# Identification and Assignment of the Absolute Configuration of Biologically Active Methyl-Branched Ketones from Limnephilid Caddis Flies

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*Dedicated to Prof. Dr. Peter Köll on the occasion of his 60th birthday*

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Glands of the 4th and 5th abdominal sternite of the caddis flies *Potamophylax latipennis*, *Potamophylax cingulatus*, and *Glyphotaelius pellucidus* contain (*S*)-4-methyl-3-heptanone (**4a**), (4*S*,6*S*)-4,6-dimethyl-3-octanone (**4b**), and (4*S*,6*S*)-4,6-dimethyl-3-nonanone (**4c**). As shown by gas chromatography coupled with electrophysiological recordings, these ketones elicit a strong response in the insects' antennae. The structural assignment of the compounds was achieved on the basis of mass spectra, enantioselective synthesis, and gas chromatography on a chiral stationary phase.

## Introduction

Caddis flies (Trichoptera) are phylogenetically considered as the sister order of butterflies and moths (Lepidoptera).[1] Recent investigations showed, that primitive moths of the family Eriocraniidae and caddisflies exhibit similarities in physiology, morphology, and systems of chemical communication. While more advanced lepidopteran species produce sex pheromones containing long-chain unsaturated acetates, aldehydes, and primary alcohols in glands located near the ovipositor, caddis flies and eriocraniid moths possess glands in the 4th and 5th abdominal segment where they mainly produce unbranched, short-chain methylketones and methylcarbinols.[2–4] However, in the limnephilid caddis fly, *Hesperophylax occidentalis*, a branched ketone, 6-methyl-3-nonanone with an unknown stereochemistry, was reported to be the sex-pheromone.[5] In the present paper we describe the identification of similar branched compounds in three other species of the family Limnephilidae, *Potamophylax latipennis*, *Potamophylax cingulatus*, and *Glyphotaelius pellucidus*.

## Results and Discussion

Preliminary electroantennographic (EAG) recordings carried out on male antennae showed an activity with the extracts of females of both *Potamophylax* species. Further analysis by gas chromatography with electroantennographic detection (GC-EAD)[6] showed two compounds eliciting a response of the male antennae.

Upon GC-MS analysis of the extracts, the two EAD-active main components and one additional minor compound could be identified. They showed similar mass spectra and, therefore, were believed to be structurally related. The mass spectra of these compounds were characterised by a prominent $m/z = 86$ fragment, suggesting the compounds to represent 4-ketones or 3-ketones with methyl branching in position 2 or 4, as this fragment is the result of a typical McLafferty rearrangement at the carbon–oxygen double bond. The base peak at $m/z = 57$ results from an α-cleavage relative to the carbonyl carbon, indicating a 3-ketone and excluding, at the same time, the structure of a 2-methyl-3-alkanone (which would have yielded $m/z = 71$). Thus, the compounds were likely to represent 4-methyl-3-ketones. A comparison of mass spectral data[7] and gas chromatographic retention times using a synthetic sample proved the first eluting compound to be 4-methyl-3-heptanone (**4a**). The two remaining ketones, with molecular ions of $m/z = 156$ and 170, respectively, were proposed to be 4,6-dimethyl-3-octanone (**4b**) and 4,6-dimethyl-3-nonanone (**4c**) based on a comparison of the retention times of singly and doubly branched 3-alkanones. Further structural proof was obtained by coinjection with synthetic samples. The mass spectrum of **4c** is shown in Figure 1.

The assignment of the absolute configurations of the compounds was achieved by gas chromatography using a modified cyclodextrin, octakis-(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin, as the stationary phase. Enantiomers and diastereomers could be well separated. The natural products were shown to have (4*S*)- and (4*S*,6*S*)-configuration, respectively (see Figure 2). Both racemic and enantiopure material for comparison was obtained synthetically, as described below.

