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Synthesis of the Enantiomers of 21-Methyl-7-hentriacontanone and a Stereoisomeric Mixture of 5-Acetoxy-19-methylnonacosane, Candidates for the Female Sex Pheromone of the Screwworm Fly…

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Synthesis of the Enantiomers of 21-Methyl-7-hentriacontanone and a Stereoisomeric Mixture of 5-Acetoxy-19-methylnonacosane, Candidates for the Female Sex Pheromone of the Screwworm Fly, *Cochliomyia hominivorax**

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The enantiomers of 21-methyl-7-hentriacontanone (1), which might show weak bioactivity as the female sex pheromone of the screwworm fly (*Cochliomyia hominivorax*), were synthesized by starting from the enantiomers of citronellal. (±)-Citronellol was converted to a racemic and diastereomeric mixture of 5-acetoxy-19-methylnonacosane (2), which was considered to be a candidate for the female sex pheromone of *C. hominivorax*. Synthetic 2 exhibited no pheromone activity against male *C. hominivorax*.

Key words: *Cochliomyia hominivorax*; methyl-branched ketone; methyl-branched secondary acetate; pheromone; screwworm fly

The New World screwworm fly (*Cochliomyia hominivorax*) is a troublesome pest to livestock in Central and South America. In order to eradicate this fly, a sterile male release program was successfully executed in that region. Possible incompatibility of the sex pheromones in released flies versus wild flies, however, may cause problems to render the program unsuccessful. Accordingly, in 2001, Carlson at the United States Department of Agriculture started his endeavors to clarify the pheromone system of *C. hominivorax*.

Pomonis *et al.* were the first to study the pheromone of *C. hominivorax*, and reported in 1993 the identification of sixteen compounds in a pheromonally active HPLC fraction extracted from the females.[1] Unfortunately, they were unable to identify the compound(s) responsible for the pheromone activity, because no bioactivity could be observed in peaks trapped either by GC or by recombination of the trapped capillary GC peaks, presumably due to thermal decomposition in the course of GC separation.

Carlson then requested us to synthesize the five compounds, (±)-**1**, **3**, **4**, **5** and **6**, (Fig. 1) out of the sixteen candidates reported by Pomonis.[1] These five compounds have been synthesized as stereoisomeric mixtures[2] and bioassayed in the United States.[3] The result was very encouraging to reveal the strong pheromone activity of 6-acetoxy-19-methylnonacosane (**3**) against male *C. hominivorax* at 1–6 μg, causing copulatory response.[3] 7-Acetoxy-15-methylnonacosane (**6**) was also active but less potent.

Although 7-acetoxy-19-methylnonacosane (**4**) and 8-acetoxy-19-methylnonacosane (**5**) were devoid of pheromone activity, 21-methyl-7-hentriacontanone (**1**) did not seem to be inert, seeming to be very slightly active (Carlson, D. A. personal communication dated March 11, 2002). We therefore thought that the enantiomers of **1** should be synthesized to clarify the matter. Another synthetic target suggested by Carlson was 5-acetoxy-19-methylnonacosane (**2**). This isomer of **3** is one of Pomonis's sixteen com-

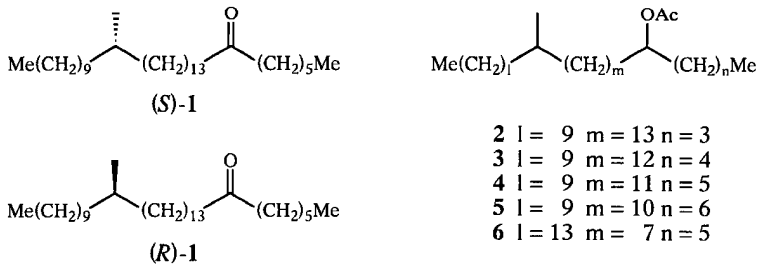

Fig. 1. Structures of Components **1**–**6** of the Female Sex Pheromone of the Screwworm Fly, *Cochliomyia hominivorax*.

* Pheromone Synthesis, Part 222. For Part 221, see Masuda, Y., Fujita, K., and Mori, K., *Biosci. Biotechnol. Biochem.*, **67**, 1744–1750 (2003).

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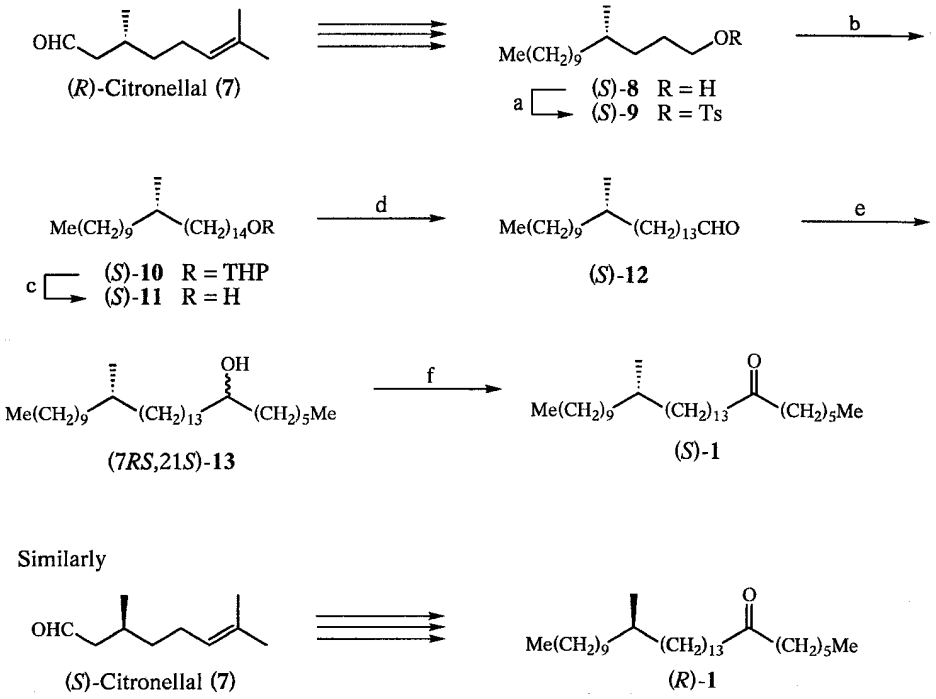


