(*S*)-2-Pentyl (*R*)-3-Hydroxyhexanoate, a Banana Volatile and Its Olfactory Recognition by the Common Fruit Fly, *Drosophila melanogaster*

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The volatile organic compounds emitted from ripening bananas that elicit an antennal response from the common fruit fly, *Drosophila melanogaster*, were analyzed by a combination of gas chromatographic−electroantennographic detection, mass spectrometry, and ^{1}H NMR spectroscopy. These analyses revealed that the headspace of ripening bananas contains a number of EAD-active components including the new ester (*S*)-2-pentyl (*R*)-3-hydroxyhexanoate, the structural assignment of which was confirmed by chemical synthesis.

Fruit flies in the family Drosophilidae are a nuisance in homes, restaurants, fruit markets, and canneries, and wherever fruit and vegetable matter is left exposed.[1] Early research directed at identifying the natural volatiles that lure fruit flies to rotting organic material, with the intention of exploiting these compounds in commercial traps, led to the discovery of various attractants including EtOH, HOAc, EtOAc, and acetaldehyde.[2] More recently, it was revealed that overripe mango fruit produces the fruit fly attractive volatiles EtOH, HOAc, amyl acetate, 2-phenylethanol, and phenylethyl acetate.[3] It has also been demonstrated that *Drosophila melanogaster* is attracted by volatile compositions that include a short-chain carboxylic acid, a short-chain alcohol, a volatile aryl-substituted alcohol, a nitrogen compound, a sugar, a terpene, EtOAc, 2-phenylethyl acetate, and H_2O.[4] Despite these discoveries, the development of effective means to remove *Drosophila* from areas of food preparation and storage remains an important challenge. Given that banana mash fermented by bakers' yeast has been used as a bait to attract fruit flies since the 1930s,[5] as a prelude to the development of an efficient semiochemical lure for *Drosophila,* we initiated an investigation of antenna-stimulating volatiles produced by ripening bananas.[6] The results of this study as well as the isolation, structural elucidation, and synthesis of (*S*)-2-pentyl (*R*)-3-hydroxyhexanoate, a new natural product, are reported herein.

Approximately 50 ripening bananas were aerated individually for three days, and the volatile organic compounds were collected on Porapak Q (ethylvinylbenzene−divinylbenzene polymer) and subsequently extracted into pentane. Gas chromatographic−electroantennographic detection (GC-EAD) analyses[7] of the volatiles revealed that many components elicited a response from *D. melanogaster* antennae (Figure 1). With the exception of one compound, the structures of all antennal stimulatory volatile constituents were assigned on the basis of their characteristic retention indices and MS fragmentation patterns,[8] and assignments were confirmed by comparison with authentic standards. The behavioral activity of each candidate semiochemical is typically determined by preparing a synthetic blend that mimics in concentration and composition the antennal-stimulatory volatiles and by bioassaying this synthetic blend as well as blends from which specific compounds (e.g., alcohols, esters, or hydrocarbons) are eliminated.[9] While the structurally uncharacterized compound (t_R = 10.69 min, Figure 1) elicited a relatively weak antennal response (approximately 0.2 mV), this was not necessarily indicative of the compound's behavioral significance.[10] Consequently, a confident structural assignment and synthetic source for this new candidate semiochemical were required. In its mass spectrum (Figure 2) the fragmentation ion *m*/*z* 89 was suggestive of a butyrate, which is commonly found in banana volatiles[6] and the molecular ion *m*/*z* 203 (M + 1) was consistent with the chemical formula $C_{11}H_{22}O_3$, indicating an additional alcohol function. Moreover, the retention indices for this compound on DB-23 (1838), DB-5 (1347), DB-210 (1657), and DB-17 (1480) were consistent with those of a polar ester, such as a butyrate with an OH group in the alcohol or acid portion. While the fragmentation ion *m*/*z* 133 (loss of 69 from the molecular ion *m*/*z* 203) suggested an ester derived from pentanol, and *m*/*z* 45 further suggested a 2-pentyl ester,[11] the molecular mass of the candidate structure (2-pentyl hydroxybutyrate) deduced from the MS data was not a match with that of the unknown. With this in mind, the gas chromatographic retention indices for 2-heptyl 3-hydroxybutyrate, which has a molecular weight consistent with that of the unknown, were measured on DB-23 (1861), DB-5 (1345), DB-210 (1672), and DB-17 (1482) columns. These data closely resembled those of the unknown, but the mass spectrum of this substance lacked a strong *m*/*z* 89 ion. Considering that the MS information derived from the unknown appeared insufficient to assign a molecular structure and that many hydroxy esters seemed plausible, we decided to isolate this substance and to elucidate its molecular structure by ^{1}H NMR spectroscopy. Normal-phase flash chromatographic separation (Et_2O/pentane) of the crude mixture of volatiles followed by reversed-phase HPLC afforded a small amount (300 ng as determined by GC analysis with an internal standard) of this unidentified volatile. ^{1}H NMR spectroscopy with extended acquisition time (11 000 scans, 600 MHz TCI Cryoprobe) permitted the detection of a number of signals related to the natural product. However, the 300 ng sample also contained relatively large amounts of residual solvents and their associated impurities that masked key resonances. The presence of an ester function was suggested by a multiplet that resonated at δ 4.95 (acyloxy methine) and two doublets of doublets with resonances at δ 2.46 and 2.36 (α-methylene). Importantly, the multiplicity and splitting pattern of the latter two resonances were consistent with those of a β-hydroxy ester, and both signals showed a 1D TOCSY correlation to a multiplet that resonated at δ 3.96. On the basis of an additional 1D TOCSY correlation between the acyloxy methine proton and a methyl resonance at δ 1.20 (doublet), we were able to construct the partial structure depicted in Figure 3. Further observation of 1D TOCSY correlations from the acyloxy methine and carbinol protons to at least two methyl resonances centered around δ 0.90 reduced to 22 the number of potential structural isomers for the ester, but due to the limited amount of material, a confident

