TOTAL SYNTHESIS OF FUMITREMORGINS AND VERRUCULOGENS†

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Abstract——The syntheses of fumitremorgin B(**49b**), C (**54**), verruculogen TR-2(**101**), and related compounds, all of which pentacyclic tremorgenic mycotoxins are reviewed. Major topics include construction of the pentacyclic ring system, stereoselective formation of 1,3-disubstituted β-carboline, introduction of a double bond and *cis*-glycol to the ring C of the pentacycle.

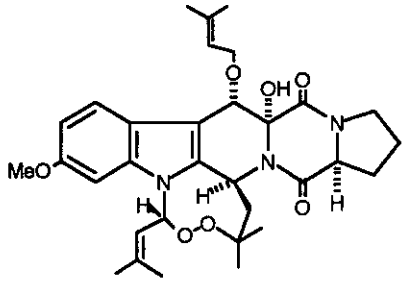
Contents:

I. Introduction.

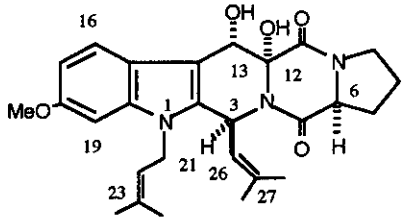
The tremorgenic mycotoxins fumitremorgin A and B were isolated in 1971 from *Aspergillus fumigatus* growing on rice and miso, a popular food in Japan by Yamazaki and coworkers.[1] The closely related mycotoxins verruculogen, acetoxyverruculogen, verruculogen TR-2, and fumitremorgin C have also been isolated from various *Aspergillus* and *Penicillium* species.[2] The structures of these mycotoxins have been determined mostly by X-ray analysis and NMR

† This paper is dedicated to the memory of the late Professor Shun-ichi Yamada.

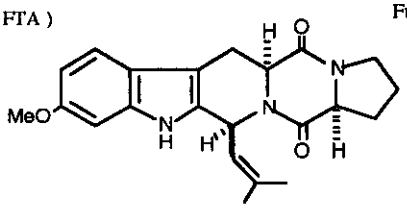
studies.[3] These mycotoxins have a pentacyclic ring system derived from 6-methoxy-tryptophan, proline and isoprene units. The absolute configurations were determined by the optical activity of proline isolated by severe hydrolysis of fumitremorgin A and B.[1](Scheme 1)



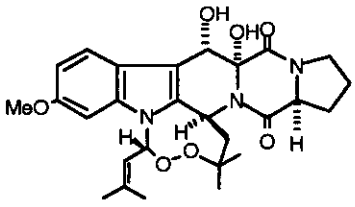
Fumitremorgin A (FTA)



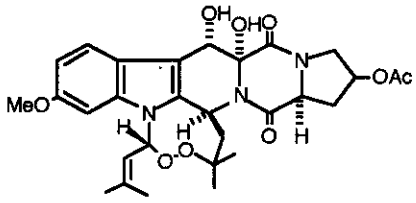
Fumitremorgin B (FTB)



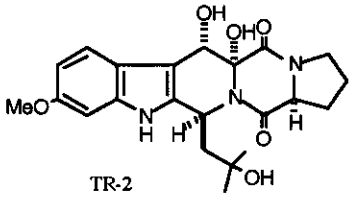
Fumitremorgin C (SM-Q) (FTC)



Verruculogen



Acetoxyverruculogen



TR-2

Scheme 1 Tremorgenic mycotoxins

Intraperitoneal administration of these mycotoxins to experimental animals produce tremor with intermittent convulsion. The mode of action of these compounds is not well understood, but is believed to involve inhibition of the presynaptic release of γ-aminobutyric acid in the central nervous system.[4] Therefore, these mycotoxins are called tremorgenic mycotoxins. The total syntheses of fumitremorgin B (FTB), TR-2, fumitremorgin C (FTC) and related compounds have been reported by several research groups, including our own group . However, fumitremorgin A and verruculogen which have an endoperoxide moiety, have not

yet been synthesized . In this review, we describe these total synthesis, focusing our own results.

Problems to be solved in the synthesis of fumitremorgins are : 1) introduction of a 6-methoxy group into tryptophan; 2) construction of a pentacyclic ring system ; 3) introduction of *cis* glycol at the12- and 13- positions ; 4) formation of a double bond at the12- and 13-positions for item 3 above ; 5) stereoselective synthesis of 1,3-*cis* substituted β-carbolines; 6) introduction of an isobutenyl or 2-hydroxybutyl group at the 1-position of the β-carboline moiety; and 7) a biomimetic or an efficient convergent synthesis. Each group refered to here has successfully synthesized the mycotoxins by resolving some of these problems.

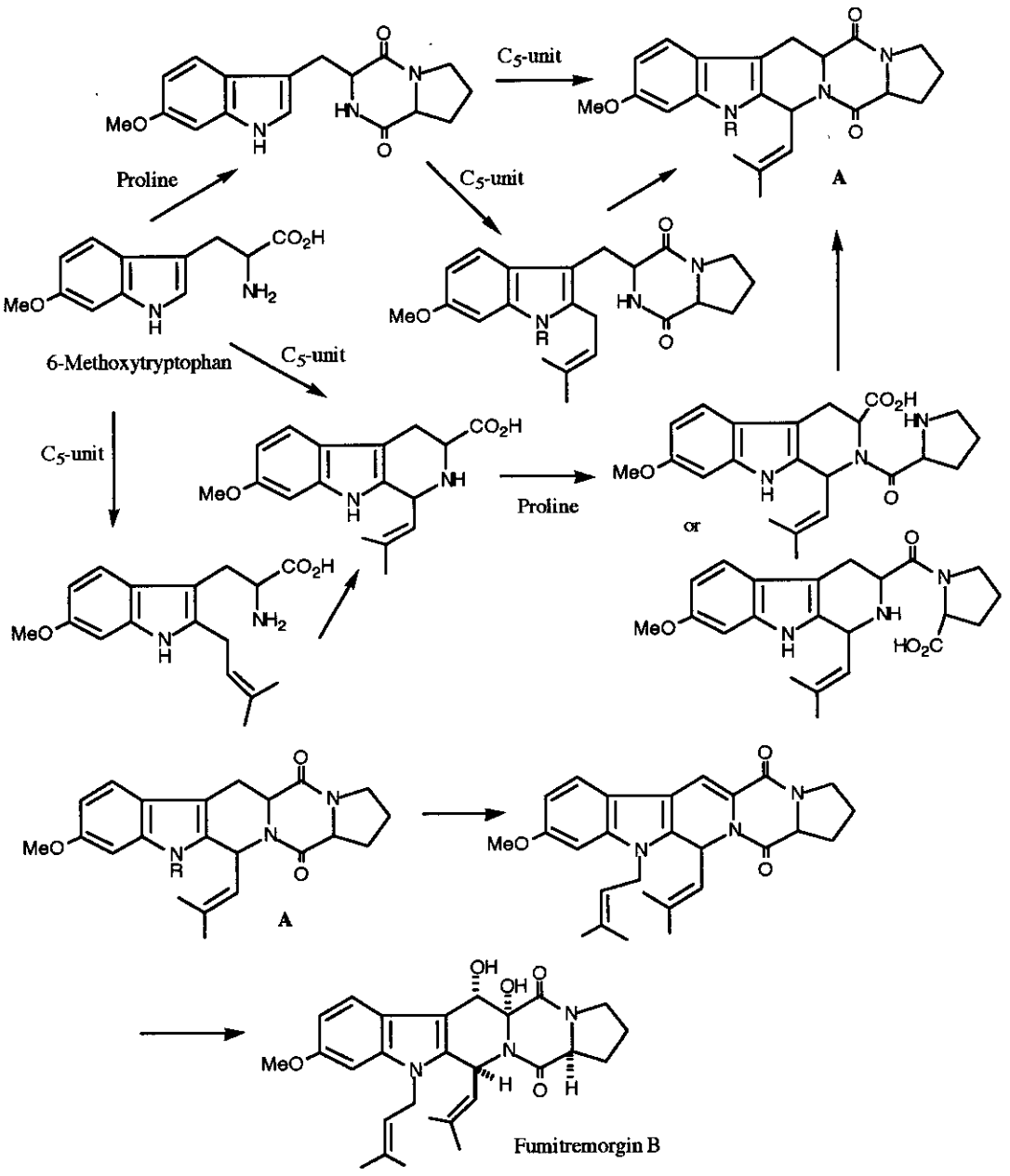
II. Total synthesis of FTB and FTC by our group: Biomimetic synthesis.

We chose fumitremorgins as targets of total synthesis not only because of their indolic structure and their biological activities, but also because these mycotoxins have been isolated and their structures have been determined at our university by Yamasaki's group.

II-1 Biomimetic construction of the parent pentacyclic ring system.

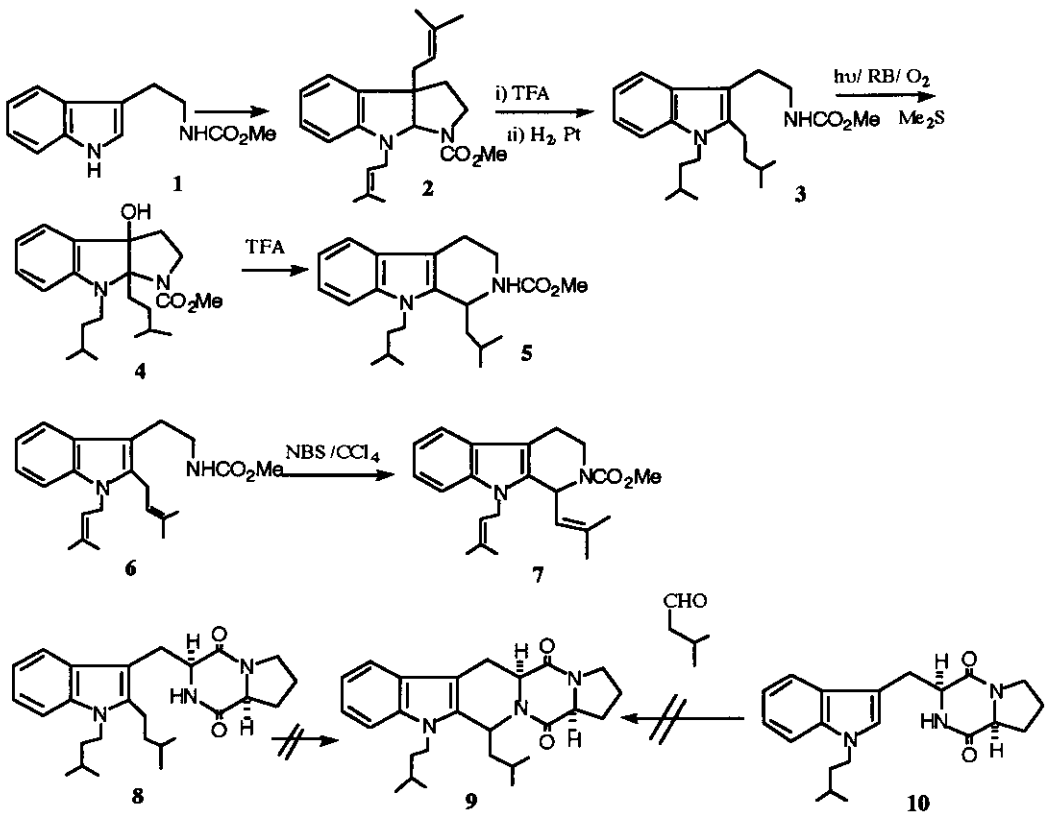
Yamazaki and his coworkers have verified that tryptophan, mevalonolactone, and proline are incorporated into fumitremorgins. [1,5] Several biosynthetic pathways can be proposed, as shown in Scheme 2.

Cyclotryptophylproline and 2-prenylated tryptophan derivatives have been isolated as natural products.[6,7a,14a] Pentacyclic compound (**A**) *via* prenylated diketopiperazine was considered to be an attractive intermediate towards FTB . Since we have developed a method for synthesizing 6-methoxy-L-tryptophan from tryptophan *via* a tryptophan cyclic tautomer,[7] the next problem was the formation of the pentacyclic ring system (**A**), preferably *via* a biomimetic pathway. Therefore, we first examined a model reaction for a rather new type of cyclization to give β-carboline from 2-prenyltryptophan derivatives. We found that 1-isobutyl-9-isopentyl-THC (**5**)[tetrahydro-β-carboline] could be obtained by an acid-catalyzed rearrangement of 3a-hydroxypyrrolo[*2,3-b*]indole(**4**), which was obtained by the dye-sensitized photooxygenation of 1,2-diisopentyltryptamine(**3**). Compound (**3**) was prepared by prenylation of the tryptamine(**1**) to give **2**, which was followed by the acid-catalyzed rearrangement and hydrogenation, as shown in Scheme 3.[8] Furthermore, bromination of *N*b-methoxycarbonyl-1,2-diprenyltryptamine(**6**) prepared by the acid-catalyzed rearrangement of **2** with NBS in carbon tetrachloride gave the corresponding THC (**7**) in moderate yield.[9] However, the pentacyclic compound (**9**) was not obtained by similar photooxygenation of the 1,2-diisopentyl-cyclotryptophylproline (**8**) followed by acid treatment.