Scheme 1. Synthesis of the Enantiomers of 21-Methyl-7-hentriacontanone (**1**).
Reagents: (a) TsCl, C_5H_5N (quant.). (b) $THPO(CH_2)_{11}MgBr$, Li_2CuCl_4, THF. (c) TsOH, MeOH, THF (75%, 2 steps). (d) PCC, MS 4A, NaOAc, CH_2Cl_2 (78%). (e) $Me(CH_2)_5MgBr$, THF (89%). (f) Jones CrO_3, acetone (70%).

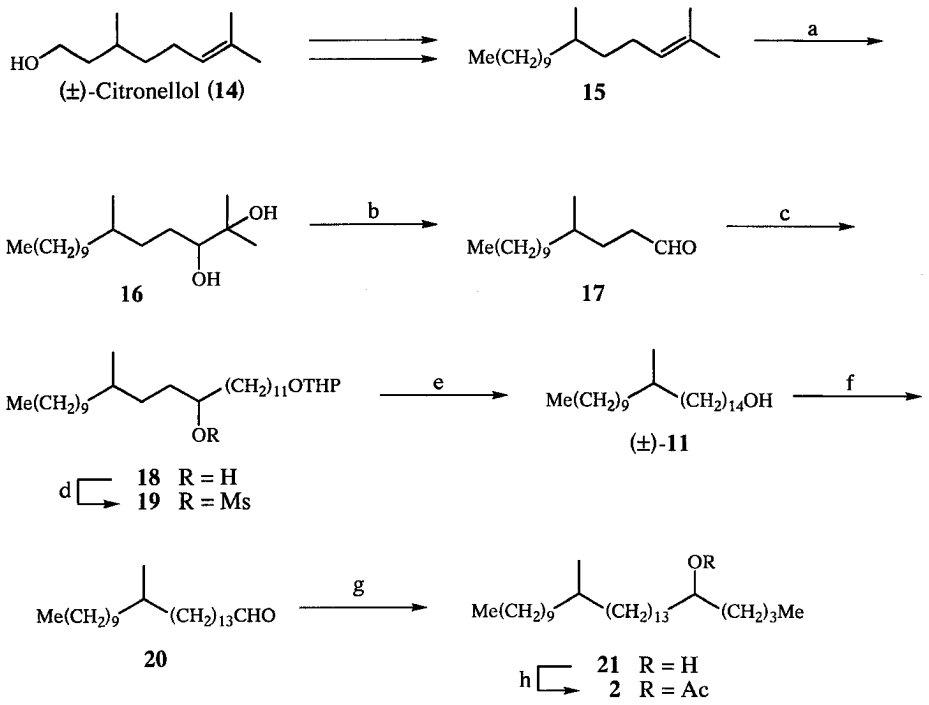
pounds,[1] and may also work as a pheromone component. The present paper describes the synthesis of (*S*)-**1** and (*R*)-**1**, and also the synthesis of a racemic and diastereomeric mixture of **2**.

Synthesis of the Enantiomers of 21-Methyl-7-hentriacontanone (1)

Commercially available enantiomers of citronellal (**7**, 97% e.e.; Takasago) were the most appropriate starting materials for the synthesis of (*R*)- and (*S*)-**1**, because conversion of **7** to tosylate **9** *via* alcohol **8** was already known (Scheme 1).[4] Treatment of (*S*)-**9** with 11-tetrahydropyranyl(THP)oxyundecylmagnesium bromide in the presence of dilithium tetrachlorocuprate according to Schlosser[5] afforded (*S*)-**10**. Removal of the THP group of **10** with *p*-toluenesulfonic acid (TsOH) in methanol furnished crystalline alcohol (*S*)-**11**. This was oxidized with pyridinium chlorochromate (PCC) to give aldehyde (*S*)-**12**. The Grignard reaction of (*S*)-**12** with hexylmagnesium bromide furnished alcohol (7*RS*, 21*S*)-**13** as a crystalline mixture of diastereomers. Finally, alcohol **13** was oxidized with Jones chromic acid to give (*S*)-21-methyl-7-hentriacontanone (**1**), mp 42–43°C, $[\alpha]_D^{25}$ −0.1 (*c* 5.3, hexane). The overall yield of (*S*)-**1** was 36% based on (*S*)-**8** (6 steps). Similarly, (*S*)-citronellal (**7**) yielded (*R*)-**1**, mp 42–43°C, $[\alpha]_D^{21}$ +0.1 (*c* 4.4, hexane).

