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Total Synthesis of (+)-Fumitremorgin B, Its Epimeric Isomers, and Demethoxy Derivatives

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Abstract: Total synthesis of the title compounds is described. The key intermediate, dehydro-pentacyclic 13, is prepared in a sequence involving Pictet-Spengler reaction and DDQ oxidation. The key step in the synthesis was the dihydroxylation of 13 to afford the cis-diol 54, which was performed by direct oxidation with osmium tetroxide, whereas treatment of 13 with N-bromo-succinimide provided the trans-diol 41. Subsequent selective prenylation of 41 and 54 gave 13-epi-fumitremorgin B (45) and fumitremorgin B (1), respectively. 13-Epi-compound 45 is also converted into fumitremorgin B (1) by oxidation followed by reduction.

Fumitremorgin B (FTB) (1) is a structually unique and potentially biologically important family of mycotoxins. There are currently six known natural products from a variety of Aspergillus and Penicillium species in this family[1-6] (Chart I), all of which are characterized by the presence of 2,5-piperazinedione ring formed from 6-methoxy-L-tryptophan and L-proline and cause severe tremorgenic reactions in mice on either oral or intraperitoneal administration.[1c,2b]

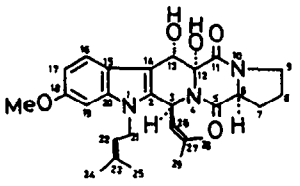
The structures of FTB (1) and fumitremorgin A (2a) were elucidated by Yamazaki[1a,1b,1c,2a,2b] and Clardy[2c] in 1974 and 1975, independently. Verruculogens, 2b[3a] and 2c[4], and TR-2 (3)[5] possess similar structures and biological activities.

The occurrence of FTB (1) and TR-2 (3) in the same culture of A. caespitosus and the efficiency of biosynthetic incorporation of TR-2 (3) into verruculogen (2b) demonstrated their biosynthetic relationships.[1e] Furthermore, fumitremorgin C (4) has been recently isolated.[6]

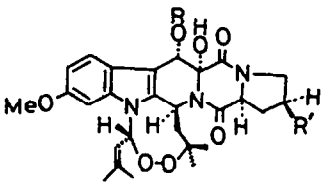
Due to the obvious structural similarities of 1, 2, and 3, it seemed attractive to approach their synthesis through 1.

Total synthesis of 2 and 3 has not yet been reported among these compounds, although a few groups have made considerable progress in this area.[7] Recently, the total synthesis of 1, based on the condensation of 3-formylindole with glycylproline diketopiperazine, was reported by Goto and Nakatsuka.[8] More recently, we completed our total synthesis of 1 by a different approach.[9] In this paper, the full account of our synthesis of FTB (1) and related compounds is reported.

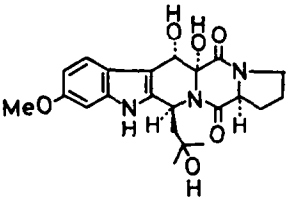
Chart I



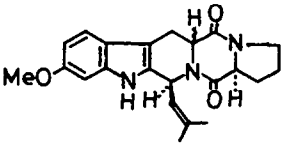
1 Fumitremorgin B



2 a: R= , R'=H Fumitremorgin A
b: R=R'=H Verruculogen (TR-1)
c: R=H, R'=OAc Acetoxyverruculogen

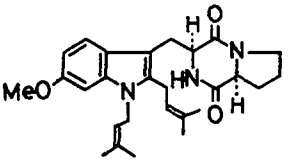


3 TR-2



4 Fumitremorgin C

Scheme I



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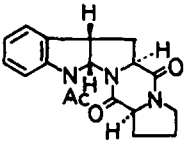

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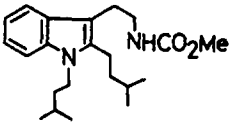

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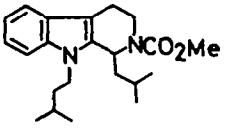

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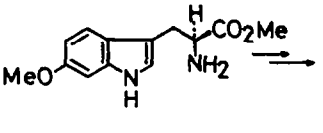

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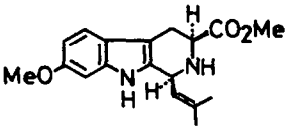
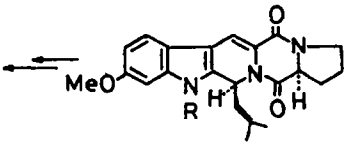
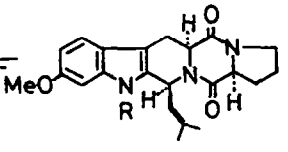


11

Fumitremorgins



13 R=H
14 R=



4a R=H
12 R=

Results and Discussion

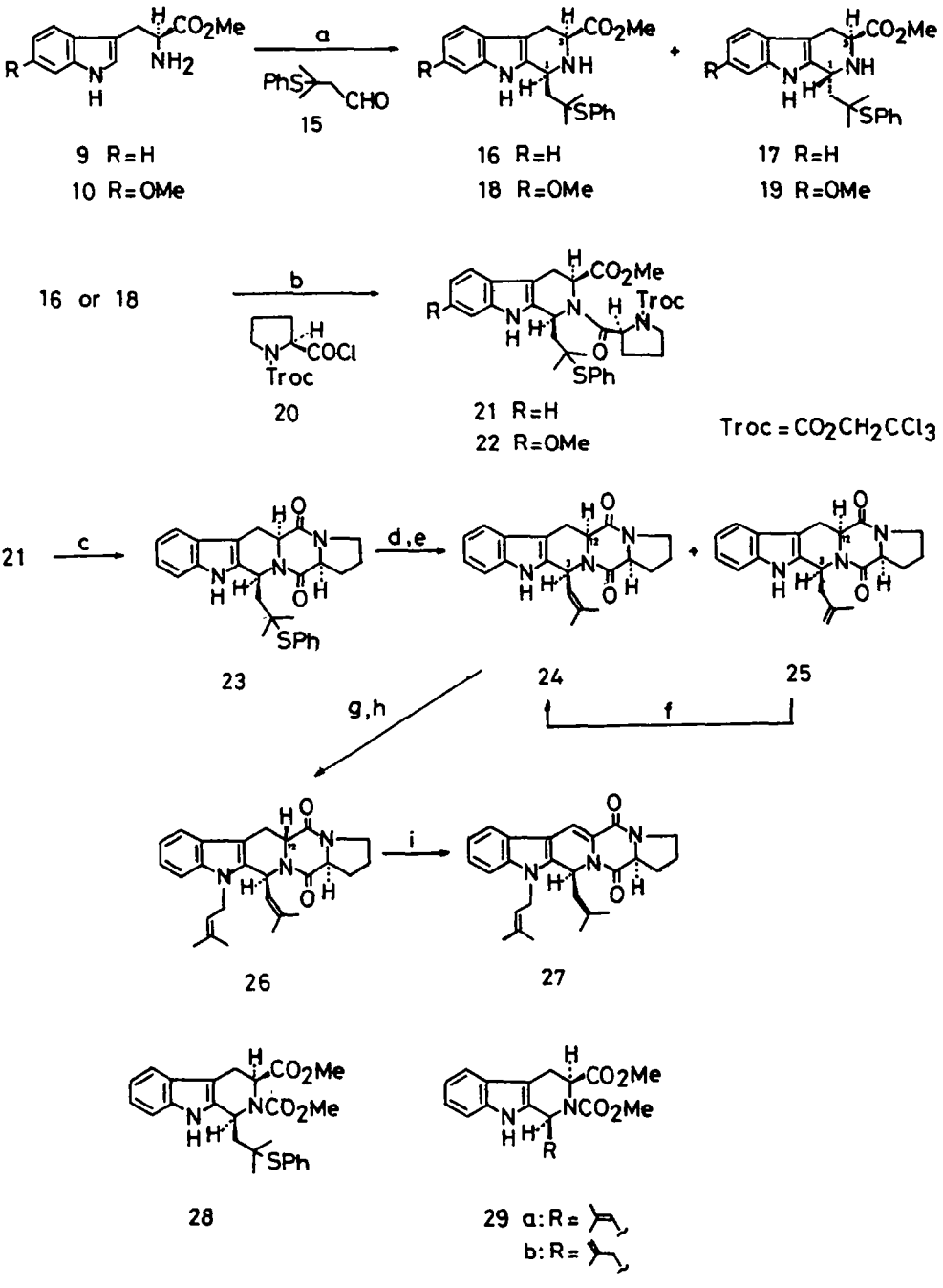
Our original plan to 1 (Scheme I) required the pentacycle 4 or 12 as the key intermediate which had called for the oxidative cyclization of prenylated cyclo-(6-methoxy-L-tryptophyl-L-prolyl) 5 derived from the methoxylation of the cyclic tautomer 6.[10a,b] We have obtained the tetrahydro-ß-carboline 8 by the oxidative cyclization of 1,2-diisopentyltryptamine derivative 7 as a preliminary study for a total synthesis of 1.[11] However, a similar oxidation of the tetrahydro derivative of 5 to the corresponding pentacyclic compound was unsuccessful.[12]

Our new approach to FTB (1) was based on the synthesis of the common ring system, optically active pentacycle 4a or 12 from 6-methoxy-L-tryptophan and L-proline *via* Pictet-Spengler reaction[13] and subsequent dehyrogenation to 13 or 14 followed by hydroxylation. The introduction of the 6-methoxy group was carried out *via* the cyclic tautomer of Nb-methoxycarbonyl-tryptophan ester, a method which we had previously reported to be an efficient means of introducing a methoxy group into the 6-position of tryptophan.[14,15] In order to obtain a pentacyclic intermediate such as 13 or 14, the optically active *cis*-1,3-disubstituted-ß-carbolines 16 and 18 (Scheme II) were chosen as precursors, since they could be obtained by the Pictet-Spengler reaction of L-tryptophan methyl ester 9 and 10 with an appropriate aldehyde, according to a method developed in this laboratory.[13] We applied similar reaction conditions using 3 mole equivalents of trifluoroacetic acid (TFA) for the Pictet-Spengler reaction of 9 and 15 and a comparable result was obtained.[13] Thus, the reaction of 9 with 3-methyl-3-phenylthiobutanal 15 in CH_2Cl_2 in the presence of TFA at room temperature afforded the *cis* isomer 16 ($[\alpha]_D$ -98.7°)[16] and the *trans* isomer 17 ($[\alpha]_D$ +4.3°) in 58% and 31% yields, respectively. In contrast, the reaction of 10 with 15 under the similar conditions gave quite low yields of 18 and 19 and a complex reaction mixture was obtained. This may due to the lability of methoxylated indoles towards acid, although the 6-methoxy group presumably facilitated the Pictet-Spengler cyclization leading to ß-carbolines. Indeed, better results were obtained with 10 when one equivalent of TFA was used, to give 18 ($[\alpha]_D$ -93.2°) and 19 ($[\alpha]_D$ +19.5°) in 54% and 18% yields, respectively.

The relative stereochemistry of the *cis* and *trans* isomers could be readily deduced on the basis of the ^{13}C-NMR data (see Experimental Section). There is a clear upfield shift of both the carbons at 1 and 3 positions in the *trans* isomer 17 relative to the *cis* isomer 16 due to steric shielding.[18,19] Although only modest stereoselectivity was observed in the Pictet-Spengler reaction, the desired *cis* isomers were produced as the major products, which were derived from attack of the indole double bond at the C-3 position on 9 and 10, from the top face of the C=N bond,[20] resulting in the more favorable transition state having a 1,3-diequatorial conformation.

