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# Synthesis of disparlure analogues, using resolution on microcrystalline cellulose triacetate-I

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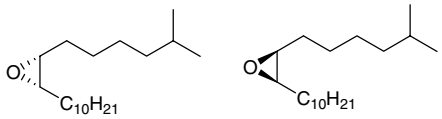
**Abstract**—The gypsy moth, *Lymantria dispar*, uses a chiral epoxide, (+)-(7*R*,8*S*)-2-methyl-7,8-epoxyoctadecane, (+)-disparlure, as its main sex attractant. The moths can detect both enantiomers of disparlure and respond differently to each one. In an effort to understand the structure–activity relationships of the gypsy moth olfactory system, we prepared the analogues of (+)- and (−)-disparlure. The key intermediate in route to the analogues was 2-epoxytridecan-1-ol. Herein we report the resolution of 2-epoxytridecan-1-yl esters on microcrystalline cellulose triacetate and the synthesis of 5-oxa and (5*Z*)-ene analogues of (+)- and (−)-disparlure. An effort to make 5-aza analogues resulted in the formation of *anti*-5-(1-hydroxy-1-undecyl)-3-(3-methylbutyl)oxazolidin-2-one. The analogues were tested for their electroantennogram responses and for their ability to bind to pheromone-binding protein 1 (PBP1). We found that the 5-oxa analogues gave strong responses and that the antenna and the PBP1 no longer distinguish the enantiomers of the 5-oxa analogues. The analogues all bound the PBP1 with similar affinity to (−)-disparlure.


## 1. Introduction

The main component of the gypsy moth, *Lymantria dispar*, sex attractant pheromone is (+)-(7*R*,8*S*)-epoxy 2-methyloctadecane [(+)-disparlure], (+)-**1**.[1–3] This compound is required for upwind flight of male moths to the pheromone-emitting females. The enantiomer (−)-**1** is neither attractive nor repellent by itself, but when presented simultaneously with (+)-**1**, it cancels upwind flight behavior in the males.[4] Studies on the olfactory mechanisms of these moths have revealed that there are distinct neurons, housed in separate populations of sensory hairs, that respond to one of the two disparlure enantiomers.[2] Furthermore, the two pheromone-binding proteins (PBPs) of the gypsy moth bind both enantiomers, although PBP1 prefers to bind (−)-**1**, while PBP2 prefers to bind (+)-**1**.[5]

Disparlure enantiomers have been synthesized individually by asymmetric epoxidation[6–8] or asymmetric dihydroxylation.[9] Compound (+)-**1** has also been prepared from L-(+)-tartaric acid,[10,11] (−)-2-deoxy-D-ribose,[12] (*S*)-(+)-glutamic acid,[13] and tri-*O*-acetyl-D-galactal.[14] Chiral auxiliaries have also been used in several syntheses.[6,7,9,15,16] The resolutions of key intermediates have also been reported, for example, pig pancreatic lipase has been used to resolve 1,4-diacetoxy-*cis*-2,3-epoxybutane;[17] Amano PS lipase has been used to resolve (*syn*)-ethyl-3-chloro-2-hydroxytridecanoate;[18] *cis*-4-bromo-2,3-epoxybutyl-(1*S*)-10-camphorsulfonate diastereomers have been resolved by fractional crystallization and are now available commercially,[19] and β-hydroxysulfide intermediates have been resolved as (*R*)-1-(1-naphthyl)ethyl isocyanate derived carbamates.[20] We chose to resolve *cis*-2,3-epoxytridecan-1-yl *p*-bromobenzoate **2c** on microcrystalline cellulose triacetate I (MCTA-I). Herein, we report the synthesis of both



**(+)-1** **(-)-1**

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enantiomers of several disparlure analogues, using ester **2c** resolved on MCTA-I. We also report the electrophysiological and pheromone-binding protein 1 (PBP1) binding activity of the analogues.

## 2. Results and discussion

### 2.1. Resolution on MCTA-I

MCTA-I is a widely used, economical chiral stationary phase for both analytical and preparative separations.[21–23] Structure–activity relationships have been undertaken with derivatives of *trans*-2-phenyl-1-cyclohexanols, glycerol, 1-phenyl-2-propanol, 3-phenyl-1,2-propanediol (chromatographed as the 1,3-dioxanes), 1,2- and 1,3-diols, 2,3-epoxypropan-1-ol (oxyranylmethanol), 4-hydroxy-cyclopent-2-enone,[23] and γ- and δ-lactones.[22] A variety of compounds with aryl moieties have also been separated.[24] Apart from a pyranyl diol,[25] 1-fluorenyl-1-ethanol and 1′-ethyl-2′,2′,2′-trifluoroethylanthracene,[26] alcohols generally do not separate readily on MCTA-I, although the corresponding benzoate esters have been found to separate cleanly.[21,23] Within one series of aryl-containing compounds, a relationship was seen with respect to the electronic and/or steric character of the substituent on the aryl moiety. Amongst the benzoate esters, *p*-chloro and *p*-bromo esters often ranked highly in their separation and resolution factors. Usually within a series, the elution order of the enantiomers remained constant across the series.[23] Both shape and electronic interactions appear to govern the extent to which enantiomers separate on MCTA-I.[23,24,27]