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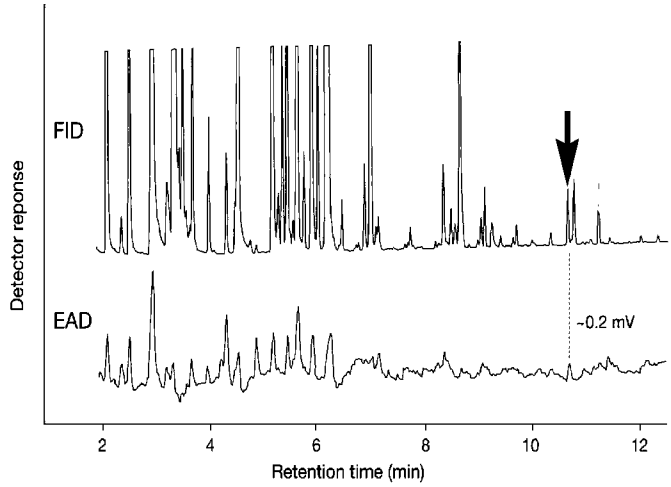


antenna-stimulating compounds	t_R (min)
isobutyl acetate	2.00
ethyl butyrate	2.49
butyl acetate	2.63
2-pentyl acetate	3.04
hexanol	3.31
isoamyl acetate	3.44
2-heptanol	3.77
isobutyl isobutyrate	3.96
2-hexyl acetate	4.39
isobutyl butyrate	4.61
3-butenyl butyrate	4.94
butyl butyrate	5.25
isoamyl isobutyrate	5.51
2-pentyl butyrate	5.69
2-heptyl acetate	5.94
3-methyl-1-butyl butyrate	6.25
2-phenylethanol	7.18
hexyl butyrate	8.38
unknown	10.69
methyl eugenol	11.46

Figure 1. Representative recording of flame ionization detector (FID) and electroantennographic detector (EAD: *D. melanogaster* antenna) responses to volatile organic compounds collected from ripening bananas. Unidentified substance is indicated with arrow (↓). Chromatography: DB-5 column; splitless injection; temperature of injection port and FID, 240 °C; temperature program, 1 min at 50 °C, then 10 °C/min to 280 °C.

