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Article

# Studies towards the Identification of the Sex Pheromone of *Thyrinteina arnobia*

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A lagarta parda *Thyrinteina arnobia* (Lepidoptera: Geometridae), é considerada no Brasil uma importante praga de plantas nativas, como *Psidium guajava*, e exóticas, como espécies de *Eucalyptus*. Neste trabalho é relatado o isolamento dos componentes feromonais de *T. arnobia,* através de técnicas de extração de glândulas e micro-extração em fase sólida (SPME) de fêmeas virgens. As amostras coletadas foram analisadas por cromatografia a gás acoplada a um detector eletroantenográfico (CG-EAD) e espectrometria de massas (CG-EM). Foram observadas duas respostas eletroantenográficas em antenas de machos de *T. arnobia* e as análises por CG-EM sugeriram a estrutura do 3,4-epoxi-6,9-eneicosadieno como componente majoritário. A síntese racêmica deste epoxidieno foi realizada em 10 etapas com rendimento global de 28%. Foram também sintetizados os quatro estereoisômeros do epoxidieno a partir dos respectivos epoxiálcoois enantiomericamente enriquecidos.

The eucalyptus brown-looper *Thyrinteina arnobia* (Lepidoptera: Geometridae) is considered an important pest in Brazilian native plants, e.g. *Psidium guajava*, and exotic plants, such as *Eucalyptus* species. In this work we describe the isolation of the pheromone components of *T. arnobia*, using glands extract and solid phase micro extraction (SPME) of virgin females. The samples were analyzed by gas chromatography with an electroantennographic detector (GC-EAD), and mass spectrometry (GC-MS). Two reproducible electroantennographic responses were elicited in the male antenna of *T. arnobia* and one of them was identified as 3,4-epoxy-6,9-heneicosadiene by CG-MS. The racemic synthesis of this epoxydiene was carried out in 10 steps and 28% overall yield. The four stereoisomers of the epoxydiene were also synthesized employing the corresponding enantiomeric enriched epoxyalcohols.

**Keywords:** electroantennography, *Thyrinteina arnobia*, sex pheromone, 3,4-epoxy-*Z*6,*Z*9-heneicosadiene, asymmetric synthesis

## Introduction

The eucalyptus brown looper, *Thyrinteina arnobia* (Lepidoptera: Geometridae) is the most harmful of the *Eucalyptus* pests in Brazil and causes severe losses in the wood production through defoliation.[1] Several strategies have been tried and considerable effort spent on the study of this insect behavior[2] and development of methods to control this pest, specially employing biological control.[3] However, no practical and environmentally acceptable manner has been found.[4] Control is made very difficult by the huge area of plantations and by the height of the trees.

Insect pest management, monitoring and control programs utilizing sex pheromones as behavior modifying chemicals have become important for several insect groups, particularly moths.[5] Ando *et al.* reported that hydrocarbons with a homoconjugated polyene system and the monoepoxy derivatives are important components of sex pheromones produced by several geometrid moths.[6]

Therefore, we have investigated the sex pheromone composition of *T. arnobia*, analyzed electrophysiological responses of co-specific males and developed an efficient synthetic route for the preparation of the possible major pheromone component in regard to the applicability in integrated pest management.

## Results and Discussion

The isolation of the *T. arnobia* pheromone components was carried out using two different techniques: gland extract and solid phase micro extraction (SPME) of virgin females.[7] The samples were analyzed by gas

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chromatography using electroantennographic detector (GC-EAD), and two compounds elicited strong and reproducible antennal responses (Figure 1). We have performed the co-injection of the female gland extract with a mixture of hydrocarbon standards in order to determine the Kovats retention index.[8] There were found the values of 2264.7 and 2265.5 for the compounds with retention time (rt) = 14.47 and 14.55 min, respectively. GC-MS analysis showed an *m/z* = 306 for the major component (rt: 14.5 min). Thus, based on the carefully comparison with the MS data from the literature[9,10] and in the Kovats retention index we proposed that the major component would be the 3,4-epoxy-6,9-heneicosadiene (**1**). Due to the very low concentration of the minor component (retention time: 14.4 min) in the extract it was not possible to propose its chemical structure; however it seems to be an isomer of compound **1**.

