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Model Studies Related to the Total Synthesis of the Fumitremorgins; the Pictet-Spengler Cyclisation and the Formation and Intramolecular Acylation of a 1,2-Dihydro-β-Carboline Derivative

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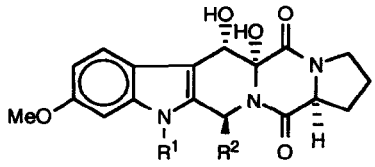
Abstract The preparations of the tetrahydro-β-carbolines **8**, **9b**, and **9d** are described The Pictet-Spengler reaction of *L*-tryptophyl-*L*-proline methyl ester with 3-methylbutanal gave the tetrahydro-β-carbolines **20** and **21**, subsequent acid-catalysed cyclisation afforded the fumitremorgin analogues **22** and **23** The 2-(*p*-toluenesulphonyl)tetrahydro-β-carboline **27a** furnished the unsaturated pentacycle **28a** upon treatment with alkali

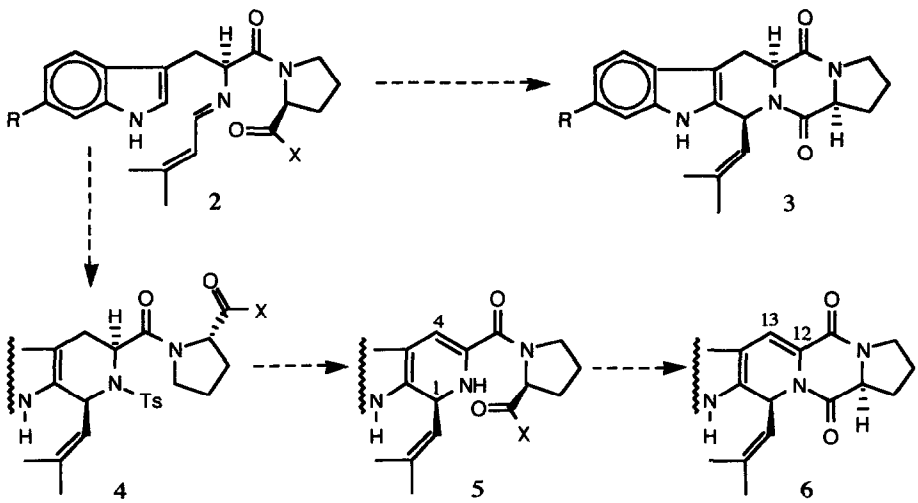
INTRODUCTION

Fumitremorgin B[1] **1a** is a member of the fumitremorgin group of mycotoxins that are synthesised by common moulds of the *Penicillium* and *Aspergillus* genera [2] The unique carbon skeleton and functionality of these compounds, together with their unusual tremor-inducing properties, render them attractive targets for total synthesis



1 a, $R^1 = CH_2C{=}CMe_2$, $R^2 = CH{=}CMe_2$
b, $R^1 = H$, $R^2 = CH_2CMe_2OH$

Prior to our studies in this area, Oikawa *et al* had reported the synthesis of some model compounds[3] but no definitive account of their work has been published Our synthetic studies were based on the expectation that a suitably functionalised imine **2a** or **2b** would undergo acid-catalysed Pictet-Spengler cyclisation followed by dioxopiperazine formation to furnish fumitremorgin C **3a**[2] or its demethoxy analogue **3b** respectively (**Scheme 1**) We also hoped that Pictet-Spengler cyclisation of the imines **2a** and **2b** could be initiated by *p*-toluenesulphonyl chloride[4] to furnish the 2-(*p*-toluenesulphonyl)tetrahydro-β-carbolines **4** Base-catalysed elimination[4] of *p*-toluenesulphinic acid from compound **4a** and imine/enamine tautomerisation would furnish the 1,2-dihydro-β-carboline **5a**. It was anticipated that the latter compound would undergo smooth cyclisation onto a suitably activated proline carboxyl function to afford the 12,13-didehydropentacycle **6a**, suitable for conversion to fumitremorgin B



SCHEME 1 a, R = OMe
b, R = H

We report below some model reactions in the demethoxy-series that underline the scope and limitation of these ideas Some of our results were summarised earlier in preliminary communications [5,6] Since the publication of the latter communication, several groups have reported model studies related to the total synthesis of fumitremorgins [7-12] Total syntheses of fumitremorgins B **1a**[13,14] and C **3a**[15,16] and of the related mycotoxin TR-2 **1b**[17] have also been reported

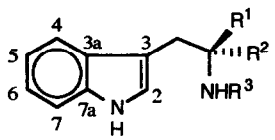
RESULTS AND DISCUSSION

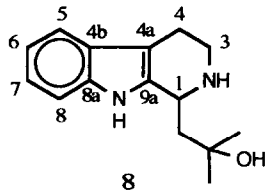
Our early experiments were performed on tryptamine **7a** and its simple derivatives Tryptamine hydrochloride reacted with 3-methyl-2-butenal, in aqueous phosphate buffer at pH 6 2, to furnish the tertiary alcohol **8**, in moderate yield, rather than the expected tetrahydro-β-carboline **9a** It seems most probable that the observed product **8** arose *via* Michael addition of water to the intermediate conjugated imine **10a**, followed by normal Pictet-Spengler cyclisation of the resultant β-hydroxy-imine The structure of the natural fumitremorgin TR-2 **1b**[18] suggests that this reaction sequence may have biosynthetic significance.

Alternatively tryptamine condensed with 3-methyl-2-butenal, in chloroform or benzene, to form the oily imine **10a** which failed to undergo Pictet-Spengler cyclisation under acid catalysis in a range of aprotic solvents However, treatment of the crude imine with *p*-toluenesulphonyl chloride in pyridine, followed by aqueous work-up, furnished the desired 2-(*p*-toluenesulphonyl)tetrahydro-β-carboline **9b** and N_b-(*p*-toluenesulphonyl)tryptamine **7b** in yields of 45 and 17% respectively The preparation of tetrahydro-β-carbolines **8** and **9b** constituted the first successful Pictet-Spengler cyclisations of tryptamine with an aliphatic α,β-unsaturated aldehyde After publication of our preliminary communication,[5] the chloroformate-induced Pictet-Spengler cyclisation of imine **10a** was reported [19]

Encouraged by our results in the tryptamine series, we investigated the reaction of 3-methyl-2-butenal with derivatives of tryptophan *L*-Tryptophan methyl ester **7c** condensed smoothly with 3-methyl-2-butenal in benzene to give the crystalline imine **10b**, which furnished N_b-(dimethylallyl)-*L*-tryptophan methyl ester **7d** upon reduction with sodium borohydride However the imine **10b** failed to undergo acid-catalysed Pictet-Spengler cyclisation in aprotic solvents under a wide range of conditions This imine also

failed to undergo Pictet-Spengler cyclisation when treated with *p*-toluenesulphonyl chloride in pyridine or in pyridine/benzene mixtures Aqueous work-up of the resultant tarry mixtures afforded N_b-(*p*-toluenesulphonyl)-*L*-tryptophan methyl ester **7e** as the major product and no trace of the desired product **9c** could be found It was established by ^{1}H-NMR that the imine **10b** was stable in d_5-pyridine and the imine could be recovered unchanged after two days in solution in dry pyridine by removal of the solvent *in vacuo*





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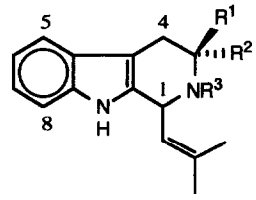
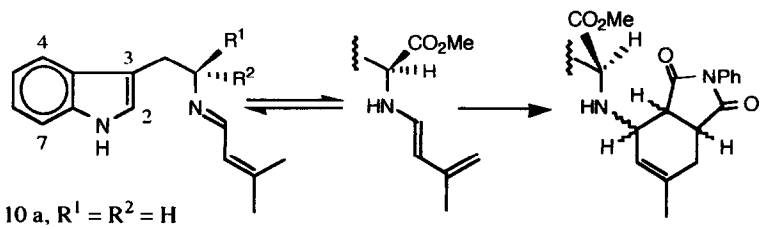


9

7 a, $R^1 = R^2 = R^3 = H$
b, $R^1 = R^2 = H$, $R^3 = Ts$
c, $R^1 = CO_2Me$, $R^2 = R^3 = H$
d; $R^1 = CO_2Me$, $R^2 = H$, $R^3 = CH_2CH{=}CMe_2$
e, $R^1 = CO_2Me$, $R^2 = H$, $R^3 = Ts$
f, $R^1 = R^2 = H$, $R^3 = CH_2Ph$
g, $R^1 = CO_2Me$, $R^2 = H$, $R^3 = CH_2Ph$
h, $R^1 = R^2 = CO_2Et$, $R^3 = H$
i, $R^1 = R^2 = CO_2Et$, $R^3 = CHO$

a; $R^1 = R^2 = R^3 = H$
b, $R^1 = R^2 = H$, $R^3 = Ts$
c, $R^1 = CO_2Me$, $R^2 = H$, $R^3 = Ts$
d, $R^1 = R^2 = CO_2Et$, $R^3 = H$

Two non-crystalline isomers, $C_{27}H_{27}N_3O_4$, were formed in equal yield, together with N_b-(*p*-toluenesulphonyl)-*L*-tryptophan methyl ester, when *N*-phenylmaleimide was added to a solution of the imine **10b** and *p*-toluenesulphonyl chloride in pyridine at room temperature These two isomers were the sole products of reaction when *p*-toluenesulphonyl chloride was omitted from the reaction mixture The spectroscopic data (experimental) are consistent with the formulation of these isomers as products **11a** and **11b** of Diels-Alder cycloaddition between *N*-phenylmaleimide and the dienamine tautomer **12** of the imine[20] (**Scheme 2**)



10 a, $R^1 = R^2 = H$
b, $R^1 = CO_2Me$, $R^2 = H$
c, $R^1 = R^2 = CO_2Et$
d, $R^1 = CONH_2$, $R^2 = H$

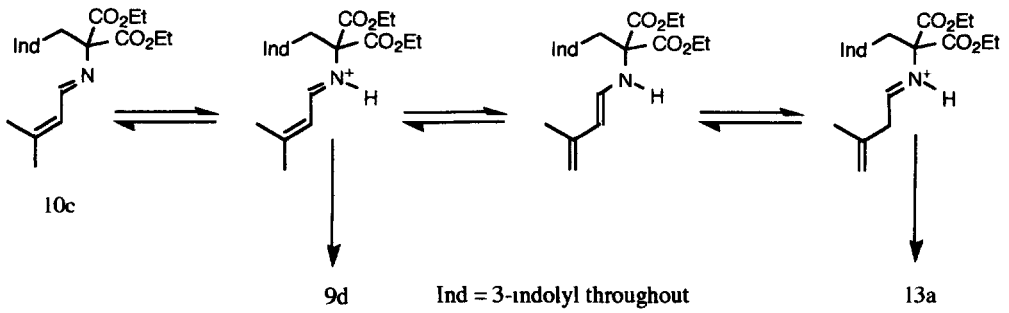
12

11 a & b

SCHEME 2

It has been reported that N_b-benzyltryptamine **7f** and N_b-benzyltryptophan methyl ester **7g** undergo facile Pictet-Spengler reaction with a range of aldehydes in refluxing toluene [21] In our hands, both failed to give products of Pictet-Spengler cycloaddition with 3-methyl-2-butenal The reluctance of the latter aldehyde to undergo the acid-catalysed Pictet-Spengler reaction with tryptophan derivatives in aprotic solvents is noteworthy in view of the ease of the Pictet-Spengler reaction between the same derivatives and

3-methylbutanal (*vide infra*). Whichever aldehyde is used, the protonated imine is an obligatory intermediate in these reactions,[22] and the lower reactivity of the α,β-unsaturated imine may simply reflect the greater delocalisation of positive charge in its conjugate acid The placement of an additional electron-withdrawing substituent in the vicinity of the protonated imine nitrogen should increase the positive charge on the imine carbon and thus promote the Pictet-Spengler cyclisation Accordingly we prepared the amino-diester **7h** *via* acid-catalysed ethanolysis of the known[23] formamido-diester **7i** The amino-diester condensed smoothly with 3-methyl-2-butenal to furnish the crystalline imine **10c** which was recovered unchanged after prolonged refluxing in benzene. Gratifyingly, addition of a catalytic amount of benzoic acid to the refluxing solution resulted in rapid and quantitative Pictet-Spengler cyclisation to give a mixture of the desired tetrahydro-β-carboline **9d** and the isomeric compound **13a**, in the ratio *ca* 6 1 (^{1}H-NMR) The same isomeric mixture was prepared more conveniently by condensation of 3-methyl-2-butenal with the amino-diester **7h** in refluxing benzene in the presence of a catalytic amount of benzoic acid The major tetrahydro-β-carboline **9d**, contaminated with traces of **13a**, could be crystallised directly from the mixture in *ca* 65% yield but complete removal of the minor product required lengthy and tedious fractional crystallisation The minor component **13a** was isolated as a glass by flash chromatography of the mother liquors Presumably **13a** arises from acid-catalysed equilibration of the conjugated imine **10c** with its dieneamine tautomer, and Pictet-Spengler cyclisation of the latter after protonation of the α-carbon (**Scheme 3**)