Scheme 2 Possible Biosynthetic Pathway of Fumitremorgin B

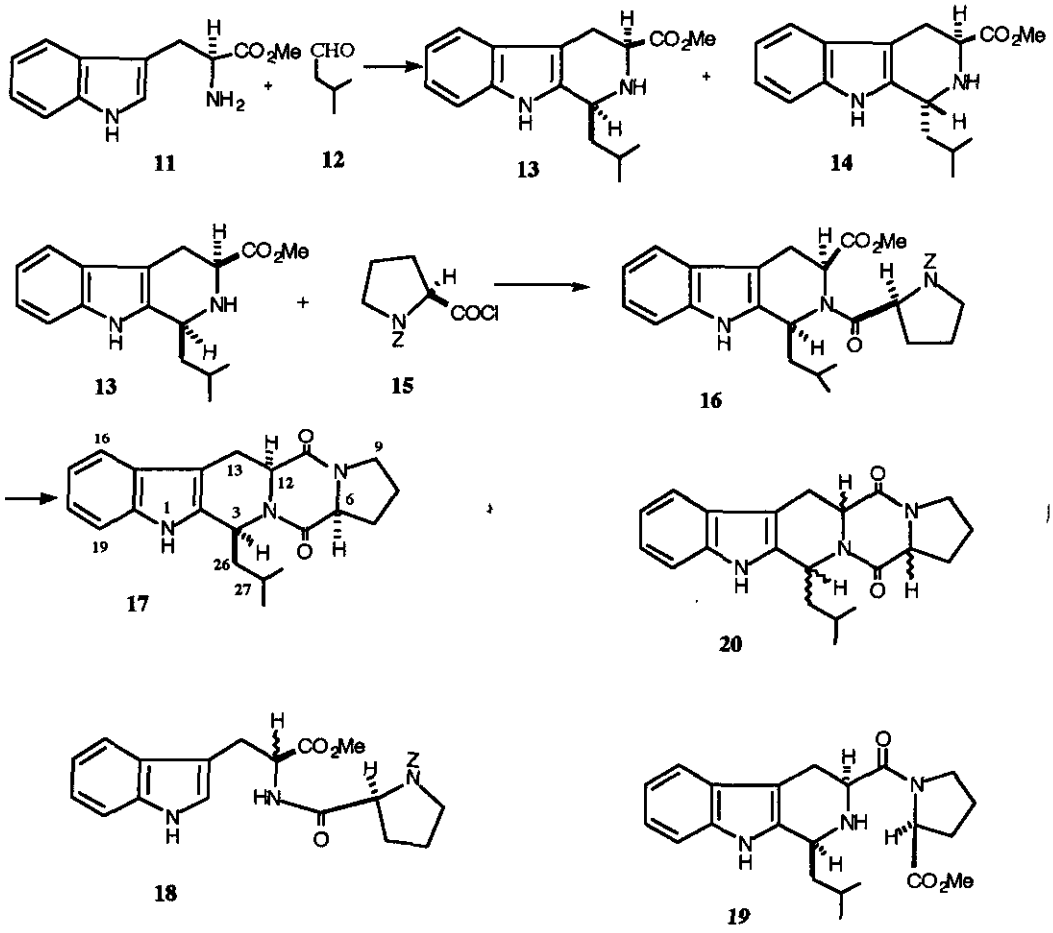
The cyclization of **8** by other oxidizing agents such as NBS failed to give the pentacyclic compound (**9**). Another attempt to produce the pentacyclic compound by the Pictet-Spengler(P-S) reaction of cyclo-L-tryptophyl-L-proline (**10**) with 3-methylbutanal was also unsuccessful . The corresponding cyclic tautomer of the diketopiperazine was obtained by the P-S reaction of **10** with 85% phosphoric acid without intervention of the aldehyde.[7]



Scheme 3

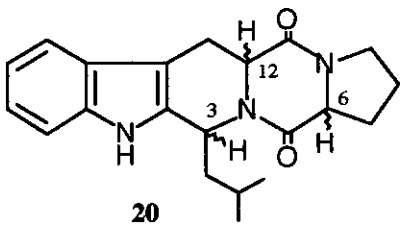
Therefore, we used a step-wise method to prepare the pentacyclic compounds *via* THC prepared by the P-S reaction of tryptophans. Since only a few examples of the P-S reaction using optically active tryptophan derivatives were known at the beginning of our study,[10] we examined racemization and the stereoselectivity of the reaction under various reaction conditions.[11] The P-S reaction of L-tryptophan methyl ester(**1 1**) with 3-methylbutanal(**1 2**) in boiling benzene (42 h) proceeded smoothly, as reported by Cook in the case of racemic tryptophans.[12] The 1,3-*cis*- (**1 3**) and *trans* -β-carbolines(**1 4**) were obtained in good yield (70%) in a nearly equal ratio, but racemization was severe. The stereochemistry of both isomers was confirmed by the ^{13}C-NMR data reported by Cook and co-workers.[13] With the addition of toluenesulfonic acid or trifluoroacetic acid, racemization decreased with a decrease in the duration of reflux (2 h or 0.3 h). However, the stereoselectivity of the reaction was not improved . The reaction in methylene chloride in the presence of TFA(6 mol equiv.) at room temperature gave a mixture of THCs (**1 3**, **1 4**) in excellent yields(95%), with the predominant formation of the desired 1,3-*cis* isomer (**1 3**) in a 2 to 1 ratio to the *trans* isomer (**1 4**). The stereoselectivity of the 1,3-*cis* isomer (**1 3**) was still not satisfactory, but 62% of the *cis* isomer(**1 3**) was isolated for the next step. The high optical purity of the both isomers was confirmed by NMR using the chiral shift reagent. Furthermore, similar results, except for the

sign of the rotation , for both THCs were obtained in the reaction with the D-tryptophan derivative.[11]



Scheme 4

The coupling reaction of the 1,3-*cis* isomer(**13**) with *N*-benzyloxycarbonyl(Z)-L-prolinyl chloride(**15**) proceeded smoothly to give the corresponding dipeptide(**16**) in excellent yield. On the other hand, the coupling reaction using Z-L-proline by diphenyl phosphorazide (DPPA) or 2,2'-dipyridyl disulfide-triphenylphosphine was unsuccessful. [11] Similar results were reported by Ottenheijm (cf. IV-2). This is probably due to the presence of steric hindrance around the β-nitrogen of the carboline ring. Removal of the protective group by catalytic hydrogenation gave the *cis,cis*-pentacyclic compound (**17**) accompanied by spontaneous cyclization . This spontaneous cyclization was in contrast to the cyclization of *N*-(Z-prolyl)-tryptophan methyl ester(**18**), in which refluxing in toluene is required after deprotection of the Z group.[14] A similar thermal reaction was required in the cyclization of the dipeptide(**19**) between the ester of β-carboline and the proline-nitrogen (cf. VI).



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Comp No	Relative stereochemistry		Absolute configuration		
	position 3-12	position 12-6	position 12	position 6	Prepared from
17	*cis*	*cis*	α-H	α-H	L-Trp-L-Pro
20a	*trans*	*cis*	α-H	α-H	L-Trp-L-Pro
20b	*cis*	*trans*	α-H	β-H	L-Trp-D-Pro
20c	*cis*	*trans*	β-H	α-H	D-Trp-L-Pro
20d	*trans*	*trans*	β-H	α-H	D-Trp-L-Pro

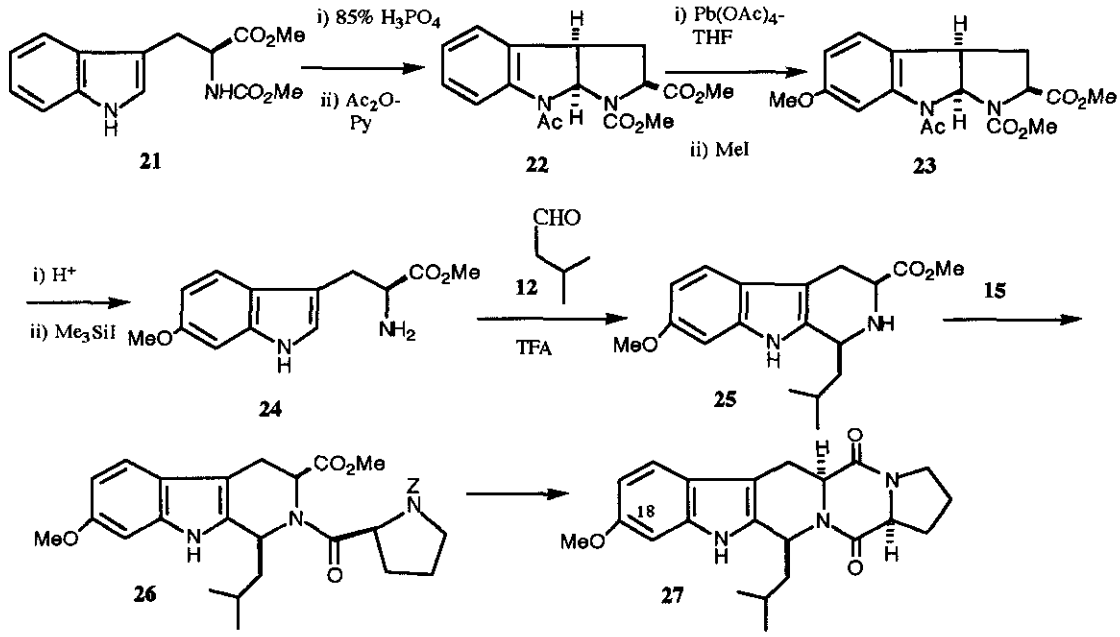
Table 1 Stereoisomers of pentacyclic compounds.

We prepared all of the possible stereoisomers of the pentacyclic compounds (**17** and **20**) using 1,3- *cis*- and *trans*- THC prepared from L- and D-tryptophan and -proline. These are shown in Table 1. These pentacyclic compounds(**17** and **20**) were obtained as crystals and could be readily differentiated by HPLC. Both of the *cis-trans* isomers(**20b**, **20c**) showed the same properties, except for the sign of the rotation, which indicates that racemization did not occur during these reactions. [11]

Epimerization of these pentacyclic compounds with 0.1M sodium hydroxide in methanol showed that the *cis-cis* isomer (**17**) epimerized to give the *trans-trans* isomer (**20d**) with inversion of the configuration at C-12 and the *trans-cis* isomer(**20a**) gave the *trans-trans* isomer (*ent* **20d**) by epimerization at the C-6 position. These epimerization studies demonstrated that facile epimerization to *trans*-diketopiperazine did occur and that the *trans-trans* isomer(**20d**) is the most stable isomer .[11]

Following the above procedures, we prepared the18-methoxy-pentacyclic compound (**27**). *N*-Methoxycarbonyl-6-methoxy-L-tryptophan methyl ester was prepared from *N*-methoxycarbonyl-L-tryptophan methyl ester (**21**) *via* the corresponding cyclic tautomer (**22**) as we reported previously. [7, 15] Oxidation of the cyclic tautomer (**22**) with lead tetraacetate in TFA followed by methylation gave the 6-methoxy derivative (**23**, 60%). Ring-opening of **23** in sulfuric acid and methanol gave *N*-methoxycarbonyl-6-methoxytryptophan methyl ester in excellent yield. The *N*-carbamate group was selectively removed by trimethylsilyl iodide.[16] The P-S reaction of the 6-methoxytryptophan methyl ester(**24**), followed by coupling with *N*-

Z-L-prolinyl chloride (**15**) and cyclization as above gave the 18-methoxy-pentacyclic compound (**27**) in good yield .



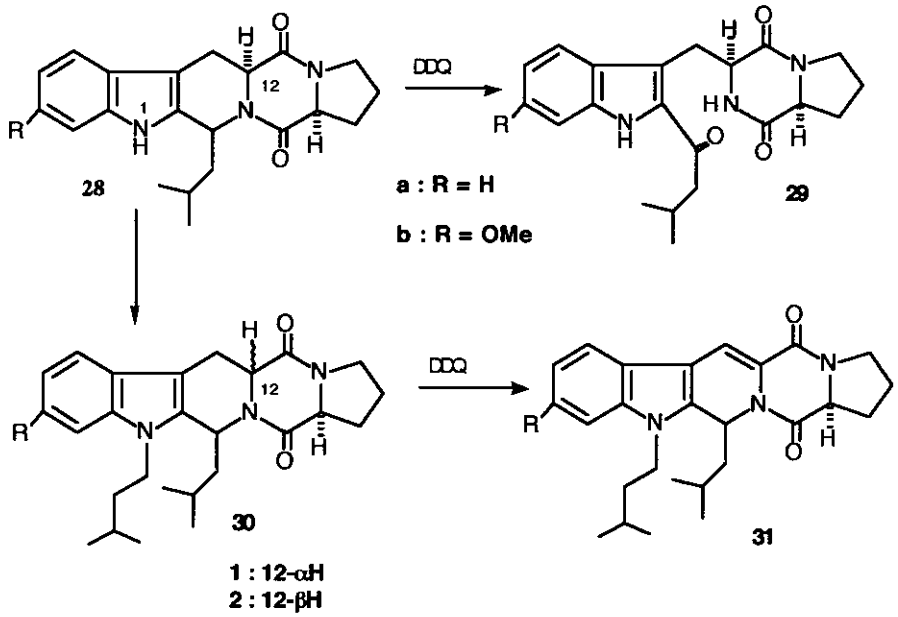
Scheme 5

II-2 Oxidation of the pentacyclic compound to the 12,13-dehydro derivative.

