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A SYNTHESIS OF SO-CALLED FUMITREMORGIN C

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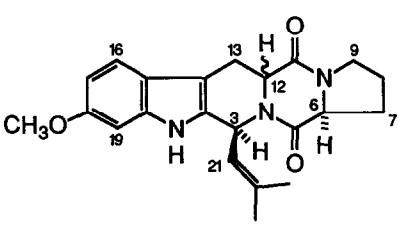
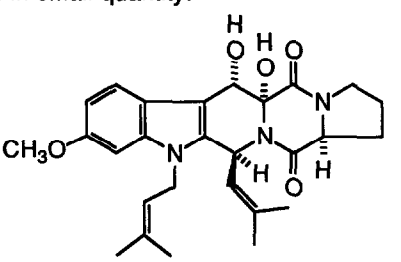
Summary: 12α- and 12β-Fumitremorgin C (**1** and **2**) were prepared from the N-prolyl-7-methoxy-β-carboline **4**, an intermediate to the synthesis of fumitremorgin B.

Fumitremorgin C (SM-Q, mp 125-130°C), one of the tremorgenic mycotoxins, was isolated from *Aspergillus fumigatus* Fres. in 1977.[1] Its structure (**1** or **2**) was first reported in a book[2] with spectral data, and the configuration at the C-12 was not specified. As fumitremorgin C is the simplest member of fumitremorgin family and its stereochemistry remains to be solved, several synthetic reports have been published. Demethoxy fumitremorgin C was prepared by Cava[3] (demethoxy **1**) and Ottenheijm[4] (demethoxy **2**). Recently Ottenheijm group has reported[5] synthesis of fumitremorgin C (**1** and **2**) applying their cyclo addition reaction of 3, 4-dihydro-β-carboline N-oxide, although **1** was obtained as an oil in small quantity.



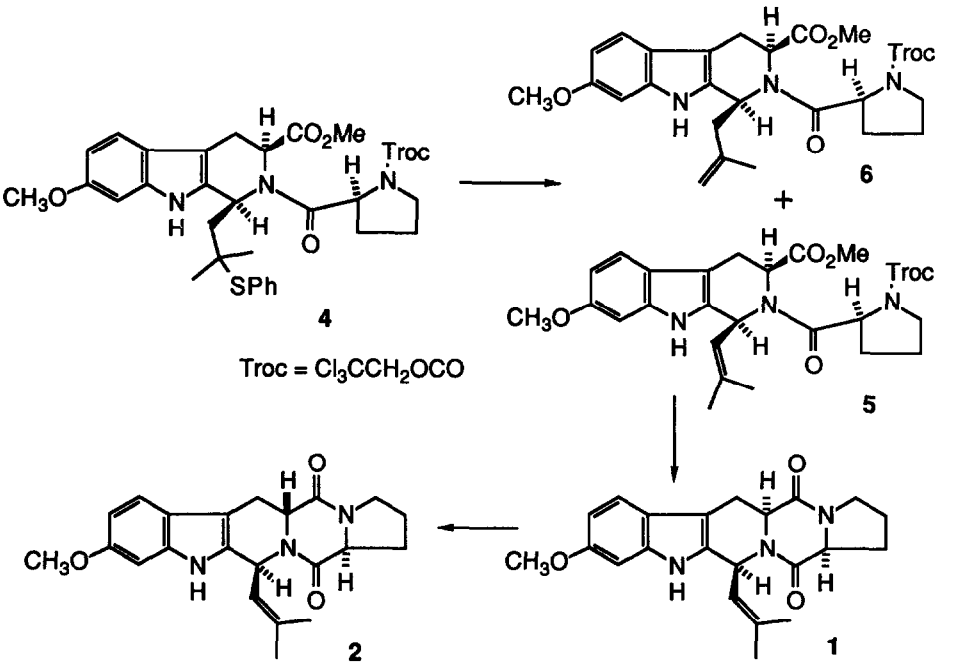
1 12α-Fumitremorgin C
2 12β-Fumitremorgin C



3 Fumitremorgin B

We have reported the synthesis of fumitremorgin B (**3**)[6] and the pentacyclic parent ring systems.[7] We report here the synthesis of two possible isomers of fumitremorgin C (**1** and **2**) from the dipeptide **4**, which was the synthetic intermediate to fumitremorgin B, as a part of synthetic study to elucidate the structure-activity relationship of tremorgenic fumitremorgins. The oxidative elimination and cyclization of **4** will provide fumitremorgin C.

