

Improved Synthesis and Deployment of (2*S*,3*R*)-2-(2*Z*,5*Z*-Octadienyl)-3-nonyloxirane, a Pheromone of the Pink Moth, *Lymantria mathura*

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We report two new syntheses of (2*S*,3*R*)-2-(2*Z*,5*Z*-octadienyl)-3-nonyloxirane, the main sex pheromone component of the pink moth, *Lymantria mathura*. The key step in the first route was the construction of (Z,Z)-1-bromo-1,4-heptadiene (**6**), which was coupled in the final step with 2-iodomethyl-3-nonyloxirane **4** via a Grignard reaction. The second approach employed alkylation of 1,4-heptadienyllithium with epoxy triflates **7** in ether/hexane and provided the pheromone in $\geq 37\%$ overall yield from alcohol **2**. The 4:1 ratio of pheromone enantiomers, reportedly the most attractive to pink moth males, can be directly crafted from appropriately selected Sharpless asymmetric epoxidation conditions.

KEYWORDS: Pink moth; *Lymantria mathura*; (2*S*,3*R*)-2-(2*Z*,5*Z*-octadienyl)-3-nonyloxirane; (3*Z*,6*Z*,9*S*,10*R*)-9,10-epoxy-3,6-nonadecadiene; pheromone; syntheses

INTRODUCTION

The pink moth, also known as the rosy Russian gypsy moth (*Lymantria mathura* Moore), is a widespread pest in Asia, including Russia, China, Japan, and India. It is a polyphagous defoliator of hardwood forest and orchard trees, but it rarely rises to pest status in its native range. Females of *L. mathura* are readily attracted to artificial lights (1), and they and their egg masses have been detected on ships originating from Asian seaports bound for the United States and Canada. Newly hatched larvae can readily disperse from these ships by ballooning on wind currents to habitats favorable for establishment and development (2). Traps baited with *L. mathura* pheromone can play an essential part in monitoring at possible introduction sites.

The main component of the pink moth pheromone was identified by Oliver et al. (3) as (2*S*,3*R*)-2-(2*Z*,5*Z*-octadienyl)-3-nonyloxirane (**1b**). This compound was active in electrophysiological tests, whereas the enantiomer **1c** evoked weaker responses that were speculated to result from the presence of $\sim 5\%$ of **1b** as a contaminant in the sample of **1c**. Both the single enantiomer **1b** and the racemate were active in our initial field tests, as was the racemic monoepoxide mixture from random epoxidation of the parent triene. In contrast, Gries et al. (4)

identified both **1b** [Gries et al. (4) referred to *S,R* oxirane **1b** as (–)-mathuralure whereas it is dextrorotatory as are *S,R* diene epoxides in general (see, e.g., ref 5)] and **1c** in the insect abdominal tips using chiral gas chromatography (GC) and reported that neither the individual enantiomers nor the racemate was attractive to male moths in field tests but that a mixture of **1b** and **1c** in a 4:1 ratio—as produced by females—was active in their field trials.

The exact percentage of enantiomer **1c** required for maximum attractiveness remains unclear. Questions of practical importance are whether the racemic epoxide **1** is active enough to be used for monitoring of pink moth populations and whether the 4:1 ratio of pheromone enantiomers could be conveniently produced from a single stereoselective reaction.

Syntheses of both enantiomers of epoxide **1** have been accomplished (3, 5) based on a method developed by Mori et al. (6, 7) for analogous pheromones. The route combines the Sharpless asymmetric epoxidation of (2*Z*,5*Z*,8*Z*)-undecatrien-1-ol and the coupling of epoxy tosylates with dialkyl cuprates. Even though the epoxidation did not provide very high asymmetric induction (84% ee), optically pure epoxy alcohols were obtained by repeated crystallizations of the corresponding 3,5-dinitrobenzoates (6, 7). The requirement for (2*Z*,5*Z*,8*Z*)-undecatrien-1-ol constitutes a limitation of this route, as its precursor, 2,5,8-undecatrien-1-ol, is unstable and because Lindlar semihydrogenation was not entirely selective, providing trienol of $\sim 90\%$ purity (6). Alternative reductions were no better: P2–Ni reduction afforded a low yield [24% (8)], and

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borane-dimethyl sulfide reduction, besides being cumbersome for preparative scale reactions, also afforded only 47% yield (5). The Wittig reaction offers another approach to oxiranes with "skipped" diene substituents (9, 10). However, general inaccessibility of the required unsaturated reagents, low temperatures ($-100\text{ }^{\circ}\text{C}$), and moderate yields often make the Wittig approaches less attractive than some offered by acetylenic chemistry. Here, we wish to report two new syntheses of both enantiomers of **1** based on the Sharpless asymmetric epoxidation, one using a novel preparation of (*Z,Z*)-1-bromo-1,4-heptadiene (**6**) and coupling of that compound with iodoepoxide **4** via a Grignard reaction, and the second employing alkylation of 1,4-heptadiynyllithium with epoxytriflate **7** to produce the key intermediate, diyne epoxide **8**. Because a 4:1 ratio of the two enantiomers has been reported (4) to be the most effective, we also adopted the practice of intentionally selecting epoxidation conditions that would normally be considered slightly suboptimal for maximizing the content of (*S,R*)-epoxide **1b** but that directly provided the desired 4:1 composition.

