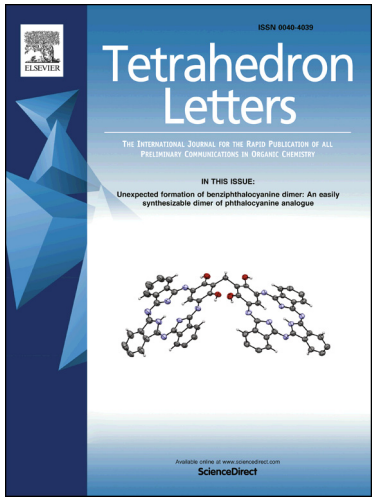

Enantioselective total synthesis of *cis*-(+)- and *trans*-(+)-disparlure

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Enantioselective total synthesis of *cis*-(+)- and *trans*-(+)-disparlure

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Dedicated to Dr. Pradeep Kumar (CSIR-NCL, Pune, India) on his 60th Birthday.

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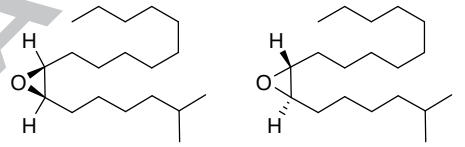
ABSTRACT

An expedient enantioselective synthetic approach for the gypsy moth sex-attractant pheromone *cis*-(+)-**1** and *trans*-(+)-disparlure **2** is described employing the optimized combination of organocatalytic MacMillan's self aldol reaction, Wittig olefination, regioselective ring opening of an epoxide and Mitsunobu esterification reactions as key steps.

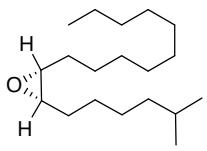
Introduction

Over the last decades, *cis*-(+)-disparlure **1** has been used worldwide as a pesticide against the gypsy moth, *Lymantria disar L.*, a widespread pest causing damage to the wild ecosystem of Europe, Africa, and North America (Figure 1).[1] The straight chain lepidopteran sex pheromone *cis*-(+)-disparlure **1** was isolated by Bierl and co-workers from the *Porthetria disar L.*, female gypsy moths.[2] Iwaki and co-workers established the absolute configuration of *cis*-(+)-disparlure **1** *via* its synthesis from (*S*)-glutamic acid.[3] The *cis*-(+)-disparlure **1** is required for the upwind flight of male moths to the pheromone releasing females and binds selectively to PBP1 protein, while the *cis*-(-)-disparlure **3** cancels the upwind flight behavior in the males which binds selectively to PBP2 protein of gypsy moth.[4]

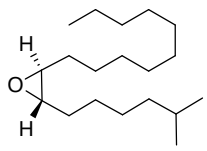


(*R*,*S*)-(+)-disparlure **1**

(*R*,*R*)-(+)-disparlure **2**



(*S*,*R*)-(-)-disparlure **3**



(*S*,*S*)-(-)-disparlure **4**

Figure 1: Structures of stereoisomers of disparlures (**1**-**4**).

Therefore, *cis*-(+)-disparlure **1** has been used to confuse and preventing male moths from locating and mating with females or leading male moths into traps for the protection of forests.[5] The *cis*-(+)-disparlure **1** and its analogues (**2**-**4**) have been synthetic targets of considerable interest for academia and agriculture due to their astonishing biological properties combined with attractive structural features. Various elegant syntheses of *cis*-(+)-disparlure **1** and its analogues (**2**-**4**) mainly based on chiral pool approaches have been documented in the literature.[6] Very recently, Fernandes and co-workers reported the stereoselective synthesis of *cis*-(+)-disparlure **1** and its analogues (**2**-**3**) using a domino Pd-catalyzed recombinant γ-isomerization/Wacker oxidation reactions of γ-vinyl-γ-butyrolactone as key steps.[6a] As part of our research program towards the asymmetric synthesis of bioactive compounds,[7] we report herein, a novel synthesis of *cis*-(+)-**1** and *trans*-(+)-disparlure **2** employing the MacMillan's self aldol reaction, Wittig olefination, regioselective ring opening of an epoxide and Mitsunobu esterification reactions as key steps.