In 1977, Oikawa and Yonemitsu reported the selective smooth oxidation of tetrahydrocarbazole to the 4-one derivative and methyl indole-3-propionate to the α,β-unsaturated ester using 2,3-dichloro-5,6-dicyanoquinone (DDQ) ,[17] and later succeeded in the similar oxidation of the pentacyclic compound to give the 12,13-dehydro derivative, although the details were not published .[18] DDQ oxidation of the 12αH-pentacyclic compound (**28a,b**) in dichloromethane-acetic acid or aqueous acetonitrile did not give the desired 12,13-dehydro derivative , but did give the 2-acylindole derivative (**29a,b**) through oxidative cleavage of the THC ring .[11]

Similar results were obtained in the oxidation with lead tetraacetate. However, DDQ oxidation of 12β-H-1-isopentyl derivatives (**30a,b-2**) gave the desired 12,13-dehydro derivatives (**31a,b**) , while the corresponding 12α-derivative (**30a-1**) did not give the dehydro derivative (**31a**) . While the stereoselectivity of this oxidation is unclear, the conformation around the C-ring of the pentacyclic compound may play an important role. The 12β-H-1-isopentyl derivatives (**30a,b-2**) were obtained by epimerizaion of the corresponding 12α-H-derivative (**30a-1**) or isopentylation of **28a,b** by isopentyl bromide with sodium hydride in DMF, during which epimerization at the 12 position occurred. Rapid prenylation of the NH-

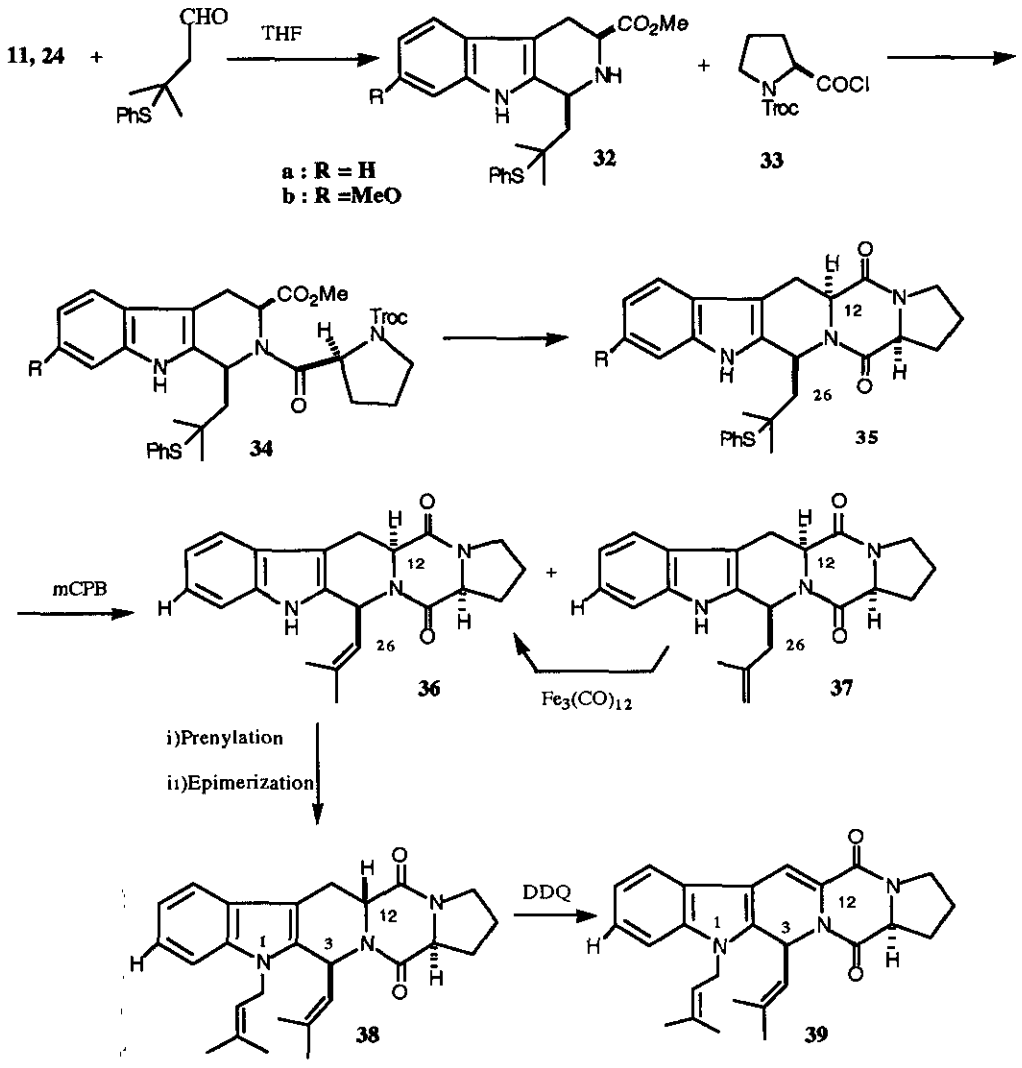
compound (**28a**) with prenyl bromide followed by catalytic reduction gave the 12α-H-1-isopentyl derivative (**30a-1**).[11]



Scheme 6

The next step was preparation of the key intermediate (**39**) for the total synthesis of FTB, which includes a double bond at the12,13-position and has 1-isopentenyl and 3-isobutenyl groups.[19] The P-S reaction of tryptophan methyl ester (**11**) with 3-phenylthio-3-methyl-butanal and subsequent acylation of THC (**32a**) with *N*-2,2,2-trichloroethoxycarbonyl(Troc)-prolinyl chloride (**33**) gave the corresponding dipeptide (**34a**). Removal of the *N*-protecting group in **34a** with zinc gave the corresponding pentacyclic compound (**35a**) along with spontaneous cyclization . The oxidative removal of the phenylthio group in **35a** gave two isomeric olefins(**36,37**) in which the undesired exocyclic olefin (**37**) was found to be a major isomer. This selectivity is probably due to the bulkiness around C-26. Isomerizaion of the isomeric mixture with an iron carbonyl [20] gave the desired endo-olefin (**36**) in 60% yield from the phenylthio derivative (**35a**) . Similar reactions with the 6-methoxytryptophan (**24**)gave **34b** and **35b**.

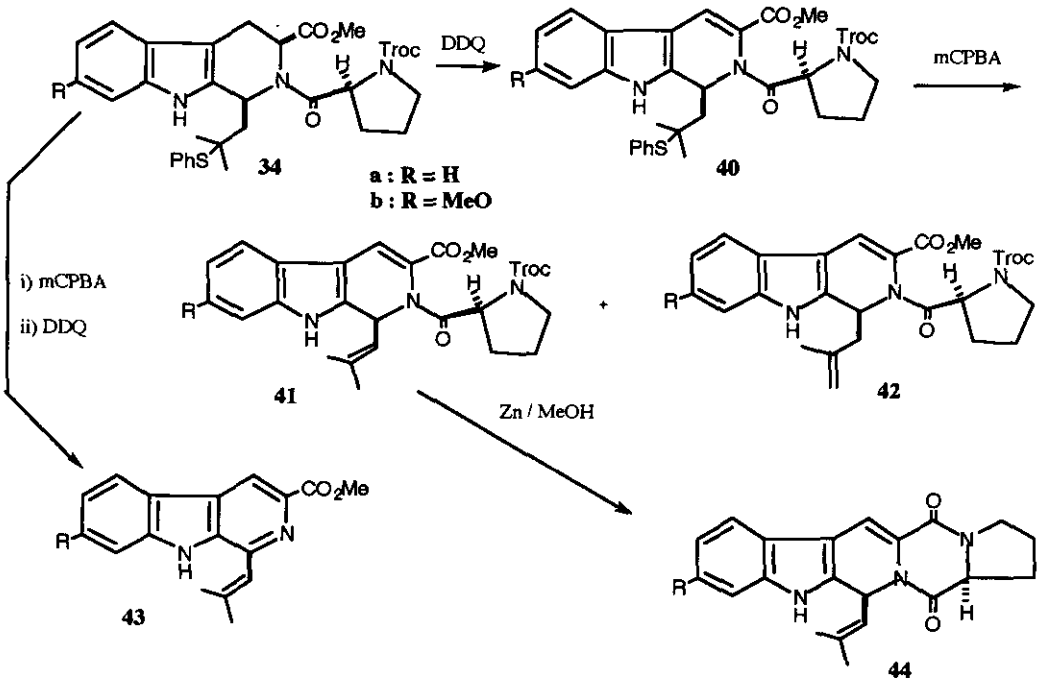
Prenylation of the 12α-H-pentacyclic compound (**36**) followed by epimerization with 0.1N sodium hydroxide gave the 12β-H isomer (**38**) in good yield . DDQ oxidation of this diene derivative (**38**) gave the 12,13-dehydro derivative (**39**), as described above, in 39% yield (by NMR), but isolation of **39** from the starting material (**38**) was difficult. Furthermore, improvement of the reaction conditions was unsuccessful. Therefore, dehydrogenation must be carried out at the dipeptide stage, which has more flexible conformations than the pentacyclic stage (**38**).



Scheme7

II-3 Total synthesis of FTB

Dehydrogenation of the dipeptide (**34a**) with DDQ in dichloromethane at room temperature gave the desired dehydro derivative (**40a**) *in 60% yield. Similar oxidation of the methoxy* derivative (**34b**) gave a lower yield of the dehydro derivative (**40b**, 30% yield in chloroform) probably due to increased susceptibility of **34b** towards DDQ oxidation by the addition of the methoxy group. Oxidative removal of the phenylthio group in **40** gave the desired endo-olefin as the major product (**41a**, 54%; **41b**,51%) . The exo-olefin (**42**) was obtained as a minor product, unlike the above case. This result supports the notion that the C-26 position in the pentacyclic compound shows severe steric hindrance which causes preferential formation of the exo-olefin (*vide supra*) . (Scheme 8)



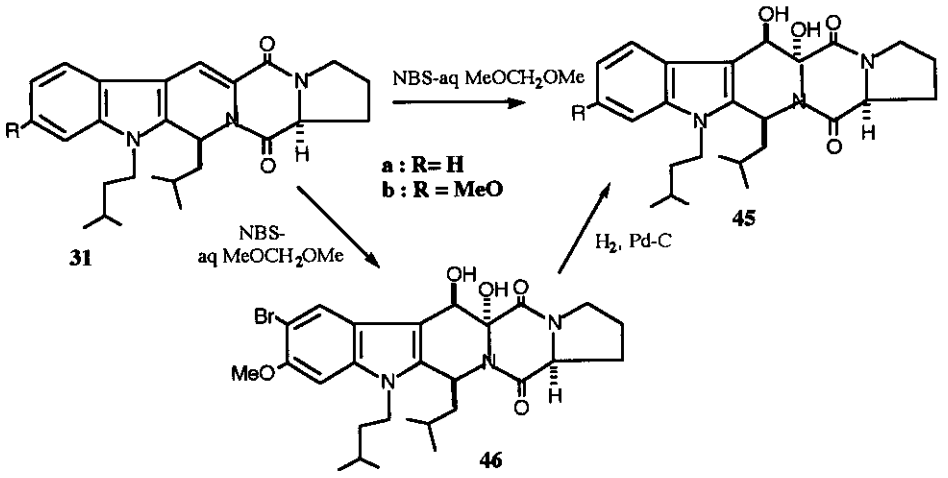
Scheme 8

The order of the oxidation is important. Oxidative removal of the phenylthio group in the dipeptide (**34a**) followed by DDQ oxidation gave the deacylated aromatized β-carboline (**43a**) as the major product in addition to a 2-acyl derivative (similar to **29**). The 1-isobutenyl-THC (similar to **52**) obtained by oxidative removal of the phenylthio group in **34** has two allylic positions and accelerated the oxidation at the 1,2-position to give **43,** even though the nitrogen was acylated. (Scheme 8) Removal of the protective group at the nitrogen in **41** with zinc in boiling methanol and subsequent spontaneous cyclization gave the pentacyclic key intermediate (**44a,b**) in good yied.[19]

We are now at the crucial step to introduce the *cis* -glycol at positions 12 and 13 . Model oxidations of the dehydro-demethoxy compound (**31a**) with Woodward *cis*-hydroxylation, *m*-CPBA, or potassium permanganate failed to give the desired *cis* -glycol . However, NBS-oxidation in aqueous dimethoxymethane [21] of **31a** gave the12α,13β-*trans* -glycol (**45a**) instead of the *cis* -glycol in 85% yield.

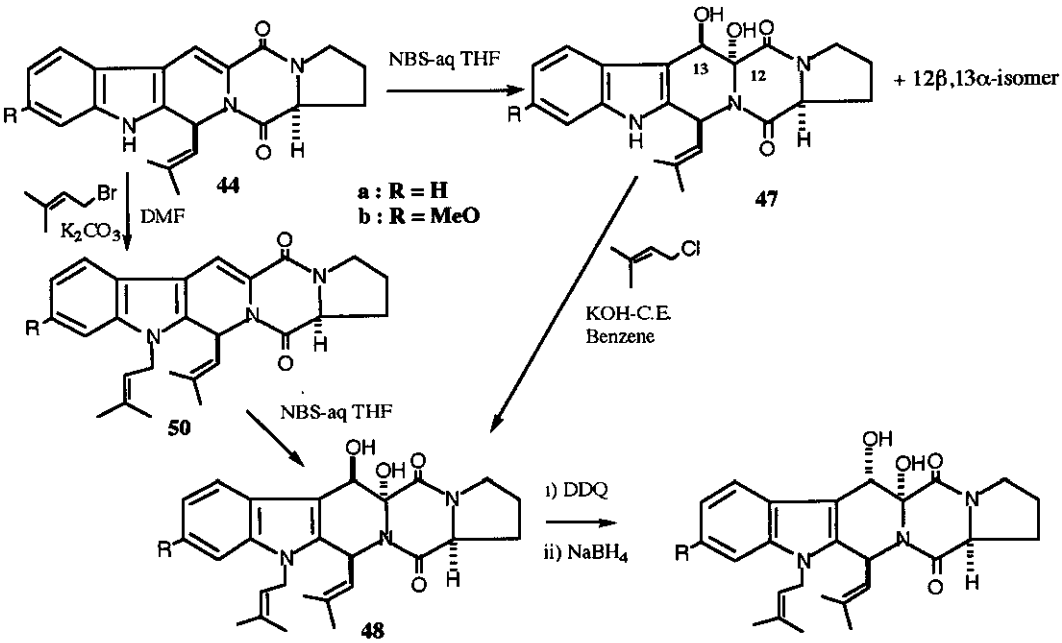
Similar oxidation of **31b** gave the brominated *trans*-glycol (**46**) in 58% yield, which in turn gave the debrominated compound (**45b**) upon catalytic hydrogenation .[11]

The improved NBS-oxidation of 12,13-dehydro-isobutenyl pentacyclic compound (**44**) in aqueous THF gave the 12α,13β-*trans*-dihydroxy derivatives in good yields (**47a**, 65%; **47b**, 77%) with the 12β,13α-isomer as a minor product. The yield of brominated product in the oxidation of the methoxy derivative (**44b**) was only 4% when a limited amount of NBS was



