

## A Synthesis of Talaromycin B

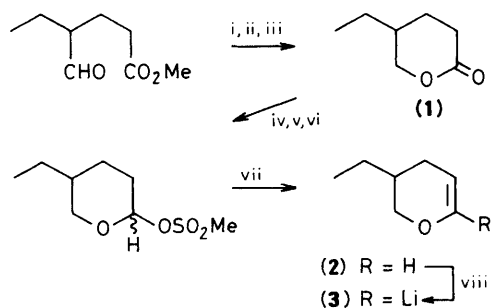
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The nucleophilic cleavage of the oxirane (**4**) by the organocuprate derived from 6-lithio-3-ethyl-3,4-dihydro-2*H*-pyran (**3**) was the key step in a synthesis of racemic talaromycin B (**7**).

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.<sup>1</sup> 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.<sup>2</sup> We report a brief synthesis<sup>3</sup> of talaromycin B which confirms the relative stereochemistry.

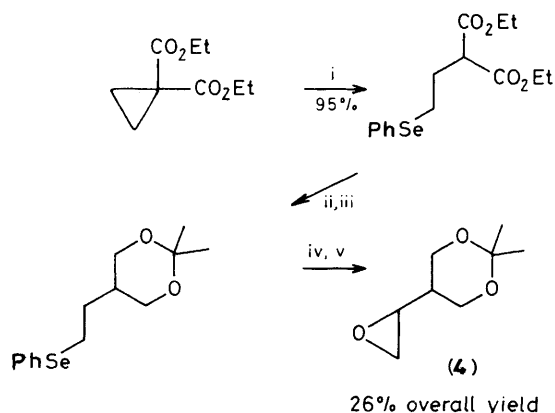
The key dihydropyran (**2**) [59% overall from (**1**); b.p. 140–141 °C at 760 mmHg;  $\nu_{\max}$  (film) 3 070m, 1 650s, and 1 078s  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (90 MHz,  $\text{CDCl}_3$ ) 6.3 (1H, m), 4.65 (1H, m), 4.0 (1H, dd with further fine splitting,  $J$  10,  $J'$  2 Hz), 3.5 (1H, 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,  $\text{C}_7\text{H}_{12}\text{O}$



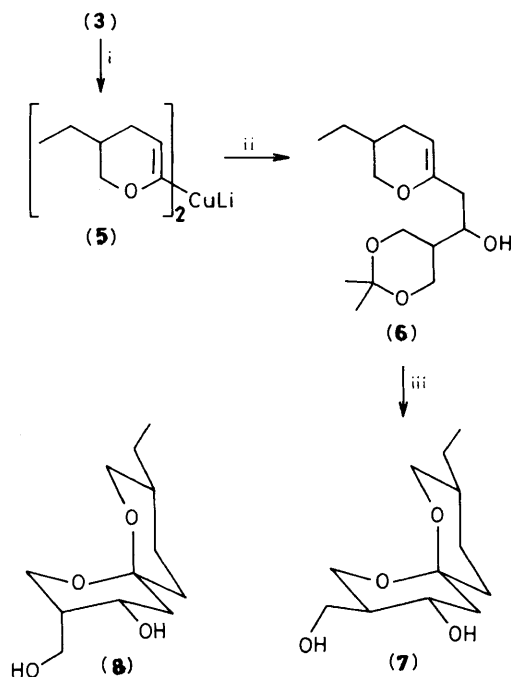
**Scheme 1.** Reagents: i,  $\text{H}_2$ ,  $\text{PtO}_2$ – $\text{SnCl}_2$ –60% aq. EtOH; ii, NaOH, room temperature; iii, conc. HCl; iv,  $\text{Bu}_2\text{AlH}$ –toluene,  $-78^\circ\text{C}$ ; v, aq. AcOH; vi,  $\text{MeSO}_2\text{Cl}$ –pyridine; vii,  $100$ – $110^\circ\text{C}$ , pyridine,  $1\frac{1}{2}$  h; viii,  $\text{Bu}^t\text{Li}$ –tetrahydrofuran.

requires  $M$  112.088 81] and the oxirane (**4**) [b.p.  $110$ – $115^\circ\text{C}$  (bath) at 18 mmHg;  $\nu_{\max}$  (film) 1 268, 1 250, 1 200, and 830  $\text{cm}^{-1}$  (all s);  $\delta_{\text{H}}$  (90 MHz,  $\text{CDCl}_3$ ) 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,  $\text{C}_8\text{H}_{14}\text{O}_3$  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.<sup>4</sup> Central to the use of such acyl



**Scheme 2.** Reagents: i,  $\text{PhSeNa}$ –EtOH, room temperature, 18 h; ii,  $\text{LiAlH}_4$ – $\text{Et}_2\text{O}$ , reflux, 4 h; iii, 2-methoxypropene,  $\text{H}^+$ – $\text{CH}_2\text{Cl}_2$ ; iv,  $\text{H}_2\text{O}_2$  (excess), pyridine (2 equiv.)– $\text{CH}_2\text{Cl}_2$ ; v,  $m\text{-ClC}_6\text{H}_4\text{CO}_3\text{H}$ – $\text{CH}_2\text{Cl}_2$ .



**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<sup>5</sup> prepared from 6-lithio-3,4-dihydro-2*H*-pyrans cleanly cleave monosubstituted oxiranes.<sup>6</sup> Thus metallation of the dihydropyran (2) with 1.3 equivalents of Bu<sup>t</sup>Li in tetrahydrofuran<sup>7</sup> 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<sup>1</sup> 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;  $\nu_{\text{max}}$  (KBr) 3 350, 1 380, 1 187, 1 085, 1 075, 1 060, 1 040, 1 035, 895, and 870 cm<sup>–1</sup> (all s);  $\delta_{\text{C}}$  (22.6 MHz, CDCl<sub>3</sub>) 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<sub>12</sub>H<sub>22</sub>O<sub>4</sub> requires  $M$  230.151 80]. The 400 MHz <sup>1</sup>H n.m.r. spectrum was identical in every detail with published spectra of natural talaromycin B.<sup>1,2</sup>

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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