An Efficient Enantioselective Synthesis of (+)-Disparlure

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Synthesis of (+)-disparlure, **1**, the sex pheromone of gypsy moth (*Lymantria dispar*), commenced from *cis*-vinyl epoxide **4** which was prepared by our asymmetric chloroallylboration in 99% de and 94% ee. Hydroboration of **4** using dicyclohexylborane in THF, followed by sodium perborate oxidation gave a crystalline *cis*-3,4-epoxy alcohol **3** whose enantiomeric purity was enhanced by recrystallization. Conversion of **3** to (+)-disparlure was via alkylation of the tosylate. (+)-Disparlure was produced in four steps with an overall yield of 27% and ≥99.5% ee.

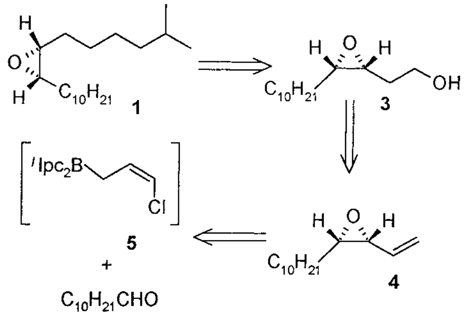
Introduction

(+)-Disparlure, **1**, (+)-(7*R*,8*S*)-*cis*-7,8-epoxy-2-methyloctadecane, is the sex pheromone of female gypsy moth, *Lymantria dispar* (L). The pheromone is required to be nearly enantiopure to elicit attraction. Many syntheses of (+)-**1** using chiral natural products,[1,2] asymmetric induction (Sharpless asymmetric epoxidation[3] and asymmetric dihydroxylation[4]), and catalytic biotransformation[5] have been reported.

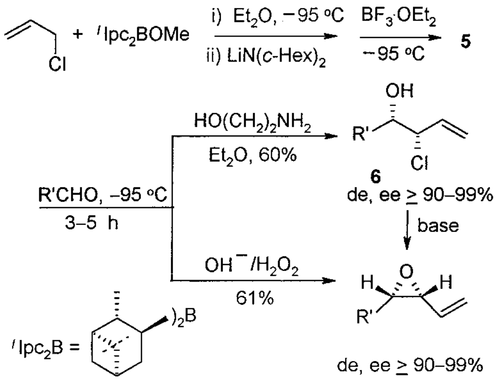
In the present work we have applied our recently developed chloroallylboration of aldehydes to the preparation of (+)-**1**. The envisioned strategy involved hydroboration of *cis*-vinyl epoxide **4** to give *cis*-3,4-epoxy alcohol **3** which, upon tosylation followed by cuprate alkylation, would yield (+)-**1** (Scheme 1). We considered it likely that **3** would be crystalline and that enantiomeric purity could be enhanced at this stage. The current synthesis is noteworthy because of the low number of steps and high enantiomeric purity of (+)-**1** produced.

A. Preparation of *cis*-Vinyl Epoxide. We have recently[6] demonstrated that reaction of aldehydes with (*Z*)-(*γ*-chloroallyl)diisopinocampheylborane, **5**, furnish *syn*-vinylchlorohydrins or *cis*-vinyl epoxides with high stereoselectivity (≥90% de, 90−99% ee). Cyclization of *syn*-vinylchlorohydrins with potassium carbonate in methanol also gives the corresponding *cis*-vinyl epoxides (Scheme 2). Employment of this process, using commercially available undecanyl aldehyde gave the desired *cis*-vinyl epoxide **4** in 63% yield (99% de, 94% ee). Intermediate **4** could be obtained directly from the above reaction by oxidation workup or by base-induced cyclization of *syn*-α-chlorohydrin **6** (R′ = $C_{10}H_{21}$) produced via ethanolamine workup.