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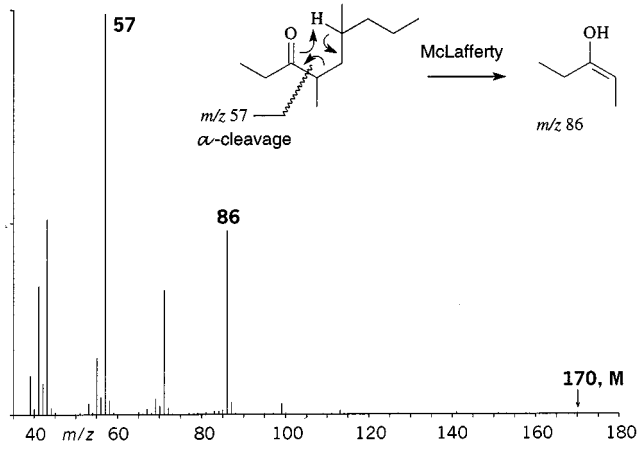



Figure 1. Mass spectrum of 4,6-dimethyl-3-nonanone (**4c**)

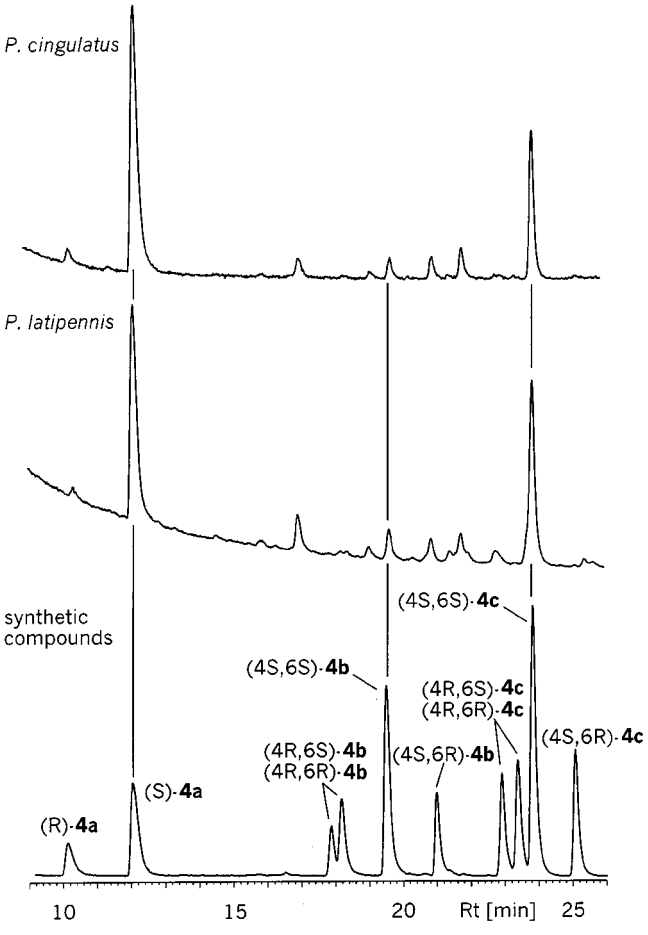
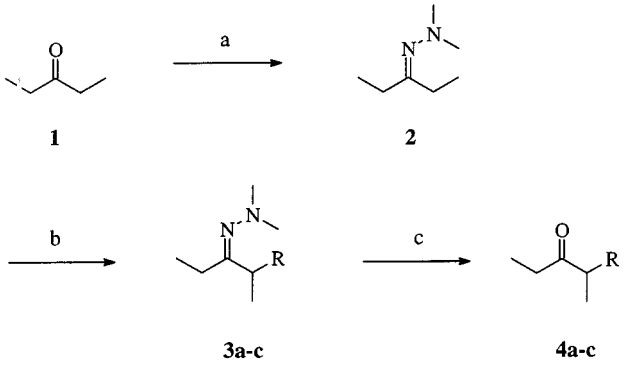



Figure 2. Gas chromatographic determination of the absolute configurations of compounds **4a**−**c** in females of *Potamophylax* spp.; additional peaks in the chromatograms of the extracts represent components which are different from the ketones described here; for conditions see Exp. Sect.