MATERIALS AND METHODS

Melting points and boiling points are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded with tetramethylsilane as an internal standard on a Bruker QE-300 spectrometer. ^1H NMR coupling constants are reported in Hz. GC analyses were performed on a Shimadzu 17A gas chromatograph using a $60\text{ m} \times 0.25\text{ mm}$ RTX-1701 column (Restek Corporation) and H_2 as the carrier gas. Optical purities of the epoxyalcohols were determined on a Chiraldex B-DM GC column (β -cyclodextrin, dimethyl), $30\text{ m} \times 0.25\text{ mm}$ (Advanced Separation Technologies, Inc). Electron impact ionization mass spectra (70 eV) were obtained with a Hewlett-Packard 5971 GC-MS equipped with a $30\text{ m} \times 0.25\text{ mm}$ DB-5MS column (J&W Scientific). Chemical ionization spectra were recorded on a Shimadzu GCMS-QP 5050A equipped with a $30\text{ m} \times 0.25\text{ mm}$ DB-5MS column, using ammonia as the reagent gas. Specific rotations were measured on a Perkin-Elmer 241 polarimeter. Combustion analyses were conducted by Galbraith Laboratories Inc. (Knoxville, TN). Flash chromatography was carried out with 230–400 mesh silica gel (Whatman). The reagents were purchased from Aldrich Chemical Co. unless otherwise specified. Anhydrous *tert*-butyl hydroperoxide was purchased from Fluka Chemical Corp. Tetrahydrofuran (THF) and ether were freshly distilled from sodium-benzophenone ketyl under N_2 . Methylene chloride and hexamethylphosphoramide (HMPA, highly toxic!) were distilled from P_2O_5 . 2-Dodecyn-1-ol was synthesized from 1-undecyne and paraformaldehyde (11). (*Z*)-2-Dodecen-1-ol (**2**) was prepared by reduction of 2-dodecyn-1-ol with activated zinc (12). 1,4-Heptadiyne was synthesized by alkylation of 1-butylnmagnesium bromide with propargyl tosylate catalyzed by copper(I) bromide (13). Ethyl (*Z*)-3-bromo-2-propenoate was made by hydrobromination of ethyl 2-propynoate (14), and the latter was reduced with lithium aluminum hydride to (*Z*)-3-bromo-2-propen-1-ol (15). Copper(I) iodide and copper(I) bromide were purified according to Kauffman and Teter (16). Mention of a proprietary company or product does not imply endorsement by the U.S. Department of Agriculture.

(2*S*,3*R*)-3-Nonyloxiranemethanol (3b). A. Compound **3b** was synthesized according to a literature procedure (11) from (*Z*)-2-dodecen-1-ol (**2**) but using 1 equiv of titanium tetra(isopropoxide) and 1.12 equiv of (*L*)-diethyl tartrate. The reaction was run for 4 days at $-20\text{ }^{\circ}\text{C}$ and afforded 66% of the epoxy alcohol of 80% ee after crystallization from cyclohexane. Further crystallizations gave little or no improvement of the optical purity; hence, the crude mixture of epoxyalcohols (2.70 g, 9:1 *SR/RS*) was dissolved in benzene (10 mL) and pyridine (5 mL). The solution was stirred in an ice bath while a solution of 3,5-dinitrobenzoyl chloride (from 15 mmol of 3,5-dinitrobenzoic acid and oxalyl chloride) in about 15 mL of benzene was added dropwise. The ice bath was removed, and the mixture was stirred at room temperature for 1.5 h, added to ice, and partitioned between ethyl acetate and water. The crude product (5.17 g) was flash chromatographed on silica gel

(5–20% ethyl acetate in hexanes). The desired ester (2.76 g, R_f 0.20, 10% ethyl acetate in hexanes) was recrystallized from hexane plus 5% ether to give 1.33 g of dinitrobenzoate of 97% ee, as determined by GC analysis of the parent alcohol on a Chiraldex B-DM column. Another crystallization from methanol provided 0.50 g of dinitrobenzoate of 99% ee. This was dissolved in methanol (5 mL) and treated with 1 N sodium hydroxide (1.6 mL). After it was stirred at room temperature for 1 h, the mixture was partitioned between ice water and ether. The organic layer was rinsed again with dilute sodium hydroxide, water, and finally with brine, then was dried (Na_2SO_4) and concentrated to provide 0.24 g of a white solid that was recrystallized from hexane to give 0.20 g of **3b** of 99% ee; mp $58\text{ }^{\circ}\text{C}$, $[\alpha]_D^{25} -3.5^{\circ}$ (c 1.1, CHCl_3). GC-MS (CI, NH_3 , m/z): 200 (M^+), 202 ($\text{M}^+ + 2$), 218 ($\text{M}^+ + 18$). GC-MS (EI): 169 ($\text{M}^+ - 31$, 2), 109 (5), 97 (45), 83 (100), 69 (72), 55 (78), 43 (48). MS (EI) data are in agreement with literature (11).

