into **1** would, however, require selective enzymatic oxidation of one of the two terminal methyl groups.

A steady release of stylopsal by mature *Stylops muelleri* females has been observed until mating, which is followed by a release of all remaining **1** at once.[27] Mated females contain only trace amounts of **1**, which results in a loss of interest of males.[27] This behavior as well as ultrastructural observations at the stylopsal-producing Nassonov gland in virgin and mated females,[28] strongly suggest that sequestration of stylopsal occurs in the gland prior to mating. Careful analysis of the chromatogram and mass spectra of the various fatty acid methyl esters (FAME) obtained by transesterification of the triacyl glycerols of the fat body of *Strepsiptera* females revealed the presence of C15 ester **13** and C16 ester **20**, representing respectively 0.5 and 1.1% of all the FAME from the fat body extract (Figure 5).

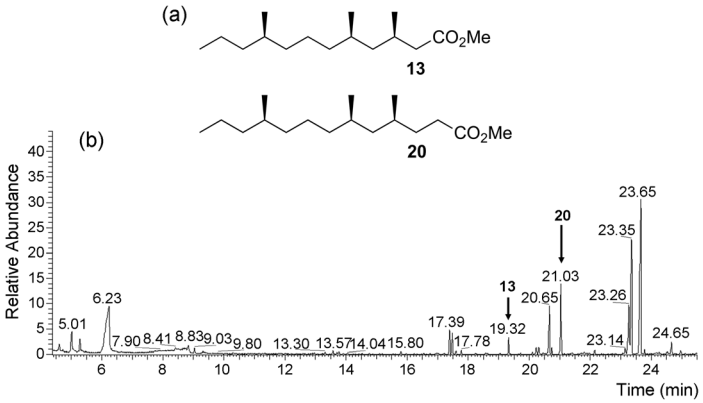
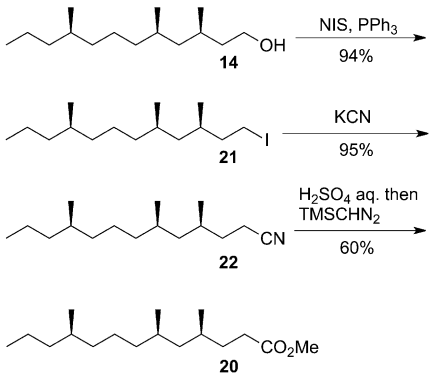



Figure 5. a) Two notable FAME found in the extract obtained by transesterification of the fat body contents of female *Stylops muelleri*. b) Gas chromatogram of the FAME.

The structure of FAME (3*R*,5*R*,9*R*)-**13** could be confirmed by comparison of retention times and mass spectra with those of the corresponding intermediate of the total synthesis (see above) (Figure 6). Coinjection of synthetic (3*R*,5*R*,9*R*)-**13** and the FAME from the fat body extract led to a virtually unchanged mass spectrum over the whole range of the coeluted peak.

As for the synthesis of FAME **20**, the direct precursor to the pheromone, alcohol (3*R*,5*R*,9*R*)-**14**, was iodinated under Appel type conditions (Scheme 6). The resulting iodide **21** was converted into nitrile **22** using potassium cyanide under standard Kolbe conditions. Hydrolysis of the nitrile function




Scheme 6. Synthesis of FAME **20**.

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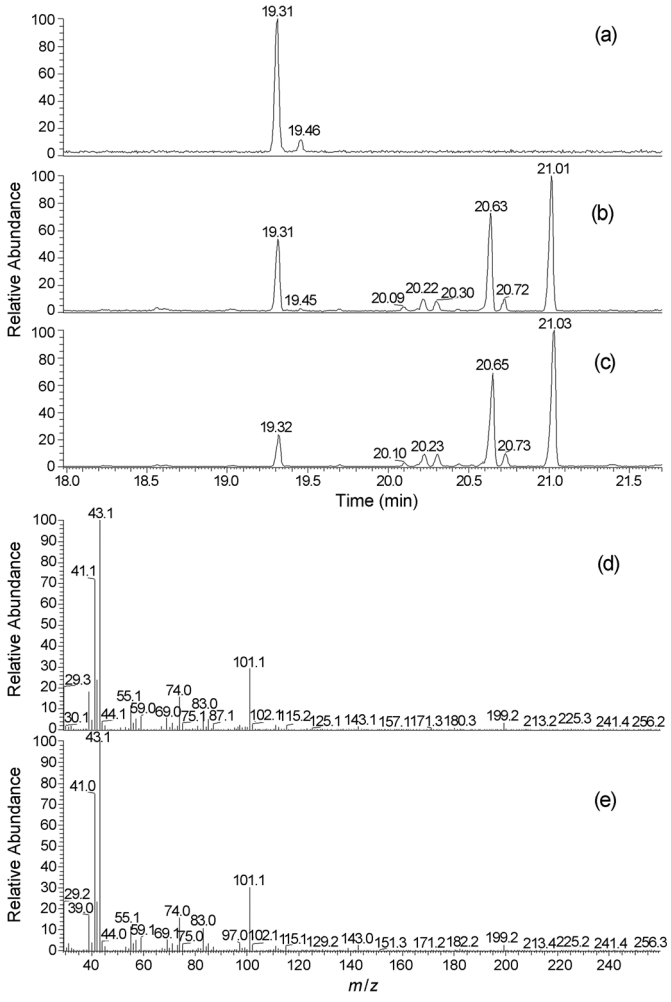


