Concise Total Synthesis of (+)-Disparlure and its *trans*-Isomer Using Asymmetric Organocatalysis

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Abstract: The efficient enantioselective synthesis of (+)-disparlure and its *trans*-isomer is described. This approach involves tandem asymmetric organocatalytic α-aminoxylation–allylation of an aldehyde and olefin cross metathesis using Grubbs' catalyst as key steps.

Key words: disparlure, total synthesis, organocatalysis, asymmetric synthesis, olefin cross metathesis

(+)-Disparlure (**1**) (Figure 1), structurally known as (7*R*,8*S*)-7,8-epoxy-2-methyloctadecane, is the sex-attractant pheromone emitted by the female gypsy moth, *Porthetria dispar* (L.).[1] This gypsy moth is a seriously harmful pest, causing severe forest losses during outbreaks in Europe, Asia, and North America. It has been shown that the (–)-enantiomer antagonizes the effect of (+)-disparlure and is slightly repellent by itself.[2] Both of the enantiomers bind differently to two pheromone-binding proteins (PBPs) found in gypsy moth antennae, PBP1 and PBP2. The (–)-enantiomer has a higher affinity for PBP1, while the (+)-enantiomer has a higher affinity for PBP2.[3] For these reasons, disparlure has been the target of numerous syntheses,[4,5] in which most of the approaches for the construction of the two asymmetric centers take advantage of asymmetric epoxidation (AE),[5f] asymmetric dihydroxylation (AD),[5g,i,l] asymmetric chloroallylation,[5d] chiral stannanes,[5c] enzymatic procedures,[5e,j,k] or chiral pool materials.[5a,b,h]

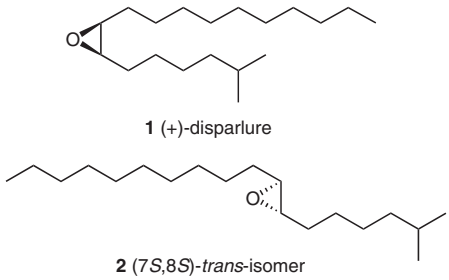
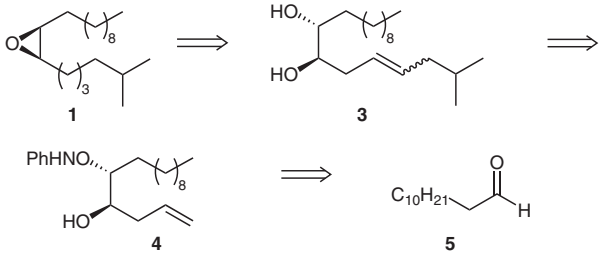


Figure 1

Herein, as part of a program for the synthesis of biologically active natural products based on asymmetric organocatalysis,[6] we describe the efficient synthesis of (+)- and (–)-disparlure and their *trans*-isomers based on asymmetric organocatalysis and olefin cross metathesis.

The retrosynthetic plan for (+)-disparlure (**1**) is outlined in Scheme 1. We envisaged that disparlure could be obtained from the diol **3** by stereoselective construction of an epoxide ring at a late stage. Diol **3** could be derived from homoallylic alcohol **4** via cross metathesis with 4-methylpent-1-ene. The key intermediate **4** can be synthesized through a proline-catalyzed tandem asymmetric α-aminoxylation–allylation of dodecanal (**5**).[6b,7,8]



Scheme 1 Retrosynthetic analysis

This retrosynthetic concept for (+)-disparlure (**1**) was put into practice as depicted in Scheme 2. Homoallylic alcohol **4** was prepared in 65% yield from dodecanal (**5**) and nitrosobenzene (**6**) using L-proline as the catalyst followed by in situ indium-mediated allylation by a modification of the original tandem α-aminoxylation–allylation reaction.[7] This reaction in the solvent dimethyl sulfoxide did not proceed cleanly; there was formation of a homodimerized aldol as a side product, and the desired product **4** was isolated only in 15% yield. However, when the initial solvent was changed to chloroform, the reaction proceeded cleanly and the product **4** was isolated in good yield with a 4:1 diastereoselectivity. The products *syn*-**4** and *anti*-**4** were separated by column chromatography and showed excellent enantiomeric excesses (98% ee in both cases). At this stage, we could not define which isomer, *syn* or *anti*, was the major product, so we supposed that the *syn*-isomer was the major product according to the literature;[6b,7] however, it was found at the final stage that the major product was in fact the *anti*-isomer.[9]

The hydroxy group in homoallylic alcohol **4** was protected using *tert*-butyldimethylsilyl triflate to afford **7** in 97% yield. The phenylamino group in **7** was removed using a zinc-catalyzed N–O cleavage reaction, which was followed by tosylation, to give **9** in 98% yield over two steps.