B. The following epoxidation conditions were used specifically to prepare **3b** of about 60% ee. Alcohol **2** (263 mg, 1.43 mmol) was epoxidized with anhydrous *t*- $\text{C}_4\text{H}_9\text{OOH}$ (521 μL of 5.5 M in decane, 2.86 mmol) in the presence of titanium tetra(isopropoxide) (421 μL , 1.43 mmol) and (*L*)-diisopropyl tartrate (201 mg, 0.86 mmol, 0.6 equiv) in dichloromethane (20 mL) at $-18\text{ }^{\circ}\text{C}$ for 120 h. The alcohol-catalyst-tartrate mixture was "aged" for 30 min before addition of peroxide as prescribed (11, 17). The mixture was then treated with 10% (*L*)-tartaric acid (3 mL) for 1 h at -23 to $-25\text{ }^{\circ}\text{C}$, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 . The combined organic extract was washed with water, dried (Na_2SO_4), concentrated, dissolved in ether (7–10 mL), and stirred with 1 N NaOH (3 mL) at $0\text{ }^{\circ}\text{C}$ for 30 min. The layers were separated, the aqueous layer was extracted with ether, and then the combined ethereal extracts were washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography (hexane/ethyl acetate, 3:2) afforded 204 mg (71%) of the mixture of epoxy alcohols **3b** and **3c** in the ratio 18.4:81.5 (63% ee).

(2*R*,3*S*)-3-Nonyloxiranemethanol (3c). Compound **3c** was prepared analogously to the *S,R*-enantiomer using (*D*)-diethyl tartrate; $[\alpha]_D^{25} +3.6^{\circ}$ (c 1.0, CHCl_3), and racemic (*cis*)-3-nonyloxiranemethanol (**3a**) was synthesized in 80% yield by epoxidation of (*Z*)-2-dodecenol with *m*-chloroperbenzoic acid in methylene chloride at $0\text{ }^{\circ}\text{C}$ as described by Magnusson et al. (18).

***cis*-2-Iodomethyl-3-nonyloxirane (4a)**. A solution of **3a** (200 mg, 1.0 mmol) in benzene (10 mL) plus ether (20 mL) was treated with imidazole (272 mg, 4.0 mmol) and triphenylphosphine (394 mg, 1.50 mmol) following Marshall et al. (19). A solution of iodine (375 mg, 1.48 mmol) in ether (6 mL) was added dropwise at 5 – $10\text{ }^{\circ}\text{C}$. After the addition was complete, the mixture was stirred at room temperature for 1 h, then much of the solvent was removed and replaced with 1:1 ether-petroleum ether. The soluble portion was filtered into a separatory funnel and rinsed with water and saturated sodium bicarbonate, then dried (Na_2SO_4), and concentrated. The residue was flash chromatographed (0–10% ethyl acetate in hexanes) to give 266 mg of pure iodooxirane **4a** (86%, R_f 0.41, 5% ethyl acetate in hexanes). ^1H NMR: 0.87 (t, 3H), 1.30 (m, 14H), 1.50 (m, 2H), 2.95–3.10 (m, 2H), 3.25–3.35 (m, 2H). GC-MS (CI, NH_3): 328 ($\text{M}^+ + 18$). GC-MS (EI): 183 (29, $\text{M}^+ - 1$), 97 (47), 69 (75), 55 (78), 83 (100). Anal. calcd for $\text{C}_{12}\text{H}_{23}\text{IO}$: C, 46.46; H, 7.47. Found: C, 46.91; H, 7.55.

(2*R*,3*R*)-2-Iodomethyl-3-nonyloxirane (4b) and (2*S*,3*S*)-2-Iodomethyl-3-nonyloxirane (4c). Compounds **4b,c** were prepared in an analogous manner from the respective chiral epoxyalcohols; $[\alpha]_D^{25} +65.0^{\circ}$ (c 1.0, CHCl_3) for **4b** and -63.0° (c 1.2, CHCl_3) for **4c**.

(*Z*)-1,3-Dibromopropene (5). To a solution of triphenylphosphine (27.5 g, 0.11 mol) in dry dichloromethane (125 mL) was added bromine (5.4 mL, 0.11 mol) dissolved in dry dichloromethane (10–15 mL) at 0 to $-5\text{ }^{\circ}\text{C}$. (*Z*)-3-Bromo-2-propen-1-ol (13.7 g, 0.10 mmol) in CH_2Cl_2 (20 mL) was added slowly to the resulting suspension at $-20\text{ }^{\circ}\text{C}$. After it was stirred for 0.5–1.0 h at that temperature, the mixture was quenched with 2–3 mL of MeOH and carefully concentrated on a rotary evaporator (bath temp 25 – $30\text{ }^{\circ}\text{C}$). The residue was suspended in pentane ($\sim 200\text{ mL}$) and filtered, and the solid $(\text{Ph})_3\text{PO}$ was washed with pentane ($2 \times 40\text{ mL}$). The combined pentane extracts were rinsed with saturated NaHCO_3 , dried (Na_2SO_4), concentrated, and distilled to

give **5** (15.0 g, 75%, >98% purity); bp 58–60 °C/25 mmHg. GC-MS (EI): 202, 200, 198 (21, 40, and 19%, M⁺), 121 (100, M⁺-Br) and 119 (98, M⁺-Br).

