Concise Synthesis of (4*R*,9*Z*)-Octadec-9-en-4-olide, the Female Sex Pheromone of *Janus integer*[‡]

Kenji Mori*[a]

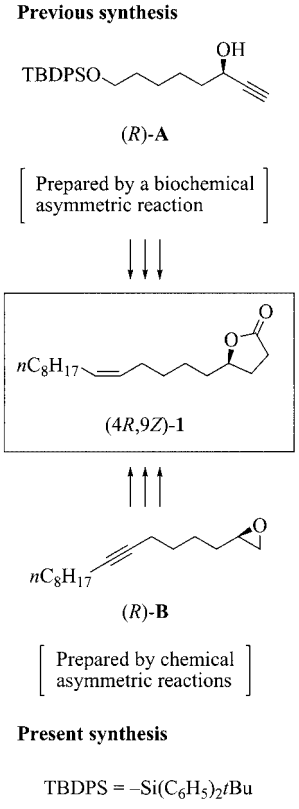
Keywords: Dihydroxylation / Epoxides / Lactones / Natural products / Pheromones

(4*R*,9Z)-Octadec-9-en-4-olide, the female sex pheromone of the currant stem girdler (*Janus integer*), was synthesized in gram quantities by employing Sharpless asymmetric dihydroxylation (AD) and Jacobsen hydrolytic kinetic resolution (HKR). Crystalline (*R*)-hexadec-7-yne-1,2-diol (87 % *ee*), obtained by AD and purified by recrystallization, was converted into (*R*)-1,2-epoxyhexadec-7-yne (87 % *ee*), which was further purified to 96 % *ee* by HKR. The epoxide was converted into the target lactone in 14 % overall yield based on hex-5-en-1-ol (11 steps).

Introduction

In 2001 Cossé et al. isolated and identified (*Z*)-octadec-9-en-4-olide (**1**) as a female-specific and antennally active compound from the female currant stem girdler, *Janus integer* Norton (Hymenoptera: Cephidae), a pest of red currant in North America.[1] It was then found to be the sex pheromone of that insect, and its (*R*) absolute configuration was proposed on the basis of the synthesis of a trace amount of (*R*)-**1** starting from (*S*)-glutamic acid.[2] Subsequently we developed another synthesis, which enabled us to obtain both (*R*)- and (*S*)-**1** in 50–100 mg quantities.[3] By bioassay of our synthetic samples, (*R*)-**1** was definitely confirmed as the sex pheromone of *J. integer*, while (*S*)-**1** was pheromonally inactive. To test the feasibility of utilizing (*R*)-**1** as the pest managing agent against *J. integer* in the U.S.A., Dr. D. G. James at Washington State University asked me to synthesize gram quantities of (*R*)-**1**. This paper describes a successful account of the synthesis of (*R*)-**1** in an amount (4 g) sufficient for a practical field test.

As shown in Scheme 1, the key intermediate in our previous synthesis[3] was acetylenic alcohol (*R*)-**A**, prepared by enzymatic kinetic resolution of (±)-**A** with lipase PS(Amano) and vinyl acetate. In the current synthesis, epoxide (*R*)-**B** was envisaged as the key intermediate, to be prepared by Sharpless asymmetric dihydroxylation (AD)[4] and Jacobsen hydrolytic kinetic resolution (HKR).[5,6] The HKR process was to enable the enrichment of the enantiomeric purity of (*R*)-**B** prepared by AD. The results detailed below confirm the practicality of these asymmetric processes.



Scheme 1. Structure of the target pheromone and two strategies for its synthesis.

Results and Discussion

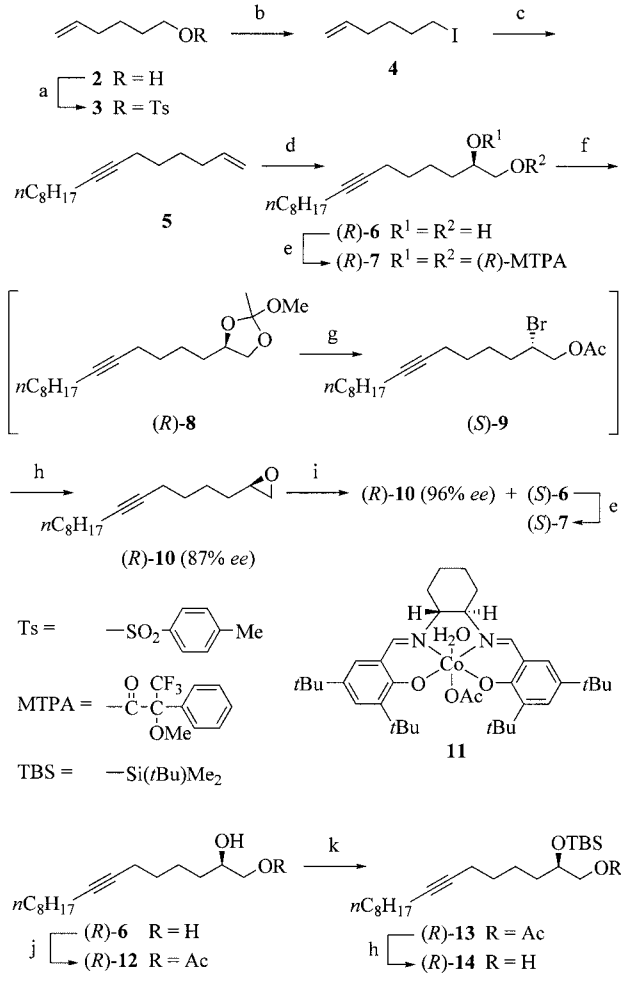
Scheme 2 summarizes the synthesis and purification of the key epoxide (*R*)-**10**. Commercially available hex-5-en-1-ol (**2**) was converted into the corresponding iodide **4** in 92% yield via tosylate **3**. Alkylation of dec-1-yne with *n*-butyl-

