Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 3773–3784

Synthesis of disparlure analogues, using resolution on microcrystalline cellulose triacetate-I

James A. H. Inkster,[a] Ivy Ling,[b] Nicolette S. Honson,[b] Loïc Jacquet,[c] Regine Gries[d] and Erika Plettner[b,*]

[a]*TRIUMF, 4004 Wesbrook Mall, Vancouver, B.C., Canada V6T 2A3*
[b]*Department of Chemistry, Simon Fraser University, 8888 University Drive, Burnaby, B.C., Canada V5A 1S6*
[c]*Camfil-Farr France, 77l81 Bld de la République, 92257 La Garenne Colombes Cedex, France*
[d]*Department of Biological Sciences, Simon Fraser University, 8888 University Drive, Burnaby, B.C., Canada V5A 1S6*

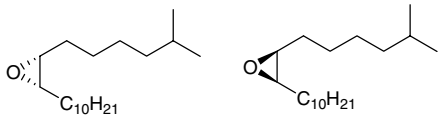
Received 18 June 2005; accepted 18 October 2005

Abstract—The gypsy moth, *Lymantria dispar*, uses a chiral epoxide, (+)-(7*R*,8*S*)-2-methyl-7,8-epoxyoctadecane, (+)-disparlure, as its main sex attractant. The moths can detect both enantiomers of disparlure and respond differently to each one. In an effort to understand the structure–activity relationships of the gypsy moth olfactory system, we prepared the analogues of (+)- and (−)-disparlure. The key intermediate in route to the analogues was 2-epoxytridecan-1-ol. Herein we report the resolution of 2-epoxytridecan-1-yl esters on microcrystalline cellulose triacetate and the synthesis of 5-oxa and (5*Z*)-ene analogues of (+)- and (−)-disparlure. An effort to make 5-aza analogues resulted in the formation of *anti*-5-(1-hydroxy-1-undecyl)-3-(3-methylbutyl)oxazolidin-2-one. The analogues were tested for their electroantennogram responses and for their ability to bind to pheromone-binding protein 1 (PBP1). We found that the 5-oxa analogues gave strong responses and that the antenna and the PBP1 no longer distinguish the enantiomers of the 5-oxa analogues. The analogues all bound the PBP1 with similar affinity to (−)-disparlure.

1. Introduction

The main component of the gypsy moth, *Lymantria dispar*, sex attractant pheromone is (+)-(7*R*,8*S*)-epoxy 2-methyloctadecane [(+)-disparlure], (+)-**1**.[1–3] This compound is required for upwind flight of male moths to the pheromone-emitting females. The enantiomer (−)-**1** is neither attractive nor repellent by itself, but when presented simultaneously with (+)-**1**, it cancels upwind flight behavior in the males.[4] Studies on the olfactory mechanisms of these moths have revealed that there are distinct neurons, housed in separate populations of sensory hairs, that respond to one of the two disparlure enantiomers.[2] Furthermore, the two pheromone-binding proteins (PBPs) of the gypsy moth bind both enantiomers, although PBP1 prefers to bind (−)-**1**, while PBP2 prefers to bind (+)-**1**.[5]

Disparlure enantiomers have been synthesized individually by asymmetric epoxidation[6–8] or asymmetric dihydroxylation.[9] Compound (+)-**1** has also been prepared from L-(+)-tartaric acid,[10,11] (−)-2-deoxy-D-ribose,[12] (*S*)-(+)-glutamic acid,[13] and tri-*O*-acetyl-D-galactal.[14] Chiral auxiliaries have also been used in several syntheses.[6,7,9,15,16] The resolutions of key intermediates have also been reported, for example, pig pancreatic lipase has been used to resolve 1,4-diacetoxy-*cis*-2,3-epoxybutane;[17] Amano PS lipase has been used to resolve (*syn*)-ethyl-3-chloro-2-hydroxytridecanoate;[18] *cis*-4-bromo-2,3-epoxybutyl-(1*S*)-10-camphorsulfonate diastereomers have been resolved by fractional crystallization and are now available commercially,[19] and β-hydroxysulfide intermediates have been resolved as (*R*)-1-(1-naphthyl)ethyl isocyanate derived carbamates.[20] We chose to resolve *cis*-2,3-epoxytridecan-1-yl *p*-bromobenzoate **2c** on microcrystalline cellulose triacetate I (MCTA-I). Herein, we report the synthesis of both



(+)-1 **(-)-1**

* Corresponding author. Tel.: +1 604 291 3586; fax: +1 604 291 3765; e-mail: plettner@sfu.ca

0957-4166/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.10.031

enantiomers of several disparlure analogues, using ester **2c** resolved on MCTA-I. We also report the electrophysiological and pheromone-binding protein 1 (PBP1) binding activity of the analogues.

2. Results and discussion

2.1. Resolution on MCTA-I

MCTA-I is a widely used, economical chiral stationary phase for both analytical and preparative separations.[21–23] Structure–activity relationships have been undertaken with derivatives of *trans*-2-phenyl-1-cyclohexanols, glycerol, 1-phenyl-2-propanol, 3-phenyl-1,2-propanediol (chromatographed as the 1,3-dioxanes), 1,2- and 1,3-diols, 2,3-epoxypropan-1-ol (oxyranylmethanol), 4-hydroxy-cyclopent-2-enone,[23] and γ- and δ-lactones.[22] A variety of compounds with aryl moieties have also been separated.[24] Apart from a pyranyl diol,[25] 1-fluorenyl-1-ethanol and 1′-ethyl-2′,2′,2′-trifluoroethylanthracene,[26] alcohols generally do not separate readily on MCTA-I, although the corresponding benzoate esters have been found to separate cleanly.[21,23] Within one series of aryl-containing compounds, a relationship was seen with respect to the electronic and/or steric character of the substituent on the aryl moiety. Amongst the benzoate esters, *p*-chloro and *p*-bromo esters often ranked highly in their separation and resolution factors. Usually within a series, the elution order of the enantiomers remained constant across the series.[23] Both shape and electronic interactions appear to govern the extent to which enantiomers separate on MCTA-I.[23,24,27]

Our results with esters **2a**,**b**, and **2c** are consistent with these previous studies, with the enantiomers of the *p*-bromobenzoate separating best and the enantiomers of the acetate separating least (Table 1), with the (−)-enantiomer eluting first always. Alcohol **3** was retained, but did not separate on MCTA-I (Table 1). The *p*-bromobenzoates separated with near-baseline resolution, and the pooled fractions of each enantiomer had none of the opposite enantiomer detectable by the GC method. From the specific rotation and the MTPA ester of alcohol (−)-**3**, the ee of its precursor, ester (+)-**2c**, must have been ⩾97%. Ester (−)-**2c** had a similarly high ee, as could be inferred from the MTPA ester of alcohol (+)-**3** and the similar rotations of opposite sign obtained for ethers (−)-**5** and (+)-**5**, and epoxides (−)-**7** and (+)-**7**, obtained from (−)-**3** and (+)-**3**, respectively (Scheme 1).

2.2. Synthesis of disparlure and the analogues

Ester **2c** could be readily saponified, without significant Payne rearrangement.[28,29] Alcohol **3** was then converted to ether **5** by deprotonation of the alcohol with NaH, followed by reaction with the primary alkyl bromide to furnish the ether. Similar conditions have been used previously to alkylate 2,3-epoxy primary alcohols in high yield.[29] Alcohol **3** was also converted to aldehyde **6**. Aldehyde **6** was sufficiently stable to be purified by flash chromatography, but it could not be stored for extended periods of time. Thus, intermediate **6** was reacted immediately in the next step, either via a Wittig reaction to give **7** or a reductive amination to afford **8**. During purification of compound **8** by flash chromatography, oxazolidinone **9** was formed by absorption of CO_2 from air (Scheme 2). Compound **9** accumulated as a white solid in the fractions. A similar reaction with CO_2 has been reported for allylamines reacted with I_2 under a CO_2 atmosphere.[30] The approach used here gave epoxy alcohols (+)-**3** and (−)-**3** in high enantiomeric purity (⩾97% ee). Furthermore, ^{1}H NMR data of the MTPA esters **4a** and **4b** of alcohols (−)-**3** and (+)-**3**, respectively, were consistent with previously reported data,[8] while the specific rotations of (−)-**3**, (+)-**7**, and (−)-**7** are in accordance with previously reported values.[6,8,14]

