

103. A Short Synthesis of 3-Methyl-5-(2,3,6-trimethylphenyl)-1-penten-3-ol, a Sesquiterpene Isolated from *Laurencia Nidifica*

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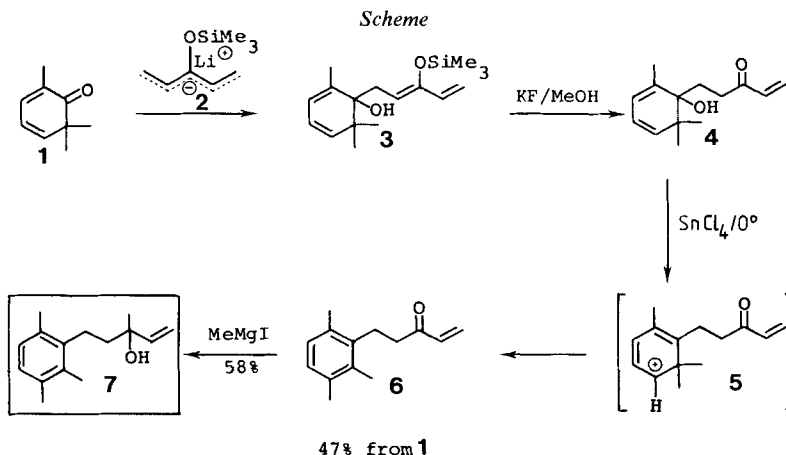
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Summary

The racemic sesquiterpenoid alcohol **7** was synthesized in four steps (27% overall yield) from the cyclohexadienone **1**. The key steps are the regioselective addition of the pentadienyllithium **2** to **1** and the *Lewis*-acid induced aromatization **4** → **6**.

Introduction. – The structure of the sesquiterpene alcohol **7**, isolated from extracts of the dried Hawaiian marine algae *Laurencia nidifica*, has been assigned on the basis of spectral data [1]¹⁾. Its racemate has been synthesized recently from 5,8-dimethyltetralone by a sequence of ten steps in an overall yield of 4.23% [2]. This paper describes a much more direct and efficient synthesis of (±)-**7** using 3-trimethylsilyloxy-pentadienyllithium as a suitable C₅-building block²⁾.



¹⁾ To our knowledge the chiroptic properties and absolute configuration of natural **7** have not been reported.

²⁾ For electrophilic substitutions of pentadienyllithium derivatives see [3] [4]; for applications to the syntheses of norpatchoulanol and α -himachalene see [5] [6].

Transformation of the dienone 1 to the sesquiterpene ($\pm$)-7 (Scheme). Silylation of 1,4-pentadien-3-ol with trimethylsilylacetamide furnished, after distillation, the crude 3-trimethylsilyloxy-1,4-pentadiene (76%); this compound is somewhat less stable than the more expensive triethylsilyl ether²) and was therefore freshly prepared before further use. Deprotonation with *s*-butyllithium in cyclohexane/tetrahydrofuran at -78° gave a solution of the pentadienyllithium **2** to which the easily accessible cyclohexadienone **1** [7] (0.64 mol-equiv.) was added at -78° . The rapidly formed crude adduct **3** underwent smooth Si/O-cleavage with potassium fluoride in methanol at 0° giving the sensitive hydroxy-enone **4**. Compound **4** could be purified and characterized but, owing to its ready convertibility to **6**, was treated directly with SnCl_4 (0.28 equiv.). This led to smooth dehydration giving the aromatic compound **6**, presumably *via* the transient cation **5**³). Accordingly, the pure enone **6** was obtained after simple chromatography in 47% overall yield from **1** without isolation of intermediates and with unambiguous regiochemical control over all four aromatic substituents. 1,2-Addition of methylmagnesium iodide to the enone **6** gave the alcohol **7** (58%). The IR., $^1\text{H-NMR}$., and mass spectra of synthetic ($\pm$)-**7** are identical with those of the natural sesquiterpene. In summary, the above route provides the racemic sesquiterpene **7** in 27% overall yield from **1** and further illustrates the utility of pentadienyllithium derivatives.

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Experimental Part

General. 'Usual work-up' means pouring the reaction mixture into a cold, well-stirred sat. aqueous NH_4Cl -solution, extracting with ether, washing the combined organic layers with sat. NaHCO_3 - and sat. aqueous NaCl -solution, drying (Na_2SO_4) and removing the solvent *i.V.* IR. spectra: in CCl_4 unless otherwise specified, $\bar{\nu}_{\text{max}}$ in cm^{-1} . $^1\text{H-NMR}$. spectra: in CDCl_3 at 100 MHz unless otherwise specified, internal standard tetramethylsilane ($\delta=0$ ppm); abbreviations: *s* singlet, *d* doublet, *t* triplet, *m* multiplet, *J* spin-spin coupling constant (Hz). MS.: signals are given in *m/z* (rel.%).

