Synthesis of (2*R*,4*R*)-Supellapyrone, the Sex Pheromone of the Brownbanded Cockroach, *Supella longipalpa*, and Its Three Stereoisomers[‡]

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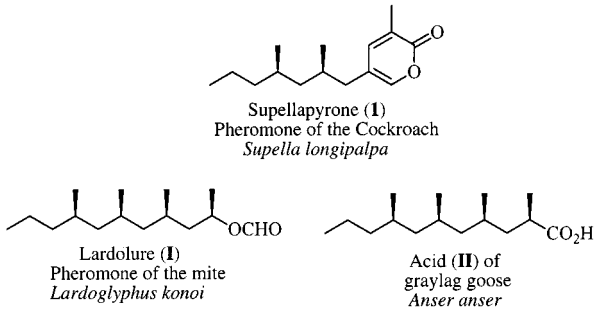
Supellapyrone [(2*R*,4*R*)-5-(2,4-dimethyl)-3-methyl-2*H*-pyran-2-one (**1**)], the female sex pheromone of the brownbanded cockroach (*Supella longipalpa*), and its three stereoisomers were synthesized by employing lipase-catalyzed desymmetrization or enantiomer separation of *syn*- or *anti*-2,4-dimethylpentane-1,5-diol (**9**) as the key step.

Introduction

In 1993, Roelofs and his co-workers isolated the female sex pheromone of the brownbanded cockroach (*Supella longipalpa*), named it supellapyrone, and identified it as 5-(2,4-dimethylheptyl)-3-methyl-2*H*-pyran-2-one (**1**, Scheme 1).[1] They synthesized a racemic and diastereomeric mixture of all four possible stereoisomers of **1**, which was shown to be bioactive.[1] The relative and absolute configuration of supellapyrone was subsequently determined by Meinwald and his co-workers as (2*R*,4*R*)-**1** by a combination of synthesis, GC analysis on a chiral stationary phase and electrophysiological measurements, although they did not synthesize each of the four stereoisomers of **1**.[2,3]



Scheme 1. Structures of supellapyrone (**1**) and related compounds

We became interested in synthesizing supellapyrone (**1**), because its proposed structure suggested a biogenetic relationship with two other polyketides, lardolure (**I**)[4,5] and (2*R*,4*R*,6*R*,8*R*)-2,4,6,8-tetramethylundecanoic acid (**II**),[6] both of which had been synthesized by Mori et al. Lardolure (**I**) is the aggregation pheromone of the acarid mite (*Lardoglyphis konoi*),[4,5] while **II** is the acid component of the preen-gland wax of the graylag goose (*Anser anser*).[6] We speculated that the natural pheromone might be (2*R*,4*R*)-**1**, and synthesized racemic (2*R**,4*R**)-**1**.[7] The ^{1}H NMR spectrum of our synthetic (2*R**,4*R**)-**1** agreed well with that of the natural pheromone.[7] We subsequently synthesized optically active (2*R*,4*R*)-**1**,[8] but did not prepare the other three stereoisomers of **1**. However, it became necessary to synthesize all of them, because Leal et al. pointed out the possibility that (2*S*,4*R*)-**1** might be an antagonist to the natural (2*R*,4*R*)-**1**.[3] Bioassay of all of four stereoisomers of **1** will definitely clarify the stereochemistry-pheromone activity relationships, which can be revealed only through experiments.[9]

Scheme 2 shows the retrosynthetic analysis of supellapyrone (**1**). After some preliminary model experiments, it was decided that the δ-lactone system of **1** could be constructed by the intramolecular Reformatsky reaction of **A**. The bromo ester **A** could be prepared from the diol **B** and 2-bromopropanoyl bromide (**C**). The former could be synthesized from alcohol **D** and dimethyl malonate (**E**). The *syn*-dimethylated alcohol **D** and its opposite enantiomer could be derived from mesitol (**F**) or *meso*-anhydride **G**. The two *anti*-dimethylated diastereomers of **D** could be prepared from (±)-**G**′.

Results and Discussion

Synthesis of the Chiral Building Block D [(2*R*,4*R*)-7] from Mesitol

Conversion of mesitol (**2**) to the hydroxy ester (2*R**,4*S**,6*S**)-**3** (Scheme 3) was carried out as previously reported.[4] The enzymatic enantiomer separation of (±)-**3** and the later steps leading to (2*R*,4*R*)-supellapyrone (**1**) were reported in 1994 as a preliminary communication.[8] Treatment of (±)-**3** with vinyl acetate in the presence of lipase AK afforded the acetate (2*S*,4*R*,6*R*)-**4** in 42% yield (ca. 100% *ee*), leaving (2*R*,4*S*,6*S*)-**3** intact (46% yield; 98% *ee*). The ester (2*R*,4*S*,6*S*)-**3** was hydrolyzed with lithium hydroxide without racemization at C-2, and the resulting hydroxy acid (2*R*,4*S*,6*S*)-**5** was purified by recrystallization. After ester-

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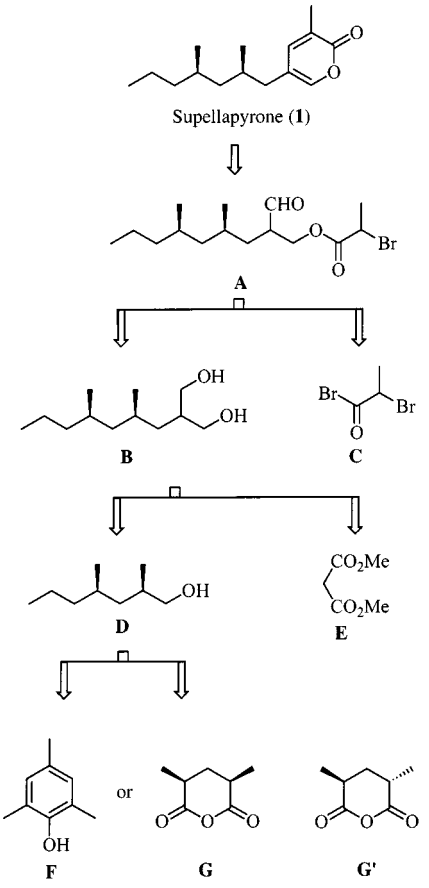


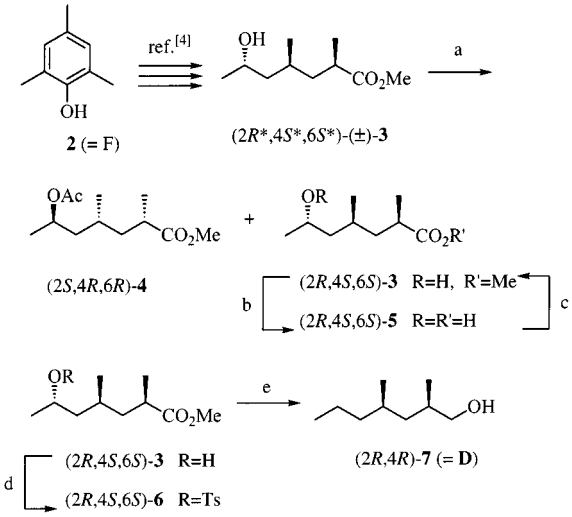
Scheme 2. Retrosynthetic analysis of supellapyrone (**1**)

ification of **5** with diazomethane to give back the methyl ester (2*R*,4*S*,6*S*)-**3**, its hydroxy group at C-6 was removed reductively via the corresponding tosylate (2*R*,4*S*,6*S*)-**6** by treatment with lithium aluminum hydride to give the desired building block (2*R*,4*R*)-**7** in 8% overall yield from mesitol (**2**, 9 steps). The diastereomeric as well as the enantiomeric purity of (2*R*,4*R*)-**7** was ca. 100% owing to the careful purification of the acid (2*R*,4*S*,6*S*)-**5** by recrystallization.

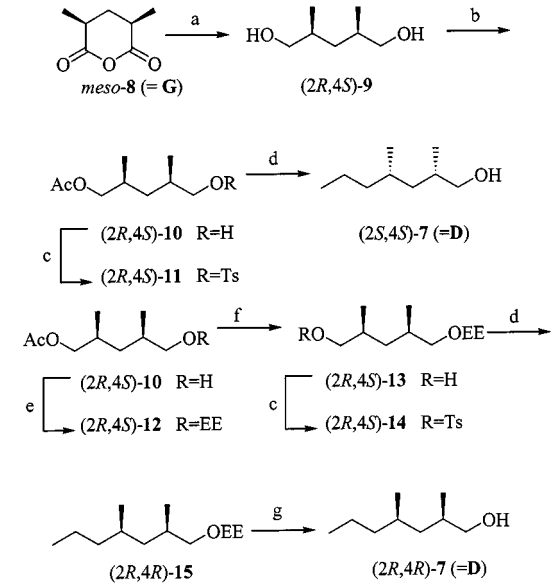
Synthesis of the Chiral Building Block D (2,4-*syn*-7) from *meso*-2,4-Dimethylglutaric Anhydride

The synthesis of **7** described above has two drawbacks: (i) The route is lengthy and inefficient, and (ii) it gives only the (2*R*,4*R*) and (2*S*,4*S*) isomers of **7**. We therefore turned our attention to more traditional ways of desymmetrizing or resolving *meso*- or (±)-2,4-dimethylpentane-1,5-diol (**9**) by means of lipases or esterases. This enzymatic method was first pioneered in 1984 by Sih and co-workers.[10]

Scheme 4 summarizes the conversion of *meso*-2,4-dimethylglutaric anhydride (**8** = **G**)[11] into the enantiomers of *syn*-2,4-dimethyl-1-heptanol (**7** = **D**). Reduction of *meso*-**8** with lithium aluminum hydride furnished (2*R*,4*S*)-**9**, which was desymmetrized by treatment with vinyl acetate and lipase AK to give the monoacetate (2*R*,4*S*)-**10** (98.3−98.4% *ee*).[12] Tosylation of (2*R*,4*S*)-**10** was followed by chain-elongation of the resulting tosylate (2*R*,4*S*)-**11** with excess ethylmagnesium bromide in the presence of dilithium tetrachlorocuprate[13] to give (2*S*,4*S*)-**7** in 50% overall yield based on *meso*-**8** (4 steps).