The *cis* isomers 16 and 18 were in turn condensed with trichloroethoxy-carbonyl(Troc)-L-prolyl chloride 20 in the presence of Et_3N in CH_2Cl_2 to give 21 and 22 in 99% and 92% yields, respectively. Reductive deprotection of the dipeptide 21 with Zn in refluxing MeOH resulted in the formation of the pentacycle 23 in 68% yield, indicating that deprotection of 21 was immediately followed by spontaneous cyclization. Subsequent dehydrosulfenylation of 23 afforded a mixture of the isomeric olefins 24 and 25 in 98% yield.[21] However, the reaction proceeded in undesirable fashion giving rise to the wrong isomer, the *exo* olefin 25 as the major product. The ratio of the *endo* isomer 24 to the

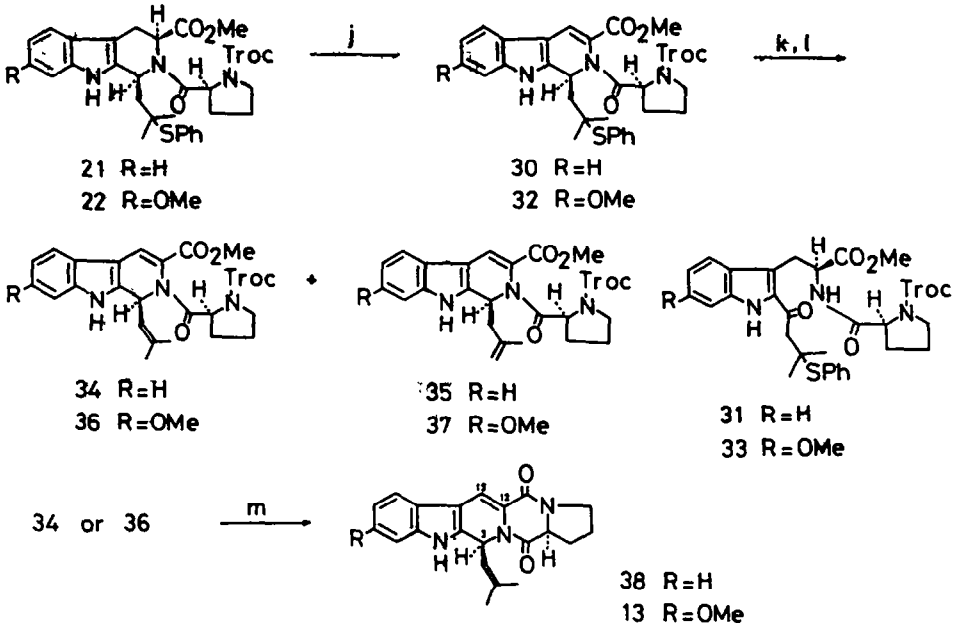
Scheme II[a]



Scheme II[a]

[a]Reagents: R=H (a) 15 (1.2 equiv), TFA (3 equiv), CH_2Cl_2, room temperature, 1 h; (b) 20 (1.2 equiv), Et_3N (1.3 equiv), CH_2Cl_2, room temperature, 2 h; (c) Zn (10 equiv) MeOH–CH_2Cl_2 (2:1), reflux, 2 h; (d) MCPBA (1.07 equiv), CH_2Cl_2, 0°C, 10 min; (e) toluene, reflux, 0.5 h; (f) $Fe_3(CO)_{12}$ (2.5 equiv), DME, reflux, 24 h; (g) NaH (2 equiv), DMF, room temperature, 45 min, *3,3-dimethylallyl bromide (1.5 equiv), DMF, room temperature*, 1 h; (h) aqueous NaOH, MeOH, reflux, 8.5 h (i) DDQ (2 equiv), CH_3CN–H_2O (7:3), room temperature, 4.5 h. R=OMe (a) 15 (1.3 equiv), TFA (1.1 equiv), CH_2Cl_2, room temperature, 1 h; (b) 20 (1.5 equiv), Et_3N (1.8 equiv), CH_2Cl_2, room temperature, 2 h.

Scheme III*



Scheme III*

*Reagents: R=H (j) DDQ (1.05 equiv), CH_2Cl_2, room temperature, 0.5 h; (k) MCPBA (1.05 equiv), $NaHCO_3$ (5 equiv), CH_2Cl_2, 0°C, 10 min; (l) toluene, reflux, 40 min; (m) Zn (10 equiv) MeOH, reflux, 65 min. R=OMe (j) Method A; DDQ (1.05 equiv), CCl_4-$CHCl_3$ (1:1), -10°C→room temperature, 110 min; Method B; DDQ (1.05 equiv), $CHCl_3$, -10°C, 80 min; (k) MCPBA (1 equiv), $NaHCO_3$ (5 equiv), CH_2Cl_2, 0°C, 15 min; (l) toluene, reflux, 50 min; (m) Zn (10 equiv), MeOH, reflux, 0.5 h.

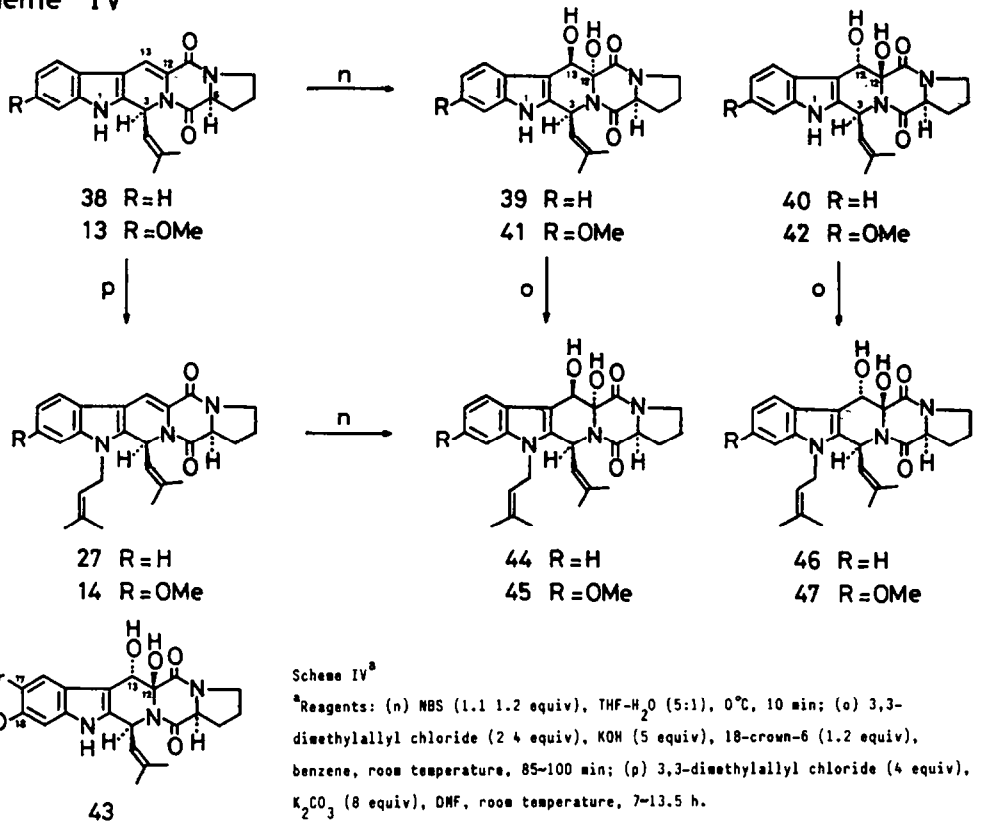
exo isomer 25 was 1:8-1:9 as evidenced by the ^{1}H-NMR analysis [C_3-H: 24, δ 6.03 (d, J=9.5Hz); 25, δ 5.48 (dd, J=4.3 and 8.9Hz)]. The isomerization[22] of 25 to 24 was carried out by treating the mixture with $Fe_3(CO)_{12}$ in refluxing DME,[26] converting the ratio to 6:1. This level of improvement of the isomeric ratio greatly facilitated the separation of 24 and 25 by fractional crystallization and chromatography and the desired 24 was isolated as a white powder in 60% yield, together with a 12% yield of 25. Prenylation of 24 with 3,3-dimethylallyl bromide gave N-prenylated derivative and no epimerization of the C-12 position was detected under these conditions. Therefore, the crude product was epimerized with NaOH in MeOH to the 12ß-isomer 26, since the 12α-isomers have been shown to resist dehydrogenation by DDQ.[13]

Dehydrogenation of the 12ß-isomer 26 in aqueous CH_3CN with DDQ (2 equiv) led to the key intermediate 27 as an inseparable mixture with the starting material 26 with a maximum yield of only 39% (estimated by the ^{1}H-NMR spectrum) despite considerable effort at optimization.

Therefore, attention was focused on a more efficient conversion of the dipeptides 21 and 22 to the key intermediates 38 and 13.

As an alternate sequence (Scheme III), we examined the dehydrogenation of the dipeptide 21 with DDQ to 30 in various solvents and the best result was obtained when CH_2Cl_2 was used. THF can also be employed as the solvent but CH_3CN and MeOH gave poor results. Reaction of 21 with DDQ (1.05 equiv) in CH_2Cl_2 afforded the corresponding dehydrogenated compound 30 in 64% yield which showed an expected UV spectrum[13] (224, 268, 284^{sh}, and 366 nm) for this unique

Scheme IV[a]



Scheme IV[a]

[a]Reagents: (n) NBS (1.1 1.2 equiv), THF-H_2O (5:1), 0°C, 10 min; (o) 3,3-dimethylallyl chloride (2 4 equiv), KOH (5 equiv), 18-crown-6 (1.2 equiv), benzene, room temperature, 85~100 min; (p) 3,3-dimethylallyl chloride (4 equiv), K_2CO_3 (8 equiv), DMF, room temperature, 7~13.5 h.

chromophore. In addition to 30, a trace amount of 1-(2-methyl-2-phenylthiopropyl)-3-methoxycarbonyl-ß-carboline[27] and 2-acylindole derivative 31 were obtained. On the other hand, in a similar reaction of 22 with DDQ in CH_2Cl_2 produced 2-acylindole 33 predominantly and 32 became the minor product. However, the yield of 32 was slightly improved when $CHCl_3$ or CCl_4-$CHCl_3$ mixture was used instead of CH_2Cl_2. Thus, treating of 22 with DDQ (1.05 equiv) in CCl_4-$CHCl_3$ mixed solvent (Method A)[28] or in $CHCl_3$ (Method B) gave 32 in 20 31% yield. This material also exhibited a characteristic UV spectrum (222, 238^{sh}, 259^{sh}, 265.5, 297, and 374 nm) corresponding to that of 30.

Oxidation of 30 with MCPBA (1 equiv) in CH_2Cl_2 followed by refluxing the diastereomeric sulfoxides in toluene without purification gave the two isomeric olefins 34 and 35 in 54% and 26% yields, respectively. However, attempted dehydrosulfenylation of 21 prior to DDQ dehydrogenation failed and 1-isobutenyl-3-methoxycarbonyl-ß-carboline[29] (31%) and a small amount of 2-acylindolic compounds were formed. Likewise, dehydrosulfenylation of 32 gave the endo-olefin 36 and the exo-olefin 37 in 51% and 18% yields, respectively. The structures of the olefins were determined by the ^{1}H-NMR spectrum after their conversion to 38 and 13. Thus, the endo-olefins 34 and 36 were reduced with Zn in refluxing MeOH, giving rise to the key intermediates 38 (mp 287°C) and 13 (mp 241-242°C) in 77% and 84% yields, respectively. The 270 MHz NMR spectrum of 38 displayed two methyl protons as two singlets (δ 1.65 and 2.02), a vinyl proton as a doublet of triplets (δ 5.26), C_3-H as a doublet (δ 6.68, J=9.8Hz), and C_{13}-H as a singlet (δ 7.35). A similar spectrum was obtained from 13, except for the aromatic

protons.

With the key intermediates 27, 38, and 13 in hand, the stage was set to carry out the dihydroxylation at the 12 and 13 positions. Initial attempts to hydroxylate model compounds by conventional methods using OsO_4, $KMnO_4$, and other oxidants failed completely.[12] However, unexpectedly, the trans-diol (12α, 13ß) 39 (Scheme IV) was formed in 65% yield, instead of the expected bromohydrin, together with the isomeric trans-diol (12ß, 13α) 40 in 30% yield, when bromination of 38 with NBS (1.1 equiv) in THF-H_2O (5:1) was carried out according to Corey's method.[30]

Mechanistic considerations led us to assign the trans stereochemistry as depicted for 39 and 40 as explained later. Further verification of the structures assigned to the trans-diols 39 and 40 followed from the spectral data (UV, IR, Mass, and ^{1}H-NMR). The UV spectrum changed to an indolic chromophore. The mass spectrum of 39 showed dehydration peaks (m/z 363 and 345) besides a molecular ion peak (m/z 381). The ^{1}H-NMR spectrum of 39 displayed the C_{12}-OH as an exchangeable doublet at δ 3.97 with J=3.1Hz, and the C_{13}-H as a doublet at δ 5.70, whereas the ^{1}H-NMR spectrum of 40 showed the C_{12}-OH peak at lower field (δ 4.47, s) and the C_{13}-OH at higher field (δ 2.40). The remarkable differences of the chemical shifts of the hydroxy groups in 39 and 40 must arise from the stereochemical interrelationships among the hydroxy groups and the carbonyl groups.[2b]

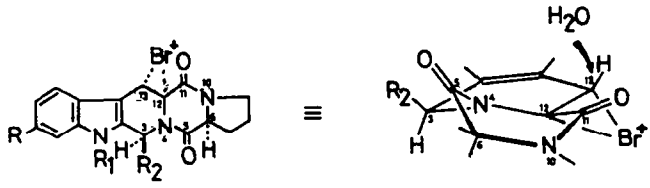
Similar treatment of 13 with NBS (1.2 equiv) gave the trans-diol (12α, 13ß) 41 (77%) accompanied with the isomeric trans-diol (12ß, 13α) 42 (10%) and the bromo-trans-diol (12ß, 13α) 43 (4%), which was formed from bromination of the activated benzene ring by the presence of 6-methoxy group.[31]

Prenylation of the diols with 3,3-dimethylallyl chloride allowed selective allylation to yield N-prenylated product even in the presence of excess chloride, whereas use of dimethylallyl bromide gave the corresponding N,O-diprenylated compound.[32] Treatment of 39 with dimethylallyl chloride (2 equiv) and KOH in the presence of 18-crown-6 in benzene readily gave demethoxy-13-epi-fumitremorgin B (44) in 84% yield. Similar treatment of 41 gave 13-epi-fumitremorgin B (45) in 65% yield. Prenylation of the minor isomer 40 under similar conditions also provided the corresponding N-prenylated compound, demethoxy-12-epi-fumitremorgin B (46) in 46% yield.

Formation of the trans-diols 39 and 41 is explained by bromine attack from the less hindered α-side to form the bromonium ion 48 (Chart II) which undergo ring opening by H_2O at the C-13 position in diaxial orientation to give the trans-bromohydrins (12α-Br, 13ß-OH) followed by spontaneous solvolysis (from the less hindered side) to give the major trans-diols 39 and 41. Alternatively, bromine attack from the unfavorable ß-side gave the minor trans-diols 40 and 42 via the corresponding bromohydrins (12ß-Br, 13α-OH).

