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Pheromone synthesis. Part 244: Synthesis of the racemate and enantiomers of (11*Z*,19*Z*)-CH503 (3-acetoxy-11,19-octacosadien-1-ol), a new sex pheromone of male *Drosophila melanogaster* to show its (*S*)-isomer and racemate as bioactive☆

Kenji Mori [a,*], Yasumasa Shikichi [a], Shruti Shankar [b,c], Joanne Y. Yew [b,c,*]

[a] *Photosensitive Materials Research Center, Toyo Gosei Co., Ltd, Wakahagi 4-2-1, Inzai-shi, Chiba 270-1609, Japan*
[b] *Temasek Life Sciences Laboratory, 1 Research Link, National University of Singapore, Singapore 117604*
[c] *Department of Biological Sciences, 14 Science Drive 4, National University of Singapore, Singapore 117546*

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Jacobsen's hydrolytic kinetic resolution (HKR) of epoxide
Pheromone

ABSTRACT

The enantiomers of (11*Z*,19*Z*)-3-acetoxy-11,19-octacosadien-1-ol were synthesized from the enantiomers of 3,4-epoxy-1-butanol PMB ether. Its racemate was also synthesized. Its (*S*)-isomer and racemate were shown to possess the same pheromone activity as CH503, a long-lived inhibitor of male courtship in *Drosophila melanogaster*, although the racemate was less active.

1. Introduction

In many species of insects, chemical communication is mediated by hydrocarbons found on the surface of their cuticles. In the fruit fly *Drosophila melanogaster*, the characteristic female compounds, (7*Z*,11*Z*)-7,11-pentacosadiene, (7*Z*,11*Z*)-7,11-heptacosadiene and (7*Z*,11*Z*)-7,11-nonacosadiene, serve as attractant for males (Fig. 1).[2] In addition, the volatile male-specific pheromone (*Z*)-vaccenyl acetate [(*Z*)-11-octadecenyl acetate] promotes male–male aggression in *D. melanogaster*.[3]

In 2009 Yew et al. isolated and identified 3-acetoxy-11,19-octacosadien-1-ol (**1**, Fig. 1) as a male-produced and long-lived pheromone named CH503 that inhibits male courtship.[4] This compound is transferred from males to females during mating, and remains on the surface of females for at least ten days. Therefore, after mating, female attractiveness to males decreases and remains depressed for nine to ten days. Unfortunately, the geometries of the two double bonds as well as the absolute configuration at C-3 of **1** remained unknown.

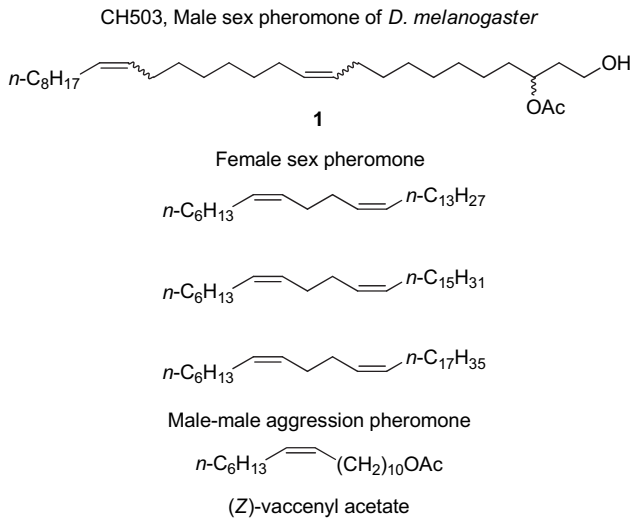

Figure 1. Structure **1** proposed for a new male sex pheromone CH503 of *D. melanogaster* and the structures of known pheromones of *D. melanogaster*.

☆ For Part 243, see Ref. 1.

* Corresponding authors. Tel.: +81 3 3816 6889; fax: +81 3 3813 1516 (K.M.); fax: +65 6872 7554 (J.Y.Y.); e-mail addresses: kjk-mori@arion.ocn.ne.jp (K. Mori), joanne@tll.org.sg (J.Y. Yew).

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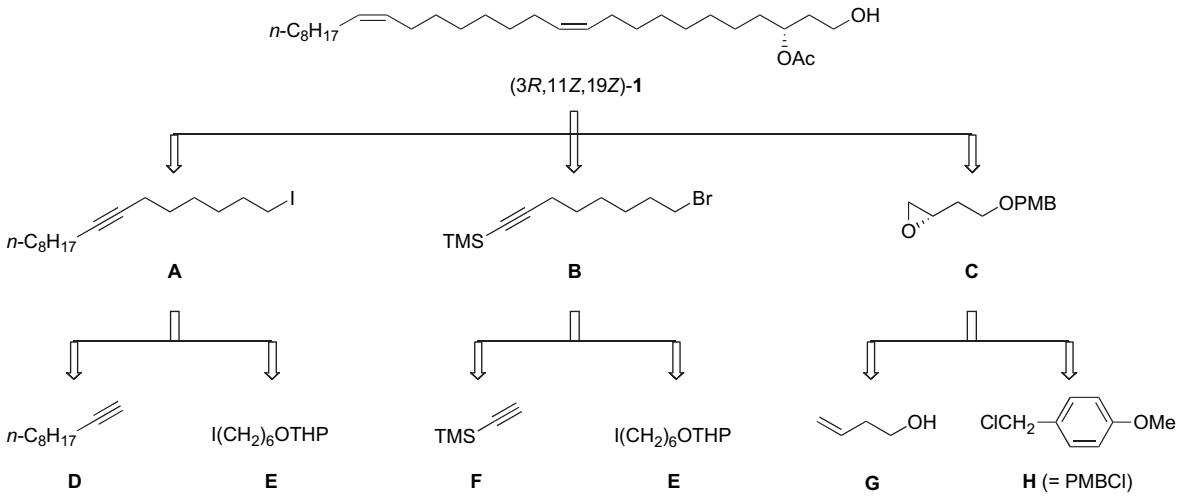
In continuation of our long-term studies on the absolute configuration of pheromones,[5] we became interested in synthesizing **1** with known geometries and absolute configuration so as to establish the stereochemistry of the naturally occurring CH503. Since *Z*-disubstituted alkenes are more prevailing among insects including *D. melanogaster* as shown in Figure 1, we decided to synthesize the racemate and enantiomers of (11*Z*,19*Z*)-3-acetoxy-11,19-octacosadien-1-ol (**1**).

Scheme 1 shows our retrosynthetic analysis of (3*R*,11*Z*,19*Z*)-**1**. The molecule **1** can be dissected into three building blocks **A**, **B**, and **C**. The two acetylenic building blocks **A** and **B** would be synthesized from each two starting materials **D**, **E** and **F**, **E**, respectively. The optically active epoxide **C** would be prepared by Jacobsen's hydrolytic kinetic resolution (HKR)[6–8] of (±)-**C**, which would be synthesized from **G** and **H**. This plan was realized as detailed in the present paper, and (3*S*,11*Z*,19*Z*)-**1** was definitely bioactive, while (3*RS*,11*Z*,19*Z*)-**1** was less bioactive.



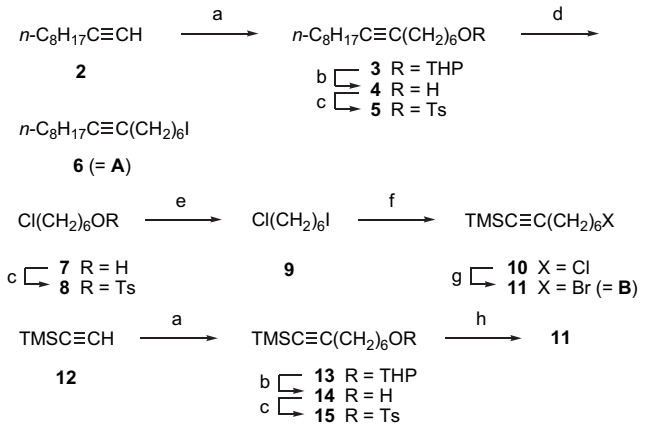
Scheme 1. Retrosynthetic analysis of (*R*)-**1**.

2. Results and discussion

2.1. Synthesis of the building blocks A (=6) and B (=11)

Scheme 2 summarizes the synthesis of the building blocks **A** (=**6**) and **B** (=**11**). 7-Hexacosynyl iodide (**6**), the building block **A**, was prepared from commercially available 1-decyne (**2**). Alkylation of **2** with *n*-butyllithium and 6-tetrahydropyranyloxyhexyl iodide afforded **3**, which was deprotected to give 7-hexacosyn-1-ol (**4**). The corresponding tosylate **5** was treated with sodium iodide to give the desired building block **6** (=**A**) in 48% overall yield based on **2** (four steps).

