Notes

A Novel Synthesis of *(S)*- and *(R)*-1-Methyl-2-cyclohexen-1-ol, Aggregation Pheromones of *Dendroctonous pseudotsugae*

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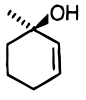
The aggregation pheromone system of the female Douglas-fir beetle (*Dendroctonous pseudotsugae* Hopkins) is a complex mixture of compounds mostly represented by *(S)*- and *(R)*-1-methyl-2-cyclohexen-1-ol (**1**) of unknown enantiomeric composition.[1] The interesting biological activities of these natural pheromones have prompted extensive synthetic efforts.[2]

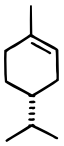
In this paper, we describe a new enantioselective approach to *(R)*-**1** and *(S)*-**1** using as the key feature the regio- and stereospecific hydroxyselenenylation of limonene degradation products.

Recently, we reported the interaction of benzeneselenenyl chloride with trisubstituted olefins in the presence of water as a simple procedure to generate a tertiary carbinol center of predictable chirality.[3] The reaction exhibits a complete diasteroselectivity when applied to a carbocyclic system forced into a rigid conformation (e.g., **2** → **3**).[3]

(S)-1



(R)-1



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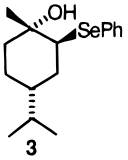

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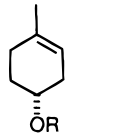
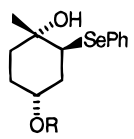
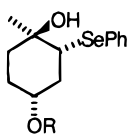
Our approach to the synthesis of *(S)*-**1** started with the hydroxyselenenylation of 4-methyl-3-cyclohexenol (**4a**) prepared by a 5-step degradation of *(R)*-(+)-limonene.[4] Treatment of **4a** with benzeneselenenyl chloride in the presence of water gave a (5:6) mixture of diastereomers **5a** and **6a**, separated by column chromatography. The lack of diastereoselectivity observed in the hydroxyselenenylation of **4a** compared with the transformation **2** → **3** permitted the preparation of both the enantiomers of **1**. Thus oxidation of **5b** derived from **5a** to the corresponding selenoxide followed by the *syn*-elimination procedure[5] yielded **7**. Subsequent reductive elimination of the acetoxy group of **7** with lithium in ammonia[6] led to *(S)*-**1** contaminated by the isomeric olefin *(S)*-**8**. The pure *(S)*-**1**, whose analytical and spectroscopic data were in accord with those reported,[1,2] was obtained in 68% yield after $SiO_2/AgNO_3$ column chromatography. Applying the same procedure the pheromone *(R)*-**1** was obtained from **6a**.



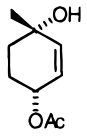
4a: R = H
4b: R = Ac



5a: R = H
5b: R = Ac



6a: R = H
6b: R = Ac



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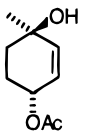

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The above procedure for the preparation of *(R)*- and *(S)*-**1** involved tedious chromatographic separation of stereoisomers **5a** and **6a**. In an attempt to increase the diastereoselectivity of the hydroxyselenenylation reaction, the alcoholic group of **4a** was transformed into a bulkier group by acetylation (**4b**). Unexpectedly, the interaction of **4b** with benzeneselenenyl chloride and water afforded **6b** as a single diastereomer. The structure of selenide **6b** was proposed on the basis of NMR studies and confirmed by chemical transformation into *(R)*-**1** by the previous route. The diasterofacial outcome of the 1,2-*trans* hydroxyselenenylation process (with the phenylselenium group *syn* to the acetoxy group) in the formation of **6b** is postulated to arise from the preferential approach of PhSeCl, which adopts a quasi-axial position in the transition state, to the olefinic bond. The reaction would then proceed *via* participation of a lone pair of electrons on the carbonyl oxygen which would direct the phenylseleno moiety to the α-face of the cycloalkene, as depicted in Scheme 1. The assistance of a homoallylic acetate in orienting the diastereoselectivity of the hydroxyselenenylation of olefins is unprecedented.[7]

The stereoselective synthesis of *(S)*-**1** was also achieved starting from **10**, available in three steps from *(R)*-limonene.[8] The hydroxyselenenylation of **10** afforded a single compound, whose spectroscopic data were in accord with structure **11**. Thus the acetyl group at C(4) acted as a conformational holding group mimicing the isopropyl

(1) Ryker, L. C.; Libbey, L. M.; Rudinsky, J. A. *Environ. Entomol.* **1979**, *8*, 789. Libbey L. M.; Oehlschlager, A. C.; Ryker, L. C. *J. Chem. Ecol.* **1983**, *9*, 1533.