Extracts of male *P. latipennis* contain (*S*)-4-methyl-3-heptanone (**4a**), but not the dimethylketones. An analysis of *Glyphotaelius pellucidus* extracts showed that both males and females produce (4*S*,6*S*)-4,6-dimethyl-3-octanone (**4b**) and (4*S*,6*S*)-4,6-dimethyl-3-nonanone (**4c**), and that both elicit responses of the male antennae in EAD experiments. While in males both are major components, females produce less 4,6-dimethyl-3-octanone (**4b**). The biological function of these ketones is still unknown. The role of these compounds in intraspecific communication is presently under investigation.

## Synthesis of Racemic Ketones

Racemates of the ketones **4** were obtained by using the dimethylhydrazone method introduced by Corey and Enders.[8] The dimethylhydrazone **2** of 3-pentanone (**1**) was alkylated with the respective alkyl halides and the product **3** cleaved by reaction with sodium periodate (Scheme 1).



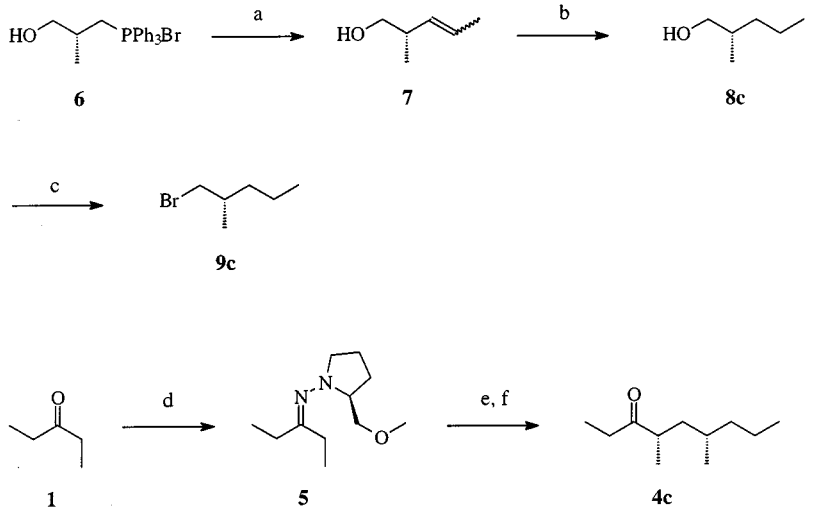

| 3, 4, 9 | a | b | c |
|---|---|---|---|
| R | *n*-propyl | 2-methylbutyl | 2-methylpentyl |

(a) N,N-dimethylhydrazine, 60 °C (b) LDA, R-Br (**9a-c**), THF, -78 °C (c) sodium periodate, phosphate buffer pH 7, MeOH

Scheme 1. Synthesis of racemic ketones **4a**−**c**

## Enantioselective Synthesis of the Ketones

The (*S*) configuration at C-4 was generated by enantioselective alkylation of the SAMP hydrazone **5** of 3-pentanone (**1**), according to the method of Enders et al.[9] (*S*)-4-Methyl-3-heptanone [(*S*)-**4a**], showing an enantiomeric excess of 97%, was synthesized as described previously.[10] In the case of the dimethylketones, the (*S*)-configuration in position 6 of the final product was introduced with the alkylating agent. (*S*)-1-Bromo-2-methylbutane (**9b**), used for the synthesis of (4*S*,6*S*)-4,6-dimethyl-3-octanone [(4*S*,6*S*)-**4b**] was obtained by bromination of commercially available (*S*)-2-methylbutan-1-ol (**8b**) by the method of Wijnberg et al.[11] (*S*)-2-Methylpentan-1-ol (**8c**), necessary for the synthesis of (4*S*,6*S*)-4,6-dimethyl-3-nonanone [(4*S*,6*S*)-**4c**], was produced by Wittig reaction of [(*R*)-3-hydroxy-2-methylpropyl]triphenylphosphonium bromide (**6**) with acetaldehyde, followed by catalytic hydrogenation of the resulting mixture of (*E*)- and (*Z*)-(*S*)-2-methyl-3-penten-1-ol (**7**). The alcohol **8c** was subsequently converted into the corresponding bromide **9c** as described above (Scheme 2).



