Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 2187–2193

# Concise total synthesis of (3*Z*,6*Z*,9*S*,10*R*)-9,10-epoxy-1,3,6-heneicosatriene, sex pheromone component of *Hyphantria Cunea*

Chao Che[a,b] and Zhong-Ning Zhang[a,*]

[a]*State Key Laboratory of Integrated Management of Pest Insects and Rodents, Institute of Zoology, Chinese Academy of Sciences, No. 19, Zhongguancun Road, Beijing 100080, People's Republic of China*
[b]*Graduate School of the Chinese Academy of Sciences, Beijing 100039, People's Republic of China*

Received 17 September 2004; revised 13 December 2004; accepted 15 December 2004

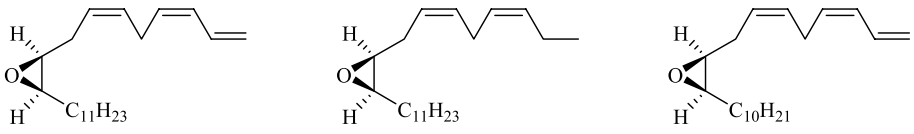
Available online 21 January 2005

**Abstract**—The total synthesis of (3*Z*,6*Z*,9*S*,10*R*)-9,10-epoxy-1,3,6-heneicosatriene, sex pheromone component of *Hyphantria cunea*, using a convergent synthetic strategy, was achieved through the regioselective coupling of the two fragments, chiral epoxy tosylate and 1,4-diyne. The former fragment was synthesized in two efficient and convenient approaches starting from the same available material using Sharpless AE kinetic resolution as the key step.


## 1. Introduction

Optically active epoxides are an important class of natural products encountered as sex pheromones of Lepidopteran pests,[1] self-defensive substances against rice blast disease[2] and antifeedants.[3] The principal member of Lepidopteran epoxy pheromones, (3*Z*,6*Z*,9*S*,10*R*)-9,10-epoxy-1,3,6-henicosatriene **1**, featured a disubstituted chiral epoxide as the central structural element, was first assigned in 1989 in the sex pheromone gland of *Hyphantria cunea*[4] (Fig. 1). Subsequently, **1** was also found in the sex pheromone secretion of *Diacrisia oblique*.[5]

As compared with the synthesis of other members of chiral epoxide pheromones, the synthesis of **1** was more challenging due to the labile 1,3,6-triene subunit. To date, only two studies on the asymmetric synthesis of **1** have been published.[6] These methods suffered from some limitations, mostly importantly being long reaction sequences, very low total yield and/or uncontrolled semihydrogenation of conjugated terminal enyne. Our interest in the synthesis of **1** arises from several considerations. Firstly, due to the strong dependence of pheromone activity on the configuration, the stereoselective synthesis of **1** is of great interest and allows further exploration of the mechanism of pheromone–receptor interaction and the relationship between structure and biological activity. Furthermore, an efficient and concise procedure to **1** would make it possible to allow its use as a pest control agent in pheromone traps, which could lead to environmental-friendly pest management. Moreover, the novel structure itself poses intrinsic problems for a total synthesis. Herein, we describe a concise synthesis of **1**.




(9S, 10R)-**1** (9S, 10R)-**2** (9S, 10R)-**3**

**Figure 1.** Sex pheromone epoxy components of *Hyphantria cunea.*

*Keywords*: Sex pheromone; Hyphantria cunea; Total synthesis.
* Corresponding author. Tel. +86 10 62612241; fax: +86 10 62565689; e-mail: zhangzn@ioz.ac.cn

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.12.060

## 2. Results and discussion

Our synthetic strategy was based on two main building blocks, that is, epoxy-tosylate (2*S*,3*S*)-**4** and 1,4-diyne **5** (Fig. 2). We envisaged that the former could be coupled with diynyl trifluoroborates which were readily generated in situ by the addition of $BF_3 \cdot Et_2O$ to diynyllithiums and mediated the regioselective ring cleavage of oxirane.[7] Our initial experiments involved the use of 1,4-heptdiyne **5a**. The coupling proceeded smoothly to afford the desired ring-opening product. In contrast, the coupling of (2*S*,3*S*)-**4** with **5b** under the similar condition had proven abortive. Repeated attempts by the modification of numerous experimental variations in base, reaction solvent and temperature, failed to furnish the product. Presumably, the introduction of electron-withdrawing vinyl led to the isomerization of molecules mainly due to deprotonation of a methylene between two triple bonds. To probe the effects of structural variations of 1,4-diyne on the course of coupling, additional two 1,4-diyne (**5c**, **5d**) were studied. Only **5d** underwent the coupling to deliver the desired product **6d**. In addition, 1,4-enyne **5e** was synthesized and employed in the coupling reaction. To our delight, we observed that (2*S*,3*S*)-**4** underwent, on treatment of **5e**, a smooth ring-opening to furnish **6e** (Fig. 3).

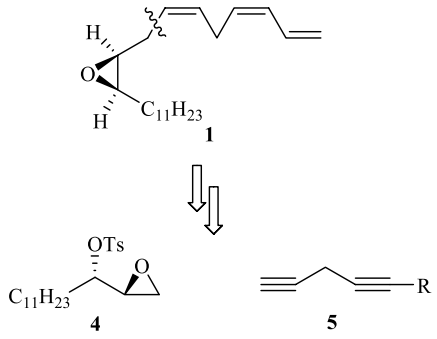
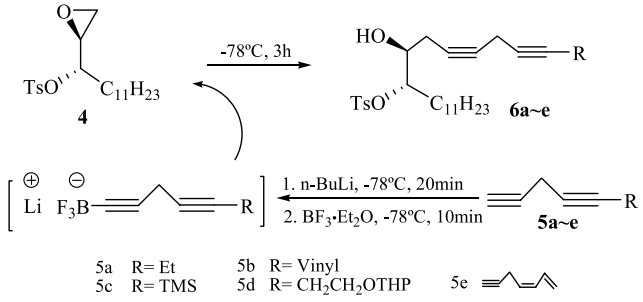



**Figure 2.** Retrosynthetic analysis of (9*S*,10*R*)-**1**.

As matters developed, it seemed that there were two possible routes to the target molecule, respectively derived from the intermediate **6e** and **6d** (Scheme 1). The former which might appear to be a more direct one, however, was not successful on the step of catalytic hydrogenation. We therefore adopt the route b employing **6d** as the intermediate. We found that the presence of THP protecting group in **6d** was unfavorable for the formation of oxirane. After removal of THP protecting group in **6d**, the resulting diol underwent cyclization in the presence of $K_2CO_3$ to afford **9** in good yield. The hydrogenation of **9** over Lindlar catalyst provided **10**, which was converted into the corresponding bromide **11**. The following elimination afforded the target molecule in good yield.