[‡] Pheromone Synthesis, 229. Part 228: K. Mori, *Tetrahedron: Asymmetry* **2005**, *16*, 685–692.

[a] Insect Pheromone and Traps Division, Fuji Flavor Co., Ltd., Midorigaoka 3-5-8, Hamura-City, Tokyo 205–8503, Japan
Fax: +81-42-555-7920;
E-mail: kjk-mori@arion.ocn.ne.jp

  DOI: 10.1002/ejoc.200400830

lithium and **4** furnished enyne **5** in 71% yield. Sharpless AD of **5** with AD-mix-β®[4] afforded crystalline (*R*)-diol **6** (about 75% *ee*) in 84% yield. The enantiomeric purity of (*R*)-**6** was analyzed by HPLC after derivatization to the corresponding bis-(*R*)-α-methoxy-α-trifluoromethylphenylacetate (MTPA ester) **7**.[7]



Scheme 2. Synthesis of (*R*)-1,2-epoxyhexadec-7-yne (**10**). Reagents: (a) TsCl, C_5H_5N; (b) NaI, DMF (92%, 2 steps); (c) $nC_8H_{17}C{\equiv}CH$, *n*BuLi, THF (71%); (d) AD-mixβ®, *t*BuOH, H_2O, 0–5 °C, 6 h, then room temp. overnight; recrystallization from hexane [1× (84%) for (*R*)-**6** of 75% *ee*; 2× (60%) for (*R*)-**6** of 87% *ee*; 5× (20%) for (*R*)-**6** of 98% *ee*]; (e) (*S*)-MTPACl, DMAP, C_5H_5N; (f) $MeC(OMe)_3$, PPTS, CH_2Cl_2; (g) AcBr, CH_2Cl_2; (h) K_2CO_3, MeOH [87%. for (*R*)-**10,** 3 steps; quant. for (*R*)-**14**,]; (i) Jacobsen's (*R*,*R*)-salen cobalt catalyst (**11**), 0.4 equiv. H_2O, THF [72% of (*R*)-**10** (96% *ee*) and 20% of (*S*)-**6** (49% *ee*)]; (j) lipase PS, CH_2=CHOAc, iPr_2O (99%); (k) TBSCl, imidazole, DMF (86%).

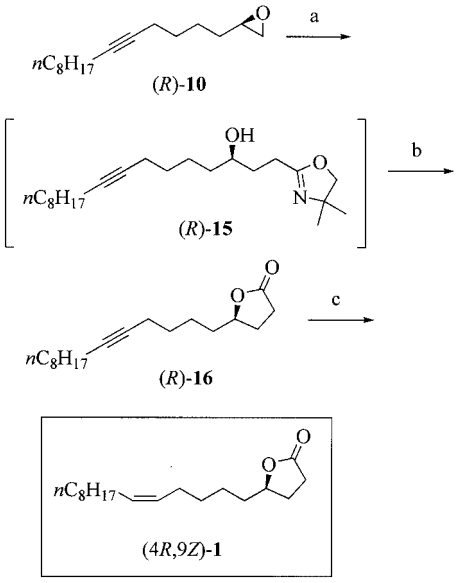
Conversion of diol (*R*)-**6** into epoxide (*R*)-**10** was executed by the method of Kolb and Sharpless.[8] Accordingly, recrystallized (*R*)-**6** (87% *ee*, vide infra) was treated with trimethyl orthoacetate and pyridinium *p*-toluenesulfonate (PPTS) to give water-labile orthoacetate (*R*)-**8**, to which acetyl bromide was added. The resulting (*S*)-1-acetoxy-2-bromo compound **9** [contaminated with (*R*)-2-acetoxy-1-bromo isomer] was mixed with potassium carbonate in aqueous methanol, without purification, to provide epoxide (*R*)-**10** (= **B**) in 87% yield based on (*R*)-**6**. The enantiomeric purity of (*R*)-**10** could be determined by GC analysis on a chiral stationary phase: octakis(2,3-di-*O*-methoxymethyl-6-*O*-*tert*-butyldimethylsilyl)-γ-cyclodextrin (MOM-TBDMS-GCD). A sample of (*R*)-**10** (87% *ee*) prepared from recrystallized (*R*)-**6** was subjected to further purification by Jacobsen's HKR in the presence of his (*R*,*R*)-salen cobalt catalyst **11**.[5,6] Treatment of (*R*)-**10** in THF with 0.7 mol% of **11** and 0.4 equiv. of water for 3 days at room temperature (25 °C) was followed by chromatographic workup to give (*R*)-**10** (96% *ee*, 72% yield) together with crystalline (*S*)-**6** (49% *ee*, 20%). Purification of (*R*)-**10** by Jacobsen's procedure was time-saving and more efficient than the purification of (*R*)-**6** by recrystallization.