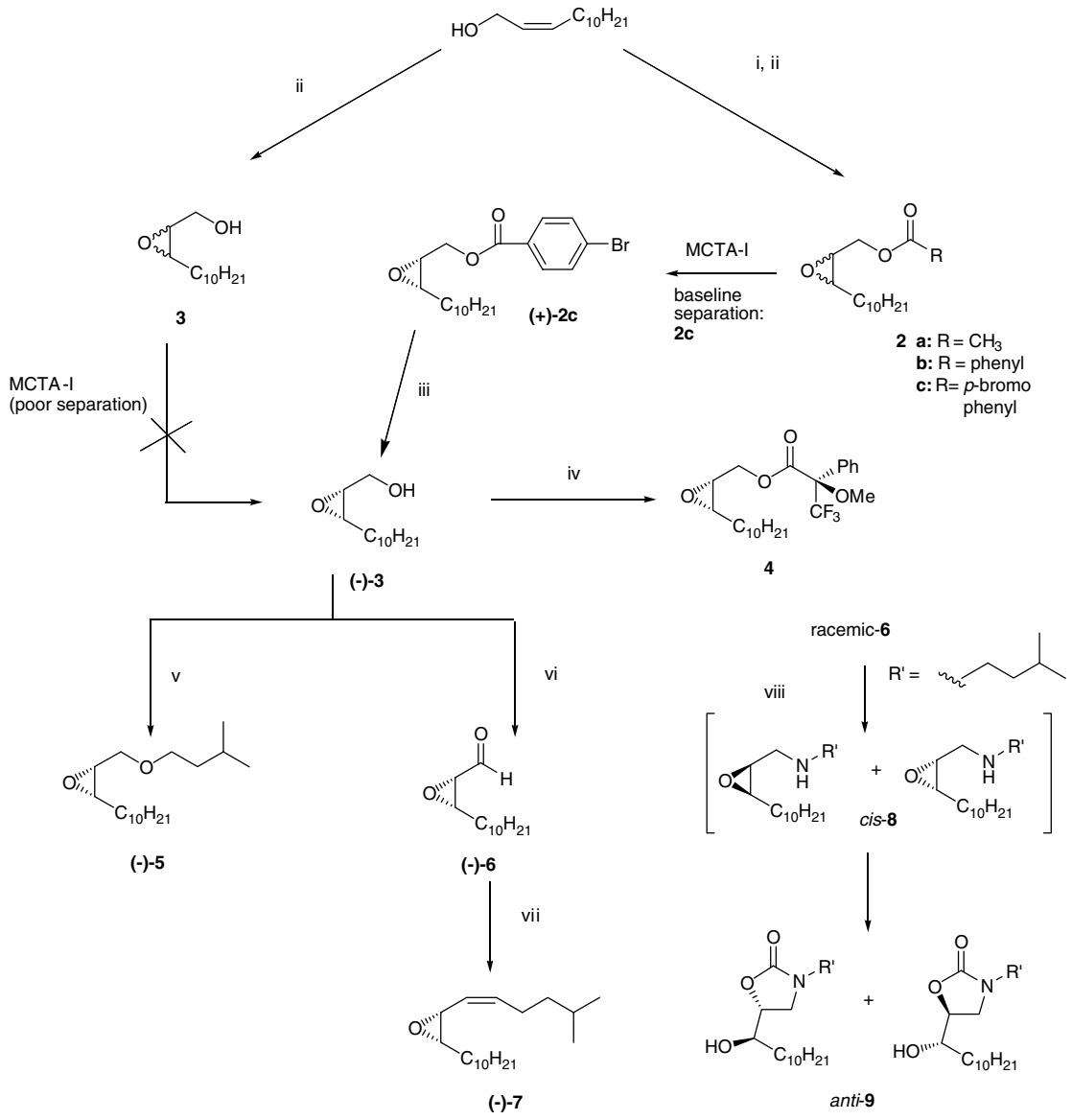
Table 1. Separation of esters **2a**–**c** and alcohol **3** on MCTA-I

Compound	Column[a]	Temperature (°C)	Solvent	Flow (mL/min)	Retention times (h)	R[b]	α[c]
2a	Medium	30	Ethanol–water 9:1	0.1	3.5 3.8	0.2	1.1
2b	Medium	30	Ethanol–water 9:1	0.1	4.7 5.3	0.7	1.1
2c	Medium	30	Ethanol–water 9:1	0.1	6.3 9.5	1.0	1.5
3	Medium	20	Hexane–ether 4:1	0.1	11 13	0.6	1.2
2c	Large	50	Ethanol–water 9:1	1.0	6.5 8.4	1.1	1.3
2c	Large	50	Ethanol–water 9:1	0.5	13.8 16.8	1.1	1.2
2c	Large	50	Ethanol–water 9:1	0.5	14.3 18.3	1.0	1.3

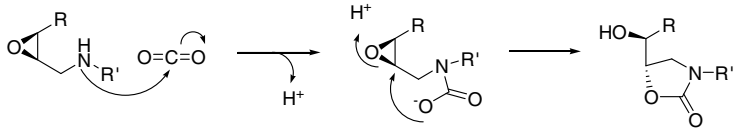
[a] See text; the medium-sized column was used to separate 10–30 mg, and the large column was used to separate typically 100–200 mg of racemic material.

[b] Resolution (R), estimated as = separation between peaks/(1.7 × average peak width at half height).[21]

[c] Separation factor $\alpha \approx$ retention time (late)/retention time (early).[21] Strictly, the separation factor α is the ratio of the retention factors, $k = (t - t_o)/t_o$, where t is the retention time of the compound and t_o is the retention time of an unretained substrance. However, we do not know any substance that is completely unretained on MCTA-I.[38]



Scheme 1. Synthesis of disparlure analogues from ester **2c**, resolved on a column of microcrystalline cellulose triacetate I (MCTA-I). Reagents and conditions: (i) the appropriate acyl chloride, pyridine, CH_2Cl_2, DMAP; (ii) *m*-CPBA; (iii) 1 M KOH in EtOH; (iv) MTPA-Cl, pyridine, CCl_4; (v) (1) NaH in DMF, (2) $(CH_3)_2CH(CH_2)_2Br$; (vi) PCC, CH_2Cl_2; (vii) (1) $(Ph)_3P(CH_2)_3CH(CH_3)_2$, THF, *n*-BuLi; (2) **6**; (viii) (1) $(CH_3)_2CH(CH_2)_2NH_2$, CH_2Cl_2, molecular sieves; (2) $NaBH_4$, MeOH.



Scheme 2. Possible mechanism of oxazolidinone **9** formation by reaction of **8** with CO_2.

2.3. Physiological and biochemical assays

The analogues were tested by GC-electroantennographic detection (GC-EAD); the only compounds that gave a signal were ether analogues (−)-**5** and (+)-**5** (Table 2). The dose–responses for the analogues were obtained from electroantennogram (EAG) recordings (Fig. 1). EAG traces reveal the summed responses from sensory hairs located between the reference and recording electrodes.[31] The dose–response for (−)-**5** [the ether analogue of (+)-**1**] was slightly lower overall than the dose–response for (+)-**1** (Fig. 2). This response pattern can also be seen in the saturation study (Table 3), where (−)-**5** gave smaller responses than (+)-**1** with respect to depolarization, hyperpolarization and recovery time (all $P < 0.05$, *t*-test). The analogue of (−)-**1**, (+)-**5**,

Table 2. GC-electroantennogram detector (GC-EAD) responses

Compound[a]	Response[b]
(+)-Disparlure **1**	++++
(−)-Disparlure **1**	+++
(−)-Ether **5**	++
(+)-Ether **5**	+
(−)-(5*Z*)-Ene **7**	None
(+)-(5*Z*)-Ene **7**	None
(±)-Oxazolidinone **9**	None
(−)-**3**	None
(+)-**3**	None

[a] 100 ng of each compound was injected.
[b] '+' Indicate that a GC-EAD peak was observed at the correct retention time. The number of '+' indicates the relative magnitude of the response. At least four injections were done for each compound.

showed a similar dose–response to (−)-**1** (Fig. 2), which was weaker than the response towards (+)-**1** (Table 3, depolarization, hyperpolarization, and recovery time, all $P < 0.05$, *t*-test) and not significantly different from the response to (−)-**5** (Table 3, depolarization, hyperpolarization, and recovery time, all $P > 0.05$, *t*-test). Thus, the introduction of the oxygen atom at the 5-position of the pheromone structure lowered the ability of the moth antenna to distinguish between the enantiomers of compound **5**, compared to the biologically active compounds (+)-**1** and (−)-**1** (Fig. 2, Table 3). The (5*Z*)-alkene analogues (−)-**7** and (+)-**7** gave no GC-EAD response and the EAG responses did not differ from hexane controls. Thus, (−)-**7** and (+)-**7** were not investigated further. Racemic oxazolidinone **9** showed no significant increase in the response to increasing the dose (Fig. 2). General odorants gave much weaker responses than epoxides **1**, ethers **5**, or oxazolidinone **9** (Fig. 2).

We hoped to find compounds that interfered with pheromone signaling in one or more insect species. Such interference could occur on two levels: (1) the peripheral level, where the compound would interfere with one (or more) molecular process(es) in the antenna of the insect and cause adaptation, or (2) the level of the brain, where the downstream response of pheromone olfactory neurons would be impaired by the perception of the compound. The latter mechanism is utilized by insects in recognition of pheromone blends from other related species.[32,33] Adaptation should manifest itself in EAG experiments, in which the analogue and pheromone (+)-**1** are passed in an alternating fashion over an antenna. If inhibition is successful, then one expects decreased depolarization, decreased hyperpolarization and increased recovery times for both (+)-**1** and the test compound. None of the analogues tested caused significant decreases in depolarization and hyperpolarization. Furthermore none of the analogues caused a significant increase in recovery times (Table 3, all $P > 0.05$, *t*-test). Thus, none of the compounds tested were a potential olfactory inhibitor at the peripheral level, even though the compounds bind to the pheromone-binding protein (see below). The second form of olfactory inhibition, at the level of the brain, should manifest itself in behavioral and field tests. Such inhibition requires that the test compound be detected by the insect. Ethers (+)-**5** and (−)-**5** are good candidates for this type of olfactory inhibition, because they give significant EAG responses by themselves (Fig. 2, Table 3). These two compounds will be tested further in future experiments.