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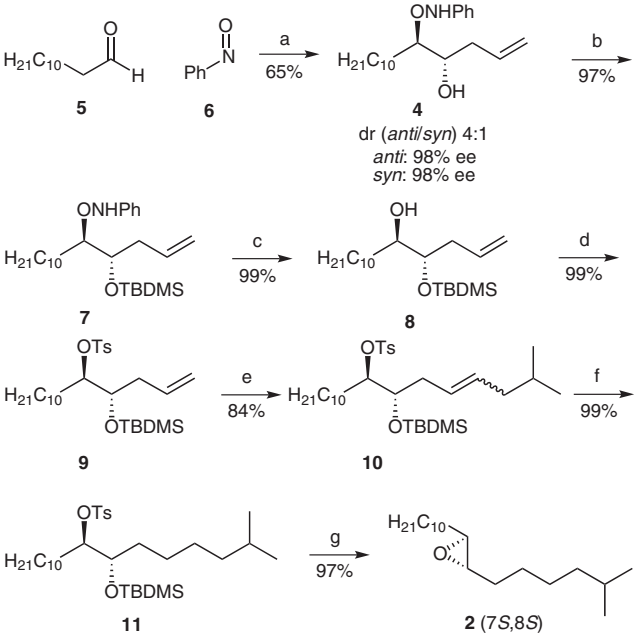
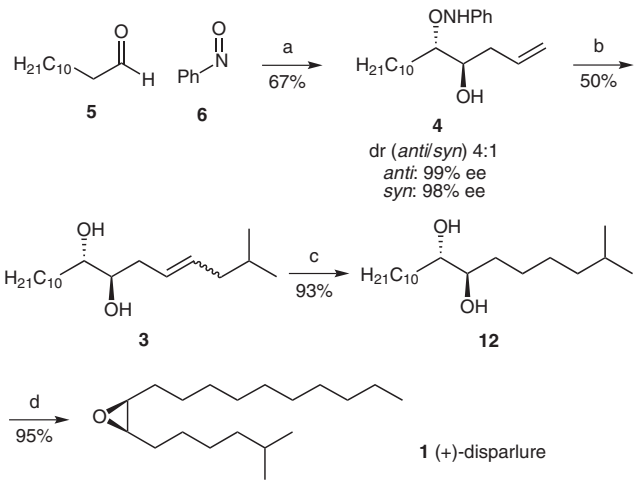
The conversion of compound **9** into the alkene **10** was achieved by olefin cross metathesis[10] with 4-methylpent-1-ene in the presence of 5 mol% of Grubbs' second-generation catalyst in 84% yield.[11] Finally, palladium-catalyzed hydrogenation of **10** followed by treatment with tetrabutylammonium fluoride gave compound **2** in 96% yield over two steps. Compound **2** was defined as the (7*S*,8*S*)-*trans*-isomer of disparlure after comparing the spectroscopic data and optical rotation of the material with reported values in the literature[5l,12] {$[\alpha]_D^{26}$ –25.8 (*c* 1.9, CCl_4) [Lit.[11] $[\alpha]_D$ –26.6 (*c* 0.5, CCl_4)]}. From these results, we were able to establish that the major diastereomer in the tandem α-aminoxylation–allylation reaction was the *anti*-homoallylic alcohol **4**.[9] From this synthetic route, the (7*R*,8*R*)-*trans*-isomer of disparlure was also prepared from the aldehyde dodecanal (**5**), using D-proline as catalyst instead of L-proline, in seven steps and 50% overall yield {$[\alpha]_D^{26}$ +26.9 (*c* 1.0, CCl_4) [Lit.[12] $[\alpha]_D$ +27.5 (*c* 0.5, CCl_4)]}.