Expoxy tosylate (2*S*,3*S*)-**4** was a vital intermediate in the synthesis of epoxy pheromones and several approaches to it have been reported. However, the methods either employed expensive chiral catalyst system,[8] or were prohibitively lengthy and impractical for large scale preparation.[7b,9] Given those considerations, the present synthesis of (2*S*,3*S*)-**4** employed readily available material and utilized the Sharpless AE kinetic resolution as the key step (Scheme 2, (±)-**12**→(*S*)-**12**). In order to obtain (*S*)-**12** with high enantiomeric excess, the catalytic selectivities of various D-(−)-tartrate esters, diethyl (DET), diisopropyl (DIPT), dicyclohexyl (DCHT), dicyclododecyl tartrate (DCDT) were investigated, and the sterically demanding D-(−)-DCHT gave the best result.[10] Thus, the asymmetric epoxidation of alkenol (±)-**12** using D-(−)-DCHT as ligand gave (*S*)-**12** with excellent yield and enantioselectivity (98.2% ee) upon 50.8% completion of the reaction. Epoxidation on (*S*)-**12** with *m*-CPBA gave a 2:1 ratio of threo to erythro epoxy alcohols (3*S*)-**13**. The compound (3*S*)-**13** were converted into diastereomeric tosylates, which was flash chromatographed to afford (2*S*,3*S*)-**4**. To circumvent the drawbacks of kinetic resolution, on the other hand, we employed an inversion of the configuration[11] to convert (2*S*,3*R*)-**13**, the epoxy product of kinetic resolution, into (2*S*,3*S*)-**14** without the loss of material. Thus, the chemical yields were markedly beyond the 50% limitation set for kinetic resolution. The cleavage of the acetyl group in (2*S*,3*S*)-**14** provided the epoxy alcohols (2*S*,3*S*)-**13**, which were converted to (2*S*,3*S*)-**4** in good yield. The specific optical rotation of (2*S*,3*S*)-**4** was very close to that in the literature {$[\alpha]_D^{25} = +8.8$ ($c=1$, $CHCl_3$); lit.[8] $[\alpha]_D^{20} = +8.6$ ($c=1$, $CHCl_3$)}.

In conclusion, we have developed two efficient and convenient procedures for the synthesis of (2*S*,3*S*)-epoxy



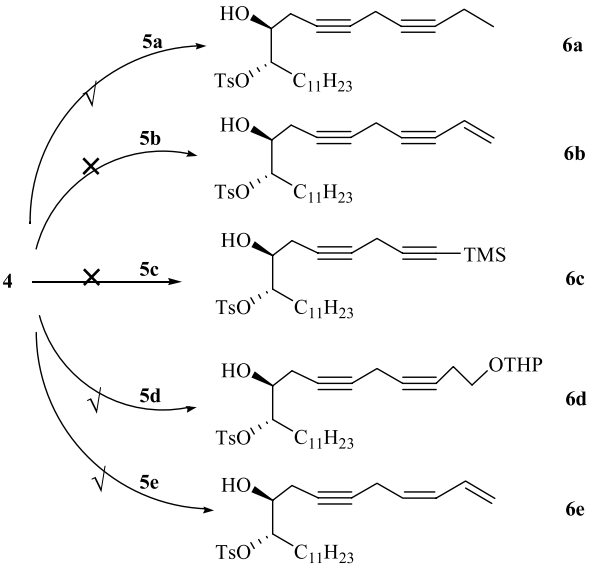
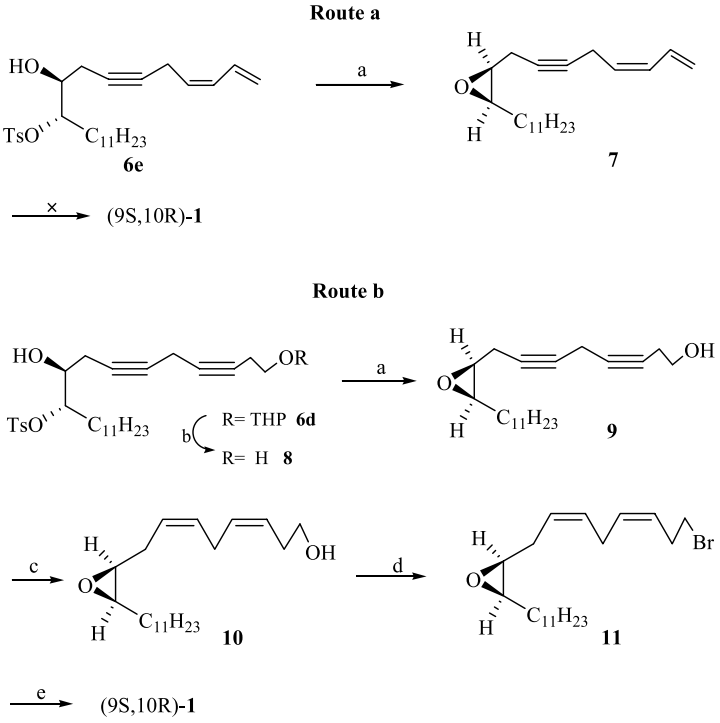
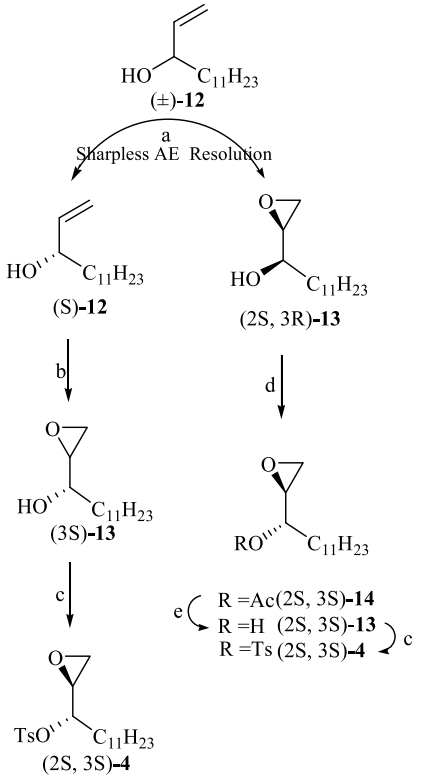




**Figure 3.** Coupling of various 1,4-diyne with (2*S*,3*S*)-**4**.




**Scheme 1.** Synthesis of (9*S*,10*R*)-**1**. Reagents and conditions: (a) $K_2CO_3$, $CH_3OH$, rt, 30 min; (b) PTSA, $CH_3OH$, rt, 5 h; (c) $H_2$, Pd-$CaCO_3$, quinoline, $CH_3OH$, rt; (d) (i) MsCl, $Et_3N$, $CH_2Cl_2$, 0 °C→rt, 1 h; (ii) LiBr, $NaHCO_3$, THF, 8 h. (e) $K_2CO_3$, $CH_3OH$, rt, 48 h. PTSA, *p*-toluenesulfonic acid.




