Bioscience, Biotechnology, and Biochemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/tbbb20

Synthesis of (4R,6S,7R)-7-Hydroxy-4,6-dimethyl-3-nonanone and (3R,5S,6R)- 6-Hydroxy-3,5-dimethyl-2-octanone, the Pheromone Components of the…

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Published online: 22 May 2014.

To cite this article: Yui MASUDA, Ken FUJITA & Kenji MORI (2003) Synthesis of (4R,6S,7R)-7-Hydroxy-4,6-dimethyl-3-nonanone and (3R,5S,6R)- 6-Hydroxy-3,5-dimethyl-2-octanone, the Pheromone Components of the…, Bioscience, Biotechnology, and Biochemistry, 67:8, 1744-1750, DOI: 10.1271/bbb.67.1744

To link to this article: http://dx.doi.org/10.1271/bbb.67.1744

Biosci. Biotechnol. Biochem., **67** (8), 1744–1750, 2003

Synthesis of (4*R*,6*S*,7*R*)-7-Hydroxy-4,6-dimethyl-3-nonanone and (3*R*,5*S*,6*R*)-6-Hydroxy-3,5-dimethyl-2-octanone, the Pheromone Components of the Bostrychid Beetle, *Dinoderus bifoveolatus**

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Received March 7, 2003; Accepted April 23, 2003

(4*R*,6*S*,7*R*)-7-Hydroxy-4,6-dimethyl-3-nonanone and (3*R*,5*S*,6*R*)-6-hydroxy-3,5-dimethyl-2-octanone, the pheromone components of the bostrychid beetle, *Dinoderus bifoveolatus*, as well as their (4*R*,6*S*,7*S*)- and (3*R*,5*S*,6*S*)-isomers were synthesized from (2*R*,4*S*,5*R*)- and (2*R*,4*S*,5*S*)-2,4-dimethyl-5-heptanolide, respectively.

Key words: bostrychid beetle; nor-serricornin stereoisomer; pheromone; serricornin stereoisomer

In 1999, Francke and his co-workers found a stereoisomer of serricornin, the cigarette beetle pheromone, as a pheromone component of the bostrychid beetle, *Dinoderus bifoveolatus* (Francke, W., personal communication dated April 15, 1999).[1)] They then detected a stereoisomer of nor-serricornin in the same beetle, and finally clarified the structures of the two pheromone components as (4*R*,6*S*,7*R*)-7-hydroxy-4,6-dimethyl-3-nonanone (**1**) and (3*R*,5*S*,6*R*)-6-hydroxy-3,5-dimethyl-3-octanone (**2**) as shown in Fig. 1 (Francke, W., personal communication dated February 5, 2001).[1)]

In connection with our recent synthesis of serricornin [(4*S*,6*S*,7*S*)-7-hydroxy-4,6-dimethyl-3-nonanone],[2)] we accomplished the synthesis of (4*R*,6*S*,7*R*)-**1** and (3*R*,5*S*,6*R*)-**2**, as well as their stereoisomers (4*R*,6*S*,7*S*)-**1′** and (3*R*,5*S*,6*S*)-**2′**. To facilitate their gas chromatographic (GC) comparison with Francke's natural products, our final targets were corresponding acetates **3**, **4**, **3′** and **4′** (Fig. 1), which were known to be separable by GC.

Scheme 1 summarizes our synthesis of intermediates (2*R*,4*S*,5*R*)-**12** and (2*R*,4*S*,5*S*)-**11′**. Starting chiral building block **7** was obtained by lipase AK-catalyzed asymmetric acetylation of *meso*-2,4-dimethyl-1,5-pentanediol (**6**) derived from *meso*-2,4-dimethylglutaric anhydride (**5**).[3)] Protection of the free hydroxy group of **7** as a *t*-butyldimethylsilyl (TBS) ether yielded **8**, which was treated with potassium carbonate in methanol to give alcohol **9**. Oxidation of **9** with tetra(*n*-propyl)ammonium perruthenate (TPAP)[4)] afforded aldehyde **10**. Treatment of **10** with ethylmagnesium bromide gave alcohol **11** as a diastereomeric mixture at C-5. Its asymmetric acetylation with vinyl acetate and lipase PS-D (Amano) was followed by chromatographic purification to furnish acetate (2*R*,4*S*,5*R*)-**12** and recovered (2*R*,4*S*,5*S*)-**11′**.

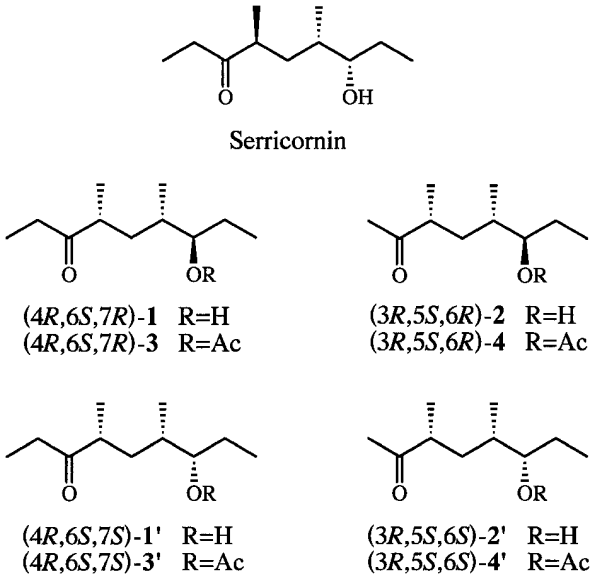

Fig. 1. Structures of Serricornin, the Pheromone Components of a Bostrychid Beetle (**1** and **2**), and Their Stereoisomers (**1′** and **2′**).

