

A Practical Approach to Enantiomerically Pure cis-Epoxides. Synthesis of (+)-Disparlure.

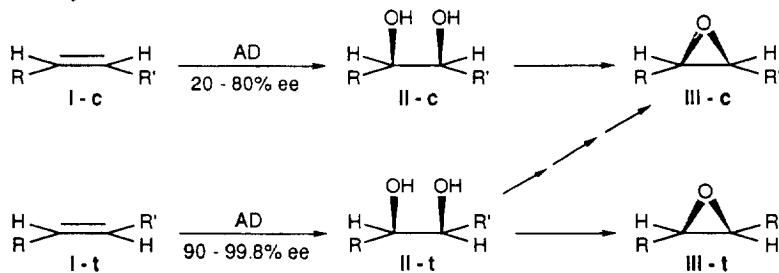
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Abstract: An efficient synthesis of (+)-disparlure has been achieved in >99.8% ee via the Sharpless asymmetric dihydroxylation followed by Mitsunobu inversion of one hydroxyl group and conversion of the resultant erythro diol to the cis epoxide.

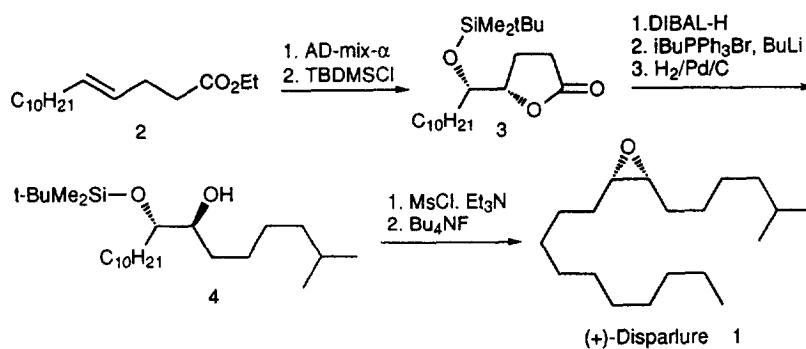
Construction of enantiomerically pure, disubstituted cis-epoxides represents a key issue in the synthesis of many low molecular weight natural products, such as insect pheromones and other semiochemicals.¹ A typical example is (+)-disparlure, the sex attractant emitted by the female gypsy moth, *Porthetria dispar* (L.), whose structure has been established as (+)-(7R,8S)-cis-7,8-epoxy-2-methyloctadecane (**1**).² Because of the growing demand for this pheromone in very high enantiomeric purity for pest control, many syntheses of (+)-disparlure have been reported. The classical approaches employ enantiopure natural products as starting materials, such as L-glutamic acid,^{1a} L-(+)-tartaric acid,³ D-(+)-glyceraldehyde,⁴ D-glucose,⁵ and D-ribose.⁶ Alternative approaches are based on enantiomerically pure sulfoxides,⁷ and the Sharpless asymmetric epoxidation reaction.⁸

Disubstituted cis-epoxides, **III-c**, can be easily obtained with high stereospecificity from erythro diols, **II-c**, in a three-step, one-pot procedure.⁹ This transformation, combined with the Sharpless asymmetric dihydroxylation (AD) of Z-alkenes, **I-c**, could therefore be the strategy of choice (Scheme 1). However, the AD reaction, which has been optimized to remarkably high levels of enantioselectivity with E-alkenes, has not reached a comparable efficiency with Z-alkenes to date.¹⁰



