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A new diastereoselective entry to the (1*S*,4*R*)- and (1*S*,4*S*)-isomers of 4-isopropyl-1-methyl-2-cyclohexen-1-ol, aggregation pheromones of the ambrosia beetle *Platypus quercivorus*

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ABSTRACT

A concise diastereoselective and enantiopure route to the (1*S*,4*R*)- and (1*S*, 4*S*)-isomers of 4-isopropyl-1-methyl-2-cyclohexen-1-ol via a palladium-catalysed deoxygenation of the enol triflate derived from limonene glycol.

1. Introduction

Over the past two decades, the epidemic mortality of the deciduous oak *Quercus crispula* has posed a significant threat to Japan's forest ecosystem.[1] The dieback is caused by the fungus *Raffaela quercivorus*, which is transmitted by the ambrosia beetle *Platypus quercivorus* (Murayama). It has recently been revealed that the invasion of *Q. crispula* and subsequent boring by the beetles are mediated by the semiochemicals (1*S*,4*R*)-4-isopropyl-1-methyl-2-cyclohexen-1-ol (*cis*-2-menthen-1-ol, **1**), and (1*S*,4*S*)- and (1*R*,4*R*)-4-isopropyl-1-methyl-2-cyclohexen-1-ol (*trans*-2-menthen-1-ol, **2** and **2′**) (Fig. 1), first isolated and reported by Nakashima et al.[2] The isomer (1*S*,4*R*)-**1** is the major aggregation pheromone of the ambrosia beetle. (1*S*,4*S*)-**2** and (1*R*,4*R*)-**2′** were also identified as minor components of *P. quercivorus*, although their precise semiochemical role is yet to be determined.

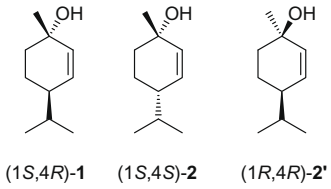
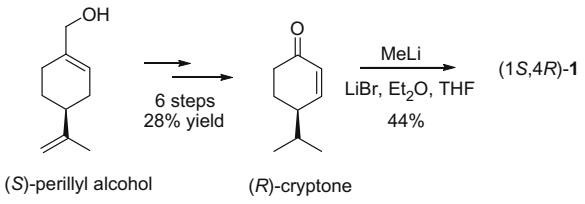


Figure 1. The frass volatiles of *P. quercivorus*.

Mori confirmed the absolute stereochemistry via the total synthesis of all three of these pheromones **1**, **2** and **2′**,[3] thus allowing field bioassays to be conducted on the synthetic pheromone (1*S*,4*R*)-**1** and confirming its role as a conspecific beetle aggregation sex pheromone. The (1*S*,4*R*)-**1** isomer lured 14.4 times as many ambrosia beetles (*P. quercivorus*) versus any other beetle species, and 3.32 times as many males to females.[4]

The synthesis of highly enriched single enantiomers of these molecules **1** and **2** has not been facile.[3] Base-promoted isomerisation of epoxides typically leads to the undesired *exo*-alkene.[5] The (1*S*,4*R*)-**1** isomer can be synthesised in one step by methylation of (*R*)-cryptone. However, this reaction is unselective, and produces a diastereomeric mixture of (1*S*,4*R*)-**1** and (1*R*,4*R*)-**2′** from which (1*S*,4*R*)-**1** could be obtained in a 44% yield after chromatographic purification and distillation (Scheme 1).[3] The enantiomeric purity of (1*S*,4*R*)-**1** was determined as 93.3% ee and it was contaminated with small amounts of (1*R*,4*R*)-**2′**. Furthermore the synthesis of (*R*)-cryptone is accomplished in six steps (28% overall yield), utilising (*S*)-perillyl alcohol as the chiral pool starting material, via a modified literature procedure for the preparation of 4-isopropenyl-2-cyclohexenone.[6]



Scheme 1. Mori's methylation of (*R*)-cryptone to afford the synthetic pheromone **1**.[3]

The (1*S*,4*S*)-**2** and (1*R*,4*R*)-**2′** isomers were synthesised by Mori from the desired enantiomer of limonene oxide (3:2 mixture of *cis*- and *trans*-diastereomers) utilising Sharpless' organoselenium chemistry on dihydrolimonene oxide (Scheme 2). A regio- and diastereomeric mixture of phenylselenohydrins was obtained, from which the desired selenide could be separated by chromatography. The presence of pyridine was essential for the success of the