(2) Mori, K.; Harza, B. G.; Pfeiffer, R. J.; Gupta, A. K.; Lindgren, B. S. *Tetrahedron* **1987**, *43*, 2249. Mori, K.; Ogoche, J. I. J. *Liebigs Ann. Chem.* **1988**, 903. Hamon, D. P. G.; Massy-Westropp, R. A.; Newton, J. L. *Tetrahedron Asymmetry* **1990**, *1*, 771.

(3) Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Rosati, O. *Tetrahedron Lett.* **1989**, 3175.

(4) Cane, D. E.; Yang, G.; Coates, R. M.; Pyun, H.-J; Hohn, T. M. *J. Org. Chem.* **1992**, *57*, 3454.

(5) Sharpless, K. B.; Gordon, K. M.; Lauer, R. F.; Patrick, D. W.; Young, M. W. *Chem. Scr.* **1975**, *8a*, 9.

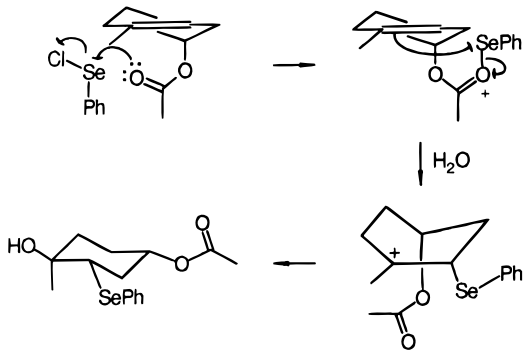
(6) Ceccherelli, P.; Curini, M.; Tingoli, M.; Pellicciari, R. *J. Chem. Soc., Perkin Trans. I* **1980**, 1924.

(7) For the regio- and stereoselectivity of PhSeCl additions to allylic acetates, see: Liotta, B.; Zima, G.; Saindane, M. *J. Org. Chem.* **1982**, *47*, 1258. Haughan, A. F.; Sweeney, J. B. *Tetrahedron: Asymmetry* **1994**, *5*, 177.

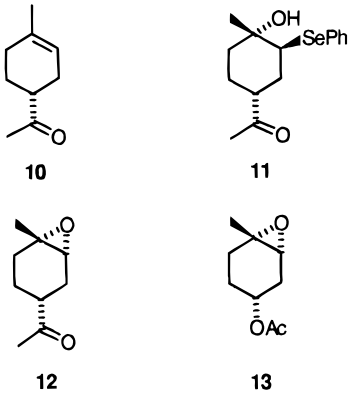
(8) Delay F.; Ohloff, G. *Helv. Chim. Acta* **1979**, *62*, 2168.

0022-3263/96/1961-2882$12.00/0

Scheme 1



properties of **2**. The olefin **7** was readily obtained from **11** *via* epoxide **12**[8] which in turn was secured by alkaline treatment of selenoxide of **11** in methanol.[9] *m*-CPBA oxidation of **12** afforded **13**,[8] and S_N2 displacement at C(2) of the epoxide ring with the phenylselenenyl anion[10] yielded the selenide **5b**, easily transformed into the pheromone *(S)*-**1** following the above procedure.



In summary we have demonstrated that both the enantiomers of 1-methyl-2-cyclohexen-1-ol (**1**) were synthetized in the diastereoselective manner from *(R)*-(+)-limonene. The present work proved the utility of the hydroxyselenenylation process for the construction of a chiral allylic and tertiary hydroxy group. The ability of the *homo*-allylic acetate to govern the diastereofacial selectivity of olefin selenation bodes well for further stereospecific applications.

Experimental Section

General. The same general procedures were followed as described previously.[11] *(R)*-(+)-limonene was purchased from Fluka.

Preparation of *β*-Hydroxy Selenides. Benzeneselenenyl chloride (1.1 mmol) was added to a stirring solution of the olefin (1 mmol) in 10 mL of a 5:1 mixture of CH_3CN-H_2O. The solution was stirred at room temperature for 30 min and then neutralized with a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with water, dried, and evaporated. Column chromatography ($CH_2Cl_2-CH_3OH$ 98:2) gave *β*-hydroxy selenides as pale yellow compounds.

***(1S,2S,4R)*-1-Methyl-2-(phenylselenyl)cyclohexane-1,4-diol (5a):** 35%; ^{1}H NMR *δ* 1.35 (s, 3 H), 3.61 (dd, 1 H, *J* = 12.0, 5.0 Hz), 4.01 (m, 1 H), 7.18−7.71 (m, 5 H); ^{13}C NMR *δ* 134.0, 129.1, 127.4, 127.3, 72.5, 66.5, 53.7, 39.7, 33.6, 30.4, 24.1. Anal. Calcd for $C_{13}H_{18}O_2Se$: C, 54.54; H, 6.34. Found: C, 54.61; H, 6.31.