**Scheme 2.** Synthesis of (2*S*,3*S*)-**4**. Reagents and conditions: (a) 4 Å MS, D-(−)-DCHT, Ti(O-*i*-Pr)$_4$, TBHP, $CH_2Cl_2$, −20 °C (refrigerator); (b) *m*-CPBA, $CH_2Cl_2$, rt, 24 h; (c) (i) TsCl, powered KOH, $Et_2O$, −5 °C→0 °C, 3 h; (ii) flash chromatography employed to separate diastereoisomer; (d) AcOH, $PPh_3$, DIAD, THF, rt, 24 h; (e) $K_2CO_3$, $CH_3OH$, 0 °C, 1 h. D-(−)-DCHT, dicyclohexyl D-(−)-tartrate; TBHP, *tert*-butyl hydroperoxide; DIAD, diisopropyl azodicarboxylate.

tosylate starting from the same available material, and then explored the possibility of its coupling with 1,4-diyne or 1,4-enyne via alkylative epoxide rearrangement, through which (3*Z*,6*Z*,9*S*,10*R*)-9,10-epoxy-1,3,6-heneicosatriene **1**, the sex pheromone component of *Hyphantria cunea*, was successfully synthesized. The implementation of the new efficient approach to **1** would pave the way to the synthesis of other members of those highly stereoselective chemoreception insect pheromones or other structurally related polyacetylenic natural products.

## 3. Experimental

### 3.1. General methods

NMR spectra were recorded on a Bruker AMX-400 spectrometer using TMS as internal standard. All the coupling constants are reported in Hz. $^{13}C$ NMR spectra were recorded on the same instrument, and chemical shifts were measured relative to residual solvent resonances ($\delta$ ($CDCl_3$)=77.0). IR spectra were determined by Bruker Tensor 27 spectrometer. High-resolution mass spectra were obtained on a Micromass UK GCT-MS instrument with EI ionization methods. The optical rotations were determined for solution in $CDCl_3$ at 25 °C by using a Perkin–Elmer Model 241-Mc automatic polarimeter. Elemental microanalyses were performed by Italian Carloerba ST-2 analyzer. Melting points were determined on a Yanagimoto apparatus and were uncorrected. 1,4-Diyne and 1,4-enyne **5a**–**5e** were synthesized based on the general procedures described in the literature.[12] Anhydrous solvents were prepared as follows: THF and diethyl ether were freshly distilled under $N_2$ from Na/benzophenone. $CH_2Cl_2$ was

distilled under $N_2$ over $CaH_2$ and stored over 4 Å molecular sieves. Purification of products was performed by flash column chromatography on silica gel (200–300 mesh).

**3.1.1. (*S*)-Tetradec-1-en-3-ol (*S*)-12 and (2*S*,3*R*)-1,2-epoxy-3-tetradecanol (2*S*,3*R*)-13.** To a stirred and cooled (−20 °C) suspension of activated powered 4 Å molecular sieves (2.1 g) in 40 mL dry $CH_2Cl_2$ under nitrogen were added D-(−)-DCHT (0.44 g, 1.4 mmol) and Ti(O-*i*-Pr)$_4$ (0.284 g, 1 mmol) and stirred for 20 min. Then compound (±)-**12** (2.12 g, 10 mmol) and 0.4 mL *n*-dodecane (internal standard for GC monitoring of percent conversion) were added and stirred for further 30 min, during which a small aliquot (ca. 0.1 mL) was taken for a $T_0$GC sample. The reaction was then treated with a solution of TBHP in toluene (0.7 equiv, 3.3 M) added by gastight syringe. The reaction mixture was kept at −20 °C (refrigerator) and monitored by GC. When the conversion reached 50%, the reaction was quenched with an aqueous solution of $FeSO_4$ and citric acid and stirred for 30 min. The organic phase was separated and the aqueous phase was extracted twice with $CH_2Cl_2$. The combined organic phases were washed with saturated brine and dried over $Na_2SO_4$. The crude product was then purified by flash chromatography (petroleum ether/ether, 2/1) to give (*S*)-**12** (0.9 g, 87% based on 50.8% conversion) and (2*S*,3*R*)-**13** (1.06 g, 91% based on 50.8% conversion). (*S*)-**12**, a colorless oil, $[\alpha]_D^{25}=+5.5$ ($c=1$, $CHCl_3$), lit.[6b] $[\alpha]_D^{25}=+5.2$ ($c=1$, $CHCl_3$); IR (neat) $\nu$ 3390, 3020, 2930, 1650 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 5.86 (ddd, $^3J_{trans}=17.1$ Hz, $^3J_{cis}=10.4$ Hz, $^3J=6.3$ Hz, 1H, $CH_2$=C*H*), 5.18 (dt, $^3J_{trans}=17.1$ Hz, $^2J=^4J=1.4$ Hz, 1H, C*H*H=CH), 5.08 (dt, $^3J_{cis}=10.4$ Hz, $^2J=^4J=1.4$ Hz, 1H, CH*H*=CH), 4.05–4.12 (m, 1H, C*H*OH), 1.45–1.56 (m, 2H, C$H_2$CHOH), 1.26 (br, s, 18H, $(CH_2)_9$), 0.88 (t, $J=6.9$ Hz, 3H, $CH_3$); $^{13}$C NMR ($CDCl_3$) $\delta$ 141.3, 114.3 (CH=$CH_2$), 73.2 (CHOH), 37.0, 31.9, 29.6, 29.5, 29.3, 25.3, 22.6, 14.0; Anal. Calcd for $C_{14}H_{28}O$: C, 79.18; H, 13.29. Found: C, 79.28; H, 13.12. (2*S*,3*R*)-**13**, white solid, mp 47–49 °C; $[\alpha]_D^{25}=-12.5$ ($c=1$, $CHCl_3$); IR (neat) $\nu$ 3310, 2910 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 3.81–3.83 (m, 1H, C*H*OH), 3.00–3.02 (m, 1H, oxirane CH), 2.81 (dd, $^2J=5.1$ Hz, $^3J=3.2$ Hz, 1H, oxirane $CH_2$), 2.72 (dd, $^2J=5.1$, $^3J=4.0$ Hz, 1H, oxirane, $CH_2$), 1.46–1.55 (m, 2H, C$H_2$CHOH), 1.26 (br, s,18H, $(CH_2)_9$), 0.88 (t, $J=6.7$ Hz, 3H, $CH_3$); $^{13}$C NMR ($CDCl_3$) $\delta$ 68.4 (CHOH), 54.6, 43.4 (CH(O)CH), 33.4, 31.9, 29.6, 29.5, 29.3, 25.2, 22.6, 14.0; Anal. Calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36. Found: C, 73.55; H, 12.14.

