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A TOTAL SYNTHESIS OF d,l-SPORIDESMIN B

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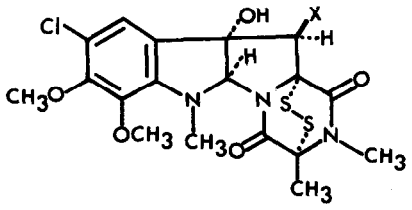
We have recently reported a formal total synthesis[1] of sporidesmin A[2] 1, a toxic major metabolite of Pithomyces chartarum, which causes the serious disease in sheep, known as "facial eczema" in New Zealand. In this communication we wish to describe a total synthesis of d,l-sporidesmin B[2] 2, one of toxic minor metabolites of Pithomyces, starting from the acetate 3a[1], an intermediate in the sporidesmin A synthesis.

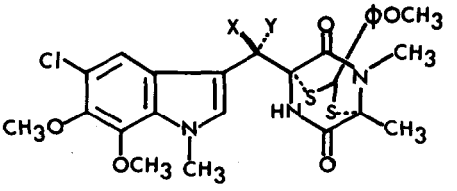
The acetate 3a was reduced to the methylene derivative 4[3] (mp 206-8°C; yield 90 %) by sodium cyanoborohydride (excess) in acetic acid at room temperature[4]. Oxidation of 4 by benzoyl peroxide[5] (excess) in dimethoxyethane containing a small amount of 4,4'-thiobis(6-t-butyl-3-methylphenol)[6] at 90°C for 2 hr yielded a mixture of the benzoates 5[7] (mp 232-4°C; yield 20 %) and 6[8] (mp 136-140°C; yield < 1.5 %). The benzoate 5 was identical (nmr[9], ir, ms, and tlc) with the authentic sample, derived from natural sporidesmin B[10] 2 in three steps [(i) sodium borohydride in methanol at 0°C, (ii) anisaldehyde and boron trifluoride etherate in methylene chloride at 0°C, and (iii) benzoyl chloride in pyridine at 0°C].

A mechanism of the oxidative cyclization (i.e., 4 → 5) was not studied extensively, but an ionic rather than radical fission of the oxidant is obviously important from the following observations; namely, (i) the oxidation proceeds in a similar velocity either in the



1 X = OH : sporidesmin A

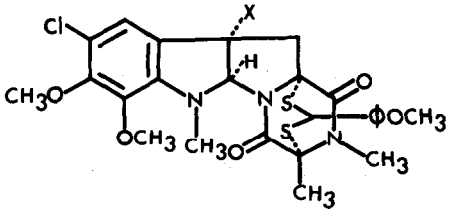
2 X = H : sporidesmin B



3a X = OAc, Y = H

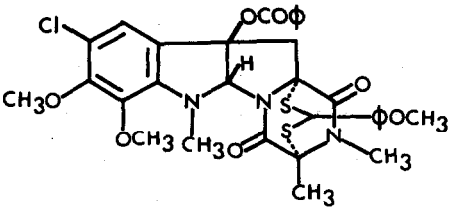
3b X = H, Y = OAc

4 X = Y = H



5 X = OCOØ

7 X = OH



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presence or in the absence of the radical scavenger, and (ii) the oxidation takes place at 0°C in methyelene chloride containing a small amount of hydrogen chloride or trifluoroacetic acid. A stereochemical course of the oxidative cyclization could be understood as follows. In the unnatural configuration (see Figure 2), the indole residue is parallel with the thioacetal residue, that causes steric compression. On the other hand such steric compression is not present in the natural configuration (see Figure 1). When stereochemical situation in the transition state of the oxidative cyclization is proposed to be close to that of the

product 5 or 6, the process to the natural configuration would be more preferred than the one to the unnatural configuration.