8-Trimethylsilyl-7-octynyl bromide (**11**), the building block **B**, was prepared in two different manners. Firstly, commercially available 6-chloro-1-hexanol (**7**) was converted to 6-chlorohexyl iodide (**9**) via tosylate **8**. Alkylation of trimethylsilyl(TMS)acetylene (**12**) with *n*-butyllithium and **9** gave chloride **10**, which was treated with lithium bromide to give **11**. The product **11** by this route, however, was a mixture of **10**, **11** and the corresponding iodide. Pure **11** could be prepared by the second route starting from TMS acetylene (**12**). Alkylation of **12** with *n*-butyllithium and 6-tetrahydropyranyloxyhexyl iodide gave **13**, whose deprotection was followed by tosylation to give **15** via **14**. Treatment of tosylate **15** with lithium bromide afforded pure 8-trimethylsilyl-7-octynyl bromide **11**(=**B**) in 83% overall yield based on **12** (four steps).



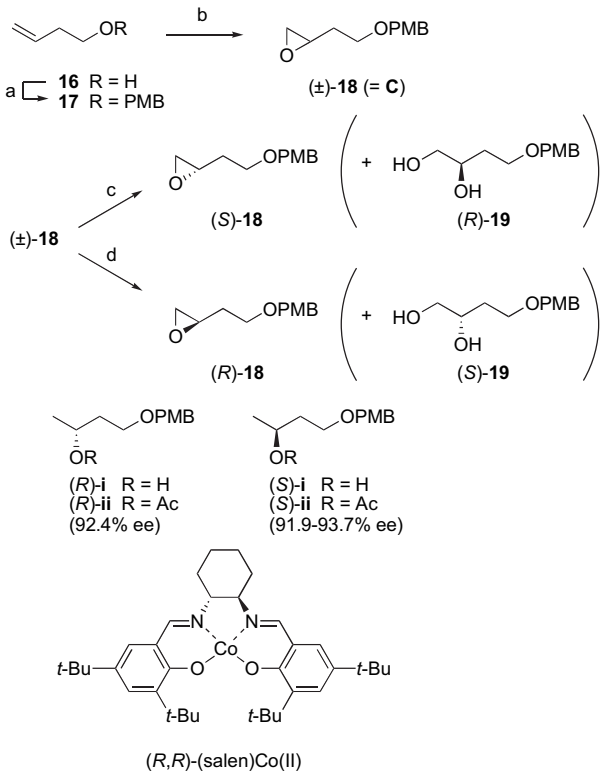
Scheme 2. Synthesis of the building blocks **A** (=**6**) and **B** (=**11**). Reagents: (a) *n*-BuLi, $I(CH_2)_6OTHP$, THF, HMPA (93% for **3**; quant. for **13**); (b) TsOH, MeOH (82% for **4**; 91% for **14**); (c) TsCl, C_5H_5N (88% for **5**; quant. for **8**; 95% for **15**); (d) NaI, DMF (72%); (e) NaI, Me_2CO (82%); (f) TMSC≡CH, *n*-BuLi, THF, HMPA (quant.); (g) LiBr, Me_2CO, DMF (83%); (h) LiBr, DMF (96%).

2.2. Synthesis of the building block C (=18)

As shown in Scheme 3, synthesis of the building block **C**, 3,4-epoxy-1-butanol p-methoxybenzyl(PMB) ether (**18**), started from 3-buten-1-ol (**16**). *p*-Methoxybenzylation of **16** with PMB chloride and potassium *tert*-butoxide in DMF gave **17**, whose epoxidation with *m*-chloroperbenzoic acid (MCPBA) afforded (±)-**18**.[9]

HKR[6] of (±)-**18** was executed according to Jacobsen's improved procedures by means of (salen)Co(III)OTs catalyst.[7,8] Treatment of (±)-**18** with (*R*,*R*)-(salen)Co(III)OTs and water furnished (*R*)-**18**, $[\alpha]_D^{25}$ +13.6 (*c* 3.44, $CHCl_3$); Ref. 11 $[\alpha]_D^{25}$ +10.6 (*c* 1.08, $CHCl_3$), which could be separated from diol (*S*)-**19** by SiO_2 chromatography. Similarly, treatment of (±)-**18** with (*S*,*S*)-(salen)Co(III)OTs and water afforded (*S*)-**18**, $[\alpha]_D^{22}$ −13.6 (*c* 4.09, $CHCl_3$); Ref. 10 $[\alpha]_D^{10}$ −12.3 (*c* 1.00, $CHCl_3$), and (*R*)-**19**. The overall yield of (*R*)-**18** was 44–48% based on **16** (three steps), while that of (*S*)-**18** was 47% (three steps).

The enantiomeric purities of (*R*)- and (*S*)-**18** were estimated as 91.9–93.7% ee and 92.4% ee, respectively, by GC-analysis of acetate **ii** prepared via **i** by $LiAlH_4$ reduction followed by acetylation of **18**. It should be added that the enantiomers of **18** as well as those of **i** could not be separated by chiral GC.



Scheme 3. Synthesis of the building block **C** (=**18**). Reagents: (a) *t*-BuOK, PMBCl, THF, DMF (90%); (b) MCPBA, CH_2Cl_2 (76%); (c) (*S*,*S*)-(salen)Co(II), TsOH, CH_2Cl_2, air; then (±)-**18**, H_2O (69%); (d) (*R*,*R*)-(salen)Co(II), TsOH, CH_2Cl_2, air; then (±)-**18**, H_2O (65–70%).

2.3. Synthesis of (*R*)-, (*S*)- and (±)-1 [(11*Z*,19*Z*)-CH503]

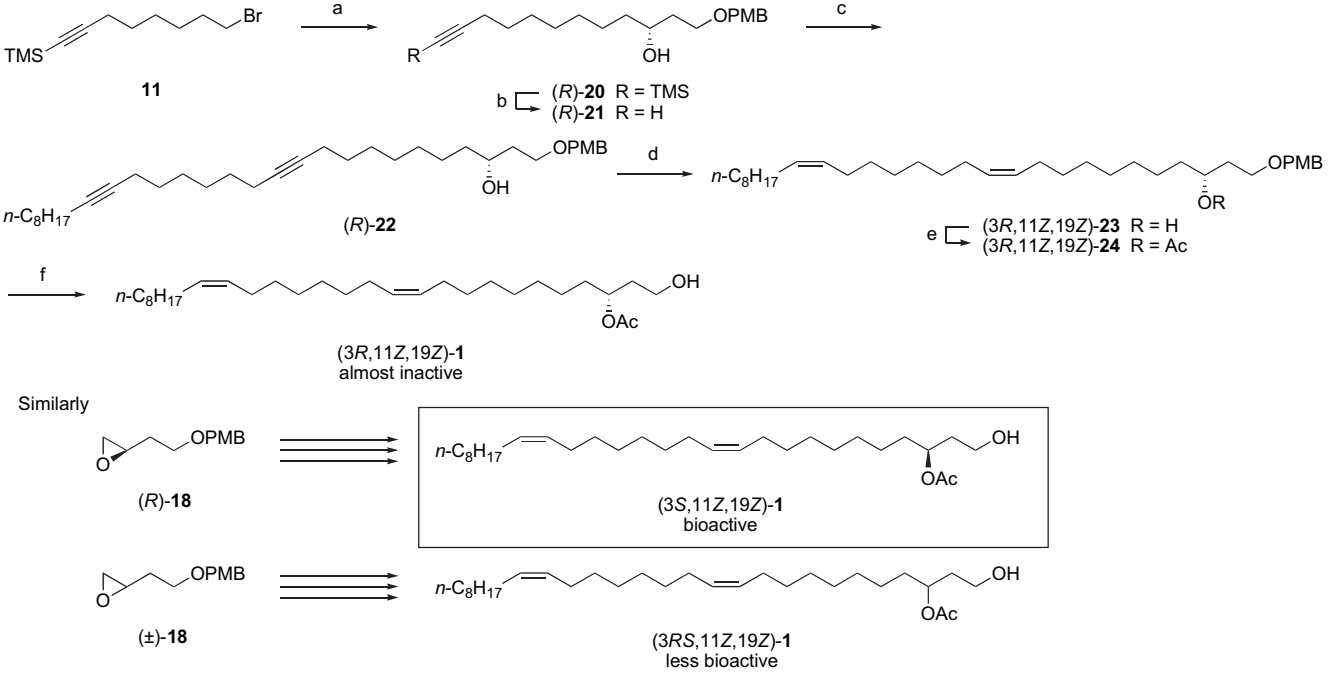
Scheme 4 summarizes the synthesis of (*R*)-, (*S*)-, and (±)-**1** by employing the three building blocks **6**, **11**, and **18**.

