*Journal of the Korean Chemical Society*
**2024**, *Vol. 68, No. 3*
Printed in the Republic of Korea
https://doi.org/10.5012/jkcs.2024.68.3.131

## Communications

# Formal Synthesis of Sex Pheromone of Gypsy Moth (+)-Disparlure from L-(+)-Tartaric Acid

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(Received January 23, 2024; Accepted March 23, 2024)

**ABSTRACT.** A simple strategy for the formal synthesis of the sex pheromone of gypsy moth (+)-disparlure from L-(+)-tartaric acid is described herein. The key steps include the mono-esterification and regioselective ring-opening of an epoxide using a Grignard reagent. The strategy of conferring asymmetry using 2-butanone enables mono-esterification in high yield and reduces the number of steps. Subsequently, (+)-disparlure is synthesized via the regioselective ring opening of the epoxide.

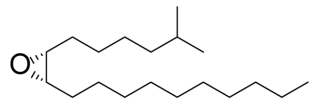
**Key words:** Gypsy moth, Pheromones, (+)-Disparlure, L-Tartaric acid, Mono-esterification

## INTRODUCTION

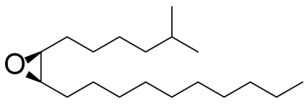
For centuries, harmful insects have damaged forests, timber, and human health. The gypsy moth, *Lymantria dispar L.*, is a harmful pest that severely damages forests in Europe, Asia, and North America. Generally, insecticides can control pests but can also adversely affect the environment and health. Accordingly, safer alternatives to insecticides for reducing pests have been intensively investigated. Insect pheromones have been focused on owing to their activeness at extremely low concentrations, nontoxicity, and species-specific nature. (+)-Disparlure **1** (*Fig.* 1), also known as (7*R*,8*S*)-7,8-epoxy-2-methyloctadecane, is the sex pheromone emitted by the female gypsy moth.[1] The (+)-enantiomer has been proven to be more active than the (−)-enantiomer.[2] A recent study demonstrated that two pheromone-binding proteins from the gypsy moth exhibited different binding affinities for both enantiomers of disparlure. The (+)-enantiomer showed a higher affinity for pheromone binding protein 2, whereas the (−)-enantiomer showed a higher affinity for pheromone binding protein 1.[3] Hence, (+)-disparlure has been used to investigate the populations, trapping, and monitoring of the gypsy moth.[4-6]

To date, many studies pertaining to the synthesis of (+)-disparlure **1** have been reported.[7-22] The enantiopure (+)-disparlure can be synthesized via chiral stannanes,[14] asymmetric dihydroxylation,[12,13,23,24] enzymatic procedures,[25-29] asymmetric chloroallylboration,[30] Sharpless asymmetric epoxidation,[9,13,19,31-33] enantiopure sulfoxides,[34-36] asymmetric chloroallylation,[30] and asymmetric organocatalysis.[17] The use of chiral pool starting materials[11,18,23] for the synthesis of disparlure, such as carbohydrates,[11,12,15,20,37,38] L-glutamic acid,[2] and L-tartaric acid[7,8,10,16] has been widely adopted.

The epoxide (2*S*,3*S*)-3,4-epoxy-1,2-O-isopropylidenebutane-1,2-diol **10** features two chiral centers at C-2 and C-3 and has been utilized as an chiral intermediate to synthesis insect pheromones.[39] The inexpensive and natural form of optically active L-(+)-tartaric acid **3** renders it an



(+)-Disparlure **1**



(-)-Disparlure **2**

***Figure* 1.** Structures of (+)-disparlure **1** and (−)-disparlure **2**.

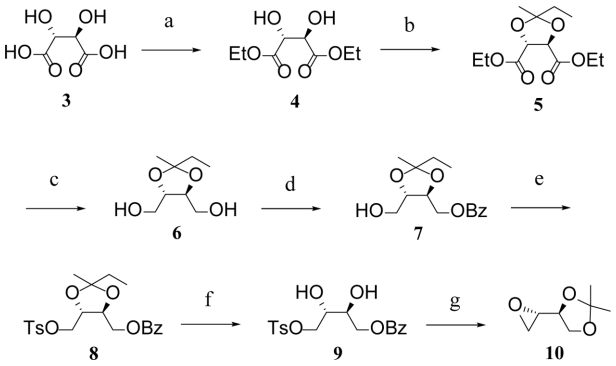
[a]Gi Baek Gwon and Hang Soo Kim contributed equally to this work

excellent starting material for the synthesis of chiral epoxide **10**. In previous studies, a symmetric diol derivative synthesized from L-(+)-tartaric acid **3** was used as an intermediate to synthesize epoxide **10**.[39,40] However, the study described a strategy of using asymmetric diol derivative to reduce the synthetic step and obtain high yields of mono-ester. Herein, we report a method of synthesizing (2*S*,3*S*)-3,4-epoxy-1,2-O-isopropylidenebutane-1,2-diol **10** via mono-esterification from L-(+)-tartaric acid **3**. Additionally, we describe the synthesis of optically pure (+)-disparlure **1** via the regioselective ring opening of an epoxide using a Grignard reagent.

