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SYNTHETIC STUDIES ON FUMITREMORGIN I.

SYNTHESIS OF (±)-12-DEOXY-12-EPIFUMITREMORGIN B

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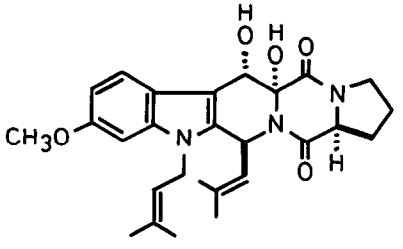
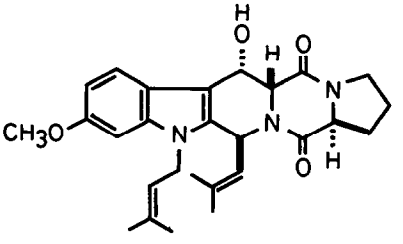
Abstracts: Diketopiperazine derivative **5** containing an oxidized prenyl moiety was prepared. The aldol product of **5** and a functionarized indole-3-aldehyde **7** was a mixture of four stereoisomers, which were converted to a single terahydro-β-carboline derivative, 12-deoxy-12-epifumitremorgin B (**2**), in good yield.

Fumitremorgin A[1] and B[2] are potent tremorgic mycotoxins produced by Aspergillus fumigatus. Verruclogen[3], which possesses a similar structure and biological activity, was also produced by Penicillium verruclosum. Their highly oxidized structures containing two isoprenyl units and diketopiperezine moiety prompted us to initiate their syntheses. Although a few synthetic studies[4] toward them have been reported recently, a total synthesis has not been accomplished. We have reported a novel synthetic method[5,6] of indole alkaloids which involves an anion formation at the α-position of protected amino acids followed by condensation with a protected indole-3-aldehyde. In this paper, we report a synthesis of (±)-12-deoxy-12-epifumitremorgin B (**2**).



Fumitremorgin B (1)



2

Glycylproline diketopiperazine (**5**) containing an oxidized prenyl moiety was synthesized as follows: Glycylproline diketopiperazine was prenylated with 1.2 eq. sodium hydride and 1.2 eq. 3,3-dimethylallyl bromide in dimethylformamide to afford N-prenyldiketopiperazine **3**[8] (84%). Treatment of **3**

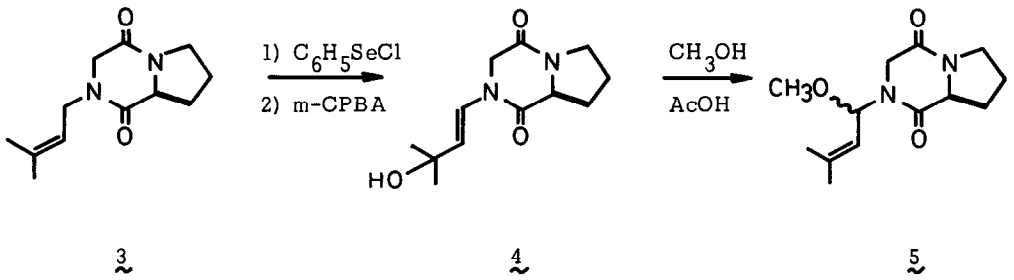
with phenylselenenyl chloride in CH_3CN-H_2O (3:1) and oxidative cleavage with m-chloroperbenzoic acid afforded tertiary alcohol **4**[8] (80%). Treatment of **4** in methanol with acetic acid at 25°C gave compound **5** (67%) which has a methoxy group at α-position of the amide nitrogen. Although **5** was a mixture of two stereoisomers, **5a** and **5b**, which were easily separable by silica gel column chromatography (ratio 3:2), it was employed for the next aldol condensation without separation [**5a** (major isomer): MS m/z 252 (M^+); ^{1}H-NMR($CDCl_3$) δ(ppm) 1.72(3H, s), 1.75(3H, s), 1.92-2.48(4H, m), 3.19(3H, s), 3.40-3.72(2H, m), 3.87(2H, AB-type, J=6 Hz), 4.09(1H, t, J=7 Hz), 5.16(1H, br.d, J=8 Hz), 6.16(1H, d, J=8 Hz). **5b**(minor isomer): MS m/z 252 (M^+); ^{1}H-NMR($CDCl_3$) δ(ppm) 1.66(3H, s), 1.74 (3H, s), 1.82-2.56(4H, m), 3.24(3H, s), 3.28-3.76(2H, m), 3.86(2H, s), 4.20(1H, t, J=7 Hz), 5.23(1H, d, J=7 Hz), 6.19(1H, d, J=7 Hz)].

