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TOTAL SYNTHESIS OF FUMITREMORGIN B

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Summary : A total synthesis of a tremorgenic mycotoxin, fumitremorgin B is described.

Fumitremorgin B **1b**, isolated by Yamazaki and coworkers[1] in 1974 from cultures of Aspergillus fumigatus, causes severe tremorgenic reactions in experimental animals. The structure of **1b** was also established by Yamazaki on the basis of chemical investigation and X-ray analysis.[2] Total synthesis of **1b**, based on the condensation of 3-formylindole with glycylproline diketopiperazine, was recently reported by Goto and Nakatsuka.[3] In this paper, we report an alternative synthesis of fumitremorgin B **1b**.

Details on the biosynthetic pathway to **1b** remain unknown but L-tryptophan, L-proline, and mevalonic acid have been shown to be the precursors for **1b**.[4] We have recently reported the synthesis of the basic ring system of **1**, namely optically active pentacycles from L- or D-tryptophan and L-proline.[5]

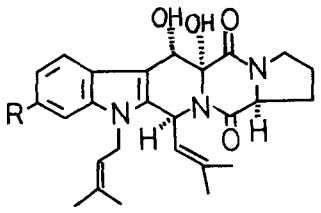
We now accomplished the total synthesis of **1** by modifying the above synthetic route. Pictet-Spengler(PS) condensation of L-tryptophan methyl ester **2a** with 3-methyl-3-phenylthiobutanal **3**(1.2 eq.) in the presence of trifluoroacetic acid(TFA)(3 eq.) in CH_2Cl_2 at room temperature(r.t.) for 1 hr afforded 1,3-cis-ß-carboline **4a**(58%) as the major product, along with the trans isomer **5a**(31%)[**4a**:$[\alpha]_D^{21}$ -98.7°(c 0.461, MeOH); νmax (neat) 3380, 1730 cm^{-1} ; m/z 394(M^+); δ 1.45(3H, s, Me), 1.47(3H, s, Me), 1.88(1H, dd, J=7.3, 15.4Hz, C_{10}-H), 2.03(1H, br-s, N_2-H), 2.19(1H, dd, J=2.6, 15.4Hz, C_{10}-H), 2.83(1H, ddd, J=2.6, 11.1, 15.0Hz, C_4-H), 3.11(1H, ddd, J=1.7, 4.3, 15.0Hz, C_4-H), 3.82(1H, dd, J=4.3, 11.1Hz, C_3-H), 3.82(3H, s, OMe), 4.55(1H, m, C_1-H)].[6] The reaction of **4a** with trichloroethoxycarbonyl(Troc)-L-prolyl chloride(1.2 eq./Et_3N, 1.3 eq./CH_2Cl_2) gave the cis-dipeptide **4b** quantitatively. Similarly, **5b** was obtained from **5a**(98%). Subsequent dehydrogenation of **4b** with DDQ(1.1 eq.) in CH_2Cl_2 at r.t. gave the dehydrodipeptide **6a**(64%; λmax 224, 268, 284sh, 366nm)[7] which was dehydrosulfenylated(i, MCPBA-$NaHCO_3$-CH_2Cl_2; ii, toluene reflux)[8] to give **7a**(54%) and **7b**(26%). Deprotection of **7a** with Zn(10 eq.) in refluxing MeOH was followed by spontaneous cyclization to give the pentacyclic compound **8a**

[77%; mp 287°C(dec.); $[\alpha]_D^{24}$ +253.8°(c 0.340, $CHCl_3$); λmax nm(ε) 234(28100), 262sh(15100), 282sh(13700), 369(16300); m/z 347(M^+); δ 1.65(3H, s, Me), 2.02(3H, s, Me), 1.90-2.20(3H, m, C_7-H, C_8-H_2), 2.39-2.48(1H, m, C_7-H), 3.63-3.76(2H, m, C_9-H_2), 4.14(1H, dd, J=7.0, 10.1Hz, C_6-H), 5.26(1H, dt-like, J=1.2, 9.8Hz, C_{21}-H), 6.68(1H, d, J=9.8Hz, C_3-H), 7.19-7.24(2H, m, C_{17}-H, C_{18}-H), 7.35(1H, s, C_{13}-H), 7.33-7.38(1H, m, C_{19}-H), 7.65(1H, m, C_{16}-H), 8.32(1H, br-s, NH)].