On the other hand, 38 and 13 were prenylated prior to the hydroxylation to give 27 and 14 in 80% and 78% yields, respectively, by treating with either dimethylallyl chloride or bromide in DMF in the presence of K_2CO_3. Subsequent dihydroxylation of 27 and 14 with NBS in THF-H_2O (5:1) led to inferior yields of 44 and 45, in part due to the oxidation of the N-prenyl groups. However, the isomeric diols 46 and 47 were not formed, suggesting that the N-prenyl group is prevented the bromine attack from the ß-side.

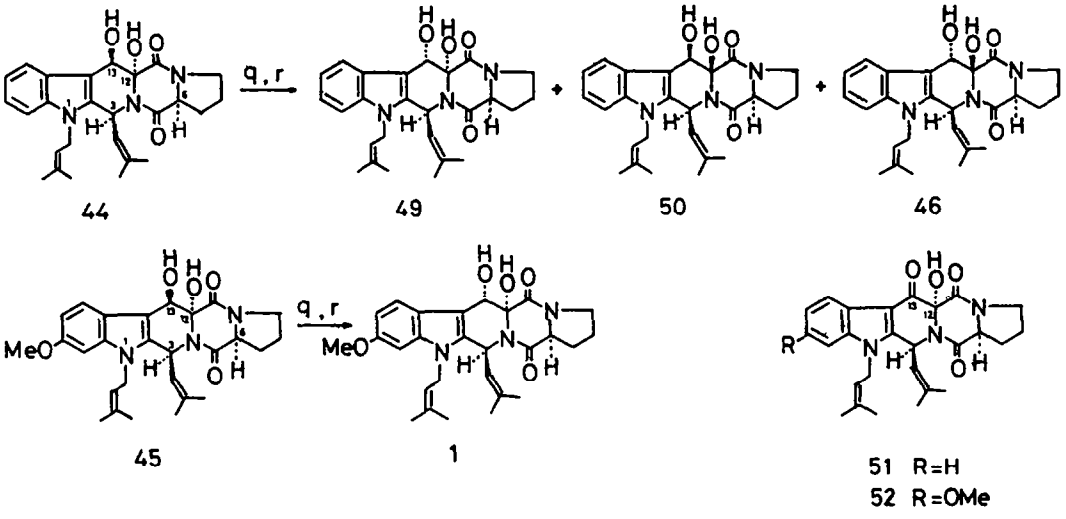
Chart II



48

R=H, OMe ; R_1=H, ⟩═⟨ ; R_2= ⟩═⟨

Scheme V[a]



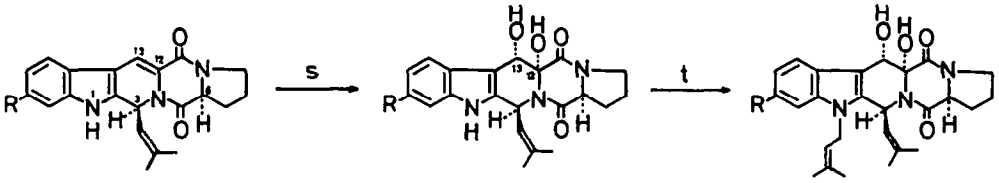
44 49 50 46

45 1 51 R=H 52 R=OMe

Scheme V[a]

[a]Reagents: (q) DDQ (3 equiv), CH_3CN-H_2O (10:1), 70°C, 80–90 min; (r) $NaBH_4$ (excess), MeOH, -10°C, 7 min.

Scheme VI[a]



38 R=H 53 R=H 49 R=H

13 R=OMe 54 R=OMe 1 R=OMe

Scheme VI[a]

[a]Reagents: (s) OsO_4 (0.14–0.15 equiv), N-methylmorpholine N-oxide (1.5 equiv), pyridine (1.1 equiv), THF-H_2O (10:1), room temperature, 4–6 h; (t) 3,3-dimethylallyl chloride (2–3 equiv), KOH (5 equiv), 18-crown-6 (1.2 equiv), benzene, room temperature, 1.5 h.

Having secured the trans configuration of the two hydroxy groups in these NBS oxidation products, we turned our attention to the conversion of the trans-diols to the corresponding α-cis-diols. Numerous efforts for this direct conversion were totally unsuccessful. Another approach was based on the oxidation of the trans-diols to the ketols (51 and 52)[33] followed by reduction with $NaBH_4$, which turned out to give the desired α-cis-diols (Scheme V).

For this purpose, we examined DDQ oxidation of 44 in various conditions.[34] Thus, the reaction of 44 with DDQ (3 equiv) in CH_3CN-H_2O (10:1) at 70°C for 90 min resulted in a complex mixture involving the desired ketol 51.[35] Without purification, the mixture was reduced with $NaBH_4$ to give the expected α-cis-diol, demethoxy FTB (49) in 4% yield. However, the major products were the ß-cis-diol 50 and the isomeric trans-diol 46 obtained in 25% and 30% yields, respectively, suggesting that undesirable epimerization at the C-12 position readily occured during oxidation and reduction.[36] The structure of demethoxy FTB (49) was confirmed by spectral data comparison with that of FTB (1). The trans-diol 46 was identical with that prepared from prenylation of 40.

Encouraged by the result of these model studies, we carried out a similar oxidation and reduction of 45 and fumitremorgin B (1) was obtained in 3% yield and the corresponding ß-cis-diol and the isomeric trans-diol were not isolated.[37] Identity of this material was established by comparison of spectral data and melting point with that of the natural product.

The fact that the overall yield of this process was disappointingly low and that is proved to be exceedingly troublesome prompted us to reinvestigate the direct OsO_4 oxidation of 38 and 13. After numerous efforts under a variety of conditions, the direct α-cis hydroxylation was achieved (Scheme VI). The reaction of 38 with catalytic OsO_4 (0.14 equiv), N-methylmorpholine N-oxide (1.5 equiv), and pyridine (1.1 equiv) in THF-H_2O (10:1) at room temperature afforded the α-cis-diol 53 in 32% yield accompanied by other oxidation products.[38] Subsequent prenylation of 53 afforded demethoxy-fumitremorgin B (49) in 72% yield, which was identical with that obtained by the previous method. The final two chemical reactions of 13, leading to fumitremorgin B (1), were performed in the analogous manner to give the expected α-cis-diol 54 in 10% yield. This was readily prenylated to give fumitremorgin B (1) in optically active form in 66% yield. The synthetic 1 was identical in all appropriate respects (mp, mmp, IR, UV, ^{1}H-NMR, and CD spectra, chromatographic mobility) with natural fumitremorgin B by direct comparison.

Efforts to refine the synthesis of 1 and to prepare analogues for biological screening and mechanism of action studies are under way.

Experimental Section

Melting points were determined with Yamato MP-1 and Yanagimoto micro melting point apparatus, and are uncorrected. UV spectra were recorded with Hitachi 323 and 340, or a Shimazu 240 spectrophotometers. IR spectra were obtained with a Hitachi 260-10 or an Analect FX-6200 FT-IR spectrophotometer. Mass spectra (MS) were recorded on a Hitachi M-60 or a JOEL JMS-HX 100 mass spectrometer. ^{1}H-NMR spectra were recorded at 270MHz with a JOEL JNM-FX 270 or a JOEL JNM-GX 270 spectrometer. ^{13}C-NMR spectra were recorded at 67.5MHz. All chemical shifts are reported downfield from an internal Me_4Si standard and given as δ values (ppm). Optical rotations were recorded with a JASCO DIP-140 polarimeter. CD spectra were taken with a JASCO J-500A polarimeter. Microanalyses were performed on a Perkin-Elmer 240 C, H, and N analyzer and a Yokokawa IC-100 ion chromatographic analyzer. Unless otherwise noted, electronic spectra (λ in nm) refer to solutions in 95% EtOH, IR spectra (ν in cm^{-1}) to KBr disks, and NMR spectra to solutions in $CDCl_3$.

N-2,2,2-Trichloroethoxycarbonyl-L-proline and its acid chloride (20). A solution of 2,2,2-trichloroethyl chloroformate (46.4 g, 210 mmol) in ether (80 ml), and 2N NaOH (105 ml) were added dropwise simultaneously to a vigorously stirred solution of L-proline (23.0 g, 200 mmol) in 2N NaOH (100 ml) and ether (40 ml) with ice-cooling over a period of 25 min. The reaction mixture was stirred for a further 10 min under ice-cooling and for 50 min at room temperature. The aqueous layer was washed with ether (100 ml), then acidified with conc. HCl to pH 1 under ice-cooling and extracted with ether (300 ml x 2). The combined ether layer was washed with water and brine, dried, and concentrated to give a colorless viscous oil (54.8 g), which was triturated with hexane to give the acid (50.4 g, 87%) as colorless crystals: mp 59-64°C; $[\alpha]_D^{28}$ -48.2° (c 0.52, MeOH); IR 3500-2500, 1720, 1415.

The acid was dissolved in excess thionyl chloride (2-3 ml to 1 g acid) at room temperature and the reaction mixture was left for overnight. Excess thionyl chloride was evaporated and dried under vaccum to leave 20 as a colorless oil quantitatively which was used without any further purification for the subsequent reaction.

Pictet-Spengler reaction of L-tryptophan methyl ester (9). Trifluoroacetic acid (17.0 g, 149 mmol) was added to a stirred solution of 9 (10.0 g, 45.8 mmol) and 15 (10.7 g, 55.0 mmol)[39] in CH_2Cl_2 (200 ml) with ice-cooling. The reaction mixture was stirred at room temperature for 1 h, then diluted with CH_2Cl_2 (200 ml) and washed with saturated $NaHCO_3$ solution (200 ml) and brine (100 ml). The organic layer was dried and concentrated to give a pale yellow caramel (22.0 g), which was chromatographed (SiO_2, 700 g; AcOEt-hexane, 1:3). First elution gave 16 (10.2 g). Second elution gave a mixture of 16 and 17 (1.9 g), which was rechromatographed (SiO_2, 100 g; the same eluent) to give 16 (0.3 g) and 17 (0.9 g). Third elution gave 17 (4.7 g). Total yields; 16 (10.5 g, 58%), 17 (5.6 g, 31%). 16: a pale yellow caramel; $[\alpha]_D^{21}$ -98.7° (c 0.46, MeOH); UV 226, 275, 283^{sh}, 291.5; IR(neat) 3380^{br}, 1730; MS m/z(rel intensity) 394(21, M^+), 229(100); ^{1}H-NMR 1.45 (3H, s, Me), 1.47 (3H, s, Me), 1.88 (1H, dd, J=7.3, 15.4 Hz, C_{10}-H), 2.03 (1H, brs, N_2-H, exchangeable), 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), 7.06-7.18 (2H, m, aromH), 7.34-7.48 (5H, m, aromH), 7.59-7.63 (2H, m, aromH), 7.83 (1H, brs, N_9-H, exchangeable); ^{13}C-NMR 25.83 (t, C-4), 28.82 and 31.30 (q, C-12 and C-13), 47.97 (t, C-10), 48.81 (s, C-11), 50.74 (d, C-1), 52.15 (q, OMe), 56.55 (d, C-3), 108.15 (s, C-4a), 110.80 (d, C-8), 117.91 (d, C-5), 119.52 (d, C-6), 121.68 (d, C-7), 127.21 (s, C-4b), 128.82 (d, C-2' and C-6'), 129.03 (d, C-4'), 131.82 (s, C-1'), 135.56 and 135.79 (s, C-8a and C-9a), 137.23 (d, C-3' and C-5'), 173.66 (s, CO). 17: a pale yellow caramel; $[\alpha]_D^{22}$ +4.3° (c 0.76, MeOH); UV 226, 274.5, 283^{sh}, 291; IR(neat) 3400^{br}, 1730; MS m/z(rel intensity) 394(24, M^+), 229(100); ^{1}H-NMR 1.42 (3H, s, Me), 1.44 (3H, s, Me), 2.01 (3H, m, C_{10}-H_2, N_2-H, exchangeable), 2.89 (1H, ddd, J=1.3, 8.2, 15.2Hz, C_4-H), 3.10 (1H, dd, J=4.8, 15.3Hz, C_4-H), 3.77 (3H, s, OMe), 3.90 (1H, dd, J=5.0, 8.6Hz, C_3-H), 4.61 (1H, t-like, C_1-H), 7.05-7.17 (2H, m, aromH), 7.33-7.47 (5H, m, aromH), 7.56-7.60 (2H, m, aromH), 7.74 (1H, brs, N_9-H, exchangeable); ^{13}C-NMR 25.19 (t, C-4), 28.82 and 30.90 (q, C-12, C-13), 47.80 (t, C-10), 49.37 (s, C-11), 48.11 (d, C-1), 52.26 (d, C-3), 52.69 (q, OMe), 107.20 (s, C-4a), 110.80 (d, C-8), 117.91 (d, C-5), 119.41 (d, C-6), 121.68 (d, C-7), 127.01 (s, C-4b), 128.77 (d, C-2' and C-6'), 128.85 (d, C-4'), 132.05 (s, C-1'), 135.71 and 135.82 (s, C-8a and C-9a), 137.00 (d, C-3' and C-5'), 174.15 (s, CO).