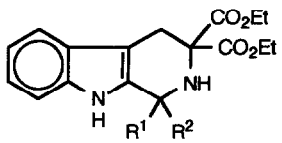


SCHEME 3

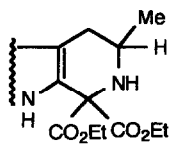
The ease of the Pictet-Spengler reaction between 3-methyl-2-butenal and the amino-diester **7h** prompted us to examine the reaction between the latter amine and other carbonyl compounds In particular, benzaldehyde reacted with **7h** in refluxing benzene with azeotropic removal of water, to furnish quantitatively (t l c) the 1-phenyltetrahydro-β-carboline **13b** within 2 h Presumably adventitious traces of benzoic acid were sufficient to catalyse cyclisation of the intermediate imine In a parallel experiment, in which benzaldehyde was allowed to react with tryptophan methyl ester under the same conditions, only the expected benzaldimine was formed Subsequent Pictet-Spengler cyclisation of the latter was extremely slow, even after the deliberate addition of benzoic acid to the refluxing solution, in confirmation of the observations of other workers [22] Acid-catalysed Pictet-Spengler reaction of the amino-diester **7h** with acetone and with acetaldehyde furnished the expected tetrahydro-β-carbolines **13c** and **13d** respectively The 1,1-di(ethoxycarbonyl)-tetrahydro-β-carboline **14** was prepared by unexceptional means to aid in NMR assignments

Following our disappointing experiences with the reaction of 3-methyl-2-butenal with tryptophan derivatives, summarised above, we turned our attention to the more amenable though less synthetically useful Pictet-Spengler reactions with 3-methylbutanal in order to test some of the ideas presented in the introduction 3-Methylbutanal condensed smoothly with *L*-tryptophan methyl ester in refluxing benzene, in

the presence of a catalytic amount of benzoic acid, to furnish the expected *cis*- and *trans*-tetrahydro-β-carbolines, **15a** and **16a** respectively, in the molar ratio 52.48 (as determined by ^{1}H-NMR) as the sole products. The pure *cis* and *trans* compounds were conveniently isolated in yields of 39 and 31% respectively by fractional crystallisation and were identified unambiguously by ^{13}C-NMR [24] Neither product showed significant optical rotation and both were shown to be racemic by examination of their ^{1}H-NMR spectra recorded in $CDCl_3$ in the presence of the chiral shift reagent *tris*(3-heptafluorobutyryl-*d*-camphorato)europium(III) [Eu(hfbc)$_3$]. In the case of both the *cis* and *trans* racemates, the chemical shift of the methyl ester protons for each enantiomer showed a good linear relationship with the mole ratio of shift reagent to substrate over the range examined (Figures 1 and 2 respectively) Alternatively, when the *cis*- and *trans*-tetrahydro-β-carbolines were isolated by flash chromatography, ^{1}H-NMR in the presence of Eu(hfbc)$_3$ revealed that both products had been formed in about 15% enantiomeric excess, and it was clear that we had previously selectively crystallised the racemic compounds from a partially racemic mixture



13 a, R^1 = H, R^2 = $CH_2C(Me)=CH_2$
b, R^1 = Ph, R^2 = H
c, R^1 = R^2 = Me
d, R^1 = H, R^2 = Me



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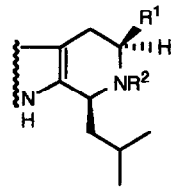

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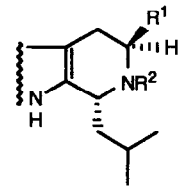


16

a, R^1 = CO_2Me, R^2 = H
b, R^1 = $CONH_2$, R^2 = H
c, R^1 = CO_2Me, R^2 = Ts

The Pictet-Spengler reaction between 3-methylbutanal and *L*-tryptophan methyl ester also occurred in refluxing benzene at apparently the same rate in the *absence* of benzoic acid to furnish the *cis*- and *trans*-tetrahydro-β-carbolines **15a** and **16a** in the same ratio as before Presumably the cyclisation step was catalysed under these conditions by adventitious 3-methylbutanoic acid The *cis*- and *trans*-tetrahydro-β-carbolines were isolated by flash chromatography as before, each in about 40% enantiomeric excess Nakagawa *et al* reported that the same tetrahydro-β-carbolines were formed in 22% enantiomeric excess under the latter conditions.[8]

During the course of our studies Massiot *et al.*[25] reported that an imine derived from an aliphatic aldehyde and *L*-tryptophanamide furnished the homochiral *cis*-tetrahydro-β-carboline, in 70% yield, upon Pictet-Spengler cyclisation catalysed by trifluoroacetic acid in dichloromethane at 0°C. At the time we ascribed the lack of racemisation in that reaction to the use of a 3-carboxamide, in which the α-proton was expected to be less acidic than that of an ester. It was subsequently shown that high enantiomeric excesses can also be achieved in the Pictet-Spengler cyclisation, under similar conditions, of imines derived from *L*-tryptophan methyl ester [8,26] In our hands 3-methylbutanal reacted with *L*-tryptophanamide to furnish a crystalline imine Treatment of the latter in dichloromethane with trifluoroacetic acid at 0°C gave a crystalline mixture of the *cis*- and *trans*-tetrahydro-β-carbolines **15b** and **16b**, in the ratio 85 15 This mixture was optically active, with $[a]_D$ -126 5°, though the degree of enantiomeric excess was not determined Authentic samples of the racemic *cis* and *trans* carboxamides were prepared from the esters **15a** and **16a** respectively, by reaction with methanolic ammonia, for t l c comparisons Not surprisingly the imine derived from the condensation of 3-methyl-2-butenal and *L*-tryptophanamide failed to undergo Pictet-Spengler cyclisation

For the synthesis of model compounds related to pentacycle **3**, the hydrobromide salt of *L*-tryptophyl-*L*-proline methyl ester was prepared as described by Swelim *et al* [27] Careful neutralisation of an aqueous solution of the salt liberated the free dipeptide ester **17** which was extracted immediately into

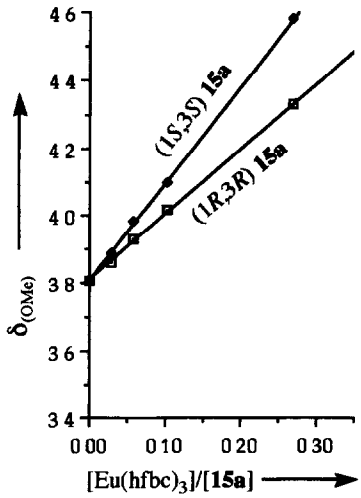


Figure 1 ^{1}H-NMR, dependence of δ_{OMe} for enantiomers of **15a** on molar ratio of Eu(hfbc)$_3$ to racemic **15a**

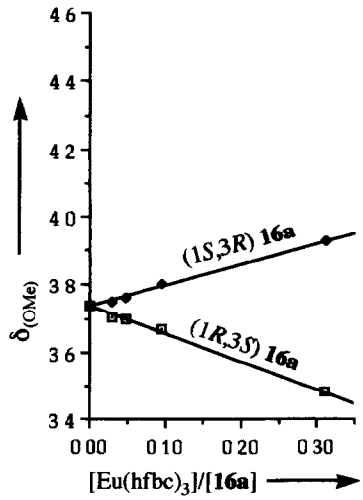


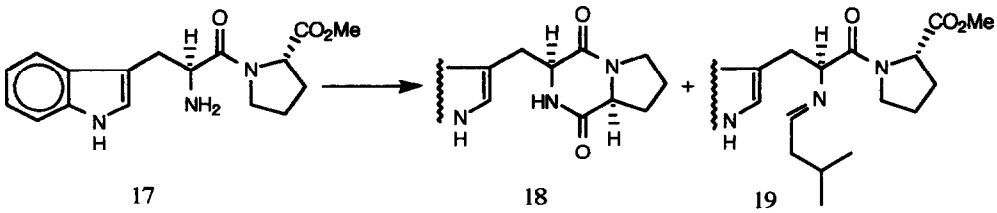
Figure 2 ^{1}H-NMR, dependence of δ_{OMe} for enantiomers of **16a** on molar ratio of Eu(hfbc)$_3$ to racemic **16a**

dichloromethane and crystallised As anticipated, solutions of this dipeptide ester in organic solvents were extremely labile, and self-condensation occurred slowly at room temperature to form the cyclic dipeptide **18** [28] Fortunately the dipeptide-ester was stable indefinitely in the crystalline state The ^{1}H- and ^{13}C-NMR spectra of the dipeptide ester in d$_6$-d m s o were complicated by the doubling of many resonances as a result of *cis-trans* isomerism about the peptide bond and also by slow intramolecular condensation to afford the cyclic dipeptide In order to ensure that the dipeptide-ester had not been partially epimerised, a sample was cyclised quantitatively in refluxing benzene to furnish the known *cis*-dioxopiperazine **18** which was shown to be completely free of its *trans*-diastereoisomer [29]

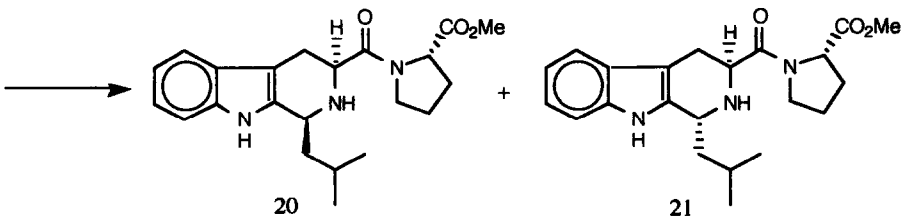
With the stereochemical integrity of the dipeptide-ester **17** thus assured, we set about the synthesis of the pentacycle **22** (**Scheme 4**) Dipeptide-ester **17** was allowed to condense with 3-methylbutanal in cold dichloromethane, in the presence of 4Å molecular sieves, to afford a solution containing the imine **19** The solution was cooled to 0°C and one equivalent of trifluoroacetic acid was added The reaction mixture was then allowed to warm to room temperature overnight Work-up afforded an amorphous solid which was shown by t l c and ^{1}H-NMR to consist mainly of the expected tetrahydro-β-carbolines **20** and **21**, in the ratio 85 15, together with the cyclic dipeptide **18** and unreacted aldehyde Acid-catalysed cyclisation of the mixed tetrahydro-β-carboline derivatives in refluxing toluene and 2-butanol[30] gave a mixture containing the pentacycles **22** and **23**, in the ratio 85 15, as the major components Fractional crystallisation of this mixture furnished the pure 3*S*,6*S*,12*S*-pentacycle **22**, m p 293-298°C, [a]$_D$ -83 9°, in 40% yield without recourse to chromatography The minor 3*R*,6*S*,12*S*-pentacycle **23**, still contaminated with traces of **22**, was isolated by flash chromatography The synthesis of these two pentacycles by a significantly different approach was reported subsequently by Nakagawa *et al* [8]

Pentacycle **22** was quantitatively isomerised by refluxing ethanolic alkali to furnish a third isomer which was less polar on t l c than either **22** or **23** Epimerisation can only have occurred at C-6 and/or at C-12 under these conditions The new pentacycle was assigned the 3*S*,6*S*,12*R*-configuration **24** since examination of molecular models showed that the 3*S*,6*R*,12*S*-diastereomer would be no less strained and far more sterically crowded, whilst the enantiomer **23** of the 3*S*,6*R*,12*R*-diastereomer was already in hand

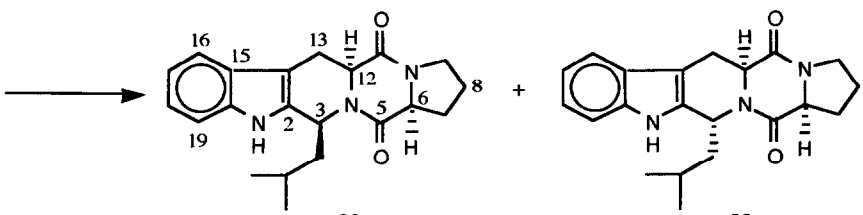
Following the successful synthesis of pentacycles related to **3** we turned our attention to models for