As to the enantiomeric purity of (*R*)- and (*S*)-**1**, there had been no good method to estimate it directly until very recently. The enantiomeric purity (97% e.e.) of the starting citronellal (**7**) was thought to be preserved in final product **1**, because there was no step in the course of the synthesis to cause racemization. In this particular case, the specific rotation values of (*R*)- and (*S*)-**1** were so small that they could not tell us anything about the purity of the enantiomers of **1**. Fortunately, however, Ohrui *et al.* have developed an excellent method for estimating the stereochemical purity of compounds with a methyl-branched and long alkyl chain whose branching point was located far from the functional groups.[6] Ohrui's method has recently been applied to the structural elucidation of plakoside A, a marine galactosphingolipid.[7] Professor Ohrui kindly estimated the enantiomeric purity of the enantiomers of **11** and that of (7*RS*, 21*S*)- and (7*RS*, 21*R*)-**13**. Their stereochemical purity values at the methyl-branching carbon was as follows: (*R*)-**11** = 96.7% e.e.; (*S*)-**11** = 97.1% e.e.; (7*RS*, 21*R*)-**13** = 96.6% e.e.; and (7*RS*, 21*S*)-**13** = 96.7% e.e. As we expected, no racemization took place in the course of the synthesis. Application of Ohrui's analytical method to our study of the *C. hominivorax* pheromone will be thoroughly discussed in our forthcoming paper on the synthesis of the four stereoisomers of 6-acetoxy-19-methylnonacosane (**3**) (Mori, K., Ohrui, H., *et al.*: to be submitted to *Eur. J. Org. Chem.*).

Very recently, Carlson *et al.* have repeated the bioassay of (±)-**1** against *C. hominivorax* males.



Scheme 2. Synthesis of the Stereoisomeric Mixture of 5-Acetoxy-19-methylnonacosane (**2**).
Reagents: (a) OsO_4, NMO, *tert*-BuOH, acetone, H_2O (75% based on **14**, 3 steps). (b) $HIO_4 \cdot 2H_2O$, THF (quant.). (c) $THPO(CH_2)_{11}MgBr$, THF (90%). (d) MsCl, C_5H_5N (quant.). (e) i) $LiAlH_4$, THF; ii) dil HCl; iii) SiO_2 chromatog; iv) recrystallization (67%). (f) PCC, MS 4A, NaOAc, CH_2Cl_2 (73.5%). (g) $Me(CH_2)_3MgBr$, THF (73%). (h) Ac_2O, DMAP, C_5H_5N (96%).

They could not get any copulatory activity with (±)-**1** in individual bioassays. Its activity was seen only when a group test was used with several stimulatory materials. According to Carlson, there may be a "group effect" causing nearby males to copulate with decoys or objects that are near a "real" mating. This may mean that some olfactory stimulant is released from engaged male genitalia that causes nearby males to become excited (Carlson, D. A., personal communication dated November 22, 2002).

Synthesis of a Stereoisomeric Mixture of 5-Acetoxy-19-methylnonacosane (2)

As just described for the synthesis of **1**, Schlosser's copper-catalyzed carbon-carbon linking reaction[5] was employed for chain-elongation of **8** to give **11**. This reaction proved extremely useful in our synthesis of aliphatic insect pheromones.[2,4] However, it sometimes failed to give the chain-elongated product in an acceptable yield, although we were unable to identify the reason for this failure. We observed a low yield more often in the case of a Grignard reagent with an ω-tetrahydropyranyloxy group than in the case of a conventional alkylmagnesium bromide. In addition, for the conversion of **9** to **10**, almost four equivalents of 11-tetrahydropyranyloxyundecylmagnesium bromide had to be used to give coupling product **10** in a good yield, and this caused difficulty in separating **11** from 1-undecanol derived from the excess Grignard reagent. To circumvent the use of the sometimes-capricious copper-catalyzed reaction, we synthesized (±)-15-methylpentacosan-1-ol (**11**) in a different way as shown in Scheme 2.

(±)-Citronellol (**14**) was converted to **15** as reported previously.[2] Dihydroxylation of **15** with osmium tetroxide and *N*-methylmorpholine *N*-oxide (NMO) afforded a diastereomeric mixture of diol **16** as crystals. Treatment of **16** with periodic acid dihydrate in tetrahydrofuran (THF) gave aldehyde **17**. This was treated with the Grignard reagent prepared from 1.5 equivalents of 11-tetrahydropyranyloxyundecyl bromide and magnesium to give **18** in a 90% yield. Mesylation of **18** with methanesulfonyl (= mesyl, Ms) chloride afforded **19**, which was reduced with lithium aluminum hydride. The resulting (±)-15-methylpentacosyl tetrahydropyranyl ether was treated with hot hydrochloric acid to furnish (±)-**11** in a 67% yield after conventional chromatographic purification and recrystallization. Thus, (±)-**11** could be readily and reproducibly prepared without very careful and time-consuming chromatographic purification, avoiding the use of a large excess of 11-tetrahydropyranyloxydecylmagnesium bromide.

Oxidation of (±)-**11** with PCC afforded aldehyde (±)-**20**. Treatment of (±)-**20** with butylmagnesium bromide gave a racemic and diastereomeric mixture of 19-methylnonacosan-5-ol (**21**) as crystals, mp 34–35°C. Acetylation of **21** with acetic anhydride

and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in pyridine furnished final product **2**. The overall yield of 5-acetoxy-19-methylnonacosane (**2**) was 23% based on (±)-citronellol (**14**; 11 steps). A bioassay of **2** showed it to be totally inactive as the sex stimulant against male *C. hominivorax*.[3)]

Conclusion

Synthesis of pheromone candidates (*R*)-**1**, (*S*)-**1** and **2** of the screwworm fly was achieved. As to the synthesis of **2**, a practical and reproducible chain-extension process was devised by employing the Grignard reaction and subsequent deoxygenation of the resulting secondary alcohol [**17**→**18**→**19**→(±)-**11**].

Since (±)-**1** and **2** were biologically inactive, we can now concentrate our efforts on the synthesis of the stereoisomers of **3** and **6** so as to clarify the stereochemistry-pheromone activity relationships in *C. hominivorax*. Indeed, the stereochemistry of **3** is important in its pheromone activity as was evident by the recent observation that (6*S*, 19*R*)-**3** was about three times more active than a stereoisomeric mixture of **3** (Carlson, D. A., personal communication dated April 17, 2003). Although (±)-**1** was pheromonally inactive, a bioassay of the enantiomers of **1** will be conducted shortly with the hope that it might tell us something about its stereochemistry-bioactivity relationship.