After becoming aware of *anti*-homoallylic alcohol **4** as the major product, we carried out the synthesis of (+)-disparlure (**1**) using an altered pathway. *anti*-Homoallylic alcohol (4*R*,5*S*)-**4** was prepared from dodecanal (**5**) and nitrosobenzene (**6**) using the catalyst D-proline followed by in situ indium-mediated allylation in excellent ee (99% ee) (Scheme 3). At this stage, we carried out the olefin cross metathesis of homoallylic alcohol **4** with 4-methylpent-1-ene. Interestingly, under the metathesis conditions, diol **3** was obtained in 50% isolated yield, which indicates that N–O bond cleavage accompanied the metathesis reaction.[13,14] Next, palladium-catalyzed hydrogenation of **3** afforded known alcohol **12** in 93% yield, which was converted into (+)-disparlure (**1**) using the established three-step, one-pot procedure [$MeC(OEt)_3$, TMSCl, KOH][15] in 95% yield {$[\alpha]_D^{22}$ +0.8 (*c* 0.5, CCl_4) [Lit.[5c] $[\alpha]_D$ +0.9 (*c* 1.1, CCl_4)]}. (–)-Disparlure could also be prepared from dodecanal (**5**) with this synthetic route in six steps and 30% overall yield using the catalyst L-proline in the tandem α-aminoxylation–allylation reaction {$[\alpha]_D^{22}$ –0.7 (*c* 0.5, CCl_4) [Lit.[5c] $[\alpha]_D$ –0.9 (*c* 0.21, CCl_4)]}.

In summary, concise and efficient syntheses of (+)- and (–)-disparlure and their *trans*-isomers were accomplished in high overall yields from commercially available dodecanal (**5**). Key steps in the syntheses involved tandem asymmetric organocatalytic α-aminoxylation–allylation of the aldehyde, which was shown to be a highly effective means for preparing chiral diols, and cross metathesis using Grubbs' catalyst. Further application of this versatile strategy to biologically significant molecules of more structural complexity and diversity is now in progress.



Scheme 2 Stereoselective synthesis of the (7*S*,8*S*)-*trans*-isomer of disparlure. *Reagents and conditions*: (a) 1. L-proline (10 mol%), $CHCl_3$, 2. allyl bromide, In, NaI, DMSO; (b) TBDMSOTf, Et_3N, CH_2Cl_2; (c) Zn, AcOH–EtOH; (d) TsCl, DMAP, CH_2Cl_2; (e) 4-methylpent-1-ene, Grubbs II catalyst (5 mol%), CH_2Cl_2; (f) 10% Pd/C, H_2, hexane; (g) TBAF, THF.



Scheme 3 Stereoselective synthesis of (+)-disparlure. *Reagents and conditions*: (a) 1. D-proline (10 mol%), $CHCl_3$, 2. allyl bromide, In, NaI, DMSO; (b) 4-methylpent-1-ene, Grubbs II catalyst (5 mol%), CH_2Cl_2; (c) 10% Pd/C, H_2, MeOH; (d) 1. $MeC(OEt)_3$, PPTS, toluene, 2. TMSCl, CH_2Cl_2, 3. KOH, THF.

All reactions were performed using flame- or oven-dried glassware under an atmosphere of dry nitrogen. Commercial reagents were purified prior to use according to the guidelines of Perrin and Armarego.[16] Organic solutions were concentrated under reduced pressure using a Büchi rotary evaporator. All organic solvents were distilled prior to use. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32–64 mesh silica gel 63. Thin-layer chromatography was performed on EM Reagents 0.25-mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching and anisaldehyde staining. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Varian Mercury 300 (300 and 75 MHz) and Bruker 400 (400 and 100 MHz) spectrometers as noted, and are internally referenced to residual proton solvent signals. Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), inte-

gration. Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Jasco 610 FT-IR spectrometer using KBr salt plates or as films, and are reported in terms of frequency of absorption (cm^{-1}). Mass spectroscopic data were obtained at the Korea Research Institute of Chemical Technology Facility. Optical rotations were recorded on a Jasco P-1010 polarimeter (WI lamp, 589 nm). HPLC analysis was performed on a Shimadzu LC-20A Prominence HPLC system using Chiralcel columns AD (25 cm) and AD guard (5 cm), as noted.