Further conversion of **12** and **11′** to the target molecules is shown in Scheme 2. Removal of the TBS

* Pheromone Synthesis, Part 221. For Part 220, see Muto, S., and Mori, K., *Biosci. Biotechnol. Biochem.*, **67**, 1559–1567 (2003).

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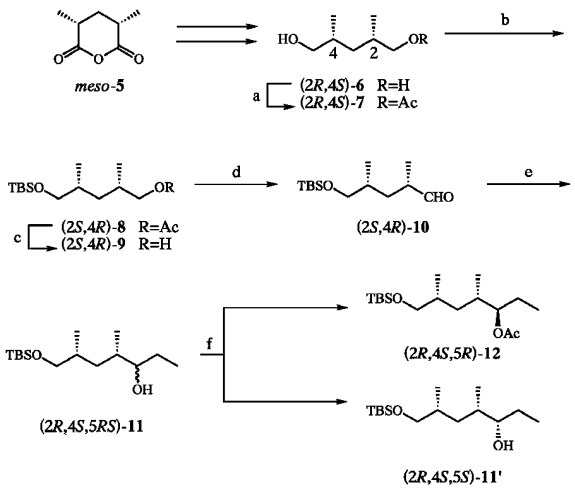
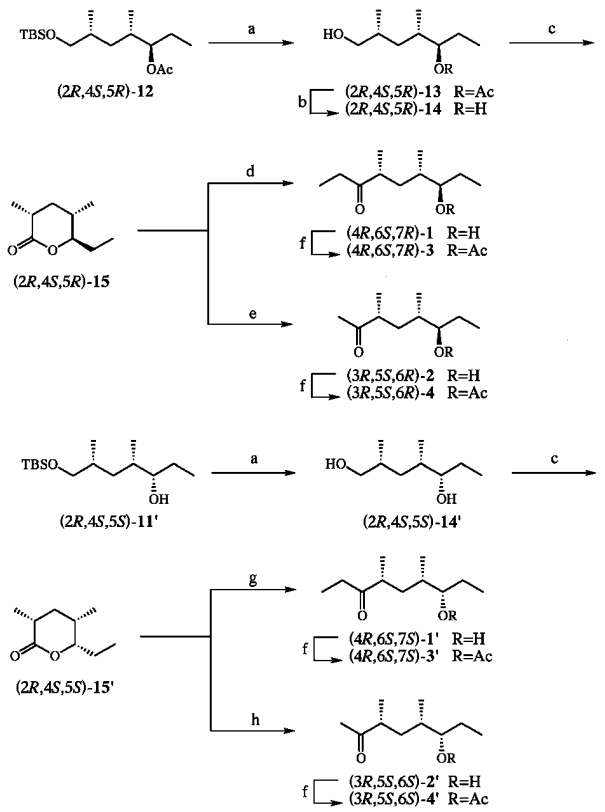


Scheme 1. Synthesis of the Intermediates, (2*R*,4*S*,5*R*)-**12** and (2*R*,4*S*,5*S*)-**11**′.

Reagents: (a) CH_2=CHOAc, lipase AK (86%).[2] (b) TBSCl, imidazole, DMF (95%). (c) K_2CO_3, MeOH (96%). (d) TPAP, NMO, CH_2Cl_2. (e) EtMgBr, THF (2 steps, 73%). (f) CH_2=CHOAc, lipase PS-D (27% for **12**; 64% for **11**′).



Scheme 2. Synthesis of the Target Molecules, **1**, **2**, **1**′ and **2**′.

Reagents: (a) TBAF, THF (quant. for **13**; 92% for **14**′). (b) KOH, MeOH (87%). (c) TPAP, NMO, CH_2Cl_2 (79% for **15**; 78% for **15**′). (d) EtMgBr, THF. (e) MeMgBr, THF. (f) Ac_2O, C_5H_5N (2 steps, 65% for **3**; 70% for **4**; 36% for **3**′; 40% for **4**′). (g) EtLi, Et_2O. (h) MeLi, Et_2O.

protective groups of **12** with tetra(*n*-butyl)ammonium fluoride (TBAF) gave diol monoacetate **13**, which was saponified to diol **14**. TPAP oxidation of **14** to lactone **15** was followed by its treatment with ethylmagnesium bromide to furnish pheromone component (4*R*,6*S*,7*R*)-**1**. Hydroxy ketone **1** was acetylated to give acetate **3** in a 6.9% overall yield based on (2*R*,4*S*)-**6** (11 steps). Similarly, treatment of **15** with methylmagnesium bromide afforded another pheromone component, (3*R*,5*S*,6*R*)-**2**. Acetylation of **2** gave **4** in a 7.6% overall yield based on (2*R*,4*S*)-**6** (11 steps).

To synthesize stereoisomers **1**′ and **2**′ of the pheromone components, **11**′ was treated with TBAF to give **14**′. This was oxidized with TPAP to yield **15**′. When lactone **15**′ was treated with ethyl- or methylmagnesium bromide, diols **A** and **B** (see Fig. 2) were obtained as the major products [23% (together with 8% of **1**′ and 52% of recovered **15**′) and 42% (together with 11% of **2**′ and 37% of recovered **15**′) respective yields.] instead of desired hydroxy ketones **1**′ and **2**′. Fortunately, however, treatment of **15**′ with ethyl- or methyllithium gave hydroxy ketones **1**′ and **2**′ in moderate yields, which afforded acetates **3**′ and **4**′ upon acetylation.