The pheromone-binding proteins (PBPs) in the sensillar lymph are the first components of the insect olfactory system that interact with the pheromone.[34] We screened analogues that showed EAG activity for their ability to bind PBP1. We used a fluorescent probe displacement assay, that can quickly give a ranking of kinetic affinity of a PBP for various ligands.[35] PBP1 bound the fluorescent probe with good affinity (1.5 μM) while PBP2 did not bind the probe. PBP1 is the more discriminatory of the two PBPs, and binds preferentially (−)-**1**.[5] Interestingly, PBP1 binds (−)-**5** and (+)-**5** with nearly the same affinity as (−)-**1** (Table 4). The affinity of PBP1 for (+)-**1** was much weaker than for (−)-**1**, consistent with what is known about this PBP from equilibrium binding assays.[5] Oxazolidinone **9** also bound to PBP1, with approximately the same affinity as (7*Z*) 2-methyl-

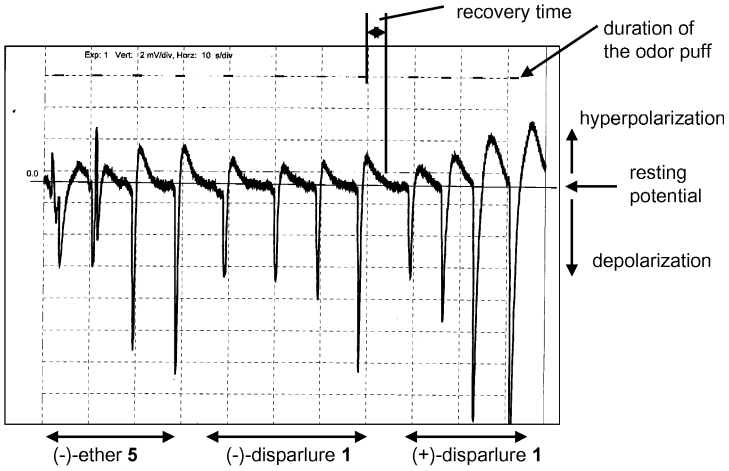


Figure 1. Electroantennogram (EAG) experiment. The four peaks in each group correspond to 1, 10, 100, and 1000 ng of the odorant applied to a filter paper and delivered to the antenna in a puff of air. The first odorant in this case was (−)-**5**, the second was (−)-**1** and the third was (+)-**1**. The duration of the air puffs is indicated by the bars at the top.

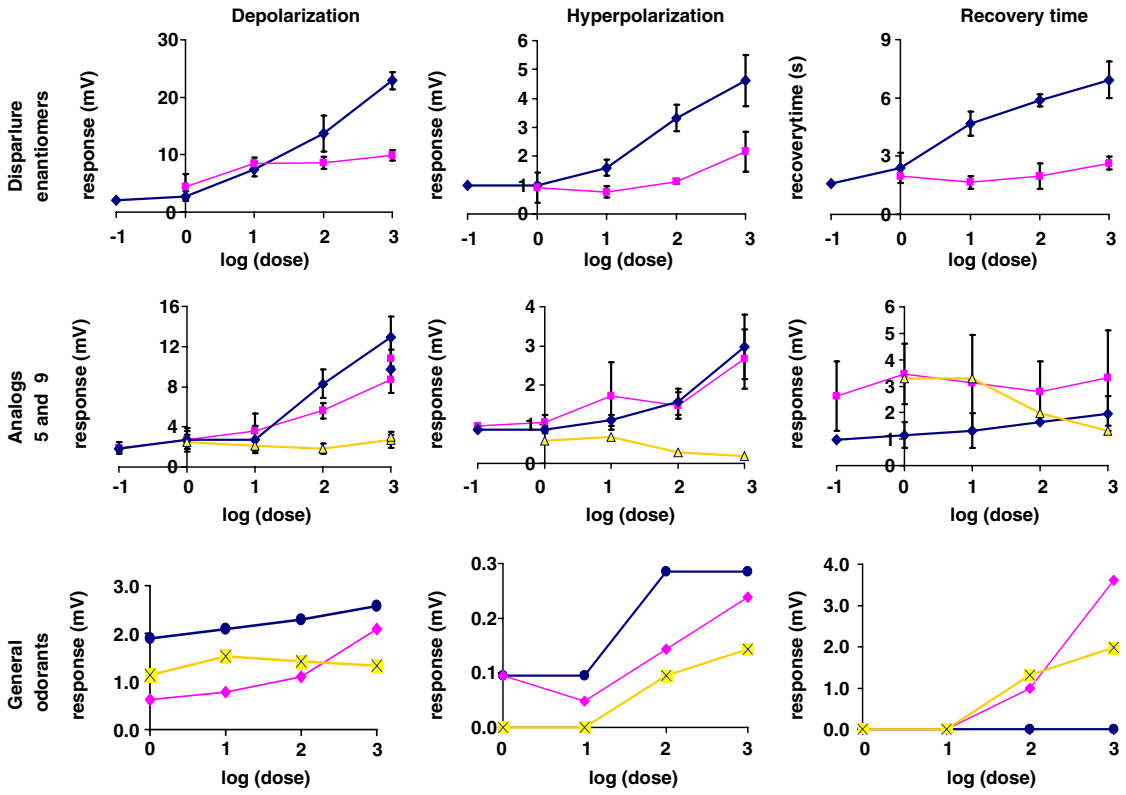


Figure 2. Dose–responses for (+)-**1**, (−)-**1**, (−)-**5**, (+)-**5**, racemic **9**, and three general odorants (camphor, geraniol, and menthol). Row 1: diamonds (+)-**1**, squares (−)-**1**; Row 2: diamonds (−)-**5**, squares (+)-**5**, triangles **9**; Row 3: circles camphor, diamonds geraniol, crosses menthol. Mean ± S.E. for compounds (+)- and (−)-**1**, (+)- and (−)-**5**, and **9** ($n = 5$–12) and mean ± range for the general odorants ($n = 3$).

octadec-7-ene, the parent hydrocarbon of epoxides (+)-**1** and (−)-**1**[36] and also a weak odorant in the gypsy moth.[4]

3. Conclusions

We have used MCTA-I chiral resolution of a racemic ester to prepare enantiomerically pure *cis*-(2,3)-epoxytridecan-1-ol, **3**. This alcohol was converted to various analogues of disparlure. Amongst these analogs, the 5-oxa forms of disparlure, (−)-**5** and (+)-**5**, had the highest electroantennogram activity and bound to the pheromone-binding protein 1 (PBP1). None of the analogues caused adaptation of isolated gypsy moth antennae.

4. Experimental

4.1. General

Solvents were distilled prior to use: THF was distilled over Na/benzophenone, ethyl acetate, and hexane were distilled in glass with a 40 cm long Vigreaux column prior to use. Thin-layer chromatography (TLC) was run on plates with aluminum backing and fluorescein as a fluorescent indicator (Merck). Most compounds were visible under UV light on these TLC plates, but for confirmation, plates were also stained with either phosphomolybdic acid or anisaldehyde stain. NMR spectra were obtained on a Brucker 400 MHz instrument with the $CHCl_3$ band as a reference. Melting points are uncorrected. Optical rotations were obtained on a Perkin–Elmer Polarimeter 340 thermostatted to 20 °C, using the sodium D line. Routine gas chromatography and GC-EAD was done on a HP 5890A gas chromatograph, fitted with a split/splitless injector, a flame ionization detector (FID) and a DB-5 column (30 m × 0.25 mm i.d., film thickness 0.25 μm). The GC was operated in the splitless mode, using the following temperature program: 100 °C (5 min), 10°/min to 200 °C (4 min), 50°/min to 250 °C (20 min). Chiral analytical GC was performed on a Varian 3400 GC with a split/splitless injector, a FID and a CycloSil-B (30m × 0.25 mm i.d., film thickness 0.25 μm, JW Scientific, Folsom CA) column. The GC was operated at 170 °C isothermally, at 20 psi head pressure. Quantities of (+)-**1** and of (−)-**1**, prepared by hydrogenation of (−)-**7** and (+)-**7**, were too small to obtain specific rotations. We used commercial (+)-**1** (Aldrich) for EAG studies. The (−)-**1** for the EAG studies was obtained from Dr. G. Gries (S.F.U.).