(Z,Z)-1-Bromo-1,4-heptadiene (6). An oven-dried flask equipped with a thermometer, mechanical stirrer, dry ice condenser, rubber septum, and N₂ inlet was loaded with dry THF (100 mL) and cooled to -20 to -25 °C. A previously prepared, freezer-cooled solution of 1-butyne (GFS Chemicals, Powell, OH) in THF (23 mL, 115.5 mg/mL, 49.0 mmol) was added quickly via syringe. A solution of ethylmagnesium bromide in ether (16 mL, 3 M, 48 mmol) was added slowly at -25 to 0 °C, and the resulting mixture was warmed to ambient temperature, heated at 35–40 °C for ~40 min, and cooled again to -20 °C. Copper(I) iodide (457 mg, 2.4 mmol) was added followed by dry HMPA (17.2 mL, 96 mmol), and the suspension was stirred at -20 to -25 °C for 0.5 h. A solution of **5** (4.85 g, 24.3 mmol) in THF (ca. 10 mL) was added at -25 °C, and the mixture was stirred at that temperature for 3–4 h during which time a thick white precipitate formed. GC analysis indicated that the reaction was essentially complete. The reaction mixture was poured into saturated NH₄Cl, treated with a solution of potassium cyanide (5.80 g in 35 mL H₂O), and extracted with pentane (3 × 50 mL). The organic extract was washed with saturated NH₄Cl solution, dried (Na₂SO₄), and concentrated to leave crude product (4.30 g) containing 92% (Z)-1-bromo-1-hepten-4-yne. Because the bromoenyne is very unstable in air, most of the sample was reduced to the corresponding diene without purification following a procedure of Brown and Ahuja (20) as modified by Millar and Oehlschlager (21). [An analytical sample of the (Z)-1-bromo-1-hepten-4-yne of 94% purity was obtained by flash chromatography using pentane. ¹H NMR (CDCl₃): 1.10 (t, J = 7.5, H-7), 2.14 (tq, ³J = 7.5, ⁵J = 2.5, H-6), 3.05 (m, H-3), 6.14 (dt, J₂₋₁ ~ J₂₋₃ = 7.0, H-2), 6.20 (dt, J = 7.0 and 1.5, H-1). MS (EI): 172, 174 (both 6%, M⁺), 93 (100), 91 (53), 77 (76), 78 (25), 65 (21)]. A suspension of nickel acetate tetrahydrate (3.10 g, 12.4 mmol) in ethanol (30 mL, 95%) was cooled in an ice bath and reduced with a sodium borohydride solution in ethanol (1 M, 25 mL, 25.0 mmol). After H₂ evolution ceased, ethylenediamine (1.67 mL, 25.0 mmol) and finally crude bromoheptyne (4.30 g) dissolved in ethanol (10 mL) were added. The mixture was stirred under a H₂ atmosphere at 0–5 °C and monitored by GC until hydrogenation was complete. The reaction products were filtered under N₂ pressure through activated granular charcoal, and the solids were washed with ethanol (3 × 35 mL). The filtrate was diluted with ice water (~200 mL) and extracted with pentane (6 × 50 mL), and the combined pentane extracts were washed with 3% HCl and water and then dried over Na₂SO₄. The pentane was removed by careful distillation through a 15 cm Vigreux column under N₂, and the residue was distilled using a water aspirator. Bromide **6** (1.94 g, 46% from **5**) of 93–95% purity was collected at 72–74 °C/31 mmHg and used in the next step. It is more stable than the enyne precursor and could be stored in a freezer for several months without noticeable change. A sample of >98% purity was obtained by flash chromatography of crude material on 15% AgNO₃-SiO₂ with pentane. ¹H NMR (CDCl₃): 1.00 (t, J = 7.5, H-7), 2.10 (dq, J₁ = J₂ = 7.2, H-6), 2.94 (dd, J₁ = J₂ = 7.0, H-3), 5.26–5.38 (m, 1H), 5.40–5.51 (m, 1H), 6.06 (dt, J₁ = J₂ = 7.0, H-2), 6.15 (dt, J = 7.0 and 1.5, H-1). The data are in close agreement with literature values (22). MS (EI): 174, 176 (each 11%, M⁺), 145 (5), 147 (5), 132 (70), 134 (69), 95 (100), 67 (49), 55 (66).