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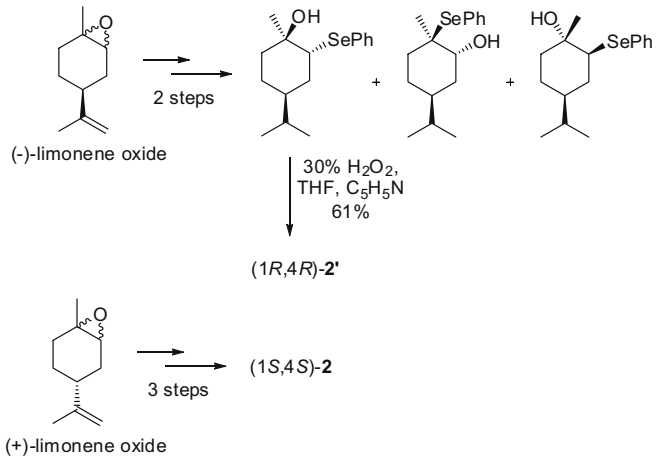
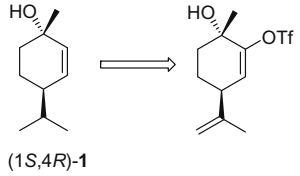


Scheme 2. Mori's synthetic strategy for accessing the minor constituents.

selenoxide elimination, otherwise acid-catalysed allylic rearrangement products of **2** ensued. The enantiomeric purity of (1*S*,4*S*)-**2** and (1*R*,4*R*)-**2**′ was 94.5% and 94.3%, respectively.[3]

In light of the problems associated with the current synthesis, we hoped to gain access to the pheromones (1*S*,4*R*)-**1** and (1*S*,4*S*)-**2** both enantiomerically and diastereomerically pure via the hydrolytic by-products isolated from the kinetic separation of the commercial mixture of *cis* and *trans* (+)- or (−)-limonene oxide.

Limonene oxide has only recently begun to enjoy widespread use as a chiral pool reagent, unlike other monoterpene building blocks popularised in total synthesis such as carvone,[7] peryillyl alcohol,[8] isopulegol[9] and limonene.[10] We believe that limonene oxide has not been adopted as an enantiomerically pure building block in total synthesis because the commercially available (+)- or (−)-limonene oxide is a diastereomeric mixture (approximately a 1:1 mixture of *cis* and *trans* epoxides) and there are relatively few practical and preparative routes to obtain the desired diastereoisomer.[11–13] Recently we reported a highly diastereoselective hydrolytic kinetic separation of the commercial mixture of *cis* and *trans* limonene oxide to afford either *trans*-diequatorial-1,2-dihydrolimonene or *trans*-diaxial-1,2-dihydrolimonene, depending on the reaction protocol employed.[14] Herein, we report a highly diastereoselective, novel second total synthesis of the volatile pheromones (1*S*,4*R*)-**1** and (1*S*,4*S*)-**2** of the beetle *P. quercivorus* utilising either the *trans*-diaxial diol or the *trans*-diequatorial diol as the chiral pool building block (Scheme 3). The key step in the synthetic route was a Stille type reduction of the enol triflate with an organostannane/silane (Scheme 4). The deoxygenation of ketones to the corresponding olefin via a $Pd^{[0]}$catalysed enol triflate reduction has been well studied,[15] and it was anticipated that we could utilise similar chemistry in the synthesis of the pheromones **1** and **2**. If successful, this would be a novel route for the synthesis of tertiary endocyclic allylic alcohols, which is complementary to the organoselenium chemistry.



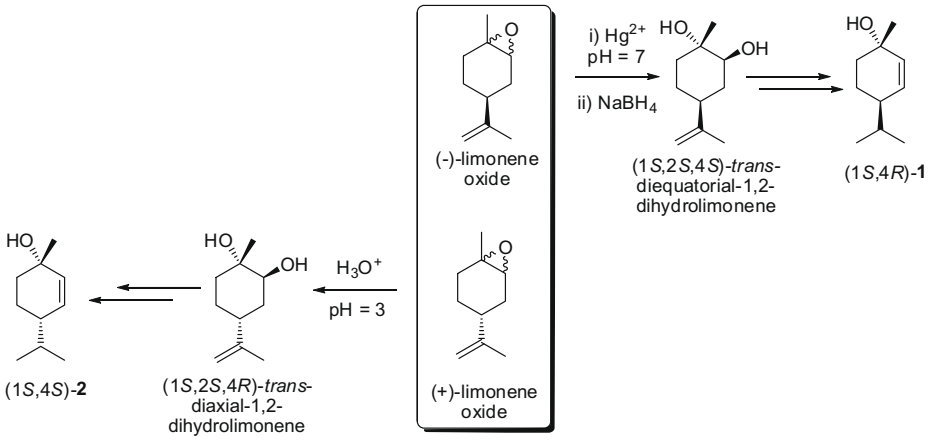
Scheme 4. Key synthetic strategy for the synthesis of compounds **1** and **2**.

