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Facile Synthesis of Regioselectively Deuteriated (3R)-(-)-[8,8,8-$^2H_3$]Linalool

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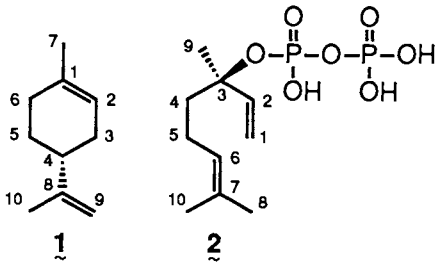
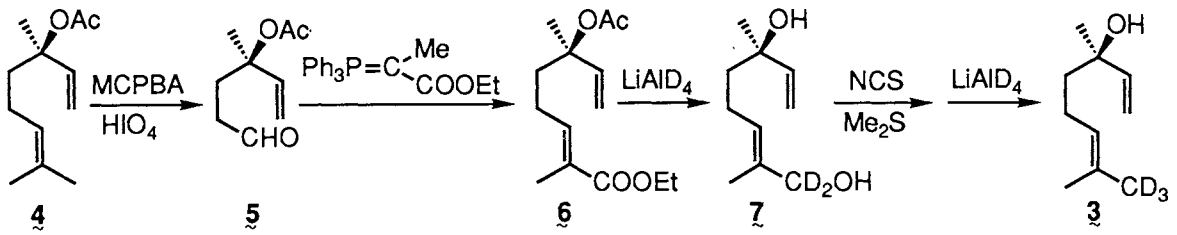
Regioselectively deuteriated (3R)-(-)-[8,8,8-$^2H_3$]-linalool was synthesized from (4R)-(-)-4-acetyl-3-methyl-5-hexenal, which was prepared from (3R)-(-)-linalyl acetate, with the synthesis of (2E,6R)-(-)-2,6-dimethyl-2,7-[1,1-$^2H_2$]octadiene-1,6-diol as the key step.

In the course of studies on the biosynthesis of cyclic monoterpenoids having a p-menthane skeleton, e.g. limonene (1),[1-3] we found that only (3R)-isomer of linalyl diphosphate (LPP; 2) was converted into (4R)-(+)-limonene (1) with the enzyme preparation from Citrus unshiu.[4] In order to examine the stereospecificity of the hydrogen elimination from the 8- or 10-position of 2 during the formation of the 8(9)-double bond of 1, we needed regioselectively deuteriated (3R)-(-)-[8,8,8-$^2H_3$]LPP (2). We now have established the facile synthetic method of (3R)-(-)-3,7-dimethyl-1,6-[8,8,8-$^2H_3$]octadien-3-ol ((3R)-(-)-[8,8,8-$^2H_3$]linalool) (3), which can be converted to LPP (2).



1 2

The regioselectively deuteriated linalool (3) is synthesized from naturally occurring (3R)-(-)-linalyl acetate (4), as shown in Scheme 1. Following the method



4 5 6 7 3

Scheme 1.