(2S,3R)-2-(2Z,5Z-Octadienyl)-3-nonyloxirane (1b). 1,2-Dibromoethane (0.94 g, 5 mmol) was added under a N₂ atmosphere to magnesium turnings (1.03 g, 42.4 mmol) in THF (15 mL). After the exothermic reaction ceased, a solution of **6** (5.0 g, 28.6 mmol) in THF (15 mL) was added dropwise over 0.5 h, maintaining the reaction temperature between 60 and 65 °C. Upon completion of the bromide addition, the dark brown mixture was stirred at 60–70 °C for 0.5 h, then cooled to ambient temperature, diluted with THF (20 mL), and cannulated into a dropping funnel. In a separate oven-dried flask were placed CuI (0.248 g, 1.3 mmol), THF (10 mL), and HMPA (10 mL). The mixture was stirred at 20–25 °C to form a faint green solution to which **4b** (5.10 g, 16.5 mmol) in THF (10 mL) was added in one portion. The resulting mixture was cooled to -30 °C, and the Grignard reagent was slowly added maintaining the temperature from -25 to -30 °C. The resulting yellow suspension was stirred at -20 °C for 1

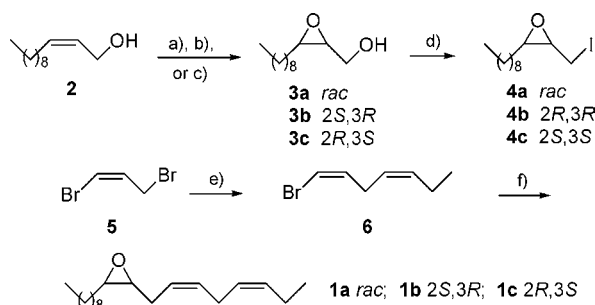
h, poured into saturated NH₄Cl (~100 mL), and extracted with ether/hexane, 1:1 (3 × 50 mL). The organic extract was dried over Na₂SO₄, concentrated, and flash chromatographed with hexane/ethyl acetate, 98:2, to give 3.75 g of material, containing ~15% unreacted iodoepoxide **4b**. This was dissolved in dry DMF (25 mL) and treated with anhydrous lithium acetate (0.6 g) at 78–80 °C for 12 h to convert starting iodoepoxide to the corresponding acetate. The reaction mixture was added to water (~40 mL) and extracted with ether/hexane 1:1 (3 × 30 mL), and the extract was dried, concentrated, and flash chromatographed with hexane/ethyl acetate, 95:5 to 90:10. The coupling products (2.44 g, 53% yield based on initial amount of **4b**) containing 83% of **1b** were isolated from the less polar fraction [(2S,3R)-3-Nonyloxiranemethanol acetate (0.62 g) was isolated from a more polar fraction. GC-MS (CI, NH₃): 243 (M + 1), 260 (M + 18). Hydrolysis (aqueous NaOH/MeOH) and subsequent chromatography facilitated the recovery of optically pure **3b** that could be reused.] The main impurity (~10%) had the same molecular weight as **1b** based on GC-MS (CI, NH₃): 261 (M - 17), 279 (M + 1), 296 (M + 18). Further purification by flash chromatography on 15% AgNO₃-SiO₂, hexane/ethyl acetate, 9:1, gave **1b** (1.79 g, 39%) of 98% chemical purity and ≥99% ee as determined by conversion to diastereomeric aziridines following (23); [α]_D²⁵ +5.3° (c 1.0, CHCl₃). Lit. (5) [α]_D²³ +3.5° (c 8.57, CHCl₃). GC-MS (CI, NH₃): 261 (M - 17), 279 (M + 1), 296 (M + 18). ¹H NMR (CDCl₃): 0.89 (t, J = 7.0, H-19), 0.98 (t, J = 7.5, H-1), 1.26 (br s, 14H), 1.53 (m, H-11), 2.08 (dq, J₁ = J₂ = 7.5, H-2), 2.23 (ddd, ²J = 14.5, ³J₁ = ³J₂ = 6.5, H_A-8), 2.41 (ddd, ²J = 14.5, ³J₁ = ³J₂ = 6.5, H_B-8), 2.81 (dd, ³J₁ = ³J₂ = 6.5, H-5), 2.92 (m, 2H, H-9, 10), 5.26–5.53 (m, 4H, H-3, 4, 6, 7). ¹³C NMR: 14.1, 14.2 (C-1, 19), 20.6, 22.7, 25.8, 26.3, 26.6, 27.8, 29.3, 29.5, 29.6 (double intensity), 31.9 (CH₂), 56.4, 57.2 (C-9, 10), 124.3, 126.8, 130.8, 132.3 (C-3, 4, 6, 7). Both ¹H and ¹³C NMR data are in close agreement with literature values for an analogous C-21 dienic epoxide (5, 22).

(2R,3S)-2-(2Z,5Z-Octadienyl)-3-nonyloxirane (1c). Compound **1c** was synthesized in an analogous manner from **6** (1.6 equiv) and **4c**; [α]_D²⁵ -4.3° (c 1.15, CHCl₃). Lit. (5) [α]_D²³ -4.3° (c 8.89, CHCl₃).