Pictet-Spengler reaction of 6-methoxy-L-tryptophan methyl ester (10). Trifluoroacetic acid (451 mg, 3.95 mmol) was added to a stirred solution of 10 (882 mg, 3.55 mmol) and 15 (879 mg, 4.52 mmol) in CH_2Cl_2 (20 ml) as above and after work-up a pale yellow caramel (1590 mg), which was chromatographed (SiO_2, 120 g; AcOEt-hexane, 1:2) to give 18 as a pale yellow caramel (817 mg, 54%): $[\alpha]_D^{24}$ -93.2° (c 0.69, MeOH); UV 226.5, 266, 273^{sh}, 298, 308; IR 3330^{br}, 1710, 1620; MS m/z(rel intensity) 424(11, M^+), 315(17), 259(100), 199(54); ^{1}H-NMR 1.44 (3H, s, Me), 1.46 (3H, s, Me), 1.86 (1H, dd, J=7.0, 15.3Hz, C_{10}-H), 2.04 (1H, brs, N_2-H, exchangeable), 2.17 (1H, dd, J=2.7, 15.3Hz, C_{10}-H), 2.79 (1H, ddd, J=2.7, 11.3, 15.0Hz, C_4-H), 3.06 (1H, ddd, J=1.8, 4.3, 15.0Hz, C_4-H), 3.81 (3H, s, OMe), 3.83 (3H, s, OMe), 3.74-3.85 (1H, overlapped with OMe peaks, C_3-H), 4.51 (1H, m, C_1-H), 6.77 (1H, dd, J=2.5, 8.6Hz, C_6-H), 6.79 (1H, d, J=1.8Hz, C_8-H), 7.3-7.7 (6H, m, C_5-H and PhS), 7.79 (1H, brs, N_9-H, exchangeable). 19: a pale yellow crystals (277 mg, 18%). Recrystallization from AcOEt-hexane gave colorless needles: mp 148-150°C; $[\alpha]_D^{24}$ +19.5° (c 1.05, MeOH); UV 226, 267, 272^{sh}, 298, 306^{sh}; IR 3320, 1730, 1620; MS m/z(rel intensity) 424(10, M^+), 315(14), 259(100), 199(47); ^{1}H-NMR 1.41 (3H, s, Me), 1.43 (3H, s, Me), 1.98-2.01 (2H, m, C_{10}-H_2), 2.41 (1H, brs, N_2-H, exchangeable), 2.84 (1H, ddd, J=1.5, 8.6, 15.3Hz, C_4-H), 3.05 (1H, dd, J=4.9, 15.3Hz, C_4-H), 3.76 (3H, s, OMe), 3.82 (3H, s, OMe), 3.88 (1H, dd, J=4.9, 8.5Hz, C_3-H), 4.56 (1H, t-like, J=4.5Hz, C_1-H), 6.75 (1H, dd, J=2.4, 8.2Hz, C_6-H), 6.78 (1H, d, J=1.5Hz, C_8-H), 7.31-7.60 (6H, m, C_5-H and PhS), 7.63 (1H, brs, N_9-H, exchangeable). Anal. Calcd for $C_{24}H_{28}N_2O_3S$: C, 67.90; H, 6.65; N, 6.60. Found: C, 68.03; H,

6.66; N, 6.61.

Condensation of 18 with 20 to 21. A solution of 20 (15.4 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a stirred solution of 18 (5.05 g, 12.8 mmol) and triethylamine (1.71 g, 16.9 mmol) in CH_2Cl_2 (50 ml) under ice-cooling over a period of 7 min. The reaction mixture was stirred for 30 min and allowed to warm to room temperature for 2 h, then diluted with CH_2Cl_2 and washed successively with water, saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried and concentrated to give a slightly yellow amorphous solid (9.38 g), which was purified by chromatography (SiO_2, 100 g; AcOEt-hexane, 1:2) to give 21 as a slightly yellow amorphous solid (8.44 g, 99%): $[\alpha]^{25}_D$ -88.4° (c 0.99, MeOH); UV 223, 274, 282^{sh}, 290; IR 3440^{br}, 1715, 1640; MS m/z(rel intensity) 669(1, M^++4), 667(2, M^++2), 665(2, M^+), 557(2), 555(2), 502(11), 500(12), 393(100), 311(52), 246(41), 244(44), 229(63), 169(40), 151(53), 133(24), 131(25), 70(81).

Condensation of 18 with 20 to 22. A solution of 20 (20.9 mmol) in CH_2Cl_2 (15 ml) was added (15 min) dropwise to a stirred solution of 18 (5.87 g, 13.8 mmol) and triethylamine (2.54 g, 25.1 mmol) in CH_2Cl_2 (200 ml) and treated as above to give a pale yellow amorphous solid (11.6 g), which was purified by chromatography (SiO_2, 290 g; AcOEt-hexane, 1:2) to give 22 as a pale yellow amorphous solid (8.83 g, 92%): $[\alpha]^{24}_D$ -63.8° (c 1.07, MeOH); UV 223.5, 268, 273^{sh}, 297, 306^{sh}; IR 3440^{br}, 1720, 1650^{sh}, 1630; MS m/z(rel intensity) 699(4, M^++4), 697(10, M^++2), 695(10, M^+), 532(35), 530(35), 423(85), 341(49), 313(36), 259(99), 246(45), 244(47), 199(43), 151(65), 133(31), 131(33), 70(100).

Deprotection and cyclization of 21 to 23. To a solution of 21 (8.00 g, 12.0 mmol) in MeOH-CH_2Cl_2 (2:1)(500 ml) was added Zn^{40} (7.80 g, 120 mmol). The reaction mixture was refluxed for 2 h and was filtered through Celite. Concentration under reduced pressure afforded a residue, which was dissolved in 5% aqueous HCl and was extracted with CH_2Cl_2. The combined organic layer was washed with saturated $NaHCO_3$ solution, brine, and dried, and concentrated. Crystallization of the residue (4.90 g) from MeOH afforded 23 (3.69 g) as colorless powder: mp 251-252.5°C; $[\alpha]^{22}_D$ -94.5°. Concentration of the mother liquor gave a residue (1.21 g) which was chromatographed on silica gel (30 g, AcOEt-hexane, 1:1) to give 6-epimer of 23 (0.24 g, 4%) and 23 (0.04 g). Total yield of 23, 3.73 g (68%). Recrystallization from AcOEt gave colorless needles: mp 244-245.5°C; $[\alpha]^{17}_D$ -100.5° (c 0.2, $CHCl_3$); UV (ε) 222(49600), 273(9500), 279(9300), 290(7000); IR 3310, 1670, 1650; MS m/z(rel intensity) 459(7, M^+), 294(100), 169(63); ^{1}H-NMR 0.87 (3H, s, Me), 1.27 (3H, s, Me), 1.84 (1H, dd, J=10.1, 14.0Hz, S-C-$\underline{CH}_2$), 1.94-2.07 (2H, m, C_8-H_2), 2.24 (1H, dd, J=4.3, 14.0Hz, S-C-$\underline{CH}_2$), 2.28-2.42 (2H, m, C_7-H_2), 3.14 (1H, dd, J=11.9, 15.9Hz, C_{13}-H), 3.55-3.64 (3H, m, C_9-H_2, C_{13}-H), 4.01-4.12 (2H, m, C_6-H, C_{12}-H), 5.93 (1H, dd, J=4.3, 10.1Hz, C_3-H), 7.14-7.61 (9H, m, aromH), 8.75 (1H, brs, N-H, exchangeable). Anal. Calcd for $C_{27}H_{29}N_3O_2S$: C, 70.56; H, 6.36; N, 9.14. Found: C, 70.41; H, 6.36; N, 9.02.

Dehydrosulfenylation of 23 to 25 and 24. To a solution of 23 (3.77 g, 8.21 mmol) in CH_2Cl_2 (200 ml) was added 85% MCPBA (1.78 g, 8.78 mmol) under ice-cooling. The reaction mixture was stirred for 10 min, then diluted with CH_2Cl_2 (200 ml), washed with 10% Na_2SO_3 solution, brine, dried and concentrated. The residue (4.04 g) was dissolved in toluene (110 ml), and was refluxed for 30 min, then a solution of AcOEt-hexane (2:1)(5 ml) was added to the reaction mixture. The resulting crystals were filtered to give a mixture of 24 and 25 (2.55 g) as a colorless powder. Purification of a residue (1.40 g) by chromatography (SiO_2, 60 g; AcOEt-hexane, 4:1) gave a mixture of 24 and 25 (0.27 g). Total yield of the isomers 24 and 25 (1:8-1:9), 2.82 g (98%). The ratio of 24 and 25 was obtained from ^{1}H-NMR spectrum of the above mixture [24, δ 6.04 (d); 25, δ 5.48 (dd)].

Isomerization of 25 to 24 by $Fe_3(CO)_{12}$. A mixture of 24 and 25 (2.80 g, 8.02 mmol) and $Fe_3(CO)_{12}$ (6.05 g, 12.02 mmol) in DME (200 ml) was refluxed for 4 h. Additional $Fe_3(CO)_{12}$ (4.04 g, 8.02 mmol) was added to the reaction mixture which was further refluxed for 20 h and filtered through Celite. The Celite was washed with AcOEt-hexane (4:1), CH_2Cl_2, and then MeOH. The combined organic layer was evaporated. The residue was chromatographed (SiO_2, 60 g) twice. Eluted with CH_2Cl_2 and MeOH-CH_2Cl_2 yielded a 6:1 ratio of 24 and 25 (2.71 g, 97%). Fractional crystallization from $CHCl_3$ and rechromatography gave 24 (1.69 g, 60%) as colorless powder and 25 (0.33 g, 12%). Recrystallization of 24 from MeOH gave a colorless powder: mp 288-290.5°C (dec); $[\alpha]^{24}_D$ +19.1° (c 0.11, $CHCl_3$); UV (ε) 224.5(36700), 276^{sh}(9400), 283(9800), 291(8100); IR 3260, 1640; MS m/z(rel intensity) 349(100, M^+), 294(62); ^{1}H-NMR 1.65 (3H, s, Me), 2.01 (3H, s, Me), 1.93-2.17 (2H, m, C_8-H_2), 2.25 (1H, m, C_7-H), 2.40 (1H, m, C_7-H), 3.13 (1H, dd, J=11.6, 15.9Hz, C_{13}-H), 3.55 (1H, dd, J=4.9, 15.9Hz, C_{13}-H), 3.64 (2H, m, C_9-H_2), 4.09-4.23 (2H, m, C_6-H, C_{12}-H), 4.93 (1H, dd, J=1.2, 9.5Hz, vinyl-H), 6.03 (1H, d, J=9.5Hz, C_3-H), 7.12-7.22 (2H, m, C_{17}-H, C_{18}-H), 7.35 (1H, dd, J=1.8, 6.7Hz, C_{19}-H), 7.58 (1H, d, J=6.7Hz, C_{16}-H), 7.87(1H, brs, N-H, exchangeable). Anal. Calcd for $C_{21}H_{23}N_3O_2$: C, 72.18; H, 6.63; N, 12.03. Found: C, 71.88; H, 6.69; N, 11.80. Recrystallization of 25 from MeOH-isopropyl ether gave a colorless powder: mp 243.5-245°C; UV 225, 276^{sh}, 280^{sh},

284, 291.5; IR 3270, 1650; MS m/z(rel intensity) 349(8, M^+), 294(100), 169(86); ^{1}H-NMR 1.69 (3H, s, Me), 2.02 (2H, m, C_8-H_2), 2.28 (2H, m, C_7-H and allyl-H), 2.43 (1H, m, C_7-H), 2.67 (1H, dd, J=4.0, 12.5Hz, allyl-H), 3.13 (1H, dd, J=11.8, 15.7Hz, C_{13}-H), 3.55 (1H, dd, J=5.2, 15.9Hz, C_{13}-H), 3.65 (2H, m, C_9-H_2), 4.11 (2H, m, C_6-H, C_{12}-H), 4.57 (1H, s, vinyl-H), 4.83 (1H, s, vinyl-H), 5.48 (1H, dd, J=4.3, 8.9Hz, C_3-H), 7.12-7.23 (2H, m, C_{17}-H, C_{18}-H), 7.36 (1H, d, J=6.9Hz, C_{19}-H), 7.58 (1H, d, J=7.6Hz, C_{16}-H), 8.13 (1H, brs, N-H, exchangeable). Anal. Calcd for $C_{21}H_{23}N_3O_2$: C, 72.18; H, 6.63; N, 12.03. Found: C, 71.55; H, 6.69; N, 11.71.

