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Asymmetric Synthesis of (*S*)-1-Methyl-2-cyclohexen-1-ol, a Constituent of the Aggregation Pheromone of *Dendroctonus pseudotsugae*

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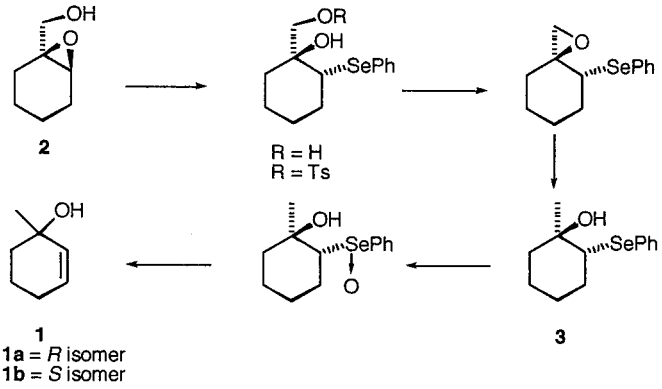
Abstract—1-Methyl-2-cyclohexen-1-ol has been prepared by a three step synthesis from 1-methylcyclohexene, in greater than 94% e.e., via a 'merged substitution–elimination reaction' between NaSePh and 2-methyl-2-hydroxycyclohexyl *p*-toluenesulphonate. © 2000 Elsevier Science Ltd. All rights reserved.

One of the constituents of the pheromone system of the beetle *Dendroctonus pseudotsugae Hopkins*, an economically important pest of the Douglas fir tree, (*pseodotsugae menziesi*) is the aggregation pheromone 1-methyl-2-cyclohexen-1-ol **1**.[1] Although the structure **1** is simple the preparation of highly enriched single enantiomers of this molecule has proved difficult. The main reasons for this relate to the *tertiary* allylic nature of the hydroxyl group. Syntheses of the optically active pheromone **1**, which have been developed, involve the conversion of optically active intermediates, prepared by classical resolution,[2] enzymatically,[3,4] from the chiral pool[5] or by multistep asymmetric syntheses.[6,7] It is somewhat ironic therefore that, inspite of all this effort, the aggregation pheromone found naturally is of only 10% e.e.[8]

Before the configurational constitution of the natural pheromone was known, we had developed an asymmetric synthesis that would allow the preparation of either enantiomer of this molecule.[6] The synthesis was somewhat long and inefficient. In the context of pedagogy, it needs to be made clear that, if industry is to make use of asymmetric synthesis as a principle tool, neophytes must be trained to think about routes which are short, simple and efficient as possible. It should also be emphasised that this is not necessarily a trivial exercise. For these reasons, it was considered worthwhile to pursue an alternative route to the enantiomers of this molecule. We report here the details of work that has been communicated briefly[9] in which enantiomers of this molecule can be obtained in high enantiomeric excess (e.e.) in just three steps from achiral 1-methylcyclohexene. The



Scheme 1.

Keywords: asymmetric synthesis; hydroxylation; elimination reactions; pheromones.

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challenge of this asymmetric synthesis has been pedagogically both useful and exciting and it has led to some interesting chemistry.

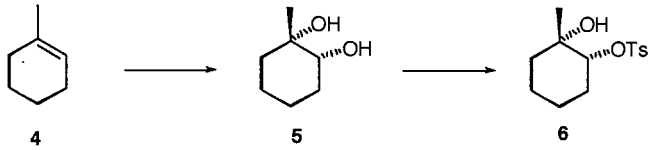
Our earlier approach to this pheromone had been through functional group interconversions from an enantio-enriched epoxy alcohol **2** prepared by a Sharpless asymmetric epoxidation reaction (Scheme 1). A selenyl substituent was introduced by an S_N2 displacement on the epoxide ring in the epoxy alcohol **2**. Subsequent stereocontrolled functional group interconversions yielded the key selenyl ether alcohol derivative **3**. Rapid developments in the Sharpless asymmetric dihydroxylation reaction, culminating in the report of a practical process,[10] led us to consider the formation of the same selenyl ether alcohol **3** (or its enantiomer) in an alternative way. It was conceivable that this key intermediate could be prepared by way of an S_N2 displacement, by NaSePh, of the tosylate moiety in the diol derivative **6**. Of course, it was recognised that both the epoxide **2** and the tosylate **6** are pseudo neopentyl in nature. However, a study of models had shown that distortion caused by the three-membered epoxide ring in the epoxide **2** should make the rear-side of that molecule accessible and in this case the reaction with NaSePh did go smoothly. The rear-side of the tosylate moiety in the molecule **6** is much more severely hindered but NaSePh is a very powerful nucleophile. What would be the outcome of such a reaction? Only a few steps would be necessary to produce the required tosylate **6** (Scheme 2) therefore this reaction was investigated.