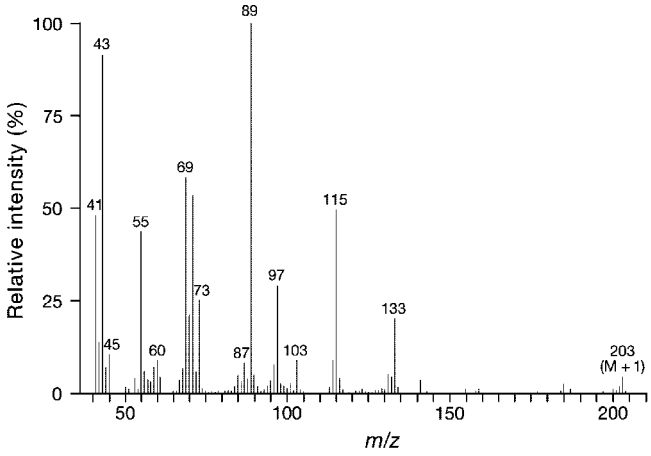


Figure 2. Saturn 2000 ion trap mass spectrum of (*S*)-2-pentyl (*R*)-3-hydroxyhexanoate (**5**).

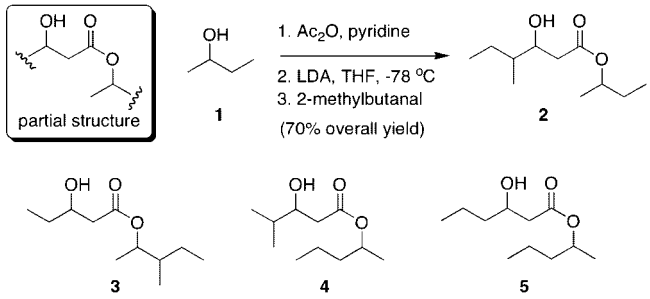
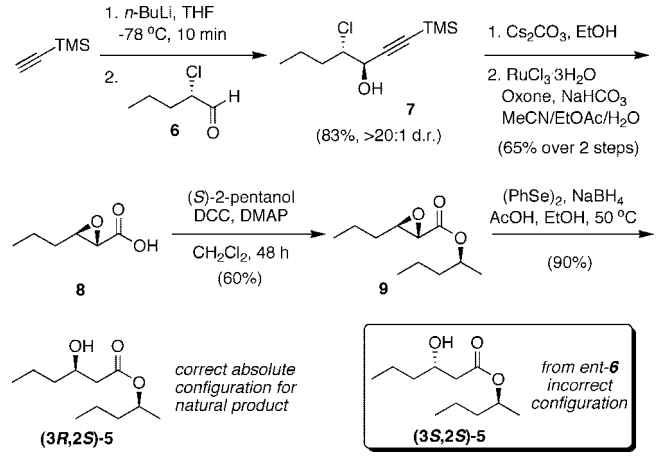


Figure 3. Synthesis and structures of candidate β-hydroxy esters **2**−**5**.

structural assignment would ultimately rely on comparison with synthetic standards.

In order to gain further insight into the structure of this new volatile ester, the synthesis and spectroscopic analysis of a small family of synthetic β-hydroxy esters (MW = 202) was carried out. As detailed in Figure 3, acetylation of 2-butanol provided an acetate (not shown), the subsequent treatment of which with LDA followed by 2-methylbutanal afforded the β-hydroxy ester **2** as a mixture of diastereomers. Alternatively, acetylation of 3-methyl-2-pentanol or 2-pentanol followed by sequential treatment with LDA and propanal or isobutyraldehdye afforded the β-hydroxy esters **3** and **4**,

Scheme 1. Synthesis of (*S*)-2-Pentyl (*R*)-3-Hydroxyhexanoate



respectively, as diastereomeric mixtures. While ^{1}H NMR spectra of esters **2**−**4** indicated that none of these substances possessed the connectivity of the natural product, similarities in the chemical shifts of the alkoxy fragment in **4** with those of the natural product suggested the later substance was derived from 2-pentanol, which was consistent with the MS data (*vide supra*). On the basis of this observation, the isomeric β-hydroxy ester **5** was synthesized, and the planar structure for the natural product was unambiguously assigned as 2-pentyl 3-hydroxyhexanoate. This is the first example of this compound as a synthetic or natural product.[12] As the four stereoisomers represented by **5** proved to be inseparable by HPLC, assignment of both the relative and absolute configuration of the natural product would require the stereoselective syntheses of these compounds.