Experimental

Melting point (mp) data are uncorrected. IR spectra were measured with a Horiba FT-720 spectrometer. ^{1}H-NMR spectra were recorded at 300 MHz by a Varian Mercury-300 spectrometer (TMS at $\delta=0.00$ or $CHCl_3$ at $\delta=7.26$ as an internal standard). ^{13}C-NMR spectra were recorded at 75 MHz also by the Varian Mercury-300 spectrometer ($CDCl_3$ at $\delta=77.0$ as an internal standard). Optical rotation values were measured with a Jasco DIP-320 polarimeter, and refractive index data were measured with an Atago DMT-1 refractometer.

(S)-15-Methyl-1-pentacosanol [(S)-11]. *p*-Toluenesulfonyl chloride (2.3 g, 12 mmol) was added portionwise to a stirred and ice-cooled solution of (*S*)-**8** (2.3 g, 10 mmol) in dry pyridine (10 ml) at 0–5°C. Stirring was continued for 30 min at 0°C and then for 1 h at room temperature. The mixture was then poured into ice-water and extracted with hexane-diethyl ether. The extract was successively washed with ice-cooled dil. HCl, water, sat. $NaHCO_3$ aq. and brine, dried with $MgSO_4$, and concentrated *in vacuo*. Resulting (*S*)-**9** [3.9 g, quant., IR ν_{max} (film) cm^{-1}: 1175 (s), 660 (s), 553 (s)] was dissolved in dry THF (40 ml) and stirred at −78°C under Ar. To this was added a solution of the Grignard reagent prepared from 11-THPO$(CH_2)_{11}$Br (11.0 g, 33 mmol) and Mg (960 mg, 40 mmol) in dry THF (35 ml) through a syringe. A solution of Li_2CuCl_4 in THF (0.1 M, 1 ml) was then added to the stirred and cooled mixture. The reaction temperature was gradually raised overnight from −78°C to room temperature. The mixture was poured into ice and sat. NH_4Cl aq., and then extracted with hexane. The extract was washed with brine, dried with $MgSO_4$, and concentrated *in vacuo* to give crude (*S*)-**10** (9.9 g), IR ν_{max} (film) cm^{-1}: 1120 (m), 1080 (m), 1020 (s). *p*-Toluenesulfonic acid monohydrate (0.1 g) was added to a solution of crude (*S*)-**10** (9.9 g) in MeOH (90 ml) and THF (50 ml). The mixture was stirred at 60°C for 1.5 h, neutralized with Na_2CO_3, and concentrated *in vacuo*. The residue was diluted with water and extracted with hexane-diethyl ether. The extract was successively washed with water and brine, dried with $MgSO_4$, and concentrated *in vacuo*. The residue (7.2 g) was chromatographed over SiO_2 (50 g in hexane). Elution with hexane-diethyl ether (20:1) gave (*S*)-**11** (2.97 g, 75%) as a solid. This was recrystallized from hexane-acetone to give fine needles, mp 42–43°C, $[\alpha]_D^{25}$ +0.15 (*c* 4.84, hexane). IR ν_{max} (nujol) cm^{-1}: 3370 (m), 1060 (s), 725 (s). NMR δ_H ($CDCl_3$): 0.83 (3H, d, $J=6.3$ Hz, 15-Me), 0.88 (3H, t, $J=7.0$ Hz, 25-H), 1.00–1.10 (2H, m), 1.10–1.40 (41H, br), 1.56 (2H, seemingly q, $J=7.2$ Hz, 2-H), 1.61 (1H, s, OH), 3.64 (2H, t, $J=6.9$ Hz, 1-H). NMR δ_C ($CDCl_3$): 14.1, 19.7, 22.64, 22.68, 25.7, 27.1, 29.35, 29.43, 29.59, 29.61, 29.65, 29.67, 29.69, 29.70, 29.72, 30.0, 31.6, 31.9, 32.7, 32.8, 37.1, 63.1. *Anal.* Found: C, 81.88; H, 14.51%. Calcd. for $C_{26}H_{54}O$: C, 81.60; H, 14.22%.

(R)-15-Methyl-1-pentacosanol [(R)-11]. In the same manner as that described for (*S*)-**11**, (*R*)-**8** (2.3 g) gave (*R*)-**11** (1.8 g, 46%) as needles from hexane-acetone, mp 44–45°C, $[\alpha]_D^{24}$ −0.11 (*c* 5.20, hexane). Its IR, ^{1}H- and ^{13}C-NMR spectra were identical with those reported for (*S*)-**11**. *Anal.* Found: C, 81.80; H, 14.47%. Calcd. for $C_{26}H_{54}O$: C, 81.60; H, 14.22%.

(S)-15-Methylpentacosanal [(S)-12]. Powdered sodium acetate (240 mg, 2.9 mmol) and powdered MS 4A (100 mg) were added to a solution of (*S*)-**11** (1.9 g, 5.0 mmol) in dry CH_2Cl_2 (25 ml). The suspension was stirred vigorously at 0–5°C. To this was added PCC (2.8 g, 13 mmol), and the dark mixture was stirred for 30 min at 0–5°C and then for 3 h at room temperature. The mixture was filtered through SiO_2 (20 g in diethyl ether), and the SiO_2 column was washed with diethyl ether. The combined filtrate and washings were concentrated *in vacuo*. The residue was chromatographed over SiO_2 (30 g in hexane). Elution with hexane-ethyl acetate (20:1) afforded (*S*)-**12** (1.5 g, 78%) as a waxy solid, $[\alpha]_D^{25}$ +0.15.

