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An enantiodivergent synthesis of both (+)- and (−)-disparlure from (*R*)-2,3-cyclohexylideneglyceraldehyde

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ABSTRACT

Reduction of ketone **3** derived from (*R*)-2,3-cyclohexylideneglyceraldehyde **1** with some common hydrides took place with *syn*-selectivity. The resulting major product **4a** has been exploited as a common chiral template to prepare both enantiomers **Ia**,**b** of disparlure.

1. Introduction

The gypsy moth is a seriously harmful pest, causing severe forest losses during outbreaks in Europe, Asia, and North America. (+)-Disparlure **Ia** (Fig. 1), structurally known as (7*R*,8*S*)-7,8-epoxy-2-methyloctadecane, is the sex-attractant pheromone emitted by the female gypsy moth, *Lymantria dispar*.[1] It has been shown that the (−)-enantiomer **Ib** antagonizes the effect of (+)-disparlure and is slightly repellent by itself.[2] Both the enantiomers bind differently to two pheromone-binding proteins (PBP1 and PBP2) that are found in gypsy moth antennae. Compounds **Ia** and **Ib** have higher affinity for PBP2 and PBP1, respectively.[3] Thus, a practical synthesis of both enantiomers of disparlure in enantiomerically pure form assumes considerable significance to have a detailed study of their structure–activity relationship and also for a thorough control of gypsy moth pests in the forest. Accordingly, efforts have been directed toward the synthesis of both enantiomers **Ia** and **Ib**[4,5a–l] and several analogues.[5m–o] Understandably, for the synthesis of both these enantiomers the prime requisite is to introduce its two stereo-centers in the linear carbon chain, which has been accomplished in a different manner by various synthetic groups, viz asymmetric epoxidation (AE),[5f] asymmetric dihydroxylation (AD),[5g,i,l] asymmetric chloroallylation,[5d] use of chiral stannanes,[5c] enzymatic procedures,[5e,j,k] or through the exploitation of chiral pool materials.[5a,b,h] However, owing to their high importance there is a scope for the development of a new strategy for the efficient synthesis of both the enantiomers **Ia** and **Ib** of disparlure.

In our ongoing program regarding the synthesis of bioactive compounds, we have been exploiting (*R*)-2,3-cyclohexylideneglyceraldehyde **1**[6a] as a useful template for the asymmetric construction of different structural units during our syntheses of different biomolecules.[6] Compound **1** has various operational advantages due to its easy accessibility on a multi-gram scale, good reactivity both in aqueous and anhydrous media, and being less prone to polymerization. Furthermore, the higher stability of its ketal functionality compared to the corresponding acetonide derivative[7] enabled us earlier[6] to manipulate all the hydroxyls of its alkylation products selectively. The present work describes our endeavor to explore the potential of **1** once again to develop a practically viable strategy for the syntheses of both **Ia** and **Ib**.

2. Results and discussion

Retro synthetic analysis (Scheme 1) of both (+)- and (−)-disparlure **I** suggested that both these enantiomers could be obtained from two differently protected forms **10a** and **11b** of the same *syn* diol that could be accessed from **1** through **4a**. It needs to be re-stated that compound **4a** had been prepared earlier in good yield and highly stereo-selective *syn* reduction of ketone **3**[6k] derived from **1** (Table 1, entry A). Now, with a view to developing a somewhat practical synthesis of disparlure, it was performed under three different operationally simpler procedures using common hydrides, viz $LiAlH_4$ (Table 1, entry B), $NaBH_4$ (Table 1, entry C), and $LiAlH_4$/LI[8] (Table 1, entry D) and their results are shown in Table 1.

In all the three cases (Table 1, entries b–d) reduction of **3** yielded **4a** in good yields, but with nearly the same degrees of moderate *syn*-selectivity. Among the three, $LiAlH_4$ reduction appeared to be most suitable for our purpose as it took place with the highest yield and best *syn*-selectivity. Thus, despite achieving less *syn*-selectivity compared to a K-selectride reduction,[6k] the operationally simpler $LiAlH_4$ reduction of **3** appeared to be preferable in our goal to establish a practical synthesis of **Ia** and **Ib**. Furthermore, somewhat less *syn*-selectivity in this case could be offset by the easy column chromatographic separation of our desired isomer **4a** from the *anti*-**4b** compound to obtain a substantial amount of it in homochiral form.