The asymmetric dihydroxylation reaction of 1-methylcyclohexene **4** has been reported. The reaction with AD β-mix goes with an e.e. of 52% but no detailed experimental procedure was given for this reaction.[11] Due to the water solubility and considerable volatility of the product diol **5**, we have found it necessary to modify somewhat the standard work-up procedure for this reaction. The wash with potassium hydroxide, which is normally used to remove methanesulphonamide, is omitted and no water is added during work-up. Because of the volatility of the diol, all solvents are removed by fractional distillation at each stage of the purification. With these precautions the diol is obtained, in 85% yield, after chromatography and sublimation. The e.e. for the diol can be determined by chiral shift NMR experiments on the corresponding *secondary* monoacetate. It was found to be the same, within experimental error, as the value determined by the use of chiral HPLC.[11] The racemic diol, needed to establish the analytical procedure, was prepared, in 65% yield, by the use of catalytic OsO_4 and NMO.[12]

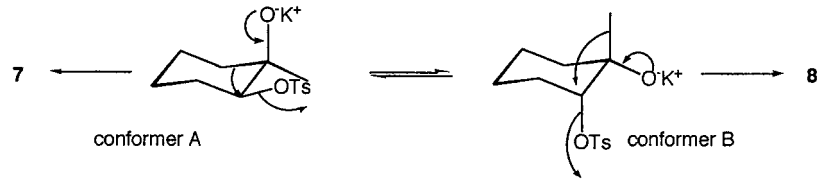
The optically active and racemic hydroxy tosylates **6** were prepared by standard procedures.[13] Conveniently it was found that the e.e. for these tosylate derivatives could also be obtained by chiral shift NMR experiments. Separation of the aromatic signals of the racemic compound into two pairs of apparent doublets was observed and baseline separation of the downfield pair could be obtained. It was then shown that recrystallisation of the optically active hydroxy tosylate gave rise to enantiomeric enrichment. The racemate was the first to crystallise and was separated. Upon concentration of the mother liquors the enriched tosylate crystallised and was found to be 75–80% e.e. On a larger scale run, it was found that three recrystallisations of the enriched tosylate from the mother liquors gave, in an overall yield of 37%, material which was 94±3% e.e.

Treatment of the racemic hydroxy tosylate **6** with KO*t*Bu in THF gave a mixture of the ketones **7** and **8** in a ratio of ≈8:1. These were identified in the following manner. The ^{1}H NMR spectrum showed a doublet at δ 1.0 and a singlet at δ 2.16 consistent with the signals expected for the methyl groups in the ketones **8** and **7**, respectively. A multiplet at δ 2.85 was consistent with the methine proton next to the carbonyl group in ketone **7**. GLC analysis showed two peaks. The minor peak had an identical retention time on co-injection with an authentic sample of 2-methylcyclohexanone. Preparation of 2,4-DNP hydrazone derivatives, followed by several recrystallisations of the product, gave, in 60% yield, the derivative of acetylcyclopentane, mp 127–128°C (lit. 127°C).[14] The ^{1}H NMR spectrum was consistent with this structure.

The hydroxy tosylate **6** does not react with NaSePh, generated, in situ, by the reaction of Ph_2Se_2 with $NaBH_4$ in EtOH, under the conditions (room temp.) that the epoxide **2** reacts smoothly. However, initially when the reaction mixture was then heated to reflux three volatile products were obtained which were isolated, in low yield, by removal of the solvent by distillation. The minor products were shown by NMR resonances and GLC analysis to be the rearrangement products **7** and **8** described above. The major product was the racemic pheromone **1** as elucidated from its NMR spectra. In particular, the ^{1}H NMR spectrum (200 MHz) showed a singlet for a methyl group at δ1.29, a methylene envelope between δ 1.5 and 1.8, a multiplet at δ 2.10 consistent with the allylic protons, and two olefinic resonances. The olefinic resonances consisted of a doublet at δ 5.63 which showed further long range coupling (J=10 and 1 Hz) and a doublet of triplets at δ 5.76 (J=4 and 10 Hz). Decoupling irradiation at δ 2.1 simplified the olefinic resonances to an AB quartet. This spectrum is consistent with that reported (but obtained at lower field strength) where the olefinic resonances were not well resolved.[2] An authentic sample of the racemic allylic alcohol **1** was obtained by the reaction of cyclohex-2-enone with MeMgI. The preparation of this larger sample also allowed the procedure for the isolation and purification of this volatile compound to be optimised for small scale preparations.

