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Synthesis of (1*S*,4*R*)-4-isopropyl-1-methyl-2-cyclohexen-1-ol, the aggregation pheromone of the ambrosia beetle *Platypus quercivorus*, its racemate, (1*R*,4*R*)- and (1*S*,4*S*)-isomers☆

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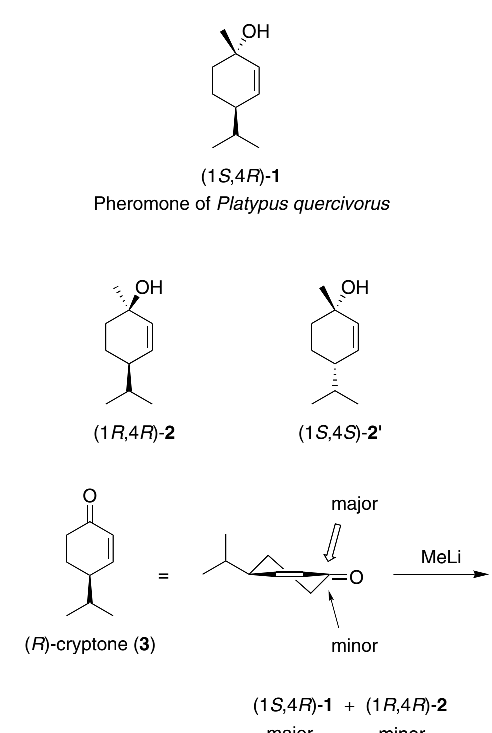
Abstract—(*S*)-Perillyl alcohol was converted to (*R*)-cryptone (91.5–93% ee) in six steps, which was then treated with methyllithium to give (1*S*,4*R*)-4-isopropyl-1-methyl-2-cyclohexen-1-ol, the aggregation pheromone of the ambrosia beetle *Platypus quercivorus*. The racemic pheromone was also prepared by methylation of (±)-cryptone. Both (1*R*,4*R*)- and (1*S*,4*S*)-isomers (98% ee) of the pheromone were synthesized from the enantiomers of dihydrolimonene oxide.

1. Introduction

Over the last decade, deciduous oak (*Quercus crispula*) dieback has been prevalent in northern Japan on the Japan Sea side, as reported by Kamata et al.[2,3] The disease is quite problematic and is capable of damage Japan's forest eco-system. Recent studies on this disease revealed that the dieback is caused by an ambrosia beetle *Platypus quercivorus* Murayama (Coleoptera: Platypodidae), which is the vector of *Raffaelea quercivora*, one of the ambrosia fungi, which causes oak dieback. In order to monitor the population of the beetle *P. quercivorus*, its chemical communication system was studied by Nakashima et al., who isolated and identified (1*S*,4*R*)-4-isopropyl-1-methyl-2-cyclohexen-1-ol (*cis*-2-menthen-1-ol, **1**, Scheme 1) as its male-produced aggregation pheromone.[4,5]

The synthesis of (1*S*,4*R*)-**1** in gram quantities was studied in order to examine its applicability as the population monitoring agent against *P. quercivorus*. Since (1*R**,4*R**)-4-isopropyl-1-methyl-2-cyclohexen-1-ol (**2** or **2′**) was detected as a minor component of the frass volatiles of *P. quercivorus*,[6] **2** and **2′** were also chosen as synthetic targets so as to deter-



Scheme 1. Structure and synthetic plan of the target molecules.

☆ Pheromone synthesis, Part 232. For Part 231, see Ref. 1.
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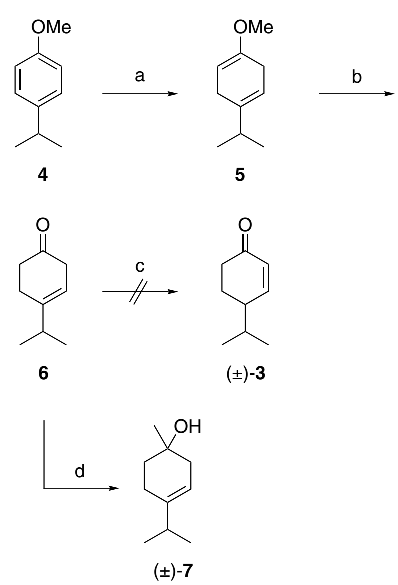
mine definitely the absolute configuration of the minor component. Clarification of the biological role of **2** or **2′** either as a synergist or as an inhibitor of the pheromone activity of **1** was important from a practical point of view. Another practical consideration was to develop an efficient synthesis of (±)-**1** to evaluate its pheromone activity under field conditions. Herein, we report the synthesis of (±)-**1**, (1*S*,4*R*)-**1**, (1*R*,4*R*)-**2**, and (1*S*,4*S*)-**2′** in amounts sufficient for field bioassay. The simple and key strategy was to prepare (1*S*,4*R*)-**1** or (±)-**1** by methylation of (*R*)-cryptone (**3**) or (±)-**3** as shown in Scheme 1. Methylation of **3** would give **1** as the major product due to the steric hindrance caused by the axial H-atom at C-6 of **3**.

2. Results and discussion

2.1. Synthesis of (±)-4-isopropyl-1-methyl-3-cyclohexen-1-ol

The first attempt to prepare (±)-cryptone **3** is shown in Scheme 2. According to Soffer and Jevnik, *p*-isopropylanisole **4** can be subjected to the Birch reduction to give **5**.[7] Treatment of **5** with dil HCl gave poor results, and (±)-**3** could not be obtained. Accordingly, **5** was hydrolyzed with aqueous oxalic acid to give pure **6**, whose isomerization to (±)-**3** was attempted under several different conditions with no useful result. Nukada kindly carried out the semi-empirical MO calculation of the heat of formation of **3** and that of **6** employing MOPAC (AM1 Hamiltonian). The heat of formation of **3** was −49.0 kcal/mol, while that of **6** was −52.5 kcal/mol, meaning that the β,γ-unsaturated ketone **6** was 3.5 kcal/mol more stable than the α,β-unsaturated ketone **3**, and therefore the former could not be isomerized to **3**.

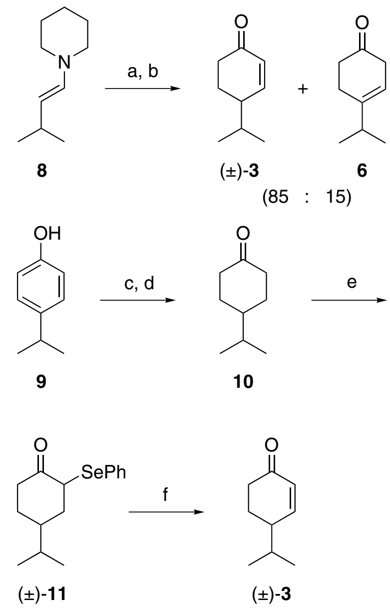


Scheme 2. Synthesis of (±)-1-methyl-4-isopropyl-3-cyclohexen-1-ol (**7**). Reagents and conditions: (a) Li, *t*-BuOH, liq. NH_3, THF, 90%; (b) $(CO_2H)_2 \cdot 2H_2O$, MeOH, H_2O, room temp, 40 min, 64%; (c) dil HCl, no reaction; (d) MeMgI, Et_2O, 22% after SiO_2 chromatography and distillation.

At this stage, it became relevant to know whether (±)-4-isopropyl-1-methyl-3-cyclohexen-1-ol **7** could attract *P. quercivorus* or not. Treatment of **6** with MeMgI yielded (±)-**7**.[8] Kamata's bioassay of (±)-**7** showed it to be totally inactive.

