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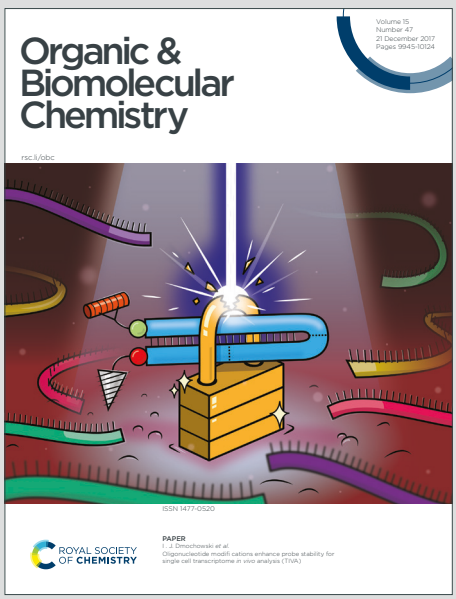

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Total synthesis of four stereoisomers of methyl 4,8,12-trimethylpentadecanoate, major component of the sex pheromone of the stink bug *Edessa meditabunda*

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Daiane Szczerbowski[a,b], Stefan Schulz[b] and Paulo Henrique Gorgatti Zarbin[a*]

[a]Laboratório de Semioquímicos, Chemistry Department, Federal University of Paraná, 81531-990 Curitiba, Brazil
[b]Institute of Organic Chemistry, Technische Universität Braunschweig, 38106 Braunschweig, Germany
*pzarbin@ufpr.br

Abstract

The male produced sex pheromone of the stink bug *Edessa meditabunda* was previously identified as a mixture of the esters methyl 4,8,12-trimethylpentadecanoate (**1**) and methyl 4,8,12-trimethyltetradecanoate (**2**), produced in a ratio of 92:8, respectively. Bioassays showed that the synthetic major compound alone is sufficient to elicit a response from females, and that it is as attractive as the natural extract. Here we present a stereoselective synthesis of four stereoisomers of methyl 4,8,12-trimethylpentadecanoate. The synthetic route was based on the connection of three chiral building blocks. High stereoisomeric purity was achieved by using commercially available compounds with defined stereochemistry, (*R*) and (*S*)-citronellol and methyl (*S*)-3-hydroxy-2-methylpropionate. Different stereoisomers were synthesized by swapping the sequence by which the building blocks were inserted into the synthetic route. The key steps in the synthesis were coupling reactions using the Fouquet-Schlosser variant of the Grignard reaction. Although the absolute configuration of the natural product remained elusive due to chromatographic inseparability of the stereoisomers, the syntheses gave access to both enantiomers of the biosynthetically most likely stereoisomer *syn*,*syn*-**1**, while all other stereoisomers can be efficiently synthesized by our straightforward approach.

Introduction

In the last decades there was an increase in the interest of studying semiochemicals, compounds transmitting information between living individuals, e.g. pheromones,[1] and to understand the role of chemical communication in insects that are pests in agriculture.[2] These substances can be applied in the field as an alternative to the use of agrochemicals, leading potentially to an improvement of crop production, with lower environmental impact and reduced costs compared to insecticides.[3] Usually, semiochemicals are isolated in very low amounts and consequently must be synthesized to get access to material for various studies. In pheromone chemistry, synthesis has three main purposes: providing synthetic standards to prove structure proposals, supply material for bioassays in the lab and in the field, and allow studies in structure-activity-relationships.[4]

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Brazil is the second major producer of soybean in the world. Every year, great losses in the production are caused by a variety of insects. The stink bug *Edessa meditabunda* is one of these pests that attack soybean crops. The insects feeds not only on the soybean pods but also suck the sap of the stems, causing serious injuries to the plant.[5] The male specific sex pheromone of *E. meditabunda* was previously identified as a mixture of two compounds, the major one being methyl 4,8,12-trimethylpentadecanoate (**1**) that is accompanied by methyl 4,8,12-trimethyltetradecanoate (**2**) (Figure 1).[6] Synthesis of a mixture of racemic stereoisomers and bioassays proved that the major compound alone elicits a response from females.[6]

It is well established that chirality plays a key role in pheromonal systems of insects, and the correct stereochemistry can be crucial for high attractiveness.[7] Therefore, we developed an efficient stereoselective approach to the synthesis of pure stereoisomers of **1** and prepared both enantiomers with *syn*,*syn*-configuration as well as an *anti*,*syn*- and a *syn*,*anti*-diastereomer. The structure of **1**, and its co-occurrence with **2,** strongly point to the fatty acid pathway for the biosynthesis of these compounds, involving malonate- and methylmalonate-units.[8] Among the possible stereoisomers of the molecule, we predominantly aimed at the synthesis of the two *syn*,*syn*-stereoisomers, because we believe that one of them might be the natural product, as in the stink bug *Pallantia macunaima*.[9, 10]

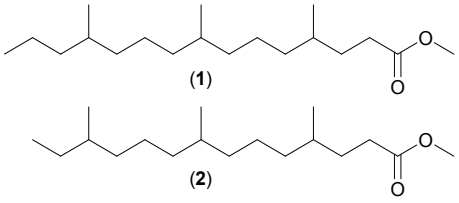

Figure 1: Sex pheromone components of males of *Edessa meditabunda*.

Results and discussion

Retroanalysis of the target compound (**1)** showed that it can be divided into three building blocks (**A**, **B** and **C**), as shown in Scheme 1. A convergent and economic synthesis was planned, with repeated use of the same building block in different syntheses. Chiral pool starting materials were selected for a high enantiomeric excess, which was needed to scrutinize the compounds' biological activities. The two outer building blocks (**A** and **B**) can be traced back to citronellol, which is available in both enantiomeric forms in high stereochemical purity. The middle part can be derived from building block **C**, a stereochemically pure, but regiochemically differentiated compound readily obtainable from commercial Roche ester, methyl (*S*)-3-hydroxy-2-methylpropionate.

To establish the strategy, we aimed to synthesize building blocks **B** and **C** only in the *S*-configuration. The key steps of coupling reactions between the blocks were achieved

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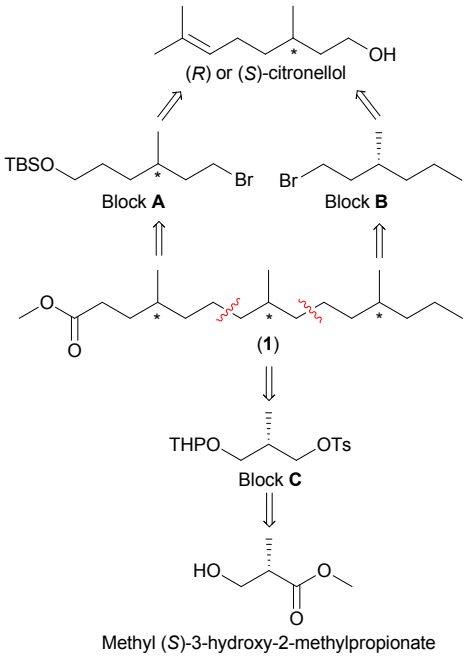
using the Fouquet-Schlosser variant of the Grignard reaction.[11] With the building blocks obtained we could synthesize four possible stereoisomers of **1**. However, this synthetic approach can easily be extended to all stereoisomers by using building blocks **B** and **C** in the *R*-configuration. Optimization of all steps in the synthetic route was initially performed by using racemic compounds.



Scheme 1: Retrosynthetic analysis of the major pheromone component **1.**

The building block (*S*)-**6** and its enantiomer (*R*)-**6** (Block **A**) were obtained from (*S*)- and (*R*)-citronellol (**3)** respectively, as shown in Scheme 2. Bromination of **3** by the Appel reaction afforded the products in 92% yield for the *S*-enantiomer and 93% for *R*.[12] The following ozonolysis of the double bond furnished alcohol (*S*)-**5** in 92% yield after reductive treatment with sodium borohydride.[13] Final protection with *tert*-butyldimethylsilyl chloride (TBSCl) produced building blocks (*S*)-**6** and (*R*)-**6** in good overall yield, 75% and 78% respectively.[14]

Building block (*S*)-**8** (Block **B**) was needed only in *S*-configuration. The intermediate (*S*)-**5** served as branching point, as shown in Scheme 2. In this case, the hydroxyl group of (*S*)-**5** was first converted into the tosylate, forming compound (*S*)-**7** in 88% yield.[15] For the selective removal of the tosyl group, $LiAlH_4$ reduction as reported by Krishnamurthy was used.[16] They propose that ether solvents with lower solving power for the Li ion, e.g. diethyl ether, lead to preferred removal of the tosylate group as compared to bromide as leaving group. This selectivity is attributed to the complexation of a lithium ion to the tosyl group, thus enhancing its leaving ability and directing the hydride attack to the carbon next to it. The only product isolated was (*S*)-**8** without any by-products. The moderate yield (76%) can be attributed to the high volatility of **8** that led to some loss during workup.

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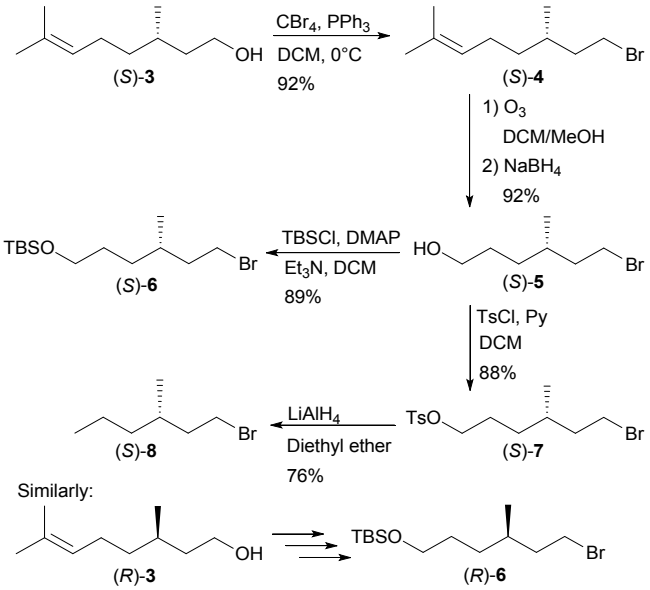

Scheme 2: Synthesis of chiral building blocks (*S*)-**6**, (*R*)-**6**, and (*S*)-**8**.