Oxidative removal of the phenylthio group in the dipeptide **4**,[6] which was prepared from 6-methoxy-L-tryptophan methyl ester by two steps, was accomplished by oxidation with m-chloroperbenzoic acid followed by thermolysis in toluene to give the desired endo-olefin **5** (72%) and the exo-olefin **6** (24%). Deprotection of **5** with Zn in refluxing methanol followed by spontaneous cyclization gave fumitremorgin C **1** (96%), mp 259.5-260.5°C, $[\alpha]_D$ -13°. The melting point of synthetic sample was much higher than that of reported natural sample, although the spectral data including the specific rotation were nearly identical with those of **1** reported by



Ottenheijm.[5] Based on our previous study,[7] **1** was refluxed in methanol with 0.1 N-sodium hydroxide to give the C-12 epimer **2** (80%), mp 245.0-247.5°C, $[\alpha]_D$ +239°. Spectral data of **2** are similar to those of reported value.[5]

Comparison of spectral data of **1** and **2** with those of reported natural fumitremorgin C showed that synthetic **1** is more similar to natural fumitremorgin C than **2**. However, complete identification was not possible, as the natural sample was not available and the specific rotation was not reported.

Experimental section

All melting points are uncorrected. The UV spectra were taken with a Hitachi 323 spectrophotometer, and the IR spectra with Hitachi 260-10 and 295 spectrophotometers. The mass spectra were recorded on Hitachi M-60 and 7M spectrometers. The NMR spectra were recorded on JNM-FX-270 and GSX-400 apparatus in $CDCl_3$ solution using tetramethylsilane as an internal standard. The specific rotation was taken with a *DIP*-140 polarimeter using a 10 cm cell. Silica gel BW-820MH or BW-200 (Fuji-Davison) was used for silica gel column chromatography. Kieselgel GF_{254} type 60 (Merck) was used for preparative thin layer chromatography.

Desulfenylation of 4 to 5 and 6

mCPBA (85%, 321 mg, 1.86 mmol) was added portionwise to a stirred suspension of **4** (1020 mg, 1.46 mmol) and $NaHCO_3$ (618 mg, 7.36 mmol) in CH_2Cl_2 (25 ml) under ice-cooling. The mixture was stirred for 15 min under ice-cooling, then diluted with CH_2Cl_2 (50 ml), washed with H_2O (15 ml), 10% Na_2SO_3 solution (20 ml), and H_2O (15 ml), and dried over $MgSO_4$. Evaporation

of the solvent gave a residue (1100 mg), which was dissolved in toluene and refluxed for 1 h. The solvent was evaporated *in vacuo* to give a residue, which was chromatographed on a silica gel column (AcOEt : hexane = 1 : 2) to give the exo-olefin **6** (206 mg, 24%) as a less polar fraction and the endo-olefin **5** (622 mg, 72%) as a more polar fraction. **6** : pale yellow amorphous solid. UV λmax (EtOH) nm: 224, 267, 272^{sh}, 297, 306^{sh}. Mass *m/z* (%): 587 (M^++2, 4.90), 585 (M^+, 5.49), 536 (3.98), 534 (27.99), 532 (82.46), 530 (84.44), 313 (48.83), 259 (100). **5** : colorless plate from AcOEt-hexane, mp 187.0-188.5°C (dec.). UV λ_{max} (EtOH) nm: 223.5, 265, 273^{sh}, 298, 306^{sh}. IR ν^{max} (KBr) cm^{-1}: 3610, 3410, 3230, 1740, 1720, 1635, 1415. Mass *m/z* (%): 587 (M^++2, 4.08), 585 (M^+, 4.11), 532 (4.59), 530 (4.57), 313 (100). Exact-mass: Calcd for $C_{26}H_{30}N_3O_6{}^{35}Cl_3$; 585.1200, found; 585.1192, calcd for $C_{26}H_{30}N_3O_6{}^{35}Cl_2{}^{37}Cl$; 587.1171, found; 587.1167.

