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Enantiodivergent Synthesis of Both Enantiomers of Gypsy Moth Pheromone Disparlure

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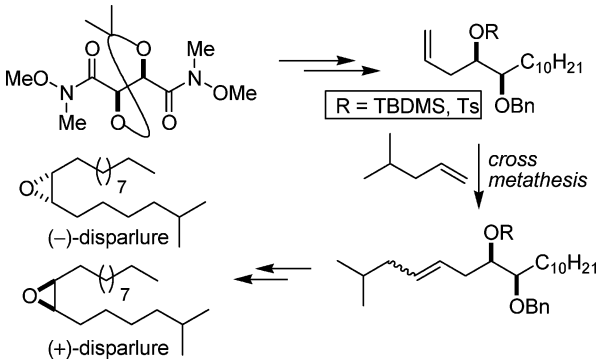
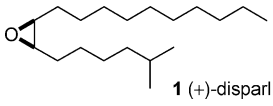


Enantiodivergent synthesis of both (−)- and (+)-disparlure, a bioactive pheromone, possessing a *cis*-epoxide has been accomplished. The key step involves the cross metathesis of a chiral homoallylic alcohol derived from L-(+)-tartaric acid.

Disparlure (*cis*-7,8-epoxy-2-methyloctadecane) **1** is the sex pheromone produced by the female gypsy moth, *Porthetria dispar L.*, a widespread forest pest, which causes severe forest losses during outbreaks.[1] Iwaki et al. established the configuration of **1** by synthesis and also observed that natural (+)-**1** is relatively more active than the (−)-enantiomer.[2] It has been recently shown that the two pheromone binding proteins from the gypsy moth bind differently for both enantiomers of disparlure.[3] Because of the different bioactivity associated with both antipodes, disparlure has been a synthetic target for a long time.[4] Of the many enantioselective syntheses disclosed for **1**, most of the approaches utilize chiral pool starting materials,[5a,i] chiral stannanes,[5c] asymmetric chloroallylboration,[5d] besides Sharpless asymmetric epoxidation,[5f] dihydroxylation,[5h,j,m] and enzymatic procedures.[5b,k]

Our interest in the synthesis of bioactive natural products from chiral pool tartaric acid resulted in the synthesis of a number of pheromones.[6] Herein, we disclose the synthesis of both enantiomers of **1**, utilizing cross metathesis of a homoallylic alcohol, derived from L-(+)-tartaric acid. As shown in retrosynthesis (Scheme 1), synthesis of both enantiomers of disparlure is envisaged from the diol **8**, by stereoselective cyclization of **8** to either enantiomer of the epoxide. Synthesis of diol **8** was anticipated from cross metathesis of homoallylic alcohol **7** and 4-methyl-1-pentene. Allylation of benzyloxyaldehyde **6** was identified for the synthesis of homoallylic alcohol **7**. Synthesis of aldehydes similar to **6** from tartaric acid has been established in our laboratory.[7]



1 (+)-disparlure

The synthetic sequence commenced with the addition of *n*-decylmagnesium bromide to the bis-Weinreb amide **2**[8] derived from L-(+)-tartaric acid, affording the diketone **3** in 92% yield. Under conditions that were optimized for the reduction of similar ketones, reduction of diketone **3** with K-selectride furnished the 1,4-diol **4** as the single diastereomer.[9] Protection of 1,4-diol **4** as the dibenzyl ether and further deprotection of the acetonide resulted in 1,2-diol **5** in 89% yield. Treatment of diol **5** with $Pb(OAc)_4$ produced the aldehyde **6**, which on allylation with allyltributyltin under Keck allylation[10] conditions afforded the homoallylic alcohol **7** (Scheme 2), in 79% yield in two steps. Homoallylic alcohol **7** served as the precursor for the synthesis of both enantiomers of **1**.The synthesis of (−)-disparlure (Scheme 3) was accomplished as follows. Homoallylic alcohol **7** was converted to the tosylate **9**, which underwent facile cross