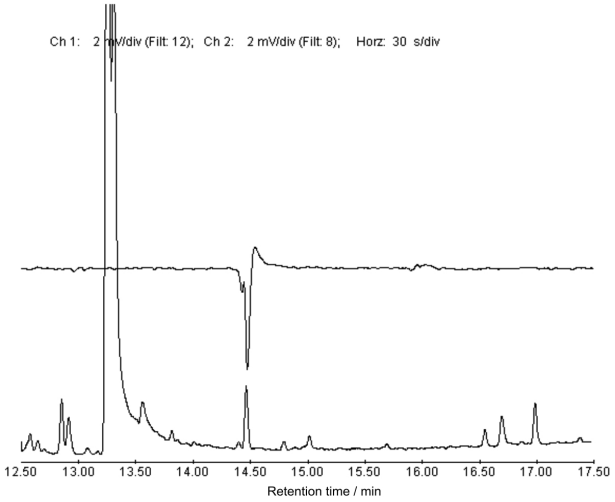


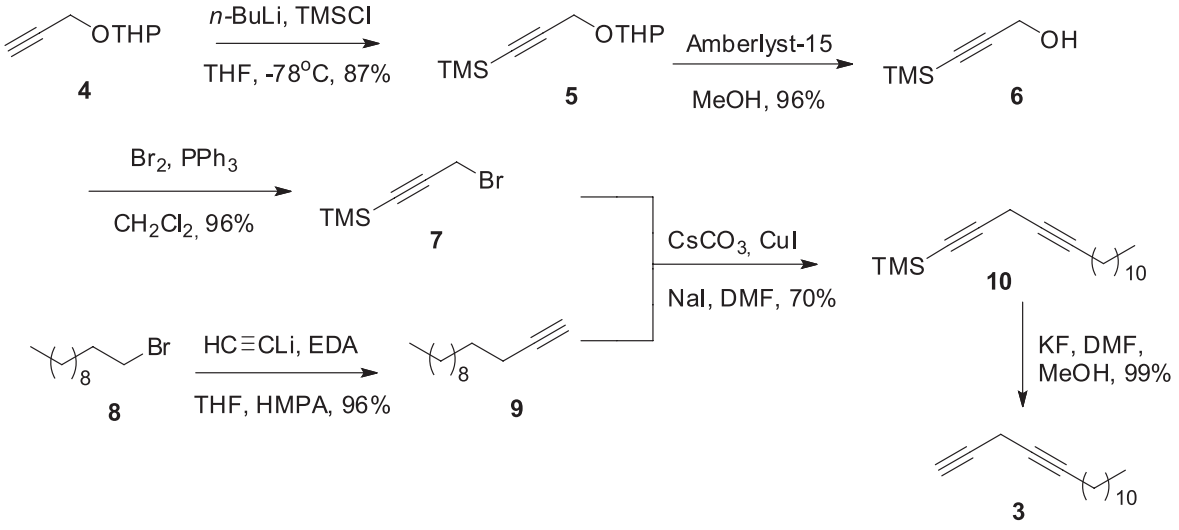

**Figure 1.** GC-EAD response of *T. arnobia* male antennae to virgin female gland extract.

In order to contribute with the identification of the pheromone components, we have synthesized a mixture of the three positional isomers of epoxyheneicosadiene from linolenic acid in 5 steps as described by Ando *et al.*[6] GC-MS and GC-EAD analyses corroborated the hypothesis that the epoxydiene **1** would be one of the possible pheromone component.

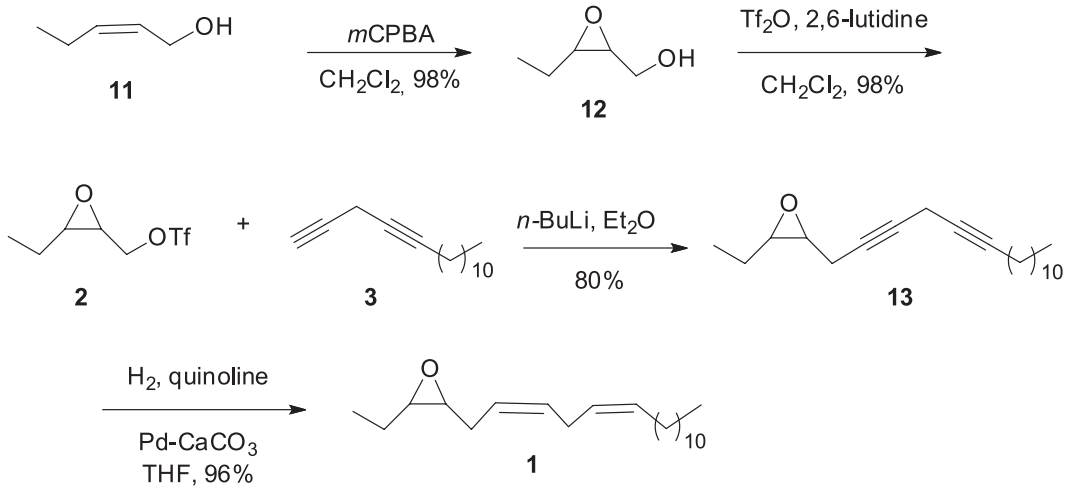
Epoxydiene **1** was described by Wong *et al*. as sex attractant for Geometrid and Noctuid moths.[11] Millar *et al*. have synthesized two stereoisomers of epoxydiene **1** and other related epoxydienes,[9] which are sex attractants of different insect species of the Geometridae family.[12]

In order to prepare a sufficient amount of compound **1** to confirm the structure of pheromone major component, and carry out electroantennographic bioassays as well as field tests, we proposed a convergent synthetic route, where the key step is the coupling of epoxytriflate **2** with diyne **3**.[13] Diyne **3** was prepared by the reaction of 3-bromo-1-trimethylsilyl-1-propyne (**7**) with 1-tridecyne (**9**) (Scheme 1),[14] which were straightforward prepared and are also commercially available. The diyne **3** is quite unstable even at low temperature; therefore, it has to be freshly prepared by deprotecting compound **10** just before the coupling reaction.

Compound **2** was prepared starting from commercially available *Z*-2-penten-1-ol (**11**),[15,16] and then the synthesis of racemic **1** was accomplished by the reaction of the corresponding acetylide of diyne **3** with epoxytriflate **2**,[17] followed by hydrogenation of the triple bonds (Scheme 2). It is worth to note that we have also tried the coupling reaction of diyne **3** with the 1,2-epoxy-3-tosylate using *n*-BuLi and $BF_3.OEt_2$ without success.[13,16] GC-MS analysis of synthetic epoxydiene **1** was identical to the major component isolated from *T. arnobia* females.




**Scheme 1.** Synthesis of diyne **3**.




**Scheme 2.** Synthesis of racemic epoxydiene **1**.

To accomplish the stereoselective version, all stereoisomers of epoxyalcohol **12** were also synthesized employing two different methodologies. The Sharpless asymmetric epoxidation[18,19] of *Z*- and *E*-2-penten-1-ol (**11**) delivered the corresponding epoxyalcohols **12** in 70-76% yield and 80-90% ee (Scheme 3, Table 1).

**Table 1.** Synthesis of the four stereoisomers of epoxyalcohol **12** via Sharpless epoxidation

| Epoxyalcohol **12** | 2-penten-1-ol | Diisopropyl tartrate | Yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|
| (2*S*,3*R*)- | *Z*- | L(+)-DIPT | 75 | 85 |
| (2*R*,3S)- | *Z*- | D(-)-DIPT | 70 | 90 |
| (2*S*,3*S*)- | *E*- | L(+)-DIPT | 76 | 80 |
| (2*R*,3*R*)- | *E*- | D(-)-DIPT | 72 | 82 |

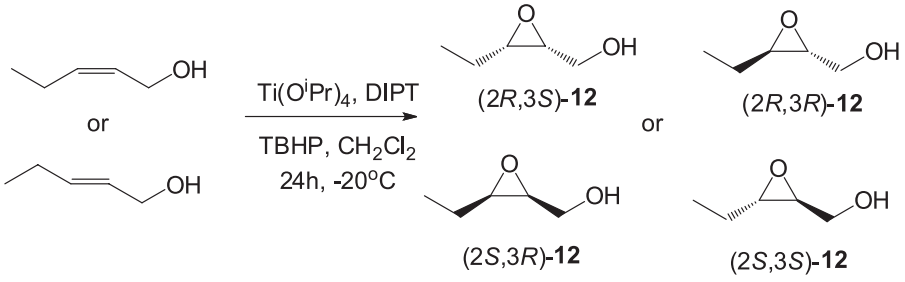
[a]after purification by flash column chromatography. [b]enantiomeric excess measured by comparison of the $[\alpha]_D$ values with literature.[20-22]