***(1R,2R,4R)*-1-Methyl-2-(phenylselenyl)cyclohexane-1,4-diol (6a):** 42%; ^{1}H NMR *δ* 1.38 (s, 3 H), 3.20 (dd, 1 H, *J* = 13.0, 4.0 Hz), 3.65 (m, 1 H), 7.20−7.70 (m, 5 H); ^{13}C NMR *δ* 132.8, 127.5, 126.6, 126.1, 70.7, 68.2, 54.1, 39.8, 35.1, 30.4, 21.6. Anal. Calcd for $C_{13}H_{18}O_2Se$: C, 54.54; H, 6.34. Found: C, 54.58; H, 6.32.

***(1S,2S,4R)*-1-Methyl-2-(phenylselenyl)-4-acetylcyclohexan-1-ol (11):** 87%; ^{1}H NMR *δ* 1.41 (s, 3 H), 1.98 (m, 1 H), 2.18 (s, 3 H), 2.41 (m, 1 H), 2.74 (m, 1 H), 3.46 (dd, 1 H, *J* = 6.8, 3.8 Hz), 7.21−7.71 (m, 5 H); ^{13}C NMR *δ* 210.8, 133.8, 129.6, 129.1, 127.4, 71.7, 53.6, 46.4, 34.9, 30.8, 27.9, 27.6, 23.3. Anal. Calcd for $C_{15}H_{20}O_2Se$: C, 57.68; H, 6.46. Found: C, 57.71; H, 6.44.

Preparation of Acetates. To a solution of the alcohol (1 mmol) in 5 mL of CH_2Cl_2 were added NEt_3 (1.5 mmol), Ac_2O (1.5 mmol), and a catalytic amount of 4-pyrrolidinopyridine were added. The solution was stirred at room temperature for 1 h and then diluted with water (10 mL). The combined organic layers were washed with water, dried, and evaporated to yield the acetate as a yellow oil.

***(1S,2S,4R)*-4-Acetoxy-1-methyl-2-(phenylselenyl)cyclohexan-1-ol (5b):** 97%; ^{1}H NMR *δ* 1.31 (s, 3 H), 1.93 (s, 3 H), 3.51 (dd, 1 H, *J* = 13.0, 4.0 Hz), 4.93 (m, 1 H), 7.18−7.72 (m, 5 H); ^{13}C NMR *δ* 169.9, 133.8, 129.1, 128.7, 127.2, 71.7, 69.3, 53.0, 35.9, 33.9, 27.0, 24.0, 20.8. Anal. Calcd for $C_{15}H_{20}O_3Se$: C, 54.87; H, 6.14. Found: C, 54.84; H, 6.18.

***(1R,2R,4R)*-4-Acetoxy-1-methyl-2-(phenylselenyl)cyclohexan-1-ol (6b):** 98%; ^{1}H NMR *δ* 1.32 (s, 3 H), 2.05 (s, 3 H), 3.21 (dd, 1 H, *J* = 12.0, 4.0 Hz), 4.79 (m, 1 H), 7.2−7.7 (m, 5 H); ^{13}C NMR *δ* 170.1, 134.1, 129.0, 128.8, 127.5, 71.7, 71.4, 55.3, 37.4, 36.0, 28.1, 23.2, 21.0. Anal. Calcd for $C_{15}H_{20}O_3Se$: C, 54.87; H, 6.14. Found: C, 54.84; H, 6.16.

Preparation of Olefines from Selenides. To a stirred solution of the selenide (1 mmol) in THF (5 mL) at room temperature was added 30% hydrogen peroxide (10 mmol). After stirring for 3 h at 50 °C, the solvent was distilled, water (10 mL) was added to the residue, and the resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine and dried. Removal of the solvent and chromatography of the residue ($CH_2Cl_2-CH_3OH$ 98:2) gave the olefins as oils.

***(1S,4R)*-4-Acetoxy-1-methyl-2-cyclohexen-1-ol (7):** 81%; ^{1}H NMR *δ* 1.21 (s, 3 H), 2.0 (s, 3 H), 5.11 (m, 1 H), 5.58 (dd, 1 H, *J* = 10.0, 3.0 Hz), 5.73 (d, 1 H, *J* = 10.0 Hz); ^{13}C NMR *δ* 170.4, 137.5, 126.7, 68.2, 67.3, 34.3, 28.3, 25.2, 21.0. Anal. Calcd for $C_9H_{14}O_3$: C, 63.49; H, 8.30. Found: C, 63.35; H, 8.35.