2.2. Synthesis of (±)-cryptone and its conversion to (1*S**,4*R**)-4-isopropyl-1-methyl-2-cyclohexen-1-ol

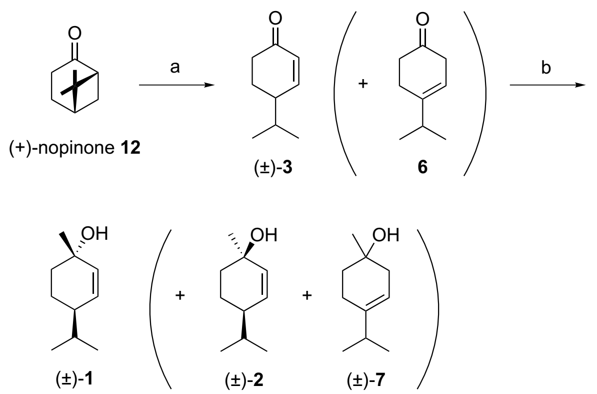
Among the many methods for the preparation of (±)-cryptone **3**,[9–11] Stork's enamine procedure[12] was examined due to its applicability in a large scale preparation (Scheme 3). Accordingly, the known enamine **8** was treated with methyl vinyl ketone. After acid treatment of the resulting adduct, it was obtained as a mixture of (±)-**3** and **6** (85:15 as revealed by the NMR signals of their olefinic protons). These two isomers were reported to be separable by careful fractional distillation,[9] although no separation was attempted in the present case.



Scheme 3. Synthesis of (±)-cryptone **3**. Reagents and conditions: (a) $CH_2{=}CHCOMe$, room temp, 1 day; (b) dil HCl, room temp, 3 days, then reflux, 30 min, 54%; (c) H_2, PtO_2, AcOH, room temp, 62%; (d) Jones CrO_3, acetone, 0–5 °C, 10 min, 76%; (e) PhSeCl, EtOAc, room temp, 40 min, 40–55%; (f) 30% H_2O_2, 0–35 °C, 1.5 h, 70%.

The next attempt to obtain pure (±)-**3** was to employ the standard organoselenium chemistry of Sharpless et al.[13] for the conversion of 4-isopropylcyclohexanone **10** to (±)-**3** (Scheme 3). Commercially available *p*-isopropylphenol **9** was hydrogenated over PtO_2 in AcOH, and the resulting alcohol was oxidized with Jones chromic acid to give **10**. Treatment of **10** with phenylselenenyl chloride afforded pure (±)-**11** after chromatographic purification. Subsequent oxidation of (±)-**11** with H_2O_2 furnished (±)-**3** with no contamination of the β,γ-unsaturated ketone **6**. Although the chemical purity of (±)-**3** obtained by this method was satisfactory, it took four steps to convert **9** into (±)-**3** with an overall yield of 13–18%. It was therefore necessary to explore a much more efficient method to prepare (±)-**3**.

Scheme 4 shows the method finally adopted for the preparation of (±)-**1**. Wallach was the first to prepare (±)-cryptone **3** by treating (+)-nopinone **12** with acid.[14] Since then, this reaction has only been employed occasionally.[15,16]



Scheme 4. Synthesis of (1*S**,4*R**)-(±)-4-isopropyl-1-methyl-2-cyclohexen-1-ol **1**. Reagents and conditions: (a) $AlCl_3$, CH_2Cl_2, 0–5 °C, 70 min, 89%; (b) MeLi, LiBr, Et_2O, THF, −40 °C to room temp, 44% of **1** and 10% of **2**.

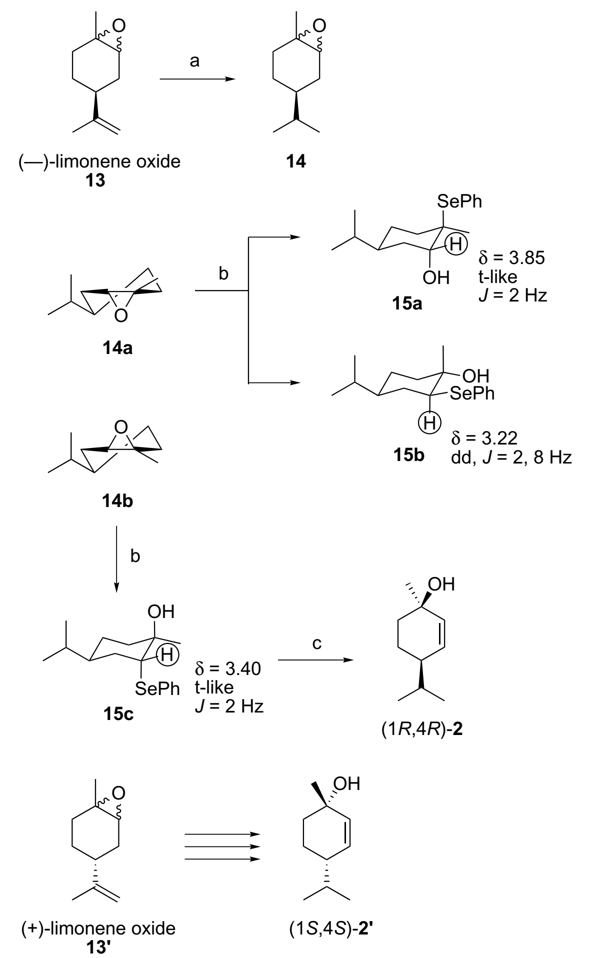
When (+)-**12** was treated with $AlCl_3$ in CH_2Cl_2, (±)-**3** was obtained in about 90% yield with purity of no less than 80–85%. The contaminant was its more stable isomer **6**. In spite of this unsatisfactory purity of the resulting (±)-**3**, the present preparation starting from (+)-nopinone (**12**) was chosen as the method of choice owing to its simplicity.

Methyllithium in Et_2O containing LiBr was then added to (±)-**3** to give a mixture of the desired product (±)-**1**, its stereoisomer (±)-**2** and alcohol (±)-**7** derived from the contaminating ketone **6**. Fortunately, (±)-**1** could be separated from (±)-**2** and (±)-**7** by SiO_2 chromatography, and gram quantities of (±)-**1** could be secured after distillation. Its EI-MS was identical to that of the sex pheromone of *P. quercivorus*. The pheromone activity of (±)-**1** against *P. quercivorus* was confirmed by Professor Kamata's bioassay. It was also possible to purify (±)-**2** by careful SiO_2 chromatography followed by distillation. However, only a very small amount of (±)-**2** was obtained by this method. Accordingly, even with a supply of optically active cryptone **3**, it proved difficult to synthesize optically active **2** in a sufficient amount for field bioassay. It, therefore, became necessary to develop a different method for the preparation of the enantiomers of **2**.

2.3. Synthesis of (1*R*,4*R*)-and (1*S*,4*S*)-4-isopropyl-1-methyl-2-cyclohexen-1-ol

The synthesis of 1-oxygenated menthane compounds has been studied for many years.[17] Klein and Ohloff prepared both (1*R*,4*R*)- and (1*S*,4*S*)-4-isopropyl-1-methyl-2-cyclohexen-1-ols **2** and **2′** by starting from the enantiomers of piperitone.[18] Unfortunately in Japan, pure enantiomers of piperitone were unavailable. Another preparative method for (1*S*,4*S*)-**2′** was reported by Schenck et al., who employed photosensitized oxygenation of (+)-dihydrolimonene (carvomenthene) as the preparative method.[19] This method, however, furnishes a mixture of six products, and is inappropriate for the synthesis of enantiomerically pure **1** and **2** in amounts sufficient enough for biological evaluation.

A new method was therefore developed for the preparation of gram quantities of (1*R*,4*R*)- and (1*S*,4*S*)-**2** as shown in Scheme 5. The key step was the application of Sharpless' organoselenium chemistry[20] to convert **14b** to (1*R*,4*R*)-**2** via phenylselenide **15c**.

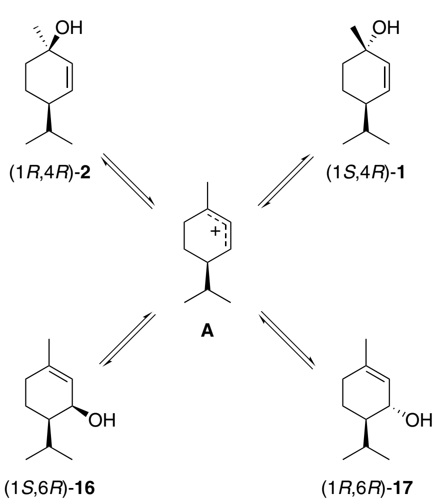


Scheme 5. Synthesis of (1*R*,4*R*)- and (1*S*,4*S*)-4-isopropyl-1-methyl-2-cyclohexen-1-ol **2** and **2′**. Reagents and conditions: (a) H_2, PtO_2, MeOH, 92%; (b) Ph_2Se_2, $NaBH_4$, EtOH, reflux, 2 h, 44% of **15c**; (c) 30% H_2O_2, THF, C_5H_5N, room temp, 1 h, 61%.