17 18 19

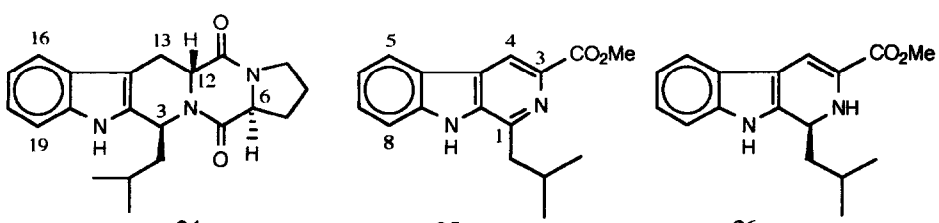


20 21



22 23

SCHEME 4

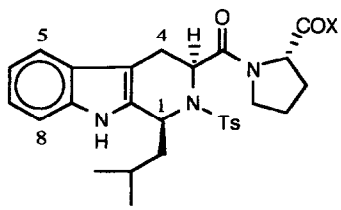


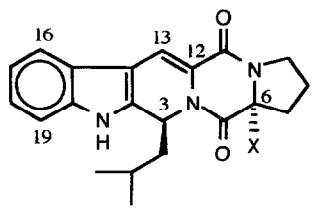
24 25 26

the proposed reaction sequence **4** to **5** to **6** The racemic *cis*- and *trans*-tetrahydro-β-carbolines **15a** and **16a** were each converted by standard methods to their *N*-*p*-toluenesulphonyl derivatives **15c** and **16c** It is worthy of comment that the ^{13}C resonances for both C-1 and C-3 of the *trans* product appeared at higher frequency than each of those for the *cis* product Therefore the relative stereochemistry of 1,3-disubstituted 2-(*p*-toluenesulphonyl)tetrahydro-β-carbolines cannot be assigned using the rule proposed by Bailey *et al*[31] Both the *cis*- and *trans*-2-(*p*-toluenesulphonyl)tetrahydro-β-carbolines were converted quantitatively into the β-carboline **25** upon refluxing with ethanolic alkali in air The intermediate 1,2-dihydro-β-carboline **26** was detected by ^1H-NMR [δ 6 7 (1H, s, H-4)][32] when the elimination of *p*-toluenesulphinic acid from the *cis*-*p*-

toluenesulphonyl derivative **15c** was conducted under an atmosphere of nitrogen

Encouraged by these observations, we prepared the 2-(*p*-toluenesuphonyl)tetrahydro-β-carboline **27a** from the mixed tetrahydro-β-carbolines **20** and **21**, in 50% overall yield from *L*-tryptophyl-*L*-proline methyl ester The derivative **27a** was then refluxed with sodium ethoxide in ethanol under an atmosphere of nitrogen The elimination of *p*-toluenesulphinic acid was accompanied by intramolecular acylation of the putative intermediate 1,2-dihydro-β-carboline to furnish the yellow fluorescent pentacycle **28a** in quantitative yield This pentacycle crystallised from ethanol in beautiful yellow cubes, which lost solvent of crystallisation upon exposure to air to leave a pale yellow amorphous powder It was clear from t l c and from the spectroscopic data that a single pentacycle had been formed, and the ^{1}H- and ^{13}C-NMR spectra were completely consistent with the structure assigned However when the elimination of *p*-toluenesulphinic acid was conducted in [*OH*-$^{2}H_{1}$]ethanol as solvent the proline α-proton (H-6) of the product pentacycle **28b** was completely exchanged for deuterium. Therefore it was necessary to demonstrate that the product was the desired 3*S*,6*S*-pentacycle **28** and not the 3*S*,6*R*-epimer





27 a, X = OMe
b, X = OH
c, X = NH_2

28 a, X = H
b, X = D

To this end numerous unsuccessful attempts were made to prepare the pentacycle **28a** under conditions that did not equilibrate H-6 with solvent protons In the course of these studies, the carboxylic acid **27b** and carboxamide **27c** were prepared The latter compound afforded the same pentacycle **28a**, in lower yield, when refluxed with one equivalent of sodium ethoxide in ethanol However the formation of **28** was accompanied again by complete exchange of H-6 when the reaction was conducted in [*OH*-$^{2}H_{1}$]ethanol with less than one equivalent of alkali An alternative approach called for the reduction of the 12(13) double bond of **28a** to furnish pentacycle **22** Unfortunately the didehydro-pentacycle **28a** was resistent to hydrogenation over palladium black or Adams catalyst[33] at pressures of up to 70 atmospheres However acid-catalysed hydrolysis of the didehydro-pentacycle afforded *L*-proline, which is consistent with the configuration depicted in **28a** Independent support for this configuration derives from molecular mechanics calculations using PCMODEL, which revealed that the enthalpy of formation of the 3*S*,6*S* compound **28a** is some 15 5 kJmol^{-1} lower than that of the 3*S*,6*R*-diastereoisomer, in confirmation of our earlier qualitative prediction,[6] based on the study of Dreiding models, that the desired isomer was the thermodynamically more stable

12,13-Didehydropentacycles related in structure to **6** and **28** have been utilised by other workers as key intermediates in the total synthesis of natural fumitremorgins[13,14,17] and their analogues [3,8,11] The 12(13) double bond was generated in those studies by dehydrogenation of a saturated pentacycle with DDQ,[3,8] by dehydrogenation of a 2-prolyl-tetrahydro-β-carboline derivative with DDQ[13] or with benzeneseleninic anhydride,[11] by acid-catalysed dehydration of a functionalised β-hydroxy-*D*-tryptophyl-*L*-proline cyclic anhydride and tandem closure of ring C,[14] and by oxidation of a saturated pentacycle with hexachloro-2,4-cyclohexadieneone [17] Our approach,[6] described above, provides a high yield alternative to these methods which should be applicable to the total synthesis of both fumitremorgin B and TR-2

EXPERIMENTAL

Organic extracts were routinely dried over $MgSO_4$ and evaporated to dryness on a rotary evaporator. T.l.c was performed on 0.25 mm thick silica gel layers containing a fluorescent indicator precoated on plastic sheets, supplied by Camlab, Cambridge; compounds were visualised by fluorescence under UV light (254 nm), or by spraying with a cerium (IV) preparation [$Ce(SO_4)_2$ (10g), trichloroacetic acid (100 g) in boiling water (400 cm^3), clarified by the addition of conc. sulphuric acid] followed by heating to 100° C Microanalyses were performed by Butterworth Laboratories Ltd., Middlesex. Melting points were recorded on a Reichert hot stage m.p apparatus and are uncorrected. Optical rotations were recorded with a Perkin Elmer 141 polarimeter Molecular modelling was carried out using the program PCMODEL (version 3.2),[34] which uses the MMX force field.[35]

Except where stated otherwise, ^{1}H-NMR spectra were recorded at 90 MHz with a Perkin Elmer R32 spectrometer for $CDCl_3$ solutions with internal tetramethylsilane lock Alternatively ^{1}H-NMR spectra were recorded at 60 MHz using a Perkin Elmer R12 spectrometer, at 220 MHz using a Perkin Elmer R34 spectrometer, or at 250 MHz using a Bruker ACF250 spectrometer. Except where stated otherwise, Fourier transform ^{1}H-decoupled ^{13}C-NMR spectra were recorded at 22 6 MHz with a JEOL FX-90Q spectrometer for $CDCl_3$ solutions with internal tetramethylsilane Multiplicities were taken from the off-resonance decoupled spectra and/or from ^{1}H-undecoupled spectra Otherwise, ^{13}C-NMR spectra were recorded at 63 MHz on a Bruker ACF250 spectrometer

1-(2-Hydroxy-2-methyl)propyl-1,2,3,4-tetrahydro-β-carboline (8)

Tryptamine hydrochloride (982 mg) and potassium dihydrogen phosphate (1.403 g) were dissolved in water (40 cm^3) and the pH was adjusted to 6 2 by the addition of 1 *M* aqueous sodium hydroxide. The solution was degassed with oxygen-free nitrogen and 3-methyl-2-butenal (848 mg) was added. The mixture was swirled gently until a homogeneous solution resulted, then left under nitrogen at 25°C for 16 days. The resultant mixture was filtered at the pump to remove an unidentified red-brown precipitate (420 mg), m.p. 146°C. The filtrate was extracted with benzene to yield a yellow-brown oil (104 mg) which was discarded. The aqueous phase was brought to pH 10 by the addition of 0 880 ammonia solution and was extracted with ether. The extract was dried and evaporated *in vacuo* to furnish a colourless solid (741 mg) which consisted of a mixture of tryptamine and the tetrahydro-β-carboline **8** in the molar ratio 5:7 (^{1}H-NMR). Repeated recrystallisation of this solid from benzene/ether, followed by sublimation (180°C, 0.1 mmHg) furnished the *title compound*, m.p. 194-195.5°C, that was homogeneous by t l c and NMR. (Found: M^+, 244.1575 $C_{15}H_{20}N_2O$ requires M, 244 158); δ_H 1 29 (3H, s, Me), 1.42 (3H, s, Me), 1.7-2 15 [2H, AB part of ABX, (collapsed to AB quartet, δ_A 1 84, δ_B 1.95, J_{AB} 14.5 Hz, on decoupling at δ 4.38), $CHC\underline{H}_2$], 2 75 [2H, m, (simplified on decoupling at δ 3 15, sharpened on decoupling at δ 4.38), $C\underline{H}_2CH_2N$], 3.15 [2H, m (simplified on decoupling at d 2.75), $CH_2C\underline{H}_2N$], 3.6 (2H, br, NH + OH), 4.38 [1H, X part of ABX, J_{AX} 5 1, J_{BX} 9.3 Hz (collapsed to singlet on decoupling at 1.85, sharpened on decoupling at δ 2 75), $C\underline{H}CH_2$], 7 0-7.55 (4H, m, aromatic H), 8 15 (1H, br s, NH), δ_C 22.4 (t, C-4), 29 0 (q, Me), 31.3 (q, Me), 39 7 (t, C-3 or $\underline{C}H_2CMe_2OH$), 44 6 (t, $\underline{C}H_2CMe_2OH$ or C-3), 49.5 (d, C-1), 70 6 (s, COH), 108.7 (s, C-4a), 110 8 (d, C-8), 118.0 (d, C-5), 119 4 (d, C-7), 121.7 (d, C-6), 127 4 (s, C-4b), 135.6 (2C, s, C-8a and 9a)

1-(2-Methyl-1-propenyl)-2-(*p*-toluenesulphonyl)-1,2,3,4-tetrahydro-β-carboline (9b)

A solution of tryptamine (481 mg) and 3-methyl-2-butenal (277 mg) in benzene (35 cm^3) was refluxed for 2 5 h in the presence of crushed 4Å molecular sieves After filtration the pale orange solution was evaporated *in vacuo* to furnish the imine **10a** as an oil (728 mg), δ_H (60 MHz) 1.80 (6H, s, CMe_2), 3.08 (2H, m, $C\underline{H}_2CH_2N$), 3.80 (2H, m, $CH_2C\underline{H}_2N$), 6.06 (1H, d, ^{3}J 9.5 Hz, N=CHC$\underline{H}$), 6 8-7.8 (5H, m, aromatic H), 8 10 (1H, d, ^{3}J 9.5 Hz, N=C$\underline{H}$CH), and 9.0 (1H, br s, NH) The crude imine (693 mg)

and *p*-toluenesulphonyl chloride (544 mg) were dissolved in pyridine (3 cm^3) at room temperature under an atmosphere of nitrogen After nine days, the black opaque reaction mixture was diluted with ether and the resulting solution was washed with 0.5 *M* hydrochloric acid; a black tar which precipitated was discarded The organic extract was dried and evaporated to dryness *in vacuo* The residue (702 mg) was submitted to preparative t.l.c on silica gel, eluted with ethyl acetate/benzene (8:92 by volume). The fraction with Rf 0 2 was identified as N_b-(*p*-toluenesulphonyl)tryptamine **7b** (156 mg, 16.5%) The fraction with Rf 0.55 furnished the *title compound* (471 mg, 45%) m.p 175-176°C (prisms, from ethyl acetate/light petroleum) (Found. C, 69.5; H, 6.5, N, 7 6%; M^+, 380.155. $C_{22}H_{24}N_2O_2S$ requires C, 69.4, H, 6.4; N, 7 4%, M, 380.156), δ_H 1.60 (3H, s, *E*-Me), 1.93 (3H, s, *Z*-Me), 2.30 (3H, s, *Ts*-Me), 2.65 (2H, m, $C\underline{H}_2CH_2N$), 3.25 (1H, m, $CH_A\underline{H}_BN$), 4.10 [1H, m, (collapsed to doublet, ^2J 13 Hz, on decoupling at δ 2.65), $CH_A\underline{H}_BN$], 5 10 (1H, br d, ^3J 10 Hz, =C<u>H</u>CHN), 5.85 [1H, d, ^3J 10 Hz, (collapsed to singlet on decoupling at δ 5.10), =CHC<u>H</u>N], 6 9-7 5 (6H, m, aromatic H), 7.64 (2H, d, ^3J 8.5 Hz, H-3 and H-5 of Ts), 7 8 (1H, s, NH), δ_C 18 4 (q, *Z*-Me), 21.3 (t, C-4), 21.5 (q, *Ts*-Me), 25.8 [q, (collapsed to singlet on SFORD at δ_H 1.60), *E*-Me], 40.6 (t, C-3), 51.1 [d, (collapsed to singlet on SFORD at δ_H 5 85), C-1], 107.9 (s, C-4a), 110.9 (d, C-8), 118.2 (d, C-5), 119.5 (d, C-7), 121.5 [d, (collapsed to singlet on SFORD at δ_H 5 10), =CH-], 121.9 (d, C-6), 126.8 (s, C-4b), 127 0 [2C, d, (collapsed to singlet on SFORD at δ_H 7.64), C-3 and C-5 of Ts], 129.3 (2C, d, C-2 and C-6 of Ts), 132.5 (s, C-9a or $Me_2\underline{C}$=), 136.1 (2C, s, C-8a and $Me_2\underline{C}$= or C-9a), 138 0 (s, C-4 of Ts), 143 0 (s, C-1 of Ts).