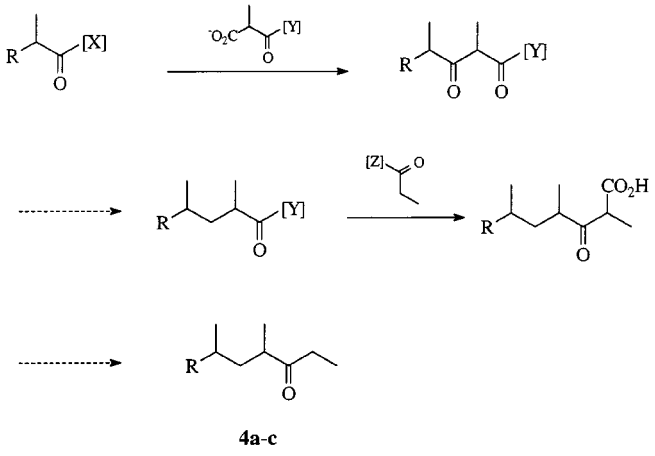

(a) BuLi, MeCHO, THF, -25 °C (b) Pd/C, 35 bar $H_2$, hexane (c) $PPh_3$, $Br_2$, $CH_2Cl_2$, 0 °C
(d) SAMP, 60 °C (e) LDA, **9c**, $Et_2O$, -110 °C (f) $O_3$, $CH_2Cl_2$

Scheme 2. Enantioselective synthesis of **4c**

Branched ketones similar to those described here have also been identified in other insects.[12] (*S*)-4-Methyl-3-heptanone (**4a**) is the typical alarm pheromone of many *Atta* ants[13] and has also been found in daddy long legs (*Leiobunum* spp.; Arachnida: Opiliones) along with (6*E*)-4,6-dimethyl-6-octen-3-one ("leiobunone").[14] Although the enantiomers of leiobunone have been synthesized, the absolute configuration of the natural product is still unknown.[15] The branched ketones **4b** and **4c** were previously identified from the desert wasp *Dasymutilla occidentalis*, but again, the absolute configuration could not be determined.[16] The biological significance of all these compounds is unknown. Another doubly branched ketone, 4,6-dimethyl-4-octen-3-one ("manicone"), was identified as an alarm pheromone from *Manica* ants,[17] and was found to have a (4*E*,6*S*)-configuration.[18]

As for the biosynthesis of the compounds identified here, methyl branching in the ketones is presumably introduced by replacement of an acetate (malonate) by a propanoate (or methylmalonate) unit along a polyketide route. This is depicted in Scheme 3, where [X], [Y], and [Z] are activators.

The ethylketone moiety might be formed from a propanoate unit entering in the last condensation step in a "head-to-head" coupling. Subsequent loss of a carbon atom through decarboxylation would yield the 3-alkanone structure.[19] Accordingly, (*S*)-4-methyl-3-heptanone (**4a**) would be derived from condensation of three propanoate units, while the biosynthesis of (4*S*,6*S*)-4,6-dimethyl-3-octanone (**4b**) would start with an acetate unit, followed by elongation with three propanoates. In a further step, the ketones can be reduced to the corresponding branched 3-alkanols, which we found in another caddis fly species, *Limnephilus lunatus* (to be published).




