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A Facile Synthetic Method for (3Z, 6Z, 9S, 10R)-9, 10-Epoxy-3, 6-heneicosadiene, Sex Pheromone Component of *Hyphantria Cunea (Drug)*

Chao CHE, Zhong Ning ZHANG*

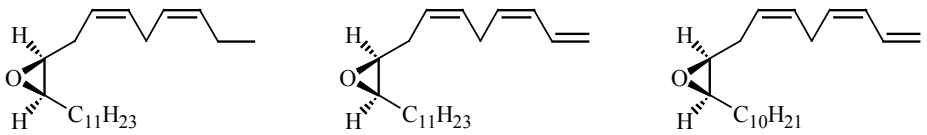
State Key Laboratory of Integrated Management of Insects and Rodents, Institute of Zoology, Chinese Academy of Sciences, Beijing 100080
Graduate School of the Chinese Academy of Sciences, Beijing 100039

Abstract: Total synthesis of (3Z, 6Z, 9S, 10R)-9, 10-epoxy-3, 6-heneicosadiene, sex pheromone component of *Hyphantria cunea (Drug)*, was achieved using Sharpless AE kinetic resolution and alkylative epoxide rearrangement as key steps.

Keywords: Sex pheromone, *Hyphantria cunea (Drug)*, Sharpless kinetic resolution, asymmeric synthesis.

Fail webworm *Hyphantria cunea (Drug)* is a notorious pest known as the American white moth which attack many crops. Earlier studies[1-3] have shown that the pheromones of *Hyphantria cunea (Drug)* are constituted with five components: (3Z, 6Z, 9*S*, 10*R*)-9, 10-epoxy-3, 6-heneicosadiene **1**, (3Z, 6Z, 9*S*, 10*R*)-9, 10-epoxy-1, 3, 6-heneicosatriene **2**, (3Z, 6Z, 9*S*, 10*R*)-cis-9, 10-epoxy-1, 3, 6-icosatriene **3**, (9Z, 12Z)-octadecadienal **4** and (9Z, 12Z, 15Z)-octadecatrienal **5**. Three of them have a similar structure which incorporates an unsaturated chain and a saturated long chain substituted chiral oxirane (**Figure 1**). In view of its novel structure and interesting biological activity, the total synthesis of these compounds has attracted a significant amount of attention[2-6]. However, the syntheses suffer from long reaction sequence and low yield. Herein, we presented a concise total synthesis of component **1** using Sharpless asymmetric epoxide (AE) kinetic resolution as a key step**.**

