Synthesis of (4*R*,9*Z*)-9-Octadecen-4-olide, the Female Sex Pheromone of *Janus integer*, and Its Enantiomer[‡]

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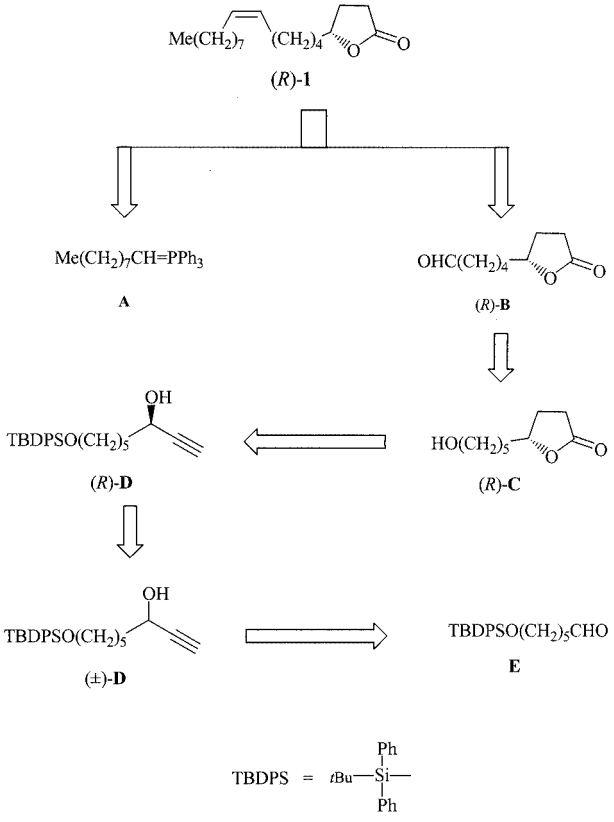
Enantiomer separation of (±)-8-*tert*-butyldiphenylsilyloxy-1-octyn-3-ol was achieved by lipase-mediated asymmetric acetylation. The resolved (*R*)-alkynol was converted into (4*R*,9Z)-9-octadecen-4-olide, which was identical with the female sex pheromone of the currant stem girdler (*Janus integer*). The absolute configuration of the natural pheromone was thus established as *R*. (4*S*,9Z)-9-Octadecen-4-olide was also synthesized, and found to be pheromonally inhibitory.

Introduction

In 2001 Cossé et al. isolated and identified (*Z*)-9-octadecen-4-olide (**1**, Scheme 1) as a female-specific and antennally active compound from the currant stem girdler, *Janus integer* Norton (Hymenoptera: Cephidae), which is an occasional pest of red currant in North America.[1] They synthesized (±)-**1**, whose sex pheromone properties were demonstrated by field experiments, and showed that the natural **1** contained only a single enantiomer as analyzed by GC on a chiral stationary phase.[1] In order to clarify the absolute configuration of the natural pheromone, we undertook the synthesis of both enantiomers of **1** with unambiguous stereochemistry. This paper describes the synthesis of (*R*)- and (*S*)-**1**, the former of which was proved to be the natural pheromone by GC comparison and field bioassay.

Scheme 1 shows our retrosynthetic analysis of (*R*)-**1**. The (*Z*)-double bond at C-9 of (*R*)-**1** can be constructed by (*Z*)-selective olefination[2] between Wittig reagent **A** and lactonic aldehyde (*R*)-**B**. The aldehyde (*R*)-**B** may be obtained by oxidation of the hydroxy lactone (*R*)-**C**. The key intermediate in the preparation of (*R*)-**C** is the acetylenic alcohol (*R*)-**D**, which is available by optical resolution of (±)-**D**. The acetylenic alcohol (±)-**D** can be prepared by ethynylation of the known aldehyde **E**.[3]

As to the key optical resolution, we proposed to employ biocatalysis.[4] As early as 1978, we attempted to use biocatalysis for the preparation of optically active acetylenic alcohols.[5] Asymmetric hydrolysis of the corresponding acetates of (±)-acetylenic alcohols with *Bacillus subtilis* var.



Scheme 1. Structure and retrosynthetic analysis of the female sex pheromone (*R*)-**1** of *Janus integer*

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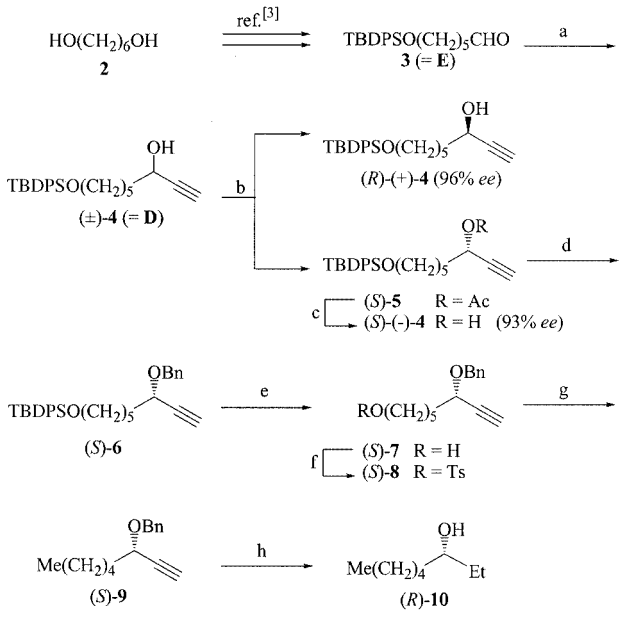
Niger, however, was not highly enantioselective.[5] At present, an appropriate lipase for asymmetric acetylation of (±)-acetylenic alcohols can be selected from commercially available lipases. Accordingly, we decided to adopt a biocatalytic approach, although there are several good methods[6] for chemical asymmetric synthesis of optically active **D**.