Scheme 1

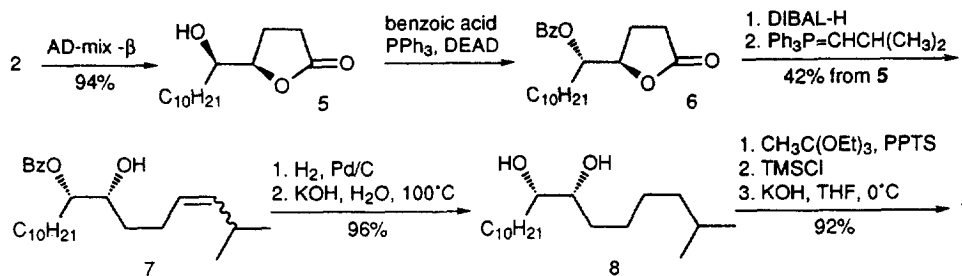
The alternative approach, based on the AD reaction with *E*-alkenes, which produces *threo* diols, requires regioselective functionalization of the two hydroxyl groups in order to achieve inversion at the desired position. We have recently reported on the syntheses of all four isomers of disparlure, including the biologically active one, using that strategy (Scheme 2).¹¹ Starting with (*E*)-ethyl pentadec-4-enoate, **2**, and using AD-mix- α afforded an (*S,S*)-hydroxylactone with 95% ee (and with > 99.5% ee after single recrystallization) followed by silylation to give **3**. The latter was converted to **4** via a three-step sequence, including reduction to lactol with DIBAL-H, Wittig olefination, and catalytic hydrogenation. Finally, the regioselective cyclization to **1** was achieved by mesylation of the free alcohol and desilylation of the silyl ether with tetrabutylammonium fluoride.



Scheme 2

Although our synthetic disparlure was found to be enantiomerically pure,¹² attempts to scale up the synthesis to gram quantities afforded the pheromone with lower enantiomeric purity (80-95%). Assuming that the problem arises from partial exchange of the silyl group between the two vicinal oxygen atoms of **4**, probably under base catalysis, we repeated the reaction using *t*-butyldiphenylsilyl ether, which is known to be more immune to such isomerizations.¹³ Unfortunately, neither this approach nor the employment of tetrahydropyranyl ether as a protecting group afforded the final product with more than 95% ee.

Here we report on an improved approach to (+)-disparlure, one that can be carried out on a large scale without loss of enantiomeric purity (Scheme 3). This strategy employs an easily available *threo*-diol with a regioselective inversion of the configuration at one center to give *erythro*-diol.¹⁴



Scheme 3

Reaction of **2** with AD-mix- β afforded (R,R)-hydroxylactone **5** in 98% ee. Mitsunobu reaction¹⁵ of hydroxylactone **5** with three equivalents each of PPh₃, benzoic acid and DEAD in dry benzene afforded **6** with complete inversion of configuration as was evident from NMR.^{16,17} Reduction of **6** at -78°C with 2 equiv DIBAL-H afforded the corresponding lactol without cleavage of the benzoate ester. Wittig reaction of the latter with isobutylidetriphenylphosphorane afforded olefin **7** as a 1:4 mixture of the E and Z isomers.¹⁸ Catalytic hydrogenation of **7** in methanol over 10% palladium on carbon yielded 8-benzoyloxy-2-methyloctadecan-7-ol, which was then hydrolyzed in hot aqueous KOH to give the erythro diol, **8**.¹⁹ Diol **8** was recrystallized from methanol and then converted to (+)-disparlure in a three-step procedure involving treatment with triethyl orthoacetate and PPTS in refluxing toluene, then with TMSCl, and finally with KOH in cold THF.⁹ Purification of the crude product by column chromatography (silica gel) afforded **1** in > 99.8% ee.¹² This product was found to be identical (¹H NMR, ¹³C NMR, IR, [α]_D, MS) with an authentic sample of (+)-disparlure.²⁰

