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Allylic oxidation in terpenoids: Synthesis of (±)-*E*-linalool-1-oic acid, (±)-*E*-9-hydroxylinalool and (±)-7-hydroxyterpineol

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Abstract. (±)-*E*-linalool-1-oic acid, (±)-*E*-9-hydroxylinalool and (±)-7-hydroxyterpineol 1, 2 and 3, respectively, have been synthesised by allylic oxidation of olefins by selenium dioxide catalysed by pyridine/*t*-butyl hydroperoxide in high yields.

Keywords. Allylic oxidation; (*E*)-9-hydroxylinalool; (*E*)-linalool-1-oic acid; 7-hydroxyterpineol.

1. Introduction

Carbonyl, hydroxyl and carboxylic acid functional group α- to the double bond are very common among terpenoids. To incorporate such functional groups, a wide variety of reagents such as CrO_3-pyridine, H_2O_2 cetyltrimethyl ammonium chlorochromate (Aggarwal *et al* 1995) and selenium dioxide, to count only a few, are used which possess individualistic advantages. Among these substances selenium dioxide is the most versatile and finds wide application in incorporating hydroxyl, carbonyl and carboxylic acid functionality α- to the double bond. Allylic oxidations by SeO_2 are very selective (Rappaport and Bhalerao 1971) and under different conditions yield different products in varying yields having mostly (*E*)-geometry (Marshall *et al* 1987). Allylic oxidation by SeO_2 has been used to advantage in the synthesis of three naturally occurring terpenoids, viz., (±)-linalool-1-oic acid (1), (±)-9-hydroxylinalool (2) and (±)-7-hydroxyterpineol (3).

Recently, Nicoletti *et al* (1989) isolated linalool-1-oic acid as a free natural product for the first time from *Kickxia spuria*. The acid 1 has been isolated (Konoshima and Sawada 1984) earlier in glycosidic form from fruits of *Gymnocladus chinesis* and, very recently, in the free form from *Artemisis siberi* (Marco *et al* 1993). 7-Hydroxyterpineol (3) and 9-hydroxylinalool (2) were isolated (Bohlmann *et al* 1991) from aerial parts of *Artemisia xerophytica*. The structural assignments of these compounds were done on the basis of spectral data. Although the C-4 centre in 3 represents a stereogenic centre, neither has optical rotation been reported nor has absolute stereochemistry been assigned, indicating thereby that the isolated natural product is racemic. Literature does not seem to record any attempt towards the synthesis of 3, while the only synthesis reported (Sharma *et al* 1994) for 2 in one pot has low yield. The only synthesis reported (Carda *et al* 1994, 1995) for 1 utilizes a long reaction sequence involving protection,

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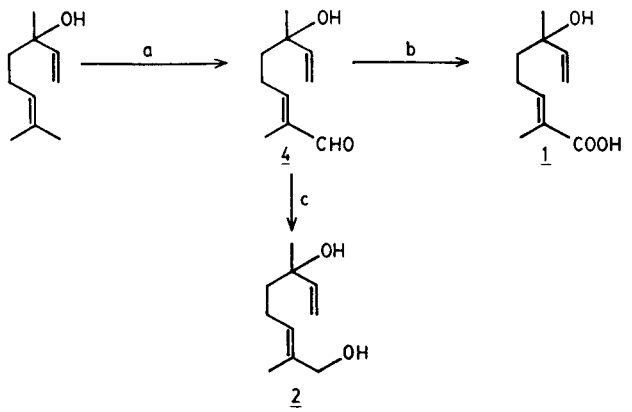
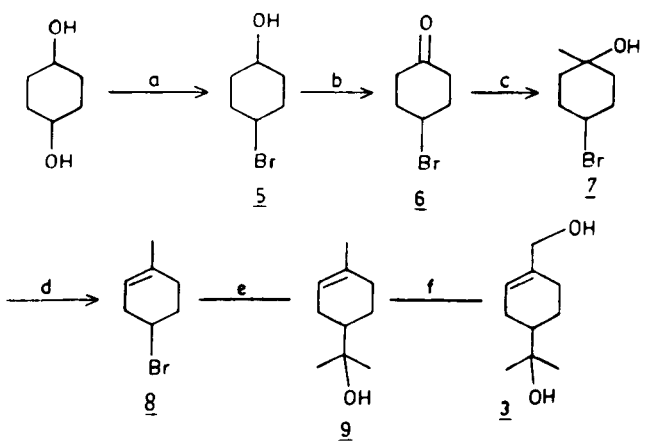