Recently, we have reported a new organocatalyst **14** for the asymmetric epoxidation of enals in green conditions.[23] We then applied this methodology for the synthesis of (*R,R*)- and (*S,S*)-**12** starting from *trans*-pentenal with good yields (79% and 81%), and excellent diastereoisomeric ratio (*anti*:*syn* 93:7) and enantiomeric excess (95% and 96%, respectively) followed by an *in-situ* reduction with $NaBH_4$ (Scheme 4). Having in hands the stereoisomers of epoxyalcohol **12** in their enantioenriched forms, the four stereoisomers of epoxydiene **1** were prepared in the same range of yield, following the same route described for the synthesis of the racemic epoxydiene.

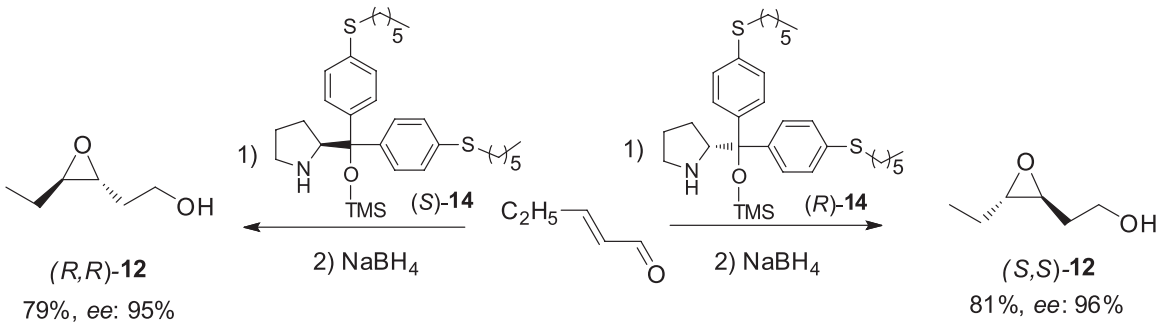
Racemic *cis*-epoxydiene **1** was employed in an EAG experiment with *T. arnobia* male antennae. Mean depolarizations achieved in response to the test compound are shown in Figure 2. Electroantennographic responses were significantly higher than that for the control (hexane). This result indicates that *T. arnobia* male adults recognize the synthetic compound **1**.

Batista-Pereira[2] observed that some *T. arnobia* females exhibited calling behavior and mated in the first hour immediately after emergence. These observations could indicate that it would start to produce pheromone before adults emerge from the pupae, i.e., in the stage of pupae. In order to evaluate this hypothesis, we used the technique of SPME in an attempt to collect the possible bioactive compounds emitted by the pupae.

The experiments of GC-EAD with dynamic headspace extraction of volatiles of female pupae of *T. arnobia* showed electrophysiological activity in the antenna of male co-specific. The pupae dynamic headspace had a single




**Scheme 3.** Synthesis of the four stereoisomers of epoxyalcohol **12**




**Scheme 4.** Organocatalytic synthesis of (*R,R*)- and (*S,S*)-**12**.

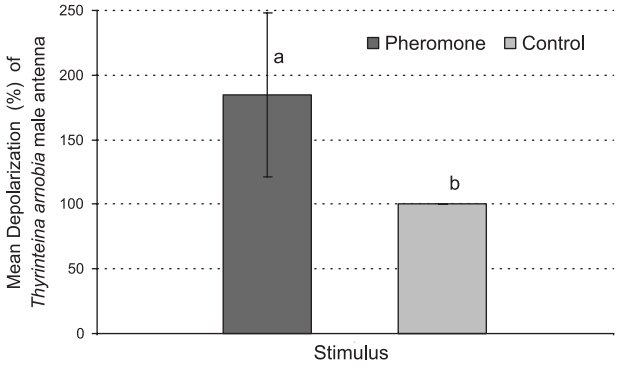



**Figure 2.** Mean EAG (± SD) elicited from *T. arnobia* male antennae, at concentration of 100 mg $mL^{-1}$ of synthetic epoxydiene **1** and control (hexane). Mean values marked with the same letter are not significantly different at $P < 0.05$, on the basis of the Tukey test (N = 10 antennae).

response, possibly related to the major compound **1** of the pheromone blend, i.e., presented the same retention time (14.5 min) of second bioactive peak of EAD of *T. arnobia* females gland extracts. The experiments were repeated, obtaining consistently the same results.

There are some reports about pheromones produced by pupae. Inoue and Hamamura extracted sex pheromone from female pupae of *Bombyx mori*.[24] It was found that the sex pheromone was detected at the final stage of pupa, 1 to 2 days prior to the adult emergence, and it was only located in the abdominal tip of the pupa. Studies with the pine sawfly pheromone, precursor 3,7-dimethyl-2-pentadecanol (diprionol),[5] was realized by GC in different body parts of virgin female *Neodiprion sertifer*.[25] About one-third of the total amount (approx. 10 ng per female) was found in each of head and thorax, abdominal segments 1-3, and the remaining abdomen. Diprionol was also found in the respective parts of pupae, but in lower amounts.

This research also showed the extreme sensitivity of *T. arnobia* antenna to the pheromone blend. This statement becomes evident when analyzing the responses of the FID and the antenna. Although the amount of the pheromone components was below the detection limit of FID, the antenna always showed electrophysiological response, revealing the great power of detection of the antenna. In the literature a correlated case was described, in which the elucidation of the pheromone was performed only based on the retention time provided by the antenna, and then checking the response of the antenna to standard compounds.[26]

In conclusion, very efficient racemic and asymmetric synthesis of 3,4-epoxy-*Z*6,*Z*9-heneicosadiene (**1**) were carried out in 10 steps and 28% overall yield. The racemic compound has shown EAG responses against male *T. arnobia* antennae. The four stereoisomers of epoxydiene **1** will be employed in EAD experiments and field tests in order to determine the absolute configuration of the natural product and prove its biological role as component of *T. arnobia* pheromone blend.