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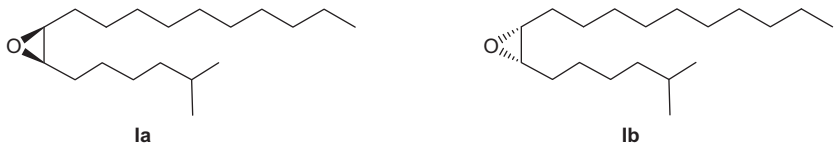
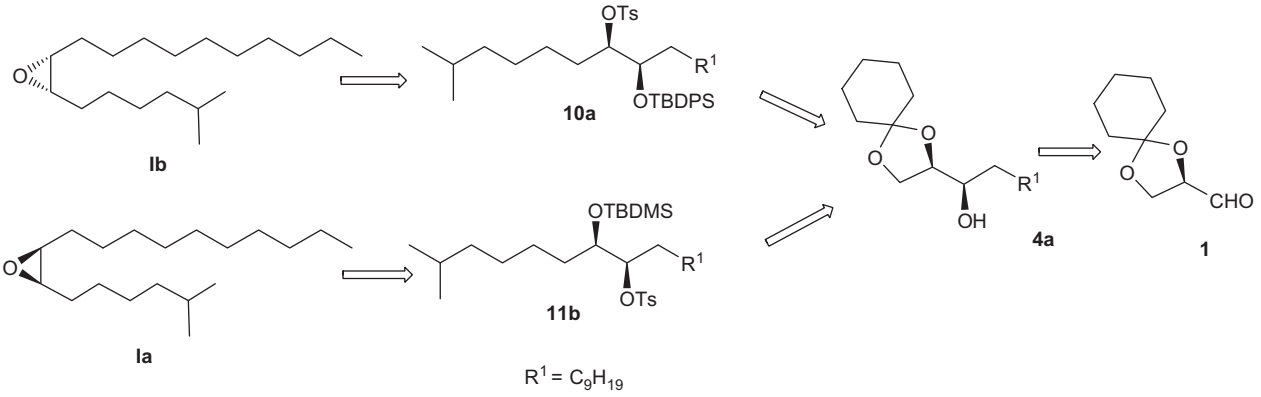


Figure 1. Both enantiomers of disparlure.



Scheme 1. Retro-synthesis of (−) and (+)-disparlure.

Table 1
Hydride reduction of **3**

Entry	Hydride	Yield (%)	Stereoselectivity **4a**:**4b**	Reference
A	K-selectride	95	91.7:8.3	6k
B	$LiAlH_4$	91.3	65.8:34.2	
C	$NaBH_4$	81.3	62:38	
D	$LiAlH_4$–LiI	85.9	63.4:36.6	

Silylation of **4a** and deketalisation of the resulting silyl-ether **5a** under acidic conditions afforded diol **6a** in good yield. This was converted into epoxide **8a** in two steps, viz regioselective tosylation at its primary hydroxyl and base treatment of the product **7a**. The epoxide **8a** was treated with 4-methypentylmagnesium bromide in the presence of copper (I) catalyst to afford the alcohol **9a**. This was tosylated which took place quantitatively and the resulting product **10a** was desilylated on treatment with TBAF to directly afford **Ib** in good yield whose spectroscopic and rotation data were found to be in accordance with the reported ones[5a] (Scheme 2).

Benzylation of **4a**, followed by acid mediated deketalisation of the resulting **5b** afforded diol **6b** in good yield. This was converted into epoxide **8b** in two steps, viz regioselective tosylation at its primary hydroxyl and base treatment of the product **7b**. Now, as carried out earlier for the preparation of **9a**, copper (I) catalyzed reaction of epoxide **8b** with 4-methypentylmagnesium bromide afforded the alcohol **9b**. This was silylated upon treatment with TBDMS-Cl and the resulting product **10b** was subjected to hydrogenation producing a known alcohol **11a**[5a] following debenzylation at the C-8 hydroxyl. Next, the hydroxyl of **11a** was tosylated, and this took place quantitatively to yield **11b** which was subjected to desilylation on treatment with TBAF to afford **Ia** in good yield whose spectroscopic and rotation data were found to be in accordance with the reported ones (Scheme 2).[5a]

