Pheromone Synthesis, CXCV[+]

Synthesis of (1*R**,3*R**,7*R**)-3-Methyl-α-himachalene, the Racemate of the Male-Produced Sex Pheromone of the Sandfly *Lutzomyia longipalpis* from Jacobina, Brazil

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Keywords: Cycloadditions / Leishmaniasis / *Lutzomyia longipalpis* / Pheromones / Sandfly

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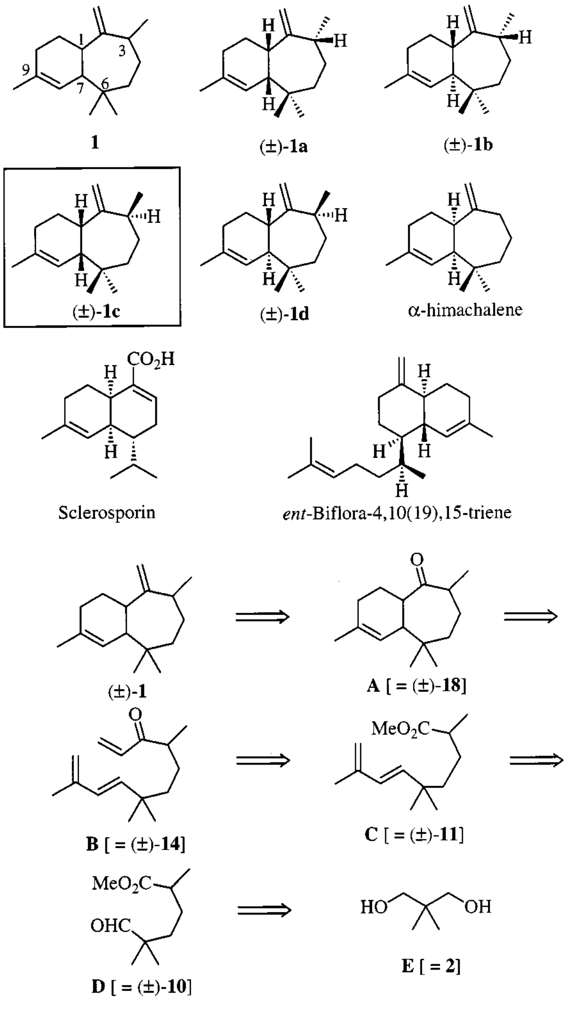
Four stereoisomers (**1a–d**) of (±)-3-methyl-α-himachalene were synthesized by employing the intramolecular Diels–Alder reaction of (±)-**14** to (±)-**18** as the key-step. The male-produced sex pheromone of the sandfly *Lutzomyia longipalpis* was shown to possess the structure and relative configuration as depicted in **1c**.

Introduction

The leishmaniases are parasitic diseases with a wide range of clinical symptoms such as cutaneous, mucocutaneous, and visceral, and the suffering they cause threatens 350 million people in 88 countries around the world[1]. The sandfly *Lutzomyia longipalpis* is the only vector of the protozoan parasite *Leishmania chagasi*, the causative agent of visceral leishmaniasis in South and Central America[2]. In 1994 Hamilton et al. isolated the sex pheromone of male *Lutzomyia longipalpis* from Jacobina, Brazil, and confirmed its activity by bioassay[3]. Subsequently in 1996, 3-methyl-α-himachalene {2-methylene-3,6,6,9-tetramethylbicyclo[5.4.0]undec-8-ene (**1**), stereochemistry unknown} was proposed as the structure of that pheromone on the basis of its MS and ^{1}H-NMR studies[4]. α-Himachalene is a sesquiterpene isolated from Himalayan deodar *Cedrus deodara*[5], and its absolute configuration was determined as depicted in Scheme 1 by CD studies of its degradation products[6].

We became interested in the synthesis of **1** so as to verify the structural proposal. Because the stereochemistry of the naturally occurring **1** was unknown, it was necessary at first to determine its relative configuration by synthesizing all of the four possible stereoisomers **1a**−**1d** as the racemates. With this objective in mind, we planned the synthesis of **1** as shown in Scheme 1. The target molecule (±)-**1** can be prepared by methylenation of the ketone **A**, which in turn is to be provided by an intramolecular Diels−Alder reaction of **B**. Intramolecular Diels−Alder reaction is a well-known reaction in terpene synthesis, and we ourselves previously employed it in the synthesis of sclerosporin[7] and *ent*-biflora-4,10(19),15-triene[8]. Indeed, all of the three existing syntheses of α-himachalene[9−11], including the enantioselective one[11], were based on this reaction. The precursor **B** is derivable from the dienoic ester **C**, which is obtainable from **D** by Wittig reaction. 2,2-Dimethyl-1,3-propanediol (**E**) was chosen as the starting material to furnish



Scheme 1. Structures of the stereoisomers of 3-methyl-α-himachalene and their synthetic plan

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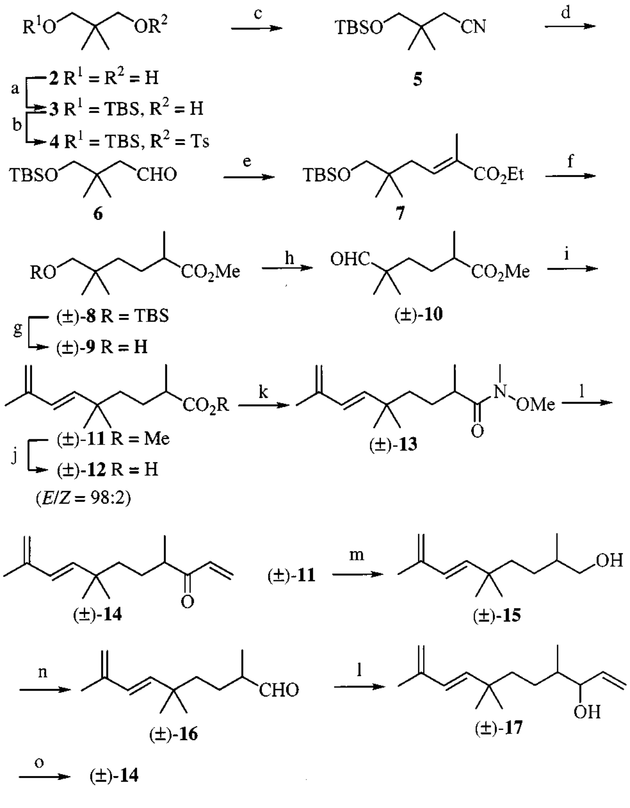
D. This plan was realized as described below, and the relative configuration of the naturally occurring pheromone was determined as depicted in **1c** by direct comparison with an authentic sample.

Results and Discussion

Synthesis of Precursor B [(±)-14]