The structures **A** and **B** of the foregoing diols were supported by their IR and ^{1}H-NMR data, indicating the absence of the carbonyl groups and the presence of two ethyl or methyl groups at the terminal position. A possible mechanism is shown in Fig. 2 for the formaition of diol **A** by the addition of ethylmagnesium bromide to lactone **15**′. In the case of lactone **15**, the hydroxy ketone, (4*R*,6*S*,7*R*)-**1**, could be smoothly generated *via* stable salts **C** and **D** with an equatorial ethyl group at C-5. In the case of the epimeric lactone **15**′, its ethyl group at C-5 adopts an axial orientation in its chair conformation. Accordingly, resulting magnesium salts **E** and **F** were unstable due to severe steric repulsion, and generated **G**, which could be attacked further by the second Grignard reagent to give **H**, affording diol **A** after the usual work-up. Thus, the stereochemical difference between **15** and **15**′ deeply affected the course of the Grignard addition.

In conclusion, we synthesized pheromone components **1** and **2** of the bostrychid beetle, *Dinoderus bifoveolatus*, as well as their stereoisomers **1**′ and **2**′ in short steps. Acetates **3** and **4** respectively derived from **1** and **2** have been found to be identical with the acetates of the natural pheromone components by a GC-MS analysis in Germany.[1]

Experimental

Melting point (mp) data were measured with a Yanaco MP-S3 instrument and are uncorrected. IR spectra were measured with a Jasco FT/IR-460 spectrometer. ^{1}H-NMR spectra were recorded at 400 MHz with a Jeol JNM-LA400 spectrometer and at 500 MHz with a Jeol JNM-LA500 spectrometer. The peak for $CHCl_3$ in $CDCl_3$ (at δ 7.26), was used

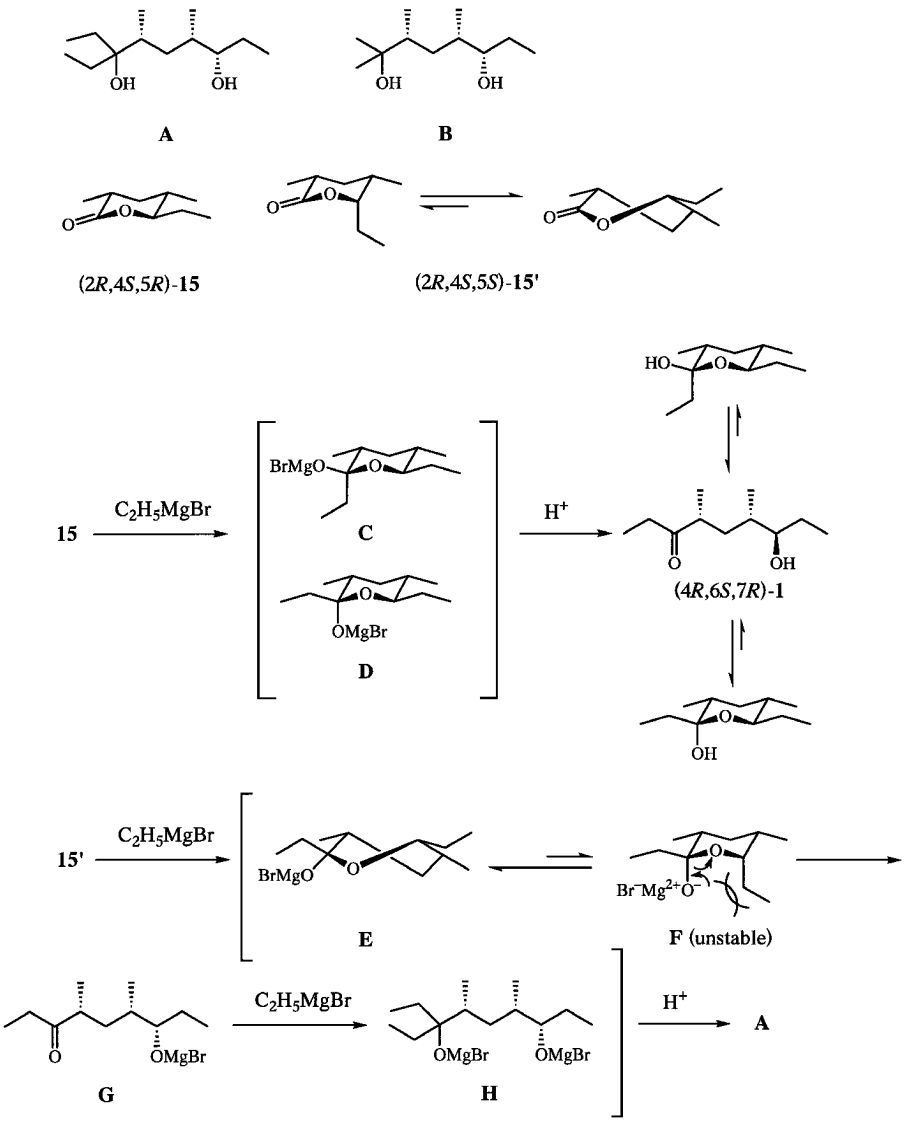


Fig. 2. Structures of Diols **A** and **B**, and a Possible Mechanism for the Formation of Diol **A** by the Addition of Ethylmagnesium Bromide to Lactone **15'**.

for the internal standard. ^{13}C-NMR spectra were recorded at 100 MHz with a Jeol JNM-LA400 spectrometer and at 126 MHz with a Jeol JNM-LA500 spectrometer. The peak for $CDCl_3$ (at δ 77.0) was used for the internal standard. Optical rotation data were measured with a Jasco P-1010 polarimeter. Column chromatography was carried out with Merck Kieselgel 60 Art 1.07734, and TLC analyses were performed with Merck 60F-254 silica gel plates.