Results and Discussion

Our synthetic approach for the enantioselective synthesis of disparlure (**1**-**4**) was envisioned *via* the retrosynthetic route as shown in Scheme 1. The epoxide derivative **5** was visualized as a synthetic intermediate from which disparlure (**1**-**4**) could be synthesized *via* Grignard reaction followed by functional group manipulations. The epoxide derivative **5** in turn could be obtained from triol derivative **6** *via* terminal epoxide formation and subsequent standard organic transformations. The triol derivative **6** could be assembled from mono-protected terminal alcohol **7** by oxidation followed by MacMillan's self-aldol

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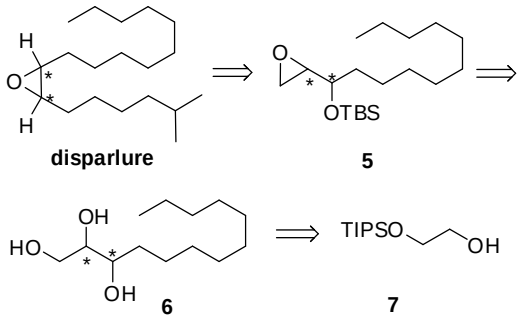
reaction and subsequently Wittig olefination. All the stereoisomers of disparlure (**1**-**4**) could be synthesized using this approach by simply changing the L- and D-proline, respectively, during organocatalyzed MacMillan's self aldol reaction and/or by Mitsunobu inversion reaction.

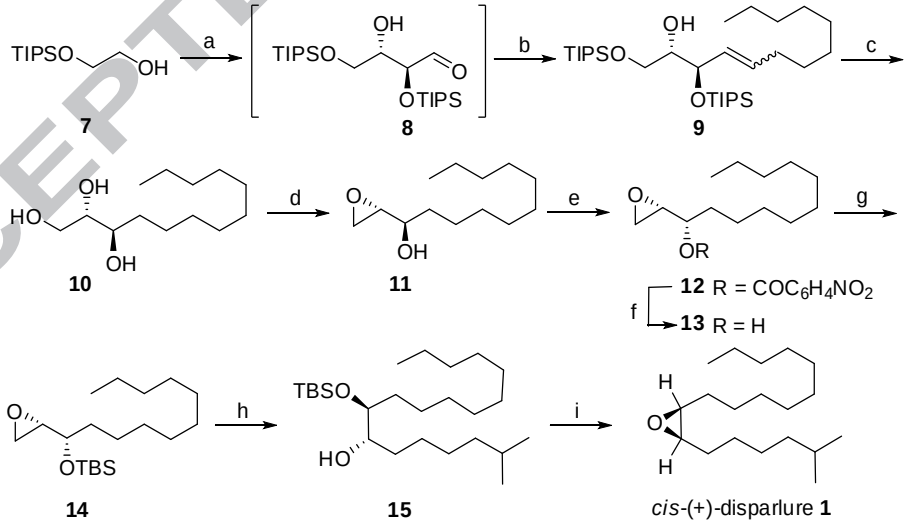


Scheme 1: Retrosynthetic approach for disparlure (**1**-**4**).

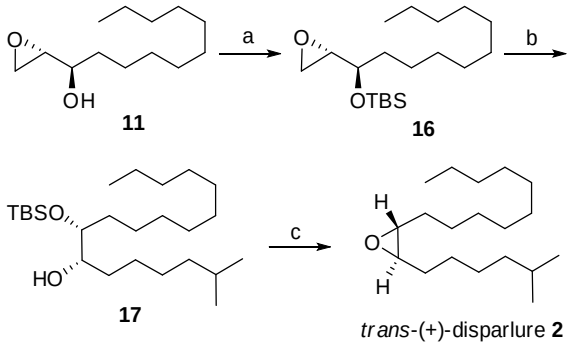
As outlined in Scheme 2, the synthesis of *cis*-(+)-disparlure **1** commenced with readily available monosilylated ethylene glycol **7**, which can be easily synthesized from base catalyzed selective protection of ethylene glycol with TIPSCl. Oxidation of monosilylated alcohol **7** under Swern conditions,[8] subsequent asymmetric MacMillan's self aldol reaction in the presence of catalytic amount of L-proline afforded the *anti*-diastereomer **8** as the major product along with its column separable *syn*-diastereomer in 4:1 ratio and 90% combined isolated yield, following the known literature procedure.[9] With enantiomerically pure *anti*-diastereomer **8** in hand, it was then subjected to Wittig olefination with (nonyl)triphenylphosphonium bromide using KHMDS to furnish the olefin **9** in 65% yield. Since the incipient olefin would be eventually hydrogenated for the synthesis of the target compound, we did not analyse the olefin geometry of **9**.