4.2. Synthesis of *cis*-2,3-epoxytridecan-1-yl *p*-bromobenzoate, 2c

4.2.1. Propargyl alcohol tetrahydropyranyl ether. Neat dihydropyran (7.51 g, 11.2 mol) was placed in a round-bottomed flask and cooled to 0 °C. A small crystal of TsOH catalyst was added; when the crystal was nearly dissolved, propargyl alcohol (5.00 g, 11.2 mol) was added and the solution was left to stir for $2\frac{1}{2}$ h. The reaction was quenched with 10% $NaHCO_3$ solution

Table 3. EAG data for alternating stimuli of (+)-**1** and various test compounds[a]

Test compound	Measurement	n[b]	Response to first stimulus		Size of subsequent responses, relative to the response to the first stimulus[c] (%)				Size of test compound response relative to the response to (+)-**1**[d] (%)		
			(+)-**1**	Compound	Second		Third				
					(+)-**1**	Compound	(+)-**1**	Compound	First	Second	Third
Clean air	Depolarization (mV)	6	19.7 ± 4.1	5.7 ± 1.5	102 ± 2	95 ± 10	105 ± 10	105 ± 9	23 ± 5	22 ± 5	25 ± 6
(−)-**1**	Depolarization (mV)	4	22.0 ± 2.3	7.3 ± 0.9	95 ± 3	110 ± 9	95 ± 4	105 ± 7	33 ± 1	38 ± 2	36 ± 2
(−)-**5**	Depolarization (mV)	13	24.9 ± 2.7	9.7 ± 1.0	95 ± 1	98 ± 3	93 ± 2	95 ± 6	39 ± 1	40 ± 2	40 ± 2
(+)-**5**	Depolarization (mV)	12	27.8 ± 2.7	10.8 ± 0.9	97 ± 2	96 ± 7	97 ± 3	89 ± 7	40 ± 2	39 ± 2	37 ± 2
9	Depolarization (mV)	5	10.9 ± 0.5	3.0 ± 0.2	101 ± 4	110 ± 18	102 ± 3	82 ± 7	28 ± 1	30 ± 4	23 ± 2
Clean air	Hyperpolarization (mV)	6	6.3 ± 1.9	2.6 ± 0.2	113 ± 15	99 ± 23	128 ± 27	97 ± 25	40 ± 13	32 ± 9	30 ± 7
(−)-**1**	Hyperpolarization (mV)	4	7.7 ± 0.9	3.9 ± 0.3	106 ± 3	82 ± 3	100 ± 8	69 ± 14	52 ± 4	39 ± 2	35 ± 7
(−)-**5**	Hyperpolarization (mV)	13	8.5 ± 1.0	3.6 ± 0.3	109 ± 6	99 ± 9	103 ± 6	103 ± 11	47 ± 6	39 ± 4	43 ± 3
(+)-**5**	Hyperpolarization (mV)	12	9.7 ± 1.1	2.8 ± 0.4	108 ± 3	144 ± 22	101 ± 5	118 ± 22	31 ± 4	36 ± 4	34 ± 5
9	Hyperpolarization (mV)	5	5.3 ± 0.1	2.0 ± 0.1	106 ± 3	93 ± 6	104 ± 0	102 ± 8	38 ± 1	33 ± 2	38 ± 3
Clean air	Recovery time (s)	6	7.9 ± 1.2	7.3 ± 1.1	103 ± 8	83 ± 17	108 ± 13	75 ± 10	73 ± 23	55 ± 14	51 ± 15
(−)-**1**	Recovery time (s)	4	9.3 ± 0.8	8.0 ± 0.8	105 ± 6	83 ± 9	88 ± 5	89 ± 31	86 ± 9	69 ± 10	82 ± 10
(−)-**5**	Recovery time (s)	13	9.9 ± 0.9	7.0 ± 0.8	103 ± 9	97 ± 9	92 ± 8	93 ± 13	69 ± 6	69 ± 10	76 ± 12
(+)-**5**	Recovery time (s)	12	9.8 ± 0.8	6.2 ± 0.8	104 ± 9	115 ± 29	93 ± 8	102 ± 11	62 ± 6	61 ± 8	76 ± 10
9	Recovery time (s)	5	7.3 ± 0.5	6.3 ± 0.6	103 ± 11	92 ± 6	77 ± 23	111 ± 19	86 ± 8	76 ± 3	94 ± 19

[a] Pheromone (+)-**1** and the test compound were passed over the antenna in 2.5 s puffs, alternating between (+)-**1** and the test compound, three times. Between puffs the antenna was allowed to recover to the resting potential. The first stimulus of a series was always with (+)-**1**. The dose of both compounds was 1 μg, delivered on a filter paper in a cartridge.

[b] Data shown is the mean ± S.E. for n replicates.

[c] Determined relative to the first stimulus of either (+)-**1** or the test compound.

[d] Determined for the first, second and third pairs of (+)-**1** and test compound stimuli.

Table 4. PBP1 binding with various ligands[a]

Ligand	IC_{50} (nM)	Emission maximum (nm)
(+)-Disparlure (+)-**1**	100	389
(−)-Disparlure (−)-**1**	4.7	380
(−)-Epoxy ether (−)-**5**	8.5	381
(+)-Epoxy ether (+)-**5**	13.2	381
(±)-Oxazolidinone **9**	22.6	380
Geraniol	260	381
Menthol	212	381
(1*R*)-(+)-Camphor	168	382
(7*Z*)-2-Methyloctadec-7-ene	26.4	381

[a] Determined with a 1-NPN competitive displacement assay.

(20 mL), diluted with ether (90 mL), and washed twice with 10% $NaHCO_3$ (20 mL). The aqueous portion was back-extracted and the organic layers combined, washed once with brine (10 mL), dried over Na_2SO_4, and purified by flash-chromatography on a silica column (1:1 hexane–ether) to give 12.24 g of the title compound (98% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47–1.68 (m, 4H), 1.69–1.78 (m, 1H) 1.78–1.85 (m, 1H) 2.41 (t, $J = 2.2$ Hz, 1H), 3.54 (m, 1H), 3.84 (m, 1H), 4.23 (dd, $J = 15.8$, 2.2 Hz, 1H), 4.30 (dd, $J = 15.8$, 2.6 Hz, 1H), 4.82 (t, $J = 3.3$ Hz, 1H).

4.2.2. 2-Tridecyn-1-ol tetrahydropyranyl ether. Protected propargyl alcohol (3.0816 g, 22.0 mmol) in THF (10 mL) was placed into a dry three-necked round-bottomed flask. The solution was stirred under argon at −50 °C (acetone/dry ice bath) for 5 min. Upon addition of *n*-butyllithium (13 mL, 22.1 mmol, 1.7 M in pentane), the solution turned orange. After 1 h, a solution of 1-bromodecane (4.8134 g, 21.8 mmol) in HMPA (12 mL) was added and the mixture allowed to warm to room temperature. The reaction was stirred for $5\frac{1}{2}$ h. The reaction was quenched with 0.5 M aqueous Na_2CO_3 (10 mL), diluted with ether (90 mL), and washed twice with 10% aqueous Na_2CO_3 (10 mL). The aqueous portion was back-extracted and the organic portions combined, washed with brine (10 mL), dried over Na_2SO_4, and purified by flash-chromatography (7:1 hexane–ether) to afford the title compound (5.0449 g, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.875 (t, $J = 7.0$ Hz, 3H), 1.12–1.45 (br s, 14H), 1.45–1.67 (m, 6H), 1.73 (m, 1H), 1.85 (m, 1H), 2.20 (tt, $J = 7.0$, 2.2 Hz, 2H), >3.52 (m, 1H) 3.84 (m, 1H) 4.20 (dt, $J = 15.1$, 2.2 Hz, 1H), 4.29 (dt, $J = 15.1$, 2.2 Hz, 1H), 4.81 (t, $J = 3.3$ Hz, 1H).

4.2.3. (2*Z*)-Tridecen-1-ol. To a round-bottomed flask fitted with a balloon and rubber septum was added 2-tridecyn-1-ol tetrahydropyranyl ether (5.6 g, 20 mmol) in 20 mL distilled hexane. Lindlar's catalyst (Pd, 5 wt % on $CaCO_3$ poisoned with Pb, 0.1058 g) was added, the flask filled with H_2 and the reaction left to stir under H_2, until the balloon no longer deflated at an appreciable rate. The product was filtered with hexane through silica gel to remove the catalyst and then concentrated. A portion of hydrogenated material from a trial reaction was added (5.78 g, 20.6 mmol total), and the pooled product dissolved in MeOH (40 mL). TsOH (0.6 g, 3 mmol) was added, and the reaction stirred for 3 h 20 min. The reaction was quenched with aqueous Na_2CO_3, adjusted to pH 10, diluted with ethyl acetate (60 mL), washed twice with aqueous Na_2CO_3 (pH 10). The aqueous portion was back-extracted twice, and the organic portion pooled, washed with brine (30 mL), dried over Na_2SO_4, and concentrated. Flash-chromatography on silica gel (10:1 hexane–ethyl acetate) yielded the title compound (3.90 g, 96% yield), as a yellow oil. The reaction was also achieved by H_2 reduction on Pd/C poisoned with quinoline, yielding a mixture of *Z*- (~80%) and *E*-isomers. Purification of the alkenol on a silica column containing 5% silver nitrate (93:6:1 hexane–ether–toluene) yielded >96% *Z*-compound. ^{1}H NMR (400 MHz, $CDCl_3$): *Z*-isomer δ 0.88 (t, $J = 7.4$ Hz, 3H), 1.25 (br s, 14H), 1.35 (m, 2H), 1.54 (br, OH), 2.06 (dt, $J = 7.4$, 7.0 Hz, 2H), 4.19 (d, $J = 6.6$ Hz, 2H), 5.57 (m, 2H).