For the construction of the last chiral building block, (*S*)-**12** (Block **C**), commercially available methyl (*S*)-3-hydroxy-2-methylpropionate ((*S*)-**9**) was used, a compound often used in the stereoselective synthesis of pheromones.[8, 17-19] The first step was the protection of the hydroxyl group using dihydropyran (DHP) and *p*-toluenesulfonic acid (*p*-TSA), to furnish compound (*S*)-**10** in 95% yield. Reduction of the ester group with $LiAlH_4$ led to alcohol (*R*)-**11** (92%),[20] that was converted into the corresponding tosylate, building block (*S*)-**12**, in 74% overall yield through the three steps (Scheme 3).

After the synthesis of all building blocks, coupling reactions following the synthetic route shown in Scheme 4 led to the first two stereoisomers, (4*R*,8*S*,12*S*)-**1**, an *anti,syn*-stereoisomer, and (4*S*,8*S*,12*S*)-**1**, a *syn,syn*-stereoisomer. The Grignard reagent of bromide (*S*)-**6** was prepared in THF and reacted with tosylate (*S*)-**12** under Li_2CuCl_4 catalysis at -78°C. The orthogonally protected diol (2*R*,6*R*)-**13**, obtained in 70% yield, allowed access to different stereoisomers of **1**, depending on the elaboration of the two protecting groups. Selective removal of the THP group was achieved by application of the method of Kim et al. using anhydrous magnesium bromide in THF, furnishing the alcohol (2*R*,6*R*)-**14** in high yield (87%).[21] No TBS cleavage or diol formation was observed.

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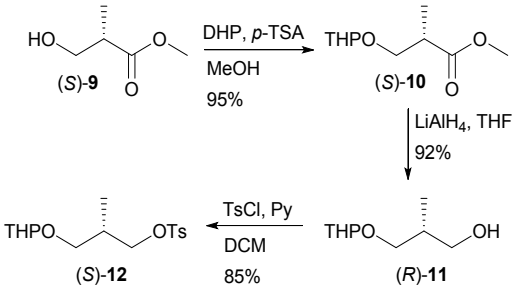
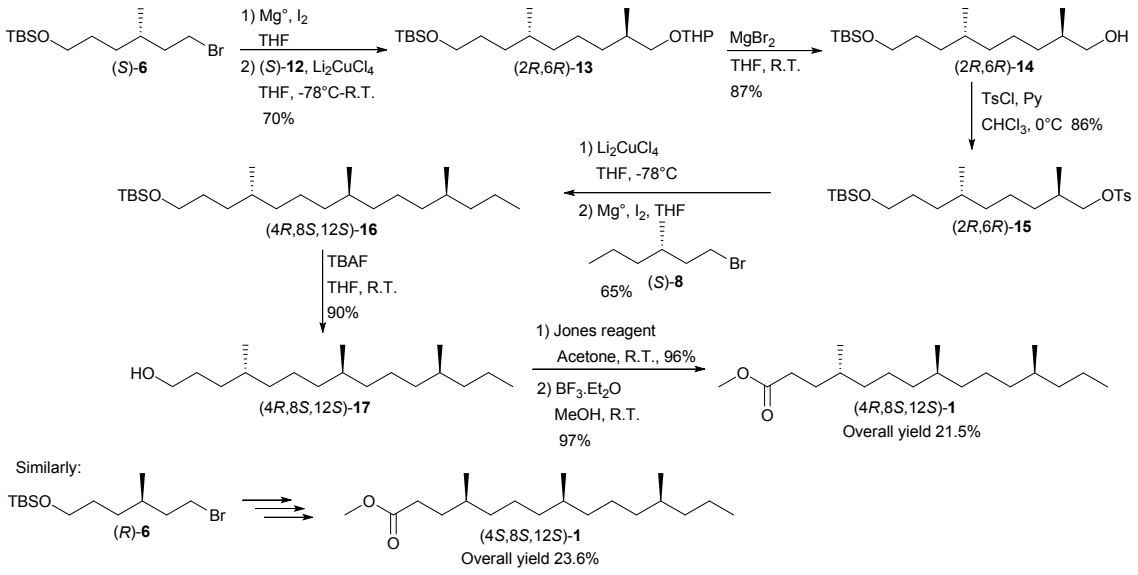


Scheme 3: Synthesis of chiral building block (*S*)-**12**.

Tosylate (2*R*,6*R*)-**15** was obtained in 86% yield and coupled with the Grignard reagent of bromide (*S*)-**8**, leading to the first trimethylated compound, (4*R*,8*S*,12*S*)-**16** in 65% yield. Deprotection of the hydroxyl group was achieved by using tetrabutylammonium fluoride solution (TBAF), furnishing alcohol (4*R*,8*S*,12*S*)-**17** in 90% yield. The last steps of the synthesis were oxidation to the corresponding acid, using Jones reagent, followed by esterification applying $BF_3.Et_2O$ in methanol, which finally lead to the first stereoisomer of compound **1**, *anti,syn*-configured methyl (4*R*,8*S*,12*S*)-trimethylpentadecanoate. The overall yield for the synthesis of this stereoisomer was 21.5% over 10 steps in its longest sequence. Through the same synthetic strategy, but starting with bromide (*R*)-**6**, the *syn,syn*-stereoisomer (4*S*,8*S*,12*S*)-**1** was obtained in 23.6% overall yield. Both isomers showed the same retention index and similar mass spectra and IR spectra as the natural compound.



Scheme 4: Synthetic route for stereoisomers (4*R*,8*S*,12*S*)-**1** and (4*S*,8*S*,12*S*)-**1**.

For the synthesis of the other two stereoisomers, key compound **13** should be deprotected by removal of the TBS group (Scheme 5). Now the alcohol could be

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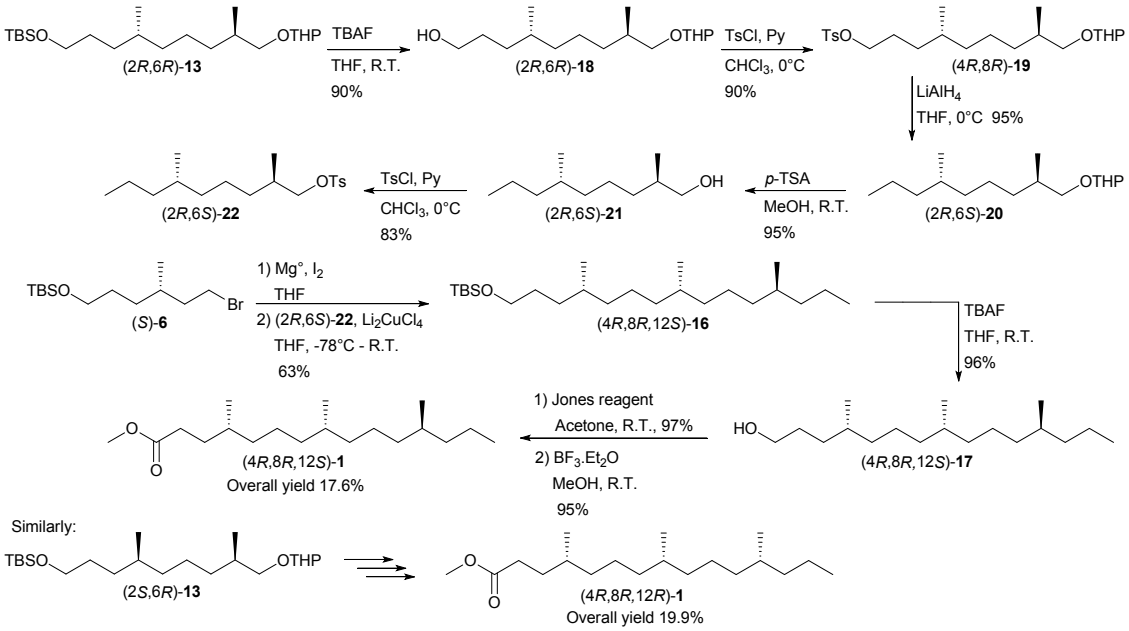
reduced via its tosylate, delivering the terminal end of **1** and placing the two stereogenic centers at this reduced end. In this manner, we would obtain the methyl groups at C-8 and C-12 in the opposite configuration of the previous synthesis, without the necessity to obtain building blocks **8** and **12** in *R*-configuration.

Starting from (2*R*,6*R*)-**13**, the TBS group was selectively removed by using TBAF, furnishing alcohol (2*R*,6*R*)-**18** in 90% yield. Tosylation (90%) and reduction with $LiAlH_4$ in THF were simple, furnishing acetal (2*R*,6*S*)-**20** in 95% yield. Subsequently, acidic methanolysis followed by tosylation of the obtained alcohol (2*R*,6*S*)-**21** furnished tosylate (2*R*,6*S*)-**22** in 83% yield. Coupling with the Grignard reagent generated from bromide (*S*)-**6** under the described conditions**,** yielded (4*R*,8*R*,12*S*)-**16** in 63% yield. Subsequently, the synthesis followed the route as already described for the other two stereoisomers. First, the hydroxyl group was deprotected using TBAF solution, followed by Jones oxidation and finishing with esterification with $BF_3{\cdot}Et_2O$ in methanol. Thus, the third stereoisomer was obtained, *syn,anti*-ester (4*R*,8*R*,12*S*)-**1** in 17.6% overall yield in 13 steps over the longest sequence. Similarly, following the same route but starting with intermediate (2*S*,6*R*)-**13**, the last stereoisomer**,** *syn,syn*-ester (4*R*,8*R*,12*R*)-**1** was synthesized in 19.9% overall yield. Both stereoisomers showed a similar retention index and similar mass spectra and IR spectra as the natural compound.