| | 4a | 4b | 4c |
|---|---|---|---|
| R | H | ethyl | *n*-propyl |

Scheme 3. Possible pathways for the biosynthesis of the methyl-branched ketones **4a**–**c**

## Experimental Section

Caddis flies were collected in 1997 and 1998 at locations near Lund, Sweden. Extracts were prepared by dissecting the 4th and 5th abdominal sternite and extracting them for 30 min. in a small amount (usually 10–30 μL) of dichloromethane. Extracts were subsequently analysed by injecting a 1 μL sample into a gas chromatograph (Hewlett–Packard 5890) coupled to a mass spectrometer (VG70–250SE), or concentrated and then submitted to GC-MS analysis.

All syntheses were carried out under argon. Solvents were distilled prior to use and dried according to standard procedures. For column chromatography, Merck silica gel (0.040−0.063 mm) was used. Mass spectra were recorded by using a combination GC8008/MD800 (Fisons) equipped with fused silica capillaries coated with DB5 (30 m × 0.25 mm ID; programmed from 60 to 300 °C at 5 °C/min.) or 60% octakis-(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin in OV1701 (25 m × 0.25 mm ID; programmed from 40 to 120 °C at 2 °C/min.). NMR spectra were recorded with a Bruker AMX400 using TMS as the internal standard. Optical rotatory values were obtained with a Perkin−Elmer 341 in 10 cm cuvettes at 20 °C.

**1-Bromo-2-methylbutane (*rac*-9b):** Bromine (1.51 mL, 29 mmol) was added slowly to a solution of triphenylphosphane (7.60 g, 29 mmol) in 25 mL dry dichloromethane at 0 °C. Subsequently, 2-methylbutan-1-ol (**8b**; 3.11 mL, 29 mmol) was added dropwise at the same temperature. After 1 h the mixture was allowed to warm to room temperature, most of the dichloromethane was distilled off, and 20 mL pentane was added. The solution was stored for about 12 h in the refrigerator to allow the produced triphenylphosphane oxide to precipitate. The white precipitate was filtered off, carefully washed with pentane, and the filtrate was concentrated. The residue was distilled to yield 2.41 g (55 %) of a colorless liquid. $bp_{760}$ = 118 °C. − $^1$H NMR (400.1 MHz, $CDCl_3$): δ = 3.40 (dd, *J* = 9.7, *J* = 5.1 Hz, H-1a), 3.34 (dd, *J* = 9.7, *J* = 6.1 Hz, H-1b), 1.76−1.67 (m, 1 H, H-2), 1.53−1.44 (m, 1 H, H-3), 1.34−1.23 (m, 1 H, H-3), 1.01 (d, *J* = 6.6 Hz, 3 H, H-2′), 0.91 (t, *J* = 7.6 Hz, 3 H, H-4). − $^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 41.1 (−, C1), 36.8 (+, C2), 27.6 (−, C3), 18.4 (+), 11.3 (+). − MS (70 eV): *m*/*z* = 39 (25), 41 (63), 42 (19), 43 (49), 53 (6), 55 (36), 56 (10), 57 (35), 69 (4), 70 (4), 71 (100), 72 (5), 93 (3), 95 (3), 107 (2), 109 (2), 121 (6), 123 (6), 150 (3) [$M^+$].