2. Results and discussion

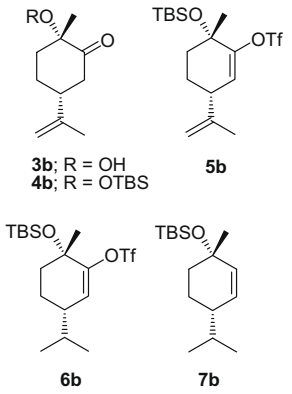
2.1. Total synthesis of the (1*S*,4*R*)- and (1*S*,4*S*)- isomers of 4-isopropyl-1-methyl-2-cyclohexen-1-ol

Our initial attempts to synthesis the required enol triflate were with the unprotected analogue (Scheme 4). The first step was oxidation of the (1*S*,2*S*,4*S*)-*trans*-diequatorial diol to the corresponding hydroxy ketone **3a**. Standard oxidation conditions for secondary alcohols, pyridinium chlorochromate (PCC), Swern conditions and TEMPO/TCCA gave poor product purity and yields of the ketol **3a**. The use of IBX (*o*-iodoxybenzoic acid)[16] gave superior yields and product purity (>95%) while ketol **3a** was typically used without further purification (Scheme 5). Ketol **3b** was obtained in excellent yields using the same conditions.

Our attempts to synthesise the enol triflate directly from either ketol **3a** or **3b** using KHMDS (2 equiv) and *N*-phenylbistrifluorosulfonamide ($PhNTf_2$) were unsuccessful. The corresponding *tert*-butyldimethylsilyl derivatives **4a** and **4b** reacted cleanly under similar conditions, but with 1 equiv of base, to give either the *tert*-butyldimethylsilyloxy enol triflate **5a** or **5b**. Selective reduction of the *exo*-cyclic olefin was achieved with Adam's catalyst (PtO_2)[3] under an atmosphere of hydrogen. Under these conditions, racemisation of the 4-position of the enol triflates **6a** and **6b** does not occur.[17]



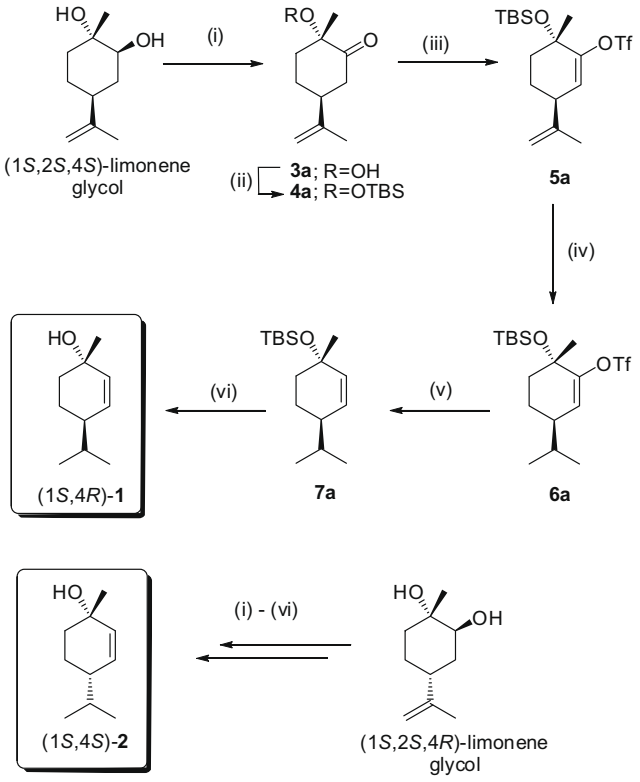
Scheme 3. Complementary routes to compounds **1** and **2** from (+)- or (−)-limonene oxide.



The synthesis of the *endo*-cyclic allylic ether **7a** or **7b** by Stille reduction of the enol triflate was successful [$Pd(PPh_3)_4$ (20 mol %), LiCl and 5 M equiv of either Bu_3SnH or Et_3SiH, in DMF at 75 °C, 2 h,[18] as determined via ^1H NMR analysis of the crude reaction sample. However, the excess starting material and by-products of the reaction (Bu_3SnH/Bu_3SnCl or Et_3SiCl) could not be removed by chromatography due to the similarity of their polarity to the TBS-protected pheromone **7a** or **7b** on silica. Fluorolytic methods ($KF_{(aq)}$ or 10% KF/silica) to remove the excess Bu_3SnCl or Et_3SiCl were investigated; however, neither of these were successful.[19,20] In an effort to separate the alkylsilanes or stannanes, an in situ deprotection of **7a** and **7b** was attempted, thus allowing their separation from the pheromone. However, even 7 equiv of TBAF and prolonged heating were unsuccessful in removing the *tert*-butyldimethylsilyl protecting group. This is presumably due to a competing side reaction of TBAF with residual organostannanes/silanes.