Commercially available (−)-limonene oxide **13** (*cis*/*trans* = ca. 3:2, 99% ee) was hydrogenated over PtO_2 in MeOH to give (−)-dihydrolimonene oxide as a mixture of **14a** and **14b** (2:3). The hydrogen at C-2 of **14a** absorbed at $\delta = 3.02$ (0.4H, t, *J* 1.5 Hz) in its ^{1}H NMR spectrum, while that of **14b** showed its signal at $\delta = 2.97$ (0.6H, d, *J* 5.4 Hz). This mixture of **14a** and **14b** was treated with NaSePh generated from Ph_2Se_2 and $NaBH_4$ in EtOH. Epoxide **14a** generated selenides **15a** and **15b**, while epoxide **14b** furnished selenide **15c**. These three products could be characterized by comparing their ^{1}H NMR data as depicted in Scheme

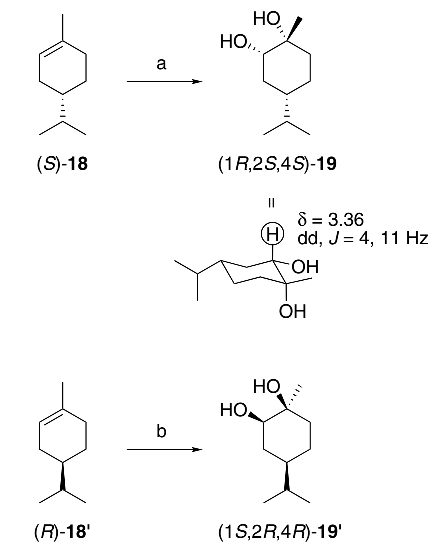
5. Unfortunately, **15a** and **15b** could not be purified due to their poor separation by SiO_2 chromatography. The desired isomer **15c**, however, could be purified by SiO_2 chromatography to give pure **15c** in 44% yield based on the mixture of **14a** and **14b**. Although the H_2O_2 oxidation of the mixture of **15a** and **15b** did not give useful results, the oxidation of **15c** with H_2O_2 could be carried out successfully in the presence of pyridine in THF to give (1*R*,4*R*)-**2**, $[\alpha]_D^{22} = +10.3$ (hexane), in 61% yield. Its EI-MS was identical with that of the minor component of the frass volatiles of *P. quercivorus*. In the same manner, (+)-limonene oxide **13′** was converted to (1*S*,4*S*)-**2′**, $[\alpha]_D^{26} = -10.2$ (hexane). The enantiomeric purities of (1*R*,4*R*)-**2** and (1*S*,4*S*)-**2′** were analyzed by GC on a chiral stationary phase by Dr. S. Tamogami, and found to be 98.3–98.7% ee and 97.8–98.2% ee, respectively. The overall yield of (1*R*,4*R*)-**2** was 25% based on **13** (three steps).

It is worthy of note that the presence of pyridine was essential for the success of the selenoxide elimination reaction (**15c** → **2**). The product obtained in the absence of pyridine was shown to be a mixture of all the four compounds **1**, **2**, **16**, and **17** in a ratio of 12.2%, 66.8%, 8.5%, and 7.5% together with some impurities (5%). In the presence of pyridine, (1*R*,4*R*)-**2** and (1*S*,4*S*)-**2′** were obtained with the purities of 94.3% and 94.5%, respectively, as analyzed by GC–MS. In the absence of pyridine, the acidity of the phenylselenenic acid generated causes an allylic rearrangement of **2** (Scheme 6). Accordingly, (1*R*,4*R*)-**2** gives the delocalized cation **A**, which affords a mixture of (1*R*,4*R*)-**2**, (1*S*,4*R*)-**1**, (1*S*,6*R*)-**16**, and (1*R*,6*R*)-**17**.



Scheme 6. Phenylselenenic acid-catalyzed allylic rearrangement of (1*R*,4*R*)-**2**.

Another attempt was made to prepare the enantiomers **2** and **2′** via the enantiomers of diol **19** (Scheme 7). Sharpless asymmetric dihydroxylation[21] of (*S*)-dihydrolimonene **18** afforded crystalline (1*R*,2*S*,4*S*)-4-isopropyl-1-methylcyclohexane-1,2-diol **19** in 42% yield. The assigned structure **19** was consistent with the observed ^{1}H NMR signal due to C*H*OH ($\delta = 3.36$, dd, *J* 4, 11 Hz) and the $[\alpha]_D$ value [observed: −10.3 ($CHCl_3$); Ref. 22: −10.1]. Similarly, asymmetric dihydroxylation of (*R*)-dihydrolimonene **18′** gave **19′**,



Scheme 7. Asymmetric dihydroxylation of the enantiomers **18** and **18′** of dihydrolimonene. Reagents and conditions: (a) AD-mix-α®, $MeSO_2NH_2$, *t*-BuOH, H_2O, 42%; (b) AD-mix-β®, $MeSO_2NH_2$, *t*-BuOH, H_2O, 40%.

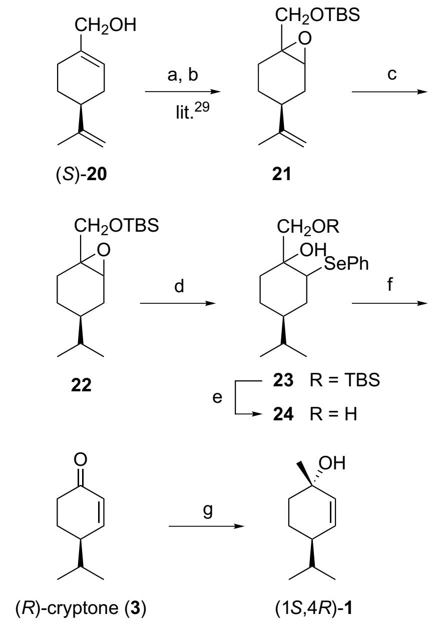
$[\alpha]_D^{21} = +9.3$ ($CHCl_3$) (Ref. 23: +8.2). Attempts were made to convert **19** to **2** by tosylation followed by elimination or by phenylselenenylation (PhSeCN, Bu_3P) followed by oxidation. Neither of these attempts were successful.

2.4. Synthesis of (*R*)-cryptone and its conversion to (1*S*,4*R*)-4-isopropyl-1-methyl-2-cyclohexen-1-ol, the pheromone of *P. quercivorus*

(*R*)-Cryptone **3** was isolated from the essential oil of *Eucalyptus cneorifolia* in Australia, and reported to possess an $[\alpha]_D$ value of −119.3 (EtOH)[24] or −91.7 (EtOH).[25] Lavender oil also contains enantiomerically impure (*R*)-cryptone, $[\alpha]_D^{21} = -27$ ($CHCl_3$).[26] Various syntheses of optically active cryptone have been reported to date. Kato et al. recorded a multi-step conversion of (+)-nopinone **12** into (*R*)-cryptone (**3**, 86% ee)[27] Asymmetric deprotonation of 4-isopropylcyclohexanone enabled Koga et al. to prepare (*S*)-**3** in 67% ee.[28] Fuchs et al. synthesized (*R*)-**3** of 94.7% ee ($[\alpha]_D$ not reported) employing Jacobsen's asymmetric epoxidation as the key step.[29] Very recently, Högberg et al. used lipase-catalyzed kinetic resolution for the preparation of (*R*)-**3** {76% ee; $[\alpha]_D^{20} = -69.7$ (EtOH)} and (*S*)-**3** {98% ee; $[\alpha]_D^{20} = +89.9$ (EtOH)}.[30] All of these published methods, however, seem to be unsuitable for preparing (*R*)-**3** in gram quantities due to low overall yield and/or experimental difficulty in a large-scale preparation.

It appeared that a slight modification of the method developed by Stevens and Albizati for the preparation of 4-isopropenyl-2-cyclohexenone[31] might be useful for a gram-scale preparation of (*R*)-**3**, because the starting (*S*)-perillyl alcohol is commercially available. As shown in Scheme 8, work along this line was successful to enable a gram-scale synthesis of (*R*)-cryptone **3** and its conversion to the desired pheromone (1*S*,4*R*)-**1**.