Scheme 3. Synthesis of the building block (2*R*,4*R*)-**7**: reagents: (a) CH_2=CHOAc, lipase AK, hexane [42% of (2*S*,4*R*,6*R*)-**4**; 46% of (2*R*,4*S*,6*S*)-**3**]; (b) LiOH, THF/H_2O (99%), then recrystallization from Et_2O/hexane (51%); (c) CH_2N_2, Et_2O (99%); (d) TsCl, C_5H_5N (quant.); (e) $LiAlH_4$, Et_2O (83%)



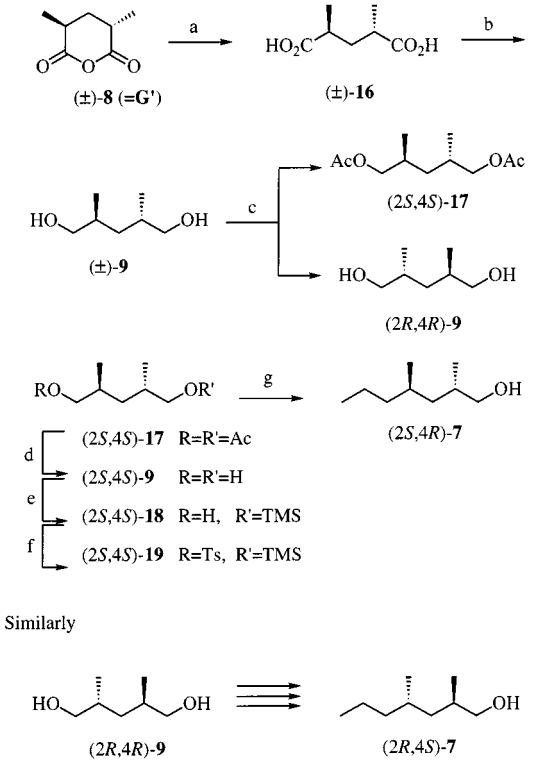
Scheme 4. Alternative synthesis of the building blocks (2*R*,4*R*)- and (2*S*,4*S*)-**7**: reagents: (a) $LiAlH_4$, THF (80%); (b) CH_2=CHOAc, lipase AK, THF (72%); (c) TsCl, C_5H_5N (quant.); (d) EtMgBr, Li_2CuCl_4, THF [87% for (2*S*,4*S*)-**7**; 77% for (2*R*,4*R*)-**15**]; (e) CH_2=CHOEt, TsOH (96%); (f) K_2CO_3, MeOH (98%); (g) TsOH, MeOH (78%)

The opposite enantiomer (2*R*,4*R*)-**7** was also prepared from the monoacetate (2*R*,4*S*)-**10**. Protection of the free hydroxy group of (2*R*,4*S*)-**10** as the ethoxyethyl (EE) ether was followed by treatment of the resulting (2*R*,4*S*)-**12** with potassium carbonate in methanol to give the alcohol (2*R*,4*S*)-**13**. This was tosylated and the resulting tosylate (2*R*,4*S*)-**14** was treated with ethylmagnesium bromide under Schlosser conditions[13] to give (2*R*,4*R*)-**15**. Subsequent removal of the EE protecting group of **15** afforded (2*R*,4*R*)-**7** in 33% overall yield based on *meso*-**8** (7 steps). It is there-

fore clear that the method shown in Scheme 4 is a more direct and efficient preparation of (2*R*,4*R*)-**7** than that shown in Scheme 3.

Synthesis of the Enantiomers of the Chiral Building Block D (2,4-*anti*-7) from (±)-2,4-Dimethylglutaric Anhydride

The synthesis of the enantiomers of 2,4-*anti*-**7** is summarized in Scheme 5. The crude and racemic anhydride (±)-**8** was hydrolyzed with boiling water and the resulting diacid was purified by recrystallization to give pure (±)-**16**. Reduction of (±)-**16** with borane−dimethyl sulfide furnished the diol (±)-**9**. Treatment of (±)-**9** with vinyl acetate in the presence of lipase AK was repeated twice to effect almost perfect enantiomer separation to give the diacetate (2*S*,4*S*)-**17** (ca.100% *ee*) and the diol (2*R*,4*R*)-**9** (ca. 100% *ee*), each in 26% yield.

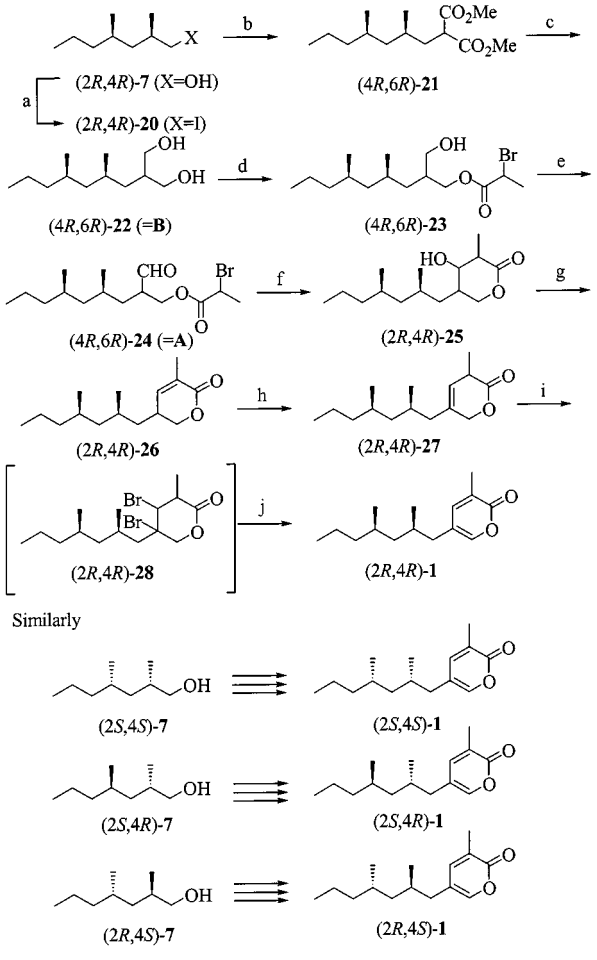


Scheme 5. Synthesis of the building blocks (2*S*,4*R*)- and (2*R*,4*S*)-**7**: reagents: (a) H_2O, heat; then recrystallization from $CHCl_3$ (20%); (b) $BH_3{\cdot}SMe_2$, THF (80%); (c) $CH_2{=}CHOAc$, lipase AK (twice) [26% of (2*S*,4*S*)-**17**; 26% of (2*R*,4*R*)-**9**]; (d) K_2CO_3, MeOH (99%); (e) *n*BuLi, TMSCl, THF (88%); (f) TsCl, Et_3N, $CHCl_3$ (quant.); (g) (1) EtMgBr, Li_2CuCl_4, THF, (2) dil. HCl (87%)

Potassium carbonate in methanol converted the diacetate (2*S*,4*S*)-**17** into the parent diol (2*S*,4*S*)-**9**, which was monosilylated with 1 equiv. of trimethylsilyl (TMS) chloride and *n*-butyllithium to give the mono-TMS ether (2*S*,4*S*)-**18**. The corresponding tosylate (2*S*,4*S*)-**19** was chain-elongated with ethylmagnesium bromide in the presence of dilithium tetrachlorocuprate[13] to give (2*S*,4*R*)-**7** with concomitant removal of the TMS group during workup. The overall yield of (2*S*,4*R*)-**7** was 16% based on (±)-**16** (6 steps) Similarly, the alcohol (2*R*,4*S*)-**7** was prepared from (2*R*,4*R*)-**9** in 18% overall yield based on (±)-**16** (5 steps).

Synthesis of (2*R*,4*R*)-Supellapyrone (1) and Its Three Stereoisomers

With all four stereoisomers of 2,4-dimethyl-1-heptanol (**7**) in hand, we began the conversion of **7** into the final product **1** as shown in Scheme 6. Treatment of alcohol (2*R*,4*R*)-**7** with iodine and triphenylphosphane in the presence of imidazole gave the iodide (2*R*,4*R*)-**20**. Alkylation of dimethyl malonate (**E**) with (2*R*,4*R*)-**20** afforded the malonate (4*R*,6*R*)-**21**. This malonate was reduced with sodium borohydride in methanol/THF[14] to give the diol (4*R*,6*R*)-**22** (= **B**). Acylation of the diol (4*R*,6*R*)-**22** with 1 equivalent of 2-bromopropanoyl bromide (**C**) employing 1 equivalent of *n*-butyllithium as base furnished the monoacylated diol (4*R*,6*R*)-**23**. This was oxidized with pyridinium chlorochromate (PCC) to afford aldehyde (4*R*,6*R*)-**24**, the precursor for the key cyclization reaction. Various other oxidants were also examined, and PCC was proved to be the best choice.



Scheme 6. Synthesis of supellapyrone (2*R*,4*R*)-**1** and its stereoisomers: reagents: (a) I_2, Ph_3P, imidazole, DMF (99%); (b) $CH_2(CO_2Me)_2$, NaH, THF (76%); (c) $NaBH_4$, THF/MeOH (85%); (d) *n*BuLi, MeCHBrCOBr, THF (78%); (e) $CrO_3{\cdot}HCl{\cdot}C_5H_5N$ (PCC), MS 4 Å, $CHCl_3$; (f) SmI_2, THF [71% based on (4*R*,6*R*)-**23**]; (g) MsCl, DMAP, $CHCl_3$ (63%); (h) $KN(SiMe_3)_2$, THF/HMPA; then dil. HCl (74%); (i) Br_2

Prior to achieving the successful Reformatsky-type reaction with samarium(II) iodide for the cyclization of

(4*R*,6*R*)-**24** to yield (2*R*,4*R*)-**25**, we attempted, in vain, an intramolecular Horner−Wadsworth−Emmons reaction of the phosphonate ester derived from **23** followed by oxidation to furnish an α,β-unsaturated δ-lactone. Compound **24** was then treated with magnesium in THF to realize an intramolecular Barbier-type reaction, which was also not successful. We therefore turned our attention to the intramolecular Reformatsky-type reaction by employing zinc or the zinc−copper couple. The reaction did not take place with zinc, but it did occur with the zinc−copper couple. This reaction, however, was difficult to reproduce. It was finally found that samarium(II) iodide in THF[15] was the best reagent to achieve the cyclization of (4*R*,6*R*)-**24** to (2*R*,4*R*)-**25** in a reproducible and acceptable yield of 71%. Dehydration of (2*R*,4*R*)-**25** was best achieved with mesyl chloride in dichloromethane in the presence of excess 4-(dimethylamino)pyridine (DMAP) to give the α,β-unsaturated δ-lactone (2*R*,4*R*)-**26** in 63% yield. A more conventional method for the dehydration of **25** by treatment with *p*-toluenesulfonic acid in boiling benzene furnished **26** in a less satisfactory yield of 40%.