REAGENTS - a: SeO_2, t-BuO_2H, CH_2Cl_2, 15°, 2hr
b. t-BuOH, $(CH_3)_2C{=}CHCH_3$, $NaClO_2$, NaH_2PO_4
c: $NaBH_4$ MeOH, 0°

Scheme 1.



REAGENTS - a: HBr, reflux, benzene
b: PCC, CH_2Cl_2, 0°
c: MeMgI, ether, 0°, N_2 atm
d: Oxalic acid, CCl_4
e: (i) Mg, THF, N_2 atm
(ii) 0°, acetone
f: (i) SeO_2, Pyridine abs. ethanol
(ii) LAH, ether, 0°

Scheme 2.

deprotection of hydroxyl group, starting from linalool. Herein, we report a facile synthesis of these compounds through oxidation by SeO_2. The reaction sequence employed is shown in schemes 1 and 2.

2. Results and discussion

Linalool was oxidised to (*E*)-2,6-dimethyl-3-hydroxy-2,7-octadienal with SeO_2, *t*-BuOOH in CH_2Cl_2. The resulting dienal was characterized by a PMR signal corresponding to the formyl group at 9·7 and an IR characteristic band at 1685 cm^{-1}.

Although the product could not be obtained with high purity because of hydroperoxide, yet the reduction of the resulting α,β-unsaturated dienal 4 with sodium borohydride at 0° yielded 9-hydroxylinalool (2). Oxidation of α,β-unsaturated dienal 4 with sodium chlorite (Pinnick *et al* 1981), and sodium dihydrogenphosphate yielded linalool-1-oic acid (1). The structures of these target molecules were confirmed through their spectral studies.

Using α-terpineol, synthesised through a new route as an intermediate, herein the first synthesis of this natural product has been achieved confirming the structure 3. Cyclohexan-1,4-diol was monobrominated selectively (Kang *et al* 1985) using 48% HBr in refluxing benzene using a Dean and Stark water separator. The bromo alcohol 5 was oxidised to 4-bromo cyclohexanone using PCC (Piancatelli *et al* 1982) in anhydrous dichloromethane at 0°. Bromoketone 6 was characterised by its IR signal at 1730 cm^{-1}. The purified bromoketone 6 was subjected to Grignard reaction with methylmagnesium iodide to afford 4-bromo-1-methyl cyclohexanol 7. Subsequent dehydration of *t*-alcohol 7 with anhydrous oxalic acid (Clarke and Davis 1941; Carlin and Constantine 1947) at 180° yielded 4-bromo-1-methylcyclohexene which was converted into Grignard reagent in THF and allowed to react with acetone to afford terpineol 9. Pure terpineol 9 was subjected to allylic oxidation (Borowiecki and Reca 1971) using SeO_2 and anhydrous pyridine in absolute ethanol to get a mixture of 3 alongwith the corresponding aldehyde as a major product. The crude mixture was subjected to reduction with LAH in ether in obtain the title compound, 7-hydroxy terpineol 3.