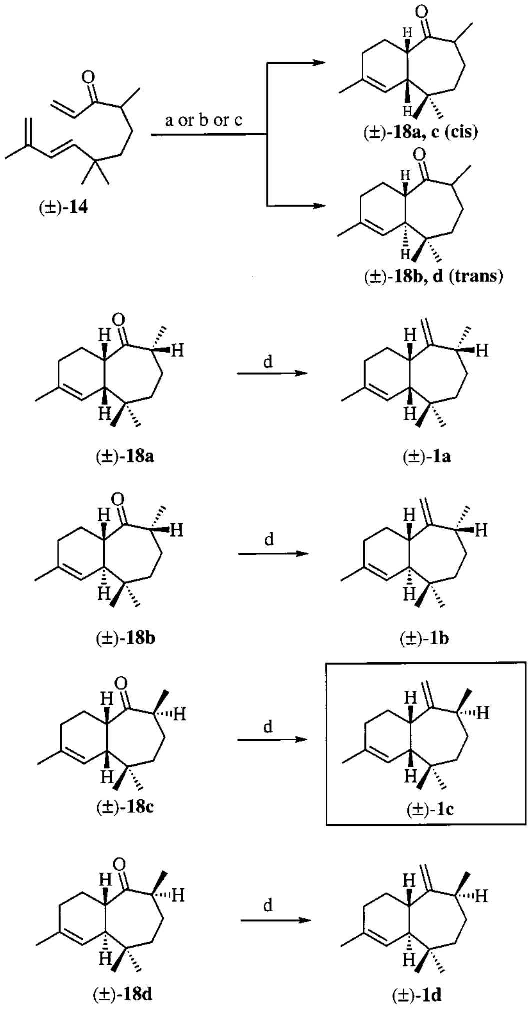
Scheme 2 summarizes the synthesis of the key precursor **B** [(±)-**14**] for the intramolecular Diels−Alder reaction. In order to discriminate the two hydroxy groups of the diol **2**, it was treated with 1.1 equiv. of *tert*-butyldimethylsilyl(TBS) chloride in the presence of 1.0 equiv. of sodium hydride to give the mono TBS ether **3**[12]. Tosylation of **3** was followed by treatment of the resulting tosylate **4** with sodium cyanide to furnish the nitrile **5**. Reduction of **5** with diisobutylaluminum hydride (DIBAL) afforded the aldehyde **6**, which was converted into the α,β-unsaturated ester **7** by a Wittig reaction. The olefinic double bond of **7** was reduced with dissolving magnesium in methanol[13][14] to give ester (±)-**8**. Desilylation of (±)-**8** and Swern oxidation of the hydroxy ester (±)-**9** yielded the aldo ester (±)-**10**. Olefin formation by the Wittig reaction converted (±)-**10** to the dienoic ester (±)-**11**, whose (*E*)/(*Z*) ratio was 98:2 as determined by GC analysis. The corresponding acid (±)-**12**, obtained by alkaline hydrolysis of (±)-**11** was then processed according to the general procedure of Weinreb for the conversion of acid to ketone[15]. The acid (±)-**12** thus yielded the *N*-methoxy-*N*-methylamide (±)-**13** by treatment with *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), *N*-ethyldiisopropylamine and *N*,*N*-4-dimethylaminopyridine (DMAP) in dichloromethane. Treatment of (±)-**13** with vinylmagnesium bromide furnished the desired precursor (±)-**14** in 17.4% overall yield based on **2** (12 steps). More conventional conversion of (±)-**11** to (±)-**14** was also executed as follows. Reduction of (±)-**11** with lithium aluminum hydride gave the alcohol (±)-**15**, which was oxidized with pyridinium chlorochromate (PCC) to furnish the aldehyde (±)-**16**. This was treated with vinylmagnesium bromide to give the alcohol (±)-**17**. Finally, the Dess−Martin oxidation[16] of (±)-**17** afforded the precursor (±)-**14**. In this case, overall yield of (±)-**14** was 16.3% (13 steps) based on **2**.



Scheme 2. Synthesis of the acyclic precursor for the Diels−Alder reaction; reagents: (a) NaH, TBSCl, THF (96%). − (b) TsCl, C_5H_5N, $CHCl_3$. − (c) NaCN, DMSO, (94%, 2 steps). − (d) i) DIBAL, CH_2Cl_2; ii) H_3O^+ (90%). − (e) $Ph_3P{=}C(Me)CO_2Et$, C_6H_6 (74%). − (f) Mg, MeOH (88%). − (g) HF/H_2O, MeCN (93%). − (h) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N (83%). − (i) $CH_2{=}C(Me)CH{=}PPh_3$, THF. − (j) KOH, MeOH (72%, 2 steps). − (k) i) EDCI, MeO(Me)NH·HCl, *i*Pr_2NEt, DMAP, CH_2Cl_2 (82%). − (l) $CH_2{=}CHMgBr$, THF [72% for (±)-**14**; 70% for (±)-**17** (2 steps)]. − (m) $LiAlH_4$, Et_2O (92%). − (n) PCC, MS 4-Å, CH_2Cl_2. − (o) Dess−Martin periodinane, C_5H_5N, CH_2Cl_2 (86%)

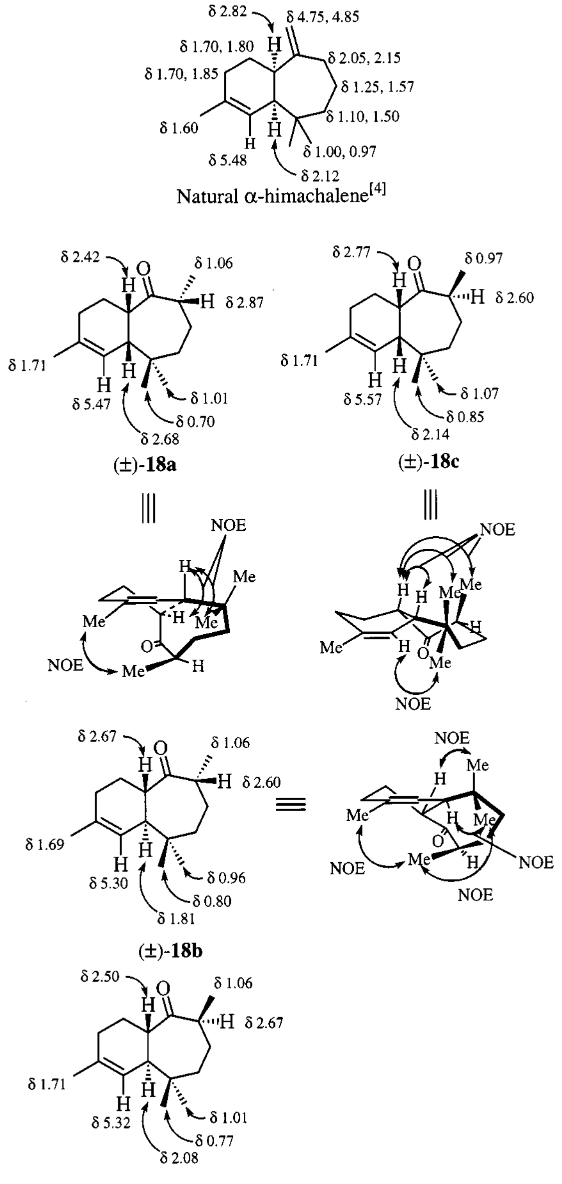
The Key Intramolecular Diels−Alder Reaction and the Relative Configuration of the Four Products (±)-18a−d

The final two steps leading to the racemic stereoisomers (±)-**1a−d** of the pheromone are summarized in Scheme 3. When a solution of the acyclic precursor (±)-**14** in benzene was heated under reflux, Diels−Alder reaction did not take place completely. This was in contrast with our past experience in the synthesis of sclerosporin[7] and *ent*-biflora-4,10(19),15-triene[8], in which their acyclic precursors spontaneously gave the octalin ring systems even at room temperature. However, when a xylene solution of (±)-**14** was heated at 130°C, the expected cycloaddition took place to give a mixture of the four stereoisomers of (±)-**18** in 56% yield. ¹H-NMR spectroscopy was useful for the determination of the ratio of (±)-**18a**,**c** (*cis*-isomers) and (±)-**18b**,**d** (*trans*-isomers). Because the proton at C-8 of α-himachalene was known to absorb at δ = 5.48[4], the *cis* isomers (±)-**18a**,**c** were thought to be those which showed signals at δ = 5.47 and 5.57, while those with the signals at δ = 5.30 and 5.32 were considered to be the *trans*-isomers (±)-**18b**,**d**. Other conditions for the Diels−Alder reaction were also evaluated. First, the Lewis-acid catalyzed cycloaddition of (±)-**14** (*E*/*Z* = 89:11 as determined by ¹H-NMR analysis) was executed in the presence of diethylaluminum chloride in dichloromethane at −78 °C to 0 °C[17]. Both the yield of (±)-**18** and *cis*/*trans* selectivity increased to 74% and 81:19, respectively. The effect of lithium perchlorate as its 5.0 M solution in diethyl ether[18][19] was then examined in the presence of 1.0 mol-% (+)-camphorsulfonic acid at room temperature to give (±)-**18** in much better yield (93%) and even higher selectivity (87:13). The purpose of our present study, however, was to determine the relative configuration of the natural pheromone. We therefore had to secure all the possible stereoisomers of **1**. Accordingly, the procedure to heat up (±)-**14** in xylene alone was chosen to give a mixture of (±)-**18a–d**.