(*S*)-Perillyl alcohol **20** was epoxidized and silylated to give the known unsaturated epoxide **21**.[31] This was hydro-



Scheme 8. Synthesis of (*R*)-cryptone **3** and its conversion to the pheromone (1*S*,4*R*)-**1**, Reagents and conditions: (a) *t*-BuOOH, VO(acac)$_2$, toluene, room temp, 2.5 h, quant.; (b) TBSCl, imidazole, DMF, quant.; (c) H_2, PtO_2, hexane, EtOAc (1:1), quant.; (d) Ph_2Se_2, NaH, THF, HMPA, reflux, 3 h; (e) TBAF, THF, room temp; (f) $NaIO_4$, THF, H_2O, room temp, 1.5 h, 28% based on **22** (three steps); (g) MeLi, LiBr, Et_2O, THF, 44%.

genated over PtO_2, and the resulting saturated epoxide **22** treated with NaSePh (prepared from Ph_2Se_2 and NaH[32,33]) in THF and HMPA to give phenylselenide **23**. The reactivity of NaSePh prepared in this manner was higher than that prepared from Ph_2Se_2 and $NaBH_4$ in EtOH.[32,33] Desilylation of **23** with tetrabutylammonium fluoride (TBAF) in THF furnished diol **24**. Intermediates **21**–**24** were prepared and used as stereoisomeric mixtures. Oxidation of **24** with sodium periodate in aqueous THF gave (*R*)-cryptone **3**, $[\alpha]_D^{19} = -86.8$ (EtOH), after chromatographic purification and distillation. The overall yield of (*R*)-**3** was 28% based on (*S*)-**20** (six steps), and its enantiomeric purity was 91.5–93% ee as determined by GC analysis on a chiral stationary phase.

Finally, methylation of (*R*)-**3** with methyllithium was followed by chromatographic purification and distillation to give (1*S*,4*R*)-**1**, $[\alpha]_D^{19} = -68.7$ (hexane); $[\alpha]_D^{19} = -65.9$ ($CHCl_3$) {Ref. 19: $[\alpha]_D = +69$ ($CHCl_3$) for (1*R*,4*S*)-**1**}, in 44% yield. Its enantiomeric purity was determined as 93.3% ee by GC analysis. Details of the GC analysis of **1**, **2**, and **3** are described in the Experimental. 2,3-Dimethoxymethyl-6-*tert*-butyldimethylsilyl-γ-cyclodextrin or Chiramix®[34] was employed as the chiral stationary phase to achieve base-peak separations of the enantiomers of **1**, **2**, and **3**.

3. Conclusion

(1*S*,4*R*)-4-Isopropyl-1-methyl-2-cyclohexen-1-ol **1** and its (1*R*,4*R*)- and (1*S*,4*S*)-isomers **2** and **2′** were synthesized in amounts sufficient for their biological evaluation. A multi-gram-scale synthetic route for (*R*)-cryptone **3** was developed. Racemates of **1** and **2** were also prepared for their biological evaluation. The pheromone activity of these compounds against *P. quercivorus* will be tested and reported in due course. The biological study will hopefully enable us to develop practical pheromone traps against that pest insect.

4. Experimental

4.1. General

Melting points (Yanaco MP-S3) and boiling points are uncorrected values. Optical rotations were measured on a Jasco DIP-320 polarimeter. IR spectra were recorded on a Horiba FT-720 spectrometer. ^{1}H NMR spectra (300 MHz, TMS at $\delta = 0.00$ or $CHCl_3$ at $\delta = 7.26$ as internal standard) and ^{13}C NMR spectra (75 MHz, $CDCl_3$ at $\delta = 77.0$ as internal standard) were recorded on a Varian Mercury-300 spectrometer. Column chromatography was carried out on Merck Kieselgel 60 Art 1.07734.

4.2. 4-Isopropyl-3-cyclohexenone 6

To a solution of **5** (6.0 g, 39.5 mmol) in MeOH (40 mL) was added a solution of oxalic acid dihydrate (0.7 g, 5.6 mmol) in H_2O (9 mL). The mixture was stirred for 40 min at room temp, diluted with H_2O, and then extracted with Et_2O. The extract was washed with H_2O, $NaHCO_3$ (aq solution), and brine, dried over $MgSO_4$, and concentrated in vacuo to give 4.3 g (74%) of crude **6**. This was distilled in vacuo to furnish 3.5 g (64%) of **6** as a colorless oil, bp 70–71 °C/4 Torr; $n_D^{24} = 1.4699$; Ref. 7: $n_D^{20} = 1.4710$; Ref. 8: $n_D^{22} = 1.4817$. ν_{max} (film): 1720 (s, CO), 1465 (m), 1195 (m), 802 (m); δ_H ($CDCl_3$): 1.04 (6H, d, *J* 6.9, $CH(CH_3)_2$), 2.24–2.30 (1H, m, $CH(CH_3)_2$), 2.30–2.43 (2H, m, $C{=}CCH_2$), 2.45–2.51 (2H, m, CH_2CH_2CO) 2.83–2.87 (2H, m, $C{=}CHCH_2CO$), 5.46 (1H, t-like, *J* 2, C=CH); δ_C ($CDCl_3$): 21.0, 26.3, 29.5, 34.7, 38.8, 39.5, 115.4, 144.5, 211.4. Anal. Calcd for $C_9H_{14}O$ (138.2): C, 78.21; H, 10.21. Found C, 75.45; H, 9.98. This ketone was so volatile that correct analytical data could not be obtained.

4.3. (±)-4-Isopropyl-1-methyl-3-cyclohexen-1-ol 7

A solution of **6** (2.76 g, 20 mmol) in dry Et_2O (10 mL) was added dropwise to a stirred and ice-cooled solution of the Grignard reagent prepared from MeI (4.3 g, 30 mmol) and Mg (0.72 g, 30 mmol) in dry Et_2O (10 mL). The mixture was stirred at 0–5 °C for 30 min, at room temperature for 5 h, then poured into ice and NH_4Cl (aq solution) and extracted with Et_2O. The extract was washed with a diluted aqueous solution of $Na_2S_2O_4$, $NaHCO_3$ (aq solution), and brine, dried (K_2CO_3), and concentrated in vacuo to give 2.72 g (88%) of crude **7**. This was chromatographed over SiO_2 (40 g). Elution with hexane/EtOAc (10:1) gave purified **7**, which was distilled to give pure **7** (900 mg, 22%) as a colorless oil, bp 80–81 °C/4 Torr; $n_D^{24} = 1.4748$, ν_{max} (film): 3370 (s, OH), 1130 (s, C–O), 1100 (s, C–O), 922 (m), 880 (m); δ_H ($CDCl_3$): 1.10 (6H, d, *J* 6.9, $CH(CH_3)_2$), 1.57 (3H, s, $C(OH)CH_3$), 1.60–1.75 (3H, m), 1.96–2.26

(5H, m), 5.30 (1H, m, C=CH); δ_C ($CDCl_3$): 21.41, 21.49, 23.7, 28.2, 34.7, 35.6, 39.8, 68.7, 115.9, 142.8 MS (70 eV, EI): *m/z* (%): 154 (2) [M^+]. 136 (34), 121 (43), 107 (29), 93 (34), 81 (100). GC (TC-WAX at 100–190 °C, +3 °C/min): t_R 15.8 min (92.2%). Anal. Calcd for $C_{10}H_{18}O$ (154.2): C, 77.86; H, 11.76. Found C, 77.56; H, 11.89.