Figure 6. Partial gas chromatograms of a) (3*R*,5*R*,9*R*)-**13**, b) coinjection of (3*R*,5*R*,9*R*)-**13** and FAME from the fat body extract, and c) FAME from the fat body extract. Mass spectrum of d) synthetic (3*R*,5*R*,9*R*)-**13** and e) the coeluted peak ($t_R = 19.31$ min) resulting from coinjection.

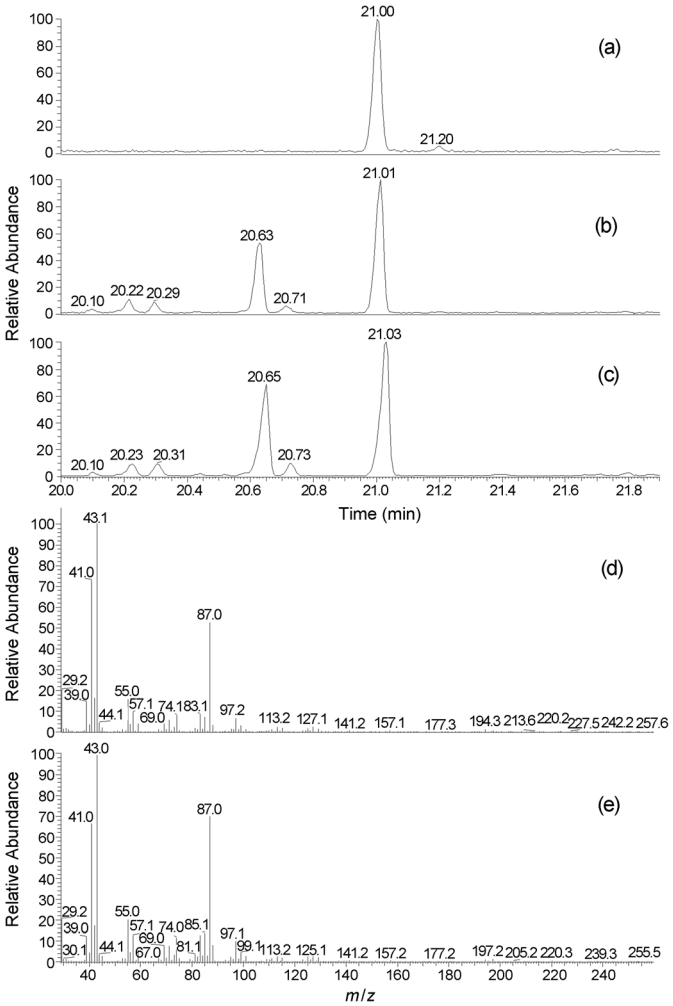


Figure 7. Partial gas chromatograms of a) (4*S*,6*R*,10*R*)-**20**, b) coinjection of (4*S*,6*R*,10*R*)-**20** and FAME from the fat body extract, and c) FAME from the fat body extract. Mass spectrum of d) synthetic (4*S*,6*R*,10*R*)-**20** and e) the coeluted peak ($t_R = 21.03$ min) resulting from coinjection.

and esterification of the resulting crude carboxylic acid provided methyl ester **20**.

The retention times and mass spectra of (4*S*,6*R*,10*R*)-**20** matched those of the natural FAME from the fat body extract (Figure 7). No change in the spectrum was observed over the whole range of the coeluted peak upon coinjection of **20** and the FAME from the fat body extract. Although the amounts of FAME of interest in the extract were sufficient for detection, the relative quantities with respect to the other components in the extract made it technically impossible to analyze the contents by chiral GC for confirmation of the absolute configuration of the detected FAME. It may however be assumed that both detected FAME present the same absolute configuration as that of the biogenetically related stylopsal.

It is noteworthy that alcohol **14** was not found within the different extracts. Moreover, no biosynthetically related compounds were found in extracts of the fat body of the host bees, suggesting that the biosynthesis of the pheromone is carried out entirely and *de novo* by the female (see the Supporting Information).[29] From the information gathered, a polyketide synthesis can be assumed to take place to form a C16 carboxylic acid derivative **15**, which is converted into stylopsal (**1**) according to pathway (a). It may then be further degraded to C15 carboxylic acid derivative **13**. The exact course of the events leading to the formation of stylopsal, including the enzymatic apparatus needed for the formation of precursors and end-products are, however, impossible to claim at this stage. Further work is underway to answer these questions and the results will be reported in due course.

## Conclusion

The absolute configuration of stylopsal, the first identified sex pheromone of a twisted-wing parasite, was unequivocally established by total synthesis, GC analyses, and bioassays.