***rac*-4,6-Dimethyl-3-octanone (*rac*-4b):** To a stirred solution of diisopropylamine (1.16 mL, 8 mmol) in 100 mL dry tetrahydrofuran was added butyllithium (1.6 M solution in hexane; 5.00 mL, 8 mmol) at 0 °C and the mixture stirred for 15 min. Subsequently, 3-pentanone-dimethylhydrazone (**2**; 1.03 g, 8 mmol) was added, and the mixture was stirred for an additional 2 h at the same temperature. The solution was then cooled to −78 °C and, *rac*-**9b** (1.20 g, 8 mmol) was added. This mixture was stirred for about 12 h and then allowed to warm to room temperature. It was then poured into a mixture of 150 mL water and 50 mL dichloromethane, and the layers were separated. The aqueous layer was extracted three times with 50 mL portions of dichloromethane. The combined organic layers were washed with brine, dried with anhydrous magnesium sulfate, and concentrated. The residue was dissolved in 50 mL of methanol and 10 mL of 1M phosphate buffer (pH 7), and 30 mmol of sodium periodate in 80 mL water was added. This mixture was stirred for 3 h. The precipitate was filtered off and washed with dichloromethane. The filtrate was extracted with dichloromethane, and the combined organic layers were washed with brine, dried and concentrated. The residue was chromatographed on silica (hexane/ethyl acetate, 50:1) to yield 540 mg (44 %) of *rac*-**4b**. − $^1$H NMR (400.1 MHz, $CDCl_3$): δ = 2.69−2.60 (m, 1 H, H-4), 2.54−2.36 (m, 2 H, H-2), 1.74−1.65 (m, 1 H, H-6), 1.37−1.24 (m, 4 H, H-5,7), 1.04 (pseudo-t, 6 H, H-4′,6′), 0.90−0.83 (m, 6 H, H-1,8). − $^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 216.0 (o), 43.9 (+), 40.4 (−), 34.2 (−), 32.3 (+), 22.7 (−), 19.3 (+), 17.4 (+), 14.1 (+), 7.8 (+). − MS (70 eV): *m*/*z* = 39 (11), 41 (27), 43 (7), 55 (14), 57 (100), 71 (2), 86 (23), 99 (2), 127 (1), 156 (0.1) [$M^+$].

**1-Bromo-2-methylpentane (*rac*-9c):** This synthesis was essentially the same as for *rac*-**9b**. Bromine (0.53 mL, 10 mmol), triphenylphosphane (2.63 g, 10 mmol), and 2-methylpentan-1-ol (815 mg, 8.0 mmol) yielded 1.04 g (78 %) of *rac*-**9c**. − $^1$H NMR (400.1 MHz, $CDCl_3$): δ = 3.40 (dd, $^3J_{1a,2}$ = 5.1, $^2J_{1a,1b}$ = 9.7 Hz, 1 H, H-1a), 3.32 (dd, $^3J_{1b,2}$ = 6.1, $^2J_{1b,1a}$ = 9.7 Hz, 1 H, H-1b), 1.86−1.75 (m, 1 H, H-2), 1.47−1.16 (m, 4 H, H-3,4), 1.01 (d, $^3J_{2',2}$ = 6.6 Hz, 3 H, H-2′), 0.91 (t, $^3J_{5,4}$ = 7.1 Hz, 3 H, H-5). − $^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 41.8 (−), 37.0 (−), 35.0 (+), 20.0 (−), 18.8 (+), 14.4 (+). − MS (70 eV): *m*/*z* = 39 (23), 41 (58), 42 (20), 43 (100), 55 (11), 57 (6), 69 (5), 71, (9), 85 (55), 93 (1), 95 (1), 121 (1), 123 (1), 164 (0.2) [$M^+$], 166 (0.2) [$M^+$].

