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Birch Reduction of 3,4-Dihydro-8-hydroxy-3-methylisocoumarin (Mellein). Expeditious Syntheses of (±)-Ramulosin and a Spruce Budworm Toxin

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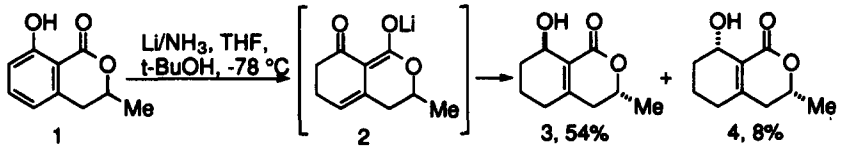
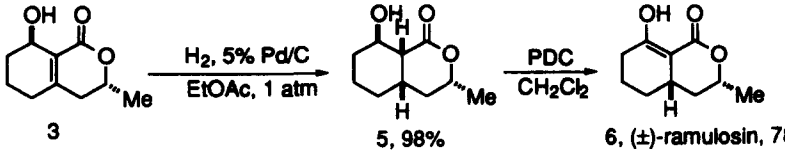
Abstract: A three-step conversion of (±)-mellein (1) to (±)-ramulosin (6) in 41% overall yield is described. A synthesis of the spruce budworm toxin 7 also is reported. © 1997 Elsevier Science Ltd.

We wish to report the stereoselective Birch reduction of 3,4-dihydro-8-hydroxy-3-methylisocoumarin (1)[1] the racemate of a natural phytotoxin called mellein.[2] To 27 mg of Li in NH_3 (20 mL) cooled to -78 °C was added a solution of 1 (35 mg) and t-BuOH (0.07 mL) in THF (1.5 mL). The mixture was stirred at -78 °C for 3 h, then sufficient piperylene was added to dissipate the blue color of the solution. Solid NH_4Cl was added, the cooling bath was removed and the NH_3 was allowed to evaporate. The residue was diluted with H_2O and the mixture was extracted with CH_2Cl_2 (2 x 5 mL). The extract was dried over anhydrous Na_2SO_4, evaporated and chromatographed on silica gel to give 3,8-*trans*-8-hydroxy-3-methyl-3,4,5,6,7,8-hexahydroisocoumarin (3, 54%)[3] and the *cis*-isomer 4 (8%).[4]

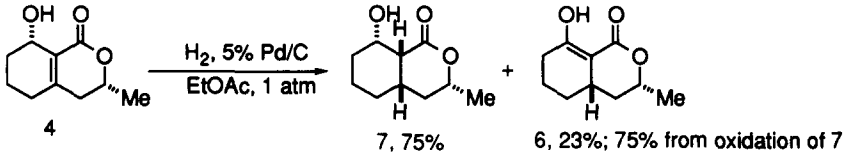


Simple phenols are ionized in NH_3 and consequently are resistant to Birch reduction except at very high concentrations of Li (~ 3M).[5] Dihydroisocoumarin 1 is reactive with dilute solutions of Li in NH_3 because the radical dianion generated by addition of an electron to the phenoxide ion of 1 is stabilized by the lactone carbonyl group. It also is noteworthy that there is good stereoselectivity for reduction of the intermediate keto dienolate 2 or related species. A high degree of 1,5-intraannular chirality transfer has been observed for Birch reductions of 8-aryl-3,4-dihydro-3-methylisocoumarins.[6]



Ramulosin (6) has been isolated from the fungus Pestalotia ramulosa.[7] The structural similarity of 6 to the antitumor antibiotic bactobolin[8] has made this relatively simple δ-lactone an important synthetic target.[9] Hydrogenation of allylic alcohol 3 in EtOAc with 5% Pd/C occurs exclusively at the β-face of the

double bond to give **5** as a single diastereomer in 98% yield.[10] Oxidation of **5** in CH_2Cl_2 with PDC gave (±)-ramulosin (**6**) in 78% yield after flash chromatography on silica gel.