Epoxide (*S*)-**18** was added to the Grignard reagent prepared from **11** and Mg in THF in the presence of CuBr to give alcohol (*R*)-**20**. Treatment of (*R*)-**20** with potassium carbonate in methanol furnished acetylenic alcohol (*R*)-**21** in 76% yield based on (*S*)-**18** (two steps). Alkylation of the dianion prepared from (*R*)-**21** and *n*-butyllithium with 7-hexadecynyl iodide (**6**) gave (*R*)-**22** in 45% yield as a low-melting solid, $[\alpha]_D^{22}$ +6.71 (*c* 3.02, hexane). Hydroboration-protonolysis[12] of (*R*)-**22** gave (*R*)-**23** in 65% yield, $[\alpha]_D^{24}$ +4.77 (*c* 2.36, hexane), which was acetylated with acetic anhydride and pyridine to give (*R*)-**24** in 90% yield, $[\alpha]_D^{20}$ −10.4 (*c* 3.88, hexane). Finally, removal of the PMB protective group of (*R*)-**24** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[13] furnished (3*R*,11*Z*,19*Z*)-**1** in 47% yield as a colorless oil, $[\alpha]_D^{22}$ −8.21 (*c* 2.29, hexane). The overall yield of (3*R*,11*Z*,19*Z*)-**1** was 9.4% based on **11** (six steps). Similarly (3*S*,11*Z*,19*Z*)-**1** was obtained as a colorless oil, $[\alpha]_D^{24}$ +7.78 (*c* 2.50, hexane), in 17% overall yield based on **11** (six steps). Racemic **1** was also synthesized by starting from (±)-**18**. The IR, ^1H, and ^{13}C NMR, and EIMS spectra of (*R*)-, (*S*)-, and (±)-**1** support the structure (11*Z*,19*Z*)-**1**. The TMS ethers of (*R*)-, (*S*)-, and (±)-**1** were estimated as 97.8%, 98.9%, and 97.6% pure, respectively, by their GC–MS analysis, and they showed the EIMS identical to that of the TMS ether of the naturally occurring CH503. It should be added that **1** shows unusually abundant M^+ peak in its EIMS, indicating a strong hydrogen-bonding between the hydroxy group and the carbonyl group (see Experimental).

^1H and ^{13}C NMR measurements of (*S*)-**1** in $CDCl_3$ after 100 days' storage at room temperature (20–23 °C) revealed that (*S*)-**1** [δ_H 2.08 (OAc); δ_C 171.8 (C=O)] slowly isomerized to its 1-acetyl isomer [δ_H 2.06 (OAc); δ_C 171.2 (C=O)], yielding a 2:1 mixture of the 1-acetyl isomer and (*S*)-**1**. This isomerization might have been caused by a trace amount of HCl in $CDCl_3$. This acetyl transfer might also operate enzymatically to inactivate the pheromone in the female flies.

2.4. Evaluation of pheromone activity of (*R*)-, (*S*)-, and (±)-1

Table 1 shows the percentage of trials in which male *D. melanogaster* exhibited courtship behavior toward a female fly perfumed with (3*S*,11*Z*,19*Z*)-, (3*R*,11*Z*,19*Z*)- or (3*RS*,11*Z*,19*Z*)-**1**.



Scheme 4. Synthesis of (*R*)-, (*S*)-, and (±)-**1**. Reagents: (a) Mg, THF, CuBr, (*S*)-**18**; (b) K_2CO_3,MeOH [76% for (*R*)-**21**; 92% for (*S*)-**21**, two steps]; (c) *n*-BuLi (2 equiv), THF, HMPA, **6** [45% for (*R*)-**22**; 57% for (*S*)-**22**]; (d) (i) $(cyclohexyl)_2BH$ (8 equiv), THF; (ii) AcOH, heat; (iii) NaOH, H_2O_2[65% for (*R*)-**23**; 79% for (*S*)-**23**]; (e) Ac_2O, DMAP, C_5H_5N [90% for (*R*)-**24**; 53% for (*S*)-**24**]; (f) DDQ, CH_2Cl_2, H_2O [47% for (*R*)-**1**; 77% for (*S*)-**1**].

Table 1
Percentage of trials in which male *D. melanogaster* exhibited courtship behavior toward a female fly perfumed with (3*S*,11*Z*,19*Z*)-CH503, (3*R*,11*Z*,19*Z*)-CH503, or the racemic mixture of CH503(**1**)

Concentration (ng)[a]	(3*S*,11*Z*,19*Z*)-**1** (n=20)[b]	(3*R*,11*Z*,19*Z*)-**1** (n=20)[b]	(3*RS*,11*Z*,19*Z*)-**1** (n=20)[b]
800	20%**	60%**	15%**
400	30%**	80%*	55%**
200	45%*	90%	65%*
100	45%*	100%	50%*
50	45%*	95%	90%
0	82%(n=39)	100%(n=40)	95%(n=40)

[a] Amount deposited on the surface of each female fly.
[b] Significant when compared to trials using non-perfumed female targets (* $p<0.01$; ** $p<0.001$, Fisher exact probability test).

The data show that (3*S*,11*Z*,19*Z*)-**1** is pheromonally active, and inhibits the male courtship initiation, while (3*R*,11*Z*,19*Z*)-**1** is almost inactive. The racemate is less active than the (*S*)-isomer. Roughly speaking, the levels of CH503 (**1**) appear to be within the same range as the levels of (*Z*)-vaccenyl acetate (52.6±25.8 ng per adult male) in the male fly.[14] If this is taken as a rough estimate of CH503 amounts in a single male fly, the natural CH503 and (3*S*,11*Z*,19*Z*)-**1** have about the same bioactivity. Details of biological evaluation will be published separately in due course.

2.5. Quantification of endogenous level of CH503

We then analyzed the endogenous levels of CH503 to support our idea that the natural CH503 and (3*S*,11*Z*,19*Z*)-**1** have about the same bioactivity. Quantification of endogenous levels of CH503 in virgin male flies was performed by HPTLC separation of crude extract followed by densitometry of the CH503-containing band. The band was identified based on similar retention time to synthetic (3*S*,11*Z*,19*Z*)-CH503. Previous analysis by mass spectrometry of the lipid band from crude extract showed that the major component is CH503.[4] A calibration curve was constructed using 100 ng to 2000 ng of synthetic (3*S*,11*Z*,19*Z*)-**1**. The curve showed good correlation ($R^2 \geq 0.99$) and was expressed by a second order calibration function. Using this function, the average amount of CH503 from crude cuticular extract was shown to be 36 ng (±7.3, S.E.M.) per adult male fly.

The behavioral data indicate that 50 ng of (3*S*,11*Z*,19*Z*)-**1** on the surface of a female fly is sufficient to inhibit male courtship performance. Thus, the amounts of CH503 that could potentially be transferred to a female fly after successful mating is within the range that is expected to have a behavioral effect. This means that the bioactivity of (3*S*,11*Z*,19*Z*)-**1** is about the same as that of the natural CH503. It is therefore highly probable that the natural CH503 is (3*S*,11*Z*,19*Z*)-**1**.

3. Conclusion

The enantiomers and the racemate of (11*Z*,19*Z*)-3-acetoxy-11,19-octacosadien-1-ol (CH503, **1**) were synthesized through a convergent route. The overall yield of (3*S*,11*Z*,19*Z*)-**1** was 8.2% (ten steps) based on 1-decyne (**2**). The enantiomeric purities of (3*S*,11*Z*,19*Z*)- and (3*R*,11*Z*,19*Z*)-**1** were thought to be about 92% ee, reflecting those of (*R*)- and (*S*)-**18**, the optically active starting epoxides.

(3*S*,11*Z*,19*Z*)-**1** was pheromonally as active as the natural CH503. The racemate of **1** was less bioactive, while (3*R*,11*Z*,19*Z*)-**1** was almost biologically inactive. It is therefore almost certain that the naturally occurring CH503 is (3*S*,11*Z*,19*Z*)-**1**. The final conclusion about this identity will be given after synthesis and biological evaluation of (3*S*,11*E*,19*E*)-, (3*S*,11*E*,19*Z*)-, and (3*S*,11*Z*,19*E*)-**1**. We are currently engaged in this endeavor to definitely conclude the stereochemistry–bioactivity relationships among the stereoisomers of **1**.

4. Experimental

4.1. General

Boiling and melting points are uncorrected values. Refractive indices (n_D) were measured on an Atago DMT-1 or DR-M2 refractometer. Optical rotations were measured on a Jasco P-1020 polarimeter. IR spectra were measured on a Jasco FT/IR-410 spectrometer. ^{1}H NMR spectra (400 MHz, TMS at δ=0.00 as internal standard) and ^{13}C NMR spectra (100 MHz, $CDCl_3$ at δ=77.0 as internal standard) were recorded on a Jeol JNM-AL 400 spectrometer. GC–MS were measured on Agilent Technologies 5975 inert XL. HRMS were recorded on a Jeol JMS-SX 102A. Column chromatography was carried out on Merck Kieselgel 60 Art 1.07734.