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Stylopsal and three configurational isomers were prepared in 11 steps in the longest linear sequence in 16–21% overall yield. Gas chromatographic investigations showed that the natural material has 3*R*,5*R*,9*R* configuration. This is supported by GC/EAD investigations in which this isomer elicited a strong response at the male antennae, whereas the corresponding (3*S*,5*S*,9*R*)-diastereomer was much less active. In field tests, the synthetic (3*R*,5*R*,9*R*)-diastereomer was highly attractive to male *Stylops muelleri*, thus further supporting the structure of stylopsal. Analytical and synthetic studies revealed that the pheromone is likely to be biosynthesized through a polyketide pathway to a 4,6,10-trimethyltridecanoic acid derivative as a central intermediate. Overall, as simple as the life of this entirely host-dependent female organism appears, it undertakes the effort to produce a relatively complex stereochemically defined potent female sex pheromone to maximize success of reproduction. Further research concerning the biosynthesis of the pheromone and the peculiar biology of *Strepsiptera* is underway.

## Experimental Section

For general analytical and experimental conditions see the Supporting Information.

***tert*-Butyl-[(3*S*,4*Z*,7*R*)-3,7-dimethyldec-4-enyloxy]diphenylsilane, (3*S*,4*Z*,7*R*)-11**: *n*BuLi (1.6 M in hexanes, 655 μL, 1.05 mmol) was added dropwise to a suspension of phosphonium salt (*R*)-**3** (537 mg, 1.1 mmol) in anhydrous THF (5 mL) cooled to −78 °C under a nitrogen atmosphere, and the resulting deep-orange mixture was stirred at this temperature for 30 min. In a separate flask, to a solution of alcohol (*S*)-**10** (342 mg, 1.0 mmol) in anhydrous $CH_2Cl_2$ (5 mL) were successively added *N*-methylmorpholine *N*-oxide (NMO; 106 mg, 1.05 mmol), activated powdered molecular sieves 4 Å (100 mg), and TPAP (18 mg, 0.05 mmol) portionwise, resulting in the formation of a deep-green mixture. After stirring for 15 min, the black solution was transferred into the phosphorane solution by using a cannula. The cooling bath was removed, and stirring was continued for 30 min. Dilution with $Et_2O$ (10 mL), filtration over a pad of silica gel, concentration in vacuo, and flash column chromatography (hexane/EtOAc, 50:1) afforded olefin (3*S*,4*Z*,7*R*)-**11** as a colorless oil (385 mg, 91%; *E*/*Z* = 10:90). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.67 (dd, *J* = 6.6, 1.3 Hz, 4H; $H_{Ar}$), 7.43–7.33 (m, 6H; $H_{Ar}$), 5.29 (dt, *J* = 10.9, 7.3 Hz, 1H; H-5), 5.12 (dd, *J* = 10.9, 9.7 Hz, 1H; H-4), 3.64 (t, *J* = 6.5 Hz, 2H; H-1), 2.73–2.61 (m, 1H; H-3), 2.05 (dddd, *J* = 14.3, 7.5, 6.3, 1.5 Hz, 1H; H-6a), 1.83 (dtd, *J* = 14.3, 7.3, 1.5 Hz, 1H; H-6b), 1.60–1.38 (m, 3H; H-7, H-2), 1.38–1.19 (m, 4H; H-8, H-9), 1.04 [s, 9H; $C(CH_3)_3$], 0.91 (d, *J* = 6.7 Hz, 3H; $CH_3$-3), 0.87 (t, *J* = 6.8 Hz, 3H; H-10), 0.82 ppm (d, *J* = 6.7 Hz, 3H; $CH_3$-7); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 136.4 (CH-4), 135.6 ($C_{Ar}$), 134.2 ($C_{Ar}$), 129.5 ($C_{Ar}$), 127.5 ($C_{Ar}$), 127.4 (CH-5), 62.2 ($CH_2$-1), 40.2 ($CH_2$-6), 38.9 ($CH_2$-2), 34.7 (CH-3), 33.2 (CH-7), 28.1 ($CH_2$-8), 26.9 [$C(CH_3)_3$], 21.1 ($CH_2$-9), 20.2 ($CH_3$-7), 19.6 ($CH_3$-3), 19.2 [$C(CH_3)_3$], 14.3 ppm ($CH_3$-10); IR (film): $\tilde{\nu}_{max}$ = 2956, 2929, 2858, 1462, 1428, 1110, 823, 737, 701, 613 cm$^{-1}$; MS (EI): *m*/*z* (%): 365 (100), 287 (27), 281 (25), 225 (18), 203 (36), 199 (74), 183 (64), 135 (18); HRMS (ESI+): *m*/*z* calcd for $[C_{28}H_{42}ONaSi]^+$: 445.2897; found: 445.2893.