The seemingly simple final dehydrogenation of (2*R*,4*R*)-**26** to (2*R*,4*R*)-supellapyrone (**1**) was rather difficult to achieve, and demanded considerable experimentation. A successful three-step conversion was found: (i) Deconjugation of the α,β-unsaturated lactone (2*R*,4*R*)-**26** with potassium hexamethyldisilazide (KHMDS) in THF/HMPA followed by quenching with dilute hydrochloric acid to give the β,γ-unsaturated δ-lactone (2*R*,4*R*)-**27** in 74% yield, (ii) bromination of (2*R*,4*R*)-**27** with bromine, and (iii) dehydrobromination of the resulting dibromide **28** with 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) in chloroform to furnish (2*R*,4*R*)-supellapyrone (**1**), $[\alpha]_D^{23} = +5.20$ (Et_2O) [ref.[8]: $[\alpha]_D^{19} = +5.3$ (Et_2O)], in 15% overall yield based on (2*R*,4*R*)-**7** (10 steps) or 5% overall yield based on the *meso*-anhydride **8** (17 steps). Its ^1H NMR spectrum agrees well with the published spectrum[1] of the natural pheromone. Our synthetic (2*R*,4*R*)-**1** was > 99% chemically pure and its diastereomeric purity was 99.2% *de*, both determined by GC, while its enantiomeric purity was 98.2−98.3% *ee*, as estimated by that of the key intermediate (2*R*,4*R*)-**7**.

The other three stereoisomers of supellapyrone, (2*S*,4*S*)-, (2*S*,4*R*)-, and (2*R*,4*S*)-**1**, were also synthesized from the corresponding three key intermediates, (2*S*,4*S*)-, (2*S*,4*R*)-, and (2*R*,4*S*)-**7**. They could be secured with the same degree of chemical, diastereomeric and enantiomeric purities as those of (2*R*,4*R*)-**1**. The diastereomers such as (2*R*,4*R*)- and (2*R*,4*S*)-**1** could be cleanly separated by GC (DB-wax column) and showed subtle but definitive differences in their ^1H and ^{13}C NMR spectra (see Exp. Sect.).

Conclusion

The synthesis described above allowed us to secure the four stereoisomers of supellapyrone (**1**). Especially noteworthy are the successful use of lipase AK in achieving desymmetrization or enantiomer separation of *syn*- or *anti*-2,4-dimethylpentane-1,5-diol (**9**) and the high efficiency of samarium(II) iodide in effecting the Reformatsky-type reaction. Our synthetic samples of the stereoisomers of **1** are now being bioassayed in the U.S.A. (Prof. C. Schal), and the results will be published in due course.

Experimental Section

General: Melting points (uncorrected values): Yanaco MP-S3. − IR: Jasco A-102 and Jasco FT/IR-410. − ^1H NMR: Jeol JNM-EX90A (90 MHz), Jeol JNM-AL300 (300 MHz), Jeol JNM-LA400 (400 MHz) and Jeol JNM-LA500 (500 MHz) (TMS at δ = 0 or $CHCl_3$ at δ = 7.26 or C_6D_6 at δ = 7.15 as internal standard). − ^{13}C NMR: Jeol JNM-LA400 (100.40 MHz) and Jeol JNM-LA500 (125.65 MHz) (C_6D_6 at δ = 77.0 as internal standard). − Optical rotation: Jasco DIP-1000 or Jasco P-1020. −HRMS: Jeol JMS-SX102A. − Column chromatography: Merck Kieselgel 60 Art 1.07734. − TLC: 0.25 mm Merck Silica gel plates (60F−254).

Enantiomeric Separation of (±)-(2*R,4*R**,6*S**)-Methyl 6-Hydroxy-2,4-dimethylheptanoate (3):** To a stirred solution of hydroxy ester **3** (13.6 g, 72.1 mmol) in hexane (100 mL) were added vinyl acetate (30.0 mL, 353 mmol) and lipase AK (850 mg). This mixture was stirred for 2 weeks at room temperature and the lipase was filtered off. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (250 g, hexane/ethyl acetate, 20:1) to give acetate **4** (6.92 g, 42%), and hydroxy ester **3** (6.19 g, 46%), both as oils. These were directly employed in the next step.

(2*R*,4*S*,6*S*)-3: IR (film): $\tilde{\nu}_{max} = 3450\ cm^{-1}$ (s, O−H), 1740 (s, C=O), 1200 (s, C−O), 1175 (s), 1150 (s). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.2 Hz, 3 H, 4-CH_3), 1.15 (d, *J* = 6.8 Hz, 3 H, 2-CH_3), 1.18 (d, *J* = 6.2 Hz, 3 H, 7-H_3), 1.2−2.0 (m, 6 H, 3, 5-H_2, 4-H, OH), 2.54 (qd like, *J* = 6.7, 2.1 Hz, 1 H, 2-H), 3.67 (s, 3 H, OCH_3), 3.85 (m, 1 H, 6-H).

(2*S*,4*R*,6*R*)-4: IR (film): $\tilde{\nu}_{max} = 1745\ cm^{-1}$ (s, C=O), 1730 (s, C=O), 1250 (s). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 5.5 Hz, 3 H, 4-CH_3), 1.14 (d, *J* = 6.7 Hz, 3 H, 2-CH_3), 1.19 (d, *J* = 6.2 Hz, 3 H, 7-H_3), 1.2−2.0 (m, 5 H, 3,5-H_2, 4-H), 2.02 (s, 3 H, Ac), 2.52 (m, 1 H, 2-H), 3.66 (s, 3 H, OCH_3), 5.03 (m, 1 H, 6-H).

(2*S*,4*S*,6*R*)-Methyl 6-Hydroxy-2,4-dimethylheptanoate (3): To a stirred solution of ester **4** (5.69 g, 24.7 mmol) in dry methanol (200 mL) was added K_2CO_3 (3.41 g, 24.7 mmol) at room temperature. This mixture was stirred for 6.5 h, and acidified with HCl (6 M), concentrated in vacuo, diluted with water, and extracted with diethyl ether. The extract was washed with water, saturated aqueous $NaHCO_3$ solution and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (60 g, hexane/ethyl acetate, 10:1) to give hydroxy ester **3** (4.36 g, 94%), which was employed directly in the next step.

(2*R*,4*R*,6*S*)-6-Hydroxy-2,4-dimethylheptanoic Acid (5): To a stirred solution of hydroxy ester **3** (5.95 g, 31.6 mmol) in THF (70 mL) was added an aqueous solution of LiOH (1.58 M, 60 mL, 94.9 mmol). The mixture was stirred for 12 h at room temperature. It was acidified with HCl (6 M), concentrated in vacuo to give a crude mixture of **5** (5.41 g, 98%). This was recrystallized twice from hexane/diethyl ether (8:1) to give pure hydroxy acid **5** (2.76 g, 51%) as needles; m.p. 83−85 °C (ref.[5] m.p. 83.5−85 °C). − $[\alpha]_D^{24} = -4.04$ (*c* = 8.66 in $CHCl_3$) {ref.[5] $[\alpha]_D^{23} = -4.2$ (*c* = 8.69 in $CHCl_3$)} . − IR (KBr): $\tilde{\nu}_{max} = 3350\ cm^{-1}$ (s, O−H), 2650 (s),

1680 (s, C=O), 1280 (s), 1110 (s), 1085 (s). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.5 Hz, 3 H, 4-CH_3), 1.186 (d, *J* = 7.1 Hz, 3 H, 2-CH_3), 1.189 (d, *J* = 5.9 Hz, 3 H, 7-H_3), 1.3−1.8 (m, 5 H, 3,5-H_2, 4-H), 2.56 (qt, *J* = 6.9, 1.7 Hz, 1 H, 2-H), 3.91 (qt, *J* = 5.7, 3.8 Hz, 1 H, 3-H), 5.70 (br. s, 2 H, CO_2H, OH).

(2*S*,4*S*,6*R*) Isomer: In the same manner as described above, (2*S*,4*S*,6*R*)-**3** (4.36 g, 23.2 mmol) gave **5** (2.39 g, 59%) as needles; m.p. 82−84.5 °C (ref.[5] m.p. 83−85 °C). − $[\alpha]_D^{25}$ = +3.97 (*c* = 8.49 in $CHCl_3$) {ref.[5] $[\alpha]_D^{23}$ = +4.3 (*c* = 8.50 in $CHCl_3$)}.

(2*R*,4*S*,6*S*)-Methyl 6-Hydroxy-2,4-dimethylheptanoate (3): To a solution of (2*R*,4*S*,6*S*)-**5** (1.60 g, 9.18 mmol) in diethyl ether (100 mL) was added an excess amount of diazomethane solution in diethyl ether. This solution was stirred for 1 h at room temperature and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (30 g, hexane/ethyl acetate, 10:1) to give (2*R*,4*S*,6*S*)-**3** (1.71 g, 99%); n_D^{22} = 1.4395. − $[\alpha]_D^{27}$ = −6.55 (*c* = 1.26 in $CHCl_3$). − $C_{10}H_{20}O_3$ (188.3): C 63.80, H 10.71; found C 63.42, H 10.69. − A sample was converted into the corresponding (*R*)-MTPA ester and analyzed by HPLC [column: Senshu Pac silica 1251-N, 4.6 mm × 25 cm; solvent, *n*-hexane/THF, 40:1, flow rate: 1.6 mL/min; detection, 254 nm], t_R = 11.8 min [> 99.9% *ee*]. (2*S*,4*S*,6*R*) isomer: t_R = 10.2 min.

(2*S*,4*R*,6*R*) Isomer: (2*S*,4*R*,6*R*)-Hydroxy acid **5** (2.03 g, 11.7 mmol) was methylated with diazomethane to give hydroxy ester (2*S*,4*R*,6*R*)-**3** (2.09 g, 95%); n_D^{22} = 1.4385. − $[\alpha]_D^{27}$ = +6.70 (*c* = 1.60 in $CHCl_3$). − $C_{10}H_{20}O_3$ (188.3): C 63.80, H 10.71; found C 63.85, H 10.55. − This was analyzed in the same manner as above to determine the enantiomeric purity [> 99.9% *ee*] by HPLC.

(2*R*,4*R*)-2,4-Dimethyl-1-heptanol (7): *p*-Toluenesulfonyl chloride (6.60 g, 34.6 mmol) was added portionwise to a stirred solution of (2*R*,4*S*,6*S*)-**3** (5.01 g, 26.6 mmol) in dry pyridine (15 mL) at 0 °C. This mixture was allowed to warm to 5 °C, stirred for 16 h, then poured into saturated aqueous $CuSO_4$ solution, and extracted with diethyl ether. The extract was washed with saturated aqueous $CuSO_4$ solution, water and brine. The extract was dried with $MgSO_4$ and concentrated in vacuo to give crude **6** (9.22 g, quant.) This tosylate was used without further purification. To an ice-cooled and stirred suspension of $LiAlH_4$ (2.02 g, 53.2 mmol) in diethyl ether (100 mL) was added dropwise a solution of **6** (9.22 g, ca. 26.6 mmol) in diethyl ether (30 mL). This mixture was allowed to warm to room temperature and stirring was continued for 1.5 h. It was then cooled to 0 °C again, quenched with water and aqueous NaOH solution (15%), filtered through Celite, and the filtrate was concentrated in vacuo. The residue was distilled to give **7** (3.20 g, 83%) as an oil; b.p. 103.5−104 °C/28 Torr. − n_D^{22} = 1.4331. − $[\alpha]_D^{25}$ = +14.6 (*c* = 1.09 in $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 3330 cm^{-1} (s, O−H), 1035 (s, C−O). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 4.5 Hz, 3 H, 4-CH_3), 0.88 (t, *J* = 5.3 Hz, 3 H, 7-H_3), 0.93 (d, *J* = 5.6 Hz, 3 H, 2-CH_3), 1.0−2.0 (m, 9 H, 3,5,6-H_2, 2,4-H, OH), 3.36 (dd, *J* = 10.5, 6.4 Hz, 1 H, 1-H), 3.54 (dd, *J* = 10.6, 5.3 Hz, 1 H, 1-H). − $C_9H_{20}O$ (144.3): C 74.93, H 13.97; found C 74.54, H 13.60.