Preparation of the Imine (10b)

L-Tryptophan methyl ester (4.36 g) was dissolved in warm dry benzene (80 cm^3) containing 4Å molecular sieves (5 g) in suspension. The solution was cooled to room temperature and 3-methyl-2-butenal (1 85 g) in dry benzene (5 cm^3) was added with gentle stirring Fine crystals began to precipitate after about 20 m After 2 h the stirred suspension of crystals was decanted free from molecular sieves and filtered under suction to furnish the *imine* (4.52 g, 80%), m p 126-127°C (m p 131-132 5°C after recrystallisation from ethyl acetate/light petroleum), $[a]_D^{25}$ -165° (c 1 1, CH_2Cl_2), $[a]_D^{24}$ -214.5° (c 0.9, pyridine) (Found M^+, 284 153 $C_{17}H_{20}N_2O_2$ requires M, 284.1525), δ_H ($CDCl_3$) 1 66 (3H, s, Me), 1.81 (3H, s, Me), 3 17 and 3 50 (each 1H, A and B parts respectively of ABX, J_{AB} 14 5, J_{AX} 8, J_{BX} 5 Hz, CH_2), 3 72 (3H, s, CO_2Me), 4 15 (1H, X part of ABX, J_{AX} 8, J_{BX} 5 Hz, C<u>H</u>CO_2Me), 6.03 (1H, br d, J 9 Hz, N=CHC<u>H</u>), 6 9-7 75 (5H, m, aromatic H), 7 78 (1H, d, J 9 Hz, N=C<u>H</u>CH), 8 53 (1H, br s, NH), δ_H (d_5-pyridine) 1.56 (3H, s, Me), 1 63 (3H, s, Me), 3 62 (3H, s, CO_2Me), 3 46 and 3 78 (each 1H, A and B parts respectively of ABX, J_{AB} 14, J_{AX} 8, J_{BX} 6 Hz, CH_2), 4 49 (1H, X part of ABX, J_{AX} 8, J_{BX} 6 Hz, C<u>H</u>CO_2Me), 6 13 (1H, br d, J 9 Hz, N=CHC<u>H</u>=), 7.15-7.95 (5H, m, aromatic H), 8 13 (1H, d, J 9 Hz, N=C<u>H</u>CH=), δ_C 18 5 (q, *Z*-Me), 26 6 (q, *E*-Me), 30 0 (t, CH_2), 52 2 (q, MeO), 73.8 (d, α-C), 111.0 (s, C-3), 111.2 (d, C-7), 118 8 (d, C-4), 119 3 (d, C-6), 121.8 (d, C-5), 123 6 (d, C-2), 125 0 (d, <u>C</u>H=CMe_2), 127.3 (s, C-3a), 136.3 (s, C-7a), 148 8 (s, =<u>C</u>Me_2), 161.9 (d, CH=N), 173.0 (s, C=O)

N_b-(3,3-Dimethylallyl)-*L*-Tryptophan Methyl Ester (7d)

Sodium borohydride (692 mg) was added in portions over 3 h to a stirred solution of the imine **10b** (4 200 g) in anhydrous methanol (70 cm^3), at 0°C, in the presence of 4Å molecular sieves (4 g) After a further hour, the molecular sieves were removed, the solution was evaporated to dryness, and the residue partitioned between benzene and water The benzene extract was evaporated to dryness *in vacuo* and the solid residue crystallised from chloroform/light petroleum to give the almost pure product (3 237 g, 77%), m p 101-103°C Recrystallisation from ethyl acetate/light petroleum furnished the *title compound*, m p 103.5-104°C (thick needles), $[a]_D^{21}$ +16 5° (c 1.1, MeOH) (Found C, 71 5, H, 8 0, N, 10.1%, M^+, 286 168 $C_{17}H_{22}N_2O_2$ requires C, 71.3, H, 7 7, N, 9 8%, M, 286.168), δ_H (60 MHz) 1 55 (3H, s, Me), 1 66 (3H, s, Me), 1 77 (1H, br s, NH), 3.15 (4H, m, 2 x CH_2), 3 62 (3H, s, CO_2Me), 3.7 (1H, m, CHN), 5 2 (1H, br t, ^3J 6 Hz, C<u>H</u>=C), 6 9-7 7 (5H, m, aromatic H), 8 55 (1H, br s, indole NH), δ_C 17 8

(q, Z-Me), 25 7 (q, *E*-Me), 29 4 (t, β-CH_2), 45.7 (t, -$NHCH_2$-), 51.6 (q, OMe), 61 5 (d, α-CH), 111 1 (d, C-7), 111.3 (s, C-3), 118.7 (d, C-4), 119 4 (d, C-6), 122.0 (d, C-5), 122 4 (d, CH=CMe_2), 122.8 (d, C-2), 127 5 (s, C-3a), 135 0 (s, =CMe_2), 136.2 (s, C-7a), 175 5 (s, C=O).

Attempted Pictet-Spengler Cyclisation of the Imine (10b)

p-Toluenesulphonyl chloride (351 mg) was stirred overnight with a solution of the imine (502 mg) in anhydrous pyridine (5 cm^3) under an atmosphere of dry nitrogen The reaction mixture turned bright red within two minutes and had become black after 18 h. After a further 9 days at room temperature the solvent was removed *in vacuo* and the tarry residue was partitioned between benzene and 0 5 *M* hydrochloric acid The organic phase was subjected to preparative t l.c on silica gel, eluted with ethyl acetate/benzene (1.4 by volume), to furnish N_b-(*p*-toluenesulphonyl)-*L*-tryptophan methyl ester (280 mg), Rf 0 45, $[a]_D^{24}$ -28 9° (c 0 5, EtOH) [which was identical (t.l.c. and ^{1}H-NMR) to an authentic sample, of $[a]_D^{24}$ -29.6° (c 0 6, EtOH)], and several unidentified substances

Reaction Between the Imine (10b) and *N*-Phenylmaleimide

p-Toluenesulphonyl chloride (340 mg) and *N*-phenylmaleimide (311 mg) were added sequentially to a solution of the imine **10b** (505 mg) in dry pyridine (5 cm^3) under nitrogen The resultant solution was stirred for 12 h at room temperature, then the solvent was removed *in vacuo* T l c (ethyl acetate/benzene, 2·3 by volume) on the residue showed the presence of two major products with Rf 0.3 and 0 5 respectively, together with traces of N_b-(*p*-toluenesulphonyl)tryptophan methyl ester (Rf 0 75) and less polar substances Preparative t l.c with the same eluent furnished the *Diels-Alder adducts* **11a** (260 mg, 32%) and **11b** (265 mg, 33%), both as foams, which were homogeneous on t.l c.

Adduct 11a gave Rf 0 5 (Found: M^+, 457 200 $C_{27}H_{27}N_3O_4$ requires M, 457 200), δ_H 1 75 (3H, s, Me), 3 60 (3H, s, OMe) superimposed on 2 0-4 0 (9H, overlapping m), 5 7 (1H, br s, =CH-), 6 85-7 7 (10H, overlapping m, aromatic), 8.17 (1H, br s, indole NH), δ_C 23 2 (q, Me), 28 0 (t, CH_2), 29 4 (t, β-CH_2), 38 8 (d, CHCON), 43 4 (d, CHCON), 51 8 (q, OMe), 53 2 (d, CHN), 61 5 (d, α-CH), 110 5 (s, C-3), 111 1 (d, C-7), 118 7 (d, C-4), 119.3 (d, C-6), 121.8 (d, C-5), 123 0 (d, C-2), 125.3 (d, CH=), 126 4 (2C, d, C-2 and C-6 of Ph), 127 5 (s, C-3a), 128 4 (d, C-4 of Ph), 129.1 (2C, d, C-3 and C-5 of Ph), 131 9 (s, =CMe), 136 1 (s, C-7a), 136 6 (s, C-1 of Ph), 175 3 (s, CO_2Me), 177 3 (s, C=O), 179 2 (s, C=O).

Adduct 11b gave Rf 0 3 (Found M^+, 457 201 $C_{27}H_{27}N_3O_4$ requires M, 457 200), δ_H 1.62 (3H, s, Me), 2 1-2 7 (3H, m), 2 8-3 5 (4H, m), 3 68 (3H, s, OMe) superimposed on 3 5-3 95 (2H, m), 5 42 (1H, br s, CH=), 6 95-7 7 (10H, overlapping m, aromatic H), 8.32 (1H, br s, indole NH), δ_C 23 0 (q, Me), 28 5 (t, CH_2), 29 5 (t, β-CH_2), 39 2 (d, CHCON), 44 4 (d, CHCON), 51 9 (q, OMe), 52 4 (d, CHN), 59 4 (d, α-CH), 110 7 (s, C-3), 111 4 (d, C-7), 118.5 (d, C-4), 119 3 (d, C-6), 121.9 (d, C-5), 123 6 (d, C-2), 124 7 (d, CH=), 126.6 (2C, d, C-2 and C-6 of Ph), 127 1 (s, C-3a), 128.5 (d, C-4 of Ph), 129 1 (2C, d, C-3 and C-5 of Ph), 131 9 (s, =CMe), 136.3 (s, C-7a), 137 2 (s, C-1 of Ph), 174 9 (s, CO_2Me), 177 3 (s, C=O), 178 9 (s, C=O)

The two Diels-Alder adducts were formed as the sole products when the imine **10b** was allowed to react with *N*-phenylmaleimide in pyridine in the absence of *p*-toluenesulphonyl chloride

Preparation of the Amino-diester (7h)

Diethyl formamidomalonate (11 670 g) and gramine (10 015 g) were stirred vigorously with ethanolic sodium ethoxide (prepared from 1 345 g sodium in 500 cm^3 anhydrous ethanol) for 30 m at room temperature Dimethyl sulphate (8 0 cm^3) was added dropwise over 30 m and the resultant solution was stirred at room temperature overnight The crystalline precipitate was removed by filtration, washed with water until the washings were neutral, then dried in air at 70°C, and recrystallised from ethanol to furnish the formamido-diester **7i** (16 516 g, 87%), m p 180-181°C (lit.[23] 180-181°C)

A solution of the latter compound (8.500 g) in dry ethanol (80 cm^3) was refluxed with conc. hydrochloric acid (6 6 cm^3) for 2 h, then evaporated to dryness *in vacuo* and dried over phosphorous pentoxide The oily residue was crystallised from anhydrous ethanol and ether to give the hydrochloride salt of the amine **7h** (6.950 g, 80%), m p 128-130°C. A solution of the latter compound in water (100 cm^3) was shaken with ether while an excess of conc aqueous ammonia was added. The organic extract was washed with water, dried, and evaporated to dryness *in vacuo* to furnish the amine **7h** as a colourless oil (5 581 g, 90%) (Found: M^+, 304 142. Calc for $C_{16}H_{20}N_2O_4$: M, 304 142), δ_H (60 MHz) 1.22 (6H, t, ^3J 7 Hz, CH_3CH_2 x 2), 2.00 (2H, s, NH_2), 3.52 (2H, s, CH_2), 4 20 (4H, q, ^3J 7 Hz, CH_3CH_2 x 2), 6 9-7 75 (5H, m, aromatic H), 8.35 (1H, br s, indole NH), which was used without purification in the reactions described below

Pictet-Spengler Cyclisation of Amino-diester (7h) with 3-Methyl-2-butenal

(a) A solution of 3-methyl-2-butenal (1.368 g) and the amine **7h** (4.507 g) in benzene (75 cm^3) was refluxed for 2 h with entrapment of water using a Dean-Stark apparatus Benzoic acid (360 mg) was then added and the solution was refluxed for a further 6 h The resulting dark-yellow solution was washed sequentially with 5% aqueous sodium bicarbonate and water, and the solvent was then removed *in vacuo* T l c. [eluted with ethyl acetate and benzene (1 9 by volume)] and ^{1}H-NMR revealed that the oily product consisted mainly of the tetrahydro-β-carboline **9d** (Rf 0.33) and its isomer **13a** (Rf 0.40) in the mole ratio *ca* 6:1 The oil was submitted to fractional crystallisation from benzene/light petroleum to furnish *1-(2-methyl-1-propenyl)-3,3-di(ethoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline* **9d** (3 590 g, 65%), m p. 136-137°C (Found. C, 68.45, H, 6 9; N, 7 4%, M^+, 370 1875 $C_{21}H_{26}N_2O_4$ requires C, 68.1; H, 7 1, N, 7 6%, M, 370 189), δ_H 1 21 (3H, t, ^3J 7.2 Hz, CH_3CH_2), 1 35 (3H, t, ^3J 7.2 Hz, CH_3CH_2), 1.86 and 1.93 (each s, Me_2C=C), 2 93 (1H, br s, NH), 3 1-3.85 [2H, m (resembling an AB quartet with additional fine structure), δ_A 3 23 (long-range coupled to CHNH, ^5J 2 5 Hz), δ_B 3.72 (long-range coupled to CHNH, ^5J 1 5 Hz), $^2J_{AB}$ 15 5 Hz, CH_2], 4 0-4 45 (4H, m, CH_3CH_2 x 2), 5.15 [1H, A part of AB quartet (sharpened on irrad at δ 3 23), $^3J_{AB}$ 9 2 Hz, NCHCH=], 5 35 [1H, B part of AB quartet (sharpened on irrad at δ 1 9), $^3J_{AB}$ 9.2 Hz, NCHCH=], 7 05-7 65 (4H, m, aromatic H), 7 73 (1H, br s, NH); δ_C 14.0 (2C, q, CH_3CH_2 x 2), 18 2 (q, *Z*-Me), 25 9 (q, *E*-Me), 27 1 (t, C-4), 48 5 (d, C-1), 61 8 (t, OCH_2), 62 2 (t, OCH_2), 67 0 (s, C-3), 105 9 (s, C-4a), 110 7 (d, C-8), 118 2 (d, C-5), 119.3 (d, C-7), 121 5 (d, C-6), 124 7 (d, CH=), 127.4 (s, C-4b), 133 6 (s, C-9a), 136 2 (s, C-8a), 137.6 (s, $=CMe_2$), 169.7 (s, C=O), 170 3 (s, C=O).