4.2.4. (2*Z*)-Tridecen-1-yl *p*-bromobenzoate. Into a dry round-bottomed flask containing pyridine (25 mL), (2*Z*)-tridecen-1-ol (1.3012 g, 6.56 mmol) was added, followed by *p*-bromobenzoyl chloride (1.5910 g, 7.25 mmol) and the reaction left to stir at room temperature for 16 h. The reaction was quenched with 0.1 M HCl (10 mL), diluted with ether (75 mL), and washed twice with 0.1 M HCl (10 mL) and once with ice water (10 mL). The aqueous portion was back-extracted and the organic portions combined, washed once with brine (10 mL), dried over $MgSO_4$, and purified by flash-chromatography on silica gel (7:1 hexane–ether) to afford 2-tridecen-1-yl *p*-bromobenzoate (1.8678 g, 75% yield), a colorless oil. GC–MS (EI): *m*/*z* (rel. abundance %) 353 (2%, $M^+-C_2H_4$), 351 (1%, $M^+-C_2H_4$), 301 (6%, M^+-Br), 201 (21%), 203 (20%) 183 (95%, $COC_6H_6Br^+$), 185 (100%, $COC_6H_6Br^+$), 155 (10%), 157 (12%). IR (KBr, cm^{-1}): 3078 (=C–$H_{str.}$), 2926, 1723 (C=O), 1583, 1437, 1269, 1098, 703, 517 (C–Br). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, $J = 7.2$ Hz, 3H), 1.24 (br s, 14 H), 1.48 (m, 2H), 2.17 (dt, $J = 6.5$, 4.0 Hz, 2H), 4.85 (d, $J = 5.5$ Hz, 2H), 5.68 (m, 2H), 7.56 (br d, $J = 8$ Hz, 2H), 7.90 (br d, $J = 8$ Hz, 2H).

4.2.5. Esters for MCTA-I separation

4.2.5.1. *cis*-2,3-Epoxytridecan-1-yl acetate, (±)-2a. Racemic epoxy alcohol (±)-**3** (70.3 mg, 0.33 mmol) was dissolved in 2 mL of CH_2Cl_2 and 0.3 mL of pyridine. To this solution, 30 mg (0.34 mmol) of acetyl chloride was added, followed by a crystal of 4-*N*,*N*-dimethylaminopyridine (DMAP). The reaction was stirred for 1 h at room temperature. The organic solution was washed with water and 0.1 M HCl, and the solution then dried over Na_2SO_4. After purification on a small column of silica gel (8:1 hexane–ether), 47 mg (50%) of acetate **2a** were obtained. GC–MS (EI): *m*/*z* (rel. abundance %) 257 (10%, M+1), 197 (3%), 123 (3%), 115 (38%), 109 (8%), 97 (11%), 95 (17%), 83 (6%), 81 (7%), 67 (5%), 55 (21%), 43 (100%).

We compared the results obtained for various esterifications of epoxy alcohol **3** against esterification of (2*Z*)-tridicen-1-ol followed by epoxidation of the ester, and found that the latter procedure gave cleaner products.

As a result, this method was adopted for esters **2b** and **2c**.

4.2.5.2. *cis*-2,3-Epoxytridecan-1-yl benzoate (±)-2b. (2*Z*)-Tridecen-1-ol (300 mg, 1.5 mmol) was reacted with 333 mg (1.5 mmol) of benzoyl chloride, as described above, to give 192 mg (0.5 mmol, 33%) of the benzoate. ^{1}H NMR (400 MHz, $CDCl_3$): (major isomer, *Z*, 93%) δ 0.86 (t, $J = 6.5$ Hz, 3H), 1.25 (m, 14H), 1.40 (m, 2H), 2.16 (br q, $J \sim 5$ Hz, 1.9H), 4.86 (d, $J = 6.5$ Hz, 1.9H), 5.68 (m, 1.9H), 7.4 (br t, $J = 9$ Hz, 2H), 7.55 (br t, $J = 9$ Hz, 1H), 8.02 (br d, $J = 9$ Hz, 2H). (*minor isomer*, *E*, 7%) same as *Z*, except: δ 2.07 (m, 0.1H, H-4), 4.75 (d, $J = 6.5$ Hz, 0.1H, H-1), 5.88 (m, 0.1H, H-2 and H-3).

(*Z*)-2-Tridecen-1-yl benzoate (47 mg, 0.16 mmol), dissolved in 2 mL of CH_2Cl_2, was added to *m*-CPBA (32 mg, 0.16 mmol) in 2 mL of CH_2Cl_2. The mixture was stirred at room temperature for 4.5 h, after which the organic solution was washed with water, followed by NaOH (1 M). The organic phase was dried and the product was purified on silica gel (3:1 hexane–ether). The small amount of *trans* epoxide, that formed from the minor *E* isomer, readily separated from the major *cis* epoxide during chromatography. After evaporation of the solvent, 10 mg (0.04 mmol, 20%) of the pure *cis* benzoate **2b** was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, $J =$ Hz, 3H), 1.29 (m, 16H), 1.60 (m, 2H), 3.06 (m, $J = 13.6$ Hz, ~5–6 Hz, 1H), 3.31 (m, $J = 13.6$ Hz, ~5–6 Hz, 1H), 4.30 (dd, $J = 11$ Hz, 6.5 Hz, 1H), 4.56 (dd, $J = 11$ Hz, 4.5 Hz, 1H), 7.46 (br t, $J = 7.3$ Hz, 2H), 7.58 (br t, $J = 7.3$ Hz, 1H), 8.08 (br d, $J = 7.3$ Hz, 2H).

4.2.5.3. *cis*-2,3-Epoxytridecan-1-yl *p*-bromobenzoate (±)-2c. In a dry round-bottomed flask containing 5 mL of CH_2Cl_2, pure (*Z*)-2-tridecen-1-yl *p*-bromobenzoate (0.1064 g, 0.279 mmol) was added, followed by solid $NaHCO_3$ (0.0611 g, 0.727 mmol). After the addition of *m*-CPBA (0.0529 g, 0.306 mmol), the reaction was left to stir for 2 h, after which another half equivalent of *m*-CPBA was added, followed by another half equivalent after 3 h. The reaction was left for 16 h. The reaction was quenched with ice water (10 mL), diluted with ether (60 mL), and washed three times (ice water (10 mL), 10% Na_2SO_3 (10 mL), and 10% $NaHCO_3$ (10 mL)). The aqueous portion was back-extracted and the organic portions combined, washed once with brine (10 mL), dried over $MgSO_4$, and purified by flash-chromatography (7:1 hexane–ethyl acetate) to afford (±)-**2c** (0.1069, 96% yield), a white solid, mp: 48.5–49 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, $J = 7.0$ Hz, 3H), 1.2–1.41 (br, 16H), 1.59 (m, 2H), 3.07 (m, 1H), 3.31 (dt, $J = 7.0$, 4.4 Hz, 1H), 4.28 (dd, $J = 12.1$, 7.4 Hz, 1H), 4.57 (dd, $J = 12.1$, 4.4 Hz, 1H), 7.59 (d, $J = 8.5$, 2H), 7.94 (d, $J = 8.5$, 2H).

4.3. Resolution on microcrystalline cellulose triacetate-I (MCTA-I)

For trial runs, racemic epoxy esters **2a**–**c** in 0.5 mL butanol were injected onto a semi-preparative column (ID = 0.9 cm, length = 60 cm) of MCTA-I (25–40 μm, EM Science, Gibbstown NJ), equilibrated with distilled ethanol–water (9:1). The column was jacketed and kept at a constant temperature of 30 °C using a recirculating heater/pump (Haake E2). The flow rate was 0.1 mL/min. Ester **2a** did not separate significantly, while ester **2b** showed moderate separation. Ester **2c** was more retained and eluted with baseline separation in two cases and with only a small overlap in two other cases. As the esters are not separated on the chiral GC column, samples of the representative fractions were hydrolyzed and the resulting alcohol **3** analyzed by chiral GC (CycloSil B). An attempt to separate alcohol **3** directly by chromatography on MCTA-I was not successful.

For preparative runs, a representative procedure was given. Racemic epoxy ester **2c** (0.1610 g) in 5 mL butanol was injected onto a large column (ID = 2.5 cm, length = 100 cm) of MCTA-I (as above). The solvent was distilled ethanol–water (9:1), the flow rate was 0.5 mL/min and the temperature was 50 °C. (2*S*,3*R*)-(−)-**2c** (0.0546 g collected) eluted from 12:30 h to 15 h; (2*R*,3*S*)-(+)-**2c** eluted from 15:30 h to 17:45 h (0.0822 g collected). Samples of relevant column fractions were transesterified for GC analysis of enantiomeric excess prior to pooling. A representative procedure is as follows: a 20 μL sample was placed in an ampoule, followed by 1 M KOH (10 μL) in ethanol. The ampoules were sealed and vortexed, then left for 1 $\frac{1}{2}$ h. Then the ampoule was opened and water (10 μL) was added, followed by ethyl acetate (100 μL). The sample was shaken for 30 s, the lower aqueous portion removed with a syringe, and another 10 μL of water was added. After two more washes, the ethyl acetate was transferred into a dry ampoule containing a small amount of Na_2SO_4. The ampoule was sealed and left for 1 h. The extract was transferred to a fresh ampoule and concentrated to ~2 μL, using a water aspirator, prior to analysis. Fractions that contained one enantiomer were pooled and the intermediate fractions, with both enantiomers, were recycled. (2*R*,3*S*)-(+)-**2c**: $[\alpha]_D^{20} = +9.4$ (*c* 0.80, $CHCl_3$). (2*S*,3*R*)-(−)-**2c**: $[\alpha]_D^{20} = -9.3$ (*c* 1.12, $CHCl_3$).

