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RELATIVE AND ABSOLUTE STEREOCHEMISTRY OF THE MELANOGENESIS INHIBITORS OH-3984 K1 AND K2. PARTIAL SYNTHESIS FROM ALBOCYCLINE

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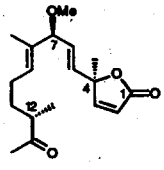
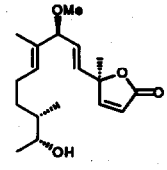
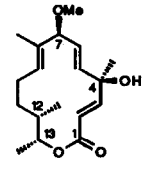
Abstract: The transformation of the macrolide antibiotic albocycline (3) to the recently isolated melanin synthesis inhibitors OH-3984 K1 (1) and K2 (2) has established the relative and absolute configurations of 1 (4*R*, 7*R*, 12*S*) and 2 (4*R*, 7*R*, 12*S*, 13*R*).

Our search for new melanin synthesis inhibitors recently led to the isolation of OH-3984 K1 (1) and K2 (2), together with the known, closely related macrolide antibiotic albocycline (3), from a fermentation broth of *Streptomyces* sp. OH-3984.[1] Compounds 1 and 2 suppress the melanogenesis of B16 melanoma cells with no inhibitory effect on cell growth at concentrations of 7.5 and 3.8 μg/ml, respectively.[1] In our initial studies, the planar structures of 1 and 2 were deduced via extensive spectroscopic analysis, but their stereochemistry remained unknown.[2] Earlier an X-ray crystallographic analysis of the derived *p*-bromobenzoate revealed the (4*R*, 7*R* 12*S*, 13*R*) absolute configuration of albocycline (3).[3] Herein we describe the chemical conversion of 3 to both OH-3984 K1 and K2, permitting the assignment of relative and absolute stereochemistry for 1 and 2.

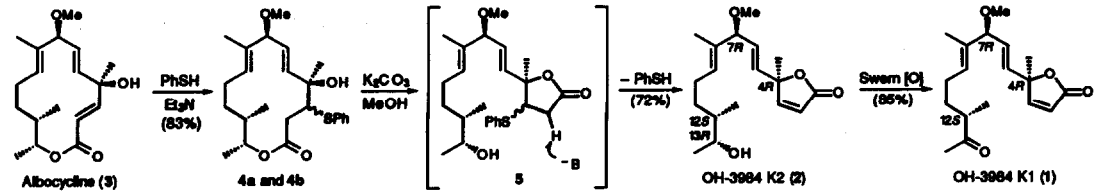

OH-3984 K1 (1)


OH-3984 K2 (2)


Albocycline (3)

Albocycline (3) was transformed to OH-3984 K2 (2) via 1,4-addition[4] of thiophenol to the α, β-unsaturated lactone moiety, followed by base-induced translactonization[5] and elimination of PhSH (Scheme 1). OH-3984 K2 (2) then furnished K1 (1) upon Swern oxidation.[6,7]

Scheme 1



Both synthetic 1 and 2 proved to be indistinguishable from the corresponding natural products by ^{1}H-NMR, ^{13}C-NMR, and IR, as well as high resolution mass spectrometry and optical rotation {synthetic 1: $[\alpha]_D^{19}$ -155.7° (*c* 1.0, EtOH); lit[2] $[\alpha]_D^{24}$ -154.9° (*c* 0.366, EtOH); synthetic 2: $[\alpha]_D^{19}$ -172.0° (*c* 1.0, EtOH); lit[2] $[\alpha]_D^{24}$ -167.9° (*c* 0.927, EtOH)}. Accordingly, the relative and absolute configurations of OH-3984 K1 (1) and K2 (2) are (4*R*, 7*R*, 12*S*) and (4*R*, 7*R*, 12*S*, 13*R*), respectively. The conversion of albocycline (3) to 2 (60% overall yield) and to 1 (51% overall yield) will also enable us to prepare additional quantities of the latter compounds, as required for more detailed biological evaluation.

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7. Physical data for **4a**: TLC R_f 0.75 (10% acetone/chloroform); colorless oil; $[\alpha]_D^{24}$ -73.7° (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 3475, 2975, 1725, 1440, 1375, 1230, 1170 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.42-7.38 (m, 2 H), 7.24-7.13 (m, 3 H), 5.94 (dd, *J* = 15.8, 5.0 Hz, 1 H), 5.49 (d, *J* = 15.8 Hz, 1 H), 5.19 (br d, *J* = 8.9 Hz, 1 H), 4.73 (m, 1 H), 4.01 (d, *J* = 5.0 Hz, 1 H), 3.63 (dd, *J* = 9.1, 3.6 Hz, 1 H), 3.13 (s, 3 H), 2.71 (dd, *J* = 15.2, 3.3 Hz, 1 H), 2.49 (dd, *J* = 15.2, 8.6 Hz, 1 H), 2.22 (m, 1 H), 2.00 (m, 1 H), 1.75 (m, 1 H), 1.53 (s, 3 H), 1.47 (m, 1 H), 1.34 (s, 3 H), 1.28 (m, 1 H), 0.98 (d, *J* = 6.6 Hz, 3 H), 0.88 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 171.9, 136.2, 135.4, 133.5, 131.9, 131.7, 129.7, 128.5, 127.7, 87.9, 74.7, 71.9, 58.3, 56.1, 38.7, 35.6, 31.7, 26.5, 23.4, 15.3, 14.0, 11.7; high resolution mass spectrum (EI, 70 eV) *m/z* 418.2175 (M^+; calcd. for $C_{24}H_{34}O_4S$: 418.2178). Physical data for **4b**: TLC R_f 0.68 (10% acetone/chloroform); white, amorphous solid, mp 108-110 °C ($CHCl_3$); $[\alpha]_D^{21}$ +40.0° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3475, 2940, 1725, 1435, 1375, 1230, 1170 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.39-7.36 (m, 2 H), 7.25-7.15 (m, 3 H), 5.83 (dd, *J* = 15.5, 6.9 Hz, 1 H), 5.51 (d, *J* = 15.8 Hz, 1 H), 5.31 (t, *J* = 7.6 Hz, 1 H), 4.40 (m, 1 H), 3.97 (d, *J* = 6.9 Hz, 1 H), 3.35 (dd, *J* = 5.6, 3.0 Hz, 1 H), 3.15 (s, 3 H), 2.74 (dd, *J* = 16.5, 4.0 Hz, 1 H), 2.47 (dd, *J* = 16.5, 5.6 Hz, 1 H), 2.12 (m, 1 H), 1.88 (m, 1 H), 1.59 (m, 1 H), 1.54 (s, 3 H), 1.43 (s, 3 H), 1.27 (q, *J* = 5.7 Hz, 2 H), 1.10 (d, *J* = 6.3 Hz, 3 H), 0.83 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 171.5, 136.2, 135.9, 135.7, 132.1, 129.3, 129.0, 128.1, 127.2, 87.6, 75.0, 74.6, 56.0, 55.7, 37.8, 36.3, 32.5, 28.4, 22.4, 17.9, 15.6, 11.4; high resolution mass spectrum (EI, 70 eV) *m/z* 418.2173 (M^+; calcd. for $C_{24}H_{34}O_4S$: 418.2178).

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