4.2. 7-Hexadecyn-1-ol tetrahydropyranyl ether 3

A solution of *n*-BuLi in hexane (1.6 M, 48 mL, 77 mmol) was added dropwise to a stirred and cooled solution of 1-decyne (**2**, 10.6 g, 76.7 mmol) in dry THF (56 mL) and HMPA (13 mL) at −70 to −40 °C under Ar. The mixture was warmed to −10 °C over 15 min, and then cooled again to −70 °C. A solution of 6-iodo-1-hexanol THP ether (18.4 g, 58.9 mmol) in dry THF (13 mL) was added dropwise to the stirred and cooled solution at −70 °C, and the temperature was gradually raised to room temperature. After stirring for 1.5 h at room temperature, the mixture was stirred and heated at reflux for 1.5 h. After cooling, the mixture was diluted with water and extracted with hexane. The combined hexane solution was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (21.4 g) was chromatographed over SiO_2 (200 g). Elution with hexane/EtOAc (20:1) gave 17.7 g (93%) of **3** as a colorless oil, n_D^{21} 1.4647; ν_{max} (film): 1136 (m), 1120 (m), 1078 (m), 1034 (m); δ_H ($CDCl_3$): 0.88 (3H, t, *J* 6.8, CH_2CH_3), 1.21–1.67 (24H, m), 1.67–1.77 (1H, m), 1.77–1.90 (1H, m), 2.10–2.18 (4H, m, C≡CCH_2×2), 3.36–3.41 (1H, m), 3.47–3.53 (1H, m), 3.70–3.76 (1H, m), 3.84–3.90 (1H, m), 4.58 (1H, t, *J* 4.4).

4.3. 7-Hexadecyn-1-ol 4

p-Toluenesulfonic acid monohydrate (1.3 g, 6.8 mmol) was added to a solution of **3** (17.7 g, 54.9 mmol) in methanol (250 mL). The solution was stirred and heated under reflux for 6 h. It was then diluted with water, and extracted with Et_2O. The combined Et_2O solution was successively washed with $NaHCO_3$ solution, and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (14.0 g) was chromatographed over SiO_2 (200 g). Elution with hexane/EtOAc (10:1–5:1) gave 10.7 g (82%) of **4** as an oil, which solidified in a refrigerator. ν_{max} (film): 3338 (s, O–H), 1055 (m, C–O); δ_H ($CDCl_3$): 0.88 (3H, t, *J* 6.8, CH_2CH_3), 1.22–1.62 (20H, m), 2.12–2.15 (4H, m, C≡CCH_2×2), 3.62–3,68 (2H, m, CH_2OH). HRMS calcd for $C_{16}H_{30}O$: 238.2297, found: 238.2293.

4.4. 7-Hexadecynyl tosylate 5

Tosyl chloride (12.8 g, 67.1 mmol) was added portionwise to a stirred and ice-cooled solution of **4** (10.7 g, 44.9 mmol) in dry pyridine (70 mL) at 5–10 °C. After stirring for 3 h at 5–10 °C, water was added to the mixture until the precipitates were dissolved, and stirring was continued for 5 min. It was then diluted with water and extracted with Et_2O. The combined Et_2O solution was successively washed with water, dil $CuSO_4$ solution, water, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (16.2 g) was chromatographed over SiO_2 (200 g). Elution with hexane/EtOAc (20:1) gave 15.5 g (88%) of **5** as a colorless oil, n_D^{19} 1.4980; ν_{max} (film): 1599 (m, arom. C=C), 1363 (s, SO_2), 1178 (s, SO_2), 1099 (m, C–O), 1020 (w), 962 (m), 916 (m), 814 (m), 663 (m), 555 (m); δ_H ($CDCl_3$): 0.88 (3H, t, *J* 6.8, CH_2CH_3), 1.21–1.54 (18H, m),

1.59–1.71 (2H, m), 2.08–2.14 (4H, m, C≡CCH$_2$×2), 2.45 (3H, s), 4.02 (2H, t, *J* 6.4, CH$_2$OTs), 7.35 (2H, d, *J* 8.0), 7.79 (2H, d, *J* 8.4).

4.5. 7-Hexadecynyl iodide 6

Powdered sodium iodide (3.8 g, 25 mmol) was added portionwise to a solution of **5** (3.9 g, 9.9 mmol) in DMF (20 mL) at room temperature. After exothermic reaction, the mixture was stirred and heated at 80 °C for 4 h. After cooling, the mixture was diluted with water, and extracted with Et$_2$O. The combined Et$_2$O solution was successively washed with water, dil $Na_2S_2O_3$ solution, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (3.3 g) was chromatographed over SiO_2 (60 g). Elution with hexane/EtOAc (100:1) gave 2.5 g (72%) of **6** as a colorless oil (this solidified in a deep freezer). n_D^{19} 1.4973; ν_{max} (film): 2927 (s), 2854 (s), 1462 (m), 1198 (m), 723 (m), 598 (w); δ_H ($CDCl_3$): 0.88 (3H, t, *J* 7.0, CH$_2$*CH*$_3$), 1.22–1.54 (18H, m), 1.79–1.88 (2H, m), 2.11–2.20 (4H, m, C≡CCH$_2$×2), 3.19 (2H, t, *J* 7.0, CH$_2$I); δ_C ($CDCl_3$): 7.1, 14.1, 18.65, 18.74, 22.6, 27.7, 28.8, 28.9, 29.10, 29.12, 29.2, 30.0, 31.8, 33.4, 79.7, 80.4. HRMS calcd for $C_{16}H_{29}I$: 348.1314, found: 348.1325.

4.6. 6-Chlorohexyl tosylate 8

Tosyl chloride (40.0 g, 210 mmol) was added portionwise to a stirred and ice-cooled solution of **7** (25.1 g, 185 mmol) in dry pyridine (80 mL) at 10–15 °C. After the addition, the mixture was stirred for 1.5 h at 0–5 °C. It was then diluted with ice-water, and extracted with Et$_2$O. The extract was washed with water, dil HCl, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo to give 52.0 g (quant.) of **8** as an oil. ν_{max} (film): 1599 (w), 1358 (s), 1188 (s), 1176 (s), 956 (m), 816 (m), 663 (m), 555 (m); δ_H ($CDCl_3$): 1.30–1.42 (4H, m), 1.62–1.78 (4H, m), 2.45 (3H, s, ArCH$_3$), 3.49 (2H, t, *J* 6.4), 7.35 (2H, d, *J* 8.4), 7.79 (2H, d, *J* 8.4). This was employed for the next step without further purification.

4.7. 6-Chlorohexyl iodide 9

Sodium iodide (30.0 g, 200 mmol) was added to a solution of **8** (52.0 g, 185 mmol) in acetone (160 mL). The mixture was stirred and heated under reflux for 30 min until solid sodium tosylate precipitated. The mixture was cooled and diluted with water. The lower layer was separated, and the upper aqueous layer was extracted with hexane. The combined organic solution was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to give 36.7 g (82%) of **9** as a colorless oil. Bp 90–92 °C/4 Torr, n_D^{24} 1.5158; ν_{max} (film): 2933 (s), 2858 (s), 727 (m), 650 (m); δ_H ($CDCl_3$): 1.38–1.52 (4H, m), 1.74–1.90 (4H, m), 3.20 (2H, t, *J* 6.8, CH$_2$I), 3.54 (2H, t, *J* 6.4, CH$_2$Cl); GC–MS [column: HP-5MS 5% phenylmethylsiloxane, 30 m×0.25 mm i.d.; press: 60.7 kPa; temp: 70–230 °C (+10 °C/min)]: t_R 7.28 min [1.4%, Cl(CH$_2$)$_6$Cl], 10.00 (97.4%, **9**), 12.57 [1.2%, I(CH$_2$)$_6$I]. MS of **9** (70 eV, EI): *m*/*z*: 246 (6) [M^+, $C_6H_{12}ICl$], 155 (8), 119 (25), 83 (64), 55 (100), 43 (22) 41 (35). HRMS calcd for $C_6H_{12}ICl$: 245.9672, found: 245.9672.

4.8. 8-Trimethylsilyl-7-octynyl chloride 10

A solution of *n*-BuLi in hexane (1.6 M, 95.6 mL, 153 mmol) was added dropwise to a stirred and cooled solution of TMSC≡CH (15.0 g, 153 mmol) in dry THF (120 mL) and HMPA (12 mL) at −20 to −10 °C under Ar. The stirred mixture was then cooled to −78 °C. A solution of **9** (36.6 g, 148 mmol) in dry THF (10 mL) was added dropwise to the stirred mixture over 5 min, which was then left to stand 3 days at room temperature. The mixture was diluted with water, and extracted with hexane. The hexane solution was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo to give 41.0 g (quant.) of crude **10**. ν_{max} (film): 2956 (s), 2937 (s), 2860 (m), 2175 (m), 1250 (s), 843 (s), 760 (s). This was employed in the next step without further purification.

