Pergamon

Tetrahedron 55 (1999) 1763–1780

TETRAHEDRON

Cycloaddition Reactions of Aldimines of 1,5-Ketoaldehydes. Applications in the Synthesis of Polycyclic Nitrogen Heterocycles.

Ronald Grigg*, Mark Thornton-Pett and Gnanamoly Yoganathan

Molecular Innovation, Diversity and Automated Synthesis (MIDAS) Centre,
School of Chemistry, The University of Leeds, Leeds LS2 9JT.

Received 14 September 1998; revised 16 November 1998; accepted 10 December 1998

Abstract: Aliphatic aldimines of a range of cyclic and acyclic 1,5-ketoaldehydes undergo metal catalysed regio- and stereo-specific imine → azomethine ylide → cycloaddition cascades. Acid catalysed cyclisations of the NH group of the pyrrolidine products onto the ketone functionality results in novel tri- and tetra-cyclic nitrogen heterocycles.

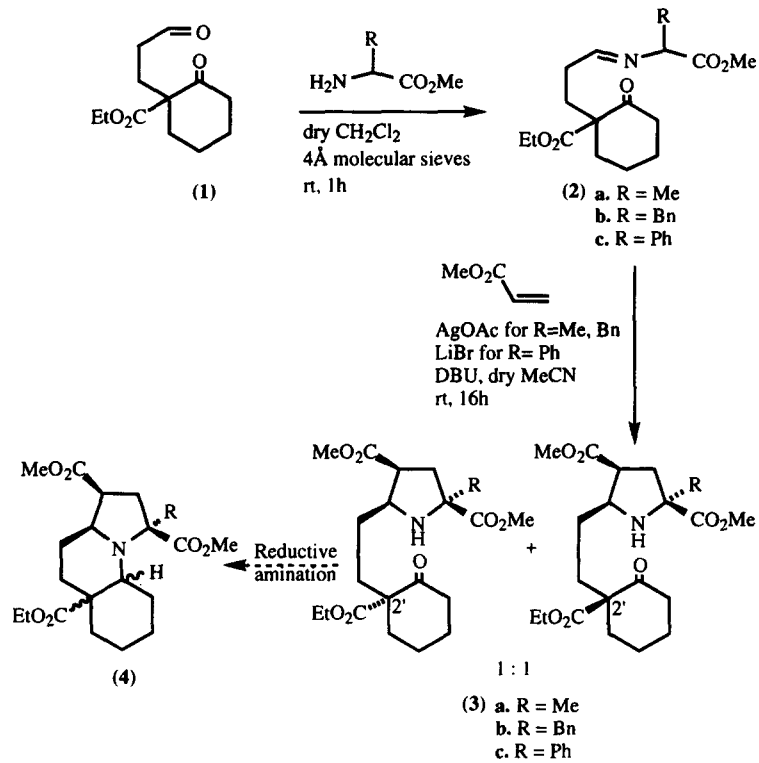
Novel methods for the construction of complex heterocyclic ring remains an area of continuing interest and innovation. The combination of two ring forming reactions into a sequential process offers a particularly powerful method for the construction of ring systems possessing a high degree of complexity. We have developed a novel regio- and stereo-specific methodology involving imine → azomethine ylide → cycloaddition cascade processes for the synthesis of highly functionalised pyrrolidines.[1] Following an exploration of imines of 1,5-dialdehydes[2] we now report the combination of such cascades employing monoimines of 1,5-ketoaldehydes with acid catalysed ring forming processes involving cyclisation of the NH moiety of the pyrrolidines onto a proximate carbonyl group. The products from these processes are tricyclic enamines and tetracyclic enamino ketones and differ substantially from those arising from 1,5-dialdehydes.[2]

Reactions with cyclic 1,5-ketoaldehydes

Our initial work focused on the synthesis of the basic tricyclic indolizidine ring system found in a number of alkaloids such as gephyrotoxin and related alkaloids.[3] 1,5-Ketoaldehydes, in which the ketone moiety resides in a cycloalkanone, were selected as starting materials. Such substrates are readily available *via* Michael addition of suitable cycloalkanones to acrolein.

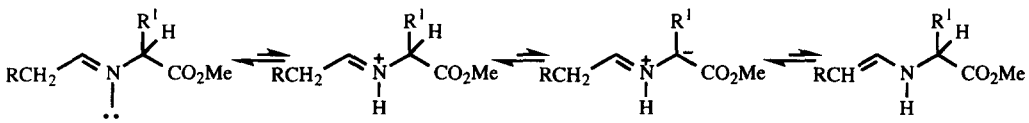
Treatment of **1**[4] with a series of α-aminoesters in the presence of 4Å molecular sieves in dry CH_2Cl_2 at room temperature for 1h gave the corresponding aliphatic aldimines **2a-c** in 89 - 92% yield.

0040-4020/99/$ - see front matter
PII: S0040-4020(98)01189-2



Scheme 1

The imine → azomethine ylide → cycloaddition cascade process can be achieved under thermal conditions or *via* metal ion catalysis at room temperature.[2] The milder conditions of the latter methodology are particularly valuable for cascades involving aliphatic aldimines. These latter substrates often give poor yields by the thermal 1,2-prototropy route due to imine ⇌ enamine tautomerism (**Scheme 2**) with consequent side reactions (eg - enamine Michael addition).[5]



Scheme 2

The 1,3-dipolar cycloaddition reaction of aliphatic aldimines **2a-c** with methyl acrylate in the presence of AgOAc/DBU or LiBr/DBU in dry MeCN at room temperature for 16h resulted in 1 : 1 diastereomeric mixtures of cycloadducts **3a-c** in 60 - 64% yield.

The ^{1}H n.m.r. spectra of the cycloadducts can be deceptively simple in $CDCl_3$ but the peaks of the individual diastereomers are clearly visible in C_6D_6 as illustrated for cycloadducts **3b** in **Figure 1**.

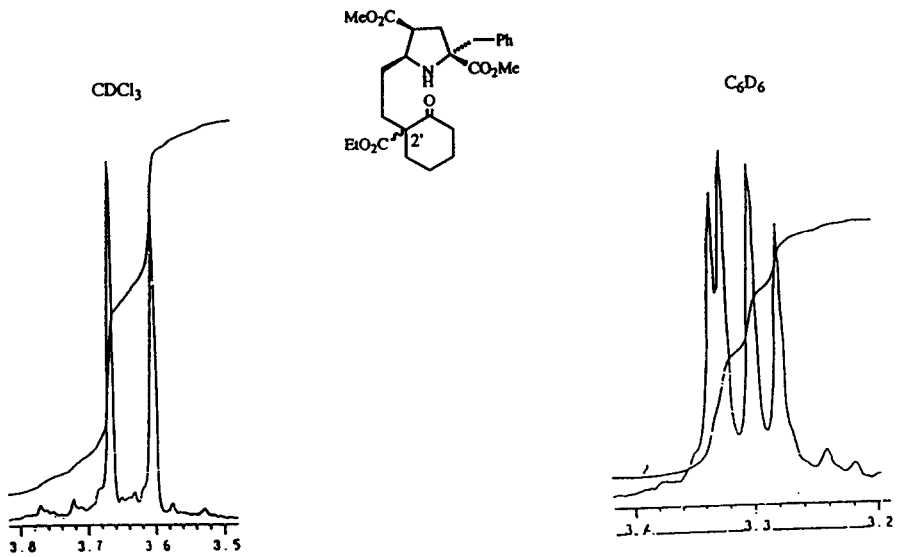
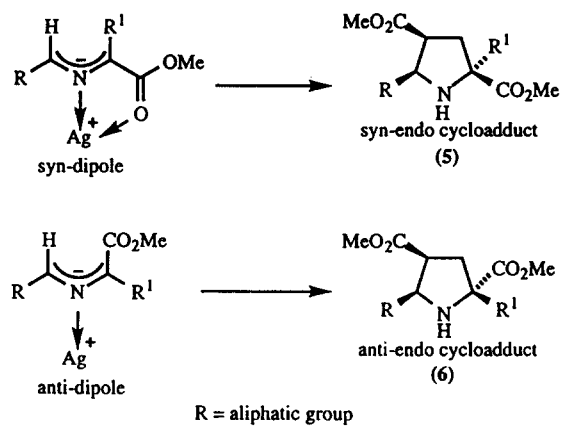


Figure 1. Effect of solvent on the methyl ester region of the ^{1}H n.m.r. spectra of the mixture of diastereomers 3b