Results and Discussion

As shown in Scheme 2, the first stage of the synthesis was the preparation of (±)-**4**, its lipase-catalyzed asymmetric acetylation to give the recovered **4** and the acetylated **5**, and determination of the absolute configuration of the acetylated **5** as (*S*) by its conversion into a compound with known stereochemistry such as (*R*)-3-octanol (**10**). 1,6-Hexanediol (**2**) was converted into the known aldehyde **3** (= **E**) according to the procedure described by Posner and Johnson.[3] Addition of lithium acetylide ethylenediamine complex to **3** gave 8-*tert*-butyldiphenylsilyloxy-1-octyn-3-ol, (±)-**4**.



Scheme 2. Lipase-catalyzed asymmetric acetylation of (±)-**4**, and determination of the absolute configuration of the acetylated (*S*)-**5** by its conversion into (*R*)-**10**: reagents. (a) $HC{\equiv}CLi{\cdot}H_2N(CH_2)_2NH_2$, THF (62%); (b) Lipase AH-S (Amano), $CH_2{=}CHOAc$; SiO_2 chromatography [3 times, 29% for (*R*)-**4**]; (c) K_2CO_3, MeOH (24%, 2 steps × 2 times); (d) NaH, BnBr, THF, DMF (85%); (e) TBAF, THF (81%); (f) TsCl, C_5H_5N, DMAP, CH_2Cl_2 (89%); (g) $LiAlH_4$, THF (quant.); (h) H_2, 5% Pd-C, EtOH (33%)

Burgess and Jennings previously reported that asymmetric acetylation of 1-octyn-3-ol with lipases was not favorable to resolution, giving recovered (*R*)-1-octyn-3-ol of only 23% *ee*.[7] Nevertheless, we screened various lipases available in our laboratory (mainly Amano lipases) with the hope of achieving better resolution. Table 1 summarizes the results. Fortunately, lipase AH-S (Amano) afforded the recovered (+)-**4** with 82% *ee* even after a single acetylation in vinyl acetate.

Other promising but less satisfactory enzymes were lipase PS-C and lipase AK-20. However, the acetylations took place much more sluggishly with these two enzymes. As mentioned by Burgess,[7] we also experienced unfavorable resolution in the case of some simpler 1-alkyn-3-ols. Success in the case of (±)-**4** was presumably due to the presence of an extremely bulky *tert*-butyldiphenylsilyl (TBDPS) group at the terminal position of the alkyl group to make possible a better fit of (−)-**4** with the active site of lipase AH-S. In a preparative-scale experiment, the enzymatic acetylation with vinyl acetate and lipase AH-S was repeated three times to give (+)-**4** (96% *ee*) in 29% yield and the acetylated product **5**, which was treated with potassium carbonate in methanol to give (−)-**4** (93% *ee*) in 24% yield.

As to the absolute configuration of the recovered (+)-**4**, it was assumed to be (*R*) according to the empirical rule proposed by Burgess and Johnson.[7] This was verified by converting (−)-**4** to (−)-3-octanol with known (*R*) configuration.[8] (−)-Alcohol **4** of 70% *ee* was used for this experiment, and benzylated to furnish **6**. Removal of the TBDPS protective group of **6** was followed by tosylation of the resulting alcohol **7**. Reduction of tosylate **8** with lithium aluminum hydride gave **9**,[9] hydrogenolysis of which furnished (*R*)-(−)-3-octanol (**10**). Accordingly, the (*S*) configuration was assigned to **5**, (−)-**4**, **6**, **7**, **8** and **9**, and the recovered (+)-acetylenic alcohol **4** was (*R*)-**4**, as expected.