An alternate reagent for the palladium-catalysed reduction of enol triflates is a trialkylammonium formate—palladium complex.[21–23] This reagent can be used for the efficient and straightforward reduction of enol triflates to alkenes, it is also tolerant of a wide range of functional groups including tertiary alcohols and esters. Treatment of enol triflate **6a** or **6b** with HCO_2H and PPh_3 in the presence of $Pd(OAc)_2$ and PPh_3 gave the desired olefin in good yields after a simple extraction and elution through a short silica plug in neat hexane.

Finally, the *tert*-butyldimethylsilyloxy pheromone **7a** or **7b** was deprotected; TBAF (1.5 equiv) in refluxing THF gave the synthetic pheromones (1*S*,4*R*)-**1** or (1*S*,4*S*)-**2**, respectively, in excellent yields (>90%). No racemisation, which would produce diastereomers, was observed throughout the synthesis. The enantiomeric excess of the pheromones (1*S*,4*R*)-**1** or (1*S*,4*S*)-**2** was 98–99% ee, identical to that of the chiral pool reagent (+)- or (−)-limonene oxide. Furthermore, we have established an alternate route for the synthesis of tertiary allylic alcohols that does not use the conventional organoselenium chemistry.



Scheme 5. Total synthesis of the synthetic pheromones **1** and **2**. Reagents and conditions: (i) IBX, EtOAc, reflux, **3a** 93%, **3b** 98%; (ii) TBSOTf, 2,6-lutidine, DCM, −78 °C to rt, **4a** 61%, **4b** 99%; (iii) KHMDS, THF, −78 °C then $PhNTf_2$, −78 °C to rt, **5a** 91%, **5b** 82%; (iv) 1 mol % PtO_2, H_2, MeOH, **6a** 75%, **6b** 88%; (v) 5 mol % $Pd(OAc)_2$, PPh_3, DIPEA, formic acid, DMF, 70 °C, **7a** 75%, **7b** 88%; (vi) TBAF, THF, reflux, **1** 81%, **2** 91%.

3. Conclusion

The pheromones (1*S*,4*R*)-*cis*-2-menthen-1-ol **1** and (1*S*,4*S*)-*trans*-2-menthen-1-ol **2** were synthesised in high diastereoselectivity (>98% de), enantiomeric purity (98–99% ee) and good overall yields (32% **1**, 45% **2** from *trans*-1,2-dihydrolimonene). Utilising this synthetic sequence, the synthesis of all components of the volatiles of *P. quercivorus* in high enantiomeric purity is now possible. This will facilitate further field studies on the roles of the minor constituents of *P. quercivorus,* which will aid in evaluating their activity, with the eventual hope of improved trapping techniques being developed, thereby addressing the invasion and epidemic mortality of the deciduous oak *Q. crispula* by the ambrosia beetle.

4. Experimental

4.1. General

All reagents were purchased from the Aldrich Chemical Co. and used without further purification. Solvents were dried, when necessary, by standard methods. Organic solutions were dried over $MgSO_4$. The progress of the reactions was monitored by thin layer chromatography (TLC) on Merck 60 F240 precoated silica gel polyester plates, and products were visualized with vanillin dip. Flash chromatography was performed with Davisil LC60A, 40–63 μm silica media.

Proton (^1H) and carbon (^{13}C) NMR spectra were recorded in $CDCl_3$ on either a Bruker AM300, Bruker AV400 or Varian DRX 500 spectrometer operating at 300, 400 and 500 MHz, respectively, for proton and 75, 100 and125 MHz for carbon nuclei. Chemical shifts (δ) are expressed in parts per million (ppm) and referenced to residual solvent signal as the internal standard. Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer RXI FTIR Spectrometer as thin films on NaCl plates. Low resolution mass spectrometry (ESI) was performed on a Micromass Platform QMS spectrometer. High resolution mass spectra (HRMS) were recorded on either a Bruker BioApex 47e FTMS fitted with an analytical electrospray source using NaI for accurate mass calibration or a Waters GC-TOF. Low resolution (EI) mass spectra were recorded on a VG Micromass 70/70F mass spectrometer with an ion source temperature of 200 °C and electron impact energy of 70 eV. Optical rotations were obtained using a PolAAR 2001 automatic polarimeter, using a 1 dm cell with chloroform as a solvent, at a wavelength of 589 nm (sodium D line).

