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Sequential 1,3-Dipolar Cycloaddition-Pictet-Spengler Spirocyclisation Reactions of Metallo-Azomethine Ylides from Aliphatic Aldimines

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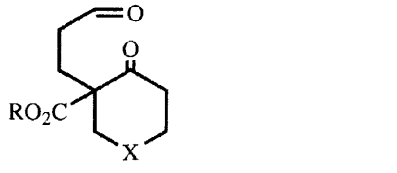
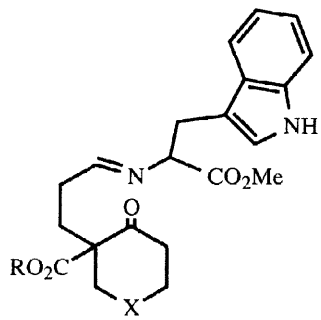
Abstract: Combinations of imine → azomethine ylide → cycloaddition cascades with acid catalysed Pictet-Spengler spirocyclisation occurs regio- and stereoselectively to afford novel polycyclic spirocycles containing three new rings and five stereocentres

Keywords : Metallo-azomethine ylides, Pictet-Spengler reaction, cycloaddition, cascade reaction.

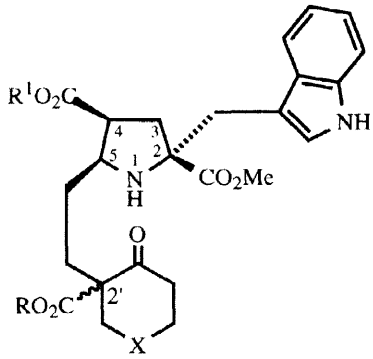
In the course of work directed towards the construction of a series of polycyclic nitrogen heterocycles[1] the imines **2a** (95%) and **2b** (83%) were prepared, starting from 1,5-ketoaldehydes[2] **1a** and **1b** and tryptophan methyl ester. The imine → azomethine ylide → cycloaddition cascade reaction of these imines with a range of dipolarophiles gave the cycloadducts **3a-d** in 57 - 68% yield as 1 : 1 mixtures of diastereomers.



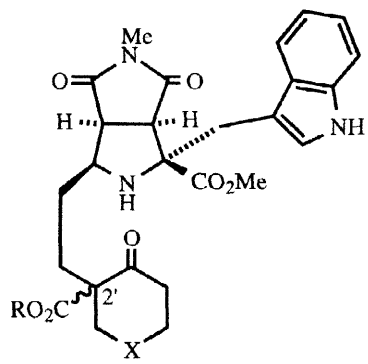
(1) **a.** X = CH_2, R = Et
b. X = NBn, R = Me



(2) **a.** X = CH_2, R = Et
b. X = NBn, R = Me



(3) **a.** X = CH_2, R = Et, R^1 = Me
b. X = NBn, R = Me, R^1 = Me
c. X = CH_2, R = Et, R^1 = (-)-menthyl



(3d) X = CH_2, R = Et

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Cycloaddition of imine **2a** with (1R,2S,5R)-menthyl acrylate (AgOAc, DBU, dry MeCN, rt, 16h) also resulted in a 1 : 1 diastereomeric mixture of enantiopure cycloadducts, due to the asymmetric 2'-carbon centre in **3c**, in 57% yield .

The absolute configuration of the pyrrolidine moiety of the diastereomeric cycloadducts **3c** is assigned as 2R,4S,5S based, by analogy, on the absolute configuration of two cycloadducts of (1R,2S,5R)-menthyl acrylate which were established by X-ray crystallography.[3] The regio- and endo-specificity of the cycloaddition reaction together with the absolute configuration of the pyrrolidine ring in the cycloadduct and the facial shielding effect of the menthyl isopropyl moiety are accommodated in the transition state shown in Figure 1 for the formation of **3c**.

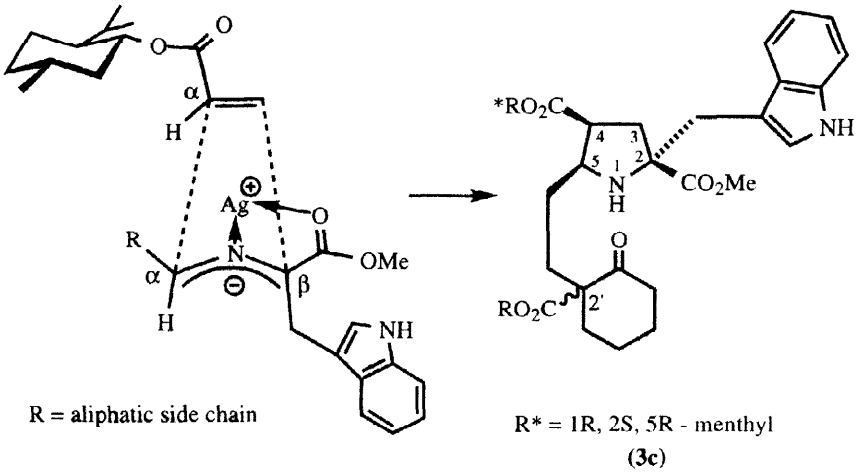
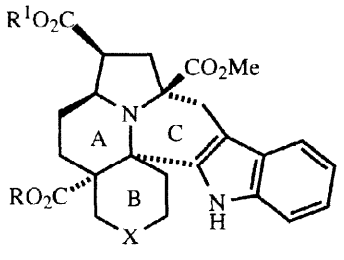


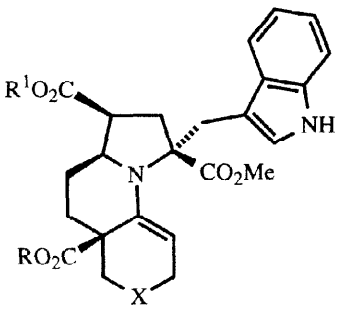
Figure 1

The endo-transition state involves attack on the $(C\alpha)_{re}$ - $(C\beta)_{si}$ face of the E,E-dipole by the less hindered $(C\alpha)_{re}$ face of the s-cis acrylate. The menthyl isopropyl group effectively shields the si-face in the s-cis acrylate.

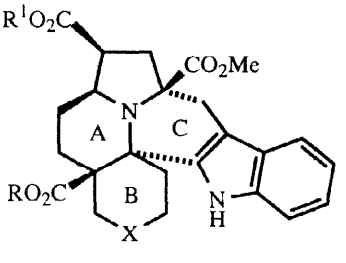
Treatment of cycloadducts **3a,b&d** with a catalytic amount of p-TsOH in boiling toluene for 48h provided the spirocyclic nitrogen heterocycles **4a,b&d** in 54 - 58% yield based on the 2'R-diastereomer. The 1 : 1 diastereomer mixture of cycloadducts **3c** resulted in enantiomerically pure **4c** in 50% yield based on the 2'R-diastereomer. No enamines **5a-d**, derived from the 2'S-diastereomer were detected in the crude products.



