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TOTAL SYNTHESIS OF FUMITREMORGIN B[1]

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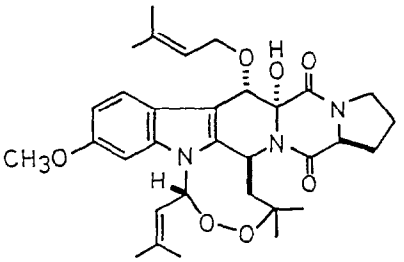
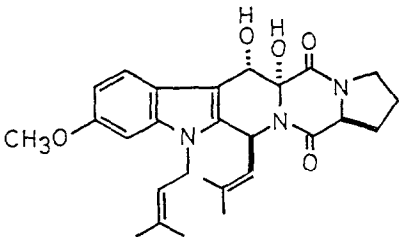
Abstract: Total synthesis of fumitremorgin B, one of the potent tremorgic mycotoxins, was achieved in 7 steps.

Fumitremorgins A[3] (1) and B[4] (2) are potent tremorgic mycotoxins produced by Aspergillus fumigatus. Verruculogen,[5] which possesses a similar structure and biological activities, was also produced by Penicillium verruclosum.

Although a few synthetic studies[6,7,8] toward them have been appeared recently, a total synthesis of them has not been accomplished because of their highly oxidized structures. We have recently reported a novel synthetic method of indole alkaloids and found a facil synthetic rout of tetrahydro-β-carboline derivative, (±)-12-deoxy-12-epi-fumitremorgin B (I).[2] In this paper, we report first total synthesis of optically active fumitremorgin B (2) by selective oxidation of dehydro-β-carboline derivative 9a.



Fumitremorgin A (1)



Fumitremorgin B (2)

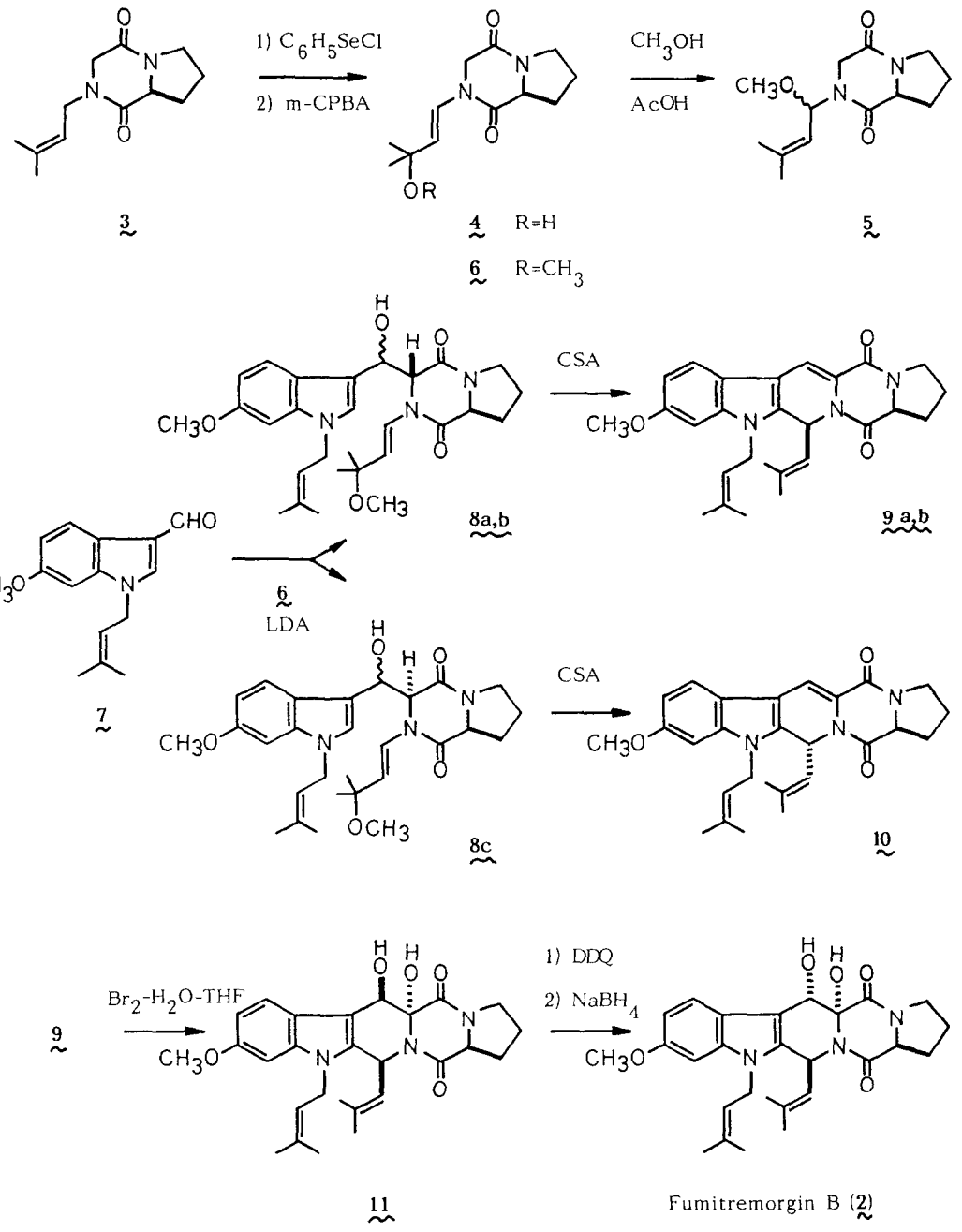
In the previous report, we achieved the synthesis of I by condensation of oxidized diketopiperazine derivative 5 with substituted indole-3-aldehyde 7 and subsequent acid treatment with camphorsulfonic acid. On the purpose of shortening of synthetic steps, we chose tert-methoxy derivative 6 instead of 5. 6 was obtained by treatment of N-dimethylallyl glycylproline diketopiperazine 3 with phenylselenenyl chloride in methanol and oxidative removement[10] of phenyl selenenyl group with m-CPBA in 96% overall yield [6: oil; MS m/z 252(M^+); ^{1}H-NMR($CDCl_3$) ppm 1.32(6H, s), 1.80-2.60(4H, m), 3.13(3H, s), 3.40-4.30(5H, m), 5.08(1H, d, J=15 Hz), 7.28(1H, d, J=15 Hz)].