(4*S*,5*R*)-5-(*N*-Phenylaminooxy)pentadec-1-en-4-ol (4)

To a soln of dodecanal (**5**; 1.50 mL, 6.0 mmol) and nitrosobenzene (**6**; 540 mg, 5.0 mmol) in $CHCl_3$ (3.5 mL), L-proline (60 mg, 0.50 mmol) was added. After being stirred for 4 h at 0 °C, the reaction mixture was diluted with DMSO (10 mL), which was followed by the addition of allyl bromide (0.65 mL, 7.5 mmol), NaI (1.12 g, 7.5 mmol), and indium (860 mg, 7.5 mmol) at r.t., and stirring for 1.5 h. The reaction mixture was quenched with 0.5 M aq HCl (30 mL) and the aqueous layer was extracted with EtOAc (2 × 40 mL). The combined organic layer was washed with brine (40 mL), dried (anhyd $MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (EtOAc–hexanes, 1:9) to afford the title compound (4*S*,5*R*)-**4** [yield: 870 mg (52%)] and the more quickly eluting (4*R*,5*R*)-isomer [yield: 218 mg (13%)]. The diastereomeric ratio was determined from the ^1H NMR spectrum of the crude product. The enantiomeric excess of the *anti*- and the *syn*-diastereomer was measured by HPLC analysis after separation of the isomers using column chromatography.

***anti*-(4*S*,5*R*)-4**

$[\alpha]_D^{26}$ +33.7 (*c* 1.0, $CHCl_3$).

HPLC (Chiralcel AD; *i*-PrOH–hexanes, 2:98; 1 mL/min): t_R (major) = 11.7 min, t_R (minor) = 15.5 min; 98% ee.

IR (KBr): 3414, 3276, 2923, 2853, 1602, 1494, 1466 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.62 (dd, *J* = 7.2, 8.7 Hz, 2 H), 6.94–7.00 (m, 3 H), 5.82–5.96 (m, 1 H), 5.11–5.20 (m, 2 H), 4.01 (dt, *J* = 2.4, 6.0 Hz, 1 H), 3.85–3.90 (m, 1 H), 2.30 (ddd, *J* = 1.2, 7.2, 8.4 Hz, 2 H), 1.23–1.72 (m, 19 H), 0.88 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.6, 135.3, 129.2, 122.6, 118.0, 115.2, 86.1, 72.5, 37.1, 32.1, 30.0, 29.9, 29.8, 29.6, 28.5, 26.6, 22.9, 14.3.

HRMS: *m*/*z* [M^+] calcd for $C_{21}H_{35}NO_2$: 333.2668; found: 333.2680.

***syn*-(4*R*,5*R*)-4**

HPLC (Chiralcel AD; *i*-PrOH–hexanes, 2:98; 1 mL/min): t_R (major) = 10.6 min, t_R (minor) = 12.9 min; 98% ee.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.24–7.29 (m, 2 H), 6.94–7.00 (m, 3 H), 5.84–5.95 (m, 1 H), 5.12–5.20 (m, 2 H), 3.82–3.88 (m, 1 H), 3.73–3.79 (m, 1 H), 2.22–2.47 (m, 2 H), 1.18–1.72 (m, 19 H), 0.88 (t, *J* = 6.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.5, 134.9, 129.2, 122.7, 118.0, 115.3, 85.7, 72.9, 38.4, 32.1, 30.0, 29.83, 29.78, 29.69, 29.57, 25.8, 22.9, 14.3.

(4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*N*-phenylaminooxy)pentadec-1-ene (7)

To a soln of (4*S*,5*R*)-**4** (500 mg, 1.5 mmol) in CH_2Cl_2 (7.0 mL) at 0 °C was added Et_3N (0.42 mL, 3.0 mmol), followed by TBDMSOTf (0.41 mL, 1.8 mmol), and the mixture was stirred for 30 min. The reaction mixture was quenched with sat. NH_4Cl soln (15 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layer was washed with brine (20 mL), dried (anhyd $MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (EtOAc–hexanes, 1:99) to afford compound **7** as a pale yellow oil; yield: 675 mg (97%).

$[\alpha]_D^{26}$ +12.7 (*c* 1.0, $CHCl_3$).