Actually, although the diol (*R*)-**6** could be purified by recrystallization from hexane, the recovery of the purified **6** was low due to its high solubility and low melting point. Diol (*R*)-**6** of 87% *ee* could be obtained in 60% yield based on **5**, while that of 98% *ee* could be secured only in 20% yield.

Two unsuccessful attempts were made to purify (*R*)-**6** enzymatically. Treatment of diol (*R*)-**6** with lipase PS and vinyl acetate in diisopropyl ether afforded monoacetate (*R*)-**12** of no improved enantiomeric purity. In this particular case, the stereochemistry at C-2 of **6** did not affect the rate of acetylation of the hydroxy group at C-1. The sterically more demanding *tert*-butyldimethylsilyl (TBS) group was then attached to (*R*)-**12** to give (*R*)-**13**, which was treated with potassium carbonate in aqueous methanol to furnish (*R*)-**14**. Attempted lipase-catalyzed acetylation of (*R*)-**14** with lipase PS and vinyl acetate did not proceed at all, presumably due to excessively severe steric hindrance caused by the TBS group. The enzymatic approach was therefore abandoned. It should be added that the lipase-catalyzed kinetic resolution of 1-TBSoxyhexadec-7-yn-2-ol might be possible, in view of a recent publication dealing with a similar substrate.[9]

Scheme 3 shows the conversion of epoxide (*R*)-**10** into the target lactone (4*R*,9*Z*)-**1**. Classic treatment of (*R*)-**10** with diethyl sodiomalonate in ethanol[10] did not give a good result in this case. Although many methods for the synthesis of lactonic pheromones from epoxides have been employed,[11] Meyers' oxazoline alkylation method[12,13] was adopted to convert (*R*)-**10** into (*R*)-octadec-9-yn-4-olide (**16**) via (*R*)-**15**. Accordingly, epoxide (*R*)-**10** was added to the anion generated from 2,4,4-trimethyl-2-oxazoline by treatment with *n*-butyllithium, and the resulting (*R*)-**15** was heated with dilute hydrochloric acid to give (*R*)-**16** in 58% yield based on (*R*)-**10**. Finally, semihydrogenation of (*R*)-**16** over Lindlar's catalyst (Pd–$CaCO_3$–Pb^{2+}) in hexane at –5 to 0 °C under atmospheric pressure afforded (4*R*,9*Z*)-octadec-9-en-4-olide (**1**) in 94% yield. Its GC analysis revealed it to be of 96% *ee* with a *Z*/*E* ratio of 13:1.

In conclusion, a concise synthesis of *Janus integer* pheromone (4*R*,9*Z*)-**1** was achieved in an overall yield of 14% based on hex-5-en-1-ol **2** (11 steps). The result of the field test will be reported in due course.



Scheme 3. Synthesis of (4*R*,9*Z*)-octadec-9-en-4-olide (**1**). Reagents: (a) 2,4,4-trimethyl-2-oxazoline, *n*BuLi, THF, –78 °C to room temp.; (b) dil. HCl, THF, 60 °C, 30 min (58%, 2 steps); (c) H_2, Lindlar Pd–$CaCO_3$–Pb^{2+}, hexane, –5 to 0 °C (94%).

Experimental Section

General: IR: Horiba FT-720. ^{1}H NMR: Varian Mercury 300 (300 MHz) (TMS at δ = 0.00 ppm or $CHCl_3$ at δ = 7.26 ppm as internal standard). ^{13}C NMR: Varian Mercury 300 (75 MHz) ($CDCl_3$ at δ = 77.0 ppm as internal standard). Melting points (Yanaco MP-S3) and boiling points: Uncorrected values. n_D: Atago DNT-1. $[\alpha]_D$: Jasco DIP-320. CC: Merck Kieselgel 60 Art 1.07734.

Hex-5-enyl Tosylate (3): TsCl (55 g, 294 mmol) was added portionwise to a stirred and ice-cooled solution of **2** (25.4 g, 254 mmol) in dry pyridine (150 mL). The mixture was stirred for 3 h at 0–5 °C, poured into ice and dil. HCl., and extracted with hexane. The extract was washed successively with water, sat. $NaHCO_3$ solution, and brine, dried with $MgSO_4$, and concentrated in vacuo to give 64.5 g (quant.) of **3** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (apparently quint, J = 6 Hz, 2 H), 1.61 (apparently quint, J = 6 Hz, 2 H), 2.01 (dt, J = 6, 6 Hz, 2 H), 2.42 (s, 3 H, $ArCH_3$), 4.01 (t, J = 6 Hz, 2 H, 1-H_2), 4.95 (m, 2 H, 6-H_2), 5.70 (m, 1 H, 5-H), 7.36 (d, J = 6 Hz, 2 H, Ar), 7.80 (d, J = 6 Hz, 2 H, Ar) ppm. IR (film): $\tilde{\nu}$ = 1640 (w, C=C), 1595 (m, Ar), 1360 (s), 1175 (s), 935 (s), 665 (s), 555 (s) cm^{-1}. This compound was employed for the next step without further purification.