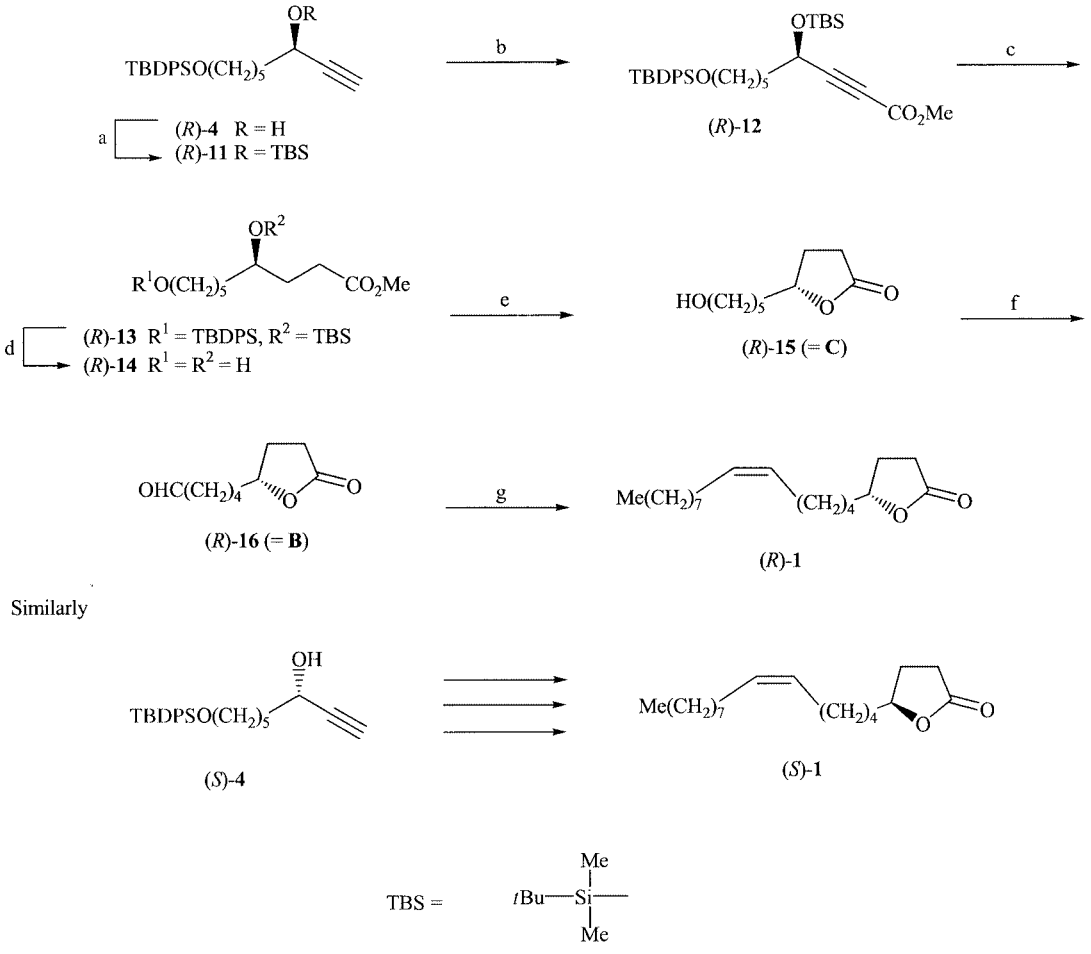
Scheme 3 summarizes the conversion of the alkynyl alcohol **4** to the desired lactone **1**. The free hydroxy group of (*R*)-**4** was first protected as the *tert*-butyldimethysilyl (TBS) ether to give (*R*)-**11**. Treatment of (*R*)-**11** with butyllithium and methyl chloroformate furnished acetylenic ester (*R*)-**12**. This ester was hydrogenated over Adams' platinum oxide to afford saturated ester (*R*)-**13**. Fortunately, no appreciable hydrogenolysis of the C−O bond at C-4 took place. Deprotection of the two silyl protective groups of (*R*)-**13** was achieved with tetrabutylammonium fluoride (TBAF) to give a mixture of hydroxy ester (*R*)-**14** and hydroxy lactone (*R*)-**15**. The mixture was subjected to alkaline hydrolysis with potassium hydroxide, and the resulting potassium salt of the hydroxy acid was acidified with hydrochloric acid to give hydroxy lactone (*R*)-**15**. Oxidation of (*R*)-**15** with pyridinium chlorochromate (PCC) afforded lactonic aldehyde (*R*)-**16**.

Finally, Wittig reaction of (*R*)-**16** with (triphenyl)nonylenephosphorane under Bestmann's salt-free conditions[2] furnished (4*R*,9*Z*)-9-octadecen-4-olide (**1**), $[\alpha]_D^{26} = +24$ (c = 0.50, $CHCl_3$). It showed IR, ^1H and ^{13}C NMR spectral properties and elemental analytical data in good agreement with the expected structure **1**. In particular, its mass spectrum was identical to the published spectrum of the natural **1**. Dr. A. Cossé kindly carried out the GC analysis of (*R*)-**1** under the reported conditions with a β-DEX 225 column,[1] and proved it to be highly pure (95.9% *ee*; *E*/*Z* = 1.6:98.4). More importantly, he found (*R*)-**1** to be the naturally occurring enantiomer. The overall yield of (*R*)-**1** was

Table 1. Screening of enzymes for asymmetric acetylation of (±)-**4**

Entry[a]	Enzyme[b]	Reaction time (h)	Enantiomeric purity (% *ee*) of (+)-**4**[c]
1	Lipase AH-S	22	82
2	Lipase AH	244	15
3	Lipase PS	246	no reaction
4	Lipase PS-C	101	71
5	Lipase PS-D	77	45
6	Lipase MY	197	20
7	Lipase AF-2	197	no reaction
8	Lipase AK-20	76	69
9	Lipase FAD-15	197	9

[a] All the reactions were carried out at room temperature (20−22 °C) employing neat vinyl acetate as the acetyl donor. [b] Enzymes were mainly the generous gift of Amano Enzyme Inc. [c] Determined by HPLC analysis on Chiralcel-OD® (see Exp. Sect.).



Scheme 3. Synthesis of the enantiomers of (*Z*)-9-octadecen-4-olide (**1**): reagents: (a) TBSCl, imidazole, DMF (94%); (b) BuLi, $ClCO_2Me$, THF (94%), (c) H_2, PtO_2, hexane (89%), (d) TBAF, THF; (e) 1) KOH, MeOH, H_2O; 2) dil. HCl (79%; 3 steps); (f) PCC, 4-Å molecular sieves, CH_2Cl_2 (68%); (g) $Me(CH_2)_8PPh_3Br$, NaHMDS, hexane, THF, −100 °C (68%)

5.1% based on **3** (nine steps). Similarly (*S*)-**1** (94.9% *ee*; *E*/*Z* = 1.6:98.4), $[\alpha]_D^{25} = -23$ (*c* = 1.00, $CHCl_3$), was synthesized from (*S*)-**4** in 6.7% overall yield (10 steps).

In conclusion, both the enantiomers of (*Z*)-9-octadecen-4-olide (**1**) were synthesized, and (*R*)-**1** was identical to the natural pheromone by GC comparison. Lipase AH-S was found to be an appropriate enzyme for asymmetric acetylation of the acetylenic alcohol (*S*)-**4**. Field bioassay of the enantiomers of **1** in the USA revealed (*R*)-**1** to be pheromonally active, while (*S*)-**1** was found to be a pheromone

inhibitor, making (±)-**1** only ca. 10% as active as (*R*)-**1**. It should be added that Bohlmann and Abraham reported in 1979 the isolation of (−)-9-octadecen-4-olide [(*S*)-**1**] from the aerial parts of a South African plant, *Helichrysum hypocepharum* (Compositae).[10] Their ^{1}H NMR spectroscopic data for (−)-**1** coincided with ours. The plant thus produces the opposite (*S*)-enantiomer of the (*R*)-pheromone [(*R*)-**1**] of *Janus integer*.