4.4. (±)-Cryptone 3 by Stork's enamine procedure

Enamine **8** (bp 102–103 °C/35 Torr) was prepared from isovaleraldehyde and piperidine according to Stork et al.[12] Methyl vinyl ketone (6.7 g, 96 mmol) was added dropwise to stirred ice-cooled enamine **8** (14.5 g, 95 mmol) over 45 min. The mixture was then stirred overnight at room temp. After 1 day, it was acidified with 10% HCl (185 mL), and the mixture was stirred for 3 days under Ar at room temperature. The stirred mixture was then heated at reflux for 30 min. After cooling, it was extracted with Et_2O. The extract was washed with dil HCl, H_2O, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was distilled to give 7.1 g (54%) of (±)-**3** contaminated with **6**, bp 83–86 °C/4 Torr; $n_D^{27} = 1.4773$. Acid treatment causes isomerization of (±)-**3** to **6**. Their ratio could be analyzed by ^{1}H NMR measurement comparing the areas of the signals [C=C*H* and CH(C*H*$_3$)$_2$] due to (±)-**3** and **6**, respectively, and found to be 85:15–75:25. ν_{max} (film): 1720 (m, CO of **6**), 1682 (s, CO of **3**), 833 (m), δ_H ($CDCl_3$): 0.95 (3H, d, *J* 6.9, CHC*H*$_3$), 0.97 (3H, d, *J* 6.9, CHC*H*$_3$), 1.04 [d, *J* 6.9, CH(C*H*$_3$)$_2$ of **6**], 1.69–1.87 (2H, m, CH$_2$C*H*$_2$), 1.95–2.05 (1H, m, C*H*CH$_3$), 2.25–2.40 (2H, m, COCH$_2$), 2.46–2.55 (1H, m, C=CHC*H*), 2.83–2.87 (m, C=CHC*H*$_2$CO of **6**), 5.46 (t-like, *J* 2, C=CH of **6**), 6.00 (1H, ddd, *J* 10.2, 2.7, 0.9, COC*H*=CH), 6.91 (1H, ddd, *J* 10.2, 2.4, 1.8, COCH=C*H*). Anal. Calcd for $C_9H_{14}O$ (138.2): C, 78.21; H, 10.21. Found C, 77.03; H, 10.09. Due to the high volatility of (±)-**3** and **6**, correct analytical data could not be obtained.

4.5. (±)-4-Isopropyl-2-phenylselenenylcyclohexanone 11

4-Isopropylcyclohexanone **10** was prepared from commercially available *p*-isopropylphenol, by its hydrogenation over PtO_2 in AcOH followed by Jones oxidation, as a colorless oil, bp 62–64 °C/3 Torr; $n_D^{24} = 1.4574$. ν_{max} (film): 1716 (s, CO), 1176 (m); δ_H ($CDCl_3$): 0.93 (6H, d, *J* 6.6, CH(C*H*$_3$)$_2$), 1.38–1.65 (5H, m), 1.95–2.06 (1H, m), 2.25–2.44 (4H, m); δ_C ($CDCl_3$): 19.9, 29.6, 31.7, 41.0, 42.5, 212.6.

PhSeCl (5.0 g, 26 mmol) was added to a stirred solution of **10** (3.2 g, 23 mmol) in EtOAc (75 mL) at room temperature. With the exothermic reaction, the color of the red reaction mixture turned yellow within 5 min. Stirring was continued for 40 min, and the mixture then partitioned between hexane and H_2O. The organic layer was separated, washed with H_2O, $NaHCO_3$ (aq solution), and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed over SiO_2 (100 g). Elution with hexane/EtOAc (10:1) yielded 3.1 g (46%) of (±)-**11** as a slightly yellowish oil, $n_D^{24} = 1.5012$; ν_{max} (film): 1708 (s, CO), 740 (s). Anal. Calcd for $C_{15}H_{20}OSe$ (295.3); C, 61.01; H, 6.83. Found C, 61.10; H, 6.54.

4.6. (±)-Cryptone 3 by organoselenium chemistry

To a stirred and ice-cooled solution of (±)-**11** (3.0 g, 10 mmol) in THF (40 mL) was added dropwise 30% H_2O_2 (7 mL, 62 mmol). The stirring was continued for 2 h at room temp. The mixture was then concentrated in vacuo, diluted with H_2O, and extracted with Et_2O. The extract was washed with $NaHCO_3$ (aq solution), and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed over SiO_2 (50 g). Elution with hexane/EtOAc (20:1) afforded 1.0 g (70%) of crude (±)-**3**. This was distilled to give pure (±)-**3** (435 mg, 31%) as a colorless oil, bp 70–71 °C/3 Torr; $n_D^{27} = 1.4852$; ν_{max} (film): 3032 (w), 2958 (s), 2873 (m), 1682 (s, CO), 1466 (m), 1388 (m), 1245 (m), 956 (w), 833 (m); δ_H ($CDCl_3$): 0.95 (3H, d, *J* 6.9, CHC*H*$_3$), 0.97 (3H, d, *J* 6.9, CHC*H*$_3$), 1.69–1.87 (2H, m, CH$_2$C*H*$_2$), 1.95–2.05 (1H, m, C*H*CH$_3$), 2.25–2.40 (2H, m, COC*H*$_2$), 2.46–2.55 (1H, m, C=CHC*H*), 6.00 (1H, ddd, *J* 10.2, 2.7, 0.9, COC*H*=CH), 6.91 (1H, ddd, *J* 10.2, 2.4, 1.8, COCH=C*H*); δ_C ($CDCl_3$): 19.4, 19.6, 25.2, 31.5, 37.4, 42.4, 129.7, 154.4, 200.2. Anal. Calcd for $C_9H_{14}O$ (138.2): C, 78.21; H, 10.21 Found C, 75.52; H, 9.87. Due to the high volatility of (±)-**3**, correct analytical data could not be obtained.

4.7. (±)-Cryptone 3 from (+)-nopinone 12

Powdered $AlCl_3$ (10.0 g, 72.5 mmol) was added to a stirred and ice-cooled solution of (+)-nopinone (**12**, Aldrich, 5.3 g, 38 mmol) in CH_2Cl_2 (50 mL) at 0–5 °C under Ar. The reaction was exothermic, and the mixture was warmed up to 20 °C for several seconds. Stirring was continued for 70 min at 0–5 °C. The mixture was then poured into ice and dil HCl, and extracted with CH_2Cl_2. The organic solution was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was distilled to give 4.7 g (89%) of (±)-**3** contaminated with 15–20% of **6**. Its IR, ^{1}H and ^{13}C NMR data were almost identical with those of (±)-**3** prepared by other methods. GC (TC-WAX 100–190 °C, +3 °C/min): t_R 13.85 min (19.5%, **6**), 16.73 min (80.5%, **3**). MS (70 eV, EI) of **3**: *m/z* (%): 138 (17) [M^+], 96 (83), 95 (100), 81 (20), 67 (52), 66 (23), 65 (23), 53 (18); MS (70 eV, EI) of **6**: *m/z* (%): 138 (41) [M^+], 96 (22), 95 (21), 81 (100), 67 (40), 53 (24).

4.8. (1*S**,4*R**)-(±)-4-Isopropyl-1-methyl-2-cyclohexen-1-ol 1 and its (1*R**,4*R**)-isomer 2