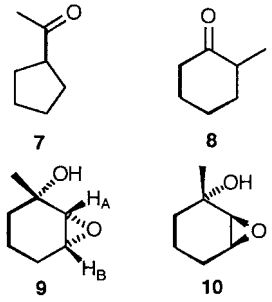


Scheme 2.



Scheme 3.

The amounts of the two minor products in the above reaction varied between experiments and it was reasoned that, because NaSePh is such a weak base and unlikely to remove a proton from an alcohol, it is likely that the by-products arose from adventious base. Indeed, when the glassware was washed with NH_4Cl solution and then water before being dried for use, the products **7** and **8** no longer formed during the reaction. It was also determined that no reaction took place when the tosylate **6** was refluxed alone in EtOH.



Treatment of the optically active tosylate **6** (75–80% e.e.) with NaSePh under these conditions gave, in 23% yield, the optically active pheromone **1b**$[\alpha]_D=-55$ (lit. +75.8 for *R* isomer >96% e.e.). On a larger scale, and with further optimisation of the procedure, the optically active tosylate **6** (94% e.e.) was converted to the allylic alcohol **1b** in 78% isolated yield. Because the determination of the e.e. with our polarimeter was likely to be inaccurate an alternative method for the estimation of the e.e. was sought. The enantiomeric purity of the *tertiary* allylic alcohol **1** could not be obtained directly by chiral shift NMR experiments and we did not have access to complexation GC.[2] Conversion of the alcohol **1b** to the epoxide with MCPBA at RT gives a mixture of the epoxides **9** and **10** in the ratio of 93:7 as determined by ^1H NMR. Reaction of the alcohol **1b** under slow addition of MCPBA in Et_2O at 0°, and buffered with $NaHCO_3$, gives the epoxide **9** in 70% yield whereas the minor diastereomer is no longer detected. Chiral shift NMR experiments on the epoxide **9** confirmed that the enantiomeric purity from the tosylate had been maintained (94% e.e.).

Discussion

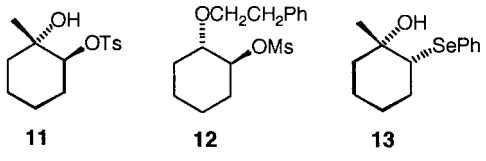
The rearrangement of the hydroxy tosylate **6** with base gives the products of anion pinacol rearrangements.[15,16] The stereoelectronic requirements for such a reaction are that rearrangement is favoured when the leaving group and the migrating bond are antiperiplanar.[17] This cyclohexyl tosylate is conformationally mobile therefore two products are possible. The major product, acetylcyclopentane **7**, arises from the conformer A (Scheme 3) where both the methyl group and the tosyl group are equatorial, whereas the minor isomer **8** arises from the conformation B where these groups are both axial. The major conformation for this ring system would be conformer A and the position of equilibrium would be similar to that found for methylcyclohexane ($K\approx20$) since the conformational effects of the O^-K^+ and OTs would largely cancel. It is unlikely that the energies of activation for these two rearrangement reactions are enormously different, therefore, it is not surprising that the major product from the rearrangement reaction is acetylcyclopentane **7**.

The mechanism for the elimination reaction observed is intriguing. The reaction of the tosylate **6** with NaSePh in EtOH is not an E1 mechanism for the following reasons. The qualitative observation is that the half-life for the reaction is concentration dependent; also no products from pinacol rearrangement are observed when care is taken to remove adventitious base; and furthermore the tosylate **6** is recovered unchanged after reflux in EtOH. The question arises, therefore, as to why selenide anion a powerful nucleophile to carbon, but non-nucleophilic to hydrogen attached to the oxygen of an alcohol, should suddenly change allegiance and become a nucleophile to hydrogen attached to carbon. Winstein, in a paper published in 1956,[18] first drew attention to the dichotomy of weak bases but good nucleophiles which promote elimination reactions when he wrote about merged substitution–elimination reactions. Since then there has been considerable debate[19,20] as to the veracity of his suggestion but, in our opinion, no clear explanation has been given for what is actually occurring in these reactions. Since our example appears to be one of the more extreme examples of this phenomenon, we hope that our observations will rekindle debate on this subject.