(2*S*,4*S*) Isomer: (2*S*,4*R*,6*R*)-**3** (2.04 g, 10.8 mmol) was treated as above to give (2*S*,4*S*)-**7** (1.06 g, 71%); b.p. 101−103 °C/26 Torr. − n_D^{25} = 1.4323. − $[\alpha]_D^{25}$ = −14.9 (*c* = 1.04 in $CHCl_3$). − $C_9H_{20}O$ (144.3): C 74.93, H 13.97; found C 74.91, H 13.78. − Its IR and ^{1}H NMR spectra were identical with those of (2*R*,4*R*)-**7**.

(2*R*,4*S*)-5-Acetoxy-2,4-dimethyl-1-pentanol (10): Lipase AK 20 (250 mg) was added to a cooled and stirred solution of *meso*-diol **9** (5.18 g, 39.2 mmol) in THF (50 mL) at 0 °C. Vinyl acetate (3.7 mL, 43 mmol) was added to the mixture, which was stirred for 3 d at 5 °C. Vinyl acetate (1.5 mL, 17 mmol) was added again, and the mixture was stirred for 2 d, filtered through Celite, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (50 g, hexane/ethyl acetate, 20:1) to give (2*R*,4*S*)-**10** (4.95 g, 72%) as an oil; n_D^{25} = 1.4378. − $[\alpha]_D^{25}$ = +10.6 (*c* = 1.88 in $CHCl_3$). {ref.[12] $[\alpha]_D^{20}$ = +10.4 (*c* = 1.2 in $CHCl_3$).} − IR (film): $\tilde{\nu}_{max}$ = 3425 cm^{-1} (s, O−H), 1740 (s, C=O), 1245 (s), 1040 (s, C−O). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 6.4 Hz, 6 H, 2,4-CH_3), 1.0−2.0 (m, 5 H, 3-H_2, 2,4-H), 2.45 (s, 3 H, Ac), 3.45 (br. d, *J* = 3.9 Hz, 2 H, 5-H_2), 3.82 (dd, *J* = 6.2, 10.6 Hz, 1 H, 1-H), 3.98 (dd, *J* = 5.2, 10.6 Hz, 1 H, 1-H). − A sample was converted into the corresponding benzoate to determine its enantiomeric purity by HPLC. [column: Chiralcel®-OD, 4.6 mm × 25 cm; solvent: *n*-hexane/ethanol, 30:1, flow rate: 0.5 mL/min; temperature: 5 °C; detection: 254 nm], t_R = 17.8 min [(2*S*,4*R*) isomer, 1.0%] 22.7 [(2*R*,4*S*) isomer, 99.0%]. The enantiomeric purity of (2*R*,4*S*)-**10** was found to be 98.0% *ee*.

(2*S*,4*S*)-2,4-Dimethyl-1-heptanol (7): To a stirred solution of (2*R*,4*S*)-**10** (2.35 g, 13.5 mmol) in dry pyridine (12 mL) was added *p*-toluenesulfonyl chloride (3.09 g, 16.2 mmol) at 0 °C. After 18 h, the reaction mixture was quenched with water, and extracted with diethyl ether. The extract was washed with saturated aqueous $CuSO_4$ solution, water, saturated aqueous $NaHCO_3$ solution and brine. The extract was dried with Na_2SO_4 and concentrated in vacuo to give (2*R*,4*S*)-**11**, which was used without further purification. To a stirred solution of (2*R*,4*S*)-**11** in THF (27 mL) was added dropwise a solution of ethylmagnesium bromide in THF (1.0 M, 68 mL, 68 mmol) and a solution of Li_2CuCl_4 in THF(0.1 M, 16 mL, 1.6 mmol) at −78 °C under argon. The mixture was then gradually warmed to 5 °C. After 18 h, saturated aqueous NH_4Cl solution was added. The mixture was diluted with water, and extracted with diethyl ether. The extract was washed with saturated aqueous NH_4Cl solution, water, aqueous saturated $NaHCO_3$ solution and brine. The extract was dried with Na_2SO_4 and concentrated in vacuo. The residue was distilled under reduced pressure to furnish (2*S*,4*S*)-**7** (1.70 g, 87%) as an oil; b.p. 107−108 °C/34 Torr. Its IR and ^{1}H NMR spectra are identical to those of (2*R*,4*R*)-**7**.

(2*R*,4*S*)-5-Acetoxy-2,4-dimethylpentyl 1′-Ethoxyethyl Ether (12): To a stirred solution of (2*R*,4*S*)-**10** (4.98 g, 28.6 mmol) in ethyl vinyl ether (15 mL) was added *p*-toluenesulfonic acid monohydrate (14 mg, 0.074 mmol) at 0 °C. After 1.5 h, the mixture was quenched with saturated aqueous $NaHCO_3$ solution, diluted with water and extracted with diethyl ether. The extract was washed with water, saturated aqueous $NaHCO_3$ solution and brine. The extract was dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (100 g, hexane/ethyl acetate, 50:1) to give (2*R*,4*S*)-**12** (6.72 g, 96%) as an oil; b.p. 92−94 °C/2 Torr. − n_D^{24} = 1.4270. − $[\alpha]_D^{25}$ = +3.39 (*c* = 4.68 in $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 1740 (s, C=O), 1240 (s), 1135 (s), 1090 (s, C−O), 1040 (s, C−O). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 6.4 Hz, 6 H, 2,4-CH_3), 1.20 (t, *J* = 7.0 Hz, 3 H, 2′′-H_3), 1.34 (d, *J* = 5.3 Hz, 3 H, 2′-H_3), 1.0−2.0 (m, 4 H, 3-H_2, 2,4-H), 2.05 (s, 3 H, Ac), 3.0−3.8 (m, 6 H, 1,5,1′′-H_2), 3.93 (dd, *J* = 6.2, 11.6 Hz, 1 H, 1′′-H), 4.66 (q, *J* = 5.3 Hz, 1 H, 1′-H). − $C_{13}H_{26}O_4$ (246.2): calcd. C 63.38, H 10.64; found C 63.33, H 10.34.

(2*R*,4*S*)-5-Hydroxy-2,4-dimethylpentyl 1′-Ethoxyethyl Ether (13): A solution of (2*R*,4*S*)-**12** (6.20 g, 25.2 mmol) in methanol (25 mL) was stirred with K_2CO_3 (4.53 g, 32.8 mmol) at room temperature. After 17 h, the mixture was diluted with water, concentrated in vacuo to remove methanol, and extracted with chloroform. The extract was washed with brine, dried with a mixture of Na_2SO_4 and

K_2CO_3, and concentrated in vacuo. The residue was purified by silica gel column chromatography (30 g, hexane/ethyl acetate, 20:1) to give (2*R*,4*S*)-**13** (5.02 g, 98%) as an oil; b.p. 100 °C/3 Torr. − n_D^{24} = 1.4338. − $[\alpha]_D^{24}$ = +4.29 (*c* = 3.38 in $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 3420 cm^{-1} (s, O−H), 1135 (s, C−O), 1045 (s, C−O). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.6 Hz, 6 H, 2,4- CH_3), 0.9−1.8 (m, 3 H, 3-H_2, 2,4-H, OH), 1.20 (t, *J* = 7.1 Hz, 3 H, 2′′-H_3), 1.30 (d, *J* = 5.5 Hz, 3 H, 2′-H_3), 3.0−3.8 (m, 5 H, 1,5,1′′-H_2), 3.66 (q, *J* = 5.5 Hz, 1 H, 1′-H). − $C_{11}H_{24}O_3$ (204.3): calcd. C 64.67, H 11.84; found C 64.95, 11.99.

(2*R*,4*R*)-1-(1′-Ethoxyethoxy)-2,4-dimethyl-1-heptane (15): To a stirred solution of (2*R*,4*S*)-**13** (3.20 g, 15.6 mmol) in dry pyridine (18 mL) was added *p*-toluenesulfonyl chloride (3.57 g, 18.7 mmol) at 0 °C. After 40 h, the mixture was diluted with water, and extracted with diethyl ether. The extract was washed with saturated aqueous $CuSO_4$ solution, water, saturated aqueous $NaHCO_3$ solution and brine. The extract was dried with Na_2SO_4 and concentrated in vacuo. The residual crude (2*R*,4*S*)-**14** was used without further purification. − IR (film): $\tilde{\nu}_{max}$ = 1600 cm^{-1} (m, aromatic), 1175 (s, C−O), 1095 (s, SO_2), 965 (s), 815 (s), 665 (s). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.4 Hz, 3 H, 4-CH_3), 0.9−2.0 (m, 4 H, 3-H_2, 2,4-H), 0.91 (d, *J* = 6.6 Hz, 3 H, 2-H_3), 1.19 (t, *J* = 7.0 Hz, 3 H, 2′′-H_3), 1.27 (d, *J* = 5.3 Hz, 3 H, 2′-H_3), 2.45 (s, 3 H, Ar-CH_3), 3.0−4.2 (m, 6 H, 1,5,1′′-H_2), 4.63 (q, *J* = 5.3 Hz, 1 H, 2′-H), 7.35 (d, *J* = 8.1 Hz, 2 H, Ar-H), 7.79 (d, *J* = 11.6 Hz, 2 H, Ar-H). − To a stirred solution of crude (2*R*,4*S*)-**14** in THF (47 mL) were added dropwise a solution of ethylmagnesium bromide in THF (0.5 M, 95 mL, 48 mmol) and a solution of Li_2CuCl_4 in THF (0.1 M, 5.0 mL, 0.5 mmol) at −78 °C under argon. The mixture was stirred for 17 h at 5 °C, and then quenched with saturated aqueous NH_4Cl solution. The mixture was diluted with water and extracted with diethyl ether. The extract was washed with saturated aqueous NH_4Cl solution, water, saturated aqueous $NaHCO_3$ solution and brine. The extract was dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (50 g, hexane/ethyl acetate, 80:1) to give ether (2*R*,4*R*)-**15** (2.61 g, 77%) as an oil. − n_D^{25} = 1.4219. − $[\alpha]_D^{25}$ = −0.73 (*c* = 10.2 in $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 1140 cm^{-1} (s, C−O), 1100 (s), 1065 (s, C−O). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 5.2 Hz, 3 H, 4- CH_3), 0.88 (t, *J* = 5.2 Hz, 3 H, 7-H_3), 0.92 (d, *J* = 6.6 Hz, 3 H, 2- CH_3), 1.0−2.0 (m, 8 H, 3,5,6-H_2, 2,4-H), 1.16 (t, *J* = 7.2 Hz, 3 H, 2′′-H_3), 1.30 (d, *J* = 5.3 Hz, 3 H, 2′-H_3), 3.0−3.8 (m, 4 H, 1,2′′-H_2), 4.67 (q, *J* = 5.3 Hz, 1 H, 1′-H). − This was directly used in the next step.

