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

Sung-Gon Kim*

Department of Chemistry, College of Natural Science, Kyonggi University, San 94-6, Iui-dong, Yeongtong-gu, Suwon 443-760, Korea
Fax +82(31)2499631; E-mail: sgkim123@kgu.ac.kr

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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 (7R,8S)-7,8-epoxy-2-methyloctadecane, is the sex-attractant pheromone emitted by the female gypsy moth, Porthetria dispar (L.). 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. 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. For these reasons, disparlure has been the target of numerous syntheses, in which most of the approaches for the construction of the two asymmetric centers take advantage of asymmetric epoxidation (AE), asymmetric dihydroxylation (AD), asymmetric chloroallylation, enzymatic procedures, or chiral pool materials.

This retrosynthetic concept for (+)-disparlure (1) was put into practice as depicted in Scheme 2. Homooallylic 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. 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, however, it was found at the final stage that the major product was in fact the anti-isomer.

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.
The conversion of compound 9 into the alkene 10 was achieved by olefin cross metathesis\textsuperscript{10} with 4-methylpent-1-ene in the presence of 5 mol% of Grubbs’ second-generation catalyst in 84\% yield.\textsuperscript{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 (7S,8S)-trans-isomer of disparlure after comparing the spectroscopic data and optical rotation of the material with reported values in the literature\textsuperscript{5c}\textsuperscript{12} 
\[ [\alpha]_D^{26} = -25.8 (c 1.9, CCl_4) \text{[Lit.]} \] 
\[ [\alpha]_D^{26} = -26.6 (c 0.5, CCl_4) \text{[Lit.]} \] 
\[ [\alpha]_D^{26} = +25.7 (c 0.5, CCl_4) \]. From these results, we were able to establish that the major diastereomer in the tandem a-amination–allylation reaction was the anti-homoallylic alcohol 4.\textsuperscript{9} From this synthetic route, the (7R,8R)-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 \[ [\alpha]_D^{26} = +26.9 (c 1.0, CCl_4) \text{[Lit.]} \] 
\[ [\alpha]_D^{26} = +27.5 (c 0.5, CCl_4) \].

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 (4R,5S)-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.\textsuperscript{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)]\textsubscript{3}, TMSCl, KOH\textsuperscript{15} in 95\% yield \[ [\alpha]_D^{22} = +0.8 (c 0.5, CCl_4) \text{[Lit.]} \] 
\[ [\alpha]_D^{22} = +0.9 (c 1.1, CCl_4) \text{[Lit.]} \]. (+)-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 a-amination–allylation reaction \[ [\alpha]_D^{22} = -0.7 (c 0.5, CCl_4) \text{[Lit.]} \] 
\[ [\alpha]_D^{22} = -0.9 (c 0.21, CCl_4) \text{[Lit.]} \].

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 a-amination–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.

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 Armaragro.\textsuperscript{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 13C 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-
(4S,5R)-5-allyl-5-(N-phenylamino)pentadec-1-en-4-ol (4)

To a solution of dodecanal (5; 1.50 mL, 6.0 mmol) and nitrosobenzene (6; 540 mg, 5.0 mmol) in CHCl3 (3.5 mL), p-toluenesulfonyl chloride (355 mg, 0.69 mmol) in CH2Cl2 (7.0 mL) was added Et3N (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. NH4Cl solution (15 mL) and the aqueous layer was extracted with CH2Cl2 (2 × 20 mL). The combined organic layer was washed with brine (20 mL), which was followed by anhyd MgSO4, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (EtOAc–hexanes, 1:9) to afford compound 7 as a pale yellow oil; yield: 675 mg (97%).

HRMS: m/z [M+] calcd for C27H49NO2Si: 447.3531; found: 447.3531.

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

To a solution of 8 (303 mg, 0.85 mmol) in CH2Cl2 (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. NH4Cl solution (15 mL) and the aqueous layer was extracted with CH2Cl2 (2 × 20 mL). The combined organic layer was washed with brine (20 mL), dried (anhyd MgSO4), 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: 494 mg (99%).

HRMS: m/z [M+1] calcd for C21H35NO2Si: 356.3111; found: 356.3091.
40 °C and stirred for 5 h. The solvent and remaining 4-methylpent-1-one 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, 2926, 2856, 1463, 1364, 1264 cm⁻¹.

1H NMR (300 MHz, CDCl₃): 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).

13C NMR (75 MHz, CDCl₃): δ = 134.6, 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), 86.4 (minor), 86.2, 74.3 (minor), 74.1, 42.3, 38.4, 36.8 (minor), 33.0 (minor), 32.1, 32.8, 29.7, 29.3, 29.68, 29.57, 29.51, 28.8 (minor), 28.6, 28.0 (minor), 27.8, 26.1, 26.0, 25.4 (minor), 25.3, 22.9, 22.60, 22.55, 21.8, 18.3, 14.3, 14.3, –4.5.

(7RS,8S)-7-(tert-Butyldimethylsiloxy)-2-methyl-8-(p-tolylsulfo-nolyl)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 H₂ 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, 1:99) to afford compound 11 as a colorless oil; yield: 278 mg (99%).

IR (film): 3290, 3215, 2986, 2850, 1470 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 3.86–3.92 (m, 1 H), 3.81–3.84 (m, 2 H), 3.55–3.70 (m, 2 H), 2.98–3.23 (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).

13C NMR (100 MHz, CDCl₃): 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), 22.9, 22.26, 14.1.

(7RS,8S)-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 H₂ 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%).

IR (film): 3303, 2956, 2915, 2820, 1469 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 3.58–3.61 (m, 2 H), 2.31 (br s, 1 H), 2.19 (br s, 1 H), 1.95–1.60 (m, 27 H), 0.82–0.91 (m, 9 H).

13C NMR (100 MHz, CDCl₃): δ = 74.7, 38.9, 31.9, 31.18, 31.15, 29.7, 29.6, 29.3, 27.9, 26.3, 26.1, 21.69, 22.64, 22.61, 14.1.

References


(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 CHCl3–DMSO cosolvent system. From this, we deduce that the reversal of selectivity compared with previous results6b,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 a-oxygenated aldehydes; see: Paquette, L. A.; Mitzel, T. M. J. Am. Chem. Soc. 1996, 118, 1931.


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


(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.