Scheme 3. Synthesis of the stereoisomers of (±)-3-methyl-α-himachalene; reagents: (a) xylene, 130°C (56%; *cis*/*trans* = 52:48). – (b) Et_2AlCl CH_2Cl_2, –78 °C – 0 °C (74%; *cis*/*trans* = 81:19). – (c) $LiClO_4$, 1.0 mol-% CSA, Et_2O, room temp. (92%; *cis*/*trans* = 82:18). (d) Tebbe reagent $[Cp_2Ti(Cl)CH_2AlMe_2]$, THF, toluene, –40 °C – room temp. (quant.)

The next problem was the separation of each of the stereoisomers. Conventional silica gel chromatography separated the mixture into two spots, one with R_f = 0.64 and the other with R_f = 0.61 (hexane/ethyl acetate = 10:1). These were further separated by MPLC to give four products (±)-**18a**, (±)-**18b**, (±)-**18c** and (±)-**18d** in the order of elution. The major product (±)-**18a** and (±)-**18c** were obtained pure as judged from ^{1}H-NMR spectra, while (±)-**18b** and (±)-**18d** were contaminated with a small amount of (±)-**18a** and (±)-**18c**, respectively. The relative configuration of these stereoisomers of (±)-**18** was then clarified by their detailed 500 MHz ^{1}H-NMR analysis (NOESY) as shown in Scheme 4. In both of the major ketones (±)-**18a** and (±)-**18c** a nuclear Overhauser effect (NOE) could be observed between the protons at C-1 and C-7, indicating their ring-juncture to be *cis*. In the case of (±)-**18a**, another NOE could be observed between the protons of the methyl group at C-3 and those of the methyl group at C-9. The relative configuration of (±)-**18a** was therefore assigned as shown in Scheme 4. We gave the depicted relative configuration to (±)-**18c**, because an NOE was observed between the protons of the methyl group at C-3 and the proton at C-1. The structure (±)-**18b** was assigned to one of the *trans*-isomers and the relative configuration was determined as shown in Scheme 4 for the following reasons. An NOE could be observed between the proton at C-1 and those of the β-methyl group at C-6, and also between the protons of α-methyl group and the proton at C-7. One other NOE could also be observed between the protons of α-methyl group at C-6 and those of methyl group at C-3. The remaining isomer



Scheme 4. Structures and ^{1}H-NMR data of the four stereoisomers of (±)-**18**

was considered to possess the relative configuration as depicted in (±)-**18d**.

Synthesis of the Four Stereoisomers (±)-1a−d of the Racemic Pheromone and their Comparison with the Naturally Occurring Pheromone

The Tebbe reagent [μ-chlorobis(chloropentadienyl)-(dimethylaluminum)-μ-methylenetitanium][20][21] successfully converted the ketones **18** to **1** as reported by Evans et al. in their synthesis of α-himachalene[11]. Each of the stereoisomers (±)-**18a−d** gave the corresponding stereoisomers (±)-**1a−d** of the pheromone in quantitative yield (Scheme 3). The overall yield of (±)-**1** (as a stereoisomeric mixture) was 16.0% via (±)-**13** (based on **2**, 14 steps), or 15.0% via (±)-**17** (based on **2**, 15 steps). The ^{1}H-NMR data of (±)-**1a-d** (Table 1) were carefully compared with the published data[4] of the natural pheromone. Together with the mass spectral comparison, (±)-**1c** was shown to be the racemate of the pheromone. Indeed the ^{1}H-NMR spectrum of (±)-**1c** was identical to the authentic spectrum of the natural pheromone supplied by Prof. J. A. Pickett. Direct GC comparison of (±)-**1c** with the natural pheromone confirmed their identity, and our (±)-**1c** was bioactive as the sandfly sex pheromone. The result of these comparisons and bioassays will be published separately as a joint communication with Pickett et al.[22] In conclusion, our synthesis of (1*R**,3*R**,7*R**)-3-methyl-α-himachalene (**1c**) has definitely established the structure and relative configuration of the male-produced sex pheromone of *Lutzomyia longipalpis* from Jacobina, Brazil, as depicted in **1c**. We are currently synthesizing the enantiomers of **1c** in order to determine the absolute configuration of the pheromone.

Table 1. ^{1}H NMR data of the stereoisomers of (±)-**1** (500 MHz, $CDCl_3$)

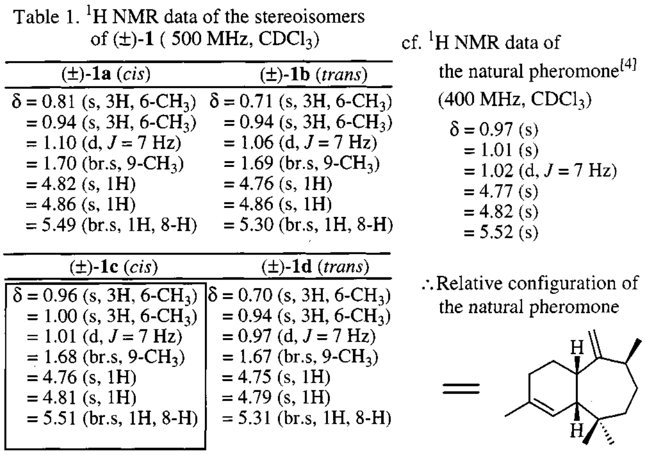


Table 1. ^{1}H NMR data of the stereoisomers of (±)-**1** (500 MHz, $CDCl_3$)

(±)-**1a** (*cis*)	(±)-**1b** (*trans*)
δ = 0.81 (s, 3H, 6-CH_3)	δ = 0.71 (s, 3H, 6-CH_3)
= 0.94 (s, 3H, 6-CH_3)	= 0.94 (s, 3H, 6-CH_3)
= 1.10 (d, *J* = 7 Hz)	= 1.06 (d, *J* = 7 Hz)
= 1.70 (br.s, 9-CH_3)	= 1.69 (br.s, 9-CH_3)
= 4.82 (s, 1H)	= 4.76 (s, 1H)
= 4.86 (s, 1H)	= 4.86 (s, 1H)
= 5.49 (br.s, 1H, 8-H)	= 5.30 (br.s, 1H, 8-H)

(±)-**1c** (*cis*)	(±)-**1d** (*trans*)
δ = 0.96 (s, 3H, 6-CH_3)	δ = 0.70 (s, 3H, 6-CH_3)
= 1.00 (s, 3H, 6-CH_3)	= 0.94 (s, 3H, 6-CH_3)
= 1.01 (d, *J* = 7 Hz)	= 0.97 (d, *J* = 7 Hz)
= 1.68 (br.s, 9-CH_3)	= 1.67 (br.s, 9-CH_3)
= 4.76 (s, 1H)	= 4.75 (s, 1H)
= 4.81 (s, 1H)	= 4.79 (s, 1H)
= 5.51 (br.s, 1H, 8-H)	= 5.31 (br.s, 1H, 8-H)

cf. ^{1}H NMR data of the natural pheromone[4] (400 MHz, $CDCl_3$)

δ = 0.97 (s)
= 1.01 (s)
= 1.02 (d, *J* = 7 Hz)
= 4.77 (s)
= 4.82 (s)
= 5.52 (s)

∴Relative configuration of the natural pheromone =

Experimental Section

General: Boiling points: Uncorrected values. − IR: Jasco IRA-102. − ^{1}H NMR: Jeol JNM-EX 90A (90 MHz), Jeol JNM-LA 500 (500 MHz), (TMS at $\delta_H = 0.00$ or $CHCl_3$ at $\delta_H = 7.26$ as an internal standard). − ^{13}C NMR: Jeol JNM-LA 500 (126 MHz), ($CDCl_3$ at $\delta_C = 77.0$ as an internal standard). − MS: Jeol JMS-SX 102A and Hitachi M-80B. − CC: Merck Kieselgel 60, Art. No. 1.07734. − TLC: 0.25 mm Merck silica gel plates (60F-254).