4.9. 8-Trimethylsilyl-7-octynyl bromide 11 from 10

Lithium bromide (40 g, 460 mmol) was added to a solution of **10** (41.0 g, 148 mmol) in acetone (150 mL) and DMF (20 mL). The mixture was stirred and heated under reflux for 1.5 h, and 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. The residue was distilled to give 31.0 g (ca. 83%) of a mixture of **10**, **11** and the corresponding iodide as a colorless oil. Bp 95–110 °C/6 Torr, n_D^{23} 1.4732; ν_{max} (film): 2956 (s), 2937 (s),2860 (m), 2173 (s), 1250 (s), 843 (vs), 760 (s); δ_H ($CDCl_3$): 0.14 (9H, s, $SiMe_3$), 1.37–1.57 (6H, m), 1.75–1.92 (2H), 2.23 (2H, t, *J* 7.2, C≡C*CH*$_2$), 3.19 (0.1H, t, *J* 7.2, CH$_2$I), 3.41 (1.1H, t, *J* 6.8, CH$_2$Br), 3.54 (0.8H, t, *J* 6.8, CH$_2$Cl); GC–MS [same conditions as described for **9**]: t_R 11.00 min (33.6%, **10**), 12.08 (48.6%, **11**), 13.23 (7.8%, the corresponding iodide). MS of **10** (70 eV, EI): *m*/*z*: 201 (4) [M^+–CH_3], 107 (44), 95 (28), 93 (100), 79 (11), 73 (20), 69 (5), 59 (4), 55 (5). MS of **11** (70 eV, EI): *m*/*z*: 247 (4) [M^+–CH_3], 245 (4) [M^+–CH_3], 165 (7), 139 (100), 137 (100), 107 (87), 73 (30). MS of the iodide (70 eV, EI): *m*/*z*: 308 (1.5) [M^+], 193 (32), 185 (100), 107 (31), 73 (55). HRMS of **11** calcd for $C_{10}H_{18}BrSi$ (M^+–CH_3): 245.0361, found: 245.0351.

4.10. 8-Trimethylsilyl-7-octyn-1-ol tetrahydropyranyl ether 13

In the same manner as described above for **3**, TMSC≡CH (**12**, 11.8 g, 120 mmol) in dry THF (90 mL) and HMPA (20 mL) was treated with *n*-BuLi in hexane (1.6 M, 75 mL, 0.12 mol) and 6-iodo-1-hexanol THP ether (25.0 g, 80.1 mmol) in dry THF (20 mL) to give 23.6 g (quant.) of crude **13** as an oil, n_D^{18} 1.4609; ν_{max} (film): 2175 (s, C≡C), 1250 (m), 1138 (m, C–O–C), 1120 (m, C–O–C), 1078 (m, C–O–C), 1036 (m, C–O–C), 843 (s), 760 (m), 640 (m); δ_H ($CDCl_3$): 0.15 (9H, s, $SiMe_3$), 1.33–1.47 (4H, m), 1.47–1.66 (8H, m), 1.68–1.76 (1H, m), 1.78–1.88 (1H, m), 2.22 (2H, t, *J* 7.2, C≡C*CH*$_2$), 3.36–3.41 (1H, m), 3.47–3.53 (1H, m), 3.71–3.77 (1H, m), 3.83–3.91 (1H, m), 4.56–4.61 (1H, t-like). This was employed for the next step without further purification.

4.11. 8-Trimethylsilyl-7-octyn-1-ol 14

p-Toluenesulfonic acid monohydrate (1.8 g, 9.5 mmol) was added to a solution of crude **13** (21.6 g, 73.3 mmol) in methanol (200 mL). The solution was stirred at room temperature for 1 h. It was then diluted with water, and extracted with Et$_2$O. The combined Et$_2$O solution was successively washed with water, $NaHCO_3$ solution, and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (17.9 g) was chromatographed over SiO_2 (200 g). Elution with hexane/EtOAc (10:1–5:1) gave 13.2 g (91%, two steps) of **14** as a colorless oil, n_D^{16} 1.4593; ν_{max} (film): 3342 (s, O–H), 2175 (s, C≡C), 1250 (s), 1057 (m, C–O), 843 (s), 760 (m), 640 (m); δ_H ($CDCl_3$): 0.15 (9H, s, $SiMe_3$), 1.33–1.47 (4H, m), 1.50–1.62 (4H, m), 2.23 (2H, t, *J* 7.0, C≡C*CH*$_2$), 3.65 (2H, t, *J* 6.6, *CH*$_2$OH). HRMS calcd for $C_{10}H_{19}OSi$ (M^+–CH_3): 183.1205, found: 183.1196.

4.12. 8-Trimethylsilyl-7-octynyl tosylate 15

In the same manner as described above for **5**, **14** (14.1 g, 71.1 mmol) in dry pyridine (90 mL) was treated with tosyl chloride (20.3 g, 106 mmol) to give 23.9 g (95%) of crude **15** as a colorless oil, n_D^{16} 1.5028; ν_{max} (film): 2173 (s, C≡C), 1599 (m, arom, C=C), 1362 (s, SO_2), 1250 (m), 1178 (s, SO_2), 1097 (m, C–O), 1020 (w), 964 (m), 918 (m), 843 (s), 760 (m), 663 (m), 555 (m); δ_H ($CDCl_3$): 0.14 (9H, s, $SiMe_3$), 1.27–1.38 (4H, m), 1.42–1.52 (2H, m), 1.60–1.70 (2H, m), 2.18 (2H, t, *J* 7.0, C≡C*CH*$_2$), 2.45 (3H, s), 4.02 (2H, t, *J* 6.6, *CH*$_2$OTs),

7.35 (2H, d, *J* 8.0), 7.79 (2H, d, *J* 8.4). This was employed for the next step without further purification.

4.13. 8-Trimethylsilyl-7-octynyl bromide 11 from 15

Powdered lithium bromide (10.5 g, 121 mmol) was added portionwise to a solution of crude **15** (23.6 g, 66.9 mmol) in DMF (140 mL). The solution was stirred at room temperature for 4 h. It was then diluted with water, and extracted with Et_2O. The combined Et_2O solution was successively washed with dil $Na_2S_2O_3$, water, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (17.1 g) was chromatographed over SiO_2 (200 g). Elution with hexane/EtOAc (50:1) gave 16.8 g (96%) of **11** as a colorless oil, n_D^{16} 1.4760; ν_{max} (film): 2175 (s, C≡C), 1250 (s), 843 (s), 760 (m), 640 (m), 563 (w); δ_H ($CDCl_3$): 0.15 (9H, s, $SiMe_3$), 1.37–1.48 (4H, m), 1.48–1.58 (2H, m), 1.84–1.91 (2H, m), 2.23 (2H, t, *J* 7.2, C≡CCH_2), 3.41 (2H, t, *J* 7.0, CH_2Br); δ_C ($CDCl_3$): 0.17, 19.7, 27.6, 27.8, 28.2, 32.6, 33.7, 84.4, 107.2. HRMS calcd for $C_{10}H_{18}BrSi$: (M^+-CH_3): 245.0361, found: 245.0359.

4.14. 1-*p*-Methoxybenzyloxy-3-butene 17

Powdered potassium *tert*-butoxide (26.8 g, 240 mmol) was added to a solution of **16** (14.0 g, 194 mmol) in dry THF (200 mL) and DMF (40 mL). The mixture was stirred at room temperature to give a homogeneous solution. *p*-Methoxybenzyl chloride (29.2 g, 199 mmol) was added dropwise to the stirred mixture. When the exothermic reaction subsided, the mixture with suspended KCl was stirred and heated at 55 °C for 1 h, and then concentrated in vacuo. The residue was diluted with water, and extracted with hexane. The hexane solution was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to give 33.0 g (90%) of **17** as a colorless oil. Bp 111–115 °C/4 Torr; ν_{max} (film): 1641 (w), 1614 (m), 1585 (w), 1514 (s), 1248 (s), 1097 (s), 1036 (s), 822 (m); δ_H ($CDCl_3$): 2.33–2.39 (2H, m), 3.49 (2H, t, *J* 6.8, CH_2OPMB), 3.80 (3H, s, $ArOCH_3$), 4.45 (2H, s, $ArOCH_2$), 5.00–5.12 (2H, m), 5.78–5.90 (1H, m), 6.87 (2H, dd, *J* 2.0, 0.4, arom. H), 7.26 (2H, d, *J* 8.4, arom. H).