reported in the literature,[5] 4 (n_D^{25} 1.4473; d_4^{25} 0.8991; $[\alpha]_D^{25}$ -7.1° (neat)(lit.[6] -7.7°); 99.9% pure on GLC) was converted into (4R)-(-)-4-acetyl-3-methyl-5-hexenal (5) ($[\alpha]_D^{25}$ -8.25° (c 2.0, Hexane); m/z 94 (M^+-AcOH)) by oxidation with m-chloroperbenzoic acid and periodic acid in 54% yield. Wittig reaction[7] of aldehyde (5) (5 mmol) with ethyl 2-triphenyl(phosphoranyidene)-propionate (6.3 mmol) in dichloromethane (15 cm^3) at -20 °C gave a mixture of ethyl (2E,6R)-(-)-6-acethyl-2,6-dimethyl-2,7-octadienoate (6) and its (2Z)-isomer (95:5 on GLC) in 85% yield. The mixture was subjected to column chromatography on silica gel to give the ester (6) ($[\alpha]_D^{25}$ -4.4° (c 4.1, Hexane); m/z 194 (M^+-AcOH); IR (neat) 1730 and 1705 cm^{-1} (ester)). Reduction of 6 (2.5 mmol) with lithium aluminum deuteride (99.5% ^2H-enrichment; 6.4 mmol) in ether (10 cm^3) gave (2E,6R)-(-)-2,6-dimethyl-2,7-[1,1-$^2H_2$]-octadiene-1,6-diol (7) ($[\alpha]_D^{25}$ -16.9° (c 1.18, MeOH) (lit.[8] -12.8° for the non-deuteriated compound); ^1H NMR (270 MHz, $CDCl_3$) δ 1.30 (s, 3H, 10-H_3), 1.58 (m, 2H, 4-H), 1.66 (s, 3H, 9-H_3), 2.08 (m, 2H, 5-H), 5.08 (dd, 1H, J=1.5 and 10.7 Hz, 8-H(trans)), 5.22 (dd, 1H, J=1.5 and 17.6 Hz, 1-H(cis)), 5.41 (dt, 1H, J=1.5 and 7.3 Hz, 3-H), and 5.92 (dd, 1H, J=10.7 and 17.6 Hz, 7-H)] in 99% yield. The ^2H NMR spectrum of 7 showed a signal at δ 3.98 assignable to the deuterium atoms at the hydroxymethyl group. The deuterium-enrichment for 7 was found to be 99.5% by mass spectral analysis. Although it was reported that non-labeled (2E,6R)-(-)-2,6-dimethyl-2,7-octadiene-1,6-diol could be synthesized by the oxidation of linalool with SeO_2[9,10] or by the biological transformation of linalool with living cells,[8,11,12] these methods are recognized to give a low yield. Therefore, the method employing the Wit-

tig reaction described above was demonstrated to be superior for the synthesis of the optically active diol.

The deuteriated diol (7) (2.0 mmol) was converted into (2E,6R)-(-)-2,6-dimethyl-2,7-[1,1-$^2H_2$]octadiene-1-chloride by treatment of N-chlorosuccinimide (2.5 mmol) with dimethyl sulfide (0.22 mmol) in dichloromethane (15 cm^3) at -40 °C, and then the chloride was reduced with lithium aluminum deuteride (99.5% ^{2}H-enrichment; 5.0 mmol) to give (3R)-(-)-3,7-dimethyl-1,6-[8,8,8-$^2H_3$]octadien-3-ol ((3R)-(-)-[8,8,8-$^2H_3$]-linalool) (3)[13] (98.5% ^{2}H-enrichment; $[\alpha]_D^{25}$ -19.1° (c 1.3, Hexane) (lit.[14] -20.1°) in 14.5% yield. A signal at δ 1.68 in the ^{2}H NMR spectrum of 3 indicated that the 8-methyl group of linalool was deuteriated. The overall yield of (3R)-(-)-[8,8,8-$^2H_3$]linalool (3) from (3R)-(-)-linalyl acetate (4) was 7.4%.

Thus, the availability of (3R)-(-)-[8,8,8-$^2H_3$]linalool (3), which can be phosphorylated[15] to yield the diphosphate (2), will facilitate our studies on the stereochemistry of the biosynthesis of p-menthane derivatives.

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13) Duteriated linalool (3): IR (neat); 3400 (OH) and 1630 cm^{-1} (C=C); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.28 (s, 3H, 9-H_3), 1.56 (m, 2H, 4-H), 1.60 (s, 3H, 10-H_3), 2.02 (m, 2H, 5-H), 5.06 (dd, 1H, J=1.5 and 10.8 Hz, 1-H(trans)), 5.12 (dt, 1H, J=1.5 and 7.1 Hz, 6-H), 5.19 (dd, 1H, J=10.8 and 17.6 Hz, 2-H), and 5.21 (dd, 1H, J=1.5 and 17.6 Hz, 1-H(cis)); ^{2}H NMR (76.7 MHz, $CDCl_3$) δ 1.68 (bs, 8-Me); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 17.6 (C-10), 22.8 (C-5), 25.6 (bm, C-8), 27.9 (C-9), 42.1 (C-4), 73.5 (C-3), 111.7 (C-1), 124.3 (C-6), 131.9 (C-7), 145.1 (C-2); MS (rel. int.) m/z 157 (M^+, 1%), 139 (M^+-H_2O, 18), and 93 (100).

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