3-*tert*-Butyldimethylsilyloxy-2,2-dimethyl-1-propanol (3): To a suspension of sodium hydride (8.44 g, 211 mmol, about 60% suspension in mineral oil) in dry THF (300 mL) was added 2,2-dimethyl-1,3-propanediol (20.0 g, 192 mmol) at 0 °C. After stirring at 0 °C for 1 h, TBSCl (29.0 g, 192 mmol) was added to the resulting suspension, and it was stirred for 3 h at room temp. The mixture was diluted with water and the aqueous layer was extracted with ether. The combined organic layers were washed with a satd. aqueous sodium hydrogen carbonate solution, dried with magnesium sulfate and concentrated in vacuo. The residue was purified by distillation to give 40.3 g (96%) of **3** as a colorless oil, b.p. 61−65 °C/3 Torr, $n_D^{23} = 1.4355$. − IR (film): $\nu_{max} = 3400$ cm^{-1} (s, br. O−H), 1250 (m, Si−CH_3). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.06 [s, 6 H, $Si(CH_3)_2$], 0.88 (s, 6 H, 2-CH_3 × 2), 0.90 [s, 9 H, $SiC(CH_3)_3$], 2.82 (t, 1 H, *J* = 5.4 Hz, OH), 3.46 (s, 2 H, 3-H_2), 3.46 (d, 2 H, *J* = 5.4 Hz, 1-H_2).

3-*tert*-Butyldimethylsilyloxy-2,2-dimethylpropyl *p*-Toluenesulfonate (4): To a solution of **3** (20.0 g, 91.6 mmol) in $CHCl_3$ (200 mL) were added pyridine (74 mL, 0.91 mol) and tosyl chloride (21.0 g, 110 mmol) at 0 °C. The suspension was stirred at 0−4 °C for 18 h. The reaction mixture was diluted with water and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with a saturated aqueous $CuSO_4$ solution, water, a satd. aqueous sodium hydrogen carbonate solution and brine, dried with sodium sulfate, and concentrated in vacuo to give ca. 35 g of **4** as an oil. This was immediately used in the next step without further purification, IR (film): $\nu_{max} = 1360$ cm^{-1} (s, SO_2), 1250 (m, Si−CH_3), 1180 (s, SO_2).

4-*tert*-Butyldimethylsilyloxy-3,3-dimethybutanenitrile (5): To a solution of **4** (ca. 35 g) in DMSO (300 mL) was added sodium cyanide (95% purity, 5.30 g, 103 mmol). The mixture was stirred for 8 h at about 120−140 °C. The reaction mixture was diluted with water at 0 °C, and stirred for 1 h. The aqueous mixture was extracted with ethyl acetate. The combined organic layers were washed with a saturated sodium hydrogen carbonate solution, water, and brine, dried with sodium sulfate, and concentrated in vacuo. The residue was distilled to give 18.4 g (94%, 2 steps) of **5** as a colorless oil, b.p. 68−71 °C/2 Torr, $n_D^{25} = 1.4156$. − IR (film): $\nu_{max} = 2325$ cm^{-1} (w, CN), 1260 (m, Si−CH_3). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.05 [s, 6 H, $Si(CH_3)_2$], 0.90 [s, 9 H, $SiC(CH_3)_3$], 1.02 (s, 6 H, 2-CH_3 × 2), 2.30 (s, 2 H, 1-H_2), 3.34 (s, 2 H, 3-H_2). − Due to the volatility of **5**, no correct combustion analytical data could be obtained.

4-*tert*-Butyldimethylsilyloxy-3,3-dimethylbutanal (6): To a solution of **5** (19.8 g, 87.1 mmol) in dry CH_2Cl_2 (200 mL) was added dropwise DIBAL in hexane (0.94 M solution, 97 mL, 91 mmol) at −78°C under Ar. The mixture was stirred for 1 h at −78 °C and 5 h at 0−4 °C. The reaction mixture was poured into sat. NH_4Cl solution and diluted with diethyl ether. To this mixture was added a satd. Rochelle's salt solution and the mixture was stirred at room temp. until it separated into two phases. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with water and brine, dried with sodium sulfate, and concentrated in vacuo. The residue was purified by chromatography on silica gel (200 g, elution with hexane/ethyl acetate, 100:1) to give 18.0 g (90%) of **6** as a colorless oil. This was immediately used in the next step without further purification, $n_D^{24} = 1.4328$. − IR (film): $\nu_{max} = 2750$ cm^{-1}(w, aldehyde C−H), 1725 (vs, C=O), 1260 (m, $\mathrm{Si{-}CH_3}$). − ^{1}H NMR (90 MHz, $\mathrm{CDCl_3}$): δ = 0.07 [s, 6 H, $\mathrm{Si(CH_3)_2}$], 0.89 [s, 9 H, $\mathrm{SiC(CH_3)_3}$], 1.02 (s, 6 H, 2-$\mathrm{CH_3}$ × 2), 2.28 (d, 2 H, *J* = 3.1 Hz, 2-$\mathrm{H_2}$), 3.35 (s, 2 H, 4-$\mathrm{H_2}$), 9.84 (t, 1 H, *J* = 3.1 Hz, CHO).

Ethyl (*E*)-6-*tert*-Butyldimethylsilyloxy-2,5,5-trimethyl-2-hexenoate (7): To a solution of **6** (18.0 g, 78.1 mmol) in benzene (200 mL) was added ethoxycarbonylethylidenetriphenylphosphorane (94% purity, 31.5 g, 81.7 mmol) and the mixture stirred under reflux for 5 h, and then concentrated under reduced pressure. The residue was filtered and the filter cake was washed with hexane. The filtrate was concentrated in vacuo, and the residue purified by distillation to give 18.2 g (74%) of **7** as a colorless oil, b.p. 113 °C/1 Torr. − n_D^{23} = 1.4466. − IR (film): ν_{max} = 1710 cm^{-1} (vs, C=O), 1650 (m, C=C), 1260 (m, $\mathrm{Si{-}CH_3}$). − ^{1}H NMR (90 MHz, $\mathrm{CDCl_3}$): δ = 0.03 [s, 6 H, $\mathrm{Si(CH_3)_2}$], 0.87 (s, 6 H, 6-$\mathrm{CH_3}$ × 2), 0.89 [s, 9 H, $\mathrm{SiC(CH_3)_3}$], 1.29 (t, 3 H, *J* = 7.2 Hz, $\mathrm{OCH_2C}H_3$), 1.82 (br. d, 3 H, *J* = 1 Hz, 2-$\mathrm{CH_3}$), 2.13 (d, 2 H, *J* = 8.1 Hz, 4-$\mathrm{H_2}$), 3.25 (s, 2 H, 6-$\mathrm{H_2}$), 4.19 (q, 2 H, *J* = 7.2 Hz, $\mathrm{OC}H_2\mathrm{CH_3}$), 6.85 (dt, 1 H, *J* = 1 Hz, 8.1 Hz, 3-H). − $\mathrm{C_{17}H_{34}O_3Si}$ (314.5): calcd. C 64.92, H 10.90; found C 64.89, H 10.69.