Condensation of 6 with substituted indole-3-aldehyde 7 with LDA at -78 °C gave three products [8a(50%), 8b(11%), and 8c(15%)] after silica gel column cromatography [8a: oil; MS m/z 495(M^+); ^{1}H-NMR($CDCl_3$) ppm 1.02(3H, s), 1.10(3H, s), 1.68(3H, s), 1.73(3H, s), 1.10-2.20(4H, m), 2.95(3H, s), 3.00(1H, br.t, J=6 Hz), 3.22(1H, br.t, J=10 Hz), 3.36(1H, br.d, J=5.6 Hz), 3.46(1H, br.t, J=10 Hz), 3.76(3H, s), 4.47(2H, d, J=6.8 Hz), 4.66(1H, d, J=3,6 Hz), 4.98(1H, d, J=15.3 Hz), 5.17(1H, br.t, J=6.8 Hz), 5.38(1H, dd, J=3.6 and 5.1 Hz), 6.63(1H, d, J=2.0 Hz), 6.69(1H, dd, J=8.7 and 2.0 Hz), 6.81(1H, s), 7.05(1H, d, J=15.3 Hz), 7.39(1H, d, J=8.4 Hz)]. Stereochemistry of these isomers were determined after subsequent cyclization reaction.

Compounds 8ab gave the same product by the treatment with camphorsulfonic acid in dichloromethane at 10 °C in 88% and 80% yield. But very interestingly, the product was obtained as two kinds of crystals, 9a and 9b, by usual recrystallization with methanol (9a:9b=1:2) [9a: mp 192°C; MS m/z 445(M^+); ^{1}H-NMR($CDCl_3$) ppm 1.64(3H, s), 1.72(3H, s), 1.87(3H, s), 2.00(3H, s), 1.80-2.60(4H, m), 3.60-3.80(2H, m), 3.84(3H, s), 4.12(1H, dd, J=7.1 and 8.8 Hz), 4.57(2H, d, J=6.0 Hz), 5.10(1H, br.t, J=6.0 Hz), 5.22(1H, dt, J=10.2, and 1.3 Hz), 6.67(1H, d, J=10.2 Hz), 6.72(1H, d, J=2.2 Hz), 6.85(1H, dd, J=8.5 and 2.2 Hz), 7.31(1H, s), 7.54(1H, d, J=8.5 Hz); 9b: mp 213°C]. ^{1}H-NMR, MS, UV spectra and RF values of 9a and 9b were completely identical each other. ^{1}H-NMR mesurements of 9a and 9b in the presence of optically active shift reagent [$Eu(TFC)_3$] suggested that 9a is optically active and 9b is racemic compound respectively. Dehydration of 8c with CSA gave another isomer 10.