4.4. *cis*-2,3-Epoxytridecan-1-ol, 3

4.4.1. Racemic (±)-3 by direct epoxidation of (2*Z*)-tridecen-1-ol. Racemic epoxy alcohol was obtained by direct epoxidation of (2*Z*)-tridecen-1-ol. A typical procedure is as follows. *m*-CPBA (0.9718 g, 5.63 mmol) was added in small portions over 2 h to a solution of (*Z*)-tridecen-1-ol (0.5354 g, 2.70 mmol) in CH_2Cl_2 (14 mL) while the reaction was kept at 0 °C. The reaction was allowed to warm to room temperature over another 2 h, then diluted with CH_2Cl_2, chilled, and filtered. The product mixture was washed twice with saturated aqueous Na_2CO_3, the aqueous portion back-extracted, and the organic portions pooled and washed with brine. Recrystallization from pentane afforded (±)-**3** (0.5752 g, 99%).

4.4.2. Alcohol 3 by transesterification of epoxy ester 2c. Epoxy ester (±)-**2c** (0.6058 g, 1.52 mmol) was dissolved in a solution of 1 M KOH in ethanol. After

2 h, the reaction was quenched with ice, diluted with 130 mL ethyl acetate, and washed twice with water (5 mL). The organic portions were pooled and washed with brine, then concentrated and purified by flash-chromatography (4:1 hexane–ethyl acetate) to afford the title compound epoxy alcohol (±)-**3** (0.3040 g, 93% yield), a white solid. Mp: 56–57 °C. (lit. 59.5–60 °C,[18] 61–63 °C,[8] 63 °C[14]). Similar procedures were carried out for the (−)- and (+)-epoxy alcohols, starting from enantiomerically pure (2*R*,3*S*)-(+)-**2c** and (2*S*,3*R*)-(−)-**2c**, respectively. Enantiomeric excess of the corresponding epoxy alcohols (2*R*,3*S*)-(−)-**3** and (2*S*,3*R*)-(+)-**3** was estimated at >97% by chiral GC and from the specific rotation. Chiral GC (CycloSil B): (2*S*,3*R*)-(+)-**3** 15.191 min, (2*R*,3*S*)-(−)-**3** 15.399 min.

GC–MS (EI): *m*/*z* (rel. abundance %) 215 (1%, M^++1), 197 (1%), 183 (1%), 111 (17%), 97 (70%), 83 (57%) 55 (100%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, $J = 6.6$ Hz, 3H), 1.16–1.38 (br s, 16H), 1.38–1.63 (m 3H), 3.03 (m, 1H), 3.15 (dt, $J = 7.0$, 4.0 Hz, 1H), 3.68 (ddd, $J = 12.1$, 7.0, 5.1 Hz, 1H), 3.86 (ddd, $J = 12.1$, 7.4, 4.0 Hz, 1H). (lit.[18,8]). ^{13}C NMR (400 MHz, $CDCl_3$): 14.05, 22.64, 26.61, 27.93, 29.27, 29.37, 29.49, 31.84, 56.72, 57.29, 60.92. (lit.[14]). (2*S*,3*R*)-(+)-**3**: $[\alpha]_D^{20} = +7.9$ (*c* 1.85, $EtOH_{abs}$), ee 97% (lit. (2*R*,3*S*)-(−)-**3**: $[\alpha]_D^{20} = -7.8$ (*c* 1.0, $EtOH_{abs}$),[6] (2*S*, 3*R*)-(+)-**3** $[\alpha]_D^{20} = +7.8$ (*c* 1.28, EtOH),[8] both ee 95%, (2*R*,3*S*)-(−)-**3** $[\alpha]_D^{20} = -7.95$ (*c* 1.76, EtOH)[14]).

4.4.3. MTPA esters of (+)-3 and (−)-3, (2′*R*,2*S*,3*R*)-4 and (2′*R*,2*R*,3*S*)-4. Optically-active (+)-**3** (10 mg) was mixed with pyridine (300 μL) and 400 μL α-methoxy-α-trifluoromethylphenylacetic chloride, (*S*)-MTPA-Cl, in CCl_4 (600 μL). The reaction mixture was left to stir overnight, after which it was concentrated and purified twice by flash-chromatography (2:1 hexane–ether, 7:1 hexane–ether). Identical steps were carried out with (−)-**3**. The 4.3–4.6 ppm region of the ^{1}H NMR of the MTPA ester of (+)-**3**, (2′*R*,2*S*,3*R*)-**4**, and for the MTPA ester of (−)-**3**, (2′*R*,2*R*,3*S*)-**4**, was consistent with literature data.[8]

^{1}H NMR (400 MHz, $CDCl_3$): (2′*R*,2*S*,3*R*)-**4** δ 0.88 (t, $J = 7.1$ Hz, 3H), 1.1–1.38 (br s, 14H), 1.50 (m, 2H), 1.68 (m, 2H), 3.02 (m, 1H), 3.20 (dt, $J = 7.1$, 4.3 Hz, 1H), 3.58 (s, 3H), 4.38 (dd, $J = 12.0$, 6.8 Hz, 1H), 4.45 (dd, $J = 12.0$, 4.6 Hz, 1H), 7.37–7.44 (m, 3H), 7.49–7.56 (m, 2H). (2′*R*,2*R*,3*S*)-**4** δ 0.88 (t, $J = 7.1$, 3H), 1.1–1.38 (br s, 14H), 1.50 (m, 2H), 1.63 (m, 2H), 3.02 (m, 1H), 3.22 (dt, $J = 6.8$, 4.6 Hz, 1H), 3.88 (s, 3H), 4.34 (dd, $J = 12.0$, 6.8 Hz, 1H), 4.50 (dd, $J = 12.0$, 4.6 Hz, 1H), 7.37–7.44 (m, 3H), 7.48–7.56 (m, 2H).

4.5. *cis*-(2,3)-Epoxy-1-(3-methylbutoxy)-tridecane, (±)-5

A dry flask was charged with racemic epoxy alcohol (±)-**3** (0.3666 g, 1.71 mmol) in dry DMF. NaH (0.2147 g, 60% in mineral oil, 5.64 mmol) was washed twice with hexane and added as a slurry in DMF, dropwise at 0 °C, under argon. The reaction was stirred vigorously. After 3 h, 1 equiv of NaH (68.4 mg, 60% in mineral oil, 1.7 mmol) was added, and an hour later 3-methyl-1-bromobutane (0.5511 g, 3.64 mmol, Aldrich) in DMF added dropwise to the alkoxide (total solvent ~35 mL DMF). The reaction was allowed to warm to room temperature. After 15 h, the reaction was quenched with ice water (5 mL), diluted with ether (60 mL) and washed twice [ice water (5 mL), 10% $NaHCO_3$ (10 mL)]. The combined organic portions were back-extracted, concentrated and purified by flash-chromatography (2:1 hexane–ethyl acetate) to afford (±)-**5** (0.2998 g, 62% yield), as a colorless oil. Chiral GC (CycloSil B): (2*R*,3*S*)-(−)-**7**: 45.39 min, (2*S*,3*R*)-(+)-**7**: 45.93 min. GC–MS (EI): *m*/*z* (rel. abundance %) 285 (1%, M^++1), 266 (5%, $M^+ - H_2O$), 227 (5%), 215 (20%), 197 (38%), 179 (14%), 137 (12%), 123 (25%), 111 (16%), 109 (27%), 97 (33%), 95 (27%), 81 (23%), 71 (100%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, $J = 7.1$ Hz, 3H), 0.90 (dd, $J = 6.8$ Hz, 6H) 1.16–1.38 (br s, 16H), 1.38–1.59 (m, 4H), 1.71 (m, 1H), 2.97 (m, 1H), 3.13 (dt, $J = 6.2$, 4.3 Hz, 1H), 3.41–3.52 (m, 2H), 3.56 (dt, $J = 9.2$, 6.8 Hz, 1H), 3.63 (dd, $J = 11.1$, 4.3, 2H). Anal. Calcd for $C_{18}H_{36}O_2$ (284.48): C, 76.00; H, 12.76. Found: C, 75.84; H, 12.94. Similar procedures were carried out for the (+)- and (−)-epoxy ethers, starting from optically pure (2*S*,3*R*)-(+)-**3** and (2*R*,3*S*)-(−)-**3**, respectively. (2*S*,3*R*)-(+)-**5**: $[\alpha]_D^{20} = +1.2$ (*c* 0.59, $CHCl_3$). (2*R*,3*S*)-(−)-**5**: $[\alpha]_D^{20} = -1.2$ (*c* 0.18, $CHCl_3$).