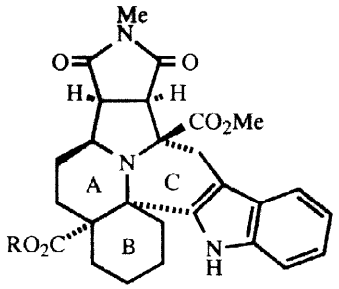
(4)a. X = CH_2, R = Et, R^1 = Me
b. X = NBn, R = Me, R^1 = Me
c. X = CH_2, R = Et, R^1 = (-)-menthyl



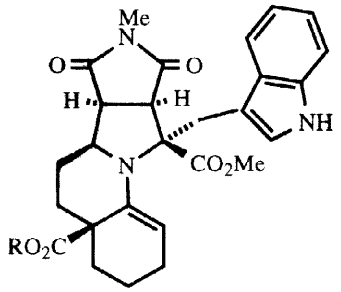
(5)a. X = CH_2, R = Et, R^1 = Me
b. X = NBn, R = Me, R^1 = Me
c. X = CH_2, R = Et, R^1 = (-)-menthyl



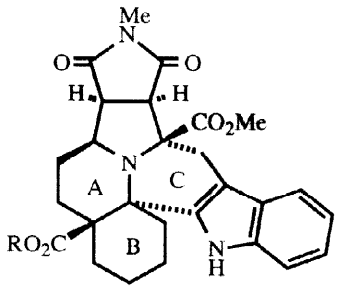
(6)a. X = CH_2, R = Et, R^1 = Me
b. X = NBn, R = Me, R^1 = Me
c. X = CH_2, R = Et, R^1 = (-)-menthyl



(4d)

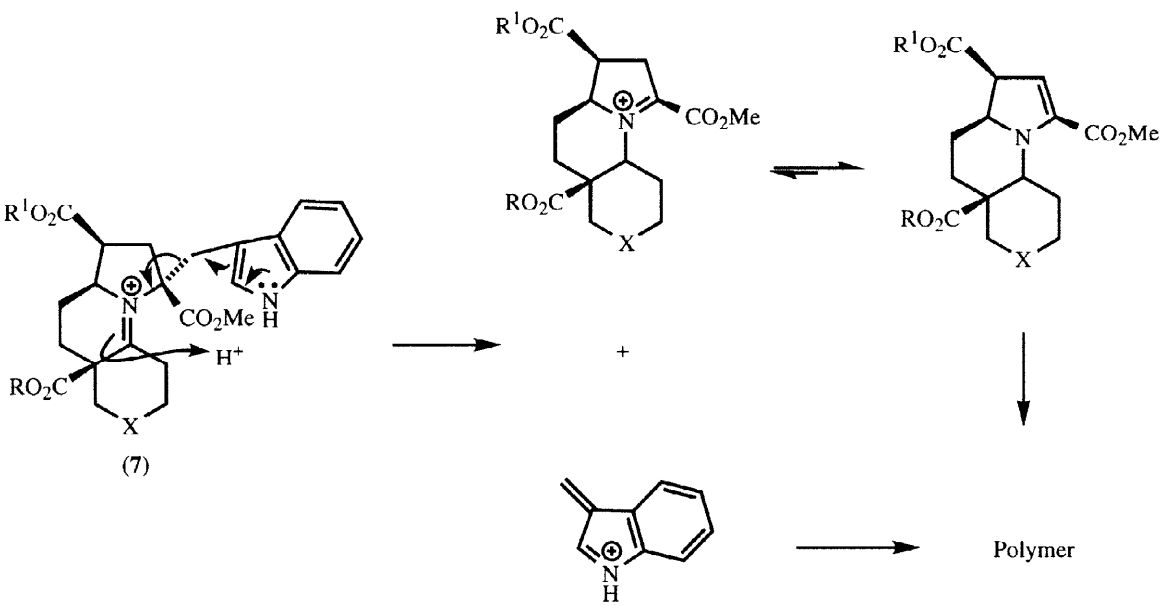


(5d)



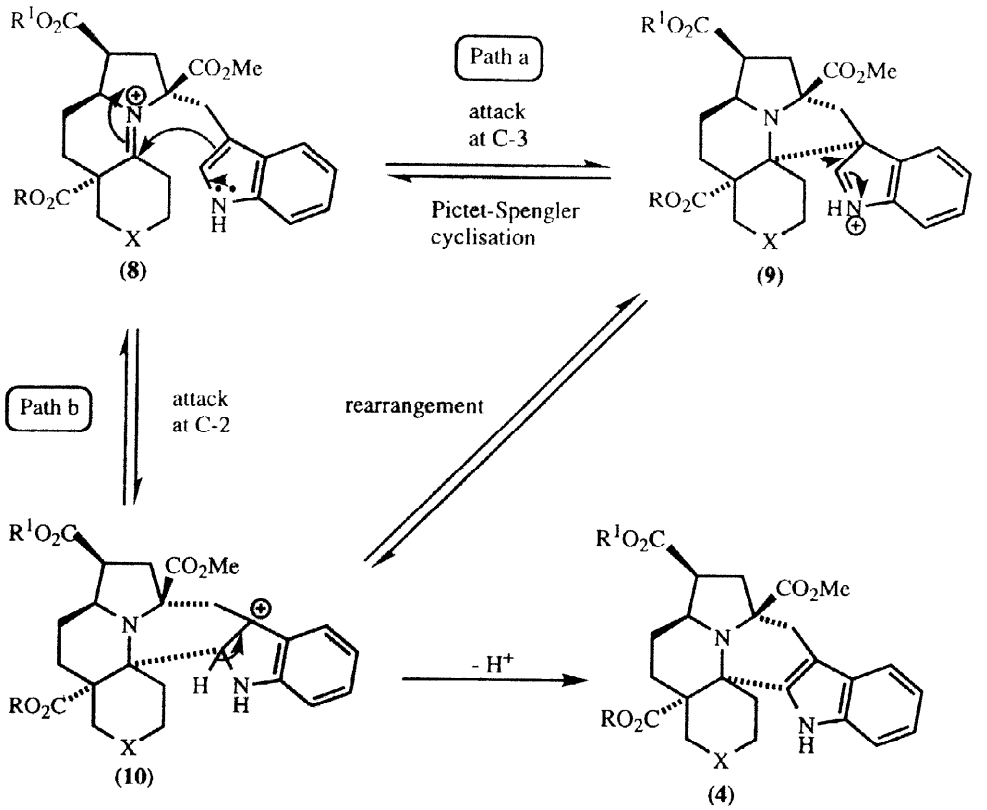
(6d)