Figure 1

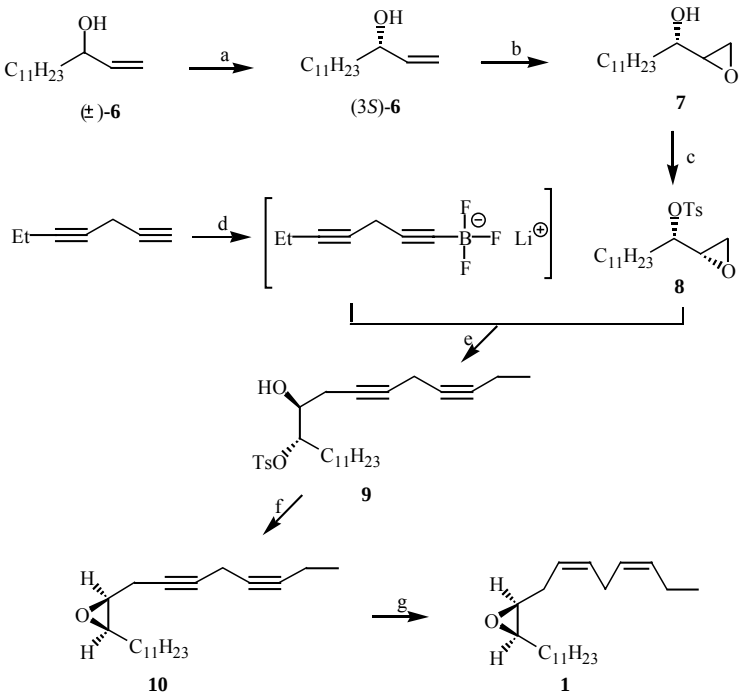


compound **1** compound **2** compound **3**

* Email: zhangzn@panda.ioz.ac.cn

The first stage of the synthesis involved the development of an efficient asymmetric synthesis of (2*S*, 3*S*)-1,2-epoxy-tetradecan-3-ol tosylate **8**. Several approaches to the epoxytosylate have been reported[7-9]. However, carbohydrates or an expensive chiral catalyst system were required in these methods. The process was lengthy and impractical for large scale preparation. Given those considerations, the present synthesis of (2*S*, 3*S*)-**8** employed easily available material and utilized a Sharpless AE kinetic resolution as a key step (**Scheme 1**, (±)-**6**→ (3*S*)-**6**). In order to obtain (3*S*)-**6** with high enantiomeric excess, the catalytic selectivities of various D-(-)-tartrate esters, such as diethyl (DET), diisopropyl (DIPT), dicyclohexyl (DCHT), dicyclododecyl tartrate (DCDT), were investigated, and the sterically demanding D-(-)-DCHT gave the best result. Thus, the asymmetric epoxidation of alkenol (±)-**6** using D-(-)-DCHT as ligand gave (3*S*)-**6** with excellent enantioselectivity (>99% ee.)[10] and yield (85%, based on the 54.6% conversion). Epoxidation on (3*S*)-**6** with *m*-CPBA gave the mixture of threo to erythro epoxy alcohols **7** in 2:1 ratio, and the compound **7** were converted to the diastereomeric tosylates, followed by flash chromatography afforded (2*S*, 3*S*)-epoxy -tosylates **8**, which is the vital intermediates in the synthesis of **1**. The specific optical rotation of **8** was very close to that in the literature { $[\alpha]_D^{20}$ +8.75 (*c* 2, $CHCl_3$), lit. $[\alpha]_D^{20}$ +8.3 (*c* 1, $CHCl_3$)[4]}.

Scheme 1



Reagents and conditions: a) 4Å molecular sieves, D-(-)-DCHT, $Ti(O\text{-}i\text{-}Pr)_4$, TBHP, CH_2Cl_2, -20℃; b) *m*-CPBA, CH_2Cl_2, rt.; c)TsCl, TEA, CH_2Cl_2, 5℃; d) BuLi, $BF_3{\cdot}OEt_2$, THF, -78℃; e)THF, -78℃, 3h; f) CH_3OH, K_2CO_3; g) $Pd/CaCO_3$, H_2

The second stage of the synthesis involved the coupling of the two fragments, the epoxytosylate **8** and 1,4-heptdiyne. The crucial coupling was achieved through an alkylative epoxide rearrangement of the epoxytosylate and diynyl trifluoroborates, which were readily generated *in situ* by the addition of $BF_3{\cdot}Et_2O$ to diynyllithiums. This reaction proceeded readily and regioselectively. Thus, the epoxytosylate **8** was opened to afford compound **9**; this intermediate could be isolated or used directly for the next reaction without further purification. Treatment of **9** with K_2CO_3 in methanol gave epoxydiyne **10** in 70% yield in two steps. Catalytic hydrogenation of **10** over Lindlar catalyst easily gave the target epoxydiene **1**, and its spectral data were identical with the reported data[2].

In conclusion, we have developed an efficient and convenient method for asymmetric synthesis of (2*S*, 3*S*)-1,2-epoxy-tetradecan-3-ol tosylate from which pheromone component **1** of *Hyphantria cunea (Drug)* was successfully synthesized. Studies toward the synthesis of the analogues of **1** are underway.

References and Note

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10. The e.e. value was determined by ^{31}P NMR after preparation of phosphorous derivatives with (1*R*, 2*R*)-diaminomethylcyclohexane and PCl_3 *in situ*.

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