***tert*-Butyl-[(3*R*,7*R*)-3,7-dimethyldecyloxy]diphenylsilane, (3*R*,7*R*)-7**: *With palladium on charcoal*: Olefin (3*S*,4*Z*,7*R*)-**11** (380 mg, 0.9 mmol) was dissolved in degassed EtOAc (3 mL) and hydrogenated over 10% Pd/C (38 mg, 10% w/w) under hydrogen (10 bar) in an autoclave at RT for 1.5 h. Upon completion of the reaction as indicated by GC, the mixture was filtered over a pad of silica gel and the solvent was removed in vacuo. Flash column chromatography (hexane/EtOAc, 50:1) afforded (3*R*,7*R*)-**7** as a colorless oil (363 mg, 95%).

*With Raney nickel*: A mixture of olefin (3*S*,4*Z*,7*R*)-**11** (200 mg, 0.47 mmol) and activated Raney nickel (200 μL) in anhydrous ethanol (4 mL) was stirred at RT under hydrogen (10 bar) in an autoclave for 5 h. Upon completion of the reaction as indicated by GC, the mixture was filtered over a pad of silica gel and the solvent was removed in vacuo. Flash column chromatography (hexane/EtOAc, 50:1) afforded (3*R*,7*R*)-**7** as a colorless oil (192 mg, 96%). $[\alpha]_D^{20}$ = −2.3 (*c* = 0.310, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.72–7.67 (m, 4H; $H_{Ar}$), 7.45–7.35 (m, 6H; $H_{Ar}$), 3.77–3.65 (m, 2H; H-1), 1.68–1.55 (m, 2H; H-2), 1.46–1.06 (m, 12H; H-3, H-4, H-5, H-6, H-7, H-8, H-9), 1.07 [s, 9H; $C(CH_3)_3$], 0.89 (t, *J* = 7.1 Hz, 3H; H-10), 0.85 (d, *J* = 6.6 Hz, 3H; $CH_3$-3), 0.83 ppm (d, *J* = 6.6 Hz, 3H; $CH_3$-7); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 135.6 ($C_{Ar}$), 134.2 ($C_{Ar}$), 129.5 ($C_{Ar}$), 127.6 ($C_{Ar}$), 62.3 ($CH_2$-1), 39.7 ($CH_2$-2), 39.4 ($CH_2$-8), 37.4 ($CH_2$-6), 37.3 ($CH_2$-4), 32.5 (CH-7), 29.4 (CH-3), 26.9 [$C(CH_3)_3$], 24.4 ($CH_2$-5), 20.2 ($CH_2$-9), 19.8 ($CH_3$-3), 19.7 ($CH_3$-7), 19.2 [$C(CH_3)_3$], 14.4 ppm ($CH_3$-10); IR (film): $\tilde{\nu}_{max}$ = 2956, 2927, 2858, 1462, 1428, 1378, 1108, 823, 736, 700, 614 cm$^{-1}$; MS (ESI+): *m*/*z* (%): 447 (100), 359 (13), 315 (11), 301 (7), 273 (5), 217 (10), 153 (5); HRMS (ESI+): *m*/*z* calcd for $[C_{28}H_{44}ONaSi]^+$: 447.3054; found: 447.3055.

**(3*R*,7*R*)-3,7-Dimethyldecan-1-ol, (3*R*,7*R*)-12**: TBAF (1 M in THF, 1.28 mL, 1.28 mmol) was added to a solution of silyl ether (3*R*,7*R*)-**7** (360 mg, 0.85 mmol) in THF (2 mL) at RT. After stirring for 2 h, the mixture was diluted with $Et_2O$ (5 mL), filtered over a pad of silica gel, and concentrated in vacuo. Purification by flash column chromatography (hexane/EtOAc, 5:1) afforded alcohol (3*R*,7*R*)-**12** as a pungent colorless oil (152 mg, 96%). $[\alpha]_D^{20}$ = +2.7 (*c* = 1.31, $CHCl_3$) {lit.: $[\alpha]_D^{20}$ = +1.90 (*c* = 1.86, $CHCl_3$)}. The spectral data matched those reported in the literature.[30]