(2*R*,4*R*)-2,4-Dimethyl-1-heptanol (7): A stirred solution of (2*R*,4*R*)-**15** (3.19 g, 14.8 mmol) in methanol (15 mL) was treated with *p*-toluenesulfonic acid monohydrate (14 mg, 0.074 mmol) at room temperature for 20 h. The mixture was quenched with saturated aqueous $NaHCO_3$ solution, diluted with water, and extracted with diethyl ether. The extract was washed with water, saturated aqueous $NaHCO_3$ solution and brine. The extract was dried with $MgSO_4$ and concentrated in vacuo. The residue was distilled under reduced pressure to furnish alcohol **7** (1.67 g, 78%) as an oil; b.p. 106−107 °C/32 Torr. − Its IR and ^1H NMR spectra are the same as those of an authentic sample.

(2*R,4*S**)-2,4-Dimethylglutaric Acid (16):** A mixture of crude (±)-**8** (87.3 g) and water (100 mL) was boiled for 2 h, and cooled to room temperature. The resulting solid was collected and recrystallized twice from chloroform to give pure (±)-diacid **16** (33.5 g, 12.8% from *meso* and racemic mixture of diacid); m.p. 143−145 °C (ref.[11] m.p. 139−141 °C).

(2*R,4*R**)-2,4-Dimethyl-1,5-pentanediol (9):** To a stirred solution of (±)-**16** (19.0 g, 118 mmol, ca. 100% *de*) in THF (240 mL) was added a THF solution of borane−dimethyl sulfide (2.0 M, 130 mL, 260 mmol) at −10 °C. The mixture was gradually allowed to warm to room temperature. After 13 h, the mixture was quenched with water, and extracted with diethyl ether. The extract was washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (300 g, chloroform/methanol, 5:1) to give known (±)-**9**[11] (12.5 g, 80%) as an oil. − n_D^{24} = 1.4531 (ref.[11] n_D^{25} = 1.4515). − IR (film): $\tilde{\nu}_{max}$ = 3350 cm^{-1} (br. s), 1030 (s, C−O). − ^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.7 Hz, 6 H, 2,4-CH_3), 1.23 (t, *J* = 6.8 Hz, 2 H, 3-H_2), 1.77 (sext, *J* = 6.6 Hz, 2 H, 2,4-H), 1.86 (br. s, 2 H, OH), 3.47 (d, *J* = 6.4 Hz, 4 H, 1,5-H_2). − ^{13}C NMR (100.40 MHz, $CDCl_3$): δ = 16.3, 32.8, 36.7, 68.8.

Enantiomeric Separation To Give (2*R*,4*R*)-9 and (2*S*,4*S*)-17: To a stirred solution of (±)-**9** (18.8 g, 142 mmol) in THF (150 mL), were added lipase AK 20 (0.82 g) and vinyl acetate (12.7 mL, 149 mmol) at 0 °C. The mixture was stirred for 22 h at 5 °C. The lipase was filtered off, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (200 g, hexane/ethyl acetate, 10:1) to give (2*R*,4*R*)-**9** (6.41 g, 34%), monoacetate (4.74 g, 19%). Further elution (hexane/ethyl acetate, 3:1) provided (2*S*,4*S*)-**17** (13.9 g, 45%).

Purification of (2*R*,4*R*)-9: A stirred solution of (2*R*,4*R*)-**9** (3.14 g, 23.8 mmol) in THF (30 mL) was treated with lipase AK 20 (0.14 g) and vinyl acetate (1.00 mL, 11.9 mmol) in the same manner as above to give (2*R*,4*R*)-**9** (2.43 g, 77%) as an oil. − n_D^{23} = 1.4520. − $[\alpha]_D^{22}$ = −37.5 (*c* = 1.08 in $CHCl_3$). − Its IR and ^1H NMR spectra are identical to those of (2*R*,*4*R**)-**9**. An analytical sample was converted into the corresponding diacetate. − $C_{11}H_{20}O_4$ (216.3): C 61.69, H 9.32; found C 60.75, H 9.71. − The diol **9** was so hygroscopic that correct combustion analytical data could not be obtained. The corresponding dibenzoate was prepared as usual and analyzed by HPLC [column: Chiralcel®-OD, 4.6 mm × 25 cm; solvent: *n*-hexane/ethanol, 100:1, flow rate: 0.3 mL/min; temperature: 5 °C; detection: 254 nm], t_R = 31.6 min [(2*R*,4*R*) isomer, ca. 100%].

Purification of (2*S*,4*S*)-2,4-Dimethyl-1,5-pentanediol Diacetate (17): A solution of crude (2*S*,4*S*)-**17** (13.5 g, 62.3 mmol) in methanol (125 mL) was treated with K_2CO_3 (21.7 g, 150 mmol) in the same manner as for the purification of (2*S*,4*R*)-**13** to give (2*S*,4*S*)-**9** (8.12 g, 99%). A solution of (2*S*,4*S*)-**9** (8.12 g, 36.3 mmol) in THF (80 mL) was treated with lipase AK 20 (0.24 g) and vinyl acetate (10.4 mL, 122 mmol), in the same manner as in the preparation of (2*R*,4*R*)-**9**, to give (2*S*,4*S*)-**17** (7.86 g, 59%) and monoacetate (3.24 g, 30%). This (2*S*,4*S*)-**17** was analyzed by HPLC [column: Chiralcel®-OD, 4.6 mm × 25 cm; solvent: *n*-hexane/ethanol, 100:1, flow rate: 0.3 mL/min; temperature: 5 °C; detection: 210 nm], t_R = 24.3 min [(2*S*,4*S*)-**17**, ca. 100%]. The diacetate (2*S*,4*S*)-**17** was obtained as an oil; n_D^{22} = 1.4373. − $[\alpha]_D^{22}$ = +7.67 (*c* = 1.32 in $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 1745 cm^{-1} (s, C=O), 1230 (s, C−O), 1040 (s, C−O). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.7 Hz, 6 H, 2,4-CH_3), 1.19 (t, *J* = 7.3 Hz, 2 H, 3-H_2), 1.84 (sext-like, J = 7.1 Hz, 2H, 2,4-H), 2.05 (s, 6 H, Ac), 3.89 (d, J = 6.4 Hz, 4 H, 1,5-H_2). − $C_{11}H_{20}O_4$ (216.3): calcd. C 61.09, H 9.32; found C 61.06, H 9.67.

(2*R*,4*R*)-2,4-Dimethyl-5-trimethylsilyloxy-1-pentanol (18): To a stirred solution of (2*R*,4*R*)-**9** (4.41 g, 33.4 mmol) in THF (70 mL) was added a solution of *n*-butyllithium in hexane (2.52 M, 14.6 mL, 37.4 mmol) at −78 °C under argon. After 20 min, trimethylsilyl

chloride (4.45 mL, 35.1 mmol) was added dropwise, and the mixture was stirred for 1.5 h. It was then quenched with saturated aqueous $NaHCO_3$ solution, and extracted with diethyl ether. The extract was washed with brine, dried with a mixture of Na_2SO_4 and K_2CO_3, and concentrated in vacuo. The residue was purified by silica gel column chromatography (45 g, hexane/ethyl acetate, 5:1, containing ca. 0.1% triethylamine) to give (2*R*,4*R*)-**18** (1.86 g, 27%) and recovered diol **9** (2.78 g, 63%). The product **18** was an unstable oil. − IR (film): $\tilde{\nu}_{max}$ = 3365 cm^{-1} (s, O−H), 2955 (s), 1255 (s, C−O), 1090 (s), 845 (s), 750 (s). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.11 [s, 9 H, $Si(Me)_3$], 0.86 (d, *J* = 6.5 Hz, 3 H, 4-CH_3), 0.89 (d, *J* = 6.8 Hz, 3 H, 2-CH_3), 1.13 (dq, *J* = 13.1, 4.6 Hz, 1 H, 3-H), 1.22 (dq, *J* = 13.1, 4.9 Hz, 1 H, 3-H), 1.56 (s, 1 H, OH), 1.75 (m, 2 H, 2,4-H), 3.38 (m, 2 H, 5-H_2), 3.46 (m, 2 H, 1-H_2). − This was used directly in the next step.

(2*S*,4*S*) Isomer: In the same manner as described above, (2*S*,4*S*)-**9** (6.35 g, 48.0 mmol) gave (2*S*,4*S*)-**18** (1.86 g, 42%) and recovered diol **9** (52%).

(2*S*,4*R*)-2,4-Dimethyl-1-heptanol (7): *p*-Toluenesulfonyl chloride (7.70 g, 40.4 mmol) was added portionwise to a stirred solution of (2*S*,4*S*)-**18** (4.13 g, 20.2 mmol) and triethylamine (14.1 mL, 101 mmol) in chloroform (30 mL) at 0 °C. This mixture was warmed to 5 °C and stirred for 14 h. The mixture was then diluted with water and extracted with chloroform. The extract was washed with saturated aqueous $CuSO_4$ solution, water, saturated aqueous $NaHCO_3$ solution and brine. The extract was dried with Na_2SO_4 and concentrated in vacuo. This tosylate **19** was used without further purification. − IR (film): $\tilde{\nu}_{max}$ = 1595 cm^{-1} (w), 1175 (s), 655 (s). − To a stirred solution of (2*S*,4*S*)-**19** in THF (20 mL) were added dropwise a solution of ethylmagnesium bromide in THF (1.0 M, 100 mL,100 mmol) and a solution of Li_2CuCl_4 in THF (0.5 M, 2.0 mL, 1.0 mmol) at −78 °C. The mixture was allowed to warm to 5 °C very slowly. After 18 h, the mixture was quenched with a saturated aqueous NH_4Cl solution and extracted with diethyl ether. The extract was washed with aqueous HCl (1 M) and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by distillation to give (2*S*,4*R*)-**7** (2.54 g, 87%) as an oil; b.p. 104 °C/22 Torr. − n_D^{22} = 1.4320. − $[\alpha]_D^{25}$ = +26.6 (*c* = 1.17 in $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 3345 cm^{-1} (s, O−H), 1035 (s, C−O). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.8−1.0 (m, 9 H, 2,4-CH_3,7-H_3), 1.0−1.5 (m, 6 H, 3,5,6-H_2), 1.6−2.0 (m, 3 H, 2,4-H, OH), 3.43 (d, *J* = 6.2 Hz, 1 H, 1-H), 3.45 (d, *J* = 6.4 Hz, 1 H, 1-H). − $C_9H_{20}O$ (144.3): C 74.93, H 13.97; found C 74.74, H 13.82.