Experimental Section

General Remarks: IR: Jasco FT/IR-460 Plus. ^{1}H NMR: Jeol EX-90A (90 MHz), JNM-AL300 (300 MHz), JNM-LA400 (400 MHz) or JNM-LA500 (500 MHz), with $CHCl_3$ at δ = 7.26 ppm used as the internal standard. ^{13}C NMR: JNM-LA400 (100 MHz), with $CHCl_3$ at δ = 77.0 ppm used as the internal standard. MS: Hitachi M-80B. Refractive index (n_D): Atago DMT-1 refractometer. Optical rotation: Jasco DIP-1000 polarimeter.

(±)-8-*tert*-Butyldiphenylsilyloxy-1-octyn-3-ol [(±)-4]: A solution of (±)-**3**[3] (11.5 g, 32.5 mmol) in dry THF (120 mL) was added to a stirred suspension of 90% HC≡CLi·$H_2N(CH_2)_2NH_2$ (16.6 g, 162 mmol) in dry THF (150 mL) at room temperature under argon. After stirring for 1.5 h at room temperature, the mixture was poured into a saturated aqueous $NaHCO_3$ solution and water, and the resulting mixture was extracted with Et_2O. The combined extract was successively washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (250 g, hexane/EtOAc, 20:1) to give 7.56 g of (±)-**4** (62%) as a colorless oil, n_D^{25} = 1.5167. IR (film): $\tilde{\nu}_{max.}$ = 3395 (m, O−H), 3305 (m, C≡C−H), 1110(s, Si−O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (s, 9 H, TBDPS), 1.20−1.89 (m, 9 H, 4-H, 5-H, 6-H, 7-H, OH), 2.46 (d, *J* = 1.5 Hz, 1 H, 1-H), 3.66 (t, *J* = 6.3 Hz, 2 H, 8-H), 4.35 (dt, *J* = 1.5, 6.6 Hz, 1 H, 3-H), 7.26−7.44 (m, 6 H, TBDPS), 7.65−7.68 (m, 4 H, TBDPS) ppm. $C_{24}H_{32}O_2Si$ (380.6): calcd. C 75.74, H 8.47; found C 75.64, H 8.82.

(*R*)-8-*tert*-Butyldiphenylsilyloxy-1-octyn-3-ol [(*R*)-4] and (*S*)-8-*tert*-Butyldiphenylsilyloxy-1-octyn-3-ol [(*S*)-4]: Lipase AH-S (2.00 g) was added to a solution of (±)-**4** (10.0 g, 26.4 mmol) in vinyl acetate (600 mL), and the mixture was stirred for 22 h at room temperature. The enzyme was filtered off through a Celite pad and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (200 g, hexane/EtOAc, 20:1) to give crude (*R*)-**4** (5.03 g, 50%) and (*S*)-6-acetoxy-1-*tert*-butyldiphenylsilyloxy-7-octyne [(*S*)-**5**] (5.45 g, 49%). The crude (*R*)-**4** was acetylated according to this procedure twice more to give 2.94 g of (*R*)-**4** [total for all three times; 29% based on (±)-**4**] as a colorless oil. K_2CO_3 (2.67 g, 19.4 mmol) was added to a solution of (*S*)-**5** (5.45.g, 12.9 mmol) in MeOH (50 mL). After stirring for 2 h at room temperature, the mixture was poured into water and extracted with Et_2O. The combined extract was successively washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (100 g, hexane/EtOAc, 20:1) to give 4.55 g (93%) of (*S*)-**4** as a colorless oil. This was resolved once more according to the same procedure as that described for the enzymatic resolution and methanolysis to give 2.40 g of (*S*)-**4** [2 steps × 2 times, 24%, based on (±)-**4**] as a colorless oil. (*R*)-**4**: n_D^{25} = 1.5172. $[\alpha]_D^{26}$ = −0.5 (*c* = 1.18, $CHCl_3$). $C_{24}H_{32}O_2Si$ (380.6): calcd. C 75.74, H 8.47; found C 75.50, H 8.69. Its IR and NMR spectra were identical to those of (±)-**4**. The enantiomeric purity of (*R*)-**4** was estimated to be 96.4% *ee* by HPLC analysis (column: Chiralcel OD® 4.6 mm × 25 cm; solvent: hexane/ethanol, 90:1; flow rate: 0.45 mL/min; detection at 254 nm); t_R 36.1 min (98.2%) [(*S*)-**4**: t_R 39.5 min (1.8%)]. (*S*)-**4**: n_D^{26} = 1.5166. $[\alpha]_D^{26}$ = +0.5 (*c* = 1.12, $CHCl_3$). $C_{24}H_{32}O_2Si$ (380.6): calcd. C 75.74, H 8.47; found C 75.52, H 8.53. Its IR and NMR spectra were identical to those of (±)-**4**. Following the same procedure as for the analysis of (*R*)-**4**, enantiomeric purity of (*S*)-**4** was determined as 93.4% *ee*. t_R 39.5 min (95.7%) [(*R*)-**4**: t_R 36.7 min (3.2%)].