**(2*E*,5*R*,9*R*)-Methyl 5,9-dimethyldodec-2-enoate, (2*E*,5*R*,9*R*)-6**: NMO (53 mg, 0.52 mmol), activated powdered molecular sieves 4 Å (50 mg), and TPAP (9 mg, 0.05 mmol) were successively added portionwise to a solution of alcohol (3*R*,7*R*)-**12** (93 mg, 0.5 mmol) in anhydrous $CH_2Cl_2$ (5 mL), resulting in the formation of a deep-green mixture. After stirring for 15 min, methoxycarbonylmethylenetriphenylphosphorane (200 mg, 0.6 mmol) was added to the black solution in one portion as a solid and stirring was continued overnight. Filtration over a pad of silica gel, concentration in vacuo, and flash column chromatography afforded α,β-unsaturated ester (2*E*,5*R*,9*R*)-**6** as a colorless oil (107 mg, 89%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.95 (dt, *J* = 15.4, 7.5 Hz, 1H; H-3), 5.81 (d, *J* = 15.6 Hz, 1H; H-2), 3.72 (s, 3H; $OCH_3$), 2.20 (m, 1H; H-4a), 2.07–1.98 (m, 1H; H-4b), 1.68–1.53 (m, 1H; H-5), 1.44–1.00 (m, 11H; H-6, H-7, H-8, H-9, H-10, H-11), 0.89 (d, *J* = 6.6 Hz, 3H; $CH_3$-5), 0.87 (t, *J* = 7.3 Hz, 3H; H-12), 0.83 ppm (d, *J* = 6.6 Hz, 3H; $CH_3$-9); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 167.0 (C-1), 148.6 (CH-3), 121.9 (CH-2), 51.3 ($OCH_3$), 39.7 ($CH_2$-4), 39.3 ($CH_2$-10), 37.2 ($CH_2$-6), 36.9 ($CH_2$-8), 32.5 (CH-5), 32.4 (CH-9), 24.4 ($CH_2$-7), 20.1 ($CH_2$-11), 19.6 ($CH_3$-5), 19.5 ($CH_3$-9), 14.4 ppm ($CH_3$-12); IR (film): $\tilde{\nu}_{max}$ = 2955, 2926, 2872, 1727, 1657, 1460, 1436, 1379, 1321, 1269, 1195, 1171, 1131, 1043, 983 cm$^{-1}$. MS (EI): *m*/*z* (%): 240 (6), 209 (13), 142 (15), 100 (100), 85 (34), 71 (28), 57 (41), 43 (46); HRMS (EI): *m*/*z* calcd for $[C_{15}H_{28}O_2]^+$: 240.2089; found: 240.2088.

**(3*R*,5*R*,9*R*)-Methyl 3,5,9-trimethyldodecanoate, (3*R*,5*R*,9*R*)-13**: A solution of (*R*)-Tol-BINAP (30.6 mg, 0.045 mmol) and $CuBr{\cdot}SMe_2$ (6.2 mg, 0.03 mmol) in anhydrous $CH_2Cl_2$ (0.7 mL) was stirred for 20 min and anhydrous *t*BuOMe (2 mL) was added. The bright-yellow solution was cooled to −20 °C and MeMgBr (3 M in $Et_2O$, 0.130 mL, 0.39 mmol) was added. After stirring for 5 min, a solution of (2*E*,5*R*,9*R*)-**6** (75 mg, 0.3 mmol) in *t*BuOMe (1 mL) was added dropwise over 30 min. Stirring was continued for 1 h, and the reaction mixture was quenched with MeOH (0.5 mL) and a saturated $NH_4Cl$ solution (2 mL). The layers were separated and the aqueous layer was extracted with $Et_2O$ (3 × 3 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated in vacuo. Flash column chromatography (pentane/$Et_2O$, 50:1) afforded ester (3*R*,5*R*,9*R*)-**13** as a colorless oil (69 mg, 86%, dr = 96:4). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 3.66 (s, 3H; $OCH_3$), 2.31 (m, 1H; H-2a), 2.07 (m, 2H; H-2b, H-3), 1.45 (m, 1H; H-5), 1.38 (m, 1H; H-9), 1.35–1.16 (m, 8H; H-4a, H-6a, H-7, H-8a, H-10a, H-11), 1.11–0.95 (m, 4H; H-4b, H-6b, H-8b, H-10b), 0.92 (d, *J* = 6.4 Hz, 3H; $CH_3$-3), 0.88 (t, *J* = 7.0 Hz, 3H; H-12), 0.86 (d, *J* = 6.6 Hz, 3H; $CH_3$-5), 0.84 ppm (d, *J* =

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6.6 Hz, 3H; $CH_3$-9); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 174.00 (C=O), 51.52 ($CH_3O$), 44.91 ($CH_2$-4), 41.78 ($CH_2$-2), 39.60 ($CH_2$-10), 37.62 ($CH_2$-8), 37.27 ($CH_2$-6), 32.74 (CH-9), 30.31 (CH-5), 28.13 (CH-3), 24.46 ($CH_2$-7), 20.64 ($CH_3$-3), 20.36 ($CH_2$-11), 20.33 ($CH_3$-5), 19.93 ($CH_3$-9), 14.62 ppm ($CH_3$-12); IR (film): $\tilde{\nu}_{max}$ = 2926, 1741, 1460, 1192, 1009, 740 cm$^{-1}$; MS (CI+): *m/z* (%): 257 (100), 255 (42), 241 (14), 225 (8); HRMS (CI+): *m/z* calcd for $[C_{16}H_{33}O_2]^+$: 257.2481; found: 257.2478.