IR (KBr): 2926, 2855, 1602, 1496, 1463, 1254 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.21–7.27 (m, 3 H), 6.90–6.97 (m, 3 H), 5.79–5.93 (m, 1 H), 5.02–5.12 (m, 2 H), 3.93–3.98 (m, 1 H), 3.78–3.82 (m, 1 H), 2.22–2.40 (m, 2 H), 1.27–1.69 (m, 18 H), 0.93 (s, 9 H), 0.89 (t, *J* = 6.9 Hz, 3 H), 0.09 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.1, 136.0, 129.1, 121.8, 117.1, 114.6, 86.9, 74.3, 37.9, 32.2, 30.1, 29.9, 29.8, 29.7, 29.6, 26.8, 26.2, 22.9, 18.4, 14.4, –4.0, –4.1.

HRMS: *m*/*z* [M^+] calcd for $C_{27}H_{49}NO_2Si$: 447.3533; found: 447.3531.

(4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)pentadec-1-en-5-ol (8)

To a soln of **7** (640 mg, 1.4 mmol) in EtOH–AcOH (3:1, 14 mL) was added Zn powder (910 mg, 14 mmol). The mixture was stirred for 18 h at r.t., and the resulting suspension was filtered through a pad of Celite® and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (EtOAc–hexanes, 2:98) to afford compound **8** as a colorless oil; yield: 494 mg (99%).

$[\alpha]_D^{26}$ +0.50 (*c* 1.6, $CHCl_3$).

IR (KBr): 3051, 2929, 2856, 1474, 1264 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.75–5.89 (m, 1 H), 5.01–5.09 (m, 2 H), 3.55–3.67 (m, 2 H), 2.14–2.34 (m, 2 H), 2.11 (br s, 1 H), 1.13–1.52 (m, 18 H), 0.90 (s, 9 H), 0.85 (t, *J* = 6.9 Hz, 3 H), 0.64 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.8, 117.0, 75.3, 74.8, 36.2, 32.13, 32.11, 30.0, 29.83, 29.79, 29.6, 26.3, 26.1, 22.9, 18.3, 14.3, –4.1, –4.3.

HRMS: *m*/*z* [M^+] calcd for $C_{21}H_{44}O_2Si$: 356.3111; found: 356.3091.

(4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*p*-tolylsulfonyloxy)pentadec-1-ene (9)

To a soln of **8** (303 mg, 0.85 mmol) in CH_2Cl_2 (7.0 mL) was added DMAP (830 mg, 6.8 mmol), followed by TsCl (812 mg, 4.3 mmol), and the mixture was refluxed for 18 h. The reaction mixture was quenched with sat. NH_4Cl soln (15 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layer was washed with brine (20 mL), dried (anhyd $MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (EtOAc–hexanes, 2:98) to afford compound **9** as a colorless oil; yield: 430 mg (99%).

$[\alpha]_D^{26}$ +16.3 (*c* 1.0, $CHCl_3$).

IR (KBr): 2958, 2928, 2856, 1599, 1466, 1359, 1263 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.1 Hz, 2 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 5.65–5.79 (m, 1 H), 5.00–5.08 (m, 2 H), 4.45 (dt, *J* = 2.4, 9.0 Hz, 1 H), 4.00 (dt, *J* = 2.1, 6.9 Hz, 1 H), 2.43 (s, 3 H), 2.07–2.25 (m, 2 H), 1.60–1.73 (m, 1 H), 1.40–1.50 (m, 1 H), 1.05–1.34 (m, 16 H), 0.89 (t, *J* = 6.6 Hz, 3 H), 0.86 (s, 9 H), 0.06 (s, 3 H), 0.03 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.6, 134.7, 134.3, 129.8, 128.1, 117.9, 86.1, 73.8, 39.4, 32.1, 29.8, 29.7, 29.64, 29.55, 29.48, 26.1, 25.3, 22.9, 21.8, 18.3, 14.3, –4.3, –4.4.

HRMS: *m*/*z* [M^+] calcd for $C_{28}H_{50}O_4SSi$: 510.3199; found: 510.3196.

(7*S*,8*R*)-7-(*tert*-Butyldimethylsilyloxy)-2-methyl-8-(*p*-tolylsulfonyloxy)octadec-4-ene (10)

To a soln of **9** (355 mg, 0.69 mmol) in CH_2Cl_2 (7.0 mL) was added 4-methylpent-1-ene (0.44 mL, 3.5 mmol), followed by Grubbs II catalyst (29 mg, 0.035 mmol). The reaction mixture was warmed to

40 °C and stirred for 5 h. The solvent and remaining 4-methylpent-1-ene were removed under reduced pressure. The crude material was purified by flash column chromatography (EtOAc–hexanes, 2:98) to afford compound **10** as a colorless oil; yield: 327 mg (84%).