Thus the products with the cis-decalin core **4a-d** (AB rings) are observed whilst the products with a trans-decalin (AB rings) core **6a-d** are not observed. Normally trans-decalins are more stable but inspection of molecular models of **4** and **6** show clearly that the additional fused rings create considerable steric strain in the C ring of **6**. This latter unfavourable strain is clearly present in the transition state leading to **6** and accounts for its failure to form. Failure to detect the enamines **5a-d** is believed to be due to the fragmentation-polymerisation of the precursor iminium ion **7** (arrows) (Scheme 1) which intervenes due to the disfavoured cyclisation of **7**. Formation of **4a-d** occurs *via* a conventional Pictet-Spengler cyclisation (Scheme 2). The intermolecular version of this reaction (condensation of tryptophan derivatives with aldehydes) has been extensively studied and has long been an important reaction for the synthesis of indole alkaloids.[4] The first step of the reaction involves the formation of iminium ion **8** following which two pathways could operate in the key Pictet-Spengler cyclisation. This cyclisation has generally been thought to proceed *via* a spiroindolenine intermediate **9**[4,5] followed by rearrangement of **9** (Path a) to **10**. However the cyclisation can also occur by direct attack at C-2 of the indole to give **10** (Path b).[6] Loss of H^+ from **10** gives the spirocycle **4**.



(7)

Scheme 1



Scheme 2

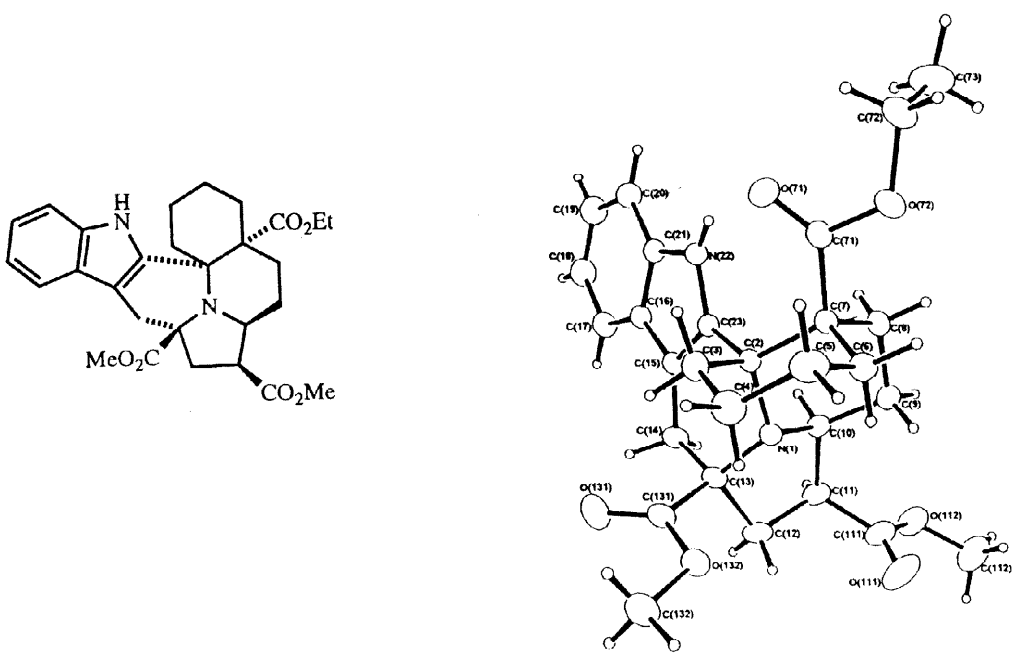
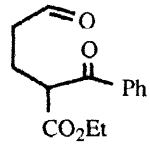
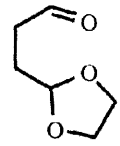


Figure 2. X-Ray crystallographic structure of 4a

Only the 2'R-diastereomer undergoes cyclisation to the spirocycle **4a**. In NOEDS studies on **4a** irradiation of the signal for the CH_2 of the 2'-ethoxycarbonyl group causes 1% enhancement of the signal for the NH of the indolyl moiety. This result suggests that the ethoxycarbonyl and indolyl groups are cis related. X-Ray crystallographic studies of **4a** confirmed the cis-azadecalin skeleton **4a** (Figure 2). The combination of imine cycloaddition with the Pictet-Spengler reaction results in the formation of three rings and four stereocentres and steric constraints in the Pictet-Spengler cyclisation originating at a remote centre result in precise selection of only one diastereomer of **3a-d**.

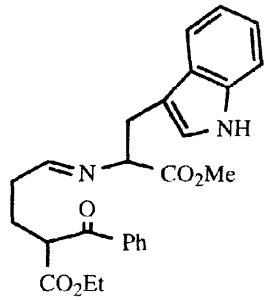


(11)

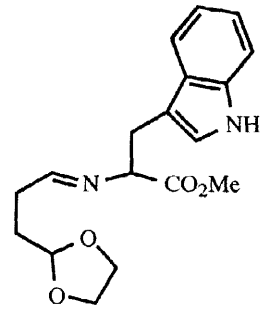


(12)

The 1,5-ketoaldehyde **11** and the monoprotected dialdehyde **12** were also subjected to a similar study. Both **11**[2] and **12**[7] reacted with tryptophan methyl ester in the presence of 4Å molecular sieves and anhydrous $MgSO_4$ respectively at room temperature to give the aliphatic aldimines **13** and **14** in 82% and 85% yield respectively.

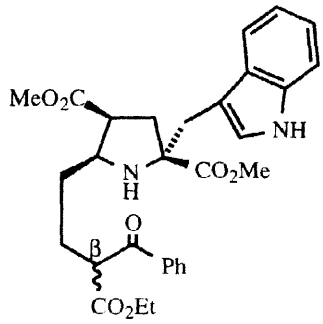


(13)

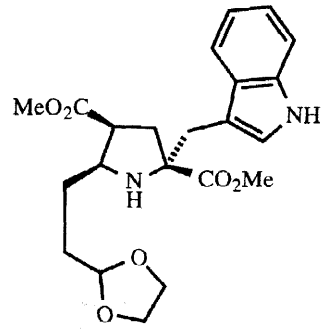


(14)

The AgOAc catalysed cycloaddition reaction of imine **13** with methyl acrylate in the presence of DBU proceeded in 65% yield to give a 1 : 1 mixture of diastereomeric cycloadducts **15** (due to the asymmetric β-carbon). Imine **14** underwent 1,3-dipolar cycloaddition with methyl acrylate in the presence of NEt_3 to give the cycloadduct **16** in 67% yield.