Our results with esters **2a**,**b**, and **2c** are consistent with these previous studies, with the enantiomers of the *p*-bromobenzoate separating best and the enantiomers of the acetate separating least (Table 1), with the (−)-enantiomer eluting first always. Alcohol **3** was retained, but did not separate on MCTA-I (Table 1). The *p*-bromobenzoates separated with near-baseline resolution, and the pooled fractions of each enantiomer had none of the opposite enantiomer detectable by the GC method. From the specific rotation and the MTPA ester of alcohol (−)-**3**, the ee of its precursor, ester (+)-**2c**, must have been ⩾97%. Ester (−)-**2c** had a similarly high ee, as could be inferred from the MTPA ester of alcohol (+)-**3** and the similar rotations of opposite sign obtained for ethers (−)-**5** and (+)-**5**, and epoxides (−)-**7** and (+)-**7**, obtained from (−)-**3** and (+)-**3**, respectively (Scheme 1).

### 2.2. Synthesis of disparlure and the analogues

Ester **2c** could be readily saponified, without significant Payne rearrangement.[28,29] Alcohol **3** was then converted to ether **5** by deprotonation of the alcohol with NaH, followed by reaction with the primary alkyl bromide to furnish the ether. Similar conditions have been used previously to alkylate 2,3-epoxy primary alcohols in high yield.[29] Alcohol **3** was also converted to aldehyde **6**. Aldehyde **6** was sufficiently stable to be purified by flash chromatography, but it could not be stored for extended periods of time. Thus, intermediate **6** was reacted immediately in the next step, either via a Wittig reaction to give **7** or a reductive amination to afford **8**. During purification of compound **8** by flash chromatography, oxazolidinone **9** was formed by absorption of $CO_2$ from air (Scheme 2). Compound **9** accumulated as a white solid in the fractions. A similar reaction with $CO_2$ has been reported for allylamines reacted with $I_2$ under a $CO_2$ atmosphere.[30] The approach used here gave epoxy alcohols (+)-**3** and (−)-**3** in high enantiomeric purity (⩾97% ee). Furthermore, $^1$H NMR data of the MTPA esters **4a** and **4b** of alcohols (−)-**3** and (+)-**3**, respectively, were consistent with previously reported data,[8] while the specific rotations of (−)-**3**, (+)-**7**, and (−)-**7** are in accordance with previously reported values.[6,8,14]

**Table 1.** Separation of esters **2a**–**c** and alcohol **3** on MCTA-I

| Compound | Column[a] | Temperature (°C) | Solvent | Flow (mL/min) | Retention times (h) | $R$[b] | $\alpha$[c] |
|---|---|---|---|---|---|---|---|
| **2a** | Medium | 30 | Ethanol–water 9:1 | 0.1 | 3.5<br>3.8 | 0.2 | 1.1 |
| **2b** | Medium | 30 | Ethanol–water 9:1 | 0.1 | 4.7<br>5.3 | 0.7 | 1.1 |
| **2c** | Medium | 30 | Ethanol–water 9:1 | 0.1 | 6.3<br>9.5 | 1.0 | 1.5 |
| **3** | Medium | 20 | Hexane–ether 4:1 | 0.1 | 11<br>13 | 0.6 | 1.2 |
| **2c** | Large | 50 | Ethanol–water 9:1 | 1.0 | 6.5<br>8.4 | 1.1 | 1.3 |
| **2c** | Large | 50 | Ethanol–water 9:1 | 0.5 | 13.8<br>16.8 | 1.1 | 1.2 |
| **2c** | Large | 50 | Ethanol–water 9:1 | 0.5 | 14.3<br>18.3 | 1.0 | 1.3 |

[a] See text; the medium-sized column was used to separate 10–30 mg, and the large column was used to separate typically 100–200 mg of racemic material.

[b] Resolution ($R$), estimated as = separation between peaks/(1.7 × average peak width at half height).[21]

[c] Separation factor $\alpha \approx$ retention time (late)/retention time (early).[21] Strictly, the separation factor $\alpha$ is the ratio of the retention factors, $k = (t - t_o)/t_o$, where $t$ is the retention time of the compound and $t_o$ is the retention time of an unretained substrance. However, we do not know any substance that is completely unretained on MCTA-I.[38]