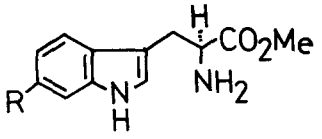
Based on the above results, the synthesis of our key intermediate **8b** was effectively accomplished by the similar reaction sequence. The PS reaction of **2b**[5] with 3(TFA, CH_2Cl_2) gave **4c**[58%; $[\alpha]_D^{24}$ -93.2°(c 0.687, MeOH)] and **5c**[20%; $[\alpha]_D^{24}$ +19.5°(c 1.05, MeOH)]. Treatment of **4c** with Troc-L-prolyl chloride afforded **4d**(92%). Dehydrogenation of **4d** with DDQ gave **6b**(20-30%) which was dehydrosulfenylated to give **7c**(51%) and **7d**(18%). Reductive deprotection(Zn, MeOH, reflux) followed by cyclization of **7c** resulted in the formation of the key intermediate **8b**[84%; mp 241-242°C(dec.); $[\alpha]_D^{24}$ +313.2°(c 0.152, $CHCl_3$); λmax nm(ε) 234(25400), 268.5(16400), 299(14000), 377.5(13500); m/z 377(M^+); δ 3.82(3H, s, OMe), 4.13(1H, m, C_6-H), 6.63(1H, d, J=9.9Hz, C_3-H), 7.29(1H, s, C_{13}-H)].

Having versatile intermediates **8** in hand, we turned our attention to the oxidation to the corresponding cis-diols **1**. After several attempts, selective dihydroxylation at 12 and 13 position of **8a** was achieved in one step. Thus, treatment of **8a** with OsO_4(0.14 eq.) in the presence of N-methylmorpholine N-oxide(1.54 eq.) and pyridine(1.1 eq.) in THF-H_2O(10:1) at r.t. for 6 hr gave a 32% yield of **9a**[mp 209-210°C; νmax(KBr) 3400, 1650cm^{-1}; m/z 381(M^+), 364(M^+-OH), 363(M^+-H_2O), 347(M^+-2xOH); δ 4.18(1H, br-s, C_{12}-OH, exchangeable), 4.43(1H, dd, J=7.0, 9.5Hz, C_6-H), 4.71(1H, d, J=2.8Hz, C_{13}-OH, exchangeable), 5.79(1H, dd, J=1.2, 2.8Hz, C_{13}-H), 5.92(1H, dd, J=1.2, 9.5Hz, C_3-H), 7.95(1H, dd-like, J=1.5, 7.0Hz, C_{16}-H)]. Prenylation of **9a** with dimethylallyl chloride(KOH, 18-crown-6, benzene)gave demethoxy-fumitremorgin B **1a** 72%; mp 213-214°C; λmax 227.5, 278sh, 284.5, 293nm; νmax (KBr) 3450, 1680sh, 1658cm^{-1}; m/z 449(M^+); δ 4.03(1H, s, C_{12}-OH, exchangeable), 4.46(1H, dd, J=7.5, 9.3Hz, C_6-H), 4.74(1H, d, J=2.7Hz, C_{13}-OH, exchangeable), 5.81(1H, dd, J=0.9, 2.7Hz, C_{13}-H), 6.01(1H, dd, J=0.9, 10.1Hz, C_3-H)]. The final two chemical reactions of **8b** leading to fumitremorgin B **1b** were performed in the similar manner, involving the OsO_4 oxidation to the cis-diol **9b**[10%; mp 199-200°C; λmax 222.5, 260sh, 270.5, 296, 303sh nm; νmax (KBr) 3350, 1640cm^{-1}] followed by prenylation to yield fumitremorgin B **1b**[66%; mp 210-211°C; CD(c 0.976x10^{-4}, EtOH) [θ](nm) + 0.84x10^4(215), -1.62x10^4(230), +2.21x10^4(273), +1.03x10^4(288), +1.13x10^4(299)]. Chromatographic mobility, mp and IR, mass, NMR,and CD spectra of the synthetic **1b** were indistinguishable from those of natural specimen.

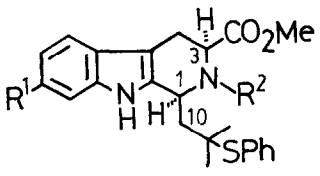
As an alternative method for the introduction of the two hydroxyl groups at 12 and 13 positions, bromination of **8a** with NBS(1.1 eq.) in THF-H_2O(5:1) was carried out according to Corey's methods[9]. However, unexpectedly, the trans-diol(12α, 13ß) **10a** was obtained in 66% yield, instead of the expected bromohydrin, together with the isomeric trans-diol(12ß, 13α) **11a**(31%).