4.6. *cis*-(2,3)-Epoxytridecan-1-al, (±)-6

Racemic epoxy alcohol (±)-**3** (0.1866 g, 0.87 mmol) in CH_2Cl_2 (32 mL) was cooled to 0 °C and a suspension of PCC (1.708 g, 7.92 mmol) in CH_2Cl_2 (3 mL) was added dropwise. After 1 h, the reaction was brought to room temperature. After 3 h 40 min, 3 mL hexane was added to precipitate the solid, and the solution was passed through a column of silica with ethyl acetate. The solution was concentrated and immediately purified by flash-chromatography (4:1 hexane–ethyl acetate) to afford (±)-**7** (0.1194 g, 65% yield), a yellow oil. ^{1}H NMR (100 MHz, $CDCl_3$): δ 0.90 (t, $J = 6.6$ Hz, 3H), 1.2–1.4 (br, 16H), 1.5–1.7 (m, 2H), 3.3 (t, $J = 5.1$ Hz, 1H), 3.4 (m, $J = 5.1$ Hz, 2H), 9.5 (d, $J = 5.0$ Hz, 1H).[18,8]

4.7. 4-Methylpentan-1-ol

Crushed magnesium turnings (5.9 g, 0.24 mol) were added to a dry flask, then cooled under argon. Dry ether (40 mL) was added, followed by a 20 mL aliquot of isoamyl bromide (30.1 g, 0.20 mol) in 60 mL ether. The reaction was cooled to 0 °C. One small flake of I_2 was added and the remainder of the alkyl halide solution added dropwise over 20 min, during which time the reaction became turbid gray. The reaction was gently heated at reflux for 45 min, then cooled to room temperature and dry paraformaldehyde (11.5 g, 0.38 mol) was added and the reaction was left 4.5 h. The reaction was quenched with 6 M HCl (100 mL), diluted with ether (200 mL), and washed twice with 6 M HCl (100 mL and 20 mL). The aqueous portion was back-extracted and the organic portions combined, washed

with brine (10 mL), and dried over Na_2SO_4. The crude product was vacuum-distilled (15 mmHg), collecting between 53 and 69 °C, to afford 4-methylpentan-1-ol (9.71 g, 48% yield), a colorless liquid. (Note: this compound has become available commercially). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (d, $J = 6.6$ Hz, 6H), 1.18–1.27 (m, 2H), 1.41 (br, OH), 1.5–1.62 (m, 3H), 3.63 (t, $J = 6.6$ Hz, 2H).

4.8. 1-Bromo-4-methylpentane

Neat 4-methylpentan-1-ol (8.08 g, 79.1 mmol) was placed in a round-bottomed flask fitted with a drying tube and a NaOH trap. The reaction was cooled to 0 °C and PBr_3 (5.0 mL, 102 mmol) added dropwise with stirring. After 15 min, the orange mixture was removed from the ice bath and the reaction stirred for 25 h. The reaction was quenched with ice water (10 mL), diluted with ether (90 mL) and washed twice with water (10 and 7.5 mL). The aqueous portion was back-extracted and the organic portions combined, washed once with brine (7.5 mL), dried over Na_2SO_4, and distilled, collecting between 161 and 165 °C, to give 1-bromo-4-methylpentane (6.67 g, 23% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (d, $J = 6.6$, i-$(CH_3)_2$, 6H), δ 1.30 (dt, $J = 8.8$, 7.0 Hz, H-3, 2H), 1.47–1.63 (m, H-4, 1H), 1.86 (m, H-2, 2H), 3.39 (t, $J = 6.6$ Hz, H-1, 2H).

4.9. 4-Methylpentyl triphenylphosphonium bromide

Triphenylphosphine (0.4651 g, 1.77 mmol) in dry benzene (3 mL) was refluxed under argon for 1 h. 1-Bromo-4-methylpentane (0.1171 g, 0.79 mmol) was added in benzene (2 mL) and the solution stirred at reflux for 8 h, after which the reaction was cooled to room temperature and left stirring under argon for 16 h. The viscous yellow-orange oil was transferred in CH_2Cl_2, concentrated, and washed three times in ether (previously dried over $MgSO_4$) to remove triphenylphosphine oxide. The product was placed in hexane (2 mL) and gently heated in a hot water bath, then the warm solvent was decanted. The product, a pale orange solid, was dried under vacuum to give the title compound (0.2374 g, 78% yield), mp: 234.5–235.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.763 (d, $J = 6.4$ Hz, 6H), 1.44–1.54 (m, 3H), 1.54–1.67 (m, 2H), 3.79 (m, 2H), 7.69 (m, 6H), 7.78 (m, 3H), 7.85 (m, 6H).

4.10. (−)-2-Methyl-(5*Z*,7*R*,8*S*)-epoxyoctadec-5-ene, (−)-7

4-Methylpentyl triphenylphosphonium bromide (0.1195 g, 0.28 mmol) was placed in a dry three-necked flask and heated gently for 40 min under vacuum. Dry THF (2 mL) was added via cannula and the reaction put under argon and brought to −78 °C. A solution of *n*-butyllithium (0.12 mL, 0.2 mmol, 1.6 M in hexane) was added dropwise by syringe and the reaction was left to stir for $1\frac{1}{2}$ h, during which time the solution became dark orange. Epoxy aldehyde (−)-**6** (0.0293 g, 0.14 mmol) in THF (2 mL) was added dropwise. The reaction was kept at −78 °C for 3 h, after which it was left to warm to room temperature overnight. The reaction was diluted with ether (20 mL) and washed once with water (2 mL). The aqueous portion was back-extracted once, and the organic portions pooled, dried over $MgSO_4$, concentrated. GC and NMR analysis revealed that the product contained 82% (*Z*) and 18% (*E*)-isomer. The isomers were separated by flash-chromatography (5:1 hexane–ethyl acetate) to afford (−)-(5*Z*)-**7** (0.2370 g, 61% yield), a colorless oil. GC–MS (EI): *m*/*z* (rel. abundance %) 281 (5%, M^++1), 236 (14%), 169 (23%), 95 (100%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83–0.92 (m, 9H), 1.2–1.37 (br, 18H), 1.37–1.65 (m, 3H), 2.20 (m, H-4, 2H), 3.07 (m, 1H), 3.64 (ddd, $J = 8.5$, 4.4, 1.1 Hz, 1H), 5.19 (ddt, $J = 11.0$, 8.5, 1.5 Hz, 1H), 5.75 (dtd, $J = 11.0$, 7.7, 1.1 Hz, 1H) (lit.[8]). ^{13}C NMR (400 MHz, $CDCl_3$): δ 14.05, 22.41, 22.64, 25.72, 26.29, 27.54, 28.23, 29.28, 29.40, 29.51, 31.86, 38.68, 52.79, 58.60, 123.66, 137.51 (lit.[14]). $[\alpha]_D^{20} = -40.5$ (*c* 0.82, $CHCl_3$) (lit.[14]). $[\alpha]_D^{20} = -39.5$ (*c* 0.80, $CHCl_3$). The same procedure was used to synthesize (±)-**7** and (+)-**7**, yielding compounds with identical NMR spectra. Specific rotation of (+)-**7**: $[\alpha]_D^{20} = +43.8$ (*c* 0.80, $CHCl_3$).

4.11. (2,3)-Epoxy-1-(3-methyl-aminobutyl) tridecane (±)-8, and *anti*-5-(1-hydroxy-undecyl)-3-(3-methylbutyl)oxazolidin-2-one, (±)-9

A dry round-bottomed flask filled with activated molecular sieves was flushed with argon and racemic epoxy aldehyde **6** (0.2126 g, 1.00 mmol) dissolved in dry CH_2Cl_2 (10 mL), added via cannula. 3-Methylbutan-1-amine (0.0894 g, 1.03 mmol, Aldrich) in CH_2Cl_2 (2 mL) was added dropwise, and the mixture stirred for 14 min. The reaction mixture was filtered to remove the sieves and concentrated to give 0.2449 g crude epoxy imine. The imine was dissolved in abs. MeOH (8 mL) and $NaBH_4$ (0.1033 g, 2.73 mmol) was added over 15 min, with stirring. After a total of 45 min, the reaction was quenched with water (5 mL), diluted with ethyl acetate (90 mL), and washed once with water (5 mL) and twice with aqueous $NaHCO_3$ buffer (pH 9, 5 mL). The aqueous portions were back-extracted and the organic portions pooled, washed with brine, and concentrated to give 0.2129 g of crude (±)-**8**. Flash-chromatography on silica gel (5:1 $CHCl_3$–MeOH) yielded epoxy amine (±)-**8** (0.1830 g, 64% yield) as a colorless oil. Upon standing, **8** converted to *anti*-hydroxyoxazolidinone (±)-**9**, a white solid, which was recrystallized twice from hexanes (0.1115 g, 53% yield), mp: **9** 82.5–83 °C. GC–MS (EI): **8** *m*/*z* (rel. abundance %) 282 (6%, M^+-1), 266 (6%, M^+-OH), 224 (100%), 140 (38%), 112 (85%), 84 (46%); compound **9** *m*/*z* (rel. abundance %) 327 (1%, M^+), 279 (15%), 167 (44%), 149 (100%). IR (KBr, cm^{-1}): **9** 3356, 2959, 2923, 2851, 1713 (CO), 1470, 1347, 1280, 1208, 1141, 1079, 1007, 759, 718, 626. ^{1}H NMR (400 MHz, $CDCl_3$): **8** δ 0.84–0.94 (m 9H), 1.18–1.38 (br s, 18H), 1.38–1.47 (m, 2H), 1.52 (m, 2H), 1.64 (m, 1H), 1.72–2.4 (br, NH), 2.64–2.76 (m, 2H), 2.96 (m, 1H), 3.12 (m, 1H). Compound **9** δ: 0.88 (t, $J = 7.0$ Hz, 3H), 0.93 (d, $J = 6.6$ Hz, 6H), 1.12–1.35 (br s, 18H), 1.38–1.46 (m, 2H), 1.81–1.91 (m, 1H), 3.27 (m, 2H), 3.40 (m, 1H),

3.50–3.59 (m, 2H), 4.38 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): **9** 157.51 (C=O), 75.37, 72.41, 46.12, 42.48, 35.94, 32.60, 31.87, 29.58, 29.52, 29.45, 29.30, 25.66, 25.41, 22.64, 22.36, 14.07. Anal. Calcd for $C_{19}H_{37}NO_2$ **9** (327.28): C, 69.68; H, 11.39; N, 4.28. Found: C, 69.79; H, 11.51; N, 4.13.