Hex-5-enyl Iodide (4): Powdered sodium iodide (80 g, 533 mmol) was added to a stirred solution of **3** (64.5 g, 254 mmol) in DMF (220 mL). After the exothermic reaction, the mixture was stirred for 4 d at room temp. It was then poured into water, and extracted with pentane. The pentane extract was washed successively with water, sodium thiosulfate solution, and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was distilled to give 49.3 g (92% based on **2**) of **4**, b.p. 84–85 °C/40 Torr. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (apparently quint, J = 6 Hz, 2 H), 1.80 (apparently quint, J = 6 Hz, 2 H), 2.04 (dt, J = 6, 6 Hz, 2 H), 3.18 (t, J = 6 Hz, 2 H, 1-H_2), 5.00 (m, 2 H, 6-H_2), 5.80 (m, 1 H, 5-H) ppm. IR (film): $\tilde{\nu}$ = 3075 (m), 2930 (s), 2885 (m), 1640 (m, C=C), 1215 (s), 1170 (s), 990 (m), 915 (s) cm^{-1}. This compound was immediately used for the next step.

Hexadec-1-en-7-yne (5): *n*BuLi (1.6 M in hexane, 36.5 mL, 58.4 mmol) was added at –78 °C under Ar to a stirred and cooled (dry ice/acetone) solution of dec-1-yne (8.0 g, 58 mmol) in dry THF (120 mL). The mixture was stirred at –78 to 20 °C for 1 h. Then **4** (13.0 g, 62 mmol) was added dropwise by syringe, and the mixture was stirred and heated under reflux (65 °C) for 3 h. It was left to stand at room temp. for 2 d, and was then poured into ice and sat. NH_4Cl solution, and extracted with pentane. The extract was washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was distilled to give 9.1 g (71%) of **5**, b.p. 124–127 °C/4 Torr. n_D^{22} = 1.4567. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, J = 6.6 Hz, 3 H, 16-H_3), 1.18–1.40 [1.28 (br. s), m, 12 H], 1.40–1.55 (m, 4 H), 2.08 (m, 2 H), 2.10–2.20 (m, 4 H), 4.91–5.05 (m, 2 H, 1-H_2), 5.70–5.88 (m, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 18.6, 18.7, 22.7, 28.0, 28.6, 28.9, 29.13, 29.14, 29.2, 31.8, 33.3, 79.9, 80.4, 114.4, 138.7 ppm. IR (film): $\tilde{\nu}$ = 3075 (w), 2930 (s), 2860 (s), 1645 (m, C=C), 1460 (s), 990 (m), 910 (s) cm^{-1}. $C_{16}H_{28}$ (220.4): calcd. C 87.19, H 12.81: found C 86.89, H 12.92. HRMS (EI) $[M]^+$ ($C_{16}H_{28}$): calcd. 220, 2191; found 220. 2187.

(*R*)-Hexadec-7-yne-1,2-diol (6): AD-mix-β® (33.7 g) was added to a stirred mixture of *t*BuOH (120 mL) and water (120 mL), and the stirring was continued to generate a reddish biphasic mixture. This was then cooled in an ice-bath, and **5** (5.3 g, 24 mmol) was added dropwise. The stirring was continued for 6 h at 0–5 °C and then overnight at room temp. to give a yellowish suspension. The excess oxidant was then destroyed by addition of Na_2SO_3 (36 g) with stirring and ice-cooling over 30 min. The mixture was concentrated in vacuo, and extracted with ethyl acetate. The extract was washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residual semi-solid was recrystallized from hexane to give crude (*R*)-**6** (5.1 g, 84%, 75% *ee*), $[\alpha]_D^{20}$ = +4.7 (c = 3.7, MeOH). A second recrystallization of 6.4 g of crude (*R*)-**6** gave 4.6 g (60% based on **5**, 87% *ee*) of the diol, $[\alpha]_D^{22}$ = +6.2 (c = 3.2, MeOH). In another experiment, recrystallization was repeated five times to give (*R*)-**6** of 98% *ee*, $[\alpha]_D^{21}$ = +7.4 (c = 3.2, MeOH), in 20% yield based on **5**, as leaflets, m.p. 50.5–52.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.3 Hz, 3 H, 16–H_3), 1.20–1.40 [1.27 (br. s), m, 16 H], 1.40–1.60 (m, 4 H), 2.09–2.19 (m, 4 H), 3.44 (dd, J = 11, 11 Hz, 1 H, 1-H), 3.66 (dd, J = 11, 11 Hz, 1 H, 1–H), 3.73 (m, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 18.6, 18.7, 22.6, 24.7, 28.9, 29.0, 29.11, 29.13, 29.2, 31.8, 32.6, 66.8, 72.2, 79.7, 80.6 ppm. IR (nujol): $\tilde{\nu}$ = 3370 (s, OH), 3295 (sh.), 1115 (m), 1070 (m), 1000 (m), 860 (s), 725 (s) cm^{-1}. $C_{16}H_{30}O_2$ (254.4): calcd. C 75.53, H 11.89; found C 75.23, H 12.11.