A solution of MeLi in Et_2O (containing LiBr, 1.0 M, 60 mL, 60 mmol) was added dropwise to a stirred and cooled (dry ice–acetone) solution of (±)-**3** (containing 19.5% of **6**, 4.6 g, 33 mmol) in THF (50 mL) at −40 °C under Ar. The mixture was stirred for 30 min at −40 to 0 °C, and then for 1 h at room temp. It was then poured into ice and NH_4Cl (aq solution), and extracted with Et_2O. The extract was washed with brine, dried over K_2CO_3, and concentrated in vacuo. The residue was chromatographed over SiO_2 (120 g). Elution with hexane/EtOAc (15:1) first gave (±)-**2** (0.8 g, 16%) and then (±)-**1** (2.7 g, 53%) contaminated with small amounts of (±)-**2** and (±)-**7**. Crude (±)-**2** was distilled in vacuo to give 0.50 g (10%) of (±)-**2**, bp 73–74 °C/4 Torr; $n_D^{26} = 1.4722$; ν_{max} (film): 3340 (s, OH), 2958 (s), 2873 (s), 1678 (w), 1461 (m), 1369 (m), 1122 (m), 906 (m), 733 (m), δ_H ($CDCl_3$): 0.88 (3H, d, *J* 6.9, CHC*H*$_3$) 0.90 (3H, d, *J* 6.9, CHC*H*$_3$), 1.26 (3H, s, C(OH)C*H*$_3$), 1.38–1.70 (5H, m), 1.80–1.92 (2H, m), 5.66 (2H, s-like, C*H*=C*H*); δ_C ($CDCl_3$): 19.2, 19.6, 21.6, 29.6, 31.7, 37.2, 42.1, 67.4, 133.2, 133.5. GC (TC-Wax, 100–190 °C, +3 °C/min): t_R 12.94 min [91.5% (±)-**2**]; MS (70 eV, EI): *m/z* (%): 154 (13) [M^+], 139 (78), 121 (50), 111 (72), 95 (61), 94 (73), 93 (79), 79 (100), 77 (73), 69 (51), 67 (49), 55 (53). Anal. Calcd for $C_{10}H_{18}O$ (154.2): C, 77.86; H, 11.76. Found C, 77.79; H, 11.43. Distillation of crude (±)-**1** gave 2.23 g (44%) of (±)-**1** [92% purity with 6% of (±)-**7** and 2% of (±)-**2** as analyzed by GC], bp 78–79 °C/4 Torr; $n_D^{28} = 1.4728$; ν_{max} (film): 3367 (s, OH), 2958 (s), 2870 (s), 1651 (w), 1462 (m), 1369 (m), 1122 (s), 984 (m), 918 (m), 806 (w); δ_H ($CDCl_3$): 0.87 (3H, d, *J* 6.6, CHC*H*$_3$), 0.89 (3H, d, *J* 6.6, CHC*H*$_3$), 1.27 (3H, s, C(OH)C*H*$_3$), 1.30–2.10 (7H, m), 5.60 (2H, s-like, C*H*=C*H*); δ_C ($CDCl_3$): 19.4, 19.7, 23.5, 28.5, 31.7, 38.0, 41.7, 69.6, 131.3, 134.6. GC (TC-WAX, 100–190 °C, +3 °C/min): t_R 17.36 min (92%). MS (70 eV, EI): *m/z* (%): 154 (9) [M^+], 139 (100), 136 (46), 121 (73), 111 (62), 95 (58), 93 (87), 91 (56), 83 (64), 81 (58), 79 (62), 77 (78), 69 (71), 67 (53), 55 (71). Anal. Calcd for $C_{10}H_{18}O$ (154.2): C, 77.86; H, 11.76. Found C, 77.71; H, 11.48.

If the chromatographic purification was omitted and the product purified by distillation only, then 7.55 g (86%) of 82% pure (±)-**1** (contaminated with 10% of **7** and 4% of **2**) was obtained by starting from 8.0 g of 80% pure (±)-**3**. GC (TC-WAX, 100–190 °C, +3 °C/min): t_R 13.04 (4%, **2**), 13.26 (10%, **7**), 14.65 (82%, **1**). Calcd for $C_{10}H_{18}O$ (154.2): C, 77.86; H, 11.76. Found C, 77.35; H, 11.26.

4.9. Enantiomers of dihydrolimonene oxide 14 and 14′

4.9.1. (*R*)-(−)-Isomer 14. Adams's PtO_2 (50 mg) was added to a solution of (−)-limonene oxide **13** (Aldrich, 99% ee; 6.4 g, 42 mmol) in MeOH (30 mL). The mixture was stirred under H_2 (balloon) for 2 h at room temperature. The hydrogenation was exothermic, and about 1 L of H_2 was consumed. The mixture was then diluted with hexane and filtered through Celite. The filtrate was concentrated in vacuo, and the residue was distilled to give 6.0 g (92%) of **14**, bp 87–88 °C/24 Torr; $n_D^{24} = 1.4490$; $[\alpha]_D^{19} = -65.5$ (*c* 3.05, hexane); ν_{max} (film): 2958 (s), 2873 (s), 1018 (m), 841 (m), 760 (m), 671 (m): δ_H ($CDCl_3$): 0.83 (3.2H, d, *J* 6.9, CHC*H*$_3$), 0.84 (1.4H, d, *J* 6.9, CHC*H*$_3$), 0.85 (1.4H, d, *J* 6.6, CHC*H*$_3$), 0.90–1.20 (2H, m), 1.30 [3H, s, C(OH)C*H*$_3$], 1.32–1.68 (4H, m), 1.80–2.14 (2H, m), 2.97 (0.6H, d, *J* 5.4, OCH of **14b**), 3.02 (0.4H, t, *J* 1.5, OCH of **14a**); δ_C ($CDCl_3$): 19.3, 19.7, 22.5, 23.1, 24.4, 24.9, 27.9, 29.2, 30.9, 31.6, 32.3, 35.1, 39.2, 57.6, 57.8, 59.6, 61.0. Anal. Calcd for $C_{10}H_{18}O$ (154.2): C, 77.86; H, 11.76. Found C, 77.82; H, 11.97.

4.9.2. (*S*)-(+)-Isomer 14′. (+)-Limonene oxide (**13′**, Aldrich, 98% ee; 6.4 g, 42 mmol) yielded 5.4 g (83%) of (*S*)-(+)-**14′**, bp 87–88 °C/25 Torr; $n_D^{24} = 1.4490$; $[\alpha]_D^{19} = +64.4$ (*c* 2.39, hexane). Its spectral data were identical with those of **14**. Anal. Calcd for $C_{10}H_{18}O$ (154.2): C, 77.86; H, 11.76. Found C, 77.66; H, 12.32.

4.10. 4-Isopropyl-1-methyl-2-phenylselenenylcyclohexan-1-ol 15c and 15c′

4.10.1. (1*R*,2*R*,4*S*)-Isomer 15c. $NaBH_4$ (1.7 g, 45 mmol) was added portionwise to a stirred and ice-cooled suspension of Ph_2Se_2 (7.0 g, 22 mmol) in 95% EtOH (100 mL) at 0–5 °C under Ar. The mixture was stirred for 30 min to dissolve solid Ph_2Se_2, giving a homogeneous solution. To this stirred solution of NaSePh was added a solution of (−)-dihydrolimonene oxides **14a** and **14b** (5.7 g, 37 mmol) in 95% EtOH (20 mL) at room temp. The mixture was stirred and heated at reflux for 2 h. White semi-solid precipitates were generated at the end of this period. The mixture was then concentrated in vacuo to remove EtOH, and the residue was diluted with water. The resulting mixture was extracted with hexane. The extract was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo to give about 12.15 g of the residue. Its ^1H NMR analysis revealed the presence of **15a**, **15b**, and **15c** in a ratio of approximately 2:1:3 as estimated by the comparison of the signals due to their C*H*OH or C*H*SePh proton as shown in Scheme 5. The residue (12.15 g) was purified by chromatography over SiO_2 (150 g). Elution with hexane/EtOAc (20:1) first gave 4.6 g of a mixture of **15a** and **15b** contaminated with a small amount of **15c**, then 3.6 g of **15c** contaminated with a small amount of **15a** and **15b**, and finally **15c** (4.1 g). It was impossible to separate **15a** from **15b** cleanly by open column SiO_2 chromatography. The middle fraction was rechromatographed over SiO_2 (80 g) to give 0.9 g of pure **15c**. The combined yield of **15c** was 5.0 g (44%), which was obtained as a yellowish oil, $n_D^{24} = 1.5062$; $[\alpha]_D^{21} = -103.2$ (*c* 3.83, hexane). ν_{max} (film): 3352 (s, OH), 3058 (w), 1577 (m), 737 (s), 690 (m); δ_H ($CDCl_3$): 0.80 (3H, d, *J* 6.6, CHC*H*$_3$), 0.85 (3H, d, *J* 6.6, CHC*H*$_3$), 1.26 (2H, m), 1.37 (3H, s, C(OH)-C*H*$_3$), 1.40–2.08 (7H, m), 3.40 (1H, t-like, CHSePh) 7.24–7.27 (3H, m, arom-H) 7.50–7.60 (2H, m, arom-H); δ_C ($CDCl_3$): 14.1, 20.2, 22.6, 24.7, 31.6, 32.5, 35.2, 39.1, 54.9, 72.8, 127.4, 129.0, 130.8, 134.3. Anal. Calcd for $C_{16}H_{22}OSe$ (309.3): C. 62.13; H, 7.17. Found C, 61.64; H, 7.58.

4.10.2. (1*S*,2*S*,4*R*)-Isomer 15c′. In the same manner, (+)-dihydrolimonene oxides **14a′** and **14b′** (6.1 g, 40 mmol) afforded 5.2 g (43%) of **15c′** as a yellowish oil, $n_D^{24} = 1.5062$, $[\alpha]_D^{21} = +110.5$ (*c* 2.84, hexane). Its spectral data were identical with those of **15c**. Anal. Calcd for $C_{16}H_{22}OSe$ (309.3); C, 62.13; H, 7.17. Found C, 61.80; H, 7.58.