(*S*)-3-Benzyloxy-8-*tert*-butyldiphenylsilyloxy-1-octyne [(*S*)-6]: NaH (60% suspension in mineral oil, 30 mg, 0.94 mmol) was added to a stirred and ice-cooled solution of (*S*)-**4** (70% *ee*, 190 mg, 0.50 mmol) in THF (3 mL) and *N*,*N*-dimethylformamide (DMF, 1 mL). Benzyl bromide (169 mg, 0.98 mmol) was then added dropwise to the mixture at 0 °C. After stirring for 3 h at room temperature, the mixture was poured into water, and extracted with EtOAc. The combined organic phases were successively washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (6.0 g, hexane/EtOAc, 40:1) to give 200 mg (85%) of (*S*)-**6** as a colorless oil, n_D^{25} = 1.5177. $[\alpha]_D^{25}$ = −40 (*c* = 0.91, $CHCl_3$). IR (film): $\tilde{\nu}_{max.}$ = 3305 (w, C≡C−H), 1110 (s, Si−O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (s, 9 H, *t*Bu), 1.34−1.54 (m, 6 H, 2-H, 3-H, 4-H), 1.56−1.80 (m, 2 H, 5-H), 2.46 (d, *J* = 2.1 Hz, 1 H, 8-H), 3.64 (t, *J* = 6.3 Hz, 2 H, 1-H), 4.05 (dt, *J* = 2.1, 4.5 Hz, 1 H, 6-H), 4.49 (d, *J* = 11 Hz, 1 H, OC*H*$_2$Ph), 4.80 (d, *J* = 11 Hz, 1 H, OC*H*$_2$Ph), 7.34−7.42 (m, 9 H, OCH$_2$*Ph*, TBDPS), 7.64−7.67 (m, 4 H, TBDPS) ppm. $C_{31}H_{38}O_2Si$ (470.7): calcd. C 79.10, H 8.14; found C 78.80, H 8.34.

(*S*)-6-Benzyloxy-7-octyn-1-ol [(*S*)-7]: A solution of TBAF in THF (1.0 M, 690 μL, 0.69 mmol) was added to a stirred and ice-cooled solution of (*S*)-**6** (250 mg, 0.53 mmol) in THF (3 mL). After stirring for 12 h at room temperature, the mixture was poured into ice water and extracted with EtOAc. The combined organic phases were successively washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (5.0 g, hexane/EtOAc, 10:1) to give 100 mg (81%) of (*S*)-**7** as a colorless oil, n_D^{23} = 1.5151. $[\alpha]_D^{26}$ = −86 (*c* = 1.00, $CHCl_3$). IR (film): $\tilde{\nu}_{max.}$ = 3365 (s, O−H), 3290 (w, C≡C−H), 1070(s, Si−O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.37 (quintet, *J* = 7.6 Hz, 2 H, 3-H), 1.47−1.60 (m, 4 H, 2-H, 4-H), 1.71−1.83 (m, 2 H, 5-H), 2.47 (d, *J* = 1.5 Hz, 1 H, 8-H), 3.63 (q, *J* = 6.1 Hz, 2 H, 1-H), 4.08 (dt, *J* = 6.4, 1.5 Hz, 1 H, 6-H), 4.50 (d, *J* = 8.9 Hz, 1 H, OC*H*$_2$Ph), 4.80 (d, *J* = 8.9 Hz, 1 H, OC*H*$_2$Ph), 7.28−7.36 (m, 5 H, OCH$_2$*Ph*) ppm. $C_{15}H_{20}O_2$ (232.3): calcd. C 77.55, H 8.68; found C 77.26, H 8.81.

(*S*)-6-Benzyloxy-7-octynyl Tosylate [(*S*)-8]: Pyridine (42 μL, 0.53 mmol), DMAP (15 mg, 0.12 mmol) and TsCl (116 mg, 0.61 mmol) were added to a stirred and ice-cooled solution of (*S*)-**7** (75 mg, 0.32 mmol) in CH_2Cl_2 (2 mL). After stirring for 17 h at 4 °C, the mixture was poured into water and extracted with EtOAc. The combined organic phases were successively washed with 1 M HCl, saturated aqueous $NaHCO_3$ solution and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (3.0 g, hexane/EtOAc, 30:1) to give 111 mg (89%) of (*S*)-**8** as a colorless oil, n_D^{23} = 1.5178. $[\alpha]_D^{26}$ = −52 (*c* = 1.00, $CHCl_3$). IR (film): $\tilde{\nu}_{max.}$ = 3285 (w, C≡C−H), 1360 (s, S=O), 1175 (s, S=O), 1070 (s, Si−O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30−1.73 (m, 8 H, 2-H, 3-H, 4-H, 5-H), 2.44 (s, 3 H, Ar-*Me*), 2.46 (d, *J* = 2.1 Hz, 1 H, 8-H), 4.01 (t, *J* = 6.6 Hz, 2 H, 1-H), 3.99−4.03 (m, 1 H, 6-H), 4.48 (d, *J* = 12 Hz, 1 H, OC*H*$_2$Ph), 4.79 (d, *J* = 12 Hz, 1 H, OC*H*$_2$Ph), 7.32−7.34 (m, 7 H, OCH$_2$*Ph*, *Ar*-Me), 7.78 (d, *J* = 8.4 Hz, 2 H, *Ar*-Me) ppm. $C_{22}H_{26}O_4S_2$ (386.5): calcd. C 68.37, H 6.78; found C 68.26, H 6.86.

(*S*)-3-Benzyloxy-1-octyne [(*S*)-9]: A solution of (*S*)-**8** (100 mg, 0.26 mmol) in THF (2 mL) was added dropwise to a stirred and ice-cooled suspension of $LiAlH_4$ (39 mg, 1.03 mmol) in THF (3 mL). After stirring under reflux for 0.5 h, the reaction mixture was cooled to 0 °C. Water (0.1 mL), 15% aqueous NaOH solution (0.1 mL) and water (0.1 mL) were added to the mixture, and it was filtered through a Celite pad. The filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (3.0 g, hexane/EtOAc, 60:1) to give 56 mg (quant.) of (*S*)-**9** as a colorless oil, n_D^{22} = 1.4929. $[\alpha]_D^{23}$ = −49 (*c* = 0.55, $CHCl_3$). IR (film): $\tilde{\nu}_{max.}$ = 3305 (w, C≡C−H), 1090 (s, C−O−C) cm^{-1}. ref.[9] $[\alpha]_D^{25}$ = −49.2 (*c* = 0.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.2 Hz, 3 H, 8-H), 1.23−1.52 (m, 6 H, 5-H, 6-H, 7-H), 1.69−1.81 (m, 2 H, 4-H), 2.47 (d, *J* = 2.1 Hz, 1 H, 1-H), 4.07 (dt, *J* = 2.1, 6.6 Hz, 1 H, 3-H), 4.51 (d, *J* = 12 Hz, 1 H, OCH_2Ph) 4.81 (d, *J* = 12 Hz, 1 H, OCH_2Ph), 7.28−7.36 (m, 5 H, OCH_2Ph) ppm. Its IR and NMR spectra were identical to those in ref.[9] $C_{15}H_{20}O$ (216.3): calcd. C 83.28, H 9.32; found C 83.15, H 9.54.