***(1R,4R)*-4-Acetoxy-1-methyl-2-cyclohexen-1-ol (9):** 80%; ^{1}H NMR *δ* 1.35 (s, 3 H), 2.05 (s, 3 H), 5.25 (m, 1 H), 5.71 (dd, 1 H, *J* = 10.0, 3.0 Hz), 5.85 (d, 1 H, *J* = 10.0 Hz); ^{13}C NMR *δ* 170.7, 138.1, 125.9, 67.6, 67.4, 34.4, 28.4, 25.8, 21.1. Anal. Calcd for $C_9H_{14}O_3$: C, 63.49; H, 8.30. Found: C, 63.54; H, 8.26.

***(1S,4R)*-4-Acetyl-1-methyl-2-cyclohexen-1-ol (12):** 90%; ^{1}H NMR *δ* 1.31 (s, 3 H), 2.21 (s, 3 H), 3.02 (m, 1 H), 5.82 (bs, 2 H); ^{13}C NMR *δ* 209.3, 135.4, 125.2, 66.9, 49.3, 35.8, 28.7, 21.4. Anal. Calcd for $C_9H_{14}O_2$: C, 70.08; H, 9.16. Found: C, 70.14; H, 9.11.

Reductive Elimination of Allylic Acetates with Li/NH_3. A solution of the acetate (1 mmol) in THF (5 mL) was added during 20 min to a solution of Li (10 mmol) in liquid ammonia (20 mL), and the reaction mixture was stirred at −40 °C for 10 min. A few drops of bromobenzene were added to the mixture, the ammonia was evaporated in a stream of nitrogen, and a 0.5 N sulfuric acid solution (3 mL) was added to the residue. The resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were washed with water, dried, and evaporated. Column chromatography of the residue on a silica gel/$AgNO_3$ (10%) ($CH_2Cl_2-CH_3OH$ 98:2) gave olefins as colorless oils.

***(S)*-1-Methyl-2-cyclohexen-1-ol (1):** 65%; $[\alpha]^{20}_D$ −75.6° (Et_2O), with the same spectral data as those reported;[1] ^{13}C NMR *δ* 133.7, 129.0, 67.2, 37.8, 29.3, 25.0, 19.4.

***(S)*-1-Methyl-3-cyclohexen-1-ol (8):** 28%; $[\alpha]^{20}_D$ −66.4° (Et_2O); ^{1}H NMR *δ*;[12] ^{13}C NMR *δ* 125.6, 123.7, 68.3, 39.5, 34.7, 28.6, 23.0.

(9) Ceccherelli, P.; Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Tetrahedron Lett.* **1995**, 5079.

(10) Kametani, T.; Kurobe, H.; Nemoto, H. *J. Chem. Soc., Perkin Trans. I* **1981**, 756.

(11) Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Rosati, O.; Wenkert, E. *J. Org. Chem.* **1991**, *56*. 7065.

(12) Staroscik, J. A.; Rickborn, B. *J. Org. Chem.* **1992**, *37*, 738.

***(R)*-1-Methyl-2-cyclohexen-1-ol (1):** 63%; $[\alpha]^{20}_D$ + 75.8° (Et_2O); for spectral data *vide supra*.

***(R)*-1-Methyl-3-cyclohexen-1-ol (8):** 27%; $[\alpha]^{20}_D$ + 66.2° (Et_2O); for spectral data *vide supra*.

***m*-CPBA Oxidation of Ketone 12.** A solution of *m*-CPBA (55%) (1.3 g, 7.5 mmol) in CH_2Cl_2 (10 mL) was added to a stirred solution of **12** (0.24 g, 1.5 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The mixture was then allowed to reach room temperature and stirred for 3 days. After addition of saturated solution of Na_2SO_3, the organic phase was separated, washed with water, dried, and evaporated, yielding **13** as a colorless oil (0.18 g, 70%): ^{1}H NMR δ 1.39 (s, 3 H), 2.12 (s, 3 H), 3.19 (dd, 1 H, J = 4.0, 1.5 Hz), 3.52 (dd, 1 H, J = 4.0, 2.0 Hz), 5.11 (dt, 1H, J = 8.0, 2.0 Hz); ^{13}C NMR δ 170.7, 70.1, 66.2, 60.9, 55.8, 35.5, 26.9, 26.8, 21.0. Anal. Calcd for $C_9H_{14}O_4$: C, 58.04; H, 7.58. Found: C, 58.11; H, 7.52.

Reaction of Epoxy Acetate 13 with Phenylselenium Anion. To a stirred suspension of diphenyl diselenide (0.2 g, 0.61 mmol) in EtOH (4 mL) was added $NaBH_4$ (0.05 g, 1.28 mmol) at room temperature. After 30 min a solution of **15** (0.2 g, 1.18 mmol) in EtOH (2 mL) was added, and the reaction mixture was refluxed for 1 h, then poured into brine (20 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried and evaporated to yield **6b** (0.31g, 93%).

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