Determination of the Enantiomeric Purity of (*R*)-Hexadec-7-yne-1,2-diol (6): In the usual manner,[7] samples of **6** were treated with (*S*)-MTPACl and DMAP in pyridine to give (*R*)-MTPA esters **7**. These were analyzed by HPLC (PEGASIL silica®, 25 cm × 4.6 mm; eluent: hexane/EtOAc, 50:1; flow rate: 1.0 mL min^{-1}). Compound (*R*)-**6** obtained immediately after AD: t_R = 45.9 (87.5%), 49.2 (12.5%) min; 75% *ee*. (*R*)-**6** obtained after two recrystallizations: t_R = 46.2 (93.5%), 49.4 (6.5%) min; 87% *ee*. (*R*)-**6** obtained after five recrystallizations: t_R = 47.0 (98.9%), 50.5 (1.1%) min; 98% *ee*. ^{1}H NMR analysis of **7** did not give useful information, due to the complexity of the spectrum.

(*R*)-1,2-Epoxyhexadec-7-yne (10)

(i) Preparation of Orthoacetate (*R*)-8: PPTS (30 mg, 0.1 mmol) was added to a stirred solution of (*R*)-**6** (87% *ee*, 3.45 g, 13.6 mmol) and trimethyl orthoacetate (3.5 g, 18.4 mmol) in CH_2Cl_2 (30 mL), and the solution was left to stand overnight in a refrigerator. The solution was then concentrated in vacuo, and the residue was

stirred and heated at 50–60 °C in vacuo (20 Torr) to remove MeOH, affording 5.2 g (quant.) of oily (*R*)-**8**. IR (film): $\tilde{\nu}$ = 1240 (m), 1155 (s), 1055 (s), 890 (m) cm^{-1}. This orthoester was labile against water, and was used immediately in the next step.

(ii) Preparation of Acetoxy Bromide (*S*)-9: Acetyl bromide (1.5 mL, about 2.5 g, 20 mmol) was added at 0–5 °C to a stirred and ice-cooled solution of (*R*)-**8** (5.2 g, 13.6 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred for 1 h at 0–5 °C, and was then concentrated in vacuo to give about 5.9 g (quant.) of (*S*)-**9** as a yellowish oil. IR (film): $\tilde{\nu}$ = 1745 (s, C=O), 1375 (m), 1235 (s), 1025 (m) cm^{-1}. This bromide was used in the next step without further purification.

(iii) Preparation of Epoxide (*R*)-10: A solution of (*S*)-**9** (5.9 g, 13.6 mmol) in THF (10 mL) was added dropwise to a stirred suspension of K_2CO_3 (4.5 g, 19 mmol) in MeOH (30 mL) and water (5 mL). The mixture was stirred and heated at 50 °C for 1 h, and concentrated in vacuo. The residue was diluted with water and extracted with EtOAc. The extract was 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/EtOAc (100:1) afforded 2.9 g (91% based on **6**) of oily (*R*)-**10** (87% *ee*), n_D^{21} = 1.4608. $[\alpha]_D^{26}$ = +7.5 (*c* = 3.1, Et_2O).

(iv) Purification of (*R*)-10 by Jacobsen's HKR: A mixture of (*R*,*R*)-salen cobalt catalyst (Aldrich, 130 mg, 0.2 mmol), toluene (0.8 mL), and acetic acid (15 μL) was stirred for 1 h, while open to the air at room temp (25 °C). The solvent was then removed in vacuo to dry up the dark brown residue **11**. To this was added a solution of (*R*)-**10** (87% *ee*, 6.5 g, 27.5 mmol) in dry THF (13 mL) and water (0.18 mL, 10 mmol). The resulting dark solution was stirred for 3 d at room temp (24–25 °C) and was then poured onto a column of SiO_2 (50 g) in hexane. Elution with hexane/EtOAc (100:1) gave crude (*R*)-**10** (5.1 g). Subsequent elution with hexane/EtOAc (1:1) gave crude (*S*)-**6** (1.4 g). Recrystallization of (*S*)-**6** from EtOAc/hexane furnished 1.36 g (20%) of (*S*)-**6** [49% *ee* as determined by HPLC analysis of (*S*)-**7**: t_R = 46.1 (25.4%), 49.3 (74.6%) min] as leaflets, m.p. 45–46 °C. $[\alpha]_D^{24}$ = –3.6 (*c* = 3.37, MeOH). Its IR and NMR spectra were identical to those of (*R*)-**6**. Further purification of (*R*)-**10** was executed by SiO_2 (35 g) chromatography. Elution with hexane/EtOAc (75:1) gave 4.7 g (72%) of pure (*R*)-**10** (96% *ee*), n_D^{25} = 1.4596. $[\alpha]_D^{22}$ = +7.93 (*c* = 3.12, Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3 H, 16-H_3), 1.20–1.60 [1.27 (br. s), 1.50 (br. s), m, 18 H], 2.10–2.18 (m, 4 H), 2.47 (apparently dd, *J* = 2.7, 5.1 Hz, 1 H, 1-H), 2.75 (apparently dd, *J* = 5.1, 5.1 Hz, 1 H, 1-H), 2.92 (m, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 18.65, 18.72, 22.6, 25.1, 28.8, 28.9, 29.09, 29.11, 29.2, 31.8, 32.0, 47.0, 52.2, 79.6, 80.6 ppm. IR (film): $\tilde{\nu}$ = 3045 (w), 2930 (s), 1460 (m), 1335 (w), 1260 (w), 1130 (w), 920 (m), 835 (m), 725 (w) cm^{-1}. $C_{16}H_{28}O$ (236.4): calcd. C 81.29, H 11.94; found C 80.92, H 12.22.