Repetition of the synthesis of **5** starting with (*S*)-2-pentanol provided an inseparable mixture of diastereomeric hydroxy esters that, when compared to natural **5** by chiral GC,[13] confirmed the configuration of the acyloxy methine stereocenter as *S*. On the basis of this result, syntheses of both the *R*- and *S*-configured β-hydroxy esters were carried out. While the α,β-epoxy acid **8** required to access **5** is available via Sharpless asymmetric epoxidation of 2-hexen-1-ol followed by oxidation of the alcohol function,[14,15] an alternative route to this substance (Scheme 1) exploits methodology developed in one of our laboratories for the synthesis of *trans*-epoxides.[16] Thus, addition of the lithium anion derived from trimethylsilyl acetylene to (*S*)-2-chloropentanal (**6**) provided the

chlorohydrin **7** in excellent yield (dr > 20:1). Following epoxide formation (Cs_2CO_3, EtOH), the alkyne function was oxidatively cleaved[17] to provide the desired α,β-epoxy acid **8** in good overall yield. Completion of the synthesis of the (*R*)-β-hydroxy ester involved esterification with (*S*)-2-pentanol and a subsequent regioselective reduction[18] of the epoxide. Following a similar sequence of reactions that started with (*R*)-2-chloropentanal, the (*S*)-β-hydroxy ester (3*S*,2*S*)-**5** (see inset in Scheme 1) was also constructed. Although the ^{1}H and ^{13}C NMR spectra derived from (3*R*,2*S*)-**5** and (3*S*,2*S*)-**5** were indistinguishable, chiral GC analysis[13] allowed confident configurational assignment of the natural product as (*S*)-2-pentyl (*R*)-3-hydroxyhexanoate.[19]

In summary, the volatile organic compounds emitted from ripening bananas that elicit an antennal response from the common fruit fly, *D. melanogaster*, have been identified by a combination of GC-EAD analysis, MS, NMR spectroscopy, and synthesis. These efforts resulted in the isolation of submicrogram quantities of the new antenna-stimulating ester (*S*)-2-pentyl (*R*)-3-hydroxyhexanoate, the structural assignment of which was confirmed by synthesis. Notably, the stereoselective synthesis of this compound involved the development of a new method to access α,β-epoxy acids. Bioassaying the behavioral response of *D. melanogaster* to individual components and/or blends of the antenna-stimulating banana volatiles[9] identified in this study may lead to the development of effective lures for the common fruit fly.

Experimental Section

General Experimental Procedures. All reactions were performed under an atmosphere of dry Ar using oven-dried glassware. THF, Et_2O, and CH_2Cl_2 were used directly from an MBraun solvent purifier system (MB-SP Series). Commercial anhydrous EtOH (reagent grade) was used without further purification. Caledon pentane non-UV was distilled prior to use. Flash chromatography was carried out with 230−400 mesh silica gel (E. Merck, silica gel 60). Chiral GC analyses were preformed on a Hewlett-Packard 5890 gas chromatograph equipped with a flame ionization detector and a custom-made chiral GC column coated with a 1:1 mixture of heptakis(2,6-di-*O*-methyl-3-*O*-pentyl)-β-cyclodextrin and OV-1701 (30 m length, 0.320 mm i.d., 0.25 μm film).[13] NMR spectra were recorded using deuterochloroform ($CDCl_3$) as the solvent on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (600 MHz), Varian Inova 500 (500 MHz), or Varian MercuryPlus (400 MHz). Signal positions (δ) are given in parts per million from TMS and were measured relative to the signal of the solvent ($CDCl_3$: δ 7.26, ^{1}H NMR; δ 77.0, ^{13}C NMR). Infrared (IR) spectra were recorded on a MB-series Bomem/Hartman & Braun Fourier transform spectrophotometer with internal calibration as films between sodium chloride plates. Selected, characteristic absorption data are provided for each compound. Chemical ionization (CI) mass spectra were recorded on a Varian 4000 mass spectrometer at 70 eV. High-resolution fast atom bombardment (HR-FABMS) mass spectra were recorded on a JEOL JMS-AX505HA mass spectrometer at 3 kV. Optical rotations were measured on a Perkin-Elmer polarimeter 341.

Collection of Volatiles from Bananas. A single yellow-ripe banana was placed in a Pyrex glass aeration chamber (15.5 cm inner diameter (i.d.) × 20 cm). For 12 days, a water-driven aspirator drew purified air at 1 L/min through the chamber and a downstream Pyrex glass column (140 × 5 mm i.d.) filled with Porapak Q (50−80 mesh, Waters, Milford, MA). Every 24 h, volatiles were eluted from Porapak Q with 2 mL of freshly distilled pentane.