6-Methoxy-1-prenylindole-3-aldehyde **7** [mp 67°C; MS m/z 243(M^+); ^{1}H-NMR($CDCl_3$) δ(ppm) 1.92 (6H, s), 3.96(3H, s), 4.74(2H, d, J=7 Hz), 5.50(1H, t, J=7 Hz), 6.90(1H, d, J=2 Hz), 7.04(1H, dd, J=2, 9 Hz), 7.71(1H, s), 8.26(1H, d, J=9 Hz), 9.98(1H, s)]. was prepared in 80% yield from 6-methoxyindole-3-aldehyde **6** by alkylation with 3,3-dimethylallyl bromide in the presence of potassium carbonate.

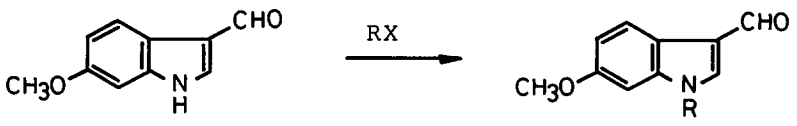
Aldol condensation of the N-prenyldiketopiperazine **5** with the aldehyde **7** was achieved as reported previously.[5,6] Thus, to a THF solution of **5** was added 1.2 eq. lithium diisopropylamide at -78°C, followed by addition of THF solution of **7** to afford the desired product **9**[8][oil; MS m/z 495(M^+)] in 59% yield. **9** was a mixture of four stereoisomers, all of which have trans stereochemistry[9] on the diketopiperazine ring. Although these stereoisomers were separable by silica gel TLC, the mixture was employed for the next cyclization step without seperation. Treatment of **9** with a catalytic amount of camphorsulfonic acid in dichloromethane at 25°C gave in 80% yield a single product (**2**) [mp 220°C; IR(KBr) ν_{max} 3450, 1660 cm^{-1}; UV(MeOH) λ_{max} nm(ε) 208(36600), 224(40900), 264(5940), 272(6500), 294(7340); MS m/z 463(M^+); ^{1}H-NMR($CDCl_3$) δ(ppm) 1.72(3H, s), 1.75(3H, s), 1.83(3H, s), 1.92(3H, s), 1.6-2.6(4H, m), 3.5-3.8(2H, m), 3.84(3H, s), 4.30(1H, t, J=7 Hz), 4.36(1H, d, J=2 Hz), 4.51(2H, d, J=6 Hz), 5.11(1H, br.t, J=7 Hz), 5.23(1H, d, J=9 Hz), 5.41(1H, br.s), 6.57(1H, d, J=9 Hz), 6.71(1H, d, J=2 Hz), 6.81(1H, dd, J=2, 8 Hz), 7.50(1H, d, J=8 Hz)]. Surprisingly in this reaction the four stereoisomers gave a single tetrahydro-β-carboline derivative in good yield. Acid treatment of **9** in MeOH gave a single methoxy derivative (**11**)[10] [MS m/z 477(M^+)] in 85% yield.

The stereochemistry of **2** and **11** were determined as follows; N-pivaloyl derivative **10**;[8] was synthesized in 65% yield by the simillar condensation of **5** and **8**[8], which was prepared from **6** in 85% yield. Tetrahydro-β-carboline derivative **12**[8] [mp 241-242°C] was prepared in 54% yield by acid treatment followed by removal of the pivaloyl moiety. The stereochemistry of **12**[12] was determined by X-ray crystalographic analysis[13] as depicted. By comparison of ^{1}H-NMR spectra of **2**, **11** and **12**, stereochemistry of these tetrahydro-β-carboline derivatives was concluded to be identical each other. Consequently, the structure of **2** was determined to be (±)-12-deoxy-12-epi-fumitremorgin B.

Our synthetic rout for tetrahydro-β-carboline derivatives is very useful not only for the synthesis of fumitremorgin A and B but also other indole alkaloids containing a similar carbon skeleton.