**3.1.2. (3*S*)-1,2-Epoxy-3-tetradecanol (3*S*)-13.** A solution of (*S*)-**12** (2.12 g, 10 mmol) in 20 mL of anhydrous $CH_2Cl_2$ was cooled to 0 °C and stirred vigorously under nitrogen atmosphere. To this was added a solution of 75% *m*-CPBA (3.23 g, 14 mmol) in $CH_2Cl_2$. The resulting white mixture was warmed to room temperature and stirred for 24 h. The solution was filtered and washed with three 20 mL portions of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CH_2Cl_2$, and the combined organic layers were dried over anhydrous $Na_2SO_4$. After the concentration and purification by flash chromatography (petroleum ether/ether, 2/1) epoxy alcohol (3*S*)-**13** (1.9 g, 84%) was obtained as a colorless oil which solidified upon standing at room temperature. The ratio of threo to erythro epoxy alcohols was determined to be ca. 2:1 by $^1$H NMR integration of the carbinol methine proton resonances. IR (neat) $\nu$ 3310, 2910 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 3.84 and 3.43 (2m, 1H, C*H*OH) (1:2), 2.96–3.04 (m, 1H, oxirane CH), 2.82 (dd, $^2J=4.9$ Hz, $^3J=4.1$ Hz, 1H, oxirane $CH_2$), 2.72 (dd, $^2J=4.9$ Hz, $^3J=2.7$ Hz, 1H, oxirane, $CH_2$), 1.55–1.60 (m, 2H, C$H_2$CHOH), 1.26 (br, s,18H, $(CH_2)_9$), 0.88 (t, $J=6.9$ Hz, 3H, $CH_3$); Anal. Calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36. Found: C, 73.55; H, 12.14.

**3.1.3. (2*S*,3*S*)-1,2-Epoxy-3-acetyloxytetradecane (2*S*,3*S*)-14.** To a solution of the epoxy alcohol (2*S*,3*R*)-**13** (1.14 g, 5 mmol) in anhydrous THF (100 mL) was added AcOH (1.50 g, 25 mmol) and $PPh_3$ (5.24 g, 20 mmol), followed by the addition of diisopropylazodicarboxylate (3.03 g, 15 mmol) over a period of 5 min. The orange-red color of diisopropylazodicarboxylate faded immediately with slight liberation of heat. The solution was stirred at room temperature for 1 day. The mixture was diluted with ether (100 mL) then washed with $H_2O$ and brine. The aqueous washings were extracted with ether (50 mL) and the extraction was washed with brine. The combined organic layers were dried over anhydrous $Na_2SO_4$. The solvent was removed at reduced pressure. Flash chromatography (petroleum ether/ether, 5/1) of the residue afforded (2*S*,3*S*)-**14** (0.90 g, 67%) as a colorless oil. $[\alpha]_D^{25}=+2.7$ ($c=1$, $CHCl_3$); IR (neat) $\nu$ 2930, 1730 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 4.68–4.73 (m, 1H, C*H*OAc), 3.05–3.08 (m, 1H, oxirane CH), 2.82 (dd, $^2J=4.8$ Hz, $^3J=4.1$ Hz, 1H, oxirane $CH_2$), 2.63 (dd, $^2J=4.8$ Hz, $^3J=2.6$ Hz, 1H, oxirane $CH_2$), 2.08 (s, 3H, O=C*CH*$_3$), 1.63–1.66 (m, 2H, C$H_2$CHOAc), 1.26 (br, s, 18H, $(CH_2)_9$), 0.88 (t, $J=6.7$ Hz, 3H, $CH_3$); $^{13}$C NMR ($CDCl_3$) $\delta$ 170.3 (O=C); 74.0 (CHOAc); 52.9, 44.8 (CH(O)CH); 31.8, 31.3, 29.5, 29.4, 29.3, 29.2, 25.1, 22.6, 20.9, 14.0; Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 70.92; H, 11.07.

**3.1.4. (2*S*,3*S*)-1,2-Epoxy-3-tetradecanol (2*S*,3*S*)-13.** To a solution of (2*S*,3*S*)-**14** (0.54 g, 2 mmol) in methanol (10 mL) was added anhydrous $K_2CO_3$ (0.5 g) at 0 °C while stirring. The mixture was stirred at 0 °C for 1 h, and then filtered. Concentration of the filtrate and purification by flash chromatography (petroleum ether/ether, 1/1) gave (2*S*,3*S*)-**13** (0.43 g, 94%) as a white solid, mp 40–42°C; $[\alpha]_D^{25}=+1.6$ ($c=1$, $CHCl_3$); IR (neat) $\nu$ 3310, 2910 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 3.41–3.43 (m, 1H, C*H*OH), 2.97–2.99 (m, 1H, oxirane CH), 2.83 (dd, $^2J=4.8$ Hz, $^3J=4.2$ Hz, 1H, oxirane $CH_2$), 2.71 (dd, $^2J=4.8$ Hz, $^3J=2.7$ Hz, 1H, oxirane, $CH_2$), 1.57–1.61 (m, 2H, C$H_2$CHOH), 1.26 (br, s, 18H, $(CH_2)_9$), 0.88 (t, $J=6.8$ Hz, 3H, $CH_3$); $^{13}$C NMR ($CDCl_3$) $\delta$ 71.7 (CHOH), 55.4, 45.1 (CH(O)CH), 34.3, 31.9, 29.6, 29.5, 29.4, 29.3, 25.3, 22.6, 14.0; Anal. Calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36. Found: C, 73.55; H, 12.14.