Scheme 5: Synthesis of stereoisomers (4*R*,8*R*,12*S*)-**1** and (4*R*,8*R*,12*R*)-**1** using intermediates (2*R*,6*R*)-**13** and (2*S*,6*R*)-**13**.

All stereoisomers showed similar mass and infrared spectra as the natural compound. The products were obtained in very high ee, because the stereogenic centers introduced

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by the chiral pool approach remained untouched during the syntheses. This is important because it turned out that there is currently no method to directly determine the ee of the compounds (see below).

We then tried to use the synthetic products for elucidation of the stereochemistry of natural **1** by chromatography. It is not trivial to separate stereoisomers of methyl-branched long-chain aliphatic compounds,[8] especially if the first methyl group is in γ-position to the functional group. Various attempts were performed, using either enantioselective GC with different columns or employing chiral derivatization reagents, such as (*S*)-2-acetoxypropionyl chloride or (*R*)-trans-chrysanthenoyl chloride,[22-24] in both GC and HPLC. For these derivatizations alcohols **17** were used instead of **1**, because an alcohol group in the analyte is needed for their use. Natural **1** can readily be transformed into **17** by reduction. All these methods proved unsuccessful. This was also true for the HPLC method developed by Ohrui et. al that had been successfully applied to various structures similar to compound **1**.[25-27] Further analytical studies are, therefore, necessary to achieve a good chromatographic separation of the stereoisomers that will allow to determine the absolute configuration of the male pheromone of *Edessa meditabunda*.

The understanding of the biosynthetic pathway leading to **1** might give some indications on the stereochemistry of the natural pheromone. The structure of **1** and its co-occurrence with **2** straightforwardly hint towards the fatty acid biosynthetic pathway. Biological synthesis of fatty acids is based on variations of a conserved set of chemical reactions in all organisms, regardless of the natural diversification in its structural organization.[28, 29] We hypothesize that the biosynthesis of compound **1** is initiated with a methylmalonyl-CoA starting unit, which leads to the main chain with 15 carbon atoms (Scheme 6 A). Malonyl-CoA units are inserted to elongate the chain, adding two carbons. The methyl groups are introduced by insertion of a methylmalonyl-CoA unit into the growing chain (Scheme 6 A). The stereochemistry of the methyl branch is likely controlled by a stereoselective NADPH-catalyzed reduction of the resulting α,β-unsaturated thioester by the enoyl-ACP reductase domain of the fatty acid synthase (FAS) (Scheme 6 B).[30] All these processes of the biosynthesis involve the action of a cascade of enzymes that are repeatedly used during one elongation cycle (Scheme 6 B). In the case of our target compound (**1**), the same enoyl-ACP reductase domain will reduce all three different 2-methylalkenoyl motifs encountered during the biosynthesis of **1**. Therefore, it is most likely that all three stereogenic centers generated by the enzyme have the same configuration. With this rationalization, we believe that the natural stereoisomer produced by the organism might be a *syn*,*syn*-stereoisomer, either (4*R*,8*R*,12*R*)-**1** or (4*S*,8*S*,12*S*)-**1**. This hypothesis is strongly supported by other species of stink bugs that had methyl branched compounds identified as sex pheromone. After determination of absolute configuration, all the molecules showed to be *syn, syn* isomers.[9, 10] Compound **2** might be formed as described, using malonate-CoA instead of methylmalonate-CoA as starting unit.

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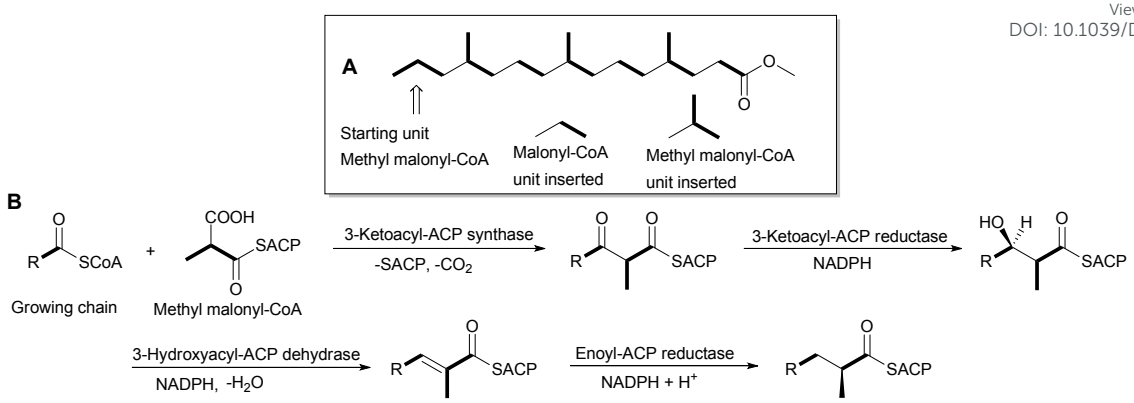

Scheme 6: A) Proposed biosynthetic building blocks in the biosynthesis of compound **1**. B) Enzymes involved in the incorporation of a new methylmalonyl-CoA unit in the growing chain leading to the methyl branches.

Conclusions

In summary, we developed the total synthesis of the two *syn*-*syn*-enantiomers of methyl 4,8,12-trimethylpentadecanoate (**1**), the most likely stereoisomeric arrangement in natural **1**. In addition, pure stereoisomers with *anti*,*syn*- and *syn*,*anti*-configuration were produced. A convergent synthetic route was developed, employing compounds from the chiral pool, (*R*) and (*S*)-citronellol (**3**) and methyl (*S*)-3-hydroxy-2-methylpropionate (**9**), thus ensuring a high ee of the target compounds. The three chiral building blocks obtained (**6**, **8** and **12**) were coupled through a Fouquet-Schlosser Grignard approach. The longest sequence of the route had 13 steps, and it was possible to obtain the target compounds in good overall yields ranging from 17.6% to 23.6%. Our approach can be modified to the synthesis of other stereoisomers and may also be used in the synthesis of structurally related compounds. More studies are necessary to achieve chromatographic separation of the stereoisomers of alcohol **17** or of **1**, to elucidate the absolute configuration of the natural pheromone. The four synthetic compounds will now be used in olfactometer tests, aiming to establish the stereochemistry-biological activity relationship for this pheromone.

Experimental

General information

When necessary, reagents and solvents used in the reactions were purified following methods described in the literature.[31] Anhydrous reactions were performed in flame dried glassware under an argon atmosphere. GC-MS analyses were performed in a Shimadzu QP2010 Plus mass spectrometer (EI 70 eV), coupled with a Shimadzu GC-2010 gas chromatograph. The samples were analysed using a capillary column RTX-5 (30m x 0,25mm i.d. x 0,25µm film thickness; Restek Chromatography Products, EUA),

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with a helium flow of 1 mL/min. The oven was initially held at 50°C, kept for one minute, followed by an increase of 7°C/min until finally 250°C were achieved, followed by 5 min isothermal period. GC/FTIR analysis were performed on a Shimadzu GC-2010 gas chromatograph coupled to a DiscovIR-GC (Spectra Analysis) detection system. The oven program started with 100°C for 1 minute, increasing with a rate of 10°C/min until 270°C were obtained, followed by a 10 min hold period. The samples were analysed using a capillary column RTX-5 (30m x 0,25mm i.d. x 0,25µm film thickness; Restek Chromatography Products, EUA), with a helium flow of 1 mL/min. NMR analyses were performed on Bruker ARX-200 and Bruker DPX-300 spectrometers. The chemical shifts (δ) are expressed in ppm and the coupling constants (*J*) are expressed in Hertz (Hz). All spectra were recorded in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. HRMS Spectra were measured with a Bruker Daltonics micrOTOF II-ESI-TOF mass spectrometer.

Experimental procedure

Preparation of Li_2CuCl_4 solution (0.1 M):[32] Lithium chloride (0.34 g, 8 mmol) was added to a flask, previously dried for 12 h at 200°C and equipped with a magnetic stirring bar. The system was submitted to vacuum and heated at 120°C for 3 h. After this period, the flask was cooled to room temperature and the pressure was equalized by the introduction of argon. Anhydrous $CuCl_2$ (0.536 g, 4 mmol) was added to the flask and the mixture was submitted to vacuum for additional 2 h at room temperature. Argon was introduced to the flask, anhydrous THF (40 mL) was added and the mixture was stirred for 1 h. The solution was stored under an argon atmosphere at room temperature.

Preparation of Jones reagent: Chromium trioxide (10 g, 0.1 mol) was dissolved in water (14 mL) and cooled in an ice bath. A solution of H_2SO_4 (8.7 mL, 0.16 mol, 18 M solution) and water (28 mL) are carefully added with manual stirring.

