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# A short and efficient synthesis of (+)-disparlure and its enantiomer

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**Abstract**—A short and highly efficient approach was applied for the total synthesis of the gypsy moth sex pheromone (+)-disparlure and its enantiomer from isopropylidene D- and L-erythrose, using a common strategy.


(7*R*,8*S*)-(+)-7,8-Epoxy-2-methyloctadecane **1**, also known as (+)-disparlure, is the single sex attractant pheromone emitted by the female gypsy moth, *Lymantria* (*Porthetria*) *dispar*[1] (Fig. 1). The gypsy moth is a seriously harmful pest affecting a variety of forest, shade, and orchard trees in Europe and North America. For this reason, numerous syntheses of (+)-disparlure have been reported so far, in order to use the synthetic material in field tests aimed at population monitoring.

Initial efforts produced racemic disparlure.[1,2] However, epoxide **1** is required to be nearly enantiopure to elicit male attraction since its enantiomer, (−)-disparlure **2**, has an opposite effect on the male population.[3] The need for enantiopure material led several groups to address this problem.[4,5] Among the different solutions proposed to prepare enantiopure (+)-disparlure the most common ones utilize an asymmetric epoxidation reaction[5f] (resembling a possible biosynthetic pathway[6]) or dihydroxylation,[5j] as the key step for the construction of the two asymmetric centers present in the natural product. Other routes employ chiral stannanes,[5b] enantiopure sulfoxides,[7] asymmetric chloroallylboration[5c] or the use of enzymatic procedures.[5h,8] Chiral pool approaches have been very popular, as well, using mainly carbohydrates,[5g,9] L-glutamic acid,[10] and L-tartaric acid[11] as the starting materials of choice. Relatively less work has been directed towards the preparation of the unnatural (−)-enantiomer.[12] The syntheses of analogues,[13] *trans*-isomers[5k] and labeled compounds,[14] have also been reported. In general, the use of asymmetric reactions, although often very simple, always have the drawback of producing material which is contaminated with the (−)-enantiomer, even in small quantities. On the other hand, the chiral auxiliary and chiral pool schemes were often rather costly and lengthy.

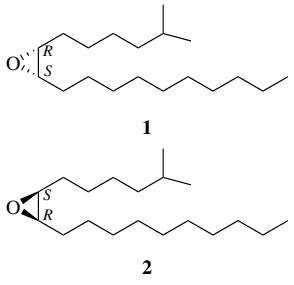


**Figure 1.** Structures of (+)-disparlure **1** and (−)-disparlure **2**.

In continuation of our natural product synthesis program, employing acetonides of D- and L-erythroses as starting materials,[15] we wish to report here a new, short, and very efficient approach for the synthesis of both enantiomers of disparlure.

The common strategy for the target compounds (Scheme 1) involves the construction of an epoxide ring at a late stage from the appropriately protected diols **4**, bearing the correct *cis*-stereochemistry in each case. The required aliphatic $C_7$ and $C_{10}$ chains were planned to be introduced by successive Wittig olefinations and double alkene reduction, leading finally back to protected erythroses **6**. It thus became obvious, that the stereochemistry of **6** could be directly transferred to the target epoxides **3**.

*Keywords*: Disparlure; Erythrose; Wittig olefination; Epoxide.
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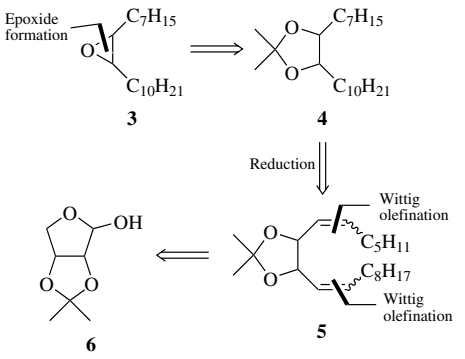
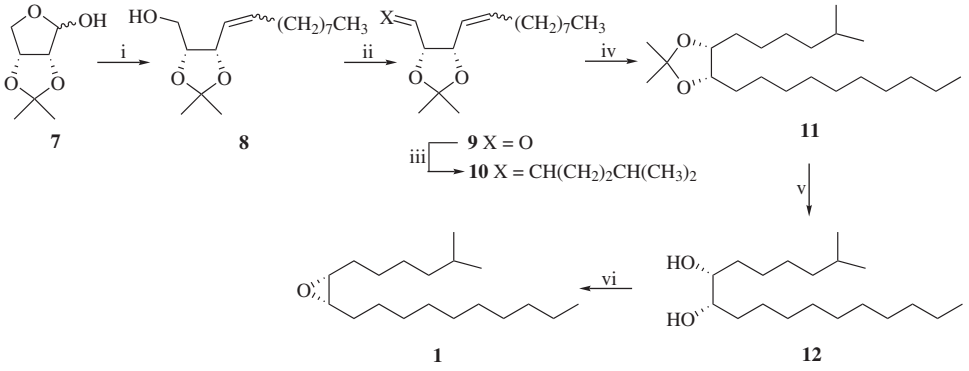