Analyses of Volatiles. The volatile extracts eluted from the Porapak Q with pentane were concentrated to a volume of 1 mL and analyzed by coupled GC-EAD[7] employing a Hewlett-Packard (HP) 5890 gas chromatograph fitted with a GC column (30 m × 0.32 mm i.d.) coated with DB-5 (J&W Scientific, Folsom, CA). For GC-EAD recordings a fruit fly's head with both antennae intact was severed from the body and inserted into the opening of a glass capillary electrode (0.58 mm i.d. × 65 mm length) (A-M Systems, Inc., Calsborg, WA) filled with saline solution.[20] The tip of one antenna was removed by spring microscissors (Fine Science Tools Inc., North Vancouver, British Columbia, Canada) and then placed into the opening of the recording electrode mounted on a portable micromanipulator and positioned in front of a constant stream (250 mL/min) of warm (20 °C) nonhumidified air (Praxair Canada Inc., Mississauga, Ontario, Canada), which delivered the GC column eluent through a custom-built interface kept a 250 °C. Antennal receptor potentials (measured in mV by a custom-built amplifier) elicited by specific compounds were recorded by a HP 3392A chart recorder. Identical retention times of compounds detected by the flame ionization detector of the GC and by the insect antenna allowed assignment of antennal responses to specific compounds in the eluent. Volatiles that elicited responses from antennae were analyzed by GC-MS, employing a Varian Saturn 2000 ion trap GC-MS fitted with a DB-5 column. As (*S*)-2-pentyl (*R*)-3-hydroxyhexanoate occurred in greatest relative abundance between 24 and 48 h, in 50 additional aerations of single bananas, volatiles were Porapak Q-collected for 3 days.

Isolation of (*S*)-2-Pentyl (*R*)-3-Hydroxyhexanoate. Single or combined Porapak Q volatile extracts were evaporated to dryness under a stream of N_2 (5 min). The samples were reconstituted in 100 μL of pentane and fractionated on silica gel (50 g) in a glass column (14 × 0.5 cm i.d.). After prerinsing the silica with pentane, the extract was applied and then successively eluted with 2 mL of pentane, 1 mL of pentane/Et_2O (9:1), and 4 mL of pentane/Et_2O (3:1). The pentane/Et_2O (3:1) fraction was further purified by reversed-phase HPLC (Nova Pak C_{18}, 3.9 × 300 mm column) using a H_2O/MeCN (2:3) mobile phase. (*S*)-2-Pentyl (*R*)-3-hydroxyhexanoate eluted between 6.25 and 6.5 min. For characterization data see below.

Representative Procedure for the Synthesis of the β-Hydroxy Esters 2−4. Synthesis of 2-Butyl 3-Hydroxy-4-methylhexanoate (2). To a cold (−78 °C), stirred solution of diisopropylamine (0.66 mL, 4.7 mmol) in THF (40 mL) was added *n*-butyllithium (2.5 M solution in hexanes, 1.9 mL, 4.7 mmol). After 30 min at −78 °C, the reaction mixture was warmed to 0 °C for an additional 15 min. The resulting slightly yellow solution was cooled to −78 °C, and *sec*-butyl acetate (500 mg, 4.31 mmol) was added followed after 15 min by the addition of 2-methylbutanal (0.55 mL, 5.17 mmol). The resulting mixture was stirred for an additional 30 min, after which time it was warmed to 0 °C and treated with saturated aqueous NH_4Cl (10 mL). The mixture was then diluted with Et_2O (20 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), and concentrated to provide a crude yellow oil. Purification of the crude material by flash chromatography (silica gel, 10:1 hexanes/EtOAc) afforded (2-butyl)-3-hydroxy-4-methylhexanoate (**2**) as a mixture of four diastereomers. ^{1}H NMR (500 MHz) δ: 4.90 (m, 4H), 3.94 (m, 2H), 3.85 (m, 2H), 3.00 (m, 2H), 2.83 (m, 2H), 2.49−2.35 (m, 8H), 1.66−1.43 (m, 16H), 1.22 (d, 12H, J = 6.2 Hz), 1.17 (m, 4H), 0.93−0.88 (m, 36H). ^{13}C NMR (100 MHz) (all resolved carbon resonances reported) δ: 173.2, 173.2, 173.1, 173.1, 72.6, 72.6, 71.6, 71.5, 70.9, 70.9, 39.7, 39.7, 39.7, 39.0, 39.0, 38.1, 28.7, 25.4, 24.9, 19.3, 19.3, 14.3, 14.3, 13.7, 13.7, 11.6, 11.6, 11.4, 9.6. IR (neat): 3494, 2967, 2878, 1714, 1463, 1380, 1278, 1183, 1095, 1061, 1028 cm^{-1}. Exact mass calcd for $C_{11}H_{23}O_3$: 203.1647 (M + H); found 203.1651.