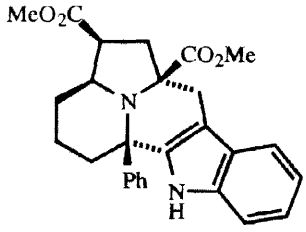


(15)

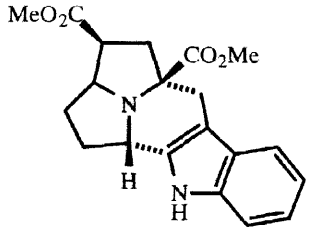


(16)

Acid catalysed cyclisation of the 1 : 1 diastereomeric mixture of cycloadducts **15** in the presence of a catalytic amount of p-TsOH in boiling toluene for 36h resulted in formation of the nitrogen heterocycle **17** in 59% yield. Acid catalysed hydrolysis of the acetal group in **16** in the presence of sodium cyanoborohydride resulted in **18** in 69% yield *via* an intramolecular Pictet-Spengler reaction. Surprisingly none of the simple reductive amination product was observed[7] indicating cyclisation is significantly faster than reduction.

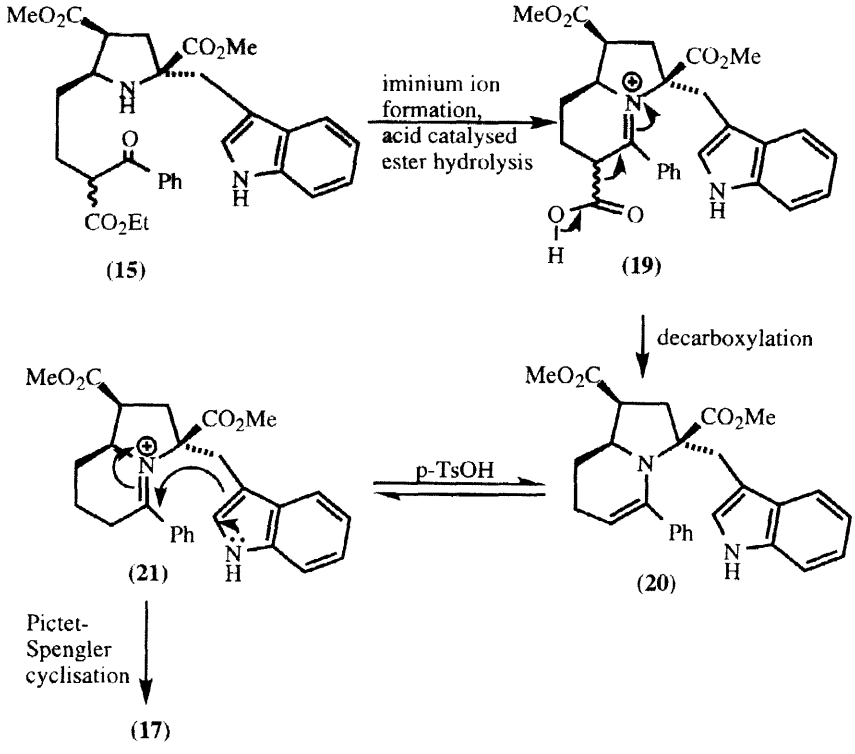


(17)



(18)

The genesis of **17** (Scheme 3) involves the formation of the appropriate iminium ion followed by acid catalysed ester hydrolysis giving **19**. Decarboxylation of **19** results in formation of the enamine **20** which equilibrates with iminium ion **21** which undergoes Pictet-Spengler cyclisation (Scheme 3).



Scheme 3

Experimental. Melting points were obtained on a Reichert hot-stage apparatus and are uncorrected. Optical rotations were measured at ambient temperature using an Optical Activity Ltd., AA-1000 polarimeter. Microanalysis were obtained using a Carlo Erba MOD 1106 instrument. Mass spectral data were recorded on a V.G.Autospec instrument operating at 70eV. Accurate molecular weights were determined using perfluorokerosine as an internal standard. Nuclear magnetic resonance spectra were recorded on QE300 and

Bruker WP400 instruments operating at 300 and 400MHz respectively. Deuterochloroform was used as the solvent with tetramethylsilane as the internal standard. Chemical shifts are given in parts per million (δ) down field from tetramethylsilane and coupling constants are given in Hz. The following abbreviations are used : s=singlet, d=doublet, t=triplet, q=quartet, dd=double doublet, m=multiplet. Solvents were purified according to standard procedures.[8] The term ether refers to diethyl ether and petroleum ether refers to the fraction with boiling point 40-60^{0}C. Flash chromatography employed silica gel 60 (230-400 mesh).

General Procedure for Preparation of Aliphatic Aldimines. α-Aminoester hydrochloride in dry CH_2Cl_2 was shaken with concentrated aqueous ammonia solution. The CH_2Cl_2 layer was separated, dried ($MgSO_4$) and evaporated to dryness under reduced pressure at room temperature to afford the aminoester free base. A mixture of aldehyde (1 eq), α-aminoester (1.05 eq) and activated 4Å molecular sieves in dry CH_2Cl_2 (5 ml for 1 mmol aldehyde) was stirred at room temperature for 1h. After the removal of molecular sieves by filtration the solvent was evaporated (bath temperature ≤ 30^{0}C) and the crude product was used for the next step without purification due to thermal and chromatographic instability.

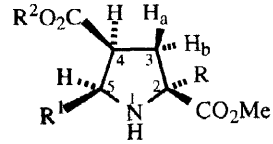
Methyl N-[3-(1'-ethoxycarbonyl-2'-oxocyclohexyl)-propylidine]-tryptophanate (2a). Aldehyde **1a** (1.50 g, 6.64 mmol) and racemic tryptophan methyl ester (1.52 g, 6.70 mmol) gave the crude imine as a pale yellow viscous gum (2.69 g, 95%). δ 8.25(s, 1H, NH), 7.61(d, 1H, J 6.7Hz, indole-H), 7.15(m, 5H, indole-H and HC=N), 4.18(m, 2H, O$\underline{CH_2}$Me), 4.00(dd, 1H, J 4.7, 9.4Hz, NCH), 3.76(s, 3H, OMe), 3.44(dd, 1H, J 4.7, 14.5Hz, indole-CH), 3.12(dd, 1H, J 9.4, 14.5Hz, indole-CH), 2.49-1.41(m, 12H, 6 x CH_2) and 1.25(t, 3H, J 6.8Hz, OCH$_2\underline{Me}$); ***m/z***(%) 426(M^+, 8), 296(7), 202(5), 197(3), 130(100), 124(7) and 55(6).

Methyl N-[3-(1'-benzyl-3'-methoxycarbonyl-4'-oxopiperidyl)-propylidine]-tryptophanate (2b). Aldehyde **1b** (3.20 g,10.56 mmol) and racemic tryptophan methyl ester (2.41 g, 11.09 mmol) gave the crude imine as a pale yellow viscous gum (4.39 g, 83%). δ 8.48(s, 1H, NH), 7.28(m, 11H, PhH, indole-H and HC=N), 3.83(m, 1H, NCH), 3.74 and 3.68(2 x s, 2 x 3H, 2 x OMe), 3.14(m, 6H, $PhCH_2$, indole-CH_2 and CH_2) and 2.04(m, 8H, 4 x CH_2); ***m/z***(%) 503(M^+, 6), 444(5), 412(6), 373(46), 130(100), 91(78), 77(10), 65(10) and 51(4).