## Experimental

### General Remarks

Unless otherwise noted, all commercially available reagents were purchased from Aldrich Chemical Co. Reagents and solvents were purified when necessary according to the usual procedures described in the literature. The IR spectra refer to films and were measured on a Bomem M102 spectrometer. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker ARX-200 (200 and 50 MHz, respectively) and DRX-400 (400 and 100 MHz, respectively) spectrometers. Mass spectra were recorded on a Shimadzu GCMS-QP5000. HPLC chromatograms were obtained on a Shimadzu apparatus, LC-10AT Pump, SPD-10A UV-Vis Detector, SCL-10A System Controller, using a Chiralpak AD-H (4.6 mm∅ × 250 mmL, particle size 5 μm) or a Chiralcel OD-H or OD (4.6 mm∅ × 250 mmL, particle size 5 μm). Optical rotations were measured with a Perkin-Elmer Polarimeter, Mod. 241, at 589 nm, 30 °C or Polartronic H, Schmidt Haensch, at 589 nm, 23 °C. Melting point was obtained on a MQAPF-301 apparatus. High-resolution mass spectra were recorded

on a Bruker - AutoFlex Speed, MALDI-TOF/TOF MS (λ = 355 nm, f = 500 Hz, matrix HCCA, calibration standard TPP, PEG 600). Analytical thin-layer chromatography was performed on a 0.25 μm film of silica gel containing fluorescent indicator $UV_{254}$ supported on an aluminum sheet (Sigma-Aldrich). Flash column chromatography was performed using silica gel (Kieselgel 60, 230-400 mesh, E. Merck). Gas chromatography was performed in a Shimadzu GC-17A with $H_2$ as carrier gas and using a DB-5 column.

Insects: *T. arnobia* specimens were obtained from the Insect Bioassay Laboratory at the Federal University of São Carlos, SP, Brazil where they were reared on artificial diets.[4] established in the Insect Bioassay Laboratory at the Federal University of São Carlos, SP, Brazil. Pupae were sexed and placed individually in plastic vials (6 cm × 6 cm ID) for emergence of adults. Male and female pupae were maintained in a growth chamber at 25 ± 1 °C and 60 ± 5 % r.h., in a 12:12 L:D photoperiod.

Pheromone Extraction: During peak calling activity, about fourth hour of the 1st scotophase,[2] abdominal tips with pheromone glands of virgin female moths were removed, placed into a 2.0 mL vial and extracted for 30 min with pentane (100 μL). The extract was transferred to a clean conical dark microvial with Teflon®-lined screw caps, concentrated under a stream of $N_2$, and stored at –20 °C until analyzed. Five extracts of pheromone glands were prepared containing 24, 30, 30, 31 and 36 glands respectively, which varied with the availability of calling females within a particular batch.

Collection of pheromone by dynamic SPME: Solid phase microextraction (SPME; Supelco) was used to collect pheromone compounds emitted by virgin female moths. The SPME fiber (100 μm polydimethylsiloxane coating) was conditioned before use at 250 °C for 10 min in a GC injector. Virgin female moths were placed in an aeration chamber (7.0 cm × 5.5 cm ∅) fitted with a glass inlet tube and an outlet tube. The apparatus was flushed with charcoal-purified air at 5-10 mL $min^{-1}$ (through the inlet tube) with the SPME fiber placed in the outlet tube of the vial to collect the emitted volatiles overnight. In analogous fashion, pupae were placed in an aeration chamber (6.0 cm × 1.8 cm ∅, air flow at 2.5-3.0 mL $min^{-1}$) and pheromone from the effluvia was collected by dynamic SPME.

*Electroantennography*: Antennae of 1-2 day old male moths were used for electroantennographic experiments (EAG) and electroantennographic detection (EAD) in a Syntech electroantennography system.[27] Each antenna was pulled from the head with forceps and a few segments were cut off at the base and the tip.[7] The antenna was then fixed between two stainless steel electrodes by pushing the base and tip into droplets of an electrically conductive gel (Spectra 360® electrode gel) applied to the metal electrodes. The antennal responses were amplified and recorded with a data acquisition controller and software EAG.

EAG experiments were performed in order to elucidate the selectivity of the antennal receptors of *T. arnobia*. The EAG response was evaluated as follows: the volatile compounds or control were released from Pasteur pipettes containing a piece of filter paper (ca. 0.8 $cm^2$) previously impregnated with 10 μL of a freshly prepared 100 mg $mL^{-1}$ solution of synthetic epoxydiene **1** in hexane, after the solvent had evaporated. The puff containing the test compound was delivered into a continuously humidified and purified air stream (1.2 L $min^{-1}$) passing for 0.3 seconds through the impregnated filter paper in the pipettes. Control stimulation was made at the beginning and the end of each series of EAG experiments. EAG amplitudes in response to the test compound were expressed in relation to the responses to the control (hexane), because of the large differences in overall sensitivity between individual antennae, and to compensate the decline in antennal sensitivity during a measuring session. In this normalization procedure, the responses to the control were defined as 100%. The values obtained between two calibration references (controls) were calculated by linear interpolation between those references values. The Syntech EAG software calculated the normalized values automatically. The epoxydiene **1** was tested on 10 antennae each of male *T. arnobia*. The mean normalized responses of the different compounds were submitted to ANOVA for statistical analysis and compared by the Tukey test ($P < 0.05$).