**Scheme 1.** Retrosynthetic analysis.

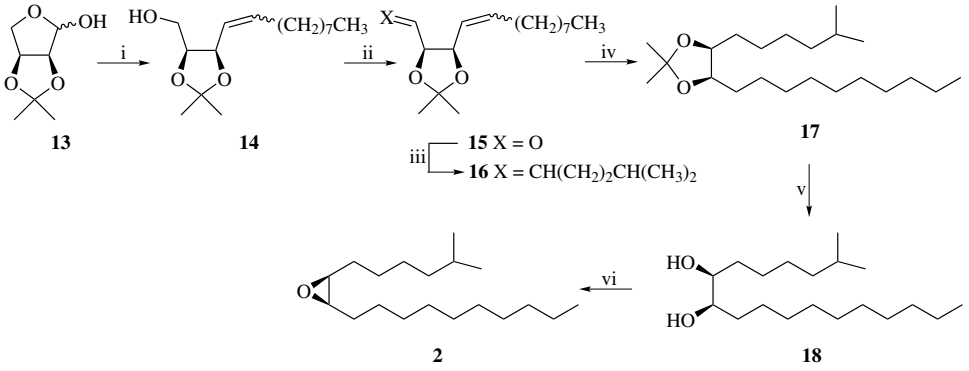
To investigate the feasibility of this retrosynthetic plan, acetonides **7** and **13**, both available in multigram quantities from D- and L-arabinose,[16] respectively, were initially subjected to a Wittig olefination upon treatment with the unstable phosphonium ylide derived from nonyl bromide, yielding a mixture of geometrical isomers **8** and **14**, in each case (Schemes 2 and 3).[17] These mixtures were next used to prepare aldehydes **9** and **15** applying standard Swern oxidation conditions and the latter were employed, without isolation, in the second Wittig olefination with the unstable phosphonium ylide derived from 1-bromo-4-methylpentane.[18]

It is worth noting that at this stage dienes **10** and **16** were an inseparable mixture of all four possible geometrical isomers.[19] However, there was no obvious reason to separate this mixture and identify its components since the following reduction step afforded protected diols **11** and **17**, respectively. These reductions were best performed using Ra-Ni whereas Pd/C catalytic hydrogenations proved to be too sluggish, yielding complicated mixtures after prolonged times and incomplete reactions.

Having acetonides **11** and **17** in hand, we smoothly prepared the corresponding diols **12** and **18** upon acidic hydrolysis. Then, these diols were used to reach the desired compounds using a well established procedure,[5d,20] which involves a three-step sequence: successive treatment with triethyl orthoacetate, TMSCl, and finally KOH in THF. Pure epoxides **1** and **2** were obtained after column chromatography on silica gel and were found to have identical physical and spectroscopic




**Scheme 2.** Synthesis of (+)-disparlure **1**. Reagents and conditions: (i) $Ph_3P^+(CH_2)_8CH_3Br^-$, *n*-BuLi, THF, 0 °C to room temperature, 95%; (ii) $(COCl)_2$, DMSO, $CH_2Cl_2$ then $Et_3N$, −55 °C to room temperature; (iii) $Ph_3P^+(CH_2)_3CH(CH_3)_2Br^-$, *n*-BuLi, THF, 0 °C to room temperature, 91% overall from **8**; (iv) $H_2$, Ra-Ni, MeOH, room temperature, 98%; (v) 37% HCl, THF/$H_2O$ (2:1), room temperature, 98%; (vi) (a) $CH_3C(OEt)_3$, PPTS, toluene, 110 °C; (b) TMSCl, $CH_2Cl_2$, room temperature; (c) 1 N KOH in MeOH, THF, 0 °C to room temperature, 90%.




**Scheme 3.** Synthesis of (−)-disparlure **2**. Reagents and conditions: (i) $Ph_3P^+(CH_2)_8CH_3Br^-$, *n*-BuLi, THF, 0 °C to room temperature, 97%; (ii) $(COCl)_2$, DMSO, $CH_2Cl_2$ then $Et_3N$, −55 °C to room temperature; (iii) $Ph_3P^+(CH_2)_3CH(CH_3)_2Br^-$, *n*-BuLi, THF, 0 °C to room temperature, 90% overall from **14**; (iv) $H_2$, Ra-Ni, MeOH, room temperature, 96%; (v) 37% HCl, THF/$H_2O$ (2:1), room temperature, 99%; (vi) (a) $CH_3C(OEt)_3$, PPTS, toluene, 110 °C; (b) TMSCl, $CH_2Cl_2$, room temperature; (c) 1 N KOH in MeOH, THF, 0 °C to room temperature, 88%.

properties to those reported in the literature.[5b] {For **1**: $[\alpha]_D$ +0.9 (*c* 1.1, $CCl_4$), lit.[5b] $[\alpha]_D$ +0.9 (*c* 1.1, $CCl_4$); for **2**: $[\alpha]_D$ −0.8 (*c* 1, $CCl_4$), lit.[5b] $[\alpha]_D$ −0.9 (*c* 0.21, $CCl_4$)}.

Although, the general synthetic scheme described above furnished in a straightforward way the desired (+)-disparlure and its enantiomer in almost 75% overall yields from D- and L-erythrose precursors we were also keen to explore the possibility of performing the same sequence of reactions with minimum isolation of the intermediates. Indeed, we were pleased to observe that similar results were obtained without isolation of any of the intermediates before epoxide formation. Thus, steps (i)–(iv) were repeated with simple filtration of the resulting reaction mixtures through a short pad of silica gel in each case. This was enough to remove organic and inorganic salts as well as polar phosphorus entities. According to this modified experimental procedure, which demands only two chromatographic separations, (+)-disparlure and its enantiomer were obtained in overall yields of more than 70%.

The work described in this article presents a short and efficient synthetic approach toward the preparation of (+)-disparlure **1** and its enantiomer **2** making use of readily available, multigram quantities of D- and L-erythrose derived chirons and employing a common retrosynthetic route. The overall yields for both targets are in the range of 70–75% in a six-step sequence involving a minimum number of purifications and relatively simple and inexpensive procedures.

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