Scheme 9

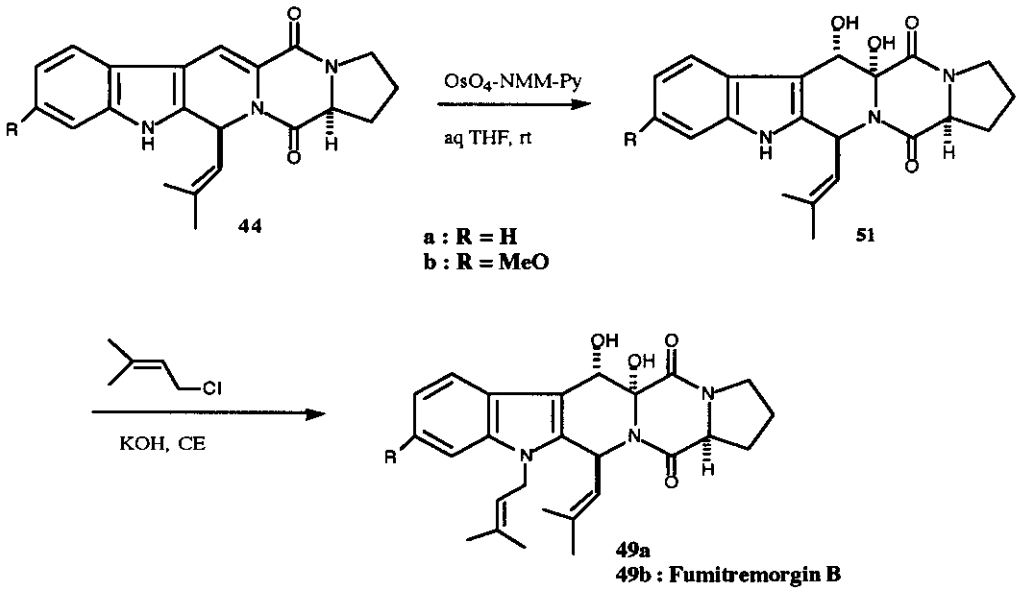
used. *N*a-prenylation of **47** with prenyl chloride-NaOH-crown ether-benzene gave the corresponding **48** (a,84%; b,65%), while *O*- and *N*-diprenylation occurred with prenyl bromide-DMF-NaH. The final step for the synthesis of FTB was epimerization of the12β-hydroxide to the α-isomer, which was successful only by DDQ oxidation of **48** followed by sodium borohydride reduction. However, the yield of FTB (**49b**,3%) and the demethoxy FTB (**49a**,4%) was poor . The 12β,13β- and 12β,13α-dihydroxy isomers were isolated in the



Scheme 10

case of the demethoxy derivative, indicating that partial epimerization occurred at the 12 position in the 13-oxo intermediate. NBS-oxidation of the *N*a-prenyl-12,13-dehydro derivative gave poor results due to the presence of the oxidation-sensitive *N*a-prenyl group, which has no severe steric hindrance.[19] (Scheme 10)

To improve the final step, we re-examine the *cis* -dihydroxylation of the 12,13-dehydro-compound (**44**) and found that oxidation with osmium tetroxide (catalytic amount)-*N*-methylmorpholine *N*-oxide-pyridine-aqueous THF gave the 12α,13α-*cis*-dihydroxy derivative (**51**) in better yield (**a**, 32%; **b**, 10%). Prenylation at the *N*a-position with prenyl chloride-KOH-18-crown ether-6 at room temperature gave FTB (**49b**, 60%) and the demethoxy FTB (**49a**, 72%). Thus, the total synthesis was completed.[19] The deprenyl derivative (**51b**) was later isolated from *Aspergillus fumigatus* and determined to be 12,13-dihydroxyfumitremorgin C by comparing the spectral data with those of our synthetic compound.[22]

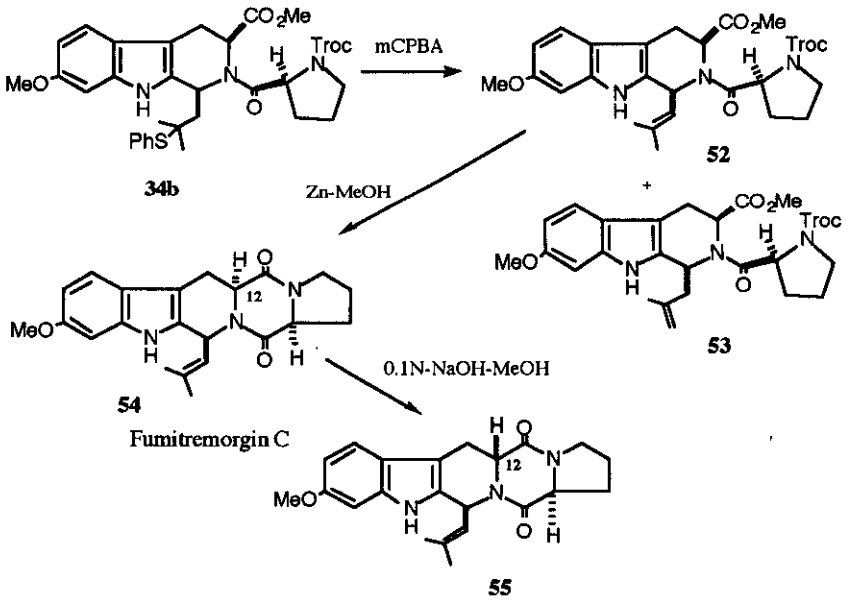


Scheme 11

II-4 Total synthesis of FTC

After completion of the total synthesis of FTB, we used these intermediates in the synthesis of FTC. Although FTC has a less complicated structure, the stereochemistry at the 12-position has not yet been established (cf. ref. 27c and 31b). (Scheme 12) Although the 12α-(**54**) and β-isomers (**55**) have already synthesized by the Ottenheijm-Hermkens group (cf. IV-4), the12α-isomer (**54**) was obtained only as an oil, unlike the natural product. The oxidative removal of the phenylthio-group in **34b** obtained above gave a mixture of the endo- (**52**) and

exo-olefins (**53**) , and the desirable endo-olefin (**52**) was obtained as the major product (74%), as described above. The reductive removal of the Troc groups in **52** resulted in spontaneous cyclization to give 12α-FTC (**54**) as crystals. Epimerization of 12α-isomer (**54**) with 0.1 N sodium hydroxide gave 12β-FTC (**55**), also as crystals. The melting point of natural FTC did not agree with that of either isomer, but the spectral data of the 12α-isomer closely resembled those of natural FTC.[23] Since neither the natural product nor its optical rotation value was available, rigorous identification was not possible. However, both the Ottenheijm-Hermkens group and our group concluded that the 12α-isomer is the natural product .



Scheme 12

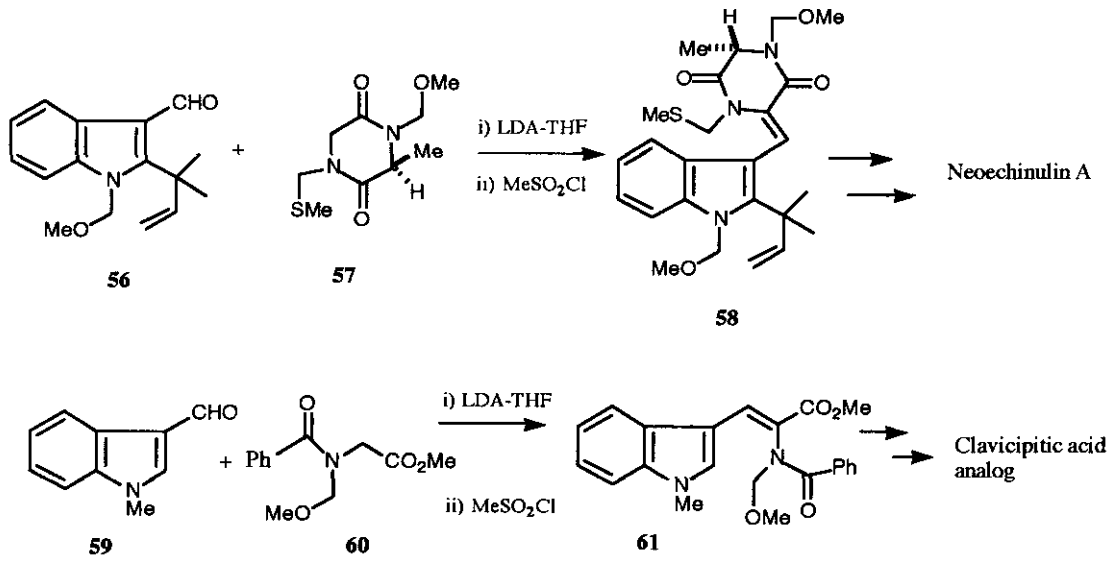
III Total synthesis of FTB by the Goto-Nakatsuka group : A convergent synthesis.

A characteristic feature of their synthesis of FTB is that they used a convergent method instead of a linear synthesis taken by most of the other groups.

III-1 Condensation of the indole-3-aldehyde with the active methylene of an α-amino acid derivative

The Goto-Nakatsuka group established an aldol-type condensation between indole-3-aldehydes (**56**,**59**) and a diketopiperazine (**57**) or a *N*-benzoylglycine derivative (**60**) in the synthesis of neoechinulin A and a clavicipitic acid analog. 3-Indolemethylidenediketopiperazine(**58**) and a dehydrotryptophan derivative (**61**) were obtained by condensation with LDA in THF.[24] (Scheme 13)

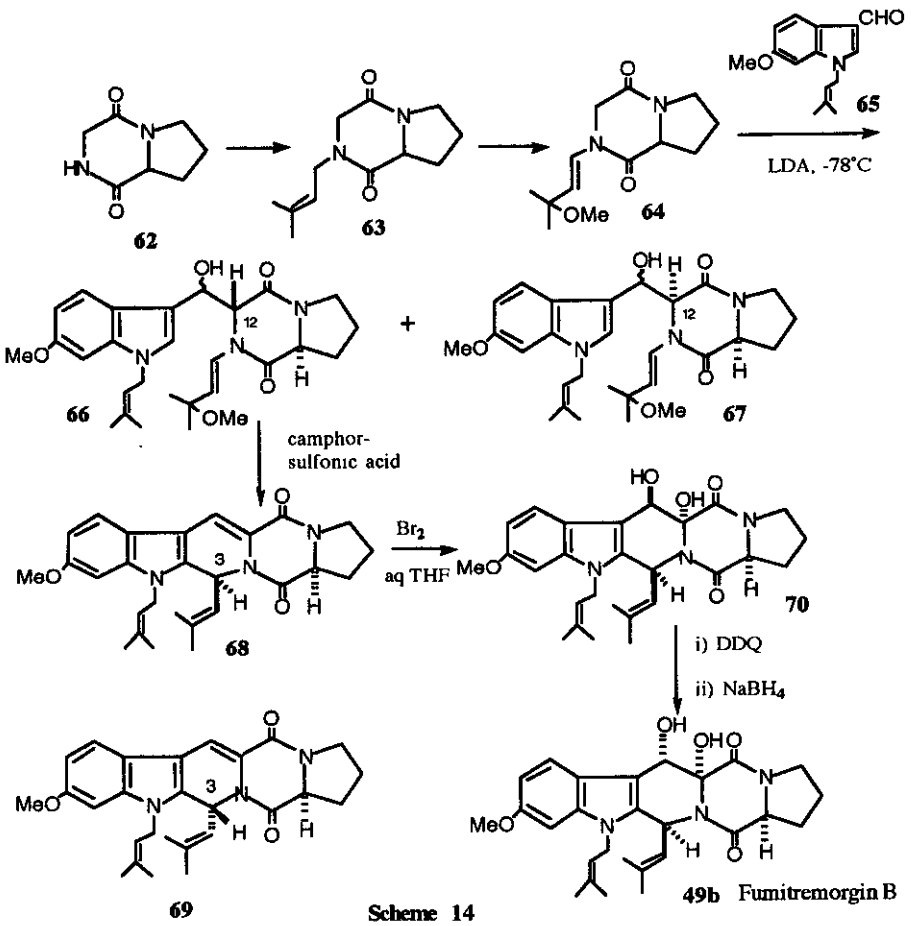
For the total synthesis of FTB, the diketopiperazine moiety was prepared from cycloglycinyl-L-proline (**62**). *N*-Prenylation of the diketopiperazine (**62**) followed by oxidation with phenylselenyl chloride-methanol gave the methoxy-enamine (**64**), which was partially racemized . Aldol condensation of the methoxy-enamine (**64**) with the indole-3-aldehyde (**65**) by LDA at -78°C gave two 12β-H isomers (**66**, 50% and 11%) and a 12α-H isomer (**67**, 15%). (Scheme 14)



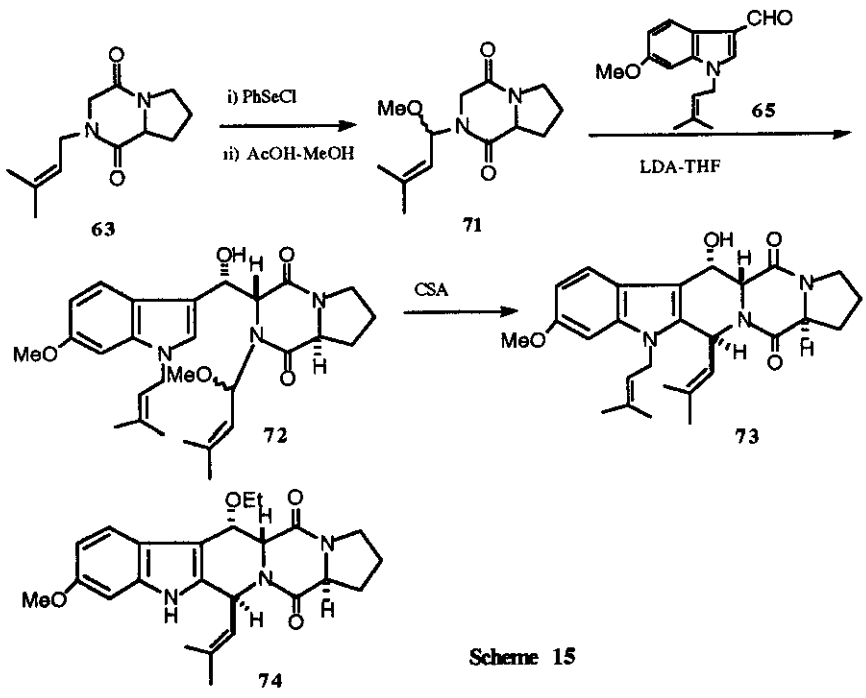
Scheme 13

Acid (camphorsulfonic acid) treatment of **66** gave the pentacyclic key intermediate (**68**) by P-S-type cyclization and dehydration. The pentacyclic compound (**68**) obtained was a mixture of optically active and racemic compounds, which were separated by crystallization. On the other hand, similar acid treatment of the 12α-isomer (**67**) gave the 3α-isopentenyl-pentacyclic compound (**69**). Hydroxylation of **68** with bromine in aqueous THF gave the *trans*-12α,13β-dihydroxy derivative (**70**) in 64% yield. This result is similar to ours , but better yield. It is likely that NBS oxidation of **68** occurred at the 1-prenyl group also(see above). Epimerization at the13β-hydroxy group in **70** proceeded successfully to give FTB (**49b**) as a sole product by DDQ oxidation followed by reduction with $NaBH_4$, as in our case but with a better yield. [25] (Scheme 14) FTB was synthesized by the Goto-Nakatsuka group and our group independently at almost the same time.