3-Trimethylsilyloxy-1,4-pentadiene. 1,4-Pentadien-3-ol (2.6 g, 31 mmol) and trimethylsilyl acetamide (4.85 g, 37 mmol) were heated in pentane (20 ml) under reflux for 1 h. The mixture was allowed to cool to 25° over 2 h, then kept at 0° for 24 h and filtered through a small amount of SiO_2 . Fractional distillation of the evaporated filtrate afforded the crude, unstable 3-trimethylsilyloxy-1,4-pentadiene as a colourless oil (3.6 g, 76%), b.p. $99-101^\circ/760$ Torr. - IR.: 2790, 2155, 1125, 990, 930. - $^1\text{H-NMR}$.: 0.13 (*s*, 9 H); 4.62 (*t* $\times$ *m*, $J=5.5$, 1 H); 5.09 (*d* $\times$ *t*, $J=10$ and 2, 2 H); 5.22 (*d* $\times$ *t*, $J=17$ and 2, 2 H); 5.86 (*d* $\times$ *d* $\times$ *d*, $J=5.5$, 10 and 17, 2 H). - MS.: 156 ($\text{C}_8\text{H}_{16}\text{OSi}^+$; 19), 155 (38), 147 (81), 141 (100), 129 (24).

5-(2,3,6-Trimethylphenyl)-1-penten-3-one (6). 1.1N *s*-Butyllithium in cyclohexane (5.14 ml, 5.65 mmol) was added to a stirred solution of freshly prepared 3-trimethylsilyloxy-1,4-pentadiene (879 mg, 5.63 mmol) in THF (8 ml) at -78° under argon. After stirring this mixture for 15 min at -78° 2N 2,6,6-trimethylcyclohexa-2,4-dienone (**1**) [7] in THF (1.8 ml, 3.6 mmol) was added dropwise until the orange colour of the solution had faded. The mixture was then immediately submitted to work-up to give the crude hydroxysilyl ether **3** which was dissolved in methanol (20 ml). After addition of KF (310 mg, 5.35 mmol) at 0° the mixture was stirred at

³) For a similar aromatization observed during a synthesis of patchoulenol see [8].

0°-+5° for 1 h and then submitted to the usual work-up giving the crude 5-(1-hydroxy-2,6,6-trimethylcyclohexa-2,4-dienyl)-1-penten-3-one (**4**) a sample of which was chromatographed (neutral Al₂O₃, activity II, benzene/ethyl acetate 9:1) for characterization [Oil. - IR.: 3410, 2940, 1690, 1405. - ¹H-NMR.: 1.04 (s, 3 H); 1.09 (s, 3 H); 1.82 (s, 3 H); 1.7-2.0 (2 H); 2.25 (m, 1 H); 2.54 (s, 1 H, disappears on exchange with D₂O); 2.77 (m, 1 H); 5.3-6.6 (6 H)]. Stannic chloride (260 mg, 1 mmol) was added to a stirred solution of the crude hydroxy-trienone **4** in ether (20 ml) at 0°. Stirring the mixture at 0° for 30 min followed by the usual work-up and chromatography (SiO₂, hexane/ether 9:1) gave the aromatic compound **6** as an oil (336 mg, 47% from **1**). - IR.: 1710, 1694, 1625, 1408, 1100, 960. - ¹H-NMR.: 2.26 (s, 3 H); 2.30 (s, 3 H); 2.34 (s, 3 H); 2.6-2.7 (4 H); 5.91 (m, 1 H); 6.1-6.7 (2 H); 7.0 (s, 2 H). - MS.: 202 (C₁₄H₁₈O⁺, 21), 184 (33), 169 (19), 147 (16), 133 (49), 132 (100).

3-Methyl-5-(2,3,6-trimethylphenyl)-1-penten-3-ol (**7**). A solution of the enone **6** (326 mg, 1.6 mmol) in ether (1 ml) was added to a solution of the Grignard reagent prepared from methyl iodide (355 mg, 2.5 mmol) and magnesium turnings (72 mg, 3 mmol) in ether (5 ml) at -30° under argon. The mixture was kept at -30° for 30 min and at 0° for 1 h. The usual work-up followed by chromatography (neutral Al₂O₃, activity III, hexane/ether 9:1→3:1) gave the title compound as a viscous oil (202 mg, 58%). - IR.: 3610, 2970, 2920, 1465, 1000, 925. - IR. (CS₂): 790. - ¹H-NMR.: 1.36 (s, 3 H); 1.59 (s, 1 H, disappears on exchange with D₂O); 1.5-1.8 (2 H); 2.20 (s, 3 H); 2.24 (s, 3 H); 2.28 (s, 3 H); 2.5-2.9 (2 H); 5.14 (d×d, J=2 and 10, 1 H); 5.30 (d×d, J=2 and 17, 1 H); 6.04 (d×d, J=10 and 17, 1 H); 6.91 (s, 2 H). (60 MHz, CCl₄): 1.30 (s, 3 H); 1.4-1.8 (3 H); 2.14 (s, 3 H); 2.18 (s, 3 H); 2.20 (s, 3 H); 2.5-2.8 (2 H); 5.01 (d×d, J=2 and 10); 5.17 (d×d, J=2 and 17); 5.92 (d×d, J=10 and 17); 6.67 (s, 2 H). - MS.: 218 (C₁₅H₂₂O⁺, 31), 200 (8), 185 (19), 147 (100), 133 (85), 132 (67), 120 (16), 119 (17).

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