Fractions rich in the minor component were submitted to flash chromatography on silica gel, eluted with ethyl acetate/benzene (1 9 by volume), to furnish *1-(2-methyl-2-propenyl)-3,3-di(ethoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline* **13a** as a glass, which was homogeneous by t l c. and NMR (Found M^+, 370 1875 $C_{21}H_{26}N_2O_4$ requires M, 370.189), δ_H (250 MHz) 1.20 (3H, t, J 7 1 Hz, CH_3CH_2), 1.36 (3H, t, J 7.1 Hz, CH_3CH_2), 1.90 (3H, s, CH_3C=), 2.47 (1H, dd, J 14.0 and 7 9 Hz) and 2 67 (1H, dd, J 14 0 and 5 6 Hz) (CH_2CH), 3.1 (1H, br. s, NH), 3 21 (1H, dd, ^2J 15.3, ^5J 2 4 Hz) and 3 78 (1H, dd, ^2J 15 3, ^5J 1 6 Hz) [C(4)H_2], 4.1-4 4 (4H, m, CH_2O x 2), 4 55 (1H, m, H-1), 5 07 (2H, s, CH_2=C), 7 2 (2H, m, aromatic H), 7 3 (1H, m, aromatic H), 7 6 (1H, m, H-8), 8 34 (1H, s, NH); δ_C (63 MHz) 14 0 (2C, CH_3CH_2 x 2), 22.5 (CH_3C=), 27.3 (C-4), 43 7 (CH_2C=), 47.0 (C-1), 61 9 (OCH_2), 62 3 (OCH_2), 67.0 (C-3), 106.3 (C-4a), 110 9 (C-8), 113 9 (CH_2=), 118.1 (C-5), 119.3 (C-7), 121.6 (C-6), 126.9 (C-4b), 134.1 (C-9a), 136.1 (C-8a), 142.2 (C=CH_2), 169.8 (C=O), 170.2 (C=O)

(b) 3-Methyl-2-butenal (115 mg) was stirred for 6 h at room temperature with a solution of the amino-diester **7h** (380 mg) in benzene (10 cm^3) in the presence of 4Å-molecular sieves (1 g) The solution was filtered, evaporated *in vacuo*, and crystallised from benzene/light petroleum to furnish the *imine* **10c** (336 mg, 73%), m.p. 77-78°C (Found M^+, 370.189 $C_{21}H_{26}N_2O_4$ requires M, 370 189); δ_H (60 MHz) 1.15 (6H, t, ^3J 7 Hz, CH_3CH_2 x 2), 1 72 and 1.82 (each 3H, each s, Me_2C=), 3.63 (2H, s, CH_2), 4.14 (4H, q, ^3J 7 Hz, CH_3CH_2 x 2), 6.08 (1H, br d, ^3J 9 Hz, N=CHCH), 6.9-7 65 (5H, m, indole CH), 8 16 (1H, d,

^3J 9 Hz, N=CH), 8.3 (1H, br s, NH)

A solution of this imine (401 mg) and benzoic acid (28 mg) in anhydrous benzene (30 cm^3) was refluxed for 7 h to give the same mixture of isomeric tetrahydro-β-carbolines as that described in (a) above Fractional crystallisation of the crude product from benzene-light petroleum furnished the tetrahydro-β-carboline **9d**, m.p. 136-137°C, in 68% yield

3,3-Di(ethoxycarbonyl)-1-phenyl-1,2,3,4-tetrahydro-β-carboline (13b)

A solution of benzaldehyde (701 mg) and the amino-diester **7h** (2 013 g) in benzene (30 cm^3) was refluxed for 2 h with removal of water using a Dean-Stark apparatus The solvent was removed *in vacuo* to leave an oil which was crystallised from benzene-light petroleum to furnish the *title compound* (1.511 g, 58%), m.p. 118-119°C (Found. C, 70.3, H, 6 1, N, 7 1%, M^+, 392.172 $C_{23}H_{24}N_2O_4$ requires C, 70 4, H, 6.2; N, 7.1%; M, 392.174), δ_H 1 14 (3H, t, ^3J 7 Hz, CH_3), 1.26 (3H, t, ^3J 7 Hz, CH_3), 3.14 (1H, br s, NH), 3.2-3 9 (2H, AB part of ABX, δ_A 3.32, δ_B 3.73, $^2J_{AB}$ 15, $^5J_{AX}$ 3, $^5J_{BX}$ 2 Hz, C(4)H_2), 3.95-4.40 (4H, m, CH_3CH_2 x 2), 5.43 (1H, X part of ABX, CHNH), 7 0-7 65 (10H, overlapping m, aromatic H + NH), δ_C 14 0 (2C, q, Me x 2), 27.1 (t, C-4), 55 4 (d, C-1), 61 8 (t, OCH_2), 62.2 (t, OCH_2), 67.3 (s, C-3), 106.8 (s, C-4a), 110 8 (d, C-8), 118.2 (d, C-5), 119.4 (d, C-7), 121 8 (d, C-6), 127.1 (s, C-4b), 128.7 (5C, d, Ph), 133 5 (s, C-9a), 136 4 (s, C-8a), 141.5 (s, C-1 of Ph), 169 3 (s, C=O), 170.4 (s, C=O)

3,3-Di(ethoxycarbonyl)-1,1-dimethyl-1,2,3,4-tetrahydro-β-carboline (13c)

A solution of the amine **7h** (13.102 g) in acetone (150 cm^3) was refluxed with glacial acetic acid (2 cm^3) for 48 h The solvent was removed *in vacuo* and the residue recrystallised from acetone and light petroleum to furnish the *title compound* (4.65 g, 31%), m p 170-173°C, which was homogeneous by t.l.c. and NMR (Found: M^+, 344.175 $C_{19}H_{24}N_2O_4$ requires M, 344 174), δ_H (220 MHz) 1 26 (6H, t, J 7 Hz, CH_3CH_2 x 2), 1 45 (6H, s, Me_2), 2 65 (1H, s, NH), 3.31 (2H, s, CH_2), 4 25 (4H, q, J 7 Hz, OCH_2 x 2), 7.15-7 4 (3H, m, H-5,6,7), 7.60 (1H, m, H-8), 7.9 (1H, s, H-9), δ_C 13 9 (2C, q, CH_3CH_2 x 2), 27.3 (t, C-4), 30 6 (2C, q, Me_2), 50 5 (s, C-1), 61 9 (2C, t, OCH_2 x 2), 65.0 (s, C-3), 104.9 (s, C-4a), 110.7 (d, C-8), 118.4 (d, C-5), 119 5 (d, C-7), 121.7 (d, C-6), 127 0 (s, C-4b), 136 0 (s, C-8a), 138 1 (s, C-9a), 171.0 (2C, s, C=O x 2)

3,3-Di(ethoxycarbonyl)-1-methyl-1,2,3,4-tetrahydro-β-carboline (13d)

A solution of the amine **7h** (1 020 g) and acetaldehyde (161 mg) in dry benzene (30 cm^3) was stirred at room temperature for 3 h in the presence of 4Å molecular sieves Benzoic acid (102 mg) was then added and the reaction mixture was refluxed for 8 h The mixture was subsequently cooled to room temperature and filtered The filtrate was washed in turn with 5% aqueous sodium hydrogen carbonate, then water, and evaporated *in vacuo* to furnish the *title compound* (982 mg, 89%) as an oil, which was homogeneous on t l c. (Found· M^+, 330 158. $C_{18}H_{22}N_2O_4$ requires M, 330.158); δ_H 1 12 (3H, t, ^3J 7.1 Hz, CH_3CH_2), 1.30 (3H, t, ^3J 7 1 Hz, CH_3CH_2), 1 44 (3H, d, ^3J 6.7 Hz, CH_3CH), 2 67 (1H, br s, NH), 3 12 [1H, dd, ^2J 15.2 Hz, ^5J 2 4 Hz, C(4)H_AH_B], 3 66 [1H, dd, ^2J 15 2 Hz, ^5J 1 6 Hz, C(4)H_AH_B], 3 95-4 6 [5H, overlapping m, CH_3CH_2 x 2 and H-1], 7 0-7 65 (4H, m, aromatic H), 7 82 (1H, s, H-9), δ_C 14 0 (2C, q, CH_3CH_2 x 2), 21 3 (q, CH_3), 27 3 (t, C-4), 45.3 (d, C-1), 61 8 (t, OCH_2), 62.2 (t, OCH_2), 67 1 (s, C-3), 105 8 (s, C-4a), 110.7 (d, C-8), 118 2 (d, C-5), 119 4 (d, C-7), 121 6 (d, C-6), 127 1 (s, C-4b), 135 1 (s, C-9a), 136.2 (s, C-8a), 169 9 (s, C=O), 170 2 (s, C=O)

1,1-Di(ethoxycarbonyl)-3-methyl-1,2,3,4-tetrahydro-β-carboline (14)

A solution of α-methyltryptamine[36] (960 mg) and diethyl 2-oxopropandioate (1 055 g) in benzene (40 cm^3) was refluxed for 2 h with collection of water by means of a Dean-Stark trap Benzoic acid was added and refluxing continued for a further 8 h The reaction mixture was worked up as described above to

give the *title compound* (1 096 g, 60%), m p 126-127°C (Found: C, 65.1; H, 6.9; N, 8.2%, M^+, 330.159 $C_{18}H_{22}N_2O_4$ requires C, 65.4, H, 6 7, N, 8.5%, M, 330.158), δ_H 1.30 (3H, t, ^3J 7 2 Hz, CH_3CH_2), 1.35 (3H, t, ^3J 7 2 Hz, CH_3CH_2), 1.41 (3H, d, ^3J 6.1 Hz, CH_3CH), 2.34-3 00 (3H, overlapping m, CH_2CH + NH), 3.35 (1H, m, CH_2CH), 4.3 (4H, m, CH_3CH_2 x 2), 7.0-7.6 (4H, m, aromatic H), 8.56 (1H, s, H-9), δ_C 14 0 (2C, q, CH_3CH_2 x 2), 22 0 (q, CH_3), 29.6 (t, C-4), 47.3 (d, C-3), 62.5 (t, OCH_2), 62.7 (t, OCH_2), 67 9 (s, C-1), 111 2 (d, C-8), 112.5 (s, C-4a), 118 6 (d, C-5), 119 3 (d, C-7), 122.5 (d, C-6), 126 2 (s, C-4b and C-9a), 136.5 (s, C-8a), 168.2 (s, C=O), 169.7 (s, C=O).