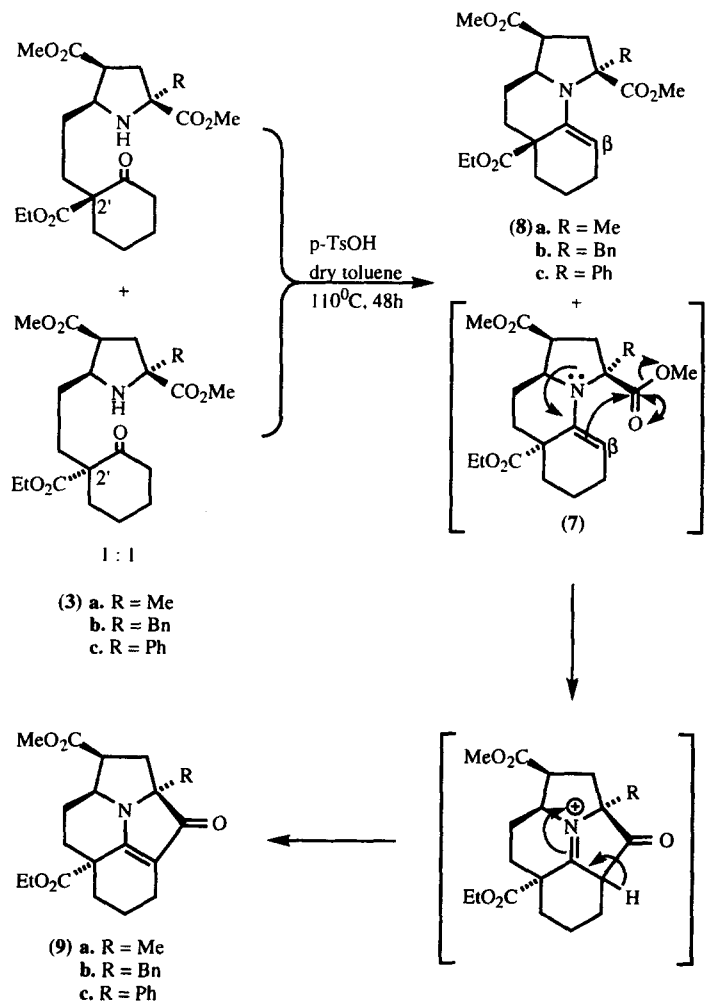
Previous work in our group showed that the Ag(I) catalysed cycloaddition reactions in MeCN result in mixtures of syn-endo **5** and anti-endo **6** cycloadducts due to the lack of stereoselectivity in the azomethine ylide forming step of the cascade. When related cycloaddition cascades were carried out in toluene it had proved possible to suppress formation of anti-endo cycloadduct[6]. However, when the imine **2b** was subjected to the cycloaddition cascade in dry toluene a 1: 1 diastereomeric mixture of cycloadducts **3b** was obtained.



The formation of diastereomeric mixtures of cycloadducts **3a-c** in these cases is not due to the formation of syn- and anti-dipoles but rather arises solely from the asymmetric carbon centre (2') adjacent to the carbonyl functionality in the cyclohexanone ring which, not unsurprisingly, exerts no diastereoselectivity. All efforts to separate the 1 : 1 diastereomeric mixtures of cycloadducts **3a-c** by column chromatography using different solvent systems failed.

We next attempted cyclisation via reductive amination of the carbonyl group **3** → **4** (**Scheme 1**). Several methods employing sodium cyanoborohydride[7,8] were initially tried without any success. The failure of this process in our system is presumably due to the sterically hindered carbonyl functionality in the cycloadduct **3**.

Application of standard methodology (catalytic p-TsOH in boiling toluene[9,10]) for enamine formation to the 1 : 1 mixtures of cycloadducts **3a-c** over 48h gave mixtures of enamines **8a-c** together with polycyclic nitrogen heterocycles **9a-c** (62 - 68%, based on one diastereomer) depending on the 2'-stereochemistry of the cycloadducts **3a-c** (**Scheme 3**). The enamines **8a-c** decomposed on attempted column chromatography on flash silica or neutral alumina. The stereochemistry of **9b** was established by X-ray crystallographic studies (**Figure 2**). Replacing boiling toluene by boiling benzene resulted in recovery of starting material.



Scheme 3

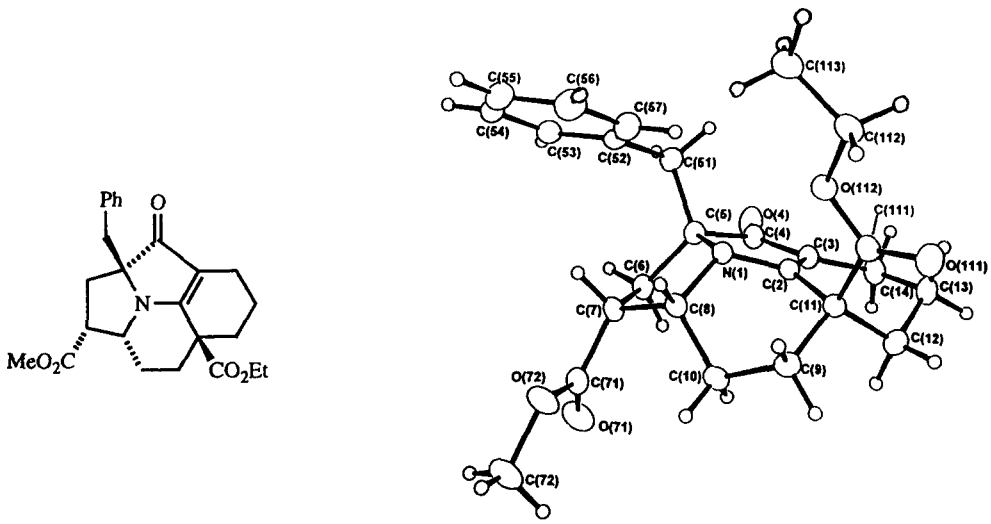
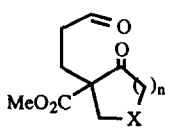
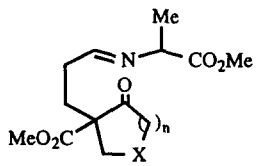


Figure 2. X-Ray crystallographic structure of 9b

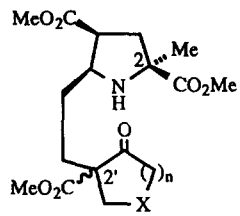
Thus one diastereomer undergoes double cyclisation to **9** whilst the other diastereomer undergoes conventional enamine forming cyclisation to **8**. Molecular models show this difference is due to the close proximity of the enamine β-carbon in **7**, but not in **8**, to the pyrrolidine C(2)- ester carbonyl group .



(**10**) **a.** X = CH_2, n = 1
b. X = CH_2, n = 3
c. X = NBn, n = 2
d. X = O, n = 2
e. X = S, n = 2



(**11**) **a.** X = CH_2, n = 1
b. X = CH_2, n = 3
c. X = NBn, n = 2
d. X = O, n = 2
e. X = S, n = 2

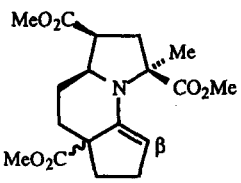


(**12**) **a.** X = CH_2, n = 1
b. X = CH_2, n = 3
c. X = NBn, n = 2
d. X = O, n = 2
e. X = S, n = 2

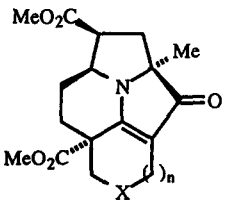
The 1,5-ketoaldehydes **10a-e**[4,11] were similarly reacted with alanine methyl ester in the presence of 4Å molecular sieves in dry CH_2Cl_2 at room temperature for 1h to give the aliphatic aldimines **11a-e** in 75 - 93% yield.

The imines **11a-d** reacted regio- and stereo-selectively with methyl acrylate in the presence of AgOAc and DBU in dry MeCN at room temperature over 16h to give cycloadducts **12a-d** in 61 - 65% yield as 1 : 1 diastereomeric mixtures of cycloadducts due to the asymmetric 2'-carbon centre. Imine **11e** failed to undergo a AgOAc catalysed cycloaddition reaction probably due to the strong coordination of the Ag(I) cation to sulfur[12] preventing the usual metallo-dipole formation.