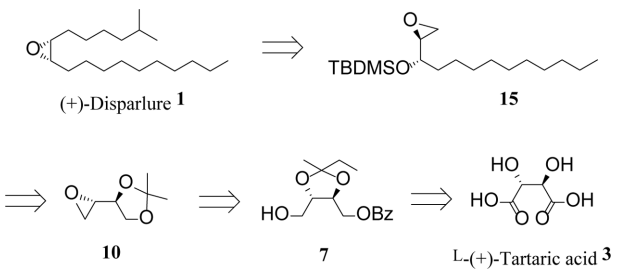
## RESULTS AND DISCUSSION

A strategy for the retrosynthesis of enantioselective (+)-disparlure (**1**) is shown in *Scheme* 1. Researchers have demonstrated that (+)-disparlure can be synthesized via the regioselective ring opening of a TBS-protected epoxide derivative using a Grignard reagent.[21] The TBDMS-protected epoxide derivative compound **15** can be obtained from compound **10** via carbon chain elongation with the Grignard reagent. Meanwhile, we expect that the epoxide (2S,3S)-3,4-epoxy-1,2-O-isopropylidenebutane-1,2-diol **10** can be obtained via mono-tosylation with another alcohol group protected by a benzoate. The key intermediate, compound **7**, can be accessed via the mono-esterification of L-(+)-tartaric acid **3**.

As in *Scheme* 2, the present synthetic strategy begins with the preparation of diethyl L-(+)-tartrate (compound **4)** derived from L-(+)-tartaric acid (compound **3)**, which can be easily synthesized via acid-catalyzed Fischer esterification in 100% yield. In previous studies, acetone or 2,2-dimethoxypropane (2,2-DMP) was used to obstruct the secondary alcohol group, which can undergo undesired reactions. The symmetric structure would be difficult to mono-esterify in high yield[41-43] or additional hydrolysis steps would be required to obtain the mono-ester.[39,40] Several researchers investigated the use of enzymes such as lipase because the mono-synthesis reaction should be conducted without any custom apparatus.[44,45] However, the approach showed limitations pertaining to dynamic kinetic resolution and industrial scale.[46] Therefore, in this study, 2-butanone was substituted with acetone or 2,2-DMP to obtain the asymmetric structure, which can be performed at the industrial scale. The reaction of diethyl L-(+)-tartrate with 2-butanone using *p*-TsOH in benzene furnished compound **5** in 94% yield. Subsequently, a reductive reaction was performed using LAH and dry THF to obtain the diol derivative (compound **6**) in 92% yield. The asymmetric structure resulted in a high mono-esterification yield. The mono-benzoate (compound **7**) was successfully obtained using benzoyl chloride and pyridine at 0 ℃ to room temperature (90% yield). Compound **8** was obtained in 90% yield via tosylation using TsCl and pyridine. Deprotection of the acetonide with HCl provided a diol derivative (Compound **9)** in 89% yield. Compound **9** was then reacted with $Na_2CO_3$ to produce an epoxide derivative, followed by treatment with 2,2-DMP and acid catalysis to afford compound **10** as a key chiral building block (68% yield over two steps).

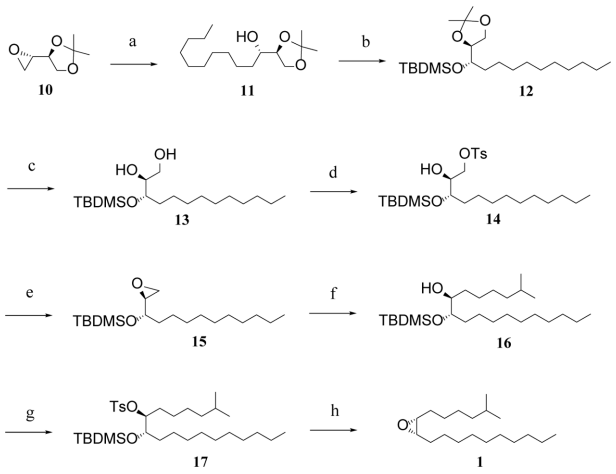



***Scheme* 2.** Synthesis of (2*S*,3*S*)-3,4-epoxy-1,2-O-isopropylidenebutane-1,2-diol **10**. (a) $H_2SO_4$, $CH_3CH_2OH$, benzene, 80 ℃, 15 h, 100%; (b) 2-butanone, *p*-TsOH, benzene, 80 ℃, 15 h, 94%; (c) LAH, dry THF, 66 ℃, 4 h, 92%; (d) BzCl, pyridine, 0 ℃ to rt, 4 h, 90%; (e) *p*-TsCl, pyridine, dry $CH_2Cl_2$, 0 ℃ to rt, 72 h, 90%; (f) TFA, 0 ℃, 3 h, 89%; (g) i) $Na_2CO_3$, $CH_3OH$, rt, 26 h, ii) 2,2-dimethoxypropane, $H_2SO_4$, dry acetone, rt, 1 h, 68% (over two steps).