Prenylation of 24 to 26. To a stirred suspension of NaH (52.9% oil dispersion, 82 mg, 1.81 mmol) in DMF (1 ml) was added a solution of 24 (317 mg, 0.91 mmol) in DMF (12 ml) at room temperature under an argon atmosphere. After 45 min stirring, 3,3-dimethylallyl bromide (203 mg, 1.36 mmol) in DMF (1 ml) was added. The reaction mixture was stirred for 1 h at room temperature, quenched with saturated aqueous NH_4Cl, and then extracted with AcOEt. The combined organic layer was washed with water and brine, dried, and concentrated. The crude N-prenylated 24 (398 mg, 100%, caramel) was crystallized from AcOEt-hexane, to give 26 as colorless scales: mp 175-176°C; $[\alpha]^{24}_D$ +29.0° (c 0.10, $CHCl_3$); UV (ε) 228.5(38300), 278.5^{sh}(9200), 285(10100), 293(8800); IR 1640, 1430, 1360; MS m/z(rel intensity) 417(100, M^+), 346(48); ^{1}H-NMR 1.64 (3H, s, Me), 1.68 (3H, s, Me), 1.85 (3H, s, Me), 2.02 (3H, s, Me), 2.0 (2H, m, C_8-H_2), 2.3 (1H, m, C_7-H), 2.4 (1H, m, C_7-H), 3.14 (1H, dd, J=11.8, 15.7Hz, C_{13}-H), 3.56-3.66 (3H, m, C_9-H_2, C_{13}-H), 4.13 (2H, m, C_6-H, C_{12}-H), 4.63 (2H, d-like, C_{21}-H_2), 4.85 (1H, d, J=10.1Hz, C_{26}-H), 5.07 (1H, t-like, C_{22}-H), 6.14 (1H, d, J=10.1Hz, C_3-H), 7.10-7.26 (3H, m, C_{17}-H, C_{18}-H, C_{19}-H), 7.58 (1H, d, J=6.7Hz, C_{16}-H). Anal. Calcd for $C_{26}H_{31}N_3O_2$: C, 74.79; H, 7.48; N, 10.06. Found: C, 74.53; H, 7.49; N, 9.86.

A solution of N-prenylated 24 (42 mg, 0.10 mmol) in MeOH (10 ml) and 0.1N NaOH (1 ml) was refluxed for 8.5 h. After being quenched with AcOH, the solvent was evaporated. The residue was taken up with CH_2Cl_2. Work-up in usual manner gave 26 (44 mg, 100%) as a colorless waxy solid: ^{1}H-NMR 1.70 (3H, s, Me), 1.76 (3H, s, Me), 1.82 (3H, s, Me), 1.92 (3H, s, Me), 1.92-2.08 (3H, m, C_7-H, C_8-H_2), 2.47 (1H, m, C_7-H), 2.96 (1H, dd, J=12.6, 15.0Hz, C_{13}-H), 3.36 (1H, dd, J=4.3, 15.3Hz, C_{13}-H), 3.82 (1H, m, C_9-H), 3.76 (1H, m, C_9-H), 4.10 (1H, dd, J=5.8, 9.8Hz, C_6-H), 4.45 (1H, dd, J=4.3, 12.2Hz, C_{12}-H), 4.57 (2H, d, J=6.4Hz, C_{21}-H_2), 5.12 (1H, t-like, C_{22}-H), 5.36 (1H, d, J=8.9Hz, C_{26}-H), 6.51 (1H, d, J=8.9Hz, C_3-H), 7.07-7.26 (3H, m, C_{17}-H, C_{18}-H, C_{19}-H), 7.46 (1H, d, J=7.6Hz, C_{16}-H).

Dehydrogenation of 26 by DDQ to 27. A mixture of 26 (110 mg, 0.26 mmol) and DDQ (122 mg, 0.52 mmol) in CH_3CN-H_2O (7:3)(10 ml) was stirred for 4.5 h at room temperature and the solvent was evaporated. Chromatography of the residue on a short alumina column and elution with CH_2Cl_2 yielded a mixture of 27 and 26 (79 mg), which was rechromatographed (SiO_2, 10 g; AcOEt-hexane, 2:1) to give a 58:42 ratio of 27 and 26 (73 mg). Complete separation of 27 and 26 was unsuccessful. The ratio of 27 (39%) and 26 (29%) was determined by the ^{1}H-NMR spectrum, [C_{26}-H :27, δ 5.22 (d); 26, 5.36(d). C_3-H: 27, δ 6.71 (d); 26, 6.51(d). C_{16}-H: 27, δ 7.66 (m); 26, 7.46 (d)]. The yields were obtained based on the ratio.

Dehydrogenation of 21 to 30. DDQ (13.3 g, 57.6 mmol) was added at once to a stirred solution of 21 (36.6 g, 54.9 mmol) in CH_2Cl_2 (280 ml). The reaction mixture was stirred at room temperature for 30 min, then passed through a column (Al_2O_3, 100 g; CH_2Cl_2 and AcOEt). The filtrate was concentrated to give a red brown amorphous solid (31.1 g), which was chromatographed (SiO_2, 700 g; AcOEt-hexane, 1:2). First elution gave a dehydrogenated product 30 (23.3 g, 64%) as a red brown amorphous solid: UV 224, 268, 284^{sh}, 366; IR 3440^{br}, 1710, 1650^{sh}, 1620^{sh}, 1600^{sh}; MS m/z(rel intensity) 665(1, M^++2), 663(1, M^+), 500(4), 498(4), 391(9), 246(22), 244(23), 227(100), 195(8), 168(16), 133(12), 131(13), 70(34). Second elution gave a small amount of a mixture of unkown products. Third elution gave an oxidative cleavage product 31 (10%) as a pale yellow amorphous solid: UV 215, 239, 319; IR 3420^{br}, 1720, 1650; MS m/z(rel intensity) 683(1, M^++2), 681(1, M^+), 573(2), 571(2), 283(28), 246(14), 244(15), 225(65), 212(100), 184(28), 170(27), 110(31), 83(56), 70(62).

Dehydrogenation of 22 to 32. Method A: DDQ (1.93 g, 8.33 mmol) was added to a solution of 22 (5.52 g, 7.92 mmol) in CCl_4 (25 ml) under an argon atmosphere. The resulting mixture was stirred at room temperature for 10 min, then cooled under an ice-salt bath. Chilled $CHCl_3$ (25 ml) was added *via* syringe into the reaction mixture, which was stirred at the same temperature for 60 min, at 0°C for 30 min, and at room temperature for 20 min. Alumina (17 g) was added to the reaction mixture, which was filted and washed with $CHCl_3$ in several times. Evaporation of the combined filtrate gave a red brown amorphous solid (5.27 g), which was chromatographed (SiO_2, 150 g; AcOEt-hexane, 1:2). First elution gave a dehydrogenated product 32 (1.29 g, 23%) as a red brown amorphous solid: UV 222, 238^{sh}, 259^{sh}, 265.5, 297, 374; IR 3430^{br}, 1710, 1620, 1600^{sh}; MS m/z(rel intensity) 695(1, M^++2), 693(1, M^+), 530(3), 528(3), 421(6), 257(100), 255(11), 198(16), 133(13), 131(14), 70(42). Second elution gave recovered 22 as a red brown amorphous solid (1.21 g, 22%). Third elution

gave an oxidative cleavage product 33 (1.15 g, 20%) as a brown amorphous solid: UV 219, 261, 269^{sh}, 343; IR 3420^{br}, 1720, 1650^{sh}, 1630; MS m/z(rel intensity) 713(2, M^++2), 711(2, M^+), 603(6), 601(6), 313(22), 255(60), 242(77), 214(41), 200(22), 110(100), 83(75), 70(70).

Method B: DDQ (2.40 g, 10.4 mmol) was added at once to a solution of 22 (6.88 g, 9.87 mmol) in $CHCl_3$ (30 ml) with ice-salt cooling under an argon atmosphere. The mixture was stirred at same temperature for 80 min. The starting material 22 was disappeared on a TLC plate (SiO_2; AcOEt-hexane, 1:2). The reaction mixture was passed through a short column of alumina and the filtrate was concentrated to give a dark red brown amorphous solid (6.79 g), which was chromatographed (SiO_2, 200 g; AcOEt-hexane, 1:2). First elution gave a dehydrogenated product 32 (2.09 g, 31%) as a red brown amorphous solid. Other elution gave more polar products; unknown products and an oxidative cleavage product 33.

Dehydrosulfenylation of 30 to 34 and 35. 85% MCPBA (0.73 g, 3.60 mmol) was added portionwise slowly to a stirred suspension of 30 (2.28 g, 3.43 mmol) and $NaHCO_3$ (1.44 g, 17.1 mmol) in CH_2Cl_2 (30 ml) under ice-cooling. The reaction mixture was stirred for 10 min, then diluted with CH_2Cl_2 (200 ml), washed successively with water, saturated $NaHCO_3$ solution, water, brine, dried, and concentrated. The residue (2.28 g) was dissolved in toluene (50 ml), which was refluxed for 40 min and then concentrated. The mixture was chromatographed (SiO_2, 100 g; AcOEt-hexane, 1:2) twice to give 34 (1.03 g, 54%)(more polar isomer) and 35 (0.49 g, 26%)(less polar isomer). 34: a pale red brown amorphous solid; UV 231.5, 266, 278^{sh}, 284^{sh}, 364; IR 3440^{br}, 1710, 1650^{sh}, 1620, 1600^{sh}; MS m/z(rel intensity) 553(2, M^++3), 553(2, M^++1), 406(2), 309(9), 281(100), 246(30), 244(31), 227(38), 167(14), 133(23), 131(24), 114(11), 95(11), 70(61). 35: a pale yellow brown amorphous solid, which was crystallized from isopropyl ether to give pale yellow crystals: mp 215-216°C; UV 231, 265.5, 278^{sh}, 284^{sh}, 364; IR 3440^{br}, 1710, 1650, 1620, 1600^{sh}; MS m/z(rel intensity) 500(4), 498(4), 281(6), 248(11), 246(31), 244(33), 227(100), 195(15), 168(21), 167(19), 133(18), 131(19), 114(8), 95(7), 70(44). Anal. Calcd for $C_{25}H_{26}Cl_3N_3O_5$: C, 54.12; H, 4.72; N, 7.57; Cl, 19.17. Found: C, 53.66; H, 4.56; N, 7.62; Cl, 18.92.

Dehydrosulfenylation of 32 to 36 and 37. 85% MCPBA (0.40 g, 1.98 mmol) was added portionwise slowly to a stirred suspension of 32 (1.38 g, 1.98 mmol) and $NaHCO_3$ (0.83 g, 9.88 mmol) in CH_2Cl_2 (30 ml) as above and the similar treatment gave a diastereomeric mixture of sulfoxides (1.05 g) as a pale yellow amorphous solid, which was dissolved in toluene (30 ml) and the mixture was refluxed for 50 min and then concentrated. The mixture was chromatographed (SiO_2, 50 g; AcOEt-hexane, 2:3) twice to give 36 (0.59 g, 51%)(more polar isomer) and 37 (0.21 g, 18%)(less polar isomer). 36: a pale yellow amorphous solid; UV 234, 266.5, 298.5, 374; IR 3440^{br}, 1710, 1630, 1600^{sh}; MS m/z(rel intensity) 585(5, M^++3), 583(5, M^++1), 436(4), 339(45), 311(100), 257(68), 246(41), 244(42), 197(18), 133(33), 131(35), 114(15), 95(17), 70(92). 37: a pale yellow amorphous solid, which was crystallized from isopropyl ether to give pale yellow crystals: mp 202-203°C; UV 233.5, 265.5, 298.5, 373; IR 3440^{br}, 1710, 1650^{sh}, 1630, 1600^{sh}; MS m/z(rel intensity) 530(5), 528(5), 311(8), 257(100), 248(9), 246(25), 244(26), 225(15), 198(27), 197(18), 133(18), 131(19), 114(8), 95(9), 70(47). Anal. Calcd for $C_{26}H_{28}Cl_3N_3O_6$: C, 53.39; H, 4.83; N, 7.18; Cl, 18.18. Found: C, 53.14; H, 4.78; N, 7.19; Cl, 18.30.

Deprotection and cyclization of 34 to 38. To a solution of 34 (900 mg, 1.62 mmol) in MeOH (25 ml) was added Zn dust[40] (1060 mg, 16.2 mmol) and the mixture was refluxed for 65 min. The hot solution was filtered on Celite and washed with hot MeOH. The combined MeOH was concentrated and treated with CH_2Cl_2-5% aqueous HCl. The CH_2Cl_2 layer was washed successively with 5% aqueous HCl, water, saturated $NaHCO_3$ solution, brine, dried, and concentrated. The crystalline solid was washed with AcOEt-isopropyl ether to give 38 (433 mg, 77%) as pale yellow crystals. Recrystallization from $CHCl_3$ gave pale yellow crystals: mp 287°C (dec); $[\alpha]_D^{24}$ +253.8° (c 0.34, $CHCl_3$); UV (ε) 234(28100), 262^{sh}(15100), 282^{sh}(13700), 369(16300); IR 3200, 1670, 1640, 1605; MS m/z(rel intensity) 347(92, M^+), 292(30), 264(71), 250(100), 222(36), 221(28), 207(33), 206(26), 205(22), 195(86), 167(83); ^{1}H-NMR 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, vinyl-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, brs, NH, exchangeable). Anal. Calcd for $C_{21}H_{21}N_3O_2$: C, 72.60; H, 6.09; N, 12.10. Found: C, 72.22; H, 6.13; N, 11.96.