**(3*S*,5*S*,9*R*)-Methyl 3,5,9-trimethyldodecanoate, (3*S*,5*S*,9*R*)-13**: Following the same procedure with (2*E*,5*S*,9*R*)-**6** (75 mg, 0.3 mmol) and (*S*)-Tol-BINAP as the chiral ligand, (3*S*,5*S*,9*R*)-**13** was obtained as a colorless oil (55 mg, 69%, dr = 93:7). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 3.66 (s, 3H; $OCH_3$), 2.31 (m, 1H; H-2a), 2.07 (m, 2H; H-2b, H-3), 1.45 (m, 1H; H-5), 1.38 (m, 1H; H-9), 1.35–1.16 (m, 8H; H-4a, H-6a, H-7, H-8a, H-10a, H-11), 1.11–0.95 (m, 4H; H-4b, H-6b, H-8b, H-10b), 0.92 (d, *J* = 6.4 Hz, 3H; $CH_3$-3), 0.88 (t, *J* = 7.0 Hz, 3H; H-12), 0.86 (d, *J* = 6.6 Hz, 3H; $CH_3$-5), 0.84 ppm (d, *J* = 6.6 Hz, 3H; $CH_3$-9); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 174.01 (C=O), 51.52 ($CH_3O$), 44.98 ($CH_2$-4), 41.80 ($CH_2$-2), 39.73 ($CH_2$-10), 37.54 ($CH_2$-8), 37.18 ($CH_2$-6), 32.70 (CH-9), 30.27 (CH-5), 28.13 (CH-3), 24.44 ($CH_2$-7), 20.61 ($CH_3$-3), 20.38 ($CH_2$-11), 20.27 ($CH_3$-5), 19.83 ($CH_3$-9), 14.62 ppm ($CH_3$-12); IR (film): $\tilde{\nu}_{max}$ = 2926, 1741, 1460, 1192, 1009, 740 cm$^{-1}$; MS (CI+): *m/z* (%): 257 (100), 255 (40), 241 (15), 225 (8); HRMS (CI+): *m/z* calcd for $[C_{16}H_{33}O_2]^+$: 257.2481; found: 257.2482.

**(3*R*,5*R*,9*R*)-3,5,9-Trimethyldodecan-1-ol, (3*R*,5*R*,9*R*)-14**: Anhydrous THF (1.5 mL) and a solution of ester (3*R*,5*R*,9*R*)-**13** (66 mg, 0.257 mmol) in THF (1 mL) were added to a solution of $LiAlH_4$ (2 M in THF, 0.129 mL, 0.257 mmol) cooled to 0 °C, under an inert atmosphere. The cooling bath was removed and stirring was continued at ambient temperature for 2 h. The flask was again immersed in an ice-water bath and methanol (1.5 mL) was added in small portions followed by aqueous $H_2SO_4$ (1 M, 5 mL). The resulting mixture was transferred to a separation funnel, the layers were separated, and the aqueous layer was extracted with $Et_2O$ (2×3 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (2×3 mL), dried over anhydrous $MgSO_4$, and concentrated. Flash column chromatography (pentane/$Et_2O$, 3:1) afforded alcohol (3*R*,5*R*,9*R*)-**14** as a colorless oil (45 mg, 77%; dr = 96:4). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 3.71 (ddd, *J* = 10.4, 7.7, 5.8 Hz, 1H; H-1a), 3.66 (ddd, *J* = 10.4, 7.3, 6.7 Hz, 1H; H-1b), 1.65 (m, 1H; H-3), 1.62 (m, 1H; H-2a), 1.49 (m, 1H; H-5), 1.38 (m, 1H; H-9), 1.35–1.14 (m, 10H; H-2b, H-4a, H-6a, H-7, H-8a, H-10a, H-11, OH), 1.11–1.00 (m, 3H; H-6b, H-8b, H-10b), 0.97 (m, 1H; H-4b), 0.89 (d, *J* = 6.7 Hz, 3H; $CH_3$-3), 0.88 (t, *J* = 7.0 Hz, 3H; H-12), 0.85 (d, *J* = 6.5 Hz, 3H; $CH_3$-5), 0.84 ppm (d, *J* = 6.6 Hz, 3H; $CH_3$-9); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 61.43 ($CH_2$-1), 45.54 ($CH_2$-4), 40.04 ($CH_2$-2), 39.59 ($CH_2$-10), 37.65 ($CH_2$-8), 37.39 ($CH_2$-6), 32.74 (CH-9), 30.24 (CH-5), 27.18 (CH-3), 24.52 ($CH_2$-7), 20.49 ($CH_3$-3), 20.46 ($CH_3$-5), 20.35 ($CH_2$-11), 19.93 ($CH_3$-9), 14.61 ppm ($CH_3$-12); IR (film): $\tilde{\nu}_{max}$ = 3322, 2925, 1460, 1377, 1157, 741 cm$^{-1}$; MS (CI+): *m/z* (%): 228 (16), 227 (100), 211 (50), 155 (47), 141 (66), 127 (74), 113 (73), 99 (71), 97 (89), 85 (76), 71 (57); HRMS (CI+): *m/z* calcd for $[C_{15}H_{31}O]^+$: 227.2375; found: 227.2376.