IR (KBr): 2955, 2927, 2856, 1463, 1360, 1264, 1176 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.1 Hz, 2 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 5.23–5.46 (m, 2 H), 4.41–4.47 (m, 1 H), 3.92–4.01 (m, 1 H), 2.43 (s, 3 H), 2.00–2.21 (m, 2 H), 1.73–1.92 (m, 2 H), 1.39–1.72 (m, 3 H), 1.04–1.33 (m, 16 H), 0.84–0.96 (m, 18 H), 0.05 (s, 3 H), 0.02 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.6, 141.0 (minor), 134.8, 132.7, 131.5 (minor), 129.9 (minor), 129.8, 128.2, 128.1 (minor), 126.5, 125.3 (minor), 122.5 (minor), 86.4 (minor), 86.2, 74.3 (minor), 74.1, 42.3, 38.4, 36.8 (minor), 33.0 (minor), 32.1, 29.8, 29.73, 29.68, 29.57, 29.51, 28.8 (minor), 28.6, 28.0 (minor), 27.8, 26.1, 26.0 (minor), 25.4 (minor), 25.3, 22.9, 22.60, 22.55, 21.8, 18.3, 14.3, –4.3, –4.5.

(7*S*,8*R*)-7-(*tert*-Butyldimethylsilyloxy)-2-methyl-8-(*p*-tolylsulfonyloxy)octadecane (11)

To a soln of **10** (280 mg, 0.49 mmol) in hexane (5 mL) was added 10% Pd/C (0.1 w/w, 28 mg) and the mixture was stirred for 2 h under H_2 atmosphere. Then, the Pd/C was filtered off and the reaction solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (EtOAc–hexanes, 2:98) to afford compound **11** as a colorless oil; yield: 278 mg (99%).

$[\alpha]_D^{26}$ +14.3 (*c* 1.1, $CHCl_3$).

IR (KBr): 2957, 1463, 1364, 1188, 1176, 1097 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.4 Hz, 2 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 4.45 (dt, *J* = 2.4, 9.0 Hz, 1 H), 3.86–3.92 (m, 1 H), 2.44 (s, 3 H), 1.05–1.71 (m, 27 H), 0.87–0.95 (m, 18 H), 0.05 (s, 3 H), 0.02 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.6, 134.9, 129.8, 128.2, 86.9, 74.5, 39.1, 34.6, 32.2, 29.8, 29.72, 29.65, 29.5, 28.3, 28.1, 27.6, 26.1, 25.4, 22.91, 22.87, 22.8, 21.8, 18.4, 14.3, –4.1, –4.5.

HRMS: *m*/*z* [M^+] calcd for $C_{32}H_{60}O_4SSi$: 568.3982; found: 568.3987.

(7*S*,8*S*)-*trans*-7,8-Epoxy-2-methyloctadecane (2)

To a soln of **11** (225 mg, 0.40 mmol) in THF (4 mL) was added 1.0 M TBAF in THF (1.6 mL, 1.6 mmol) at 0 °C. After being stirring for 18 h at r.t., the reaction mixture was quenched with H_2O (10 mL) and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layer was washed with brine (20 mL), dried (anhyd $MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (EtOAc–hexanes, 2:98) to afford compound **2** as a colorless oil; yield: 110 mg (97%).

$[\alpha]_D^{26}$ –25.8 (*c* 1.9, CCl_4) [Lit.[11] $[\alpha]_D$ –26.6 (*c* 0.5, CCl_4)].

^1H NMR (300 MHz, $CDCl_3$): δ = 2.62–2.67 (m, 2 H), 1.17–1.58 (m, 27 H), 0.85–0.91 (m, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 59.1, 39.1, 32.39, 32.36, 32.1, 29.81, 29.77, 29.67, 29.5, 28.1, 27.4, 26.5, 26.3, 22.9, 22.7, 14.3.