Methyl N-(4-benzoyl-4-ethoxycarbonylbutylidine)-tryptophanate (13). Aldehyde **11** (2.00 g, 8.06 mmol) and racemic tryptophan methyl ester (1.85 g, 8.47 mmol) gave the crude imine as a pale yellow gum (2.96 g, 82%). δ 8.26(s, 1H, NH), 7.46(m, 11H, ArH, indole-H and HC=N), 4.33(m, 1H, $\underline{CH}CO_2Et$), 4.08(m, 2H, O$\underline{CH_2}$Me), 3.83(dd, 1H, J 4.8, 7.6Hz, NCH), 3.71(s, 3H, OMe), 3.29(dd, 1H, J 4.8, 14.4Hz, indole-CH), 3.06(dd, 1H, J 7.6, 14.4Hz, indole-CH), 2.03(m, 4H, 2 x CH_2) and 1.15(t, 3H, J 7.1Hz, OCH$_2\underline{Me}$); ***m/z***(%) 448(M^+, 1), 130(100), 105(31), 77(21) and 51(5).

Methyl N-[3-(1',3'-dioxolan-2'-yl)-propylidine]-tryptophanate (14).[9] Aldehyde **12** (0.77 g, 5.92 mmol) and racemic tryptophan methyl ester (1.55 g, 7.11 mmol) gave the crude imine as a pale yellow oil (1.60 g, 82%). δ 8.12(s, 1H, NH), 7.68(t, 1H, J 9.1Hz, HC=N), 7.48(m, 5H, indole-H), 4.84(t, 1H, J 4.9Hz, OCHO), 3.92(dd, 1H, J 4.5, 8.9Hz, NCH), 3.89(m, 4H, 2 x OCH_2), 3.69(s, 3H, OMe), 3.50(dd, 1H, J 4.5, 14.3Hz, indole-CH), 3.22(dd, 1H, J 8.9, 14.3Hz, indole-CH) and 1.73(m, 4H, 2xCH_2); ***m/z***(%) 330(M^+, 5), 271(59) and 212(100).

Numbering of Pyrrolidine Ring



General Procedure for Metal Catalysed Cycloaddition Reactions. A mixture of imine (1 eq), AgOAc or LiBr (1.2 eq), appropriate dipolarophile [methyl acrylate (1.5 eq) or NMM (1.5 eq) or (1R,2S,5R)-menthyl acrylate (1 eq)] and DBU or NEt_3(1.2 eq) in dry MeCN (5 ml for 1 mmol imine) (protected from the light with aluminium foil when AgOAc was used as catalyst) was stirred at room temperature for 16h. The reaction was then quenched by addition of saturated aqueous ammonium chloride solution and the mixture was extracted with ether (2 x) or CH_2Cl_2 (2 x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and solvent evaporated. The residue was purified by flash chromatography to afford the cycloadduct.

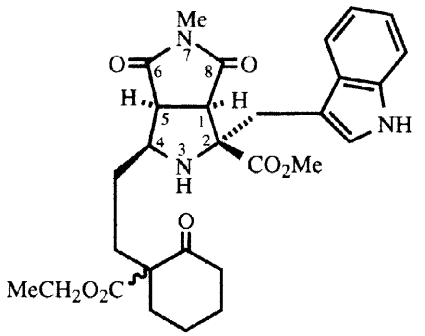
Dimethyl 2-(3'-indolylmethyl)-c-5-[1"-(1'''-ethoxycarbonyl-2'''-oxocyclohexyl)-ethyl]-pyrrolidine-r-2-,c-4-dicarboxylate (3a). Aldimine **2a** (2.69 g, 6.31 mmol), AgOAc (1.26 g, 7.58 mmol), DBU (1.53 g, 7.58 mmol) and methyl acrylate (0.82 g, 9.47 mmol) gave, after work up followed by flash chromatography eluting with ether, the **product** as a yellow viscous gum (2.07 g, 64%). (Found : C,65.6; H,7.2; N,5.25. $C_{28}H_{36}N_2O_7$ requires C,65.6; H,7.05; N,5.45%); δ (mixture of diastereoisomers) 8.55(s, 1H, NH), 7.62 and 7.26(2 x d, 2 x 1H, J 7.6Hz, 2 x indole-H), 7.07(m, 3H, indole-H), 4.15(m, 2H, OCH_2Me), 3.59(s, 6H, 2 x OMe), 3.19(d, 1H, J 14.2Hz, indole-CH), 3.12(m, 1H, 5-H), 3.02(d, 1H, J 14.2Hz, indole-CH), 2.84(m, 1H, 4-H), 2.63(m, 1H, 3-H_a), 2.42(m, 4H, 2 x CH_2), 2.12(m, 1H, 3-H_b), 1.83(m, 7H, 3 x CH_2 and NH), 1.32(m, 2H, CH_2) and 1.22(t, 3H, J 7.2Hz, OCH_2Me); δ (^{13}C) (mixture of diastereoisomers) 207.66(cyclohexanone-CO), 176.26, 173.76 and 171.61(3 x ester-CO), 135.62, 127.97, 123.67, 121.31, 118.90, 110.90 and 110.58(Ar), 69.91, 62.25(5-C), 61.06(OCH_2Me), 60.39, 52.09 and 51.20(2 x OMe), 47.76(4-C), 40.87, 38.78(3-C), 35.94(indole-CH_2), 35.63, 32.29, 27.39, 26.16 and 22.36(CH_2) and 13.96(OCH_2Me); ***m/z***(%) 513(M^++1, 52), 453(11), 382(100), 170(4), 130(39) and 55(6).

Dimethyl 2-(3'-indolylmethyl)-c-5-[1"-(1'''-benzyl-3'''-methoxycarbonyl-4'''-oxopiperidyl)-ethyl]-pyrrolidine-r-2-,c-4-dicarboxylate (3b). Aldimine **2b** (4.39 g, 8.73 mmol), AgOAc (1.75 g, 10.47 mmol), DBU (1.59 g,10.47 mmol) and methyl acrylate (1.13 g, 13.09 mmol) gave, after work up followed by flash chromatography eluting with ether, the **product** as a pale yellow semi solid (3.19 g, 62%). (Found : C,67.0; H,6.75; N,6.9. $C_{33}H_{39}N_3O_7$ requires C,67.2; H,6.65; N,7.15%); δ (mixture of diastereoisomers) 8.15(s, 1H, NH), 7.27(m, 10H, ArH and indole-H), 3.65(d, 1H, J 13.1Hz, indole-CH), 3.62(s, 3H, OMe), 3.55(d, 1H, J 13.1Hz, indole-CH), 3.52 and 3.48(2 x s, 2 x 3H, 2 x OMe), 3.43(m, 2H, $PhCH_2$), 3.25(m, 2H, CH_2), 3.01(m, 2H, 5-H and NH), 2.80(m, 1H, 4-H), 2.51(m, 1H, 3-H_a), 2.30(m, 2H, CH_2) and 1.71(m, 7H, 3-H_b and 3 x CH_2); ***m/z***(%) 589(M^+, 1), 530(6), 459(51), 130(32), 91(100), 77(8), 65(11), 51(4) and 39(6).

