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SYNTHETIC APPROACH TO THE TOTAL SYNTHESIS OF FUMITREMORGINS II SYNTHESIS OF OPTICALLY ACTIVE PENTACYCLIC INTERMEDIATES AND THEIR DEHYDROGENATION

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Summary : Optically active pentacycles(13-18) were synthesized from L- and D-tryptophans, two of which (13 and 15) were alkylated and dehydrogenated to 21 and 22, respectively.

Fumitremorgin B 1 is a tremorgenic toxin produced by the Aspergillus fumigatus.[1] The structure of 1 has been determined by Yamazaki and coworkers[2] and 1 has been one of our synthetic target molecules.[3] While a few attemps to synthesize 1 has been reported[4],no total synthesis has yet been published of any of the fumitremorgin family.

We have previously reported a new ß-carboline synthesis.[5] Recent Harrison's publication[6] prompted us to report our synthetic approach to optically active pentacyclic compounds of general form(13-18), as promissing intermediates leading to optically pure fumitremorgins and dehydrogenation of these compounds.

The Pictet-Spengler reaction has been employed to prepare 1,2,3,4-tetrahydro-ß-carbolines.[7] However, little is known about the racemization during the Pictet-Spengler reaction of L- or D-tryptophan ester with an aldehyde to the corresponding 1,3-cis- and trans-disubstituted-1,2,3,4-tetrahydro-ß-carbolines.[6,8] We now obtained optically active 1,3-cis-ß-carbolines as a major isomer by the Pictet-Spengler reaction of L- and D-tryptophan methyl esters 2 and 6-methoxy-L-tryptophan methyl ester 3.

According to Cook's conditions,[9] we first carried out the reaction of 2a and isovaleraldehyde in boiling benzene without or with TsOH and we obtained the cis isomer 4a and the trans isomer 5a in about same ratio which were, however, shown to be racemized to a greater extent by NMR spectrum and the $[\alpha]_D$ value.[10] We obtained 4a(62%,$[\alpha]_D^{21}$ -121°)[11),12)] predominantly without significant racemization together with 5a(33%,$[\alpha]_D^{25}$ +51°),[12)] when the reaction of 2a with isovaleraldehyde in CH_2Cl_2 in the presence of trifluoroacetic acid(TFA) (5.7 mole equivalents, r.t. 2 hr). Similar reaction of D-tryptophan methyl ester 2b with isovaleraldehyde gave 4b(64%,

$[\alpha]_D^{16}$ +120.7°) as a major isomer and **5b**(34%, $[\alpha]_D^{11}$ -52.4°). These results made us to examine the corresponding reaction of 6-methoxy-L-tryptophan methyl ester **3**[13] with isovaleraldehyde in similar conditions. The reaction proceeded with predominant formation of **6**(53%, mp 151-152°, $[\alpha]_D^{9}$ -122.3°),[12] accompanied by the formation of **7**(30%, mp 151.5-153.5°, $[\alpha]_D^{16}$ +58.4°).[12]

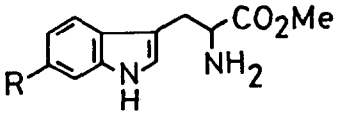
Coupling reaction of **4** or **6** with proline was then accomplished by use of the acid chloride. Treatment of **4a** with Z-L-prolyl chloride in CH_2Cl_2-Et_3N gave **8a**(92%, mp 192.5-193.5°, $[\alpha]_D^{12}$ -48.8°). Deprotection of **8a**(10% Pd/C, $HCOONH_4$, MeOH, r.t.)[16] was followed by spontaneous cyclization to give the parent pentacyclic compound **13**(95%).[17] Likewise, **4b** and **5a** could be converted into the corresponding pentacycles **16** via **8b** and **14** via **9a**, respectively. The dipeptide **11** was also obtained by the reaction of **6** with Z-L-prolyl chloride which was subjected to hydrogenolysis to give **15** (95%, mp 272-275°, $[\alpha]_D^{32}$ -80.6°). A simple two-step sequence has been developed to prepare 1,3-trans-oriented dipeptide **9a** in stereoselective fashion ; predominant formation of **9a**(41%, mp 207-208°, $[\alpha]_D^{13}$ -104.7°) was achieved by the direct cyclization of the imminium salt **12**, which was prepared by the condensation of **2a** with isovaleraldehyde (CH_2Cl_2, molecular sieves-4A, r.t, 12hr) followed by the acylation with Z-L-prolyl chloride. A similar series of reactions starting from **2b** led to the formation of **17** via **9b**.