2-(2,5-Octadiynyl)-3-nonyloxirane (8a). To a solution of **3a** (2.14 g, 10.70 mmol) in dry CH₂Cl₂ (35 mL) containing 2,6-lutidine (1.26 g, 11.77 mmol) was added triflic anhydride (1.98 mL, 11.77 mmol) in CH₂Cl₂ at -60 °C. The solution was stirred for 0.5 h while slowly warming to -45 °C, and then ice water and pentane were added, and the layers were separated. The aqueous layer was extracted twice with pentane, and then the pentane extracts were washed with aqueous NaHSO₄ and aqueous NaHCO₃, dried with Na₂SO₄, and concentrated. Flash chromatography (hexane/ethyl acetate, 9:1) afforded pure triflate **7a** (3.24 g, 91%). MS (CI, NH₃): 350 (M⁺ + 18).

To a solution of 1,4-heptadiyne (202 mg, 2.2 mmol) in dry ether (5 mL) at -78 °C was slowly added a hexane solution of butyllithium (1.8 mL, 1.11 M, 2.0 mmol) keeping the temperature around -75 °C. After the mixture was stirred at -78 °C for 1.5 h, a pale yellow suspension formed to which was added triflate **7a** (330 mg, 1.0 mmol) dissolved in dry ether (1 mL). The solution was allowed to warm to -50 to -40 °C (whereupon a white precipitate separated) and placed overnight in a freezer at -25 °C. The resulting thick suspension was poured into saturated NH₄Cl and extracted with ether/hexane (1:1), and the organic extract was washed with aqueous NH₄Cl, dried with Na₂SO₄, and concentrated. Flash chromatography (hexane/ethyl acetate, 95:5) gave diyne oxirane **8a** (220 mg, 80% yield, 98% purity). GC-MS (CI, NH₃): 275 (M⁺ + 1), 292 (M⁺ + 18). ¹H NMR (CDCl₃): 0.87 (t, J = 6.5, 3H), 1.12 (t, J = 7.5, 3H), 1.15–1.60 (br m, 14H), 1.50 (m, 2H), 2.17 (br q, H-7'), 2.27 (br dd, ²J = 17.1, ³J = 7.0, 1H, H-1'), 2.56 (ddt, ²J = 17.1, ³J = 5.5, ⁵J = 2.6, 1H, H-1'), 2.94 (dt, ³J = 5.5, 4.5, 1H, H-3), 3.13 (m, 3H, H-2, H-4'). The signals are in close agreement with the literature data for an analogous diyne oxirane (22). Anal. calcd for C₁₉H₃₀O: C, 83.15; H, 11.02. Found: C, 82.89; H, 11.00.

cis-2-(2Z,5Z-Octadienyl)-3-nonyloxirane (1a). Oxirane **8a** (296 mg, 1.08 mmol) was dissolved in a mixture of methanol (13 mL) and cyclohexene (0.5 mL) plus quinoline (40 μL) and stirred in the presence of 5% Pd on CaCO₃ (31 mg, Lindlar catalyst, lead poisoned, Strem Chemicals, Newburyport, MA) in a hydrogen atmosphere. After about 1 h, the reaction was complete by GC analysis. The mixture was filtered

Scheme 1^a

^a Reagents and conditions: (a) MCPBA, CH₂Cl₂, (80%). (b) 1. *t*-BuOOH/Ti(O-*i*-Pr)₄/(*D*)- or (*L*)-DET (**3b**, 66%, 80% ee); 2. 3,5-(NO₂)₂C₆H₃COCl/Py, crystallization, NaOH/MeOH, (99% ee for **3b** and **3c**). (c) *t*-BuOOH, 1 equiv Ti(O-*i*-Pr)₄, 0.6 equiv (*L*)-DIPT (**3b**, 71%, 63% ee). (d) Ph₃P, imidazole, I₂ (86%). (e) 1. EtC≡CMgBr, CuI/HMPA; 2. H₂, P2-Ni (46% from **5**). (f) 1. Mg, THF, reflux; 2. 0.58 equiv **4**, CuI, HMPA/THF, -30 to -25 °C, AgNO₃-SiO₂ (39% from **4**).

through a short pad of Celite, the pad was rinsed with 5 mL of MeOH, the filtrate was concentrated, and the residue was flash chromatographed with hexane/ethyl acetate, 30:1, plus 0.1% MeOH to give 280 mg (93%) of oxirane **1a** of 95% purity. A product of 99% purity was obtained by chromatography on 15% AgNO₃-SiO₂ as described above. The spectral data of **1a** and chiral epoxide **1b** were identical.

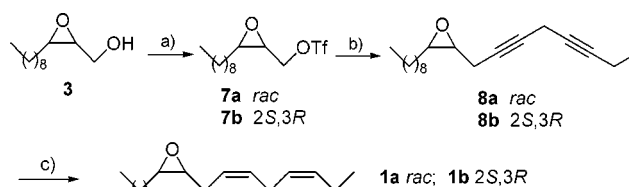
Analogous to the above procedures, chiral epoxyalcohol **3b** of 63% ee (2.14 g, 10.7 mmol) was converted to the corresponding triflate (3.20 g, 91%), which was alkylated with 2.0 equiv of 1,4-heptadiynyllithium to give **8b** (1.96 g, 74%). Reduction of the latter with Lindlar catalyst afforded **1b** (1.55 g, 78%) of 97% chemical purity.