(7*R*,8*S*)-2-Methyloctadec-4-ene-7,8-diol (3)

To a soln of (4*R*,5*S*)-**4** (450 mg, 1.34 mmol) in CH_2Cl_2 (14 mL) was added 4-methylpent-1-ene (0.86 mL, 6.7 mmol), followed by Grubbs' catalyst (2nd generation) (56 mg, 0.067 mmol). The reaction mixture was warmed to 40 °C and stirred for 8 h. The solvent and remaining 4-methylpent-1-ene were removed under reduced pressure. The crude material was purified by flash column chromatography (EtOAc–hexanes, 15:85) to afford compound **3** as a white solid; yield: 200 mg (50%).

IR (film): 3290, 3213, 2958, 2916, 2850, 1470 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.35–5.65 (m, 2 H), 3.55–3.70 (m, 2 H), 2.13–2.35 (m, 2 H), 2.10 (br s, 2 H), 1.90–1.98 (m, 2 H), 1.23–1.68 (m, 19 H), 0.86–0.92 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.8, 132.7 (minor), 126.9, 125.7 (minor), 74.03 (minor), 73.97 (minor), 73.8, 73.4, 42.0, 36.5 (minor), 34.6, 31.9, 31.6, 29.7, 29.6, 29.3, 29.2 (minor), 28.6 (minor), 28.3, 26.0, 22.7, 22.4 (minor), 22.29, 22.26, 14.1.

(7*R*,8*S*)-2-Methyloctadecane-7,8-diol (12)

To a soln of **3** (162 mg, 0.54 mmol) in MeOH (7 mL) was added 10% Pd/C (0.1 w/w, 16 mg) and the mixture was stirred for 3 h under H_2 atmosphere. Then, the Pd/C was filtered off and the reaction solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (EtOAc–hexanes, 15:85) to afford compound **12** as a white solid; yield: 150 mg (93%).

Mp 86–87 °C (Lit.[5g] 85–88 °C); $[\alpha]_D^{22}$ +1.88 (*c* 0.5, $CHCl_3$).

IR (film): 3303, 2956, 2915, 2820, 1469 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.58–3.61 (m, 2 H), 2.31 (br s, 1 H), 2.19 (br s, 1 H), 1.15–1.60 (m, 27 H), 0.82–0.91 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 74.7, 38.9, 31.9, 31.18, 31.15, 29.7, 29.6, 29.3, 27.9, 27.4, 26.3, 26.1, 22.69, 22.64, 22.61, 14.1.

(+)-Disparlure [(7*R*,8*S*)-*cis*-7,8-Epoxy-2-methyloctadecane, 1]

To a soln of **12** (75 mg, 0.25 mmol) in toluene (1.5 mL) was added triethyl orthoacetate (0.24 mL, 1.25 mmol), followed by PPTS (2 mg). The reaction mixture was warmed to 110 °C and stirred for 1.5 h. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (1.5 mL), TMSCl (0.32 mL, 2.5 mmol) was added, and the mixture was stirred for 15 h at r.t. Then, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (EtOAc–hexanes, 1:99) to afford the acetoxy chloride isomers as a colorless oil. The acetoxy chloride isomers were dissolved in THF (1.5 mL), which was followed by the addition of 1 N KOH in MeOH (0.72 mL) and stirring for 2 h at r.t. Then, the reaction mixture was quenched with H_2O (10 mL) and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layer was washed with brine (20 mL), dried (anhyd $MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (EtOAc–hexanes, 2:98) to afford compound **1** as a colorless oil; yield: 67 mg (95%).

$[\alpha]_D^{22}$ +0.8 (*c* 0.5, CCl_4) [Lit.[5c] $[\alpha]_D$ +0.9 (*c* 1.1, CCl_4)].

^1H NMR (400 MHz, $CDCl_3$): δ = 2.88–2.92 (m, 2 H), 1.16–1.60 (m, 27 H), 0.84–0.90 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 57.2, 38.9, 31.9, 29.7, 29.6, 29.3, 27.9, 27.8, 27.3, 26.9, 26.6, 22.68, 22.61, 22.60, 14.1.

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References

(1) Bierl, B. A.; Beroza, M.; Collier, C. W. *Science* **1970**, *170*, 87.
(2) Miller, J. R.; Mori, K.; Roelofs, W. L. *J. Insect Physiol.* **1977**, *23*, 1447.
(3) Pettner, E.; Lazar, J.; Prestwich, E. G.; Prestwich, G. D. *Biochemistry* **2000**, *39*, 8953.
(4) For reviews, see: (a) Mori, K.; Tashiro, T. *Curr. Org. Synth.* **2004**, *1*, 11. (b) Mori, K. *Acc. Chem. Res.* **2000**, *33*, 102.

