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SYNTHESIS OF (R)-1-METHYL-2-CYCLOHEXEN-1-OL, A CONSTITUENT OF THE AGGREGATION PHEROMONES OF DENDROCTONUS PSEUDOTSUGAE

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ABSTRACT

An efficient route for the synthesis of (R)-(+)-1-methyl-2-cyclohexen-1-ol from 1-cyclohexenemethanol using the Sharpless epoxidation method as the source of chirality is described.

As part of a study on the asymmetric synthesis of pheromones we report the synthesis of one enantiomer of 1-methyl-2-cyclohexen-1-ol **1**, an aggregation pheromone of the female Douglas-fir beetle, by a route which is suitable for the preparation of either enantiomer. The pheromone system of this beetle (*Dendroctonus pseudotsugae Hopkins*) is a complex mixture of compounds which includes 1-methyl-2-cyclohexen-1-ol, 3-methyl-2-cyclohexen-1-one, 3-methyl-2-cyclohexen-1-ol (seudenol), verbenone, *trans*-verbenol, 3-penten-1-ol and frontalin.[1] The enantiomeric constitution of the naturally occurring pheromone **1** is unknown. Although the structure of **1** is simple the preparation of pure enantiomers has been difficult and the methods reported have been based on natural seudenol[2] (not optically pure) or seudenol arising from enzymatic hydrolysis of racemic seudenyl acetate with pig liver esterase.[3] In the present work, the Sharpless epoxidation method[4] has been used to obtain the epoxy alcohol **3** which was transformed further to yield the pheromone, (R)-1-methyl-2-cyclohexen-1-ol, of high optical purity (**Scheme 1**).

The allylic alcohol **2**, prepared by reduction of methyl 1-cyclohexene-1-carboxylate with lithium aluminium hydride, was treated with t-butyl hydroperoxide, titanium tetra-iso-propoxide and diethyl

L-(+)-tartrate to yield the epoxy alcohol **3**.[4] After conversion of this epoxy alcohol **3** into its p-nitrobenzoate **4**, two recrystallisations from ethanol gave the pure derivative **4**, m.p. 94-96° (lit.[4] 92-93°). Hydrolysis of **4** with IM sodium hydroxide in ethanol yielded the pure epoxy alcohol **3** which was converted into its acetate **5** (acetic anhydride-pyridine) for the determination of its enantiomeric excess, in the presence of the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium (III) [Eu(hfc)$_3$], according to the method described.[5] Only one enantiomer could be detected under conditions where the resonances of both enantiomers in the racemate were clearly resolved (300 MHz). The epoxy alcohol **3** and its p-nitrobenzoate **4** are therefore considered to be greater than 97% e.e.

Both opening of the epoxide and cleavage of the ester occurred during reaction of p-nitrobenzoate **4** with an excess of the reagent prepared from diphenyl diselenide and sodium borohydride in ethanol solution.[6] Flash chromatography (ethyl acetate-light petroleum, 2:3) gave the required diol **6**† in 93% yield together with a small amount of the product expected from Payne rearrangement of the epoxy alcohol **3**.[7]

The diol **6** was converted (TsCl, Et_3N, DMAP) into the tosylate **7** which was treated, without purification, with potassium carbonate in methanol to yield the crude epoxide **8** which was then reduced with lithium aluminium hydride in ether. This reaction afforded the expected product **9**† and some of the primary alcohol **10***. Acetylation of the mixture with acetic anhydride in pyridine allowed easy chromatographic separation (ethyl acetate-light petroleum, 15:85) of the required product **9** (65% yield from the diol **6**) from the acetate **11**†.

Oxidation of the selenide **9** with m-chloroperoxybenzoic acid in dichloromethane gave the selenoxide **12** (86%) which was predominantly one diastereomer by ^{1}H n.m.r. (300 MHz). Recrystallisation (dichloromethane-ether) gave a sample, m.p. 123-125° †. Thermal elimination was achieved by refluxing the selenoxide **12** in carbon tetrachloride in the presence of triethylamine for 75 min. After isolation, the product was flash chromatographed (ethyl acetate-light petroleum, 15:85) and the solvent was removed through a short fractionating column packed with glass helices. The pheromone, (R)-(+)-1-methyl-2-cyclohexen-1-ol was recovered in 91% yield. Distillation at 20 mm (heated block) gave a product with $[\alpha]_D^{20}$ + 79.8 (C = 2.58 in ether) (lit.[2,3] $[\alpha]_D$ + 75.8 in ether) and with the same spectral data as those recorded.[2,3] Based on the rotation values, this enantiomer has an e.e. of at least 95%.

Clearly, the method described above for the preparation of the (R)-(+)-isomer can be used to obtain its enantiomer by substituting diethyl D-(-)-tartrate in the Sharpless epoxidation of 1-cyclohexenemethanol **2**.