4.11. 4-Isopropyl-1-methyl-2-cyclohexen-1-ol 2 and 2′

4.11.1. (1*R*,4*R*)-Isomer 2. H_2O_2 (30%, 17 mL, 150 mmol) was added dropwise to a stirred and ice-cooled solution of **15c** (7.6 g, 24.6 mmol) in a mixture of THF (50 mL) and pyridine (10 mL). The reaction was exothermic. The mixture was stirred for 1 h at room temp, and then stirred and heated under reflux for 1 h. Subsequently, it was concentrated in vacuo, diluted with H_2O, and extracted with hexane. The hexane solution was washed with K_2CO_3 (aq solution), $CuSO_4$ (aq solution), and brine, dried over K_2CO_3, and concentrated in vacuo. The residue (about

5 g) was chromatographed over SiO_2 (100 g). Elution with hexane/EtOAc (30:1) afforded 3.4 g of crude **2** in later fractions. This was distilled to give 2.3 g (61%) of (1*R*,4*R*)-**2** as a colorless oil, bp 66–68 °C/3 Torr; $n_D^{24} = 1.4718$; $[\alpha]_D^{22} = +10.3$ (*c* 4.28, hexane); $[\alpha]_D^{20} = +11.4$ (*c* 1.67, $CHCl_3$). Its spectral data were identical with those of (±)-**2**. GC (TC-WAX, 100–190 °C, +3 °C/min): $t_R = 15.91$ min [94.3%, (1*R*,4*R*)-**2**]. Anal. Calcd for $C_{10}H_{18}O$ (154.2): C, 77.86; H, 11.76. Found C, 77.61; H, 11.84.

4.11.2. (1*S*,4*S*)-Isomer 2′. In the same manner, **15c′** (3.8 g, 12.3 mmol) was oxidized with 30% H_2O_2 (10 mL, 88 mmol) in THF (50 mL) and pyridine (10 mL). The crude product was purified by SiO_2 chromatography and distillation to give 1.5 g (79%) of (1*S*,4*S*)-**2′** as a colorless oil, bp 73–74 °C/4 Torr; $n_D^{24} = 1.4712$; $[\alpha]_D^{26} = -10.2$ (*c* 4.12, hexane); $[\alpha]_D^{20} = -12.0$ (*c* 2.06, $CHCl_3$). Its spectral data were identical with those of (±)-**2**. GC (TC-WAX, 100–190 °C, +3 °C/min): $t_R = 15.81$ min [94.5%, (1*S*,4*S*,)-**2′**]. Anal. Calcd for $C_{10}H_{18}O$ (154.2): C, 77.86; H, 11.76. Found C, 77.80; H, 11.89.

4.11.3. Isomerization in the absence of pyridine. If the above reaction was executed in the absence of pyridine, isomerization of (1*R*,2*R*)-**2** took place due to the acidity of the generated phenylselenenic acid to give a mixture of (1*R*,4*R*,)-**2** ($t_R = 16.13$ min; 66.8%), (1*S*,4*R*)-**1** ($t_R = 18.04$ min; 12.2%), (1*S*,6*R*)-**16** ($t_R = 19.69$ min; 8.5%), and (1*R*,6*R*)-**17** ($t_R = 21.79$ min; 7.5%) together with 5% of six unidentified compounds as analyzed by GC–MS (TC-WAX 100–190 °C, +3 °C/min). In the case of (1*S*,4*S*)-**2′**, the reaction in the absence of pyridine furnished a mixture of (1*S*,4*S*)-**2′** ($t_R = 16.16$ min; 51.2%), (1*R*,4*S*)-**1′** ($t_R = 18.09$ min; 23.9%), (1*R*,6*S*)-**16′** ($t_R = 19.71$ min; 7.6%), and (1*S*,6*S*)-**17′** ($t_R = 21.82$ min; 13.3%) together with 4% of seven unidentified compounds. Addition of pyridine to avoid the acid-catalyzed allylic rearrangement was therefore the key to the success of the synthesis. The four alcohols **1**, **2**, **16**, and **17** were identified by their MS. MS (70 eV, EI) of **16**: *m*/*z*: 154 (6.3) [M^+], 139 (49), 84 (100), 83 (56), 79 (25), 77 (26), 55 (31). MS (70 eV, EI) of **17**: *m*/*z*: 154 (9) [M^+], 139 (43), 91 (19), 84 (100), 83 (56), 79 (24), 77 (61), 55 (37). The retention time of **17** (17.98 min) was longer than that of **16** (15.88 min) due to the presence of the equatorial OH at C-2 of **17**.

4.12. 4-Isopropyl-1-methylcyclohexane-1,2-diols 19 and 19′

4.12.1. (1*R*,2*S*,4*S*)-Isomer 19. (*S*)-(−)-Dihydrolimonene was prepared from (*S*)-(−)-limonene (Aldrich, 6.0 g) by partial hydrogenation over PtO_2 (130 mg) in MeOH (15 mL). After dilution with hexane, the mixture was filtered through Celite to remove Pt, and the filtrate concentrated in vacuo to give crude **18** (6.0 g). AD-mix α® (Aldrich, 30 g) and $MeSO_2NH_2$ (3.2 g) were added to a mixture of *t*-BuOH (90 mL) and H_2O (100 mL), and the red mixture was stirred for 30 min at 0–5 °C to generate a biphasic (red and colorless) oxidant for AD. A solution of **18** (6.0 g, 44 mmol) in *t*-BuOH (10 mL) was added to the mixture, and stirring was continued for 3 h at 0–5 °C and for 2 days at room temperature causing the mixture to turn yellow in color. Subsequently, Na_2SO_3 (30 g) was added, and the mixture was stirred for 30 min at room temp. It was then concentrated in vacuo to remove *t*-BuOH. The residue was diluted with H_2O and extracted with Et_2O. The Et_2O solution was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was tritulated with hexane to give 3.2 g (42%) of crude **19**. Recrystallization from hexane yielded 1.96 g of pure **19** as needles, mp 72–73 °C; $[\alpha]_D^{22} = -10.3$ (*c* 2.28, $CHCl_3$) {Ref. 22 mp 82–83 °C; $[\alpha]_D = -10.1$ ($CHCl_3$)}. ν_{max} (nujol): 3336 (s, OH), 1165 (m), 1068 (m), 926 (m), 737 (m). δ_H ($CDCl_3$): 0.88 [6H, d, *J* 6.6, $CH(CH_3)_2$], 1.04–1.20 (1H, br), 1.26 [3H, s, $C(OH)CH_3$], 1.27–1.54 (5H, m) 1.60–1.86 (5H, m), 3.36 (1H, dd, *J* 4, 11, C*H*OH); δ_C ($CDCl_3$): 19.8, 19.9, 24.2, 27.1, 32.4, 34.0, 37.3, 42.7, 71.0, 75.5. Anal. Calcd for $C_{10}H_{20}O_2$ (172.3): C, 69.72; H, 11.70. Found C, 69.46; H, 12.11.

4.12.2. (1*S*,2*R*,4*R*)-Isomer 19′. Similarly, 7.0 g of (*R*)-**18′** was oxidized with 30 g of AD-mix β® in the presence of $MeSO_2NH_2$ (3.2 g) in *t*-BuOH (100 mL) and H_2O (100 mL) to give 3.5 g (40%) of crude **19′**. This was recrystallized from hexane to give 2.5 g of pure **19′** as needles, mp 74.5–75.0 °C; $[\alpha]_D^{21} = +9.3$ (*c* 3.30, $CHCl_3$) {Ref. 23 mp 82–83 °C; $[\alpha]_D^{29} = +8.2$}. Its spectral properties were identical with those of **19**. Anal. Calcd for $C_{10}H_{20}O_2$ (172.3): C, 69.72; H, 11.70. Found C, 69.50; H, 12.12.