**3.1.5. (2*S*,3*S*)-1,2-Epoxy-3-tosyloxytetradecane (2*S*,3*S*)-4.** To a solution of epoxy alcohols (3*S*)-**13** (2.28 g, 10 mmol) in 50 mL of anhydrous $Et_2O$ was added tosylchloride (2.85 g, 15 mmol) and the mixture was cooled to −5 to −10 °C. Freshly and finely machine-powdered KOH (6 g) was added with efficient stirring over 15 min while maintaining the temperature between −5 and 0 °C. The mixture was stirred for additional 2 h at 0 °C and then poured into 50 mL of ice water. After vigorous shaking, the layers were separated. The organic layer and two ethereal

extracts were washed with brine and dried over anhydrous $Na_2SO_4$. Concentration and purification by flash chromatography (petroleum ether/ether, 2/1) yielded threo-epoxy tosylate (2*S*,3*S*)-**4** (1.72 g) as white solid and erythro-epoxy tosylate (0.94 g) as colorless oil. Threo-epoxy tosylate (2*S*,3*S*)-**4**, mp 66–68 °C; $[\alpha]_D^{25}=+8.8$ ($c=1$, $CHCl_3$), lit.[8] mp 71–72 °C, $[\alpha]_D^{20}=+8.6$ ($c=1$, $CHCl_3$); IR (KBr) $\nu$ 3050, 2925, 1595 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.81 (d, $J=$ 8.3 Hz, 2H, 2,6-Ar), 7.32 (d, $J=8.3$ Hz, 2H, 3,5-Ar), 4.34 (dt, $J=6.3$, 7.2 Hz, 1H, C*H*OTs), 3.03–3.06 (m, 1H, oxirane CH), 2.78 (t, $^2J=^3J=4.6$ Hz, 1H, oxirane $CH_2$), 2.63 (dd, $^2J=4.6$ Hz, $^3J=2.6$ Hz, 1H, oxirane $CH_2$), 2.44 (s, 3H, Ar–*$CH_3$*), 1.66–1.70 (m, 2H, C*$H_2$*CHOTs), 1.26 (br, s, 18H, $(CH_2)_9$), 0.88 (t, $J=6.6$ Hz, 3H, $CH_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 144.5, 134.3, 129.6, 127.8 (Ar); 83.4 (CHOTs); 52.6, 44.8 (CH(O)CH); 31.9, 31.8, 29.5, 29.4, 29.2, 29.1, 24.8, 22.6, 21.6, 14.1; Anal. Calcd for $C_{21}H_{34}O_4S$: C, 65.93; H, 8.96. Found: C, 65.98; H, 8.93.

The same procedure as described above was applied for the conversion of (2*S*,3*S*)-**13** to (2*S*,3*S*)-**4**.

### 3.2. Typical procedure for the preparation of 6a, 6d and 6e

**3.2.1. (*Z*,9*S*,10*S*)-9-Hydroxy-10-tosyloxyhenicosa-1,3-dien-6-yne 6e.** A solution of **5e** (0.28 g, 3 mmol) in 15 mL of anhydrous THF was stirred at −78 °C as a solution of *n*-BuLi in hexanes (1 mL, 2.5 mmol) was added slowly by syringe. The resulting dark green solution was stirred for 15 min, and then $BF_3\cdot Et_2O$ (0.31 mL, 2.5 mmol) was added via syringe. After another 15 min, a solution of **4** (0.38 g, 1 mmol) in 4 mL of THF was added also by syringe, and the reaction mixture was stirred for further 3 h at −78 °C. The reaction mixture was then quenched with 10 mL saturated $NH_4Cl$. The aqueous layer was separated and extracted with ether (10 mL×2). The combined organic layer was dried over anhydrous $Na_2SO_4$, and concentrated to afford a brown residue which was purified through flash chromatography (petroleum ether/ether, 1/1) to give **6e** (0.37, 79%) as a colorless oil. $[\alpha]_D^{25}=-4.1$ ($c=1$, $CHCl_3$); IR (neat) $\nu$ 3524, 3080, 3030, 2925, 2285 (weak), 1645, 1597 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.82 (d, $J=8.3$ Hz, 2H, 2,6-Ar), 7.33 (d, $J=8.3$ Hz, 2H, 3,5-Ar), 6.63 (dddd, $^3J_{trans}=16.7$ Hz, $^3J_{cis}=10.2$ Hz, $^3J=10.7$ Hz, $^4J=1.0$ Hz, 1H, CH=CHC*H*=$CH_2$), 6.05 (t, $^3J=^3J_{cis}=10.7$ Hz, 1H, CH=C*H*CH=$CH_2$), 5.44 (dt, $^3J_{cis}=10.7$ Hz, $^3J=7.2$ Hz, 1H, C*H*=CHCH=$CH_2$), 5.25 (d, $^3J_{trans}=16.7$ Hz, 1H, CH=CHCH=C*H*H), 5.17 (d, $^3J_{cis}=10.2$ Hz, 1H, CH=CHCH=CH*H*), 4.62–4.67 (m, 1H, C*H*OTs), 3.76–3.80 (m, 1H, C*H*OH), 3.04 (dd, $^3J=7.2$ Hz, $^4J=1.8$ Hz, 2H, HC≡CC*$H_2$*C=CH), 2.44 (s, 3H, Ar–*$CH_3$*), 2.35–2.37 (m, 2H, C≡CC*$H_2$*CHOH), 1.50–1.70 (m, 2H, TsOCHC*$H_2$*), 1.26 (br, s, 18H, $(CH_2)_9$), 0.88 (t, $J=6.6$ Hz, 3H, $CH_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 144.7, 134.1, 129.8, 127.9 (Ar); 131.3, 130.4, 126.3, 118.7 (2C=C); 84.7 (TsOCH); 81.0, 76.7 (C≡C); 70.4 (CHOH); 31.9, 30.6, 29.6, 29.5, 29.4, 29.3, 29.2, 24.9, 23.9, 22.7, 22.6, 21.7, 17.6, 14.1; HRMS (*m*/*z*) Calcd for $C_{28}H_{42}O_4S$ 474.2804, found 474.2801.

Compounds **6a** and **6d** were prepared in the same manner to that described above.