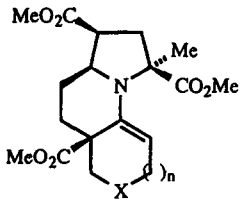
The acid catalysed cyclisation reaction of 1 : 1 diastereomeric mixture of cycloadducts **12a** resulted in a diastereomeric mixture of enamines **13**. Further cyclisation is prevented by the rigid framework impeding close approach of the enamine β-carbon and the proximal 2-methoxycarbonyl group. The purification of the diastereomeric mixture of enamines by column chromatography resulted in < 5% purified product due to extensive decomposition on the column.



(13)

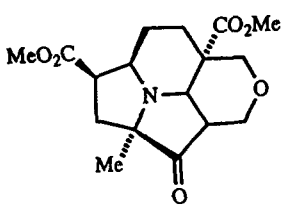


(14) a. X = CH_2, n = 2
b. X = NBn, n = 1
c. X = O, n = 1



(15) a. X = CH_2, n = 2
b. X = NBn, n = 1
c. X = O, n = 1

Cyclisation of the 1 : 1 diastereomeric mixtures of cycloadducts **12b-d** under our standard cyclisation conditions provided the polycyclic nitrogen heterocycles **14a-c** in 68 - 76% yield. No enamines **15a-c** were detected in the crude products. The X-ray crystal structure of polycyclic nitrogen heterocycle **14c** is shown in **Figure 3**.



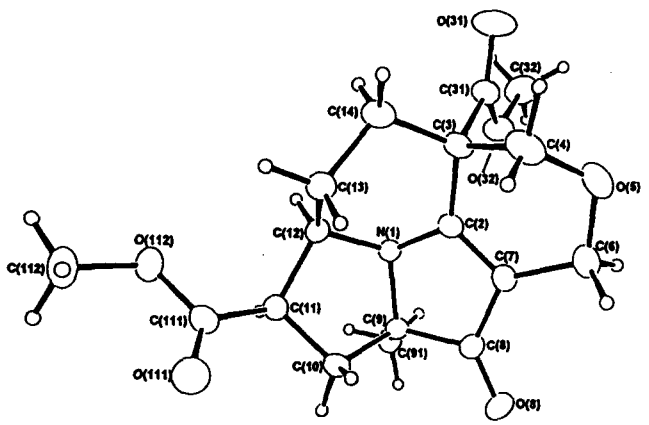
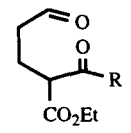


Figure 3. X-Ray crystallographic structure of 14c

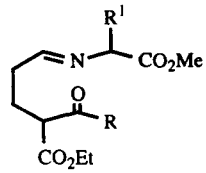
Reactions with acyclic 1,5-ketoaldehydes

The acyclic 1,5-ketoaldehydes[4] **16a** and **16b** were also prepared by surface mediated Michael addition reaction of the corresponding β-ketoesters with acrolein and then reacted with a series of α-aminoesters in the

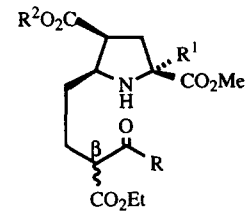
presence of 4Å molecular sieves at room temperature for 1h to give the aliphatic aldimines **17a-c** in 82 - 89% yield.



(16) **a.** R = Ph
b. R = 3-furyl



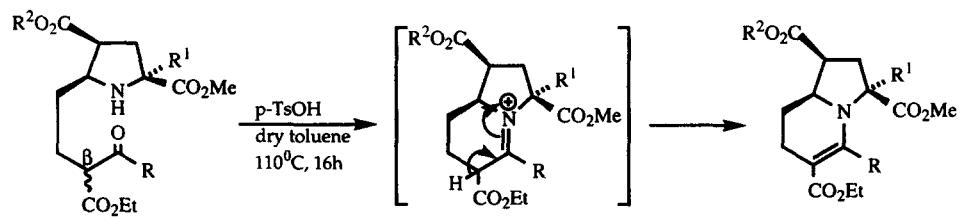
(17) **a.** R = Ph, R^1 = Me
b. R = Ph, R^1 = Bn
c. R = 3-furyl, R^1 = Me



(18) a. R = Ph, R^1 = Me, R^2 = Me
b. R = Ph, R^1 = Bn, R^2 = (-)-menthyl
c. R = 3-furyl, R^1 = Me, R^2 = Me

The AgOAc catalysed cycloaddition reaction of imines **17a** and **17c** with methyl acrylate in the presence of DBU proceeded in good yields to give 1 : 1 diastereomeric mixtures of syn-endo cycloadducts **18a** and **18c** (due to asymmetric β-carbon). Similarly the cycloaddition of imine **17b** with (-)-menthyl acrylate under standard cycloaddition conditions resulted in an analogous 1 : 1 diastereomeric mixture of cycloadducts **18b** in 59% yield. We have previously shown that the AgOAc catalysed cycloaddition of imines to menthyl acrylate furnishes enantiopure cycloadducts.[3]

Acid catalysed cyclisation of the 1 : 1 diastereomeric mixtures of cycloadducts **18a** and **18c** in the presence of a catalytic amount of p-TsOH in boiling toluene for 16h resulted in the formation of indolizidines **20a** and **20c** in 68% and 66% yields respectively *via* the iminium ion intermediate **19**. Enantiopure indolizidine **20b** was obtained, as expected, in 67% yield from the 1 : 1 diastereomeric mixture of cycloadducts **18b** since the C(6)- asymmetric centre is removed (**Scheme 4**).



(18) a. R = Ph, R^1 = Me, R^2 = Me
b. R = Ph, R^1 = Bn, R^2 = (-)-menthyl
c. R = 3-furyl, R^1 = Me, R^2 = Me

(19)

(20) a. R = Ph, R^1 = Me, R^2 = Me
b. R = Ph, R^1 = Bn, R^2 = (-)-menthyl
c. R = 3-furyl, R^1 = Me, R^2 = Me

Scheme 4

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[14]. The term ether refers to diethyl ether and petroleum ether refers to the fraction with boiling point 40-60°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°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)-propylidene]-alaninate (2a). Aldehyde **1**[4] (1.00 g, 4.42 mmol) and racemic alanine methyl ester (0.48 g, 4.65 mmol) gave the crude imine as a pale yellow oil (1.27 g, 92%). δ 7.65(t, 1H, J 4.6Hz, HC=N), 4.18(m, 2H, O<u>CH</u>$_2$Me), 3.87(q, 1H, J 6.8Hz, <u>CH</u>Me), 3.69(s, 3H, OMe), 2.53(m, 8H, 4 x CH_2), 1.70(m, 4H, 2 x CH_2), 1.37(d, 3H, J 6.8Hz, CH<u>Me</u>) and 1.24(t, 3H, J 7.2Hz, OCH$_2$<u>Me</u>); ***m/z***(%) 311(M^+, 1), 142(7), 55(7), 45(5) and 42(12).

Methyl N-[3-(1'-ethoxycarbonyl-2'-oxocyclohexyl)-propylidene]-phenylalaninate (2b). Aldehyde **1** (1.50 g, 6.64 mmol) and racemic phenylalanine methyl ester (1.25 g, 6.97 mmol) gave the crude imine as a pale yellow gum (2.35 g, 91%). δ 7.18(m, 6H, ArH and HC=N), 4.32(m, 2H, O<u>CH</u>$_2$Me), 3.88(dd, 1H, J 4.7, 9.4Hz, NCH), 3.73(s, 3H, OMe), 3.24(dd, 1H, J 4.6, 13.4Hz, PhCH), 2.97(dd, 1H, J 9.5, 13.4Hz, PhCH), 2.46-1.43(m, 12H, 6 x CH_2) and 1.24(t, 3H, J 7.3Hz, OCH$_2$<u>Me</u>); ***m/z***(%) 387(M^+, 1), 328(2), 314(1), 296(7), 98(3), 91(60), 88(100), 83 (7), 77(19), 65(19), 55(23), 51(11) and 42(13).

Methyl N-[3-(1'-ethoxycarbonyl-2'-oxocyclohexyl)-propylidene]-phenylglycinate (2c). Aldehyde **1** (1.00 g, 4.42 mmol) and racemic phenylglycine methyl ester (0.77 g, 4.65 mmol) gave the crude imine as a pale yellow gum (1.47 g, 89%). δ 7.74(t, 1H, J 4.6Hz, HC=N), 7.35(m, 5H, ArH), 4.94 (s, 1H, PhCH), 4.19(m, 2H, O<u>CH</u>$_2$Me), 3.72(s, 3H, OMe), 2.53-1.46(m, 12H, 6 x CH_2), and 1.27(t, 3H, J 7.2Hz, OCH$_2$<u>Me</u>); ***m/z***(%) 373(M^+, 4), 314(69), 300(13), 296(16), 164(3), 77(30), 65(4) and 51(7).