3. Experimental

Boiling points are uncorrected. IR spectra were recorded on a Perkin–Elmer 1430 spectrophotometer (wave number in cm^{-1}). PMR and ^{13}C NMR spectra were recorded on a Varian EM-360 (60 MHz) and Bruker AC 300F 300 MHz spectrometer using $CDCl_3$ as solvent and tetramethylsilane as an internal standard. Chemical shifts are given in PPM (δ-scale). Mass spectra (MS) were recorded at 70 eV using a VG-Analytical 11-250-J70-S spectrometer. Silica gel (Acme 100–200 mesh) was used for column chromatography. Unless stated otherwise, all organic extracts were dried over sodium sulphate.

3.1 *6-Hydroxy-2,6-dimethyl octa-2,7-dienal (4)*

A solution of linalool (2·05 g, 13·3 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a stirred mixture of SeO_2 (150 mg, 1·35 mmol) and 70% *t*-butyl hydroperoxide (4·8 ml, 40 mmol) in CH_2Cl_2 (25 ml) at 15°C. After being stirred at that temperature for 3 hours, the reaction mixture was diluted with ether (100 ml), washed with 10% aqueous KOH, water, brine and then dried over anhydrous magnesium sulphate. Evaporation of the solvent under reduced pressure afforded the crude product as an oil contaminated with a small amount of *t*-butyl hydroperoxide. Purification of the crude product over silica gel using hexane–ethyl acetate (9:1) as eluent afforded pure 4 (1·77g, 79·3%). IR spectrum (neat): 3405, 2920, 1685, 1635, 1410, 1070, 910. PMR spectrum: 9·3δ(*s*, 1H, CHO), 5·7δ(*m*, 1H, olefinic), 5·2δ(*dt*, 2H, $J = 12, 5, 3$), 4·96δ(*t*, 1H, $J = 9$), 3·8δ(*brs*, 1H, OH, D_2O exchangeable), 2·2δ(*m*, 2H), 1·7δ(*s*, 3H), 1·43δ(*m*, 2H) and 1·2(*s*, 3H). ^{13}C NMR: 195·6, 144·7, 144·1, 143·5, 125·8, 77·5, 41·6, 27·7, 23·8, 12·8. MS: 168$[M]^+$, 151, 150, 135, 123, 111, 93, 81, 71, 85, 59.

3.2 *Linalool-1-oic acid* (1)

The dienal 4 (0·202 g, 1·2 mmol) was dissolved in 25 ml of *t*-butyl alcohol and 10 ml of 2-methyl-2-butene. A solution of sodium chlorite (1·0 g, 11 mmol) and sodium dihydrogenphosphate (1·0 g, 8·3 mmol) in 10 ml of water was added dropwise for 15 minutes. The pale yellow reaction mixture was stirred at room temperature overnight. The volatile components were then removed under vacuum, the residue dissolved in 30 ml of water and finally extracted with hexane. The aqueous layer was acidified to *p*H 3 with HCl and extracted with ether, and the ether layer washed with cold water and dried. Evaporation of the solvent gave the pure acid 1 (0·204 g, 92·7%). IR spectrum: 3420–3250 (*br*), 2940, 1705, 1635, 1410; 1060, 905. PMR spectrum: 7·93δ(*br s*, 1H, COOH, D_2O exchangeable), 5·73δ(*m*, 1H), 5·3(*dt*, 2H, $J = 17, 6, 3$), 5·06δ(*br t*, 1H), 2·3δ(*m*, 2H), 3·8δ(*br s*, 1H, OH, D_2O exchangeable) 1·63δ(*s*, 3H), 1·43δ(*m*, 2H), 1·26δ(*s*, 3H). ^{13}C NMR: 176·5, 144·8, 144·2, 125·9, 113·7, 76·2, 42·7, 27·3, 23·8, 11·9. MS: 183$[M]^+$, 1666, 143, 110, 99, 85, 81, 71, 59.