(2S,4R)-1-Acetoxy-5-tert-butyldimethylsilyloxy-2,4-dimethylpentane (8). To a stirred solution of (2*R*,4*S*)-**7** (5.06 g, 29.0 mmol) and imidazole (2.35 g, 34.5 mmol) in DMF (50 ml) was added TBSCl (4.82 g, 31.9 mmol) at 0°C. The reaction mixture was stirred for 4 h at room temperature and then quenched with water. It was extracted with diethyl ether, and the resulting extract was successively washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel to give **8** (7.92 g, 95%) as a colorless oil, n_D^{24} 1.4309. $[\alpha]_D^{24}$ +5.40 (*c* 1.10, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 1745 (s, C=O), 1235 (s, C–OAc), 1095 (s, Si–O). NMR δ_H (400 MHz, $CDCl_3$): 0.005 (6H, s, Si–CH_3), 0.85–0.95 (1H, m, 3-H$_a$), 0.87 (9H, s, *t*-Bu), 0.88 (3H, d, *J*=5.9 Hz, 4-CH_3), 0.92 (3H, d, *J*=6.8 Hz, 2-CH_3), 1.43 (1H, quintet like, *J*=6.8 Hz, 3-H$_b$), 1.67 (1H, octet, *J*=6.6 Hz, 4-H), 1.87 (1H, octet like, *J*=6.8 Hz, 2-H), 2.07 (3H, s, OAc), 3.33 (1H, dd, *J*=9.8, 6.6 Hz, 5-H$_a$), 3.40 (1H, dd, *J*=9.8, 5.4 Hz, 5-H$_b$), 3.79 (1H, dd, *J*=10.7, 6.8 Hz, 1-H$_a$), 3.93 (1H, dd, *J*=10.7, 5.7 Hz, 1-H$_b$). *Anal.* Found: C, 62.30; H, 11.49%. Calcd. for $C_{15}H_{32}O_3Si$: C, 62.45; H, 11.18%.

(2S,4R)-5-tert-Butyldimethylsilyloxy-2,4-dimethyl-1-pentanol (9). To a stirred solution of **8** (5.06 g, 17.5 mmol) in MeOH (35 ml) was added K_2CO_3

(2.66 g, 19.3 mmol) at room temperature. The mixture was stirred for 12 h at room temperature, before the solvent was removed under reduced pressure. The concentrate was diluted with water and extracted with diethyl ether. The resulting extract was successively washed with water, sat. $NaHCO_3$ aq. and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel to give **9** (4.18 g, 96%) as a colorless oil, n_D^{24} 1.4368. $[\alpha]_D^{24}$ −1.89 (*c* 1.15, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 3340 (br.m, O–H), 1095 (s, Si–O). NMR δ_H (400 MHz, $CDCl_3$): 0.004 (6H, s, Si–CH_3), 0.87–0.94 (1H, m, 3-H$_a$), 0.88 (9H, s, *t*-Bu), 0.89 (3H, d, J = 3.4 Hz, 4-CH_3), 0.93 (3H, d, J = 6.6 Hz, 2-CH_3), 1.42 (1H, m, 3-H$_b$), 1.63–1.82 (3H, m, 1-OH, 2-, 4-H), 3.32–3.53 (4H, m, 1-, 5-H_2). *Anal.* Found: C, 63.14; H, 12.47%. Calcd. for $C_{13}H_{30}O_2Si$: C, 63.35; H, 12.27%.

(2R,4S,5RS)-1-tert-Butyldimethylsilyloxy-5-hydroxy-2,4-dimethylheptane (11). To a stirred solution of **9** (2.28 g, 9.25 mmol) in CH_2Cl_2 (23 ml) were added NMO (1.63 g, 13.9 mmol) and TPAP (135 mg, 0.38 mmol) at room temperature. The mixture was stirred for 0.5 h at room temperature, and then filtered through silica gel. The filtrate was concentrated under reduced pressure. To a stirred solution of residual aldehyde **10** in THF (10 ml) was added EtMgBr in THF (1.0 M, 30 ml, 30 mmol) at 0°C. The mixture was stirred for 0.5 h at room temperature, quenched by adding sat. NH_4Cl aq. at 0°C, and extracted with diethyl ether. The extract was successively washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel to give **11** (1.84 g, 2 steps, 73%) as a colorless oil, n_D^{20} 1.4446. $[\alpha]_D^{24}$ −9.6 (*c* 1.00, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 3365 (br.w, O–H), 1095 (m, Si–O). NMR δ_H (400 MHz, $CDCl_3$): 0.03 (6H, s, Si–CH_3), 0.83–0.99 (10H, m, 2-CH_3, 3-H$_a$, 4-CH_3, 7-H_3), 0.88 (9H, s, *t*-Bu), 1.40–1.74 (5H, m, 2-H, 3-H$_b$, 4-H, 6-H_2), 3.31–3.47 (3H, m, 1-H_2, 5-H). The proton of OH could not be located. *Anal.* Found: C, 65.62; H, 12.62%. Calcd. for $C_{15}H_{34}O_2Si$: C, 65.53; H, 12.48%.