Methyl N-[3-(1'-methoxycarbonyl-2'-oxocyclopentyl)-propylidene]-alaninate (11a). Aldehyde **10a** (1.50 g, 7.58 mmol) and racemic alanine methyl ester (0.82 g, 7.95 mmol) gave the crude imine as a pale

yellow oil (1.99 g, 93%). δ 7.69(t, 1H, J 4.3Hz, HC=N), 3.90(q, 1H, J 6.8Hz, CHMe), 3.73 and 3.72(2 x s, 2 x 3H, 2 x OMe), 2.11(m, 10H, 5 x CH_2) and 1.40(d, 3H, J 6.8Hz, CHMe); ***m/z***(%) 283(M^+, 4), 268(3), 252(3), 224(75),110(15), 87(11) and 82(100).

Methyl N-[3-(1'-methoxycarbonyl-2'-oxocycloheptyl)-propylidene]-alaninate (11b). Aldehyde **10b** (2.00 g, 8.85 mmol) and racemic alanine methyl ester (0.96 g, 9.29 mmol) gave the crude imine as a pale yellow gum (2.45 g, 89%). δ 7.73(t, 1H, J 4.4Hz, HC=N), 3.94(q, 1H, J 6.8Hz, CHMe), 3.77 and 3.75(2 x s, 2 x 3H, 2 x OMe), 2.42(m, 6H, 3 x CH_2) 1.70(m, 8H, 4 x CH_2) and 1.44(d, 3H, J 6.8Hz, CHMe); ***m/z***(%) 311(M^+, 4), 252(53), 224(9) and 88(7).

Methyl N-[3-(1'-benzyl-3'-methoxycarbonyl-4'-oxopiperidyl)-propylidene]-alaninate (11c). Aldehyde **10c** (3.00 g, 9.90 mmol) and racemic alanine methyl ester (1.07 g, 10.40 mmol) gave the crude imine as a pale yellow gum (3.36 g, 88%). δ 7.66(s, 1H, HC=N), 7.28(m, 5H, ArH), 3.88(q, 1H, J 6.9Hz, CHMe), 3.73 and 3.71(2 x s, 2 x 3H, 2 x OMe), 3.58(m, 2H, $PhCH_2$), 3.40(d, 1H, J 11.6Hz, NCH), 2.96 and 2.43(2 x m, 2 x 2H, 2 x CH_2), 2.22(d, 1H, J 11.6Hz, NCH), 1.93(m, 4H, 2 x CH_2) and 1.38(d, 3H, J 6.9Hz, CHMe); ***m/z***(%) 388(M^+, 1), 357(1), 329(20), 301(8), 297(5), 260(15) and 91(100).

Methyl N-[3-(3'-methoxycarbonyl-4'-oxotetrahydropyranyl)-propylidene]-alaninate (11d). Aldehyde **10d** (0.76 g, 3.55 mmol) and racemic alanine methyl ester (0.38 g, 3.73 mmol) gave the crude imine as a pale yellow oil (0.80 g, 75%). δ 7.70(s, 1H, HC=N), 4.52(d, 1H, J 11.6Hz, OCH), 3.91(q, 1H, J 6.6Hz, CHMe), 3.79 and 3.73(2 x s, 2 x 3H, 2 x OMe), 3.45(d, 1H, J 11.6Hz, OCH), 2.88-1.60(m, 8H, 4 x CH_2) and 1.41(d, 3H, J 6.6Hz, CHMe); ***m/z***(%) 297(M^+-2, 1), 207(5), 179(7), 98(4), 87(8), 55(51) and 44(100).

Methyl N-[3-(3'-methoxycarbonyl-4'-oxotetrahydrothiopyranyl)-propylidene]-alaninate (11e). Aldehyde **10e** (1.00 g, 4.38 mmol) and racemic alanine methyl ester (0.47 g, 4.57 mmol) gave the crude imine as a pale yellow oil(1.14 g, 84%). δ 7.70(t, 1H, J 4.6Hz, HC=N), 3.91(q, 1H, J 6.8Hz, CHMe), 3.79 and 3.73(2 x s, 2 x 3H, 2 x OMe), 3.27-2.13(m, 10H, 5 x CH_2) and 1.36(d, 3H, J 6.8Hz, CHMe); ***m/z***(%) 315(M^+, 7), 256(56), 210(4), 142(68), 87(8) and 55(43).

Methyl N-(4-benzoyl-4-ethoxycarbonylbutylidene)-alaninate (17a). Aldehyde **16a**[4] (1.00 g, 4.03 mmol) and racemic alanine methyl ester (0.44 g, 4.23 mmol) gave the crude imine as a pale yellow oil (1.19 g, 89%). δ 7.75(m, 6H, PhH and HC=N), 4.51(m, 1H, $CHCO_2Et$), 4.13(m, 2H, OCH_2Me), 3.92(q, 1H, J 6.9Hz, CHMe), 3.72(s, 3H, OMe), 2.35(m, 4H, 2 x CH_2), 1.39(d, 3H, J 6.9Hz, CHMe) and 1.17(t, 3H, J 7.1Hz, OCH_2Me); ***m/z***(%) 333(M^+, 7), 274(20), 260(32), 256(6), 228(25), 105(100), 77(65), 51(23) and 39(10).

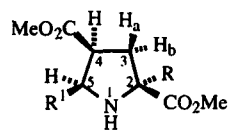
Methyl N-(4-benzoyl-4-ethoxycarbonylbutylidene)-phenylalaninate (17b). Aldehyde **16a** (0.50 g, 2.01 mmol) and racemic phenylalanine methyl ester (0.38 g, 2.12 mmol) gave the crude imine as a pale yellow oil (0.67 g, 82%). δ 7.23(m, 11H, ArH and HC=N), 4.39(m, 1H, $CHCO_2Et$), 4.14(m, 2H, OCH_2Me), 3.81(dd, 1H, J 4.9, 8.3Hz, NCH), 3.73(s, 3H, OMe), 3.17(dd, 1H, J 4.6, 13.3Hz, PhCH),

2.92(dd, 1H, J 7.6, 13.3Hz, PhCH), 2.16(m, 4H, 2 x CH_2) and 1.17(t, 3H, J 7.1Hz, $OCH_2\underline{Me}$); ***m/z***(%) : 409(M^+, 1), 318(1), 105(62), 91(51), 77(49), 65(20), 51(32) and 39(14).

Methyl N-[4-(3'-furoyl)-4-ethoxycarbonylbutylidene]-alaninate (17c). Aldehyde **16b** (1.00 g, 4.20 mmol) and racemic alanine methyl ester (0.45 g, 4.41 mmol) gave the crude imine as a pale yellow oil (1.19 g, 88%). δ 8.36(s, 1H, furyl-H), 7.73(t, 1H, J 3.6Hz, HC=N), 7.45 and 6.82(2 x s, 2 x 1H, furyl-H), 4.16(m, 3H, $\underline{CH}CO_2Et$ and $O\underline{CH_2}Me$), 3.93(q, 1H, J 6.7Hz, $\underline{CH}Me$), 3.74(s, 3H, OMe), 2.95(m, 4H, 2 x CH_2), 1.41(d, 3H, J 7.2Hz, $CH\underline{Me}$) and 1.21(t, 3H, J 7.0Hz, $OCH_2\underline{Me}$); ***m/z***(%) 323(M^+, 5), 264(7), 95(100) and 67(6).

General Procedure for Metal Catalysed Cycloaddition Reactions. A mixture of imine (1 eq), AgOAc or LiBr (1.2 eq), methyl acrylate (1.5 eq) and DBU (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.

Numbering of Pyrrolidine Ring.



Dimethyl 2-methyl-c-5-[1'-(1"-ethoxycarbonyl-2"-oxocyclohexyl)-ethyl]-pyrrolidine-r-2-,c-4-dicarboxylate (3a). Aldimine **2a** (1.27 g, 4.08 mmol), AgOAc (0.82 g, 4.90 mmol), DBU (0.75 g, 4.90 mmol) and methyl acrylate (0.53 g, 6.12 mmol) gave, after work up followed by flash chromatography eluting with ether, the **product** (1.00 g, 62%) as a pale yellow gum. (Found : C,60.3; H,7.9; N,3.4. $C_{20}H_{31}NO_7$ requires C,60.45; H,7.85; N,3.5%); δ (mixture of diastereoisomers) 4.21(m, 2H, $O\underline{CH_2}Me$), 3.77 and 3.64(2 x s, 2 x 3H, 2 x OMe), 3.27(q, 1H, J 6.6Hz, 5-H), 2.99(m, 1H, 4-H), 2.52(m, 4H, 3-H_a, NH and CH_2), 1.73(m, 11H, 3-H_b and 5 x CH_2), 1.40(s, 3H, Me) and 1.21(t, 3H, J 7.3Hz, $OCH_2\underline{Me}$); ***m/z***(%) 398(M^++1, 38), 338(100), 320(30), 292(14), 200(36), 55(7) and 42(6).