Complete β-facial selectivity also was observed for hydrogenation of **4** to give (±)-ramulosin (**6**, 23%)[11] and **7** (75%), the racemate of a spruce budworm toxin recently isolated from conifer endophyte strains of Conoplea elegantula.[12] Oxidation of **7** with PDC also gave (±)-ramulosin (**6**) in 75% yield. Since both enantiomers of mellein are available from natural sources,[2] the conversions of **1** to **6** and **7** represent formal asymmetric syntheses of these δ-lactones.

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3. **3** (mp 63.5 °C): R_f 0.45 (2:1 hexane:acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.50 (br, 1 H, H_8), 4.47 (m, 1 H, H_3), 3.37 (br, 1 H, OH), 2.32 (dd, J = 17.6, 11.6 Hz, 1 H, H_4), 2.24 (m, 1 H, H_5), 2.21 (dd, J = 17.6, 3.7 Hz, 1 H, H_4), 2.12 (ddd, J = 19.3, 4.6, 4.5 Hz, 1 H, H_5), 2.01 (m, 1 H, H_7), 1.84 (m, 1 H, H_6), 1.66 (m, 1 H, H_7), 1.58 (m, 1 H, H_6), 1.40 (d, J = 6.3 Hz, 3 H, Me); ^{13}C NMR (500 MHz, $CDCl_3$) δ 165.98, 153.81, 126.76, 73.03, 63.89, 35.61, 30.48, 29.72, 20.43, 18.66; MS (CI-DIP, $C_{10}H_{14}O_3$) m/z 183 (M+1), 165, 121; Anal. Calcd for $C_{10}H_{14}O_3 \cdot 0.1\ H_2O$: C, 65.25; H, 7.78. Found: C, 65.17; H, 7.85.
4. **4** (oil): R_f 0.47 (2:1 hexane:acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.50 (m, 1 H, H_3), 4.47 (m, 1 H, H_8), 3.51 (s, 1 H, OH), 2.37 (dd, J = 17.8, 12.2 Hz, 1 H, H_4), 2.22-2.15 (m, 3 H), 1.98-1.94 (m, 1 H), 1.82-1.75 (m, 1 H), 1.68-1.63 (m, 2 H), 1.40 (d, J = 6.3 Hz, 3 H, Me); ^{13}C NMR (500 MHz, $CDCl_3$) δ 167.09, 154.88, 125.49, 73.38, 62.10, 35.97, 30.39, 29.23, 20.42, 16.52; Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.63; H, 7.84.
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10. **5** (oil): R_f 0.50 (2:1 hexane:acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.41 (m, 1 H, H_3), 4.05 (m, 1 H, H_8), 3.05-2.90 (br, 1 H, OH), 2.57 (dd, J = 6.6, 6.4 Hz, 1 H, H_{8a}), 2.42-2.39 (br, 1 H, H_{4a}), 1.95 (br, 1 H, H_7), 1.87 (ddd, J = 14.4, 6.6, 3.4 Hz, 1 H, H_4), 1.62-1.56 (br, 2 H, H5, H7), 1.45-1.26 (br, 4 H), 1.32 (d, J = 6.3 Hz, 3 H, Me); ^{13}C NMR (500 MHz, $CDCl_3$) δ 174.03, 75.67, 66.12, 46.38, 34.74, 31.18, 31.06, 29.28, 21.20, 18.88; MS (CI-DIP, $C_{10}H_{16}O_3$) m/z 185 (M+1), 167, 123.
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12. (a) Findlay, J. A.; Buthelezi, S.; Lavoie, R.; Peña-Rodriguez, L.; Miller, J. D. *J. Nat. Prod.* **1995**, *58*, 1759. (b) Attempted synthesis of **7** by Mitsonobu reaction of **5** with 4-nitrobenzoic acid gave dehydration to the α,β-unsaturated lactone (84%).

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