1R,2S,5R-Menthyl 2-(3'-indolylmethyl)-r-2R-methoxycarbonyl-c-5S-[1"-(1'''-ethoxycarbonyl-2'''-oxocyclohexyl)-ethyl]-pyrrolidine-c-4S-carboxylate (3c). Aldimine **2a** (5.50 g, 12.91 mmol), AgOAc (2.59 g, 15.49 mmol), DBU (2.36 g, 15.49 mmol) and 1R, 2S, 5R-menthyl acrylate (2.72 g, 12.91 mmol) gave, after work up followed by flash chromatography eluting with 1 : 1 v/v ether-petroleum ether, the **product** as a yellow viscous gum (4.68 g, 57%). (Found : C,69.55; H,8.0; N,4.15. $C_{37}H_{52}N_2O_7$ requires C,69.75; H,8.25; N,4.4%); $[\alpha]_D$ -41.1 (c 1.06, $CHCl_3$); δ (mixture of

diastereoisomers) 8.16(s, 1H, NH), 7.63 and 7.31(2 x d, 2 x 1H, J 7.5Hz, 2 x indole-H), 7.10(m, 3H, indole-H), 4.64(m, 1H, OCH), 4.17(m, 2H, O$\underline{CH_2}$Me), 3.60(s, 3H, OMe), 3.57 and 3.22(2 x m, 2 x 1H, 2 x indole-CH), 3.17(m, 1H, 5-H), 2.86(m, 1H, 4-H), 2.58(m, 1H, 3-H_a), 2.45(m, 4H, aliphatic-H), 2.13(m, 1H, 3-H_b), 1.64(m, 13H, aliphatic-H and NH), 1.25(t, 3H, J 7.1Hz, OCH$_2$$\underline{Me}$) and 0.94(m, 14H, aliphatic-H); ***m/z***(%) : 636(M^+, 1), 506(100), 170(6), 130(41), 83(15) and 55(11).

Methyl 2-(3'-indolylmethyl)-4-[1"-(1'''-ethoxycarbonyl-2'''-oxocyclohexyl)ethyl]-7-methyl-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane-2-carboxylate (3d).



Aldimine **2a** (5.50 g, 12.91 mmol), AgOAc (2.59 g, 15.49 mmol), DBU (2.36 g, 15.49 mmol) and NMM (1.58 g, 14.20 mmol) gave, after work up followed by flash chromatography eluting with ether, the **product** as a pale yellow semi solid (4.71 g, 68%). (Found : C,64.5; H,6.25; N,7.55. $C_{29}H_{35}N_3O_7$ requires C,64.8; H,6.55; N,7.8%); δ (mixture of diastereoisomers) 8.26(s, 1H, NH), 7.60(m, 1H, indole-H), 7.35(m, 4H, indole-H), 4.20(m, 2H, O$\underline{CH_2}$Me), 3.71(s, 3H, OMe), 3.65(m, 1H, 4-H), 3.53(m, 1H, indole-CH), 3.39(m, 2H, 5-H and indole-CH), 3.12(m, 1H, 1-H), 2.91(s, 3H, NMe), 2.48(m, 4H, 2 x CH_2), 2.30(s, 1H, NH), 1.66(m, 8H, 4 x CH_2) and 1.25(t, 3H, J 7.0Hz, OCH$_2$$\underline{Me}$); ***m/z***(%) 536($M^+$-1, 4), 407(30), 406(100), 130(71), 55(10) and 42(4).

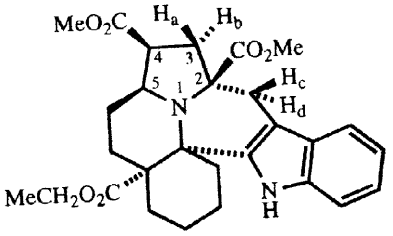
Dimethyl 2-(3'-indolylmethyl)-c-5-(1"-benzoyl-1"-ethoxycarbonylprop-3"-yl)-pyrrolidine-r-2-,c-4-dicarboxylate (15). Aldimine **13** (2.96 g, 6.61 mmol), AgOAc (1.32 g, 7.93 mmol), DBU (1.21 g, 7.93 mmol) and methyl acrylate (0.85 g, 9.91 mmol) gave, after work up followed by flash chromatography eluting with ether, the **product** as a pale yellow viscous gum (2.29 g, 65%). (Found : C,66.2; H,6.3; N,5.1. $C_{30}H_{34}N_2O_7$. $0.5H_2O$ requires C,66.3; H,6.5; N,5.15%); δ (mixture of diastereoisomers) 8.32(s, 1H, NH), 7.48(m, 10H, PhH and indole-H), 4.29(t, 1H, J 7.1Hz, $\underline{CH}CO_2Et$), 4.12(q, 2H, J 7.2Hz, O$\underline{CH_2}$Me), 3.61 and 3.58(2 x s, 2 x 3H, 2 x OMe), 3.20(m, 2H, 5-H and indole-CH), 3.02(d, 1H, J 14.1Hz, indole-CH), 2.83(m, 1H, 4-H), 2.63(m, 1H, 3-H_a), 2.32(m, 3H, CH_2 and 3-H_b), 1.32(m, 3H, NH and CH_2) and 1.15(t, 3H, J 7.2Hz, OCH$_2$$\underline{Me}$); ***m/z***(%) : 535($M^+$+1, 1), 475(7), 429(12), 404(78), 130(94), 105(100), 77(39) and 51(6).

Dimethyl 2-(3'-indolylmethyl)-c-5-[2'-(1",3"-dioxolan-2"-yl)-ethyl]-pyrrolidine-r-2-,c-4-dicarboxylate (16).[9] Aldimine **14** (1.95 g, 5.91 mmol), AgOAc (1.18 g, 7.09 mmol), NEt_3 (0.72 g, 7.09 mmol) and methyl acrylate (0.76 g, 8.86 mmol) gave, after work up followed by flash chromatography eluting with 5 : 1 v/v ether-petroleum ether, the **product** (1.65 g, 67%) which crystallised from ether-petroleum ether as colourless rods, m.p. 181-182^{0}C. (Found : C,63.35; H,6.95; N,6.5. $C_{22}H_{28}N_2O_6$ requires C,63.45; H,6.75; N,6.7%); δ 8.12(s, 1H, indole-H), 7.52(m, 5H, indole-H), 4.78(t, 1H, J 4.8Hz, OCHO), 3.89(m, 4H, 2 x OCH_2), 3.83 and 3.71(2x s, 2 x 3H, 2 x OMe), 3.48(dd, 1H, J 4.5, 14.3Hz, indole-CH), 3.34(m,

1H, 5-H), 3.20(dd, 1H, J 8.9, 14.3Hz, PhCH), 3.17(m, 1H, 4-H), 2.59(dd, 1H, J 5.6, 12.9Hz, 3-H_b), 1.89(m, 1H, 3-H_a) and 1.77(m, 4H, 2 x CH_2); ***m/z***(%) 416(M^+, 2), 357(50), 298(100) and 179(72).