3.3 *9-Hydroxylinalool* (2)

To the crude 4 (1·77 g) in methanol 20 ml at 0° was added in small lots $NaBH_4$ (115 mg, 3 mmol) with stirring. After stirring for an hour, the reaction mixture was concentrated and the residue dissolved in ether. The ether layer was then washed with water and brine and finally dried. Removal of solvent followed by column chromatographic purification over silica gel using hexane–ethylacetate (9:1) as eluent afforded pure 2(1·692 g, 87·3%). IR spectrum: 3480, 2970, 1550, 1460, 1380, 1260, 1015. PMR spectrum: 5·77δ(*dd*, 1H, olefinic, $J = 15, 9$), 5·22δ(*dd*, 1H, $J = 15, 3$), 5·07δ(*dd*, 1H, $J = 12, 3$), 4·93δ(*t*, 1H, $J = 9$), 3·99δ(*br s*, 3H, CH_2OH), 2·96δ(*br s*, 1H, OH, D_2O exchangeable), 2·08δ(*m*, 2H, CH_2), 1·66δ(*br s*, 3H, CH_3), 1·58δ(*m*, 2H), 1·30δ(*s*, 3H, CH_3). MS: 170 $[M^+]$, 85, 71.

3.4 *4-Bromocyclohexanol* (5)

Hydrobromic acid (48%, 11·42 ml) was added to a solution of 1,4-cyclohexanediol (11·6 g, 0·1 mol) and benzene (200 ml) and the mixture was heated to reflux for 15 h while trapping the water formed using a Dean and Stark water separator. The resulting reaction mixture was washed with 6N NaOH solution, water and brine and then dried. Evaporation of the solvent followed by chromatographic purification using hexane–ether (9:1) as eluent yielded pure 5 (17·06 g, 95·3%). TLC: $R_f = 0·43$ (hexane:ethyl acetate::9:1) IR spectrum: 3440, 2980, 2890, 1270, 1070, 465. PMR spectrum: 4·47δ(*br s*, 1H, OH, D_2O exchangeable) 3·96δ(*m*, 1H, CHOH), 3·53δ(*m*, 1H, CHBr), 2·06δ(*m*, 4H, 2xCH_3), 1·93δ(*m*, 4H, 2xCH_3).

3.5 *4-Bromocyclohexanone* (6)

Bromoalcohol 5 (8·95 g, 0·05 mol) in CH_2Cl_2 (50 ml) was added to a well-stirred mixture of pyridinium chlorochromate (16·25 g, 0·075 mol) in anhydrous CH_2Cl_2 (150 ml) at 0°. The mixture was stirred and the progress of the reaction monitored by tlc. After the completion of the reaction, the reaction mixture was diluted with ether (200 ml). The supernant layer was decanted from the black gummy residue to yield 6 (5·95 g, 67·2%) after removal of the solvent. TLC: $R_f = 0·51$, 5% ethyl acetate). IR spectrum: 3440, 2970, 1730, 1450, 1270, 1120, 1070. PMR spectrum: 3·8δ(*m*, 1H, CHBr), 2·2δ(*m*, 8H).

3.6 *4-Bromo-1-methylcyclohexanol* (7)

A solution of 6 (2·65 g, 0·015 mol) in ether (15 ml) was added dropwise to a well-stirred ice-cooled solution of methylmagnesium iodide, prepared from activated Mg turnings (0·384 g, 0·016 mol) and MeI (1·0 ml, 3·41 g, 0·024 mol) in ether (20 ml), and the contents were left overnight at room temperature. The resulting solution was decomposed with a saturated solution of NH_4Cl, extracted with ether, washed with water and brine, and then dried. Evaporation of solvent yielded 7 (2·34 g, 80·8%). IR spectrum: 3340, 2960, 1450, 1380, 1260, 1150, 1010, 970, 920. PMR spectrum: 3·9δ(*m*, 1H, CHBr), 2·6δ(*br s*, 1H, OH, D_2O exchangeable), 1·9δ(*m*, 4H), 1·6δ(*m*, 4H), 1·1δ(*s*, 3H).