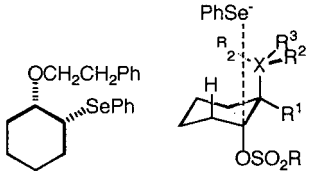
Under the same conditions, with NaSePh, as when the tosylate **6** gives only the elimination product **1**, both the racemic isomeric *trans*-tosylate **11** and the racemic mesylate **12** undergo clean substitution reactions to give the selenide derivatives **13**[21] and **14**, respectively. It has been shown[17] that for the 4-*t*-butylcyclohexyl derivatives the axial tosylate reacts faster than the equatorial tosylate in S_N2 reactions. Conformational mobility is clearly demonstrated for the tosylate **6**, even at room temperature, since the compounds **7** and **8** come from two different chair conformers of the alkoxide. From a study of models it is seen that when the leaving group is axial not only is the rear-side attack less hindered but, the nucleophile, the reaction centre and the leaving group can stay co-linear throughout the reaction.[†]

[†] A study of a model (axial leaving group down) shows that the reacting centre can move up smoothly towards the nucleophile as overlap of the orbitals takes place. This would give the product in the boat conformation. No such smooth pathway exists for the equatorial leaving group. We believe that this requirement would also account for the known *trans*-diaxial opening of cyclic epoxides.

Perhaps herein lies an explanation for our observations. It is likely that the selenide ion follows a trajectory co-incident with the dipole axis of the molecule and that, in both the compounds **11** and **12**, the propensity for carbon nucleophilicity is not thwarted by steric barriers since only lone pairs (see **15**) would hinder the approach. In the case of the tosylate **6**, however, the methyl group would clearly present an obstacle to rear-side attack. The deflected nucleophile might then encounter the hydrogen atom, held in an *anti-periplanar* relationship to the leaving group, with sufficient energy to overcome the barrier to elimination and this then becomes the lower energy process.



11 **12** **13**



14 **15**

In conclusion, therefore, we have developed a three step asymmetric synthesis of the pheromone, from achiral starting materials. The route is probably far more efficient than any to date and will be extremely efficient if further developments to the Sharpless procedure allow a more enantioselective preparation of the diol **5**. Furthermore the synthesis has revealed an intriguing elimination reaction which may help to unravel the paradoxes arising in the mechanism of weak-base elimination reactions.

Experimental

General procedure

Mp were taken on a Kofler hot stage apparatus under a Reichert microscope and are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian spectrometer at 200 or 300 MHz, as indicated. Optical rotations were measured with a Perkin–Elmer 141MC Polarimeter. MS were recorded on a VG ZAP 2HF mass spectrometer. Elemental analyses were carried out by the University of Otago, Department of Chemistry, Dunedin, New Zealand. Flash chromatography was performed with Merck Kieselgel 60 (230–400 mesh ASTM). TLC was performed with Merck DC Alufolien Kieselgel 60 F_{254} which were visualised either with UV light or by immersion in acidic ammonium molybdate solution. Other anhydrous solvents and reagents were prepared according to standard laboratory procedures.[22]

(1*S*,2*R*)-1-Methyl-cyclohexan-1,2-diol (5). A mixture of AD-mix-β (35.8 g), *t*-BuOH (125 mL), H_2O (125 mL), and $MeSO_2NH_2$ (2.45 g, 25.7 mmol) was cooled to 0°C, where upon some of the dissolved salts precipitated. 1-Methylcyclohexene (Aldrich, 3.0 mL, 23.4 mmol) was added and the reaction mixture stirred with a mechanical stirrer (500 rpm) for 48 h at 0°C. Sodium sulphite (37.9 g, 300 mmol) was added and the mixture allowed to warm to ambient temperature, and then stirred for a further 30 min. The aqueous phase re-extracted with CH_2Cl_2 (4×50 mL). The combined organic fractions were dried and solvent removed by distillation through a column packed with glass helices to give a yellow oil. Purification by flash chromatography (EtOAc/hexanes, 10/90, v/v) gave the *title compound* as yellow crystals. Sublimation at 60°C/0.5 mm Hg gave white crystals (1.9 g, 85%), mp 67–68°C. δ_H (200 MHz): 1.24 (s, 3H, Me), 1.2–1.6 (complex, methylene envelope, 8H), 1.8 (br s, 1H, –OH), 1.9 (br s, 1H, –OH), 3.4 (dd, *J*=3.9, 8.9 Hz, 1H, H2). δ_c: 21.5, 23.1, 26.5, 30.3, 36.8, 71.6, 74.8. ν_{max}: 3550(m, 2 peaks), 3475(w), 2975(s), 1040(m) cm^{-1}. *m/z*: 130($M^{+\cdot}$,14%), 112(29), 71(100). Lit:[23] δ_H: δ 1.25 (s, 3H), 1.0–1.9 (m, 8H), 3.38 (m, 1H) mp 69–70°C.