Methyl (*R)-6-*tert*-Butyldimethylsilyloxy-2,5,5-trimethylhexanoate (8):** A small amount of dry MeOH (ca. 30 mL) was added carefully to magnesium (13.0 g, 535 mmol) and the mixture stirred on a water bath. The reaction mixture was then gently refluxed, and to this mixture was added dropwise a solution of **7** (17.0 g, 54.0 mmol) in dry MeOH (300 mL) at room temp. After the mixture was stirred for 2 d. at room temp, it was then diluted with diethyl ether and poured into aqueous 3 M hydrochloric acid carefully at 0 °C. The aqueous layers was saturated with sodium chloride and extracted with diethyl ether. The combined organic layers were washed with water and brine, dried with sodium sulfate, and concentrated in vacuo. The residue was purified by distillation to give 14.4 g (88%) of **8** as a colorless oil, b.p. 102−104°C/2 Torr. − n_D^{23} = 1.4319 − IR (film): ν_{max} = 1750 cm^{-1} (vs, C=O), 1260 (m, $\mathrm{Si{-}CH_3}$), 1110 (s). − ^{1}H NMR (90 MHz, $\mathrm{CDCl_3}$): δ = 0.01 [s, 6 H, $\mathrm{Si(CH_3)_2}$], 0.81 (s, 6 H, 5-$\mathrm{CH_3}$ × 2), 0.88 [s, 9 H, $\mathrm{SiC(CH_3)_3}$], 1.14 (d, 3 H, *J* = 7.1 Hz, 2-$\mathrm{CH_3}$), 1.01−1.60 (m, 4 H, 3-$\mathrm{H_2}$, 4-$\mathrm{H_2}$), 2.15−2.50 (m, 1 H, 2-H), 3.21 (s, 2 H, 6-$\mathrm{H_2}$), 3.66 (s, 3 H, $\mathrm{OCH_3}$). − $\mathrm{C_{16}H_{34}O_3Si}$ (302.53) calcd. C: 63.52, H:11.33; found C:63.14, H:11.01.

Methyl (*R)-6-Hydroxy-2,5,5-trimethylhexanoate (9):** To a solution of **8** (11.6 g, 38.3 mmol) in $\mathrm{CH_3CN}$ (100 mL) was added 46% hydrofluoric acid (4.15 mL) at 0 °C. The mixture was stirred at 0−4 °C for 14 h, then diluted with ether, washed with a satd. aqueous sodium hydrogen carbonate solution and separated. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with a satd. sodium hydrogen carbonate solution and brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was purified by distillation to give 6.67 g (93%) of **9** as a colorless oil, b.p. 90−93 °C/2.5 Torr. − n_D^{23} = 1.4435. − IR (film): ν_{max} = 3450 cm^{-1} (s, OH), 1740 (vs, C=O). − ^{1}H NMR (90 MHz, $\mathrm{CDCl_3}$): δ = 0.86 (s, 6 H, 5-$\mathrm{CH_3}$ × 2), 1.16 (d, 3 H, *J* = 7.1 Hz, 2-$\mathrm{CH_3}$), 1.01−1.60 (m, 4 H, 3-$\mathrm{H_2}$, 4-$\mathrm{H_2}$), 2.15−2.50 (m, 1 H, 2-H), 3.32 (br. d, 2 H, *J* = 5.4 Hz, 6-$\mathrm{H_2}$), 3.68 (s, 3 H, -$\mathrm{OCH_3}$). − $\mathrm{C_{10}H_{20}O_3}$ (188.27): calcd. C 63.80, H 10.71; found C 63.43, H 10.61.

Methyl (*R)-2,5,5-Trimethyl-6-oxohexanoate (10):** To a solution of oxalyl chloride (4.3 mL, 49 mmol) in dry $\mathrm{CH_2Cl_2}$ (20 mL) at −60°C was added a solution of dry DMSO (7.1 mL, 0.10 mol) in dry $\mathrm{CH_2Cl_2}$ (20 mL). After stirring for 20 min at −60 °C, a solution of **9** (3.12 g, 16.6 mmol) in dry $\mathrm{CH_2Cl_2}$ (20 mL) was added dropwise. The reaction mixture was stirred at −40 °C for 40 min, warmed at 0 °C and $\mathrm{Et_3N}$ (23 mL, 0.17 mol) was added. The mixture was diluted with water and the aqueous layer was extracted with $\mathrm{CH_2Cl_2}$. The combined organic layers were washed with water and brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was diluted with hexane and filtered through Celite. The filtrate was purified by chromatography on silica gel (30 g, elution with hexane/ethyl acetate, 200:1) to give 2.56 g (83%) of **10** as a colorless oil. This was immediately used in the next step without further purification, n_D^{24} = 1.4344. − IR (film): ν_{max} = 2700 cm^{-1} (w, aldehyde C−H), 1730 (vs, C=O). − ^{1}H NMR (90 MHz, $\mathrm{CDCl_3}$): δ = 1.05 (s, 6 H, 5-$\mathrm{CH_3}$ × 2), 1.15 (d, 3 H, *J* = 7.1 Hz, 2-$\mathrm{CH_3}$), 3.68 (s, 3 H, $\mathrm{OCH_3}$), 9.43 (s, 1 H, CHO).

(2*R,6*E*)-2,5,5,8-Tetramethyl-6,8-nonadienoic Acid (12):** To a suspension of methallyltriphenylphosphonium chloride (3.66 g, 10.8 mmol) in dry THF (30 mL) at 0 °C was added a solution of *t*BuOK (1.21 g, 10.8 mmol) in dry THF (15 mL) dropwise and the mixture was stirred for 1 h at room temp. To this mixture was added dropwise a solution of **10** (1.34 g, 7.19 mmol) in dry THF (20 mL). The mixture was stirred under reflux for 24 h. and then poured into sat. $\mathrm{NH_4Cl}$ solution and stirred for 1 h at room temp. before extraction with ethyl acetate. The combined organic layers were washed with brine, dried with magnesium sulfate, and concentrated in vacuo to give methyl ester **11**. The residue was diluted with MeOH (20 mL) and 5% KOH in MeOH (50 mL) was added. The mixture was stirred under reflux for 5 h. and then diluted with water. The aqueous mixture was washed with toluene to remove non-acidic compounds before it was acidified with dil. hydrochloric acid, and extracted with chloroform. The combined organic layers were washed with water and brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was purified by chromatography on silica gel (30 g, elution with hexane/ethyl acetate, 5:1) to give 1.08 g of **12** (72%) as a colorless oil.

Methyl (2*R,6*E*)-2,5,5,8-Tetramethyl-6,8-nonadienoate (11):** n_D^{23} = 1.4695. − IR (film): ν_{max} = 1740 cm^{-1} (vs, C=O), 1640 (m, C=C), 1610 (w, C=C). − ^{1}H NMR (500 MHz, $\mathrm{CDCl_3}$): δ = 1.01 (s, 6 H, 5-$\mathrm{CH_3}$ × 2), 1.13 (d, 3 H, *J* = 7 Hz, 2-$\mathrm{CH_3}$), 1.23−1.45 (m, 3 H, 3-$H_a\mathrm{H_b}$, 4-$\mathrm{H_2}$), 1.53−1.67 (m, 1 H, 3-$\mathrm{H_a}H_b$), 1.83 (s, 3 H, 8-$\mathrm{CH_3}$), 2.37 (dq, 1 H, *J* = 7 Hz, *J'* = 14 Hz, 2-H), 3.67 (s, 3 H, $\mathrm{OCH_3}$), 4.89 (s, 1 H, 9-$H_a\mathrm{H_b}$), 4.90 (s, 1 H, 9-$\mathrm{H_a}H_b$), 5.57 (d, 1 H, *J* = 16 Hz, 6-H), 6.04 (d, 1 H, *J* = 16 Hz, 7-H). − $\mathrm{C_{14}H_{24}O_2}$ (224.34) calcd. C: 74.95, H: 10.78; found C: 74.61, H: 10.98.