3. Conclusion

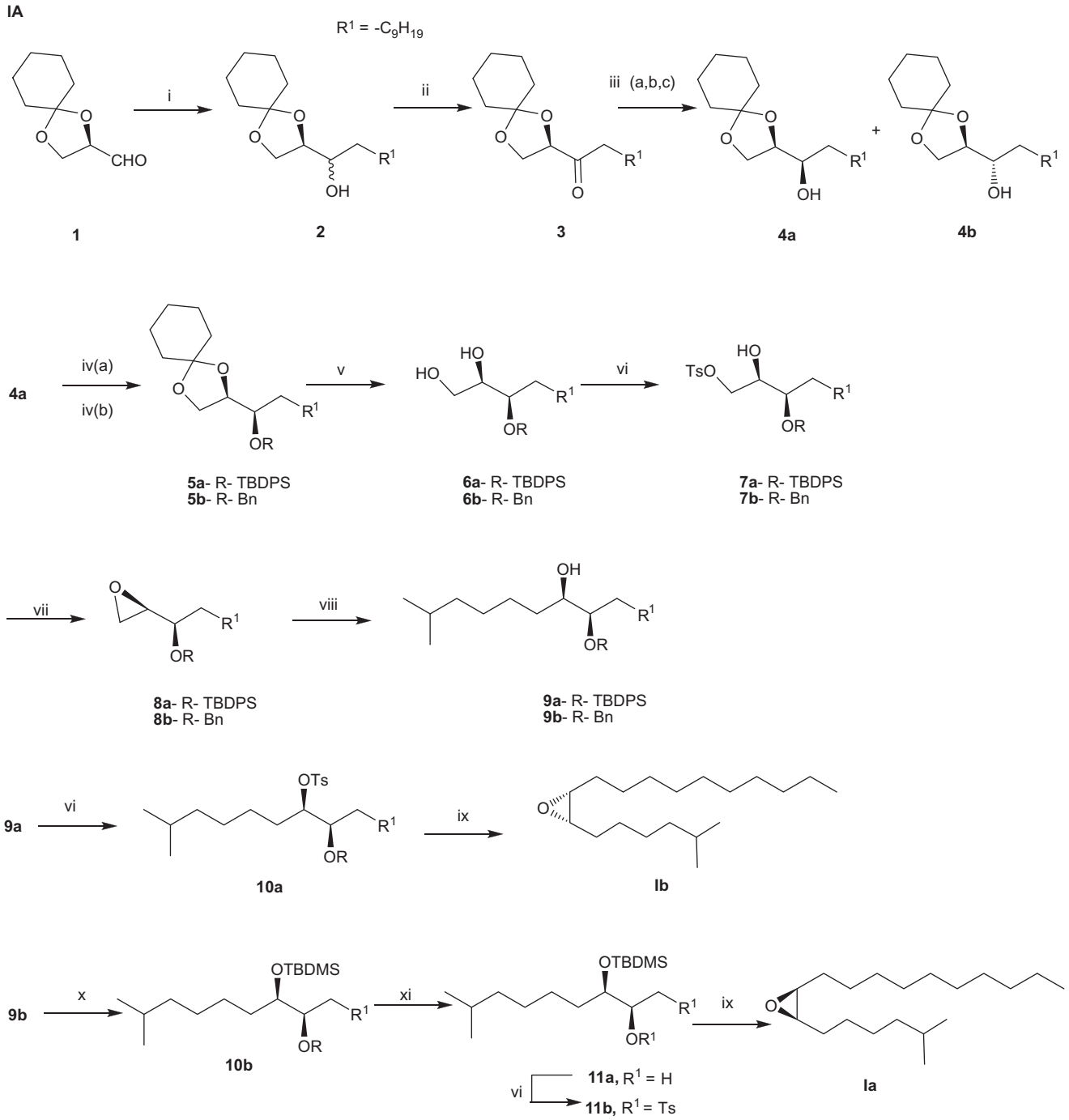
A simple route to an enantiodivergent synthesis of both enantiomers **Ia** and **Ib** of disparlure has been established through the functional and stereoselective manipulation of a common intermediate **4a**, a partially protected 1,2-*syn*-diol derived from **1**.[6a] As could be evident here, the partial protection of the *syn* diol moiety in **4a** enabled us to smoothly obtain another set of partially protected diols **9a** and **11a**, the advanced precursors of **Ib** and **Ia**, respectively. Notably, using an $LiAlH_4$ reduction of ketone **3** (Table 1, entry B) the overall yield of **4a** has been considerably increased to 60% in two practically viable steps (steps ii and iii, Scheme 2) starting from Grignard product **4**. Accordingly, the overall yields of **Ia** and **Ib** in this protocol were found to be 10.75% and 13.97%, respectively, which were comparable with most of the reported approaches.[5] The efficacy of the present route was due to many operational advantages associated with easily available **1**[6a] as mentioned earlier and its being comprised of a series of operationally simple and scaleable reactions. In view of this, despite the presence of a moderately *syn*-selective reduction of ketone **3** (Table 1, entry B), utilizing the present route has significant advantages to achieve the practical syntheses of both **Ia**/**Ib**, compared to all other reported syntheses.[5] Understandably, beginning with the major Grignard product *anti*-**4b** there is a scope to prepare the *trans* isomers[5o] of both **Ia** and **Ib** following the same reactions protocol as described here.

4. Experimental

Chemicals used as starting materials are commercially available and were used without further purification. All solvents used for the extraction and chromatography were distilled twice at atmospheric pressure prior to use. The ^1H and ^{13}C NMR spectra were recorded with a Bruker Ac-200 (200 MHz) instrument in $CDCl_3$. The organic extracts were desiccated over dry Na_2SO_4.

4.1. Reduction of compound 3 with $LiAlH_4$

To a stirred solution of **3** (6.2 g, 0.02 mol) in THF (100 ml) at 0 °C was added $LiAlH_4$ (760 mg, 0.02 mol) in several portions over a period of 1 h. The mixture was stirred at 0 °C for 1.5 h until the reaction was completed (TLC). The reaction was then quenched by the dropwise addition of aqueous saturated Na_2SO_4 that destroyed the excess hydride to form a white precipitate. It was then filtered through a sintered funnel and washed with EtOAc.