**(3*S*,5*S*,9*R*)-3,5,9-Trimethyldodecan-1-ol, (3*S*,5*S*,9*R*)-14**: Following the same procedure with (3*S*,5*S*,9*R*)-**13** (55 mg, 0.214 mmol), (3*S*,5*S*,9*R*)-**14** was obtained as a colorless oil (37 mg, 76%; dr = 93:7). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 3.71 (ddd, *J* = 10.5, 7.7, 5.8 Hz, 1H; H-1a), 3.66 (ddd, *J* = 10.5, 7.3, 6.7 Hz, 1H; H-1b), 1.65 (m, 1H; H-3), 1.62 (m, 1H; H-2a), 1.50 (m, 1H; H-5), 1.38 (m, 1H; H-9), 1.35–1.18 (m, 10H; H-2b, H-4a, H-6a, H-7, H-8a, H-10a, H-11, OH), 1.12–1.01 (m, 3H; H-6b, H-8b, H-10b), 0.98 (m, 1H; H-4b), 0.89 (d, *J* = 6.7 Hz, 3H; $CH_3$-3), 0.88 (t, *J* = 7.0 Hz, 3H; H-12), 0.85 (d, *J* = 6.6 Hz, 3H; $CH_3$-5), 0.84 ppm (d, *J* = 6.6 Hz, 3H; $CH_3$-9); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 61.46 ($CH_2$-1), 45.61 ($CH_2$-4), 40.12 ($CH_2$-2), 39.74 ($CH_2$-10), 37.58 ($CH_2$-8), 37.31 ($CH_2$-6), 32.70 (CH-9), 30.21 (CH-5), 27.18 (CH-3), 24.51 ($CH_2$-7), 20.48 ($CH_3$-3), 20.41 ($CH_3$-5), 20.37 ($CH_2$-11), 19.84 ($CH_3$-9), 14.62 ppm ($CH_3$-12); IR (film): $\tilde{\nu}_{max}$ = 3322, 2925, 1460, 1377, 1157, 741 cm$^{-1}$; MS (CI+): *m/z* (%): 228 (16), 227 (100), 211 (86), 155 (36), 141 (63), 127 (72), 113 (68), 99 (75), 97 (72), 85 (75), 71 (52); HRMS (CI+): *m/z* calcd for $[C_{15}H_{31}O]^+$: 227.2375; found: 227.2381.

**(3*R*,5*R*,9*R*)-3,5,9-Trimethyldodecanal, (3*R*,5*R*,9*R*)-1 (stylopsal)**: A solution of alcohol (3*R*,5*R*,9*R*)-**14** (11 mg, 0.048 mmol) in hexane (0.5 mL) was added to a solution of Dess–Martin periodinane (31 mg, 0.072 mmol) in $CH_2Cl_2$ (0.5 mL) under an argon atmosphere, followed by the addition of water (ca. 1 μL). The resulting mixture was stirred at RT for 2 h, then $CH_2Cl_2$ (0.5 mL) and a 0.5 M solution of $Na_2S_2O_3$ in saturated $NaHCO_3$ (1 mL) were successively added. The mixture was stirred vigorously until the organic layer became clear, then the layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3×1 mL). The combined organic layers were washed with water (1 mL), brine (1 mL), and dried over $MgSO_4$. Concentration in vacuo and purification by flash column chromatography (pentane/$Et_2O$, 20:1) afforded aldehyde (3*R*,5*R*,9*R*)-**1** (8 mg, 73%; dr = 96:4) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 9.76 (dd, *J* = 2.5, 1.9 Hz, 1H; H-1), 2.39 (m, 1H; H-2a), 2.18 (m, 1H; H-2b), 2.15 (m, 1H; H-3), 1.46 (m, 1H; H-5), 1.38 (m, 1H; H-9), 1.35–1.15 (m, 8H; H-4a, H-6a, H-7, H-8a, H-10a, H-11), 1.12–1.01 (m, 4H; H-4b, H-6b, H-8b, H-10b), 0.96 (d, *J* = 6.5 Hz, 3H; $CH_3$-3), 0.88 (t, *J* = 7.0 Hz, 3H; H-12), 0.87 (d, *J* = 6.6 Hz, 3H; $CH_3$-5), 0.84 ppm (d, *J* = 6.6 Hz, 3H; $CH_3$-9); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 203.36 (CH-1), 51.19 ($CH_2$-2), 45.06 ($CH_2$-4), 39.60 ($CH_2$-10), 37.62 ($CH_2$-8), 37.32 ($CH_2$-6), 32.74 (CH-9), 30.32 (CH-5), 25.99 (CH-3), 24.47 ($CH_2$-7), 20.88 ($CH_3$-3), 20.37 ($CH_2$-11), 20.27 ($CH_3$-5), 19.94 ($CH_3$-9), 14.63 ppm ($CH_3$-12); IR (film): $\tilde{\nu}_{max}$ = 2925, 2710, 1727, 1460, 740 cm$^{-1}$; MS (CI+): *m/z* (%): 227 (100), 207 (19), 183 (22), 182 (24), 153 (12), 139 (24), 125 (36), 111 (43), 97 (39), 83 (23); HRMS (CI+): *m/z* calcd for $[C_{15}H_{31}O]^+$: 227.2375; found: 227.2372.