Pictet-Spengler Reaction Between 3-Methylbutanal and *L*-Tryptophan Methyl Ester

(a) 3-Methylbutanal (3 560 g) was added to a warm solution of *L*-tryptophan methyl ester (8.009 g) in dry benzene (100 cm^3) which was refluxed for 2 h with collection of water using a Dean-Stark apparatus Benzoic acid (320 mg) was then added and the solution refluxed for a further 36 h The cooled reaction mixture was washed with 5% aqueous sodium bicarbonate solution, followed by water, and evaporated *in vacuo* to give a crystalline residue, t l c [ethyl acetate/benzene (1:4 by volume)] on which showed only two significant products, with Rf 0.30 (for the *cis* product **15a**) and 0.23 (for the *trans* compound **16a**) The *cis/trans* ratio was approximately 52 48 (^{1}H-NMR) The mixture was crystallised once from benzene and then submitted to fractional crystallisation from methanol to furnish racemic *cis-3-(methoxycarbonyl)-1-(2-methylpropyl)-1,2,3,4-tetrahydro-β-carboline* **15a** (4.062 g, 39%), m.p. 147°C, $[a]_D^{25}$ -1.0° (c 1, EtOH) (Found C, 71 7; H, 7 9, N, 9 75%, M^+, 286 168 $C_{17}H_{22}N_2O_2$ requires C, 71 3; H, 7 7, N, 9 8%; M, 286 168), δ_H 1.01 and 1 04 (each 3H, each d, ^3J 6 5 Hz, CMe_2), 1 55-2 25 (4H, overlapping m, CH_2CHMe_2 + NH), 2.82 [1H, ddd, ^2J 15.3, ^3J 11.3, ^5J 2.5 Hz, C(4)-H_AH_B], 3 12 [1H, ddd, ^2J 15.3, ^3J 4.3, ^5J 2.0 Hz, C(4)-H_AH_B], 3.79 [1H, dd, ^3J 11.3 and 4 3 Hz, H-3], 3 81 (3H, s, CO_2Me), 4.2 (1H, m, H-1), 7 0-7 55 (4H, m, aromatic H), 7 78 (1H, br s, H-9), δ_C 21 7 (q, CH_3), 23.8 (q, CH_3), 24.3 (d, $CHMe_2$), 26.0 (t, C-4), 44 4 (t, CH_2), 50 5 (d, C-1), 52.1 (q, OMe), 56.4 (d, C-3), 107.7 (s, C-4a), 110.7 (d, C-8), 117 9 (d, C-5), 119 5 (d, C-7), 121 6 (d, C-6), 127 2 (s, C-4b), 135 8 (s, C-9a), 136 0 (s, C-8a), 173 8 (s, C=O)

The combined mother liquors were submitted to fractional crystallisation from benzene/light petroleum to give the *racemic trans-3-(methoxycarbonyl)-1-(2-methylpropyl)-1,2,3,4-tetrahydro-β-carboline* **16a** (3 209 g, 31%), m p 118°C, $[a]_D^{25}$ +0.2° (c 1, EtOH) (Found C, 71.3, H, 7 8; N, 9.8%; M^+, 286 168 $C_{17}H_{22}N_2O_2$ requires C, 71 3, H, 7 7, N, 9.8%, M, 286 168), δ_H 1 00 (3H, d, J 6.7 Hz, $CHCH_3$), 1.03 (3H, d, J 6 7 Hz, $CHCH_3$), 1.3-2 2 (3H, m, CH_2CHMe_2), 2 2 (1H, s, NH), 2 8-3.3 [2H, AB part of ABX, C(4)-H_2], 3 75 (3H, s, CO_2Me), 3 98 (1H, X part of ABX, J_{AX} + J_{BX} 12 4 Hz, H-3), 4.28 (1H, m, H-1), 7 05-7 6 (4H, m, aromatic H), 7 7 (1H, br s, H-9); δ_C 21 6 (q, CH_3), 23.6 (q, CH_3), 24.6 (d, CH), 25 0 (t, C-4), 44 4 (t, CH_2), 48 1 (d, C-1), 52.0 (q, OCH_3), 52 3 (d, C-3), 106.7 (s, C-4a), 110 7 (d, C-8), 117 9 (d, C-5), 119.3 (d, C-7), 121 5 (d, C-6), 127 1 (s, C-4b), 135.8 (s, C-9a), 136.0 (s, C-8a), 174.3 (s, C=O)

(b) The reaction between *L*-tryptophan methyl ester and 3-methylbutanal was performed in the presence of benzoic acid as described above but care was taken to avoid fractionating the crude reaction mixture (or the purified products) by crystallisation. The total crude reaction mixture was submitted to flash chromatography over silica gel eluted with ethyl acetate/benzene (1 5 by volume) to afford the *cis*-tetrahydro-β-carboline **15a**, $[a]_D^{25}$ -21.3° (c 1 8, EtOH) and the *trans* diastereomer **16a**, $[a]_D^{25}$ +6 9° (c 1 0, EtOH). The ^{1}H-NMR of each diastereomer in the presence of Eu(hfbc)$_3$ revealed that they had both been isolated in about 15% enantiomeric excess

(c) The reaction between *L*-tryptophan methyl ester and 3-methylbutanal was performed as described above but *in the absence of benzoic acid The total crude reaction mixture was submitted to flash* chromatography over silica gel eluted with ethyl acetate/benzene (1 5 by volume) to afford the *cis*-tetrahydro-β-carboline **15a**, $[a]_D^{25}$ -65.3° (c 1 2, EtOH) and the *trans* diastereomer **16a**, $[a]_D^{25}$ +20.3° (c 0 9, EtOH)

^{1}H-NMR in the presence of Eu(hfbc)$_3$ revealed that they had both been isolated in about 40% enantiomeric excess.

Pictet-Spengler Cyclisation of *L*-Tryptophanamide with 3-Methylbutanal

A solution of *L*-tryptophanamide (5 405 g) and 3-methylbutanal (2.550 g) in dry benzene was refluxed for 2 h with collection of water using a Dean-Stark trap The solution was concentrated *in vacuo* and the residue crystallised from benzene to furnish the *imine* (6 204 g, 85%), m p. 139-140°C, $[a]_D^{25}$ -27.3° (c 1, CH_2Cl_2) (Found: M^+, 271 168 $C_{16}H_{21}N_3O$ requires M, 271 1685); δ_H 0.74 (6H, d, J 7 Hz, 2 x Me), 1.5-2 05 (3H, m, C$\underline{H}_2$C$\underline{H}$Me$_2$), 3 05 [1H, dd, J 14 and 10 Hz, C(4)-H$_A$], 3 51 [1H, dd, J 14 and 3 5 Hz, C(4)-H$_B$], 3 87 [1H, dd, J 10 and 3 5 Hz, H-3], 5 8 and 6 8 (each 1H, br, NH_2), 6 9-7 75 (6H, overlapping m, aromatic H and CH=N), 8 2 (1H, br s, indole NH)

Trifluoroacetic acid (1.140 g) was stirred at room temperature with a solution of the imine (2 850 g) in dichloromethane (305 cm^3) for 24 h. The solution was then washed with 5% aqueous sodium bicarbonate, followed by water, dried, and evaporated to dryness. The solid residue was crystallised once from benzene to furnish a mixture (2.480 g, 87%), m p. 183-184°C, $[a]_D^{25}$ -126 5°, of the *cis* and *trans* tetrahydro-β-carbolines **15b** and **16b** in the ratio 17.3 (estimated by ^{13}C-n m r), unchanged on repeated recrystallisation (Found. C, 71 25, H, 8 0, N, 15 7, M^+, 271 168 Calc for $C_{16}H_{21}N_3O$ C, 70 8, H, 7 8, N, 15 5, M, 271 1685), δ_C (d_6-d m s o) 21 6 (q, Me), 23 8 (d, C$\underline{H}$Me$_2$), 24 0 (q, Me), 25.7 (t, C-4), 43.3 (t, CH_2), 50 7 (d, C-1), 57 0 (d, C-3), 106 9 (s, C-4a), 111 0 (d, C-8), 117.3 (d, C-5), 118.3 (d, C-7), 120 4 (d, C-6), 127 0 (s, C-4b), 135.9 (s, C-9a), 137 6 (s, C-8a), 175 2 (s, C=O), [and resonances due to the minor component at δ 24 3, 24 8, 48 1 (d, C-1), 51 9 (d, C-3), 106.2 (s), 137 8]

Racemic *Cis*- and *Trans*-Tetrahydro-β-carbolinecarboxamides 15b and 16b

A solution of the racemic ester **15a** (450 mg) in dry methanol (10 cm^3) was saturated with gaseous ammonia at 0°C. After 2 days at room temperature the reaction mixture was evaporated to dryness *in vacuo* to furnish the *cis-carboxamide* (380 mg), Rf 0 45 [t l c eluted with ethanol/chloroform (1 9 by volume)] (Found· M^+, 271 168. Calc for $C_{16}H_{21}N_3O$, 271 1685)

The racemic *trans* ester **16a** was similarly converted to the *trans-carboxamide* **16b**, m p 234-235°C, Rf 0 55 [t l c eluted with ethanol/chloroform (1 9 by volume)] (Found M^+, 271 167 Calc for $C_{16}H_{21}N_3O$, 271 1685)

Reaction Between *L*-Tryptophanamide and 3-Methylbut-2-enal

A solution of *L*-tryptophanamide (900 mg) and 3-methylbut-2-enal (410 mg) in benzene (50 cm^3) was refluxed for 2 h, then the solvent was removed *in vacuo* to give the crude imine **10d** (1 205 g) as an amorphous solid, δ_H 1.49 (3H, s, Me), 1 78 (3H, s, Me), 3 07 (1H, dd, J 14 and 10 Hz, C$\underline{H}_A$H$_B$CH), 3 52 (1H, dd, J 14 and 3 5 Hz, CH$_A$$\underline{H}_B$CH), 3 94 (1H, dd, J 10 and 3 5 Hz, CH$_2$C$\underline{H}$), 5.89 (1H, d, J 10 Hz, N=CHC$\underline{H}$=), 6 2 (1H, br, NH), 7 49 (1H, d, J 10 Hz, N=C$\underline{H}$CH=) superimposed on 6 8-7 75 (6H, m, indole CH + amino NH), 8.57 (1H, br s, indole NH) This imine failed to undergo Pictet-Spengler cyclisation under any of the conditions that were attempted

***L*-Tryptophyl-*L*-proline Methyl Ester (17)**

The hydrobromide salt of the title compound was prepared as described by Swelim *et al*[27] and had m p. 202-205°C (from EtOH-ether) (lit[27] m p 200-205°C), $[a]_D^{25}$ -6 9° (c 1, H_2O) This salt (1 802 g) was dissolved in water (10 cm^3) and the solution was shaken vigorously with dichloromethane (50 cm^3) while excess of a 10% aqueous solution of sodium bicarbonate was added in small portions The aqueous layer was re-extracted with dichloromethane (50 cm^3) and the combined organic extract was washed once with water (20 cm^3), dried over $MgSO_4$, and evaporated to dryness *in vacuo* at 0°C The residue was crystallised with care from benzene to give the *title compound* (945 mg, 67%), m p 138-139°C, $[a]_D^{25}$ -5.6° (Found M^+, 315 1575 $C_{17}H_{21}N_3O_3$ requires M, 315 158)

A sample of the dipeptide ester **17** (324 mg) was refluxed with benzene (35 cm^3) for 3.5 h. The solvent was removed *in vacuo* and the residue recrystallised from acetone to furnish *L*-tryptophyl-*L*-proline cyclic anhydride **18**, m p 174-175°C, $[a]_D^{25}$ -104 6° (c 0 6, AcOH) (lit [28] m p 174°C, $[a]_D^{22}$ -101°) (Found· M^+, 283 132 Calc for $C_{16}H_{17}N_3O_2$ M, 283 132).

Pentacycle (22)

3-Methylbutanal (1 351 g) was added at room temperature to a stirred solution of *L*-tryptophyl-*L*-proline methyl ester (4 503 g) in dichloromethane (200 cm^3) in the presence of 4Å molecular sieves (10 g). The resulting solution of the imine was cooled in a ice-bath then trifluoroacetic acid (1.620 g) was added. The reaction mixture was left to warm up to room temperature overnight The mixture was freed from molecular sieves by filtration, washed with 5% aqueous sodium bicarbonate solution, then washed with water, dried over magnesium sulphate, and evaporated to dryness *in vacuo* to leave an amorphous substance (4.976 g), referred to below as 'Mixture X' T l.c [eluted with ethanol and chloroform (4·96 by volume)] and ^{1}H-NMR revealed that this mixture consisted mainly of the required *cis*-tetrahydro-β-carboline **20** (Rf 0 3) and the *trans* diastereoisomer **21** (Rf 0 25) in the ratio *ca* 85·15 (Found M^+, 383.221. Calc for $C_{22}H_{29}N_3O_3$ 383.221) together with traces of the cyclic anhydride **18** (Rf 0 15)

Mixture X (2 50 g) was dissolved in formic acid (20 cm^3) and the solution kept at room temperature for 20 minutes The formic acid was then removed *in vacuo* at room temperature The residue was dissolved in a mixture of 2-butanol (80 cm^3) and toluene (20 cm^3) and the solution was refluxed for 2 h, after which time unreacted tetrahydro-β-carbolines **20** and **21** could not be detected by t l.c The solvent was removed *in vacuo* to give a crystalline mixture (2 153 g) of the diastereoisomeric pentacycles **22** and **23**, in the ratio 85 15, together with traces of the cyclic anhydride **18** A single crystallisation from ethanol gave the diastereoisomeric mixture (1 845 g), free from the latter compound Fractional crystallisation from ethanol then furnished the pure *pentacycle* **22**, [1 003 g, 40% from **17**], m.p 293-298°C (decomp), $[a]_D$ -83 9° (c, 0 5, $CHCl_3$), (Found C, 72.0, H, 7 3, N, 11.8, M^+, 351 195 $C_{21}H_{25}N_3O_2$ requires C, 71 8, H, 7.2; N, 11.95%; M, 351.195), δ_H 0 80 (3H, d, J 6.5 Hz, Me), 1.04 (3H, d, J 6 5 Hz, Me), 1 4-2.65 [7H, overlapping m, C(7)-H_2, C(8)-H_2, and CH_2CHMe_2], 3.14 [1H, dd, J 11 and 16 Hz, C(13)-H_AH_B], 3 4-3 8 [3H, m, C(13)-H_AH_B and C(9)-H_2], 4.08 (2H, m, H-6 and H-12), 5 52 (1H, dd, J 4 and 9 Hz, H-3), 7 1-7 65 (4H, m, H-16, H-17, H-18, and H-19), 8 6 (1H, br s, H-1), δ_C (d_6-d.m s o.) 20.9 (t, C-8), 22.0 (q, Me), 22 6 (t, C-13), 23 5 (q, Me), 24 1 (d, CH), 27 8 (t, C-7), 44 7 (t, C-9), 46 1 (t, CH_2), 49.8 (d, C-3), 55 9 (d, C-12), 58.4 (d, C-6), 105 1 (s, C-14), 111 2 (d, C-19), 117 6 (d, C-16), 118 6 (d, C-18), 120 7 (d, C-17), 125.8 (s, C-15), 135.0 (s, C-2), 135.8 (s, C-20), 165.5 (s, C=O), 169 0 (s, C=O)