3-Methyl-2-pentyl 3-Hydroxypentanoate (3) (mixture of four diastereomers). ^{1}H NMR (500 MHz) δ: 4.87−4.78 (m, 4H), 3.85 (m, 4H), 3.16 (m, 4H), 2.42 (dd, 4H, J = 3.3, 16.2 Hz), 2.33 (ddd, 4H, J = 1.0, 8.9, 16.2 Hz), 1.57−1.34 (m, 16H), 1.13−1.01 (m, 16H), 0.90 (t, 12H, J = 7.5 Hz), 0.83 (m, 24H). ^{13}C NMR (150 MHz) (all resolved carbon resonances reported) δ: 173.4, 173.4, 173.3, 173.3, 72.8, 72.7, 71.6, 71.6, 71.0, 71.0, 39.7, 39.7, 39.7, 39.0, 39.0, 38.1, 28.8, 25.5, 25.0, 19.5, 19.5, 14.4, 14.4, 13.9, 13.8, 11.8, 11.5, 9.7. IR (neat): 3444, 2965, 2879, 1730, 1463, 1380, 1179, 1026, 983 cm^{-1}. Exact mass calcd for $C_{11}H_{23}O_3$: 203.1647 (M + H); found 203.1654.

2-Pentyl 3-Hydroxy-4-methylpentanoate (4) (mixture of two diastereomers). ^{1}H NMR (600 MHz) δ: 4.96 (apparent sextet, 2H, J = 6.1 Hz), 3.76 (m, 2H), 3.00 (m, 2H), 2.47 (dd, 2H, J = 2.4, 16.2 Hz), 2.37 (dd, 2H, J = 9.7, 16.2 Hz), 1.70 (m, 2H), 1.58 (m, 2H), 1.46 (m, 2H), 1.38−1.27 (m, 4H), 1.21 (dd, 6H, J = 0.7, 6.1 Hz), 0.95−0.89 (m, 18H). ^{13}C NMR (150 MHz) (all resolved carbon resonances reported) δ: 173.2, 173.2, 72.7, 72.7, 71.3, 38.6, 38.0, 33.1, 20.0, 19.9, 18.6, 18.6, 18.3, 17.8, 17.8, 13.9. IR (neat): 3466, 2961, 2875, 1731, 1468, 1382, 1327, 1282, 1186, 1121, 1106, 1056 cm^{-1}. Exact mass calcd for $C_{11}H_{23}O_3$: 203.1647 (M + H); found 203.1653.

(*S*)-2-Chloropentanal (6). To a cold (0 °C), stirred solution of pentanal (430 mg, 5.0 mmol) in CH_2Cl_2 (20 mL) were added D-prolinamide (57.5 mg, 0.5 mmol) and NCS (870 mg, 6.5 mmol). The reaction mixture was stirred for 1 h and then slowly warmed to

room temperature over the course of 3 h, at which temperature it was stirred until complete consumption of pentanal (as determined by ^{1}H NMR spectroscopy). The mixture was diluted with pentane (20 mL), cooled (−78 °C), filtered through a fritted funnel, and concentrated on a rotary evaporator in an ice water bath. The resulting oil was dissolved in pentane (20 mL), cooled (−78 °C), filtered through a fritted funnel, and concentrated on a rotary evaporator in an ice−water bath to give (*S*)-2-chloropentanal (**6**) (600 mg, >97% yield, 85% enantiomeric excess[21]) as a clear oil. ^{1}H NMR (500 MHz) δ: 9.44 (d, 1H, J = 2.5 Hz), 4.14 (ddd, 1H, J = 2.5, 5.0, 7.5 Hz), 1.90 (m, 1H), 1.77 (m, 1H), 1.47 (m, 2H), 0.91 (t, 3H, J = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 195.2, 63.6, 33.8, 18.7, 13.2. IR (neat): 2963, 2936, 2876, 2849, 1735, 1466, 1434, 1382, 1262, 1206, 1055 cm^{-1}. Exact mass calcd for $C_5H_{10}ClO$: 121.5868; found 121.5870. $[\alpha]_D^{25}$ −11.4 (*c* 0.6, $CHCl_3$).