### 2-[(3-Trimethylsilylprop-2-yn-1-yl)oxy]tetrahydro-2H-pyran (**5**)[28]

To a solution of tetrahydro-2-(2-propynyloxy)-2H-pyran (**4**) (4.752 g, 33.94 mmol) in dry THF (34.0 mL) was added a 2.5 M solution of *n*-BuLi in hexanes (20.4 mL, 50.9 mmol) at -78 °C under $N_2$. The mixture was stirred 15 min, and then TMSCl (5.529 g, 50.9 mmol) was added. The temperature was left to rise to rt and after 4 hr a 10% aqueous solution of HCl (30 mL) was added at 0 °C. After separation of the phases, the aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over $Na_2SO_4$. After concentration, the residue was purified by column chromatography (hexane/ethyl acetate 9:1) to afford compound **5** in 87% yield (6.258 g, 29.52 mmol). IR (film) $\nu_{max}/cm^{-1}$: 2956; 2175; 1249; 1130; 1029; 842; 759.$^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.17 (s, 9H), 1.55-1.83 (m, 6H), 3.47-3.58 (m, 1H), 3.84 (ddd, 1H, *J* 11.6, 8.4, 3.1), 4.25 (d, 2H, *J* 4.1), 4.82 (t, 1H, *J* 3.4).$^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 101.55, 96.73, 90.79,

61.87, 54.77, 30.22, 25.37, 18.98, -0.06 (3C). GC-MS (70 eV) *m/z* (%): 211 M-H, 1) 173 (11), 111 (37), 101 (49), 85 (100), 73 (75), 55 (61).

### 3-Trimethylsilyl-prop-2-yn-1-ol (**6**)[29]

In a flask containing methanol (4.0 mL) and Amberlyst-15 (0.025 g) under $N_2$, compound **5** (0.250 g, 1.17 mmol) was added dropwise at 0 °C. The mixture was stirred at 40 °C for 8 hr, then the resin was filtered, and washed with ethyl acetate (10 mL). A 10% aqueous solution of HCl (10 mL) was added and the organic layer was extracted with ethyl acetate (3 × 10 mL), and dried over $Na_2SO_4$. After concentration, the residue was purified by column chromatography (hexane/ethyl acetate 9:1) to afford compound **6** in 96% yield (0.143g, 1.12 mmol). IR (film) $\nu_{max}$/cm$^{-1}$: 3367, 2960, 2175, 1251, 1041, 842. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.18 (s, 9H), 1.82 (s, 1H), 4.27 (s, 2H).$^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 103.85, 90.67, 51.62, -0.24 (3C).GC-MS (70 eV) *m/z* (%): 128 ($M^+$, 1), 113 (100), 85 (93), 75 (66), 61 (68).

### 3-Bromo-1-trimethylsilylprop-1-yne (**7**)[30]

To a solution of triphenylphosphine (9.735 g, 37.11 mmol) in dry dichloromethane (46.0 mL) under $N_2$, bromine (5.438 g, 34.03 mmol) was added at 0 °C. After 30 min, when the solution color changed from orange to white, compound **6** (3.960 g, 30.93 mmol) was slowly added. The mixture was stirred for 1 h, and then it was washed with water (3 × 30 mL) and a 10% aqueous solution of HCl (2 × 20 mL).The aqueous layer was extracted with ethyl acetate (3 × 20 mL), and then the combined organic layers was dried over $Na_2SO_4$ and concentrated in vacuum. The residue was purified by column chromatography, using hexane as eluent, to afford compound **7** in 70% yield (4.125 g, 21.6 mmol). IR (film) $\nu_{max}$,/cm$^{-1}$: 2957, 2180, 1251, 1204, 1041, 844, 760. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.18 (s, 9 H), 3.90 (s, 2 H).$^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 99.97, 92.12, 14.51, –0.42 (3C).GC-MS (70 eV) *m/z* (%): 192 (1), 190 (1), 177 (100), 175 (93), 149 (78), 147 (69), 123 (14), 111 (28), 96 (26), 83 (32), 66 (19), 53 (35).

### Tridec-1-yne (**9**)[31]

To a solution of lithium acetylide-ethylenediamine complex 85% (1.174 g, 12.75 mmol) in dry THF (25.5 mL) and HMPA (4.25 mL), 1-bromoundecane (**8**) (2.00 g, 8.50 mmol) was slowly added at -78 °C under $N_2$. The temperature was raised to rt and the mixture was stirred for 8 hr. Then a 10% solution of HCl (10 mL) was added. The organic layer was separated and the aqueous phase extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $Na_2SO_4$. After concentration, the residue was purified by column chromatography using hexane as eluent to afford compound **9** in 96% yield (1.468 g, 8.16 mmol). IR (film) $\nu_{max}$/cm$^{-1}$: 3313, 2925, 2854, 2119, 1465, 628. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.88 (t, 3H, *J* 6.8), 1.27 (bs, 18H); 1.91 (t, 1H, *J* 2.6), 2.16 (dt, 2H, *J* 6.8, 2.6). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 84.52, 67.93, 31.91, 29.63 (2C), 29.53, 29.35, 29.14, 28.77, 28.53, 22.66, 18.38, 14.02. GC-MS (70 eV) *m/z* (%): 123 (1), 109 (14), 95 (45), 81 (100), 67 (55), 55 (65).

### 1-Trimethylsilyl-hexadeca-1,4-diyne (**10**)

To a mixture containing previously dried cesium carbonate (1.792 g, 5.5 mmol), sodium iodide (0.823 g, 5.5 mmol), dry copper (I) iodide (1.047 g, 5.5 mmol), DMF (11.0 mL), and tridecyne (**9**) (1.010 g, 5.5 mmol), bromide **7** (1.050 g; 5.5 mmol) was slowly added under $N_2$ at 0 °C. After 24 h at rt, a saturated solution of ammonium chloride (20 mL) was added. The organic layer was separated and the aqueous phase extracted with ethyl acetate (3 × 30 mL). Combined organic layers were dried over $Na_2SO_4$ and concentrated. The residue was purified by column chromatography using hexane as eluent to afford compound **10** in 70% yield (1.116 g, 3.8 mmol). IR (film) $\nu_{max}$/ cm$^{-1}$: 2925, 2183, 1625, 1249, 1012, 842. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.16 (s, 9H), 0.88 (t, 3H, *J* 6.6), 1.27 (bs, 18H), 2.15 (tt, 2H, *J* 6.8, 2.4), 3.17 (t, 2H, *J* 2.4).$^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 105.20, 84.47, 80.98, 73.26, 31.90, 29.62 (2C), 29.55, 29.33, 29.15, 28.05, 28.69, 22.26, 18.70, 14.05, 10.82, -0.13 (3C).GC-MS (70 eV) *m/z*(%): 275 (5), 247 (1), 217 (4), 177 (10), 131 (25), 117 (18), 83 (28), 73 (100), 59 (82).