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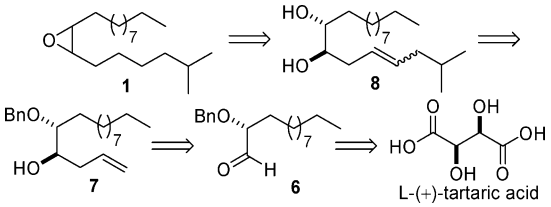
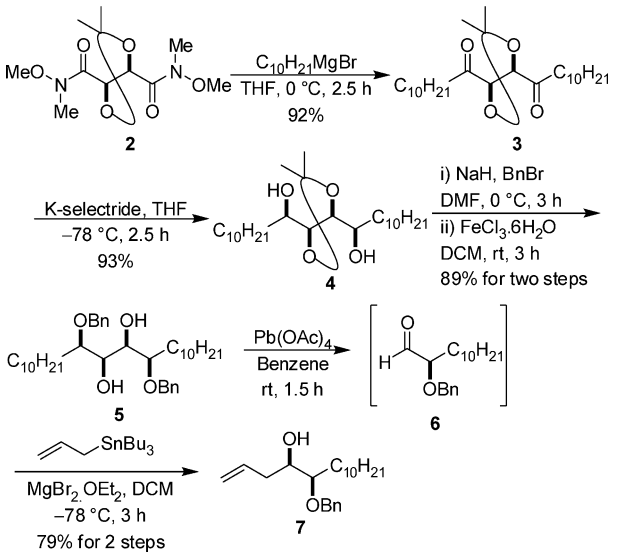
SCHEME 1. Retrosynthesis of Disparlure

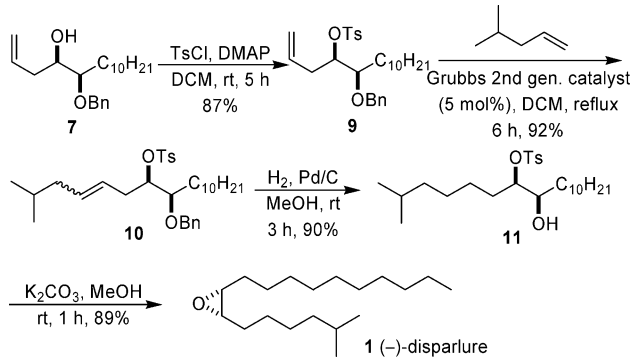


SCHEME 2. Stereoselective Synthesis of Homoallylic Alcohol 7

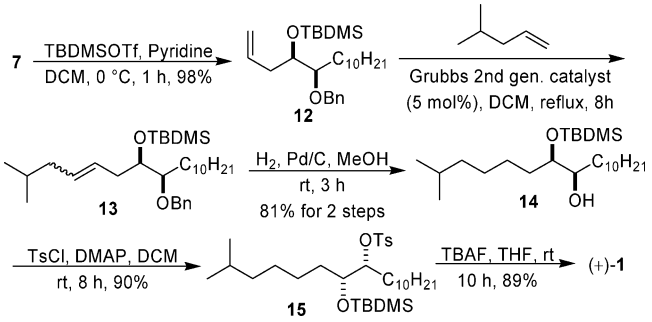


metathesis[11] with 4-methyl-1-pentene in presence of 5 mol % of Grubbs second generation catalyst to afford the alkene **10**[12] in 92% yield. Hydrogenation of the alkene **10** with Pd/C led to the formation of hydroxytosylate **11**,[13] which on treatment with K_2CO_3 furnished (−)-**1** in 89% yield: $[\alpha]_D$ −1.0 (*c* 1.7, CCl_4); lit.[5c] $[\alpha]_D$ −0.9 (*c* 0.21, CCl_4); the spectral data of which are identical to those reported in literature.[5c]For the synthesis of (+)-**1** (Scheme 4), the alcohol group in homoallylic alcohol **7** was protected as the *tert*-butyldimethylsilyl ether under standard conditions to yield **12** in 98% yield. Cross metathesis of **12** with 4-methyl-1-pentene resulted in alkene **13**,[14] which on hydrogenation with Pd/C afforded the alcohol **14** in 81% yield in two steps. Reaction of **14** with TsCl and DMAP produced