Scheme 1



Scheme 2



B. Hydroboration of *cis*-Vinyl Epoxide 4. Initial reactions examined hydroboration of **4** with 9-BBN and $BH_3{\cdot}SMe_2$, followed by oxidation with $NaOH/H_2O_2$. No *cis*-3,4-epoxy alcohol **3** was isolated. Hydroboration of **4** with 9-BBN followed by oxidation with various oxidation reagents ($NaOAc/H_2O_2$, $NaBO_3$) did not yield expected **3** either. Polar product similar to that expected from epoxide opening was detected. It is reported that reaction of vinyl epoxide with 9-BBN or $BH_3{\cdot}SMe_2$ leads to opening of the epoxide.[7a] According to the proposed mechanism, the borons of 9-BBN and $BH_3{\cdot}SMe_2$ coordinate with the epoxide oxygen lone pair electrons promoting opening.

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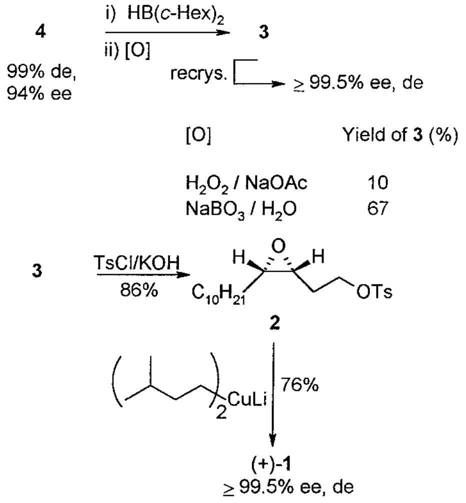
10.1021/jo9820871 CCC: $18.00

Scheme 3



Since the boron of dicyclohexylborane is more sterically encumbered, it would not be expected to coordinate as strongly with the epoxide oxygen lone pair electrons. Therefore, ring opening should be a slower process.[7b] Hydroboration using HB(c-Hex)$_2$ followed by addition of NaOH/H$_2$O$_2$ also failed to produce **3**. The failure of hydroboration of **4** in the foregoing reactions could be because of complications during the oxidation due to the sensitivity of the epoxide to strong base.[8] Thus, we reexamined hydroboration of **4** using dicyclohexylborane in several solvents and determined that the reaction proceeded well in THF but was much slower in Et$_2$O, pentane, or toluene. Oxidation with various reagents gave **3**. Surprisingly, NaOAc/H$_2$O$_2$, which is useful for organoboranes with base-sensitive functional groups did not give a good result. Sodium perborate[9] is the reagent of choice providing **3** in 67% yield (Scheme 3).[10]

Two recrystallizations from 1% ether in hexane solution yielded **3** (mp: 38.5−39.5 °C) in enantiopure form.[11]

C. Synthesis of (+)-Disparlure. Tosylation of *cis*-3,4-epoxy alcohol **3** with tosyl chloride in pyridine for 2 days gave a low yield of **2** (50% yield). However, reaction of **3** with tosyl chloride and powdered potassium hydroxide in ethyl ether gave a good yield of **2** (86%). Cuprate-mediated alkylation of **2** furnished with (+)-**1** in 76% yield (Scheme 3). Enantiomeric purity of (+)-**1** was determined to be ≥99.5% by Oliver's method.[12]

Conclusions

cis-Vinyl epoxide **4** (94% ee) was generated by chloroallylboration of undecanaldehyde using (*Z*)-γ-chloroallylborane, **5**. Subsequent hydroboration using dicyclohexylborane in THF followed by sodium perborate oxidation gave *cis*-epoxy alcohol **3** which was converted to (+)-**1** in overall yield of 27% and ≥99.5% ee.

Experimental Section

General Chemical Procedures. THF and diethyl ether were distilled from sodium−benzophenone ketyl. Dicyclohexylamine [(c-Hex)$_2$NH] was freshly distilled from CaH$_2$ prior to use. Allyl chloride was freshly distilled over P$_2$O$_5$ prior to use. Undecanyl aldehyde was distilled prior to use. The ^{l}Ipc$_2$BOMe and 9-BBN were purchased from Aldrich and used without purification. Moisture- and air-sensitive reactions were conducted under argon in vacuum-dried glassware. A nitrogen glovebag was used to weigh moisture-sensitive compounds. Syringes and cannulas were used to transfer air-sensitive reagents.[13] Unless otherwise stated, standard workup refers the combination of organic extracts, washing with ice-cold brine, drying over anhydrous MgSO$_4$, and concentration in vacuo. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. GC analyses were conducted using a 30-m × 0.25-mm i.d. fused silica column coated with DB-1 with FID detection.