4.12. Electrophysiology

Electroantennogram (EAG) analysis was performed on a Syntech EAG system (Hilversum, The Netherlands), fitted with a CS-05 stimulus air controller and an AUTO *SPIKE* I DAC-2/3 amplification system and recording program. Isolated antennae from 1 to 3 days old gypsy moths were used. Stimuli were delivered on small filter papers in cartridges, fashioned out of a 5.5′ Pasteur pipette. Antennae were detached from the moth and cut at the tip. Each antenna was connected with the base of the antenna attached to the reference electrode and the tip attached to the recording electrode. The electrodes were Ag/AgCl, housed in glass capillaries, which were filled with EAD ringer solution.[37] For GC-EAD runs, the GC was operated in splitless mode and 100 ng of each test compound was injected.

4.13. PBP1 ligand binding screen

Pheromone-binding protein 1 (PBP1) from gypsy moth was expressed and purified as described previously.[5] Compounds were evaluated for binding by displacement of *N*-phenylnaphthylamine (1-NPN) from PBP1. The affinity of PBP1 for 1-NPN was 1.5 μM at pH 7.4 (50 mM Tris buffer, pH 7.4), as determined by titrating 1-NPN into PBP1. The displacement of 1-NPN from PBP1 by the test compounds was performed in the same buffer, as follows. In a 1 cm quartz cuvette, 2 mL of 0.3 μM PBP1 and 0.3 μM 1-NPN were incubated in the dark for 10 min. Next, 0.05, 0.1, 0.2, and 0.5 μM aliquots of test ligands (1 mM stock solutions dissolved in methanol, except for (7*Z*)-2-methyloctadec-7-ene, which was dissolved in hexane) were titrated into the solution and incubated in the dark for 10 min. After each addition, the fluorescence emission was monitored on a PTI (Quantum Master Model QM-1) fluorimeter. Excitation was at 337 nm and the emission scan monitored from 357 to 600 nm. The IC_{50} values are the competitor concentration causing a fluorescence decay of half-maximal intensity. IC_{50} values were determined directly from the nonlinear regression plots constructed using GraFit5.

Acknowledgements

We thank Dr. K. N. Slessor, for a gift of (*S*)-MTPA-Cl, Mrs. M. Tracey, for help with NMR, Mr. J. Belli, Ms. M. Chatterton and Ms. R. Thorne, for technical assistance, Dr. G. Gries, for permitting us to use his EAG apparatus and for samples of (−)-**1**, and a reviewer, for helpful comments. Funded by the Natural Sciences and Engineering Research Council (NSERC) of Canada (Grant RGPIN222923 to E.P.) and Research Corporation (Research Innovation Award RI 0519 to E.P.).

References

1. Carde, R. T.; Doane, C. C.; Baker, T. C.; Iwaki, S.; Marumo, S. *Environ. Entomol.* **1977**, *6*, 768–772.
2. Hansen, K. *Physiol. Entomol.* **1984**, *9*, 9–18.
3. Plimmer, J. R.; Schwalbe, C. P.; Paszek, E. C.; Bierl, B. A.; Webb, R. E.; Marumo, S.; Iwaki, S. *Environ. Entomol.* **1977**, *6*, 518–522.
4. Gries, G.; Gries, R.; Khaskin, G.; Slessor, K. N.; Grant, G. G.; Liska, J.; Kapitola, P. *Naturwissenschaften* **1996**, *83*, 382–385.
5. Plettner, E.; Lazar, J.; Prestwich, E. G.; Prestwich, G. D. *Biochemistry* **2000**, *39*, 8953–8962.
6. Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *103*, 464–465.
7. Mori, K.; Ebata, T. *Tetrahedron Lett.* **1981**, *22*, 4281–4282.
8. Prestwich, G. D.; Graham, S. M.; Kuo, J.-W.; Vogt, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 636–642.
9. Sinha-Bagchi, A.; Sinha, S. C.; Keinan, E. *Tetrahedron: Asymmetry* **1995**, *6*, 2889–2892.
10. Mori, K.; Takigawa, T.; Matsui, M. *Tetrahedron Lett.* **1976**, *44*, 3953–3956.
11. Mori, K.; Takigawa, T.; Matsui, M. *Tetrahedron* **1979**, *35*, 833–837.
12. Kang, S.-K.; Kim, Y.-S.; Lim, S.; Kim, K.-S.; Kim, S.-G. *Tetrahedron Lett.* **1991**, *32*, 363–366.
13. Iwaki, S.; Marumo, S.; Saito, T.; Yamada, M.; Katagiri, K. *J. Am. Chem. Soc.* **1974**, *96*, 7842–7844.
14. Tolstikov, A. G.; Khakhalina, N. V.; Odinokov, V. N.; Khalilov, L. M. *J. Org. Chem. USSR* **1989**, *25*, 263–268.
15. Marshall, J. A.; Jablonowski, J. A.; Jiang, H. *J. Org. Chem.* **1999**, *64*, 2152–2154.
16. Satoh, T.; Oohara, T.; Ueda, Y.; Yamakawa, K. *J. Org. Chem.* **1989**, *54*, 3130–3136.
17. Brevet, J.-L.; Mori, K. *Synthesis* **1992**, 1007–1012.
18. Tsuboi, S.; Yamafuji, N.; Utaka, M. *Tetrahedron: Asymmetry* **1997**, *8*, 375–379.
19. Gries, R.; Khaskin, G.; Schaefer, P. W.; Hahn, R.; Gotoh, T.; Gries, G. *J. Chem. Ecol.* **2005**, *31*, 49–62.
20. Pirkle, W. H.; Rinaldi, P. L. *J. Org. Chem.* **1978**, *44*, 1025–1028.
21. Keeling, C. I.; Ngo, H. T.; Benusic, K. D.; Slessor, K. N. *J. Chem. Ecol.* **2001**, *27*, 487–497.
22. Francotte, E.; Lohmann, D. *Helv. Chim. Acta* **1987**, *70*, 1569–1582.
23. Francotte, E.; Wolf, R. M. *Chirality* **1990**, 16–31.
24. Francotte, E.; Junker-Buchheit, A. *J. Chromatogr.* **1992**, *576*, 1–45.
25. Zajc, B.; Grahek, R.; Kocijan, A.; Lakshman, M. K.; Kosmrlij, J.; Lah, J. *J. Org. Chem.* **2003**.
26. Bevan, C. D.; Mutton, I. M. *Anal. Proc.* **1992**, *29*, 240–242.
27. Lipkowitz, K. B. *J. Chromatogr. A* **1995**, *694*, 15–37.
28. Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819–3822.
29. Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4970–4982.
30. Toda, T.; Kitagawa, Y. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 334–335.
31. De Kramer, J.; Hemberger, J. In *Pheromone Biochemistry*; Prestwich, G. D., Blomquist, G. J., Eds.; Academic Press: New York, 1987; pp 433–472.
32. Vickers, N. J.; Christensen, T. A.; Hildebrand, J. G. *J. Comp. Neurol.* **1998**, *400*, 35–56.

33. Mustaparta, H. In *Insect Pheromone Research: New Directions*; Carde, R. T., Minks, A. K., Eds.; Chapman and Hall: New York, 1997; pp 144–163.
34. Vogt, R. G.; Riddiford, L. M. *Nature* **1981**, *293*, 161–163.
35. Campanacci, V.; Krieger, J.; Bette, S.; Sturgis, J. N.; Lartigue, A.; Cambillau, C.; Breer, H.; Tegoni, M. *J. Biol. Chem.* **2001**, *276*, 20078–20084.
36. Jurenka, R. A.; Subchev, M.; Abad, J.-L.; Choi, M.-Y.; Fabrias, G. *Proc. Nat. Acad. Sci. U.S.A.* **2003**, *100*, 809–814.
37. Staddon, B. W.; Everton, I. J. *Comp. Biochem. Physiol.* **1980**, *65A*, 371–374.
38. Isaksson, R.; Erlandsson, P.; Hansson, L.; Holmberg, A.; Berner, S. *J. Chromatogr.* **1990**, *498*, 257–280.