8-Bromo-2,6-dimethyloct-2-ene [(*S*) and (*R*)-4]: A solution of triphenylphosphine (5.03 g, 19.2 mmol) in DCM (13 mL) was added to a solution of (*S*)-citronellol [(*S*)-**3**] (2.32 mL, 12.8 mmol) and tetrabromomethane (5.1 g, 15.36 mmol) in DCM (38 mL), previously cooled in an ice bath. The ice bath was removed and the reaction mixture was stirred at room temperature for one hour. The reaction mixture was monitored by TLC. The solvent was removed by rotary evaporation under reduced pressure. The crude product was purified by column chromatography using hexane as eluent. Compound (*S*)-**4** was obtained in 92% yield. $[\alpha]_D^{25}$ = +5.55 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (d, *J* = 6.5 Hz, 3H), 1.10-1.25 (m, 1H), 1.27-1.42 (m, 1H), 1.57-1.76 (m, 8H), 1.81-2.11 (m, 3H), 3.34-3.51 (m, 2H), 5.05-5.13 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 131.4, 124.4, 40.0, 36.5, 32.0, 31.3, 25.7, 25.3, 18.8, 17.6; MS (70 eV) *m/z* (%): 220 (17), 218 (17), 164 (10), 162 (10), 150 (6), 148 (6), 97 (15), 95 (9), 70 (15), 69 (100), 56 (17), 55 (47); IR (υ_{max}, cm^{-1}): 566, 647, 973, 1263, 1379, 1456, 1723, 2872, 2925, 2963, 3368.
In the same manner, (*R*)-**4** was prepared starting from (*R*)-citronellol [(*R*)-**3**] (5.5 mL, 30.3 mmol), tetrabromomethane (10.62 g, 32 mmol) and triphenylphosphine (8.43 g, 32 mmol) in 93% yield. $[\alpha]_D^{25}$ = -5.79 (*c* = 1.1, $CHCl_3$).

6-Bromo-4-methylhexan-1-ol [(*S*) and (*R*)-5]: A solution of (*S*)-**4** (2.52 g, 11.56 mmol) in a mixture of DCM (129 mL) and methanol (86 mL) was prepared in a two-necked flask and was cooled to -60°C. Ozone was bubbled in the solution at a flow rate

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of 4 mL/min for approximately 40 min or until the appearance of the characteristic blue color of ozone. Excess ozone was removed by an air stream passed through the reaction flask for 30 min at 0°C with magnetic stirring. $NaBH_4$ (4.0 g, 105.74 mmol) was added in small portions during 1 h. After reaching room temperature, the solution was stirred for an additional 1 h. Aqueous sat. NH_4Cl solution (50 mL) was carefully added and the stirring was maintained for another 30 min. The solvent was removed under reduced pressure. Water was added (50 mL) and the reaction mixture was extracted with DCM (4 x 60 mL). The organic phase was washed with brine, dried over $MgSO_4$, and the solvent was removed. The crude product was used in the next step without further purification. (*S*)-**5** was obtained in 92% yield. $[\alpha]_D^{25} = +7.42$ (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (d, *J* = 6.3 Hz, 3H), 1.11-1.29 (m, 1H), 1.32-1.77 (m, 5H), 1.79-1.98 (m, 2H), 3.36-3.53 (m, 2H), 3.63 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 63.0, 39.8, 32.3, 32.0, 31.4, 29.9, 18.8; MS (70 eV) *m/z* (%): 178 (0.2), 176 (0.2), 150 (64), 148 (64), 97 (45), 81 (16), 70 (16), 69 (100), 55 (60), 41 (42); IR (υ_{max}, cm^{-1}): 897, 1058, 1266, 1381, 1464, 2868, 2935, 2957, 3277.
In the same manner, (*R*)-**5** was prepared starting from (*R*)-**4** (2.70 g, 24.77 mmol), yield 96%. $[\alpha]_D^{25} = -7.59$ (*c* = 1.0, $CHCl_3$).

6-Bromo-4-methylhexyl-1-oxy-*tert*-butyldimethylsilane [(*S*) and (*R*)-6]: A solution of (*S*)-**5** (0.84 g, 4.3 mmol), triethylamine (1.10 mL, 5.8 mmol) and catalytic amount of DMAP in anhydrous DCM (26 mL) was cooled to 0°C. *tert*-butyldimethylsilyl chloride (0.77 g, 5.16 mmol) was added to the mixture in 3 portions with intervals of 10 min. After 18 h the reaction mixture was washed with water and brine. The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The product was purified by flash chromatography using hexane/ethyl acetate 9.5:0.5 as mobile phase. (*S*)-**6** was obtained in 89% yield. $[\alpha]_D^{25} = +2.88$ (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.87-0.95 (m, 12H), 1.11-1.27 (m, 1H), 1.31-1.45 (m, 1H), 1.47-1.61 (m, 2H), 1.65-1.78 (m, 2H), 1.81-1.98 (m, 1H), 3.36-3.51 (m, 2H), 3.61 (t, *J* = 6.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 63.3, 40.0, 32.5, 32.0, 31.4, 30.0, 26.0, 18.9, 18.3, -5.3; MS (70 eV) *m/z* (%): 251 (0.2), 169 (3), 97 (36), 75 (18), 73 (11), 69 (24), 55 (100); IR (υ_{max}, cm^{-1}): 774, 833, 1096, 1253, 1467, 2857, 2889, 2930, 2954.
In the same manner, (*R*)-**6** was prepared starting from (*R*)-**5** (1.0 g, 5.1 mmol), triethylamine (1.32 mL, 6.96 mmol) and *tert*-butyldimethylsilyl chloride (0.91 g, 6.09 mmol), yield of 88%. $[\alpha]_D^{25} = -3.01$ (*c* = 1.0, $CHCl_3$).

(*S*)-6-Bromo-4-methylhexyl tosylate [(*S*)-7]: A solution of (*S*)-**5** (1.86 g, 9.59 mmol) in chloroform (7.5 mL) was cooled in an ice bath. Pyridine (1.5 mL, 19.2 mmol) was added, followed by the addition of *p*-toluenesulfonyl chloride (2.74 g, 14.6 mmol) in small portions with magnetic stirring. After 1 h, the mixture was diluted with ethyl acetate (40 mL) and water (10 mL) was added. The organic phase was successively washed with aqueous sat. $CuSO_4$ solution and then washed with water, dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The product was purified by flash chromatography using hexane/ethyl acetate 9:1 as mobile phase. The yield was 88%. ^1H NMR (200 MHz, $CDCl_3$): δ 0.85 (d, *J* = 6.4 Hz, 3H), 1.03-1.44 (m, 2H), 1.51-1.91 (m, 5H), 2.45 (s, 3H), 3.25-3.44 (m, 2H), 4.02 (t, *J* = 6.5 Hz, 2H), 7.22-7.42 (m, 2H), 7.69-7.84 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 144.7, 133.0, 129.8, 127.8, 70.7, 39.5, 31.9, 31.7, 30.9, 26.2, 21.6, 18.5; MS (70 eV) *m/z* (%): 240 (2), 173 (38), 172 (17), 155 (30), 150 (15), 148 (15), 97 (38), 91 (100), 69 (71), 68 (26), 55

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(90); IR (υ_{max}, cm^{-1}): 736, 818, 920, 967, 1101, 1178, 1191, 1356, 1456, 1601, 2855, 2876, 2929, 2962.

(*S*)-1-Bromo-3-methylhexane [(S)-8]: A solution of (*S*)-**7** (1.5 g, 4.45 mmol) in anhydrous diethyl ether (18 mL) was added dropwise to a suspension of lithium aluminum hydride (0.253 g, 6.68 mmol) in anhydrous diethyl ether (27 mL), previously cooled to 0°C. After 30 min with stirring the reaction mixture was diluted with diethyl ether (20 mL), water was carefully added (0.25 mL), followed by sodium hydroxide solution (0.25 mL, 15% aqueous solution) and again water (0.75 mL). The mixture was allowed to warm to room temperature and stirred for 15 min. $MgSO_4$ was added and the mixture was filtered. The solvent was removed under reduced pressure at room temperature. The product was purified through flash chromatography using hexane/ethyl acetate 9:1 as mobile phase The yield was 76%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84-0.95 (m, 6H), 1.07-1.39 (m, 4H), 1.58-1.72 (m, 2H), 1.78-1.95 (m, 1H), 3.33-3.53 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.0, 38.7, 32.2, 31.4, 19.9, 18.9, 14.3; MS (70 eV) *m/z* (%): 180 (2), 178 (2), 151 (28), 149 (28), 71 (100), 70 (34), 69 (35), 57 (51), 56 (25), 55 (76), 43 (92), 41 (58); IR (υ_{max}, cm^{-1}): 648, 1379, 1461, 1782, 2871, 2927, 2958; $[\alpha]_D^{25} = +1.42$ (*c* = 1.0, $CHCl_3$).

Methyl (*S*)-2-methyl-3-(tetrahydro-2*H*-pyran-2-yloxy)-propanoate [(*S*)-10]: Dihydropyran (0.59 mL, 6.44 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added to a solution of methyl (*S*)-3-hydroxy-2-methylpropanoate [(*S*)-**9**] (1.15 g, 5.48 mmol) in DCM (5.4 mL). The reaction mixture was stirred at room temperature for 4 h. The solution was washed with brine, the organic phase was dried over anhydrous $MgSO_4$, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. The yield was 95%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20 (dd, *J* = 7.0 Hz, 1.5 Hz, 3H), 1.46-1.90 (m, 6H), 2.79 (m, 1H), 3.40-3.69 (m, 2H), 3.71 (s, 3H), 3.73-3.99 (m, 2H), 4.56-4.69 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 175.3, 99.0 and 98.4, 69.3 and 68.9, 62.1 and 61.8, 51.6, 40.2 and 40.0, 30.6 and 30.5, 25.4, 19.3 and 19.2, 14.0; MS (70 eV) *m/z* (%):201 (1), 115 (13), 101 (59), 85 (100), 69 (18), 59 (28), 57 (17), 56 (17), 41 (27); IR (υ_{max}, cm^{-1}): 906, 974, 1035, 1126, 1205, 1365, 1460, 1741, 2881, 2947, $[\alpha]_D^{25} = +7.21$ (*c* = 1.0, $CHCl_3$).