Deprotection and cyclization of 36 to 13. A solution of 36 (90 mg, 0.154 mmol) in MeOH (4 ml) was treated with Zn dust[40] (102 mg, 1.56 mmol) for 30 min as above. The similar work-up followed by chromatography (SiO_2, 10 g; AcOEt-hexane, 2:1) gave 13 (49 mg, 84%) as pale yellow crystals. Recrystallization from AcOEt gave pale yellow crystals: mp 241-242°C (dec); $[\alpha]_D^{24}$ +313.2° (c 0.15, $CHCl_3$); UV (ε) 234(25400), 267(16400), 299(14000), 377.5(13500); IR 3400^{br}, 1675, 1640^{sh}, 1600; MS m/z(rel intensity) 377(74, M^+), 322(33), 294(49), 280(100), 252(37), 251(25), 237(35), 236(16), 225(79), 197(95);

^{1}H-NMR 1.64 (3H, s, Me), 1.99 (3H, s, Me), 1.8-2.2 (3H, m, C_7-H, C_8-H_2), 2.40 (1H, m, C_7-H), 3.66-3.91 (2H, m, C_9-H_2), 3.82 (3H, s, OMe), 4.13 (1H, m, C_6-H), 5.24 (1H, d-like, J=9.6Hz, vinyl-H), 6.63 (1H, d, J=9.9Hz, C_3-H), 6.82-6.85 (2H, m, C_{17}-H, C_{19}-H), 7.29 (1H, s, C_{13}-H), 7.55 (1H, d-like, J=9.6Hz, C_{16}-H), 8.28 (1H, brs, NH, exchangeable).

Reaction of 38 with NBS. Formation of trans-diols 39 and 40. NBS (59 mg, 0.334 mmol) was added to a stirred solution of 38 (105 mg, 0.302 mmol) in THF-H_2O (5:1)(35 ml) under ice-cooling. The reaction mixture was stirred for 10 min at the same temperature, quenched with 10% aqueous Na_2SO_3 (20 ml), and extracted with CH_2Cl_2 (40 ml). The CH_2Cl_2 layer was washed with brine, dried, and concentrated. The residue (144 mg) was chromatographed (SiO_2, 10 g; CH_2Cl_2-acetone, 10:1) to give 39 (75 mg, 65%) as a less polar isomer and 40 (35 mg, 30%) as a more polar isomer. Recrystallization of 39 from isopropanol-isopropyl ether gave colorless cotton-like needles: mp 231-232°C; UV 222, 273, 278, 282.5, 290; IR 3420, 3350, 1655, 1635; MS m/z(rel intensity) 381(2, M^+), 363(2), 346(2), 345(5), 213(100), 170(66), 168(18), 167(22), 157(85), 129(24); ^{1}H-NMR 1.66 (3H, s, Me), 2.02 (3H, s, Me), 1.84-2.15 (3H, m, C_7-H, C_8-H_2), 2.45 (1H, m, C_7-H), 2.72 (1H, s, C_{12}-OH, exchangeable), 3.50-3.68 (2H, m, C_9-H_2), 3.97 (1H, d, J=3.1Hz, C_{13}-OH, exchangeable), 4.41 (1H, dd, J=6.7, 9.5Hz, C_6-H), 5.23 (1H, d, J=9.5Hz, vinyl-H), 5.70 (1H, d, J=2.8Hz, C_{13}-H), 6.01 (1H, d, J=9.5Hz, C_3-H), 7.17-7.25 (2H, m, C_{17}-H, C_{18}-H), 7.34-7.38 (1H, m, C_{19}-H), 7.71 (1H, m, C_{16}-H), 8.14 (1H, brs, NH, exchangeable). Recrystallization of 40 from isopropanol-isopropyl ether gave slightly yellow cotton-like needles: mp 212-216°C; UV 222, 273, 278, 289; IR 3380^{br}, 1660; MS m/z(rel intensity) 381(9, M^+), 213(37), 170(35), 157(34),149(62), 137(20), 129(24); ^{1}H-NMR 1.79 (3H, s, Me), 2.04 (3H, s, Me), 1.86-2.10 (3H, m, C_7-H, C_8-H_2), 2.40-2.50 (1H, m, C_7-H), 2.40 (1H, overlapped with C_7-H, C_{13}-OH, exchangeable), 3.57-3.79 (2H, m, C_9-H_2), 4.38 (1H, dd, J=6.6, 10.2Hz, C_6-H), 4.47 (1H, s, C_{12}-OH, exchangeable), 5.13 (1H, brs, C_{13}-H), 5.59 (1H, d, J=9.8Hz, vinyl-H), 6.67 (1H, d, J=9.8Hz, C_3-H), 7.11-7.22 (2H, m, C_{17}-H, C_{18}-H), 7.34 (1H, dd, J=1.8, 7.0Hz, C_{19}-H), 7.59 (1H, dd, J=1.5, 7.0Hz, C_{16}-H), 7.94 (1H, brs, NH, exchangeable).

Reaction of 13 with NBS. Formation of trans-diols 41, 42 and 43. NBS (12.0 mg, 0.067 mmol) was added to a stirred solution of 13 (21.0 mg, 0.056 mmol) in THF-H_2O (5:1)(5 ml) under ice-cooling. The reaction mixture was treated as above to give a residue (29.3 mg), which was separated by preparative TLC (SiO_2; CH_2Cl_2-acetone, 5:1, twice) to give 41 (17.7 mg, 77%), 42 (2.3 mg, 10%), and 43 (1.2 mg, 4%). Recrystallization of 41 from AcOEt gave colorless cotton-like needles: mp 224-226°C; UV 222.5, 260^{sh}, 268.5, 297, 304^{sh}; IR 3410, 3300^{sh}, 1655, 1635; MS m/z(rel intensity) 411(8, M^+), 393(2), 375(7), 356(3), 243(85), 200(100), 187(46), 159(24); ^{1}H-NMR 1.67 (3H, s, Me), 2.03 (3H, s, Me), 1.89-2.21 (3H, m, C_7-H, C_8-H_2), 2.46 (1H, m, C_7-H), 2.69 (1H, s, C_{12}-OH, exchangeable), 3.59-3.76 (2H, m, C_9-H_2), 3.83 (3H, s, OMe), 3.91 (1H, d, J=3.1Hz, C_{13}-OH, exchangeable), 4.41 (1H, dd, J=6.7, 9.2Hz, C_6-H), 5.23 (1H, d, J=9.2Hz, vinyl-H), 5.64 (1H, d, J=3.1Hz, C_{13}-H), 5.96 (1H, d, J=9.2Hz, C_3-H), 6.85 (1H, dd, J=1.8, 7.5Hz, C_{17}-H), 6.87 (1H, d, J=1.8Hz, C_{19}-H), 7.55 (1H, d, J=7.6Hz, C_{16}-H), 7.80 (1H, brs, NH, exchangeable). 42: colorless crystals: UV 224, 261.5, 268^{sh}, 296, 303^{sh}; MS m/z(rel intensity) 411(22, M^+), 356(5), 243(42), 200(100), 187(28), 159(15); ^{1}H-NMR 1.79 (3H, s, Me), 2.04 (3H, s, Me), 1.90-2.17 (3H, m, C_7-H, C_8-H_2), 2.29 (1H, brs, C_{13}-OH, exchangeable), 2.47 (1H, m, C_7-H), 3.61-3.79 (2H, m, C_9-H_2), 3.82 (3H, s, OMe), 4.39 (1H, dd, J=6.1, 10.7Hz, C_6-H), 4.43 (1H, s, C_{12}-OH, exchangeable), 5.09 (1H, brs, C_{13}-H), 5.59 (1H, d, J=9.8Hz, vinyl-H), 6.64 (1H, d, J=9.8Hz, C_3-H), 6.80 (1H, dd, J=2.1, 8.5Hz, C_{17}-H), 6.85 (1H, d, J=1.8Hz, C_{19}-H), 7.45 (1H, d, J=8.5Hz, C_{16}-H), 7.83 (1H, brs, NH, exchangeable). 43: a colorless solid: UV 224.5, 267, 303, 312^{sh}; MS m/z(rel intensity) 491(16, M^++2), 489(16, M^+), 436(6), 434(7), 323(33), 321(36), 280(61), 278(66), 111(17), 109(13), 105(14), 43(100); ^{1}H-NMR 1.79 (3H, s, Me), 2.04 (3H, s, Me), 1.90-2.18 (3H, m, C_7-H, C_8-H_2), 2.23 (1H, brs, C_{13}-OH, exchangeable), 2.50 (1H, m, C_7-H), 3.63-3.79 (2H, m, C_9-H_2), 3.88 (3H, s, OMe), 4.41 (1H, dd, J=6.1, 10.4Hz, C_6-H), 4.46 (1H, s, C_{12}-OH, exchangeable), 5.04 (1H, brs, C_{13}-H), 5.58 (1H, d, J=9.7Hz, vinyl-H), 6.60 (1H, d, J=9.5Hz, C_3-H), 6.90 (1H, s, C_{19}-H), 7.74 (1H, s, C_{16}-H), 7.88 (1H, brs, NH, exchangeable).

Prenylation of 39.--- Desethoxy-13-epi-fumitremorgin B (44). Benzene (3 ml) was added via syringe to the mixture of 39 (30 mg, 0.079 mmol), 96% powdered KOH (23 mg, 0.394 mmol), and 18-crown-6 (25 mg, 0.095 mmol) under an argon atmosphere and the mixture was stirred for 5 min. To which was added a solution of 3,3-dimethylallyl chloride (17 mg, 0.163 mmol) in benzene (1 ml) and the mixture was stirred for 85 min. After dilution with CH_2Cl_2, the mixture was washed with water and brine, dried, and concentrated. The crystalline solid was covered with hot AcOEt to give 44 as colorless cotton-like needles (30 mg, 84%): mp 254°C (dec); UV 225, 276^{sh}, 283.5, 292; IR 3440, 1660, 1630; MS m/z(rel intensity) 449(13, M^+), 431(6), 415(6), 281(100), 238(43), 225(26), 212(44), 210(39), 184(39), 170(22), 168(26), 167(21), 157(23); ^{1}H-NMR 1.67 (3H, s, Me), 1.70 (3H, s, Me), 1.86 (3H, s, Me), 2.04 (3H, s, Me), 1.90-2.20 (3H, m, C_7-H, C_8-H_2), 2.43-2.50 (1H, m, C_7-H), 2.71 (1H, s, C_{12}-OH, exchangeable), 3.68 (2H, dd, J=4.5, 9.1Hz, C_9-H_2), 4.00 (1H, d, J=3.1Hz, C_{13}-OH,

exchangeable), 4.45 (1H, dd, J=7.0, 9.8Hz, C_6-H), 4.66 (2H, d-like, J=6.1Hz, C_{21}-H_2), 5.06 (1H, t-like, C_{22}-H), 5.25 (1H, d-like, J=10.1Hz, C_{26}-H), 5.72 (1H, d, J=3.1Hz, C_{13}-H), 6.09 (1H, d, J=10.1Hz, C_3-H), 7.16-7.29 (3H, m, C_{17}-H, C_{18}-H, C_{19}-H), 7.71 (1H, dd, J=2.4, 6.4Hz, C_{16}-H).

Prenylation of 40.--- Demethoxy-12-epi-fumitremorgin B (46). The similar prenylation of 40 (50 mg, 0.131 mmol) with 3,3-dimethylallyl chloride (28 mg, 0.268 mmol) in the presence of KOH (39 mg, 0.667 mmol) and 18-crown-6 (42 mg, 0.159 mmol) gave demethoxy-12-epi-fumitremorgin B 46 (28 mg, 46%). Recrystallization of 46 from AcOEt-isopropylether-hexane gave colorless cotton-like needles: mp 206-207°C; UV 225, 275, 282, 291; IR 3440^{br}, 1660; MS m/z(rel intensity) 449(25, M^+), 431(8), 415(15), 281(100), 238(63), 225(21), 212(37), 210(35), 194(26), 184(44), 183(31), 182(56), 170(29), 168(56), 167(50), 157(21); ^{1}H-NMR 1.71 (3H, s, Me), 1.77 (3H, s, Me), 1.82 (3H, s, Me), 2.00 (3H, s, Me), 1.96 (1H, d, J=4.6Hz, C_{13}-OH, exchangeable), 1.7-2.1 (3H, m, C_7-H, C_8-H_2), 2.48 (1H, m, C_7-H), 3.61-3.77 (2H, m, C_9-H_2), 4.38 (1H, dd, J=5.9, 10.9Hz, C_6-H), 4.47 (1H, s, C_{12}-OH, exchangeable), 4.55-4.74 (2H, m, C_{21}-H_2), 5.13 (1H, partially overlapped with C_{13}-H, C_{22}-H), 5.14 (1H, d, J=5.0Hz, C_{13}-H), 5.59 (1H, d, J=9.6Hz, C_{26}-H), 6.77 (1H, d, J=9.9Hz, C_3-H), 7.05-7.34 (3H, m, C_{17}-H, C_{18}-H, C_{19}-H), 7.59 (1H, d-like, J=6.9Hz, C_{16}-H).