Many oxidative conditions of 9a was failed but bromination of 9a in THF-H_2O (8:5) at 18°C gave the desired dihydroxy compound 11 in 64% yield [11: mp 231.5-232°C; IR(KBr) ν_{max} 3470, 1660, 1635 cm^{-1}; UV λ_{max}(MeOH) nm(ε) 205(37600), 222(40000), 273(7200), 296(8880); MS m/z 479(M^+); ^{1}H-NMR ($CDCl_3$) ppm 1.67(3H, s), 1.71(3H, s), 1.87(3H, s), 2.03(3H, s), 1.80-2.60(4H, m), 2.74(1H, s), 3.69(2H, m), 3.85(3H, s), 3.97(1H, d, J=2.9 Hz), 4.45(1H, t, J=8.0 Hz), 4.59(2H, d, J=6.0 Hz), 5.06(1H, br.t, J=6.0 Hz), 5.23(1H, dt, J=10.0 and 1.5 Hz), 5.67(1H, d, J=2.9 Hz), 6.06(1H, d, J=10.0 Hz), 6.74(1H, d, J=2.2 Hz), 6.86(1H, dd, J=8.5 and 2.2 Hz), 7.58(1H, d, J=8.5 Hz)]. Unfortunately, compound 11 was not fumitremorgin B (2) but its stereoisomer. In this brominating reaction, a small amount of further brominated compound was obtained but this was easily separated by silica gel TLC.

By the comparison of spectral data of 11 and fumitremorgin B (2), 11 was seemed to be isomer concerning the stereochemistry of its secondary hydroxy group. So, we tried many oxidation condition of the secondary alcohol of 11 but all atempts were failed except DDQ oxidation.[9] DDQ oxidation of 11 in CCl_4-$(ClCH_2)_2$ (4:1) at 60 °C for 100 min afforded its ketone derivative in 18% yield (mp 225.5-226.5 °C). Subsequent reduction of the ketone derivative with $NaBH_4$ in MeOH at 0 °C for 10 min afforded single product. Chromatography on silica gel TLC gave pure optically active fumitremorgin B in quantitative



3

4 R=H

6 R=CH_3

5

8a,b

9 a,b

7

8c

10

9

11

Fumitremorgin B (2)

yield [mp 212-213°C; IR($CHCl_3$) ν_{max} 3500, 1665 cm^{-1}; UV λ_{max}(MeOH) nm(ε) 203 (36000), 225(36500), 275(7900), 295(8700); MS m/z 479(M^+); ^{1}H-NMR($CDCl_3$) ppm 1.62(3H, s), 1.69(3H, s), 1.84(3H, s), 1.98(3H, s), 1.60-2.60(4H, m), 3.63(2H, m), 3.82(3H, s), 4.00(1H, br.s), 4.45(1H, dd, J=9.0 and 7.0 Hz), 4.53(2H, d, J=6.0 Hz), 4.70(1H, d, J=2.7 Hz), 4.69(1H, dt, J=10.5 and 1.3 Hz), 5.03(1H, br.t, J=6.0 Hz), 5.76(1H, d, J=2.7 Hz), 5.96(1H, d, J=10.5 Hz), 6.69(1H, d, J=2.3 Hz), 6.79(1H, dd, J=8.7 and 2.3 Hz), 7.84(1H, d, J=8.7 Hz)]. These spectroscopic data, CD spectra and TLC of synthetic and natural fumitremorgin B were completely identical each other. Further synthetic studies on fumitremorgin A and verruclogen are now in progress.

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10. In this step, a part of compound 6 isomerized to D-proline derivative.

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