(2*R*,4*S*) Isomer: In the same manner as described above, (2*R*,4*R*)-**18** (1.86 g, 9.1 mmol) gave (2*R*,4*S*)-**7** (1.17 g, 89%) as an oil; b.p. 110−111 °C/37 Torr. − n_D^{23} = 1.4326. − $[\alpha]_D^{25}$ = −28.3 (*c* = 0.665 in $CHCl_3$). − Its IR and ^1H NMR spectra are identical to those reported for (2*S*,4*R*)-**7**. − $C_9H_{20}O$ (144.3): C 74.93, H 13.97; found C 74.62, H 13.90.

(2*R*,4*R*)-2,4-Dimethylheptyl Iodide (20): To a stirred solution of (2*R*,4*R*)-**7** (3.16 g, 22 mmol), imidazole (1.80 g, 26 mmol) and triphenylphosphane (6.32 g, 24 mmol) in DMF (30 mL) was added dropwise a solution of iodine (6.12 g, 24 mmol) in DMF (20 mL) at 0 °C. This solution was warmed to room temperature and stirred for 2 h, poured into saturated aqueous $Na_2S_2O_3$ solution, and extracted with hexane. The extract was washed with aqueous $Na_2S_2O_3$ solution, water and brine. The extract was dried with $MgSO_4$ and concentrated in vacuo. The residue was filtered through silica gel to give iodide **20** (5.50 g, 99%) as an oil. An analytical sample was purified by distillation; b.p. 80−81 °C/12 Torr. − n_D^{25} = 1.4852. − $[\alpha]_D^{25}$ = −5.22 (*c* = 1.51 in $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 1195 cm^{-1}. − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.8−1.0 (m, 9 H, 2,4-CH_3, 7-H_3), 1.0−1.8(m, 8 H, 3,5,6-H_2, 2,4-H), 3.11 (dd, *J* = 5.1, 9.6 Hz, 1 H, 1-H), 3.30 Hz (dd, *J* = 4.3, 9.6 Hz, 1 H, 1-H). − $C_9H_{19}I$ (254.2): C 42.53, H 7.54; found C 42.86, H 7.92.

(2*S*,4*S*) Isomer: In the same manner as described above, (2*S*,4*S*)-**7** (1.01 g, 6.99 mmol) gave **20** (1.52 g, 85%) as an oil; b.p. 78−80 °C/11 Torr. − n_D^{26} = 1.4864. − $[\alpha]_D^{26}$ = +5.38 (*c* = 1.66 in $CHCl_3$). − Its IR and ^1H NMR spectra are identical to those reported for (2*R*,4*R*)-**20**. − $C_9H_{19}I$ (254.2): C 42.53, H 7.54; found C 42.17, H 7.81.

(2*R*,4*S*) Isomer: In the same manner as described above, (2*R*,4*S*)-**7** (1.17 g, 8.11 mmol) gave **20** (2.10 g, quant.) as an oil; b.p. 77−80 °C/12 Torr. − n_D^{24} = 1.4861. − $[\alpha]_D^{25}$ = +2.11 (*c* = 1.10 in $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 1195 cm^{-1}. − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.75−1.0 (m, 9 H, 2,4-CH_3, 7-H_3), 1.0−1.8 (m, 8 H, 3,5,6-H_2, 2,4-H), 3.43 (d, *J* = 6.2 Hz, 1 H, 1-H), 3.46 (d, *J* = 5.9 Hz, 1 H, 1-H). − $C_9H_{19}I$ (254.2): C 42.53, H 7.54; found C 42.40, H 7.44.

(2*S*,4*R*) Isomer: In the same manner as described above, (2*S*,4*R*)-**7** (1.76 g, 17.6 mmol) gave **20** (4.50 g, quant.); b.p. 74−76 °C/12 Torr. − n_D^{26} = 1.4855. − $[\alpha]_D^{25}$ = −1.96 (*c* = 1.04 in $CHCl_3$). − Its ^1H NMR spectrum is identical to that reported for (2*R*,4*S*)-**20**. − $C_9H_{19}I$ (254.2): C 42.53, H 7.54; found C 42.44, H 7.89.

(4*R*,6*R*)-Dimethyl 2-Methoxycarbonyl-4,6-dimethylnonanoate (21): To a stirred suspension of sodium hydride (60% in mineral oil, 0.33 g, 13 mmol) in THF (28 mL), was added dimethyl malonate (1.17 g, 8.8 mmol), and stirring was continued for 1 h under argon. A solution of (2*R*,4*R*)-**20** (1.50 g, 5.9 mmol) in THF (5.0 mL) was added dropwise to the stirred mixture, which was heated at reflux for 13.5 h. It was then quenched with a saturated NH_4Cl solution, diluted with water, and extracted with diethyl ether. The extract was washed with water and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (30 g, hexane/ethyl acetate, 20:1) to give (4*R*,6*R*)-**21** (1.16 g, 76%) as an oil. − n_D^{26} = 1.4370. − $[\alpha]_D^{26}$ = −9.80 (*c* = 1.13 in $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 1755 cm^{-1} (s, C=O), 1740 (s, C=O), 1255 (s), 1200 (s, C−O), 1155 (s). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.7−1.0 (m, 9 H, 4,6-CH_3, 9-H_3), 1.0−2.1 (m, 10 H, 3,5,7,8-H_2, 4,6-H), 3.51 (dd, *J* = 5.8, 9.0 Hz, 1 H, 2-H), 3.73 (s, 6 H, OCH_3). − $C_{14}H_{26}O_4$ (258.4): calcd. C 65.09, H 10.14; found C 65.06, H 10.25.

(4*S*,6*S*) Isomer: In the same manner as described above, (2*S*,4*S*)-**20** (2.28 g, 9.0 mmol) gave (4*S*,6*S*)-**21** (2.03 g, 88%) as an oil. − n_D^{23} = 1.4365. − $[\alpha]_D^{26}$ = +9.48 (*c* = 1.10 in $CDCl_3$). − Its IR and ^1H NMR spectra are identical to those reported for (4*R*,6*R*)-**21**. − $C_{14}H_{26}O_4$ (258.4): calcd. C 65.09, H 10.14; found C 65.09, H 9.86.

(4*R*,6*S*) Isomer: In the same manner as described above, (2*R*,4*S*)-**20** (2.10 g, ca. 8.11 mmol) gave (4*R*,6*S*)-**21** (1.45 g, 69%) as an oil. − n_D^{22} = 1.4362. − $[\alpha]_D^{22}$ = −11.4 (*c* = 1.17 in $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 1750 cm^{-1} (s, C=O), 1740 (s, C=O), 1200 (s, C−O), 1155 (s), 1055 (m, C−O). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.7−1.0 (m, 9 H, 4,6-CH_3, 9-H_3), 1.0−2.0 (m, 10 H, 3,5,7,8-H_2, 4,6-H), 3.49 (t, *J* = 7.1 Hz, 1 H, 2-H), 3.73 (s, 6 H, OCH_3). − $C_{14}H_{26}O_4$ (258.4): calcd. C 65.09, H 10.14; found C 65.17, H 9.98.

(4*S*,6*R*) Isomer: In the same manner as described above, (2*S*,4*R*)-**20** (4.50 g, ca. 17.6 mmol) gave (4*S*,6*R*)-**21** (3.24 g, 71%) as an oil. − n_D^{26} = 1.4366. − $[\alpha]_D^{24}$ = +11.9 (*c* = 1.13 in $CHCl_3$). − Its IR and ^1H NMR spectra are identical to those reported for (4*R*,6*S*)-**21**. − $C_{14}H_{26}O_4$ (258.4): calcd. C 65.09, H 10.14; found C 65.25, H 10.02.

(4*R*,6*R*)-2-Hydroxymethyl-4,6-dimethylnonan-1-ol (22): A mixture of (4*R*,6*R*)-**21** (2.04 g, 7.9 mmol) and $NaBH_4$ (1.5 g, 39 mmol) in THF (60 mL) was stirred and heated at reflux for 1 h. Dry methanol (12.5 mL) was then added over 1 h, and refluxing was continued for another 1 h. The mixture was then cooled to room temperature, acidified with dil. HCl, and extracted with diethyl ether. The extract was washed with HCl (6 M), and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (40 g, hexane/ethyl acetate, 5:1) to give (4*R*,6*R*)-**22** (1.36 g, 85%) as an oil. − n_D^{26} = 1.4544. − $[\alpha]_D^{26}$ = −7.30 (*c* = 1.12 in $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 3350 cm^{-1} (s, O−H), 1030 (s), 970 (s). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.7−1.0 (m, 9 H, 4,6-Me,9-H_3), 1.0−2.0 (m, 11 H, 2,4,6-H, 3,5,7,8-H_2), 2.28 (br. s, 2 H, OH), 4.15−4.45 (m, 4 H, 1,1′-H_2). − An analytical sample was converted into the corresponding diacetate. − $C_{14}H_{26}O_4$ (286.4): calcd. C 67.10, H 10.56; found C 66.72, H 10.99.

(4*S*,6*S*) Isomer: In the same manner as described above, reaction of (4*S*,6*S*)-**21** (2.03 g, 7.8 mmol) gave (4*S*,6*S*)-**22** (1.35 g, 85%) as an oil. − n_D^{23} = 1.4540. − $[\alpha]_D^{26}$ = +6.89 (*c* = 1.30 in $CHCl_3$). − Its IR and ^1H NMR spectra are identical to those reported for (2*R*,4*R*)-**22**. − Its diacetate was analyzed. − $C_{14}H_{26}O_4$ (286.4): calcd. C 67.10, H 10.56; found C 67.41, H 10.50.

(4*R*,6*S*) Isomer: In the same manner as described above, (4*R*,6*S*)-**21** (3.05 g, 11.8 mmol) gave (4*R*,6*S*)-**22** (2.16 g, 90%) as an oil. − n_D^{22} = 1.4533. − $[\alpha]_D^{24}$ = −16.2 (*c* = 1.02 in $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 3350 cm^{-1} (s, O−H), 1030 (s, C−O), 960 (s). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.7−1.0 (m, 9 H, 4,6-CH_3, 9-H_3), 1.0−1.7 (m, 10 H, 3,5,7,8-H_2, 4,6-H), 1.7−2.0 (m, 1 H, 2-H), 2.26 (br. s, 2 H, OH), 3.4−4.0 (m, 4 H, 1,1′-H_2). − Its diacetate was analyzed. − $C_{14}H_{26}O_4$ (286.4): calcd. C 67.10, H 10.56; found C 66.70, H 10.17.