***rac*-4,6-Dimethyl-3-nonanone (*rac*-4c)**: According to the procedure described above for *rac*-**4b**, **2** (3.60 g, 28 mmol), and *rac*-**9c** (4.60 g, 28 mmol) were reacted and, after oxidative cleavage, yielded 1.68 g (35 %) of *rac*-**4c**. − $^1$H NMR (400.1 MHz, $CDCl_3$): δ = 2.70−2.57 (m, 1 H, H-4), 2.54−2.37 (m, 2 H, H-2), 1.72−1.64 (m, 1 H, H-6), 1.47−1.19 (m, 6 H, H-5,7,8), 1.05 (d, *J* = 7.1 Hz, 3 H, H-4′), 1.04 (d, *J* = 6.1 Hz, 3 H, H-6′), 0.87 (t, *J* = 7.6 Hz, 3 H), 0.86 (t, *J* = 7.6 Hz, 3 H). − $^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 215.6 (o), 43.9 (+), 40.8 (−), 34.2 (−), 30.3 (+), 20.0 (−), 19.9 (−), 17.4 (+), 16.3 (+), 14.3 (+), 7.8 (+). − MS (70 eV): *m*/*z* = 41 (29), 43 (47), 55 (13), 57 (100), 69 (5), 71 (31), 86 (49), 87 (4), 99 (4), 113 (2), 127 (1), 141 (1), 155 (1), 170 (1) [$M^+$].

**(*S*)-1-Bromo-2-methylbutane [(*S*)-9b]:** The synthesis was essentially the same as for *rac*-**9b**. Bromine (1.51 mL, 29 mmol), triphenylphosphane (7.60 g, 29 mmol), and (*S*)-2-methylbutan-1-ol (**8b**; 3.11 mL, 29 mmol) yielded 2.41 g (55 %) of (*S*)-**9b**. Same NMR and MS data as for *rac*-**9b**, $[\alpha]_D$ = +3.8 (*c* = 5.0, $CHCl_3$) (ref.:[20] +3.74).

**(4*S*,6*S*)-4,6-Dimethyl-3-octanone [(4*S*,6*S*)-4b]:** To a stirred solution of diisopropylamine (1.30 mL, 9 mmol) in 50 mL dry diethyl ether was added butyllithium (1.6 M solution in hexane; 5.65 mL, 9 mmol) at 0 °C. After 15 min. of additional stirring, 3-pentanone-SAMP-hydrazone (**5**; 1.76 g, 9 mmol) in 10 mL dry diethyl ether was added dropwise. The mixture was stirred at 0 °C for 4 h, then cooled to approx. −110 °C (pentane/liq. nitrogen), and (*S*)-**9b** (1.40 g, 9 mmol) was added dropwise. The mixture was stirred for about 12 h and allowed to warm to room temperature. It was then poured into a mixture of 150 mL diethyl ether/30 mL water and extracted three times with 20 mL portions of diethyl ether. The combined organic extracts were washed with 30 mL water, dried with anhydrous magnesium sulfate, and concentrated. The crude product was dissolved in 40 mL dry dichloromethane, cooled to −60 °C, and ozone was passed through the solution until it turned green. It was then warmed to room temperature, and the solvent was distilled off. The residue was chromatographed on silica (hexane/ethyl acetate, 50:1) to yield 356 mg (26 %) of (4*S*,6*S*)-**4b**. Same NMR and MS data as for *rac*-**4b**. − $[\alpha]_D$ = +21.0 (*c* = 1.3, hexane), *ee* (chiral GC) = 98 %. − HR-MS: calcd. 156.1514; found 156.1517.

**(2*S*)-2-Methyl-3-penten-1-ol (7):** To a suspension of [(*R*)-3-hydroxy-2-methylpropyl]triphenylphosphonium bromide (**6**; 10.0 g, 24,1 mmol) in 100 mL dry tetrahydrofuran, was added butyllithium (1.6 M solution in hexane; 30.0 mL, 48 mmol) at −25 °C. After stirring for 10 min., freshly distilled acetaldehyde (2.00 mL, 35.5 mmol) was added at the same temperature. The reaction mixture was then allowed to warm to room temperature. Subsequently, 100 mL of saturated aqueous ammonium chloride was added, and the mixture was extracted three times with 50 mL portions of a 1:1 (v/v) pentane/diethyl ether mixture. The combined organic extracts were dried with magnesium sulfate and concentrated under reduced pressure. The precipitated triphenylphosphane oxide was filtered off and washed carefully with pentane. The filtrate was again con-