### Hexadeca-1,4-diyne (**3**)[9]

To a solution of diyne **10** (0.418 g, 1.44 mmol) in methanol (2.8 mL) and DMF (0.7 mL), potassium fluoride was added (0.167 g, 2.8 mmol). The mixture was stirred at 40 °C for 3 h, and then water (10 mL) was added. The organic layer was separated and the aqueous phase extracted with ethyl acetate (3 × 10 mL). Combined organic layers were dried over $Na_2SO_4$ and concentrated. The residue was purified by column chromatography using hexane as eluent to afford compound **3** in 99% yield (0.309 g; 1.42 mmol). IR (film) $\nu_{max}$/cm$^{-1}$: 3313, 2923, 1718, 1465, 640. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.88 (t, 3H, *J* 6.8), 1.26 (bs, 18H), 2.05 (t, 1H, *J* 2.6), 2.15 (tt, 2H, *J* 6.8, 2.6), 3.14 (q, 2H, *J* 2.6). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 81.34, 79.00, 72.98, 68.27, 31.93, 29.63 (2C), 29.53, 29.35, 29.15, 28.88, 28.70, 22.69, 18.69, 14.09, 9.56. GC-MS (70 eV) *m/z* (%):175 (1), 161 (2), 147 (6), 133 (19), 119 (36), 105 (50), 91 (100), 67 (46), 55 (53).

### 3,4-Anhydro-1,2-dideoxypentitol (**12**)

Alcohol **11** (0.502 g; 5.8 mmol) was diluted in dry methylene chloride (5.8 mL). Then a solution of MCPBA (1.307 g, 7.5 mmol) in dry methylene chloride (7.5 mL) was added at 0 °C and $N_2$. The mixture was stirred for 2 h at rt, then a saturated solution of sodium carbonate (10 mL) was added. After separation of the phases, the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated solution of sodium metabisulfite (2 × 10 mL) and dried over $Na_2SO_4$. After concentration, the residue was purified by column chromatography (hexane/ethyl acetate 7:3) to afford epoxyalcohol **12** in 98% yield (0.576 g, 5.7 mmol). IR (film) $\nu_{max}$/cm$^{-1}$: 3413, 2962, 2923, 2850, 2360, 2341, 1791, 1731, 1558, 1463, 1259, 1074, 800. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 1.05 (t, 3H, *J* 7.5), 1.60-1.70 (m, 2H), 2.95-3.05 (m, 1H), 3.12-3.24 (m, 1H), 3.60-3.73 (m, 1H), 3.77-3.91 (m, 1H).$^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 60.42, 58.24, 57.13, 21.07, 10.44. GC-MS (70 eV) *m/z* (%): 83 (0.5), 71 (1), 59 (100), 41 (85).

### 3-epoxialcohol **12** via Sharpless epoxidation:[19]

In a flask containing molecular sieves 4 Å (100 mg), anhydrous dichloromethane (20 mL) was added under argon and cooled to −20 °C then diisopropyl tartrate (0.083 mL, 0.49 mmol) and $Ti(O^iPr)_4$ (0.095 mL, 0.33 mmol) were added. The mixture was stirred for 20 min then TBHP (2.51 mL, 12.96 mmol, 5.5 M in dry toluene) was added. After 20 min a solution of *E*- or *Z*-pent-2-en-ol (6.48 mmol, 0.65 mL) in anhydrous dichloromethane (5 mL) was added dropwise. The mixture was stirred for 24 h at −20 °C, then a saturated solution of $Na_2SO_3$ (5 mL) was added and stirred for 1 h at rt. The resulting suspension was washed with dichloromethane (30 mL) and filtered over celite. The solution was then cooled to 0 °C and an aqueous solution of NaOH (30%, 4.5 mL) was added and the resulting mixture stirred for 30 min. The organic layer was extracted with dichloromethane (3 × 20 mL) and dried with anhydrous $Na_2SO_4$. The solvent was evaporated under vacuum and the crude product was purified by flash column chromatography in silica gel and hexane:ethyl acetate (8:2) as eluent.

(2*S*,3*R*)-**12**: $[\alpha]_D^{30}$ -10.0 (*c* 1.0, $CH_2Cl_2$), lit.[20]: $[\alpha]_D^{21}$ −11.8 (*c* 1.7, $CH_2Cl_2$). (2*R*,3*S*)-**12**: $[\alpha]_D^{30}$ +10.7 (*c* 1.0, $CH_2Cl_2$), lit.[21]: $[\alpha]_D^{21}$ +11.9 (*c* 2.0, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.05 (t, 3H, *J* 7.6); 1.48-1.66 (m, 2H); 2.98-3.04 (m, 1H); 3.14-3.20 (m, 1H); 3.68 (dd, 1H, *J* 12.0, 4.0); 3.83 (dd, 1H, *J* 11.8, 6.8). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 60.24; 58.17; 56.93; 20.81; 10.43. MS (relative intensity %): *m/z* 83 (0,5); 71 (1); 59 (100); 41 (85).

(2*S*,3*S*)-**12**: $[\alpha]_D^{30}$ −24.9 (*c* 1.0, EtOH), lit.[22]: $[\alpha]_D^{21}$ −31.3 (*c* 0.56, EtOH). (2*R*,3*R*)-**12**: $[\alpha]_D^{30}$ +25.5 (*c* 1.0, EtOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.02 (t, 3H, *J* 7.6); 1.55-1.66 (m, 2H); 2.93-2.98 (m, 2H); 3.60-3.68 (m, 1H); 3.89-3.96 (m,1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 61.76; 58.12; 57.02; 24.59; 9.79. MS (relative intensity %): *m/z* 83 (0.5); 71 (1); 59 (100); 41 (85).

### (2R,3R)- and (2S,3S)-**12** via organocatalysis:[23]

In a 5 mL vial, the catalyst (*R*)- or (*S*)-**14** (107 mg, 10 mol%, 0.2 mmol) was dissolved in ethanol and distilled water (3.0 mL, 1.0 mL), followed by addition of *trans*-2-pentenal (167 mg, 2.0 mmol) and $H_2O_2$ (35% aqueous solution, 0.5 mL, 6.0 mmol). The resulting mixture was stirred for 16 h. Water (7 mL) was added and extracted with diethylether (3 × 30 mL). The organic phase was dried over $MgSO_4$ and concentrated. The residue was dissolved in methanol (14 mL), cooled to 0 °C and followed by addition of $NaBH_4$ (0.201 g, 5.3 mmol). After 20 min, the reaction was quenched by water (15 mL), extracted with diethylether (3 × 20 mL), dried over $MgSO_4$ and concentrated. The epoxyalcohol was obtained in 79-81% yield (95-96% ee and 93:7 rd), as colorless oil after flash chromatography using hexane and ethyl acetate 9:1.