Prenylation of 41.--- 13-Epi-fumitremorgin B (45). Benzene (5 ml) was added via syringe to the mixture of 41 (58 mg, 0.141 mmol), 96% powdered KOH (42 mg, 0.719 mmol), and 18-crown-6 (45 mg, 0.170 mmol) under an argon atmosphere and the mixture was stirred for 2 min. A solution of 3,3-dimethylallyl chloride (30 mg, 0.287 mmol) in benzene (1 ml) was added and the reaction mixture was stirred for 100 min. Usual work-up as above gave 45 (44 mg, 65%). Recrystallization of 45 from AcOEt gave colorless cotton-like needles: mp 226-227°C; UV 226, 265^{sh}, 275, 297.5, 305^{sh}; IR 3430^{br}, 1660, 1630; MS m/z(rel intensity) 479(23, M^+), 462(2), 461(6), 445(4), 443(2), 311(100), 268(59), 242(25), 240(22), 214(26), 212(21), 200(34), 198(18), 187(14) ; ^{1}H-NMR 1.66 (3H, s, Me), 1.70 (3H, s, Me), 1.87 (3H, s, Me), 2.03 (3H, s, Me), 1.80-2.21 (3H, m, C_7-H, C_8-H_2), 2.43-2.52 (1H, m, C_7-H), 2.74 (1H, s, C_{12}-OH, exchangeable), 3.67 (2H, dd, J=4.5, 9.1Hz, C_9-H_2), 3.85 (3H, s, OMe), 3.97 (1H, d, J=3.1Hz, C_{13}-OH, exchangeable), 4.44 (1H, dd, J=7.0, 9.8Hz, C_6-H), 4.59 (2H, d-like, J=6.1Hz, C_{21}-H_2), 5.05 (1H, t-like, C_{22}-H), 5.22 (1H, d, J=10.1Hz, C_{26}-H), 5.66 (1H, d, J=3.1Hz, C_{13}-H), 6.04 (1H, d, J=9.8Hz, C_3-H), 6.73 (1H, d, J=2.1Hz, C_{19}-H), 6.85 (1H, dd, J=2.1, 8.6Hz, C_{17}-H), 7.57 (1H, d, J=8.6Hz, C_{16}-H).

Prenylation of 38 to 27. A solution of 3,3-dimethylallyl chloride (360 mg, 3.44 mmol) in DMF (1 ml) was added to a stirred suspension of 38 (300 mg, 0.864 mmol) and powdered K_2CO_3 (960 mg, 6.95 mmol) in DMF (10 ml). The reaction mixture was stirred at room temperature for 7 h, and was diluted with AcOEt. Similar work-up gave a residue (365 mg) was purified by chromatography (SiO_2, 15 g; CH_2Cl_2-acetone, 10:1) to give 27 as a pale yellow amorphous solid (288 mg, 80%): UV 239, 261^{sh}, 285^{sh}, 373; IR 1665, 1605; MS m/z(rel intensity) 415(100, M^+), 360(82), 346(17), 332(52), 318(34), 263(72), 235(32), 221(26), 206(24), 205(25), 193(21), 167(30), 166(26); ^{1}H-NMR 1.65 (3H, s, Me), 1.71 (3H, s, Me), 1.86 (3H, s, Me), 2.01 (3H, s, Me), 1.8-2.0 (3H, m, C_7-H, C_8-H_2), 2.42 (1H, m, C_7-H), 3.63-3.79 (2H, m, C_9-H_2), 4.13 (1H, dd, J=6.4, 9.8Hz, C_6-H), 4.63 (2H, d-like, J=5.8Hz, C_{21}-H_2), 5.10 (1H, t-like, C_{22}-H), 5.22 (1H, d, J=10.1Hz, C_{26}-H), 6.70 (1H, d, J=10.4Hz, C_3-H), 7.17-7.26 (3H, m, C_{17}-H, C_{18}-H, C_{19}-H), 7.37 (1H, s, C_{13}-H), 7.66 (1H, dd-like, C_{16}-H).

Prenylation of 13 to 14. A solution of 3,3-dimethylallyl chloride (103 mg, 0.985 mmol) in DMF (1 ml) was added to a stirred suspension of 13 (93 mg, 0.246 mmol) and powdered K_2CO_3 (280 mg, 2.03 mmol) in DMF (3 ml). The reaction mixture was stirred at room temperature for 13.5 h. Usual work-up as above gave 14 as a pale yellow amorphous solid (86 mg, 78%): UV 238.5, 270.5, 299.5, 381; IR 1670, 1650^{sh}, 1610; MS m/z(rel intensity) 445(100, M^+), 390(67), 376(30), 362(32), 348(59), 293(73), 265(41), 251(52), 236(37), 235(26), 223(24), 197(32), 196(26); ^{1}H-NMR 1.64 (3H, s, Me), 1.72 (3H, s, Me), 1.87 (3H, s, Me), 2.00 (3H, s, Me), 1.8-2.2 (3H, m, C_7-H, C_8-H_2), 2.42 (1H, m, C_7-H), 3.63-3.78 (2H, m, C_9-H_2), 3.85 (3H, s, OMe), 4.12 (1H, dd, J=6.4, 9.8Hz, C_6-H), 4.57 (2H, d-like, J=5.8Hz, C_{21}-H_2), 5.10(1H, m, C_{22}-H), 5.16(1H, d-like, J=10.1Hz, C_{26}-H), 6.67 (1H, d, J=10.1Hz, C_3-H), 6.72 (1H, d, J=2.4Hz, C_{19}-H), 6.85 (1H, dd, J=2.1, 8.6Hz, C_{17}-H), 7.31 (1H, s, C_{13}-H), 7.53 (1H, d, J=8.5Hz, C_{16}-H).

Conversion of demethoxy-13-epi-fumitremorgin B (44) to demethoxy-fumitremorgin B (49). DDQ (95 mg, 0.410 mmol) was added to a stirred suspension of 44 (92 mg, 0.205 mmol) in CH_3CN-H_2O (10:1)(15 ml) and the mixture was heated at 70°C. After 60 min DDQ (47 mg, 0.202 mmol) was added to the reaction mixture, which was heated at 70°C for 30 min and passed through a short column on neutral alumina (elution with THF and CH_2Cl_2) and the elution was concentrated. The residue was dissolved in MeOH (1 ml) and cooled under an ice-salt bath. Excess $NaBH_4$ was added and the whole was stirred for 7 min and diluted with CH_2Cl_2. Usual work-up gave a residue which was separated by preparative TLC (SiO_2; AcOEt-hexane, 3:1) to give 49 (4 mg, 4%), 50 (23 mg, 25%), 46 (28 mg, 30%), and the unknown product (8 mg). Recrystallization of 49 from MeOH

gave colorless needles: mp 210-211°C; UV 227.5, 277, 283.5, 293; MS m/z(rel intensity) 449(14, M^+), 432(11), 431(5), 415(5), 323(34), 290(16), 281(100), 238(38), 225(20), 212(37), 210(33), 184(36), 182(20), 170(22), 168(27), 167(23), 157(19); ^{1}H-NMR 1.63 (3H, s, Me), 1.69 (3H, s, Me), 1.84 (3H, s, Me), 2.00 (3H, s, Me), 1.8-2.2 (3H, m, C_7-H, C_8-H_2), 2.46 (1H, m, C_7-H), 3.65 (2H, dd, J=4.9, 8.9Hz, C_9-H_2), 4.03 (1H, brs, C_{12}-OH, exchangeable), 4.46 (1H, dd, J=7.3, 9.8Hz, C_6-H), 4.60 (2H, d-like, J=5.8Hz, C_{21}-H_2), 4.71 (1H, d, J=10.1Hz, C_{26}-H), 4.74 (1H, d, J=2.7Hz, C_{13}-OH, exchangeable), 5.04 (1H, t-like, C_{22}-H), 5.81 (1H, d, J=2.8Hz, C_{13}-H), 6.01 (1H, d, J=10.1Hz, C_3-H), 7.10-7.25 (3H, m, C_{17}-H, C_{18}-H, C_{19}-H), 7.99 (1H, dd, J=1.2, 7.0Hz, C_{16}-H). Recrystallization of 50 from MeOH-isopropyl ether gave colorless needles: mp 213.5-215.5°C; UV 226.5, 276^{sh}, 283, 292; IR 3430^{br}, 1650; MS m/z(rel intensity) 449(8, M^+), 281(100), 238(40), 225(19), 212(39), 210(33), 208(14), 196(15), 194(17), 184(39), 182(21), 170(23), 168(32), 167(22), 157(21); ^{1}H-NMR 1.70 (3H, s, Me), 1.78 (3H, s, Me), 1.81 (3H, s, Me), 1.86 (3H, s, Me), 1.9-2.2 (3H, m, C_7-H, C_8-H_2), 2.48 (1H, m, C_7-H), 2.82 (1H, d, J=9.8Hz, C_{13}-OH, exchangeable), 3.65 (1H, m, C_9-H), 3.84 (1H, m, C_9-H), 4.21 (1H, dd, J=6.1, 9.8Hz, C_6-H), 4.60 (2H, m, C_{21}-H_2), 4.94 (1H, s, C_{12}-OH, exchangeable), 5.10 (1H, t-like, C_{22}-H), 5.23 (1H, dd, J=0.9, 9.7Hz, C_{13}-H), 5.68 (1H, d-like, J=9.5Hz, C_{26}-H), 6.56 (1H, dd, J=0.9, 9.5Hz, C_3-H), 7.08-7.26 (3H, m, C_{17}-H, C_{18}-H, C_{19}-H), 7.81 (1H, d, J=7.0Hz, C_{16}-H). Recrystallization of 46 from AcOEt-hexane gave colorless cotton-like needles: mp 208-209°C. The UV, MS, and ^{1}H-NMR spectra were identical with those described above.

Conversion of 13-epi-fumitremorgin B (45) to fumitremorgin B (1). DDQ (35 mg, 0.151 mmol) was added to a stirred solution of 45 (36 mg, 0.075 mmol) in CH_3CN-H_2O (10:1)(4 ml) and the mixture was heated at 70°C. After 60 min of heating, DDQ (17 mg, 0.073 mmol) was added to the reaction mixture. The whole was heated at 70°C for 20 min and passed through a short column on neutral alumina (elution with THF and CH_2Cl_2) and the elution was concentrated. The residue was dissolved in MeOH (1 ml) and cooled in an ice-salt bath. Excess $NaBH_4$ was added and the whole was stirred for 8 min and diluted with CH_2Cl_2. The mixture was washed with water (x2) and brine, dried and concentrated. The resulting residue was separated by preparative TLC (SiO_2; AcOEt-hexane, 3:1) to give 1 (1.1 mg, 3%), and the byproduct (20 mg).[37] Recrystallization of 1 from MeOH gave colorless needles: mp 205-207°C (lit.[1c] mp 211-212°C); UV 226, 277.5, 297, 306^{sh}; ^{1}H-NMR 1.63 (3H, s, Me), 1.70 (3H, s, Me), 1.85 (3H, s, Me), 1.99 (3H, s, Me), 1.8-2.2 (3H, m, C_7-H, C_8-H_2), 2.46 (1H, m, C_7-H), 3.64 (2H, dd, J=4.9, 8.5Hz, C_9-H_2), 3.85 (3H, s, OMe), 4.00 (1H, s, C_{12}-OH, exchangeable), 4.46 (1H, dd, J=7.0, 9.5Hz, C_6-H), 4.54 (2H, d-like, J=5.8Hz, C_{21}-H_2), 4.70 (1H, d, J=2.7Hz, C_{13}-OH, exchangeable), 4.70 (1H, d-like, J=10.1Hz, C_{26}-H), 5.04 (1H, t-like, C_{22}-H), 5.77 (1H, d, J=2.7Hz, C_{13}-H), 5.97 (1H, d-like, J=10.1Hz, C_3-H), 6.70 (1H, d, J=2.4Hz, C_{19}-H), 6.80 (1H, dd, J=2.4, 8.5Hz, C_{17}-H), 7.85 (1H, d, J=8.5Hz, C_{16}-H).

Dihydroxylation of 38 with osmium tetroxide to 53. A solution of osmium tetroxide in tert-butanol[41] (4 ml) was added via syringe to a stirred suspension of 38 (400 mg, 1.15 mmol), N-methylmorpholine N-oxide monohydrate (240 mg, 1.78 mmol), and pyridine (100 mg, 1.26 mmol) in THF-H_2O (10:1)(24 ml) with ice-cooling under an argon atmosphere. After the reaction mixture was stirred for 10 min, the cold bath was removed, and the reaction mixture was stirred for an additional 6 h at room temperature. A 10% aqueous $NaHSO_3$ solution (20 ml) was added to the reaction mixture with ice-cooling. After extraction with CH_2Cl_2 (x2), the organic layer was treated as usual to give a dark brown amorphous solid (530 mg), which was chromatographed (SiO_2, 30 g; AcOEt-hexane, 2:1). First elution gave 53 (141 mg, 32%) as slightly yellow crystals. Recrystallization from AcOEt gave colorless needles: mp 209-210°C; UV 223.5, 274, 282.5, 290; IR 3400^{br}, 1650; MS m/z(rel intensity) 381(12, M^+), 364(8), 363(2), 347(6), 323(29), 213(100), 196(20), 184(20), 182(29), 180(16), 170(86), 168(29), 167(41), 158(20), 157(97), 129(25); ^{1}H-NMR 1.67 (3H, s, Me), 2.02 (3H, s,Me), 1.9-2.2 (3H, m, C_7-H, C_8-H_2), 2.46 (1H, m, C_7-H), 3.62-3.72 (2H, m, C_9-H_2), 4.18 (1H, brs, 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), 4.81 (1H, d-like, J=9.5Hz, vinyl-H), 5.79 (1H, dd, J=1.2, 2.8Hz, C_{13}-H), 5.92 (1H, dd, J=1.2, 9.5Hz, C_3-H), 7.11-7.23 (2H, m, C_{17}-H, C_{18}-H), 7.33 (1H, dd, J=1.5, 7.0Hz, C_{19}-H), 7.84 (1H, brs, NH, exchangeable), 7.95 (1H, dd, J=1.5, 7.0Hz, C_{16}-H). Second elution gave the unknown product[38] (130 mg) as a yellow brown solid.