(*R*)-2-Methyl-3-(tetrahydro-2*H*-pyran-2-yloxy)-propan-1-ol [(*R*)-11]: A solution of (*S*)-**10** (4.0 g, 19.76 mmol) in anhydrous THF (80 mL) was slowly added to a suspension of lithium aluminum hydride (1.48g, 39.47 mmol) in anhydrous THF (140 mL) at 0°C. The mixture was allowed to reach room temperature and stirred for 5 h. The reaction mixture was cooled to 0° C again, diluted with THF (70 mL), and water was carefully added (1.48 mL), followed by addition of NaOH solution (1.48 mL, 15% aqueous solution) and water again (4.44 mL). The mixture was allowed to warm to room temperature and stirred for 30 min. $MgSO_4$ was added and the mixture was filtered. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification and the yield was 92%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.93 (d, *J* = 6.9 Hz, 3H), 1.40-1.92 (m, 7H), 3.16 (s, 1H), 3.30-3.96 (m, 6H), 4.50-4.66 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 99.0 and 98.8, 71.2 and 71.1, 66.2 and 66.1, 62.1, 35.6 and 35.4, 30.3, 25.1, 19.3, 13.5 and 13.3; MS (70 eV) m/z (%): 173 (2), 144 (2), 101 (37), 85 (100), 84 (29), 67 (11), 57 (25), 56 (30), 55 (46), 41 (27); IR (υ_{max}, cm^{-1}): 1037, 1129, 1356, 1454, 2874, 2947, 3311; $[\alpha]_D^{25} = +6.17$ (*c* = 1.0, $CHCl_3$).

(*S*)-2-Methyl-3-(tetrahydro-2*H*-pyran-2-yloxy)-propyl tosylate [(S)-12]: Compound (S)-**12** was prepared in the same manner as (*S*)-**7**, starting from (*R*)-**11** (0.70 g, 4.02 mmol), pyridine (3 mL) and *p*-toluenesulfonyl chloride (0.84 g, 4.4 mmol). The product was purified through flash chromatography using hexane/ethyl acetate 8:2 as mobile phase. Compound (*S*)-**12** was obtained in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (dd, *J* = 6.9 Hz, 1.8 Hz, 3H), 1.39-1.82 (m, 6H), 2.02-2.17 (m, 1H), 2.45 (s, 3H), 3.16-3.30 (m, 1H), 3.41-3.52 (m, 1H), 3.54-3.65 (m, 1H), 3.67-3.81 (m, 1H), 3.90-4.17 (m, 2H), 4.41-4.50 (m, 1H), 7.31-7.37 (m, 2H), 7.76-7.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.6, 133.1, 129.8, 127.9, 99.1 and 98.6, 72.20 and 72.18, 68.4 and 67.9, 62.2 and 61.9, 33.6 and 33.5, 30.4, 25.4, 21.6, 19.4 and 19.3, 13.7 and 13.6; MS (70 eV) *m/z* (%): 227 (2), 173 (45), 172 (17), 155 (28), 101 (51), 91 (94), 85 (100), 84 (46), 72 (25), 65 (42), 57 (32), 55 (85), 54 (14); IR (υ_{max}, cm^{-1}): 664, 811, 966, 1174, 1357, 1598, 2874, 2942; $[\alpha]_D^{25}$ = +5.92 (*c* = 1.0, $CHCl_3$).

2,6-Dimethyl-9-(*tert*-butyldimethylsiloxy)-nonyloxy-tetrahydro-2*H*-pyran [(2*S*,6*R*) and (2*R*,6*R*)-13]: A Grignard reagent was prepared by slow addition of bromide (*S*)-**6** (1.0 g, 3.24 mmol) to magnesium turnings (0.087 g, 3.56 mmol previously dried and activated with iodine) in anhydrous THF (4.9 mL) under an argon atmosphere. The reaction mixture was stirred for 30 min after finishing the addition of the bromide. A solution of tosylate (*S*)-**12** (0.165 g, 0.5 mmol) in anhydrous THF (0.9 mL) was cooled to -78°C. After 30 min, a solution of Li_2CuCl_4 (3%, 0.15 mL, 0.1 M in THF) was added, the resulting mixture was stirred for 15 min and kept at -78°C. The previously prepared Grignard reagent of bromide (*S*)-**6** was added dropwise through a syringe to the solution, during 30 min. After the addition, the reaction mixture was kept at -78°C for 1 h. After this period the solution was allowed to reach room temperature and was stirred for 12 h. The reaction mixture was quenched by careful addition of aqueous sat. NH_4Cl solution and was extracted with ethyl acetate (3 x 5 mL). The organic phase was washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The product was purified through flash chromatography using hexane/ethyl acetate 9.5:0.5 as mobile phase. Compound (2*R*,6*R*)-**13** was obtained in 70% yield. $[\alpha]_D^{25}$ = +1.34 (*c* = 1.0, $CHCl_3$); MS (70 eV) *m/z* (%): 329 (0.4) 227 (9), 159 (100), 157 (4), 101 (25), 97 (69), 85 (97), 83 (50), 75 (83), 69 (66), 55 (64), 41 (47); IR (υ_{max}, cm^{-1}): 834, 1032, 1054, 1253, 1433, 2856, 2929; (2*R*,6*R*)-**13**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.80-1.03 (m, 15H), 1.04-1.19 (m, 3H), 1.23-1.63 (m, 12H), 1.66-1.83 (m, 3H), 3.05-3.32 (m, 1H), 3.40-3.75 (m, 4H), 3.78-4.00 (m, 1H), 4.52-4.65 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 99.0 and 98.6, 73.2 and 73.1, 63.6, 62.1 and 62.0, 37.2, 34.0, 33.4 and 33.3, 33.0, 32.6, 30.7, 30.4, 26.0 (3 x CH_3), 25.6, 24.3, 19.6, 18.3, 17.2 and 17.1, -5.28.

In the same manner, compound (2*S*,6*R*)-**13** was prepared starting from (*R*)-**6** (1.0 g, 3.26 mmol) and magnesium (0.12 g, 4.85 mmol). The suspension of the Grignard reagent formed was added to a solution of tosylate (*S*)-**12** (0.20 g, 0.61 mmol) and Li_2CuCl_4 (3%, 0.18 mL, 0.1 M in THF). The yield was 71%. $[\alpha]_D^{25}$ = +7.36 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.79-0.97 (m, 15H), 0.99-1.17 (m, 3H), 1.19-1.64 (m, 12H), 1.65-1.93 (m, 3H), 3.08-3.28 (m, 1H), 3.44-3.66 (m, 4H), 3.81-3.92 (m, 1H), 4.54-4.60 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 99.1 and 98.8, 73.2 and 73.0, 63.7, 62.2 and 62.1, 37.29 and 37,27; 34.1 and 34.0, 33.5 and 33.4, 32.90 and 32.89, 32,57 and 32,55, 30.7, 30.4, 25.9 (3 x CH_3), 25.6, 24.4 and 24.3, 19.7, 19.6 and 19.5, 18.4, 17.3 and 17.2, -5.3.

9-(*tert*-Butyldimethylsilyloxy)-2,6-dimethylnonan-1-ol [(2*R*,6*S*) and (2*R*,6*R*)-14]: Anhydrous $MgBr_2$ (0.131 g, 0.71 mmol) was added to a solution of (2*R*,6*R*)-**13** (0.095 g, 0.23 mmol) in anhydrous diethyl ether (2.7 mL) at room temperature. After stirring for 4 h water was added and the reaction mixture was extracted with ethyl acetate (3 x 4 mL). The organic phase was washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was used in the next step without further purification. Compound (2*R*,6*R*)-**14** was obtained in 87% yield. $[\alpha]_D^{25}$ = +5.27 (*c* = 1.0, $CHCl_3$); MS (70 eV) *m/z* (%): 243 (1), 227 (1), 97 (88), 95 (22), 83 (64), 75 (69), 69 (100), 57 (27), 55 (76), 41 (21); IR (υ_{max}, cm^{-1}): 1042, 1063, 1384, 1468, 2858, 2871, 2931, 3288; (2*R*,6*R*)-**14:** ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.80-1.00 (m, 15H), 1.04-1.18 (m, 2H), 1.21-1.43 (m, 6H), 1.45-1.74 (m, 4H), 3.33-3.51 (m, 2H), 3.59 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 68.3, 63.6, 37.2, 35.7, 33.4, 33.0, 32.5, 30.4, 26.0, 24.3, 19.6, 18.3, 16.5, -5.28.
In the same manner, compound (2*R*,6*S*)-**14** was prepared starting from (2*R*,6*S*)-**13** (0.127 g, 0.31 mmol) and $MgBr_2$ (0.175 g, 0.95 mmol), in 90% yield. $[\alpha]_D^{25}$ = +6.46 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.03-0.16 (m, 6H), 0.80-1.01 (m, 15H), 1.04-1.22 (m, 4H), 1.23-1.47 (m, 6H), 1.49-1.70 (m, 2H), 3.33-3.54 (m, 2H), 3.59 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 68.3, 63.6, 37.2, 35.7, 33.5, 32.9, 32.5, 30.3, 25.9, 24.3, 19.7, 18.3, 16.6, -5.31.