4.2. (2*S*,5*S*)-2-Hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohexanone 3a

To a solution of *trans*-diequatorial-1,2-dihydrolimonene[14] (1.47 g, 8.63 mmol) in EtOAc (40 mL) was added iodoxybenzoic acid (IBX) (6.28 g, 22.4 mmol). After the heterogeneous solution was refluxed for 12 h, it was cooled to ambient temperature and filtered through a sintered funnel. The residue was washed with EtOAc (20 mL), the filtrate dried and concentrated in vacuo to afford the *title compound* as a colourless oil (1.36 g, 93% yield), which was typically used without further purification. An analytical sample was obtained by purification of a small portion by flash column chromatography (25% EtOAc: 75% hexanes). $[\alpha]_D^{20} = +2.5$ (*c* 1.0 $CHCl_3$). ^{1}H NMR (500 MHz) δ 1.41 (s, 3H), 1.64–1.72 (m, 2H), 1.75 (s, 3H), 1.90 (m, 1H), 2.18 (m, 1H), 2.35–2.40 (m, 2H), 2.52–2.55 (m, 2H), 4.75 (s, 1H), 4.80 (m, 1H). ^{13}C NMR (125 MHz) δ 18.7, 26.5, 30.1, 39.0, 41.3, 42.9, 68.0, 113.2, 145.3, 214.0. IR (film): 3486 (m), 2972 (m), 2856 (w), 1715 (s) cm^{-1}. MS (ESI) *m/z*: 207.10 $(M+K)^+$. HRMS (ESI) calcd for $C_{10}H_{17}O_2$ $(M+H)^+$ *m/z* 169.1223, found: 169.1223.

4.3. (2*S*,5*R*)-2-Hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohexanone 3b

The above procedure was repeated with *trans*-diaxial-1,2-dihydrolimonene,[14] the *title compound* was obtained as a colourless oil in a 98% yield. $[\alpha]_D^{20} = -49.2$ (*c* 1.1 $CHCl_3$,). ^{1}H NMR (500 MHz) δ 1.36 (s, 3H), 1.70 (m, Hz, 3H), 1.75–2.05 (complex, 4H), 2.58 (dd, *J* = 5.6, 13.6 Hz, 1H), 2.66 (m, 1H), 2.78 (ddd, *J* = 1.6, 5.4, 13.6 Hz, 1H), 2.96 (br s, 1H), 4.69 (d, *J* = 0.5 Hz, 1H), 4.86 (d, *J* = 0.5 Hz, 1H). ^{13}C NMR (125 MHz) δ 21.8, 25.3, 25.5, 37.4, 41.7, 44.3, 75.9, 112.2, 146.3, 213.7. IR (film): 3348 (br s), 3157 (m) 3057 (w), 2860 (w), 1711 (s) cm^{-1}. HRMS (ESI) calcd for $C_{10}H_{16}NaO_2$ $(M+Na)^+$ 191.1043, found: 191.1041.

4.4. (2*S*,5*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-methyl-5-(prop-1-en-2-yl)cyclohexanone 4a

To a solution of the hydroxy ketone **3a** (1.26 g, 7.49 mmol) 2,6-lutidine (2.0 mL, 17.3 mmol) in dry DCM (20 mL), at −78 °C under an atmosphere of nitrogen, was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (2.2 mL, 3.9 mmol) dropwise. The solution was allowed to warm to room temperature over 1.5 h. The reaction mixture was quenched with cold 1 M $HCl_{(aq)}$ (1 × 20 mL), washed with brine (3 × 20 mL), dried and concentrated in vacuo and subsequently subjected to flash column chromatography (10% EtOAc: 90% hexanes), to afford the *title compound* as a colourless oil (1.29 g, 61%). $[\alpha]_D^{20} = -41.3$ (*c* 2.3, $CHCl_3$). ^{1}H NMR (200 MHz) δ 0.08 (s, 3H), 0.11 (s, 3H), 0.86 (s, 9H), 1.36 (s, 3H), 1.66 (m, 1H), 1.72 (s, 3H), 1.76 (m, 1H), 1.90–1.97 (m, 2H), 2.39–2.47 (m, 2H), 2.53–2.57 (m, 1H), 4.72 (s, 1H), 4.78 (m, 1H). ^{13}C NMR (125 MHz) δ −2.4, −2.1, 18.6, 21.2, 25.7, 26.2, 27.4, 41.1, 43.6, 45.7, 79.2, 110.7, 147.1, 211.3. IR (film): 2950 (m), 2935 (s), 2856 (m), 1728 (s), 1472 (w), 1462 (m), 1360 (w), 1253 (s), 1207 (m) cm^{-1}.

4.5. (2*S*,5*R*)-2-(*tert*-Butyldimethylsilyloxy)-2-methyl-5-(prop-1-en-2-yl)cyclohexanone 4b

The above procedure was repeated with the hydroxy ketone **3b**, the *title compound* was obtained as a colourless oil in a 99% yield. $[\alpha]_D^{20} = +59.8$ (*c* 1.25, $CHCl_3$). ^{1}H NMR (400 MHz) δ 0.02 (s, 3H), 0.12 (s, 3H), 0.91 (s, 9H), 1.30 (s, 3H), 1.42–1.63 (complex, 2H), 1.73 (s, 3H), 1.95–2.07 (m, 2H), 2.20–2.32 (m, 2H), 2.99 (m, 1H), 4.72–4.76 (m, 2H). ^{13}C NMR (100 MHz) δ −2.9, −1.8, 18.5, 20.6, 23.9, 26.16, 26.23, 41.9, 43.0, 47.6, 110.1, 147.9, 211.7. IR (film): 2857 (s), 1723 (s), 1463 (m), 1375 (m), 1254 (s), 1198 (m) cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{30}NaO_2Si$ $(M+Na)^+$ 305.1913, found: 305.1905.