The Goto-Nakatsuka group has also synthesized (±)-12-deoxy-12-epi-FTB (**73**) from **71** and **65** by a similar route. (Scheme 15) The stereochemistry of the final compound (**73**) was confirmed by X-ray analysis of an analogous compound (**74**) prepared by a similar route starting from 1-pivaloylindole-3-aldehyde instead of the 1-prenyl compound (**65**). [26]



Scheme 14

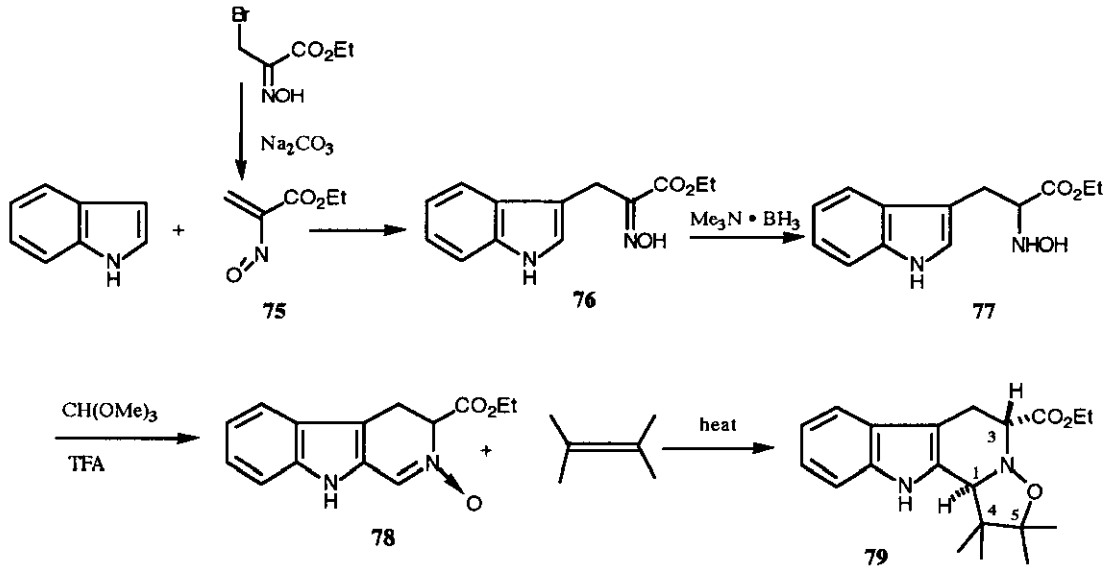


Scheme 15

IV Total synthesis of verruculogen TR-2 and FTC by the Ottenheijm-Hermkens group: Fused isoxazole compound as a protected form of 1,3-*trans*-1-hydroxyisobutyl-THC.

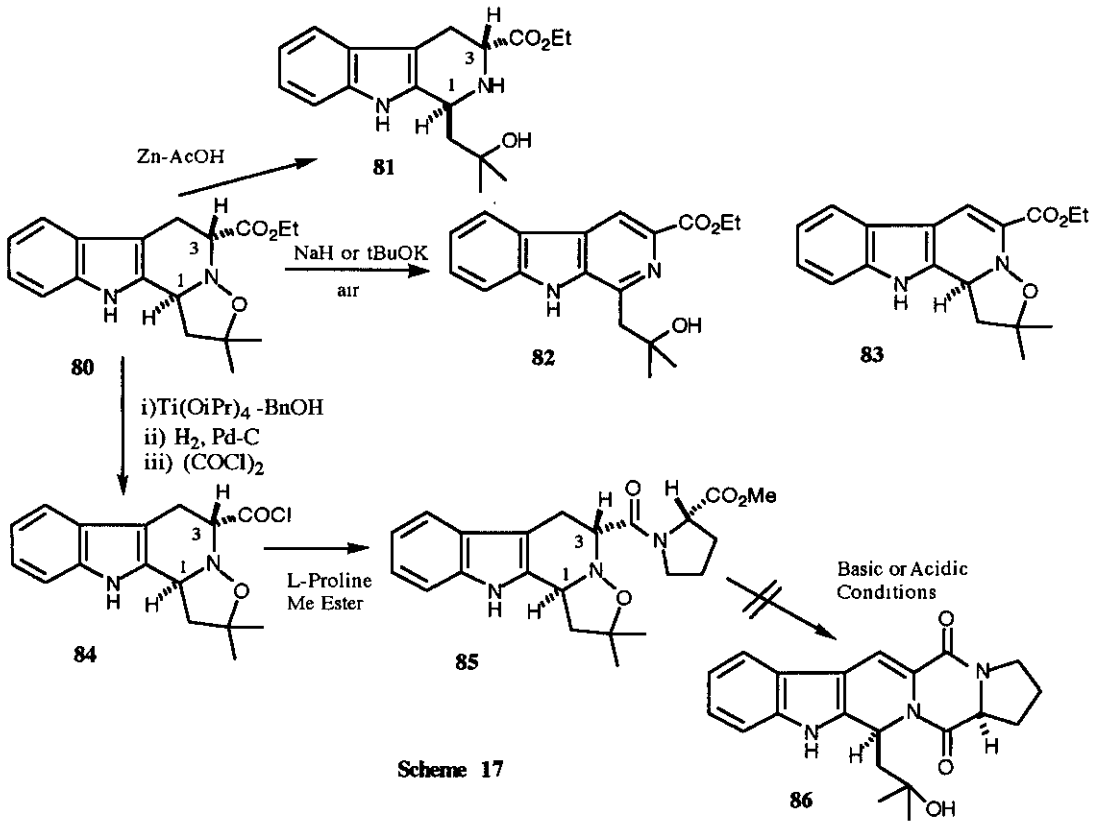
IV-1 Model Experiments

Since the P-S reaction of tryptophan derivatives with α,β-unstaturated aldehydes or β-hydroxyaldehydes was not successful, Ottenheijm's group developed the 1,3-dipolar cycloaddition of the nitrone (**7 8**) with alkenes to form the fused isoxazolidine (**7 9**), which is an excellent precursor of the 1,3-*trans*-1-hydroxyisobutyl-THC.[27] Condensation of indole with the nitroso-acrylate (**7 5**, obtained from β-bromopyruvate oxime with base) gave the β-indolypyruvate oxime (**7 6**), which in turn gave *N*-hydroxytryptophan ester (**7 7**) upon reduction with a triethylamine-borane complex. The Bischler-Napieralski-type reaction of **7 7** with methyl orthoformate in the presence of TFA gave the nitrone (**7 8**) in excellent yield . The 1,3-dipolar cycloaddition of the nitrone (**7 8**) with various alkenes gave the fused isooxazolidines (**7 9**), which were protected forms of 3-(β-hydroxyethyl)-THCs. [27 a, b] (Scheme 16) The fused isoxazolidine (**8 0**) obtained from **7 8** and 2-butene was rather stable towards reducing reagents such as aluminum amalgam, Raney Ni, and catalytic hydrogenation, probably due to the steric hindrance caused by the *gem*-dimethyl group. However, upon reduction with zinc in acetic acid, **8 0** gave the 1,3-*trans*-1-(β-hydroxyethyl)-THC ester (**8 1**), which was an attractive precursor of TR-2. Although this β-carboline (**8 1**) was obtained as a racemate, this result opens a new route to the synthesis of TR-2. [27c]



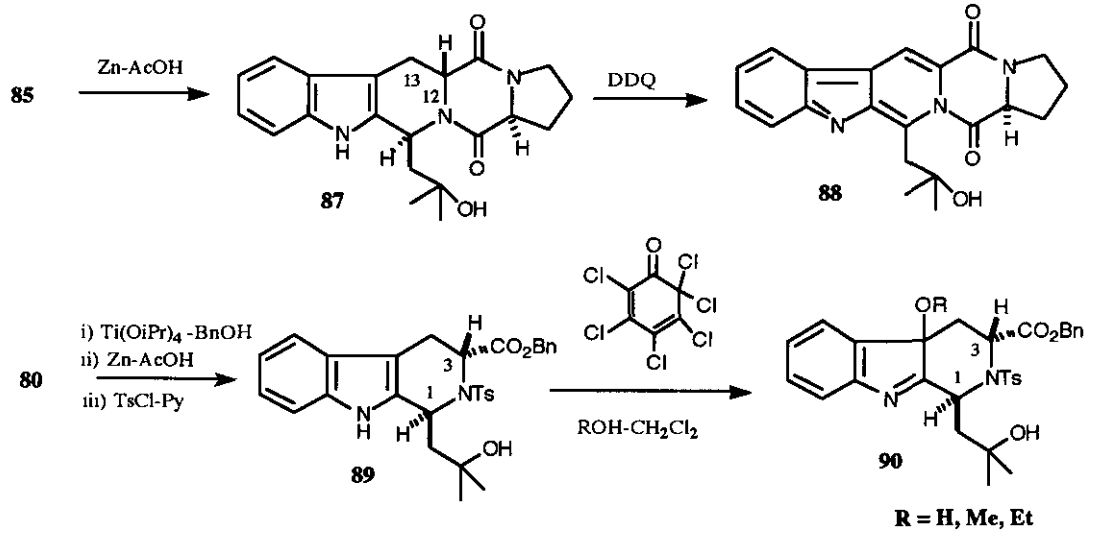
Scheme 16

They also examined methods to introduce a double bond at the 12- and 13-positions of the pentacyclic compound as a precursor of TR-2. [28] To introduce a double bond into the β-carboline, they first oxidized the fused isoxazolidine(**80**) by air under alkaline condition. They obtained the aromatized compound (**82**) instead of the desired 3,4-dehydro derivative (**83**) accompanied by cleavage of the isoxazolidine ring.[28b] To stop the reaction at the 3,4-dehydro stage, they attempted to trap the 3,4-dehydro derivative as the 2-acyl-β-carboline, as described by Harrison (cf. VI). They oxidized a dipeptide (**85**) obtained from **80** under various basic conditions, expecting to isolate a dehydro derivative such as the pentacyclic compound (**86**), but an untractable reaction mixture was obtained. [28b] (Scheme 17)
Ottenheijm's group also examined the DDQ oxidation of the 12β-H-pentacyclic compound (**87**). However, they obtained only an over-oxidized compound (**88**), even using one equivalent of DDQ. This result is somewhat inconsistent with our results, although the substituent also differed slightly (see above). They finally found that the oxidation of 2-tosyl-β-carboline (**89**) with 2,3,4,5,6,6-hexachlorocyclohexadien-1-one in methanol gave the methoxyindolenine(**90**,R = Me) which is an attractive precursor for the dehydro derivative, in excellent yield. [28]