9-(*tert*-Butyldimethylsilyloxy)-2,6-dimethylnonyl tosylate [(2*R*,6*S*)- and (2*R*,6*R*)-15]: Compounds **15** were prepared in the same manner as described for compound (*S*)-**7**, starting from (2*R*,6*R*)-**14** (0.050 g, 0.17 mmol), pyridine (0.03 mL), and *p*-toluenesulfonyl chloride (0.040 g, 0.21 mmol). The product was purified through flash chromatography using hexane/ethyl acetate 9.5:0.5 as mobile phase. Compound (2*R*,6*R*)-**15** was obtained in 86% yield. $[\alpha]_D^{25}$ = -1.54 (*c* = 1.0, $CHCl_3$); MS (70 eV) *m/z* (%): 287 (1), 271 (2), 230 (16), 229 (100), 227 (10), 111 (15), 97 (64), 91 (18), 83 (39), 75 (59), 69 (49), 55 (31); (2*R*,6*R*)-**15**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.05-0,019 (m, 6H), 0.83-1.08 (m, 15H), 1.11-1.40 (m, 9H), 1.44-1.63 (m, 3H), 2.50 (s, 3H), 3.56-3.76 (m, 2H), 3.81-4.08 (m, 2H), 7.34-7.54 (m, 2H), 7.79-8.03 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 144.6, 133.2, 129.8, 127.9, 75.2, 63.6, 37.0, 32.9, 32.8, 32.5, 30.3, 26.0, 24.0, 21.6, 19.6, 18.3, 16.4, -5.3.
In the same manner, compound (2*R*,6*S*)-**15** was prepared starting from (2*R*,6*S*)-**14** (0.057 g, 0.19 mmol), pyridine (0.05 mL) and *p*-toluenesulfonyl chloride (0.048 g, 0.25 mmol), in 88% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.03-0.18 (m, 6H), 0.76-0.98 (m, 15H), 0.99-1.17 (m, 4H), 1.21-1.40 (m, 6H), 1.42-1.62 (m, 2H), 2.44 (s, 3H), 3.52-3.70 (m, 2H), 3.74-3.97 (m, 2H), 7.29-7.46 (m, 2H), 7.73-7.89 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 144.6, 133.2, 129.8, 127.9, 75.1, 63.6, 36.9, 32.9, 32.9, 32.8, 32.4, 30.3, 25.9, 23,9, 21.6, 19.6, 18.3, 16.4, -5.27.

4,8,12-Trimethylpentadecyloxy-*tert*-butyldimethylsilane [(4*R*,8*S*,12*S*), (4*S*,8*S*,12*S*), (4*R*,8*R*,12*S*) and (4*R*,8*R*,12*R*)-16]: Compounds **16** were prepared in the same manner as described for the stereoisomers of compound **13**. Bromide (*S*)-**8** (0.40 g, 2.22 mmol) and magnesium turnings (0.09 g, 3.30 mmol) were used. The suspension of the Grignard reagent formed was added to a solution of tosylate (2*R*,6*R*)-**15** (0.067 g, 0.22 mmol) and Li_2CuCl_4 (3%, 0.09 mL, 0.1 M in THF). The product was purified through flash chromatography using hexane as mobile phase. Compound (4*R*,8*S*,12*S*)-**16** was obtained in 65% yield. $[\alpha]_D^{25}$ = +0.95 (*c* = 1.0, $CHCl_3$); MS (70 eV) *m/z* (%): 384 (1), 369 (2), 329 (7), 328 (29), 327 (100), 139 (18), 125 (47), 111 (87), 97 (99), 83 (60), 75 (88), 71 (54), 69 (52), 57 (55), 43 (45); IR (υ_{max}, cm^{-1}): 777, 837, 940, 1099, 1252,

1379, 1467, 2858, 2896, 2928, 2957; (4*R*,8*S*,12*S*)-**16**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.79-0.94 (m, 21H), 1.03-1.14 (m, 4H), 1.18-1.38 (m, 15H), 1.43-1.60 (m, 4H), 3.59 (t, J = 6.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 63.7, 39.4, 37.5, 37.5, 37.4, 34.7, 34.5, 33.1, 32.8, 32.6, 32.5, 31.6, 30.4, 26.0, 25.3, 24.5, 22.7, 20.7, 20.2, 19.7, 18.4, 14.4, -5.3.

In the same manner, compound (4*S*,8*S*,12*S*)-**16** was prepared starting from bromide (*S*)-**8** (0.30 g, 1.68 mmol) and magnesium turnings (0.061 g, 2.5 mmol). The suspension of the Grignard reagent formed was added to a solution of tosylate (2*R*,6*S*)-**15** (0.052 g, 0.17 mmol) and Li_2CuCl_4 (3%, 0.08 mL, 0.1 M in THF). Compound (4*S*,8*S*,12*S*)-**16** was obtained in 63% yield. $[\alpha]_D^{25}$ = +2.19 (c = 1.0, $CHCl_3$).

In the same manner, compound (4*R*,8*R*,12*S*)-**16** was prepared starting from bromide (*S*)-**6** (0.123 g, 0.40 mmol) and magnesium turnings (0.02 g, 0.73 mmol). The suspension of the Grignard reagent formed was added to a solution of tosylate (2*R*,6*S*)-**22** (0.018 g, 0.055 mmol) and Li_2CuCl_4 (3%, 0.025 mL, 0.1 M in THF). Compound (4*R*,8*R*,12*S*)-**16** was obtained in 63% yield. $[\alpha]_D^{25}$ = -1.66 (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.78-0.93 (m, 21H), 1.00-1.17 (m, 4H), 1.19-1.44 (m, 15H), 1.46-1.62 (m, 4H), 3.59 (t, J = 6.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 63.7, 39.5, 37.5, 37.4, 37.4, 34.2, 33.0, 32.8, 32.61, 32.57, 32.5, 30.4, 30.4, 29.5, 26.0, 24.5, 20.2, 19.8, 19.7, 19.6, 19.2, 14.4, -5.2.

In the same manner, compound (4*R*,8*R*,12*R*)-**16** was prepared starting from bromide (*S*)-**6** (0.185 g, 0.60 mmol) and magnesium turnings (0.025 g, 0.90 mmol). The suspension of the Grignard reagent formed was added to a solution of tosylate (2*R*,6*R*)-**22** (0.030 g, 0.09 mmol) and Li_2CuCl_4 (3%, 0.04 mL, 0.1 M in THF). Compound (4*R*,8*R*,12*R*)-**16** was obtained in 70% yield. $[\alpha]_D^{25}$ = -2.30 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.82-0.92 (m, 19H), 0.98-1.19 (m, 4H), 1.21-1.42 (m, 15H), 1.44-1.61 (m, 4H), 3.59 (t, J = 6.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 63.7, 39.4, 37.4, 34.2, 32.9, 32.8, 32.6, 32.6, 32.5, 30.4, 29.5, 26.0, 24.5, 20.2, 19.8, 19.2, 18.4, 14.4, -5.3.

4,8,12-Trimethylpentadecan-1-ol [(4*R*,8*S*,12*S*), (4*S*,8*S*,12*S*), (4*R*,8*R*,12*S*) and (4*R*,8*R*,12*R*)-17]: A solution of Bu_4NF (0.19 mL, 0.19 mmol, 1 M in THF) was added to a solution of (4*R*,8*S*,12*S*)-**16** (0.051 g, 0.13 mmol) in anhydrous THF (0.5 mL) at room temperature. After stirring for 4 h water was added (1 mL) and the reaction mixture was extracted with ethyl acetate (3 x 2 mL). The organic phase was washed with aqueous sat. $NaHCO_3$ solution and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The product was purified through flash chromatography using hexane/ethyl acetate 9.5:0.5 as mobile phase. Compound (4*R*,8*S*,12*S*)-**17** was obtained in 90% yield. $[\alpha]_D^{25}$ = +3.07 (c = 1.0, $CHCl_3$); MS (70 eV) *m/z* (%): 269 (1), 252 (1), 154 (22), 111 (38), 98 (25), 97 (49), 85 (51), 84 (57), 83 (57), 71 (56), 70 (49), 69 (100), 57 (73), 56 (43), 55 (73), 43 (71), 41 (51); IR (υ_{max}, cm^{-1}): 737, 1063, 1381, 1466, 2846, 2859, 2872, 2928, 2962, 3278; (4*R*,8*S*,12*S*)-**17**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.79-0.92 (m, 12H), 1.00-1.19 (m, 5H), 1.20-1.46 (m, 15H), 1.48-1.65 (m, 3H), 3.63 (t, J = 6.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 63.5, 39.4, 37.5, 37.4, 37.3, 37.3, 33.0, 32.8, 32.6, 32.5, 30.4, 24.5, 24.4, 20.1, 19.7, 19.6, 14.4.

In the same manner, compound (4*S*,8*S*,12*S*)-**17** was prepared starting from (4*S*,8*S*,12*S*)-**16** (0.012 g, 0.03 mmol) and Bu_4NF (0.045 mL, 0.045 mmol, 1 M in THF), in 92% yield. $[\alpha]_D^{25}$ = +1.15 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.71-0.88 (m,

12H), 0.91-1.08 (m, 6H), 1.10-1.37 (m, 15H), 1.41-1.58 (m, 3H), 3.56 (t, J = 6.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 63.5, 39.4, 37.5, 37.4, 37.37, 37.32, 32.9, 32.8, 32.7, 32.5, 30.4, 24.4, 24.3, 20.1, 19.8, 19.7, 19.6, 14.4.

In the same manner, compound (4*R*,8*R*,12*S*)-**17** was prepared starting from (4*R*,8*R*,12*S*)-**16** (0.012 g, 0.03 mmol) and Bu_4NF (0.045 mL, 0.045 mmol, 1 M in THF), in 96% yield. $[\alpha]_D^{25}$ = -1.66 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.79-0.93 (m, 12H), 0.96-1.12 (m, 6H), 1.18-1.37 (m, 15H), 1.42-1.59 (m, 3H), 3.63 (t, J = 6.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 63.4, 39.5, 37.5, 37.4, 37.3, 32.9, 32.8, 32.7, 32.5, 30.4, 29.7, 24.4, 24.1, 20.2, 19.7, 19.65, 19.63, 14.4.

In the same manner, compound (4*R*,8*R*,12*R*)-**17** was prepared starting from (4*R*,8*R*,12*R*)-**16** (0.020 g, 0.052 mmol) and Bu_4NF (0.078 mL, 0.078 mmol, 1 M in THF), in 90% yield. $[\alpha]_D^{25}$ = -1.05 (*c* = 1.0, $CHCl_3$).