4.6. (3*S*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-6-methyl-3-(prop-1-en-2-yl)cyclohex-1-enyl trifluoromethane-sulfonate 5a

A solution of the TBS-ether **4a** (1.10 g, 3.89 mmol) in anhydrous THF (5 mL) was cooled to −78 °C, and potassium bistrimethylsilylamide (0.5 M solution in toluene, 8.6 mL, 4.22 mmol) was added dropwise under an atmosphere of nitrogen; stirring was maintained at this temperature for 30 min, after which *N*-phenyl-bis(trifluoromethanesulfonimide) (1.53 g, 4.28 mmol) in anhydrous THF (5 mL) was introduced via a syringe to the −78 °C solution of the potassium enolate. Stirring was continued whilst warming to ambient temperatures over 2.5 h, after which the reaction was deemed to have gone to completion via TLC analysis. The reaction mixture was quenched with water (10 mL), diluted with ether (50 mL) and was washed with saturated brine (3 × 20 mL). The organic phase was dried, concentrated, and subjected to flash column chromatography (5% EtOAc: 95% hexanes) to yield the *title compound* as colourless oil (1.48 g, 91% yield). Alternatively, dissolution of the crude residue in MeOH precipitated residual *N*-phenyltrifluorosulfonimide, which then afforded the *title compound* after filtration and removal of solvent in vacuo. The material obtained was of acceptable purity (>90% by ^{1}H NMR analysis). $[\alpha]_D^{20} = -66.15$ (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz) δ 0.11 (s, 3H), 0.13 (s, 3H), 0.87 (s, 9H), 1.43 (s, 3H), 1.56 (m, 1H), 1.75 (s, 3H), 1.83–1.88 (m, 2H), 1.95 (m, 1H), 2.97 (m, 1H), 4.70 (m, 1H), 4.85 (m, 1H), 5.67 (d, *J* = 4.0 Hz, 1H). ^{13}C NMR (100 MHz) δ −2.3, −2.1, 18.4, 21.6, 23.8, 25.8, 25.9, 26.8, 37.7, 42.7, 72.0, 112.7, 120.8, 145.5, 152.8. IR ($CDCl_3$): 2956 (w), 2931 (w), 2858 (w), 1260(m), 1248 (m), 1215 (s), 1143 (s) cm^{-1}. HRMS (EI) calcd for $C_{16}H_{27}F_3O_4SSi$ $(M-CH_4)$**.** 399.1268, found: 399.1241 (6%), 357.0830 (84), 207.0271 (37), for 133.1351 (100).

4.7. (3*R*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-6-methyl-3-(prop-1-en-2-yl)cyclohex-1-enyl trifluoromethane-sulfonate 5b

The above procedure was repeated with the TBS-ether **4b**, the *title compound* was obtained as a colourless oil in an 82% yield. $[\alpha]_D^{20} = +5.8$ (*c* 1.25, $CHCl_3$). ^{1}H NMR (500 MHz) δ 0.047 (s, 3H), 0.054 (s, 3H), 0.08 (s, 9H), 1.36 (s, 3H), 1.60–1.68 (m, 2H), 1.67 (s, 3H), 2.03 (m, 1H), 2.94 (m, 1H) 4.84 (s, 1H), 4.87 (m, 1H), 5.63 (d, *J* = 2.5 Hz, 1H). ^{13}C NMR (125 MHz) δ −2.3, −2.1, 18.4, 20.8, 24.2, 25.9, 26.6, 38.9, 44.0, 71.6, 112.4, 117.4, 121.7, 146.6, 152.7. IR (film): 2954 (s), 2932 (s), 2859 (s), 1249 (s), 1211 (s), 1145 (s) cm^{-1}. MS (EI) *m/z* 399.1 $((M-CH_4)^{+\cdot}, 4\%)^+$, 357.1(58), 207.1 (25), 133.2 (100). HRMS (ESI) calcd for $C_{17}H_{33}F_3NO_4SSi$ $(M+NH_4)^+$ 434.1852, found: 432.1848.