4.15. 1-*p*-Methoxybenzyloxy-3,4-epoxybutane 18

*4.15.1. Compound (±)-**18**.* MCPBA (65% purity, 52.0 g, 196 mmol) was added portionwise to a stirred and ice-cooled solution of **17** (32.0 g, 167 mmol) in dry CH_2Cl_2 (350 mL) at 5–15 °C. The mixture was stirred for 30 min at 0–5 °C and for 4.5 h at room temperature. It was then filtered and the filter cake of *m*-chlorobenzoic acid was washed with hexane. The organic solution was washed with dil $Na_2S_2O_3$, dil NaOH and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (100 g). Elution with hexane/EtOAc (10:1) gave 26.5 g (76%) of (±)-**18** as an oil, ν_{max} (film): 1612 (m), 1585 (m), 1514 (s), 1248 (vs), 1093 (s), 1036 (s), 823 (s); δ_H ($CDCl_3$): 1.72–1.80 (1H, m), 1.85–1.94 (1H, m), 2.50–2.53 (1H, m), 2.75–2.79 (1H, m), 3.02–3.10 (1H, m, epoxy-H), 3.57–3.62 (2H, m), 3.80 (3H, s, OCH_3), 4.46 (2H, s), 6.88 (2H, dt, *J* 2.4, 6.8, arom. H), 7.26 (2H, d, *J* 8.4, arom. H); GC–MS [same conditions as described for **9**]; t_R 15.09 min [95.0%, (±)-**18**]. MS of (±)-**18** (70 eV, EI): *m*/*z*: 208 (12) [M^+], 177 (6), 137 (31), 136 (16), 135 (22), 121 (100), 109 (6), 91 (6), 78 (9), 77 (11).

*4.15.2. Compound (R)-**18**.* A mixture of (*R*,*R*)-*N*,*N*′-bis(3,5-di-*t*-butylsalicylidene)-1,2-cyclohexanediamino cobalt(II) [(*R*,*R*)-(salen)Co(II)] (229 mg, 0.4 mmol) and *p*-TsOH·H_2O (76 mg, 0.4 mmol) in dry CH_2Cl_2 (5 mL) was stirred for 30 min under air. Its color changed from red to greenish black. After removing the stirring bar, the greenish black mixture was concentrated in vacuo. The residual black solid was dried in vacuo for 30 min. (±)-Epoxide **18** (13.2 g, 63.5 mmol) and water (0.58 mL, 32 mmol) were then added to it, and the mixture was stirred vigorously for 20 h. The initial hydrolysis was exothermic. The mixture was dissolved in a small amount of EtOAc and chromatographed over SiO_2 (100 g). Elution with hexane/EtOAc (10:1) gave crude (*R*)-**18** as a red-colored oil. Further elution with EtOAc gave (*S*)-**19** as a dark oil. The crude (*R*)-**18** was distilled in vacuo to give (*R*)-**18** (4.28–4.64 g, 65–70%) as a colorless oil. Bp 111–113 °C/1–2 Torr; $[\alpha]_D^{25}$ +13.6 (*c* 3.44, $CHCl_3$) or bp105–108 °C/1 Torr; $[\alpha]_D^{21}$ +12.7 (*c* 4.42, $CHCl_3$). Ref. 11 $[\alpha]_D^{25}$ +10.6 (*c* 1.08, $CHCl_3$). Its IR and ^{1}H NMR data were identical to those reported previously.[10,11]

*4.15.3. Compound (S)-**18**.* Similarly, by employing a catalyst prepared from (*S*,*S*)-(salen)Co(II) (229 mg, 0.4 mmol) and *p*-TsOH·H_2O (76 mg, 0.4 mmol), (±)-**18** (13.1 g, 63 mmol) was hydrolyzed with water (0.58 mL, 32 mmol) to give (*S*)-**18** (4.53 g, 69%) as a colorless oil. Bp 118–121 °C/2 Torr; $[\alpha]_D^{22}$ −13.6 (*c* 4.09, $CHCl_3$). Ref. 10 $[\alpha]_D^{20}$ −12.3 (*c* 1.00, $CHCl_3$). Further elution with EtOAc gave (*R*)-**19** as a dark oil.

4.16. Determination of the enantiomeric purities of (*R*)- and (*S*)-18

Compound(*R*)- and (*S*)-**18** (ca. 50 mg each) were reduced with $LiAlH_4$ in THF to give (*S*)- and (*R*)-**i**, respectively, which were acetylated with Ac_2O/C_5H_5N to give (*S*)- and (*R*)-**ii**. Enantioselective GC of **ii**: [instrument: Agilent 7890 GC; column: CHIRAMIX® 30 m×0.25 mm i.d.; column temperature: 40–180 °C (+0.7 °C/min); carrier gas: He, 0.7 mL/min]: t_R 179.8 min [(*S*)-**ii**], 180.7 [(*R*)-**ii**]. The enantiomeric purity of (*R*)-**18** was 92.4% ee, and that of (*S*)-**18** was 91.9–93.7% ee.

4.17. 11-Dodecyne-1,3-diol 1-*p*-methoxybenzyl ether 21

*4.17.1. Compound (R)-**21**.* A Grignard reagent was prepared from **11** (15.5 g, 62 mmol) and Mg turnings (1.7 g, 70 mmol) in dry THF (35 mL). CuBr (0.86 g, 6 mmol) was added to the stirred and cooled Grignard reagent at −30 °C under Ar. After stirring for 30 min at −30 °C, a solution of (*S*)-**18** (4.50 g, 21.6 mmol) in dry THF (10 mL) was added dropwise to the stirred mixture at −40 to −30 °C. The reaction was exothermic. The mixture was stirred overnight with gradual raise of the temperature from −30 °C to room temperature. It was then diluted with ice and satd NH_4Cl solution, and extracted with Et_2O. The Et_2O solution was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo to give crude (*R*)-**20** (12.3 g), ν_{max} (film): 3466 (br O–H), 2956 (s), 2931 (s), 2858 (s), 2173 (m,C≡C), 1614 (w, arom. C=C), 1514 (m), 1250 (s), 843 (vs), 760 (m). This was dissolved in MeOH (100 mL) and water (6 mL), to which was added K_2CO_3 (5.0 g, 36 mmol). 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 Et_2O. The Et_2O solution was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (7.7 g) was chromatographed over SiO_2 (100 g). Elution with hexane/EtOAc (5:1) gave (*R*)-**21** [5.21 g, 76% based on (*S*)-**18**] as a colorless oil, n_D^{20} 1.5042; $[\alpha]_D^{22}$ +6.84 (*c* 3.68, hexane); ν_{max} (film): 3437 (br, O–H), 3311 (m, C≡C–H), 1612 (m, arom. C=C), 1514 (s), 1248 (s), 1092 (m), 1038 (m), 822 (m); δ_H ($CDCl_3$): 1.25–1.60 (12H, m), 1.70–1.80 (2H, m), 1.93 (1H, t, *J* 2.8, C≡CH), 2.15–2.23 (2H, m), 2.94 (1H, OH), 3.58–3.65 (1H, m), 3.65–3.72 (1H, m), 3.78 (1H, m), 3.80 (3H, s, OCH_3), 4.45 (2H, s, OCH_2Ar), 6.87 (2H, d, *J* 8.4, arom. H), 7.24 (2H, d, *J* 8.4, arom. H). HRMS calcd for $C_{20}H_{30}O_3$: 318.2195, found: 318.2202.

*4.17.2. Compound (S)-**21**.* Similarly, **11** (15.5 g, 62 mmol) and (*R*)-**18** (4.68 g 22.5 mmol) afforded (*S*)-**21** [6.56 g, 92% based on (*R*)-**18**], n_D^{26} 1.4948; $[\alpha]_D^{23}$ −6.91 (*c* 3.25, hexane). Its IR and ^{1}H NMR data were identical to those of (*R*)-**21**. HRMS calcd for $C_{20}H_{30}O_3$: 318.2195, found: 318.2202.

*4.17.3. Compound (±)-**21**.* Similarly, **11** (5.00 g, 20 mmol) and (±)-**18** (3.12 g, 15 mmol) gave (±)-**21** [4.42 g, 70% based on (±)-**18**],

n_D^{23} 1.5030. Its IR and ^{1}H NMR data were identical to those of (*R*)-**21**. HRMS calcd for $C_{20}H_{30}O_3$: 318.2195, found: 318.2201.