RESULTS AND DISCUSSION

Synthesis of both enantiomers and racemic **1** via a copper(I)-catalyzed Grignard coupling is illustrated in **Scheme 1**. (*Z*)-2-Dodecen-1-ol was epoxidized either with MCPBA in the achiral route or via the Sharpless asymmetric epoxidation protocol (17) affording epoxyalcohols **3**. The optical purities of **3b** and **3c** (~80% ee) were further enriched by recrystallization of their respective 3,5-dinitrobenzoates to 99% ee (judged by GC analyses of the regenerated alcohols **2a** and **2b** on a Chiraldex B-DM column) following published procedures (3, 6).

We examined a variety of conditions in order to fine-tune the asymmetric epoxidation to produce the desired 4:1 (60% ee) ratio of epoxides **3**, which was expected to remain unchanged throughout the synthesis. It turned out that running the epoxidation of **2** in the presence of 1 equiv of titanium tetra(isopropoxide) and 0.57–0.70 equiv of (*L*)-diisopropyl tartrate, with other conditions as described in the original version (24), furnished **3b** of 55–65% ee (with 0.60 equiv of tartrate the ee was 63%). The epoxyalcohols **3** were smoothly converted to the corresponding iodo epoxides **4** using iodine/triphenylphosphine/imidazole (19, 25).

For synthesis of the second building block **6**, we used (*Z*)-1,3-dibromopropene **5**, easily prepared in three steps from ethyl 2-propynoate in 45% yield (14, 15). Initial attempts toward cuprous chloride-catalyzed alkylation (26) of 1-butyne with **5** resulted in a partial (~5%) *Z/E* isomerization, along with some (12%) homocoupling of the alkyne. We found that the *Z* configuration remained virtually intact and the homocoupling could be contained to ~5% if 1-butyne was alkylated with **5** via a Grignard reagent in the presence of CuI in THF/HMPA at -30 to -20 °C. Thus, crude (*Z*)-1-bromo-1-hepten-4-yne of 92% purity was prepared but it was too unstable in air to isolate so it was hydrogenated without purification with P2-Ni catalyst

Scheme 2^a

^a Reagents and conditions: (a) (Tf)₂O, 2,6-lutidine (91%). (b) Two equiv EtC≡CCH₂C≡CLi, ether/hexane, -70 to -40 °C (80%). (c) H₂, Pd-CaCO₃, MeOH/cyclohexene (93%, 95% purity).

to bromodiene **6**. The yield of distilled **6** after the two-step process was 46%, an improvement over the previously reported yield of less than 20% resulting from hydroboration of 1-bromo-1,4-heptadiyne (22).

In the final step, bromodiene **6** was converted to a Grignard reagent in refluxing THF and added to iodoepoxide **4b** (0.58 equiv) in the presence of 10% CuI in HMPA/THF at -30 °C following the original alkylation procedure of Nicolaou et al. (27), which was also employed by Mori and Brevet in pheromone chemistry (25). Some unreacted **4b** was converted to the corresponding acetate and removed from the coupling products by flash chromatography affording **1b** in 53% yield but only 83% purity. The **1b** was further purified on AgNO₃-SiO₂ to give material of 98% purity in 39% yield based on starting **4b**. The main impurity formed during the coupling had the same molecular weight as **1b** and apparently originated from *Z/E* isomerization at C-1 during Grignard formation. Partial loss of geometric purity (though to a lesser extent) was reported also by Mori and Brevet (25), who conducted a similar coupling with a Grignard reagent prepared from (*Z*)-1-bromo-1-butene at room temperature. Our attempts to prepare the Grignard reagent from **6** at room temperature resulted in lower yields of **1**.

The second synthesis involved construction of diyne epoxide **8** (**Scheme 2**) and stereospecific semihydrogenation to epoxydiene **1**, an approach frequently employed in preparations of epoxydiene pheromones such as (*Z,Z*)-*cis*-2-(2,5-octadienyl)-3-undecyloxirane, the principal sex pheromone component of several lepidopteran species (22, 28, 29). Different schemes toward the construction of the diyne epoxides have been described—for example, *cis*-9-heneicosene-3,6-diyne was epoxidized with *m*-chloroperbenzoic acid toward preparation of an achiral pheromone (28). One chiral synthesis utilized the reaction of 1,4-heptadiynyllithium with (*2R,3R*)-1,2-epoxy-3-tetradecanol benzoate (29) in the key step. Yet another scheme made use of alkylation/rearrangement of chiral 1,2-epoxy-3-alkan-1-ol tosylates with 1,4-heptadiynyllithium, with the epoxide construction carried out in situ (22). To incorporate the Sharpless epoxidation into such a scheme, the most straightforward approach appeared to be utilization of iodoepoxide **4** in the displacement reaction with an anion of 1,4-heptadiyne. This type of displacement, however, has frequently been unsuccessful, resulting instead in the reductive epoxide opening to allylic alcohols as discussed by Millar and Underhill (21, 30) [see also (31) and references therein]. Wasserman and Oku (32) and others (31, 33, 34) have described successful alkylation of alkyne anions with epoxytriflates. Epoxytriflates **7** were easily prepared from alcohols **3** and were stable to chromatography and storage in a refrigerator. However, our attempts to react 1,4-heptadiynyllithium (generated from 1,4-heptadiyne and BuLi) with triflate **7a** under the conditions described in the literature (THF/HMPA, ether/HMPA, or pure THF) resulted in complex mixtures even at -80 °C, apparently through proto-