(1*S*,2*RS*) 1-Methyl-cyclohexan-1,2-diol (5r). 1-Methylcyclohexene (2.5 mL, 21.2 mmol) and an aqueous solution of 40.85 mg/mL OsO_4 (0.7 mL, 28 mg, 0.11 mmol) were added to NMO (3.71 g, 31.6 mmol) in H_2O (2 mL) and acetone (12 mL) and the reaction mixture stirred vigorously overnight. A slurry of fluorisil (1.75 g) and sodium hydrosulfite (0.59 g) were added, the mixture stirred for 30 min at ambient temperature, filtered through a pad of celite. Solvent was removed by distillation through a short fractionating column packed with glass helices. The pot residue was extracted with CH_2Cl_2 (3×10 mL), the combined organic extracts were dried and solvent was removed by distillation. Flash chromatography (EtOAc/hexanes, 30/70, v/v) gave the *title compound* (2.06 g, 75%). Further purification by sublimation at 50°C/0.5 mm Hg gave white crystals (1.75 g, 63%), mp 67–68°C. The spectral data corresponded with the data for the (1*S*,2*R*) enriched isomer.

(1*R*,2*S*)-(2-Methyl-2-hydroxy)cyclohexyl *p*-toluenesulfonate (6). A solution of the optically enriched diol **5** (2.59 g, 19.9 mmol) dissolved in pyridine (45 mL) was cooled to 0°C. To this was added tosyl chloride (5.38 g, 28.2 mmol) and the reaction mixture was then kept at 5°C for 15 h, poured over a slurry of ice, and extracted with CH_2Cl_2 (3 mL×50). The organic phase was washed successively with 7.5% HCl (3 mL×50) and saturated aq. $NaHCO_3$, dried and the solvent removed. Purification by flash chromatography (EtOAc/hexanes, 20/80, v/v) gave the *title compound* as white crystals (4.61 g, 82%), mp. 80–81°C. δ_H (200 MHz): 1.14 (s, 3H, CH_3), 1.2–1.8 (8H, complex, methylene envelope), 1.59 (s, 1H, HO), 2.45 (s, 3H, Ar-CH_3), 4.36 (dd, *J*=9.9, 4.0 Hz, 1H, H1), 7.34 (d, *J*=8.2 Hz, 2H, Ar), 7.80 (d, *J*=8.2 Hz, 2H, Ar). δ_c (50 MHz): 20.7, 21.6, 23.5, 26.9, 28.0, 37.5, 70.6, 87.0, 127.7, 129.8, 134.4, 144.7. $\nu_{max:}$ 3600(s), 2850(s), 1600(s), 1500(m), 1260(m), 1180(w) cm^{-1}. *m/z*: 285($M^{+\cdot}$,5%), 284(11), 155(68), 111(40), 44(100). Anal Calcd for $C_{14}H_{20}O_4S$: C, 59.13; H, 7.03. Found: C, 58.94; H, 6.98. Chiral shift NMR (200 MHz) analysis of the tosylate (12 mg) with $Eu(hfc)_3$ (12 mg) in CCl_4 (0.5 mL) and C_6D_6 (0.08 mL) gave with baseline separation, two broad *d* at δ 7.92 and δ 8.12 for the *d* originally at δ 7.80. By the method of cutting and weighing of the broad *d* resonances at δ 7.91 and δ 8.12 an enantiomeric excess of 55±3% was estimated. Recrystallisation from hexanes–Et_2O gave crystals which were

filtered and shown to be the racemate. Concentration of the mother liquor gave the optically active tosylate as crystals (75% e.e.). Further recrystallisations (×3) of the optically enriched material gave, in a 37% recovery yield, the tosylate, 94% e.e.

(1*RS*,2*SR*)-2-Methyl-2-hydroxycyclohexyl *p*-toluenesulphonate (6r). The above procedure was repeated with the racemic diol **5r** (1.56 g, 12.01 mmol), pyridine (20 mL) and tosyl chloride (3.10 g, 1.36 mmol). Purification by chromatography, (EtOAc/hexanes, 30/70, v/v) gave the *title compound* as white crystals (3.21 g, 94%), mp 80–81°C. The spectral data corresponded with the data for the (1*S*,2*R*) isomer.