(2*R,6*E*)-12:** n_D^{23} = 1.4806. − IR (film): ν_{max} = 3000 cm^{-1} (m, br. $\mathrm{CO_2}$ H), 1710 (s, C=O), 1640 (m, C=C), 1610 (w, C=C). − ^{1}H NMR (500 MHz, $\mathrm{CDCl_3}$): δ = 1.02 (s, 6 H, 5-$\mathrm{CH_3}$ × 2), 1.17 (d, 3 H, *J* = 7 Hz, 2-$\mathrm{CH_3}$), 1.23−1.45 (m, 3 H, 3-$H_a\mathrm{H_b}$, 4-$\mathrm{H_2}$), 1.53−1.67 (m, 1 H, 3-$\mathrm{H_a}H_b$), 1.83 (s, 3 H, 8-$\mathrm{CH_3}$), 2.34−2.45 (m, 1 H, 2-H), 4.89 (s, 1 H, 9-$H_a\mathrm{H_b}$), 4.90 (s, 1 H, 9-$\mathrm{H_a}H_b$), 5.57 (d, 1 H, *J* = 16 Hz, 6-H), 6.05 (d, 1 H, *J* = 16 Hz, 7-H). − $\mathrm{C_{13}H_{22}O_2}$ (210.31) calcd. C: 74.24, H: 10.54; found C: 73.89, H: 10.64.

Determination of the Selectivity of Olefin Formation for (2*R,6*E*)-11:** The selectivity of the formation of (±)-**11** was determined by GC analysis. GC (column: TC-WAX®, 0.53 mm × 15 m, 70°C + 3°C/min; carrier gas: He, press 1.6 kg/cm^2). t_R = 5.91 min [2%, (6*Z*)-**11**], t_R = 7.43 min [98%, (6*E*)-**11**]. Therefore the (*E*)/(*Z*) ratio of **11** was estimated to be 98:2.

(2*R,6*E*)-*N*-Methyl-*N*-methoxy-2,5,5,8-tetramethyl-6,8-nonadienamide (13):** To a solution of **12** (163 mg, 0.775 mmol) in dry $\mathrm{CH_2Cl_2}$ (5 mL) at 0°C was added *i*$\mathrm{Pr_2NEt}$ (160 μL, 0.940 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (91 mg, 0.93 mmol) EDCI (156 mg, 0.81 mmol) and a catalytic amount of DMAP. After the reaction mixture was stirred for 18 h at room temp, it was diluted with water. The aqueous layer was extracted with $\mathrm{CH_2Cl_2}$.

The combined organic layers were washed with water and brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was purified by chromatography on silica gel (5 g, elution with hexane/ethyl acetate, 10:1) to give 161 mg (82%) of **13** as a colorless oil, $n_D^{24} = 1.4808$. − IR (film): $\nu_{max} = 1670\ cm^{-1}$ (vs, C=O), 1610 (m, C=C). − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.01 (s, 6 H, 5-CH_3), 1.11 (d, 3 H, J = 5.5 Hz, 2-CH_3), 1.23−1.45 (m, 3 H, 3-H_aH_b, 4-H_2), 1.53−1.67 (m, 1 H, 3-H_aH_b), 1.83 (s, 3 H, 8-CH_3), 2.78 (br. s, 1 H, 2-H), 3.18 (s, 3 H, N-CH_3), 3.68 (s, 3 H, N-OMe), 4.89 (s, 1 H, 9-H_aH_b), 4.90 (s, 1 H, 9-H_aH_b), 5.58 (d, 1 H, J = 16 Hz, 6-H), 6.04 (d, 1 H, J = 16 Hz, 7-H). − $C_{15}H_{27}O_2N$ (253.38): calcd. C 71.10, H 10.74, N 5.53; found C 71.35, H 10.75, N 5.70.

(2*R,6*E*)-2,5,5,8-Tetramethyl-6,8-nonadien-1-ol (15):** To a stirred slurry of $LiAlH_4$ (92% purity, 42 mg, 1.0 mmol) in dry diethyl ether (10 mL) at 0 °C, a solution of **11** (457 mg, 2.04 mmol) in diethyl ether (5 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 3 h. Excess $LiAlH_4$ was destroyed by careful addition of water (0.4 mL), an aqueous sodium hydroxide solution (15%, 0.4 mL) and water (1.2 mL). The mixture was diluted with diethyl ether, filtered through Celite, and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica gel (10 g, elution with hexane/ethyl acetate, 10:1) to give 368 mg (92%) of **15** as a colorless oil, $n_D^{23} = 1.4802$. − IR (film): $\nu_{max} = 3350\ cm^{-1}$ (s, O−H), 1640 (m, C=C), 1610 (w, C=C). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.91 (d, 3 H, J = 7 Hz, 2-CH_3), 1.02 (s, 6 H, 5-CH_3 × 2), 1.18−1.44 (m, 5 H, 2-H, 3,4-H_2), 1.83 (s, 3 H, 8-CH_3), 3.35−3.55 (m, 2 H, 1-H_2), 4.88 (s, 1 H, 9-H_aH_b), 4.89 (s, 1 H, 9-H_aH_b), 5.59 (d, 1 H, J = 16 Hz, 6-H), 6.04 (d, 1 H, J = 16 Hz, 7-H). − $C_{13}H_{24}O$ (196.33): calcd. C 79.53, H 12.32; found C 79.15, H 12.60.

(2*R,6*E*)-2,5,5,8-Tetramethyl-6,8-nonadienal (16):** To a mixture of **15** (294 mg, 1.50 mmol) and powdered MS 4-Å (500 mg) in CH_2Cl_2 (20 mL) was added pyridinium chlorochromate (98% purity, 494 mg, 2.25 mmol) and the mixture stirred for 8 h. The residue was filtered through silica gel (30 g, elution with diethyl ether) to give 290 mg of **16** as an oil. This was immediately used in the next step without further purification − IR (film): $\nu_{max} = 1730\ cm^{-1}$ (vs, C=O), 1640 (m, C=C), 1610 (w, C=C). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.91 (d, 3 H, J = 7 Hz, 2-CH_3), 1.02 (s, 6 H, 5-CH_3 × 2), 1.18−1.44 (m, 5 H, 2-H, 3-H, 3, 4-H_2), 1.84 (s, 3 H, 8-CH_3), 2.27 (br. s, 1 H, 2-H), 4.89 (s, 1 H, 9-H_aH_b), 4.90 (s, 1 H, 9-H_aH_b), 5.58 (d, 1 H, J = 16 Hz, 6-H), 6.04 (d, 1 H, J = 16 Hz, 7-H), 9.60 (d, 1 H, J = 9 Hz, C*H*O).

(4*R,8*E*)-4,7,7,10-Tetramethyl-1,8,10-undecatrien-3-ol (17):** To a solution of **16** (crude 290 mg) in dry THF (15 mL) at −20 °C was added vinylmagnesium bromide (0.98 M in THF solution, 2.3 mL, 2.3 mmol). Then the mixture was allowed to warm up to room temp. and stirred for 2 h. before it was poured into a sat. NH_4Cl solution. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was purified by chromatography on silica gel (20 g, elution with hexane/ethyl acetate, 30:1) to give 40 mg of recovered alcohol **15** and 200 mg (as diastereomeric mixture at C-3 and C-4, 70% based on consumed **15**, in 2 steps) of **17** as a colorless oil. − IR (film): $\nu_{max} = 3450\ cm^{-1}$ (s, O−H), 1640 (m, C=C), 1610 (w, C=C). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.87, 0.88 (each d × 2, 3 H, J = 7 Hz, 4-CH_3 as diastereomeric mixture), 1.02 (s, 6 H, 7-CH_3 × 2), 0.80−1.12 (m, 1 H, 5-H_aH_b), 1.20−1.35 (m, 1 H, 5-H_aH_b), 1.35−1.55 (3 H, m, 4-H, 6-H_2), 1.56 (br, d. 1 H, J = 4 Hz, 3-OH), 1.83 (s, 3 H, 10-CH_3), 3.80−4.20 (m, 1 H, 3-H), 4.87 (s, 1 H, 11-H_aH_b), 4.89 (s, 1 H, 11-H_aH_b), 5.15 (br. dt, 1 H, J = 2 Hz, J' = 5 Hz, 1-H_aH_b), 5.22 (d, 1 H, J = 17 Hz, 1-H_aH_b), 5.59 (d, J = 16 Hz, 8-H), 5.85 (ddd, 1 H, J = 5 Hz, J' = 11 Hz, J''' = 17 Hz, 2-H), 6.04 (d, 1 H, J = 16 Hz, 9-H). − $C_{15}H_{26}O$ (222.4) calcd. C: 81.02, H: 11.79; found C: 80.65, H: 11.51.