(3*R*,4*S*)-4-Chloro-3-hydroxy-1-(trimethylsilyl)-1-heptyne (7). To a cold (−78 °C), stirred solution of trimethylsilylacetylene (98 mg, 1 mmol) and dry THF (10 mL) was added *n*-butyllithium (0.54 mL, 1.84 M in hexanes, 1.0 mmol). After 10 min, a solution of (2*S*)-2-chloropentanal (**6**) (132 mg, 1.1 mmol) in THF (1.0 mL) was added, and the resulting mixture was stirred for 10 min. The solution was then treated with saturated aqueous NH_4Cl (10 mL) and diluted with Et_2O (10 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL), and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), and concentrated to give the crude chlorohydrin (>20:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy). Purification of the crude product by flash chromatography (silica gel, 15:1 hexanes/EtOAc) afforded (3*R*,4*S*)-4-chloro-3-hydroxy-1-trimethylsilyl-1-heptyne (**7**) (180 mg, 83%) as a colorless oil. ^{1}H NMR (500 MHz) δ: 4.51 (dd, 1H, J = 3.5, 8.3 Hz), 4.03 (m, 1H), 2.43 (t, 1H, J = 8.3 Hz), 1.81 (m, 2H), 1.62 (m, 1H), 1.45 (m, 1H), 0.96 (t, 3H, J = 7.4 Hz), 0.19 (s, 9H). ^{13}C NMR (150 MHz) δ: 101.7, 92.0, 66.5, 66.4, 35.4, 19.7, 13.5, −0.3. IR (neat): 3367, 2961, 2875, 2177, 1466, 1382, 1251, 1123 cm^{-1}. Exact mass calcd for $C_{10}H_{18}ClSi$: 201.0861 (M − OH); found 201.0867. $[\alpha]_D^{25}$ −11.1 (*c* 8.7, $CHCl_3$).

(2*S*,3*R*)-2,3-Epoxyhexanoic Acid (8). To a solution of (3*R*,4*S*)-4-chloro-3-hydroxy-1-trimethylsilyl-1-heptyne (**7**) (90 mg, 0.4 mmol) in ethanol (4 mL) was added Cs_2CO_3 (202 mg, 0.6 mmol), and the reaction mixture was stirred for 16 h at room temperature. The mixture was treated with H_2O (5 mL) and diluted with pentane (10 mL), and the phases were separated. The aqueous phase was extracted with pentane (3 × 10 mL), and the combined organic phases were washed with brine (3 × 15 mL), dried ($MgSO_4$), and concentrated to give a crude epoxide, which was used without further purification.

To a cold (0 °C), stirred solution of the crude epoxide in a 1.5:1:0.3 mixture of MeCN/H_2O/EtOAc (11.5 mL) were added Oxone (834 mg, 1.4 mmol) and $NaHCO_3$ (342 mg, 4.1 mmol). After 5 min, $RuCl_3 \cdot 3H_2O$ (3 mg, 0.01 mmol) was added and the reaction mixture was stirred at 0 °C for 1 h. The mixture was then treated with 10% aqueous $NaHSO_3$ (10 mL), acidified with 2 N aqueous HCl to pH < 2, and diluted with EtOAc (15 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 10 mL), and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Purification of the crude product by flash chromatography (Iatrobeads, 2.5% MeOH in CH_2Cl_2) afforded (2*R*,3*R*)-2,3-epoxyhexanoic acid (**8**) (35 mg, 65% over two steps) as a clear oil. ^{1}H NMR (600 MHz) δ: 8.11 (br s, 1H), 3.26 (s, 1H), 3.20 (t, 1H, J = 4.8 Hz), 1.68−1.46 (m, 4H), 0.98 (t, 3H, 7.4 Hz). ^{13}C NMR (150 MHz) δ: 174.8, 58.9, 52.5, 33.3, 19.0, 13.7. IR (neat): 2963, 2876, 1730, 1462, 1383, 1198, 899 cm^{-1}. Exact mass calcd for $C_6H_{11}O_3$: 131.0708 (M + H); found 131.0703. $[\alpha]_D^{25}$ +11.6 (*c* 8.0, $CHCl_3$).