Synthesis of acetylcyclopentane (7) and 2-methyl-cyclohexanone (8). To the tosylate **6r** (1.79 g, 6.32 mmol) dissolved in dry THF (20 mL) was added *t*-BuOK (1.50 g, 13.35 mmol). After stirring at ambient temperature for 24 h the white solution was worked up by addition of CH_2Cl_2 (10 mL), washed with H_2O and the aqueous phase extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were filtered through a pad of celite, dried and solvent removed to give a colourless oil (644 mg, 5.75 mmol, 91%) composed of **7** and **8**. δ_H (200 MHz):1.0 (d), 1.5–2.0 (complex, methylene envelope), 2.16 (s), 2.85 (m). The ratio of the integration for the resonances at δ 1.0 and 2.16 were ≈1:8. Ketones **7** and **8** were separated by GLC analysis (15% FFAP column, 2 m, at 130°C) and the compound **8** was identified by co-injection with authentic material.

Formation of 2,4-dinitrophenyl hydrazone of acetylcyclopentane

To a mixture of methyl-cyclopentyl-ketone **7** and 2-methyl-cyclohexanone **8** (401 mg, 3.58 mmol) was added Brady's reagent (9 mL) and the reaction mixture heated on a H_2O bath for 20 min then left sitting at ambient temperature overnight. The orange crystals were filtered, washed with 5% aq. $NaHCO_3$ and H_2O. Several recrystallisations from ethanol gave the *title compound* as orange crystals (621 mg, 2.15 mmol, 60%), mp 127–128°C. δ_H (200 MHz):1.5–2.0 (complex, 8H, methylene envelope), 2.06 (s, 3H, CH_3), 2.85 (m, 1H, H1), 7.96 (d, J=10.0 Hz, 1H, Ar), 8.32 (dd, J=3.0 and 10.0 Hz, 1H, Ar), 9.15 (d, J=3.0 Hz, 1H, Ar), 11.05 (br s, 1H, N*H*). ν_{max}: 3300(w), 2900(s), 1610 (m), 1580(m), 1500(w), 1250(m) cm^{-1}. Lit:[14] Mp 127°C.

(1*S*)-1-Methyl-2-cyclohexen-1-ol (1). To a dried roundbottom flask, previously washed with sat. NH_4Cl and H_2O, was added dry ethanol (14 mL) and Ph_2Se_2 (1.39 g, 4.48 mmol) and the mixture placed under N_2. To this was added $NaBH_4$ (557.2 mg, 14.73 mmol) at a rate to keep the reaction mixture below reflux. To the clear solution was added the tosylate **6** (2.07 g, 7.29 mmol) and the mixture was then refluxed for 3 h, then allowed to stir for 12 h. Removal of ethanol by distillation at atmospheric pressure through a vacuum-jacketed column gave a yellow solution. The residue was evaporatively distilled (kugelrohr) 120°/35 mm Hg to give the *title compound* as a colourless liquid (636.2 mg, 78%), $[\alpha]_D$=−55. δ_H (200 MHz): 1.29 (s, 3H, CH_3), 1.5–1.8 (methylene envelope+OH, 5H), 2.1 (m, 2H, H4), 5.60 (dm, J=10.0 Hz, 1H, H3), 5.75 (td, J=4.0 and 10.0 Hz, 1H, H2). Spectral data was consistent with that reported. Decoupling at δ 2.1 reveals the peaks at δ 5.75, 5.60 as an AB quartet. δ_c (50 MHz): 19.6, 25.1, 29.3, 37.9, 67.9, 129.1, 133.7. *m/z*: 112($M^{+\cdot}$,5%), 97(100), 95(24), 84(44), 79(29), 69(88), 54(36), 48(23).

(1*SR*)-1-Methyl-2-cyclohexen-1-ol (1r). CH_3I (2.2 mL, 35.09 mmol) was added dropwise to Mg (910.1 mg, 37.43 mmol), activated with I_2, in dry Et_2O (40 mL). The mixture was then stirred for 2 h. 2-Cyclohexene-1-one (2.0 mL, 20.6 mmol) was added dropwise. After the reaction, sat. NH_4Cl was added, the organic phase was separated, extracted with 10% $NaHCO_3$ and H_2O, dried and solvent removed by distillation through a vacuum jacketed column to yield a yellow oil (2.04 g). The crude mixture was purified by flash chromatography (EtOAc/hexanes/Et_3N, 20/75/5, v/v), (solvent removed by distillation), and short path distillation 60°C/42 mm Hg to give, in ~65% yield, the *title compound* as a clear oil (1.54 g, 13.73 mmol) with a small amount of triethylamine left as a stabiliser. Spectral data was identical with the pheromone **1b** previously synthesised.