Fractions rich in the less polar, minor component were submitted to chromatographic purification to furnish the pentacycle **23**, δ_H 1.0 (6H, m, Me_2), 1 4-2 6 [7H, overlapping m, C(7)-H_2, C(8)-H_2, and CH_2CHMe_2], 2 85 [1H, dd, J 12 and 16 Hz, C(13)-H_AH_B], 3.2-4 35 [4H, overlapping m, H-6, C(9)-H_2, and C(13)-H_AH_B], 4 47 (1H, dd, J 12 and 4 5 Hz, H-12), 6 00 (1H, br t, J 6.5 Hz, H-3), 7 0-7.7 (4H, m, aromatic H), δ_C (d_6-d.m.s.o) 21.0 (t, C-8), 22.3 (q, Me), 23 2 (q, Me), 24 8 (d, CH), 27 9 (t, C-7), 29.3 (t, C-13), 43.5 (t, CH_2), 44.5 (t, C-9), 46 8 (d, C-3), 52.6 (d, C-12), 58 4 (d, C-6), 104.8 (s, C-14), 111 0 (d, C-19), 117 6 (d, C-16), 118 7 (d, C-18), 121 0 (d, C-17), 126 1 (s, C-15), 136.0 (s, C-20), 133 9 (s, C-2), 164.0 (s, C=O), 164 7 (s, C=O)

Base-catalysed Isomerisation of Pentacycle (22)

Pentacycle **22** (130 mg) and potassium tert-butoxide (5 0 mg) were dissolved in dry ethanol (20 cm^3) and the solution refluxed for 3 h with monitoring by t.l c. [eluant ethanol and chloroform (2·98 by volume)]. During this time the starting pentacycle **22** (Rf 0 5) was quantitatively replaced by a single product (Rf 0.6) The solvent was then removed *in vacuo*, and the residue partitioned between water and chloroform. The organic extract afforded the *epimeric pentacycle* **24** as an amorphous powder; δ_H 0 96 (3H, d, J 6 Hz, Me), 1.08 (3H, d, J 6 Hz, Me), 1.5-2.7 [7H, m, C(7)-H_2, C(8)-H_2, and CH_2CHMe_2],

2.92 (1H, dd, J 13 and 15 Hz, C(13)-$\underline{H}_A H_B$], 3.33 [1H, dd, J 4.5 and 15 Hz, C(13)-$H_A\underline{H}_B$], 3.5-3.95 [2H, m, C(9)-H_2], 4.1 (1H, m, H-6), 4.42 (1H, dd, J 4.5 and 13 Hz, H-12), 5.85 (1H, br d, J 8 Hz, H-3), 7 05-7 55 (4H, m, aromatic H), 8.26 (1H, br s, NH); δ_C 22.0 (t, C-8), 22.2 (q, Me), 23.3 (q, Me), 25.2 (d, CH), 25.9 (t, C-7), 30.0 (t, C-13), 43.1 (t, CH_2), 45 4 (t, C-9), 48.1 (d, C-3), 55.2 (d, C-12), 58.8 (d, C-6), 106 4 (s, C-14), 110.9 (d, C-19), 118.0 (d, C-16), 119.8 (d, C-18), 122.1 (d, C-17), 126 4 (s, C-15), 134.0 (s, C-2), 136.0 (s, C-20), 165 0 (s, C=O), 166.7 (s, C=O)

Racemic *Cis*- and *Trans*-3-(Methoxycarbonyl)-1-(2-methylpropyl)-2-(*p*-toluenesulphonyl)-1,2,3,4-tetrahydro-β-carbolines (15c) and (16c)

A solution of the racemic *cis*-tetrahydro-β-carboline **15a** (500 mg) and *p*-toluenesulphonyl chloride (335 mg) in dry benzene (15 cm^3) containing pyridine (1 5 cm^3) was refluxed for 3 h Solvent was then removed *in vacuo* and the residue partitioned between water and ethyl acetate The organic phase was washed with dilute hydrochloric acid, followed by water, dried, and evaporated *in vacuo* The oily product was crystallised from benzene and recrystallised from methanol to furnish the *cis-p-toluenesulphonyl derivative* **15c** (490 mg, 64%), m p. 157-158°C (Found. C, 65.2, H, 6 3, N, 6 2%, M^+, 440 1755. $C_{24}H_{28}N_2O_4S$ requires C, 65.4, H, 6 4; N, 6 4, M, 440.177); δ_H (60 MHz) 0 98 (3H, d, J 6 Hz, Me), 1.06 (3H, d, J 6 Hz, Me), 1.4-2 15 (3H, m, $C\underline{H}_2C\underline{H}Me_2$), 2.25 (3H, s, Ts-Me), 2.55 [1H, dd, J 16.5 and 7.5 Hz, C(4)$\underline{H}_A H_B$], 3 29 [1H, br d, J 16.5 Hz, C(4)$H_A\underline{H}_B$], 3.66 (3H, s, CO_2Me), 5.03 (1H, br d, J 7 5 Hz, H-3), 5.2 (1H, m, H-1), 6.9-7.75 (8H, overlapping m, aromatic H), 7.83 (1H, s, H-9), δ_C (d_6-d m.s.o.) 19 5 (t, C-4), 20.8 (q, Ts-Me), 21 5 (d, $\underline{C}HMe_2$), 23.4 (q, Me), 23.7 (q, Me), 44.9 (t, CH_2), 51.1 (d, C-1), 52.2 (d, C-3), 52.4 (q, OMe), 103.6 (s, C-4a), 111 0 (d, C-8), 117.6 (d, C-5), 118.4 (d, C-7), 121 0 (d, C-6), 125.9 (s, C-4b), 126.6 (2C, d, C-3 and C-5 of Ts), 129.6 (2C, d, C-2 and C-6 of Ts), 132.4 (s, C-9a), 135.9 (s, C-8a), 136.7 (s, C-4 of Ts), 143.3 (s, C-1 of Ts), 171.4 (s, C=O).

Similarly, the racemic *trans*-tetrahydro-β-carboline **16a** furnished the *trans-p-toluenesulphonyl derivative* **16c**, m.p 201-202°C (Found: C, 65.5; H, 6.25, N, 6 3%; M^+, 440 177 $C_{24}H_{28}N_2O_4S$ requires C, 65 4, H, 6.4, N, 6.4; M, 440 177); δ_C (d_6-d m s o) 20.9 (2C, q, Ts-Me and CH$\underline{Me}$), 22.8 (t, C-4), 23 4 (q, Me), 24 0 (d, CH), 42.9 (t, CH_2), 52.1 (q, OMe), 53.4 (d, C-1), 54.1 (d, C-3), 106.0 (s, C-4a), 111 0 (d, C-8), 117 5 (d, C-5), 118.5 (d, C-7), 120 9 (d, C-6), 126 4 (s, C-4b), 127 5 (2C, d, C-3 and C-5 of Ts), 129 2 (2C, d, C-2 and C-6 of Ts), 134.6 (s, C-9a), 135.8 (s, C-8a), 136.7 (s, C-4 of Ts), 143.7 (s, C-1 of Ts), 170.3 (s, C=O)

3-(Methoxycarbonyl)-1-(2-methylpropyl)-β-carboline (25)

A solution of sodium methoxide (prepared *in situ* from 21 mg sodium) and the racemic *cis*-2-(*p*-toluenesulphonyl)-1,2,3,4-tetrahydro-β-carboline **15c** (400 mg) in dry methanol (11 cm^3) was refluxed for 3 h to give a bright yellow fluorescent solution Solvent was removed *in vacuo* and the residue partitioned between water and ethyl acetate. The organic extract gave a solid which was crystallised from ethyl acetate-light petroleum to furnish the *β-carboline* (220 mg, 86%), m.p. 146-147°C (Found· C, 72.0; H, 6 45, N, 10.1%, M^+, 282 136. $C_{17}H_{18}N_2O_2$ requires C, 72.3, H, 6 4, N, 9.9%, M, 282.137), δ_H 0 58 (6H, d, J 6.5 Hz, CH$\underline{Me}_2$), 2.15 (1H, m, $C\underline{H}Me_2$), 2 90 (2H, d, J 7 Hz, $C\underline{H}_2CH$), 3.97 (3H, s, CO_2Me), 7 25-7 8 (3H, m, aromatic CH), 8 21 (1H, d, J 8 Hz, H-8), 8.87 (1H, s, H-4), 10 8 (1H, br s, H-9); δ_C 22.2 (2C, q, Me x 2), 28 7 (d, $\underline{C}HMe_2$), 42.9 (t, CH_2), 52.4 (q, OMe), 112.6 (d), 116 5 (d, C-4), 120 5 (d), 121.7 (d), 121 9 (s), 128.4 (s), 128 6 (d), 136.4 (s), 136.8 (s), 141.2 (s), 145.9 (s), 167 1 (s, C=O)

The *trans*-2-(*p*-toluenesulphonyl)tetrahydro-β-carboline **16c** furnished the same β-carboline **25** upon reaction with sodium methoxide under the same conditions.

2-(*p*-Toluenesulphonyl)tetrahydro-β-carboline (27a)

p-Toluenesulphonyl chloride (785 mg) was added to a solution of Mixture X, that was described above, (1 500 g), in pyridine (4.0 cm^3) and benzene (50 cm^3) The reaction mixture was stirred and heated

at 70°C for 8 h. The dark red solution was evaporated to dryness *in vacuo*, and the residue was diluted with water and extracted with ethyl acetate. The organic extract was washed with 2 *M* hydrochloric acid, then with water, dried, and evaporated to dryness. Fractional crystallisation of the residue from benzene furnished the *title compound* (1 153 g, 50% from **17**) as colourless crystals, m.p. 246-247°C, $[a]_D$ -15.8° (c 0.5, $CHCl_3$) (Found. M^+, 537.228. $C_{29}H_{35}N_3O_5S$ requires M, 537.230), δ_H 0 94 (3H, d, J 7 Hz, Me), 1 12 (3H, d, J 7 Hz, Me), 2 16 (3H, s, Ts-Me) superimposed on 1.3-2.5 (8H, overlapping m, C(4)-H_AH_B, C(1)-C<u>H</u>C<u>H</u>$_2$, and proline C<u>H</u>$_2$C<u>H</u>$_2$), 3.16 [1H, d, J 16 Hz, C(4)-H_A<u>H</u>$_B$], 3 65 (3H, s, OMe), 3 9-4.5 (3H, overlapping m, proline CHN and CH_2N), 5.0-5.3 (2H, overlapping m, H-1 and H-3), 6.9-7 7 (9H, overlapping m, aromatic H and NH); δ_C (d_6-d.m.s.o.) 19.1 (t, C-4), 20.7 (q, Ts-Me), 21.2 (q, Me), 23.6 (q, Me), 24.0 (d, CH), 24.6 (t, proline C-4), 28.3 (t, proline C-3), 43 5 (t, CH_2), 47.3 (t, proline C-5), 51.5 (d, C-1 or C-3), 51 7 (q, OMe), 51.9 (d, C-3 or C-1), 59.7 (d, proline C-2), 104 9 (s, C-4a), 110.7 (d, C-8), 117.5 (d, C-5), 118.0 (d, C-7), 120.7 (d, C-6), 126.0 (s, C-4b), 127 0 (2C, d, Ts C-3 and C-5), 129.3 (2C, d, Ts C-2 and C-6), 131.5 (s, C-9a), 135.7 (2C, s, C-8a and Ts C-4), 143.4 (s, Ts C-1), 168.0 (s, C=O), 172.0 (s, C=O).