(*c* 4.56, hexane). IR ν_{max} (film) cm^{-1}: 2715 (w), 1730 (s), 720 (m). NMR δ_H ($CDCl_3$): 0.83 (3H, d, J= 6.3 Hz, 15-Me), 0.87 (3H, t, J=6.6 Hz, 25-H), 1.00–1.15 (2H, m), 1.20–1.40 (39H, br), 1.62 (2H, t, J=7.2 Hz, 3-H), 2.41 (2H, dt, J=1.4, 7.5 Hz, 2-H), 9.76 (1H, t, J=1.4 Hz 1-H). NMR δ_C ($CDCl_3$): 14.1, 19.7, 22.1, 22.7, 27.1, 29.2, 29.35, 29.42, 29.58, 29.63, 29.65, 29.66, 29.68, 29.70, 29.73, 30.0, 31.9, 32.7, 37.1, 43.9, 202.9. *Anal.* Found: C, 82.10; H, 13.94%. Calcd. for $C_{26}H_{52}O$: C, 82.03; H, 13.77%.

(R)-15-Methylpentacosanal [(R)-12]. In the same manner as that described for (*S*)-**12**, (*R*)-**11** (1.3 g) gave (*R*)-**12** (1.25 g, 97%) as a waxy solid, $[\alpha]_D^{25}$ −0.04 (*c* 5.10, hexane). Its IR, ^1H- and ^{13}C-NMR spectra were identical with those reported for (*S*)-**12**. *Anal.* Found: C, 82.28; H, 13.37%. Calcd. for $C_{26}H_{52}O$: C, 82.03; H, 13.77%.

(7RS, 21S)-21-Methyl-7-hentriacontanol [(7RS, 21S)-13]. A Grignard reagent was prepared from hexyl bromide (1.7 g, 10 mmol) and Mg (270 mg, 11 mmol) in dry THF (10 ml) under Ar. A solution of (*S*)-**12** (1.5 g, 3.9 mmol) in dry THF (10 ml) was added dropwise to the stirred and ice-cooled Grignard reagent under Ar at 0–5°C. The mixture was left to stand overnight at room temperature, then poured into ice and sat. NH_4Cl aq., and extracted with hexane. The extract was successively washed with water and brine, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (30 g in hexane). Elution with hexane-ethyl acetate (20:1) gave (7*RS*, 21*S*)-**13** (1.6 g, 89%) as a solid. Recrystallization from hexane-acetone afforded fine needles, mp 41–44°C, $[\alpha]_D^{24}$ −0.8 (*c* 8.23, hexane). IR ν_{max} (nujol) cm^{-1}: 3350 (m), 1135 (m), 1080 (m), 720 (s). NMR δ_H ($CDCl_3$): 0.83 (3H, d, J=6.3 Hz, 21-Me), 0.88 (6H, t, J=7.2 Hz, 1-H, 31-H), 1.00–1.10 (4H, m), 1.18–1.50 (51H, m), 1.59 (1H, s, OH), 3.58 (1H, m, 7-H). NMR δ_C ($CDCl_3$): 14.08, 14.11, 19.7, 22.62, 22.69, 25.61, 25.65, 27.1, 29.36, 29.37, 29.62, 29.64, 29.66, 29.68, 29.69, 29.70, 29.72, 30.0, 31.8, 31.9, 32.7, 37.1, 37.5, 72.0. *Anal.* Found: C, 82.66; H, 14.83%. Calcd. for $C_{32}H_{66}O$: C, 82.32; H, 14.25%.

(7RS, 21R)-21-Methyl-7-hentriacontanol [(7RS, 21R)-13]. In the same manner as that described for (7*RS*, 21*S*)-**13**, (*R*)-**12** (0.92 g) gave (7*RS*, 21*R*)-**13** (0.80 g, 71%) as a solid. Recrystallization from hexane-acetone yielded fine needles, mp 40–43°C, $[\alpha]_D^{20}$ +0.7 (*c* 5.20, hexane). Its IR, ^1H- and ^{13}C-NMR spectra were identical with those reported for (7*RS*, 21*S*)-**13**. *Anal.* Found: C, 82.39; H, 14.49%. Calcd. for $C_{32}H_{66}O$: C, 82.32; H, 14.25%.

(S)-21-Methyl-7-hentriacontanone [(S)-1]. Jones chromic acid (2.67 M, 1.0 ml, 2.67 mmol = 3 equiv.) was added dropwise to a stirred and ice-cooled solution of (7*RS*, 21*S*)-**13** (1.21 g, 2.59 mmol) in acetone (100 ml) at 0–5°C. After the mixture had been stirred for 30 min at 0–5°C, MeOH was added to destroy excess CrO_3. The mixture was concentrated *in vacuo*, and the residue was partioned between hexane and water. The hexane extract was successively washed with water and brine, dried with $MgSO_4$, and concentrated *in vacuo* to give crude (*S*)-**1** as a solid. Recrystallization from acetone gave pure (*S*)-**1** (0.84 g, 70%) as fine needles, mp 42–43°C, $[\alpha]_D^{25}$ −0.1 (*c* 5.3, hexane). IR ν_{max} (film) cm^{-1}: 2962 (m), 2918 (s), 2850 (s), 1703 (s), 1468 (s), 1412 (m), 1379 (m), 1128 (w), 987 (w), 721 (m). NMR δ_H ($CDCl_3$): 0.83 (3H, d, J=6.6 Hz, 21-Me), 0.88 (6H, t, J= 6.9 Hz, 1-H, 31-H), 1.00–1.10 (2H, m), 1.18–1.40 (45H, br., centered at 1.25), 1.55 (4H, seemingly t, J=7.5 Hz, 5-H, 9-H), 2.38 (4H, t, J=7.5 Hz, 6-H, 8-H). NMR δ_C ($CDCl_3$): 14.0, 14.1, 19.7, 22.5, 22.7, 23.84, 23.89, 27.1, 28.9, 29.27, 29.35, 29.42, 29.48, 29.61, 29.65, 29.67, 29.69, 29.70, 29.72, 30.0, 31.6, 31.9, 32.7, 37.1, 42.8, 48.1, 65.3, 211.8. *Anal.* Found: C, 82.90; H, 14.31%. Calcd. for $C_{32}H_{64}O$: C, 82.64; H, 13.88%.