Scheme 17

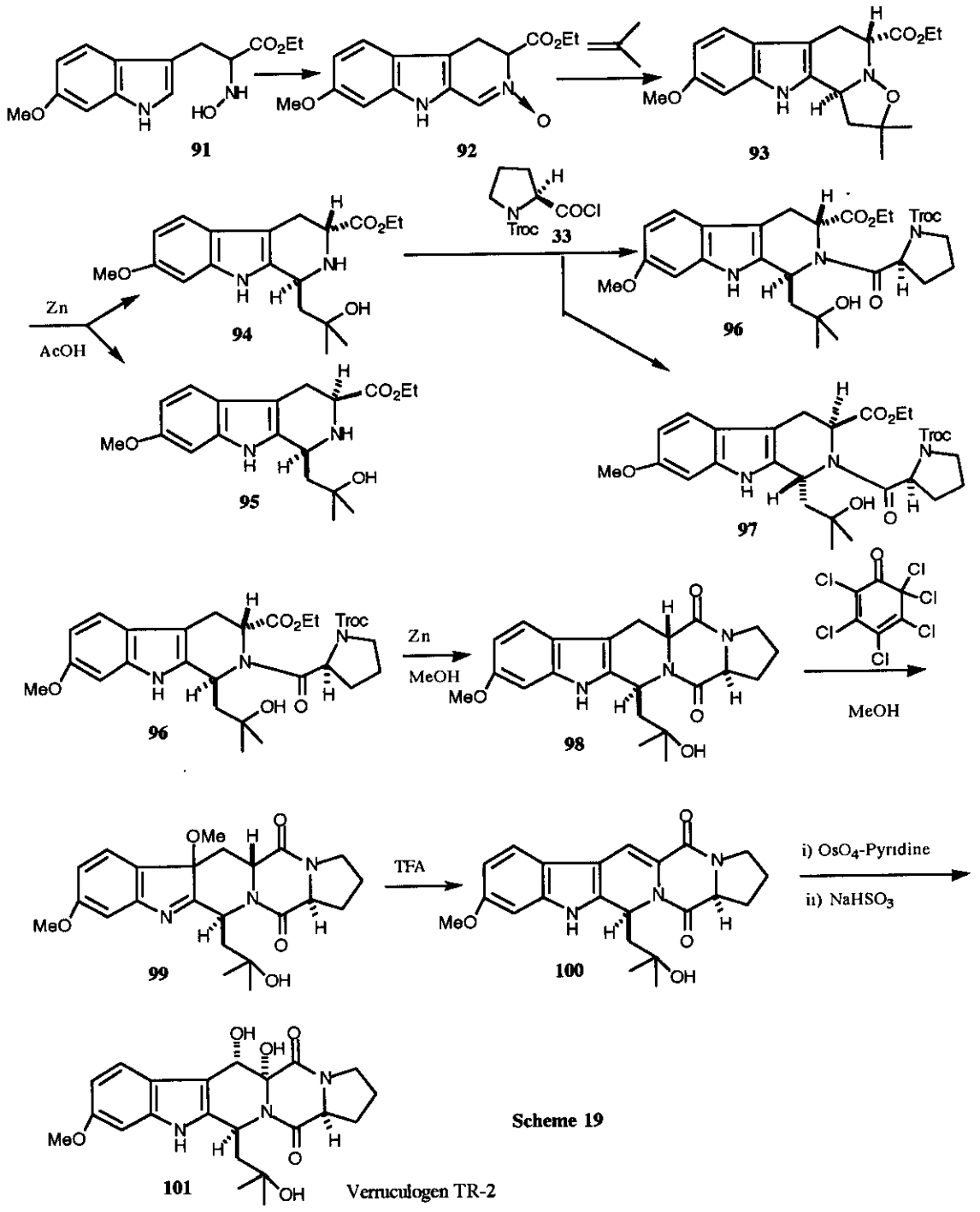
The *N*-chloro derivative was considered to be an intermediate of the reaction, and an alcohol attacked the 3-position of the indole as a nucleophile. [28,29]



Scheme 18

IV-2 Total synthesis of TR-2

They were now ready for the total synthesis of TR-2. Michael addition of 6-methoxyindole with ethyl nitroso-acrylate followed by reduction with a triethylamine-borane complex as described above gave the *N*-hydroxytryptophan (**91**). Bischler-Napieralski reaction of **91** with methyl orthoformate in the presence of TFA gave the nitrone (**92**) in excellent yield. The 1,3-dipolar cycloaddition of this nitrone (**92**) with isobutene in toluene at 120°C in a pressure vessel gave a fused isoxazolidine (**93**) which in turn gave the1,3-*trans*-1-hydroxyisobutyl-THC (**94**) in excellent yield and the 1,3-*cis* -isomer (**95**) as a minor product , both in racemic forms. It is not clear that epimerization occurred in either the fused isoxazolidine (**93**) or the β-carboline (**94**). The methoxy-THC (**94**) was condensed with *N*-Troc-L-prolinyl chloride (**33**) in dichloromethane in the presence of triethylamine to give a mixture of the two optical active diastereomers (**96,97**). Removal of the Troc group in the dipeptide (**96**) with zinc in boiling methanol gave the pentacyclic compound (**98**) by spontaneous cyclization of the intermediate amino ester. Oxidation of **98** with hexachlorocyclohexadiene in dichloromethane-methanol gave the methoxyindolenine (**99**) in 73% yield, which in turn gave the desired 12,13-dehydro derivative (**100**) upon treatment with TFA in 46% yield . Oxidation in ethanol gave a less satisfactory result. The yield of **100** could be increased to 80% by acid treatment of the recovered methoxyindolenine (**98**). The final *cis*-dihydroxylation of **100** with osmium tetroxide following Boyd's procedure(cf. VIII) gave the target molecule, verruculogen TR-2 (**101**), in 22% yield. (Scheme 19)

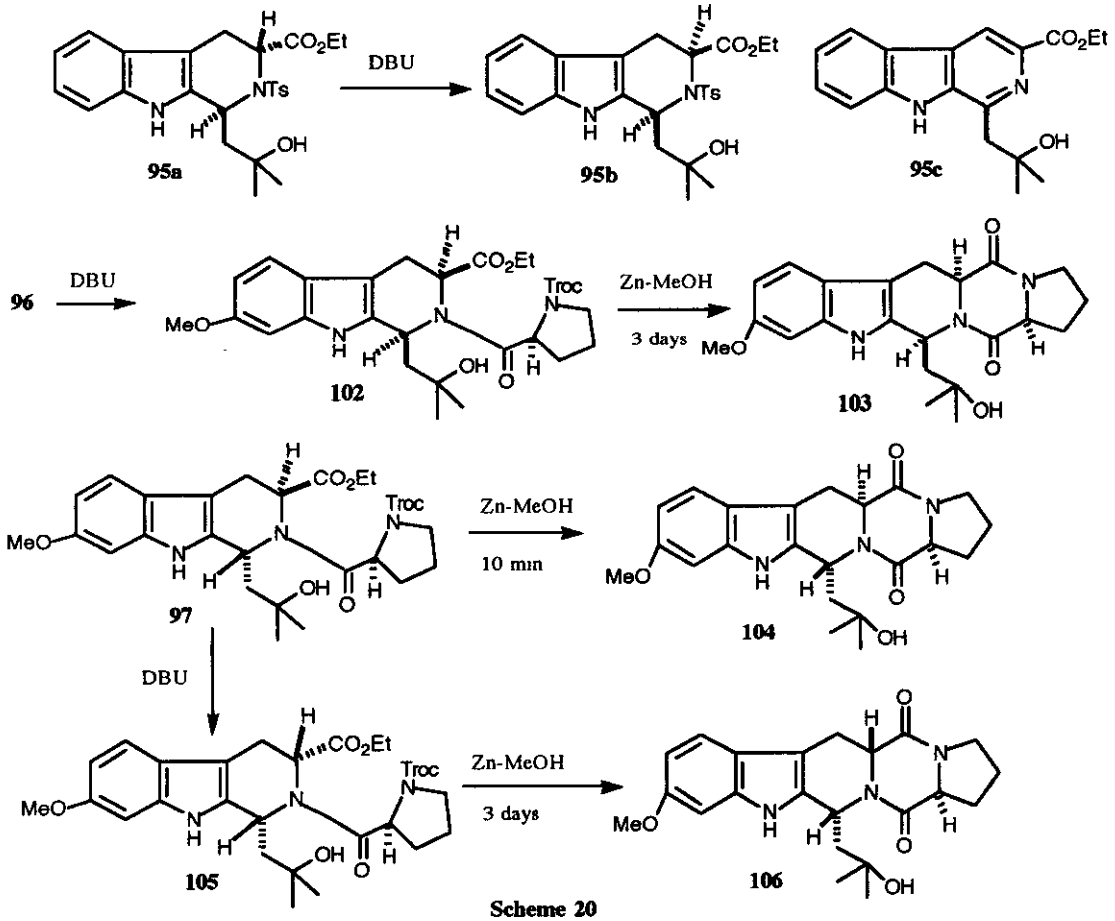


Scheme 19

IV-3 Synthesis of FTC

Ottenheijm's group also synthesized FTC from intermediates of TR-2. Since the configuration of the 12-position of FTC has not been established, they prepared all of the possible stereoisomers of the pentacyclic compound with a hydroxyisobutyl group at the 3-position.

They examined epimerization at the 3-position of the 1,3-*trans*-*N*b-tosyl-THC (**95a**) as a model reaction for dipeptides (**96,97**). Epimerization of **95a** did not proceed with triethylamine, while the aromatized β-carboline (**95c**) was obtained with sodium ethoxide. Furthermore, epimerization in the isoxazolidine derivative (**84**) was also not successful. However, epimerization of **95a** to **95b** did occur with DBU. Deuteration at the 3-position using deuteriomethanol verified the position of the epimerization.[30] The*trans-ttans*-pentacycle (**98**) was prepared as described above. (Scheme 19) Epimerization of the 3-position of the dipeptide (**96**) with DBU in chloroform gave the 3α-H-isomer (**102**) in 50% yield. The 3α-H-dipeptide (**102**) gave the corresponding *cis-cis*- pentacycle (**103**) in 63% yield upon removal of the protective group, but cyclization required 3-days of reflux. Another 1,3-*trans* -dipeptide (**97**) similarly gave the *trans-cis* -pentacycle (**104**) in quantitative yield. The *cis-trans*- pentacycle (**106**) was obtained from **97** by epimerization (67%) with DBU followed by deprotection-cyclization (45%) with zinc in boiling methanol for 3 days. Ottenheijm's group failed to epimerize at the 12-position of **103** and **104** with DBU (cf. our results; II-1. II-4).[30] (Scheme 20)

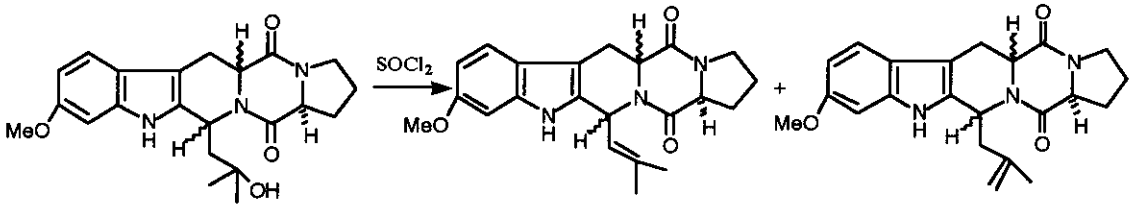


Scheme 20

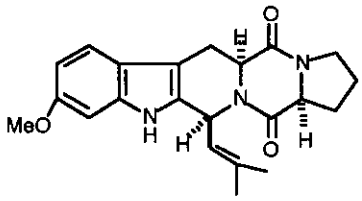
The presence of steric hindrance between the 1-substituent and the prolinyl group in 1,3-*cis* dipeptides such as **102** and **105** inhibited cyclization compared to the spontaneous cyclization in 1,3-*trans*-dipeptides (**96**,**97**). Since we did not observe such inhibition in the cyclization of 1,3-*cis*-dipeptides (Schemes 4 and 12, Table 1)), steric hindrance may be greater with a 1-hydroxyisobutyl substituent than with a simple 1-isobutyl or isobutenyl substituent in the THC. The same four pentacycles were prepared from **94** and **95** with Z-prolinyl chloride in a similar manner. Deprotection-cyclization of the 1,3-*cis*-dipeptides (not shown) under catalytic hydrogenation gave **103** and **106** in low yields (10%), which reflects the presence of the above steric hindrance .

Dehydration of the *tert*-alcohol to the alkene remained the final step in the synthesis of FTC. The same difficulty that we encountered (cf. II-2) was observed in the dehydration with thionyl chloride . Dehydration of both of the 3,12-*trans*-pentacycles (**98**, **104**) with thionyl chloride gave trisubstituted alkenes (**55**, **108**) as major isomers, however, the desired trisubstitued alkenes (**54**, **111**) were obtained only as minor products in the dehydration of 3,12-*cis*-pentacycles (**103**, **106**). (Table 2) They compared the spectral data of these endo-alkenes with those of natural FTC and concluded that natural FTC is the 3,6,12-α-H isomer(**54**). [30]

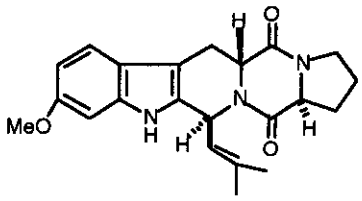
The Ottenheijm-Hermkens group also prepared demethoxy-12β-FTC (**113**) from **81** by a route similar to that shown above. [27c]



98 3α-H,12β-H	**55** 3α-H,12β-H	**107** 3α-H, 12β-H
3,12-*trans*	65%	11%
104 3β-H, 12α-H	**108** 3β-H, 12α-H	**109** 3β-H, 12α-H
3,12-*trans*	28%	13%
103 3α-H, 12α-H	**54** 3α-H, 12α-H	**110** 3α-H, 12α-H
3,12-*cis*	4% **FTC**	44%
106 3β-H, 12β-H	**111** 3β-H, 12β-H	**112** 3β-H, 12β-H
3,12-*cis*	3%	16%