**3.2.2. (9*S*,10*S*)-9-Hydroxy-10-tosyloxyhenicosa-3,6-diyne 6a.** Colorless oil (0.40 g, 84%); $[\alpha]_D^{25}=-11.7$ ($c=$ 1, $CHCl_3$); IR (neat) $\nu$ 3410, 3065, 2925, 2210 (weak), 1595 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.81 (d, $J=8.3$ Hz, 2H, 2,6-Ar), 7.33 (d, $J=8.3$ Hz, 2H, 3,5-Ar), 4.63–4.67 (m, 1H, C*H*OTs), 3.88 (dt, $J=3.9$, 6.9 Hz, 1H, C*H*OH), 3.11–3.13 (m, 2H, C≡CC*$H_2$*C≡C), 2.45 (s, 3H, Ar–C*$H_3$*), 2.34–2.37 (m, 2H, C≡CC*$H_2$*CHOH), 2.16–2.19 (m, 2H, C≡CC*$H_2$*-$CH_3$), 1.51–1.60 (m, 2H, TsOCHC*$H_2$*$CH_2$), 1.26 (br, s, 18H, $(CH_2)_9$), 1.12 (t, $J=7.5$ Hz, 3H, C≡C$CH_2$C*$H_3$*), 0.88 (t, $J=$ 6.8 Hz, 3H, $CH_3$); Anal. Calcd for $C_{28}H_{42}O_4S$: C, 70.85; H, 8.92. Found: C, 70.56; H, 8.68.

**3.2.3. (9*S*,10*S*)-9-Hydroxy-10-tosyloxy-1-(tetrahydro-2*H*-pyran-2-yloxy)henicosa-3,6-diyne 6d.** Colorless oil (0.42 g, 73%); $[\alpha]_D^{25}=-18.6$ ($c=1$, $CHCl_3$); IR (neat) $\nu$ 3430, 3065, 2925, 2216 (weak), 1598 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.83 (d, $J=8.2$ Hz, 2H, 2,6-Ar), 7.35 (d, $J=$ 8.2 Hz, 2H, 3,5-Ar), 4.63–4.66 (m, 2H, C*H*OTs, OC*H*O), 3.80–3.91 (m, 2H, C≡C$CH_2$C*$H_2$*OTHP), 3.69–3.73 (m, 1H, C*H*OH), 3.11–3.15 (m, 2H, C≡CC*$H_2$*C≡C), 2.49 (dt, $^3J=$ 7.1 Hz, $^5J=2.1$ Hz, 2H, HOCHC*$H_2$*C≡C), 2.45 (s, 3H, Ar–C*$H_3$*), 2.36 (t, $J=6.2$ Hz, 2H, C≡CC*$H_2$*$CH_2$OTHP), 1.50–1.80 (m, 8H, TsOCHC*$H_2$*, $(CH_2)_3$), 1.26 (br, s, 18H, $(CH_2)_9$), 0.88 (t, $J=6.4$ Hz, 3H, $CH_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 144.8, 134.1, 129.7, 127.9 (Ar); 98.7 (OCHO), 84.6 (TsOCH); 77.6, 75.7, 75.2, 68.5 (2C≡C); 70.3 (CHOH); 65.7, 62.2 ($2CH_2O$); 31.9, 30.6, 30.5, 29.6, 29.5, 29,3, 29.2, 25.4, 24.9, 23.8, 22.7, 21.6, 20.2, 19.4, 19.3, 14.1, 9.8, 9.6; Anal. Calcd for $C_{33}H_{50}O_6S$: C, 68.95; H, 8.77. Found: C, 68.77; H, 8.73.

**3.2.4. (*Z*,9*S*,10*R*)-9,10-Epoxyhenicosa-1,3-dien-6-yne 7.** To a solution of **6e** (0.47 g, 1 mmol) in 10 mL of anhydrous methanol was added anhydrous $K_2CO_3$ (0.4 g) with stirring at room temperature. After 30 min, the reaction mixture was filtered. Concentration of the filtrate and purification by flash chromatography (petroleum ether/diethyl ether, 10/1) afforded **7** (0.25 g, 82%) as a colorless oil which solidified upon standing at room temperature. $[\alpha]_D^{25}=+21.4$ ($c=1$, $CHCl_3$); IR (neat) $\nu$ 3030, 2925, 2285 (weak), 1645 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 6.63 (ddd, $^3J_{trans}=16.7$ Hz, $^3J_{cis}=$ 10.2 Hz, $^3J=10.7$ Hz, 1H, CH=CHC*H*=$CH_2$), 6.04 (t, $^3J=^3J_{cis}=10.7$ Hz, 1H, CH=C*H*CH=$CH_2$), 5.44 (dt, $^3J_{cis}=10.7$ Hz, $^3J=7.2$ Hz, 1H, C*H*=CHCH=$CH_2$), 5.24 (d, $^3J_{trans}=16.7$, 1H, CH=CHCH=C*H*H), 5.16 (d, $^3J_{cis}=10.2$ Hz, 1H, CH=CHCH=CH*H*), 3.06–3.12 (m, 3H, C≡CC*$H_2$*CH=CH, oxirane CH), 2.95 (dt, $J=4.2$, 5.5 Hz, 1H, oxirane CH), 2.52–2.58 (ddt, $^2J=17$ Hz, $^3J=$ 5.5 Hz, $^5J=2.7$ Hz, 1H, C≡CC*H*HCH(O)CH), 2.22–2.28 (ddt, $^2J=17$, $^3J=7.2$ Hz, $^5J=2.5$ Hz, 1H, C≡CCH*H*CH(O)CH), 1.50–1.56 (m, 2H, CH(O)CHC*$H_2$*), 1.26 (br, s, 18H, $(CH_2)_9$), 0.88 (t, $J=6.6$ Hz, 3H, $CH_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 131.3, 130.3, 126.5, 118.5 (2CH=CH); 79.9, 75.4 (C≡C); 57.1, 55.3 (CH(O)CH); 31.9, 29.7, 29.6, 29.5, 29.3, 27.6, 26.5, 22.7, 18.8, 17.7, 14.1; HRMS (*m*/*z*) Calcd for $C_{21}H_{34}O$ 302.2610, found 302.2613.