Scheme 2. Synthesis of (−) and (+)-disparlure. Reagents and conditions: (i) Ref. 6k; (ii) Ref. 6k; (iii) (a) $LiAlH_4$, Dry THF, 0 °C, 91%; (b) $NaBH_4$, MeOH, 0 °C, 81%; (c) $LiAlH_4$, LiI, Et_2O, −40 to −78 °C, 86%; (iv) (a) TBDPSCl, imidazole, DMAP, Dry CH_2Cl_2, 95%; (b) $PhCH_2Br$, NaH, Dry THF, 60 °C, 90%; (v) aq TFA (80%), CH_2Cl_2, 0 °C, 80%; (vi) TsCl, Dry Py, DMAP, 0 °C, quantitatively; (vii) K_2CO_3, Dry CH_3OH, 85%; (viii) $(CH_3)_2CH(CH_2)_2CH_2MgBr$, Cu, Dry THF, −60 °C, 70%; (ix) TBAF, Dry THF, 0 °C, 75%; (x) TBDMS-Cl, imidazole, DMAP, Dry CH_2Cl_2, 90%; (xi) Pd/C, H_2 gas, C_2H_5OH, 85%.

The organic filtrate was washed with water, brine, and dried over Na_2SO_4. Solvent removed under reduced pressure afforded the residue which was purified by column chromatography (silica gel; 0–15% EtOAc in petroleum ether) to afford pure **4a**[6k] (3.75 g, yield 59.7%) and **4b**[6k] (1.95 g, yield 31.2%), both as colorless oils.

4.2. Reduction of compound 3 with $NaBH_4$

To a stirred solution of **3** (6.2 g, 0.022 mol) in MeOH (50 ml) at 0 °C was added $NaBH_4$ (740 mg, 0.02 mol) in several portions over a period of 20 min. The mixture was stirred at 0 °C for 2 h. Solvent was removed under reduced pressure. The residue was taken in $CHCl_3$. The organic solution was washed with water, brine, and dried over Na_2SO_4. Solvent removed under reduced pressure to afford the residue which was purified by column chromatography (silica gel; 0–15% EtOAc in petroleum ether) to afford pure **4a** (3.14 g, yield 50.3%) and **4b** (2.0 g, yield 31%).

4.3. Reduction of compound 3 with $LiAlH_4$/LiI

To a stirred solution of **3** (3.1 g, 0.011 mol) in diethyl ether (20 ml) was added LiI (13.4 g, 0.1 mol) and the mixture was stirred

at −40 °C for 5 min. Then it was cooled to −78 °C and $LiAlH_4$ (3.8 g, 0.1 mol) was added in several portions over a period of 20 min. The mixture was stirred at −78 °C for 30 min and quenched by the addition of aqueous saturated Na_2SO_4 that decomposed the excess hydride to form a white precipitate. It was then filtered through a sintered funnel and washed with EtOAc. The organic filtrate was washed with water, brine, and dried over Na_2SO_4. Solvent removed under reduced pressure afforded a residue which was purified by column chromatography (silica gel; 0–15% EtOAc in petroleum ether) to afford pure **4a** (1.7 g, yield 54.5%) and **4b** (980 mg, yield 31.4%).

4.4. (2*R*,3*R*)-1,2-*O*-Cyclohexylidene-3-*O*-*tert*-butydiphenylsilyl-tridecane-1,2,3-triol 5a

To a stirred solution of **4a** (2.5 g, 8.0 mmol) in CH_2Cl_2 (75 mL) containing imidazole (0.82 g, 12.01 mmol) were added TBDPSCl (2.64 g, 9.6 mmol) and a catalytic amount (150 mg) of DMAP. The mixture was stirred for a further 10 h and then poured in water, the organic layer separated and the aqueous layer was extracted with $CHCl_3$. The combined organic extracts were washed with water, brine, and dried. Solvent removal under reduced pressure followed by column chromatography of the residue (Silica gel, 0–10% EtOAc in Hexane) afforded pure **5a** (4.19 g, yield 95%), as a colorless thick oil. $[\alpha]_D^{25} = +3.75$ (*c* 0.7, $CHCl_3$); ^{1}H NMR: δ 0.88 (t, *J* = 6.8 Hz., 3H), 1.0–1.2 (m, 27H), 1.3–1.6 (m, 10H), 3.63–3.78 (m, 2H), 3.86–3.93 (m, 1H), 4.08–4.17 (m, 1H), 7.25–7.43 (m, 6H), 7.67–7.71 (m, 4H). ^{13}C NMR: 14.1, 19.5, 22.7, 23.7, 23.8, 25.0, 25.2, 27.0, 29.3, 29.4, 29.50, 29.58, 29.66, 31.9, 32.7, 34.5, 36.0, 65.2, 74.2, 77.9, 109.7, 127.32, 127.36, 129.4, 134.3, 136.01, 136.07. Anal. Calcd for $C_{35}H_{54}O_3Si$: C, 76.31; H, 9.88. Found: C, 76.57; H, 9.55.