Dimethyl 2-benzyl-c-5-[1'-(1"-ethoxycarbonyl-2"-oxocyclohexyl)-ethyl]-pyrrolidine-r-2-,c-4-dicarboxylate (3b). Aldimine **2b** (2.35 g, 6.07 mmol), AgOAc (1.22 g, 7.29 mmol), DBU (1.11 g, 7.29 mmol) and methyl acrylate (0.78 g, 9.11 mmol) gave, after work up followed by flash chromatography eluting with ether, the **product** (1.73 g, 60%) as a pale yellow gum. (Found : C,65.95; H,7.6; N,2.8. $C_{26}H_{35}NO_7$ requires C,65.95; H,7.45; N,2.95%); δ (mixture of diastereoisomers) 7.21(m, 5H, ArH), 4.17(m, 2H, $O\underline{CH_2}Me$), 3.65 and 3.58(2 x s, 2 x 3H, 2 x OMe), 3.05(m, 1H, 5-H), 2.97(d, 1H, J 13.0Hz, PhCH), 2.83(m, 2H, PhCH and 4-H), 2.58(m, 1H, 3-H_a), 2.44(m, 5H, NH and 2 x CH_2), 2.19(m, 3H, 3-H_b and CH_2), 1.63(m, 6H, 3 x CH_2) and 1.24(t, 3H, J 7.1Hz, $OCH_2\underline{Me}$); δ (^{13}C) (mixture of diastereoisomers)

207.60(cyclohexanone-CO), 175.66, 173.71 and 171.64(3 x ester-CO), 136.87, 130.15, 127.87 and 126.57(Ar), 69.98, 62.31(5-C), 61.14($O\underline{CH_2}Me$), 60.44, 52.08 and 51.31(2 x OMe), 47.59(4-C), 46.21(CH_2), 40.98(3-C), 39.22($PhCH_2$), 35.98, 32.30, 27.48, 26.15 and 22.48(5 x CH_2) and 14.06($OCH_2\underline{Me}$); ***m/z***(%) 474(M^++1, 18), 414(33), 382(100), 91(47), 65(7), 55(16), 42(9) and 39(6); υ_{max} (film) 3600-3300, 2900, 1725, 730 and 700 cm^{-1}.

Dimethyl 2-phenyl-c-5-[1'-(1"-ethoxycarbonyl-2"-oxocyclohexyl)-ethyl]-pyrrolidine-r-2-,c-4-dicarboxylate (3c). Aldimine **2c** (1.47 g, 3.94 mmol), LiBr (0.41 g, 4.72 mmol), DBU (0.72 g, 7.29 mmol) and methyl acrylate (0.51 g, 5.91 mmol) gave, after work up followed by flash chromatography eluting with ether, the **product** (1.16 g, 64%) as a pale yellow gum. (Found : C,65.4; H,7.2; N,2.75. $C_{25}H_{33}NO_7$ requires C,65.35; H,7.25; N,3.05%); δ (mixture of diastereoisomers) 7.68(d, 2H, J 7.5Hz, ArH), 7.28(m, 3H, ArH), 4.22(m, 2H, $O\underline{CH_2}Me$), 3.69 and 3.66(2 x s, 2 x 3H, 2 x OMe), 3.12(m, 2H, 5-H and 3-H_a), 2.94(m, 1H, 4-H), 2.47(m, 4H, NH, 3-H_b and CH_2), 1.87(m, 10H, 5 x CH_2) and 1.28(t, 3H, J 7.0Hz, $OCH_2\underline{Me}$); ***m/z***(%) 460(M^++1, 79), 400(100), 382(5), 77(10) and 65(4).

Dimethyl 2-methyl-c-5-[1'-(1"-methoxycarbonyl-2"-oxocyclopentyl)-ethyl]-pyrrolidine-r-2-,c-4-dicarboxylate (12a). Aldimine **11a** (1.99 g, 7.03 mmol), AgOAc (1.41 g, 8.44 mmol), DBU (1.28 g, 8.44 mmol) and methyl acrylate (0.91 g, 10.55 mmol) gave, after work up followed by flash chromatography eluting with ether, the **product** (1.58 g, 61%) as a pale yellow oil. (Found : C,58.5; H,7.55; N,3.5. $C_{18}H_{27}NO_7$ requires C,58.5; H,7.35; N,3.8%); δ (mixture of diastereoisomers) 3.77, 3.69 and 3.65(3 x s, 3 x 3H, 3 x OMe), 3.27(m, 1H, 5-H), 3.10(m, 1H, 4-H), 2.46(m, 5H, 3-H_a and 2 x CH_2), 1.75(m, 8H, 3-H_b, NH and 3 x CH_2) and 1.40(s, 3H, Me); ***m/z***(%) 370(M^++1, 51), 354(4), 310(17) 200(4) and 83(6).

Dimethyl 2-methyl-c-5-[1'-(1"-methoxycarbonyl-2"-oxocycloheptyl)-ethyl]-pyrrolidine-r-2-,c-4-dicarboxylate (12b). Aldimine **11b** (2.45 g, 7.87 mmol), AgOAc (1.58 g, 9.44 mmol), DBU (1.44 g, 9.44 mmol) and methyl acrylate (1.02 g, 11.80 mmol) gave, after work up followed by flash chromatography eluting with ethyl acetate, the **product** (1.90 g, 61%) as a pale yellow gum. (Found : C,60.35; H,7.6; N,3.25. $C_{20}H_{31}NO_7$ requires C,60.45; H,7.85; N,3.5%); δ (mixture of diastereoisomers) 3.89, 3.81 and 3.74(3 x s, 3 x 3H, 3 x OMe), 3.36(m, 1H, 5-H), 3.07(m, 1H, 4-H), 2.64(m, 4H, NH, 3-H_a and CH_2), 2.13(m, 5H, 3-H_b and 2 x CH_2), 1.78(m, 8H, 4 x CH_2) and 1.50(s, 3H, Me); ***m/z***(%) 398(M^++1, 1), 382(1), 366(1), 338(100), 200(41), 140(18), 43(76), 55(11) and 42(12).

Dimethyl 2-methyl-c-5-[1'-(1"-benzyl-3"-methoxycarbonyl-4"-oxopiperidyl)-ethyl]-pyrrolidine-r-2-,c-4-dicarboxylate (12c). Aldimine **11c** (3.36 g, 7.), AgOAc (1.73 g, 10.39 mmol), DBU (1.58 g, 10.39 mmol) and methyl acrylate (1.12 g, 12.99 mmol) gave, after work up followed by flash chromatography eluting with ether, the **product** (2.58 g, 63%) as a pale yellow viscous gum. (Found : C,63.15; H,7.1; N,5.95. $C_{25}H_{34}N_2O_7$ requires C,63.25; H,7.2; N,5.9%); δ (mixture of diastereoisomers) 7.28(m, 5H, ArH), 3.75 and 3.72(2 x s, 2 x 3H, 2 x OMe), 3.68(m, 2H, $PhCH_2$), 3.59(s, 3H, OMe), 3.38(m, 1H, 5-H), 3.22(m, 1H, 4-H), 2.97(m, 4H, 2 x CH_2), 2.38(m, 5H, 3-H_a, 3-H_b, NH and CH_2), 1.90 and 1.54(2 x m, 2 x 2H, 2 x CH_2) and 1.38(s, 3H, Me); ***m/z***(%) 474(M^+, 1), 415(98), 383(11), 356(23), 297(19), 91(100), 77(4), 65(10) and 39(4).