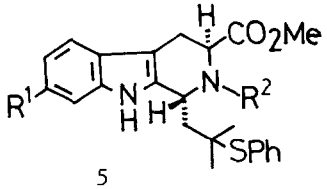
1 a, R=H
b, R=OMe Fumitremorgin B



2 a, R=H
b, R=OMe

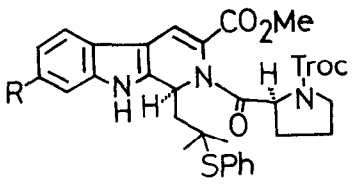


4

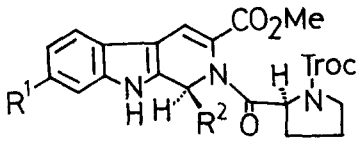


5

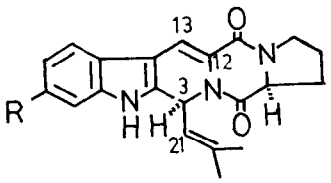
a, $R^1=R^2=H$
b, $R^1=H$, R^2=Troc-L-prolyl
c, R^1=OMe, $R^2=H$
d, R^1=OMe, R^2=Troc-L-prolyl



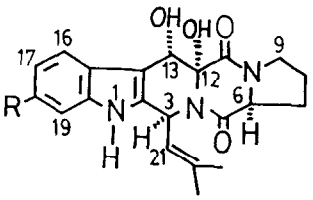
6 a, R=H
b, R=OMe



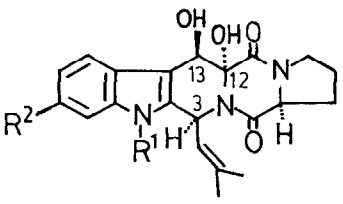
7 a, $R^1=H$, R^2= 
b, $R^1=H$, R^2= 
c, R^1=OMe, R^2= 
d, R^1=OMe, R^2= 



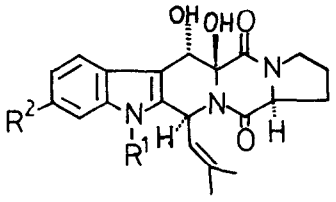
8 a, R=H
b, R=OMe



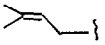
9 a, R=H
b, R=OMe



10



11

a, $R^1=R^2=H$
b, R^1=  , $R^2=H$
c, $R^1=H$, R^2=OMe
d, R^1=  , R^2=OMe

Similar treatment of **8b** with NBS gave the trans-diol(12α, 13ß) **10c**[77%; mp 224-226°C; δ 2.69(1H, s, C_{12}-OH, exchangeable), 3.91(1H, d, J=3.1Hz, C_{13}-OH, exchangeable), 5.64(1H, d, J=3.1Hz, C_{13}-H), 5.96(1H, d, J=9.2Hz, C_3-H)] as the major product accompanied by the isomeric trans-diol(12ß, 13α) **11c**(10%). Prenylation of **10a** with dimethylallyl chloride gave demethoxy-13-epi-fumitremorgin B **10b**[84%; mp 254°C(dec.)] while **11a** gave demethoxy-12-epi-fumitremorgin B **11b**(46%; mp 206-7°C). Likewise, prenylation of **10c** afforded 13-epi-fumitremorgin B **10d**[65%; mp 226-227°C; δ 2.74(1H, s, C_{12}-OH, exchangeable), 3.85(3H, s, OMe), 3.97(1H, d, J=3.1Hz, C_{13}-OH, exchangeable), 5.66(1H, d, J=3.1Hz, C_{13}-H), 6.04(1H, d, J=9.8Hz, C_3-H)].

The oxidation of **10b** with DDQ in CH_3CN-H_2O(10:1, 70°C) followed by $NaBH_4$ reduction in MeOH provided demethoxyfumitremorgin B **1a**(4%). A similar oxidation and reduction sequence of **10d** gave fumitremorgin B **1b**(3%). The application of the present method to the synthesis of related biologically interesting natural products is underway and will be reported in due course.

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References and Notes

1. M. Yamazaki, S. Suzuki, and K. Miyaki, Chem.Pharm.Bull., 19, 1739(1971).
2. References were cited in the previous report[5].
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4. M. Yamazaki, H. Fujimoto, and T.Kawasaki, Tetrahedron Lett., 1241(1975).
5. M. Nakagawa, H. Fukushima, T. Kawate, M. Hongu, S. Kodato, T. Une, M. Taniguchi, and T. Hino, Tetrahedron Lett., 27, 3235(1986).
6. All the ^{1}H-NMR spectra were recorded in $CDCl_3$.
7. All the UV spectra were taken in EtOH.
8. Dehydrosulfenylation prior to DDQ oxidation of **4b** failed to give **7a** and 1-isobutenyl-2-methoxycarbonyl-ß-carboline was formed(31%).
9. E. J. Corey and J. Das, Tetrahedron Lett., 4217(1982).