54 Fumitremorgin C



113 Demethoxy-12β-FTC

Table 2

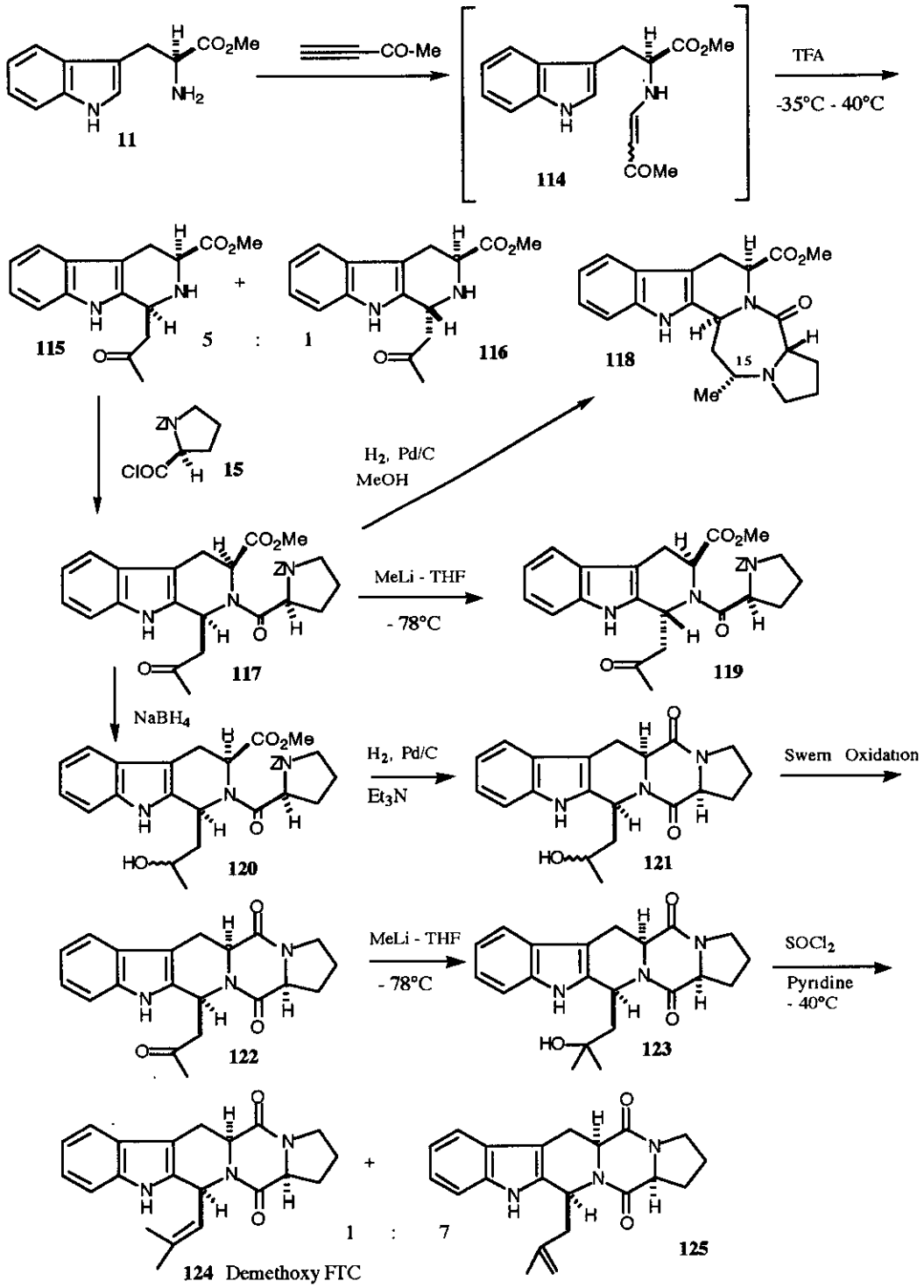
V. Synthesis of demethoxy-FTC by Bailey's group: The P-S reaction with acetylenic carbonyl compounds.

Bailey and his group applied the P-S reaction [10d] to the synthesis of 1,3-disubstituted THCs.[31] Furthermore, they developed a modified P-S reaction using acetylenic ester to prepare optically active 1,3-disubstituted THCs. They devised a synthesis of FTC by applying the stereoselective P-S reaction, since its stereochemistry was ambiguous.[32c,d] They also tried to establish a method for preparing analogs of FTC with regard to the prenyl moiety.

They first carried out the P-S reaction of L-tryptophan ester (**11**) with ethyl propiolate to give 1,3-*cis*-1-methoxycarbonylmethyl-THC,[32a,b] which was transformed into the 3-methoxycarbonylmethyl pentacyclic compound such as **121** in Scheme 21 by conventional methods . However, the proper methyl nucleophile for *trans*forming the ester group in the pentacycle to the *tert*-alcohol could not be found. Therefore, they used butyn-2-one instead of ethyl propiolate in the P-S reaction to give 1,3-*cis*- and 1,3-*trans* -THCs (**115**,**116**) in a 5 : 1 ratio . Coupling of the *cis*-THC (**115**) with *N*-benzyloxycarbonyl-L-prolinyl chloride (**15**) proceeded smoothly to gave the corresponding dipeptide (**117**). They met some difficulties in the formation of a pentacyclic compound. The catalytic hydrogenation of **117** to remove the Z-group gave the undesired pentacycle (**118**), which has a seven-membered ring, by condensation of the ketone with the amine followed by further reduction. To prevent the undesired cyclization as well as to approach the isobutenyl group, **117** was methylated with methyllithium . However, only epimerization at the 1 position of THC *via* cleavage of the 1,2-bond was observed, and not formation of a *tert*-alcohol. Therefore, the ketone in **117** was reduced with sodium borohydride to give the secondary alcohol (**120**). Cyclization of **120** proceeded smoothly with catalytic hydrogenation to give a pentacyclic compound (**121**). (cf. IV-4). Swern oxidation of the pentacycle (**121**) followed by methylation with methyllithium gave the *tert*-alcohol (**123**). The stereochemistry of **122** was determined by X-ray analysis. Dehydration of the *tert*-alcohol (**123**) with thionyl chloride gave demethoxy-FTC (**124**) as a minor product, which is similar to the result obtained in FTC by Ottenheijm's group. This synthetic route may be useful for preparing analogues of FTC and TR-2.[32]

VI Some model experiments by Harrison's group: Modified Pictet-Spengler reactions and formation of the 12,13-dehydro pentacycle.

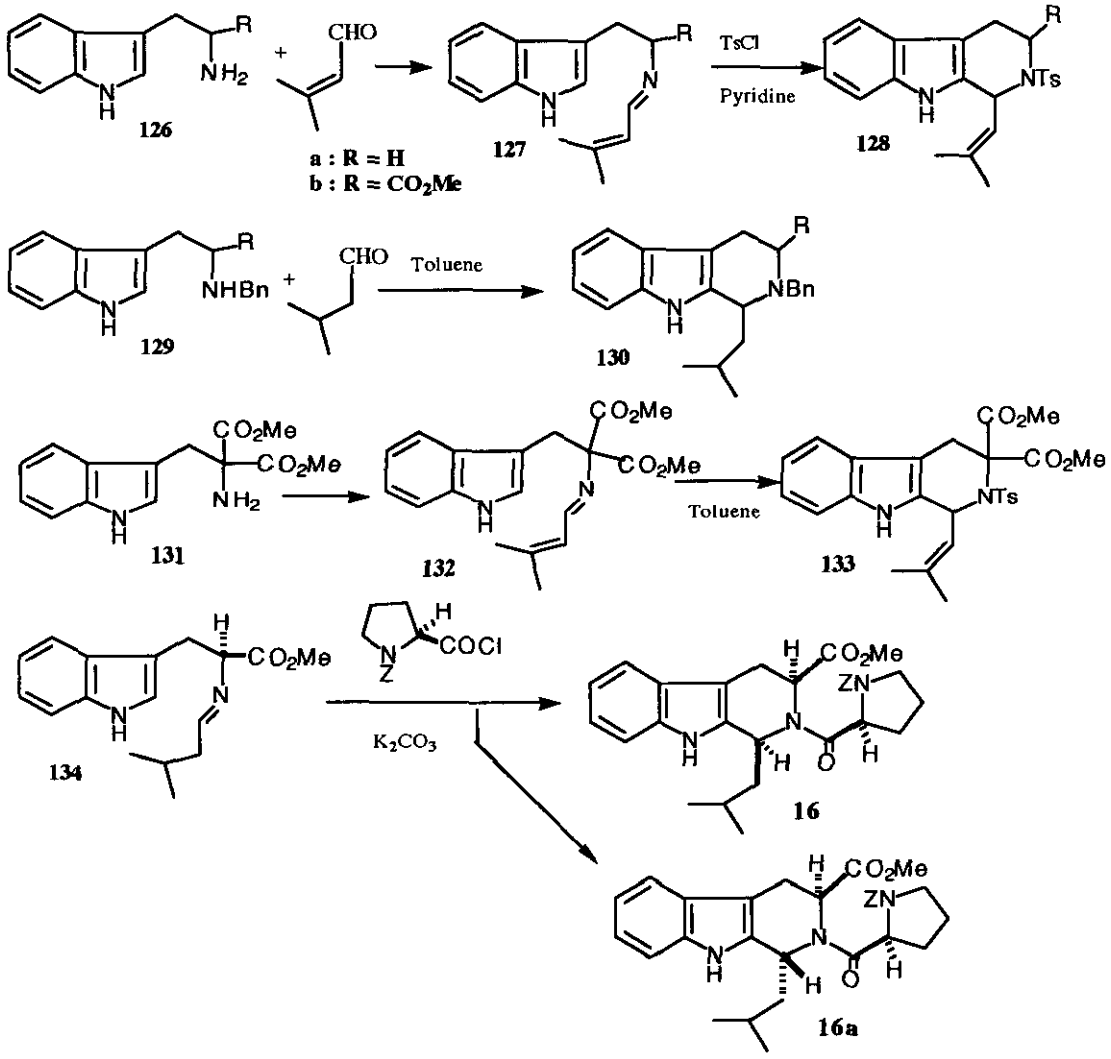
Harrison and co-workers developed the first successful P-S reaction of tryptamine with 3-methyl-2-butenal.[33] Treatment of the imine (**127a**) prepared from tryptamine (**126a**) and 3-methyl-2-butenal with toluenesulfonyl chloride in pyridine gave the 1-isobutenyl-THC (**128a**) in 45% yield, while the acid-catalyzed P-S reaction did not give the desired compound. Alkyl chloroformates have also been shown to be effective in these P-S reactions.[34] However, a similar reaction of the imine (**127b**) prepared from tryptophan ester (**126b**) and 3-methyl-2-butenal with toluenesulfonyl chloride did not give **128b**, and only *N*-tosyltryptophan ester was



Scheme 21

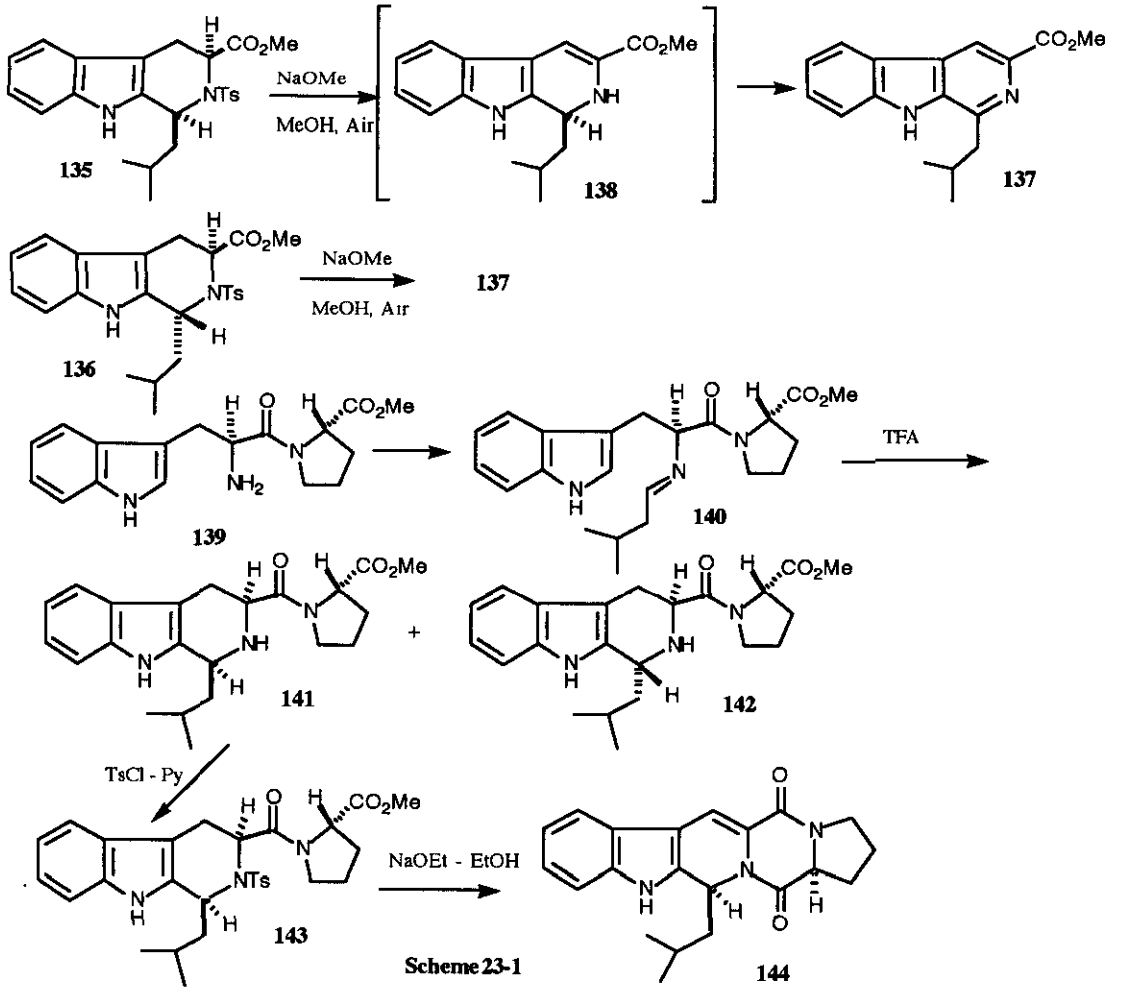
obtained.[35] Furthermore, the P-S reaction of *N*-benzyltryptamine (**129a**) or tryptophan (**129b**) with 3-methyl-2-butanal in boiling toluene gave the THC (**130**) following Cook's

procedure,[36] but a similar reaction with 3-methyl-2-butenal failed to give the corresponding THC. They suggested that failure of the P-S reaction was due to delocalization of the carbon-cation of the imine by the presence of an additional double bond. Therefore, the addition of a more electro-negative group near the imine may facilitate the P-S reaction. They prepared an aminomalonate analog of tryptophan (**131**) and the corresponding imine (**132**) with 3-methyl-2-butenal. Boiling of this imine (**132**) in toluene in the presence of a catalytic amount of benzoic acid gave a mixture of the desired endo-olefinicTHC (**133**) and the isomeric exo-olefin in a ratio of *ca.* 6 : 1. These results provide valuable information regarding the P-S reaction, but they did not develop a new way to synthesize fumitremorgins.[35] We examined this modified P-S reaction to prepare pentacycles. The imine (**134**) prepared from tryptophan ester with 3-methylbutanal gave the THC (**16** and **16a**) upon treatment with prolinyl chloride (**15**).