4.5. (2*R*,3*R*)-3-*O*-*tert*-Butydiphenylsilyl-tridecane-1,2,3-triol 6a

To a stirred and cooled (0 °C) solution of **5a** (4 g, 7.26 mmol) in CH_2Cl_2 (75 mL) was added 80% aqueous TFA (10 mL) in portions. After stirring the mixture for 2.5 h for completion of the reaction (by TLC), $NaHCO_3$ was added to decompose the excess TFA, followed by the addition of water. The mixture was extracted with $CHCl_3$. The combined organic extracts were washed with water and brine, and dried over Na_2SO_4. Solvent removal under reduced pressure followed by column chromatography (silica gel, 5% MeOH in $CHCl_3$) of the residue afforded pure **6**a (2.73 g, yield 80%). $[\alpha]_D^{25} = -20$ (*c* 0.8, $CHCl_3$); ^{1}H NMR: δ 0.86 (t, *J* = 6.8 Hz, 3H), 1.0–1.3 (m, 27H), 1.66 (br s, 2H), 3.5–3.8 (m, 4H), 7.3–7.5 (m, 6H), 7.7–7.9 (m, 4H). ^{13}C NMR: 14.0, 19.4, 22.6, 24.8, 27.0, 29.30, 29.38, 29.4, 31.8, 33.2, 64.3, 73.26, 73.84, 127.5, 127.7, 129.7, 129.8, 133.1, 133.6, 135.7, 135.8. Anal. Calcd for $C_{29}H_{46}O_3Si$: C, 73.99; H, 9.85. Found: C, 74.28; H, 9.62.

4.6. (2*R*,3*R*)-1,2-Epoxy-3-*O*-*tert*-butyldiphenylsilyl-tridecane-3-ol 8a

To a cooled (0 °C) solution of **6a** (2.7 g, 5.73 mmol) in pyridine (10 mL) containing DMAP (50 mg) was slowly added *p*-toluenesulfonylchloride (1.093 g, 5.73 mmol) over a period of two hours. The mixture was stirred at 0 °C for 2 h. After completion of the reaction (monitored with TLC), it was quenched by the addition of water and extracted with $CHCl_3$. The organic layer was washed successively with 5% aqueous HCl, water, brine, and then dried over Na_2SO_4. The solvent was removed under reduced pressure to obtain the crude residue which was quickly purified by passing through a short silica gel column eluting first with 10% diethyl ether in hexane and then with 5–15% EtOAc in hexane to obtain **7a** in quantitative yield. This was immediately dissolved in MeOH (15 mL) and mixed with solid K_2CO_3 (1.10 g, 8 mmol). The mixture was stirred at room temperature for three hours. The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$. The organic layer was washed successively with water, 5% aqueous HCl, water, brine, and then dried over Na_2SO_4. Solvent removal under reduced pressure and column chromatography of the residue (silica gel, 0–5% EtOAc in hexane) afforded pure compound **8a** (1.53 g, yield 85%) as a colorless liquid. $[\alpha]_D^{25} = -16.8$ (*c* 0.9, $CHCl_3$); ^{1}H NMR: δ 0.89 (t, *J* = 6.8 Hz., 3H), 1.0–1.5 (m, 27H), 2.44–2.46 (m, 1H), 2.70–2.74 (m, 1H), 3.03–3.07 (m, 1H), 3.33–3.67 (m, 1H). 7.2–7.4 (m, 6H), 7.6–7.7 (m, 4H). ^{13}C NMR: 14.1, 19.4, 22.7, 24.9, 26.9, 27.0, 29.3, 29.4, 29.5, 31.9, 34.7, 44.8, 55.6, 75.2, 127.40, 127.47, 129.5, 133.9, 134.2, 136.0. Anal. Calcd for $C_{29}H_{44}O_2Si$: C, 76.93; H, 9.80. Found: C, 77.19; H, 9.59.