3.7 *4-Bromo-1-methylcyclohexene* (8)

A mixture of 7 (1·93 g, 0·01 mol), anhydrous CCl_4 (25 ml) and anhydrous oxalic acid (3·6 g, 0·04 mol) was heated in an oil bath maintained at 175–180° for 8 h. The reaction was monitored by tlc. The resulting mixture was filtered, the solid residue washed with CCl_4 and the resulting filtrate washed with 5% aqueous $NaHCO_3$ and then water, and finally dried over anhydrous $CaCl_2$. Solvent removal followed by column chromatography over silica gel using hexane ether (9·8:0·2) as eluent yielded 8 (1·55 g, 88·5%). TLC: $R_f = 0·70$ in 5% benzene. IR spectrum: 2960, 1450, 1270, 1180, 1105, 1025. PMR spectrum: 5·3δ(*t*, 1H, $J = 4$), 4·2δ(*m*, 1H, CHBr), 2·5δ(*m*, 2H), 2·1δ(*m*, 4H), 1·7δ(*s*, 3H).

3.8 *α-Terpineol* (9)

A solution of acetone (1 ml) in THF (5 ml) was added dropwise to a well-stirred ice-cooled solution of Grignard reagent, prepared from activated Mg turnings (0·132 g, 5·5 mmol) and bromide 8 (0·963 g, 5·5 mmol) in anhydrous THF (15 ml) and the contents were stirred overnight at room temperature. The resulting solution was decomposed with a saturated solution of NH_4Cl, extracted with ether, washed with water and then dried. Solvent removal followed by chromatographic purification over silica gel using hexane–ethyl acetate (9·5:0·5) as eluent afforded pure α-terpineol 9 (0·53 g, 62·6%). IR spectrum: 3440, 2950, 1660, 1450, 1250, 1180, 1070. PMR spectrum: 5·5δ(*t*, 1H, $J = 5$) 4·1δ(*br s*, 1H, OH, D_2O exchangeable), 2·1δ(*m*, 2H), 1·95δ (*m*, 4H), 1·8δ(*s*, 3H), 1·5δ(*m*, 1H), 1·2δ(*s*, 3H), 1·1δ(*s*, 3H). MS: 154[M^+], 134, 121, 79.

3.9 *7-Hydroxyterpineol* (3)

A mixture of α-terpineol 9 (0·793 g, 5·15 mmol), sublimed SeO_2 (0·28 g, 2·5 mmol) and anhydrous pyridine (0·25 g, 3·1 mmol) in absolute ethanol (15 ml) was heated under reflux for 4·5 h. The solvent was removed in vacuum and the residue was extracted with CH_2Cl_2. The combined extracts were washed with water and brine, and then dried over anhydrous $CaCl_2$. Solvent removal gave a crude mixture of hydroxyterpineol along with a major amount of the corresponding aldehyde, which was then reduced as such. To a cooled suspension of LAH (0·076, 2·0 mmol) in ether (10 ml) at 0° was added dropwise crude product obtained above (0·67 g) in ether (10 ml) and stirred for an hour at 0°. The reaction mixture was decomposed with a saturated solution of sodium potassium tartrate, then extracted with chloroform, washed with brine and dried over anhydrous $CaCl_2$. Evaporation of the solvent afforded the pure compound 3 (0·557 g, 63·6%). IR spectrum: 3380, 2920, 1610, 1070, 970, 730. PMR spectrum: 5·6δ(*br s*, 1H), 4·1δ(*br s*, 1H, OH, D_2O exchangeable), 3·8δ(*s*, 2H), 2·6δ(*br s*, 1H), 2·1δ(*m*, 2H), 1·95δ(*m*, 4H), 1·5δ(*m*, 1H), 1·2δ(*s*, 3H), 1·1δ(*s*, 3H). MS: 170[M^+], 150, 121, 81, 79.

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