(4*R*,8*S*,12*S*), (4*S*,8*S*,12*S*), (4*R*,8*R*,12*S*) and (4*R*,8*R*,12*R*)-4,8,12-Trimethylpentadecanoic acid: Jones reagent was added dropwise to a solution of alcohol (4*R*,8*S*,12*S*)-**17** (0.032 g, 0.12 mmol) in acetone (2 mL) at room temperature, until the characteristic orange color remained. After stirring for 20 min water was added (2 mL) and the reaction mixture was extracted with hexane (3 x 2 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was used in the next step right after preparation, without further purification. The yield was 96% for (4*R*,8*S*,12*S*)-4,8,12-trimethylpentadecanoic acid. $[\alpha]_D^{25}$ = +1.61 (*c* = 1.0, $CHCl_3$); MS (70 eV) *m/z* (%): 41 (48), 43 (100), 55 (66), 57 (92), 69 (46), (77), 73 (62), 85 (64), 99 (31), 127 (18), 143 (27), 224 (1), 227 (17), 255 (1), 284 (6); IR (υ_{max}, cm^{-1}): 949, 1214, 1287, 1378, 1462, 1710, 2857, 2870, 2924, 2957.

In the same manner, (4*S*,8*S*,12*S*)-4,8,12-trimethylpentadecanoic acid was prepared starting from (4*S*,8*S*,12*S*)-**17** (0.007 g, 0.027 mmol), in 96% yield. $[\alpha]_D^{25}$ = +5.86 (*c* = 1.0, $CHCl_3$).

In the same manner, (4*R*,8*R*,12*S*)-4,8,12-trimethylpentadecanoic acid was prepared starting from (4*R*,8*R*,12*S*)-**17** (0.007 g, 0.027 mmol), in 97% yield. $[\alpha]_D^{25}$ = -2.57 (*c* = 1.0, $CHCl_3$).

In the same manner, (4*R*,8*R*,12*R*)-4,8,12-trimethylpentadecanoic acid was prepared starting from (4*R*,8*R*,12*R*)-17 (0.012 g, 0.046 mmol), in 95% yield. $[\alpha]_D^{25}$ = -5.80 (*c* = 1.0, $CHCl_3$). HRMS: Calculated for $C_{18}H_{35}O_2$ $[M-H]^-$ 283.2643; found 283.2631.

Methyl 4,8,12-trimethylpentadecanoate [(4*R*,8*S*,12*S*), (4*S*,8*S*,12*S*), (4*R*,8*R*,12*S*) and (4*R*,8*R*,12*R*)-1]: $BF_3{\cdot}Et_2O$ (0.041 mL, 0.33 mmol) was added to a solution of (4*R*,8*S*,12*S*)-4,8,12-trimethylpentadecanoic acid (0.031 g, 0.11 mmol) in anhydrous methanol (1 mL). This mixture was stirred for 14 h at room temperature. After this period aqueous sat. $NaHCO_3$ solution was added and the reaction mixture was extracted with hexane (3 x 2 mL). The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. It was not necessary to purify the final compound. Compound (4*R*,8*S*,12*S*)-**1** (*anti,syn*-stereoisomer) was obtained in 97% yield. $[\alpha]_D^{25}$ = +1.39 (*c* = 1.0, $CHCl_3$); MS (70 eV) *m/z* (%): 43 (42), 57 (34), 74 (32), 87 (100), 157 (18), 227 (4), 241 (12), 269 (1), 298 (2); IR (υ_{max}, cm^{-1}): 1713, 1196, 1379, 1435, 1463, 1743, 2847, 2860, 2873, 2929, 2957; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.77-0.91 (m, 12H), 1.01-1.14 (m, 4H), 1.18-1.49 (m, 16H), 1.58-1.73 (m, 1H), 2.21-2.40 (m, 2H),

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3.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7, 51.5, 39.5, 37.6, 37.5, 37.4, 37.1, 32.9, 32.5, 32.3, 32.1, 29.8, 24.6, 24.4, 20.2, 19.8, 19.3, 19.3, 14.5.

In the same manner, compound (4*S*,8*S*,12*S*)-**1** (*syn,syn*-stereoisomer) was obtained from (4*S*,8*S*,12*S*)-4,8,12-trimethylpentadecanoic acid (0.007 g, 0.025 mmol) and $BF_3.Et_2O$ (0.009 mL, 0.075 mmol), in 96% yield. $[\alpha]_D^{25}$ = +1.37 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.78-0.93 (m, 12H), 1.01-1.12 (m, 4H), 1.19-1.47 (m, 16H), 1.63-1.72 (m, 1H), 2.23-2.38 (m, 2H), 3.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6, 51.4, 39.4, 37.5, 37.4, 37.3, 37.0, 32.8, 32.5, 32.4, 31.9, 29.7, 24.5, 24.3, 20.1, 19.8, 19.7, 19.3, 14.4.

In the same manner, compound (4*R*,8*R*,12*S*)-**1** (*syn,anti*-stereoisomer) was obtained from (4*R*,8*R*,12*S*)-4,8,12-trimethylpentadecanoic acid (0.007 g, 0.025 mmol) and $BF_3.Et_2O$ (0.009 mL, 0.075 mmol), in 95% yield. $[\alpha]_D^{25}$ = -2.05 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.77-0.90 (m, 12H), 1.01-1.13 (m, 4H), 1.19-1.51 (m, 16H), 1.60-1.74 (m, 1H), 2.21-2.38 (m, 2H), 3.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6, 51.5, 39.5, 37.5, 37.5, 37.3, 37.0, 32.8, 32.5, 32.4, 32.0, 29.8, 24.5, 24.4, 20.2, 19.8, 19.5, 19.2, 14,5.

In the same manner, compound (4*R*,8*R*,12*R*)-**1** (*syn,syn*-stereoisomer) was obtained from (4*R*,8*R*,12*R*)-4,8,12-trimethylpentadecanoic acid (0.012 g, 0.044 mmol) and $BF_3.Et_2O$ (0.016 mL, 0.13 mmol), in 97% yield. (4*R*,8*R*,12*R*)-**1**: $[\alpha]_D^{25}$ = -1.43 (*c* = 0.57, $CHCl_3$).

2,6-Dimethyl-9-(tetrahydro-2*H*-pyran-2-yloxy)-nonan-1-ol [(2*R*,6*R*) or (2*S*,6*R*)-18]: Compounds **18** were prepared in the same manner as described for the stereoisomers of compound **17**. Compound (2*R*,6*R*)-**18** was prepared starting from (2*R*,6*R*)-**13** (0.075 g, 0.20 mmol) and Bu_4NF (0.3 mL, 0.30 mmol, 1 M in THF). The product was purified through flash chromatography using hexane/ethyl acetate 9:1 as mobile phase. Compound (2*R*,6*R*)-**18** was obtained in 90% yield. MS (70 eV) *m/z* (%): 55 (45), 57 (20), 69 (29), 85 (100), 101 (10), 187 (1), 199 (1); IR (υ_{max}, cm^{-1}): 1026, 1060, 1120, 1459, 2868, 2927, 3396; (2*R*,6*R*)-**18**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.71-0.91 (m, 6H), 0.95-1.35 (m, 9H), 1.40-1.88 (m, 9H), 2.98-3.22 (m, 1H), 3.33-3.60 (m, 4H), 3.69-3.86 (m, 1H), 4.43-4.58 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 98.9 and 98.7, 73.2 and 73.0, 63.0, 62.0 and 61.9, 37.1, 33.9, 33.31 and 33.26, 33.0, 32.5, 30.6, 30.2, 25.4, 24.2, 19.5, 19.45 and 19.39, 17.1 and 17.0.

In the same manner, compound (2*S*,6*R*)-**18** was prepared starting from (2*S*,6*R*)-**13** (0.154 g, 0.39 mmol) and Bu_4NF (0.51 mL, 0.51 mmol, 1 M in THF), in 89% yield. $[\alpha]_D^{25}$ = -5.14 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82-0.98 (m, 6H), 1.06-1.46 (m, 9H), 1.47-1.91 (m, 9H), 3.07-3.31 (m, 1H), 3.44-3.65 (m, 4H), 3.80-3.93 (m, 1H), 4.52-4.61 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 98.9 and 98.7, 73.1 and 72.9, 63.2, 62.1 and 62.0, 37.2, 34.0 and 33.9, 33.4 and 33.3, 32.8, 32.5, 30.6, 30.2, 25.4, 24.2 and 24.1, 19.6, 19.5 and 19.4, 17.2 and 17.1.

4,8-Dimethyl-9-(tetrahydro-2*H*-pyran-2-yloxy)-nonyl tosylate [(4*R*,8*R*) and (4*S*,8*R*)-19]: Compounds **19** were prepared in the same manner as for compound (*S*)-**7**. Compound (4*R*,8*R*)-**19** was prepared starting from (2*R*,6*R*)-**18** (0.049 g, 0.18 mmol), pyridine (0.3 mL) and *p*-toluenesulfonyl chloride (0.045 g, 0.23 mmol). The product was purified through flash chromatography using hexane/ethyl acetate 9:1 as mobile phase, giving (4*R*,8*R*)-**19** in 89% yield. MS (70 eV) *m/z* (%): 39 (27), 41 (57), 55 (66), 67 (29), 69 (63), 84 (62), 85 (100), 91 (52), 97 (47), 101 (12), 109 (16), 11 (17), 123

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(8), 155 (12), 173 (16), 252 (6), 396 (1); IR (υ_{max}, cm^{-1}): 662, 1030, 1175, 1359, 2870, 2927.

In the same manner, compound (4*S*,8*R*)-**19** was prepared starting from (2*S*,6*R*)-**18** (0.070 g, 0.26 mmol), pyridine (0.5 mL) and *p*-toluenesulfonyl chloride (0.079 g, 0.41 mmol), in 90% yield. $[\alpha]_D^{25}$ = +7.24 (*c* = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.77-0.84 (m, 3H), 0.87-0.96 (m, 3H), 1.04-1.38 (m, 9H), 1.48-1.86 (m, 9H), 2.45 (s, 3H), 3.09-3.27 (m, 1H), 3.44-3.65 (m, 2H), 3.80-3.91 (m, 1H), 3.97-4.05 (t, *J* = 6.6 Hz, 2H), 4.52-4.60 (m, 1H), 7.31-7.38 (m, 2H), 7.76-7.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.6, 133.3, 129.8, 127.9, 99.1 and 98.8, 73.1 and 73.0, 71.1, 62.2 and 62.1, 37.1 and 37.0, 34.0 and 33.9, 33.4, 33.3, 32.4, 32.27 and 32.25, 30.7, 26.4, 25.5, 24.3 and 24.2, 21.6, 19.6, 19.5 and 19.4, 17.2 and 17.1.