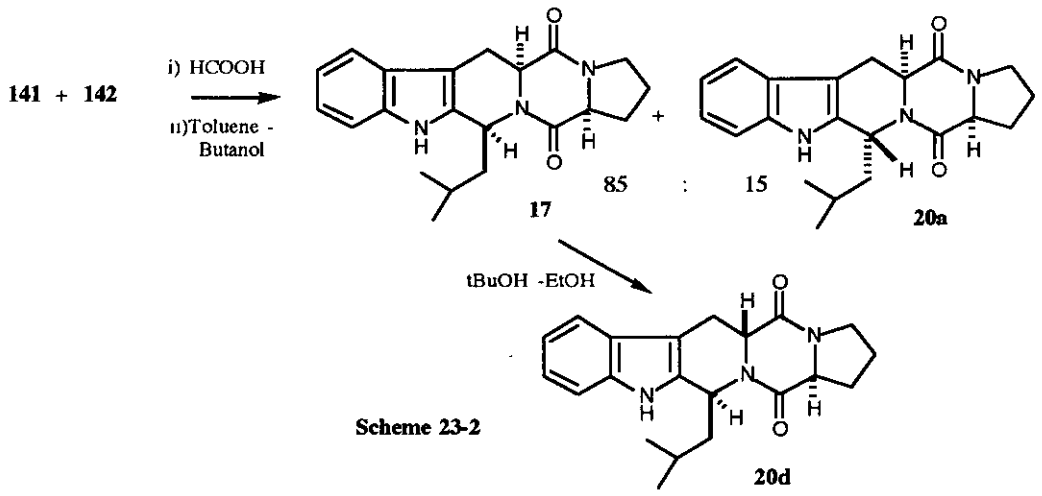


Scheme 22

Unfortunately, the undesired 1,3-*trans* derivative (**16a**) was obtained as a major compound.[11] Furthermore, the attempted reaction of **134** with *N*-carbonyl-L-proline anhydride to give a pentacycle such as **17** in one step was unsuccessful .[11] (Scheme 22)
Harrison's group prepared racemic 2-tosyl-1,3-*cis*- (**135**) and *trans*-THCs (**136**) by the P-S reaction using Cook's procedure followed by tosylation. When both compounds were treated with boiling NaOMe-MeOH in air, the aromatized β-carboline (**137**) was obtained in excellent yield. However, a similar reaction of **135** under nitrogen clarified that the 1,2-dihydro-β-carboline (**138**) acted as an intermediate by an NMR study. This fact suggested that the formation of **138** may be induced by the basic elimination of the tosyl group in **135** as *p*-toluenesulfinyl acid and isomerization, indicating the possibility of developing a nemethodfor the formation of the double bond at the 12,13- position of pentacyclic compounds[35] (Scheme 23).



Scheme 23-1



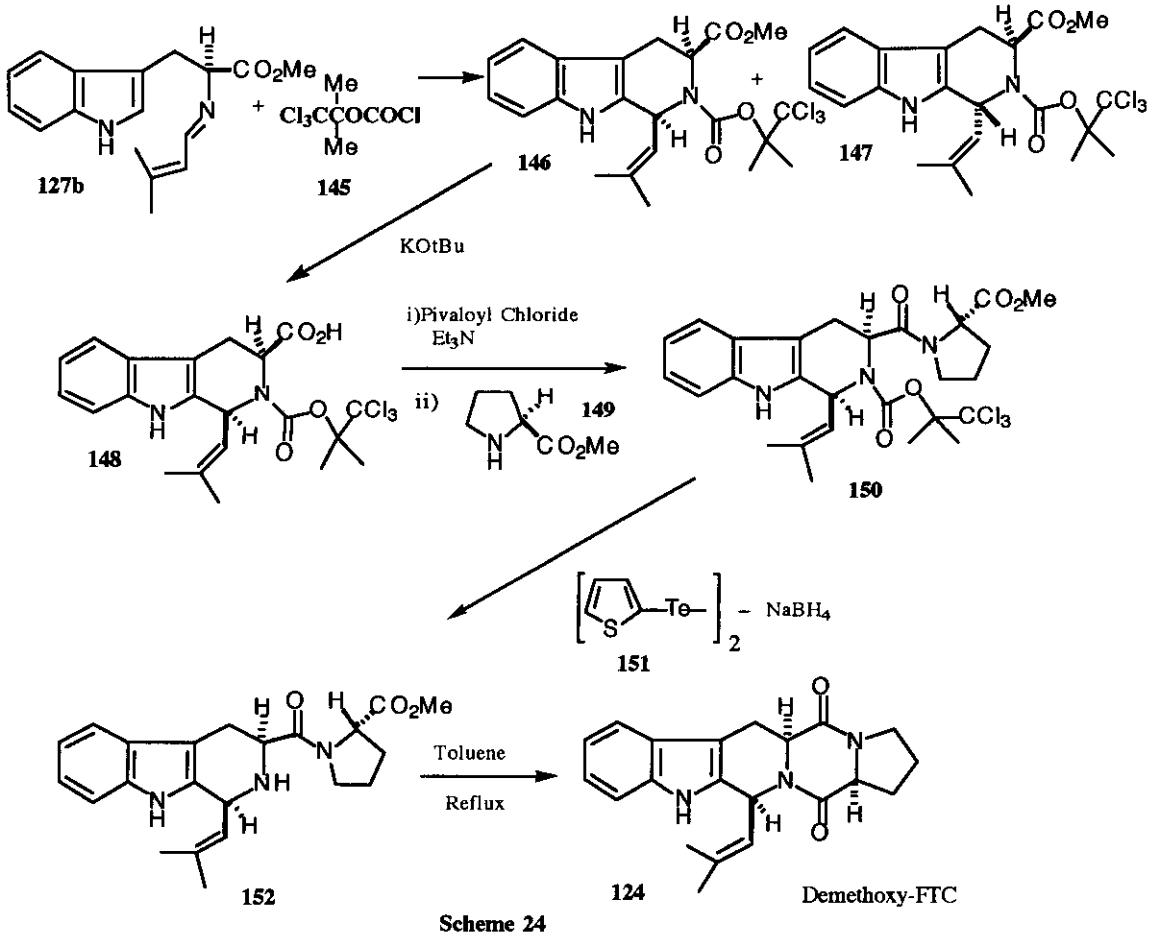
Scheme 23-2

Therefore, they prepared the L-tryptophyl-L-proline (**139**) and its imine (**140**) with 3-methylbutanal. Cyclization of **140** with TFA gave a mixture of 1,3-*cis* - (**141**) and 1,3-*trans* -THC dipeptide (**142**) in a ratio of 85 : 15.[37] The mixture was tosylated to give 1,3-*cis*-2-tosyl-THC (**143**) in 40% yield from the dipeptide. Elimination of the tosyl group in **143** with NaOMe-MeOH in nitrogen gave the 12,13-dehydro pentacycle (**144**) *via* cyclization of the intermediate, 1,2-dihydro-β-carboline. Since the catalytic hydrogenation of **144** was not successful and a similar cyclization with sodium ethoxide in deuteroethanol gave the 6-deutero compound, which suggested epimerization at the 6-position, this stereochemistry was confirmed by the isolation of L-proline upon hydrolysis as well as by a molecular mechanics calculation using PCMODEL, which showed that the (3S,6S)- isomer (**144**) is more stable than the (3S,6R)-isomer. Harrison's group prepared saturated pentacycle(**17** and **20a**) from **139** by refluxing a mixture of **141** and **142** in toluene-butanol after treatment with formic acid.[38] This cyclization was in contrast to that of **16** (cf. II-1). The *cis-cis* -pentacycle (**17**) was epimerized to the *trans-trans* -pentacycle (**20d**) in boiling *tert*-BuOK-EtOH, similar to our result.

VII Synthesis of demethoxy-FTC by Cava's group.[38]

Unlike Harrison's example, P-S cyclization of the imine (**127b**) prepared from tryptophan ester and 3-methyl-2-butenal with 2,2,2-trichloro-*tert*-butoxycarbonyl chloride (**145**) instead of tosyl chloride gave a mixture of 1,3-*trans* - (**147**) and 1,3-*cis*- (**146**)-THCs in 70% yield in a ratio of 2 : 1. Furthermore, they claimed that only 1,3-*trans*-THC was obtained unexpectedly when cyclization was carried out with 2,2,2,-trichloroethoxycarbonyl (Troc) chloride.
The minor *cis*-β-carboline (**146**) was hydrolyzed with potassium *tert*-butoxide-H_2O (2 equivalents)[39] to give a free carboxylic acid (**148**), which was coupled with L-proline ester (**149**) to give **150** *via* a mixed anhydride with pivaloyl acid. Removal of the *N*-protective group with dithienyl ditelluride (**151**)-$NaBH_4$[40] gave the NH derivative (**152**). Reflux of this

dipeptide (**152**) in toluene gave the demethoxy-FTC (**124**) in 78% yield. Neither the spectral data of the final compound nor a discussion of the configuration at the 12-position of natural FTC were provided in their communication.

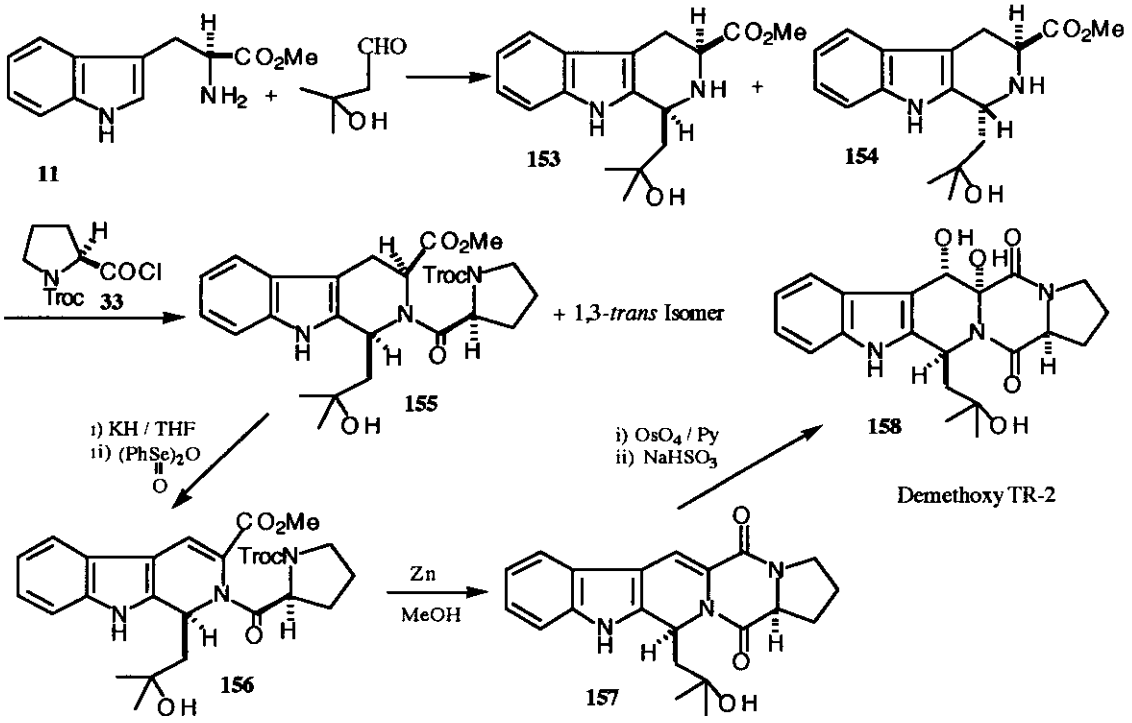


Scheme 24

VIII Synthesis of demethoxy-TR-2 by Boyd and Thompson : The P-S reaction with 3-hydroxy-3-methylbutanal and dehydrogenation of the 3,4-positions of β-carboline.[41]

Boyd ad Thompson examined the P-S reaction of tryptophan with β-hydroxy aldehyde, which had not been investigated sufficiently.[42] The P-S reaction of L-tryptophan methyl ester (**11**) hydrochloride with 3-hydroxy-3-methylbutanal in aqueous solution gave an inseparable mixture of 1,3-*cis*-(**153**) and *trans*-(**154**)-THCs in 71% yield in a ratio of 1.9 : 1. Changing the reaction temperature and pH did not change the ratio of **153** and **154**. The mixture of amino esters (**153**, **154**) was coupled with *N*-Troc-L-prolinyl chloride (**33**) to give

a separable mixture of dipeptides(**155** and an isomer) in 69% yield. This coupling reaction did not proceed with *N*-Troc-L-proline-DCC or the *p*-nitrophenyl ester, indicating a high degree of steric hindrance around the 2-position of the THC .



Scheme 25

Both we and Ottenheijm's group obtained similar results (see above). To introduce the double bond at the 3,4-position of the 1,3-*cis*-THC (**155**), they applied benzeneselenic anhydride oxidation of the carbanion at the 3-position to give **156**. Further aromatization was prevented by the acylated nitrogen at the 2-position, as in previous cases. Removal of the *N*-protective group in **156** smoothly gave the12,13-dehydro-pentacycle (**157**). The final step to demethoxy-TR-2 was *cis*-dihydroxylation of the dehydro derivative (**157**). Osumium tetroxide oxidation following the Sharpless procedure [43] gave demethoxy TR-2 (**158**) in 75% yield. The stereochemistry of these THCs was determined by X-ray analysis of the pentacycle obtained from the 1,3-*trans* -dipeptide. However, the stereochemistry of the final product remained to be re-examined, because the NMR spectral data of the final product (**158**) did not agree with those of synthetic TR-2 given by Ottenheijm's group, and this discrepancy could not be attributed to the presence of a methoxy group.[28]

IX CONCLUSION

Tremorgenic mycotoxins such as FTB and TR-2 have attracted the attention of many synthetic organic chemists due to their complicated structures and biological activities. This review

emphasized that these synthetic strategies largely depended on the background research of the respective groups. Most of these synthetic studies were carried out iindependently in about 1985.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

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