Pentacycle (28)

The *p*-toluenesulphonamide **27a** (1 940 g) and sodium ethoxide (242 mg) were dissolved in ethanol (190 cm^3) and the solution refluxed for 3 h under an atmosphere of nitrogen The yellow fluorescent solution was evaporated to dryness *in vacuo* and the residue partitioned between water and chloroform. The organic extract was washed with water, dried, and evaporated to dryness *in vacuo*. Crystallisation of the solid product from ethanol gave yellow cubes which on drying lost ethanol of crystallisation to afford *the didehydropentacycle* **28a** as a yellow powder (930 mg, 74%), m.p. 284-290°C (decomp.), $[a]_D$ 214.7° (c 0.2, $CHCl_3$) (Found: C, 71.95; H, 6.6, N, 12.2, M^+, 349 179. $C_{21}H_{23}N_3O_2$ requires C, 72.2; H, 6 6; N, 12.0; M, 349.179); δ_H (d_6-dmso) 0 89 (3H, d, J 6 Hz, Me), 0 92 (3H, d, J 6 Hz, Me), 1.3-2.6 [7H, overlapping m, C(3)-C<u>H</u>$_2$C<u>H</u>, C(7)-H_2, and C(8)-H_2], 3.3-3.8 (2H, m, C(9)-H_2), 4.25 (1H, m, H-6), 6 00 (1H, t, J 7 Hz, H-3), 7 24 (1H, s, H-13) superimposed on 7 0-7.3 (2H, m, aromatic H), 7 45 (1H, m, aromatic H), 7 75 (1H, m, aromatic H), 11 65 (1H, s, NH), δ_C (d_6-d.m.s.o.) 21 4 (t, C-8), 22.6 (q, Me), 22 9 (q, Me), 23.8 (d, CH), 28.6 (t, C-7), 43.3 (t, CH_2), 44 4 (t, C-9), 48 3 (d, C-3), 58.1 (d, C-6), 105 4 (s, C-12), 110 3 (d, C-13), 111.9 (d, C-19), 118.1 (d, C-16), 120.2 (d, C-18), 121.8 (d, C-17), 122 3 (s, C-14), 123 7 (s, C-15), 136 0 (s, C-20), 136.4 (s, C-2), 158 7 (s, C=O), 166.4 (s, C=O).

Carboxamide (27c)

Aqueous sodium hydroxide (65 cm^3, 0 1 *M*) was added dropwise over 30 m to a vigorously stirred solution of the methyl ester **27a** (3.225 g) in dioxane (260 cm^3) The mixture was diluted with water (50 cm^3) and stirring continued at room temperature for 18 h Solvent was then removed *in vacuo* and the residue partitioned between water and ethyl acetate. The aqueous layer was acidified with dilute hydrochloric acid and extracted with dichloromethane. The extract was washed with water, dried, evaporated *in vacuo*, and the residue crystallised from benzene to furnish the *carboxylic acid* **27b** (2 54 g, 81%), m.p. 160-163°C (Found C, 63 9, H, 6 25, N, 8.1%, M^+, 523.217. $C_{28}H_{33}N_3O_5S$ requires C, 64.2, H, 6.35; N, 8.0%; M, 523.214); δ_H 0 94 (3H, d, J 6 Hz, Me), 1.10 (3H, d, J 6 Hz, Me), 2 14 (3H, s, Ts-Me) superimposed on 1.4-2.6 [8H, overlapping m, C(1)-C<u>H</u>$_2$C<u>H</u>, C(4)-<u>H</u>$_A$H$_B$, proline C(3)-H_2, and proline C(4)-H_2], 3 15 [1H, d, J 16 Hz, C(4)-H_A<u>H</u>$_B$], 3.8-4.5 [3H, overlapping m, proline C(2)-H and proline C(5)-H_2], 5.0-5.35 (2H, overlapping m, H-1 and H-3), 6 7-7 4 (6H, overlapping m, aromatic H), 7 55 (2H, d, J 8 Hz, Ts-H_2), 7 80 (1H, s, NH), δ_C (d_6-d.m.s.o) 19.4 (t, C-4), 21 0 (q, Me), 21.4 (q, Me), 23 8 (q, Me), 24 3 (d, CH), 24 8 (t, proline C-4), 28.8 (t, proline C-3), 43.8 (t, CH_2), 47 6 (t, proline C-5), 51 8 (d, C-1 or C-3), 52.3 (d, C-3 or C-1), 60 1 (d, proline C-2), 105 2 (s, C-4a), 111.0 (d, C-8), 117 8 (d, C-5), 118 4 (d, C-7), 121 0 (d, C-6), 126.3 (s, C-4b), 127.3 (2C, d, Ts C-3 and C-5), 129 6 (2C, d, Ts C-2 and C-6), 131.8 (s, C-9a), 135 9 (s, C-8a), 136 1 (s, Ts C-4), 143.8 (s, Ts C-1),

168.2 (s, C=O), 173.4 (s, C=O).

Oxalyl chloride (0.2 cm^3) was added to a solution of the carboxylic acid (600 mg) in warm anhydrous benzene (35 cm^3) and the reaction mixture was stirred at 45°C for 2 h. The mixture was then evaporated to dryness *in vacuo*, the residue redissolved in benzene (30 cm^3) and the solution saturated with gaseous ammonia. After removal of the solvent *in vacuo* the crystalline residue was recrystallised from ethanol and ether to furnish *the carboxamide* (402 mg), m.p 226-227°C (Found: C, 64.0, H, 6 5; N, 10.9%, M^+, 522 232. $C_{28}H_{34}N_4O_4S$ requires C, 64.3, H, 6.6, N, 10 7%, M, 522 230); δ_H (d_6 dmso) 0.88 (3H, d, J 6 Hz, Me), 1 10 (3H, d, J 6 Hz, Me), 2.15 (3H, s, Ts-Me) superimposed on 1.3-2 5 [9H, overlapping m, C(1)-C$\underline{H_2}$C$\underline{H}$, C(4)-$\underline{H_A}H_B$, proline C(3)-H_2, proline C(4)-H_2 and NH], 2.90 [1H, d, J 16 Hz, C(4)-$H_A\underline{H_B}$], 3 30 (1H, s, NH), 4 0 [3H, overlapping m, proline C(2)-H and proline C(5)-H_2], 5 05 (1H, br m, H-1), 5.28 (1H, br d, J 7 Hz, H-3), 6 7-7 4 (6H, overlapping m, aromatic H), 7 58 (2H, d, J 8 Hz, Ts-H_2), 10 52 (1H, s, H-9)

Reaction of the Carboxamide (27c) with Sodium Ethoxide in [*OH*-$^2H_1$]Ethanol

The (*p*-toluenesulphonyl)carboxamide **27c** (522 mg, 1 0 mmol) and sodium ethoxide (54 mg, 0 8 mmol) were dissolved in [*OH*-$^2H_1$]ethanol (35 cm^3) and the solution was refluxed under nitrogen for 9 h T l.c of the resultant solution, eluted with ethyl acetate/benzene (1 4 by volume) showed the pentacycle (Rf 0 55) as the major component together with unreacted carboxamide (Rf 0.3) The solution was evaporated to dryness and the residue partitioned between water and chloroform The organic extract was washed with water, dried, and evaporated to dryness Crystallisation of the crude product twice from ethanol furnished the [$^2H_1$]pentacycle **28b** (171 mg, 48%), m p 285-290°C (Found. M^+, 350.185 Calc for $C_{21}H_{22}{}^2H_1N_3O_2$ M, 350 185).

Acid-Catalysed Hydrolysis of Pentacycle (28a)

A suspension of the pentacycle (225 mg) in 6 *M* hydrochloric acid (150 cm^3) was refluxed for 36 h with vigorous stirring The mixture was then evaporated to dryness *in vacuo* and the residue was triturated with water (20 cm^3). The water-soluble material (126 mg) was submitted to preparative t.l c on silica gel, eluted with butanol/acetic acid/water (3 1·1, by volume) The band with Rf 0 45 was extracted with ethanol and furnished proline (53 mg), $[a]_D$ -30.5° (c 0 5, H_2O), -17 0° (c 0.5, 2 *M* HCl), -34.9° (c 0 5, 2 *M* NaOH). Authentic *L*-proline had $[a]_D$ -87.4° (c 0 5, H_2O), -53.1° (c 0 5, 2 *M* HCl), -103 1° (c 0 5, 2 *M* NaOH)

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REFERENCES

1 M Yamazaki, K Suzuki, H Fujimoto, T Akiyama, U Sankawa, and Y Itaka, *Chem Pharm Bull*, 1980, **28**, 861-865

2 M Yamazaki, Chapter 6 in "The Biosynthesis of Mycotoxins A Study in Secondary Metabolism", Ed P S Steyn, Academic Press, New York, 1980, pp 193-222

3 Y Oikawa, T Yoshioka, and O. Yonemitsu, Tennen Yuki Kagobutsu Toronkai Koen Yoshishu, 1978, 22-27 (*Chem Abstr*, 1979, **90**, 152436)

4 R B. Woodward, M P Cava, W D. Ollis, A Hunger, H U Daeniker, and K. Schenker, *Tetrahedron*, 1963, **19**, 247-288

5 D M Harrison, *Tetrahedron Lett*, 1981, **22**, 2501-2504

6 D M Harrison and R B Sharma, *Tetrahedron Lett*, 1986, **27**, 521-524

7 S Nakatsuka, H Miyazaki, K Teranishi, and T Goto, *Tetrahedron Lett*, 1986, **27**, 2391-2394

8 M Nakagawa, H Fukushima, T Kawate, M Hongu, S Kodato, T Une, M Taniguchi, and T. Hino, *Tetrahedron Lett.*, 1986, **27**, 3235-3238; M. Nakagawa, H. Fukushima, T Kawate, M. Hongu, T Une, S. Kodato, M. Taniguchi, and T Hino, *Chem Pharm. Bull.*, 1989, **37**, 23-32.

9 R. Plate, P. H H Hermkens, H. Behm, H. C J Ottenheijm, *J Org Chem*, 1987, **52**, 560-564.

10 G J. O'Malley and M. P Cava, *Tetrahedron Lett*, 1987, **28**, 1131-1134.

11 S A. Boyd and W. J Thompson, *J Org Chem*, 1987, **52**, 1790-1794.

12 P D. Bailey, S P. Hollinshead, and N. R. McLay, *Tetrahedron Lett*, 1989, **30**, 6421-6422

13 M. Nakagawa, S. Kodato, M Hongu, T Kawate, and T. Hino, *Tetrahedron Lett.*, 1986, **27**, 6217-6220; S. Kodato, M. Nakagawa, M. Hongu, T. Kawate, and T. Hino, *Tetrahedron*, 1988, **44**, 359-377

14 S Nakatsuka, K Teranishi, and T. Goto, *Tetrahedron Lett.*, 1986, **27**, 6361-6364.

15 P H H Hermkens, R Plate, and H C J Ottenheijm, *Tetrahedron*, 1988, **44**, 1991-2000

16 T. Hino, T Kawate, and M Nakagawa, *Tetrahedron*, 1989, **45**, 1941-1944

17 P H. H. Hermkens, R. Plate, and H. C J Ottenheijm, *Tetrahedron Lett*, 1988, **29**, 1323-1324; P H H Hermkens, R Plate, C G Kruse, H W Scheeren, and H. C J. Ottenheijm, *J Org Chem.*, 1992, **57**, 3881-3887

18 P S Steyn, R Vleggaar, and C. J Rabie, *Phytochemistry*, 1981, **20**, 538-539

19 E Yamanaka, N Shibata, and S Sakai, *Heterocycles*, 1984, **22**, 371-374

20 cf H. R Snyder, R B. Hasbrouck, and J F Richardson, *J Am Chem Soc*, 1939, **61**, 3558-3560.

21. F Ungemach, M. DiPierro, R. Weber, and J M. Cook, *J Org Chem.*, 1981, **46**, 164-168

22. R Grigg, H Q N Gunaratne, and E McNaghten, *J Chem. Soc, Perkin Trans I*, 1983, 185-187, cf M. Jawdosiuk and J M. Cook, *J Org Chem.*, 1984, **49**, 2699-2701

23 U Hengartner, A D Batcho, J F. Blount, W Leimgruber, M E Larscheid, and J W. Scott, *J Org Chem*, 1979, **44**, 3748-3752

24 F Ungemach, D Soerens, R Weber, M. DiPierro, O Campos, P Mokry, J. M Cook, and J V Silverton, *J Am Chem Soc.*, 1980, **102**, 6976-6984.

25 G Massiot and T Mulamba, *J Chem. Soc, Chem. Commun.*, 1983, 1147-1149.

26 P D Bailey, S P Hollinshead, and N. R McLay, *Tetrahedron Lett*, 1987, **28**, 5177-5180.

27 A A Swelim, A I Khodair, and S Sallay, Bull Fac Sci, Assiut Univ, 1975 (Pub 1978), **4**, 233-245 (*Chem Abstr*, 1979, **91**, 21100)

28 P S Steyn, *Tetrahedron*, 1973, **29**, 107-120

29 P G. Sammes and A. C Weedon, *J Chem Soc, Perkin Trans I*, 1979, 3048-3052

30 D E. Nitecki, B. Halpern, and J W. Westley, *J Org Chem*, 1968, **33**, 864-866

31 P D Bailey and S P Hollinshead, *J Chem Soc, Chem. Commun*, 1985, 1575-1576

32 cf C J Moody and J G Ward, *J Chem. Soc, Perkin Trans I*, 1984, 2895-2901

33 cf J. S Davies and M. N Ibrahim, *Tetrahedron Lett*, 1977, 1453-1454, N Izumiya, S Lee, T. Kanmera, and H. Aoyagi, *J Am Chem. Soc*, 1977, **99**, 8346-8348

34 Serena Software, Box 3076, Bloomington, Indiana 47402-3076, U S A.

35 J J Gajewski, K E. Gilbert, and J. McKelvey, *Advances in Molecular Modelling*, 1990, **2**, 65

36 E. H P Young, *J Chem Soc*, 1958, 3493-3496.