***cis*-(3*R*,4*R*)-3,4-Epoxy-1-tetradecene, 4.** To a stirred and cooled (−95 °C) mixture of ^{l}Ipc$_2$BOMe (11.5 mmol) and allyl chloride (15 mmol) in anhydrous ether (50 mL) was added a solution of LiN(c-Hex)$_2$ (15 mmol) in THF (25 mL). After stirring for 1 h, BF$_3$·OEt$_2$ (30 mmol) and undecanyl aldehyde (11.5 mmol) were added sequentially. The reaction was continued at −95 °C for 4 h. Solvents were removed in vacuo at room temperature, and the residue was triturated with *n*-pentane (40 mL) and allowed to settle (12 h). The supernatant was transferred to another predried flask by cannula. The residue was further treated with pentane (2 × 30 mL), and the pentane extracts were combined. Removal of pentane in vacuo furnished a semisolid.

Oxidation of Boron Intermediate. The residue obtained from chloroallylboration reaction was dissolved in THF (20 mL) with stirring and cooled to 0 °C. Then, 3 M NaOH (12 mL) and 30% H$_2$O$_2$ (12 mL) were sequentially added. The reaction mixture was allowed to warm to room temperature (14 h). Standard workup followed by flash chromatography yielded a colorless liquid **4** (1.32 g, 63% yield). $[\alpha]^{23}_{D}$ +21.09 (c = 8.81, CH$_2$Cl$_2$); ^{13}C NMR (CDCl$_3$, ppm) 132.78, 120.13, 58.79, 57.17, 31.90, 29.58, 29.53, 29.42, 29.30, 27.75, 26.29, 22.66, 14.04. ^{1}H NMR (CDCl$_3$, ppm) 5.69 (ddd, J = 17.2, 10.4, 7.2 Hz, 1H), 5.46 (ddd, J = 17.2, 1, 1 Hz, 1H), 5.34 (ddd, J = 10.2, 1, 1 Hz, 1H), 3.39 (dd, J = 7.2, 4.3 Hz, 1H), 3.06 (m, 1H), 1.58−1.26 (m, 18H), 0.87 (t, J = 6.8 Hz, 3H); CIMS m/z (isobutane, rel intensity) 211 (M$^+$ + 1, 18), 169 (100). Anal. Calcd for C$_{14}$H$_{26}$O: C, 79.94; H, 12.46. Found: C, 79.80; H, 12.55. Enantiomeric purity was determined to be 94% by ^{1}HNMR analysis using chiral shift reagent Eu(hfc)$_3$.

***cis*-(3*R*,4*R*)-3,4-Epoxytetradecan-1-ol, 3.** Dicyclohexylborane is prepared from freshly distilled cyclohexene and BH$_3$·SMe$_2$. Further purification by sublimation is performed. A solution of epoxide **4** (420 mg, 2 mmol) in THF (1 mL) was added to 2 mmol of dicyclohexylborane−THF solution (2 mL) via syringe while stirring. Stirring was continued for 4 h at room temperature. The reaction was quenched by addition of 910 mg of NaBO$_3$·H$_2$O and 0.5 mL of H$_2$O. The mixture was stirred overnight, and then 4 g of anhydrous K$_2$CO$_3$ was added. After 2 h, the mixture was diluted with 15 mL of anhydrous Et$_2$O. Solid was removed by filtration and washed with Et$_2$O. Concentration of the filtrate in vacuo, followed by flash chromatography using hexane:Et$_2$O, 7:3, as eluant yielded 291 mg of **3** (67% yield), mp 33−37.5 °C. Two cycles of recrystallization from 1% Et$_2$O in hexane gave mp 37.7−38.5 °C. $[\alpha]^{23}_{D}$ −8.34 (c = 6.32, Et$_2$O); ^{13}C NMR (CDCl$_3$, ppm) 60.81, 56.68, 54.94, 31.88, 30.68, 29.66, 29.56, 29.53, 29.49, 29.28, 27.96, 26.46, 22.63, 14.01. ^{1}H NMR (CDCl$_3$, ppm) 3.86 (m, 2H), 3.09 (dt, J = 8.0, 4.4 Hz, 1H), 2.93 (td, J = 5.6, 4.4 Hz, 1H), 1.92−1.26 (m, 21H), 0.87 (t, J = 6.8 Hz, 3H). IR (film) 3308, 2917, 2850, 1417, 1068, 1047, 843 cm^{-1}. CIMS m/z (isobutane, rel intensity) 229 (M$^+$ + 1, 100), 211 [(M$^+$ − 18) + 1, 95]. Anal. Calcd for C$_{14}$H$_{28}$O$_2$: C, 73.63; H, 12.36. Found: C, 73.80; H,