(2R,4S,5R)-5-Acetoxy-1-tert-butyldimethylsilyloxy-2,4-dimethylheptane (12). Lipase PS-D (Amano Enzyme, Inc.; 0.70 g) was suspended in a solution of **11** (6.93 g, 25.2 mmol) in vinyl acetate (50 ml), and the mixture was stirred at room temperature for 11 days. The mixture was filtered through Celite, and the Celite layer was washed with diethyl ether. The combined filtrate and washings were concentrated under reduced pressure. The residue was chromatographed on silica gel to give the corresponding acetate (2.88 g, 36%). After deacetylation, Lipase PS-D (0.24 g) was suspended in a solution of the corresponding alcohol (2.40 g, 20.8 mmol) in vinyl acetate (25 ml), and the mixture was stirred at room temperature for 5 days. The mixture was filtered through Celite, and the Celite layer was washed with diethyl ether. The combined filtrate and washings were concentrated under reduced pressure. The residue was chromatographed on silica gel to give **12** (2.13 g, total 27%) as a colorless oil, n_D^{24} 1.4339. $[\alpha]_D^{24}$ −13.1 (*c* 1.04, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 1740 (s, C=O), 1245 (s, C–OAc), 1095 (s, Si–O). NMR δ_H (400 MHz, $CDCl_3$): 0.03 (6H, s, Si–CH_3), 0.84–0.94 (10H, m, 2-CH_3, 4-CH_3, 3-H$_a$, 7-H_3), 0.88 (9H, s, *t*-Bu), 1.40–1.59 (3H, m, 3-H$_b$, 6-H_2), 1.60–1.74 (1H, m, 2-H), 1.76–1.81 (1H, m, 4-H), 2.07 (3H, s, OAc), 3.34 (1H, dd, J = 9.8, 6.1 Hz, 1-H$_a$), 3.41 (1H, dd, J = 9.8, 5.4 Hz, 1-H$_b$), 4.71 (1H, dt like, J = 8.3, 4.6 Hz, 5-H). The diastereomeric excess was analyzed by GC [DB-WAX® column (0.25 mm × 60 m), 80–150°C, +20°C/min; He carrier gas at 1.0 kg/cm^2], (2*R*,4*S*,5*R*)-**12**: t_R = 27.53 min (99.12%); (2*R*,4*S*,5*S*)-**12**: t_R = 26.93 min (0.87%). The diastereomeric excess of (2*R*,4*S*,5*R*)-**12** was therefore 98.3% d.e. *Anal.* Found: C, 64.42; H, 11.19%. Calcd. for $C_{17}H_{36}O_3Si$: C, 64.50; H, 11.46%.

(2R,4S,5R)-5-Acetoxy-2,4-dimethyl-1-heptanol (13). To a stirred mixture of (2*R*,4*S*,5*R*)-**12** (1.00 g, 3.16 mmol) in dry THF (6 ml) was added TBAF in THF (1.0 M, 3.8 ml, 3.8 mmol) at 0°C under Ar, and stirring was continued for 12 h at room temperature. The reaction mixture was poured into water and extracted with diethyl ether. The extract was successively washed with sat. $NaHCO_3$ aq. and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel to give **13** (647 mg, quant.) as a colorless oil, n_D^{21} 1.4459. $[\alpha]_D^{21}$ +17.3 (*c* 1.00, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 3450 (br.s, O–H), 1735 (s, C=O), 1245 (s, C–OAc). NMR δ_H (500 MHz, $CDCl_3$): 0.87 (3H, t, J = 7.3 Hz, 7-CH_3), 0.89 (3H, d, J = 6.8 Hz, 4-CH_3), 0.97 (3H, d, J = 6.7 Hz, 4-CH_3), 1.31 (1H, dt like, J = 5.6, 1.9 Hz, 3-H_aH_b), 1.42 (1H, ddd, J = 13.8, 7.6, 5.6 Hz, 3-H_aH_b), 1.48–1.57 (2H, m, 6-H_2), 1.70 (1H, octet-like, J = 6.4Hz, 2-H), 1.83 (1H, m, 4-H), 2.06 (3H, s, OAc), 3.40 (1H, dt, J = 10.4, 6.1 Hz, 1-H_aH_b), 3.52 (1H, dt, J = 10.4, 5.5 Hz, 1-H_aH_b), 4.71 (1H, dt, J = 8.3, 4.9 Hz, 5-H). The proton of OH could not be located. *Anal.* Found: C, 65.12; H, 11.23%. Calcd. for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96%.

(2R,4S,5R)-2,4-Dimethyl-1,5-heptanediol (14). A solution of **13** (647 mg, 3.20 mmol) and KOH in MeOH (1.0 M, 9.0 ml, 9.0 mmol) was stirred for 12 h at room temperature. The reaction mixture was poured into water and extracted with diethyl ether, and the solvent was removed under reduced pressure. The concentrate was diluted with water and extracted with diethyl ether. The resulting extract was successively washed with water, sat. $NaHCO_3$ aq. and

brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel to give **14** (647 mg, 87%) as a colorless oil, n_D^{21} 1.4586. $[\alpha]_D^{21}$ −11.8 (*c* 1.00, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 3335 (s, O–H). NMR δ_H (500 MHz, $CDCl_3$): 0.91 (3H, d, J=6.8 Hz, 4-CH_3), 0.96 (3H, t, J=7.4 Hz, 7-H_3), 0.97 (3H, d, J=6.7 Hz, 2-CH_3), 0.93–0.99 (1H, m, 3-H_a), 1.32–1.45 (1H, m, 3-H_b), 1.49–1.59 (2H, m, 6-H_2), 1.60–1.67 (1H, m, 4-H), 1.67–1.76 (1H, m, 2-H), 3.34 (1H, ddd, J=8.9, 5.5, 3.4 Hz, 5-H), 3.45 (1H, dd, J=10.7, 6.1 Hz, 1-H_a), 3.53 (1H, dd, J=10.7, 4.9 Hz, 1-H_b). *Anal.* Found: C, 67.24; H, 12.53%. Calcd. for $C_9H_{20}O_2$: C, 67.45; H, 12.58%.