(R)-21-Methyl-7-hentriacontanone [(R)-1]. In the same manner as that described for (*S*)-**1**, (7*RS*, 21*R*)-**13** (0.80 g) gave (*R*)-**1** (0.75 g, 94%) as a solid. Recrystallization from acetone afforded fine needles, mp 42–43°C. $[\alpha]_D^{21}$ +0.1 (*c* 4.4, hexane). Its IR, ^1H- and ^{13}C-NMR spectra were identical with those reported for (*S*)-**1**. *Anal.* Found: C, 82.91; H, 13.98%. Calcd. for $C_{32}H_{64}O$: C, 82.64; H, 13.88%.

(3RS, 6RS)-2,6-Dimethylhexadecane-2,3-diol (16). Crude and oily **15** (30.3 g) was prepared from **14** (8.8 g, 57 mmol) according to ref. 2. A solution of OsO_4 (150 mg, 0.6 mmol) in *tert*-BuOH (15 ml) and NMO (50% aq., 26.0 g, 111 mmol) were added to a stirred solution of crude **15** (30.3 g) in a mixture of acetone (240 ml), *tert*-BuOH (100 ml) and H_2O (60 ml). Stirring was continued for 3 days at room temperature. The color of the mixture changed from dark brown to almost colorless. Solid $Na_2SO_3 \cdot 7H_2O$ (15 g) was added to the stirred mixture. After 30 min, the solvents were removed *in vacuo*. The residue was diluted with water, and extracted with ethyl acetate. The extract was successively washed with water and brine, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (180 g in hexane). After washing out the hydrocarbons with hexane, **16** (12.1 g, 75% based on **14**, 3 steps) was eluted with hexane-ethyl acetate (10:1 − 5:1). Partially solidified **16** was recrystallized from acetone to give crystalline **16** (5.3 g, 33%) as prisms, mp 55–56°C. IR ν_{max} (nujol) cm^{-1}: 3400 (m), 1050 (s). NMR δ_H ($CDCl_3$): 0.87 (3H, d, J=6.9 Hz, 6-Me), 0.88 (3H, t, J=6.6 Hz, 16-H), 1.16 (3H, s, 1-H or 2-Me), 1.22

(3H, s, 1-H or 2-Me), 1.10–1.50 (24H, br., centered at 1.26), 1.96 (1H, s, OH), 2.11 (1H, s, OH), 3.34 (1H, m, 3-H). NMR δ_C ($CDCl_3$): 14.1, 19.5, 22.7, 23.2, 26.5, 27.1, 29.1, 29.3, 29.64, 29.68, 29.7, 30.0, 31.9, 32.8, 34.0, 37.2, 73.2, 78.9. *Anal.* Found: C, 75.71; H, 13.50%. Calcd. for $C_{18}H_{38}O_2$: C, 75.46; H, 13.37%.

(RS)-4-Methyltetradecanal (17). A solution of **16** (11.4 g, 39.9 mmol) in THF (50 ml) was added dropwise to a stirred and ice-cooled solution of $HIO_4 \cdot 2H_2O$ (9.5 g, 41.7 mmol) in THF (150 ml). Stirring was continued for 1 h at 0–5°C to precipitate HIO_3. The mixture was diluted with water and extracted with hexane. The extract was successively washed with water, $NaHCO_3$ aq., water and brine, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (100 g in hexane). Elution with hexane-ethyl acetate (50:1) gave **17** (8.9 g, 99%) as an oil which solidified in a refrigerator. IR ν_{max} (film) cm^{-1}: 2710 (w), 1728 (s), 721 (w). NMR δ_H ($CDCl_3$): 0.87 (3H, d, J=6.3 Hz, 6-Me), 0.88 (3H, t, J=6.0 Hz, 16-H), 1.14 (2H, m), 1.22–1.38 (16H, m), 1.40–1.50 (2H, m, 4-H), 1.60–1.72 (2H, m, 3-H), 2.32–2.52 (2H, m, 2-H), 9.77 (1H, t, J=1.0 Hz 1-H). NMR δ_C ($CDCl_3$): 14.1, 19.3, 22.7, 26.9, 28.9, 29.3, 29.6, 29.9, 31.9, 32.4, 36.7, 41.7, 203.0. *Anal.* Found: C, 79.72; H, 13.62%. Calcd. for $C_{15}H_{30}O$: C, 79.57; H, 13.36%.

