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# A STEREOSPECIFIC SYNTHESIS OF (+)-DISPARLURE, SEX ATTRACTANT OF THE GYPSY MOTH

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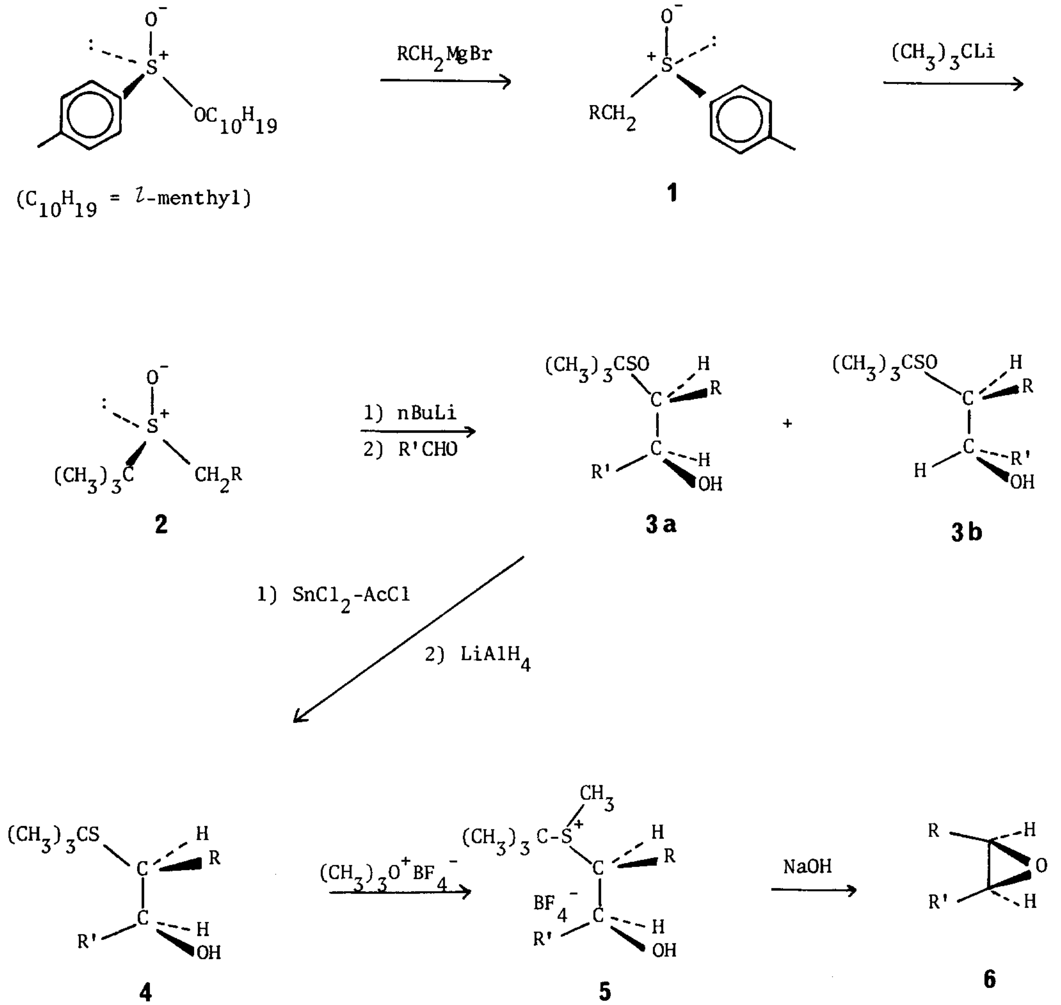
Disparlure, *cis*-7,8-epoxy-2-methyloctadecane, was identified as the female-produced sex pheromone of the gypsy moth, *Lymantria dispar* L., by Bierl, Beroza and Collier.[1] The 7R,8S enantiomer of disparlure was synthesized by Marumo[2] and Mori[3] and found to be more attractive to males than the racemate.[4] The elegant assignment of the absolute stereochemistry of all of the stereoisomers of the epoxide by the stereospecific syntheses of the Japanese groups, and the need for large quantities of (+)-disparlure for biological evaluation prompted us to develop a shorter stereospecific route for large scale synthesis of these materials. We now describe a synthesis of 7R,8S-epoxy-2-methyloctadecane in about 15% overall yield in six steps from *l*-menthyl-*p*-toluenesulfinate, patterned after the stereospecific epoxide synthesis of Durst[5] and Johnson,[6] as diagramed in the Chart. The synthesis has been conducted on a scale to yield five grams of (+)-disparlure and smaller quantities of (-)-disparlure and the (+)-*trans* isomer, and seems adaptable for much larger quantities. It also could be easily adapted to the synthesis of analogues.