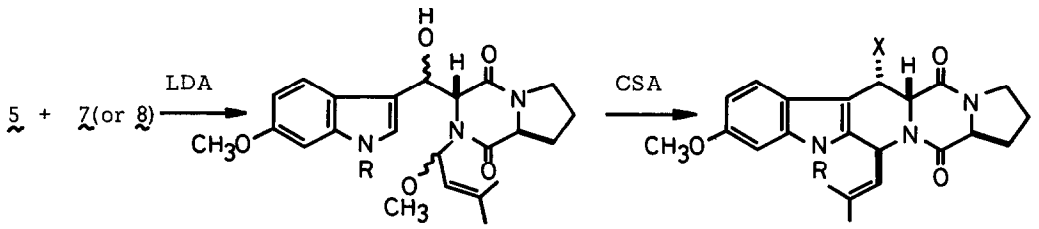
3 4 5



6

7 R = $CH_2CH{=}C(CH_3)_2$

8 R = $COC(CH_3)_3$



9 R = $CH_2CH{=}C(CH_3)_2$

10 R = $COC(CH_3)_3$

2 R = $CH_2CH{=}C(CH_3)_2$, X = OH

11 R = $CH_2CH{=}C(CH_3)_2$, X = OCH_3

12 R = H, X = OC_2H_5

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(7) a) Pictet-Spengler reaction; see E. Yamanaka, N. Shibata and S. Sakai, Heterocycles, **22**, 371 (1984); b) Bischler-Napieraski reaction; see A. Ishida, T. Nakamura, K. Irie and T. Ohishi, Chem. Pharm. Bull., **33**, 3237 (1985), and references cited therein.

(8) Satisfactory spectral data were obtained for all new compounds described.

(9) An aldol condensation of lithium enolate of **5** occurred on a less hindered side. a) S. Nakatsuka K. Sasaki, K. Yamaguchi and T. Goto, Chemistry Lett., 695 (1981); b) S. Nakatsuka and T. Goto. Heterocycles. **21**. 61 (1984).

(10) **11**: MS m/z 477(M^+); ^{1}H-NMR($CDCl_3$) δ(ppm) 1.72(6H, s), 1.82(3H, s), 1.92(3H, s), 1.5-2.5(4H, m), 3.35(3H, s), 3.78(3H, s), 3.5-3.8(2H, m), 4.22(1H, t, J=7 Hz), 4.30(1H, d, J=2 Hz), 4.46(2H, br.s), 4.95(1H, d, J=2 Hz), 5.06(1H, t, J=7 Hz), 5.14(1H, d, J=9 Hz), 6.50(1H, d, J=9 Hz), 6.60(1H, d, J=2 Hz), 6.74(1H, dd, J=2, 8 Hz), 7.40(1H, d, J=8 Hz).

(11) **12**: MS m/z 423(M^+); ^{1}H-NMR($CDCl_3$) δ (ppm) 1.10(3H, t, J=7 Hz), 1.74(3H, s), 1.98(3H, s), 1.8-2.6(4H, m), 3.66(2H, q, J=7 Hz), 3.5-3.8(2H, m), 3.83(3H, s), 4.28(1H, t, J=6.5 Hz), 4.34(1H, d, J=2 Hz), 5.06(1H, d, J=2 Hz), 5.24(1H, d, J=9 Hz), 6.56(1H, d, J=9 Hz), 6.80(1H, dd, 2, 8 Hz), 6.82(1H, d, J=2 Hz), 7.44(1H, d, J=8 Hz), 7.80(1H, br.s).

(12) Unfortunately, X-ray analysis data expressed **12** to be not an optically active but DL-form. We assume racemization occurred during the preparation of **5**.

(13) The X-ray diffraction data were collected by use of an automated four-circle diffractometer, RIGAKU AFC-5, set on a rotating anode X-ray generator, RIGAKU RU-200, with a graphite monochromated Cu radiation (Cu Ka=1.5418A). All computation were carried out at the Computation Center of Nagoya University using CRYSTAN SYSTEM [C. Katayama, N. Sakabe, and K. Sakabe, Acta Crystallogr., Sect. A, **28**, s207 (1972)].

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