Determination of the Enantiomeric Purity of 1,2-Epoxyhexadec-7-yne (10): Samples of **10** were analyzed by GC on a chiral stationary phase by Dr. S. Tamogami of T. Hasegawa Co., Ltd. (instrument: Agilent 6890N; column: 50% MOM-TBDMS-GCD, 30 m × 0.25 mm, df = 0.25 μm; column temp: 40–180 °C (+0.5 °C min^{-1}); carrier gas: N_2; flow rate: 0.6 mL min^{-1}; detector: FID; injection temp: 230 °C; detector temp: 250 °C). Compound (*R*)-**10** prior to Jacobsen's HKR: t_R = 254.3 (93.5%), 259.4 (6.5%) min; 87% *ee*. Compound (*R*)-**10** after Jacobsen's HKR: t_R = 254.2 (98.0%), 259.4 (2.0%) min; 96% *ee*.

(*R*)-1-Acetoxyhexadec-7-yn-2-ol (12): Lipase PS (Amano, 1.2 g) was added to a stirred solution of crude (*R*)-**6** (75% *ee*, 2.0 g, 7.9 mmol) and vinyl acetate (50 mL) in iPr_2O (100 mL). Stirring was continued for a week at room temp. (20 °C), and the mixture was filtered through Celite. The filtrate was concentrated in vacuo. The residual oil (2.3 g, 99%) was homogeneous, and was identified as (*R*)-**12**. n_D^{26} = 1.4638. $[\alpha]_D^{24}$ = +0.8 (*c* = 3.2, hexane). ^{1}H NMR (300 MHz $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3 H, 16-H_3), 1.20–1.40 [1.27 (br. s), m, 15 H], 1.40–1.60 (m, 4 H), 2.10 (s, 3 H, Ac), 2.10–2.25 (m, 4 H), 3.86 (m, 1 H, 2-H), 3.96 (dd, *J* = 11, 11 Hz, 1 H, 1-H), 4.18 (dd, *J* = 11, 11 Hz 1 H, 1-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 18.7, 20.8, 22.6, 24.6, 28.9, 29.0, 29.1, 29.2, 31.8, 32.7, 66.7, 68.7, 69.8, 72.1, 79.6, 80.6, 171.2 ppm. IR (film): $\tilde{\nu}$ = 3480 (m, OH), 1745 (s, C=O), 1240 (s) cm^{-1}. HRMS (EI) $[M]^+$ ($C_{18}H_{32}O_3$): calcd. 296.2351; found 296.2357.

(*R*)-1-Acetoxy-2-*tert*-butyldimethylsilyloxyhexadec-7-yne (13): TBSCl (1.6 g, 10 mmol) was added to a stirred and ice-cooled solution of (*R*)-**12** (2.2 g, 7.4 mmol) and imidazole (2.7 g, 40 mmol) in dry DMF (30 mL). The mixture was stirred for 3 d at room temp (20 °C), poured into ice water, and extracted with hexane. The extract was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (40 g). Elution with hexane/EtOAc (50:1) gave 2.6 g (86%) of (*R*)-**13**, n_D^{26} = 1.4547. $[\alpha]_D^{22}$ = –2.4 (*c* = 3.2, hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.08 [s, 6 H, $Si(CH_3)_2$], 0.88 (br. s, 12 H, *t*Bu, 16-H_3), 1.20–1.55 (m, 18 H), 2.05 (s, 3 H, Ac), 2.08–2.20 (m, 4 H), 3.84 (m, 1 H, 2-H), 3.92 (dd, *J* = 11, 11 Hz, 1 H, 1-H), 4.40 (dd, *J* = 11, 11 Hz, 1 H, 1-H) ppm. IR(film): $\tilde{\nu}$ = 1745 (s, C=O), 1235 (s), 1120 (m), 1045 (m), 835 (s), 775 (m) cm^{-1}. HRMS (EI) $[M]^+$ ($C_{24}H_{46}O_3Si$): calcd. 410.3216; found 410.3223.