CHART


(C$_{10}$H$_{19}$ = *l*-menthyl)
RCH$_2$MgBr
1
(CH$_3$)$_3$CLi
2
1) nBuLi
2) R'CHO
3a
+
3b
1) SnCl$_2$-AcCl
2) LiAlH$_4$
4
(CH$_3$)$_3$O$^+$BF$_4^-$
5
NaOH
6

Diastereomerically pure *l*-menthyl-*p*-toluenesulfinate was prepared as described by Phillips[7a] and Herbrandson.[7b] The final product, obtained after eight recrystallizations from acetone/water, exhibited $[\alpha]_D^{25}$= -199.7° (acetone, c=2), lit. $[\alpha]_D^{25}$= -199.2° (acetone, c=2).[7b] Treatment with 6-methylheptylmagnesium bromide in dry ether under nitrogen at rm temp gave sulfoxide **1** (R = $(CH_3)_2CH(CH_2)_4$),[8,9] which was purified by sublimation of the menthol and column chromatography of the residue (alumina, 1:1 hexane/ether, followed by 100% ether). The product, obtained in 65% yield from the sulfinate, had $[\alpha]_D^{25}$= 138.5° (acetone, c=2). Reaction of **1** with t-butyllithium according to Lockard[10] gave sulfoxide **2** (R = $(CH_3)_2CH(CH_2)_4$) (115% crude yield), which was used for the next reaction without purification because of its moderate stability. Configurational assignments are as given by Mislow[8b] and Lockard,[10] assuming inversion at each displacement. Generation of the lithium salt of **2** in dry ether under nitrogen with n-butyllithium/hexane, followed by reaction with undecanal[5,6] gave a mixture of diastereomers, which could be separated easily into two main components (both showed m/e 388 in the ms) by column chromatography (silica gel, ether). The second eluting diastereomer **3b**,[9] obtained in 30% yield, crystallizes when kept in the refrigerator. It afforded the (+)-*trans*-diastereomer of disparlure, $[\alpha]_D^{25}$= 22.2° ($CCl_4$, c=10), when it was carried through the remainder of the synthesis. The first eluting material, obtained in about 45% yield as a pale yellow oil,[9] $[\alpha]_D^{25}$= 18.9° ($CCl_4$, c=10), must be **3a** (R = $(CH_3)_2CH(CH_2)_4$, R' = $CH_3(CH_2)_9$), since it ultimately gave the desired (+)-*cis*-disparlure. It could be purified further by careful medium pressure liquid chromatography to remove small amounts (about 2%) of other impurities (possibly other diastereomers), but the disparlure finally obtained from such highly purified material was indistinguishable in its optical rotation, gc purity, ir and nmr spectra, and effectiveness as an attractant in the field from disparlure obtained from **3a** not so treated. Reduction of **3a** by stannous chloride-acetyl chloride[11] in pyridine-acetonitrile-DMF at 0°C for approximately 1.5 hr gave the corresponding acetoxysulfide with only a very minute amount of undesirable side products. The crude product was directly cleaved by lithium aluminum hydride and purified by column chromatography (silica gel, benzene) to give **4** (R = $(CH_3)_2CH(CH_2)_4$, R' = $CH_3(CH_2)_9$)[9] (ms m/e 372) in 84-6% yield from **3a**. Alkylation of **4** with trimethyloxonium fluoborate[12] (1.5 equivalent in 1:1 $CH_2Cl_2$:$CH_3NO_2$, 30 min at 0°C, 15 minute removal of solvent at 0°C *in vacuo*) afforded the salt **5** (R = $(CH_3)_2CH(CH_2)_4$, R' = $CH_3(CH_2)_9$) which was dissolved in dichloromethane without further purification and treated with 0.5 N aqueous sodium hydroxide at 0-25°C for 10-12 hr. Purification of the dichloromethane soluble product by column chromatography (silica gel, benzene) and molecular distillation gave 7R,8S-disparlure, **6** (R = $(CH_3)_2CH(CH_2)_4$, R' = $CH_3(CH_2)_9$), in 55% yield from **4**, as a colorless oil, $[\alpha]_D^{25}$= 0.48° ($CCl_4$, c=10), $[\alpha]_D^{25}$= 0.231° (neat), ir, nmr, and mass spectra identical with those of racemic material. Capillary gc analysis under conditions which would have revealed the presence of the *trans* isomer gave no indication of this material, and showed less than 1% contamination with peaks from other impurities. When the synthesis was conducted with undecylmagnesium bromide in the first step and 6-methylheptanal in the third step, the final products, obtained in comparable yield were (+)-*trans* epoxide and (-)-disparlure (7S,8R-epoxy-2-methyloctadecane), $[\alpha]_D^{25}$= -0.25°, ($CCl_4$, c=10), ir, nmr, and mass spectra identical with those of racemic material.

Because of the low specific rotation of optically active samples of disparlure, possible contamination with small amounts of materials with high specific rotation renders the observed values meaningless as indicators of even relative stereochemical purity. However, field tests, to be described separately,[13] indicate an attractancy in North America to wild male gypsy moths for our (+)-disparlure indistinguishable from that of samples of Marumo's[2] or Mori's[3] material. In addition, our (-) material is indistinguishable from Mori's as an antagonist of attraction when emitted with (+)-disparlure. The spectra and experimental details of our synthesis will be discussed in full in another publication.

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