(12RS, 15RS)-15-Methylpentacosane-1,12-diol 1-Tetrahydropyranyl Ether (18). A Grignard reagent was prepared under Ar by adding a solution of 11-THPO$(CH_2)_{11}$Br (10.7 g, 30 mmol) in dry THF (40 ml) to Mg (800 mg, 33 mmol) at 60°C in the presence of a few mg of iodine. A solution of **17** (4.7 g, 21 mmol) in dry THF (10 ml) was added dropwise to the stirred and ice-cooled solution of the Grignard reagent at 0–5°C under Ar, and the mixture was left to stand for 2 days. It was then poured into ice and sat. NH_4Cl aq., and extracted with hexane. The extract was successively washed with water and brine, dried with $MgSO_4$ and concentrated *in vacuo*. The residual oil (15 g) was chromatographed over SiO_2 (100 g in hexane). Elution with hexane-ethyl acetate (10:1) gave 9.3 g (90%) of **18** as an oil which solidified upon storage in a refrigerator. This solid was triturated with pentane, and filtered to give 3.9 g (38%) of crystalline **18**. Recrystallization from pentane gave needles, mp 43–45°C. IR ν_{max} (film) cm^{-1}: 3400 (m), 1122 (m), 1074 (m), 1025 (s). NMR δ_H ($CDCl_3$): 0.86 (3H, d, J=6.9 Hz, 15-Me), 0.88 (3H, t, J=7.0 Hz, 25-H), 1.05–1.40 (43H, m), 1.50–1.60 (4H, m, 2-H, 5′-H), 1.62–1.86 (2H, m, 3′-H), 3.35–3.40 (1H, dt, J=6.6, 9.6 Hz, 1-H), 3,42–3.65 (3H, m, 12-H, 3′-H), 3.68–3.80 (1H, dt, J=6.6, 9.6 Hz, 1-H) 3.82–3.92 (2H, m, 6′-H), 4.58 (1H, t, J=3.6 Hz, 2′-H). NMR δ_C ($CDCl_3$): 14.1, 19.58, 19.64, 19.7, 22.7, 25.5, 25.61, 25.65, 26.2, 27.00, 27.04, 29.3, 29.45, 29.55, 29.59, 29.63, 29.69, 29.71, 30.0, 30.3, 30.7, 31.9, 32.6, 32.77, 32.82, 32.86, 32.9, 34.87, 34.92, 36.88, 36.95, 37.1, 37.4, 37.5, 62.3, 63.4, 67.7, 72.3, 72.4, 98.8. Oily **18** was used for the next step without further purification.

(12RS, 15RS)-12-Methanesulfonyloxy-15-methylpentacosan-1-ol Tetrahydropyranyl Ether (19). Methanesulfonyl chloride (1.5 ml, 2.2 g, 19.4 mmol) was added dropwise to a stirred and ice-cooled solution of **18** (3.0 g, 6.0 mmol) in CH_2Cl_2 (15 ml) and dry pyridine (10 ml). The mixture was kept in a refrigerator for 3 days, poured into ice-water, and extracted with hexane. The extract was successively washed with water, $CuSO_4$ aq., water and brine, dried with $MgSO_4$, and concentrated *in vacuo* to give **19** (3.5 g, quant.) as an oil. IR ν_{max} (film) cm^{-1}: 1350 (m), 1175 (s), 900 (s), 530 (s). NMR δ_H ($CDCl_3$): 0.87 (3H, d, J=6.3 Hz, 15-Me), 0.89 (3H, t, J=6.9 Hz, 25-H), 1.10–1.45 (43H, m), 1.48–1.62 (4H, m, 2-H, 5′-H), 1.62–1.86 (2H, m, 3′-H), 3.00 (3H, s, SO_2Me), 3.34–3.42 (1H, dt, J=6.6, 9.0 Hz, 1-H), 3.46–3.55 (2H, m, 2-H, 4′-H), 3.68–3.78 (1H, dt, J=6.6, 9.0 Hz, 1-H), 3.82–3.92 (2H, m, 6′-H), 4.58 (1H, t, J=4.5 Hz, 2′-H), 4.64–4.74 (1H, seemingly quint., J=6.0 Hz, 12-H). This compound was employed immediately for the next step.

(RS)-15-Methylpentacosan-1-ol [(±)-11]. A solution of **19** (3.5 g, 6.0 mmol) in dry THF (20 ml) was added dropwise to a stirred and ice-cooled suspension of $LiAlH_4$ (1.0 g, 26 mmol) in THF (50 ml) at 0–5°C. The mixture was stirred and heated under reflux for 1.5 h. It was then ice-cooled, and water (5 ml) was added dropwise to destroy the excess $LiAlH_4$. The mixture was acidified with dil. HCl (conc. HCl:H_2O=1:1, 30 ml), stirred and heated under reflux for 30 min, cooled, and extracted with hexane. The extract was successively washed with water, sat. $NaHCO_3$ aq. and brine, dried with $MgSO_4$, and concentrated *in vacuo* to give 2.5 g of a crude oil. This oil was chromatographed over SiO_2 (70 g in hexane). Elution with hexane-ethyl acetate (15:1) gave 1.95 g (88%) of (±)-**11** as a solid. Recrystallization from acetone gave (±)-**11** (1.52 g, 67%) as prisms, mp 35–36°C. IR ν_{max} (film) cm^{-1}: 3400 (m), 1060 (s), 720 (s), 600 (s). NMR δ_H ($CDCl_3$): 0.83 (3H, d, J=6.3 Hz, 15-Me), 0.88 (3H, t, J=6.3 Hz, 25-H), 1.00–1.20 (2H, m), 1.20–1.50 (42H, br. s), 1.50–1.70 (2H, m, 2-H), 3.64 (2H, t, J=6.6 Hz, 1-H). NMR δ_C ($CDCl_3$): 14.1, 19.7, 22.65, 22.69, 25.7, 27.1, 29.36, 29.60, 29.62, 29.67, 29.69, 29.70, 29.71, 29.74, 31.6, 31.9, 32.7, 32.8, 37.1, 63.1. *Anal.* Found: C, 81.68; H, 14.49%. Calcd. for $C_{26}H_{54}O$: C, 81.60; H, 14.22%.