Furthermore, the reaction of **4a** with Z-D-prolyl chloride provided **10**. Hydrogenolysis of **10** afforded **18**(mp 264-266°, $[\alpha]_D^{27}$ -95.1°). Comparison of the $[\alpha]_D$ value of **18** with that of its enantiomer **16**(mp 263.5-266°, $[\alpha]_D^{25}$ +95.3°) suggests that little or no racemization occurred under these reaction conditions.

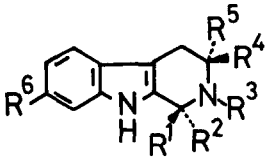
When the cis-diketopiperazine derivative **13** was treated with isopentyl bromide(1.2 equiv.) in DMF(r.t., 40 min.) in the presence of NaH(1.1 equiv.), **19**($[\alpha]_D^{21}$ +112.0°) was formed exclusively(95%), indicating that N-alkylation was accompanied by the simultaneous epimerization at C-12 position. Similar reaction of **15** provided **20**($[\alpha]_D^{19}$ +125.9°) in 98% yield.[18]

Attempted dehydrogenation of pentacycles(**13**, **15**, and N-isopentyl derivative of **13**) having cis diketopiperazine moiety with DDQ failed to give the corresponding 12,13-dehydro derivatives. Treatment of the 12-epimeric isomer, **19**, with DDQ in CH_3CN-H_2O(7 : 3), however, resulted in the formation of the expected dehydrogenated compound **21**(λmax 236, 261, 367 nm; νmax 1690, 1620 cm^{-1} ; δ($CDCl_3$) 7.39(s, C_{13}-H) ; m/z 419 M^+ ; $[\alpha]_D^{18}$ +145.8°) in 58% yield. Similaly **20** underwent selective dehydrogenation to **22**(λmax 219, 236sh, 268, 298, 376 nm; δ($CDCl_3$) 7.33(s, C_{13}-H); m/z (%) 449(14) M^+, 392(100), $[\alpha]_D^{16}$ +137.4°) in 62% yield.[19]

The present study provides clear guidelines for the synthesis of pentacyclic intermediates to fumitremorgines. Our extension and application of these results toward the total synthesis of **1** will be reported.

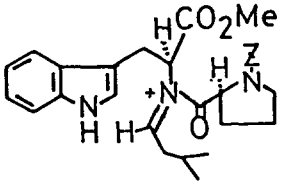


2a, R=H, L-Tryptophan
b, R=H, D-Tryptophan
3, R=OMe, L-Tryptophan

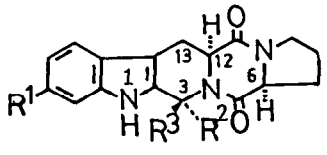


4a- 11

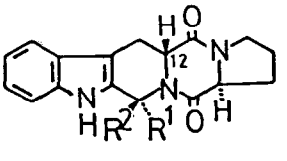
	R^1	R^2	R^3	R^4	R^5	R^6
4a	i-Bu	H	H	CO_2Me	H	H
4b	H	i-Bu	H	H	CO_2Me	H
5a	H	i-Bu	H	CO_2Me	H	H
5b	i-Bu	H	H	H	CO_2Me	H
6	i-Bu	H	H	CO_2Me	H	OMe
7	H	i-Bu	H	CO_2Me	H	OMe
8a	i-Bu	H	Z-L-Pro	CO_2Me	H	H
8b	H	i-Bu	Z-L-Pro	H	CO_2Me	H
9a	H	i-Bu	Z-L-Pro	CO_2Me	H	H
9b	i-Bu	H	Z-L-Pro	H	CO_2Me	H
10	i-Bu	H	Z-D-Pro	CO_2Me	H	H
11	i-Bu	H	Z-L-Pro	CO_2Me	H	OMe