SCHEME 3. Synthesis of (−)-Disparlure 1



SCHEME 4. Synthesis of (+)-Disparlure 1



the tosylate **15** in 90% yield. Treatment of **15** with TBAF furnished (+)-**1** in 89% yield: $[\alpha]_D$ +1.0 (*c* 1.5, CCl_4); lit.[5c] $[\alpha]_D$ +0.9 (*c* 1.1, CCl_4).In summary, a facile enantiodivergent synthesis of the bioactive pheromone, disparlure, was achieved. Homoallylic alcohol derived from chiral pool L-(+)-tartaric acid served as the key building block for the synthesis of both (−)- and (+)-disparlure, involving cross metathesis as the pivotal step.

Experimental Section

(4*R*,5*R*)-5-(Benzyloxy)pentadec-1-en-4-ol (7): To a solution of **5** (0.2 g, 0.34 mmol) in 3 mL of benzene at room temperature was added $Pb(OAc)_4$ (0.27 g, 0.6 mmol) under argon atmosphere. The reaction mixture was stirred for 1.5 h at the same temperature, quenched with water (0.2 mL), and stirred for 10 min at room temperature. The reaction mixture was filtered through a short pad of Celite, and the Celite pad was washed with CH_2Cl_2 (25 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to yield α-benzyloxyaldehyde **6** as a colorless oil. It was subjected to the next reaction without purification.

A suspension of aldehyde **6** (obtained above) and $MgBr_2{\cdot}Et_2O$ (0.23 g, 0.9 mmol) in 3 mL of CH_2Cl_2 at −78 °C was stirred under argon atmosphere for 1 h. Allyltributyltin (0.3 mL, 0.9 mmol) was introduced dropwise over a period of 5 min at the same temperature. The reaction mixture was stirred for 2 h, poured into water (10 mL), and extracted with ether (3 × 8 mL). Combined ethereal extracts were washed with 1% aqueous NH_3 (three times) to remove tin impurities, brine, and dried over Na_2SO_4. Evaporation of solvent followed by column chromatography of the resulting residue using petroleum ether/EtOAc (96:4) as an eluent yielded **7** as a colorless oil in 79% (for two steps, 0.18 g): $[\alpha]_D$ −18.8 (*c* 1, $CHCl_3$); IR (neat) 3442, 2952, 2854, 1456, 1090, 1070, 912, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 5.94−5.78 (m, 1H), 5.14−5.06 (m, 2H), 4.65 (d, J = 11.4 Hz, 1H), 4.50 (d, J = 11.4 Hz, 1H), 3.67−3.60 (m, 1H), 3.36−3.28 (m, 1H), 2.39−2.18 (m, 3H), 1.71−1.49 (m, 2H), 1.41−1.18 (m, 16H), 0.88 (t, J = 7.2

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(12) Evaluation of the ratio of *E*/*Z* regioisomers in **10** resulting from the cross metathesis was inconclusive from NMR. No further efforts were made to estimate the *E*/*Z* ratio. The stereochemistry of the double bond is of no consequence because it is saturated in the next step by hydrogenation.

(13) A minor amount (6%) of product resulting from the displacement of the tosyl group is also observed.

(14) It was difficult to separate the product alkene **13** from homoallylic alcohol **12** at this stage. However, further hydrogenation of the alkene **13** resulted in the alcohol **14**, which was easily purified.

Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4 (Cq), 134.9 (CH), 128.4 (CH), 127.8 (CH), 127.7 (CH), 117.2 (CH_2), 81.4 (CH), 72.3 (CH_2), 71.9 (CH), 38.0 (CH_2), 31.9 (CH_2), 30.1 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 25.1 (CH_2), 22.6 (CH_2), 14.0 (CH_3); HRMS for $C_{22}H_{36}O_2$ + Na calcd 355.2613; found 355.2612.