(2*R*,3*R*)-**12**: $[\alpha]_D^{23}$ +21.00 (*c* 0.0003, ethyl acetate). (2*S*,3*S*)-**12**: $[\alpha]_D^{23}$ −21.97 (*c* 0.0003, ethyl acetate). HPLC analysis of the corresponding benzoate derivatives of (2*R*,3*R*)- and (2*S*,3*S*)-**12**, using chiral OD-H column ($\lambda$ = 254 nm), hexane:ethanol (98:2 ratio) as eluent (1.0 mL min$^{-1}$), showed 95% and 96% ee, respectively. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 4.06 (dd, 1H, *J* 12.0, 4.0, *syn*), 3.91 (d, 1H, *J* 12.0, *anti*), 3.78 (dd, 1H, *J* 12.0, 8.0, *syn*), 3.62 (d, 1H, *J* 12.0, *anti*), 3.19-3.14 (m, 1H, *syn*), 2.97-2.93 (m, 2H, *anti*), 2.85-2.81 (m, 1H, *syn*), 1.96 (bs, 2H, *anti* and *syn*), 1.66-1.58 (m, 2H, *anti*), 1.29-1.25 (m, 2H, *syn*), 1.07-0.98 (m, 3H, *anti*), 0.89-0.84 (m, 3H, *syn*).$^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 61.77, 58.17, 57.05, 24.59, 9.80.

### 3,4-Anhydro-1,2-dideoxy-5-O-(trifluoroacetyl)pentitol (**2**)[32]

To a solution of epoxyalcohol **12** (0.500 g, 4.89 mmol), 2,6-lutidine (0.577 g, 5.38 mmol), in dry dichloromethane (15.0 mL), triflic anhydride (1.517 g, 5.38 mmol) was added at −60 °C under $N_2$. After 1 hr, the mixture was neutralized with a 10% aqueous solution of HCl. The organic layer was separated and aqueous phase extracted with dichloromethane (3 × 20 mL). Combined organic layers were dried over $Na_2SO_4$ and concentrated in vacuum. The residue was purified by column chromatography using hexane : dichloromethane (6 : 4) as eluent to afford compound **2** in 98% yield (1.142 g, 4.88 mmol). IR (film) $\nu_{max}$/ cm$^{-1}$: 2978, 1415, 1210, 1144, 943, 616. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 1.08 (t, 3H, *J* 7.3), 1.45-1.72 (m,

2H), 3.08 (dt, *J* 1H, 6.6, 4.1), 3.30 (dt, 1H, *J* 7.1, 4.3), 4.50 (dd, 1H, *J* 11.0, 7.0), 4.69 (dd, 1H, *J* 11.0, 3.8). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 121.80, 115.45, 102.93, 74.86, 57.94, 52.58, 21.17, 10.31. GC-MS (70 eV) *m/z* (%):191 (31), 99 (69), 85 (72), 69 (100), 61 (95).

2-ethyl-3-heptadeca-2,5-diyn-1-yloxirane (**13**)

To a solution of freshly prepared diyne **3** (0.077 g, 0.35 mmol) in dry ethyl ether (0.85 mL) at –78 °C and under $N_2$, a 1.0 M solution of *n*-BuLi in hexanes (0.36 mL, 0.36 mmol) was slowly added. The mixture was stirred for 1 hr, and then a solution of racemic epoxytriflate **2** (0.074 g, 0.31 mmol) in dry THF (0.32 mL) was added dropwise. The temperature was raised to –45 °C and after 6 h, a saturated solution of ammonium chloride (5.0 mL) was added. The organic layer was separated and aqueous phase extracted with ethyl ether (3 × 10 mL), dried over $Na_2SO_4$ and concentrated in vacuum. The residue was purified by column chromatography using hexane:dichloromethane (6:4) as eluent to afford compound **13** in 80% yield (0.077 g, 0.25 mmol). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.88 (t, 3H, *J* 6.7), 1.07 (t, 3H, *J* 7.5), 1.26 (bs, 20H), 2.15 (tt, 2H, *J* 6.8, 2.4), 2.54 (ddd, 1H, *J* 5.1, 2.7, 2.4), 2.62 (ddd, 1H, *J* 5.1, 2.4, 2.7), 2.92 (dd, 2H, *J* 6.3, 2.4), 3.13 (m, 2H).$^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 80.77, 76.86, 75.24, 73.87, 58.06, 55.13, 31.88, 29.60 (2C), 29.50, 29.30, 29.12, 28.88, 28.73, 22.64, 20.91, 18.68 (2C), 14.02, 10.44, 9.72.GC-MS (70 eV) *m/z* (%): 302 ($M^+$, 4), 273 (15), 245 (1), 231 (1), 217 (1), 203 (2), 175 (11), 161 (22), 147 (34), 133 (33), 109 (72), 81 (100), 67 (37), 55 (75).

*2*-ethyl -3-[(2Z,5Z)-heptadeca-2,5-dien-1-yl]-oxirane (**1**)[9,10]