**(3*S*,5*S*,9*R*)-3,5,9-Trimethyldodecanal, (3*S*,5*S*,9*R*)-1**: Following the same procedure with (3*S*,5*S*,9*R*)-**14** (15 mg, 0.066 mmol), (3*S*,5*S*,9*R*)-**1** was obtained as a colorless oil (12 mg, 81%; dr = 93:7). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 9.76 (dd, *J* = 2.5, 1.9 Hz, 1H; H-1), 2.39 (m, 1H; H-2a), 2.18 (m, 1H; H-2b), 2.15 (m, 1H; H-3), 1.47 (m, 1H; H-5), 1.37 (m, 1H; H-9), 1.35–1.21 (m, 8H; H-4a, H-6a, H-7, H-8a, H-10a, H-11), 1.13–1.02 (m, 4H; H-4b, H-6b, H-8b, H-10b), 0.96 (d, *J* = 6.5 Hz, 3H; $CH_3$-3), 0.88 (t, *J* = 7.0 Hz, 3H; H-12), 0.87 (d, *J* = 6.6 Hz, 3H; $CH_3$-5), 0.84 ppm (d, *J* = 6.6 Hz, 3H; $CH_3$-9); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 203.36 (CH-1), 51.21 ($CH_2$-2), 45.13 ($CH_2$-4), 39.73 ($CH_2$-10), 37.54 ($CH_2$-8), 37.24 ($CH_2$-6), 32.70 (CH-9), 30.28 (CH-5), 25.99 (CH-3), 24.47 ($CH_2$-7), 20.85 ($CH_3$-3), 20.38 ($CH_2$-11), 20.21 ($CH_3$-5), 19.84 ($CH_3$-9), 14.63 ppm ($CH_3$-12); IR (film): $\tilde{\nu}_{max}$ = 2925, 2710, 1727, 1460, 740 cm$^{-1}$; MS (CI+): *m/z* (%): 227 (100), 207 (19), 183 (22), 182 (24), 153 (12), 139 (24), 125 (36), 111 (43), 97 (39), 83 (23); HRMS (CI+): *m/z* calcd for $[C_{15}H_{31}O]^+$: 227.2375; found: 227.2379.

**(4*S*,6*R*,10*R*)-Methyl 4,6,10-trimethyltridecanoate, (4*S*,6*R*,10*R*)-20**: A solution of $H_2SO_4$ (1 M, 0.5 mL) was added to a solution of nitrile **22** (15 mg, 0.063 mmol) in acetic acid (0.2 mL) and the temperature was maintained at 70 °C for 4 h. After cooling to RT, the reaction mixture was extracted with EtOAc (3×1 mL) and the organic layer was dried over $MgSO_4$ and concentrated in vacuo. The intermediate crude carboxylic acid (15 mg) was dissolved in benzene (0.3 mL) and methanol (0.09 mL), followed by addition of a trimethylsilyldiazomethane solution (2 M in $Et_2O$, 0.06 mL, 0.117 mmol). The resulting solution was stirred at RT for 1 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution (0.5 mL) and extracted with $Et_2O$ (3×1 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography (pentane/$Et_2O$, 20:1) afforded methyl ester **20** (11 mg, 60%) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 3.67 (s, 3H; $OCH_3$), 2.37 (ddd, *J* = 15.6, 9.7, 5.9 Hz, 1H; H-2a), 2.29 (ddd, *J* = 15.6, 9.4, 6.4 Hz, 1H; H-2b), 1.69 (m, 1H; H-4), 1.51 (m, 2H; H-6, H-10), 1.42–1.14 (m, 10H; H-3, H-5a, H-7a, H-8, H-9a, H-11a, H-12), 1.12–1.00 (m, 3H; H-7b, H-9b, H-11b), 0.96 (m, 1H; H-5b), 0.90–0.84 ppm (m, 12H; $CH_3$-4, $CH_3$-6, $CH_3$-10, H-13); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 174.79 (C=O), 51.66 ($CH_3O$), 44.99 ($CH_2$-5), 39.61 ($CH_2$-11), 37.67 ($CH_2$-9), 37.47 ($CH_2$-7), 32.75 (CH-10), 31.99 ($CH_2$-3), 31.90 ($CH_2$-2), 30.23 (CH-6), 29.96 (CH-4), 24.50 ($CH_2$-8), 20.39 ($CH_3$-4), 20.36 ($CH_2$-12), 20.12 ($CH_3$-6), 19.93 ($CH_3$-10), 14.62 ppm ($CH_3$-13); IR (film): $\tilde{\nu}_{max}$ = 2925, 1743, 1460, 1435, 1378, 1253, 1193, 1170, 1118 cm$^{-1}$; MS (CI+): *m/z* (%): 299 (20), 271 (100), 269 (51), 255 (15), 197 (5); HRMS (CI+): *m/z* calcd for $[C_{17}H_{35}O_2]^+$: 271.2637; found: 271.2645.

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