(2R,4S,5R)-2,4-Dimethyl-5-heptanolide (15). To a stirred solution of **14** (448 mg, 2.80 mmol) in CH_2Cl_2 (6 ml) were added NMO (1.31 g, 11.2 mmol) and TPAP (74.6 mg, 0.212 mmol) at room temperature. The mixture was stirred for 12 h at room temperature, filtered through silica gel, and the silica gel layer was washed with CH_2Cl_2. The combined filtrate and washings were concentrated under reduced pressure. The residue was chromatographed on silica gel to give **15** (344 mg, 79%) as a colorless solid, mp 32–33°C. $[\alpha]_D^{20}$ +32.6 (*c* 1.10, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 1730 (s, C=O). NMR δ_H (400 MHz, $CDCl_3$): 0.97 (3H, d, J=6.8 Hz, 4-CH_3), 1.00 (3H, t, J=7.3 Hz, 5-CH_2CH_3), 1.28 (3H, d, J=7.1 Hz, 3-CH_3), 1.30–1.40 (1H, m, 4-H), 1.50–1.62 (1H, m, 5-CH_aCH$_3$), 1.74–1.85 (2H, m, 3-H_a, 5-CH_bCH$_3$), 1.90 (1H, ddd, J=13.2, 6.3, 3.2 Hz, 3-H_b), 2.49 (1H, ddq, J=7.1, 6.8, 6.3 Hz, 2-H), 3.90 (1H, ddd, J=10.0, 7.1, 2.9 Hz, 5-H). *Anal.* Found: C, 69.20; H, 10.56%. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32%.

(4R,6S,7R)-7-Acetoxy-4,6-dimethyl-3-nonanone (3). To a stirred solution of **15** (100 mg, 0.64 mmol) in dry Et_2O (10 ml) was added a solution of EtMgBr in THF (0.89 M, 0.76 ml, 0.67 mmol) at −78°C. The mixture was stirred for 0.5 h at room temperature, quenched by adding sat. NH_4Cl aq. at 0°C, and extracted with diethyl ether. The extract was successively washed with water and brine, dried with Na_2SO_4, and concentrated under reduced pressure, before pyridine (5 ml) and Ac_2O (1 ml) were added to residual **1** at 0°C. The mixture was stirred for 48 h at room temperature, quenched by adding water at 0°C, and extracted with diethyl ether. The extract was successively washed with water, sat. $CuSO_4$ aq., sat. $NaHCO_3$ aq. and brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel to give **3** (95 mg, 2 steps, 65%) as a pale yellow oil, n_D^{21} 1.4355. $[\alpha]_D^{20}$ +12.1 (*c* 1.05, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 1735 (s, C=O), 1720 (s, C=O), 1245 (s, C–OAc). NMR δ_H (400 MHz, $CDCl_3$): 0.857 (3H, t, J=7.6 Hz, 9-H_3), 0.86 (3H, d, J=7.1 Hz, 6-CH_3), 1.04 (3H, t, J=7.2 Hz, 1-H_3), 1.10 (3H, d, J=7.1 Hz, 4-CH_3), 1.46–1.65 (4H, m, 5-, 8-H_2), 1.79–1.87 (1H, m, 6-H), 2.06 (3H, s, OAc), 2.40 (1H, dq, J=17.8, 7.2 Hz, 2-H_a), 2.52 (1H, dq, J=17.8, 7.2 Hz, 2-H_b), 2.66 (1H, ddq, J=9.2, 7.1, 4.6 Hz, 4-H), 4.67 (1H, dt, J=7.8, 4.9 Hz, 7-H). NMR δ_C (100 MHz, $CDCl_3$): 7.7, 10.0, 15.8, 18.1, 21.1, 23.3, 34.0, 34.1, 35.4, 43.8, 78.9, 171.0, 215.0. *Anal.* Found: C, 68.21; H, 10.41%. Calcd. for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59%.

(3R,5S,6R)-6-Acetoxy-3,5-dimethyl-2-octanone (4). To a stirred solution of **15** (100 mg, 0.64 mmol) in dry Et_2O (10 ml) was added a solution of MeMgBr in THF (0.93 M, 0.72 ml, 0.67 mmol) at −78°C. The mixture was stirred for 0.5 h at room temperature, quenched by adding sat. NH_4Cl aq. at 0°C, and extracted with diethyl ether. The extract was successively washed with water and brine, dried with Na_2SO_4, and concentrated under reduced pressure, before pyridine (5 ml) and Ac_2O (1 ml) were added to residual **2** at 0°C. The reaction mixture was stirred for 48 h at room temperature, quenched by adding water at 0°C, and extracted with diethyl ether. The extract was successively washed with water, sat. $CuSO_4$ aq., sat. $NaHCO_3$ aq. and brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel to give **4** (97 mg, 2 steps, 70%) as a pale yellow oil, n_D^{21} 1.4365. $[\alpha]_D^{20}$ +20.4 (*c* 1.00, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 1735 (s, C=O), 1720 (s, C=O), 1245 (s, C–OAc). NMR δ_H (400 MHz, $CDCl_3$): 0.86 (3H, t, J=7.8 Hz, 8-H_3), 0.87 (3H, d, J=7.1 Hz, 5-CH_3), 1.05–1.13 (1H, m, 4-H_a), 1.12 (3H, d, J=6.8 Hz, 3-CH_3), 1.48–1.68 (3H, m, 4-H_b, 7-H_2), 1.77–1.84 (1H, m, 5-H), 2.07 (3H, s, OAc), 2.13 (3H, s, 1-H_3), 2.63 (1H, ddq, J=9.2, 6.8, 4.9 Hz, 3-H), 4.68 (1H, dt, J=7.8, 4.9 Hz, 6-H). NMR δ_C (100 MHz, $CDCl_3$): 9.9, 15.7, 17.7, 21.1, 23.3, 27.8, 33.9, 35.3, 44.9, 78.8, 171.1, 212.6. *Anal.* Found: C, 67.46; H, 10.50%. Calcd. for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35%.