Deprotection and cyclization of 5 to 12α-fumitremorgin C 1

Zn dust (61 mg, 9.36 mmol) was added to a solution of **5** (544 mg, 0.93 mmol) in MeOH (50 ml), and the mixture was refluxed for 90 min. Inorganic material was filtered through Celite pad and washed with hot MeOH. Combined solvent was evaporated to give a residue, which was dissolved in CH_2Cl_2 (200 ml) and washed with 5% HCl solution (30 ml), sat. $NaHCO_3$ solution (30 ml), and brine (30 ml), and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was chromatographed on a silica gel column (AcOEt : hexane = 2 : 3 - 1: 0) to give **1** as a pale yellow amorphous solid (399 mg, 96%). Repeated crystallization from AcOEt gave colorless powder, mp 259.5-260.5°C (dec.). $[\alpha]_D{}^{28}$ -13° (c 0.53, MeOH). UV λ_{max} (EtOH) nm: 225, 264^{sh}, 273.5, 299, 307.5^{sh}. IR ν^{max} (KBr) cm^{-1}: 3180^{br}, 1680, 1660. ^{1}H-NMR δ ppm: 1.65 (3H, d, J=1.53 Hz, CH_3), 1.99 (3H, d, J=1.22 Hz, CH_3), 1.88-2.11 (2H, m, C_8-H_2), 2.19-2.31 (1H, m, C_7-Ha), 2.36-2.47 (1H, m, C_7-Hb), 3.10 (1H, ddd, J=0.92, 11.60, and 15.87 Hz, C_{13}-Ha), 3.52 (1H, dd, J=4.88 and 15.87 Hz, C_{13}-Hb), 3.62-3.67 (2H, m, C_9-H_2), 3.83 (3H, s, OCH_3), 4.08-4.21 (2H, m, C_6-H and C_{12}-H), 4.91 (1H, ddd, J=1.22, 1.52, and 9.46 Hz, C_{21}-H), 5.98 (1H, d, J=9.46 Hz, C_3-H), 6.82 (1H, dd, J=2.44 and 8.54 Hz, C_{17}-H), 6.86 (1H, d, J=1.83 Hz, C_{19}-H), 7.44 (1H, d, J=8.54 Hz, C_{16}-H), 7.77 (1H, brs, NH). ^{13}C-NMR (100.40 MHz) δ ppm: 18.10 (q, Me), 21.95 (t, C-13), 23.06 (t, C-8), 25.72 (q, Me), 28.59 (t, C-7), 45.41 (t, C-9), 51.03 (d, C-3), 55.77 (q, OMe), 56.79 (d, C-12), 59.23 (d, C-6), 95.31 (d, C-19), 106.25 (s, C-14), 109.49 (d, C-17), 118.88 (d, C-16), 120.76 (s, C-15), 124.19 (d, C-21), 132.20 (s, C-2 or C-22), 133.98 (s, C-22 or C-2), 137.05 (s, C-20), 156.53 (s, C-18), 165.74 (s, CO), 169.52 (s, CO). Mass *m/z* (%): 381 (M^++2, 6.60), 380 (M^++1, 41.60), 379 (M^+, 100), 364 (42.55), 324 (63.36), 281 (75.96). Anal. calcd for $C_{22}H_{25}N_3O_3$: C, 69.64; H, 6.64; N, 11.07. Found: C, 69.44; H, 6.64; N, 10.96.

Epimerization of 1 to 2

0.1 N-NaOH aq. solution (15 ml) was added to a solution of **1** (143 mg, 0.38 mmol) in MeOH (15 ml). The mixture was refluxed for 3 h. Acetic acid (1 ml) was added under ice-cooling and the solvent was evaporated. The residue was dissolved with CH_2Cl_2 (100 ml), and washed with sat. $NaHCO_3$ solution (30 ml) and brine (30 ml), and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was separated by preparative tlc (silica gel, AcOEt : hexane = 4 : 1) to give **2** as a white solid (117 mg, 82%) and recovered **1** (3 mg, 2%). Crystallization of **2** from AcOEt gave pale yellow prisms, mp 245.0-247.5°C (dec.). $[\alpha]_D{}^{28}$ +239° (c 0.11, MeOH). UV λ_{max} (EtOH) nm:

226, 265^{sh}, 272^{sh}, 297, 306^{sh}. IR ν^{max} (KBr) cm^{-1}: 3260^{br}, 1665. ^{1}H-NMR δ ppm: 1.76 (3H, d, J=1.22 Hz, CH_3), 1.97 (3H, d, J=1.22 Hz, CH_3), 1.9-2.2 (3H, m, C_7-Ha and C_8-H_2), 2.4-2.6 (1H, m, C_7-Hb), 2.90 (1H, ddd, J=1.53, 12.21, and 15.25 Hz, C_{13}-Ha), 3.31 (1H, dd, J=3.96 and 15.25 Hz, C_{13}-Hb), 3.60 (1H, m, C_9-Ha), 3.76 (1H, m, C_9-Hb), 3.83 (3H, s, OCH_3), 4.12 (1H, m, C_6-H), 4.41 (1H, ddd, J=0.91, 3.97, and 12.21 Hz, C_{12}-H), 5.35 (1H, td, J=1.22 and 9.15 Hz, C_{21}-H), 6.44 (1H, d, J=9.46 Hz, C_3-H), 6.78 (1H, dd, J=2.13 and 8.54 Hz, C_{17}-H), 6.82 (1H, d, J=1.83 Hz, C_{19}-H), 7.32 (1H, d, J=8.54 Hz, C_{16}-H), 7.68 (1H, brs, NH). ^{13}C-NMR (100.40 MHz) δ ppm: 18.73 (q, Me), 22.01 (t, C-13), 25.94 (q, Me), 26.02 (t, C-8), 29.83 (t, C-7), 45.49 (t, C-9), 47.80 (d, C-3), 55.71 (q, OMe), 56.41 (d, C-12), 58.76 (d, C-6), 95.09 (d, C-19), 106.90 (s, C-14), 109.36 (d, C-17), 118.72 (d, C-16), 120.85 (d, C-21), 121.02 (s, C-15), 131.85 (s, C-2 or C-22), 136.93 (s, C-22 or C-2), 139.08 (s, C-20), 156.62 (s, C-18), 164.97 (s, CO), 165.29 (s, CO). Mass *m/z* (%) : 381 (M^++2, 5.83), 380 (M^++1, 35.61), 379 (M^+, 91.66), 364 (44.69), 324 (80.97), 281 (100). Anal. calcd for $C_{22}H_{25}N_3O_3$: C, 69.64; H, 6.64; N, 11.07. Found: C, 69.50; H, 6.59; N, 10.92.

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