To a solution of diyne **13** (0.010 g, 0.03 mmol) and quinoline (0.002 g) in dry THF (0.30 mL) under $H_2$, 10% Pd/$CaCO_3$ (0.003 g) was added. The mixture was stirred for 1 h, and then was filtered over silica gel and washed with ethyl ether (2 × 10 mL).The organic layer was neutralized with a 10% solution of HCl, extracted with ethyl ether (3 × 10 mL), dried over $Na_2SO_4$ and concentrated in vacuum. The residue was purified by column chromatography using hexane : dichloromethane (6 : 4) as eluent to afford racemic epoxydiene **1** in 96% yield (0.009 g, 0.029 mmol). IR (film) $\nu_{max}$/cm$^{-1}$: 3011, 2957, 2924, 2853, 1465, 1379, 818, 803, 720. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.88 (t, 3H, *J* 6.8), 1.05 (t, 3H, *J* 7.6), 1.26-1.34 (bs, 18H), 1.48-1.65 (m, 2H), 2.05 (q, 2H, *J* 6.8), 2.22 (dt, 1H, *J* 14.4, 6.8), 2.41 (dt, 1H, *J* 14.4, 6.4), 2.80 (t, 2H, *J* 6.0), 2.90 (dt, 1H, *J* 6.4, 4.4), 2.95 (dt, 1H, *J* 6.4, 4.4), 5.29-5.50 (m, 4H).$^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 130.85, 130.74, 127.21, 124.19, 58.35, 56.60, 31.95, 29.69 (4C), 29.37, 29.35,27.64, 27.30, 26.26, 25.83, 22.71, 21.08, 14.13, 10.64. GC-MS (70 eV) *m/z* (%): 306 ($M^+$, 0.7), 277 (0.5), 248 (0.5), 234 (5), 220 (2), 205 (0.5), 191 (0.5), 161 (1).166 (1), 151 (2), 135 (5), 121 (8), 107 (11), 93 (35), 79 (100), 67 (50), 55 (1).

Synthesis of enantiomeric enriched epoxydiene **1**

In a flask under $N_2$ atmosphere, freshly prepared 1,4-hexadecadiyne **3** (0.218 g; 1 mmol) was dissolved in dry THF (4 mL).Then a solution of *n*-BuLi in hexane (2.01 M; 0.44 mL; 0.9 mmol) was slowly added at –78 °C. The resulting brown solution was stirred for 30 min a –78 °C. Freshly prepared enantiomeric enriched epoxytriflate **2** (0.351 g; 1.5 mmol) in dry THF (2 mL) was slowly added and the resulting slightly yellow solution was stirred for 90 min a –78 ºC. Then a saturated solution of $NH_4Cl$ (4 mL) was added and the mixture was allowed to warm until rt and extracted with a mixture of hexane/ethyl ether (1:1) (3 × 20 mL). The combined organic layers were washed with saturated solution of $NH_4Cl$ (20 mL) and dried with anhydrous $MgSO_4$. The solution was concentrated under vacuum and the crude product was employed in the following step without further purification.

A flask containing the Lindlar catalyst (5% Pd in $CaCO_3$ with Pb) (0.027 g) and freshly distilled quinoline (35 µL, 0.3 mmol) was submitted to vacuum for 15 min. Then a solution of freshly prepared epoxydiyne **13** (0.272 g, 0.9 mmol) in dry THF (1mL), degasified using an ultrasound bath, was added. The mixture was stirred under $H_2$ atmosphere at rt and the progress of the reaction was followed by TLC. After 1 h the starting material was fully consumed, and then the mixture was filtered over celite 545, washing with ethyl ether (30 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated in the rotaevaporator without heating. The crude product was purified by flash column chromatography in silica gel using hexane/dichloromethane 95:5 as eluent. The stereoisomers of epoxydiene **1** were obtained in 50-63% yield over two steps.

(2*S*,3*R*)-**1**: $[\alpha]_D^{23}$ +2.6 (*c* 0.004, $CH_2Cl_2$), lit.[9] $[\alpha]_D^{23}$ +2.6 (*c* 2.74, $CH_2Cl_2$), (2*R*,3*S*)-**1**: $[\alpha]_D^{23}$ –7.4 (*c* 0.002, $CH_2Cl_2$), lit.[9] $[\alpha]_D^{23}$ –2.4 (*c* 2.92, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.88 (t, 3H, *J* 6.8); 1.05 (t, 3H, *J* 7.2); 1.26-1.34 (bs, 18H), 1.48-1.65 (m, 2H); 2.05 (q, 2H, *J* 8.4); 2.20-2.24 (m, 1H); 2.39-2.41 (m, 1H); 2.80 (t, 2H, *J* 6.8 Hz); 2.87-2.98 (m, 1H); 2.95 (dt, 1H, *J* 6.4, 4.4); 5.26-5.58 (m, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 130.83; 130.74; 127.20; 124.20; 58.34; 56.57; 34.69; 31.94; 29.69 (2C); 29.65; 29.57; 29.35; 27.31; 26.20; 25.84; 24.33; 22.70; 21.09; 14.11; 10.62. MS (relative intensity %): *m/z* 306 (0.7); 277 (0.5); 248 (0.5); 234(5); 220 (2); 205 (0.5); 191 (0.5); 161

(1); 166 (1); 151 (2); 135 (5); 121 (8); 107 (11); 93 (35); 79 (100); 67 (50); 55 (1).

From Sharpless epoxidation: (2*R*,3*R*)-**1**: $[\alpha]_D^{23}$ +11.5 (*c* 0.002, $CH_2Cl_2$), (2*S*,3*S*)-**1**: $[\alpha]_D^{23}$ –3.55 (*c* 0.004, $CH_2Cl_2$). From organocatalysis: (2*R*,3*R*)-**1**: $[\alpha]_D^{23}$ +4.79 (*c* 0.015, $CH_2Cl_2$), (2*S*,3*S*)-**1**: $[\alpha]_D^{23}$ –5.35 (*c* 0.015, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.88 (t, 3H, *J* 6.8); 0.99 (t, 3H, *J* 7.6); 1.26-1.34 (m, 18H), 1.48-1.65 (m, 2H); 2.05 (q, 2H, *J* 8.4); 2.24-2.30 (m, 1H); 2.40-2.42 (m, 1H); 2.67-2.75 (m, 2H); 2.79 (t, 2H, *J* 6.8); 5.26-5.58 (m, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 131.04; 130.68; 127.29; 123.73; 59.54; 57.66; 31.94; 29.69 (2C); 29.69; 29.65; 29.57; 29.36; 29.34; 27.30; 25.79; 25.03; 22.70; 21.09; 14.11; 9.88. MS (relative intensity %): *m/z* 306 (0.7); 277 (0.5); 248 (0.5); 234(5); 220 (2); 205 (0.5); 191 (0.5); 161 (1); 166 (1); 151 (2); 135 (5); 121 (8); 107 (11); 93 (35); 79 (100); 67 (50); 55 (1).

## Supplementary Information

Supplementary data (GC-EAD, GC-MS, NMR and FTIR spectra) are available free of charge at http://jbcs.sbq.org.br as PDF file.

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