2-(2,6-dimethylnonyloxy)-tetrahydro-2*H*-pyran [(2*R*,6*S*) and (2*R*,6*R*)-20]: Compounds **20** were prepared in the same manner as (*S*)-**10**. Compound (2*R*,6*S*)-**20** was prepared starting from (4*R*,8*R*)-**19** (0.060 g, 0.15 mmol) and $LiAlH_4$ (0.011 g, 0.30 mmol). The product was purified through flash chromatography using hexane as mobile phase, yielding (2*R*,6*S*)-**20** in 95% yield. $[\alpha]_D^{25}$ = +2.19 (*c* = 1.0, $CHCl_3$); MS (70 eV) *m/z* (%): 53 (2), 55 (22), 57 (33), 69 (7), 71 (13), 85 (100), 101 (4), 198 (1); IR (υ_{max}, cm^{-1}): 817, 968, 1099, 1180, 1190, 1358, 1469, 1603, 2858, 2874, 2929, 2968; (2*R*,6*S*)-**20**: ^1H NMR (200 MHz, $CDCl_3$): δ 0.78-0,99 (m, 9H), 1.01-1.45 (m, 11H), 1.49-1.97 (m, 7H), 3.05-3.33 (m, 1H), 3.40-3.71 (m, 2H), 3.77-3.98 (m, 1H), 4.50-4.67 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 99.0 and 98.7, 73.2 and 73.1, 62.1 and 62.0, 39.4, 37.3, 34.0, 33.4, 33.3, 32.4, 30.7, 25.5, 24.3, 20.1, 19.6, 17.2 and 17.1, 14.3.

In the same manner, compound (2*R*,6*R*)-**20** was prepared starting from (4*S*,8*R*)-**19** (0.10 g, 0.24 mmol) and $LiAlH_4$ (0.018 g, 0.48 mmol), in 96% yield. $[\alpha]_D^{25}$ = +2.31 (*c* = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.73-0.96 (m, 9H), 1.00-1.15 (m, 3H), 1.18-1.45 (m, 8H), 1.50-1.95 (m, 7H), 3.03-3.33 (m, 1H), 3.40-3.70 (m, 2H), 3.75-4.00 (m, 1H), 4.47-4.67 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 99.0 and 98.7, 73.2 and 73.0, 62.1 and 62.0, 39.4 and 39.3, 37.34 and 37.33, 34.1 and 34.0, 33.5, 33.4, 32.46 and 32.45, 30.7, 25.5, 24.4 and 24.3, 20.1, 19.7 and 19.5, 17.3 and 17.2, 14.4.

2,6-Dimethylnonan-1-ol [(2*R*,6*R*) and (2*R*,6*S*)-21]: Catalytic amount of *p*-TSA was added to a solution of (2*R*,6*S*)-**20** (0.066 g, 0.26 mmol) in methanol (1 mL) at room temperature. The evolution of the reaction was monitored by TLC. After 4 h the solvent was remover under reduced pressure and the residue was dissolved in ethyl acetate (4 mL). The organic phase was washed with aqueous sat. $NaHCO_3$ solution and brine, dried over $MgSO_4$ and the solvent removed. The crude product was used in the next step without further purification and the yield was 95% for (2*R*,6*S*)-**21**. $[\alpha]_D^{25}$ = + 12.47 (*c* = 1.0, $CHCl_3$); MS (70 eV) *m/z* (%): 43 (83), 55 (75), 57 (61), 69 (100), 70 (69), 71 (53), 84 (71), 85 (49), 97 (28), 111 (86), 126 (5), 154 (2), 171 (1); IR (υ_{max}, cm^{-1}): 738, 1036, 1378, 1462, 2870, 2925, 2956, 3335; (2*R*,6*S*)-**21**: ^1H NMR (200 MHz, $CDCl_3$): δ 0.73-0.99 (m, 8H), 1.01-1.17 (m, 3H), 1.18-1.42 (m, 8H), 1.50-1.78 (m, 2H), 1.88 (s, 1H), 3.30-3.61 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 68.4, 39.4, 37.3, 35.7, 33.4, 32.4, 24.3, 20.1, 19.6, 16.5, 14.3.

In the same manner, compound (2*R*,6*R*)-**21** was prepared starting from (2*R*,6*R*)-**20** (0.050 g, 0.19 mmol), in 94% yield. $[\alpha]_D^{25}$ = + 7.12 (*c* = 1.0, $CHCl_3$) ^1H NMR (300 MHz, $CDCl_3$): δ 0.79-0.96 (m, 9H), 0.97-1.15 (m, 3H), 1.17-1.45 (m, 8H), 1.51-1.68 (m, 2H), 3.40 (dd, *J* = 10.5 Hz, 6.6 Hz, 1H), 3.52 (dd, *J* = 10.5 Hz, 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 68.4, 39.3, 37.3, 35.8, 33.5, 32.6, 24.4, 20.1, 19.7, 16.6, 14.4.

2,6-Dimethylnonyl tosylate [(2*R*,6*S*) or (2*R*,6*R*)-22]: Compounds **22** were prepared in the same manner as (*S*)-**7**. Compound (2*R*,6*S*)-**22** was prepared starting from (2*R*,6*S*)-**21** (0.042 g, 0.25 mmol), pyridine (0.04 mL) and p-toluenesulfonyl chloride (0.048 g, 0.25 mmol). The product was purified through flash chromatography using hexane/ethyl acetate 9.5:0.5 as mobile phase, giving (2*R*,6*S*)-**22** in 83% yield. $[\alpha]_D^{25}$ = -1.27 (*c* = 1.0, $CHCl_3$); MS (70 eV) *m/z* (%): 43 (38), 55 (37), 69 (52), 84 (52), 91 (88), 97 (20), 111 (75), 154 (41), 155 (63), 173 (100), 228 (1), 327 (1); IR (υ_{max}, cm^{-1}): 665, 961, 1174, 1360, 2870, 2927, 2966; (2*R*,6*S*)-**22**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.81 (d, *J* = 6.5 Hz, 3H), 0.84-0.91 (m, 6H), 0.94-1.12 (m, 3H), 1.15-1.36 (m, 8H), 1.68-1.85 (m, 1H), 2.45 (s, 3H), 3.80 (dd, *J* = 9.3 Hz, 6.5 Hz, 1H), 3.89 (dd, *J* = 9.3 Hz, 5.7 Hz, 1H), 7.31-7.37 (m, 2H), 7.76-7.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.5, 133.2, 129.8, 127.9, 75.2, 39.4, 37.0, 32.9, 32.8, 32.4, 24.0, 21.6, 20.1, 19.5, 16.4, 14.4.
In the same manner, compound (2*R*,6*R*)-**22** was prepared starting from (2*R*,6*S*)-**21** (0.032 g, 0.19 mmol), pyridine (0.36 mL) and p-toluenesulfonyl chloride (0.058 g, 0.30 mmol), in 85% yield. $[\alpha]_D^{25}$ = -3.46 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.79 (d, *J* = 6.5 Hz, 3H), 0.83-0.92 (m, 7H), 0.93-1.12 (m, 4H), 1.13-1.40 (m, 9H), 1.69-1.84 (m, 1H), 2.45 (s, 3H), 3.80 (dd, *J* = 9.3 Hz, 6.5 Hz, 1H), 3.89 (dd, *J* = 9.3 Hz, 5.7 Hz, 1H), 7.31-7.38 (m, 2H), 7.76-7.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.6, 133.2, 129.8, 127.9, 75.1, 39.3, 37.0, 32.9, 32.8, 32.3, 24.0, 21.6, 20.1, 19.6, 16.5, 14.4.

Conflicts of interest

There are no conflicts to declare.

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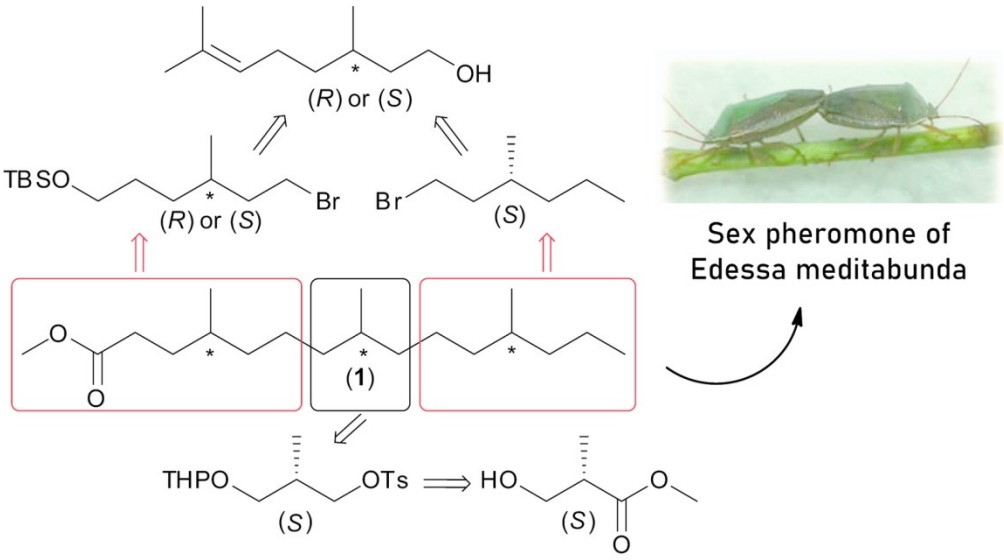

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