(7*R*,8*R*)-8-(Benzyloxy)-7-(*p*-toluenesulfonyloxy)-2-methyloctadec-4-ene (10): A mixture of **9** (50 mg, 0.1 mmol), 4-methyl-1-pentene (0.07 mL, 0.5 mmol), and Grubbs second generation catalyst (5 mg, 0.005 mmol) in 1 mL of CH_2Cl_2 was refluxed for 6 h. The solvent was removed, and the syrup thus obtained was chromatographed using petroleum ether/EtOAc (97:3) as an eluent to yield **10** in 92% (51 mg) as a colorless oil, as an *E*/*Z* mixture (the ratio of the geometrical isomers is inconclusive from ^{1}H NMR; since the next step is the reduction of the double bond, no efforts were made to separate the *E*/*Z* isomers and is used as such in the next step): IR (neat) 2924, 2853, 1599, 1455, 1367, 1188, 1176, 1098, 1055, 899 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 8.4 Hz, 2H), 7.37−7.24 (m, 7H), 5.41−5.27 (m, 1H), 5.18−4.96 (m, 1H), 4.58−4.50 (m, 1H), 4.51 (s, 2H), 3.57−3.49 (m, 1H), 2.51−2.40 (m, 1H), 2.42 (s, 3H), 2.28−2.19 (m, 1H), 1.83−1.12 (m, 21H), 0.92−0.80 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4 (Cq), 138.3 (Cq), 134.2 (Cq), 133.1 (CH), 129.6 (CH), 128.3 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 125.1 (CH), 83.0 (CH), 78.8 (CH), 72.6 (CH_2), 41.9 (CH_2), 32.7 (CH_2), 31.9 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.2 (CH), 25.5 (CH_2), 22.7 (CH_2), 22.3 (CH_3), 22.2 (CH_3), 21.6 (CH_3), 14.1 (CH_3).

(7*R*,8*R*)-7-(*p*-Toluenesulfonyloxy)-2-methyloctadecan-8-ol (11): To a solution of **10** (40 mg, 0.07 mmol) in 2 mL of methanol at room temperature was added activated 10% Pd/C (20 mg). The reaction mixture was stirred for 3 h under hydrogen atmosphere (balloon) at the same temperature. After the reaction was complete (TLC), it was filtered through a short pad of Celite and the Celite pad was washed with ether (15 mL). Evaporation of solvent followed by column chromatography of the resulting residue using petroleum ether/EtOAc (94:6) yielded **11** as a colorless solid in 90% (30 mg) yield: mp 40.4−41.5 °C; $[\alpha]_D$ +12.3 (*c* 2.4, $CHCl_3$); lit.[15] mp 41.0−41.5 °C; $[\alpha]_D$ −12.3 (*c* 2.0, $CHCl_3$) for the enantiomer; IR (neat) 3393, 2924, 2853, 1600, 1455, 1364, 1175, 1019, 896 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 4.49 (dt, J = 6.0, 5.4 Hz, 1H), 3.50−3.68 (br m, 1H), 2.45 (s, 3H), 1.79 (d, J = 6.6 Hz, OH, exchangeable with D_2O), 1.75−0.95 (m, 27H), 0.88 (t, J = 7.2 Hz, 3H), 0.83 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7 (Cq), 134.3 (Cq), 129.7 (CH), 127.7 (CH), 86.7 (CH), 71.8 (CH), 38.6 (CH_2), 32.9 (CH_2), 31.9 (CH_2), 30.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 27.8 (CH), 27.1 (CH_2), 25.5 (CH_2), 25.1 (CH_2), 22.7 (CH_2), 22.5 (CH_3), 21.6 (CH_3), 14.1 (CH_3).

