A Synthesis of Talaromycin B

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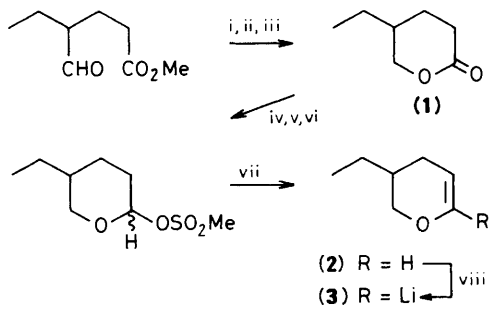
The nucleophilic cleavage of the oxirane (**4**) by the organocuprate derived from 6-lithio-3-ethyl-3,4-dihydro-2*H*-pyran (**3**) was the key step in a synthesis of racemic talaromycin B (**7**).

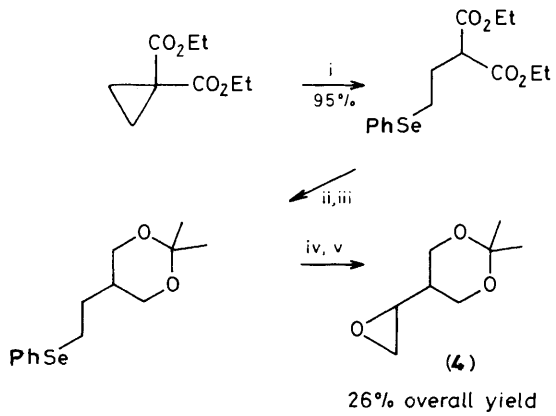
The fungus *Talaromyces stipitatus* infects wood-shavings-based chicken litter. Two isomeric toxic metabolites have been isolated from cultures of *T. stipitatus* which appear to block outward potassium fluxes and thus lead to muscle dysfunction.[1] Talaromycins A (**8**) and B (**7**) were identified as the toxic metabolites by an elegant application of two-dimensional n.m.r. cross relaxation spectroscopy.[2] We report a brief synthesis[3] of talaromycin B which confirms the relative stereochemistry.

The key dihydropyran (**2**) [59% overall from (**1**); b.p. 140—141 °C at 760 mmHg; ν_{max} (film) 3 070m, 1 650s, and 1 078s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 6.3 (1H, m), 4.65 (1H, m), 4.0 (1H, dd with further fine splitting, *J* 10, *J'* 2 Hz), 3.5 (1H, dd with further splitting, *J* 10, *J'* 8 Hz), 1.15—2.2 (5H, m), and 0.95 (3H, distorted t, *J* 7 Hz); M^+ 112.0888, $C_7H_{12}O$ requires *M* 112.088 81] and the oxirane (**4**) [b.p. 110—115 °C (bath) at 18 mmHg; ν_{max} (film) 1 268, 1 250, 1 200, and 830 cm^{-1} (all s); δ_H (90 MHz, $CDCl_3$) 3.7—4.2 (4H, m), 3.03 (1H, ddd, *J* 7, *J'* 4.5, *J''* 4.0 Hz), 2.72 (1H, dd, *J* 4.5, *J'* 4.0 Hz), 2.54 (1H, dd, *J* 4.5, *J'* 3.0 Hz), 1.4 (6H, s), and 1.4—1.7 (1H, m); M^+ 158.0941, $C_8H_{14}O_3$ requires *M* 158.094 288] were prepared by standard procedures as shown in Schemes 1 and 2, respectively.