General Procedure for Acid Catalysed Cyclisation Reactions. Cycloadduct (1 eq) and p-TsOH (0.1 eq) were mixed in dry toluene (5 ml for 1 mmol cycloadduct) in a round bottom flask equipped with a reflux condenser. A guard tube was attached to the top of the condenser and the mixture was stirred and boiled under reflux for the appropriate time. The reaction mixture was then cooled and the solvent removed under reduced pressure. The residue was partitioned between brine (10 ml for 1 mmol cycloadduct) and CH_2Cl_2 (20 ml for 1 mmol cycloadduct), the organic layer separated and the water layer extracted with a further portion of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed. The residue was purified by column chromatography.

Spirocyclic Nitrogen Heterocycle (4a).



Proton irradiated	Enhancement (%)							
	NH	H_c	5-H	4-H	3-H_a	H_d	3-H_b	$OCH_2\underline{Me}$
$O\underline{CH_2}Me$	1							5
5-H				4		5		
4-H			2			1	5	
3-H_a		5					20	
H_d		14	4				4	
3-H_b				8	26	4		

Prepared from the 1 : 1 diastereomeric mixture of cycloadducts **3a** (1.00 g, 1.92 mmol) and p-TsOH (0.04 g, 0.19 mmol). Work up after 48h gave a mixture of spirocyclic nitrogen heterocycle **4a** and decomposition products. Flash chromatography eluting with 1 : 1 v/v ether-petroleum ether, afforded **4a** [0.27 g, 56% (yield based on one diastereomer)] which crystallised from ethyl acetate as colourless prisms, m.p. 147-149°C. (Found : C,68.1; H,6.85; N,5.35. $C_{28}H_{34}N_2O_6$ requires C,68.0; H,6.95; N,5.65%); δ 9.45(s, 1H, NH), 7.50 and 7.48(2 x d, 2 x 1H, J 7.6Hz, 2 x indole-H), 7.14 and 7.07(2 x t, 2 x 1H, J 7.0Hz, 2 x indole-H), 4.29(m, 2H, $O\underline{CH_2}Me$), 3.77(d, 1H, J 14.3Hz, H_c), 3.73 and 3.70(2 x s, 2 x 3H, 2 x OMe), 3.13(m, 1H, 5-H), 3.04(m, 1H, 4-H), 2.87(dd, 1H, J 5.9, 12.4Hz, 3-H_a), 2.81(m, 1H, CH), 2.77(d, 1H, J 14.3Hz, H_d), 2.41(m, 1H, CH), 2.07(dd, 1H, J 9.3, 12.4Hz, 3-H_b), 1.98(m, 2H, CH_2), 1.63(m, 6H, 3 x CH_2), 1.34(t, 3H, J 7.1Hz, $OCH_2\underline{Me}$) and 1.19(m, 2H, CH_2); δ (^{13}C) 178.31, 175.71, 174.02(3 x ester-CO), 136.29, 135.38, 127.11, 121.36, 118.92, 117.79, 111.19 and 106.30(Ar) , 65.95, 63.30, 61.14($O\underline{CH_2}Me$), 60.58(5-C), 52.33, 52.17 and 51.51(2 x OMe), 43.89(4-C), 41.92(3-C), 34.34, 31.35 and 31.01(3 x CH_2), 24.74(indole-CH_2), 23.15, 22.48 and 21.51(3 x CH_2) and 14.10($OCH_2\underline{Me}$); ***m/z***(%) 494(M^+, 26), 449(6), 435(100), 421(99), 364(5), 362(6) and 130(9).

Spirocyclic Nitrogen Heterocycle (4b). Prepared from the 1 : 1 diastereomeric mixture of cycloadducts **3b** (0.50 g, 0.85 mmol) and p-TsOH (0.02 g, 0.08 mmol). Work up after 48h gave a mixture of spirocyclic nitrogen heterocycle **4b** and decomposition products. Flash chromatography eluting with ether, afforded **4b** [0.13 g, 54% (yield based on one diastereomer)] as a colourless powder, m.p. 116°C. (Found : C,69.05; H,6.7; N,7.05. $C_{33}H_{37}N_3O_6$ requires C,69.35; H,6.5; N,7.35%); δ 9.75(s, 1H, NH), 7.28(m, 9H, PhH and indole-H), 3.77(d, 1H, J 14.6Hz, indole-CH), 3.73, 3.71 and 3.68(3 x s, 3 x 3H, 3 x OMe), 3.61(d, 1H, J 13.0Hz, CH), 3.36(m, 2H, $PhCH_2$), 3.07(m, 2H, 5-H and 4-H), 2.86(dd, 1H, J 5.8, 12.4Hz, 3-H_a),

2.75(m, 4H, indole-CH and 3 x CH), 4.17(dd, 1H, J 8.9, 12.4Hz, 3-H_b), 1.93(m, 2H, CH_2) and 1.44(m, 4H, 2 x CH_2); ***m/z***(%) 571(M^+, 78), 512(94), 480(61), 441(6), 130(10), 91(100) and 65(5).

Spirocyclic Nitrogen Heterocycle (4c). Prepared from the 1 : 1 diastereomeric mixture of cycloadducts **3c** (0.02 g, 0.31 mmol) and p-TsOH (0.01 g, 0.03 mmol). Work up after 48h gave a mixture of spirocyclic nitrogen heterocycle **4c** and decomposition products. Flash chromatography eluting with 1 : 1 v/v ether-petroleum ether, afforded **4c** [0.05 g, 50% (yield based on one diastereomer)] as a colourless powder, m.p. 160-163^{0}C, $[\alpha]_D$ -27.1 (c 0.62, $CHCl_3$). (Found (H.R.M.S) : 618.3678. $C_{37}H_{50}N_2O_6$ requires 618.3668) δ 8.17(s, 1H, NH), 7.66 and 7.35(2 x d, 2x1H, J 7.8Hz, 2 x indole-H), 7.14 and 7.13(m, 2H, indole-H), 4.59(m, 1H, OCH), 4.16(m, 2H, O<u>CH$_2$</u>Me), 3.77(s, 3H, OMe), 3.72(d, 1H, J 14.9Hz, H_c), 3.32(m, 1H, 5-H), 3.21(d, 1H, J 14.9Hz, H_d), 2.89(m, 1H, 4-H), 2.24(m, 5H, 3-H_a, 3-H_b and aliphatic-H), 1.51(m, 10H, aliphatic-H), 1.27(t, 3H, J 7.1Hz, OCH$_2$<u>Me</u>) and 0.90(m, 17H, aliphatic-H); ***m/z***(%) 618(M^+, 7), 545(8), 488(100), 486(4), 435(6) and 130(29).