Dihydroxylation of 13 with osmium tetroxide to 54. A solution of osmium tetroxide in tert-butanol[41] (3 ml) was added to 13 (300 mg, 0.795 mmol), N-methylmorpholine N-oxide monohydrate (162 mg, 1.20 mmol), and pyridine (70 mg, 0.885 mmol) in THF-H_2O (10:1)(18 ml) as above. The mixture was stirred for 4 h at room temperature. Similar work-up gave a dark brown amorphous solid (340 mg), which was chromatographed (SiO_2, 20 g; AcOEt-hexane, 2:1). First elution gave 54 (32 mg, 10%) as slightly yellow crystals. Recrystallization from AcOEt-isopropryl ether gave colorless needles: mp 199-200°C; UV 222.5, 260^{sh}, 270.5, 298, 303^{sh}; IR 3350^{br}, 1640; MS m/z(rel intensity) 411(23, M^+), 394(7), 393(2), 377(3), 356(16),

264(19), 243(80), 200(100), 188(16), 187(48), 159(20); ^{1}H-NMR 1.67 (3H, s, Me), 2.01 (3H, s, Me), 1.9-2.2 (3H, m, C_7-H, C_8-H_2), 2.49 (1H, m, C_7-H), 3.65 (2H, m, C_9-H_2), 3.84 (3H, s, OMe), 4.11 (1H, s, C_{12}-OH, exchangeable), 4.43 (1H, dd, J=6.7, 9.2Hz, C_6-H), 4.66 (1H, d, J=2.8Hz, C_{13}-OH, exchangeable), 4.80 (1H, d-like, J=9.5Hz, vinyl-H), 5.75 (1H, dd, J=1.2, 2.8Hz, C_{13}-H), 5.88 (1H, dd, J=1.2, 9.5Hz, C_3-H), 6.81 (1H, dd, J=2.1, 8.5Hz, C_{17}-H), 6.85 (1H, d, J=2.1Hz, C_{19}-H), 7.65 (1H, brs, NH, exchangeable), 7.80 (1H, d, J=8.5Hz, C_{16}-H). Second elution gave the unknown products mixture[38] (total 153 mg).

Prenylation of 53 to demethoxy-fumitremorgin B (49). Benzene (8 ml) was added via syringe to a mixture of 53 (80 mg, 0.210 mmol), 96% powdered KOH (61 mg, 1.04 mmol), and 18-crown-6 (67 mg, 0.254 mmol) under an argon atmosphere and the reaction mixture was stirred for a few min. A solution of 3,3-dimethylallyl chloride (44 mg, 0.421 mmol) in benzene (1 ml) was added. After 60 min stirring, a solution of 3,3-dimethylallyl chloride (22 mg, 0.210 mmol) in benzene (0.5 ml) was added to the reaction mixture, which was stirred for an additional 30 min. Usual work-up gave 49 (68 mg, 72%) as yellow crystals. Recrystallization from MeOH gave slightly yellow needles: mp 213-214°C; UV 227.5, 278^{sh}, 284.5, 293; IR 3450^{br}, 1680^{sh}, 1658, 1610^{sh}; MS m/z(rel intensity) 449(16, M^+), 432(4), 431(3), 415(6), 323(12), 281(100), 238(59), 225(19), 212(39), 210(35), 184(43), 182(21), 170(25), 168(33), 167(24), 157(22); ^{1}H-NMR 1.64 (3H, s, Me), 1.69 (3H, s, Me), 1.84 (3H, s, Me), 2.00 (3H, s, Me), 1.8-2.2 (3H, m, C_7-H, C_8-H_2), 2.46 (1H, m, C_7-H), 3.64 (2H, dd, J=4.9, 8.9Hz, C_9-H_2), 4.03 (1H, s, C_{12}-OH, exchangeable), 4.46 (1H, dd, J=7.5, 9.3Hz, C_6-H), 4.61 (2H,d-like, J=5.8Hz, C_{21}-H_2), 4.71 (1H, d-like, J=10.1Hz, C_{26}-H), 4.74 (1H, d, J=2.7Hz, C_{13}-OH, exchangeable), 5.04 (1H, t-like, C_{22}-H), 5.81 (1H, dd, J=0.9, 2.7Hz, C_{13}-H), 6.01 (1H, dd, J=0.9, 10.1Hz, C_3-H), 7.10- 7.24 (3H, m, C_{17}-H, C_{18}-H, C_{19}-H), 7.99 (1H, d-like, J=7.3Hz, C_{16}-H). CD (c 1.042x10^{-4} g/ml, EtOH) [θ](nm): +23300(209)(positive maximum), -13810(225)(negative maximum), -3030(325)(positive maximum), -9060(242)(negative maximum), +28040(273)(positive maximum). Anal. Calcd for $C_{26}H_{31}N_3O_4$: C, 69.46; H, 6.95; N, 9.35. Found: C, 69.32; H, 7.01; N, 9.60.

Prenylation of 54 to fumitremorgin B (1). Benzene (3 ml) was added to a mixture of 54 (31 mg, 0.075 mmol), 96% powdered KOH (22 mg, 0.376 mmol), and 18-crown-6 (24 mg, 0.091 mmol) as above and the reaction mixture was stirred for a few min. A solution of 3,3-dimethylallyl chloride (16 mg, 0.153 mmol) in benzene (1 ml) was added and the mixture was stirred for 90 min. Usual work-up gave a residue which was purified by chromatography (SiO_2, 10 g; CH_2Cl_2-acetone, 10:1) to give 1 (24 mg, 66%) as pale yellow crystals. Recrystallization of 1 from MeOH gave slightly yellow needles: mp 210-211°C (lit.[1c] mp 211-212°C); UV 228.5, 267^{sh}, 277.5, 297, 305^{sh}; IR 3440^{br}, 1680^{sh}, 1660, 1620; MS m/z(rel intensity) 479(44, M^+), 462(9), 461(4), 445(4), 311(100), 268(76), 242(37), 240(25), 214(37), 212(20), 200(36), 198(26), 197(12), 187(18); ^{1}H-NMR 1.63 (3H, s, Me), 1.70 (3H, s, Me), 1.85 (3H, s, Me), 1.99 (3H, s, Me), 1.9-2.2 (3H, m, C_7-H, C_8-H_2), 2.47 (1H, m, C_7-H), 3.64 (2H, dd, J=4.9, 8.5Hz, C_9-H_2), 3.84 (3H, s, OMe), 4.01 (1H, s, C_{12}-OH, exchangeable), 4.45 (1H, dd, J=6.7, 9.8Hz, C_6-H), 4.54 (2H, d-like, J=5.2Hz, C_{21}-H_2), 4.70 (1H, d, J=2.8Hz, C_{13}-OH, exchangeable), 4.70 (1H, d-like, J=10.1Hz, C_{26}-H), 5.04 (1H, t-like, C_{22}-H), 5.77 (1H, dd, J=0.9, 2.8Hz, C_{13}-H), 5.97 (1H, dd, J=0.9, 10.1Hz, C_3-H), 6.70 (1H, d, J=2.1Hz, C_{19}-H), 6.80 (1H, dd, J=2.1, 8.6Hz, C_{17}-H), 7.85 (1H, d, J=8.6Hz, C_{16}-H). CD (c 0.976x10^{-4} g/ml, EtOH) [θ] (nm): +8350(215)(positive maximum), -16220(230)(negative maximum), +22110(273)(positive maximum), +10320(288)(negative maximum), +11300(299)(positive maximum).

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(22) This unexpected result prompted us to investigate a suitable condition to isomerize the exo olefin to the endo olefin. Attempted isomerization of **29b** to **29a** by conventional methods employing transition metal catalysts[23] such as $RhCl(PPh_3)_3$,[24] $PdCl_2$, $PdCl_2(PhCN)_2$[25] failed completely. In contrast, reaction of **29b** with $Fe_3(CO)_{12}$ produced a mixture of **29a** and **29b** (7:3) in 83% yield.

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(27) UV λ_{max}(EtOH) 224.5, 268^{sh}, 274, 290^{sh}, 306, 336, 350 nm; IR ν_{max}(KBr) 3350, 1710 cm^{-1}.

(28) $CHCl_3$ was used as a cosolvent since DDQ is sparingly soluble in CCl_4 and, therefore, the reaction in CCl_4 was sluggish even at room temperature (see Experimental Section).

(29) mp 201.5-202 °C (from benzene-hexane); UV λ_{max}(EtOH) 237.5, 281, 349.5 nm.

(30) E. J. Corey and J. Das, Tetrahedron Lett., 23, 4217 (1982).

(31) The corresponding brominated diol of **41** was not isolated under these conditions but the use of larger amounts of NBS produced this bromination. Thus, a trace amount of the brominated diol (12α, 13β) may be present in **41**.

(32) Prenylation of **39** with 3,3-dimethylallyl bromide (2 equiv) under similar conditions gave **44** (34%) and N,O-diprenylated product (47%): mp 194-197 °C (from isopropylether); UV λ_{max}(EtOH) 225.5, 276.5^{sh}, 284, 292 nm; IR ν_{max}(KBr) 3440, 1660 cm^{-1}; MS m/z(rel intensity) 517(2, M^+), 500(7), 433(7), 432(7), 431(7), 280(86), 252(100), 212(51), 210(21), 184(56), 182(19), 168(29), 167(19), 157(11); ^{1}H-NMR δ($CDCl_3$) 1.37 (3H, s, Me), 1.58 (3H, s, Me), 1.66 (3H, s, Me), 1.68 (3H, s, Me), 1.85 (3H, s, Me), 2.03 (3H, s, Me), 1.9-2.2 (3H, m, C_7-H, C_8-H_2), 2.46 (1H, m, C_7-H), 3.68 (2H, dd, J=2.3, 9.4Hz, C_9-H_2), 3.75 (2H, d-like, J=6.7Hz, C_{30}-H_2), 4.00 (1H, d, J=2.8Hz, C_{13}-OH, exchangeable), 4.33 (1H, dd, J=7.0, 10.0Hz, C_6-H), 4.65 (2H, d-like, J=5.2Hz, C_{21}-H_2), 4.95-5.04 (2H, m, C_{22}-H, C_{31}-H), 5.23 (1H, d-like, J=10.1Hz, C_{26}-H), 5.82 (1H, d, J=2.7Hz, C_{13}-H), 6.12 (1H, d, J=10.1Hz, C_3-H), 7.13-7.25 (3H, m, C_{17}-H, C_{18}-H, C_{19}-H), 7.68 (1H, m, C_{16}-H). The similar treatment of **39** with 3,3-dimethylallyl bromide (1 equiv) gave **44** and N,O-diprenylated compound, along with recovered **39**. To our surprise, O-prenylation occurred at the tert-hydroxy group (C_{12}-OH) as shown by the coupling between the C_{13}-H and C_{13}-OH.

(33) As preliminary experiment, the oxidation of **39** to the corresponding **51** type ketone employing usual oxidizing agents (e.g. CrO_3/pyridine, PDC, MnO_2) for an alcohol to ketone failed and DDQ oxidation of **39** also unsuccessful.

(34) We thank Professor T. Goto and S. Nakatsuka for giving us an information about the DDQ oxidation.

(35) The ketol **51** was not isolated in the pure form, but the UV spectrum of the reaction mixture showed the absorption spectrum corresponding to 3-acylindoles: UV λ_{max}(EtOH) 249.5, 269.5, 308 nm.

(36) **50** was not detected by TLC analysis during DDQ oxidation, indicating that **44** readily isomerized to the undesired isomer **46**, which was in turn was oxidized and reduced to give **50**.

(37) Instead of the corresponding isomeric diols, such as **50** and **46**, another compound, which was assumed to be the dehydrated product, was obtained in about 48% yield. UV λ_{max}(EtOH) 218.5, 277, 294^{sh} nm; IR ν_{max}(KBr) 1700^{sh}, 1665, 1630, 1620 cm^{-1}; MS m/z(rel intensity) 461(100, M^+); ^{1}H-NMR δ($CDCl_3$) 1.24 (3H, s, Me), 1.57 (3H, s, Me), 1.72 (3H, s, Me), 1.82 (3H, s, Me), 1.8-2.2 (3H, m, C_7-H, C_8-H_2), 2.46 (1H, m, C_7-H), 3.57 (1H, m, C_9-H), 3.77-3.90 (1H, m, C_9-H), 3.81 (3H, s, OMe), 4.18-4.38 (3H, m, C_6-H, C_{21}-H_2), 5.13 (1H, m, C_{22}-H), 5.18 (1H, d-like, J=8.9Hz, C_{26}-H), 5.34 (1H, d, J=9.2Hz, C_3-H), 5.72 (1H, s, C_{12}-H), 6.37 (1H, d, J=2.1Hz, C_{19}-H), 6.50 (1H, dd, J=2.1, 8.2Hz, C_{17}-H), 6.96 (1H, d, J=8.2Hz, C_{16}-H). Surprisingly, this compound resisted the $NaBH_4$ reduction.

(38) Byproducts appeared to be derived from the oxidative cleavage of 2,3-bond of the indole moiety by OsO_4.

(39) P. A. Grieco and M. Miyashita, J. Org. Chem., 40, 1181 (1975).

(40) Zn dust was activated before use; L. F. Fieser and M. Fieser, Reagents for Organic Synthesis, 1, p1276 (1967).

(41) OsO_4 was added as a 1% solution in tert-butanol. This OsO_4 solution was prepared according to Sharpless and Akashi's method.[42]

(42) K. B. Sharpless and K. Akashi, J. Am. Chem. Soc., 98, 1986 (1976) and references cited therein.