(*R*)-2-*tert*-Butyldimethylsilyloxyhexadec-7-yn-1-ol (14): K_2CO_3 (1.2 g, 8.7 mmol) was added to a stirred solution of (*R*)-**13** (2.0 g, 4.9 mmol) in THF (5 mL), MeOH (15 mL), and H_2O (1 mL). The mixture was stirred and heated at 50 °C for 1.5 h, and was then concentrated in vacuo. The residue was diluted with water and extracted with hexane. The extract was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo to give 1.8 g (quant.) of (*R*)-**14**, n_D^{26} = 1.4594. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.08 [s, 6 H, $Si(CH_3)_2$], 0.88 (t, *J* = 6.9 Hz, 3 H, 16-H_3), 0.90 (s, 9 H, *t*Bu), 1.20–1.60 (m, 18 H), 2.10–2.22 (m, 4 H), 2.40 (s, 1 H, OH), 3.38 (dd, *J* = 11, 11 Hz, 1 H, 1-H) 3.62 (dd, *J* = 11, 11 Hz, 1 H, 1-H), 3.78 (m, 1 H, 2-H) ppm. IR (film): $\tilde{\nu}$ = 3580 (w), 3460 (m, OH), 1255 (s), 1120 (s), 835 (s), 780 (s) cm^{-1}. HRMS (EI) $[M]^+$ ($C_{22}H_{44}O_2Si$): calcd. 368.3111; found 368.3112.

(*R*)-Octadec-9-yn-4-olide (16): A solution of *n*BuLi in hexane (1.6 M, 12.5 mL, 20 mmol) was added dropwise at –78 °C under Ar to a stirred and cooled solution of 2,4,4-trimethyl-2-oxazoline (2.3 g, 20 mmol) in THF (12 mL). The solution was stirred at –78 °C for 30 min. A solution of (*R*)-**10** (96% *ee*, 2.8 g, 12 mmol) in THF (3 mL) was then added dropwise to the stirred and cooled solution at –78 to –70 °C. The mixture was stirred at –78 °C for 30 min, and gradually warmed to room temp (22 °C) over 3 h. It was then acidified with 3 M HCl (about 50 mL), and diluted with THF (30 mL). The resulting acidic and homogeneous solution was stirred and heated under reflux (60–70 °C) for 30 min. The solution was concentrated in vacuo to remove THF and was extracted with hexane. The hexane extract was washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed over SiO_2 (20 g, hexane). Elution with hexane/EtOAc (10:1) afforded 1.93 g (58%) of (*R*)-**16** as a colorless oil, n_D^{22} = 1.4732. $[\alpha]_D^{23}$ = +21.7 (*c* = 3.21, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3 H, 18-H_3), 1.20–1.70 [1.28 (br. s), m, 18 H], 1.70–1.80 (m, 1 H), 1.80–1.95 (m, 1 H), 2.10–2.20 (m, 4 H, 8-H_2, 12-H_2), 2.33 (ddt, *J* = 6, 7, 11 Hz, 1 H, 3-H), 2.53 (ddd, *J* = 0.6, 7, 11 Hz, 2 H, 2-H_2), 4.49 (quint, *J* = 6 Hz, 1 H, 4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 18.5, 18.6, 22.6, 24.3,

27.9, 28.6, 28.7, 28.77, 28.78, 28.9, 29.1, 31.7, 35.0, 79.4, 80.6, 80.8, 177.1 ppm. IR (film): $\tilde{\nu}$ = 2990 (s), 2860 (s), 1778 (s, C=O), 1460 (m), 1355 (w), 1175 (s), 1020 (w), 915 (w), 805 (w), 725 (w), 650 (w) cm^{-1}. $C_{18}H_{30}O_2$ (278.4): calcd. C 77.65, H 10.80; found C 77.47, H 10.96. HRMS (EI) $[M]^+$ ($C_{18}H_{30}O_2$): calcd. 278.2246; found 278.2243.