**3.2.5. (9*S*,10*S*)-1,9-Dihydroxy-10-tosyloxyhenicosa-3,6-diyne 8.** PTSA (catalytic) was added to a solution of **6d** (1.15 g, 2 mmol) in 30 mL of methanol and stirred for 5 h at room temperature. Methanol was removed under reduced pressure and the residue was dissolved in ether. The ether

layer was washed with water, saturated aqueous $NaHCO_3$, brine respectively and dried over anhydrous $Na_2SO_4$. Concentration at reduced pressure and purification by flash chromatography (petroleum ether/ether, 1/4) afforded **8** (0.89 g, 91%) as a colorless oil. $[\alpha]_D^{25}=-8.6$ ($c=1$, $CHCl_3$); IR (neat) $\nu$ 3390, 3065, 2925, 2217 (weak), 1598 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.83 (d, $J=8.3$ Hz, 2H, 2,6-Ar), 7.35 (d, $J=8.3$ Hz, 2H, 3,5-Ar), 4.64–4.66 (m, 1H, C*H*OTs,), 3.79–3.82 (m, 1H, C*H*OH), 3.71 (t, $J=6.2$ Hz, 2H, C≡CCH$_2$C*H*$_2$OH), 3.13–3.15 (m, 2H, C≡CC*H*$_2$-C≡C), 2.42–2.47 (m, 5H, Ar–C*H*$_3$, HOCHC*H*$_2$C≡C), 2.36–2.38 (m, 2H, C≡CC*H*$_2$CH$_2$OH), 1.50–1.60 (m, 2H, TsOCHCH*H*$_2$), 1.26 (br, s, 18H, $(CH_2)_9$), 0.88 (t, $J=6.6$ Hz, 3H, $CH_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 144.8, 134.1, 129.7, 127.8 (Ar); 84.6 (CHOTs); 77.3, 76.1, 75.8, 68.7 (2C≡C); 70.3 (CHOH); 61.0 ($CH_2OH$); 31.9, 30.5, 29.6, 29.5, 29.3, 29.2, 24.9, 23.7, 23.0, 22.9, 22.7, 21.6, 14.1, 9.8, 9.6; Anal. Calcd for $C_{28}H_{42}O_5S$: C, 68.54; H, 8.63. Found: C, 68.41; H, 8.74.

**3.2.6. (9*S*,10*R*)-9,10-Epoxyhenicos-3,6-diyn-1-ol 9.** The procedure described for the preparation of **7** was followed. White solid (0.26 g, 83%), mp 48–50 °C; $[\alpha]_D^{25}=+23.5$ ($c=1$, $CHCl_3$); IR (KBr) $\nu$ 3390, 2930, 2280 (weak) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 3.71 (t, $J=6.2$ Hz, 2H, C*H*$_2$OH), 3.14–3.17 (m, 2H, C≡CC*H*$_2$C≡C), 3.11 (dt, $J=5.5$ Hz, 1.6, 1H, oxirane CH), 2.95 (dt, $J=4.5$, 5.5 Hz, 1H, oxirane CH), 2.29 and 2.52 (2m, 2H, C≡CC*H*$_2$CH(O)CH), 2.45 (tt, $^3J=6.2$ Hz, $^5J=2.3$ Hz, 2H, C≡CC*H*$_2$CH$_2$OH), 1.48–1.53 (m, 2H, CH(O)CHC*H*$_2$CH$_2$), 1.26 (br, s, 18H, $(CH_2)_9$), 0.88 (t, $J=6.6$ Hz, 3H, $CH_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 77.1, 76.3, 76.2, 75.7 (2C≡C); 61.1 ($CH_2OH$); 57.1, 55.0 (CH(O)CH); 31.9, 29.6, 29.5, 29.4, 29.3, 27.5, 26.4, 23.1, 22.7, 18.7, 14.1, 9.8; HRMS (*m*/*z*) Calcd for $C_{21}H_{34}O_2$ 318.2559, found 318.2553.

**3.2.7. (3*Z*,6*Z*,9*S*,10*R*)-9,10-Epoxyhenicos-3,6-dien-1-ol 10.** Lindlar catalyst (5% palladium on $CaCO_3$, poisoned with lead, 15 mg) and 5 mg quinoline was placed in a 50 mL flask equipped with side arm and a rubber septum. The flask was alternately evacuated and filled with hydrogen several times. A solution of **9** (0.32 g, 1 mmol) in 20 mL of methanol was added via syringe and the suspension was stirred at room temperature until required amount of hydrogen gas (44.8 mL). The reaction mixture was filtered and concentrated under reduced pressure to afford **10** in almost quantitative yields. White solid, mp 39–42 °C; $[\alpha]_D^{25}=-2.5$ ($c=1$, $CHCl_3$); IR (neat) $\nu$ 3300, 3025, 2920, 1645 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.39–5.57 (m, 4H, C*H*=C*H*CH$_2$C*H*=C*H*) 3.66 (t, $J=6.3$ Hz, 2H, C*H*$_2$OH), 2.83–2.97 (m, 4H, C*H*(O)C*H*, CH=CHC*H*$_2$CH=CH), 2.25 and 2.39 (2m, 2H, CH=CHC*H*$_2$CH(O)CH), 2.35–2.41 (m, 2H, HC=CHC*H*$_2$CH$_2$OH), 1.46–1.55 (m, 2H, CH(O)CHC*H*$_2$CH$_2$), 1.26 (br, s, 18H, $(CH_2)_9$), 0.88 (t, $J=6.6$ Hz, 3H, $CH_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 130.7, 130.3, 126.0, 124.6 (2C=C); 62.2 ($CH_2OH$); 57.2, 56.4 (CH(O)CH); 31.9, 30.9, 29.6, 29.5, 29.4, 27.8, 26.6, 26.3, 25.9, 22.7, 14.1; HRMS (*m*/*z*) Calcd for $C_{21}H_{38}O_2$ 322.2872, found 322.2874.