(5) For recent syntheses of disparlure, see: (a) Prasad, K. R.; Anbarasan, P. *J. Org. Chem.* **2007**, *72*, 3155. (b) Koumbis, A. E.; Chronopoulos, D. D. *Tetrahedron Lett.* **2005**, *46*, 3453. (c) Marshall, J. A.; Jablonowski, J. A.; Jiang, H. *J. Org. Chem.* **1999**, *64*, 2152. (d) Hu, S.; Jayaraman, S.; Oehlschlager, A. C. *J. Org. Chem.* **1999**, *64*, 3719. (e) Tsuboi, S.; Yamafuji, N.; Utaka, M. *Tetrahedron: Asymmetry* **1997**, *8*, 375. (f) Li, L. H.; Wang, D.; Chan, T. H. *Tetrahedron Lett.* **1997**, *38*, 101. (g) Sinha-Bagchi, A.; Sinha, S. C.; Keinan, E. *Tetrahedron: Asymmetry* **1995**, *6*, 2889. (h) Paolucci, C.; Mazzini, C.; Fava, A. *J. Org. Chem.* **1995**, *60*, 169. (i) Ko, S. Y. *Tetrahedron Lett.* **1994**, *35*, 3601. (j) Tsuboi, S.; Furutani, H.; Ansari, M. H.; Sakai, T.; Utaka, M.; Takeda, A. *J. Org. Chem.* **1993**, *58*, 486. (k) Brevet, J.-L.; Mori, K. *Synthesis* **1992**, 1007. (l) Keinan, E.; Sinha, S. C.; Sinha-Bagchi, A.; Wang, Z.-M.; Zhang, X.-L.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 6411.

(6) (a) Kim, S.-G.; Park, T.-H. *Tetrahedron: Asymmetry* **2008**, *19*, 1626. (b) Kim, S.-G.; Park, T.-H.; Kim, B. J. *Tetrahedron Lett.* **2006**, *47*, 6369. (c) Kim, S.-G.; Kim, J.; Jung, H. *Tetrahedron Lett.* **2005**, *46*, 2437. (d) For a review on total synthesis based on asymmetric organocatalysis, see: de Figueiredo, R. M.; Christmann, M. *Eur. J. Org. Chem.* **2007**, 2575.

(7) Zhong, G. *Chem. Commun.* **2004**, 606.

(8) For selected examples of proline-catalyzed asymmetric α-aminoxylation of aldehydes, see: (a) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808. (b) Zhong, G. *Angew. Chem. Int. Ed.* **2003**, *42*, 4247. (c) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293.

(9) Even in the case of the use of only DMSO as solvent, the major product was the *anti*-isomer with 4:1 (*anti*/*syn*) diastereoselectivity, similar to the result with the $CHCl_3$–DMSO cosolvent system. From this, we deduce that the reversal of selectivity compared with previous results[6b,7] (2:3, *anti*/*syn*, in our cases) comes from the use of different aldehyde substrates, not a solvent effect. The major isomer could be inverted according to the substrates used in the indium-mediated allylation of α-oxygenated aldehydes; see: Paquette, L. A.; Mitzel, T. M. *J. Am. Chem. Soc.* **1996**, *118*, 1931.

(10) For selected articles on olefin cross metathesis, see: (a) Cossy, J.; BouzBouz, S.; Hoveyda, A. H. *J. Organomet. Chem.* **2001**, *624*, 327. (b) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360. For a recent review, see: (c) Connon, S. J.; Blechert, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900.

(11) The ratio of *E*/*Z*-regioisomers in **10** (1:5), which was estimated by ^{13}C NMR spectroscopy, was not important because the double bond was reduced by hydrogenation in the next step.

(12) Iwaki, S.; Marumo, S.; Saito, T.; Yamada, M.; Katagiri, K. *J. Am. Chem. Soc.* **1974**, *96*, 7842.

(13) We have found that Grubbs' catalyst cleanly cleaved the N–O bond of **4** to furnish diol in the case of the absence of a cross-metathesis partner; detailed results will be published in due course.

(14) For an example of the use of Grubbs' catalyst as a reagent for N-deallylation, see: Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *Org. Lett.* **2001**, *3*, 3781.

(15) Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515.

(16) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, **1988**.