Attempted formation of (1*SR*)-1-methyl-2-cyclohexenol (1r) by solvolysis

The racemic tosylate **6r** (153 mg, 0.53 mmol) in dry ethanol (4 mL) in a dried roundbottom flask, initially washed with sat. NH_4Cl and H_2O, was refluxed for 4 h under a N_2 atmosphere. CH_2Cl_2 (50 mL) was added to the reaction mixture, the reaction mixture washed with H_2O (2×40 mL), the organic extract dried and solvent removed at atmospheric pressure by distillation as above. The ^1H NMR showed no traces of the alkene, only the tosylate present (103 mg, 67% recovered).

(1*SR*,2*RS*,3*RS*)-2,3-Epoxy-1-methyl-cyclohexanol (9r). A solution of $NaHCO_3$ (0.63 M, 2 mL) was added to the racemic alcohol **1r** (149 mg, 1.32 mmol) dissolved in Et_2O (2 mL) and the solution was cooled to −5°C. *m*CPBA (Aldrich 85%, 377.4 mg, ~1.86 mmol) was added portionwise over 5 min and the biphasic solution was then stirred at ambient temperature for 3 h. CH_2Cl_2 (20 mL) was added to the mixture, it was washed with 1 M aq. NaOH (20 mL), H_2O (20 mL), dried, and solvent removed. Purification by flash chromatography (EtOAc/hexanes, 30/70, v/v) yielded the *title compound* as a colourless liquid (145 mg, 84%). δ_H (300 MHz):1.2–2.1 (methylene envelope, 6H), 1.33 (s, 3H, CH_3), 2.40 (br s, 1H, OH), 3.10 (d, J=4.0 Hz, 1H, H2), 3.36 (m, 1H, H3). δ_c (75 MHz): 16.5, 23.8, 26.0, 36.0, 56.1, 59.2, 68.8. Chiral shift analysis of the epoxide (11 mg) with Eu(hfc)$_3$ (7 mg) in CCl_4 (0.5 mL) and C_6D_6 (0.08 mL) gave separation of the epoxy protons initially at δ 2.40 and δ 3.10 into two pairs of peaks with baseline resolution of the upfield pair.

(1*S*,2*R*,3*R*)-2,3-Epoxy-1-methyl-cyclohexanol (9). The above procedure was repeated with aq. $NaHCO_3$ (0.63 M, 2 mL), the enantioriched alcohol **1** (101 mg, 0.89 mmol), Et_2O (3 mL), *m*CPBA (Aldrich 85%, 201 mg, ~0.99 mmol) at −5°C. Purification by flash chromatography (EtOAc/hexanes, 30/70, v/v) yielded the *title*

compound as a colourless liquid (63 mg, 55%), care was taken to include all fractions containing the epoxide to avoid enrichment by fractionation. Chiral shift analysis of the epoxide (4 mg) with $Eu(hfc)_3$ (3 mg) in CCl_4 (0.5 mL) and C_6D_6 (0.08 mL) gave similar separation of the epoxy protons as obtained for the racemic compound. The enantiomeric excess (94±3% e.e.) measured was unchanged from the optically enriched tosylate sample employed (94±3% e.e.).

***trans*-2-(Phenylselenyl)cyclohexyl(2′-phenylethyl) ether (14).** trans-*2-(2-Phenylethoxy)-cyclohexan-1-ol.* To a solution of sodium hydride, (oil removed with dry benzene, 159 mg, 6.60 mmol) in THF (6 mL) and HMPA (0.4 mL) was added 2-phenylethanol (0.25 mL, 2.10 mmol). The solution was refluxed and to this was added dropwise cyclohexane oxide (0.2 mL, 1.98 mmol) and further refluxed overnight. CH_2Cl_2 (10 mL) was added and the solution washed with sat. NH_4Cl (10 mL), the aqueous layer further extracted with CH_2Cl_2 (2×10 mL), the organic phase was dried and solvent removed. The crude product was purified by flash chromatography (EtOAc/hexanes, 20/80, v/v) then further by distillation (120°C/0.1 mm Hg) to give, as a clear oil, *trans*-2-(2-phenylethoxy)-cyclohexan-1-ol (130 mg, 0.59 mmol, 29%). δ_H (200 MHz):1.09 (m, 4H, methylene), 1.69 (m, 2H, methylene), 1.9–2.1 (m, 2H, methylene), 2.52 (br s, 1H, OH), 2.90 (t, J=7.0 Hz, 2H, H2′), 3.05 (m, 1H, H1 or H2), 3.37 (m, 1H, H1 or H2), 3.57 (dt, J=7.4 and 9.1 Hz, 1H, H1′, diastereotopic), 3.95 (dt, J=6.6 and 9.2 Hz, 1H, H1′, diastereotopic), 7.28 (m, 5H, Ar-H). δ_C (50 MHz):23.9, 24.2, 29.2, 31.9, 36.7, 69.5, 73.7, 84.1, 126.3, 128.4, 128.9, 139.0. $\nu_{max}(CDCl_3)$: 3550 (m), 3400 (w), 2900 (s), 1600(m), 1500(m), 1260(m) cm^{-1}. *m/z*(FAB): 221 (MH^+,9%), 203(5), 121(3), 105(100).