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References and Notes

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16. Diethylazodicarboxylate (DEAD) (0.950 mL, 6 mmol) was added slowly to an ice cooled solution of **5** (512 mg, 2 mmol), triphenylphosphine (1.57 g, 6 mmol) and benzoic acid (732 mg, 6 mmol) in dry benzene (10 mL). The mixture was stirred for 90 min at room temperature and then filtered through a short bed of silica gel using hexane:ethyl acetate 85:15 to give **6** (452 mg, 63%) in the form of a colorless oil. $^1\text{H NMR}$: 8.00 (dd, $J=8.4$, 2.0 Hz, 2H), 7.55 (m, 1H), 7.43 (m, 2H), 5.33 (dt, $J=8.4$, 4.8 Hz, 1H), 4.64 (td, $J=7.1$, 4.8 Hz, 1H), 2.64-2.45 (m, 2H), 2.38-2.13 (m, 2H), 1.77-1.64 (m, 2H), 1.46-1.18 (m, 16H), 0.84 (t, $J=7.1$ Hz, 3H). $^{13}\text{C NMR}$: 176.53, 165.81, 133.28, 129.62, 128.48, 128.16, 80.23, 74.16, 31.84, 30.22, 29.51, 29.47, 29.36, 29.26, 28.02, 25.13, 22.64, 14.03 ppm.
17. The two carbinol signals in the $^1\text{H NMR}$ spectrum of **6**: 5.33 (dt) and 4.64 (td), characterizes the *erythro* stereochemistry. In contrast, the *threo* diastereomer, obtained by esterification of **5** with benzoyl chloride in pyridine, exhibits two signals at 5.26 and 4.73 with identical multiplicity (ddd, $J=8.4$, 5.6, 3.0 Hz, 1H).
18. DIBAL-H (4 mL, 4 mmol) was added slowly to a cold (-78°C) solution of **6** (452 mg) in THF (5 mL), the mixture was stirred at the same temperature for 2 h and then work-up with aqueous NH_4Cl (1 mL) and diethyl ether to give the corresponding lactol (431 mg, 95%). *n*-BuLi (2 mL of 2.5M solution in hexane, 5.0 mmol) was added to a solution of isobutyltriphenylphosphonium bromide (1.99g, 5 mmol) in THF (10 mL) at 0°C , and the mixture was stirred for 1.5 h. Solution of above mentioned crude lactol (431 mg) in dry THF (2 mL) was added, the mixture was stirred for 2 h and then worked up with aqueous NH_4Cl and ether, followed by chromatography over silica gel (hexane:ethyl acetate 9:1) affording 8-benzoyloxy-7-hydroxy-2-methyloctadec-3-ene, **7** (334 mg, 70%). $^1\text{H NMR}$: 8.05 (m, 2H), 7.55 (m, 1H), 7.43 (m, 2H), 5.46-5.14 (m, 2H), 5.11 (m, 1H), 3.82 (m, 1H), 2.68-1.36 (m, 8H), 1.30-1.18 (m, 16H), 0.95-0.83 (pair of doublets and triplets, 9H).
19. A solution of **7** (334 mg) was mixed with 10% Pd-C (80 mg) in methanol (5 mL) and stirred under hydrogen atmosphere for 16 h, filtered through celite, and the solvent was removed in vacuo. The residue was heated with 3N aqueous KOH at 100°C for 24 h, extracted with ether, passed through silica gel using ethyl acetate, and recrystallized from methanol to give diol **8** (240 mg, 98%). mp $85-88^\circ\text{C}$. $^1\text{H NMR}$: 3.61 (br m, 2H), 1.80 (br m, 2H), 1.60-1.12 (br m, 27H), 0.88 (t, $J=6.7$ Hz, 3H), 0.86 (d, $J=6.6$ Hz, 6H). MS: 323 ($\text{M}+\text{Na}^+$).
20. A solution of **8** (125 mg, 0.42 mmol), triethylorthoacetate (0.4 mL, 5.5 eq), PPTS (3 mg) in toluene (2 mL) was refluxed at 110°C for 90 min. The solvent was removed in vacuo, the residue was dissolved in dichloromethane (2 mL), TMSCl (0.4 mL, 4.08 mmol) was added and the mixture was stirred at room temperature for 12 h. Solvent was removed in vacuo and the residue was passed through a short bed of silica gel (hexane:ethylacetate; 19:1) affording two acetoxy chloride isomers in the form of a colorless oil (144 mg). $^1\text{H NMR}$: 5.06-5.00 (m, 1H), 3.94-3.86 (m, 1H), 2.08 (s, 3H), 1.74-1.44 (m, 6H), 1.40-1.12 (br s, 21H), 0.88-0.82 (pair of doublets and triplets, 9H). The latter mixture was dissolved in THF (2 mL), stirred with 1N methanolic KOH (1.2 mL) at room temperature for 2 h, then worked-up with ether and water and subjected to column chromatography (silica gel, hexane:ethylacetate 19:1) to give **1** (110 mg, 92%).