(4*R,8*E*)-4,7,7,10-Tetramethyl-1,8,10-undecatrien-3-one (14): (i)** To a solution of **13** (160 mg, 0.629 mmol) in dry THF (5 mL) at −20°C was added vinylmagnesium bromide (1.04 M in THF solution, 3.0 mL, 3.12 mmol). The mixture was allowed to warm up to room temp. and stirred for 6 h. before it was poured into a sat. NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, dried with magnesium sulfate, and concentrated in vacuo to give 100 mg (72%) of **14** as a colorless oil. This was immediately used in the next step without further purification. − **(ii) Dess−Martin Oxidation via 17:** A suspension of Dess−Martin periodinane (282 mg, 0.663 mmol) in CH_2Cl_2 (11 mL) was added dropwise to a solution of **17** (80 mg, 0.36 mmol) in CH_2Cl_2 (5 mL). This was stirred for 1 h at room temp. before it was diluted with diethyl ether and quenched by adding a satd. aqueous sodium hydrogen carbonate /sodium bisulfate solution (1:1, 20 mL), and the resulting mixture was stirred for 5 min. Upon further dilution with diethyl ether, the mixture was washed with a satd. sodium hydrogen carbonate solution, brine, dried with magnesium sulfate and concentrated in vacuo to give 68 mg (86%) of **14** as an oil. This was immediately used in the next step without further purification, $n_D^{24} = 1.4969$. − IR (film): $\nu_{max} = 1700\ cm^{-1}$ (vs, C=O), 1640, (w, C=C), 1610 (w, C=C).

3,6,6,9-Tetramethylbicyclo[5.4.0]undecan-2-one (18a-d): i) Thermal Conditions: A solution of **14** (180 mg, 0.810 mmol) in xylene (5 mL) was stirred under reflux for 2 d. The mixture was filtered through silica gel, eluted with hexane/ethyl acetate 100:1 to give 100 mg (56%) of **18** as a stereoisomeric mixture. This residue was separated by medium pressure liquid chromatography (MPLC, silica gel 50±20 µm: 20 g, elution with hexane/ethyl acetate 300:1, pressure: 30 MPa, elution rate: 12 mL/1 min) to give 4 mg of pure **18a**, 5 mg of crude **18b**, 4 mg of pure **18c** and 4 mg of crude **18d**. These ratios were determined by ^1H-NMR analysis (500 MHz, $CDCl_3$). − **ii) Et_2AlCl Conditions:** To a solution of **17** (19 mg, 0.085 mmol, E/Z = 89:11) in CH_2Cl_2 (1 mL) was added a solution of Et_2AlCl in hexane (0.95 M solution, 0.4 mL, 0.38 mmol) at −78 °C. The reaction mixture was allowed to warm up to 0 °C and it was stirred for 1 h. To this mixture was added a satd. Rochelle′s salt solution and the mixture was stirred at room temp. until it separated into two phases. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was purified by chromatography on silica gel (2 g, elution with hexane/ethyl acetate, 100:1) to give 14 mg (74%, *cis*/*trans* = 81:19 as determined by ^1H-NMR analysis) of **18** as a stereoisomeric mixture. − **(iii) $LiClO_4$−CSA Conditions:** To a solution of dry $LiClO_4$ (23.7 g, 223 mmol) in dry diethyl ether (43 mL) and CSA (5 mg) in dry THF (0.04 mL) was added dropwise a solution of **17** (491 mg, 2.23 mmol, E/Z = 84:16) in dry diethyl ether (10 mL). The reaction mixture was stirred for 18 h at room temp. Then it was cooled at 0 °C and diluted with water, and filtered through Celite. The filtrate was separated into the organic and aqueous layers, and the latter was extracted with diethyl ether. The combined organic layers were washed with brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was purified by chromatography on silica gel (20 g, elution with hexane/ethyl acetate, 100:1) to give 450 mg (92%, *cis*/*trans* = 82:18 as determined by ^1H-NMR analysis) of **18** as a stereoisomeric mixture. This residue was also purified by medium pressure liquid chromatography (MPLC, silica gel 50±20 µm, 40 g, elution with hexane/ethyl acetate, 300:1, pressure: 30 MPa, elution rate: 12 mL/1 min) to give 131 mg of **18a** and 75 mg of **18c**.

18a: R_f = 0.64 (hexane/ethyl acetate = 10:1). − n_D^{23} = 1.5034. − IR (film): ν_{max} = 2980 cm^{-1}(s), 2950 (s), 2900 (s), 1700 (vs, C=O), 1450 (m), 1390 (m), 1370 (m), 1360 (m), 1340 (w), 1320 (w), 1300 (w), 1280 (w), 1260 (w), 1230 (w) 1210 (w), 1180 (m), 1150 (w), 1140 (m), 1110 (w), 1060 (m), 1040 (m), 1020 (w), 1010 (w), 1000 (w), 980 (w), 950 (w), 930 (w), 920 (m), 880 (w), 860 (m), 810 (w), 770 (w), 720 (w). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.70 (s, 3 H, β-6-CH_3) 1.01 (s, 3 H, α-6-CH_3), 1.06 (d, *J* = 6.5 Hz, 3 H, 3-CH_3), 1.27−1.37 (m, 1 H, *J* = 4 Hz, *J'* = 11 Hz, 4-H_aH_b), 1.43−1.58 (m, 3 H, 5-H_2,11-H_{ax}), 1.63−1.71 (m, 1 H, 4-H_aH_b), 1.71 (br. s, 3 H, 9-CH_3), 1.84−1.94 (m, 1 H, 10-H_{eq}), 2.01 (br. dd, *J* = 6 Hz, *J'* = 16.5 Hz, 1 H, 10-H_{ax}), 2.15−2.21 (m, 1 H, 11-H_{eq}), 2.42 (ddd, *J* = 3 Hz, *J'* = 7 Hz, *J'''* = 12 Hz, 1 H, 1-H), 2.68 (br. s, 1 H, 7-H), 2.83−2.91 (dq, *J* = 4 Hz, *J'* = 6.5 Hz, 1 H, 3-H), 5.47 (br. s or m, 1 H, 8-H). − ^{13}C NMR (126 MHz, $CDCl_3$) δ = 17.0, 20.2, 23.1, 23.9, 29.6, 31.0, 31.6, 37.8, 42.2, 43.7, 44.2, 51.3, 122.0, 135.3, 216.1. − $C_{15}H_{24}O$: calcd. 220.1828; found 220.1826 (HRMS). − Due to the volatility of **18a**, no correct combustion analytical data could be obtained.

18b: R_f = 0.64 (hexane/ethyl acetate = 10:1). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.80 (s, 3 H, β-6-CH_3), 0.96 (s, 3 H, α-6-CH_3), 1.06 (d, *J* = 6.5 Hz, 3 H, 3-CH_3), 1.17−1.27 (m, 1 H, 4-H_aH_b), 1.34−1.44 (m, 2 H, 5-H_2), 1.55−1.61 (m, 1 H, 11-H_aH_b), 1.69 (br. s, 3 H, 9-CH_3), 1.77−1.93 (m, 3 H, 7-H, 10-H_2, 11-H_aH_b), 2.15−2.24 (m, 1 H, 4-H_aH_b), 2.56−2.64 (m, 1 H, 3-H), 2.64−2.70 (m, 1 H, 1-H), 5.30 (br. s., 1 H, 8-H).