(RS)-15-Methylpentacosanal [(±)-20]. Powdered sodium acetate (240 mg, 2.9 mmol) and powdered MS 4A (100 mg) were added to a solution of (±)-**11** (1.1 g, 2.9 mmol) in dry CH_2Cl_2 (25 ml). The ice-cooled suspension was stirred vigorously at 0–5°C. To this was added PCC (3.0 g, 14 mmol), and the dark-colored mixture was stirred for 20 min at 0–5° and then for 2 h at room temperature. The mixture was then diluted with diethyl ether (200 ml) and filtered through SiO_2 (20 g in diethyl ether). The SiO_2 column was washed with diethyl ether (100 ml). The combined filtrate and washings were concentrated *in vacuo* to give a residual oil (1.1 g). This oil was chromatographed over SiO_2 (30 g in hexane). Elution with hexane-ethyl acetate (15:1) gave (±)-**20** (0.8 g, 73.5%) which solidified in a refrigerator. IR ν_{max} (film) cm^{-1}: 2710 (w), 1730 (s), 720 (m). NMR δ_H ($CDCl_3$): 0.83 (3H, d, J=6.3 Hz, 15-Me), 0.88 (3H, t, J=6.6 Hz, 25-H), 1.00–1.07 (2H, m), 1.20–1.40 (39H, br. s), 1.63 (2H, seemingly quint., J=7.5 Hz, 3-H), 2.42 (2H, dt, J=1.8, 7.5 Hz, 2-H), 9.76 (1H, t, J=1.8 Hz, 1-H). NMR δ_C ($CDCl_3$): 14.1, 19.7, 22.1, 22.7, 27.1, 29.2, 29.36, 29.43, 29.58, 29.64, 29.66, 29.67, 29.69, 29.71, 29.73, 30.0, 31.9, 32.7, 37.1, 43.9, 203.0. *Anal.* Found: C, 81.80; H, 13.40%. Calcd. for $C_{26}H_{52}O$: C, 82.03; H, 13.21%.

(5RS, 19RS)-19-Methylnonacosan-5-ol [(5RS, 19RS)-21]. A Grignard reagent was prepared from butyl bromide (1.5 g, 11 mmol) and magnesium (300 mg, 12 mmol) in dry THF (20 ml) under Ar. A solution of (±)-**20** (0.8 g, 2.1 mmol) in dry THF (10 ml) was added dropwise to the stirred and ice-cooled Grignard reagent under Ar at 0–5°C. The mixture was stirred for 30 min at 0–5°C and for an additional 30 min at room temperature. It was then poured into ice and sat. NH_4Cl aq., and extracted with hexane. The extract was successively washed with water and brine, dried with $MgSO_4$, and concentrated *in vacuo* to give 920 mg (99.6%) of crude **21** as a solid. Recrystallization from acetone afforded pure **21** (670 mg, 73%) as fine needles, mp 34–35°C. IR ν_{max} (film) cm^{-1}: 3325 (s), 3255 (s), 1135 (m), 1070 (m), 720 (s). NMR δ_H ($CDCl_3$): 0.84 (3H, d, J=6.3 Hz, 19-Me), 0.88 (3H, t, J=6.9 Hz, CH_2CH_3), 0.91 (3H, t, J=6.9 Hz, CH_2CH_3), 1.00–1.15 (2H, m), 1.18–1.50 (49H, m), 1.59 (1H, s, OH), 3.59 (1H, m, 5-H). NMR δ_C ($CDCl_3$): 14.08, 14.11, 19.7, 22.7, 22.8, 27.8, 29.4, 29.62, 29.63, 29.66, 29.70, 29.73, 30.0, 31.9, 32.7, 37.1, 37.2, 37.5, 72.0. *Anal.* Found: C, 82.24; H, 14.27%. Calcd. for $C_{30}H_{62}O$: C, 82.11; H, 14.24%.

(5RS, 19RS)-5-Acetoxy-19-methylnonacosane [(5RS, 19RS)-2]. Acetic anhydride (1.0 ml) and DMAP (50 mg) were added to a stirred and ice-cooled solution of **21** (250 mg, 0.57 mmol) in CH_2Cl_2 (5 ml) and pyridine (2.5 ml). The mixture was stirred for 1.5 h at room temp, poured into ice-water, and extracted with hexane. The extract was washed successively with dil. HCl, sat. $NaHCO_3$ aq. and brine, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (8 g in hexane). Elution with hexane-ethyl acetate (70:1) gave **2** (263 mg, 96%) as an oil, n_D^{21} 1.4527. IR ν_{max} (film) cm^{-1}: 1737 (s), 1238 (s), 1020 (m), 721 (w). NMR δ_H ($CDCl_3$): 0.83 (3H, d, J=6.6 Hz, 19-Me), 0.89 (3H, t, J=6.3 Hz, CH_2CH_3), 0.90 (3H, t, J=6.3 Hz, CH_2CH_3), 1.00–1.15 (2H, m), 1.18–1.40 (45H, m), 1.44–1.58 (4H, m, 4-H, 6-H), 2.03 (3H, s, $COCH_3$), 4.86 (1H, seemingly quint., J=6.3 Hz, 5-H). NMR δ_C ($CDCl_3$): 14.0, 14.1, 19.7, 21.3, 22.6, 22.7, 25.3, 27.1, 27.5, 29.4, 29.5, 29.6, 29.66, 29.67, 29.68, 29.70, 29.71, 29.74, 30.0, 32.7, 33.8, 34.1, 37.1, 74.4, 170.9. MS (EI) m/z (relative intensity): 57 (100), 73 (90), 89 (95), 97 (50), 111 (30), 129 (45), 131 (42), 154 (4), 167 (20), 182 (6), 420 (3, M^+-AcOH). *Anal.* Found: C, 80.15; H, 13.65%. Calcd. for $C_{32}H_{64}O_2$: C, 79.93; H, 13.42%.

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