(2R,4S,5S)-1-tert-Butyldimethylsilyloxy-5-hydroxy-2,4-dimethylheptane (11′). Lipase PS-D (Amano Enzyme, Inc.; 96 mg) was suspended in a solution of **11** (1.84 g, 6.70 mmol) in vinyl acetate (18.5 ml), and the mixture was stirred at room temperature for 2 days. Additional lipase PS-D (90 mg) was then added to the reaction mixture. After stirring for 9 days, the mixture was filtered through Celite, and the Celite layer was washed with diethyl ether. The combined filtrate and washings were concentrated under reduced pressure. The residue was chromatographed on silica gel to give **11′** (1.19 g, 64%) as a colorless oil, n_D^{24} 1.4438. $[\alpha]_D^{24}$ +7.62 (*c* 1.45, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 3385 (br.m, O–H), 1090 (s, Si–O). NMR δ_H (400 MHz, $CDCl_3$): 0.03 (6H, s, Si–CH_3), 0.85 (3H, d, J=6.8 Hz, 4-CH_3), 0.88 (3H, d, J=6.6 Hz,

2-CH_3), 0.88 (9H, s, *t*-Bu), 0.89–0.98 (1H, m, 3-H_a), 0.93 (3H, t, J = 8.8 Hz, 7-H_3), 1.40–1.54 (4H, m, 3-H_b, 5-OH, 6-H_2), 1.55–1.64 (1H, m, 4-H), 1.68 (1H, octet, J = 6.4 Hz, 2-H), 3.34–3.50 (3H, m, 1-H_2, 5-H). The diastereomeric excess was analyzed by GC [DB-WAX® column (0.25 mm × 60 m), 80–150°C, +20°C/min; He carrier gas at 1.0 kg/cm^2], (2*R*,4*S*,5*R*)-**11**: t_R = 30.58 min (0.48%); (2*R*,4*S*,5*S*)-**11′**: t_R = 30.35 min (99.5%). The diastereomeric excess of (2*R*,4*S*,5*S*)-**11′** was therefore 99.0% d.e. *Anal.* Found: C, 65.46; H, 12.24%. Calcd. for $C_{15}H_{34}O_2Si$: C, 65.63; H, 12.48%.

(2R,4S,5S)-2,4-Dimethyl-1,5-heptanediol (14′). To a stirred mixture of **11′** (1.00 g, 3.64 mmol) in dry THF (6 ml) was added TBAF in THF (1.0 M, 4.4 ml, 4.4 mmol) at 0°C under Ar, and stirring was continued for 5 h at room temperature. The reaction mixture was poured into water and extracted with diethyl ether. The extract was successively washed with sat. $NaHCO_3$ aq. and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel to give **14′** (538 mg, 92%) as a colorless oil, n_D^{21} 1.4576. $[\alpha]_D^{22}$ −3.8 (*c* 1.05, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 3350 (br.s, O–H). NMR δ_H (500 MHz, $CDCl_3$): 0.86 (3H, d, J = 6.7 Hz, 4-CH_3), 0.94 (3H, d, J = 6.5 Hz, 2-CH_3), 0.95 (3H, t, J = 7.4 Hz, 7-CH_3), 0.94–1.03 (1H, m, 3-H_a), 1.46 (2H, quint, J = 7.4 Hz, 6-H_2), 1.52–1.60 (3H, m, 3-H_b, 1-, 5-OH), 1.65 (1H, ddq like, J = 7.1, 6.7, 3.4 Hz, 4-H), 1.74 (1H, octet, J = 6.5 Hz, 2-H), 3.44–3.53 (3H, m, 1-H_2, 5-H). *Anal.* Found: C, 67.30; H, 12.43%. Calcd. for $C_9H_{20}O_2$: C, 67.45; H, 12.58%.

(2R,4S,5S)-2,4-Dimethyl-5-heptanolide (15′). To a stirred solution of **14′** (538 mg, 3.37 mmol) in CH_2Cl_2 (7 ml) were added NMO (1.58 g, 13.5 mmol) and TPAP (96 mg, 0.27 mmol) at room temperature. The reaction mixture was stirred for 12 h at room temperature, filtered through silica gel, and the silica gel layer was washed with CH_2Cl_2. The combined filtrate and washings were concentrated under reduced pressure. The residue was chromatographed on silica gel to give **15′** (417 mg, 78%) as a colorless oil, n_D^{20} 1.4564. $[\alpha]_D^{20}$ −108 (*c* 1.10, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 1740 (s, C=O), 1245 (s, C–OAc). NMR δ_H (400 MHz, $CDCl_3$): 0.90 (3H, d, J = 7.1 Hz, 4-CH_3), 0.99 (3H, t, J = 7.3 Hz, 5-CH_2CH_3), 1.02–1.14 (1H, m, 4-H), 1.19 (3H, d, J = 6.6 Hz, 2-CH_3), 1.54 (1H, ddq, J = 7.3, 6.8, 4.9 Hz, 5-CH_aCH$_3$), 1.72 (1H, ddq, J = 8.6, 7.3, 6.8 Hz, 5-CH_bCH$_3$), 2.09–2.20 (1H, m, 3-H_a), 2.32 (1H, dt like, J = 13.7, 8.8 Hz, 3-H_b), 2.53–2.64 (1H, m, 2-H), 4.18 (1H, ddd, J = 8.6, 4.9, 3.2 Hz, 5-H). *Anal.* Found: C, 69.32; H, 10.61%. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32%.