4.8. (3*R*,6*S*)-6-*tert*-Butyldimethylsilyloxy)-3-isopropyl-6-methylcyclohex-1-enyl trifluoromethanesulfonate 6a

A solution of enol triflate **5a** (1.38 g, 3.32 mmol) and PtO_2 (7.5 mg, 1 mol %) in absolute methanol (15 mL), under an atmosphere of hydrogen, was stirred at room temperature for 3 h, after which time the reaction had gone to completion (TLC analysis, 100% hexane). Filtration of the crude reaction mixture through a bed of Celite followed by concentration of the filtrate in vacuo afforded the *title compound* as a colourless oil (1.28 g 93% yield), which was used without further purification. $[\alpha]_D^{20} = -21.7$ (*c* 2.65, $CHCl_3$). ^{1}H NMR (400 MHz) δ 0.11 (s, 6H), 0.88, (s, 9H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 1.38–1.45 (complex, 4H), 1.66 (m, 1H), 1.75 (m, 1H), 1.85–2.00 (m, 2H), 2.19–2.26 (m, 1H) 5.60 (dd, *J* = 3.0, 0.6 Hz, 1H). ^{13}C NMR (100 MHz) δ −2.2, −2.1, 18.4, 19.8, 19.9, 23.0, 24.9, 26.8, 31.9, 39.6, 41.8, 72.5,

120.3, 121.3, 152.4. IR (film): 2959 (s), 2933 (s), 2865 (sh), 2859 (s), 1248 (s), 1211, 1146 (s) cm^{-1}. HRMS (EI) calcd for $C_{16}H_{28}F_3O_4SSi$ $(M-CH_4)^{+\cdot}$ 401.1430, found: 401.1408 (11%), 359.1017 (83), 135.1534 (100).

4.9. (3*S*,6*S*)-6-*tert*-Butyldimethylsilyloxy)-3-isopropyl-6-methylcyclohex-1-enyl trifluoromethanesulfonate 6b

The above procedure was repeated with the enol triflate **5b**, the *title compound* was obtained as a colourless oil in an 81% yield. $[\alpha]_D^{20} = -35.5$ (*c* 1.55, $CHCl_3$). ^1H NMR (500 MHz) δ 0.10 (s, 3H), 0.12 (s, 3H), 0.86 (s, 9H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H), 1.4 (s, 3H), 1.51 (m, 1H), 1.60–1.64 (m, 2H), 1.75 (m, 1H), 1.97 (m, 1H), 2.16 (m, 1H), 5.59 (d, *J* = 2 Hz, 1H). ^{13}C NMR (125 MHz) δ −2.4, −2.2, 18.3, 19.4, 19.7, 20.6, 25.9, 26.7, 32.0, 39.6, 42.9, 71.7, 119.1, 122.3, 152.6. IR (film): 2959 (s), 2932 (s), 2859 (s), (s), 1210 (s), 1173 (m), 1145 (s), cm^{-1}. MS (EI) *m/z* 401.1 ($C_{16}H_{28}F_3O_4SSi\cdot-CH_4$, 6%)$^+$, 359.1 (44), 265 (18), 251 (30), 207 (49), 183 (24), 135 (100). HRMS (EI) calcd for $C_{16}H_{28}F_3O_4SSi$ $(M-CH_4)^{+\cdot}$ 401.1430, found: 401.1410 (6%), 359.0930 (90), 265.0194 (26), 251.0470 (52), 207.0099 (78), 135.1462 (100).

4.10. (1*S*,4*R*)-*tert*-Butyl((1*S*,4*S*)-4-isopropyl-1-methylcyclohex-2-enyloxy)dimethylsilane 7a

Following a modified procedure of both Cacchi et al.[21,22] and Liu et al.,[23] to a stirred solution of the dihydroenoltriflate **6a** (1.15 g, 2.76 mmol), DIPEA (2.1 mL, 6.03 mmol), $Pd(OAc)_2$ (31 mg, 148 μmol) and triphenylphosphine (72 mg, 275 μmol) in dry DMF (20 mL), under an atmosphere of nitrogen, was slowly added 98%formic acid (208 μL, 5.50 mmol). The reaction temperature was warmed to 70 °C with the aid of an external oil bath, and maintained at this temperature for 2 h. After this period, complete conversion to the *title compound* was observed via TLC analysis. The reaction mixture was diluted with water (40 mL), extracted into hexanes and dried, after which it was subjected directly to a short silica gel plug in neat hexanes, to afford a clear volatile oil (556 mg, 75% yield) after concentration of the solvent under reduced pressure (330 mbar, 40 °C). $[\alpha]_D^{20} = -77.3$ (*c* 2.07, $CHCl_3$). ^1H NMR (500 MHz) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.86 (s, 9H), 0.86 (d, *J* = 8.5 Hz, 3H), 0.88 (d, *J* = 8.5 Hz, 3H), 1.23 (s, 3H), 1.32 (m, 1H), 1.57 (m, 1H), 1.67–1.80 (m, 3H), 1.92 (m, 1H), 5.49 (ddd, *J* = 1.0, 2.4, 10.3 Hz, 1H), 5.60 (ddd, *J* = 1.3, 2.6, 10.3 Hz, 1H). ^{13}C NMR (100 MHz) δ −1.9, −1.8, 19.6, 20.0, 22.9, 24.0, 26.1, 30.3, 32.1, 38.7, 41.9, 72.3, 129.9, 136.1. IR (film): 3021 (w), 2958 (s), 2930 (s), 2858 (s), 1130 (s) cm^{-1}. ESI (MS) *m/z*: 301.08 $(M+MeOH+H)^+$ HRMS (EI) calcd for $C_{15}H_{29}OSi$ $(M-CH_4)^{+\cdot}$ 253.1988 $(M-CH_4)^{+\cdot}$, found: 253.1988 (12%), 211.1770 (31), 135.1405 (28), 93.1008 (73), 75.0529 (100).