trans-*(2-Phenylethoxy)cyclohexyl methanesulphonate (12).* To the above alcohol (103 mg, 0.47 mmol) in CH_2Cl_2 (2.2 mL) and Et_3N (0.095 mL, 0.68 mmol), cooled to 0°C, was added dropwise mesyl chloride (0.05 mL, 0.65 mmol) and let stir for 20 min. Then CH_2Cl_2 (10 mL) and ice water (5 mL) were added to the reaction mixture and the organic layer was separated, washed with cold 15% HCl, cold sat. $NaHCO_3$ and cold brine, dried and the solvent removed to give the *trans*-(2-phenylethoxy)cyclohexyl methanesulfonate **12** as a colourless oil (138 mg, 0.46 mmol) in a 99% yield. δ_H (200 MHz):1.31 (m, 4H, methylene), 1.72 (m, 2H, methylene), 2.17 (m, 2H, methylene), 2.78 (s, 1H, CH_3), 2.86 (t, J=6.8, 2H, H2′), 3.31 (m, 1H, H2), 3.69 (dt, J=9.0 and 7.9, 1H, H1′, diastereotopic), 3.82 (dt, J=7.7 and 9.3 Hz, 1H, H1′, diastereotopic), 4.32 (ddd, J=4.8, 8.6 and 10.4, 1H, H1), 7.23 (5H, m, Ar-H). δ_C (50 MHz):23.0, 23.5, 29.8, 31.9, 36.4, 37.6, 69.7, 79.1, 84.3, 125.9, 128.1, 128.7, 138.8. ν_{max}: 3000(m), 2900(s), 2800(m), 1600(w), 1500(m), 1440(m), 1400(m), 1350(br, s), 1150(s), 1100(m), 950(s), 920(s), 870(m), 810(m), 740(s) cm^{-1}. *m/z*(FAB): 299(MH^+,8%), 275(3), 203(51), 177(28), 135(22), 117(35), 105(100).

trans-*2-(Phenylselenyl)cyclohexyl(2′-phenylethyl) ether (14).* Solid $NaBH_4$ (105 mg, 2.78 mmol) was added to a solution of Ph_2Se_2 (253 mg, 0.81 mmol) in dry ethanol (4 mL) at a rate to keep the reaction mixture below reflux. The above mesylate **12** (280 mg, 0.94 mmol) was added and the reaction mixture refluxed for 6 h. Then CH_2Cl_2 (10 mL) was added and the solution was washed with sat. $NaHCO_3$ (10 mL), H_2O (50 mL), dried, and solvent removed to give a yellow solid which was purified by flash chromatography (CH_2Cl_2/hexanes 20/80, v/v), to give, in a 53% yield, the *title compound* as a clear oil (176 mg, 0.49 mmol). δ_H (200 MHz):1.33–2.04 (m, 8H, methylene envelope), 2.93 (t, J=7.3 Hz, 2H, H2′), 3.49 (m, 1H, H1), 3.68 (m, 3H, H2 and H1′), 7.26 (m, 8H, Ar-H and Se–Ar-H), 7.62 (m, 2H, Se–Ar-H). δ_C (50 MHz):21.1, 25.2, 29.4, 30.3, 36.6, 49.4, 69.7, 78.4, 126.0, 126.9, 128.2, 128.8, 129.0, 130.7, 134.1, 139.2. $\nu_{max}(CDCl_3)$: 2800(s), 1600(s), 1570(m), 1500(s), 1420(s), 1350(s), 1290(s), 1230(s), 1160(s) cm^{-1}. *m/z*(FAB): 360(MH^+,20%), 256(15), 239(41), 105(100). Analytical results were not obtained.

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