The cleavage of silyl ether in compound **9** with TBAF and subsequent hydrogenation under 1 atm pressure in the presence of a catalytic amount of Pd/C furnished the triol derivative **10** in 90% yield. Our next endeavour was to carry out the terminal epoxide formation using 1,2-diol. Towards this end, triol **10** on base catalyzed selective monotosylation with $TsCl/NEt_3$ in the presence of catalytic amount of dibutyltin oxide followed by base treatment delivered the terminal epoxide **11** in 76% yield. The free hydroxyl group of compound **11** on treatment with *p*-nitrobenzoic acid (PNBA) and diisopropyl azodicarboxylate (DIAD) under the Mitsunobu esterification conditions successfully furnished the ester **12**, which on basic hydrolysis synthesized the inverted alcohol **13** in 95% yield. Treatment of alcohol **13** with TBSCl using the basic conditions of imidazole/DMAP synthesized the protected derivative **14** in 89% yield. The epoxide **14** on Cu(I)-catalyzed regioselective ring-opening with *iso*-hexylMgBr at -60 °C, furnished the alcohol **15** in 81% yield. Finally, the free hydroxyl group of compound **15** was subjected to *O*-tosylation using TsCl/DMAP and subsequent silyl ether cleavage using TBAF delivered the sex pheromone *cis*-(+)-disparlure **1** in 85% yield {$[\alpha]_D^{25}$ +1.2 (*c* 1.1, CCl_4) [Lit.[6a] +1.6 (*c* 1.1, CCl_4)]}. The spectroscopic and physical data of *cis*-(+)-disparlure **1** were found to be in full accordance with those documented in the literature.[3,6]

For synthesis of *trans*-(+)-disparlure **2**, the free hydroxyl group of compound **11** on treatment with TBSCl under the basic conditions of imidazole/DMAP furnished the silyl ether derivative **16** in 87% yield (Scheme 3). The *trans*-(+)-disparlure **2** was synthesized from compound **16** following an analogous series of reactions as shown in Scheme 2, {$[\alpha]_D^{25}$ +27.8 (*c* 0.5, CCl_4) [Lit.[3] +27.5 (*c* 0.5, CCl_4)]}. The spectroscopic and physical data of *trans*-(+)-disparlure **2** were found to be in full accordance with the literature data.[3,6]



Scheme 2: *Reagents and conditions*: (a) i) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78 °C, 2 h, ii) L-proline (10 mol%), DMF, rt, 24 h, 72%; (b) KHMDS, $C_9H_{19}PPh_3Br$, THF, -78 °C to rt, 4 h, 65%; (c) i) TBAF, THF, rt, 12 h; ii) H_2, Pd/C, EtOAc, rt, 8 h, 90% (over two steps); (d) i) TsCl, NEt_3, Bu_2SnO (10 mol%), dry CH_2Cl_2, 0 °C to rt, 2 h, ii) KOH, Et_2O, rt, 12 h, 76% (over two steps); (e) PPh_3, PNBA, DIAD, toluene, 0 °C to rt, 2 h, 97%; (f) $LiOH.H_2O$, THF:MeOH:H_2O (3:2:1), rt, 1 h, 95%; (g) TBSCl, imidazole, DMAP, dry CH_2Cl_2, 0 °C to rt, 14 h, 89%; (h) *iso*-hexylMgBr, dry THF, CuI, -60 °C, 6 h, 81%; (i) i) TsCl, DMAP, dry CH_2Cl_2, 0 °C to rt, 24 h, ii) TBAF, THF, rt, 6 h, 85% (over two steps).



Scheme 3. *Reagents and conditions*: (a) TBSCl, imidazole, DMAP, dry CH_2Cl_2, 0 ^oC to rt, 14 h, 87%; (b) *iso*-hexylMgBr, dry THF, CuI, -60 ^oC, 6 h, 85%; (c) i) TsCl, DMAP, dry CH_2Cl_2, 0 ^oC to rt, 24 h, ii) TBAF, THF, rt, 6 h, 84% (over two steps).

In conclusion, enantioselective synthesis of *cis*-(+)-**1** and *trans*-(+)-disparlure **2** have been achieved from readily available starting materials employing the organocatalyzed MacMillan's self aldol reaction, Wittig olefination, regioselective ring opening of an epoxide and Mitsunobu esterification reactions as key steps. Moreover, the synthetic strategy described has significant potential for stereochemical variation and gives further access to other stereoisomers as well as various other analogues of disparlure.

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Supplementary Material

Supplementary Supplementary material (detailed experimental and spectral analysis) associated with this article can be found in the online version, at http://....

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Highlights

1. *cis*-(+)-Disparlure, a female gypsy moths sex pheromone
2. A concise and efficient asymmetric general approach for disparlure
3. Organocatalytic MacMillan's self aldol reaction and Wittig olefination key steps
4. Regioselective ring opening of an epoxide and Mitsunobu esterification reactions