4.18. 11,19-Octacosadiyne-1,3-diol 1-*p*-methoxybenzyl ether 22

*4.18.1. Compound (R)-**22**.* A solution of *n*-BuLi in hexane (1.6 M, 17.5 mL, 28 mmol) was added dropwise to a stirred and cooled solution of (*R*)-**21** (3.90 g, 12.9 mmol) in dry THF (30 mL) and HMPA (3 mL) at −40 °C under Ar. The mixture solidified due to the formation of the dilithium salt of (*R*)-**21**. The mixture was warmed to −15 °C, and then cooled again to −40 °C. A solution of **6** (4.52 g, 13 mmol) in dry THF (10 mL) was added dropwise to the mixture, which was left to stand overnight with gradual raise of the temperature to room temperature. The solid mixture turned to a suspension of the lithium salt of (*R*)-**22** at −40 °C, and became homogeneous at −10 °C. The mixture was diluted with satd NH_4Cl solution and ice, and extracted with hexane. The hexane solution was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (7.1 g) was chromatographed over SiO_2 (80 g). Elution with hexane/EtOAc (10:1–5:1) gave (*R*)-**22** (3.15 g, 45%) as a low-melting solid, mp 29.5–30 °C; $[\alpha]_D^{22}$ +6.71 (*c* 3.02, hexane); ν_{max} (film): 3437 (br. O–H), 2929 (s), 2856 (s), 1614 (m, arom. C=C), 1587 (w), 1514 (m), 1464 (m), 1248 (s), 1092 (m), 1038 (m), 822 (m); δ_H ($CDCl_3$): 0.88 (3H, t, *J* 6.8, CH_2CH_3), 1.22–1.52 (32H, m), 1.70–1.75 (2H, m), 2.10–2.20 (8H, m), 2.90 (1H, d-like, *J* 3.2), 3.58–3.64 (1H, m), 3.65–3.72 (1H, m), 3.73–3.80 (1H, br), 3.80 (3H, s, OCH_3), 4.45 (2H, s, OCH_2Ar), 6.87 (2H, d, *J* 8.4, arom. H), 7.25 (2H, d, *J* 8.4, arom. H). HRMS calcd for $C_{36}H_{58}O_3$: 538.4386, found: 538.4369.

*4.18.2. Compound (S)-**22**.* Similarly, (*S*)-**21** (6.41 g, 20.3 mmol) and **6** (7.3 g, 21 mmol) gave (*S*)-**22** (6.14 g, 57%) as a low-melting solid, mp 28–30 °C; $[\alpha]_D^{22}$ −5.64 (*c* 2.34, hexane). Its IR and ^{1}H NMR data were identical to those of (*R*)-**22**. HRMS calcd for $C_{36}H_{58}O_3$: 538.4386, found: 538.4380.

*4.18.3. Compound (±)-**22**.* Similarly, (±)-**21** (2.16 g, 7.2 mmol) and **6** (2.42 g, 6.8 mmol) afforded (±)-**22** (1.10 g, 30%) as an oil, n_D^{23} 1.4981. Its IR and ^{1}H NMR spectra were identical to those of (*R*)-**22**. HRMS calcd for $C_{36}H_{58}O_3$: 538.4386, found: 538.4391.

4.19. (11*Z*,19*Z*)-11,19-Octacosadiene-1,3-diol 1-*p*-methoxybenzyl ether 23

*4.19.1. Compound (R)-**23**.* Borane/dimethyl sulfide complex ($BH_3 \cdot Me_2S$, 1.6 mL, 24 mmol) was added dropwise to a stirred and ice-cooled solution of cyclohexene in dry THF (2 M, 24 mL, 48 mmol) at 0–10 °C under Ar. After 10 min, the solution turned to a paste-like suspension of colorless and crystalline dicyclohexylborane. A solution of (*R*)-**22** (1.64 g, 3.05 mmol) in dry THF (10 mL) was added dropwise to the stirred and ice-cooled suspension of the foregoing dicyclohexylborane at 5–15 °C. Stirring was continued for 30 min at 0–5 °C, and then for 1.5 h at room temperature, when the mixture became almost homogeneous. AcOH (7 mL) was added dropwise to the stirred and ice-cooled mixture, which was then stirred and heated at 50 °C for 1 h. The stirred mixture was then ice-cooled to 5–10 °C, and a solution of NaOH (15 g) in water (40 mL) was added slowly. Subsequently, 30% H_2O_2 (8 mL) was added dropwise to the mixture, and it was stirred for 10 min at room temperature. The mixture was diluted with water, and extracted with hexane. The hexane solution was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo to give 7.8 g of the residue, whose major component was cyclohexanol. It was chromatographed over SiO_2 (50 g). Elution with hexane/EtOAc (15:1) gave (*R*)-**23** (1.08 g, 65%) as a colorless oil, n_D^{25} 1.4890; $[\alpha]_D^{24}$ +4.77 (*c* 2.36, hexane); ν_{max} (film): 3373 (br, O–H), 3003 (w), 2925 (vs), 2854 (vs), 1614 (w), 1587 (w), 1514 (m), 1464 (m), 1248 (s), 1072 (m), 1039 (m), 970 (w), 822 (w), 721 (w); δ_H ($CDCl_3$): 0.88 (3H, t, *J* 6.8, CH_2CH_3), 1.10–1.60 (26H, m), 1.68–1.78 (4H, m), 1.85–1.92 (1H, m), 1.94–2.08 (10H, m), 2.88 (1H, s), 3.56–3.64 (2H, m), 3.64–3.72 (1H, m), 3.73–3.80 (1H, br), 3.80 (3H, s, $ArOCH_3$), 4.45 (2H, s, OCH_2Ar), 5.35 (4H, m, 2×CH=CH), 6.87 (2H, d, *J* 8.8, arom. H), 7.25 (2H, d, *J* 8.8, arom. H). HRMS calcd for $C_{36}H_{62}O_3$: 542.4699, found: 542.4704.

*4.19.2. Compound (S)-**23**.* Similarly, (*S*)-**22** (2.42 g, 4.5 mmol) was treated with dicyclohexylborane prepared from $BH_3 \cdot Me_2S$ (2.4 mL, 36 mmol) and cyclohexene (2 M in THF, 36 mL, 72 mmol). Further manipulation yielded (*S*)-**23** (1.92 g, 79%) as a colorless oil, n_D^{23} 1.4834; $[\alpha]_D^{21}$ −5.04 (*c* 2.23, hexane). Its IR and ^{1}H NMR spectra were identical to those of (*R*)-**23**. HRMS calcd for $C_{36}H_{62}O_3$: 542.4699, found: 542.4694.

*4.19.3. Compound (±)-**23**.* Similarly, (±)-**22** (1.038 g, 1.93 mmol) afforded 0.830 g (79%) of (±)-**23**, n_D^{22} 1.4832. Its IR and ^{1}H NMR spectra were identical to those of (*R*)-**23**. HRMS calcd for $C_{36}H_{62}O_3$: 542.4699, found: 542.4670.

4.20. (11*Z*,19*Z*)-3-Acetoxy-11,19-octacosadien-1-ol *p*-methoxybenzyl ether 24

*4.20.1. Compound (R)-**24**.* Acetic anhydride (3 mL) and DMAP (10 mg) were added to a solution of (*R*)-**23** (1.15 g, 2.1 mmol) in dry pyridine (6 mL) with shaking at room temperature. The mixture was left to stand for 3 days at room temperature. It was then diluted with ice-water, and extracted with Et_2O. The Et_2O solution was successively washed with aq $CuSO_4$ solution, water, satd $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo to give 1.38 g of crude (*R*)-**24**. This was chromatographed over SiO_2 (15 g). Elution with hexane/EtOAc (10:1) furnished (*R*)-**24** (1.11 g, 90%) as a colorless oil, n_D^{26} 1.4820; $[\alpha]_D^{20}$ −10.4 (*c* 3.88, hexane). ν_{max} (film): 3003 (m), 2927 (s), 2854 (s), 1738 (s, C=O), 1653 (w), 1614 (m), 1587 (w), 1514 (m), 1464 (m), 1363 (m), 1244 (s), 1097 (m), 1041 (m), 1024 (m), 820 (w), 723 (w); δ_H ($CDCl_3$): 0.88 (3H, t, *J* 6.8, CH_2CH_3), 1.20–1.45 (30H, m), 1.50–1.58 (2H, m), 1.80–1.90 (2H, m), 1.99 (3H, s, $COCH_3$), 1.95–2.10 (8H, m), 3.40–3.50 (2H, m, CH_2OH), 3.80 (3H, s, OCH_3), 4.40 (2H, s, $ArCH_2O$), 5.02 (1H, m, CHOAc), 5.35 (4H, s-like, 2×CH=CH), 6.87 (2H, d, *J* 8.4, arom. H), 7.24 (2H, d, *J* 8.4, arom. H). HRMS calcd for $C_{38}H_{64}O_4$: 584.4805, found: 584.4786.

*4.20.2. Compound (S)-**24**.* Similarly, (*S*)-**23** (1.80 g, 3.3 mmol) was acetylated to give (*S*)-**24** (1.03 g, 53%) as a colorless oil, n_D^{23} 1.4870; $[\alpha]_D^{24}$ +11.6 (*c* 3.76, hexane). Its IR and ^{1}H NMR spectra were identical to those of (*R*)-**24**. HRMS calcd for $C_{38}H_{64}O_4$: 584.4805, found: 584.4814.