Dimethyl 2-methyl-c-5-[1'-(3"-methoxycarbonyl-4"-oxotetrahydropyranyl)-ethyl]-pyrrolidine-r-2-,c-4-dicarboxylate (12d). Aldimine **11d** (0.80 g, 2.68 mmol), AgOAc (0.54 g, 3.21 mmol), DBU (0.49 g, 3.21 mmol) and methyl acrylate (0.35 g, 4.01 mmol) gave, after work up followed by flash chromatography eluting with ethyl acetate, the **product** (0.67 g, 65%) as a pale yellow gum. (Found : C,56.55; H,6.7; N,3.45. $C_{18}H_{27}NO_8$ requires C,56.1; H,7.05; N,3.65%); δ (mixture of diastereoisomers) 4.48(d, 1H, J 11.5Hz, OCH), 4.17(m, 1H, 5-H), 3.77 and 3.73(2 x s, 2 x 3H, 2 x OMe), 3.69(m, 2H, CH_2), 3.66(s, 3H, OMe), 3.41(m, 1H, OCH), 3.37(m, 1H, 4-H), 2.84(m, 4H, 3-H_a, CH and CH_2), 1.76(m, 4H, 3-H_b, NH and CH_2), 1.40(s, 3H, Me) and 1.27(m, 1H, CH); ***m/z***(%) 384(M^+-1, 11), 326(10), 252(7), 208(6), 200(9), 193(8), 185(8) and 158(6).

Dimethyl 2-methyl-c-5-(1'-benzoyl-1'-ethoxycarbonylprop-3'-yl)-pyrrolidine-r-2-,c-4-dicarboxylate (18a). Aldimine **17a** (1.19 g, 3.58 mmol), AgOAc (0.72 g, 4.30 mmol), DBU (0.65 g, 4.30 mmol) and methyl acrylate (0.46 g, 5.37 mmol) gave, after work up followed by flash chromatography eluting with ether, the **product** (1.07 g, 71%) as a pale yellow oil. (Found : C,63.2; H,6.7; N,3.15. $C_{22}H_{29}NO_7$ requires C,63.0; H,6.95; N,3.35%); δ (mixture of diastereoisomers) 7.69(m, 5H, ArH), 4.30(m, 1H, $\underline{CH}CO_2Et$), 4.13(m, 2H, $O\underline{CH_2}Me$), 3.73(s, 3H, OMe), 3.67(s, 1H, NH), 3.56(s, 3H, OMe), 3.13(m, 1H, 5-H), 2.96(m, 1H, 4-H), 2.55(m, 1H, 3-H_a), 2.13(m, 2H, CH_2), 1.88(m, 1H, 3-H_b), 1.44(m, 5H, Me and CH_2) and 1.21(t, 3H, J 7.3Hz, $OCH_2\underline{Me}$); ***m/z***(%) 419(M^+, 4), 374(5), 360(100), 315(21), 314(73), 200(3), 141(39), 105(96), 77(63), 51(16) and 39(9).

1R,2S,5R-Menthyl 2-benzyl-r-2R-methoxycarbonyl-c-5S-(1'-benzoyl-1'-ethoxycarbonylprop-3'-yl)-pyrrolidine-c-4S-carboxylate (18b). Aldimine **17b** (0.67 g, 3.58 mmol), AgOAc (0.33 g, 1.97 mmol), DBU (0.30 g, 1.97 mmol) and menthyl acrylate (0.35 g, 1.64 mmol) gave, after work up followed by flash chromatography eluting with ether, the **product** (0.60 g, 59%) as a pale yellow oil , $[\alpha]_D$ -25.2 (c 1.86, $CHCl_3$). (Found : C,71.65; H,7.75; N,2.3. $C_{37}H_{49}NO_7$ requires C,71.7; H,7.95; N,2.25%); δ (mixture of diastereoisomers) 7.56(m, 10H, ArH), 4.63(m, 1H, OCH), 4.45(m, 1H, $\underline{CH}CO_2Et$), 4.14(q, 2H, J 7.0Hz, $O\underline{CH_2}Me$), 3.67(s, 3H, OMe), 3.13(m, 1H, 5-H), 2.95(m, 3H, $PhCH_2$ and 4-H), 2.66(m, 1H, 3-H_a), 2.21-1.21(m, 11H, 3-H_b, NH and aliphatic-H), 1.17(t, 3H, J 7.0Hz, $OCH_2\underline{Me}$) and 0.59(m, 13H, aliphatic-H); ***m/z***(%) 620(M^++1, 27), 574(5), 560(19), 528(100), 436(6), 105(46) and 77(13).

Dimethyl 2-methyl-c-5-(1'-(3"-furoyl)-1'-ethoxycarbonylprop-3'-yl)-pyrrolidine-r-2-,c-4-dicarboxylate (18c). Aldimine **17c** (1.19 g, 3.68 mmol), AgOAc (0.74 g, 4.42 mmol), DBU (0.67 g, 4.42 mmol) and methyl acrylate (0.48 g, 5.53 mmol) gave, after work up followed by flash chromatography eluting with ether, the **product** (1.00 g, 66%) as a pale yellow oil. (Found : C,59.35; H,6.55; N,3.45. $C_{20}H_{27}NO_8$ requires C,58.7; H,6.55; N,3.45%); δ (mixture of diastereoisomers) 8.17(s, 1H, furyl-H), 7.46 and 6.79(2 x s, 2 x 1H, 2 x furyl-H), 4.16(q, 2H, J 7.2Hz, $O\underline{CH_2}Me$), 3.92(t, 1H, J 7.4Hz, $\underline{CH}CO_2Et$), 3.76 and 3.61(2 x s, 2 x 3H, 2 x OMe), 3.33(m, 1H, 5-H), 3.01(m, 1H, 4-H), 2.99(s, 1H, NH), 2.59(m, 1H, 3-H_a), 2.11(m, 2H, CH_2), 1.92(dd, 1H, J 7.3, 13.9Hz, 3-H_b), 1.43(m, 5H, Me and CH_2) and 1.21(t, 3H, J 7.2Hz, $OCH_2\underline{Me}$); ***m/z***(%) 408(M^+-1, 1), 200(7), 95(22) and 41(4).

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.

Tetracycle (9a). Prepared from the 1 : 1 diastereomeric mixture of cycloadducts **3a** (1.00 g, 2.53 mmol) and p-TsOH (0.05 g, 0.25 mmol). Work up after 48h gave a mixture of **9a**, enamine **8a** and decomposition products. Flash chromatography, eluting with ether, afforded **9a** [0.05 g, 68% (yield based on one diastereomer)] as a colourless solid, m.p. 112-114^{0}C. (Found : C,65.4; H,7.35; N,4.2. $C_{19}H_{25}NO_5$ requires C,65.7; H,7.25; N,4.05%); δ 4.13(q, 2H, J 7.2Hz, O$\underline{CH_2}$Me), 3.70(m, 1H, 5-H), 3.58(s, 3H, OMe), 3.35(q, 1H, J 7.9Hz, 4-H), 2.13(m, 5H, 3-H_a and 2xCH_2), 1.84(dd, 1H, J 6.5, 13.5Hz, 3-H_b), 1.72(m, 2H, CH_2), 1.42(m, 4H, 2 x CH_2), 1.29(s, 3H, Me) and 1.19(t, 3H, J 7.2Hz, OCH$_2\underline{Me}$); ***m/z***(%) 347(M^+, 39), 319(6), 274(21), 260(17), 246(100), 215(4) and 187(29).

Tetracycle (9b). Prepared from the 1 : 1 diastereomeric mixture of cycloadducts **3b** (1.73 g, 3.66 mmol) and p-TsOH (0.07 g, 0.37 mmol). Work up after 48h gave a mixture of **9b**, enamine **8b** and decomposition products. Flash chromatography, eluting with ether, afforded **9b** [0.51 g, 66% (yield based on one diastereomer)] which crystallised from ether as colourless plates, m.p. 106-108^{0}C. (Found : C,70.9; H,6.95; N,3.4. $C_{25}H_{29}NO_5$ requires C,70.9; H,6.9; N,3.3%); δ 7.20(m, 5H, ArH), 4.13(q, 2H, J 7.1Hz, O$\underline{CH_2}$Me), 3.50(s, 3H, OMe), 3.33(m, 1H, 5-H), 2.91 and 2.81(2 x d, 2 x 1H, J 13.6Hz, 2 x PhCH), 2.61(q, 1H, J 7.7Hz, 4-H), 2.09(m, 5H, 3-H_a and 2 x CH_2), 1.95(dd, 1H, J 7.7, 13.7Hz, 3-H_b), 1.67(m, 2H, CH_2), 1.37(m, 4H, 2 x CH_2) and 1.21(t, 3H, J 7.1Hz, OCH$_2\underline{Me}$); δ (^{13}C) 205.29(CO), 173.78 and 172.78(2 x ester-CO), 172.44 and 136.57(2 x =C), 131.10, 127.81, 126.43 and 112.63(Ar), 77.80(2-C), 61.25(O$\underline{CH_2}$Me), 58.15(5-C), 51.68(OMe), 48.95(4-C), 45.53(C-CO_2Et), 41.72(PhCH_2), 34.39, 31.02, 30.00, 22.07, 18.91 and 18.68(6 x CH_2) and 14.09(OCH$_2\underline{Me}$); ***m/z***(%) 423(M^+, 34), 350(6), 332(100), 259(5), 200(4), 91(19), 77(4) and 65(4); υ_{max} (nujol) 2900, 1710, 1650, 720 and 690 cm^{-1}.