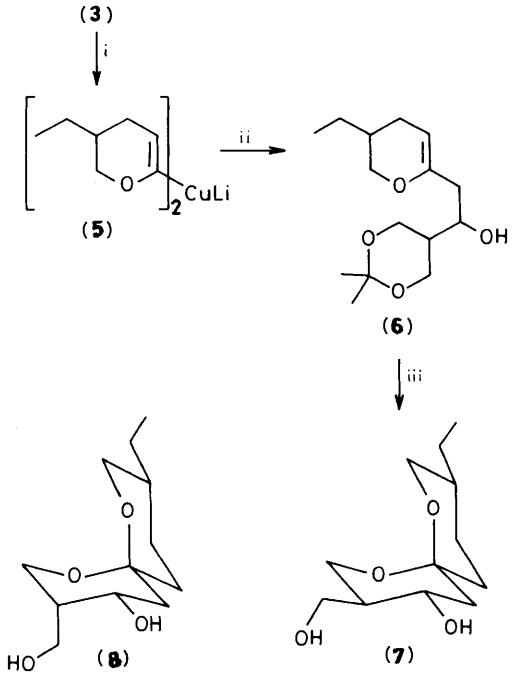
The fulcrum of our synthetic plan involved the use of a 6-lithio-3,4-dihydro-2*H*-pyran as a masked bifunctional carbonyl anion equivalent.[4] Central to the use of such acyl



Scheme 1. *Reagents:* i, H_2, PtO_2–$SnCl_2$–60% aq. EtOH; ii, NaOH, room temperature; iii, conc. HCl; iv, Bu^i_2AlH–toluene, −78 °C; v, aq. AcOH; vi, $MeSO_2Cl$–pyridine; vii, 100–110 °C, pyridine, 1½ h; viii, Bu^tLi–tetrahydrofuran.



Scheme 2. *Reagents:* i, PhSeNa–EtOH, room temperature, 18 h; ii, $LiAlH_4$–Et_2O, reflux, 4 h; iii, 2-methoxypropene, H^+–CH_2Cl_2; iv, H_2O_2 (excess), pyridine (2 equiv.)–CH_2Cl_2; v, *m*-$ClC_6H_4CO_3H$–CH_2Cl_2.



Scheme 3. *Reagents:* i, CuI; ii, (**4**) (0.66 equiv.), 0—20 °C; iii, aq. HCl.

anion equivalents for the synthesis of the 4-hydroxy-1,7-dioxaspiro[5.5]undecane moiety of talaromycin B is the recent discovery that relatively stable organocuprates[5] prepared from 6-lithio-3,4-dihydro-2*H*-pyrans cleanly cleave monosubstituted oxiranes.[6] Thus metallation of the dihydropyran (**2**) with 1.3 equivalents of Bu^{t}Li in tetrahydrofuran[7] gave (**3**) which was converted into the organocuprate (**5**) with CuI (Scheme 3). Reaction of (**5**) with 0.66 equivalents of the oxirane (**4**) at 0—20 °C gave the unstable intermediate (**6**) which without purification was treated with aqueous HCl. As expected, hydrolysis of the 1,3-dioxane moiety of (**6**) was accompanied by ring closure to the more thermodynamically stable[1] talaromycin B (**7**). Chromatographic purification on silica gel G eluting with 5 : 2 (v/v) benzene–dioxane gave (**7**) in 23% overall yield from (**2**) and (**4**). Recrystallisation from ethyl acetate–hexane gave pure (**7**) [m.p. (sealed tube) 135—136.5 °C; ν_{max} (KBr) 3 350, 1 380, 1 187, 1 085, 1 075, 1 060, 1 040, 1 035, 895, and 870 cm^{-1} (all s); δ_C (22.6 MHz, $CDCl_3$) 96.8, 65.9, 64.8, 61.4, 60.85, 45.9, 44.1, 36.6, 35.1, 25.1, 24.7, and 11.1 p.p.m. M^+ 230.151 36, $C_{12}H_{22}O_4$ requires M 230.151 80]. The 400 MHz ^{1}H n.m.r. spectrum was identical in every detail with published spectra of natural talaromycin B.[1,2]

By this route gram quantities of (**7**) can be prepared from cheap, readily available starting materials. Further applications of lithiated dihydropyrans to the synthesis of natural 4-hydroxy-1,7-dioxaspiro[5.5]undecanes are under investigation.

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