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(11) As the enantiomeric purity of (+)-**1** is ≥99.5% based on the method of Oliver (see ref 12), it is reasonable to assume **3** possessing enantiomeric purity of ≥99.5%.

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12.45. Alternatively, **3** can be synthesized from hydroboration of protected *syn*-chlorohydrin **6** (R′ = $C_{10}H_{21}$) by a one-pot three-step process.[10]

***cis*-(3*R*,4*R*)-3,4-Epoxytetradecanyl tosylate, 2.** A solution of **3** (228 mg, 1 mmol) in anhydrous ether (2 mL) was cooled to −5 °C. *p*-Toluenesulfonyl chloride (190 mg, 1 mmol) was added, followed by the addition of powdered KOH in small portions over 15 min. After 4 h, the reaction was quenched with ice−water (10 mL). The aqueous layer was extracted with ether (3 × 10 mL). The combined ether extract was dried over anhydrous Na_2SO_4. Solvent removal followed by column chromatography yielded **2** (328 mg, 86% yield). $[\alpha]^{23}_{D}$ +9.16 (*c* = 2.62, Et_2O); ^{13}C NMR ($CDCl_3$, ppm) 129.85, 127.90, 67.71, 56.90, 53.24, 31.88, 29.53, 29.48, 29.43, 29.26, 27.91, 27.75, 26.41, 22.62, 21.58, 14.04. ^1H NMR ($CDCl_3$, ppm) 7.80 (d, *J* = 16 Hz, 2H), 7.36 (d, *J* = 16 Hz, 2H), 4.19 (m, 2H), 2.92 (m, 1H), 2.93 (m, 1H), 2.44 (s, 3H), 1.98 (m, 1H), 1.76 (m, 1H), 1.43−1.26 (m, 18H), 0.89 (t, *J* = 6.8 Hz, 3H). Anal. Calcd for $C_{21}H_{34}O_4S$: C, 65.93; H, 8.96. Found: C, 66.07; H, 8.89.

(+)-(7*R*,8*S*)-*cis*-7,8-Epoxy-2-methyloctadecane, 1. Isopentyllithium in hexane (5.44 mL, 4 mmol) was added to a stirred slurry of cuprous iodide (385 mg, 2 mmol) in Et_2O (15 mL) at −40 °C. After stirring for 30 min, the flask was warmed to 0 °C for 5 min and then cooled to −78 °C, and a solution of tosylate **2** (382 mg, 1 mmol) in Et_2O (5 mL) was added dropwise. After 30 min stirring, the reaction was allowed to warm to room temperature. The reaction was quenched with saturated aqueous ammonium chloride at 0 °C. The organic extract was separated, and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic extract was washed with brine (2 × 15 mL) and then dried over Na_2SO_4. Column chromatography over silica gel (hexane:Et_2O, 100:1) gave **1** (204 mg, 76% yield). $[\alpha]^{23}_{D}$ +0.61 (*c* = 5.06, CCl_4), (lit.[3a] $[\alpha]^{23}_{D}$ +0.6, *c* = 5.6, CCl_4). ^1H NMR and ^{13}C NMR spectra of **1** are identical to those reported.[3a]

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