4.7. (7*R*,8*R*)-2-Methyl-8-*O*-*tert*-butyldiphenylsilyl-7,8-octadecanediol 9a

A Grignard suspension of 1-bromo-4-methylpentane in THF (50 mL) was prepared from the bromide (1.64 g, 9.94 mmol) and Mg (0.29 g, 11.92 mmol) in the usual manner. The suspension was cooled (−50 °C) and Cu(I) bromide (0.712 g, 4.97 mmol) was added to it. The mixture was stirred for 15 min. To the resultant black suspension at −50 °C was added compound **8a** (1.5 g, 3.31 mmol) in THF (40 mL). The mixture was stirred at the same temperature for 1 h and then overnight at room temperature. The reaction was quenched by the addition of aqueous saturated NH_4Cl (10 mL) and extracted with EtOAc. The organic layer was washed with 5% aqueous HCl, water, brine, and then dried over Na_2SO_4. Solvent removal under reduced pressure and column chromatography of the residue (silica gel, 0–10% EtOAc in hexane) afforded pure **9a** (1.24 g, yield 70%) as a colorless liquid. $[\alpha]_D^{25} = +4.7$ (*c* 1.07, $CHCl_3$); ^{1}H NMR: δ 0.86 (m, 9H), 0.97–1.52 (m, 36H), 2.2 (br s, 1H), 3.53 (m, 1H), 3.6 (m, 1H). 7.2–7.4 (m, 6H), 7.6–7.7 (m, 4H). ^{13}C NMR: 14.0, 19.5, 22.6, 24.8, 26.0, 27.1, 27.3, 27.8, 29.2, 29.3, 29.4, 29.5, 31.8, 33.4, 33.9, 38.9, 72.7, 76.2, 127.4, 127.6, 129.6, 129.7, 133.5, 134.1, 135.9. Anal. Calcd for $C_{35}H_{58}O_2Si$: C, 78.00; H, 10.85. Found: C, 78.27; H, 10.62.

4.8. (−)-Disparlure Ib

To a cooled (0 °C) solution of **9a** (1.2 g, 2.23 mmol) in pyridine (8 mL) containing a catalytic amount (100 mg) of DMAP was slowly added *p*-toluenesulfonylchloride (0.51 g, 2.67 mmol). The mixture was stirred at 0 °C for 9 h. After the completion of the reaction (monitored with TLC), it was quenched by the addition of water and extracted with $CHCl_3$. The organic layer was washed successively with 5% aqueous HCl, water, brine, and then dried over Na_2SO_4. Removal of solvent under reduced pressure afforded the crude residue which was quickly purified by passing through a short silica gel and eluting first with 5% diethyl ether in hexane to remove unreacted *p*-toluenesulfonylchloride that was used in excess and then with 10% EtOAc in hexane to obtain **10a** in quantitative yield. Compound **10a** was found to be unstable on long standing and hence the majority of it was immediately used for the next reaction. However, a small portion of it was used for characterization. $[\alpha]_D^{25} = +6.5$ (*c* 2.6, $CHCl_3$); ^{1}H NMR: δ 0.84 (m, 9H), 1.0–1.2 (m, 36H), 2.41 (s, 3H), 3.84 (m, 1H), 4.43 (m, 1H), 7.2–7.6 (m, 14H). ^{13}C NMR: 14.0, 19.2, 21.4, 22.5, 22.6, 25.5, 26.9, 27.6, 27.9, 29.2, 29.3, 29.4, 31.8, 38.6, 72.7, 84.4, 127.4, 127.5, 127.6, 127.9, 129.4, 129.5, 129.6, 133.5, 133.7, 134.2, 135.9, 144.0.

To a solution of **10a** (1.35 g, 1.95 mmol) in 10 mL of THF was added TBAF (2.7 mL, 3.9 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 4 h at room temperature. After completion of the reaction (indicated by TLC), it was poured into water and extracted with ether. The combined ethereal extract

was washed with water and brine and dried over Na_2SO_4. Evaporation of solvent followed by column chromatography with (0–10% EtOAc in hexane) yielded pure **Ib** (0.41 g, yield 75%) a colorless oil. $[\alpha]_D^{25} = -1.1$ (*c* 1.4, CCl_4); lit.[5a] $[\alpha]_D^{25} = -1.0$ (*c* 1.7, CCl_4); ^{1}H NMR: δ 0.84–0.87 (m, 9H), 1.15–1.56 (m, 27H), 2.87–2.91 (m, 2H). ^{13}C NMR: 13.9, 22.4, 22.5, 26.5, 26.7, 27.2, 27.7, 27.8, 29.2, 29.4, 31.8, 38.8, 57.0.

4.9. (2*R*,3*R*)-1,2-*O*-Cyclohexylidene-3-*O*-benzyl-tridecane-1,2,3-triol 5b

To a suspension of sodium hydride (0.52 g, 50% suspension in oil, 10.77 mmol) and dry THF (50 ml), **4a** (2.8 g, 8.97 mmol) in dry THF (50 ml) was added dropwise over a period of 10 min under an argon atmosphere. The mixture was heated at 60 °C for 1 h that was accompanied with the liberation of H_2 gas. The mixture was cooled to room temperature followed by the addition of benzyl bromide (1.84 g, 10.77 mmol) in THF (50 ml) to it. The mixture was stirred for I h and then brought to 60 °C and heated for a further 2 h. On completion of the reaction (monitored with TLC), it was cooled with ice-water, quenched by the addition of water, and extracted with EtOAc. The organic layer was washed successively with water, 5% aqueous HCl, water, brine, and then dried over Na_2SO_4. Solvent removal under reduced pressure and column chromatography of the residue (silica gel, 0–10% EtOAc in hexane) afforded pure compound **5b** (3.25 g, yield 90%) as a colorless liquid. $[\alpha]_D^{25} = +16.9$ (*c* 1.5, $CHCl_3$); ^{1}H NMR: δ 0.89 (t, *J* = 6.6 Hz., 3H), 1.2–1.4 (m, 18H), 1.4–1.6 (m, 10H), 3.42 (m, 1H), 3.65–3.69 (m, 1H), 3.98–4.02 (m, 1H), 4.1–4.2 (m, 1H), 4.63 (d, *J* = 12.8 Hz, 1H), 4.82 (d, *J* = 12.8 Hz, 1H), 7.2–7.4 (m, 5H). ^{13}C NMR: 14.0, 22.6, 23.8, 24.0, 25.2, 25.5, 29.2, 29.5, 30.8, 31.8, 34.9, 36.3, 65.7, 72.9, 78.4, 80, 109.8, 127.4, 127.7, 127.9, 128.2, 138.9. Anal. Calcd for $C_{26}H_{42}O_3$: C, 77.56; H, 10.51. Found: C, 77.71; H, 10.27.