centrated under reduced pressure, and the crude product was chromatographed on silica gel (pentane/diethyl ether, 3:1), yielding 1.27 g (53 %) of **7** as a mixture of stereoisomers. − $^1$H NMR (400.1 MHz, $CDCl_3$): δ = 5.69−5.51 (m, 2 H, H-4), 5.28 (dd, 1 H, H-$3_{trans}$) *J* = 15.3, *J* = 7.6, 5.17 (pseudo-t, 1 H, H-$3_{cis}$), 3.55−3.43 (m, 2 H, H-1), 3.39−3.31 (m, 2 H, H-1), 2.82−2.67 (m, 1 H, H-2), 2.38−2.24 (m, 1 H, H-2), 1.68 (t, 6 H, H-5), 0.98 (t, 6 H, H-2′). − MS: *m*/*z* = 39 (27), 41 (100), 42 (8), 43 (10), 53 (8), 55 (10), 57 (6), 58 (4), 67 (10), 69 (63), 70 (9), 71 (6), 82 (8), 100 (3) [$M^+$].

**(*S*)-2-Methyl-1-pentanol (8c):** Compound **7** (1.20 g, 12.0 mmol) in 20 mL hexane was hydrogenated for 3.5 h at 35 bar with palladium on charcoal (10 % Pd) as catalyst. The reaction mixture was filtered through silica gel (diethyl ether), dried with anhydrous magnesium sulfate, and concentrated to give 860 mg (70 %) of **8c**. − $[\alpha]_D$ = −8.2 (*c* = 1.48, $CHCl_3$) {ref.:[21] −13 (*c* = 1.08, $CHCl_3$, 578 nm)}. − $^1$H NMR (400.1 MHz, $CDCl_3$): δ = 3.51 (dd, $^3J_{1a,2}$ = 5.6 Hz, $^2J_{1a,1b}$ = 10.6 Hz, 1 H, H-1a), 3.42 (dd, $^3J_{1b,2}$ = 6.6 Hz, $^2J_{1b,1a}$ = 10.6 Hz, 1 H, H-1b), 1.69−1.58 (m, 1 H, H-2), 1.44−1.31 (m, 4 H, H-3,4), 0.95−0.86 (m, 6 H, H-2′,5) - $^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 68.5 (−), 35.5 (−), 35.4 (+), 20.1 (−), 16.6 (+), 14.3 (+). − MS: *m*/*z* = 39 (17), 41 (41), 42 (21), 43 (100), 53 (3), 55 (33), 56 (26), 57 (5), 59 (2), 69 (31), 70 (33), 71 (35), 84 (9), 85 (1), 102 (0.1) [$M^+$].

**(*S*)-1-Bromo-2-methylpentane [(*S*)-9c]:** The synthesis was essentially the same as for *rac*-**9b**. Bromine (0.53 mL, 10 mmol), triphenylphosphane (2.63 g, 10 mmol), and **8c** (815 mg, 8.0 mmol) yielded 1.04 g (78 %) of (*S*)-**9c**. Same NMR and MS data as for *rac*-**9c**, $[\alpha]_D$ = −1.5 (*c* = 7.97, $CHCl_3$) {ref.:[22] −0.9 (*c* = 50, diethyl ether)}.

**(4*S*,6*S*)-4,6-Dimethyl-3-nonanone [(4*S*,6*S*)-4c]:** In a reaction carried out analogously to the synthesis of (4*S*,6*S*)-**4b**, 670 mg (3.4 mmol) of **5** and 730 mg (4.4 mmol) of (*S*)-**9c** yielded 332 mg (57 %) of (4*S*,6*S*)-**4c**. Same NMR and MS data as for *rac*-**4c**. − $[\alpha]_D$ = +11.6 (*c* = 0.85, $CH_2Cl_2$), *ee* (chiral GC) = 97%. − HR-MS: calcd. 170.1670; found 170.1705.

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