(*S*)-2-Pentyl (2*R*,3*R*)-2,3-expoxyhexanoate (9). To a solution of epoxy acid **8** (100 mg, 0.77 mmol) in CH_2Cl_2 (10 mL) were added (2*S*)-2-pentanol (92 μL, 0.85 mmol), DCC (238 mg, 1.2 mmol), and DMAP (9 mg, 0.08 mmol). The resulting mixture was stirred at room temperature for 48 h, filtered through a plug of Celite, and concentrated. Purification of the crude product by flash chromatography (silica gel, CH_2Cl_2) afforded (*S*)-2-pentyl (2*R*,3*R*)-2,3-expoxyhexanoate (**9**) (92 mg, 60%) as a clear oil. ^{1}H NMR (500 MHz) δ: 5.00 (apparent sextet, 1H, J = 6.3 Hz), 3.18 (d, 1H, J = 1.9 Hz), 3.12 (dt, 1H, J = 1.9, 6.2 Hz), 1.67−1.45 (m, 6H), 1.33 (m, 2H), 1.23 (d, 3H, J = 6.3 Hz), 0.97 (t, 3H, J = 7.2 Hz), 0.91 (t, 3H, J = 7.3 Hz). ^{13}C NMR (100 MHz) δ: 169.0, 72.3, 58.2, 53.2, 37.9, 33.4, 19.8, 19.1, 18.6, 13.8, 13.7. IR (neat): 2961, 2875, 1749, 1465, 1381, 1290, 1244, 1200, 1121 cm^{-1}. Exact mass calcd for $C_{11}H_{21}O_3$ (M + H): 201.1491; found 201.1487. $[\alpha]_D^{25}$ +14.3 (*c* 10.0, $CHCl_3$).

Preparation of (*S*)-2-Pentyl (*R*)-3-hydroxyhexanoate (5). To a solution of diphenyldiselenide (47 mg, 0.15 mmol) in EtOH (2 mL) was added $NaBH_4$ (13 mg, 0.34 mmol). After gas evolution had subsided the reaction was cooled to 0 °C and HOAc (12 μL, 0.4 mmol) was added. The reaction mixture was stirred for 5 min, a solution of epoxy ester **9** (20 mg, 0.1 mmol) in a 1:0.5 mixture of THF/EtOH (1.5 mL) was added, and the resulting mixture was stirred at 50 °C for 24 h. The reaction mixture was then cooled, purged with air for 5 min, and concentrated. Purification of the crude product by flash chromatography (silica gel, 15:1 hexanes/EtOAc) afforded (*S*)-2-pentyl (*R*)-3-hydroxyhexanoate (**5**) (18 mg, 90%) as a clear oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.97 (apparent sextet, 1H, J = 6.3 Hz), 4.00 (m, 1H), 3.01 (d, 1H, J = 3.8 Hz), 2.48 (dd, 1H, J = 2.9, 16.4 Hz), 2.38 (dd, 1H, J = 9.2, 16.4 Hz), 1.61−1.27 (m, 8H), 1.22 (d, 3H, J = 6.3 Hz), 0.93 (t, 3H, J = 7.2 Hz), 0.91 (t, 3H, 7.1 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 173.1, 71.5, 67.9, 41.7, 38.8, 38.2, 20.2, 18.9, 18.8, 14.2, 14.1. IR (neat): 3450, 2932, 2874, 1731, 1466, 1379, 1176, 1120, 1019, 996 cm^{-1}. Exact mass calcd for $C_{11}H_{23}O_3$: 203.1647 (M + H); found 203.1630. $[\alpha]_D^{25}$ +3.4 (*c* 10.0, $CHCl_3$).

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Supporting Information Available: ^{1}H NMR and 1D TOCSY spectra recorded on the natural product and ^{1}H and ^{13}C NMR spectra for all new synthetic compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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