(4*S*,6*R*) Isomer: In the same manner as described above, (4*S*,6*R*)-**21** (1.45 g, 5.62 mmol) gave (4*S*,6*R*)-**22** (1.04 g, 92%) as an oil. − n_D^{22} = 1.4549. − $[\alpha]_D^{24}$ = +19.0 (*c* = 1.14 in $CHCl_3$). − Its IR and ^1H NMR spectra are identical to those reported for (2*R*,4*S*)-**22**. Its diacetate was analyzed. − $C_{14}H_{26}O_4$ (286.4): calcd. C 67.10, H 10.56; found C 66.82, H 10.74.

(4*R*,6*R*)-2-Hydroxymethyl-4,6-dimethylnonyl 2-Bromopropanoate (23): To a stirred and cooled solution of (4*R*,6*R*)-**22** (0.51 g, 2.6 mmol) in THF (15 mL) at −78 °C, was added dropwise a solution of *n*-butyllithium in *n*-hexane (1.60 M, 1.80 mL, 2.9 mmol) under argon. After 1 h at −78 °C, a solution of 2-bromopropanoyl bromide in THF (1.0 M, 2.6 mL, 2.6 mmol) was added dropwise to the mixture. The solution was stirred at −78 °C for 30 min, and a saturated aqueous NH_4Cl solution was added. The mixture was extracted with diethyl ether. The extract was washed with water, a saturated aqueous $NaHCO_3$ solution and brine. The extract was dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (10 g, hexane/ethyl acetate, 15:1) to give (4*R*,6*R*)-**23** (0.67 g, 78%) as an oil. − n_D^{23} = 1.4703. − $[\alpha]_D^{24}$ = −8.19 (*c* = 1.41 in $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 3450 cm^{-1} (s, O−H), 1740 (s, C=O). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.7−1.0 (m, 9 H, 4,6-CH_3, 9-H_3), 1.0−2.1 (m, 11 H, 3,5,7,8-H_2, 2,4,6-H), 1.83 (d, *J* = 6.8 Hz, 3 H, 3′′-H_3), 3.58 (br. t, *J* = 5.5 Hz, 2 H, 1′-H_2), 4.1−4.3 (m, 1 H, OH), 4.39 (q, *J* = 6.8 Hz, 1 H, 2′′-H). − HRFAB-MS [$C_{15}H_{29}BrO_3$ + H]: calcd. 337.1378; found 337.1384.

(4*S*,6*S*) Isomer: In the same manner as described above, (4*S*,6*S*)-**22** (0.67 g, 3.3 mmol) gave (4*S*,6*S*)-**23** (0.82 g, 74%) as an oil. − n_D^{23} = 1.4711. − $[\alpha]_D^{25}$ = +8.10 (*c* = 1.30 in $CHCl_3$). − Its IR and ^1H NMR spectra are identical to those reported for (4*R*,6*R*)-**23**. − HRFAB-MS [$C_{15}H_{29}BrO_3$ + H]: calcd. 337.1378; found 337.1382.

(4*R*,6*S*) Isomer: In the same manner as described above, (4*R*,6*S*)-**22** (514 mg, 2.54 mmol) gave (4*R*,6*S*)-**23** (361 mg, 42%) and the recovered **22** (315 mg, 61%). (4*R*,6*S*)-**23** was obtained as an oil. − n_D^{26} = 1.4686. − $[\alpha]_D^{25}$ = −6.71 (*c* = 1.02 in $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 3400 cm^{-1} (s, O−H), 1740 (s, C=O). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.7−1.0 (m, 9 H, 4,6-CH_3,9-H_3), 1.0−2.1 (m, 11 H, 3,5,7,8-H_2, 2,4,6-H), 1.84 (d, *J* = 6.8 Hz, 3 H, 3′′-H_3), 3.5−3.7 (m, 1 H, OH), 3.46 (t, *J* = 6.4 Hz, 2 H, 1′-H), 3.70 (t, *J* = 5.9 Hz, 2 H, 1-H), 4.30 (q, *J* = 6.9 Hz, 1 H, 2′′-H). − HRFAB-MS [$C_{15}H_{29}BrO_3$ + H]: calcd. 337.1378; found 337.1387.

(4*S*,6*R*) Isomer: In the same manner as described above, (4*S*,6*R*)-**22** (989 mg, 4.88 mmol) gave (4*S*,6*R*)-**23** (4.28 g, 26%) and the recovered diol (690 mg, 69%). − n_D^{26} = 1.4671. − $[\alpha]_D^{25}$ = +7.95 (*c* = 1.10 in $CHCl_3$). − Its IR and ^1H NMR spectra are identical to those reported for (4*R*,6*S*)-**23**. − HRFAB-MS [$C_{15}H_{29}BrO_3$ + H]: calcd. 337.1378; found 337.1373.

(2*R*,4*R*)-5-(2,4-Dimethylheptyl)-3,4,5,6-tetrahydro-4-hydroxy-3-methyl-2*H*-pyran-2-one (25): To a stirred mixture of (4*R*,6*R*)-**23** (416 mg, 1.23 mmol) and powdered MS 4 Å (0.61 g) in dichloromethane (6.2 mL), was added portionwise PCC (370 mg, 1.7 mmol) at 0 °C. The mixture was warmed to room temperature, and stirred for 1.5 h. It was then filtered through Florisil, and the solid was washed with diethyl ether. The combined filtrate and washings were concentrated in vacuo to give (4*R*,6*R*)-**24** (420 mg), which was used without further purification. To a stirred solution of the aldehyde **24** in THF (15 mL), was added dropwise a solution of SmI_2 in THF (0.1 M, 25 mL, 2.5 mmol) at 0 °C under argon. After 1 h, the reaction flask was opened to quench SmI_2 with O_2, warmed to room temperature, and diluted with a saturated aqueous NH_4Cl solution. The mixture was extracted with diethyl ether. The extract was washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was filtered through silica gel to afford crude (2*R*,4*R*)-**25** (268 mg, 80%) as an oil, which was used without further purification. − IR (film): $\tilde{\nu}_{max}$ = 3450 cm^{-1} (s, O−H), 1740 (s, C=O), 1730 (s, C=O). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.7−1.0 (m, 12 H, 3,2′,4′-CH_3,7-H_3), 1.0−1.5 (m, 11 H, 1′,3′,5′,6′-H_2, 2′,4′-H, OH), 1.6−1.9 (m, 1 H, 5-H), 2.4−2.8 (br. s, 1 H, 3-H), 3.6−4.5 (m, 3 H, 4,6-H).

(2*S*,4*S*) Isomer: In the same manner as described above, (4*S*,6*S*)-**23** (824 mg, 2.44 mmol) gave (4*S*,6*S*)-**25** (381 mg, 61%) as an oil. Its IR and ^1H NMR spectra are identical to those reported for (2*R*,4*R*)-**25**.

(2*R*,4*S*) Isomer: In the same manner as described above, (4*R*,6*S*)-**23** (361 mg, 1.07 mmol) gave (4*R*,6*S*)-**25** (143 mg, 55%) as an oil. Its IR and ^1H NMR spectra are identical to those reported for (2*R*,4*R*)-**25**.

(2*S*,4*R*) Isomer: In the same manner as described above, (4*S*,6*R*)-**23** (428 mg, 1.27 mmol) gave (4*S*,6*R*)-**25** (148 mg, 48%) as an oil. Its IR and ^1H NMR spectra are identical to those reported for (2*R*,4*R*)-**25**.

(2*R*,4*R*)-5-(2,4-Dimethylheptyl)-5,6-dihydro-3-methyl-(2*H*)-pyran-2-one (26): To a stirred solution of (2*R*,4*R*)-**25** (214 mg, 0.84 mmol) and 4-dimethylaminopyridine (0.26 g, 2.1 mmol) in chloroform (4.0 mL) was added dropwise methanesulfonyl chloride (81 μL, 1.0 mmol) at 0 °C. After 30 min, the mixture was allowed to warm to room temperature. After 12 h, it was diluted with water, and extracted with chloroform. The extract was washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue

was purified by silica gel column chromatography (4.0 g, hexane/ethyl acetate, 30:1) to give (2*R*,4*R*)-**26** (125 mg, 63%) as an oil. − n_D^{23} = 1.4727. − $[\alpha]_D^{25}$ = −3.56 (*c* =1.04 in $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 1725 cm^{-1} (s, C=O), 1135 (s). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.7 Hz, 3 H, 4′-CH_3), 0.89 (t, *J* = 11.6 Hz, 3 H, 7′-H_3), 0.90 (d, *J* = 10.7 Hz, 3 H, 2′-CH_3), 0.95−1.65 (m, 10 H, 1′,3′,5′,6′-H_2, 2′,4′-H), 1.92 (dt, *J* = 4.6, 1.5 Hz, 3 H, 3-CH_3), 2.57 (br. s, 1 H, 5-H), 4.05 (dt, *J* = 7.7, 10.1 Hz, 1 H, 6-H), 4.35 (ddd, *J* = 11.0, 7.4, 4.9 Hz, 1 H, 6-H), 6.53 (d, *J* = 22.9 Hz, 1 H, 4-H). − $C_{15}H_{26}O_2$ (238.4): calced. C 75.58, H 10.99; found C 75.58, H 10.86.

(2*S*,4*S*) Isomer: In the same manner as described above, (2*S*,4*S*)-**25** (381 mg, 1.49 mmol) gave (2*S*,4*S*)-**26** (251 mg, 71%) as an oil. − n_D^{25} = 1.4721. − $[\alpha]_D^{25}$ = +2.90 (*c* = 1.14 in $CHCl_3$). − Its IR and ^1H NMR spectra are identical to those reported for (2*R*,4*R*)-**26**. − $C_{15}H_{26}O_2$ (238.4): calcd. C 75.58, H 10.99; found C 75.57, H 10.84.

(2*R*,4*S*) Isomer: In the same manner as described above, (2*R*,4*S*)-**25** (143 mg, 0.59 mmol) gave (2*R*,4*S*)-**26** (72 mg, 51%) as an oil. − n_D^{23} = 1.4683. − $[\alpha]_D^{25}$ = −26.9 (*c* = 1.10 in $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 1725 cm^{-1} (s, C=O), 1135 (s). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 6.4 Hz, 3 H, 4′-CH_3), 0.88 (t, *J* = 7.3 Hz, 3 H, 7′-H_3), 0.88 (d, *J* = 10.7 Hz, 3 H, 2′-CH_3), 1.0−1.4 (m, 8 H, 3′,5′,6′-H_2, 1′,2′,4′-H), 1.50 (dq, *J* = 20.8, 7.3 Hz, 1 H, 1′-H), 1.92 (q, 1.5 Hz, 3 H, 3-CH_3), 2.57 (br. s, 1 H, 5-H), 4.05 (ddd, *J* = 11.0, 7.3, 5.3 Hz, 1 H, 6-H), 4.35 (quint-like, *J* = 5.5 Hz, 1 H, 6-H), 6.53 (br. d, *J* = 15.3 Hz, 1 H, 4-H). − $C_{15}H_{26}O_2$ (238.4): calcd. C 75.58, H 10.99; found C 75.26, H 10.46.