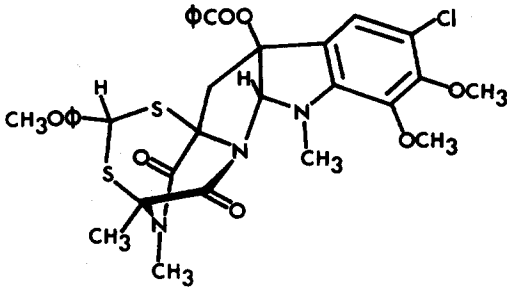

Figure 1

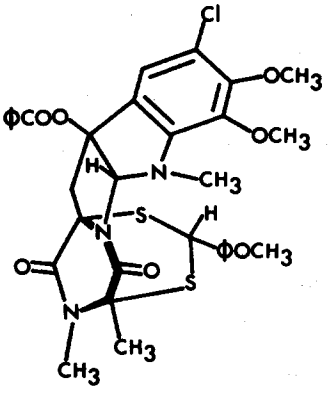

Figure 2

Hydrolysis of benzoyl group in 5 by 1 N aq. KOH in THF - MeOH (2 : 1) at 0°C for 4 hr gave the alcohol 7[11] (mp 145-150°C dec.; yield 80 %). m-Chloroperbenzoic acid oxidation of 7 in methylene chloride at 0°C, followed by treatment with boron trifluoride etherate (3 %) in methylene chloride at 20°C for 4 hr afforded d,l-sporidesmin B 2[12] (needles from ether: mp 181-2°C dec.; yield 32 %). Synthetic substance was identified with natural sporidesmin B 2 by comparison of spectroscopic data (ir[13], nmr, ms, and uv) and tlc behavior (silica gel).

References and Footnotes

1. Y. Kishi, S. Nakatsuka, T. Fukuyama, and M. Havel, J. Am. Chem. Soc., 95, 6493 (1973).
2. Sporidesmins. Part I to XIII. The latest report: S. Safe, and A. Taylor, J. Chem. Soc. Perkin Trans. I, 472 (1972).
3. MS: 563 & 561 (M^+), and 379 & 377; $\delta^{CDCl_3}_{ppm}$ 1.84 (3H, s), 3.24 (3H, s), 3.60 (2H, s), 3.78 (3H, s), 3.90 (3H, s), 3.94 (3H, s), 4.00 (3H, s), 5.06 (1H, s), 6.34 (1H, broad s), 6.81

and 7.29 (2H+2H, AB, J=9 Hz), 6.93 (1H, s), and 7.23 (1H, s); ν_{max}^{KBr} 3280, 1685, 1255, and 1040 cm^{-1}.

4. A treatment of the acetate 3a by acetic acid in methylene chloride at room temperature yields an equilibrium mixture of the acetate 3a (ca. 1 part; mp 176-8°C) and the epi-acetate 3b (ca. 2 parts; mp 208-210°C).
5. Y. Kanaoka, M. Aiura, and S. Hariya, J. Org. Chem., 36, 458 (1971).
6. Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama, T. Goto, S. Inoue, S. Sugiura, and H. Kakoi, Chem. Commun., 64 (1972).
7. MS: 683 & 681 (M^+), 561 & 559, and 377 & 375; $\delta_{ppm}^{CDCl_3}$ 1.92 (3H, s), 3.10 and 3.30 (1H+1H, AB, J=16 Hz), 3.17 (3H, s), 3.50 (3H, s), 3.77 (3H, s), 3.87 (6H, s), 5.95 (1H, s), 6.07 (1H, s), 6.80 and 7.26 (2H+2H, AB, J=9 Hz), 6.96 (1H, s), and 7.3-8.0 (5H, m); ν_{max}^{KBr} 1730, 1685, 1280, 1255, and 1035 cm^{-1}.
8. MS: 683 & 681 (M^+), 561 & 559, and 377 & 375; ν_{max}^{KBr} 1730, 1685, 1275, 1260, and 1030 cm^{-1}.
9. We thank Japan Electron Optics Laboratory Co., Ltd. for the measurement of the FT-nmr spectra.
10. We are indebted to Dr. E. P. White, Ruakura Animal Research Station, New Zealand, for his generous gift of natural sporidesmin B.
11. MS: 579 & 577 (M^+), 395 & 393, and 243 & 241; $\delta_{ppm}^{CDCl_3}$ 1.90 (3H, s), 2.86 (2H, broad s), 3.16 (3H, s), 3.34 (3H, s), 3.77 (3H, s), 3.81 (3H, s), 3.84 (3H, s), 5.03 (1H, s), 5.41 (1H, s), 6.83 and 7.33 (2H+2H, AB, J=9 Hz), and 7.02 (1H, s); ν_{max}^{KBr} 3400 (broad), 1680, 1260, and 1035 cm^{-1}.
12. MS: 459 & 457 (M^+), 395 & 393, and 243 & 241; $\delta_{ppm}^{CDCl_3}$ 2.03 (3H, s), 2.74 and 3.27 (1H+1H, AB, J=16 Hz), 2.97 (1H, broad s), 3.06 (3H, s), 3.29 (3H, s), 3.82 (3H, s), 3.88 (3H, s), 5.43 (1H, s), and 7.10 (1H, s); ν_{max}^{KBr} 3410, 1700, 1675, and 1035 cm^{-1}.
13. The ir spectrum of synthetic d,l-sporidesmin B in KBr disk was found to be identical with that of natural sporidesmin B in all respects.