**3.2.8. (3*Z*,6*Z*,9*S*,10*R*)-1-Bromo-9,10-epoxyhenicos-3,6-diene 11.** To an ice-cooled solution of **10** (1.61 g, 5 mmol) in $CH_2Cl_2$ (30 mL) containing triethylamine (1.01 g, 10 mmol) was added methanesulfonyl chloride (0.74 g, 6.3 mmol) with stirring. The mixture was stirred for additional 1 h, and then washed with water. The methylene chloride solution was dried over anhydrous $Na_2SO_4$ and concentrated to give an oil residue. The residue was dissolved in dry THF (10 mL), and added anhydrous LiBr (1.72 g, 20 mmol) and $NaHCO_3$ (1.76 g, 15 mmol) at 0 °C. The mixture was stirred for 8 h at room temperature and then filtered. Concentration of the filtrate and flash chromatography (petroleum ether/ether, 10/1) afforded **11** (1.57 g, 82%) as a colorless oil. $[\alpha]_D^{25}=+4.2$ ($c=1$, $CHCl_3$); IR (neat) $\nu$ 3030, 2925, 1640 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.41–5.54 (m, 4H, C*H*=C*H*CH$_2$C*H*=C*H*), 3.38 (t, $J=7.1$ Hz, 2H, C*H*$_2$Br), 2.79–2.96 (m, 4H, oxirane, CH=CHC*H*$_2$CH=CH), 2.63 (dt, $J=6.5$ Hz, 7.0, 2H, CH=CHC*H*$_2$CH$_2$Br), 2.29 and 2.37 (2m, 2H, CH(O)CHC*H*$_2$CH=CH), 1.50–1.55 (m, 2H, CH(O)-CHC*H*$_2$CH$_2$), 1.26 (br, s, 18H, $(CH_2)_9$), 0.89 (t, $J=6.6$ Hz, 3H, $CH_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 130.5, 130.1, 126.5, 124.3 (2C=C); 57.3, 56.4 (CH(O)CH); 31.9, 30.8, 29.9, 29.6, 29.5, 29.4, 29.3, 26.0, 25.9, 22.6, 14.1; HRMS (*m*/*z*) Calcd for $C_{21}H_{37}OBr$ 384.2028, found 384.2031.

**3.2.9. (3*Z*,6*Z*,9*S*,10*R*)-9,10-Epoxy-1,3,6-henicostriene 1.** To a solution of **11** (0.38 g, 1 mmol) in 10 mL anhydrous methanol was added anhydrous $K_2CO_3$ (0.4 g) with stirring at room temperature. After 48 h, the reaction mixture was filtered. Concentration of the filtrate and purification by flash chromatography (petroleum ether/ether, 20/1) afforded **1** (0.26 g, 86%) as a colorless oil. $[\alpha]_D^{25}=-0.6$ ($c=3$, $CHCl_3$), lit.[6a] $[\alpha]_D^{16}=-0.41$ ($c=1.97$, $CHCl_3$); IR (neat) $\nu$ 3030, 2925, 1640 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 6.64 (dddd, $^3J_{trans}=16.8$ Hz, $^3J_{cis}=10.1$ Hz, $^3J=10.9$ Hz, $^4J=1.1$ Hz, 1H, CH=CHC*H*=CH$_2$), 6.01 (t, $J=10.9$ Hz, 1H, CH=C*H*CH=CH$_2$), 5.38–5.55 (m, 3H, C*H*=C*H*CH$_2$-C*H*=CH), 5.23 (dd, $^3J_{trans}=16.8$ Hz, $^2J=1.8$ Hz, 1H, CH=CHCH=C*H*H), 5.14 (d, $^3J_{cis}=10.1$ Hz, 1H, CH=CHCH=CH*H*), 2.80–2.96 (m, 4H, oxirane, CH=CHC*H*$_2$CH=CH), 2.29 and 2.39 (2m, 2H, CH(O)CHC*H*$_2$CH=CH), 1.55–1.60 (m, 2H, CH(O)-CHC*H*$_2$), 1.26 (br, s, 18H, $(CH_2)_9$), 0.89 (t, $J=6.7$ Hz, 3H, $CH_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 131.8, 130.1, 129.9, 129.5, 124.4, 117.6 (3C=C); 57.2, 56.4 (CH(O)CH); 31.9, 29.9, 29.6, 29.5, 29.4, 29.3, 26.2, 26.0, 22.7, 14.1; HRMS (*m*/*z*) Calcd for $C_{21}H_{36}O$ 304.2766, found 304.2770.

## Acknowledgements

We thank Beijing forestry station for generous financial support of the study.

## References and notes

1. (a) Hill, A. S.; Kovalev, B. G.; Nikolaeva, L. N.; Reolofs, W. L. *J. Chem. Ecol.* **1982**, *8*, 383–396. (b) Wong, J. W.; Underhill, E. W.; Mckenzie, S. L.; Chisholm, M. D. *J. Chem. Ecol.* **1985**, *11*, 726–756. (c) Millar, J. G.; Underhill, E. W.; Giblin, M.; Barton, D. *J. Chem. Ecol.* **1987**, *13*, 1371–1383. (d) Brevet, J. L.; Mori, K. *Synthesis* **1992**, 1007–1012.

2. Yadav, J. S.; Radhakrishna, P. *Tetrahedron* **1990**, *46*, 5825–5832.
3. Grandjean, D.; Pale, P.; Chuche, J. *Tetrahedron Lett.* **1992**, *33*, 5355–5358.
4. Toth, M.; Buser, H. R.; Pena, A.; Arn, H.; Mori, K.; Takeuchi, T.; Nikolaeva, L. N.; Kovalev, B. G. *Tetrahedron Lett.* **1989**, *30*, 3405–3408.
5. Persoons, C. J.; Yadav, J. S.; Prasad, A. R.; Subhashini, S.; Prasoona, A. L.; Jyothi, K. N. *IOBC/WPRS Bull.* **1993**, *16*, 136–140.
6. (a) Mori, K.; Takeuchi, T. *Liebigs Ann. Chem.* **1989**, 453–457. (b) Yadav, J. S.; Valli, M. Y.; Prasad, A. R. *Tetrahedron* **1998**, *54*, 7551–7562.
7. (a) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391–394. (b) Bell, T. W.; Ciaccio, J. A. *J. Org. Chem.* **1993**, *58*, 5153–5162.
8. (a) Zhang, Z. B.; Wang, Z. M.; Wang, Y. X.; Liu, H. Q.; Lei, G. X.; Shi, M. *J. Chem. Soc., Perkin Trans. I* **2000**, 53–57. (b) Zhang, Z. B.; Wang, Z. M.; Wang, Y. X.; Liu, H. Q.; Lei, G. X.; Shi, M. *Tetrahedron: Asymmetry* **1999**, *10*, 837–840.
9. Soulié, J.; Boyer, T.; Lallemand, J. Y. *Tetrahedron: Asymmetry* **1995**, *6*, 625–636.
10. Che, C.; Zhang, Z. N.; Huang, G. L.; Wang, X. X. *Chin. J. Org. Chem.* **2004**, *24*, 1281–1283.
11. Mitsuunobu, O. *Synthesis* **1981**, 1–28.
12. Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: New York, 1988; p 227.