(*R*)-3-Octanol [(*R*)-10]: A solution of (*S*)-**9** (57 mg, 0.26 mmol) in EtOH (1 mL) was shaken under a H_2 atmosphere in the presence of 5% Pd-C (15 mg) for 21 h at room temperature. The catalyst was removed by filtration through a Celite pad, and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (5.0 g, hexane/EtOAc, 30:1) to give 11 mg (33%) of (*R*)-**10** as a colorless oil, n_D^{23} = 1.4218 (ref.[8] n_D^{22} = 1.4222). $[\alpha]_D^{22}$ = −6.5 (*c* = 0.15, $CHCl_3$). [ref.[8] $[\alpha]_D^{22}$ = −9.7 (*c* = 0.93, $CHCl_3$)]. Its IR and NMR spectra were identical to those in ref.[8]

(*R*)-3-*tert*-Butyldimethylsilyloxy-8-*tert*-butyldiphenylsilyloxy-1-octyne [(*R*)-11]: TBSCl (1.17 g, 7.77 mmol) was added to a stirred and ice-cooled solution of (*R*)-**4** (2.69 g, 7.07 mmol) and imidazole (529 mg, 7.77 mmol) in DMF (30 mL). After stirring for 22 h at room temperature, the mixture was poured into water and extracted with Et_2O. The combined extract was successively washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (100 g, hexane/EtOAc, 50:1) to give 3.29 g (94%) of (*R*)-**11** as a colorless oil, n_D^{26} = 1.5090. $[\alpha]_D^{26}$ = +19 (*c* = 0.82, $CHCl_3$). IR (film): $\tilde{\nu}_{max.}$ = 3310 (w, C≡C−H), 1110 (s, Si−O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.11 (s, 3 H, TBS), 0.13 (s, 3 H, TBS), 0.90 (s, 9 H, TBS), 1.05 (s, 9 H, TBDPS), 1.41−1.68 (m, 8 H, 2-H, 3-H, 4-H, 5-H), 2.37 (d, *J* = 1.9 Hz, 1 H, 8-H), 3.66 (t, *J* = 6.3 Hz, 2 H, 1-H), 4.32 (dt, *J* = 1.9, 6.4 Hz, 1 H, 6-H), 7.35−7.42 (m, 6 H, TBDPS), 7.65−7.68 (m, 4 H, TBDPS) ppm. $C_{30}H_{46}O_2Si_2$ (494.9): calcd. C 72.81, H 9.37; found C 73.08, H 9.63.

(*S*)-3-*tert*-Butyldimethylsilyloxy-8-*tert*-butyldiphenylsilyloxy-1-octyne [(*S*)-11]: Using the method described for the preparation of (*R*)-**11**, (*S*)-**4** (540 mg, 1.41 mmol) yielded 648 mg (quant.) of (*S*)-**11** as a colorless oil, n_D^{26} = 1.5110. $[\alpha]_D^{26}$ = −20 (*c* = 1.01, $CHCl_3$). $C_{30}H_{46}O_2Si_2$ (494.9): calcd. C 72.81, H 9.37; found C 72.78, H 9.47. Its IR and NMR spectra were identical to those of (*R*)-**11**.

Methyl (*R*)-4-*tert*-Butyldimethylsilyloxy-9-*tert*-butyldiphenylsilyloxy-2-nonynoate [(*R*)-12]: A solution of *n*BuLi in hexane (1.55 M, 8.46 mL, 13.1 mmol) was added to a stirred and cooled solution of (*R*)-**11** (3.23 g, 6.53 mmol) in THF (30 mL) at −78 °C under argon. After stirring for 30 min at −78 °C, $ClCO_2Me$ (1.01 mL, 13.1 mmol) was added dropwise. The mixture was allowed to warm to room temperature with stirring for 3 h. It was then quenched with water and extracted with Et_2O. The combined extracts were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (100 g, hexane/EtOAc, 75:1) to give 3.38 g (94%) of (*R*)-**12** as a colorless oil, n_D^{26} = 1.5062. $[\alpha]_D^{26}$ = +10 (*c* = 1.01, $CHCl_3$). IR (film): $\tilde{\nu}_{max.}$ = 2235 (m, C≡C), 1720 (C=O), 1250 [s, C(=O)−O], 1110 cm^{-1} (s, Si−O). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.11 (s, 3 H, TBS), 0.15 (s, 3 H, TBS), 0.91 (s, 9 H, TBS), 1.05 (s, 9 H, TBDPS), 1.24−1.70 (m, 6 H, 5-H, 6-H, 7-H, 8-H), 3.65 (t, *J* = 6.3 Hz, 2 H, 9-H), 3.77 (s, 3 H, CO_2Me), 4.43 (t, *J* = 6.6 Hz, 1 H, 4-H), 7.35−7.42 (m, 6 H, TBDPS), 7.65−7.68 (m, 4 H, TBDPS) ppm. $C_{32}H_{48}O_4Si_2$ (552.9): calcd. C 69.51, H 8.75; found C 69.48, H 9.07. This was employed in the next step without further purification.