4.10. (2*R*,3*R*)-3-*O*-Benzyl-tridecane-1,2,3-triol 6b

To a stirred and cooled (0 °C) solution of **5b** (3.2 g, 7.95 mmol) in CH_2Cl_2 (50 mL) was added 80% aqueous trifluoroacetic acid (15 mL) in portions. The mixture was stirred for 2.5 h at 0 °C until its completion (by TLC). Solid $NaHCO_3$ (5 g) was added to it to decompose the excess TFA, followed by the addition of water. The mixture was extracted with $CHCl_3$. The combined organic extract was washed with water and brine, and dried over Na_2SO_4. Removal of the solvent in vacuum followed by column chromatography (silica gel, 5% MeOH in $CHCl_3$) of the residue afforded pure **6b** (2.05 g, yield 80%) as a colorless thick oil. $[\alpha]_D^{22} = +4.5$ (*c* 2.01, $CHCl_3$); ^{1}H NMR: δ 0.88 (t, *J* = 6.6 Hz., 3H), 1.2–1.4 (m, 18H), 2.09 (s, 2H), 3.64–3.66 (m, 4H), 4.47 (d, *J* = 12.8 Hz, 1H), 4.68 (d, *J* = 11.3 Hz, 1H), 7.2–7.4 (m, 5H). ^{13}C NMR: 14.1, 22.7, 25.3, 29.3, 29.6, 29.9, 30.3, 31.9, 64.0, 72.4; 73.2, 79.9, 127.8, 127.9, 128.4, 138.3. Anal. Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.75; H, 10.37.

4.11. (2*R*,3*R*)-1,2-Epoxy-3-*O*-benzyl-tridecane-3-ol 8b

To a cooled (0 °C) solution of **6b** (2 g, 6.21 mmol) in pyridine (10 mL) containing DMAP as a catalyst was added *p*-toluenesulfonylchloride (1.18 g, 6.21 mmol). The mixture was stirred at 0 °C for 2 h. After completion of the reaction (monitored with TLC), it was quenched by the addition of water and extracted with $CHCl_3$. The organic layer was washed successively with 5% aqueous HCl, water, brine, and then dried. The solvent was removed under reduced pressure to obtain the crude residue which was quickly purified by passing through a short plug of silica gel and eluting with 5–15% EtOAc in hexane to obtain **7b** in quantitative yield. This was immediately dissolved in MeOH (20 mL) and mixed with solid K_2CO_3 (1.2 gm, 8.68 mmol). The mixture was stirred at room temperature for three hours. The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$. The organic layer was washed successively with water, 5% aqueous HCl, water, brine, and then dried over Na_2SO_4. The solvent was removed under reduced pressure and column chromatography of the residue (silica gel, 0–5% EtOAc in hexane) afforded pure compound **8b** (1.08 g, yield 85%) as a colorless liquid. $[\alpha]_D^{25} = +16.7$ (*c* 1.08, $CHCl_3$); ^{1}H NMR: δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.2–1.5 (m, 18H), 2.47–2.50 (m, 1H), 2.7–2.8 (m, 1H), 3.02 (m, 2H), 4.58 (d, *J* = 11.8 Hz, 1H), 4.84 (d, *J* = 11.3 Hz, 1H), 7.2–7.4 (m, 5H). ^{13}C NMR: 13.9, 22.5, 25.4, 29.2, 29.5, 31.8, 32.3, 42.9, 54.9, 71.5, 80.4, 127.2, 127.6, 128.1, 138.7. Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 78.70; H, 10.81.