(4*R*,9*Z*)-Octadec-9-en-4-olide (1): Lindlar's Pd catalyst (Aldrich, 5 wt.-% on $CaCO_3$, poisoned with lead, 49 mg) was added to a solution of (*R*)-**16** (96% *ee*, 500 mg, 1.8 mmol) in hexane (10 mL). The suspension was cooled with an ice/salt bath (–5 to 0 °C), and was vigorously stirred under H_2 (1 atm) for 75 min. The catalyst was then removed by filtration through a small column of SiO_2 (2 g), and the column was washed with hexane. The hexane solution was concentrated in vacuo, and the residue was chromatographed over SiO_2 (5 g in hexane). Elution with hexane/EtOAc (10:1) afforded 450 mg (94%) of (4*R*,9*Z*)-**1**. When hydrogenation was executed at room temperature (20–25 °C), the product **1** was impure, and contaminated with substantial amounts of (*R*)-octadecan-4-olide and (4*R*,9*E*)-octadec-9-en-4-olide. In order to avoid loss of the material by overreduction and isomerization, the Lindlar hydrogenation of (*R*)-**16** was carried out repeatedly in small portions. By repeating this hydrogenation three times, 1.72 g of (*R*)-**16** gave 1.50 g (91%) of (4*R*,9*Z*)-**1** as a colorless oil, which solidified in a deep freezer (–20 °C), n_D^{25} = 1.4670. $[\alpha]_D^{23}$ = +24.2 (*c* = 3.20, $CHCl_3$) {ref.:[3] $[\alpha]_D^{25}$ = +24 (*c* = 0.50, $CHCl_3$)}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3 H, 18-H_3), 1.20–1.80 [1.27 (br. s), m, 18 H], 1.81–1.90 (m, 1 H), 1.96–2.10 (m, 4 H, 8-H_2, 11-H_2), 2.32 (ddt, *J* = 6, 7.5, 13 Hz, 1 H, 3-H), 2.53 (ddd, *J* = 1.3, 7.5, 9.2 Hz, 2 H, 2-H_2), 4.48 (quint, *J* = 6 Hz, 1 H, 4-H), 5.35 (ddt, *J* = 7, 12, 18 Hz, 2 H, 9-H, 10-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.7, 24.9, 27.0, 27.1, 27.2, 28.0, 28.8, 29.3, 29.4, 29.5, 29.7, 31.9, 35.5, 80.9, 129.1 [(9*Z*) isomer, major, 95%], 129.4 [(9*E*) isomer, very minor, 5%], 130.5 [(9*Z*) isomer, major, 95%], 130.7 [(9*E*) isomer, very minor, 5%], 177.2 ppm. IR (film): $\tilde{\nu}$ = 2925 (s), 2855 (s), 1780 (s, C=O), 1650 (w, C=C), 1460 (m), 1355 (m), 1285 (w), 1175 (s), 1020 (m), 915 (m), 825 (w), 720 (m) cm^{-1}. GC analysis on a BDEX-225 column of this sample by Dr. Bartelt (U.S. Department of Agriculture) revealed its composition as follows: (4*R*,9*Z*)-**1** = 90.4%; (4*R*,9*E*)-**1** = 5.7%; (*R*)-octadecan-4-olide = 3.9%. The purity of the sample was therefore >98% *ee*, *Z*/*E* = 16:1, unsaturated lactone/saturated lactone = 24.6:1. $C_{18}H_{32}O_2$ (280.4); calcd. C 77.09, H, 11.50; found C 76.96, H 11.64. HRMS (EI) $[M]^+$ ($C_{18}H_{32}O_2$): calcd. 280.2402; found 280.2402.

Acknowledgments

My thanks are due to Drs. R. J. Bartelt (U.S. Department of Agriculture) and S. Tamogami (T. Hasegawa Co., Ltd.) for GC analyses of (4*R*,9*Z*)-**1** and (*R*)-**13**, respectively. Determination of the enantiomeric purity of **6** was kindly carried out by Dr. T. Tashiro (RIKEN). I appreciate the support of this work by Mr. M. Hagiwara, Drs. T. Chuman, and S. Muto, Fuji Flavor Co., Ltd.

[1] A. A. Cossé, R. J. Bartelt, D. G. James, R. J. Petroski, *J. Chem. Ecol.* **2001**, *27*, 1841–1851.
[2] D. G. James, R. J. Petroski, A. A. Cossé, B. W. Zilkowski, R. J. Bartelt, *J. Chem. Ecol.* **2003**, *29*, 2189–2199.
[3] C. Shibata, K. Mori, *Eur. J. Org. Chem.* **2004**, 1083–1088.
[4] H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2485– 2547.
[5] M. Tokunaga, J. F. Larrow, F. Kakiuchi, E. N. Jacobsen, *Science* **1997**, *277*, 936–938.
[6] E. N. Jacobsen, *Acc. Chem. Res.* **2000**, *33*, 421–431.
[7] J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512–519.
[8] H. C. Kolb, K. B. Sharpless, *Tetrahedron* **1992**, *48*, 10515–10530.
[9] Y. Aoyagi, Y. Saitoh, T. Ueno, M. Horiguchi, K. Takeya, R. M. Williams, *J. Org. Chem.* **2003**, *68*, 6899–6904.
[10] T. Sugai, K. Mori, *Agric. Biol. Chem.* **1984**, *48*, 2497–2500.
[11] K. Mori, in *The Total Synthesis of Natural Products*, vol. 9 (Ed.: J. ApSimon), John Wiley & Sons, New York, **1992**, 216–273.
[12] A. I. Meyers, E. D. Mihelich, R. L. Nolen, *J. Org. Chem.* **1974**, *39*, 2783–2787.
[13] P. H. G. Zarbin, A. R. M. Oliveira, F. Simonelli, J. A. F. P. Villar, O. Delay, Jr., *Tetrahedron Lett.* **2004**, *45*, 7399–7400.

Received: November 22, 2004