(2*S*,4*R*) Isomer: In the same manner as described above, (2*S*,4*R*)-**25** (148 mg, 0.61 mmol) gave (2*S*,4*R*)-**26** (73 mg, 50%)as an oil. − n_D^{23} = 1.4680. − $[\alpha]_D^{25}$ = +27.0 (*c* = 1.10 in $CHCl_3$). − Its IR and ^1H NMR spectra are identical to those reported for (2*R*,4*S*)-**26**. − $C_{15}H_{26}O_2$ (238.4): calcd. C 75.58, H 10.99; found C 75.38, H 10.78.

(2*R*,4*R*)-5-(2,4-Dimethylheptyl)-3-methyl-2*H*-pyran-2-one (Supellapyrone, 1)

(a): To a stirred solution of α,β-unsaturated lactone (2*R*,4*R*)-**26** (51 mg, 0.21 mmol) in THF (0.75 mL) and hexamethylphosphoric triamide (HMPA, 0.15 mL), was added dropwise a solution of potassium hexamethyldisilazide in toluene (0.5 M, 0.84 mL, 0.42 mmol). After 1 h, HCl (1 M, 0.1 mL) was added, and 30 s later saturated aqueous $NaHCO_3$ solution (1.0 mL) was added. The mixture was allowed to warm to room temperature, diluted with water, and extracted with diethyl ether. The extract was washed with water, saturated aqueous $NaHCO_3$ solution and brine. The extract was dried with Na_2SO_4, and concentrated in vacuo. The residue was filtered through a silica gel column to give (2*R*,4*R*)-**27** (37 mg, 74%) as an oil, which was used without further purification. − IR (film): $\tilde{\nu}_{max}$ = 1745 cm^{-1} (s, C=O), 1200 (m, C−O). − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.8−0.9 (m, 9 H, 2′,4′-CH_3, 7-H_3), 0.9−1.7 (m, 8 H, 3′,5′,6′-H_2, 2′,4′-H), 1.36 (d, *J* = 7.4 Hz, 3 H, 3-CH_3), 1.78 (dd, *J* = 9.0, 13.5 Hz, 1 H, 1′-H), 2.07 (dt, *J* = 6.0, 13.5 Hz, 1 H, 1′-H), 3.04 (br. s, 1 H, 3-H), 4.63−4.80 (m, 2 H, 6-H), 5.45 (s, 1 H, 4-H).

(2*S*,4*S*) Isomer: In the same manner as described above, (2*S*,4*S*)-**26** (26 mg, 0.11 mmol) gave (2*S*,4*S*)-**27** (21 mg, 81%) as an oil. Its IR and ^1H NMR spectra are identical to those reported for (2*R*,4*R*)-**27**.

(2*R*,4*S*) Isomer: In the same manner as described above, (2*R*,4*S*)-**26** (35 mg, 0.15 mmol) gave (2*R*,4*S*)-**27** (24 mg, 68%). − IR (film): $\tilde{\nu}_{max}$ = 1745 cm^{-1} (s, C=O), 1160 (m). − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 6.2 Hz, 3 H, 4′-CH_3), 0.83 (d, *J* = 6.4 Hz, 3 H, 2′-CH_3), 0.88 (t, *J* = 7.0 Hz, 3 H, 7-H_3), 1.0−1.25 (m, 4 H, 5′,6′-H_2), 1.28 (dt, *J* = 14.9, 7.0 Hz, 2 H, 3′-H_2), 1.36 (d, *J* = 7.4 Hz, 3 H, 3-CH_3), 1.49 (sext-like, *J* = 6.8 Hz, 1 H, 4′-H), 1.61 (sext-like, *J* = 6.3 Hz, 1 H, 2′-H), 1.87 (dd, *J* = 14.2, 8.0 Hz, 1 H, 1′-H), 2.00 (dt, *J* = 14.0, 4.9 Hz, 1 H, 1′-H), 3.05 (m, 1 H, 3-H), 4.68 (d, *J* = 15.5 Hz, 1 H, 6-H), 4.75 (d, *J* = 15.5 Hz, 1 H, 6-H), 5.45 (s, 1 H, 4-H).

(2*S*,4*R*) Isomer: In the same manner as described above, (2*S*,4*R*)-**26** (22 mg, 0.092 mmol) gave (2*S*,4*R*)-**27** (16 mg, 67%) as an oil. Its IR and ^1H NMR spectra are identical to those reported for (2*R*,4*S*)-**27**.

(b): To a solution of (2*R*,4*R*)-**27** (37 mg, 0.16 mmol) in chloroform (0.30 mL) was added dropwise a solution of bromine in carbon tetrachloride (0.55 M, 0.40 mL, 0.22 mmol) at 0 °C. After 30 min, the solution was warmed to room temperature and stirred for 17.5 h in the dark, and then concentrated in vacuo. The residue was rapidly diluted with chloroform (0.30 mL), and DBU (96 μL, 0.64 mmol) was added. The mixture was stirred for 1 h at room temperature. It was poured into a saturated aqueous NH_4Cl solution, and extracted with diethyl ether. The extract was washed with a saturated aqueous NH_4Cl solution, water and brine. The extract was dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (1.0 g, hexane/ethyl acetate, 30:1) to give (2*R*,4*R*)-**1** (23 mg, 61%) as an oil. − n_D^{26} = 1.4950. − $[\alpha]_D^{23}$ = +5.20 (*c* = 1.15 in diethyl ether). − IR (film): $\tilde{\nu}_{max}$ = 2955 cm^{-1} (s), 2925 (s), 1715 (s, C=O), 1650 (m), 1570 (m), 1455 (m), 1380 (m), 1265 (m), 1160 (m), 1040 (m), 990 (m), 760 (m). − ^1H NMR (500 MHz, C_6D_6): δ = 0.61 (d, *J* = 6.4 Hz, 3 H, 2′CH_3), 0.75−0.85 (m, 1 H, 5′-H), 0.80 (dd, *J* = 12.2, 2.3 Hz, 3 H, 4′-CH_3), 0.90 (t, *J* = 10.4 Hz, 3 H, 7′-H_3), 0.97−1.1 (m, 1 H, 5′-H), 1.04 (q, *J* = 7.3 Hz, 1 H, 6′-H), 1.15−1.35 (m, 3 H, 3′,4′,6′-H), 1.377 (q-like, *J* = 5.5 Hz, 2 H, 1′,3′-H), 1.384 (dd, *J* = 21.4, 8.9 Hz, 1 H, 2′-H), 1.78 (dq, *J* = 3.35, 12.2 Hz, 1 H, 1′-H), 1.86 (d, *J* = 0.6 Hz, 3 H, 3-CH_3), 6.32 (q, *J* = 1.2 Hz, 1 H, 4-H), 6.55 (br. s, 1 H, 2-H). − ^{13}C NMR (125.65 MHz, C_6D_6): δ = 14.6, 17.1, 19.6, 20.2, 30.0, 30.3, 36.6, 39.2, 44.7, 117.2, 125.7, 140.5, 146.1, 162.0. − The spectral data of (2*R*,4*R*)-**1** are identical to those reported previously.[1,2,7,8] − HREI-MS [$C_{15}H_{24}O_2$]: calcd. 236.1776; found 236.1776.

(2*S*,4*S*) Isomer: In the same manner as described above, (2*S*,4*S*)-**27** (49 mg, 0.21 mmol) gave (2*S*,4*S*)-**1** (40 mg, 81%) as an oil. − n_D^{26} = 1.4923. − $[\alpha]_D^{23}$ = −5.82 (*c* = 1.11 in diethyl ether). − Its IR, ^1H and^{13}C NMR spectra are identical to those reported for (2*R*,4*R*)-**1**. − HREI-MS [$C_{15}H_{24}O_2$]: calcd. 236.1776; found 236.1777.

(2*R*,4*S*) Isomer: In the same manner as described above, (2*R*,4*S*)-**27** (24 mg, 0.10 mmol) gave (2*R*,4*S*)-**1** (15 mg, 64%) as an oil. − n_D^{24} = 1.5159. − $[\alpha]_D^{23}$ = 29.1 (*c* = 0.75 in $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 2955 cm^{-1} (s), 2925 (s), 1715 (s), 1650 (m), 1570 (m), 1455 (m), 1380 (m), 1265 (m), 1160 (m), 1040 (m), 990 (m), 760 (m). − ^1H NMR (500 MHz, C_6D_6): δ = 0.61 (d, *J* = 6.4 Hz, 3 H, 2′-CH_3), 0.75 (d, *J* = 6.4 Hz, 3 H, 4′-CH_3), 0.90 (t, *J* = 7.1 Hz, 3 H, 7′-H_3), 0.85−0.95 (m, 2 H, 5′-H_2), 1.0−1.1 (m, 1 H, 6′-H), 1.1−1.35 (m, 3 H, 2′,4′,6′-H), 1.38 (td, *J* = 12.5, 5.5 Hz, 2 H, 3′-H_2), 1.47 (dd, *J* = 13.8, 8.2 Hz, 1 H, 1′-H), 1.70 (dd, 14.1, 5.8 Hz, 1 H, 1′-H), 1.85 (s, 3 H, 3-CH_3), 6.29 (br. s, 1 H, 4-H), 6.54 (br. s, 1 H, 2-H). − ^{13}C NMR (125.65 MHz, C_6D_6): δ = 14.5, 17.1, 18.8, 19.3, 20.5, 30.0, 37.6, 40.5, 44.3, 116.5, 124.8, 140.5, 146.1, 161.7. − HREI-MS [$C_{15}H_{24}O_2$]: calcd. 236.1776; found 236.1776.

(2*S*,4*R*) Isomer: In the same manner as described above, (4*S*,6*R*)-**27** (16 mg, 0.062 mmol) gave (2*S*,4*R*)-**1** (16 mg, quant.) as an oil.

− n_D^{24} = 1.5168. − $[\alpha]_D^{23}$ = +27.0 (c = 0.85 in $CHCl_3$). − Its IR, ^1H and ^{13}C NMR spectra are identical to those reported for (2*R*,4*S*)-**1**. − HREI-MS [$C_{15}H_{24}O_2$]: calcd. 236.1776; found 236.1771.

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