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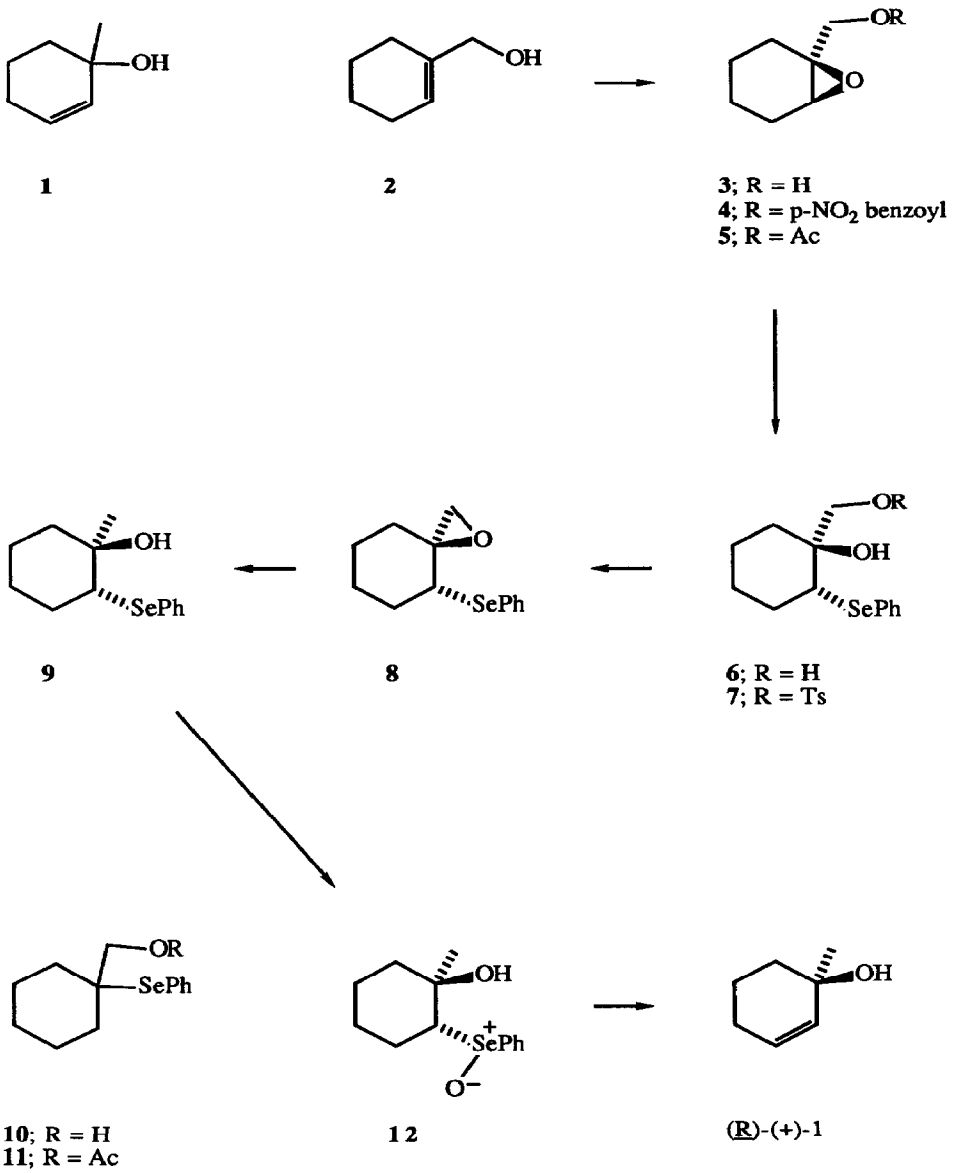
* This could have arisen from hydride reduction of a selenonium salt, formed by intra-molecular opening of the epoxide **8** by the selenium.


OH
OH
OR
O
1
2
3; R = H
4; R = p-NO2 benzoyl
5; R = Ac
OR
OH
SePh
6; R = H
7; R = Ts
O
SePh
OH
SePh
8
9
OR
SePh
OH
SePh
O−
10; R = H
11; R = Ac
12
OH
(R)-(+)-1

Scheme 1

ACKNOWLEDGEMENT

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† 300 MHz ^{1}H n.m.r. data:

[1S, 2R]-1-(Hydroxymethyl)-2-(phenylselenyl)cyclohexanol **6** δ ($CDCl_3$): 1.3-2.3, complex (methylene envelope); 3.36, dd, 8.7 and 4.1 Hz (H2); 3.61 and 3.77, ABq, 11.4 Hz (diastereotopic CH_2O); 7.28, m and 7.59, m (aromatic).

[1R, 2R]-1-Methyl-2-(phenylselenyl)cyclohexanol **9** δ ($CDCl_3$): 1.29, s (CH_3); 1.2-2.3, complex, (methylene envelope); 2.62, s (OH); 3.21, dd, 3.9 and 7.5 Hz (H2); 7.25, m and 7.59, m (aromatic).

1-(Phenylselenyl)cyclohexylmethyl acetate **11** 60 MHz δ ($CDCl_3$): 1.2-2.3, complex (methylene envelope); 2.03, s (CH_3); 4.10, s (CH_2); 7.2-7.8, complex (aromatic).

[1R, 2R]-1-Methyl-2-(phenylseleninyl)cyclohexanol **12** δ ($CDCl_3$): 1.3-2.0, complex (methylene envelope and OH); 1.68, s (CH_3); 3.09, m (H2); 7.57, m and 7.79, m (aromatic).

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