Methyl (*S*)-4-*tert*-Butyldimethylsilyloxy-9-*tert*-butyldiphenylsilyloxy-2-nonynoate [(*S*)-12]: Using the method described for the preparation of (*R*)-**12**, (*S*)-**11** (668 mg, 1.34 mmol) yielded 746 mg (quant.) of (*S*)-**12** as a colorless oil, n_D^{25} = 1.5082. $[\alpha]_D^{25}$ = −19 (*c* = 1.00, $CHCl_3$). This value was not consistent with that of (*R*)-**12**. The reason could not be clarified. $C_{32}H_{48}O_4Si_2$ (552.9): calcd. C 69.51, H 8.75; found C 69.45, H 8.75. Its IR and NMR spectra were identical to those of (*R*)-**12**. This was employed in the next step without further purification.

Methyl (*R*)-4-*tert*-Butyldimethylsilyloxy-9-*tert*-butyldiphenylsilyloxy-2-nonanoate [(*R*)-13]: A solution of (*R*)-**12** (92 mg, 0.17 mmol) in hexane (1 mL) was shaken under a H_2 atmosphere in the presence of PtO_2 (1 mg) for 22 h at room temperature. The catalyst was removed by filtration through a Celite pad, and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (3.0 g, hexane/EtOAc, 75:1) to give 82 mg (89%) of (*R*)-**13** as a colorless oil, n_D^{26} = 1.5064. $[\alpha]_D^{26}$ = −5.4 (*c* = 1.04, $CHCl_3$). IR (film): $\tilde{\nu}_{max.}$ = 1740 (s, C=O), 1255 [s, C(=O)−O], 1110 (s, Si−O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.41 (s, 3 H, TBS), 0.45 (s, 3 H, TBS), 0.89 (s, 9 H, TBS), 1.06 (s, 9 H, TBDPS), 1.26−1.81 (m, 10 H, 3-H, 5-H, 6-H, 7-H, 8-H), 2.29−2.39 (m, 2 H, 2-H), 3.66 (t, *J* = 6.4 Hz, 2 H, 9-H) 3.68 (s, 3 H, CO_2Me), 3.65−3.70 (m, 1 H, 4-H), 7.27−7.44 (m, 6 H, TBDPS), 7.67−7.69 (m, 4 H, TBDPS) ppm. $C_{32}H_{52}O_4Si_2$ (556.9): calcd. C 69.01, H 9.41; found C 69.29, H 9.62.

Methyl (*S*)-4-*tert*-Butyldimethylsilyloxy-9-*tert*-butyldiphenylsilyloxy-2-nonanoate [(*S*)-13]: Using the method described for the preparation of (*R*)-**13**, (*S*)-**12** (700 mg, 1.26 mmol) yielded 698 mg of (*S*)-**13** (99%) as a colorless oil, n_D^{23} = 1.5063. $[\alpha]_D^{23}$ = +5.5 (*c* = 0.20, $CHCl_3$). $C_{32}H_{52}O_4Si_2$ (556.9): calcd. C 69.01, H 9.41; found C 69.04, H 9.64. Its IR and NMR spectra were identical to those of (*R*)-**13**.

(*R*)-9-Hydroxy-4-nonanolide [(*R*)-15]: A solution of TBAF in THF (1.0 M, 5.39 mL, 5.39 mmol) was added to a stirred and ice-cooled solution of (*R*)-**13** (1.00 g 1.80 mmol) in THF (10 mL). After stirring for 20 h at room temperature, the mixture was poured into ice water and extracted with EtOAc. The combined extracts were washed with brine, dried with $MgSO_4$, and concentrated in vacuo to give 800 mg of a crude mixture of (*R*)-**14** and (*R*)-**15** as a colorless oil. This was employed in the next step without further purification. A solution of KOH (151 mg, 2.70 mmol) in water (2 mL) was added to a stirred and ice-cooled solution of the crude mixture of (*R*)-**14** and (*R*)-**15** (800 mg) in MeOH (10 mL). After stirring for 30 min at room temperature, it was evaporated to remove MeOH and brought to pH 2 with 3 M HCl. The mixture was stirred at room temperature for 2 h, and then extracted with Et_2O. The combined extracts were successively washed with saturated aqueous $NaHCO_3$ solution and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (50 g, hexane/EtOAc, 10:1) to give 244 mg (2 steps, 79%) of (*R*)-**15** as a colorless oil, n_D^{26} = 1.4680. $[\alpha]_D^{26}$ = +36 (*c* = 1.08, $CHCl_3$). IR (film): $\tilde{\nu}_{max.}$ = 3405 (s, O−H), 1760 (s, C=O), 1190 [s, C(=O)−O] cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25−1.90 (m, 10 H, 3-H, 5-H, 6-H, 7-H, 8-H, OH), 2.33 (ddt, *J* = 6.1, 7.3, 19.3 Hz, 1 H, 3-H), 2.54 (dd, *J* = 7.3, 9.3 Hz, 2 H, 2-H), 3.65 (t, *J* = 6.6 Hz, 2 H, 9-H), 4.49 (quint, *J* = 6.1 Hz, 1 H, 4-H) ppm. $C_9H_{16}O_3$ (172.2): calcd. C 62.77, H 9.36; found C 62.65, H 9.09.

(*S*)-9-Hydroxy-4-nonanolide [(*S*)-15]: Using the method described for the preparation of (*R*)-**15**, (*S*)-**13** (660 mg, 1.19 mmol) yielded 134 mg (2 steps, 66%) of (*S*)-**15** as a colorless oil, n_D^{25} = 1.4681. $[\alpha]_D^{25}$ = −36 (*c* = 1.08, $CHCl_3$). $C_9H_{16}O_3$ (172.2): calcd. C 62.77, H 9.36; found C 62.54, H 9.38. Its IR and NMR spectra were identical to those of (*R*)-**15**.