*4.20.3. Compound (±)-**24**.* Similarly, (±)-**23** (776 mg, 1.43 mmol) was acetylated to give (±)-**24** (714 mg, 85%) as a colorless oil, n_D^{22} 1.4832. Its IR and ^{1}H NMR spectra were identical to those of (*R*)-**24**. HRMS calcd for $C_{38}H_{64}O_4$: 584.4805, found: 584.4807.

4.21. (11*Z*,19*Z*)-3-Acetoxy-11,19-octacosadien-1-ol (CH503) 1

*4.21.1. Compound (R)-**1**.* 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 600 mg, 2.6 mmol) was added to a stirred and ice-cooled solution of (*R*)-**24** (1.10 g, 1.9 mmol) in CH_2Cl_2 (40 mL) and water (4 mL) at 0–5 °C. The mixture was stirred for 15 min at 0-5 °C and then for 40 min at room temperature. The initial greenish black solution turned to a light brown suspension of crystalline 2,3-dichloro-5,6-dicyano-1,4-hydroquinone. The reaction was quenched by adding satd $NaHCO_3$ solution and Et_2O, and the mixture was extracted with Et_2O. The Et_2O solution was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (20 g). Elution with hexane/EtOAc (15:1) gave *p*-methoxybenzaldehyde (0.24 g). Subsequent elution with hexane/EtOAc (10:1) afforded (*R*)-**1** (410 mg,

47%) as a colorless oil, n_D^{25} 1.4692; $[\alpha]_D^{22}$ −8.21 (*c* 2.29, hexane); ν_{max} (film): 3458 (br, O–H), 3005 (m), 2925 (s), 2854 (s), 1738 (s, C=O), 1655 (w, C=C), 1464 (m), 1375 (m), 1244 (s, C–O), 1055 (m), 1022 (m), 723 (m); δ_H ($CDCl_3$): 0.88 (3H, t, *J* 6.8, CH_2CH_3), 1.20–1.40 (31H, m), 1.50–1.70 (2H, m), 1.85–1.89 (1H, m), 1.92–2.05 (8H, m), 2.08 (3H, s, $COCH_3$), 2.42 (1H, t-like), 3.48–3.58 (1H, m, CH*H*OH), 3.60–3.68 (1H, m, C*H*HOH), 4.98–5.07 (1H, m, CHOAc), 5.30–5.40 (4H, m, 2×CH=CH); δ_C ($CDCl_3$): 14.1, 21.1, 22.7, 25.4, 27.2, 29.17, 29.30, 29.34, 29.38, 29.50, 29.71, 29.75, 31.9, 34.6, 37.5, 58.5, 71.5, 129.64, 129.66, 129.75, 129.77, 171.8; MS (EI): *m*/*z*: 465 (30), 464 (100) [M^+], 447 (31), 446 (90), 405 (34), 404 (96), 387 (28), 386 (84), 377 (11), 376 (25), 360 (16), 358 (9.5), 287 (15), 273 (17), 261 (11), 259 (14), 248 (11), 247(19), 236 (15), 234 (12), 233 (17), 222 (18), 208 (17), 194 (11), 180 (10), 163 (17), 149 (35), 135 (56), 121 (56), 109 (58), 95 (96), 81 (95), 69 (65), 67 (81), 55 (61). HRMS calcd for $C_{30}H_{56}O_3$: 464.4229, found: 464.4228. *GC–MS of the TMS ether of* (*R*)-***1***: [column: HP-5MS 5% phenylmethylsiloxane, 30 m×0.25 mm i.d.; press: 52.7 kPa; temp: 50–325 °C (+15 °C/min)]: t_R 23.45 min (97.8%). MS of the TMS ether of (*R*)-**1** (EI, 70 eV): *m*/*z*: 536 (3) [M^+, $C_{33}H_{64}O_3Si$], 476 (9), 386 (15), 287 (12), 273 (15), 259 (10), 163 (13), 149 (30), 135 (63), 117 (100), 103 (92), 81(63), 67 (50), 55 (46), 43 (28).

*4.21.2. Compound (S)-**1**.* Similarly (*S*)-**24** (1.00 g, 1.7 mmol) was treated with DDQ (600 mg, 2.6 mmol) in CH_2Cl_2 (40 mL) and water (4 mL) to give (*S*)-**1** (543 mg, 77%), n_D^{22} 1.4690; $[\alpha]_D^{24}$ +7.78 (*c* 2.50, hexane). Its IR, ^1H and ^{13}C NMR and EIMS spectra were identical to those of (*R*)-**1**. HRMS calcd for $C_{30}H_{56}O_3$: 464.4229, found: 464.4224. *GC–MS of the TMS ether of (S)-**1***: [same conditions as for the TMS ether of (*R*)-**1**]; t_R 23.39 min (98.9%). MS of the TMS ether of (*S*)-**1** (EI, 70 eV): *m*/*z*: 536 (3) [M^+, $C_{33}H_{64}O_3Si$], 476 (5), 386 (8), 287 (8), 273 (9), 259 (8), 163 (10), 149 (21), 135 (52), 117 (100), 103 (89), 81 (51), 73 (59), 67 (50), 55 (45), 43 (38).

*4.21.3. Compound (±)-**1**.* Similarly, (±)-**24** (625 mg, 1.07 mmol) was treated with DDQ (380 mg, 1.65 mmol) in CH_2Cl_2 (27 mL) and water (3 mL) to give (±)-**1** (355 mg, 72%) as a colorless oil, n_D^{22} 1.4671. Its IR, ^1H and, ^{13}C NMR, and MS data were identical to those of (*R*)-**1**. HRMS calcd for $C_{30}H_{56}O_3$: 464.4229, found: 464.4212. GC–MS of the TMS ether of (±)-**1** [same conditions as for the TMS ether of (*R*)-**1**]: t_R 23.41 min (97.6%). HRMS calcd for $C_{33}H_{64}O_3Si$: 536.4625, found 536.4625.

4.22. Biological experiments

4.22.1. Fly stocks and husbandry. CantonS flies used for the assay were raised at 25 °C on cornmeal agar food. Socially naïve flies aged between 4–6 days were used for the assay.

4.22.2. Courtship behavior assays with perfumed targets. Courtship assays were performed in chambers of 10 mm diameter and 3 mm depth. A perfumed female target and 4–6 days old socially naïve male were placed in each chamber and videotaped for 30 min. Wet filter paper was put into each chamber to maintain humidity. Female flies were perfumed with various concentrations of (3*R*,11*Z*,19*Z*)-**1**, (3*S*,11*Z*,19*Z*)-**1**, or (3*RS*,11*Z*,19Z)-**1**. The perfuming method has been described elsewhere.[4,15] Briefly, glass vials (Wheaton, USA) were coated with 20 μg, 10 μg, 5 μg, or 1.25 μg of each isomer or of the racemic mixture diluted in 200 μl hexane (Optima grade, Fisher Scientific, USA) and the solvent evaporated. Six live females were placed in each vial and gently vortexed for three 20 s bouts with a 20 s pause in between. It is estimated that approximately 25% of the vial contents are transferred to the flies.[15] Control flies were vortexed in a vial in which hexane had been placed and evaporated. The heads of perfumed flies were crushed immediately before the assay.

4.22.3. Statistical analysis. The distribution of pairs in which courtship was observed was analyzed using a Fisher exact probability test.[16]

4.22.4. Quantification of endogenous levels of CH503 by densitometry. Cuticular lipid extracts were prepared from 30 virgin male CantonS flies, 4–6 days old. Three replicate samples were made. Thirty live flies were placed in hexane (200 μL) for 15 min at room temperature, and hexane solution was evaporated in a gentle stream of N_2. The residue was re-dissolved in 30 μL of hexane prior to high performance thin layer chromatography (HPTLC) analysis. A 100 μg/mL solution of synthetic (3*S*,11*Z*,19*Z*)-**1** was also prepared in hexane and applied to the HPTLC plate in the following amounts: 2000 ng, 1000 ng, 300 ng, 100 ng. HPTLC separation was performed on glass-backed silica gel plates (10×10 cm), coated with 0.2 mm of silica gel 60; Merck, Germany, (Catalog No. 1.05633.0001) using a running solvent consisting of hexane/diethyl ether/methanol (85:5:10, each by volume). Following separation, the plate was stained with a solution of primuline (0.01% in 20% acetone; Sigma-Aldrich, USA). UV densitometric quantification of primuline fluorescence was performed using a CD60 TLC densitometer (Desaga, Germany) and the software package Desaga ProQuant. The HPTLC plate was scanned at λ=345 nm with slit dimensions 0.02 mm×6 mm. Standard curves were fitted using Microsoft Excel.

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