(4R,6S,7S)-7-Acetoxy-4,6-dimethyl-3-nonanone (3′). To a stirred solution of **15′** (82 mg, 0.52 mmol) in dry Et_2O (10 ml) was added EtLi in Et_2O [1.39 M, 0.42 ml, 0.58 mmol; prepared from Li (787 mg) in dry Et_2O (20 ml) and EtBr (5.00 g) in dry Et_2O (10 ml)] at −78°C. The mixture was stirred for 5 min at −78°C, quenched by adding water at 0°C, and extracted with diethyl ether. The extract was successively washed with water and brine, dried with Na_2SO_4, concentrated under reduced pressure, and then pyridine (5 ml) and Ac_2O (1 ml) were added to residual **1′** at 0°C. The reaction mixture was stirred for 12 h at room temperature, quenched by adding water at 0°C, and extracted with diethyl ether. The extract was successively washed with water, sat. $CuSO_4$ aq., sat. $NaHCO_3$ aq. and brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel to give **3′** (48 mg, 2 steps, 36%) as a pale yellow oil, n_D^{21} 1.4386. $[\alpha]_D^{20}$ −4.4 (*c* 1.00, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 1735 (s, C=O), 1720 (s, C=O), 1245 (s, C–OAc). NMR δ_H (400 MHz, $CDCl_3$): 0.87 (3H, t, J = 7.6 Hz, 9-H_3), 0.89 (3H, d, J = 6.8 Hz, 6-CH_3), 1.03 (3H, t, J = 7.4 Hz, 1-H_3), 1.06 (3H, d, J = 7.1 Hz, 4-CH_3), 1.50–1.65 (4H, m, 5-, 8-H_2), 1.71–1.78 (1H, m, 6-H), 2.06 (3H, s, OAc), 2.39 (1H, dq, J = 17.8, 7.4 Hz, 2-H_a), 2.49 (1H, dq, J = 17.8, 7.4 Hz, 2-H_b), 2.69 (1H, ddq, J = 7.1, 5.4, 2.7 Hz, 4-H), 4.47 (1H, ddd, J = 8.5, 4.7, 4.1 Hz, 7-H). NMR δ_C (100 MHz, $CDCl_3$): 7.8, 10.1, 14.6, 17.3, 21.1, 24.1, 33.5, 34.3, 36.3, 43.3, 76.7, 171.1, 215.1. *Anal.* Found: C, 68.36; H, 10.77%. Calcd. for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59%.

(3R,5S,6S)-6-Acetoxy-3,5-dimethyl-2-octanone (4′). To a stirred solution of **15′** (35 mg, 0.224 mmol) in dry Et_2O (10 ml) was added EtLi in Et_2O [1.04 M, 0.22 ml, 0.23 mmol; prepared from Li (787 mg) in dry Et_2O (20 ml) and EtBr (5.00 g) in dry Et_2O (10 ml)] at −78°C. The mixture was stirred for 5 min at −78°C, quenched by adding water at 0°C, and extracted with diethyl ether. The extract was successively washed with water and brine, dried with Na_2SO_4, and concentrated under reduced pressure, before pyridine (5 ml) and Ac_2O (1 ml) were added to residual **2′** at 0°C. The reaction mixture was stirred for 12 h at room temperature, quenched by adding water at 0°C, and extracted with diethyl ether. The extract was successively washed with water, sat. $CuSO_4$ aq., sat. $NaHCO_3$ aq. and brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel to give **4** (19 mg, 2 steps, 40%) as a pale yellow oil, n_D^{21} 1.4372. $[\alpha]_D^{20}$ −30.6 (*c* 0.85, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 1735 (s, C=O), 1720 (s, C=O), 1245 (s, C–OAc). NMR δ_H (500 MHz, $CDCl_3$): 0.87 (3H, t, J = 7.7 Hz, 8-H_3), 0.89 (3H, d, J = 6.7 Hz, 5-CH_3), 1.03–1.11 (1H, m, 4-H_a), 1.08 (3H, d, J = 6.7 Hz, 3-CH_3), 1.48–1.69

(3H, m, 5-H, 7-H_2), 1.74 (1H, ddd, J=14.1, 8.3, 6.1 Hz, 4-H_b), 2.07 (3H, s, OAc), 2.12 (3H, m, 1-H_3), 2.67 (1H, sextet, J=7.3 Hz, 3-H), 4.76 (1H, dt, J=8.3, 4.6 Hz, 6-H). NMR δ_C (100 MHz, $CDCl_3$): 10.1, 14.5, 17.0, 21.1, 24.1, 28.0, 33.5, 36.1, 44.4, 77.7, 171.1, 212.6. *Anal.* Found: C, 67.42; H, 10.50%. Calcd. for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35%.

Acknowledgments

We thank Prof. W. Francke (University of Hamburg) for kindly sharing his results in the structural elucidation of **1** and **2**. Our thanks are also due to Dr. Y. Hirose (Amano Enzyme, Inc.) for his kindly presenting lipase AK.

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