Tetracycle (9c). Prepared from the 1 : 1 diastereomeric mixture of cycloadducts **3c** (1.16 g, 2.52 mmol) and p-TsOH (0.05 g, 0.25 mmol). Work up after 48h gave a mixture of **9c**, enamine **8c** and decomposition products. Flash chromatography, eluting with ether, afforded **9c** [0.32 g, 62% (yield based on one diastereomer)] as pale yellow prisms, m.p. 142-144^{0}C. (Found : C,70.4; H,6.5; N,3.4. $C_{24}H_{27}NO_5$ requires C,70.4; H,6.65; N,3.4%); δ 7.59(d, 2H, J 7.3Hz, ArH), 7.30(m, 3H, ArH), 4.26(m, 2H, O$\underline{CH_2}$Me), 3.89(m, 1H, 5-H), 3.65(s, 3H, OMe), 3.27(q, 1H, J 7.9Hz, 4-H) 2.48-1.39(m, 12H, 3-H_a, 3-H_b and 5xCH_2) and 1.35(t, 3H, J 7.0Hz, OCH$_2\underline{Me}$); ***m/z***(%) 409(M^+, 68), 381(28), 380(100), 378(6), 336(13), 77(7) and 39(3).

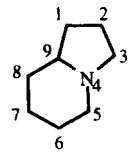
Enamine (13). Prepared from the 1 : 1 diastereomeric mixture of cycloadducts **12a** (0.50 g, 1.36 mmol) and p-TsOH (0.03 g, 0.14 mmol). Work up after 16h gave a diastereomeric mixture of enamines **13** and decomposition products (yield of crude product 62%). Chromatography on neutral alumina, eluting with ether, afforded **13** (< 5%). δ 4.59(m, 1H, C=CH), 3.79, 3.75 and 3.62(3 x s, 3 x 3H, 3 x OMe), 3.20(m, 2H, 5-H and 4-H), 2.33(m, 6H, 3-H_a, 3-H_b and 2 x CH_2), 1.61(m, 4H, 2 x CH_2) and 1.40(s, 3H, Me); ***m/z***(%) 351(M^+, 10), 292(100), 233(9) and 174(7).

Tetracycle (14a). Prepared from the 1 : 1 diastereomeric mixture of cycloadducts **12b** (1.90 g, 4.79 mmol) and p-TsOH (0.09 g, 0.48 mmol). Work up after 48h gave a mixture of **13b** and decomposition products. Flash chromatography, eluting with ethyl acetate, afforded **13b** [0.63 g, 76% (yield based on one diastereomer)] which crystallised from ether as colourless prisms, m.p. 104-106^{0}C. (Found : C,64.2; H,7.15; N,3.85. $C_{19}H_{25}NO_5$. 0.5H_2O requires C,64.05; H,7.35; N,3.9%); δ 3.95(q, 1H, J 6.9Hz, 5-H), 3.61(s, 3H, OMe), 3.57(m, 1H, 4-H), 3.52(s, 3H, OMe), 2.44(m, 1H, CH), 1.98(m, 3H, 3-H_a and CH_2), 1.78(m, 3H, 3-H_b and CH_2), 1.62(m, 3H, CH and CH_2), 1.39(m, 2H, CH_2), 1.21(s, 3H, Me) and 1.05(m, 2H, CH_2); δ (^{13}C) 201.05(CO), 175.33 and 172.20(2 x ester-CO), 171.34 and 112.44(2 x =C), 72.94(2-C), 53.85(5-C), 52.14 and 51.46(2 x OMe), 51.18(C-CO_2Me), 51.11(4-C), 36.08(CH_2), 34.49(3-C), 32.01, 28.01, 26.97, 21.95 and 20.84(5 x CH_2) and 18.39(Me); ***m/z***(%) 347(M^+, 22), 288(6), 260(100) and 202(45).

Tetracycle (14b). Prepared from the 1 : 1 diastereomeric mixture of cycloadducts **12c** (0.47 g, 1.00 mmol) and p-TsOH (0.02 g, 0.10 mmol). Work up after 48h gave a mixture of **13c** and decomposition products. Flash chromatography, eluting with ethyl acetate, afforded **13c** [0.15 g, 72% (yield based on one diastereomer)] as a pale yellow solid, m.p. 138-140^{0}C. (Found : C,66.35; H,6.6; N,6.35. $C_{24}H_{28}N_2O_5$. 0.5H_2O requires C,66.5; H,6.75; N,6.45%); δ 7.30(m, 5H, ArH), 3.80(m, 2H, 5-H and NCH), 3.69 and 3.66(2 x s, 2 x 3H, 2 x OMe), 3.56(m, 2H, 4-H and NCH), 3.26 and 2.96(2 x d, 2 x 1H, J 14.4Hz, 2 x PhCH), 1.80(m, 8H, 3-H_a, 3-H_b, and 3 x CH_2) and 1.40(s, 3H, Me); ***m/z***(%) 424(M^+, 19), 396(9), 337(10), 306(12), 274(10), 91(100), 77(5), 65(12) and 51(3).

Tetracycle (14c). Prepared from the 1 : 1 diastereomeric mixture of cycloadducts **12d** (0.40 g, 1.04 mmol) and p-TsOH (0.02 g, 0.10 mmol). Work up after 48h gave a mixture of **14c** and decomposition products. Flash chromatography, eluting with ethyl acetate, afforded **14c** [0.12 g, 68% (yield based on one diastereomer)] which crystallised from CH_2Cl_2 as colourless prisms, m.p. 172-173^{0}C. (Found : C,59.35; H,6.6; N,3.8. $C_{17}H_{21}NO_6$. 0.5H_2O requires C,59.3; H,6.45; N,4.05%); δ 4.55 and 4.35(2 x d, 2 x 1H, J 14.4Hz, 2 x OCH), 4.27(d, 1H, J 11.0Hz, OCH), 3.90(m, 1H, 5-H), 3.79 and 3.69(2 x s, 2 x 3H, 2 x OMe), 3.57(m, 1H, 4-H), 3.17(d, 1H, J 11.0Hz, OCH), 1.81(m, 5H, 3-H_a, 3-H_b, CH and CH_2), 1.41(s, 3H, Me) and 1.31(m 1H, CH); ***m/z***(%) 335(M^+, 87), 307(18), 276(34), 248(100), 217(4), 202(8) and 189(4).

Numbering of Indolizidine Ring.



Dimethyl 3-methyl-5-phenyl-6-ethoxycarbonylindolizid-5-ene-1,3-dicarboxylate (20a). Prepared from the 1 : 1 diastereomeric mixture of cycloadducts **18a** (0.40 g, 0.95 mmol) and p-TsOH (0.02 g, 0.10 mmol). Work up after 16h followed by flash chromatography eluting with ether, afforded **20a** (0.26 g, 68%) as a pale yellow oil. (Found : C,66.1; H,6.8; N,3.2. $C_{22}H_{27}NO_6$ requires C,65.8; H,6.8; N,3.5%); δ 7.14(m, 5H, ArH), 3.67(m, 5H, OMe and $O\underline{CH_2}Me$), 3.42(m, 4H, OMe and 9-H), 2.83(dd, 1H, J 5.9, 12.5Hz, 2-H_a), 2.65(m, 1H, 1-H), 2.22(m, 1H, CH), 1.92(dd, 1H, J 6.7, 12.5Hz, 2-H_b), 1.72(m, 2H, CH_2), 1.25(m, 4H, Me and CH) and 0.74(t, 3H, J 7.1Hz, $OCH_2\underline{Me}$); ***m/z***(%) 401(M^+, 11), 342(100), 328(7) and 77(7).