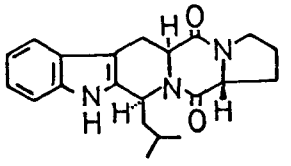
12



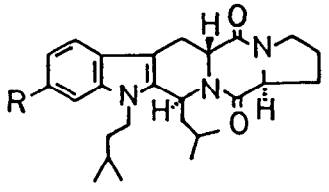
13, R^1=R^2=H, R^3=CH_2CHMe_2
14, R^1=R^3=H, R^2=CH_2CHMe_2
15, R^1=OMe, R^2=H, R^3=CH_2CHMe_2



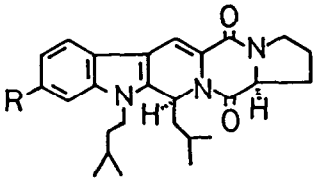
16, R^1=CH_2CHMe_2, R^2=H
17, R^1=H, R^2= CH_2CHMe_2



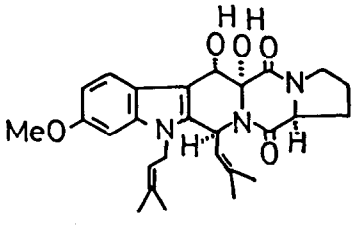
18



19, R=H
20, R=OMe



21, R=H
22, R=OMe



1
Fumitremorgin B

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10. 4a : 21.7% e.e.(without TsOH), 80.2% e.e.(with TsOH).
11. All new compounds gave IR, UV, ^{1}H-NMR, ^{13}C-NMR, and Mass spectra that are consistent with the structures assigned. Crystalline compounds gave satisfactory elemental analysis. Optical rotations were taken in MeOH.
12. The NMR spectrum using the chiral shift reagent(tris(3-heptafluoro-butyryl-d-camphorato)europium(III)) showed the absence of the other enantiomer.
13. The optically active 6-methoxytryptophan ester was synthesized according to our method[14] and the reference[15].
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17. 13, mp 289-290°, $[\alpha]_D^{18}$ -76.3° ; νmax (KBr) 3260 (NH), 1665 (CO) cm^{-1}.
18. 20, colorless amorphous powder; λmax (EtOH) nm 230, 277, 296, 307sh; νmax (KBr) 1660 cm^{-1} ; ^{1}H-NMR δ($CDCl_3$) 0.94, 1.01, 1.02,and 1.15(12H,d,J= 6.3 Hz, Me), 1.5-2.15(9H,m, C_7-H_AH_B-CH_2, Me_2CHCH_2), 2.50(1H,m, $C_7H_AH_B$), 2.91 (1H,dd,J=15.0, 12.4Hz, C_{13}-H_AH_B), 3.29(1H,dd,J=15.5, 4.6Hz, $C_{13}H_AH_B$),3.60 (1H,m, N_{10}-CH_AH_B), 3.80(1H,m, N_{10}-CH_AH_B), 3.88(3H,s, OMe), 3.90-4.15(3H, ,m, N_1-CH_2, C_6-H), 4.46(1H,dd,J=12.0, 4.5Hz, C_{12}-H), 5.88(1H,d,J=10.2Hz, C_3-H), 6.75-6.80(2H,m, C_{17}-H, C_{19}-H), 7.30(1H,d,J=8.9Hz, C_{16}-H) ; Exact mass : calcd. for $C_{27}H_{37}N_3O_3$ 451.2837. Found, 451.2828.
19. The reaction mixture was treated with 5% HCl before work-up.

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