(−)-Disparlure (*cis*-7,8-Epoxy-2-methyloctadecane) (1): To a solution of **11** (25 mg, 0.055 mmol) in 1 mL of methanol was added potassium carbonate (12 mg, 0.08 mmol) at room temperature under inert atmosphere. The reaction mixture was stirred for 1 h at the same temperature, poured into water (4 mL), and extracted with ether. The combined ethereal layer was washed with brine and dried over Na_2SO_4. Evaporation of solvent followed by column chromatography of the resulting residue using petroleum ether/EtOAc (99:1) yielded (−)-**1** as a colorless oil in 89% (14 mg): $[\alpha]_D$ −1.0 (*c* 1.7, CCl_4); lit.[5c] $[\alpha]_D$ −0.9 (*c* 0.21, CCl_4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.91−2.87 (m, 2H), 1.57−1.15 (m, 27H), 0.90−0.84 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.2 (CH), 38.9 (CH_2), 31.9 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.9 (CH), 27.8 (CH_2), 27.3 (CH_2), 26.8 (CH_2), 26.6 (CH_2), 22.7 (CH_2), 22.6 (CH_3), 14.1 (CH_3).

(7*R*,8*R*)-7-(*tert*-Butyldimethylsilyloxy)-2-methyloctadecan-8-ol (14): A mixture of **12** (60 mg, 0.13 mmol), 4-methyl-1-pentene (0.09 mL, 0.67 mmol), and Grubbs second generation catalyst (6 mg, 0.0065 mmol) in 1 mL of CH_2Cl_2 was refluxed for 8 h. After the reaction was complete (indicated by TLC), it was concentrated to a syrup. Column chromatography of the syrup using petroleum ether/EtOAc (98:2) as an eluent yielded **13**, admixed with a small amount of **12** which was not separable by column chromatography. It was subjected to the next reaction without further purification.

To a solution of the crude **13** obtained above in 2.5 mL of methanol at room temperature was added activated 10% Pd/C (30 mg). The reaction mixture was stirred for 3 h under hydrogen atmosphere (balloon) at the same temperature. After the reaction was complete (TLC), it was filtered through a short pad of Celite and the Celite pad was washed with ether (15 mL). Residue obtained after evaporation of solvent was purified by column chromatography using petroleum ether/EtOAc (98:2) to yield **14** as a colorless oil in 81% (45 mg): $[\alpha]_D$ −3.8 (*c* 3.2, $CHCl_3$); IR (neat) 3439, 2927, 2856, 1463, 1255, 1084, 836, 775 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.44−3.31 (m, 2H), 2.06 (d, J = 6.9 Hz, 1H, exchangeable with D_2O), 1.61−1.05 (m, 27H), 0.86−0.75 (m, 18H), 0.01 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 75.1 (CH), 72.6 (CH), 38.9 (CH_2), 36.1 (CH_2), 34.1 (CH_2), 33.9 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 27.9 (CH), 27.6 (CH_2), 25.9 (CH_2), 25.8 (CH_3), 25.2 (CH_2), 22.6 (CH_2), 22.5 (CH_3), 18.1 (Cq), 14.1 (CH_3), −4.1 (CH_3), −4.6 (CH_3); HRMS for $C_{25}H_{54}O_2$-Si + Na calcd 415.3971; found 415.3978.

(+)-Disparlure (*cis*-7,8-Epoxy-2-methyloctadecane) (1): To a solution of **15** (30 mg, 0.05 mmol) in 1.5 mL of THF was added TBAF (0.15 mL, 0.15 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 10 h at room temperature. After the reaction was complete (indicated by TLC), it was poured into water (5 mL) and extracted with ether (3 × 8 mL). The combined ethereal extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvent followed by column chromatography using petroleum ether/EtOAc (99:1) as an eluent yielded (+)-**1** in 89% as a colorless oil: $[\alpha]_D$ +1.0 (*c* 1.5, CCl_4); lit.[5c] $[\alpha]_D$ +0.9 (*c* 1.1, CCl_4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.93−2.88 (m, 2H), 1.59−1.15 (m, 27H), 0.91−0.84 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.2 (CH), 38.9 (CH_2), 31.9 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.9 (CH−), 27.8 (CH_2), 27.3 (CH_2), 26.8 (CH_2), 26.6 (CH_2), 22.6 (CH_2), 22.5 (CH_3), 14.1 (CH_3).

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Supporting Information Available: Experimental procedures and spectroscopic data for the compounds and copies of ^{1}H NMR and ^{13}C NMR spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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