4.12. (7*R*,8*R*)-2-Methyl-8-*O*-benzyl-7,8-octadecanediol 9b

Following the same procedure as reported for the preparation of **9a**, $(CH3)_2CH(CH_2)_2CH_2MgBr$, prepared from Mg (0.28 g, 11.82 mmol), 1-bromo-4-methylpentane (1.63 g, 9.85 mmol) in THF (25 mL) was reacted with Cu(I) bromide (0.72 g, 5.01 mmol) at −50 °C. To the resultant black suspension at −50 °C was added **8b** (1 g, 3.28 mmol) in THF (30 mL). After the usual work up and solvent removal under reduced pressure, the residue was purified by column chromatography (silica gel, 0–5% EtOAc in hexane) to obtain pure **9b** (0.9 g, yield 70%) as a colorless liquid. $[\alpha]_D^{25} = +10.3$ (*c* 1.16, $CHCl_3$); ^{1}H NMR: δ 0.87 (m, 9H), 1.2–1.7 (m, 27H), 1.77 (s, 1H), 3.24 (m, 1H), 3.57 (m, 1H), 4.47 (d, *J* = 12.8 Hz, 1H), 4.66 (d, *J* = 11.3 Hz, 1H), 7.2–7.3 (m, 5H). ^{13}C NMR: 14.1, 22.5, 25.1, 25.9, 27.3, 27.8, 29.2, 29.5, 29.8, 30.2, 31.8, 33.4, 38.9, 72.3; 72.6, 82.3, 127.5, 127.7, 128.3, 138.5. Anal. Calcd for $C_{26}H_{46}O_2$: C, 79.94; H, 11.87. Found: C, 79.71; H, 11.69.

4.13. (7*R*,8*R*)-2-Methyl-7-*O*-*tert*-butyldimethylsilyl-7,8-octadecanediol 11a

To a stirred solution of **9b** (0.9 g, 2.30 mmol) and *tert*-butyldimethylsilyl chloride (0.41 g, 2.76 mmol) in CH_2Cl_2 (50 mL) was added imidazole (0.24 g, 3.45 mmol). The mixture was stirred for a further 10 h at room temperature and treated with water. The organic layer was separated and washed with water, brine, and dried. Solvent removal under reduced pressure afforded the residue which was purified by column chromatography (silica gel, 0–10% EtOAc in petroleum ether) to afford compound **10b** (1.04 g, yield 90%).

To a solution of **10b** (1 g, 1.98 mmol) in ethanol (10 mL) was added activated 10% Pd/C (50 mg). The reaction mixture was stirred under a hydrogen atmosphere (balloon) for 3 h at room temperature. After completion of the reaction (TLC), it was filtered through a short pad of Celite which was then thoroughly washed with diethyl ether. Solvent removal under reduced pressure and column chromatography (silica gel, 0–10% EtOAc in hexane) of the residue afforded a known **11a** (0.69 g, yield 85%) in pure form as an oil. $[\alpha]_D^{25} = -4.2$ (*c* 2.8, $CHCl_3$); lit[5a] $[\alpha]_D^{25} = -3.8$ (*c* 3.2, $CHCl_3$); ^{1}H NMR: δ 0.06 (s, 6H), 0.87 (m, 9H), 1.2–1.5 (m, 36H), 1.77 (s, 1H), 3.45 (m, 2H). ^{13}C NMR: −4.6, −4.1, 14.0, 18.1, 22.5, 22.6, 25.3, 25.9, 27.6, 27.9, 29.3, 29.6, 29.7, 31.9, 33.9, 34.1, 38.9, 72.7; 75.2.

4.14. (+)-Disparlure Ia

To a cooled (0 °C) solution of **11a** (0.65 g, 1.57 mmol) in pyridine (4 mL) containing DMAP as a catalyst was slowly added *p*-toluenesulfonylchloride (0.328 g, 1.723 mmol). The mixture was stirred at 0 °C for 6 h. After completion of the reaction (monitored with TLC), it was quenched by the addition of water and extracted with $CHCl_3$. The organic layer was washed successively with 5%

aqueous HCl, water, brine, and then dried. The solvent was removed under reduced pressure to obtain the crude residue which was quickly purified by passing through a short silica gel and eluting first with 5% EtOAc in hexane to remove the *p*-toluenesulfonylchloride that was used in excess and then with (0–10% EtOAc in hexane) to obtain **11b** in quantitative yield.

To a solution of **11b** (0.70 g, 1.23 mmol) in THF (5 mL) was added TBAF (1.4 mL, 2.46 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 5 h at that temperature and then for 1 h more at room temperature. It was poured into water and extracted with diethyl ether. The combined ethereal extract was washed successively with water, brine, and dried over Na_2SO_4. Solvent removal under reduced pressure afforded the residue which was purified by column chromatography (silica gel; 0–10% EtOAc in hexane) to afford pure **Ia** (0.26 g, yield 75%). $[\alpha]_D^{25} = +1.1$ (*c* 1.7, CCl_4); lit.[5a] $[\alpha]_D^{25} = +1.0$ (*c* 1.5, CCl_4); ^{1}H NMR: δ 0.84–0.87 (m, 9H), 1.11–1.59 (m, 27H), 2.86–2.90 (m, 2H). ^{13}C NMR: 14.0, 22.5, 22.6, 26.5, 26.8, 27.2, 27.8, 29.2, 29.5, 31.8, 38.9, 57.1.

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