(*R*)-9-Oxo-4-nonanolide [(*R*)-16]: PCC (84 mg, 0.39 mmol) was added to a stirred and ice-cooled suspension of powdered molecular sieves 4 Å (20 mg) in a solution of (*R*)-**15** (53 mg, 0.30 mmol) in dry CH_2Cl_2 (1 mL). After stirring for 1.5 h at room temperature, the mixture was diluted with Et_2O and filtered through silica gel (2 g), and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (1.0 g, hexane/EtOAc, 20:1) to give 36 mg (68%) of (*R*)-**16** as a colorless oil, n_D^{26} = 1.4749. $[\alpha]_D^{26}$ = +53 (*c* = 0.64, $CHCl_3$). IR (film): $\tilde{\nu}_{max.}$ = 2725 [m, C(=O)−H], 1770 (s, C=O), 1720 [C(=O)−H], 1180 [s, C(=O)−O] cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.39−1.88 (m, 9 H, 3-H, 5-H, 6-H, 7-H, 8-H), 2.32 (ddt, *J* = 6.7, 7.3, 20.2 Hz, 1 H, 3-H), 2.47 (dt, *J* = 1.5, 7.5 Hz, 2 H, 9-H), 2.52 (dd, *J* = 7.3, 9.5 Hz, 2 H, 2-H), 4.48 (quint. like, *J* = 6.7 Hz, 1 H, 4-H), 9.77 (t, *J* = 1.5 Hz, 1 H, CHO). This was employed in the next step without further purification.

(*S*)-9-Oxo-4-nonanolide [(*S*)-16]: Using the method described for the preparation of (*R*)-**16**, (*S*)-**15** (50 mg, 0.29 mmol) yielded 39 mg (80%) of (*S*)-**16** as a colorless oil, n_D^{26} = 1.4659. $[\alpha]_D^{26}$ = −41 (*c* = 1.04, $CHCl_3$). This value was not consistent with that of (*R*)-**16**. The reason could not be clarified. Its IR and NMR spectra were identical to those of (*R*)-**16**. This was employed in the next step without further purification.

(4*R*,9*Z*)-9-Octadecen-4-olide [(*R*)-1]: A solution of $NaN(SiMe_3)_2$ in toluene (1.0 M, 8.09 mL, 8.09 mmol) was added to a stirred suspension of dry nonyltriphenylphosphonium bromide (5.22 g, 10.8 mmol) in dry hexane (50 mL) and the mixture was stirred and refluxed for 3 h under argon. The resulting orange solution was transferred to another flask through a cannula under argon, and was added dropwise to a solution of (*R*)-**16** (90 mg, 0.53 mmol) in dry THF (2 mL) at −100 °C under argon. The reaction mixture was allowed to warm to room temperature with stirring for 30 min, then quenched with a saturated aqueous NH_4Cl solution, and extracted with Et_2O. The combined extracts were successively washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (20 g, hexane/EtOAc, 40:1) to give 110 mg (68%) of (*R*)-**1** as a colorless oil, n_D^{26} = 1.4706. $[\alpha]_D^{26}$ = +24 (*c* = 0.50, $CHCl_3$). IR (film): $\tilde{\nu}_{max.}$ = 2925 (s, C−H), 2855 (s, C−H), 1780 (s, C=O), 1460 (m, CH_2), 1385 (w, C−H) 1350 (w, C−H), 1175 [s, C(=O)−O), 1020 (w, C−H), 915 (w, C−H), 720 (w, CH_2) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.0 Hz, 3 H, 18-H), 1.27−1.76 (m, 19 H, 3-H, 5-H, 6-H, 7-H, 12-H, 13-H, 14-H, 15-H, 16-H, 17-H), 1.81−1.89 (m, 1 H, 3-H), 1.99−2.06 (m, 4 H, 8-H, 11-H), 2.32 (ddt, *J* = 6.5, 7.5, 13 Hz, 1 H, 3-H), 2.53 (ddd, *J* = 1.3, 7.5, 9.2 Hz, 2 H, 2-H), 4.48 (quint, *J* = 6.5 Hz, 1 H, 4-H), 5.35 (dtt, *J* = 7.1, 12, 18 Hz, 2 H, 9-H, 10-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.10, 14.11, 22.7, 24.9, 27.0, 27.2, 28.0, 28.9, 29.3, 29.4, 29.5, 29.7, 31.9, 35.5, 81.0, 129.1, 130.5, 177.3 ppm. MS (EI, 70 eV): *m*/*z* (%) = 41 (94), 55 (93), 67 (100), 81 (100), 95 (79), 109 (44), 122 (30), 136 (44), 154 (30), 168 (12), 181 (7), 207 (7), 220 (17), 280 (40) [M$^+$] $C_{18}H_{32}O_2$ (280.5): calcd. C 77.09, H 11.50; found C 77.21, H 11.42. The enantiomeric excess of (*R*)-**1** was determined as 95.9% *ee* and the *E*/*Z* ratio was 1.6:98.4 by GC analysis (Dr. A. Cossé).

(4*S*,9*Z*)-9-Octadecen-4-olide [(*S*)-1]: Using the method described for the preparation of (*R*)-**1**, (*S*)-**16** (39 mg, 0.29 mmol) yielded 55 mg (86%) of (*S*)-**1** as a colorless oil, n_D^{26} = 1.4681. $[\alpha]_D^{26}$ = −23 (*c* = 1.00, $CHCl_3$). Its IR and NMR and MS spectra were identical to those of (*R*)-**1**. $C_{18}H_{32}O_2$ (280.5): calcd. C 77.09, H 11.50; found C 76.82, H 11.79. The enantiomeric excess of (*S*)-**1** was determined as 94.9% *ee* and the *E*/*Z* ratio was 1.6:98.4 by GC analysis (Dr. A. Cossé).

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