Table 1. Trapping of *L. mathura* Males with a 4:1 Blend of **1b** and **1c** between July 7 and July 21, 2002, in Terney, Russian Far East

treatment	dispenser	loading (mg)	mean no. males captured per trap ^a
1b/1c (4:1)	cotton wick ^b	1	1.38 bc ^c
1b/1c (4:1)	string ^d	1	5.67 a
1b/1c (4:1)	string ^d	2.5	6.07 a
hexane	cotton wick		0.00 c

^a Test was run using traps with six replicates \times seven observations for each treatment (42 observations/treatment). ^b A 100 μ L solution of pheromone was injected into \sim 10 mm slice of standard dental cotton roll. ^c Means followed by the same letter are not significantly different according to a Scheffe's test at the .05 level of significance. Analysis done with the log (number of males captured + 1), actual means presented. ^d Prepared according to Leonhardt et al. (35); loading 64 μ g pheromone per cm.

tropic rearrangements of the base-sensitive 1,4-diyne group. The side reactions were slowed dramatically when the alkylation was conducted in a less polar ether/hexane mixture. Thus, reaction of 2.2 equiv of 1,4-heptadiyne and 2.0 equiv of BuLi at -75 $^{\circ}$ C, followed by addition of the triflates **7a** or **7b**, slowly raising the temperature to about -40 $^{\circ}$ C, and continuing the alkylation at -25 $^{\circ}$ C resulted in complete conversion of triflate and 80% yield of diyne epoxides **8a** and **8b** isolated in high purity (98–99%) by flash chromatography. When the alkylation was conducted with 1.5 equiv of BuLi, the yield dropped to 65–70%. We also found that the ether should be freshly distilled from sodium-benzophenone ketyl to obtain reproducible results and that the reaction should be driven to completion since unreacted triflates complicated chromatographic purification.

In the last step, the diyne epoxides **8** were hydrogenated with a Lindlar catalyst in the presence of quinoline in cyclohexene/MeOH to give racemic **1a** or the 2*S*,3*R* enantiomer **1b** in 90–93% yield. The optical purities of both enantiomers of **1** synthesized by two routes were confirmed by conversion of the epoxides to diastereomeric aziridines and GC analysis (23). The enantiomeric excesses of **1b** and **1c** from both methods were found to be \geq 99%, consistent with the optical purities of the starting epoxy alcohols **3a** and **3b**, and thus indicating that there was no loss of chirality during alkylation. The most practical composition for attracting *L. mathura*, epoxide **1b** of \sim 63% ee, was prepared in an overall yield of 37% from alcohol **2** using the tuned asymmetric epoxidation conditions.

In summary, we examined the applicability of two routes toward the preparation of the main component of the *L. mathura* pheromone. Both methods conveniently provided \sim 4:1 ratio of *S,R* and *R,S* enantiomers of **1** using the tuned Sharpless asymmetric epoxidation. However, the sequence illustrated in **Scheme 1** appeared to be limited mainly because of incomplete stereoselectivity of the copper(I)-catalyzed coupling reaction. On the other hand, the second synthesis advantageously used a straightforward alkylation of 1,4-heptadiynyllithium with epoxytriflate **7** in ether–hexane and an uncomplicated semi-hydrogenation of diyne epoxide **8** thus offering a higher overall yield. It also seemed to overcome the shortcomings of the existing route mentioned in the Introduction, which also included burdensome organocuprate chemistry in assembling a 19 carbon skeleton (3, 5). As compared to other syntheses of chiral diene epoxides, our approach benefits from the tuned Sharpless asymmetric epoxidation, whereas the potential of alternative methods in direct preparation of the desired ratio of the enantiomers of oxirane **1** remains to be shown.

Multigram quantities of pheromone have been prepared and tested in Russia in 2002 and 2003. Detailed results of field

bioassays with the individual enantiomers of the pheromone and the mixtures thereof will be published elsewhere. **Table 1** presents trapping data of *L. mathura* with a 4:1 mixture of **1b** and **1c** impregnated on cotton wicks and PVC-coated string dispensers prepared according to Leonhardt et al. (35).

Despite the low moth population, string dispensers caught significantly greater numbers of male pink moths than cotton wicks that had been used in the previous study (3). It is reasonable to anticipate that the string, or twine, formulation could serve as a standard lure for detection and monitoring of *L. mathura* since it has also been particularly effective for (+)-disparlure, a pheromone of similar molecular weight used by the gypsy moth, *Lymantria dispar* (35).

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