1R, 2S, 5R-Menthyl 3-benzyl-3R-methoxycarbonyl-5-phenyl-6-ethoxycarbonylindolizid-5-ene-1S-carboxylate (20b). Prepared from the 1 : 1 diastereomeric mixture of cycloadducts **18b** (0.20 g, 0.32 mmol) and p-TsOH (0.01 g, 0.03 mmol). Work up after 16h, followed by flash chromatography eluting with 1 : 1 v/v ether-petroleum ether, afforded **20b** (0.13 g, 67%) as a pale yellow gum, $[\alpha]_D$ +55.3 (c 1.36, $CHCl_3$). (Found : C,72.95; H,8.0; N,2.3. $C_{37}H_{47}NO_6$. $0.5Et_2O$ requires C,73.3; H,8.2; N,2.2%); δ 7.34(m, 10H, ArH), 4.52(m, 1H, OCH), 3.74(m, 2H, $O\underline{CH_2}Me$), 3.63(s, 3H, OMe), 3.51(m, 1H, 9-H), 2.83(m, 2H, $PhCH_2$), 2.49(m, 1H, 1-H) and 2.26-0.56(m, 27H, 2-H_a, 2-H_b, $OCH_2\underline{Me}$ and aliphatic-H); ***m/z***(%) 601(M^+, 18), 542(15), 510(100), 91(29) and 77(7).

Dimethyl 3-methyl-5-(2'furyl)-6-ethoxycarbonylindolizid-5-ene-1,3-dicarboxylate (20c). Prepared from the 1 : 1 diastereomeric mixture of cycloadducts **18c** (0.40 g, 0.98 mmol) and p-TsOH (0.02 g, 0.10 mmol). Work up after 16h, followed by flash chromatography eluting with ether, afforded **20c** (0.26 g, 69%) as a pale yellow gum. [Found (H.R.M.S) : 391.1631. $C_{20}H_{25}NO_7$ requires 391.1631]; δ 7.43(m, 3H, furyl-H), 3.87(m, 2H, $O\underline{CH_2}Me$), 3.76 and 3.59(2 x s, 2 x3 H, 2 x OMe), 3.50(m, 1H, 9-H), 2.78(dd, 1H, J 5.2, 12.5Hz, 2-H_a), 2.65(m, 1H, 1-H), 2.19(m, 2H, CH_2), 1.94(dd, 1H, J 6.7, 12.5Hz, 2-H_b), 1.61(m, 2H, CH_2), 1.38(s, 3H, Me) and 0.98(t, 3H, J 7.1Hz, $OCH_2\underline{Me}$); ***m/z***(%) : 391(M^+, 19), 346(12), 332(100) and 318(7).

X-ray Crystallography - Data for both compounds were collected at 200 K on a Stoe STADI4 4-circle diffractometer using ω-θ scans and graphite monochromated Cu-K_α radiation (λ=1·54184 Å). Both data sets were collected for absorption using azimuthal ψ-scans. Full details of crystal data, data collection and structure refinement are given in Table 1.

The structures of both compounds were solved by direct methods using SHELXS-86[15] and were refined by full-matrix least squares (based on F^2) using SHELXL-97[16]. In both cases non-hydrogen atoms were refined with anisotropic displacement parameters and hydrogen atoms were constrained to idealised positions using a riding model with free rotation for methyl groups.

Complete atomic co-ordinates, anisotropic displacement parameters and interatomic distances and angles have been deposited with the Cambridge Crystallographic Data Centre.

Table 1. Crystal Data for Compounds **9b** and **14c**

	9b	**14c**
formula	$C_{25}H_{29}NO_5$	$C_{17}H_{21}NO_6$
f.w.	423.49	335.35
crystal dimensions, mm	0.45 x 0.38 x 0.20	0.62 x 0.46 x 0.30
crystal system	orthorhombic	monoclinic
space group	*Pbca*	$P2_1/a$
a, Å	15.101(3)	8.4584(7)
b, Å	16.446(3)	13.0885(7)
c, Å	17.564(3)	14.8129
β, °	-	96.078(6)
V, Å^3	4362.0(14)	1630.7(2)
Z	8	4
D_{calcd}, g cm^{-3}	1.29	1.37
μ, mm^{-1}	0.726	1.366
F(000)	1816	712
max., min. transmission factors	0.838, 0.736	0.870, 0.592
θ_{max}°	32.33	32.26
Total data collected	4488	4874
R_{int}[a]	0.0283	0.0407
Unique reflections	3509	2562
'Observed' refections[b]	2361	2359
number of parameters, *p*	283	221
goodness of fit on F^2, *s*[c]	1.025	1.064
R_1[d]	0.0494	0.0486
wR[e]	0.1427	0.1280
weighting parameters[f]	0.083, 1.0704	0.0496, 0.7007
extinction coefficient[g]	0.00073	0.0038(4)
largest diff, peak and hole, eÅ^{-3}	0.241, -0.284	0.216, -0.163

Footnotes

a) $R_{int} = \Sigma|F_o^2 - F_o^2(mean)|/\Sigma[F_o^2]$

b) $F_c^2 > 2.0\sigma(F_c^2)$

c) $s = [\Sigma[w(F_o^2-F_c^2)^2]/(n-p)]^{1/2}$

d) $R_1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$

e) $wR = [\Sigma[wF_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2}$

f) $w = [\sigma^2(F_o^2) + (aP)2 + bP]^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$

g) $F_c' = kF_c[1+0.001*F_c^2\lambda^3/\sin 2\theta]^{-1/4}$

Acknowledgements: We thank Leeds University for support.

References

1. Grigg, R.; Sridharan, V., *Advances in Cycloaddition*, Ed. D.P.Curran, JAI Press, **1993,** Vol.3, p.161-204.
2. Grigg, R.; Hargreaves, S.; Redpath, J.; Turchi, S.; Yoganathan, G., *Synthesis*, In press.
3. Daly, J.W.; Witkop, B.; Tokuyama, T.; Nishikawa, T.; Karle, I.L., *Helv. Chem. Acta.*, **1977,** *60*, 1128-1140.
4. Ranu, B.C.; Bhar, S.; Sarkar, D.C., *Tetrahedron Lett.*, **1991,** *32*, 2811-2812.
   Ranu, B.C.; Bhar, S., *Tetrahedron* , **1992,** *48*, 1327-1332.
   Cope, C.; Synerholm, M.E., *J. Am. Chem. Soc.*, **1950,** *72*, 5228-5232.
   Baker, B.R.; Shapiro, H.S., *J. Med. Chem.*, **1963,** *6*, 664-669.
5. Audisio, G.; Porzio, W.; Zetta, J.; Ferruti, P., *J. Chem. Soc., Perkin Trans. 11*, **1979,** 1391-1394.
6. Grigg, R.; Montgomery, J.; Somasunderam, A., *Tetrahedron*, **1992,** *48*, 10431-10442.
7. Borch, R.F.; Bernstein, M.D.; Durst, H.D., *J. Am. Chem. Soc.*, **1971,** *93*, 2897-2904.
   Lane, C.F., *Synthesis*, **1975,** 135-146.
8. Manescalchi, F.; Nardi, A.R.; Savoia, D., *Tetrahedron Lett.*, **1994,** *35*, 2775-2778.
   Mattson, R.J.; Pham, K.M.; Leuck, D.J.; Cowen, K.A., *J. Org. Chem.*, **1990,** *55*, 2552-2554.
9. Ihara, M.; Taniguchi, T.; Makita, K.; Takano, M.; Ohnishi, M.; Taniguchi, N.; Fukumoto, K.; Kabuto, C., *J. Am. Chem. Soc.*, **1993,** *115*, 8107-8115.
   Rejek, M.; Wimmer, Z.; Saman, D.; Ricankova, M.; Nemec, V., *Helv. Chem. Acta.*, **1994,** *77*, 1241-1255.

10. Hayakawa, K.; Takewaki, M.; Fujimoto, I.; Kanematsu, K., *J. Org. Chem.*, **1986,** *51,* 5100-5105.

11. Vebrel, J.; Carrie, R., *Bull. Soc. Chim. Fr.*, **1982,** 161-166.
Ghosh, A.K.; Liu, W., *J. Org. Chem.*, **1995,** *60,* 6198-6201.
Corey, E.J.; Pine, S.G., *Tetrahedron Lett.*, **1983,** 2821-2824.

12. Savic, V., *Ph. D. Thesis,* University of Leeds, **1994,** p.71.

13. Barr, D.A.; Dorrity, M.J.; Grigg, R.; Hargreaves, S.; Malone, J.F.; Montgomery, J.; Redpath, J. Stevenson, P.; Thornton-Pett, M., *Tetrahedron,* **1995,** *51,* 273-294.

14. Gordon, A.J.; Ford, R.A., *The Chemist's Companion,* John Wiley & Sons, **1972,** p.431 and p.434.

15. Sheldrick, G.M., *Acta. Crystallogr., Sect A,* **1990,** *46,* 467.

16. Sheldrick, G.M., SHELXL-97, Program for refinement of crystal structures, University of Gottingen.