Spirocyclic Nitrogen Heterocycle (4d). Prepared from the 1 : 1 diastereomeric mixture of cycloadducts **3d** (1.00 g, 1.86 mmol) and p-TsOH (0.04 g, 0.19 mmol). Work up after 48h gave a mixture of spirocyclic nitrogen heterocycle **3d** and decomposition products. Flash chromatography eluting with ether, afforded **3d** [0.28 g, 58% (yield based on one diastereomer)] which crystallised from ether as colourless needles, m.p. 162-165^{0}C. (Found : C,67.05; H,6.4; N,8.1. $C_{29}H_{33}N_3O_6$ requires C,66.8; H,6.5; N,7.8%); δ 9.45(s, 1H, NH), 7.48 and 7.30(2 x d, 2 x 1H, J 7.6Hz, indole-H), 7.12 and 7.05(2 x t, 2 x 1H, J 7.0Hz, indole-H), 4.30(m, 2H, O<u>CH$_2$</u>Me), 4.09(m, 2H, H_c and 4-H), 3.61(s, 3H, OMe), 3.12(m, 2H, 5-H and 1-H), 3.04(s, 3H, NMe), 2.86(d, 1H, J 12.9Hz, H_d), 2.30(m, 4H, 2 x CH_2) and 1.50(m, 11H, OCH$_2$<u>Me</u> and 4 x CH_2); ***m/z***(%) 519(M^+, 75), 474(12), 460(46), 446(100), 389(7), 387(9), 328(3) and 130(14).

Polycyclic Nitrogen Heterocycle (17). Prepared from the 1 : 1 diastereomeric mixture of cycloadducts **15** (1.00 g, 1.87 mmol) and p-TsOH (0.04 g, 0.19 mmol). After 36h, work up followed by flash chromatography eluting with 4 : 1 v/v ether-petroleum ether, afforded **15** (0.49 g, 59%) as a yellow semi solid. (Found (H.R.M.S) : 444.2051. $C_{27}H_{28}N_2O_4$ requires 444.2049); δ 8.06(s, 1H, NH), 7.55 and 7.39(2 x d, 2 x 1H, J 7.3Hz, 2 x indole-H), 7.19(m, 7H, indole-H and PhH), 3.75(s, 3H, OMe), 3.55(d, 1H, J 14.1Hz, indole-CH), 3.09(m, 2H, 5-H and 4-H), 2.87(dd, 1H, J 4.6, 12.7Hz, 3-H_a), 2.81(s, 3H, OMe), 2.73(d, 1H, J 14.1Hz, indole-CH) and 1.46(m, 7H, 3-H_b and 3 x CH_2); ***m/z***(%) 444(M^+, 11), 385(37), 130(11), 77(62), 51(37) and 39(33).

Polycyclic Nitrogen Heterocycle (18).[9] A solution of cycloadduct **16** (1.40 g, 3.37 mmol) in THF (55 ml) and 0.1M HCl (11 ml) was stirred at room temperature for 4h and neutralised by the addition of 0.1M NaOH solution. Sodium cyanoborohydride (0.42 g, 6.73mmol) was then added and stirring continued for a further 12h. The solvent was evaporated and the residue was treated with brine (10 ml). The mixture was extracted with CH_2Cl_2 (3 x 10ml) and the combined extracts dried ($MgSO_4$), filtered and the solvent evaporated. The residue was purified by flash chromatography eluting with 9 : 2 v/v ethyl acetate-ether, to afford **18** (0.82 g, 69%) as a colourless oil. (Found : C,67.85; H,6.75; N,8.0. $C_{20}H_{22}N_2O_4$ requires C,67.6; H,6.5; N,7.9%); δ 7.52(m, 4H, indole-H), 4.80(t, 1H, J 3.0Hz, NCH), 3.84 and 3.76(2 x s, 2 x 3H, 2 x OMe), 3.48(dd, 1H, J 4.5, 14.3Hz, indole-CH), 3.40(m, 1H, 5-H), 3.20(dd, 1H, J 8.9, 14.3Hz, indole-CH), 3.14(m, 1H, 4-H), 2.81(dd, 1H, J 5.7, 13.0Hz, 3-H_b), 1.82(m, 1H, 3-H_a) and 1.62(m, 4H, 2 x CH_2); ***m/z***(%) 354(M^+, 9), 296(40) and 237(100).

Single crystal X-ray diffraction analysis of 4a - Crystallographic data were measured on a Stoe STADI4 4-circle diffractometer using Cu-K_α radiation (λ=1·54184 Å) and an ω-θ scanning method. The data were corrected for absorption empirically using azimuthal ψ-scans. The structure was solved by direct methods using SHELXS-86[10] and refined by full-matrix least-squares (on F^2) using SHELXL-93.[11] The weighting scheme used was $w = [\sigma^2(F_o^2) + (xP)_2 + yP]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$. The solution gave two molecules in the asymmetric unit which differ only by the relative conformations of side groups. All non-hydrogen atoms were refined with anisotropic displacement parameters whilst hydrogen atoms were constrained to predicted positions using a riding model. The residuals wR_2 and R_1, given below, are defined as $wR_2 = [\Sigma[wF_o^2 - F_c^2)^2]/\Sigma[w(F_o^4)]]^{1/2}$ and $R_1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$.

Crystal data for 4a - $C_{28}H_{34}N_2O_6$, 0.58 X 0.44 X 0.30 mm, M = 494.57, triclinic, space group P-1, a = 12.0677(3), b = 12.0629(4), c = 18.9238(6) Å, α = 95.740(3)°, β = 102.408(2)°, γ = 107.629(2)°, U = 2523.42(13) Å^3, Z = 4, D_C = 1.30 Mg m^{-3}, μ = 0.747 mm^{-1}, $F(000)$ = 1056, T =293K.

Data collection - Graphite monochromated Cu-$K\alpha$ radiation, λ = 1.54184 Å, scan speeds 1.5 - 8.0° min^{-1}, ω scan widths 1.05° + α-doublet splitting, $4.0 < 2\theta < 130.0°$, 8142 unique data collected, 6462 reflections with $F_o > 4.0\ \sigma(F_o)$.

Structure Refinement - Number of parameters = 674, isotropic extinction parameter, x = 0.0048(2), goodness of fit, s = 1.032; weighting parameters x,y = 0.0628, 0.8596; wR_2 = 0.1174, R_1 = 0.0411.

Supplementary data, which includes hydrogen co-ordinates, all thermal parameters and complete sets of bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre and are available on request.

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