18c: R_f = 0.61 (hexane/ethyl acetate = 10:1). − n_D^{24} = 1.5016. − IR (film): ν_{max} = 3000 cm^{-1} (s), 2950 (s), 2900 (s), 2850 (s), 1700 (vs, C=O), 1450 (m), 1390 (w), 1380 (w), 1340 (w), 1320 (w), 1280 (w), 1230 (w), 1210 (w), 1170 (w), 1160 (w), 1140 (w), 1120 (w), 1070 (w), 1040 (w), 1020 (w), 1000 (w), 960 (w), 930 (w) 900 (w), 870 (w), 840 (w), 830 (w) 790 (w), 770 (w) 740 (w), 710 (w). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85 (s, 3 H, β-6-CH_3), 0.97 (d, *J* = 6.5 Hz, 3 H, 3-CH_3), 1.07 (s, 3 H, α-6-CH_3), 1.17−1.37 (m, 2 H, 4-H_2), 1.39−1.45 (m, 1 H, 5-H_aH_b), 1.71 (br. s., 3 H, 9-CH_3), 1.66−1.88 (m, 4 H, 5-H_aH_b, 10-H_2, 11-H_aH_b), 2.05−2.10 (m, 1 H, 11-H_aH_b), 2.14 (br. s, 1 H, 7-H), 2.63−2.71 (m, 1 H, 3-H), 2.74−2.79 (m. 1 H, 1-H), 5.57 (br. s., 1 H, 8-H). − ^{13}C NMR (126 MHz, $CDCl_3$) δ = 17.1, 24.0, 24.7, 27.0, 29.7, 30.9, 31.6, 36.0, 37.3, 45.3, 46.3, 48.1, 122.4, 134.3, 219.4. − $C_{15}H_{24}O$: calcd. 220.1828; found 220.1822. (HRMS). − Due to the volatility of **18c**, no correct combustion analytical data could be obtained.

18d: R_f = 0.61 (hexane/ethyl acetate = 10:1). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.77 (s, 3 H, β-6-CH_3), 1.01 (s, 3 H, α-6-CH_3), 1.06 (d, *J* = 6.8 Hz, 3 H, 3-CH_3), 1.20−1.35 (m, 2 H), 1.35−1.50 (m, 2 H), 1.67 (br. s, 3 H, 9-CH_3), 1.75−1.92 (m, 2 H), 1.90−2.04 (m, 1 H), 2.05−2.10 (m, 1 H, 7-H), 2.45−2.55 (m, 1 H, 1-H), 2.60−2.73 (m, 1 H, 3-H), 5.32 (br. s, 1 H, 8-H).

2-Methylene-3,6,6,9-tetramethylbicyclo[5.4.0]undec-8-ene (1) [3-Methyl-α-himachalene]: (i) Thermal Conditions: To a solution of **18a** (3 mg, 0.01 mmol) in dry THF (1 mL) was added Tebbe reagent (0.5 M in toluene, 0.1 mL, 0.05 mmol) at −40 °C. The mixture was stirred for 1 h at this temperature and then for 8 h at room temp. 15% NaOH solution (0.1 mL) was added at 0°C and the mixture filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was chromatographed on silica gel (1 g, pentane) to give 3 mg (quant.) of **1a**. Other stereoisomers **1b-d** were also prepared under these conditions. − **(ii) $LiClO_4$−CSA Conditions:** In the same manner as described above, **18a** (23 mg, 0.10 mmol) was converted into 16 mg (70%) of **1a**, and **18c** (32 mg, 0.15 mmol) was converted into 21 mg (66%) of **1c**.

1a: n_D^{24} = 1.4990. − IR (film): ν_{max} = 3100 cm^{-1} (w), 3075 (w), 2950 (s), 2850 (s), 2725 (w), 1630 (m, C=C), 1460 (s), 1450 (s), 1380 (m), 1370 (m), 1360 (m), 1320 (w), 1260 (w), 1240 (w), 1220 (w), 1190 (w), 1160 (w), 1140 (w), 1120 (w), 1105 (w), 1060 (w), 1040 (w), 1030 (w), 1020 (w), 1000 (w), 990 (w), 650 (w), 620 (w), 890 (s), 860 (w), 850 (w), 830 (w), 810 (w), 760 (w), 720 (w). − ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.81 (s, 3 H, β-6-CH_3), 0.94 (s, 3 H, α-6-CH_3), 1.10 (d, *J* = 7 Hz, 3 H, 3-CH_3), 1.20−1.36 (m, 3 H), 1.48−1.55 (m, 1 H), 1.70 (br. s, 3 H, 9-CH_3), 1.75−1.82 (m, 1 H), 1.93−2.06 (m, 3 H), 2.34 (br. s, 1 H, 7-H), 2.36−2.46 (m, 1 H, 3-H), 4.82 (s, 1 H, 2-CH_aH_b), 4.86 (s, 1 H, 2-CH_aH_b), 5.49 (br. s., 1 H, 8-H). − ^{13}C NMR (126 MHz, $CDCl_3$) δ = 21.8, 23.8, 23.9, 25.2, 30.3, 32.0, 34.0, 37.4, 37.9, 42.4, 44.15, 44.20, 105.4, 123.6, 133.8, 158.9. − $C_{16}H_{26}$: calcd. 218.2036; found 218.2035. − Due to the volatility of **1a**, no correct combustion analytical data could be obtained.

1b: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.71 (s, 3 H, β-6-CH_3), 0.94 (s, 3 H, α-6-CH_3), 1.06 (d, *J* = 7 Hz, 3 H, 3-CH_3), 1.69 (br. s, 3 H, 9-CH_3), 4.76 (s, 1 H, 2-CH_aH_b), 4.86 (s, 1 H, 2-CH_aH_b), 5.30 (br. s., 1 H, 8-H).

1c: n_D^{24} = 1.5036. − IR (film): ν_{max} = 3100 (w), 3000 (s), 2950 (s), 2900 (s), 1650 (w, C=C), 1630 (w, C=C), 1470 (w), 1450 (m), 1440 (w), 1400(w), 1380 (w), 1370 (w), 1350 (w), 1340 (w), 1310 (w), 1280 (w), 1220 (w), 1190 (w), 1170 (w), 1150 (w), 1130 (w), 1080 (w), 1060 (w), 1030 (w), 1010 (w), 1000 (w), 980 (w), 960 (w), 950 (w), 910 (w), 890 (s), 870 (w), 830 (w), 800 (w), 750 (w), 730 (w), 700 (w). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96 (s, 3 H, β-6-CH_3), 1.00 (s, 3 H, α-6-CH_3), 1.01 (d, *J* = 7 Hz, 3 H, 3-CH_3), 1.08−1.15 (m, 1 H), 1.47−1.53 (m, 1 H), 1.58−1.66 (m, 1 H), 1.68 (br. s, 3 H, 9-CH_3), 1.72−1.88 (m, 4 H), 2.13 (br. s, 1 H, 7-H), 2.22−2.34 (m, 1 H, 3-H), 2.82 (br. s, 1 H, 1-H), 4.76 (s, 1 H, 2-CH_aH_b), 4.81 (s, 1 H, 2-CH_aH_b), 5.51 (br. s, 1 H, 8-H). − {lit[4]. δ = 0.97 (s), 1.01 (s), 1.02 (d, *J* = 7 Hz), 2.30 (m), 2.81 (m), 4.77 (s), 4.82 (s), 5.52 (s)}. − ^{13}C NMR (126 MHz, $CDCl_3$) δ = 21.6, 24.2, 25.0, 26.7, 32.0, 35.2, 36.37, 36.42, 36.7, 37.8, 41.5, 47.5, 107.1, 123.9, 134.1, 162.2. − $C_{16}H_{26}$: calcd. 218.2036; found 218.2030 (HRMS). − Due to the volatility of **1c**, no correct combustion analytical data could be obtained.

1d: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.70 (s, 3 H, β-6-CH_3), 0.94 (s, 3 H, α-6-CH_3), 0.97 (d, *J* = 7 Hz, 3 H, 3-CH_3), 1.67 (br. s, 3 H, 9-CH_3), 4.75 (s, 1 H, 2-CH_aH_b), 4.79 (s, 1 H, 2-CH_aH_b), 5.31 (br. s, 1 H, 8-H).

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