***Scheme* 1.** Retrosynthetic analysis of (+)-disparlure **1**.

Our synthetic approach for the synthesis of (+)-disparlure **1** from (2*S*,3*S*)-3,4-epoxy-1,2-O-isopropylidenebutane-1,2-diol **10** is shown in *Scheme* 3. (+)-Disparlure **1** was easily synthesized via the Grignard reaction for carbon chain elongation, epoxide formation, and alcohol protection. As a first reaction for adding the carbon frame, $Li_2CuCl_4$-catalyzed regioselective ring-opening reaction with $C_9H_{19}MgBr$ at −76 ℃ was performed, which afforded




***Scheme* 3.** Synthesis of (+)-disparlure **1**. (a) $Li_2CuCl_4$, $C_9H_{19}MgBr$, dry $Et_2O$, −78 ℃ to rt, 4 h, 70%; (b) TBDMSCl, imidazole, TEA, dry DMF, rt, 6 h, 95%; (c) 50% aq TFA, $CH_2Cl_2$, rt, 1 h, 85%; (d) *p*-TsCl, pyridine, dry $CH_2Cl_2$, 0 ℃ to rt, 72 h, 80%; (e) $K_2CO_3$, $CH_3OH$, rt, 3 h, 89%; (f) iso-hexylMgBr, CuI, dry $Et_2O$, −78 ℃ to rt, 6 h, 78%; (g) *p*-TsCl, DMAP, dry $CH_2Cl_2$, 0 ℃ to rt, 90 h, 85%; (h) TBAF, dry THF, 0 ℃ to rt, 18 h, 95%.

compound **11** in 70% yield. Thereafter, the secondary hydroxyl group in compound **11** was protected with TBDMSCl using imidazole and triethylamine to afford compound **12** in 95% yield. Hydrolysis under weakly acidic conditions using trifluoroacetic acid (TFA) afforded compound **13** in 85% yield. Compound **14** was obtained via mono-tosylation with TsCl and pyridine in 80% yield and then treated with $K_2CO_3$ to obtain an epoxide derivative (compound **15**, 89% yield). Garg *et al.* described (+)-disparlure **1** can be synthesized from TBS-protected epoxide derivative.[21] Although TBDMS was used instead of TBS, (+)-disparlure **1** could be synthesized from compound **15** through the same synthetic procedure. Compound **15** was treated with iso-hexylMgBr in the presence of a Cu(I) catalyst to afford compound **16** via regioselective ring opening in 78% yield. The free hydroxyl group of compound **16** was tosylated using TsCl and DMAP, furnishing compound **17** in 85% yield. Finally, compound **17** was subjected to desilylation using TBAF to obtain the desired target compound, (+)-disparlure **1**, in 95% yield $[\alpha]_D^{25}$ = +1.0 (c = 1.9, $CHCl_3$), ref.[22] $[\alpha]_D^{26}$ = +0.8 (c = 0.3, $CHCl_3$)]}. The spectroscopic and optical rotation data for (+)-disparlure **1** agreed well with reported values.[22]

In summary, we achieved the facile synthesis of sex pheromone of gypsy moth (+)-disparlure **1** via the monoesterification and regioselective ring opening of an epoxide, using the chiral pool starting material L-(+)-tartaric acid **3**. The epoxide (2*S*,3*S*)-3,4-epoxy-1,2-O-isopropylidenebutane-1,2-diol **10** has been used as an important chiral building block for synthesizing biologically active materials.[47]

This epoxide comprises two chiral centers; hence, it can have four stereoisomers. In this study, the epoxide **10** was synthesized without inverting the stereogenic center of the two chiral centers from L-tartaric acid **3**. The strategy of conferring asymmetry to 2-butanone enabled a high overall yield for synthesizing epoxide **10** by providing monoesterification in high yield and reduced the number of steps, as compared with adopting a symmetric structure using acetone or 2,2-DMP. We expect this simple optically selective synthetic approach to be useful for synthesizing chiral building blocks as well as benefit the insect-pheromone industry.

**Acknowledgments.** This research was supported by the Basic Science Research Program and the Engineering Research Center Program (2018R1A5A1025511) of the National Research Foundation of Korea (NRF), funded by the Ministry of Education.

**Supporting Information.** Additional Supporting Information is available online at the end of this article.

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