4.11. (1*S*,4*S*)-*tert*-Butyl((1*S*,4*S*)-4-isopropyl-1-methylcyclohex-2-enyloxy)dimethylsilane 7b

The above procedure was repeated with the dihydroenoltriflate **6b**, the *title compound* was obtained as a colourless oil in 88% yield. $[\alpha]_D^{20} = -49.75$ (*c* 2.07, $CHCl_3$). ^1H NMR (500 MHz) δ 0.04 (s, 3H), 0.07 (s, 3H), 0.85 (s, 9H) 0.88 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), 1.25 (s, 3H), 1.38 (dt, *J* = 3.0, 12.5 Hz, 1H), 1.48–1.66 (m, 3H), 1.78–1.85 (m, 2H) 5.59–5.65 (complex, 2H). ^{13}C NMR (125 MHz) δ −1.7, 14.4, 19.7, 20.1, 21.9, 22.9, 26.1, 31.2, 31.9, 32.2, 39.1, 42.7, 70.0, 132.2, 134.4. IR (film): 3021 (w), 2957 (s), 2930 (s), 2858 (m), 1131 (m) cm^{-1}. MS (EI) 253.2 ($(M-CH_4)^{+\bullet}$, 12%), 211.2 (57), 13.2 (43), 93.1 (44), 75.1 (100). HRMS (EI) calcd for $C_{15}H_{29}OSi$ $(M-CH_4)^{+\cdot}$ 253.1988, found: 253.1956 (7%), 211.1815 (41), 135.1434 (23), 93.1005 (57), 75.0566 (100).

4.12. (1*S*,4*R*)-4-Isopropyl-1-methyl-2-cyclohexen-1-ol 1

Tetrabutylammonium fluoride (1.0 M in THF; 1.5 mL, 1.5 mmol) was added to a stirred solution of the *tert*-butyldimethylsilyloxy pheromone **7a** (268 mg, 1 mmol) in anhydrous THF (5 mL) under an atmosphere of nitrogen; the reaction mixture was brought to reflux and maintained at this temperature for 18 h. After this time, the reaction was cooled and carefully concentrated in vacuo (357 mbar, 40 °C), and the resulting residue was subjected directly to flash column chromatography (15% EtOAc: 75% hexanes); affording the synthetic pheromone (140 mg, 91% yield) as a colourless oil. $[\alpha]_D^{20} = -72.4$ (*c* 1.0, $CHCl_3$) lit. −65.9 (Ref. 3 $CHCl_3$ *c* 1.17, 96.67% ee). ^1H NMR (500 MHz) δ 0.86 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 1.27 (s, 3H), 1.38 (m, 1H), 1.55–1.66 (m, 2H), 1.67 (br s, 1H), 1.73 (m, 1H), 1.86 (ddd, *J* = 2.8, 5.9, 12.6 Hz, 1H), 1.94 (m, 1H), 5.58–5.64 (m, 2H). ^{13}C NMR (125 MHz) δ 19.6, 20.0, 23.8, 28.7, 32.0, 38.3, 41.9, 69.9, 131.5, 134.8.

4.13. (1*S*,4*S*)-4-Isopropyl-1-methyl-2-cyclohexen-1-ol 2

The above procedure was repeated with the *tert*-butyldimethylsilyloxy pheromone **7b**, the *title compound* was obtained as a colourless oil in an 81% yield. $[\alpha]_D^{20} = -11.5$ (*c* 1.0, $CHCl_3$) lit. −12.0 (Ref. 3 $CHCl_3$, *c* 2.06, 98.66% ee). ^1H NMR (500 MHz) δ 0.89 (d, *J* = 7 Hz, 3H), 0.91 (d, *J* = 7 Hz, 3H), 1.27 (s, 3H), 1.43 (m, 1H), 1.46 (br s, 1H), 1.52 (dt, *J* = 3.0, 13.5 Hz, 1H), 1.59–1.67 (m, 2H), 1.81–1.90 (m, 2H), 5.64–5.70 (complex, 2H). ^{13}C NMR (125 MHz) δ 19.5, 19.9, 21.8, 29.8, 31.9, 37.5, 42.3, 67.7, 133.5, 133.8.

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