4.13. (4*S*)-1-*tert*-Butyldimethylsilyloxymethyl-1,2-epoxy-4-isopropylcyclohexane 22

(*S*)-Perillyl alcohol **20** (Aldrich, 30 g) was oxidized with *t*-BuOOH to give 37.7 g of crude epoxy alcohol, which was silylated with TBSCl to furnish 57.3 g (quant.) of the known **21** after SiO_2 chromatography.[31] Adams's PtO_2 (300 mg) was added to a solution of **21** (57.3 g, 0.2 mol) in hexane (100 mL) and EtOAc (100 mL), and the mixture vigorously stirred under H_2 for 2 h at room temp, allowing the consumption of about 5 L of H_2. The hydrogenation was exothermic. The mixture was then filtered through Celite to remove Pt, and the Celite layer was washed with hexane. The combined filtrate and washings were concentrated in vacuo to give 56.9 g (quant.) of **22** as a colorless oil, $n_D^{22} = 1.4572$; $[\alpha]_D^{19} = -25.7$ (*c* 2.64, EtOH); $[\alpha]_D^{17} = -23.3$ (*c* 3.12, $CHCl_3$); ν_{max} (film): 1255 (m), 1100 (m), 837 (s), 780 (s); δ_H ($CDCl_3$): 0.04 and 0.05 (6H, each s, $SiCH_3$), 0.82 (3H, d, *J* 6, $CHCH_3$), 0.83 (3H, d, *J* 6, $CHCH_3$), 0.88 [9H, s, $C(CH_3)_3$], 1.20–1.70 (6H, m), 1.90–2.12 (4H, m), 3.13 (1H, br s), 3.56 (2H, d, *J* 5, CH_2O), 3.62 (1H, br s); δ_C ($CDCl_3$): −5.4, −5.3, 18.3, 19.6, 24.8, 25.8, 25.9, 25.95, 26.8, 31.7, 35.8, 58.0, 60.1, 67.1. Anal. Calcd for $C_{16}H_{32}O_2Si$: (284.5): C, 67.55; H, 11.34. Found C, 66.81; H, 11.72.

4.14. (4*S*)-1-*tert*-Butyldimethylsilyloxymethyl-4-isopropyl-2-phenylselenenylcyclohexan-1-ol 23

To a stirred suspension of NaH (50% in mineral oil, 3.4 g, 71 mmol) in dry THF (70 mL) was added slowly a solution of Ph_2Se_2 (10.7 g, 34 mmol) in THF (30 mL) at gentle reflux under Ar. With exothermic H_2 evolution, the orange solution turned to white and voluminous suspension of NaSePh. CAUTION. Care should be taken not to make the reaction too vigorous to control. After stirring and heating under reflux for 1.5 h, HMPA (7 mL) was added to the mixture to dissolve NaSePh. To the resulting homogeneous solution was added dropwise with stirring a solution of **22** (15.4 g, 54 mmol) in dry THF (35 mL), and the mixture was stirred and heated under reflux for 3 h under Ar. Subsequently, the mixture was cooled, diluted with ice-water, and extracted with hexane. The extract was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to give crude **23** (25 g, quant.) as an oil, $n_D^{22} = 1.5132$; $[\alpha]_D^{15} = +12.2$ (*c* 2.79, $CHCl_3$); ν_{max} (film): 3433 (m), 1577 (w), 1253 (m), 1084 (m), 837 (s), 779 (m), 737 (m), 690 (m). Anal. Calcd for $C_{22}H_{38}O_2SeSi$; (441.5): C, 59.84; H, 8.67. Found C, 59.11; H, 8.25.

4.15. (4*S*)-1-Hydroxymethyl-4-isopropyl-2-phenylselenenyl-cyclohexan-1-ol 24

A solution of TBAF in THF (1 M, 70 mL, 70 mmol) was added to a stirred solution of crude **23** (25 g, 54 mmol) in THF (70 mL) and the dark-colored mixture was left to stand overnight at room temperature. It was then diluted with H_2O and extracted with Et_2O. The extract was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo to give a crude oil (25 g) containing **24**, ν_{max} (film): 3430 (s), 1577 (w), 1253 (s), 1064 (s), 837 (s), 779 (s). This was employed in the next step without further purification.

4.16. (*R*)-Cryptone (4-isopropyl-2-cyclohexenone) 3

Solid sodium periodate (50 g, 234 mmol) was added in one portion to a stirred and ice-cooled solution of crude **24** (25 g, 54 mmol) in THF (300 mL) and H_2O (60 mL). The resulting solution soon became pasty with precipitated $NaIO_3$. After stirring for 1.5 h at room temp, the mixture was diluted with Et_2O and $NaHCO_3$ (aq solution). The Et_2O layer was separated and the aq layer was extracted with Et_2O. The combined Et_2O solution was washed with H_2O and brine, dried with $MgSO_4$, and concentrated in vacuo to give 21.3 g of an oil. This was chromatographed over SiO_2 (110 g). Elution with hexane/EtOAc (15:1) yielded fractions with ν_{max} (film): 1682. These were combined and distilled in vacuo to give 2.1 g (28% based on **22**, three steps) of (*R*)-**3**, bp 80–82 °C/6 Torr; $n_D^{22} = 1.4816$; $[\alpha]_D^{19} = -86.8$ (*c* 1.06, EtOH). Its spectral properties were identical with those of (±)-**3**.

4.17. (1*S*,4*R*)-4-Isopropyl-1-methyl-2-cyclohexen-1-ol 1

In the same manner as described for the preparation of (±)-**1**, (*R*)-**3** (3.6 g) was converted to (1*S*,4*R*)-**1** (1.8 g, 45%) by treatment with MeLi followed by chromatographic purification and distillation, bp 80–81 °C/5 Torr; $n_D^{22} = 1.4732$; $[\alpha]_D^{19} = -68.7$ (*c* 1.42, hexane); $[\alpha]_D^{19} = -65.9$ (*c* 1.17, $CHCl_3$) {Ref. 19 $[\alpha]_D = +69$ for (1*R*,4*S*)-**1**}. Its IR, ^1H NMR, ^{13}C NMR, and mass spectra were identical with those of (±)-**1**. GC (TC-WAX, 100–190 °C, +3 °C/min): $t_R = 18.25$ min (92.8%).

4.18. Determination of the enantiomeric purities of 1, 2, and 3 by GC analysis

4.18.1. GC analysis of 1 and 2. Instrument: Agilent 6890. Column: Chiramix®[34] (0.25 mm i.d. × 30 m). Column temp: 40–180 °C (+0.7 °C/min). Carrier gas: N_2, 0.7 mL/min. Detector: FID. Injection temp: 230 °C. Detector temp: 250 °C.

(±)-**1**: t_R 113.54 min [(1*S*,4*R*)-**1**], 114.54 min [(1*R*,4*S*)-**1′**] (base peak separation).
(1*S*,4*R*)-**1**: 96.67% of (1*S*,4*R*)-**1** and 3.33% of (1*R*,4*S*)-**1′** (93.34% ee).
(±)-**2**: t_R 108.43 min [(1*S*,4*S*)-**2′**], 109.50 min [(1*R*,4*R*)-**2**] (base peak separation).
(1*R*,4*R*)-**2**: 99.16% of (1*R*,4*R*)-**2** and 0.84% of (1*S*,4*S*)-**2′** (98.32% ee) or 99.33% of (1*R*,4*R*)-**2** and 0.67% of (1*S*,4*S*)-**2′** (98.66% ee).
(1*S*,4*S*)-**2**: 99.11% of (1*S*,4*S*)-**2′** and 0.89% of (1*R*,4*R*)-**2** (98.22% ee) or 98.92% of (1*S*,4*S*)-**2′** and 1.08% of (1*R*,4*R*)-**2** (97.84% ee).

4.18.2. GC analysis of 3. Instrument: Agilent 6890. Column: 2,3-dimethoxymethyl-6-*tert*-butyldimethylsilyl-γ-cyclodextrin (50% MOMTBDMSGC, 0.25 mm i.d. × 30 m). Column temp: 70–180 °C (+0.7 °C/min). Carrier gas, N_2, 0.7 mL/min. Detector: FID. Injection temp: 230 °C. Detector temp: 250 °C.

(±)-**3**: t_R 94.95 min [(*S*)-**3**], 96.88 min [(*R*)-**3**].
(*R*)-**3**: 95.74% of (*R*)-**3** and 4.26% of (*S*)-**3** (91.48% ee).

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